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CICLO XXX

Development of organocatalytic and stereoselective reactions

Settore scientifico-disciplinare: **CHIM/06**

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Abbreviations

e.g.	for example
ee	enantiomeric eccess
Ph	phenyl
NHC	*N*-heterocyclic carbene
eq.	equation
t-Bu	*tert*-butyl
Me	methyl
TFAA	trifluoroacetic anhydride
NMR	nuclear magnetic resonance
HBD	hydrogen bond donor
TADDOL	*α,α,α,α*-tetraaryl-1,3-dioxolane-4,5- dimethanol
PTC	phase-transfer catalysis
PT	phase-transfer
Ar	aryl
Et	ethyl
Ac	acetyl
6-APA	6-aminopenicillanic acid
ATPase	adenosinetriphosphatase
i-Pr	isopropyl
LTD4	leukotriene D4 receptor
PPTS	pyridinium *p*-toluene sulfonate
Ms	mesyl
THP	tetrahydropyran
MeOH	methanol
THF	tetrahydrofuran
EtOH	ethanol
PPAR*γ*	peroxisome proliferator-activated receptor gamma
p	*para*
Ts	tosyl
S_N2	nucleophilic substitution
DMAP	4-dimethylaminopyridine
Boc	*tert*-butyloxycarbonyl

TsOH	*p*-toluenesulfonic acid
MeCN	acetonitrile
MsOH	methanesulfonic acid
Nu	nucleophile
E	electrophile
Bn	benzyl
EtOAc	ethyl acetate
RT	room temperature
SMA	sulfa-Michael addition
mol	mole
cat.	catalyst
T	temperature
t	time
CPME	cyclopentyl methyl ether
dr	diastereomeric ratio
Et_2O	diethyl ether
DMSO	dimethyl sulfoxide
9-*epi*-QT	9-amino-(9-deoxi)-*epi*-quinine thiourea
epi	epimer
DCM	dichloromethane
Boc_2O	di-*tert*-butyl dicarbonate
DCE	1,2-dichloroethane
TFA	trifluoroacetic acid
ET(30)	electronic transition energy
h	hour
HPLC	high performance liquid chromatography
MS	molecular sieves
M	molar concentration
confing.	molecular configuration
TLC	thin layer chromatography
s	singlet
d	doublet
t	triplet
q	quartet

dd	double doublet
m	multiplet
b	broad
gCOSY	correlation spectroscopy
gHSQC	heteronuclear single-quantum correlation spectroscopy
TOCSY	total correlation spectroscopy
NOESY	nuclear overhauser effect spectroscopy
IR	infrared spectra
ESI	electrospray ionization
Et_3N	triethylamine
DMF	*N*,*N*-dimethylformamide
MS	mass spectrometry
R_f	retardation factor
m.p.	melting point
Opt. Rot.	optical rotation
API	active pharmaceutical ingredient
DET	diethyl tartrate
CHP	cumene hydroperoxide
DIPT	diisopropyl D-tartrate
m	meta
TBHP	*tert*-butyl hydroperoxide
HIV	human immunodeficiency virus
n-Bu_2O	dibutyl ether
c-Hex	cyclohexyl
Pr	propyl
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
P_1-*t*-Bu	phosphazene base P_1-*t*-Bu
P_4-*t*-Bu	phosphazene base P_4-*t*-Bu
Cy	cyclohexyl
TBAB	tetrabutylammonium bromide
conv.	conversion
ROESY	rotating frame nuclear overhauser effect spectroscopy

UPLC	ultra performance liquid chromatography

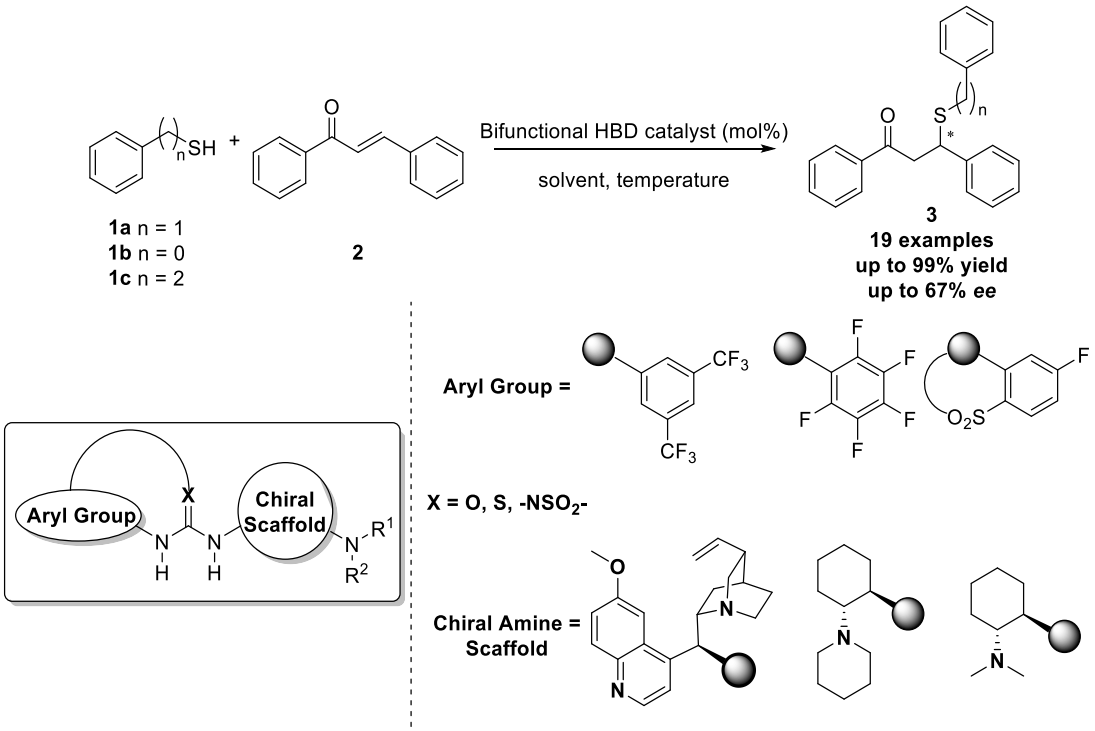
Abstract

The development of organocatalytic and stereoselective reactions is an attractive tool for the synthesis of chiral organic molecules. The benefits compared to the metal or organometallic and enzymatic catalysis are for example the potential for saving cost, time and energy, enabling easier reaction conditions, minimization in chemical waste and lack of metal impurities in the chemical compound.

The focus of this PhD thesis was the development of two organocatalytic and stereoselective reactions: the sulfa-Michael addition (SMA) and the Darzens condensation because they are interesting approaches for the synthesis of chiral drugs and, in the pharmaceutical industry, there are few Active Pharmaceuthical Ingredients (API) that are produced through stereoselective SMAs and Darzens reactions catalysed by organocatalysts. Accordingly the thesis is organized in two parts: the first one concerning the sulfa-Michael reactions and the second one in which the studies on the Darzens reaction are described. Each part is self-consistent and presents the introduction, the scope of the study, the description and critical discussion of the results, the conclusions and the detailed description of the synthetic procedures and the characterization data of the products. Moreover some representative spectra are reported at the end of each part. References are reported as notes at the end of each page. The list of abbreviations used in the thesis is reported at the beginning of the thesis.

In the field of sulfa-Michael addition (SMA), bifunctional hydrogen-bond donor (HBD) catalysis represents an approach for activating both the nucleophile and the electrophile reaction components. There are relatively few examples of stereoselective SMAs catalysed by bifunctional HBDs involving *trans*-chalcone (**2**) as Michael acceptor.

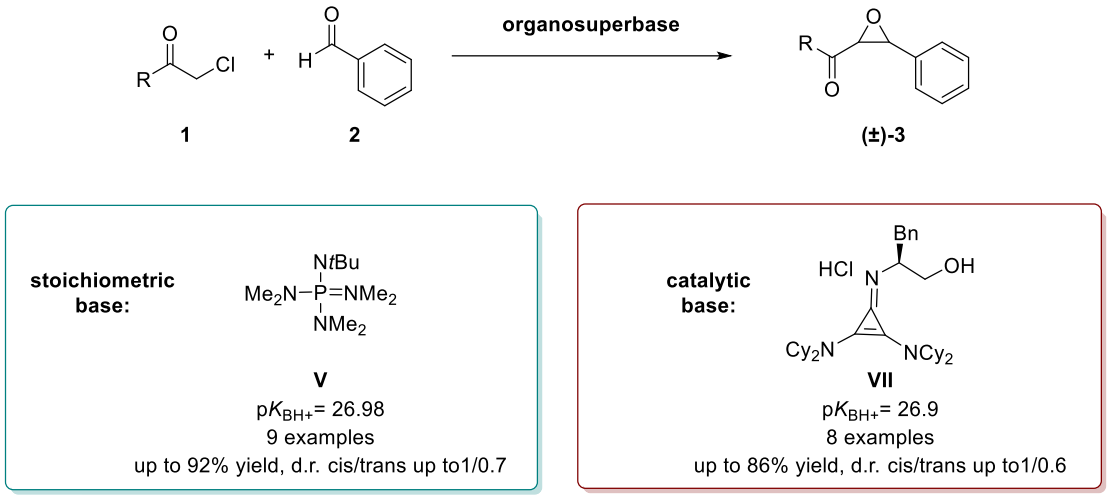
In the context of HBD catalysts optimization, a survey of literature reports suggests that increasing the acidity of the NH thiourea protons have beneficial effects on reaction rates of a number of catalysed reactions. Prompted by this information, the comparative analysis, in a single experimental setting, of some HBD catalysts in stereoselective SMAs to *trans*-chalcone (**2**) was performed, Scheme 1.



Scheme 1 Comparative analysis of some HBD catalysts in stereoselective SMAs to *trans*-chalcone (**2**) studied during the PhD.

We studied the effect of catalyst loading, solvent and temperature in the model reaction: the addition of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**). With the optimised conditions, we comparatively evaluated, in a single experimental setting, the activity of some popular HBD catalysts in the stereoselective SMA of benzenethiol (**1b**), phenylmethanethiol (**1a**) and 2-phenylethanethiol (**1c**) to *trans*-chalcone (**2**). Increasing the Brønsted acidity of the hydrogen bond donor unit gave, in some cases, faster reactions but had, in general, a negative impact on the stereoselectivity. The addition product **3b** of benzenethiol (**1b**) to *trans*-chalcone (**2**) was found to be stereochemically unstable, undergoing a *retro*-Michael reaction when left in the presence of the catalysts, such as in the case of a delayed work-up of the reaction mixture.

Regarding the Darzens condensations, these reactions are most commonly run in the presence of strong anionic bases such as alkali metal hydroxides or alkoxides, sodium amide, LDA, LiHMDS or *n*-butyllithium, very often with pre-formation of the reactive ester enolate anion. To the best of our knowledge, there are no examples of Darzens reaction involving uncharged organobase. Prompted by this information, the suitability of 'organosuperbases' with different pK_{BH^+} in the synthesis of *α,β*-epoxycarbonyl compounds was assessed, Scheme 2.



Scheme 2 Darzens condensation developed in the presence of 'organosuperbases' **V** and **VII**.

The reaction, under mild condition, proceeds in the presence of stoichiometric quantity of phosphazene P_1-*t*-Bu **V** to give the corresponding *cis*- and *trans*-epoxides **3** in good yield and short reaction time.

Although phosphazenes have great utility, both the problems of their stability and difficulties of their preparation make the identification of new superbases an important goal. To this end, cyclopropenimine **VII**, with a pK_{BH}^{+} similar to that of P_1-*t*-Bu **V**, was tested. By using a stoichiometric quantity of 'superbase' **VII**, the epoxide **3** was obtained with up to 34% yield and 1/0.85 d.r. cis/trans. By using a catalytic amount of 'superbase' **VII** (30 mol%), the *α*,*β*-epoxycarbonyl compounds **3** were obtained with up to 86% yield and 1/0.6 d.r. *cis*/*trans*; proving to be tolerant to both variations in the structure and electronic properties of the aromatic aldehydes and *α*-halo carbonyl compounds used.

Riassunto

Le reazioni organocatalitiche e stereoselettive sono delle metodologie sintetiche utili per la sintesi di molecole chirali. I benefici rispetto alla catalisi metallica o organometallica ed enzimatica sono ad esempio il basso prezzo, il risparmio di tempo ed energia, condizioni di reazione semplici, la produzione di pochi rifiuti e l'assenza di impurezze metalliche nel composto desiderato.

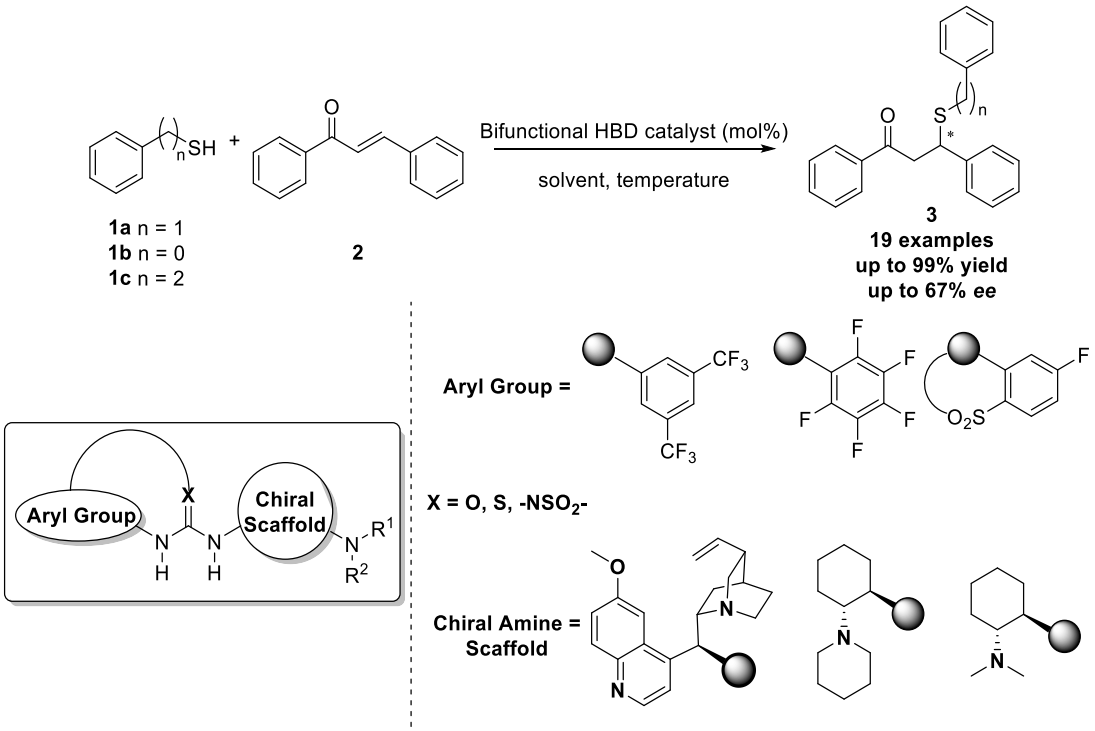
Il focus di questo dottorato è stato lo sviluppo di due reazioni organocatalitiche e stereoselettive: le addizioni di sulfa-Michael e le condensazioni di Darzens poiché rappresentano degli approcci sintetici interessanti per la sintesi di farmaci chirali e, nell'ambito farmaceutico, ci sono pochi principi attivi (API) sintetizzati con reazioni di SMAs e/o di Darzens organocatalitiche e stereoselettive.

Di conseguenza, la tesi è organizzata in due parti: la prima riguarda le reazioni di sulfa-Michael e la seconda in cui sono descritti gli studi sulla reazione di Darzens. Ogni parte è auto-coerente e presenta l'introduzione, le finalità dello studio, la descrizione e la discussione dei risultati, le conclusioni, le procedure sintetiche utilizzate e i dati di caratterizzazione dei prodotti. Inoltre gli spettri rappresentativi sono riportati alla fine di ogni parte. I riferimenti si trovano come note alla fine di ogni pagina. L'elenco delle abbreviazioni utilizzate nella tesi è descritto all'inizio della tesi.

Nell'ambito delle addizioni di sulfa-Michael (SMAs), la catalisi mediata da molecole bifunzionali donatrici di legami ad idrogeno (HBD) rappresenta un approccio interessante per l'attivazione sia della componente nucleofila che di quella elettrofila di una reazione.

Gli esempi di SMA stereoselettive catalizzate da HBD bifunzionali e aventi il *trans*-calcone (**2**) come accettore di Michael sono pochi.

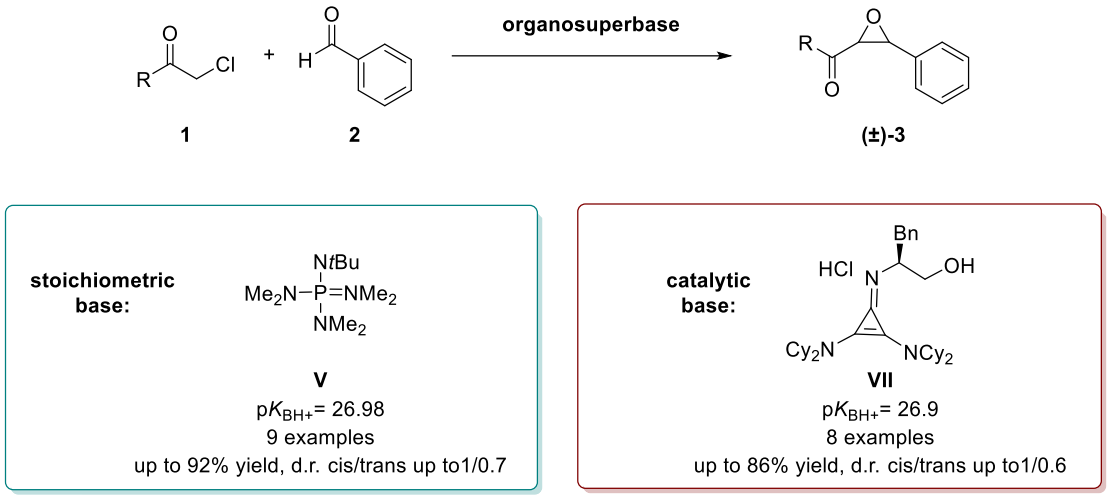
Con l'obiettivo di ottimizzare l'attivitá dei catalizzatori HBD, la letteratura suggerisce come l'aumento dell'acidità dei protoni tioureici NH abbia effetti positivi sulle velocità di alcune reazioni. Spinto da queste informazioni, si è deciso di eseguire un'analisi comparativa di alcuni catalizzatori HBD in SMA stereoselettive aventi il *trans*-calcone (**2**) come accettore di Michael, Schema 1.



Schema 1 Addizioni di sulfa-Michael promosse da catalizzatori HBD studiate durante il dottorato.

All'inizio, abbiamo studiato l'effetto della quantitá di catalizzatore, del solvente e della temperatura nella reazione modello: l'addizione del fenilmetantiolo (**1a**) al *trans*-calcone (**2**). Successivamente, con le condizioni di reazione ottimizzate, abbiamo valutato la capacità di indurre stereoselezione da parte di alcuni catalizzatori HBDs nelle SMAs stereoselettive del benzentiolo (**1b**), fenilmetantiolo (**1a**) e 2-feniletantiolo (**1c**) al *trans*-calcone (**2**). L'aumento dell'acidità di Brønsted nella porzione donatrice di legami ad idrogeno ha dato, in alcuni casi, reazioni più rapide ma, in generale, ha avuto un impatto negativo sulla stereoselettività. Inoltre, il prodotto **3b**, ottenuto dall'addizione del benzentiolo (**1b**) al *trans*-calcone (**2**) è risultato stereochimicamente instabile, poiché subisce una reazione di *retro*-Michael quando lasciato in presenza di catalizzatori, come nel caso di un ritardato work-up della reazione.

Per quanto riguarda le condensazioni di Darzens, generalmente, sono condotte in presenza di basi forti come idrossidi o alcossidi di metalli alcalini, sodio ammide, LDA, LiHMDS o *n*-butil litio. In letteratura, non ci sono esempi di reazioni di Darzens condotte in presenza di basi organiche neutre. Quindi, si è deciso di studiare la reazione di Darzens in presenza di basi organiche neutre aventi una diversa pK_{BH^+}, Schema 2.



Schema 2 Reazione di Darzens sviluppata in presenza delle basi **V** e **VII**.

La reazione, in presenza di una quantità stechiometrica di fosfazene P_1-*t*-Bu **V**, genera gli epossidi *cis* e *trans* **3** con una buona resa e con un breve tempo di reazione.

Tuttavia, sia i problemi di stabilità che le difficoltà di preparazione delle basi fosfazeniche, rendono importante l'obiettivo di identificare nuove superbasi. A tal fine, è stata valutata la ciclopropenimmina **VII**, con una pK_{BH}^{+} simile a quella di P_1-*t*-Bu **V**. Con l'impiego di una quantità stechiometrica di "superbase" **VII**, l'epossido **3** è stato ottenuto con una resa fino al 34% e 1/0.85 d.r. *cis*/*trans*. Usando una quantità catalitica di "superbase" **VII** (30 mol%), i composti *α*,*β*-epossicarbonilici **3** sono stati ottenuti con una resa fino all'86% e 1/0.6 d.r. *cis*/*trans*; dimostrando di essere tollerante sia alle variazioni strutturali che alle proprietà elettroniche delle aldeidi aromatiche e dei composti carbonilici impiegati.

Chapter 1: Organocatalysis

1.1 Introduction

Organocatalysis,[1] a catalytic method paralleling metal or organometallic[2] and enzymatic catalysis,[3] is a synthetic methodology based on the use of small organic molecules to catalyse organic transformations. The term was coined by MacMillan in 2000.[4] The field of organocatalysis has evolved over the last two decades into an attractive tool for the synthesis of chiral organic molecules.[5]

Multiple benefits compared with the other two catalytic areas have brought the acceptance of organocatalysis as a complementary branch of catalytic methods, with the potential for saving cost, time and energy, enabling easier reaction conditions, minimization in chemical waste and lack of metal impurities in the final product. In general, organic molecules are usually stable under aerobic conditions, so there is no need for ultra-dry reaction conditions and for special reaction glassware. A large number of organocatalysts are naturally available from biological sources as single enantiomers and/or easily synthesized from precursors present in nature. In addition, organocatalysts are often cheaper and less toxic than metal-based catalysts and, can be easily removed from waste streams.

The activation mode of organocatalysts, Figure 1.1, occurs either through the transient formation of covalent bonds, such as in enamine,[6] iminium[6] and carbene catalyst,[7] as well as through non-covalent interaction, such as in hydrogen bonding catalysis (*e.g.* thioureas,[8] squaramides[9] and phosphoric acids[10]) or ionic interaction (*e.g.* phase-transfer catalysts[11]). Together, these catalytic events represent the repertoire of organocatalysts currently available.

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[1] a) Qin, Y.; Zhu, L.; Luo, S. *Chem, Rev.* **2017**, *117*, 9433; b) Zhan, G.; Du, W.; Chen, Y-C. *Chem. Soc. Rev*. **2017**, *46*, 1675; c) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, 38, 217; d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

[2] a) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138; b) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369; c) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379; d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

[3] a) Lewis, J. C.; Coelho, P. S.; Arnold, F. H. *Chem. Soc. Rev.* **2011**, *40*, 2003; b) Schramm,V. L. *Chem. Rev.* **2006**, *106*, 3029; c) Ramos, M. J.; Fernandes, P. A. *Acc. Chem. Res.* **2008**, *41*, 689; d) Callender, C.; Dyer, R. B. *Acc. Chem. Res*. **2015**, *48*, 407; e) Oyama, S. T.; Somorjai, G. A. *J. Chem. Educ.* **1988**, *65*, 765; f) Hansen, D. E.; Raines, R. T. *J. Chem. Educ.* **1990**, *67*, 483.

