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Universidad del País Vasco

Euskal Herriko Unibertsitatea

ASYMMETRIC SYNTHESIS OF α-THIOFUNCTIONALIZED CARBONYL COMPOUNDS: ACCESS TO THIOEPOXIDES AND TERTIARY THIOLS

DOCTORAL THESIS

Yurre Olaizola Alvarez

Donostia, 2015

Universidad del País Vasco Euskal Herriko Unibertsitatea

CONFORMIDAD DEL DEPARTAMENTO

El Consejo del Departamento de Química Orgánica I en reunión celebrada el día 3 de marzo de 2015 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: **"Asymmetric synthesis of α-thiofunctionalized carbonyl compounds: access to thioepoxides and tertiary thiols"** dirigida por el Dr. Caludio Palomo Nicolay y la Dra. Mª Antonia Mielgo Vicente y presentada por Doña. Yurre Olaizola Alvarez ante este Departamento.

En Donostia, a 4 de marzo de 2015

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Dr. Claudio Palomo Nicolau con N.I.F. 37655199J como Director de la Tesis Doctoral: **"Asymmetric synthesis of α-thiofunctionalized carbonyl compounds: access to thioepoxides and tertiary thiols"** realizada en el Departamento Química Orgánica I, Facultad de Químicas, Universidad del País Vasco por el Doctorando Doña. Yurre Olaizola Alvarez, autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia, a 27 de febrero de 2015

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PARA SU PRESENTACION

Dra. Mª Antonia Mielgo Vicente con N.I.F. 15995379Y como Directora de la Tesis Doctoral: **"Asymmetric synthesis of α-thiofunctionalized carbonyl compounds: access to thioepoxides and tertiary thiols"** realizada en el Departamento Química Orgánica I, Facultad de Químicas, Universidad del País Vasco por el Doctorando Doña. Yurre Olaizola Alvarez, autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia, a 27 de febrero de 2015

LA DIRECTORA DE LA TESIS

M.ª Antonia Mielgo

Fdo.: Mª Antonia Mielgo Vicente

Universidad del País Vasco Euskal Herriko Unibertsitatea

ACTA DE GRADO DE DOCTOR O DOCTORA
ACTA DE DEFENSA DE TESIS DOCTORAL

DOCTORANDO/A DON/DÑA. Yurre Olaizola Alvarez

TITULO DE LA TESIS: Asymmetric synthesis of α-thiofunctionalized carbonyl compounds: access to thioepoxides and tertiary thiols

El Tribunal designado por la Comisión de Postgrado de la UPV/EHU para calificar la Tesis Doctoral arriba indicada y reunido en el día de la fecha, una vez efectuada la defensa por el/la doctorando/a y contestadas las objeciones y/o sugerencias que se le han formulado, ha otorgado por unanimidad la calificación de:

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Eskerrak

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Ciencias Químicas de San Sebastián, Universidad del País Vasco, (UPV-EHU) bajo la dirección del Dr. Claudio Palomo Nicolau y la Dra. Antonia Mielgo Vicente, a quienes expreso mi más sincero agradecimiento primero por darme la oportunidad de desarrollar esta tesis doctoral en este departamento y por su dedicación y esfuerzo durante el desarrollo de este trabajo.

I want to thank Dr. Peter I. Dalko and his group for giving me the opportunity to do a short but intense stay in his laboratory at the University of Descartes in Paris for the development of this research work. Merci de votre accueil et de votre hospitalité.

La financiación de este trabajo ha provenido de una beca predoctoral del Ministerio de Educación, Cultura y Deporte (AP2009-1486), así como de la UFI QOSYC.

Tambíen me gustaría agradecer al resto del grupo de profesores que comprenden este departamento; especialmente al Dr. Aitor Landa que ha sido compañero en todos los proyectos que he participado y me ha ayudado y enseñado mucho.

Nola ez, departamentuko beste partaide guztiei ere eskerrak eman nahi dizkiet, bertan egindako lagunei. (Bai LAGUNEI esan dot!!). Ez ditut izenak jarriko baten bat ahazteko beldurrez, asko izan baitira. Asko izan dira baita ere beraien ondoan bizitako momento onak eta beraiei esker bide hau errazagoa izan da.

Ez ditut ahaztu nahi kuadrilako lagunak, askotan galdera inkomodo ta erantzun ezinak egin arren ta zer egiten ibili naizen ulertu gabe ere beti aurrera jarraitzeko animatu nautenak.

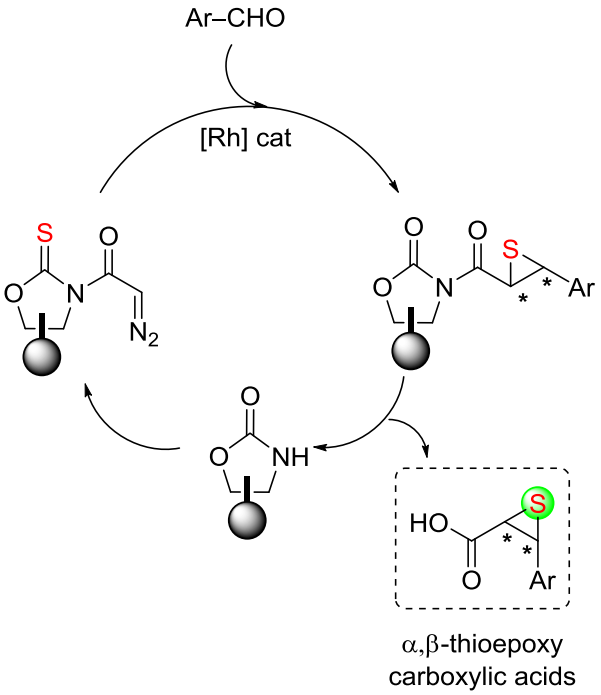
Nire eskerrik beroenak etxekoei, atxabaltakoei Ama, Aita eta Amaiari, denerako beti hor egoteagatik eta gasteizkoei emandako babes eta animoengatik. Azkenik, nere maitte Ekhiri, nerekin bizitza konpartitzeagatik, eman dizkidan zorion guztiengatik eta batez ere momentu ez hain onetan ere beti ondoan egoteagatik.

Mila esker danoi

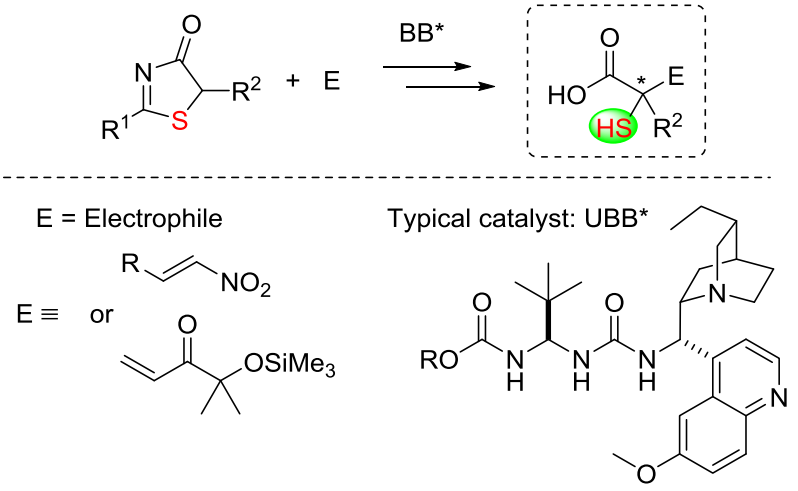
Summary

The aim of this PhD Thesis has been the development of novel methodologies for the asymmetric synthesis of some sulfur-containing carboxylic acid derivatives; more specifically, α,β-thioepoxy and α,α-disubstituted α-mercapto carboxylic acid derivatives.

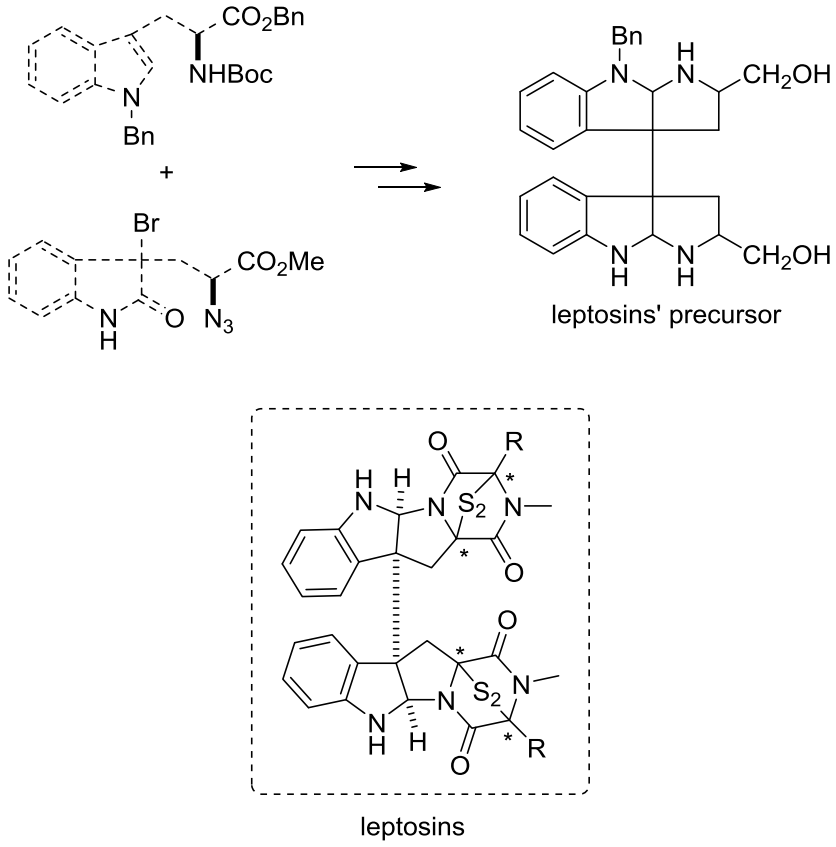
Inspired by previous work from our laboratory on the dual ability of the oxazolidin-2-thione group to act as an intramolecular sulfur-donor reagent and a stereodirecting group, we demonstrate herein that *N*-(diazoacetyl)oxazolidin-2-thiones react efficiently with aromatic aldehydes in the presence of rhodium catalyst and serve as both *C*─*C* and *C*─*S* bond forming reagents while controlling reaction stereochemistry in the stereoselective synthesis of thioepoxides. Accordingly, an unprecedented sulfur transfer process with concomitant *C*─*C* bond formation is reported for the first time.



On the other hand, the first procedure to obtain enantioenriched α-mercapto carboxylic acids from 5*H*-thiazol-4-ones, has also been described. These sulfur-based (pro)nucleophiles, which have never been used in asymmetric synthesis, can be easily deprotonated by ureidopeptide-like bifunctional Brønsted bases (UBB*) and other chiral bifunctional Brønsted bases (BB*) and added to different Michael acceptors such as nitroalkenes or α'-oxy enones.



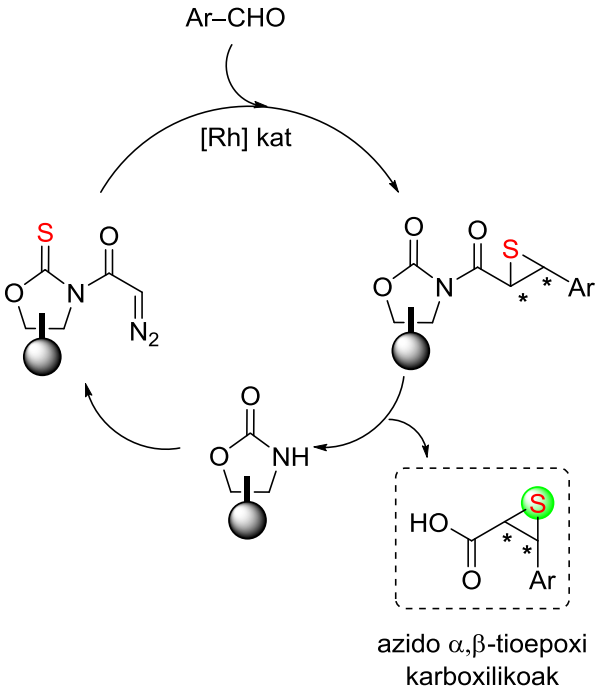
Finally, and under the guidance of Prof. Dr. Dalko from the University of Descartes in Paris, and as a complement of the previous work, preliminary research towards the synthesis of leptosins, a type of sulfur-containing *epi*(polythio)diketopiperazine (ETP) alkaloids with a broad range of biological activities, has also been undertaken.



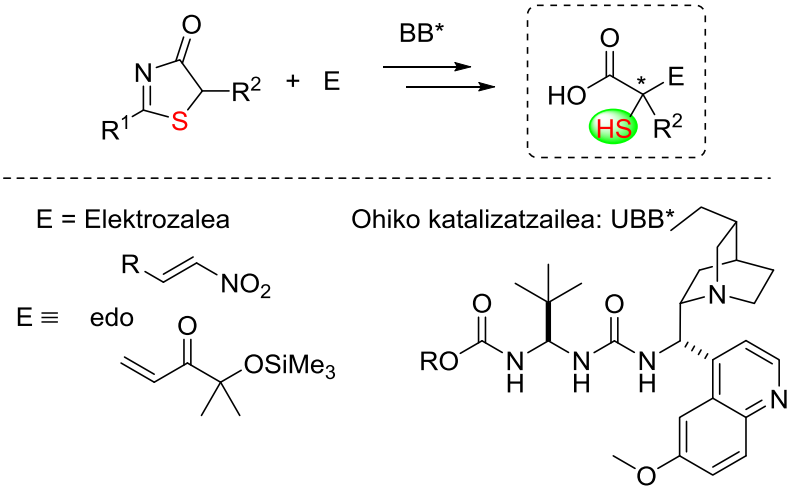
Laburpena

Tesi honen helburu nagusia sufredun azido karboxiliko jakin batzuen sintesi asimetrikorako metodologia berriak garatzea izan da. Hain zuzen ere: azido α,β-tioepoxi karboxilikoak eta azido α,α-diordezkatu α-merkapto karboxilikoak.

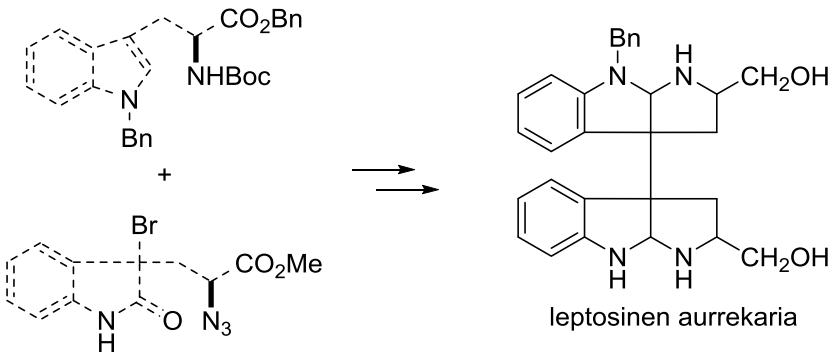
Gure ikerketa taldean oxazolidin-2-tiona taldeak duen gaitasun bikoitza erakutsi zen, alde batetik sufre-transferentziarako erreaktibo intramolekular bezala eta bestetik, erreakzioaren estereokimikaren talde zuzentzaile gisa. Lan honetan oinarriturik, Tesi honetan *N*-(diazoazetil)oxazolidin-2-tionek aldehido aromatikoekin modu eraginkorrean erreakzionatu dezaketela tioepoxidoak estereoselektiboki emateko frogatu dugu katalizatzaile moduan rodioa erabiliz. Erreakzio honetan *C–C* eta *C–S* lotura berriak prozesu berean eratzen dira eta oxazolidin-2-tionak paper bikoitza du: S-emailearena eta erreakzioaren estereokimikaren kontrolatzailearena. Halako prozesuek ez dute aurrekaririk, guk dakigula.

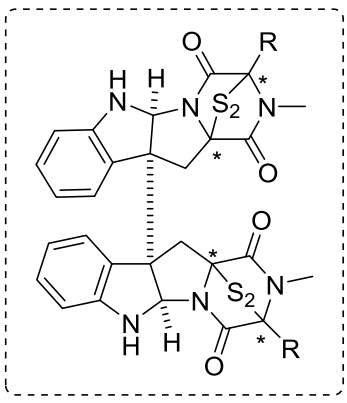


Bigarren atalean, enantioaberastutako azido α-merkapto karboxilikoak lortzeko organokatalisian oinarritutako prozedura berri bat deskribatzen da, pronukleozale bezala 5*H*-tiazol-4-onak erabiltzen diren lehendabiziko aldia izanik. Prozesu honetan pronukleozale hauek erraz deprotonatzen dira ureidopeptido motako (UBB*) eta bestelako Brønsted base bifuntzionalak (BB*) erabiliz, gero Michael hartzaile desberdinetara, esaterako nitroalkanotara eta α'-oxi enonatara adizionatzeko.



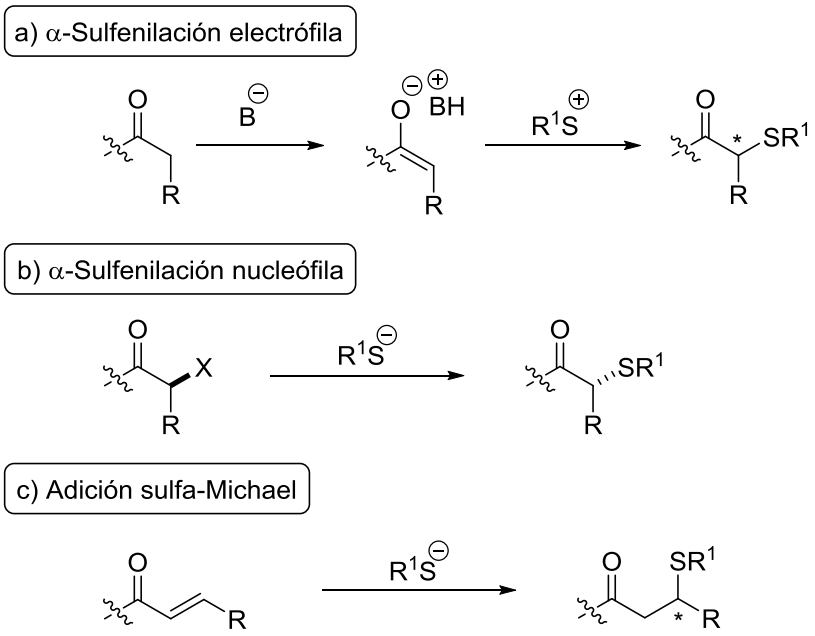
Aurreko bi atalen osagarri gisa, Pariseko Descartes Unibertsitateko Peter I. Dalko irakaslearen gidaritzapean egindako lana aurkezten da; hain zuzen ere leptosinen sintesi totalean hastapen lan bat. Sufrea duten *epi*(politio)diketopiperazina (ETP) alkaloide hauek aktibitate biologiko ezberdin ugari dituzte.





Resumen

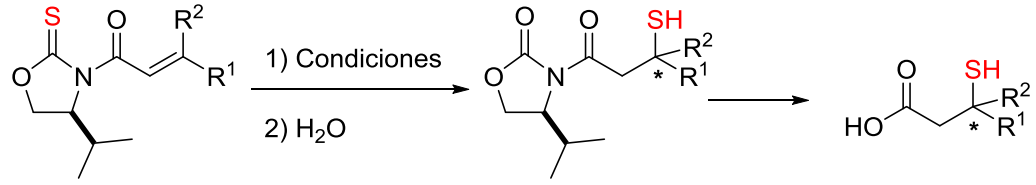
Muchos productos naturales y sustancias bioactivas, así como ligandos empleados en síntesis asimétrica son compuestos organosulfurados. Más concretamente, las unidades estructurales que contienen carbonilos tiofuncionalizados están presentes en muchos compuestos biológicamente activos y/o son importantes precursores para su síntesis. Por ello, han sido notables los esfuerzos realizados con el fin de desarrollar métodos estereocontrolados para la preparación de este tipo de unidades. Dos de las aproximaciones comunes implican, por un lado, las α-sulfenilaciones (tanto electrófilas como nucleófilas) de compuestos carbonílicos, y por otro lado, la adición conjugada de nucleófilos de azufre a aceptores de Michael (Esquema 1).



Esquema 1. Estrategias habituales para la síntesis asimétrica de compuestos carbonílicos tiofuncionalizados.

Basándose en estas estrategias se han desarrollado muchos protocolos que hoy en día proporcionan acceso a compuestos carbonílicos tiofuncionalizados. Sin embargo, a pesar del progreso en este campo, todavía hay algunas limitaciones, como por ejemplo, la ausencia de métodos para acceder a compuestos α,β-tioepoxi carbonílicos (tioepóxidos) de forma directa y estereocontrolada; así como la escasez de protocolos para preparar tioles terciarios. Así, el objetivo principal de la presente Tesis Doctoral ha sido el desarrollo de nuevas metodologías para la síntesis estereoselectiva de derivados de ácidos carboxílicos α,β-tioepoxicarbonilícos y ácidos α-mercapto α,α-disustituidos.

Trabajos previos desarrollados en nuestro grupo de investigación han demostrado la doble función del grupo oxazolidin-2-tiona, que actúa simultáneamente como inductor de la estereoquímica y como reactivo, en una reacción muy eficiente de transferencia intramolecular de azufre en *N*-enoil oxazolidin-2-tionas promovida tanto por ácidos de Lewis como de Brønsted (Esquema 2).

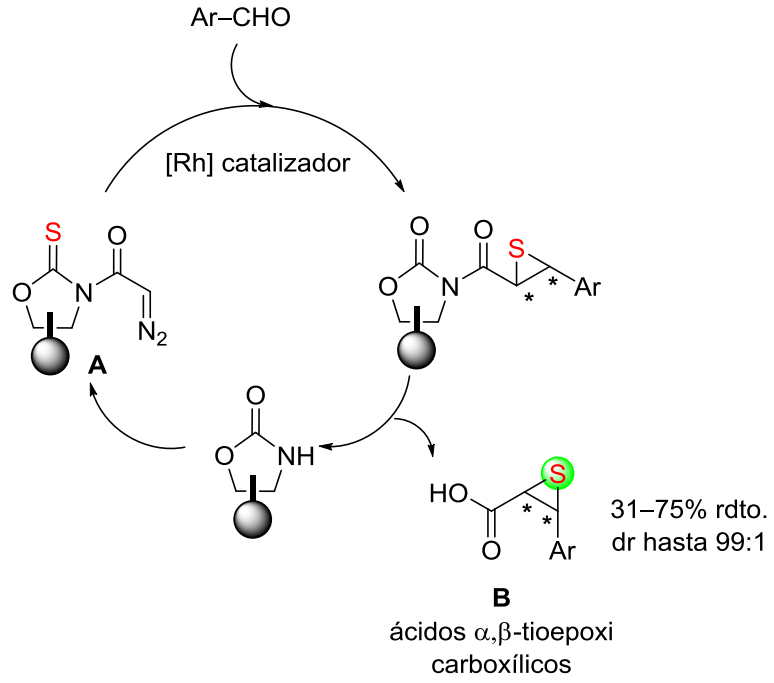


R^1= alquilo; R^2= arilo

Condiciones:
Ácidos de Lewis: $SnCl_4$ o BF_3 (2 eq.)
Ácidos de Brønsted: CF_3CO_2H (2 eq.)

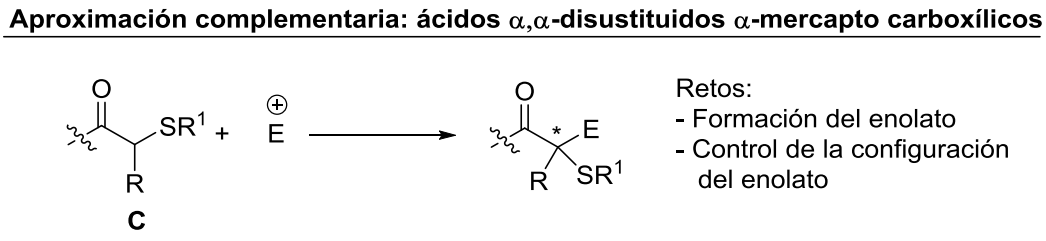
Esquema 2. β-Tiofuncionalización de compuestos carbonílicos mediante transferencia de azufre intramolecular.

Basándonos en esta reacción, en la presente Tesis demostramos que las *N*-(diazoacetil)oxazolidin-2-tionas **A** (Esquema 3) en presencia de un catalizador de Rh son sustratos eficientes para la síntesis estereoselectiva de tioepóxidos **B** en su reacción con aldehídos aromáticos. Estos diazo compuestos promueven simultáneamente la formación de enlaces *C–C* y *C–S,* y controlan además la estereoquímica del proceso. Esta síntesis asimétrica directa de tioepóxidos involucra un proceso intramolecular de transferencia de azufre sin precedentes junto con la formación simultánea de un enlace *C–C*. La escisión de la oxazolidinona permite recuperar y reciclar el auxiliar quiral y produce los correspondientes ácidos α,β-tioepoxi carboxílicos ópticamente activos con excelente estereoselectividad. Estudios de DFT proporcionan una explicación plausible para la reactividad y estereoselectividad observada en la reacción de transferencia de azufre, incluyendo la inversión de preferencia *cis/trans* observada para diferentes benzaldehídos. Los resultados de estas investigaciones se describen en el capítulo 2.



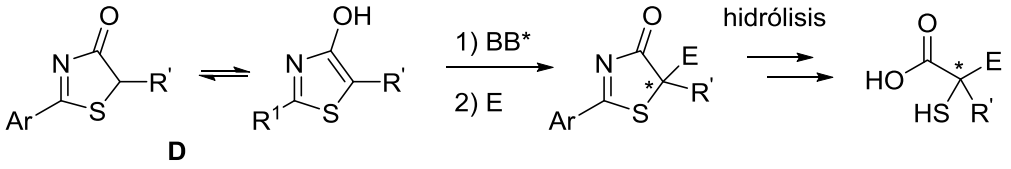
Esquema 3. Procedimiento desarrollado para la síntesis estereoselectiva de ácidos α,β-tioepoxi carboxílicos.

Por otra parte, la mayoría de los procedimiento para obtener tioles terciarios a partir de sustratos carbonílicos se basan en α-sulfenilaciones. Una aproximación complementaria para obtener este tipo de compuestos podría ser el empleo de (pro)nucleófilos del tipo **C** (Esquema 4) que contienen el átomo de azufre, y que podrían ser desprotonados por bases de Brønsted, para después ser utilizados en la reacción con un electrófilo. Las dos claves de esta propuesta son, por un lado, la búsqueda de condiciones adecuadas para la formación del enolato en presencia de bases de Brønsted, y por otro lado, el control de la configuración del enolato, un aspecto crucial para el control eficiente de la estereoselectividad del proceso.



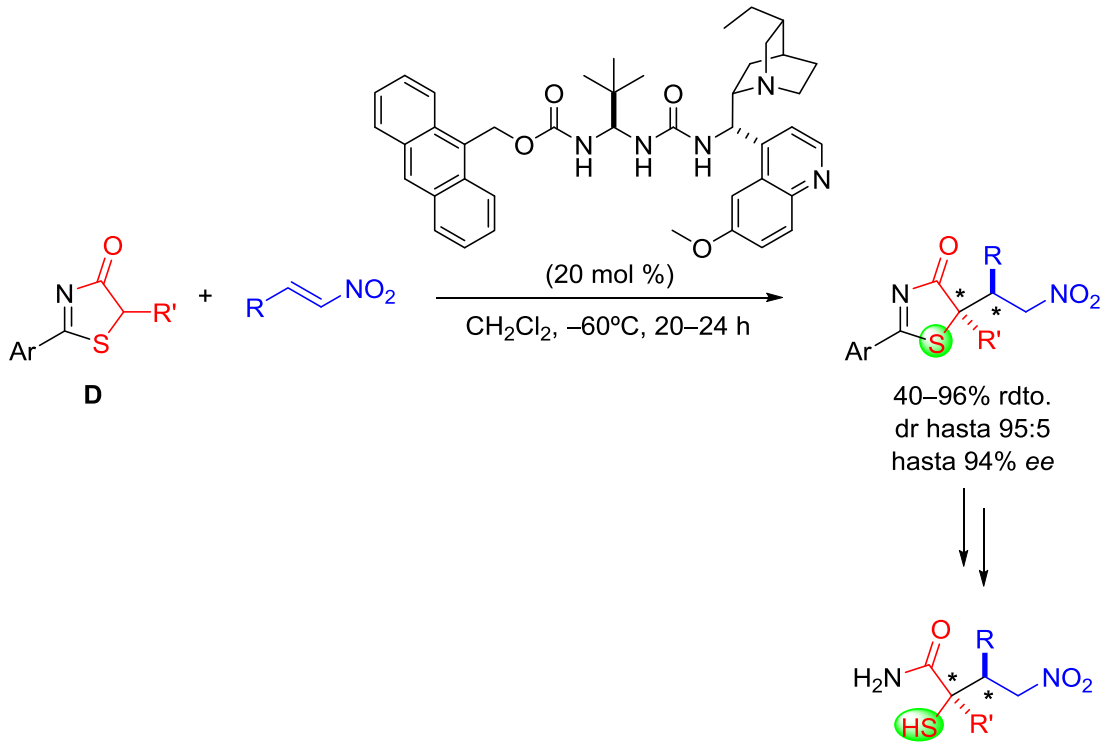
Esquema 4. Propuesta para la síntesis estereoselectiva de compuestos carbonílicos α-tiofuncionalizados α,α-disustituidos.

En este contexto, la presente Tesis describe un procedimiento para obtener ácidos α-mercapto carboxílicos enantioenriquecidos a partir de 5*H*-tiazol-4-onas **D** (Esquema 5) mediante adiciones de Michael a nitroalquenos y α'-oxi enonas. Estos resultados se describen en el capítulo 3. Estos (pro)nucleófilos que contienen azufre, hasta donde nosotros sabemos, no han sido previamente empleados en sístesis asimétrica, pero estudios de RMN han demostrado que en disolución existen en equilibrio entre la dos formas tautómeras, la forma cetónica y la forma enólica. Así, pueden desprotonarse fácilmente empleando bases de Brønsted quirales. Además, y dada la naturaleza cíclica de estos sustratos la geometría del enolato resultante está fijada lo que a su vez facilitaría el control de la estereolectividad en la reacción con diferentes electrófilos. La hidrólisis de la tiazolona en los aductos de adición porporciona el correspondiente ácido α,α-disustituido α-mercapto carboxílico portador del grupo tiol libre de forma altamente estereoselectiva. Cabe destacar que la mayoría de los procedimientos descritos en la bibliografía porporcionan tioéteres terciarios y su tranformación en derivados de tioles terciarios libres no es una reacción trivial.



Esquema 5. Propuesta desarrollada para la síntesis de ácido α,α-disustituidos α-mercapto carboxílicos.

Así, en una primera instancia se eligieron nitroalquenos como electrófilos para su utilización en la reacción de Michael. Tras un estudio de diferentes condiciones de reacción para la adición de 5*H*-tiazol-4-onas **D** a nitroalquenos, se ha demostrado que las bases de Brønsted quirales conocidas no son eficientes en el control de la estereoquímica del proceso. Sin embargo, los mejores resultados se obtuvieron con bases de Brønsted bifuncionales de tipo ureidopeptídico (UBB*) que han sido descritas en nuestro grupo de investigación (Esquema 6).



Esquema 6. Procedimiento desarrollado para la síntesis estereoselectiva de derivados de ácidos α,α-disustitudos α-mercapto carboxílicos.

En base a estos resultados y basándonos en la experiencia de nuestro grupo de investigación en el empleo de α'-hidroxi enonas en varias transformaciones como reacciones de Diels-Alder, reacciones 1,3-dipolares con nitronas y diferentes adiciones de Michael se decidió investigar la extensión de la anterior metodología a α'-hidroxi enonas como aceptores de Michael. Estos sustratos, hasta donde nosotros sabemos, no han sido empleados anteriormente en procedimientos organocatalíticos. Además estas estructuras presentan varios puntos de coordinación, así como diferentes modos de activación, debido a que pueden actuar de ambas formas, como dadores y como aceptores de enlace de hidrógeno (Figura 1).

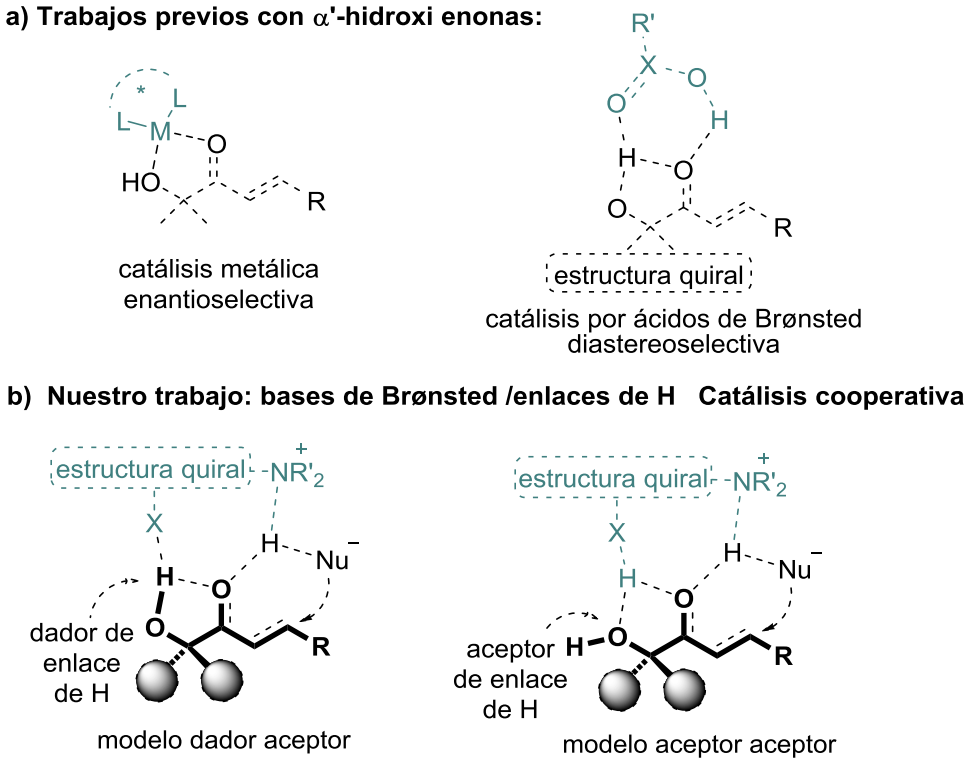
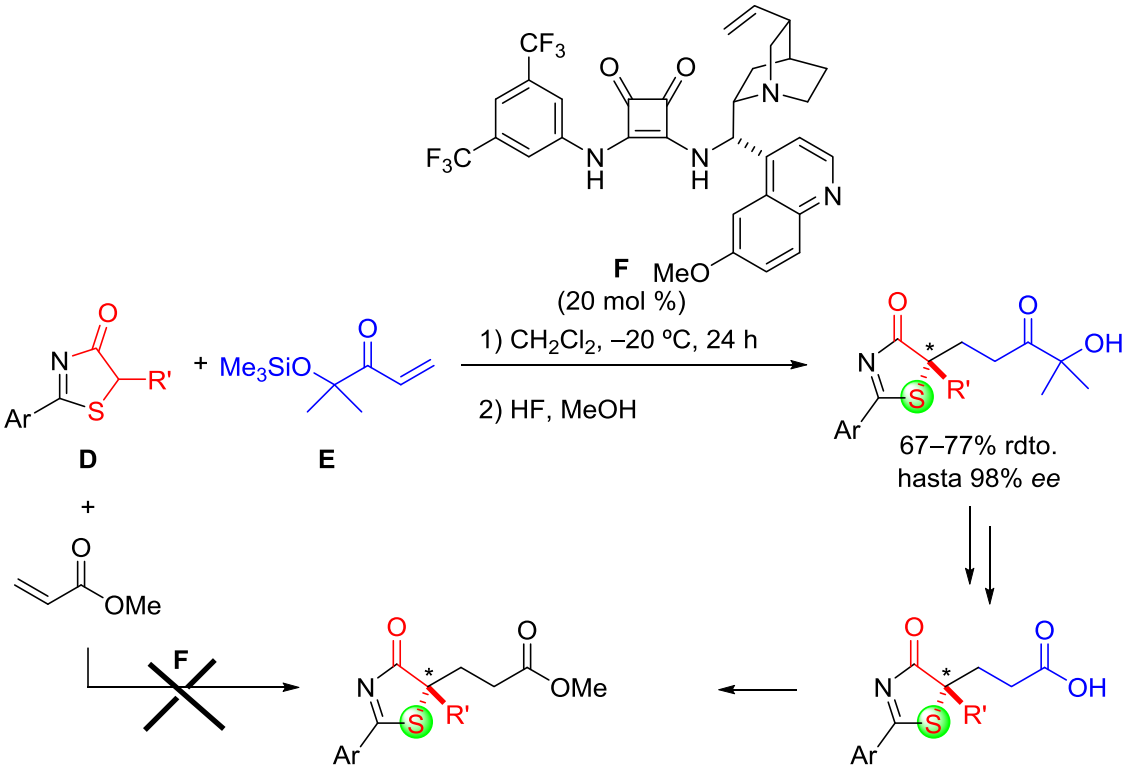


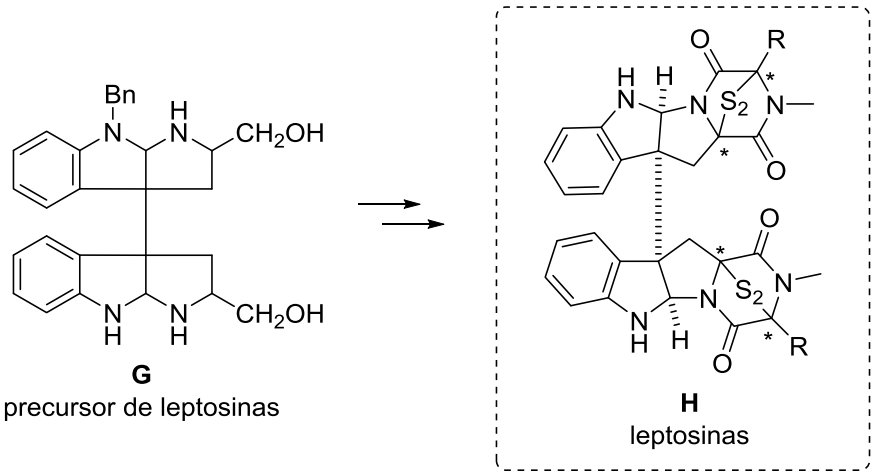
Figura 1. Diferentes modos de activación de α'-hidroxi enonas.

Sin embargo, las bases de Brønsted bifuncionales de tipo ureidopeptídico que eran eficientes en las reacciones con nitroalquenos no proporcionan resultados satisfactorios en la reacción con α'-oxi enonas **E** (Esquema 7). Afortunadamente, empleando otras bases de Brønsted bifuncionales ya conocidas como la escuaramida bifuncional **F** (Esquema 7) se obtienen buenos resultados relativos tanto a reactividad como a estereoselectividad. Además estas α'-oxi enonas pueden considerarse equivalentes sintéticos de enoato, debido a que se pueden transformar fácilmente en condiciones oxidantes en derivados de ácidos carboxílicos, siendo la acetona el único subproducto que se forma en la reacción. Estos resultados son significativos puesto que la adición de Michael de las 5*H*-tiazol-4-onas al acrilato de metilo no tiene lugar cuando se emplean las mismas condiciones de reacción (Esquema 7).



Esquema 7. Adición de Michael desarrollada de 5*H*-tiazol-4-onas **D** a α'-oxi enonas **E**.

Finalmente, bajo la dirección del Prof. Dr. Peter I. Dalko, de la Universidad de Descartes en Paris, y como trabajo complementario al previamente descrito, se ha llevado a cabo una investigación preliminar para desarrollar la síntesis total de las leptosinas **H** (Esquema 8), un tipo de alcaloides que contienen la unidad *epi*(politio)dicetopiperazina (ETP) y que presentan gran variedad de actividades biológicas. Se ha sintetizado el precursor **G** de las leptosinas **H** y asimismo se han efectuado estudios preliminares de la reacción de tiolación en un compuesto modelo. Los resultados de esta investigación se describen en el capítulo 4.



Esquema 8. Estructura general de las leptosinas y precursor sintetizado.

Abbreviations and acronyms

ACE	angiotensin converting enzyme
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Bn	benzyl
CFL	compact fluorescent lamp
DBU	1,8-diazabicycloundec-7-ene
DEAD	diethyl azodicarboxilate
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2PYR$	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
$(DHQ)_2PYR$	hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPP	diphenyl phosphoric acid
de	diastereomeric excess
DIPA	*N,N*-diisopropylamine
dr	diastereomeric ratio
ee	enantiomeric excess
EPC	enantiomerically pure compound
Eq.	equation
equiv.	equivalent
ETP	*epi*(polythio)diketopiperazine
EWG	electron-withdrawing group
h	hour(s)
HPLC	high-performance liquid chromatograpy

IBX	2-iodoxybenzoic acid
LDA	lithium diisopropylamide
LiTMP	lithium tetramethylpiperidine
min	minutes
MOM	methoxy methyl
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
PG	protecting group
Ph	phenyl
Q	quinine
QN	quinidine
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
SMA	sulfa-Michael addition
t	time
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TFA	trifluoroacetic acid
TfN_3	trifluoromethanesulfonyl azide
THF	tetrahydrofuran
TMEDA	*N,N,N'N'*-tetramethylenediamine

Index

Chapter 1:

Introduction

1. Introduction

Introduction

1.1. Organosulfur compounds

Sulfur is an essential element for life and organosulfur compounds are widely present in nature and various biological systems. Starting from simplest biomolecules, two of the twenty one proteinogenic amino acids contain sulfur (*L*-methionine **1** and *L*-cysteine **2**, Figure 1). The thiol side-chain of *L*-cysteine is known to be involved in metal-binding in proteins. On the other hand, glutathione **3** is a tripeptide that plays an important role in primary metabolism and in maintaining the intracellular redox potential.

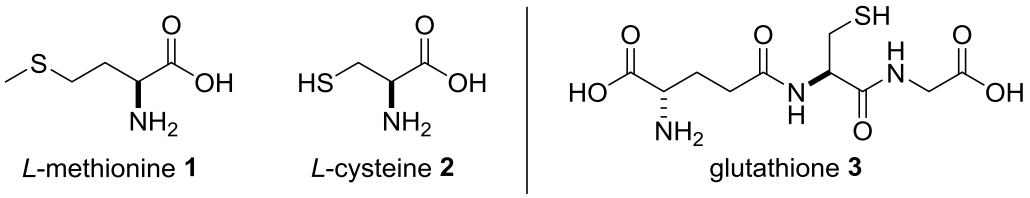


Figure 1. Sulfur containing simple biomolecules.

Sulfur is also present in many more complex compounds with biological or pharmaceutical interest.[1] In fact, nine of the top ten best-selling drugs in the world in 2013 were organosulfur compounds.[2] Figure 2 shows some examples of more complex sulfur-containing biomolecules. For example biotin **4**, also known as vitamin H, is part of the B complex group of vitamins and plays an important role in various metabolic reactions, that is why is often recommended as a dietary supplement. Esomeprazole **5** (Nexium) is a proton pump inhibitor which is used in the treatment of dyspepsia, peptic ulcer disease and gastroesophageal reflux disease and is the third best-selling drug in United States right now. Only in 2013, americans spent $1.5 billion buying large amounts of Nexium.[3] On the other hand, rosuvastatin **6** is an oral drug that is prescribed for lowering cholesterol and triglyceride levels, and it is therefore used to prevent cardiovascular diseases. Finally, singulair **7** is indicated for chronic treatment of asthma in adults.

[1] Fraústo da Silva, J. J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, **2001**.

[2] http://www.fiercepharma.com/special-reports/10-best-selling-drugs-2013.

[3] http://www.drugs.com/stats/nexium.

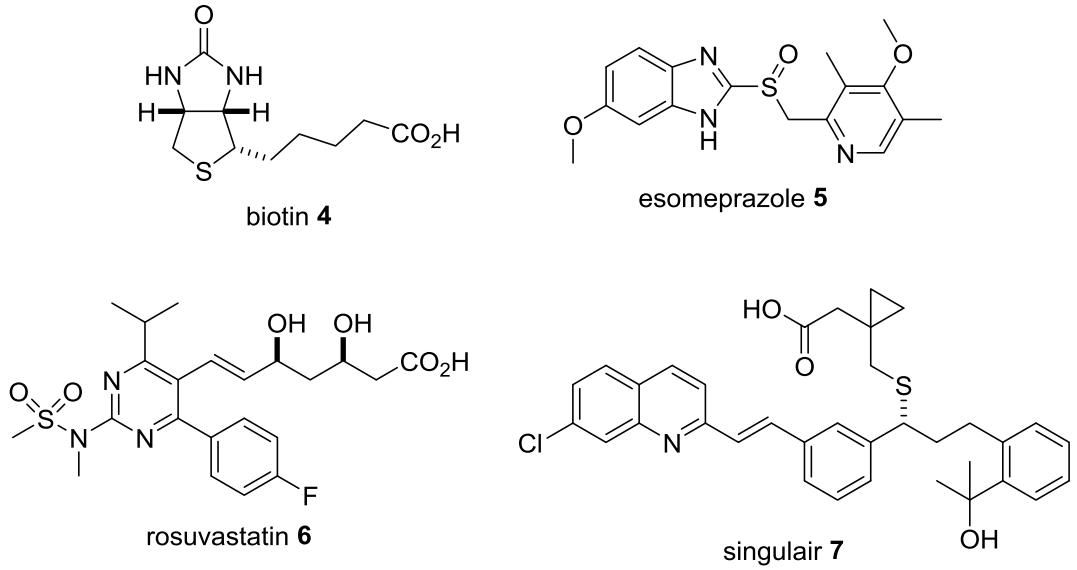
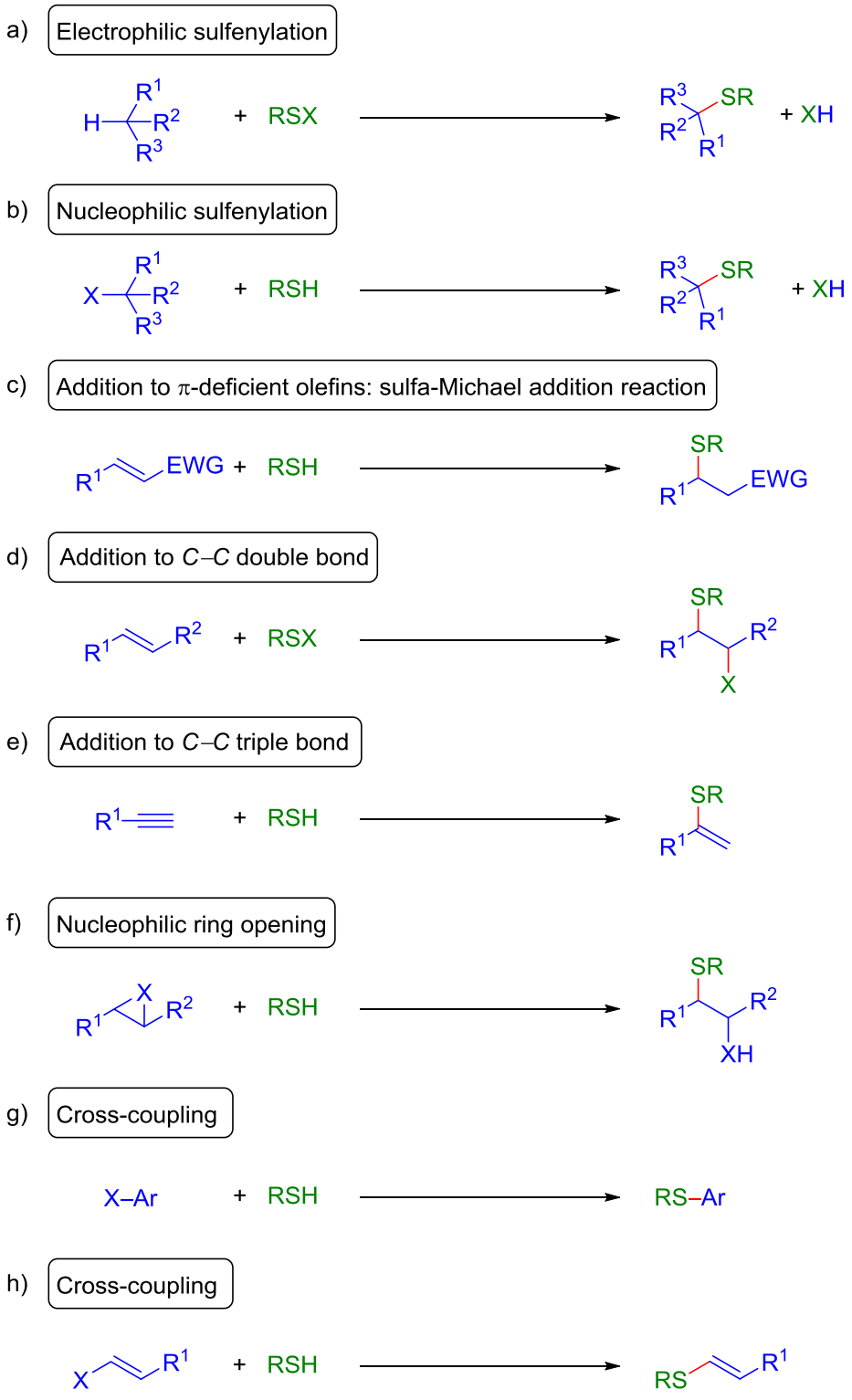


Figure 2. Sulfur containing complex biomolecules.

Because of the interest and biological values of organosulfur compounds *C–S* bond formations stand at the forefront of investigation of modern synthetic organic chemistry. Some representative strategies for *C–S* bond construction are summarized in Scheme 1.

The sulfenylation reaction is an important approach for the construction of *C–S* bonds, wherein electrophilic or nucleophilic sulfur reagents can be employed (a and b strategies, Scheme 1). On the other hand, the addition to *C–C* double bonds (c and d strategies), and particularly the sulfa-Michael addition reaction (c strategy), which involves the addition of sulfur nucleophiles to activated *C–C* double bonds, have been extensively studied. Although less investigated, other option is the hydrothiolation of *C–C* triple bonds, which can be achieved via radical pathways or organometallic catalytic processes (e strategy). Thiolysis of epoxides, aziridines or anhydrides (f strategy) also provides new *C–S* bonds and constitutes a very important and common method for their construction. Finally, an interesting alternative are cross-coupling reactions (g and h strategies), where the halide in aryl or vinyl halides is substituted by sulfur.



Scheme 1. Some representative strategies for *C–S* bond formation.

An interesting family of organosulfur compounds are thiofunctionalized carbonyl compounds; on the one hand, because this motif is present in biologically interesting and active compounds; and on the other hand, because these structures are also valuable precursors for the synthesis of other interesting or biologically active

derivatives. Both functional groups present in this type of compounds, carbonyl and thiol, provide high potential for further synthetic transformations. Some representative examples of biologically active compounds bearing thiofunctionalized carbonyl units are shown in Figure 3.

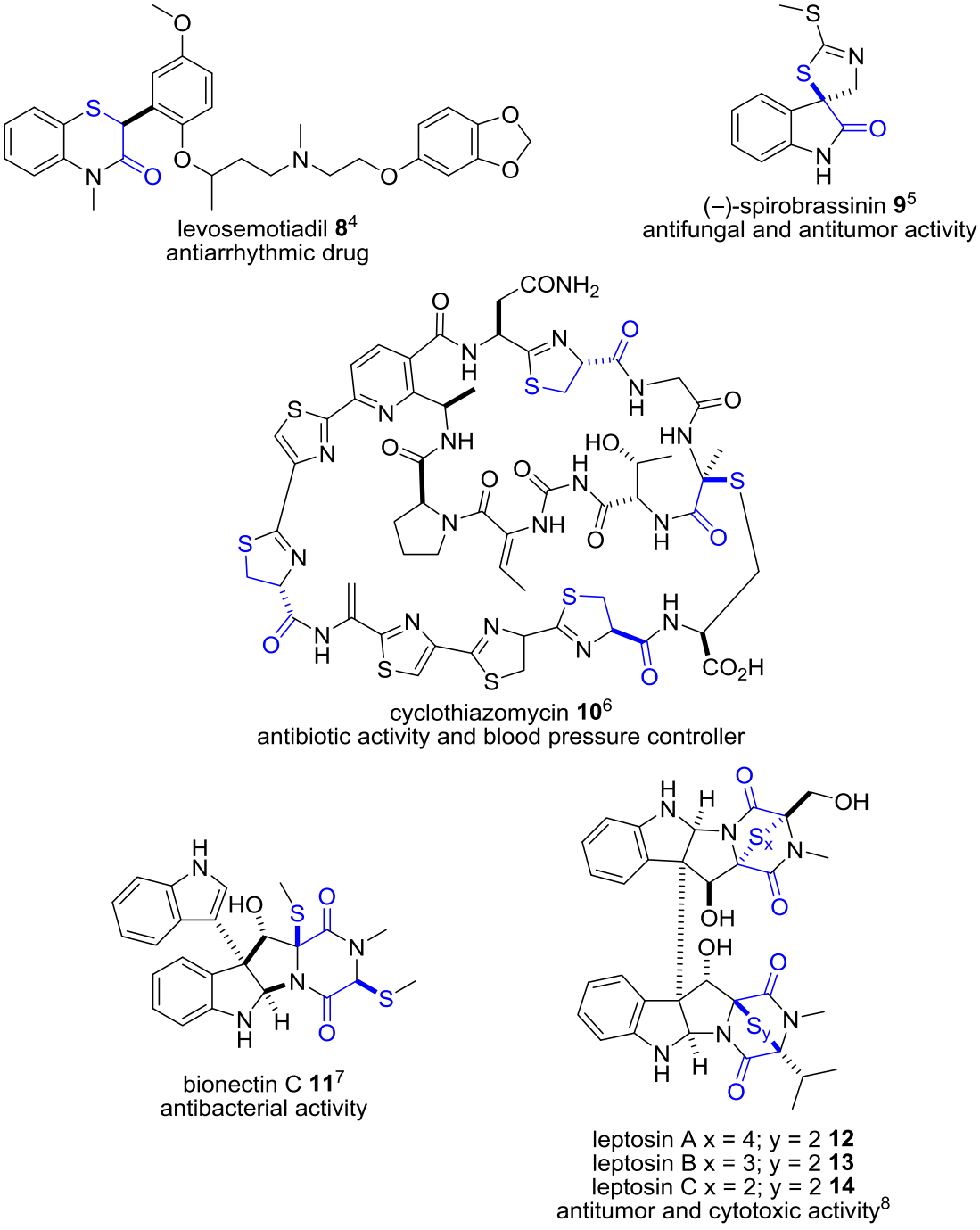
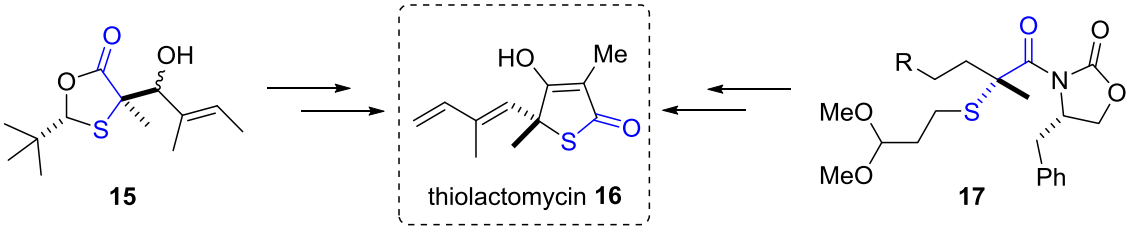


Figure 3. Representative examples of biomolecules containing the thiofunctionalized carbonyl unit.

[4] a) Meng, L. -J.; Zuo, H.; Li, Z. -B; Dupati, G.; Jang, K.; Moon, G.; Zhao, B. -X; Miao, J. -Y.; Shin, D. -S. *Res. Rep. Med. Chem.* **2013**, *3*, 11–20. b) Lakshmi, N. V.; Tamilisai, R.; Perumal, P. T. *Tetrahedron Lett*. **2011**, *52*, 5301–5307.

Another attractive compound is thiolactomycin **16** (Scheme 2), a sulfur-containing antibiotic isolated from a soil bacterium, *Nocardia* sp.,[9] which shows moderate in vitro activity against a number of pathogens and in vivo antimycobacterial activity against the virulent strain *M. tuberculosis* Erdman.[10] Thiofunctionalized derivatives **15**[11] and **17**[12] are in this case precursors in the synthesis of this antibiotic. This example shows how thiofunctionalized compounds are also valuable substrates for the synthesis of biologically active *S*-containing biomolecules.



Scheme 2. Representative examples of thiofunctionalized carbonyl compounds as precursors of thiolactomycin **16**.

Despite the prevalence of the *C–S* unit in nature and the importance of sulfur functionalities in many biological processes, the formation of *C–S* bonds has received significantly less attention than *C–N*, *C–O* and *C–C* bond construction; maybe, because the incorporation of a sulfur atom into organic molecules presents different synthetic problems. On the one hand, thiocarbonyl compounds are usually unstable and therefore difficult to synthesize; moreover, they are relatively poor electrophiles.[13] Thus, most of the general synthesis of organosulfur compounds involve reactions with sulfur-based

[5] Liu, L.; Zhang, S.-L.; Xue, F.; Lou, G.-S.; Zhang, H.-Y.; Ma, S.-C.; Duan, W.; Wang, W. *Chem. Eur. J.* **2011**, *17*, 7791–7795.

[6] Bagley, M. C.; Xiong, X. *Org. Lett*. **2004**, *6*, 3401–3404.

[7] a) Coste, A.; Kim, J.; Adams, T. C.; Movassaghi, M. *Chem. Sci*. **2013**, *4*, 3191–3197. b) Zheng, C. -J.; Kim, C. -J.; Bae, K. S.; Kim, Y. -H.; Kim, W. -G. *J. Nat. Prod*. **2006**, *69*, 1816–1819.

[8] Takahashi, C.; Minoura, K.; Yamada, T.; Numata, A.; Kushida, K.; Shingu, T.; Hagishita, S.; Nakai, H.; Sato, T.; Harada H. *Tetrahedron* **1995**, *51*, 3483–3498.

[9] Oishi, H.; Noto, T.; Sasaki, H.; Suzuki, K.; Hayashi, T.; Okazaki, H.; Ando, K.; Sawada, M. *J. Antibiot*. **1982**, *35*, 391–395.

[10] Salyden, R. A.; Lee, R. E.; Armour, J. W.; Cooper, A. M.; Orme, I. M.; Brennan, P. J.; Besra, G. S. *Antimicrob. Agents. Chemother*. **1996**, 2813–2819.

[11] McFadden, J. M.; Frehywot, G. J.; Townsend, C. A. *Org. Lett*. **2002**, *4*, 3859–3862.

[12] a) Ohata, K.; Terashima, S. *Tetrahedron Lett*. **2006**, *47*, 2787–2791. b) Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4070–4074.

[13] Okazaki, R. In *Organosulfur Chemistry*, Vol. 1; Page, P. C. B., Ed.; Academic Press: London, **1995**, pp 225–258.

nucleophiles. On the other hand, sulfur containing compounds can act as poisons for several metal systems, due to their strong coordinating and adsorptive properties.[14]

As in the case of most biomolecules, most of sulfur-containing compounds are chiral. Therefore, the development of strategies for the construction of *C–S* bonds in a highly stereoselective manner has gained considerable interest. It is worth noting that organosulfur compounds are also useful ligands in asymmetric synthesis.[15]

1.2. Strategies for the stereoselective synthesis of thiofunctionalized carbonyl compounds

1.2.1. General considerations

Chirality is an inherent property of an object that is non superimposable upon its mirror image. One example of a chiral object is a hand, a left hand cannot be superposed with a right hand. Referring to molecules, the pair of non superimposable mirror images are called enantiomers, and in the absence of a chiral environment, they display the same physical and chemical properties, only differing in the fact that they rotate the plane of polarised light in opposite directions. However, in a chiral environment, such as a biological receptor, or the active site of an enzyme, their 'handedness' becomes significant because of the potential to afford diastereomeric transition states or complexes. Therefore, whilst there are examples of enantiomers of chiral molecules having the same biological activity, there are many other cases where they differ significantly in their mode of action.[16]

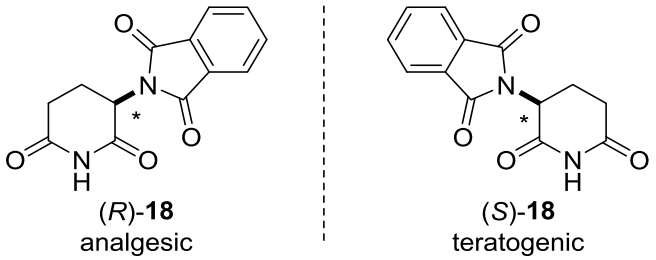


Figure 4. Enantiomers of thalidomide **18**.

One significant example of the relevance of the properties of individual enantiomers comes from the history of the drug thalidomide **18** whose two enantiomers

[14] a) Oudar, J.; Wise, H. *Deactivation and Poisoning of Catalyst*; Marcel Dekker, Inc. New York, **1985**. b) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker, Inc. New York, **1984**.

[15] *Organosulfur Chemistry in Asymmetric Synthesis*, Eds.: Toru, T.; Bolm, C., **2008**, Wiley-VCH, Weinheim.

[16] Ariens, E. J. *Trends Pharmacol. Sci.* **1986**, *7*, 200–205.

exhibit very different biological activities as shown in Figure 4, and whose prescription as racemate to pregnant women led to the birth of many malformed children during the 1960s,[17] clearly illustrating how important the use of single enantiomers as drugs can be in the treatment of diseases. Since thalidomide's tragedy the synthesis of enantiomerically pure compounds has gained considerable attention.[18]

Therefore, one of the main goals in organic chemistry over the last years has been the development of methodologies for the synthesis of enantiomerically pure chiral molecules. The concept of "*EPC-synthesis*" (Enantiomerically Pure Compound-synthesis) was first introduced by Prof. Seebach[19] in 1980, to gather all the processes for the preparation of chiral enantiopure compounds. At present the different strategies developed for this purpose can be classified into three major groups (Figure 5): *resolution of racemates*, the use of the so called "*chiral pool*" and *asymmetric synthesis*.

The so-called "*resolution of racemates*"[20] consists of preparing the desired compound as the racemic mixture and then separate the enantiomers by means of physical or chemical processes. In *dynamic kinetic resolutions*[21] both enantiomers of a racemic mixture are converted into a single stereoisomeric product. This strategy involves a combination of a standard *kinetic resolution* and *in situ* racemisation of the less reactive or nonreactive enantiomer, which must be a labile substrate for the easy conversion into the racemic mixture again.

A second option is to use a natural enantiopure compound from the "*chiral pool*"[22] as the chiral source. This compound will remain included in the structure of the final product; and therefore, is particularly useful when the desired final product and the chiral compound are structurally similar, to avoid subsequent transformations. The *chiral pool* arsenal is constituted by carbohydrates, amino acids, hydroxy acids, alkaloids and terpenes.

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[17] Later it was found that the administration of the drug as single *R* enantiomer does not constitute a solution, because under physiological conditions the compound racemizes.

[18] Stephens, T.; Brynner, R. *Dark Remedy: The impact of Thalidomide and Its Revival as a Vital Medicin*e, **2001**, Perseus, Cambridge, MA.

[19] Seebach, D.; Hungerbühler, E. *Synthesis of Enantiomerically Pure Compounds (EPC-Synthesis)* in *Modern Synthetic Methods*, Scheffold, R., Ed., **1980,** p 94, Salle + Sauerländer, Frankfurt.

[20] For general reviews on the resolution of racemates, see: a) Synoradzki, L.; Bernaś, U.; Ruśkowski, P. *Org. Prep. Proced. Inc*. **2008**, *40*, 163–200. b) Anderson, N. G. *Org. Proc. Res. Dev*. **2005**, *9*, 800–813.

[21] For general reviews on the kinetic dynamic resolution, see: a) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge. b) Matute, B. M. *An. Quim.* **2006**, *102*, 46–52.

[22] For general reviews on the strategy of chiral pool, see: a) Nicolaou, K. C.; Spyder, S. A. *Classics in Total Synthesis II*, **2003**, Wiley-VCH, Weinheim. b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis I*, **1996**, Wiley-VCH, Weinheim. c) Hanessian, S. *Pure Appl. Chem.* **1993**, *65,* 1189–1204. d) Blaser, H. -U. *Chem. Rev.* **1992**, 935–952. e) Noyori, R. *Chemical Society Reviews* **1989**, *18*, 187–208.

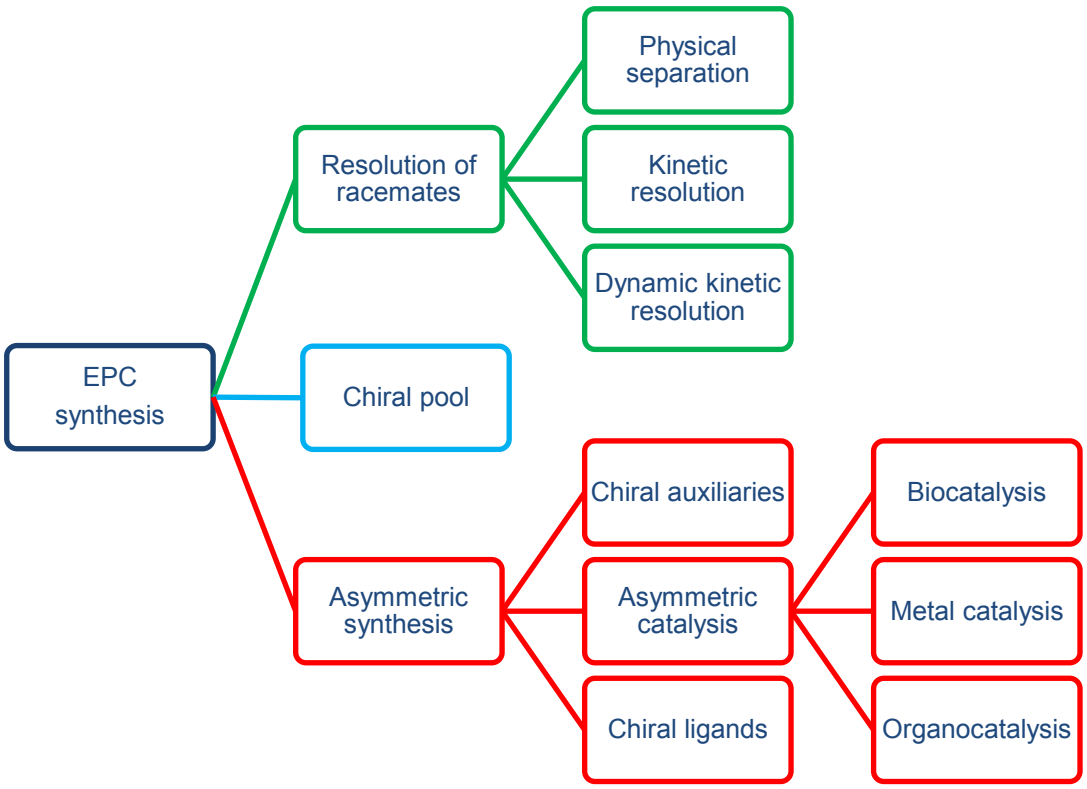


Figure 5. Synthetic approaches for EPC-synthesis.

Finally it is also possible to perform an *asymmetric synthesis*[23] by using an achiral substrate as starting material where the asymmetric induction will come from a *chiral auxiliary,*[24] from a *chiral catalyst*[25] or from a *chiral ligand*[26] (Figure 5).

[23] For general reviews on asymmetric synthesis, see: a) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis 2nd Edition*, **2012**, Pergamon Press, Oxford. b) *Asymmetric Synthesis II: More Methods and Applications*, Eds. Christmann, M.; Bräse, S., **2012**, Wiley-VHC, Weinheim, Germany. c) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials*, **2007**, Wiley-VCH, New York.

[24] For general reviews on chiral auxiliaries, see: a) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. b) ref. 23c. c) Glorious, F.; Gnass, Y. *Synthesis* **2006**, *12*, 1899–1930. d) Roos, G. *Compendium of Chiral Auxiliary Applications*, **2002**, Academic Press, New York. e) Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. *Houben–Weyl Methods in Organic Chemistry, Stereoselective Synthesis*, **1995**, Thieme-Verlag, Stuttgart. f) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, **1995**, Willey, New York.

[25] For general reviews on chiral catalysts, see: a) *Catalytic Asymmetric Synthesis* 3rd Edition, Ed. Ojima, I., **2013**, John Wily & Sons, Hoboken, New Jersey. b) *Catalytic Methods in Asymmetric Synthesis: Advanced materials, techniques and applications*, Eds. Gruttadauria, M. Giacalone, F. **2011**, John Wily & Sons, Hoboken, New Jersey. c) Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*, **2007**, Wiley-VCH, Weinhelm. d) Trost, B. M. *Proc. Natl. Acad. Sci.* **2004**, 101, 5348–5355.

[26] For general reviews on chiral ligands, see: a) *Privileged chiral ligands and catalyst*, Ed. Zhou, Q. -L., **2011**, Wiley-VCH, Weinheim. b) Schütz, T. *Synlett* **2003**, *6*, 901–902.

Chiral auxiliaries are chiral compounds or chemical units which are covalently and temporarily attached to a substrate wherein the chiral induction to the newly created stereocenter or chirality element occurs through a diastereoselective process. The auxiliary is then removed and recycled and an usual requeriment for these auxiliaries is to be cheap and accessible in both enantiomeric forms as they are employed in stoichiometric amounts. Another possibility is when the chiral information to transform an achiral substrate into a chiral product comes from a chiral reagent. This is the case of the *chiral ligands*, which are also used in stoichiometric amounts. These are enantiopure compounds which interact with a metallic center through quelation to generate a chiral reagent which transfers the information of chirality during the reaction to the product. Finally, *asymmetric catalysis* involves the use of substoichiometric amounts of an enantiopure chiral substance which speeds up the reaction and controls product's stereochemistry through enantioselective processes. In this field three different groups can be distinguished. On the one hand, *biocatalysis*,[27] also known as enzymatic catalysis or biotransformation, which makes use of protein-based catalysts (enzymes). Secondly, *metal catalysis*,[28] which is based on the use of chiral complexes of metallic species. And finally, *organocatalysis*,[29] a more recently developed methodology which employs chiral small organic molecules lacking metal elements in their active form, to catalyse chemical reactions. The field of *organocatalysis* has developed rapidly and a number of

[27] For general reviews on biocatalysis, see: a) De Gonzalo, G.; Lavandera, I.; Gotor, V. *Catalytic Methods in Asymmetric Synthesis. Advanced Materials, Techniques, and Applications* (Ed. Gruttadauria, M.; Giacalone, F.), **2011**, John Wiley & Sons, Hoboken, pp 391–527. b) *Enzyme Biocatalysis: Principles and Applications*, Ed. Illanes, A., **2008**, Springer, New York. c) Bommarius, A. S.; Riebel, B. R. *Biocatalysis: Fundamentals and Applications*, **2007**, Wiley-VCH. d) Pollard, D. J.; Woodley, J. M. *Trends Biotechnol.* **2007**, *25*, 66–73.

[28] For general reviews on *organometallic catalysis*, see: a) Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev.* **2015**, *44*, 433–448. b) Steinborn, D. *Fundamentals of Organometallic Catalysis*, **2011**, Wiley-VCH, Germany. c) Astruc, D. *Organometallic Chemistry and Catalysis*, **2007**, Springer-Verlag Berlin Heidelberg. d) Ma, J. A.; Cahard, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583. e) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*, **2004**, 2nd edition, Wiley-VCH, Weinheim. f) Ojima, I. *Catalytic Asymmetric Synthesis*, **2000**, 2nd edition, Wiley-VCH, New York. g) Special edition *"Catalytic Asymmetric Synthesis*", *Acc. Chem. Res.* **2000**, *33*, 323–440.

[29] For representative reviews on *organocatalysis*, see: a) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions and Applications,* Ed. Dalko, P. I., **2013**, Wiley-VCH Verlag GmbH & Co., Weinheim, Gernamy. b) *Stereoselective Organocatalysis: Bond formation methodologies and activation modes*, Ed. Rios Torres, R., **2013**, John Wiley & Sons, Inc.; Hoboken, New Jersey. c) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406–2447. d) Liu, W. J.; Li, N.; Gong, L. Z. *Top Organomet. Chem.* **2011**, *36*, 153–206. e) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20618–20619. f) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189. g) Dalko, P. I. *Enantioselective Organocatalysis*, **2007**, Wiley-VCH, Weinheim. h) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. i) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748.

these catalysts can now compete with the more established fields of *metal mediated* and *biocatalysis* in terms of stereocontrol.

There are some different classifications of organocatalysts; one of the most widespread is the classification depending on the interaction between the substrate and the catalyst.[30] In this sense, in general terms two types of *organocatalysis* can be differentiated: *Non covalent catalysis* and *covalent catalysis*. In *non covalent organocatalysis*, reactions are accelerated and controlled by weak interactions between the substrate and the catalyst and these can involve either the formation of hydrogen bonds,[31] or of ionic pairs, as in the case of phase transfer catalysis[32] or Brønsted base catalysis.[33] An alternative approach to *non covalent organocatalysis* is *covalent organocatalysis*, where the catalyst and the substrate react through covalent interactions to afford an activated complex. With carbonyl compounds appropriate catalysts are among others,[34] chiral amines, also named aminocatalysts,[35] which have been used with aldehydes and ketones. In these cases regarding the reactive species that is generated in the interaction between the substrate and the catalyst, different activation modes have

[30] This classification was outlined by Langebeck in 1949 in his book "*Organic Catalysts and Their Relations with Enzymes*". For a more recent classification, see: a) ref. 29h. b) ref. 29i. For an alternative classification based on the acid/base reactivity of organocatalysts, see: c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

[31] For general reviews on hydrogen bond catalysis, see: a) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem*. **2014**, 2633–2646. b) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1–22. c) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*, **2009**, Wiley-VCH, Weinheim. d) Zhang, Z.; Scheiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. e) Terada, M. *Chem. Commun.* ***2008,*** 4097–4112. f) Yu, X.; Wang, W. *Chem. Asian. J.* **2008**, *3*, 516–532. g) Akiyama, Y. *Chem. Rev.* **2007**, *107*, 5744–5758. h) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. i) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.

[32] For general reviews on phase transfer catalysis, see: a) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312–4348. b) Maruoka, K. *Asymmetric Transfer Catalysis*, **2008**, Wiley-VCH, Weinheim. c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

[33] For representative reviews on Brønsted base catalysis, see: a) Tiang, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145–200. b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653.

[34] Other catalysis types involve the use of *N*-heterocyclic carbenes, some tertiary amines and analogous, alkyl pyridines, trialkylphosphines and trialkyl amines.

[35] The aminocatalysis term was first mentioned in 2001: a) List, B. *Synlett* **2001**, 1675–1686. For reviews on aminocatalysis, see: b) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J*. **2014**, *20*, 358–368. c) Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Chem. Sci*. **2013**, *4*, 2287–2300. d) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632–649. e) Alemán, J.; Cabrera, S. *An. Quím.* **2009**, *105,* 189–197. f) ref. 29f. g) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, 39, 79–87. h) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 7876–7880.

been developed: iminium ion,[36] enamine,[37] dienamine,[38] trienamine[39] and SOMO[40] activations.

In nature, enzymes are able to combine multiple interactions acting as polyfunctional catalysts and thus increasing reaction rates and specifity. Based on this idea researchers have developed a new concept, bifunctional catalysis,[41] where both reagents, nucleophile and electrophile can be simultaneously activated by two catalytic units of the same catalyst, which can work as Lewis acid/base or Brønsted acid/base centers, improving reaction efficiency and/or selectivity. This concept has been applied to metal catalysis, organocatalysis and combination of both. Some representative examples of bifunctional catalysts are shown in Figure 6.

[36] For general reviews on iminium ion catalysis, see: a) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281–347. b) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *12*, 1759–1772. c) Pihko, P.M.; Majander, I.; Erkkila, A. *Chem. Rev.* **2007**, *107*, 5416–5470.

[37] For general reviews on enamine catalysis, see: d) Pihko, P. M.; Majander, I.; Erkkila, A. *Top. Curr. Chem.* **2010**, *291*, 29–75. b) Mukherjee, S.; Woon, J.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. c) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. d) Marigo, M.; Jorgensen, K. A. *Chem. Commun.* **2006**, 2001–2011.

[38] For general reviews on dienamine catalysis, see: a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865–887. b) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, 128, 12973–12980.

[39] For general reviews on trienamine catalysis, see: a) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709–716. b) Jia, Z. -J.; Jiang, H.; Li, J. -L.; Gschwend, B.; Li, Q. -Z.; Yin, X.; Grouleff, J.; Chen, Y. -C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053–5061.

[40] For general reviews on SOMO catalysis, see: a) Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1360–1363. b) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2007**, 46, 7356–7359. c) Young, H. -Y.; Hung, J. -B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005.

[41] For general reviews on bifunctional catalysis, see: a) Fang, X.; Wang, C. -J. *Chem. Commun.* **2015**, *51*, 1185–1197. b) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, 23, 490–508. c) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 6216–6232. d) Cucinotta, C.S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. *Chem. Eur. J.* **2009**, *15*, 7913–7921. e) Lattanzi, A. *Chem. Commun.* **2009**, 1452–1463. f) Connon, S. J. *Chem. Commun*. **2008**, 2499–2510. g) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, 45, 7496–7504.

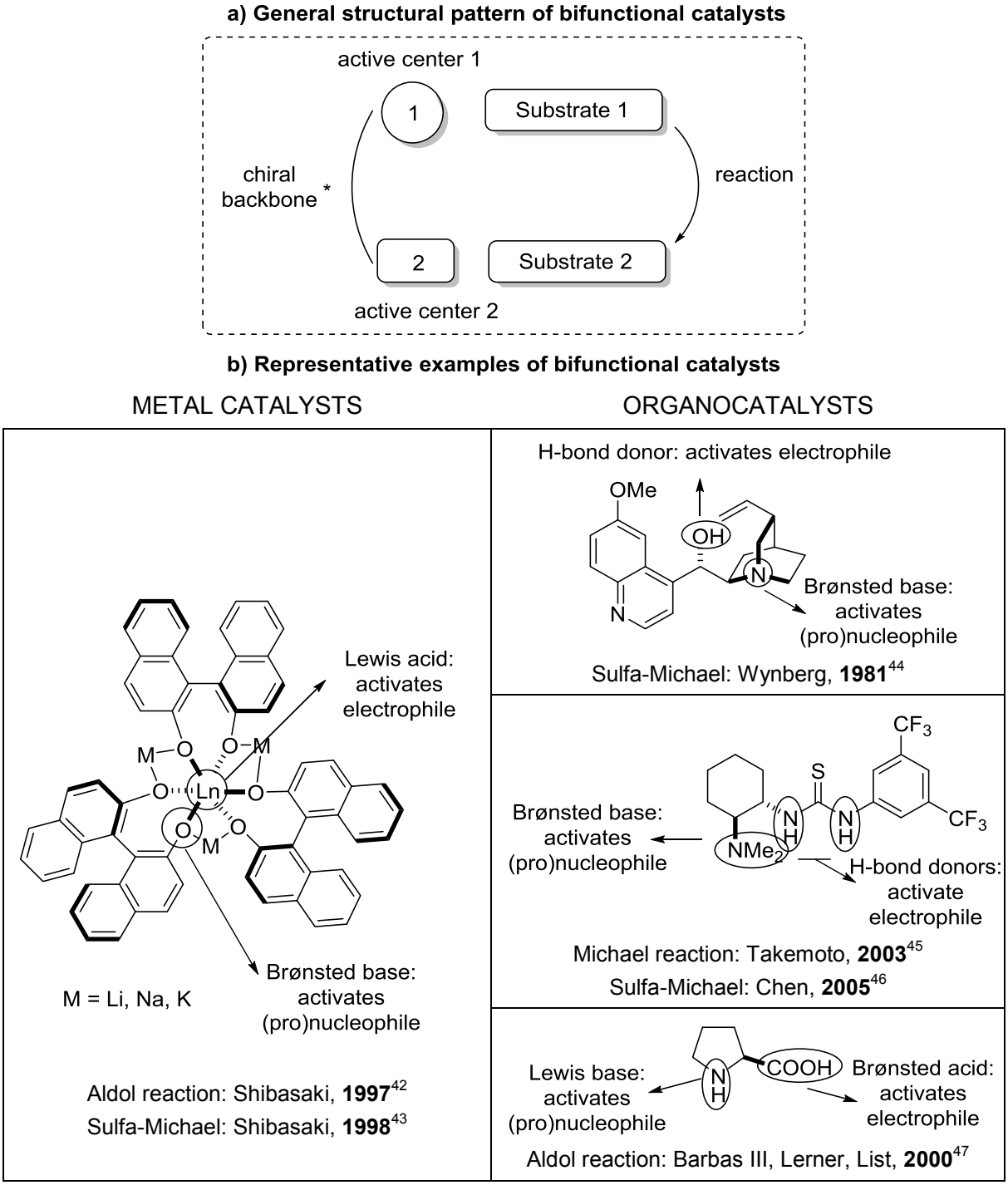


Figure 6. General structural pattern and representative examples of bifunctional catalysts, and the first reactions were they have been investigated.

[42] Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed*. **1997**, *36*, 1871–1873.

[43] Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1998**, *120*, 4043–4044.

[44] Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc*. **1981**, *103*, 417–430.

[45] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672–12673.

[46] Li, B. -J.; Jiang, L.; Liu, M.; Chen, Y. -C.; Ding, L. -S.; Wu, Y. *Synlett* **2005**, 603–606.

[47] List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc*. **2000**, *122*, 2395–2396.

Over the last years the previously described asymmetric protocols have also been investigated in the stereoselective construction of *C–S* bonds.[48] In this context, the most common strategies of this type which afford thiofunctionalized carbonyl compounds consist of the electrophilic sulfenylation of carbonyl substrates (Figure 7) and the conjugate addition of *S*-nucleophiles to unsaturated carbonyl compounds (Figure 8). The most significant contributions and limitations of these strategies described until the beginning of our research are outlined in the following sections.

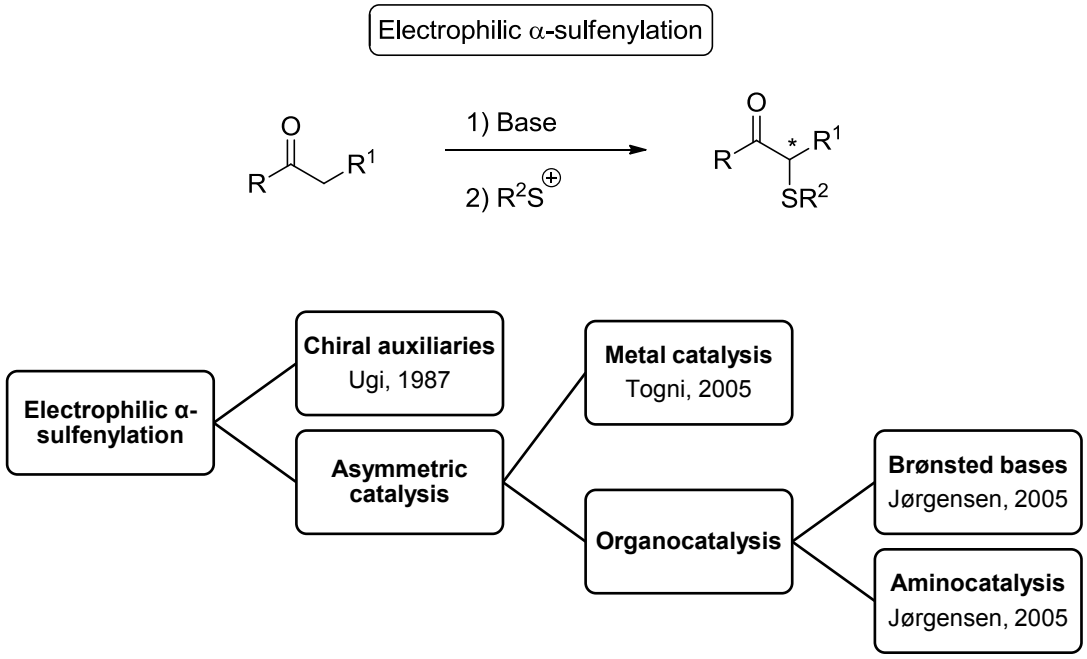


Figure 7. Strategies for the asymmetric electrophilic α-sulfenylation of carbonyl compounds and first examples of each one.

[48] For general reviews on asymmetric *C–S* bond formation, see: a) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev*. **2014**, *114*, 8807–8864. b) Heravi, M. M.; Hajiabbase, P. *Mol. Divers*. **2014**, *18*, 411–439. c) Della Sala, G.; Lattanzi, A. in Chapter 14: *C–Other atom bond formation (S, Se, B)* of ref. 29b. d) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051–2069. e) Bichler, P.; Love, J. A. *Top Organomet. Chem*. **2010**, *31*, 39–64. f) Procter, D. J. *J. Chem. Soc., Perkin. Trans. 1* **2001**, 335–354. g) Kondo, T.; Mitsudo, T. *Chem. Rev*. **2000**, *100*, 3205–3220.

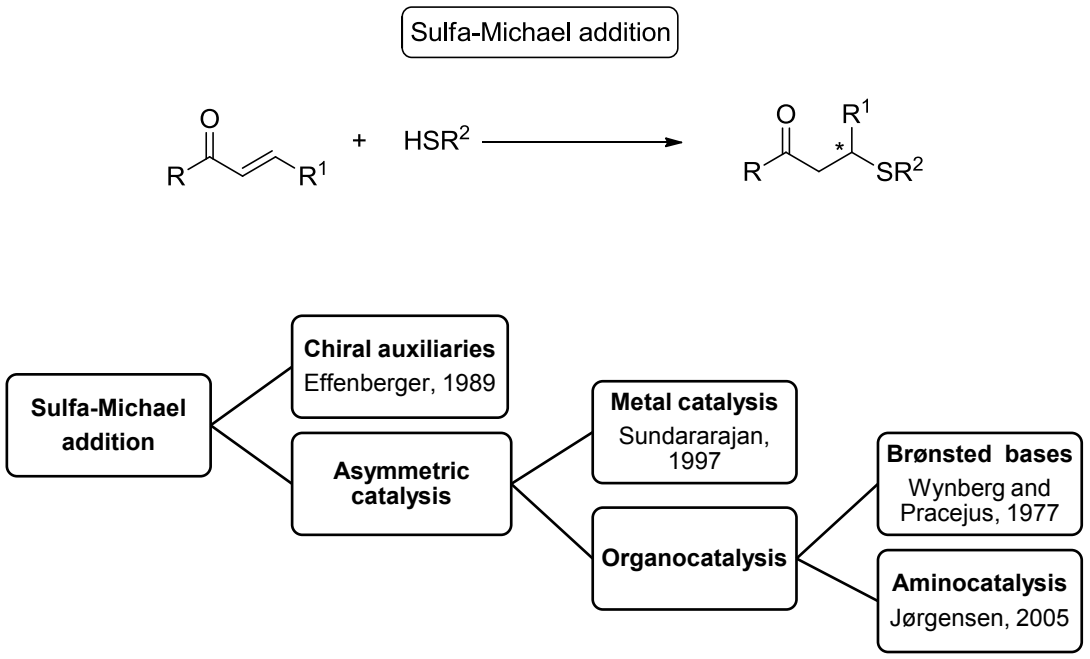
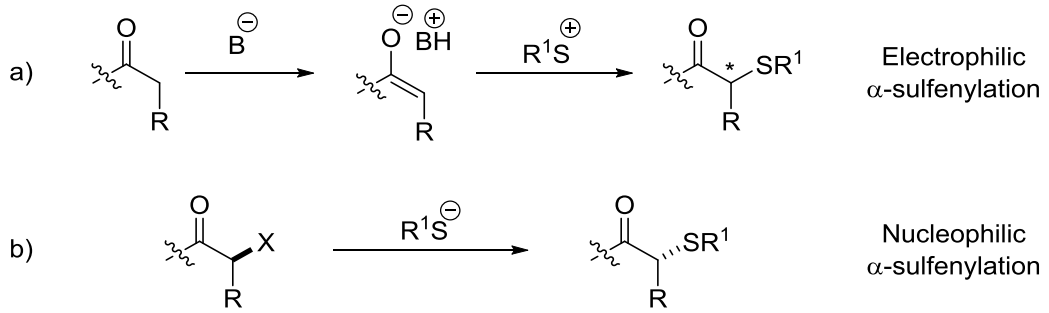


Figure 8. Strategies for the asymmetric sulfa-Michael addition to α,β-unsaturated carbonyl compounds and first examples of each one.

1.2.2. Asymmetric α-sulfenylation of carbonyl compounds

An interesting approach for the asymmetric construction of *C–S* bonds in carbonyl compounds is the α-sulfenylation reaction. Within this strategy there are two alternatives depending on the role of the sulfur reagent. On the one hand, the most investigated approach is electrophilic α-sulfenylation, where the carbonyl compound is transformed into the enolate or equivalent which then reacts with an electrophilic sulfur reagent providing the α-sulfenylated carbonyl compound (Scheme 3, a). In the other alternative, nucleophilic α-sulfenylation, a leaving group at the α-position of the carbonyl group is displaced by the nucleophilic sulfur substrate (Scheme 3, b). In both cases, the yielded product is an α-sulfenylated carbonyl compound. The latter option has been much less developed than the former one and the most significant contributions are summarized in the following section (section 1.2.2.1). These involve a strategy based on the use of a chiral auxiliary and protocols that employ enantiopure chiral compounds as starting material.



Scheme 3. Strategies for the α-sulfenylation of carbonyl compounds.

1.2.2.1. Nucleophilic α-sulfenylation

As said before, a *chiral auxiliary*[24] is an enantiopure compound that is temporarily incorporated into a prochiral starting material in order to control the stereochemical outcome of the reaction. Nowadays, different well-known *chiral auxiliaries* allow to perform selectively a great number of reactions.[49] Among them Evans' oxazolidinones[50] and Oppolzer's sultams[51] for carboxylic acids or Enders' SAMP/RAMP hydrazines[52] for aldehydes and ketones (Figure 9) constitute robust examples.

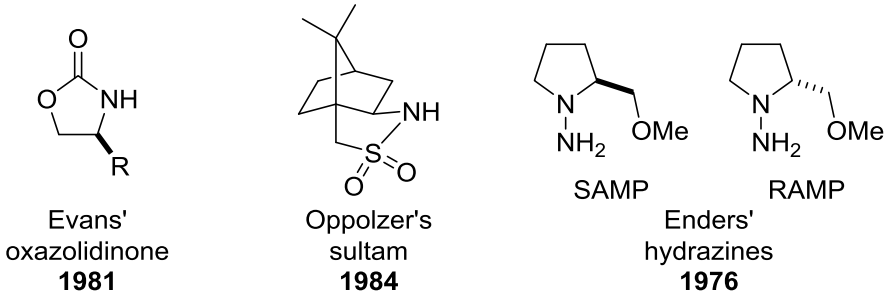


Figure 9. Representative chiral auxiliaries.

However, regarding nucleophilic α-sulfenylation based on chiral auxiliaries only one example can be found in the literature. The group of Evans described in 2000 the

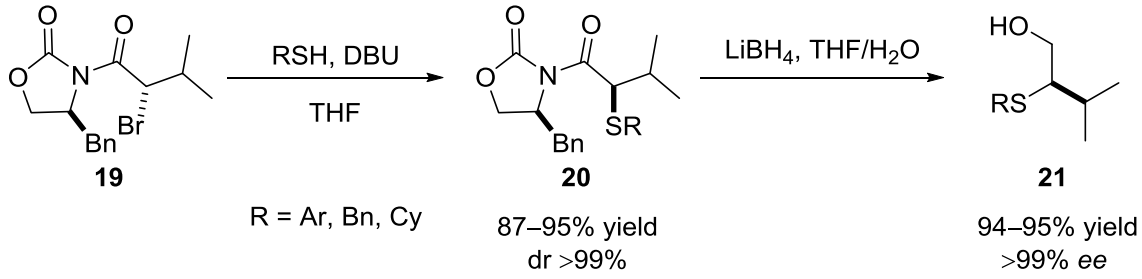
[49] Paquette, L. A. *Handbook of Reagents for Organic Synthesis*: *Chiral Reagents for Asymmetric Synthesis* **2003**, Wiley, New York.

[50] a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127. For a general review, see: b) Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Bevola, L.; Botta, B. *Current Organic Synthesis* **2007**, *4*, 81–135.

[51] a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397–1401. For a general review, see: b) Oppolzer, *Pure Appl. Chem*. **1990**, *62*, 1241–1250.

[52] a) Enders, D.; Eichenauer, H. *Angew. Chem. Int. Ed*. **1976**, *15*, 549–550. For a general review, see: b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *5*8, 2253–2329.

diastereoselective synthesis of thioethers by bromine displacement in α-bromoimides **19** with thiolates employing his oxazolidinones as chiral auxiliaries (Scheme 4). Reductive cleavage of the auxiliary with $LiBH_4$ in the final adducts gives the β-hydroxysulfides **21** in excellent enantioselectivities.[53]



Scheme 4. Nucleophilic α-sulfenylation of α-bromoimides to afford β-hydroxysulfides. **Evans, 2000**.

On the other hand, the remainder protocols for nucleophilic α-sulfenylations employ enantiopure compounds as starting materials and involve the use of α-hydroxy carbonyl derivatives or the ring-opening of epoxides. In the former strategy, the hydroxy group is first transformed into a good leaving group, such as mesylate,[54] cyclic sulfamidate[55] or phosphonic ester,[56] to perform the S_N2 reaction with a sulfur nucleophilic reagent. All the reported procedures of this type lead to tertiary thiol derivatives, whose construction is still being a challenging task in organic synthesis,[57] and they would be outlined in Chapter 3. The first example of this strategy is represented in Scheme 5 and uses mesyl chloride to run the intramolecular S_N2 reaction that takes place with complete inversion of the configuration.[54a]

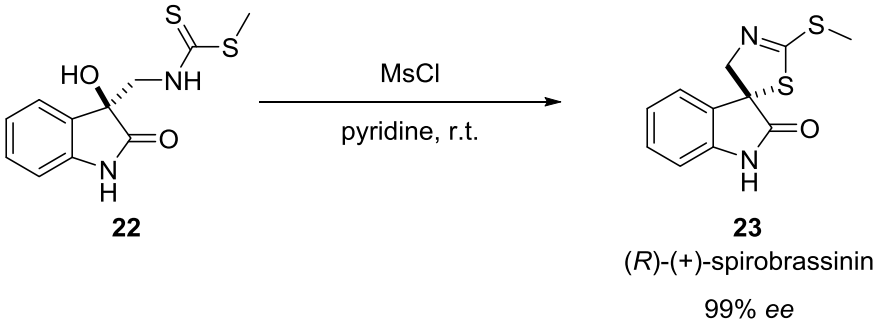
[53] Evans, D.A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.

[54] a) Monde, K.; Taniguchi, T.; Miura, N.; Nishimura, S. -I.; Harada, N.; Dukor, R. K.; Nafie, L. A. *Tetrahedron Lett*. **2003**, *44*, 6017–6020. For the transformation of α,α-dialkyl hydroxy esters into tertiary thiol derivatives, see: b) Weaver, J. D.; Morris, D. K.; Tunge, J. A. *Synlett* **2010**, 470–474.

[55] For a nucleophilic α-sulfenylation of α-methylisoserine-derived sulfamidate that provides α-sulfenyl β-amino acids: Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M. *J. Org. Chem*. **2006**, *71*, 1692–1695.

[56] For nucleophilic α-sulfenylations performed with diphenylphosphinites and an oxidant agent, see: Using benzoquinone: a) Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Chem. Lett*. **2005**, *34*, 638–639. Using azides: b) Kuroda, K.; Maruyama, Y.; Hayashi, Y.; Mukaiyama, T. *Chem. Lett*. **2008**, *37*, 836–837.

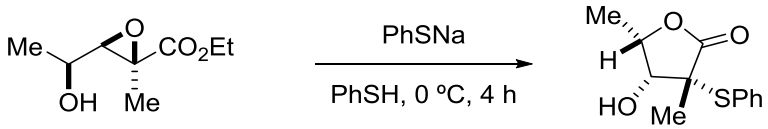
[57] For general reviews on the formation of tetrasubstituted stereocenters, see: a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Ed. Christoffers, J.; Baro, A., **2005**, Wiley-VCH, Weinheim, Germany. For organocatalytic formation of tetrasubstituted stereocenters: b) Bella, M.; Casperi, T. *Synthesis* **2009**, 1583–1614. For metal catalyzed formation of tetrasubstituted stereocenters: c) Hawner, C.; Alexakis, A. *Chem. Commun*. **2010**, *46*, 7295–7306. For a review on the formation of tetrasubstituted stereogenic carbons bearing a sulfur substituent, see: d) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem*. **2011**, *7*, 582–595.



22 **23**
(*R*)-(+)-spirobrassinin
99% *ee*

Scheme 5. Nucleophilic α-sulfenylation for the synthesis of (*R*)-(+)-spirobrassinin. **Monde, 2003**.

As far as we know, two particular examples of the ring-opening of epoxides with sulfur nucleophiles are described in the literature. Rodríguez and co-workers used sodium thiophenolate to yield α-thiofunctionalized lactone **25**, starting from epoxide **24** (Scheme 6).[58] In the other example, the epoxide opening reaction was applied to the synthesis of a biologically interesting sulfur-bridge containing dimer.[59]



24 **25**
60% yield

Scheme 6. Asymmetric synthesis of α-thiofunctionalized lactones through epoxide ring opening with sodium thiophenolate. **Rodríguez, 2007**.

The previous examples show that the strategy based on nucleophilic α-sulfenylation of carbonyl compounds has been scarcely studied and is mainly limited to enantiopure starting materials.

1.2.2.2. Electrophilic α-sulfenylation

Regarding asymmetric electrophilic α-sulfenylations, much more contributions can be found in the literature, and, as in most asymmetric organic reactions, pioneering examples are based on *chiral auxiliary* methodologies. Catalytic protocols with metal and metal-free catalysts appeared in 2005. Regarding *metal-promoted catalysis*, only few examples have been reported, probably because sulfur tends to coordinate to metal complexes, thus inhibiting the catalytic activity. Comparatively, organocatalytic α-sulfenylation reactions have been more developed, and within this field *non covalent organocatalysis* has received much attention.

[58] López, I.; Rodríguez, S.; Izquierdo, J.; González, F. V. *J. Org. Chem*. **2007**, *72*, 6614–6617.
[59] Tatsuta, K.; Suzuki, Y.; Toriumi, T.; Furuya, Y.; Hosokawa, S. *Tetrahedron Lett*. **2007**, *48*, 8018–8021.

1.2.2.2.1. Chiral auxiliary strategy

Few examples have been reported following this strategy and the most representative contributions are shown in Table 1.[60] The first example of this type was reported by Ugi in 1987,[61] using (*R*)-α-phenylethylamine as chiral auxiliary (Table 1, entry 1), although the stereocontrol turned to be poor. Later, other general auxiliaries such as Evans' oxazolidinones[62] and Enders' hydrazines[63] were also investigated in this reaction (Table 1, entries 2 and 3). Furthermore, Enders expanded successfully the scope of the α-sulfenylation reaction to ketones (Table 1, entry 4), and this constitutes a relevant contribution because, as far as we know, this represents one of the few efficient protocols for the asymmetric α-sulfenylation of ketones.[64]

The strategy of *chiral auxiliaries* presents two important drawbacks; on the one hand, stoichiometric quantities of the chiral information source are needed and, on the other hand, two additional steps, attachment and cleavage of the chiral auxiliary, are required. That is why researchers developed an alternative strategy, called *asymmetric catalysis*, in which the stereocontrol of the reaction is regulated by a chiral catalyst. As the interaction between the catalyst and the substrate is reversible the catalyst is not consumed during the process and can be introduced in a new catalytic cycle. The atom

[60] For the use of other chiral auxiliaries, see: For the diastereoselective α-sulfenylation of chiral α-amino esters Schiff bases: a) Bentama, A.; Hoarau, S.; Pappalardo, L.; Roumestant, M. L.; Viallefont, P. *Amino Acids* **1994**, *7*, 105–108. For the diastereoselective α-sulfenylation of 2-aryl-3-phenyl-1-menthopyrazoles: b) Kashima, C.; Takahashi, K.; Hosomi, A. *Heterocycles* **1996**, *42*, 241–250.

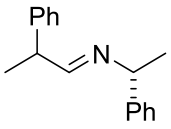
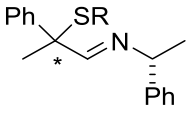
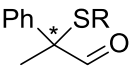
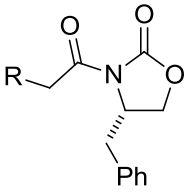
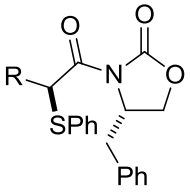
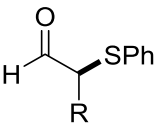
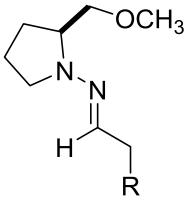
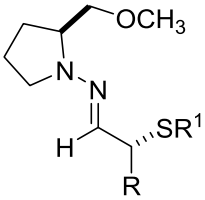
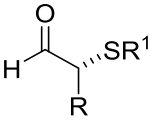
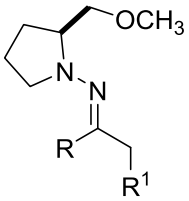
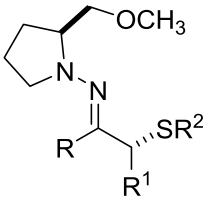
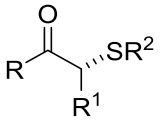
[61] Youn, J. -H.; Herrmann, R.; Ugi, I. *Synthesis* **1987**, 159–161.

[62] a) Chibale, K.; Warren, S. *Tetrahedron Lett*. **1994**, *35*, 3991–3994. For a synthetic application of α-sulfenylation which provides a key intermediate for the synthesis of the biologically active compound thiolactomycin **16** (page 8), see: b) ref. 12.

[63] a) Enders, D.; Schäfer, T.; Mies, W. *Tetrahedron* **1998**, *54*, 10239–10252. When diisopropyldisulfide was used as sulfur source low diastereomeric excess was observed.

[64] For a recent contribution which employs silyl enol ethers of ketones to afford α-sulfenylated ketones with good stereochemical results using Lewis bases as catalysts, see: a) Denmark, S. E.; Rossi, S. Webster, M. P.; Wang, H. *J. Am. Chem. Soc*. **2014**, *136*, 13016–13028. For other less successful precedents, see: For the enantioselective sulfenylation of 4-alkylcyclohexanones using chiral sulphonamides as sulfur source: b) Hiroi, K.; Nishida, M.; Nakayama, A.; Nakazawa, K.; Fujii, E.; Sato, S. *Chem. Lett*. **1979**, 969−972. For the sulfenylation of masked ketones through Evans' oxazolidinone-derived *O*-silylated imide enolates: c) Alexander, R. P.; Paterson, I. *Tetrahedron Lett*. **1985**, *26*, 5339−5340. For the α-sulfenylation of ketones which involves the reaction with tin enolates with phenylsulfenyl chloride in the presence of stoichiometric amounts of a chiral diamine: d) Yura, T.; Iwasawa, N.; Clark, R.; Mukaiyama, T. *Chem Lett*. **1986**, 1809–1812.

Table 1. Stoichiometric α-sulfenylation of carbonyl compounds.

Entry	Author	Substrate	Sulfur source	Product	Final product
1	Ugi, **1987**[61]		RSSR		 91–95% yield 13–51% *ee*
2	Warren, **1994**[62]		PhSSPh		 90–94% yield >98% *ee*
3	Enders, **1998**[63]		R^1SSR^1		 67–70% yield 45–93% *ee*
4	Enders, **1998**[63]		R^2SSR^2		 47–59% yield 92–96% *ee*

economy[65] of the process is optimal, minimizing the waste generated. An additional advantage of this methodology is the multiplication of the chirality, since stoichiometric quantities of enantioenriched products are obtained from substoichiometric quantities of catalyst. In contrast to the use of *chiral auxiliaries* that affords enantiopure compounds through diastereomeric intermediates, *asymmetric catalysis* furnishes directly enantiomers from prochiral compounds allowing the preparation of a broad variety of chiral compounds with high enantiomeric excess. It was for their work on *asymmetric catalysis*, more specifically on metal catalyzed asymmetric hydrogenation reactions, that Profs. W. S. Knowles, R. Noyori and K. B. Sharpless won the Nobel Prize in Chemistry in 2001 (Figure 10). This is a clear evidence of the importance of this field.

[65] a) Trost, B. M. *Science* **1991**, *254*, 1471–1477. b) Trost, B. M. *Angew. Chem. Int. Ed*. **1995**, *34*, 259–281. c) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246.

W. S. Knowles R. Noyori K. B. Sharpless

Figure 10. The Nobel Prize in Chemistry in 2001.

1.2.2.2.2. Metal-catalyzed α-sulfenylation

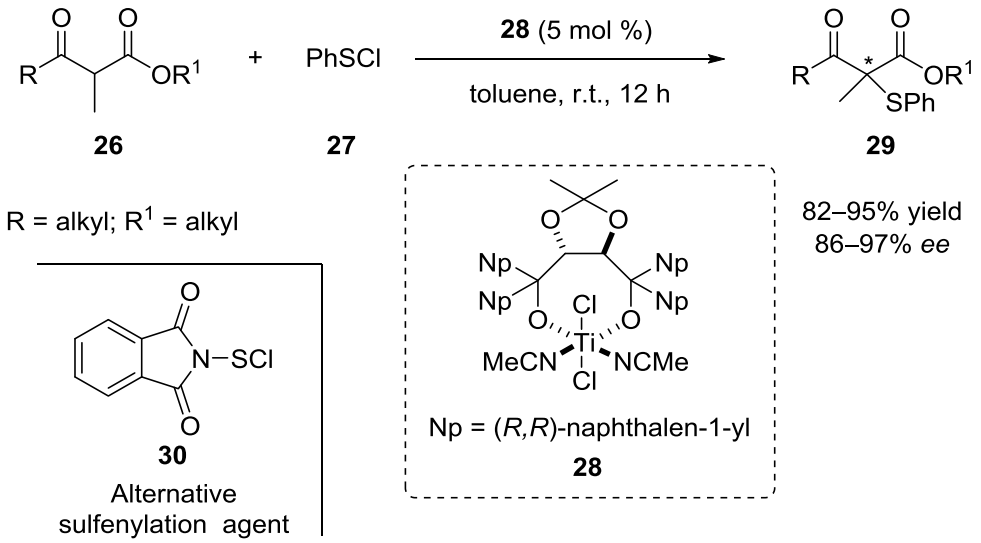
Regarding α-sulfenylation reactions of carbonyl compounds and, unlike other reactions, metal catalyzed processes have been developed in a little extent, likely because the use of sulfur-based reagents presents some limitations when Lewis acids are employed as catalyst, due to undesired association of the sulfur with the metal. A comprehensive literature search reveals the existence of only two metal-catalyzed examples which are promoted by titanium and scandium complexes, and are presented below.

Togni and co-workers reported the first example in 2005 using phenylsulfenyl chloride **27** as electrophilic sulfur source, β-keto esters **26** as substrates and the Ti(TADDOLato) complex **28** as catalyst (Scheme 7, a).[66] They assume that the β-ketoester enolate intermediate coordinates to the Ti(IV) center in a chelating fashion, inducing chirality.[67] The catalyst is compatible with the hydrogen chloride formed as by-product in the reaction, despite the absence of a base in the reaction mixture. However, the limitation of the procedure is the difficulty in transforming the thioether group. Thus, later they developed an alternative employing phthalimide-*N*-sulfenyl chloride **30** as sulfenylation agent, wherein the *S–N* bond is easier to cleavage, but unfortunately, the enantiomeric excess did not go beyond 60%.[68]

[66] Jereb, M.; Togni, A. *Org. Lett*. **2005**, *7*, 4041–4043.

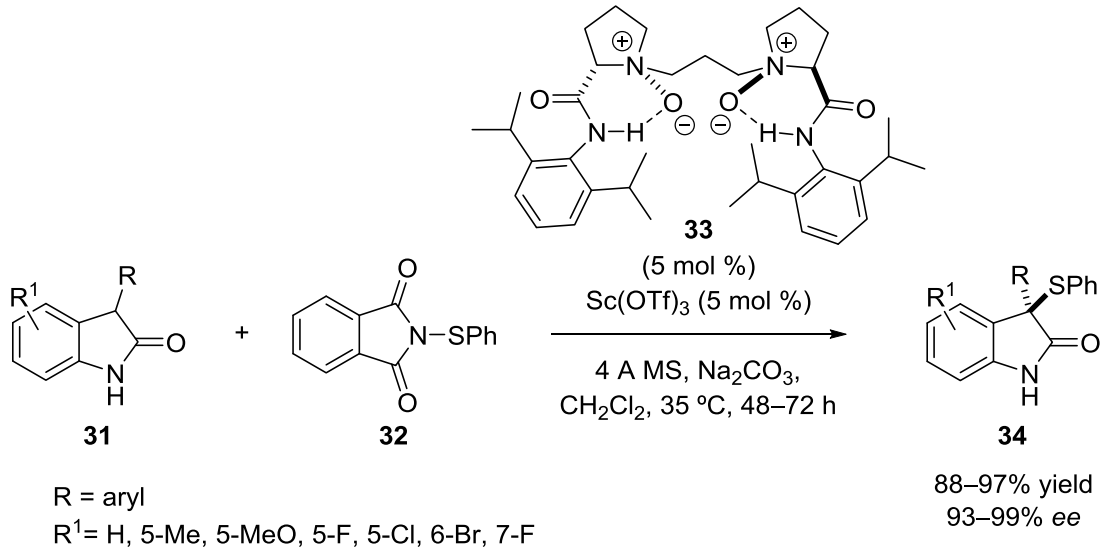
[67] Better results regarding *ee*, up to 97%, were obtained when alkyl bulky ester groups such as 1,1,2-trimethyl propyl were used : Jereb, M.; Togni, A. *Chem. Eur. J.* **2007**, *13*, 9384–9392.

[68] Srisailam, S. K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2603–2607.



Scheme 7. Ti-Catalyzed enantioselective α-sulfenylation of β-keto esters. **Togni, 2005**.

In 2012 Feng and co-workers developed an asymmetric sulfenylation of unprotected 3-substituted oxindoles **31** with *N*-(phenylthio)phthalimide **32** employing a combination of chiral *N,N′*-dioxide **33**-$Sc(OTf)_3$ complex and in this case, a stoichiometric Brønsted base (Na_2CO_3) was needed to produce enolyzation of **31** (Scheme 8).[69]



Scheme 8. Enantioselective α-sulfenylation of unprotected 3-substituted oxindoles. **Feng, 2012**.

[69] Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett*. **2012**, *14*, 2726–2729.

1.2.2.2.3. Organocatalyzed α-sulfenylation

Although chiral metal catalysts have turned to be quite efficient in chirality transfer in a wide range of asymmetric reactions, over the last years methods based exclusively on metal-free chiral organic catalysts, i.e. *organocatalysis*, have become significant and have been comparatively much developed in the case of α-sulfenylation reactions.[70] In addition, in this strategy the problem of the coordination of the sulfur atom to the metal is avoided. Within this alternative, depending on the interactions between the substrate and the catalyst two different approaches are distinguished: *non covalent organocatalysis* and *covalent organocatalysis*.

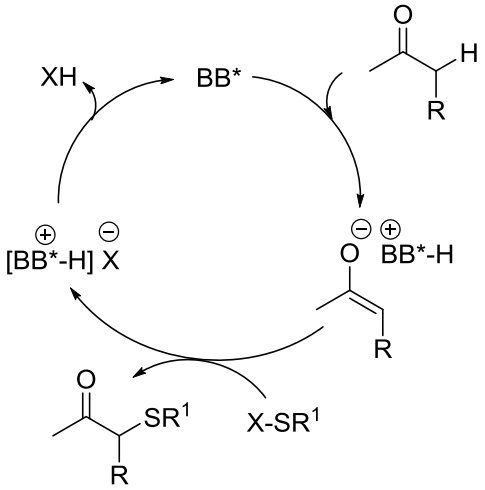
1.2.2.2.3.1. Non covalent organocatalysis

As said before, in *non covalent organocatalysis*, the interactions between the substrate and the catalyst are weak. In the case of α-sulfenylation reactions, this type of organocatalysis has been investigated essentially by using Brønsted base catalysis.[71] Chiral Brønsted bases[33] have been demonstrated capable of catalyzing a large range of asymmetric reactions. These catalysts promote deprotonation of the (pro)nucleophile through the formation of a chiral ion pair that provides an asymmetric environment for the construction of the new bond. In general, the intrinsic nondirectional nature of electrostatic interactions in ion pairing complexes makes difficult to predict the sense of stereoinduction in the final product.

The catalytic cycle of the α-sulfenylation of carbonyl compounds promoted by Brønsted bases is shown in Scheme 9. An enolizable carbonyl compound is deprotonated by a chiral Brønsted base to yield a more nucleophilic chiral species. Thanks to the chiral catalytic component of the ion pair, this reacts with the sulfur electrophile providing the enantioenriched product and releasing the Brønsted base catalyst which can then undergo a new catalytic cycle. It is worth noting that the other product generated in the reaction (XH) must be less acid than the starting carbonyl compound to avoid the protonation of the Brønsted base, and therefore the deactivation of the catalyst.

[70] For a recent review on asymmetric α-sulfenylation, see: Zhao, X.; Shen, J.; Jiang, Z. *Mini-reviews in Org. Chem*. **2014**, *11*, 424–431.

[71] An alternative for Brønsted bases in *non covalent organocatalysis* is phase transfer catalysis. For a preliminary study of diastereoselective α-sulfenylation of β-keto sulfoxides catalyzed by *N*-benzilquininium chloride under phase transfer catalysis, see: Wladislaw, B.; Marzorati, L.; Biaggio, F. C.; Vargas, R. R.; Bjorklund, M. B.; Zukerman-Schpector, J. *Tetrahedron* **1999**, *55*, 12023–12030.



Scheme 9. Brønsted base promoted catalytic cycle for the electrophilic α-sulfenylation of carbonyl compounds.

Nitrogen-containing compounds such as tertiary amines, guanidines, amidines and imidazoles are predominantly used chiral Brønsted base catalysts. In particular the cinchona family (Figure 11) occupies a central position due to its extensive versatility, stereochemical diversity and commercial availability. In fact, these compounds have been considered as one of the most privileged chiral inductors in organic synthesis.[72] Regarding the substrate, usually the (pro)nucleophiles used with Brønsted base catalysts of this type are β-dicarbonyl compounds, due to their appropriate pka's.

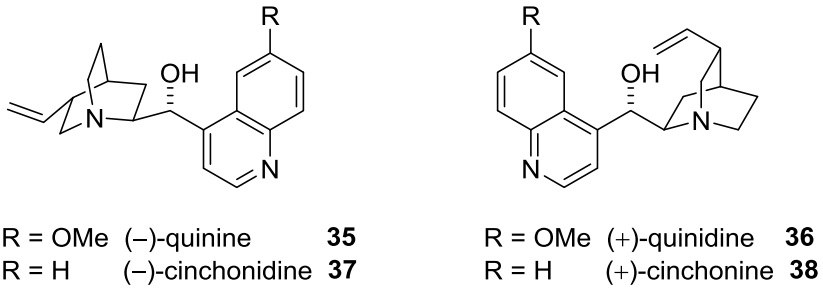


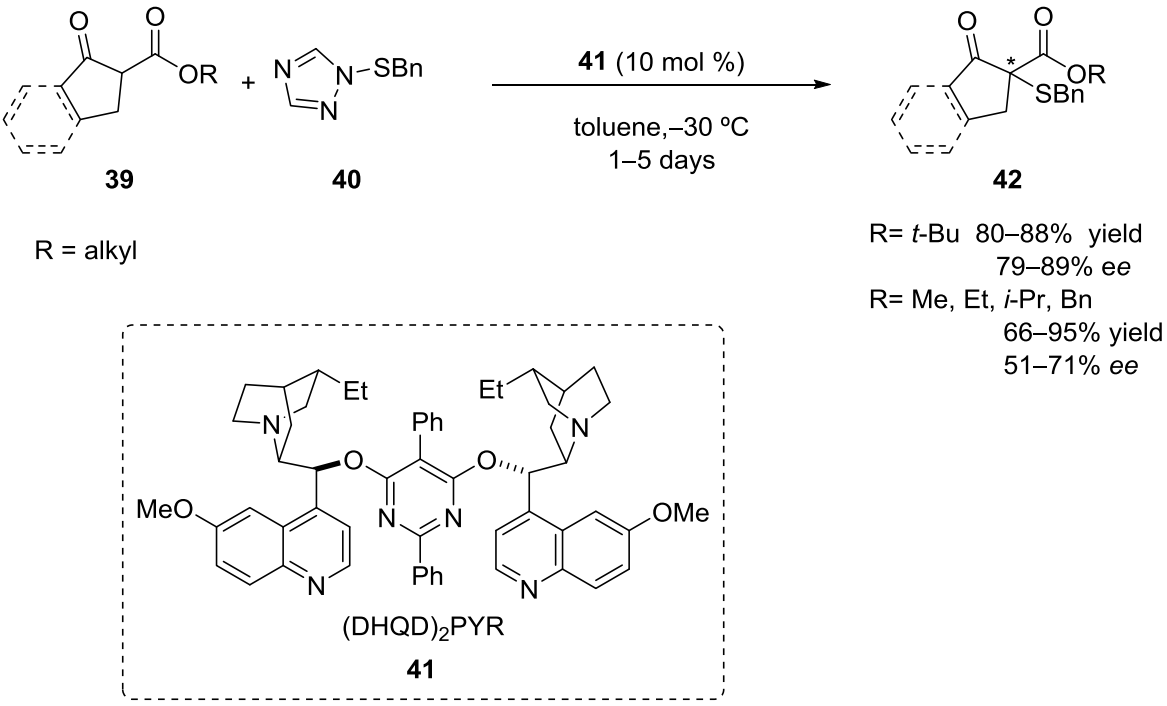
Figure 11. Cinchona alkaloids family.

The group of Jørgensen was pioneering in introducing an organocatalyst in the field of α-sulfenylation in 2005. They employed the commercially available cinchona alkaloid $(DHQD)_2PYR$ **41** as Brønsted base to perform the first α-sulfenylation of cyclic β-dicarbonyl compounds **39**. As electrophilic sulfur source the novel triazole derivative 1-benzylsulfanyl-1,2,4-triazole **40** was choosen and the reactions proceed with moderate to good yields and enantioselectivities (Scheme 10).[73,74] Following this pioneering

[72] Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299,* 1691–1693.

[73] Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689–5694.

example, other protocols promoted by bifunctional Brønsted base catalysts, which are outlined later, have also been published.



Scheme 10. Enantioselective α-sulfenylation of cyclic β-dicarbonyl compounds. **Jørgensen, 2005**.

When a given catalyst bears two catalytic sites, one that activates the (pro)nucleophile and other that interacts with the electrophile, a double simultaneous activation occurs in the asymmetric reaction process and this type of catalyst is said to be bifunctional.[41] Usually, this dual activation provides benefits in the reaction rates and stereoselectivity, due to more ordered transitions states. After the introduction of the term, this type of catalyst emerged as a powerful tool in asymmetric synthesis. Over the last years bifunctional Brønsted bases with an additional urea/thiourea or squaramide functionality as H-bond donor have emerged as potential bifunctional catalysts. Since Takemoto's design,[45] cyclohexyldiamine and cinchona based Brønsted bases[75] **43**, **44** and **45** bearing a urea/thiourea functionality were initially the most developed catalysts[76] (Figure 12). Later, in 2008 Rawal[77] presented a new bifunctional Brønsted

[74] For a related protocol for the asymmetric α-sulfenylation of substituted piperazine-2,5-diones promoted by quinine which provides moderate enantiocontrol, see: Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742–2750.

[75] a) Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967–1969. b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, *35*, 4481–4483. c) McCooey, S. H.; Connon, S. *Angew. Chem. Int. Ed*. **2005**, *44*, 6367–6370.

[76] For reviews on organocatalysis using thiourea derivative catalysts, see: a) Tsakos, M.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 10199–10222. b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid*

base **46** bearing a squaramide group as H-bond donor as another interesting bifunctional catalyst family (Figure 12).[78]

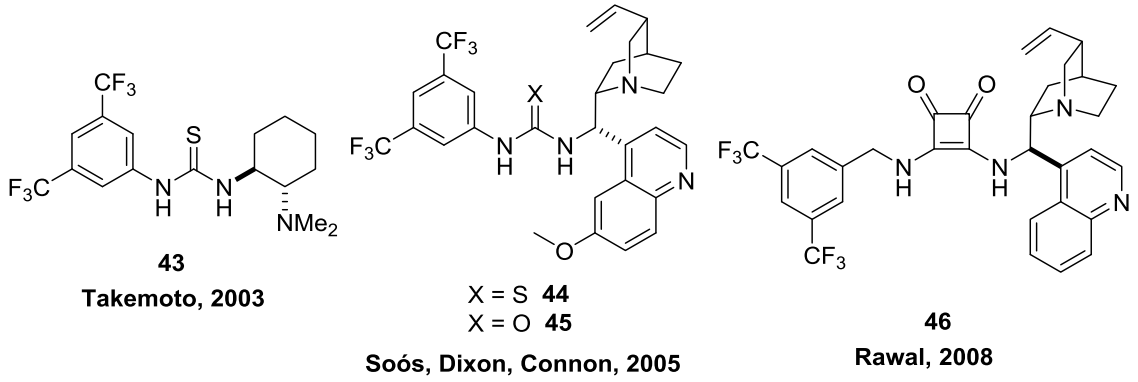


Figure 12. Representative bifunctional Brønsted base catalysts.

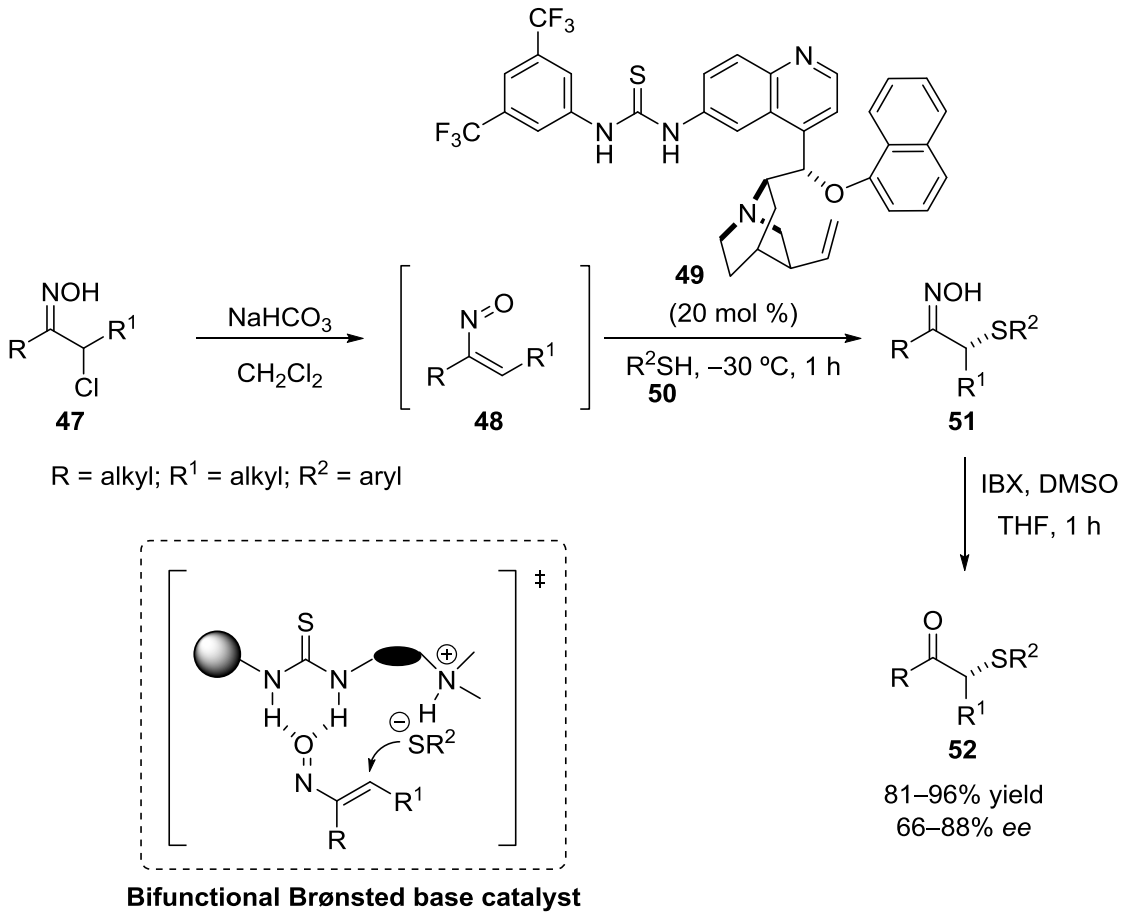
Colbart and co-workers reported the first organocatalytic asymmetric formal α-sulfenylation of ketones via sulfa-Michael addition with *in situ* formed nitrosoalkenes, catalyzed by a bifunctional Brønsted base catalyst.[79] Nitrosoalkenes **48** were generated by treating α-chloro oximes **47** with $NaHCO_3$. Then the bifunctional catalyst **49** and thiol **50** were added to the reaction mixture. According to the authors' proposal (Scheme 11), the thiourea moiety is supposed to coordinate to the oxygen of the nitroso group, while the deprotonated thiol adds to **48** giving the oxime **51**, which is then hydrolized to **52**. This represents a good and indirect alternative for the synthesis of α-thiofunctionalized ketones, for which, as said before, very limited efficient protocols have been reported (see page 21 and ref. 64).

Catalysis, and Additional Topics: Science of Synthesis, Ed.: K. Maruoka, **2012**, Thieme Verlag, Stuttgart, pp. 119–168 and pp. 437–497. c) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol*. **2011**, *1*, 1298–1310. d) ref. 31d. e) Connon, S. J. *Synlett* **2009**, *3*, 354–376. f) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn*. **2008**, *81*, 785–795. g) Connon, S. J. *Chem. Eur. J*. **2006,** *12*, 5418-5427. h) Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299–4306.

[77] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

[78] For reviews on organocatalysis using squaramide catalysts, see: a) ref. 76a. b) Aleman, J.; Parra, A.; Jiang, H.; Jorgensen, K. A. *Chem. Eur. J.* **2011**, 17, 6890–6899. c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, 40, 2330–2346.

[79] Hatcher, J. M.; Kholer, M. C.; Colbart, D. M. *Org. Lett*. **2011**, *13*, 3810–3813.



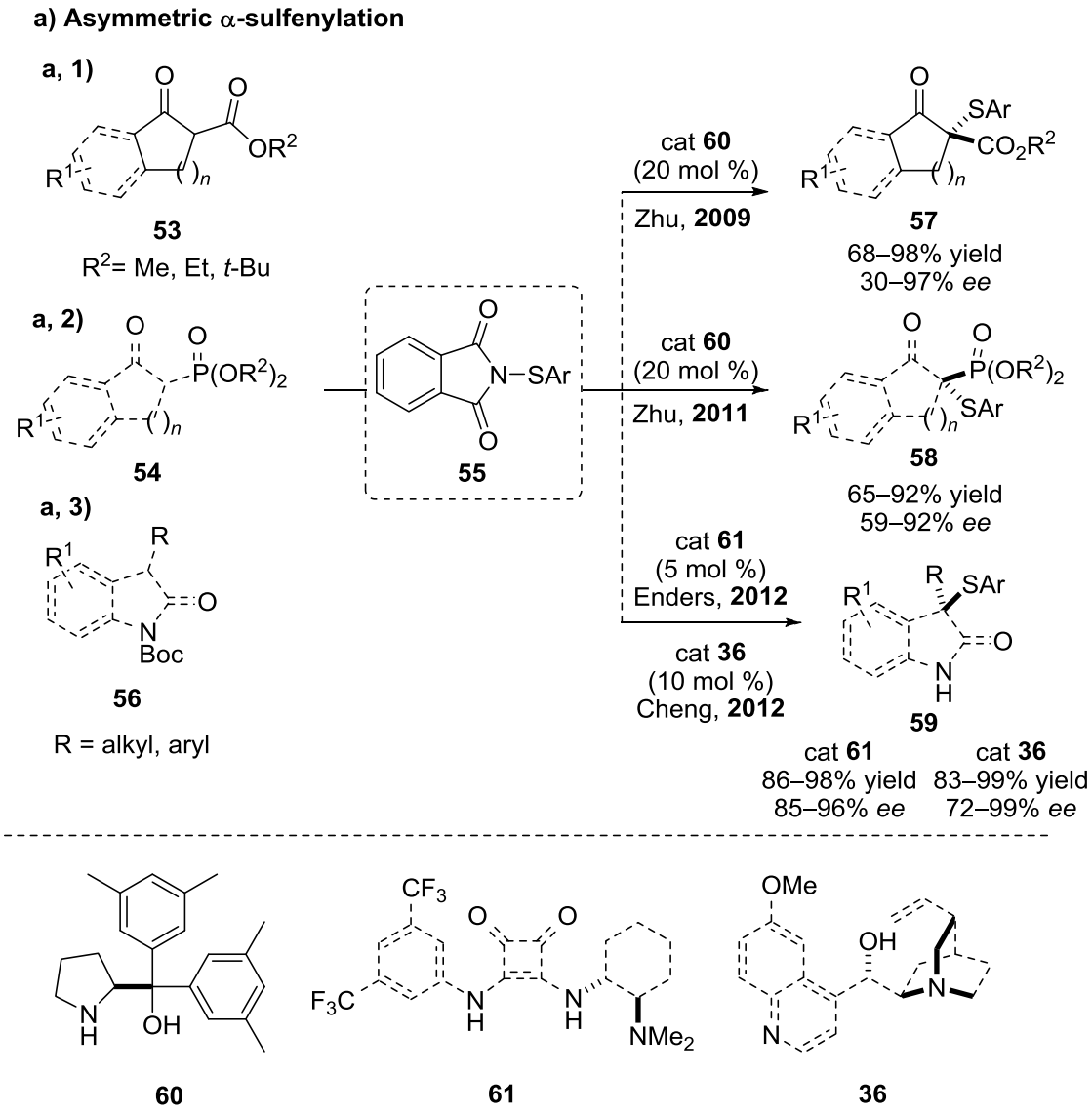
Scheme 11. Formal asymmetric α-sulfenylation of ketones via sulfa-Michael addition to nitroso alkene intermediates. **Colbart, 2011**.

Efficient α-sulfenylation reactions of 1,3-dicarbonyl cyclic compounds,[80] β-keto phosphonates[81] and 3-substituted oxindoles[82] have been described employing bifunctional Brønsted base catalysts. The most significant characteristics of these protocols are, on the one hand, the formation of tertiary thiol derivatives,[57d] for which limited synthesis exist; and, on the other hand, and, in general, the use of *N*-(arylthio)phthalimides **55** as sulfur source (Scheme 12a). Remarkably catalyst **60**, in contrast to the most known way of action of these pyrrolidines as aminocatalysts, works in these reactions as bifunctional Brønsted base as demonstrated by NMR studies. The proposed mode of action of this catalyst is depicted in Scheme 12b.

[80] Fang, L.; Lin, A.; Hu, H.; Zhu, C.; Cheng, Y. *Chem. Eur. J*. **2009**, *15*, 7039–7043.

[81] Lin, A.; Fang, L.; Zhu, X.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal*. **2011**, *353*, 545–549.

[82] a) Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. Eur. J*. **2012**, *18*, 11531–11535. b) Li, X.; Liu, C.; Xue, X. -S.; Cheng, J. -P. *Org. Lett*. **2012**, *14*, 4374–4377. For a similar efficient example which uses *N*-benzyl protected aryloxindoles as substrates, *N*-(sulfanyl)succinimides as sulfur source, and commercially available $(DHQD)_2PHAL$ as catalyst, see: c) Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett*. **2012**, *14*, 4670–4673.



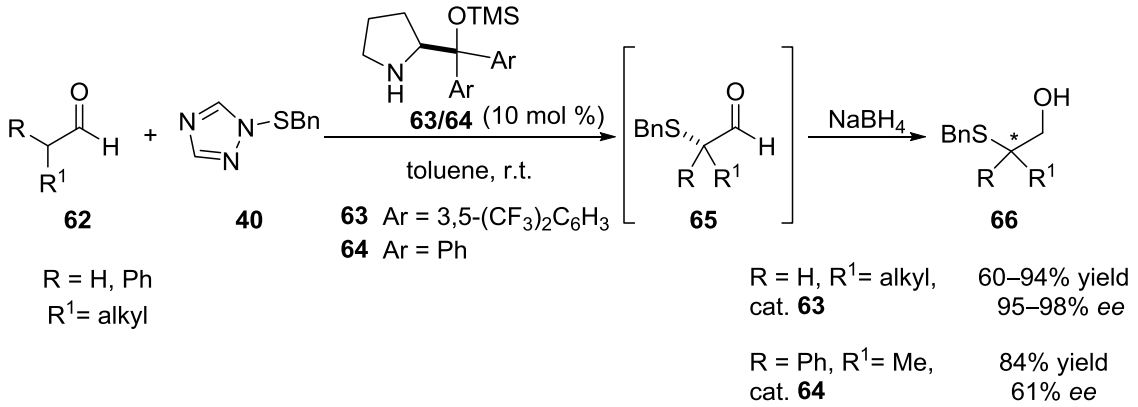
Scheme 12. a) Organocatalytic asymmetric α-sulfenylations of 1,3-dicarbonylic cyclic compounds (a,1, **Zhu**, **2009**), β-keto phosphonates (a,2, **Zhu, 2011**) and 3-substituted oxindoles (a,3, **Enders** and **Cheng**, **2012**). b) Proposed transition state for (a,1) and (a,2) reactions.

Brønsted base mono- and bifunctional catalysts are limited to relatively acidic substrates as 1,3-dicarbonyl compounds, β-ketophosphonates and oxindoles. A complementary alternative for the α-thiofunctionalization of carbonyl compounds is *covalent organocatalysis*.

1.2.2.2.3.2. Covalent organocatalysis

In *covalent organocatalysis*, the catalyst and the substrate interact covalently. In carbonyl compounds the most developed strategy is aminocatalysis and this has been applied to the α-sulfenylation of aldehydes through enamine activation. There are very few examples of this strategy and the reported ones make use of aldehydes as starting carbonyl compounds and chiral pyrrolidines as amino-catalysts.

The same group that developed the first Brønsted base catalyzed α-sulfenylation of cyclic β-dicarbonyl compounds, described in 2005 the first aminocatalyzed α-sulfenylation of aldehydes shown in Scheme 13.[83] Non ramified aldehydes react under these conditions to give in good yields and excellent enantioselectivities benzyl thioalcohols **66** after reduction of sulfenylated adducts **65**.[84] However, α-branched aldehydes seem to be not appropriate substrates for this reaction as demonstrated by the low enantioselectivity found in the case of 2-phenyl propanal.

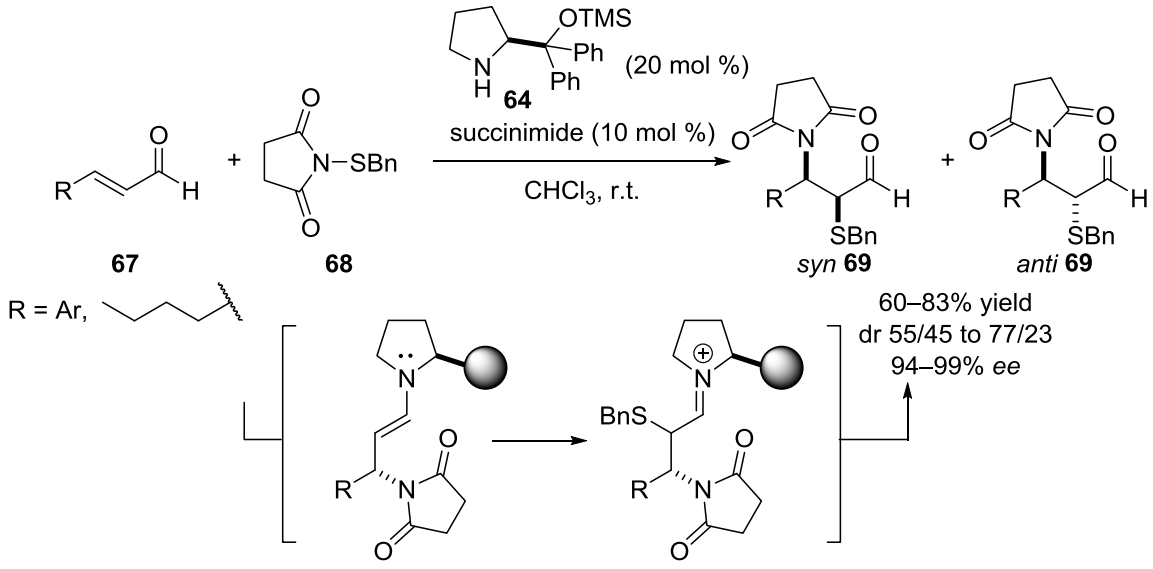


Scheme 13. Organocatalyzed α-sulfenylation of aldehydes. **Jørgensen, 2005**.

[83] a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797. b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjæersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

[84] For the synthetic applications of the sulfenylated aldehydes developed by Armstrong, see: For the synthesis of vinyl glycines: a) Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem. Int. Ed*. **2007**, *46*, 5369–5372. For the synthesis of allenamides: b) Armstrong, A. Emmerson, D. P. G. *Org. Lett*. **2009**, *11*, 1547–1150. For the synthesis of β,γ-unsaturated-α-aminophosphonates: c) Armstrong, A. Deacon, N.; Donald, C. *Synlett* **2011**, 2347–2350.

Alternatively, Córdova and co-workers developed an aminosulfenylation reaction of enals, where the sulfur-containing electrophile **68** includes a masked nitrogen nucleophilic component that is incorporated into the electrophilic enal **67** via iminium/enamine activation strategy in the presence of catalyst **64**. A small amount of succinimide was added in order to initiate the first aza-Michael reaction as shown in Scheme 14.[85] Epimerization of the α-carbon of aminoaldehydes **69** by the chiral amine catalyst was demonstrated, thus explaining the moderate diastereocontrol of the reaction.



Scheme 14. Organocatalyzed aminosulfenylation of α,β-unsaturated aldehydes. **Córdova, 2008**.

It is worth noting that very recently and after our research work Brønsted base catalyzed electrophilic α-sulfenylation of α-nitroesters,[86] azlactones[87] and 5*H*-oxazol-4-ones[88] have been published. Furthermore, α-trifluoromethylsulfenylation of β-ketoesters[89] and oxindoles[90] has also been reported.

The previous contributions show that the α-sulfenylation of carbonyl compounds is a well established and deeply investigated strategy. Although there are already some limitations regarding substrate scope, and some protocols, as for instance, metal-

[85] Zhao, G. L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468–8472.

[86] Fang, L.; Lin, A.; Shi, Y.; Cheng, Y.; Zhu, C. *Tetrahedron Lett*. **2014**, *55*, 387–389.

[87] Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett*. **2014**, *16*, 672–675.

[88] Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696–8702.

[89] a) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12856–12859. b) Wang, X.; Yang, T.; Cheng, X.; Shen, Q. *Angew. Chem. Int. Ed*. **2013**, *52*, 12860–12864.

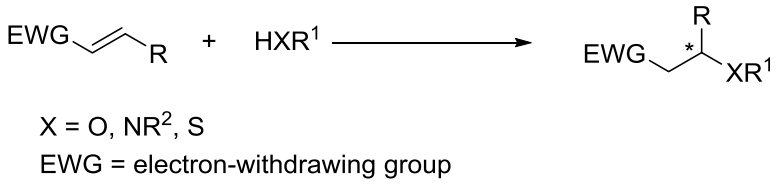
[90] a) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun*. **2014**, 2508–2511. b) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett*. **2014**, *16*, 2192–2195.

catalyzed procedures have been scarcely developed, the α-sulfenylation constitutes nowadays a useful tool to access different α-thiofunctionalized carbonyl derivatives.

Another strategy for the thiofunctionalization of carbonyl compounds is the sulfa-Michael reaction of sulfur based (pro)nucleophiles with α,β-unsaturated carbonyl compounds which affords β-thiofunctionalized carbonyl derivatives. The most significant existing contributions of this protocol are outlined in the following section.

1.2.3. Asymmetric sulfa-Michael additions to unsaturated carbonyl compounds

The Michael reaction[91] is the 1,4-addition of a nucleophile to an electrodeficient α,β-unsaturated compound and constitutes an important tool in organic chemistry for the formation of *C–C* bonds (Scheme 15). When a sulfur-containing nucleophile is used the reaction is called sulfa-Michael addition and is probably the most developed process for the asymmetric formation of *C–S* bonds, due to the diversity of nucleophilic and electrophilic reagents available for this transformation. Whilst several Michael acceptors may be employed in this reaction,[92] we will focus on α,β-unsaturated carbonyl compounds, only.

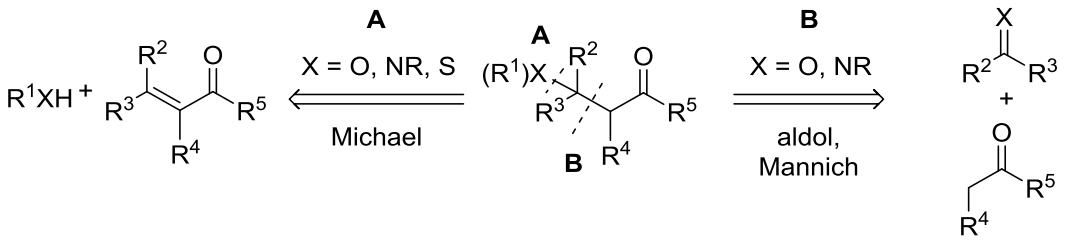


Scheme 15. General scheme of hetero-Michael addition reactions. (X = O, oxa-Michael; X = NH, aza-Michael; X = S, sulfa-Michael)

When sulfa-Michael reactions are performed using α,β-unsaturated carbonyl substrates as Michael acceptors β-sulfur-substituted derivatives are generated (Scheme 16, A). Another direct approach to synthesize these derivatives would be the aldol reaction with thiocarbonyl electrophiles (Scheme 16, B). However, this protocol is of limited synthetic utility because thiocarbonyl compounds are poor electrophiles, unstable under the aldol reaction conditions and difficult to synthesize.

[91] For general reviews on Michael reactions, see: a) Thirumalaikumar, M. *Org. Prep. Proc. Int.* **2011**, *43*, 67–129. b) Córdova, A. *Catalytic Asymmetric Conjugate Reactions*, **2010**, Wiley-VCH, Weinheim. c) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition*, **2010**, RSC Catalysis, Cambridge.

[92] For general reviews on sulfa-Michael reactions, see: a) Enders, D.; Lüttegen, K.; Narine, A. A. *Synthesis* **2007**, *7*, 959–980. b) ref. 48a.



Scheme 16. Representative strategies for the synthesis of β-hetero substituted carbonyl compounds.

Michael reactions in general and, sulfa-Michael additions in particular, constitute a very useful tool for the development of tandem[93] reactions to increase the complexity and the diversity of the final products. The first step of a sulfa-Michael addition generates an enolate or equivalent which can then undergo the reaction with another electrophile. It is for this reason that many sulfa-Michael additions described in the literature are the first reaction of a tandem sequence.[94] In these cases an additional functionality is required to perform the reaction and in most of the reported protocols of this type this functionality is incorporated in the sulfur-donor. Figure 13 (a) shows the most representative substrates of this class. Some few protocols which incorporate this extra functionality in the Michael acceptor (Figure 13, b) or in both, donor and acceptor, have also been published. Apart from few examples with chiral auxiliaries, all the transformations of this kind are organocatalyzed, either by Brønsted bases or by aminocatalysts. Interestingly these reactions lead to highly substituted heterocycles such as thiochromenes, dihydro- and tetrahydrothiophenes (Figure 13, c).

[93] In 2004 Fogg and dos Santos used the term tandem catalysis to describe coupled catalysis in which sequential transformation of the substrate occurs via two (or more) mechanistically distinct processes: a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev*. **2004**, *248*, 2365–2379. For a classification of one-pot reactions based on the catalysis type, see: b) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem*. **2012**, *10*, 211–224. For general reviews on tandem reactions, see: c) Tietze, L. F. *Domino Reactions: Concepts for Efficient Organic* **2013**, Wiley-VCH, Weinheim, Germany. d) Pellissier, H. *Asymmetric Domino reactions* **2013**, RSC Catalysis, Cambridge. e) Chapman, J. C.; Frost, C. G. *Synthesis* **2007**, 1–21. f) Tietze, L. F.; Brasche, G.; Gerike, D. M. *Domino Reactions in Organic Synthesis* **2006**, Wiley-VCH, Weinheim. g) Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Inter. Ed.* **2006**, *45*, 7134–7186. h) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. For reviews on tandem organocatalytic reactions: i) Pellissier, H. *Tetrahedron* **2013**, *69*, 7171–7210. j) Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry*, **2010**, *2*, 167–178. k) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

[94] For reviews on organocatalytic *C–S* bond forming reactions where all these tandem protocols are described, see ref. 48a and c.

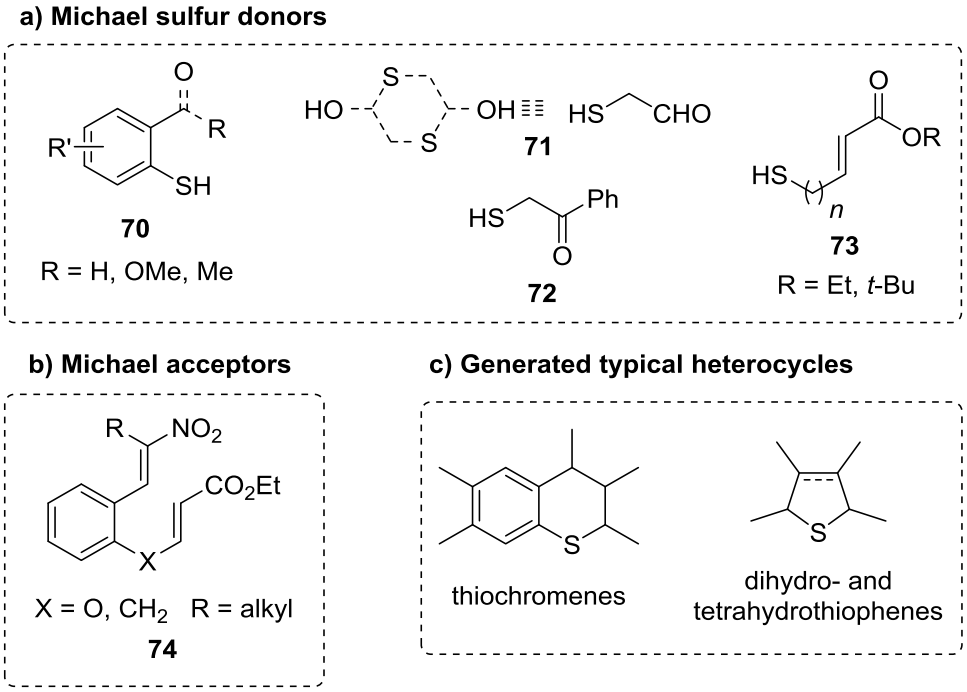


Figure 13. Common sulfur donor and acceptor substrates in tandem reactions initiated by a sulfa-Michael addition. a) Michael sulfur donors. b) Michael acceptors. c) Typical heterocycles generated in these reactions.

In the next sections the most representative sulfa-Michael reactions described at the beginning of our research for α,β-unsaturated carbonyl compounds employing different strategies are outlined. As in the case of α-sulfenylation, the most widely used strategy is organocatalysis. Even so, some procedures based on the incorporation of a chiral auxiliary or the use of metal catalysts to obtain β-thiofunctionalized enantioenriched carbonyl compounds have also been developed. It is noteworthy that when α-substituted Michael acceptors are used, after the sulfa-Michael addition the stereocontrolled protonation of the resulting enolate or equivalent intermediate must occur to obtain the enantioenriched sulfa-Michael adduct, which involves an additional challenge for these reactions.

1.2.3.1. Chiral auxiliary strategy

The stoichiometric sulfa-Michael additions developed following this strategy incorporate the chiral auxiliary in the Michael acceptor. In this context, proline- and pyrrolidine-derived auxiliaries,[95,96] (Figure 14, a), Evans' oxazolidinones[97,98] (Figure

[95] Effenberger, F.; Isak, H. *Chem. Ber*. **1989**, *122*, 553–559.

[96] Kim, B. H.; Le, H. B.; Hwang, J. K.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1215–1220.

[97] Tseng, T. -C.; Wu, M. -J. *Tetrahedron: Asymmetry* **1995**, *6*, 1633–1640.

[98] Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem*. **1995**, *60*, 6188–6190.

14, b), Oppolzer's sultams[99] (Figure 14, c) and a particular example that uses *chiro*-inositols[100] (Figure 14, d) have been investigated by using thiols and thioacids as donors and some of these cases make use of α-substituted Michael acceptors. A particular type of chiral camphor derived Michael donors have also been used in asymmetric tandem sulfa-Michael/Meerwein-Ponndorf-Verley reduction reactions.[101]

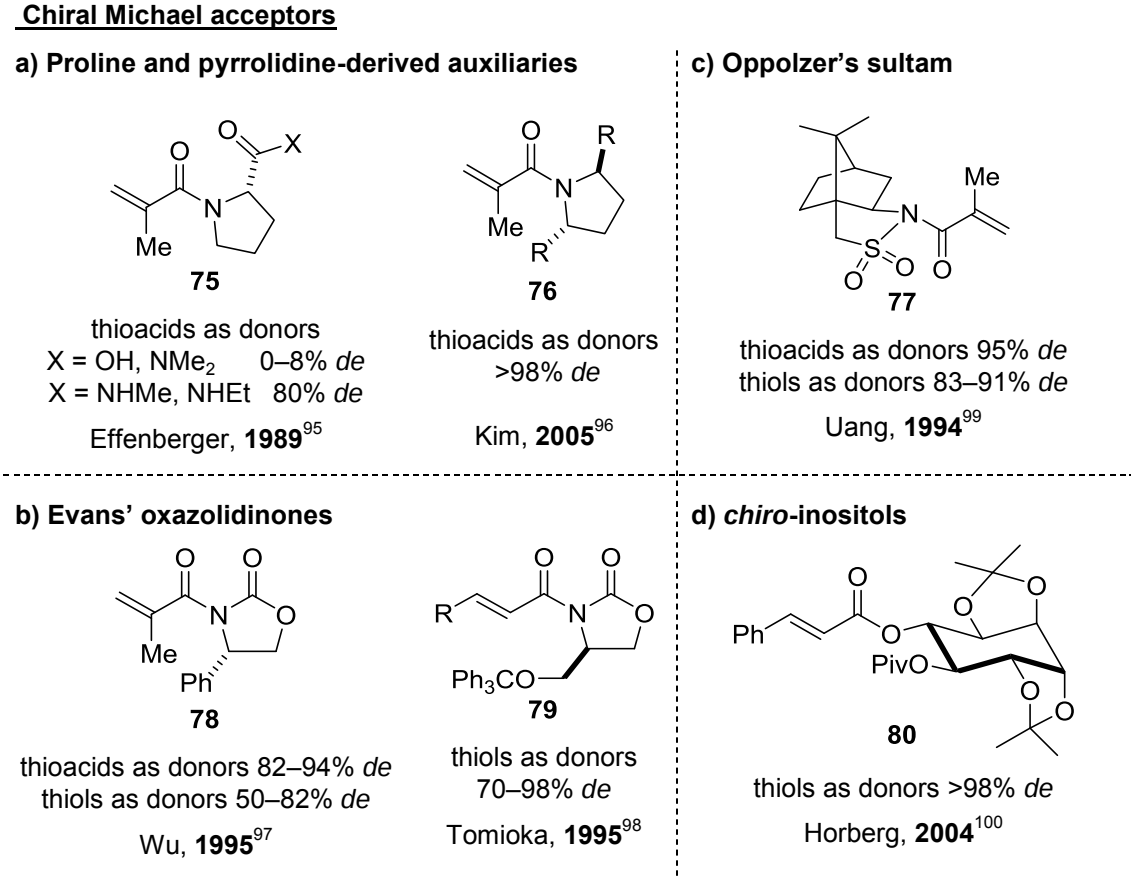


Figure 14. Chiral auxiliary based Michael acceptors for sulfa-Michael additions.

[99] Tsai, W. -J.; Lin, Y. -T; Uang, B. -J. *Tetrahedron: Asymmetry* **1994**, *5*, 1195–1198.

[100] Cousins, G.; Falshaw, A.; Horberg, J. O. *Org. Biomol. Chem*. **2004**, *2*, 2272–2274.

[101] a) Shiraki, H.; Nishide, K.; Node, M. *Tetrahedron Lett*. **2000**, *41*, 3437–3441. b) Nishide, K.; Ohsugi, S. -I.; Shiraki, H.; Tamakita, H.; Node, M. *Org. Lett*. **2001**, *3*, 3121–3124. c) Nishide, K.; Ozeki, M.; Kunishige, H.; Shigeta, Y.; Patra, P. K.; Hagimoto, Y.; Node, M. *Angew. Chem Int. Ed.* **2003**, *42*, 4515–4517. d) Ozeki, M.; Nishide, K.; Teraoka, F.; Node, M. *Tetrahedron: Asymmetry* **2004**, *14*, 895–907. e) Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett*. **2003**, *44*, 2323–2326.

1.2.3.2. Metal-catalyzed sulfa-Michael additions

Although organocatalyzed sulfa-Michael addition has been the most developed strategy to synthesize chiral sulfur-containing compounds, enantioselective metal catalyzed sulfa-Michael reactions have also been studied. Figure 15 shows the investigated Michael acceptors following this strategy which involve cyclic enones, α,β-unsaturated esters, α,β-unsaturated *N*-acyl oxazolidinones and acyclic enones as well the most representative successful metal-based catalytic systems in each case (Figure 15).

The first examples described within this methodology involved cyclic enones, probably because they are among the most reactive carbonyl Michael acceptors. Among all the catalysts explored,[102] Shibasaki's lanthanide based heterobimetallic catalyst **83** is the most general and afforded the best stereochemical results[103] (Figure 15, a,1).

In general α,β-unsaturated esters have been demonstrated to be poor electrophiles in sulfa-Michael additions and only a successful example has been developed by Tomioka[104] (Figure 15, a,2), but the catalytic system is limited to 2-(trimethylsilyl)thiophenol as sulfur donor. An alternative to solve the problem of the low electrophilicity of α,β-unsaturated esters in these reactions has been the use of α,β-unsaturated *N*-acyl oxazolidinones which upon the Michael reaction can be converted into the corresponding carboxylic acids or derivatives. One advantage of these substrates is the presence of two carbonyl sites for coordination to the metal; thus affording more rigid transition states, which in principle, could be more reactive and efficient for the control of the stereochemistry. In turn, the limitation of this alternative is the requirement of detachment of the oxazolidinone tether. Several metal-catalyzed successful protocols which employ these substrates have been reported.[105] Figure 15 (a,3) shows the first successful contribution in this field.[106]

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[102] For sulfa-Michael additions of thiols to cyclic enones, see: Promoted by aluminium heterobimetallic catalyst: a) Manickam, G.; Sundararajan, G. *Tetrahedron: Asymmetry* **1997**, *13*, 2271–2278. For an example promoted by polymer-supported heterobimetallic catalyst: b) Sundararajan, G.; Prabagaran, N. *Org. Lett*. **2001**, *3*, 389–392. Promoted by a *N,N´*-dioxide-cadmium chiral complex: c) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun*. **2000**, 1851–1852. d) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589–9594. Promoted by a chiral amino ether complex and limited to 2-substituted thiophenols: e) Nishimura, K.; Tomioka, K. *J. Org. Chem*. **2002**, *67*, 431–434.

[103] a) ref. 43. b) Emori, E.; Iida, T.; Shibasaki, M. *J. Org. Chem*. **1999**, *64*, 5318–5320.

[104] a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 12974–12975. For a study of the structural requeriments of the chiral ligand for this reaction: b) Tomioka, K.; Okuda, M.; Nishimura, K.; Manabe, S.; Kanai, M.; Nagaoka, Y.; Koga, K. *Tetrahedron Lett*. **1998**, *39*, 2141–2144. For a synthetic application of the reaction in the synthesis of biologically active compound (–)-neplanocin A: c) Nishimura, K.; Tomioka, K. *Yakugaku Zasshi* **2003**, *123*, 9–18.

[105] a) Kobayashi, S.; Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* **2001**, 983–985. b) Matsumoto, K.; Watanabe, A.; Uchida, T.; Ogi, K.; Katsuki, T. *Tetrahedron Lett*. **2004**, *45*, 2385–2388. c) Sauerland, S.

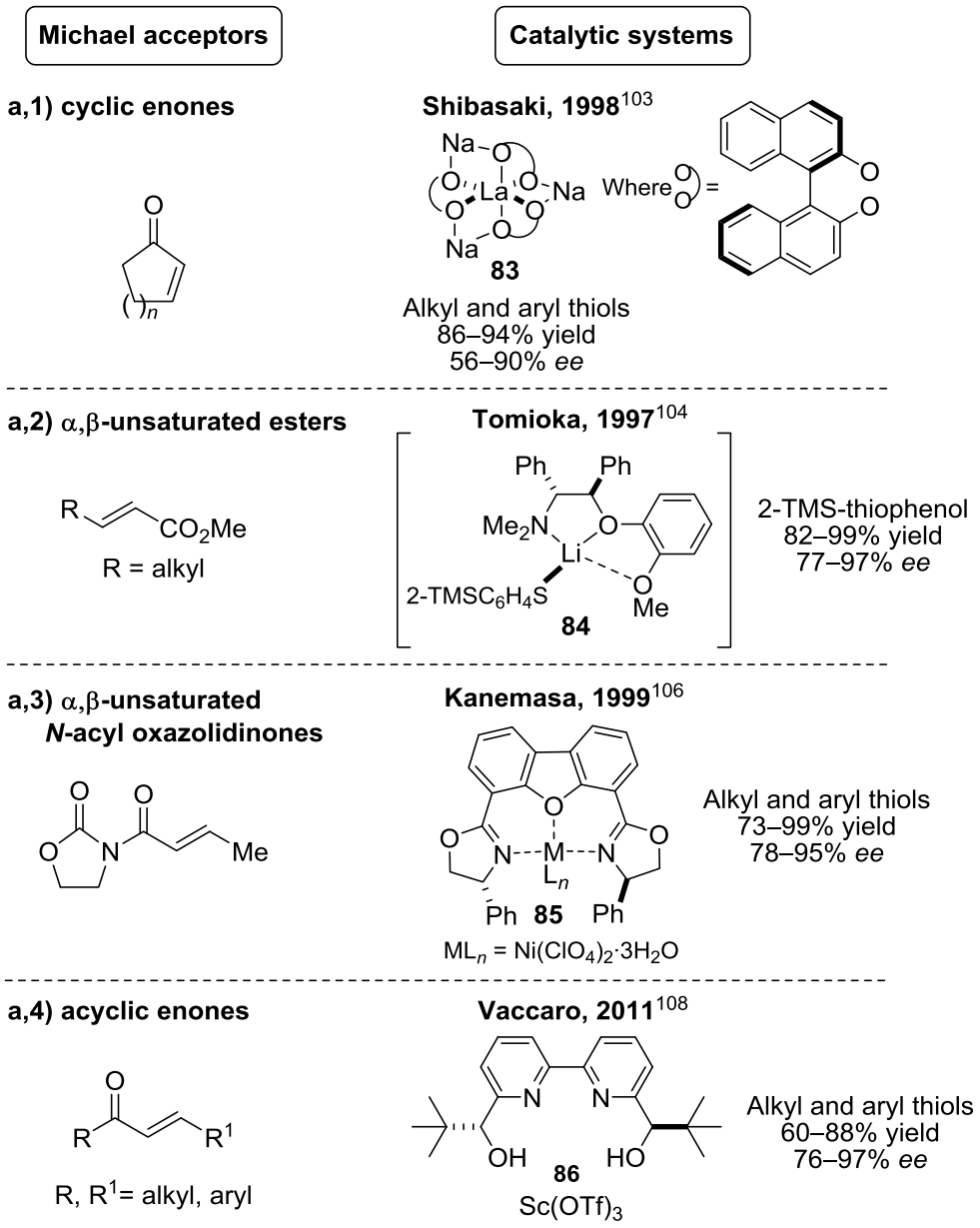


Figure 15. Successful examples of metal catalyzed sulfa-Michael additions to different Michael acceptors.

In this context, sulfa-Michael additions to acyclic enones appeared later compared with cyclic enones and α,β-unsaturated imides. Three successful examples have been reported in this field. Two of them make use of particular sulfur nucleophiles

J. K.; Kiljunen, E.; Koskinen, A. M. P. *Tetrahedron Lett*. **2006**, *47*, 1291–1293. d) Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2007**, *48*, 6480–6482. e) Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron* **2008**, *64*, 3488–3493.

[106] a) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc*. **1999**, *121*, 8675–8676. b) Kanemasa, S. *J. Synth. Org. Chem. Jpn*. **2003**, *61*, 1073–1080. c) Kanemasa, S.; Ito, K. *Eur. J. Org. Chem*. **2004**, 4741–4753.

as 2-substituted thiophenol[102e] or methyl thioglycolate.[107] The third one, more general regarding the sulfur donor, was published by Vaccaro[108] by using the catalytic system **86** (Figure 15, a,4).

Eficcient metal-based catalytic systems have been described for different Michael acceptors. However, all of them use thiols as nucleophiles and no successful examples for the addition of thioacids, which are good precursors of free mercapto derivatives have been developed following this strategy. Besides these metal-based approaches, sulfa-Michael addition reactions have also been investigated in the presence of organocatalysts. The most significant contributions in this field are summarized in the following section.

1.2.3.3. Organocatalyzed sulfa-Michael additions

As mentioned before, sulfa-Michael reactions have been mainly developed through organocatalytic protocols. As in the case of α-sulfenylations, two different approaches can be distinguished based on the type of organocatalysts used to promote the 1,4-addition, non covalent and covalent organocatalysis.

1.2.3.3.1. Non covalent organocatalysis

Organocatalyzed sulfa-Michael additions have been widely investigated with chiral Brønsted bases as catalysts. Successful examples using different Michael acceptors have been reported, as outlined below. The most successful catalysts for these transformations are shown in Figure 16. Significantly, and except **41**, all of them are thiourea/urea or squaramide based bifunctional Brønsted bases. In general, natural cinchona alkaloids have been shown to afford poor stereochemical results in these reactions as first demonstrated by Wynberg in 1977 in the sulfa-Michael addition of aromatic thiols to cyclohexanone.[109] In the following years some other papers were

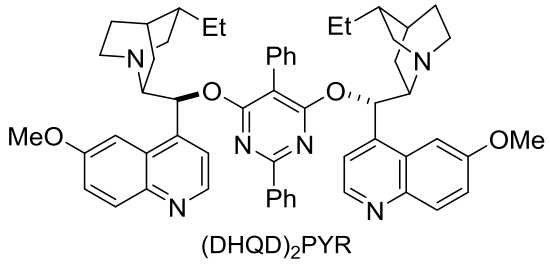
[107] Hui, Y. H.; Jiang, J.; Wang, W. T.; Chen, W. L.; Cai, Y. F.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4290–4293.

[108] a) Bonollo, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2011**, *13*, 2150–2152. For the extension of the acceptor scope to α-substituted enones, with moderate enantiocontrol, see: b) Kitanosono, T.; Sakai, M.; Ueno, M.; Kobayashi, S. *Org. Biomol. Chem.* **2012**, *12*, 7134–7147.

[109] a) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. *Tetrahedron Lett*. **1977**, *25*, 2181–2182. For a study on the superiority of cinchona alkaloids over other catalysts due to the free OH, see ref. 44.

published on cinchona alkaloid derivatives catalyzed sulfa-Michael additions, all of them with moderate stereochemical results.[110]

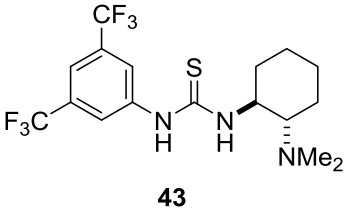
a) Monofunctional catalysts



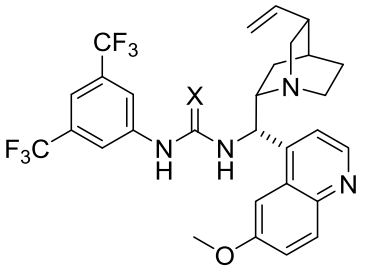
$(DHQD)_2PYR$

41

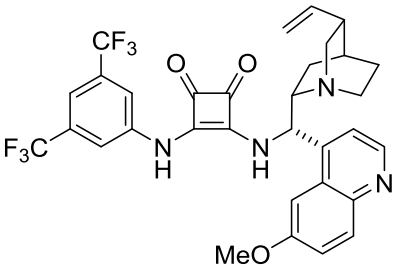
b) Bifunctional catalysts



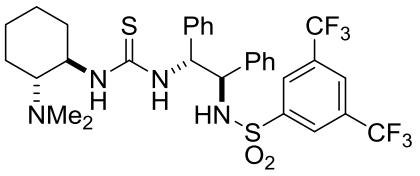
43



X = S **44**
X = O **45**



87



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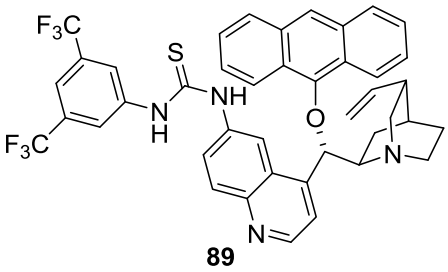

89

Figure 16. Brønsted base catalysts in successful sulfa-Michael additions.

It was not until 2002 when Deng's group reported the first highly efficient enantioselective method for cyclic enones promoted by the monofunctional

[110] For sulfa-Michael reactions which occur with moderate stereocontrol, see: For cinchona-derived catalysts: a) Kobayashi, N.; Iwai, K. *J. Org. Chem*. **1981**, *46*, 1823–1828. b) Gawronski, J.; Gaworonska, K.; Wynberg, H. *J. Chem. Soc., Chem. Commun*. **1981**, 307–308. c) Yamashita, H.; Mukaiyama, T. *Chem. Lett*. **1985**, 363–366. d) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun*. **1991**, 485–486. e) Skarżewski, J.; Zielińska-Błajet, M.; Turowska-Tyrk, I. *Tetrahedron: Asymmetry* **2001**, *12*, 1923–1928. For polymer-supported cinchona-derived catalysts: f) Kobayashi, N.; Iwasi, K. *J. Am. Chem. Soc*. **1978**, *100*, 7071–7072. g) Hodge, P.; Khoshdel, E.; Waterhouse, L. *J. Chem. Soc., Perkin Trans.* **1985**, 2327–2331. h) Inagaki, M.; Hiratake, J.; Yamamoto, Y.; Oda, J. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 4121–4126. i) Athawale, V.; Manjrekar, N. *Tetrahedron Lett*. **2001**, *42*, 4541–4543. j) Danelli, T.; Annuntziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461–467. For an example of an enzyme-catalyzed reaction: k) Kitazume, T.; Murata, K. *J. Fluorine Chem*. **1988**, *39*, 75–86.

bis(dihydroquinidinyl)pyrimidine derivative $(DHQD)_2PYR$ **41** by using thionaphtol as sulfur donor (Figure 17, a,1).[111] Later and, after Takemoto[45] included bifunctionality as a design element, efficient sulfa-Michael additions of both thiols and thioacids to different Michael acceptors were reported in the presence of the structurally related thiourea/urea or squaramide containing bifunctional catalysts **43**, **44**, **45**, **87**, **88** and **89** (Figure 16, b). Indeed, these bifunctional organocatalysts have turned to afford excellent stereochemical results, being superior to the natural cinchona alkaloids.

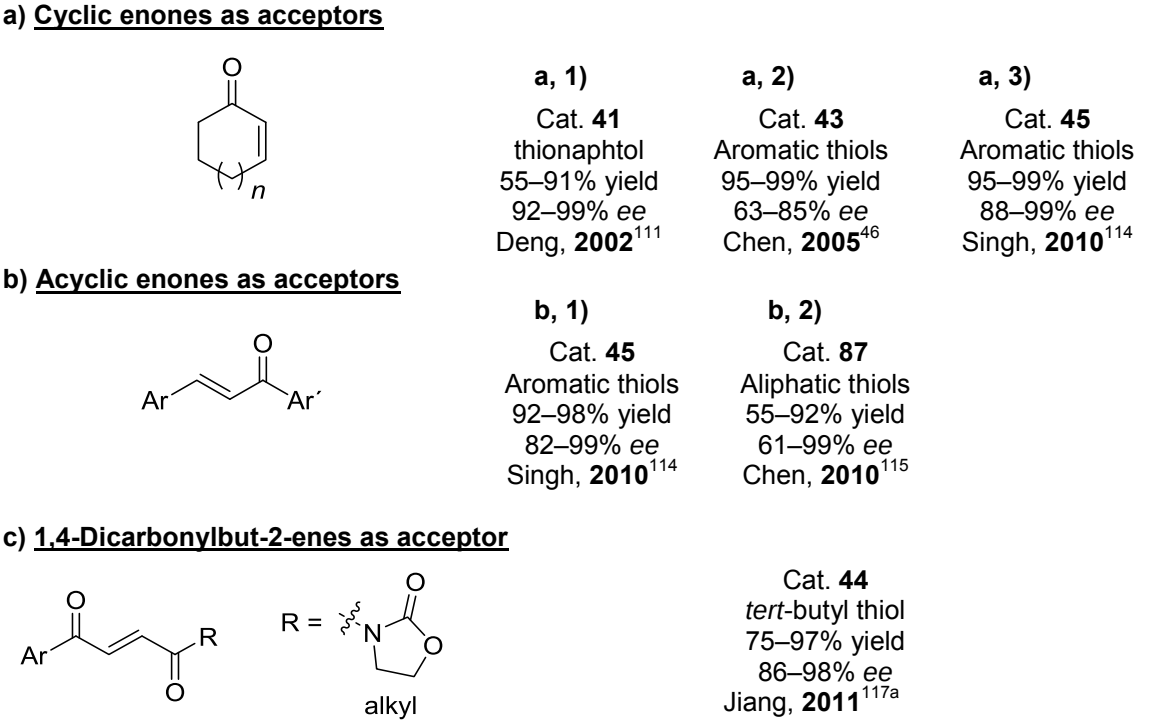

Figure 17. Successful examples of sulfa-Michael additions to cyclic and acyclic enones promoted by chiral Brønsted bases.

Both cyclic and acyclic enones have been demonstrated to be efficient acceptors for sulfa-Michael additions. The most representative successful contributions are shown in Figure 17. In this context, and although different examples of the addition of aromatic thiols to cyclic enones have been published,[112,113] among them, the most

[111] McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem. Int. Ed*. **2002**, *41*, 338–340.

[112] For examples of sulfa-Michael additions of thiophenol to cyclic enones with low enantiocontrol, see: Promoted by chiral calix[4]arenes: a) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Eur. J. Org. Chem*. **2008**, 5957–5964. b) Shirakawa, S.; Kimura, T.; Murata, S. -i.; Shimizu, S. *J. Org. Chem*. **2009**, *74*, 1288–1296. Promoted by a supported thiourea cinchona catalyst: c) Fredriksen, K. A.; Kristensen, T. E.; Hansen, T. *Beilstein J. Org. Chem*. **2012**, *8*, 1126–1133. For the sulfa-Michael addition of thioacids to cyclic and acyclic enones with moderate enantiocontrol, see: d) Rana, N. K.; Unhale, R.; Singh, V. K. *Tetrahedron Lett*. **2012**, *53*, 2121–2124.

successful stereochemical results have been obtained with **43**[46] and **45**[114] (Figure 17, a,2 and a,3). Regarding acyclic enones two efficient procedures on the addition of thiols have been reported, both promoted by bifunctional catalysts **45**[114] and **87**[115] (Figure 17, b,1 and b,2). Some examples of thioacid additions to acyclic enones have also been published, but all of them with poor stereochemical results.[116] In connection with this, one interesting protocol to increase reactivity in acyclic enones while controlling regioselectivity was reported by Jiang and co-workers[117] in 2011 by introducing an acyl motif at β-position of an acyclic enone (Figure 17, c) with excellent regio- and stereochemical results. This constitutes a very interesting alternative to produce α-thiofunctionalized carbonyl derivatives, the most prevalent motif in carbonyl units containing organosulfur bioactive molecules.

On the other hand, α,β-unsaturated esters have also turned to be poorer electrophiles in these reactions as shown by the addition of thiophenol to ethyl crotonate in the presence of bifunctional catalyst **88** (Figure 18, a).[118] A solution to this problem has been proposed following the same idea than in metal-catalyzed sulfa-Michael additions. The strategy consist of increasing the reactivity and selectivity, by using 1,3-dicarbonylic compounds such as α,β-unsaturated imides or oxazolidinone-derived imides as ester or carboxylic acid surrogates where the templates offer a two-binding points platform for coordination with appropriate H-bond donors.[119] Following this idea and using oxazolidinone derivatives as substrates Deng[120] (Figure 18, b,1) and Chen[121] (Figure 18, b,2) demonstrated the efficiency of catalysts **89** and **87** respectively in these reactions.

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[113] For a particular example of the desymmetrization of spirocyclic oxindoles through the sulfa-Michael addition of aromatic thiols with very good enantioselectivities, see: Yao, L.; Liu, K.; Tao, H. -Y.; Qiu, G. -F.; Zhou, X.; Wang, C. -J. *Chem. Commun*. **2013**, *49*, 6078–6080.

[114] Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem*. **2010**, *75*, 2089–2091.

[115] Dai, L.; Wang, S. -X.; Chen, F. -E. *Adv. Synth. Catal*. **2010**, *352*, 2137–2141.

[116] For examples of the sulfa-Michael addition of thioacids to acyclic enones with moderate enantioselectivity, see: Promoted by Takemoto's catalyst **54**: a) Li, H.; Zu, L.; Wang, J.; Wang, W. *Tetrahedron Lett*. **2006**, *47*, 3145–3148. Promoted by catalyst **56**: b) See ref. 112d.

[117] a) Zhao, F.; Zhang, W.; Yang, Y.; Pan, Y.; Chen, W.; Liu, H.; Yan, L.; Tan, C. -H.; Jiang, Z. *Adv. Synth. Catal.* **2011**, *353*, 2624–2630. For a precedent following a similar strategy by using β-ethoxy carbonyl nitroalkenes affording tertiary thioethers with excellent results, see: b) Lu, H. -H.; Zhang, F. -G.; Meng, X. -G.; Duan, S. -W.; Xiao, W. -J. *Org. Lett*. **2009**, *11*, 3946–3949. For more details on this strategy, see Chapter 3, page 95.

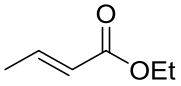
[118] Dong, X. -Q.; Fang, X.; Wang, C. -J. *Org. Lett*. **2011**, *13*, 4426–4429.

[119] For a not successful precedent on the use of acyclic imide derivatives as Michael acceptors, see: ref. 46.

[120] Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc*. **2009**, *131*, 418–419.

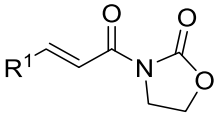
[121] Dai, L., Yang, H.; Chen, F. -E. *Eur. J. Org. Chem*. **2011**, 5071–5076.

a) Ethyl crotonate as acceptor



Cat. **88**
Thiophenol
50% yield
62% *ee*
Wang, **2011**[118]

b) α,β-Unsaturated *N*-acylated oxazolidin-2-ones as acceptors

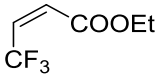


b, 1)
Cat. **89**
Aliphatic thiols
84–99% yield
87–96% *ee*
Deng, **2009**[120]

b, 2)
Cat. **87**
Alkyl and aryl thiols
53–99% yield
73–99% *ee*
Chen, **2011**[121]

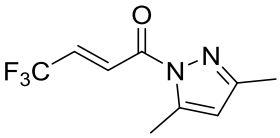
c) Fluorinated Michael acceptors

c, 1)



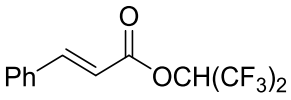
Cat. **88**
Aromatic thiols
88–96% yield
90–96% *ee*
Wang, **2011**[118]

c, 2)



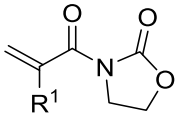
Cat. **88**
Aromatic thiols
88–96% yield
86–97% *ee*
Wang, **2012**[122]

c, 3)



Cat. **88**
Alkyl and aryl thiols
88–96% yield
86–97% *ee*
Wang, **2013**[123]

d) α-Substituted Michael acceptor



d, 1)
Cat. **44**
Alkyl and aryl thiols
82–99% yield
65–95% *ee*
Singh, **2011**[126]

d, 2)
Cat. **44**
Thioacetic acid
82–98% yield
75–97% *ee*
Singh, **2013**[127]

Figure 18. Examples of sulfa-Michael additions to different acceptors promoted by bifunctional chiral Brønsted bases.

Other alternative to increase the poor electrophilicity of α,β-unsaturated esters is to incorporate activating electron-withdrawing or coordinating groups in the Michael acceptor. Some examples of this strategy were developed by Wang and co-workers employing as acceptors β-trifluoromethyl unsaturated esters[118] (Figure 18, c,1), β-trifluoromethyl pyrazol-derived amides[122] (Figure 18, c,2) as well as hexafluoroisopropyl unsaturated esters[123] (Figure 18, c,3). When the reactions were tested with similar esters lacking fluorinated substitutents worst results regarding both,

[122] Dong, X. -Q.; Fang, X.; Tao, H. -Y.; Zhou, X.; Wang, C. -J. *Adv. Synth. Catal*. **2012**, *354*, 1141–1147.
[123] Fang, X.; Li, J.; Wang, C. -J. *Org. Lett*. **2013**, *15*, 3448–3451.

reactivity and stereoselectivity, were observed, demonstrating that the fluorinated function is critical for success.[124]

As said before, the use of α-substituted α,β-unsaturated systems involves as additional challenge, the selective protonation of the resulting enolate intermediate.[125] A successful example with these substrates was reported by Singh[126] in 2011 by using *N*-acryloyloxazolidin-2-ones for the addition of thiols (Figure 18, d,1). Furthermore, the Michael donor scope was satisfactorily extended by the same authors in 2013 to thioacetic acid (Figure 18, d,2).[127] However, to our knowledge, when we started with the research work for this PhD Thesis no successful protocols for α,β- and β,β-disubstituted substrates as Michael acceptors had been reported.

1.2.3.3.2. Covalent organocatalysis

Sulfa-Michael reactions have also been investigated through covalent organocatalysis (aminocatalysis) by using chiral secondary and primary amines. While chiral secondary amines have been mainly used in tandem reactions[128] with enals, chiral primary amines have been investigated in reactions with enones and α-branched enals.

Although Brønsted bases are suitable catalysts for sulfa-Michael additions, in 2005 Jørgensen and co-workers presented a very interesting alternative: a chiral secondary amine, which reacts with α,β-unsaturated aldehydes to provide highly electrophilic chiral iminium ions ready to undergo a nucleophilic thiol addition. They demonstrated for the first time that diarylprolinol ether **63** in combination with benzoic

[124] For an example which combines both strategies, that is, the use of *N*-acyl oxazolidinones and the incorporation of an activating electron withdrawing group to obtain amino acid derivatives with variable stereochemical results, see: Breman, A. C.; Smits, J. M. M.; de Gelder, R.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Synlett* **2012**, *23* 2195–2200.

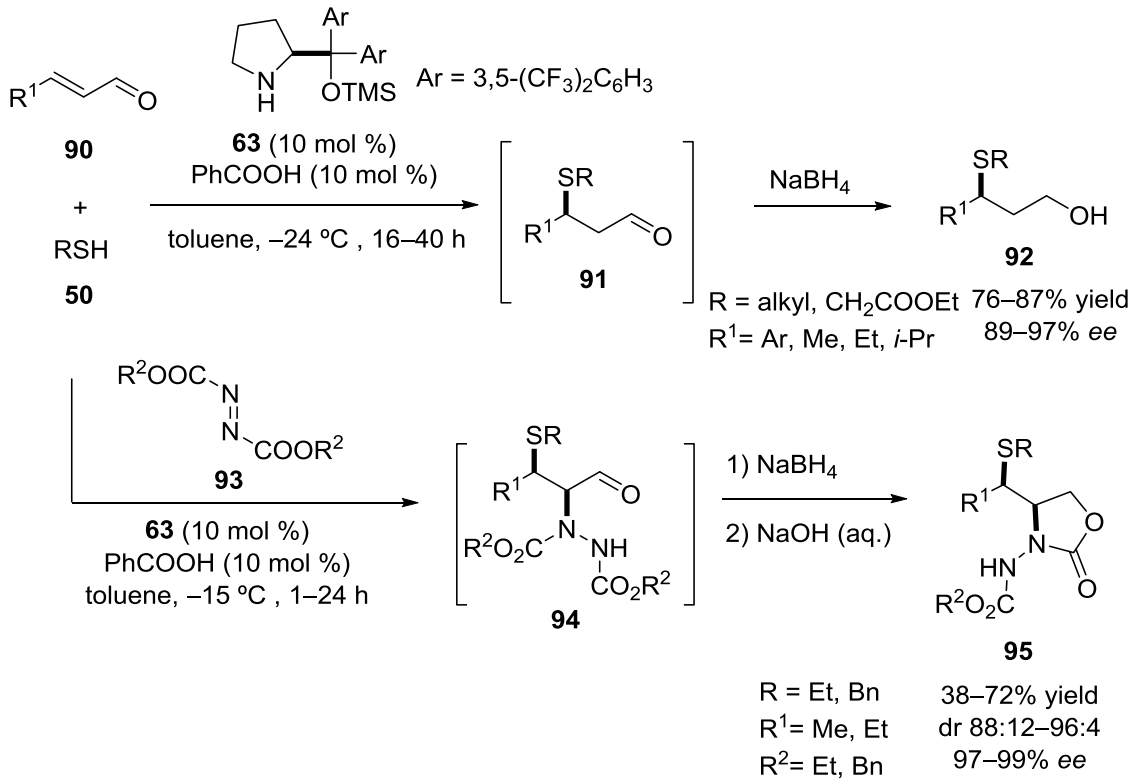
[125] For the first sulfa-Michael addition of benzyl thiol to α-phthalimidomethacrylates promoted by natural cinchona alkaloids with moderate enantioselectivities, see: a) Pracejus, H.; Wilke, F. -W.; Hanemann, K. *J. Prakt. Chem.* **1977**, *319*, 219–229. For particular efficient examples with other α-substituted acceptors by using a chiral bicyclic guanidine: b) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C. -H. *Angew. Chem. Int. Ed*. **2008**, *47*, 5641–5645. c) Lin, S.; Leow, D.; Huang, K. -W.; Tan, C. -H. *Chem. Asian. J*. **2009**, *4*, 1741–1744

[126] a) Rana, N. K.; Singh, V. K. *Org. Lett*. **2011**, *13*, 6520–6523. For an example with structurally related imides by using squaramide **87** as catalyst, see: b) Dai, L.; Yang, H.; Niu, J.; Chen, F. -E. *Synlett*. **2012**, *23*, 314–316.

[127] Unhale, R. A.; Rana, N. K.; Singh, V. K. *Tetrahedron Lett*. **2013**, *54*, 1911–1915

[128] For more information, see: a) ref. 48a and c. For a non tandem sulfa-Michael reaction between naphthalene-2-thiol and 2-cyclohexen-1-one promoted by a pyrrolidine-guanidine bifunctional catalyst working through a Brønsted base-iminium activation mode with 20% *ee*, see: b) Pansare, S. V.; Lingampally, R. *Org. Biomol. Chem*. **2009**, *7*, 319–324.

acid catalyzes the addition of thiols to aromatic and aliphatic enals **90** with high levels of enantiocontrol (Scheme 17).[129] Furthermore, they were able to take advantage of the nucleophilicity of the enamine intermediate by adding azodicarboxylate **93**, as new electrophile and developed a multicomponent reaction, which affords highly functionalized oxazolidinones **95** in excellent stereoselectivity (Scheme 17). After this work many other contributions which follow this strategy have been reported in different tandem reactions.[130]



Scheme 17. Organocatalyzed sulfa-Michael addition of thiols to enals and organocatalyzed multicomponent domino reaction. **Jørgensen, 2005**.

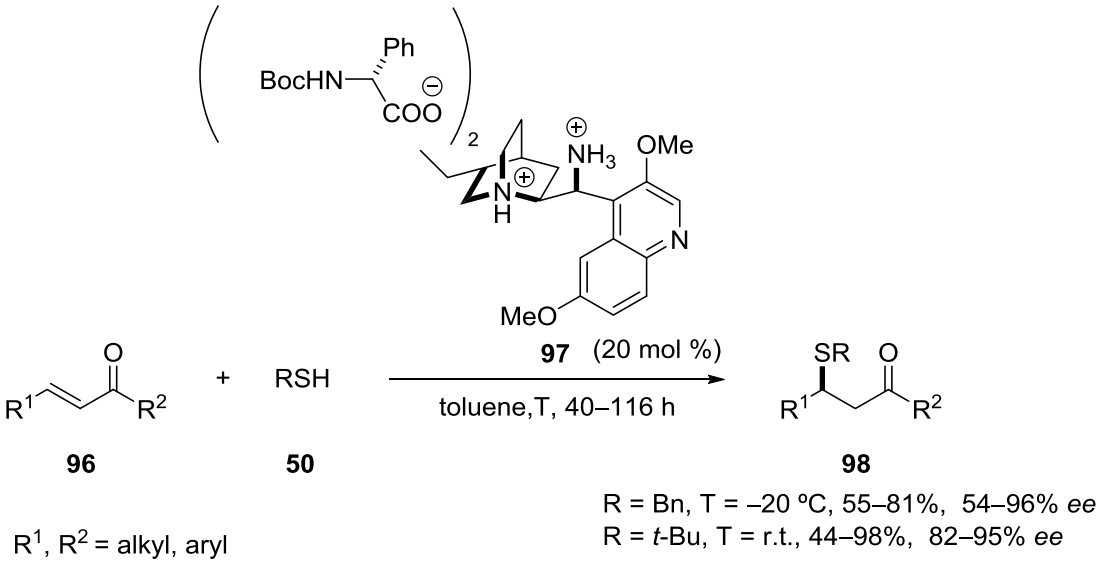
Secondary amines are suitable catalysts for the activation of α,β-unsaturated aldehydes, but usually, sterically demanding enals and α,β-unsaturated ketones are more problematic. Primary amines, however, have found to be more efficient in such cases. Regarding sulfa-Michael additions, 9-amino-(9-deoxy)-*epi*-hydroquinine salts such as **97**[131] (Scheme 18) have shown to be the most efficient promoters for reactions with

[129] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 15710–15711.

[130] For more information, see ref. 48a and c.

[131] For another example of the addition of benzyl mercaptan to cyclic enones promoted by *S*-triphenylmethyl *L*-cysteine, see: Yoshida, M.; Ohno, Y.; Hara, S. *Tetrahedron Lett*. **2010**, *51*, 5134–5136.

acyclic unsaturated ketones and α-substituted enals, as reported by Melchiorre.[132] Later, the same author extended this protocol to a tricomponent sulfa-Michael/amination tandem reaction starting from α,β-disubstituted enals.[133] Following the same strategy, in 2011 the same group described a diastereodivergent sulfa-Michael addition of alkyl thiols to α-substituted α,β-unsaturated ketones promoted by the 6'-hydroxy-9-amino-9-deoxy-*epi*-quinidine salts derived from different chiral and achiral acids.[134]



Scheme 18. Organocatalyzed sulfa-Michael addition of thiols to enones catalyzed by **97**. **Melchiorre, 2008**.

All the previous examples clearly show that the sulfa-Michael reaction is an important tool for the stereoselective formation of new *C–S* bonds and has been widely studied employing different strategies. Most of the reported strategies provide chemically stable thioether derivatives, usually more difficult to transform into the corresponding mercapto derivatives. Besides some unsolved questions within this transformation, one important limitation of sulfa-Michael reactions nowadays is the lack of general protocols for the addition to α,β- and β,β-disubstituted Michael acceptors, in part likely, because of reactivity problems associated with steric constraints and in part, because in these cases the stereochemistry of the reaction is more difficult to control.

[132] Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal*. **2008**, *350*, 49–53.

[133] Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 7892–7894.

[134] Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 17934–17941.

After our research work several papers on the sulfa-Michael addition reaction have been published using the previously described protocols, such as the chiral auxiliary strategy,[135] metal catalysis,[136] non-covalent organocatalysis[137] and covalent organocatalysis.[138] Furthermore, as mentioned before, sulfa-Michael additions are potential reactions to develop tandem reactions and recent contributions have also been described in this context, using both non-covalent[139] and covalent organocatalysts.[140]

1.2.4. Miscellaneous methods

Although the most common strategies to afford α- and β-thiofunctionalized carbonyl compounds are α-sulfenylations and sulfa-Michael addition reactions respectively, other particular reactions have also been reported to synthesize these type of compounds. These procedures are briefly discussed in this section.

Regarding protocols that provide α-thiofunctionalized carbonyl compounds, recently the group of Jørgensen reported an asymmetric organocatalytic thio-Diels Alder reaction using thiocarbonyls **99** as dienophiles and different dienals as dienes.[141] The best results to afford the sulfur-containing heterocycles were obtained with catalyst **103** (Scheme 19). In all cases a tetrasubstituted stereocenter is generated at the α position of the carbonyl group.

[135] Aydillo, C.; Compañón, I.; Avenoza, A.; Buesto, J. H.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Am. Chem. Soc*. **2014**, *136*, 789–800.

[136] White, J. D.; Shaw, S. *Chem. Sci*. **2014**, *5*, 2200–2204.

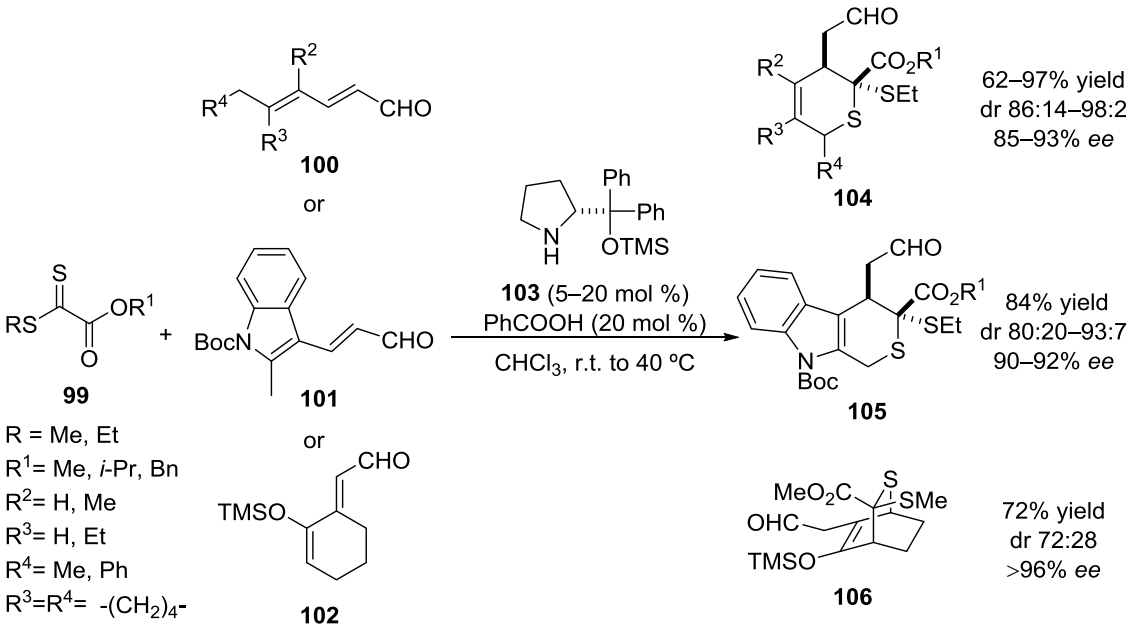
[137] a) Zhao, B. -L.; Du, D. -M. *RSC Adv*. **2014**, *4*, 27346–27353. b) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal*. **2014**, *356*, 1292–1300.

[138] Fu, N.; Zhang, L.; Luo, S.; Cheng, J. -P. *Org. Lett*. **2014**, *16*, 4626−4629.

[139] a) Huang, Y.; Zheng, C.; Chai, Z.; Zhao, G. *Adv. Synth. Catal*. **2014**, *356*, 579–583. b) Huang, Y.; Zheng, C.; Chai, Z.; Zhao, G. *Adv. Synth. Catal*. **2014**, *356*, 579–583. c) Zhao, B. -L.; Du, D. -M. *Org. Biomol. Chem*. **2014**, *12*, 1585–1594. d) Zhao, B. -L.; Liu, L.; Du, D. -M. *Eur. J. Org. Chem*. **2014**, 7850–7858. e) Li, Y. -H.; Zhao, B. -L.; Gao, Y.; Du, D. -M. *Tetrahedron: Asymmetry* **2014**, *25*, 1513–1519. f) Song, J.; Moss, J.; Yang, D. -C.; Guan, Y.; He, Y. -H. *RSC Adv*. **2014**, *4*, 54032–54038. g) Liang, J. -J.; Pan, J. -Y.; Xu, D. -C.; Xie, J. -W. *Tetrahedron Lett*. **2014**, *55*, 6335–6338.

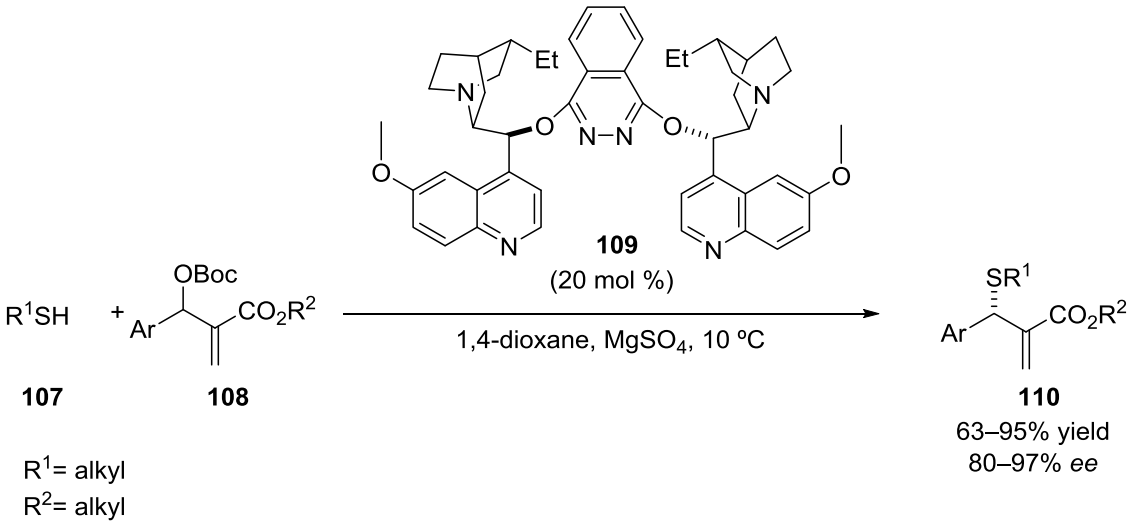
[140] Wu, L.; Wang, Y.; Zhou, Z. *Tetrahedron: Asymmetry* **2014**, *25*, 1389–1395.

[141] Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2013**, *135*, 5200–5207.



Scheme 19. Asymmetric organocatalytic thio-Diels-Alder reaction. **Jørgensen, 2013**.

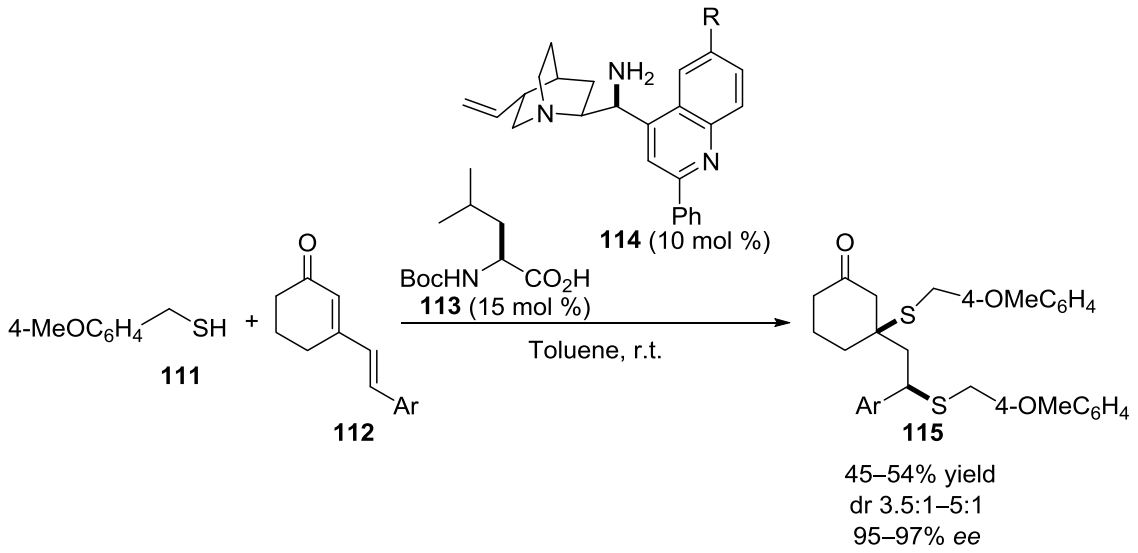
On the other hand, three other protocols to obtain β-substituted carbonyl compounds have also been described. For instance, in 2011 the group of Chen and Zhu reported the synthesis of α-methylene β-mercapto esters **110** with good yields and high enantiocontrol adding alkyl thiols **107** to Morita-Baylis-Hillman carbonates **108**. The reaction was promoted by the commercially available cinchona alkaloid $(DHQD)_2PHAL$ **109** (Scheme 20).[142]



Scheme 20. Addition of thiols to Morita-Baylis-Hillman carbonates. **Chen** and **Zhu, 2011**.

[142] Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal*. **2011**, *353*, 3301–3306.

Melchiorre and co-workers described in 2012 the 1,6-addition of thiols to cyclic dienones **112** and they were able to take advantage of the product formed in the 1,6-addition, an α,β-unsaturated carbonyl compound, to perform a cascade reaction involving both 1,6- and 1,4-addition of thiols, by simply increasing the amount of the thiol. Furthermore, the resulting products **115** were tertiary thioethers, an important challenge in organosulfur compounds, and although the observed diastereoselectivity was moderate the enantiocontrol was very high (Scheme 21).[143]



Scheme 21. The 1,6- and 1,4-addition of thiols to cyclic dienones. **Melchiorre, 2012**.

Recently, enantioselective additions of sulfonyl anion surrogates to acyclic enones generally using bifunctional Brønsted base catalysts have also been reported.[144]

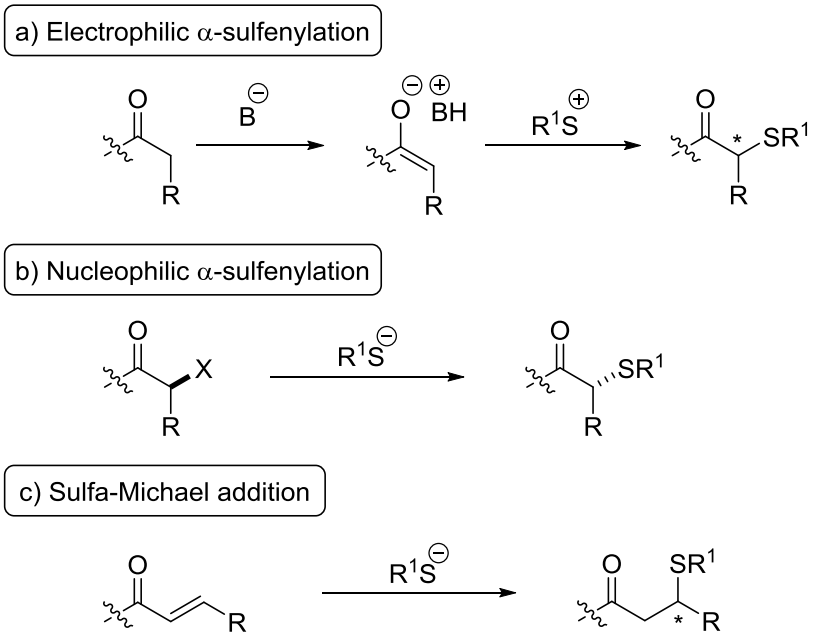
1.3. Working hypothesis and objectives

As disclosed in the previous sections and although many organosulfur compounds show biological interesting properties and are valuable synthetic compounds, the stereoselective formation of *C–S* bonds has been less studied when compared with the analogous *C–C*, *C–O* and *C–N* bonds, probably due to the previously mentioned drawbacks associated to sulfur. Mainly because thiocarbonyl compounds are usually poor electrophiles and unstable and sulfur poisons catalysts. Thus, the general aim of this Doctoral Thesis has been to develop novel methodologies for the stereoselective synthesis of thiofunctionalyzed carbonyl compounds.

[143] Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 6439–6442.

[144] a) Moccia, M.; Fini, F.; Scagnetti, M.; Adamo, M. F. A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6893–6895. b) Jin, Z.; Xu, J.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem. Int. Ed*. **2013**, *47*, 12354–12358. c) Fernández, M.; Uria, U.; Orbe, L.; Vicario, J. L.; Reyes, E.; Carrillo, M. *J. Org. Chem*. **2014**, *79*, 441–445.

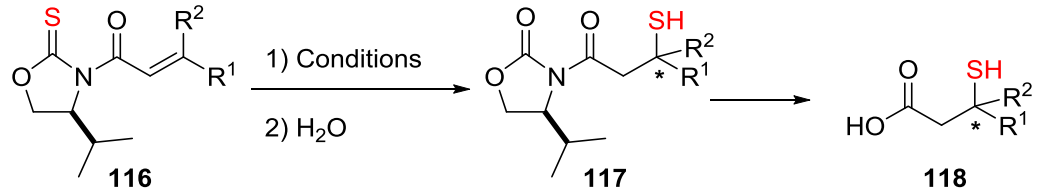
The previous precedents show that nowadays different efficient direct and catalytic protocols are available for the thiofunctionalyzation of carbonyl compounds either at the α or β position. The reported protocols involve both electrophilic and nucleophilic α-sulfenylations and mainly sulfa-Michael additions (Scheme 22). However, when we started the research work for this Thesis, and, as far as we knew, there was virtually no method to access α,β-thioepoxy carbonyl compounds in a direct and stereocontrolled way.



Scheme 22. Common strategies for the synthesis of α- and β-thiofunctionalized carbonyl compounds.

In this context, our research group has shown that the oxazolidin-2-thione group in the *N*-enoyl-oxazolidin-2-thiones **116** (Scheme 23) acts as both, intramolecular sulfur donor reagent and a stereodirecting group through an unprecedent intramolecular sulfur transfer reaction.[145]

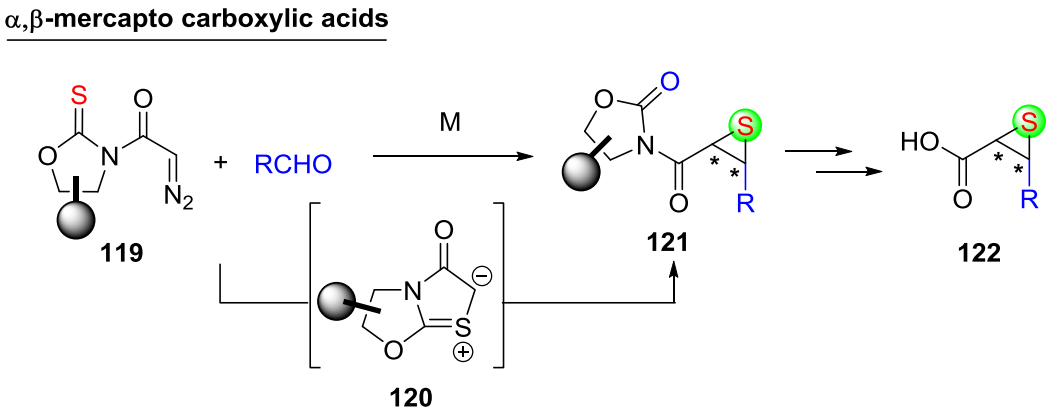
[145] a) Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc*. **2001**, *123*, 5602–5603. b) Palomo, C.; Oiarbide, M.; Dias, F.; López, R.; Linden, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 3307–3310. c) Palomo, C.; Oiarbide, M.; López, R.; González, P. B.; Gómez-Bengoa, E.; Saá, J. M.; Linden, A. *J. Am. Chem. Soc*. **2006**, *128*, 15236–15247.



Conditions:
Metal assisted: $SnCl_4$ or BF_3 (2 eq.)
Palomo, *JACS* **2001**, *123*, 5602 and *ACIE* **2004**, *43*, 3307
Brønsted acid assisted: CF_3CO_2H (2 eq.)
Palomo, *JACS* **2006**, *128*, 15236

Scheme 23. Sulfur transfer process with concomitant β-thiofunctionalization of carbonyl compounds. **Palomo, 2001, 2004** and **2006**.

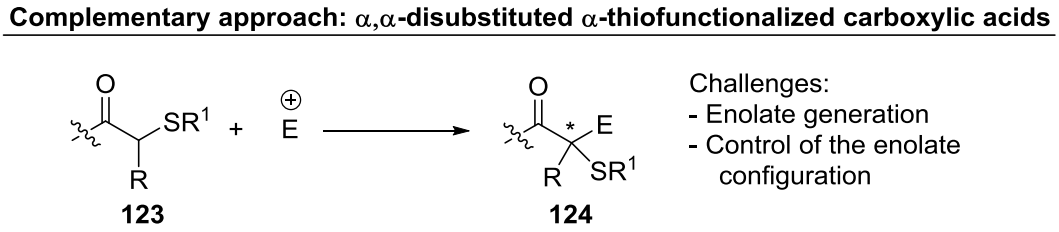
Inspired by these precedents we hypothesized that diazo derivatives of type **119** (Scheme 24) could serve as both *C–C* and *C–S* bond forming reagents in the reaction with aldehydes promoted by the appropriate metal catalyst to afford, through the formation of the thiocarbonyl ylide intermediate **120**, thiiranes **121**, coming from a formal sulfa-Michael addition. The results of this research are presented in Chapter 2.



Scheme 24. Working hypothesis for stereoselective synthesis of α,β-thioepoxy carbonyl compounds.

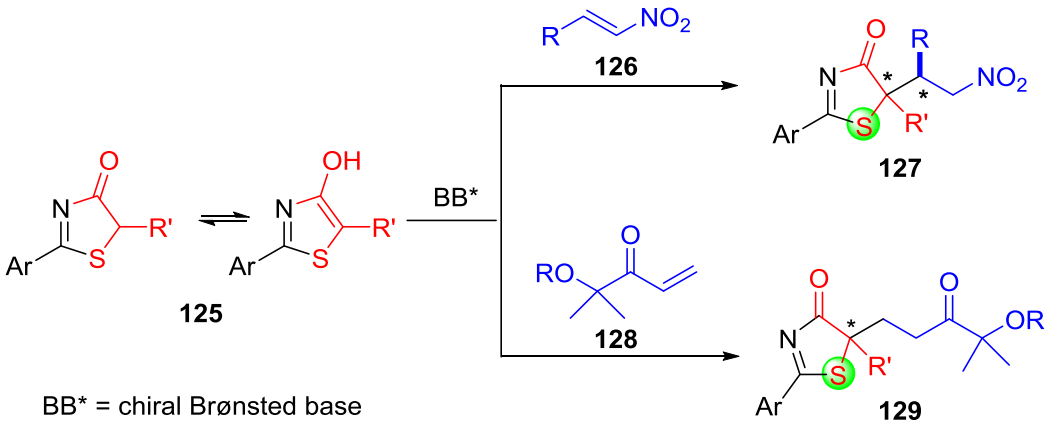
On the other hand, the precedents disclosed in the previous introduction also show that the approaches for the asymmetric synthesis of tertiary thiols are limited. Thus, as a second goal of this PhD Thesis we focused on the development of a new methodology for the catalytic synthesis of tertiary thiols of type **124** (Scheme 25). As depicted in Scheme 22 the most direct protocol for the synthesis of α,α-disubstituted α-thiofunctionalized carboxylic acids involve electrophilic and nucleophilic α-sulfenylation. A complementary alternative would be the use of sulfur-based (pro)nucleophiles which upon treatment with the appropriate Brønsted base and in the presence of a suitable Michael acceptor would undergo a Michael addition to provide

tertiary thiol derivatives (Scheme 25). The two key points for this proposal are, on the one hand, the search for the appropriate conditions for the enolate generation under Brønsted base catalysis and, secondly, the control of the enolate configuration that would be critical for stereoselectivity.



Scheme 25. Working hypothesis for stereoselective synthesis of α,α-disubstituted α-thiofunctionalized carbonyl compounds.

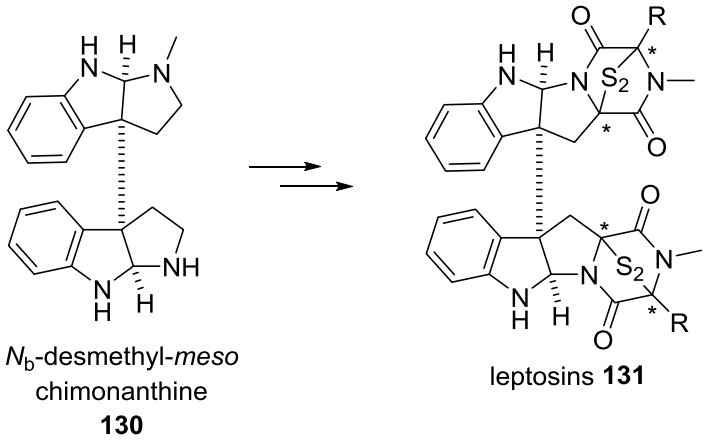
To address these problems, and for reasons that will be outlined later, we envisaged 5*H*-thiazol-4-ones **125** (Scheme 26) as new sulfur-based (pro)nucleophiles to perform Michael addition reactions with different Michael acceptors, such as nitroalkenes **126** and enones, particularly α'-oxy enones **128**. The results of this proposal are presented in Chapter 3.



Scheme 26. Proposed stereoselective synthesis of α,α-disubstituted α-thiofunctionalized carbonyl compounds.

Finally, on the basis of the obtained results during the research work conducted for this PhD Thesis, and as a third goal, we considered interesting to investigate routes towards the total synthesis of a sulfur-containing interesting biomolecule with α-thiofunctionalized carbonyl units. After literature search we found that leptosins **131** (Scheme 27) could be good candidates for this purpose because, as far as we know, no total synthesis of these type of compounds is described. Under the guidance of Prof. Dr. Peter I. Dalko from the University of Descartes, in Paris, and based on the synthesis of

N_b-desmethyl-*meso*-chimonanthine **130** published by their group in 2006,[146] we focused on the development of a new protocol to prepare these leptosins. The results of these investigations are described in Chapter 4.



Scheme 27. Structures of N_b-desmethyl-*meso*-chimonanthine and leptosins.

[146] Menozzi, C.; Dalko, P. I.; Cossy, J. *Chem. Commun*. **2006**, 4638–4640.

Chapter 2:

Asymmetric synthesis of α,β-thioepoxy carboxylic acid derivatives

2. Asymmetric synthesis of α,β-thioepoxy carboxylic acid derivatives

Asymmetric synthesis of α,β-thioepoxy carboxylic acid derivatives

2.1. Introduction

Thioepoxides or thiiranes, three membered sulfur heterocycles, are essential structures in many biologically active compounds[147] and are also valuable synthetic building blocks for the synthesis of polymers,[148] liquid crystals[149] and adhesives.[150] Particularly, α,β-thioepoxy carboxylic acids[151] serve as selective inhibitors for cysteine protease and therefore inactivate the corresponding enzyme. In view of the practical need and synthetic utility, considerable efforts have been devoted to develop efficient protocols to synthesize thiiranes.[152] The most representative strategies for this purpose are summarized in Scheme 28. For instance, one option involves the reaction of ketones with a sulfenyl lithium nucleophile of type **133** which contains an electrophilic group (E) (Scheme 28, Eq. 1).[153] Reaction of this lithium carbanion with the ketone generates alkoxide intermediate **134**, which reacts then intramolecularly with the electrophilic group E to afford, through intermediates **135** and **136**, the thiirane **137**. The previous electrophilic group has a twofold function. First, it acts as an alkoxide trap and, second, it is capable of converting the oxido function into a leaving group. Other option to access alkoxide intermediates of the same type is to start from ketones such as **139** (Scheme 28, Eq. 2) which upon reduction with sodium borohydride furnish the

[147] a) Testero, S. A.; Lee, M.; Staran, R. T.; Espahbodi, M.; Llarrull, L. I.; Toth, M.; Mobashery, S.; Chang, M. *Med Chem. Lett*. **2011**, *2*, 177–181. b) Cho, H. -J.; Jung, M. -J.; Kwon, Y.; Na, Y. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 6766–6769. c) Hutchinson, S. A.; Baker, S. P.; Linden, J.; Scammells, P. J. *Bioorg. Med. Chem*. 2004, 12, 4877–4884.

[148] a) Kudo H.; Makino, S.; Kameyama, A.; Nishikubo, T. *Macromolecules* **2005**, *38*, 5964–5969. b) Imai, T.; Hayakawa, K.; Satoh, T.; Kaga, H.; Kakuchi, T. *Polym. Sci. Pol. Chem*. **2002**, *40*, 3443–3448. c) Kameyama, A.; Murakami, Y. Nishikubo, T. *Macromolecules* **1999**, *32*, 1407–1412.

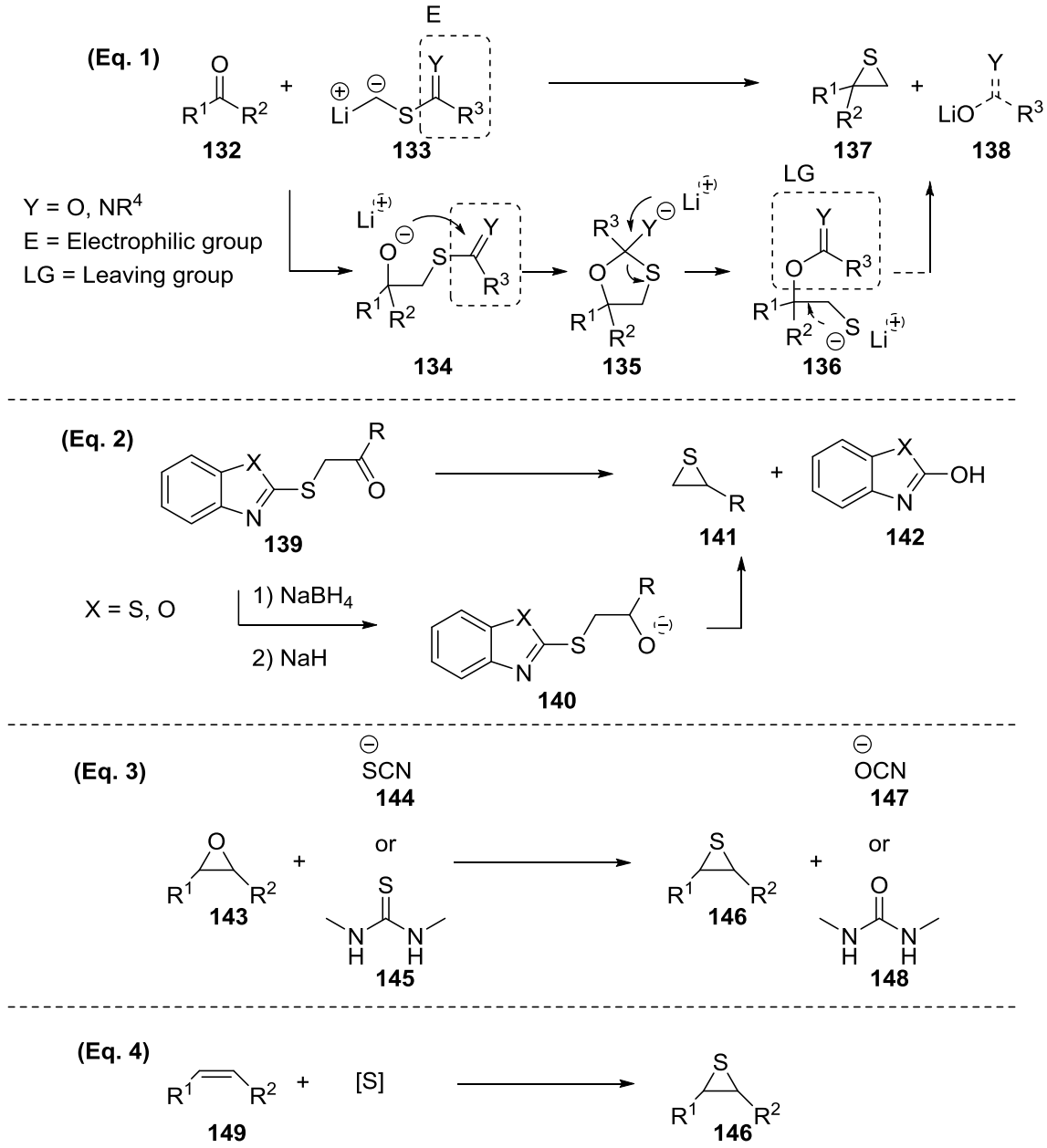
[149] a) Gay, J.; Scherowsky, G. *Synth. Commun*. **1995**, *25*, 2665–2672. b) Scherowsky, G.; Gay, J. *Liq. Cryst*. **1989**, *5*, 1253–1258. c) Gottarelli, G.; Mariani, P.; Spada, G. P.; Samori, B.; Forni, A.; Solladie, G.; Hilbert, M. *Tetrahedron* **1983**, *39*, 1337–1344.

[150] a) Kadoma, Y. *Dent. Mater. J*. **2002**, *21*, 156–169. b) Chino, K.; Suga, K.; Ikawa, M.; Satoh, H. *J. Appl. Polym. Sci*. **2001**, *82*, 2953–2957.

[151] Schirmeister, T. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 2647–2651.

[152] For a general review on thiiranes, see: a) M. Saito, J. Nakayama, "Thiiranes and Derivatives" In *Science of Syntheses, Houben-Weyl Methods of Molecular Transformations*, Eds. Bellus, D.; Jacobsen, E. N.; Ley, S. V.; Noyori, R.; Regitz, M.; Reider, P. J.; Schaumann, E.; Shinkai, I.; Thomas, E. J.; Trost, B. M. Vol. 39 (Ed. Kambe, N.), **2008**, George Thieme Velag, Stuttgart, 589–658. b) Sander, M. *Chem. Rev*. **1966**, *66*, 297–339.

[153] a) Johnson, C. R.; Tanaka, K. *Synthesis* **1976**, 413–414. b) Meyers, A. I.; Ford, M. E. *Tetrahedron Lett*. **1975**, *16*, 2861–2864.



Scheme 28. Some representative strategies for the synthesis of thiiranes.

corresponding alcohol. This by treatment with NaH generates alkoxide **140**, which evolves to the thiirane **141**.[154] On the other hand, the transformation of epoxides into thioepoxides via nucleophilic substitution reaction (Scheme 28, Eq. 3) has been the most studied alternative for thiirane synthesis, but an important drawback of this procedure is the undesirable polymerization of the resulting thioepoxide. Two different reagents have mainly been employed in this strategy. On the one hand, epoxides are

[154] a) Calò, V.; Fiandanese, V.; Nacci, A. *Tetrahedron Lett.* **1998**, *39*, 3825–3828. b) Calò, V.; Fiandanese, V.; Nacci, A.; Volpe, A. *Tetrahedron* **1996**, *52*, 2155–2166.

reacted with ammonium[155] or potassium thiocyanate.[156] Other option is to use thioureas as sulfur reagents.[157] Direct sulfur transfer to the appropriate alkenes (Scheme 28, Eq. 4) is a protocol which also provides thioepoxides. The first example of this strategy was described 50 years ago[158] and since then many examples have been published.[159] Depending on the nature of the sulfur transfer reagent the protocols used in this last alternative can be classified into two groups: stoichiometric sulfur transfer, which has been the most investigated option and, where different sulfur sources have been used, and metal-catalyzed sulfur transfer, where the sulfur sources are activated by recyclable transition metal catalysts. In general sulfur transfer reactions have been less investigated than oxygen transfer procedures, because sulfur is less electronegative, therefore electrophilic sulfur sources must be activated, as mentioned above, for example, with metals.

All the previously mentioned procedures have two important limitations. On the one hand, none of them offers a broad scope; and, on the other hand, stereoselective versions of these protocols have been hardly investigated. The few examples of asymmetric synthesis of thioepoxides described in the literature are outlined in the next section.

2.2. Protocols for the asymmetric synthesis of thiiranes

To our knowledge, the first protocol developed for the stereoselective preparation of thioepoxides was enzymatic and follows the strategy shown in Scheme 28, Eq. 2. through bioreduction of ketones **150** (Scheme 29).[160] In 1999, Scilimati's

[155] a) Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett*. **2004**, *45*, 1535–1537. b) Kazemi, F.; Kiasat, A. R. *Phosphorus Sulfur* **2003**, *178*, 1333–1337. c) Mirkhani, V.; Tangestaninejad, S.; Alipanah, L. *Synth. Commun*. **2002**, *32*, 621–626. d) Mohammdpoor-Baltork, I.; Khosropour, A. R. *Molecules* **2001**, *6*, 996–1000. e) Iranpoor, N.; Tamami, B.; Shekarriz, M. *Synth Commun*. **1999**, *29*, 3313–3321.

[156] a) Reddy, C. S.; Nagavani, S. *Heteroatom Chem*. **2008**, *19*, 97–99. b) Yadav, J. S.; Reddy, B. V. S.; Reddy, C. S.; Rajasekhar, K. *J. Org. Chem*. **2003**, *68*, 2525–2527. c) Yadav, J. S.; Reddy, B. V. S.; Baishya, G. *Synlett* **2003**, *3*, 396–398.

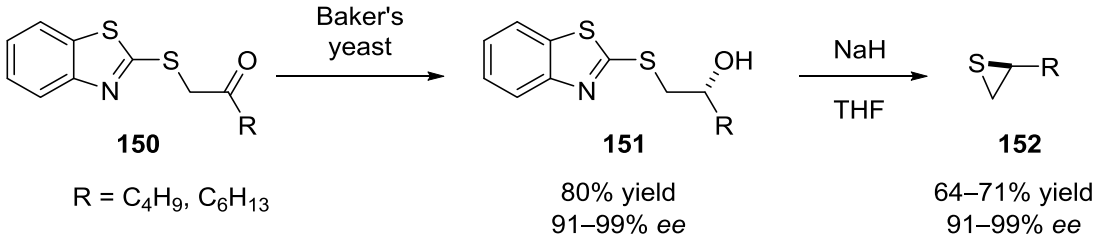
[157] a) Zeynizadeh, B.; Baradani, M. M.; Eisavi, R. *Phosphorus Sulfur* **2011**, *186*, 2208–2215. b) Eisavi, R.; Zeynizadeh, B.; Baradani, M. M. *Phosphorus Sulfur* **2011**, *186*, 1902–1909. c) Kazemi, F.; Kiasat, A. R.; Ebrahimi, S. *Synth. Commun*. **2003**, *33*, 595–600. d) Kazemi, F.; Kiasat, A. R.; Ebrahim, S. *Phosphorus Sulfur* **2001**, *176*, 135–140. e) Tangestaninjad, S.; Mirkhani, V. *Synth. Commun*. **1999**, *29*, 2079–2083.

[158] Schmidt, U.; Osterroht, C. *Angew. Chem. Int. Ed*. **1965**, *4*, 437–440.

[159] For a general review on the synthesis of thiiranes starting from alkenes, see: Adam, W.; Bargon, R. M. *Chem. Rev*. **2004**, *104*, 251–261.

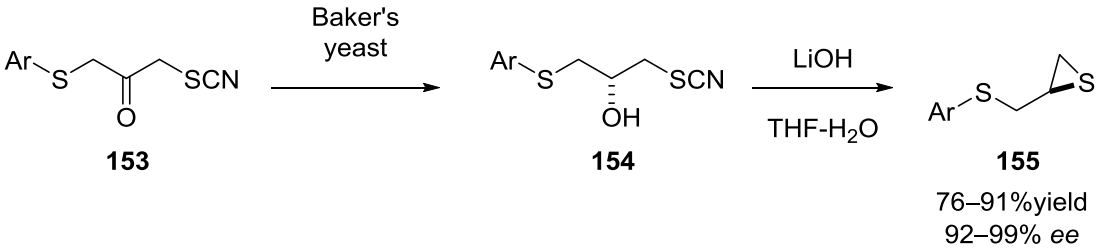
[160] Di Nunno, L.; Franchini, C.; Nacci, A.; Scilimati, A.; Sinicropi, M. S. *Tetrahedron: Asymmetry* **1999**, *10*, 1913–1926.

group reported the preparation of 1-(benzothiazol-2-ylsulfanyl)-2-alkanols **151** through a baker's yeast mediated asymmetric reduction of ketones **150** with high level of stereocontrol. These compounds turned to be good precursors for the synthesis of optically active thioepoxides **152** upon treatment with sodium hydride (Scheme 29).



Scheme 29. Synthesis of enantiomerically enriched thiiranes **152**. **Scilimati, 1999**.

More recently, Plenkiewicz,[161] following a bioreduction-based protocol, described the synthesis of enantiomerically enriched but unstable β-hydroxythiocyanates **154**, which were transformed *in situ* into thiiranes **155** by treatment with lithium hydroxide, maintaining the enantiomeric purity (Scheme 30). The cyanate formed after deprotonation of the hydroxy group is a good leaving group, thus facilitating the formation of the thiirane, which occurs with successful results.

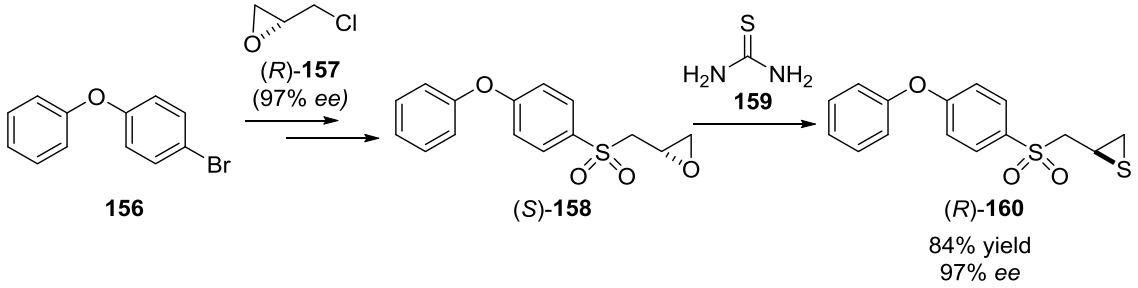


Scheme 30. Synthesis of enantiomerically enriched thiiranes **155**. **Plenkiewicz, 2007**.

The only stereoselective example found in the literature on the use of enantiomerically pure epoxides to get enantioenriched thiiranes was published in 2005 by Mobashery and co-workers.[162] They described the synthesis of both enantiomers of compound **160**, a selective inhibitor of gelatinases, starting from commercially available (*R*)- and (*S*)-epichlorohydrin **157** (Scheme 31), showing that both are equally active in the inhibition process. In this case the strategy depicted in Scheme 28, Eq. 3. was used, and the conversion of the oxirane into the thiirane ring was promoted by thiourea **159** with inversion of the stereochemistry.

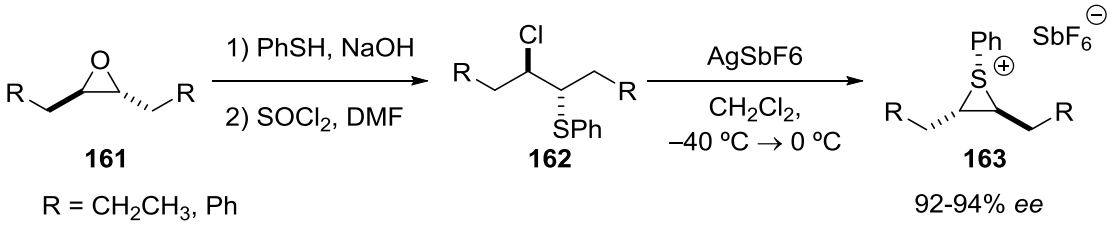
[161] a) Łukowska, E.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 493–499. b) Łukowska, E.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1202–1209.

[162] Lee, M.; Bernardo, M. M.; Meroueh, S. O.; Brown, S.; Fridman, R.; Mobashery, S. *Org. Lett*. **2005**, *7*, 4463–4465.



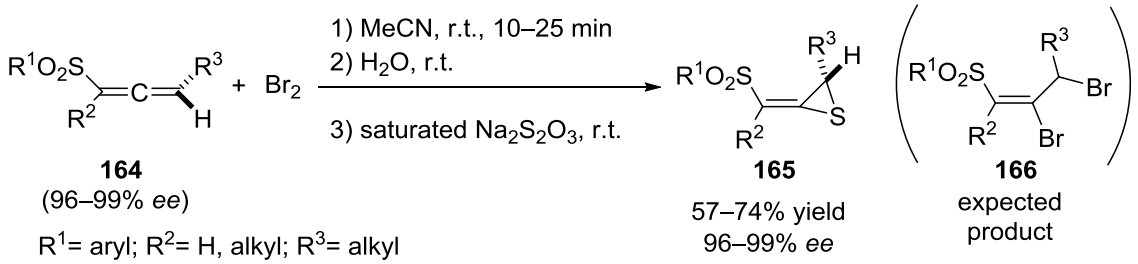
Scheme 31. Synthesis of (*R*)-2-(4-phenoxyphenylsulfonylmethyl)thiirane **160**. **Mobashery, 2005**.

More recently, in 2009, Denmark disclosed the peculiar asymmetric synthesis of configurationally stable thiiranium ions **163** by silver assisted ionization of chloro sulfide derivatives **162** under anhydrous conditions (Scheme 32).[163]



Scheme 32. Synthesis of enantiomerically enriched thiiranium ions **163**. **Denmark, 2009**.

Ma and co-workers[164] also contributed to the field by developing new strategies to provide optically active thiiranes, documenting a particular protocol to prepare alkylidenethiiranes in a highly stereoselective manner. They used enantioenriched 1,2-allenyl sulfones **164** as starting material and performed an electrophilic reaction with bromine. After quenching the reaction with saturated aqueous $Na_2S_2O_3$, instead of the expected 2,3-dibromoalkenyl sulfone **166**, the substituted 1-sulfonyl alkylidenethiirane **165** was isolated without losing the enantiopurity (Scheme 33).

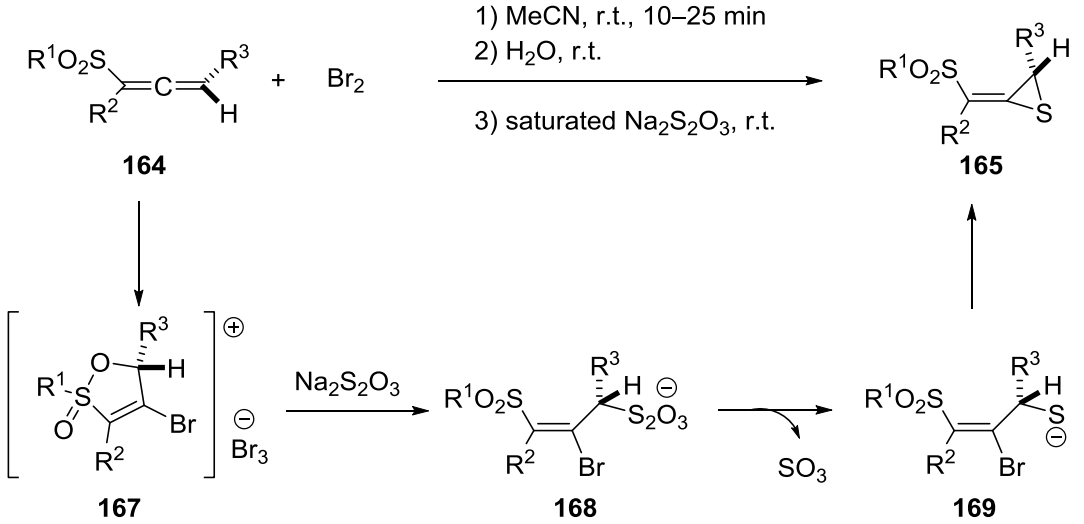


Scheme 33. Synthesis of enantiomerically enriched 1-phenylsulfonylalkylidenethiiranes **165**. **Ma, 2007**.

[163] Denmark, S. E.; Vogler, T. *Chem. Eur. J*. **2009**, *15*, 11737–11745.

[164] Zhou, C.; Fu, C.; Ma, S. *Angew. Chem. Int. Ed*. **2007**, *46*, 4379–4381.

The authors suggested the mechanism depicted in Scheme 34 for the thiirane formation. The five-membered ring intermediate **167** is supposed to be opened by treatment with $S_2O_3^{2-}$ and after release of SO_3 intramolecular conjugated addition and elimination are proposed.



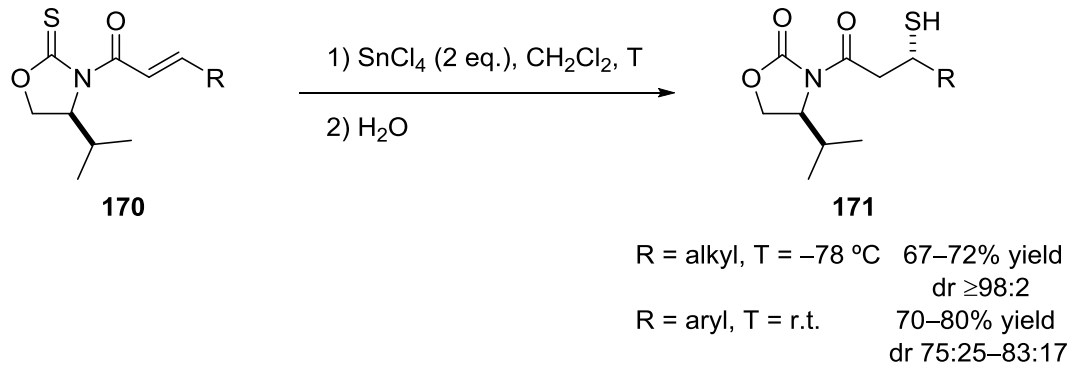
Scheme 34. Proposed mechanism for the stereoselective thiiranation of 1,2-allenyl sulfones **164** with Br_2 and $Na_2S_2O_3$. **Ma, 2007**.

As far as we know, these are the only reported asymmetric synthesis of enantiomerically enriched thiiranes. All these protocols are based on bioreductions or make use of starting enantioenriched substrates. Thus, the development of new asymmetric protocols to access thiiranes stereoselectively is highly demanding.

2.3. Precedents from our group

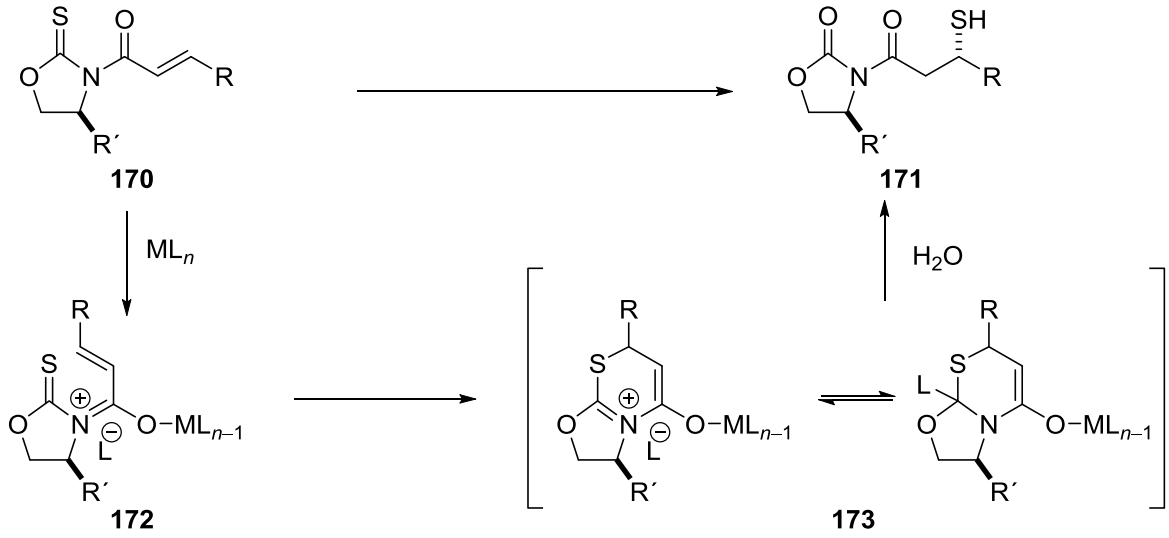
As mentioned in the introduction, our research group developed a methodology to synthesize β-mercapto carboxylic acid derivatives that relies on an intramolecular sulfur transfer in *N*-enoyl oxazolidin-2-thiones **170** (Scheme 35). In 2001 a conceptually new strategy to provide β-thio carbonyl compounds was presented by using these substrates. These compounds performed, in the presence of $SnCl_4$, a diastereoselective intramolecular sulfur migration through a formal sulfa-Michael addition. The reaction was general for both alkyl- and aryl-substituted imides and provided high levels of diastereoselection and good yields. Aryl derivatives were less reactive, and therefore higher reaction temperatures were needed, providing slightly lower stereochemical results (Scheme 35).[165] The oxazolidin-2-thione has two functions; on the one hand, it acts as sulfur-donor reagent and, on the other hand, as controller of the reaction stereochemistry.

[165] See ref. 145a, page 50.



Scheme 35. Intramolecular sulfur transfer reaction of *N*-enoyl oxazolidin-2-thiones **170** promoted by Lewis acids. **Palomo, 2001**.

It was suggested that complexation between *N*-enoyl oxazolidinon-2-thione and the Lewis acid provides intermediate **172**. Then subsequent electrocyclic cyclization and hydrolysis occurs yielding the corresponding β-mercapto imide **171** (Scheme 36).

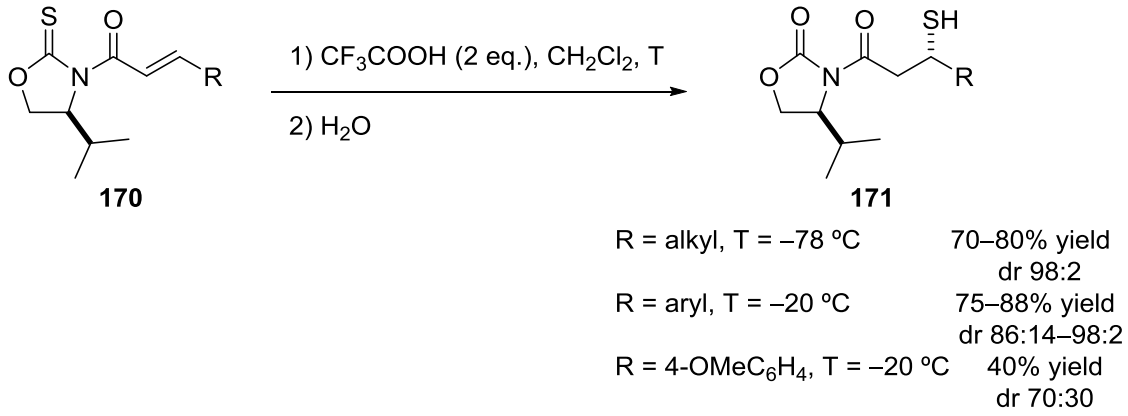


Scheme 36. Proposed course of the sulfur transfer reaction. **Palomo, 2001**.

Intervention of protons during sulfur migration reaction was evidenced, because in the presence of 2,6-di-*tert*-butylpyridine, a base that captures protons, but is apparently unable to coordinate to metals, no reaction was observed. With the intention to make the process free from metal the reaction was tested with Brønsted acids demonstrating that they were also appropriate to promote the sulfur transfer reaction with successful performance, being TFA the acid that provided the best results (Scheme 37).[166] Exceptionally, when the reaction was carried out with electron-rich aromatic substituents (4-$OMeC_6H_4$), an undesired side product, whose structure has not been elucidated, was detected and the diastereoselectivity decreased. Additionally, in the

[166] See ref. 145c, page 50.

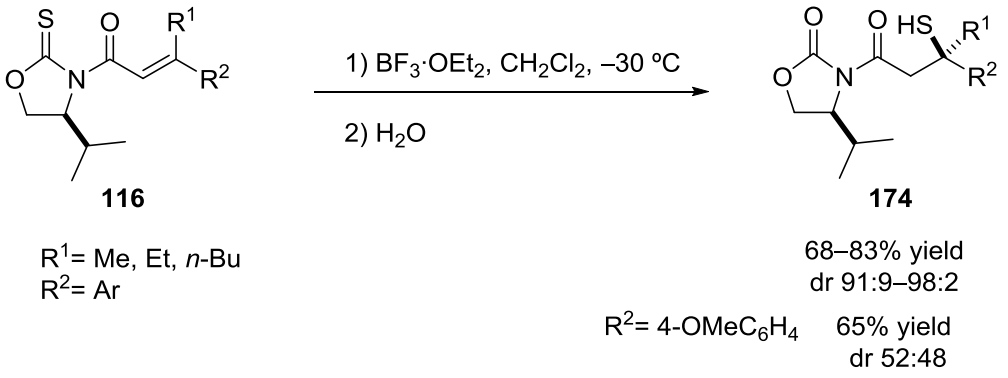
absence of Lewis or Brønsted acids no reaction was observed, even at room temperature and after long reaction times.



Scheme 37. Intramolecular sulfur transfer reaction of *N*-enoyl oxazolidin-2-thiones **170** promoted by Brønsted acids. **Palomo, 2006**.

Although is usually challenging to run stereoselective Michael additions with β,β-disubstituted Michael acceptors, on the one hand, because the reactivity is lower and, on the other hand, because of the inherent difficulty in controlling reaction stereoselectivity, our group was able to extend satisfactorily the previous methodology to this type of acceptors.

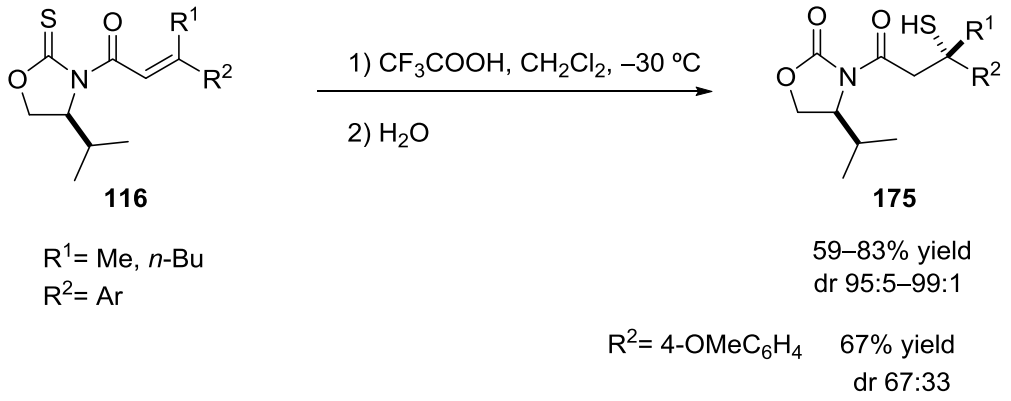
The reaction was initially performed with Lewis acids and in this case $BF_3{\cdot}OEt_2$ was found to be the most efficient promoter in terms of reactivity and stereochemistry. The corresponding tertiary thiols were isolated with good yields and high diastereomeric ratios (Scheme 38), even employing β,β-disubstituted *N*-enoyl oxazolidin-2-thiones with variable *E/Z* composition. Once again 4-$OMeC_6H_4$ substituted imide was the exception, no exhibiting diastereoselection in the reaction.[167]



Scheme 38. Intramolecular sulfur transfer reaction of β,β-disubstituted *N*-enoyl oxazolidin-2-thiones **116** promoted by Lewis acids. **Palomo, 2004**.

[167] See ref. 145b, page 50.

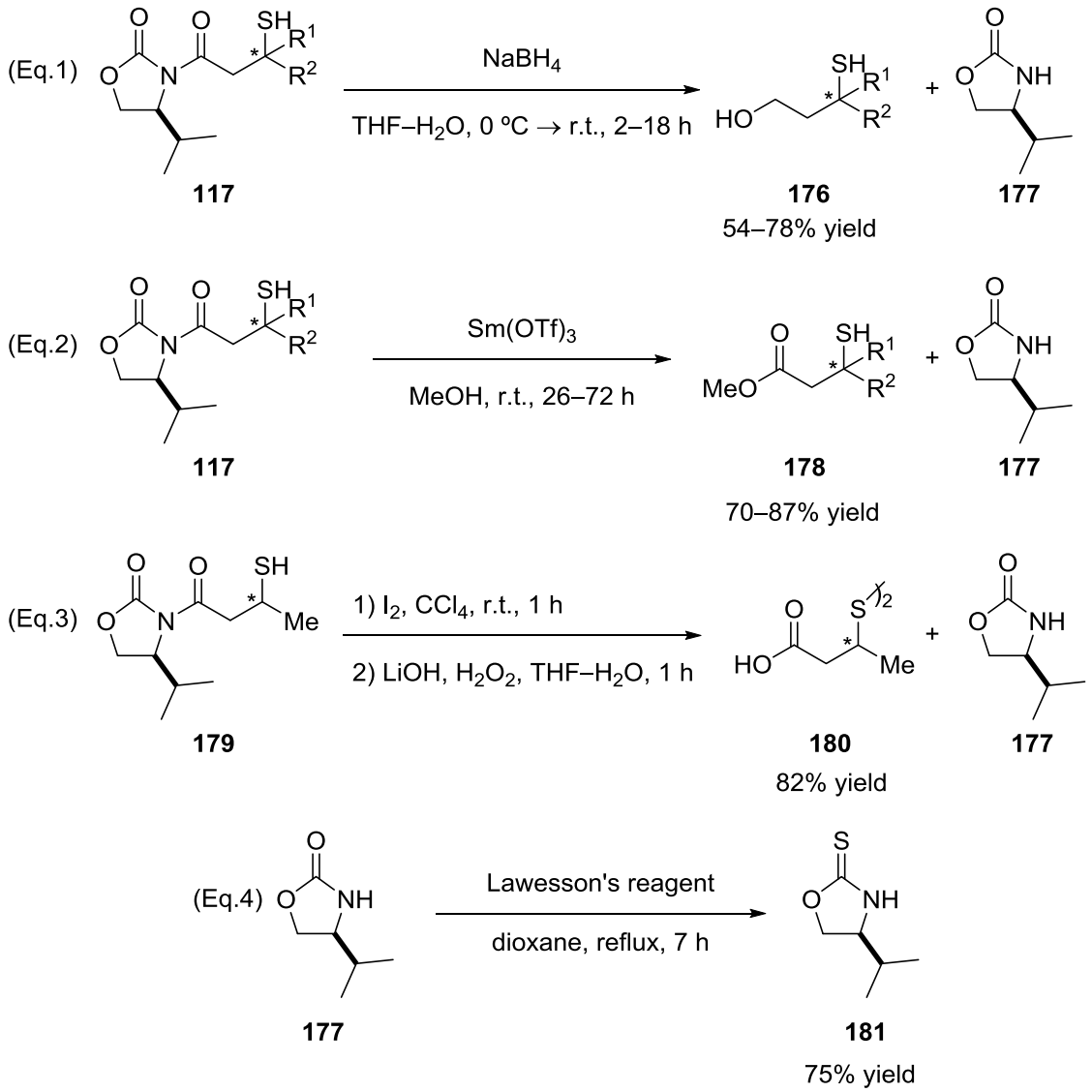
After the successful results afforded with β-monosubstituted substrates in the presence of Brønsted acids, the reaction was also tested with β,β-disubstituted imides in the presence of TFA. The sulfur migration reaction proceeded satisfactorily, although longer reaction times were needed and diastereoselectivities decreased slightly. Curiously, Brønsted acid promoted reactions showed opposite asymmetric induction, obtaining mainly the other diastereomer, thus complementing the initial methodology (Scheme 39).[168] By only changing the acid promoter and starting from the same chiral source it was possible to synthesize the desired diastereomer.



Scheme 39. Intramolecular sulfur transfer reaction of β,β-disubstituted *N*-enoyl oxazolidin-2-thiones **116** promoted by Brønsted acids. **Palomo, 2006**.

In all cases the detachment of the altered chiral auxiliary was successfully carried out, with the simultaneous release of the corresponding enantioenriched β-mercapto carboxylic acid derivative, following two ways. The first protocol uses sodium borohydride in a mixture of THF–H_2O to yield the corresponding hydroxythiols (Scheme 40, Eq. 1), whilst under the presence of $Sm(OTf)_3$ in MeOH β-mercapto carboxylic ester derivatives were isolated (Scheme 40, Eq. 2). Alternatively, before performing the cleavage of the auxiliary, it was possible to protect the thiol group as disulfide and then treat this disulfide under the standard conditions to release Evans' oxazolidinone by lithium peroxide assisted hydrolysis to afford dimeric compound **180** (Scheme 40, Eq. 3). In addition, the modified auxiliary recovered from chromatographic column was successfully transformed by treatment with Lawesson's reagent into the initial chiral auxiliary (Scheme 40, Eq. 4).

[168] See ref. 145c, page 50.

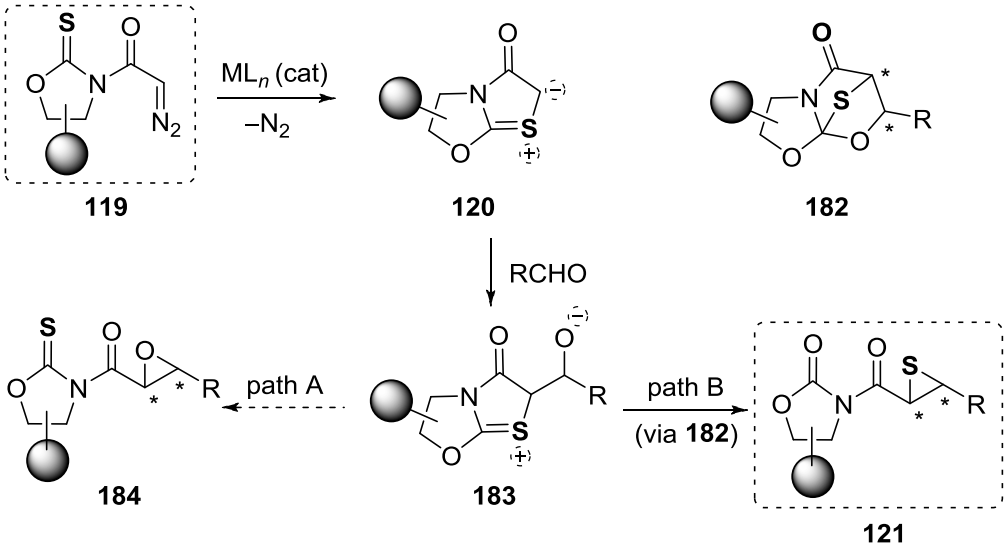


Scheme 40. Elaboration of adducts of sulfur transfer reactions and recovery of the chiral auxiliary.

2.4. Working hypothesis and synthetic plan

Inspired by the work developed in our laboratory that demonstrates the double role of the oxazolidin-2-thione group which acts as chiral auxiliary and as intramolecular sulfur-donor reagent in the previous reactions, we proposed as the first goal of this Thesis the development of a procedure to synthesize thiiranes using oxazolidin-2-thione derivatives. We hypothesized that *N*-(diazoacetyl)oxazolidin-2-thiones **119** might be suitable reagents to perform intramolecular sulfur migration forming *C–C* and *C–S* bonds asymmetrically to afford thiiranes. Our assumption was

that treatment of *N*-(diazoacetyl)oxazolidin-2-thione with an appropriate metal[169] would provide thiocarbonyl ylides **120** which upon reaction with an aldehyde would generate the zwiterionic intermediates **183**. These could follow either path A or B to afford epoxide or thioepoxide products respectively (Scheme 41). Although the epoxide formation seemed to be the simplest way for the evolution of the zwiterionic intermediate and the preferred route for both sulfide ylides[170] and carbonyl ylides,[171] we did not rule out path B, that would provide α,β-thioepoxy carbonyl compounds in a stereocontrolled fashion, likely through rearrangement of intermediate **182**.



Scheme 41. Hypothesis for the stereoselective synthesis of thiiranes by sulfur transfer with concomitant *C–C* bond formation.

[169] For *C–S* bond formation mediated by sulfur ylides derived from metal carbenes, see: a) Zhang, Y.; Wang, J. *Coord. Chem. Rev*. **2010**, *254*, 941–953. For metal-catalyzed reactions of α-diazocarbonyl compounds, see: b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev*. **2010**, *110*, 704–724. c) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev*. **2009**, *38*, 3061–3071. d) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577–6605. e) Doyle, M. P.; McKervey, A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, **1998**, Wiley-Interscience: New York. For the generation of thiocarbonyl ylides, see: f) Padwa, A. *Chem. Soc. Rev*. **2009**, *38*, 3072–3081.

[170] For a review, see: a) Aggarwal, V. K.; Crimmin, M.; Riches, S. In *Science of Synthesis*; Georg Thieme Verlag, Stuttgart, **2008**, Vol. 37, pp 321−406. For examples, see: b) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R. L.; Smith, C.; Vasse, J. -L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105−2114 and references therein. For a mechanistic investigation, see: c) Edwards, D. R.; Montoya-Peleaz, P.; Crudden, C. M. *Org. Lett*. **2007**, *9*, 5481–5484.

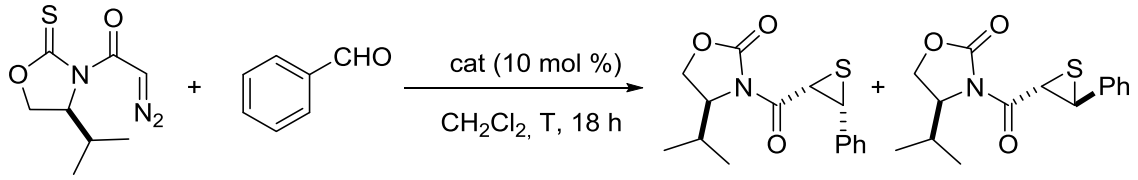
[171] a) Liu, W. -J.; Lv, B. -D.; Gong, L. -Z. *Angew. Chem. Int. Ed*. **2009**, *48*, 6503−6506. b) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett*. **2001**, *3*, 933−935.

2.5. Results and discussion

2.5.1. Catalyst screening

Dr. Landa from our laboratory started this project by performing the reaction with diazo compound **185** and benzaldehyde in the presence of $Rh_2(OAc)_4$ (entry 1) at 0 ºC. Under these conditions thioepoxide **187a** was obtained as a mixture of the *cis* and *trans* isomers and the *cis* isomer was isolated in 50% yield. Then the hydrated derivative $Rh_2(OAc)_4 \cdot 2H_2O$ (entry 2) and $Cu(acac)_2$ (entry 7) were also tested as metal catalysts. In the two cases the formation of thioepoxides **187a** in *cis/trans* ratios of 88:12 and 85:15 respectively was observed. The pure major diastereomer after purification of each crude mixture by column chromatography was obtained in 62% and 53% yields, respectively. Fortunately no oxirane product was detected in the corresponding crude reaction mixtures. Thus, some other metal catalysts were evaluated and the corresponding results are compiled in Table 2.

Table 2. Screening of catalysts for the reaction of *N*-(diazoacetyl)-2-oxazolidinethione **185** and benzaldehyde **186a**.[a]



185 **186a** ***cis*-187a** ***trans*-187a**

Entry	Catalyst	T (ºC)	*cis/trans*[b]	Yield (%)[c]
1	$Rh_2(OAc)_4$	0	86:14	50
2	$Rh_2(OAc)_4 \cdot 2H_2O$	0	88:12	62
3		–10	94:6	64[d]
4		–20	97:3	62[d]
5	$Rh_2(OCOCF_3)_4$	0	--	0[e]
6	$CoCl_2$	0	--	0
7	$Cu(acac)_2$	0	85:15	53
8	$Cu(OTf)_2$	0	--	0[e]
9	CuCl	0	91:9	40
10	$FeCl_2 \cdot 4H_2O$	0	--	0[e]
11	AuCl	0	99:1	18
12	AgOTf	0	--	0[e]
13	$Pd(OAc)_2$	0	--	17

[a] The reactions were performed on a 0.3 mmol scale; **185** (1 equiv., 0.3 mmol), **186a** (5 equiv., 1.5 mmol). [b] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [c] Yield of isolated major isomer after chromatography. [d] Using 2 mol % catalyst. [e] Extensive decomposition was observed.

These results show that the nature of the counterion of the transition metal salt used has an important influence on the catalytic activity; while $Rh_2(OAc)_4$ and $Cu(acac)_2$ demonstrated to be active and induced good reaction yields, no reaction was observed with either $Rh_2(OCOCF_3)_4$ (entry 5) or $Cu(OTf)_2$ (entry 8) salts. Other divalent metal salts which usually induce ylide formation such as $CoCl_2$, $FeCl_2{\cdot}4H_2O$ or $Pd(OAc)_2$ resulted not effective for the reaction. Variable results were obtained when salts with metals in the oxidation state +1 were employed; while AgOTf (entry 12) was not able to promote the reaction, with CuCl (entry 9) and AuCl (entry 11), although the diastereoselectivity was satisfactory, the yields were low or very low.

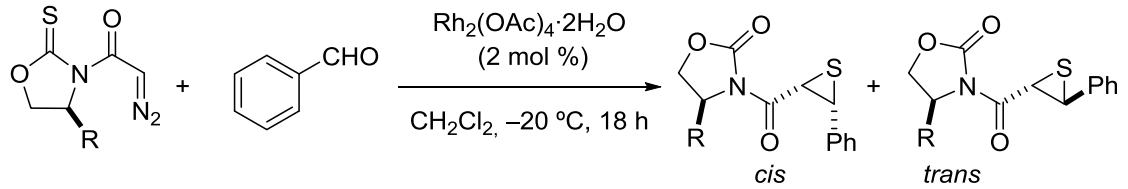
Considering the ability to promote the reaction and induce stereoselectivity, $Rh_2(OAc)_4{\cdot}2H_2O$ was the best catalyst among the tested ones. Improvements in the *cis/trans* ratio in this case were achieved when the temperature of the reaction was decreased (entries 3 and 4) and it was also demonstrated that 2 mol % of the catalyst loading was enough to perform the reaction efficiently regarding the reactivity and diastereoselectivity.

2.5.2. *N*-(diazoacetyl)-2-oxazolidinethione screening

Once the catalyst and the reaction temperature were established, the next step was the investigation of the influence of the stereodirecting group of the *N*-(diazoacetyl)-2-oxazolidinethione in the reaction (Table 3).

Comparable results were observed when diazo-oxazolidin-2-thione bearing the *tert*-butyl substituent was used (entry 2); however, the starting amino acid to prepare this diazo compound is much more expensive. In the case of diazo compounds bearing Bn (entry 3) and Ph (entry 4) groups worst results regarding both, yields and selectivities, were obtained. Therefore diazo-oxazolidinone bearing the isopropyl group was chosen as sulfur-donor reagent.

Table 3. *N*-(diazoacetyl)-oxazolidin-2-thione screening.[a]



185 R = *i*-Pr
188 R = *t*-Bu
189 R = Bn
190 R = Ph

186a

187 R = *i*-Pr
191 R = *t*-Bu
192 R = Bn
193 R = Ph

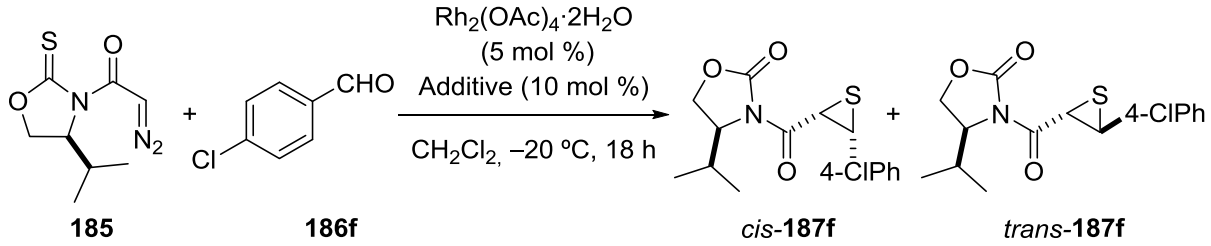
Entry	R	*cis/trans*[b]	Yield (%)[c]
1	*i*-Pr	97:3	62
2	*t*-Bu	94:6	60
3	Bn	85:15	40
4	Ph	92:8	45

[a] The reactions were performed on a 0.3 mmol scale; **185/188/189/190** (1 equiv., 0.3 mmol), **186a** (5 equiv., 1.5 mmol). [b] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [c] Yield of isolated major isomer after chromatography.

2.5.3. Solvent and additive screening

To complete the screening of the reaction conditions, several solvents were tested observing that the initially used solvent for the reaction, dichloromethane, was the best (Table 4). Slight erosion of the *cis/trans* ratio was reported when the reaction was carried out in toluene (entry 4) or 1,2-dichloroethane (entry 5). Worst results were provided by diethyl ether and only 30% of conversion was observed with tetrahydrofuran. With the intention of improving the results some additives were also tested and totally unsatisfactory results were observed with pyridine (entry 7) and phenanthroline (entry 8). Nevertheless, the addition of 2,2'-bipyridyl (entry 6) to the reaction produced slightly better selectivity but worst yield; however, we considered that the improvement in selectivity was not enough comparing with the lowering of the yield to compensate the use of this additive. Therefore subsequent reactions were carried out without additive.

Table 4. Solvent and additive screening for the reaction of *N*-(diazoacetyl)-oxazolidin-2-thione **185** and 4-chlorobenzaldehyde **186f**.[a]



185 **186f** ***cis*-187f** ***trans*-187f**

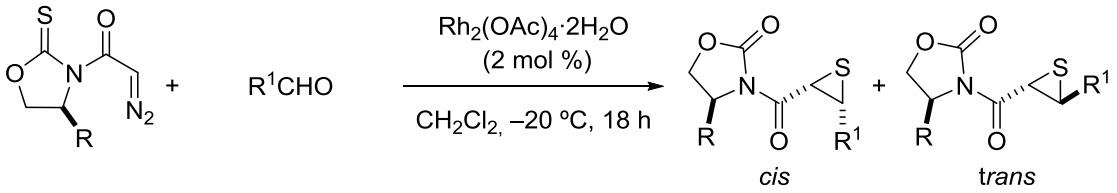
Entry	Solvent	Additive	Conv. (%)[b]	*cis/trans*[c]
1	CH_2Cl_2	none	100(63)[d]	88:12
2	THF	none	30	--
3	Et_2O	none	100	79:21
4	Toluene	none	100	85:15
5	$ClCH_2CH_2Cl$	none	100	85:15
6	CH_2Cl_2	2,2'-bipyridyl	100(55)[d]	91:9
7	CH_2Cl_2	pyridine	0[e]	--
8	CH_2Cl_2	phenanthroline	5	--

[a] The reactions were performed on a 0.30 mmol scale; **185** (1 equiv., 0.3 mmol), **186f** (5 equiv., 1.5 mmol). [b] Data refers to % of **187f** in the crude mixture determined by ^{1}H NMR. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] The number in parenthesis is the yield of isolated pure *cis* compound **187f** after column chromatography. [e] Just decomposition of **185** was observed.

2.5.4. Reaction scope

After the optimization study it was concluded that the best conditions to perform the reactions were the use of the diazo compound **185**, 3 equivalents of aldehyde, 2 mol % of $Rh_2(OAc)_4·2H_2O$ as catalyst, dichloromethane as solvent at –20 ºC. A representative selection of aldehydes was evaluated to establish the generality of this asymmetric route to thiiranes. As the results in Table 5 show, a range of aromatic aldehydes bearing either electron-donating, neutral, or electron-withdrawing substituents, all produced the corresponding α,β-thioepoxy carbonyl compounds smoothly within 16–18 h at –20 ºC.

Table 5. Scope of the reaction. [a]



185 R = *i*-Pr
188 R = *t*-Bu

186

187 R = *i*-Pr
191 R = *t*-Bu

Entry	Substrate	R^1	Product	cis/trans[b]	Yield (%)[c]
1	**185**	Ph	**187a**	93:7	65[d]
2	**185**	4-MeC_6H_4	**187b**	82:18	60
3	**185**	3,5-diMeC_6H_3	**187c**	83:17	61
4	**185**	4-$MeOC_6H_4$	**187d**	1:99	61
5	**185**	4-$TBSOC_6H_4$	**187e**	1:99	31[e]
6[f]	**185**	4-ClC_6H_4	**187f**	88:12	63
7	**185**	3-ClC_6H_4	**187g**	86:14	57
8	**185**	4-BrC_6H_4	**187h**	91:9	56
9	**185**	4-$NO_2C_6H_4$	**187i**	92:8	61
10	**185**	4-CNC_6H_4	**187j**	91:9	56
11	**185**	PhC≡C	**187k**	72:28	65
12[g]	**188**	PhC≡C	**191k**	83:17	75
13[h]	**188**	PhC≡C	**191k**	86:14	69
14[g]	**188**	3-ClC_6H_4C≡C	**191l**	85:15	60
15	**185**	3-furyl	**187m**	62:38	nd[i]
16[g]	**188**	3-furyl	**191m**	83:17	70
17	**185**	3-pyridyl	**187n**	--	0[j]

[a] Reaction conditions: **185/188** (0.5 mmol), **186** (3 equiv., 1.5 mmol), $Rh_2(OAc)_4·2H_2O$ (2 mol %), −20 ºC, 18 h in CH_2Cl_2 (1.5 mL). [b] Determined by ^1H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [c] Yields of isolated pure compounds **187/191** after column chromatography. [d] Reaction carried out at 2 mmol scale. [e] Yield not optimized; partial desilylation occurred during chromatography (SiO_2). [f] 91:9 diastereoselectivity in the presence of 2,2'-bipyridyl as additive. [g] Reaction run at −60 ºC. [h] Reaction run at −78 ºC. [i] nd: not determined [j] Unchanged starting material recovered.

In each case a mixture of *cis/trans* diastereomers was detected in the crude of the reaction and after column chromatography the major isomer was isolated in 56–75% yield. Interestingly, in most cases the *cis*-thiirane was produced as the major isomer

with *cis/trans* ratios between 97:3 and 82:18 (entries 1–3, 6–10). Assignment of the *cis/trans* relative configuration of the formed thiirane ring was primarily made by correlation of the coupling constants between the two *vec* H nucleus in ^{1}H NMR: from 7.4 Hz to 7.7 Hz for *cis*-thiirane systems and from 4.8 Hz to 4.9 Hz for the *trans* isomer. In addition, an X-ray single-crystal structure analysis of compound *cis*-**187a** served to confirm undoubtedly the proposed structure (Figure 19). Curiously, when benzaldehydes bearing electron-donating substituents such as methoxy (entry 4) and *tert*-butyldimethylsililoxy (entry 5) groups were employed exclusively *trans*-configured adduct was observed. Experiments by Landa from this laboratory corroborated this assumption and this unusual reversal of the reaction stereochemistry observed could be explained by means of a computational study as will be discussed later.

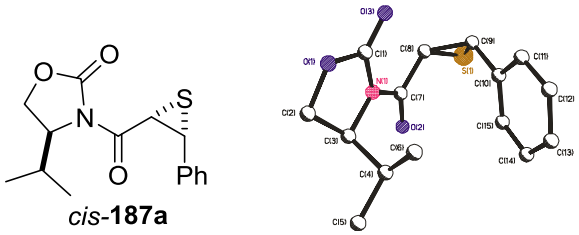


Figure 19. ORTEP diagram of compound *cis*-**187a**.

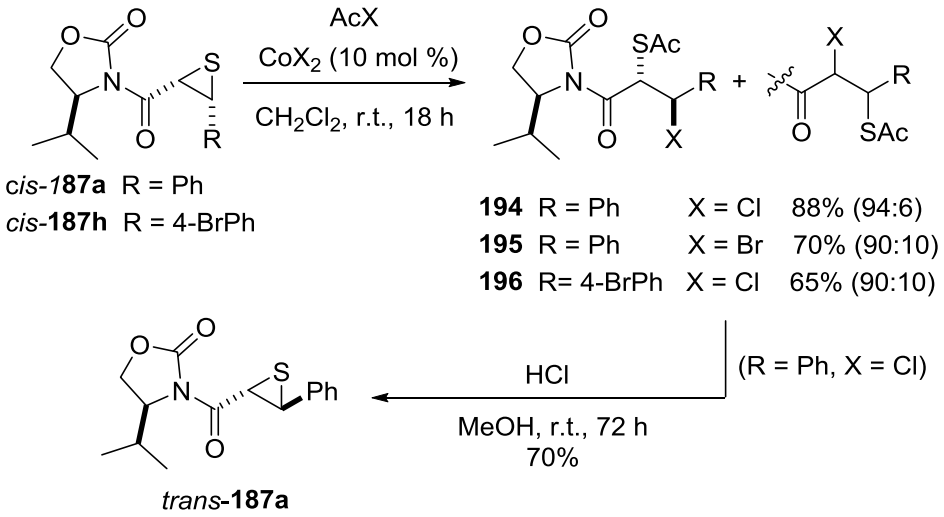
The reaction was suitable also with other non enolizable aldehydes such as alkynyl and heteroaryl aldehydes (entries 11–16). In these cases, it was necessary to carry out the reactions at lower temperatures and replace the starting material to *tert*-butyl derivative oxazolidin-2-thione to achieve successful selectivities. Exceptionally, the reaction did not work with pyridylcarbaldehyde (entry 17), probably due to the inactivation of the catalyst. Unfortunately, aliphatic aldehydes were less reactive and it turned out impossible to determine the *cis/trans* ratio by NMR.

2.5.5. Elaboration of adducts

After optimization of the reaction conditions for the sulfur-migration process and with the corresponding adducts in hand, the release of the oxazolidinone auxiliary was next investigated.

Attempts of removal of the chiral auxiliary, that is, the oxazolidinone moiety, from thiirane adducts **187**, made together with Landa and Cano from this laboratory, through imide hydrolysis or alcoholysis under standard reaction conditions, i.e. lithium hydroxide, samarium (III) or scandium (III) triflate or sodium borohydride, were completely unfruitful and only extensive desulfurization occurred. To avoid this problem we decided to open first the thioepoxides and then examine the imide hydrolysis in the ring-opened adducts. For that we followed the experimental procedure

developed by Iranpoor, Firouzabadi and Jafari[172] to transform thiiranes to β-chlorothioacetates catalyzed by $CoCl_2$. Treatment of thiiranes **187a** and **187h** with acyl halide (AcCl or AcBr) in the presence of a catalytic amount of cobalt halide ($CoCl_2$ or $CoBr_2$) in dichloromethane at room temperature provided the corresponding β-halide-α-thio imide derivatives **194–196** with good yields (65–88%) (Scheme 42). A minor amount (6–10%) of the corresponding regioisomeric ring opening product was detected by ^{1}H NMR analysis of the reaction crude in all the cases.



Scheme 42. Thiirane ring opening of adducts **187**.

The relative and absolute configuration of the major regioisomer was determined by a single crystal X-ray analysis of **194** (Figure 20), confirming that substitution at the β carbon occurred with retention of configuration, perhaps by a double inversion pathway involving a transient *C–O* adduct. Furthermore a procedure to prepare the more stable *trans* isomer was reported, and restoration of the thiirane ring was achieved treating the opened adduct with methanolic HCl at room temperature (Scheme 42). The reaction occurred efficiently and with inversion of the configuration at the β carbon.

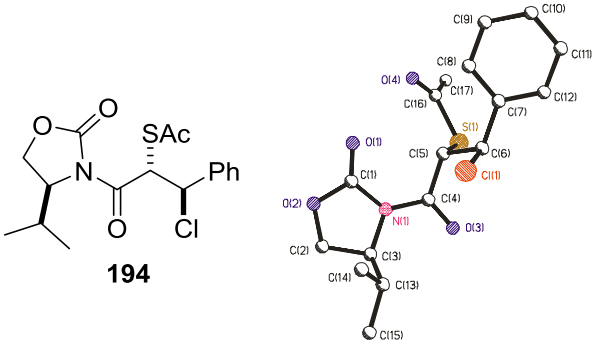
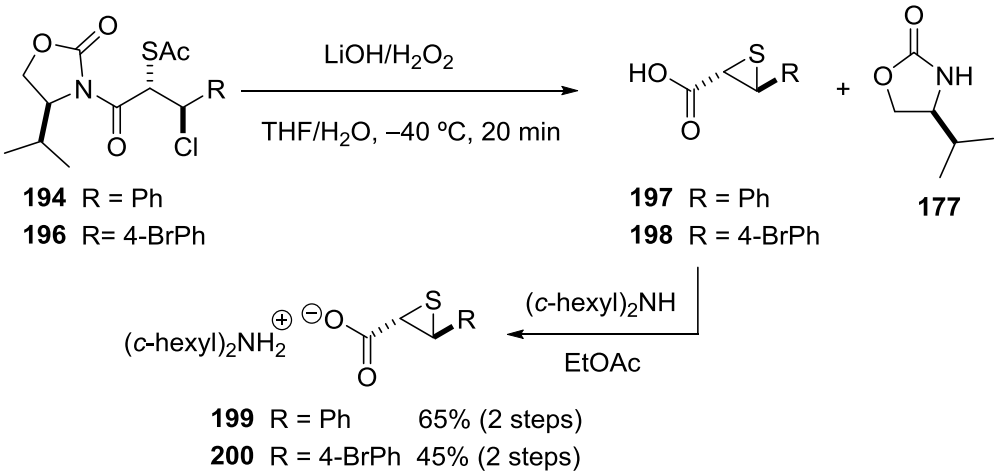


Figure 20. ORTEP diagram of compound **194**.

[172] Iranpoor, N.; Firouzabadi, H.; Jafari, A. A. *Synth. Commun.* **2003**, *33*, 2321−2327.

Finally, lithium peroxide assisted hydrolysis of the *N*-acyl oxazolidinone moiety[173] worked efficiently and proceeded with concomitant restoration of the thiirane ring, to afford the corresponding acids **197** and **198** along with the oxazolidinone **177** (Scheme 43).



Scheme 43. Removal of the auxiliary.

Unfortunately, the acids were unstable and it was not possible to purify them by column chromatography; therefore they were isolated as the stable dicyclohexylaminium salts **199** and **200** (Scheme 43), which were crystalline compounds and a single crystal X-ray analysis of **200** served to confirm the configuration of adducts (Figure 21).

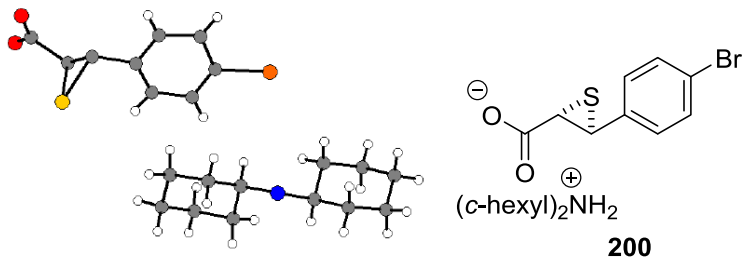
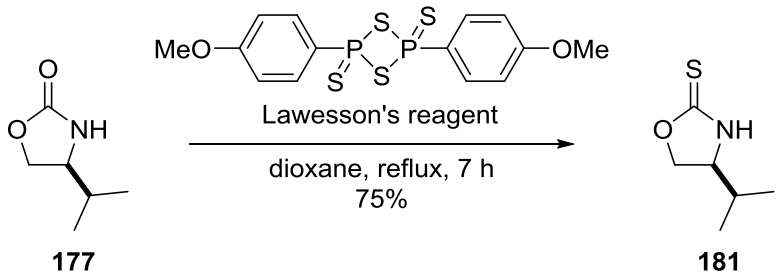


Figure 21. ORTEP diagram of compound **200**.

The oxazolidinone could be efficiently recovered and then successfully transformed into the starting auxiliary for reuse with a simple transformation of the

[173] Gage, J. R.; Evans, D. A. *Org. Synth*. **1990**, *68*, 83–91.

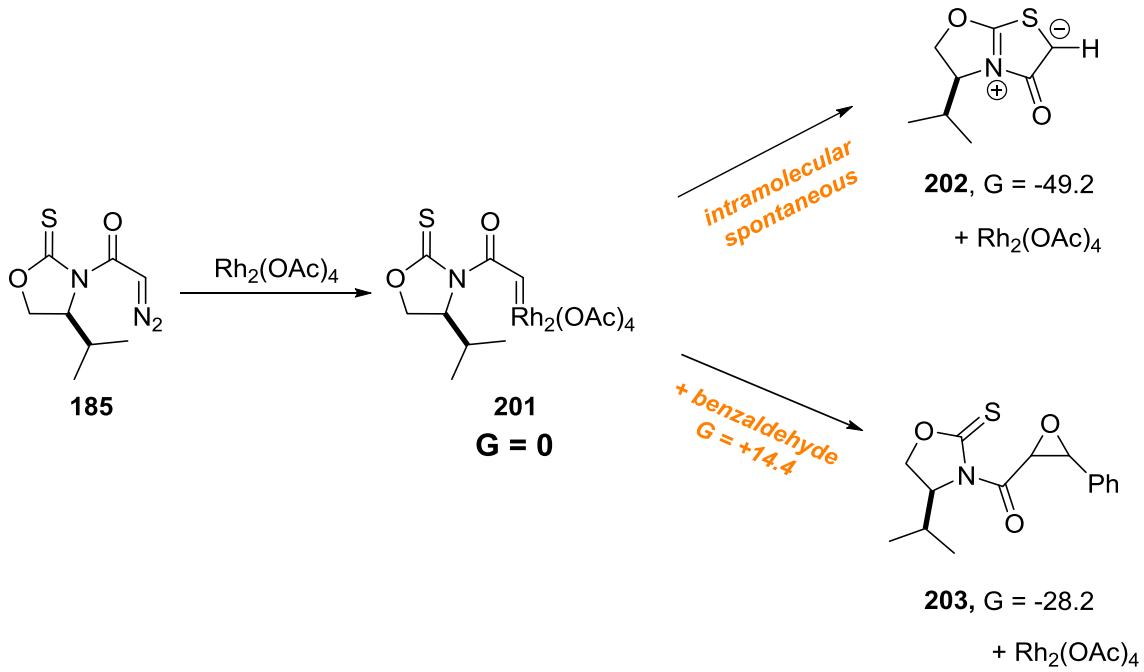
carbonyl group into the thiocarbonyl one by treatment with Lawesson's reagent (Scheme 44).[174]



Scheme 44. Recovery of the auxiliary.

2.5.6. Computational studies

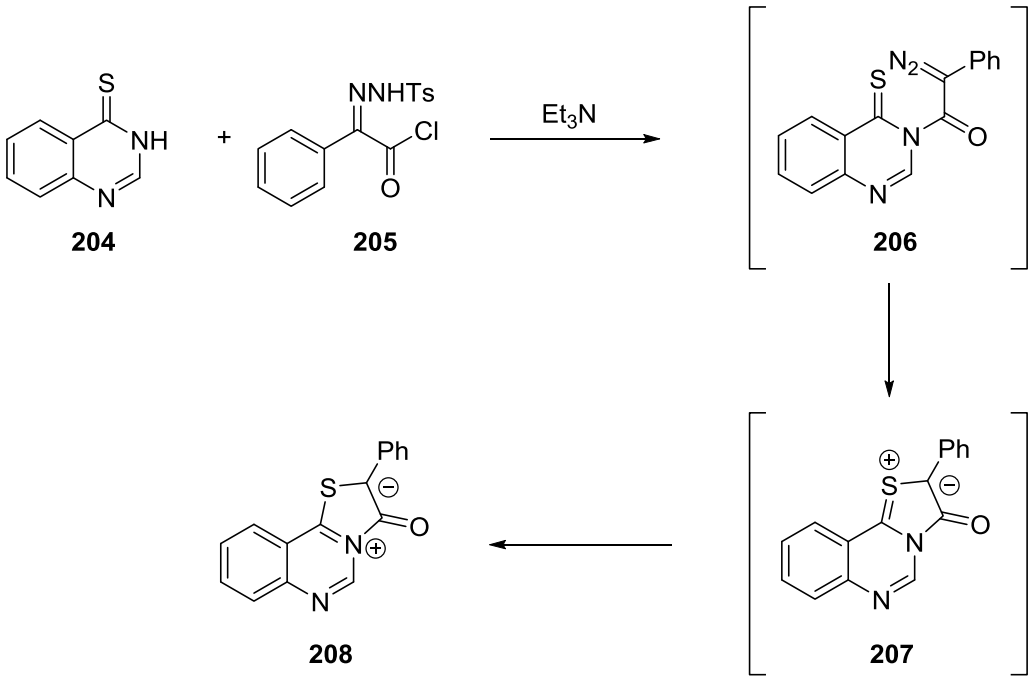
A DFT investigation was carried out by Dr. Enrique Gómez-Bengoa from our department, to find an explanation for the observed reactivity and stereoselectivity of the sulfur transfer event, including the reversal from *cis* to *trans* preference of thiirane formation experimentally documented with certain electron-rich benzaldehydes. The obtained results provided support for a plausible pathway for this intriguing thiirane-forming reaction.



Scheme 45. Comparison of the mechanism through zwitterionic **202** and epoxide **203**.

[174] a) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., **1995**, John Wiley: Chichester, Vol. 1, p 530. b) Ref 145b, page 50.

Firstly, treatment of diazo thione compound **185** with the catalyst of Rh(II) would produce the corresponding rhodium carbenoid species **201**. This intermediate could evolve into bicyclic ylide **202**[175] or could react with benzaldehyde to generate the epoxide **203** (Scheme 45), which could eventually lead to the final products. However, the intermolecular formation of the epoxide shows a measurable barrier of 14.4 Kcal/mol, whereas the intramolecular displacement of the rhodium fragment by the sulfur does not present activation barrier, probably because of the high charge delocalization exhibited by this particular ylide. In 1984, Potts[176] reported that diazothioamide compound **205** related to **185** can yield and stable aromatic mesoionic system, similar to our ylide intermediate (Scheme 46).



Scheme 46. Intramolecular carbenoid-type cyclization to obtain mesoionic ring system.

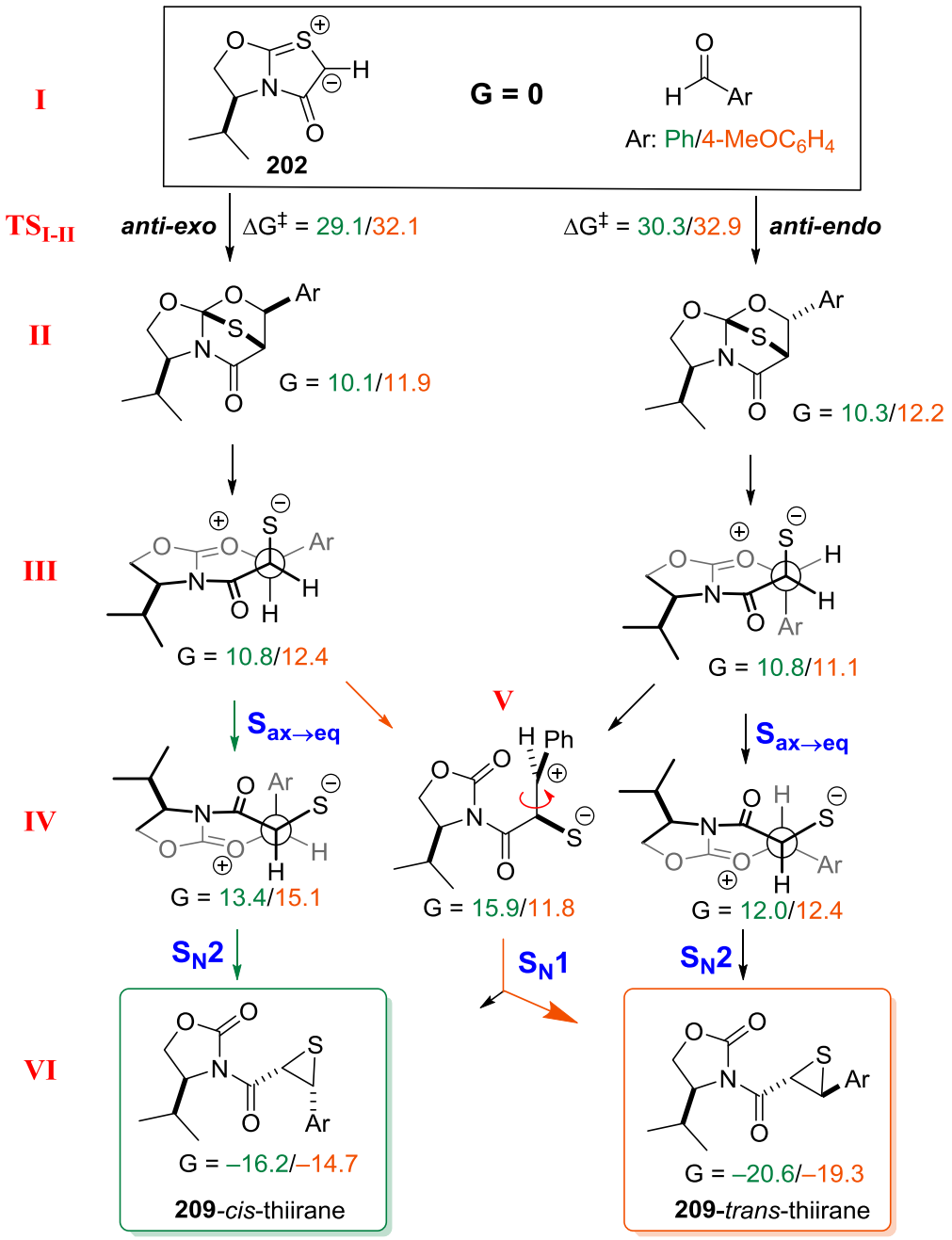
Moreover, epoxide **203** lies much higher in energy than **202** and the fact that no traces of epoxide product were detected in the reaction mixtures supported the mechanism through **202** and disfavours the epoxide pathway.

According to calculations, subsequent reaction of **202** with either benzaldehyde or *p*-anisaldehyde would generate a unique tricyclic adduct. Among the four possible relative orientations of the ylide and aldehyde component during the cycloaddition

[175] For generation, and subsequent cycloaddition, of thiocarbonyl ylides from the Rh(II)-catalyzed cyclization of diazothiocarbonyl compounds, see: a) ref. 169f, page 68. b) Padwa, A.; Flick, A. C.; Lee, H. I. *Org. Lett*. **2005**, *7*, 2925–2928. c) Padwa, A.; Kinder, F. R.; Zhi, L. *Synlett* **1991**, 287–288. d) Potts, K. T.; Houghton, E.; Singh, U. P. *J. Org. Chem*. **1974**, *39*, 3627–3631.

[176] Potts, K. T.; Murphy, P. *J. Chem. Soc. Chem. Commun*. **1984**, 1348–1349.

reaction (*anti-exo*, *anti-endo*, *syn-exo* and *syn-endo*), *anti-exo* and *anti-endo* are the preferred ones, which are represented in Scheme 47. The complementary *syn* transition states lie considerably higher in energy, probably due to unfavourable interactions between the isopropyl substituent of the ylide and the incoming aldehyde. The energy differences between two relative orientation approaches, *anti-exo* and *anti-endo* for benzaldehyde (1.2 Kcal/mol) would justify preferential formation of *anti-exo* adduct with expected diastereoselectivities near 90:10. Transformation of high energetic tricyclic intermediates into the final thiirane products would follow a more or less downhill energy profile for both cases. The first step of the transformation is a ring opening, cleaving the *C–S* bond, followed by $S_{ax \rightarrow eq}$ conformational switch, finishing by an internal S_N2 displacement that would provide the thiirane adduct. Consequently, from a tricyclic *anti-exo* intermediate the *cis*-configured thiirane would be formed; conversely, from the less-favourable *anti-endo* precursor, the *trans*-thiirane would be produced, a prediction that agrees with the experimentally observed trend for most aldehydes tested and is also consistent with the registered diastereoselectivities. Interestingly, calculations also offer a plausible explanation of the reversal of the reaction stereochemistry observed experimentally for *p*-anisaldehyde and other related electron-rich aromatic aldehydes. The first intermediate of the transformation from the tricyclic to the final products is the same for both types of aldehydes, i.e. ring opened intermediate, but in the case of benzaldehydes bearing electron-donating substituents, the thiirane generation could occur through an alternative S_N1-type pathway, which is about 2.5 Kcal/mol less favourable than S_N2 pathway for benzaldehyde, but conversely about 3.3 Kcal/mol more favourable than S_N2 pathway in the case of *p*-anisaldehyde. More simply, the electron-donating substituent of the benzaldehyde is able to stabilize the generated carbocation, therefore the lifetime is longer and has enough time to turn the *C–C* bond. Thus, as expected, S_N1-type cyclization would preferentially lead to the most stable *trans*-thiirane product, like the tricyclic *anti-endo* intermediate. Therefore, all the pathways lead to *trans*-thiirane adduct in the case of electron-rich aldehydes, that is why, only a single diastereomer could be observed in the crude reaction mixture.



Scheme 47. Principal reaction pathways found by DFT investigation at the B3LYP level of theory for the Rh-catalyzed reaction between diazocompound **185** and either benzaldehyde or *p*-anisaldehyde. Values of Gibbs energy are given in Kcal/mol.

In summary, we have reported the first Rh-catalyzed reaction of a diazoacetyl compound with aldehydes that affords thiiranes with very high stereoselectivity where chiral *N*-(diazoacetyl)oxazolidin-2-thione acts as chiral auxiliary and sulfur-donor reagent.[177] Furthermore, the removal of the oxazolidinone moiety from adducts allows

[177] Cano, I.; Gómez-Bengoa, E.; Landa, A.; Maestro, M.; Mielgo, A.; Olaizola, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed*. **2012**, *51*, 10856–10860.

recovering and recycling of the chiral auxiliary and provides the corresponding optically active thiirane carboxylic acids. This direct asymmetric synthesis of thioepoxides involves an unprecedented sulfur transfer process with concomitant *C–C* bond formation. A plausible pathway supported by a DFT investigation is presented to understand the observed reactivity and stereoselectivity, including the reversal from *cis* to *trans* preference of thiirane formation with certain electron-rich benzaldehydes.

Chapter 3:

Asymmetric synthesis of α,α-disubstituted α-mercapto carboxylic acid derivatives

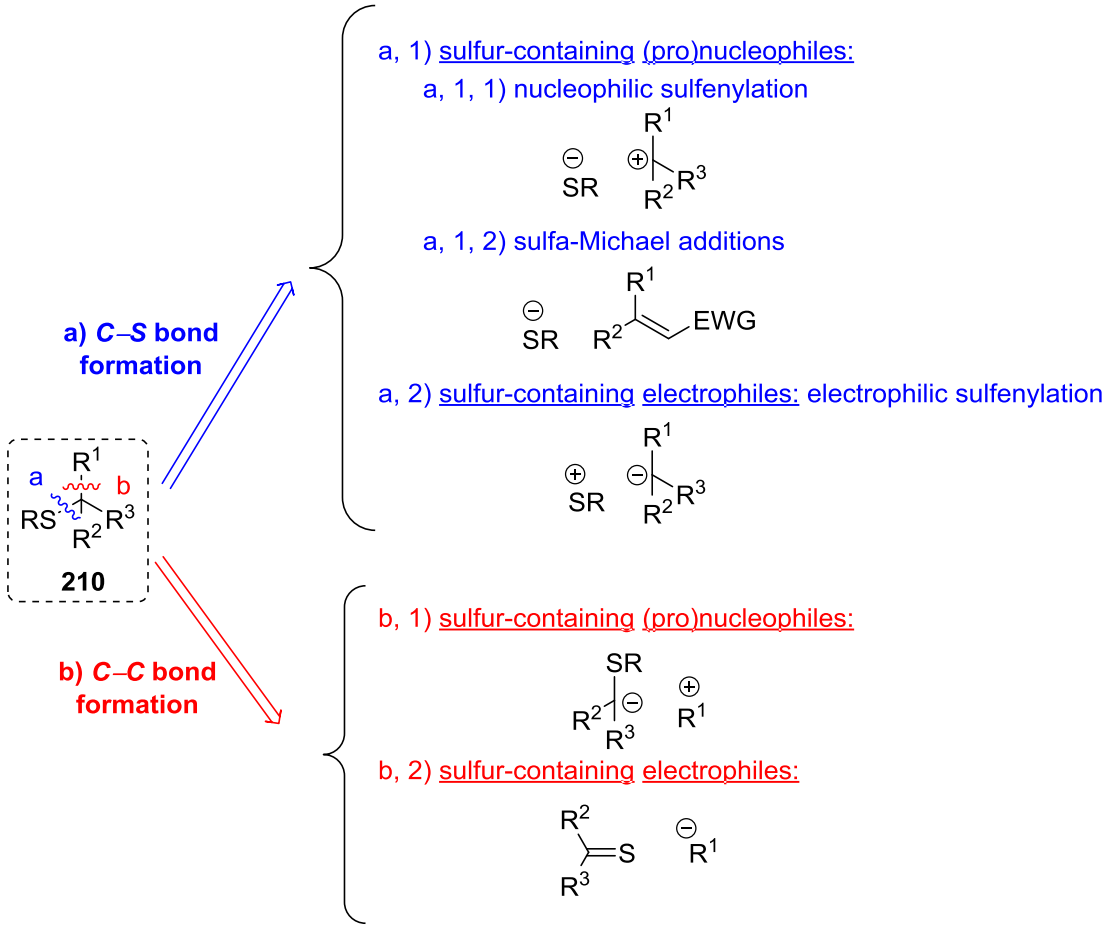
3. Asymmetric synthesis of α,α-disubstituted α-mercapto carboxylic acid derivatives

Asymmetric synthesis of α,α-disubstituted α-mercapto carboxylic acid derivatives

3.1. Introduction

As mentioned in the introduction, tertiary thiols are structural motifs present in some biologically active compounds and therefore play an important role in biological and medicinal chemistry. However, and in contrast to chiral secondary thiols, which have been the subject of many investigations, relatively few examples of asymmetric protocols for the preparation of tertiary thiols in optically pure form have been reported.[178] The known strategies to synthesize tertiary thiols can be classified into two groups (Scheme 48); in the first approach a new *C–S* bond is formed (Scheme 48, a), either through reaction of a sulfur-centered nucleophile with an electrophilic trisubstituted carbon center (nucleophilic sulfenylation, Scheme 48, a,1,1), or with a β,β-disubstituted activated alkene (sulfa-Michael addition, Scheme 48, a,1,2). Other alternative to synthesize tertiary thiols through the formation of a new *C–S* bond is the reaction between a carbanion and a sulfur electrophile (electrophilic sulfenylation, Scheme 48, a,2). Besides this, tertiary thiols can also be synthesized through the creation of a *C–C* bond (Scheme 48, b) by reacting either a secondary sulfur-containing nucleophile with the corresponding electrophile (Scheme 48, b,1) or by reaction of a carbanion with a thioketone (Scheme 48, b,2). This last alternative has not been developed mainly due to the high instability of thioketones. The asymmetric contributions to this field described until the beginning of our research are summarized in the following sections. It is worth noting that most of the examples involve reactions with carbonyl compounds.

[178] See ref. 57d, page, 19.



Scheme 48. Strategies for the asymmetric synthesis of tertiary thiols or derivatives.

3.1.1. Asymmetric synthesis of tertiary thiols or derivatives through *C–S* bond formation (a strategy)

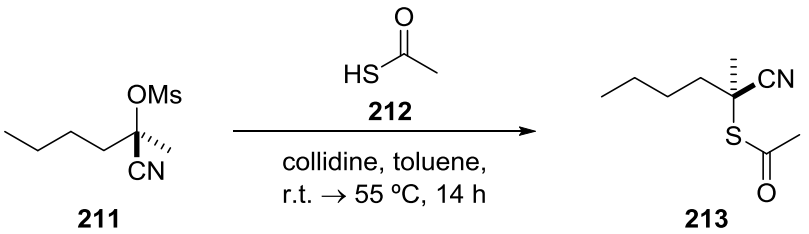
Following this strategy mainly nucleophilic and electrophilic sulfenylation reactions have been developed. However, a few examples based on the sulfa-Michael addition of sulfur nucleophiles to β,β-disubstituted activated alkenes have also been reported. All these contributions as well as their limitations are outlined below.

3.1.1.1. Nucleophilic sulfenylation

The examples described following this protocol involve most of them the use of enantiomerically pure alcohols, wherein after transformation of the hydroxy functionality into a good leaving group, react with a sulfur-based nucleophile through S_N2 displacement. Appropriate leaving groups employed in these cases are mesylates, cyclic sulfamidates and phosphonic esters. Other alternative is the ring-opening of epoxides with sulfur nucleophiles. Finally, a particular example of Mitsunobu reaction

has also been reported within this strategy. It is worth noting that all the examples of this methodology make use of enantiopure starting materials.

The first example of a nucleophilic sulfenylation that provides a tertiary thiol derivative was described by Effenberger and co-workers in 1999. They reported the nucleophilic substitution of mesyl activated cyanohydrin **211** with thioacetic acid **212** in toluene which afforded (*S*)-2-acetylthio-2-methylhexanenitrile **213** with high stereocontrol and good yield (Scheme 49).[179]



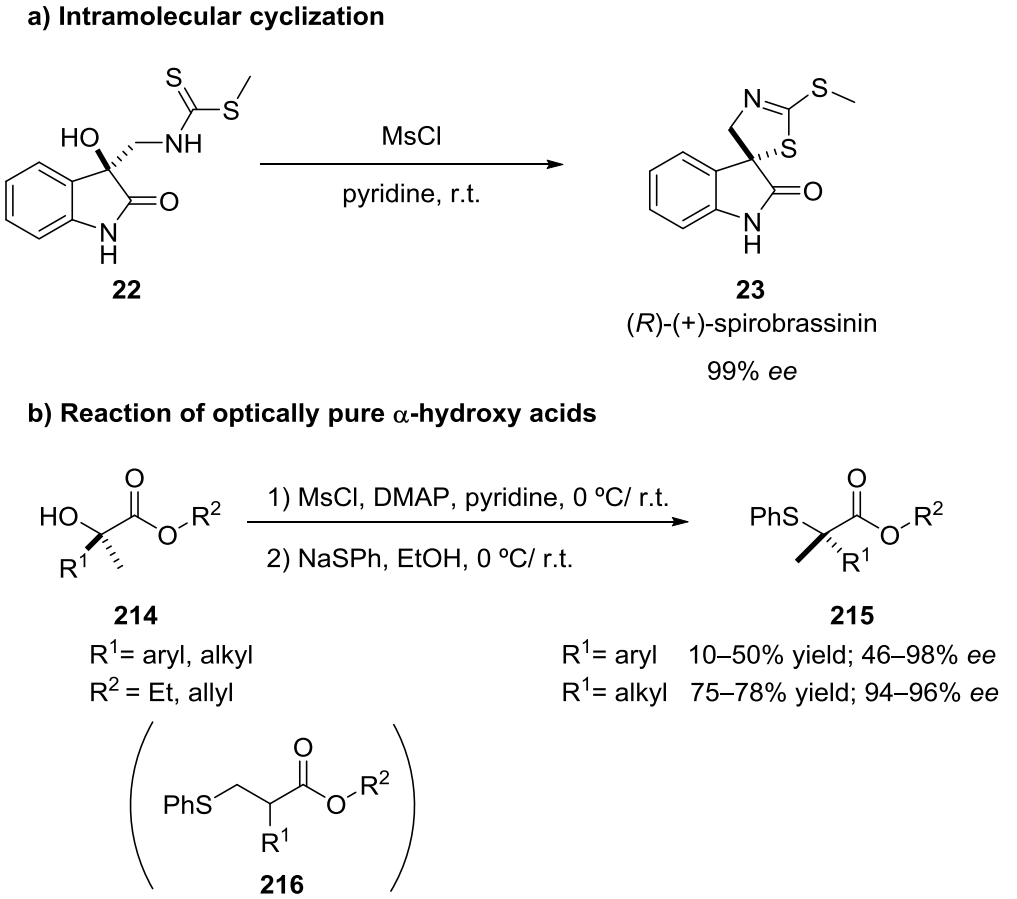
Scheme 49. Nucleophilic sulfenylation of derivative **211** with thioacetic acid. **Effenberger, 1999**.

Following the same strategy two other examples appeared later. One of them was published by Monde[180] and co-workers for the preparation of the non natural enantiomer of the antifungal (*S*)-(–)-spirobrassinin, by an intramolecular cyclization of dithiocarbamate **22** (Scheme 50, a). The reaction occurs with total stereocontrol, but the yield was not documented. The other example was published by Tunge[181] in 2010 and involves the transformation of α-aryl-α-hydroxy esters **214** (R^1= aryl) into tertiary thiol derivatives **215** by treating them with methanesulfonyl chloride followed by sodium thiophenolate (Scheme 50, b). The reaction proceeds in low yields, probably because elimination followed by conjugate addition to provide subproduct **216** occurs. Best results regarding reactivity and stereoselectivity were obtained when α,α-dialkyl hydroxy esters **214** (R^1= alkyl) were used.

[179] Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775.

[180] See ref. 54a, page 19.

[181] See ref. 54b, page 19.

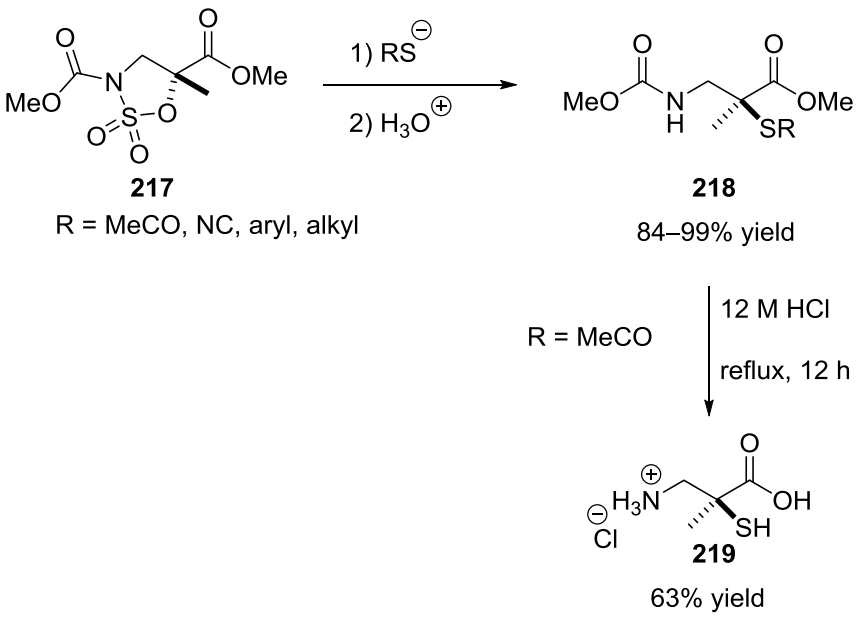


Scheme 50. Other examples of the use of mesylates for the obtention of tertiary thiol derivatives through nucleophilic sulfenylation. a) Synthesis of (*R*)-(+)-spirobrassinin **23**. **Monde, 2003**. b) Reaction of α-hydroxy esters **214** to obtained tertiary thioethers. **Tunge, 2010**.

Cyclic sulfamidates have also been successfully employed in nucleophilic sulfenylation of α-substituted β-amino acids. The group of Peregrina disclosed a protocol to this purpose by using cyclic sulfamidate **217** as starting material.[182] The method was satisfactorily applied to sulfur nucleophiles to produce α-sulfenyl β-amino acid derivatives that can be transformed into the corresponding tertiary thiol **219** upon acid treatment (Scheme 51).[183] Although different sulfur nucleophiles have been used, the procedure is limited to enantiomerically pure substrate **217**, and after hydrolysis β-mercapto amino acid **219** is obtained.

[182] Avenoza, A.; Busto, J. H.; Corzana, F.; Jiménez-Osés, G.; Peregrina, J. M. *Chem Commun*. **2004**, 980–981.

[183] See ref. 55, page 19.

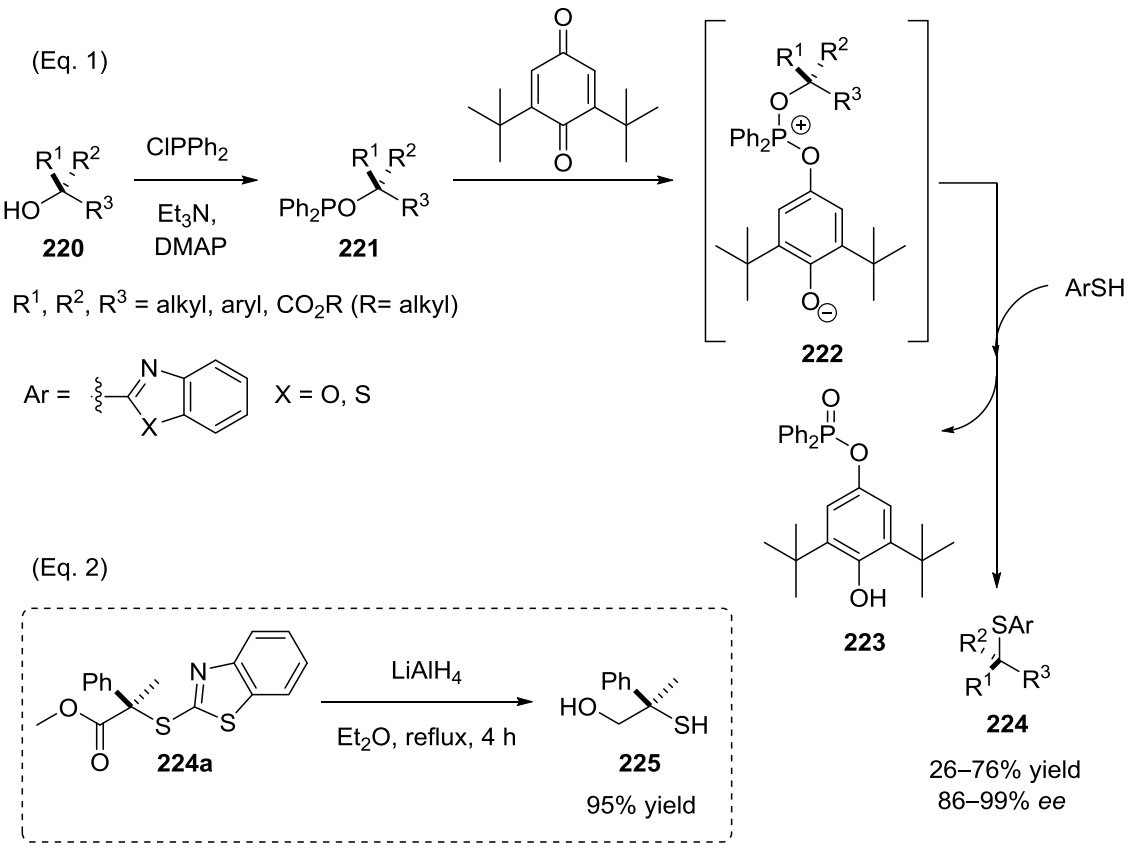


Scheme 51. Reaction of cyclic sulfamidate **217** with sulfur nucleophiles. **Peregrina, 2006**.

Mukaiyama and co-workers made use of the same idea to get sulfur-containing tetrasubstituted stereogenic carbons.[184] They transformed the tertiary alcohols **220** into alkyl diphenylphosphinites **221**. Before the S_N2 displacement, the phosphinite group should be activated through oxidation, with 2,6-di-*tert*-butyl-1,4-benzoquinone (Scheme 52, Eq. 1). The inversion reaction worked satisfactorily with a wide range of alcohols. Furthermore, treatment of adduct **224a** with $LiAlH_4$ provides the corresponding chiral tertiary thiol **225** (Scheme 52, Eq. 2).[185]

[184] a) See ref. 56a, page 19. b) Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 780–790.

[185] For the extension of this work by using phenoxydiphenyl phosphine and azide derivatives as oxidants, see: a) See ref. 56b, page 19. b) Kuroda, K.; Maruyama, Y.; Hayashi, Y. Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **2009**, *82*, 381–392. c) Mukaiyama, T. Kuroda, K.; Maruyama, Y. *Heterocycles* **2010**, *80*, 63–82.

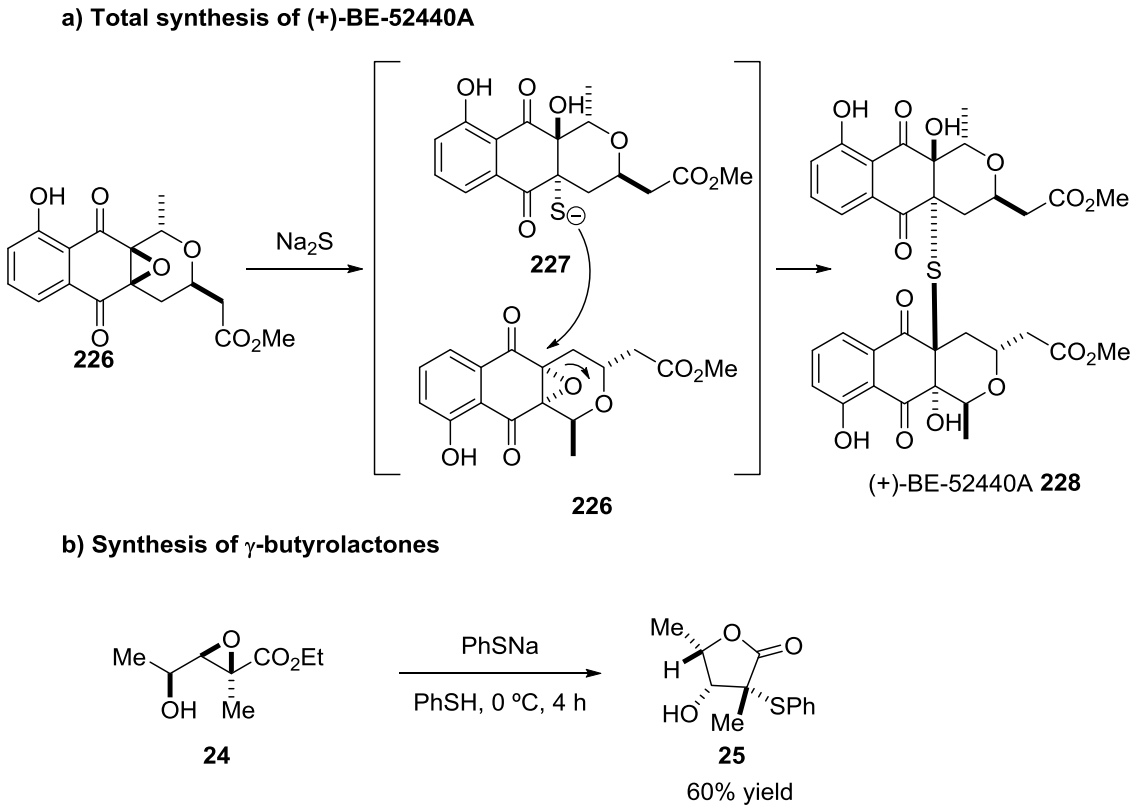


Scheme 52. Asymmetric synthesis of tertiary thiols. **Mukaiyama, 2005**.

On the other hand, and as mentioned before, the S_N2 epoxy-opening reaction with sulfur nucleophiles is another efficient alternative to yield tertiary thiols or thioethers. To the best of our knowledge, only two asymmetric protocols of this type have been reported (Scheme 53). Tatsuta and co-workers performed the total synthesis of (+)-BE-52440A **228** applying this strategy.[186] As depicted in Scheme 53 (a), the key step of the synthesis is the regioselective epoxy-opening dimerization of **226**, which occurs through a S_N2 reaction between the thiolate **227** and the epoxide **226**. Another example of this strategy was reported by Rodríguez in 2007, by treating epoxides **24** with sodium thiophenolate to provide γ-butyrolactones **25** in moderate yield (Scheme 53, b).[187]

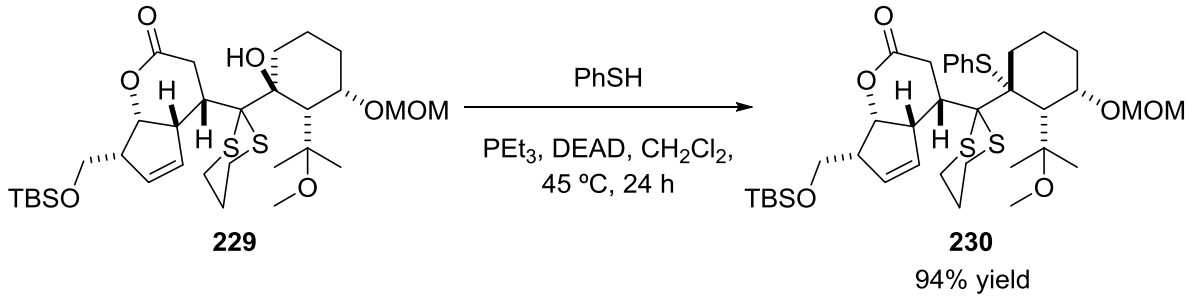
[186] See ref. 59, page 20.

[187] See ref. 58, page 20.



Scheme 53. Asymmetric S_N2 epoxy-opening reactions for the synthesis of tertiary thioethers. a) Key step of the synthesis of (+)-BE-52440A **228**. **Tatsuta, 2007**. b) Epoxide ring-opening with sodium thiophenolate in enantiomerically pure epoxides. **Rodríguez, 2007**.

Additionally, the Mitsunobu reaction is a suitable alternative to synthesize chiral secondary thiols; however, it is well known that sterically-hindered tertiary alcohols do not yield the corresponding sulfides under these conditions and the starting material or elimination products are obtained instead. Nevertheless, an exception has been reported in the literature by La Clair's group, who employed the Mitsunobu reaction starting from substrate **229** and thiophenol for the synthesis of **230** in 94% yield under mild conditions (Scheme 54).[188]



Scheme 54. Mitsunobu reaction for the synthesis of **230**. **La Clair, 2006**.

[188] La Clair, J. J. *Angew. Chem. Int. Ed*. **2006**, *45*, 2769–2773.

As a summary of this section we can say that the asymmetric synthesis of tertiary thiols through nucleophilic substitution is limited in scope to particular compounds as hydroxy derivatives or epoxides and requires starting enantiopure substrates.

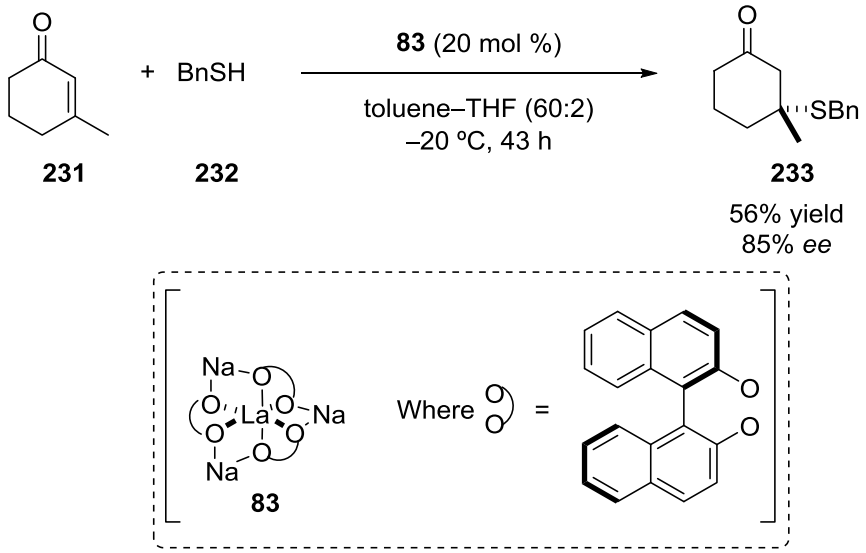
3.1.1.2. Sulfa-Michael addition

Other alternative to produce chiral tertiary thiols are sulfa-Michael additions to β,β-disubstituted Michael acceptors (Scheme 48, a,1,2). This strategy has been scarcely developed mainly due to problems associated to this type of acceptors, which are: 1) low reactivity, 2) low π-facial stereoselectivity and 3) equilibration of stereoisomers through an addition/elimination mechanism. As disclosed in Chapter 2, our group was able to perform a formal sulfa-Michael addition to β,β-disubstituted *N*-enoyl oxazolidin-2-thiones which affords β-mercapto carboxylic acid derivatives.[189] Apart from this, and to the best of our knowledge, only three asymmetric examples which afford tertiary thiol derivatives are found in the literature, which are promoted by metal-containing and metal-free catalysts and involve the use of cyclic enones, which are conformationally restricted Michael acceptors, and β-substituted nitroalkene acceptors, both known as reactive Michael acceptors.

As mentioned in the introduction, the first example of these sulfa-Michael additions was described by Shibasaki and co-workers by using heterobimetallic asymmetric complexes **83**. They reported the conjugate addition of benzyl thiol to cyclic enone **231**, to provide tertiary thioether **233** in relatively good enantioselectivity, but moderate yield (Scheme 55).[190] As far as we know, this represents the first example of a catalytic enantioselective synthesis of tertiary thiols or derivatives.

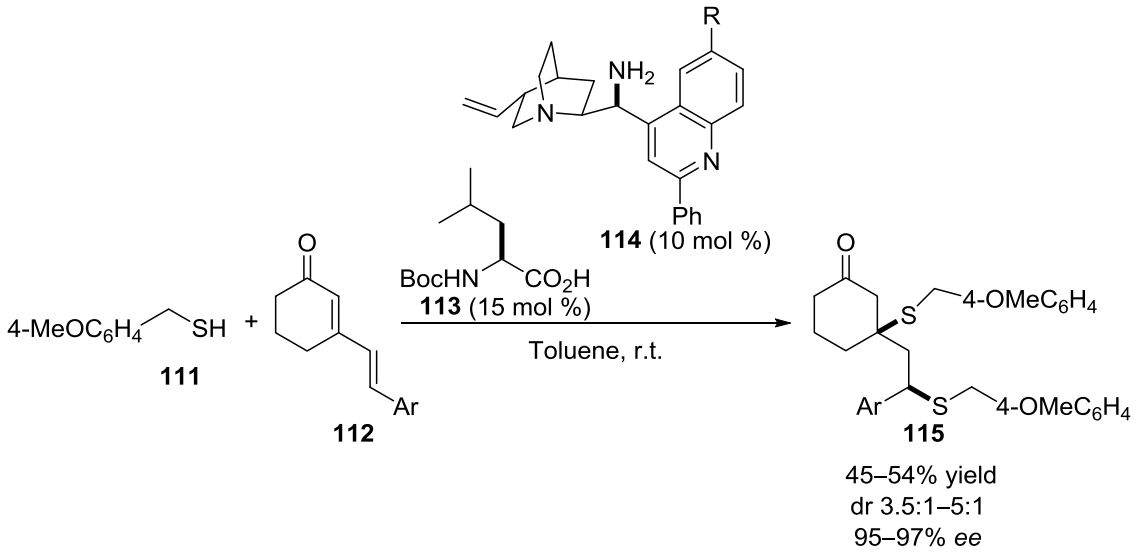
[189] See ref. 145b and c, page 50.

[190] See ref. 103, page 37.



Scheme 55. Metal-catalyzed sulfa-Michael addition. **Shibasaki, 1998**.

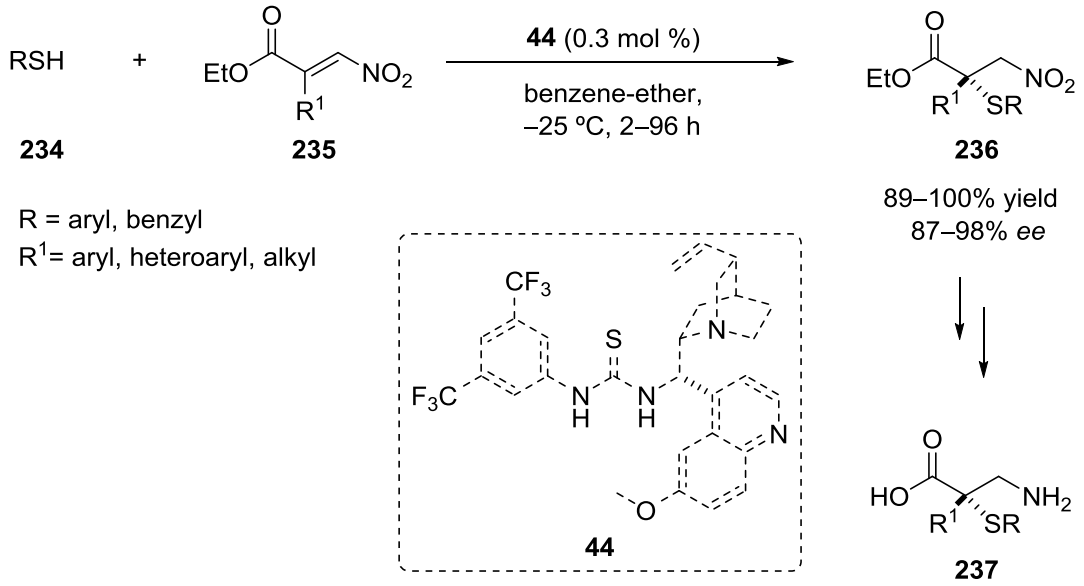
A second example of these sulfa-Michael additions by using cyclic enones was reported by Melchiorre's group in 2012. Although initially they described the 1,6-sulfa-Michael addition of thiols **111** to cyclic dienones **112**, then they realized that the α,β-unsaturated carbonyl compounds obtained after this reaction could be used to perform a subsequent 1,4-addition by the use of a large excess (12 eq.) of thiol. Following this, adducts **115** with moderate yield and diastereocontrol, but high enantioselectivity, were produced (Scheme 56).[191] After 48 h of reaction time the conversion was only partial, that explaining why the yield of the reaction did not go beyond 54%.



Scheme 56. The 1,6- and 1,4-addition of thiols to cyclic dienones. **Melchiorre, 2012**.

[191] See ref. 143, page 49.

Another interesting alternative to solve the usual problems of the conjugate additions to β,β-disubstituted activated alkenes was published in 2009 by the group of Xiao (Scheme 57). They reported the organocatalyzed addition of different thiols to a wide variety of β,β-disubstituted nitroalkenes as Michael acceptors obtaining satisfactory results. In this case the inherent low reactivity of the β,β-disubstituted Michael acceptors is compensated by the incorporation of the electron-withdrawing ethoxy carbonyl group as β-substituent. The reaction was successfully applied to prepare α-arylthio-β-amino acids preserving the enantiomeric purity.[192]



Scheme 57. Organocatalyzed sulfa-Michael addition of thiols to trisubstituted nitroalkenes. **Xiao, 2009**.

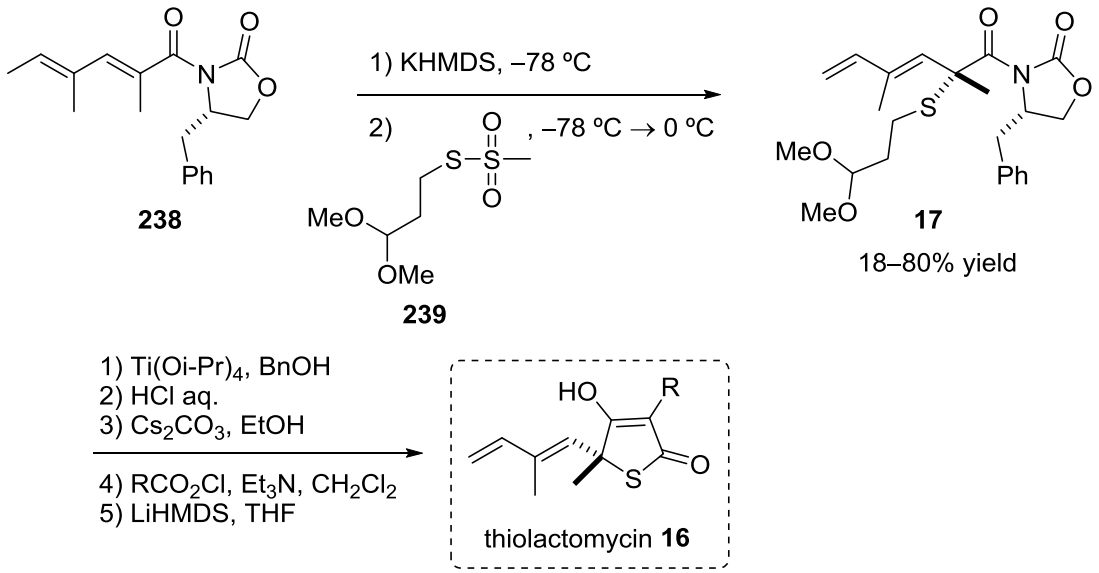
Although sulfa-Michael additions to β,β-disubstituted Michael acceptors are direct reactions to produce tertiary thiols, even today are one of the hot topics in organic chemistry. Nonetheless some examples have been described, but all of them make use of particular electrophiles.

3.1.1.3. Electrophilic sulfenylation

The asymmetric electrophilic sulfenylation is an important strategy for the construction of chiral tertiary thiols and has been deeply investigated. Although most of the examples are Brønsted base-catalyzed reactions, three protocols of metal catalysis and an example of the use of chiral auxiliaries have also been reported.

[192] See ref. 117b, page 42.

Ohata and co-workers documented the α-sulfenylation of α,α-disubstituted carbonyl compound **238** by using Evans' chiral auxiliary to prepare the key intermediate **17** for the synthesis of the biologically interesting thiolactomycin **16** (Scheme 58).[193]



Scheme 58. Asymmetric α-sulfenylation by using Evans' oxazolidinones. **Ohata, 2006**.

Regarding metal-catalyzed sulfenylations the described methods are summarized in Table 6. Two of them, the titanium(IV) catalyzed α-sulfenylation of β-ketoesters reported by Togni[194] (Table 6, entry 1), and the α-sulfenylation of 3-substituted oxindoles described by Feng[195] (Table 6, entry 3), make use of carbonyl compounds as starting material, and have been discussed in the introduction section. The third example was described by Denmark[196] and co-workers in 2011 and, to our knowledge, it is the only example of electrophilic sulfenylation which does not use a carbonyl compound as starting substrate (Table 6, entry 2). They performed the asymmetric sulfenylation of unactivated alkenes in the presence of the chiral selenophosphoramide catalyst **240** and the same sulfur source than Feng. An example of a trisubstituted olefin that leads to a tertiary thiol was presented in the work. The authors propose that the reaction with the double bond occurs first to produce the thiiranium ion and then the nucleophilic attack of the hydroxy group takes place to provide predominantly the constitutional isomer **241**. However, the reactivity was very low and therefore the reaction was run at room temperature, affording **241** in very low yield and enantioselectivity.

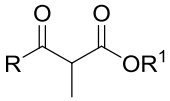
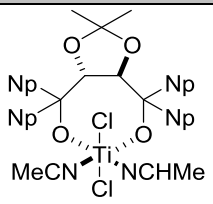
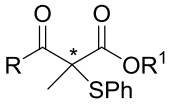
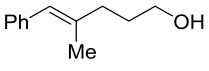
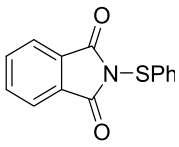
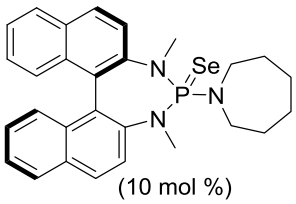
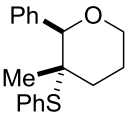
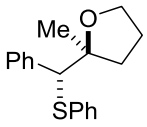
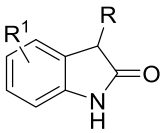
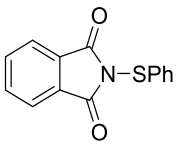
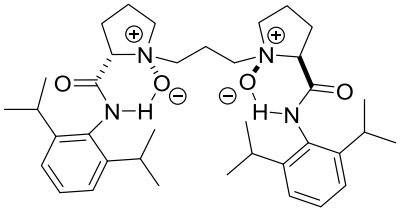
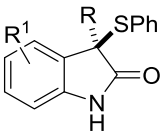
[193] See ref. 12, page 8.

[194] See ref. 66, 67 and 68, page 23.

[195] See ref. 69, page 24.

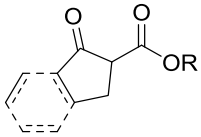
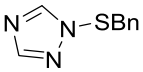
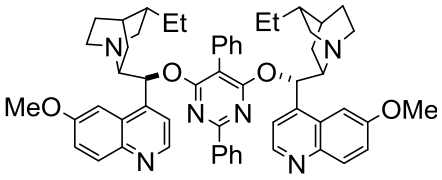
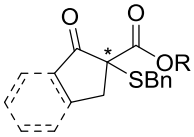
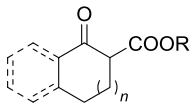
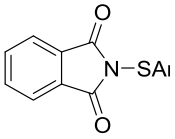
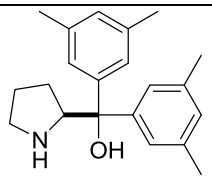
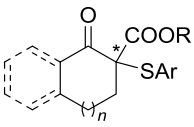
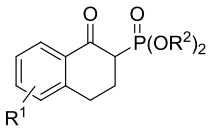
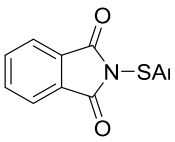
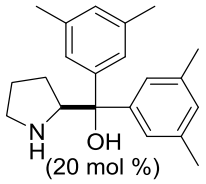
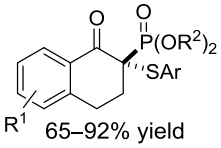
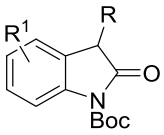
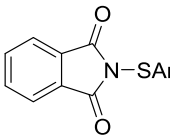
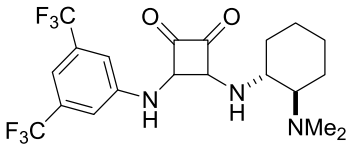
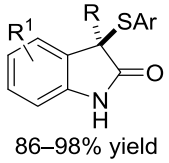
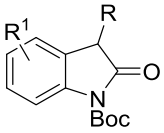
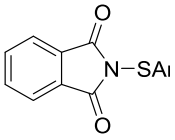
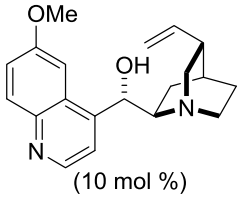
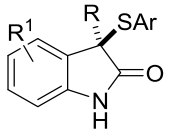
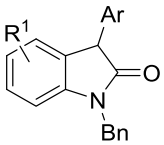
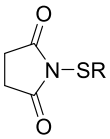
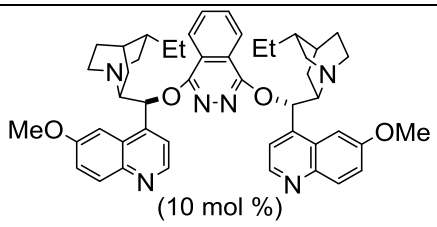
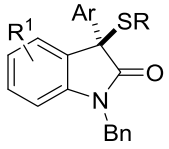
[196] Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc*. **2011**, *133*, 15308–15311.

Table 6. Metal-catalyzed sulfenylation reactions to afford tertiary thiol derivatives.

Entry Author	Carbonyl compound	Sulfur source	Catalyst	Product
entry 1 **Togni, 2005**		PhSCl	 Np = (*R*,*R*)-naphthalen-1-yl (5 mol %)	 82–95% yield 86–97% *ee*
entry 2 **Denmark, 2011**			 (10 mol %) **240**	 **241** 24%, 20% *ee*  **242** **241**:**242**; 18:1
entry 3 **Feng, 2012**			 (5 mol %) $Sc(OTf)_3$ (5 mol %)	 88–97% yield 93–99% *ee*

On the other hand, all the reported organocatalyzed electrophilic sulfenylations use carbonylic compounds as (pro)nucleophiles and chiral secondary or tertiary amines as Brønsted base catalysts. Therefore an important requeriment for the formation of the enolates is that the protons at the α position to the carbonyl must be relatively acidic, limiting thus the employed substrates to β-ketoesters, β-ketophosphonates and 3-substituted oxindoles. The results published in this field are in general very successful and are compiled in Table 7. The pioneering example was reported by Jørgensen in

Table 7. Organocatalyzed α-sulfenylation reactions to afford tertiary thiol derivatives.

Entry Author	Carbonyl compound	Sulfur source	Catalyst	Product
entry 1 **Jørgensen, 2005**			 (10 mol %)	 66–95% yield 51–91% *ee*
entry 2 **Zhu, 2009**	 *n* = 0, 1		 (20 mol %)	 *n* = 0, 1 68–98% yield 79–97% *ee*
entry 3 **Zhu, 2011**			 (20 mol %)	 65–92% yield 80–90% *ee*
entry 4 **Enders, 2012**			 (5 mol %)	 86–98% yield 85–96% *ee*
entry 5 **Cheng, 2012**			 (10 mol %)	 83–99% yield 72–99% *ee*
entry 6 **Jiang, 2012**			 (10 mol %)	 72–98% yield 85–97% *ee*

2005, the α-sulfenylation of β-dicarbonyl compounds[197] (Table 7, entry 1). An important contribution in this field was disclosed by Zhu and co-workers in 2009, who developed prolinol derivatives catalyzed α-sulfenylations of β-ketoesters[198] (Table 7,

[197] See ref. 73, page 26.

[198] See ref. 80, page 29.

entry 2), and then, they extended the reaction to β-ketophosphonates[199] (Table 7, entry 3). Later in 2012, different groups, as those of Enders[200] (Table 7, entry 4), Cheng[201] (Table 7, entry 5) and Jiang[202] (Table 7, entry 6), employed 3-substituted oxindoles as substrates.

As a summary of this section we can highlight that although the most investigated option for the asymmetric synthesis of tertiary thiols through *C–S* bond formation has been the electrophilic sulfenylation, almost all the cases are limited to compounds that bear relatively acidic protons at α position of the carbonyl group. Furthermore, as mentioned in the introduction, in general, electrophilic sulfenylations are reactions with not very good atom economy, because part of the electrophilic sulfur reagent is lost as waste in the reaction.

3.1.2. Asymmetric synthesis of tertiary thiols or derivatives through *C–C* bond formation (b strategy)

The second approach for the synthesis of tertiary thiols is to form a new *C–C* bond through a stereoselective reaction of a sulfur-containing (pro)nucleophile and the appropriate electrophile. Following this strategy alkylations, acylations, arylations, aldol/Mannich reactions, Michael additions, aminations and Diels-Alder reactions starting from a secondary sulfur-based substrate have been described. The pioneering examples were based on the use of enantiopure starting substrates and with the advent of asymmetric catalysis some examples of metal and metal-free catalyzed reactions were developed.

In 1987, Kellog[203] applied the strategy of self-reproduction of chirality developed by Seebach,[204] and described the asymmetric synthesis of tertiary thiols starting from secondary α-mercaptocarboxylic acids **243**. To the best of our knowledge this represents the first asymmetric synthesis of tertiary thiols. Secondary thiols **243** react first with pivalaldehyde **244**, providing a separable mixture of *cis* and *trans* 1,3-oxathiolan-4-ones **245**. After separation, the enolate of the major diastereomer **245** (*cis*-**245**) was generated and reaction with the electrophile E occurred controlled by the *tert*-butyl group. As different electrophiles were tested, examples of various reaction types such as alkylations, Michael-additions and aldol reactions were developed. The obtained

[199] See ref. 81, page 29.

[200] See ref. 82a, page 29.

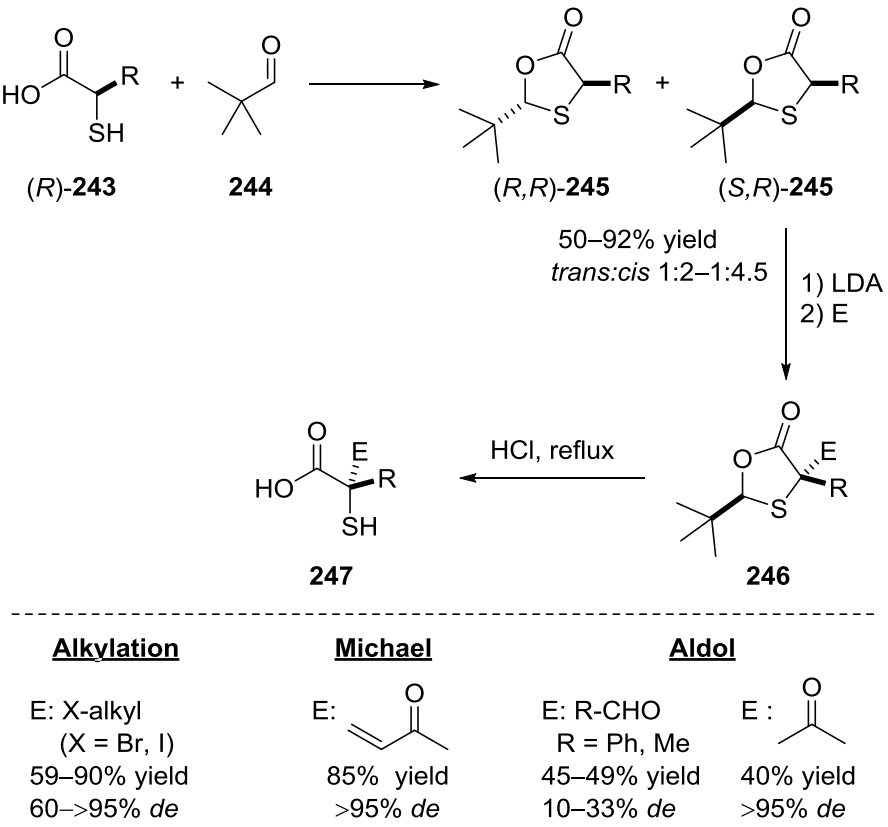
[201] See ref. 82b, page 29.

[202] See ref. 82c, page 29.

[203] Strijtveen, B.; Kellog, R. M. *Tetrahedron* **1987**, *43*, 5039–5054.

[204] Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.

results are compiled in Scheme 59. Very good yields and diastereomeric ratios were observed in alkylations and Michael reactions. However, in the case of the aldol reaction, although diastereoselectivity was very good for acetone, yields were moderate and very poor chemical and stereochemical results were obtained with aldehydes. Hydrolysis of the resulting adducts **246** produced enantiomerically enriched tertiary thiols **247**. Later, Townsend and co-workers applied this strategy to the synthesis of thiolactomycin starting from (2*S*)-thiolactic acid through an aldol reaction.[205]

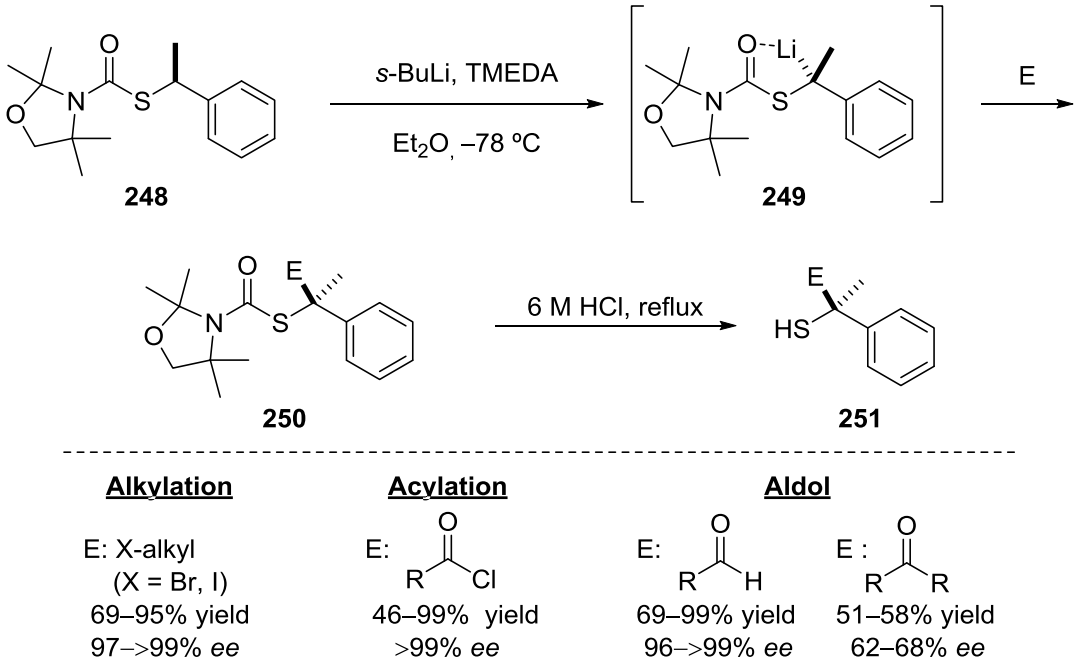


Scheme 59. Synthesis of enantiomerically enriched tertiary thiols. **Kellog, 1987**.

Ten years were needed for the publication of the next work on asymmetric synthesis of tertiary thiols through *C–C* bond formation. Hoppe and co-workers developed a protocol of alkylation, acylation and aldol reaction in 1997 using enantiomerically pure benzylic thiocarbamate **248**. The lithium derivative **249** formed by deprotonation was configurationally stable at –78 ºC and after electrophilic substitution, the corresponding adducts **250** were afforded in general in high yields and

[205] See ref. 11, page 8.

stereoselectivity, except in the case of ketones. Thiols **251** were efficiently produced by acid hydrolysis (Scheme 60).[206]



Scheme 60. Electrophilic substitution of α-sulfenylated organolithium compounds. **Hoppe, 1997**.

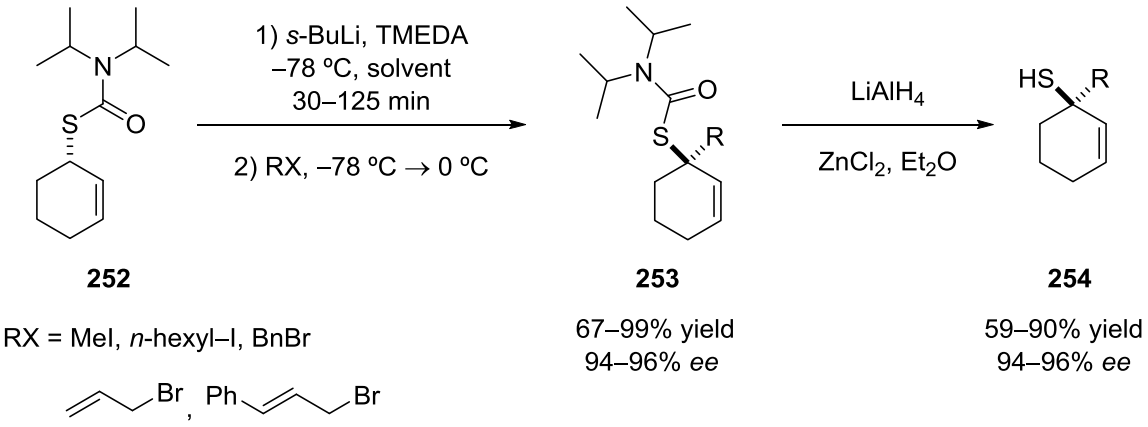
The methodology was next extended by the same authors to cyclohexenyl thiocarbamate **252** and different electrophilic reagents. The corresponding free tertiary thiol derivatives **254** were obtained in this case by treating the adducts **253** with lithium aluminium hydride (Scheme 61).[207] Some years later, in 2006, Gleason developed a synthetic application of this type of alkylations to synthesize α-quaternary carboxylic acids or α-quaternary primary alcohol derivatives,[208] and β-amino acids or β-amino alcohols.[209]

[206] a) Hoppe, D.; Kaiser, B.; Stratmann, O.; Fröhlich, R. *Angew. Chem. Int. Ed*. **1997**, *36*, 2784–2786. For the extension of the work, see: b) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Chem. Eur. J*. **2001**, *7*, 423–435.

[207] a) Marr, F.; Frölhlich, R.; Hoppe, D. *Org. Lett*. **1999**, *1*, 2081–2083. b) Marr, F.; Hoppe, D. *Org. Lett*. **2002**, *4*, 4217–4220. c) Marr, F.; Frölhlich, R.; Wibbeling, B.; Diedrich, C.; Hoppe, D. *Eur. J. Org. Chem*. **2002**, 2970–2988.

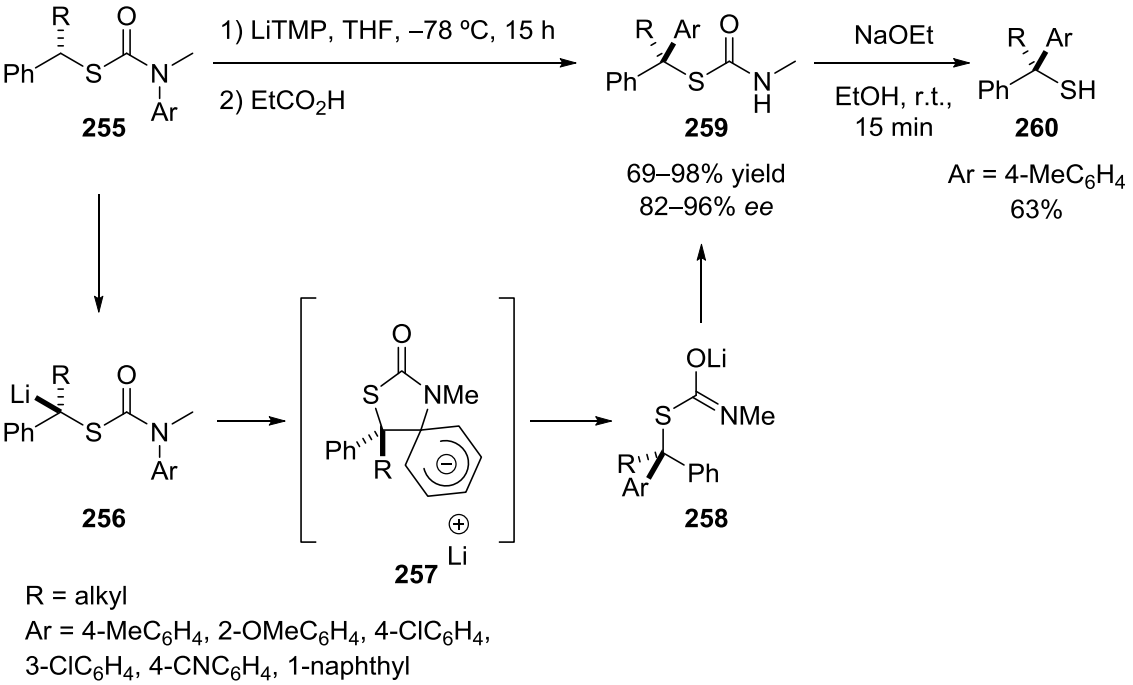
[208] Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett*. **2006**, *8*, 1359–1362.

[209] Tiong, E. A.; Gleason, J. L. *Org. Lett*. **2009**, *11*, 1725–1728.



Scheme 61. Electrophilic alkylation of α-sulfenylated organolithium compounds. **Hoppe, 1999**.

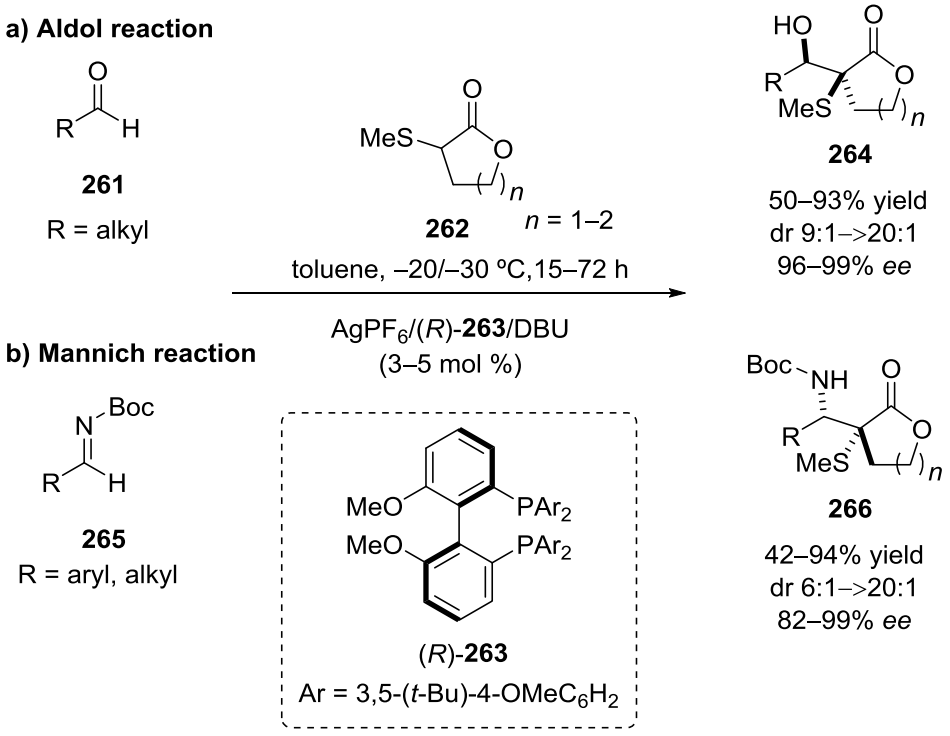
Arylation of sulfur-containing (pro)nucleophiles has also been reported as an efficient protocol to access tertiary thiols. Clayden and co-workers published a particular rearrangement of lithiated thiocarbamates **256**, which follows this strategy. The intramolecular migration of the *N*-aryl ring proceeds as depicted in Scheme 62, with retention of stereochemistry, treating substrates **255** with lithium tetramethylpiperidine. Enantiomerically enriched thiols **260** were efficiently obtained by deprotecting compound **259** under mild conditions with sodium ethoxide (Scheme 62).[210]



[210] MacLellan, P.; Clayden, J. *Chem. Commun*. **2011**, *47*, 3395–3397.

Scheme 62. Lithium thiocarbamate rearrangements to synthesize tertiary thiols. **Clayden, 2011**.

After this, it was not until 2012 that Shibasaki and co-workers described the first catalytic example of asymmetric synthesis of tertiary thiols through *C–C* bond formation. α-Sulfanyl lactones **262** (Scheme 63) were chosen as sulfur containing (pro)nucleophiles to perform the aldol and Mannich reactions catalyzed by the Lewis acid $AgPF_6$ in combination with biphep-type ligand **263** and DBU. Firstly, the reaction was carried out with different aldehydes (Scheme 63, a).[211] The authors propose a cooperative catalytic system where the interaction between silver and the sulfanyl moiety produced *in situ* chemoselective activation of the α-sulfanyl lactone and therefore easier deprotonation with the Brønsted base (DBU), even in the presence of highly enolizable aldehydes. The resulting aldols **264** are obtained in good yield and excellent stereocontrol. Then, the strategy was extended to the Mannich reaction, using the same type of substrate and *N*-Boc-aldimines (Scheme 63, b).[212] In this case the reaction proceeds also satisfactorily obtaining β-amino-α-methylthio derivatives **266** in good yields and high stereocontrol.

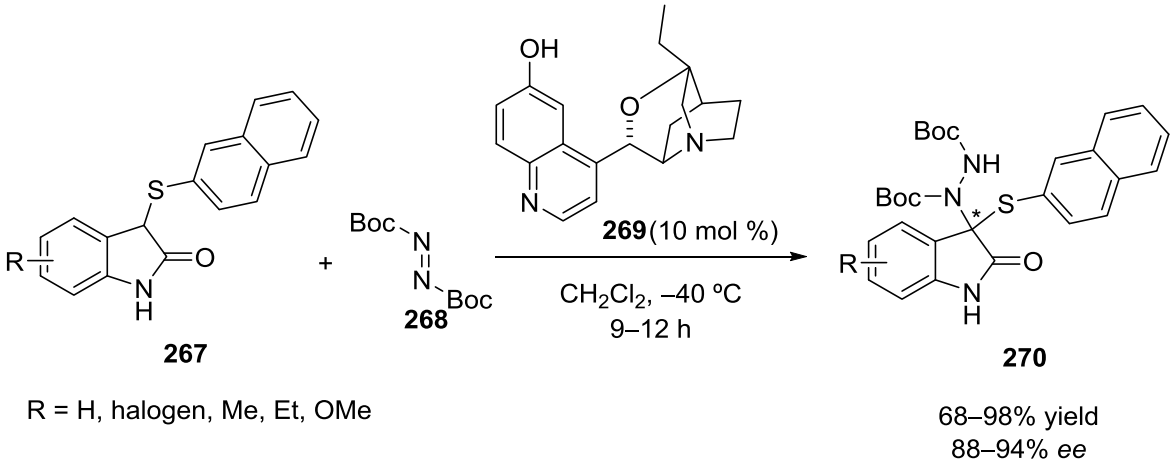


Scheme 63. Asymmetric metal-catalyzed reactions of α-sulfanyl lactones to yield tertiary thioethers. a) Asymmetric aldol reaction. b) Asymmetric Mannich reaction. **Shibasaki, 2012** and **2013**.

[211] Takechi, S.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2012**, *51*, 4218–4222.

[212] Takechi, S.; Kumagai, N.; Shibasaki, M. *Org. Lett*. **2013**, *15*, 2632–2635.

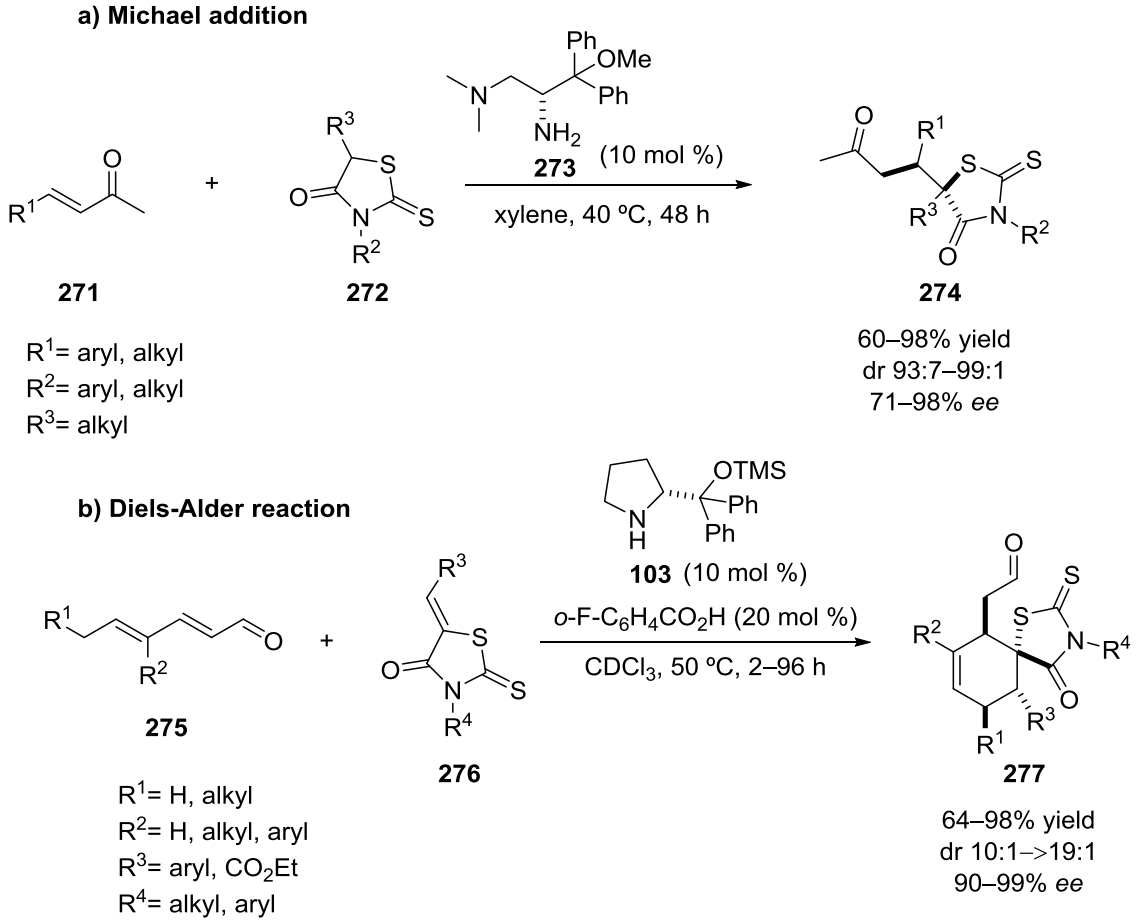
Besides alkylation/acylation/arylation and aldol/Mannich reactions of sulfur-containing (pro)nucleophiles, some particular catalytic examples of amination, Michael addition and Diels-Alder reactions of these (pro)nucleophiles have also been published. For example, Zhou described a new strategy of this type, based on the deprotonation of 3-thiooxindoles **267** and subsequent reaction with the electrophile di-*tert*-butyl azodicarboxylate **268** catalyzed by the Brønsted base **269**. The corresponding 3,3-disubstituted oxindoles featuring two heteroatoms at the C3 position were produced with good to high yields and high enantiocontrol (Scheme 64).[213]



Scheme 64. Asymmetric amination of 3-substituted oxindoles for the asymmetric synthesis of tertiary thioethers **270**. **Zhou, 2013**.

On the other hand, Ye and co-workers[214] used rhodanines as sulfur-based substrates in a Michael reaction with enones promoted by the bulky primary amine **273** as catalyst which additionally contains a tertiary amine moiety (Scheme 65, a). The corresponding tertiary thiol derivatives were obtained in good yield and very good stereoselectivity. Furthermore, the same group used rhodanine derivatives **276** as dienophiles to develop the aminocatalyzed Diels-Alder reaction with 2,4-dienals **275** that provided spirocyclic compounds **277** containing the rhodanine motif with high stereoselectivity (Scheme 65, b).[215]

[213] Zhou, F.; Zeng, X. -P.; Wang, C.; Zhao, X. -L.; Zhou, J. *Chem. Commun*. **2013**, *49*, 2022–2024.
[214] Fu, F.; Hu, H.; Gu, X.; Ye, J. *Org. Lett*. **2012**, *14*, 2038–2041.
[215] Zhu, K.; Huang, H.; Wu, W.; Wei, Y.; Ye, J. *Chem. Commun*. **2013**, *49*, 2157–2159.



Scheme 65. Rhodanines as sulfur-based (pro)nucleophiles. a) Conjugate addition of rhodanines to α,β-unsaturated ketones. b) Diels-Alder reaction of rhodanines and 2,4-dienals. **Ye, 2012** and **2013**.

All the previous examples make use of a new *C–C* bond formation to access tertiary thiols or thioethers. Nevertheless, very recently, Jørgensen's group published a complementary protocol which combines both strategies, the simultaneous formation of *C–S* bond and *C–C* bond and involves a thio-Diels-Alder reaction.[216] This example has been discussed in detail in the introduction (Scheme 19, page 48)

In this section the reported examples for the asymmetric synthesis of tertiary thiols or derivatives through *C–C* bond formation have been disclosed. Some different reactions have been applied for that; even so, this strategy has been scarcely studied and thus general protocols are still needed. Furthermore, although more recent contributions are based on the use of catalysts for chirality induction, most of the methods make use of enantiomerically pure substrates or provide thioethers, whose deprotection to the free thiol is not so trivial. Therefore, the development of new strategies to obtain free tertiary thiols is still desirable.

[216] See ref. 141, page 47.

3.2. Michael addition of 5*H*-thiazol-4-ones to nitroolefins

3.2.1. Working hypothesis and synthetic plan

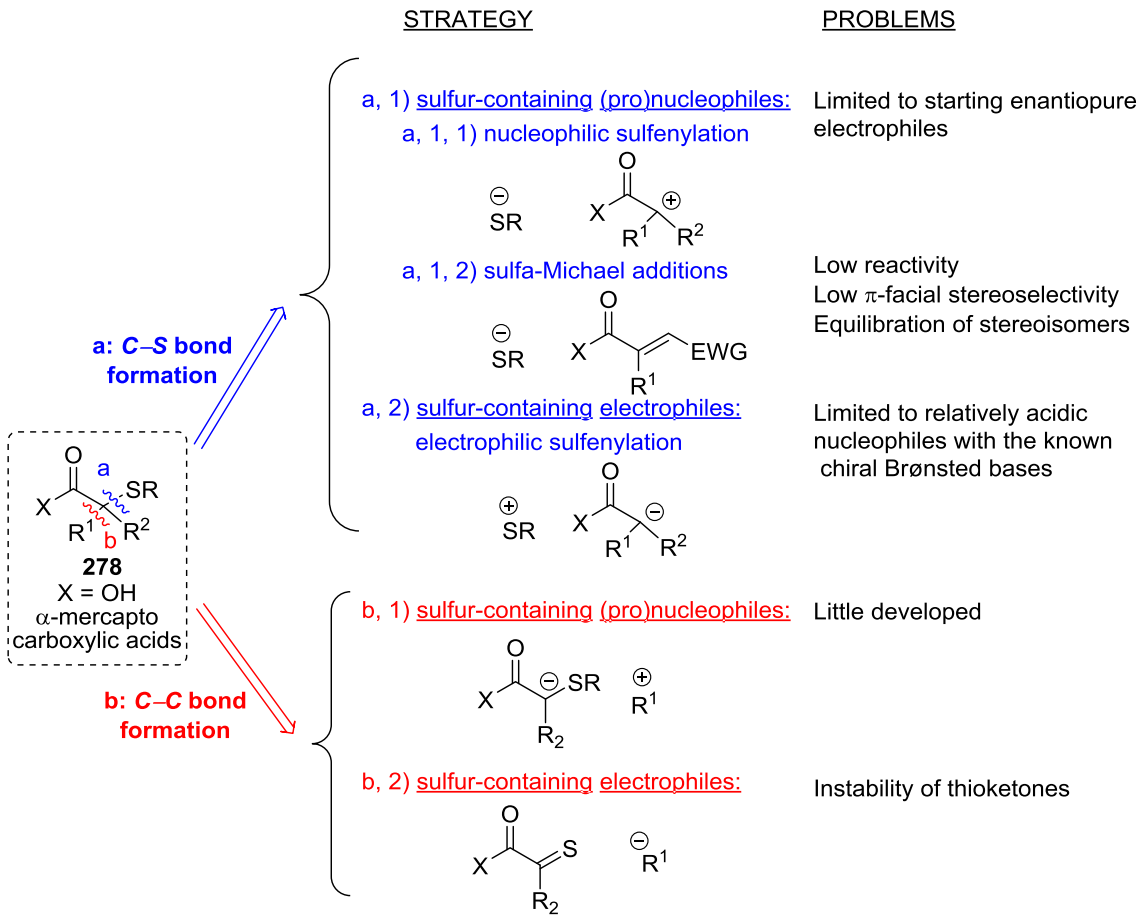
As mentioned before, only few methodologies for the catalytic enantioselective synthesis of tertiary thiols or derivatives can be found in the literature. The inherent difficulty associated with the stereoselective construction of tetrasubstituted stereogenic centers is probably the reason that accounts for the existing limited number of studies.[217] In connection with the efforts of our research group directed towards the asymmetric synthesis of organosulfur compounds, that is, β,β-disubstituted β-mercapto carboxylic acids[218] and thiiranes,[219] we focused on the catalytic asymmetric synthesis of α-mercapto carboxylic acids of type **278** (Scheme 66).

Scheme 66 shows the possible disconnections to access these compounds involving either *C–S* and *C–C* bond formation, as well as the limitations of each one according to the published precedents. Within the possibilities involving *C–S* bond formation, one option would be nucleophilic sulfenylation, which is mainly limited to starting enantiopure electrophiles; other alternative would be sulfa-Michael addition to a β,β-disubstituted Michael acceptor, which, as said before, involves different problems as low reactivity, low π-facial stereoselectivity and equilibration of stereoisomers through an addition/elimination mechanism. Finally the last possibility regarding *C–S* bond formation would be electrophilic sulfenylation, which in turn, with the known tertiary amine containing chiral Brønsted bases is limited to relatively acidic donors as 1,3-dicarbonylic compounds and related.

[217] See ref. 57, page 19.

[218] See ref. 145b and c, page 50.

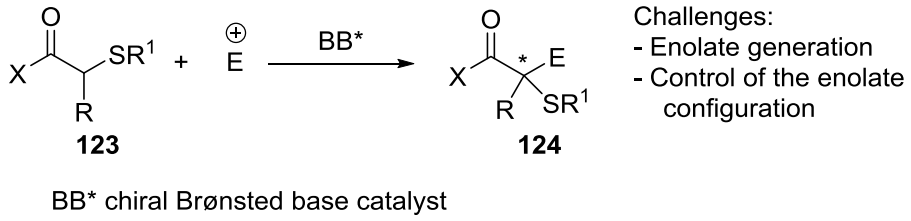
[219] See ref. 177, page 80.



Scheme 66. Strategies for the synthesis of α-mercapto carboxylic acids **278**.

On the other hand, regarding *C–C* bond formation only the reaction of sulfur-containing (pro)nucleophiles with appropriate electrophiles seems to be feasible, a strategy which has been little developed; because the reaction of nucleophiles with thioketones exhibits also different problems as disclosed in the introduction of this chapter. On this basis we focused on the b,1 disconnection (Scheme 66) and therefore on the investigation of an organocatalytic protocol for the reaction of sulfur-containing (pro)nucleophiles of type **123** with appropriate electrophiles in the presence of a chiral Brønsted base as catalyst (Scheme 25).

Approach to tertiary thiol derivatives: α,α-disubstituted α-thiofunctionalized carboxylic acids



Scheme 67. Working hypothesis for stereoselective synthesis of α,α-disubstituted α-thiofunctionalized carboxylic acid derivatives.

The main challenges of this proposal are, on the one hand, the selection of the appropriate nucleophile and electrophile; secondly, the search for conditions for enolate generation; and thirdly, the control of the enolate configuration which would be key for stereochemical success.

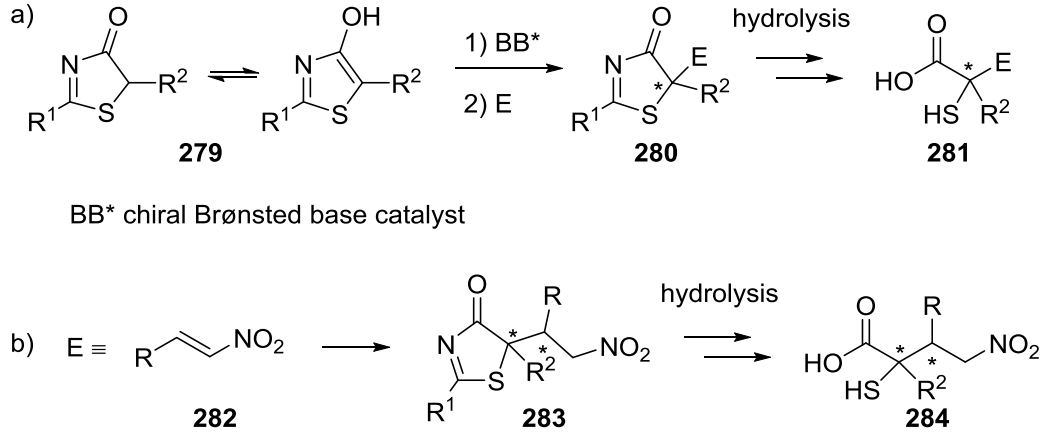
At this point, and after a comprehensive literature search we found 5*H*-thiazol-4-ones **279** (Scheme 68), which as far as we know, and in sharp contrast to the structurally related 5*H*-oxazol-4-ones[220] and 4*H*-oxazol-5-ones (azlactones),[221] have never been used in asymmetric synthesis. Interestingly, in 2011 Weiß, Beckert and Fabian[222] reported an ^{1}H NMR study of these compounds in solution which shows that they exist in equilibrium between the two tautomeric forms (Scheme 68, a). If so, this would facilitate deprotonation and further enolate generation. In addition, and due to the cyclic nature of these compounds, the geometry of the resulting enolate would be fixed, thus facilitating the control of the stereoselectivity. Other factor that can affect stereocontrol

[220] For the use of 5*H*-oxazol-4-ones in the synthesis of α,α-branched α-hydroxy acids, see: Metal catalysis: a) Trost, B. M.; Dogra, K.; Franzin, M. *J. Am. Chem. Soc*. **2004**, *126*, 1944–1945. b) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed*. **2012**, *51*, 7523–7527. c) Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed*. **2012**, *51*, 2776–2779. d) Trost, B. M.; Hirano, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 6480–6483. Organocatalysis: e) Misaki, T.; Takimotoa, G.; Sugimura, T. *J. Am. Chem. Soc*. **2010**, *132*, 6286–6287. f) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc*. **2011**, *133*, 5695–5697 g) Quiau, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett*. **2013**, *15*, 2358–2361. h) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. *Chem. Commun*. **2012**, *48*, 461–463. i) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal*. **2013**, *355*, 1505–1511.

[221] For reviews on 4*H*-oxazol-5-ones, see: a) Alba, A.-N. R.; Rios, R. *Chem. Asian J*. **2011**, *6*, 720–734. b) Mosey, R. A.; Fisk, J. S.; Tepe, J. T. *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762. For the sulfur analogs of azlactones, see: c) Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun*. **2010**, *46*, 300–302. d) Liu, X.; Deng, L.; Jiang, X.; Yan, W.; Liu, C.; Wang, R. *Org. Lett*. **2010**, *12*, 876–879. e) Liu, X.; Deng, L.; Song, H.; Jia, H.; Wang, R. *Org. Lett*. **2011**, *13*, 1494–1497. f) Liu, X.; Song, H.; Chen, Q.; Li, W.; Yin, W.; Kai, M.; Wang, R. *Eur. J. Org. Chem*. **2012**, 6647–6655.

[222] Täuscher, E.; Weiß, D.; Beckert, R.; Fabian, J.; Assumpçao, A.; Görls, H. *Tetrahedron Lett*. **2011**, *52*, 2292–2294.

is the nature of the R^1 group of the thiazolone, which could also be easily modified. Furthermore, hydrolysis of the resulting adducts would provide the α-mercapto carboxylic acids **281**, first goal of this research. This is a significant aspect of this proposal, since most of the known protocols for the synthesis of tertiary thiol derivatives, *vide supra,* provide thioethers and the obtention of free thiols from them is not a trivial transformation. On this basis we selected these thiazolones as pronucleophiles, and in a first instance nitroalkenes were chosen as electrophiles (Scheme 68, b). In this case an additional challenge would be the control of the diastereoselectivity together with enantioselectivity.



Scheme 68. a) General reaction of 5*H*-thiazol-4-ones with electrophiles and hydrolysis of the corresponding adduct. b) Proposed electrophile for first investigations.

3.2.2. Results and discussion

3.2.2.1. Catalyst screening

In order to check the validity of our hypothesis we began our study by evaluating several classical Brønsted bases for the reaction of the readily available thiazolone **285**[223] with the nitroolefin **282a** (Table 8).[224] Initially, the reaction was explored using some representative cinchona alkaloids such as, quinine **35** (entry 1), quinidine **36** (entry 2), 9-*epi*-quinine **287** (entry 3) and $(DHQ)_2PYR$ **288** (entry 4) in dichloromethane at –60 ºC. In all cases stereochemical results were disappointing with

[223] Grummt, U. -W.; Weiss, D.; Birckner, E.; Beckert, R. *J. Phys. Chem. A*. **2007**, *111*, 1104–1110.

[224] For a review on conjugate additions to nitroolefins, see: a) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627–2648. b) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601. c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem*. **2002**, 1877–1894.

poor diastereo- and enantioselectivities. Whereas quinine **35** and quinidine **36** produced total conversion after 20 h reaction time, 9-*eqi*-quinine **287** and $(DHQ)_2PYR$ **288** turned to be less reactive affording only less than 50% conversion after 48 h reaction time.

Next, on the basis of the pioneering studies of Takemoto and co-workers,[225] and subsequent seminal works by the groups of Jacobsen,[226] Soós,[227] Dixon,[228] and Connon[229] on bifunctional (thio)urea-tertiary amine catalysts,[230] we decided to test bifunctional catalyst **43**, **44** and **45**. However, as results in Table 8 show, catalyst **43** (entry 5) provided very low enantioselectivity (20% *ee*), although in quite good diastereoselectivity (83:17), whilst no stereochemical improvement was essentially observed with catalysts either **44** or **45** (entries 6 and 7), and even worst diastereoselectivities were attained. At this stage and, in view of the common strong substrate dependence in direct asymmetric *C–C* bond forming reactions catalyzed by Brønsted bases, focus to address this problem was turned to catalyst design.

[225] a) See ref. 45, page 15.

[226] Fuerst, D. E; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.

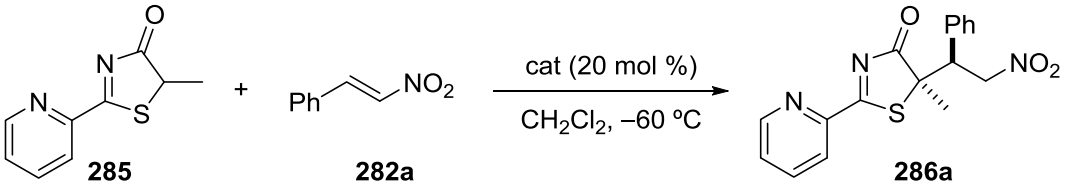
[227] See ref. 75a, page 27.

[228] See ref. 75b, page 27.

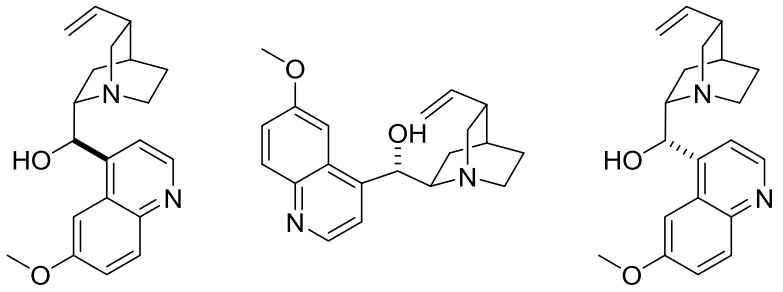
[229] See ref. 75c, page 27.

[230] See ref. 76, page 27.

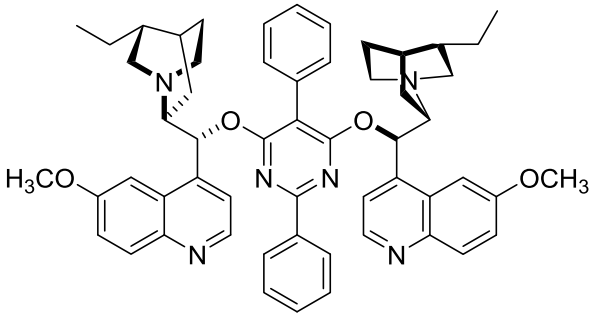
Table 8. Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-one **285** to nitrostyrene **282a**.[a]



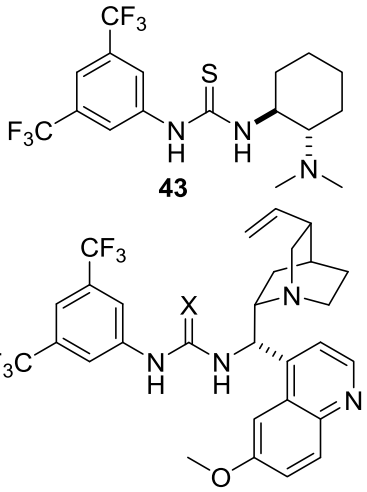
285 **282a** **286a**



Q **35** QN **36** 9-*epi*-Q **287**



(DHQ)$_2$PYR **288**



43

X = S **44**
X = O **45**

Entry	Catalyst	t (h)	Yield (%)[b]	dr[c]	*ee*[d]
1	Q	20	47	53:47	40
2	QN	20	60	75:25	-20
3	9-*epi*-Q	48[e]	27	58:42	12
4	(DHQ)$_2$PYR	48[e]	4	55:45	10
5	**43**	48	53	83:17	20
6	**44**	20	53	60:40	35
7	**45**	20	48	54:46	40

[a] Reaction conditions: **285** (0.3 mmol), **282a** (2 equiv., 0.6 mmol), catalyst (20 mol %), −60 ºC in CH_2Cl_2 (0.6 mL). [b] Yields of the isolated major isomer after column chromatography. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Less than 50% conversion related to the disappearance of the starting material.

Like catalyst **43**–**45**, most (thio)urea based Brønsted bases known to date display the 3,5-bis(trifluoromethyl)phenyl group in their structure, a key structural motif which was first introduced by Schreiner and Wittkopp in 2002 for hydrogen-bond catalysis.[231] Later, Zhong[232] and Schreiner[233] after an exhaustive study based on NMR- and IR-spectroscopy and mass-spectrometry together with DFT calculations suggested that the success of these catalysts may be attributed to the participation of three contiguous H-bond donors, both *N–H* bonds of the (thio)urea unit and the *ortho C–H* bond of the aryl group, during the electrophile activation event (Figure 22, a).

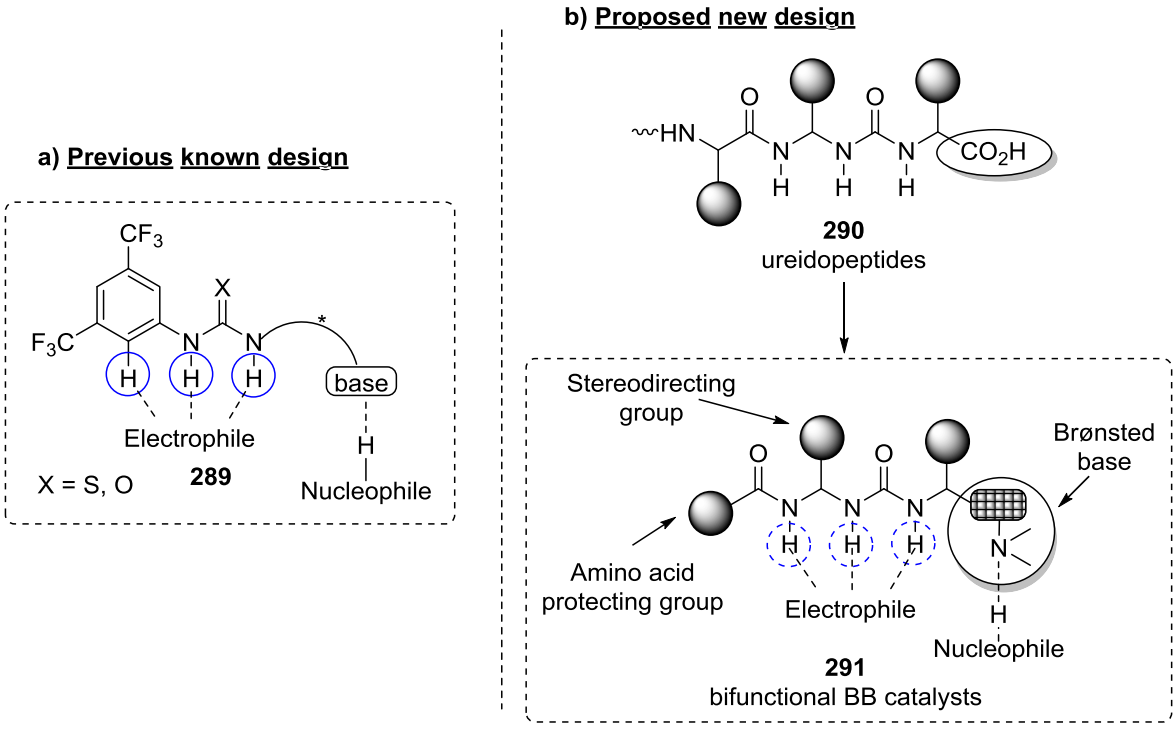


Figure 22. Ureidopeptide-based Brønsted bases. a) Previous known design. b) Proposed new design.

On the other hand, over the last years the efficacy of synthetic peptides for fine-tuning of reactivity and selectivity has been proved in several significant synthetic transformations.[234] In this context, ureidopeptides **290** (Figure 22, b), are peptidomimetics that display an urea unit in place of an amide bond and have been

[231] a) Schreiner, P. R.; Wittkopp, A. *Org. Lett*. **2002**, *4*, 217–220. b) See ref. 31d, page 13. c) Kotice, M.; Schreiner, P. R. in *Hydrogen Bonding in Organic Synthesis*, Ed. Pihko, P. M., **2009**, Wiley-VCH, Weinheim, pp 141–351.

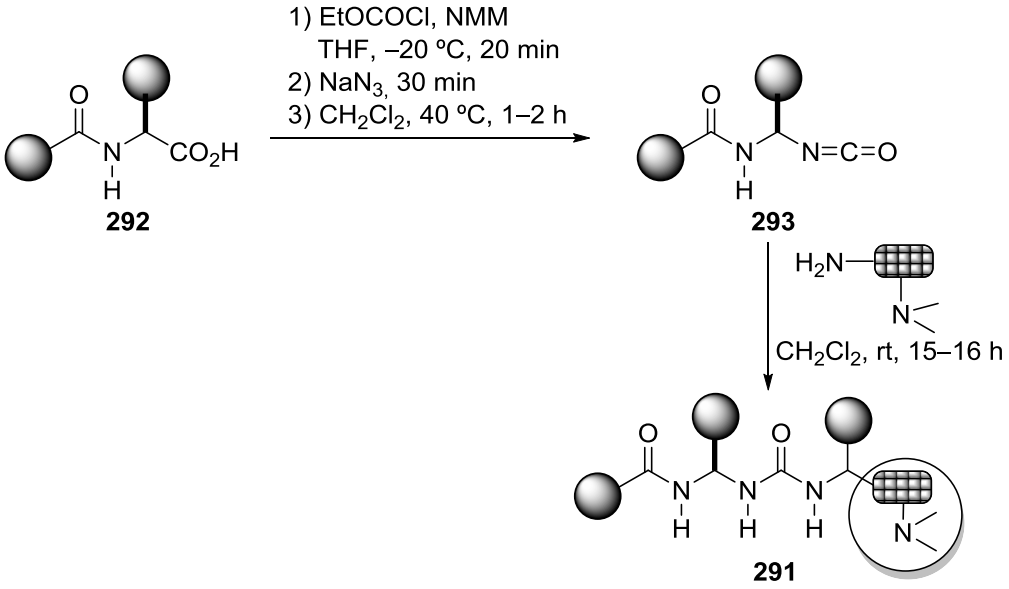
[232] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682–2685.

[233] Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem*. **2012**, 5919–5927.

[234] a) Wennemers, H. *Chem.Commun*. **2011**, *47*, 12036–12041. b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev*. **2007**, *107*, 5759–5812.

recognized for their ability to develop hydrogen bond interactions.[235] Based on this observation in our research group it was considered that replacement of the α-amino acid terminus by a Brønsted base in ureidopeptides **290** should provide new bifunctional Brønsted base catalysts **291** with several sites amenable for structural modification: the Brønsted base, the stereodirecting group between two *N–H*s and finally the protecting group of the amino acid. Therefore, from this design several different classes of ureidopeptide-based catalysts could be readily accessible from the available pools of both α-amino acids (or peptides) and primary-tertiary diamines. Additionally, these catalysts display as new features the presence of an *N,N′*-diacyl aminal unit in place of the bis(trifluoromethyl)phenyl group, and an urea moiety, providing three hydrogen bond donors that are in close proximity to an additional stereodirecting group, offering thus the opportunity of multiple H-bond interactions, increasing therefore the number of coordination patterns with the reaction substrates.

So, as part of a more general research project, our group focused on this new catalyst design with the aim of checking the efficiency of these new catalysts in different transformations. The proposed general synthetic sequence for these catalysts is outlined in Scheme 69, and involves carbamate protection of the amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base.

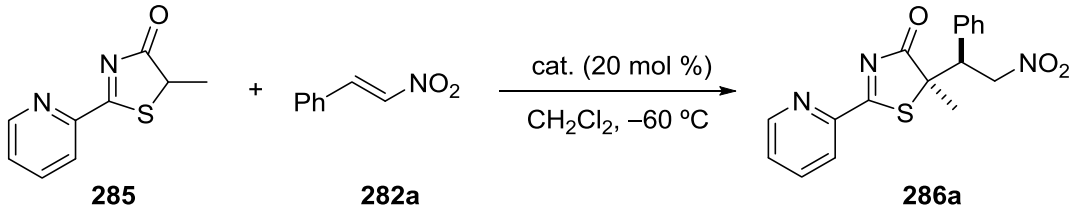


Scheme 69. Ureidopeptide-based Brønsted base bifunctional catalyst preparation.

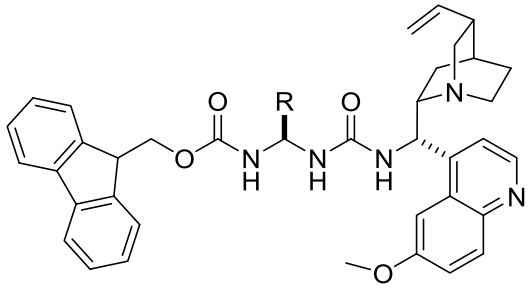
[235] a) Sureshbabu, V. V.; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705. b) Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222. c) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J. -P.; Marraud, M.; Guichard, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1893–1895. d) Semetey, V.; Hemmerlin, C.; Didierjean, C.; Schaffner, A. -P.; Giner, A. G.; Aubry, A.; Briand, J. -P.; Marraud, M.; Guichard, G. *Org. Lett.* **2001**, *3*, 3843–3846.

The first synthesis and optimization of the catalysts of this type were carried out by López and Diosdado from our research group. Following this approach catalyst **294**–**302** were prepared from several α-amino acids and 9-*epi*-9-amino-9-deoxyquinine alkaloid and explored in the reaction of thiazolone **285** and nitroolefin **282a** (Table 9). We first evaluated the influence of the substituent on the aminal moiety by comparing the results obtained with catalysts **294**–**297** (entries 1–4). These results clearly show that the nature of this substituent is really significant being the best chemical and stereochemical results obtained with the *tert*-leucine-derived catalyst **297** (entry 4). At this point, we selected catalyst **297** for further optimization and decided to change the carbamate group to test its influence. Likewise **298**–**301** *tert*-leucine derivatives were prepared and checked in the previous reaction. Benzyl and phenylethyl carbamates **298** and **299** (entries 5 and 6) afforded good diastereoselectivity, but unsatisfactory results regarding enantioselectivity (40% *ee*) and long reaction times were needed to obtain complete conversion. Further improvements were observed with naphthyl and anthracenyl carbamates **300** and **301** (entries 7 and 8), being the best results those obtained with catalyst **301**. Finally hydrogenolysis of catalyst **301** afforded catalyst **302**, which, fortunately, provided the highest diastereo- and enantioselectivities (entry 9).

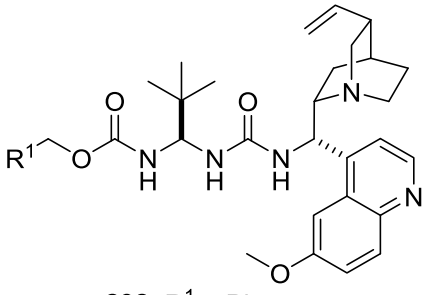
Table 9. Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-one **285** to nitrostyrene **282a**.[a]



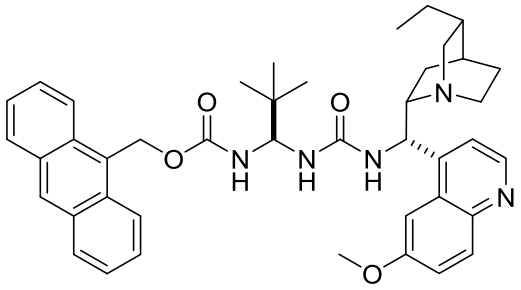
285 **282a** **286a**



294 R = $PhCH_2$
295 R = Ph
296 R = *i*-Pr
297 R = *t*-Bu



298 R^1 = Ph
299 R^1 = $PhCH_2$
300 R^1 = 2-Naph
301 R^1 = 9-Anth



302

Entry	Catalyst	t (h)	Yield (%)[b]	dr[c]	*ee*[d]
1	**294**	20	75	94:6	15
2	**295**	20	70	95:5	30
3	**296**	20	88	91:9	40
4	**297**	20	92	95:5	66
5	**298**	48	70	94:6	40
6	**299**	48	65	96:4	40
7	**300**	20	90	94:6	70
8	**301**	20	86	90:10	78
9	**302**	20	80	93:7	80

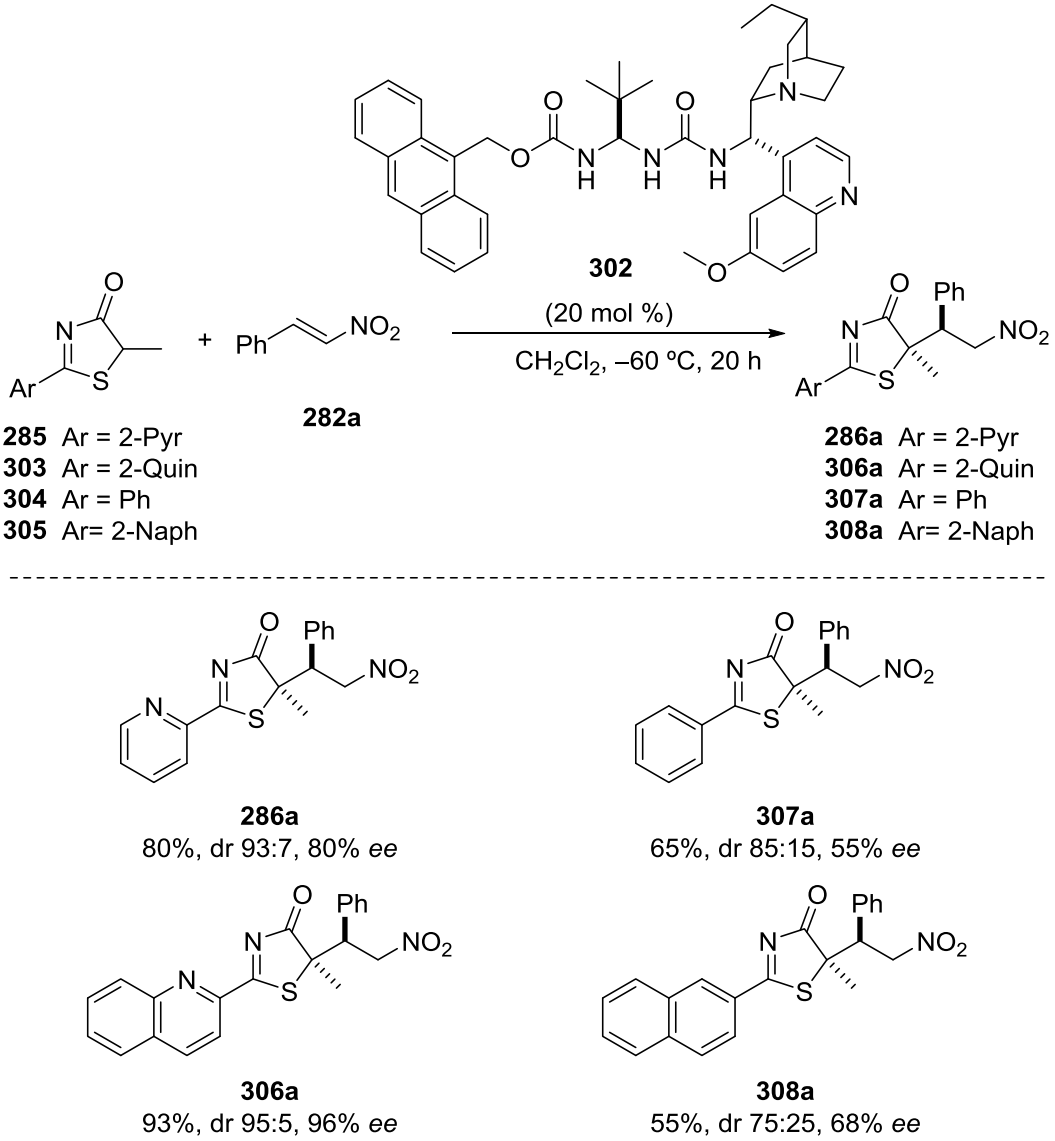
[a] Reaction conditions: **285** (0.3 mmol), **282a** (2 equiv., 0.6 mmol), catalyst (20 mol %), −60 ºC in CH_2Cl_2 (0.6 mL). [b] Yields of the isolated major isomer after column chromatography. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

3.2.2.2. 5H-Thiazol-4-one screening

Once we performed the screening of different catalysts, catalyst **302**, which produced the best results, was selected for further optimization. So, at this point, we considered the possibility of varying the substrate (Table 10) and hypothesized that the aromatic group of the thiazolone could play a significant role in the stereocontrol of the reaction. To check this, thiazolones **303**–**305** were prepared following reported procedures[236] and their reaction with nitrostyrene was survied in the presence of catalyst **302**. The corresponding results are compiled in Table 10. These results show that replacement of pyridine by a phenyl group provides worst results regarding stereoselectivity (85:15 dr, 55% *ee*). Fortunately, when quinoline-derived thiazolone **303** was tested successful results were obtained (93% yield, 95:5 dr, 96% *ee*) for **306a**. In contrast, the naphthyl-substituted substrate **305** afforded the addition product **308a** again with disappointing diastereomeric ratios (75:25) and enantioselectivities (68% *ee*), results that seem to indicate that the pyridine and quinoline nitrogen atoms of thiazolones **285** and **303** play a significant role in reaction stereocontrol. On this basis, the 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **303** was selected to study the reaction scope.

[236] For more details, see the experimental section.

Table 10. 5*H*-thiazol-4-one screening for Michael addition to nitrostyrene **282a**.[a]



[a] Reaction conditions: Thiazolone (0.3 mmol), **282a** (2 equiv., 0.6 mmol), catalyst (20 mol %), −60 ºC in CH_2Cl_2 (0.6 mL). Complete conversion related to the disappearance of the starting material. Yields of the isolated major isomer after column chromatography. The dr values were determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Previous work by Takemoto[237] (2005), Pápai[238] (2006) and Zhong[232] (2010) on the Michael addition of 1,3-dicarbonylic compounds to nitroolefins catalyzed by thiourea-based bifunctional Brønsted bases shows different proposals for the way of action of these catalysts. Firstly, in 2005, and on the basis of ^{1}H NMR studies, Takemoto porposed A model (Figure 23), wherein the malonate enolate coordinates to

[237] a) See ref. 45, page 15. For the mechanistic proposal of the reaction, see: b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119–125.

[238] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

the protonated tertiary amine and the nitroalkene is coordinated to the two urea *NH*-bonds through the two oxygens. Later, in 2006 Pápai did an exhaustive DFT study considering Takemoto's model (A) and his new proposal B. The calculations show that proposal B is energetically more favourable than A. Since then, this has been the generally assumed way of action of these bifunctional catalysts in these type of reactions. Following this, in 2010 Zhong also proposed a similar model to B (Figure 23, C proposal) supported by ^{1}H NMR and DFT studies for the conjugate addition of a related 1,3-dicarbonylic compound.

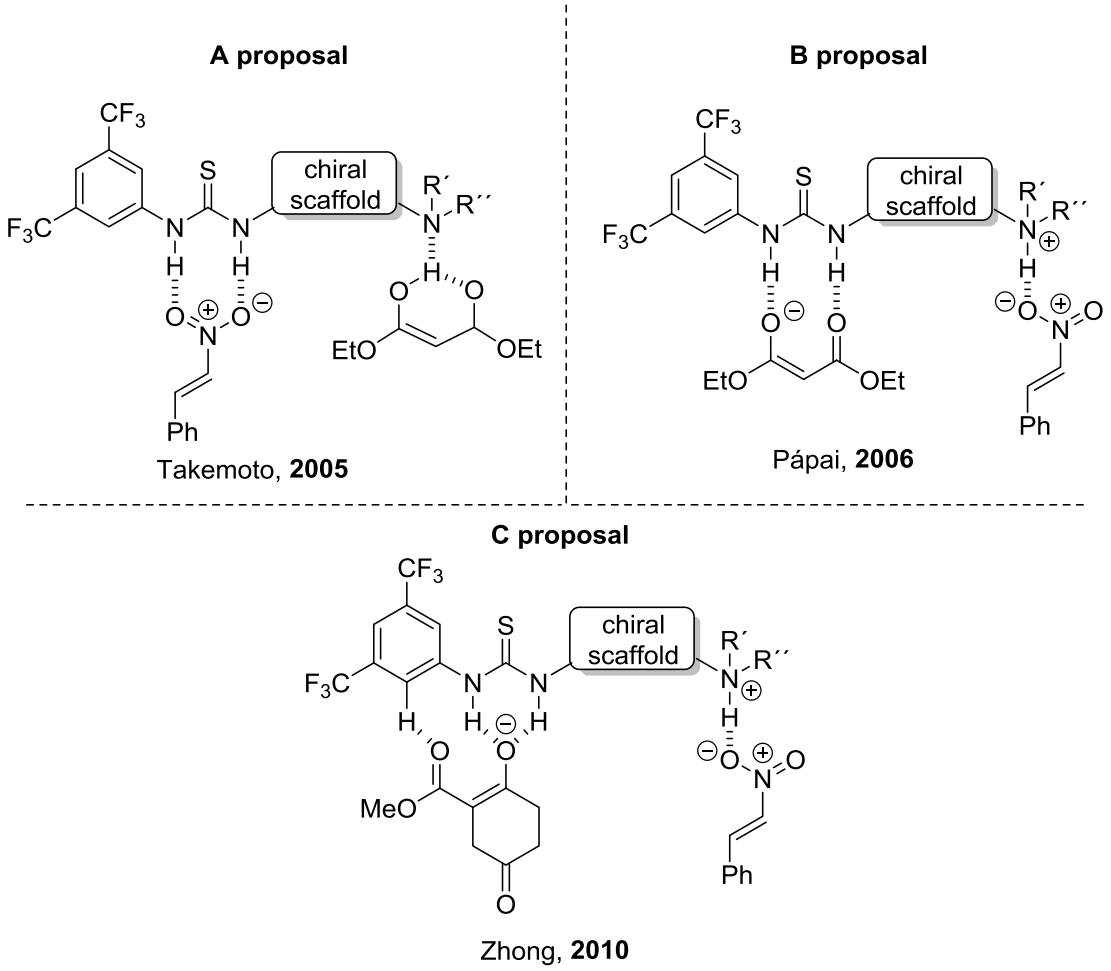


Figure 23. Proposed dual activation models for the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes promoted by thiourea based bifunctional Brønsted bases.