[4] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[5] a) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774; b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis;* Wiley-VCH: Weinheim, **2005**.

[6] a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jorgensen, K. A. *Chem. Commun*. **2011**, *47*, 632; b) Erkkilä, A.; Majander, I.; Pihko, P. M. Chem. Rev. **2007**, *107*, 5416.

[7] Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314.

[8] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; b) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

[9] a) Alemán, J.; Parra, A.; Jiang, H., Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890; b) Storer, R. I.; Aciro, C.; Jone, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330.

[10] Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227.

[11] Maruoka, K. *Asymmetric Phase Transfer Catalysis*, Wiley-VCH: Weinheim, **2008**.

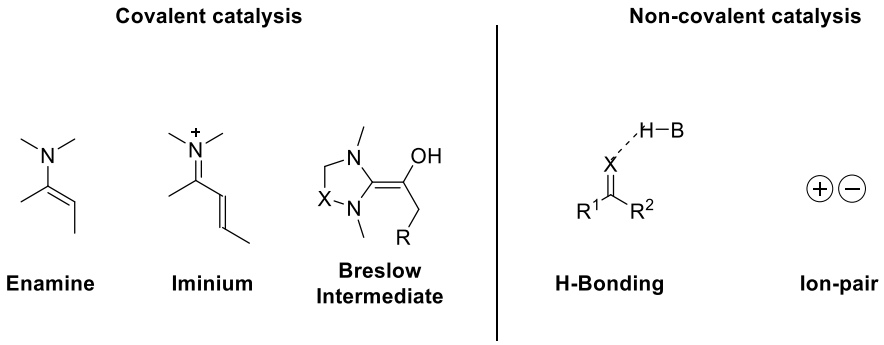
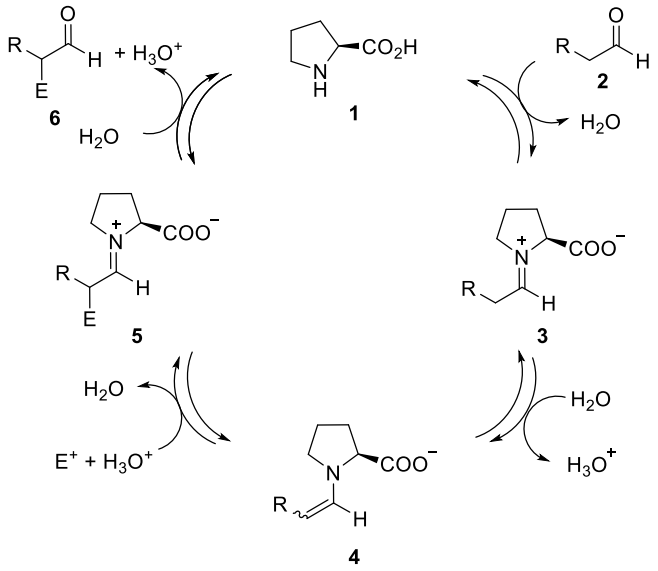


Figure 1.1 Examples of activation mode of organocatalysts.

1.2 Covalent organocatalysis

In 1971, Parrish[12] and Eder;[13] developed independently a stereoselective intramolecular aldol reaction catalysed by proline (**1**). The activation mode of **1** was later explained by Barbas, Lerner and List, Scheme 1.1, in 2000 to occur *via* an enamine mechanism.[14]



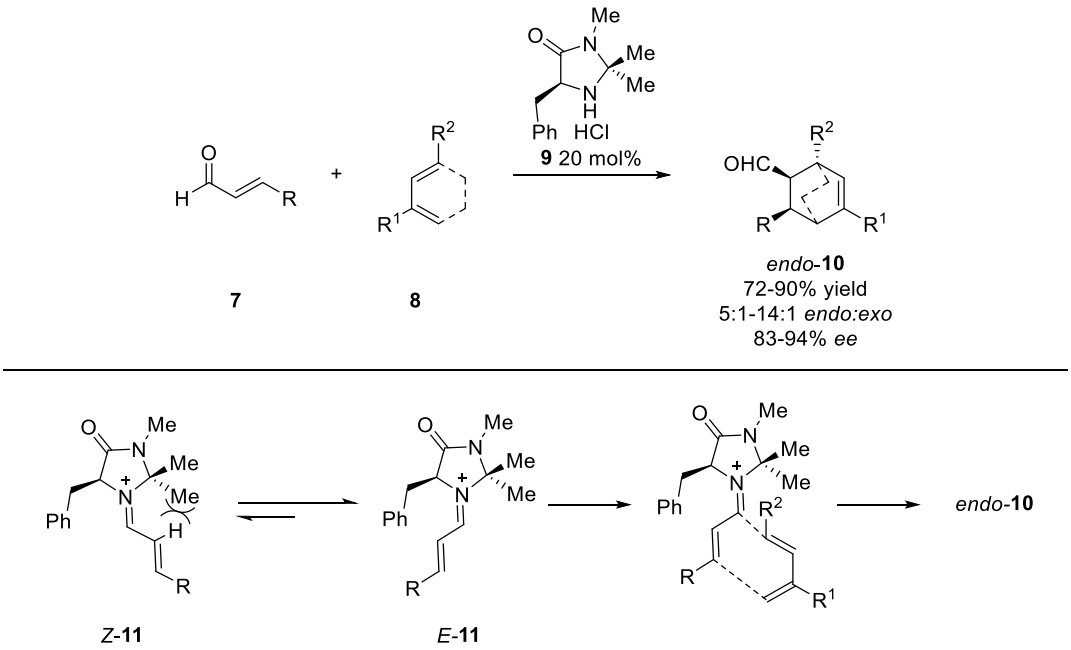
Scheme 1.1 Proline-enamine mechanism active during an organocatalytic process.

The catalytic cycle starts with the nucleophilic attack of the chiral catalyst **1** to the aldehyde **2**, forming the iminium-ion **3**. The deprotonation of iminium-ion **3** generates the reactive nucleophilic enamine intermediate **4** that can attack an electrophile reforming the iminium-ion **5**. The hydrolysis of the iminium-intermediate delivers the product **6** and the chiral catalyst, which is again available for another catalytic cycle.

[12] Hajos, Z. G.; Parrish, D. R. *German patent DE 2102623*, **1971**.
[13] Eder, U.; Sauer, G. R.; Wiechert, R. *German patent DE 2014757*, **1971**.
[14] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, 122, 2395.

Another example of covalent organocatalysis is the iminium-ion catalysis.[6] Although the 'history' of iminium catalysis does not have a specific starting date; likely, the first process involving an iminium catalysis dates back to the discovery of the Knoevenagel condensation.[15]

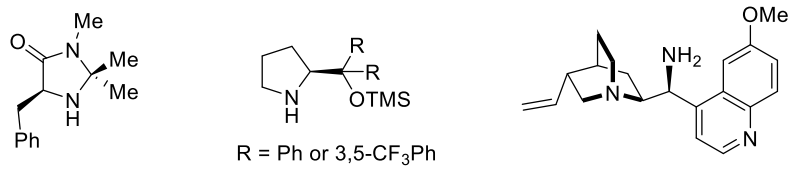
The designing, rather than discovering, of an iminium catalysis was developed by Mac-Millan and co-workers in 2000.[4] They hypothesized that the reversible formation of iminium ions from *α,β*-unsaturated aldehydes and chiral amines might emulate the equilibrium dynamics and *π*-orbital electronics that are inherent to Lewis acid catalysis. To test this hypothesis, they investigated the ability of the chiral imidazolidinone **9** to catalyse the stereoselective Diels-Alder reaction between the *α,β*-unsaturated aldehyde **7** and diene **8**, Scheme 1.2. The reaction provided cyclic *endo*-**10** with good stereoselectivity. The catalyst **9** and aldehyde **7** form, preferentially, the iminium ion *E*-**11** where the *α*-hydrogen is far away from the geminal methyl groups of imidazolidinone **9**. Therefore, the most favourable transition state leads to *endo*-**10**.



Scheme 1.2 Diels-Alder reaction catalysed by imidazolidinone **9** *via* iminium ion mechanism.

In addition to the imidazolidinone **9** family, others chiral amines were developed as iminium catalysts *e.g.* the diarylprolinol silyl ethers **12** and the diamine **13** derived from *Cinchona* alkaloids, Figure 1.2.[16]

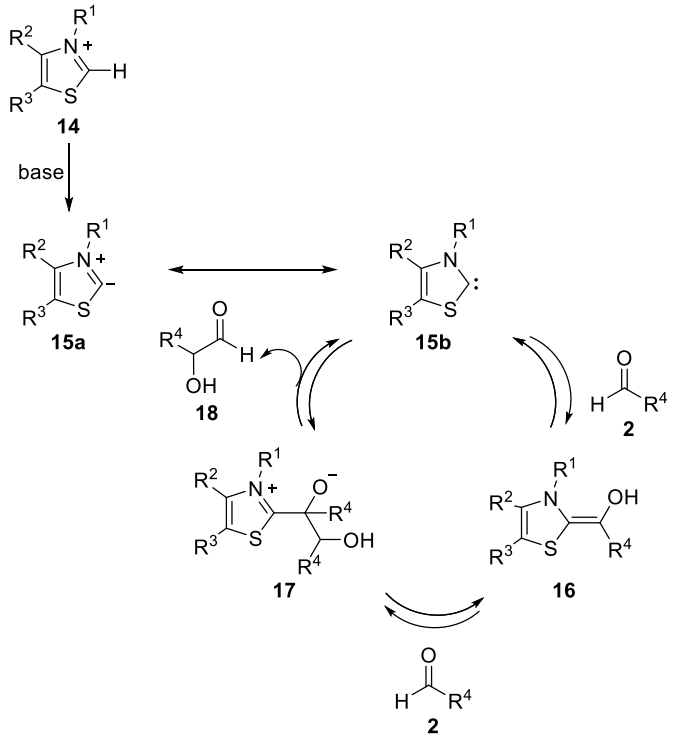
[15] Knoevenagel, E. *Chem. Ber.* **1894**, *27*, 2345.
[16] a) Marigo, M.; Wabnitz, T. C; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 794; b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; c) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu Y.; Ding, L-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816.



9 **12** **13**

Figure 1.2 Examples of iminium organocatalysts.

Among the portfolio of covalent organocatalysis, *N*-heterocyclic carbenes (NHCs), inspired by thiamine-dependent enzymatic processes, have emerged as powerful and versatile catalysts.[17] The first activation mode of NHCs was described by R. Breslow in the benzoin condensation catalysed by the thiazolium salt **14**, Scheme 1.3.[18] The deprotonation of thiazolium **14** generates the nucleophilic thiazolylidene compound **15**. The addition of the catalyst **15** to the aldehyde **2** gives the 'Breslow-intermediate' **16** which can react with another aldehyde **2** to give *α*-hydroxy-ketone **18**.



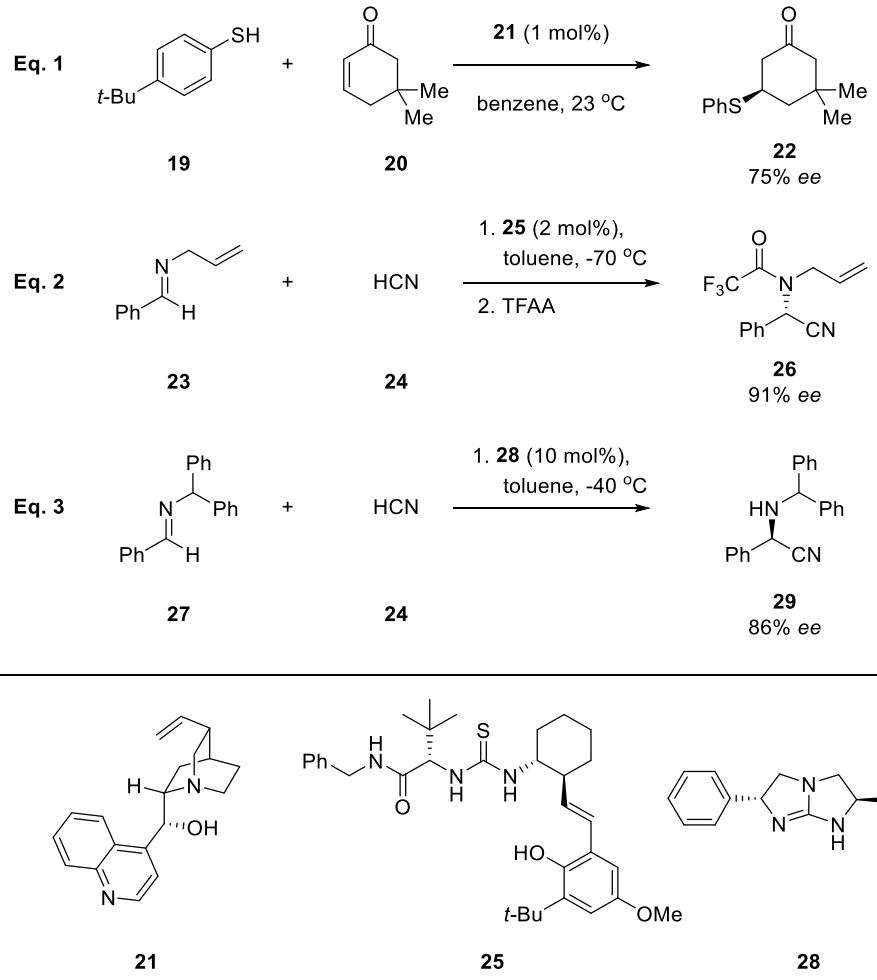
Scheme 1.3 NHCs and Breslow intermediate **16**.

[17] a) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev*. **2008**, *37*, 2691; b) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906; c) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040; d) Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed*. **2016**, *55*, 2.
[18] Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

The three catalytic covalent-mechanisms reported above represent the most investigated strategies for the stereoselective synthesis of chiral compounds and they have seen tremendous development in recent years.

1.3 Non-covalent organocatalysis

In the 1981, Wynberg reported that *Cinchona*-alkaloid **21** catalyses the stereoselective addition of thiophenol **19** to the cyclic enone **20**, Scheme 1.4, eq. 1, suggesting that the activation of the substrate and the organization of the transition state occur through hydrogen-bonding interactions.[19] However, the understanding of H-bonding catalysis was expanded in the late 1990s only, when Jacobsen,[20] Scheme 1.4, eq. 2, and Corey,[21] Scheme 1.4, eq. 3, independently developed a stereoselective Strecker reaction in the presence of hydrogen-bonding organocatalysts **25** or **28** that activate the electrophilic component of the reaction.



Scheme 1.4 Application of hydrogen-bonding organo-catalysts in stereoselective synthesis.

[19] Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.
[20] Sigman, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
[21] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

Subsequently, Jacobsen explained the activation mode of thiourea organocatalysts through NMR, kinetic, structure-activity relationship and theoretical studies, Figure 1.3.[22] In particular, the two urea protons form a dual H-bond interaction with the nitrogen atom of the enamine.

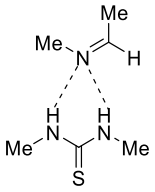


Figure 1.3 Activation mode of thiourea via H-bond interaction.

The investigation of Jacobsen has been crucial to understand this powerful activation mode and prompted the design and development of new chiral hydrogen bond donor (HBD) catalysts, Figure 1.4. The HBD catalysts discovered have a diversified range of structural and functional frameworks with different pK_a of the HBD unit and, potentially, able to catalyse a large number of reactions.[23]

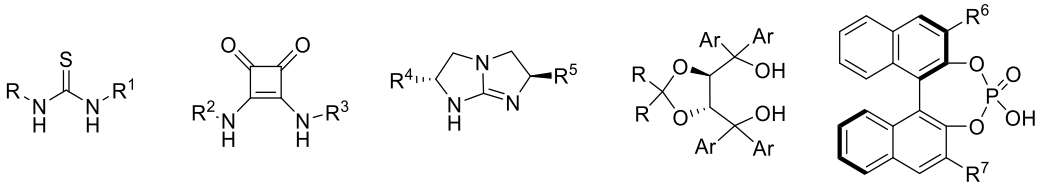
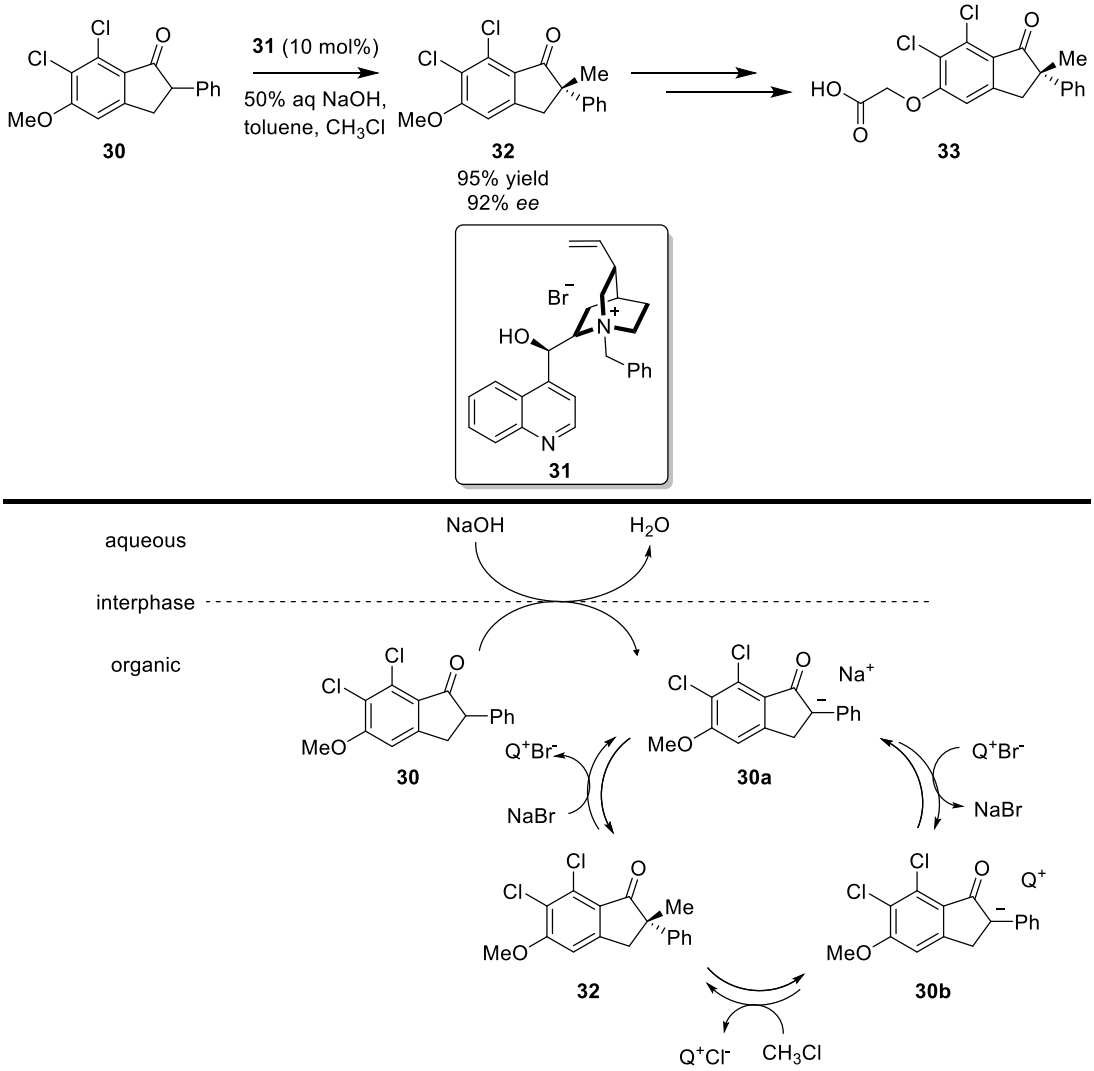


Figure 1.4 Example of some popular HBDs catalysts.

Among non-covalent organocatalytic methods, the last example reported is the phase-transfer catalysis (PTC). The first successful application of a chiral PTC was developed by Merck research group for the synthesis of indacrinone **33**, Scheme 1.5.[24] In particular, they developed the stereoselective alkylation of compound **30** in the presence of the *Cinchona*-based quaternary ammonium salts **31** to afford the product **32** in 95% yield with 92% *ee*. The quaternary *Cinchona*-ammonium cation **31** forms a nucleophilic ionic complex with the anion **30a**, generated by deprotonation with NaOH at the interphase of the organic and aqueous phases. The nucleophilic ionic complex **30b** then reacts with the electrophile to provide the product **32** leaving the catalyst **31** free in the organic phase.

[22] Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.
[23] a) Doyle, A.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; b) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633.
[24] Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.



Scheme 1.5 PTC synthesis of indacrinone **33**.

Since PTC was introduced, various types of natural and non-natural product derived chiral PT catalysts were introduced, such as *Cinchona*-ammonium salt **34**, binaphthyl-modified salt **35** and chiral crown ether **36**, Figure 1.5.[25]

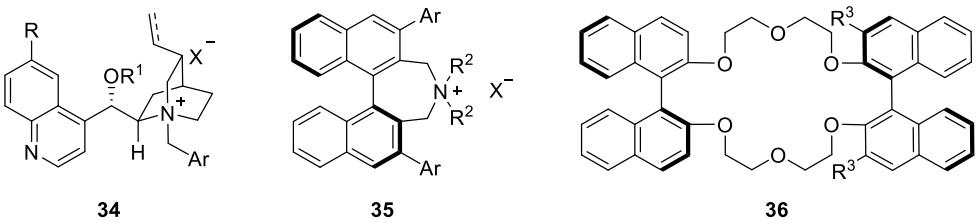


Figure 1.5 Example of some popular PT catalysts.

[25] a) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679; b) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090; c) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 2.