Taking into account these previous proposals we suggest the model outlined in Figure 24 for our reaction, in which the nitroolefin and the thiazolone are concurrently activated by the ureido-Brønsted base. The nitro group of the electrophile would interact with the cationic *N–H* group of the protonated amine, while the thiourea would coordinate to the thiazolone through the nitrogen and oxygen atoms of the thiazolone ring. An additional coordination would be possible when the substrate presents a

nitrogen atom in the structure, enhancing the fixation of the transition state, thus providing better stereocontrol during the reaction. Therefore, this model nicely accounts for the better behaviour of pyridyl and quinolyl thiazolone substrates **285** and **303** *versus* the phenyl and naphthyl based thiazolones **304** and **305**. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation remains to be clarified. Due to the flexibility of the catalyst **302** an extensive number of reaction modes have to be examined in a DFT study.

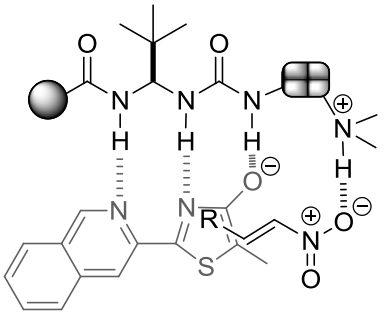
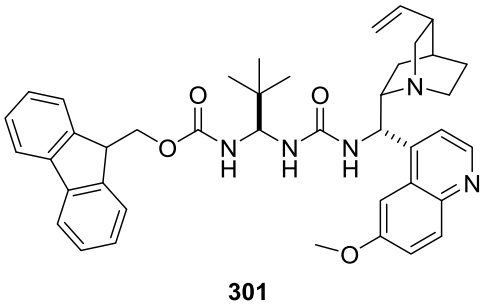


Figure 24. Proposed model for reaction activation.

In general, these catalysts were solids and Diosdado from our group obtained a single-crystal of **301** that was analyzed by X-ray revealing that in the solid state the *N–H* groups, in the *N,N′*-diacyl aminal and the urea moiety, are oriented in the same direction and that neither of them display any apparent tendency to develop intramolecular hydrogen bonds (Figure 25), being therefore accessible for coordination with the substrates. Nevertheless, in solution this orientation could differ.



301

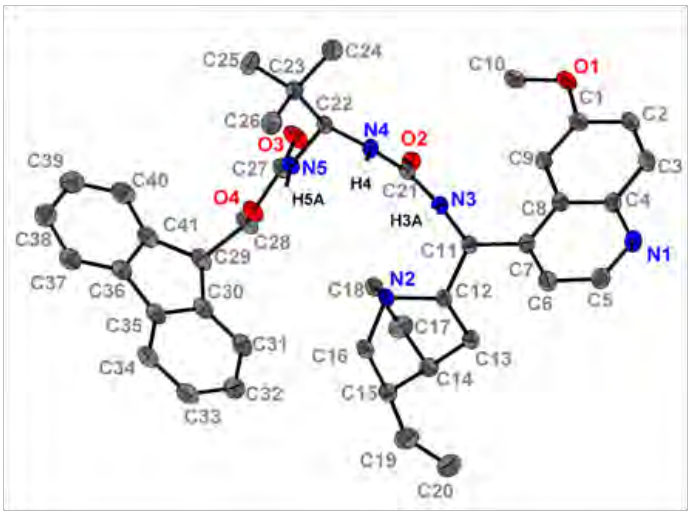


Figure 25. ORTEP diagram of compound **301**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

3.2.2.3. Reaction scope

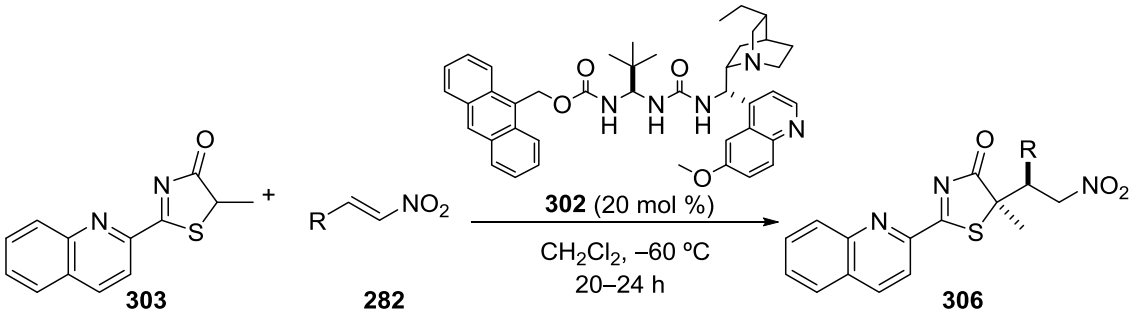
After catalyst and substrate screening, optimal reaction conditions to Michael addition of thiazolones to nitroolefins were established. On the one hand, 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **303** was found to be the most appropriate substrate, catalyst **302** (20 mol %) resulted the most effective one regarding reactivity and stereoselectivity and the reactions were conducted at –60 ºC in dichloromethane. Toluene and tetrahydrofuran were also tested as solvents, obtaining significantly worst results.

Next, we focused on the scope of the reaction with the aim of evaluating the generality of this asymmetric route to tertiary thiols respect to the nitroolefin component.[239] Therefore, a representative selection of electrophiles was evaluated and as can be seen in Table 11, nitroolefins bearing β-aryl substituents with either electron-donating or electron-withdrawing groups were almost equally tolerated, providing the corresponding adducts with diastereomeric ratios, typically greater than 95:5 and enantioselectivities up to 96%. For instance, performing the reaction with 3- and 4-methoxyphenyl substituted nitroalkenes products **306b** and **306c** were essentially produced as single diastereomers and with enantioselectivities of 92% and 94% respectively. Similar results were afforded with 3- and 4-methylphenyl substituents. Nevertheless, the *ortho*-tolyl substrate **306f** and 2,4-dimethylphenyl derivative **306g** led to unsatisfactory results. Probably, the steric hindrance provided by the substituent in position 2 had a negative effect in the organization of the transition state, producing a significant decrease in the diastereoselectivity of the reaction. In the case of the *ortho*-tolyl derivative almost no diastereocontrol was observed on the crude reaction mixture.

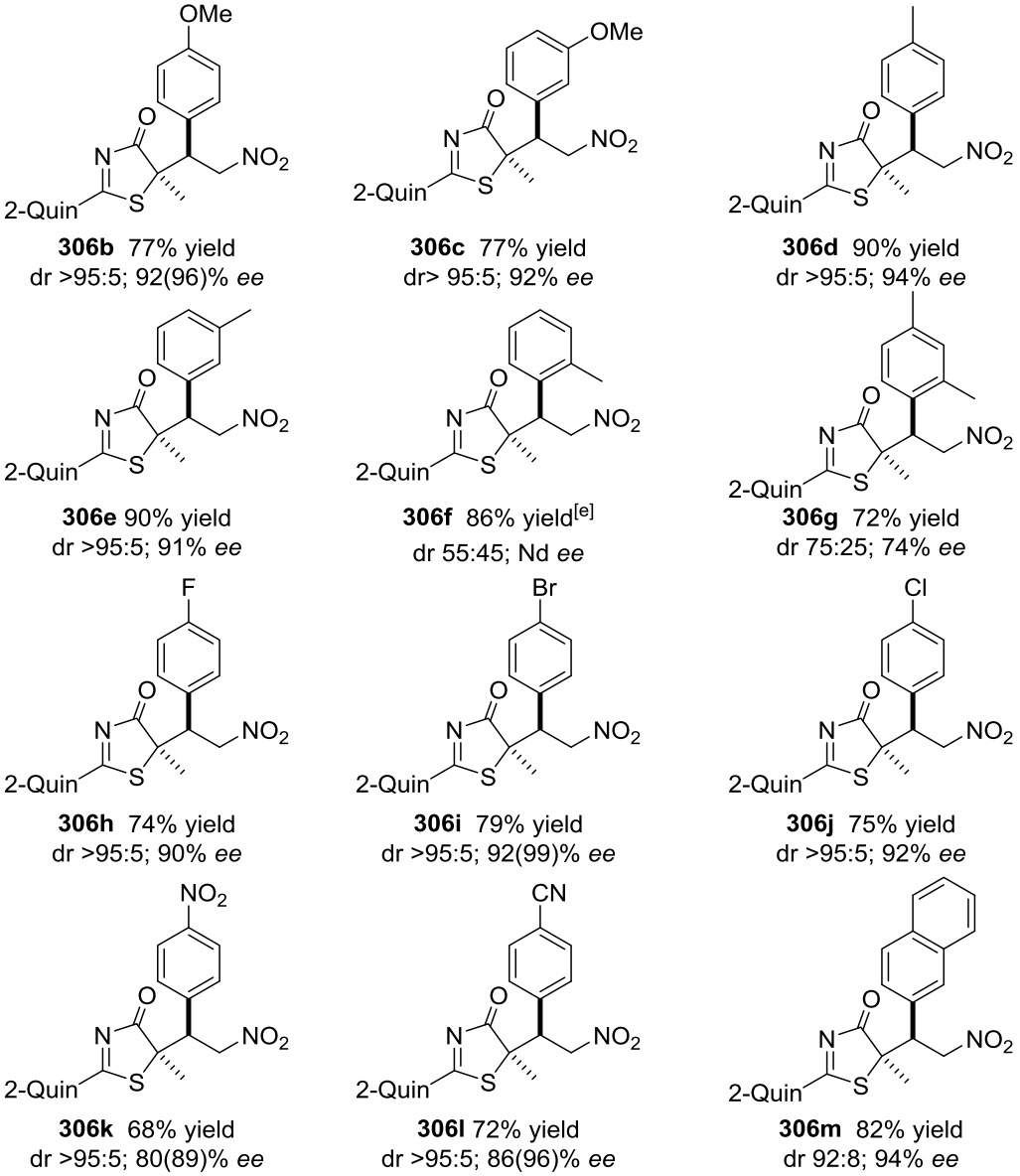
Nitroolefins **282h**, **282i** and **282j** with inductively electron-withdrawing fluoro, bromo and chloro substituents at the *para* position provided too satisfactory chemical and stereochemical results (synthesis of **306h**, **306i** and **306j**). On the other hand, electrophiles **282k** and **282l** bearing mesomeric electron-withdrawing substituents gave the corresponding adducts **306k** and **306l** with slightly reduced enantioselectivities, which could be increased after a single crystallization from diethyl ether or diisopropyl ether getting good *ee* values (data shown in Table 11). 2-Naphthyl containing nitroalkene **282m** showed similar successful results to its partner nitrostyrene.

[239] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed*. **2013**, *52*, 11846–11851.

Table 11. Scope of the conjugate addition of 5*H*-thiazol-4-one **303** to nitroolefins **282** promoted by catalyst **302**.[a-d]



303 **282** **306**



306b 77% yield
dr >95:5; 92(96)% *ee*

306c 77% yield
dr> 95:5; 92% *ee*

306d 90% yield
dr >95:5; 94% *ee*

306e 90% yield
dr >95:5; 91% *ee*

306f 86% yield[e]
dr 55:45; Nd *ee*

306g 72% yield
dr 75:25; 74% *ee*

306h 74% yield
dr >95:5; 90% *ee*

306i 79% yield
dr >95:5; 92(99)% *ee*

306j 75% yield
dr >95:5; 92% *ee*

306k 68% yield
dr >95:5; 80(89)% *ee*

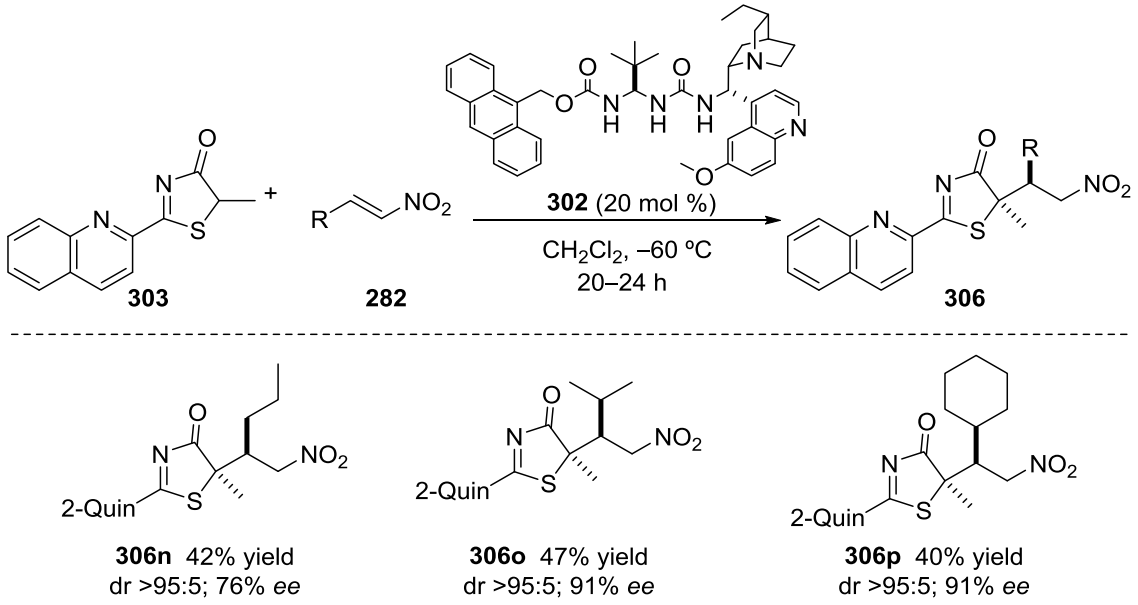
306l 72% yield
dr >95:5; 86(96)% *ee*

306m 82% yield
dr 92:8; 94% *ee*

[a] Reaction conditions: **303** (0.3 mmol), **282** (2 equiv., 0.6 mmol), catalyst (20 mol %), −60 ºC in CH_2Cl_2 (0.6 mL). [b] Yields of the isolated major isomer after column chromatography. [c] The dr values were determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Data in parentheses were obtained after crystallization from diethyl ether or diisopropyl ether. Using 10 mol % catalyst loading essentially same results were attained for **306c** and **306i**. [e] Yield refers to both diastereomers. Nd: Not determined.

The method also works with the recalcitrant β-alkyl-substituted nitroolefins (Table 12) which afford the desired adducts as single diastereomers, albeit in modest chemical yields (around 40%). The enantioselectivities documented depend on the branching of substrates, getting better results with branched nitroolefins. Thus, the unbranched aliphatic nitroolefin **282n** provided the corresponding adduct **306n** with a modest 76% *ee* value, whereas the branched aliphatic substrates **282o** and **282p** led to products **306o** and **306p**, with very good enantioselectivities (both 91% *ee*). Additionally, and as demonstrated by Etxabe and Dr. Landa from this laboratory, the method also works quite well with nitroolefins bearing β-heteroatomic groups.[240]

Table 12. Scope of the conjugate addition of 5*H*-thiazol-4-one **303** to β-alkyl-substituted nitroolefins promoted by catalyst **302**.[a-d]



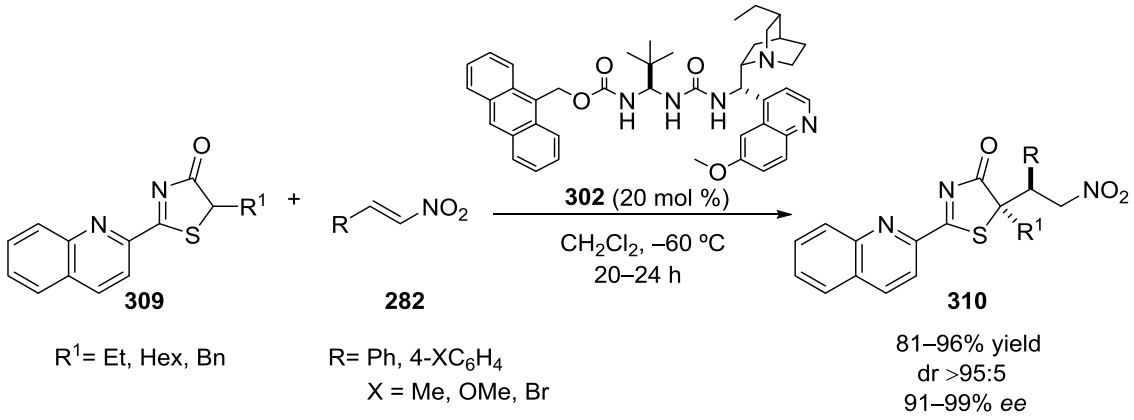
[a] Reaction conditions: **303** (0.3 mmol), **282** (2 equiv., 0.6 mmol), catalyst (20 mol %), −60 ºC in CH_2Cl_2 (0.6 mL). [b] Yields of the isolated major isomer after column chromatography. [c] The dr values were determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Using 10 mol % catalyst loading essentially same results were attained for **306o**.

It should be noted that in this study 20 mol % of catalyst has been employed, but experiments using 10 mol % of the catalyst loading with nitroolefins carrying 4-OMePh, 4-BrPh and *i*Pr β-substituents proceeded equally well without compromising either selectivity or chemical yield.

On the other hand, the generality of the reaction regarding the R^1 substituent of the thiazolone was also investigated by Etxabe and Dr. Landa (Scheme 70). Thiazolones

[240] Typically 93–96% yield, dr > 92:8, 89–92% ee. See: ref. 239.

bearing short, large and branched alkyl chains, all of them, afforded successful results regarding reactivity and selectivity.



Scheme 70. Thiazolone scope.

An interesting aspect of this methodology to synthesize tertiary thiol derivatives is the general crystallinity of both starting substrates, thiazolone **303** and most of nitroolefins, a property which is readily translated to the resulting products **306**. This attractive characteristic provided the opportunity of crystallizing the adducts; thus, as mentioned before, a single crystallization, generally from diethyl ether or diisopropyl ether, produced products with increased enantiomeric purity. Moreover, an unambiguous determination of the absolute configuration of the corresponding adducts was performed by a single-crystal X-ray analysis of **306i** (Figure 26) and by assuming a uniform reaction mechanism.

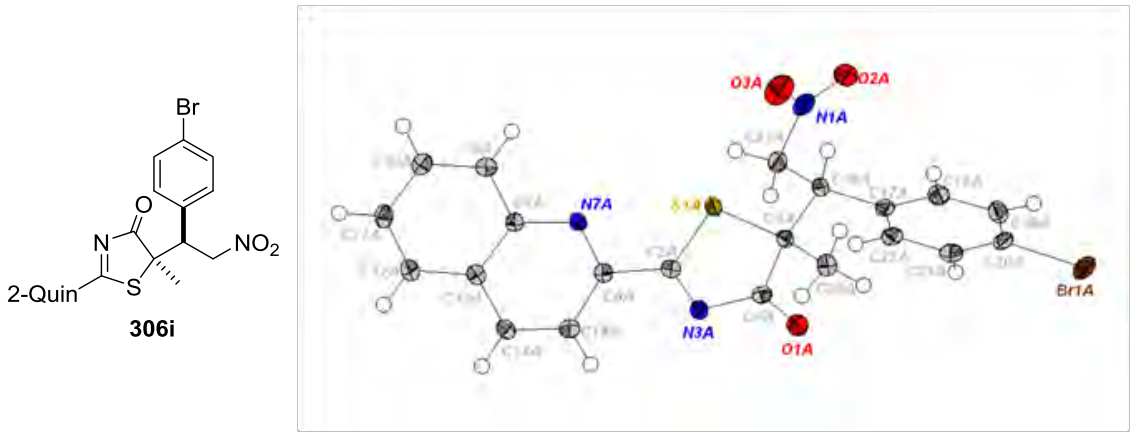
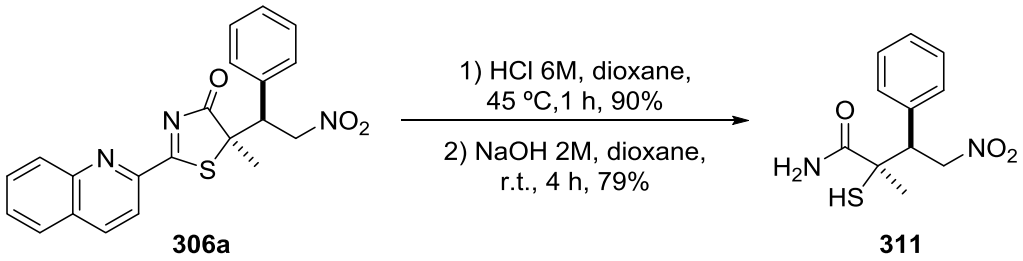


Figure 26. ORTEP diagram of compound **306i**.

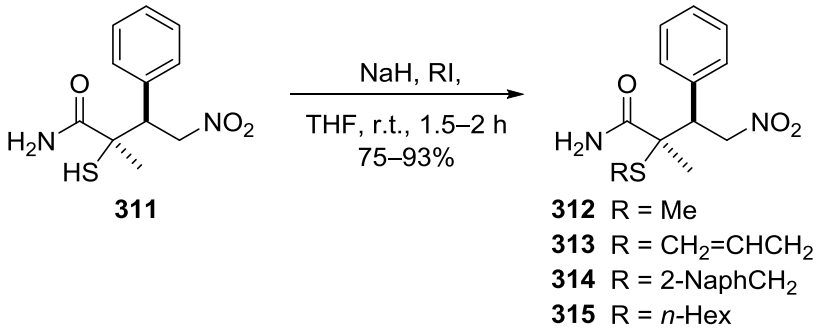
3.2.2.4. Elaboration of adducts

One of the first objectives of this project was to develop a methodology to obtain free tertiary thiols stereoselectively. We were happy to find that adduct **306a** could be transformed into the corresponding α,α-disubstituted α-mercapto carboxylic acid derivative **311**, by simple ring opening in acid medium, followed by saponification of the resulting thioester (Scheme 71), both under mild conditions, illustrating thus the utility of our procedure.



Scheme 71. Transformation of adduct **306a** into α,α-disubstituted α-mercapto carboxylic acid derivative **311**.

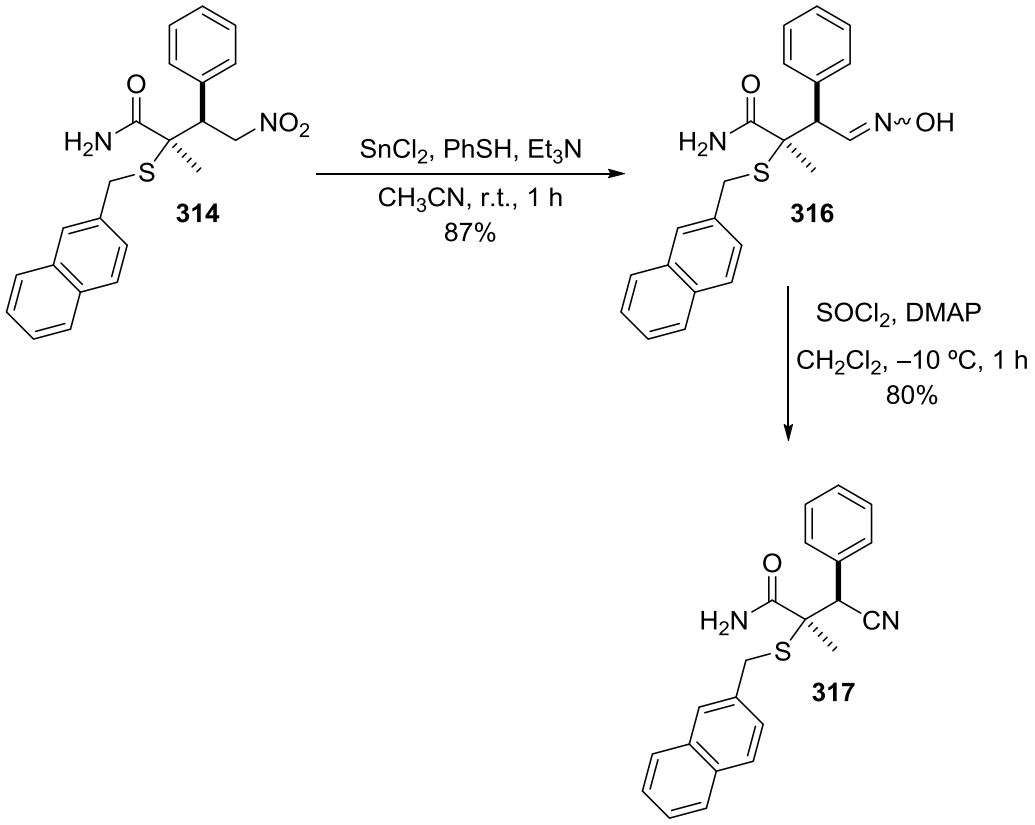
As it has been shown in the introduction of this Thesis and, more specifically in the introduction of this chapter, the majority of the methodologies for the preparation of organosulfur compounds generally afford aryl or alkyl thioethers. Interestingly, our approach provides a quick entry to mercapto compounds with the thiol group in its free form. Next, we wondered whether these adducts could be *S*-alkylated without affecting the nitro group. Apart from steric constraints it is known that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[241] Satisfactorily, treating the adduct **311** with different halides in the presence of sodium hydride the corresponding *S*-alkylated products were produced in 75–93% yield and leaving untouched the nitro group (Scheme 72).



Scheme 72. *S*-Alkylation of α,α-disubstituted α-mercapto carboxylic acid derivative **311**.

[241] Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2005**, *44*, 612–615 and references therein.

Therefore, we can say that our methodology is appropriate for the asymmetric synthesis of free tertiary thiols and also a variety of thioether derivatives from a single common intermediate. Oximes, on the other hand, may be obtained following a protocol described by Bartra and co-workers[242] (Scheme 73). After treatment of the adduct **314** with $SnCl_2$/PhSH/Et_3N in acetonitrile a *E/Z* mixture (3:1, not assigned) of product **316** was obtained with good yield. Finally, the oxime group was oxidized to nitrile using a methodology described in our group, employing thionyl chloride and dimethylaminopyridine (Scheme 73).[243]



Scheme 73. Transformation of the nitro group into nitrile through the oxime.

[242] a) Bartra, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587–594. b) Hughes, C. C.; Trauner, D. *Angew. Chem. Int. Ed*. **2002**, *41*, 4556–4559.

[243] Arrieta, A.; Palomo, C. *Synthesis* **1983**, 472–474.

3.3. Michael addition of 5*H*-thiazol-4-ones to α'-oxy enones

3.3.1. Introduction

Given that good results regarding reactivity and stereoselectivity were afforded in the Michael addition of 5*H*-thiazol-4-ones to nitroolefins catalyzed by new ureidopeptide-based Brønsted bases developed in our group, and, taking into account that these catalysts offer the opportunity of multiple H-bond interactions, we suspected that they might be suitable to coordinate to other Michael acceptors.

On the other hand, previous work developed by our group shows that α-hydroxy ketones, but more in particular their unsaturated analogues, α'-hydroxy enones, provided interesting results in different reactions[244] such as Diels-Alder reactions, cycloadditions to nitrones and different Michael additions. These achiral structures can be considered as enoate equivalents as the resulting adducts can be very easily transformed under oxidative conditions into functionalized carboxylic acid derivatives, being acetone the only organic side product formed. In addition, these are outstanding bidentate templates, due to the ability of the ketol moiety for both 1,4-metal and 1,4-proton binding (Figure 27, a) which has revealed to be critical for success. On this basis, we hypothesized that the H-bonding ability of the ketol moiety in α'-hydroxy enones could influence reactions initiated by a proton-transfer event, as Brønsted base catalyzed Michael reactions (Figure 27, b). More specifically, α'-hydroxy enones could participate as a two point H-bond donor/acceptor (DA model, Figure 27, b) or acceptor/acceptor (AA model, Figure 27, b) partner in the transition state, an interesting design element that is lacking in previous enoyl templates. On the other hand, and to the best of our knowledge, these α'-hydroxy enones have not been previously investigated in organocatalytic processes.

[244] Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev*. **2012**, *41*, 4150–4164.

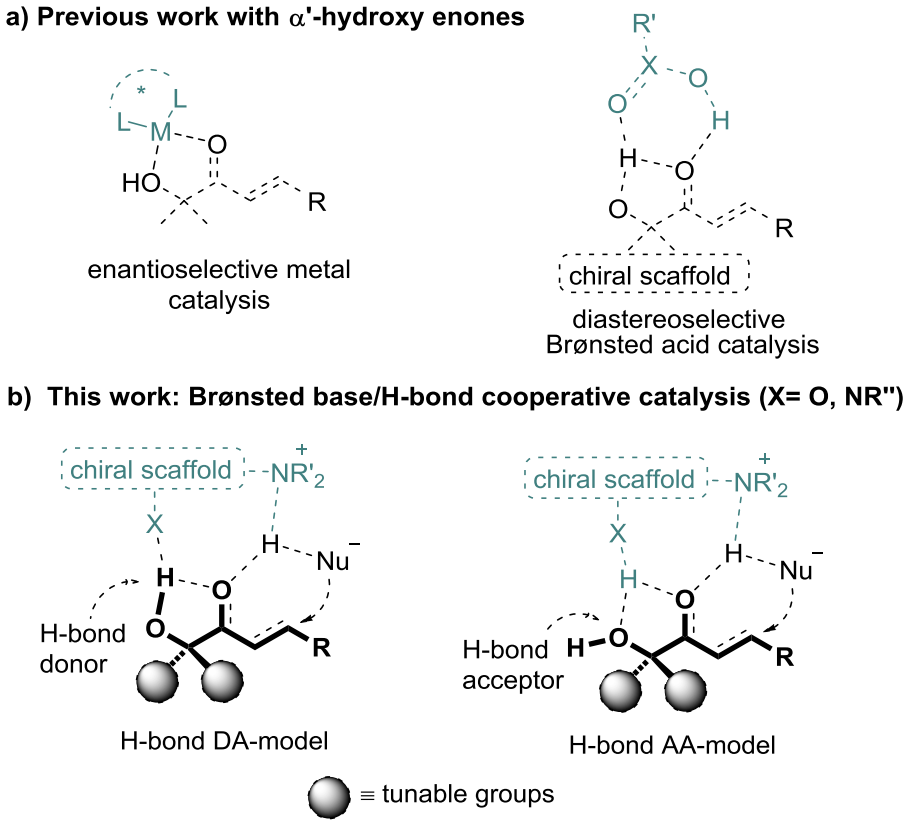
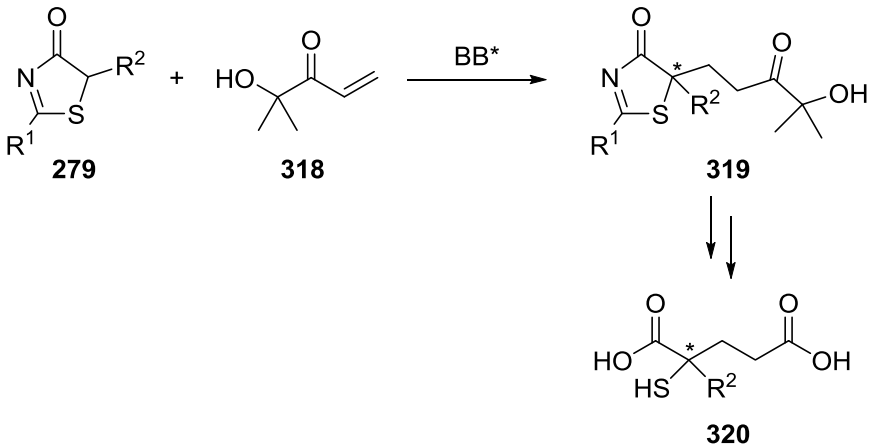


Figure 27. Different activation modes of α'-hydroxy enones.

On this basis, we selected these α'-hydroxy enones as Michael acceptors for the reaction with the previous thiazolones (Scheme 74). Additionally, this reaction involves the formation of a tetrasubstituted carbon center bearing a sulfur heteroatom, and the resulting Michael adducts could then be transformed into tertiary thiols.



Scheme 74. Proposed organocatalytic Michael addition of thiazolones to α'-oxy enones, catalyzed by chiral Brønsted bases.

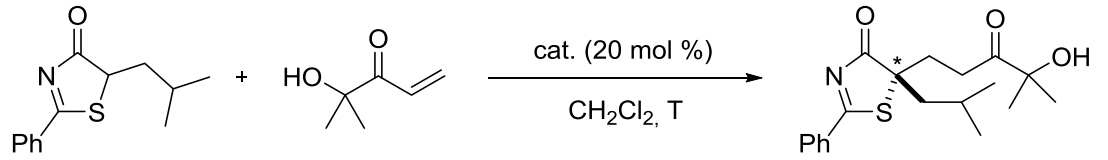
3.3.2. Results and discussion

3.3.2.1. Catalyst and Michael acceptor screening

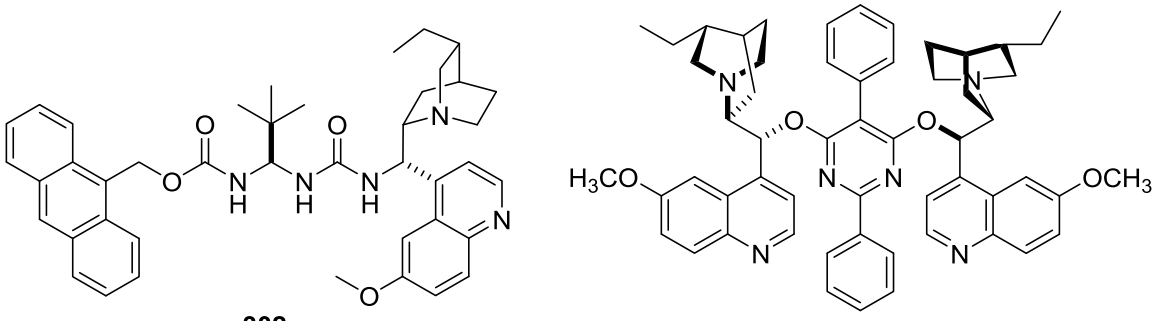
Thus, we initiated our study by performing the reaction between 5*H*-thiazol-4-one **321** and α'-hydroxy enone **322**, in the presence of the ureidopeptide-based Brønsted base catalyst **302** that previously provided the best results. However, although the expected product was obtained, the catalyst was stereochemically completely ineffective, affording the desired product with 70% yield but in racemic form (entry 1, Table 13). Then, we conducted the reaction in the presence of cinchona alkaloid derivative $(DHQ)_2PYR$ **288**, obtaining too disappointing chemical and stereochemical results. After 48 h reaction time only 50% of conversion was observed and the isolated product was again racemic (entry 2, Table 13). Subsequently, the reaction with squaramides[245] **87** and **324** was explored. Although these squaramides were able to promote the reaction and, for the first time, we observed some enantiocontrol, the enantioselectivity registered was really low (12–36% *ee*) (entries 3 and 4, Table 13).

[245] First described by Rawal and co-workers: a) See ref. 77, page 28. For reviews on organocatalysis using squaramide catalysts, see: b) ref. 76a, page 27. c) Aleman, J.; Parra, A.; Jiang, H.; Jorgensen, K. A. *Chem. Eur. J.* **2011**, 17, 6890–6899. d) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, 40, 2330–2346.

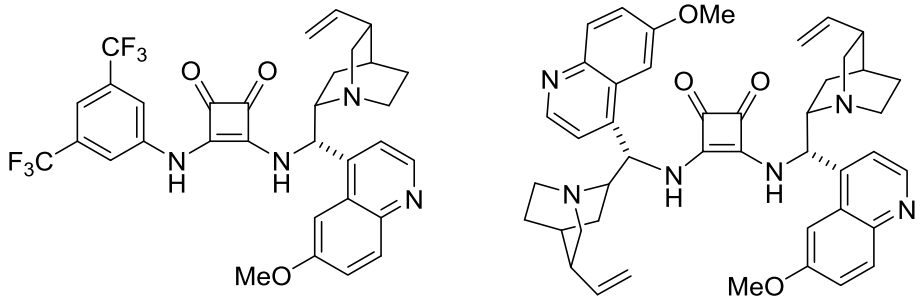
Table 13. Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-one **321** to α'-hydroxy enone **322**.[a]



321 **322** **323**



302 **288** $(DHQ)_2PYR$



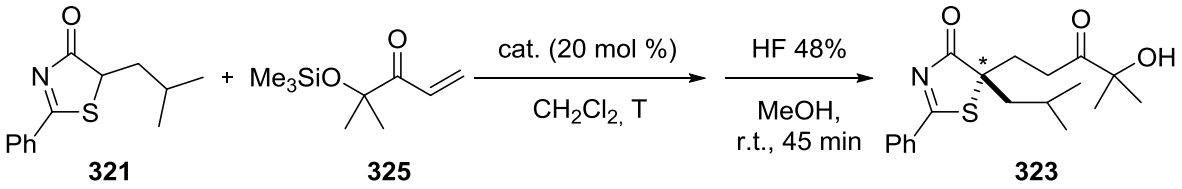
87 **324**

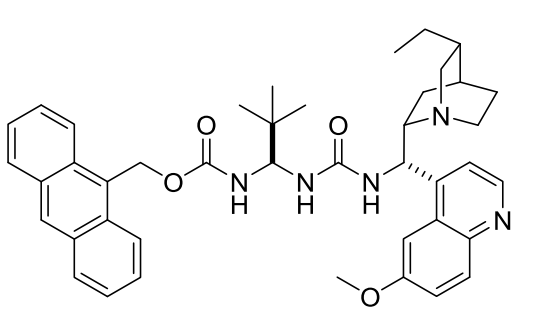
Entry	Catalyst	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)[c]	*ee*[d]
1	**302**	–60	24	100	70	0
2	**288**	–40	48	50	40	0
3	**87**	–40	24	100	72	36
4	**324**	–40	24	100	75	12

[a] Reaction conditions: **321** (0.3 mmol), **322** (3 equiv., 0.9 mmol), catalyst (20 mol %), in CH_2Cl_2 (0.9 mL). [b] Related to the disappearance of the starting material. [c] Yields of the isolated compound after column chromatography. [d] Determined by HPLC analysis on a chiral stationary phase.

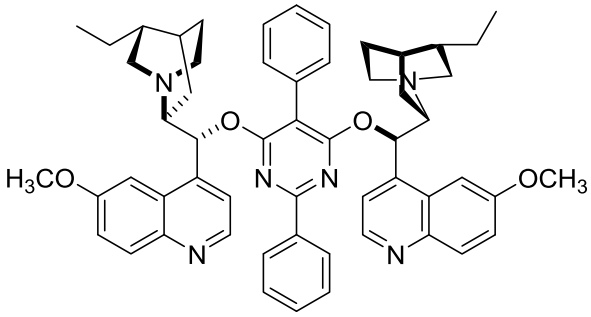
At this point we considered the possibility of modifying the Michael acceptor. The hydroxy group of this template can be easily modified, by simple silylation, without cancelling, or even increasing its capability to bind to the catalyst, a feature that adds flexibility to the template in order to adapt it optimally to different substrate/catalyst combinations.

Table 14. Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-one **321** to α'-silyloxy enone **325**.[a]

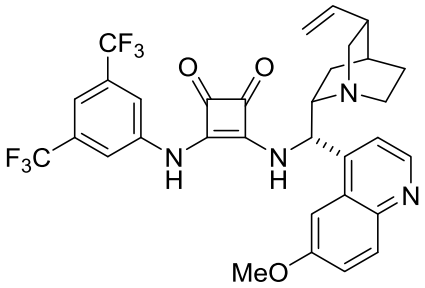




302



288 $(DHQ)_2PYR$



87

Entry	Catalyst	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)[c]	*ee*[d]
1	**302**	–20	24	0	-	-
2	**288**	0	24	0	-	-
3	**87**	–40	24	100	64	98

[a] Reaction conditions: **321** (0.3 mmol), **325** (1.5 equiv., 0.45 mmol), catalyst (20 mol %), in CH_2Cl_2 (0.9 mL). [b] Related to the disappearance of the starting material. [c] Yields of the isolated compound after column chromatography. [d] Determined by HPLC analysis on a chiral stationary phase.

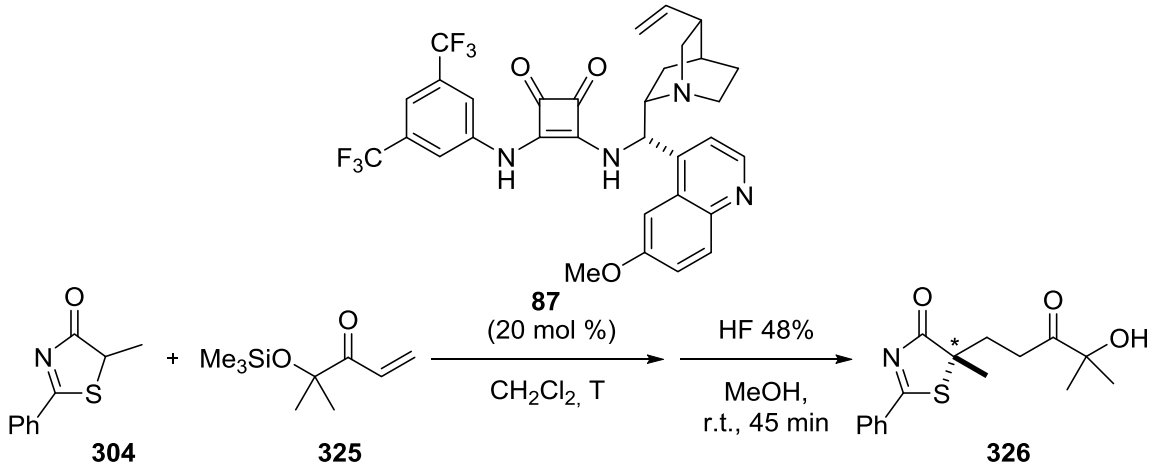
Relying on the preceding results, we tested the reaction with the new silylated Michael acceptor **325** in the presence of ureidopeptide derivative catalyst **302**, and we obtained again unsatisfying results, since only starting material was observed (entry 1, Table 14). Exactly the same results were documented when we changed the catalyst to $(DHQ)_2PYR$ **288** (entry 2, Table 14). Surprisingly, when the reaction was run with squaramide **87**, the conversion of the reaction was complete, towards the addition product. In order to determine the enantioselectivity of the reaction, we performed *in situ* desilylation of the intermediate to afford the corresponding addition adduct **323** and

after HPLC analysis we determined that the reaction occurs with excellent enantiocontrol (entry 3, Table 14). The configuration of the Michael adducts was assigned by analogy with the reaction of other (pro)nucleophiles with this enone developed in our group[246] and assuming a uniform mechanism.

3.3.2.2. Temperature screening

With the intention of improving the yield of the reaction we decided to perform it at different temperatures. We were pleasant to observe that the enantioselectivity did not vary when the reaction was performed at higher temperatures (–40 ºC or –20 ºC, Table 15, entries 1 and 2), but the yield was improved. In contrast, at room temperature a detrimental effect in the enantiocontrol was observed as the 1,4-addition adduct was obtained in 88% *ee* after desilylation (entry 3, Table 15). On this basis, –20 ºC was chosen as the best temperature to perform the reactions.

Table 15. Temperature screening for the 1,4-addition of 5*H*-thiazol-4-one **304** to α'-silyloxy enone **325**.[a]

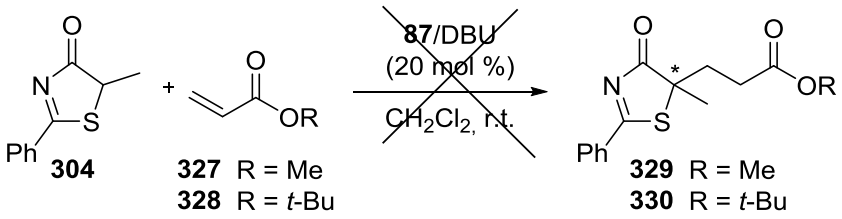


Entry	T (ºC)	t (h)	Conv. (%)[b]	Yield (%)[c]	*ee*[d]
1	–40	24	100	67	96
2	–20	24	100	77	96
3	r.t.	24	100	75	88

[a] Reaction conditions: **304** (0.3 mmol), **325** (1.5 equiv., 0.45 mmol), catalyst (20 mol %), in CH_2Cl_2 (0.9 mL). [b] Related to the disappearance of the starting material. [c] Yields of the isolated compound after column chromatography. [d] Determined by HPLC analysis on a chiral stationary phase.

[246] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc*. **2014**, *136*, 17869–17881.

It should be noted that treatment of 5-methyl-2-phenylthiazol-4(5*H*)-one **304** with either methyl acrylate **327** or *tert*-butyl acrylate **328** under the optimized conditions did not provide the corresponding addition products, even at room temperature and employing stronger bases such as 1,8-diazabicycloundec-7-ene. In every case the starting products were recovered unchanged.

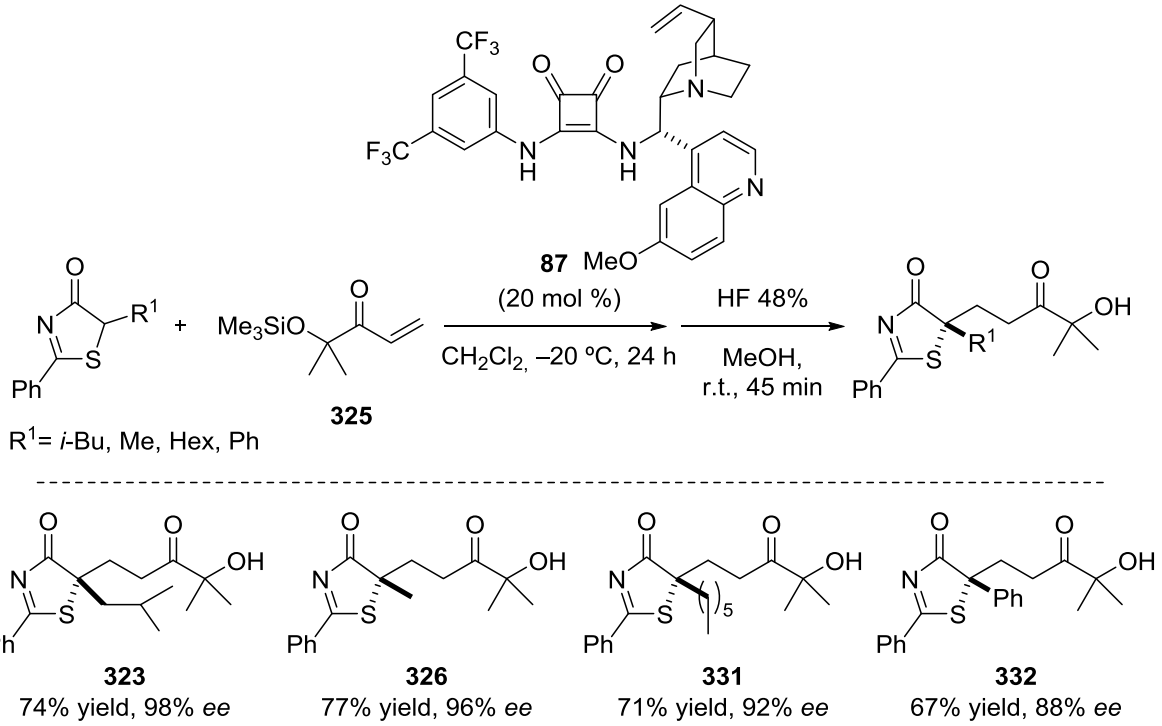


Scheme 75. Michael addition reaction of thiazolone **304** to methyl acrylate **327** and *tert*-butyl acrylate **328**.

3.3.2.3. Reaction scope

After optimization we found the best conditions for the 1,4-addition of 5*H*-thiazol-4-ones to α'-silyloxy enone **325**, to be the use of 1.5 equivalents of enone, 20 mol % of squaramide **87** in dichloromethane at –20 ºC. Therefore the reaction was then performed with different thiazolones, and the corresponding results are compiled in Table 16. These results show that the reaction proceeds satisfactorily with thiazolones bearing either short, long or ramified alkyl chains and also with aromatic substituents, providing in all cases good yields and very good to excellent enantiomeric excesses.

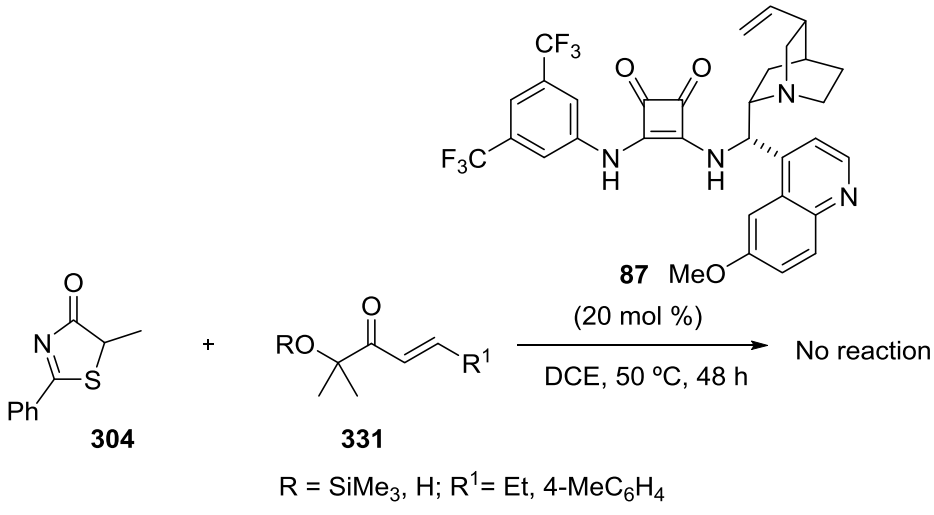
Table 16. Scope of the conjugate addition of 5*H*-thiazol-4-ones to α'-silyloxy enone **325**.[a]



[a] Reaction conditions: Thiazolone (0.3 mmol), **325** (1.5 equiv., 0.45 mmol), catalyst (20 mol %), in CH_2Cl_2 (0.9 mL) at –20 ºC. Yields of the isolated compound after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

Unfortunately, the reaction did not work with β-substituted α'-oxy enones, substituted either with alkyl or aryl groups, even performing the reactions in dichloroethane at 50 ºC (Scheme 76). In each case examined, the starting materials were recovered unchanged, probably due to steric factors.

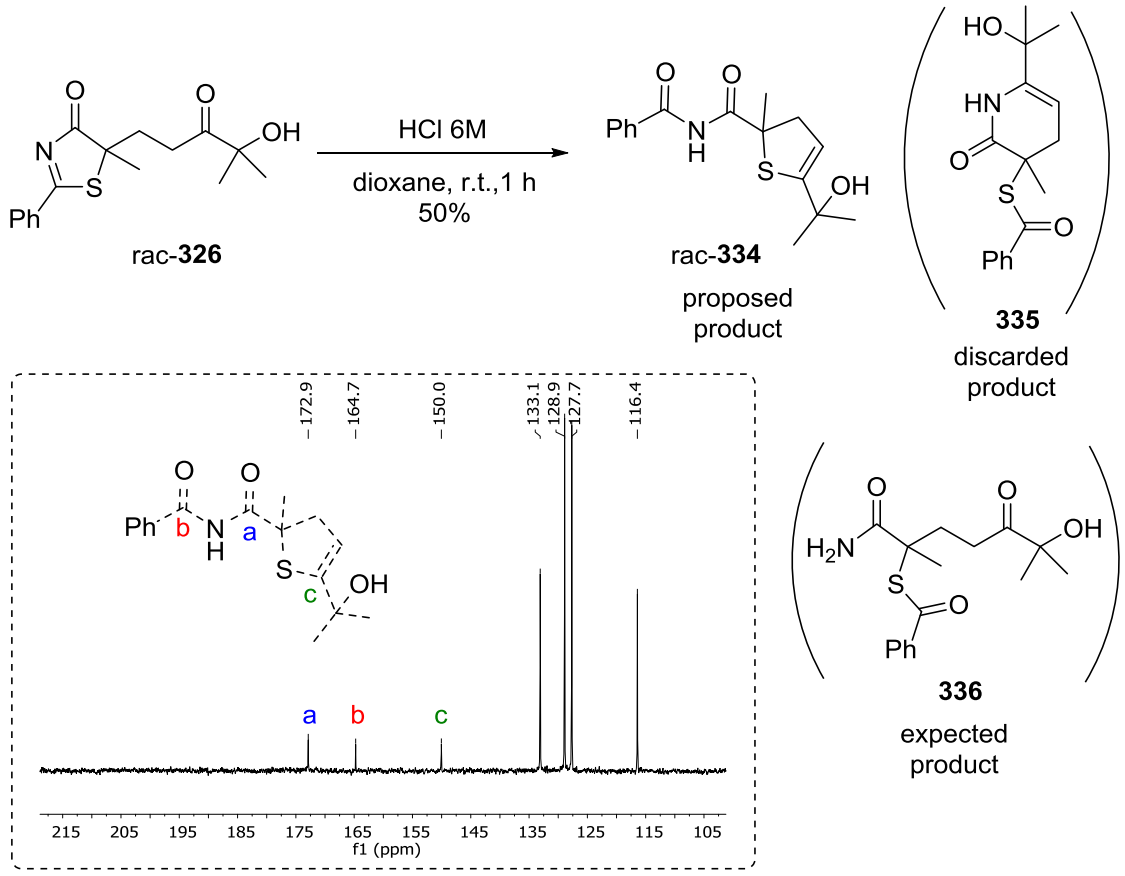
Scheme 76. Conjugate addition of 5*H*-thiazol-4-ones to β-substituted α'-oxy enones.[a]



[a] Reaction conditions: **304** (0.3 mmol), **333** (1.5 equiv., 0.45 mmol), catalyst (20 mol %), in DCE (0.9 mL) at 50 ºC.

3.3.2.4. Elaboration of adducts

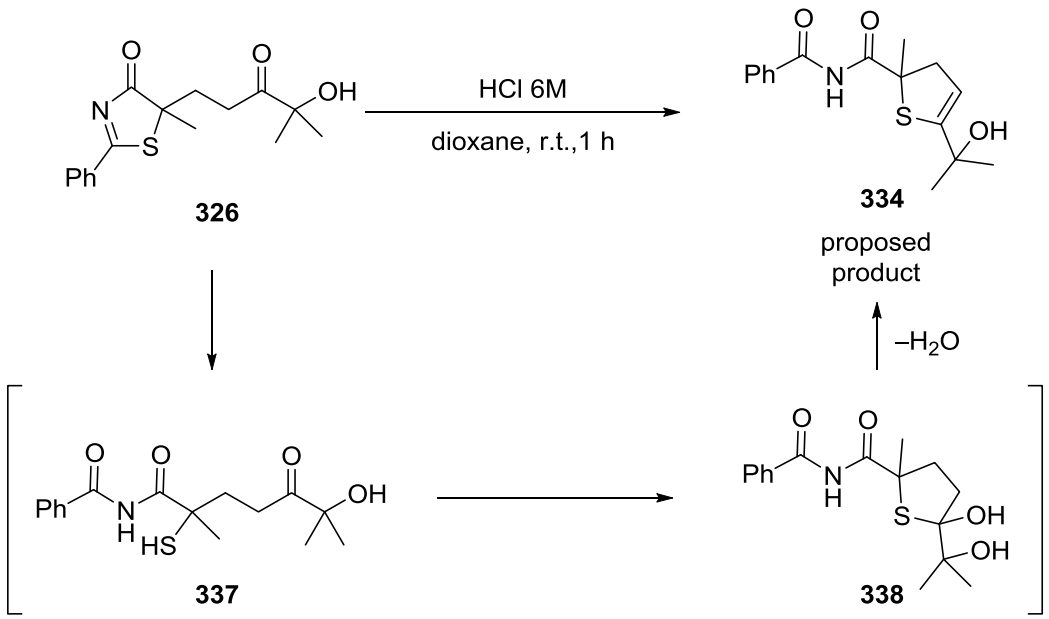
To demonstrate the synthetic utility of these adducts some transformations were performed. Firstly, the Michael addition products were treated under acidic conditions. Employing 6M or 3M HCl in dioxane at room temperature complete disappearance of the starting material was observed after 1 h. However, and, surprisingly, we could not identify the expected product **336** (Scheme 77) which bears three carbonyl groups. Our ^{13}C NMR spectrum showed only two carbonyl signals and mass analysis of the isolated compound revealed the lost of a water molecule compared with the expected product **336**.



Scheme 77. Acid hydrolysis of Michael adduct **326**.

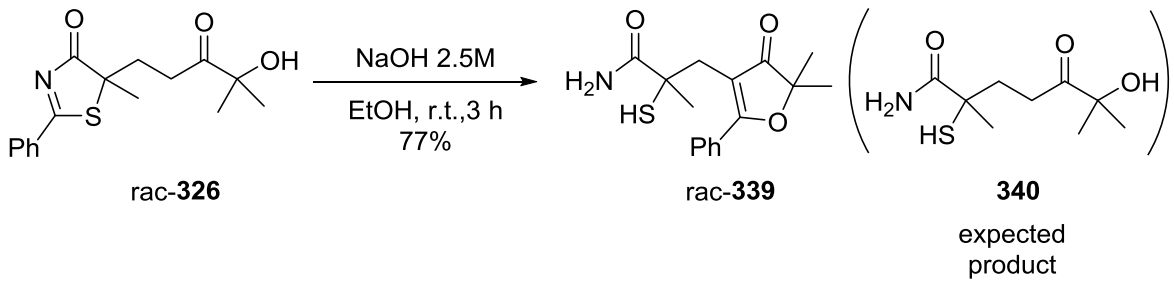
Based on the mass, NMR and IR spectra a tentative assignment was performed for the obtained product. Firstly two plausible structures **334** and **335** were proposed. However, NMR and IR spectra seemed to be more in concordance with structure **334**, as in the ^{13}C NMR spectrum no signal related to the thioether carbonyl in **335** (~190 ppm) was detected. Instead, two signals at 165 and 173 ppm were observed, both in agreement with the two imide carbonyls ("a" and "b" in Scheme 77). Furthermore the

IR signal observed at 1744 cm^{-1} is in accordance with the imide (1734 cm^{-1}) which appear higher than secondary amides (1610 cm^{-1}). Scheme 78 outlines the mechanism we suggest for the formation of *N*-benzoyl-5-(2-hydroxypropan-2-yl)-2-methyl-2,3-dihydrothiophene-2-carboxamide **334**.

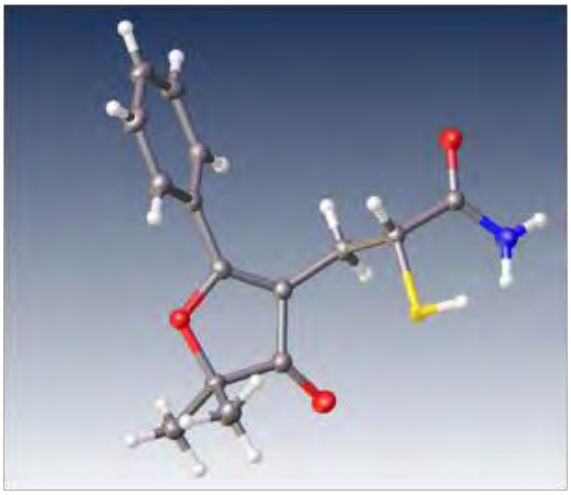


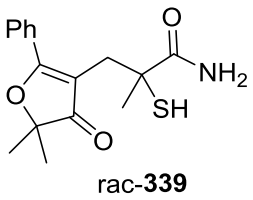
Scheme 78. Proposed mechanism for the formation of compound **334**.

Interest was then focused on basic hydrolysis and we performed the reaction with NaOH 2.5M in ethanol at room temperature. However, instead of the expected product **340**, adduct **339** was identified (Scheme 79). The structure was confirmed by single crystal X-ray analysis (Figure 28).



Scheme 79. Basic hydrolysis of compound **326**.

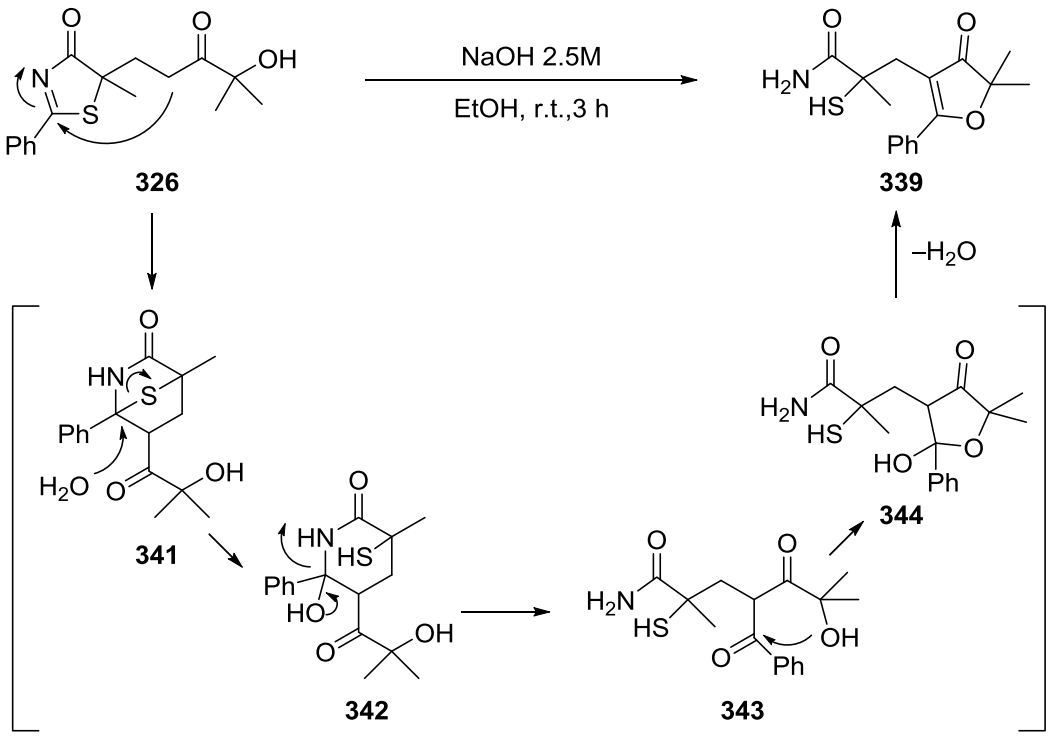




rac-**339**

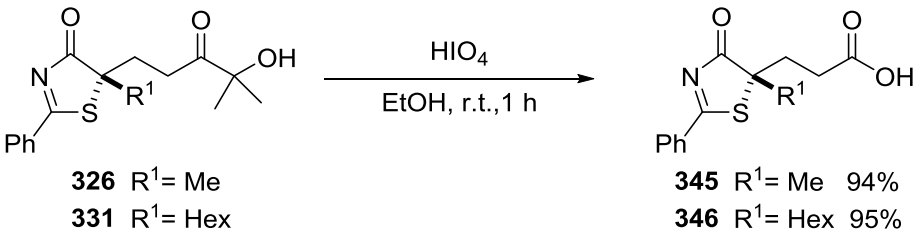
Figure 28. ORTEP diagram of compound **339**.

Scheme 80 shows a plausible mechanism for the formation of compound **339**. We propose that in the presence of NaOH the carbon adjacent to the ketone is deprotonated to produce unstable intermediate **341** which evolves to **342**. Then nucleophilic addition of the hydroxy group in **341** to the carbonyl moiety would produce **344**, which could be spontaneously dehydrated to generate adduct **339**.



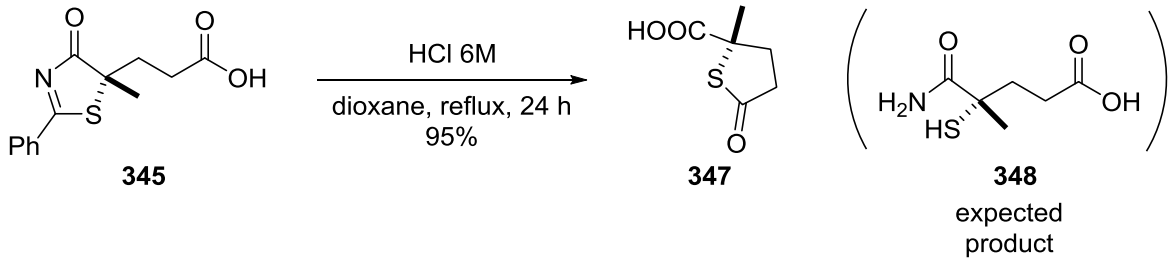
Scheme 80. Proposed mechanism for the formation of compound **339**.

In view that the ketone seemed to be a labile point in the elaboration of the Michael addition product **326**, we decided to transform first the adduct into the corresponding carboxylic acid. This was easily achieved by treatment of **326** and **331** with periodic acid in diethyl ether. Under these conditions the reaction proceeded smoothly and carboxylic acids **345** and **346** were isolated in 94% and 95% yields (Scheme 81).[247]



Scheme 81. Oxidation of **326** and **331** derivatives.

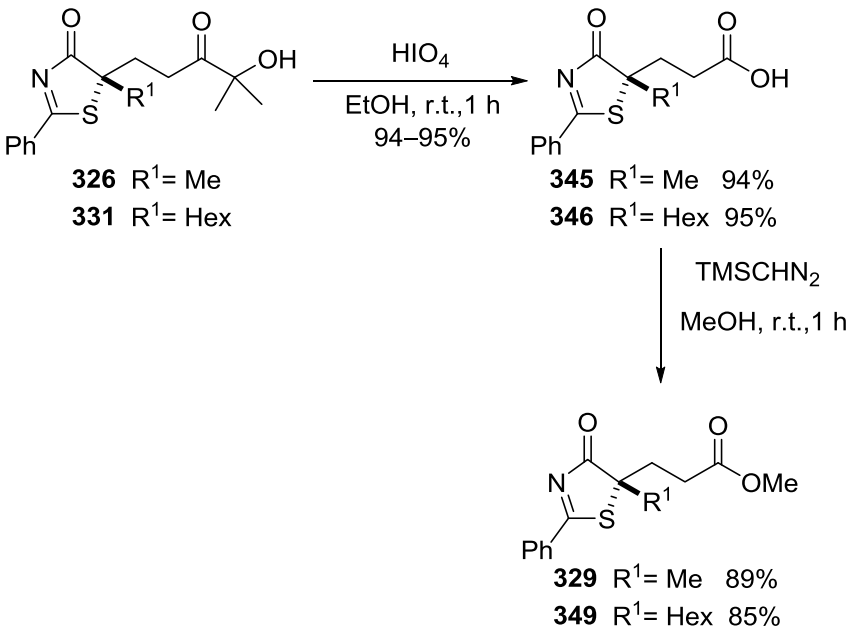
Subsequently, after treatment of carboxylic acid **326** with HCl 6M in dioxane at room temperature, no reaction was observed. Under more drastic conditions (24 h reaction time at reflux), the starting material disappeared completely. However, instead of the expected product **348**, thiolactone **347** in 95% yield was identified after mass and spectroscopic analysis (Scheme 82).



Scheme 82. Acid hydrolysis of carboxylic acid derivative **345**.

As mentioned before, no reaction was observed between thiazolone **304** and methyl acrylate **327** under the described conditions (Scheme 83). So adducts **329** and **347** were synthesized through esterification of carboxylic acid derivatives **345** and **346** by treatment with a solution of trimethylsilyldiazomethane and were obtained in very good yields (Scheme 83).[247] These results show that this new procedure constitutes an efficient protocol to perform a formal Michael addition to methyl acrylate **327**, reaction, which under other conditions is not feasible.

[247] Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

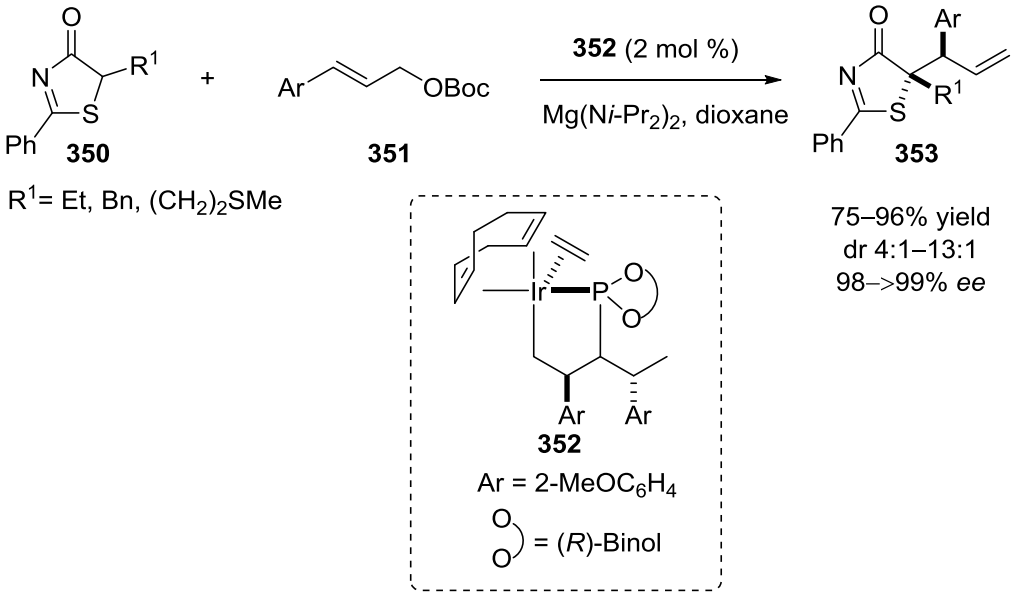


Scheme 83. Elaboration of adducts into methyl ester derivatives.

In conclusion, we have reported 5*H*-thiazol-4-ones as new prochiral substrate reagents for the asymmetric construction of tertiary thiols.[239] The direct catalytic Michael addition of this new class of pronucleophiles to nitroolefins enables access to α-mercapto carboxylic acid derivatives with two adjacent, quaternary and tertiary, stereocenters. Ureidopeptide-like Brønsted bases developed in our research group have shown to be effective catalysts to promote this transformation. The catalyst architecture can be easily modify by simply starting from the α-amino acid or peptide derived isocyanate and a survey of naturally or synthetically primary/tertiary diamines, thus opening the way for catalyst optimization in other transformations.

On the other hand, no reaction was observed when acrylate derivative esters where used as Michael acceptors for the 1,4-addition of 5*H*-thiazol-4-ones. In contrast, α-silyloxy enone has shown to be key enoate surrogate for this reaction, providing the corresponding adducts, which bear a tetrasubstituted stereogenic carbon, with successful chemical and stereochemical results.[246] The α-silyloxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity in the presence of a cinchona-based bifunctional squaramide. Surprisingly, and in contrast to the Michael addition to nitroalkenes, in this case the previous ureidopeptide-like catalysts are not efficient. Furthermore, the resulting Michael adducts can be easily transformed into the corresponding carboxylic acid derivatives through simple oxidative cleavage of the ketol unit, being acetone the only organic side product formed in the reaction.

After our publication[239] on the catalytic enantioselective synthesis of tertiary thiols from Michael addition of 5*H*-thiazol-4-ones to nitroalkenes, the group of Hartwig reported iridium-catalyzed allylic substitution with 5*H*-thiazol-4-ones (Scheme 84).[248]



Scheme 84. Ir-catalyzed allylic substitution with 5*H*-thiazol-4-ones.

[248] Chen, W.; Hartig, J. F. *J. Am. Chem. Soc*. **2014**, *136*, 377–382.

Chapter 4:

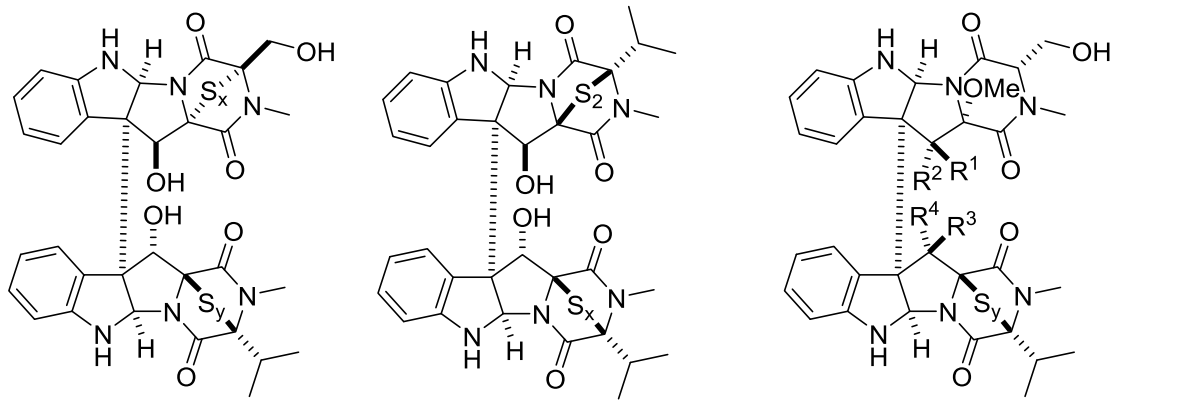
Towards the synthesis of leptosins' core

4. Towards the synthesis of leptosins' core

Towards the synthesis of leptosins' core

4.1. Introduction

In connection with our efforts centered in the development of methodologies to access thiofunctionalized carbonyl compounds, focus was also turned towards the synthesis of natural products containing thiofunctionalized carbonyl units and showing interesting biological properties. More specifically and, as part of a more general project of Dalko's group from the University of Descartes (Paris) on the synthesis of *epi*(polythio)diketopiperazine mycotoxins, and under his supervision, interest was directed to the development of a protocol to construct leptosins (Figure 29), an important class of *epi*(polythio)diketopiperazines.



leptosin A x = 4; y = 2
leptosin B x = 3; y = 2
leptosin C x = 2; y = 2
leptosin G x = 4; y = 3
leptosin G_1 x = 3; y = 3
leptosin G_2 x = 2; y = 3
leptosin H x = 2; y = 4

leptosin K x = 2
leptosin K_1 x = 3
leptosin K_2 x = 4

leptosin M $R^1 = R^4 = OH$; $R^2 = R^3 = H$; y = 4
leptosin M_1 $R^1 = R^4 = OH$; $R^2 = R^3 = H$; y = 2
leptosin N $R^1 = R^4 = H$; $R^2 = R^3 = OH$; y = 4
leptosin N_1 $R^1 = R^4 = H$; $R^2 = R^3 = OH$; y = 3

Figure 29. Part of the family of leptosins.

The *epi*(polythio)diketopiperazine (ETP) alkaloids constitute a large and diverse family of natural products produced as secondary metabolites by a number of filamentous fungi and have received substantial attention from the scientific community due to their potent biological activity and complex molecular architecture.[249] They

[249] a) Iwasa, E.; Hamashima, Y.; Sodeoka, M. *Isr. J. Chem*. **2011**, *51*, 420–433. b) Bräse, S.; Encinas, A.; Keck, J; Nising, C. F. *Chem. Rev.* **2009**, *109*, 3903–3990. c) Gardiner, D. M.; Waring, P.; Howlett, B. J.

display a broad spectrum of biological properties,[250] including antibacterial, anticancer, antiviral, antiparasitic, antifungal, antimalarial, immunosuppressive and anti-inflammatory activities, among others. Recently, it has also been reported that they inhibit a variety of cellular targets and signalling processes critical for cancer cell growth,[251] suggesting that ETPs may have utility as lead molecules for drug development and molecular tools.

The potent biological activities and complex structures that surrounds the central *epi*(polythio)diketopiperazine moiety mark ETP compounds as appealing synthetic targets and considerable efforts have thus been directed towards their synthesis. However, only few of them have been totally synthesized. A remarkable example was reported in 1970s by Fukuyama and Kishi who disclosed the total synthesis of gliotoxin **354** (Figure 30), one of the best-known ETPs, introducing the ETP fragment in masked form as a nucleophilic unit.[252] In 2009, Movassaghi described the total synthesis of dideoxyverticillin A (**355**, Figure 30)[253] and in more recent years some groups published different synthesis of other ETP natural products.[254]

Leptosins (Figure 29) are a significant group of ETP natural compounds, most of them dimeric, which contain the *epi*(polythio)diketopiperazine ring fused to a cyclotryptamine fragment, and which are produced as secondary metabolites by *Leptosphaeria* sp., originally separated from the marine alga *Sargassum tortile.*[255]

Microbiology **2005**, *151*, 1021–1032. d) Waring, P.; Eichner, R. D.; Müllbacher, A. *Med. Res. Rev.* **1988**, *8*, 499–524. e) Cole, R. J.; Cox, R. H. in *Handbook of Toxic Fungal Metabolites*, Academic Press, New York, **1981**, pp. 569–613.

[250] Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi, M. *Chem. Sci*. **2013**, *4*, 1646–1657 and references therein.

[251] Du, L.; Robles, A. J.; King, J. B.; Mooberry, S. L.; Chichewicz, R. H. *J. Nat. Prod*. **2014**, *77*, 1459–1466.

[252] a) Fukuyama, T.; Kishi, Y. *J. Am. Chem. Soc*. **1976**, *98*, 6723–6724. For a previous work on the synthesis of dehydrogliotoxin, see: b) Kishi, Y.; Fukuyama, S.; Nakatsuka, S. *J. Am. Chem. Soc*. **1973**, *95*, 6492–6493.

[253] Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238−241.

[254] a) Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, S. A. *J. Am. Chem. Soc*. **2012**, *134*, 17320−17332. b) Fujiwara, H.; Kurogi, T.; Okaya, S.; Okana, K.; Tokoyama, H. *Angew. Chem. Int. Ed*. **2012**, *51*, 13062−13065. c) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc*. **2012**, *134*, 1930−1933. d) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y. -P.; Sarlah, D. *J. Am. Chem. Soc*. **2011**, *133*, 8150−8153. e) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. *J. Am. Chem. Soc*. **2010**, *132*, 4078−4079.

[255] a) See ref. 8, page 8. b) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859–1864. c) Takahashi, C.; Nurnata, A.; Matsurnura, E.; Minoura, K.; Eto, H.; Shingu, T.; Ito, T.; Hasegawa, T. *J. Antibiot*. **1994**, *47*, 1242–1249.

Leptosins have a great structural diversity: the symmetric, heterodimeric or more complex dissymmetric natural products have a rich and versatile biological activity. Like other ETPs, these compounds possess an intramolecular polysulfide bridge at the α,α´-positions of the diketopiperazine, and although mono-, di-, tri- and tetrasulfide members are present in nature, disulfides are more prevalent.[256] It is generally assumed that several biological effects of these alkaloids are associated to the (poly)sulfide bridge, which can inactivate proteins via reaction with thiol groups of cysteine residues, generate reactive oxygen species by redox cycling mechanism,[249c] or sequester zinc from protein targets.[257] Regardless the well documented dimerization step of *L*-tryptophan,[258] the biosynthetic path was not so far elucidated and, as far as we know, only one total synthesis of this class of compounds (leptosin D **356**, Figure 30) which bears only a unit of ETP and a 3-substituted indole moiety has been recently reported by Overman.[259]

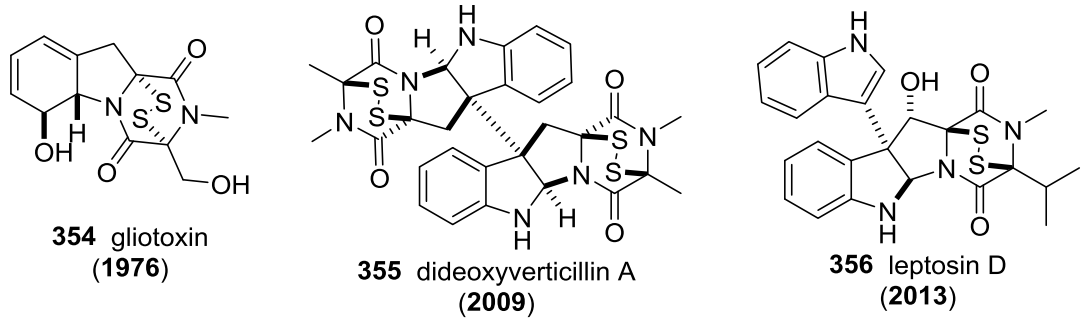


Figure 30. Some of the synthesized ETP compounds: gliotoxin (**354**), dideoxyverticillin A (**355**) and leptosin D (**356**).

4.2. Working hypothesis and synthetic plan

The group of Prof. Peter I. Dalko has experience in the synthesis of the *meso*-chimonanthine core **357** (Figure 31). In 2006 they described the total synthesis of N_b-desmethyl-*meso*-chimonanthine **130** through a seven-step convergent sequence (Scheme

[256] For general reviews, see: a) Jiang, C. -S.; Muller W. E. G.; Schröder H. C.; Guo Y. -W. *Chem. Rev*. **2012**, *112*, 2179–2207. b) Borthwick, A. D. *Chem. Rev*. **2012**, *112*, 3641–3716. c) Vigushin, D. M.; Mirsaidi, N.; Brooke, G.; Sun, C.; Pace, P.; Inman, L.; Moody, C. J.; Coombes, R. C. *Med. Oncol*. **2004**, *21*, 21–30.

[257] Cook, K. M.; Hilton, S. T.; Mecinovi, J.; Motherwell, W. B.; Figg, W. D.; Schofield, C. J. *J. Biol. Chem*. **2009**, *284*, 26831–26838.

[258] a) Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488–5508. b) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313–324.

[259] DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F. -L.; Overman, L. E. *J. Am. Chem. Soc*. **2013**, *135*, 4117–4128.

85).[260] The key step of the synthesis was inspired by the elegant synthesis of (±)-perophoramidine developed by Fuchs and Funk in 2004[261] and consists of a diastereoselective tandem [4+2] cycloaddition-cyclization of the bromooxindole **358** and the tryptamine derivative **359**. As Scheme 85 illustrates, bromooxindole **358** in the presence of an appropriate base, provides intermediate **360**, that reacts with **359** through a [4+2] cycloaddition reaction to form species **362**, which evolves to **364**, through intermediate **363**. Compound **364**, which was obtained in its racemic form as a 95:5 diastereomer mixture, was isolated and purified by column chromatography. The N_b-desmethyl-*meso*-chimonanthine core **130** was provided by reductive-cyclization from the azido group of **364**, employing Red-Al (sodium bis(2-methoxyethoxy) aluminumhydride) as reducing agent and was obtained in 57% yield.

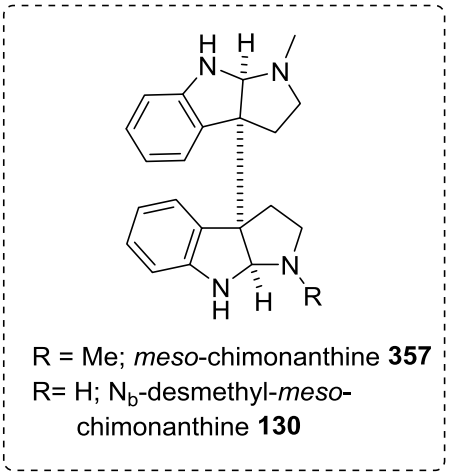
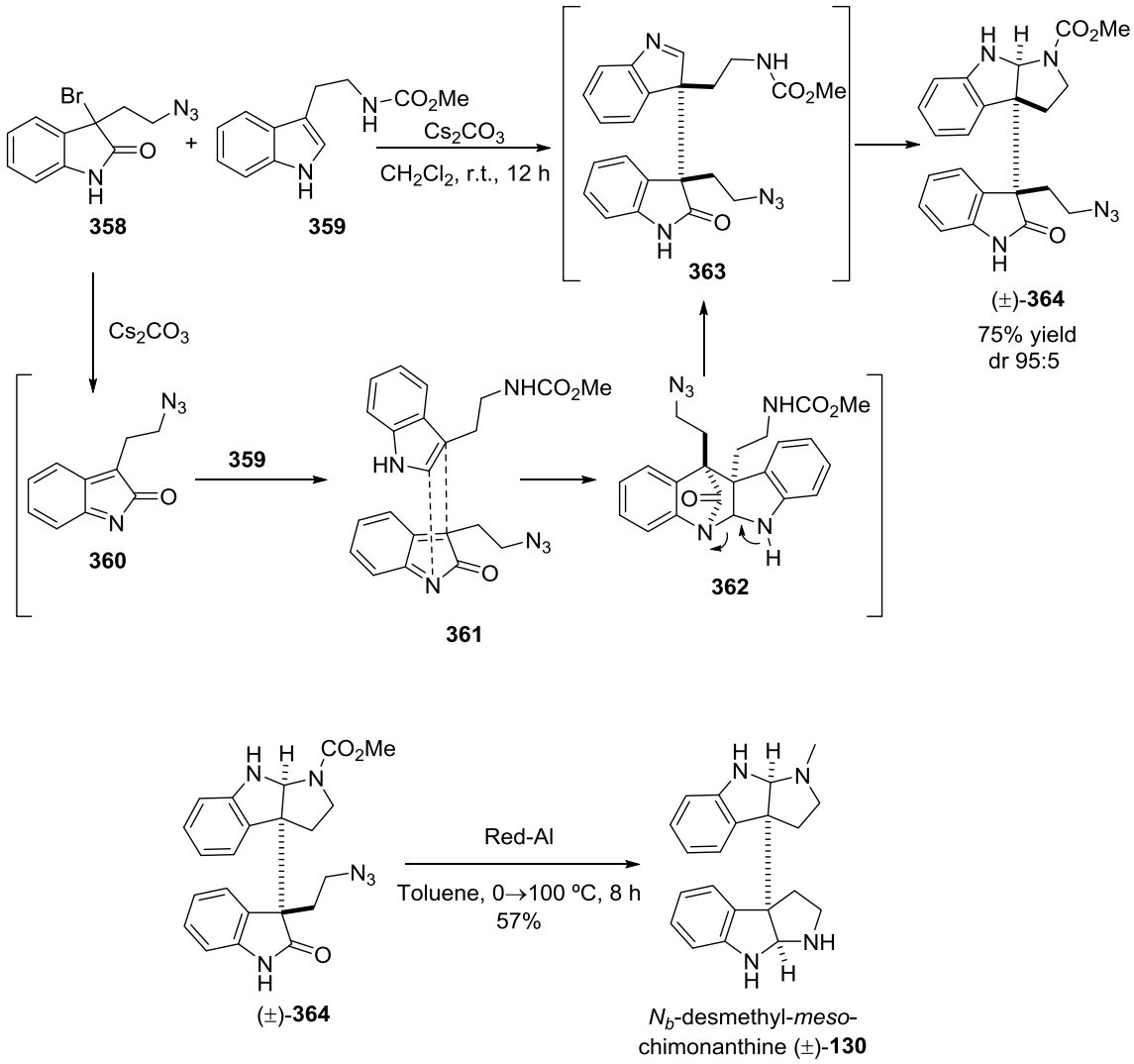


Figure 31. Structure of *meso*-chimonanthine **357** and N_b-desmethyl-*meso*-chimonanthine **130**.

A critical point of this transformation is its chemoselectivity depending on the nitrogen nucleophilicity of the tryptamine side chain **359**. It has been found that amine protection as carbamate is required for success, because when the reaction is performed with the *N*-methyl-tryptamine, the formal substitution of the bromide in **358** occurs. Additionally and for efficient formation of the corresponding diene **360** starting from bromooxindole **358** the free amide in the latter is also necessary.

[260] See ref. 146, page 53.

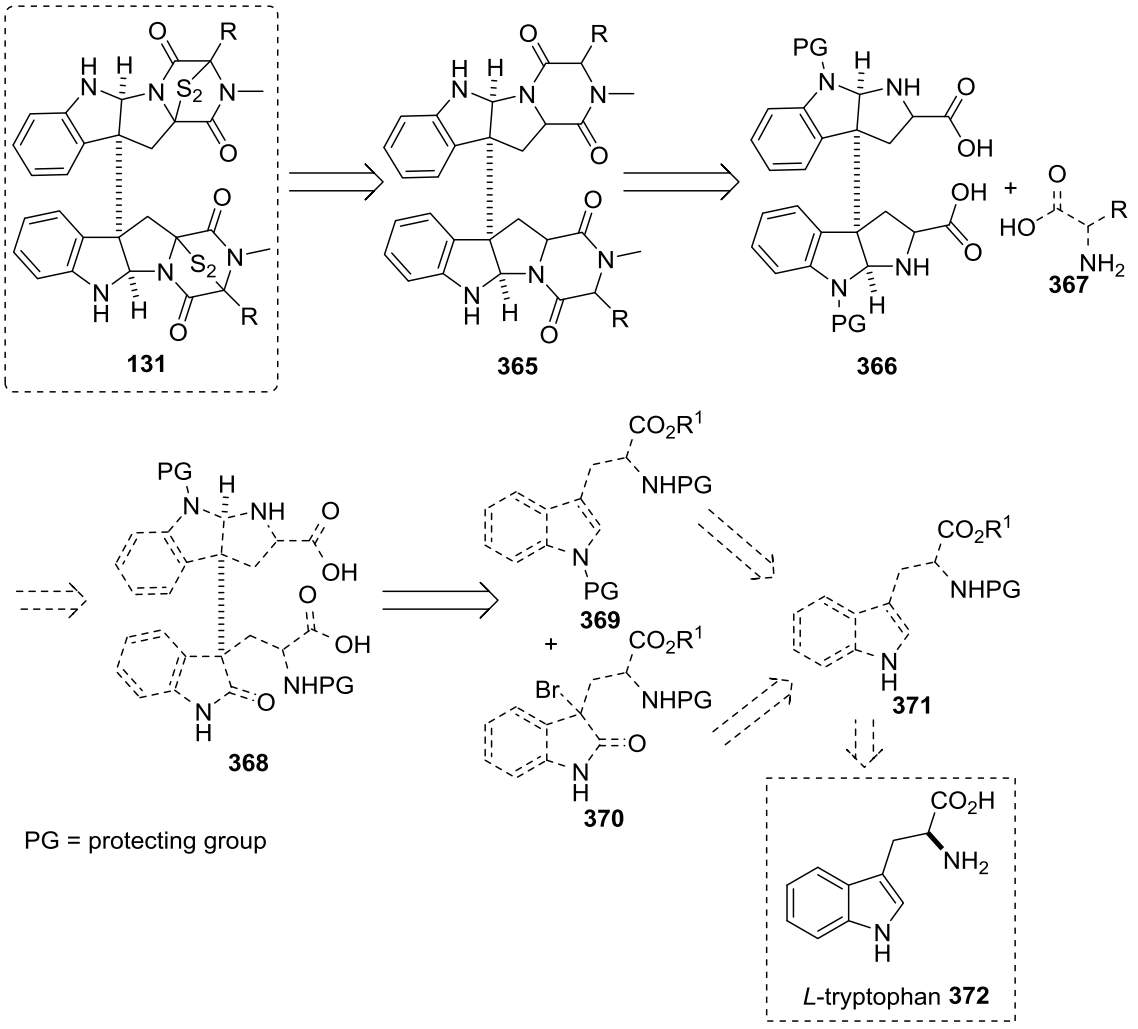
[261] Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc*. **2004**, *126*, 5068–5069.



Scheme 85. Tandem [4+2] cycloaddition-cyclization reaction to obtain the N_b-desmethyl-*meso*-chimonanthine core. **Dalko, 2006**.

On this basis, in a first instance, we focused on the synthesis of leptosins of general structure **131** (Scheme 86). It was considered that the last step of the synthesis must be the construction of the sulfur bridge due to its chemical lability. Thus the most logical pathway would be to prepare first the chimonanthine core **366**;[260] then incorporate the 2,5-diketopiperazine to obtain **365** and finally introduce the disulfide fragment. The diketopiperazine **365** necessary for the incorporation of the dithio bridge could be obtained through peptide coupling of chimonanthine **366** and the appropriate amino acid (Scheme 86). At this point and for successful incorporation of the 2,5-diketopiperazine we envisioned that the two indol nitrogens in **366** should be protected. Finally, chimonanthine **368** would be prepared following the procedure previously reported by Dalko's group starting from bromooxindole **370** and tryptamine derivative **369**, which, in turn, both of them could be obtained from *L*-tryptophan **372**. It is worth

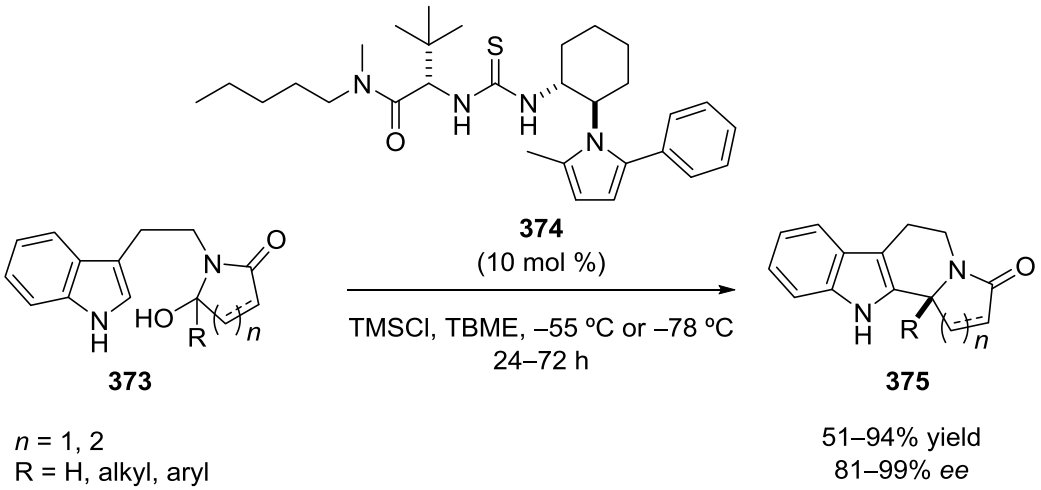
noting that the free amide is required in bromooxindole **370** to form the corresponding diene for the Diels-Alder reaction.



Scheme 86. Retrosynthetic analysis of leptosins **131**.

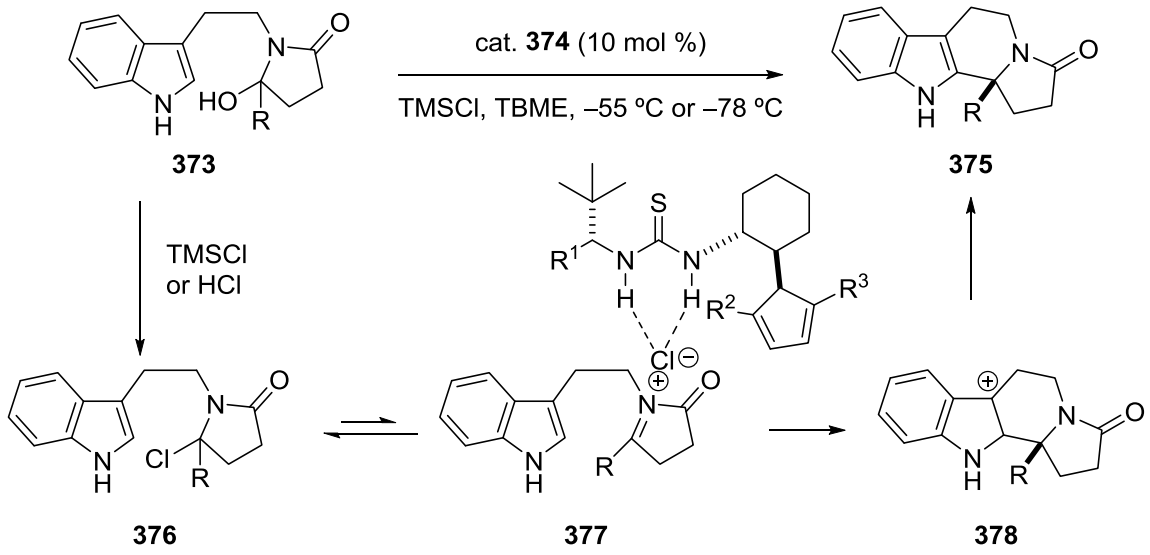
The critical step of this proposal is therefore the incorporation of the dithio bridge in the diketopiperazine derivative **365**. For this step, interest was focused on the organocatalytic Pictet-Spengler-type cyclization catalyzed by chiral thioureas and published by Jacobsen and co-workers in 2007.[262] They described the enantioselective Pictet-Spengler-type cyclization of hydroxylactams **373** through asymmetric catalysis via an anion-binding mechanism (Scheme 87). The reactive iminium ion was generated from hydroxylactam **373** in the presence of either chlorotrimethylsilane or the combination of HCl and 3 Å molecular sieves.

[262] Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2007**, *129*, 13404–13405.



Scheme 87. Asymmetric Pictet-Spengler-type cyclization of hydroxylactams **373** catalyzed by chiral thiourea **374**. **Jacobsen, 2007**.

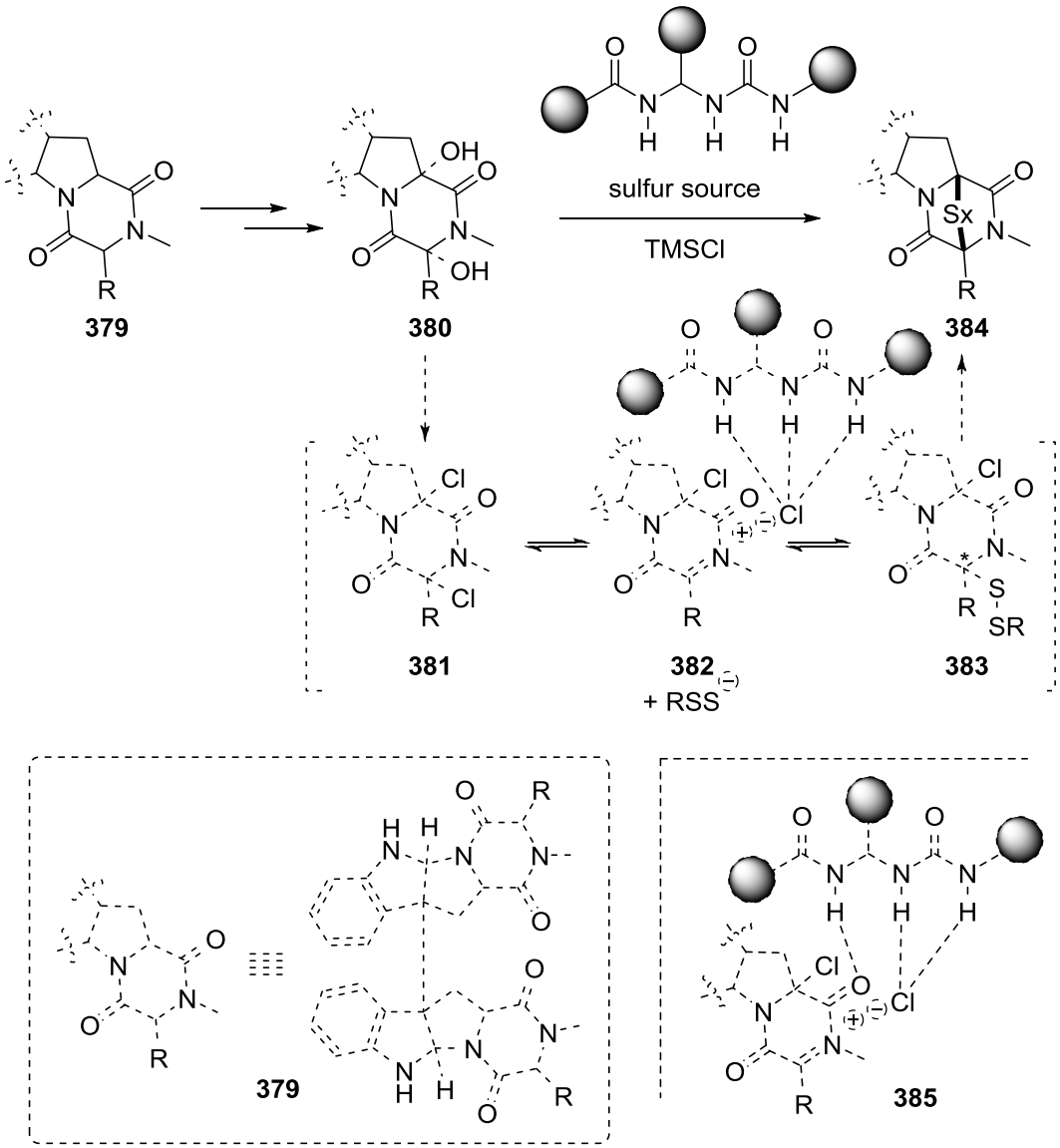
In this reaction the stereodifferentiation has been proposed to occur through the coordination between the chloride iminium counterion and the catalyst as disclosed in Scheme 88. It has been assumed that the iminium cyclization mediated by the resulting chloride anion-bound thiourea occurs asymmetrically.



Scheme 88. Proposed reaction mechanism for the asymmetric cyclization. **Jacobsen, 2007**.

Coming back to our synthetic plan, we considered that sulfur nucleophiles could be added to the reactive iminium **382**, generated from the diketopiperazine intermediate **381** (Scheme 89). On this basis, we proposed a Pictet-Spengler-type thiolation and therefore the evaluation of the addition of different nucleophilic thiol reagents to the putative iminium intermediate **382**, obtained from the dihydroxy intermediate **380**, in the presence of an appropriate H-bond donor catalyst, such as, the ureidopeptide-based

catalysts developed in our group (Scheme 89). It was hypothesized that the chloride anion could interact with the catalyst through the formation of three H-bonds as shown in Scheme 89 and could induce stereoselectivity in the process. Other possibility would be the coordination of the chloride anion through two H-bonds, while one carbonyl oxygen of the diketopiperazine moiety would interact with the remaining NH bond of the catalyst (Scheme 89, **385**). In addition, if double iminium ion formation occurs from the dichlorinated substrate **381**, this organocatalytic reaction would involve the simultaneous generation of four tetrasubstituted carbon stereocenters bearing each a sulfur atom. Two different alternatives could be investigated in this step; on the one hand, the use of a sulfur nucleophile incorporating two sulfur atoms; and on the other hand, the use of two equivalents of a nucleophile carrying only a sulfur atom and then oxidation of the corresponding dithiol to form the bridge.

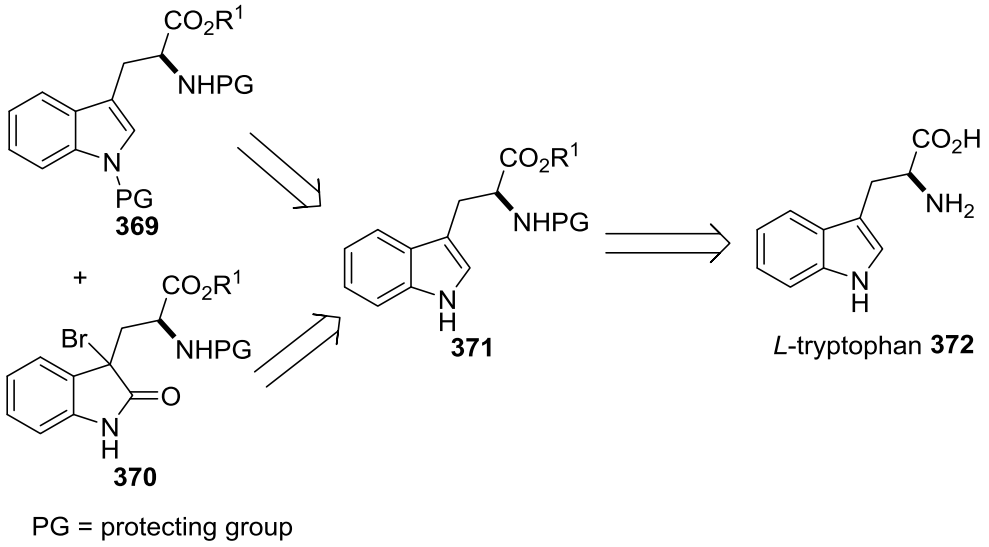


Scheme 89. Suggested reaction to construct the dithio bridge under chiral catalyst mediated organocatalytic conditions.

Thus, the main goals of this project were, on the one hand, to check the validation of the protocol developed by Dalko for the synthesis of the chimonanthine core in the preparation of leptosins or other *epi*(polythio)diketopiperazine alkaloids and; secondly, to investigate a methodology to introduce the sulfur bridge.

4.3. Results and discussion

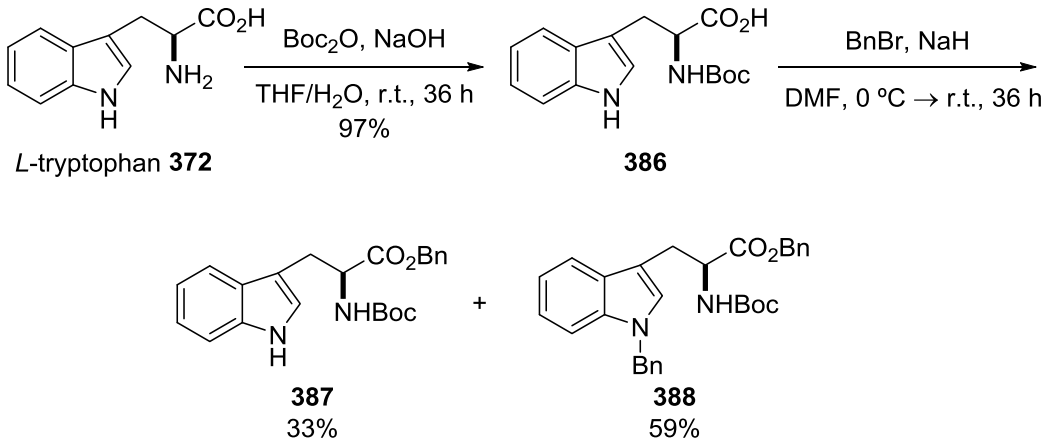
4.3.1. Synthesis of tryptophan derivatives 369 and 370



Scheme 90. Retrosynthetic analysis of **369** and **370**, precursors for the [4+2] cycloaddition-cyclization reaction.

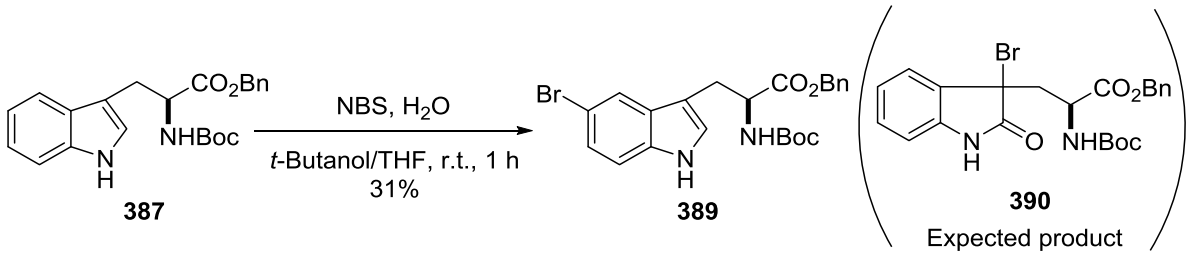
According to the disconnections proposed in Scheme 86 for the preparation of leptosins **131**, interest was first directed to precursors **369** and **370** (Scheme 90). As mentioned before, the starting material of this total synthesis was *L*-tryptophan. Compound **369** would be directly obtained from *L*-tryptophan after conventional protection protocols. And for the obtention of **370** the bromination of **371** by treatment with NBS/H_2O was planned.

The first step was the protection of all the reactive groups of the *L*-tryptophan amino acid. First of all, the primary amine was transformed into its *tert*-butyl carbamate following standard procedures and the *N*-Boc derivative **386** was obtained in 97% yield (Scheme 91). Then one-pot benzylation of both, the carboxylic acid and the tryptophan amine group in compound **386** was tried under the conditions shown in Scheme 91. However, a mixture of mono- and dibenzylated products **387** and **388** were detected in a 1:2 ratio. Even using excess of reagents this ratio could not be improved. Both compounds were separated by column chromatography.



Scheme 91. Protection of *L*-tryptophan.

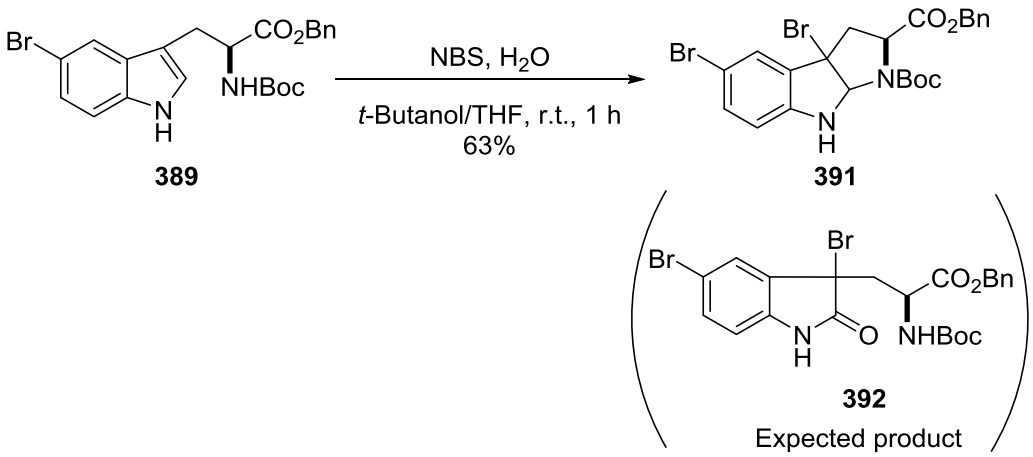
To perform then the [4+2] cycloaddition-cyclization reaction the free secondary amide in bromooxindole derivative **370** is needed, so it was considered that the monobenzylated *L*-tryptophan derivative **387** could be used to access this fragment. Thus, a solution of the tryptophan derivative **387** in *tert*-butanol-water-tetrahydrofuran was treated with *N*-bromosuccinimide (NBS) with the intention of obtaining the expected brominated product **390**.[263] However, after performing the reaction, adduct **389** was isolated instead of the expected product **390** (Scheme 92).



Scheme 92. Bromination of adduct **387**.

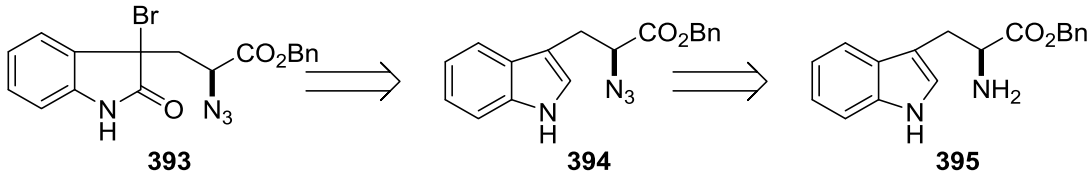
To develop the general protocol and to test the [4+2] cycloaddition-cyclization reaction it was hypothesized that brominated compound **389** could also be useful. Thus the same bromination conditions were tested starting from 5-bromo derivative **389** to produce the dibromooxindole **392**. But once again, the desired product **392** was not isolated. After ^{1}H NMR analysis adduct **391** was detected instead of product **392** (Scheme 93).

[263] a) Hinman, R. L.; Bauman, C. P. *J. Org. Chem*. **1964**, *29*, 1206–1215. b) ref. 261.

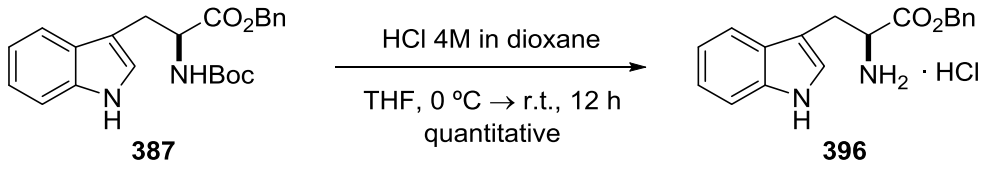


Scheme 93. Second bromination reaction.

At this point a change of the strategy was examined and replacement of the NHBoc group by the azido group was proposed to avoid the formation of the third cycle before the [4+2] cycloaddition-cyclization reaction. So focus was then turned to the synthesis of **393** (Scheme 94), considering that after performing the [4+2] cycloaddition-cyclization, it would be easy to transform the azido group into the primary amine, to perform the reductive cyclization and close the third cycle. For that, the first step was to deprotect the amine in the Boc derivative **387** under standard conditions (Scheme 95) and then transform it into the azido group.



Scheme 94. Retrosynthetic analysis of bromooxindole **393**.



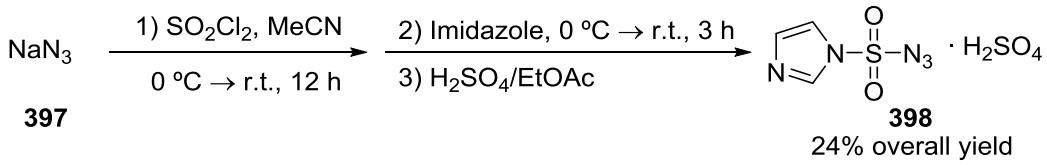
Scheme 95. Deprotection of *tert*-butoxycarbonyl group of adduct **387**.

An efficient approach for the transformation of the amino group into the azide is the diazotransfer reaction described by Shiner in 1972,[264] who utilized

[264] Cavender, C. J.; Shiner, V. J. *J. Org. Chem.* **1972**, *37*, 3567–3569.

trifluoromethanesulfonyl azide (TfN_3) as diazo donor reagent to prepare azides from aliphatic amines. Although this method has been effectively applied by other authors,[265] the explosive nature of neat TfN_3 and the expense of trifluoromethanesulfonic anhydride used in the preparation of TfN_3, made researchers look for other safer alternatives. Likewise, in 2007, Goddard-Borger[266] reported that imidazole-1-sulfonyl azide could replace the TfN_3, being this less costly to prepare, more stable, and in addition, it produces more easily removed by-products and shows comparable efficacy as diazotransfer reagent. Goddard-Borger and co-workers continued working in the field and in 2012 published a work,[267] where they warned about the danger of this compound and investigated different salt derivatives of the diazotransfer reagent developed in 2007, demonstrating that the hydrogen sulfate derivative was the safest one to handle, although usual precautions must be taken. For instance, mother liquors and other waste, which may contain the highly explosive sulfonyl diazide, should be treated with excess of sodium nitrite and acidified to destroy azide-containing species, anhydrous solvents must be used and careful attention must be paid to the stoichiometry and temperature of the reaction.

3-Azidosulfonyl-3*H*-imidazol-1-ium hydrogen sulfate **398** was prepared following the procedure described by Goddard-Borger and taking into account all the recommended safety precautions. Sodium azide was firstly treated with sulfuryl chloride, then imidazole was added and finally, sulfuric acid was incorporated slowly to precipitate the diazotransfer salt **398** (Scheme 96).



397 **398**

24% overall yield

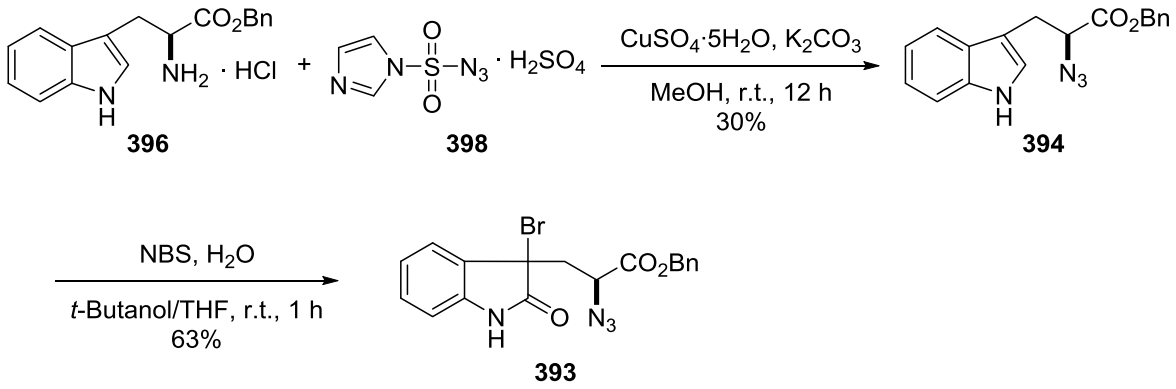
Scheme 96. Synthesis of diazotransfer reagent **398**.

[265] a) Zaloom, J.; Roberts, D. C. *J. Org. Chem*. **1981**, *46*, 5173–5176. b) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Hel*v. *Chim. Acta* **1991**, *74*, 2073–2077. c) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *37*, 6029–6032. d) Lundquist, J. T., IV; Pelletier, J. C. *Org. Lett*. **2001**, *3*, 781–783. e) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778.

[266] a) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett*. **2007**, *9*, 3797–3800. b) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett*. **2011**, *13*, 2514–2514.

[267] Fischer, N.; Goddard-Borger, E. D.; Greiner, R.; Klapötke, T. M.; Skelton, B. W.; Stierstorfer, J. *J. Org. Chem*. **2012**, *77*, 1760–1764.

Once the reagent was ready the diazotransfer reaction was performed following the published indications,[266a] and the desired product **394** was obtained in moderate yield (30%) and was then subjected to oxidative bromination conditions affording in this case the expected adduct **393** in 63% yield and as a mixture of diastereomers which was used as such in the next step (Scheme 97).

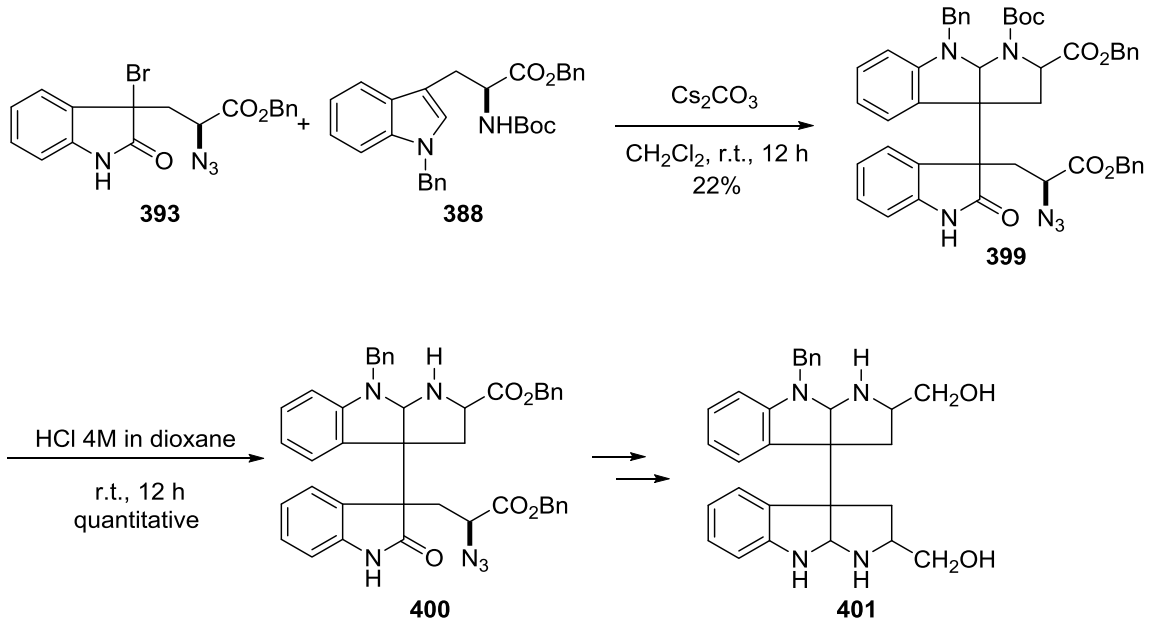


Scheme 97. Synthesis of bromooxindole **393**.

4.3.2. [4+2] Cycloaddition-cyclization reaction between 388 and 393

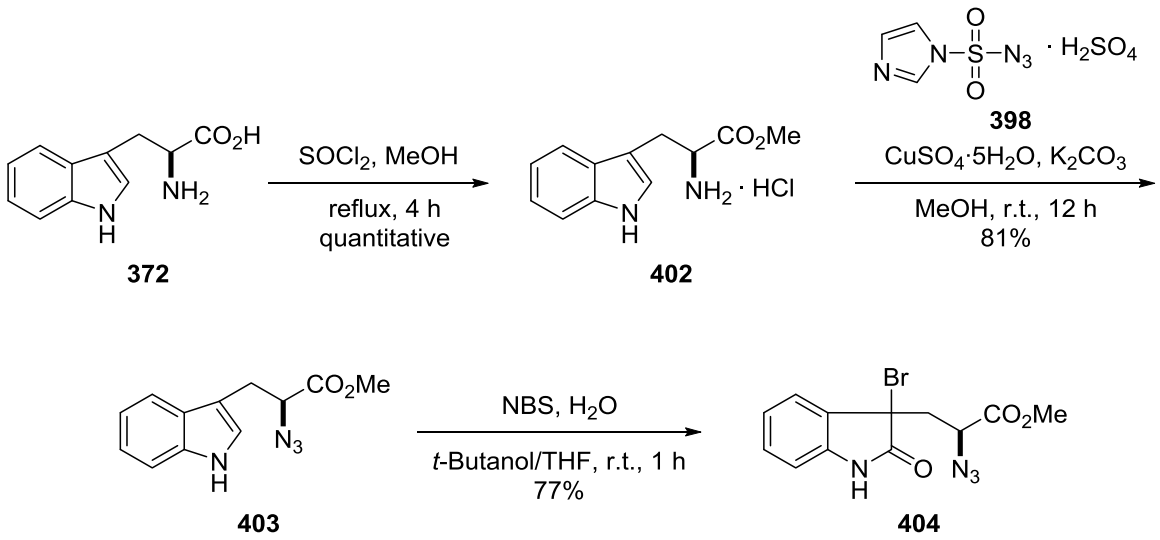
Once bromooxindole **393** and fully protected *L*-tryptophan **388** were synthesized the [4+2] cycloaddition-cyclization reaction previously developed by Dalko[268] was tested (Scheme 98). The reaction worked well but the dimeric compound **399** was obtained in very low yield (22%) and as a diastereomeric mixture whose ratio nor configuration could be determined. Even so, with this compound in hand the next reaction was investigated. The Boc group in **399** was deprotected to afford compound **400**, precursor of **401** after reductive amination followed by cyclization (Scheme 98).

[268] See ref. 146, page 53.



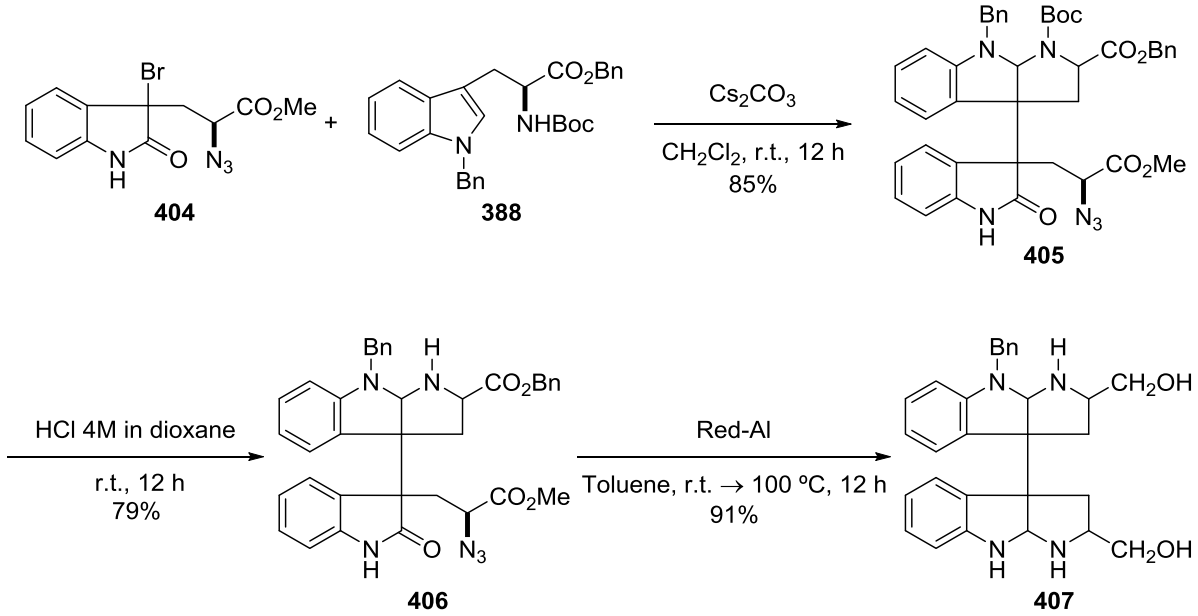
Scheme 98. Synthesis of adduct **399**, starting from *L*-tryptophan derivatives **393** and **388**.

At that time and, considering that the spectra of compounds **393** and **400** were not very clear, and after looking at them closely an important signal at 4.71 ppm was detected in all the ^{1}H NMR spectra. This signal may correspond to the methylene of benzyl alcohol and it was first observed in the ^{1}H NMR spectrum of the crude of the diazotransfer reaction. We hypothesized that, probably, under the conditions of this reaction part of the protected carboxylic acid had been deprotected providing benzyl alcohol. Thus, as alternative, replacement of the benzyl ester by the methyl ester was considered. The methyl ester derivative **402** was easily prepared starting from *L*-tryptophan (Scheme 99) and was then subjected to diazotransfer conditions and oxidative bromination, which proceeded smoothly and very cleanly to afford **404** as a mixture of diastereomers which was used as such for the cycloaddition-cyclization reaction.



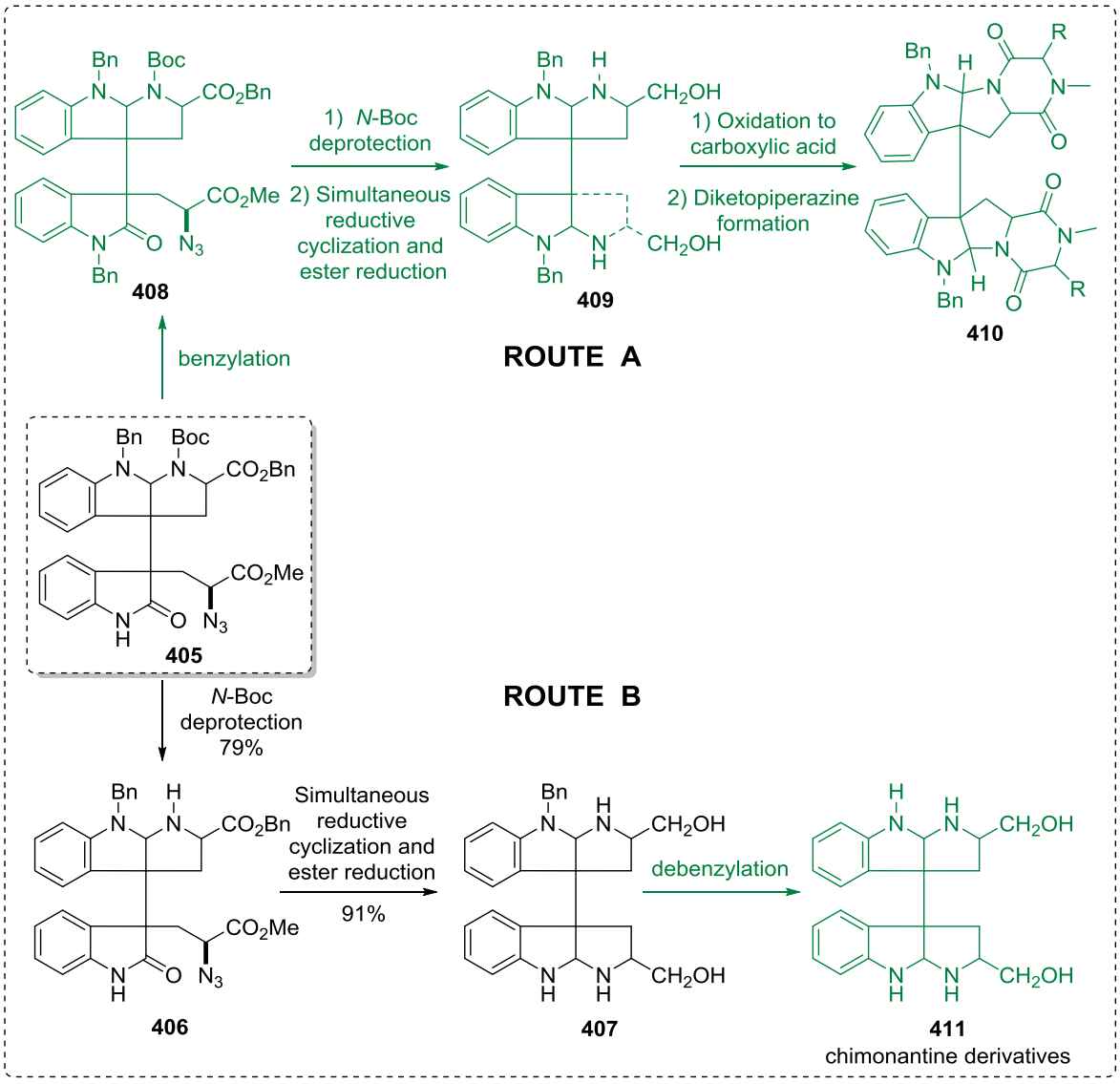
Scheme 99. Synthesis of adduct **404**.

Then the previous cycloaddition-cyclization process was again repeated, but starting from the methyl ester derivative **404** (Scheme 100). In this case the yield of the reaction was good, although a mixture of 1:1.5 of diastereomers whose configuration was not determined, was registered. After *tert*-butoxycarbonyl group deprotection, both pure diastereomers were isolated in small amounts and characterized. Treatment of adduct **406** with Red-Al in toluene promoted the reductive amination starting from the azido group with the simultaneous reduction of both ester groups to afford dimer **407**.



Scheme 100. Synthesis of adduct **407** starting from *L*-tryptophan derivatives **404** and **388**.

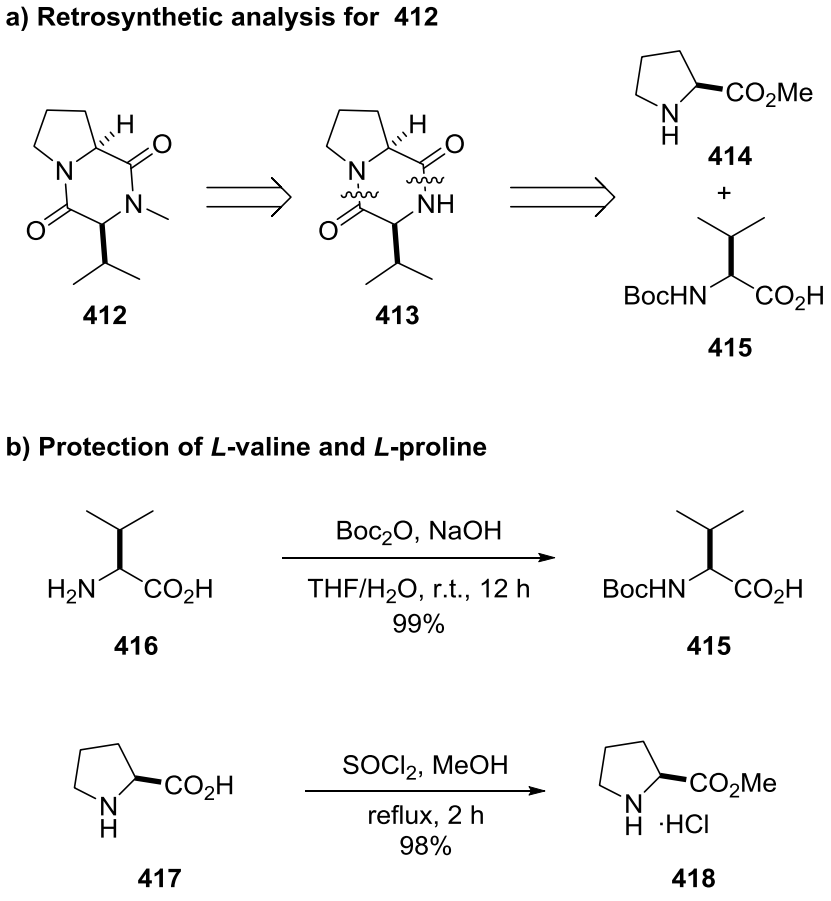
In conclusion, we can say that following Dalko's procedure compound **405** which is a very interesting intermediate for the synthesis of diketopiperazines of type **410** (Scheme 101, route A) and chimonanthine derivatives of type **411** (Scheme 101, route B) has been synthesized. Starting from **405** and, according to previously proposed retrosynthesis, diketopiperazines **410** would be easily accessible through route A. On the other hand, also starting from **405**, **407** has been prepared. This compound is in turn precursor of chimonanthine derivatives of type **411** through debenzylation under Birch reduction conditions (route B). Derivatives **411** are structural motifs of some leptosins, and bear two hydroxymethyl functionalities useful for further transformations.



Scheme 101. Synthetic applications of compound **405** towards leptosins' structures. The performed reactions are shown in black. The possible future transformations leading to diketopiperazines of type **410** and chimonanthine derivatives **411** are shown in green.

4.3.3. Optimization of conditions for thiolation in a model compound

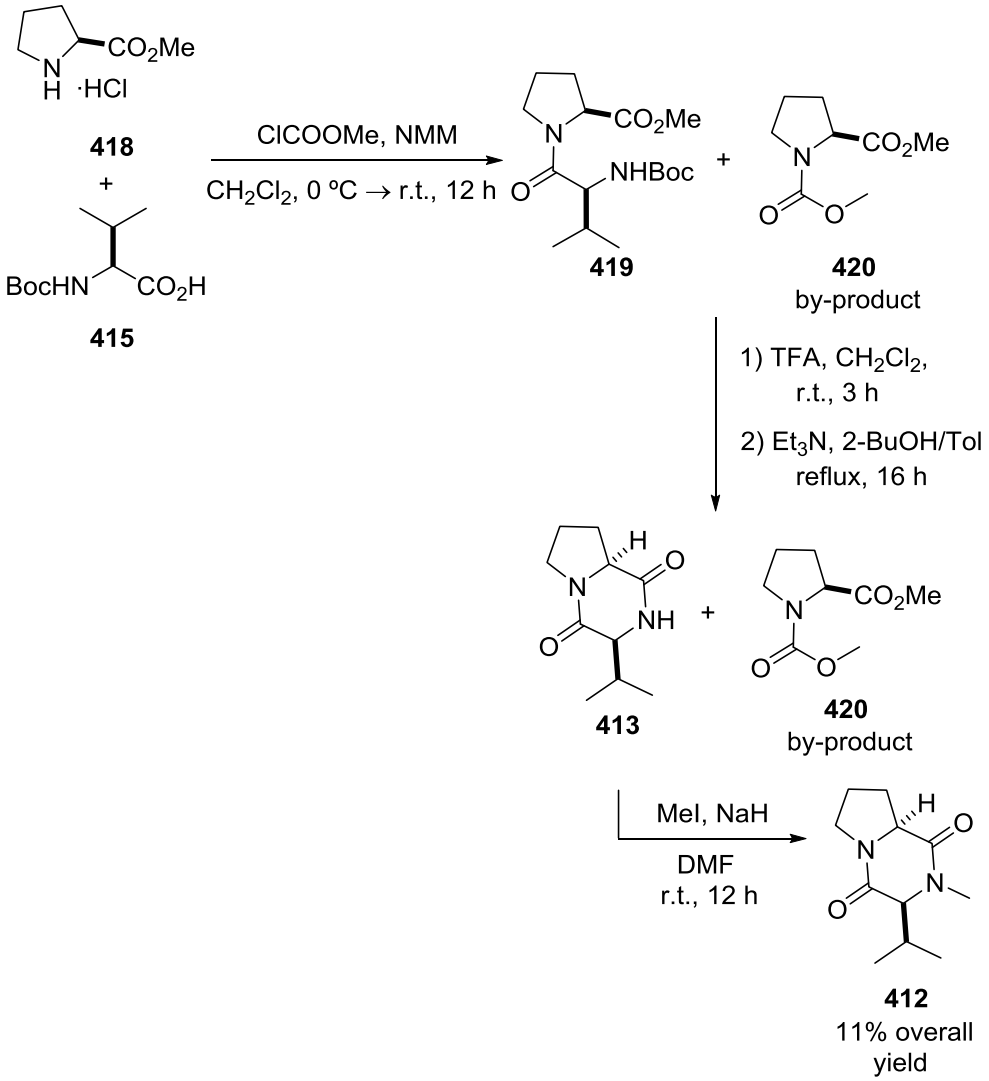
In parallel with the investigation for the synthesis of the basic structure of our target molecule, we considered the possibility of checking the conditions for the construction of the dithio bridge in model compound **412**, which can be easily prepared from *L*-proline methyl ester **414** and *N*-Boc-valine **415** (Scheme 102, a) and closely resembles the right-side structure of our target leptosins.



Scheme 102. Preparation of the precursors for the synthesis of model diketopiperazine **412**. a) Retrosynthetic analysis of **412**. b) Protection of starting amino acids.

Both, *L*-proline methyl ester **418** and *N*-Boc-valine **415** were easily prepared following conventional protocols starting from the free amino acids (Scheme 102, b). The coupling of both derivatives was carried out according to published protocols in the presence of methyl chloroformate and *N*-methylmorpholine under the conditions shown in Scheme 103. The expected diketopiperazine **413** was obtained together with by-product **420**, formed from the reaction between *L*-proline and methyl chloroformate. This mixture of compounds was subjected to Boc deprotection and then refluxed in 2-butanol/toluene in the presence of triethylamine to yield compound **413** together with

by-product **420**. Both derivatives could be separated by column chromatography and **413** was *N*-methylated using methyl iodide and sodium hydride (Scheme 103). Diketopiperazine **412** was obtained in only 11% overall yield, and was used to check the conditions for the thiolation reaction.

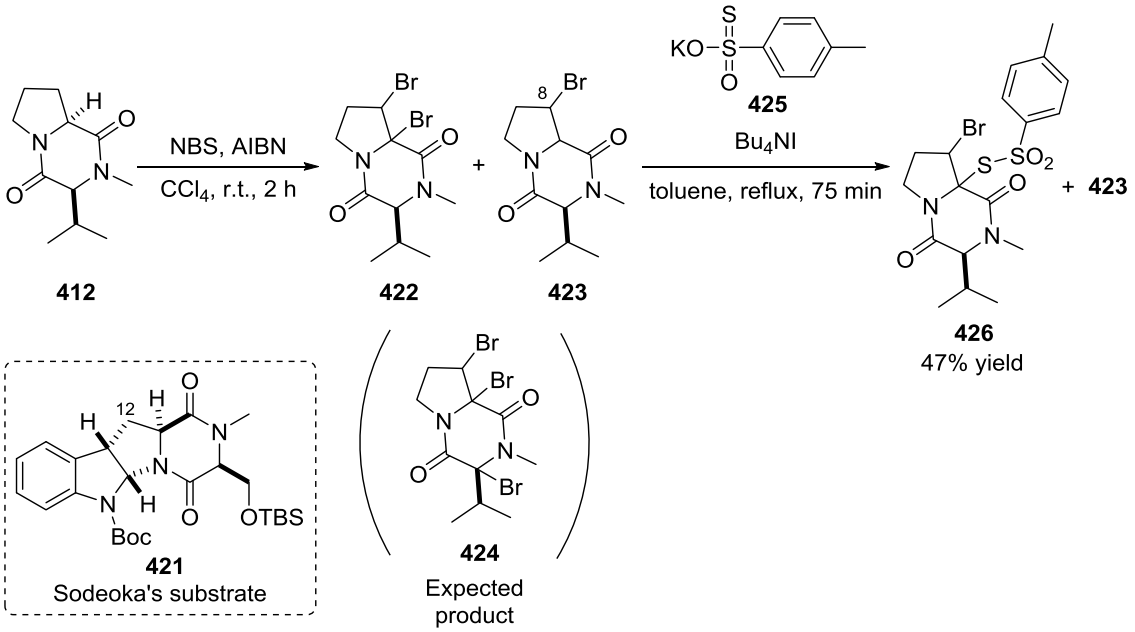


Scheme 103. Synthesis of diketopiperazine **412** through the coupling of amino acid derivatives **418** and **415**.

With diketopiperazine **412** in hand, the appropriate sulfur reagent for thiolation was first checked, for which the first step was to brominate the two key positions in diketopiperazine **412**. For this purpose we focused on the method reported by Sodeoka and co-workers,[269] where they describe the bromination of the structurally similar compound **421** (Scheme 104) by using *N*-bromosuccinimide (NBS) and 2,2'-azobisisobutyronitrile (AIBN) in carbon tetrachloride as solvent. They reported that

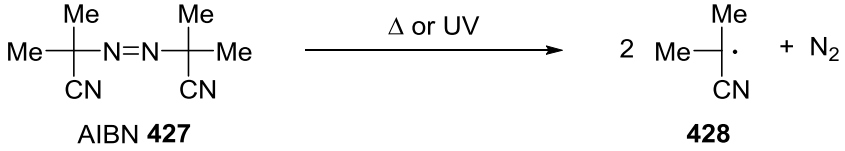
[269] Iwasa, E. Hamashima, Y.; Fujishiro, S.; Hashizume, D.; Sodeoka, M. *Tetrahedron* **2011**, *67*, 6587–6599.

although the desired bromination proceeded smoothly, unavoidably position twelve was also brominated. Considering this observation and, being our main goal to obtain the compound brominated in both α-positions to the carbonyls, we decided to employ three equivalents of NBS in the presence of AIBN as radical initiator (Scheme 104). The reaction was performed following these conditions and compounds **422** and **423** were identified in the resulting crude instead of compound **424**. As usually this type of compounds are not very stable, this mixture was used as such for the thiolation reactions in the presence of potassium *p*-toluenethiosulfonate **425** as sulfur reagent. This reagent has been described for the synthesis of dithio derivatives,[270] but has never been used to produce disulfide bridges. Under the conditions shown in Scheme 104 compound **426** was isolated in 47% yield.



Scheme 104. First approach to form the disulfide bridge in 2,5-diketopiperazine derivative **412**.

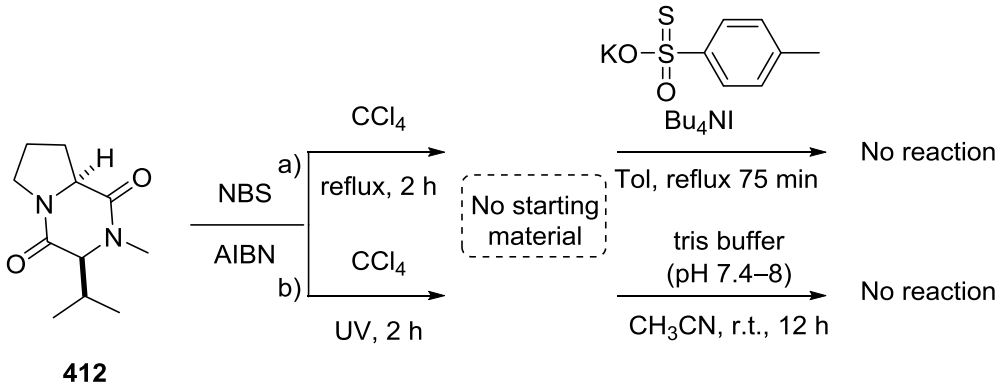
After these results we examined again the bromination reaction. AIBN is commonly used as radical initiator in radical reactions. In our first bromination trial the reaction was run at room temperature, but usually AIBN requires higher temperatures or UV light for the generation of radicals (Scheme 105).



Scheme 105. Decomposition of AIBN.

[270] Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem*. **2005**, *70*, 9740–9754.

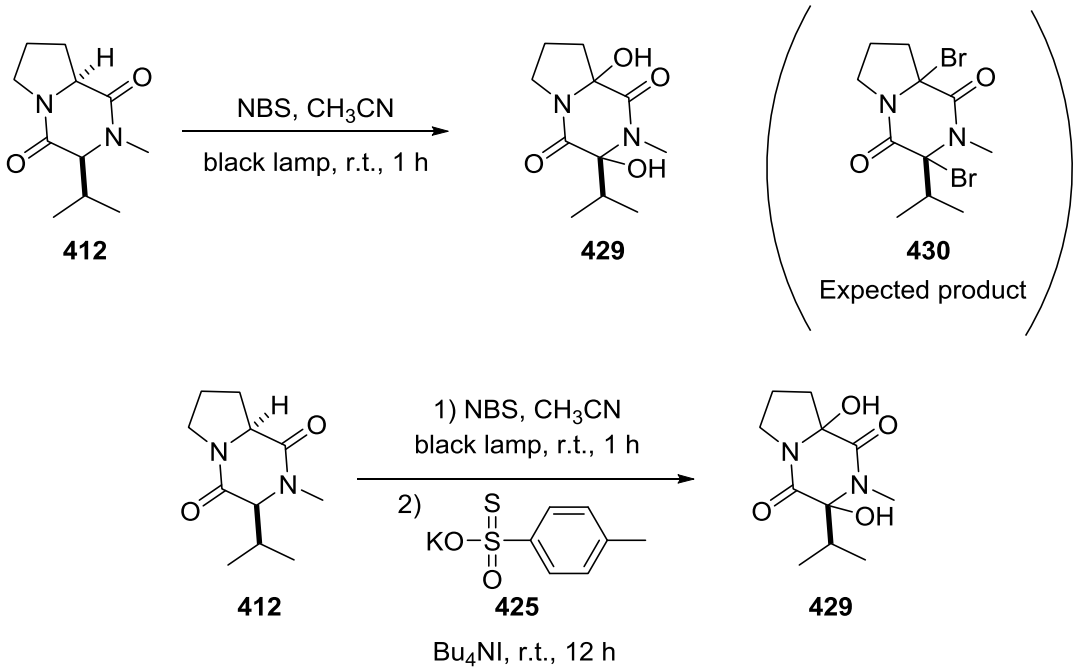
So bromination of compound **412** was again tried under two different reaction conditions: in refluxing CCl_4 (Scheme 106, a) and under UV irradiation (Scheme 106, b). After 2 hours reaction time, no starting material could be observed in the two cases, so potassium *p*-toluenethiosulfonate was added in the first case (Scheme 106, a), and a buffered aqueous solution in the second case (Scheme 106, b). In both cases the material of the first step was recovered unaltered, suggesting that the dibrominated compound was not formed during the first step or decomposed very quickly.



Scheme 106. Approaches for the thiolation of 2,5-diketopiperazine derivative **412**.

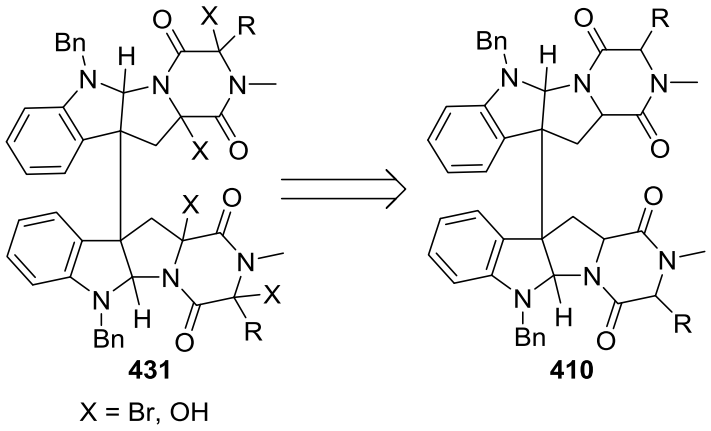
After checking the literature we found that recently Kappe[271] reported visible-light-induced bromination of benzylic compounds with NBS, a reaction which is clean, safe and economical. In this case the radical reaction is activated with a simple household compact fluorescent lamp (CFL) under mild conditions using acetonitrile as solvent. The authors evaluated three different household CFLs: a 30 W cool-white lamp, a 15 W plant-growing lamp and 25 W black-light lamp, and the best results were produced by the latter one. So the bromination reaction was tested using the black-light lamp and NBS in acetonitrile following the conditions reported by Kappe. ^{1}H NMR analysis of the resulting crude, pointed to the obtention of dihydroxy derivative **429** (Scheme 107), maybe because the glassware or the solvent were not dry enough. So the reaction was again performed taking into account this observation and using everything dry. Potassium *p*-toluenethiosulfonate **425** was added *in situ*, without isolation of the intermediate, and dihydroxy derivative **429** was again identified (Scheme 107). Curiously, under these reaction conditions (NBS and black lamp, r.t.) not bromination at position in the pyrrolidine ring seems to occur.

[271] Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. *J. Org. Chem*. **2014**, *79*, 223–229.



Scheme 107. Approaches for the thiolation of 2,5-diketopiperazine derivative **412**.

In conclusion, we can say that after these preliminary experiments we have been able to validate the previously reported Dalko's protocol for the synthesis of some intermediates of leptosins. More specifically compound **407** has been obtained in 61% overall yield and is precursor of some chimonanthine derivatives and some diketopiperazine fused chimonanthines. On the other hand, thanks to the first trials for thiolation in model compound **412**, although unfruitful, we can say that some conditions which could work for the dibromination or dihydroxylation of the diketopiperazine containing leptosins' precursor **410** (Scheme 108) have also been found. Nevertheless, further studies are still needed.



Scheme 108. Proposed synthesis of dibrominated or dihydroxylated derivative **431**.

Chapter 5:

Conclusions

New asymmetric routes to access chiral thioepoxides and tertiary thiols have been developed. Specifically, α,β-thioepoxy carboxylic acids are obtained from *N*-(diazoacetyl)oxazolidin-2-thiones and α,α-disubstituted α-mercapto carboxylic acid derivatives are prepared from 5*H*-thiazol-4-ones.

N-(diazoacetyl)oxazolidin-2-thiones are good substrates in the Rh-catalyzed reaction with benzaldehydes to provide enantioenriched thioepoxides with excellent stereocontrol. The oxazolidinethione in these substrates not only acts as chiral auxiliary, but also as sulfur donor reagent, a feature of the method that is essentially unprecedented in the field of chiral auxiliary chemistry. Removal of the oxazolidinone moiety from the adducts allows the recovery and recycling of the chiral auxiliary and affords the corresponding optically active thiirane carboxylic acids in excellent stereoselectivity. DFT studies provide a plausible rational of the observed reactivity and stereoselectivity of the sulfur transfer event, including the reversal from *cis* to *trans* preference of thioepoxide formation observed with different benzaldehydes.

The usefulness of 5*H*-thiazol-4-ones as efficient reagents in asymmetric synthesis has been demonstrated for the first time. More particularly their potential in the synthesis of tertiary thiol derivatives, for which few synthetic protocols exist, has been shown. These thiazolones add in high stereoselectivity to nitroalkenes in the presence of ureidopeptide-like bifunctional Brønsted bases, a family of novel catalysts developed in our research group. After hydrolysis of the Michael adducts α-mercapto carboxylic acid derivatives are afforded in high stereoselectivity. Furthermore, the addition of 5*H*-thiazol-4-ones to α'silyloxy enone, a key enoate surrogate, provide carboxylic acid derivatives which bear a tetrasubstituted stereogenic carbon.

Under the guidance of Prof. Dr. Peter I. Dalko from the University of Descartes in Paris, a methodology previously described for the synthesis of chimonanthine has been validated for the preparation of the structural core of leptosins. A preliminary study of the thiolation of model diketopiperazines has also been developed.

Chapter 6:

Experimental section

6. Experimental section

Experimental section

6.1. Materials and general techniques

6.1.1. Reagents, solvents and products

Reagents were purchased from different commercial suppliers (Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated.

N,N-dimethylaniline, triethylamine, acetyl chloride and acetyl bromide were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at –30 ºC under nitrogen.

Dirhodium tetraacetate dihydrate ($Rh_2(OAc)_4 \cdot 2H_2O$) was purchased from Alfa Aesar. Catalyst $(DHQ)_2PYR$ **288** was purchased from Aldrich and catalyst **43** from Strem chemicals.

When anhydrous solvents were required, they were dried following established procedures.[272] Dichloromethane and acetonitrile were distilled over CaH_2, toluene was dried over sodium and tetrahydrofuran and diethyl ether were dried by filtration through drying columns (Pure Solv It).

Thiiranes must be stored in a refrigerator and under Ar atmosphere (at –30 ºC they are stable for at least one month). They decompose over time giving off the corresponding olefins and elemental sulfur.

6.1.2. General experimental

All non-aqueous reactions were performed using oven-dried glassware, under inert atmosphere of Ar or N_2 and were magenitacally stirred unless otherwise stated.

Heat requiring reactions were performed using a hotplate with a sand bath and a condenser. Reactions requiring low temperatures were performed using cooling bath circulators *Huber* T100E and acetone or isopropanol baths.

Organic layers washed with aqueous phases were dried over $MgSO_4$ or Na_2SO_4 and filtered through cotton.

[272] Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals* 3rd Edition Butterworth-Heinemann, Oxford **1988**.

Solvent evaporation was carried out in rotavapors Büchi R-110, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when the products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (~0.5 mmHg) was employed.

Unless otherwise specified, yields refer to chromatographically purified and spectroscopically pure compounds.

6.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under ultraviolet light, Fisher Bioblock lamp VL-4LC, $\lambda = 254$ and 365 nm. In addition, TLC plates were also visualized by heating them after contact with an appropriate stain. Solution 1: potassium permanganate (1g) in 100 mL of water. Solution 2: Phosphomolybdic acid (2.5 g), ammonium cerium (IV) nitrate (1 g) in 470 mL of water and 100 mL of sulfuric acid 6% solution.

Chromatographic purification was carried out employing Merck ROCC 60 silica gel 40–63 μm as stationary phase and a suitable mixture of solvents (typically hexane/ ethyl acetate, cyclohexane/ethyl acetate or dichloromethane/methanol) as eluent. In some particular cases non acid silica gel was used, which was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 h. After filtration, the residual water was evaporated in an oven at 80 ºC during 72 h.

6.1.4. Optical rotations

Optical rotations were recorded using a Jasco P-2000 polarimeter or Perkin Elmer 341 polarimeter. Specific rotations (SR) $[\alpha]_D$ were reported in 10^{-1}deg·cm^2·g^{-1}, concentrations (c) were quoted in g/100mL, $_D$ refers to D-line of sodium (589 nm) and temperature (T) was given in degree Celcius (ºC).

6.1.5. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus and microscope and were uncorrected.

6.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer, Bruker 250 spectrometer (250 MHz for ^{1}H, 63 MHz for ^{13}C) or Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C). Chemical shifts (δ) were quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ = 7.26) and ^{13}C (δ = 77.0). The multiplicity of each signal was designed using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet; brs, broad singlet. Coupling constants (*J*) were reported in Hertz (Hz).

MestrReNova Mnova 8.1 program was used to process and edit the registered spectra.

6.1.7. Mass spectra

MS spectra were recorded on an ESI-ion trap Mass spectrometer Agilent 1100 series LC/MSD, SL model, on an UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on a Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) or in the University of Descartes (Paris).

6.1.8. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances were reported.

6.1.9. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600E, equipped with 2996 and 1998 photodiode array UV detector, using Daicel Chiralpak AD-H, OD-H, IA, IB and IC columns. Flow and solvent conditions are given for each compound.

6.1.10. X-ray diffraction analysis

The X-ray diffraction analysis experiments were conducted in the X-ray unit of University of A Coruña (UDC) and in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using difractometers for monocrystals.

6.1.11. Computational studies

All structures were optimized using the functional B3LYP[273] and the 6-31G* basis set as implemented in Gaussian 09.[274] All energy minima and transition structures were characterized by frequency analysis. The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[275] were followed to verify the energy profiles connecting each transition state to the correct associated local minima. The energies reported in this work include single-point calculations at B3LYP/6-311++G** level on the IEF-PCM solvation model (solvent = dichloromethane),[276] using the previously optimized gas-phase structures (B3LYP/6-31G*).

[273] a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

[274] Gaussian 09, Revision B.01; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, Jr. J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J. and Fox, D. J. Gaussian, Inc., Wallingford CT, **2010**.

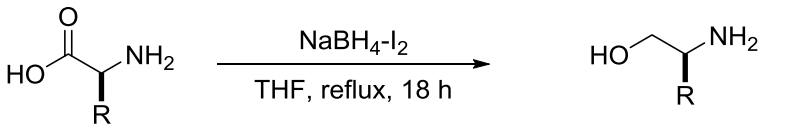
[275] Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.

[276] a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3047. b) Tomasi, J.; Mennucci, B.; Cancès, E. *J. Mol. Struct. (Theochem)* **1999**, *464*, 211–226.

6.2. Experimental section of Chapter 2

6.2.1. General procedure for synthesis of diazocompounds

6.2.1.1. General procedure for synthesis of (S)-aminoalcohols[277]



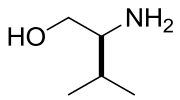
416 R = *i*-Pr
432 R = *t*-Bu
433 R = Bn
434 R = Ph

435 R = *i*-Pr 94%
436 R = *t*-Bu 88%
437 R = Bn 97%
438 R = Ph 91%

(*S*)-aminoalcohols **435**–**438** are commercially available; or may be prepared by reduction of the corresponding amino acid by treatment with $NaBH_4$-I_2 as follows. A 500 mL three-neck round-bottom flash was fitted with a magnetic stirbar, a reflux condenser, and an addition funnel. The flask was charged with sodium borohydride (2.4 equiv., 4.5 g, 120 mmol) and dry THF (130 mL). The (*S*)-amino acid (1 equiv., 50 mmol) was added in one portion and the flask was cooled to 0 ºC in an ice bath. A solution of iodine (1 equiv., 12.7 g, 50 mmol) in THF (30 mL) was poured into the addition funnel and added slowly and dropwise over 30 min resulting in vigorous evolution of hydrogen. After addition of the iodine was complete and gas evolution had ceased, the flask was heated to reflux for 18 h and then cooled to room temperature, and methanol (75 mL) was added cautiously until the mixture became clear. After stirring for 30 min, the solvent was removed by rotary evaporation leaving a white paste which was dissolved by addition of 20% aqueous KOH (100 mL). The solution was stirred for 4 h and extracted with dichloromethane (3 x 100 mL). The organic extracts were combined and dried over $MgSO_4$ and concentrated in vacuo, affording the corresponding (*S*)-aminoalcohol. All data were consistent with those previously reported.

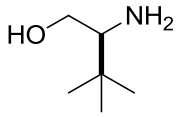
[277] McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568–3571.

(*S*)-Valinol 435[277]



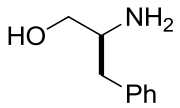
The title compound **435** was prepared from (*S*)-valine (5.8 g, 50 mmol) according to the general procedure. White solid, yield: 4.8 g, 47.0 mmol, 94%. m. p. 32–33 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.64 (dd, *J* = 10.3, 8.9 Hz, 1H), 3.27 (dd, *J* = 10.3, 8.9 Hz, 1H), 2.61–2.51 (m, 1H), 1.67 (bs, 2H), 1.59–1.49 (m, 1H), 0.93 (dd, *J* = 6.8, 4.6 Hz, 6H).

(*S*)-*tert*-Leucinol 436[277]



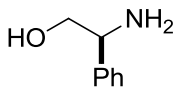
The title compound **436** was prepared from (*S*)-*tert*-leucine (6.6 g, 50 mmol) according to the general procedure. White solid, yield: 5.2 g, 44.4 mmol, 88%. m. p. 31–32 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.71 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.20 (t, *J* = 10.2 Hz, 1H), 2.50 (dd, *J* = 10.1, 3.9 Hz, 1H), 1.75 (bs, 2H), 0.90 (s, 9H).

(*S*)-Phenylalaninol 437[277]



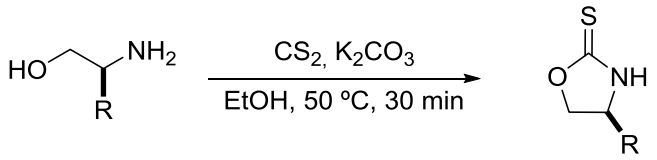
The title compound **437** was prepared from (*S*)-pehnylalanine (8.4 g, 50 mmol) according to the general procedure. White solid, yield: 7.3 g, 48.5 mmol, 97%. m. p. 91–92 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48–6.96 (m, 5H), 3.64 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.39 (dd, *J* = 10.6, 7.2 Hz, 1H), 3.22–3.03 (m, 1H), 2.79 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.53 (dd, *J* = 13.5, 8.6 Hz, 1H), 1.89 (bs, 2H).

(*S*)-Phenylglycinol 438[277]



The title compound **438** was prepared from (*S*)-pehnylglycine (7.6 g, 50 mmol) according to the general procedure. White solid, yield: 6.2 g, 45.5 mmol, 91%. m. p. 70–72 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.58–7.05 (m, 5H), 4.05 (dd, *J* = 8.2, 4.4 Hz, 1H), 3.75 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.56 (dd, *J* = 10.7, 8.2 Hz, 1H), 1.93 (bs, 2H).

6.2.1.2. General procedure for synthesis of oxazolidin-2-thiones[278]

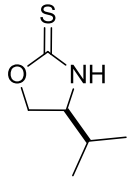


435	R = *i*-Pr	**181**	R = *i*-Pr 78%
436	R = *t*-Bu	**439**	R = *t*-Bu 72%
437	R = Bn	**440**	R = Bn 74%
438	R = Ph	**441**	R = Ph 69%

[278] Li, G.; Ohtani, T. *Heterocycles* **1997**, *45*, 2471–2474.

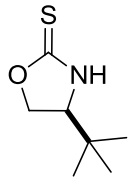
To a suspension of the corresponding (*S*)-aminoalcohol (1 equiv., 40 mmol) and potassium carbonate (0.5 equiv., 2.8 g, 20 mmol) in ethanol (400 mL), was added carbon disulfide (2 eq, 4.8 mL, 80 mmol), at 0 ºC under nitrogen atmosphere. The reaction mixture was stirred at 50 ºC for 30 min and then was cooled to 0 ºC and quenched carefully with a solution of 30% H_2O_2 (8 mL) (Note, very exotermic reaction). The resulting mixture was filtered, diluted with ethyl acetate (300 mL) and washed with water (300 mL) and brine (300 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with AcOEt/Hexane 1/4) to afford the desired product. All data were consistent with those previously reported.

(*S*)-4-Isopropyloxazolidin-2-thione 181[279]



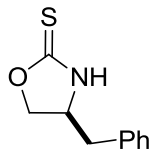
The title compound **181** was prepared from (*S*)-valinol **435** (4.1 g, 40 mmol) according to the general procedure. White solid, yield: 4.5 g, 31.2 mmol, 78%. m. p. 44–47 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.69 (t, *J* = 9.1 Hz, 1H), 4.39 (dd, *J* = 9.1, 6.7 Hz, 1H), 3.91–3.71 (m, 1H), 1.90–1.72 (m, 1H), 0.96 (dd, *J* = 13.5, 6.8 Hz, 6H).

(*S*)-4-(*tert*-Butyl)oxazolidin-2-thione 439[280]



The title compound **439** was prepared from (*S*)-*tert*-leucinol **436** (4.7 g, 40 mmol) according to the general procedure. White solid, yield: 4.6 g, 29.8 mmol, 72%. m. p. 152–154 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.62 (t, *J* = 9.6 Hz, 1H), 4.46 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.81 (dd, *J* = 9.6, 6.3 Hz, 1H), 0.94 (s, 9H).

(*S*)-4-Benzyloxazolidin-2-thione 440[279]

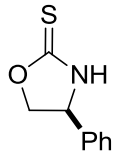


The title compound **440** was prepared from (*S*)-phenylalaninol **437** (6.0 g, 40 mmol) according to the general procedure. Yellow oil, yield: 5.7 g, 29.6 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36 (m, 3H), 7.21 (m, 2H), 4.76 (t, *J* = 8.7 Hz, 1H), 4.49−4.23 (m, 2H), 2.95 (m, 2H).

[279] Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604–6607.

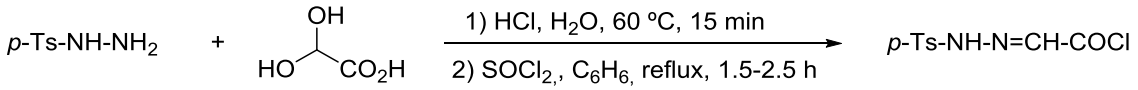
[280] Baiget, J.; Cosp, A.; Gálvez, E.; Gómez-Pinal, L.; Romea, P.; Urpí, F. *Tetrahedron*, **2008**, *64*, 5637–5644.

(*S*)-4-Phenyloxazolidin-2-thione 441[281]



The title compound **441** was prepared from (*S*)-phenylglycinol **438** (5.5 g, 40 mmol) according to the general procedure. White solid, yield: 4.9 g, 27.6 mmol, 69%. m. p. 118–120 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48–7.28 (m, 5H), 5.10 (dd, *J* = 9.1, 6.7 Hz, 1H), 5.06–4.94 (m, 1H), 4.49 (dd, *J* = 8.7, 6.6 Hz, 1H).

6.2.1.3. Procedure for the synthesis of 2-(2-tosylhydrazono)acetyl chloride[282]



A) Glyoxylic acid p-toluenesulfonylhydrazone:

To a solution of glyoxylic acid (23.5 g, 255.1 mmol) in water (500 mL) at 60 ºC was added a solution of *p*-toluenesulfonylhydrazide (46.6 g, 250.0 mmol) in 2.5 M HCl (125 mL) at 60 ºC. The resulting mixture was stirred at the same temperature until all the hydrazone, which initially separated as oil, solidified (about 15 min). The mixture was allowed to cool to room temperature and then it was stored in the fridge at 0 ºC overnight. After this time the crude was filtered, washed with cool water and allowed to dry for 2 days. The crude product was dissolved in boiling ethyl acetate (200 mL), filtered to remove any insoluble material and diluted with CCl_4 (400 mL). The solution was stored in the fridge overnight and then the precipitate was filtered off and dried (for two days at 50 ºC) to give the glyoxylic acid *p*-toluenesulfonylhydrazone as white crystals.

B) 2-(2-Tosylhydrazono)acetyl chloride:

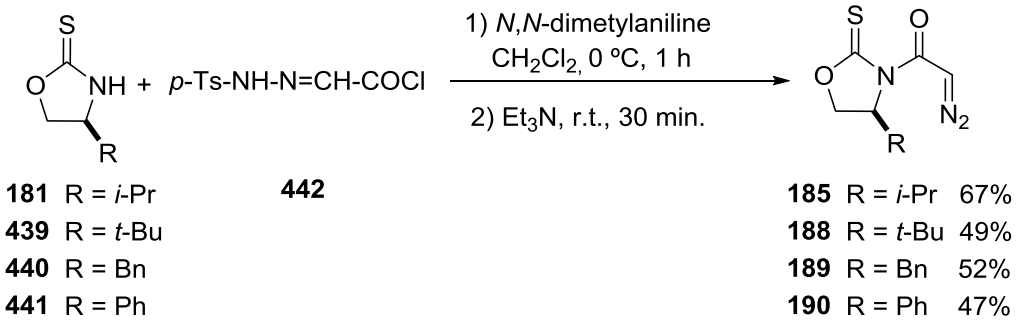
To a suspension of glyoxylic acid *p*-toluenesulfonylhydrazone (10.0 g, 41.3 mmol) in benzene (50 mL) was added thionyl chloride (2 equiv., 6 mL, 82.4 mmol). The reaction mixture was heated under reflux until vigorous gas evolution ceased and most of suspended solid was dissolved (1.5–2.5 h). The mixture was cooled to room

[281] Wu, Y.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990–3992.

[282] a) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53–60. b) *Organic Synthesis*; John Wiley & Sons, Inc.; U. S. A., **1973**; Col. Vol. 5, p 258–263.

temperature, filtered through celite and the solvent was evaporated under reduce pressure, affording 2-(2-tosylhydrazono)acetyl chloride **442**.

*6.2.1.4. Procedure for the synthesis of thionediazocompounds **185, 188–190***



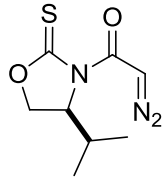
181 R = *i*-Pr
439 R = *t*-Bu
440 R = Bn
441 R = Ph

442

185 R = *i*-Pr 67%
188 R = *t*-Bu 49%
189 R = Bn 52%
190 R = Ph 47%

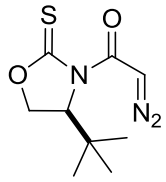
To a mixture of the corresponding *NH*-oxazolidin-2-thione (10.0 mmol) and 2-(2-tosylhydrazono)acetyl chloride **442** (1.8 equiv., 4.7 g, 18.0 mmol) in dry CH_2Cl_2 (60 mL) at 0 ºC, was added *N*,*N*-dimetylaniline (1.8 equiv., 2.3 mL, 18.0 mmol) under argon atmosphere. The resulting mixture was stirred at 0 ºC for 1 h and then triethylamine (5 equiv., 7.0 mL, 50.0 mmol) was added. The reaction was stirred at the same temperature for 30 min. Next, the temperature was allowed to rise to room temperature and the mixture was stirred for another 10 min. The reaction mixture was then quenched with water (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 x 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with AcOEt/Hexane 1/9) to afford the desired product.

(*S*)-2-Diazo-1-(4-isopropyl-2-thioxooxazolidin-3-yl)ethanone 185



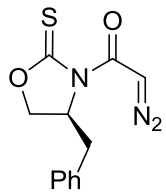
The title compound **185** was prepared from (*S*)-4-isopropyloxazolidin-2-thione **181** (1.5 g, 10 mmol) according to the general procedure. Yellow solid, yield: 1.4 g, 6.7 mmol, 67%. $[\alpha]_D^{25}$ = +132.5 (c = 1.00, CH_2Cl_2). m. p. 53–54 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.97 (s, 1H), 4.81 (dd, *J* = 9.9, 5.4 Hz, 1H), 4.39 (d, *J* = 5.4 Hz, 2H), 2.40 (m, 1H), 0.91 (dd, *J* = 17.3, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 185.3, 164.4, 67.4, 63.2, 51.1, 29.2, 18.0, 14.8. HRMS: $C_8H_{12}NO_2S$ $[M+H-2N]^+$ calcd.: 186.0584, found: 186.0586.

(*S*)-1-(4-(*tert*-Butyl)-2-thioxooxazolidin-3-yl)-2-diazoethanone 188



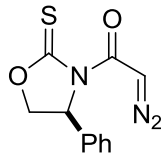
The title compound **188** was prepared from (*S*)-4-(*tert*-butyl)oxazolidin-2-thione **439** (1.6 g, 10 mmol) according to the general procedure. Brown solid, yield: 1.1 g, 4.9 mmol, 49%. $[\alpha]_D^{25}$ = +194.0 (c = 1.00, CH_2Cl_2). m. p. 63–64 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.85 (s, 1H), 4.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.47 (dd, *J* = 9.5, 1.8 Hz, 1H), 4.36 (dd, *J* = 9.5, 7.8 Hz, 1H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 186.2, 164.9, 69.2, 65.1, 51.2, 36.2, 25.6. UPLC-DAD-QTOF: $C_9H_{13}N_3NaO_2S$ $[M+Na]^+$ calcd.: 250.0626, found: 250.0620.

(*S*)-1-(4-Benzyl-2-thioxooxazolidin-3-yl)-2-diazoethanone 189



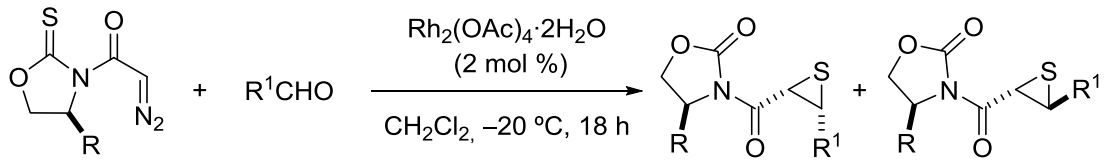
The title compound **189** was prepared from (*S*)-4-benzyloxazolidin-2-thione **440** (1.9 g, 10 mmol) according to the general procedure. Pale yellow solid, yield: 1.3 g, 5.2 mmol, 52%. $[\alpha]_D^{25}$ = +127.5 (c = 1.00, CH_2Cl_2). m. p. 66–68 ºC. ^{1}H-RMN ($CDCl_3$, 300 MHz), δ: 7.97 (s, 1H), 7.50–7.09 (m, 5H), 5.04 (m, 1H), 4.43–4.23 (m, 2H), 3.32 (dd, *J* = 3.3, 13.4 Hz, 1H), 2.82 (dd, *J* = 9.7, 13.4 Hz, 1H). ^{13}C-RMN (75 MHz, $CDCl_3$), δ: 184.7, 164.2, 135.0, 129.3, 128.9, 127.3, 70.1, 59.8, 51.2, 37.6. HRMS: $C_{12}H_{12}NO_2S$ $[M+H-2N]^+$ calcd.: 234.0589, found: 234.0599.

(*S*)-2-Diazo-1-(4-phenyl-2-thioxooxazolidin-3-yl)ethanone 190



The title compound **190** was prepared from (*S*)-4-phenyloxazolidin-2-thione **441** (1.8 g, 10 mmol) according to the general procedure. Yellow solid, yield: 1.1 g, 4.7 mmol, 47%. $[\alpha]_D^{25}$ = +211.6 (c = 1.00, CH_2Cl_2). m. p. 103–105 ºC (decomposition). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.91 (s, 1H), 7.49–7.16 (m, 5H), 5.80 (dd, *J* = 8.8, 3.5 Hz, 1H), 4.80 (t, *J* = 8.9 Hz, 1H), 4.45 (dd, *J* = 9.1, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 184.9, 163.9, 138.5, 129.3, 129.0, 126.0, 73.9, 62.1, 51.5. HRMS: $C_{11}H_{10}NO_2S$ $[M+H-2N]^+$ calcd.: 220,0427, found: 220.0444.

6.2.2. General procedure for the catalytic synthesis of thiiranes 187, 191–193



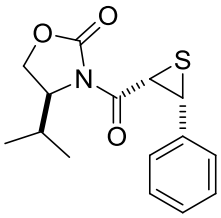
185 R = *i*-Pr
188 R = *t*-Bu
189 R = Bn
190 R = Ph

186

187 R = *i*-Pr
191 R = *t*-Bu
192 R = Bn
193 R = Ph

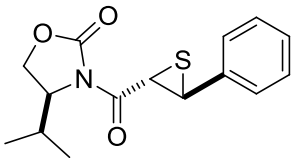
To a solution of the corresponding diazocompound **185**, **188–190** (1 equiv.) and aldehyde **186a-n** (3 equiv.) in dry CH_2Cl_2 (3 mL/mmol) at –20 ºC, was added rhodium (II) acetate dihydrate (2 mol %) under argon atmosphere. The reaction mixture was stirred overnight at the same temperature and afterwards quenched with saturated $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was analyzed by ^{1}H NMR spectroscopy in order to determine the *cis/trans* isomeric ratio produced in each case. Subsequent purification of the crude product by flash column chromatography on silica gel (eluting with AcOEt/Hexane 1/4) allowed isolation of pure major isomer (in some specific cases, minor diastereomer could also be isolated and fully characterized).

(*S*)-4-Isopropyl-3-((2*S*,3*R*)-3-phenylthiirane-2-carbonyl)oxazolidin-2-one *cis*-187a



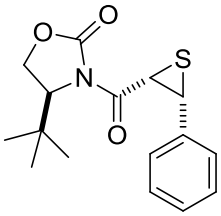
The title compound *cis*-**187a** was prepared from **185** (426 mg, 2.0 mmol) and benzaldehyde (610 μL, 6.0 mmol) according to the general procedure (1st fraction of the chromatographic column). White solid, yield: 379 mg, 1.30 mmol, 65%. $[\alpha]_D^{25}$ = +105.5 (c = 1.00, CH_2Cl_2). m. p. 96–98 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41–7.38 (m, 2H), 7.25–7.23 (m, 3H), 4.54 (d, *J* = 7.7 Hz, 1H), 4.40 (d, *J* = 7.7 Hz, 1H), 4.24–4.19 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 1H), 1.81–1.70 (m, 1H), 0.66 (d, *J* = 7.1 Hz, 3H), 0.06 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.9, 153.5, 133.8, 128.5, 128.1, 128.0, 63.6, 58.8, 43.5, 41.4, 28.0, 17.6, 13.3. HRMS: $C_{15}H_{18}NO_3S$ $[M+H]^+$ calcd.: 292.1007, found: 292.1012.

(*S*)-4-Isopropyl-3-((2*S*,3*S*)-3-phenylthiirane-2-carbonyl)oxazolidin-2-one *trans*-187a



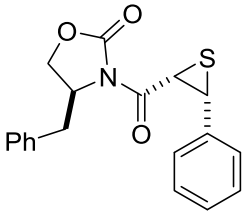
The title compound *trans*-**187a** was prepared from **185** (426 mg, 2.0 mmol) and benzaldehyde (610 μL, 6.0 mmol) according to the general procedure. Colorless oil, yield: 29 mg, 0.10 mmol, 5% (2nd fraction of the chromatographic column). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39–7.28 (m, 5H), 4.95 (d, *J* = 4.8 Hz, 1H), 4.54 (d, *J* = 4.8 Hz, 1H), 4.51–4.45 (m, 1H), 4.39–4.31 (m, 1H), 4.26 (dd, *J* = 9.1, 3.1 Hz, 1H), 2.44–2.31 (m, 1H), 0.93 (dd, *J* = 9.2, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 168.8, 153.8, 136.7, 128.7, 128.2, 127.3, 63.7, 59.0, 41.3, 36.4, 28.6, 17.9, 14.8. HRMS: $C_{15}H_{18}NO_3S$ $[M+H]^+$ calcd.:292.1007, found: 292.15.

(*S*)-4-(*tert*-Butyl)-3-((2*S*,3*R*)-3-phenylthiirane-2-carbonyl)oxazolidin-2-one *cis*-191a



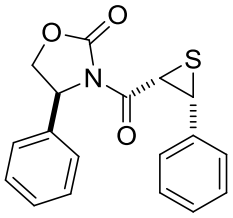
The title compound *cis*-**191a** was prepared from **188** (68 mg, 0.3 mmol) and benzaldehyde (91 μL, 0.9 mmol) according to the general procedure. White solid, yield: 55 mg, 0.18 mmol, 60%. $[\alpha]_D^{25}$ = +97.4 (c = 1.00, CH_2Cl_2). m. p. 112–115 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.49–7.44 (m, 2H), 7.29–7.20 (m, 3H), 4.51 (d, *J* = 7.7 Hz, 1H), 4.44 (d, *J* = 7.7 Hz, 1H), 4.23–4.18 (m, 2H), 4.13 (dd, *J* = 5.9, 3.0 Hz, 1H), 0.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.1, 154.7, 133.7, 128.9, 128.2, 128.0, 65.9, 62.1, 43.5, 41.8, 35.2, 25.1. HRMS: $C_{16}H_{20}NO_3S$ $[M+H]^+$ calcd.: 306.1164, found: 306.1171.

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-phenylthiirane-2-carbonyl)oxazolidin-2-one *cis*-192a



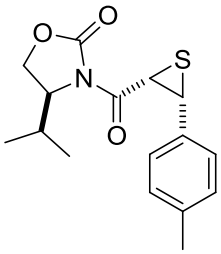
The title compound *cis*-**192a** was prepared from **189** (78 mg, 0.3 mmol) and benzaldehyde (91 μL, 0.9 mmol) according to the general procedure. White solid, yield: 41 mg, 0.12 mmol, 40%. $[\alpha]_D^{25}$ = +101.0 (c = 1.00, CH_2Cl_2). m. p. 114–117 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ. 7.48–7.43 (m, 1H), 7.36–7.20 (m, 7H), 6.95–6.89 (m, 2H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.48–4.39 (m, 2H), 4.11 (t, *J* = 8.4 Hz, 1H), 3.98 (dd, *J* = 9.1, 2.4 Hz, 1H), 2.52 (dd, *J* = 13.6, 3.2 Hz, 1H), 1.70 (dd, *J* = 13.5, 10.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.4, 153.2, 135.2, 133.8, 129.4, 129.1, 128.9, 128.6, 128.2, 127.2, 66.5, 55.4, 43.1, 41.2, 36.6. HRMS: $C_{19}H_{18}NO_3S$ $[M+H]^+$ calcd.: 340.1007, found: 340.1022.

(*S*)-4-Phenyl-3-((2*S*,3*R*)-3-phenylthiirane-2-carbonyl)oxazolidin-2-one *cis*-193a



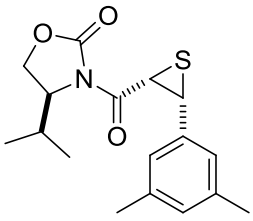
The title compound *cis*-**193a** was prepared from **190** (74 mg, 0.3 mmol) and benzaldehyde (91 µL, 0.9 mmol) according to the general procedure. White solid, yield: 45 mg, 0.14 mmol, 45%. $[\alpha]_D^{25}$ = +111.8 (c = 1.00, CH_2Cl_2). m. p. 108–110 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.49–7.05 (m, 9H), 6.57-6.48 (m, 1H), 5.29 (dd, *J* = 8.6, 3.4 Hz, 1H), 4.68 (t, *J* = 8.7 Hz, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 4.46 (d, *J* = 7.6 Hz, 1H), 4.13 (dd, *J* = 8.8, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8, 153.6, 138.0, 133.5, 129.0, 128.5, 128.3, 128.0, 125.1, 70.7, 57.8, 43.0, 41.3. HRMS: $C_{18}H_{16}NO_3S$ $[M+H]^+$ calcd.: 326.0851, found: 326.0858.

(*S*)-4-Isopropyl-3-((2*S*,3*R*)-3-(p-tolyl)thiirane-2-carbonyl)oxazolidin-2-one *cis*-187b



The title compound *cis*-**187b** was prepared from **185** (107 mg, 0.5 mmol) and 4-methylbenzaldehyde (177 µL, 1.5 mmol) according to the general procedure. White solid, yield: 92 mg, 0.30 mmol, 60%. $[\alpha]_D^{25}$ = +103.2 (c = 1.00, CH_2Cl_2). m. p. 101–103 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.27 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.36 (d, *J* = 7.6 Hz, 1H), 4.26–4.18 (m, 2H), 4.07 (d, *J* = 6.6 Hz, 1H), 2.29 (s, 3H), 1.81–1.74 (m, 1H), 0.67 (d, *J* = 7.1 Hz, 3H), 0.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.2, 153.8, 137.8, 130.8, 128.8, 128.4, 63.6, 58.8, 43.6, 41.4, 28.0, 20.9, 17.7, 13.1. HRMS: $C_{16}H_{20}NO_3S$ $[M+H]^+$ calcd.: 306.1164, found: 306.1164.

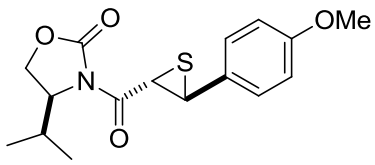
(*S*)-3-((2*S*,3*R*)-3-(3,5-Dimethylphenyl)thiirane-2-carbonyl)-4-isopropyloxazolidin-2-one *cis*-187c



The title compound *cis*-**187c** was prepared from **185** (107 mg, 0.5 mmol) and 3,5-dimethylbenzaldehyde (202 µL, 1.5 mmol) according to the general procedure. Colorless oil, yield: 98 mg, 0.31 mmol, 61%. $[\alpha]_D^{25}$ = +66.1 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.98 (s, 2H), 6.85 (s, 1H), 4.52 (d, *J* = 7.7 Hz, 1H), 4.35–4.24 (m, 2H), 4.21 (d, *J* = 8.3 Hz, 1H), 4.08 (dd, *J* = 8.1, 1.5 Hz, 1H), 2.24 (s, 6H), 1.83–1.73 (m, 1H), 0.68 (d, *J* = 7.1 Hz, 3H), 0.11 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.1, 153.8, 137.7, 133.8, 129.7, 126.2, 63.8, 58.8, 43.5,

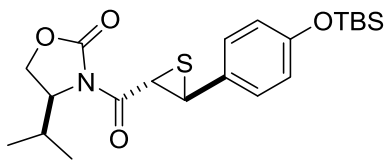
41.5, 28.2, 21.1, 17.6, 13.3. HRMS: $C_{17}H_{22}NO_3S$ $[M+H]^+$ calcd.: 320.1320, found: 320.1333.

(*S*)-4-Isopropyl-3-((2*S*,3*S*)-3-(4-methoxyphenyl)thiirane-2-carbonyl)oxazolidin-2-one *trans*-187d



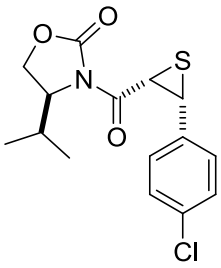
The title compound *trans*-**187d** was prepared from **185** (107 mg, 0.5 mmol) and 4-methoxybenzaldehyde (183 µL, 1.5 mmol) according to the general procedure. Colorless oil, yield: 98 mg, 0.30 mmol, 61%. $[\alpha]_D^{25}$ = –41.6 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.29 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.93 (d, *J* = 4.9 Hz, 1H), 4.52 (d, *J* = 4.9 Hz, 1H), 4.51–4.44 (m, 1H), 4.38–4.30 (m, 1H), 4.26 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.80 (s, 3H), 2.43–2.32 (m, 1H), 0.92 (dd, *J* = 8.8, 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 169.0, 159.6, 146.0, 130.4, 128.4, 114.1, 63.6, 59.0, 55.3, 41.4, 36.1, 28.5, 17.9, 14.7. HRMS: $C_{16}H_{20}NO_4S$ $[M+H-S]^+$ calcd.: 290.1387, found: 290.1392.

(*S*)-3-((2*S*,3*S*)-3-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)thiirane-2-carbonyl)-4-isopropyloxazolidin-2-one *trans*-187e



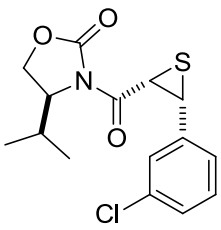
The title compound *trans*-**187e** was prepared from **185** (107 mg, 0.5 mmol) and 4-((*tert*-butyldimethylsilyl)oxy)benzaldehyde (371 µL, 1.5 mmol) according to the general procedure. Colorless oil, yield: 64 mg, 0.15 mmol, 31%. $[\alpha]_D^{25}$ = –69.1 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.22 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.92 (d, *J* = 4.9 Hz, 1H), 4.51 (d, *J* = 4.9 Hz, 1H), 4.49–4.43 (m, 1H), 4.34 (t, *J* = 8.6 Hz, 1H), 4.25 (dd, *J* = 9.0, 3.1 Hz, 1H), 2.43–2.31 (m, 1H), 0.98 (s, 9H), 0.92 (dd, *J* = 7.9, 7.1 Hz, 6H), 0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 169.0, 155.8, 153.8, 129.2, 128.4, 120.3, 63.7, 59.0, 41.5, 36.2, 28.6, 25.6, 18.2, 17.9, 14.8, -4.4. HRMS: $C_{21}H_{32}NO_4Si$ $[M+H-S]^+$ calcd.: 390.2101, found: 390.2117.

(*S*)-3-((2*S*,3*R*)-3-(4-Chlorophenyl)thiirane-2-carbonyl)-4-isopropyloxazolidin-2-one *cis*-187f



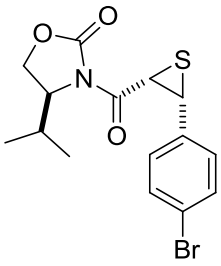
The title compound *cis*-**187f** was prepared from **185** (107 mg, 0.5 mmol) and 4-chlorobenzaldehyde (211 mg, 1.5 mmol) according to the general procedure. White solid, yield: 102 mg, 0.31 mmol, 63%. $[\alpha]_D^{25}$ = +94.4 (c = 1.00, CH_2Cl_2). m. p. 106–108 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.31 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 4.49 (d, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.27–4.18 (m, 2H), 4.12–4.03 (m, 1H), 1.84–1.70 (m, 1H), 0.67 (d, *J* = 7.1 Hz, 3H), 0.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.8, 153.8, 134.0, 132.6, 129.9, 128.2, 63.7, 58.8, 43.5, 40.6, 28.0, 17.6, 13.1. HRMS: $C_{15}H_{17}ClNO_3S$ $[M+H]^+$ calcd.: 326.0618, found: 326.0631.

(*S*)-3-((2*S*,3*R*)-3-(3-Chlorophenyl)thiirane-2-carbonyl)-4-isopropyloxazolidin-2-one *cis*-187g



The title compound *cis*-**187g** was prepared from **185** (107 mg, 0.5 mmol) and 3-chlorobenzaldehyde (211 mg, 1.5 mmol) according to the general procedure. White solid, yield: 93 mg, 0.28 mmol, 57%. $[\alpha]_D^{25}$ = +121.7 (c = 1.00, CH_2Cl_2). m. p. 83–88 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.38–7.35 (m, 1H), 7.32–7.28 (m, 1H), 7.24–7.18 (m, 2H), 4.54 (d, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.28–4.20 (m, 2H), 4.10 (d, *J* = 6.5 Hz, 1H), 1.87–1.75 (m, 1H), 0.69 (d, *J* = 7.0 Hz, 3H), 0.15 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.7, 153.8, 136.3, 134.3, 129.4, 128.3, 127.2, 63.8, 58.9, 43.4, 40.5, 28.2, 17.7, 13.4. HRMS: $C_{15}H_{17}ClNO_3$ $[M+H-S]^+$ calcd.: 294.0897, found: 294.0888.

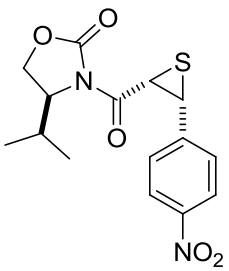
(*S*)-3-((2*S*,3*R*)-3-(4-Bromophenyl)thiirane-2-carbonyl)-4-isopropyloxazolidin-2-one *cis*-187h



The title compound *cis*-**187h** was prepared from **185** (107 mg, 0.5 mmol) and 4-bromobenzaldehyde (278 mg, 1.5 mmol) according to the general procedure. White solid, yield: 102 mg, 0.28 mmol, 56%. $[\alpha]_D^{25}$ = +85.9 (c = 1.00, CH_2Cl_2). m. p. 82–85 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.28–4.19 (m, 2H), 4.10 (d, *J* = 4.2

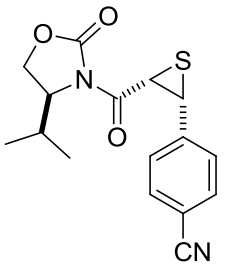
Hz, 1H), 1.85–1.72 (m, 1H), 0.70 (d, *J* = 7.1 Hz, 3H), 0.11 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.7, 153.7, 133.1, 131.1, 130.2, 122.1, 63.6, 58.8, 43.5, 40.6, 28.0, 17.6, 13.0. HRMS: $C_{15}H_{17}BrNO_3S$ $[M+H]^+$ calcd.: 340.0371, found: 340.0385.

(*S*)-4-Isopropyl-3-((2*S*,3*R*)-3-(4-nitrophenyl)thiirane-2-carbonyl)oxazolidin-2-one *cis*-187i



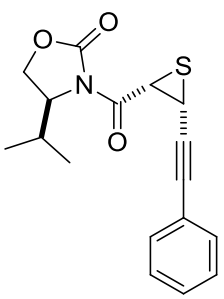
The title compound *cis*-**187** was prepared from **185** (107 mg, 0.5 mmol) and 4-nitrobenzaldehyde (227 mg, 1.5 mmol) according to the general procedure. Yellow solid, yield: 103 mg, 0.30 mmol, 61%. $[\alpha]_D^{25}$ = +80.2 (c = 1.00, CH_2Cl_2). m. p. 104–105 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.11 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H), 4.27–4.20 (m, 2H), 4.11–4.06 (m, 1H), 1.83-1.71 (m, 1H), 0.66 (d, *J* = 7.0 Hz, 3H), 0.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.4, 153.8, 147.8, 141.8, 129.7, 123.2, 63.8, 58.9, 43.5, 40.3, 28.0, 17.6, 13.3. HRMS: $C_{15}H_{17}N_2O_5$ $[M+H-S]^+$ calcd.: 305.1137, found: 305.1139.

4-((2*R*,3*S*)-3-((*S*)-4-Isopropyl-2-oxooxazolidin-3-carbonyl)thiiran-2-yl)benzonitrile *cis*-187j



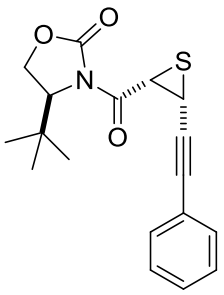
The title compound *cis*-**187j** was prepared from **185** (107 mg, 0.5 mmol) and 4-cyanobenzaldehyde (197 mg, 1.5 mmol) according to the general procedure. Yellow solid, yield: 88 mg, 0.28 mmol, 56%. $[\alpha]_D^{25}$ = +73.0 (c = 1.00, CH_2Cl_2). m. p. 102–106 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60–7.49 (m, 4H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.39 (d, *J* = 7.6 Hz, 1H), 4.28–4.21 (m, 2H), 4.14–4.06 (m, 1H), 1.83–1.70 (m, 1H), 0.69 (d, *J* = 7.1 Hz, 3H), 0.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 164.4, 153.8, 139.7, 131.8, 129.5, 118.3, 111.9, 63.8, 58.8, 43.5, 40.5, 28.0, 17.5, 13.2. HRMS: $C_{16}H_{17}N_2O_3$ $[M+H-S]^+$ calcd.: 285.1239, found: 285.1244.

(*S*)-4-Isopropyl-3-((2*S*,3*R*)-3-(phenylethynyl)thiirane-2-carbonyl)oxazolidin-2-one *cis*-187k



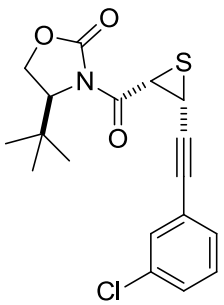
The title compound *cis*-**187k** was prepared from **185** (107 mg, 0.5 mmol) and phenylpropargyl aldehyde (183 μL, 1.5 mmol) according to the general procedure. Yellow solid, yield: 102 mg, 0.32 mmol, 65%. $[\alpha]_D^{25}$ = +93.3 (c = 1.00, CH_2Cl_2). m. p. 93–95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40–7.34 (m, 2H), 7.32–7.25 (m, 3H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.53–4.46 (m, 1H), 4.40–4.32 (m, 1H), 4.26 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.98 (d, *J* = 6.9 Hz, 1H), 2.46–2.33 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.3, 154.1, 132.1, 131.7, 128.6, 128.1, 84.4, 83.6, 64.0, 59.2, 40.0, 28.3, 26.4, 17.8, 14.3. HRMS: $C_{17}H_{18}NO_3$ $[M+H-S]^+$ calcd.: 284.1287, found: 284.1287.

(*S*)-4-(*tert*-Butyl)-3-((2*S*,3*R*)-3-(phenylethynyl)thiirane-2-carbonyl)oxazolidin-2-one *cis*-191k



The title compound *cis*-**191k** was prepared from **188** (114 mg, 0.5 mmol) and phenylpropargyl aldehyde (183 μL, 1.5 mmol) according to the general procedure. Orange solid, yield: 123 mg, 0.38 mmol, 75%. $[\alpha]_D^{25}$ = +59.8 (c = 1.00, CH_2Cl_2). m. p. 92–94 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39–7.33 (m, 2H), 7.30–7.22 (m, 3H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.45 (dd, *J* = 5.5, 3.6 Hz, 1H), 4.38–4.32 (m, 2H), 4.01 (d, *J* = 6.9 Hz, 1H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.6, 154.7, 132.1, 131.9, 128.6, 128.1, 84.6, 84.2, 66.0, 62.2, 39.7, 35.8, 27.0, 25.6. HRMS: $C_{18}H_{20}NO_3$ $[M+H-S]^+$ calcd.: 298.1438, found: 298.1456.

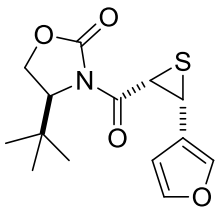
(*S*)-4-(*tert*-Butyl)-3-((2*S*,3*R*)-3-((3-chlorophenyl)ethynyl)thiirane-2-carbonyl) oxazolidin-2-one *cis*-199l



The title compound *cis*-**199l** was prepared from **188** (114 mg, 0.5 mmol) and 3-chlorophenylpropargyl aldehyde (247 mg, 1.5 mmol) according to the general procedure. Yellow oil, yield: 110 mg, 0.30 mmol, 60%. $[\alpha]_D^{25}$ = +139.6 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.34 (m, 1H), 7.30–7.16 (m, 3H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.48–4.43 (m, 1H), 4.39–4.34 (m, 2H), 3.98 (d, *J* = 6.9

Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.5, 154.7, 134.0, 131.8, 130.0, 129.4, 128.9, 123.8, 86.0, 82.6, 66.0, 62.2, 39.4, 35.8, 26.6, 25.6. HRMS: $C_{18}H_{19}ClNO_3$ $[M+H-S]^+$ calcd.: 332.1048, found: 332.1068.

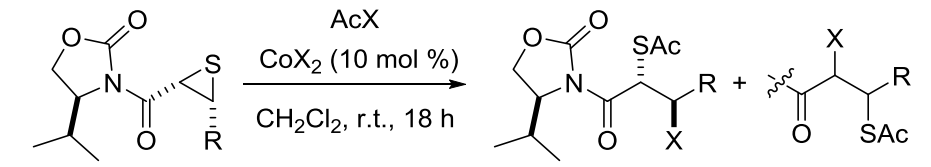
(*S*)-4-(*tert*-Butyl)-3-((2*S*,3*R*)-3-(furan-3-yl)thiirane-2-carbonyl)oxazolidin-2-one *cis*-191m



The title compound *cis*-**191m** was prepared from **188** (114 mg, 0.5 mmol) and 3-furaldehyde (130 μL, 1.5 mmol) according to the general procedure. Colorless oil, yield: 103 mg, 0.35 mmol, 70%. $[\alpha]_D^{25}$ = +101.2 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$,) δ: 7.40–7.37 (m, 1H), 7.29 (t, *J* = 1.7 Hz, 1H), 6.45 (dd, *J* = 1.7, 0.6 Hz, 1H), 4.41 (d, *J* = 7.4 Hz, 1H), 4.29–4.21 (m, 3H), 4.18 (d, *J* = 7.3 Hz, 1H), 0.64 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.4, 154.8, 143.0, 142.0, 120.7, 111.6, 66.0, 62.2, 43.1, 35.4, 33.1, 25.4. HRMS: $C_{14}H_{18}NO_4$ $[M+H-S]^+$ calcd.: 264.1230, found: 264.1243.