Chapter 2: The organic chemistry of sulfur compounds

2.1 Organosulfur drugs in the pharmaceutical industry

Organosulfur compounds are widely present in nature and various biological systems. Cysteine **1**, Figure 2.1, is involved in the biochemical pathway of almost all living organisms,[26] furthermore, synthetic organosulfur compounds, Figure 2.1, are of significant potential in pharmaceutical science, serving, for instance, as antibiotic, antidepressant and antiasthma agents.[27] In this respect it is interesting to note that all of the top ten selling drugs in 2012 were organosulfur compounds.[28]

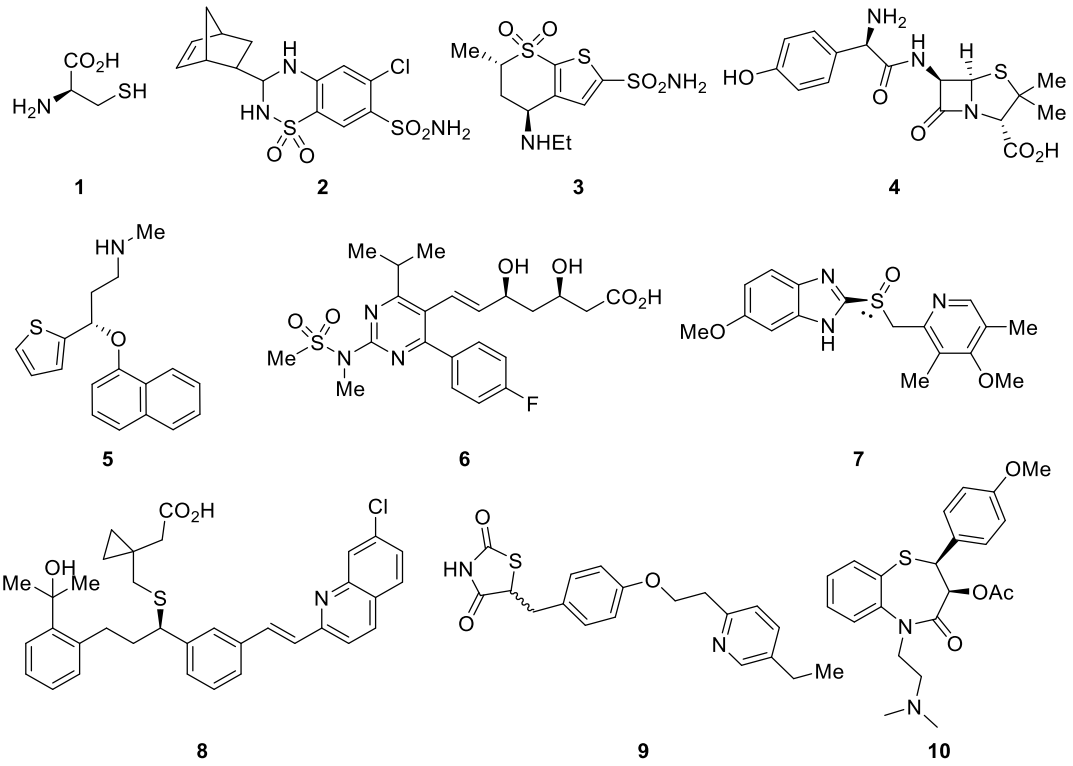
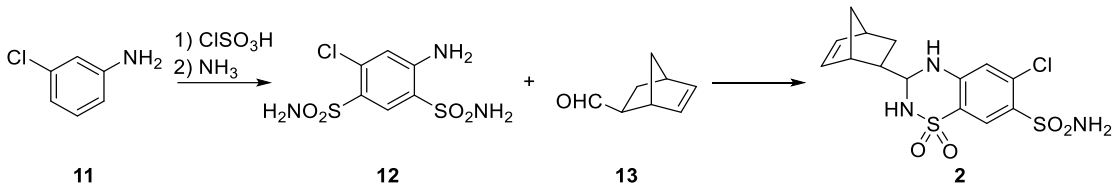


Figure 2.1 Example of biologically active organosulfur compounds present in nature and organosulfur drugs.

Sulfur containing drug may present several functional groups involving the sulfur atom namely sulfonamides, thioethers, sulfoxides and sulfones.[29] Sulfonamide drugs were the first antibiotics to be used systemically, and paved the way for the new antibiotic revolution in medicine. Nevertheless, antibiotics are not the only drugs derived from sulfonamides. For example, cyclothiazide **2**, Figure 2.1, is a diuretic and antihypertensive drug that was

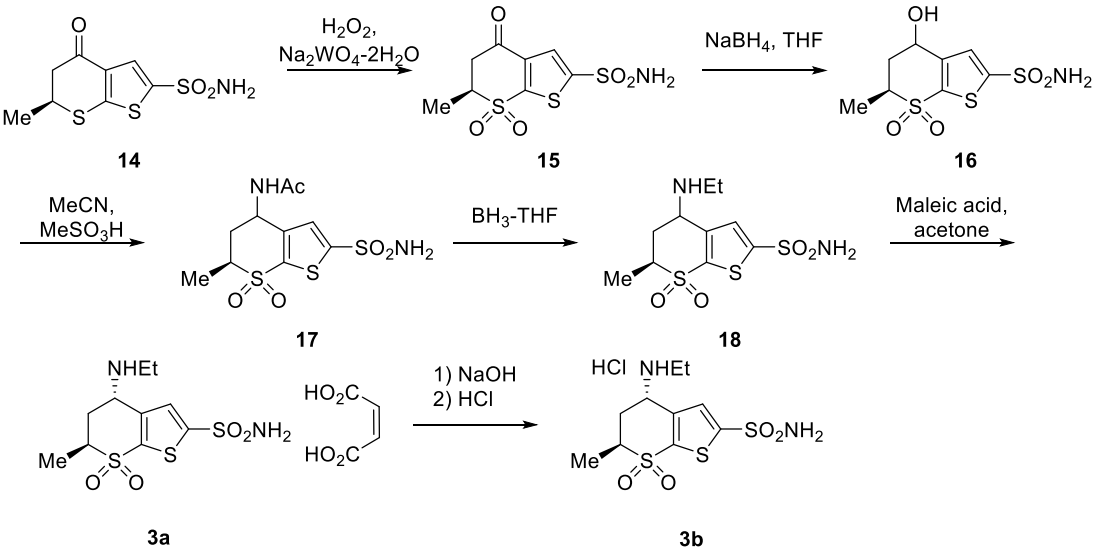
[26] Fraústo da Silva, J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, **2001**.
[27] a) Nudelman, A. *The Chemistry of Optically Active Sulfur Compounds*; Gordon and Breach: New York, **1984**; b) *Sulphur-Containing Drugs and Related Organic Compounds*; Damani, L. A., Ed.; Wiley: New York, **1989**.
[28] http://www.genengnews.com/insight-and-intelligenceand153/top-20-best-selling-drugs-of 2012/77899775/?page=2.
[29] Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200.

originally introduced in the United States in 1963 by Eli Lilly. The total synthesis, Scheme 2.1, includes the synthesis of sulfonamides **12** and the subsequent cyclization with aldehyde **13** to afford cyclothiazide **2**.[30]



Scheme 2.1 Total synthesis of cyclothiazide **2**.

Other relevant sulfur containing drug is dorzolamide **3**, Figure 2.1, first drug based on drug design and used to treat glaucoma.[31] Recently, Zach System developed a stereoselective process for the preparation of compound **14** as an intermediate in the preparation of dorzolamide **3**, Scheme 2.2.[32] In particular, the oxidation of sulfide **14** gave keto-sulfone **15** which was reduced to the hydroxyl compound **16**. Subsequently, the Ritter reaction generated *N*-acetyl compound **17** which was transformed to the amine **18**. Finally, the salification gave the desired dorzolamide **3**.



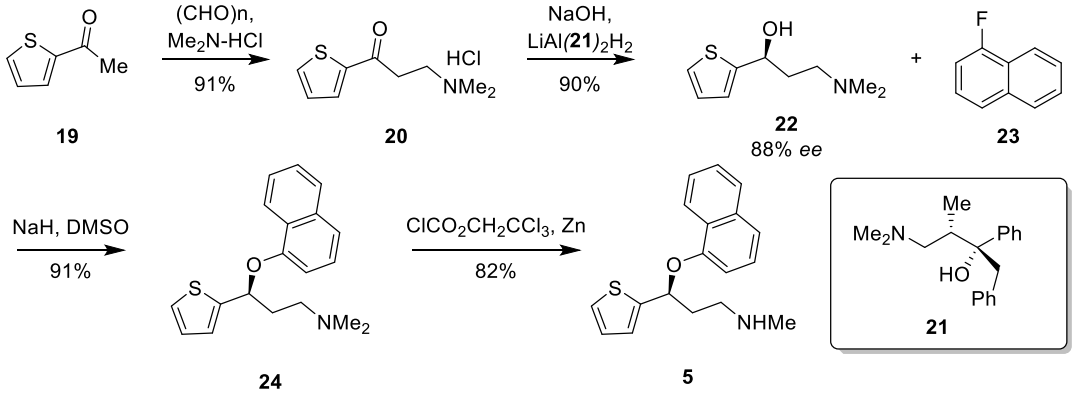
Scheme 2.2 Synthesis of dorzolamide **3**.

Well-known antibiotics containing sulfur atom are the penicillins, *e.g.* **4**, Figure 2.1, that play a significant role in fighting against syphilis, or infections caused by staphylococci and

[30] Whitehead, C. W.; Traverso, J. J.; Sullivan, H. R. Marshall, F. J. *J. Org. Chem.* **1961**, *26*, 2814.
[31] Ponticello, G. S.; Sugrue, M. F.,; Plazonnet, B.; Durand-Cavagna, G. *Pharm. Biotechnol.* **1998**, *11*, 555.
[32] Volpicelli, R.; Nardi, A.; Andretto, M.; Munari, I.; Brescello, R.; Smaniotto, A.; Cotarca, L.; Verzini, M. *WO 2014/005943*, **2014**.

streptococci. Though certain kinds of bacteria are resistant to penicillins, they are still popular antibiotics in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.[33] Penicillin is a secondary metabolite of certain species of *Penicillium* and is produced when growth of the fungi is inhibited by stress. It is not produced during active growth. The mass production of penicillins is mainly based on biosynthesis and semisynthesis. The first chemical synthesis of penicillin was accomplished by John C. Sheehan in 1957.[34] Although the initial synthesis developed by Sheehan was not appropriate for mass production, one of the intermediate compounds, 6-aminopenicillanic acid (6-APA), was the nucleus of penicillin. It can be obtained from the fermentation brew of the *Penicillium* mold and used as the main building block for the preparation of several semisynthetic penicillins.[35]

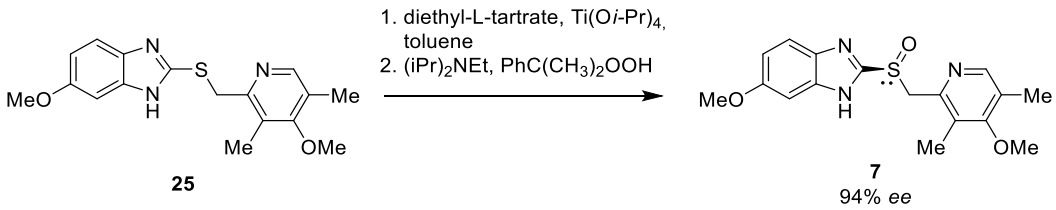
Going back to Figure 2.1, in 1988, the company Eli Lilly developed duloxetine **5**, registered trademark Cymbalta, a potent inhibitor of the serotonin and norepinephrine uptake carriers.[36] It is used for the treatment of depression, obesity, and alcoholism.[37] The stereoselective synthesis includes four-stages, Scheme 2.3.[38] In particular, ketone **20** was obtained from 2-acetylthiophene (**19**) *via* Mannich reaction. Subsequently, the stereoselective reduction of **20** gave the alcohol **22** which was used for the alkylation with 1-fluoronaphthalene (**23**) to afford compound **24**. Finally, *N*-methyl dealkylation generated the desired drug **5** with a 60% overall yield.



Scheme 2.3 Total synthesis of duloxetine **5**.

[33] Garrod, L. P. *Br. Med. J.* **1960**, *1*, 527.
[34] Sheehan, J. C.; Henery, L.; Kenneth, R. *J. Am. Chem. Soc.* **1957**, *79*, 1262.
[35] Cole, M. *Appl. Microbiol*. **1966**, *14*, 98.
[36] a) Robertson, D. W.; Wong, D. T.; Krushinski, J. H. Jr. *Eur. Pat. Appl. EP273658*, **1988**; b) Wong, D. T.; Robertson, D. W.; Bymaster, F. P.; Krushinski, J. H.; Reid, L R. *Life Sciences* **1988**, 43, 2049.
[37] Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412.
[38] Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101.

Among drugs used against acid-related diseases, AstraZeneca developed esomeprazole **7**, Figure 2.1, the (*S*)-enantiomer of omeprazole, an inhibitor of the gastric acid pump H^+/K^+-ATPase.[39] Having considered different synthetic routes,[40] they realised that the most attractive approach was the stereoselective oxidation of sulfide **25** to the corresponding sulfoxide, Scheme 2.4.[41]



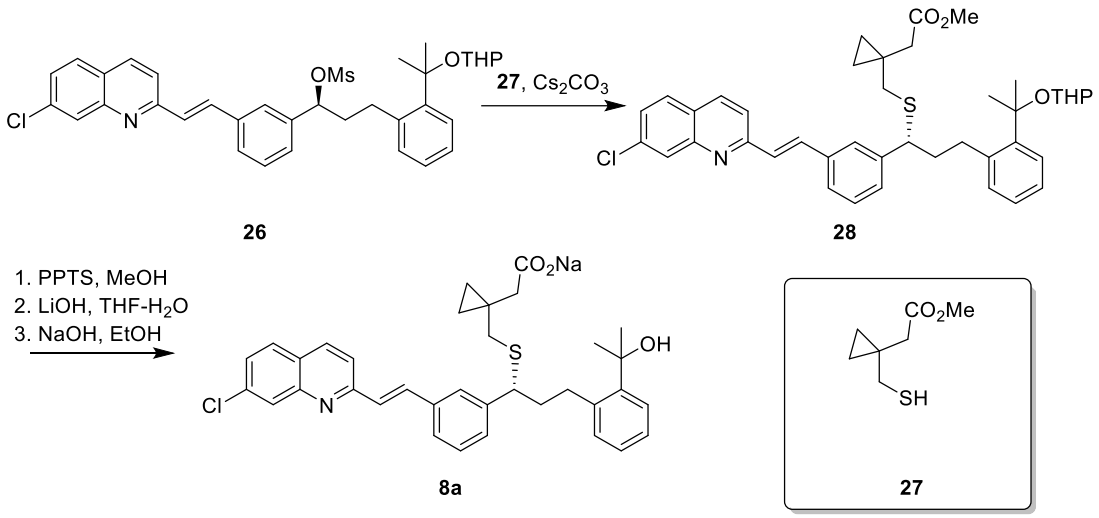
Scheme 2.4 Stereoselective oxidation of sulfide **25** in the synthesis of esomeprazole **7**.

Specifically, sulfide **25** was converted into esomeprazole **7** by using diethyl–L-tartrate/ titanium (IV) isopropoxide/water in toluene and then, *N*,*N*-diisopropyethylamine and cumene hydroperoxide were added to the reaction mixture. After work-up, the isolated product **7** was obtained with 94% *ee*.

In the early 1990s, Merck group discovered Montelukast **8**, Figure 2.1, registered trademark Singulair, a leukotriene D4 receptor antagonist (LTD4) used for the prophylaxis and chronic treatment of asthma.[42] Different chemical syntheses were reported for the preparation of Montelukast **8**.[43] In principle, the crucial step, in all syntheses, is the formation of the chemical bond between carbon and sulfur atoms.

The first method reported required the use of methanesulfonyl derivate **26** and thiol **27** in the key synthetic step, Scheme 2.5.[44] Subsequently, deprotection of the hydroxyl group with pyridinium *p*-toluene sulfonate (PPTS), hydrolysis of the methyl ester and purification of crude compound gave the sodium salt **8a**.

[39] a) Lindberg, P.; Brändström, A.; Wallmark, B.; Mattsson, H.; Rikner, L.; Hoffman, K.-J. *Med. Res. Rev.* **1990**, *10*, 1; b) Fellenius, E.; Berglindh, T.; Sachs, G.; Olbe, L.; Elander, B.; Sjöstrand, S.-E.; Wallmark, B. *Nature* **1981**, *290*, 159; c) von Unge, S.; Langer, V.; Sjölin, L. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1967.
[40] Carlsson, E. I.; Junggren, U. K.; Larsson, H. S.; von Wittken Sundell, G. W. *Patent appl. EP 074341*, **1981**.
[41] Cotton, H.; Elebring, T.; Larsson, M.; Li, L.; Sörensen, H.; von Unge, S. *Tetrahedron*: *Asymmetry* **2000**, *11*, 3819.
[42] a) Schoors, D. F.; De Smet, M.; Reiss, T.; Margolskee, D.; Cheng, H.; Larson, P.; Amin, R.; Somers, G. *Br. J. Clin. Pharmacol.* **1995**, *40*, 277; b) Markham, A.; Faulds, D. *Drugs* **1998**, *56*, 251; c) Noonan, M. J.; Chervinsky, P.; Brandon, M.; Zhang, J.; Kundu, S.; Mcburney, J.; Reiss, T. F. *Eur. Respir. J.* **1998**, *11*, 1232.
[43] Halama, A.; Jirman, J.; Boušková, O.; Gibala, P.; Jarrah, K. *Org. Process Res. Dev.* **2010**, *14*, 425.
[44] Labelle, M.; Belley, M.; Gareau, Y.; Gauthier, J. Y.; Guay, D.; Gordon, R.; Grossman, S. G.; Jones, T. R.; Leblanc, Y. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 283.

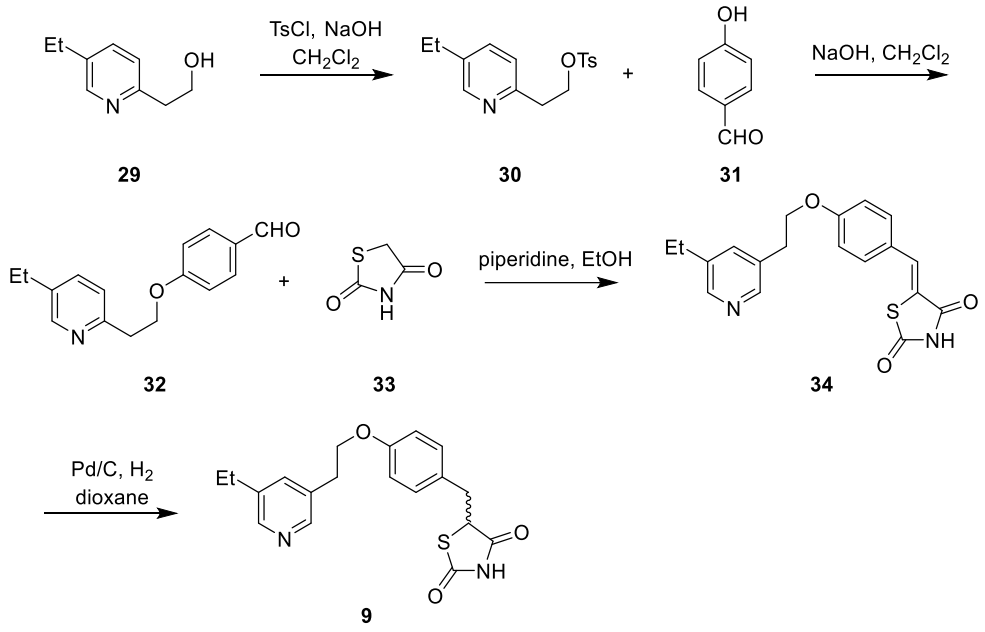


Scheme 2.5 Key steps in the total synthesis of Montelukast **8**.

In the same years, the Takeda company identified pioglitazone **9**, Figure 2.1, a benzylthiazolidinedione derivative approved with the brand name Actos and used for the treatment of diabetes.[45] Pioglitazone **9** stimulates peroxisome proliferator-activated receptor gamma (PPARγ) in order to modulate the transcription of the insulin sensitive genes that are involved in biochemical pathways of glucose and lipids.[46]

The original chemical synthesis of pioglitazone **9** is shown in Scheme 2.6.[47] The chemical route involved activation of 5-ethyl-2-pyridyl ethanol (**29**) as *p*-toluene sulfonyl ester to obtain intermediate **30**. Subsequently, this intermediate was reacted with the nucleophilic *p*-hydroxybenzaldehyde **31** in the presence of sodium hydroxide affording compound **32**. The Knoevenagel reaction between intermediate **32** and thiazolidinedione **33** gave compound **34** which was reduced in the presence of Pd/C/H_2 yielding the desired compound **9**.

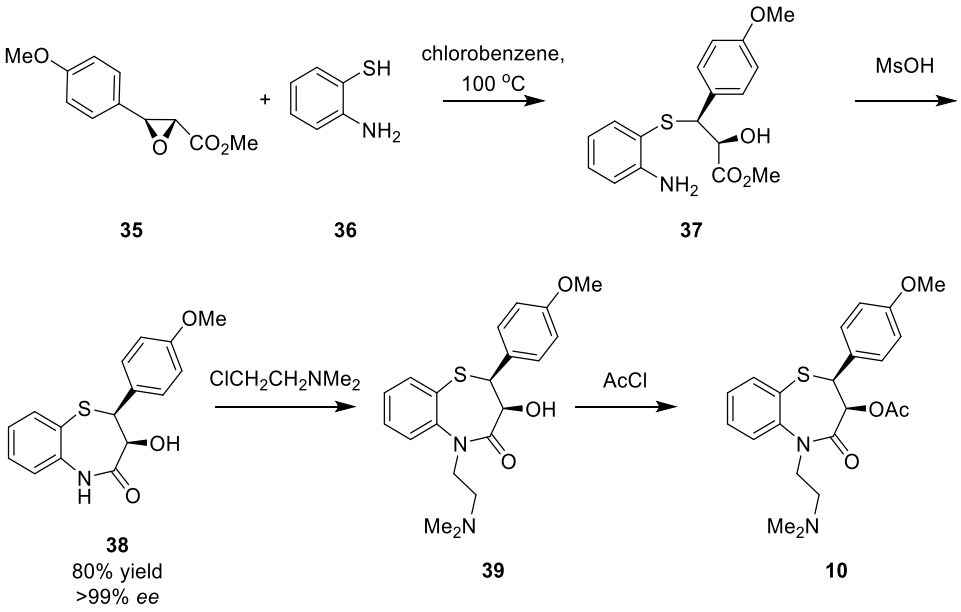
[45] Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.
[46] a) Le, A.; Pucko, W.; Szelejewski, W. *Org. Process Res. De*v. **2004**, *8*, 157,; b) Colca, J. R.; McDonald, W. G.; Waldon, D. J.; Leone, J. W.; Lull, J. M.; Bannow, C. A.; Lund, E. T.; Mathews, W. R. *Am. J. Physiol. Endocrinol. Metab.* **2004**, *286*, 60; c) Paddock, M. L.; Wiley, S. E.; Axelrod, H. L.; Cohen, A. E.; Roy, M.; Abresch, E. C.; Capraro, D.; Murphy, A. N.; Nechushtai, R.; Dixon, J. E.; Jennings, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 14342.
[47] Meguro, K.; Fujita, T.; Hatanaka, C.; Ooi, S. *U.S. Patent 4,812,570,* **1989**.



Scheme 2.6 Total synthesis of pioglitazone **9**.

Among organo-sulfur drugs, the last example reported is diltiazem **10**, Figure 2.1, a calcium antagonists used for the treatment of angina and hypertension.[48] Among diversified synthetic approaches, methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (**35**), Scheme 2.7, was recognized as a key intermediate for the chemical synthesis of diltiazem **10**.[49] In particular, the epoxide opening with 2-aminothiophenol (**36**) and the cyclization in the presence of methanesulfonic acid gave benzothioazepine **38** in 80% yield and >99% *ee*. Finally, alkylation and acetylation yielded the final product **10**.[50]

[48] a) Inoue, H.; Takeo, S.; Kawazu, M.; Kugita, H. *Yakugaku Zasshi* **1973**, *93*, 729; b) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* **1973**, *21*, 92; c) Abe, K.; Inoue, H.; Nagao, T. *Yakugaku Zasshi* **1988**, *108*, 716.
[49] a) Kugita, H.; Inoue, H.; Ikezaki, M.; Takeo, S. *Chem. Pharm. Bull*. **1970**, *18*, 2028; b) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull*. **1970**, *18*, 2284; c) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull*. **1971**, *19*, 595; d) Hashiyama, T.; Inoue, H.; Konda, M.; Takeda, M. *J. Chem. Soc., Perkin Trans 1*. **1984**, 1725; e) Hashiyama, T.; Inoue, H.; Takeda, M.; Aoe, K.; Kodera, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 421.
[50] Synthelabo, *US Patent 5,013,835*, **1991**.



Scheme 2.7 Total synthesis of diltiazem **10**.

2.2 The world of sulfur-chemistry reactions

The organo-sulfur chemistry occupies a prominent position in the race for the synthesis of valuable chemical substances, indeed, organosulfur compounds are widely present in nature and living organisms where they are pivotal compounds in many biochemical processes. Moreover, several scaffolds for fine chemicals and drugs contain sulfur functional groups in their structure as presented in Section 2.1.

Relevant functional groups presenting the sulfur atom are depicted in Figure 2.2 and they are: thiols **(a)**, disulfides **(b)**, sulfonium salts **(c)**, sulfoxides **(d)**, sulfones **(e)**, sulfonic acids **(f)**, thioacetals **(g)** and thioacids **(h),** and sulfonamides **(i)**.[51]

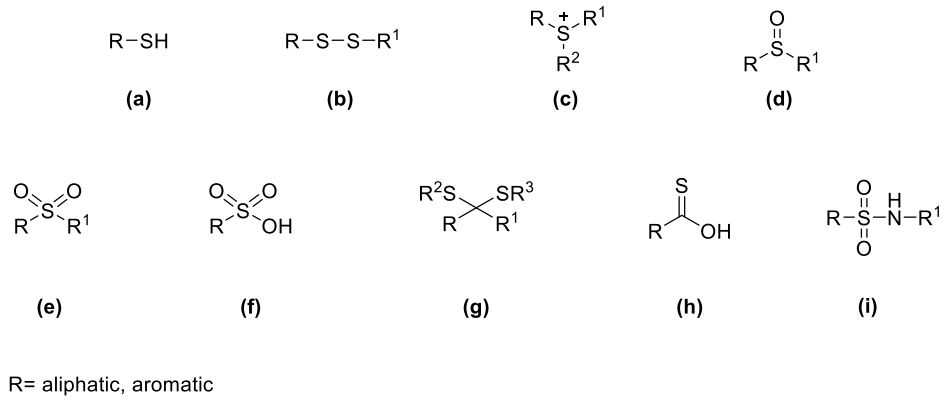


Figure 2.2 Some representative sulfur functional groups.

The chemistry of sulfur functional groups is very rich and it is out of the scope of this chapter to overview such a large part of chemistry. However, in the following sections some reactions involving thiols or sulfur electrophiles and related to the research work of this PhD thesis such as nucleophilic substitution, addition and condensation reactions are presented and discussed.

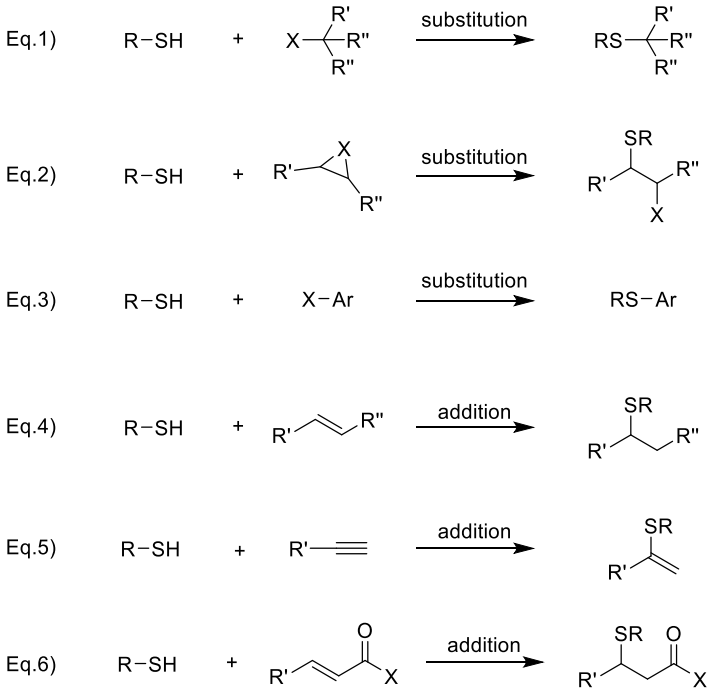
2.2.1 Thiols as nucleophiles

Thiols operate as nucleophiles in two main types of reactions: either substitutions or additions to a multiple bond, Scheme 2.8.[52]

The substitution type reaction is not restricted to carbon centres, either aliphatic or aromatic, but includes also the main group and transition elements.

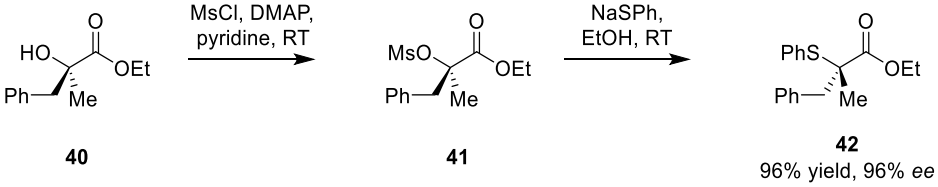
Among the different methods to form the carbon-sulfur bond, the direct substitution of leaving groups such as halides, sulfonates, *O*-phosphinite, etc., Scheme 2.8, Eq.1; by a sulfur nucleophile represents an interesting approach for the C-S bond formation.[53]

[51] Rayner, C. M.; Philip, P. *Organosulfur Chemistry*, Ed.; Academic Press: **1995**.
[52] Peach, M. E. *The Chemistry of the Thiol Group*, Patai, S., Ed.; John Wiley & Sons Ltd.: **1974**.



Scheme 2.8 Examples of reactions involving thiols as nucleophiles.

For example, the ability of sulfonates as leaving groups has allowed the preparation of tertiary thiols such as *α*-thio-esters **42**, Scheme 2.9. The displacement of the mesylate leaving group by thiophenol occurs via S_N2 mechanism. Specifically, the presence of the *α*-ester group of **41** inhibits carbocation formation and the planar ester group creates minimal steric hindrance for the nucleophile approach.[54]

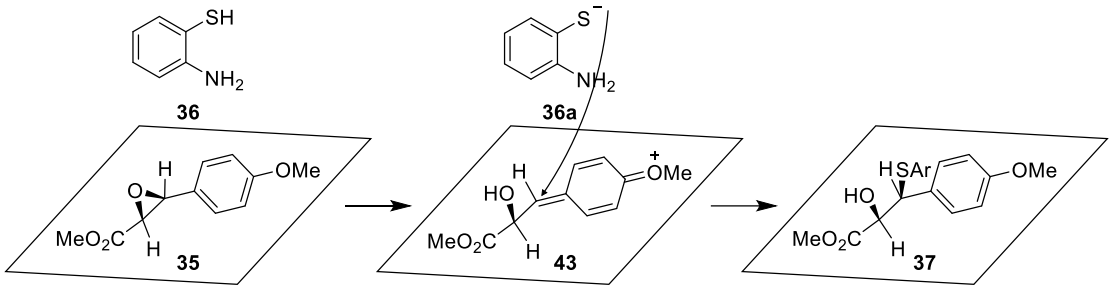


Scheme 2.9 Synthesis of *α*-thio-esters **42**.

Sulfur-based nucleophiles have been employed in nucleophilic ring opening of epoxides, Scheme 2.8, Eq. 2.[55] As mentioned in the synthesis of diltiazem **10**, Scheme 2.7, under thermal conditions, the reaction of 2-aminothiophenol (**36**) with the glycidic ester **35** proceeds with retention of configuration at the stereocenter C-3. The thiol **36** protonates the epoxide **35** from the proximal side of a plane defined by the four atoms attached to it, Scheme 2.10. The ring opening is facilitated by the *p*-methoxy group, leading to the resonance-stabilized *p*-

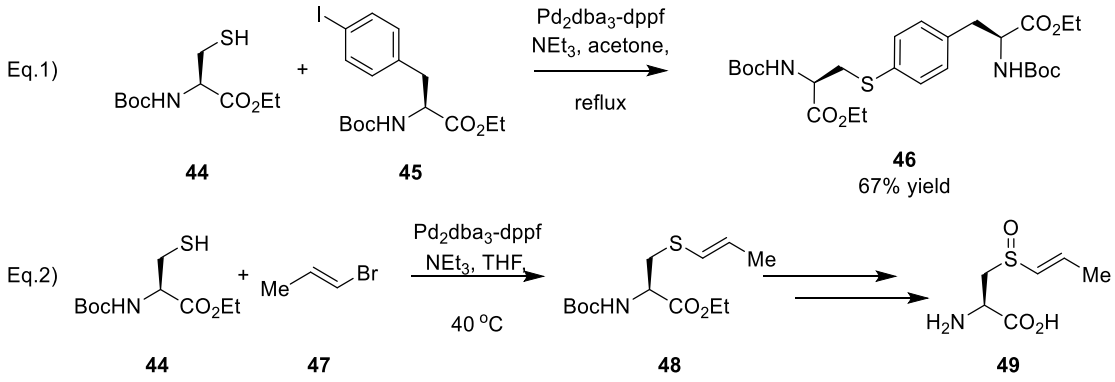
[53] Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 335.
[54] Weaver, J. D.; Morris, D. K.; Tunge, J. A. *Synlett* **2010**, 470.
[55] López, I.; Rodríguez, S.; Izquierdo, J.; González, F. V. *J. Org. Chem.* **2007**, *72*, 6614.

methoxy quinone cation **43**. The stereochemistry observed can be explained if the disappearance of the ion pair is faster than migration of thiolate **36a**.[56]



Scheme 2.10 Mechanism of ring opening **35** in the presence of thiol **36**.

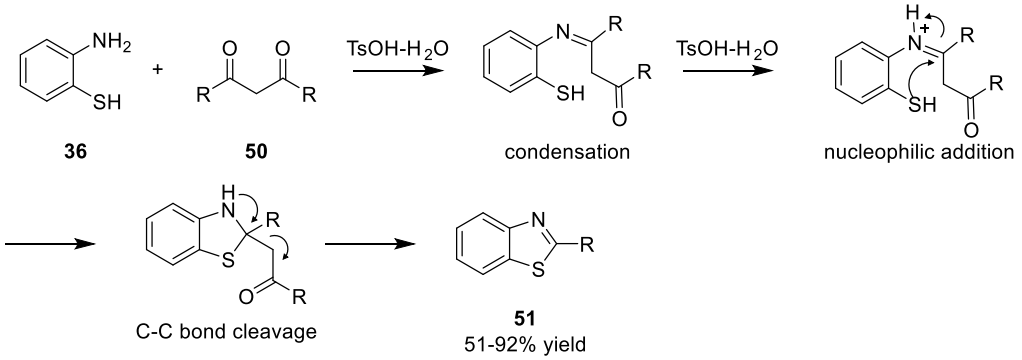
Other important substitution reactions for the formation of C-S bonds are the cross-coupling transformations, Scheme 2.8, Eq. 3.[57] In 2003, Campagne and co-workers developed the arylation of cysteine derivative **44**, Scheme 2.11, Eq.1.[58] The reactions were carried out in the presence of Pd_2dba_3/dppf system and aryl iodide **45**. This study is of interest because it allows accessing to biologically active molecules containing the cysteine core. The same catalytic condition was used for the synthesis of Isoaliin **49**, the main sulfur compound found in onions *Allium cepa*, Scheme 2.11, Eq.2.[59] The mechanism of the cross-coupling reaction of cysteine derivative was studied using both ^{31}P NMR spectroscopy and electrochemical experiments.[60]



Scheme 2.11 Synthesis of cysteine derivatives *via* cross-coupling reaction.

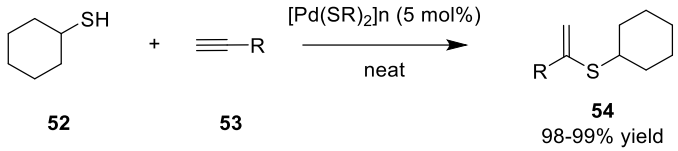
[56] Schwartz, A.; Madan, P. B.; Mohacsi, E.; O`Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851.
[57] Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.
[58] Moreau, X.; Campagne, J. J. *Organomet. Chem.* **2003**, *687*, 322.
[59] Namyslo, J.; Stanitzek, C. *Synthesis* **2006**, 3367.
[60] Moreau, X.; Campagne, J. M.; Meyer, G.; Jutand, A. *Eur. J. Org. Chem.* **2005**, 3749.

Thiols operate as nucleophiles also in addition reactions, Scheme 2.8, Eq.4 and Eq.5.[61] For example, this reaction was used for the synthesis of heterocycles such as benzothiazoles **51**, Scheme 2.12. Bao and co-workers developed the cyclization reaction of 2-aminothiophenol (**36**) with *β*-diketones **50** in the presence of the TsOH·H_2O as Brønsted acid providing various 2-substituted benzothiazoles **51** in good to excellent yields (51−92%).[62]



Scheme 2.12 Synthesis of benzothiazoles **51**.

In 2007, Ananikov and co-workers developed the additions of sulfur nucleophiles to the carbon−carbon triple bonds, Scheme 2.13. They demonstrated that Pd nanoparticles catalysed the regioselective addition of cyclohexane thiol **52** to alkyne **53** providing the vinyl sulfide **54** in good yield and selectivity.[63]



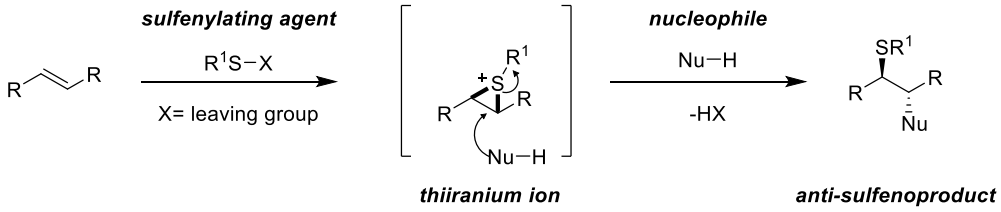
Scheme 2.13 Addition of thiols to C-C triple bonds.

2.2.2 Electrophilic sulfur reagents

Electrophilic sulfur reagents has been known since the 1960s in the context of the studies of the mechanism of the electrophilic additions of chalcogenides to carbon-carbon double and triple bonds. The intermediates thiiranium ions, also named episulfonium ions, and thiirenium ions were isolated and characterized by X-Ray analysis when the alkene or alkyne present

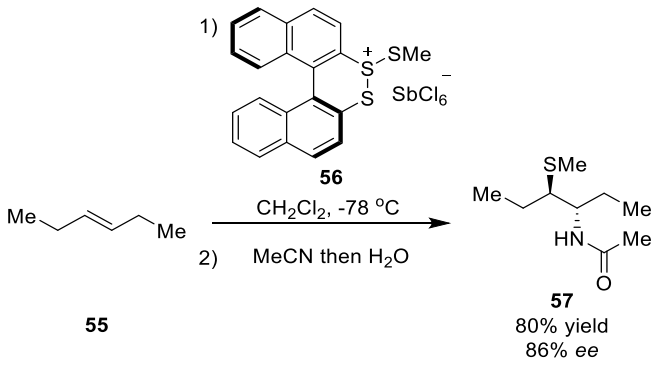
[61] Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807.
[62] Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Org. Lett.* **2014**, *16*, 764.
[63] Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y.; Timofeeva, T. V. *J. Am. Chem. Soc.* **2007**, *129*, 7252.

very bulk substituents.[64] Thiiranium ions are comparable to epoxides and aziridinium ions in their ability to undergo ring opening with a variety of nucleophiles, Scheme 2.14. Thiiranium ions are generated from reaction of alkenes with electrophilic sulfur reagents, such as sulfenyl halides, thiosulfonium salts, and sulfenamides.[65] Despite the high reactivity of thiiranium ions, they are stable at low temperature and undergo stereospecific ring opening via S_N2 mechanism by nucleophiles, providing the *anti*-sulfenofunctionalized products.[66]



Scheme 2.14 Sulfenilation of an alkene *via* the intermediate thiiranium ion.

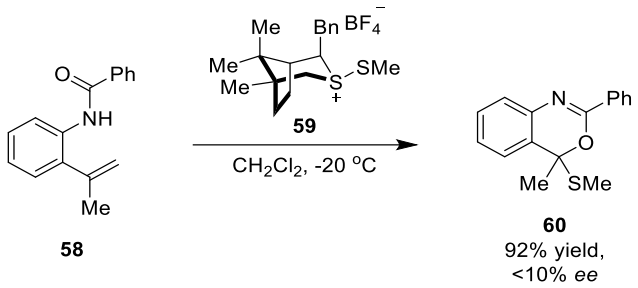
Few examples are reported for the stereoselective sulfeno-functionalization reactions *via* thiiranium ions. In 1994, Pasquato and co-workers described the first example of stereoselective sulfeno-amination of *trans*-3-hexene (**55**) in the presence of a stoichiometric amount of *S*-methylthiobinaphthyl-derivative **56**, Scheme 2.15. Opening of thiiranium ion with acetonitrile in the presence of water generated product **57** in 80% yield with 86% *ee*. The lower temperature (-78 °C) led to product **57** with higher enantiomeric purity, consistent with the temperature dependence on the thiiranium stability.[67]



Scheme 2.15 Stereoselective sulfeno-functionalization reaction developed by Pasquato.

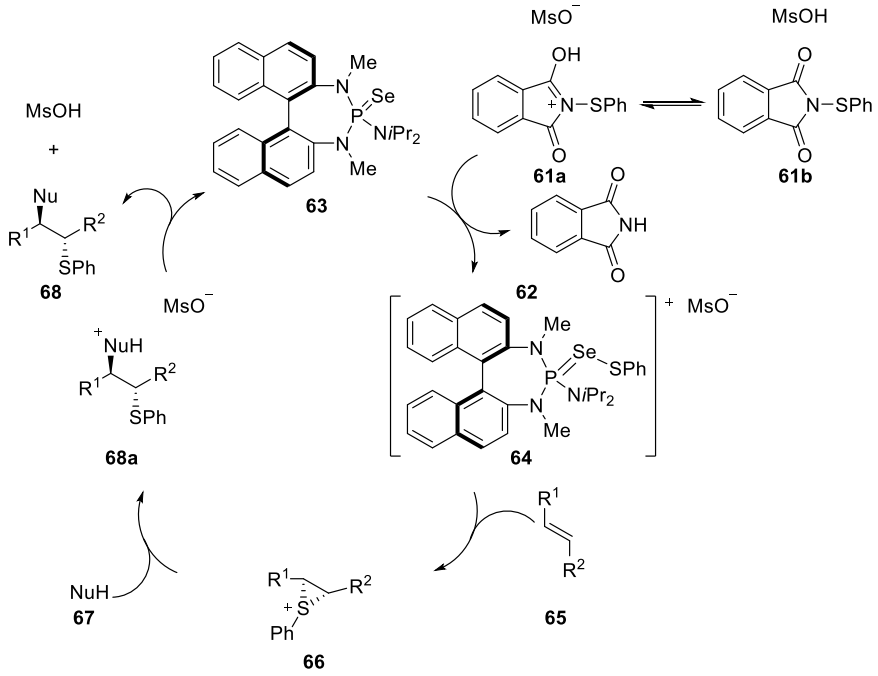
[64] a) Schmid, G. H.; Garratt, D. G. *The Chemistry of Double- Bonded Functional Groups*; John Wiley & Sons: London, **197**; b) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons, Ltd.: West Sussex, UK, **1990**; pp 403−516.
[65] Destro, R.; Lucchini, V.; Modena, G.; Pasquato, L. *J. Org. Chem.* **2000**, *65*, 3367.
[66] a) Fachini, M.; Lucchini, V.; Modena, G.; Pasi, M.; Pasquato L. *J. Am. Chem. Soc.* **1999**, *121*, 3944; b) Denmark, S. E.; Vogler, T. *Chem. Eur. J.* **2009**, *15*, 11737.
[67] Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.* **1994**, 1565.

After this publication and in the same year, Rayner reported the intramolecular ring opening of thiiranium ions generated from the chiral methylthio-sulfonium salt **59** to yield benzoxazine **60** with good yield and low stereoselectivity, Scheme 2.16.[68]



Scheme 2.16 Stereoselective sulfeno-functionalization reaction developed by Rayner.

Only 20 years later, Denmark and co-workers developed an organocatalytic and stereoselective sulfenofunctionalization reaction in the presence of selenophosphoramide **63** as catalyst, Scheme 2.17.[69] The catalytic cycle initiates with the sulfenylation of the selenophosphoramide Lewis base **63** mediated by MsOH to generate the catalytically active intermediate **64**. Subsequently, the arylsulfenyl group is transferred to the alkene **65**, forming the enantiomerically enriched thiiranium ion **66**. Its stereospecific ring opening by the nucleophile **67** delivers the product **68** and regenerates catalyst **63**. Products were obtained with good or very good chemical yields and excellent enantiomeric excess.

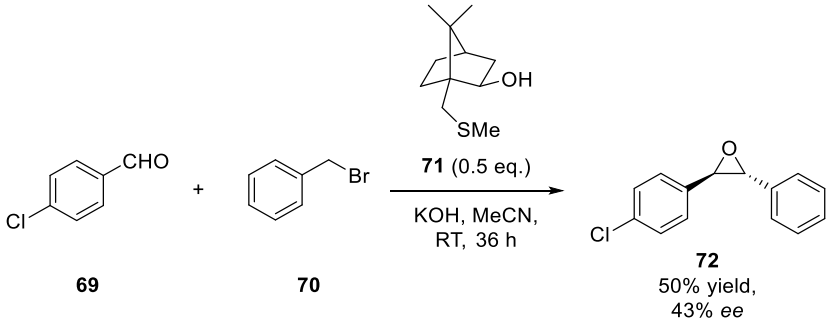


Scheme 2.17 Catalytic cycle involving the chiral selenophosphoramide **63.**

[68] Archer, N. J.; Rayner, C. M.; Bell, D.; Miller, D. *Synlett* **1994**, *1994*, 617.
[69] Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.* **2014**, *6*, 1056.

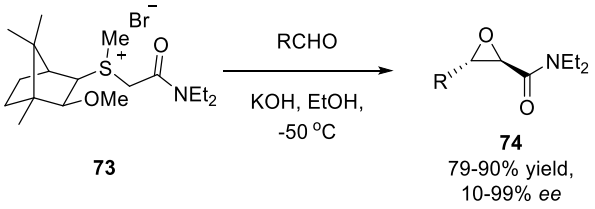
2.2.3 Thiols as reagent for the C-O and C-C bond formation

Sulfonium salts and their corresponding ylides are powerful and versatile reagents for epoxidation, cyclopropanation and aziridation reactions.[70] In 1989, Furukawa's group developed the first successful example of stereoselective epoxidation using chiral sulfonium ylides, Scheme 2.18.[71] The chiral sulfide **71**, derived from (+)-10-camphorsulfonic acid, was used to promote the reaction of aldehyde **69** and benzyl bromide **70** in the presence of KOH, through Corey-Chaykovsky mechanism, and *trans*-epoxide **72** was obtained with 47% *ee*.