6.2.3. Elaboration of adducts

*6.2.3.1. General procedure for ring opening of adducts cis-**187a** and cis-**187h**[283]*



cis-**187a** R = Ph
cis-**187h** R = 4-BrPh

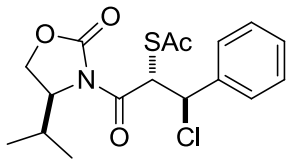
194 R = Ph X = Cl 88% (94:6)
195 R = Ph X = Br 70% (90:10)
196 R= 4-BrPh X = Cl 65% (90:10)

To a mixture of the corresponding thiirane **187** (1.0 mmol) and anhydrous $CoCl_2$ or $CoBr_2$ (0.10 mmol, 10 mol %) in dry CH_2Cl_2 (7 mL) at 0 ºC, was added acetyl chloride or acetyl bromide (2.0 mmol) under argon atmosphere. The reaction was stirred overnight at room temperature and afterwards diluted with CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$. The reaction mixture was washed with water and brine and the organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash column

[283] a) ref. 172, page 75. b) Amer, H.; Mereiter, K.; Stanetty, C.; Hofinger, A.; Czollner, L.; Beseda, I.; Jordis, U.; Kueenburg, B.; Cla*ß*en-Houben, D.; Kosma, P. *Tetrahedron* **2010**, *66*, 4390–4402.

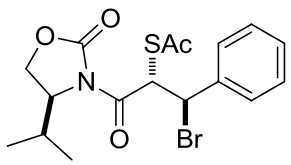
chromatography on silica gel (eluting with AcOEt/Hexane 1/4) to afford the desired product **194**–**196**.

_S_-((1_R_,2_S_)-1-Chloro-3-((_S_)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxo-1-phenylpropan-2-yl) ethanethioate 194



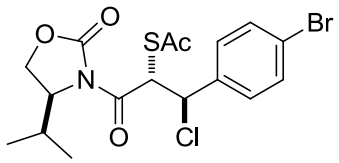
The title compound **194** was prepared from compound **187a** (291 mg, 1.0 mmol), $CoCl_2$ (13 mg, 0.10 mmol) and acetyl chloride (142 μL, 2.0 mmol) according to the general procedure. White solid, yield: 327 mg, 0.88 mmol, 88%. $[\alpha]_D^{25}$ = +37.5 (c = 1.00, CH_2Cl_2). m. p. 141–142 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52–7.46 (m, 2H), 7.39–7.31 (m, 3H), 6.47 (d, *J* = 11.1 Hz, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 4.55–4.48 (m, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 4.27 (dd, *J* = 9.0, 2.9 Hz, 1H), 2.52–2.40 (m, 1H), 2.08 (s, 3H), 0.97 (d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.6, 169.7, 153.6, 137.0, 129.3, 128.4, 128.4, 63.5, 61.6, 59.3, 49.4, 29.6, 28.6, 18.0, 15.0. HRMS: $C_{17}H_{21}ClNO_4S$ $[M+H]^+$ calcd.: 370.0874, found: 370.0869.

_S_-((1_R_,2_S_)-1-Bromo-3-((_S_)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxo-1-phenylpropan-2-yl) ethanethioate 195



The title compound **195** was prepared from compound **187a** (291 mg, 1.0 mmol), $CoBr_2$ (22 mg, 0.10 mmol) and acetyl bromide (148 μL, 2.0 mmol) according to the general procedure. White solid, yield: 289 mg, 0.70 mmol, 70%. $[\alpha]_D^{25}$ = +17.9 (c = 1.00, CH_2Cl_2). m. p. 143–148 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52–7.46 (m, 2H), 7.37–7.28 (m, 3H), 6.63 (d, *J* = 11.7 Hz, 1H), 5.30 (d, *J* = 11.6 Hz, 1H), 4.55–4.48 (m, 1H), 4.35 (t, *J* = 8.5 Hz, 1H), 4.28 (dd, *J* = 9.0, 2.9 Hz, 1H), 2.54–2.43 (m, 1H), 2.08 (s, 3H), 0.99 (dd, *J* = 6.9, 5.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.2, 169.6, 153.4, 137.4, 129.1, 128.5, 128.4, 63.4, 59.3, 51.4, 48.8, 29.4, 28.5, 17.9, 15.0. HRMS: $C_{17}H_{21}BrNO_4S$ $[M+H]^+$ calcd.: 414.0369, found: 414.0379.

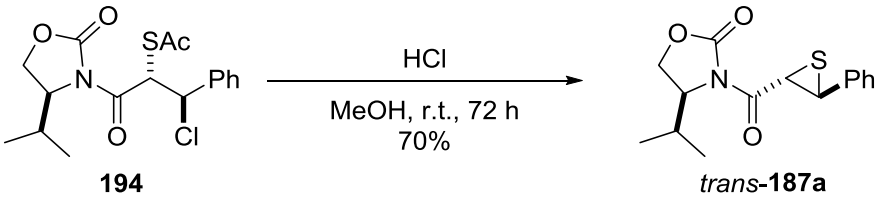
_S_-((1_R_,2_S_)-1-(4-Bromophenyl)-1-chloro-3-((_S_)-4-isopropyl-2-oxooxazolidin-3-yl)-3-oxopropan-2-yl) ethanethioate 196



The title compound **196** was prepared from compound **187h** (370 mg, 1.0 mmol), $CoCl_2$ (13 mg, 0.10 mmol) and acetyl chloride (142 μL, 2.0 mmol) according to the general procedure. White solid, yield: 292 mg, 0.65 mmol, 65%. $[\alpha]_D^{25}$ = +21.9 (c = 1.00, CH_2Cl_2). m. p. 63–64 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.46 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.41 (d, *J* = 10.3 Hz, 1H),

5.19 (d, J = 11.1 Hz, 1H), 4.52–4.45 (m, 1H), 4.33 (t, J = 8.5 Hz, 1H), 4.25 (dd, J = 9.0, 2.9 Hz, 1H), 2.50–2.35 (m, 1H), 2.09 (s, 3H), 0.94 (dd, J = 7.0, 2.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 191.0, 169.2, 153.4, 136.1, 131.5, 130.1, 123.3, 63.5, 60.9, 59.3, 49.1, 29.6, 28.5, 17.9, 14.9. HRMS: $C_{17}H_{20}BrClNO_4S$ $[M+H]^+$ calcd.: 447.9979, found: 447.9969.

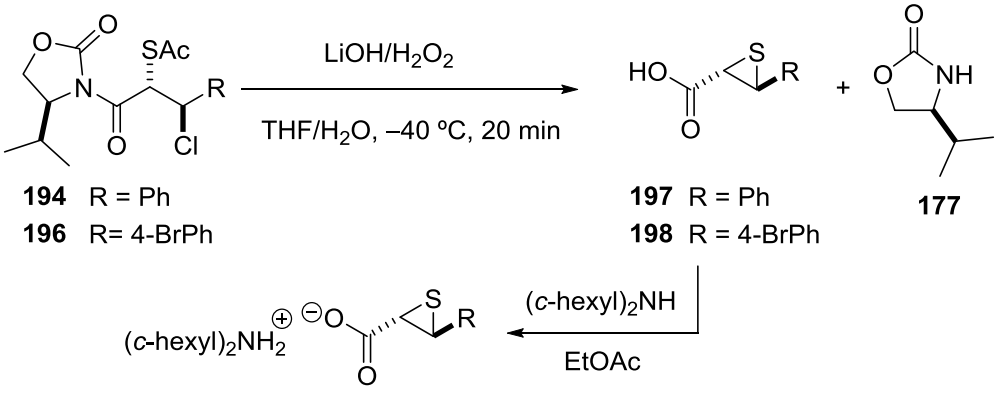
*6.2.3.2. Acid-promoted cyclization of **194** to trans-**187a***



194 *trans*-**187a**

To an ice cold solution of **194** (111 mg, 0.3 mmol) in methanol (1 mL) was added a solution of HCl in methanol (1.25 M, 1 mL). The mixture was stirred at room temperature for 72 h and then concentrated under reduced pressure. Purification by flash column chromatography (eluent: AcOEt/Hexane 1:4) gave pure *trans*-**187a** compound as an oil in 70% yield (61 mg, 0.21 mmol).

6.2.3.3. Removal of the oxazolidinone auxiliary[284]



194 R = Ph
196 R= 4-BrPh

197 R = Ph
198 R = 4-BrPh

177

199 R = Ph 65% (2 steps)
200 R = 4-BrPh 45% (2 steps)

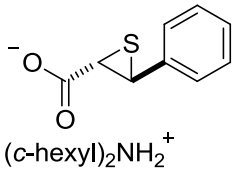
To a solution of LiOH (4 equiv., 12 mg, 0.5 mmol) in THF (2 mL) and water (0.5 mL) at 0 ºC was added a solution of 30% H_2O_2 (12 equiv., 0.17 mL, 1.5 mmol) and the resulting mixture was stirred at the same temperature for 15 min. Then the mixture

[284] Adapted from: a) Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. *J. Org. Chem.* **2000**, *65*, 9007-9012. b) ref. 145a, page 50.

was cooled to –40 ºC and a solution of the corresponding adduct **194** and **196** (1 equiv., 0.12 mmol) in 1.5 ml of THF was added. The reaction mixture was stirred at the same temperature for 20 min and afterwards 10 mL of water was added. The resulting mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the corresponding (*S*)-4-isopropyloxazolidin-2-one **177** in 90–92% yield.

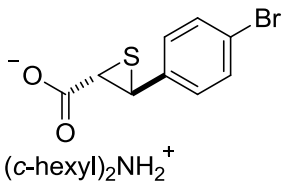
The aqueous layer was slowly acidified by dropwise addition of 6N HCl and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the corresponding carboxylic acid **197–198** as a yellow oil. The product was dissolved in EtOAc (1 mL) and dicyclohexylamine (40 µL, 0.2 mmol) was added dropwise via syringe. The derived dicyclohexylamine salt **199–200** was obtained as a solid by slow precipitation (14 h standing) from this solution.

Dicyclohexylammonium (2*S*,3*S*)-3-phenylthiirane-2-carboxylate 199



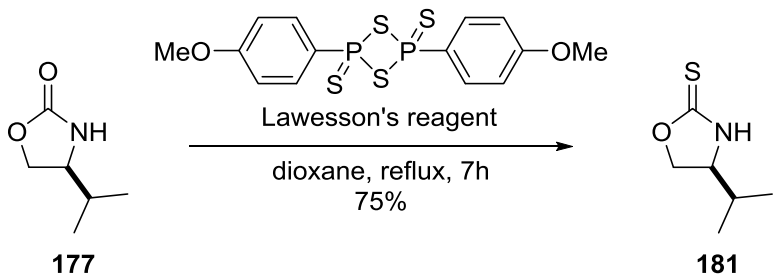
The title compound **199** was prepared from product **194** (46 mg, 0.12 mmol) according to the general procedure. White solid, yield: 29 mg, 0.08 mmol, 65%. $[\alpha]_D^{25}$ = –28.4 (c = 1.00, CH_2Cl_2). m. p. 163–165 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.32–7.20 (m, 5H), 4.11 (d, J = 5.0 Hz, 1H), 3.50–3.46 (m, 1H), 3.03–2.91 (m, 2H), 2.08–1.96 (m, 4H), 1.86–1.74 (m, 4H), 1.67–1.58 (m, 2H), 1.55–1.38 (m, 4H), 1.31–1.13 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.9, 138.8, 128.4, 127.5, 127.2, 52.9, 42.3, 42.0, 29.4, 29.4, 25.2, 24.8. HRMS: $C_9H_9O_2S$ $[M+2H-C_{12}H_{22}NH_2]^+$ calcd.: 181.0318, found: 181.0364

Dicyclohexylammonium (2*S*,3*S*)-3-(4-bromophenyl)thiirane-2-carboxylate 200



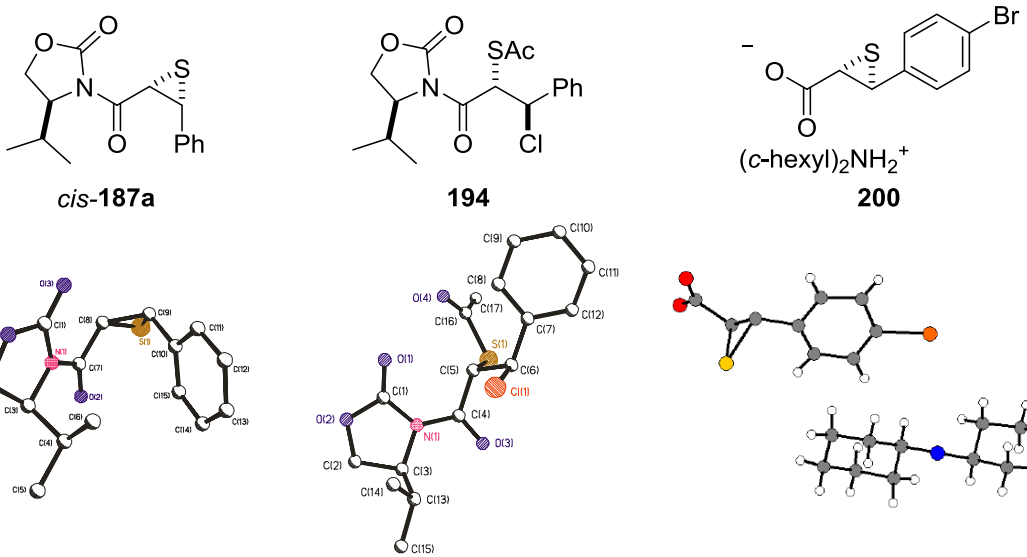
The title compound **200** was prepared from product **196** (56 mg, 0.12 mmol) according to the general procedure. White solid, yield: 25 mg, 0.06 mmol, 45%. $[\alpha]_D^{25}$ = –31.7 (c = 1.00, CH_2Cl_2). m. p. 184–186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 4.04 (d, *J* = 5.0 Hz, 1H), 3.39 (d, *J* = 5.0 Hz, 1H), 3.02–2.88 (m, 2H), 2.08–1.94 (m, 4H), 1.87–1.73 (m, 4H), 1.67–1.58 (m, 2H), 1.53–1.36 (m, 4H), 1.33–1.13 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.7, 138.0, 131.5, 128.8, 121.3, 53.0, 42.3, 41.2, 29.5, 29.4, 25.1, 24.8. HRMS: $C_9H_8BrO_2$ $[M+2H-S-C_{12}H_{22}NH_2]^+$ calcd.: 226.9702, found: 226.9715.

6.2.3.4. Recovery of the oxazolidin-2-thione auxiliary[285]



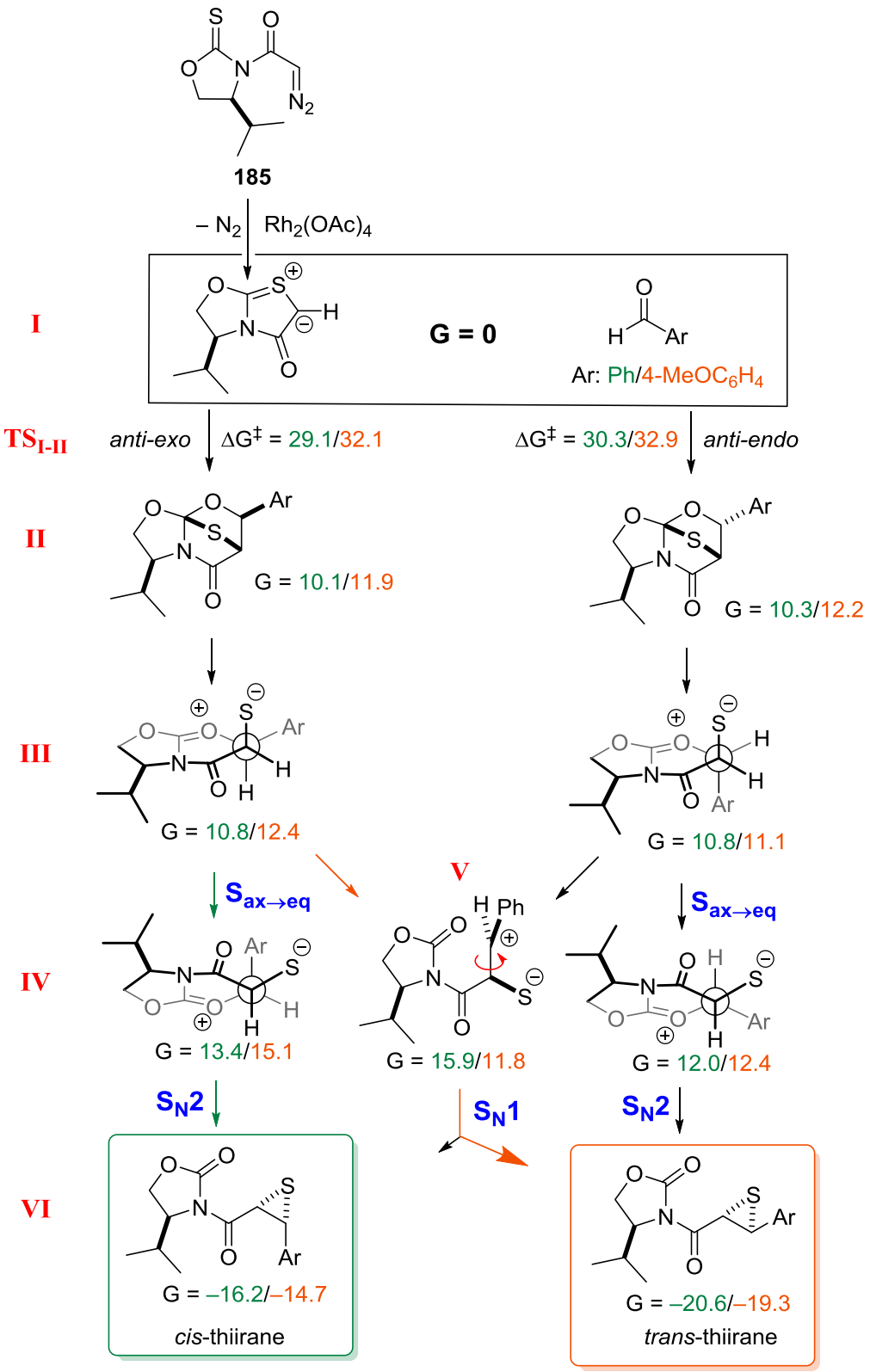
To a solution of 2-oxazolidinone **177** (1 equiv., 52 mg, 0.4 mmol) in 1,4-dioxane (2 mL) was added the Lawesson's reagent (1.5 equiv., 250.4 mg, 0.6 mmol) and the mixture was stirred at reflux temperature. Two additional portions of the Lawesson's reagent (0.6 mmol each) were successively added to the reaction mixture at 4 and at 6 h, respectively, and stirring was continued until disappearance of the starting oxazolidinone (7 h total). The reaction mixture was then cooled to room temperature, the solvent removed under reduced pressure, and the crude product was purified by flash column chromatography to afford pure (*S*)-4-isopropyloxazolidin-2-thione **181** in 75% yield (43.6 mg, 0.3 mmol).

6.2.4. ORTEP diagrams of compounds *cis*-187a, 194 and 200



[285] Adapted from: Lakshmikantham, M. V.; Chen, W.; Cava, M. P. *J. Org. Chem*. **1989**, *54*, 4746–4750.

6.2.5. Computational studies



Scheme 109. Principal reaction pathways found by DFT investigation at the B3LYP level of theory for the Rh-catalyzed reaction between diazocompound **185** and either benzaldehyde or *p*-anisaldehyde.

Table 17. Energies of the structures involved in the computational study.

	G (B3LYP/6-311++G**, IEF-PCM, CH_2Cl_2)	relative **G**	Frequency
I	-914.861019		
Benzaldehyde series			
Benzaldehyde	-345.595765		
I + Benzaldehyde	-1260.456784	0	
TS_{I-II} anti-exo	-1260.410323	29.15	-384.6
TS_{I-II} anti-endo	-1260.408515	30.29	-397.5
II exo	-1260.440763	10.05	
II endo	-1260.440432	10.26	
III exo	-1260.439590	10.79	
III endo	-1260.439545	10.82	
IV exo	-1260.435395	13.42	
IV endo	-1260.437630	12.02	
V	-1260.431414	15.92	
VI exo	-1260.482608	-16.20	
VI endo	-1260.489673	-20.64	
***p*-Methoxybenzaldehyde series**			
p-Methoxybenzaldehyde	-460.127569		
I + *p*-Methoxybenzaldehyde	-1374.988588	0	
TS_{I-II} anti-exo	-1374.937324	32.17	-171.0
TS_{I-II} anti-endo	-1374.936089	32.94	-187.2
II exo	-1374.969695	11.86	
II endo	-1374.969206	12.16	
III exo	-1374.968754	12.45	
III endo	-1374.970844	11.13	
IV exo	-1374.964540	15.09	
IV endo	-1374.968778	12.43	
V	-1374.966397	13.92	
VI exo	-1374.012006	-14.69	
VI endo	-1374.019274	-19.26	

We also sought for an alternative mechanistic scenario involving the initial reaction between the rhodium carbene **A** and benzaldehyde to generate an epoxide **B**, which could eventually lead to the final products. However, in contrast with the spontaneous intramolecular displacement of the rhodium fragment by the sulfur, the intermolecular formation of the epoxide shows a measurable barrier of 14.4 kcal/mol. Also, the epoxide **B** lies much higher in energy than **I**, supporting the aforementioned mechanism through **I**.

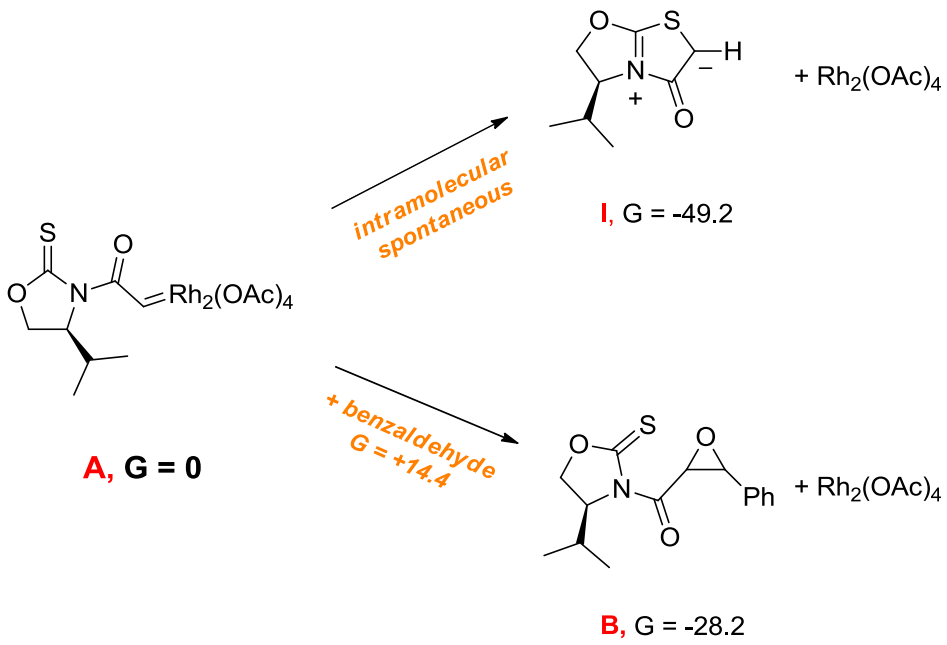


Figure 32. Comparison of the mechanisms through zwitterionic **I** and epoxide **B.**

Cartesian Coordinates of the structures involved in the computational study

I

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.114984	1.438279	-0.268518
2	6	0	1.040162	-1.611995	-0.814183
3	6	0	-0.961653	-0.912932	-0.094189
4	6	0	-2.379653	1.058706	0.169604
5	6	0	1.077165	-0.057823	-0.733006
6	6	0	2.058910	0.555004	0.288317
7	6	0	3.503605	0.357616	-0.192154
8	6	0	1.856482	0.036566	1.717355
9	1	0	-3.221182	1.701799	0.361302
10	1	0	1.821733	-2.105955	-0.243467
11	1	0	1.033573	-1.977837	-1.839170
12	1	0	1.280928	0.364796	-1.718105
13	1	0	1.843857	1.627867	0.281075
14	1	0	3.785938	-0.700071	-0.213550
15	1	0	3.652011	0.767796	-1.195068
16	1	0	4.196217	0.865806	0.482714
17	1	0	2.088859	-1.029525	1.805069
18	1	0	2.521202	0.569656	2.401230
19	1	0	0.833361	0.193744	2.068000
20	7	0	-0.332958	0.204085	-0.392549
21	8	0	-0.250043	-2.020831	-0.211516
22	8	0	-0.598602	2.537027	-0.546327
23	16	0	-2.574802	-0.688548	0.386325

TS_{I-II} anti,exo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.777088	-0.033638	-0.716079
2	6	0	0.757596	1.362065	0.251749
3	6	0	2.743321	-1.588874	-0.754426
4	6	0	0.952810	-0.924014	0.427855
5	6	0	-0.601465	0.889852	0.677919
6	6	0	5.244355	0.369684	-1.008488
7	6	0	4.035163	0.605383	-0.091831
8	6	0	4.307343	0.147863	1.346601
9	1	0	2.511588	-1.986443	-1.738975
10	1	0	3.633160	-2.062842	-0.350399
11	1	0	-1.151114	1.594045	1.293311
12	1	0	5.056622	0.736229	-2.021357
13	1	0	6.117773	0.896349	-0.617775
14	1	0	4.546248	-0.918745	1.403184
15	1	0	5.164895	0.691988	1.749003
16	1	0	3.457070	0.342298	2.005241
17	1	0	2.630270	0.366741	-1.720769
18	1	0	3.835011	1.681350	-0.073411
19	1	0	5.505248	-0.691486	-1.074312
20	7	0	1.551303	0.221804	0.063662
21	8	0	1.093620	2.486888	-0.049376
22	8	0	1.620453	-1.994617	0.129398
23	16	0	-0.374368	-0.742181	1.506989
24	6	0	-1.354061	0.512426	-0.781110
25	6	0	-2.832590	0.248957	-0.469607
26	6	0	-5.545808	-0.235268	0.070882
27	6	0	-3.343481	-1.049396	-0.514315
28	6	0	-3.698483	1.305017	-0.163731
29	6	0	-5.045378	1.067971	0.106561
30	6	0	-4.691089	-1.291985	-0.243118
31	1	0	-1.293803	1.499554	-1.287472
32	1	0	-2.672707	-1.858079	-0.777959
33	1	0	-3.319205	2.323236	-0.145327
34	1	0	-5.705166	1.897374	0.337704
35	1	0	-5.075602	-2.305734	-0.282873
36	1	0	-6.593863	-0.422511	0.277127
37	8	0	-0.682522	-0.464435	-1.375721

TS_{I-II} anti,endo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.632044	-0.540999	-0.669317
2	6	0	2.598262	-0.346223	0.253610
3	6	0	4.759315	1.443729	0.123079
4	6	0	2.667029	0.747484	1.118503
5	6	0	3.738766	1.638615	1.053593
6	6	0	4.704120	0.346848	-0.739142
7	6	0	1.436814	-1.343711	0.343815
8	1	0	1.853943	-2.347497	0.107321

9	1	0	5.594588	2.133690	0.074954
10	1	0	3.780266	2.482985	1.733625
11	1	0	5.498750	0.180440	-1.458533
12	1	0	3.604394	-1.400053	-1.334218
13	1	0	1.877867	0.879830	1.848944
14	8	0	0.671317	-1.289621	1.416735
15	6	0	-0.203760	0.210503	-0.866128
16	6	0	-2.824115	-0.239272	1.709637
17	6	0	-1.572321	-1.309679	0.195909
18	6	0	0.480538	-1.106883	-1.048894
19	6	0	-2.188583	0.850665	0.803791
20	6	0	-3.227661	1.699122	0.037565
21	6	0	-4.039810	0.883855	-0.977180
22	6	0	-2.609783	2.948015	-0.603873
23	1	0	1.032542	-1.203389	-1.977743
24	1	0	-3.906899	-0.179787	1.772949
25	1	0	-2.380234	-0.282556	2.701339
26	1	0	-1.541810	1.499947	1.394979
27	1	0	-3.911909	2.042153	0.824463
28	1	0	-3.410604	0.533816	-1.800310
29	1	0	-4.526133	0.013755	-0.526962
30	1	0	-4.826448	1.507722	-1.407058
31	1	0	-1.913161	2.687220	-1.402386
32	1	0	-3.398604	3.575199	-1.026720
33	1	0	-2.065158	3.543754	0.133617
34	7	0	-1.330914	-0.013464	-0.044787
35	8	0	-2.509121	-1.537280	1.061729
36	8	0	0.180366	1.304107	-1.211936
37	16	0	-0.805663	-2.417690	-0.867923

II exo - Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.739674	0.017361	-0.859952
2	6	0	0.829890	1.544279	0.083852
3	6	0	2.499794	-1.502174	-1.064479
4	6	0	0.609194	-0.768558	-0.022535
5	6	0	-1.280310	0.437725	-0.603403
6	6	0	-0.548942	1.090261	0.619583
7	6	0	-2.746928	0.142529	-0.387554
8	6	0	-5.481714	-0.304105	0.031070
9	6	0	-3.211038	-1.135325	-0.068455
10	6	0	-3.664716	1.192743	-0.508354
11	6	0	-5.023409	0.973336	-0.294498
12	6	0	-4.573414	-1.355763	0.138339
13	7	0	1.438614	0.391012	-0.303316
14	8	0	1.240635	2.686215	-0.020274
15	8	0	1.385756	-1.863693	-0.188545
16	8	0	-0.522748	-0.762820	-0.885244
17	16	0	-0.122465	-0.384723	1.668945
18	6	0	3.935544	0.406171	0.039466
19	6	0	3.914775	-0.266842	1.417463
20	6	0	5.255276	0.145061	-0.700265
21	1	0	2.214278	-1.728160	-2.092574
22	1	0	3.342488	-2.123164	-0.772205
23	1	0	2.870237	0.497174	-1.833587

24	1	0	-1.174486	1.109403	-1.461854
25	1	0	-1.105783	1.867452	1.130922
26	1	0	-2.508466	-1.954310	0.008195
27	1	0	-3.317340	2.186424	-0.773798
28	1	0	-5.723358	1.795683	-0.390073
29	1	0	-4.923456	-2.352434	0.382859
30	1	0	-6.539539	-0.478324	0.192181
31	1	0	3.847730	1.487532	0.190001
32	1	0	4.051726	-1.350242	1.343509
33	1	0	2.977780	-0.079363	1.946538
34	1	0	4.729480	0.122818	2.033267
35	1	0	5.411699	-0.922435	-0.886936
36	1	0	6.099348	0.498383	-0.103014
37	1	0	5.285601	0.664225	-1.662505

II endo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.710081	0.545521	0.387930
2	6	0	2.507603	0.214030	-0.248093
3	6	0	4.549731	-1.688263	0.015363
4	6	0	2.341475	-1.075206	-0.759498
5	6	0	3.359254	-2.020535	-0.628489
6	6	0	4.723284	-0.400094	0.523292
7	6	0	1.428208	1.271003	-0.345177
8	1	0	1.883697	2.236916	-0.574341
9	1	0	5.339945	-2.423704	0.114523
10	1	0	3.220925	-3.016529	-1.033954
11	1	0	5.649488	-0.129503	1.017417
12	1	0	3.858299	1.549149	0.773859
13	1	0	1.424842	-1.333509	-1.273838
14	8	0	0.472506	0.980123	-1.396271
15	6	0	-0.146678	0.106508	1.234938
16	6	0	-2.221634	-0.590693	-1.697909
17	6	0	-0.823847	0.981689	-0.811212
18	6	0	0.562708	1.448825	0.943836
19	6	0	-1.913504	-1.110479	-0.269181
20	6	0	-3.120922	-1.223441	0.691051
21	6	0	-3.994304	-2.422064	0.293323
22	6	0	-3.944476	0.065233	0.802367
23	1	0	1.092069	1.865534	1.793835
24	1	0	-3.277541	-0.613217	-1.954377
25	1	0	-1.648192	-1.127886	-2.454336
26	1	0	-1.434059	-2.090756	-0.335195
27	1	0	-2.691794	-1.437617	1.675656
28	1	0	-4.452281	-2.280924	-0.691167
29	1	0	-3.415408	-3.349725	0.266446
30	1	0	-4.804940	-2.554641	1.013921
31	1	0	-4.444453	0.311257	-0.139668
32	1	0	-4.721831	-0.055831	1.561261
33	1	0	-3.326841	0.918524	1.090549
34	7	0	-0.923667	-0.111941	0.138322
35	8	0	-1.810666	0.812802	-1.721234
36	8	0	-0.005266	-0.607267	2.210675
37	16	0	-0.821295	2.513661	0.290034

III exo - Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.924642	0.481389	-0.623622
2	6	0	-0.858236	-1.066080	-1.083675
3	6	0	-2.869039	1.975524	-0.219392
4	6	0	-0.763805	1.186960	-0.175863
5	6	0	1.291556	0.164975	-0.771431
6	6	0	0.565398	-1.184171	-0.626497
7	6	0	2.706733	0.238889	-0.282597
8	6	0	5.378675	0.285871	0.541815
9	6	0	3.020372	0.372580	1.074014
10	6	0	3.738029	0.136736	-1.221934
11	6	0	5.069627	0.150933	-0.811118
12	6	0	4.352997	0.403116	1.479989
13	7	0	-1.469209	0.170323	-0.652751
14	8	0	-1.513467	-1.849913	-1.728096
15	8	0	-1.465801	2.223128	0.177684
16	8	0	0.509166	1.241853	-0.061420
17	16	0	0.376236	-1.867686	1.069063
18	6	0	-3.723598	-0.437929	0.323212
19	6	0	-5.223854	-0.152479	0.156490
20	6	0	-3.280883	-0.346222	1.789136
21	1	0	1.255406	0.475931	-1.819146
22	1	0	1.076405	-1.886175	-1.287460
23	1	0	2.225484	0.454059	1.802358
24	1	0	3.501798	0.045911	-2.277110
25	1	0	5.861296	0.067852	-1.546687
26	1	0	4.589799	0.512815	2.532096
27	1	0	6.413903	0.306526	0.863110
28	1	0	-3.071914	2.652957	-1.045229
29	1	0	-3.483915	2.227048	0.638855
30	1	0	-3.309540	0.375872	-1.637880
31	1	0	-3.537500	-1.457175	-0.026891
32	1	0	-5.485314	0.858926	0.484157
33	1	0	-5.804195	-0.850934	0.763176
34	1	0	-5.542718	-0.266051	-0.883363
35	1	0	-2.220907	-0.584887	1.906912
36	1	0	-3.846759	-1.066577	2.384789
37	1	0	-3.471798	0.643504	2.216054

III endo - Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.040362	-0.121258	-1.612236
2	1	0	-4.762651	1.039008	-0.505026
3	1	0	-3.061278	1.199037	-0.930131
4	1	0	-4.393683	-1.967479	1.736997
5	1	0	-5.554145	-0.833257	1.038663
6	1	0	-4.831767	-2.078864	0.024216
7	1	0	-3.358113	0.258766	1.360624
8	1	0	-2.008069	-1.778389	1.234088
9	1	0	-2.961684	-2.094596	-1.527705

10	1	0	-1.678631	-3.048786	-0.733810
11	1	0	1.113617	2.028997	1.282990
12	6	0	-3.850503	0.474844	-0.713916
13	6	0	-4.630103	-1.381880	0.844212
14	6	0	-3.502216	-0.398205	0.498021
15	16	0	-0.648642	2.939396	-0.169613
16	8	0	0.557050	0.141328	-1.517536
17	8	0	-1.033335	-1.382047	-1.766647
18	8	0	-0.850415	0.595530	2.258086
19	7	0	-0.999338	-0.288856	0.157468
20	6	0	0.475838	1.631311	0.493507
21	6	0	1.381658	1.020551	-0.577524
22	6	0	-0.456374	-0.467868	-1.041518
23	6	0	-2.055866	-2.048373	-0.931357
24	6	0	-0.479909	0.654595	1.109004
25	6	0	-2.178813	-1.175981	0.341683
26	1	0	1.694639	1.808499	-1.256829
27	6	0	2.566581	0.198911	-0.138396
28	6	0	4.819571	-1.310377	0.568535
29	6	0	3.706229	0.195402	-0.952794
30	6	0	2.571606	-0.557509	1.040175
31	6	0	3.692704	-1.307587	1.389828
32	6	0	4.825681	-0.555205	-0.603818
33	1	0	3.716265	0.786816	-1.861931
34	1	0	1.716787	-0.559309	1.705717
35	1	0	3.686880	-1.884121	2.307446
36	1	0	5.701604	-0.545638	-1.241886
37	1	0	5.691319	-1.892024	0.845271

IV exo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.656793	0.255603	0.102543
2	6	0	-0.494642	1.573342	-0.465409
3	6	0	-3.025603	-0.269208	1.509328
4	6	0	-0.813394	0.185531	1.524448
5	6	0	1.481682	0.889614	0.966225
6	6	0	0.816912	1.999754	0.179917
7	1	0	-3.497689	-1.246716	1.512754
8	1	0	-3.610941	0.437792	2.092431
9	7	0	-1.238944	0.644685	0.336499
10	8	0	-0.991514	1.991122	-1.475695
11	8	0	-1.736647	-0.424084	2.213631
12	8	0	0.353218	0.293185	1.995494
13	1	0	-3.213746	1.165304	-0.121866
14	6	0	-2.833923	-0.741114	-1.061464
15	1	0	-2.400277	-0.249320	-1.936922
16	6	0	-4.332015	-0.942945	-1.334437
17	1	0	-4.468096	-1.590290	-2.203414
18	1	0	-4.841070	-1.418747	-0.490034
19	1	0	-4.833167	0.006403	-1.541639
20	6	0	-2.109532	-2.077096	-0.852943
21	1	0	-1.039064	-1.944822	-0.679252
22	1	0	-2.525686	-2.647544	-0.016961
23	1	0	-2.217522	-2.694018	-1.747876
24	1	0	0.486291	2.743999	0.917560

25	16	0	2.069176	2.784656	-0.892845
26	1	0	2.149819	1.306182	1.711016
27	6	0	2.068388	-0.316736	0.305311
28	6	0	3.159959	-2.656836	-0.779961
29	6	0	2.969843	-1.092917	1.045981
30	6	0	1.727619	-0.721203	-0.990896
31	6	0	2.270716	-1.884950	-1.528319
32	6	0	3.511267	-2.257416	0.509082
33	1	0	3.250236	-0.779855	2.045930
34	1	0	1.077520	-0.111893	-1.605079
35	1	0	2.009903	-2.181362	-2.537512
36	1	0	4.210469	-2.845842	1.091555
37	1	0	3.585440	-3.558896	-1.204546

IV endo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.139604	0.210349	-0.469974
2	6	0	0.660190	0.140668	-0.757228
3	6	0	4.048741	-0.948929	-0.029522
4	6	0	1.927452	-1.469659	0.700121
5	6	0	-1.883107	0.119071	-0.973772
6	6	0	-0.662310	-0.469579	-0.377411
7	7	0	1.812213	-0.364151	-0.155232
8	8	0	0.752945	1.045989	-1.565782
9	8	0	3.231868	-1.755120	0.859326
10	6	0	3.389772	1.564399	0.232702
11	1	0	4.925298	-0.631852	0.529650
12	1	0	4.352780	-1.580855	-0.864081
13	1	0	2.581765	2.222735	-0.099454
14	1	0	4.848769	3.168801	0.165830
15	1	0	3.201628	0.359541	-1.547721
16	1	0	5.574995	1.568513	0.040779
17	1	0	4.727770	2.266742	-1.348506
18	1	0	4.138442	0.856681	2.170188
19	1	0	3.460818	2.481929	2.191427
20	1	0	-0.720403	-0.882602	0.618932
21	1	0	2.383226	1.091365	2.122730
22	8	0	1.050617	-2.092123	1.242466
23	6	0	4.711849	2.171510	-0.259030
24	6	0	3.338517	1.483558	1.764368
25	16	0	-1.418936	-1.556263	-1.663070
26	6	0	-3.145107	0.288715	-0.200837
27	6	0	-5.526255	0.731607	1.219002
28	6	0	-3.530561	-0.578795	0.830359
29	6	0	-3.973572	1.372526	-0.515778
30	6	0	-5.155509	1.594741	0.190269
31	6	0	-4.709297	-0.356261	1.535476
32	1	0	-2.918017	-1.438921	1.076330
33	1	0	-3.689065	2.048062	-1.315473
34	1	0	-5.783834	2.440308	-0.065539
35	1	0	-4.993807	-1.034964	2.331527
36	1	0	-6.444805	0.900467	1.769262
37	1	0	-1.693969	0.899833	-1.700688

V – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.938138	-0.615728	0.529289
2	6	0	-0.850819	0.645986	1.165294
3	6	0	-3.024547	-1.992608	-0.156911
4	6	0	-0.872978	-1.255531	-0.436116
5	6	0	1.537844	-0.065832	0.822480
6	6	0	0.569729	1.038539	0.777769
7	6	0	2.864342	-0.132658	0.340061
8	6	0	5.532496	-0.365473	-0.466989
9	6	0	3.422620	0.803409	-0.569975
10	6	0	3.678551	-1.197511	0.817669
11	6	0	4.996026	-1.309210	0.418602
12	6	0	4.748490	0.683959	-0.954520
13	6	0	-3.788324	0.506311	-0.107927
14	6	0	-5.276952	0.250464	0.169588
15	6	0	-3.512993	0.713290	-1.602874
16	1	0	3.254419	-1.918309	1.507331
17	1	0	5.611795	-2.120087	0.787458
18	1	0	5.175644	1.400280	-1.645760
19	1	0	6.565842	-0.454959	-0.782418
20	1	0	-3.090493	-2.812640	0.557641
21	1	0	-3.828933	-2.072092	-0.883187
22	1	0	-3.199003	-0.697220	1.584651
23	1	0	1.279472	-0.852682	1.528268
24	1	0	-3.507777	1.423953	0.417031
25	1	0	0.927448	1.625411	1.648323
26	1	0	-5.636219	-0.655313	-0.329774
27	1	0	-5.876376	1.085341	-0.200902
28	1	0	-5.473107	0.146743	1.240634
29	1	0	2.791042	1.593074	-0.954955
30	1	0	-2.458893	0.928648	-1.794080
31	1	0	-4.090788	1.565829	-1.968612
32	1	0	-3.805243	-0.155915	-2.200542
33	7	0	-1.482948	-0.363540	0.424151
34	8	0	-1.465386	1.209253	2.050518
35	8	0	-1.769048	-2.146291	-0.878094
36	8	0	0.297188	-1.288483	-0.762996
37	16	0	0.420481	2.254653	-0.576765

VI exo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.524968	-0.150056	-0.568509
2	6	0	0.260842	-1.199813	-0.787933
3	6	0	3.575936	-0.471277	0.507305
4	6	0	1.541772	-1.110465	1.370349
5	6	0	-2.082708	-1.305964	0.389900
6	6	0	-0.838470	-1.983217	-0.109565
7	6	0	-2.328844	0.167746	0.301545

8	6	0	-2.776828	2.940411	0.298776
9	6	0	-2.353199	0.882173	-0.902305
10	6	0	-2.547839	0.858771	1.501359
11	6	0	-2.766047	2.235237	1.501326
12	6	0	-2.571383	2.258261	-0.900763
13	6	0	2.277422	1.352441	-0.836748
14	6	0	3.478176	1.951295	-1.583902
15	6	0	1.934728	2.157663	0.423461
16	1	0	-2.545439	0.314981	2.440088
17	1	0	-2.933094	2.752690	2.439261
18	1	0	-2.590843	2.797043	-1.841524
19	1	0	-2.952974	4.010109	0.294905
20	1	0	4.181924	-1.340598	0.250486
21	1	0	4.222491	0.365952	0.756999
22	1	0	2.777397	-0.635821	-1.511075
23	1	0	-2.457327	-1.740776	1.310418
24	1	0	1.415998	1.392927	-1.509228
25	1	0	-0.472773	-2.776977	0.529359
26	1	0	4.386138	1.944733	-0.972052
27	1	0	3.274074	2.990774	-1.851555
28	1	0	3.689034	1.403529	-2.506912
29	1	0	-2.214993	0.357294	-1.838960
30	1	0	1.052328	1.763363	0.933401
31	1	0	1.715852	3.193060	0.151249
32	1	0	2.763773	2.177176	1.137223
33	7	0	1.350502	-0.840698	0.009923
34	8	0	0.260615	-0.903959	-1.965303
35	8	0	2.810197	-0.801902	1.696157
36	8	0	0.742380	-1.534539	2.165551
37	16	0	-2.327611	-2.416288	-1.067410

VI endo – Benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.139718	0.210258	-0.469955
2	6	0	0.660241	0.140882	-0.757273
3	6	0	4.048682	-0.949194	-0.029638
4	6	0	1.927308	-1.469700	0.699936
5	6	0	-1.883002	0.119732	-0.973499
6	6	0	-0.662271	-0.469561	-0.377782
7	6	0	3.389903	1.564140	0.233002
8	6	0	4.712074	2.171258	-0.258522
9	6	0	3.338560	1.483039	1.764651
10	1	0	4.352549	-1.581078	-0.864292
11	1	0	4.925340	-0.632288	0.529475
12	1	0	3.201875	0.359610	-1.547671
13	1	0	2.581977	2.222599	-0.099092
14	1	0	-0.720093	-0.883533	0.618180
15	1	0	5.575113	1.567984	0.041029
16	1	0	4.849170	3.168354	0.166740
17	1	0	4.727957	2.266920	-1.347957
18	1	0	2.383311	1.090667	2.122938
19	1	0	3.460686	2.481362	2.191872
20	1	0	4.138559	0.856224	2.170413
21	7	0	1.812234	-0.364280	-0.155484
22	8	0	0.753064	1.046521	-1.565437

23	8	0	3.231721	-1.755292	0.859195
24	8	0	1.050412	-2.092040	1.242325
25	16	0	-1.419104	-1.555146	-1.664312
26	1	0	-1.693866	0.901055	-1.699819
27	6	0	-3.144996	0.288886	-0.200472
28	6	0	-5.526378	0.730757	1.219308
29	6	0	-3.529983	-0.578644	0.830874
30	6	0	-3.974019	1.372237	-0.515546
31	6	0	-5.156070	1.593943	0.190460
32	6	0	-4.708845	-0.356627	1.535948
33	1	0	-2.916980	-1.438387	1.077054
34	1	0	-3.689865	2.047832	-1.315318
35	1	0	-5.784817	2.439165	-0.065458
36	1	0	-4.992987	-1.035355	2.332113
37	1	0	-6.445013	0.899217	1.769554

TS_{I-II} anti,exo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.466309	-0.122641	-0.691304
2	6	0	1.527153	1.373584	0.290213
3	6	0	3.341609	-1.672373	-0.764053
4	6	0	1.570811	-0.924827	0.399222
5	6	0	0.134424	0.980118	0.678656
6	6	0	5.958452	0.131265	-0.943085
7	6	0	4.752383	0.426905	-0.039818
8	6	0	4.973717	-0.070646	1.393900
9	6	0	-0.616584	0.695020	-0.811347
10	6	0	-2.110410	0.509354	-0.532103
11	6	0	-4.861495	0.166190	-0.035390
12	6	0	-2.703245	-0.746531	-0.623896
13	6	0	-2.924889	1.600906	-0.200118
14	6	0	-4.281110	1.439628	0.047361
15	6	0	-4.067468	-0.931027	-0.377415
16	1	0	4.125694	0.163588	2.042255
17	1	0	3.354538	0.306796	-1.688586
18	1	0	4.618309	1.512701	-0.005277
19	1	0	6.157272	-0.942679	-1.017930
20	1	0	3.114654	-2.035736	-1.762751
21	1	0	4.190673	-2.206327	-0.346887
22	1	0	-0.382528	1.699587	1.304409
23	1	0	5.807287	0.519561	-1.953927
24	1	0	6.855760	0.600910	-0.534152
25	1	0	5.146577	-1.150578	1.434808
26	1	0	5.855963	0.413557	1.818880
27	1	0	-0.483808	1.693637	-1.280250
28	1	0	-2.085671	-1.590268	-0.907802
29	1	0	-2.494319	2.596904	-0.141848
30	1	0	-4.909757	2.286249	0.298869
31	1	0	-4.492317	-1.922559	-0.461220
32	7	0	2.249127	0.189124	0.081034
33	8	0	1.942208	2.481728	0.025905
34	8	0	2.173342	-2.028402	0.081059
35	8	0	0.009855	-0.300022	-1.423069

36	16	0	0.234649	-0.688018	1.455526
37	8	0	-6.203208	0.102854	0.225111
38	6	0	-6.851035	-1.166330	0.152040
39	1	0	-6.780738	-1.590845	-0.854123
40	1	0	-7.895930	-0.981088	0.394087
41	1	0	-6.429247	-1.869819	0.876561

TS_{I-II} anti,endo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.988076	-1.221961	-0.377962
2	6	0	1.929553	-0.802052	0.426120
3	6	0	4.298674	0.708915	0.235146
4	6	0	2.083334	0.386828	1.147270
5	6	0	3.249041	1.136256	1.056798
6	6	0	4.168570	-0.482187	-0.485320
7	6	0	0.653998	-1.635831	0.552250
8	1	0	0.944507	-2.705259	0.462070
9	1	0	3.367981	2.055379	1.619492
10	1	0	4.967502	-0.843684	-1.118399
11	1	0	2.907198	-2.152466	-0.934040
12	1	0	1.276675	0.707388	1.796398
13	8	0	-0.157582	-1.355319	1.554098
14	6	0	-0.692127	-0.060966	-0.973104
15	6	0	-3.468756	0.257705	1.459934
16	6	0	-2.289153	-1.207191	0.235375
17	6	0	-0.199698	-1.470782	-0.930671
18	6	0	-2.589464	1.087066	0.480072
19	6	0	-3.347615	1.973805	-0.531872
20	6	0	-4.000605	3.154273	0.201098
21	6	0	-4.358824	1.199116	-1.385074
22	1	0	0.376400	-1.781910	-1.794617
23	1	0	-4.531811	0.467905	1.394033
24	1	0	-3.128327	0.316315	2.489448
25	1	0	-1.882934	1.699845	1.039830
26	1	0	-2.578675	2.377214	-1.197333
27	1	0	-4.783131	2.824966	0.891885
28	1	0	-3.264460	3.728248	0.771907
29	1	0	-4.466413	3.829727	-0.520608
30	1	0	-5.176729	0.789243	-0.782484
31	1	0	-4.805788	1.867977	-2.124055
32	1	0	-3.890080	0.375758	-1.929800
33	7	0	-1.845321	-0.011124	-0.165816
34	8	0	-3.298399	-1.161392	1.049628
35	8	0	-0.164983	0.913849	-1.460808
36	16	0	-1.669553	-2.549076	-0.643827
37	8	0	5.406479	1.512635	0.209794
38	6	0	6.509402	1.125784	-0.608597
39	1	0	7.262215	1.901977	-0.479287
40	1	0	6.222324	1.070368	-1.663098
41	1	0	6.923091	0.163236	-0.289880

II exo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	3.595291	-0.326169	1.975283
2	1	0	5.355590	-0.286953	2.103474
3	1	0	4.566147	-1.640395	1.296613
4	1	0	6.802068	0.146489	0.038703
5	1	0	6.047203	0.480780	-1.523626
6	1	0	6.033747	-1.160630	-0.859956
7	1	0	4.623335	1.279880	0.351243
8	1	0	3.627796	0.524540	-1.756837
9	1	0	2.834694	-1.623308	-2.213436
10	1	0	3.898247	-2.198202	-0.905565
11	1	0	-0.322081	1.912103	1.240497
12	16	0	0.498928	-0.437455	1.603240
13	8	0	2.100019	2.663027	0.205667
14	8	0	1.947444	-1.856295	-0.345532
15	7	0	2.151192	0.392097	-0.271270
16	6	0	4.523562	-0.557317	1.448113
17	6	0	5.951630	-0.099837	-0.601615
18	6	0	4.634312	0.208365	0.124248
19	6	0	3.439035	-0.022407	-0.829270
20	6	0	0.194046	1.143860	0.675496
21	6	0	1.240564	-0.728214	-0.103210
22	6	0	3.105634	-1.500811	-1.164050
23	6	0	1.611580	1.547044	0.204055
24	8	0	0.131817	-0.575048	-0.980587
25	6	0	-0.553281	0.647650	-0.610908
26	1	0	-0.381280	1.380795	-1.406274
27	6	0	-2.037812	0.430042	-0.450679
28	6	0	-4.812005	0.122696	-0.110775
29	6	0	-2.900479	1.530840	-0.554789
30	6	0	-2.588777	-0.822142	-0.189204
31	6	0	-3.966036	-0.985363	-0.021085
32	6	0	-4.268638	1.386129	-0.382489
33	1	0	-2.498473	2.514869	-0.775248
34	1	0	-1.942043	-1.686939	-0.124386
35	1	0	-4.359190	-1.973423	0.175603
36	1	0	-4.934247	2.237293	-0.463280
37	8	0	-6.166855	0.075368	0.039967
38	6	0	-6.778174	-1.184068	0.324129
39	1	0	-6.604791	-1.899423	-0.485234
40	1	0	-7.844310	-0.983347	0.408526
41	1	0	-6.409261	-1.598571	1.267031

II endo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.021935	-0.287287	-1.108051

2	1	0	-5.142671	0.988821	-1.589431
3	1	0	-4.970273	0.572427	0.113985
4	1	0	-4.633902	3.436206	-1.055984
5	1	0	-3.100143	3.884604	-0.302246
6	1	0	-4.366720	3.099498	0.653450
7	1	0	-2.840959	1.845224	-1.694404
8	1	0	-1.475740	2.194775	0.315848
9	1	0	-1.930737	1.350706	2.445873
10	1	0	-3.630452	1.212837	1.933506
11	1	0	0.016141	-2.281520	-1.764377
12	1	0	1.139709	0.792656	1.241950
13	1	0	2.802628	-2.626957	-0.744447
14	1	0	4.938996	-1.418717	-1.024150
15	1	0	3.255863	1.994736	0.971477
16	1	0	0.707305	-2.801189	0.606399
17	16	0	-1.988210	-2.429253	-0.245825
18	8	0	-0.458013	0.375311	-2.216173
19	8	0	-2.526728	-0.514119	1.741791
20	7	0	-1.453432	0.145694	-0.133040
21	6	0	-4.420763	0.689186	-0.825306
22	6	0	-3.882363	3.120437	-0.328320
23	6	0	-3.315583	1.745964	-0.712387
24	6	0	-2.175679	1.357155	0.257672
25	6	0	-0.391996	-1.738192	-0.919089
26	6	0	-1.613247	-0.926457	0.832342
27	6	0	-2.605281	0.945088	1.690807
28	6	0	-0.759637	-0.269634	-1.228728
29	8	0	-0.351758	-1.227391	1.413824
30	6	0	0.500564	-1.756129	0.364304
31	6	0	4.096426	-0.941216	-0.538234
32	6	0	3.168343	0.989854	0.581600
33	6	0	1.959389	0.305458	0.729697
34	6	0	4.242075	0.368881	-0.060438
35	6	0	1.800708	-0.992913	0.251087
36	6	0	2.892972	-1.609277	-0.377833
37	8	0	5.462066	0.944104	-0.259933
38	6	0	5.670804	2.280512	0.199939
39	1	0	6.695120	2.529499	-0.069900
40	1	0	5.553462	2.348164	1.285554
41	1	0	4.984772	2.978151	-0.289308

III exo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	4.011893	0.360456	-2.473068
2	1	0	4.388013	-1.356412	-2.409396
3	1	0	2.791438	-0.806297	-1.909124
4	1	0	6.270563	-0.066370	0.593132
5	1	0	6.445442	-0.861088	-0.975059
6	1	0	6.100037	0.864986	-0.904219
7	1	0	4.248452	-1.393382	0.039786
8	1	0	4.074835	0.646313	1.389794
9	1	0	4.029976	2.149226	-1.140795
10	1	0	3.744022	2.810358	0.492729
11	1	0	-4.180279	-0.165344	-2.017327

12	1	0	-5.031448	0.567640	2.132557
13	1	0	-2.606523	0.610629	2.612595
14	1	0	-1.777149	-0.160004	-1.526525
15	1	0	-0.242698	-1.745100	1.672443
16	1	0	-0.432112	0.665274	1.908348
17	6	0	3.854482	-0.554624	-1.893190
18	6	0	5.885446	-0.098314	-0.429778
19	6	0	4.385856	-0.430275	-0.459680
20	16	0	0.281367	-2.028347	-0.711571
21	8	0	0.134074	1.203925	-0.000045
22	8	0	2.056850	2.184260	-0.517826
23	8	0	2.367814	-1.590101	1.905988
24	7	0	2.181751	0.262499	0.575170
25	6	0	-3.849781	-0.003969	-1.000545
26	6	0	-4.310074	0.408170	1.340298
27	6	0	-2.948404	0.429428	1.598876
28	6	0	-2.483554	0.002824	-0.724119
29	6	0	-4.770660	0.191745	0.034682
30	6	0	-2.014961	0.217829	0.574079
31	6	0	0.193771	-1.124327	0.888073
32	6	0	-0.562112	0.213974	0.920893
33	6	0	1.411929	1.191213	0.022258
34	6	0	3.492822	2.017188	-0.207025
35	6	0	1.643073	-0.915653	1.213545
36	6	0	3.620893	0.597728	0.399963
37	8	0	-6.121776	0.199084	-0.127868
38	6	0	-6.658651	-0.019967	-1.434799
39	1	0	-6.336508	0.760968	-2.129544
40	1	0	-7.739801	0.020122	-1.319656
41	1	0	-6.368428	-1.001092	-1.820918

III endo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.699219	-0.506543	-1.540492
2	1	0	-5.522393	0.462634	-0.325424
3	1	0	-3.883835	0.894219	-0.805037
4	1	0	-4.611164	-2.615034	1.659975
5	1	0	-5.959938	-1.631944	1.081132
6	1	0	-5.090750	-2.671106	-0.044841
7	1	0	-3.950512	-0.230905	1.427476
8	1	0	-2.305243	-2.012691	1.110917
9	1	0	-3.298323	-2.276890	-1.642515
10	1	0	-1.857857	-3.074311	-0.953089
11	1	0	0.197932	2.211455	1.382331
12	6	0	-4.551086	0.051153	-0.610209
13	6	0	-4.969573	-2.011887	0.821066
14	6	0	-4.022947	-0.839215	0.521426
15	16	0	-1.712326	2.952947	0.024186
16	8	0	-0.164834	0.469666	-1.547663
17	8	0	-1.512114	-1.259707	-1.873162
18	8	0	-1.506660	0.443456	2.279643
19	7	0	-1.581249	-0.309514	0.124968
20	6	0	-0.392592	1.780526	0.573759

21	6	0	0.569629	1.384560	-0.546620
22	6	0	-1.056219	-0.318478	-1.096669
23	6	0	-2.389816	-2.132841	-1.066539
24	6	0	-1.179777	0.633223	1.131150
25	6	0	-2.600707	-1.383140	0.271518
26	1	0	0.754151	2.251973	-1.173593
27	6	0	1.857168	0.702939	-0.189374
28	6	0	4.313436	-0.555680	0.358569
29	6	0	2.969886	0.903294	-1.011582
30	6	0	2.000882	-0.136839	0.927387
31	6	0	3.208724	-0.757638	1.199298
32	6	0	4.190755	0.285393	-0.753032
33	1	0	2.887280	1.556366	-1.873702
34	1	0	1.176229	-0.304678	1.609577
35	1	0	3.321185	-1.399567	2.064543
36	1	0	5.027984	0.468845	-1.411847
37	8	0	5.450403	-1.208826	0.707784
38	6	0	6.616217	-1.051977	-0.107432
39	1	0	6.435364	-1.410705	-1.124421
40	1	0	7.386186	-1.660565	0.361582
41	1	0	6.940635	-0.008168	-0.133442

IV exo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	3.512958	-0.365295	2.564427
2	1	0	3.222970	-0.849942	-1.696167
3	1	0	1.588173	0.965894	-1.793732
4	1	0	1.855866	1.464628	2.458412
5	1	0	0.631989	3.052658	1.236210
6	1	0	-1.575850	2.835953	0.405189
7	1	0	-0.289032	-3.403239	0.310442
8	1	0	-1.733846	-3.040238	1.249732
9	1	0	-0.486881	-1.803051	1.015783
10	1	0	-2.852285	-3.033811	-2.421337
11	1	0	-3.194674	-3.783854	-0.854355
12	1	0	-1.684093	-4.138669	-1.688891
13	1	0	-0.937067	-1.792191	-1.442219
14	1	0	-3.148504	-0.767204	-1.540463
15	1	0	-4.765411	-0.831914	0.177729
16	1	0	-3.924110	-2.286666	0.766966
17	6	0	3.077101	-0.072725	1.616526
18	6	0	2.925420	-0.361704	-0.778163
19	6	0	1.989906	0.671383	-0.832512
20	6	0	2.147151	0.953782	1.546703
21	6	0	3.473201	-0.741183	0.451355
22	6	0	1.577614	1.339651	0.322285
23	16	0	0.224604	3.459312	-1.172615
24	6	0	-1.021964	-2.623278	0.530814
25	6	0	-2.404995	-3.346420	-1.473420
26	6	0	-1.707303	-2.174859	-0.767013
27	8	0	-1.990505	1.205600	2.097164
28	8	0	-3.357966	-0.516685	1.654389
29	8	0	-1.119047	0.755460	-1.992561

30	7	0	-2.083759	0.213277	-0.025272
31	6	0	-0.826124	2.334497	-0.193456
32	6	0	0.573389	2.445546	0.339127
33	6	0	-2.427816	0.396244	1.319566
34	6	0	-3.802857	-1.245318	0.479726
35	6	0	-1.319554	1.059301	-0.834149
36	6	0	-2.707368	-1.011801	-0.574110
37	8	0	4.396900	-1.730701	0.613713
38	6	0	4.852859	-2.437638	-0.541149
39	1	0	4.028617	-2.958051	-1.037641
40	1	0	5.574136	-3.166100	-0.176243
41	1	0	5.342676	-1.763091	-1.249525

IV endo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-0.813567	0.321681	-2.181547
2	1	0	-4.498096	-0.755503	1.832280
3	1	0	-5.159863	1.912948	-1.472340
4	1	0	-2.912469	1.367938	-2.348493
5	1	0	-2.291933	-1.301700	0.959551
6	1	0	2.783015	1.653920	1.885144
7	1	0	-0.082367	-0.823011	0.586093
8	1	0	3.819610	3.065391	1.707088
9	1	0	4.524299	1.524013	2.184733
10	1	0	5.505531	2.007993	-1.490063
11	1	0	6.191878	1.727465	0.118024
12	1	0	4.041578	0.048268	-1.357981
13	1	0	5.432146	3.271805	-0.257964
14	1	0	3.227214	2.188730	-0.519903
15	1	0	5.138823	-1.595363	-0.075641
16	1	0	5.517258	-0.301858	1.087722
17	6	0	-4.164043	-0.280326	0.920110
18	6	0	-4.518935	1.214890	-0.947127
19	6	0	-3.256946	0.902326	-1.431256
20	6	0	-2.899338	-0.583101	0.420822
21	6	0	-4.982690	0.625990	0.235356
22	6	0	-2.419461	0.003173	-0.753947
23	16	0	-0.478487	-2.043417	-1.536686
24	6	0	3.767049	1.986100	1.543995
25	6	0	5.361613	2.193935	-0.421995
26	8	0	1.612045	-1.715961	1.706895
27	6	0	3.999182	1.674249	0.059479
28	8	0	3.817211	-1.388090	1.495118
29	8	0	1.601226	0.614702	-1.815380
30	7	0	2.507204	-0.360015	0.009298
31	6	0	0.083248	-0.646339	-0.466335
32	6	0	-1.070559	-0.273018	-1.313067
33	6	0	2.536929	-1.210249	1.124082
34	6	0	4.722296	-0.790748	0.530317
35	6	0	1.427419	-0.074195	-0.826872
36	6	0	3.853771	0.175849	-0.291944
37	8	0	-6.232460	0.991098	0.635764
38	6	0	-6.764289	0.419538	1.832842

39	1	0	-6.150285	0.677458	2.700633
40	1	0	-6.846412	-0.667920	1.748605
41	1	0	-7.756641	0.850090	1.950004

V – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-3.660594	-0.588272	0.432135
2	6	0	-1.592964	0.642212	1.149171
3	6	0	-3.732327	-1.979453	-0.220514
4	6	0	-1.582574	-1.230120	-0.507366
5	6	0	0.825233	-0.078501	0.993247
6	6	0	-0.142744	1.029058	0.882853
7	6	0	2.165660	-0.148227	0.617124
8	6	0	4.898231	-0.384442	-0.004414
9	6	0	2.814972	0.811648	-0.214098
10	6	0	2.944115	-1.247571	1.105351
11	6	0	4.273017	-1.363095	0.807498
12	6	0	4.154519	0.701643	-0.512355
13	6	0	-4.491941	0.519277	-0.254384
14	6	0	-5.983937	0.306495	0.040587
15	6	0	-4.225204	0.648978	-1.760116
16	6	0	6.933135	0.355546	-1.048674
17	1	0	4.870388	-2.186700	1.177206
18	1	0	4.623204	1.442373	-1.144760
19	1	0	-3.773913	-2.782992	0.515191
20	1	0	-4.546357	-2.091314	-0.931824
21	1	0	-3.947715	-0.641364	1.482141
22	1	0	0.491769	-0.895599	1.630595
23	1	0	-4.190021	1.455209	0.224689
24	1	0	0.126599	1.605196	1.788897
25	1	0	-6.359384	-0.622019	-0.402207
26	1	0	-6.571333	1.127253	-0.377966
27	1	0	-6.177716	0.270432	1.116439
28	1	0	2.223594	1.626298	-0.613023
29	1	0	-3.167859	0.820973	-1.974903
30	1	0	-4.780624	1.500900	-2.160281
31	1	0	-4.550339	-0.237972	-2.312914
32	1	0	2.465921	-1.992340	1.731244
33	1	0	6.523252	0.393387	-2.059347
34	1	0	7.948812	-0.029501	-1.074274
35	1	0	6.921486	1.347091	-0.592859
36	7	0	-2.202997	-0.341750	0.357712
37	8	0	6.194164	-0.580742	-0.239254
38	8	0	-2.255276	1.200423	2.005572
39	8	0	-2.485188	-2.121658	-0.953376
40	8	0	-0.418431	-1.259136	-0.835102
41	16	0	-0.160658	2.275049	-0.461563

VI exo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.707639	-1.011299	-0.574166
2	6	0	-1.319138	1.059383	-0.834080
3	6	0	-3.803257	-1.244414	0.479623
4	6	0	-2.427485	0.396479	1.319609
5	6	0	0.573857	2.445581	0.339210
6	6	0	-0.825624	2.334570	-0.193387
7	6	0	1.577936	1.339518	0.322330
8	6	0	3.473123	-0.741664	0.451391
9	6	0	1.990681	0.671711	-0.832570
10	6	0	2.146838	0.953042	1.546841
11	6	0	3.076596	-0.073653	1.616663
12	6	0	2.926022	-0.361531	-0.778230
13	6	0	-1.708019	-2.174698	-0.767088
14	6	0	-2.406014	-3.345749	-1.474077
15	6	0	-1.023335	-2.623841	0.530847
16	7	0	-2.083553	0.213518	-0.025204
17	16	0	0.225189	3.459362	-1.172513
18	1	0	1.855233	1.463550	2.458640
19	1	0	3.511967	-0.366681	2.564646
20	1	0	3.223990	-0.849370	-1.696310
21	1	0	-4.765597	-0.830514	0.177618
22	1	0	-3.925017	-2.285745	0.766727
23	1	0	-3.148645	-0.766429	-1.540509
24	1	0	0.632514	3.052607	1.236347
25	1	0	-0.937404	-1.792165	-1.441939
26	1	0	-1.575375	2.836066	0.405198
27	1	0	-3.196507	-3.782587	-0.855634
28	1	0	-1.685526	-4.138513	-1.689023
29	1	0	-2.852333	-3.032742	-2.422320
30	1	0	1.589463	0.966739	-1.793848
31	1	0	-0.488451	-1.803912	1.016538
32	1	0	-0.290360	-3.403737	0.310418
33	1	0	-1.735623	-3.041111	1.249181
34	8	0	-1.118575	0.755460	-1.992436
35	8	0	-3.358047	-0.516136	1.654376
36	8	0	-1.989798	1.205515	2.097324
37	8	0	4.396607	-1.731404	0.613742
38	6	0	4.852653	-2.438191	-0.541180
39	1	0	4.028352	-2.958084	-1.038117
40	1	0	5.573493	-3.167075	-0.176253
41	1	0	5.343007	-1.763641	-1.249186

VI endo – *p*-Methoxy-benzaldehyde

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.498212	-0.755328	1.832442
2	1	0	-5.160377	1.912100	-1.472934

3	1	0	-2.912908	1.367193	-2.348919
4	1	0	-2.291947	-1.301394	0.959901
5	1	0	-0.813779	0.321598	-2.181516
6	1	0	4.524879	1.523398	2.184890
7	1	0	3.820163	3.064964	1.707909
8	1	0	2.783548	1.653475	1.885668
9	1	0	5.505424	2.008546	-1.489930
10	1	0	5.432435	3.271901	-0.257332
11	1	0	6.192099	1.727345	0.117911
12	1	0	-0.082360	-0.822468	0.586320
13	1	0	3.227350	2.189096	-0.519294
14	1	0	4.041345	0.048773	-1.358170
15	1	0	5.517257	-0.302086	1.087431
16	1	0	5.139073	-1.595100	-0.076546
17	6	0	-4.164206	-0.280315	0.920165
18	6	0	-4.519335	1.214310	-0.947502
19	6	0	-3.257292	0.901808	-1.431531
20	6	0	-2.899454	-0.583028	0.420976
21	6	0	-4.982985	0.625716	0.235177
22	6	0	-2.419644	0.003023	-0.753936
23	16	0	-0.478260	-2.043324	-1.536270
24	8	0	1.612211	-1.716314	1.706454
25	8	0	3.817392	-1.388776	1.494266
26	8	0	1.601019	0.615452	-1.815076
27	7	0	2.507201	-0.359719	0.009277
28	6	0	3.767530	1.985730	1.544445
29	6	0	5.361768	2.194100	-0.421761
30	6	0	3.999382	1.674379	0.059792
31	6	0	0.083203	-0.645901	-0.466133
32	6	0	-1.070664	-0.272998	-1.312940
33	6	0	2.537052	-1.210510	1.123640
34	6	0	4.722386	-0.790841	0.529767
35	6	0	1.427325	-0.073676	-0.826693
36	6	0	3.853760	0.176085	-0.292059
37	8	0	-6.232774	0.990784	0.635506
38	6	0	-6.764202	0.420115	1.833194
39	1	0	-6.149859	0.678651	2.700564
40	1	0	-6.846429	-0.667399	1.749796
41	1	0	-7.756491	0.850804	1.950383

A

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.694329	1.119276	-0.200245
2	6	0	3.930286	-1.198690	0.104663
3	6	0	1.041647	0.242214	-1.728722
4	6	0	2.264661	-0.534516	-1.555322
5	6	0	3.789445	0.775252	1.280417
6	1	0	4.716389	1.292935	-0.569629
7	1	0	0.900768	0.715727	-2.704740
8	1	0	2.808873	0.774222	1.767559
9	1	0	4.503478	1.380905	1.837751
10	7	0	3.314949	-0.229456	-0.714415
11	8	0	2.094767	-1.594131	-2.152687

12	8	0	4.297302	-0.583252	1.253234
13	16	0	4.203916	-2.780034	-0.185329
14	8	0	-0.308059	1.965607	0.349683
15	6	0	-1.139895	2.356232	1.243776
16	6	0	-0.945092	3.765045	1.761719
17	1	0	-1.341530	4.471254	1.024474
18	1	0	0.117427	3.980719	1.892388
19	1	0	-1.481752	3.897931	2.701314
20	8	0	-2.105810	1.689777	1.706419
21	45	0	-0.499539	0.062624	-0.503739
22	45	0	-2.463503	-0.206815	0.951191
23	8	0	0.658671	-0.723123	1.032850
24	8	0	-1.163624	-1.028754	2.355613
25	6	0	0.945386	-1.797641	3.135342
26	1	0	2.001386	-1.598042	2.951007
27	1	0	0.654380	-1.470185	4.135715
28	1	0	0.782026	-2.878836	3.078288
29	6	0	0.070213	-1.125554	2.100118
30	8	0	-1.758640	0.845574	-1.945055
31	8	0	-3.575385	0.628321	-0.594424
32	8	0	-0.911742	-1.848040	-1.169686
33	8	0	-2.748341	-2.081700	0.142179
34	6	0	-1.919549	-2.494509	-0.719962
35	6	0	-3.007052	0.953479	-1.676374
36	6	0	-3.876129	1.503134	-2.786418
37	1	0	-4.825008	1.857008	-2.382459
38	1	0	-3.356407	2.306340	-3.312651
39	1	0	-4.075058	0.703693	-3.508054
40	6	0	-2.117240	-3.877972	-1.295618
41	1	0	-2.948313	-4.379237	-0.799587
42	1	0	-2.317484	-3.798039	-2.368171
43	1	0	-1.197481	-4.456636	-1.177512
44	6	0	2.843188	2.326325	-0.619095
45	6	0	3.128489	2.725813	-2.078298
46	6	0	3.140542	3.516118	0.311606
47	1	0	1.779938	2.087678	-0.494370
48	1	0	3.017347	1.893446	-2.779345
49	1	0	2.447497	3.521120	-2.396104
50	1	0	4.152852	3.102521	-2.180544
51	1	0	2.849790	3.311621	1.346486
52	1	0	4.205990	3.777076	0.298895
53	1	0	2.581993	4.395865	-0.020374

TS_{A-B}

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.181499	-3.538431	1.148026
2	6	0	1.995021	-2.365877	3.245154
3	6	0	1.719819	-2.223144	1.737083
4	6	0	-2.091796	2.386135	-3.506269
5	6	0	-3.032814	3.304520	2.208129
6	6	0	-2.730044	2.070391	1.393282
7	6	0	-2.134226	1.501757	-2.284710
8	8	0	-3.249265	1.029424	-1.916408
9	8	0	-1.011105	1.291194	-1.706571

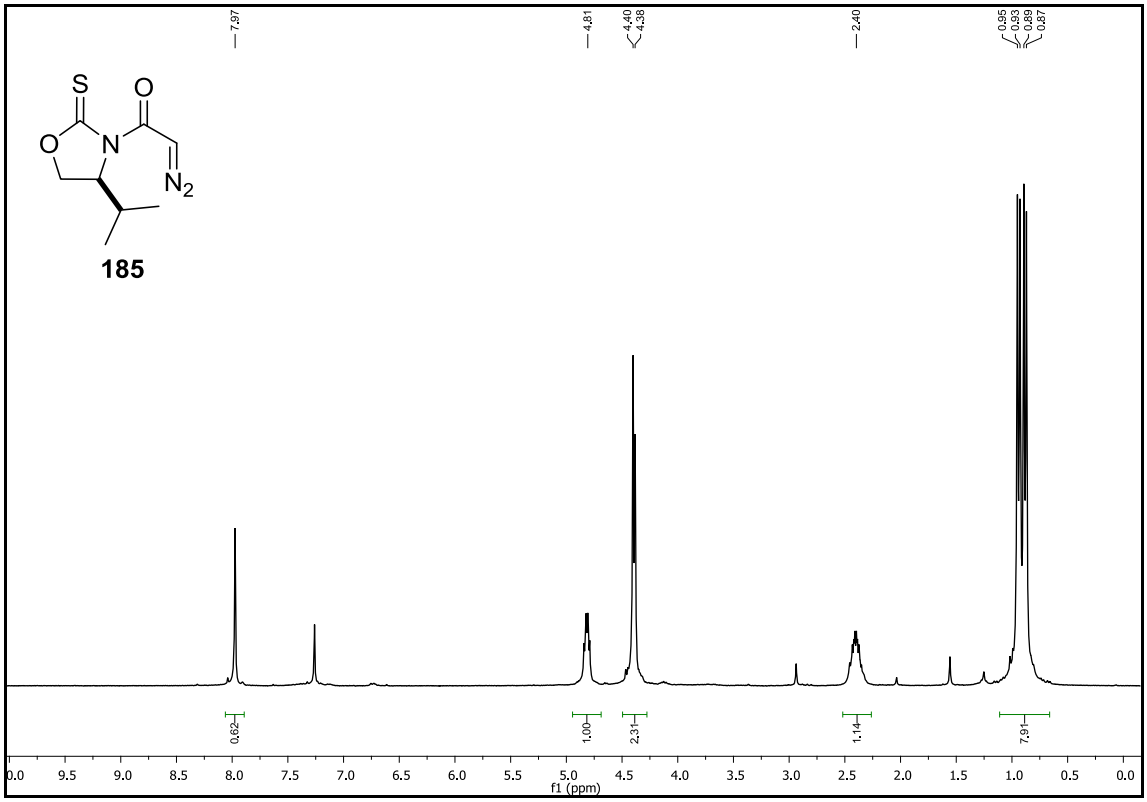
10	8	0	-3.701390	1.399284	0.933912
11	8	0	-1.492532	1.798876	1.217666
12	45	0	-3.352411	-0.234183	-0.282067
13	45	0	-0.947507	0.229621	0.033404
14	8	0	-3.302436	-1.430579	1.392746
15	6	0	-2.301861	-2.233952	3.388526
16	6	0	-2.233925	-1.489836	2.071665
17	8	0	-1.114251	-0.954501	1.773146
18	16	0	4.482863	-1.040252	-2.609974
19	8	0	4.788208	-2.255703	-0.346889
20	8	0	1.684381	-0.130203	-2.034384
21	7	0	2.856894	-1.142658	-0.343806
22	6	0	4.068405	-2.737654	0.800736
23	6	0	1.856613	-0.247825	-0.826002
24	6	0	1.058854	0.568672	0.182590
25	6	0	3.993011	-1.469282	-1.096244
26	6	0	2.996131	-1.679860	1.048575
27	6	0	-1.573398	-2.100485	-1.632785
28	6	0	-1.228141	-3.264929	-2.533658
29	8	0	-2.800689	-1.822796	-1.492507
30	8	0	-0.591618	-1.478591	-1.100781
31	6	0	1.323448	2.243675	-0.188959
32	6	0	2.751103	2.449882	0.282877
33	6	0	5.351563	3.033126	1.145098
34	6	0	2.978529	2.901365	1.595591
35	6	0	3.837449	2.300136	-0.591519
36	6	0	5.132091	2.598136	-0.161733
37	6	0	4.269508	3.187141	2.024400
38	8	0	0.467276	3.028021	0.330484
39	1	0	0.239684	-3.795702	1.640853
40	1	0	1.860908	-4.380710	1.309640
41	1	0	0.978416	-3.452224	0.076704
42	1	0	2.737200	-3.145565	3.453983
43	1	0	1.075293	-2.641902	3.768665
44	1	0	2.358736	-1.428658	3.680195
45	1	0	0.922178	-1.487631	1.620818
46	1	0	-1.357765	1.993333	-4.214722
47	1	0	-1.763387	3.387467	-3.212847
48	1	0	-3.076581	2.438240	-3.970628
49	1	0	-2.897466	4.183988	1.569893
50	1	0	-2.329864	3.387790	3.039131
51	1	0	-4.061229	3.279752	2.569677
52	1	0	-3.197308	-2.854867	3.416794
53	1	0	-1.409978	-2.845690	3.542587
54	1	0	-2.350573	-1.503270	4.202858
55	1	0	4.763924	-2.867278	1.629904
56	1	0	3.641145	-3.704267	0.523926
57	1	0	1.404013	0.511598	1.218197
58	1	0	3.432251	-0.881103	1.665857
59	1	0	-1.325129	-2.940742	-3.574923
60	1	0	-1.934465	-4.081510	-2.369305
61	1	0	-0.203685	-3.596801	-2.365872
62	1	0	1.169750	2.037547	-1.279913
63	1	0	2.124222	3.037969	2.251472
64	1	0	3.673756	1.967521	-1.609248
65	1	0	5.963012	2.480763	-0.850553
66	1	0	4.441308	3.537645	3.038141
67	1	0	6.360198	3.254862	1.482385

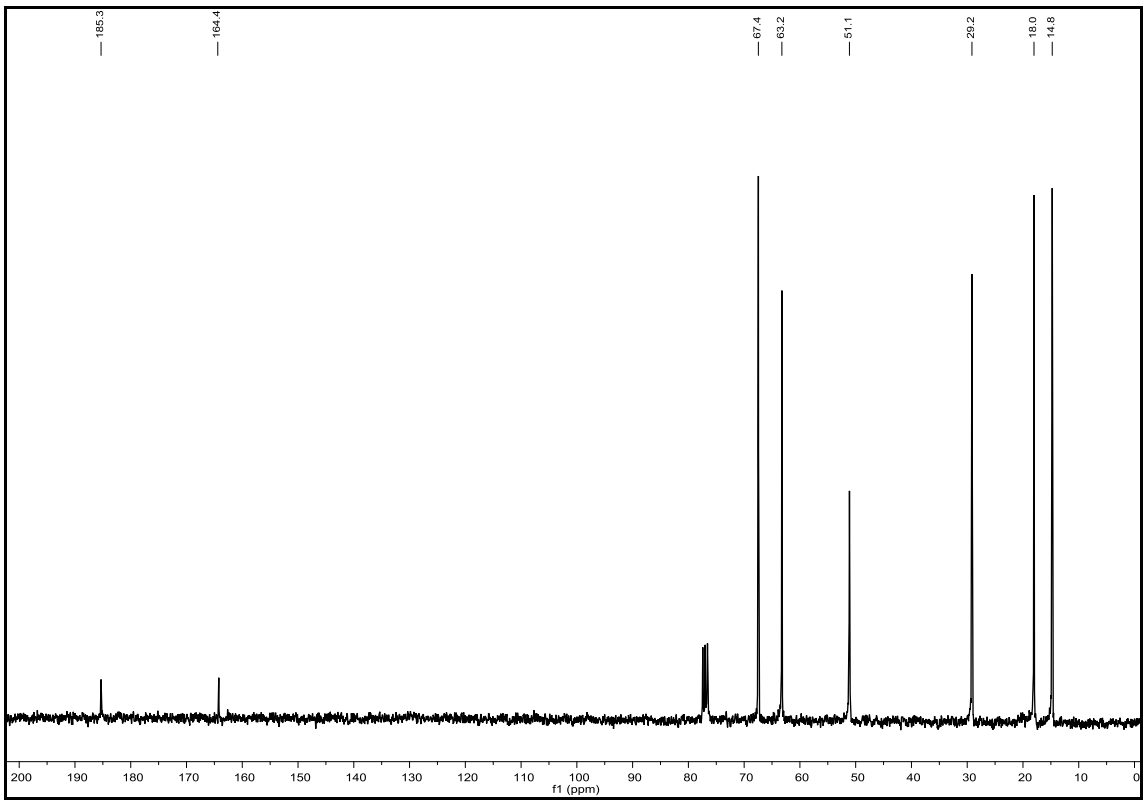
B

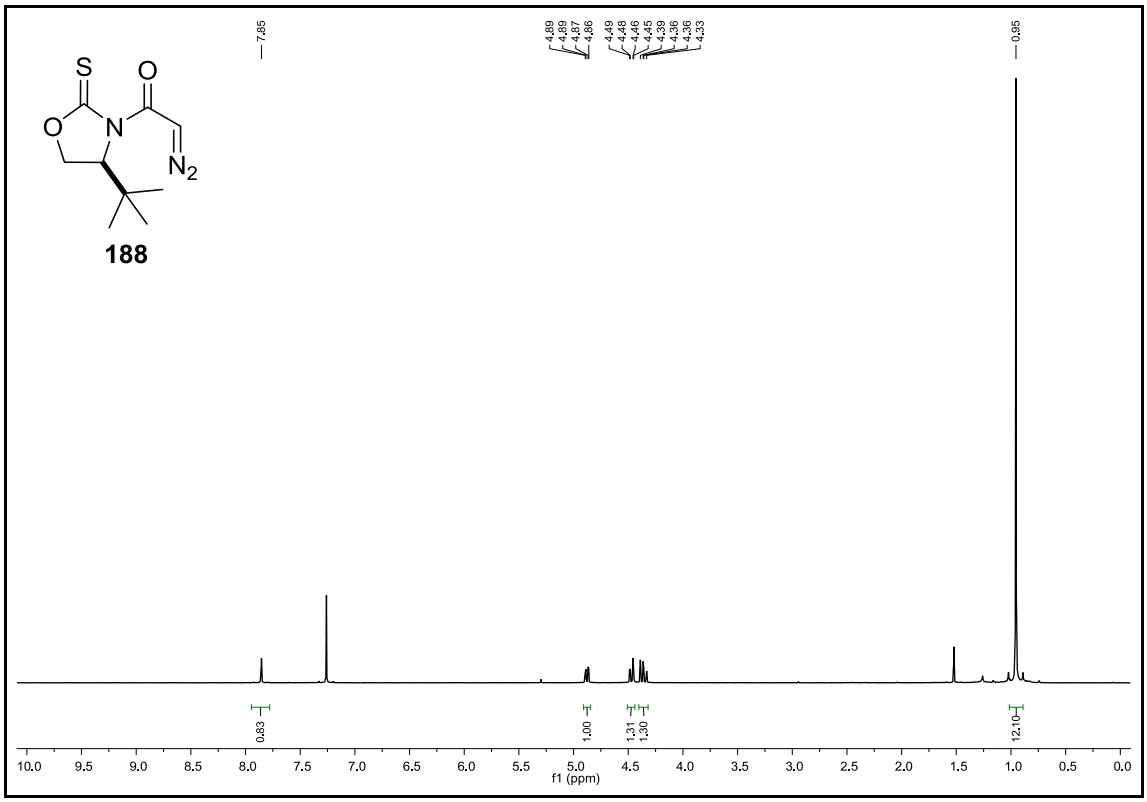
Standard orientation:

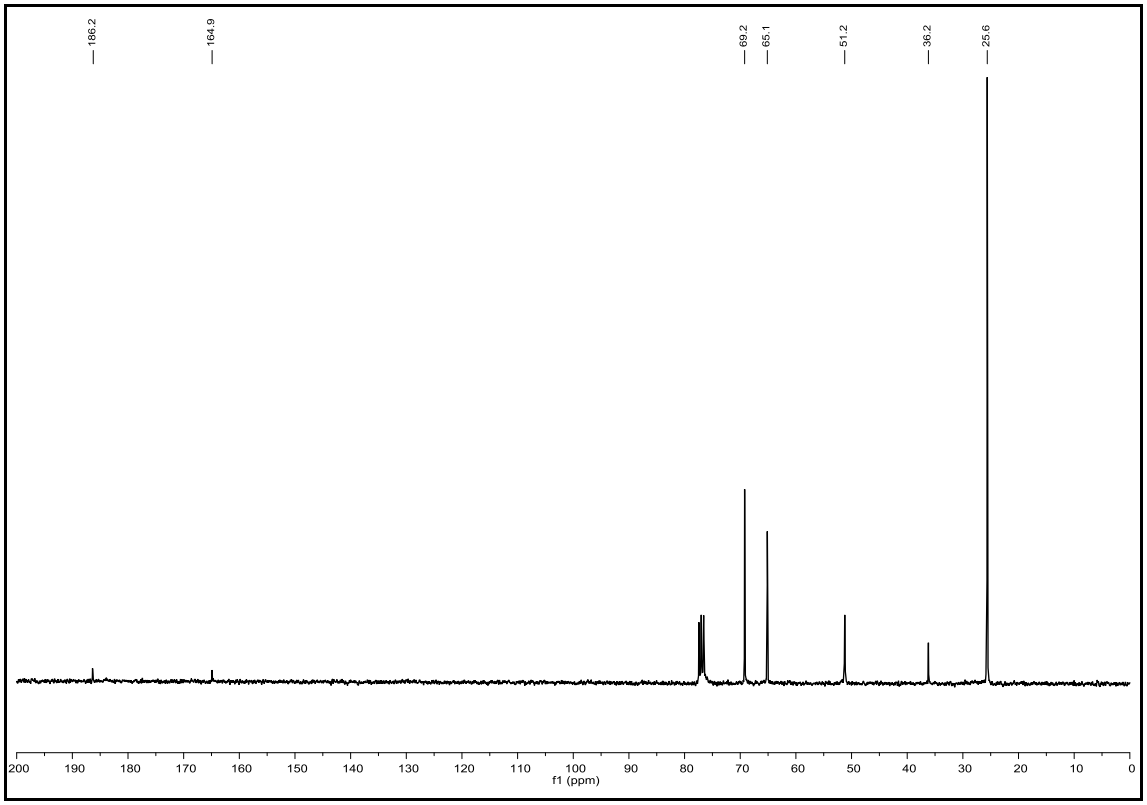
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.662234	1.559655	-0.477378
2	16	0	-1.994632	3.055286	0.083342
3	7	0	-1.176007	0.426931	0.201954
4	6	0	-0.245607	0.487332	1.261618
5	8	0	0.143318	1.521691	1.751049
6	8	0	-1.884276	1.202500	-1.767262
7	6	0	-1.378951	-0.129328	-2.004710
8	1	0	-2.018188	-0.593703	-2.755308
9	1	0	-0.351862	-0.058555	-2.379497
10	6	0	-1.449793	-0.778940	-0.619881
11	1	0	-0.653370	-1.512820	-0.478525
12	6	0	0.253351	-0.864422	1.737589
13	1	0	-0.520468	-1.576230	2.025179
14	6	0	1.576031	-1.411848	1.305821
15	1	0	1.656947	-2.501690	1.314500
16	8	0	1.380056	-0.830705	2.595409
17	6	0	-2.838952	-1.412543	-0.344301
18	1	0	-3.585020	-0.692562	-0.708017
19	6	0	-3.126030	-1.663111	1.141311
20	1	0	-4.160222	-1.997041	1.268778
21	1	0	-2.996550	-0.758983	1.741908
22	1	0	-2.482912	-2.452047	1.548840
23	6	0	-2.989128	-2.715898	-1.145559
24	1	0	-2.839311	-2.573711	-2.220405
25	1	0	-3.990981	-3.133691	-1.010281
26	1	0	-2.268617	-3.469225	-0.804508
27	6	0	2.486712	-0.732881	0.338654
28	6	0	4.182023	0.481617	-1.530594
29	6	0	2.879137	-1.423102	-0.816605
30	6	0	2.960894	0.566899	0.560308
31	6	0	3.804236	1.167042	-0.374270
32	6	0	3.718454	-0.816909	-1.750616
33	1	0	2.534355	-2.441985	-0.979882
34	1	0	2.662020	1.092085	1.459840
35	1	0	4.168561	2.174263	-0.196095
36	1	0	4.017928	-1.360514	-2.641879
37	1	0	4.840209	0.954047	-2.253693

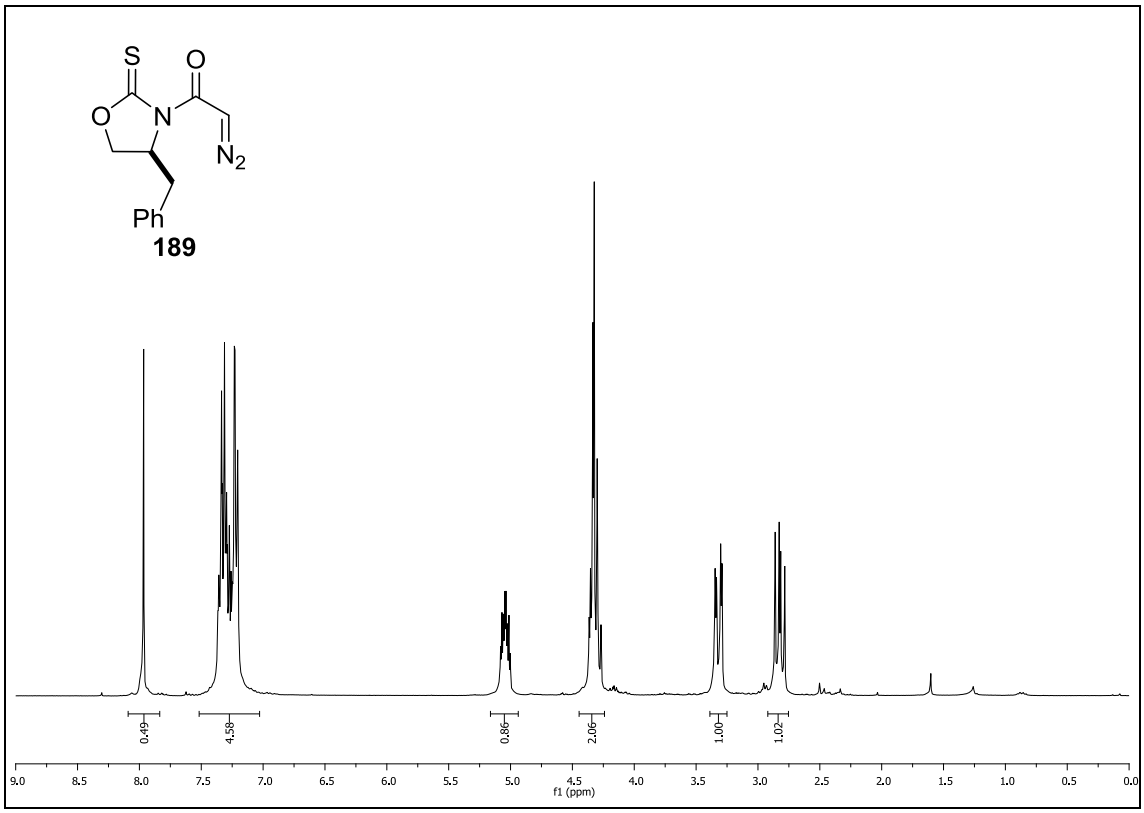
6.2.6. Representative NMR spectra

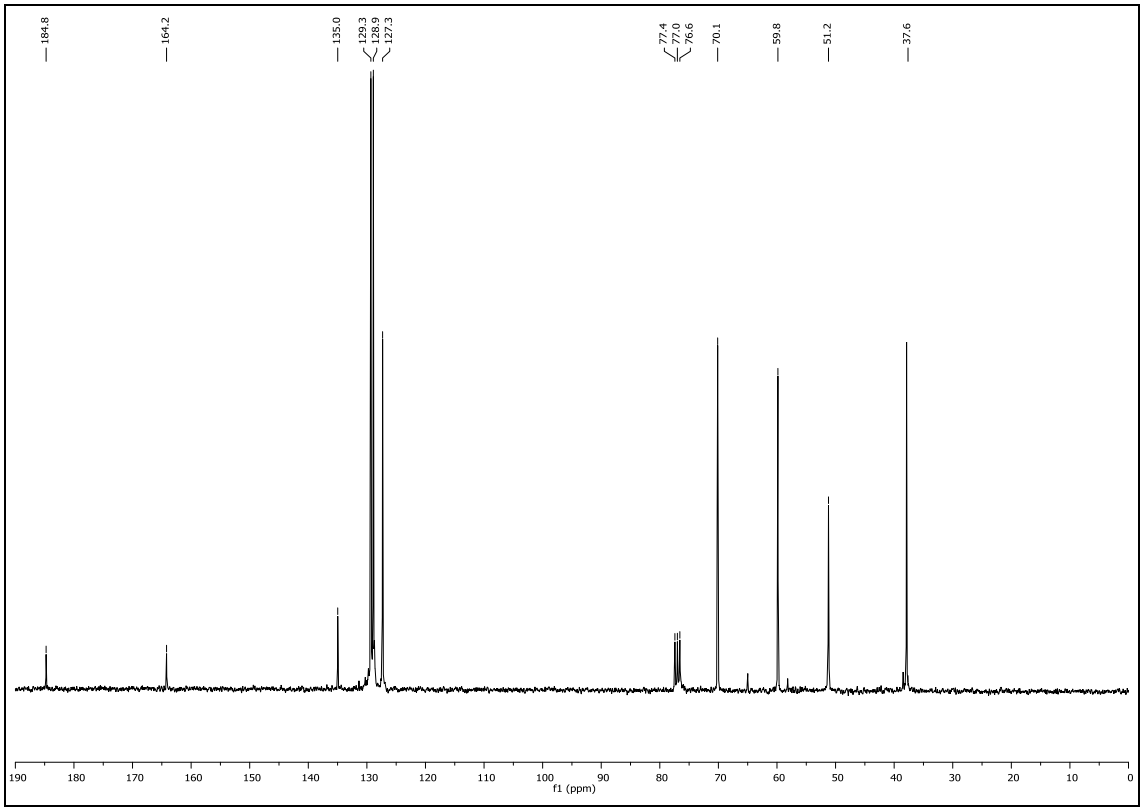


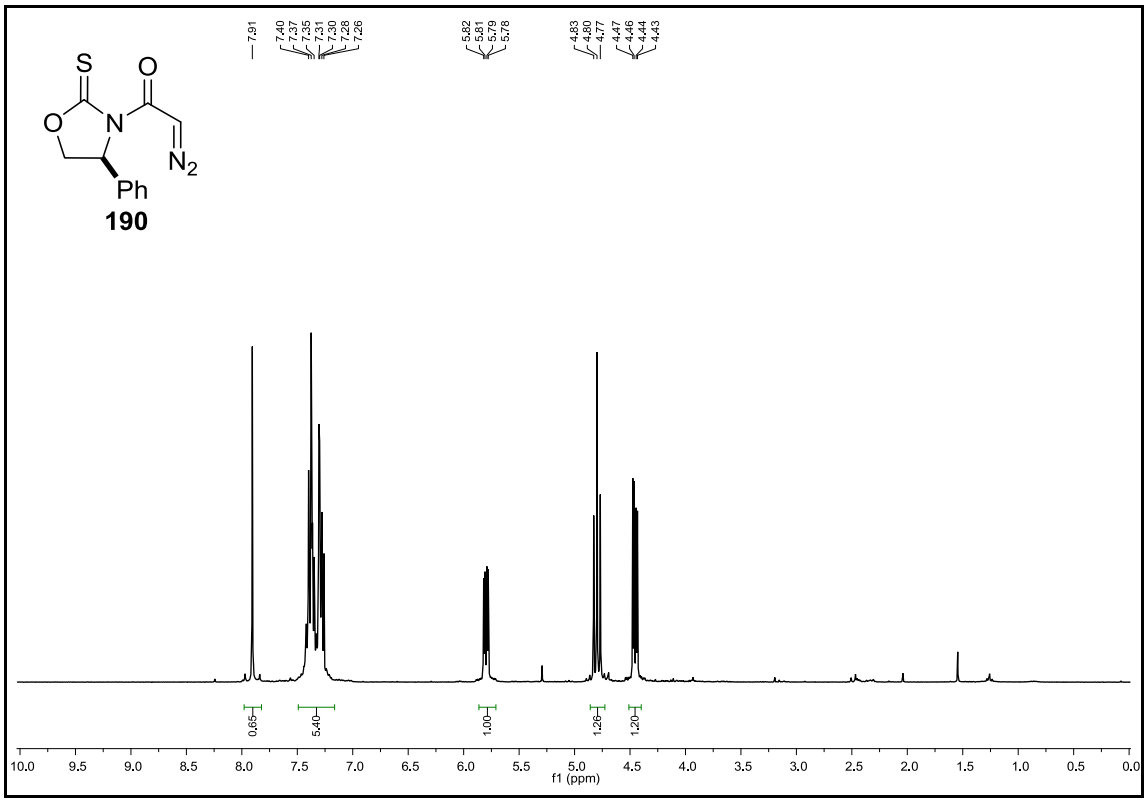


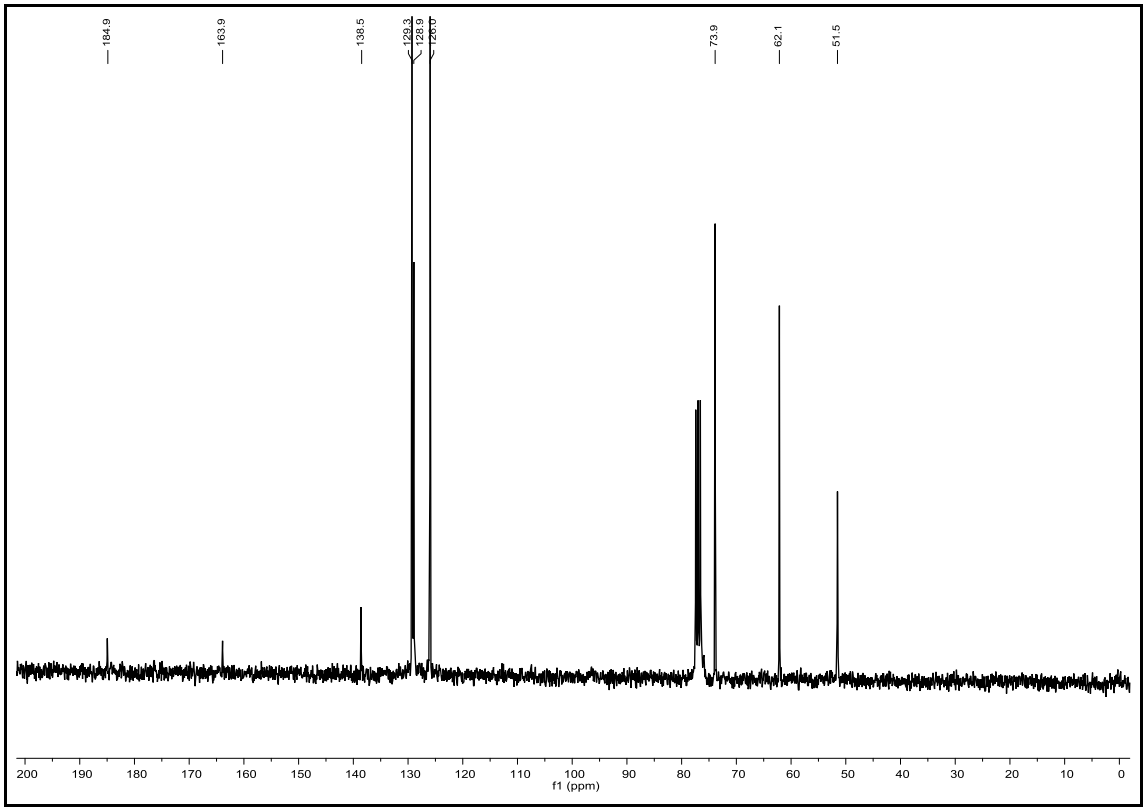

S
O
O
N
N2
188
7.85
4.89
4.89
4.87
4.86
4.49
4.48
4.46
4.45
4.39
4.36
4.36
4.33
0.95
0.83
1.00
1.31
1.30
12.10
f1 (ppm)

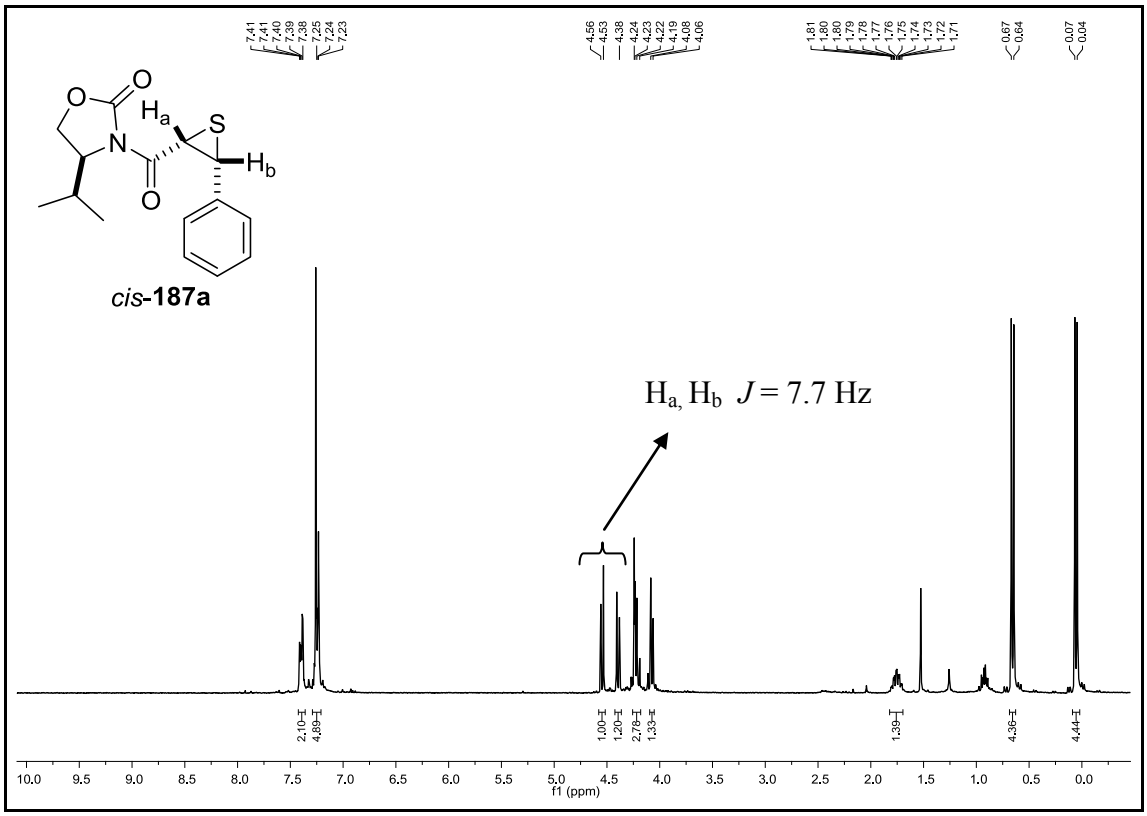

186.2
164.9
69.2
65.1
51.2
36.2
25.6
f1 (ppm)

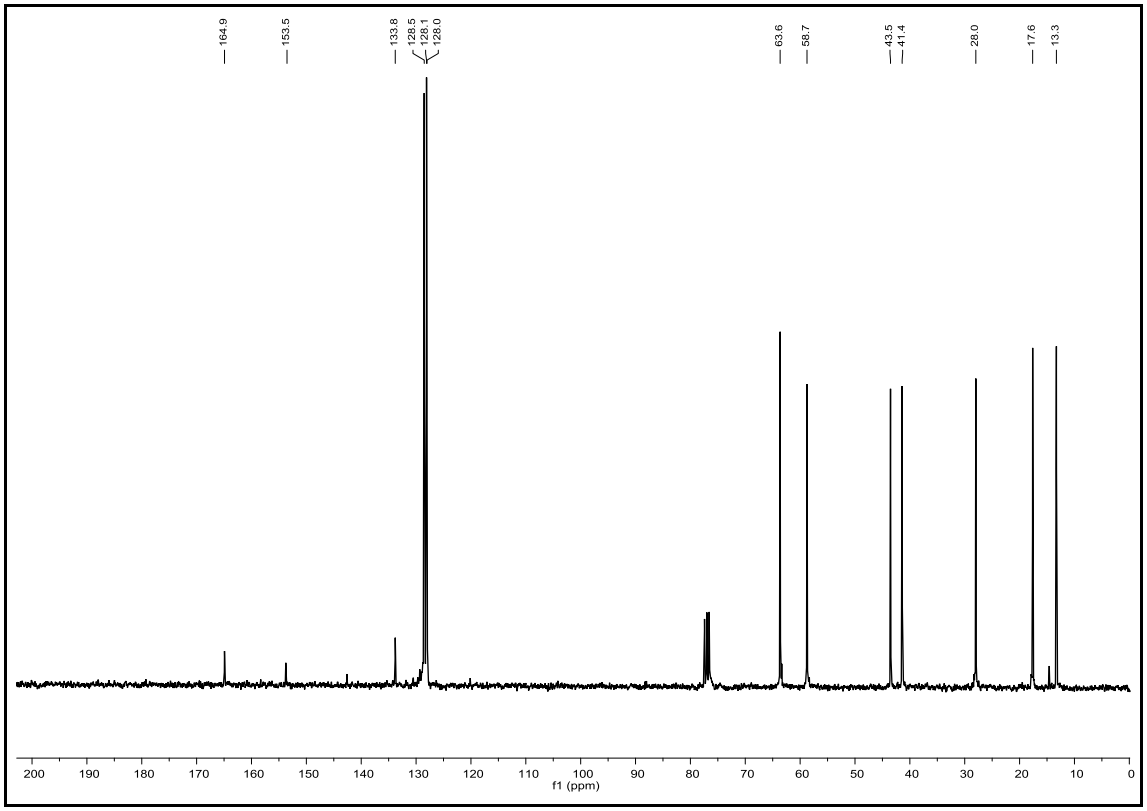

S
O
O
N
N2
Ph
189
0.49
4.58
0.86
2.06
1.00
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

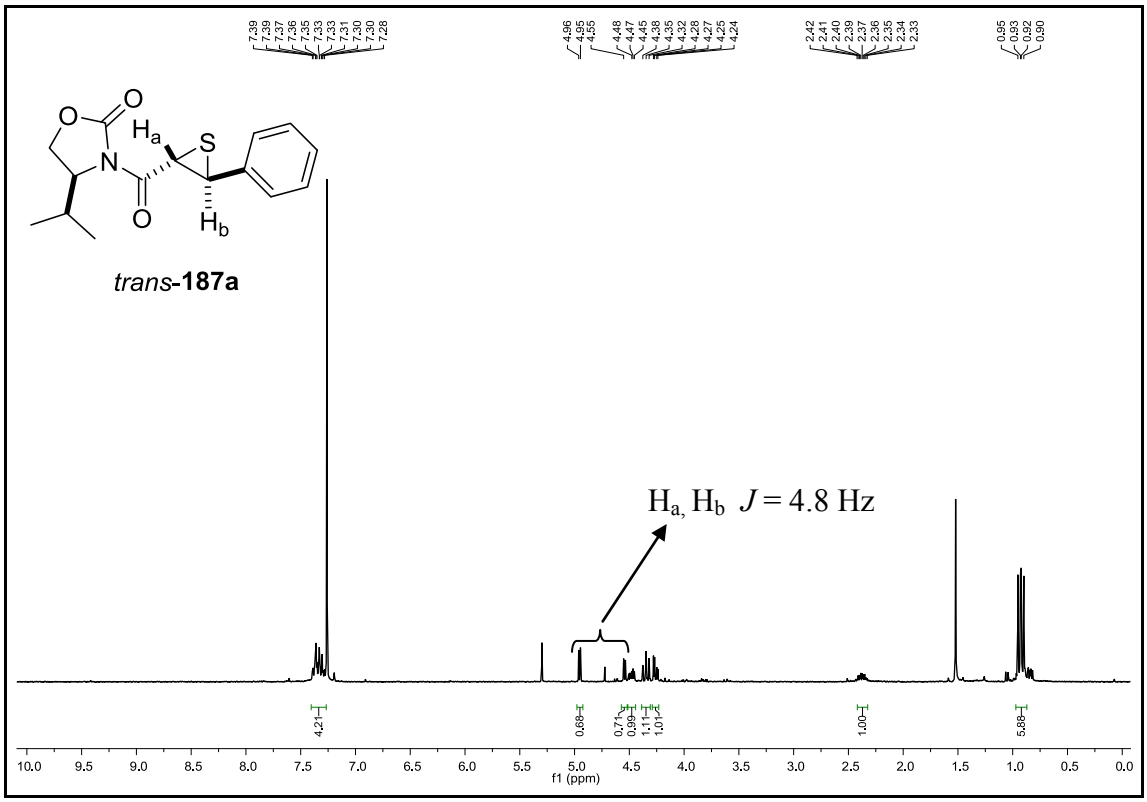

184.8
164.2
135.0
129.3
128.9
127.3
77.4
77.0
76.6
70.1
59.8
51.2
37.6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

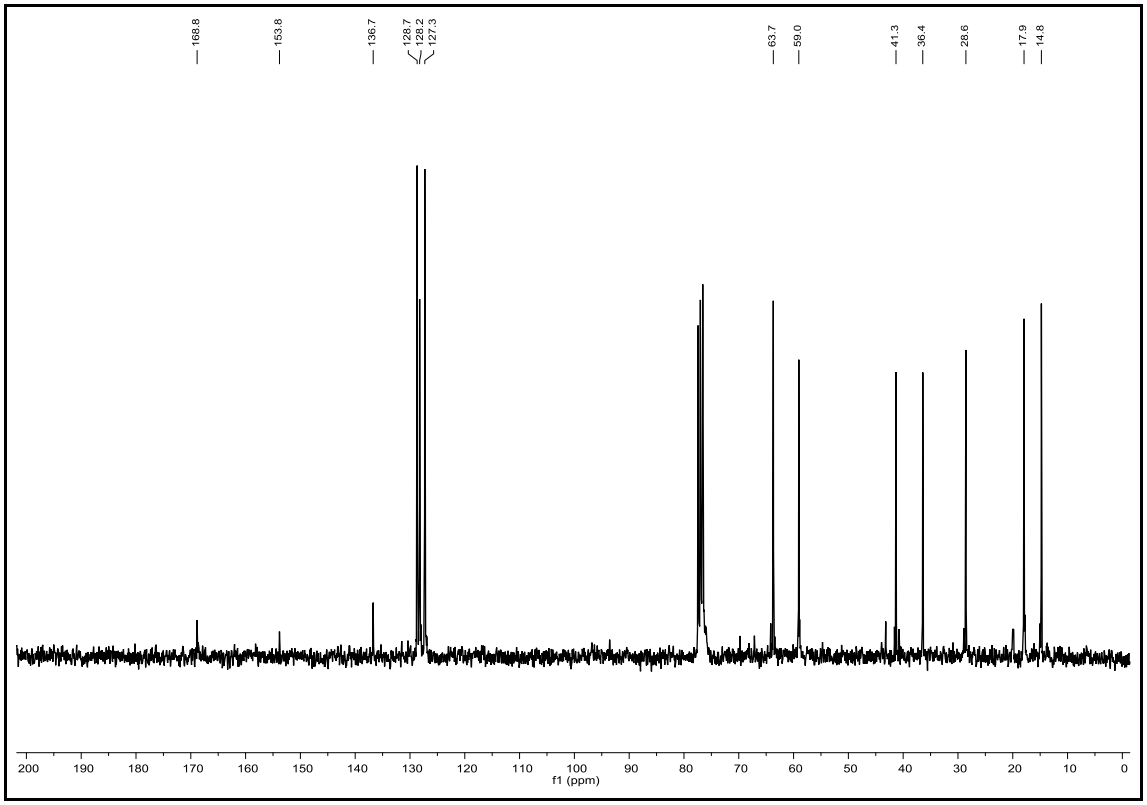

S
O
O
N
N2
Ph
190
7.91
7.40
7.37
7.35
7.31
7.30
7.28
7.26
5.82
5.81
5.79
5.78
4.83
4.80
4.77
4.47
4.46
4.44
4.43
0.65
5.40
1.00
1.26
1.20
f1 (ppm)

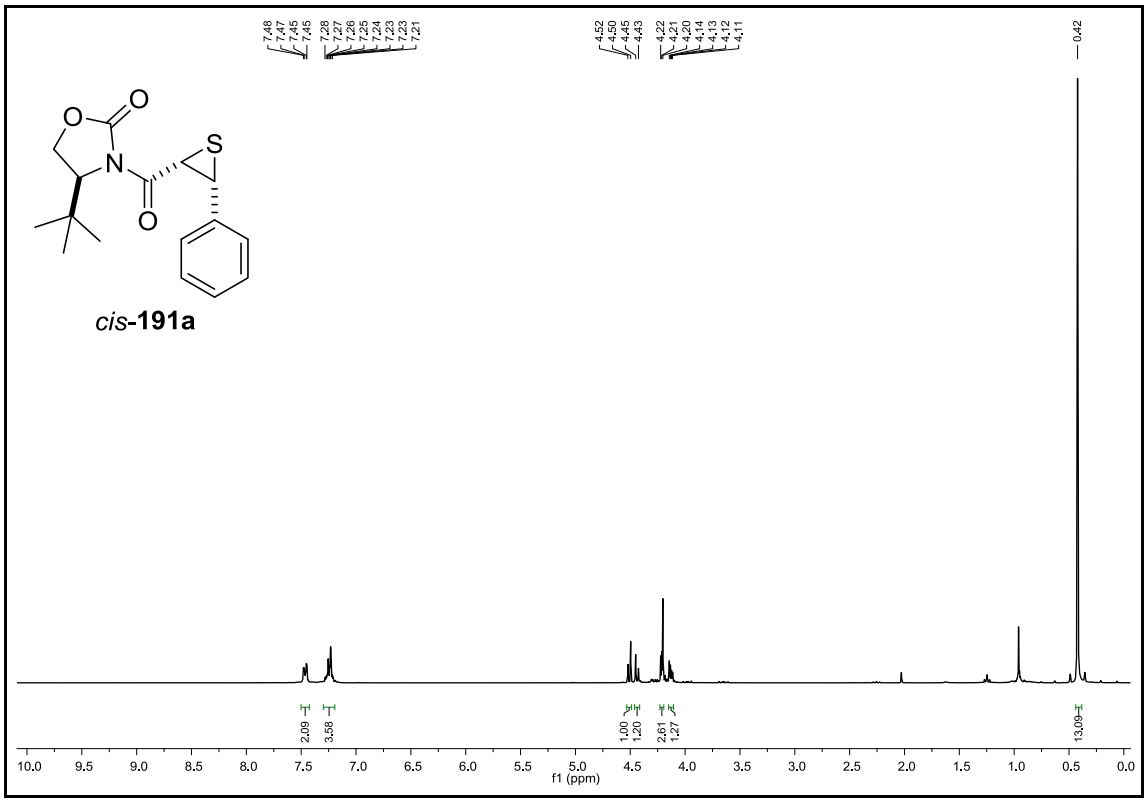

184.9
163.9
138.5
129.3
128.9
126.0
73.9
62.1
51.5
f1 (ppm)


cis-187a
Ha, Hb J = 7.7 Hz
f1 (ppm)

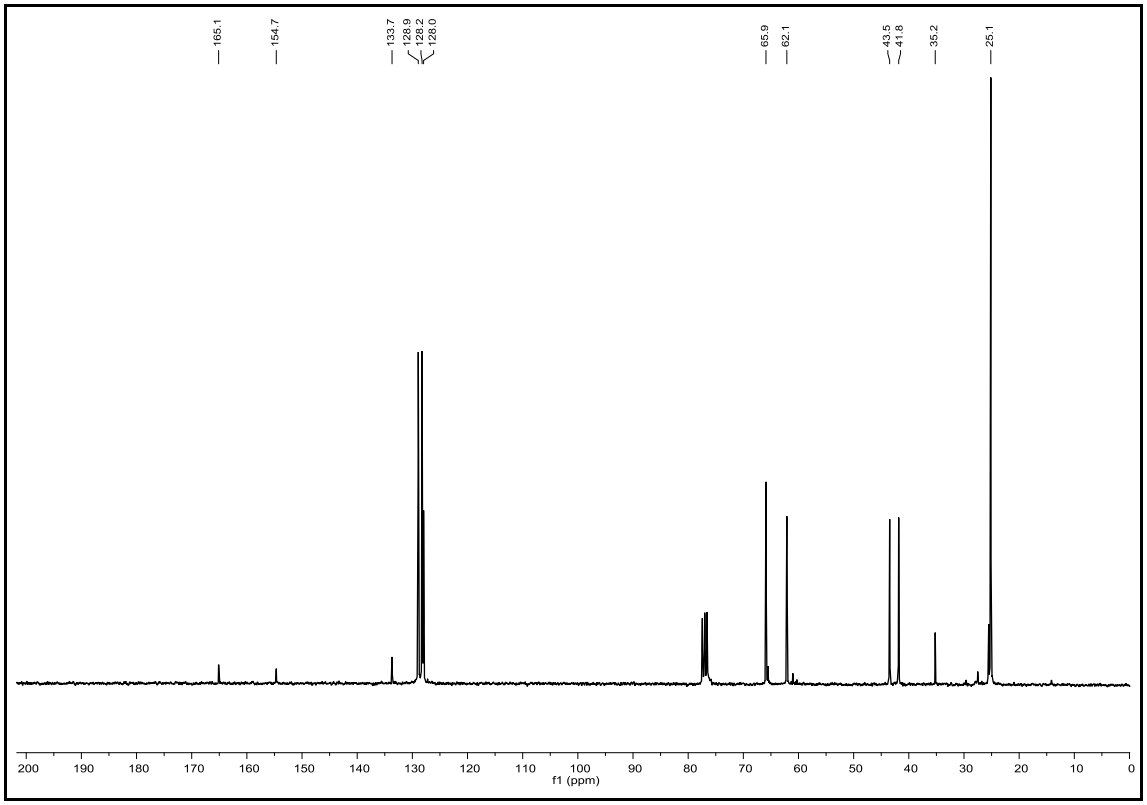

f1 (ppm)

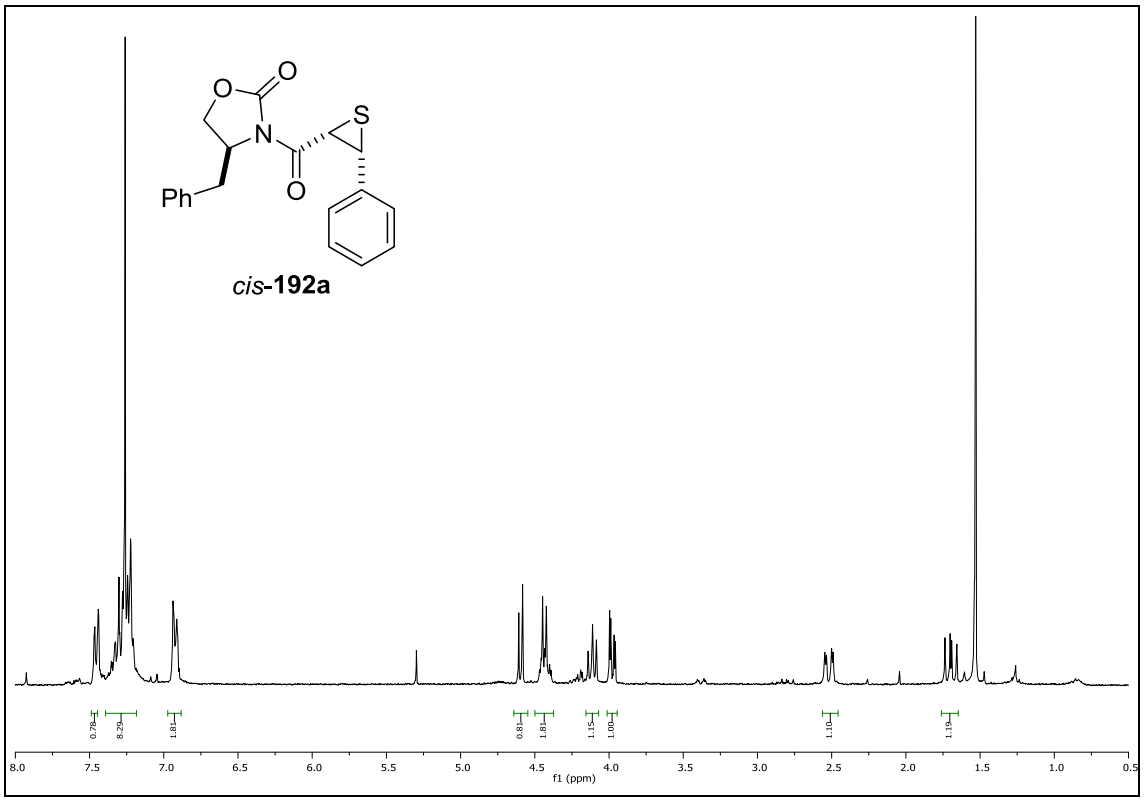

7.39
7.38
7.37
7.36
7.35
7.33
7.33
7.31
7.30
7.30
7.28
4.96
4.85
4.55
4.48
4.47
4.45
4.45
4.38
4.35
4.32
4.28
4.27
4.25
4.24
2.42
2.41
2.40
2.39
2.37
2.36
2.35
2.34
2.33
0.95
0.93
0.92
0.90
O
O
Ha
N
S
O
Hb
trans-187a
Ha, Hb J = 4.8 Hz
4.21
0.68
0.70
0.99
1.11
1.01
1.00
5.88
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

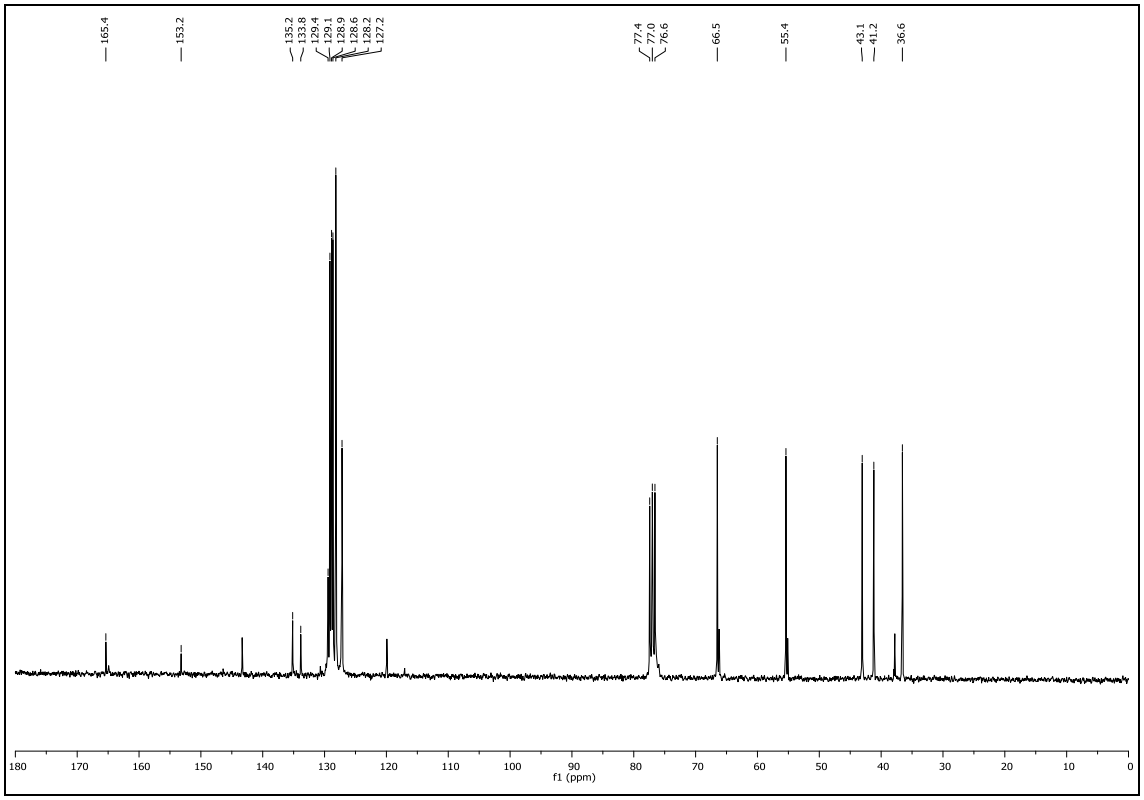

168.8
153.8
136.7
128.7
128.2
127.3
63.7
59.0
41.3
36.4
28.6
17.9
14.8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

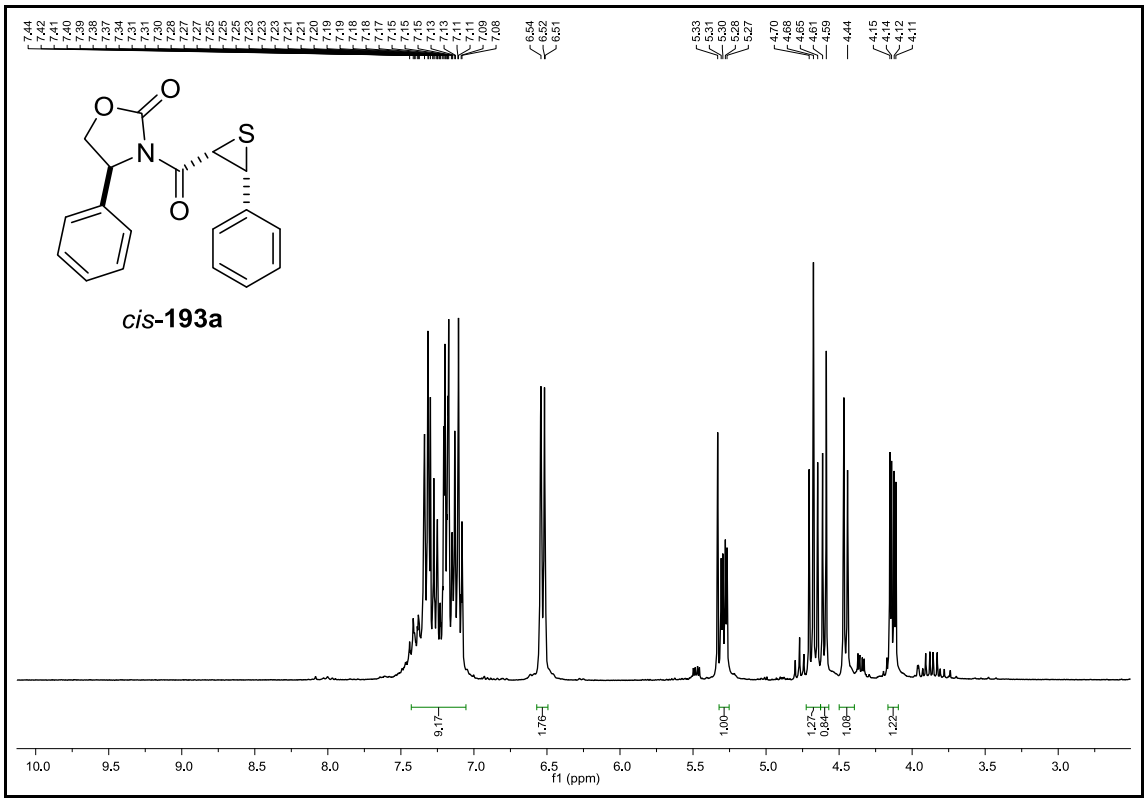

7.48
7.47
7.46
7.45
7.28
7.27
7.26
7.25
7.24
7.23
7.21
4.52
4.50
4.45
4.43
4.22
4.21
4.20
4.14
4.13
4.12
4.11
0.42
O
O
N
O
S
2.09
3.58
1.00
1.20
2.61
1.27
13.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

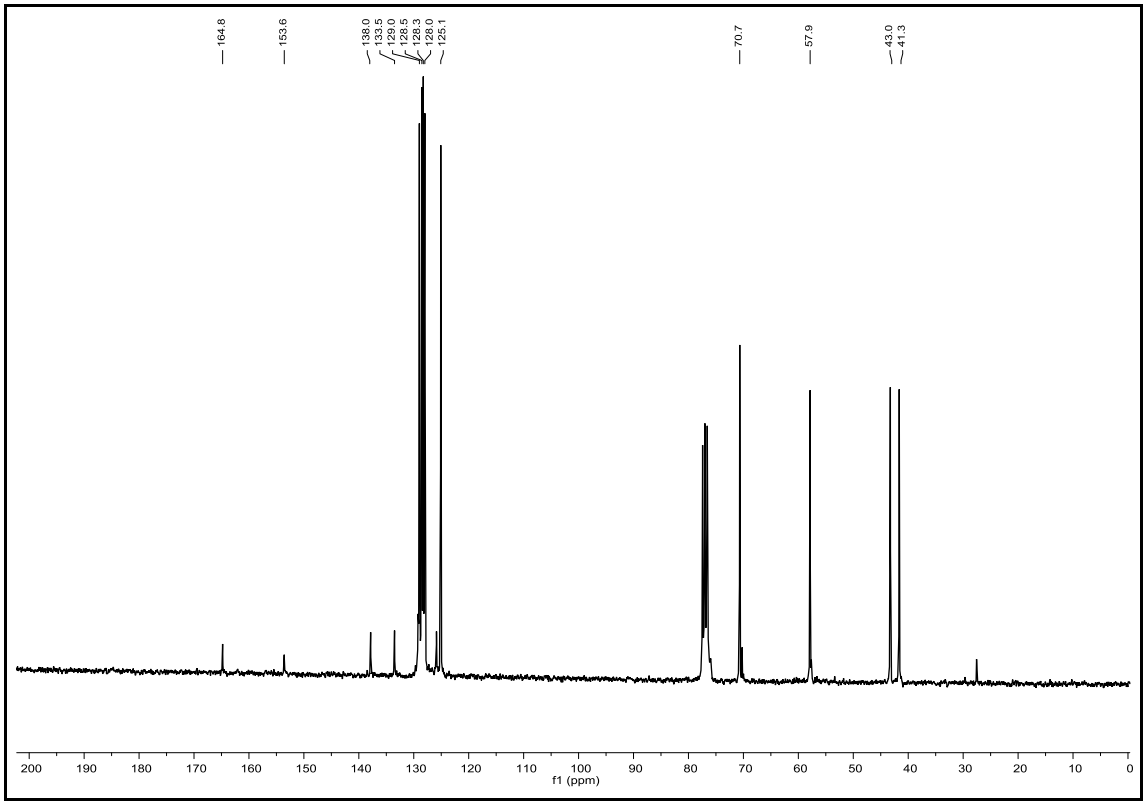
cis-**191a**

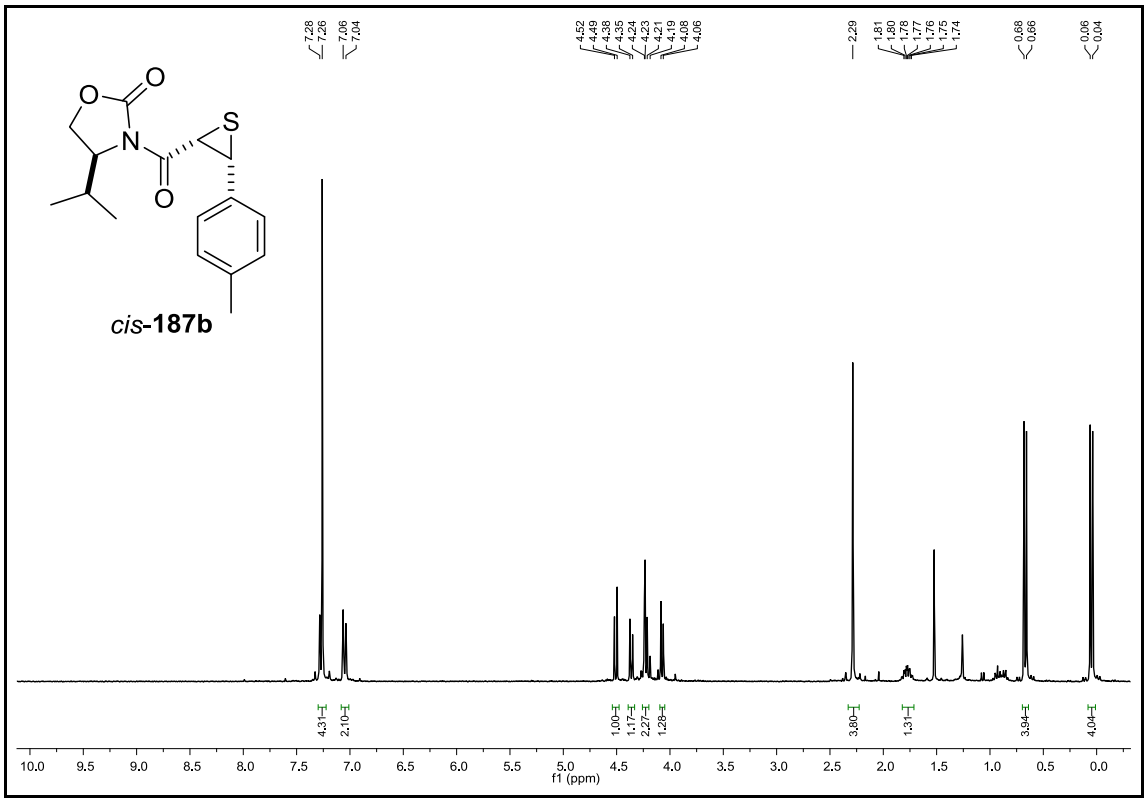

165.1
154.7
133.7
128.9
128.2
128.0
65.9
62.1
43.5
41.8
35.2
25.1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

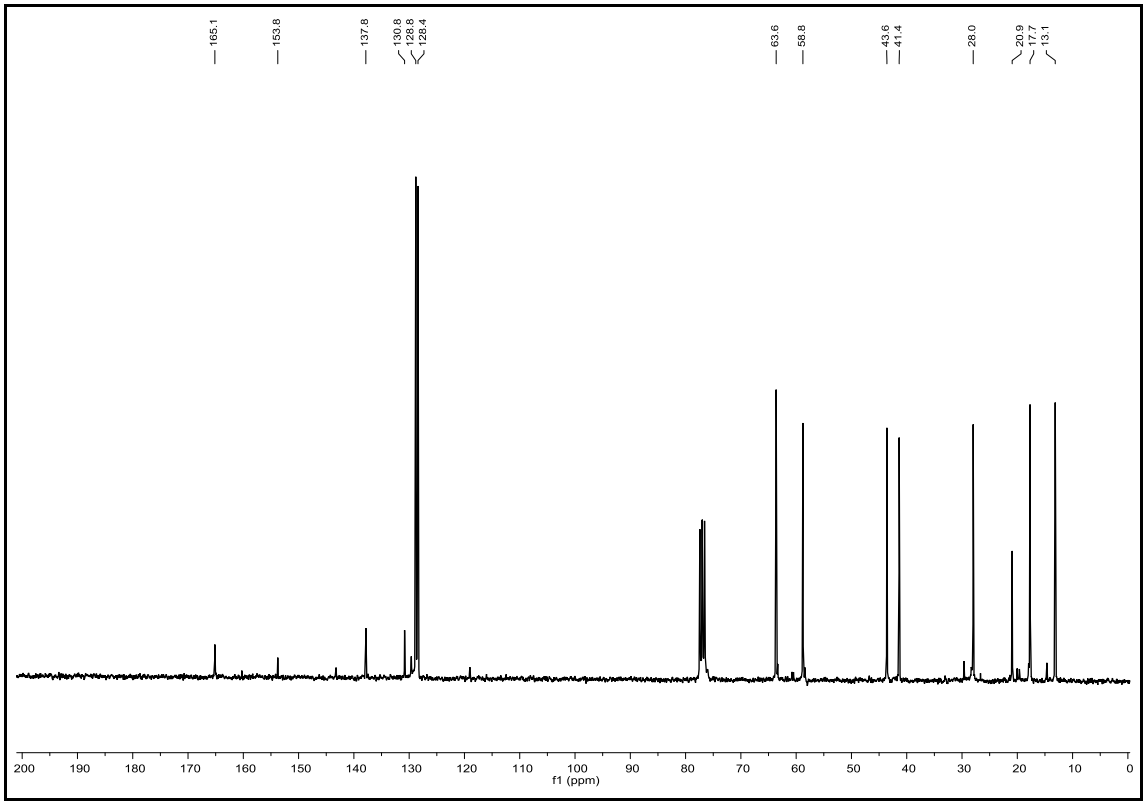

O
O
N
S
Ph
O
cis-192a
0.78
8.29
1.81
0.81
1.81
1.15
1.00
1.10
1.10
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

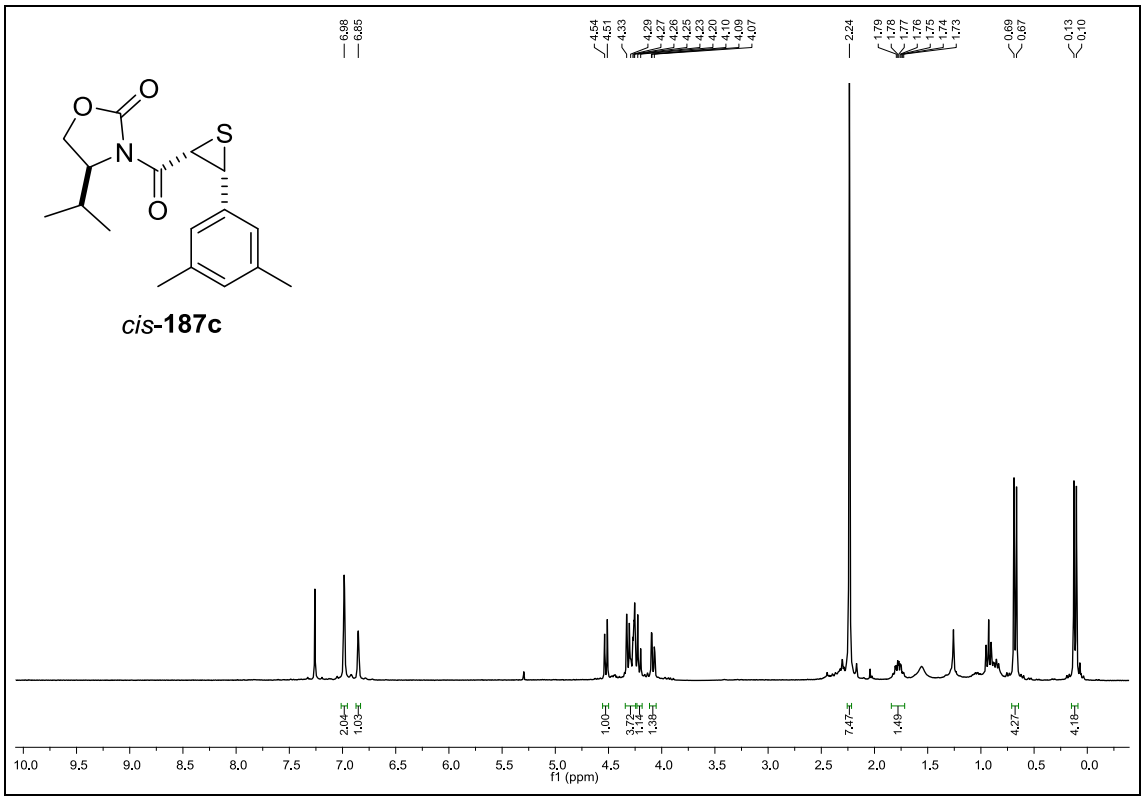

165.4
153.2
135.2
133.8
129.4
129.1
128.9
128.6
128.2
127.2
77.4
77.0
76.6
66.5
55.4
43.1
41.2
36.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

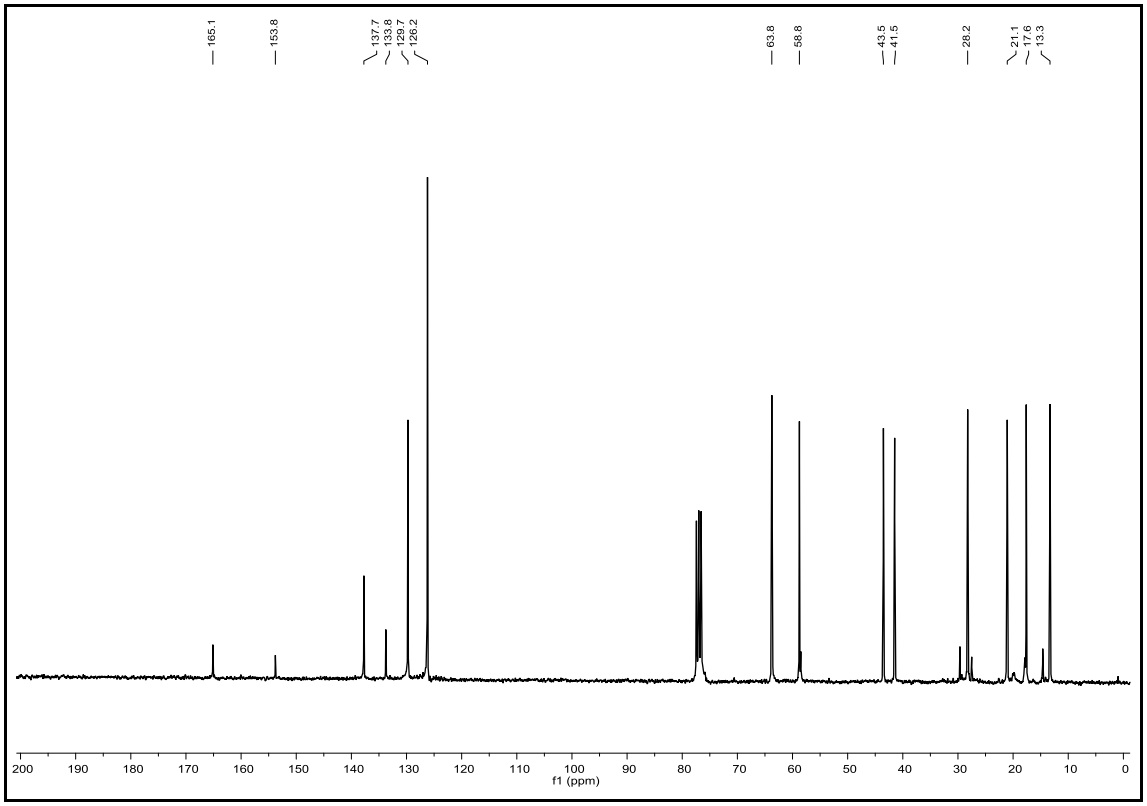

cis-193a
f1 (ppm)

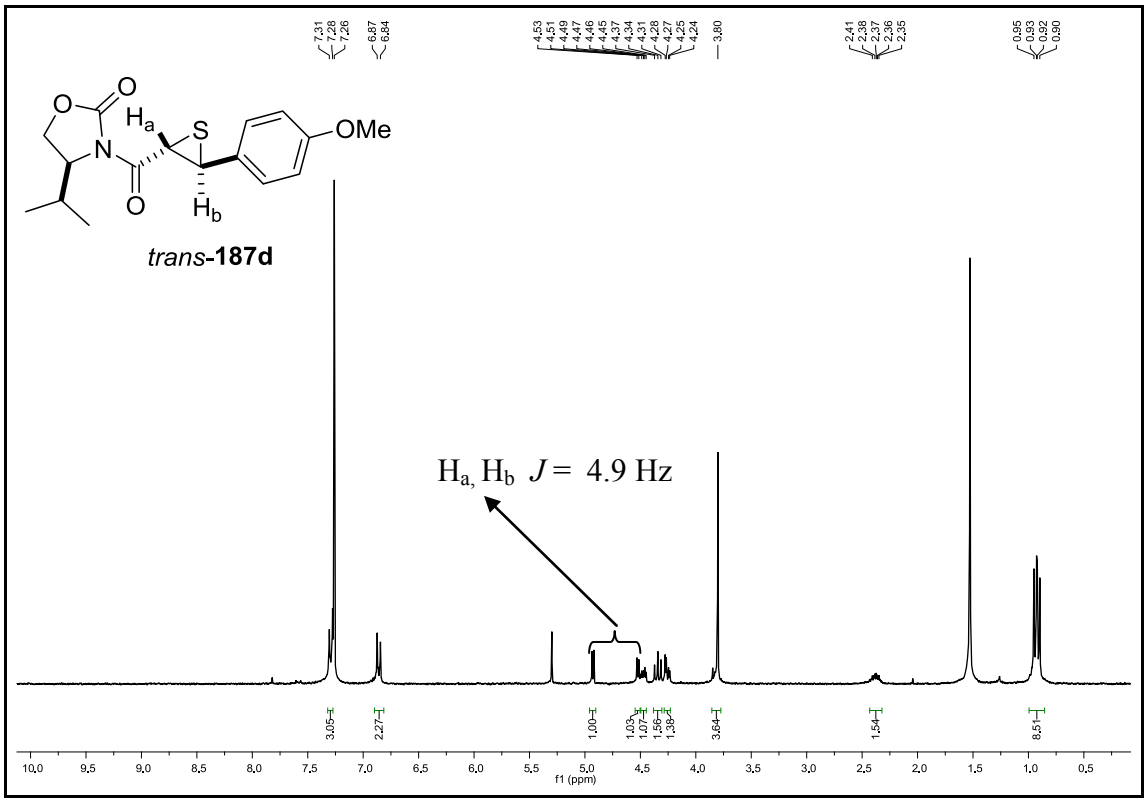

f1 (ppm)

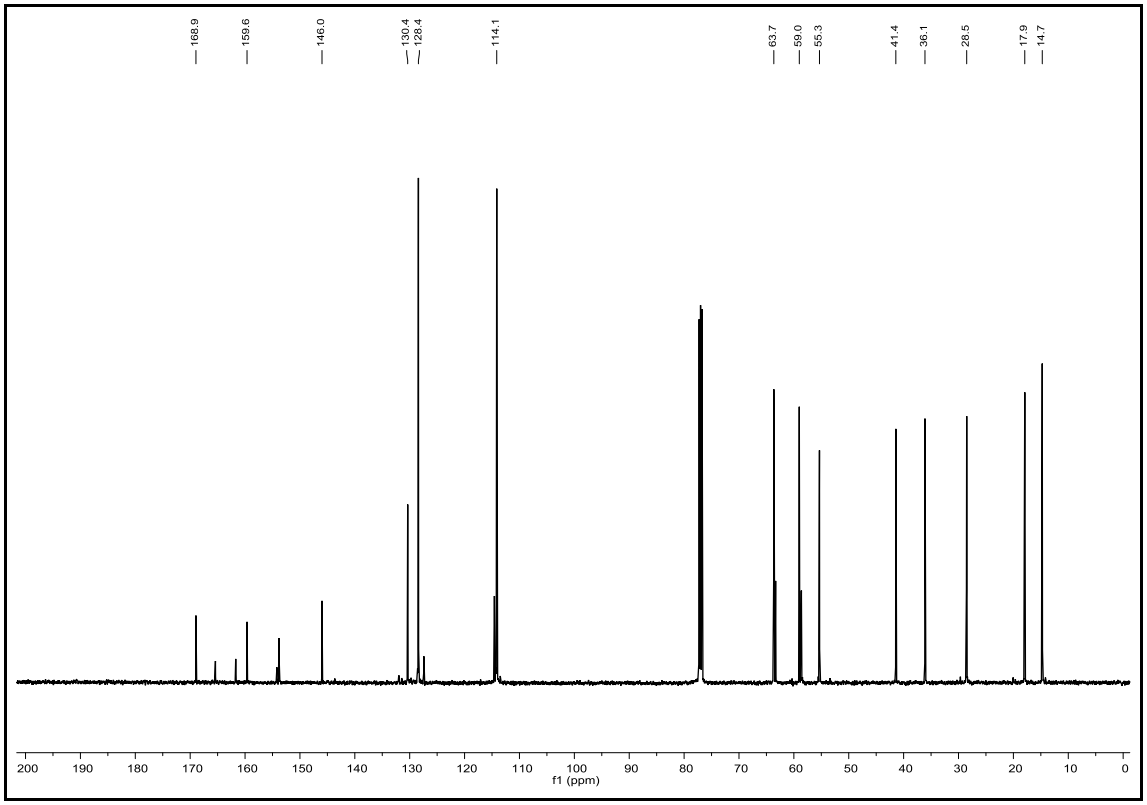

cis-187b
f1 (ppm)

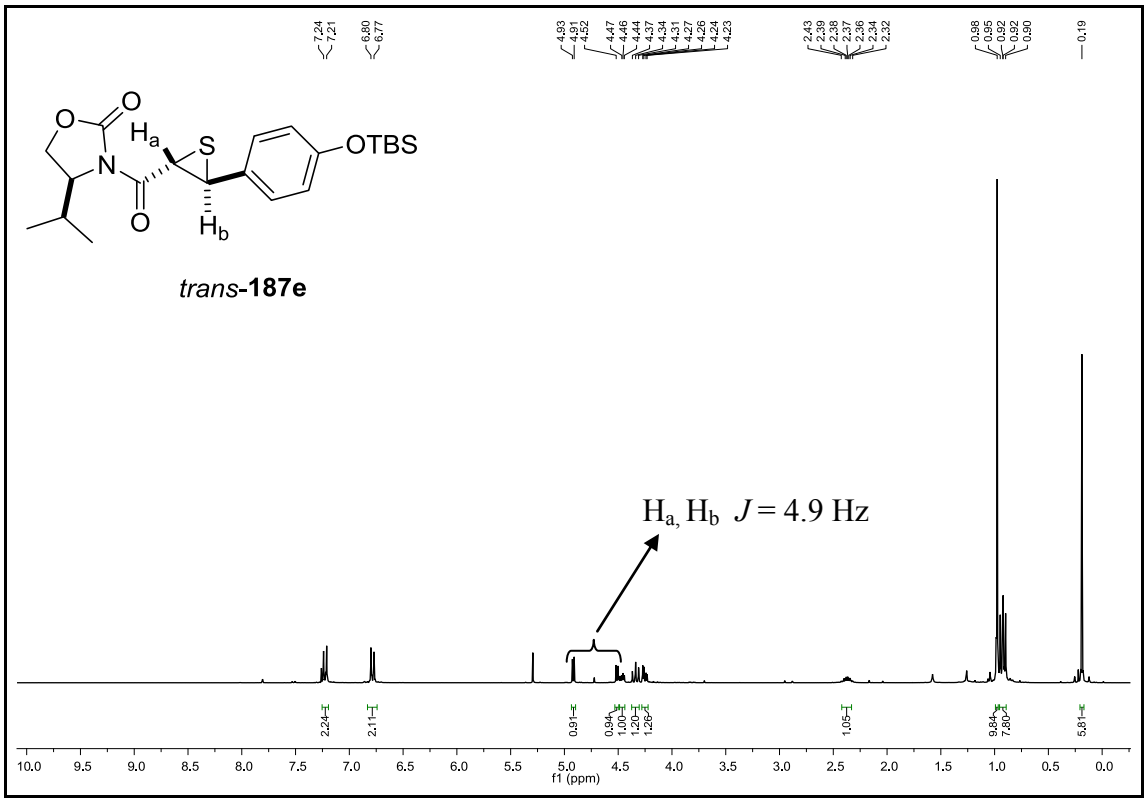

f1 (ppm)


6.98
6.85
4.54
4.51
4.33
4.29
4.27
4.26
4.25
4.23
4.20
4.10
4.09
4.07
2.24
1.79
1.78
1.77
1.76
1.75
1.74
1.73
0.69
0.67
0.13
0.10
O
O
N
O
S
cis-187c
2.04
1.03
1.00
3.72
1.14
1.38
7.47
1.49
4.27
4.18
f1 (ppm)

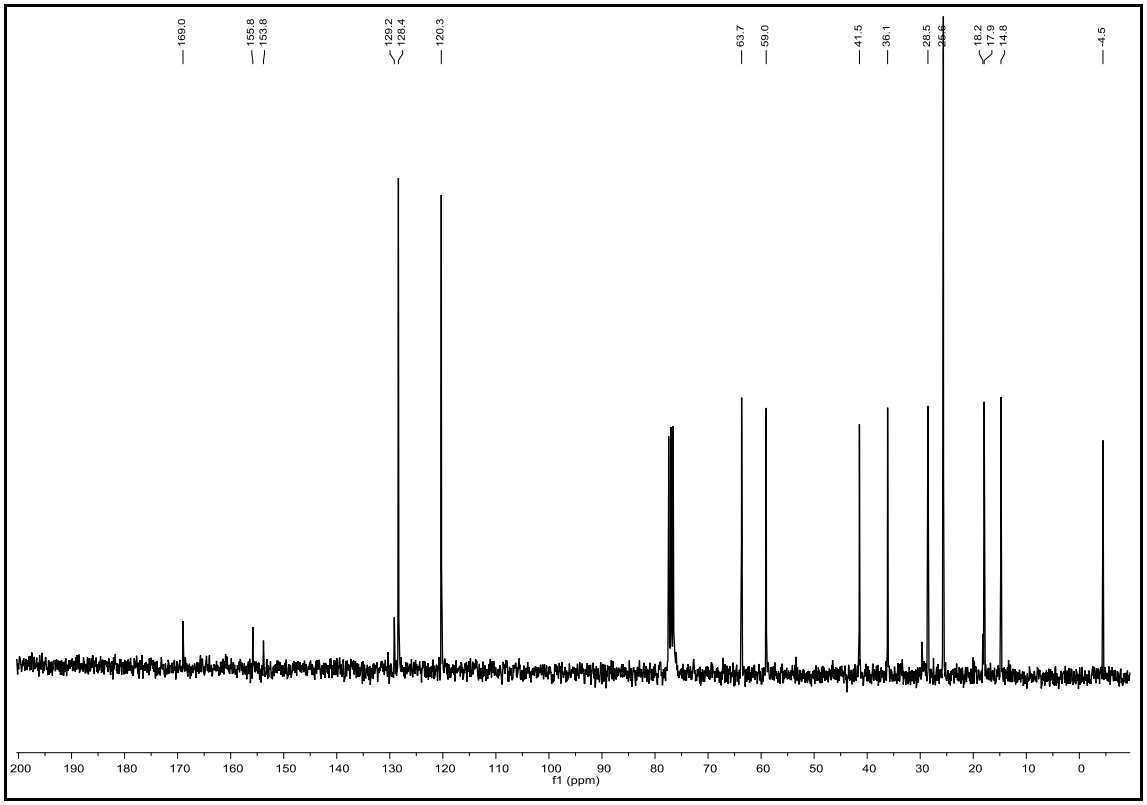

165.1
153.8
137.7
133.8
129.7
126.2
63.8
58.8
43.5
41.5
28.2
21.1
17.6
13.3
f1 (ppm)

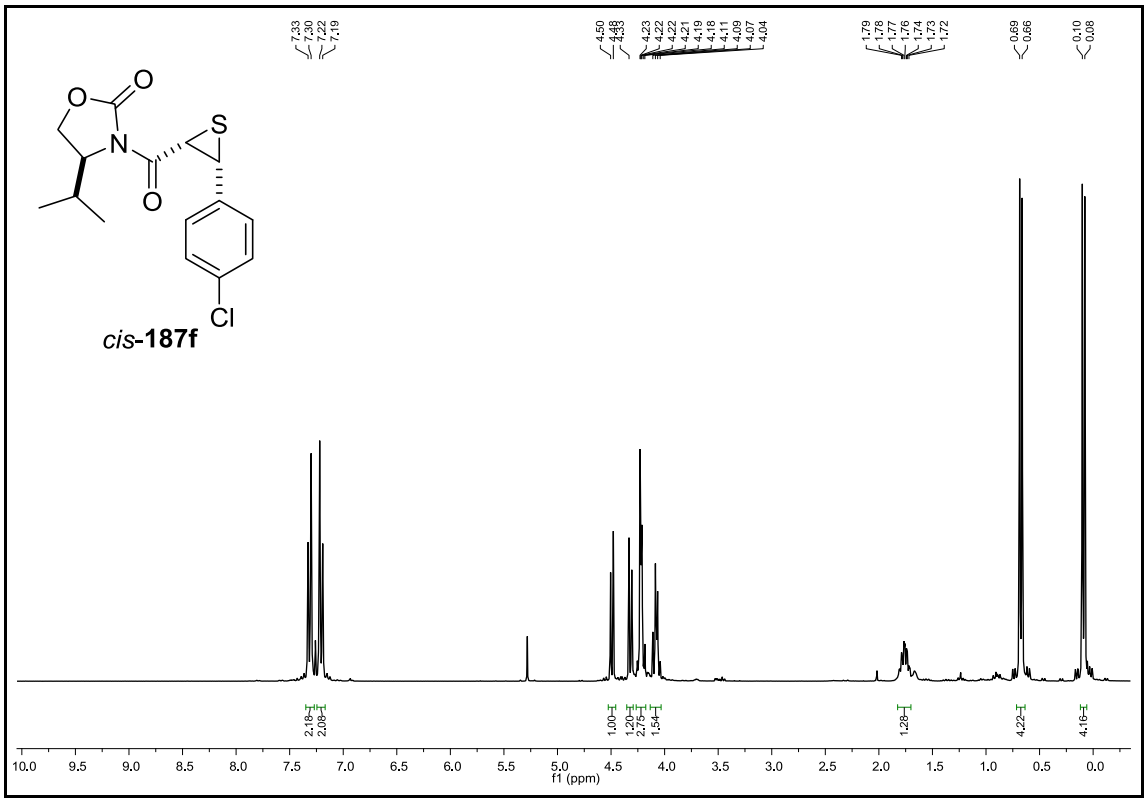

OMe
trans-187d
Ha, Hb J = 4.9 Hz
f1 (ppm)


f1 (ppm)



trans-**187e**

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4.19
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4.11
4.09
4.07
4.04
1.79
1.78
1.77
1.76
1.74
1.73
1.72
0.69
0.66
0.10
0.08
O
O
N
O
S
Cl
cis-187f
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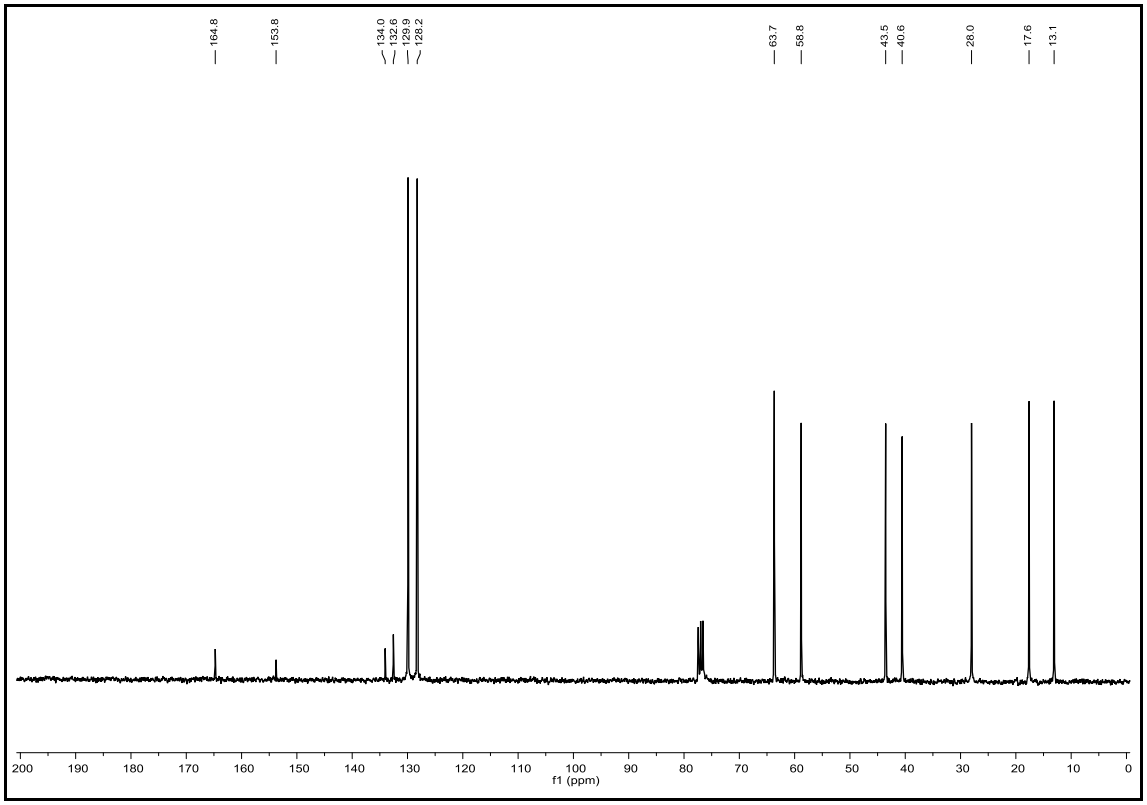
2.08
1.00
1.20
2.75
1.54
1.28
4.22
4.16
f1 (ppm)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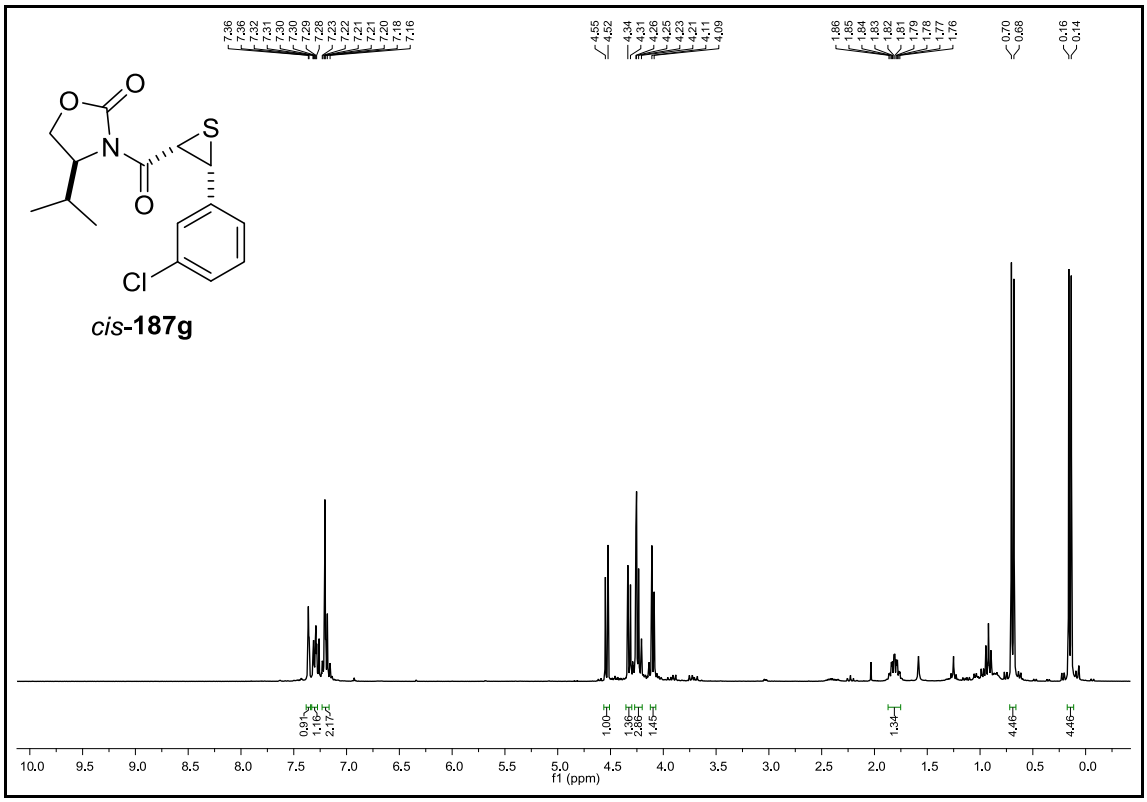
58.8
43.5
40.6
28.0
17.6
13.1
f1 (ppm)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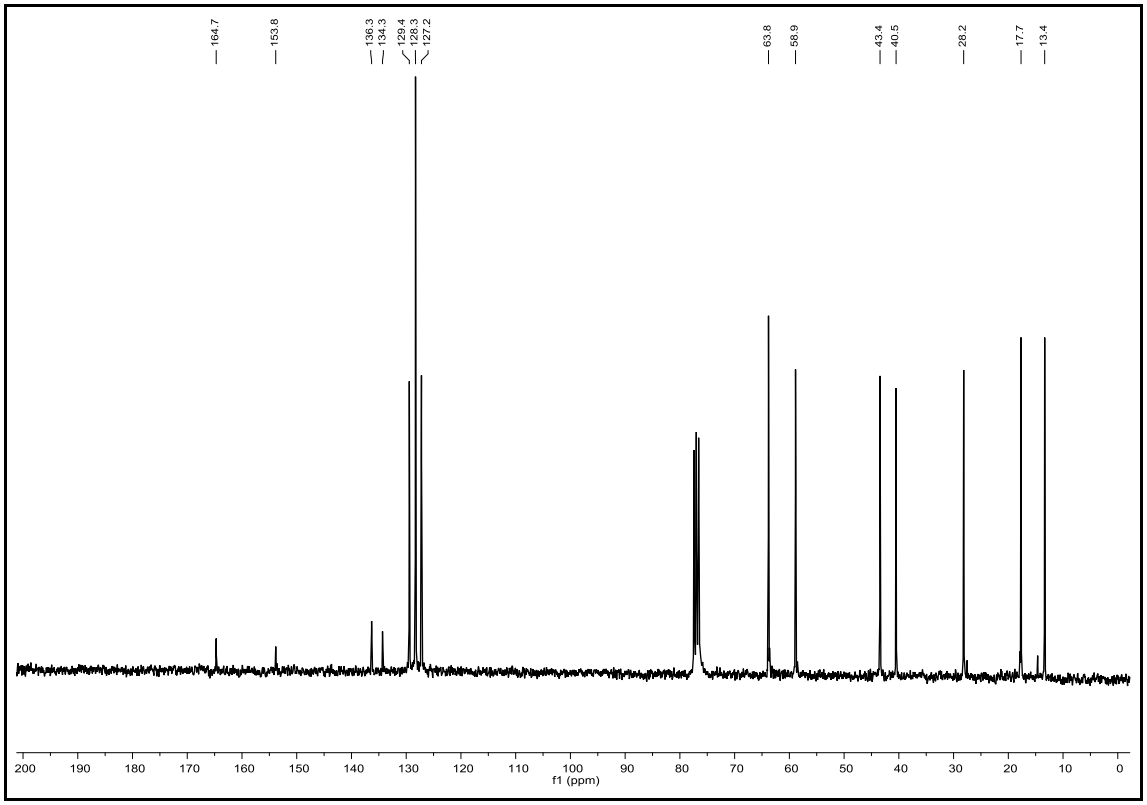
7.20
7.18
7.16
4.55
4.52
4.34
4.31
4.26
4.25
4.23
4.21
4.11
4.09
1.86
1.85
1.84
1.83
1.82
1.81
1.79
1.78
1.77
1.76
0.70
0.68
0.16
0.14
O
O
N
O
S
Cl
cis-187g
0.91
1.16
2.17
1.00
1.36
2.86
1.45
1.34
4.46
4.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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63.8
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28.2
17.7
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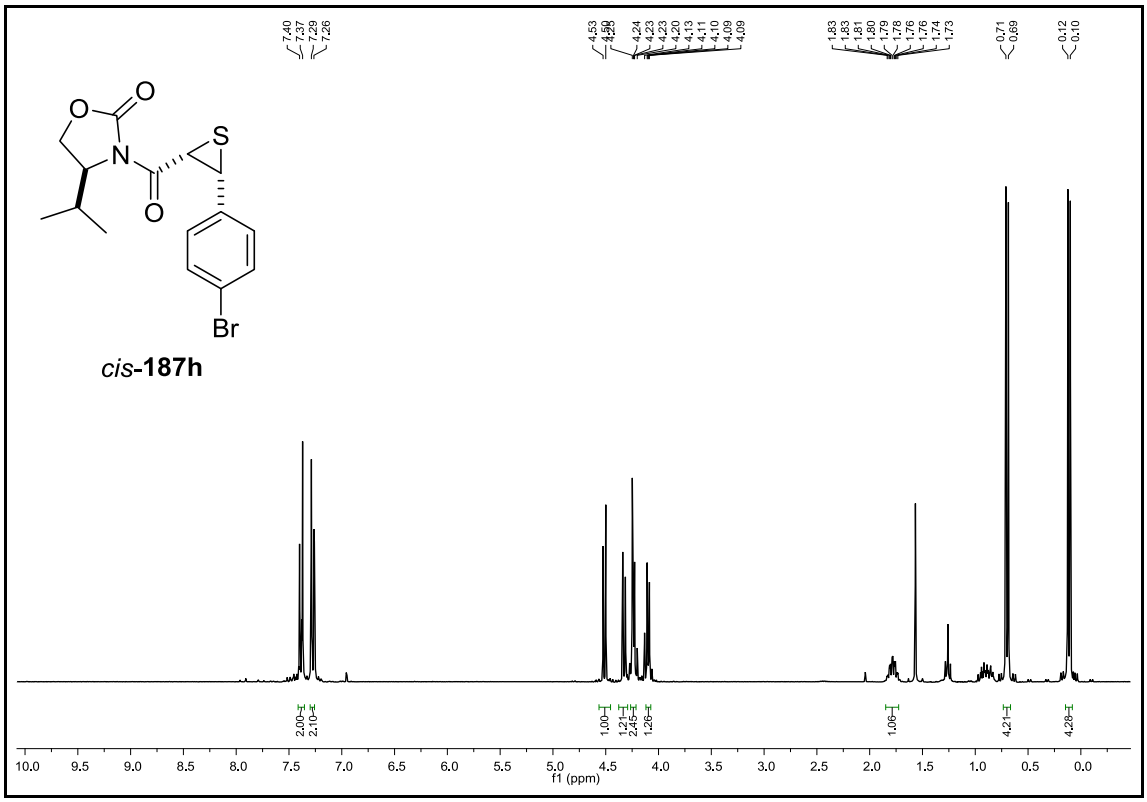
f1 (ppm)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4.51
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4.23
4.20
4.13
4.11
4.10
4.09
1.83
1.81
1.80
1.79
1.78
1.76
1.74
1.73
0.71
0.69
0.12
0.10
O
O
N
O
S
Br
cis-187h
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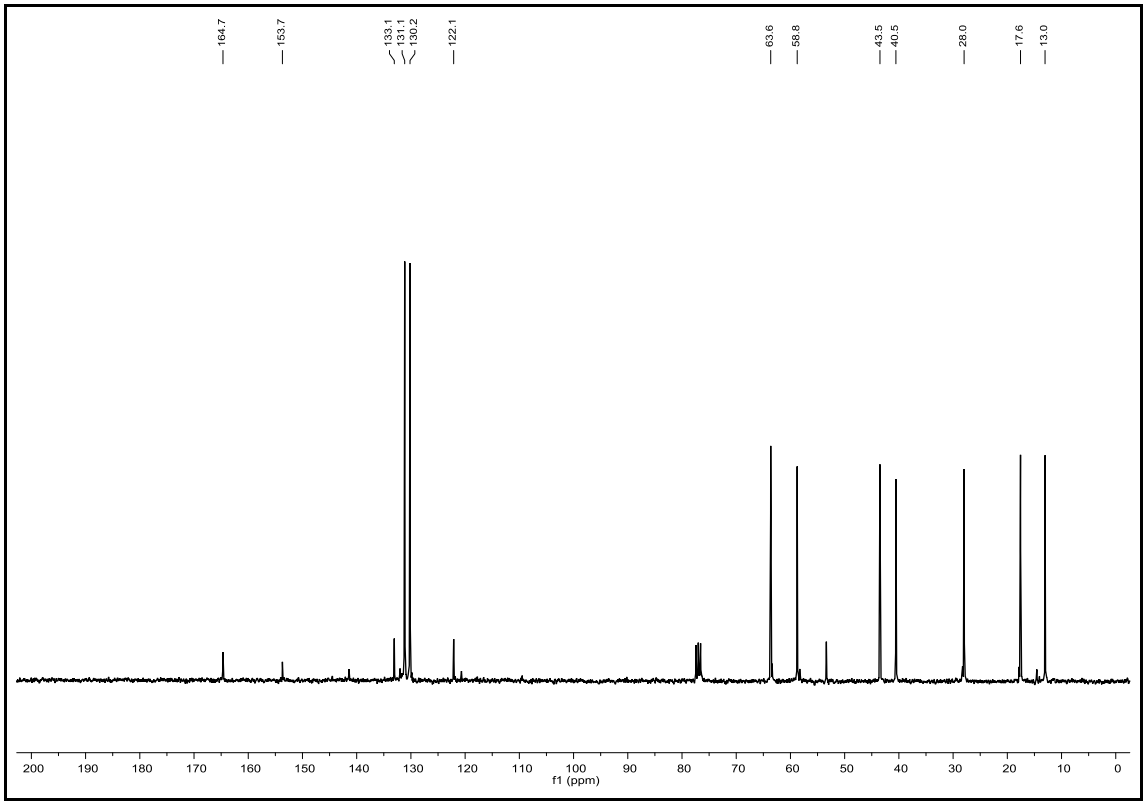
2.10
1.00
1.21
2.45
1.26
1.06
4.21
4.28
f1 (ppm)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153.7
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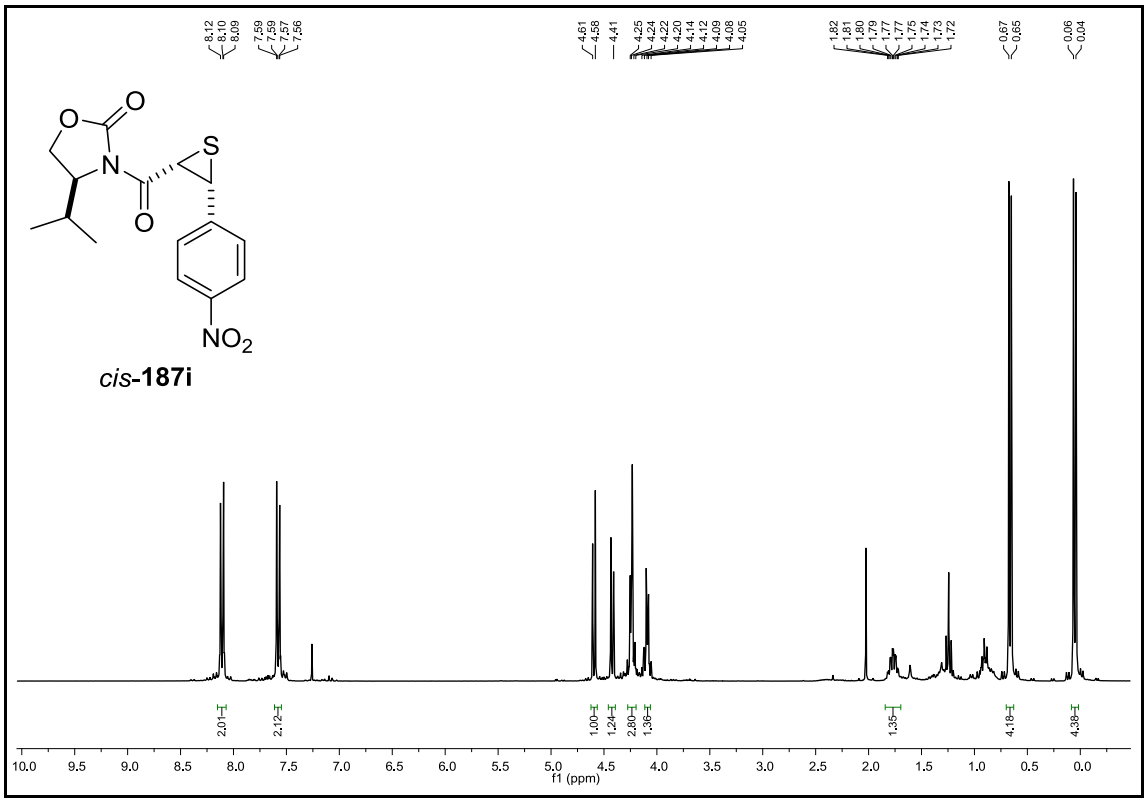
131.1
130.2
122.1
63.6
58.8
43.5
40.5
28.0
17.6
13.0
f1 (ppm)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8.09
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7.57
7.56
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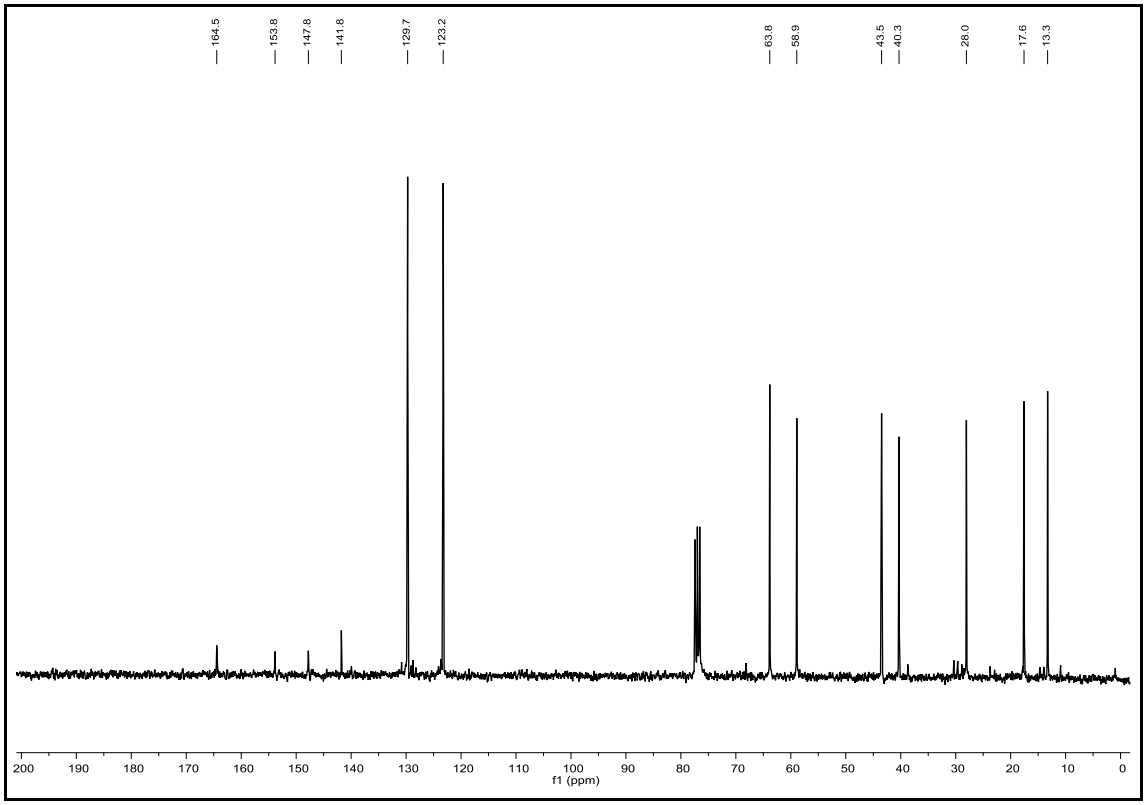
4.41
4.25
4.24
4.22
4.20
4.14
4.12
4.09
4.08
4.05
1.82
1.81
1.80
1.79
1.77
1.77
1.75
1.74
1.73
1.72
0.67
0.65
0.06
0.04
O
O
N
O
S
NO2
cis-187i
2.01
2.12
1.00
1.24
2.80
1.36
1.35
4.18
4.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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153.8
147.8
141.8
129.7
123.2
63.8
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43.5
40.3
28.0
17.6
13.3
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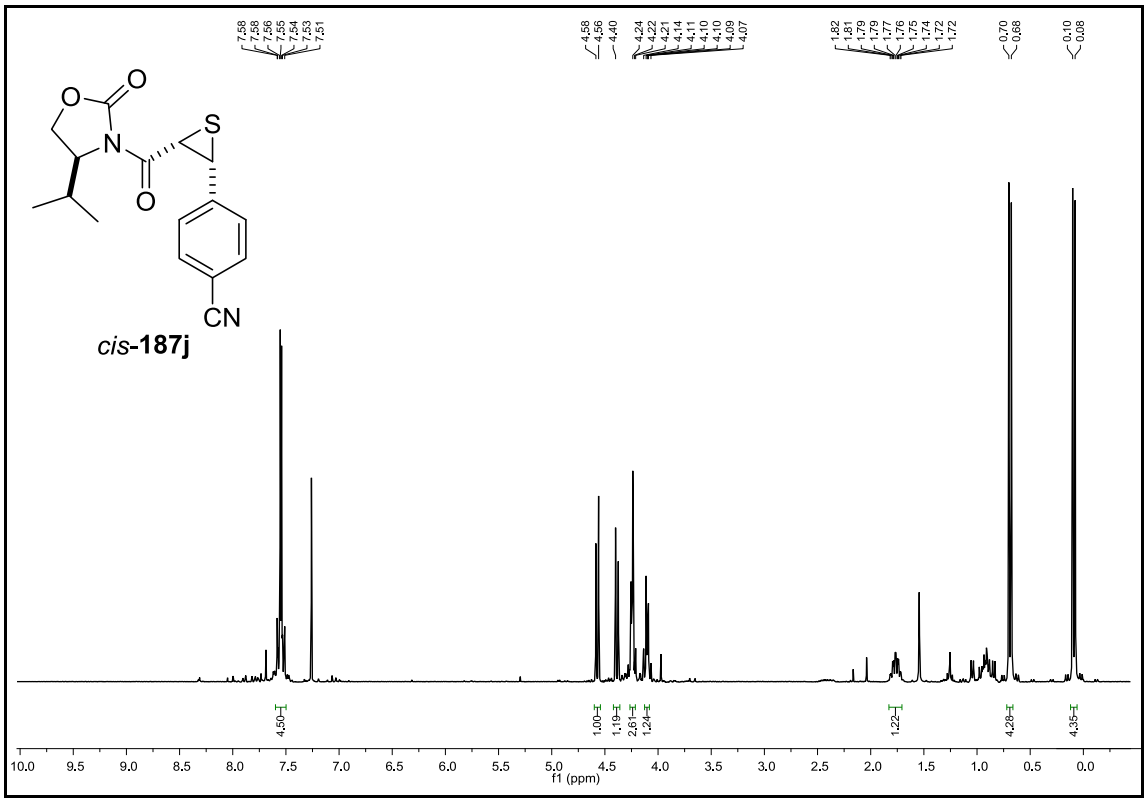
f1 (ppm)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4.40
4.24
4.22
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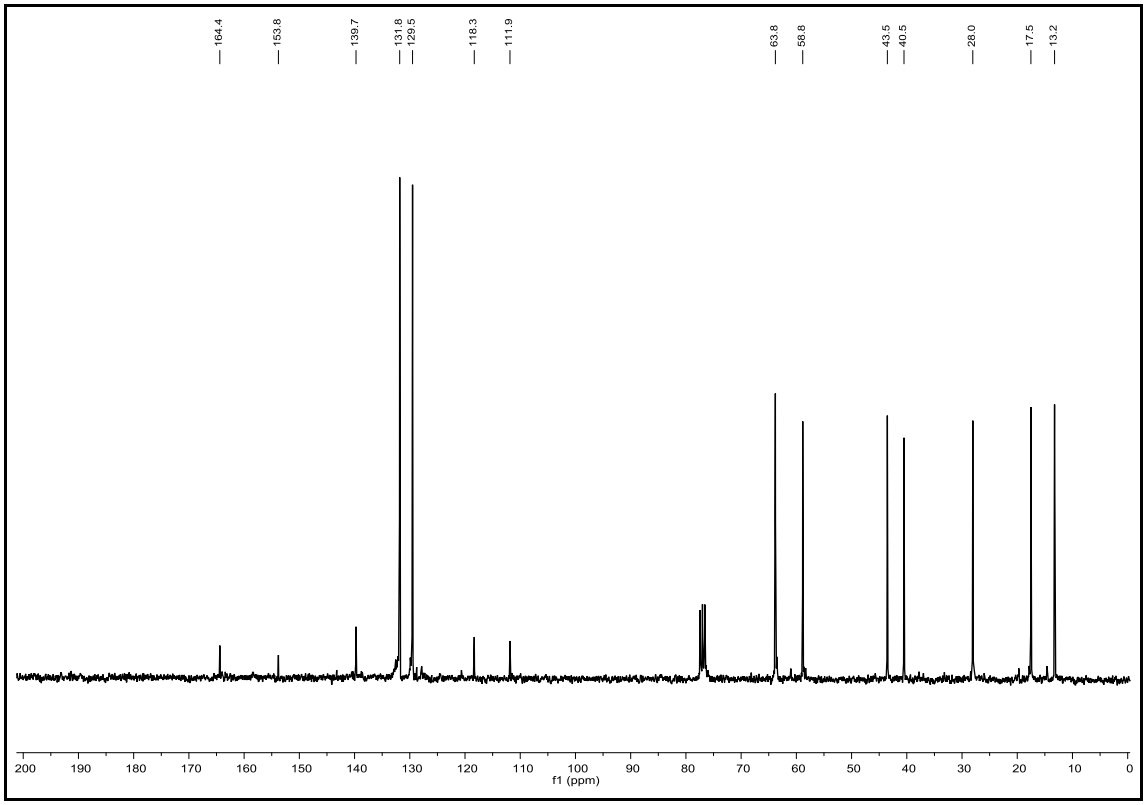
4.11
4.10
4.10
4.09
4.07
1.82
1.81
1.79
1.79
1.77
1.76
1.75
1.74
1.72
1.72
0.70
0.68
0.10
0.08
O
O
N
O
S
CN
cis-187j
4.50
1.00
1.19
2.61
1.24
1.22
4.28
4.35
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.5
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111.9
63.8
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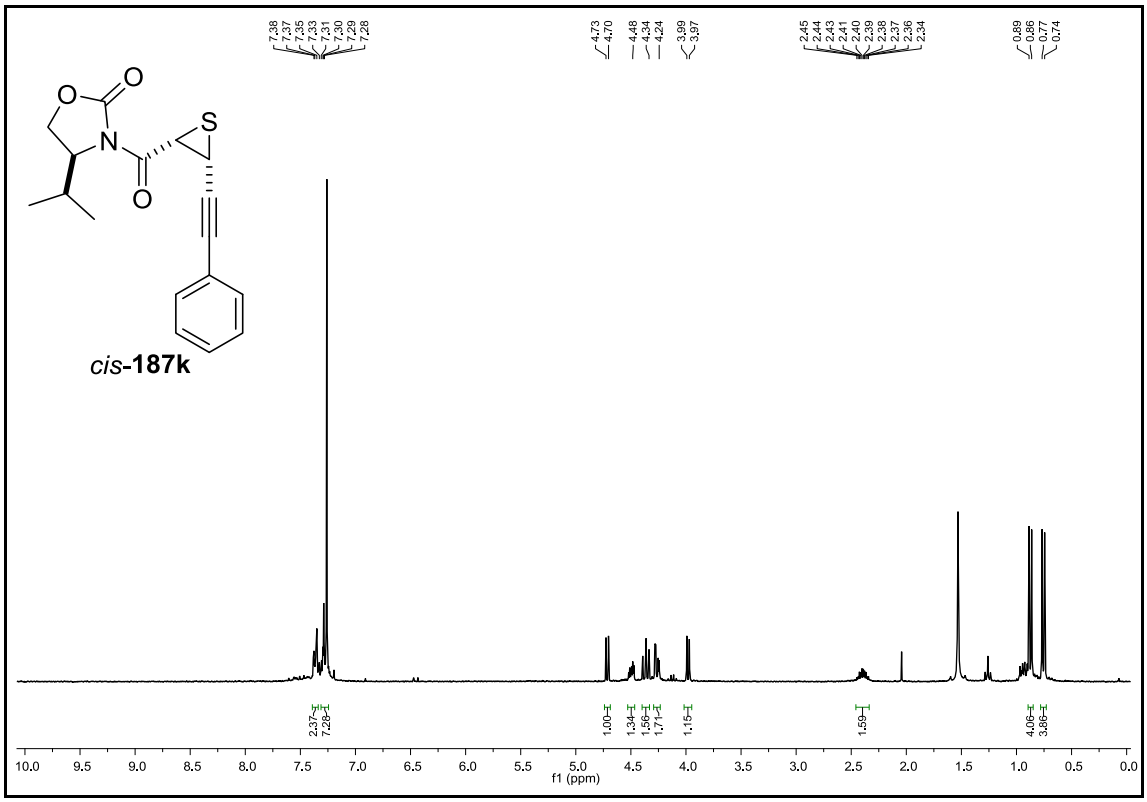
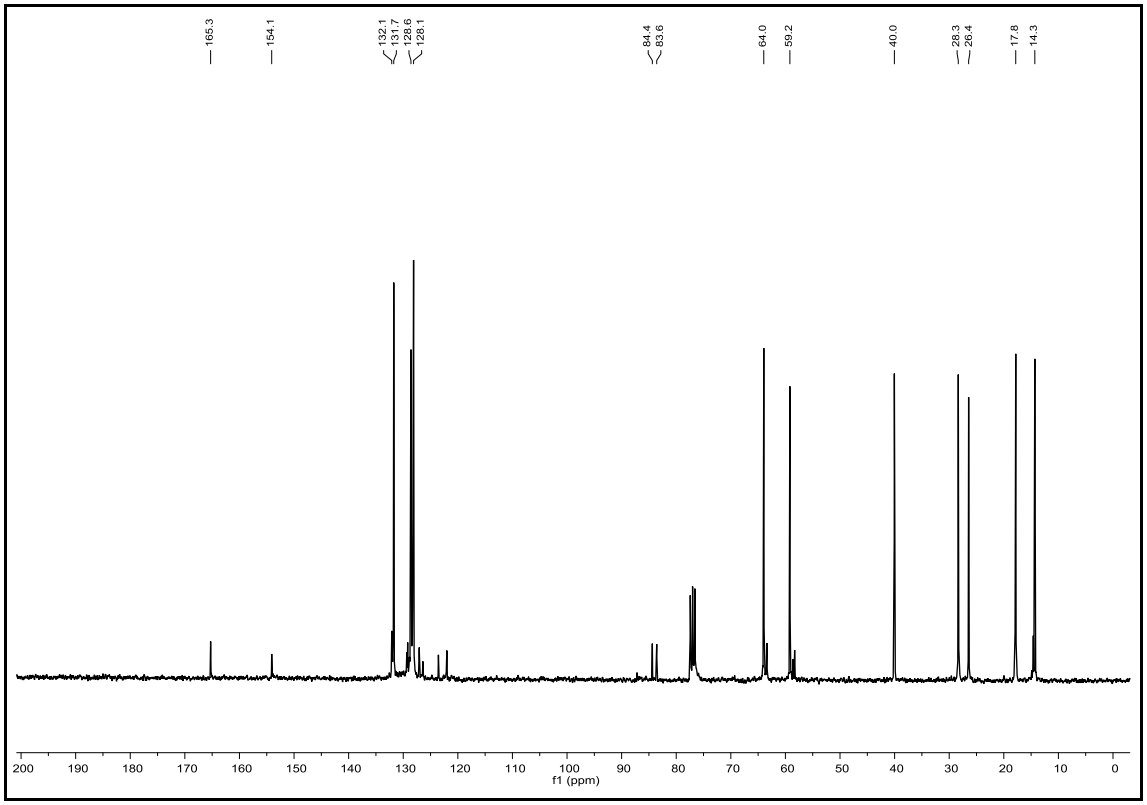
43.5
40.5
28.0
17.5
13.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