Scheme 2.18 Application of chiral sulfide **71** in an example of stereoselective epoxidation reaction.

In 2002, Aggarwal and co-workers developed a stereoselective Darzens reaction between the camphor-derived sulfonium salt **73** and several aldehydes affording *trans*-epoxides **74** with good yield and excellent stereoselectivity, Scheme 2.19.[72]

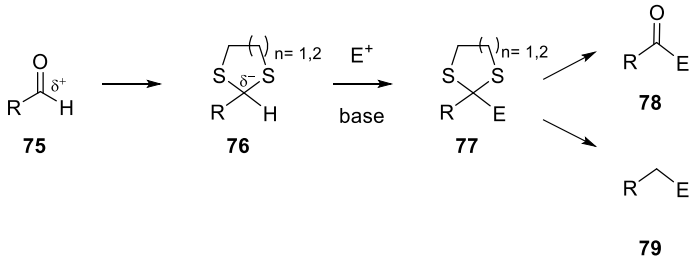


Scheme 2.19 Application of sulfonium salts for stereoselective Darzens reactions.

The last example reported is about the use of dithianes **76**, Scheme 2.20, for the carbon-carbon bond forming reaction.[73] Carbonyl compounds **75** are characterized by the presence of an electrophilic site at the carbonyl carbon. The electronic properties of this carbon can be reversed (umpolung) by transformation in dithianes **76**, discovered by Corey and Seebach.[74]

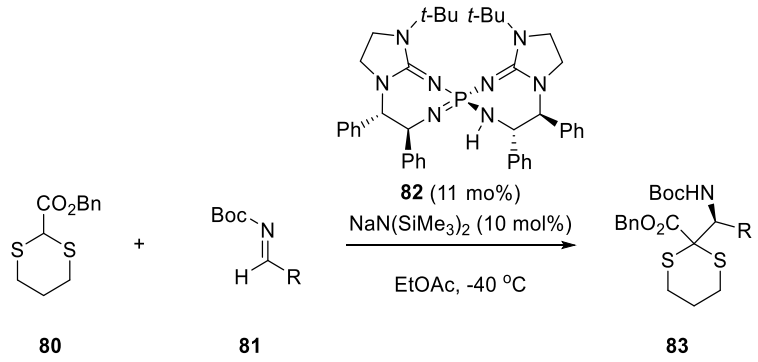
[70] Li, A. H.; Dai, L. X. *Chem. Rev.* **1997**, *97*, 2341.
[71] Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222.
[72] Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 9964.
[73] Yus, M.; Nájera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.
[74] a) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed.* **1965**, *4*, 1077; b) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed.* **1965**, *4*, 1077; c) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

These compounds are acyl anion equivalents, after reaction with an electrophile, the dithioacetal moiety **77** can be hydrolysed providing ketone **78** or it can be reductively removed to yield the compound **79**.



Scheme 2.20 Reactivity of dithianes **76** for the umpolung of carbonyl compounds.

Recently, Terada and co-workers developed a catalytic and stereoselective addition reaction of 1,3-dithiane derivatives **80** to aromatic imines **81** by using the chiral bis(guanidino)-iminophosphorane organosuperbase catalyst **82**, Scheme 2.21.[75] The reaction provided optically active *α*-amino-1,3-dithiane derivatives **83** in good yield and stereoselectivity.



Scheme 2.21 Stereoselective synthesis of *α*-amino-1,3-dithiane **83**.

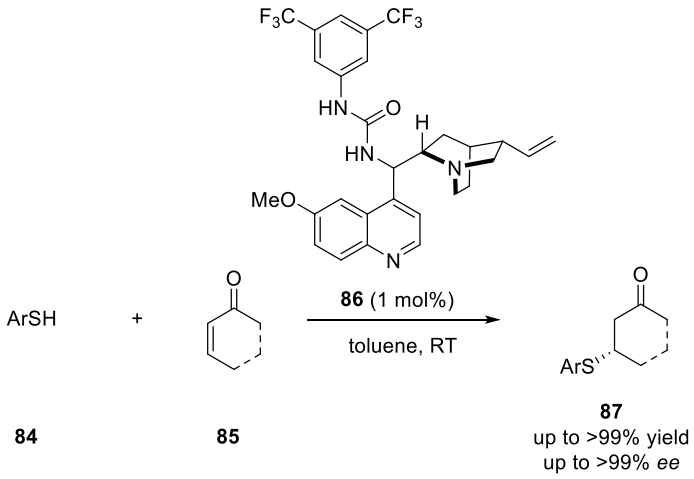
[75] Kondoh, A.; Oishi, M.; Takeda, T.; Terada, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 15836.

2.3 Organocatalytic and stereoselective sulfa-Michael additions

Among the additions of sulfur nucleophiles to electron-deficient alkenes, the 1,4-addition, the sulfa-Michael addition (SMA) plays an important role for the formation of C-S bonds and considerable efforts have been paid to improve the chemical yield and the stereoselectivity of these reactions.[76] Chiral organocatalysts including Lewis bases, Lewis base−Brønsted acid catalysts, and secondary as well as primary amines have been used in various types of stereoselective SMAs.

As reported in Section 1.3, Wynberg developed the first organocatalytic and stereoselective addition of sulfur nucleophiles to *α,β*-unsaturated carbonyl compounds in the presence of *Cinchona*-alkaloids, Scheme 1.4, eq. 1. Over the past seven-eight years, considerable efforts have been made to improve the efficiency, the stereoselectivity and the scope of SMA processes as documented by several papers appeared in the literature in this time span. I will comment, in the next few pages, the most relevant examples, in my opinion, published recently.

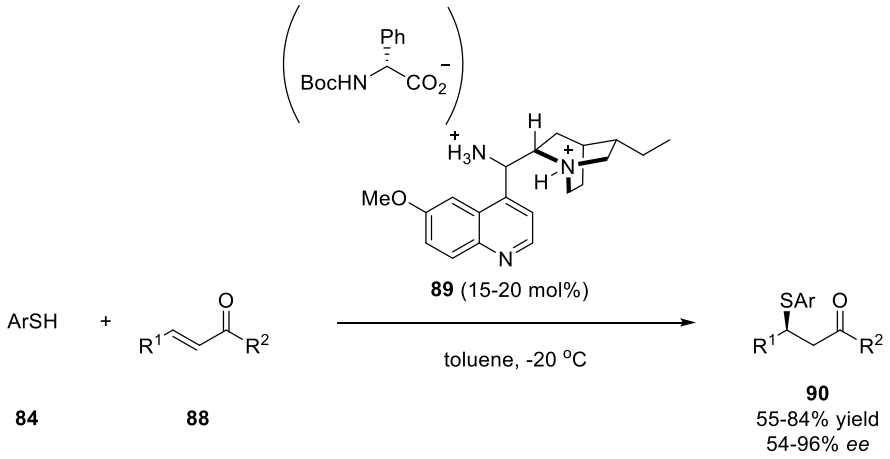
In 2010, Singh and co-workers reported the *Cinchona* alkaloid-derived urea **86** as efficient organocatalyst for stereoselective conjugate addition between thiols **84** and various *α,β*-unsaturated ketones **85** to provide optically active sulfides with high chemical yields (up to >99%) and enantiomeric excess up to >99% *ee*, Scheme 2.22. The reaction was performed with 0.1 mol% of catalyst **86** in toluene at room temperature.[77]



Scheme 2.22 Application of *Cinchona* alkaloid-derived urea **86** in stereoselective SMAs.

[76] a) D. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, *7*, 959; b) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807.
[77] Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089.

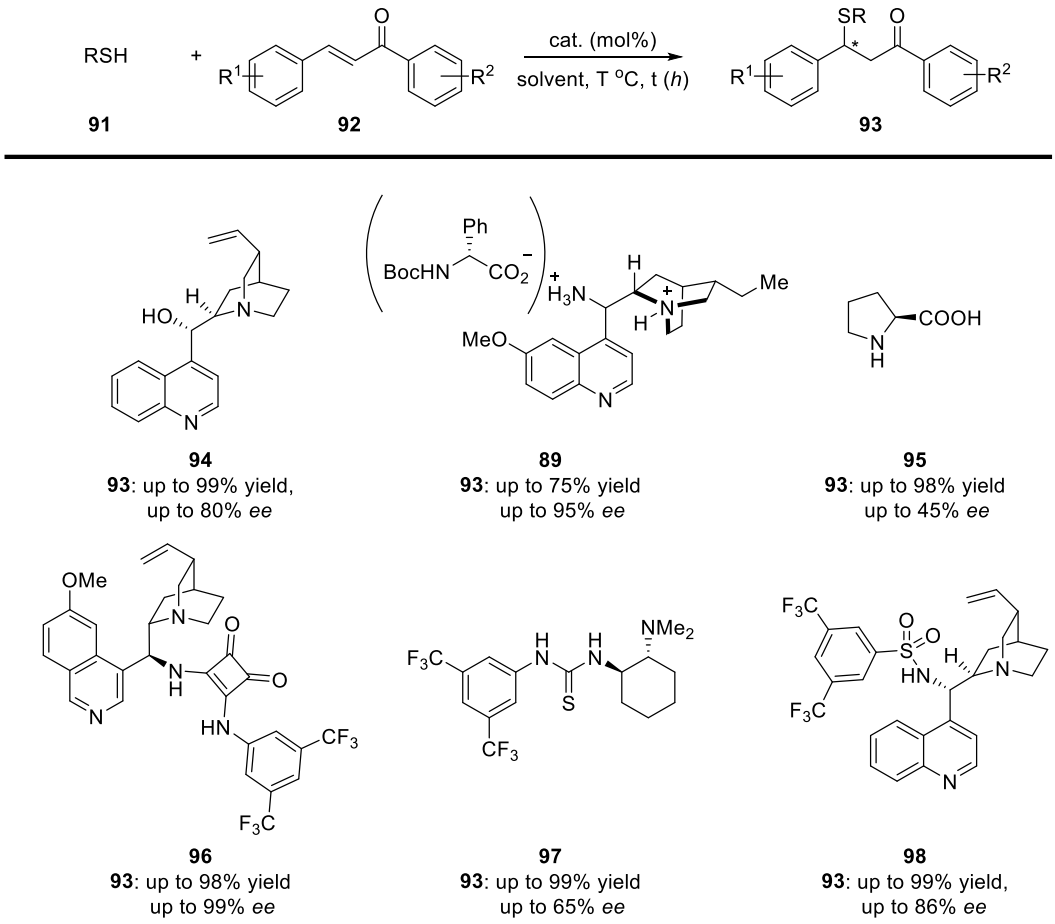
Melchiorre explored the application of *Cinchona*-derived primary amine **89** as catalyst for the 1,4-addition reaction of thiols **84** to *α,β*-unsaturated ketone **88** *via* iminium ion formations, Scheme 2.23. The reaction provided the desired product **90** from moderate to good yields and stereoselectivities.[78]



Scheme 2.23 Stereoselective SMA developed by Melchiorre and co-workers.

Among acyclic enones, an interesting Michael acceptor is the *trans*-chalcone (**92**), Scheme 2.24, since it opens the synthetic way to fine chemicals and or active pharmaceutical ingredients as for example the drug Montelukast. Skarżewski and co-workers developed the Michael addition of thiols **91** to chalcones **92** in the presence of 1.5 mol% of (+)-cinchonine (**94**) leading to the corresponding adducts **93** with an *ee* up to 80%.[79] The amino catalysis via iminium activation was employed by Melchiorre, as above mentioned, and Kumar's group.[80] In 2010, Chen and co-workers described the *Cinchona*-alkaloid based squaramide catalyst **96** allowing the preparation of Michael adducts **93** of *trans*-chalcone with excellent stereoselectivity and moderate to good yields.[81] Wang and co-workers explored the activity of Takemoto thiourea **97** for the addition of thioacetic acid to *trans*-chalcone (**92**) affording synthetically useful thioesters in excellent yields with moderate stereoselectivities.[82] Recently, Bernardi's group investigated the reaction between 2-aminothiophenol (**36**) and *trans*-chalcone (**92**) by using sulfonamide **98** derived from 9-amino-(9-deoxy)-epicinchonidine which gave the desired product with excellent yield and 86% *ee*.[83]

[78] Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49.
[79] a) J. Skarżewski, M. Zielińska-Blajet, I. Turowska-Tirk, *Tetrahedron: Asymmetry* **2001**, *12*, 1923; b) M. Zielińska-Blajet, R. Kowalczyk, J. Skarżewski, *Tetrahedron* **2005**, *61*, 5235.
[80] Kumar, A.; Akanksha *Tetrahedron* **2007**, *63*, 11086.
[81] Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2010**, *352*, 2137.
[82] H. Li, L. Zu, J. Wang, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 3145.
[83] Corti, V.; Gonzalez, P. C.; Febvay, J.; Caruana, L.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Eur. J.Org. Chem.* **2017**, 49.



Scheme 2.24 Stereoselective addition of thiols to *trans*-chalcone in the presence of catalysts **89** and **94-98**; chemical yield and stereoselectivities are also reported.

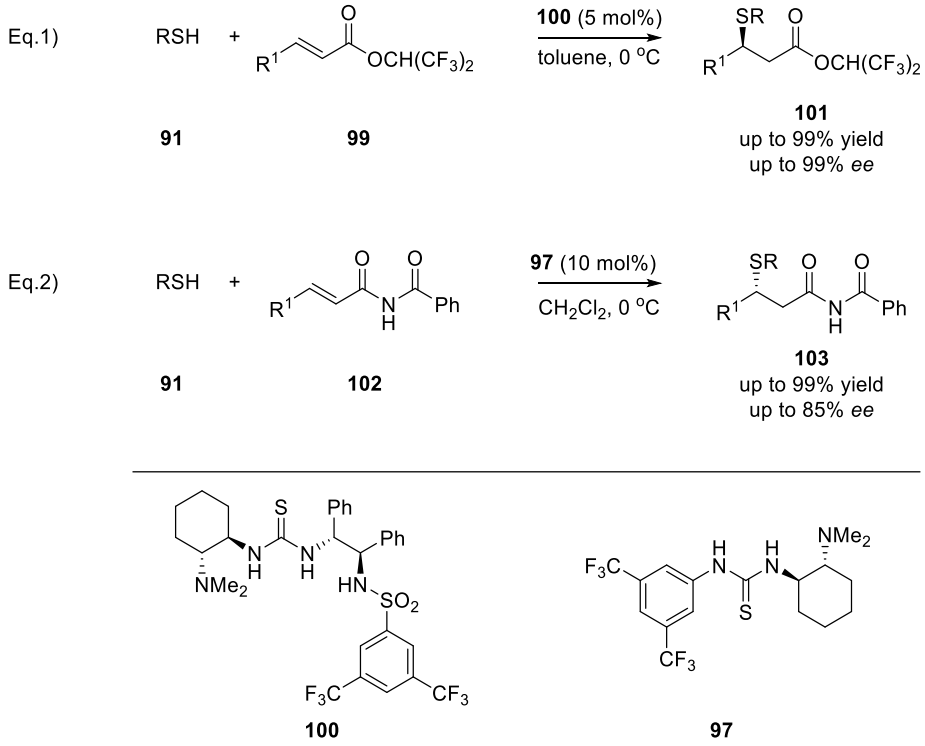
In light of the versatility of the reaction and the biological activity of *β*-mercapto carboxylic acid derivatives, Wang and co-workers developed an organocatalyzed asymmetric sulfa-Michael addition of thiols to a variety of hexafluoroisopropyl *α,β*-unsaturated esters **99**, Scheme 2.25, eq. 1. Michael adducts **101** were obtained in high yields, up to 99% with excellent stereoselectivities, up to 99% *ee*.[84]

Chen *et al.* developed the addition of thiols to *α,β*-unsaturated imides **102** in the presence of Takemoto thiourea **97** leading to the adducts **103** in high yields and moderate stereoselectivities, Scheme 2.25, eq. 2.[85]

Nitroalkenes are very common acceptors for various nucleophiles in stereoselective and non-stereoselective transformations. Among these, the stereoselective Michael addition of

[84] Fang, X.; Li, J.; Wang, C. *J. Org. Lett.* **2013**, *15*, 3448.
[85] Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett.* **2005**, 603.

thiols to nitroalkenes represents an approach to obtain chiral nitroalkanes, which can be converted into other valuable molecules.[86]

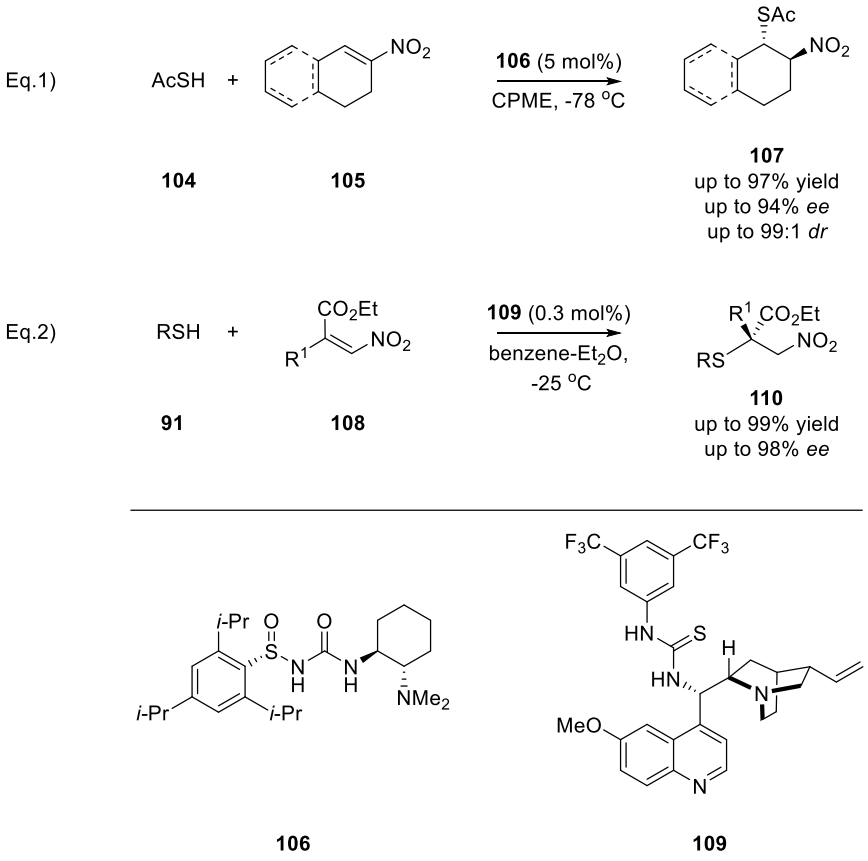


Scheme 2.25 Organocatalytic and stereoselective addition of thiols to *α,β*-unsaturated esters and imides.

In 2012, Ellman's group demonstrated the catalytic utility of the sulfinyl urea organocatalyst **106** for the stereoselective addition of thioacetic acid (**104**) to *α,β*-disubstituted nitroalkenes **105**, Scheme 2.26, eq. 1. The desired adducts **107**, bearing two stereogenic centres, were obtained in high yields, up to 97%, good stereoselectivities, up to 94% *ee* and excellent diastereomeric ratios, up to 99:1 *dr*.[87]

Xiao and co-workers reported an organocatalytic and stereoselective SMA of *β,β*-disubstituted nitroalkenes **108**, Scheme 2.26, eq. 2. Various thiols were efficiently added to the electrophilic nitroacrylates **108** using a low loading of the bifunctional-thiourea catalyst **109** derived from *Cinchona*-alkaloids to provide excellent yields (up to 99%) and high stereoselectivities (up to 98% *ee*) of the sulfa-Michael adducts **110** with a tetrasubstituted stereocenter. The addition product of this transformation was successfully transformed into new $\beta^{2,2}$-amino acids.[88]

[86] Ono. N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, **2001**.
[87] Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704.
[88] Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W. J. *Org. Lett.* **2009**, *11*, 3946.



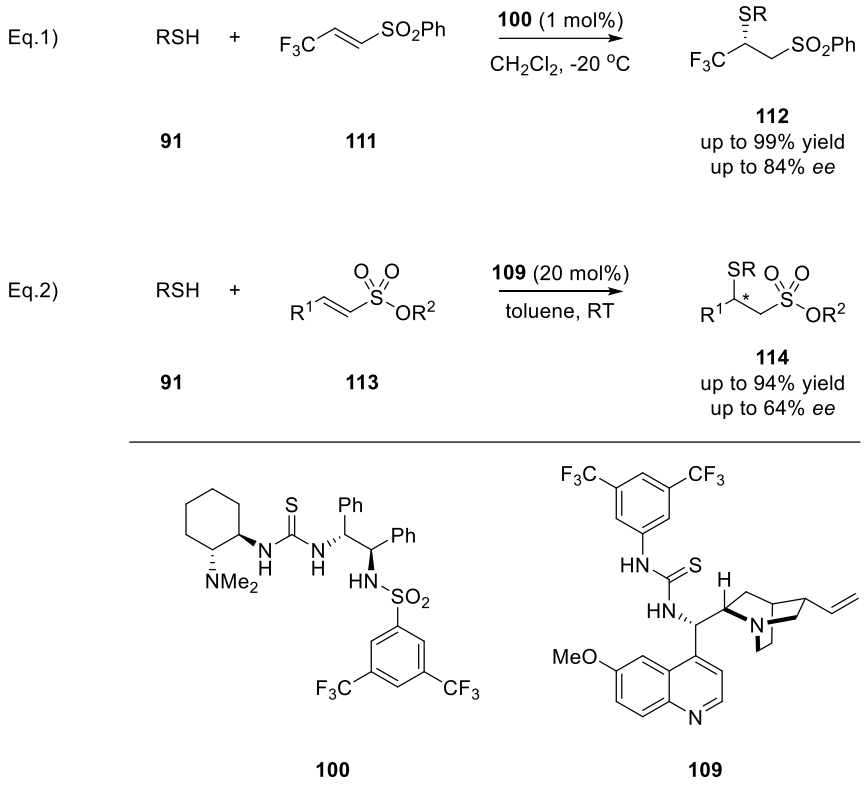
Scheme 2.26 Organocatalytic and stereoselective addition of thiols to nitroalkenes.

The last examples to report are the organocatalytic stereoselective conjugate additions of thiols to *α,β*-unsaturated sulfones and sulfonates providing a straightforward strategy to form optically active building blocks bearing sulfur containing functionalities.[89]

Wang and co-authors developed an asymmetric SMA of thiols to (*E*)-3,3,3-trifluoropropenyl phenyl sulfones **111** catalyzed by the bifunctional amine-thioureasulfonamide **100**, Scheme 2.27, eq. 1. The desired sulfones **112** bearing a trifluoromethylated stereogenic centre were obtained in high yields up to 99% with moderate stereoselectivities up to 84% *ee*.[90]

Enders and Hoffman explored the reactivity of *α,β*-unsaturated sulfonates **113** for the stereoselective SMA, Scheme 2.27, eq. 2. The *Cinchona* alkaloid-derived thiourea **109** catalyzed the SMA of thiols to various alkylsubstituted *α,β*-unsaturated sulfonates **113**, affording *β*-sulfur-substituted sulfonic acid ester products **114** in good yields, up to 94% and moderate stereoselectivities, up to 64% *ee*.[91]

[89] Alba, A.-N. R.; Companyó, X.; Rios, R. *Chem. Soc. Rev.* **2010**, *39*, 2018.
[90] Fang, X.; Dong, X.-Q.; Liu, Y.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2013**, *45*, 4509.
[91] Enders, D.; Hoffman, K. *Eur. J. Org. Chem.* **2009**, 1665.

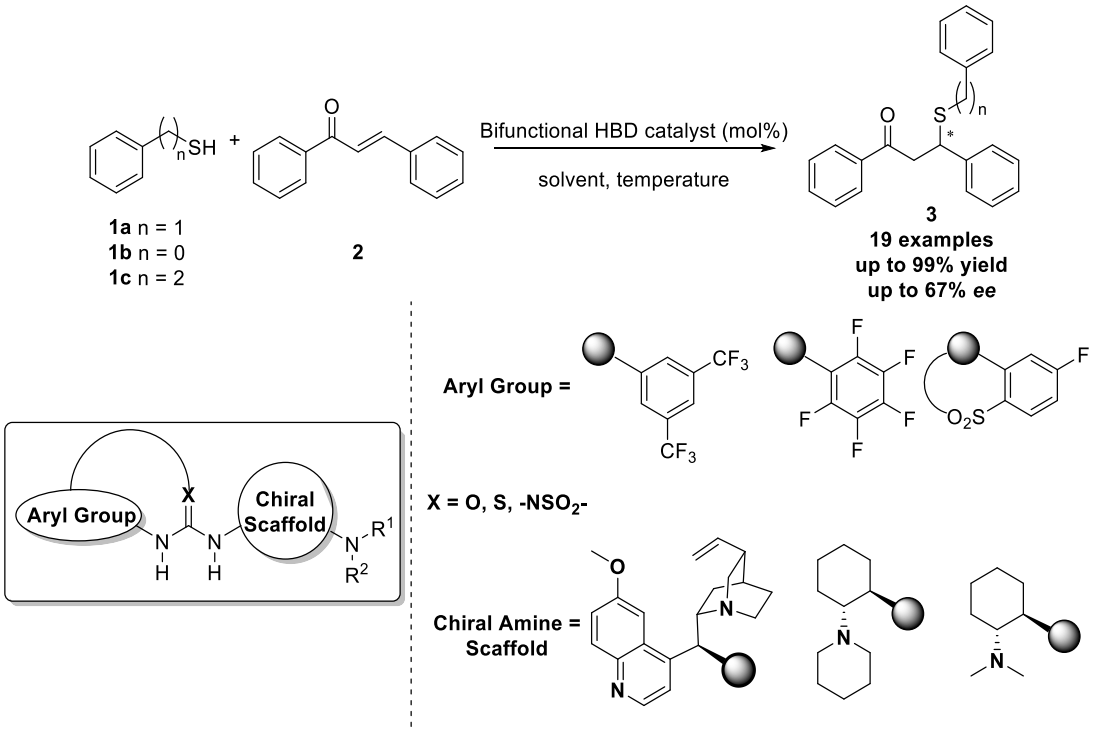


Scheme 2.27 Stereoselective addition of thiols to α,β-unsaturated sulfones and sulfonates promoted by organocatalysts **100** and **109**.

Chapter 3: sulfa-Michael addition

3.1 Object of study

Bifunctional hydrogen-bond donor (HBD) catalysis[92] represents an approach for activating both the nucleophile and the electrophile reaction components and it has been used in various types of stereoselective SMAs.[76,93]



Scheme 3.1 Comparative analysis of some HBD catalysts in the stereoselective SMAs to *trans*-chalcone (**2**) discussed in this thesis.

As previously discussed, there are relatively few examples of stereoselective SMAs catalysed by bifunctional HBDs involving *trans*-chalcone (**2**) as Michael acceptor.[79,81-83] Even fewer comparative evaluations of the most popular organocatalysts, carried out in a single experimental setting, are available for this reaction. Nevertheless, frameworks structurally related to the 3-(alkylsulfanyl)-1,3-diphenylpropan-1-ones, obtained by addition of thiols **1** to *trans*-chalcone (**2**), are of particular industrial interest because of their occurrence in the synthesis of the antiasthma agent Montelukast.[42,43] Recently these species were also proposed

[92] a) Taylor, S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; b) Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299; c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal*. **2015**, *357*, 253; d) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, **2009**; e) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; f) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967; g) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[93] a) Wang, Y.-F.; Wu, S.; Karmaker, P. G.; Sohail, M.; Wang, Q.; Chen, F.-X. *Synthesis*, **2015**, *47*, 1147; b) Duan, J.; Cheng, J.; Li, B.; Qi, F.; Li, P. *Eur. J. Org. Chem*. **2015**, *28*, 6130; c) Breman, A. C.; Telderman, S. E. M.; van Santen, R. P. M.; Scott, J. I.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *J. Org. Chem.* **2015**, *80*, 10561; d) Fukata, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc*. **2015**, *137*, 5320; e) Ding, R.; Zheng, B.; Wang, Y.; Peng, Y. *Org. Lett.* **2015**, 17, 4128; f) Zaghi, A.; Bernardi, T.; Bertolasi, V.; Bortolini, O.; Massi, A.; De Risi, C. *J. Org. Chem.* **2015**, *80*, 9176; g) Wang, R.; Liu, J.; Xu, J. *Adv. Synth. Catal*. **2015**, *357*, 159; h) Chen, J.; Meng, S.; Wang, L.; Tang, H.; Huang, Y. *Chem. Sci*. **2015**, *6*, 4184; i) Zhao, B.-L.; Du, D.-M. Asian *J. Org. Chem*. **2015**, *4*, 778.

as promising estrogen receptor ligands for breast cancer therapy because of their structural resemblance to Raloxifene and Arzoxifene[94] or precursors for antibacterial and antifungal agents.[95] Respect to other enones, *trans*-chalcone (**2**) still represents a challenging substrate, though several organocatalytic SMAs precede with excellent yield, the degree of stereoselection is generally poor. Only Chen and co-workers described a cinchona alkaloid based squaramide catalyst allowing the preparation of Michael adducts of *trans*-chalcone (**2**) with excellent stereoselectivity and moderate to good yields.[81] However, despite the large substrate and nucleophile scope of this catalyst, the Michael adduct of benzenethiol (**1a**) to *trans*-chalcone (**2**) could be obtained with 70% *ee* only. In the context of HBD catalysts optimization, while the design of the chiral scaffold for best performance remains difficult to be rationalized, physical organic chemistry approaches have provided some insights on the desirable properties of the hydrogen bond donor unit. In 2010, Luo and Cheng studying the p*K*a of a range of chiral thiourea catalysts found a linear free energy relationship between the p*K*a and both the catalytic activity and stereoselectivity in the Michael addition of malonates to nitrostyrene.[96] Furthermore, the equilibrium acidities in DMSO for a series of common thiourea catalysts have been determined by Schreiner and co-workers;[97] according to these authors, a survey of literature reports indeed suggests that increasing the acidity of the NH thiourea protons has beneficial effects on reaction rates of a number of catalysed reactions. Somewhat on this line, the acidity of some chiral Brønsted acid[98] and of a number of popular squaramide catalysts[99] have been determined as an aid to the design of novel organocatalysts. Prompted by this information, here we report the comparative analysis, in a single experimental setting, of some HBD catalysts in stereoselective SMAs to *trans*-chalcone (**2**), Scheme 3.1. We screened some popular thiourea and some structurally similar derivatives with increased Brønsted acidity of the hydrogen bond donor unit. The catalysts were screened against different nucleophiles, including phenylmethanethiol (**1a**), the rarely used benzenethiol (**1b**) and 2-phenylethanethiol (**1c**); the latter, to the best of our knowledge, was never analysed in organocatalyitic SMA reactions.

[94] Kumar, A.; Tripathi, V. D.; Kumar, P.; Gupta, L. P.; Akanksha; Trivedi, R.; Bid, H.; Nayak, V.L.; Siddiqui, J. A.; Chakravarti, B.; Saxena, R.; Dwivedi, A.; Siddiquee, M. I.; Siddiqui, U.; Konwar, R.; Chattopadhyay, N. *Bioorg. Med. Chem.* **2011**, *19*, 5409.
[95] Konduru, N. K.; Dey, S.; Sajid, M.; Owais, M.; Ahmed, N. *Eur. J. Med. Chem*. **2013**, *59*, 23-30.
[96] Li, X.; Deng, H; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 450.
[97] Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.
[98] a) Yang, C.; Xue, X.-S.; Jin, J.-L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2013**, *78*, 7076; b) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donogue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524; c) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.
[99] Ni, X.; Li, X.; Wang, Z.; Cheng, J.-P. *Org. Lett.* **2014**, *16*, 1786.

3.2 Results and discussion

3.2.1 Synthesis of catalysts

In our study we surveyed the activity of seven HBD catalysts **I-VII**, Figure 3.1A, in the stereoselective SMA of phenylmethanethiol **1a**, benzenethiol **1b**, and 2-phenylethanethiol **1c** to *trans*-chalcone **2**, Figure 3.1B. The catalysts were selected to include the most studied thioureas along with other structurally related catalysts but with increased hydrogen bond donor abilities. Namely, we analysed the activity of the Soòs catalyst **I** and that of the analogue **II** bearing the highly electron-withdrawing pentafluorophenyl group instead of the 3,5-bistrifluoromethyl moiety. The Takemoto thiourea **III**, the related catalyst **IV** that features a piperidino unit instead of the dimethylamino moiety, and the urea **V** were compared to the benzothiadiazine catalyst **VI** as an analogue with increased Brønsted acidity. In the case of the SMA of benzenethiol to *trans*-chalcone, we also tested the activity of Nagasawa catalyst **VII**.

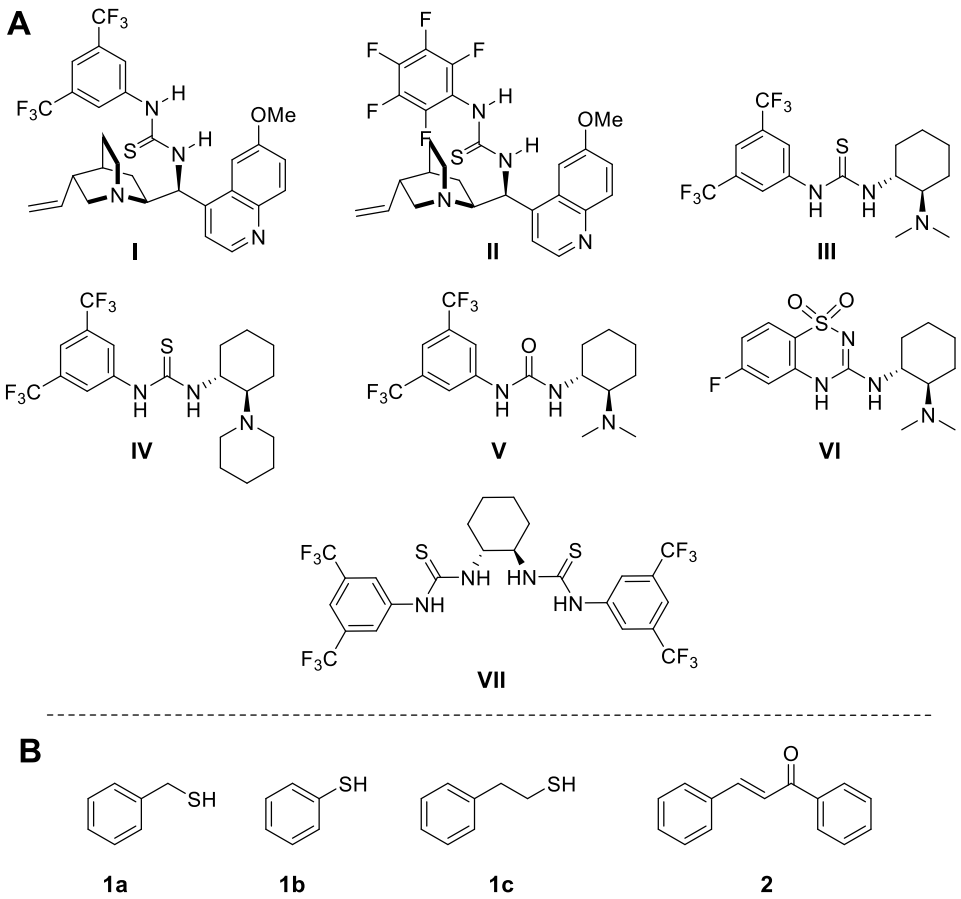
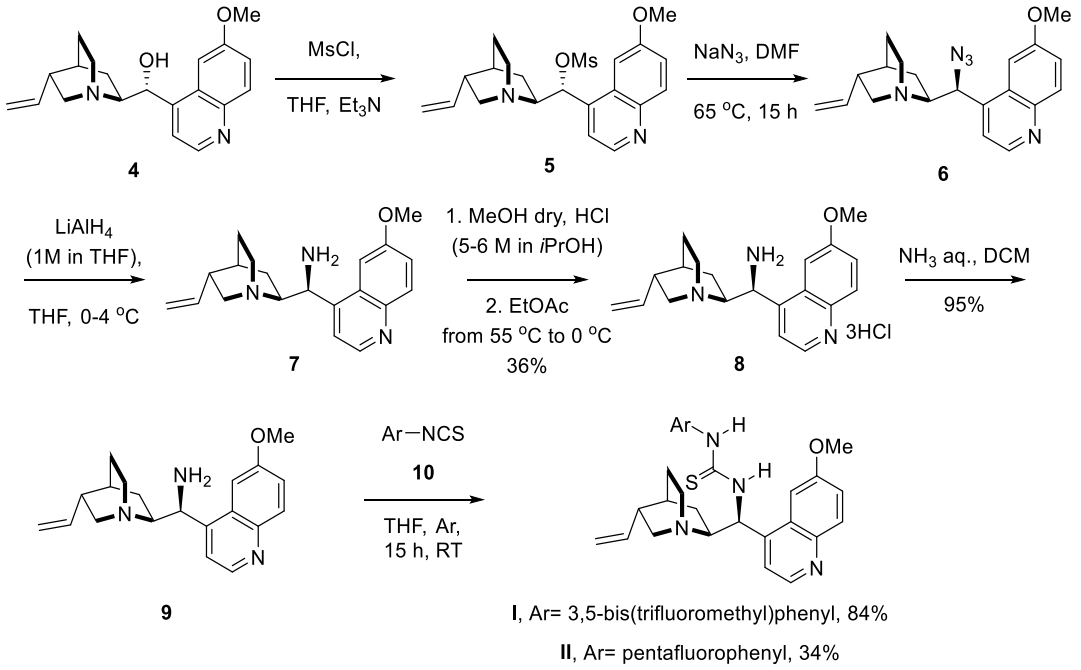


Figure 3.1 Hydrogen-bond donor catalysts and substrates used in this study.

Initiating the study, the syntheses of catalysts **I-VII** were performed according to the procedures reported in the literature. The preparation of catalysts **I-II** required six steps,

Scheme 3.2.[100] Starting from quinine **4**, the amino-group at the C-9 position was introduced by mesylation of hydoxyl group, its substitution with azide and subsequent reduction with lithium aluminium hydride providing 9-*epi*-QA **7**. The purification of 9-*epi*-QA **7** from the reaction mixture was performed by precipitation as the tri-hydrochloride salt **8**. In particular, the crude compound **7** was dissolved in dry methanol and heated at 55 °C. To this solution, hydrochloric acid in isopropanol (5-6 M) and ethyl acetate were added affording compound **8** with 36% overall yield. Then, salt **8** was suspended in dichloromethane, basified with aqueous ammonia and extracted with ethyl acetate yielding 9-*epi*-QA **9**. The reaction of phenyl isothiocyanate **10** and amine **9** in dry THF and room temperature generated the desired catalysts **I-II**.

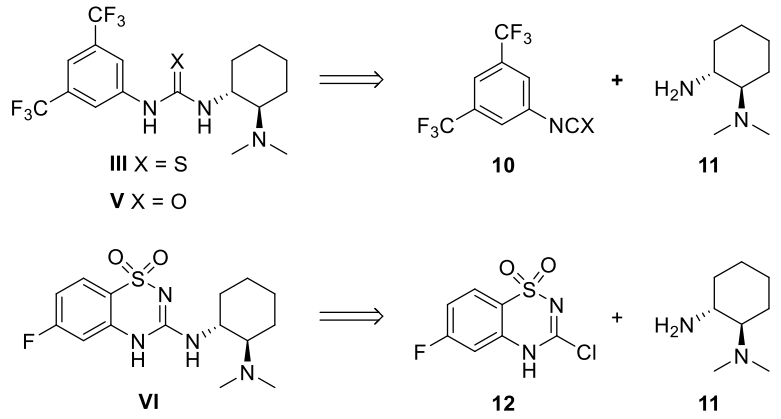


Scheme 3.2 Synthesis of catalysts **I-II**.

The synthetic pathway employed for the preparation of catalysts **III**, **V** and **VI** required the synthesis of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**),[101] Scheme 3.3.

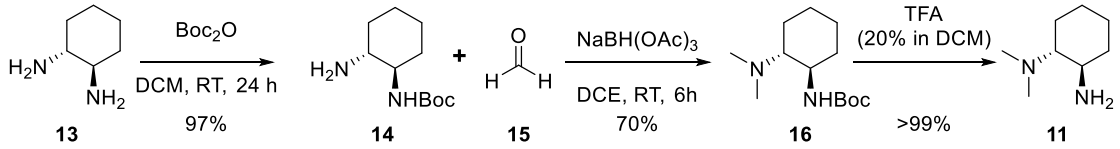
[100] a) Melchiorre P.; Bravo Lara, F.; Martin, R. *Eur. Pat. Appl*. **2014**, EP 2687527A1; b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

[101] Amarasinghe, N.-R.; Turner, P.; Todd, M.-H. *Adv. Synth. Catal.* **2012**, *354*, 2954.



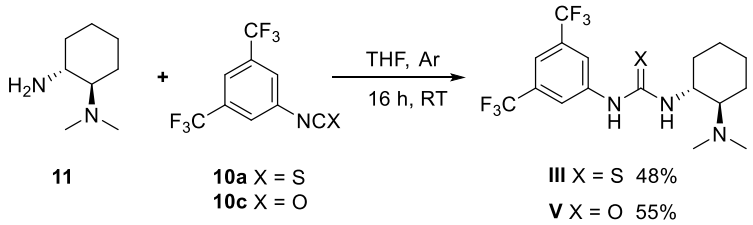
Scheme 3.3 Retrosynthetic analysis of catalysts **III**, **V** and **VI**.

As depicted in Scheme 3.4, the mono-Boc-protected diaminocyclohexane **14** was obtained in 97% yield by using 3.0 equivalents of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (**13**) and 1.0 equivalent of Boc_2O. Afterwards, the reductive amination of formaldehyde **15** with amine **14** carried out in 1,2-dichloroethane at room temperature and in the presence of sodium triacetoxyborohydride gave the dimethyl amine **16** in 70% yield. Finally, deprotection of the Boc-group with trifluoroacetic acid provided the desired amine **11** in 99% yield.



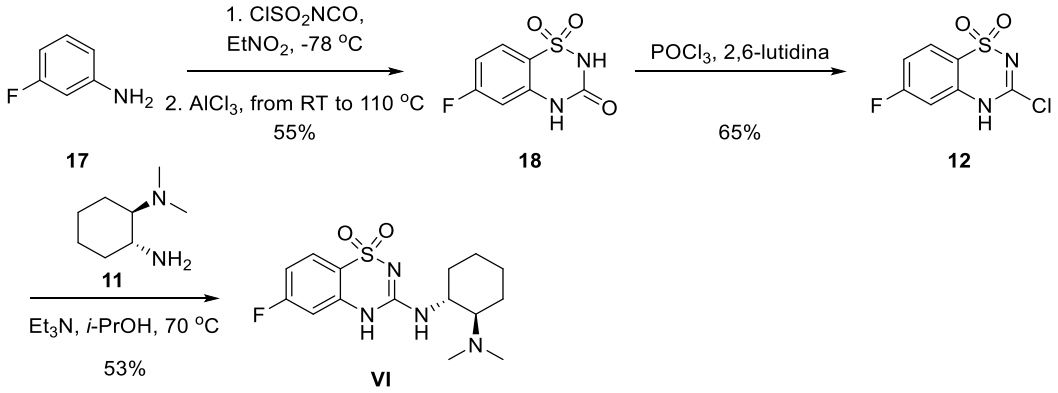
Scheme 3.4 Synthesis of amine **11**.

The reaction of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) in dry THF at room temperature gave the thiourea **III** in 48% yield. While, the reaction of dimethyl amine **11** and 3,5-bis(trifluoromethyl)phenyl isocyanate **10c** in dry THF at room temperature gaves the urea **V** in 55% yield, Scheme 3.5.[100b]



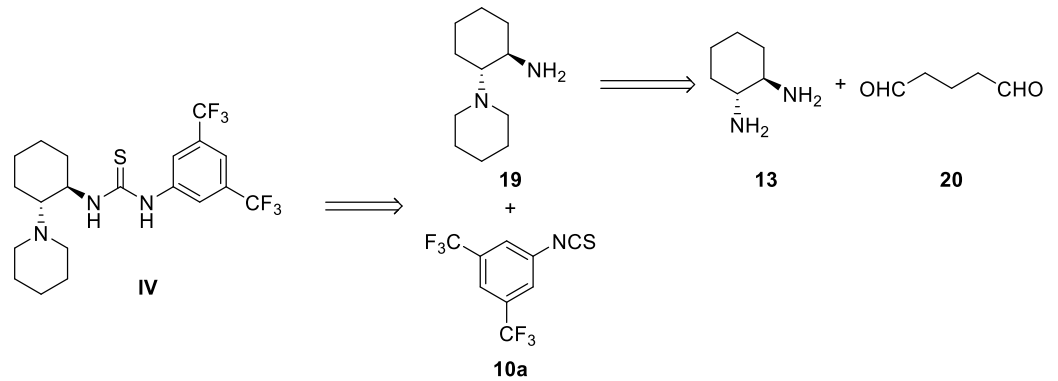
Scheme 3.5 Synthesis of catalysts **III** and **V**.

The synthesis of catalyst **VI** required the preparation of both amine **11** and compound **12**, Scheme 3.3.[102] Specifically, the reaction of 3-fluoroaniline (**17**) with chlorosulfonyl isocyanate and the subsequent intramolecular Friedel–Crafts acylation gave the product **18** with 55% yield, Scheme 3.6. Afterwards, in the presence of phosphorus oxychloride, the benzothiadiazine **12** was obtained in 65% yield. Finally, the reaction of amine **11** with benzothiadiazine **12** in isopropanol and triethylamine at 70 °C provided the catalyst **VI** in 53% yield.



Scheme 3.6 Synthesis of catalyst **VI**.

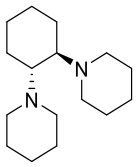
The synthetic route used for catalyst **IV** was based on the synthesis of amine **19** following the literature procedure, Scheme 3.7.[103] However, the reductive amination of glutaraldehyde **20** with amine **13** carried out in 1,2-dichloroethane at room temperature and in the presence of sodium triacetoxyborohydride did not give the desired compound **19** but the by-product **21**, Figure 3.2.



Scheme 3.7 Retrosynthetic analysis for catalysts **IV**.

[102] a) Inokuma, T.; Furukawa, M.; Takuya, U.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 10470; b) Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 11114.
[103] Yang, W.; Du, D.-M. *Adv. Synth. Catal.* **2011**, *353*, 1241.