cis-187k
f1 (ppm)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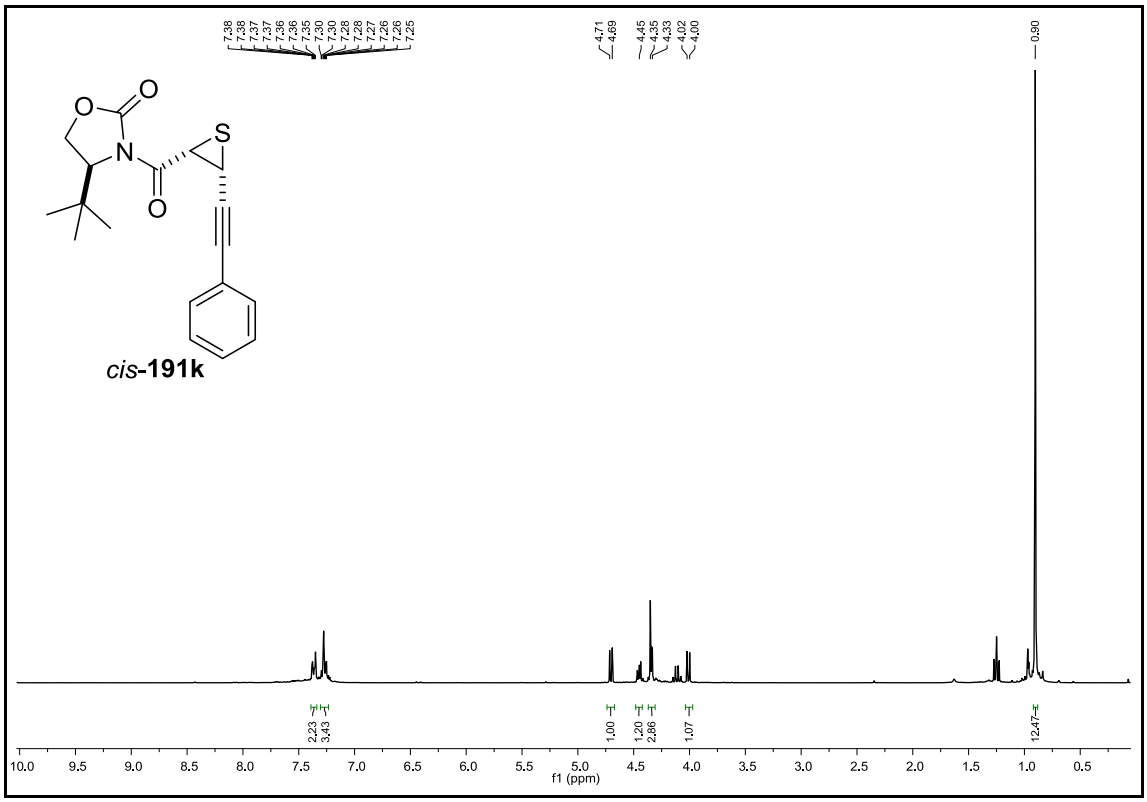
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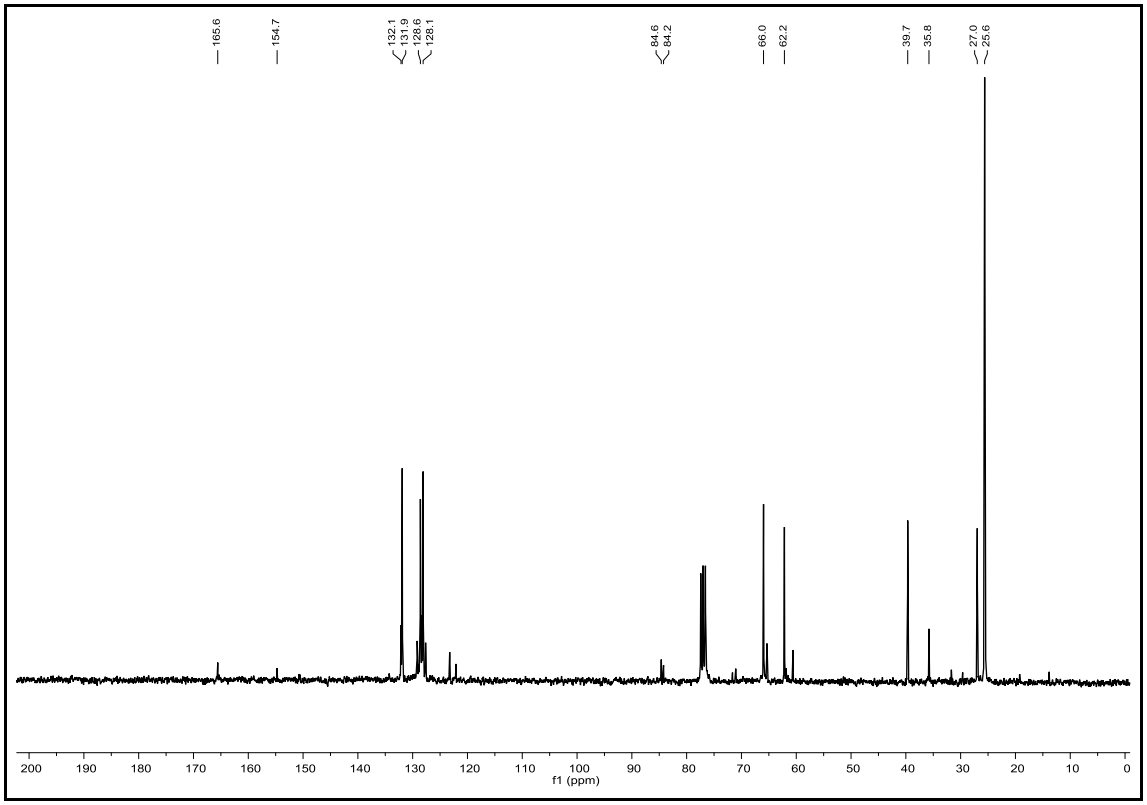
7.26
7.26
7.25
4.71
4.69
4.45
4.35
4.33
4.02
4.00
0.90
O
O
N
O
S
cis-191k
2.23
3.43
1.00
1.20
2.86
1.07
12.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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131.9
128.6
128.1
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84.2
66.0
62.2
39.7
35.8
27.0
25.6
200
190
180
170
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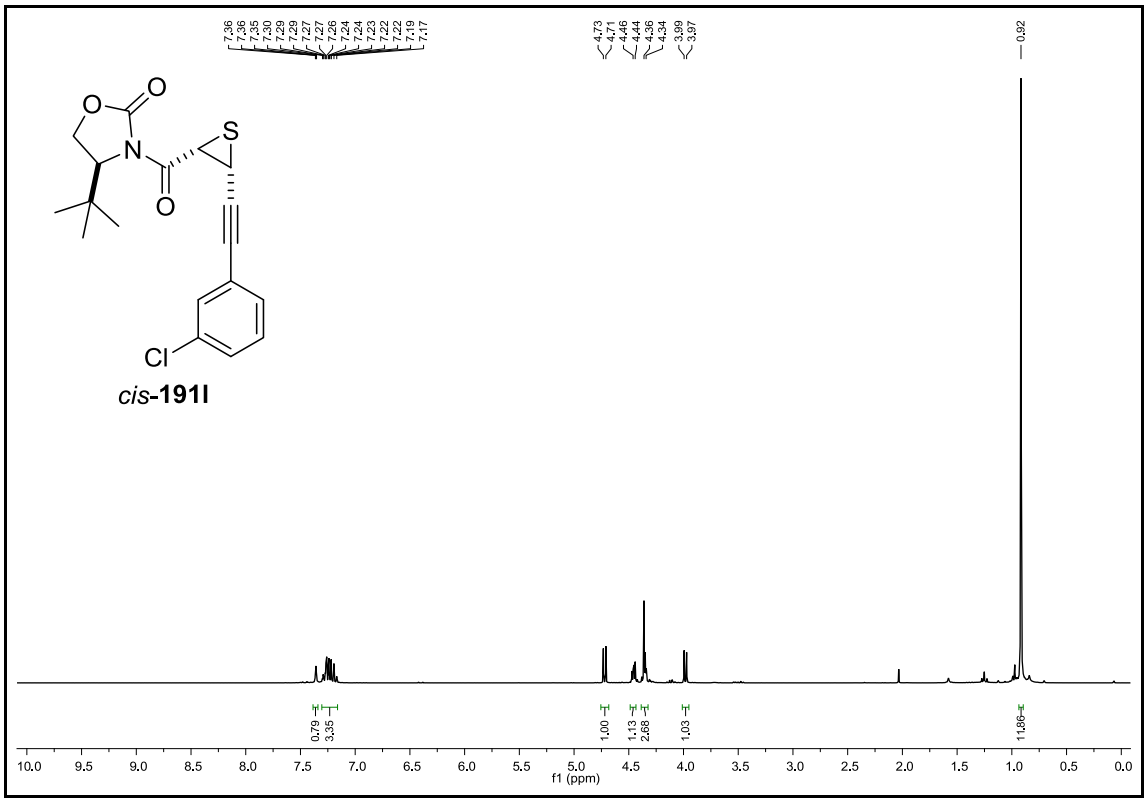
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.22
7.22
7.19
7.17
4.73
4.71
4.46
4.44
4.36
4.34
3.99
3.97
0.92
O
O
N
O
S
Cl
0.79
3.35
1.00
1.13
2.68
1.03
11.86
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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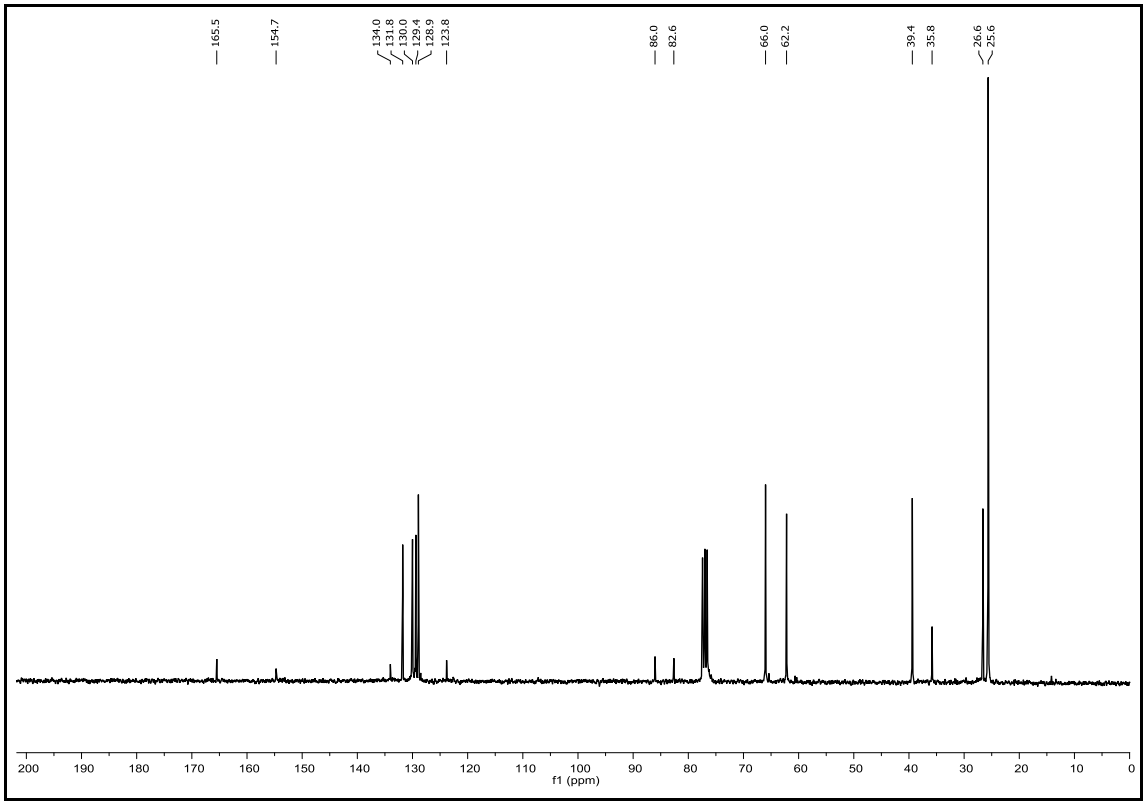
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

cis-**191l**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129.4
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123.8
86.0
82.6
66.0
62.2
39.4
35.8
26.6
25.6
200
190
180
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140
130
120
110
100
90
80
70
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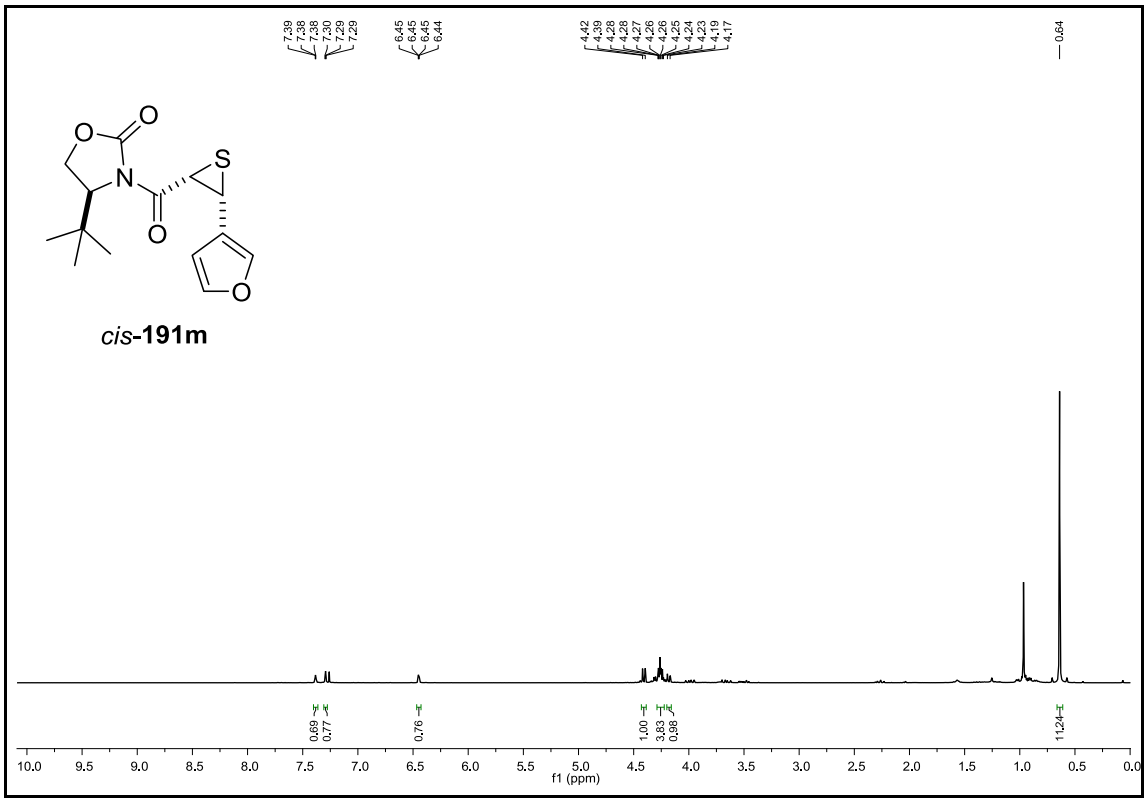
50
40
30
20
10
0
f1 (ppm)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4.28
4.27
4.26
4.26
4.25
4.24
4.23
4.19
4.17
0.64
O
O
N
O
S
O
cis-191m
0.69
0.77
0.76
1.00
3.83
0.98
1.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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2.5
2.0
1.5
1.0
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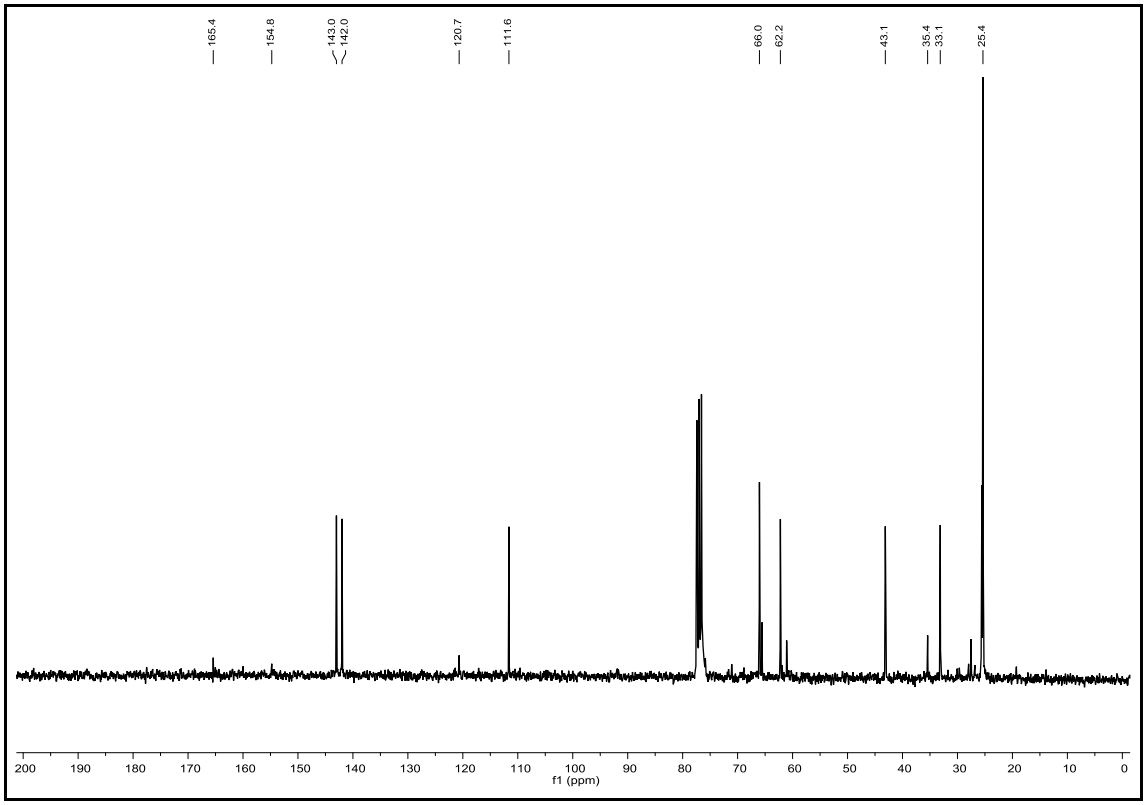
0.0
f1 (ppm)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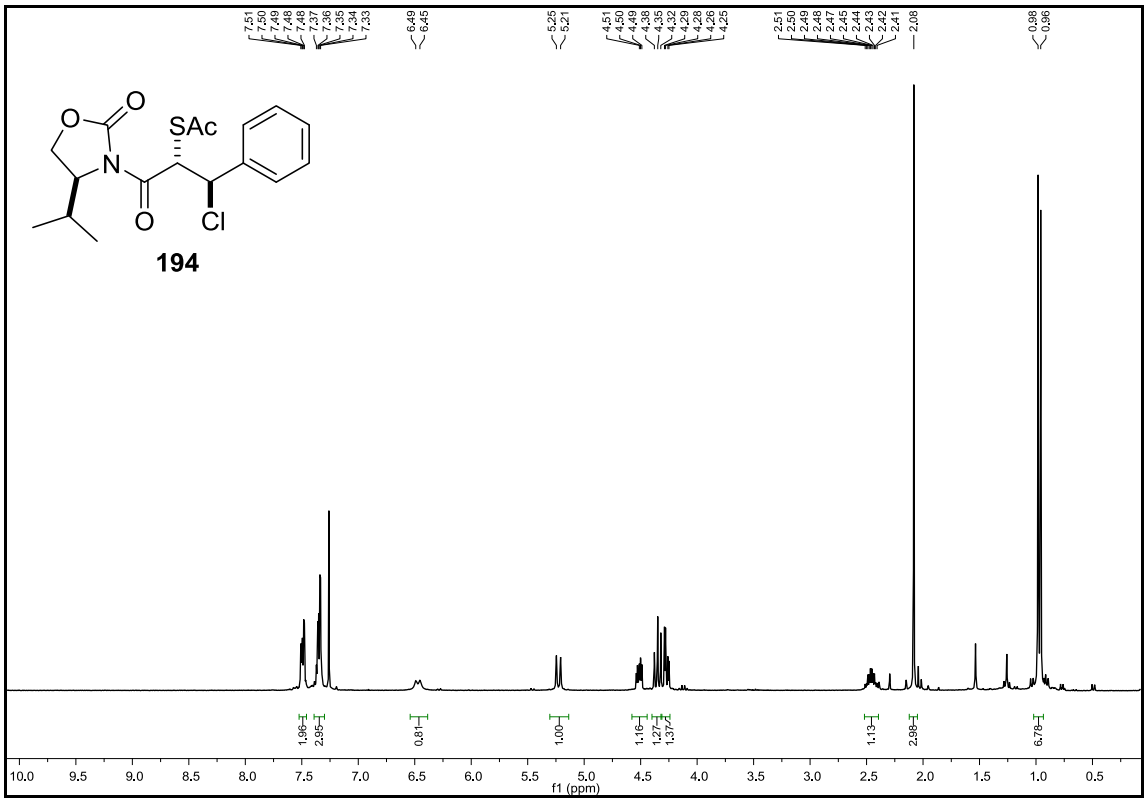
111.6
66.0
62.2
43.1
35.4
33.1
25.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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6.45
5.25
5.21
4.51
4.50
4.49
4.38
4.35
4.32
4.29
4.28
4.26
4.25
2.51
2.50
2.49
2.48
2.47
2.45
2.44
2.43
2.42
2.41
2.08
0.98
0.96
O
O
SAc
N
O
Cl
194
1.96
2.95
0.81
1.00
1.16
1.27
1.37
1.13
2.98
6.78
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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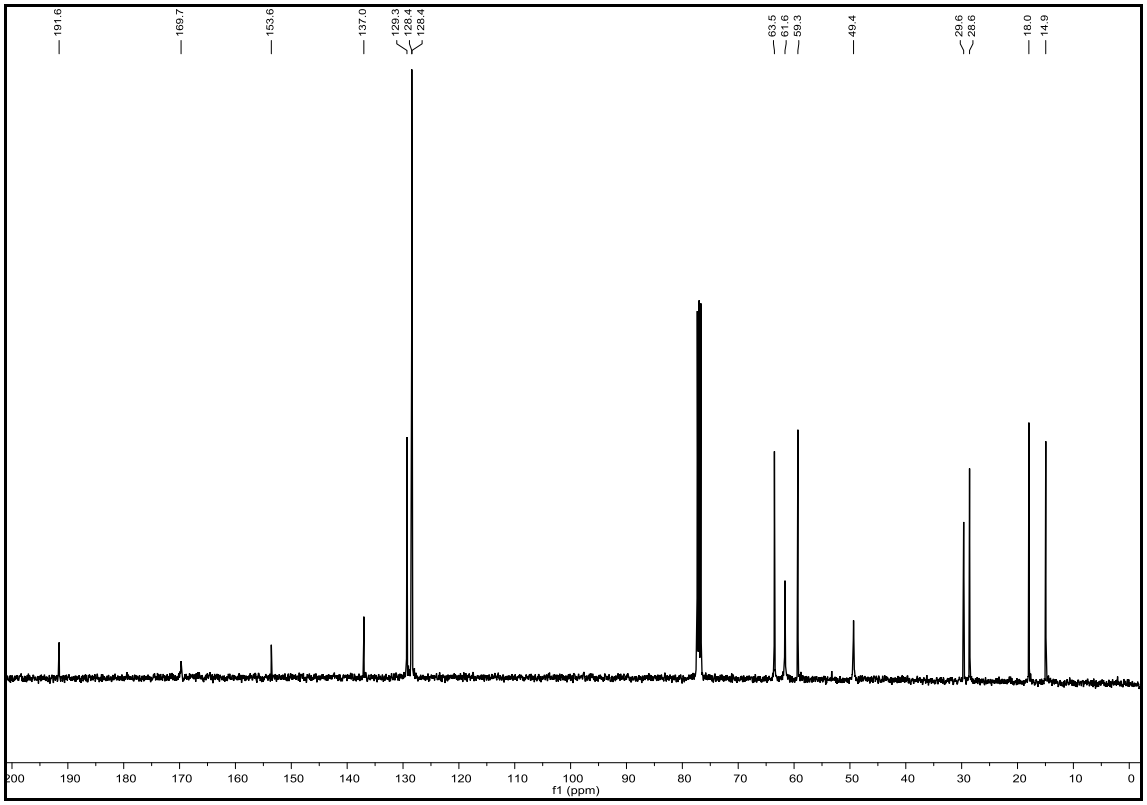
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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128.4
128.4
63.5
61.6
59.3
49.4
29.6
28.6
18.0
14.9
200
190
180
170
160
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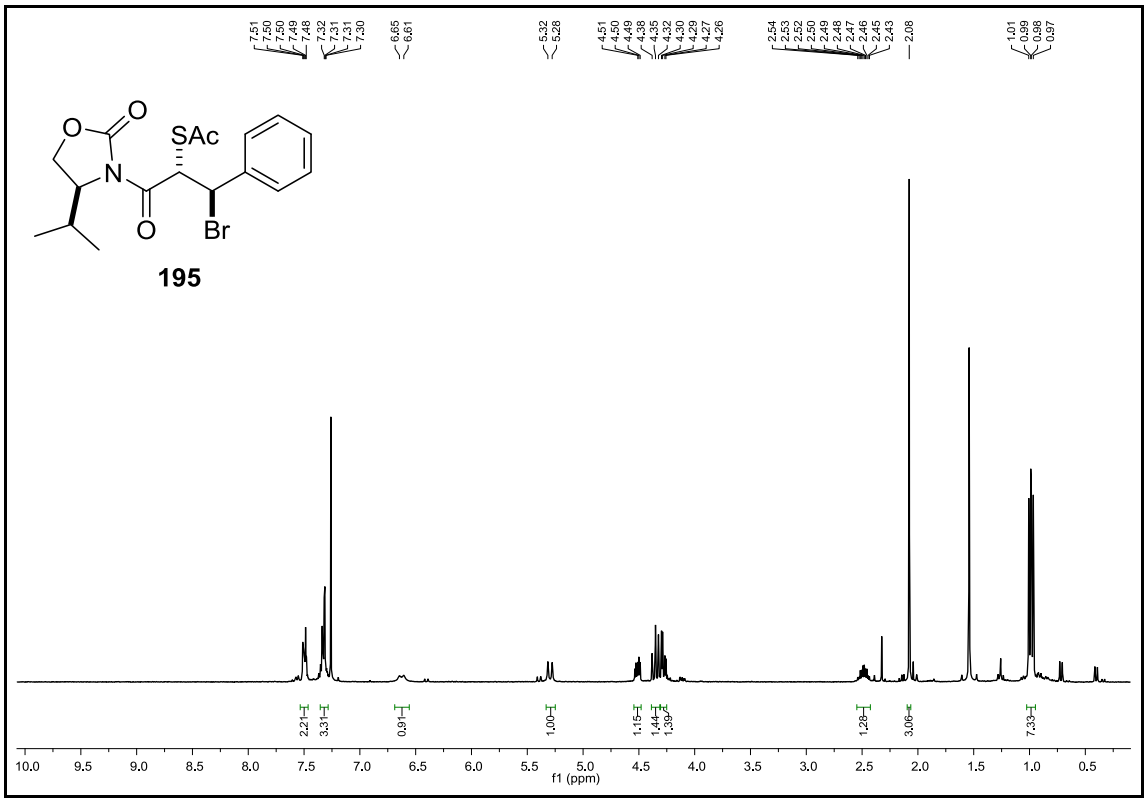
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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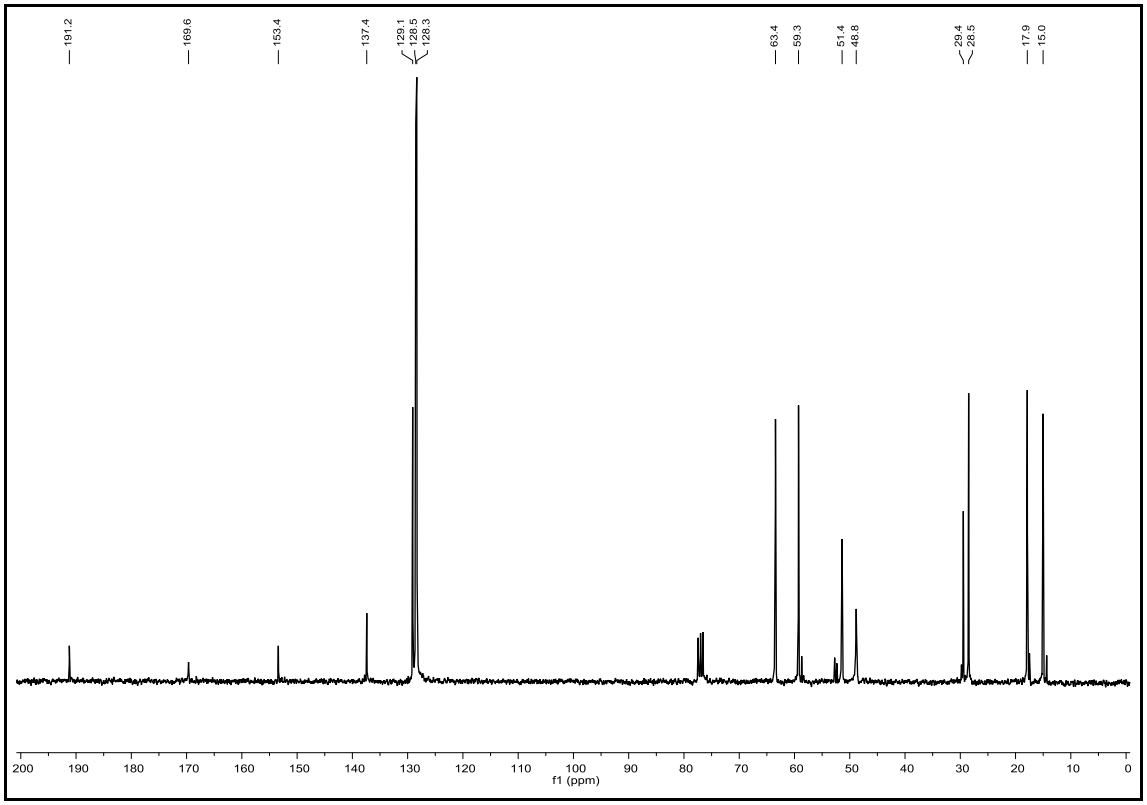
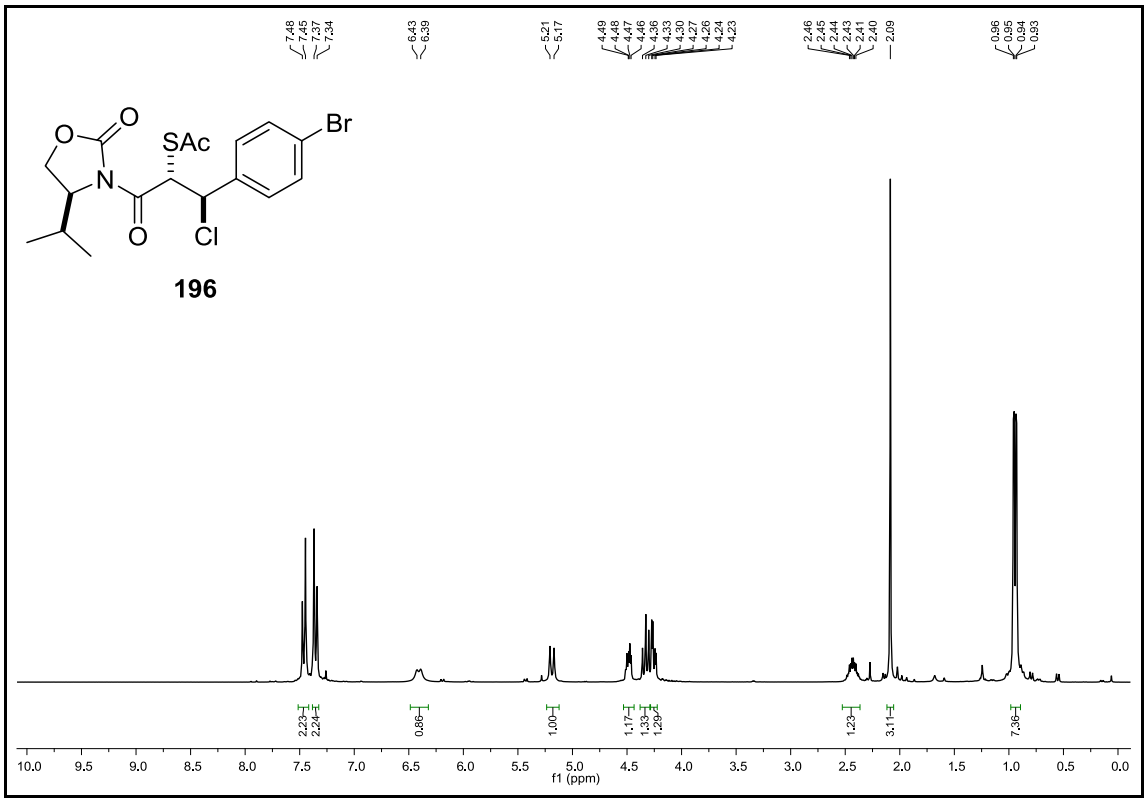

f1 (ppm)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4.48
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4.46
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4.33
4.30
4.27
4.26
4.24
4.23
2.46
2.45
2.44
2.43
2.41
2.40
2.09
0.96
0.95
0.94
0.93
O
O
N
O
SAc
Cl
Br
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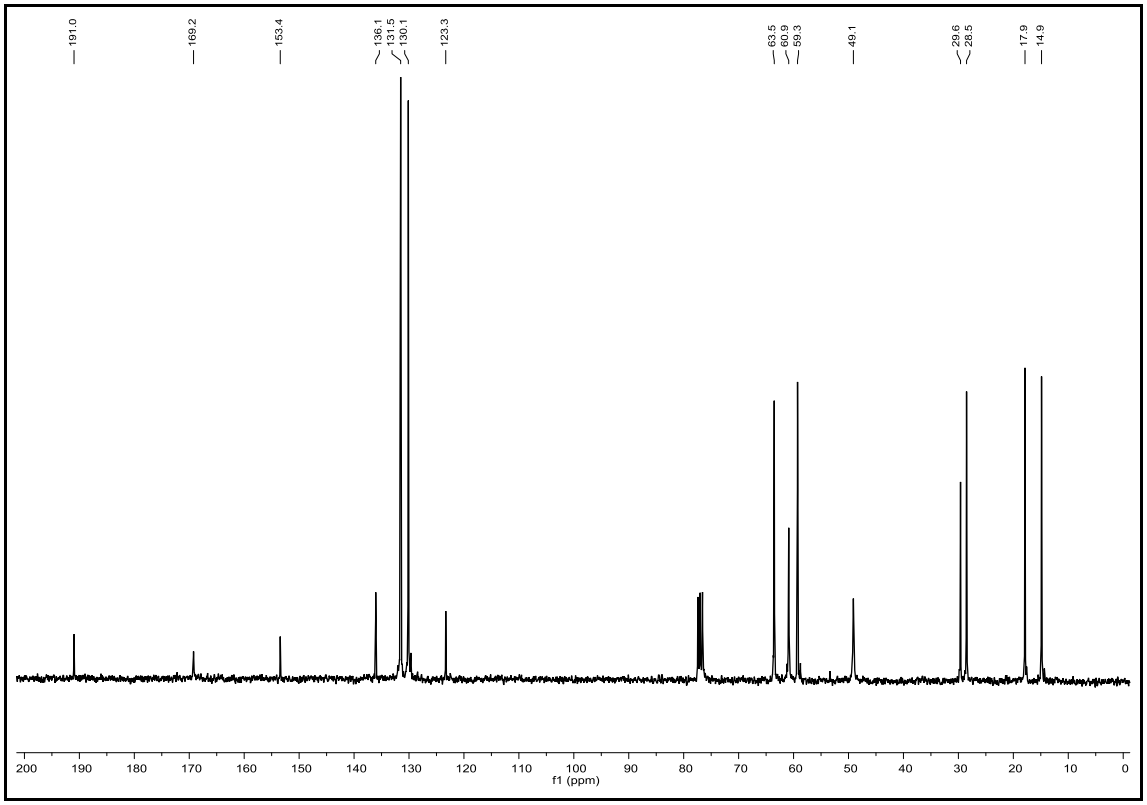
0.86
1.00
1.17
1.33
1.29
1.23
3.11
7.36
f1 (ppm)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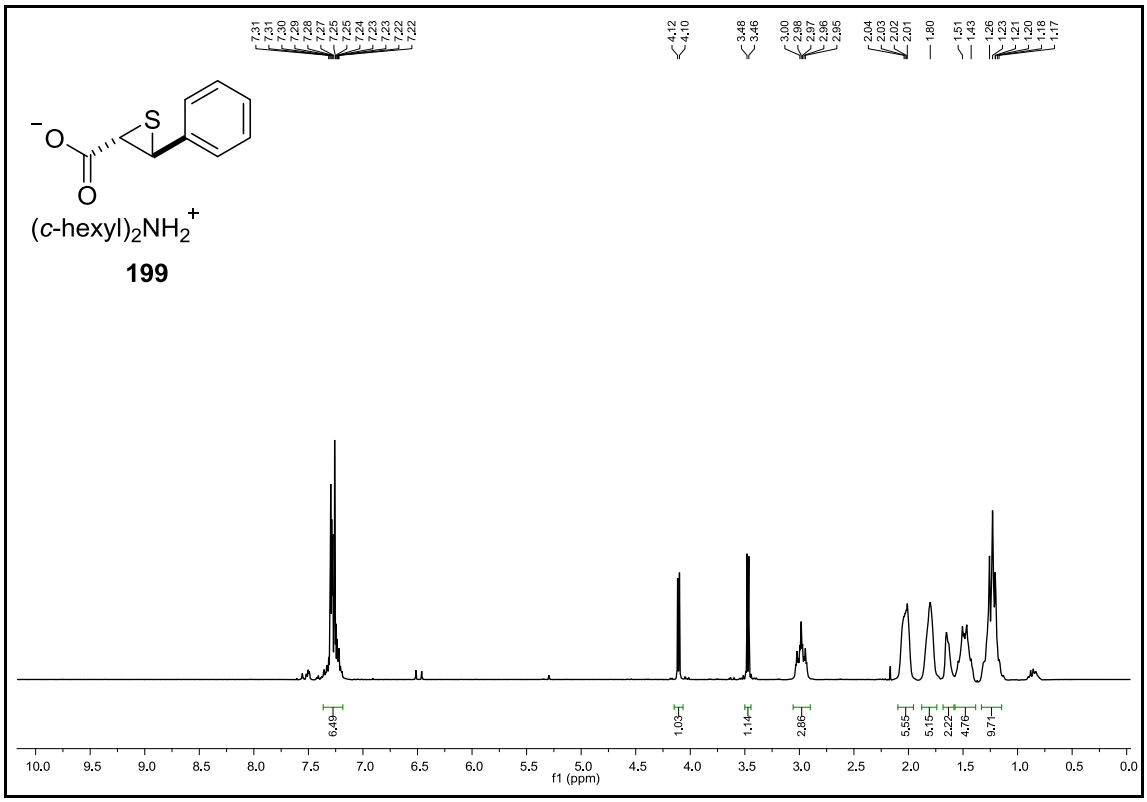
169.2
153.4
136.1
131.5
130.1
123.3
63.5
60.9
59.3
49.1
29.6
28.5
17.9
14.9
f1 (ppm)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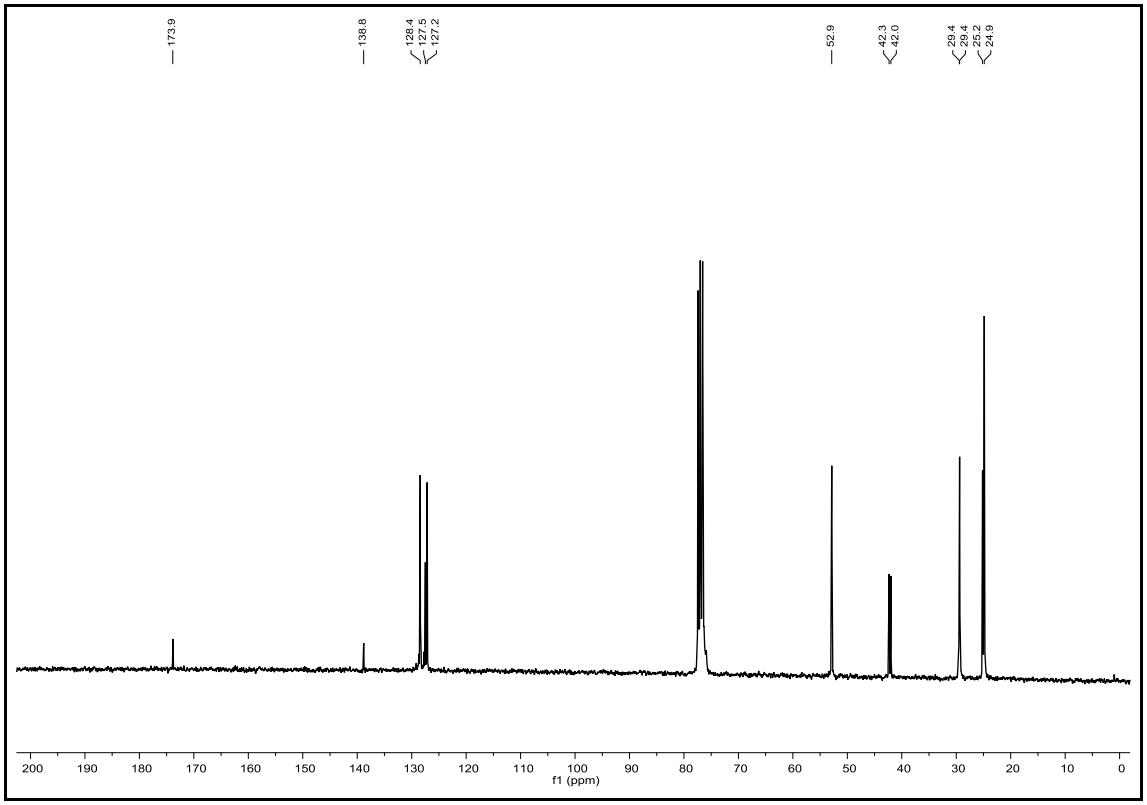
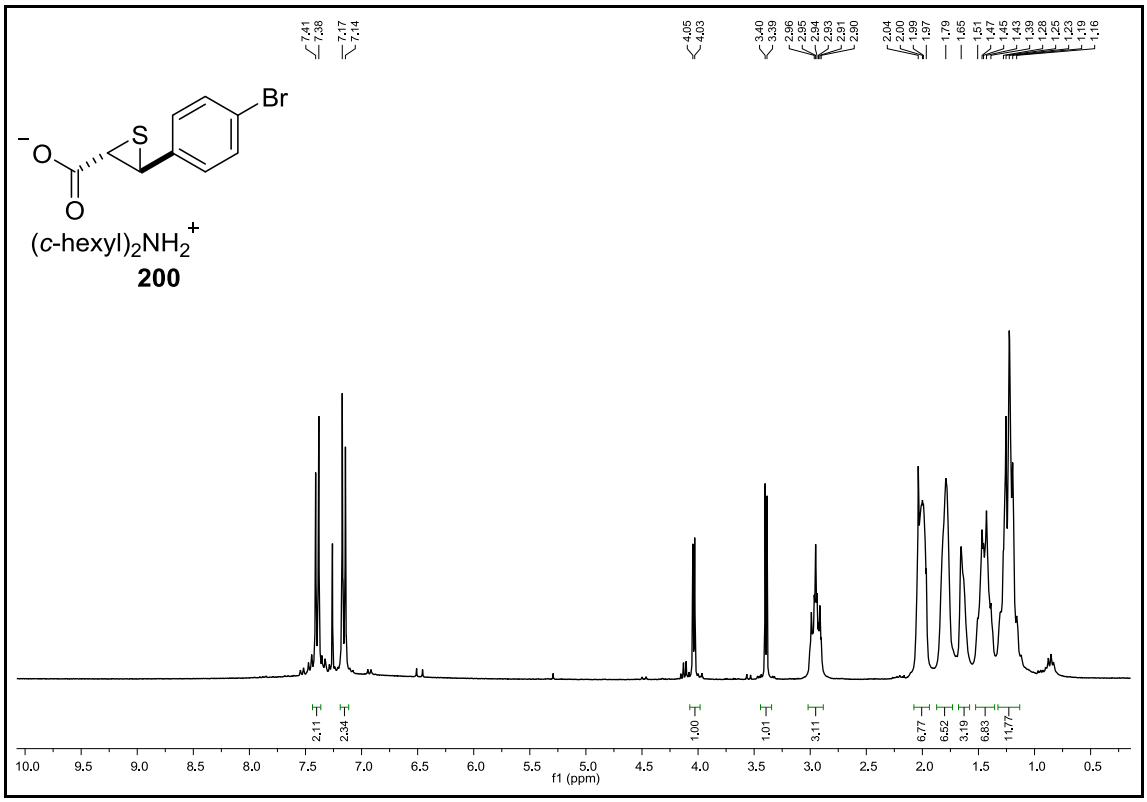
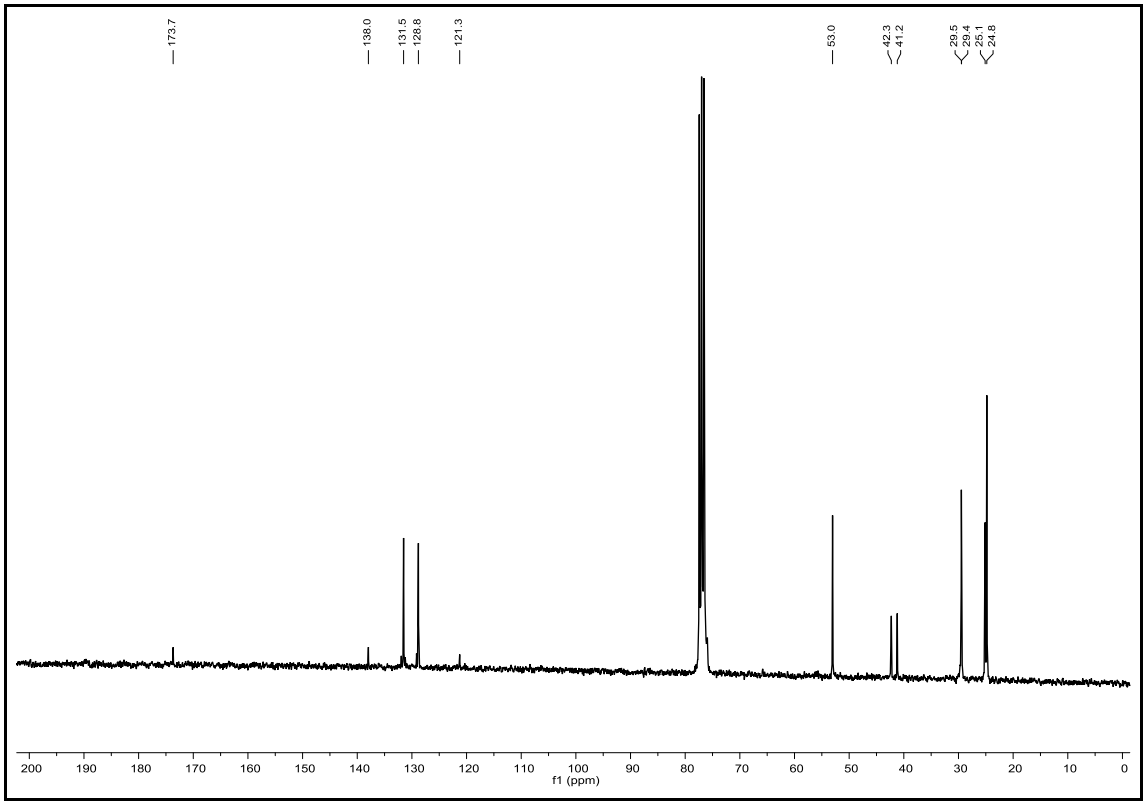
7.31
7.30
7.28
7.28
7.27
7.25
7.25
7.24
7.23
7.23
7.22
7.22
4.12
4.10
3.48
3.46
3.00
2.98
2.97
2.96
2.95
2.04
2.03
2.02
2.01
1.80
1.51
1.43
1.26
1.23
1.21
1.20
1.18
1.17
O
S
O
(c-hexyl)2NH2+
199
6.49
1.03
1.14
2.86
5.55
5.15
2.22
4.76
9.71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


173.9
138.8
128.4
127.5
127.2
52.9
42.3
42.0
29.4
29.4
25.2
24.9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

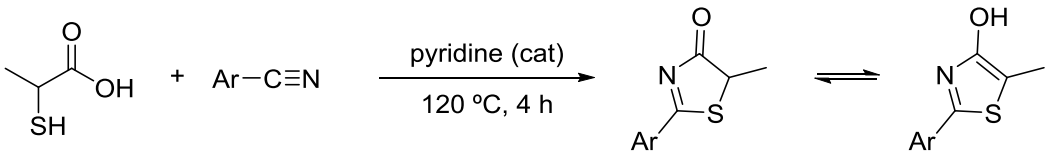

Br
S
O
O
(c-hexyl)2NH2+
200
f1 (ppm)


f1 (ppm)

6.3. Experimental section of Chapter 3

6.3.1. General procedure for the synthesis of 5*H*-thiazol-4-ones 285, 303–305, 542 and 453

6.3.1.1. General procedure A[286]



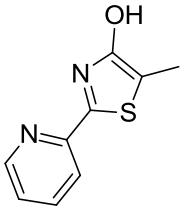
443

444 Ar = 2-Pyr
445 Ar = 2-Quin
446 Ar = 2-Ph
447 Ar = 2-Naph

285 Ar = 2-Pyr 73%
303 Ar = 2-Quin 91%
304 Ar = 2-Ph 69%
305 Ar = 2-Naph 50%

In an inert atmosphere, the corresponding carbonitrile (1 equiv.) was treated with mercaptolactic acid (1 equiv.) and pyridine (20 mol %). The mixture was stirred for 4 h at 120 ºC. During this time, a yellow mass was formed which was collected by filtration and washed with methanol, diethyl ether or diisopropyl ether. In all the cases ^{1}H NMR analysis of the resulting products in DMSO showed the presence of only the enol form.

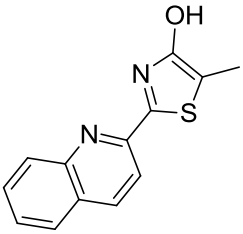
5-Methyl-2-(pyridin-2-yl)thiazol-4-ol 285[286]



The title compound **285** was prepared from pyridine-2-carbonitrile **444** (1.1 g, 10 mmol) and mercaptolactic acid **443** (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with methanol. Yellow solid, yield: 1.4 g, 7.3 mmol, 73%. m. p. 209–210 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 10.34 (s, 1H), 8.58–8.49 (m, 1H), 7.96–7.84 (m, 2H), 7.39 (ddd, *J* = 6.8, 4.8, 1.9 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.1, 158.7, 150.6, 149.5, 137.5, 124.2, 117.9, 105.8, 9.3. HRMS: $C_9H_9N_2OS$ $[M+H]^+$ calcd.: 193.0436, found: 193.0439.

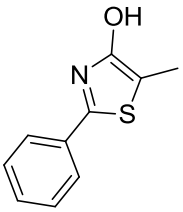
[286] Grummt, U. W.; Weiss, D.; Birckner, E.; Beckert, R. *J. Phys. Chem. A.* **2007**, *111*, 1104–1110. Keto-enol-tautomerism established by H^1-NMR using $CDCl_3$ as solvent. Using DMSO-d_6 only the enol form was detected.

5-Methyl-2-(quinolin-2-yl)thiazol-4-ol 303



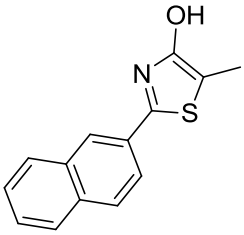
The title compound **303** was prepared from quinoline-2-carbonitrile **445** (1.5 g, 10 mmol) and mercaptolactic acid **443** (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with diethyl ether. Yellow solid, yield: 2.2 g, 9.1 mmol, 91%. m. p. 232–234 ºC. ^{1}H NMR (300 MHz, DMSO), δ: 9.59 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 6.97 (t, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.3, 158.8, 150.6, 147.1, 137.5, 130.4, 128.5, 128.0, 127.9, 126.9, 116.6, 107.2, 9.4. HRMS: $C_{13}H_{11}N_2OS$ $[M+H]^+$ calcd.: 243.0592, found: 243.0597.

5-Methyl-2-phenylthiazol-4-ol 304[287]



The title compound **304** was prepared from benzonitrile **446** (1.0 mL, 10 mmol) and mercaptolactic acid **443** (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with methanol. Yellow solid, yield: 1.3 g, 6.7 mmol, 67%. m. p. 202–204 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 10.30 (s, 1H), 7.82–7.74 (m, 2H), 7.49–7.37 (m, 3H), 2.21 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 158.8, 158.2, 133.4, 129.4, 129.1, 124.8, 102.6, 9.1. UPLC-DAD-QTOF: $C_{10}H_{10}NOS$ $[M+H]^+$ calcd.: 192.0483, found: 192.0482.

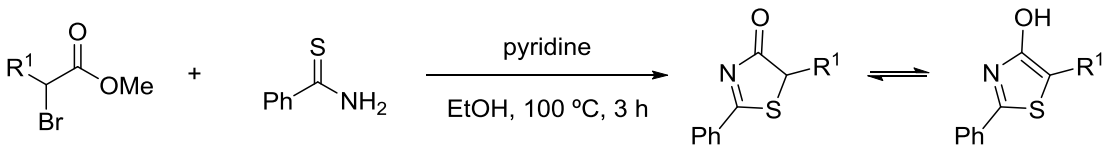
5-Methyl-2-(naphthalen-2-yl)thiazol-4-ol 305



The title compound **305** was prepared from 2-naphthonitrile **447** (1.5 g, 10 mmol) and mercaptolactic acid **443** (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with diethyl ether. Yellow solid, yield: 1.2 g, 5.0 mmol, 50%. m. p. 229–230 ºC. ^{1}H NMR (300 MHz, DMSO), δ: 10.35 (s, 1H), 8.33 (s, 1H), 8.07–7.87 (m, 4H), 7.61– 7.49 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.0, 158.2, 133.2, 132.9, 130.8, 128.8, 128.4, 127.7, 126.9, 123.6, 122.7, 103.0, 9.2. UPLC-DAD-QTOF: $C_{14}H_{12}NOS$ $[M+H]^+$ calcd.: 242.0640, found: 242.0637.

[287] Okawara, T.; Kashihara, H.; Furukawa, M. *Chem. Pharm. Bull*. **1985**, *33*, 3479–3483.

6.3.1.2. General procedure B[288]

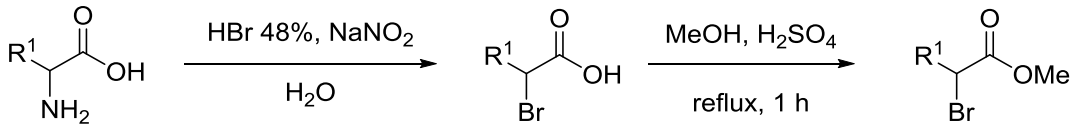


448 R^1 = *i*-Bu
449 R^1 = Hex
450 R^1 = Ph

451

321 R^1 = *i*-Bu 73%
452 R^1 = Hex 65%
453 R^1 = Ph 77%

6.3.1.2.1. Synthesis of the starting α-bromo esters[289]



2-Bromooctanoic acid (R^1 = Hex) and α-bromophenylacetic acid (R^1 = Ph) are commercially available and were purchased from commercial suppliers. 2-Bromo-4-methylpentanoic acid (R^1 = *i*-Bu) was prepared as follows.

Methyl 2-bromo-4-methylpentanoate 448[289]

Leucine (1 equiv., 5.3 g, 40 mmol) was solubilized in HBr (48%, 40 mL) and water (36 mL). The reaction mixture was cooled to 0 ºC and a solution of $NaNO_2$ (1.6 equiv., 4.4 g, 64 mmol) in water (10 mL) was added dropwise. The mixture was stirred for 2.5 h at room temperature, then concentrated and extracted with Et_2O (4 x 10 mL). The organic layers were combined and washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield 2-bromo-4-methylpentanoic acid as a colorless oil which was used in the next step without further purification. Yield: 7.6 g, 39.2 mmol, 98%.

The α-bromoacid was treated with a solution of concentrated sulphuric acid (30 μL/mmol) in methanol (2 mL/mmol) and refluxed for one hour. The solution was cooled to room temperature and concentrated under vacuum. Et_2O (20 mL) was added and the organic layer was washed with 5% aqueous solution of $NaHCO_3$ (20 mL) followed by brine (20 mL), dried over $MgSO_4$ and concentrated under vaccum. This yielded α-bromo ester **448** as a colorless oil which was used in the next step without further purification. Yield: 6.7 g, 32.2 mmol, 82%. All data were consistent with those

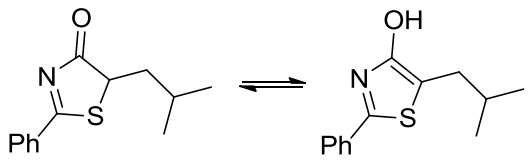
[288] Täuscher, E.; WeiB, D.; Beckert, R. Fabian, J.; Assumpção, A.; Görls, H. *Tetrahedron Lett*. **2011**, *52*, 2292–2294.
[289] Moumne, R.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2006**, *71*, 3332–3334.

previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 4.29 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 1.96–1.86 (m, 2H), 1.86 – 1.68 (m, 1H), 0.94 (dd, *J* = 13.6, 6.6 Hz, 6H).

6.3.1.2.2. General procedure B for the synthesis of 5H-thiazol-4-ones

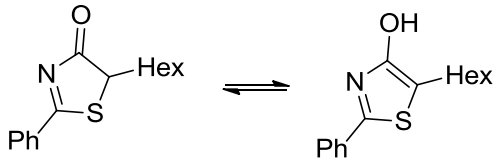
A mixture of the corresponding α-bromo methyl ester (1.1 equiv.), thioamide (1 equiv.) and pyridine (1 equiv.) was stirred under argon and slowly heated to 100–110 ºC for 3 h. After this time, ethanol was added (1.5 mL/mmol) and the mixture was stirred at room temperature for 30 min. After filtration the crude product was washed with ethanol. ^{1}H NMR analysis of the resulting products in $CDCl_3$ showed in some cases the presence of only the enol form, and in other cases the presence of both, enol and ketol forms, as indicated below.

5-Isobutyl-2-phenylthiazol-4(5*H*)-one (keto form); 5-isobutyl-2-phenylthiazol-4-ol (enol form) 321



The title compound **321** was prepared from methyl 2-bromo-4-methylpentanoate **448** (2.3 g, 11 mmol) and thioamide **451** (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid, yield: 1.7 g, 7.3 mmol, 73%. m. p. 125–127 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.20–8.10 (m, 1H), 7.88–7.80 (m, 1H), 7.72–7.61 (m, 1H), 7.57–7.48 (m, 1H), 7.47–7.35 (m, 1H), 4.26 (dd, *J* = 11.0, 4.1 Hz, 1H) (keto form), 2.63 (d, *J* = 7.0 Hz, 2H) (enol form), 2.28–2.09 (m, 2H) (keto form), 2.03–1.85 (m, 1H) (enol form), 1.83–1.66 (m, 1H) (keto form), 1.12–0.91 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.1, 194.2, 161.1, 158.4, 135.0, 133.0, 132.2, 129.7, 129.0, 129.0, 128.8, 125.7, 108.3, 54.0, 42.5, 33.3, 30.2, 28.2, 23.0, 22.2, 21.4. UPLC-DAD-QTOF: $C_{13}H_{16}NOS$ $[M+H]^+$ calcd.: 234.0953, found: 234.0960.

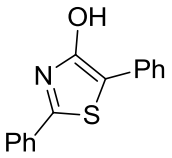
5-Hexyl-2-phenylthiazol-4(5*H*)-one (keto form); 5-hexyl-2-phenylthiazol-4-ol (enol form) 452



The title compound **452** was prepared from methyl 2-bromooctanoate **449** (2.6 g, 11 mmol) and thioamide **451** (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid, yield: 1.7 g, 6.5 mmol, 65%. m. p. 77–80 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.93–8.83 (m, 1H), 8.16–8.07 (m, 2H), 7.87–7.76 (m, 1H), 7.71–7.60 (m, 1H), 7.56–7.46 (m, 3H), 7.46–7.29 (m, 2H), 4.25 (dd, *J* = 9.2, 4.2 Hz, 1H) (keto form), 2.73 (t, *J* = 7.5 Hz, 2H) (enol form), 2.33–2.17 (m, 1H), 1.97–1.78 (m,

1H), 1.71–1.56 (m, 1H), 1.56–1.08 (m, 13H), 1.05–0.57 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.2, 193.7, 157.6, 135.0, 132.2, 129.6, 129.0, 128.7, 127.4, 125.6, 109.9, 55.6, 33.0, 31.5, 31.4, 30.9, 28.7, 28.6, 27.9, 24.3, 22.5, 22.4, 14.0, 13.9. UPLC-DAD-QTOF: $C_{15}H_{20}NOS$ $[M+H]^+$ calcd.: 262.1266, found: 262.1265.

2,5-Diphenylthiazol-4-ol 453[287]



The title compound **453** was prepared from methyl 2-bromo-2-phenylacetate **450** (2.5 g, 11 mmol) and thioamide **451** (1.4 g, 10 mmol) according to the general procedure B. The resulting solid was washed with ethanol. Yellow solid, yield: 1.9 g, 7.7 mmol, 77%. m. p. 214–216 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.01–7.90 (m, 2H), 7.89–7.79 (m, 2H), 7.54–7.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 145.8, 141.4, 129.8, 128.8, 128.5, 127.1, 126.4, 126.1, 125.5, 109.5. UPLC-DAD-QTOF: $C_{15}H_{12}NOS$ $[M+H]^+$ calcd.:254.0640, found:254.0647.

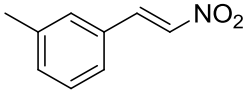
6.3.2. General procedure for the synthesis of nitroalkenes 282e–g and 282k–p

Nitroalkenes **282a–d** and **282h–j** are commercially available and were purchased from commercial suppliers. Nitroalkenes **282e–g** and **282k–p** were prepared as follows.

6.3.2.1. General procedure A[290]

Nitromethane (1 equiv., 1.1 mL, 20 mmol) was added to a stirred solution of the corresponding aldehyde (1 equiv., 20 mmol) in ethanol (35 mL) at 0 ºC, followed by dropwise addition of 10N NaOH solution (1.05 equiv., 201 mL, 21 mmol). The resulting mixture was stirred at 0 ºC for 1 hour and then a mixture of 1:1 HCl 37%: H_2O (12 mL:12 mL) was added. The reaction mixture was stirred at 0 ºC for 1 hour, then extracted with dichloromethane (3 x 50 mL), dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

1-Methyl-3-(2-nitrovinyl)benzene 282e[291]



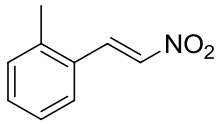
The title compound **282e** was prepared from 3-methylbenzaldehyde (2.4 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 2.5 g, 15.6 mmol, 78%. All data

[290] Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem*. **1985**, *63*, 2354–2361.

[291] Zhang, M.; Hu, P.; Zhou, J.; Wu, G.; Huang, S.; Su, W. *Org. Lett*. **2013**, *15*, 1718–1721.

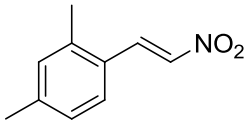
were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.98 (d, *J* = 13.7 Hz, 1H), 7.58 (d, *J* = 13.7 Hz, 1H), 7.40–7.26 (m, 4H), 2.40 (s, 3H).

1-Methyl-2-(2-nitrovinyl)benzene 282f[292]



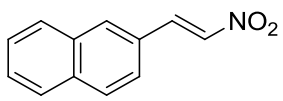
The title compound **282f** was prepared from 2-methylbenzaldehyde (2.3 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 2.7 g, 16.4 mmol, 82%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.29 (d, *J* = 13.5 Hz, 1H), 7.50–7.26 (m, 5H), 2.48 (s, 3H).

2,4-Dimethyl-1-(2-nitrovinyl)benzene 282g[293]



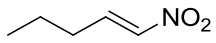
The title compound **282g** was prepared from 2,4-dimethylbenzaldehyde (2.8 mL, 20 mmol) according to the general procedure A. Yellow solid, yield: 2.5 g, 14.4 mmol, 72%. m. p. 52–54 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.28 (d, *J* = 13.5 Hz, 1H), 7.50 (d, *J* = 13.5 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.15–7.01 (m, 2H), 2.45 (s, 3H), 2.36 (s, 3H).

2-(2-Nitrovinyl)naphthalene 282m[294]



The title compound **282m** was prepared from 2-naphthaldehyde (3.1 g, 20 mmol) according to the general procedure B. Yellow solid, yield: 2.9 g, 14.6 mmol, 73%. m. p. 126–128 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.18 (d, *J* = 13.6 Hz, 1H), 8.03 (s, 1H), 7.96–7.83 (m, 3H), 7.71 (d, *J* = 13.6 Hz, 1H), 7.67–7.52 (m, 3H).

1-Nitropent-1-ene 282n[295]



The title compound **282n** was prepared from butyraldehyde (1.8 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 1.2 g, 10.4 mmol, 52%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35–7.19 (m, 1H), 6.98 (dt, *J* = 13.4, 1.4 Hz, 1H), 2.34–2.16 (m, 2H), 1.67–1.46 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

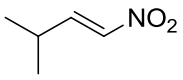
[292] Luo, M.; Yan, B. *Tetrahedron Lett*. **2010**, *51*, 5577–5580.

[293] Xu, C.; Du, J.; Ma, L.; Li, G.; Tao, M.; Zhang, W. *Tetrahedron* **2013**, *69*, 4749–4757.

[294] Jakubea, P.; Cockfield, C. M.; Hynes, P. S.; Cleator, E.; Dixon, D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 1147–1155.

[295] Lucet, D.; Sabell,e S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem*. **1999**, 2583–2591.

3-Methyl-1-nitrobut-1-ene 282o[295]

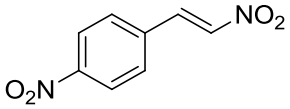


The title compound **282o** was prepared from isobutyraldehyde (1.8 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 1.0 g, 9.1 mmol, 46%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.31–7.18 (m, 1H), 6.94 (dd, *J* = 13.5, 1.4 Hz, 1H), 2.67–2.50 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H).

6.3.2.2. General procedure B[290]

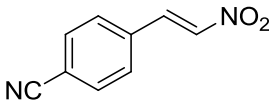
Nitromethane (1 equiv., 1.1 mL, 20 mmol) was added to a stirred solution of the corresponding aldehyde (1 equiv., 20 mmol) in 2-propanol (5 mL) at room temperature, followed by the addition of benzylamine (6.5 mol %, 0.14 mL, 1.3 mmol) and acetic acid (10 mol %, 0.12 mL, 2 mmol). The resulting mixture was stirred refluxing for 1 hour. After this time the mixture was cooled to room temperature and the precipitated solid was collected by filtration and recrystallized from ethanol to afford the corresponding nitroalkene.

1-Nitro-4-(2-nitrovinyl)benzene 282k[296]



The title compound **282k** was prepared from 4-nitrobenzaldehyde (3.0 g 20 mmol) according to the general procedure B. Yellow solid, yield: 2.5 g, 13.0 mmol, 65%. m. p. 198–200 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 13.8 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 13.8 Hz, 1H).

4-(2-Nitrovinyl)benzonitrile 282l[297]



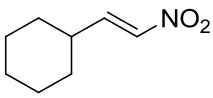
The title compound **282l** was prepared from 4-formylbenzonitrile (2.6 g, 20 mmol) according to the general procedure B. Yellow solid, yield: 2.4 g, 13.8 mmol, 69%. m. p. 193–195 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.99 (d, *J* = 13.7 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 13.8 Hz, 1H).

[296] Oh, H. K.; Yang, J. H.; Sung, D. D.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **2000**, 101–105.

[297] Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. *J. Am. Chem. Soc*. **2013**, *135*, 3355–3358.

6.3.2.3. General procedure C[295]

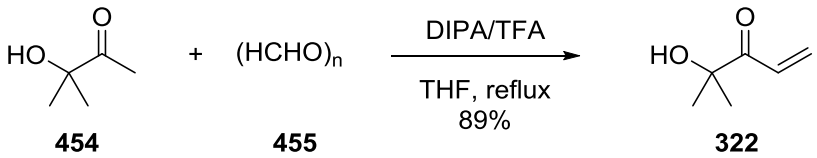
Synthesis of (2-nitrovinyl)cyclohexane 282p[295]



To a solution of the cyclohexanecarboxaldehyde (1 equiv., 1.2 mL, 10 mmol) and nitromethane (1 equiv., 0.5 mL, 10 mmol) in ethanol (2.5 mL) at 0 ºC an aqueous NaOH 1M solution (1 equiv., 1 mL, 10 mmol) was added. After 10 min under vigorous stirring the reaction mixture became yellow. Then acetic acid (1 equiv., 0.6 mL, 10 mmol) was added and the aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the corresponding nitro alcohol, which was dissolved in dichloromethane (10 mL) and cooled at 0 ºC. Then trifluoroacetic acid anhydride (1 equiv., 0.8 mL, 10 mol) and triethylamine (4 equiv., 5.5 mL, 40 mmol) were added dropwise. The reaction mixture was stirred for 1 h at 0 ºC, quenched with water (10 mL), extracted with dichloromethane (3 x 20 mL) and washed with HCl 1M (2 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the tittle compound **282p**. Yellow oil, yield: 0.74 g, 4.8 mmol, 48%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.26–7.17 (m, 1H), 6.93 (dd, *J* = 13.5, 1.3 Hz, 1H), 2.36–2.15 (m, 1H), 1.90–1.64 (m, 4H), 1.45–1.09 (m, 6H).

6.3.3. General procedure for the synthesis of α'-oxy enones 322 and 325

*6.3.3.1. Preparation of 4-hydroxy-4-methylpent-1-en-3-one **322***[298]



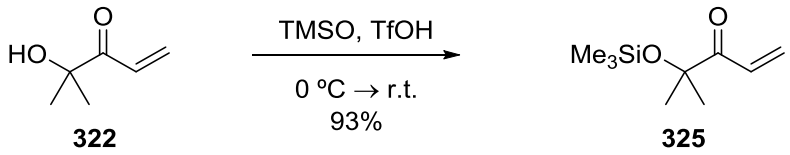
454 **455** **322**

3-Hydroxy-3-methyl-2-butanone **454** (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde **455** (2 equiv., 3 g, 100 mmol) were added to a solution of DIPA (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with HCl 1N (75 mL), NaOH 1N (75 mL) and brine (75 mL), and the organic layer was

[298] Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Comm*. **2010**, *46*, 1715–1717.

dried over $MgSO_4$. The solvent was removed using a rotavapor (230 mbar/ bath 40ºC). The residue was purified by flash column chromatography on silica gel (eluting with diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one **322** as a colorless oil. Yield: 5.0 g, 44.5 mmol, 89%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 6.79–6.67 (m, 1H), 6.53 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.85 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.83 (bs, 1H), 1.40 (s, 6H).

*6.3.3.2. Preparation of 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325***[299]



322 **325**

3-(Trimethylsilyl)-2-oxazolidinone (1.5 equiv., 3.4 mL, 22.5 mmol) and 3 drops of trifluoromethanesulfonic acid were added to 4-hydroxy-4-methylpent-1-en-3-one **322** (1 equiv., 1.68 g, 15 mmol). The reaction mixture was stirred at room temperature for 2h. After this time it was diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL); dried over $MgSO_4$ and concentred under reduced pressure (230 mbar/ bath 40ºC) to afford 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325** as a colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H).

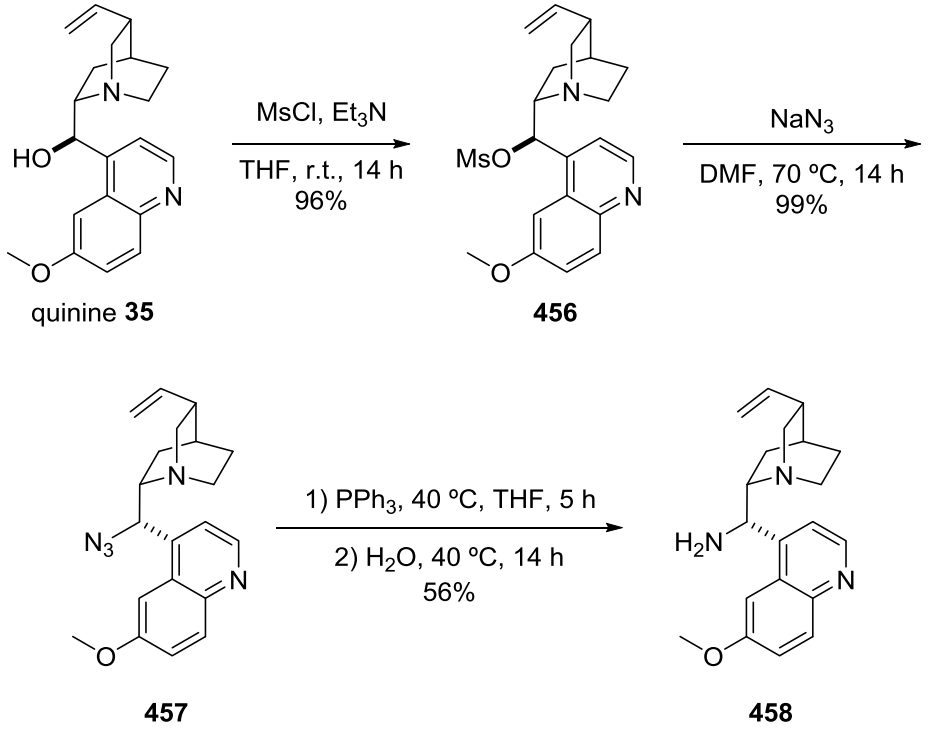
[299] Adapted from: Aizpurua, J. M.; Palomo, C.; Palomo, A. L. *Can. J. Chem*. **1984**, *62*, 336–340.

6.3.4. General procedure for the synthesis of catalysts

Catalysts **43** and **288** are commercially available and were purchased from commercial suppliers. Catalysts **44–45**, **294–302**, **87** and **324** were prepared as follows.

6.3.4.1. Preparation of 9-epi cinchona-based amines

*6.3.4.1.1. Preparation of 9-amino-(9-deoxy)epiquinine **458***[300]



1st step:[301] A mixture of quinine **35** (1 equiv., 16.2 g, 50 mmol) and triethylamine (3.6 equiv., 25.1 mL, 180 mmol) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (1.8 equiv., 7.0 mL, 90 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford crude product **456** with 96% yield, which was used in the next step without further purification.

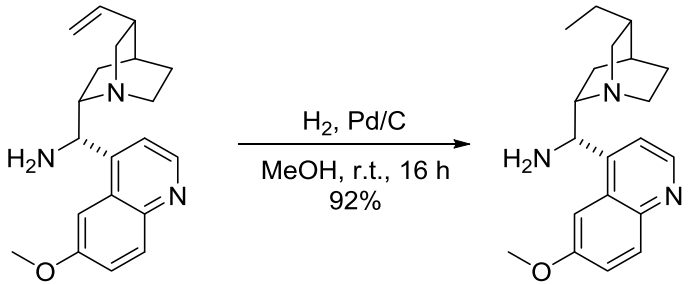
[300] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

[301] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

2nd step:[302] The crude product **456** (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 ºC and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 ºC for 16 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product **457** in quantitative yield which was used in the next step without further purification.

3rd step:[302] The crude product **457** was dissolved in THF (250 mL) and PPh_3 (1 equiv., 12.6 g, 48 mmol) was added. The reaction mixture was heated to 40 ºC and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 ºC. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 ºC and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine **458** as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.75 (d, *J* = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

*6.3.4.1.2. Preparation of 9-amino-(9-deoxy)epihydroquinine **459**[303]*



458 **459**

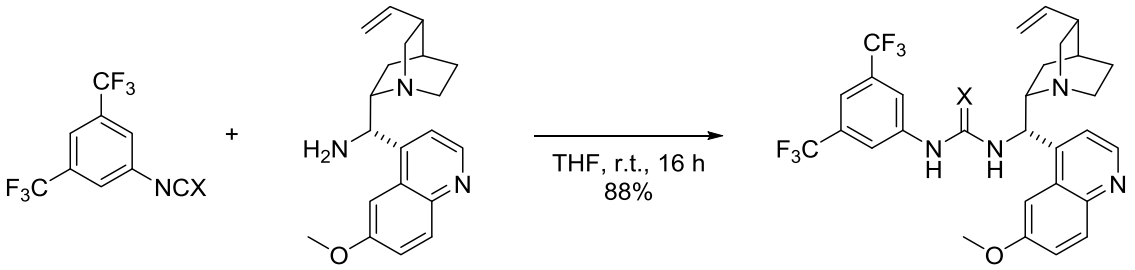
10% Palladium on carbon (10% w/w, 0.32 g) was added to a solution of 9-amino-(9-deoxy)*epi*quinine **458** (1 equiv., 3.2 g, 10 mmol) in methanol (10 mL). The

[302] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

[303] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

reaction mixture was stirred overnight under H_2 atmosphere, and then was filtered over celite and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*hydroquinine **459** as a yellow viscous oil. Yield: 3.0 g, 9.2 mmol, 92%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD), δ: 8.69 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.69 (brs, 1H), 7.61 (d, *J* = 4.7 Hz, 1H,), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.36–3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H), 3.16 (q, *J* = 10.7 Hz, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 1.62–1.58 (m, 1H), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.58–1.47 (m, 4H), 1.37–1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

*6.3.4.2. Thiourea and urea containing Brønsted base catalysts **44**[303] and **45**[304]*



460 X = S
461 X = O

458

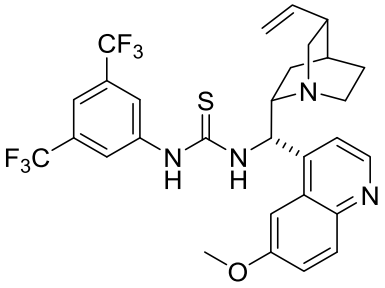
44 X = S 88%
45 X = O 82%

General procedure[303]

To a solution of 9-amino-(9-deoxy)*epi*quinine **458** (1 equiv., 1.6 g, 5 mmol) in dry THF (7.5 mL) at 0 ºC, a solution of bis(trifluomethyl)phenyl isothiocyanate **460** (1.1 equiv., 1.5 g, 5.5 mmol) or bis(trifluomethyl)phenyl isocyanate **461** (1.1 equiv., 0.6 mL, 5.5 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the title compounds **44** and **45**.

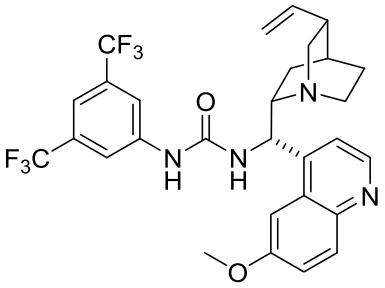
[304] Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis* **2011**, *12*, 1880–1886.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea 44



The title compound **44** was prepared from bis(trifluomethyl)phenyl isothiocyanate **460** (1.5 g, 5.5 mmol) according to the general procedure. White solid, yield: 2.6 g, 4.4 mmol, 88%. m. p. 123–125 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD), δ: 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38–2.35 (m, 1H), 1.71–1.68 (m, 2H), 1.64–1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)urea 45



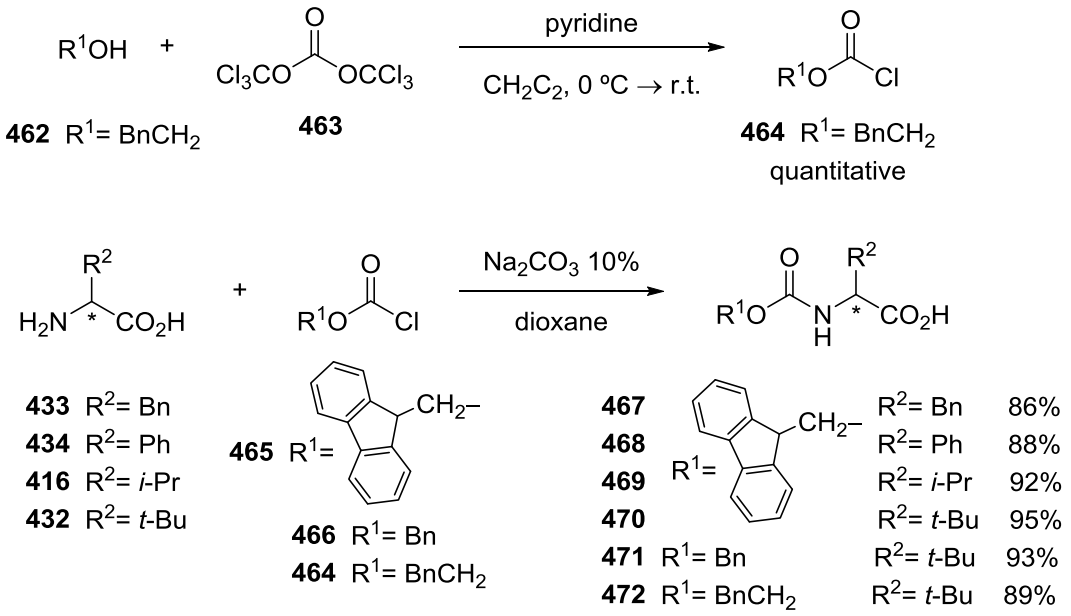
The title compound **45** was prepared from bis(trifluomethyl)phenyl isocyanate **461** (0.6 mL, 5.5 mmol) according to the general procedure. White solid, yield: 2.4 g, 4.1 mmol, 82%. m. p. 132–134 ºC. All data were consistent with those previously reported.^{1}H NMR (300 MHz, CD_3OD), δ: 8.58 (d, *J* = 4.5 Hz, 1H), 7.84–7.90 (m, 3H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 5.83–5.89 (m, 1H), 5.65 (bs, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 3.03–3.15 (m, 4H), 2.41–2.43 (m, 1H), 1.40–1.73 (m, 3H), 1.17–1.25 (m, 3H).

*6.3.4.3. Ureidopeptide-like Brønsted base catalysts **294–302***

6.3.4.3.1. Preparation of N-protected α-amino acids

Although some *N*-protected amino acids **467–471** are commercially available all of them were prepared as follows.

6.3.4.3.1.1. General procedure A, using chloroformates[305]



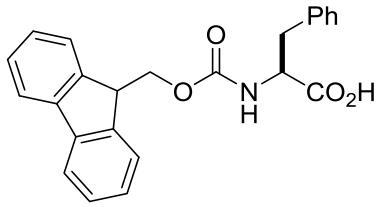
General procedure

To a stirred solution of the corresponding alcohol (1 equiv., 10 mmol) in dichloromethane (50 mL) at 0 ºC was added pyridine (1.15 equiv., 0.92 mL, 11.5 mmol) followed by triphosgene (0.4 equiv., 1.2 g, 4 mmol). The resulting mixture was stirred at room temperature overnight, and then it was partially evaporated at reduced pressure and diluted with hexane (50 mL). The solids were removed by filtration and the filtrate was evaporated to afford the corresponding chloroformate in quantitative yield, which was used as such for the next step without further purification.

To a stirred solution of the corresponding α-amino acid (1 equiv. 10 mmol) in 10% aqueous Na_2CO_3 (26 mL), and dioxane (10 mL) was slowly added at 0 ºC a solution of the corresponding chloroformate (1 equiv., 10 mmol) in dioxane (30 mL). The mixture was stirred at the same temperature for 1 h and then allowed to warm to room temperature. The solution was subsequently stirred overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL). The combined extracts were dried over $MgSO_4$, filtered off and the solvent evaporated under reduced pressure to afford the corresponding *N*-protected α-amino acids.

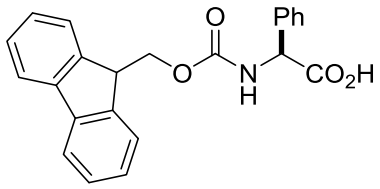
[305] Adapted from: a) Fang, L.; Yang, J.; Yang, F. *Org. Lett.* **2010**, *12*, 3124–3127. b) Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron,* **1991***, 47,* 2389–2400.

((9*H*-Fluoren-9-ylmethoxy)carbonyl)-*L*-phenylalanine 467[306]



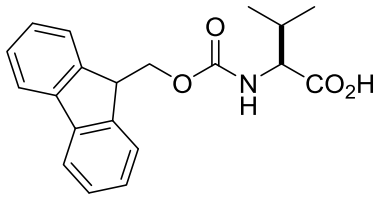
The title compound **467** was prepared from *L*-phenylalanine (1.65 g, 10 mmol) and chloroforamte **465** (2.6 g, 10 mmol) according to the general procedure A. White solid, yield: 3.3 g, 8.6 mmol, 86%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, MeOD), δ: 7.77 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.17–7.31 (m, 7H), 4.42 (dd, *J* = 4.8, 9.5 Hz, 1H),), 4.29 (dd, *J* = 7.2, 10.4 Hz, 1H), 4.22 (dd, *J* = 7.1, 10.4 Hz, 1H), 4.14 (t, *J* = 7.1 Hz, 1H), 3.21 (dd, *J* = 4.8, 13.9 Hz, 1H), 2.97 (dd, *J* = 9.5, 13.9 Hz, 1H).

((9*H*-Fluoren-9-ylmethoxy)carbonyl)-*L*-phenylglycine 468[305b]



The title compound **468** was prepared from *L*-phenylglycine (1.51 g, 10 mmol) and chloroforamte **465** (2.6 g, 10 mmol) according to the general procedure A. White solid, yield: 3.3 g, 8.8 mmol, 88%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.82–7.66 (m, 2H), 7.66–7.49 (m, 2H), 7.44–7.10 (m, 9H), 5.84–5.70 (m, 1H), 5.50–5.36 (m, 2H), 5.21–5.07 (m, 1H).

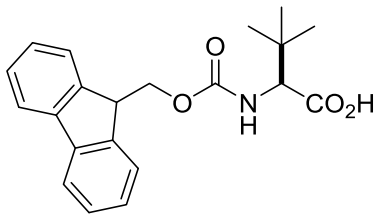
((9*H*-Fluoren-9-ylmethoxy)carbonyl)-*L*-valine 469[305b]



The title compound **469** was prepared from *L*-valine (1.17 g, 10 mmol) and chloroforamte **465** (2.6 g, 10 mmol) according to the general procedure A. White solid, yield: 3.1 g, 9.2 mmol, 92%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.76 (d, *J* = 7.5 Hz, H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.30 (dd, *J* = 15.4, 8.0 Hz, 2H), 5.25 (d, *J* = 9.0 Hz, 1H), 4.43 (d, *J* = 6.9 Hz, 1H), 4.40–4.33 (m, 2H), 4.24 (t, *J* = 7.0 Hz, 1H), 2.33–2.17 (m, 1H), 0.99 (dd, *J* = 17.8, 6.8 Hz, 6H).

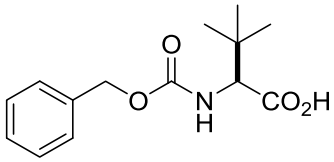
[306] Hioki, K.; Kinugasa, M.; Kishimoto, M.; Fujiwara, M.; Tani, S.; Kunishima, M. *Synthesis* **2006**, 1931–1933.

((9*H*-Fluoren-9-ylmethoxy)carbonyl)-*L-tert*-leucine 470[307]



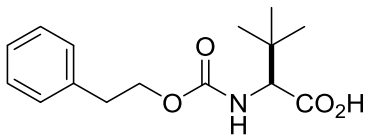
The title compound **470** was prepared from *L-tert*-leucine (1.31 g, 10 mmol) and chloroforamte **465** (2.6 g, 10 mmol) according to the general procedure A. White solid, yield: 3.4 g, 9.5 mmol, 95%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, MeOD), δ: 7.78 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 6.7 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (dt, *J* = 7.5, 1.0 Hz, 2H), 4.39–4.33 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.05 (brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

((Benzyloxy)carbonyl)-*L-tert*-leucine 471[307]



The title compound **471** was prepared from *L-tert*-leucine (1.31 g, 10 mmol) and chloroforamte **466** (1.4 mL, 10 mmol)according to the general procedure A. White solid, yield: 2.5 g, 9.3 mmol, 93%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 7.50–7.40 (m, 2H), 7.34–7.15 (m, 3H), 4.20 (d, *J* = 13.4 Hz, 1H), 3.95 (d, *J* = 16.8 Hz, 1H), 3.18 (s, 1H), 0.94 (s, 9H).

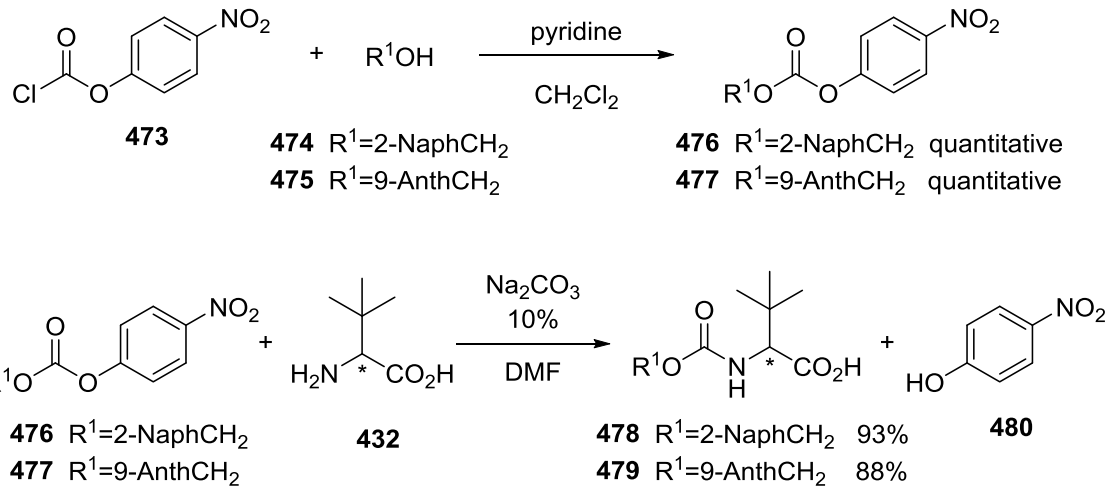
(Phenethoxycarbonyl)-*L-tert*-leucine 472



The title compound **472** was prepared from *L-tert*-leucine (1.31 g, 10 mmol) chloroforamte **467**, prepared starting from phenethyl alcohol **462** (1.2 g, 10 mmol), according to the general procedure A. White solid, yield: 2.5 g, 8.9 mmol, 89%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39–7.14 (m, 5H), 5.20 (d, *J* = 9.3 Hz, 1H), 4.31 (t, *J* = 7.8 Hz, 2H), 2.94 (t, *J* = 7.1 Hz, 2H), 1.02 (s, 9H).

[307] Pan, S. C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed*. **2007**, *46*, 612–614.

6.3.4.3.1.2. General procedure B, using 4-nitrophenyl carbonates[308]



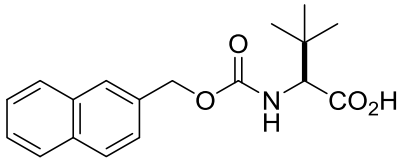
General procedure

To a stirred solution of *p*-nitrophenylchloroformate **473** (1.1 equiv. 2.2 g, 11 mmol) in dichloromethane (13.6 mL) was added pyridine (1.1 equiv., 0.9 mL, 11 mmol). The formed white slurry was cooled to 0 ºC, and the corresponding alcohol (1 equiv., 10 mmol) was added in several portions to keep the temperature at 0 ºC. After completion of the addition, the yellow mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and subsequently washed with 1 N HCl (20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

To a stirred solution of *L-tert*-leucine (1 equiv. 10 mmol) in 10% aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0 ºC a solution of the corresponding 4-nitrophenyl carbonate (1 equiv., 10 mmol) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 h and then allowed to warm to room temperature and subsequently stirred at the same temperature overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to afford the corresponding *N*-protected α-amino acids.

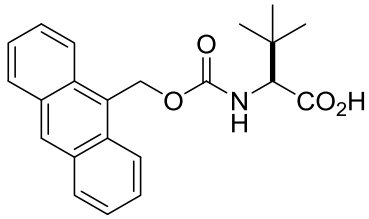
[308] Lan, P.; Porco Jr., J. A.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660–669.

((Naphthalen-2-ylmethoxy)carbonyl)-*L-tert*-leucine 478



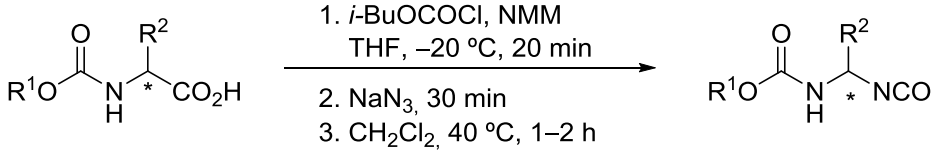
The title compound **478** was prepared from *L-tert*-leucine (1.31 g, 10 mmol) and 4-nitrophenyl carbonate **476** (3.2 g, 10 mmol), according to the general procedure B. Colorless oil, yield: 3.1 g, 9.3 mmol, 93%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.10–7.97 (m, 1H), 7.90–7.74 (m, 2H), 7.56–7.40 (m, 3H), 5.41 (d, *J* = 9.5 Hz, 1H), 5.27 (s, 2H), 4.21 (d, *J* = 9.5 Hz, 1H), 1.03 (s, 9H).

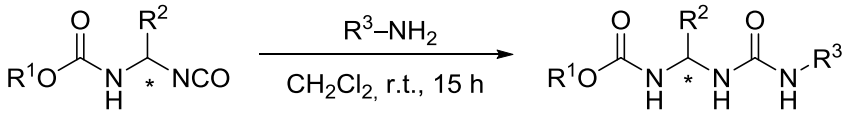
((Anthracen-9-ylmethoxy)carbonyl)-*L-tert*-leucine 479



The title compound **479** was prepared from *L-tert*-leucine (1.31 g, 10 mmol) and 4-nitrophenyl carbonate **477** (3.7 g, 10 mmol), according to the general procedure B. White solid, yield: 3.2 g, 8.8 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.65–7.54 (m, 2H), 7.53–7.46 (m, 2H), 6.18 (q, *J* = 12.1 Hz, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.28 (d, *J* = 10.2 Hz, 1H), 1.01 (s, 9H).

6.3.4.3.2. Preparation of α-amino acid derived isocyanates and coupling with 9-epi cinchona-based amines [309]





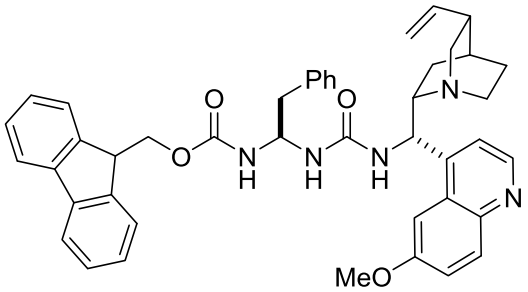
294–302

To a cooled solution of the corresponding *N*-protected α-amino acid (5 mmol, 1 equiv.) in dry THF (20 mL) were added isobutyl chloroformate (1 equiv., 0.65 mL, 5 mmol), and *N*-methylmorpholine (1 equiv., 0.6 mL, 5 mmol) and the mixture was stirred at –20 ºC for 20 min. Then, a suspension of NaN_3 (1.5 equiv., 0.48 g in 5 mL of

[309] Adapted from: Suresh Babu, V. V.; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006***, 71,* 7697–7705.

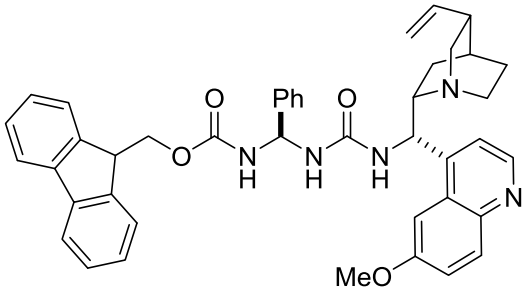
H_2O, 7.5 mmol) was added and the reaction mixture was stirred at the same temperature. After 30 min, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated under vacuum to give a yellow oil which was redissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 ºC under nitrogen for 1–2 h. The reaction was monitored by IR analysis until disappearance of the isocyanate band. After completion, the corresponding amine was added (0.7 equiv., 3.5 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluting with dichloromethane → dichloromethane/ methanol 80/20) or on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the desired catalysts **294–302**.

(9*H*-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-phenylethyl)carbamate 294



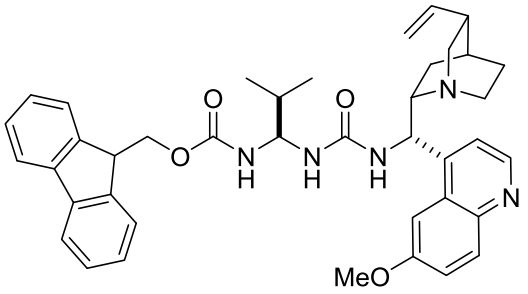
The title compound **294** was prepared from Fmoc-*L*-phenylalanine **467** (1.9 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.75 g, 2.5 mmol, 71%. $[\alpha]_D^{25}$= –12.2 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.72 (d, *J* = 4.5 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.57–7.52 (m, 2H), 7.48–7.39 (m, 3H), 7.38–7.33 (m, 4H), 7.26–7.23 (m, 4H), 7.14 (s, 2H), 6.08 (bs, 1H), 5.82–5.66 (m, 2H), 5.16 (bs, 2H), 5.03–4.96 (m, 3H), 4.41–4.33 (m, 2H), 4.22–4.12 (m, 1H), 3.97 (s, 3H), 3.27–3.04 (m, 5H) 2.77–2.68 (m, 2H), 2.34–2.27 (m, 1H), 1.69–1.62 (m, 1H), 1.45–1.36 (m, 1H), 1.00–0.93 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.8, 156.9, 155.7, 147.5, 144.8, 143.9, 143.8, 141.3, 141.2, 136.8, 131.7, 129.3, 128.5, 127.7, 127.1, 126.7, 125.0, 121.5, 120.0, 114.6, 102.0, 66.6, 60.8, 60.1, 55.7, 55.6, 47.1, 40.8, 40.2, 39.4, 27.8, 27.3, 26.01. UPLC-DAD-QTOF: $C_{44}H_{46}N_5O_4$ $[M+H]^+$ calcd: 708.3550, found: 708.3560.

(9*H*-Fluoren-9-yl)methyl ((*S*)-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)(phenyl)methyl)carbamate 295



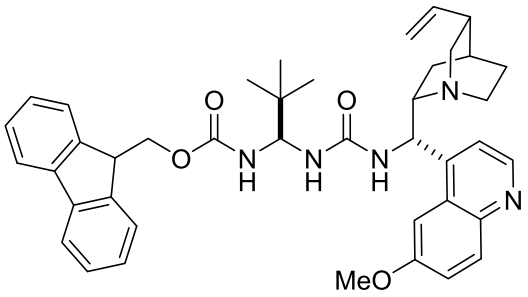
The title compound **295** was prepared from Fmoc-*L*-phenylglycine **468** (1.9 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.80 g, 2.6 mmol, 74%. $[\alpha]_D^{25}$= +18.1 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.81 (d, *J* = 4.5 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.93–7.55 (m, 4H), 7.53–7.03 (m, 12H), 5.86–5.70 (m, 1H), 5.15–4.84 (m, 4H), 4.48–4.37 (m, 1H), 4.00 (s, 3H), 3.68 (s, 1H), 3.51–3.15 (m, 3H), 3.05–2.65 (m, 3H), 2.43–2.20 (m, 1H), 1.77–1.54 (m, 3H), 1.49–1.38 (m, 1H), 0.89–0.71 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 161.0, 158.1, 147.4, 145.0, 141.3, 140.4, 132.3, 132.1, 130.7, 128.5, 127.6, 127.0, 126.4, 125.0, 121.8, 121.2, 120.9, 119.9, 114.5, 101.6, 70.5, 66.8, 66.4, 60.2, 59.1, 56.0, 55.6, 40.9, 39.4, 28.0, 27.2, 26.2. UPLC-DAD-QTOF: $C_{43}H_{44}N_5O_4$ $[M+H]^+$ calcd: 693.3315, found: 693.3322.

(9*H*-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate 296



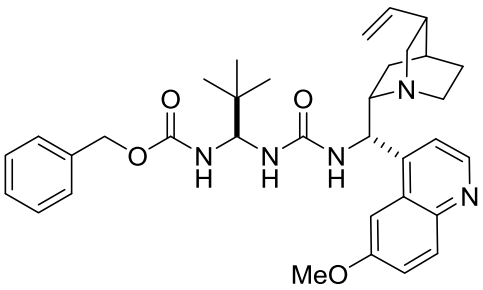
The title compound **296** was prepared from Fmoc-*L*-valine **469** (1.7 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.75 g, 2.7 mmol, 76%. $[\alpha]_D^{25}$= –35.8 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.66 (d, *J* = 3.8 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.86–7.69 (m, 3H), 7.79–7.73 (m, 2H), 7.49–7.20 (m, 7H), 6.47–6.28 (bs, 1H), 5.79–5.68 (m, 2H), 5.65–5.46 (bs, 1H), 5.40–5.19 (m, 1H), 5.03–4.95 (m, 2H), 4.80–4.57 (m, 1H), 4.48–4.26 (m, 2H), 4.19–4.15 (m, 1H), 3.96 (s, 3H), 3.28–3.20 (m, 2H), 3.17–3.02 (m, 1H), 2.75–2.70 (m, 2H), 2.60–2.54 (m, 1H), 2.38–2.22 (m, 1H), 1.66–1.58 (m, 3H), 1.53–1.35 (m, 1H), 0.87 (bs, 7H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.8, 157.4, 156.1, 147.5, 145.7, 144.7, 143.9, 143.7, 141.2, 131.6, 128.4, 127.7, 127.0, 125.0, 121.5, 119.9, 114.6, 102.0, 77.4, 77.0, 76.6, 66.7, 65.1, 60.1, 55.8, 55.6, 47.1, 40.9, 39.4, 31.9, 27.7, 27.4, 26.1, 18.7, 18.5. UPLC-DAD-QTOF: $C_{40}H_{46}N_5O_4$ $[M+H]^+$ calcd: 660.3550, found: 660.3557.

(9*H*-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 297



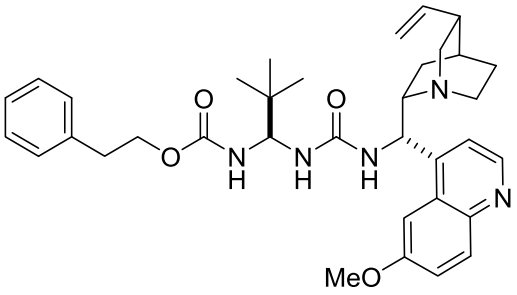
The title compound **297** was prepared from Fmoc-*L-tert*-leucine **470** (1.8 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.67 g, 2.5 mmol, 71%. $[\alpha]_D^{25}$= –16.2 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.63 (d, *J* = 4.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.83–7.72 (m, 3H), 7.62–7.55 (m, 2H), 7.47–7.31 (m, 7H), 6.41–6.26 (bs, 1H), 5.84–5.69 (m, 1H), 5.40–5.25 (m, 1H), 5.09–5.05 (bs, 1H), 5.07–4.95 (m, 3H), 4.47–4.41 (m, 1H), 4.35–4.30 (m, 1H), 4.26–4.11 (m, 1H), 3.97 (s, 3H), 3.32–3.24 (m, 2H), 3.17–3.02 (m, 1H), 2.81–2.69 (m, 2H), 2.36–2.25 (m, 1H), 1.66–157 (m, 3H), 1.48–1.38 (m, 1H), 0.92 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.2, 157.8, 156.8, 147.9, 146.3, 145.1, 144.3, 144.1, 141.8, 141.7, 132.00, 128.9, 128.1, 127.5, 125.5, 122.0, 120.4, 114.9, 102.5, 67.4, 67.1, 60.8, 56.8, 56.3, 56.0, 47.6, 41.4, 39.9, 35.8, 28.3, 27.9, 26.5, 25.8. UPLC-DAD-QTOF: $C_{41}H_{48}N_5O_4$ $[M+H]^+$ calcd: 674.3726, found: 674.3726.

Benzyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 298



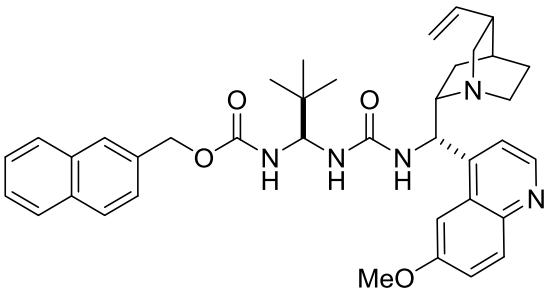
The title compound **298** was prepared from Cbz-*L-tert*-leucine **471** (1.3 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.48 g, 2.5 mmol, 72%. $[\alpha]_D^{25}$= –29.8 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.62 (d, *J* = 4.3, 1H), 8.01 (d, *J* = 9.2, 1H), 7.74 (d, *J* = 2.6, 1H), 7.39 (d, *J* = 2.7, 1H), 7.37–7.34 (m, 5H), 7.22 (d, *J* = 4.4, 1H), 6.48–6.35 (bs, 1H), 5.84–5.73 (m, 1H), 5.32–5.29 (m, 1H), 5.20 (d, *J* = 9.4, 1H), 5.08–5.05 (m, 2H), 5.04–4.95 (m, 3H), 3.97 (s, 3H), 3.30–3.23 (m, 2H), 3.12–2.99 (m, 1H), 2.80–2.70 (m, 2H), 2.34–2.27 (s, 1H), 1.68–1.64 (m, 2H), 1.62–1.56 (m, 1H), 1.45–1.38 (m, 1H), 0.82 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.2, 157.8, 156.8, 148.0, 146.5, 145.1, 141.9, 136.6, 132.6, 132.0, 129.0, 128.7, 128.6, 122.0, 119.6, 114.8, 102.5, 67.4, 67.5, 60.8, 57.0 56.4, 56.1, 41.4, 40.0, 35.8, 28.4, 27.9, 26.5, 25.7. UPLC-DAD-QTOF: $C_{34}H_{44}N_5O_4$ $[M+H]^+$ calcd: 586.3399, found: 586.3393.

Phenethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 299



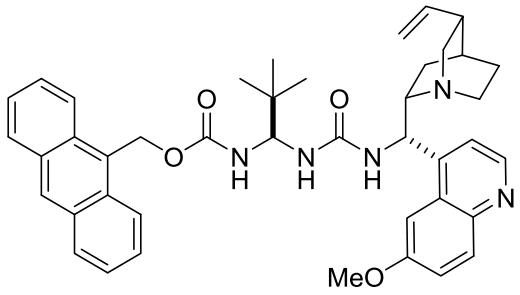
The title compound **299** was prepared from phenethoxycarbonyl-*L-tert*-leucine **472** (1.4 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 2.07 g, 2.7 mmol, 77%. $[\alpha]_D^{25}$= –25.1 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.67 (d, *J* = 4.5 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.40–7.09 (m, 7H), 6.31 (bs, 1H), 5.88–5.65 (m, 1H), 5.30 (bs, 1H), 5.05–4.90 (m, 3H), 4.32–4.12 (m, 1H), 3.95 (s, 3H), 3.32–3.16 (m, 2H), 3.16–3.04 (m, 1H), 2.94–2.82 (m, 2H), 2.82–2.64 (m, 2H), 2.33–2.22 (m, 1H), 1.68–1.50 (m, 3H), 1.49–1.37 (m, 1H), 0.97–0.71 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.8, 157.4, 156.4, 147.5, 145.9, 144.8, 141.6, 137.7, 131.6, 128.8, 128.5, 126.5, 121.6, 119.2, 114.4, 102.1, 66.5, 65.6, 60.4, 56.0, 55.6, 41.0, 39.6, 35.4, 35.4, 28.0, 27.5, 26.2, 25.3. UPLC-DAD-QTOF: $C_{35}H_{46}N_5O_4$ $[M+H]^+$ calcd: 600.3550, found: 600.3560.

Naphthalen-2-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 300



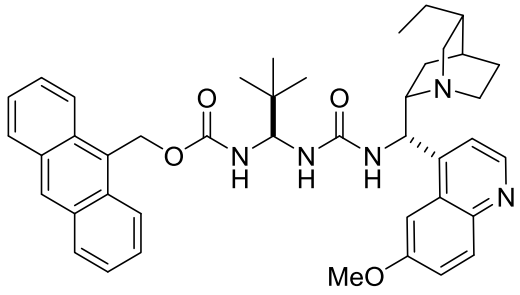
The title compound **300** was prepared from naphthlen-2-yl-methoxycarbonyl-*L-tert*-leucine **478** (1.6 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.73 g, 2.7 mmol, 78%. $[\alpha]_D^{25}$= –19.4 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.58 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.87–7.67 (m, 5H), 7.35 (dd, *J* = 9.2, 2.7 Hz, 4H), 7.24 (d, *J* = 4.6 Hz, 1H), 6.42–6.24 (bs, 1H), 5.85–5.66 (m, 1H), 5.33–5.22 (bs, 1H), 5.12–4.85 (m, 4H), 3.95 (s, 3H), 3.33–2.98 (m, 3H), 2.87–2.57 (m, 2H), 2.35–2.22 (m, 1H), 1.94–1.78 (m, 1H), 1.69–1.30 (m, 4H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.8, 157.3, 156.3, 147.1, 145.8, 144.5, 141.7, 133.2, 132.8, 131.2, 128.6, 128.0, 127.7, 127.4, 127.3, 125.9, 125.9, 125.7, 121.7, 118.5, 114.1, 102.2, 67.0, 66.0, 59.3, 55.9, 55.7, 41.1, 39.4, 35.7, 27.6, 27.3, 26.4, 25.0. UPLC-DAD-QTOF: $C_{38}H_{46}N_5O_4$ $[M+H]^+$ calcd: 636.3550, found: 636.3533.

Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 301



The title compound **301** was prepared from anthracen-9-ylmethoxycarbonyl-*L-tert*-leucine **479** (1.8 g, 5 mmol) and amine **458** (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.78 g, 2.6 mmol, 74%. $[\alpha]_D^{25}$= –2.7 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.61–8.22 (m, 4H), 8.12–7.93 (m, 3H), 7.82–7.67 (m, 1H), 7.61–7.32 (m, 5H), 7.19–7.11 (m, 1H), 6.51–6.32 (bs, 1H), 6.24–6.00 (m, 2H), 5.89–5.68 (m, 1H), 5.12–4.93 (m, 3H), 4.92–4.74 (bs, 1H), 3.96 (s, 3H), 3.39–2.98 (m, 3H), 2.97–2.56 (m, 2H), 2.46–2.22 (m, 2H), 1.92–1.54 (m, 4H), 1.45–1.29 (m, 1H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.7, 157.5, 156.5, 147.4, 144.5, 141.3, 131.4, 131.2, 130.8, 128.9, 128.5, 126.5, 125.0, 123.9, 121.6, 118.5, 114.4, 101.9, 66.7, 66.4, 59.2, 55.6, 55.2, 46.2, 40.7, 39.4, 35.2, 27.7, 27.2, 25.8, 25.1. UPLC-DAD-QTOF: $C_{42}H_{48}N_5O_4$ $[M+H]^+$ calcd: 686.3706, found: 686.3716.

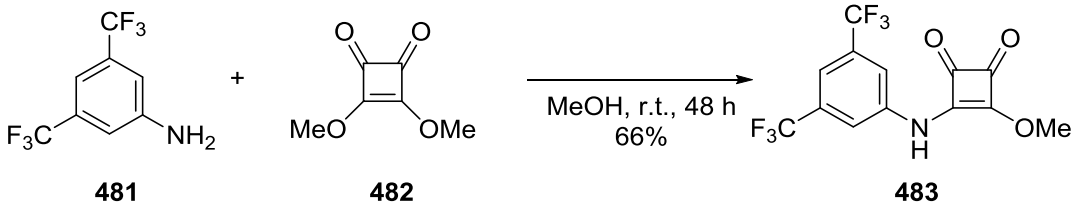
Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate 302



The title compound **302** was prepared from anthracen-9-ylmethoxycarbonyl-*L-tert*-leucine **479** (1.8 g, 5 mmol) and amine **459** (1.1 g, 3.5 mmol) according to the general procedure. White solid; yield: 1.88 g, 2.7 mmol, 78%. $[\alpha]_D^{25}$= –5.5 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.48–8.22 (m, 4H), 8.04–7.89 (m, 3H), 7.70 (s, 1H), 7.52–7.29 (m, 5H), 7.10 (d, *J* = 4.3, 1H), 6.47–6.30 (bs, 1H), 6.17–5.95 (m, 2H), 5.27–5.16 (bs, 1H), 5.12–4.94 (m, 2H), 3.94 (s, 3H), 3.30–3.07 (m, 2H), 3.05–2.86 (m, 1H), 2.72–2.33 (m, 3H), 1.65–1.33 (m, 5H), 0.90–0.67 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.7, 157.4, 156.4, 147.5, 144.6, 131.5, 131.3, 130.9, 129.0, 126.6, 126.4, 125.0, 124.0, 121.6, 102.0, 66.4, 60.3, 59.7, 57.6, 55.6, 40.9, 37.3, 35.4, 28.6, 27.4, 25.7, 25.2, 21.0, 14.2, 12.0. UPLC-DAD-QTOF: $C_{42}H_{50}N_5O_4$ $[M+H]^+$ calcd: 688.3863, found: 688.3867.

*6.3.4.4. Squaramide-based Brønsted base catalysts **87** and **324***

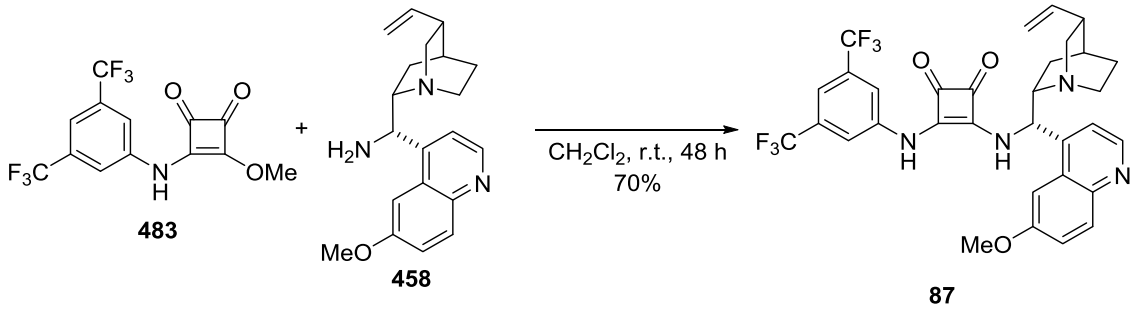
6.3.4.4.1. Preparation of squaric ester monoamine 483[310]



481 **482** **483**

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione **482** (1 equiv., 1.42 g, 10 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline **481** (1 equiv., 1.56 mL, 10 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vacuum to give title compound **483** as a white solid. Yield: 2.25 g, 6.6 mmol, 66%. m. p. 179–181 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

*6.3.4.4.2. Preparation of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione **87***[310]



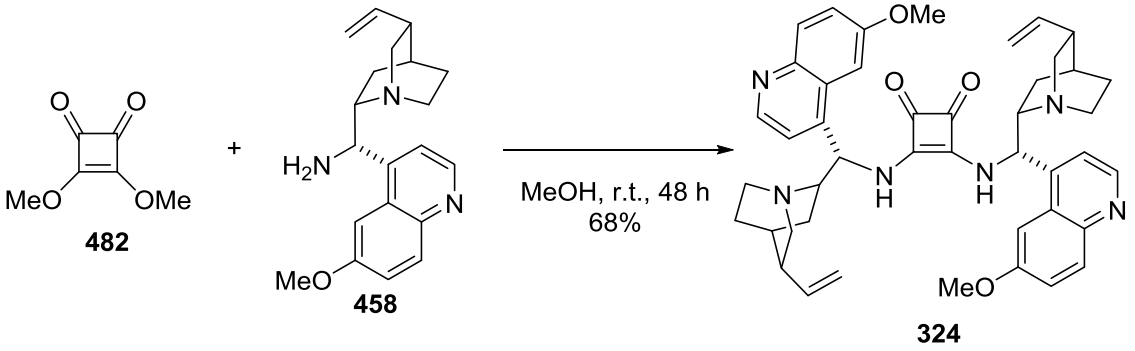
483 **458** **87**

To a solution of squaric ester monoamide **483** prepared as above (1 equiv., 2.25 g, 6.6 mmol) in dichloromethane (33 mL), 9-amino-(9-deoxy)*epi*quinine **458** (1 equiv., 2.13 g, 6.6 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford **87** as white solid. Yield: 2.91 g, 4.6 mmol, 70%. m. p. 224–225 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 9.88 (brs, 1H), 8.80 (d, J = 4.5 Hz, 1H), 8.36 (brs, 1H), 8.04–7.86 (m, 3H),

[310] Yang, W.; Du, D. M. *Org. Lett.*, **2010**, *12*, 5450–5453.

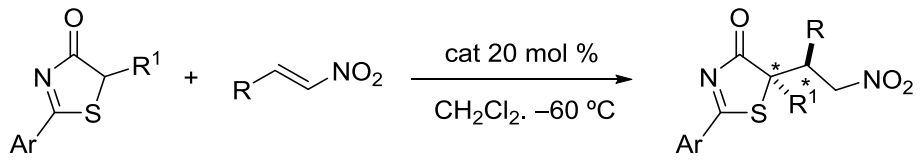
7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19–5.73 (m, 2H), 5.13–4.92 (m, 2H), 3.95 (s, 3H), 3.52–3.42 (m, 1H), 3.30–3.25 (m, 1H), 2.77–2.58 (m, 2H), 2.35–2.20 (m, 1H), 1.60–1.47 (m, 4H), 0.66 (m, 1H).

6.3.4.4.3. Prepararation of 3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl) amino)-4-(((1S)-(6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)amino) cyclobut-3-ene-1,2-dione ***324***[311]



Dimethyl squarate **482** (1 equiv., 0.5 g, 3.5 mmol) was added to a stirred solution of 9-amino-(9-deoxy)*epi*quinine **458** (2.5 equiv., 2.83 g, 8.75 mmol) in MeOH (35 mL) at room temperature. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford **324** as white solid. Yield: 1.25 g, 1.72 mmol, 68%. m. p. 266–269 ºC. All data were consistent with those previously reported.[1]H NMR (300 MHz, DMSO, 80 ºC), δ: 8.78 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 9.6 Hz, 1H), 7.80 (d, *J* = 2.3 Hz, 1H), 7.74–7.72 (m, 1H), 7.51 (d, *J* = 4.2 Hz, 1H), 7.44 (dd, *J* = 2.0, 9.6 Hz, 1H), 6.00–5.81 (m, 2H), 5.01–4.93 (m, 2H), 3.96 (s, 3H), 3.33–3.03 (m, 4H), 2.64–2.57 (m, 1H), 2.22 (m, 1H), 1.55–1.38 (m, 4H), 0.62–0.55 (m, 1H).

6.3.5. General procedure for the conjugate addition of 5*H*-thiazol-4-ones to nitroolefins



[311] Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Janga, H. B.; Song, C. E. *Chem. Commun*. **2009**, 7224–7226.

6.3.5.1. Asymmetric reaction

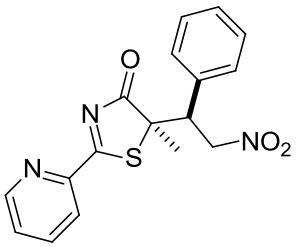
To a mixture of the corresponding thiazolone (1 equiv., 0.3 mmol) and the nitro olefin (2.0 equiv., 0.6 mmol), in dichloromethane (0.6 mL) cooled to –60 ºC the catalyst was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (monitored by ^{1}H NMR). The reaction mixture was directly purified by flash column chromatography on silica gel without previous work-up to afford the expected adducts.

6.3.5.2. Racemic reaction

Racemic compounds were prepared following the above procedure using TEA (20 mol %) as the catalyst at –20º C.

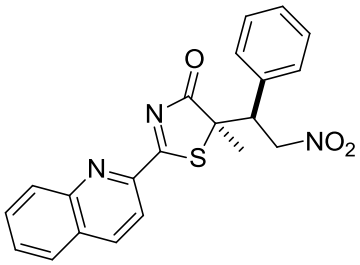
*6.3.5.3. Characterization data for compounds **286** and **306–308***

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(pyridin-2-yl)thiazol-4(5*H*)-one 286a



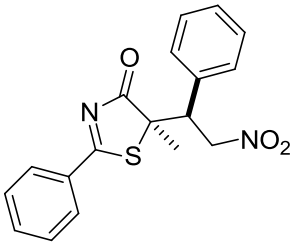
The title compound **286a** was prepared from 5-methyl-2-(pyridin-2-yl)thiazol-4-ol **285** (57.7 mg, 0.3 mmol) and nitrostyrene **282a** (89.4 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 81.9 mg, 0.24 mmol, 80%. $[\alpha]_D^{25}$= –58.2 (c = 1.00, 80% *ee*, CH_2Cl_2). m.p. 185–186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.73 (d, *J* = 4.2 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.35–7.28 (m, 2H), 7.28–7.14 (m, 3H), 5.15 (dd, *J* = 13.2, 4.7 Hz, 1H), 4.94 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 4.7 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.8, 194.1, 150.0, 148.8, 137.3, 134.2, 129.0, 128.7, 128.7, 128.5, 123.7, 75.9, 65.1, 50.2, 23.9. HRMS: $C_{17}H_{15}N_3O_3S$ $[M+H]^+$ calcd.: 342.0912, found: 342.0909. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 42.8 min (min.) and 47.2 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306a



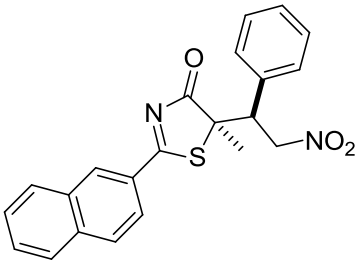
The title compound **306a** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and nitrostyrene **282a** (89.4 mg, 0.60 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 109 mg, 0.28 mmol, 93%. $[\alpha]_D^{25}$= –100.5 (c = 1.00, 98% *ee*, CH_2Cl_2). m.p. 156–158 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.38–8.16 (m, 3H), 7.95–7.78 (m, 2H), 7.76–7.64 (m, 1H), 7.43–7.32 (m, 2H), 7.31–7.12 (m, 3H), 5.19 (dd, *J* = 13.2, 4.6 Hz, 1H), 5.00 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.22 (dd, *J* = 10.7, 4.6 Hz, 1H), 1.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.9, 194.2, 148.7, 147.7, 137.4, 134.2, 134.2, 130.7, 130.4, 130.4, 129.5, 129.0, 128.7, 128.5, 127.8, 76.0, 65.1, 50.3, 24.0. UPLC-DAD-QTOF: $C_{21}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1065. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 45.5 min (min.) and 57.2 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-phenylthiazol-4(5*H*)-one 307a



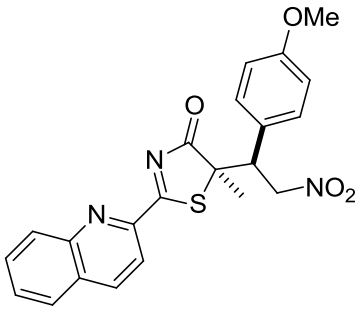
The title compound **307a** was prepared from 5-methyl-2-phenylthiazol-4-ol **304** (57.4 mg, 0.3 mmol) and nitrostyrene **282a** (89.4 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 65.9 mg, 0.2 mmol, 65%. $[\alpha]_D^{25}$= –1.7 (c = 1.00, 55% *ee*, CH_2Cl_2). m.p. 131–132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.06–7.91 (m, 2H), 7.71–7.61 (m, 1H), 7.54–7.42 (m, 2H), 7.37–7.20 (m, 5H), 5.18 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.94 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 4.6 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 193.9, 193.4, 135.4, 134.3, 131.6, 129.0, 129.0, 128.8, 128.8, 128.6, 75.8, 66.3, 50.2, 23.8. UPLC-DAD-QTOF: $C_{18}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 341.0960, found: 341.0957. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 20/80, flow rate = 0.5 mL/min, retention times: 18.1 min (min.) and 20.3 min (major.)).

(*R*)-5-Methyl-2-(naphthalen-2-yl)-5-((*S*)-2-nitro-1-phenylethyl)thiazol-4(5*H*)-one 308a



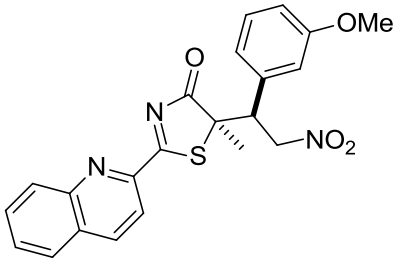
The title compound **308a** was prepared from 5-methyl-2-(naphthalen-2-yl)thiazol-4-ol **305** (86.9 mg, 0.3 mmol) and nitrostyrene **282a** (89.4 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 64 mg, 0.17 mmol, 55%. $[\alpha]_D^{25}$= –66.9 (c = 1.00, 68% *ee*, CH_2Cl_2). m.p. 85–86 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.59 (s, 1H), 8.05–7.85 (m, 4H), 7.71–7.54 (m, 2H), 7.40–7.15 (m, 5H), 5.21 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.97 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.21 (dd, *J* = 10.7, 4.6 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 193.7, 193.3, 136.7, 134.3, 132.4, 130.9, 129.8, 129.6, 129.1, 129.0, 128.8, 128.6, 128.0, 127.4, 124.0, 75.8, 66.4, 50.3, 23.9. UPLC-DAD-QTOF: $C_{22}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 391.1116, found: 391.1118. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 45.8 min (min.) and 55.8 min (major.)).

(*R*)-5-((*S*)-1-(4-Methoxyphenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306b



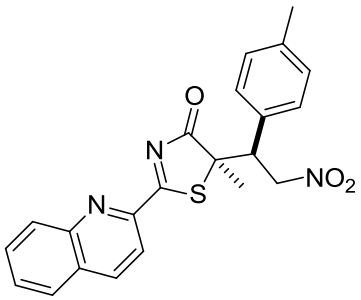
The title compound **306b** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 4-methoxy-nitrostyrene **282b** (107.5 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 97 mg, 0.23 mmol, 77%. $[\alpha]_D^{25}$= –216.6 (c = 1.00, 96% *ee*, CH_2Cl_2). m.p. 90–96 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.29–8.14 (m, 3H), 7.92–7.76 (m, 2H), 7.72–7.63 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 5.14 (dd, *J* = 13.0, 4.6 Hz, 1H), 4.93 (dd, *J* = 13.0, 10.9 Hz, 1H), 4.17 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.67 (s, 3H), 1.82 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.9, 194.3, 159.6, 148.6, 147.6, 137.3, 130.6, 130.3, 130.3, 130.1, 129.4, 127.8, 126.0, 119.5, 113.9, 76.2, 65.4, 55.0, 49.7, 24.0. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_4S$ $[M+H]^+$ calcd.: 422.1175, found: 422.1181. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, retention times: 43.4 min (min.) and 57.1 min (major.)).

(*R*)-5-((*S*)-1-(3-Methoxyphenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306c



The title compound **306c** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 3-methoxy-nitrostyrene **282c** (107.5 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 97 mg, 0.23 mmol, 77%. $[\alpha]_D^{25}$= –253.0 (c = 1.00, 94% *ee*, CH_2Cl_2). m.p. 80–81 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.31–8.13 (m, 3H), 7.92–7.75 (m, 2H), 7.72–7.62 (m, 1H), 7.18–7.07 (m, 1H), 6.98–6.86 (m, 2H), 6.80–6.70 (m, 1H), 5.17 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.97 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.68 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 194.2, 159.4, 148.7, 147.6, 137.4, 135.8, 135.8, 130.6, 130.3, 129.5, 129.4, 127.8, 121.0, 119.5, 115.0, 114.2, 76.0, 65.0, 55.1, 50.2, 24.1. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_4S$ $[M+H]^+$ calcd.: 422.1175, found: 422.1180. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, retention times: 31.3 min (min.) and 37.7 min (major.)).

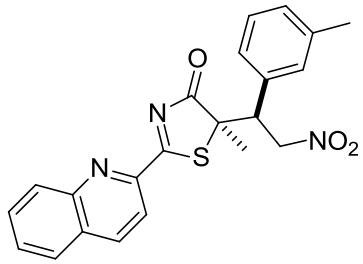
(*R*)-5-Methyl-5-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306d



The title compound **306d** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 4-methyl-nitrostyrene **282d** (98.0 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 109 mg, 0.27 mmol, 90%. $[\alpha]_D^{25}$= –236.4 (c = 1.00, 94% *ee*, CH_2Cl_2). m.p. 92–96 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.12 (m, 3H), 7.93–7.74 (m, 2H), 7.73–7.62 (m, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.18 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.97 (dd, *J* = 13.1, 10.8 Hz, 1H), 4.18 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.21 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.9, 194.3, 148.6, 147.6, 138.4, 137.3, 131.2, 130.6, 130.3, 130.2, 129.4, 129.2, 128.8, 127.7, 119.4, 76.1, 65.2, 49.9, 24.0, 20.9. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_3S$ $[M+H]^+$ calcd.: 406.1225, found: 406.1229. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H,

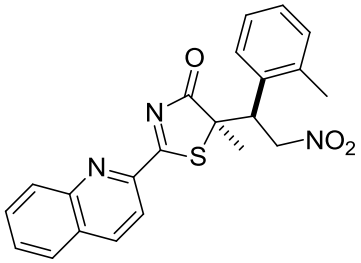
hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 46.0 min (min.) and 57.8 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-(*m*-tolyl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306e



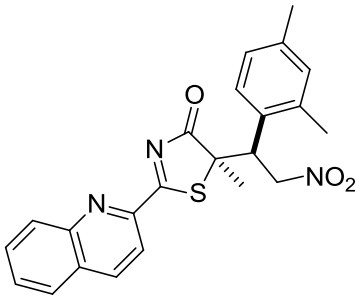
The title compound **306e** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 1-methyl-3-(2-nitrovinyl)benzene **282e** (97.9 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as yellow oil. Yield: 108 mg, 0.27 mmol, 90%. $[\alpha]_D^{25}$= –151.5 (c = 1.00, 91% *ee*, CH_2Cl_2). m.p. 76–80 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.09 (m, 3H), 7.89–7.72 (m, 2H), 7.70–7.60 (m, 1H), 7.15–6.90 (m, 4H), 5.12 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.92 (dd, *J* = 13.1, 10.7 Hz, 1H), 4.10 (dd, *J* = 10.7, 4.6 Hz, 1H), 2.18 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.9, 194.3, 148.7, 147.7, 138.2, 137.4, 134.2, 130.7, 130.4, 130.3, 130.0, 129.5, 129.4, 128.4, 127.8, 125.7, 119.5, 76.0, 65.1, 50.2, 24.0, 21.3. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_3S$ $[M+H]^+$ calcd.: 405.1147, found: 405.1150. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 85/15, flow rate = 0.5 mL/min, retention times: 31.6 min (min.) and 37.0 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-(*o*-tolyl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306f



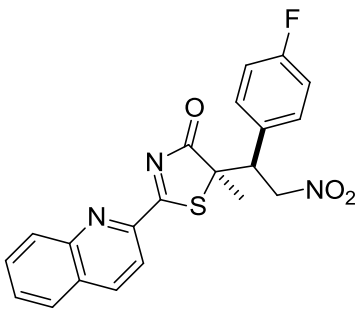
The title compound **306f** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 2-methyl-nitrostyrene **282f** (98.0 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 105 mg, 0.26 mmol, 86%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.19 (m, 3H), 7.99–7.79 (m, 3H), 7.78–7.65 (m, 1H), 7.60–7.49 (m, 1H), 7.20–6.94 (m, 3H), 5.22 (dd, *J* = 13.1, 4.3 Hz, 1H), 5.00–4.91 (m, 1H), 4.54 (dd, *J* = 11.0, 4.3 Hz, 1H), 2.47 (s, 3H), 1.90 (s, 3H).

(*R*)-5-((*S*)-1-(2,4-Dimethylphenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306g



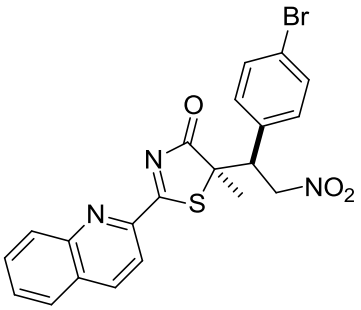
The title compound **306g** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 2,4-dimethyl-1-(2-nitrovinyl)benzene **282g** (100.6 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 90.5 mg, 0.22 mmol, 72%. $[\alpha]_D^{25}$= –108.8 (c = 1.00, 74% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.19 (m, 3H), 7.96–7.78 (m, 2H), 7.76–7.65 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.21 (dd, *J* = 13.0, 4.3 Hz, 1H), 4.92 (dd, *J* = 13.0, 11.0 Hz, 1H), 4.50 (dd, *J* = 11.0, 4.3 Hz, 1H), 2.42 (s, 3H), 2.21 (s, 3H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 194.4, 148.8, 147.8, 138.1, 137.8, 137.4, 132.4, 130.8, 130.7, 130.4, 130.4, 129.5, 127.8, 126.8, 125.5, 119.6, 76.9, 65.2, 43.5, 24.4, 20.9, 20.2. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 420.1382, found: 420.1378. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 29.8 min (min.) and 48.8 min (major.)).

(*R*)-5-((*S*)-1-(4-Fluorophenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306h



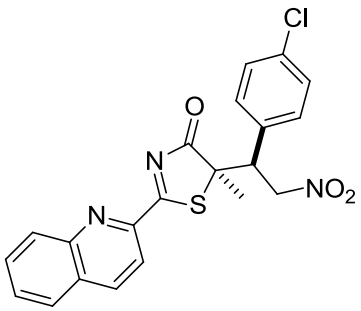
The title compound **306h** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 1-fluoro-4-(2-nitrovinyl)benzene **282h** (100.3 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 90 mg, 0.22 mmol, 74%. $[\alpha]_D^{25}$= –197.2 (c = 1.00, 90% *ee*, CH_2Cl_2). m.p. 76–79 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.31–8.13 (m, 3H), 7.91–7.78 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.39–7.28 (m, 2H), 6.94–6.84 (m, 2H), 5.14 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.94 (dd, *J* = 13.1, 11.0 Hz, 1H), 4.22 (dd, *J* = 11.0, 4.6 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 194.1, 164.3, 161.0, 148.4, 147.6, 137.4, 130.8, 130.7, 130.3, 129.5, 127.8, 119.4, 115.6, 115.4, 76.1, 65.0, 49.6, 24.2. UPLC-DAD-QTOF: $C_{21}H_{17}FN_3O_3S$ $[M+H]^+$ calcd.: 410.0975, found: 410.0968. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times: 16.3 min (min.) and 22.8 min (major.)).

(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306i



The title compound **306i** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 4-bromo-nitrostyrene **282i** (136.8 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) and finally crystallized from hexane/diisopropyl ether to give the title compound as a yellow solid. Yield: 111 mg, 0.24 mmol, 79%. $[\alpha]_D^{25}$= –270.9 (c = 1.00, 99% *ee*, CH_2Cl_2). m.p. 78–82 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.28–8.14 (m, 3H), 7.88–7.75 (m, 2H), 7.71–7.61 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.16 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.94 (dd, *J* = 13.2, 11.0 Hz, 1H), 4.19 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.9, 193.9, 148.3, 147.6, 137.3, 133.1, 131.6, 130.6, 130.6, 130.2, 130.2, 129.4, 127.7, 122.9, 119.4, 75.8, 64.7, 49.7, 24.2. UPLC-DAD-QTOF: $C_{21}H_{17}BrN_3O_3S$ $[M+H]^+$ calcd.: 470.0174, found: 470.0170. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, retention times: 36.8 min (min.) and 46.5 min (major.)).

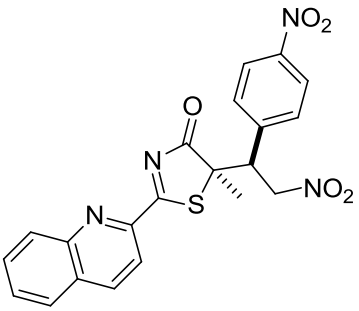
(*R*)-5-((*S*)-1-(4-Chlorophenyl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306j



The title compound **306j** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 1-chloro-4-(2-nitrovinyl)benzene **282j** (110.2 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 96 mg, 0.23 mmol, 75%. $[\alpha]_D^{25}$= –214.7 (c = 1.00, 92% *ee*, CH_2Cl_2). m.p. 72–76 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.33–8.11 (m, 3H), 7.93–7.76 (m, 2H), 7.74–7.64 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.14 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.94 (dd, *J* = 13.2, 11.0 Hz, 1H), 4.20 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 194.0, 148.4, 147.6, 137.4, 134.7, 132.6, 130.7, 130.3, 130.3, 130.3, 129.5, 128.7, 127.8, 119.5, 75.9, 64.8, 49.7, 24.2. UPLC-DAD-QTOF: $C_{21}H_{17}ClN_3O_3S$ $[M+H]^+$ calcd.: 426.0679, found: 426.0681. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H,

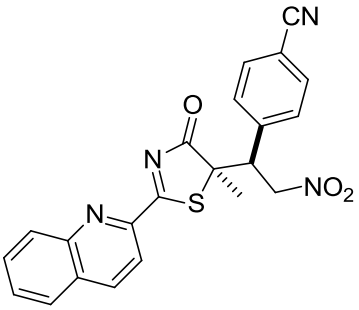
hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times: 18.5 min (min.) and 23.8 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306k



The title compound **306k** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 1-nitro-4-(2-nitrovinyl)benzene **282k** (116.5 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 89 mg, 0.20 mmol, 68%. $[\alpha]_D^{25}$= –180.3 (c = 1.00, 89% *ee*, CH_2Cl_2). m.p. 102–105 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.31 (d, *J* = 8.4 Hz, 1H), 8.20 (dd, *J* = 11.2, 8.8 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.94 – 7.80 (m, 2H), 7.78–7.68 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 5.18 (dd, *J* = 13.4, 4.5 Hz, 1H), 5.01 (dd, *J* = 13.4, 11.0 Hz, 1H), 4.36 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.2, 193.7, 148.2, 148.0, 147.8, 141.2, 137.6, 130.9, 130.5, 130.4, 130.2, 129.8, 127.9, 123.7, 119.6, 75.7, 64.4, 50.0, 24.7. UPLC-DAD-QTOF: $C_{21}H_{17}N_4O_5S$ $[M+H]^+$ calcd.: 437.0920, found: 437.0912. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 26.3 min (min.) and 37.0 min (major.)).

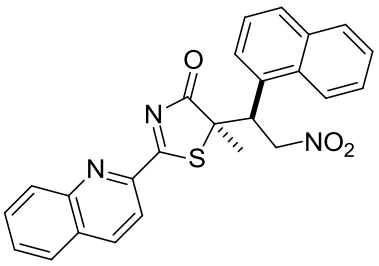
4-((*S*)-1-((*R*)-5-Methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)-2-nitroethyl) benzonitrile 306l



The title compound **306l** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 4-(2-nitrovinyl)benzonitrile **282l** (104.5 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 92 mg, 0.22 mmol, 72%. $[\alpha]_D^{25}$= –298.6 (c = 1.00, 96% *ee*, CH_2Cl_2). m.p. 171–173 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.34–8.13 (m, 3H), 7.95–7.79 (m, 2H), 7.71 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.57–7.44 (m, 4H), 5.16 (dd, *J* = 13.4, 4.5 Hz, 1H), 4.98 (dd, *J* = 13.4, 11.0 Hz, 1H), 4.29 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.1, 193.7, 148.2, 147.7, 139.3, 137.6, 132.2, 130.9, 130.3, 129.9, 129.7, 127.9, 119.5, 118.0, 112.8, 75.6, 64.4, 50.2, 24.5. UPLC-DAD-QTOF: $C_{22}H_{17}N_4O_3S$ $[M+H]^+$ calcd.: 417.1021, found: 417.1020. The enantiomeric purity of the major diastereomer was determined by HPLC

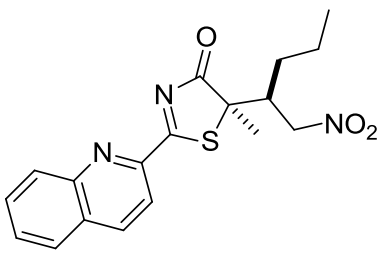
analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate = 1.0 mL/min, retention times: 21.9 min (min.) and 28.6 min (major.)).

(*R*)-5-Methyl-5-((*S*)-1-(naphthalen-1-yl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306m



The title compound **306m** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 2-(2-nitrovinyl)naphthalene **282m** (119.5 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to give the title compound as a yellow solid. Yield: 108 mg, 0.25 mmol, 82%. $[\alpha]_D^{25}$= –298.7 (c = 1.00, 94% *ee*, CH_2Cl_2). m.p. 141–143 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.23–8.04 (m, 3H), 7.86–7.59 (m, 7H), 7.56–7.45 (m, 1H), 7.44–7.32 (m, 2H), 5.29 (dd, *J*= 13.2, 4.6 Hz, 1H), 5.12 (dd, *J* = 13.2, 10.8 Hz, 1H), 4.40 (dd, *J* = 10.8, 4.6 Hz, 1H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 194.2, 148.5, 147.6, 137.3, 133.1, 132.8, 131.8, 131.8, 130.6, 130.3, 129.4, 128.8, 128.3, 128.1, 127.7, 127.4, 126.4, 126.2, 126.2, 119.4, 76.0, 65.2, 50.2, 24.2. UPLC-DAD-QTOF: $C_{25}H_{20}N_3O_3S$ $[M+H]^+$ calcd.: 442.1225, found: 442.1230. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 54.5 min (min.) and 59.5 min (major.)).

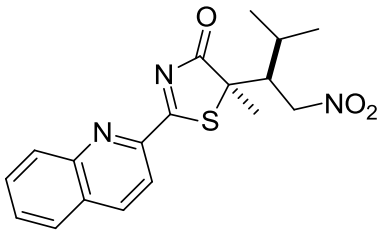
(*R*)-5-Methyl-5-((S)-1-nitropentan-2-yl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306n



The title compound **306n** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 1-nitropent-1-ene **282n** (69.1 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow oil. Yield: 45 mg, 0.13 mmol, 42%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.46–8.33 (m, 2H), 8.26–8.20 (m, 1H), 7.96–7.90 (m, 1H), 7.87–7.80 (m, 1H), 7.75–7.67 (m, 1H), 4.72 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.58 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.03–2.90 (m, 1H), 1.74 (s, 3H), 1.56–1.42 (m, 2H), 1.33–1.16 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.7, 195.9, 149.0, 147.8, 137.5, 130.8, 130.5, 129.5, 127.8, 119.7, 117.0, 75.9, 66.0, 45.1, 32.1, 24.5, 20.3, 13.8. UPLC-DAD-QTOF: $C_{18}H_{20}N_3O_3S$ $[M+H]^+$ calcd.:358.1225, found: 358.1230. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak

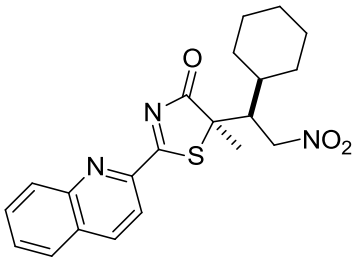
IC, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 49.7 min (major.) and 52.4 min (min.)).

(*R*)-5-Methyl-5-((S)-3-methyl-1-nitrobutan-2-yl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306o



The title compound **306o** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and 3-methyl-1-nitrobut-1-ene **282o** (69.1 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow oil. Yield: 50 mg, 0.14 mmol, 47%. $[\alpha]_D^{25}$= –4.3 (c = 1.00, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.49–8.30 (m, 2H), 8.28–8.20 (m, 1H), 7.96–7.89 (m, 1H), 7.88–7.79 (m, 1H), 7.75–7.67 (m, 1H), 4.72 (qd, *J* = 14.1, 5.0 Hz, 2H), 2.98 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.43–2.37 (m, 1H), 1.74 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.3, 195.8, 149.1, 147.8, 137.5, 130.7, 130.5, 129.5, 127.8, 119.6, 114.7, 74.1, 65.8, 49.6, 30.3, 26.3, 22.9, 19.4. UPLC-DAD-QTOF: $C_{18}H_{20}N_3O_3S$ $[M+H]^+$ calcd.:358.1225, found: 358.1226. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times: 21.6 min (major.) and 23.0 min (min.)).

(*R*)-5-((S)-1-Cyclohexyl-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one 306p



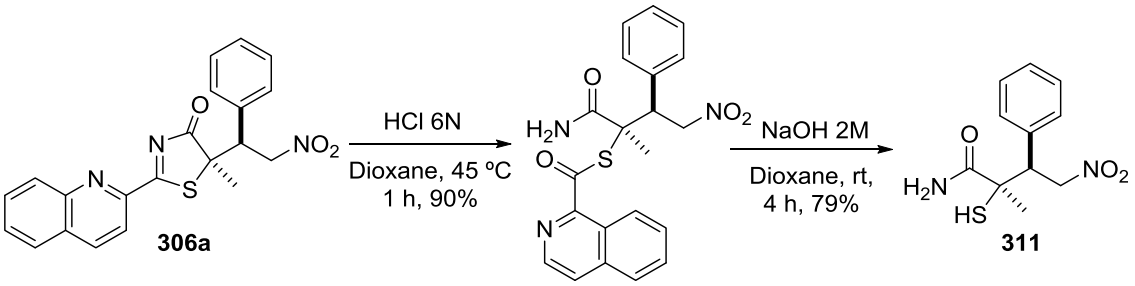
The title compound **306p** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol **303** (72.7 mg, 0.3 mmol) and (2-nitrovinyl)cyclohexane **282p** (93.1 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow oil. Yield: 48 mg, 0.12 mmol, 40%. $[\alpha]_D^{25}$= –21.1 (c = 1.00, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.50–8.34 (m, 2H), 8.30–8.17 (m, 1H), 8.01–7.91 (m, 1H), 7.90–7.80 (m, 1H), 7.75–7.68 (m, 1H), 4.84–4.64 (m, 2H), 3.04–2.90 (m, 1H), 1.73 (s, 3H), 1.68–1.45 (m, 6H), 1.30–0.85 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.1, 195.7, 149.1, 147.8, 137.5, 130.7, 130.5, 129.5, 127.8, 119.7, 117.7, 74.1, 65.7, 49.2, 40.5, 33.1, 30.0, 29.7, 26.5, 26.3, 25.8. UPLC-DAD-QTOF: $C_{21}H_{24}N_3O_3S$ $[M+H]^+$ calcd.:398.1538, found: 398.1535. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC,

hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, retention times: 51.4 min (major.) and 57.4 min (min.)).

6.3.6. Elaboration of adducts

*6.3.6.1. Hydrolysis of adduct **306a**[312]*

Synthesis of (*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide 311



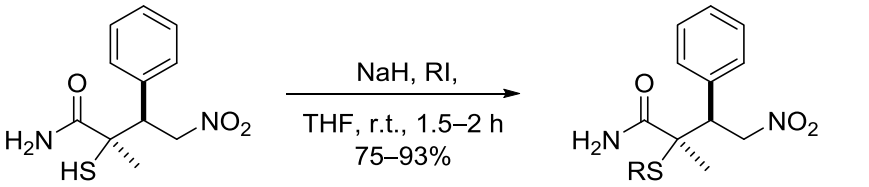
(*R*)-5-methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one **306a** (1 equiv., 361.1 mg, 0.92 mmol) was dissolved in a mixture of dioxane (5 mL) and HCl 6N (12 equiv., 1.84 mL, 11.04 mmol). The resulting solution was heated at 45 °C for 1 h. After this period the reaction mixture was cooled at 0 ºC and treated with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aqueous phase with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography on silica gel (eluting with ethyl acetate/hexane 1/1). Yellow oil, yield: 335.4 mg, 0.82 mmol, 90%.

Then, to a solution of *S*-((*2R,3S*)-1-amino-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl (1 equiv., 335 mg, 0.82 mmol) in 1.3 mL of dioxane at 0 °C was added dropwise a 2 M aqueous solution of NaOH (2.5 equiv.,1.0 mL, 2.05 mmol). The resulting mixture was stirred at room temperature for 4 h and afterwards the reaction was quenched with 2 M aq. $NaHSO_4$ (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with an aqueous solution of saturated $NaHCO_3$ (20 mL), and brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the pure product **311** as a yellow oil, which was used as such in the next step. Yield: 164.7 mg, 0.65 mmol, 79%. $[\alpha]_D^{25}$= +2.9 (c = 1.00, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35–7.28 (m, 5H), 6.42–6.31 (m, 1H), 5.52–5.41 (m, 1H), 5.14–5.05

[312] Adapted from: a) Aleman, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jorgensen, K. A. *Chem Eur. J.* **2008**, *14*, 10958–10966. b) ref. 220a, page 108.

(m, 2H), 4.22 (dd, J = 8.8, 6.1 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 175.3, 135.4, 129.1, 128.6, 128.4, 77.0, 54.0, 52.0, 26.9. UPLC-DAD-QTOF: $C_{11}H_{15}N_2O_3S$ $[M+H]^+$ calcd.: 254.0725, found: 254.0721. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 33.2 min (major.) and 48.6 min (min.)).

*6.3.6.2. S-Alkylation of α-mercapto carboxylic acid derivative **311***



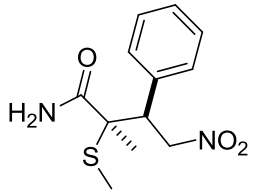
311

312 R = Me 90%
313 R = CH_2=$CHCH_2$ 93%
314 R = 2-NaphCH_2 82%
315 R = *n*-Hex 75%

General procedure

To a solution of **311** (1 equiv., 0.24 mmol) in dry THF (1mL) under argon atmosphere was added NaH 60% in mineral oil (1.2 equiv., 11 mg, 0.29 mmol). The mixture was cooled to 0 ºC and then the corresponding alkyl halide (1.2 equiv., 0.29 mmol) was added. The mixture was stirred at room temperature for 2 h and then quenched with 2 M aq. $NaHSO_4$ (5 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was separated and washed with an aqueous solution of saturated $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluting with ethyl acetate/hexane 1/1).

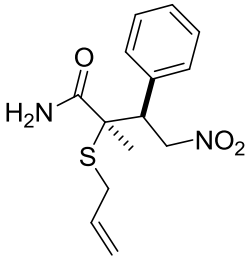
(2*R*,3*S*)-2-Methyl-2-(methylthio)-4-nitro-3-phenylbutanamide 312



The title compound **312** was prepared from (2*R*,3*S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide **311** (61 mg, 0.24 mmol) and MeI (18 μL, 0.29 mmol) according to the general procedure. Yellow oil, yield: 58.2 mg, 0.22 mmol, 90%. $[\alpha]_D^{25}$= –14.2 (c = 1.00, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.27 (m, 5H), 6.69–6.49 (m, 1H), 5.56–5.36 (m, 1H), 5.13–5.00 (m, 2H), 3.99 (dd, J = 10.2, 4.8 Hz, 1H), 2.10 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.4, 134.99,

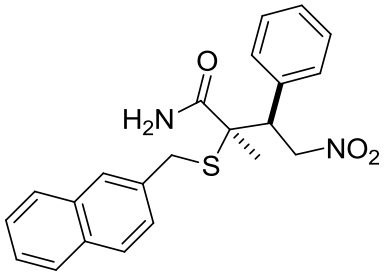
130.0, 128.5, 127.9, 94.6, 77.0, 55.7, 51.2, 21.4, 12.4. UPLC-DAD-QTOF: $C_{12}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 269.0882, found: 269.0885.

(2*R*,3*S*)-2-(Allylthio)-2-methyl-4-nitro-3-phenylbutanamide 313



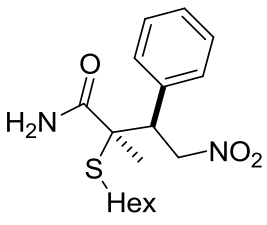
The title compound **313** was prepared from (2*R*,3*S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide **311** (61 mg, 0.24 mmol) and allyl iodide (27 μL, 0.29 mmol) according to the general procedure. Yellow oil, yield: 65.7 mg, 0.22 mmol, 93%. $[\alpha]_D^{25}$= –2.2 (c = 0.5, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36–7.27 (m, 5H), 6.63–6.48 (m, 1H), 5.56–5.41 (m, 1H), 5.29–4.98 (m, 4H), 3.99 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.34–3.11 (m, 2H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.2, 134.9, 132.8, 129.4, 128.6, 128.6, 119.0, 77.0, 56.6, 51.8, 33.2, 22.4. UPLC-DAD-QTOF: $C_{14}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 295.1116, found: 295.1118.

(2*R*,3*S*)-2-Methyl-2-((naphthalen-2-ylmethyl)thio)-4-nitro-3-phenylbutanamide 314



The title compound **314** was prepared from (2*R*,3*S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide **311** (61 mg, 0.24 mmol) and 2-(bromomethyl)naphthalene (63.7 mg, 0.29 mmol) according to the general procedure. Yellow oil, yield: 77.6 mg, 0.20 mmol, 82%. $[\alpha]_D^{25}$= +2.5 (c = 0.65, 93% *ee*, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.94–7.63 (m, 4H), 7.57–7.14 (m, 8H), 6.56 (bs, 1H), 5.69 (bs, 1H), 5.14–4.99 (m, 2H), 4.08–3.81 (m, 3H), 1.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.2, 134.9, 133.4, 133.3, 132.7, 129.4, 128.7, 128.6, 128.6, 127.8, 127.7, 127.7, 126.9, 126.5, 126.2, 77.0, 57.0, 51.7, 34.9, 22.6. UPLC-DAD-QTOF: $C_{22}H_{22}N_2O_3S$ $[M+H]^+$ calcd.: 395,1429, found: 395,1425.

(2*R*,3*S*)-2-(Hexylthio)-2-methyl-4-nitro-3-phenylbutanamide 315

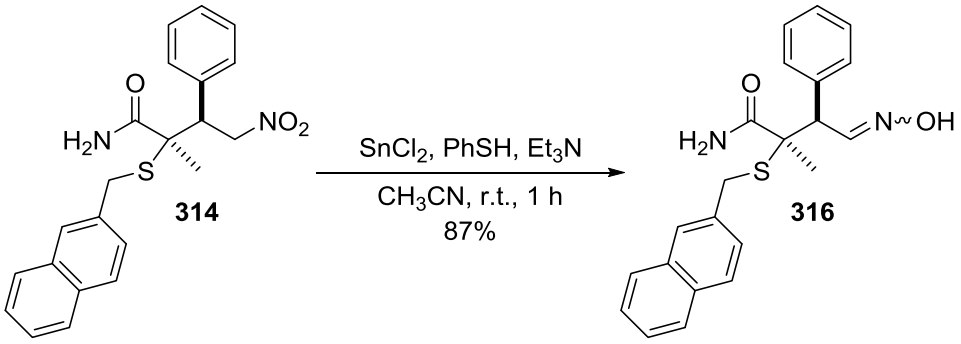


The title compound **315** was prepared from (2*R*,3*S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide **311** (61 mg, 0.24 mmol) and 1-iodohexane (43 μL, 0.29 mmol) according to the general procedure. Yellow oil, yield: 61.2 mg, 0.18 mmol, 75%. $[\alpha]_D^{25}$= +6.6 (c = 0.65, 93% *ee*, CH_2Cl_2).^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.49–7.16 (m, 5H), 6.59 (bs, 1H), 5.54 (bs, 1H), 5.14–4.95 (m, 2H), 3.97 (dd, *J* = 10.1, 4.8 Hz, 1H), 2.68–2.39 (m, 2H), 1.73–1.50 (m, 4H), 1.41–1.16 (m, 4H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.6, 135.0, 129.3, 128.4, 128.4, 77.0, 56.2,

51.7, 31.3, 29.7, 28.9, 28.7, 22.4, 22.4, 14.0. UPLC-DAD-QTOF: $C_{17}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 339,1742, found: 339,1746.

6.3.6.3. Transformation of the nitro group into oxime and nitrile groups

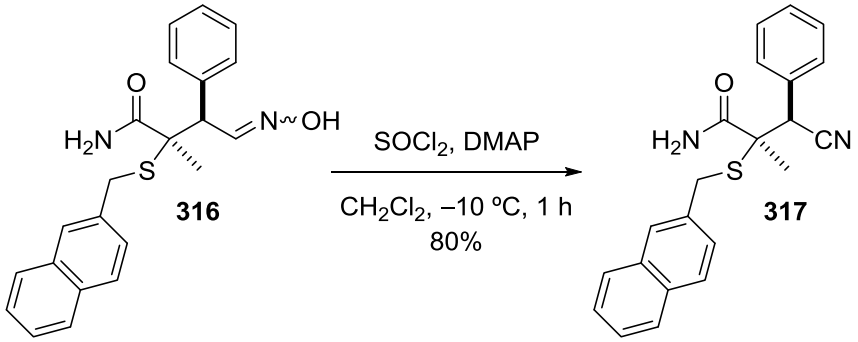
Synthesis of (2*R*, 3*S*)-4-(hydroxyimino)-2-((naphthalen-2-ylmethyl) thio)-3-phenylbutanamide 316[313]



To a solution of anhydrous $SnCl_2$ (1.5 equiv., 96.7 mg, 0.51 mmol) in 0.7 mL of CH_3CN, magnetically stirred at room temperature, PhSH (4.5 equiv., 0.16 mL, 1.53 mmol) and Et_3N (5 equiv., 0.24 mL, 1.7 mmol) were added. Then, a solution of 2-((naphthalen-2-ylmethyl)thio)-4-nitro-3-phenylbutanamide **314** (1 equiv., 129 mg, 0.34 mmol) in 1.4 mL CH_3CN was added and the resulting mixture was stirred at room temperature. After 1 h, the reaction mixture was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to give the title compound **316** as a colorless oil and as a E/Z mixture (3:1, not assigned). Yield: 91 mg, 0.24 mmol, 71%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00 (d, *J* = 8.3 Hz, 1H) (Major), 7.85–7.63 (m, 5H), 7.53–7.25 (m, 6H), 6.88 (bs, 1H), 6.57 (bs, 1H) (Major), 6.39 (bs, 1H) (Minor), 4.94 (d, *J* = 7.9 Hz, 1H) (Minor), 4.13 (d, *J* = 8.3 Hz, 1H) (Major), 3.87 (dd, *J* = 30.7, 11.5 Hz, 2H), 1.71 (s, 3H) (Minor), 1.68 (s, 3H) (Major). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 175.6 (Major), 175.5 (Minor), 149.7 (Major), 149.1 (Minor), 136.0, 133.7, 133.3, 132.5, 129.7, 128.4, 128.2, 128.2, 127.8, 127.6, 127.6, 127.0, 126.2, 126.0, 57.9 (Major), 57.6 (Minor), 53.6 (Major), 47.9 (Minor), 34.6 (Major), 31.5 (Minor), 22.6 (Minor), 21.8 (Major). UPLC-DAD-QTOF: $C_{22}H_{23}N_2O_2S$ $[M+H]^+$ calcd.: 379.1480 , found: 379.1490.

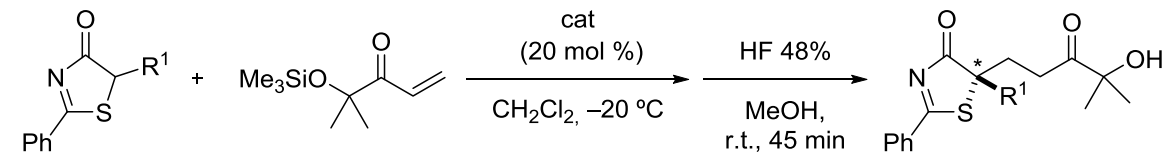
[313] See ref. 242, page 125.

Synthesis of (2*R*,3*S*)-3-cyano-2-methyl-2-((naphthalen-2-ylmethyl)thio)-3-phenylpropanamide 317[314]



Thionyl chloride (1.1 equiv., 19 μL, 0.26 mmol) was added to a stirred solution of 4-dimethylaminopyridine (1.25 equiv., 36.6 mg, 0.3 mmol) in dichloromethane (1.2 mL) at –10 ºC. The mixture containing a precipitate was stirred for 5 min. Then the aldoxime **316** (1 equiv., 91 mg, 0.24 mmol) was added and the mixture was stirred for 5 min. After, 4-dimethylaminopyridine (1.25 equiv., 36.6 mg, 0.3 mmol) was added at –10ºC. The mixture was stirred at room temperature for 30 min more. The reaction was quenched with water (2 mL) and extracted with dichloromethane (3 x 5 mL). The organic layers were washed with HCl 1M (10 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20 → 50/50) to afford **317** as yellow oil. Yield: 69.2 mg, 0.19 mmol, 80%. $[\alpha]_D^{25}$= +39.8 (c = 0.30, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.91–7.60 (m, 5H), 7.45–7.33 (m, 7H), 6.75 (bs, 1H), 6.16 (bs, 1H), 4.61 (s, 1H), 4.00–3.77 (m, 2H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.0, 133.2, 132.6, 131.0, 129.7, 128.9, 128.6, 128.4, 128.2, 127.8, 127.6, 127.2, 126.8, 126.4, 126.1, 118.8, 56.0, 45.7, 35.1, 23.4. UPLC-DAD-QTOF: $C_{22}H_{21}N_2OS$ $[M+H]^+$ calcd.: 361.1375, found: 361.1389.

6.3.7. General procedure for the conjugate addition of 5*H*-thiazol-4-ones to α'-oxy enones



304, 321, 452, 453 **325** **323, 326, 331, 332**

[314] See ref. 243, page 125.

6.3.7.1. Asymmetric reaction

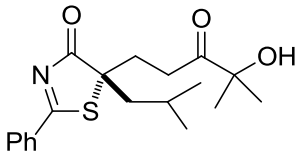
To a mixture of the corresponding thiazolone (1 equiv., 0.3 mmol) and enone **325** (1.5 equiv., 84 mg, 0.45 mmol), in dichloromethane (0.9 mL) at the corresponding temperature, the catalyst was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (monitored by ^{1}H NMR). Then, 3 mL of methanol and 0.6 mL of HF 48% were added at the corresponding temperature and the mixture was warmed to room temperature and stirred for 45 min. The reaction was treated at 0 ºC with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with CH_2Cl_2 (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20).

6.3.7.2. Racemic reaction

Racemic reactions were conducted following the procedure for the asymmetric version using 4-hydroxy-4-methylpent-1-en-3-one (3 equiv., 101 mg, 0.9 mmol), but at 0 ºC and by using TEA (20 mol %) as catalyst.

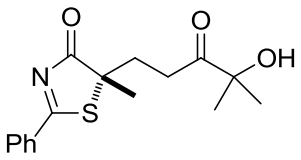
*6.3.7.3. Characterization data for compounds **323, 328–330***

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-2-phenylthiazol-4(5*H*)-one 323



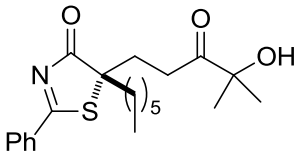
The title compound **323** was prepared from 5-isobutyl-2-phenylthiazol-4(5*H*)-one **321** (70.0 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound **323** as a colorless oil. Yield: 77.1 mg, 0.22 mmol, 74%. $[\alpha]_D^{25}$= –11.4 (c = 1.00, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.19–8.11 (m, 2H), 7.73–7.63 (m, 1H), 7.57–7.48 (m, 2H), 3.50 (s, 1H), 2.55–2.44 (m, 2H), 2.43–2.31 (m, 1H), 2.31–2.17 (m, 1H), 2.12–1.99 (m, 1H), 1.96–1.85 (m, 1H), 1.86–1.70 (m, 1H), 1.29 (s, 3H), 1.24 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 213.0, 195.5, 195.4, 135.2, 132.0, 129.1, 128.9, 76.4, 68.0, 47.9, 32.6, 30.6, 26.5, 26.5, 25.9, 24.5, 22.9. UPLC-DAD-QTOF: $C_{19}H_{26}NO_3S$ $[M+H]^+$ calcd.: 348.1633, found: 348.1638. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, retention times: 14.0 min (min.) and 16.4 min (major.)).

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5*H*)-one 326



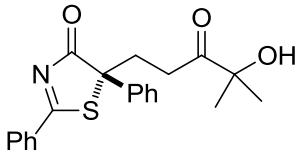
The title compound **326** was prepared from 5-Methyl-2-phenylthiazol-4-ol **304** (57.7 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound **326** as a colorless oil. Yield: 70.5 mg, 0.23 mmol, 77%. $[\alpha]_D^{25}$= –14.7 (c = 1.00, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.23–8.01 (m, 2H), 7.78–7.62 (m, 1H), 7.62–7.46 (m, 1H), 3.48 (s, 1H), 2.60–2.47 (m, 2H), 2.39–2.28 (m, 2H), 1.74 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.8, 195.1, 194.9, 135.3, 132.0, 129.1, 128.9, 76.4, 63.6, 32.9, 31.4, 26.7, 26.6, 26.5. UPLC-DAD-QTOF: $C_{16}H_{20}NO_3S$ $[M+H]^+$ calcd.: 306.1164, found: 306.1172. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, retention times: 21.6 min (min.) and 23.5 min (major.)).

(*S*)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenylthiazol-4(5*H*)-one 331



The title compound **331** was prepared from 5-hexyl-2-phenylthiazol-4(5*H*)-one **452** (78.4 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound **331** as a colorless oil. Yield: 80.0 mg, 0.21 mmol, 71%. $[\alpha]_D^{25}$= +2.0 (c = 1.00, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.20–8.09 (m, 2H), 7.74–7.63 (m, 1H), 7.57–7.48 (m, 2H), 3.51 (s, 1H), 2.59–2.48 (m, 2H), 2.47–2.33 (m, 1H), 2.33–2.21 (m, 1H), 2.05–1.91 (m, 2H), 1.29 (s, 3H), 1.27–1.14 (m, 11H), 0.82 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 213.0, 195.5, 194.9, 135.2, 132.0, 129.0, 128.9, 76.4, 69.1, 39.5, 31.8, 31.4, 31.0, 29.0, 26.5, 26.5, 25.0, 22.4, 13.9. UPLC-DAD-QTOF: $C_{21}H_{30}NO_3S$ $[M+H]^+$ calcd.: 376.1946, found: 376.1947. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, retention times: 24.7 min (major.) and 27.0 min (min.)).

(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-2,5-diphenylthiazol-4(5*H*)-one 332



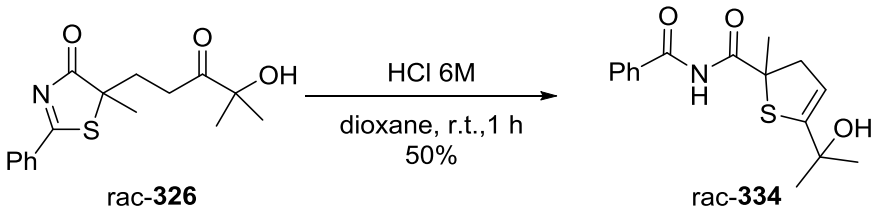
The title compound **332** was prepared from 2,5-diphenylthiazol-4-ol **453** (76.0 mg, 0.3 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **325** (83.8 mg, 0.45 mmol) according to the general procedure. The crude material

was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound **332** as a colorless oil. Yield: 73.5 mg, 0.20 mmol, 67%. $[\alpha]_D^{25}$= +54.7 (c = 1.00, 88% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.20–8.09 (m, 2H), 7.73–7.63 (m, 1H), 7.55–7.45 (m, 5H), 7.40–7.28 (m, 2H), 3.54 (s, 1H), 2.92–2.51 (m, 4H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.9, 194.7, 192.8, 138.1, 135.4, 131.7, 129.0, 128.9, 128.9, 128.4, 126.6, 76.4, 70.6, 33.1, 31.6, 26.4, 26.4. UPLC-DAD-QTOF: $C_{21}H_{22}NO_3S$ $[M+H]^+$ calcd.: 368.1320, found: 368.1324. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, retention times: 21.7 min (major.) and 29.7 min (min.)).

6.3.8. Elaboration of adducts

*6.3.8.1. Hydrolysis of adduct rac-**326***

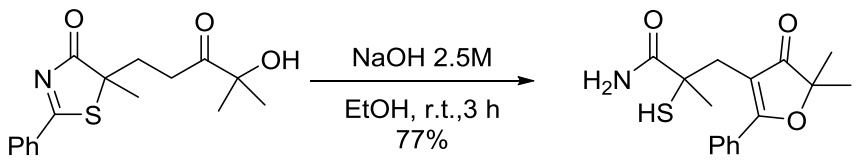
6.3.8.1.1. Method A: Acid hydrolysis[312a]



rac-**326** rac-**334**

5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5*H*)-one **326** (1 equiv., 152.6 mg, 0.5 mmol) was dissolved in a mixture of dioxane (2.7 mL) and HCl 6N (12 equiv., 1.0 mL, 6 mmol). The resulting solution was stirred at room temperature for 1 h. After this period the cooled reaction mixture was treated at 0 ºC with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane 1/1). Colorless oil, yield: 76.3 mg, 0.25 mmol, 50%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.90–7.81 (m, 2H), 7.65–7.56 (m, 1H), 7.56–7.41 (m, 2H), 5.47 (t, *J* = 2.8 Hz, 1H), 3.42 (dd, *J* = 16.8, 3.2 Hz, 1H), 2.82 (dd, *J* = 16.8, 2.4 Hz, 1H), 1.76 (s, 3H), 1.46 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 172.9, 164.7, 150.0, 133.1, 133.1, 128.9, 127.7, 116.4, 70.7, 64.0, 47.8, 29.7, 29.5, 25.0. IR υ_{max} (neat)/cm^{-1}: 3480, 3314, 2974, 2928, 1744. UPLC-DAD-QTOF: $C_{16}H_{20}NO_3S$ $[M+H]^+$ calcd.: 306.1164, found: 306.1167.

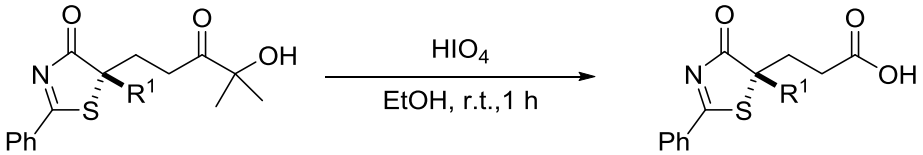
6.3.8.1.2. Method B: Saponification[315]



rac-**326** rac-**339**

To a solution of 5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5*H*)-one **326** (1 equiv., 152.6 mg, 0.5 mmol) in ethanol (5 mL), NaOH 2.5M (0.25 mL, 0.625 mmol, 1.25 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h and afterwards the reaction was quenched with 1 M aq. $KHSO_4$ (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 50/50) to give the title compound **339** as an orange solid. Yield: 117.6 mg, 0.38 mmol, 77%. m. p. 130–132 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.95–7.70 (m, 2H), 7.62–7.40 (m, 3H), 6.99 (bs, 1H), 5.78 (bs, 1H), 3.09 (s, 2H), 2.52 (s, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 181.3, 177.2, 131.6, 130.8, 128.7, 128.0, 109.0, 86.4, 52.1, 33.2, 28.4, 23.2, 23.1. UPLC-DAD-QTOF: $C_{16}H_{20}NO_3S$ $[M+H]^+$ calcd.: 306.1164, found: 306.1169.

*6.3.8.2. Elaboration of adducts **326** and **331** into carboxylic acids **345–346***[316]



326 R^1= Me
331 R^1= Hex

345 R^1= Me 94%
346 R^1= Hex 95%

General procedure

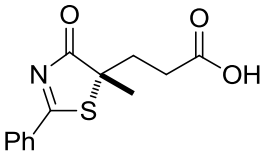
The corresponding adduct (1 equiv., 0.2 mmol) was dissolved in 1 mL of diethyl ether and periodic acid (1.2 equiv., 273.5 mg, 1.2 mmol) was added slowly. The reaction mixture was stirred at room temperature until completion (TLC analysis, 1 h). After completion, reaction was quenched with 10% aqueous sodium sulfite (5 mL) and washed with diethyl ether (5 mL). The aqueous phase was acidified to pH 2 with HCl 3M saturated with sodium chloride and extracted with ethyl acetate (3 x 10 mL). The

[315] See ref. 220a, page 108.

[316] See ref. 247, page 137.

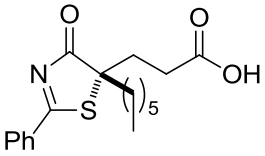
combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the crude carboxylic acid which was used in the next step without further purification.

(*S*)-3-(5-Methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid 345



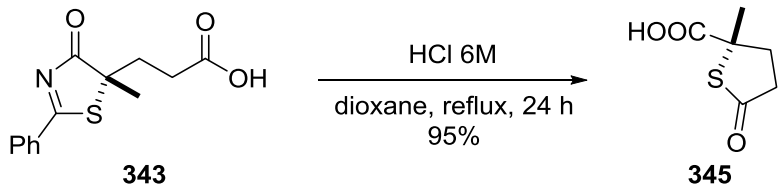
The title compound **345** was prepared from 5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-2-phenylthiazol-4(5*H*)-one **326** (61.1 mg, 0.2 mmol) according to the general procedure. Orange oil, yield: 49.5 mg, 0.19 mmol, 94%. $[\alpha]_D^{25}$= –1.2 (c = 0.72, 96% *ee*, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.21–8.03 (m, 2H), 7.82 – 7.62 (m, 1H), 7.64 – 7.43 (m, 2H), 2.59 – 2.20 (m, 4H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 194.9, 194.8, 177.5, 135.3, 132.0, 129.1, 128.9, 63.4, 33.9, 29.9, 26.3. UPLC-DAD-QTOF: $C_{13}H_{14}NO_3S$ $[M+H]^+$ calcd.: 264.0694, found: 264.0701.

(*S*)-3-(5-Hexyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid 346



The title compound **346** was prepared from 5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-2-phenylthiazol-4(5*H*)-one **331** (75.1 mg, 0.2 mmol) according to the general procedure. Orange oil, yield: 63.3 mg, 0.19 mmol, 95%. $[\alpha]_D^{25}$= +3.7 (c = 0.82, 92% *ee*, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.19–8.07 (m, 2H), 7.73–7.61 (m, 1H), 7.58–7.48 (m, 2H), 2.53–2.18 (m, 4H), 2.12–1.90 (m, 2H), 1.56–1.11 (m, 8H), 0.82 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.7, 194.2, 177.9, 135.4, 131.7, 129.0, 128.9, 68.9, 39.0, 32.8, 31.3, 29.5, 28.9, 25.0, 22.4, 13.9. UPLC-DAD-QTOF: $C_{18}H_{24}NO_3S$ $[M+H]^+$ calcd.: 334.1477, found: 334.1479.

*6.3.8.3. Conversion of thiazolone **345** into thiolactone **347***

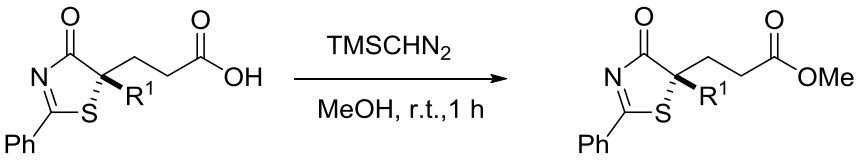


343 **345**

3-(5-Methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid **343** (1 equiv., 67.2 mg, 0.22 mmol) was dissolved in a mixture of dioxane (1.2 mL) and HCl 6N (12 equiv., 0.44 mL, 2.64 mmol). The resulting solution was stirred and refluxed for 24 h. After this period the cooled reaction mixture was treated with water (10 mL) and the product was extracted from the aq. phase with CH_2Cl_2 (3 x 10 mL) and the

combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product **345**, which was purified by flash column chromatography on silica gel (eluting with ethyl acetate/hexane 4/1). Colorless oil, yield: 33.7 mg, 0.21 mmol, 95%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.12–2.92 (m, 1H), 2.81–2.65 (m, 2H), 2.17–2.03 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 206.3, 179.0, 59.1, 42.1, 35.6, 25.8. HRMS (ESI): $C_6H_9O_3S$ $[M+H]^+$ calcd.: 161.0272, found: 161.0286.

*6.3.8.4. Conversion of carboxylic acids **345–345** into methyl ester derivatives **329** and **349***[317]



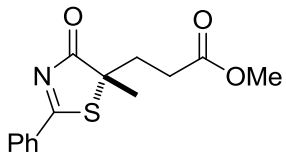
345 R^1= Me
346 R^1= Hex

329 R^1= Me 89%
349 R^1= Hex 85%

General procedure

Trimethylsilyl diazomethane 2.0 M in diethyl ether (3 equiv., 0.29 mL, 0.57 mmol) (caution: diazo derivatives are explosive under certain conditions and should be handle with care) was added dropwise to a solution of crude carboxylic acid (1 equiv., 0.19 mmol) in methanol (1.9 mL) at room temperature. After 1 h of stirring, solvents were removed under reduced pressure to afford the corresponding crude ester which was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate).

Methyl (*S*)-3-(5-methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoate 329

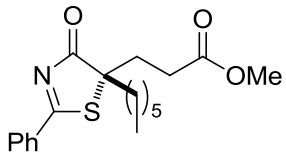


The title compound **329** was prepared from 3-(5-methyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid **345** (49.5 mg, 0.19 mmol)) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound **329** as a colorless oil. Yield: 47.0 mg, 0.17 mmol, 89%. $[\alpha]_D^{25}$= –19.2 (c = 0.92, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.15–8.03 (m, 2H), 7.71–7.60 (m, 1H), 7.56–7.43 (m, 2H), 3.61 (s, 3H), 2.41–2.21 (m, 4H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 194.9, 194.7, 172.4, 135.1, 132.0, 129.0, 128.8, 63.5, 51.7, 34.2, 30.0, 26.1. UPLC-DAD-QTOF: $C_{14}H_{16}NO_3S$ $[M+H]^+$ calcd.: 278.0851, found: 278.0852. The

[317] See ref. 247, page 137.

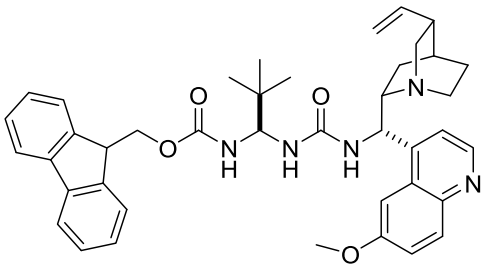
enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate = 1.0 mL/min, retention times: 15.3 min (min.) and 24.3 min (major.)).

Methyl (*S*)-3-(5-hexyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoate 349

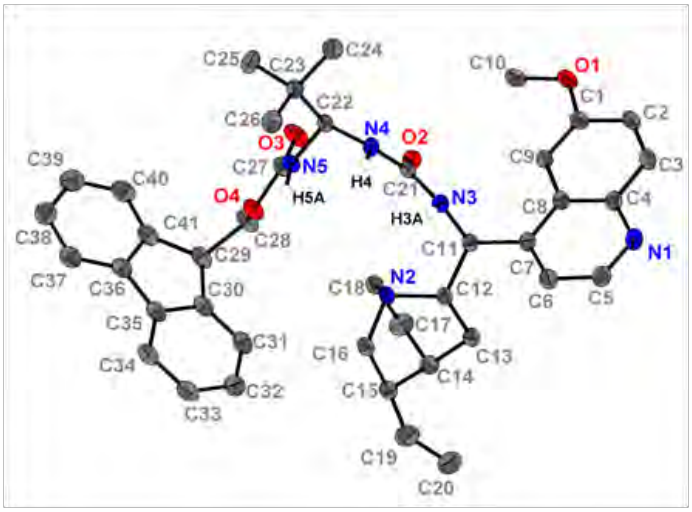


The title compound **349** was prepared from 3-(5-hexyl-4-oxo-2-phenyl-4,5-dihydrothiazol-5-yl)propanoic acid **346** (63.3 mg, 0.19 mmol)) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the title compound **349** as a colorless oil. Yield: 56.1 mg, 0.16 mmol, 85%. $[\alpha]_D^{25}$= +7.9 (c = 0.65, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.23–7.99 (m, 2H), 7.72–7.55 (m, 1H), 7.52–7.33 (m, 2H), 3.55 (s, 3H), 2.51–2.06 (m, 4H), 2.04–1.81 (m, 2H), 1.51–1.03 (m, 8H), 0.76 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.1, 194.5, 172.4, 135.0, 131.9, 128.8, 128.6, 68.9, 51.5, 38.9, 33.1, 31.2, 29.4, 28.8, 24.8, 22.2, 13.7. UPLC-DAD-QTOF: $C_{19}H_{26}NO_3S$ $[M+H]^+$ calcd.: 348.1633, found: 348.1646. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, retention times: 11.0 min (major.) and 12.7 min (min.)).

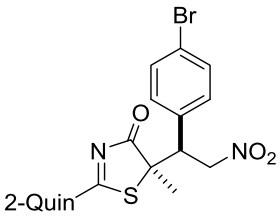
6.3.9. ORTEP diagram of compounds 301, 306i[318] and 339



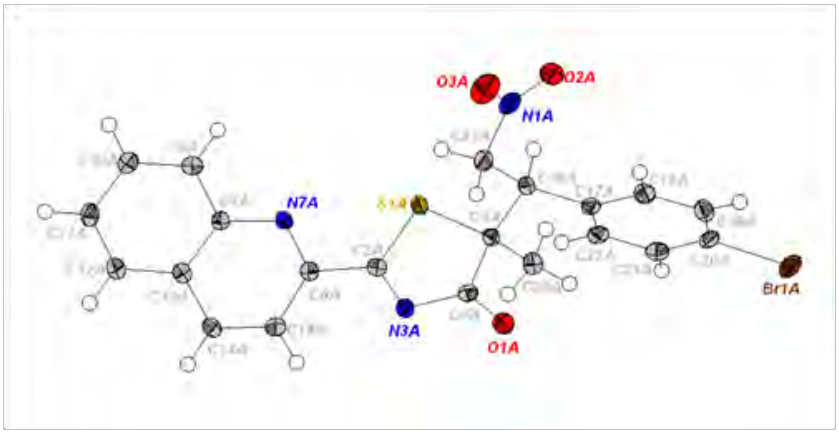
301

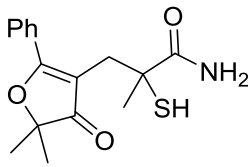


[318] CCDC 947275 contains the supplementary crystallographic data for the structural analysis of **306i** and CCDC 930440 for cat **301**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

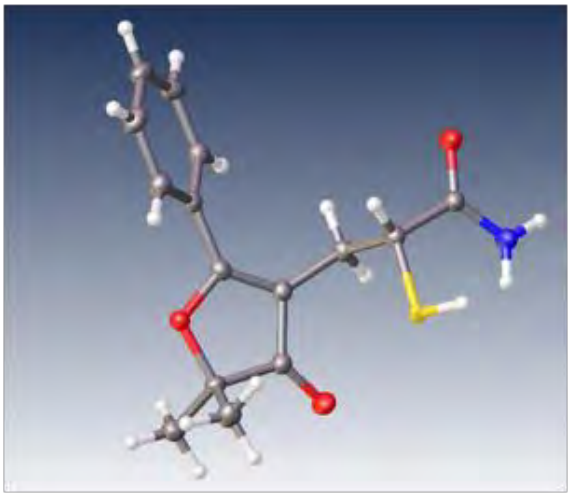


306i

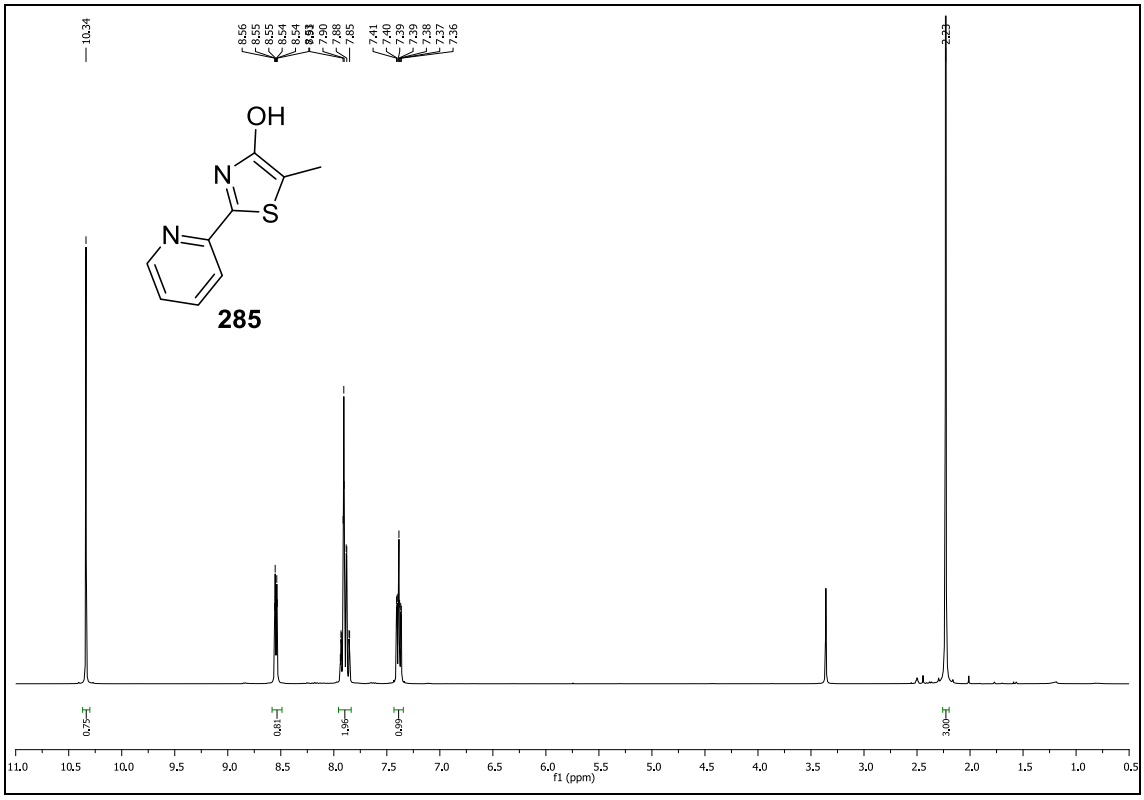


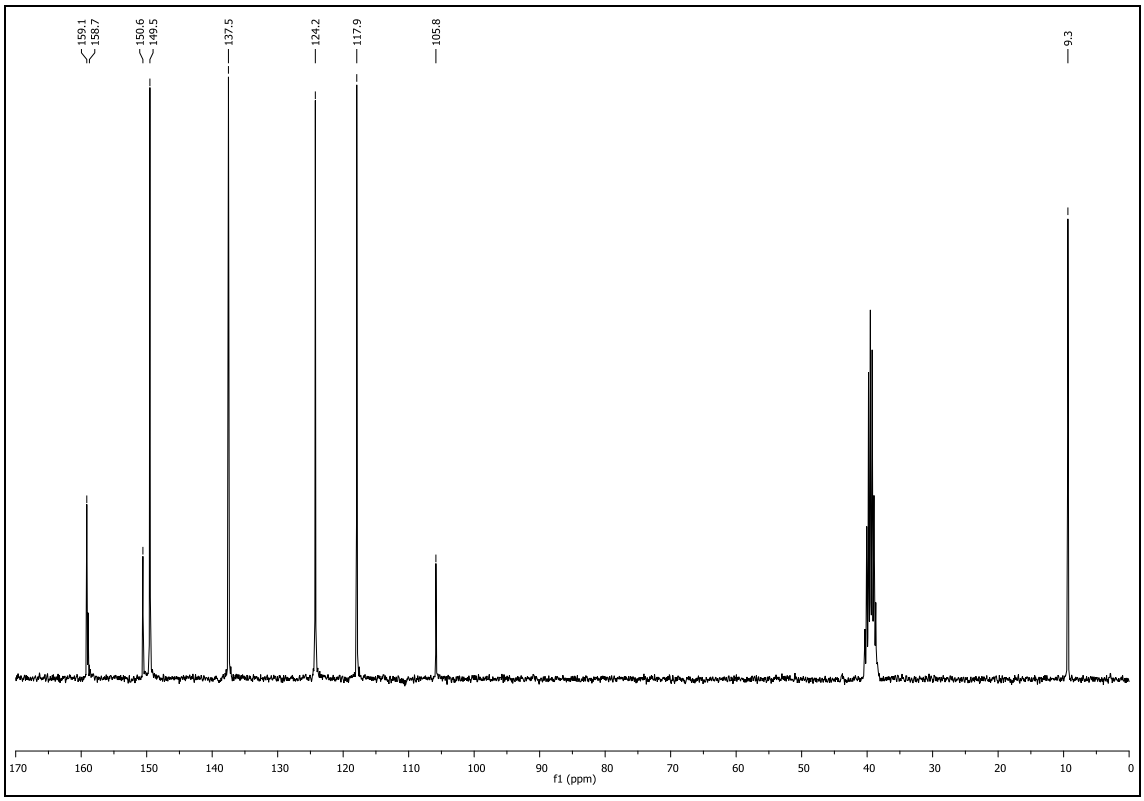


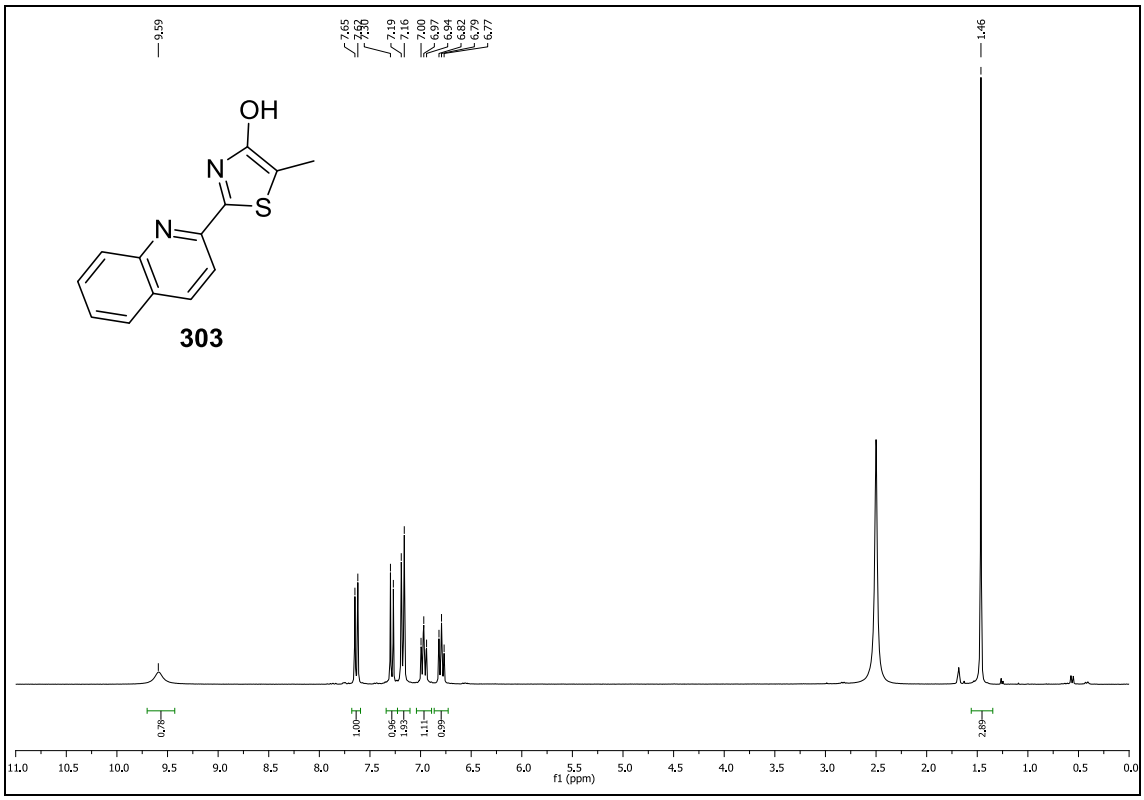
rac-**339**

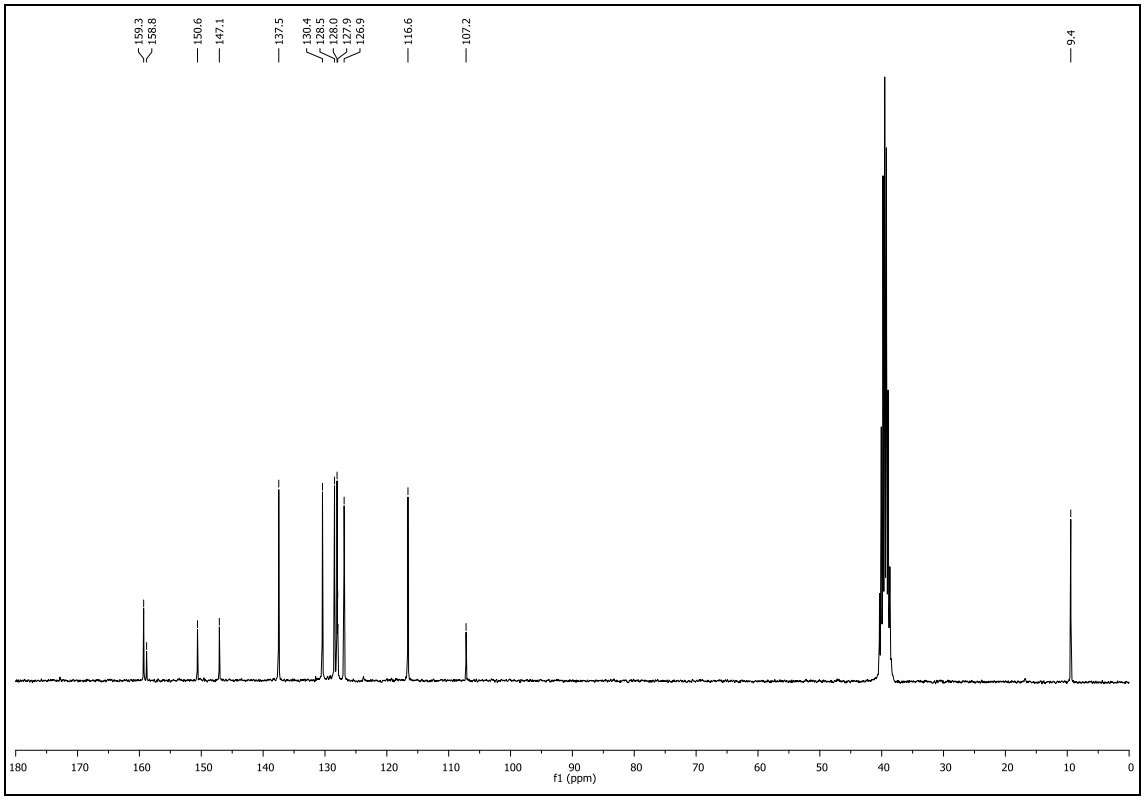


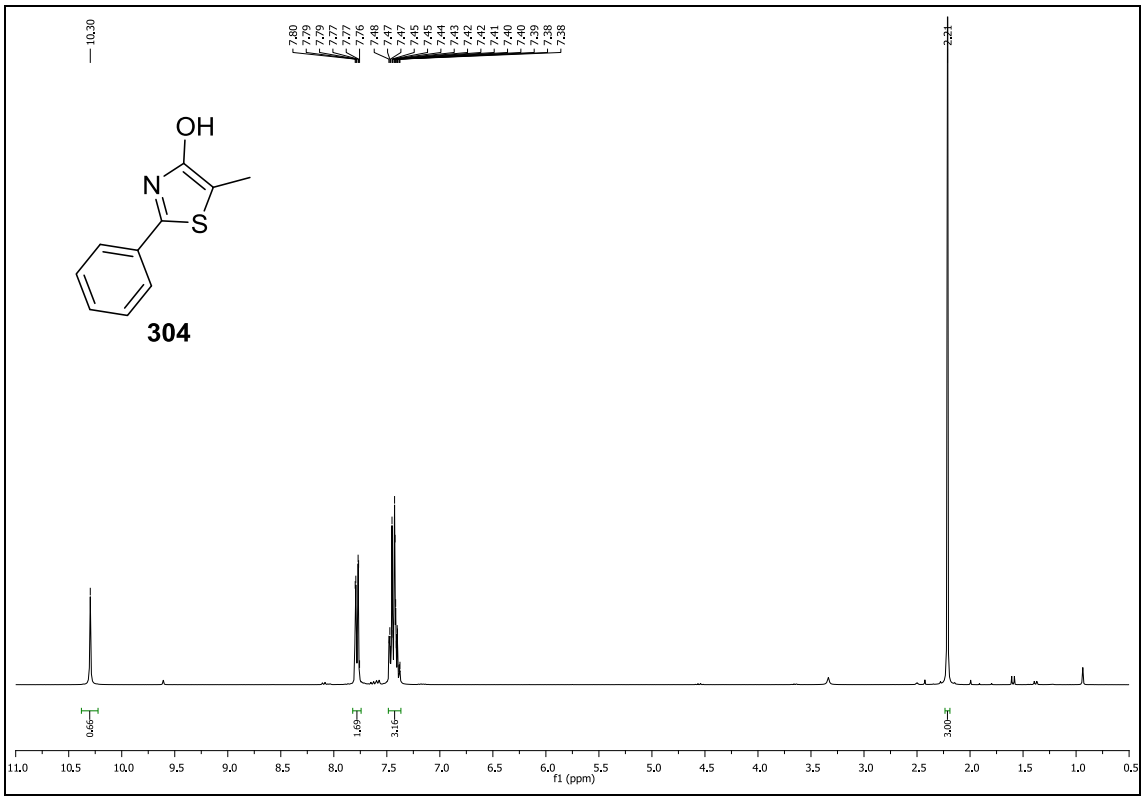
6.3.10. Representative NMR spectra

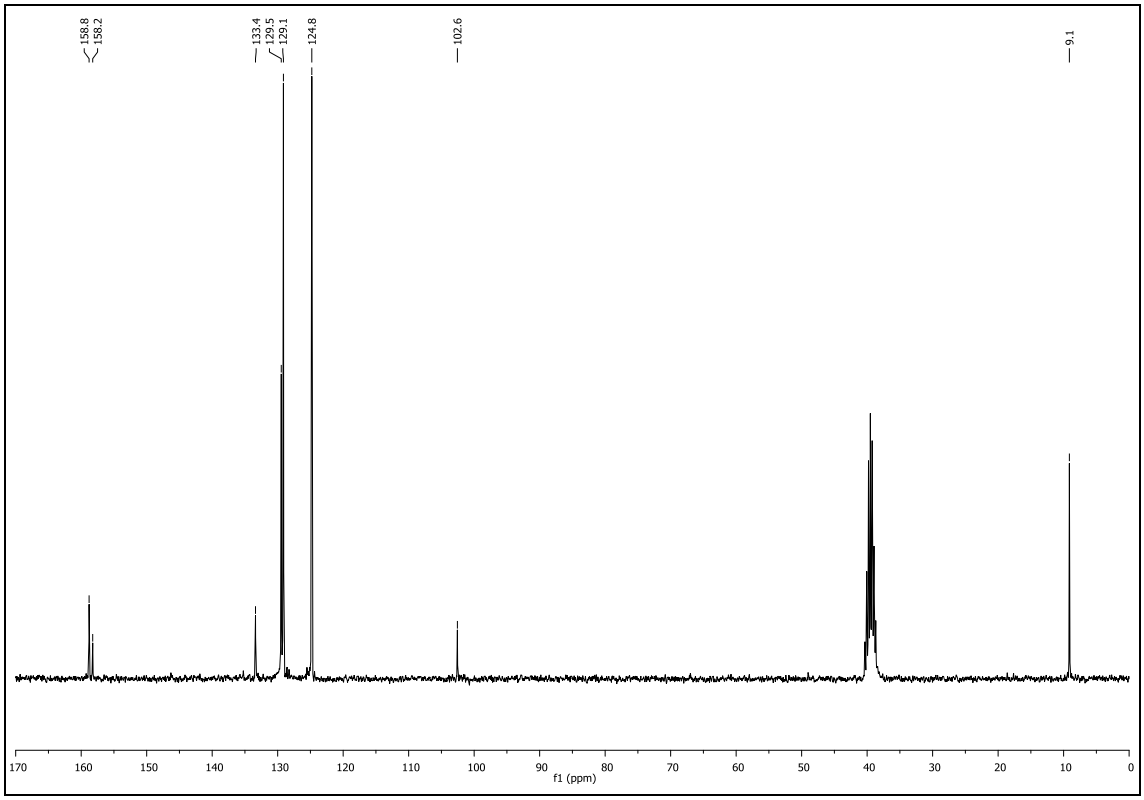





9.59
7.65
7.62
7.50
7.19
7.16
7.00
6.97
6.94
6.82
6.79
6.77
1.46
OH
N
S
N
303
0.78
1.00
0.96
1.93
1.11
0.99
2.89
f1 (ppm)


159.3
158.8
150.6
147.1
137.5
130.4
128.5
128.0
127.9
126.9
116.6
107.2
9.4
f1 (ppm)


10.30
7.80
7.79
7.79
7.77
7.77
7.76
7.48
7.47
7.47
7.45
7.45
7.44
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.38
7.38
2.21
OH
N
S
304
0.66
1.69
3.16
3.00
f1 (ppm)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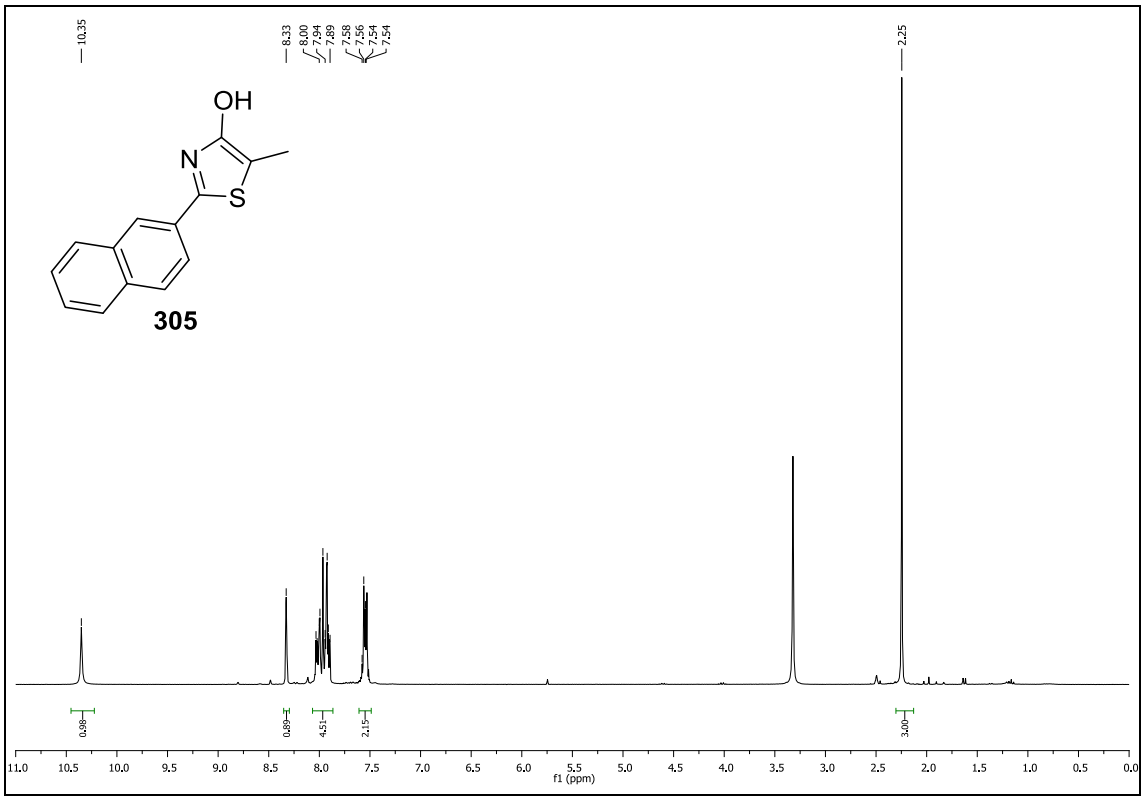
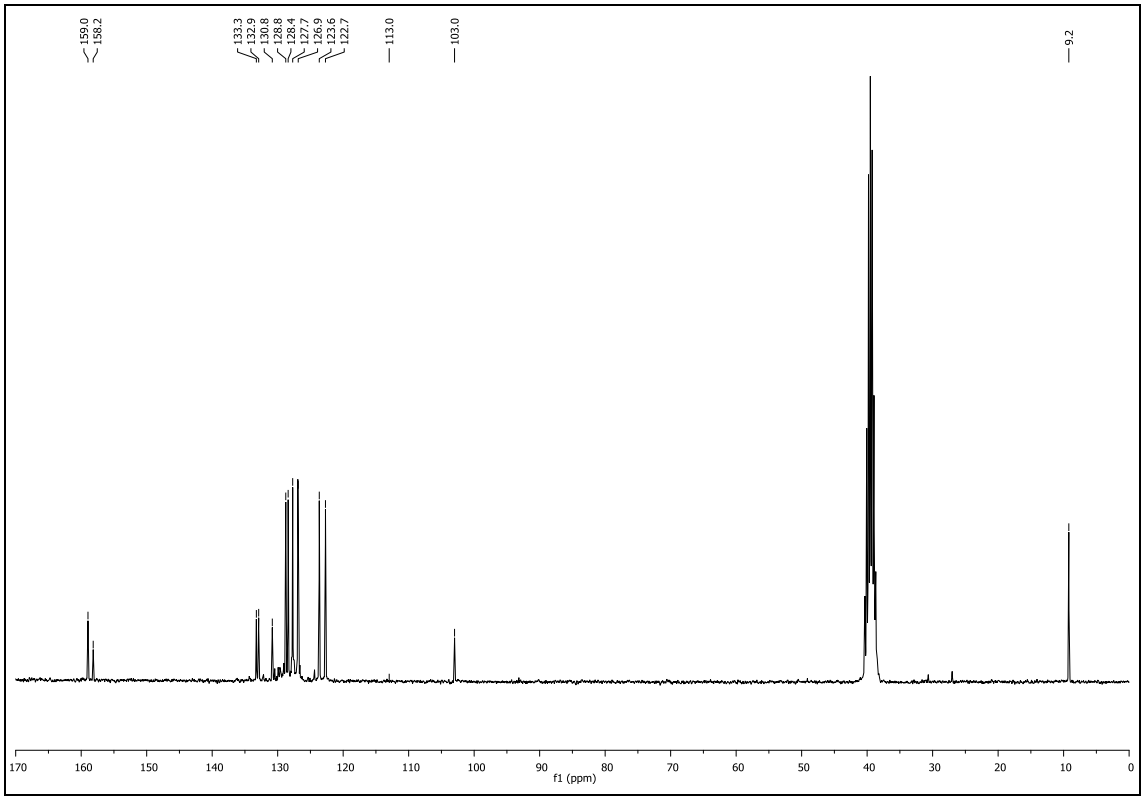
158.2
133.4
129.5
129.1
124.8
102.6
9.1
f1 (ppm)


10.35
8.33
8.00
7.94
7.89
7.58
7.56
7.54
7.54
2.25
OH
N
S
305
0.98
0.89
4.51
2.15
3.00
f1 (ppm)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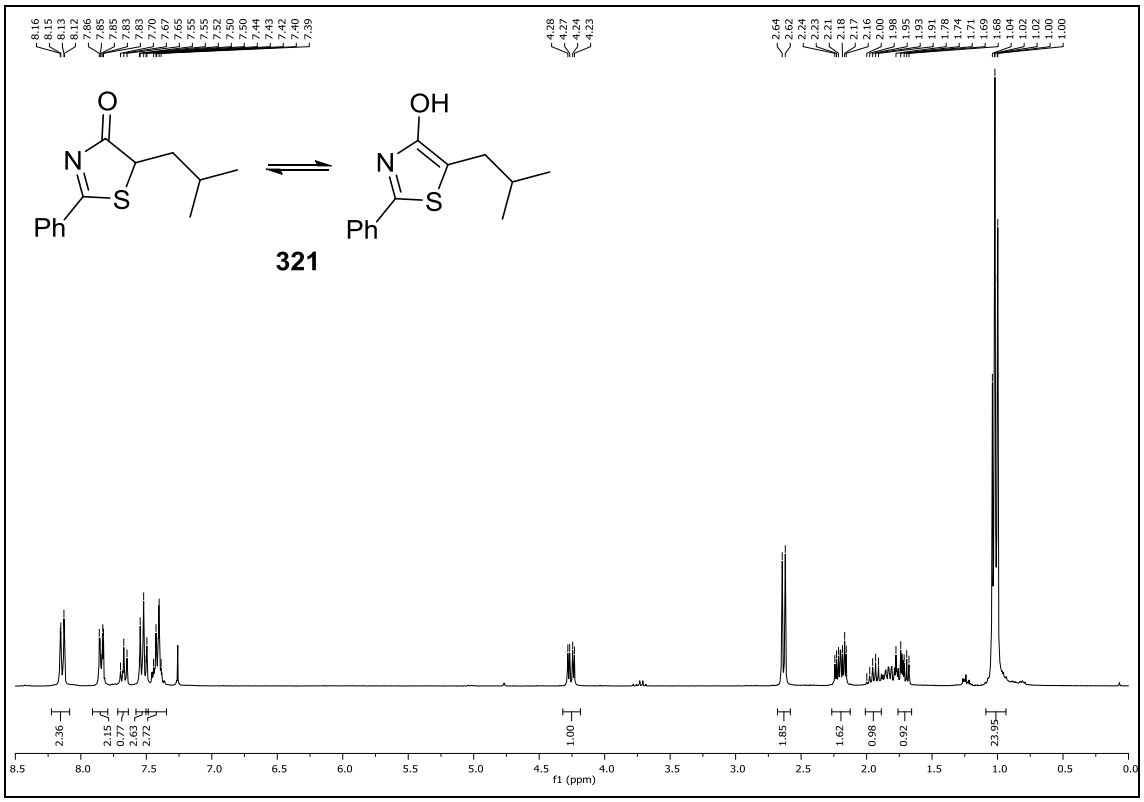
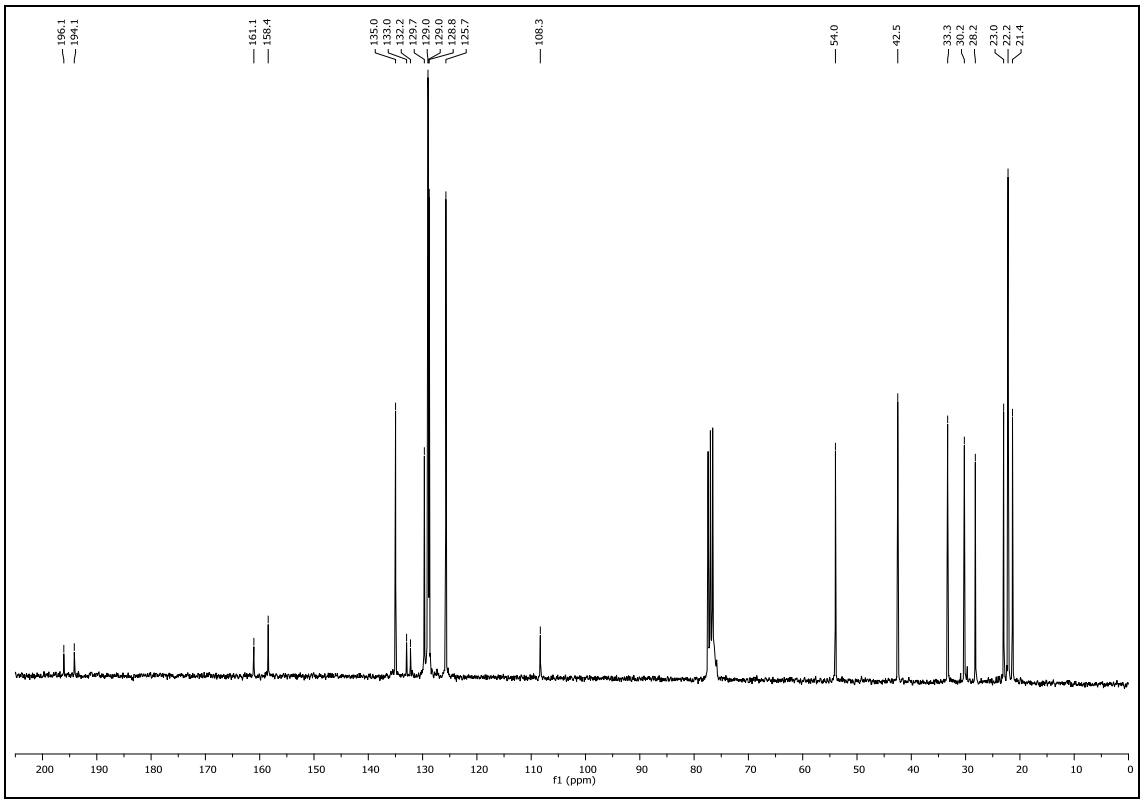
158.2
133.3
132.9
130.8
128.8
128.4
127.7
126.9
123.6
122.7
113.0
103.0
9.2
f1 (ppm)


O
N
S
Ph
OH
321
f1 (ppm)


196.1
194.1
161.1
158.4
135.0
133.0
132.2
129.7
129.0
129.0
128.8
125.7
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54.0
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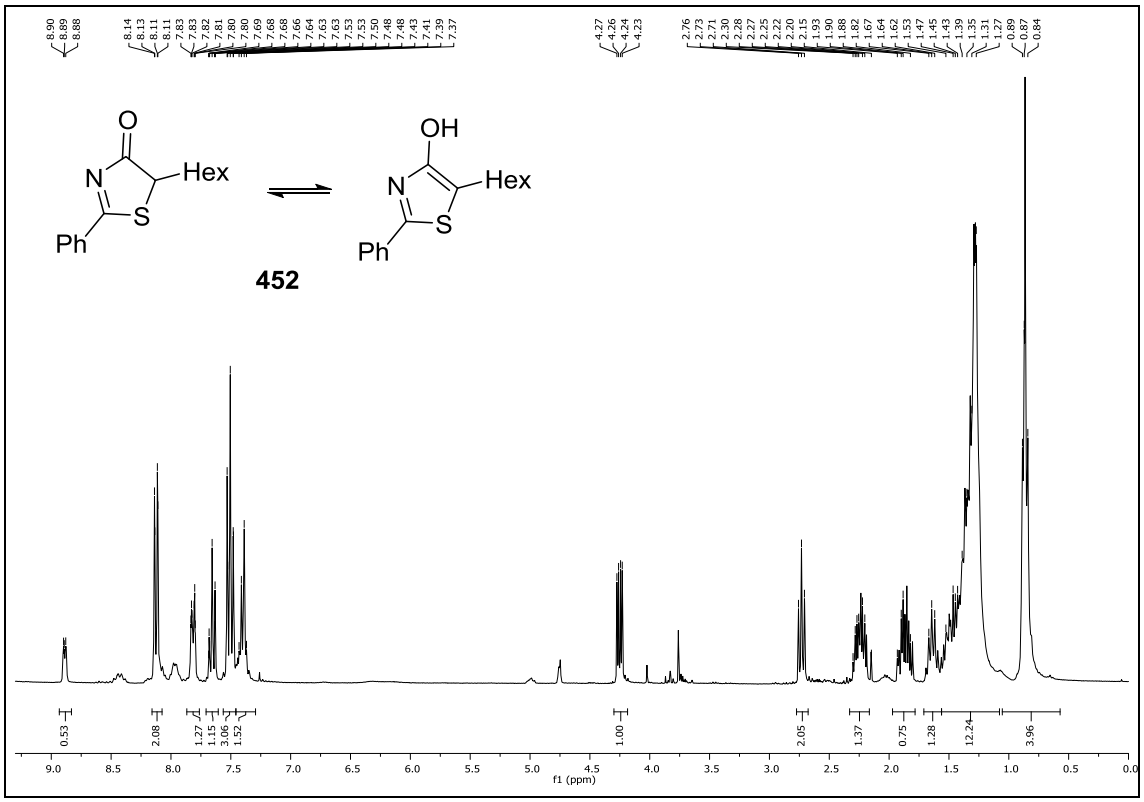
30.2
28.2
23.0
22.2
21.4
f1 (ppm)


O
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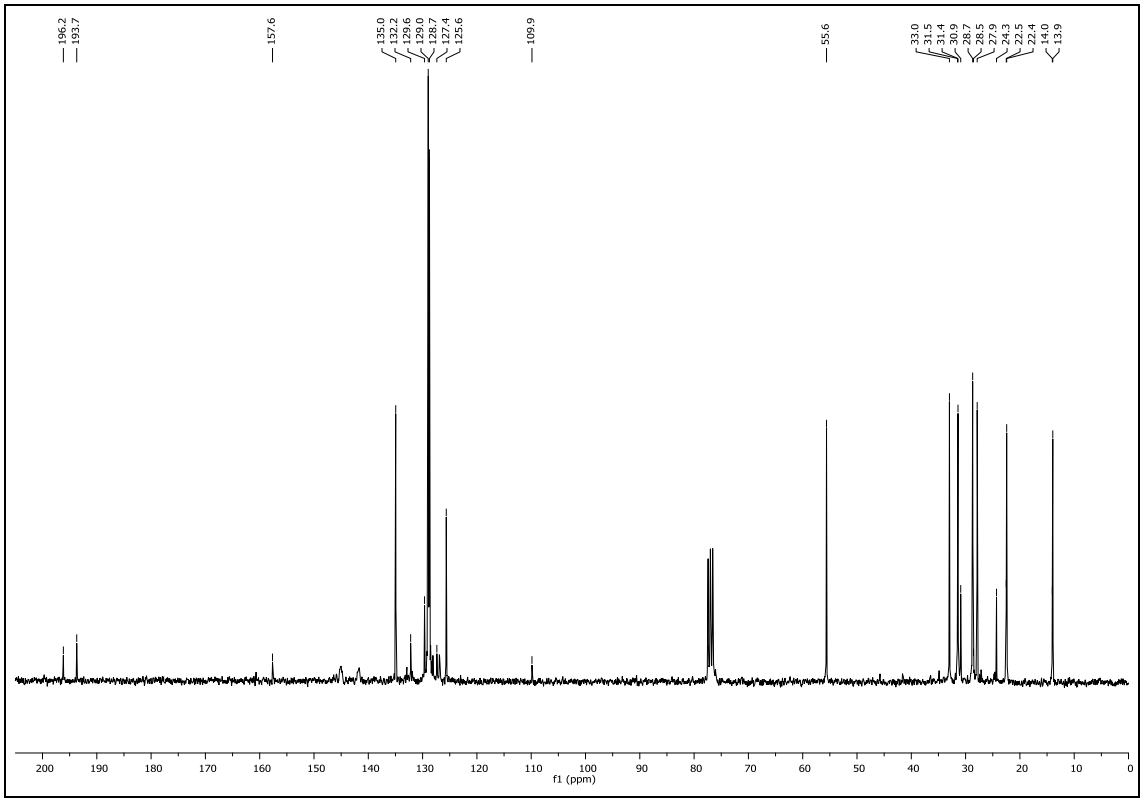
Hex
S
Ph
OH
N
Hex
S
Ph
452
f1 (ppm)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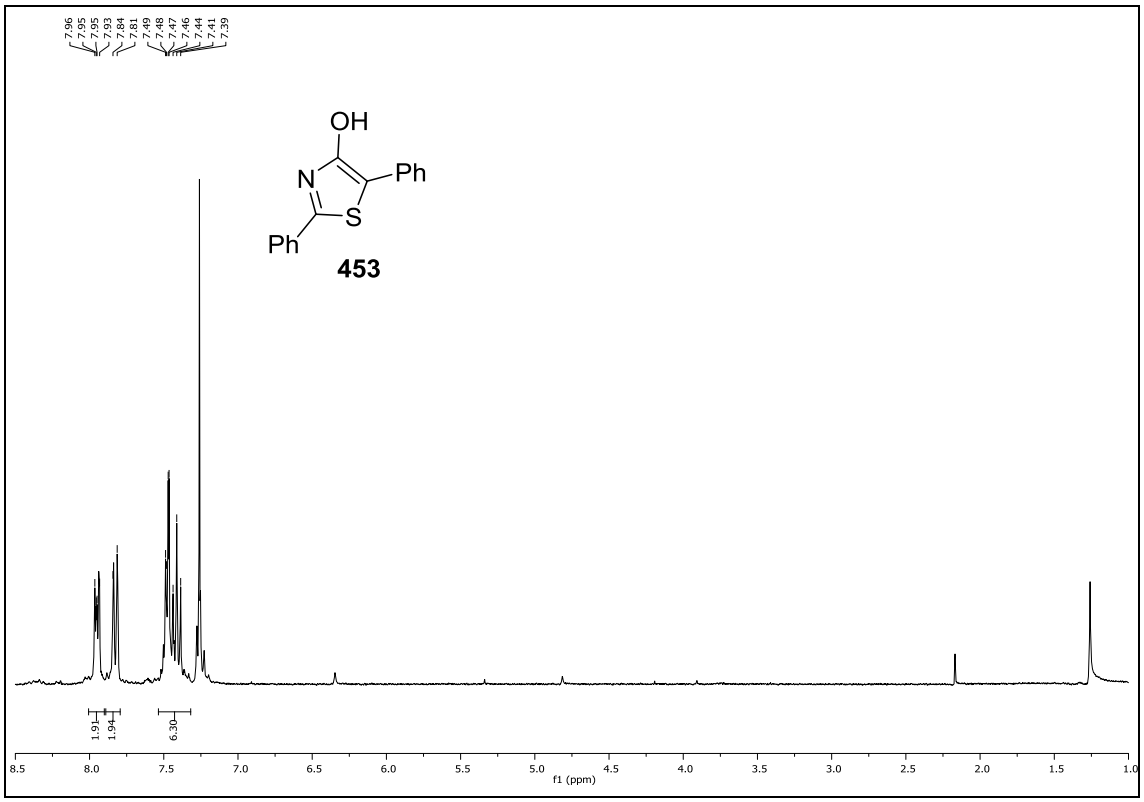
193.7
157.6
135.0
132.2
130.6
129.0
128.7
127.4
125.6
109.9
55.6
33.0
31.5
31.4
30.9
28.7
28.5
27.9
24.3
22.5
22.4
14.0
13.9
f1 (ppm)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7.95
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7.81
7.49
7.48
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7.46
7.44
7.41
7.39
OH
N
Ph
S
Ph
453
1.91
1.94
6.30
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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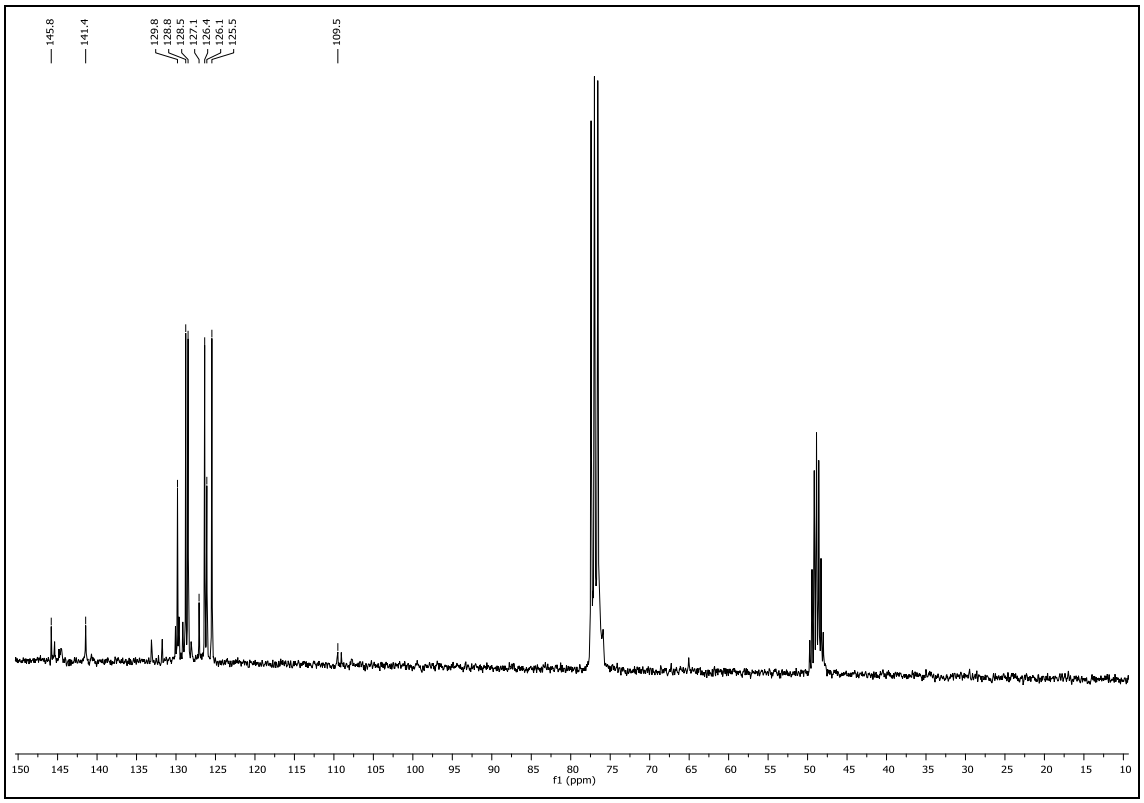
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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128.8
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127.1
126.4
126.1
125.5
109.5
150
145
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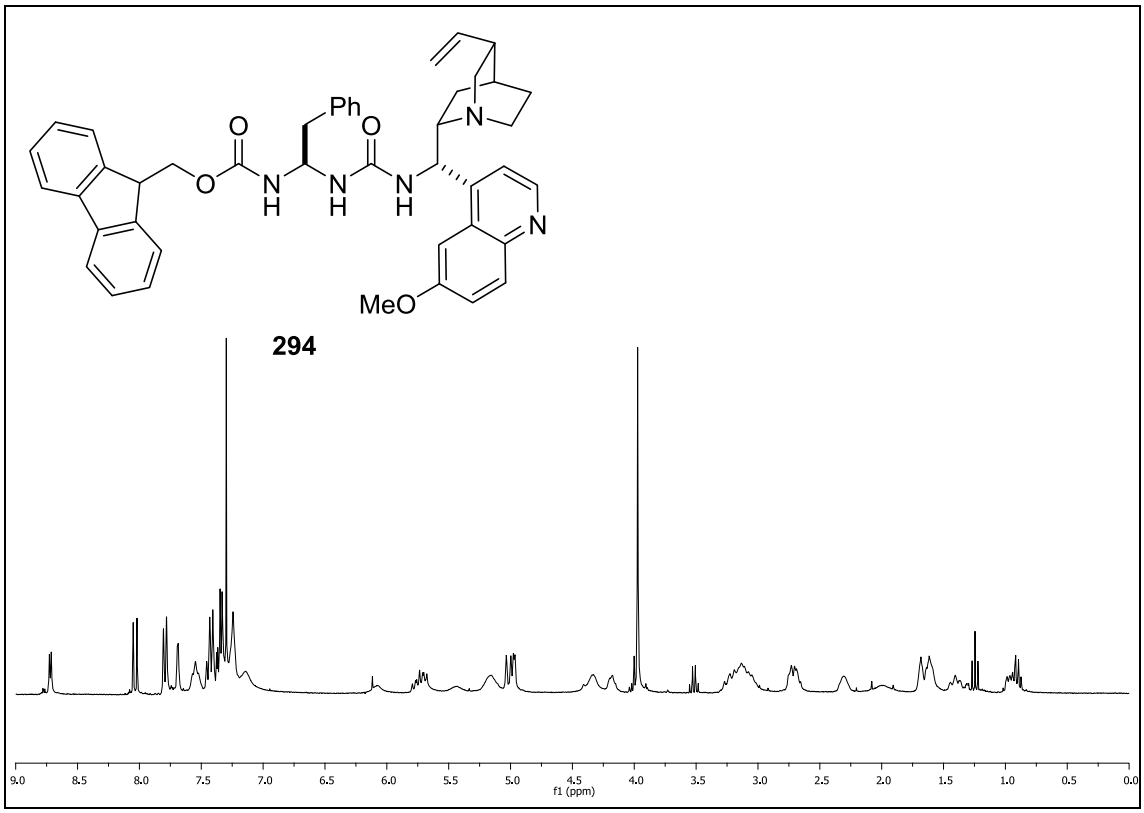
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)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H
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N
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MeO
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7.0
6.5
6.0
5.5
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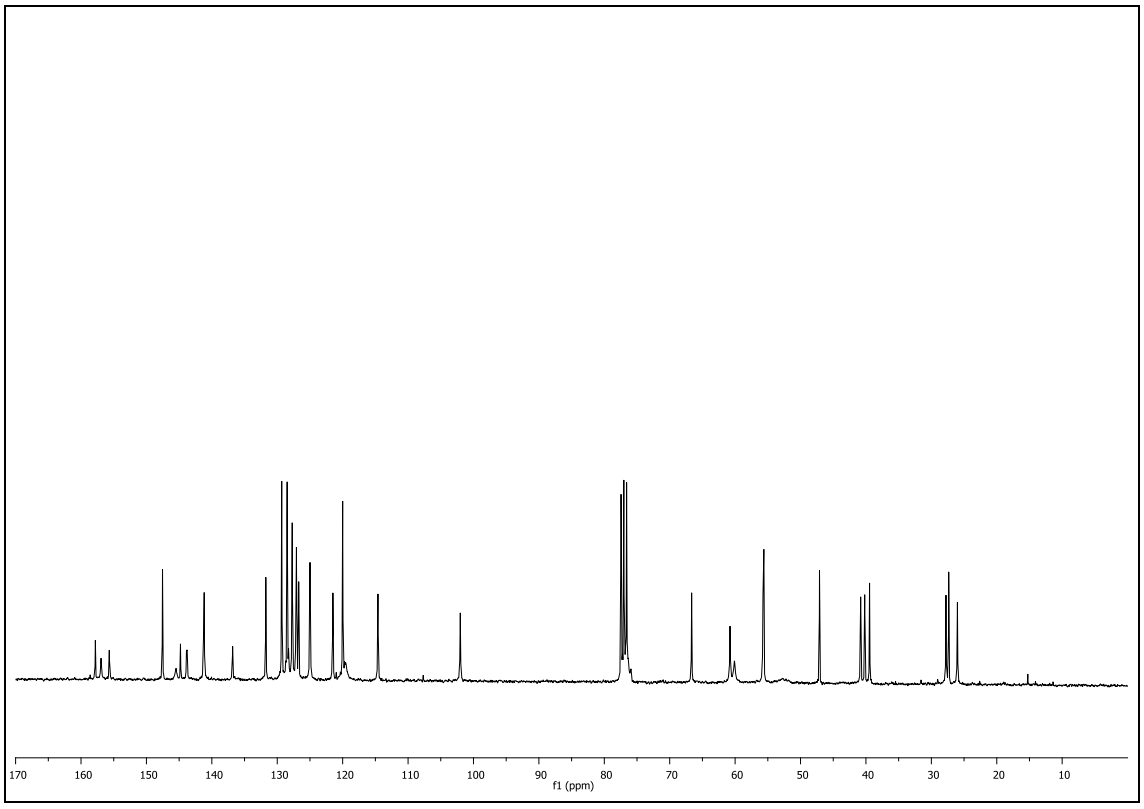
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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90
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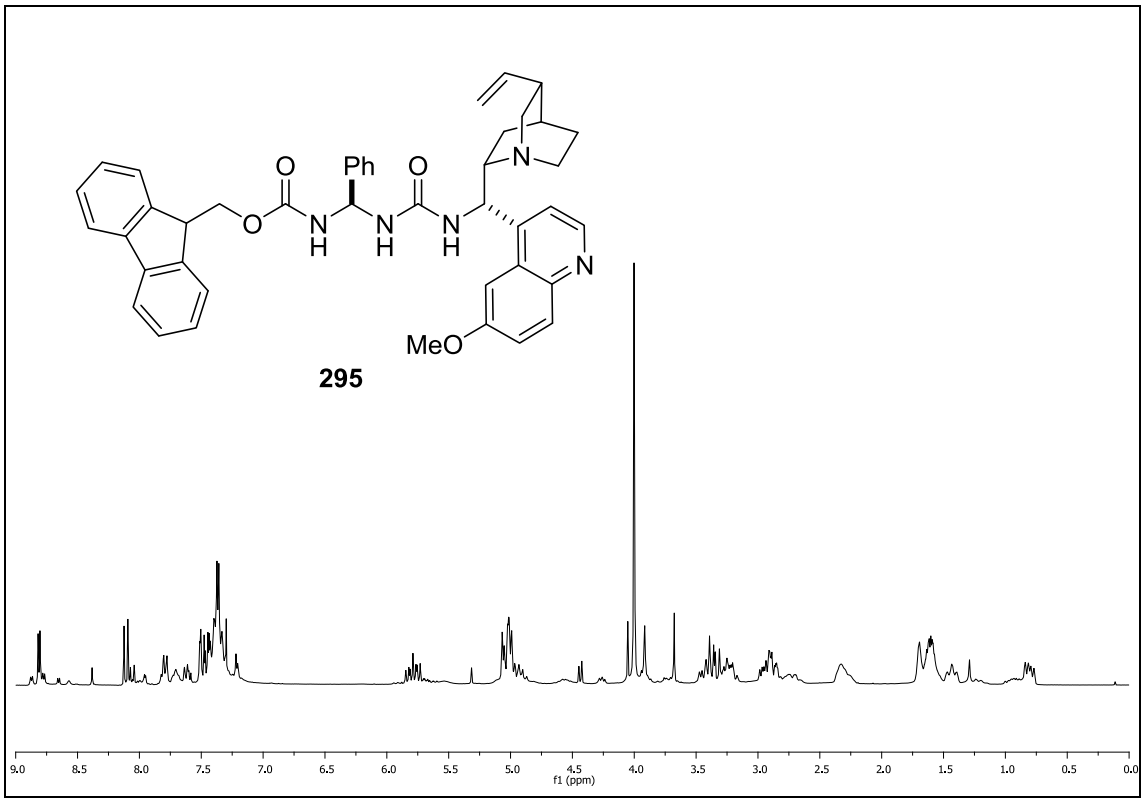
70
60
50
40
30
20
10
f1 (ppm)


O
Ph
O
N
H
N
H
N
H
O
N
MeO
295
9.0
8.5
8.0
7.5
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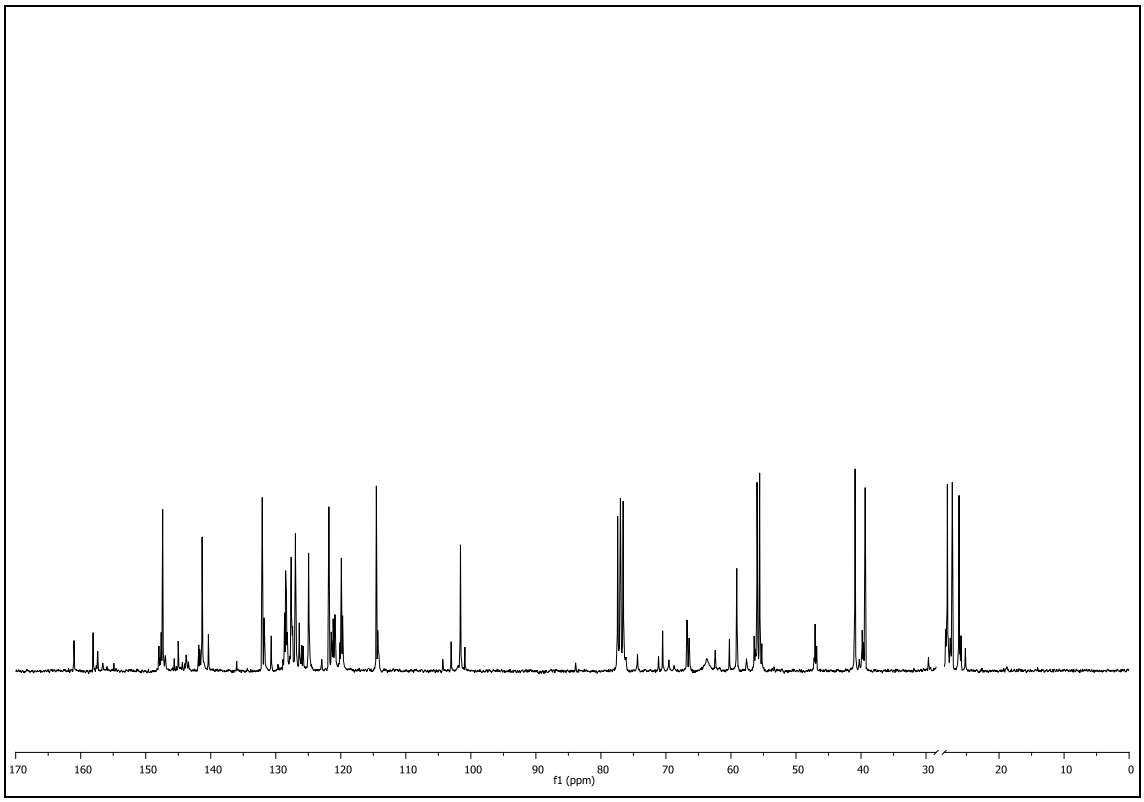
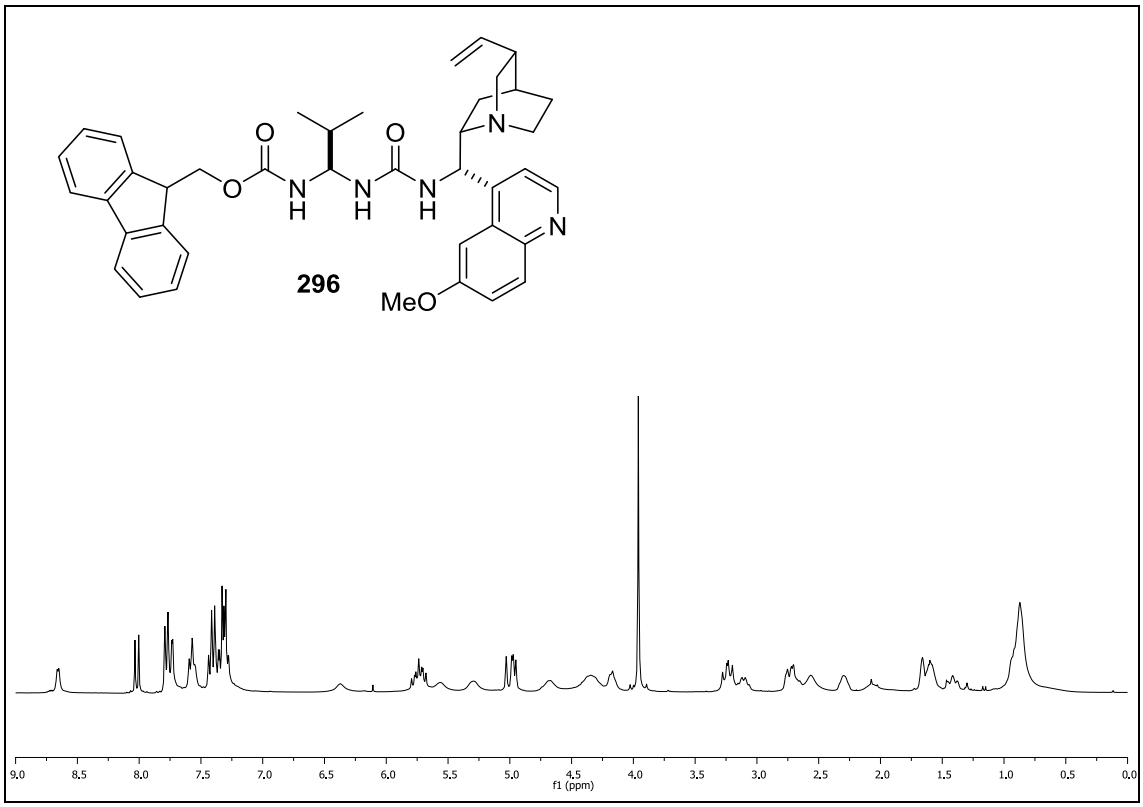
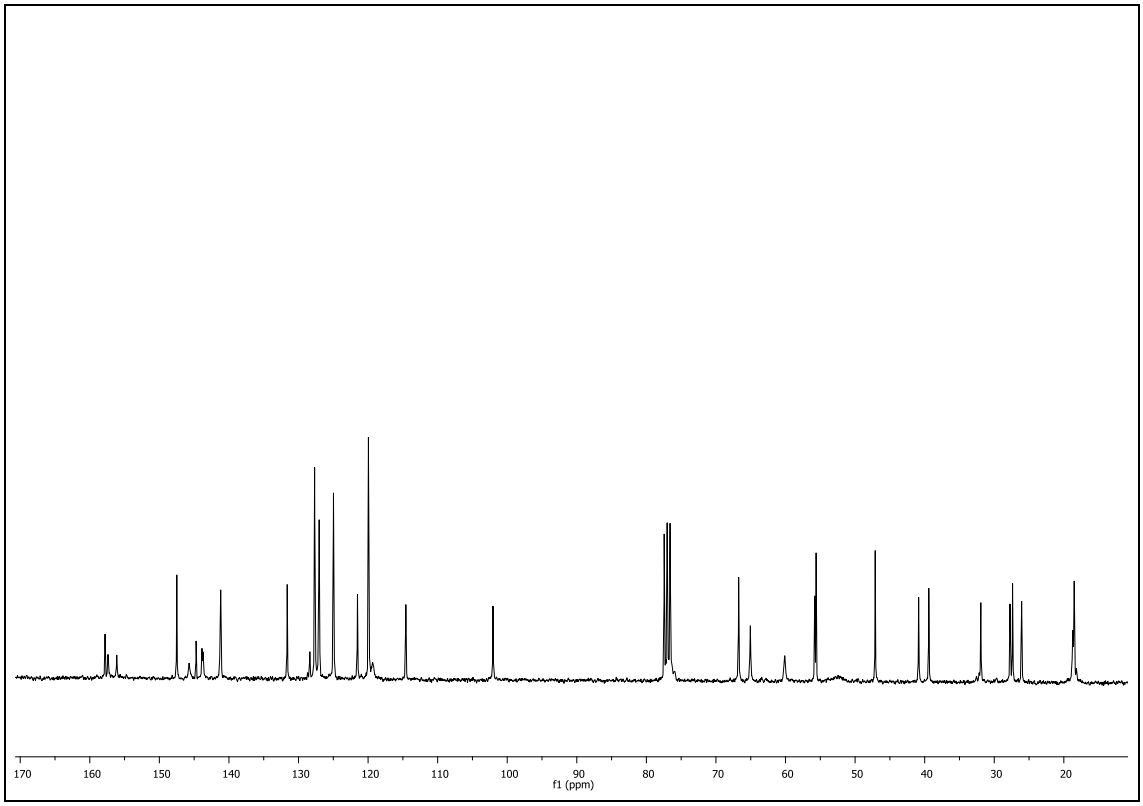
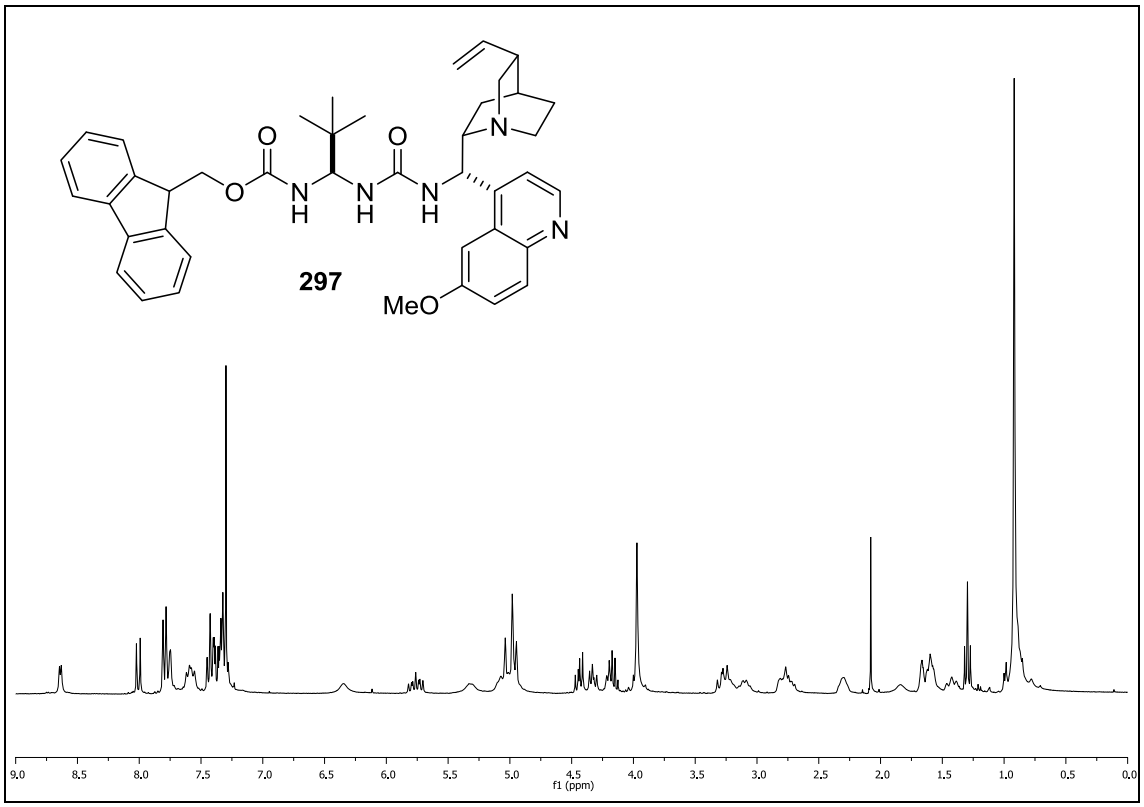
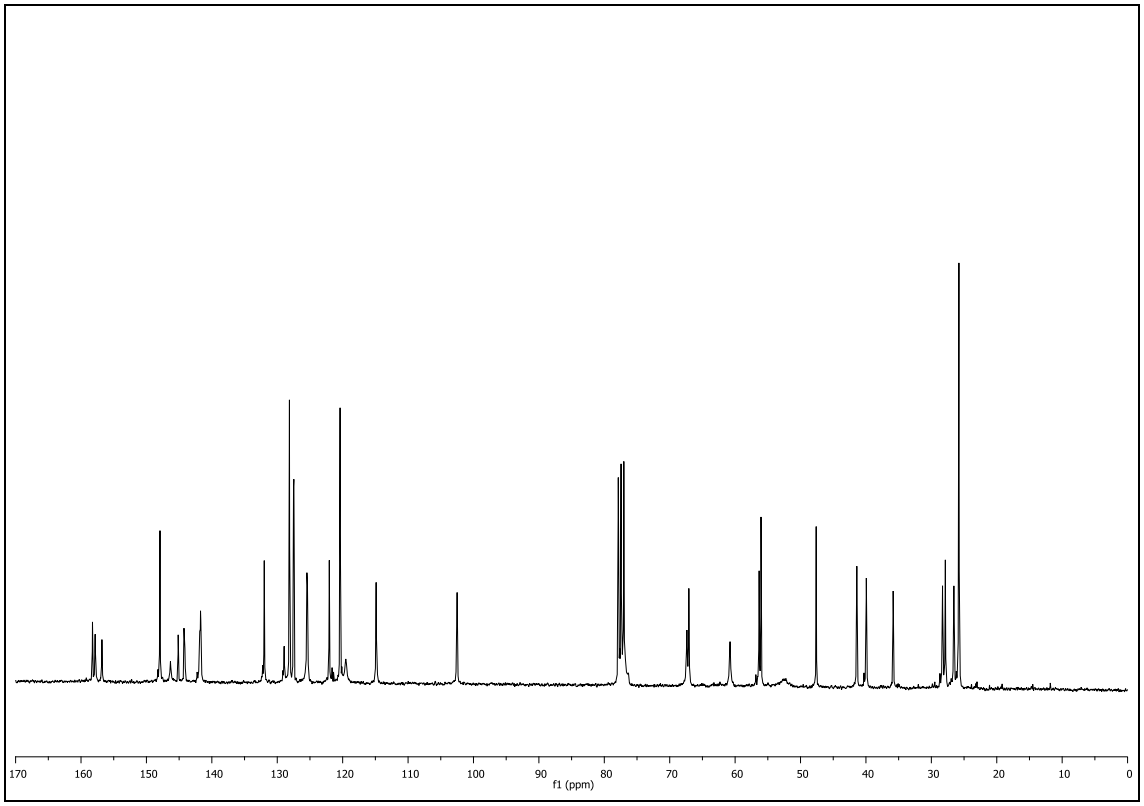
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

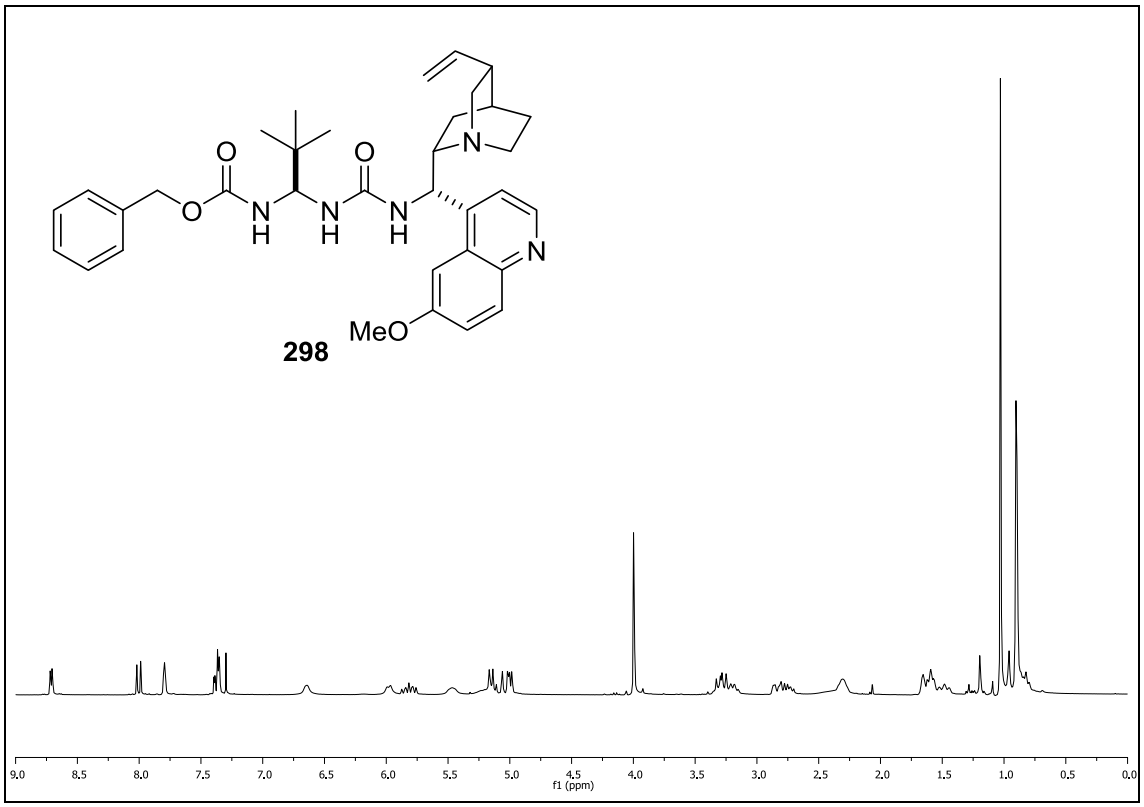

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

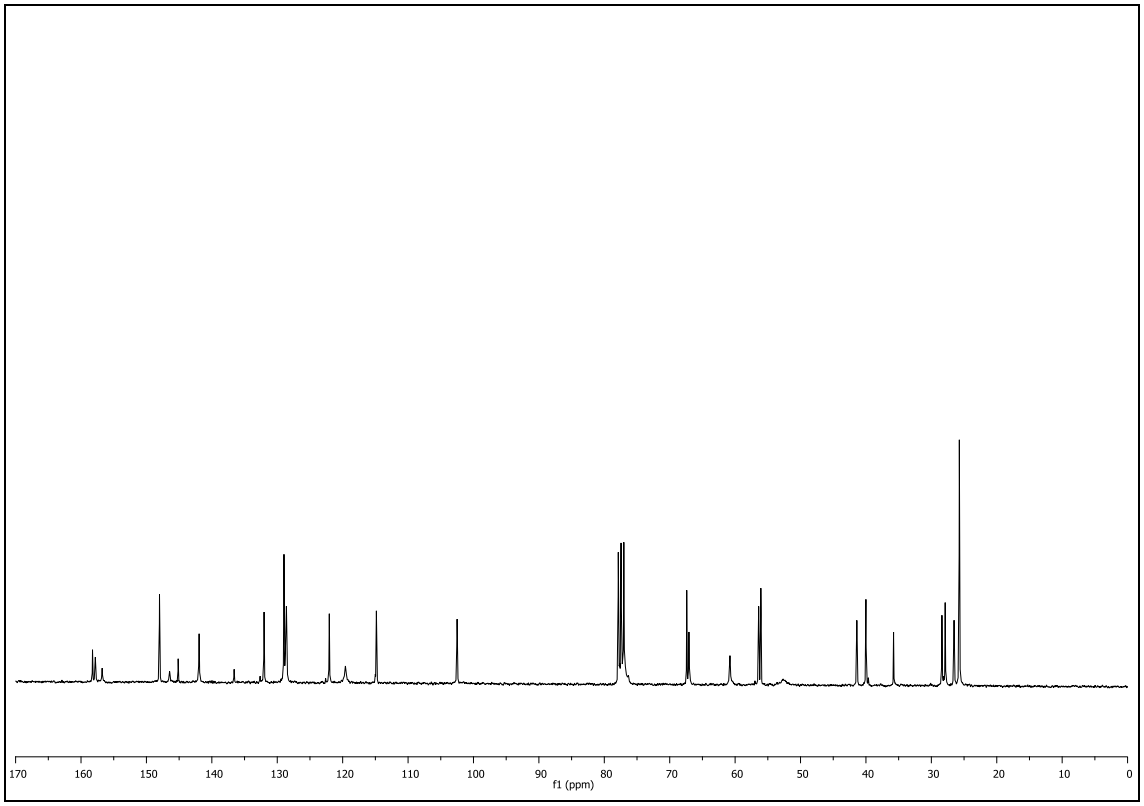

296
MeO
f1 (ppm)

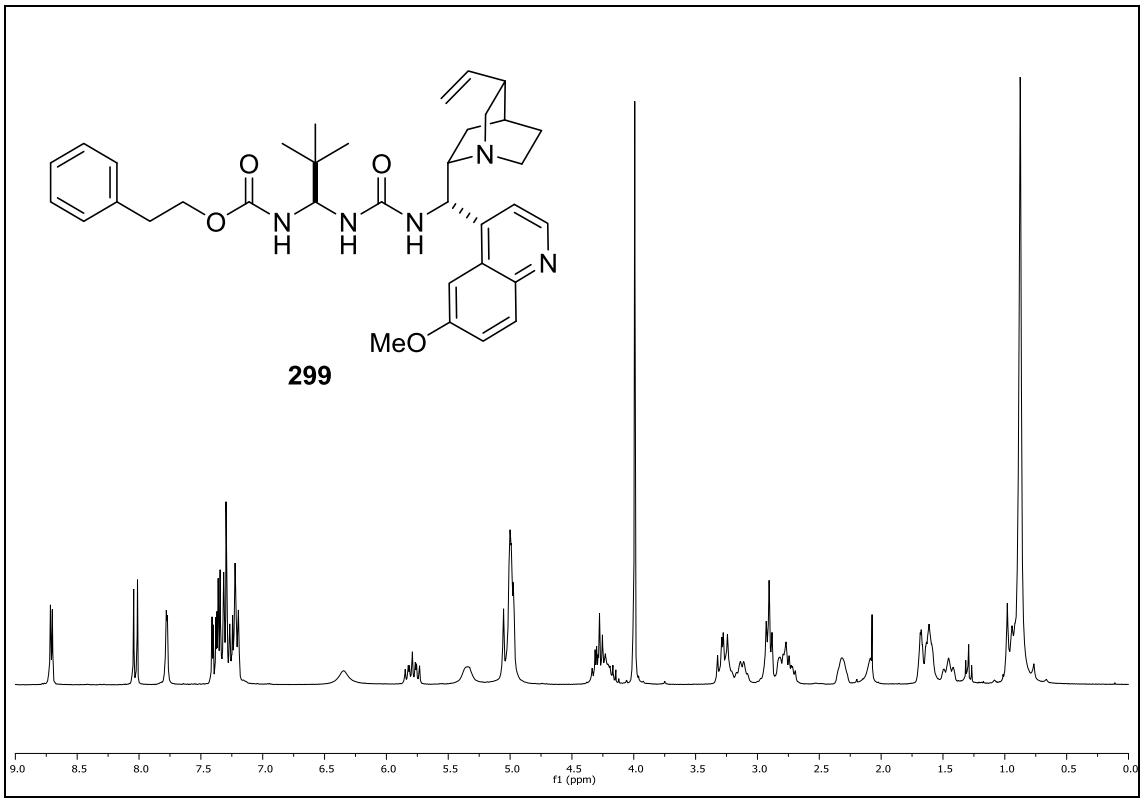

f1 (ppm)

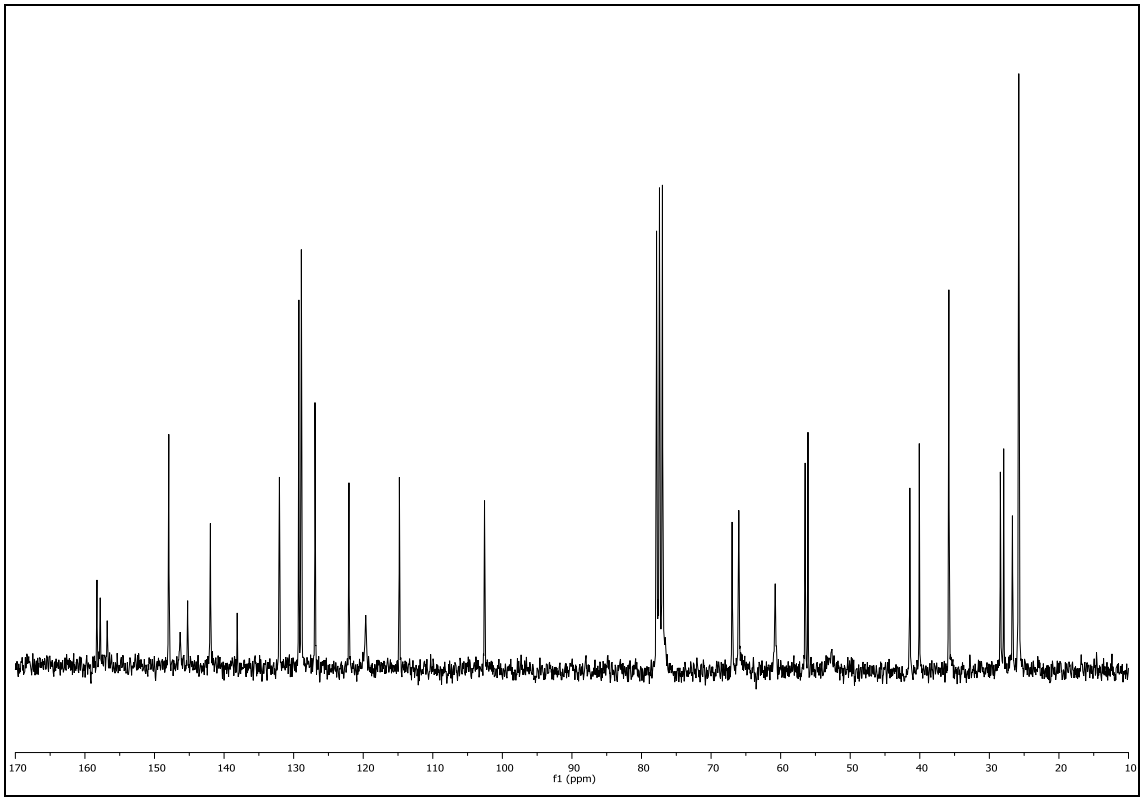

297
MeO
f1 (ppm)

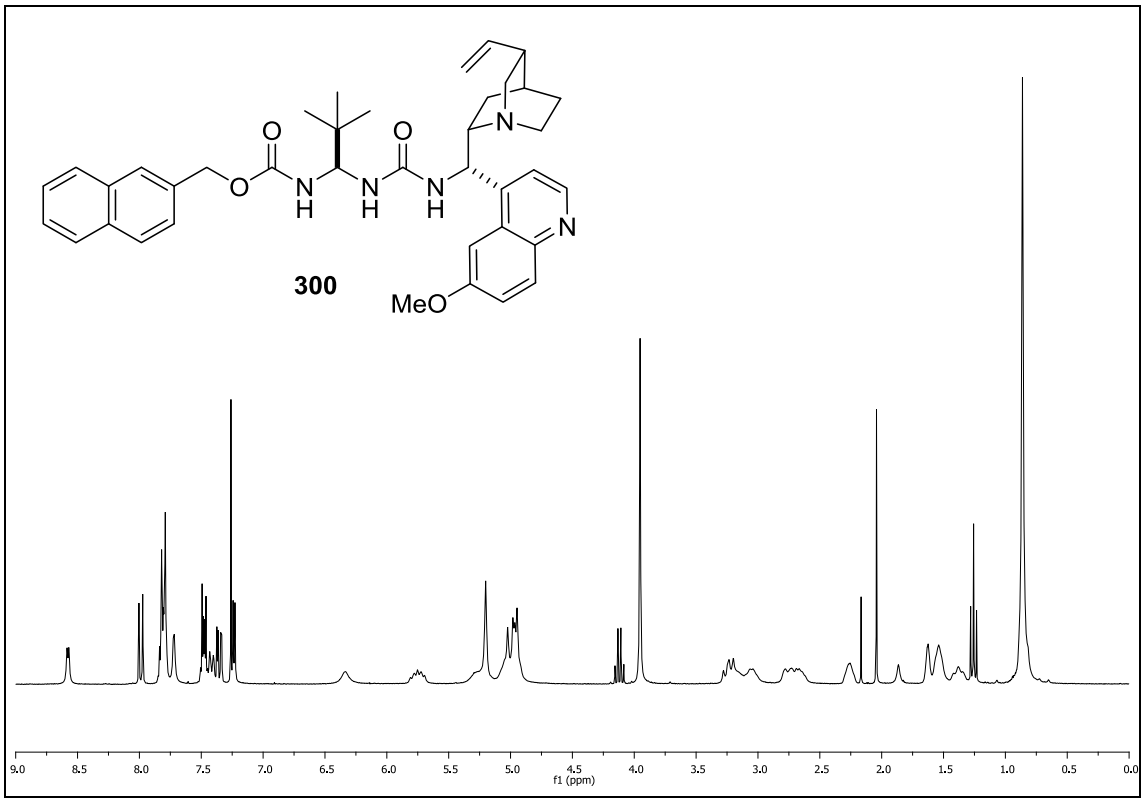

f1 (ppm)

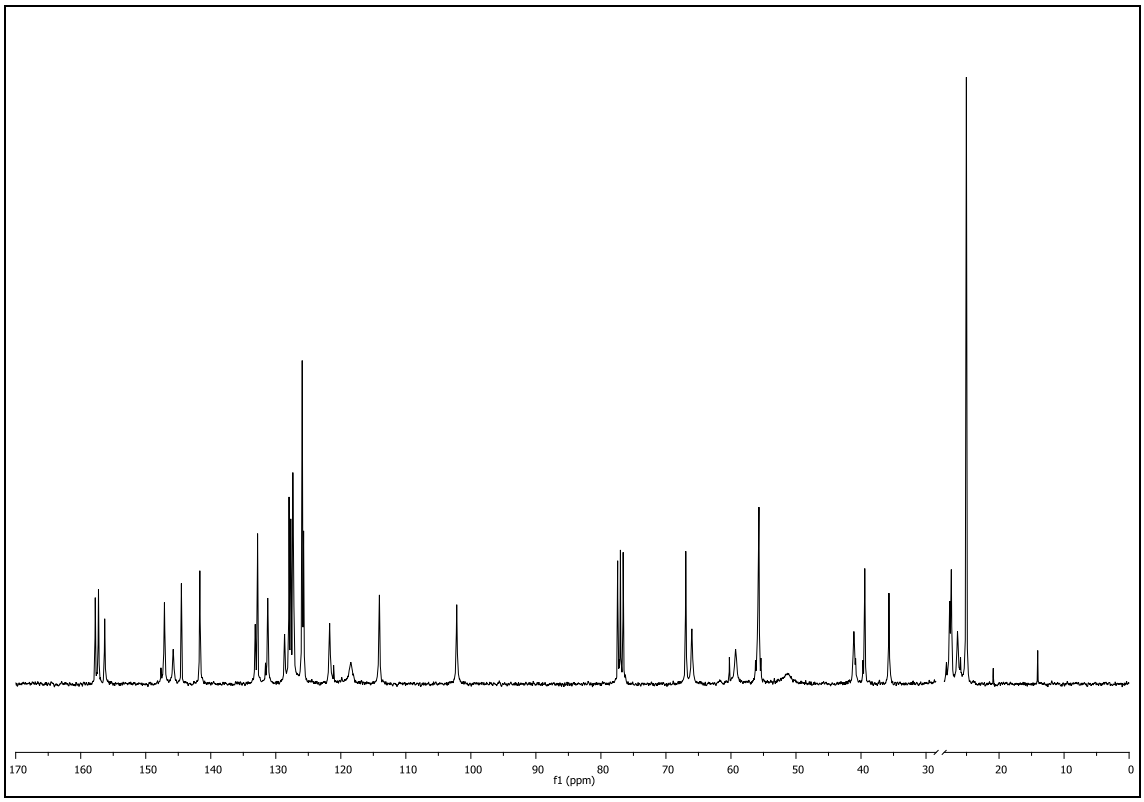

O
O
N
H
N
H
N
H
O
N
N
MeO
298
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

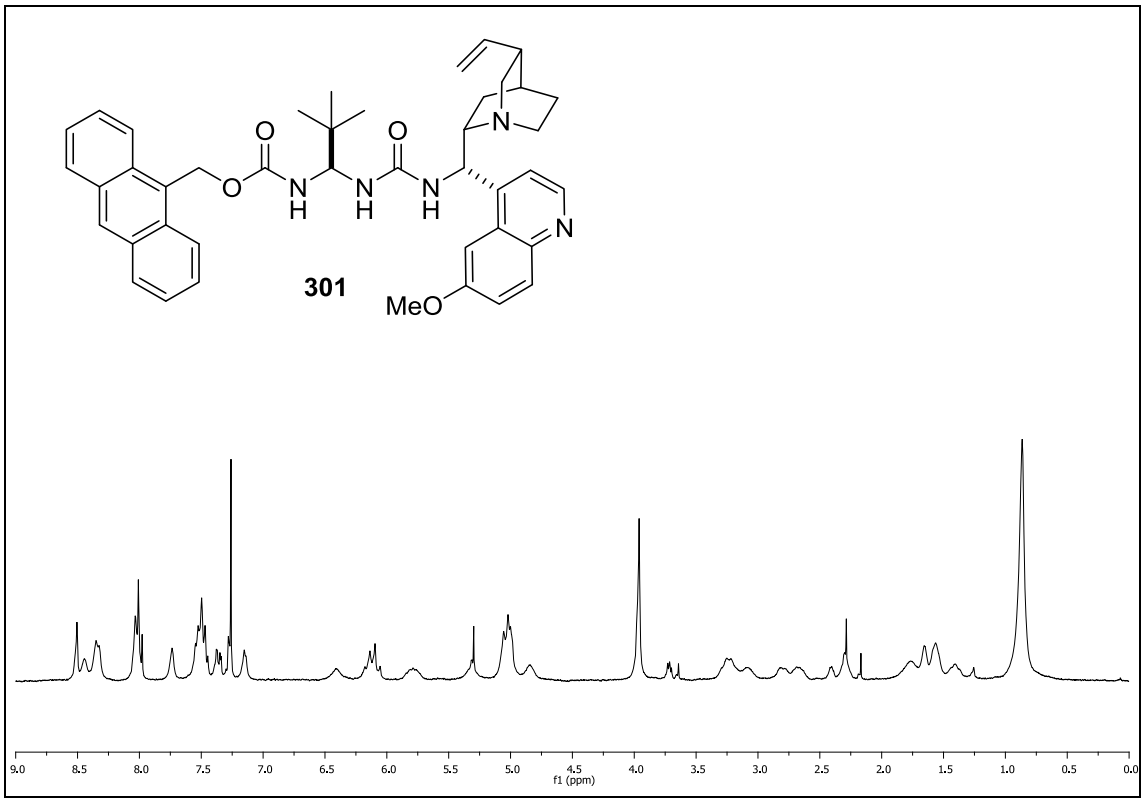

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

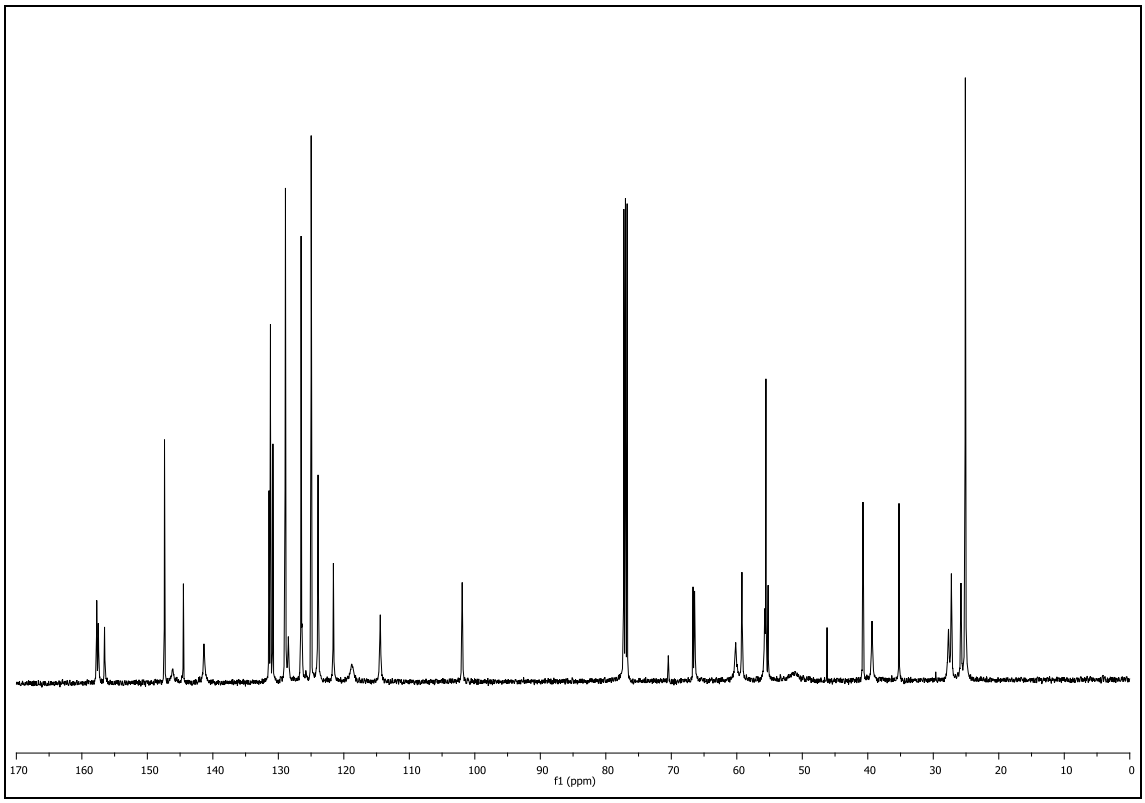

O
O
N
H
N
H
O
N
H
N
MeO
N
299
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

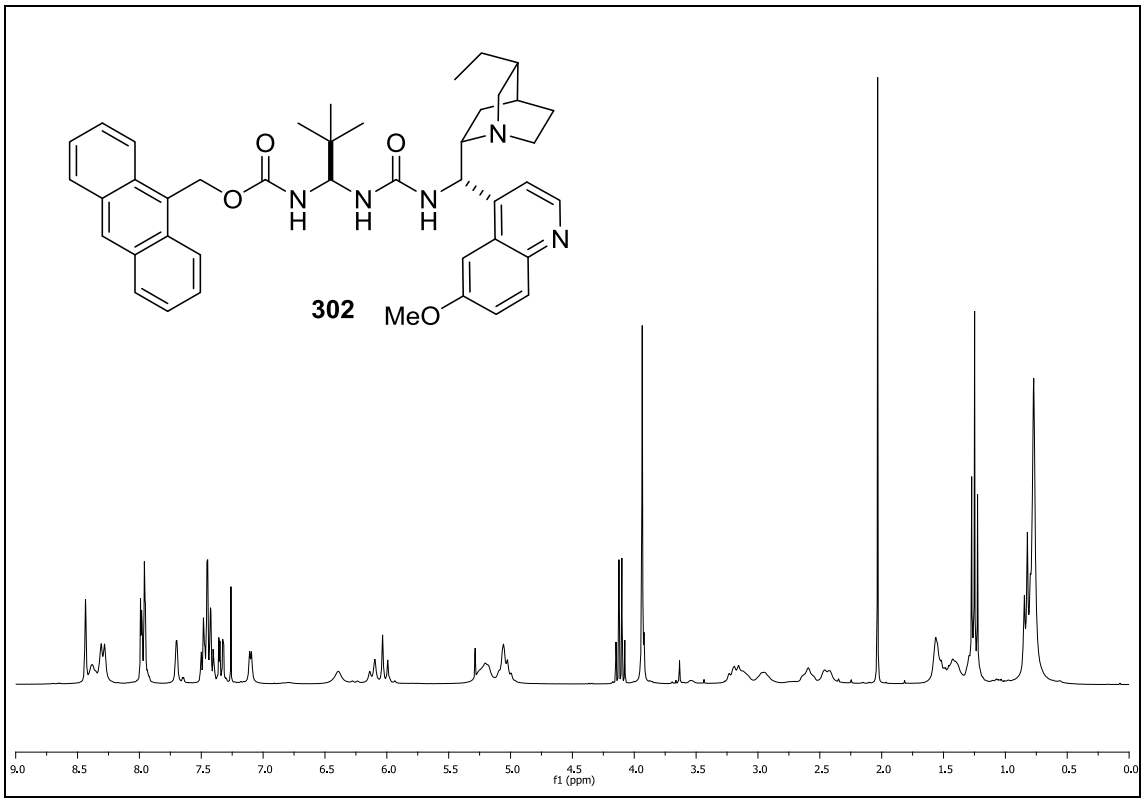

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

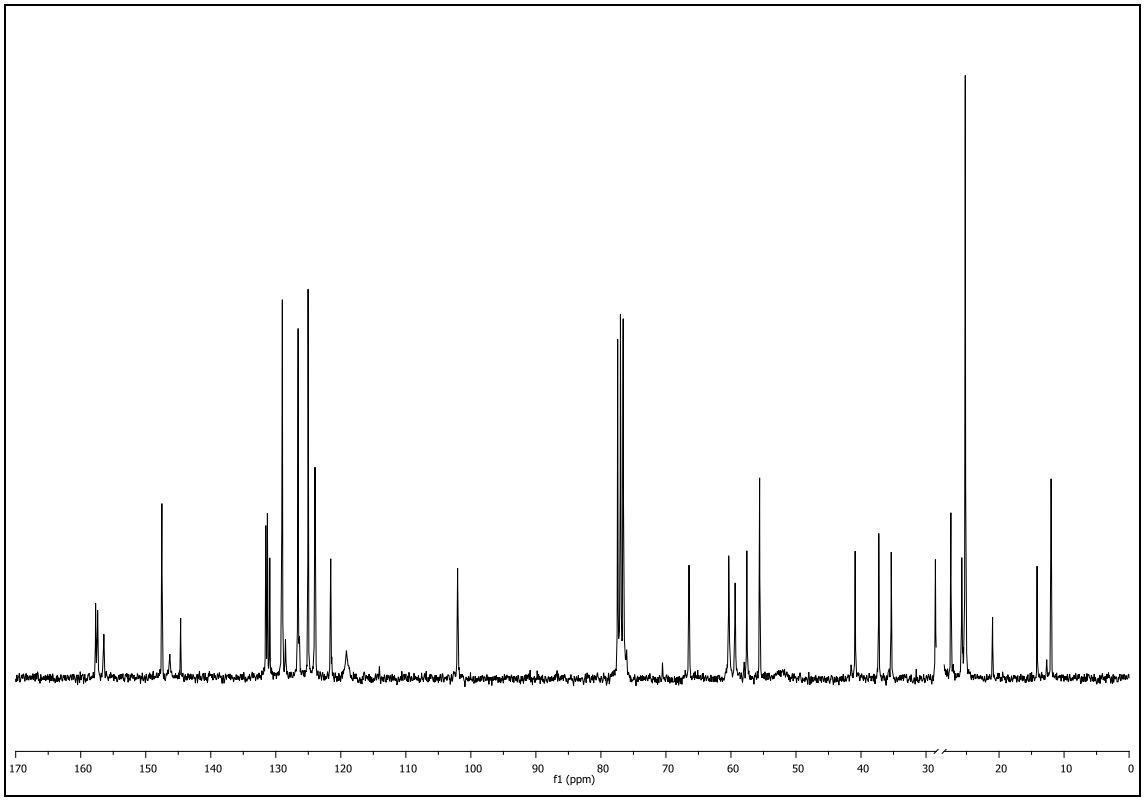

O
O
O
N
H
N
H
N
H
N
MeO
300
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

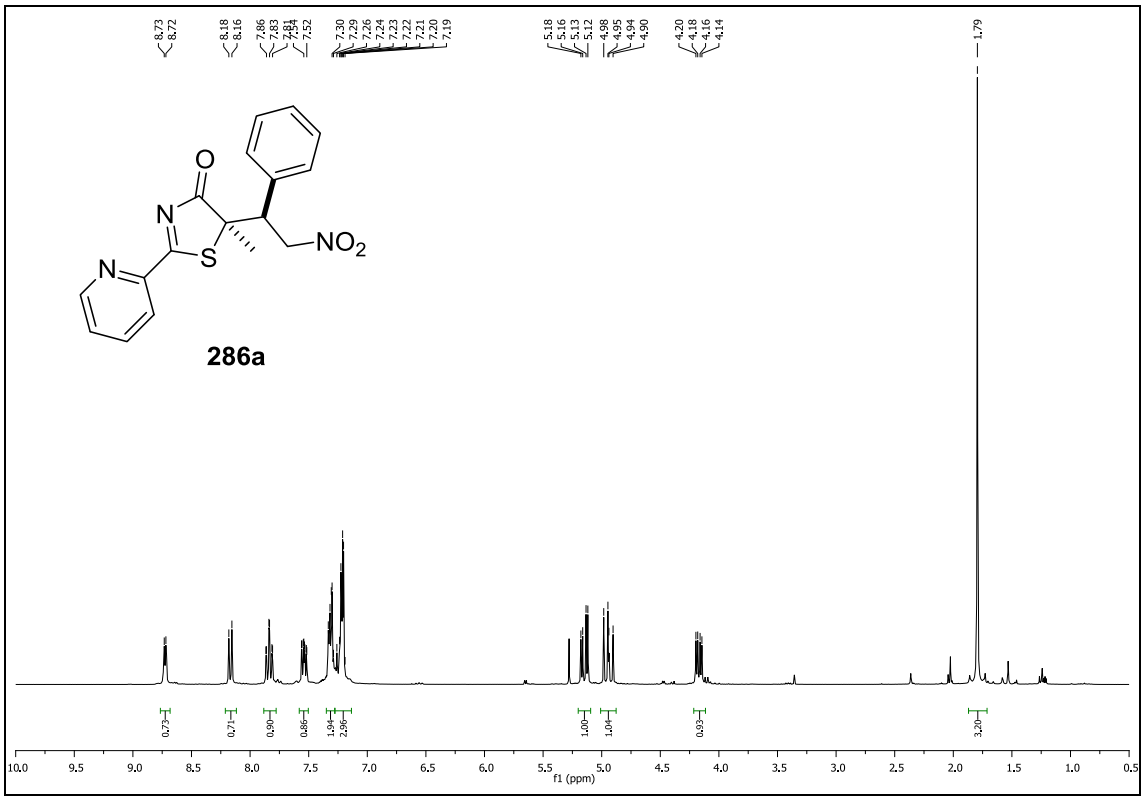

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

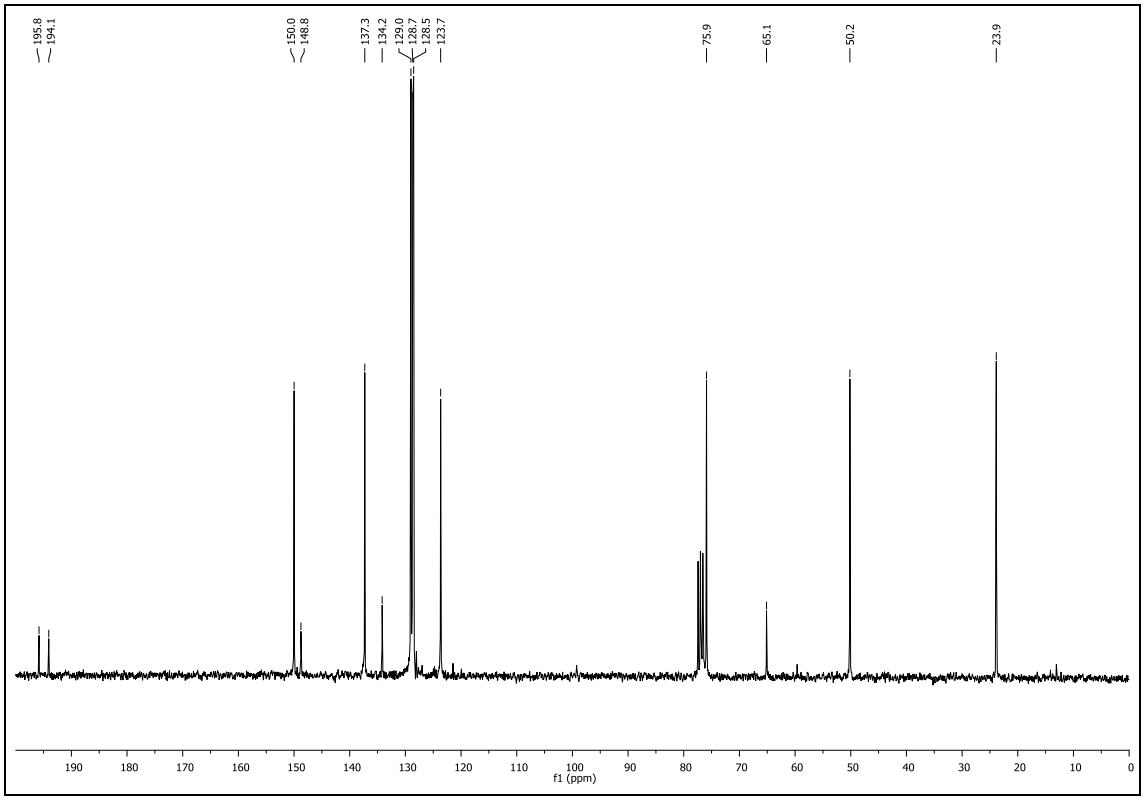

O
O
N
H
N
H
N
H
N
O
N
MeO
301
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

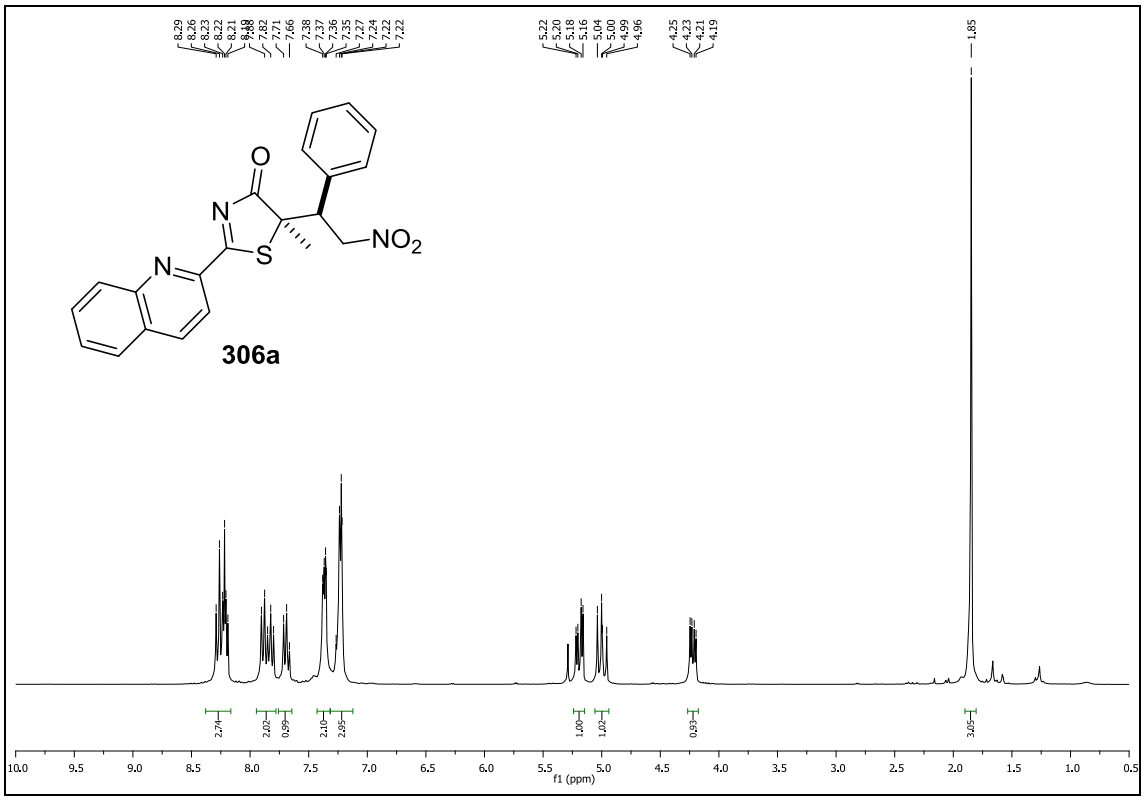

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

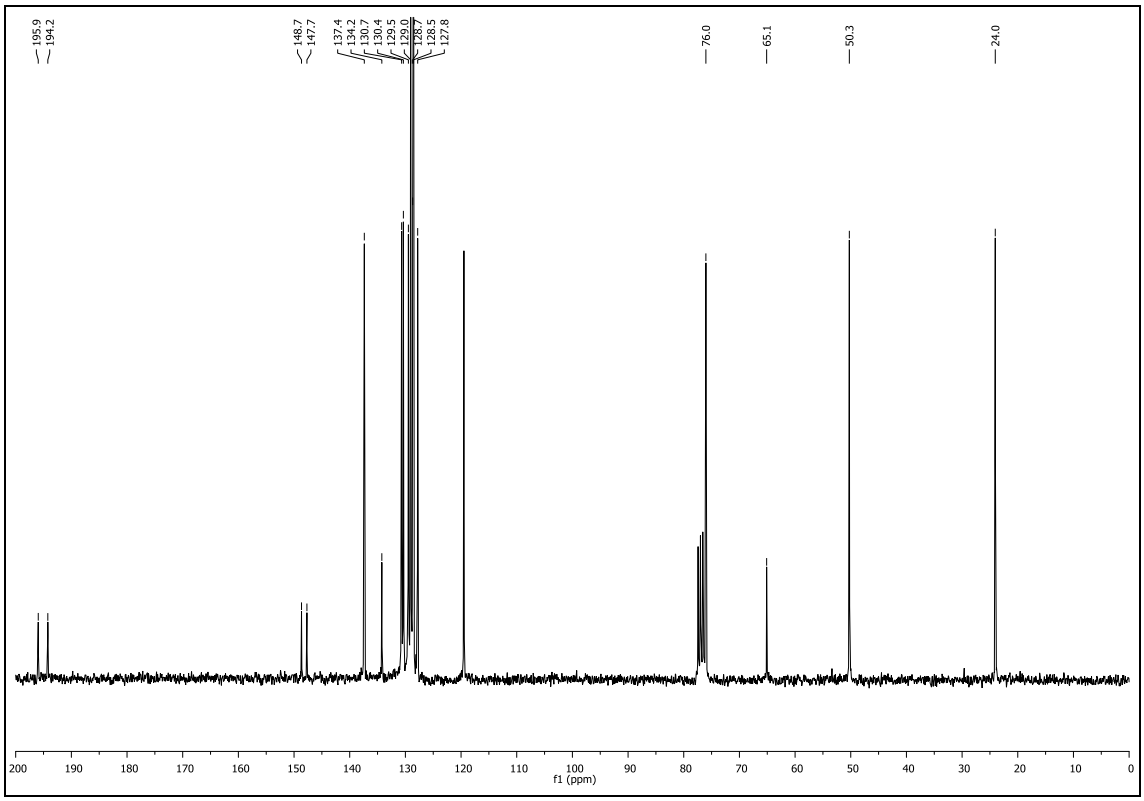

O
O
N
H
N
H
N
H
N
O
N
MeO
302
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

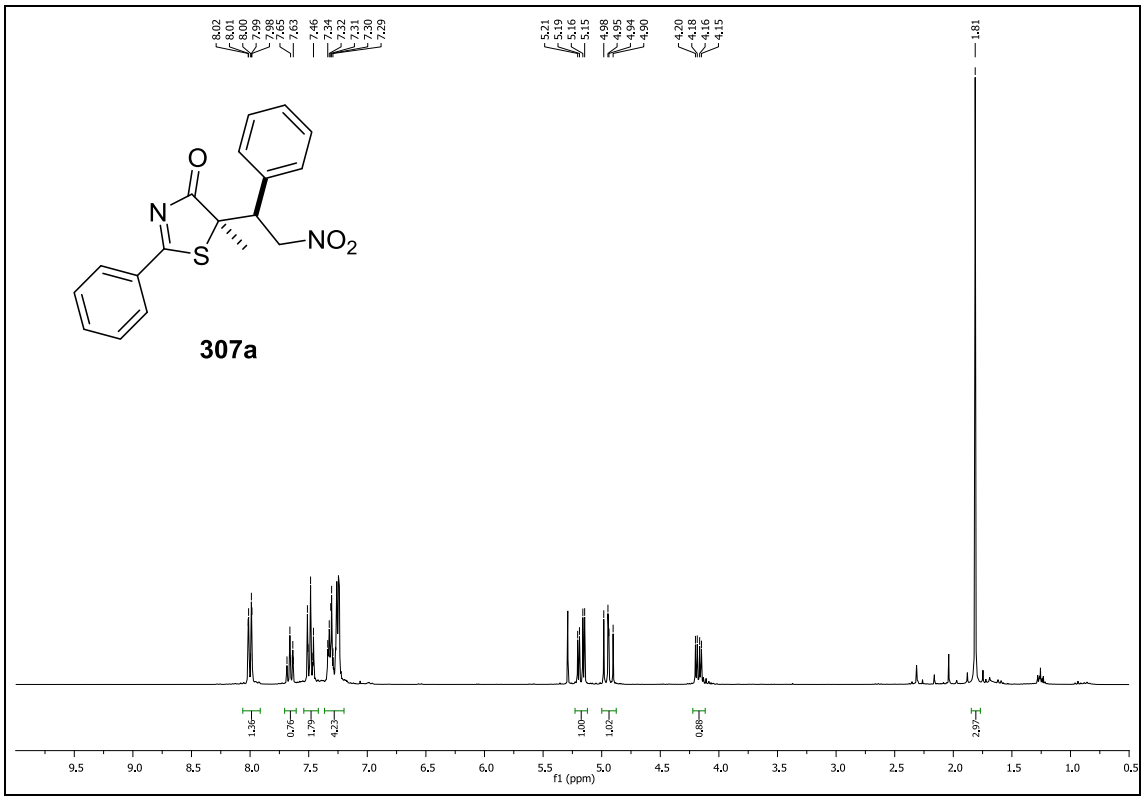

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

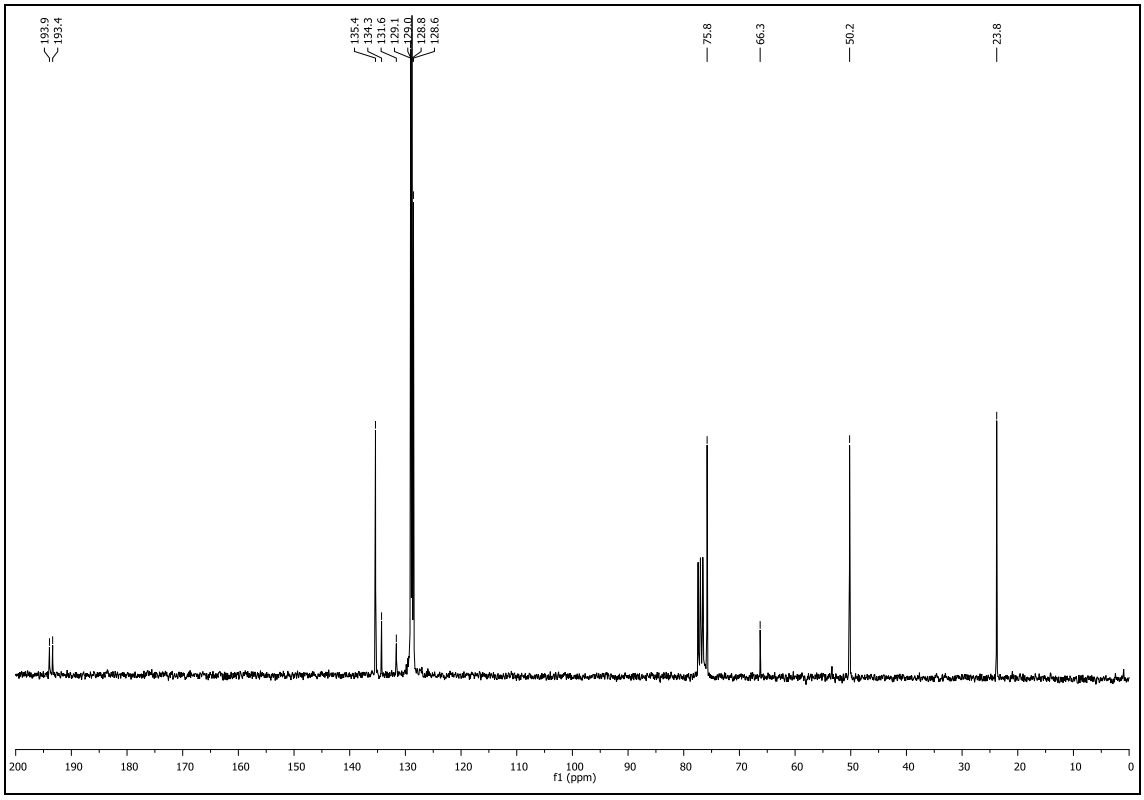

8.73
8.72
8.18
8.16
7.86
7.83
7.81
7.52
7.30
7.29
7.26
7.24
7.23
7.22
7.21
7.20
7.19
5.18
5.16
5.13
5.12
4.98
4.95
4.94
4.90
4.20
4.18
4.16
4.14
1.79
O
N
S
N
NO2
286a
0.73
0.71
0.90
0.86
1.94
2.96
1.00
1.04
0.93
3.20
f1 (ppm)

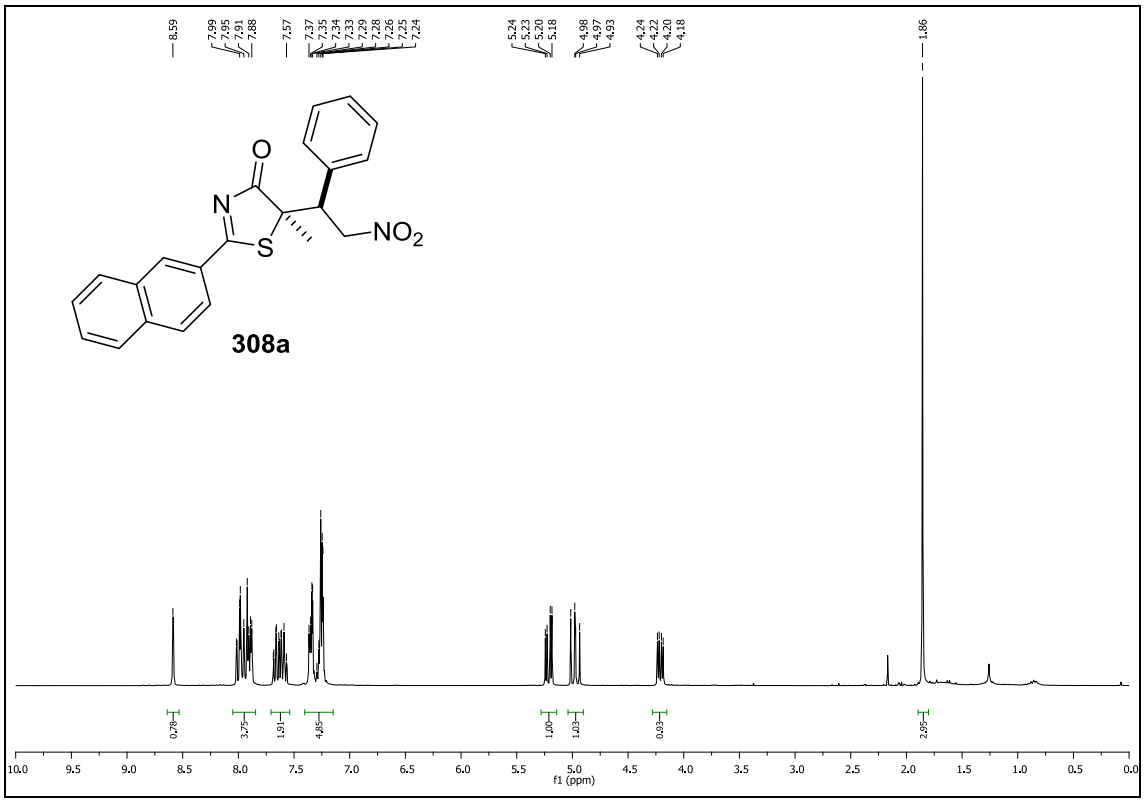

195.8
194.1
150.0
148.8
137.3
134.2
129.0
128.7
128.5
123.7
75.9
65.1
50.2
23.9
f1 (ppm)


8.29
8.26
8.23
8.22
8.21
7.82
7.71
7.66
7.38
7.37
7.36
7.35
7.27
7.24
7.22
7.22
5.22
5.20
5.18
5.16
5.04
5.00
4.99
4.96
4.25
4.23
4.21
4.19
1.85
O
N
S
N
NO2
306a
2.74
2.02
0.99
2.10
2.95
1.00
1.02
0.93
3.05
f1 (ppm)


195.9
194.2
148.7
147.7
137.4
134.2
130.7
130.4
129.5
129.0
128.7
128.5
127.8
76.0
65.1
50.3
24.0
f1 (ppm)


8.02
8.01
8.00
7.99
7.88
7.85
7.63
7.46
7.34
7.32
7.31
7.30
7.29
5.21
5.19
5.16
5.15
4.98
4.95
4.94
4.90
4.20
4.18
4.16
4.15
1.81
O
N
S
NO2
307a
1.36
0.76
1.79
4.23
1.00
1.02
0.88
2.97
f1 (ppm)


193.9
193.4
135.4
134.3
131.6
129.1
129.0
128.8
128.6
75.8
66.3
50.2
23.8
f1 (ppm)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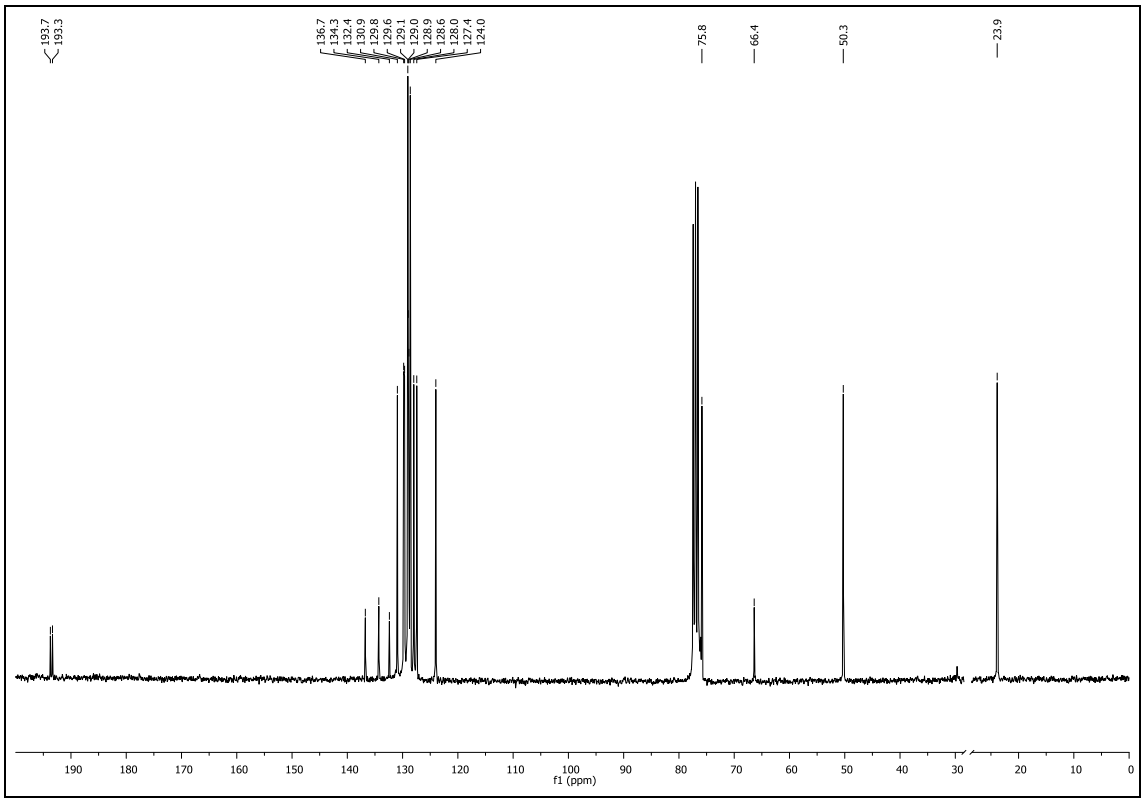
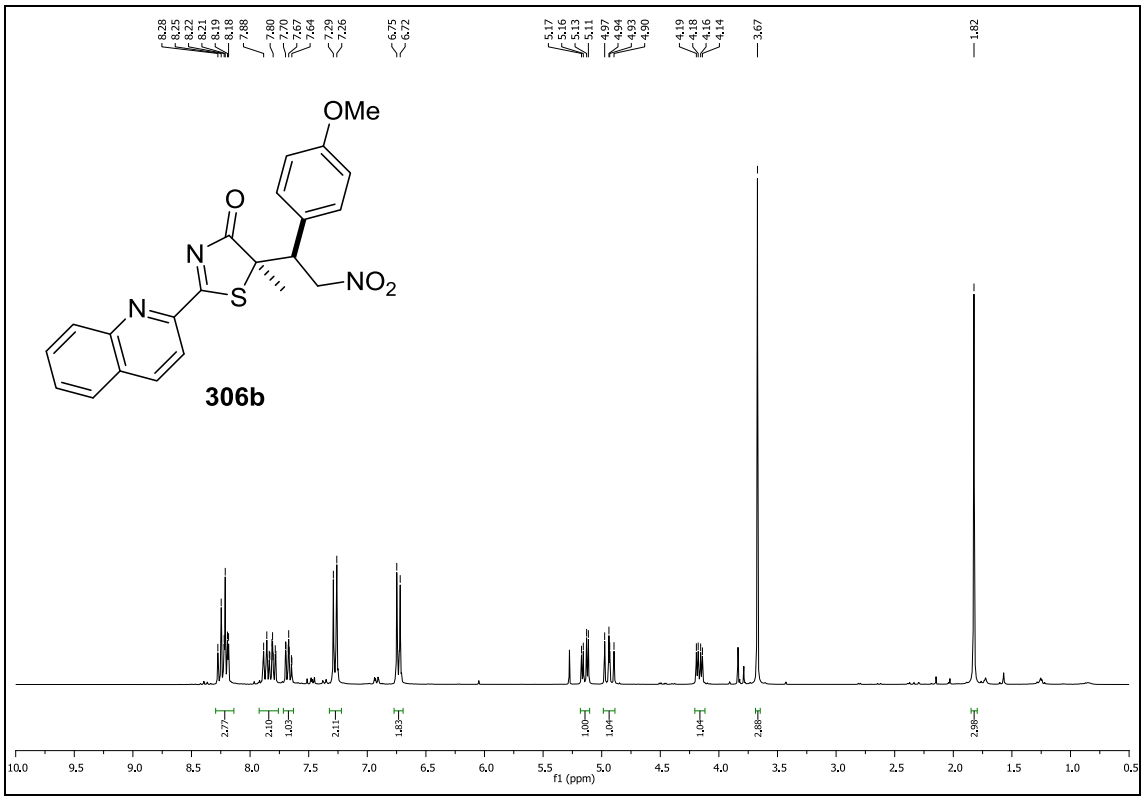
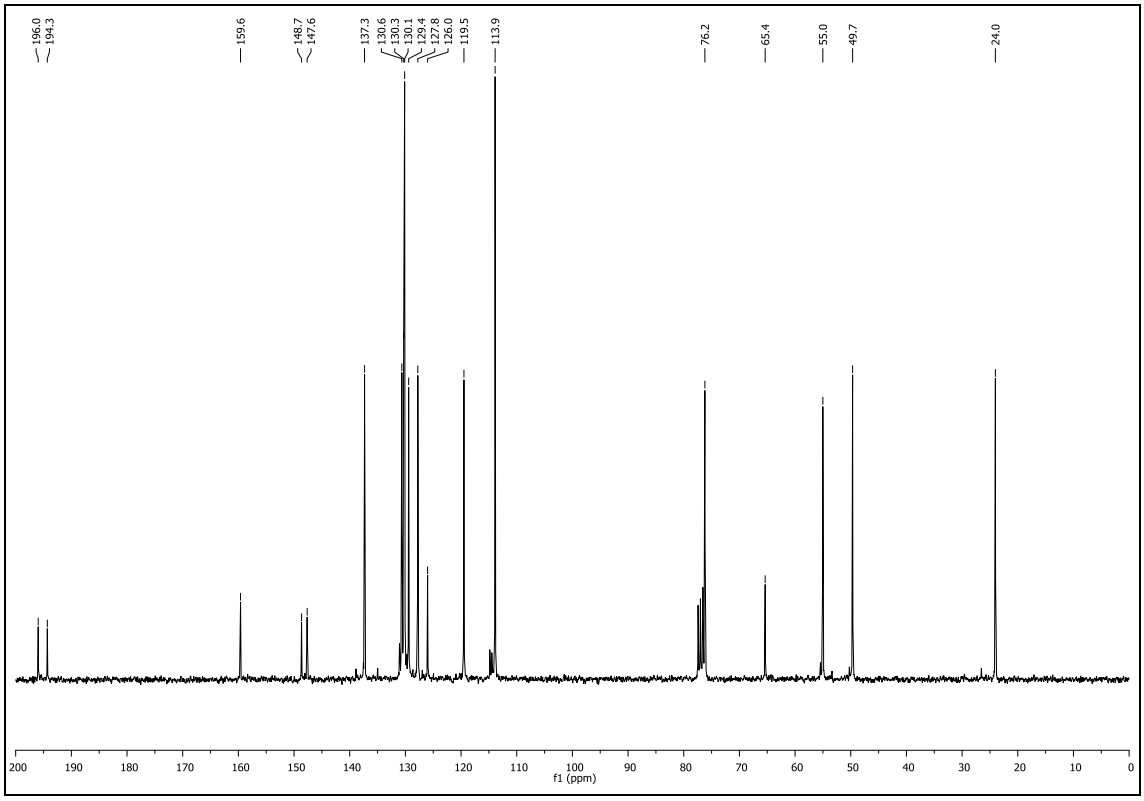
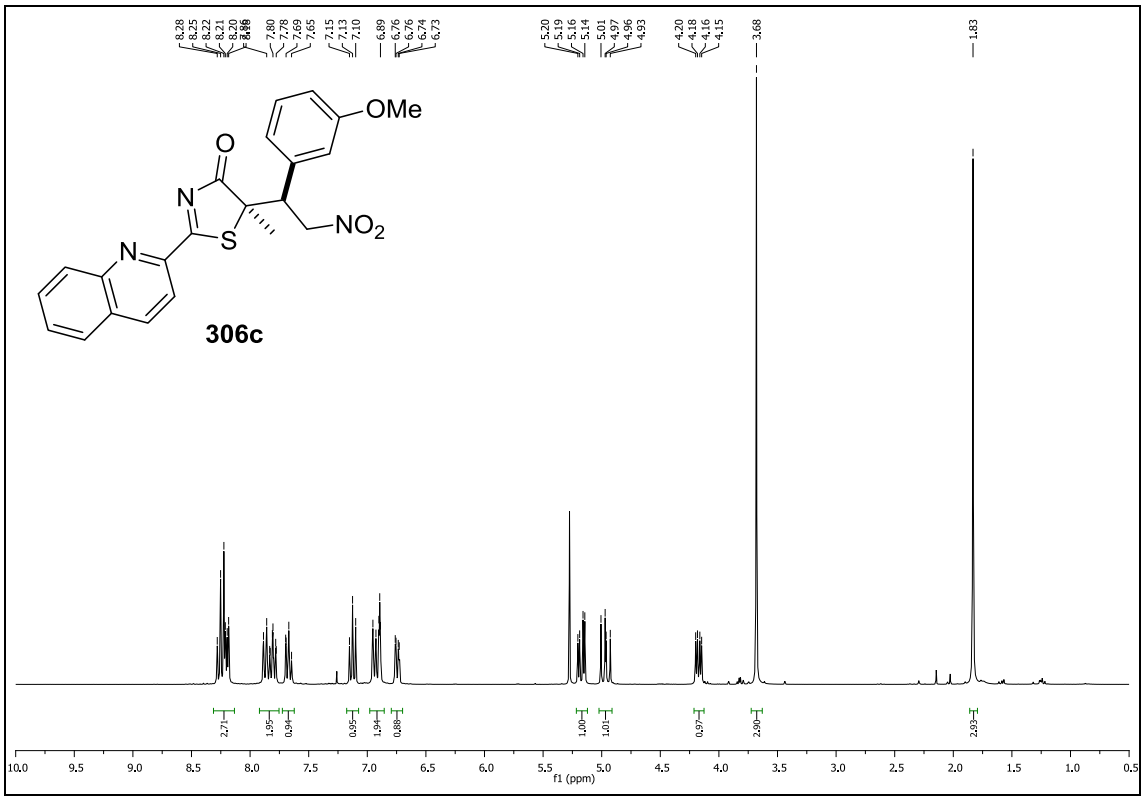
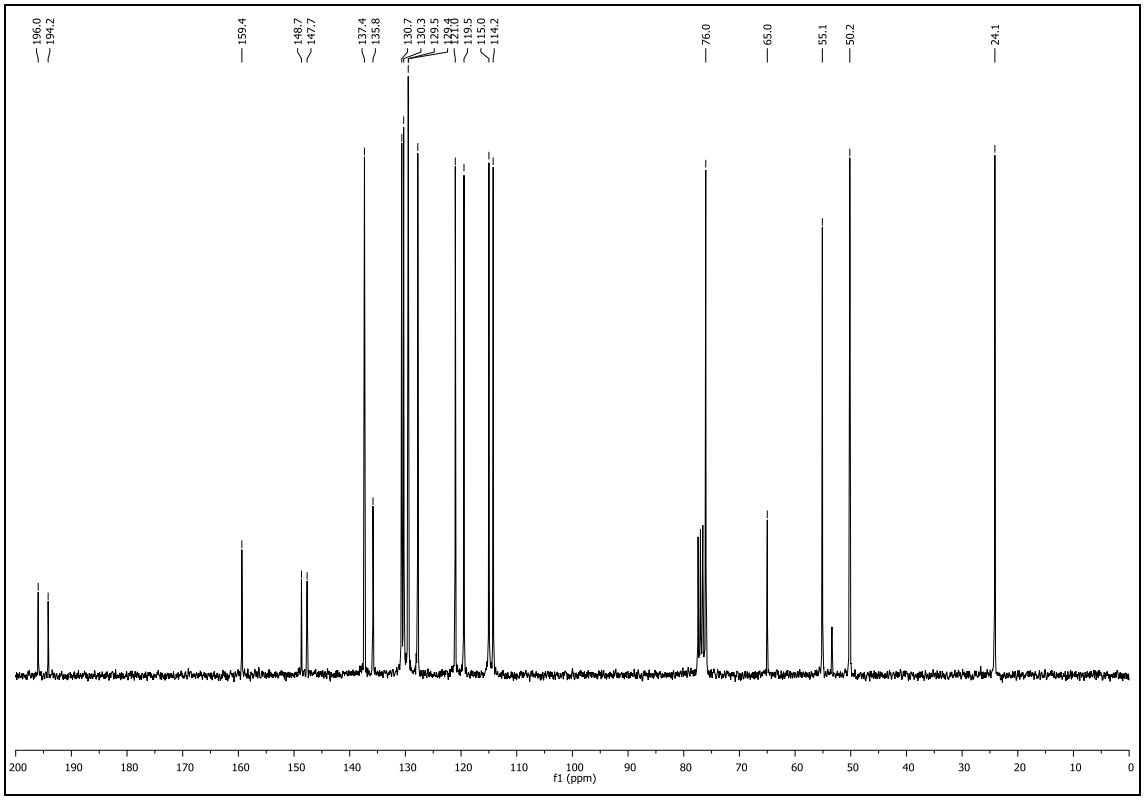
7.99
7.95
7.91
7.88
7.57
7.37
7.35
7.34
7.33
7.29
7.28
7.26
7.25
7.24
5.24
5.23
5.20
5.18
4.98
4.97
4.93
4.24
4.22
4.20
4.18
1.86
O
N
S
NO2
308a
0.78
3.75
1.91
4.85
1.00
1.03
0.93
2.95
f1 (ppm)

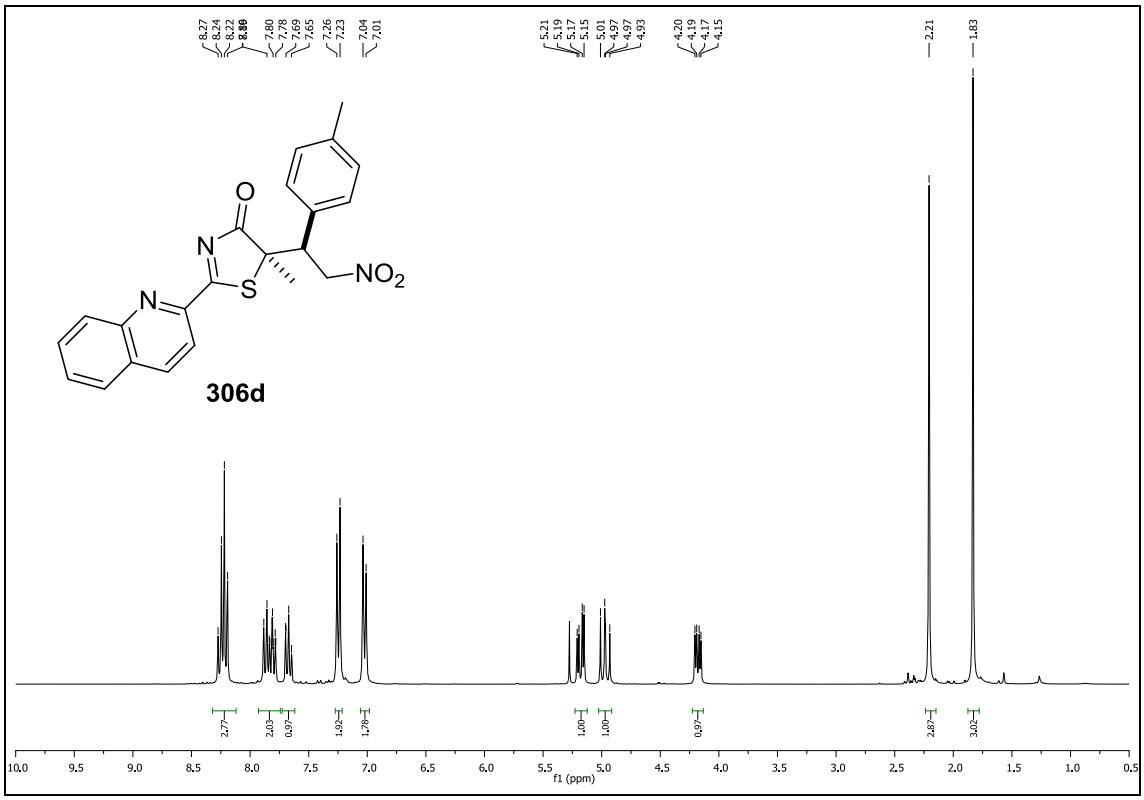

193.7
193.3
136.7
134.3
132.4
130.9
129.8
129.6
129.1
129.0
128.9
128.6
128.0
127.4
124.0
75.8
66.4
50.3
23.9
f1 (ppm)

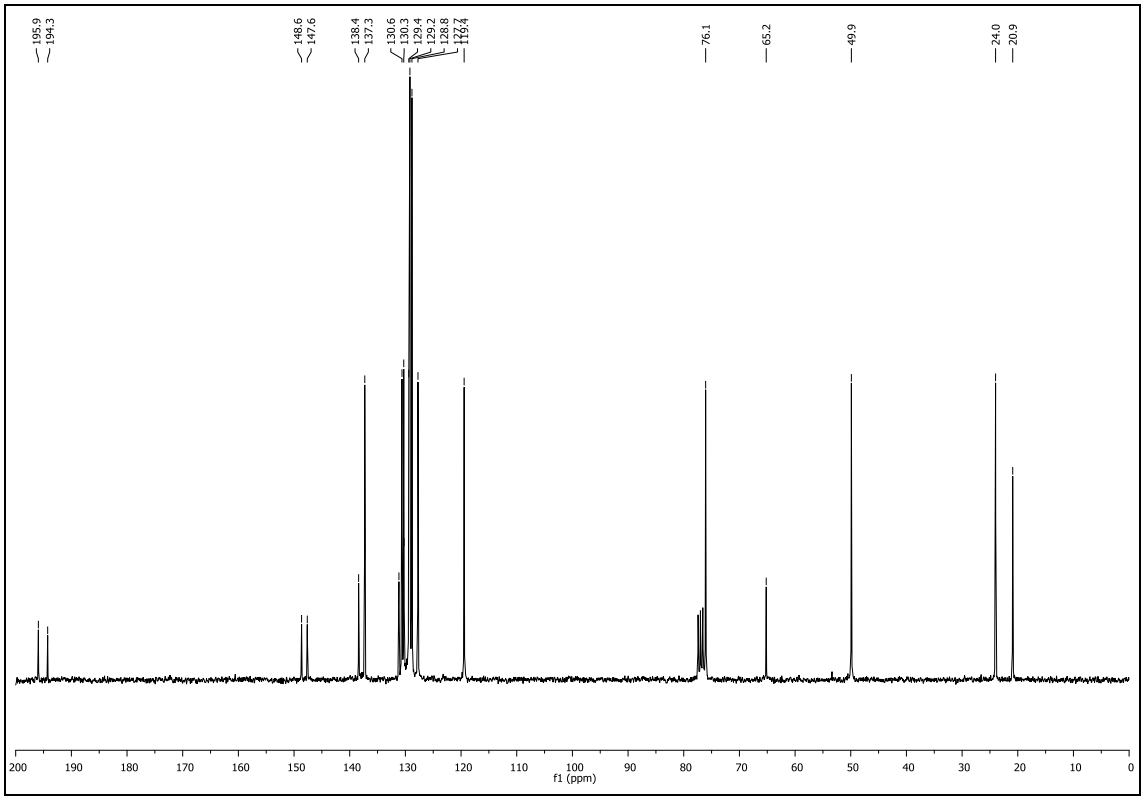

OMe
O
N
S
N
NO2
306b
f1 (ppm)

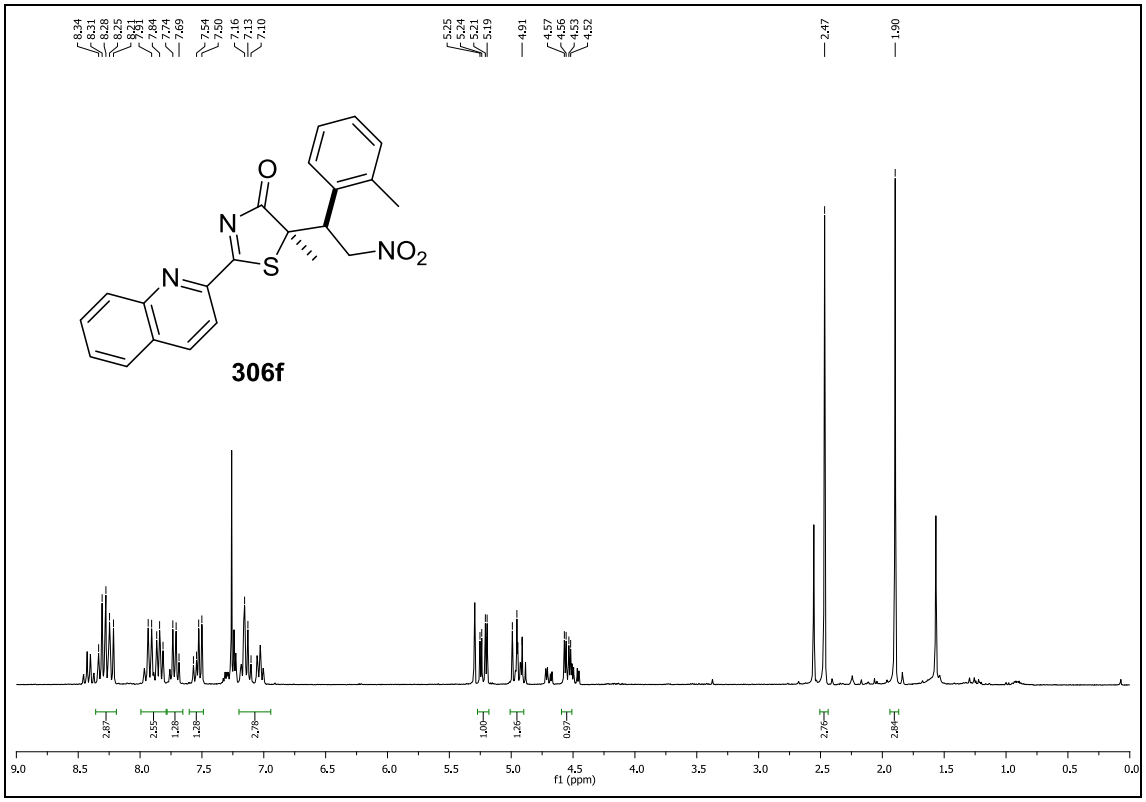

f1 (ppm)

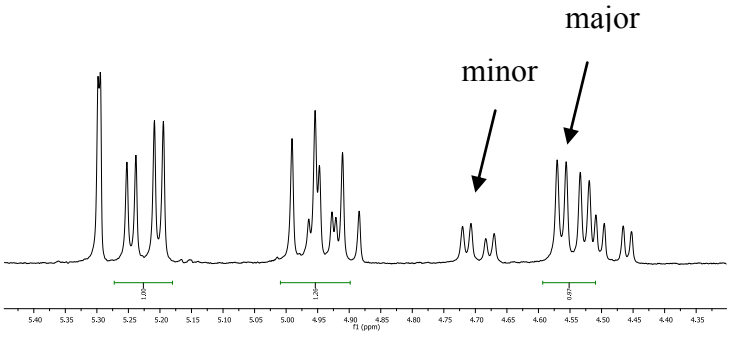

OMe
O
N
S
N
NO2
306c
f1 (ppm)

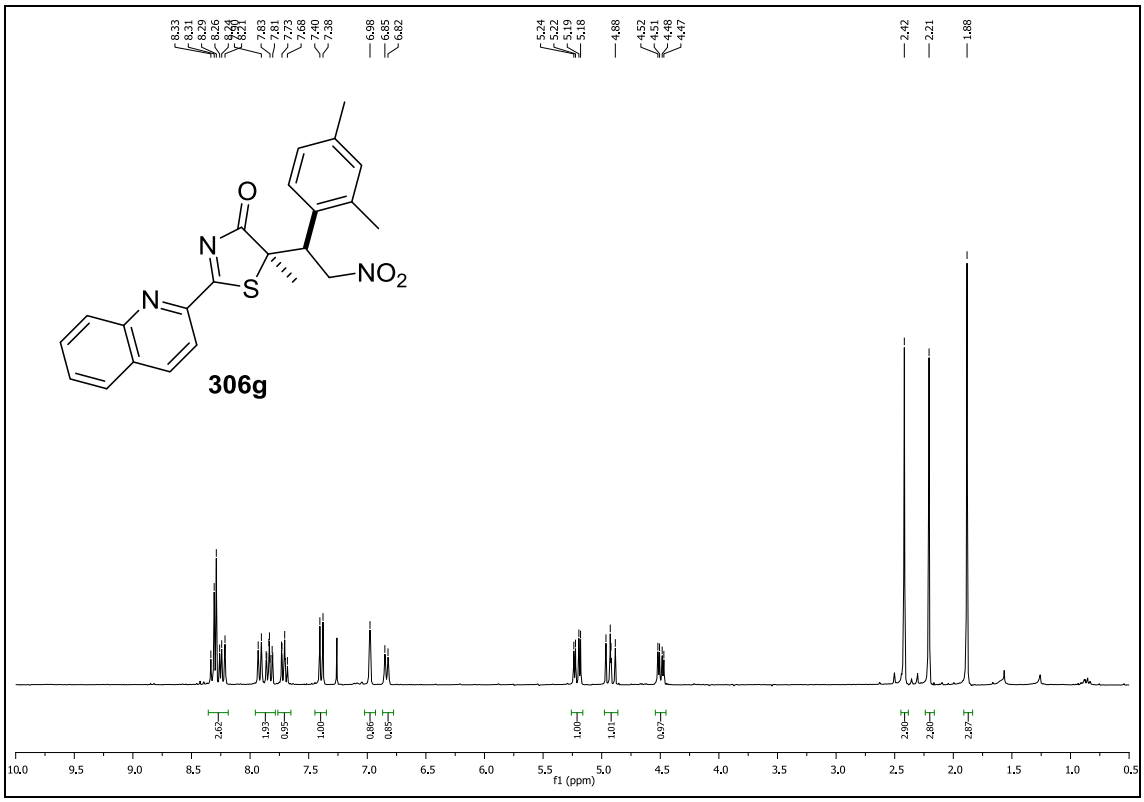

f1 (ppm)

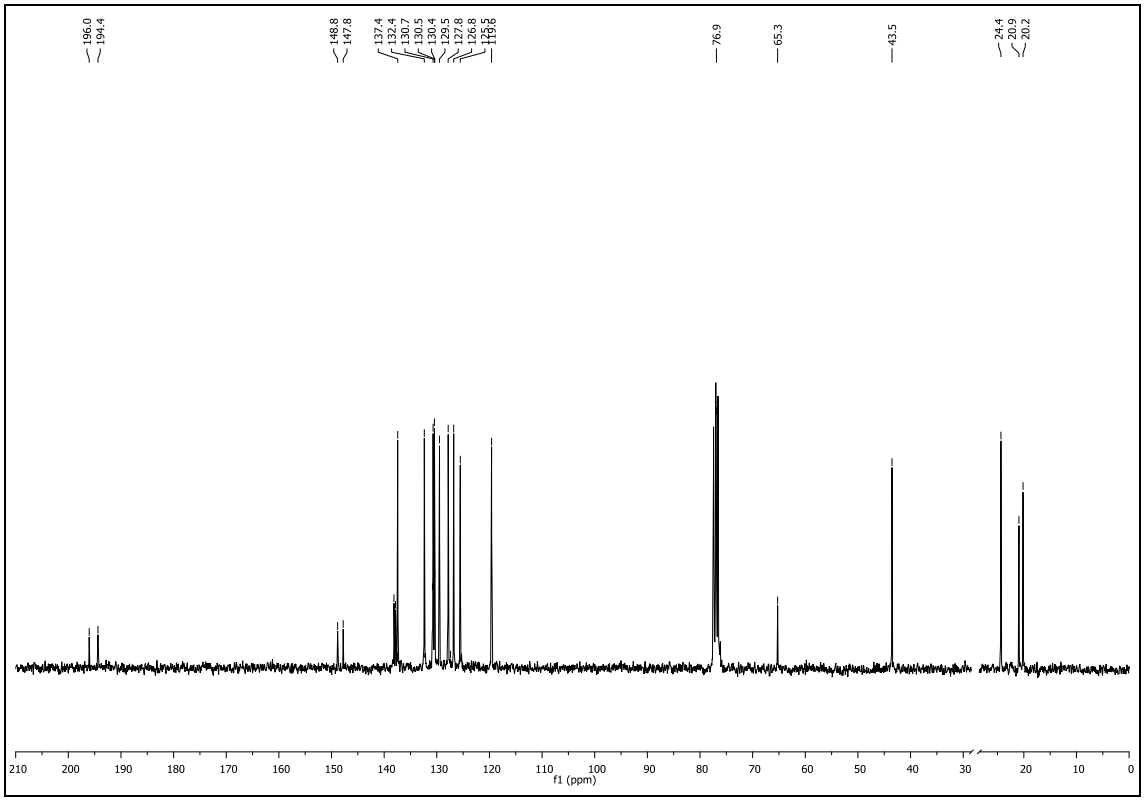

8.27
8.24
8.22
7.80
7.78
7.69
7.65
7.26
7.23
7.04
7.01
5.21
5.19
5.17
5.15
5.01
4.97
4.97
4.93
4.20
4.19
4.17
4.15
2.21
1.83
O
N
S
N
NO2
306d
2.77
2.03
0.97
1.92
1.78
1.00
1.00
0.97
2.87
3.02
f1 (ppm)

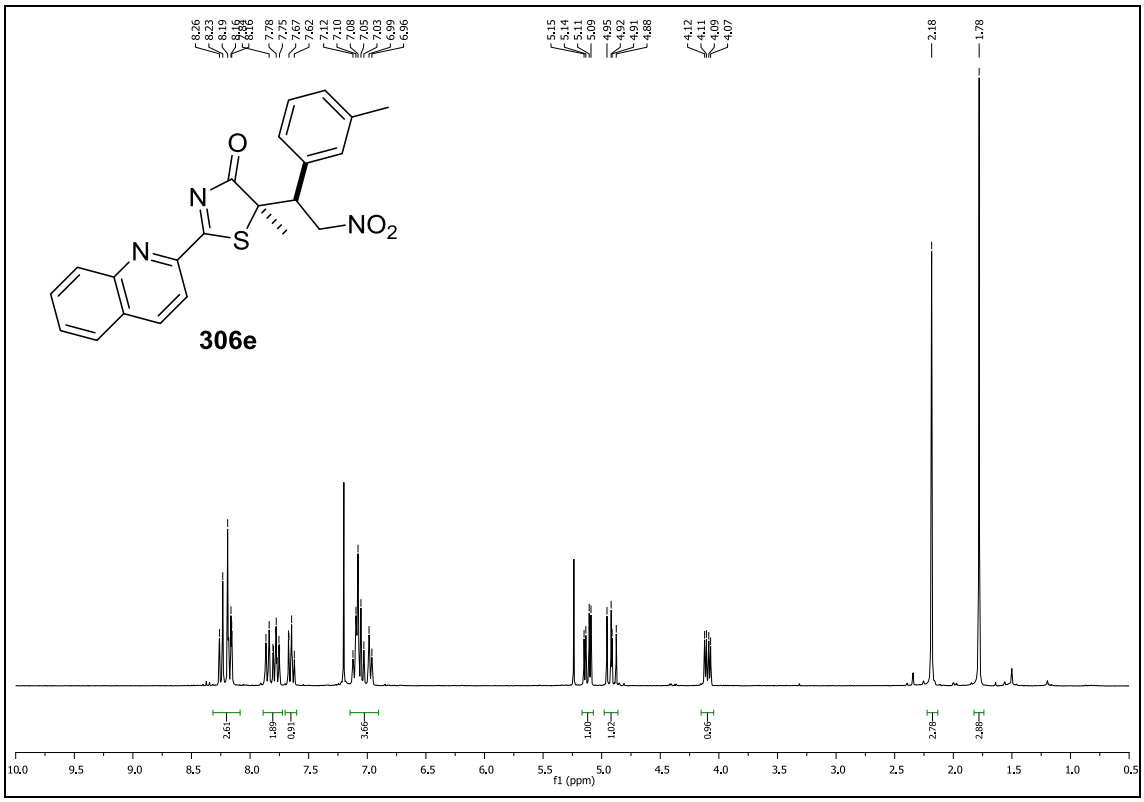

195.9
194.3
148.6
147.6
138.4
137.3
130.6
130.3
129.4
129.2
128.8
127.7
119.4
76.1
65.2
49.9
24.0
20.9
f1 (ppm)


8.34
8.31
8.28
8.25
8.21
8.21
7.84
7.74
7.69
7.54
7.50
7.16
7.13
7.10
5.25
5.24
5.21
5.19
4.91
4.57
4.55
4.53
4.52
2.47
1.90
O
N
S
N
NO2
306f
2.87
2.55
1.28
1.28
2.78
1.00
1.26
0.97
2.76
2.84
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


major
minor
1.00
1.26
0.81
5.40
5.35
5.30
5.25
5.20
5.15
5.10
5.05
5.00
4.95
4.90
4.85
4.80
4.75
4.70
4.65
4.60
4.55
4.50
4.45
4.40
4.35
f1 (ppm)


306g
f1 (ppm)


f1 (ppm)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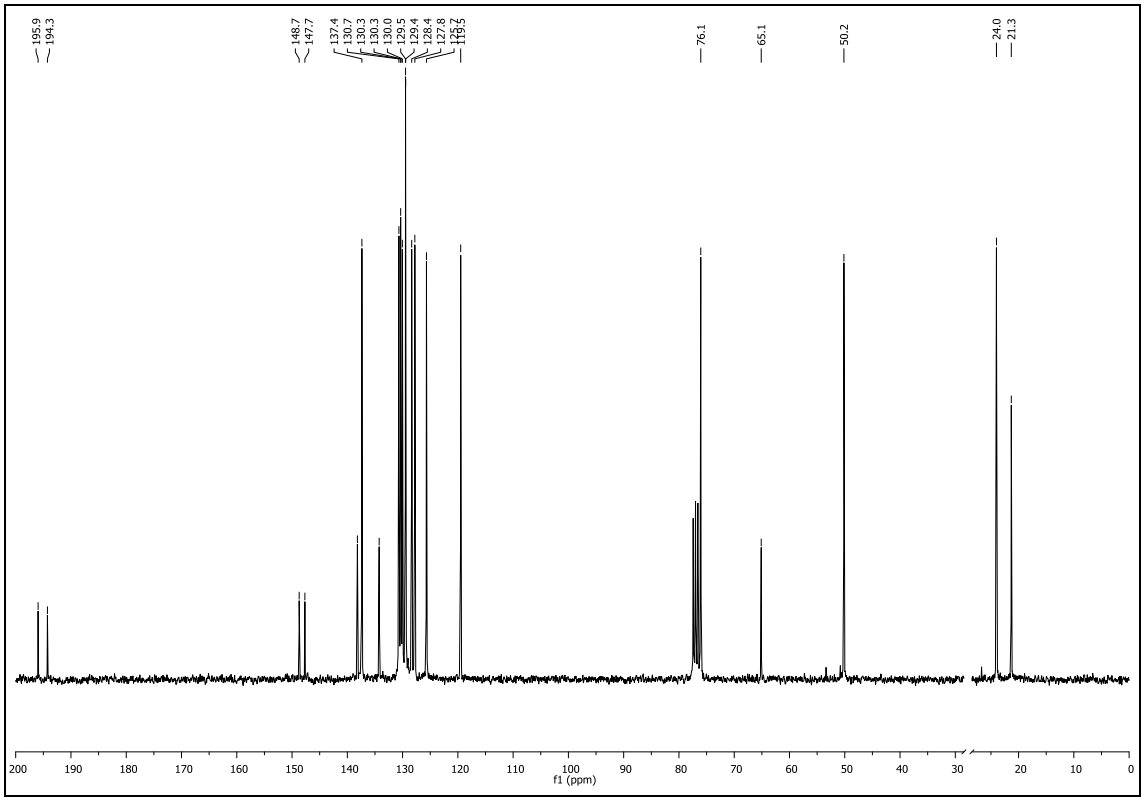
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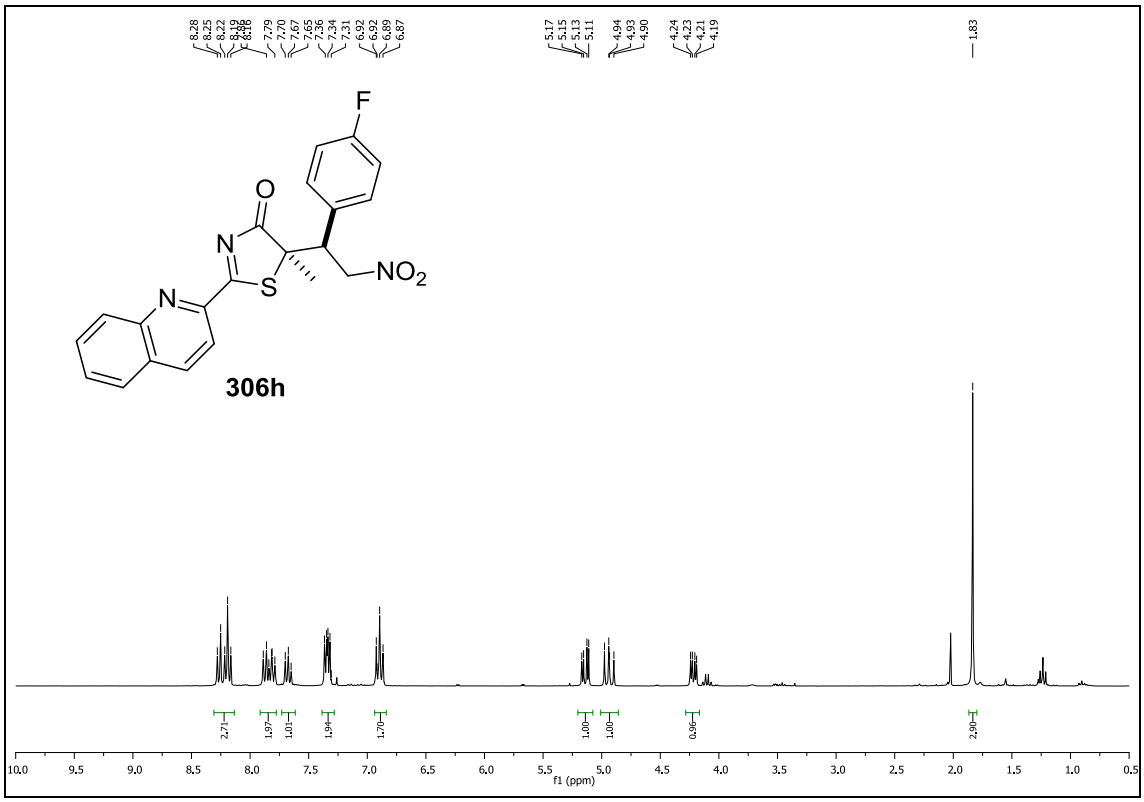
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7.31
6.92
6.92
6.89
6.87
5.17
5.15
5.13
5.11
4.94
4.93
4.90
4.24
4.23
4.21
4.19
1.83
F
O
N
S
N
NO2
306h
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1.01
1.94
1.70
1.00
1.00
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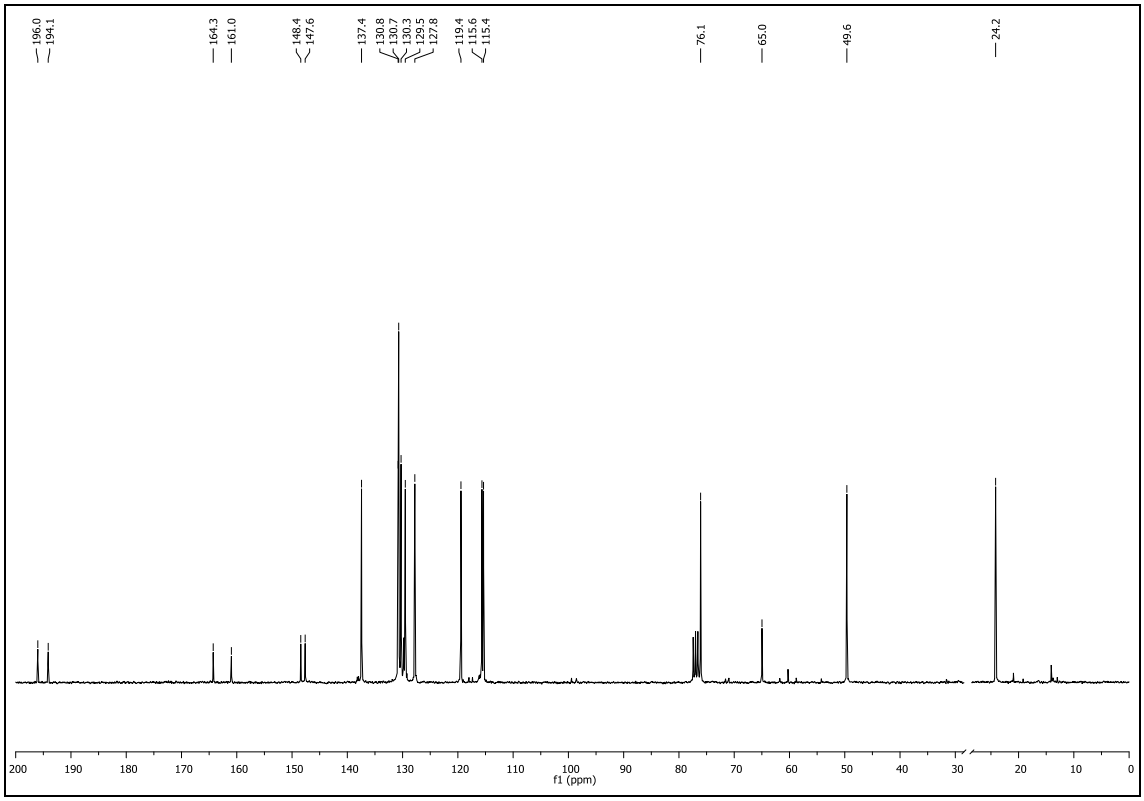
2.90
f1 (ppm)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164.3
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147.6
137.4
130.8
130.7
130.3
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127.8
119.4
115.6
115.4
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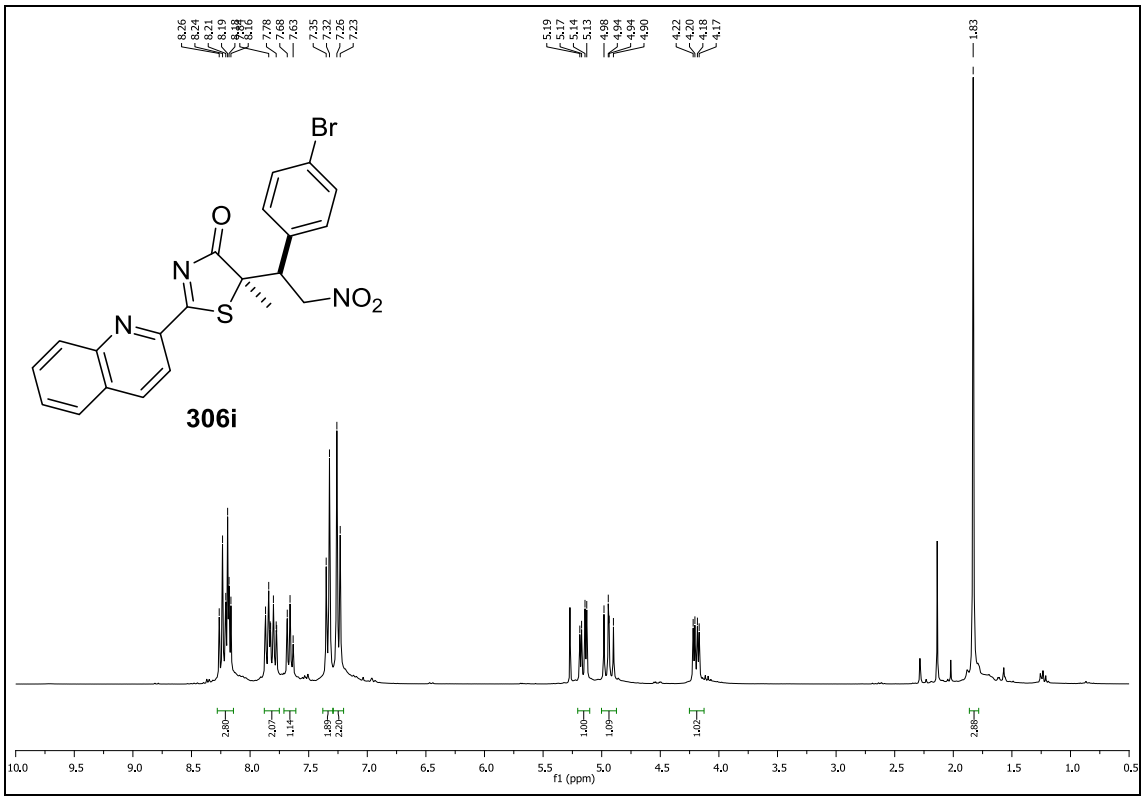
49.6
24.2
f1 (ppm)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S
N
NO2
306i
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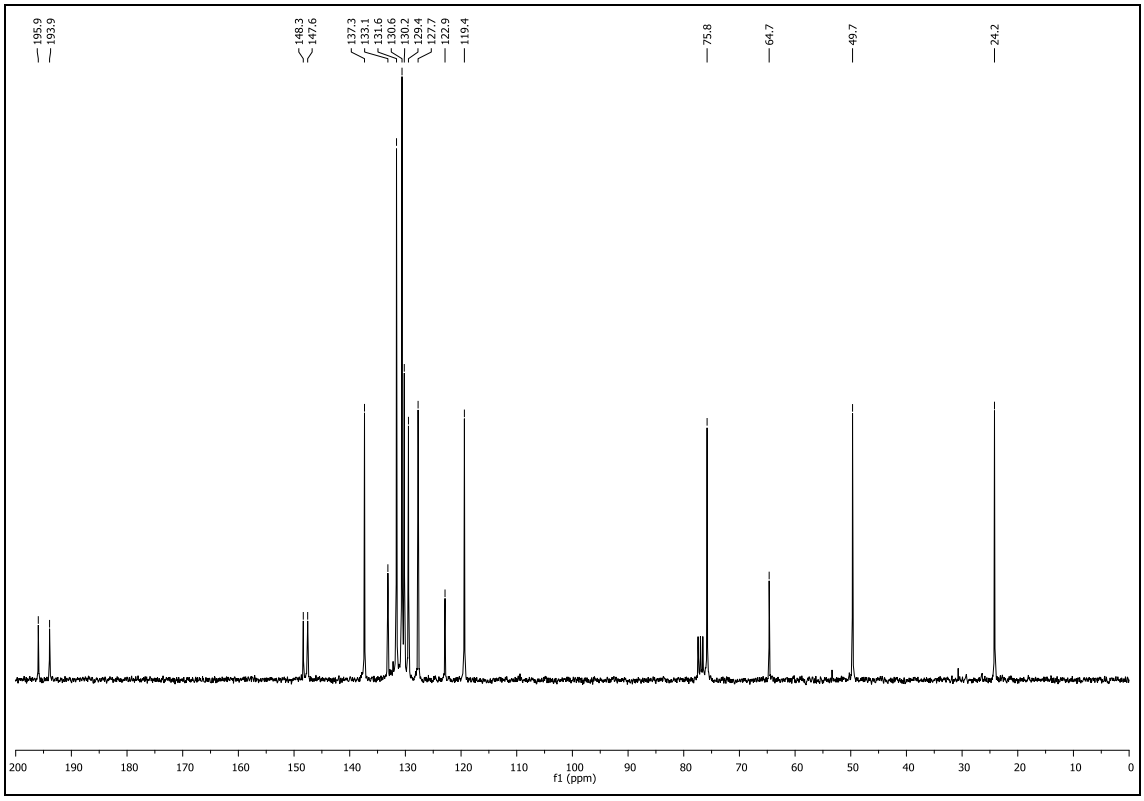
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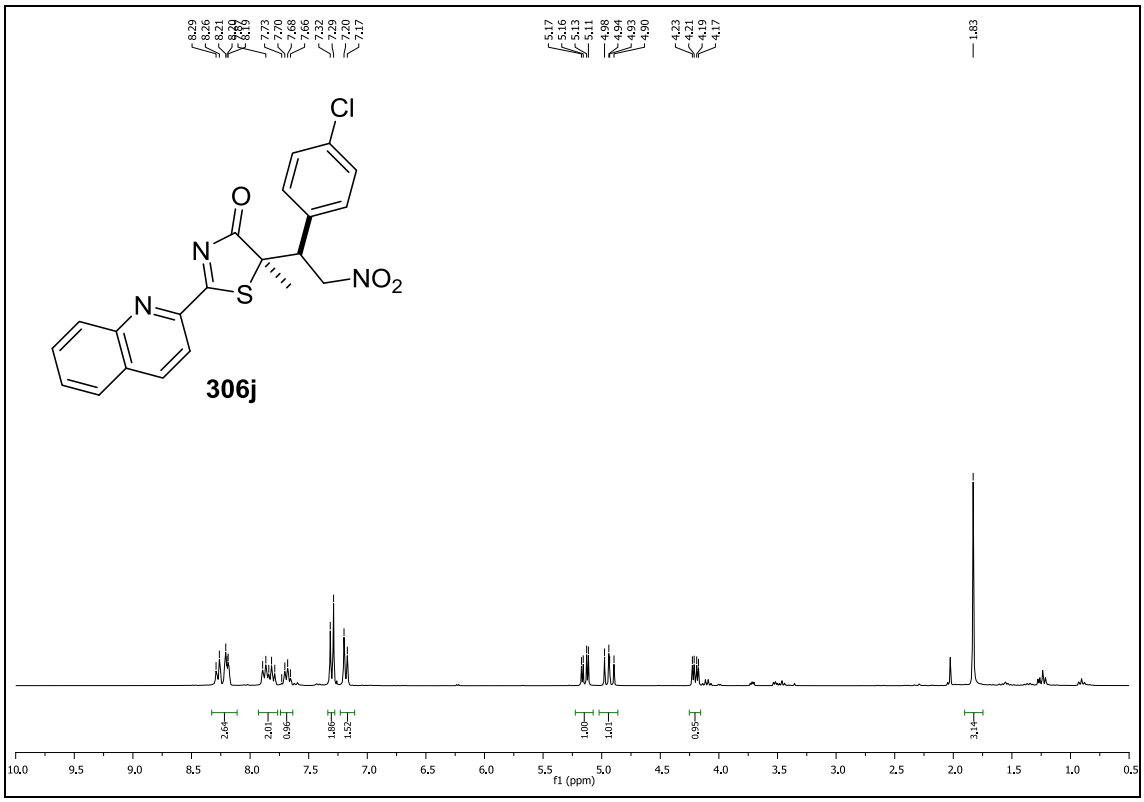
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7.17
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5.16
5.13
5.11
4.98
4.94
4.93
4.90
4.23
4.21
4.19
4.17
1.83
Cl
O
N
S
N
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1.52
1.00
1.01
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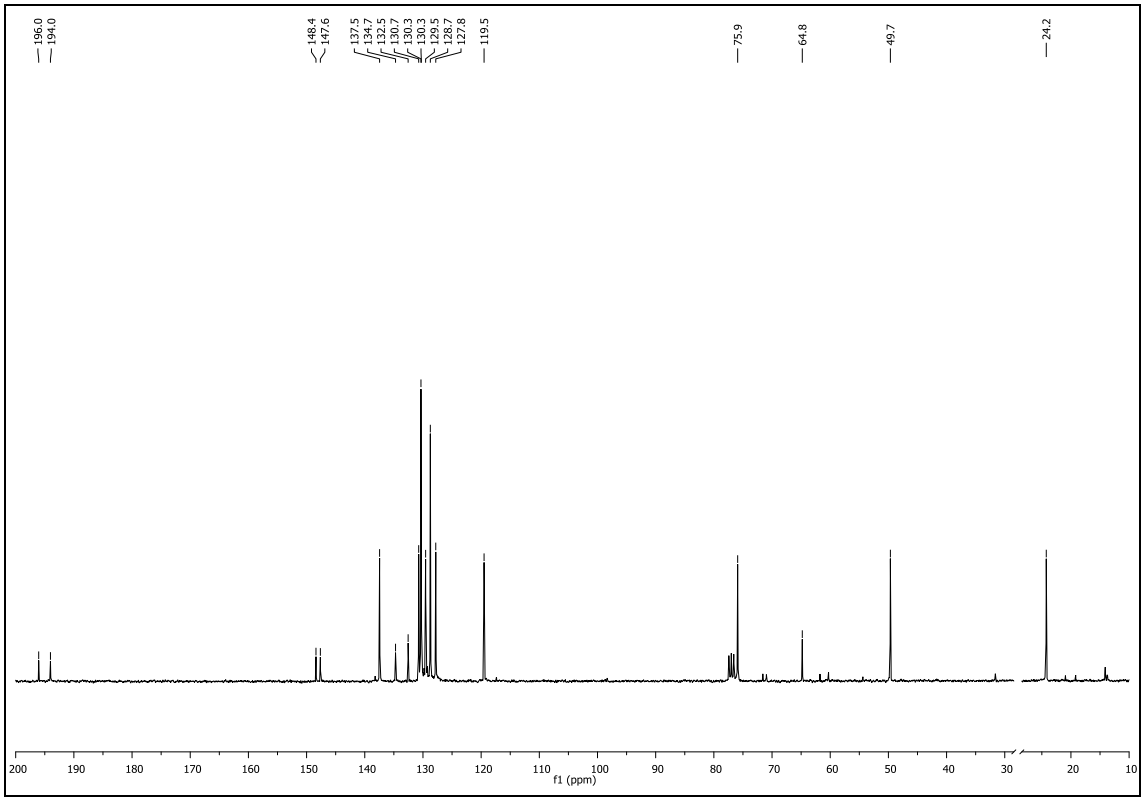
3.14
f1 (ppm)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132.5
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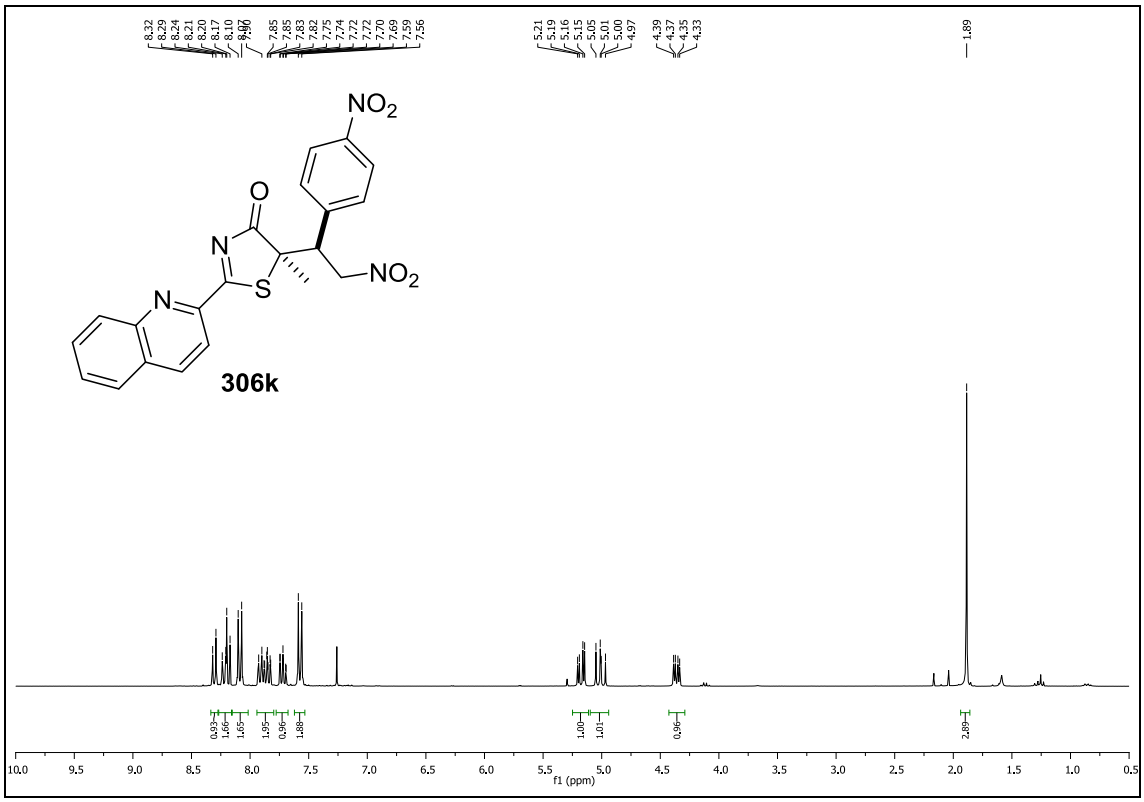
128.7
127.8
119.5
75.9
64.8
49.7
24.2
f1 (ppm)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7.75
7.74
7.72
7.72
7.70
7.69
7.59
7.56
5.21
5.19
5.16
5.15
5.05
5.01
5.00
4.97
4.39
4.37
4.35
4.33
1.89
NO2
O
N
S
N
NO2
306k
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1.65
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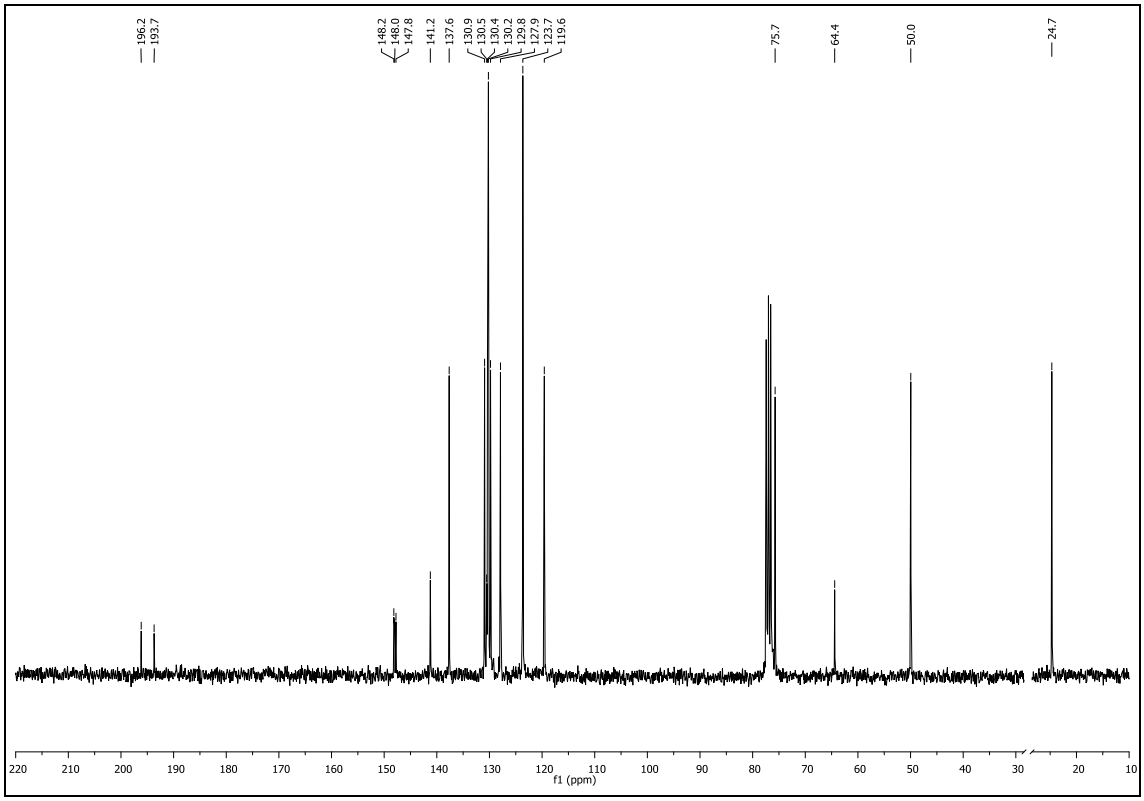
0.96
1.88
1.00
1.01
0.96
2.89
f1 (ppm)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193.7
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141.2
137.6
130.9
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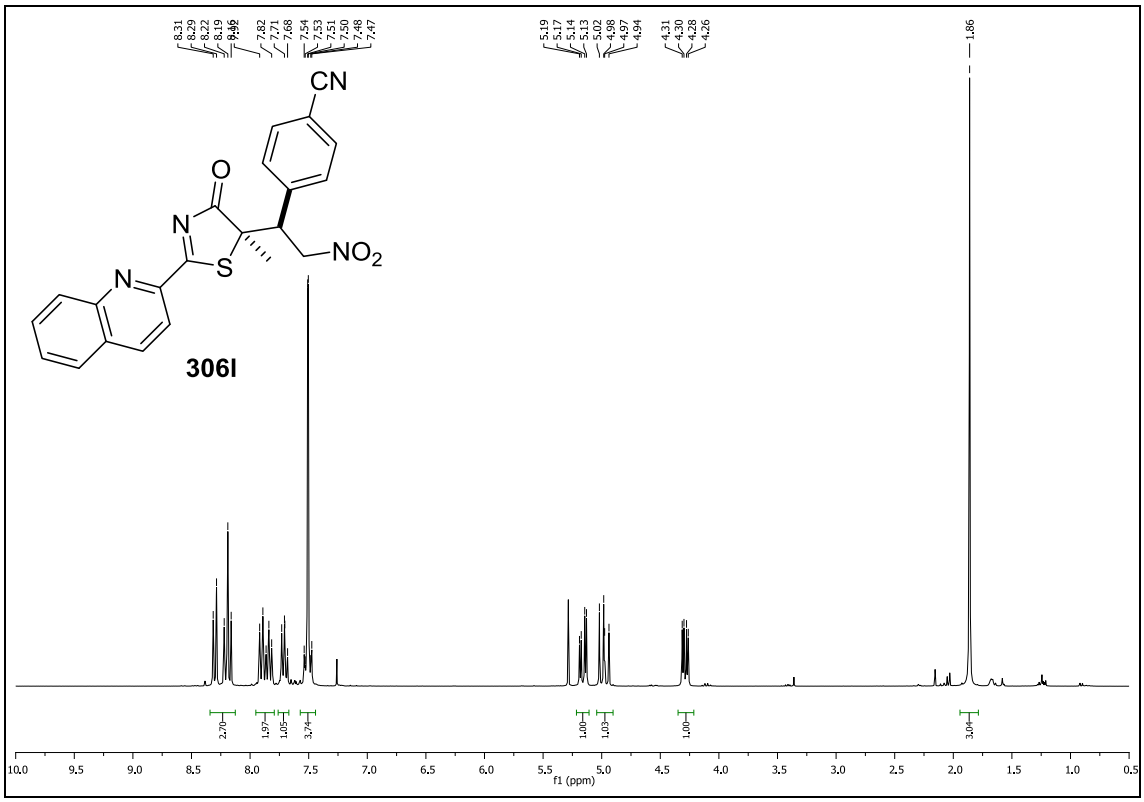
129.8
127.9
123.7
119.6
75.7
64.4
50.0
24.7
f1 (ppm)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7.48
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5.19
5.17
5.14
5.13
5.02
4.98
4.97
4.94
4.31
4.30
4.28
4.26
1.86
CN
O
N
S
NO2
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306l
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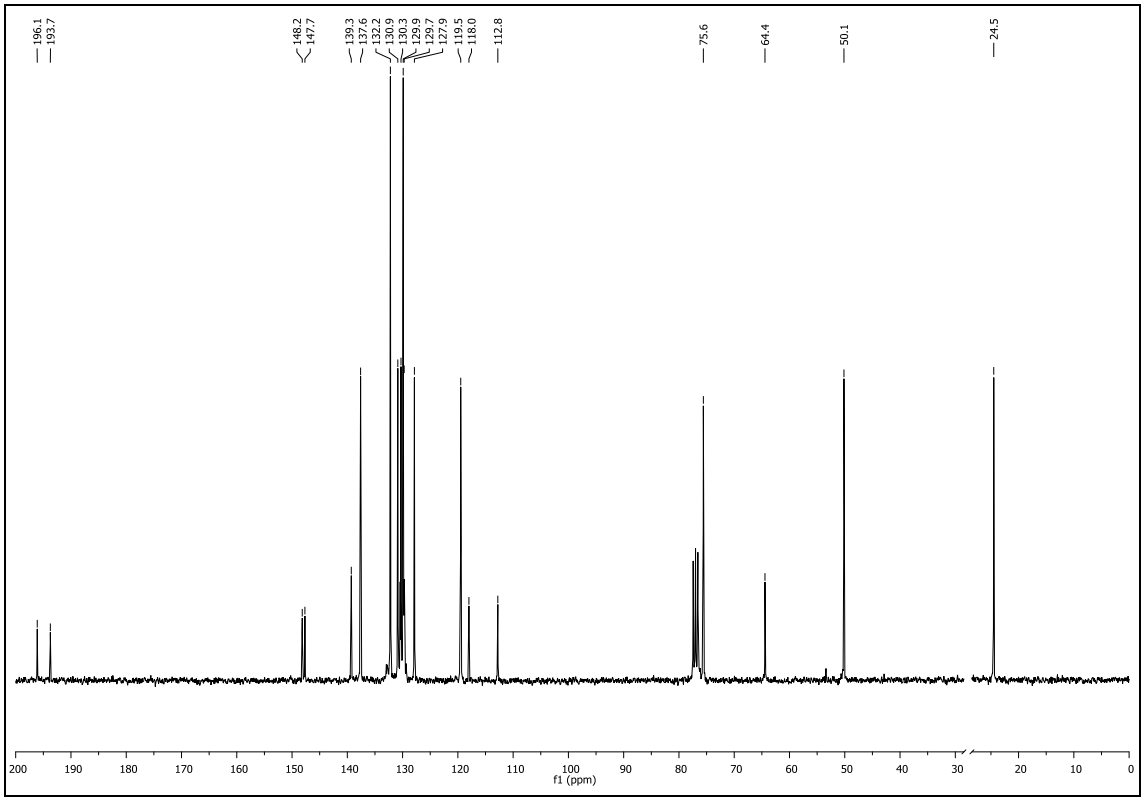
1.05
3.74
1.00
1.03
1.00
3.04
f1 (ppm)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147.7
139.3
137.6
132.2
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118.0
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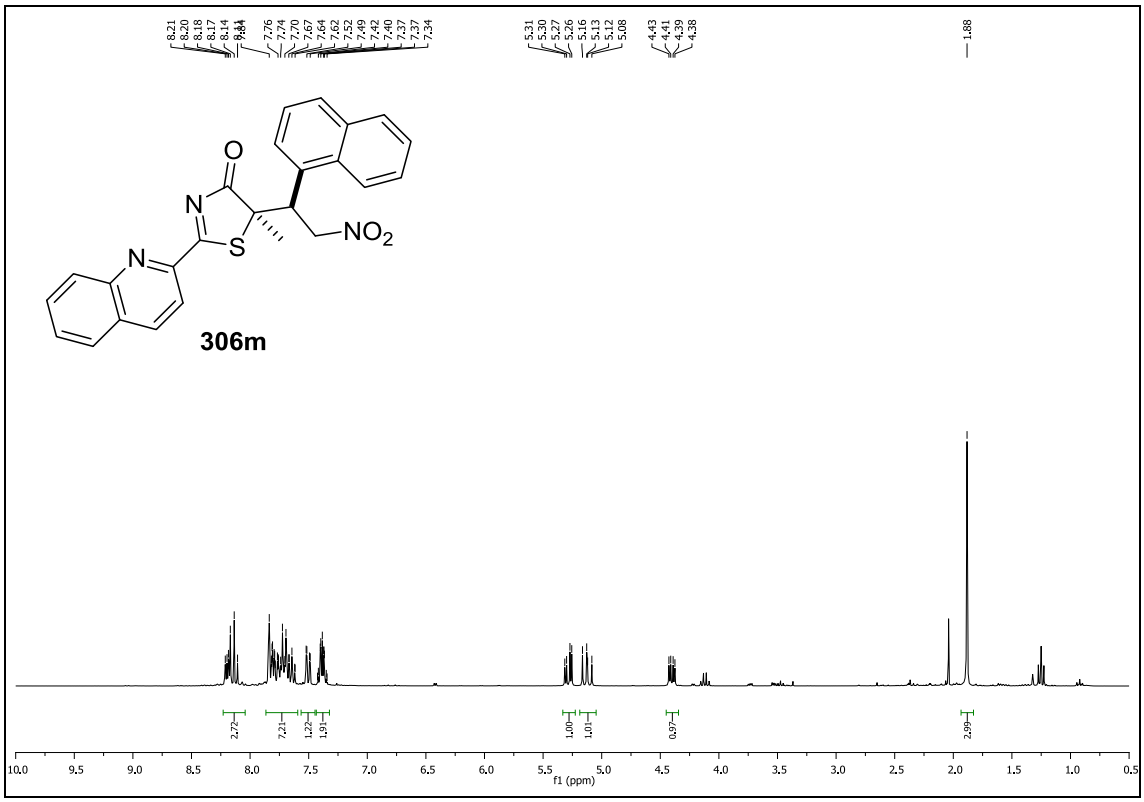
64.4
50.1
24.5
f1 (ppm)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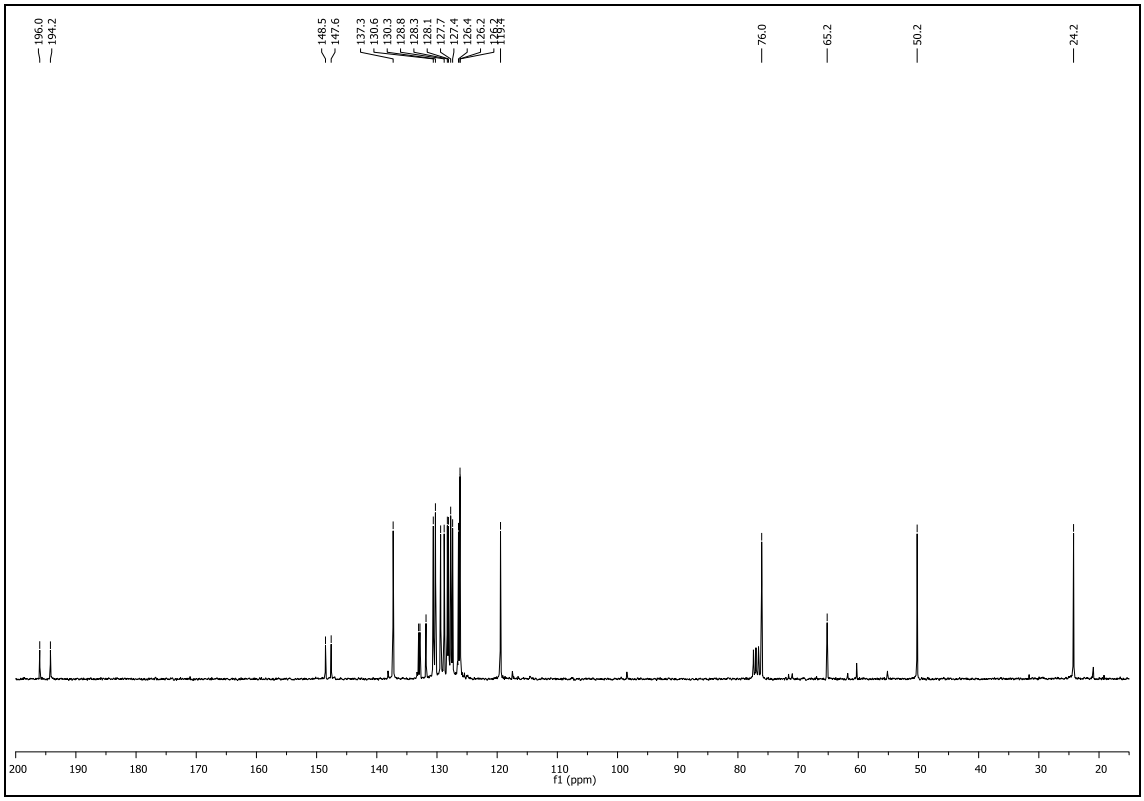
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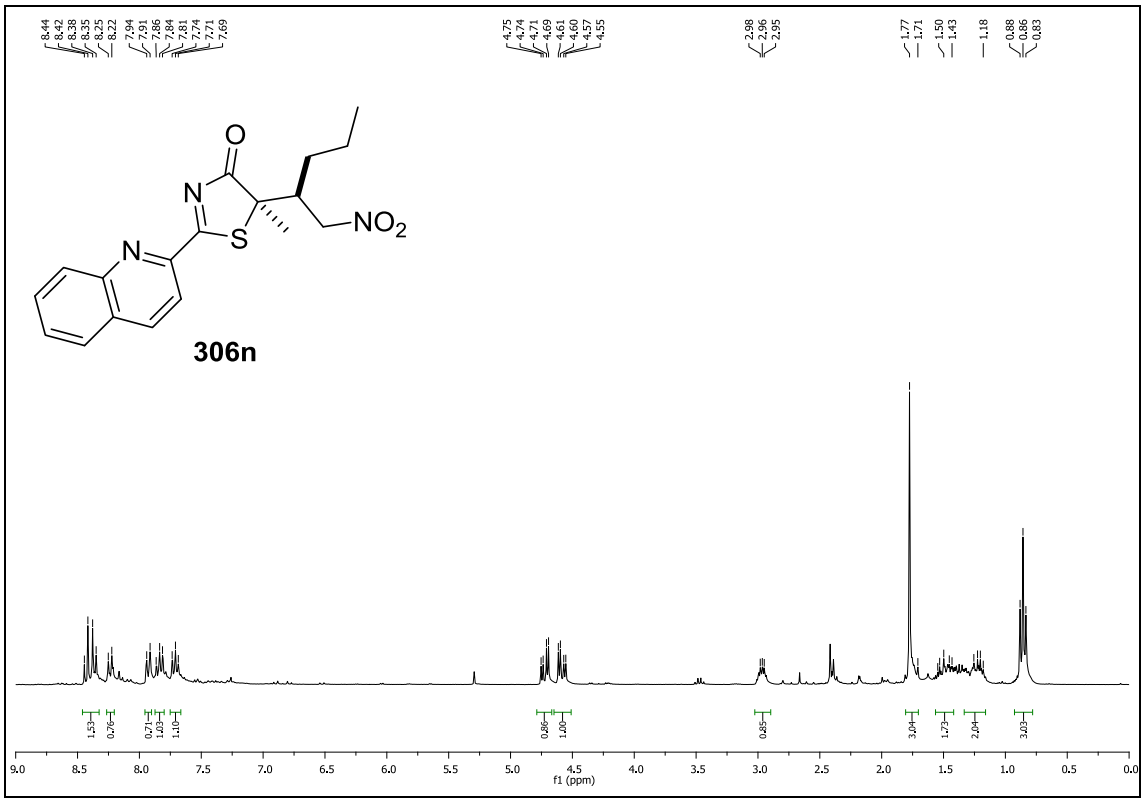
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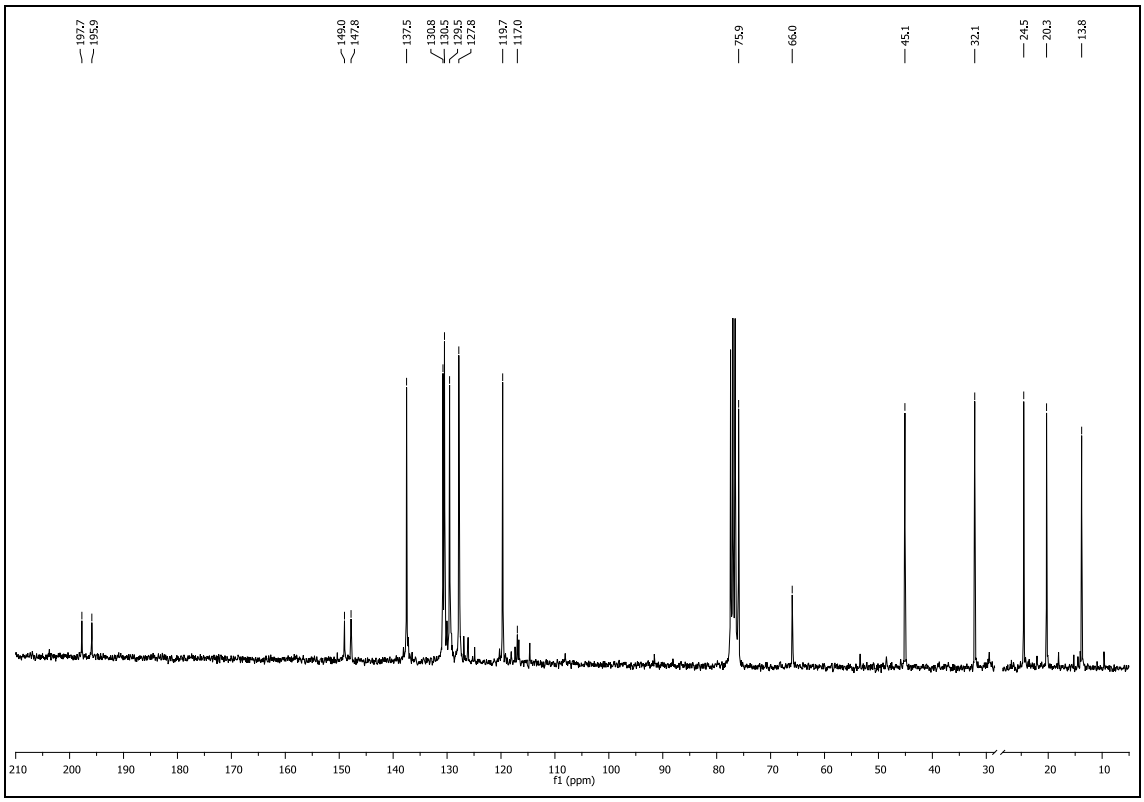
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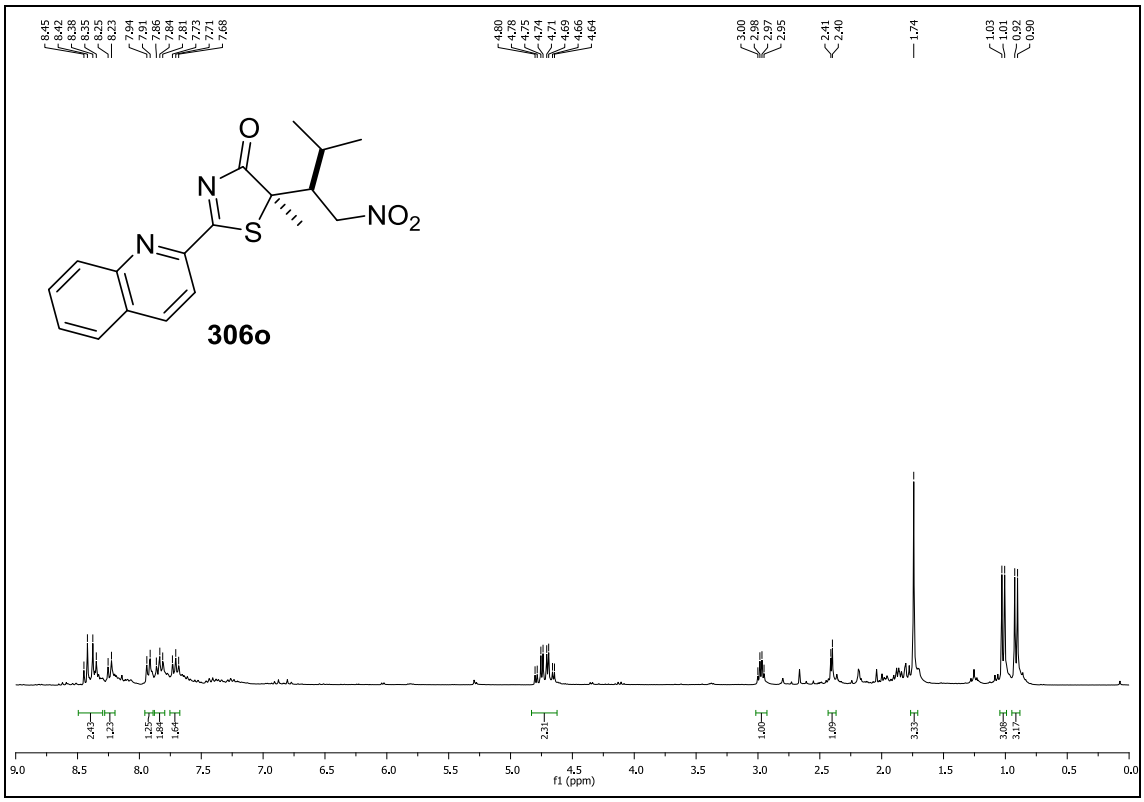
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7.68
4.80
4.78
4.75
4.74
4.71
4.69
4.66
4.64
3.00
2.98
2.97
2.95
2.41
2.40
1.74
1.03
1.01
0.92
0.90
O
N
S
N
NO2
306o
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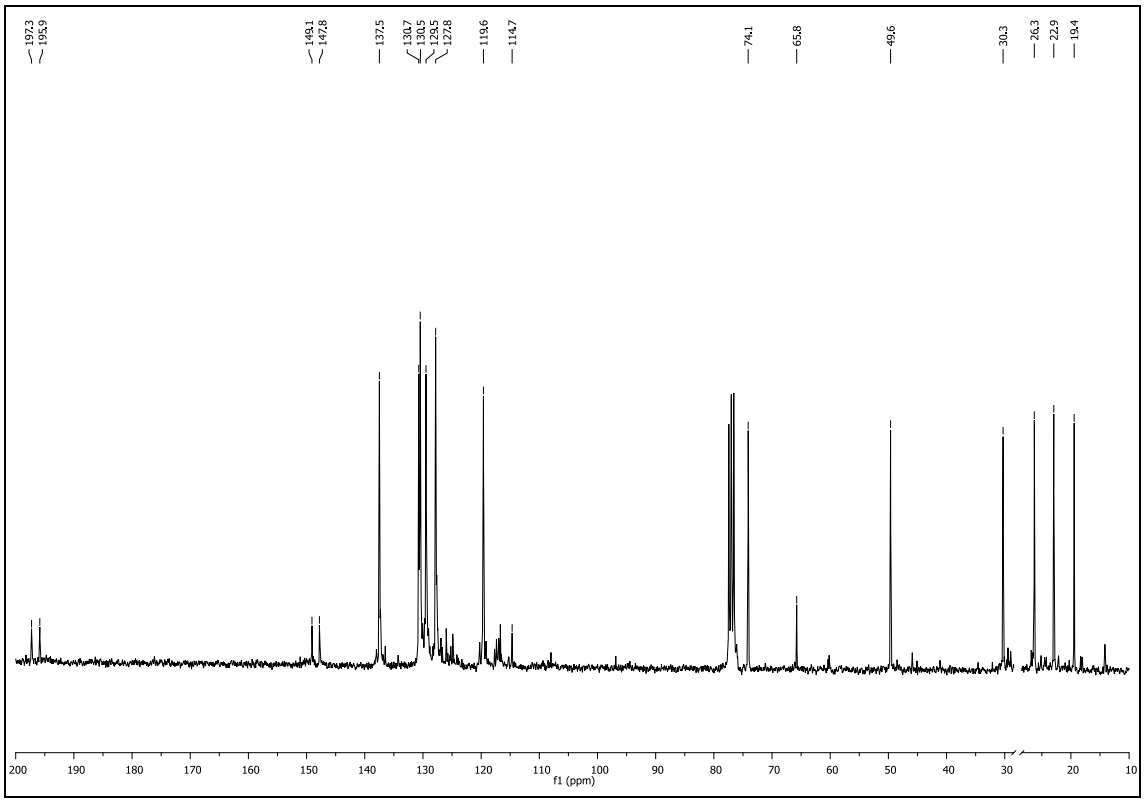
1.84
1.64
2.31
1.00
1.09
3.33
3.08
3.17
f1 (ppm)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195.9
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127.8
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114.7
74.1
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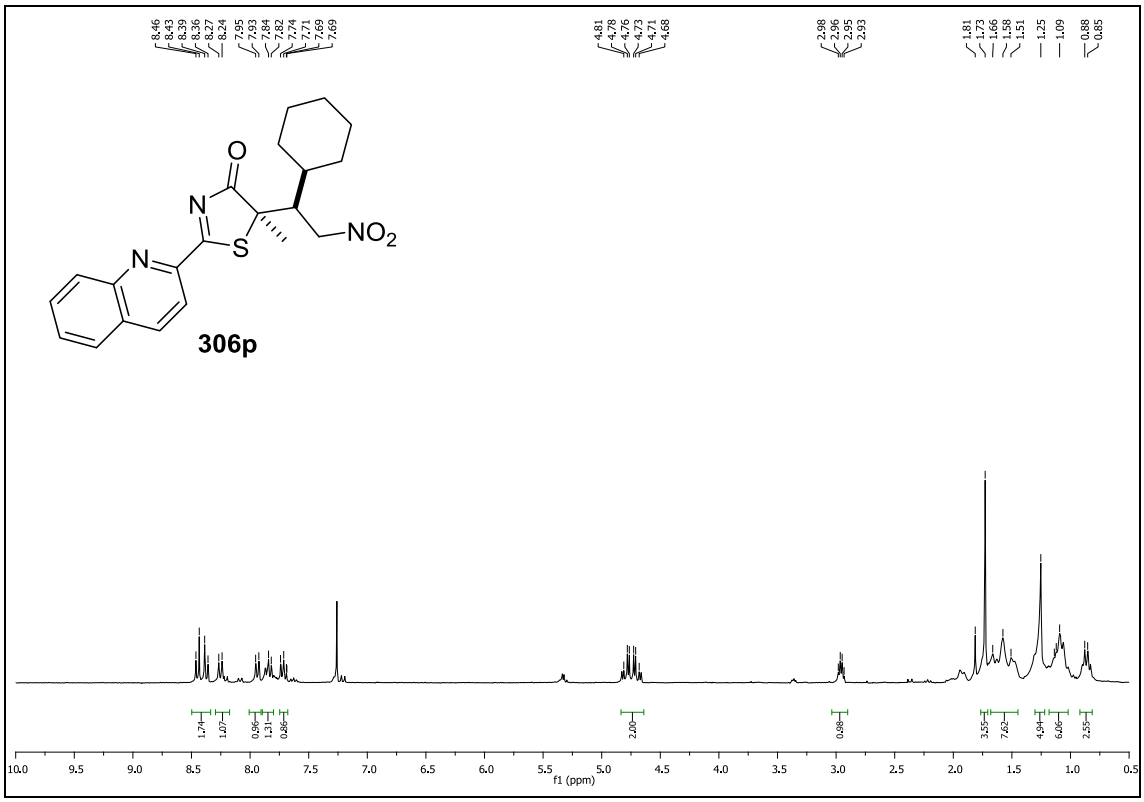
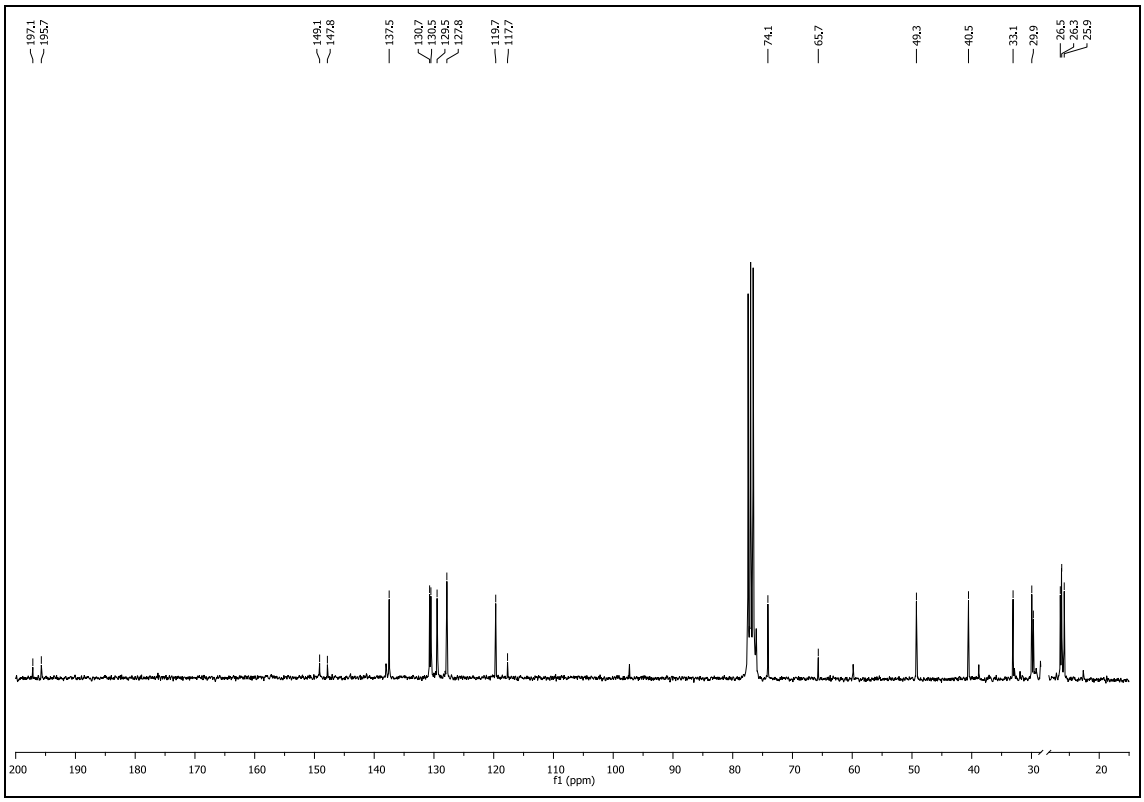
30.3
26.3
22.9
19.4
f1 (ppm)