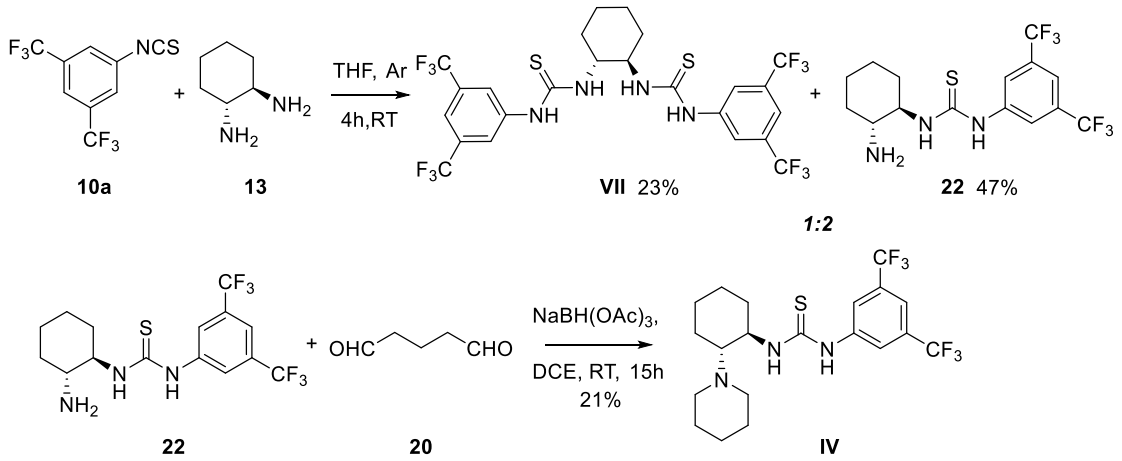
Therefore, the reaction of 1.2 equivalents of (1*R*,2*R*)-1,2-diaminocyclohexane (**13**) with 1.0 equivalent of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) in dry THF at room temperature was performed, Scheme 3.8. The reaction, after purification by flash chromatography, provided both the desired product **22** (47% yield) and the Nagasawa catalyst **VII** with 23% yield.[104]



21

Figure 3.2 By-product **21** observed during the synthesis of catalyst **IV**.

Subsequently, the reaction of compound **22** with glutaraldehyde **20** in 1,2-dichloroethane at room temperature and in the presence of sodium triacetoxyborohydride yielded the desired catalyst **IV** in 21% yield.



Scheme 3.8 Synthesis of catalysts **IV** and **VII**.

[104] Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.

3.2.2 Optimization of the reaction condition

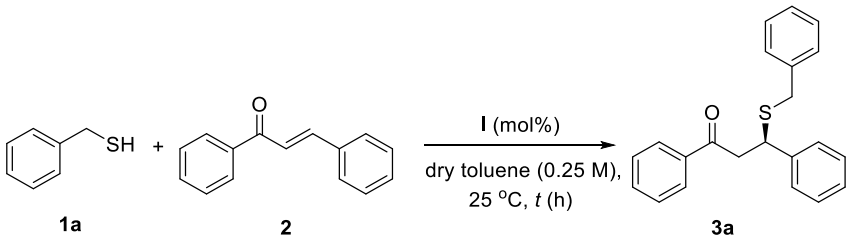
The reaction conditions were initially optimized for the addition of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**) catalysed by 9-*epi*-QT **I**.

Preliminary investigations displayed that the reaction in the presence of 0.5 mol% of catalyst **I** performed in dry toluene at 25 °C provided the desired thioether **3a** in 92% yield with 67% *ee*, Table 3.1, entry 2.

3.2.2.1 Effect of catalyst loading

Based on this result, the effect of the catalyst loading was investigated by increasing the amount of the catalyst **I** from 0.5 mol% to 1 mol% and to 5 mol%, Table 3.1.

Table 3.1 Effect of catalyst **I** loading on stereoselective sulfa-Michael addition (SMA) of benzyl thiol (**1a**) to *trans*-chalcone (**2**).[a]



entry	**I** (mol%)	*t* (h)[b]	yield (%)[c, d]	*ee* (%)[d, e, f]
1	0.1	144	89	58 (57)[g]
2	0.5	15	92	66
3	1	8	97	67
4[h]	1	8	97	67
5[h]	5	2	97	67

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1a/2** molar ratio in the presence of catalyst **I** and in 4.6 mL of dry toluene at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column. [f] The absolute configuration of the product **3a** was assigned to be (*R*) by comparison of the measured optical rotation with the value reported in the reference 81. [g] Determined by chiral HPLC analysis using a Lux cellulose III column after 48 hours. [h] SMAs were carried out on a 0.25 mmol scale.

While the increase up to 1 mol% of the catalyst produced a slight gain in the stereoselectivity and in the chemical yield, Table 3.1, entries 3-4, further addition of **I** up to 5 mol% did not produce further improvements in neither the yield nor stereoselectivity, Table 3.1, entry 5. When the reaction was carried out with 0.1 mol% of catalyst, both the stereoselectivity and the chemical yield dropped and a prolonged reaction time was required

for the completion of the process, Table 3.1, entry 1. Thus, in the presence of 1 mol% of catalyst **I**, the reaction showed to reach a stereoselectivity plateau of 67%, Figure 3.3.

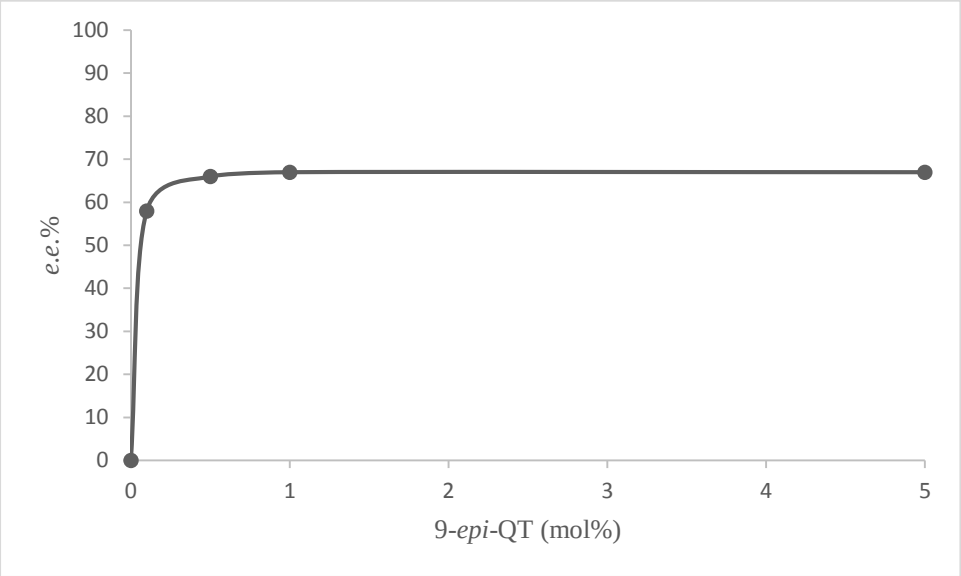


Figure 3.3 Correlation of catalyst **I** loading with stereoselectivity for SMA of benzyl thiol (**1a**) to *trans*-chalcone (**2**).

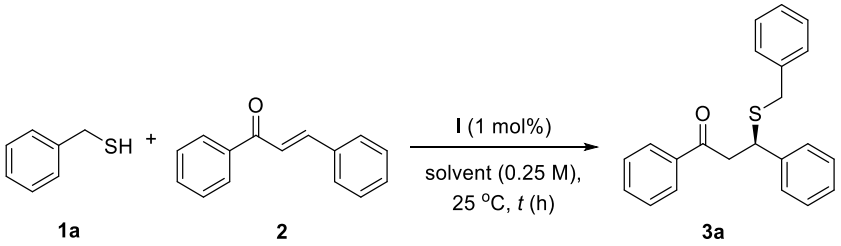
3.2.2.2 Effect of the solvent

With the optimized catalyst loading, the effects of various solvents were examined, Table 3.2. Solvents different from toluene gave lower chemical yields and stereoselectivities, with the reaction becoming more sluggish. By using dichloromethane or 1,2-dichloroethane, the Michael addition displayed a drop in both enantiomeric excess (43% *ee*) and reaction rate, Table 3.2, entries 2-4. Treatment of dichloromethane with alumina had no impact on the stereoselectivity and reaction rates. A 1:1 mixture of dry toluene and *n*-hexane gave **3a** with a similar enantiomeric excess to that of dry toluene itself, Table 3.2, entries 1 and 5. Addition of 4 Å molecular sieves to dry toluene had not effects on the stereoselectivity, Table 3.2, entry 6. By replacing dry toluene with toluene not previously dried, the *ee* values did not decrease suggesting the reaction is a fairly robust process, Table 3.2, entries 1 and 7. The observed behaviours of yields and stereoselectivities are in keeping with the reported effect of solvent polarity, expressed in terms of the ET(30) values of Dimroth and Reichardt, on the Michael additions of *β*-diketones on *β*-nitrostyrenes,[105] in the only study we are aware of in which this type of correlation is analysed. A dilution of the reaction mixture did not affect the

[105] Gavin, D.P.; Stephens, J. C. *ARKIVOC* **2010**, *9*, 407.

stereoselectivity of SMA and only resulted in prolonged reaction times, Table 3.2, entry 8. Overall, these trials identified dry toluene as the solvent of choice for further optimization.

Table 3.2 Effect of the solvent on stereoselective sulfa-Michael addition (SMA) of benzyl thiol (**1a**) to *trans*-chalcone (**2**).[a]



1a **2** **3a**

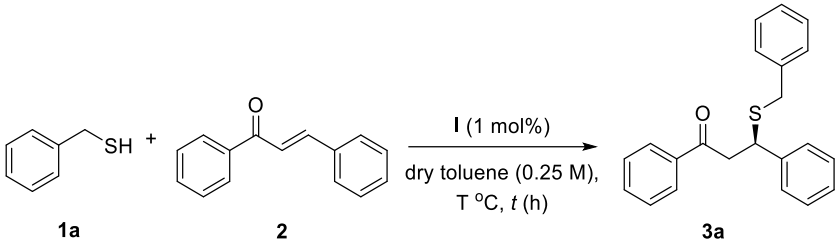
entry	solvent	*t* (h)[b]	yield (%)[c, d]	*ee* (%)[d, e]
1	dry toluene	8	97	67
2	dry CH_2Cl_2	29	97	43
3	dry DCE	29	97	43
4	dry CH_2Cl_2/Al_2O_3	29	97	42
5	dry toluene/*n*-hexane (1/1)	8	97	67
6	dry toluene/4 Å MS	8	97	65
7	toluene	8	97	66
8[f]	dry toluene	40	97	67

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1a/2** molar ratio and 1 mol% of catalyst **I** in 4.6 mL of solvent at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column. [f] 9.2 mL of solvent was used. DCE= 1,2-dichloroethane.

3.2.2.3 Effect of the temperature

By lowering the temperature to 0 °C and -20 °C, we observed a slight decrease in the stereoselectivity, while the chemical yield of the reaction was not significantly affected, Table 3.3. Although this behaviour is uncommon, the decrease in stereoselectivity at lower temperature observed here matches with information in previous reports on the catalytic activity of thioureas in the addition of thioacetic acid to enones[82] and other Michael additions[77,106] and is ascribed to a different arrangement of the transition state.[107]

Table 3.3 Effect of the temperature on stereoselective sulfa-Michael addition (SMA) of benzyl thiol (**1a**) to *trans*-chalcone (**2**).[a]



entry	temperature (°C)	*t* (h)[b]	yield (%)[c,d]	*ee* (%)[d,e]
1	25	8	97	67 ± 0.016
2	0	20	97	65 ± 0.003
3	-20	40	97	64 ± 0.006

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1a/2** molar ratio and 1 mol% of catalyst **I** in 4.6 mL of dry toluene. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column.

Overall, the best conditions required the use of 1 mol% of catalyst, dry toluene as solvent and a 0.25 M concentration of reagents and a reaction temperature of 25 °C.

[106] a) Lee, H. J.; Chae, Y. M.; Kim, D. Y. *Bull. Korean Chem. Soc*. **2011**, *32*, 2875; b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu Y. *Synlett* **2005**, 603.
[107] Rana, N. K.; Unhale, R.; Singh, V. K. *Tetrahedron Lett*. **2012**, *53*, 2121.

3.2.3 Catalyst screening

3.2.3.1 SMAs with phenylmethanethiol

With the optimised conditions we analysed the performance of catalysts **II**-**VI** aiming at assessing whether an increase of the acidity of the NH thiourea protons could have been beneficial to the stereoselectivity of the SMA, Table 3.4.

In a first attempt of increasing the Brønsted acidity of the NH thiourea protons, the 3,5-bis(trifluoromethyl)phenyl functional group was replaced with the easily accessible and highly electron-withdrawing pentafluorophenyl moiety, obtaining catalyst **II**.

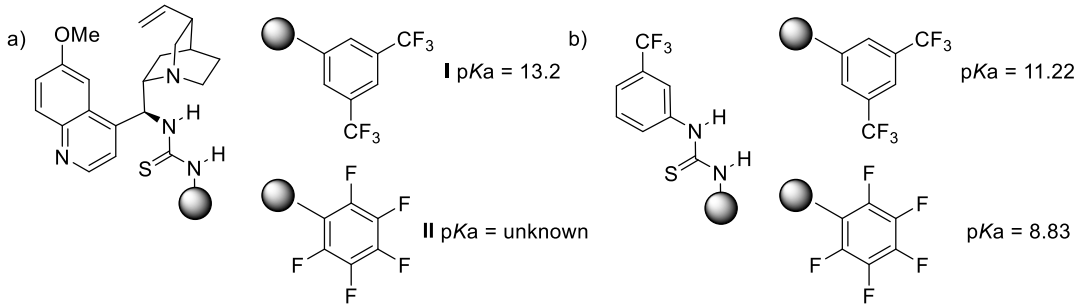


Figure 3.4 Effect of pentafluorophenyl moiety on the pK_a values of thiourea-catalysts.

The use of **II** in the stereoselective addition of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**) resulted in decreased reaction rate and selectivity. The reaction was complete in 24 hours affording the desired product in almost quantitative yield albeit with 33% *ee* only, Table 3.4, entry 3.

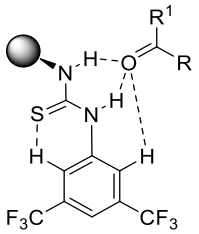
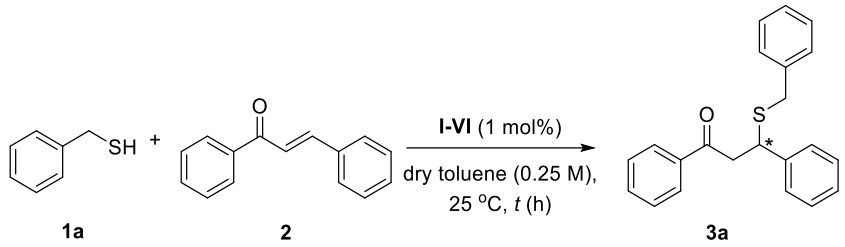


Figure 3.5 The involvement of the *ortho*-hydrogen atoms bond in the intermediate formed between the thiourea catalyst and the substrate.

Despite the increased acidity of N-H protons due to the strong electron withdrawing properties of the pentafluorophenyl moiety, an increased reaction time was necessary to achieve complete conversion and a significant decrease of the enantiomeric excess was observed. Likely this result stems from the lack of the *ortho*-H bond that may be involved in

the stabilization of the catalyst-substrate complex as for catalyst **I**, Figure 3.5, as explained by Schreiner and co-workers.[108]

Table 3.4 Stereoselective conjugate addition of benzyl thiol (**1a**) to *trans*-chalcone (**2**) catalyzed by bifunctional organocatalysts **I-VI**.[a]



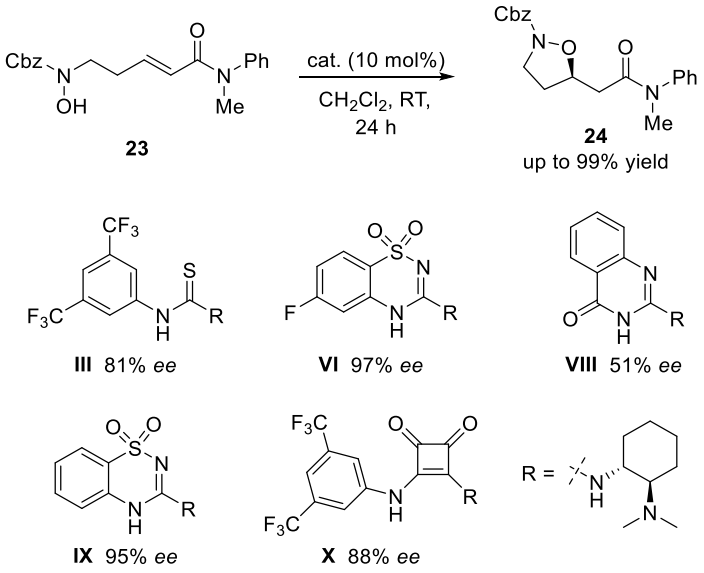
entry	cat.	*t* (h)[b]	yield (%)[c, d]	*ee* (%)[d, e]	config.[f]
1	-	336	90	-	-
2	**I**	8	97	67	*R*
3	**II**	24	99	33	*R*
4	**III**	40	99	53	*S*
5	**IV**	48	98	23	*S*
6[g]	**IV**	48	98	25	*S*
7[g, h]	**IV**	8	99	20	*S*
8	**V**	45	99	32	*S*
9	**VI**	10	99	37	*S*

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1a**/**2** molar ratio and 1 mol% of catalysts **I-VI** in 4.6 mL of dry toluene at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column. [f] The absolute configuration of the product **3a** was assigned by comparison of the measured optical rotation with the value reported in the reference 81. [g] SMAs were carried out on a 0.25 mmol scale. [h] 5 mol% of catalyst was used.

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

Retaining the 3,5-bis(trifluoromethyl)phenyl unit as a promising structural unit we turned our focus to the effect exerted by changing the thiourea unit of the HBDs catalysts. In this regard we took Takemoto's catalyst **III** as a prototype and we also analysed the related piperidino derivative **IV**; the Takemoto urea **V** was also tested for comparison, Figure 3.1. Catalysts **III** and **IV** promoted the addition of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**) with similar rates, the conversion was complete after 48 and 40 hours respectively but the stereoselectivity was significantly different. Catalyst **III** produced **3a** with 53% *ee*, while **IV** afforded the product with 25% *ee*, Table 3.4, entries 4-7. Interestingly, the Takemoto urea **V** proved to be slightly less effective than catalyst **III**, providing the product with *ee* of 32%, Table 3.4, entry 8.

Following the rationale outlined above, we sought for a catalyst with enhanced acidity of the NH urea protons and resolved to the recently proposed Takemoto benzothiadiazine **VI** that was used in the oxa-Michael addition to *α,β*-unsaturated amides and esters, Scheme 3.9.[102b] Catalyst **VI** features the same chiral scaffold of catalyst **III** but contains a hydrogen bond donor unit with higher Brønsted acidity. This catalyst, when applied to the SMA of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**), gave complete conversion of the reagents in 10 hours, very close to the time required for the reaction catalysed by **I**, but the *ee* of the product was 37% only, Table 3.4, entry 9, comparable with the stereoselectivity obtained with the Takemoto urea **V** and lower than the stereoselectivity scored by Takemoto catalyst **III**.



Scheme 3.9 Stereoselective oxa-Michael addition to *α,β*-unsaturated amides catalysed by benzothiadiazine **VI**.

When compared to catalyst **III**, the higher acidity of the NH protons of **VI** only gave a faster reaction but did not improve the stereoselectivity of the process.

At variance with catalysts **I** and **II**, the catalysts **III**-**VI** gave the addition product with *S* configuration at the newly formed stereocenter.

Overall, in the addition of phenylmethanethiol (**1a**) to *trans*-chalcone (**2**), the experimental data indicate that catalyst **I** not only displays the higher selectivity among the panel of catalysts screened, but also gives the faster reactions, in spite of the lower acidity of its NH protons with respect to catalyst **VI**.

In light of this comparative structure-activity-stereoselectivity relationship, the catalytic activity of **I-VI** was tested in both the addition of benzenethiol (**1b**), Table 3.5, and 2-phenylethanethiol (**1c**), Table 3.7, to *trans*-chalcone (**2**).

3.2.3.2 SMAs with benzenethiol

Under the optimized conditions used for nucleophile **1a**, it is noteworthy that a precipitation was observed during the addition of benzenethiol (**1b**) to *trans*-chalcone (**2**) because of the low solubility of the addition product **3b**. Therefore, a dilution to 0.125 M of *trans*-chalcone (**2**) in dry toluene was performed for reaction carried out with nucleophile **1b**. The reaction in the presence of 1 mol% of catalyst **I** provided **3b** in higher enantiomeric excess (57% *ee*) than the previously conditions (52% *ee*), and the precipitation was not detected, Table 3.5, entries 2-3.

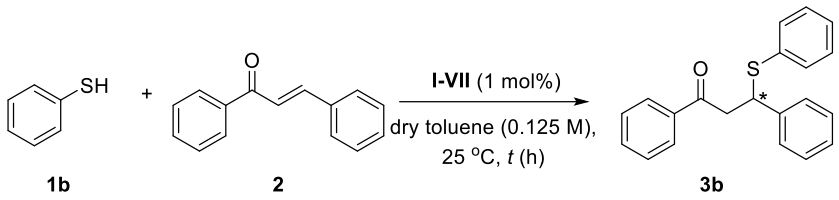
When 0.5 mol% of catalyst **I** was used, the reaction time increased from one to two hours and **3b** was obtained with 49% *ee*, Table 3.5, entry 9.

During catalyst screening, the only other catalyst displaying some stereoselectivity was the Takemoto thiourea **III** furnishing the product with a 34 % *ee*, Table 3.5, entry 5; the analogue urea **V** gave 15% *ee* only, Table 3.5, entry 7. All of the other catalysts provided limited stereoselectivity or essentially racemic materials.

Owing to the higher acidity of benzenethiol (**1b**), we included in the screening also the Nagasawa catalyst **VII**, Table 3.5, entry 11. The SMAs catalyzed by 10 mol% of **VII** provided the desired product **3b** in almost racemic mixtures.

During our studies with benzenethiol (**1b**), we noticed that a delayed work-up of the reaction mixture resulted in a slight-to-sensitive decrease of the stereoselectivity, Table 3.5, entry 10. We hypothesised that this could have been the result of a *retro*-Michael reaction. Such behaviour of **3b** could not be traced in the literature. In order to characterize the system we tested the stability of **3b** in the presence of the catalysts **I** and **III**, having two different amine moieties. For this study **3b** with 57% *ee* and catalyst **I** or **III** were co-dissolved in toluene at the same concentration used in the synthesis, after given time intervals, the reaction mixture was analysed by chiral HPLC, Table 3.6.