306p
f1 (ppm)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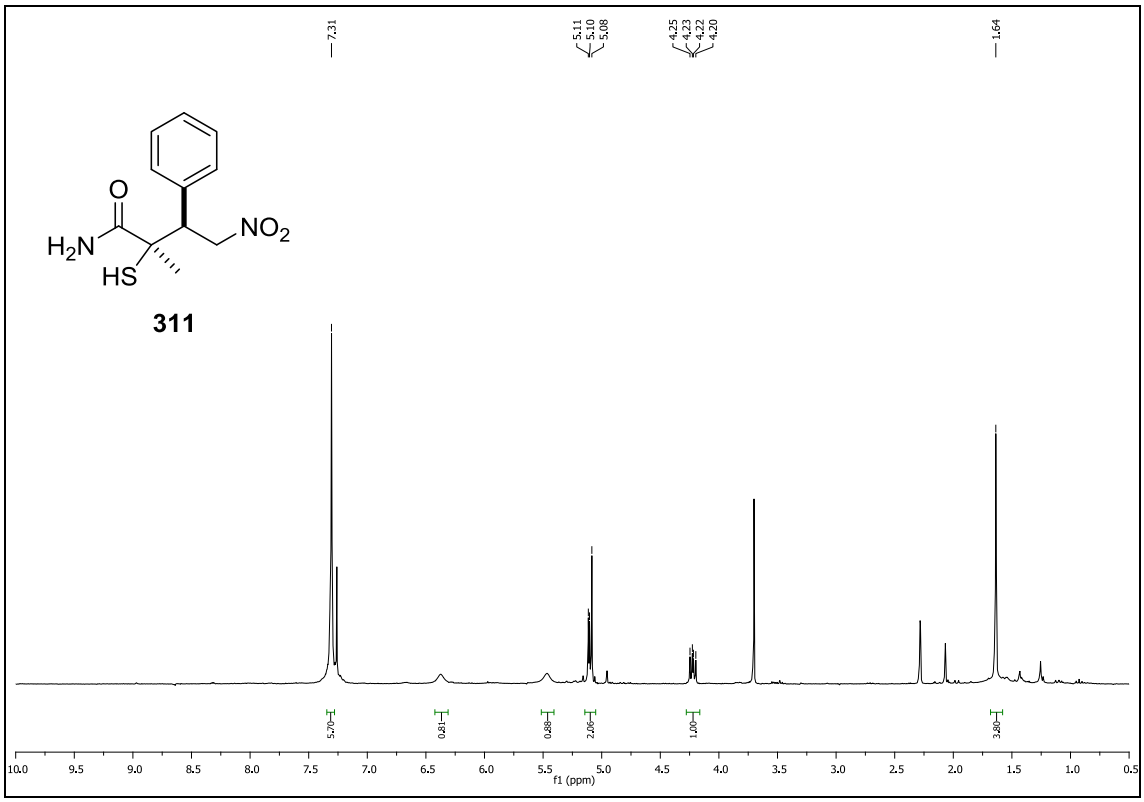
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5.08
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4.23
4.22
4.20
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HS
NO2
311
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0.88
2.00
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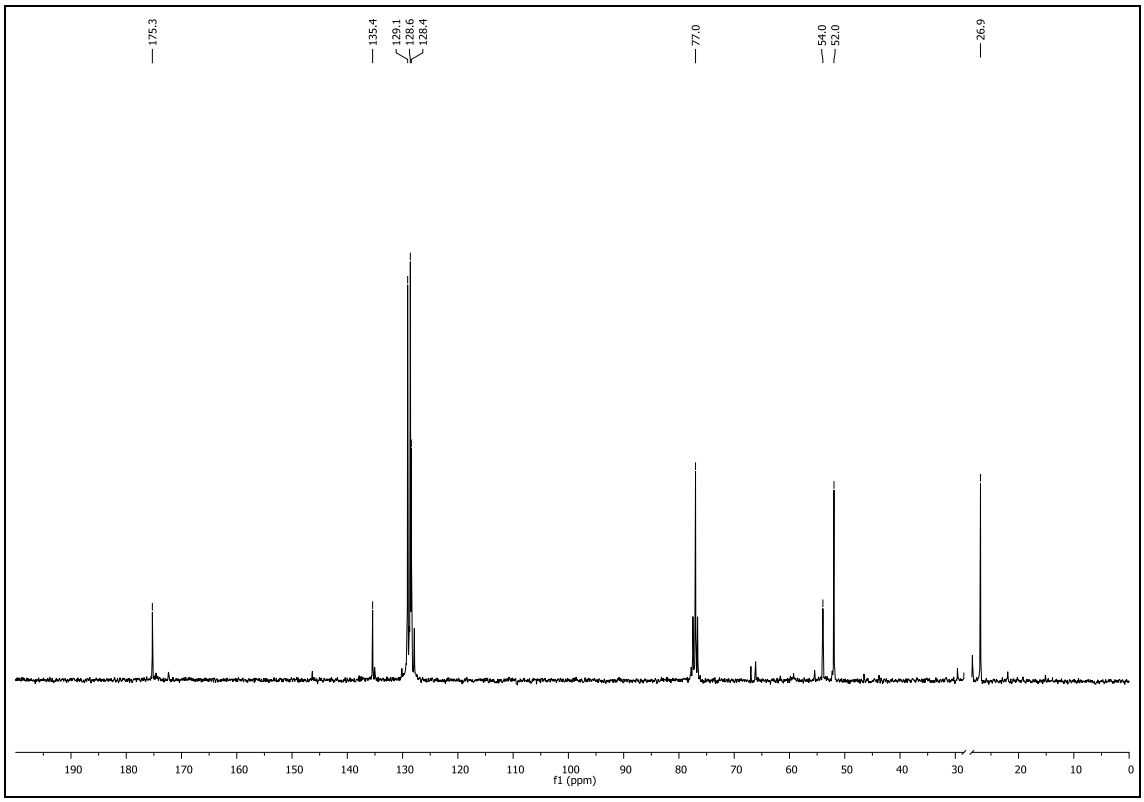
3.80
f1 (ppm)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26.9
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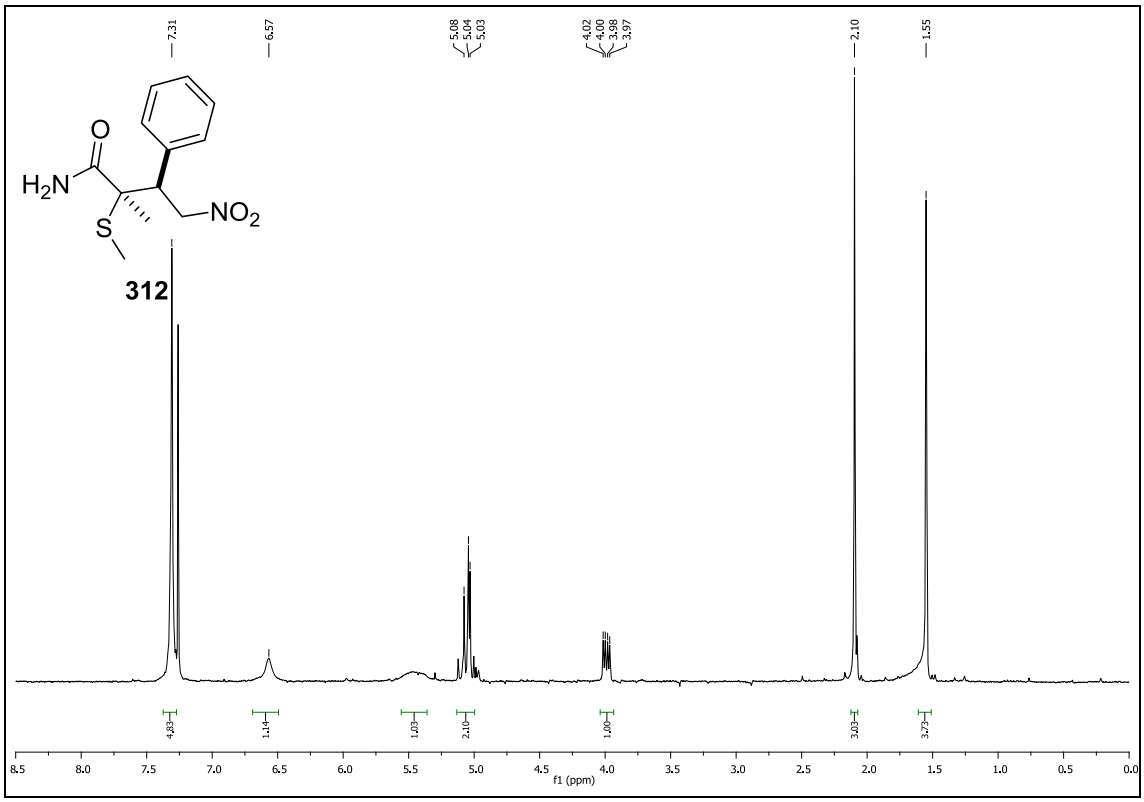
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3.98
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2.10
1.55
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S
312
4.03
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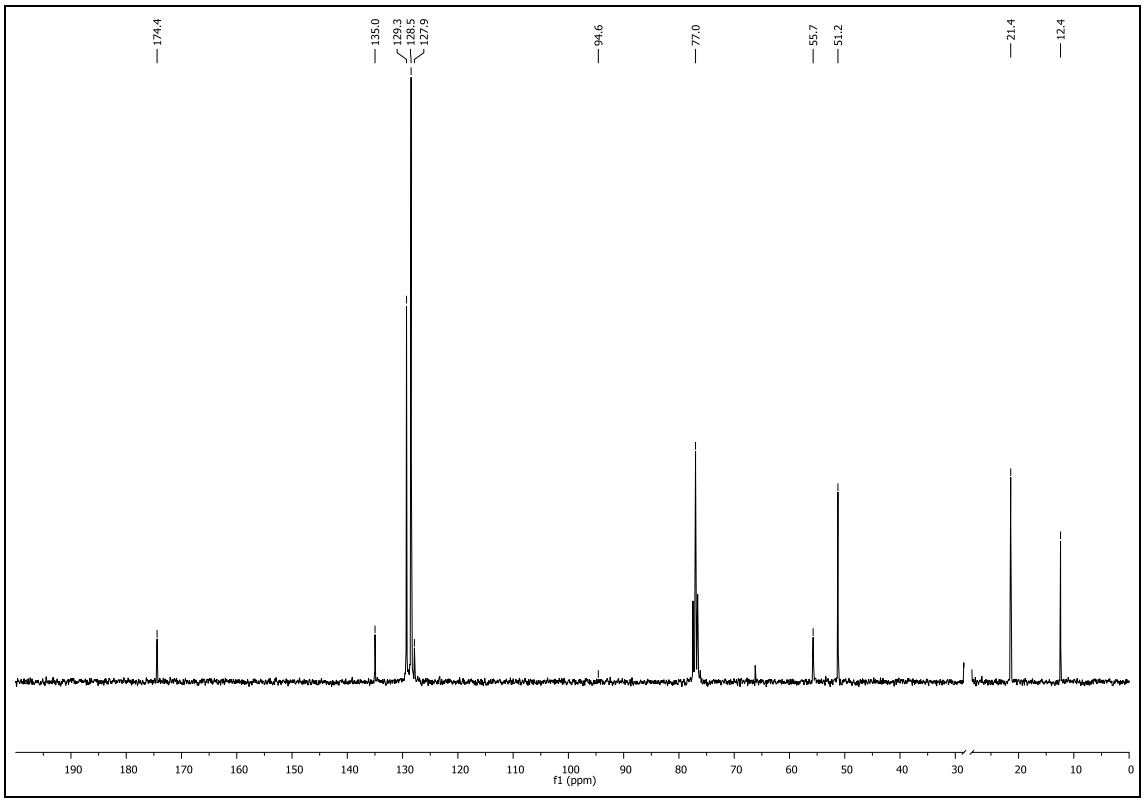
1.03
2.10
1.00
3.03
3.73
f1 (ppm)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55.7
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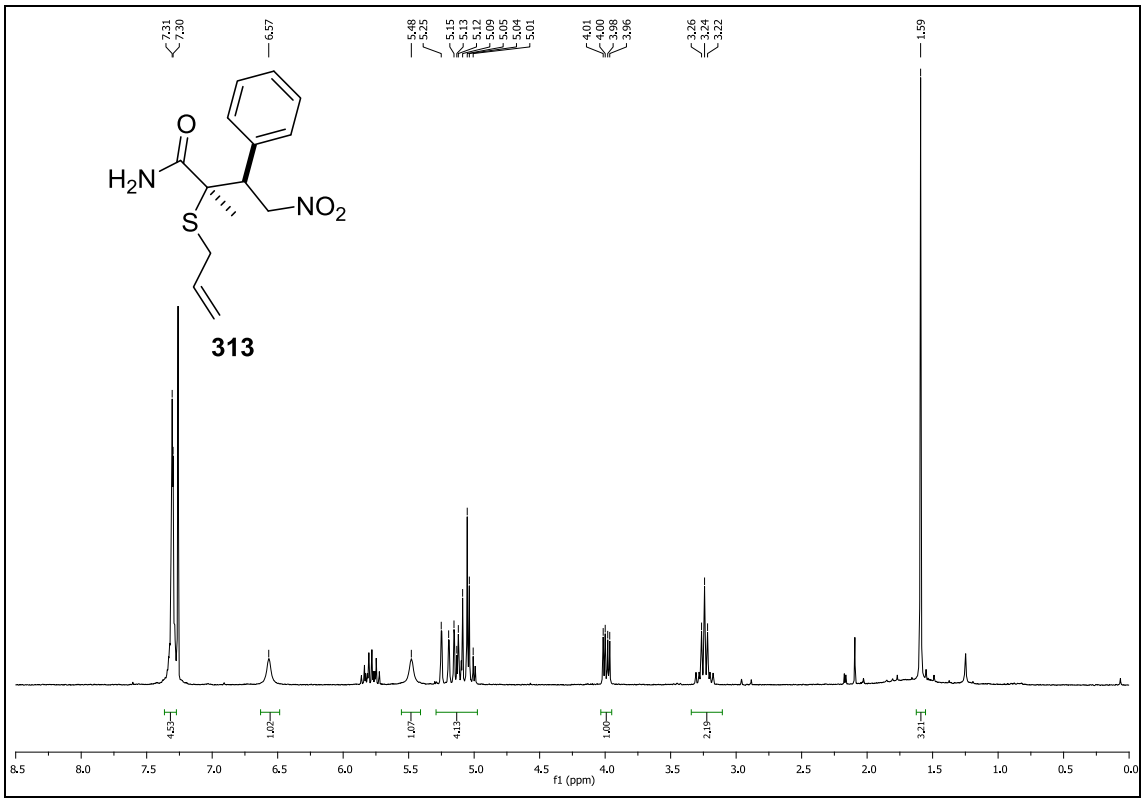
21.4
12.4
f1 (ppm)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5.04
5.01
4.01
4.00
3.98
3.96
3.26
3.24
3.22
1.59
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S
313
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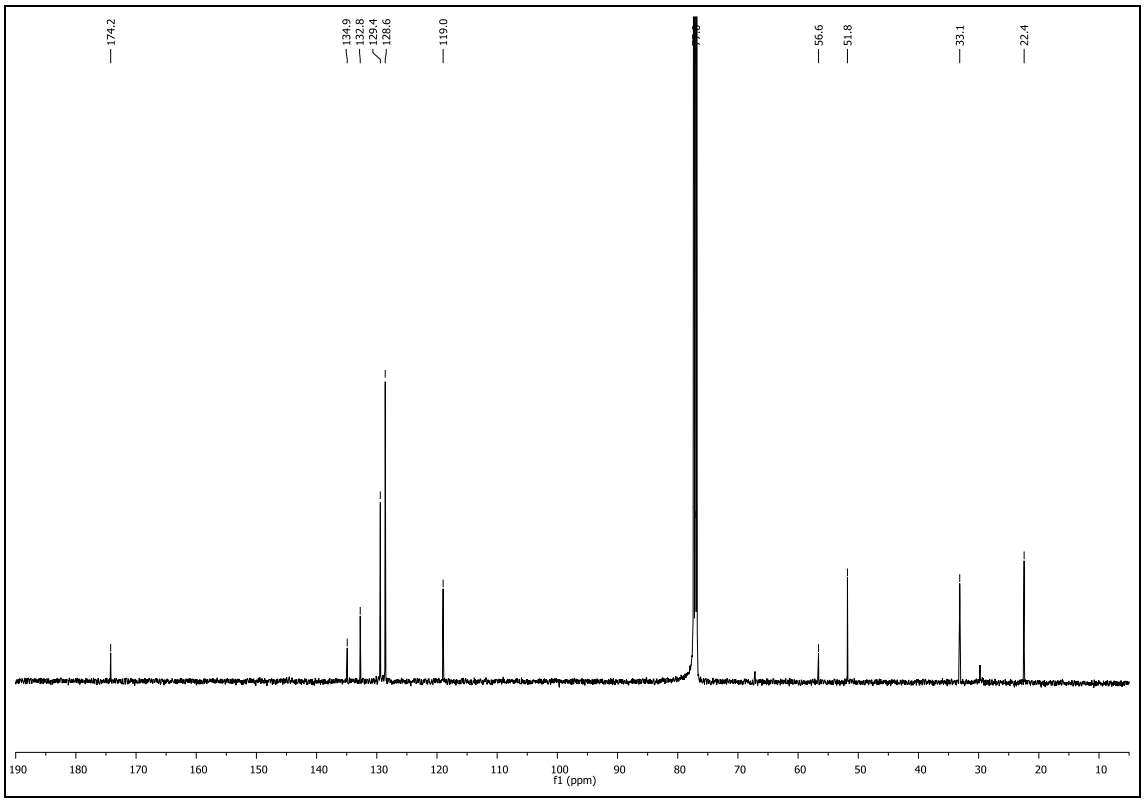
1.00
2.19
3.21
f1 (ppm)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56.6
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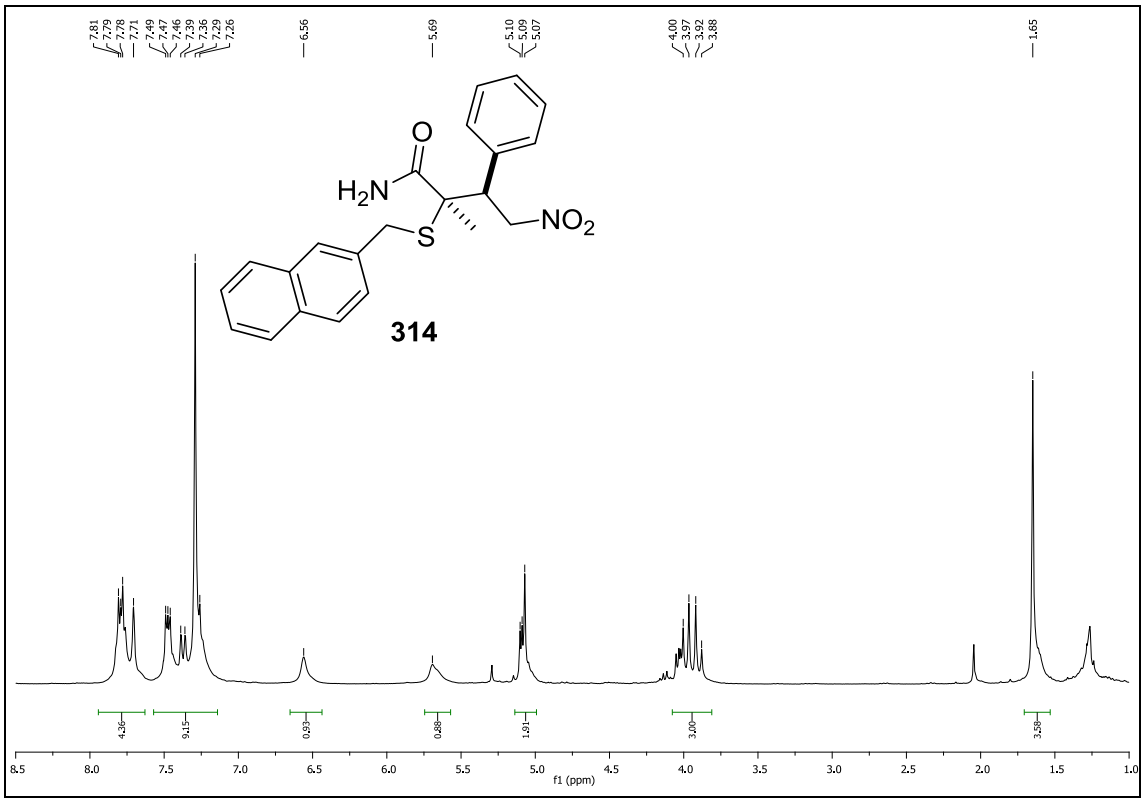
33.1
22.4
f1 (ppm)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6.56
5.69
5.10
5.09
5.07
4.00
3.97
3.92
3.88
1.65
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314
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1.91
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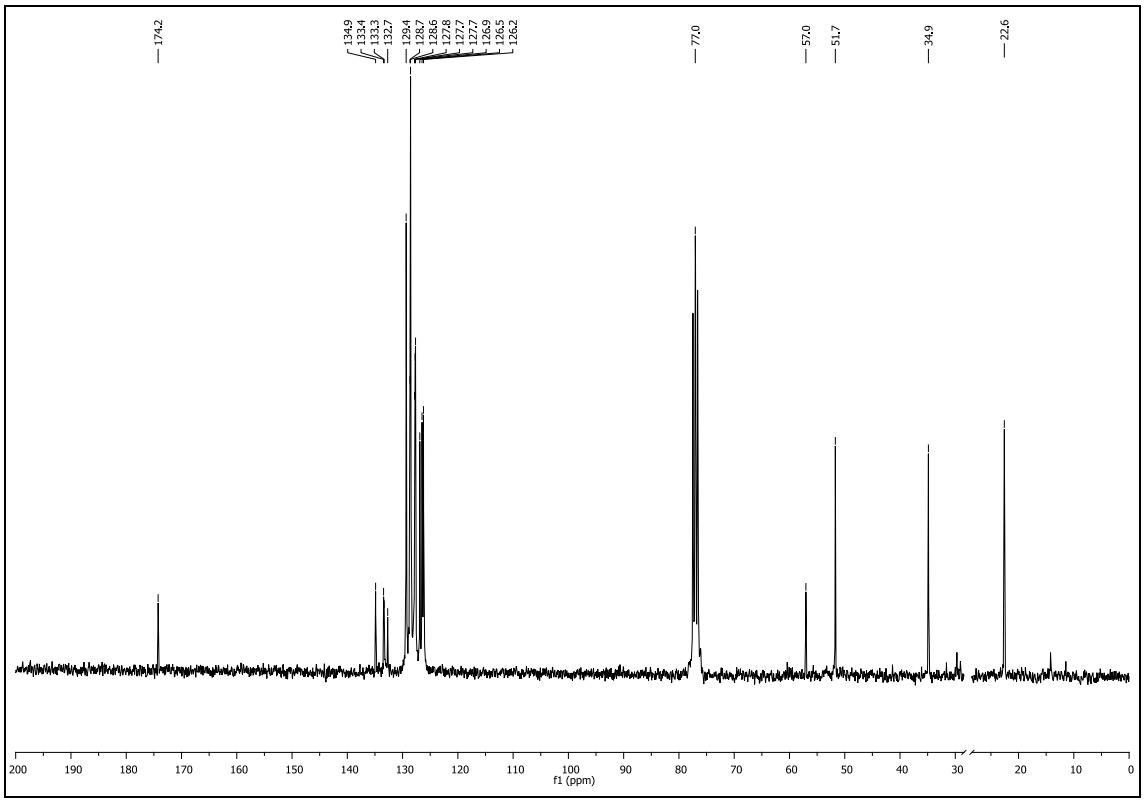
f1 (ppm)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128.6
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77.0
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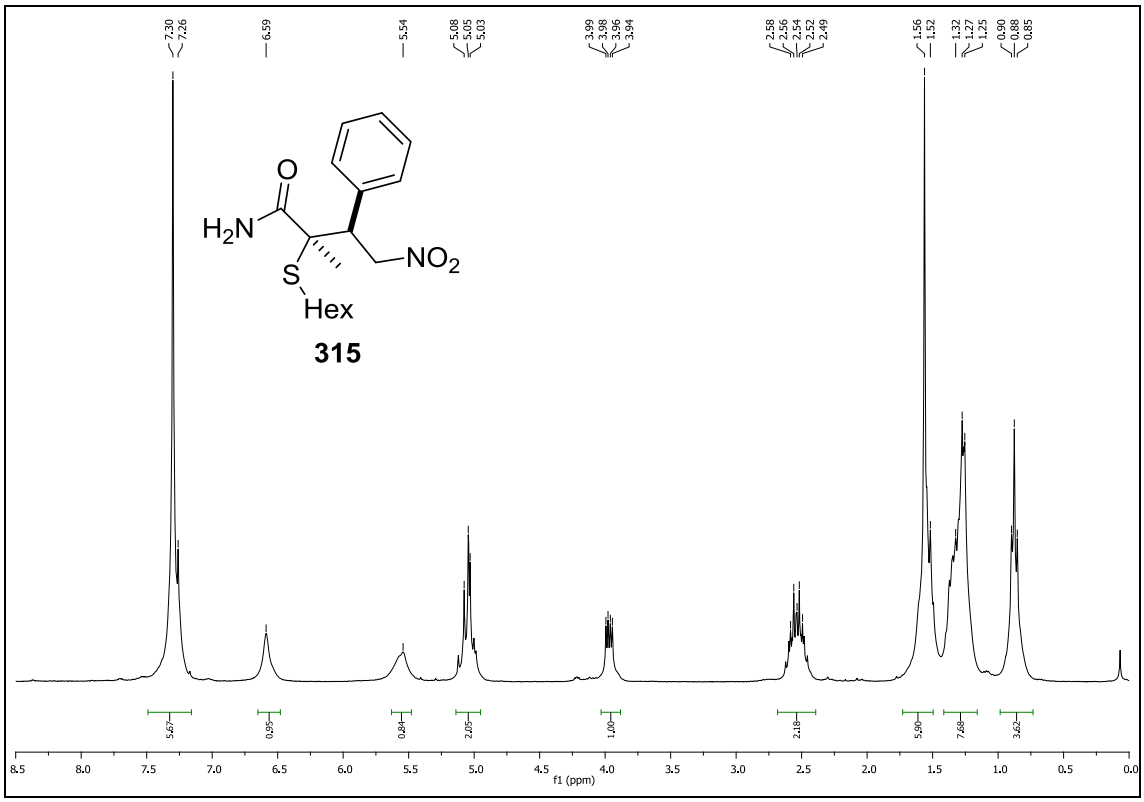
34.9
22.6
f1 (ppm)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3.94
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2.56
2.54
2.52
2.49
1.56
1.52
1.32
1.27
1.25
0.90
0.88
0.85
O
H2N
NO2
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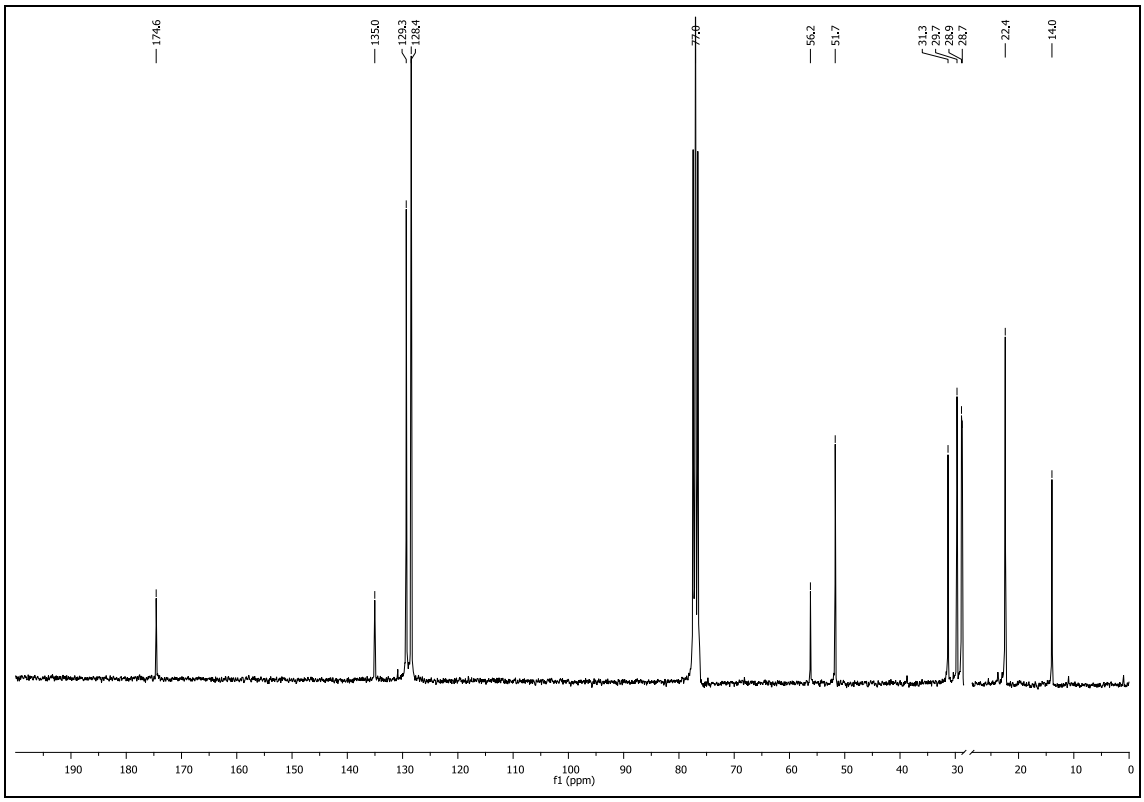
0.94
2.05
1.00
2.18
5.90
7.68
3.62
f1 (ppm)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128.4
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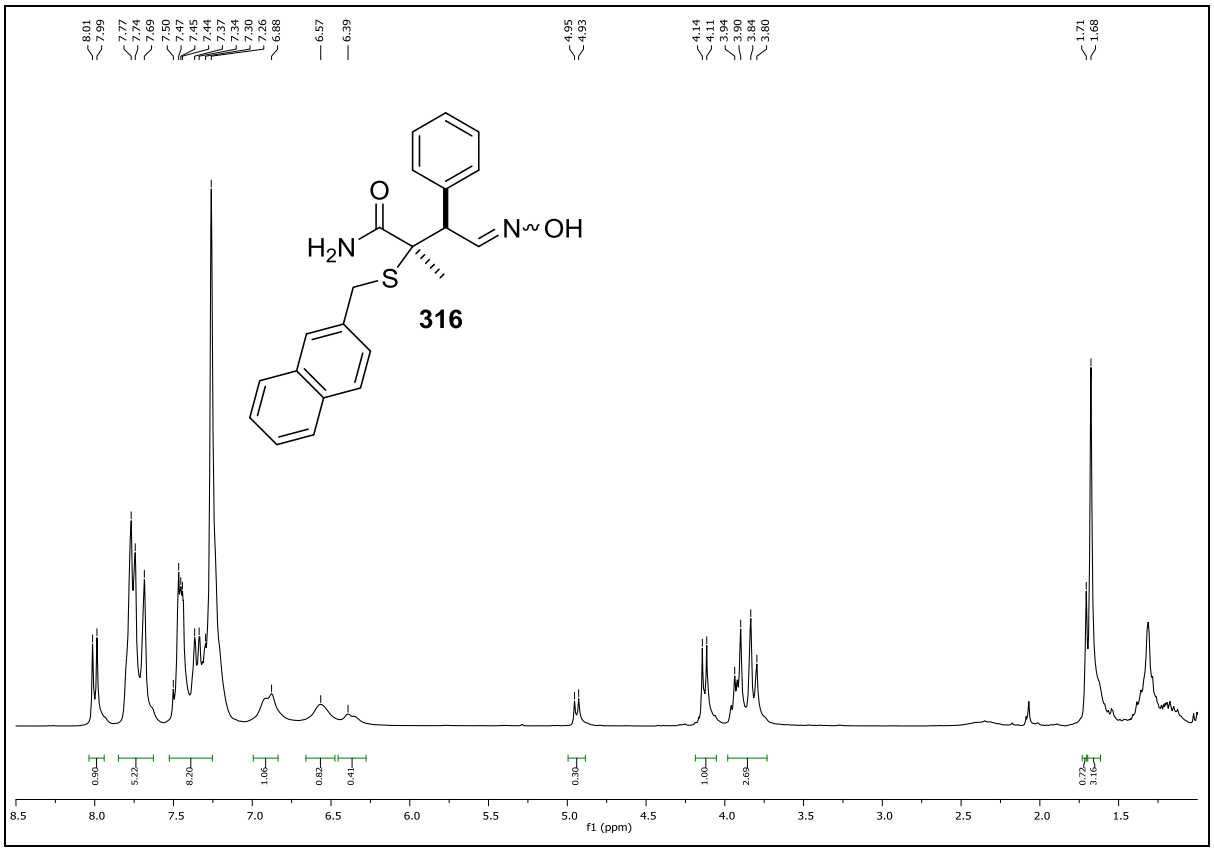
51.7
31.3
29.7
28.9
28.7
22.4
14.0
f1 (ppm)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7.34
7.30
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6.88
6.57
6.39
4.95
4.93
4.14
4.11
3.94
3.90
3.84
3.80
1.71
1.68
O
H2N
N
OH
S
316
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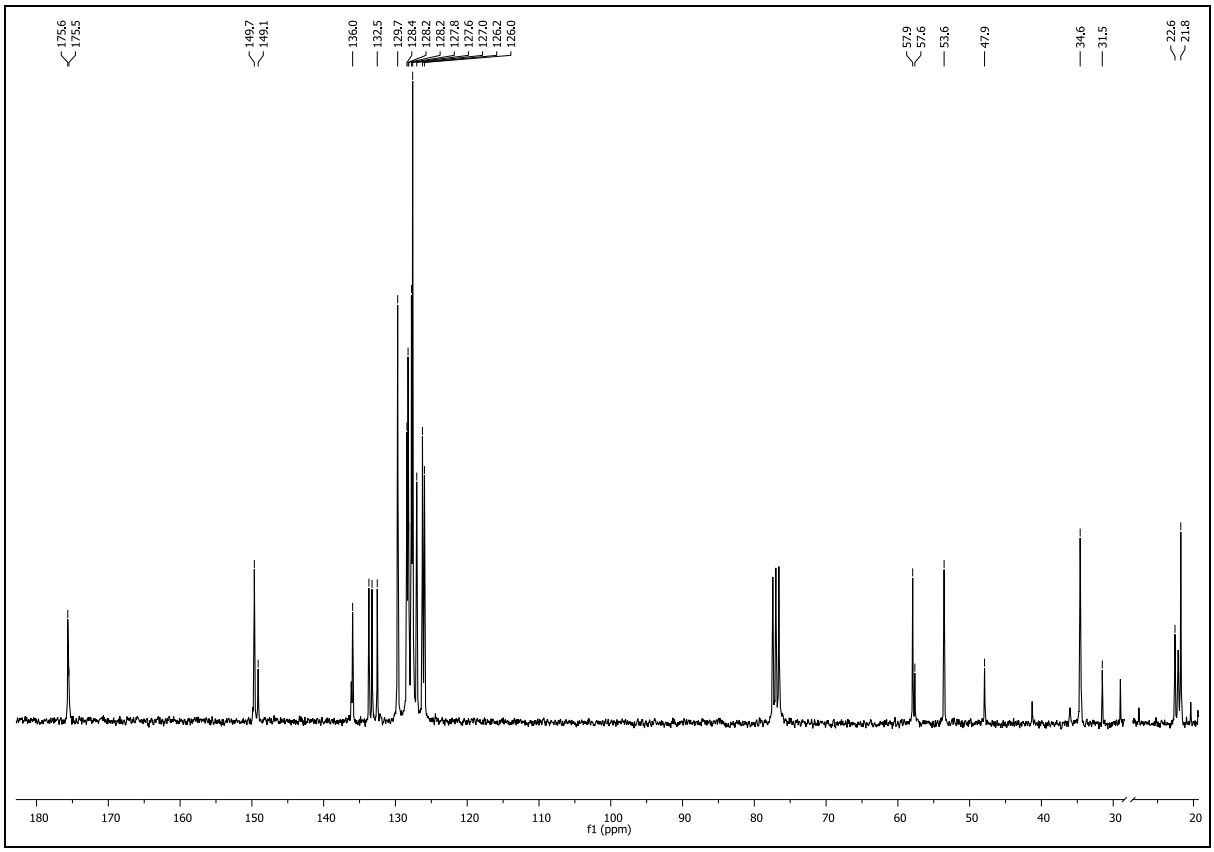
f1 (ppm)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175.5
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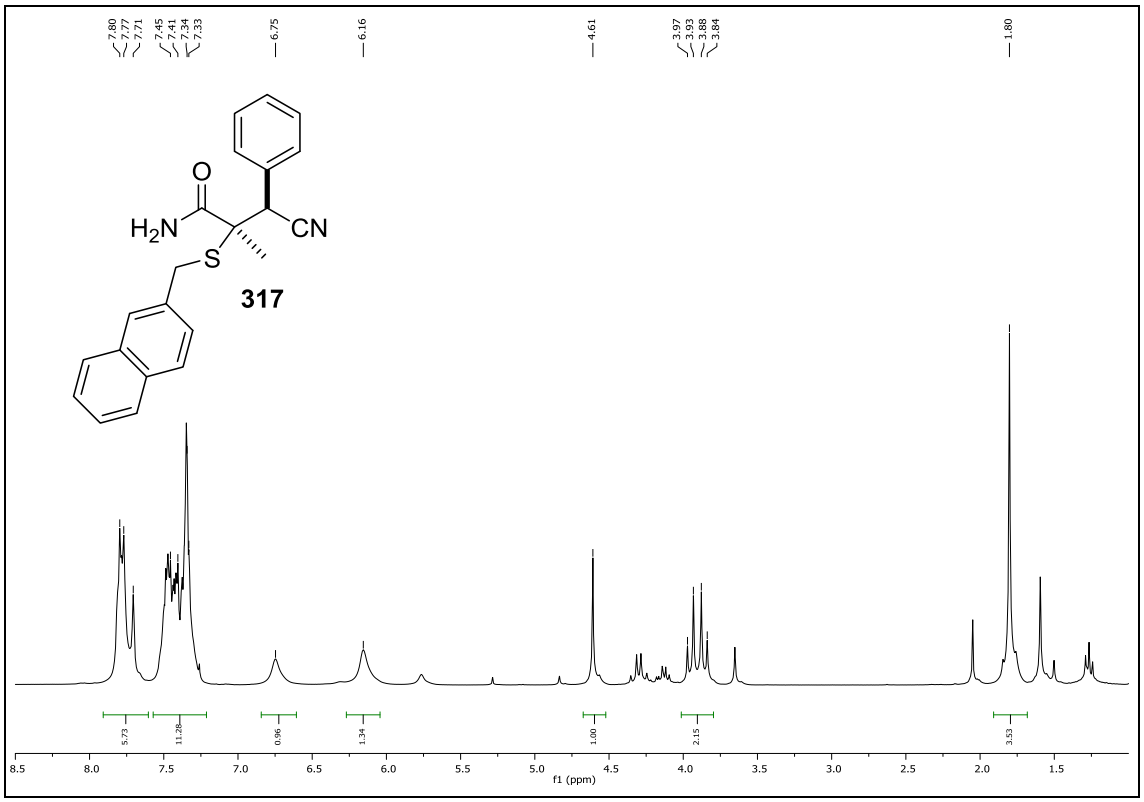
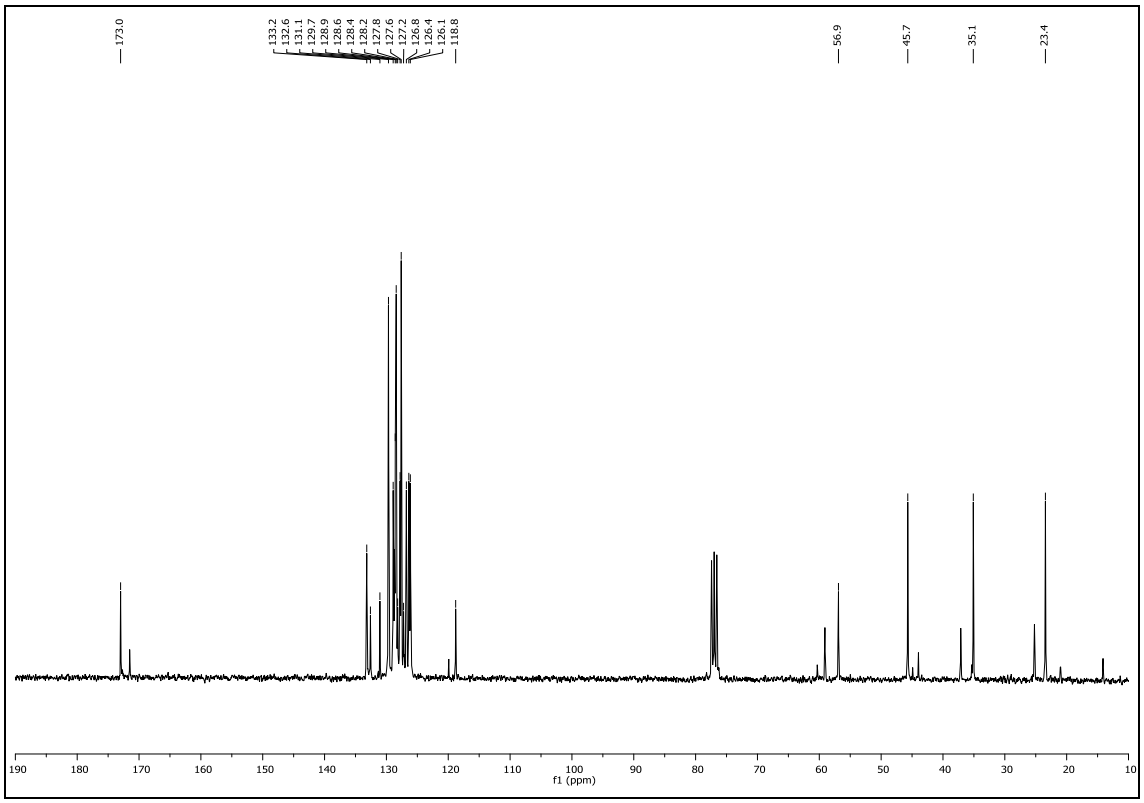
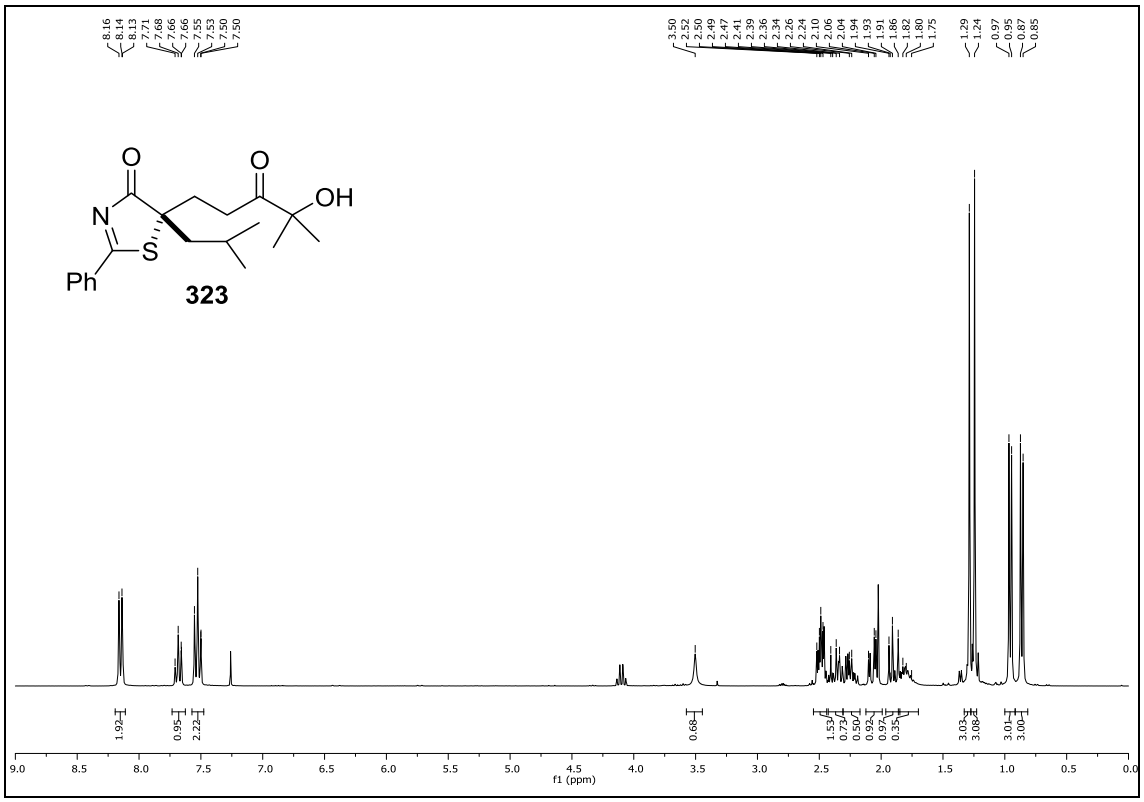
136.0
132.5
129.7
128.4
128.2
128.2
127.8
127.6
127.0
126.2
126.0
57.9
57.6
53.6
47.9
34.6
31.5
22.6
21.8
f1 (ppm)


7.80
7.77
7.71
7.45
7.41
7.34
7.33
6.75
6.16
4.61
3.97
3.93
3.88
3.84
1.80
O
H2N
CN
S
317
5.73
11.28
0.96
1.34
1.00
2.15
3.53
f1 (ppm)


173.0
133.2
132.6
131.1
129.7
128.9
128.6
128.4
128.2
127.8
127.6
127.2
126.8
126.4
126.1
118.8
56.9
45.7
35.1
23.4
f1 (ppm)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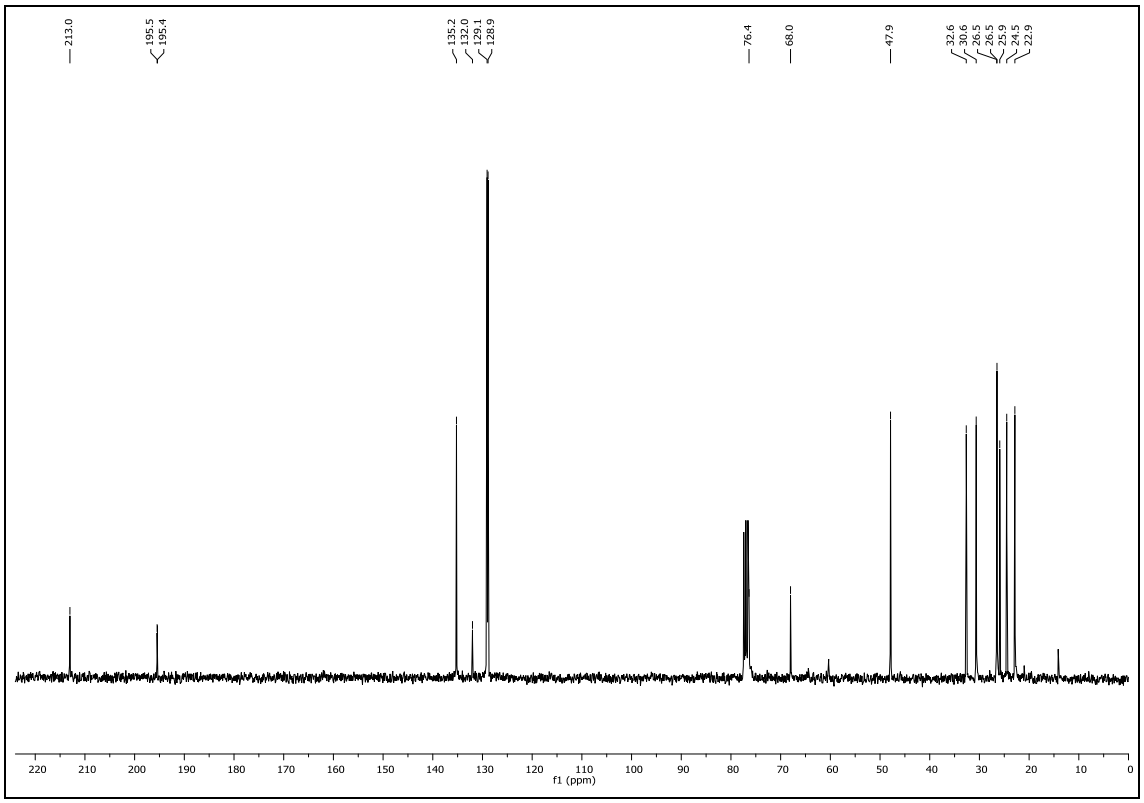
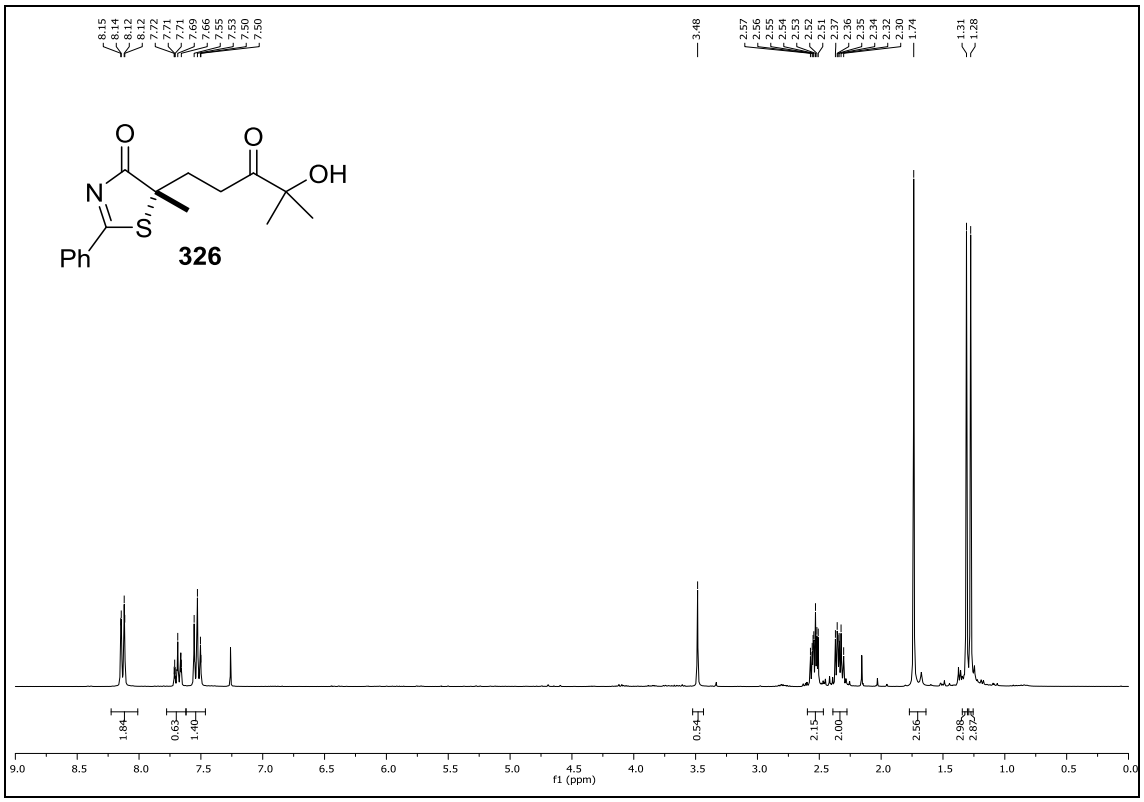
8.14
8.13
7.71
7.68
7.66
7.66
7.55
7.53
7.50
7.50
3.50
2.52
2.50
2.49
2.47
2.41
2.39
2.36
2.34
2.26
2.24
2.10
2.06
2.04
1.94
1.93
1.91
1.86
1.82
1.80
1.75
1.29
1.24
0.97
0.95
0.87
0.85
O
O
OH
N
S
Ph
323
1.92
0.95
2.22
0.68
1.53
0.73
0.50
0.92
0.92
0.35
3.03
3.08
3.01
3.00
f1 (ppm)


213.0
195.5
195.4
135.2
132.0
129.1
128.9
76.4
68.0
47.9
32.6
30.6
26.5
26.5
25.9
24.5
22.9
f1 (ppm)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8.14
8.12
8.12
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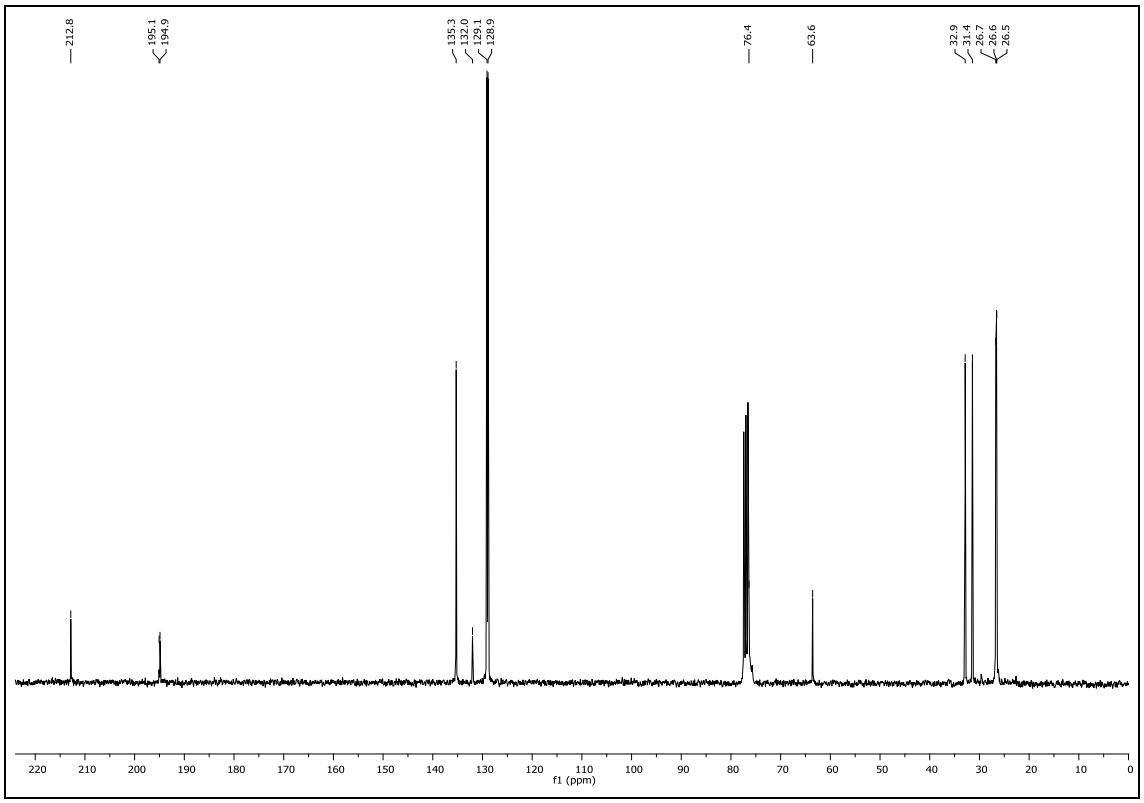
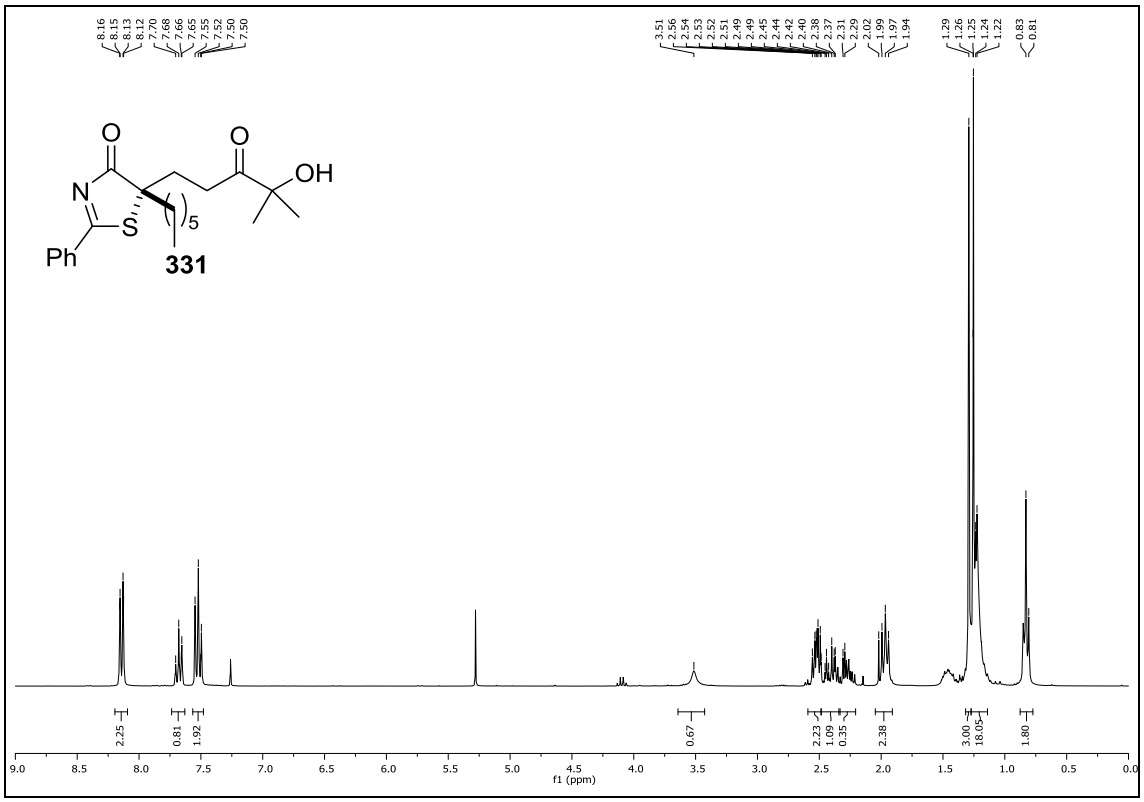
7.71
7.71
7.69
7.66
7.55
7.53
7.50
7.50
3.48
2.57
2.56
2.55
2.54
2.53
2.52
2.51
2.37
2.36
2.35
2.34
2.32
2.30
1.74
1.31
1.28
O
O
OH
N
S
Ph
326
1.84
0.63
1.40
0.54
2.15
2.00
2.56
2.98
2.87
f1 (ppm)


212.8
195.1
194.9
135.3
132.0
129.1
128.9
76.4
63.6
32.9
31.4
26.7
26.6
26.5
f1 (ppm)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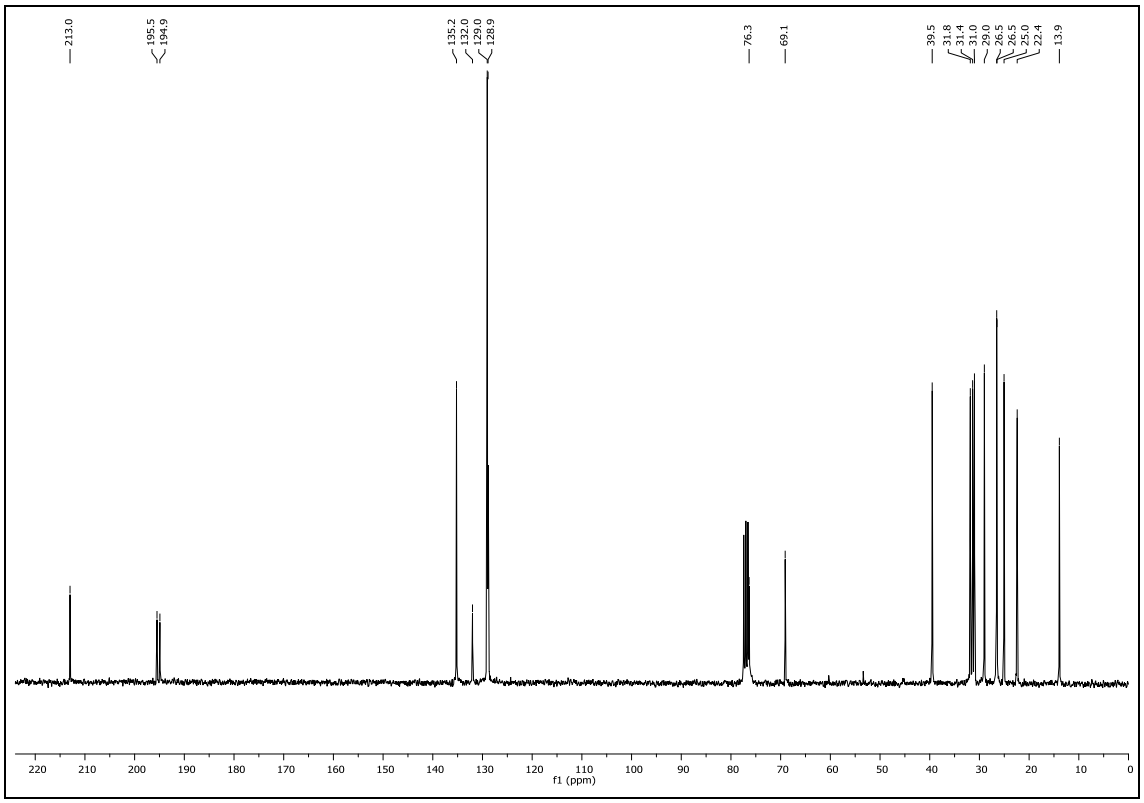
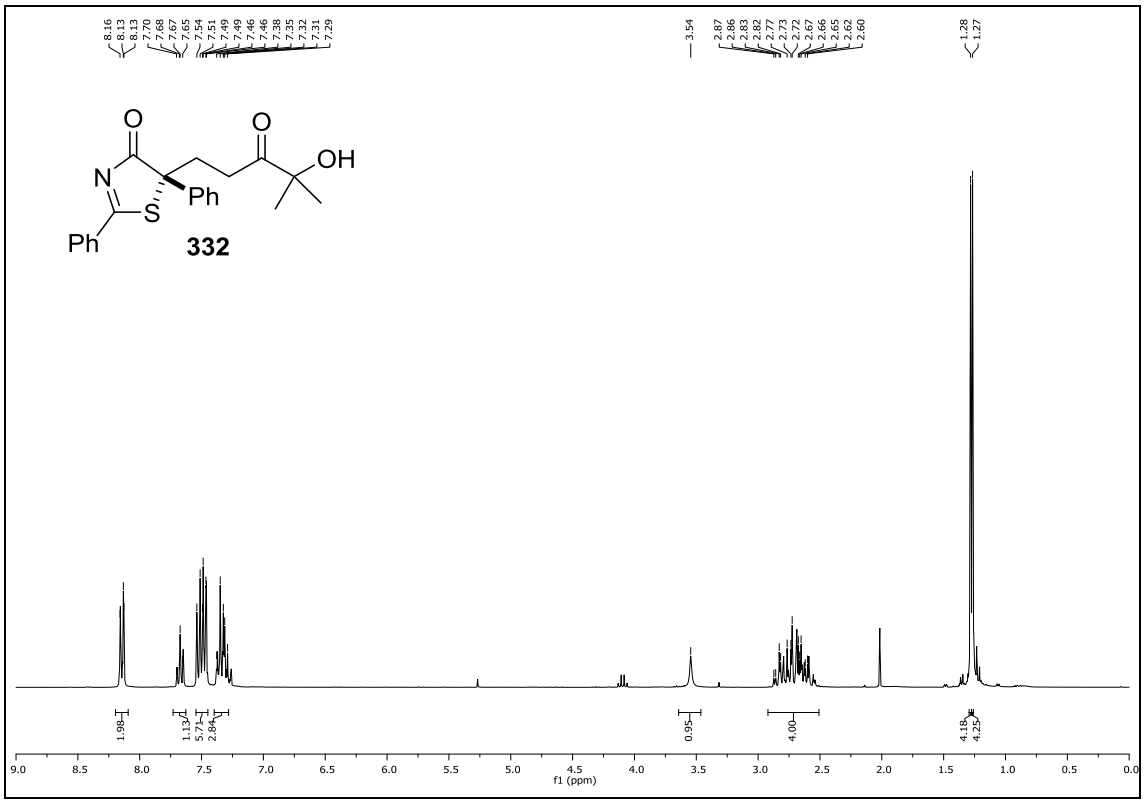
8.15
8.13
8.12
7.70
7.68
7.66
7.65
7.55
7.52
7.50
7.50
3.51
2.56
2.54
2.53
2.52
2.51
2.49
2.49
2.45
2.44
2.42
2.40
2.38
2.37
2.31
2.29
2.02
1.99
1.97
1.94
1.29
1.26
1.25
1.24
1.22
0.83
0.81
O
O
OH
N
S
5
Ph
331
2.25
0.81
1.92
0.67
2.23
1.09
0.35
2.38
3.00
18.05
1.80
f1 (ppm)


213.0
195.5
194.9
135.2
132.0
129.0
128.9
76.3
69.1
39.5
31.8
31.4
31.0
29.0
26.5
26.5
25.0
22.4
13.9
f1 (ppm)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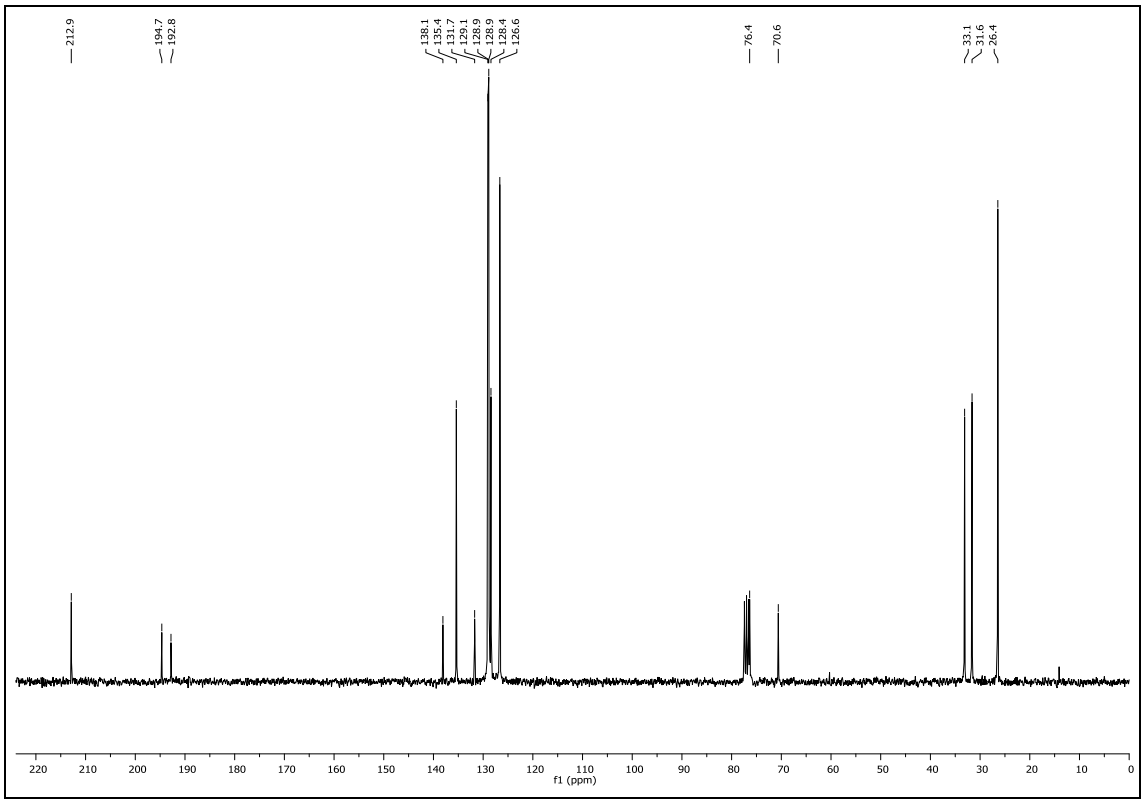
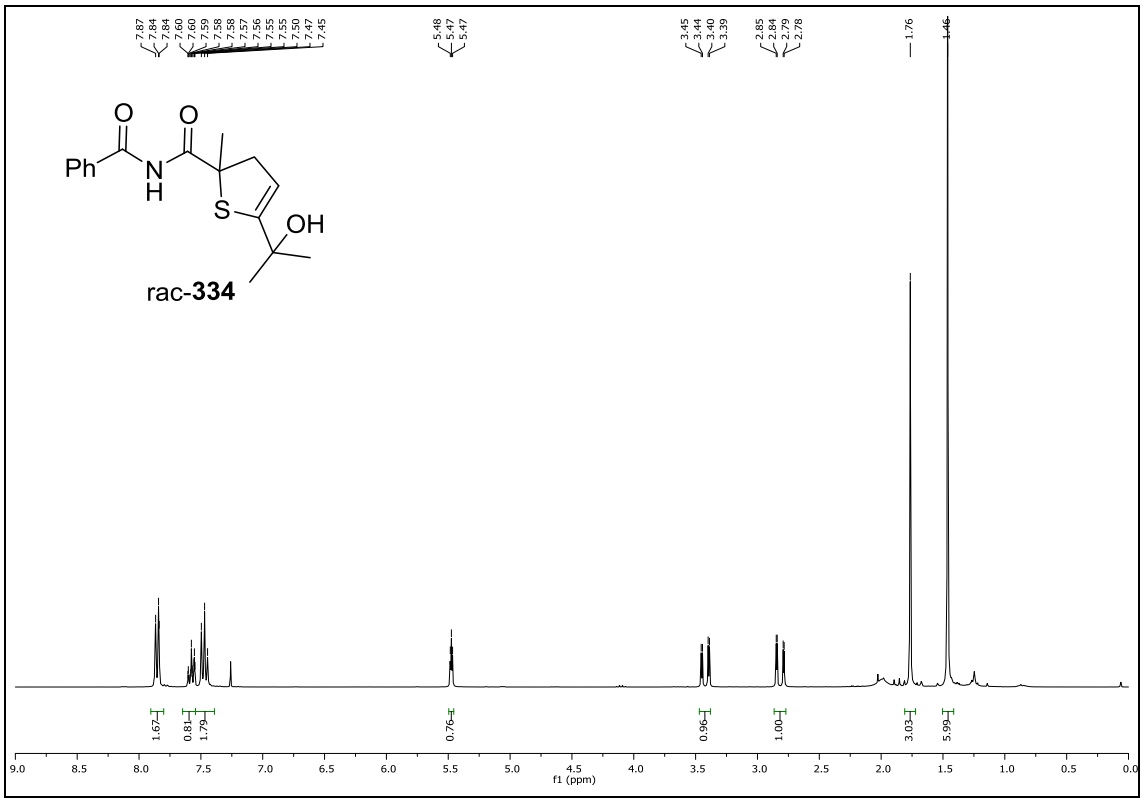
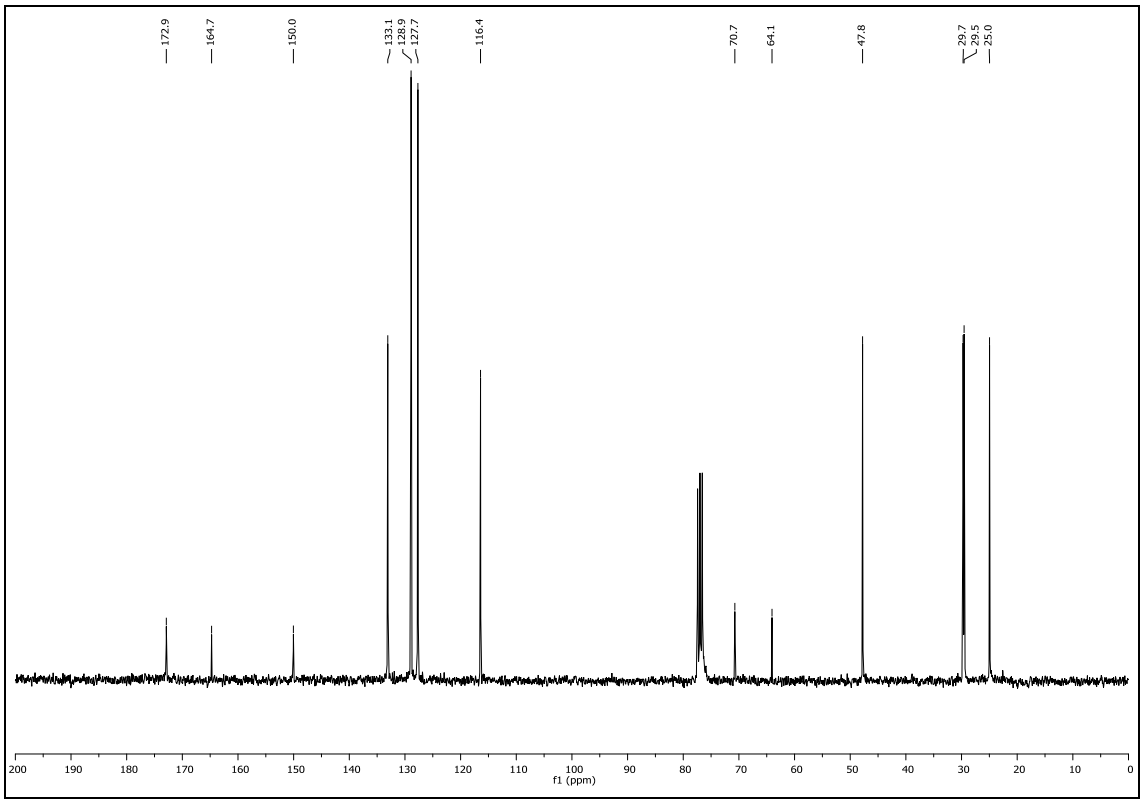
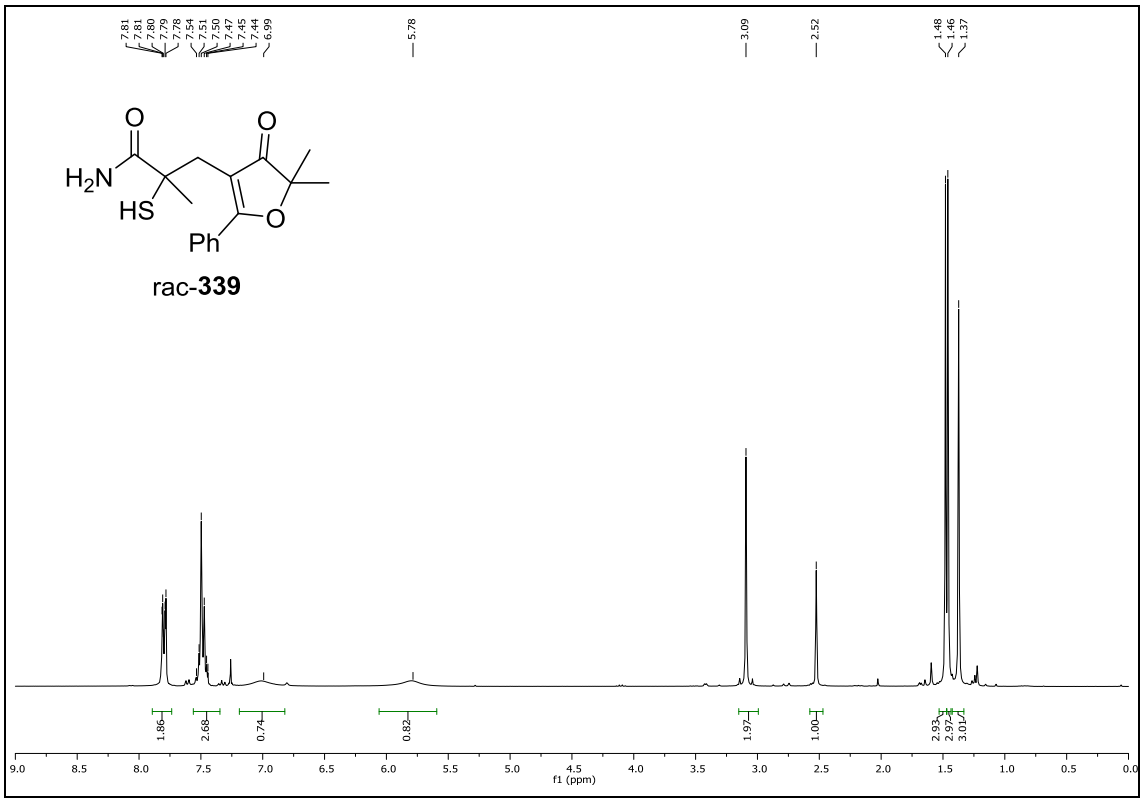
8.13
8.13
7.70
7.68
7.67
7.65
7.54
7.51
7.49
7.49
7.46
7.46
7.38
7.35
7.32
7.31
7.29
3.54
2.87
2.86
2.83
2.82
2.77
2.73
2.72
2.67
2.66
2.65
2.62
2.60
1.28
1.27
O
O
N
OH
Ph
S
Ph
332
1.98
1.13
5.71
2.84
0.95
4.00
4.18
4.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

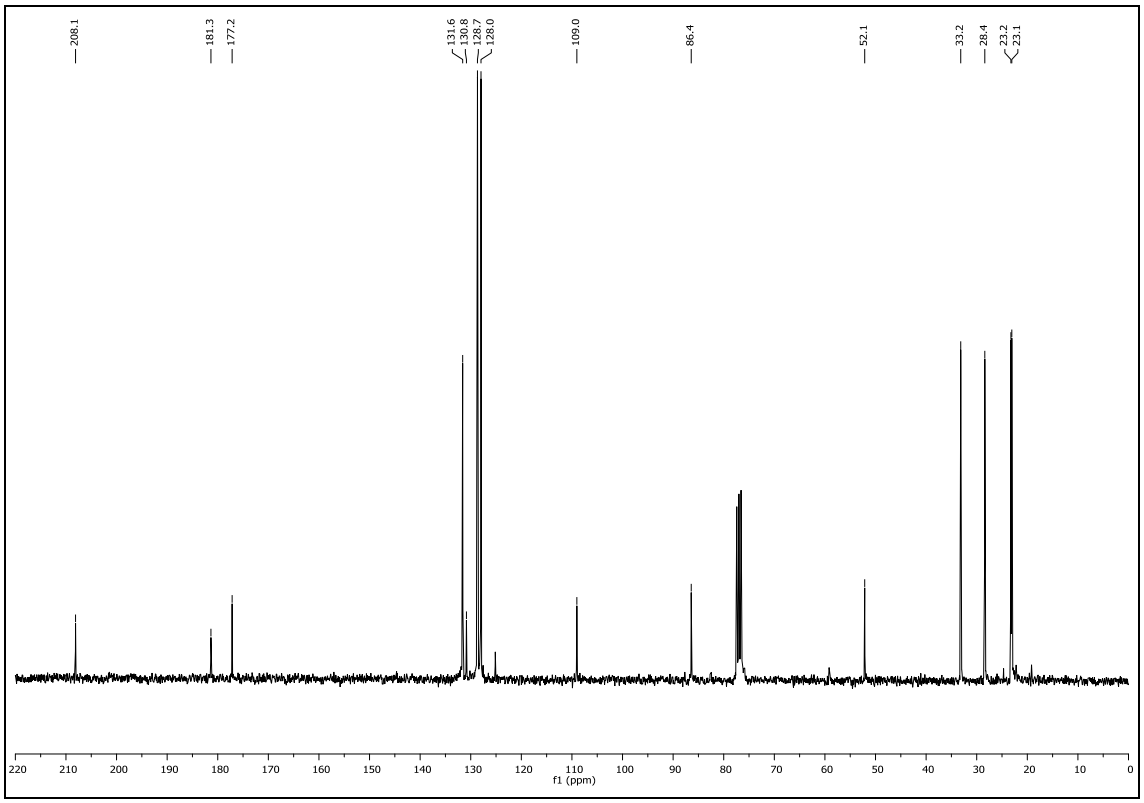

212.9
194.7
192.8
138.1
135.4
131.7
129.1
128.9
128.9
128.4
126.6
76.4
70.6
33.1
31.6
26.4
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

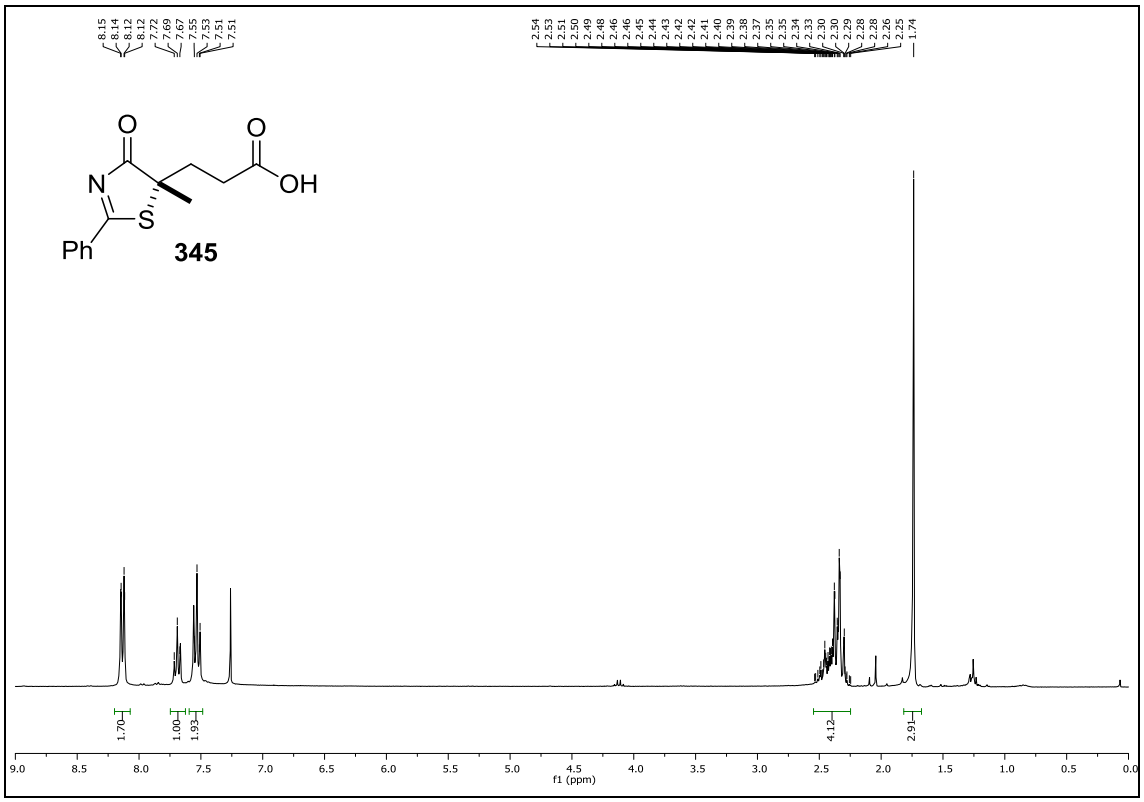

7.87
7.84
7.84
7.60
7.60
7.59
7.58
7.58
7.57
7.56
7.55
7.55
7.50
7.47
7.45
5.48
5.47
5.47
3.45
3.44
3.40
3.39
2.85
2.84
2.79
2.78
1.76
1.46
O
O
Ph
N
H
S
OH
rac-334
1.67
0.81
1.79
0.76
0.96
1.00
3.03
5.99
f1 (ppm)

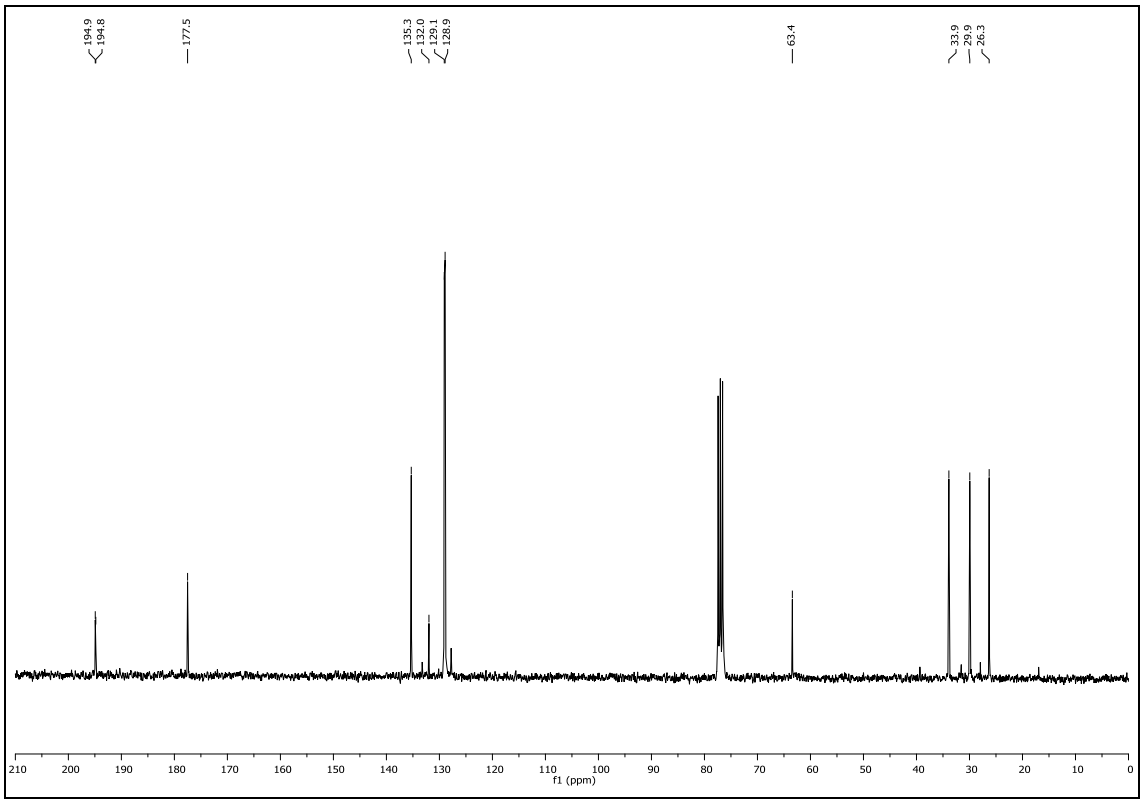

172.9
164.7
150.0
133.1
128.9
127.7
116.4
70.7
64.1
47.8
29.7
29.5
25.0
f1 (ppm)

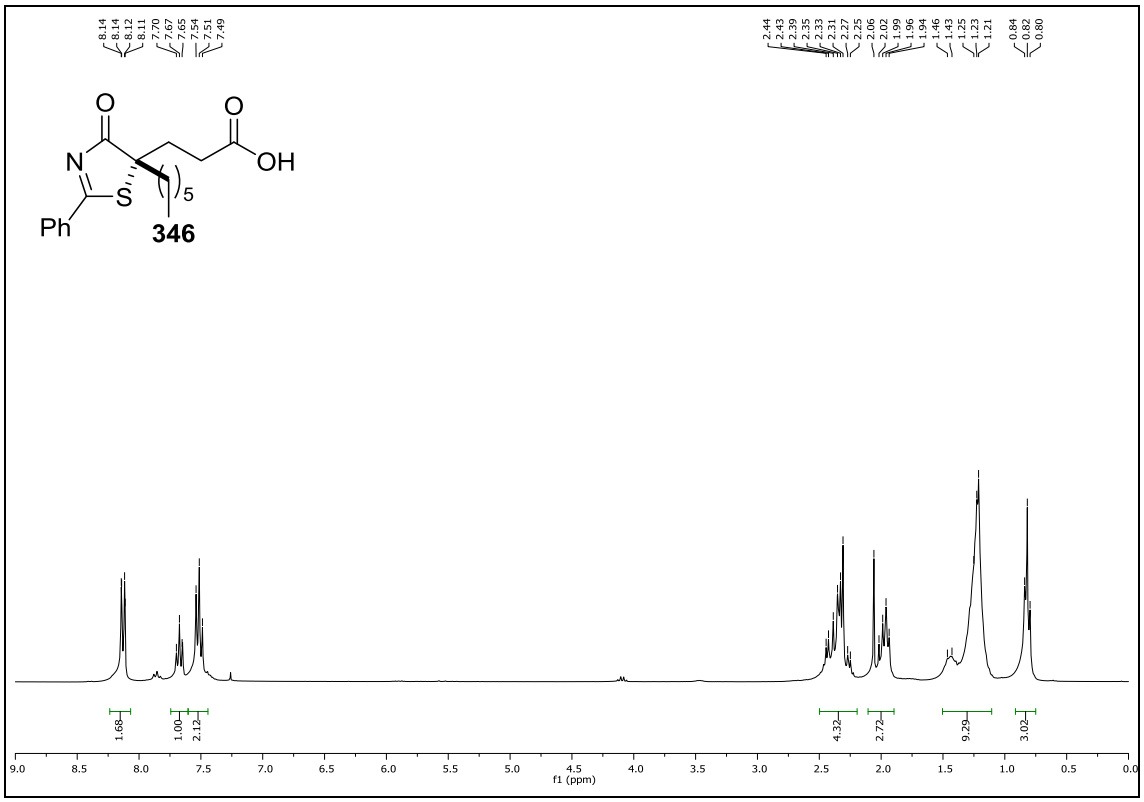

7.81
7.81
7.80
7.79
7.78
7.54
7.51
7.50
7.47
7.45
7.44
6.99
5.78
3.09
2.52
1.48
1.46
1.37
O
O
H2N
HS
O
Ph
1.86
2.68
0.74
0.82
1.97
1.00
2.93
2.97
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

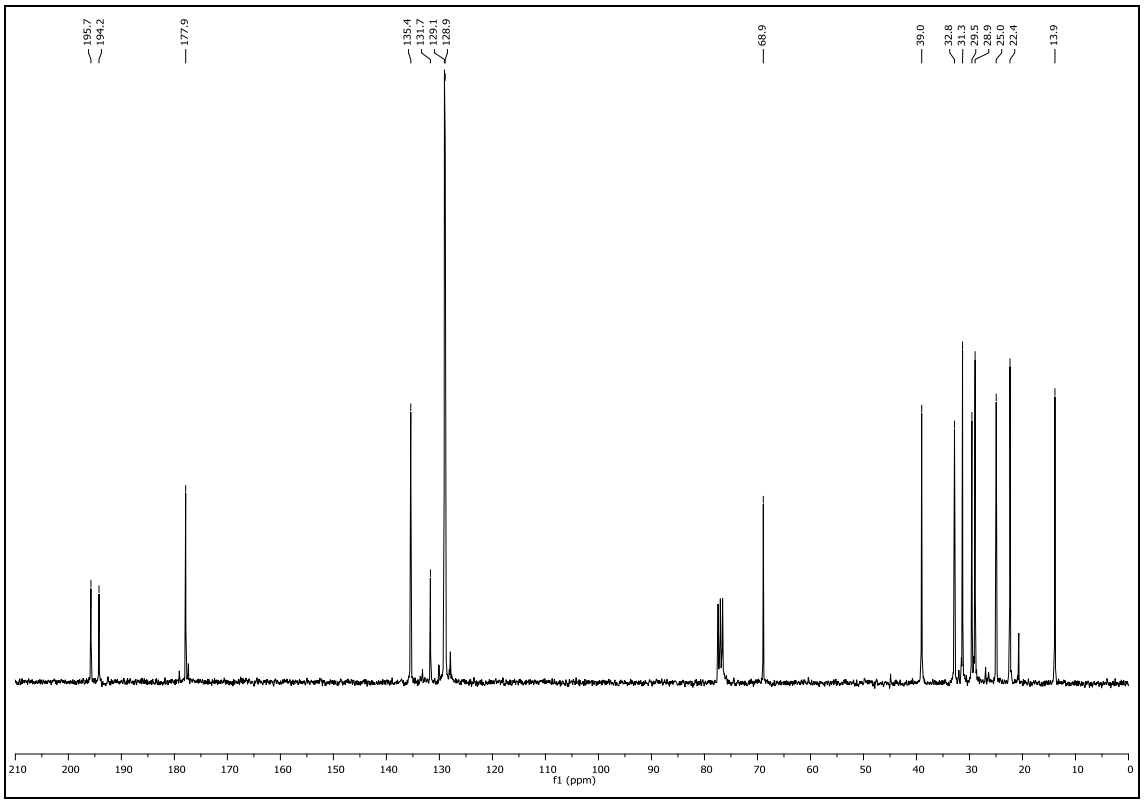
rac-**339**


208.1
181.3
177.2
131.6
130.8
128.7
128.0
109.0
86.4
52.1
33.2
28.4
23.2
23.1
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.15
8.14
8.12
8.12
7.72
7.69
7.67
7.55
7.53
7.51
7.51
2.54
2.53
2.51
2.50
2.49
2.48
2.46
2.45
2.44
2.43
2.42
2.42
2.41
2.40
2.39
2.38
2.37
2.35
2.35
2.34
2.33
2.30
2.30
2.29
2.28
2.28
2.26
2.25
1.74
O
O
N
OH
S
Ph
345
1.70
1.00
1.93
4.12
2.91
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


194.9
194.8
177.5
135.3
132.0
129.1
128.9
63.4
33.9
29.9
26.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.14
8.14
8.12
8.11
7.70
7.67
7.65
7.54
7.51
7.49
2.44
2.43
2.39
2.35
2.33
2.31
2.27
2.25
2.06
2.02
1.98
1.96
1.94
1.46
1.43
1.25
1.23
1.21
0.84
0.82
0.80
O
O
N
OH
S
5
Ph
346
1.68
1.00
2.13
4.32
2.72
9.29
3.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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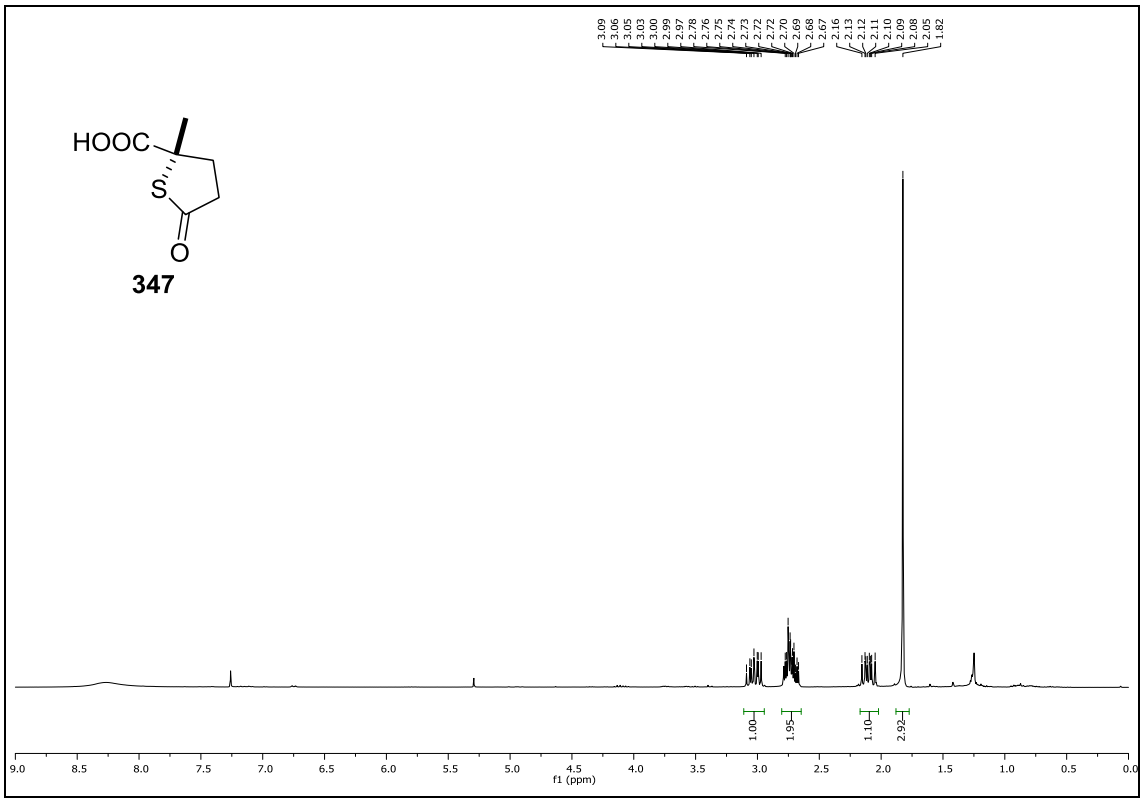
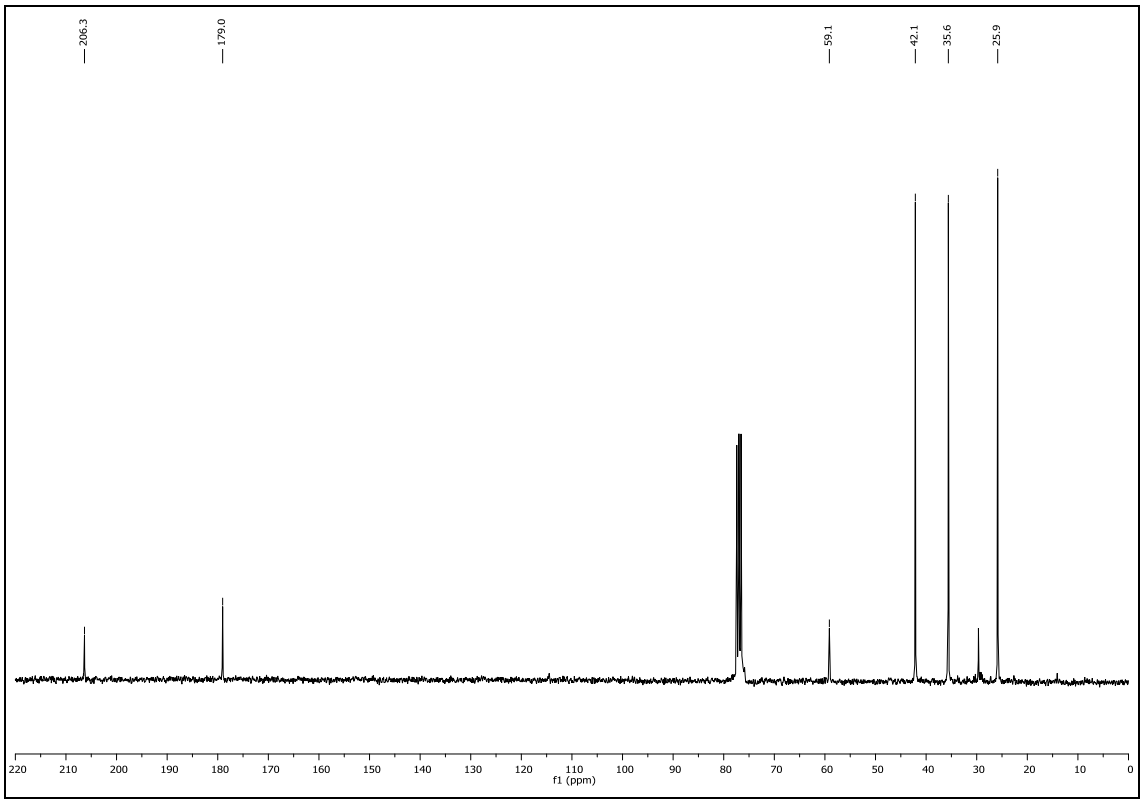
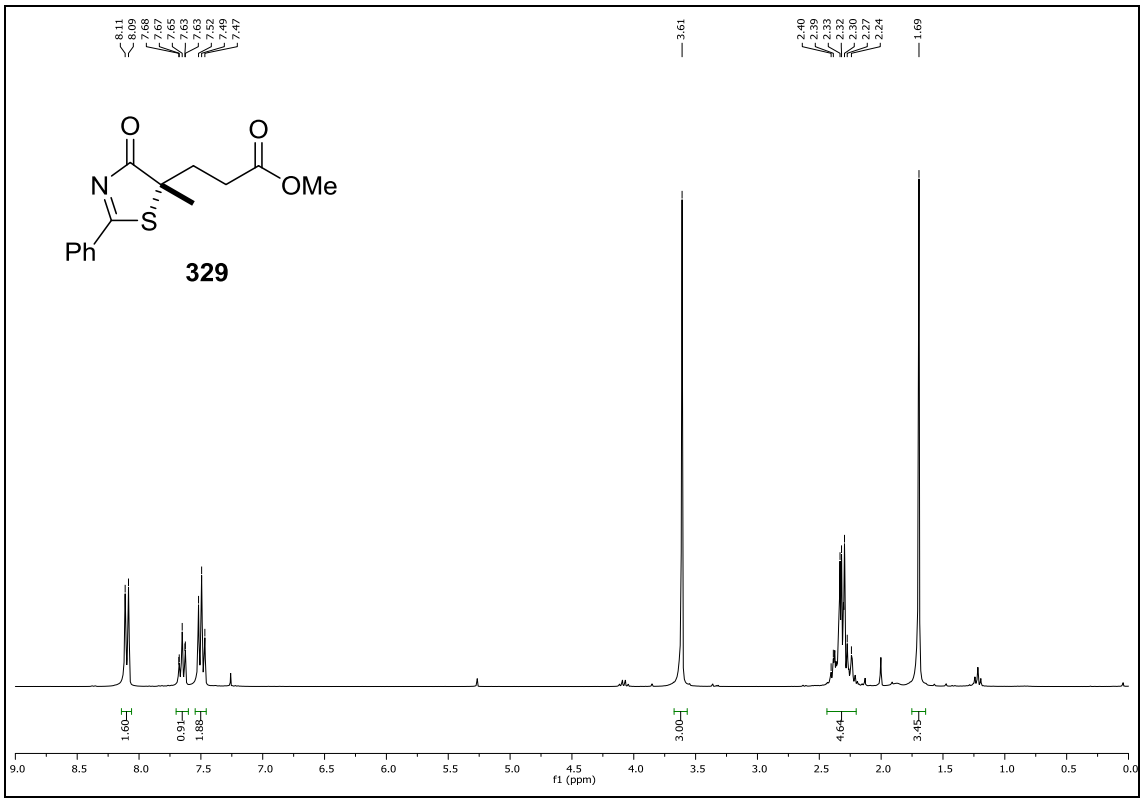
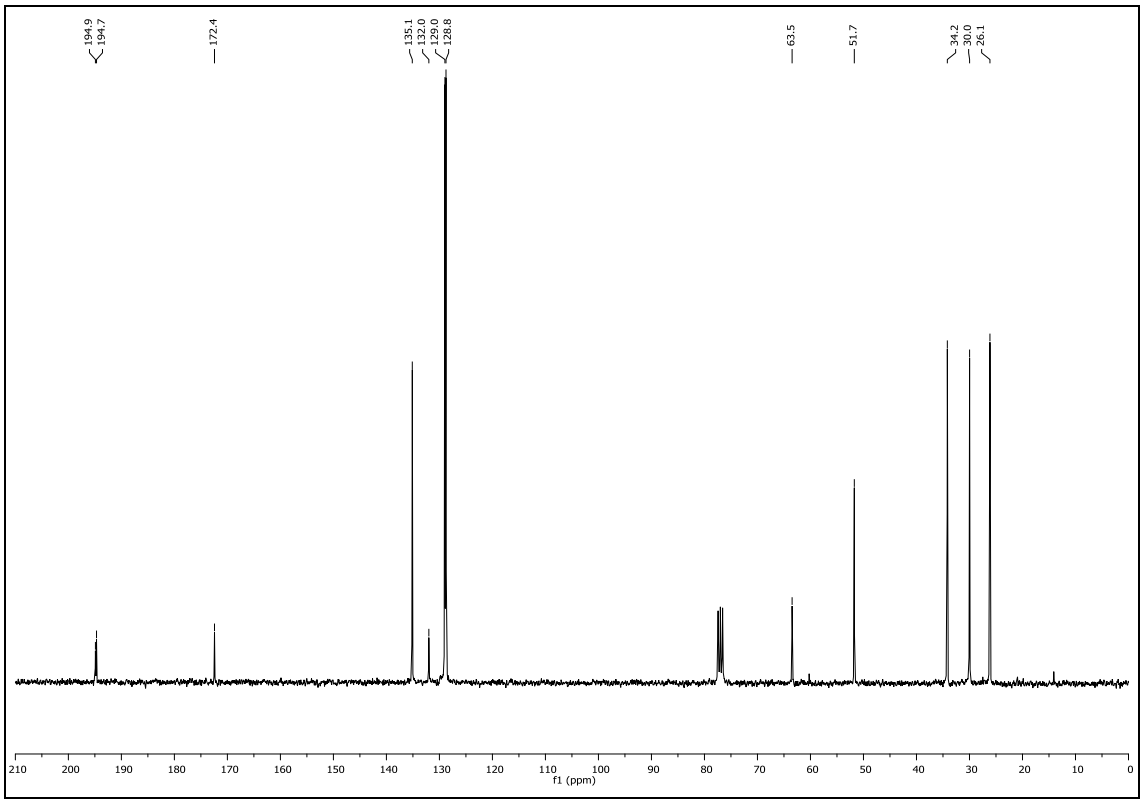
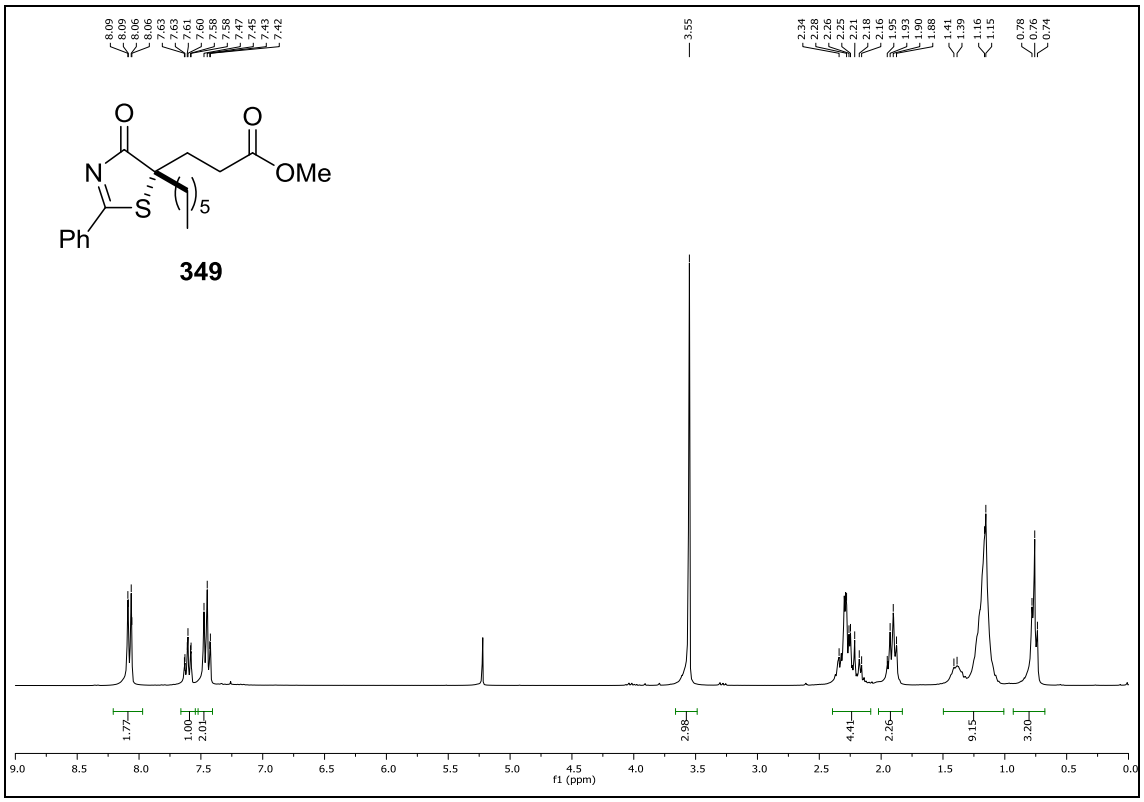
194.2
177.9
135.4
131.7
129.1
128.9
68.9
39.0
32.8
31.3
29.5
28.9
25.0
22.4
13.9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

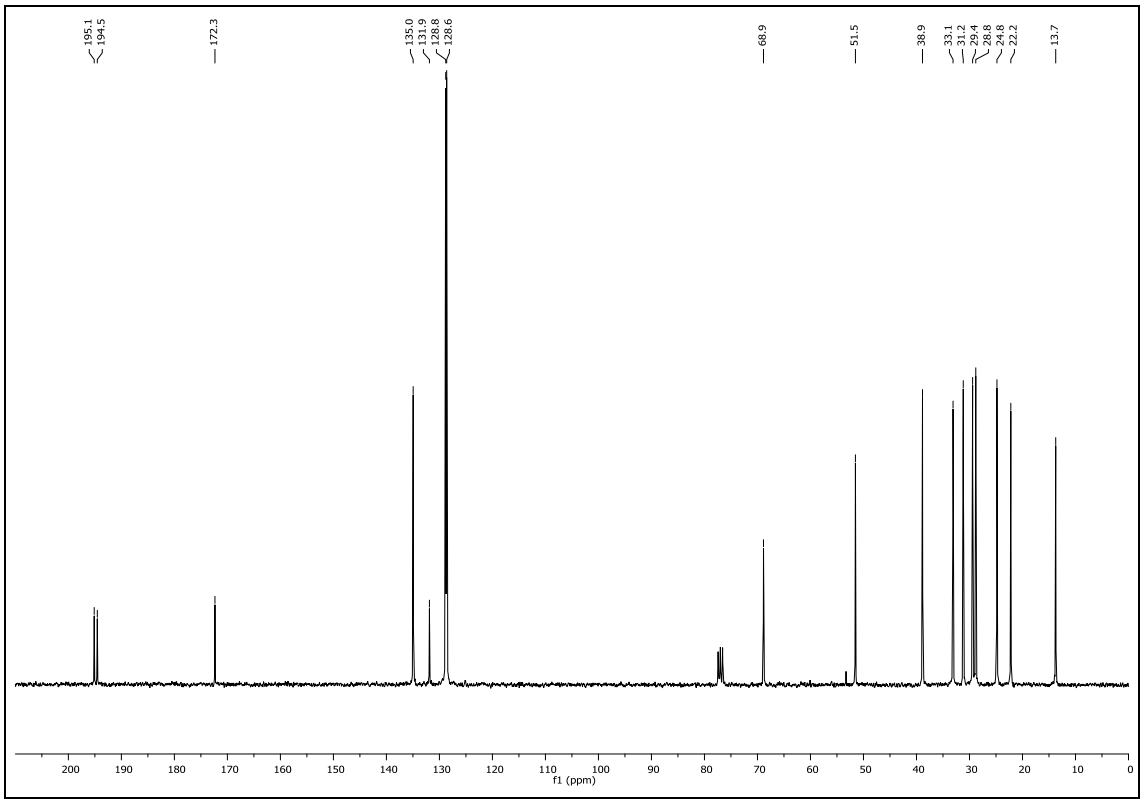

HOOC
S
O
347
3.09
3.06
3.05
3.03
3.00
2.99
2.97
2.78
2.76
2.75
2.74
2.73
2.72
2.72
2.70
2.69
2.68
2.67
2.16
2.13
2.12
2.11
2.10
2.09
2.08
2.05
1.82
1.00
1.95
1.10
2.92
f1 (ppm)


206.3
179.0
59.1
42.1
35.6
25.9
f1 (ppm)

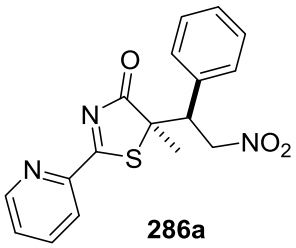

8.11
8.09
7.68
7.67
7.65
7.63
7.63
7.52
7.49
7.47
3.61
2.40
2.39
2.33
2.32
2.30
2.27
2.24
1.69
O
O
N
S
OMe
Ph
329
1.60
0.91
1.88
3.00
4.64
3.45
f1 (ppm)


194.9
194.7
172.4
135.1
132.0
130.0
128.8
63.5
51.7
34.2
30.0
26.1
f1 (ppm)


8.09
8.09
8.06
8.06
7.63
7.63
7.61
7.60
7.58
7.58
7.47
7.45
7.43
7.42
3.55
2.34
2.28
2.26
2.25
2.21
2.18
2.16
1.95
1.93
1.90
1.88
1.41
1.39
1.16
1.15
0.78
0.76
0.74
O
O
N
OMe
S
5
Ph
349
1.77
1.00
2.01
2.98
4.41
2.26
9.15
3.20
f1 (ppm)


195.1
194.5
172.3
135.0
131.9
128.8
128.6
68.9
51.5
38.9
33.1
31.2
29.4
28.8
24.8
22.2
13.7
f1 (ppm)

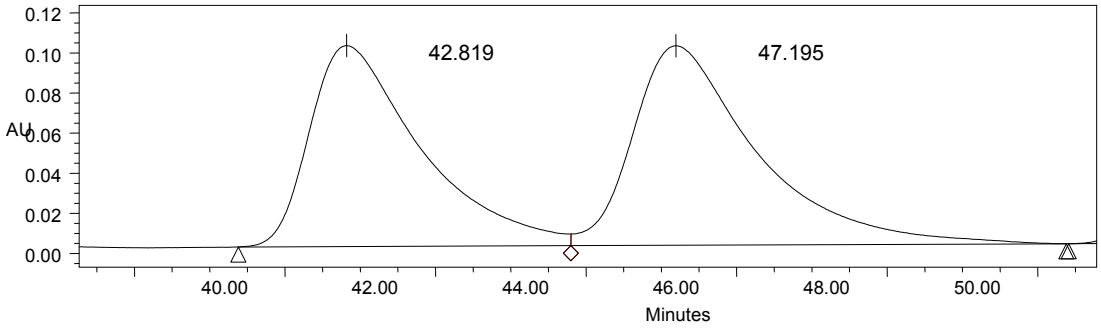
6.3.11. HPLC chromatograms



286a

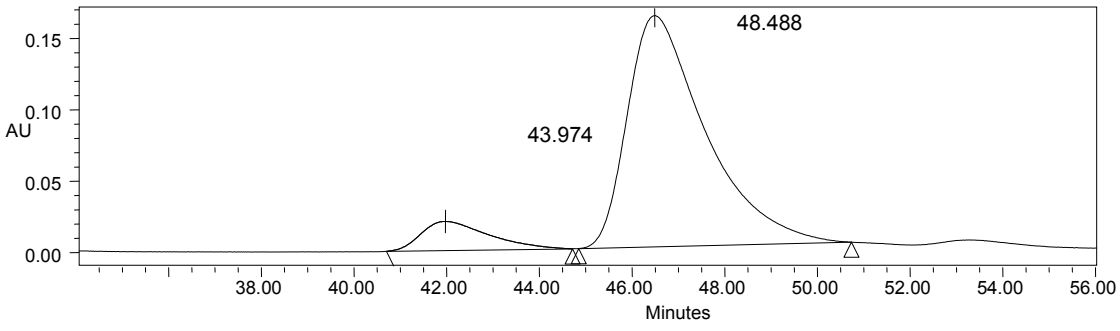
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**286a**

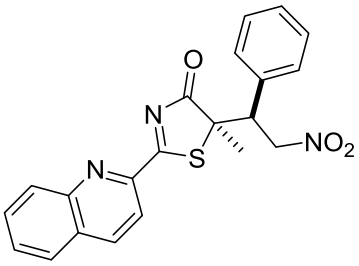


	Retention Time	% Area
1	42.819	47.48
2	47.195	52.52

286a



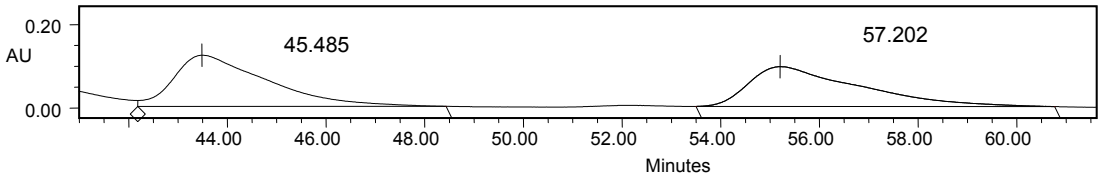
	Retention Time	% Area
1	43.974	9.78
2	48.488	90.22



306a

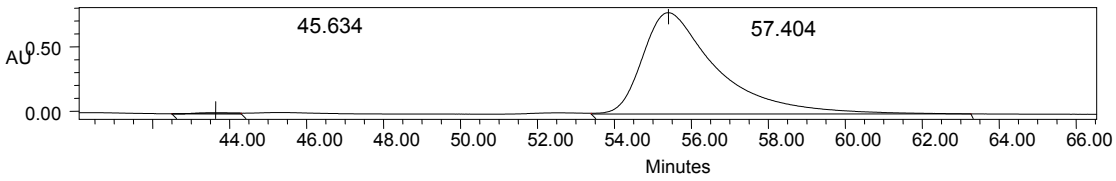
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306a**

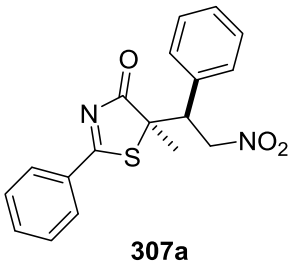


	Retention Time	% Area
1	45.485	52.22
2	57.202	47.78

306a



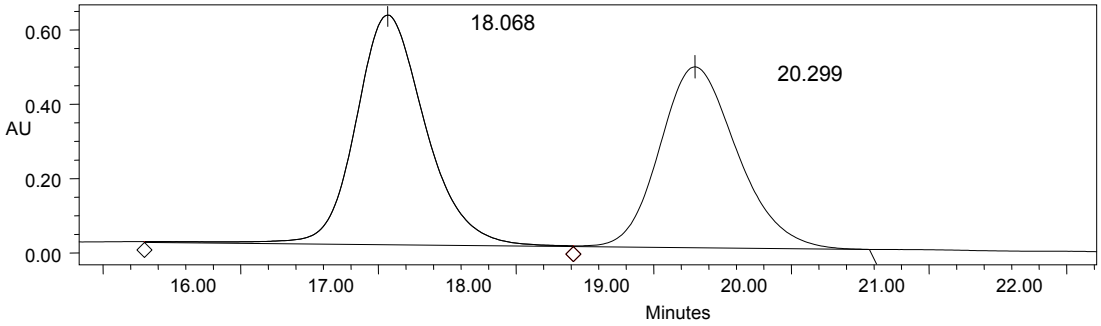
	Retention Time	% Area
1	45.634	0.48
2	57.404	99.52



307a

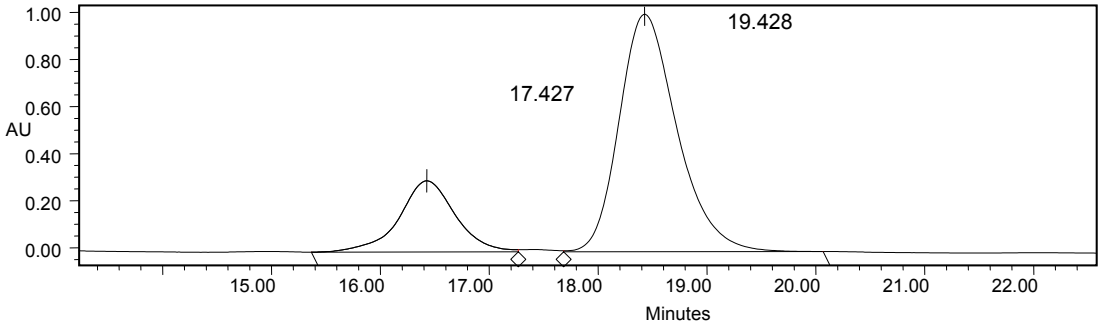
Daicel Chiralpak IC, hexane/isopropanol 20/80, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**307a**

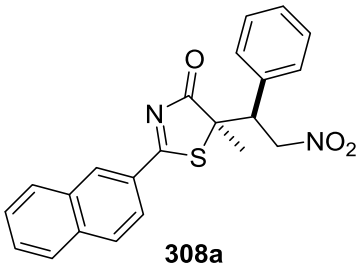


	Retention Time	% Area
1	18.068	53.41
2	20.299	46.59

307a



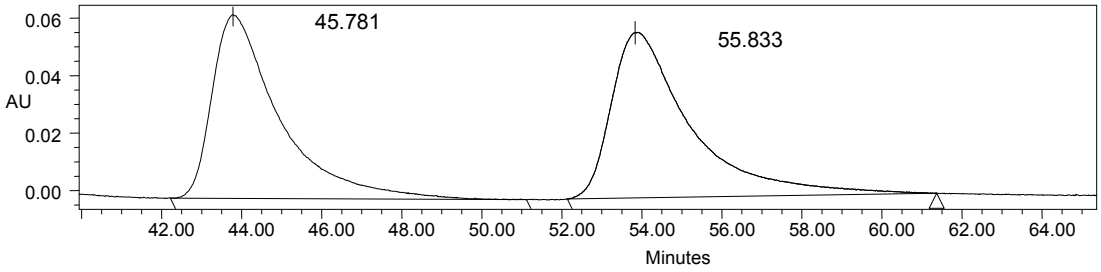
	Retention Time	% Area
1	17.427	22.55
2	19.428	77.45



308a

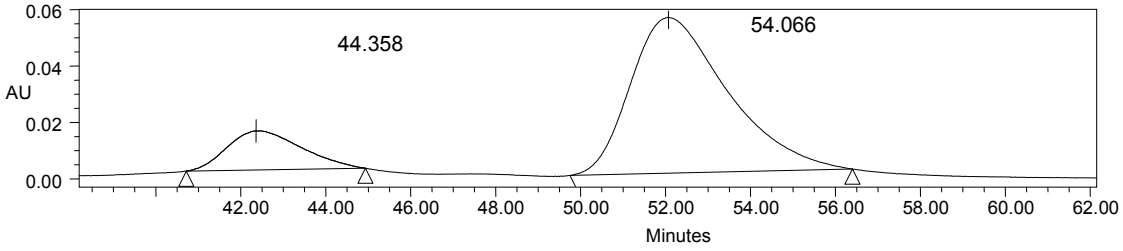
Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**308a**

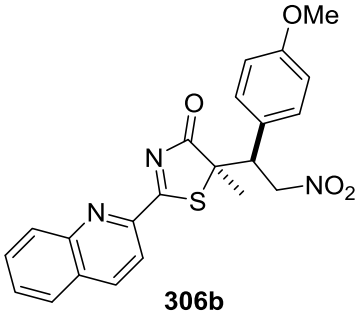


	Retention Time	% Area
1	45.781	48.55
2	55.833	51.45

308a



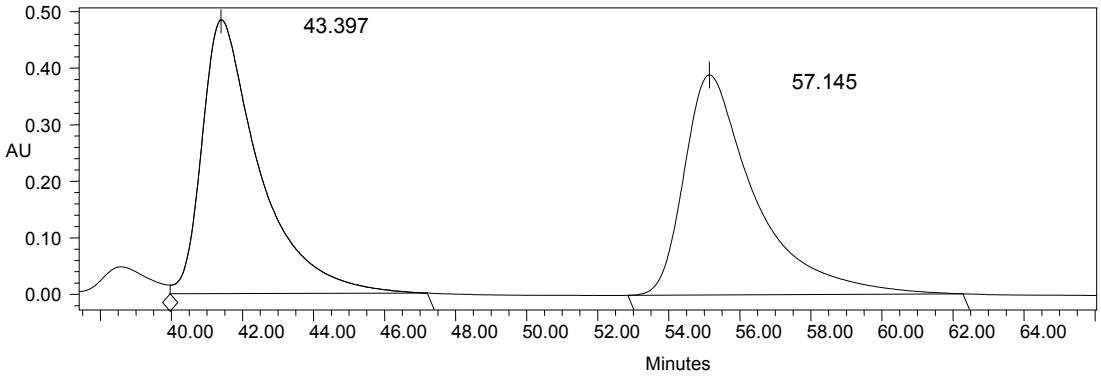
	Retention Time	% Area
1	44.358	16.08
2	54.066	83.92



306b

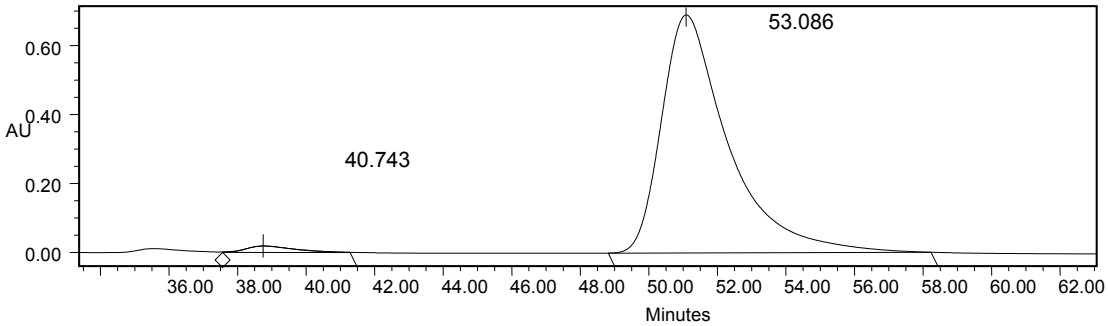
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306b**

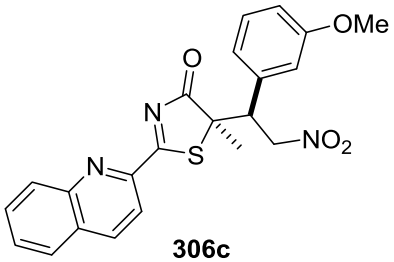


	Retention Time	% Area
1	43.397	50.21
2	57.145	49.79

306b



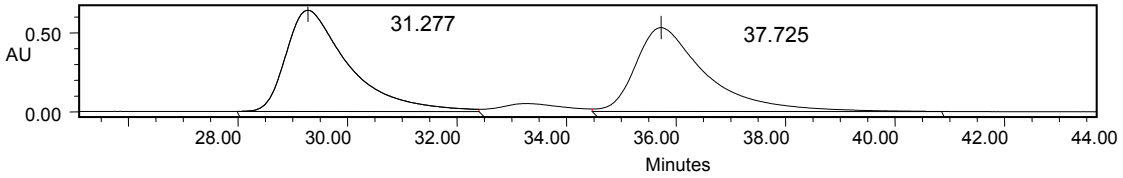
	Retention Time	% Area
1	40.743	1.90
2	53.086	98.10



306c

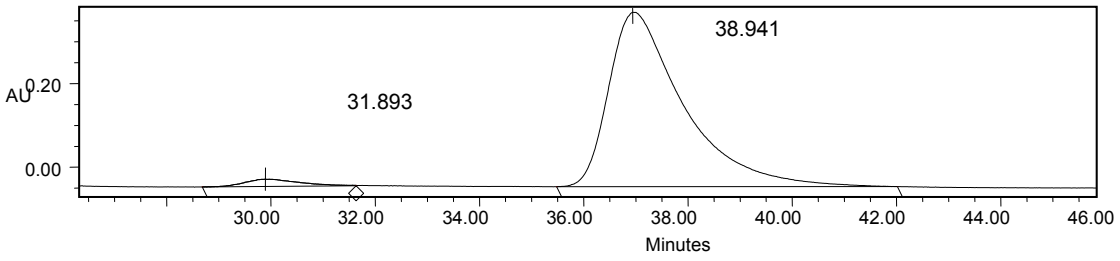
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306c**

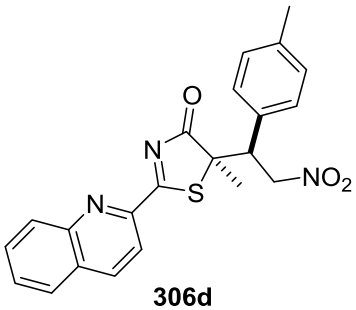


	Retention Time	% Area
1	31.277	51.80
2	37.725	48.20

306c



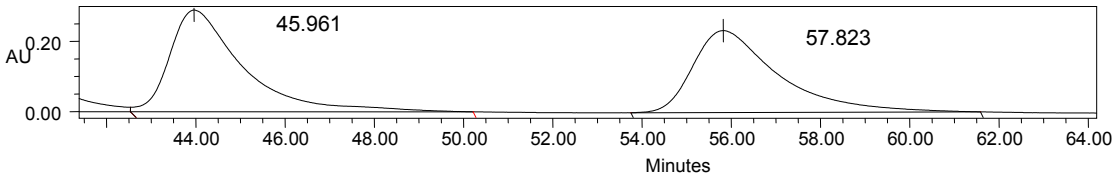
	Retention Time	% Area
1	31.893	3.03
2	38.941	96.97



306d

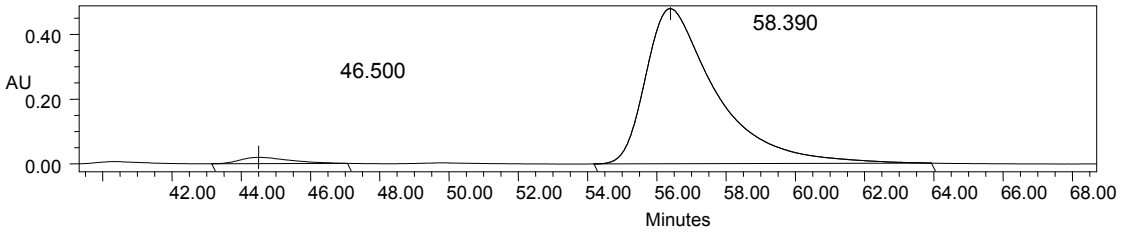
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306d**

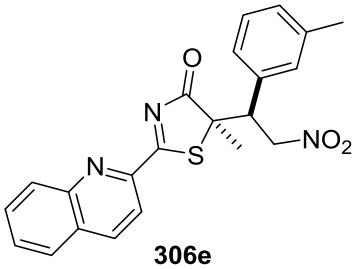


	Retention Time	% Area
1	45.961	51.59
2	57.823	48.41

306d



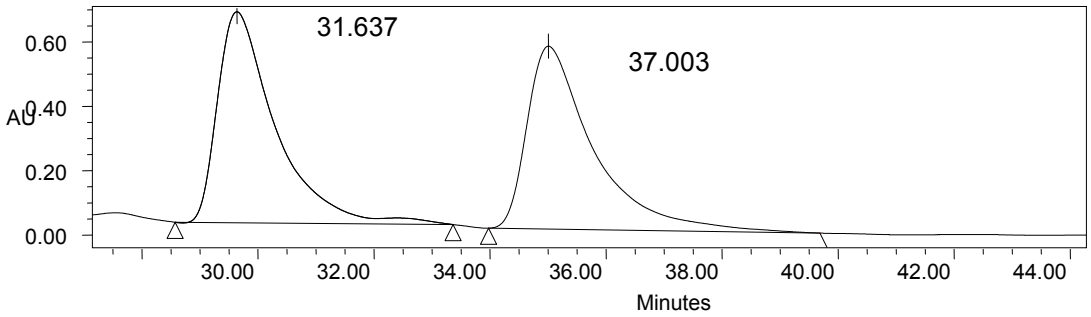
	Retention Time	% Area
1	46.500	2.80
2	58.390	97.20



306e

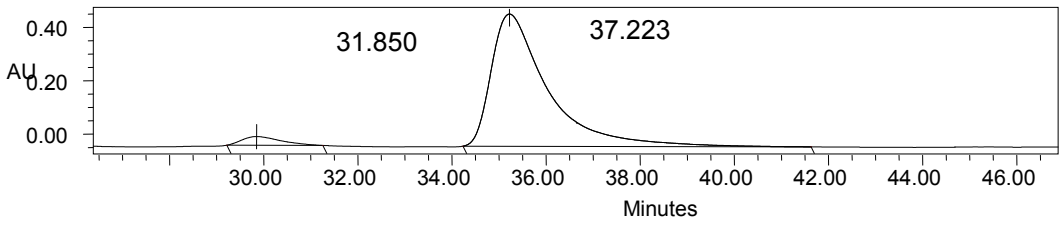
Daicel Chiralpak IA, hexane/isopropanol 85/15, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306e**

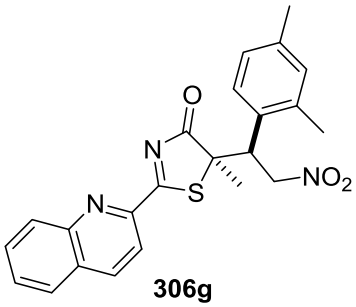


	Retention Time	% Area
1	31.637	50.23
2	37.003	49.77

306e



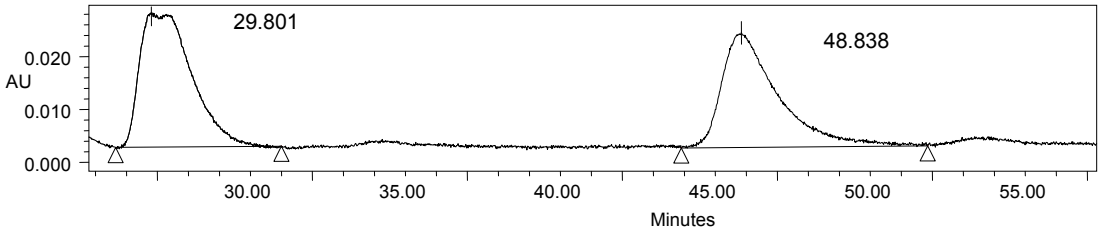
	Retention Time	% Area
1	31.850	4.34
2	37.223	95.66



306g

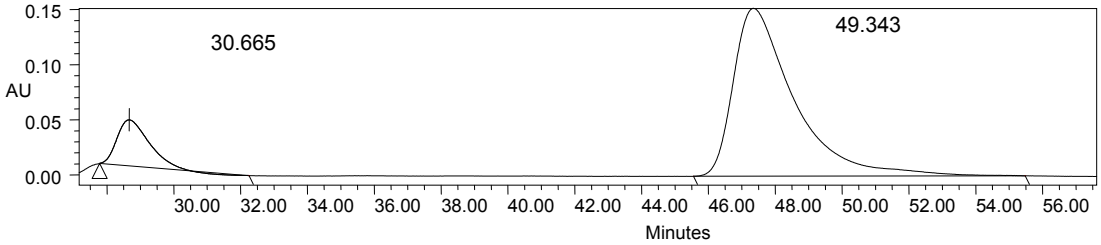
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306g**

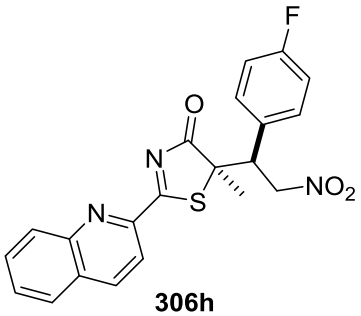


	Retention Time	% Area
1	29.801	52.17
2	48.838	47.83

306g



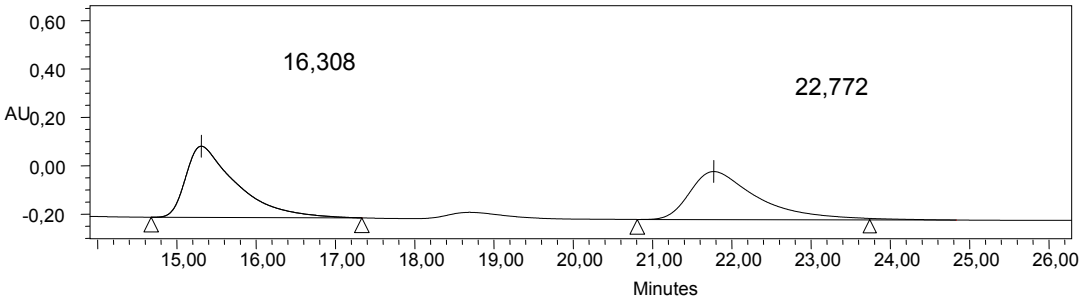
	Retention Time	% Area
1	30.665	13.15
2	49.343	86.85



306h

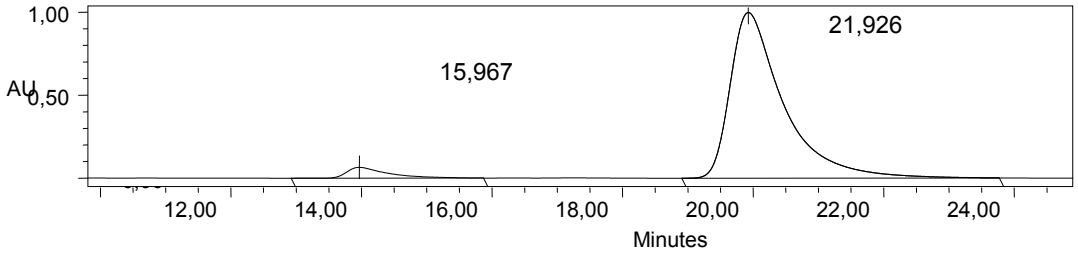
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 50/50, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306h**

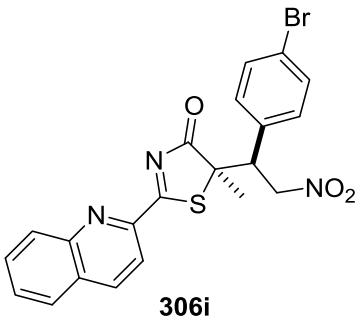


	Retention Time	% Area
1	16,308	52,31
2	22,772	47,69

306h



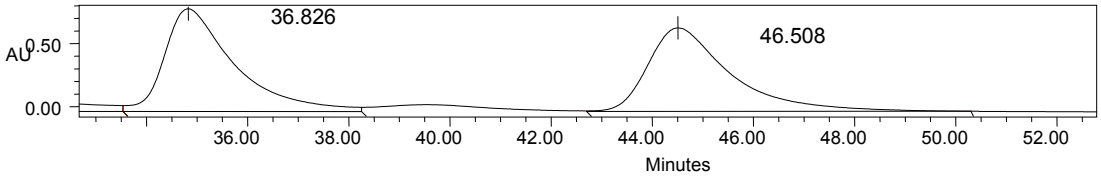
	Retention Time	% Area
1	15,967	4,74
2	21,926	95,26



306i

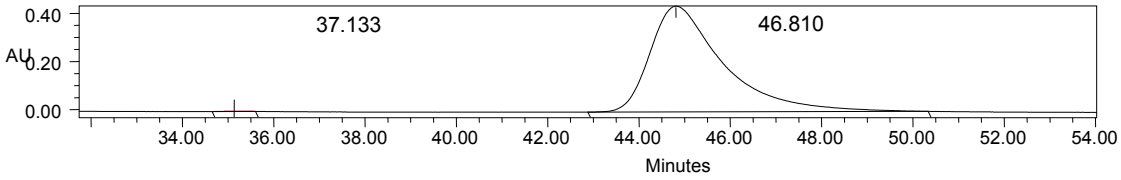
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 75/24/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306i**

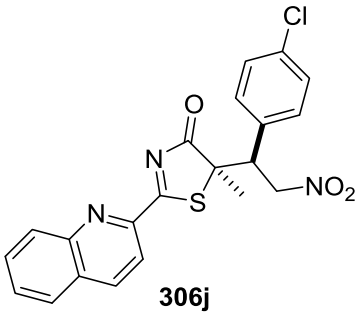


	Retention Time	% Area
1	36.826	51.28
2	46.508	48.72

306i



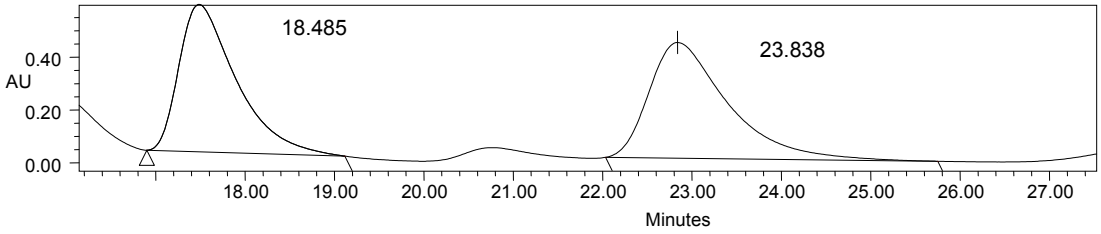
	Retention Time	% Area
1	37.133	0.07
2	46.810	99.93



306j

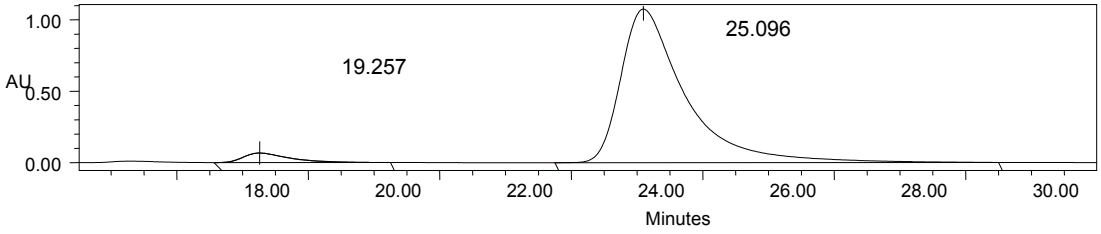
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 50/50, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306j**

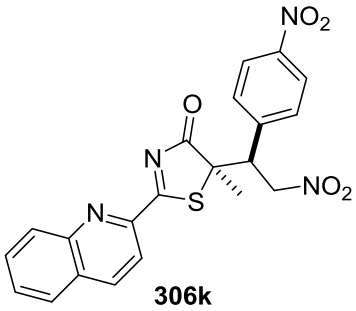


	Retention Time	% Area
1	18.485	48.17
2	23.838	51.83

306j



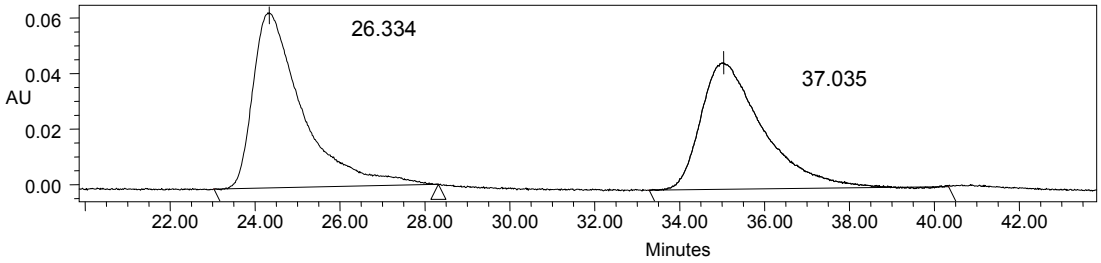
	Retention Time	% Area
1	19.257	4.28
2	25.096	95.72



306k

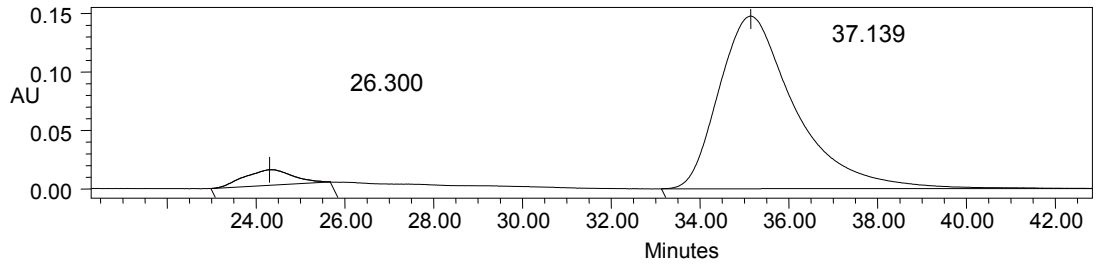
Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 50/50, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306k**

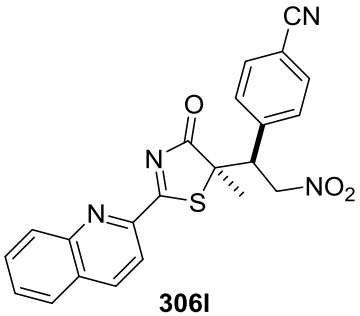


	Retention Time	% Area
1	26.334	52.34
2	37.035	47.66

306k



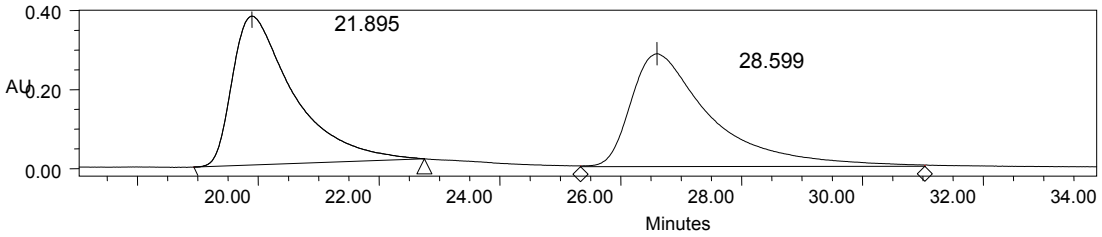
	Retention Time	% Area
1	26.300	5.41
2	37.139	94.59



306l

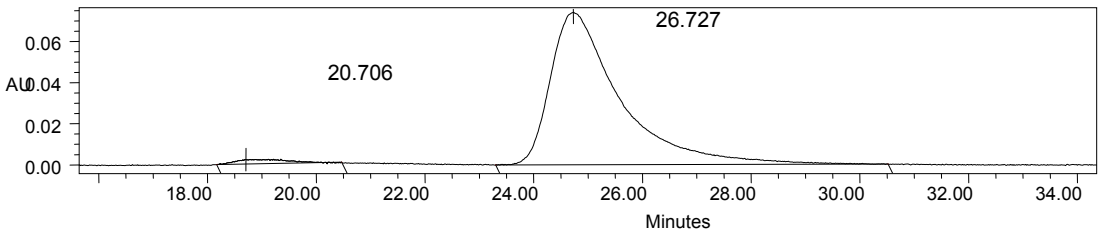
Daicel Chiralpak IA, hexane/isopropanol/ethanol 75/25, flow rate = 1.0 mL/min, λ: 210.0 nm.

rac-**306l**

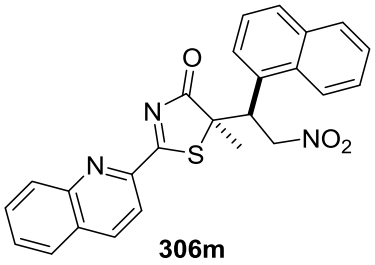


	Retention Time	% Area
1	21.895	50.26
2	28.599	49.74

306l



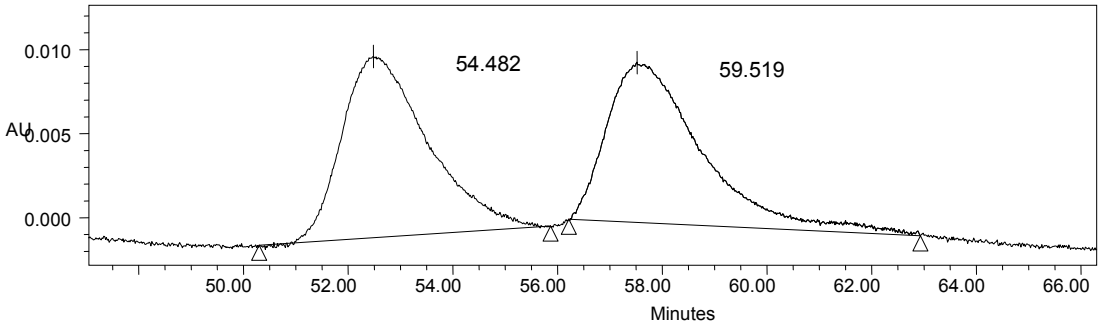
	Retention Time	% Area
1	20.706	2.12
2	26.727	97.88



306m

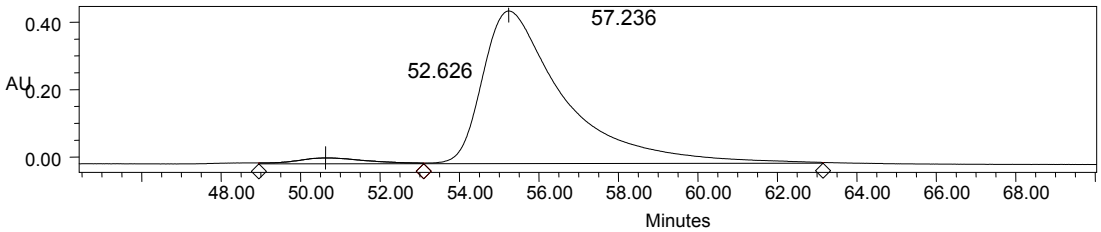
Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306m**

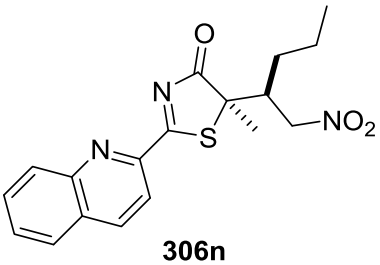


	Retention Time	% Area
1	54.482	50.72
2	59.519	49.28

306m



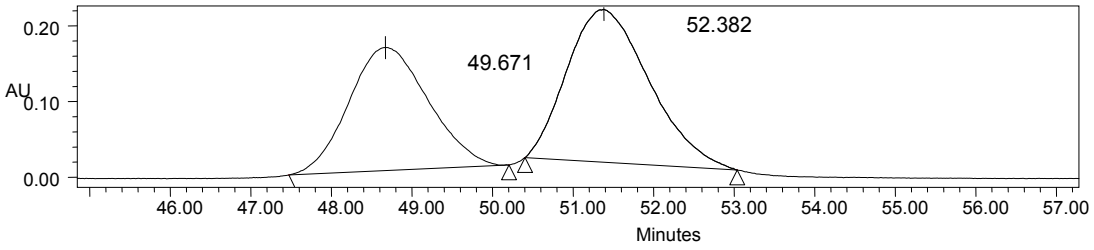
	Retention Time	% Area
1	52.626	3.14
2	57.236	96.86



306n

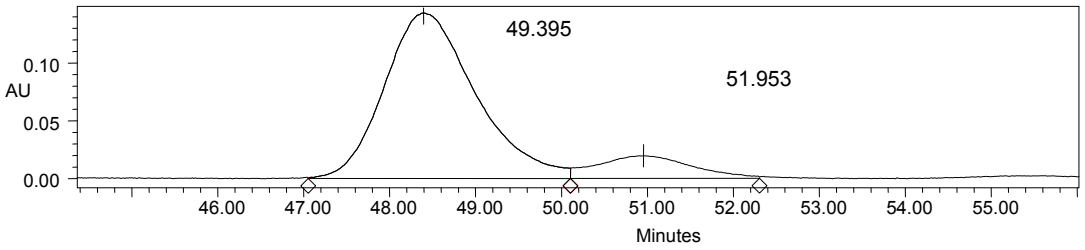
Daicel Chiralpak IC, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306n**

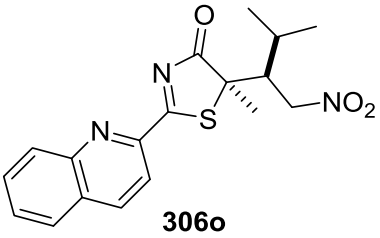


	Retention Time	% Area
1	49.671	43.73
2	52.382	56.27

306n



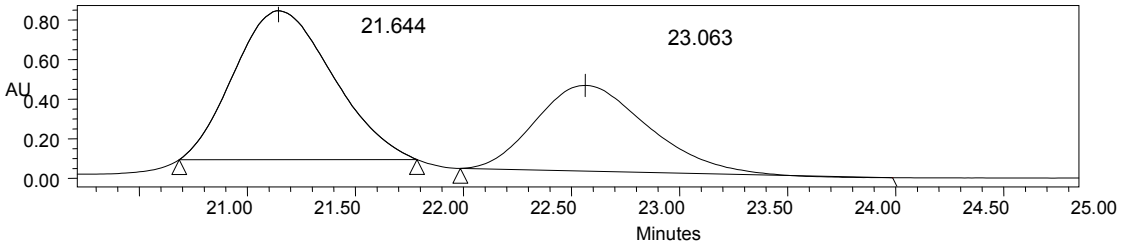
	Retention Time	% Area
1	49.395	87.61
2	51.953	12.39



306o

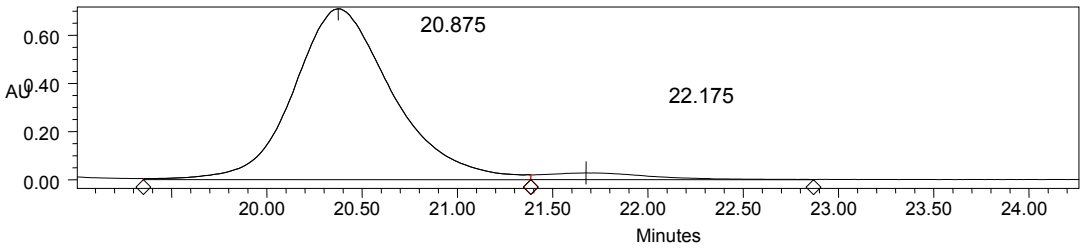
Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306o**

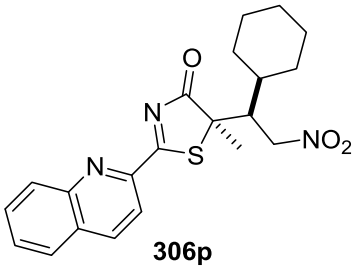


	Retention Time	% Area
1	21.644	60.31
2	23.063	39.69

306o



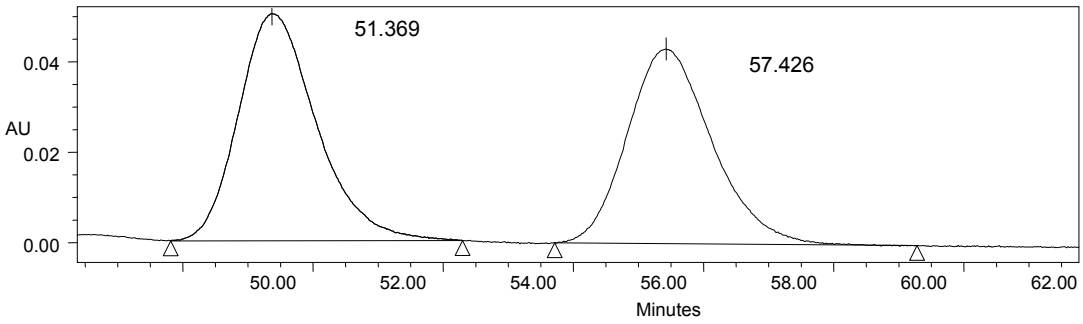
	Retention Time	% Area
1	20.875	95.87
2	22.175	4.13



306p

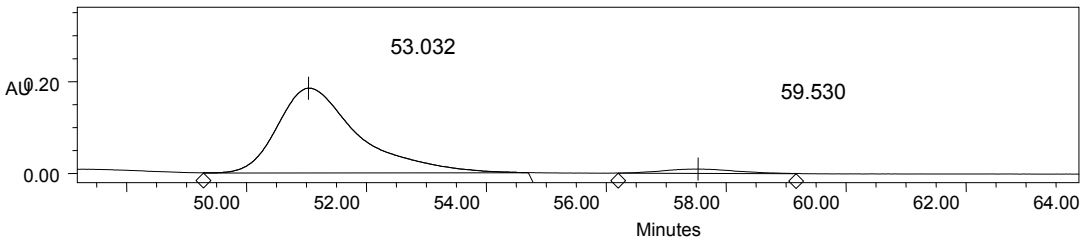
Daicel Chiralpak IC, hexane/isopropanol/ethanol 85/14/1, flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**306p**

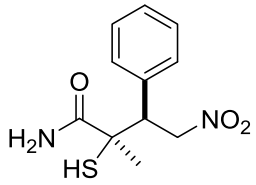


	Retention Time	% Area
1	51.369	51.82
2	57.426	48.18

306p



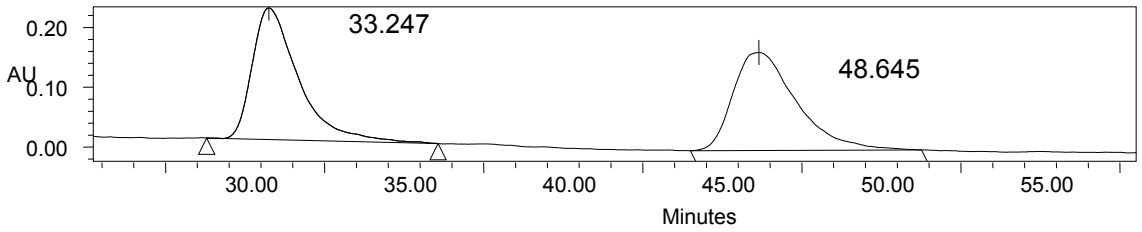
	Retention Time	% Area
1	53.032	95.49
2	59.530	4.51



311

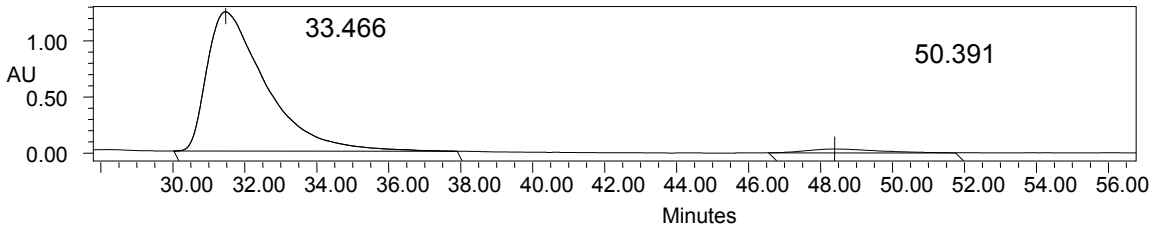
Daicel Chiralpak OD-H, hexane/isopropanol 80/20 flow rate = 0.5 mL/min, λ: 210.0 nm.

rac-**311**

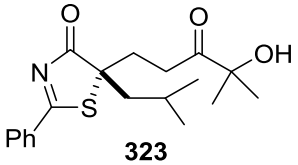


	Retention Time	% Area
1	33.247	49.51
2	48.645	50.49

311



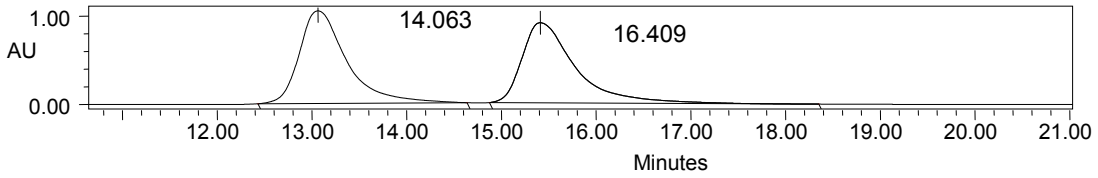
	Retention Time	% Area
1	33.466	96.64
2	50.391	3.36



323

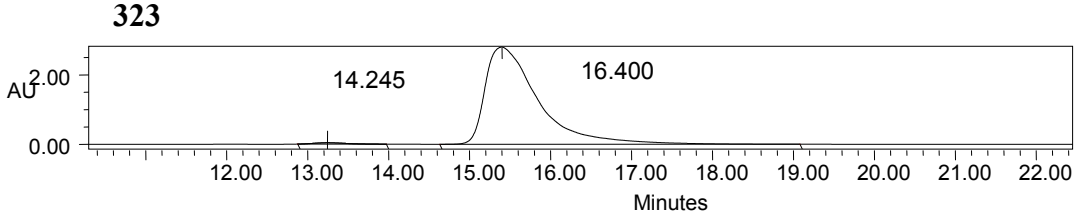
Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**323**

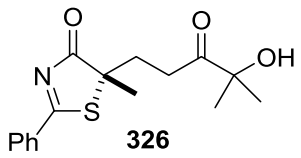


	Retention Time	% Area
1	14.063	50.60
2	16.409	49.40

323



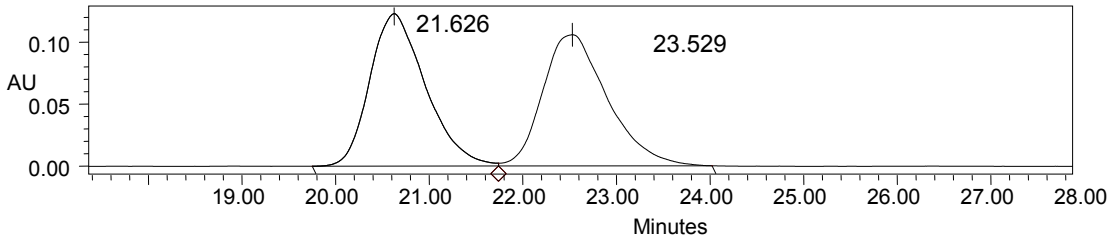
	Retention Time	% Area
1	14.245	0.88
2	16.400	99.12



326

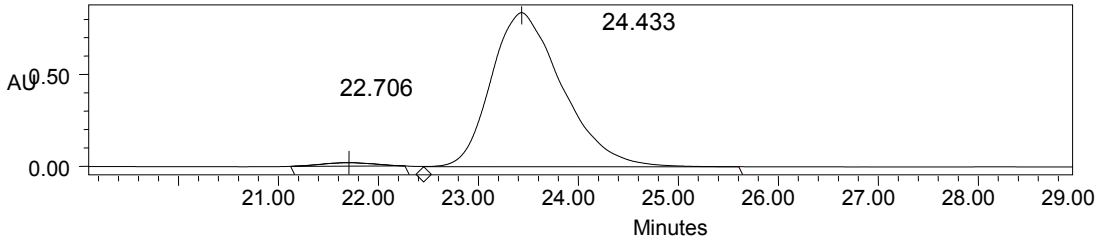
Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**326**

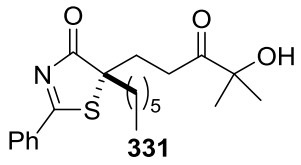


	Retention Time	% Area
1	21.626	50.09
2	23.529	49.91

326



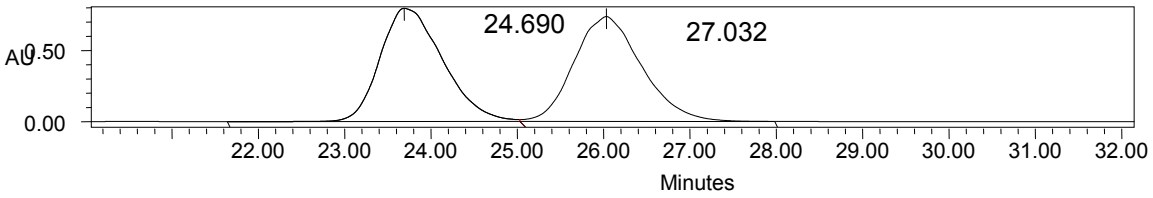
	Retention Time	% Area
1	22.706	1.65
2	24.433	98.35



331

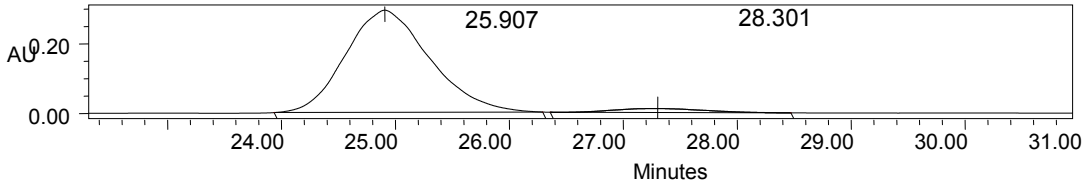
Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**331**

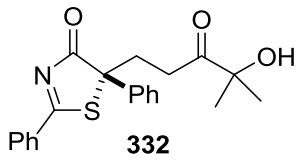


	Retention Time	% Area
1	24.690	50.03
2	27.032	49.97

331



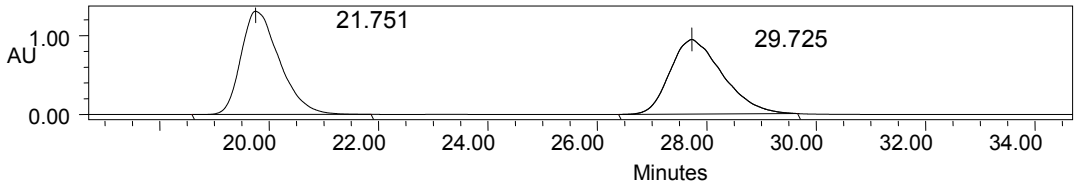
	Retention Time	% Area
1	25.907	96.00
2	28.301	4.00



332

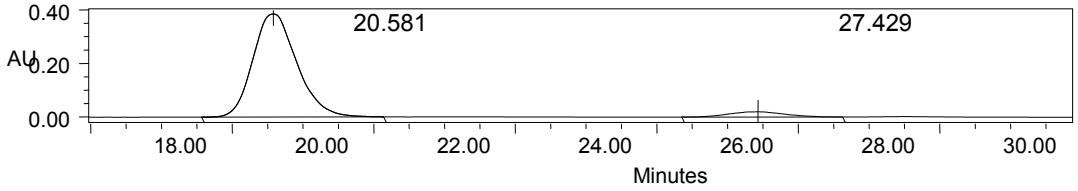
Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**332**

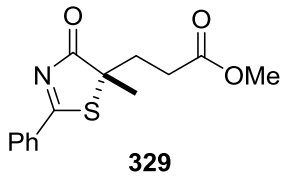


	Retention Time	% Area
1	21.751	50.39
2	29.725	49.61

332



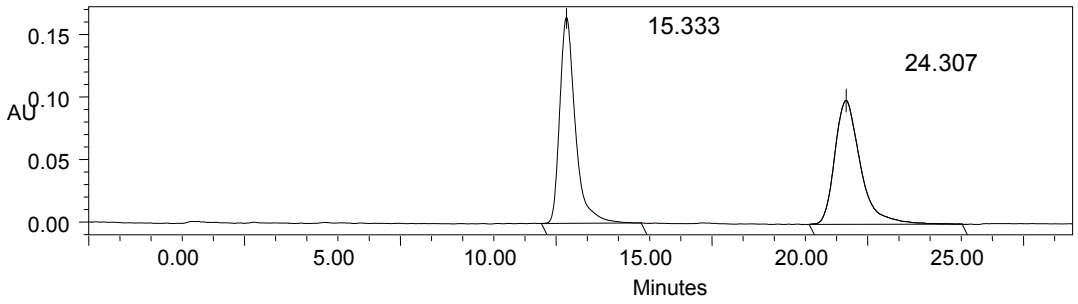
	Retention Time	% Area
1	20.581	93.87
2	27.429	6.13



329

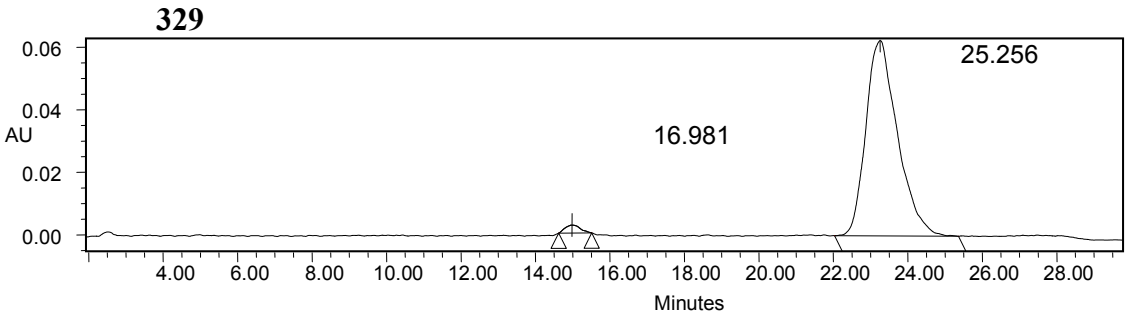
Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**329**

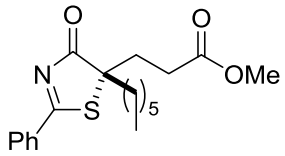


	Retention Time	% Area
1	15.333	50.15
2	24.307	49.85

329



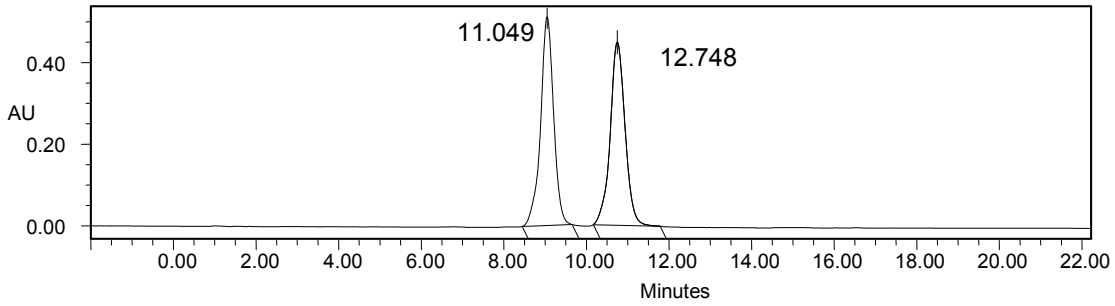
	Retention Time	% Area
1	16.981	1.91
2	25.256	98.09



349

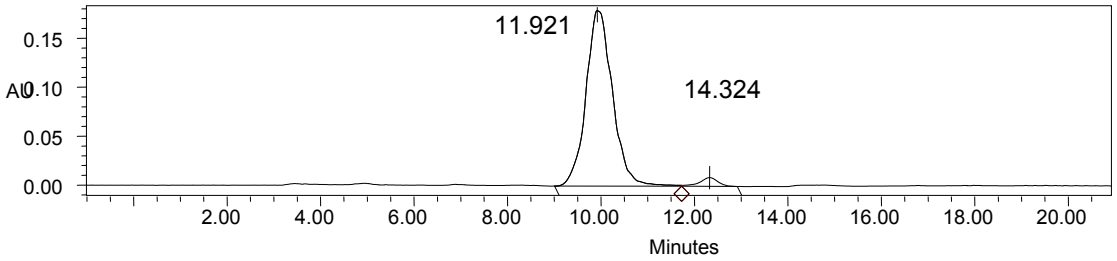
Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, λ: 272.0 nm.

rac-**349**



	Retention Time	% Area
1	11.049	49.99
2	12.748	50.01

349



	Retention Time	% Area
1	11.921	96.68
2	14.324	3.32

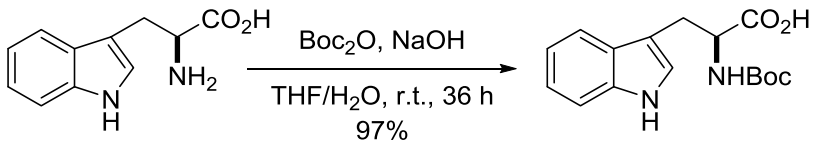
6.4. Experimental section of Chapter 4

6.4.1. Synthesis of leptosins' structural core

6.4.1.1. Preparation of starting L-tryptophan derivatives

6.4.1.1.1. L-tryptophan benzyl and methyl ester amino derivatives

*6.4.1.1.1.1. Preparation of (S)-2-((tert-butoxycarbonyl)amino)-3-(1H-indol-3-yl)propanoic acid **386**[319]*

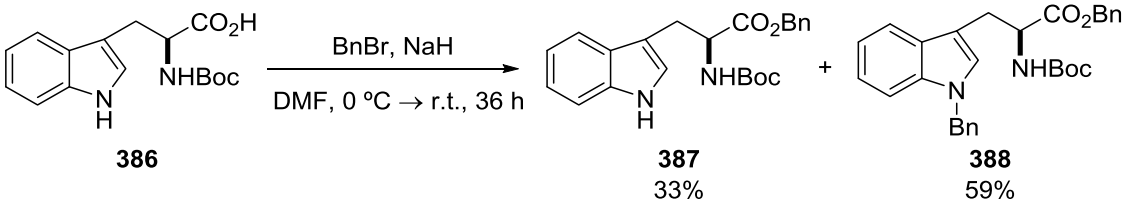


L-tryptophan **372** **386**

NaOH (1.1 equiv., 2.15 g, 53.8 mmol) and Boc_2O (1.1 equiv., 11.7 g, 53.8 mmol) were added to a stirred solution of *L*-tryptophan **372** (1 equiv., 10 g, 48.9 mmol) in THF/H_2O (240 mL:240 mL) at room temperature and the resulting solution was stirred for 36 h. After this time THF was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (100 mL). The aqueous layer was acidified with HCl 1N to pH 4, and then extracted with dichloromethane (3 x 100 mL). All the organic phases were combined and dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoic acid **386**. White solid, yield: 14.4 g, 47.3 mmol, 97%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.13–8.01 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.25–7.08 (m, 3H), 7.04–6.98 (m, 1H), 5.12–4.98 (m, 1H), 4.74–4.60 (m, 1H), 3.42–3.26 (m, 2H), 1.43 (s, 9H).

[319] Xiao, J.; Xu, J.; Cui, S.; Liu, H.; Wang, S.; Li, Y., *Org. Lett.* **2008**, *10*, 645–648.

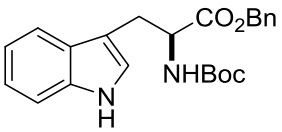
*6.4.1.1.1.2. Benzylation of N-Boc-L-Tryptophan.[320] Synthesis of **387** and **388***



386 | **387** 33% | **388** 59%

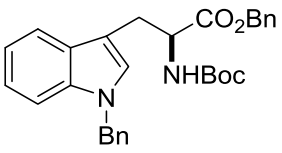
A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-Boc-*L*-tryptophan **386** (1 equiv., 1.40 g, 4.5 mmol) and DMF (4.5 mL). The resulting solution was cooled to 0 °C in an ice/water bath, and sodium hydride (60% dispersion in mineral oil, 3 equiv., 540 mg, 13.5 mmol) was added. The resulting mixture was allowed to stir at 0 °C for 30 min, then benzyl bromide (3.6 equiv., 1.92 mL, 16.2 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred until the starting material was consumed as judged by TLC analysis (36 h). The reaction was quenched with saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (6 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the resulting yellow oil crude revealed the presence of compounds **387** and **388** which were separated by flash chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1).

(*S*)-Benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate 387[321]



White solid, yield: 0.60 g, 1.5 mmol, 33%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.00 (bs, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.38–7.30 (m, 4H), 7.29–7.17 (m, 3H), 7.16–7.07 (m, 1H), 6.81 (s, 1H), 5.09 (d, *J* = 3.7 Hz, 2H), 4.79–4.61 (m, 1H), 3.29 (d, *J* = 5.3 Hz, 2H), 1.43 (s, 9H).

(*S*)-Benzyl 3-(1-benzyl-1*H*-indol-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate 388[320]

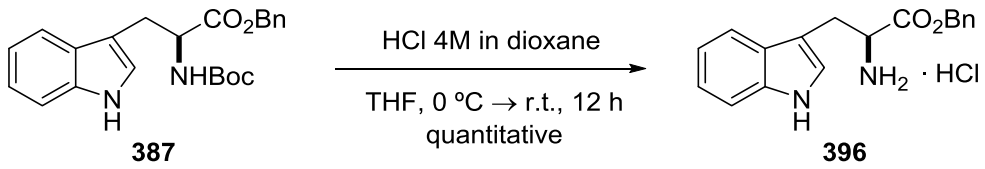


White solid, yield: 1.27 g, 2.6 mmol, 59%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.55 (d, *J* = 7.8 Hz, 1H), 7.39–6.90 (m, 14H), 6.64 (bs, 1H), 5.12 (s, 2H), 5.09–4.95 (m, 2H), 4.75–4.58 (m, 2H), 3.40–3.08 (m, 1H), 1.40 (s, 9H).

[320] Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107–5110.

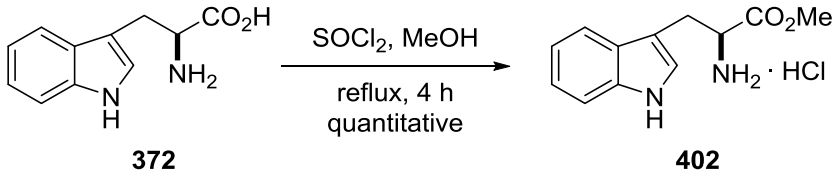
[321] Cosignani, S.; White, P. D.; Linclau, B. *J. Org. Chem*. **2004**, *69*, 5897–5905.

*6.4.1.1.1.3. Amine deprotection in adduct **387**.[322] Synthesis of **396***



To a stirred mixture of (*S*)-benzyl 2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoate **387** (1 equiv., 5.7 g, 14.5 mmol) in THF (87 mL) was added 4M HCl in dioxane (5 equiv., 18.1 mL, 72.5 mmol)**.** The reaction mixture was stirred at room temperature overnight, and then concentrated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel (eluting with dichloromethane/ methanol 98/2 → 4/1) to afford the title product (*S*)-benzyl 2-amino-3-(1*H*-indol-3-yl)propanoate hydrochloride salt **396**. White solid, yield: 4.7 g, 14.4 mmol, quantitative. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, CD_3OD), δ: 7.52 (d, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.35–7.28 (m, 3H), 7.25–7.17 (m, 2H), 7.16–7.09 (m, 1H), 7.08–6.98 (m, 2H), 5.10 (d, *J* = 2.0 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 1H), 3.36–3.25 (m, 2H).

*6.4.1.1.1.4. Preparation of (S)-methyl 2-amino-3-(1H-indol-3-yl)propanoate hydrochloride **402**[323]*



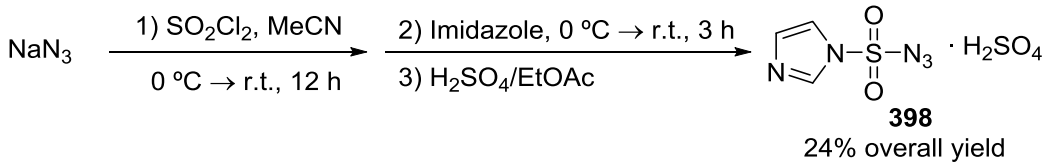
To a suspension of *L*-tryptophan **372** (1 equiv., 2.6 g, 13 mmol) in MeOH (26 mL), thionyl chloride (2.2 equiv., 2.1 mL, 28.6 mmol) was added and the mixture was refluxed for 4 h. The solution was concentred under reduced pressure and the crude material was used in next step without further purification. White solid, yield: 3.3 g, 13 mmol, quantitative. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, DMSO), δ: 11.07 (bs, 1H), 8.44 (bs, 2H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.1 Hz, 1H), 7.28–7.19 (m, 1H), 7.16–6.97 (m, 2H), 4.25 (t, *J* = 6.1 Hz, 1H), 3.67 (s, 3H), 3.28 (d, *J* = 6.2 Hz, 2H).

[322] Evans, M. J.; Morris, G. M.; Wu, J.; Olson, A. J.; Sorensend, E. J.; Cravatt, B. F. *Mol. BioSyst.* **2007**, *3*, 495–506.

[323] Zamudio-Rivera, L. S.; Beltran, H. I.; Farfan, N. *Org. Prep. Proced. Int*. **2001**, *33*, 341–349.

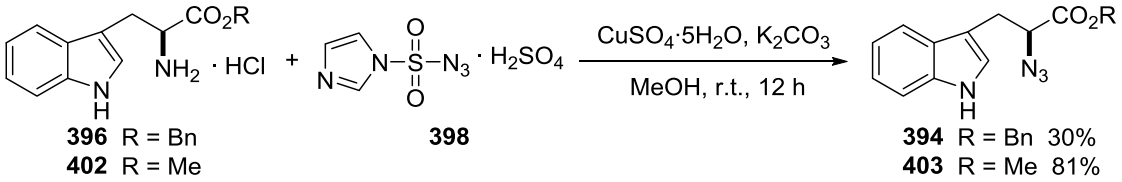
6.4.1.1.2. L-tryptophan benzyl and methyl ester azido derivatives

*6.4.1.1.2.1. Preparation of the diazotransfer reagent **398**[324]*



Sulfuryl chloride (1 equiv., 8.0 mL, 100 mmol) was added dropwise to an ice-cooled suspension of NaN_3 (1 equiv., 6.5 g, 100 mmol) in MeCN (200 mL) and the mixture was stirred overnight at room temperature. Imidazole (1.9 equiv., 13 g, 190 mmol) was added portion-wise to the ice-cooled mixture and the resulting slurry was stirred for 3 h at room temperature. The mixture was diluted with EtOAc (50 mL), washed with H_2O (2 × 200 mL) and then saturated aqueous $NaHCO_3$ (2 × 75 mL), dried over Na_2SO_4 (1 h stirring, very important for complete dryness) and filtered. Sulfuric acid (1 equiv., 10 g, 100 mmol; in 40 mL EtOAc) was added slowly to a solution of imidazole-1-sulfonyl azide in EtOAc at 0 °C. The reaction mixture was stirred for 1 h at rt. The precipitate was filtered, washed, and dried in vacuo to give 6.5 g (24 mmol, 24%) of salt **398** as a white, crystalline powder. **Caution!**. Mother liquors and other waste, which may contain the highly explosive sulfonyl diazide, were treated with excess sodium nitrite and acidified to destroy azide-containing species.

*6.4.1.1.2.2. Synthesis of azido derivatives **394** and **403**[324]*



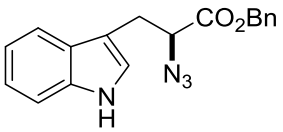
General procedure

3-Azidosulfonyl-3*H*-imidazol-1-ium hydrogen sulfate **398** (1.2 eq) was added to a mixture of the starting salt **396** or **402** (1 equiv.), K_2CO_3 (2 equiv.) and $CuSO_4.5H_2O$ (10 μmg/mmol) in MeOH (5 mL/mmol) and the mixture was stirred at room temperature overnight. The mixture was then concentrated, diluted with H_2O (3 mL/mmol), acidified with HCl 6M and extracted with EtOAc (3 × 4 mL/mmol). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude

[324] See ref. 267, page 155.

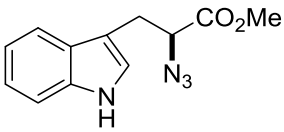
was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1) to afford the title product **394** or **403**.

(*S*)-Benzyl 2-azido-3-(1*H*-indol-3-yl)propanoate 394



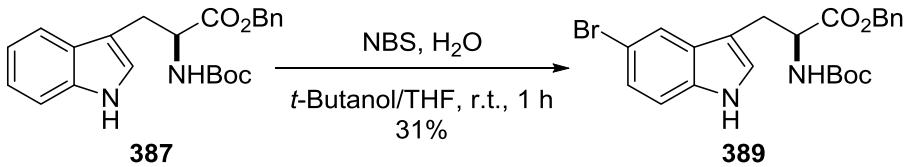
The title compound **394** was prepared from **396** (1.98 g, 6 mmol) according to the general procedure. Yellow oil, yield: 0.58 g, 1.82 mmol, 30%. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.02 (bs, 1H), 7.66–7.56 (m, 1H), 7.43–7.31 (m, 4H), 7.30–7.21 (m, 3H), 7.20 (d, *J* = 1.5 Hz, 1H), 7.18–7.12 (m, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 5.17 (s, 2H), 4.22 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.45–3.33 (m, 1H), 3.31–3.19 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 170.2, 136.1, 135.0, 128.6, 128.5, 128.3, 127.1, 123.2, 122.3, 119.7, 118.4, 111.2, 109.9, 67.4, 62.4, 27.6. HRMS: $C_{18}H_{15}N_4O_2Na$ $[M+Na]^+$ calcd: 342.3338, found: 342.3332.

(*S*)-Methyl 2-azido-3-(1*H*-indol-3-yl)propanoate 403[325]



The title compound **403** was prepared from **402** (3.3 g, 13 mmol) according to the general procedure. Orange oil, yield: 2.56 g, 10.5 mmol, 81%. $[\alpha]_D^{20}$= –9.1 (c = 1.07, $CHCl_3$). All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.16 (bs, 1H), 7.71–7.61 (m, 1H), 7.39–7.33 (m, 1H), 7.30–7.14 (m, 2H), 7.07 (d, *J* = 2.5 Hz, 1H), 4.24 (dd, *J* = 8.1, 5.5 Hz, 1H), 3.78 (s, 3H), 3.42 (dd, *J* = 15.2, 5.9 Hz, 1H), 3.26 (dd, *J* = 15.1, 7.7 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 170.8, 136.0, 126.9, 123.2, 122.1, 119.5, 118.2, 111.3, 109.7, 62.4, 52.5, 27.6. HRMS: $C_{12}H_{12}N_4O_2Na$ $[M+Na]^+$ calcd: 267.0852, found: 267.0850.

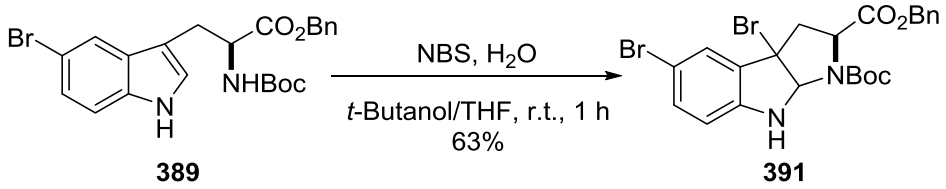
6.4.1.1.3. Bromination reactions[326]



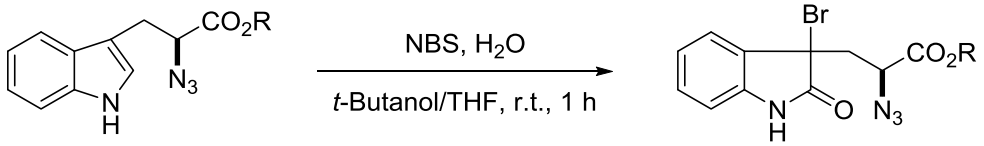
387 **389**

[325] Bencivenni,G.; Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2008**, *73*, 4721–4724.

[326] See ref. 263, page 153.



389 **391**



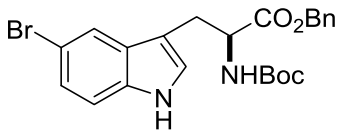
394 R = Bn
403 R = Me

393 R = Bn 63%
404 R = Me 77%

General procedure

N-Bromosuccinimide (2 equiv.) was added to a solution of the starting compound (1 equiv.) in *tert*-butanol (7 mL/mmol), THF (10 mL/mmol) and H_2O (22 μL/mmol). The mixture was stirred for 1 h at room temperature, the solution was concentred under reduced pressure and the crude material was directly purified by flash column chromatography on silica gel.

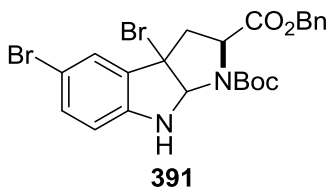
(*S*)-Benzyl 3-(5-bromo-1*H*-indol-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate 389



389

The title compound **389** was prepared from **387** (0.6 g, 1.5 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1). Yellow oil, yield: 221 mg, 0.46 mmol, 31%. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.70 (bs, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.42–7.12 (m, 7H), 6.78 (d, *J* = 2.0 Hz, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.12 (s, 2H), 4.79–4.67 (m, 1H), 3.35–3.14 (m, 2H), 1.46 (s, 9H).

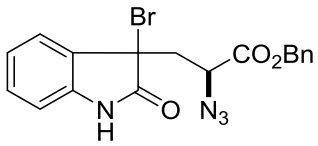
(2*S*)-2-Benzyl 1-*tert*-butyl 3a,5-dibromo-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate 391



391

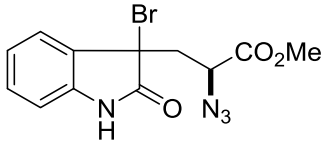
The title compound **391** was prepared from **389** (221 mg, 0.46 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 4/1). Yellow oil, yield: 161 mg, 0.29 mmol, 63%. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 7.45–7.41 (m, 1H), 7.34 (dd, *J* = 9.5, 2.4 Hz, 7H), 5.77–5.64 (m, 1H), 5.32–5.07 (m, 2H), 4.29–4.15 (m, 1H), 3.19–3.00 (m, 1H), 3.03–2.81 (m, 1H),1.34 (s, 9H).

Benzyl (2*S*)-2-azido-3-(3-bromo-2-oxoindolin-3-yl)propanoate 393



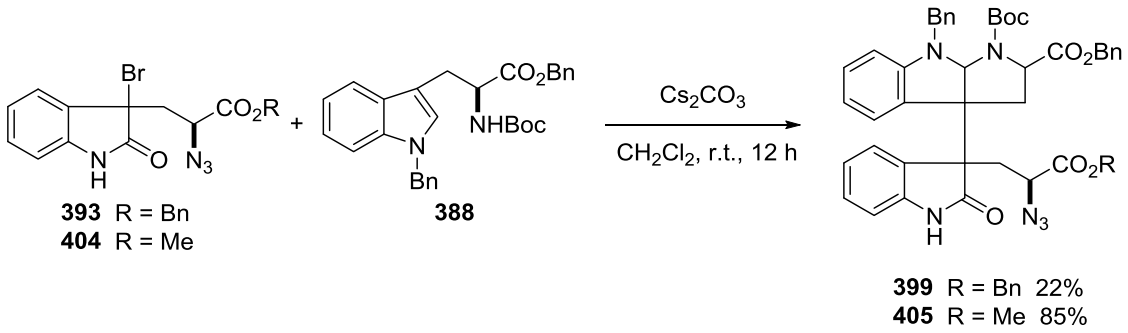
The title compound **393** was prepared from **394** (0.58 g, 1.82 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 6/1 → 1/1) to afford title compound **393** as a mixture of diastereomers (not determined), which was used as such in the following reaction. Yellow oil, yield: 0.48 g, 1.14 mmol, 63%. Data for the major diastereomer. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 9.59 (bs, 1H), 9.36 (s, 1H), 7.47–7.18 (m, 7H), 7.18–7.03 (m, 1H), 7.04–6.76 (m, 1H), 5.26–5.05 (m, 2H), 4.01 (dd, *J* = 7.3, 5.2 Hz, 1H), 3.64 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.18 (dd, *J* = 14.7, 5.2 Hz, 1H), 3.11–2.86 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 176.2, 168.7, 134.5, 130.8, 128.6, 128.4, 128.4, 128.3, 127.7, 127.5, 127.0, 124.6, 123.4, 111.5, 67.9, 59.1, 53.5, 39.7.

Methyl (2*S*)-2-azido-3-(3-bromo-2-oxoindolin-3-yl)propanoate 404



The title compound **404** was prepared from **403** (0.58 g, 1.82 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1) to afford title compound **404**, a mixture of diastereomers (dr 1:2.5 determined by ^{1}H NMR (250 MHz) analysis on the crude mixture), which was used as such in the following reaction. Orange oil, yield: 2.77 g, 8.16 mmol, 77%. Data for the major diastereomer. $[\alpha]_D^{20}$= –55.9 (c = 2.16, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 9.84 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.33–7.21 (m, 1H), 7.13–6.95 (m, 2H), 3.66 (s, 3H), 3.56 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.04–2.93 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 176.2, 169.2, 140.2, 130.7, 127.5, 124.4, 123.2, 111.4, 58.8, 53.5, 52.8, 39.6. HRMS: $C_{12}H_{12}N_4O_3Br$ $[M+H]^+$ calcd: 339.0087, found: 339.0080.

6.4.1.2. [4+2] Cycloaddition-cyclization reaction[327]

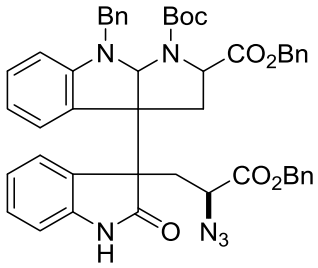


[327] See ref. 146, page 53.

General procedure

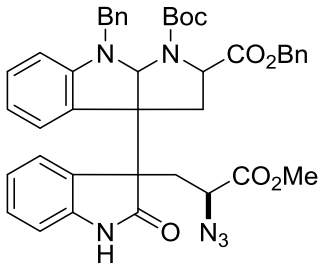
To a solution of the corresponding bromo derivative (1 equiv.) and (*S*)-benzyl 3-(1-benzyl-1*H*-indol-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate **388** (1.1 equiv.) in dry dichloromethane (10 mL/mmol), cesium carbonate (3.5 equiv.) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (10 mL/mmol) and extracted with CH_2Cl_2 (3 x 10 mL/mmol), and the combined organic layers were washed with brine (10 mL/mmol), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → 1/1) to afford the corresponding compound.

2-Benzyl 1-*tert*-butyl 3a-(3-((*S*)-2-azido-3-(benzyloxy)-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate 399



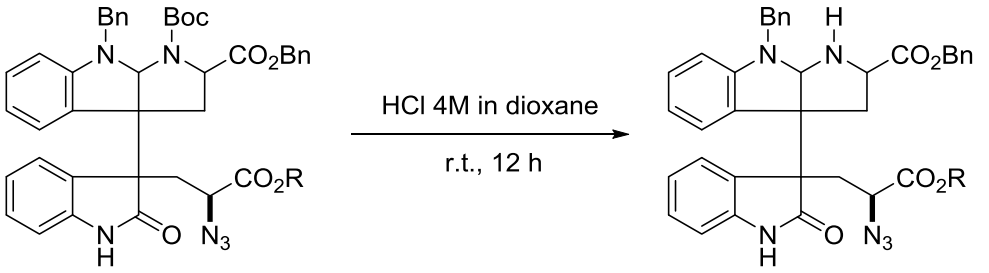
The title compound **399** was prepared from **393** (0.48 g, 1.14 mmol) according to the general procedure and after flash column chromatography was obtained as a mixture of diastereomers (not determined), together with benzyl alcohol. Yellow oil, yield: 200 mg, 0.25 mmol, 22%.

2-Benzyl 1-*tert*-butyl 3a-(3-((*S*)-2-azido-3-methoxy-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2*H*)-dicarboxylate 405



The title compound **405** was prepared from **404** (2.04 g, 6 mmol) according to the general procedure and after flash column chromatography was obtained as a mixture of diastereomers (dr 1:1.5 determined by ^{1}H NMR (250 MHz) analysis on the crude mixture). Yellow foam, yield: 3.79 g, 5.1 mmol, 85%. Data from the major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.93 (bs, 1H), 7.65–6.52 (m, 18H), 5.89 (dd, *J* = 20.6, 7.9 Hz, 2H), 5.22 (s, 1H), 4.88–4.63 (m, 2H), 4.31–4.20 (m, 1H), 3.64 (s, 3H), 3.30–3.16 (m, 1H), 2.94–2.51 (m, 4H), 1.33 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 178.3, 171.5, 170.2, 170.2, 153.8, 151.9, 139.0, 135.3, 129.9, 128.9, 128.5, 128.3, 128.3, 128.1, 127.9, 127.1, 126.9, 126.2, 126.0, 124.9, 121.9, 117.3, 110.2, 107.7, 83.5, 80.7, 66.6, 62.0, 60.5, 58.8, 53.5, 52.7, 33.4, 27.7, 26.8. HRMS: $C_{42}H_{42}N_6O_7Na$ $[M+Na]^+$ calcd: 765.3013, found: 765.3018.

*6.4.1.3. Boc deprotection in cycloadducts **399** and **405***



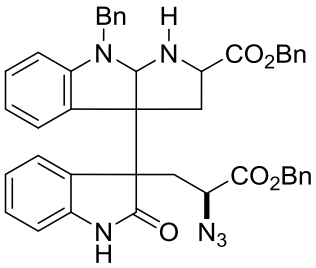
399 R = Bn
405 R = Me

400 R = Bn quantitative
406 R = Me 79%

General procedure

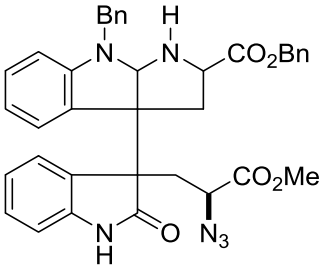
4 M HCl in dioxane (100 equiv.) was added to starting compound (1 eq). The reaction mixture was stirred at room temperature overnight and concentred under reduced pressure to yield the crude compounds **400** or **406**.

Benzyl 3a-(3-((*S*)-2-azido-3-(benzyloxy)-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate 400



The title compound **400** was prepared from **399** (200 mg, 0.25 mmol) according to the general procedure and was obtained as mixture of diastereomers (a not determined), together with benzyl alcohol. Yellow oil, yield: 180 mg, 0.25 mmol, quantitative.

Benzyl 3a-(3-((*S*)-2-azido-3-methoxy-3-oxopropyl)-2-oxoindolin-3-yl)-8-benzyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole-2-carboxylate 406



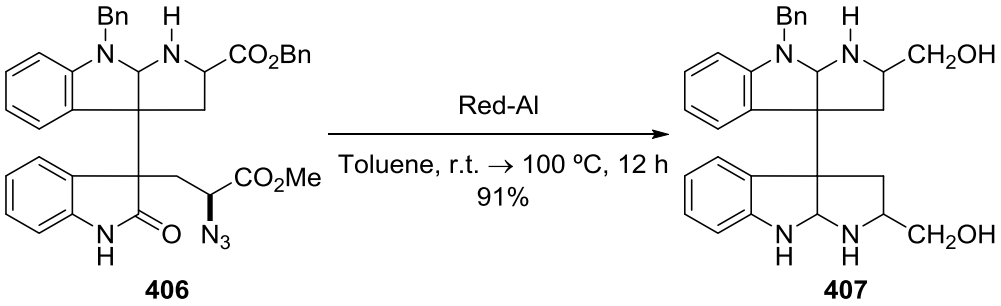
The title compound **406** was prepared from **405** (0.94 g, 1.26 mmol) according to the general procedure and after flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 6/1 → EtOAc) was obtained as a mixture of diastereomers (dr 1:1.5 determined by ^{1}H NMR (250 MHz) analysis on the crude mixture). Yellow foam, yield: 0.64 g, 1.0 mmol, 79%. A little amount of each diastereomers was separated and both diastereomers were characterized, but their configuration was not determined.

Major diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.79 (bs, 1H), 7.46–6.96 (m, 12H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.84–6.72 (m, 1H), 6.64 (s, 3H), 6.01 (d, *J* = 7.8 Hz, 1H), 4.74–4.40 (m, 2H), 4.29 (d, *J* = 16.3 Hz, 1H), 4.08–3.91 (m, 2H), 3.69 (s, 1H), 3.65 (s, 3H), 3.31–3.16 (m, 1H), 3.04–2.86 (m, 1H), 2.83–2.43 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 179.2, 173.6, 170.3, 152.2, 141.3, 138.2, 135.4, 129.8, 128.7, 128.5, 128.4, 128.3, 128.3, 128.2, 127.9, 126.8, 126.6, 126.6, 125.1, 122.26, 116.7, 110.2, 106.6, 84.4, 66.8, 61.2, 60.5, 59.0, 53.7, 52.7, 36.5, 34.3, 29.6. HRMS: $C_{37}H_{35}N_6O_5$ $[M+H]^+$ calcd: 643.2663, found: 643.2648.

Minor diastereomer: ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.16 (bs, 1H), 7.45–7.23 (m, 7H), 7.19–6.97 (m, 5H), 6.90–6.78 (m, 2H), 6.71–6.56 (m, 3H), 6.08 (d, *J* = 7.9 Hz, 1H), 5.17 (dd, *J* = 15.8, 12.2 Hz 2H), 4.76 (s, 1H), 4.38–4.04 (m, 2H), 3.71 (s, 3H), 3.71–3.54 (m, 2H), 3.29–3.05 (m, 1H), 2.92–2.68 (m, 2H), 2.60–2.37 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 178.1, 172.8, 170.2, 152.1, 140.6, 138.2, 135.4, 129.7, 129.5, 128.6, 128.4, 128.4, 128.3, 128.0, 126.8, 126.8, 126.7, 125.0, 124.5, 122.6, 116.8, 109.8, 105.9, 84.0, 66.9, 63.0, 59.4, 59.2, 54.0, 52.8, 39.9, 34.5, 26.9.

*6.4.1.4. Synthesis of **407***

(8-Benzyl-2,2',3,3',8,8a,8',8'a-octahydro-1*H*,1'*H*-[3a,3'a-bipyrrolo[2,3-b]indole]-2,2'-diyl)dimethanol 407[328]



406 **407**

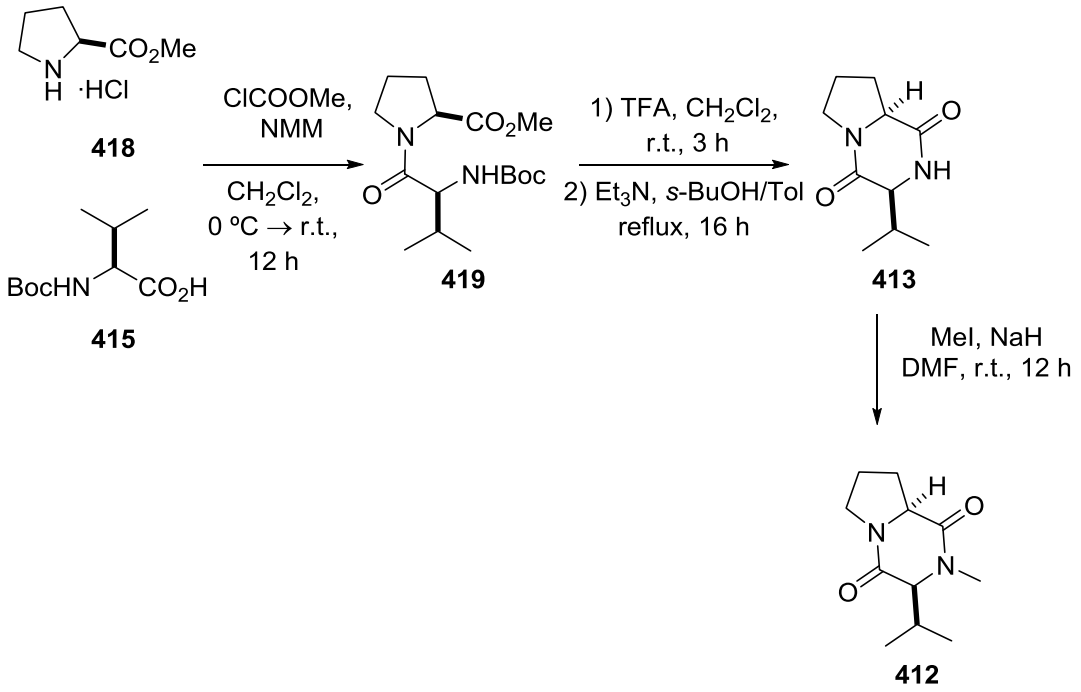
A solution of the starting compound **406** (1 equiv., 411 mg, 0.64 mmol) in toluene (10 mL) was cooled to 0 °C, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (10 equiv., 65 wt % in toluene; 1.83 mL, 6.4 mmol) was added and the resulting solution was allowed to warm to rt. Then, the mixture was heated to 100 °C and maintained at 100 °C for 24 h. After cooling to rt, the reaction was quenched with saturated aqueous sodium potassium tartrate (23 mL), diluted with ethyl acetate (46 mL), and stirred vigorously for 45 min. The mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were

[328] Joseph T. Lundquist, J. T.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781–783.

washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/ MeOH 99/1 → 4/1+ 1% Et_3N) and then was dissolved in CH_2Cl_2 and washed with brine to afford the title compound **407** as a yellow oil. Yield: 271.8 mg, 0.58 mmol, 91%. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 7.30–6.99 (m, 6H), 6.92–6.42 (m, 5H), 6.32–6.04 (m, 2H), 4.49–4.05 (m, 2H), 3.74–3.61 (m, 1H), 3.62–3.38 (m, 2H), 3.30–3.03 (m, 3H), 2.98–2.68 (m, 3H), 2.66–2.46 (m, 1H), 2.38–1.96 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 138.2, 132.8, 128.8, 128.6, 128.4, 127.4, 127.0, 126.9, 126.7, 124.9, 124.0, 119.1, 119.0, 116.8, 109.1, 105.9, 84.8, 79.2, 64.4, 62.7, 62.6, 60.5, 58.2, 49.1, 47.7, 40.0, 29.6.

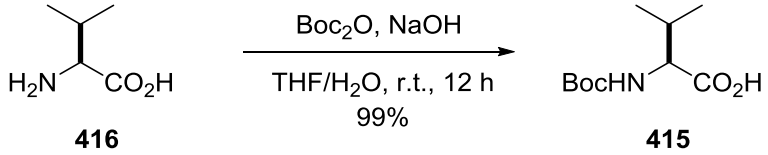
6.4.2. Thiolation of compound 412

*6.4.2.1. Synthesis of model diketopiperazine **412***



*6.4.2.1.1. Synthesis of the starting protected amino acids **415** and **418***

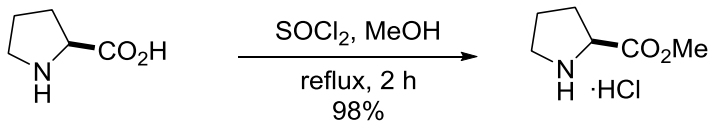
*6.4.2.1.1.1. (S)-2-((tert-Butoxycarbonyl)amino)-3-methylbutanoic acid **415**[329]*



416 **415**

NaOH (1.1 equiv., 0.88 g, 22 mmol) and Boc_2O (1.1 equiv., 4.8 g, 22 mmol) were added to a stirred mixture of *L*-valine **416** (1 equiv., 2.34 g, 20 mmol) in THF/H_2O (100 mL:100 mL) at room temperature and the resulting solution was stirred overnight. THF was removed under reduced pressure, the aqueous layer was extracted with dichloromethane (50 mL) and this organic phase was discarded. The aqueous layer was acidified with HCl 1N to pH 4, and then extracted with dichloromethane (3 x 40 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid **415**. White solid, yield: 4.3 g, 19.8 mmol, 99%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 4.99 (bs, 1H), 4.35–4.16 (m, 1H), 2.34–2.11 (m, 1H), 1.43 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 2H), 0.94 (d, *J* = 6.9 Hz, 2H).

*6.4.2.1.1.2. (S)-Methyl pyrrolidine-2-carboxylate hydrochloride **418**[330]*



417 **418**

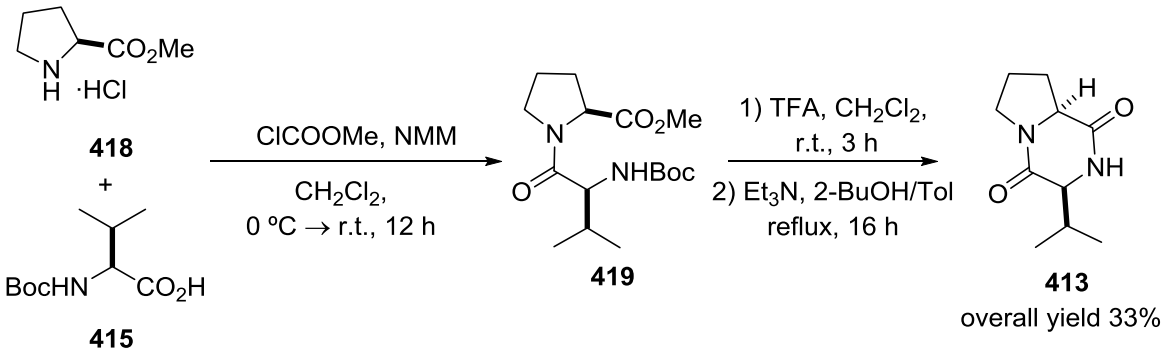
To a suspension of *L*-proline **417** (1 equiv., 2.76 g, 24 mmol) in MeOH (24 mL), thionyl chloride (1.1 equiv., 1.91 mL, 26.4 mmol) was added and the mixture was refluxed for 2 h. The resulting mixture was concentred under reduced pressure and dried in vacuum. The crude material was used in next step without further purification. White solid, yield: 3.9 g, 23.6 mmol, 98%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 3.86–3.77 (m, 1H), 3.73 (s, 3H), 3.17–3.04 (m, 1H), 3.01–2.90 (m, 1H), 2.48 (bs, 1H), 2.21–2.07 (m, 1H), 1.98–1.82 (m, 1H), 1.85–1.72 (m, 2H).

[329] Sutherland, A.; Willis, C. L. *J. Org. Chem*. **1998**, *63*, 7764–7769.

[330] Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Heterocycles* **1986**, *24*, 1045–1060.

6.4.2.1.2. Diketopiperazine formation[331]

Synthesis of (3*S*,8a*S*)-3-isopropylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione 413



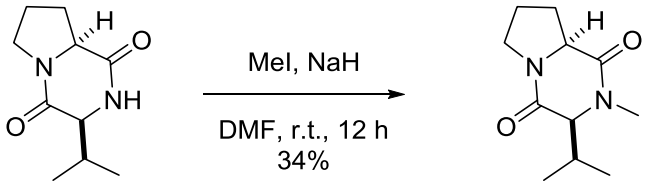
A solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid **415** (1 equiv., 4.3 g, 19.8 mmol) and *N*-methylmorpholine (2.2 equiv., 4.8 mL, 43.6 mmol) in CH_2Cl_2 (40 mL) was treated with ethyl chloroformate (1.2 equiv., 1.85 mL, 24 mmol) at 0 ºC for 10 min. (*S*)-Methyl pyrrolidine-2-carboxylate hydrochloride **418** (1.2 equiv., 3.9 g, 23.6 mmol) was then added dropwise at the same temperature and the mixture was stirred for 16 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with water (30 mL) and brine (30 mL). The organic layer was dried, and the solvent was evaporated in vacuo. The crude was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 9/1 → EtOAc) to afford compound **419**. Yellow oil, yield: 5.8 g, 17.9 mmol, 90%. A solution of amide **419** (1 equiv., 5.27 g, 16 mmol) in dry CH_2Cl_2 (54 mL) was treated with TFA (5.8 equiv., 7.11 mL, 92.8 mmol) at room temperature for 3 h. The solvent was then evaporated and the residue was dissolved in 2-butanol:toluene (32:16 mL) followed by addition of triethylamine (2 equiv., 4.5 mL, 32 mmol). The mixture was allowed to reflux for 16 h. The solution was concentred under reduced pressure and the crude was diluted with CH_2Cl_2 (50 mL) and washed with water (30 mL) and saturated $NaHCO_3$ (30 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/ MeOH 99/1 → 4/1) to afford the title compound **413** as a white solid. Yield: 1.04 g, 5.3 mmol, 33%. All the spectroscopic data were consistent with those previously reported. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 6.96 (bs, 1H), 4.01 (t, J = 8.0 Hz, 1H), 3.87 (s, 1H), 3.69–3.41 (m, 2H), 2.67–2.43 (m, 1H), 2.39–2.20 (m, 1H), 2.10–

[331] Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156–3162.

1.73 (m, 3H), 1.03 (d, J = 7.3 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 170.3, 165.0, 60.3, 58.6, 44.9, 28.4, 22.2, 18.8, 15.9.

*6.4.2.1.3. N-Methylation of diketopiperazine **413**[332]*

(3*S*,8a*S*)-3-Isopropyl-2-methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione 412



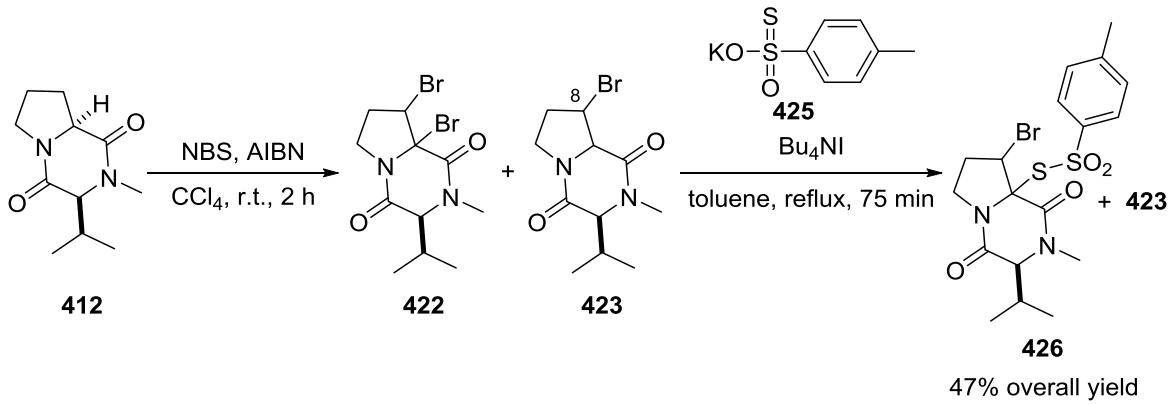
413 **412**

To a stirred solution of (3*S*)-3-isopropylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **413** (1 equiv., 1.04 g, 5.3 mmol) and MeI (3 equiv., 1.0 mL, 15.9 mmol) in DMF (10 mL), was added NaH (3 equiv., 636 mg, 15.9 mmol) at 0 ºC. The resulting mixture was stirred at room temperature overnight, and then quenched with water (10 mL). The product was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/ MeOH 99/1 → 9/1) to afford the title product **412** as a white solid. Yield: 0.38 g, 1.8 mmol, 34%. $[\alpha]_D^{20}$= +85.7 (c = 1.08, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$), δ: 3.86–3.67 (m, 1H), 3.33–3.18 (m, 2H), 3.20–3.05 (m, 1H), 2.63 (s, 3H), 2.10–1.94 (m, 1H), 1.93–1.77 (m, 1H), 1.70–1.45 (m, 3H), 0.72 (d, J = 6.9 Hz, 3H), 0.65 (d, J = 6.9 Hz, 3H).^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 166.7, 163.9, 70.0, 57.8, 44.7, 33.6, 31.0, 28.8, 21.5, 18.8, 17.8. HRMS: $C_{11}H_{19}N_2O_2$ $[M+H]^+$ calcd: 211.141, found: 211.1440.

[332] Lim, H. J.; Gallucci, J. C.; RajanBabu T. V. *Org. Lett.* **2010**, *12*, 2162–2165.

6.4.2.2. Thiolation reactions

6.4.2.2.1. Method A[333,334]

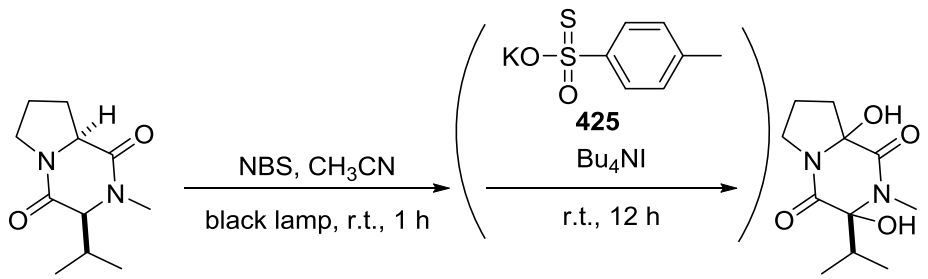


To a solution of (3*S*)-3-isopropyl-2-methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **412** (1 equiv., 100 mg, 0.48 mmol) and *N*-bromosuccinimide (3 equiv., 254 mg, 1.44 mmol) in carbon tetrachloride (10 mL) was added AIBN (0.2 equiv., 16 mg, 0.095 mmol) at room temperature. The mixture was stirred for 2 h at room temperature, then precipitated succinimide was filtered off through a cotton plug and washed with carbon tetrachloride (5 mL). Concentration in vacuo afforded the crude presumably as a mixture of brominated compounds **422** and **423** together with residual succinimide. This crude was used in the next step without further purification. A suspension of previous crude and potassium 4-methylbenzenesulfonothioate **425** (2.5 equiv., 270 mg, 1.19 mmol) in toluene (5 mL) was concentrated in vacuo to remove any water as an azeotrope. The mixture was then suspended in anhydrous toluene (5.5 mL) and tetrabutylammonium iodide (0.08 equiv., 14 mg, 0.038 mmol) was added and the mixture was heated at reflux for 75 min. The resulting suspension was filtered off through a celite plug and washed with carbon tetrachloride (5 mL). Concentration in vacuo afforded the crude which was purified by flash column chromatography on silica gel (eluting with cyclohexane/ ethyl acetate 6/1 → EtOAc) to afford compound **426** as a yellow oil. Yield: 107 mg, 0.22 mmol, 47%. ^{1}H NMR (250 MHz, $CDCl_3$), δ: 8.00 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.16–3.95 (m, 1H), 3.92–3.75 (m, 2H), 3.38–3.21 (m, 1H), 3.21–3.06 (m, 1H), 2.97 (s, 3H), 2.41 (s, 3H), 2.31–2.17 (m, 1H), 2.08–1.85 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ: 177.6, 163.5, 144.4, 138.2, 129.3, 128.3, 69.4, 43.8, 34.2, 32.8, 30.5, 29.5, 21.6, 18.5, 17.1.

[333] See ref. 269, page 161.

[334] See ref. 270, page 162.

6.4.2.2.2. Method B[335]



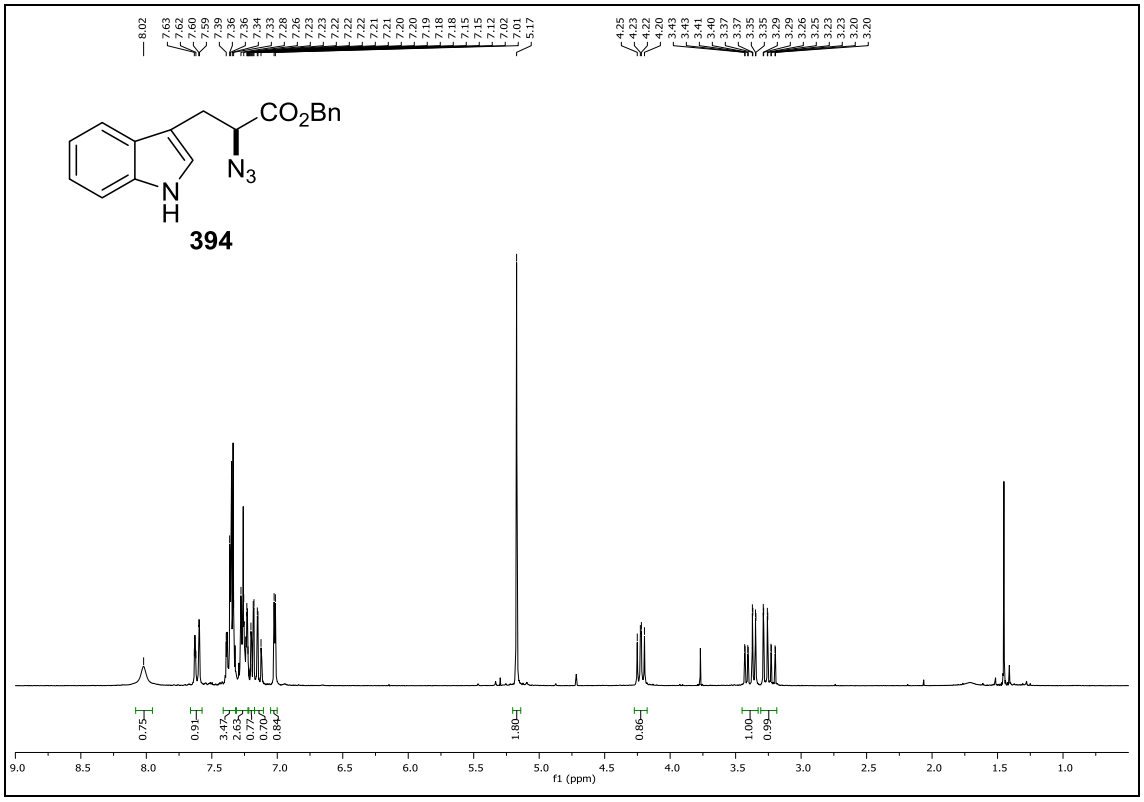
412 **429**

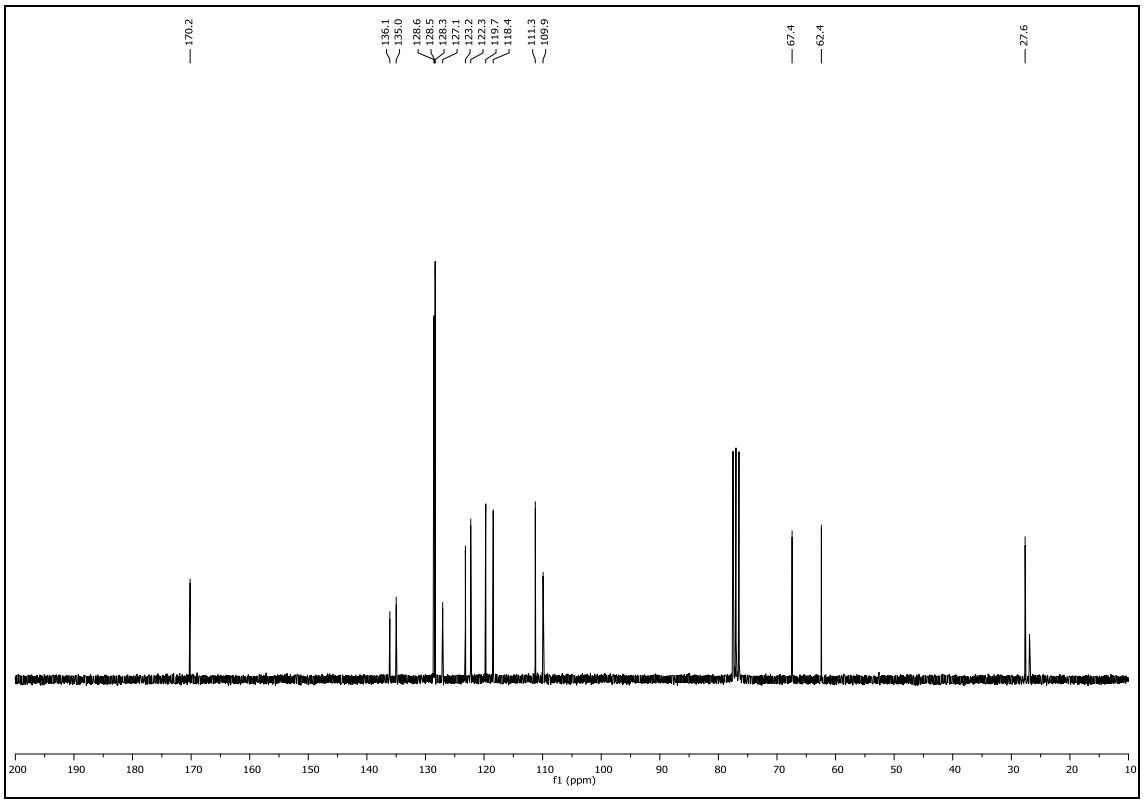
N-bromosuccinimide (2.2 equiv., 18.6 mg, 0.1045 mmol), (3*S*)-3-isopropyl-2-methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **412** (1 equiv., 10 mg, 0.0475 mmol) and acetonitrile (1 mL) were placed into a quartz cuvette. The solution was placed next to a Black lamp and after 1 h complete disappearance of the starting compound **412** was observed (followed by TLC). Concentration in vacuum afforded (3*R*)-3,8a-dihydroxy-3-isopropyl-2-methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **429** instead of the expected dibrominated compound. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.12–3.54 (m, 2H), 3.05 (s, 3H), 2.44–1.79 (m, 5H), 1.36–0.73 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 161.0, 156.0, 127.5, 111.5, 69.6, 43.9, 36.5, 34.0, 32.3, 29.7, 18.8, 17.1.

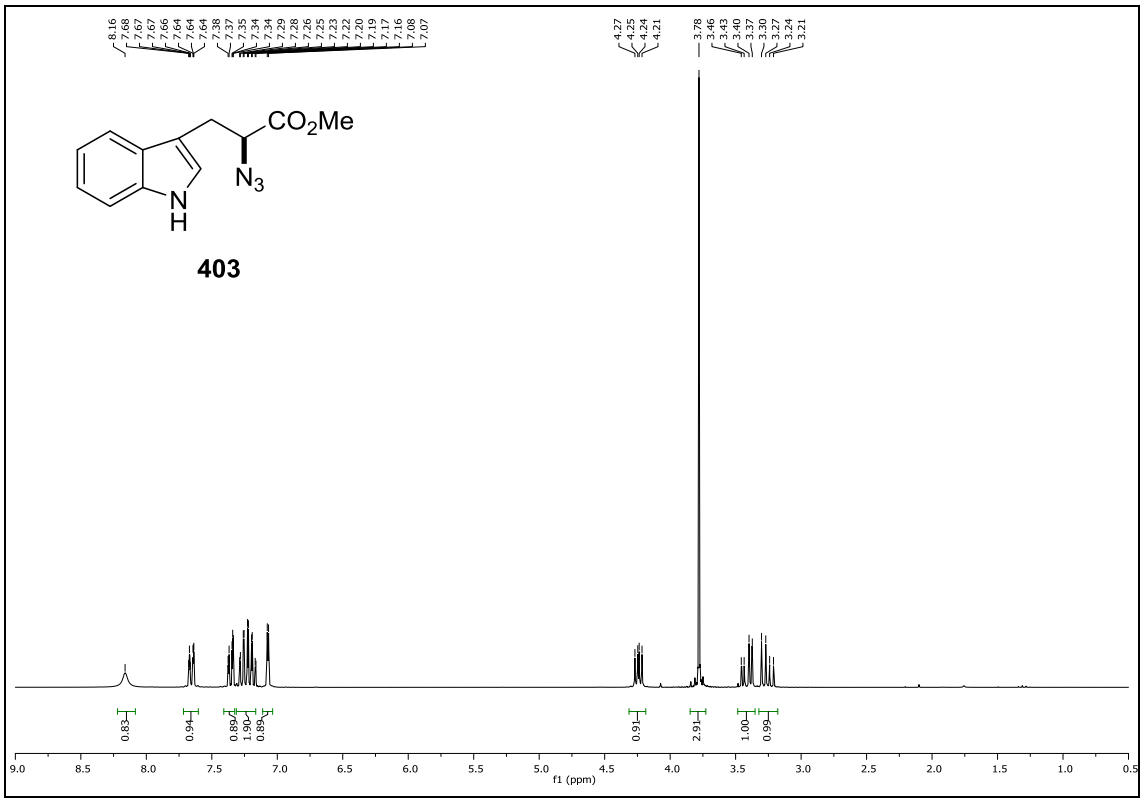
The same experiment was repeated but after complete disappearance of the starting compound **412** potassium 4-methylbenzenesulfonothioate **425** (4 equiv., 43 mg, 0.19 mmol) and tetrabutylammonium iodide (0.1 equiv., 2 mg, 0.005 mmol) were added and the mixture was stirred at room temperature overnight. The resulting suspension was concentrated under vacuum and the ^{1}H NMR spectrum of the afforded crude was the same to that of the previous crude.

[335] See ref. 271, page 163.

6.4.3. Representative NMR spectra






8.16
7.68
7.67
7.67
7.66
7.64
7.64
7.64
7.38
7.37
7.35
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7.28
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7.25
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7.17
7.16
7.08
7.07
4.27
4.25
4.24
4.21
3.78
3.46
3.43
3.40
3.37
3.30
3.27
3.24
3.21
CO2Me
N3
N
H
403
0.83
0.94
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1.90
0.89
0.91
2.91
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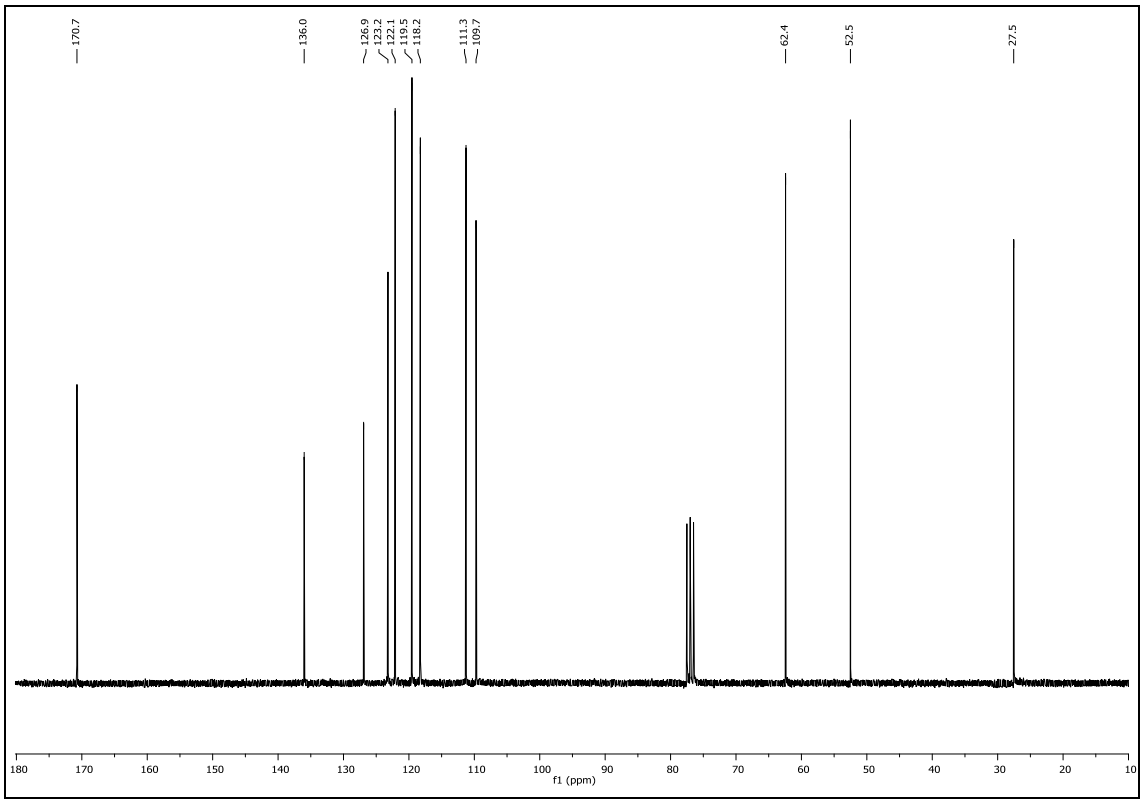
0.99
f1 (ppm)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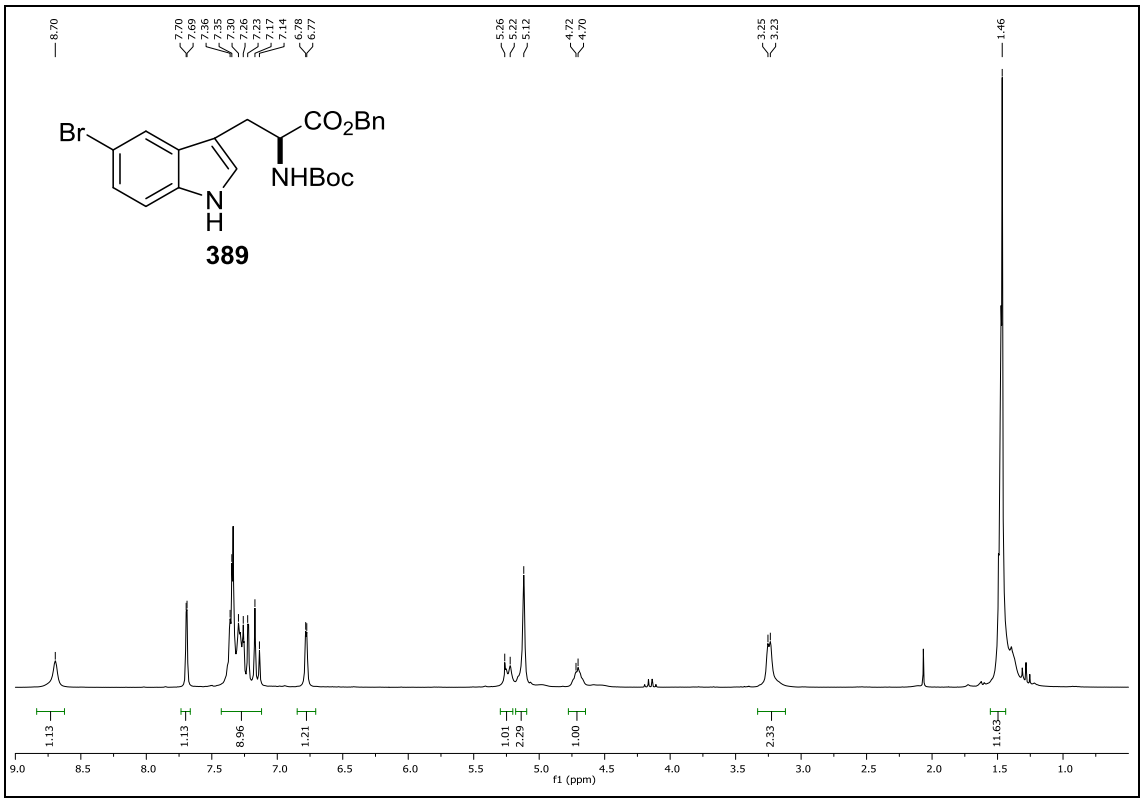
f1 (ppm)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7.23
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5.26
5.22
5.12
4.72
4.70
3.25
3.23
1.46
Br
CO2Bn
NHBoc
N
H
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1.13
8.96
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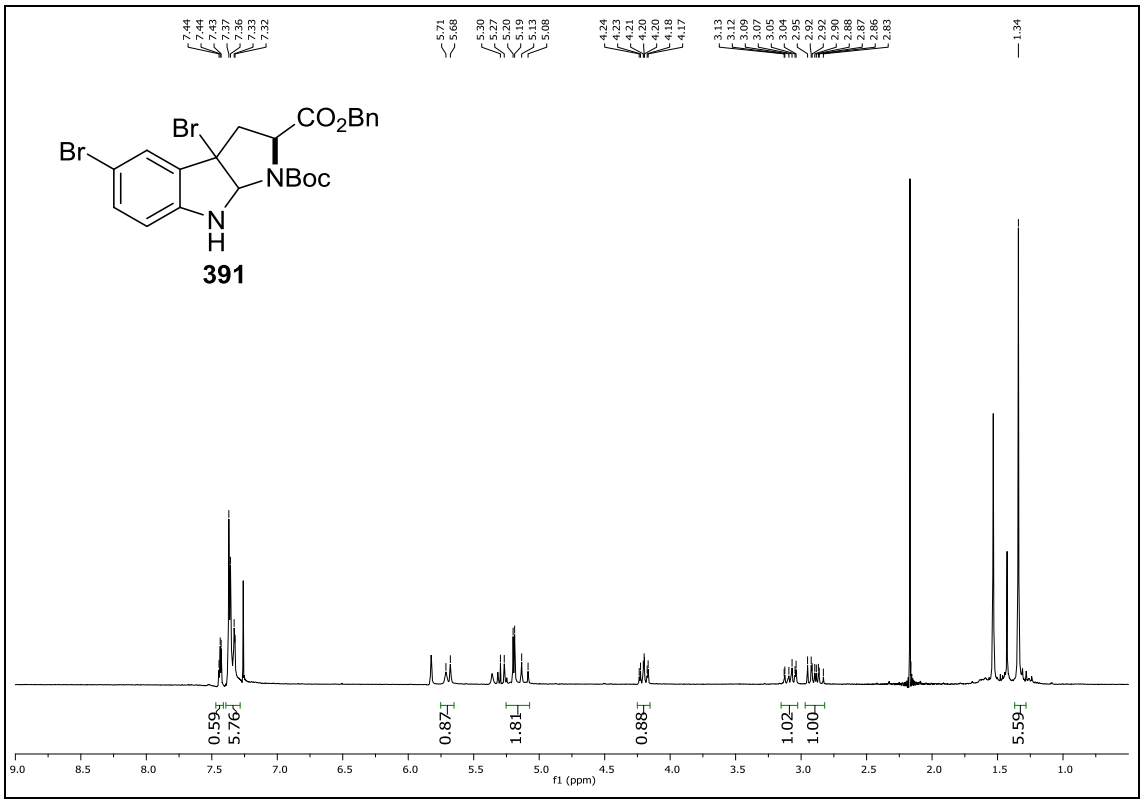
1.01
2.29
1.00
2.33
11.63
f1 (ppm)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5.30
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5.19
5.13
5.08
4.24
4.23
4.21
4.20
4.20
4.18
4.17
3.13
3.12
3.09
3.07
3.05
3.04
2.95
2.92
2.92
2.90
2.88
2.87
2.86
2.83
1.34
Br
Br
CO2Bn
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N
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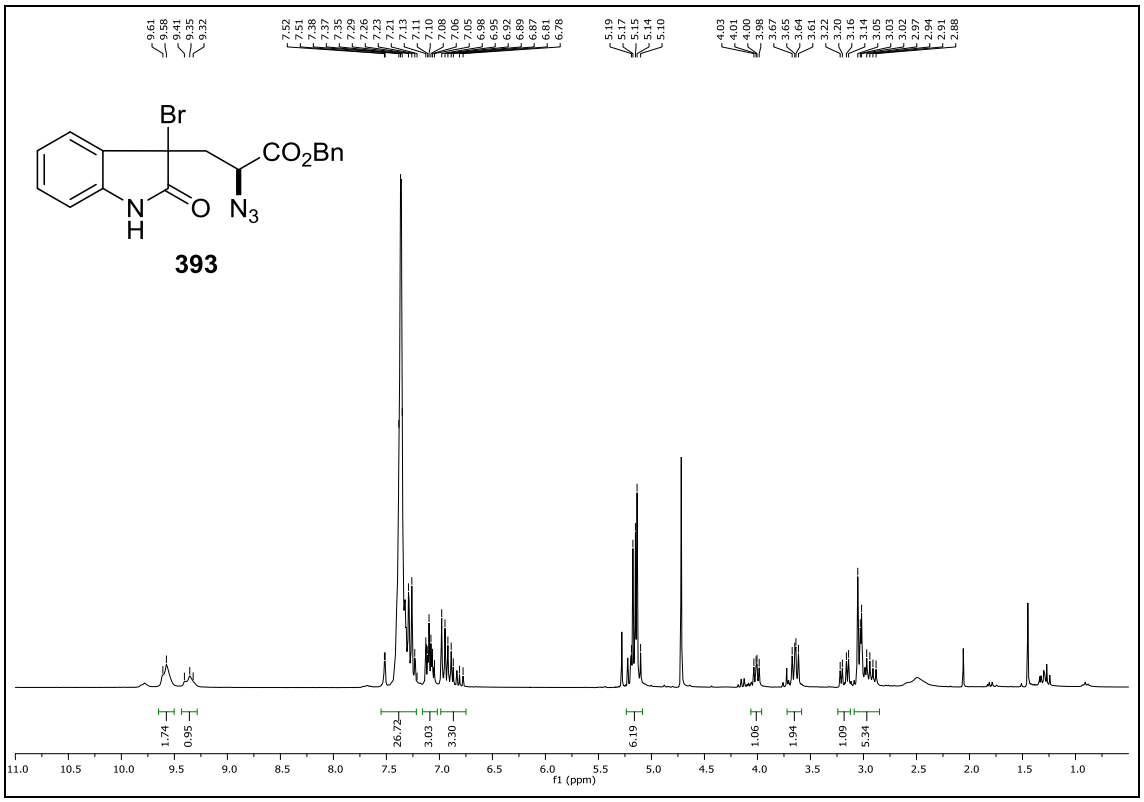
5.59
f1 (ppm)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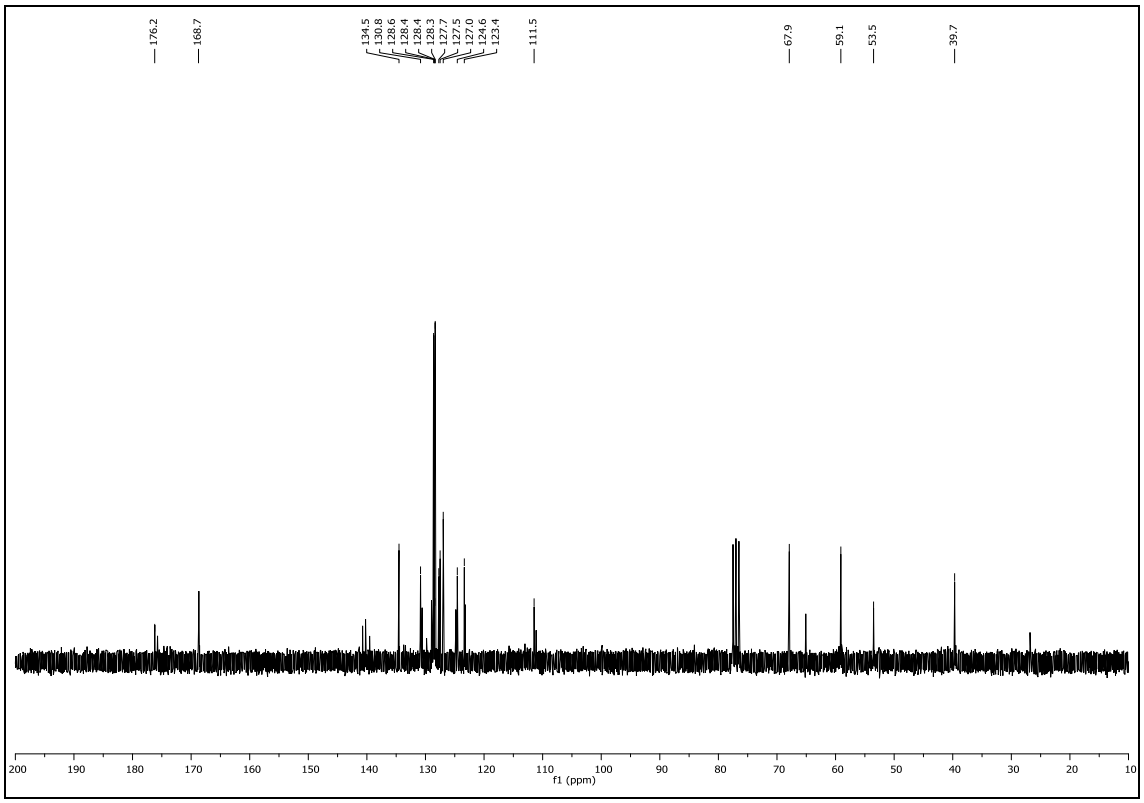
CO2Bn
N
H
O
N3
393
f1 (ppm)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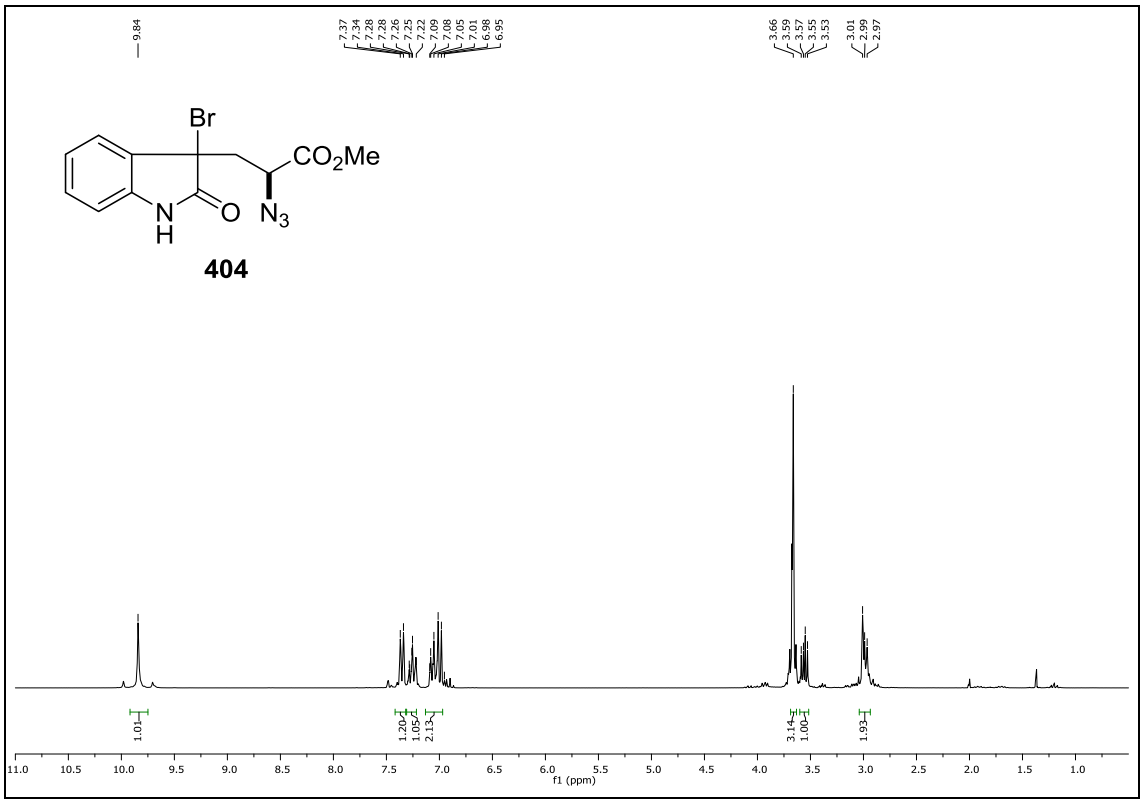
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6.95
3.66
3.59
3.57
3.55
3.53
3.01
2.99
2.97
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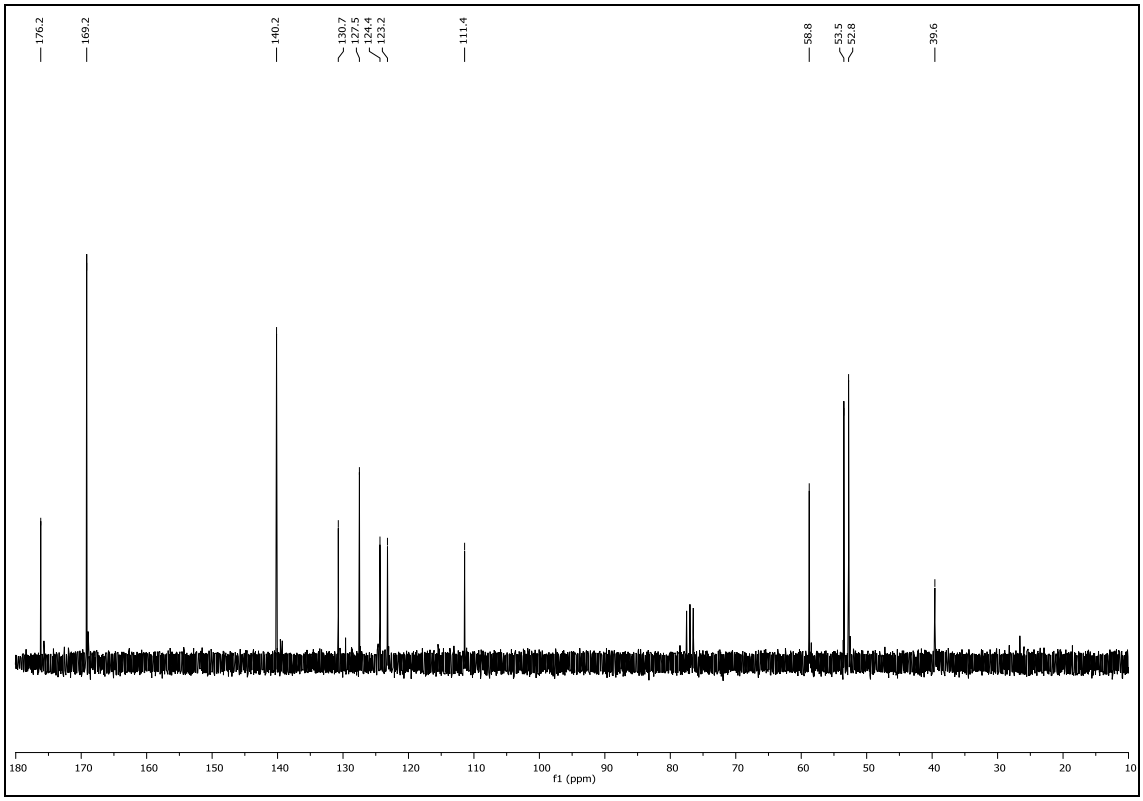
f1 (ppm)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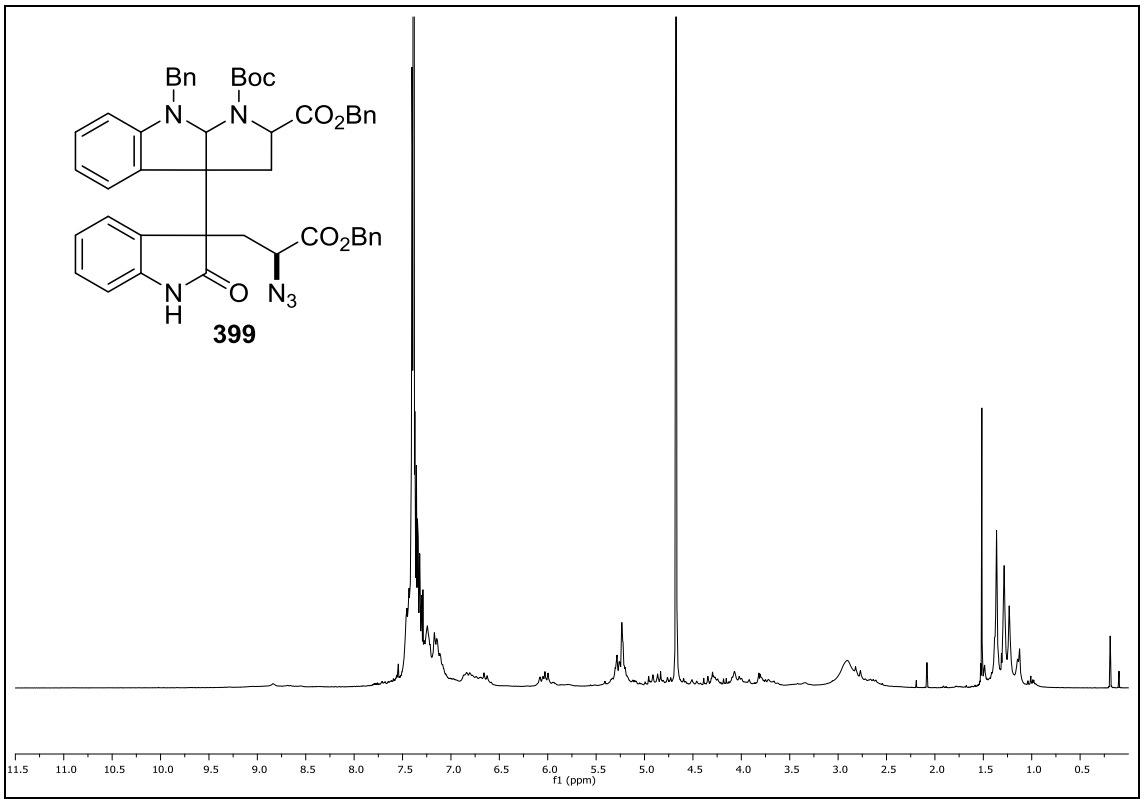
f1 (ppm)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Boc
N
N
CO2Bn
CO2Bn
N
H
O
N3
399
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11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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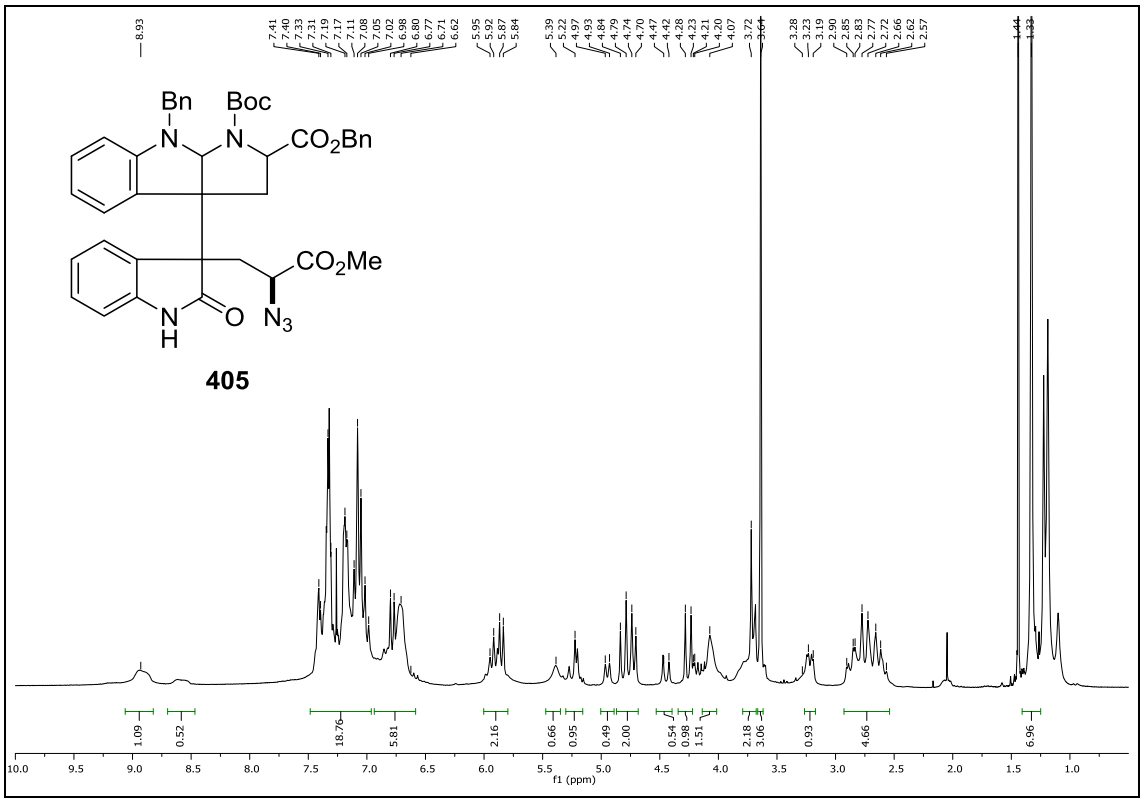
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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Boc
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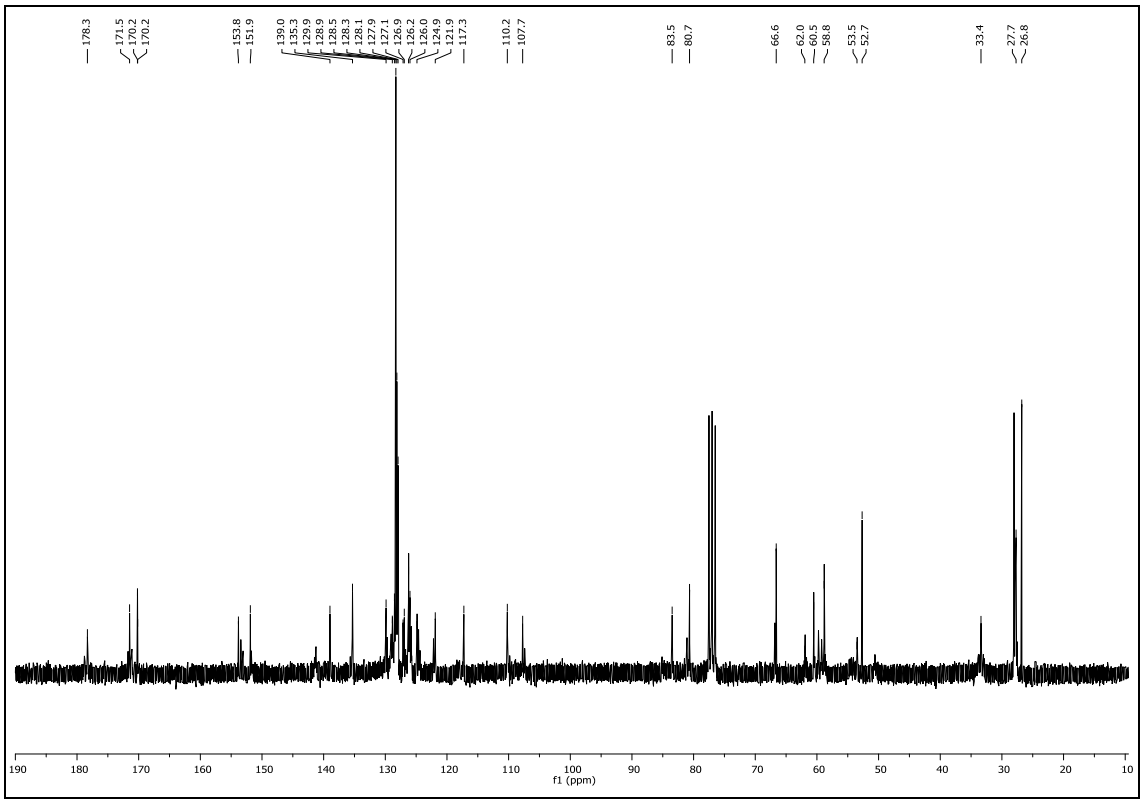
N
CO2Bn
CO2Me
N3
O
N
H
405
f1 (ppm)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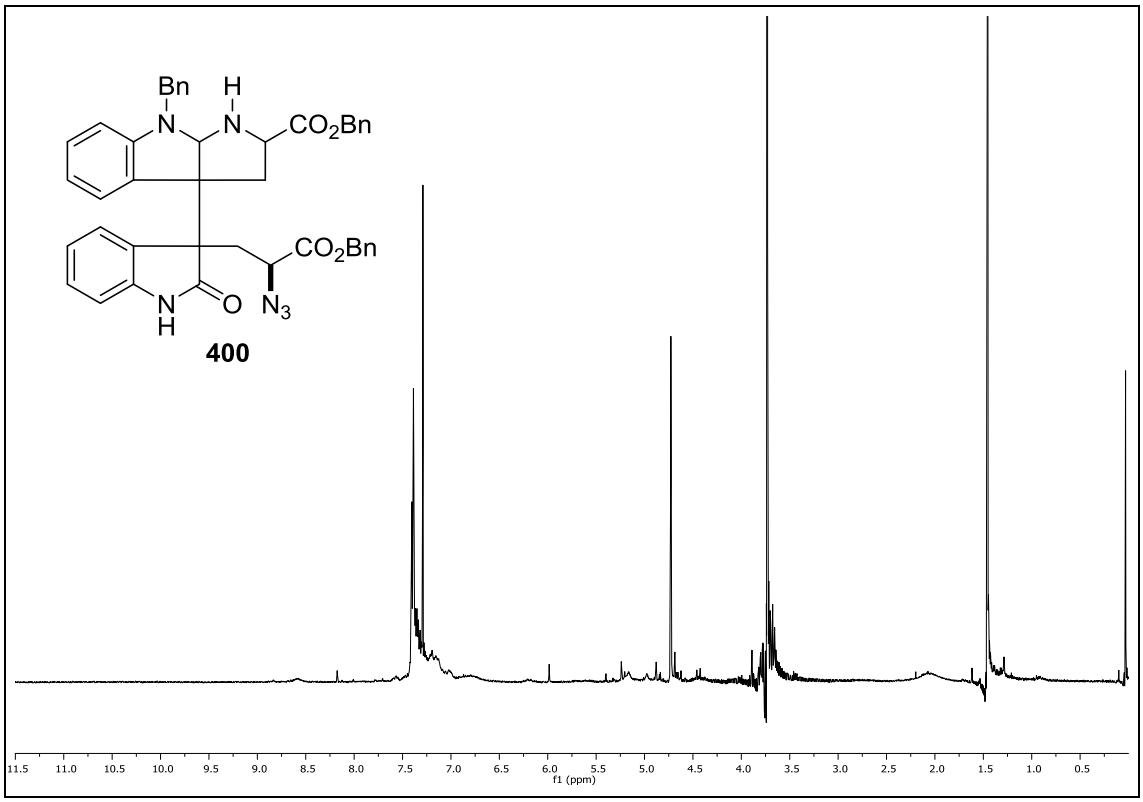
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H
N
N
CO2Bn
CO2Bn
N
H
O
N3
400
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11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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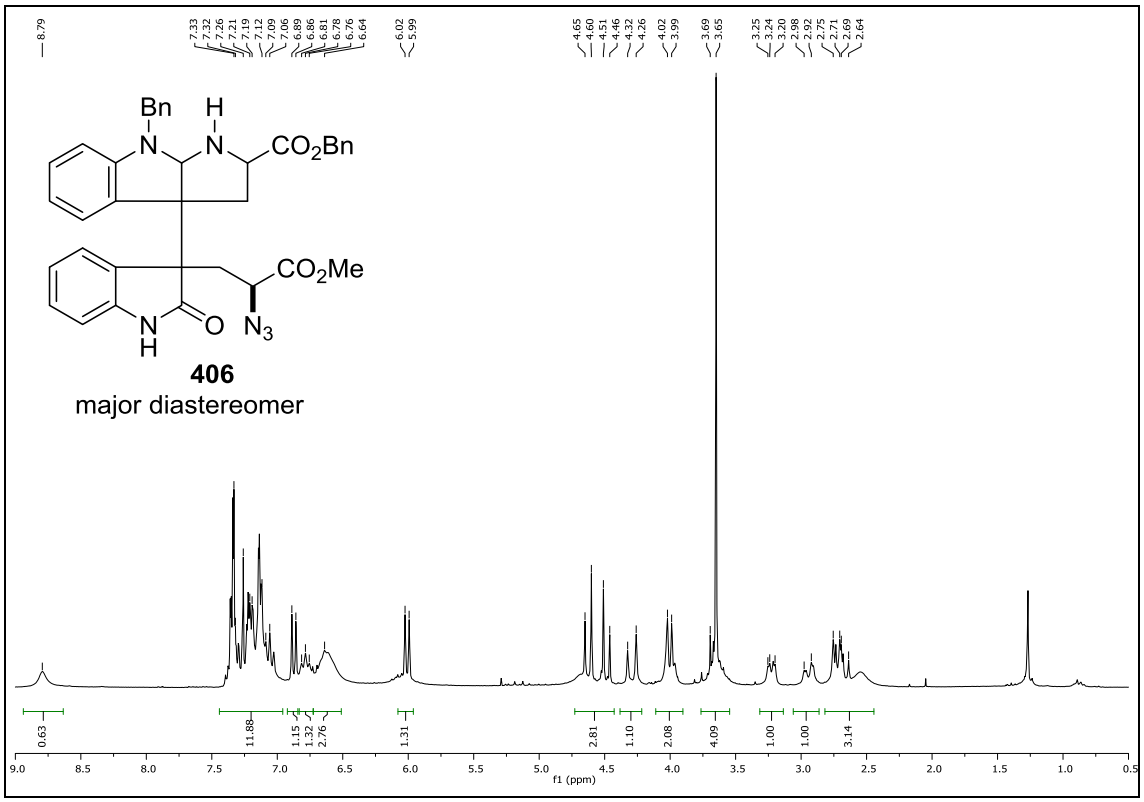
0.5
f1 (ppm)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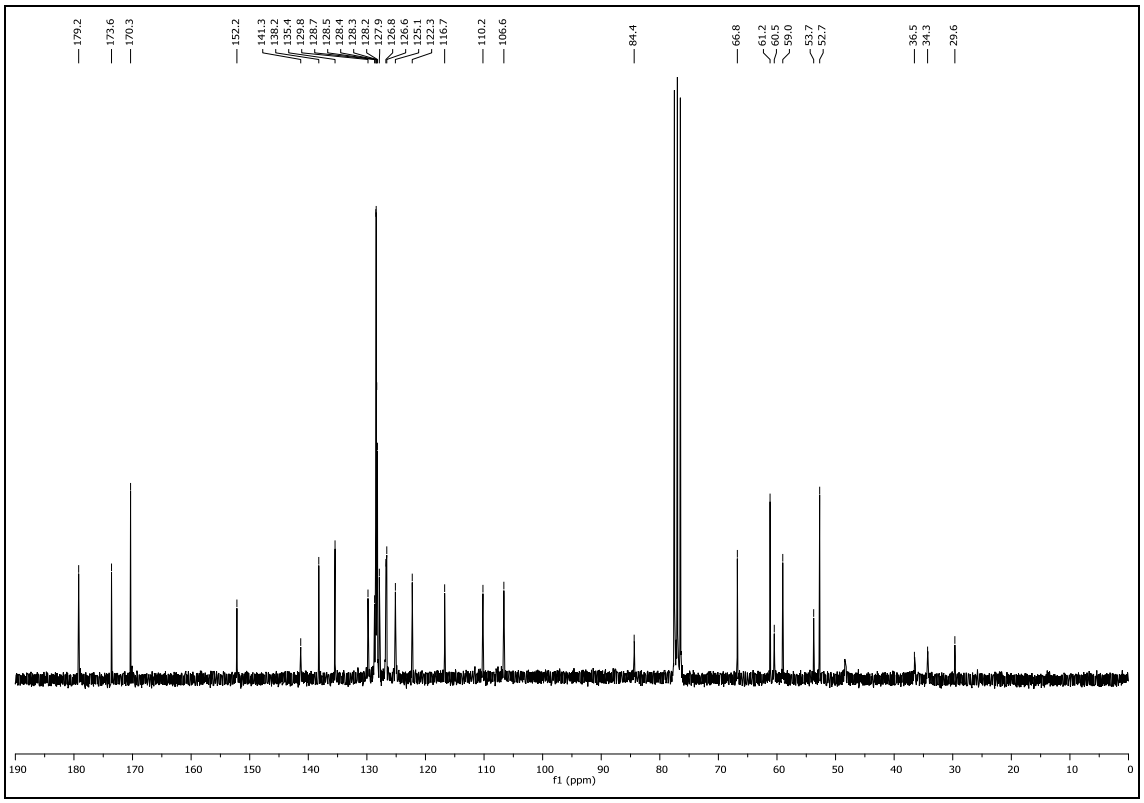
H
N
N
CO2Bn
CO2Me
N
H
O
N3
406
major diastereomer
f1 (ppm)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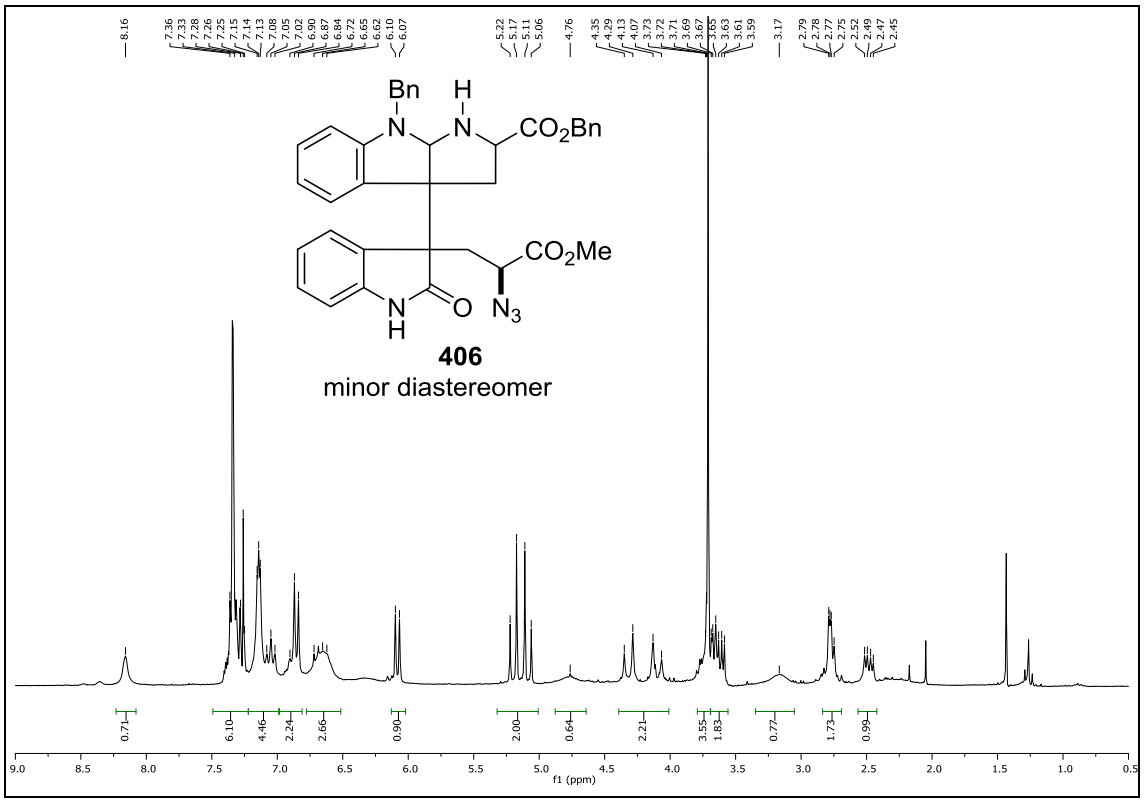
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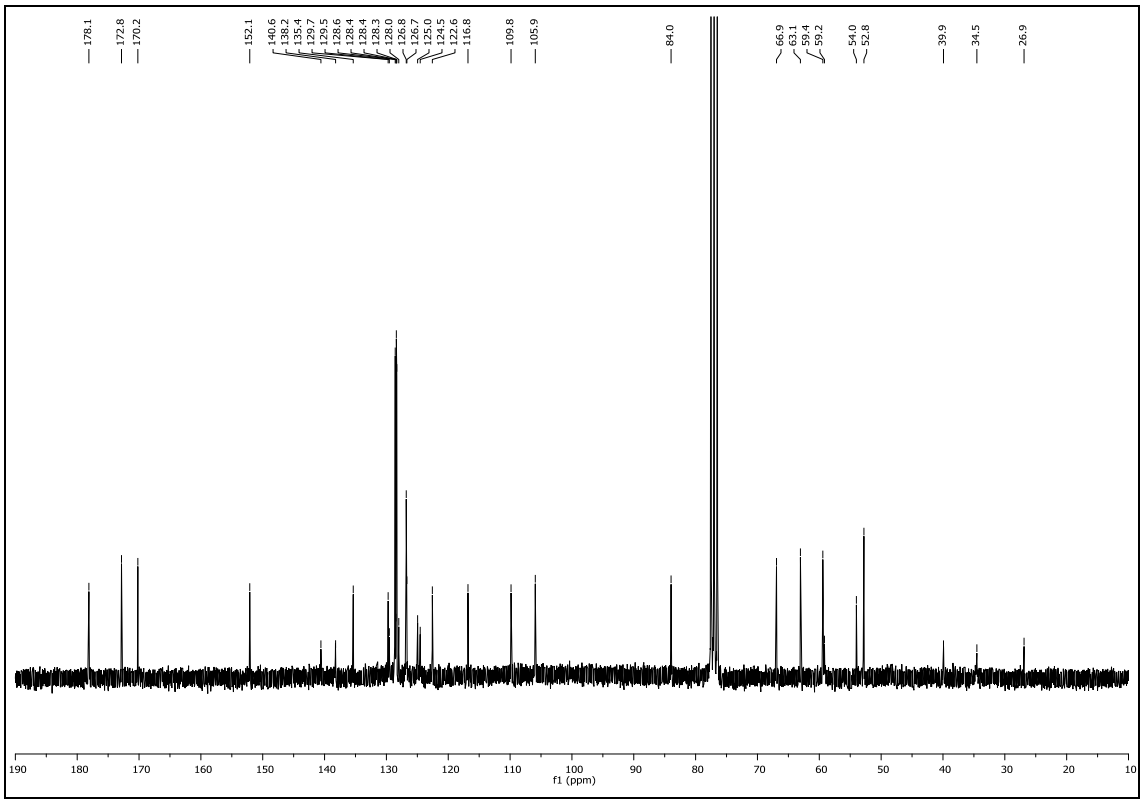
H
N
N
CO2Bn
CO2Me
N
H
O
N3
406
minor diastereomer
f1 (ppm)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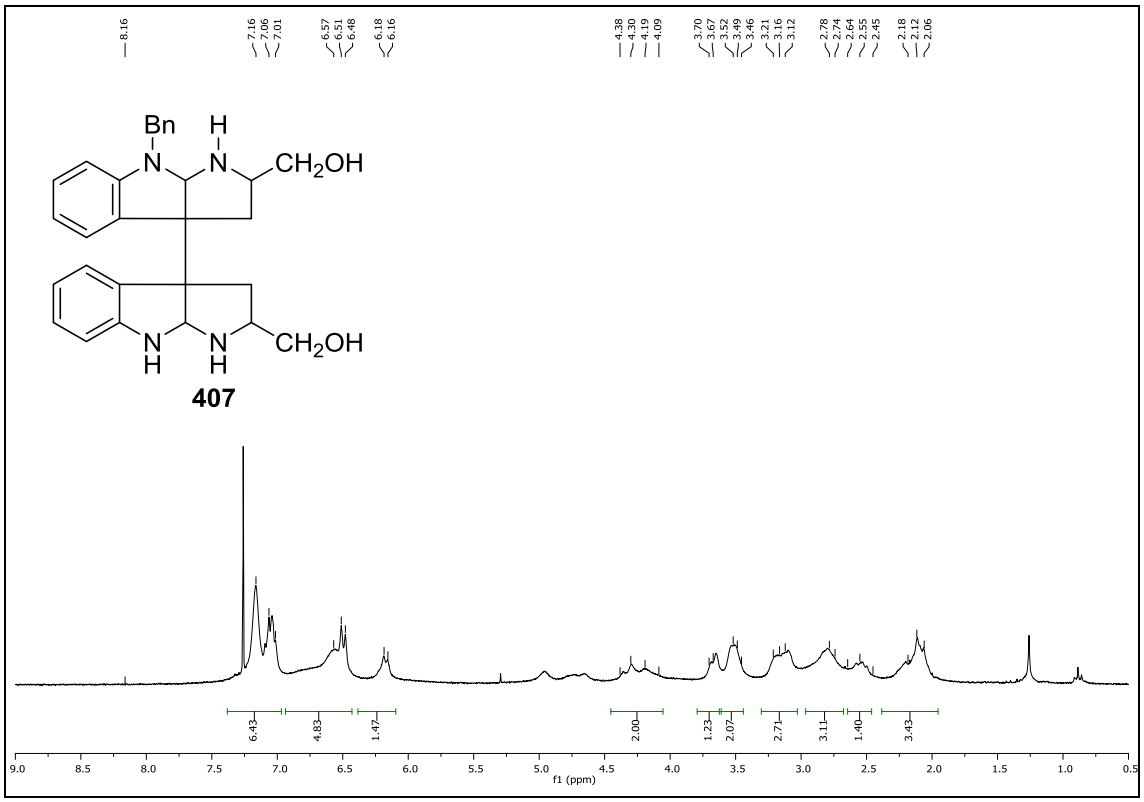
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3.70
3.67
3.52
3.49
3.46
3.21
3.16
3.12
2.78
2.74
2.64
2.55
2.45
2.18
2.12
2.06
Bn
H
N
N
CH2OH
N
H
N
H
CH2OH
407
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1.47
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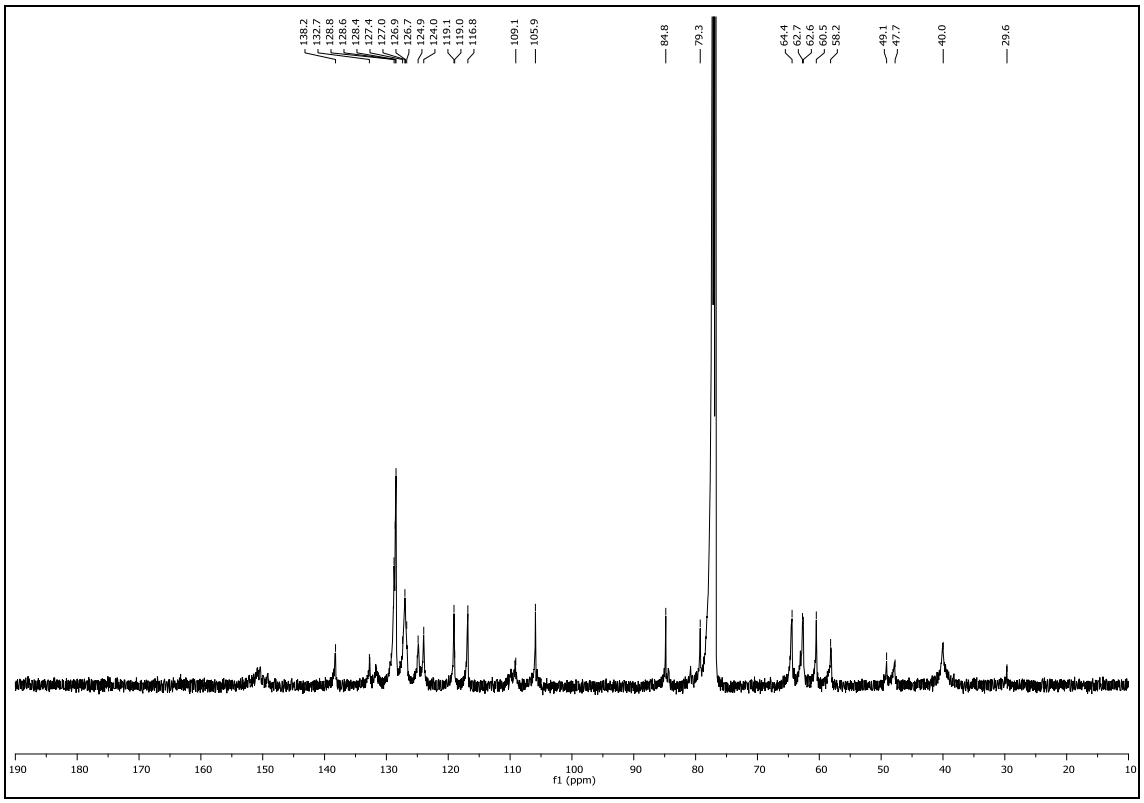
2.07
2.71
3.11
1.40
3.43
f1 (ppm)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119.0
116.8
109.1
105.9
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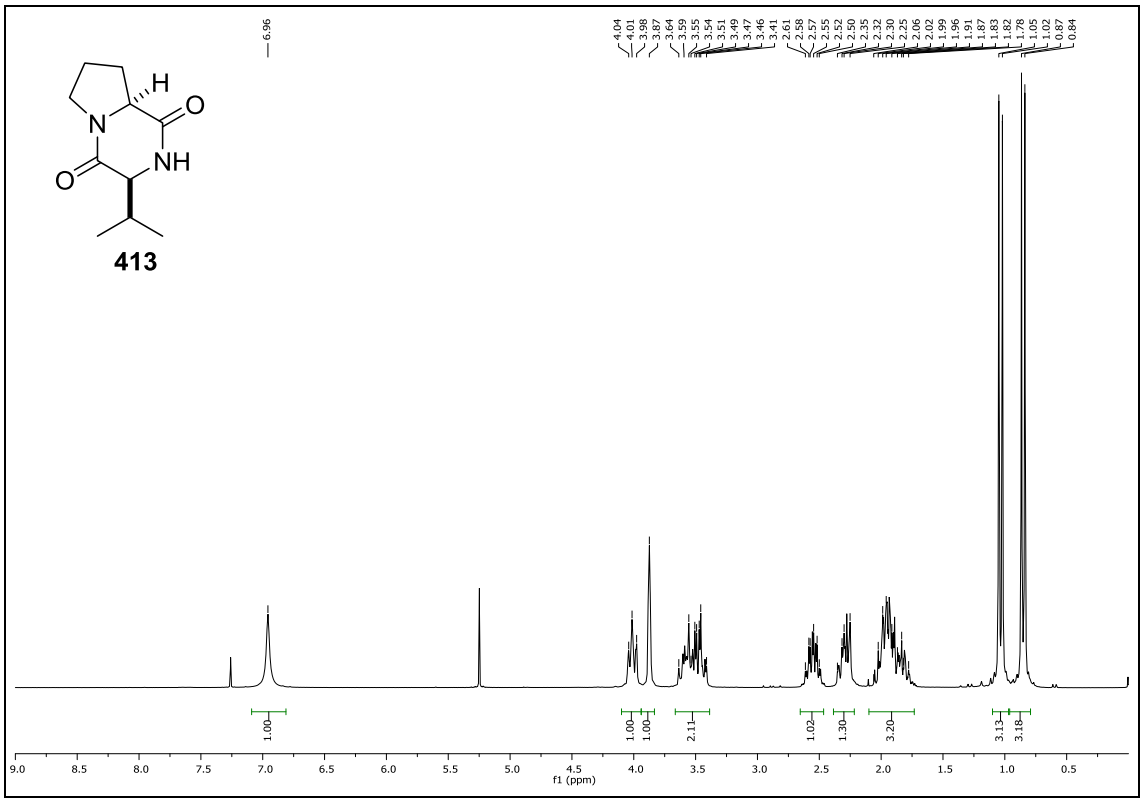
47.7
40.0
29.6
f1 (ppm)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3.47
3.46
3.41
2.61
2.58
2.57
2.55
2.52
2.50
2.35
2.32
2.30
2.25
2.06
2.02
1.99
1.96
1.91
1.87
1.83
1.82
1.78
1.05
1.02
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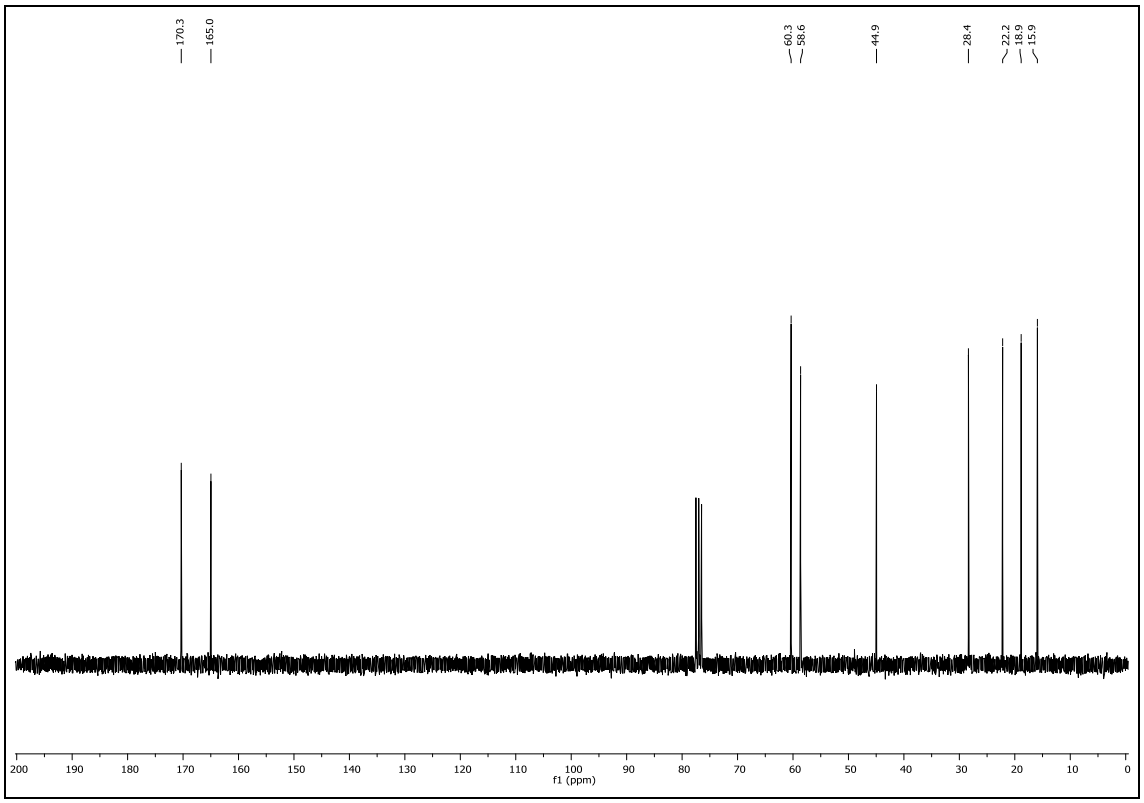
3.13
3.18
f1 (ppm)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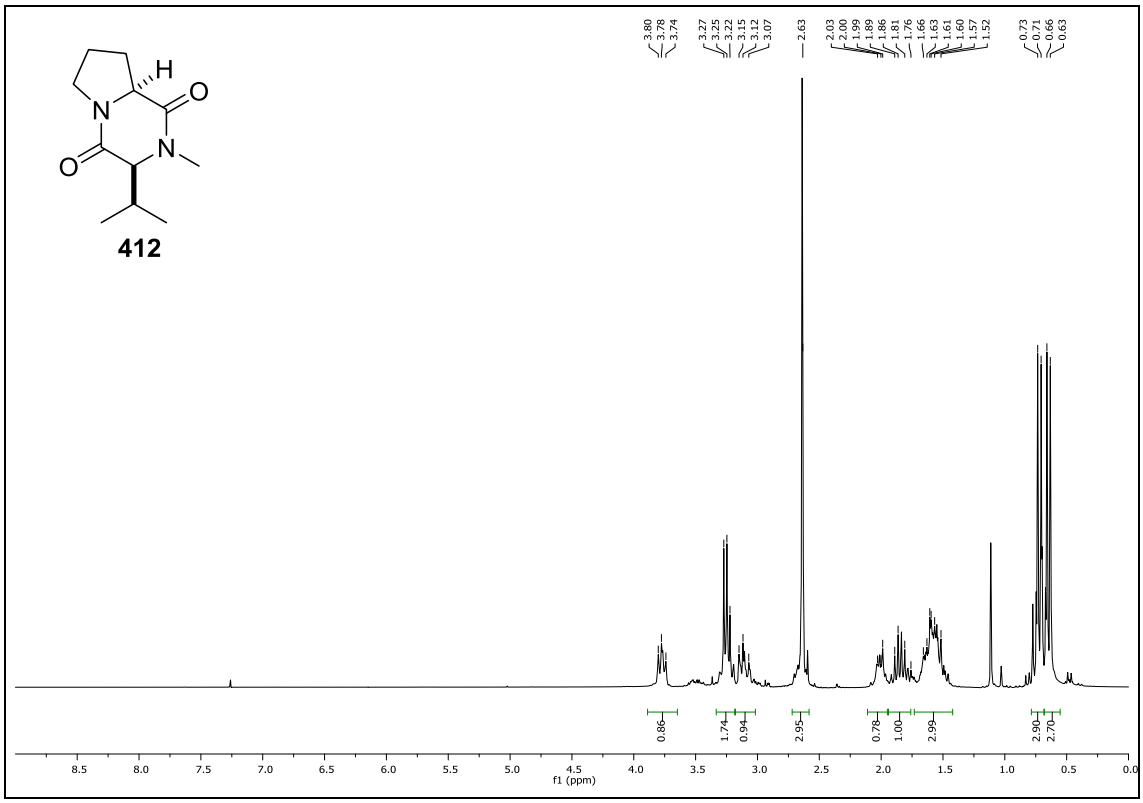
58.6
44.9
28.4
22.2
18.9
15.9
f1 (ppm)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3.74
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3.25
3.22
3.15
3.12
3.07
2.63
2.03
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1.99
1.89
1.86
1.81
1.76
1.66
1.63
1.61
1.60
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0.71
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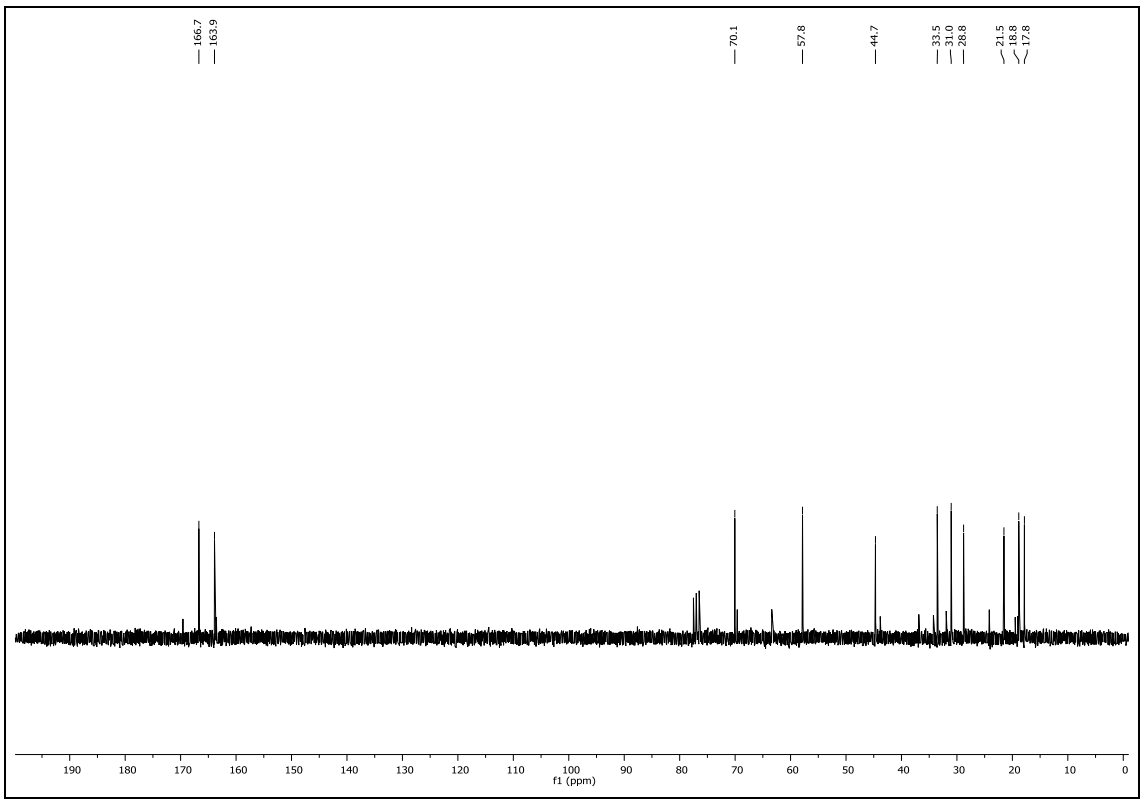
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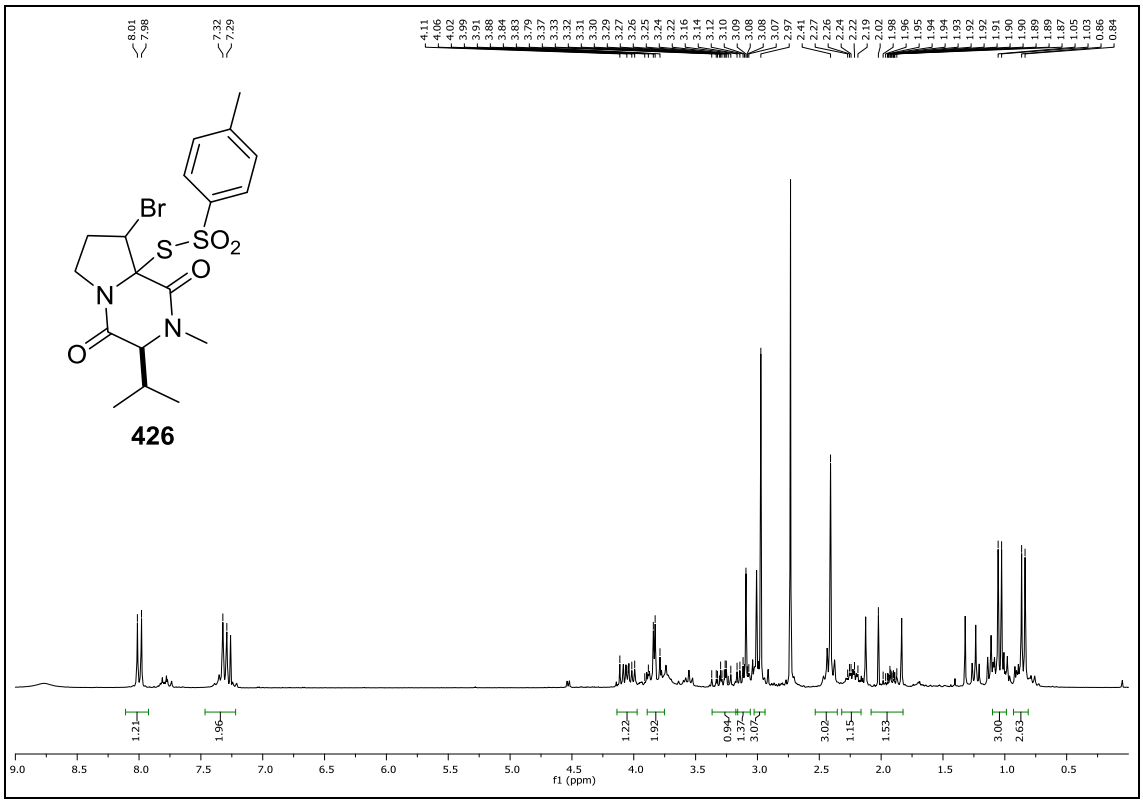
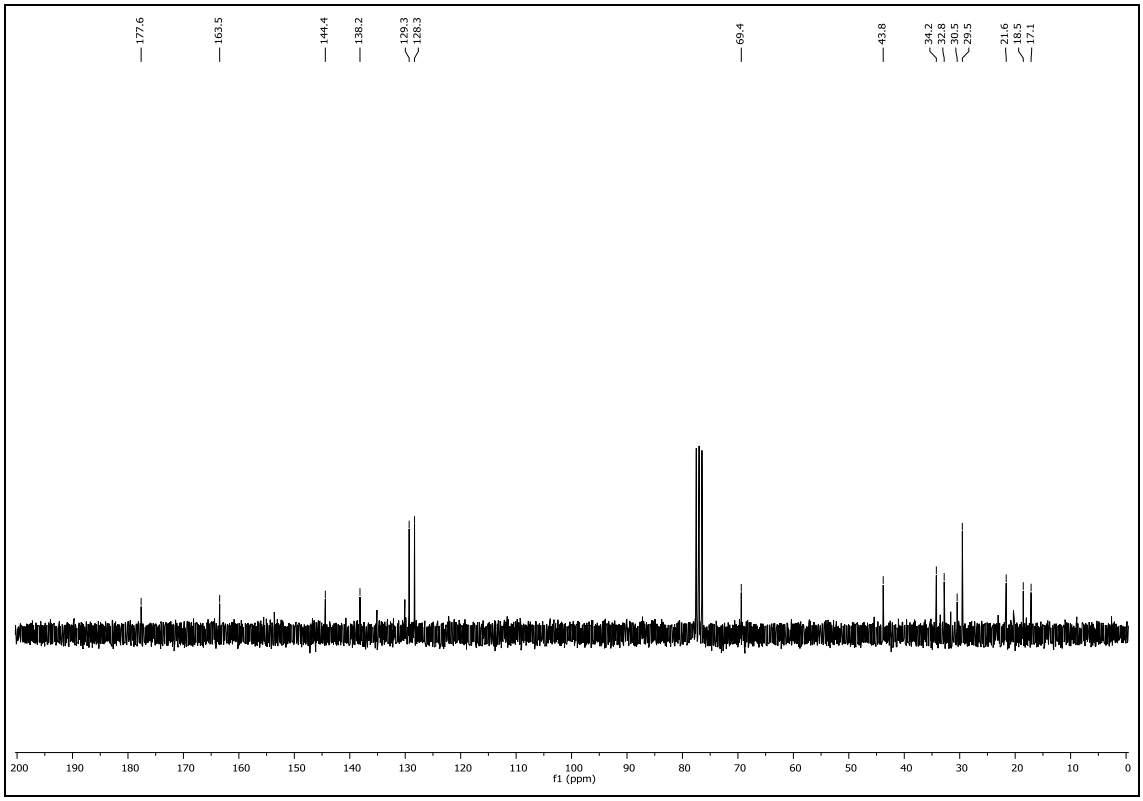
57.8
44.7
33.5
31.0
28.8
21.5
18.8
17.8
f1 (ppm)


Br
S
SO2
O
N
N
O
426
f1 (ppm)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128.3
69.4
43.8
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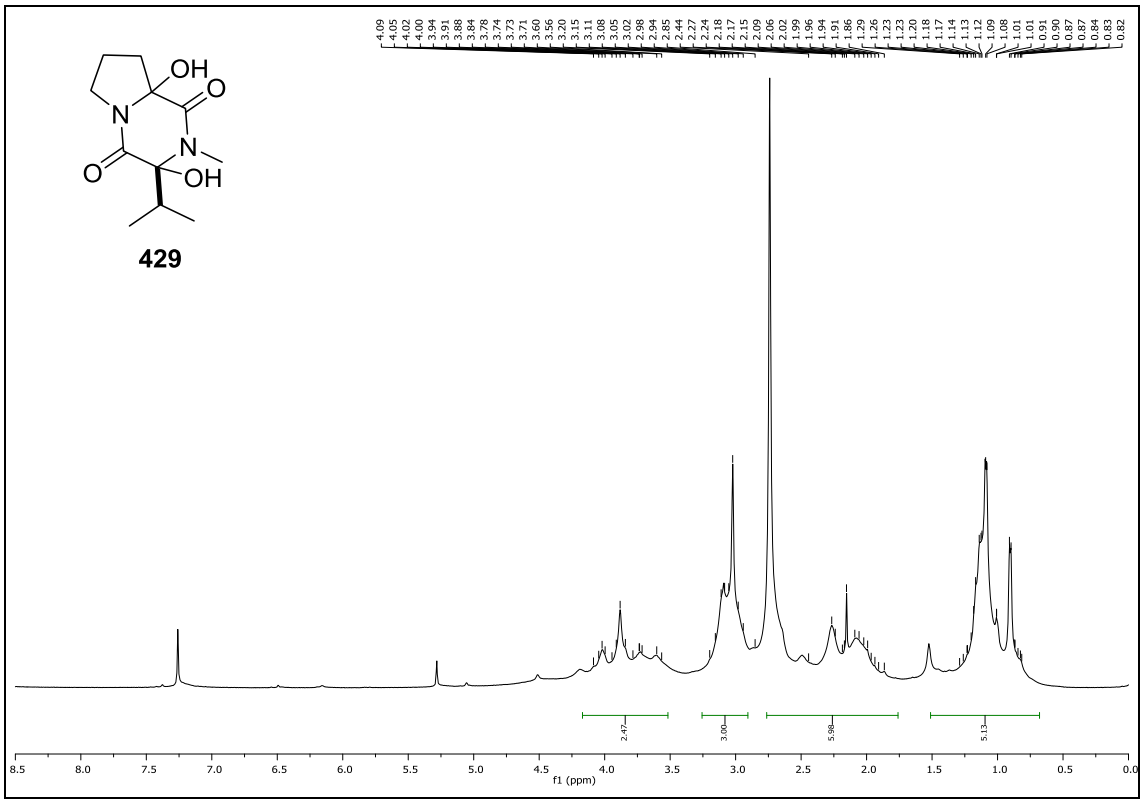
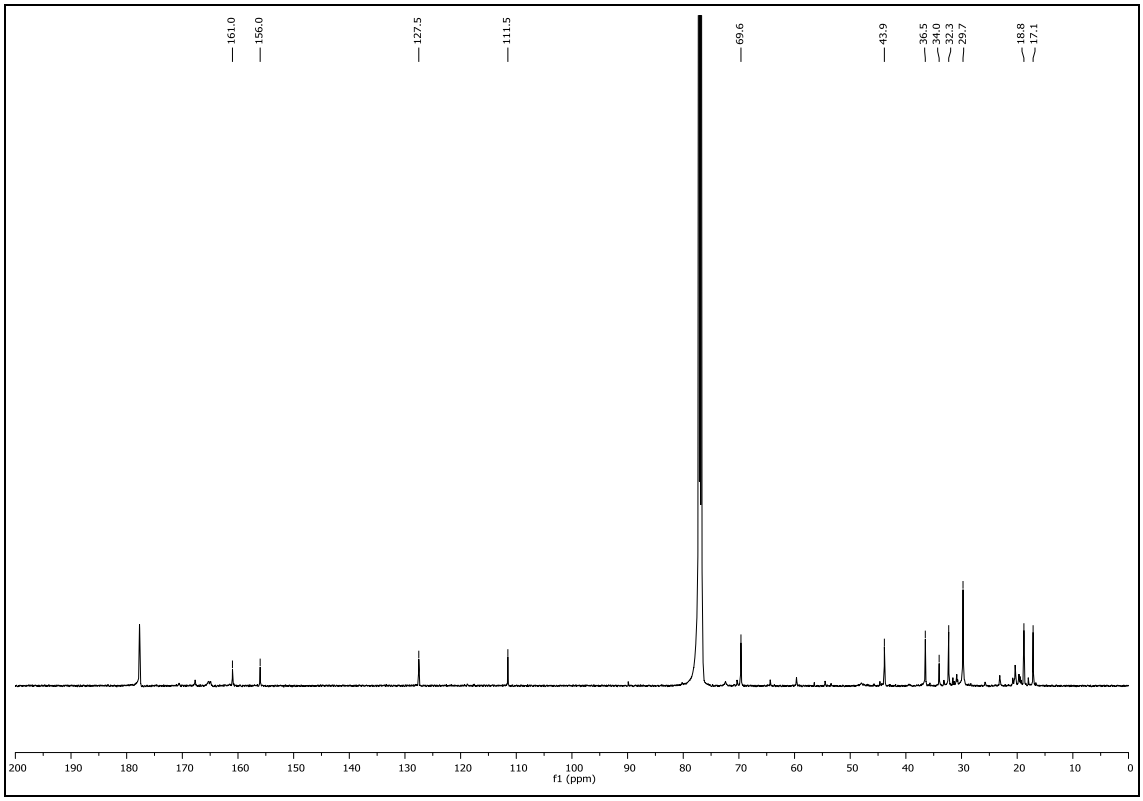
32.8
30.5
29.5
21.6
18.5
17.1
f1 (ppm)


OH
O
N
N
O
OH
429
f1 (ppm)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156.0
127.5
111.5
69.6
43.9
36.5
34.0
32.3
29.7
18.8
17.1
f1 (ppm)

Publications

Asymmetric Synthesis

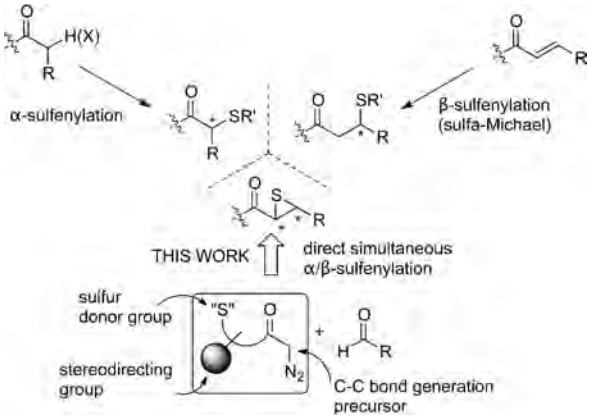
DOI: 10.1002/anie.201204771

N-(Diazoacetyl)oxazolidin-2-thiones as Sulfur-Donor Reagents: Asymmetric Synthesis of Thiiranes from Aldehydes**

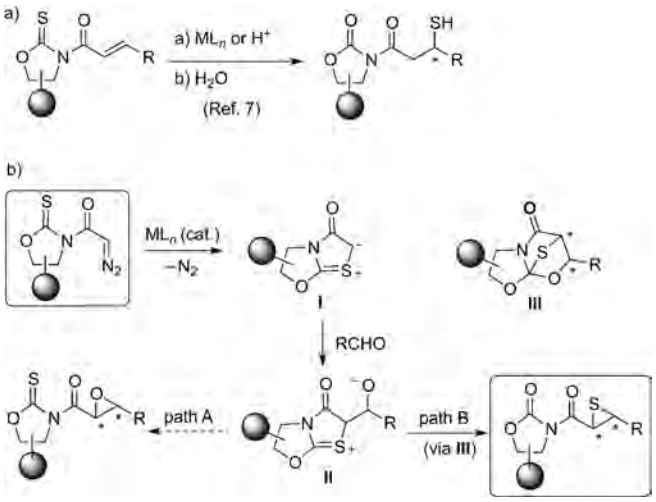
*Israel Cano, Enrique Gómez-Bengoa, Aitor Landa, Miguel Maestro, Antonia Mielgo, Iurre Olaizola, Mikel Oiarbide, and Claudio Palomo**

Sulfur-containing compounds are widespread among natural products and bioactive substances, and also useful ligands in asymmetric catalysis.[1] Therefore considerable efforts have been devoted to develop stereocontrolled C–S bond-forming procedures.[2] Two common approaches consist of the electrophilic sulfenylation of enolates or equivalents[3] and the conjugate addition of S nucleophiles to Michael acceptors;[4] these routes afford S-functionalized carbonyls at either the α or β position. Methods to access α,β-thioepoxy carbonyls[5] would not only provide versatile adducts S-functionalized at both the α and β position, but also imply generation of two contiguous stereocenters (Scheme 1). However, as far as we are aware there is virtually no method for achieving such a goal in a direct and stereocontrolled fashion.[6] Herein, we describe *N*-(diazoacetyl)oxazolidin-2-thiones as new sulfur-donor reagents that in combination with aldehydes and a Rh^{II} catalyst are capable of producing α,β-thioepoxy carbonyls in a highly stereoselective manner.

Inspired by the ability of the oxazolidin-2-thione group to act as both an intramolecular sulfur-donor reagent and a stereodirecting group (Scheme 2a),[7] we envisaged that *N*-(diazoacetyl)oxazolidin-2-thiones might serve as both C–C and C–S bond-forming reagents while controlling the reaction stereochemistry. The assumption was that thiocarbonyl ylide **I** (Scheme 2b), generated from *N*-(diazoacetyl)oxazolidin-2-thione upon treatment with a metal catalyst,[8] would react with an aldehyde to afford the zwiterionic intermediate **II**, which may follow either path A or B to provide either epoxide or thioepoxide product. Although path A (epoxide formation) seemed to be the preferred route for both sulfide ylides[9] and carbonyl ylides,[10] and implies no sulfur transfer, we speculated that path B might also be possible, likely through rearrangement of intermediate **III**.



Scheme 1. Common strategies for the stereoselective sulfenylation of carbonyls at the α or β position, and our proposal for the direct simultaneous α and β sulfenylation.



Scheme 2. Working hypothesis for stereoselective thiirane synthesis by sulfur transfer with concomitant C–C bond formation.

Starting thione diazo compounds were readily prepared by reaction of oxazolidin-2-thiones with 2-(2-tosylhydrazono)acetyl chloride in yields of 47–67%. Initial screening of catalysts and reaction conditions revealed that both Rh^{II} and Cu^{II} salts catalyzed the reaction of **1** with benzaldehyde in CH_2Cl_2 at 0°C to afford thiirane **5a** in yields from 50% to 62% upon isolation and *cis*/*trans* ratios from 85:15 to 88:12

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Manuel Lardizabal 3, 20018 San Sebastián (Spain)
E-mail: claudio.palomo@ehu.es
Dr. M. Maestro[+]
Departamento de Química Fundamental, Facultad de Ciencias
Universidade da Coruña
Campus Zapateira s/n, 15071A Coruña (Spain)

[+] X-Ray analyses.

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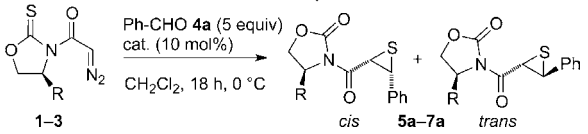
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204771.

(Table 1, entries 1, 2, and 7). Remarkably, in both cases no oxirane product was detected in the corresponding crude reaction mixtures.[10] This process is thus particularly significant in that the new C–S σ-bond formation occurs in detriment of the C–O σ-bond and with concomitant generation of two contiguous stereocenters. The nature of the counterion of the transition metal salt used has an influence on the catalytic activity: both $Rh_2(OAc)_4{\cdot}2H_2O$ and $Cu(acac)_2$ were active and induced good reaction yields, whereas no reaction at all was observed with either $Rh_2(OCOCF_3)_4$ or $Cu(OTf)_2$ salts (Table 1, entries 1, 2, and 7 vs. 5 and 8). The use of other divalent metal salts such as $CoCl_2$, $FeCl_2{\cdot}H_2O$, and $Pd(OAc)_2$, which are potentially capable of inducing ylide formation, led to sluggish reactions or no reaction at all (Table 1, entries 6, 10, 13).

On the other hand, some metals in the oxidation state +1 were also effective catalysts. For instance, although no reaction was observed with AgOTf, both CuCl and AuCl promoted the reaction to give product **5a** with *cis*/*trans* ratios of 91:9 and 99:1, respectively, albeit in these cases the yields were low (Table 1, entries 12, 9, and 11). Further optimization of the reaction conditions with $Rh_2(OAc)_4{\cdot}2H_2O$ as catalyst indicated that a lower (2 mol%) catalyst loading could be used and the *cis*/*trans* ratio could be improved by lowering the temperature (up to 97:3 *cis*/*trans* ratio; Table 1, entries 3 and 4). Finally, diazo-oxazolidinethiones **2** and **3**, bearing a *tert*-butyl and a phenyl substituent, respectively, were also tolerated, although in the case of the phenyl analogue **3** a relatively lower yield and selectivity was observed (Table 1, entries 14 and 15).

Table 1: Screening of catalysts for the reaction of *N*-(diazoacetyl)-2-oxazolidinethiones **1**–**3** and benzaldehyde.[a]

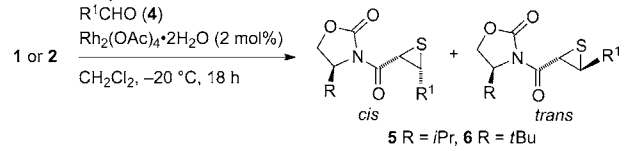


Entry	R	Substrate	Catalyst	*T* [°C]	Prod.	*cis*/*trans*[b]	Yield [%][c]
1	*i*Pr	**1**	$Rh_2(OAc)_4$	0	**5a**	86:14	50
2	*i*Pr	**1**	$Rh_2(OAc)_4{\cdot}2H_2O$	0	**5a**	88:12	62
3	*i*Pr	**1**	$Rh_2(OAc)_4{\cdot}2H_2O$	−10	**5a**	94:6	64[d]
4	*i*Pr	**1**	$Rh_2(OAc)_4{\cdot}2H_2O$	−20	**5a**	97:3	62[d]
5	*i*Pr	**1**	$Rh_2(OCOCF_3)_4$	0	**5a**	–	0[e]
6	*i*Pr	**1**	$CoCl_2$	0	**5a**	–	0
7	*i*Pr	**1**	$Cu(acac)_2$	0	**5a**	85:15	53
8	*i*Pr	**1**	$Cu(OTf)_2$	0	**5a**	–	0[e]
9	*i*Pr	**1**	CuCl	0	**5a**	91:9	40
10	*i*Pr	**1**	$FeCl_2{\cdot}4H_2O$	0	**5a**	–	0[e]
11	*i*Pr	**1**	AuCl	0	**5a**	99:1	18
12	*i*Pr	**1**	AgOTf	0	**5a**	–	0[e]
13	*i*Pr	**1**	$Pd(OAc)_2$	0	**5a**	–	17
14	*t*Bu	**2**	$Rh_2(OAc)_4{\cdot}2H_2O$	−20	**6a**	94:6	60[d]
15	Ph	**3**	$Rh_2(OAc)_4{\cdot}2H_2O$	−20	**7a**	92:8	45[d]

[a] The reactions were performed on a 0.30 mmol scale. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated major isomer after chromatography. [d] Using 2 mol% of catalyst. [e] Extensive decomposition was observed.

We next investigated the scope of the reaction with respect to the aldehyde component. As the results in Table 2 show, reactions of a range of aromatic aldehydes bearing either electron-donating, neutral, or electron-withdrawing substituents all produced the corresponding thiirane product smoothly within 16–18 h at −20 °C. In each case a mixture of *cis*/*trans* isomers was formed from which the major isomer was obtained in 57–75% yield upon isolation. Interestingly, in most cases *cis*-thiirane was obtained as the major isomer (*cis*/*trans* ratio from 97:3 to 82:18; Table 2, entries 1–3, 6–10), whereas in the case of *p*-anisidine, and *p*-*tert*-butyldimethylsilyloxybenzaldehyde, the *trans*-configured thiirane (**5d** and **5e**) was the exclusive product (Table 2, entries 4 and 5). This unusual reversal of the reaction stereochemistry observed for benzaldehydes bearing electron-donating substituents could be explained on the basis of the proposed reaction mechanism (see below). The catalytic generation of thiiranes **5** and **6** also worked for other nonenolizable aldehydes, such as alkynyl and heteroaryl aldehydes (Table 2, entries 11–16). Pyridylcarbaldehyde was an exception (Table 2, entry 17). Assignment of the *cis*/*trans* relative configuration of the formed thiirane ring was primarily made by correlation of the coupling constants between the two vicinal H nucleus in ^{1}H NMR spectroscopy: 7.4 Hz to 7.7 Hz for the *cis*-thiirane

Table 2: Scope of the reaction.[a]

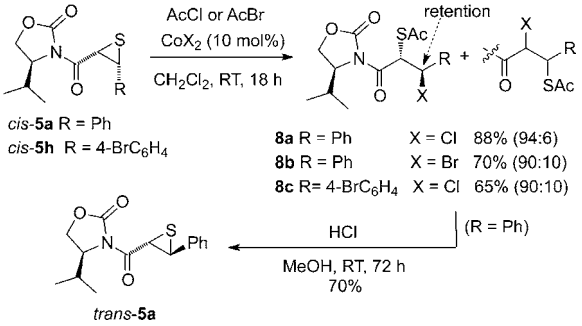


Entry	Substrate	R^1	Product	*cis*/*trans*[b]	Yield [%][c]
1	**1**	Ph	**5a**	93:7	65[d]
2	**1**	4-MeC_6H_4	**5b**	82:18	60
3	**1**	3,5-MeC_6H_3	**5c**	83:17	61
4	**1**	4-$MeOC_6H_4$	**5d**	1:99	61
5	**1**	4-$TBSOC_6H_4$	**5e**	1:99	31[e]
6[f]	**1**	4-ClC_6H_4	**5f**	88:12	63
7	**1**	3-ClC_6H_4	**5g**	86:14	57
8	**1**	4-BrC_6H_4	**5h**	91:9	56
9	**1**	4-$NO_2C_6H_4$	**5i**	92:8	61
10	**1**	4-CNC_6H_4	**5j**	91:9	56
11	**1**	PhC≡C	**5k**	72:28	65
12[g]	**2**	PhC≡C	**6k**	83:17	75
13[h]	**2**	PhC≡C	**6k**	86:14	69
14[g]	**2**	3-ClC_6H_4C≡C	**6l**	85:15	60
15	**1**	3-furyl	**5m**	62:38	n.d.[i]
16[g]	**2**	3-furyl	**6m**	83:17	70
17	**1**	3-pyridyl	**5n**	–	0[j]

[a] Reaction conditions: **1** (0.5 mmol), **4** (3 equiv, 1.5 mmol), $Rh_2(OAc)_4{\cdot}2H_2O$ (2 mol%), −20 °C, 16–18 h in CH_2Cl_2 (1 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] Yields of isolated compounds **5** or **6** after column chromatography. [d] Reaction carried out at 2 mmol scale. [e] Yield not optimized; partial desilylation occurred during chromatography (SiO_2). [f] 91:9 diastereoselectivity in the presence of 2,2′-bipyridyl as additive. [g] Reaction run at −60 °C. [h] Reaction run at −78 °C. [i] n.d. = not determined. [j] Unchanged starting material recovered.

systems; 4.80 Hz to 4.90 Hz for the *trans* isomer. In addition, an X-ray single-crystal structure analysis of compound *cis*-**5a** confirmed the proposed structure.[11]

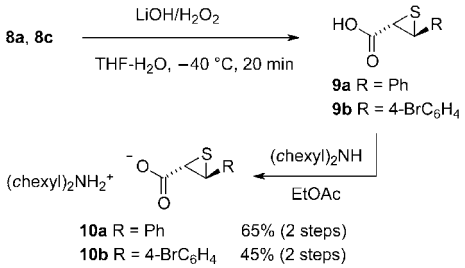
Next, reaction conditions for the selective opening of the thiirane ring and the release of the oxazolidinone auxiliary were explored. For example, treatment of thiiranes *cis*-**5a** and *cis*-**5h** with acetyl chloride in CH_2Cl_2 at room temperature in the presence of $CoCl_2$ (10 mol%), according to the procedure of Iranpoor, Firouzabadi, and Jafari,[12] gave the β-chloro-α-thio imide derivatives **8a** and **8c** in 88% and 65% yields, respectively, after chromatography (Scheme 3). Similarly,



Scheme 3. Thiirane ring opening of adducts **5**.

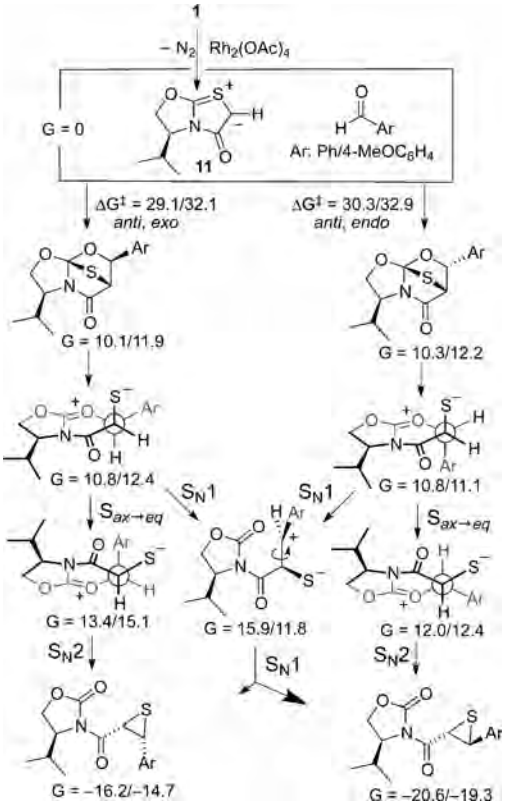
treatment of *cis*-**5a** with acetyl bromide in the presence of $CoBr_2$, as catalyst, afforded the corresponding bromo derivative **8b** in 70% yield upon isolation. In all these three cases a minor amount (6–10%) of the corresponding regioisomeric ring-opening product was also observed in the respective crude reaction mixture. It is important to note that substitution at the β carbon atom during ring opening leading to products **8** occurred with retention of configuration, perhaps by a double inversion pathway involving a transient C–O adduct. Interestingly, acid-promoted cyclization of compounds **8** to restore the thiirane ring took place very efficiently, with inversion of the configuration of β carbon atom. For instance, the treatment of **8a** with methanolic HCl afforded *trans*-**5a** in 70% yield. Accordingly, a two-step thiirane-ring isomerization from *cis* to the more stable *trans* isomer is feasible.

On the other hand, the removal of the oxazolidinone moiety from thiirane adducts **5** through imide hydrolysis or alcoholysis under standard reaction conditions led to extensive loss of the sulfur atom. This problem could be circumvented by performing imide hydrolysis on the ring-opened adducts **8** instead (Scheme 4). Thus, saponification with $LiOH/H_2O_2$ of adducts **8a** and **8c** proceeded with restoration of the thiirane ring, to afford the corresponding acids **9**, which were isolated as crystalline bench stable dicyclohexylamine salts **10**. In this transformation, oxazolidinone was also formed and it could be recovered, transformed into the thione auxiliary, and recycled.[7] Unambiguous determination of the structure of salt **10b** and compound **8a** by X-ray single-crystal structure analysis[11] further confirmed the identity of the products as well as the stereochemical outcome of the reactions involved.



Scheme 4. Recovery of the auxiliary.

A DFT investigation was carried out at the B3LYP level of theory, and provided support for a plausible pathway for this intriguing thiirane-forming reaction. Calculations predict that the corresponding rhodium carbenoid species[11] formed upon treatment of diazo thione compound **1** with $Rh_2(OAc)_4$, evolves into bicyclic ylide **11** (Scheme 5)[13] with no activation



Scheme 5. Principal reaction pathways found by DFT investigation at the B3LYP level of theory for the Rh-catalyzed reaction between diazocompound **1** and either benzaldehyde or *p*-anisaldehyde. Values of Gibbs energy are given in kcal mol^{-1}.

barrier, probably because of the high charge delocalization exhibited by this particular ylide.[14] According to calculations, subsequent reaction of **11** with either benzaldehyde or *p*-anisaldehyde would generate a unique tricyclic adduct,[15] and among the four possible relative orientations of the ylide and aldehyde component during the cycloaddition, those leading to *anti*, *exo* and *anti*, *endo* isomers are preferred. The

complementary *syn* transition states lie considerably higher in energy because unfavorable interactions between the ylide isopropyl substituent and the incoming aldehyde. The energy differences between *anti*, *exo* and *anti*, *endo* approaches for benzaldehyde and *p*-anisaldehyde, (1.2 and 0.8 kcal mol^{-1}, respectively) would justify preferential formation of the *anti, exo* adduct with expected diastereoselectivities near 90:10. Transformation of these tricyclic high energy intermediates into the final thiirane products would follow a more-or-less downhill energy profile, involving thiirane ring opening, $S_{ax\rightarrow eq}$ conformational switch, and internal S_N2 displacement. Accordingly, from a tricyclic *anti, exo* intermediate the *cis*-configured thiirane would be formed; conversely, from the less-favorable *anti, endo* precursor, the *trans*-thiirane would be formed, a prediction that agrees with the experimentally observed trend for most of the aldehydes tested. Interestingly, calculations also offer a plausible explanation of the reversal of the reaction stereochemistry observed experimentally for *p*-anisaldehyde and other related electron-rich aromatic aldehydes. Indeed, thiirane generation could occur through an alternative S_N1-type pathway, which is about 2.5 kcal mol^{-1} less favorable than the S_N2 pathway for benzaldehyde, but conversely about 3.3 kcal mol^{-1} more favorable than the S_N2 pathway for *p*-anisaldehyde. As expected, S_N1-type cyclization would preferentially lead to the most stable *trans*-thiirane product.

In conclusion, we have reported the first Rh-catalyzed reaction of a diazoacetyl compound with aldehydes that affords thiiranes, instead of oxiranes, as known before. This unusual reactivity relies on the use of *N*-(diazoacetyl)oxazolidin-2-thiones as new chiral sulfur-donor reagents and enables the direct production of optically active thiiranes with very high stereoselectivity. Work towards expanding the scope of this sulfur-transfer protocol is currently underway in our laboratory.

Experimental Section

General catalytic procedure for the synthesis of thiiranes **5**–**7**: Rhodium(II) acetate dihydrate (4.8 mg, 0.01 mmol, 2 mol%) was added to a solution of the corresponding diazocompound **1**–**3** (0.50 mmol) and aldehyde **4a**–**p** (3 equiv, 1.5 mmol) in anhydrous CH_2Cl_2 (1.5 mL) at a given temperature, under argon atmosphere. The reaction mixture was stirred for 16–18 h at the same temperature and afterwards quenched with saturated $NaHCO_3$; the organic layer was separated, dried with $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: AcOEt/hexanes, 1:4) to afford the desired product.

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[15] An alternative pathway to this tricyclic adduct would involve attack of the thione group onto the epoxide initially generated from the reaction between the aldehyde and the diazocarbonyl moiety. However, the fact that no traces of epoxide product were detected in the reaction mixtures and a 14.4 $kcal\,mol^{-1}$ energy barrier is calculated for such epoxide formation (see Ref. [11]), disfavors the epoxide pathway.

Organocatalysis

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Catalytic Enantioselective Synthesis of Tertiary Thiols From 5*H*-Thiazol-4-ones and Nitroolefins: Bifunctional Ureidopeptide-Based Brønsted Base Catalysis**

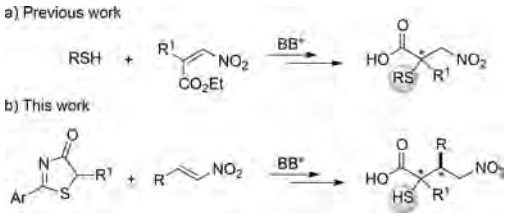
*Saioa Diosdado, Julen Etxabe, Joseba Izquierdo, Aitor Landa, Antonia Mielgo, Iurre Olaizola, Rosa López, and Claudio Palomo**

Dedicated to Professor Carmen Nájera

The direct catalytic reaction between an enolizable carbonyl compound and an electrophile under proton-transfer conditions has emerged as a challenging versatile transformation in organic synthesis.[1] Over the last years several chiral Brønsted bases have been developed to promote this transformation diastereo- and enantioselectively.[2] However, successful examples are mostly limited to 1,3-dicarbonyl compounds and acidic carbon analogues as the pronucleophilic reaction partners. 5*H*-Thiazol-4-ones, in contrast, have been well known for a long time and have found several applications in pharmaceutical and medicinal chemistry.[3] Although structurally related to 5*H*-oxazol-4-ones[4] and 4*H*-oxazol-5-ones (azlactones),[5] 5*H*-thiazol-4-ones have, as far as we know, been never been used in asymmetric synthesis in spite of the fact that they may be easily deprotonated[6] and in spite of the importance of thiols and organosulfur compounds in organic synthesis[7] and chemical biology.[8] In this context, whilst chiral secondary thiol derivatives have been the subject of most investigations, tertiary thiols have remained mostly unexplored owing to the insufficient catalytic enantioselective methodology for their preparation in optically pure form.[9]

The most general synthesis of organosulfur compounds involves reaction of a sulfur nucleophile with an electron-deficient π-olefin acceptor.[10] By using this approach Zhang and co-workers[11] reported an efficient catalytic asymmetric synthesis of tertiary thiols using chiral Brønsted bases and β-substituted β-ethoxycarbonyl nitroalkene acceptors. Conversely, tertiary thiols may be produced through conjugate additions of sulfur-based carbon pronucleophiles.[12] For instance, using rhodanines as carbon pronucleophiles and iminium catalysis, Ye and co-workers[13] have recently reported the conjugate addition and the Diels–Alder reaction to α,β-unsaturated ketones and 2,4-dienals, respectively. Tertiary thiols have also been accessed through enantioselective α-sulfenylation of aldehydes,[14a] 1,3-dicarbonyl compounds,[14b] β-keto phosphonates,[14c] and 3-substituted oxindoles.[14d–g] Other methods include thiofunctionalization of unactivated alkenes,[15a] amination of 3-thiooxindoles,[15b] and the aldol[15c] and Mannich[15d] reactions of α-sulfanyl lactones. Accordingly, whilst many methodologies for the enantioselective synthesis of secondary thiols exist, approaches for the asymmetric synthesis of tertiary thiols are clearly necessary to help fill this important gap in organic chemistry. The inherent difficulty associated with the stereoselective construction of quaternary stereogenic centers is probably the reason for the limited number of studies.[16] In connection with our efforts directed towards the asymmetric synthesis of organosulfur compounds, that is, β,β-disubstituted β-mercapto carboxylic acids[17a,b] and thiiranes,[17c] we focused on the enantioselective generation of a tetrasubstituted carbon atom at the α position of α-mercapto carboxylic acids.[18] We report herein the first highly diastereo- and enantioselective direct Michael addition of 5*H*-thiazol-4-ones to nitroolefins (Scheme 1) and it provides a quick entry to functionalized tertiary thiols. To this end, design and synthesis of ureidopeptide-based Brønsted bases, a novel subfamily of organic catalysts, are also documented for the first time.

We began our study by evaluating several Brønsted bases for the reaction of the readily available thiazolone **1**[19] with the nitroolefin **5a** (R = Ph; Scheme 2).[20] Initially, the reaction was explored using several representative cinchona alkaloids such as quinine, 9-epi-quinine, quinidine, and $(DHQ)_2PYR$ in CH_2Cl_2 at −60 °C. In every case the product



Scheme 1. Organocatalytic Michael approaches to α,α-disubstituted α-mercapto carboxylic acids mediated by chiral Brønsted bases (BB*). a) Asymmetric construction of C–S bond. b) Asymmetric construction of C–C bond.

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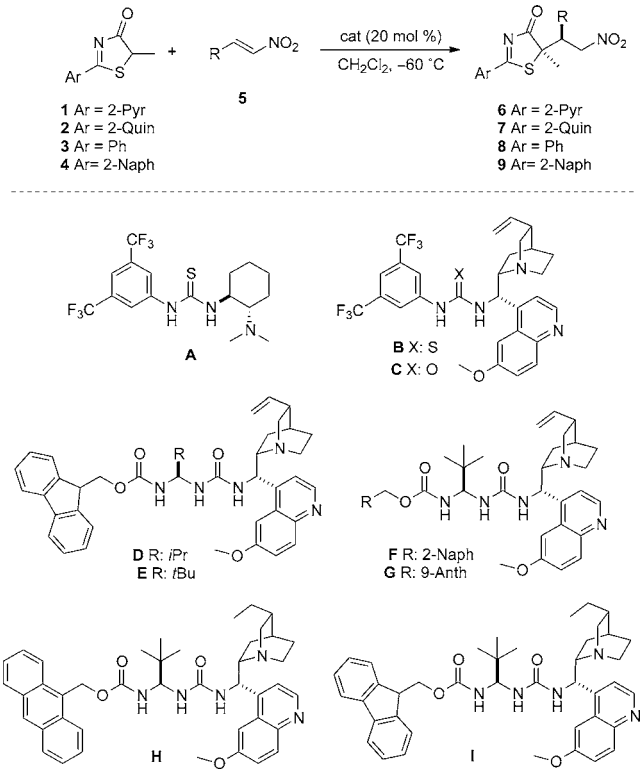


Scheme 2. Conjugate addition of 5-methyl 5*H*-thiazol-4-ones to nitro olefins promoted by chiral Brønsted bases.

6a (R = Ph) was obtained but with disappointing chemical and stereochemical results (12–40% *ee*).[21] Next, on the basis of the pioneering studies of Takemoto and co-workers, and subsequent seminal works by the groups of Jacobsen, Connon, Dixon, and Soós on bifunctional (urea)thiourea-tertiary amine catalysts,[22] we examined the catalysts **A**–**C**. However, as the results in Table 1 show **A** led to almost racemic **6a** (entry 1), whilst no improvement was essentially observed with either **B** or **C** (entries 2 and 3).

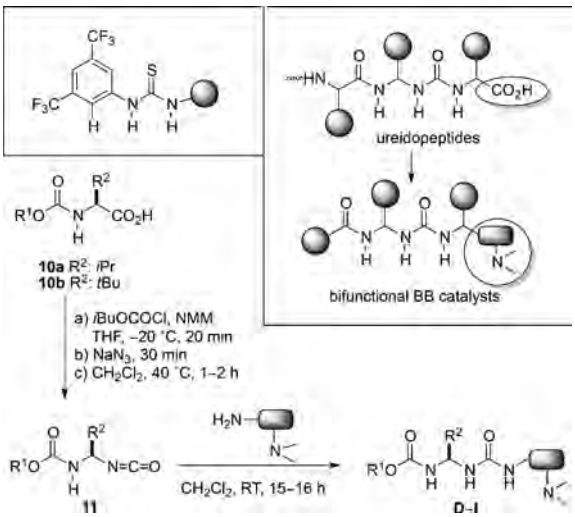
At this stage and in view of these results we focused on catalyst design. Like the catalysts **A**–**C**, most thiourea (urea)

Table 1: Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-ones **1**–**4** to nitrostyrene **5a** (R = Ph).[a]

Entry	Comp.	Cat.	Prod. (R=Ph)	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1**	**A**	**6a**	48	53	83:17	20
2	**1**	**B**	**6a**	20	53	60:40	35
3	**1**	**C**	**6a**	20	48	54:46	40
4	**1**	**D**	**6a**	20	88	91:9	40
5	**1**	**E**	**6a**	20	92	95:5	66
6	**1**	**F**	**6a**	20	90	94:6	70
7	**1**	**G**	**6a**	20	86	90:10	78
8	**1**	**H**	**6a**	20	80	93:7	80
9	**2**	**H**	**7a**	20	93	95:5	96
10	**3**	**H**	**8a**	20	65	85:15	55
11	**4**	**H**	**9a**	20	55	75:25	68

[a] Reactions conducted at −60 °C on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2). [b] Yield of the isolated major isomer. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

based Brønsted bases known to date display the 3,5-bis(trifluoromethyl)phenyl group, a structural motif which was introduced first by Schreiner and Wittkopp in 2002 for hydrogen-bond catalysis.[23] Recently, Schreiner and co-workers suggested that the success of these catalysts may be attributed in part to the participation of both N–H bonds of the thiourea unit and the *ortho* C–H bond of the aryl group during the substrate activation event.[24] Based on this observation and given the proved efficacy of synthetic peptides for fine-tuning of reactivity and selectivity of several significant synthetic transformations[25] we wondered whether the urea derivatives **D**–**I** might be more appropriate catalysts for promoting the above reaction. These products display, as new features, the presence of an N,N′-diacyl aminal unit in place of the bis(trifluoromethyl)phenyl group, and an urea moiety as hydrogen-bond donors, and both are in close proximity to an additional stereodirecting group. This type of structure closely resembles ureidopeptides (Scheme 3), which



Scheme 3. Ureidopeptide-based Brønsted bases: Catalyst preparation. NMM = *N*-methylmorpholine, THF = tetrahydrofuran.

have been recognized for their ability to develop hydrogen-bond interactions.[26] It was expected that the replacement of the α-amino acid terminus by an amino cinchona moiety in ureidopeptides should result in new bifunctional Brønsted base catalysts with several sites amenable for structural modification.

Although, several different classes of ureidopeptide-based catalysts may be made readily accessible from the available pools of both α-amino acids (or peptides) and primary-tertiary diamines, we intended first to take advantage of the tunable aminal moiety for catalyst optimization. To the best of our knowledge this family of ureidopeptide-based Brønsted base catalysts have not been previously reported. Thus, starting from valine and the *tert*-leucine derivatives **10a** and **10b**, the catalysts **D**–**I** were easily prepared by reaction of the respective intermediate isocyanates **11**[26b] with 9-epi-9-amino-9-deoxyquinine or 9-epi-9-amino-9-deoxyhydroquinine in yields within the 70–80% range for the latter step (Scheme 3). A single-crystal X-ray analysis of **E** (Figure 1)

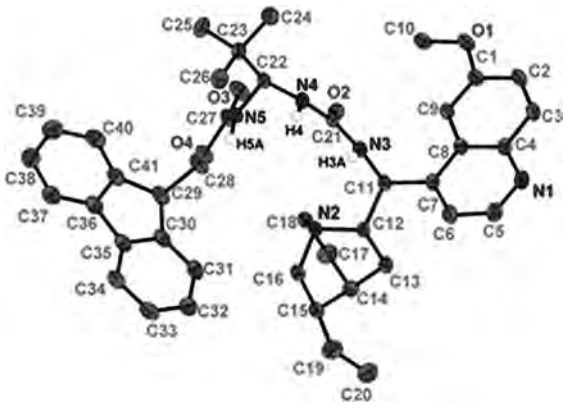


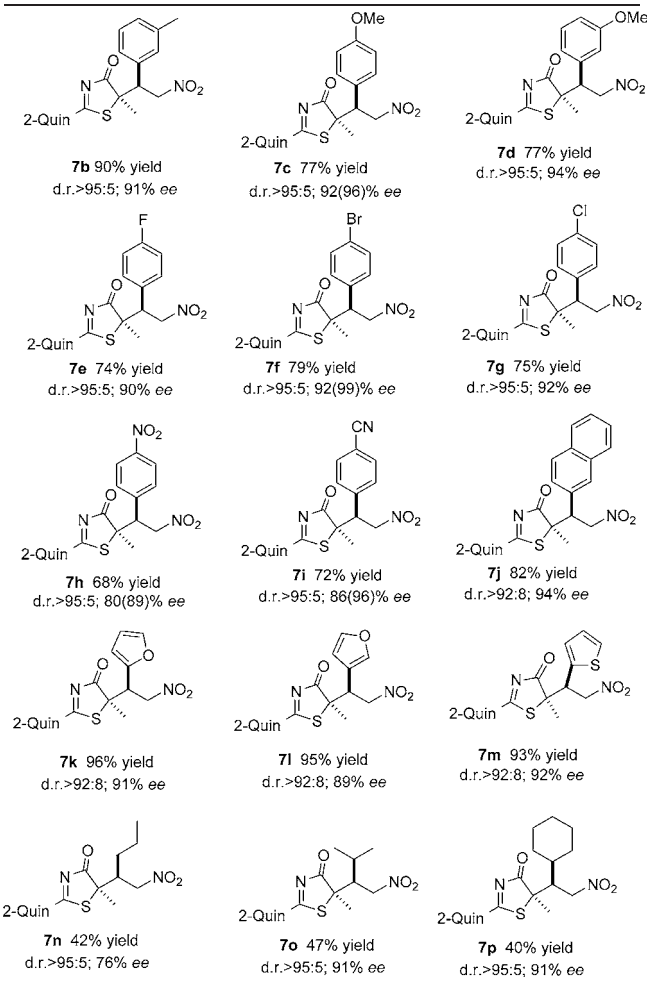
Figure 1. ORTEP representation for **E**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

shows that N-H groups, in the N,N′-diacyl aminal and the urea moiety, are oriented in the same direction and that neither of them display any apparent tendency to develop intramolecular hydrogen bonds.[21]

Experiments with these catalysts revealed an improvement in diastereoselectivity. Also, by increasing the size of the aminal substituent from isopropyl to *tert*-butyl (catalysts **D** and **E**), enantioselectivity increased up to 66%, but was still insufficient (Table 1, entries 4 and 5). Further improvements in the reaction selectivity were observed with the catalysts **F** and **G** (entries 6 and 7) and the best result was produced with the catalyst **H**, which provided the product **6a** in 80% yield and 80% *ee* (entry 8). In subsequent experiments it was found that by using the quinoline-derived thiazolone **2** and catalyst **H** the corresponding product **7a** (entry 9) was produced in 93% yield as a 95:5 mixture of diastereomers with 96% *ee* for the major isomer. In contrast, using the thiazolones **3** and **4**, the corresponding addition products **8a** and **9a** (entries 10 and 11) were formed in lower diastereomeric ratios and *ee* values, results which seem to indicate that the pyridine and quinoline nitrogen atoms of the thiazolones **1** and **2** play a significant role in reaction stereocontrol. A representative selection of nitroolefins was evaluated to establish the generality of this asymmetric route to tertiary thiols. As the data in Table 2 shows, nitroolefins bearing β-aryl substituents with either electron-donating or electron-withdrawing groups are almost equally tolerated, thus giving the corresponding adducts with good diastereomeric ratios, typically greater than 95:5 and *ee* values of up to 96%. For example, performing the reaction with the substrates **5b, 5c**, and **5d**, led to the corresponding products **7b, 7c**, and **7d** as single diastereomers with *ee* values within the 91–94% range. The nitroolefins **5e**, **5f**, and **5g** with inductively electron-withdrawing fluoro, bromo, and chloro substituents, respectively, also provided excellent chemical and stereochemical results, whereas the nitrostyrenes **5h** and **5i** bearing mesomeric electron-withdrawing substituents gave the corresponding **7h** and **7i** with slightly reduced enantioselectivities. The method also works with nitroolefins having heteroaromatic β-substituents such as for **5k, 5l**, and **5m** to afford adducts **7k, 7l**, and **7m**, respectively, with good yields and stereoselectivities. Even the recalcitrant β-alkyl-substituted nitroolefins participate in this reaction to give the desired adducts essentially as single diastereomers, albeit in modest chemical yield (typically 40%). The unbranched aliphatic nitroolefin **5n** led to the product **7n** with a modest 76% *ee*, whereas the branched aliphatic substrates **5o** and **5p** provided **7o** and **7p**, respectively, in 91% *ee*. In this study we have employed 20 mol% of catalyst but it is worth mentioning that reactions using 10 mol% of the catalyst proceeded equally well without compromising either selectivity or chemical yield (Table 2 and see the Experimental Section).

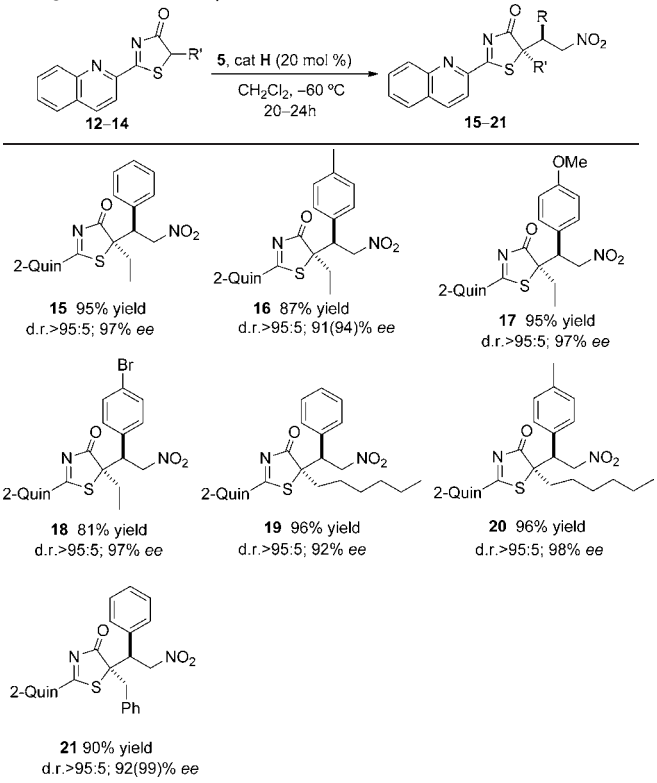
Thiazolones with short, large, and branched alkyl chains, also participate in this reaction (Table 3), and in all cases good to excellent yields were observed and the products were obtained with high enantioselectivity. The 5-ethylthiazolone **12**, for example, afforded the products **15**–**18**, essentially as

Table 2: Conjugate addition of the thiazolone **2** to nitroolefins **5** promoted by catalyst **H**.[a–d]

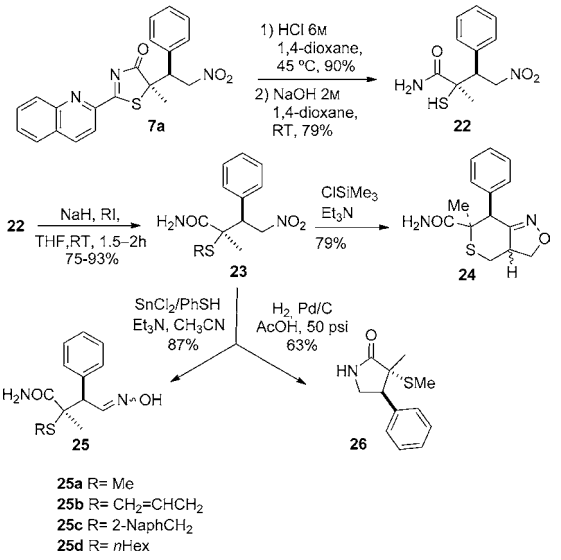


[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2) at −60°C for 20-24 h. [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^{1}H NMR (300 MHz) spectroscopy on the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Data within parentheses were obtained after crystallization from diethyl ether or diisopropyl ether. By using a 10 mol% catalyst loading, essentially the same results for **7c**, **7f**, and **7o** were attained.

Table 3: Thiazolone scope.[a–d]



[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroalkene/thiazolone/catalyst 2:1:0.2). [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase.



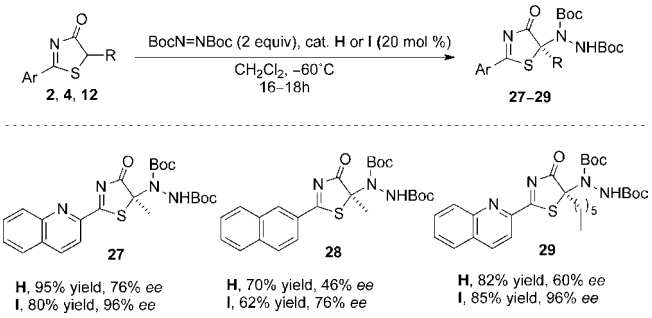
Scheme 4. Elaboration of adducts to α,α-disubstituted α-mercapto carboxylic acid derivatives.

sole diastereomers with excellent yields and 91–97% *ee*. Similarly, the hexyl (**13**) and benzyl (**14**) thiazolones, provided adducts **19, 20**, and **21** in very good yields, and diastereo- and enantioselectivities.

A practical aspect of the present methodology is the general crystallinity of the starting susbtrates, the thiazolones **2** and **12–14** and nitroolefin **5**, a property which is readily transformed into the resulting products **7** and **15–21**. Thus, a single crystallization, generally from diethyl ether or diisopropyl ether, provided products with increased enantiomeric purity. The absolute configuration of the adducts was established by a single-crystal X-ray analysis of **7f**[21] and by assuming a uniform reaction mechanism.

Transformation of the adduct **7a** into the α,α-disubstituted α-mercapto carboxylic acid derivative **22**, by simple ring opening under mild acid conditions and subsequent saponification of the resulting thioester intermediate, illustrates the utility of the method. Thus, unlike the majority of procedures for the preparation of organosulfur compounds which generally give aryl or alkyl thioethers,[9–15] our method provides a quick entry to mercapto compounds with the thiol group in its free form (Scheme 4). Therefore, the question that we examined next was to establish whether these adducts could be S alkylated without affecting the nitro group. Besides steric constraints, there is the fact that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[27] Gratifyingly, treatment of the adduct **22** with a series of halides in the presence of sodium hydride furnished the corresponding S-alkylated adducts **23** in 75–93% yields. Therefore, our approach also provides rapid access to a variety of thioether derivatives from a single common intermediate, a practical aspect that facilitates access to more elaborated products as exemplified in the formation of the tetrahydrothiopyran-fused isoxazoline **24** from **23b**. In contrast, oximes such as **25c**, may also be obtained in good yields by treatment of the respective thioether adduct with a $SnCl_2$/PhSH/Et_3N system,[28] whilst exposure to H_2 over Pd on charcoal under 50 psi enabled reduction of the nitro group to the amino function, thus leading to γ lactams.

Concerning the mechanism of these reactions,[29] we believe that the quinoline nitrogen atom of these thiazolone substrates could interact through a hydrogen bond with one of the three accessible N-H protons of the catalyst, likely with one of the aminal moieties, thereby providing a well-ordered transition state during the reaction. This assumption nicely accounts for the better behavior of quinolyl thiazolone substrates versus the 2-naphthyl thiazolone **4**. Further support for this assumption was provided from the amination reaction of the thiazolones **2**, **4**, and **12** with *tert*-butylazodicarboxylate (Scheme 5). Whilst in this case enantiocontrol proceeded better with **I** rather than with **H**, thiazolones bearing the quinoline moiety (**2** and **12**) furnished once again a better stereochemical outcome than the 2-naphthyl thiazolone **4**. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation[30] remains to be clarified. Whereas the above assumption appears reasonable for enolate ions having additional Lewis basic functionality, there is evidence from this laboratory that this structural element in the pronucleophile is not a prerequisite for catalyst efficiency and that these bifunctional ureidopeptide-based Brønsted bases are advantageous for a variety of transformations which are currently under study.[31]



Scheme 5. Catalytic enantioselective α-amination of thiazolones. Boc = *tert*-butoxycarbonyl.

In summary, we have realized the first direct catalytic Michael reaction of α-mercapto carboxylate surrogates with nitroolefins involving the construction of a fully substituted α-carbon atom. The method demonstrates the efficacy of 5*H*-thiazol-4-ones as a new class of S-carrying pronucleophiles providing α,α-disubstituted α-mercapto carboxylic acid derivatives with good yields and high diastereo- and enantioselectivities and, consequently, the method contributes to broadening the currently limited methodology available for the catalytic enantioselective synthesis of tertiary thiols. From an intuitive design we have introduced for the first time a new family of Brønsted base catalysts whose architecture can be easily modified by simply choosing the appropriate α-amino-acid-derived (or peptide) isocyanate and a survey of naturally or synthetically primary/tertiary diamines. Since strong substrate dependence is quite common in reactions promoted by Brønsted bases we believe these new catalysts may help to address this challenging issue.

Experimental Section

The catalyst **H** (67.6 mg, 0.1 mmol, 10 mol %) was added to a mixture of 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**2**) (242.3 mg, 1.0 mmol, 1 equiv) and nitrostyrene **5a** (298.3 mg, 2.0 mmol, 2 equiv) in dichloromethane (2.0 mL) cooled to −60 °C. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (16 h; monitored by ^{1}H NMR spectroscopy wherein there was disappearance of the methyl signal at $\delta = 1.46$ ppm). The crude reaction mixture was directly purified by flash column chromatography on silica gel (eluting with dichloromethane) to give adduct **7a** as a yellow solid. Yield: 364 mg, 93 %.

7a: $[\alpha]_D^{25} = -100.5$ ($c = 1.00$, 96 % *ee*, CH_2Cl_2). m.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.16 (m, 3H), 7.95–7.78 (m, 2H), 7.76–7.64 (m, 1H), 7.43–7.32 (m, 2H), 7.31–7.12 (m, 3H), 5.19 (dd, $J = 13.2$, 4.6 Hz, 1H), 5.00 (dd, $J = 13.2$, 10.7 Hz, 1H), 4.22 (dd, $J = 10.7$, 4.6 Hz, 1H), 1.85 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.9$, 194.2, 148.7, 147.7, 137.4, 134.2, 134.2, 130.7, 130.4, 130.4, 129.5, 129.0, 128.7, 128.5, 127.8, 76.0, 65.1, 50.3, 24.0 ppm. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1065. The enantiomeric purity of the major diastereomer was found to be 96 % (98 % *ee* after crystallization from diethyl ether) and was determined by HPLC analysis [Daicel Chiralpak AD-H, *n*-hexane/isopropanol/ethanol 85:14:1, flow rate = 0.5 mL min^{-1}, retention times: 45.5 min (minor) and 57.2 min (major)].

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Enantioselective Construction of Tetrasubstituted Stereogenic Carbons through Brønsted Base Catalyzed Michael Reactions: α′-Hydroxy Enones as Key Enoate Equivalent

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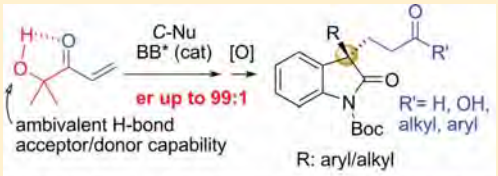
Supporting Information

ABSTRACT: Catalytic and asymmetric Michael reactions constitute very powerful tools for the construction of new C−C bonds in synthesis, but most of the reports claiming high selectivity are limited to some specific combinations of nucleophile/electrophile compound types, and only few successful methods deal with the generation of all-carbon quaternary stereocenters. A contribution to solve this gap is presented here based on chiral bifunctional Brønsted base (BB) catalysis and the use of α′-oxy enones as enabling Michael acceptors with ambivalent H-bond acceptor/donor character, a yet unreported design element for bidentate enoate equivalents. It is found that the Michael addition of a range of enolizable carbonyl compounds that have previously demonstrated challenging (i.e., α-substituted 2-oxindoles, cyanoesters, oxazolones, thiazolones, and azlactones) to α′-oxy enones can afford the corresponding tetrasubstituted carbon stereocenters in high diastereo- and enantioselectivity in the presence of standard BB catalysts. Experiments show that the α′-oxy ketone moiety plays a key role in the above realizations, as parallel reactions under identical conditions but using the parent α,β-unsaturated ketones or esters instead proceed sluggish and/or with poor stereoselectivity. A series of trivial chemical manipulations of the ketol moiety in adducts can produce the corresponding carboxy, aldehyde, and ketone compounds under very mild conditions, giving access to a variety of enantioenriched densely functionalized building blocks containing a fully substituted carbon stereocenter. A computational investigation to rationalize the mode of substrate activation and the reaction stereochemistry is also provided, and the proposed models are compared with related systems in the literature.



INTRODUCTION

Catalytic asymmetric conjugate addition reactions account as one of the most useful and atom economic approaches for the construction of new C−C and C−X bonds stereoselectively.[1] Major advances in the field have been triggered by the design and discovery of new chiral catalysts, both metal catalysts and organocatalysts, often in conjunction with the development of appropriate Michael acceptor templates.[2] The templates not only should provide gained chemical versatility to the resulting conjugate addition adducts, but also should contribute to attain optimal performance by the intervening catalyst in terms of reactivity and stereoselectivity. Ideally, strongly biased achiral templates may override otherwise observed substrate-dependent catalyst behavior, thus attenuating undesired fluctuations on the catalyst efficiency. This aid from properly design templates may result instrumental when difficult transformations, such as the enantioselective generation of tetrasubstituted carbon stereocenters, are pursued.

Among several categories of Michael acceptors, α,β-unsaturated carbonyl compounds are of prime synthetic significance. Adducts resulting from the conjugate addition of a nucleophilic reagent to α,β-unsaturated aldehydes, ketones, or carboxylic acid derivatives have all found a myriad of applications. In particular, certain carboxylic acid derivatives may afterward be converted into the corresponding aldehyde or ketone derivatives smoothly, making the former very versatile compounds. However, while both the addition reactions to α,β-unsaturated aldehydes and to ketones are well suited for iminium ion activation catalysis,[3] conjugate addition to the corresponding carboxylic acids and their derivatives is not. In this latter case, the most common activation mechanism relies upon coordination of the carbonyl group of the α,β-unsaturated carboxylic acid derivative to a Lewis acid (metal catalysis) or a H-bond donor species (organocatalysis). In this context, several two-point binding enoyl templates bearing an additional coordinating site (X, Figure 1a) tethered to the enoyl system have been developed. Compared with monodentate templates, which may lead to two degenerate C═O···metal complex geometries, thus complicating stereocontrol, bidentate templates can form chelates upon coordination to the metal as key organizational/activation element.[4] Similarly, bidentate enoyl

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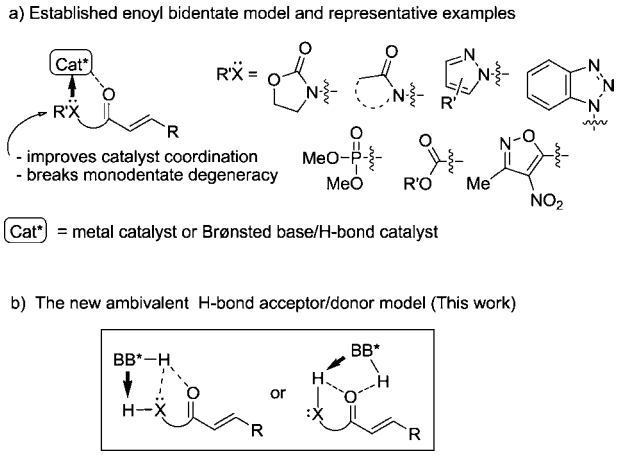

Figure 1. Bidentate enoyl templates for asymmetric catalysis: (a) previously established and (b) the new proposal. (BB* = chiral Brønsted base.)

templates may perform superiorly in conjugate addition reactions triggered by bifunctional Brønsted base–H-bond catalysts, because of the likely occurrence of double H-bond interactions between the substrate and the catalyst (Figure 1a).[1,5] This type of Brønsted base catalysis has emerged as very advantageous, not only because many Brønsted bases (BB) are commercially available and/or readily accessible, but also because the pronucleophilic reagent (NuH) does not generally need to be preactivated in a separate step.[6] However, successful BB-catalyzed enantioselective *C*–*C* bond forming conjugate addition reactions are often limited to certain inherently reactive nucleophiles (particularly 1,3-dicarbonyl compounds) and/or electrophiles (particularly nitroalkenes),[7] while in many other instances, α,β-unsaturated esters being a notable example, sluggish reactivity or poor enantiocontrol is achieved. This situation becomes more problematic when generation of all-carbon quaternary stereocenters is pursued.[8] Both reactivity attenuation by steric constraints and difficulties in controlling face selectivity in prostereogenic trisubstituted trigonal centers make this goal to be a hot topic yet.

In this study, we describe a new enoyl template model for asymmetric organocatalysis in which the bidentate substrate might engage as either H-bond donor or acceptor or both (ambivalency) during activation by the bifunctional catalyst (Figure 1b). As representatives of such a model, we show that α'-hydroxy enones perform exceedingly well in the Brønsted base-catalyzed asymmetric conjugate addition of a range of soft *C*-nucleophiles leading to tetrasubstituted carbon stereocenters in very high enantioselectivity. The chemical versatility of thus obtained adducts is also illustrated and a theoretical interpretation of the results provided.

RESULTS AND DISCUSSION

Background and Working Hypothesis. While being a prominent synthetic operation toward 1,5-dicarbonyl frameworks, successful catalytic and asymmetric methods for the constructive assembly of all-carbon quaternary centers from monodentate α,β-enones are usually restricted to 1,3-dicarbonyl substrates and related active pronucleophiles. In this context, metal-catalyzed[9] enantioselective conjugate addition of 1,3-diketones, β-ketoesters, and α-aryl cyanoesters to acrolein or vinyl ketones (mainly methyl vinyl ketone) as the Michael acceptor have been reported by the groups of Ito,[10] Shibasaki,[11] Sodeoka,[12] and Jacobsen,[13] among others.[9]

In concurrent efforts under metal-free conditions, chiral Brønsted base-catalyzed conjugate additions of enolizable carbonyl compounds have also been explored after the pioneering work by Wynberg and co-workers.[6,14] Deng and co-workers have reported conjugate additions of α-substituted β-dicarbonyl compounds and α-aryl cyanoacetates to acrolein or methyl vinyl ketone promoted by a bifunctional Cinchona based catalyst,[15,16] while Jørgensen and co-workers documented the reaction of cyclic β-keto esters with both acrolein and methyl vinyl ketone using a nonbiaryl atropisomeric Cinchona-based catalyst.[17] More recently, Rodriguez, Constantieux, and co-workers[18] extended the Brønsted base catalysis approach to cyclic β-ketoamides as nucleophiles against methyl vinyl ketone. Notwithstanding these achievements, the realization of BB-catalyzed asymmetric conjugate additions involving more reluctant substrate combinations, such as less reactive enolizable carbonyl compounds and acryloyl equivalents, remains challenging. Thus, while some ester surrogates have been applied to Brønsted base-catalyzed conjugate addition reactions,[5] to the best of our knowledge, only in three cases the generation of all-carbon quaternary centers has been documented. In a significant work, Dixon and Rigby[5m] described highly enantioselective conjugate additions of cyclic β-keto esters to naphthyl thioacrylate and *N*-acryloyl pyrrol, respectively, using a modified cinchona alkaloid as bifunctional Brønsted base catalyst. When acyclic keto esters were used as nucleophiles, yields and selectivity diminished, a limitation also noticed by Bartoli, Melchiorre and co-workers[5n] who used maleimides as competent Michael acceptors. Also, β,γ-unsaturated acyl phosphonates[5f] have been reported to be effective enoate surrogates against reactive pronucleophiles including azlactones and 1,3-dicarbonyl compounds.

In the early 1980s Heathcock and co-workers demonstrated that α'-hydroxy ketones are convenient enoate equivalents in the context of aldol addition reactions,[19] since oxidative cleavage of the ketol moiety in the corresponding aldol adducts affords β-hydroxy carboxylic acids. Focused on this observation, research from these laboratories has led to the development of metal-catalyzed conjugate addition and cycloaddition reactions of simple α'-hydroxy enones,[20] as well as Brønsted acid-catalyzed Diels–Alder reactions of chiral α'-hydroxy enones,[21,22] methods that provide, after cleavage of the ketol moiety, products in the carboxylic acid oxidation state. In these developments, the ability of the ketol moiety for both 1,4-metal and 1,4-proton binding (Figure 2a)[23] revealed to be critical for success. Based on these precedents, we hypothesized that the H-bonding ability of the ketol moiety in α'-hydroxy enones may decisively influence reactions initiated by a proton-transfer event, such as the BB-catalyzed Michael reactions (Figure 2b).[24] Specifically, the substrate α'-hydroxy enone might participate as a two-point H-bond donor/acceptor (DA-model) or acceptor/acceptor (AA-model) partner in the transition state, a diverting design element that is lacking in previous enoyl templates.[5] To the best of our knowledge, α'-hydroxy enones have not been studied within the context of organocatalytic asymmetric bond-construction processes.[25,26]

Preparation of α'-Hydroxy Enones. The α-oxy enones **1** and **3** were readily prepared[27] from the addition of lithium methoxyallene **6** to acetone and 1,3-diphenylacetone **8**, respectively, and subsequent smooth one-pot hydrolysis of the resulting intermediates, as shown in Scheme 1. Alter-

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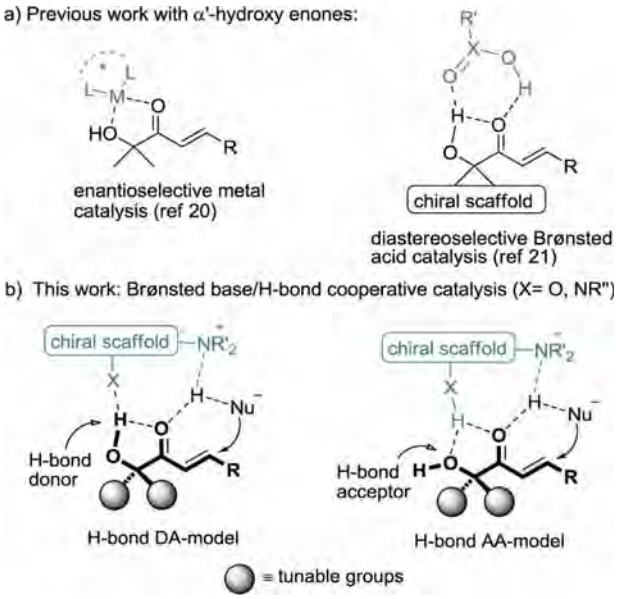
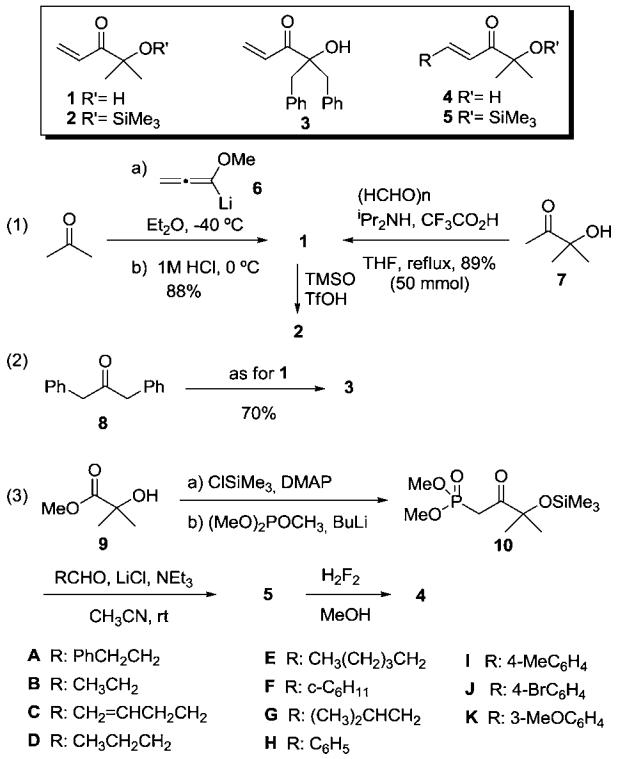


Figure 2. Two point binding α′-hydroxy enone templates for asymmetric catalysis.

Scheme 1. Preparation of α′-Hydroxy Enones[a]



[a]TMSO: *N*-(trimethylsilyl)-oxazolidin-**2**-one.

natively, enone **1** could also be prepared by the method of Connell et al.,[28] starting from the commercially available α-hydroxy ketone **7**. In both cases, compound **1** was obtained in yields between the range 80−90% at 50 mmol scale. Preparation of **2** from **1** is straightforward and quantitative by silylation with commercial *N*-trimethylsilyl oxazolidin-2-one (TMSO). For β-substituted enones **5**, the classical Horner−Wadsworth−Emmons olefination protocol from the β-keto phosphonate **10** was used. This phosphonate was in its turn prepared from commercial hydroxyester **9**.[29] Likewise, for β-aryl substituted α-hydroxy enones **4** (R = Ar), an aldol condensation of **7** with benzaldehydes may also be employed.[27]

Conjugate Additions of 3-Substituted Oxindoles. To assess the reactivity profile of these α′-hydroxy enones in Brønsted base catalysis, our study was initiated with the reaction of α′-hydroxy enone **1** and 3-substituted oxindoles. The oxindole structural motif is widely present within natural and synthetic bioactive molecules;[30] however, Brønsted base promoted reaction of 3-substituted oxindoles with alkyl vinyl ketones has met with limited success so far.[31,32] For example, it has been reported that methyl vinyl ketone (MVK),[31a,b] ethyl vinyl ketone,[31a] and phenyl vinyl ketone[31a] all provided enantiomeric excess (ee) values in the range of 60−70% in the reactions with 3-aryl oxindoles; the reactions with 3-methyl-, 3-isobutyl-, and 3-allyl oxindoles proceed with even lower ee's (of about 55%).[31c] In addressing these issues, and after screening several Brønsted base catalysts,[27] we found that the above addition reactions using **1**, conducted in the presence of 10 mol % $(DHQD)_2PYR$ (**C1**), afforded the corresponding adducts **12** in excellent yields and enantioselectivities. As the data in Table 1 show, under these conditions (−50 °C in $CHCl_3$ as solvent), oxindoles **11A−F** bearing 3-aryl substituents with either electron donating or electron withdrawing groups are tolerated with almost equal efficiency. Oxindoles with substitution at the aromatic ring also provided adducts with excellent chemical and stereochemical results. Likewise, the 3-methyl oxindoles **11Ga**, **11Gc**, and **11Gd**, which are valuable precursors of natural products, vide infra, were competent reaction partners to give the respective adducts **12Ga**, **12Gc**, and **12Gd** in good yields and enantioselectivities, typically 90% ee. Nevertheless, attempts to further expand this reaction to oxindoles bearing larger alkyl chains at the C3 position failed. Oxindoles **11H**, **11I**, **11J**, **11K**, and **11M** all provided the corresponding adducts **12** with poor enantioselectivity, typically 50% ee. While these results seem to be quite common for reactions involving 3-alkyl substituted oxindoles, very few attempts to address this deficiency have resulted with success.[32] In fact, few catalytic systems work well for both aryl- and alkyl-substituted oxindoles.[32d] Given the ready availability of α′-hydroxy enones, we focused on the α′-disubstitution pattern as an additional element for steric tuning. We were pleased to observe that the enantioselectivity was notably increased, typically from 50% ee up to 90% ee, by using α′-hydroxy enone **3**. As the results in Table 1 show, the reactions were tolerant with oxindoles bearing short, large, and ramified alkyl chains as well as alkyl chains with functional groups. These results are of special interest in that diverse functionality may be generated from a single common adduct. Thus, treatment of adducts **12Aa** and **12Gc** with $NaIO_4$ in $MeOH/H_2O$ provided the corresponding carboxylic acids **14** in yields of 98% and 94%, respectively, along with acetone as the only organic side product formed, Scheme 2. Alternatively, oxidative cleavage of adducts **13La** and **13Oa**, by treatment with periodic acid in this case, led to acids **14La** and **14Oa** in 87% and 90% yield, along with dibenzyl ketone which could be recovered and reused. On the other hand, the addition of the corresponding Grignard reagent or reduction of the carbonyl group followed by diol cleavage as above furnished the methyl and aryl ketones **15**/**16** and the aldehyde **17**, respectively, in good yields. Importantly, during the above manipulations, configurational integrity of

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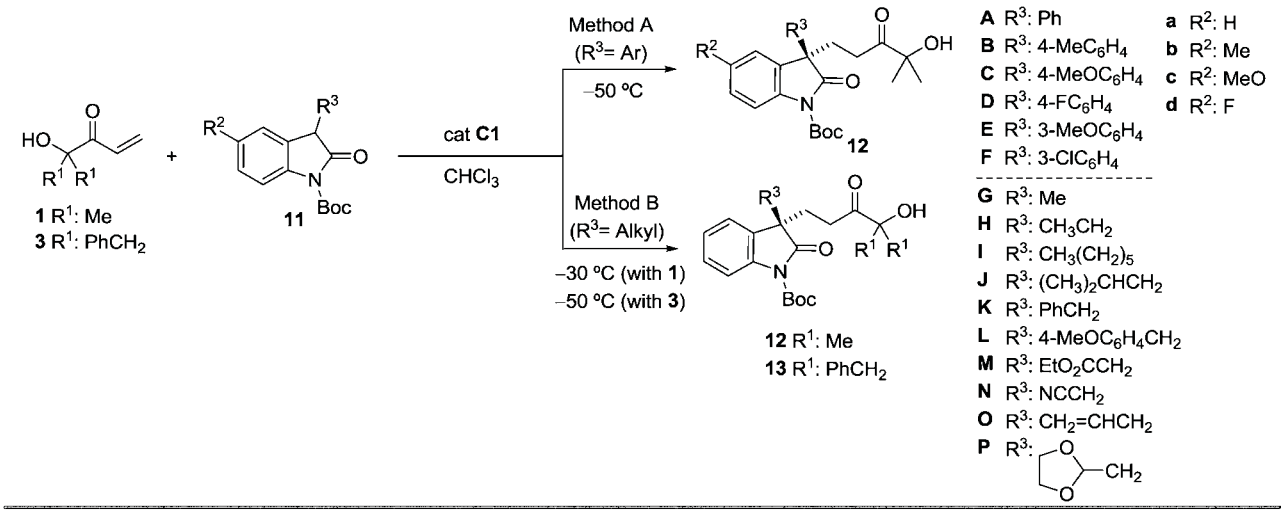
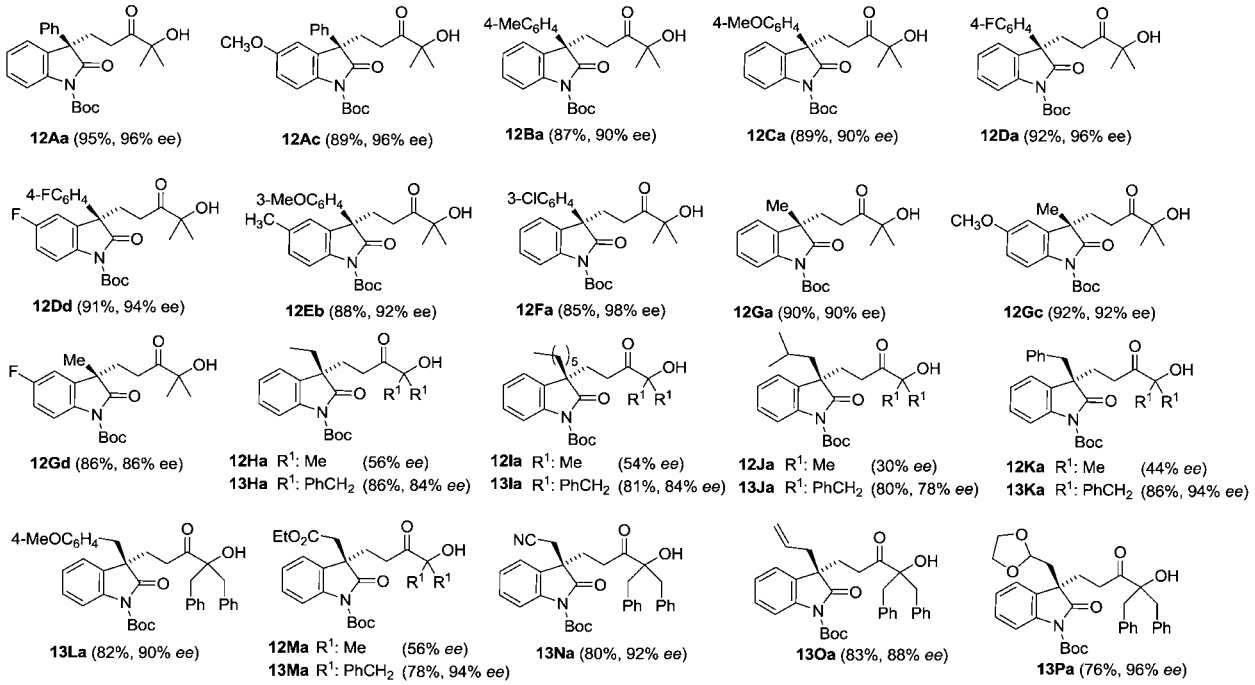
Table 1. Conjugate Additions of 3-Substituted Oxindoles to α'-Hydroxy Enones 1 and 3[a]





[a]The reactions were generally performed on a 0.30 mmol (for R^3 = Ar or Me) or 0.1 mmol (for R^3 = alkyl) scale in $CHCl_3$ (1.5 mL/mmol) using enone **1** (1.5 equiv) or **3** (3 equiv) and catalyst **C1** (10 mol % for **1**; 30 mol % for **3**). Yield of isolated product after chromatography. ee determined by HPLC analysis on chiral stationary phases.

newly generated tetrasubstituted stereogenic carbons in adducts was untouched as determined for aldehyde **17Aa** (94% ee) and acid **14Gc** (90% ee as determined in esermethole, vide infra). It is worth noting that the present method allows preparation of ketones such as **15Ga** and **16Ga**, formally derived from the less sterically demanding methyl-sustituted oxindoles, with enantioselectivities among the best reported until now.[31]

In addition, as far as we know, no asymmetric and catalytic conjugate addition of 3-substituted oxindoles to acrylate esters or their surrogates have been developed yet.[30,33] Our method may serve to remediate this deficiency by providing building blocks that can be easily transformed into biologically active compounds such as (−)-esermethole, Scheme 3,[34] an advanced intermediate for the synthesis of (−)-physostigmine.[35] Thus, Curtius rearrangement of carboxylic acid **14Gc** afforded carbamate **18**, which upon treatment with $LiAlH_4$ underwent reductive cyclization to (−)-esermethole of 90% ee.

The key role played by the $(CH_3)_2COH$ fragment of the template as a traceless activating group in the above reactions was clear from competitive experiments involving both **1** and methyl vinyl ketone (MVK), a simple enone lacking any group for additional H-bond coordination. Thus, when the reaction of oxindole **11Aa** was carried out with a 1:1 mixture of **1** and MVK in the presence of **C1** (10 mol %) at −50 °C, **12Aa** was the exclusive addition product obtained, without detecting any product from the addition reaction of **11Aa** to MVK. In

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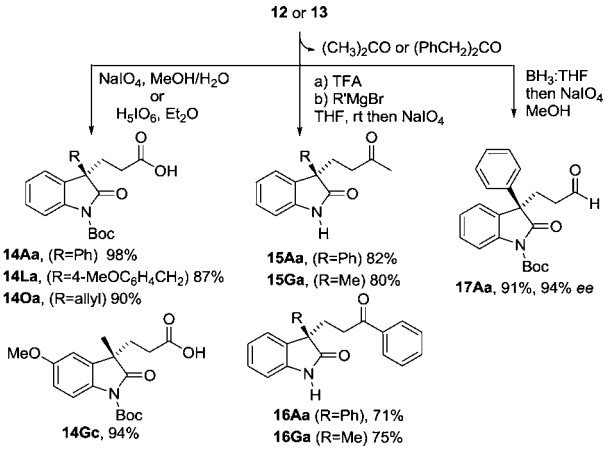
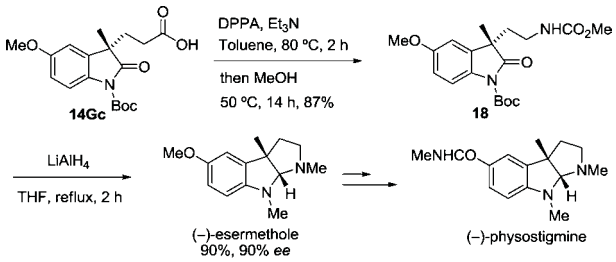
Scheme 2. Ketol Scission in Adducts 12



Scheme 3. Short Enantioselective Synthesis of (−)-Esermethole



another experiment, the reaction between oxindole **11Aa** and MVK run at −30 °C in the presence of **C1** led, after 48 h, to 35% conversion only, with an isolated product of 50% ee.

Conjugate Additions of Cyanoacetates. Encouraged by these results, we next investigated the reaction of α′-hydroxy enones with α-substituted cyanoacetates.[36,37] The problems experienced in achieving efficient chirality transfer in metal catalyzed conjugate additions with these pronucleophiles have been ascribed to the fact that cyanoacetates are incapable of two-point binding.[38] We reasoned that the capacity of α′-hydroxy enones for two-point binding (Figure 2) may ameliorate this deficiency. Indeed, we found that **1** was effective in the Brønsted base catalyzed reaction with not only α-aryl, but also α-alkyl cyanoacetates, a subclass of substituted cyanoacetates previously documented to be poorly reactive substrates,[37] particularly against alkyl vinyl ketones.[37a] After evaluation of a survey of different Brønsted bases, including **C1**, the squaramide family of catalysts pioneered by Rawal and co-workers[39] probed the most effective in these instances. Among them, catalyst **C2**[40] (Figure 3) resulted optimal for the reaction between **1** and a range of both α-aryl and α-alkyl *tert*-butyl cyanoacetates **19**. In general, the reaction with α-aryl cyanoacetates **19a−d** was performed at room temperature using 3 equiv of enone **1** to afford, after 1 h, adducts **20a−d** with excellent yields independently of the nature of the aromatic ring substitution. In contrast, most α-alkyl cyanoacetates tested showed decreased reactivity with reaction times of about 120 h required for complete conversion under the above conditions. However, by using 3-fold excess of the latter and rising the temperature to about 50 °C, full conversions of products **19e−k** were attained within about 30 h

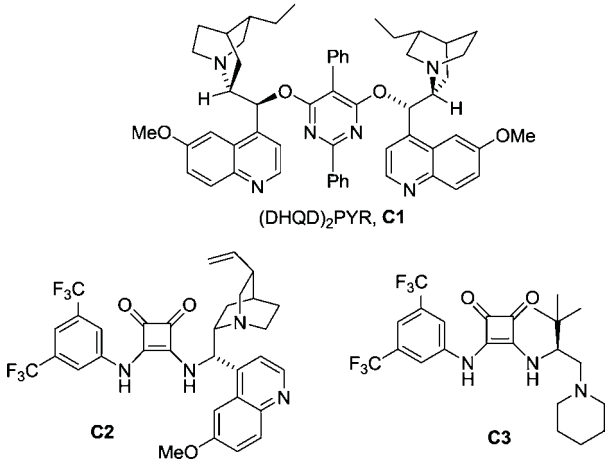


Figure 3. Catalysts employed within this work.

or less, with very high yields of isolated product and essentially perfect enantioselectivity obtained. Again, chemical manipulation of the ketol unit in adducts **20** using simple Grignard technology and/or reduction/oxidation protocols, as in Scheme 2, provided a straightforward entry to the corresponding carboxylic acids **21**, aldehydes **22**, and ketones **23**/**24**. Comparison of optical rotation value of product **23e** (see Table 2, footnote b) with literature data[10] served to set the configuration of the products and hence the stereochemical course of the above catalytic reactions. As noted above enantioselective synthesis of products like **21−24** through direct catalytic Michael reactions remains challenging. Once more, the design enone **1** demonstrated to be instrumental in achieving these levels of reactivity and selectivity. For example, when an equimolar mixture of cyanoacetate **19a**, enone **1**, and MVK was stirred at 20 °C for 30 min in the presence of 10 mol % **C2**, a 12:1 mixture of **20a** and the addition adduct from MVK, respectively, was obtained. Likewise, parallel reactions of other typical Michael acceptor templates, i.e. *N*-acryloyl oxazolidinone or *N*-acryloyl pyrazole, with cyanoacetate **19e** under the above conditions were sluggish (less than 55% conversion after 120 h at room temperature for the two cases).

Conjugate Additions of Heteroatom-Bearing Soft Carbon Nucleophiles. Besides all-carbon quaternary stereocenters, tetrasubstituted stereogenic carbons bearing a sulfur, oxygen or nitrogen heteroatom are also interesting yet difficult products to obtain as single enantiomers. Therefore, we decided to investigate the capacity of our template model to participate in Brønsted base-catalyzed conjugate additions of several heteroatom-bearing soft carbon nucleophiles. For this study 5*H*-thiazol-4-ones **25**[41] and 5*H*-oxazol-4-ones **26**[42,43] were initially selected and we found that reaction of thiazolone **25a** and oxazolone **26a** with α′-hydroxy enone **1** did proceed in the presence of several Brønsted bases, including **C1** and **C2**, but with very poor enantioselectivity. Further exploration led us to examine the modified enoyl template **2**, prepared by simple silylation of the hydroxyl group in enone **1**. To our pleasure, the reaction of 5*H*-thiazol-4-ones **25** and enone **2** catalyzed by **C2** in dichloromethane at −20 °C provided, after desilylation of the resulting intermediates, the corresponding addition products **27** in good yields and ee's up to 98%. The parent 5*H*-oxazol-4-ones **26** participated with equal chemical efficiency in the reaction with enone **2**. For example, under the above conditions, **26a** provided **28a** in 85% yield albeit in 73% ee.

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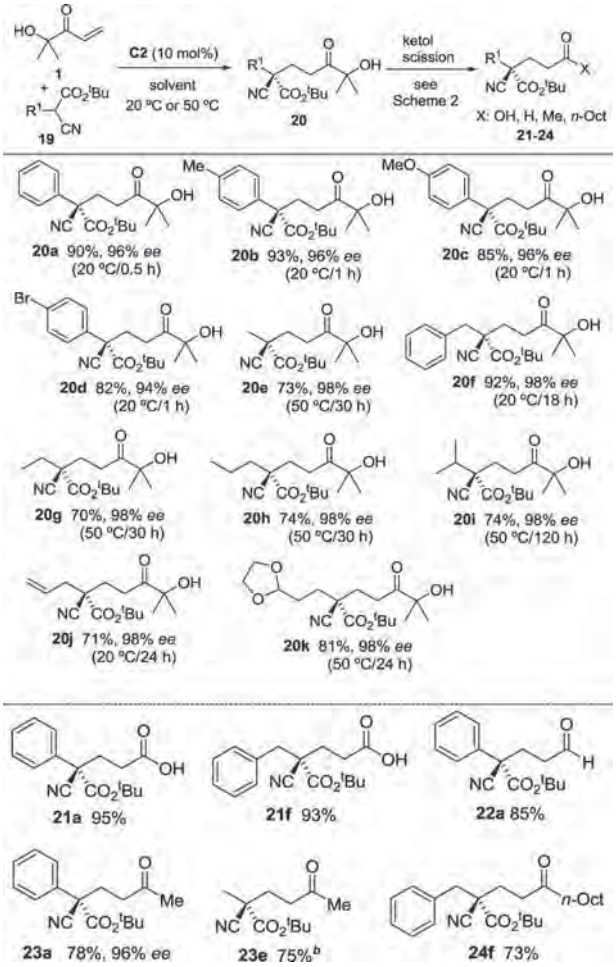
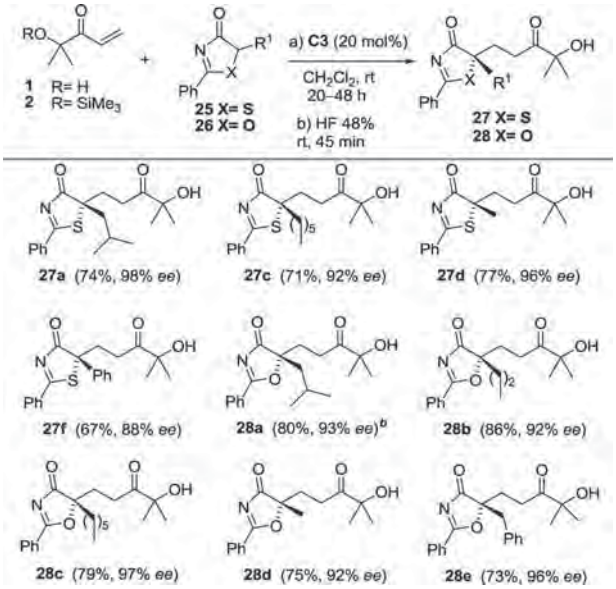
Table 2. Conjugate Addition of α-Substituted *tert*-Butyl Cyanoacetates 19 to α′-Hydroxy Enone 1 Promoted by C2[a]



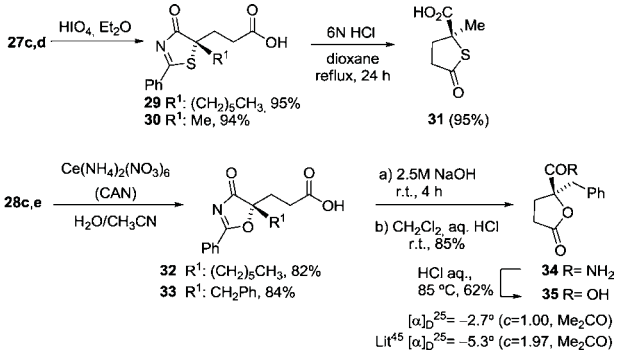
[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 at 20 °C or in $CHCl_3$ at 50 °C. Yield of isolated major isomer after chromatography. ee determined by HPLC. [b]$[\alpha]_D^{22}$ = +3.9 (*c* = 1, $CHCl_3$); lit.[10] $[\alpha]_D^{20}$= +2.7 (*c* = 5, $CHCl_3$, 81% ee).

Table 3. Conjugate Addition of 5*H*-Thiazolones 25 and 5*H*-Oxazolones 26 to α′-Silyloxy Enone 2[a]



[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.9 mL) using 1.5 equiv of enone **2**. For thiazolones **25**, reactions were conducted at −20 °C and for oxazolones **26** at rt. Yields after chromatography. ee determined by HPLC. [b]73% ee from catalyst **C2**.

Scheme 4. Elaboration of Thiazolone and Oxazolone Adducts 27 and 28



This result was further improved by using catalyst **C3**[44] (Figure 3), and the reaction between **2** and oxazolone **26a** performed at room temperature afforded, after desilylation of the resulting intermediate, adduct **28a** in 80% yield and 93% ee.

In general, excellent yields and enantioselectivities were achieved for a survey of thiazolones and oxazolones bearing either short, large, or ramified alkyl chains at the heterocyclic ring (Table 3). While these reactions were typically carried out in the presence of 20 mol % of catalyst, the catalyst loading could be reduced to 10 mol % provided the reactions were carried out at higher temperature. For example, products **28a** and **28b** were obtained in essentially same chemical yields and stereoselectivities as above when the corresponding reactions were performed in $CHCl_3$ at 40 °C during 30−40 h. Clearly, these results show that the α′−hydroxy enone template may be easily modified to better adapt to different substrate/catalyst combinations.

Transformation of adducts **27** and **28** into the corresponding carboxylic acids **29**, **30**, **32**, and **33**, Scheme 4, was easily achieved by treatment with periodic acid in the case of thiazolone adducts **27**, and with cerium ammonium nitrate (CAN) in the case of oxazolones **28**. Subsequent transformation of adduct **30** into the thiolactone **31**, as well as adduct **33** into the lactone derivative **34**, by simple ring opening under mild acid and/or basic conditions, illustrates the utility of the method. In addition, formation of known lactone **35**[45] from **34** served to establish the stereochemical course of the reactions. It should also be noted that both **25a** and **26a** upon treatment with either methyl acrylate or *tert*-butyl acrylate under the above conditions did not provided the corresponding Michael adducts.

Further exploration of the broad scope of α-silyloxy enone **2** showed that α-substituted azlactones, 4*H*-oxazol-5-ones, also fit well. For example, Table 4, the reaction between azlactones **36** and enone **2** in the presence of the catalyst **C2** or **C3** led, after desilylation of the intermediate adducts, to the corresponding products **37** with good yields and ee's. In each case, reactions proceeded with high site selectivity and no products from

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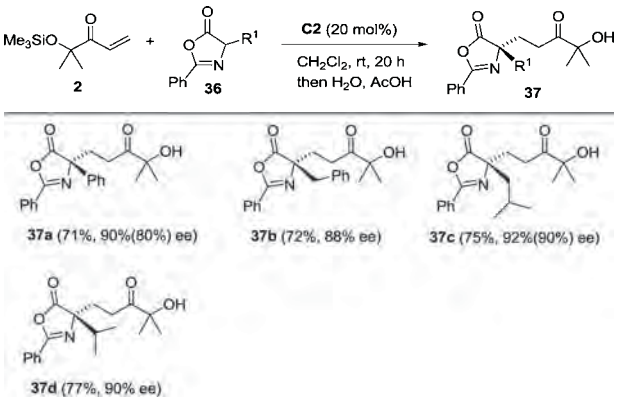
Table 4. Conjugate Addition of Azlactones[a]

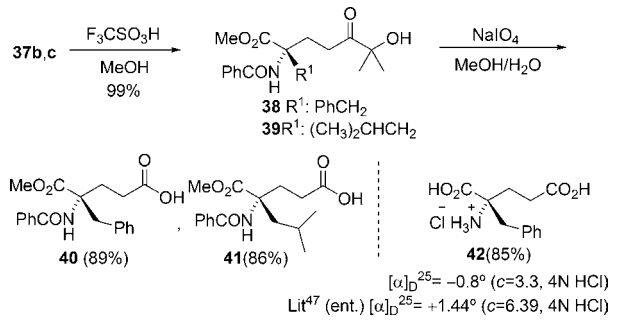


[a]The reactions were performed on a 0.30 mmol scale in CH_2Cl_2 (0.6 mL) using 3.0 equiv of enone **2**. Yield of isolated products after chromatography. ee determined by HPLC. In parentheses are ee's from catalyst **C3** (10 mol %).

reaction at the C_2-position of the azlactone ring were observed.[46]

Elaboration of thus obtained azlactone adducts afforded useful building-blocks. For instance, Scheme 5, azlactone ring

Scheme 5. Elaboration of Adducts to α,α-Disubstituted Glutamic Acid Derivatives

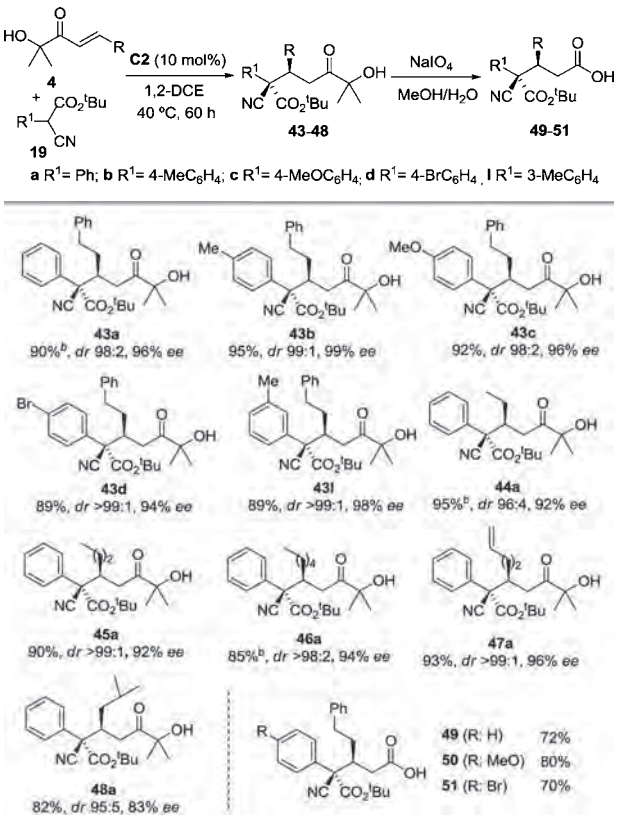


opening in **37b,c** to afford the corresponding compounds **38** and **39**, and subsequent ketol elaboration, provided acids **40** and **41**, respectively. The former was then transformed into the known glutamic acid derivative **42**[47] as a proof of the stereochemical course of the catalytic reaction.

Reactions with β-Substituted α-Oxy Enones: Generation of Adjacent Quaternary/Tertiary Stereocenters. Given the results attained with the α-oxy vinyl ketones **1** and **2**, we wondered whether this template model would be effective to generate a quaternary carbon adjacent to a tertiary stereogenic center, a synthetic task that generally presents added difficulties. To this end, we selected the reaction of α-substituted cyanoacetates owing to the inherent challenges associated with this kind of pronucleophiles, vide supra. In this context, Peters has recently addressed this issue and provided a solution to the case of reactions involving cyclic enones, that is, cyclohexenone, using metal catalysis.[38a] On the other hand, only one example of Michael reaction of α-substituted cyanoacetates with β-substituted alicyclic enones has been documented, based on salen complex catalysis.[38d]

It was gratifying to observe that α-aryl cyanoacetates **19a–d** and **19l** reacted with β-alkyl substituted α-hydroxy enones **4A–E** to furnish adducts **43–47** in good yields, Table 5. The reactions were carried out in 1,2-dichloroethane at 40 °C, and

Table 5. Conjugate Addition of Cyanoacetates to β-Substituted α-Hydroxy Enones[a]



[a]The reactions were performed on a 0.30 mmol scale in 1,2-DCE (1.2 mL) using 3.0 equiv of enone **4**, at 40 °C otherwise stated. Yield of isolated products after chromatography. ee determined by HPLC. dr determined by ^{1}H NMR or HPLC. [b]Reaction carried out at 50 °C.

generally essentially one diastereomer was produced in excellent enantiomeric excess. As exceptions, β-substituted enones **4F** and **4H**, bearing the cyclohexyl and phenyl groups, respectively, were ineffective under these conditions, while **4G** provided **48a** in good yield but diminished stereoselectivity. On the other hand, α-alkyl cyanoacetates were unreactive and did not provide the corresponding adducts. Despite these limitations, which, in their turn, confirm the difficulties associated with these problematic pronucleophiles, the method represents the first Michael addition of α-substituted cyanoacetates to β-alkyl enones catalyzed by a chiral Brønsted base, and confirms once more the excellent behavior of α′-hydroxy enones as Michael acceptors. In this respect, while no reaction was observed from **19a**, **19c**, and **19d** with methyl 5-phenylpent-2-enoate in the presence of **C2**, oxidative cleavage of **43a**, **43c**, and **43d** provided the desired carboxylic acids **49–51**. We also examined the **C2** catalyzed reaction between cyanoacetate **19a** and *trans*-3-nonen-2-one **52**, which lacks the α′-hydroxy group (Scheme 6). The reaction proceeded, but required 7 days to reach 95% of conversion and the product was formed as an 80:20 mixture of diastereomers with only modest enantioselectivity for the major isomer **53**. In sharp contrast, the reaction between **19a** and α′-hydroxy enone **4E**, as

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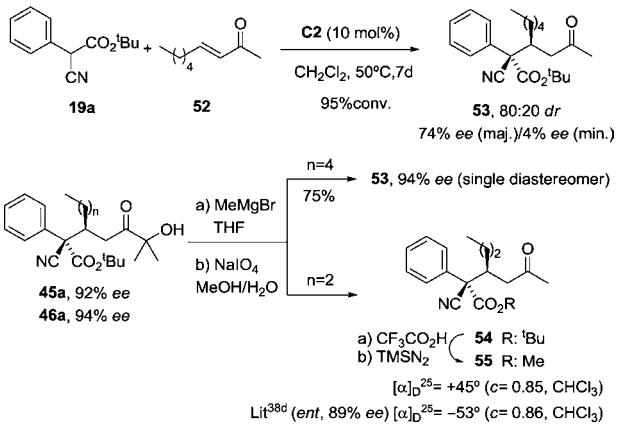
Scheme 6. Conjugate Addition of α-Substituted Cyanoacetates to Simple Enones and an Indirect Solution to the Low Inherent Stereoselectivity

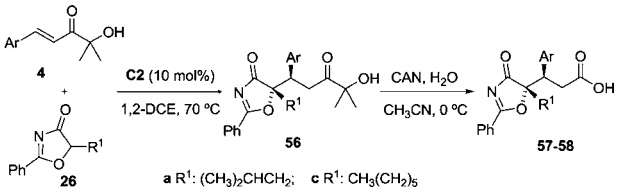


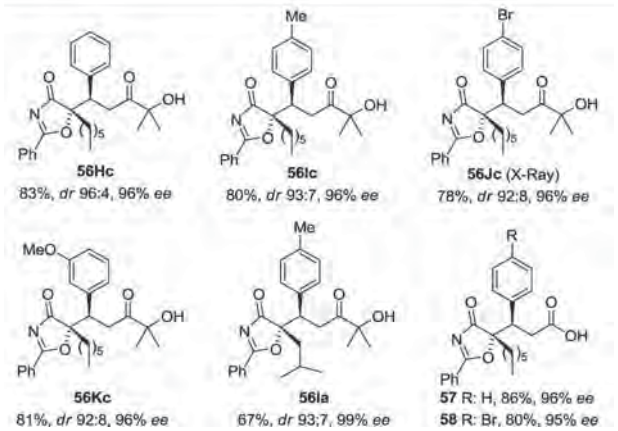
mentioned above, gave **46a** as essentially single diastereomer in 94% ee (Table 5), which enables an alternative and highly stereoselective entry to product **53** via usual alkylation and oxidative scission. Similarly, **45a** could be converted into the methyl ketone **54** and, upon subsequent transesterification, the corresponding methyl ester **55**, which exhibited essentially identical ^{1}H and ^{13}C NMR spectra to those reported in the literature,[38d] but opposite optical activity, thus confirming the stereochemical assignments for the adducts.

Oxazolones **26** also participated in the reaction with β-substituted enones **4** to give the corresponding α,α-disubstituted α-hydroxy acid precursors with an adjacent tertiary stereocenter, Table 6. However, in contrast to the case of cyanoacetates noted above, the reactions of oxazolones **26** worked well only with β-aryl enones to afford the corresponding addition products **56**. The reactions with β-alkyl enones were unproductive and the starting materials could be recovered unchanged. From these results, it is clear that for these types of substrate combinations leading to adjacent quaternary/tertiary stereocenters, there might be strong steric interactions that may justify the observed variability. Configuration of adduct **56Jc** was established by a single crystal X-ray analysis and that of the remaining adducts by assuming a uniform reaction mechanism. Additionally, conversion of **56** into the carboxylic acids **57** and **58** could be accomplished by using CAN as the optimum oxidant.

Computational Studies. With these experimental data in hand, it seemed clear that α'-oxy enones exhibit some unique reactivity as compared with ordinary enones, that is, MVK. Both higher reactivity and improved levels of enantioselectivity are observed in the BB-catalyzed reactions studied. Similarly, our experimental results indicate a distinct behavior of α'-oxy enones as compared with other typical enoyl templates previously reported for the BB-catalyzed enantioselective generation of quaternary stereogenic carbon centers. More specifically, the catalyst-controlled conjugate addition of α-substituted cyanoacetates is, as mentioned before, sluggish with the majority of Michael acceptors, while it works well with α'-oxy enones. With the aim to bring some light on such distinguishing behavior, we decided to study computationally[48] the case of the conjugate addition reactions of cyanoacetates. MVK and the two α'-oxy enones **1** and **59** were selected as the model Michael acceptors, and the relationship between their

Table 6. Conjugate Addition of Oxazolones to β-Substituted α-Hydroxy Enones[a]





[a]The reactions were performed at 70 °C on a 0.15 mmol scale in dichloroethane (0.45 mL) using 3.0 equiv of enone **4**. Yield of isolated products after chromatography. Diastereomeric ratios determined by ^{1}H NMR (300 MHz) on the crude reaction products and confirmed by HPLC. ee determined by HPLC analysis on chiral stationary phases (for compounds **57** and **58**, after derivatization to their methyl esters).

reactivity and structure was examined first. In agreement with our working hypothesis, calculations show that the intramolecular H-bond activation in **1** and **59** induces a change in a series of electronic parameters (Figure 4), explaining their higher reactivity in comparison with MVK. In particular, the electrophilicity index ω[49] for both **1**/**59** (2.0 eV) is higher than that for MVK (ω = 1.6 eV), which is consistent with the lower energy of LUMO for **1** and **59** (−1.9 eV) as compared with the LUMO of MVK (−1.5 eV), and also the more positive

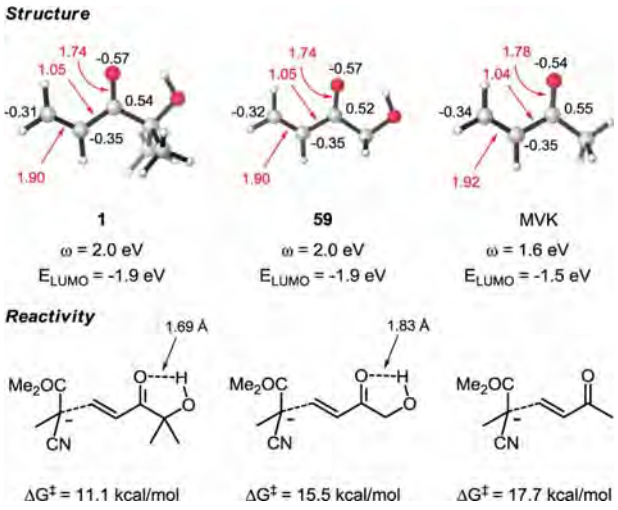


Figure 4. Structure−reactivity relationship.

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character of the β-carbon of **1** (NPA charge of −0.31) than the corresponding β-carbon of MVK (−0.34). These values correlate well with the Wiberg bond index for **1** (1.90) and MVK (1.92), respectively, indicating the diminished double bond character of the enone C═C bond in **1**.

Subsequently, the activation energy of the reaction of these three Michael acceptors with methyl α-methylcyanoacetate was computed. This barrier resulted significantly lower for α'-hydroxy enone **1** (11.1 kcal/mol) than for MVK (17.7 kcal/mol). On the other hand, although the electronic parameters of both α'-hydroxy enones **1** and **59** do not differ significantly from one another (see above), the reaction involving the latter presents an activation energy 4.4 kcal/mol higher than the reaction with **1**. This additional stabilization of the transition state (TS) for the reaction with **1** as compared with **59** is consistent with the shorter intramolecular hydrogen bond in the former case (1.69 vs 1.83 Å, Figure 1) and might be ascribed to a favorable Thorpe−Ingold effect[50] imparted by the two geminal methyl substituents in **1**.

The origin of the stereoselectivity in the **C2**-catalyzed reaction between hydroxy enone **1** and α-cyanoacetates was addressed next, and the first question to elucidate was the preferred H-bond pattern formed between the catalyst and both substrates in the TS corresponding to the *C*−*C* bond-forming step. In this respect, up to (at least) three different ternary complexes (**A**−**C**, Figure 5) have been proposed for

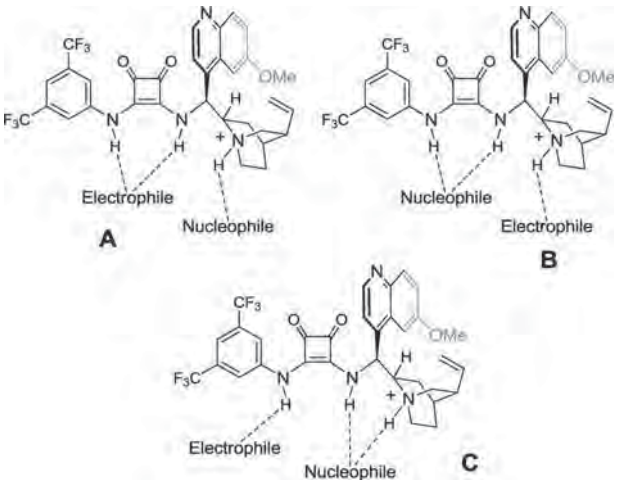

Figure 5. Three alternative substrate−catalyst combinations.

reactions involving noncovalent cooperative activation of the intervening nucleophile and electrophile, typically by a bifunctional thiourea (or squaramide)-tertiary amine catalyst.[51] Therefore, the question of whether or not a unified H-bond network model (**A**, **B**, **C**, other) could be applied to different reactions within this catalysis category seems to be still open and more data are desirable. In our case, we computed the reaction leading to adduct **20e** (Table 2), and despite much effort we were unable to find any plausible transition structure of type **B** among the several H-bond combinations studied.[52] From a look to the geometries of the resulting complexes, it seemed that once cyanoacetate is H-bonded to the catalyst there is not space available for the electrophile to interact with the same catalyst molecule. Thus, the structure closest to **B** we could find involves attack of the H-bonded cyanoacetate anion to the non complexed enone.[53] On the other hand, a single structure similar to model **C** was also found; however, it was predicted to be unrealistic due to its high activation energy.

In its turn, four feasible structures of type **A** (**TS-R$_1$**, **TS-S$_1$**, **TS-R$_2$**, **TS-S$_2$**, Figure 6) were located, in which the α'-hydroxy

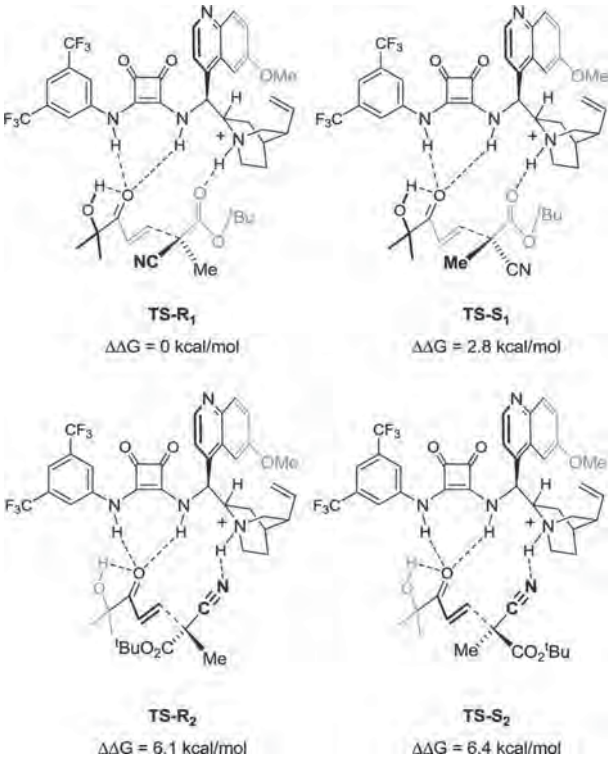

Figure 6. Located TSs for the catalytic addition reaction.

enone carbonyl is double H-bonded to the squaramide NH groups, while the protonated quinuclidine NH$^+$ might bind to either the CN or the ester group of the cyanoacetate moiety. **TS-R$_1$** is the lowest in energy and correctly explains the formation of the major isomer observed experimentally.[54] The next most feasible structure is **TS-S$_1$**. Interestingly, in both cases, the $CO_2{}^tBu$ is involved in H-bonding with the catalyst NH$^+$ moiety, while the methyl (**TS-S$_1$**) and the cyano group (**TS-R$_1$**) are, respectively, almost eclipsed with the enone double bond. The energy difference between these two structures is 2.8 kcal/mol at the M06-2X/6-311+G** computational level,[55] with the preference of **TS-R$_1$** being attributable to a larger destabilizing effect of pseudoeclipsed methyl (dihedral angle 21.9°) than pseudoeclipsed cyano (dihedral angle 33.5°). The remaining two structures, **TS-R$_2$** and **TS-S$_2$**, both involving a NH$^+$···NC interaction, lye 6.1 and 6.4 kcal/mol higher in energy than **TS-R$_1$**, respectively. From these results, some tentative conclusions may be drafted: (i) in the studied catalytic reactions, the ketol moiety of the acceptor α'-hydroxy enone plays a key role in both decreasing reaction energy barriers; (ii) among the several possible H-bond combinations for the ternary nucleophile−catalyst−electrophile complex, type **A**[51a−e] is preferred, with the squaramide group interacting with the α'-hydroxy enone (electrophile activation), and the protonated quinuclidine interacting with the cyanoacetate anion (nucleophile activation); (iii) given previous data in the literature in favor of models of type **B**[51f−k] and **C**[51l] for related catalytic reactions, we believe that a unified model cannot accommodate

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well for all reactions falling within this type of noncovalent bifunctional catalysis, and case to case analysis is required; (iv) calculations for our system confirms that H-bond with a nitrile group contributes poorly to TS stabilization as compared with H-bond to a ester group, probably due to the fact that linear arrangements, as in C≡N···HX, are more difficult to fit in the TS than angular arrangements, as in C═O···HX.[56] Eventually, the combination of these factors leads to the highly stereoselective formation of the new quaternary stereocenter in **20e**.

CONCLUSIONS

In summary, the highly stereoselective generation of tetrasubstituted carbons, including *C*−*N*, *C*−*O*, *C*−*S*, and all-carbon quaternary stereocenters, has been realized via bifunctional Brønsted base catalyzed Michael reaction of various types of hitherto challenging prostereogenic *C*-nucleophiles and α'-oxy enones as key enoate surrogates. Competitive and parallel experiments using simple enones (or esters) and the respective α'-oxy enones indicate that the α-oxy ketone moiety is crucial for achieving high levels of reactivity and stereoselectivity. The ability of α'-hydroxy enones to engage in H-bond networks as either donor or acceptor component (or both) was unknown in previous bidentate enoyl templates, and may in the future be exploited as a new design element in other organocatalytic asymmetric transformations. An additional noteworthy aspect of this design is that the *gem*-dialkylcarbinol framework of the template can be easily modified at both the carbon and oxygen sites, thus enabling easy template tuning for optimal performance. The resulting α-oxy ketone adducts can smoothly be converted into the corresponding aldehyde, ketone, or carboxylic acid derivatives through simple oxidative cleavage of the ketol unit. The present methodology thus provides access to synthetically relevant building-blocks bearing a fully substituted stereogenic carbon atom which were hitherto difficult to prepare in enantioenriched form. Studies toward broadening this methodology are currently underway.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization of compounds including NMR spectra, HPLC chromatograms, and X-ray ORTEP, as well as Cartesian coordinates of all computed stationary points, relative and absolute activation energies for all reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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