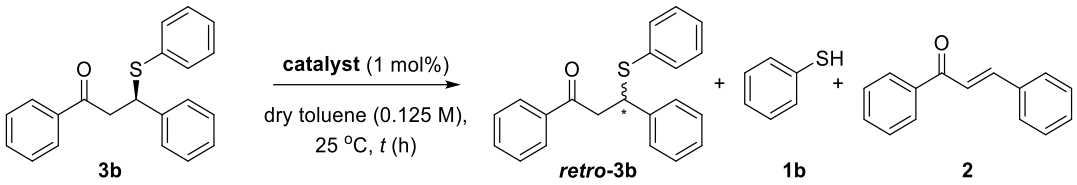
Table 3.5 Stereoselective conjugate addition of thiophenol (**1b**) to *trans*-chalcone (**2**) catalyzed by bifunctional organocatalysts **I-VII**.[a]



entry	cat.	*t* (h)[b]	yield (%)[c, d]	*ee* (%)[d, e]	config.[f]
1	-	72	94	-	-
2[g]	**I**	1	93	52 (51)[h]	*R*
3	**I**	1	95	57	*R*
4	**II**	2	97	1	-
5	**III**	2	96	34	*S*
6	**IV**	20	94	6	-
7	**V**	2	96	15	*S*
8	**VI**	2	96	6	-
9[i]	**I**	2	97	49	*R*
10[i, l]	**I**	2	95	38	*R*
11[m]	**VII**	48	94	8	-

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1b**/**2** molar ratio and 1 mol% of catalysts **I-VII** in 9.2 mL of dry toluene at RT. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column. [f] The absolute configuration of the product **3b** was assigned by comparison of the measured optical rotation with the value reported in the reference 79a. [g] 4.6 mL of solvent was used. [h] Determined by chiral HPLC analysis using a Lux cellulose III column on crude product. [i] 0.5 mol% of catalyst was used. [l] The reaction was finished after 2 hours and toluene was removed *in vacuo* after 5 hours. [m] 10 mol% of catalyst was used.

Table 3.6 *Retro*-Michael reaction of product **3b** catalyzed by bifunctional organocatalysts **I** and **III**.[a]



entry	*ee* (%) blank[b]	*ee* (%) with catalyst **I**[b]	*ee* (%) with catalyst **III**[b]	*t* (h)[c]
1	56	48	54	1
2	55	46	54	2.5
3	57	39	49	16
4	56	40	50	24
5	55	17	45	96

[a] Unless otherwise stated, *retro*-Michael reactions were carried out with 0.25 mmol of **3b** and 1 mol% of catalyst in 2 mL of dry toluene at 25 °C. [b] Determined by chiral HPLC analysis using a Lux cellulose III column. [c] Sampling time.

The measured enantiomeric excess *versus* time is reported in Figure 3.6. Inspection of Figure 3.6 reveals that the reaction rate of the *retro*-Michael process is relatively low compared with the addition process that is complete in the timespan of 1 hour (catalyst **I**) or two hours (catalyst **III**).

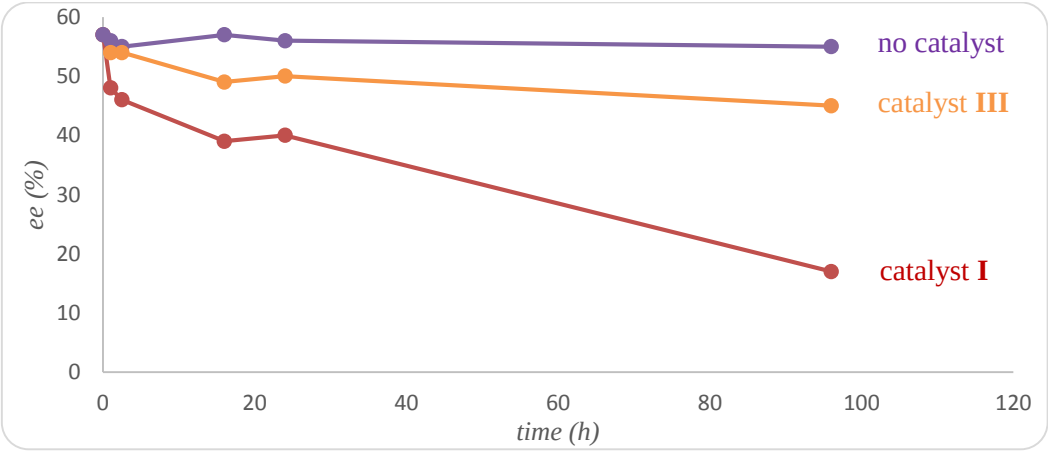


Figure 3.6 Correlation of reaction time with stereoselectivity for the *retro*-Michael reaction of **3b** in absence, violet, and in presence of catalysts **III**, orange, or **I**, red.

Subsequently, *ee* values of **3b** were determined before silica purifications of the crude reaction mixture. HPLC analysis gaves enantiomeric excess similar to that of purified compound, Table 3.5, entry 2.

Adsorption on alumina resulted in a significant formation of the enone **2**, as evidenced by ^{1}H NMR analysis, Figure 3.7, trace (b), with loss of *ee*, as from the HPLC profile, Figure 3.8, trace (a); while adsorption on silica gel revealed no formation of *trans*-chalcone (**2**) as the result of the *retro*-Michael reaction, Figure 3.7, trace (c), with no racemization of **3b**, Figure 3.8, trace (b).

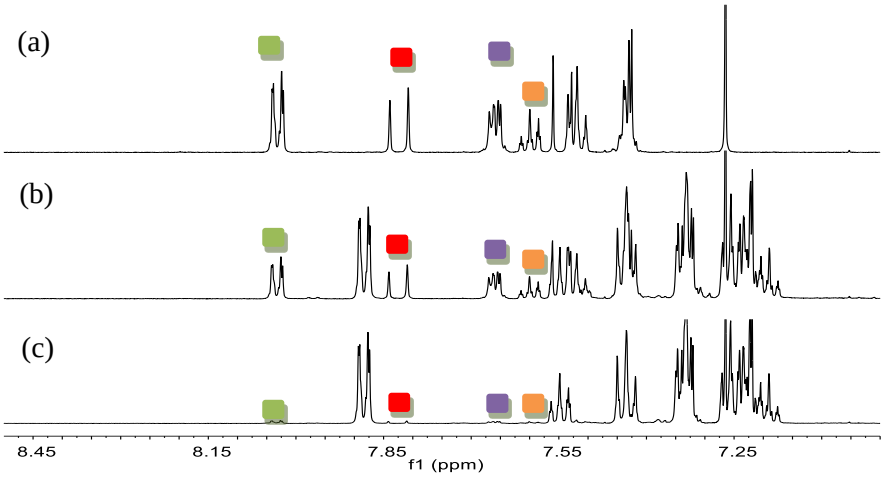


Figure 3.7 (a) ^{1}H NMR (500 MHz) spectrum of *trans*-chalcone (**2**) in $CDCl_3$; (b) ^{1}H NMR (500 MHz) spectrum of **3b**, Table 3.5, entry 2, in presence of Al_2O_3 in $CDCl_3$; (c) ^{1}H NMR (500 MHz) spectrum of **3b**, Table 3.5, entry 2, in presence of silica gel in $CDCl_3$.

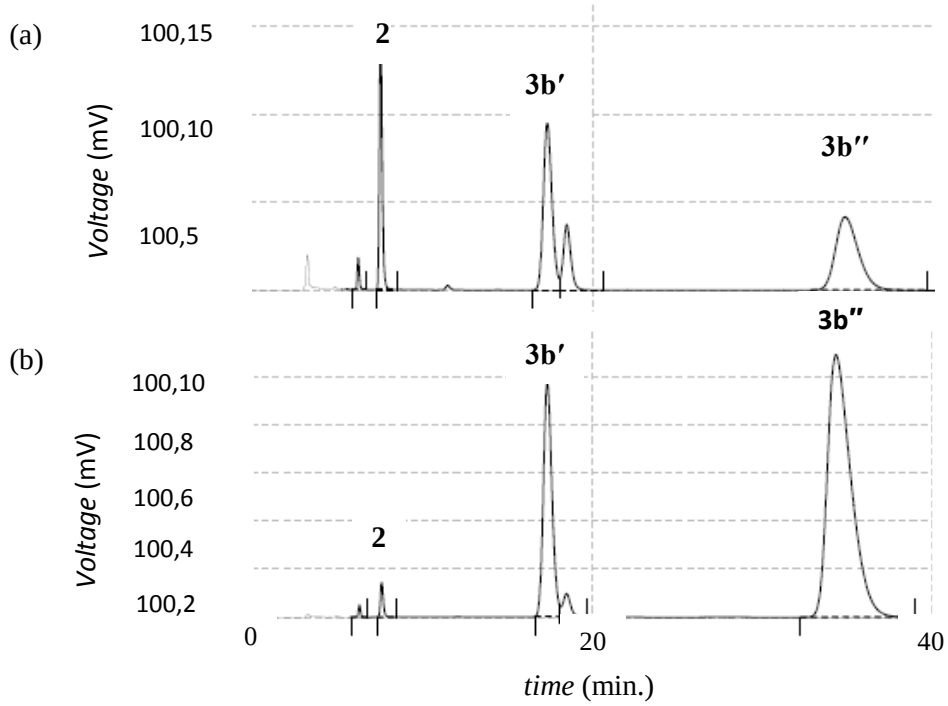
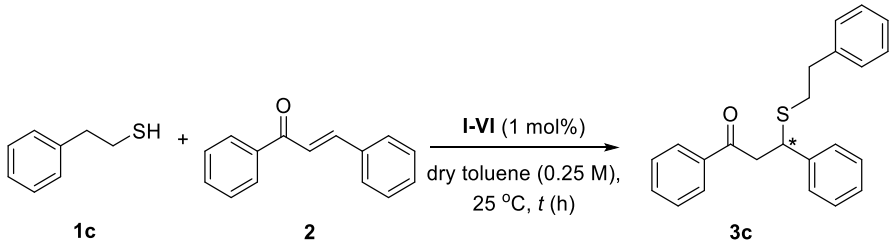


Figure 3.8 (a) Chiral HPLC spectrum of product **3b**, Table 3.5, entry 2, in presence of alumina (**2**: Rt = 7.61 min., A = 16.9 %; **3b′**: Rt = 17.33 min., A% = 32.6; unknown product: Rt = 18.46 min., A = 11.2%; **3b″**: Rt = 34.69 min.; A% = 37.8); (b) Chiral HPLC spectrum of product **3b**, Table 3.5, entry 2, in presence of silica gel (**2**: Rt = 7.62 min., A = 1.2 %; **3b′**: Rt = 17.35 min.; A% = 23.6; unknown product : Rt = 18.49 min., A = 2.2%; **3b″**: Rt = 34.32 min.; A% = 72.7).

3.2.3.3 SMAs with 2-phenylethanethiol

The stereoselective sulfa-Michael addition reactions of 2-phenylethanethiol (**1c**) to *trans*-chalcone were performed in the same conditions used for nucleophile **1a**, Table 3.7.

Table 3.7 Stereoselective conjugate addition of 2-phenylethanethiol (**1c**) to *trans*-chalcone (**2**) catalyzed by bifunctional organocatalysts **I-VI**.[a]



1c **2** **3c**

entry	cat.	*t* (h)[b]	yield (%)[c, d]	*ee* (%)[d, e]	config.[f]
1	-	648	92	-	-
2	**I**	52	94	39	*R*
3	**II**	168	95	8	-
4	**III**	168	94	16	*S*
5[g, h]	**III**	20	97	22	*S*
6	**IV**	192	95	8	-
7	**V**	168	95	9	-
8	**VI**	36	96	9 (10)[i]	-

[a] Unless otherwise stated, all SMAs were carried out on a 1.14 mmol scale using 1.25:1 **1c**/**2** molar ratio and 1 mol% of catalysts **I-VI** in 4.6 mL of dry toluene at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2-4 experiments. [e] Determined by chiral HPLC analysis using a Lux cellulose III column. [f] The absolute configuration of product **3c** was assigned to be (*R*) by comparison of the measured optical rotation with the value reported in the literature for the products **3a**-**3b**.[79a,81] [g] SMAs were carried out on a 0.25 mmol scale. [h] 5 mol% of catalyst was used. [i] Determined by chiral HPLC analysis using a Lux cellulose III column after 30 hours.

The catalysed reactions proceed slowly, although an accelerating effect of catalysts **I-VI** was clear. The reaction catalysed by **I** provided **3c** in 94% yield with 39% *ee* and was

complete in 52 hours, Table 3.7, entry 2; also in this case, Takemoto thiourea **III** was the only other catalyst enabling some stereoselectivity with the formation of **3c** with 16% *ee*, Table 3.7, entry 4. Only a modest improvement in stereoselectivity could be obtained by increasing the catalyst loading up to 5 mol%, in this case the product was isolated with a 22% *ee*, Table 3.7, entry 5. Also in this case catalysts **I** and **III** gave the products with opposite configurations.

3.4 Conclusion

The study of stereoselective sulfa-Michael addition was focused on the, model reaction of addition of phenylmethanethiol to *trans*-chalcone. In particular we investigated the effect of catalyst **I** loading, solvent and temperature.

With the optimised conditions, we comparatively evaluated, in a single experimental setting, the activity of some popular HBD catalysts in the stereoselective SMA of benzenethiol (**1b**), phenylmethanethiol (**1a**) and 2-phenylethanethiol (**1c**) to *trans*-chalcone (**2**). Soós catalyst **I** and the Takemoto thiourea **III** gave the best performances even though the degree of stereoselection was modest-to-good only. Increasing the Brønsted acidity of the hydrogen bond donor unit gave, in some cases, faster reactions but had, in general, a negative impact on the stereoselectivity. The addition product **3b** of benzenethiol (**1b**) to *trans*-chalcone (**2**) was found to be stereochemically unstable, undergoing a *retro*-Michael reaction when left in the presence of the catalysts, such as in the case of a delayed work-up of the reaction mixture. The two catalysts **II** and **VI** were employed in sulfa-Michael reactions for the first time and 2-phenylethanethiol (**1c**) was also used for the first time as nucleophile in stereoselective SMA to *trans*-chalcone (**2**).

Hopefully the results here reported are a starting point in order to increase the knowledge toward a rational choice of the best catalysts for the substrate and the nucleophile selected.

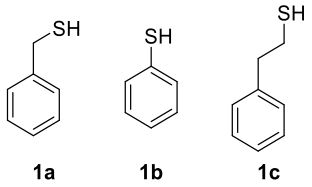
3.5 Experimental procedure

3.5.1 General experimental

Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware. Air-sensitive reagents and solutions were transferred *via* a syringe and were introduced into the apparatus through rubber septa. All reagents were purchased from Sigma-Aldrich Co. LLC. or Alfa Aesar GmbH and used as such. All solvents were purchased from Sigma-Aldrich Co. LLC or Alfa Aesar GmbH. Dry dichloromethane, dry 1,2-dichloroethane, dry DMF, THF (HPLC grade), toluene (ACS grade), and dry methanol were used as such or dried by distillation according to standard procedures (toluene and THF on Na/benzophenone). Solvents for chromatography and filtration including ethyl acetate, dichloromethane, petroleum ether and methanol were used as receveid; hexane and 2-propanol were HPLC grade. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates with visualization under short-wavelenght UV light. Additionally, spots were visualized by dipping the plates into aqueous potassium permanganate (aqueous H_2SO_4 solution of potassium permanganate) or ninhydrin reagent (*n*-butanol solution of ninhydrin and acetic acid) followed by heating. Flash column chromatography was performed using 40-63 μm silica gel using the indicated solvent mixtures. Analytical chiral HPLC analysis was carried out using Lux 5μ cellulose III column with the indicated solvents and conditions. Optical rotation data were obtained on a JASCO P-2000 polarimeter. ^{1}H NMR spectra were recorded at 400 MHz (Jeol EX-400) or 500 MHz (Varian 500 MHz). ^{13}C NMR spectra were recorded at 126 MHz (Varian 500 MHz). The proton chemical shifts were referenced to the residual non deuterated solvent (δ = 7.26 for $CDCl_3$; δ = 2.49 for DMSO *d*$_6$). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and b (broad). Coupling constants, *J*, are quoted in Hertz. ^{1}H and ^{13}C NMR assignments were supported by 2D experiments (gCOSY, gHSQC, TOCSY, NOESY sequences). Infrared spectra (IR) were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer (drop-cast films on NaCl disks). The positions of the absorption bands are reported in cm^{-1}. ESI-mass spectra were recorded on Perkin-Elmer AP II apparatus operated at 5600 eV and are reported as (*m/z*).

3.5.2 Starting materials

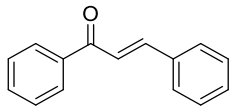
3.5.2.1 Michael donor 1a-1c



1a **1b** **1c**

Compounds **1a-1c** were commercially available, and were used as such without further purifications.

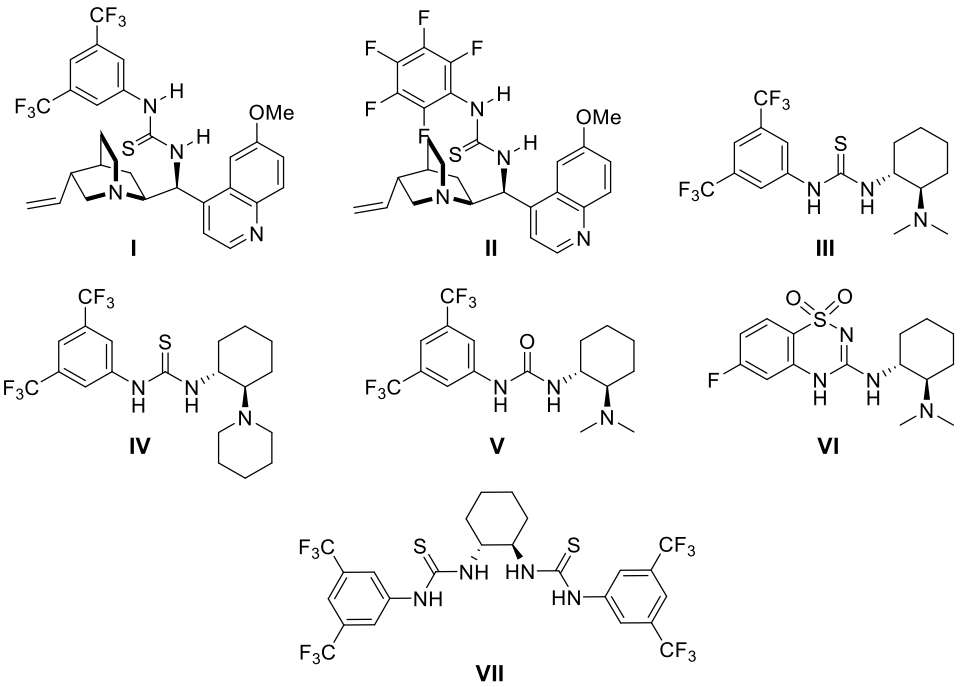
3.5.2.2 Michael acceptor 2



2

Compound **2** was commercially available, and used as such without further purifications.

3.5.2.3 Catalysts for the asymmetric sulfa-Michael addition



I **II** **III**

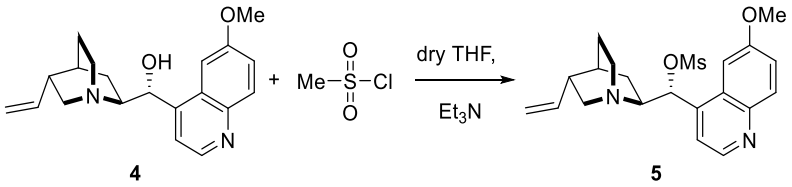
IV **V** **VI**

VII

3.5.2.3.1 Preparation, analytical and spectroscopic data of catalyst I

Catalyst **I** was prepared according to reported procedures, and its spectral data perfectly matched those reported in literature.[109]

Preparation of (*R*)-(6-methoxyquinolin-4-yl)-(8-vinylquinuclidin-2-yl)methyl methanesulfonate (5)



Into a round bottomed flask and under argon atmosphere, quinine (**4**) (500 mg, 1.54 mmol) was dissolved in dry THF (2.3 ml). Triethylamine (0.86 ml, 6.17 mmol) was added all at once at room temperature and the mixture was magnetically stirred. The flask was placed in a water-ice bath so that the internal temperature was stabilized around 0-4 °C. After 10 min methanesulfonyl chloride (0.286 ml, 3.7 mmol) dissolved in dry THF (0.9 ml) was added dropwise by aid of a dropping funnel. Additional dry THF (0.3 ml) was used to rinse the dropping funnel. After 4 hours, the reaction was quenched at 0-4 °C with the slow addition of an aqueous solution of $NaHCO_3$ (3.5% w/w) (3.5 ml) obtaining two transparent yellow phases. The organic phase was kept and the aqueous phase was extracted two times with ethyl acetate (2×1 ml). All organic layers were recombined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield crude **5** (652 mg) as a yellow oil. The crude **5** was submitted to the next reaction without any further purification.

Data for **5**:

R_f: 0.7 (9/1 CH_2Cl_2/MeOH).

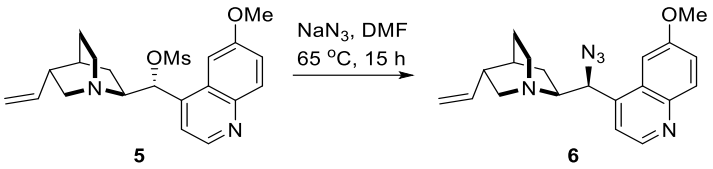
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.8 (d, *J* = 4.4 Hz, 1H), 8.05 (d, *J* = 9.6 Hz, 1H), 7.44 (bs, 1H), 7.41 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.35 (bs, 1H), 6.16 (bs, 1H), 5.83 (ddd, *J* = 17.6, 10, 7.6 Hz, 1H), 5.04-4.96 (m, 2H), 3.95 (s, 3H), 3.41 (bs, 1H), 3.16-3.03 (m, 1H), 2.97 (dd, *J* = 14, 10 Hz, 1H), 2.67-2.5 (m, 5H), 2.33-2.19 (m, 1H), 2.15-2.04 (m, 1H), 1.95-1.85 (m, 1H), 1.8-1.7 (m, 1H), 1.61 (m, 2H).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 403.5.

Found: $[M+H^+]$: 403.1.

[109] a) P. Melchiorre, L. F. Bravo, R. Martin, *Eur. Pat. Appl.* **2014**, EP 2687527A1; b) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; c) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097; d) G. Declan, J.-C. Stephens, *Arkivoc* **2011**, *9*, 407.

Preparation of 2-((*S*)-azido(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (6)



Into a round bottom flask and working under argon atmosphere, sodium azide (150 mg, 2.31 mmol) was suspended in dry DMF (1 ml) and the suspension was magnetically stirred. Crude and dry compound **5** (assumed 1.54 mmol) was dissolved in dry DMF (1.5 ml) and added all at once to the suspension of sodium azide. Additional dry DMF (0.5 ml) was used to quantitatively transfer compound **5** into the reaction flask. The mixture was heated so that the internal temperature was 65 °C. After 16 hours, the reaction was complete. The mixture was cooled in a water-ice bath so that the internal temperature was 0-4 °C. When the temperature was stabilized, the reaction was quenched by the slow addition of 1 M aqueous solution of sodium hydroxide (3 ml). The resulting mixture consisted in a yellow solution and an immiscible yellow thick oil. The mixture was transferred to a separating funnel and extracted with *tert*-butyl methyl ether (3×1 ml). The organic layers were combined, washed with 1M aqueous solution of NaOH (1 ml) and transferred to a 10 ml round bottom flask and the solvents were removed under reduced pressure. The crude product **6** was dried under high vacuum. Crude compound **6** (616 mg) was obtained as yellow oil and it was submitted to the next reaction.

Data for **6**:

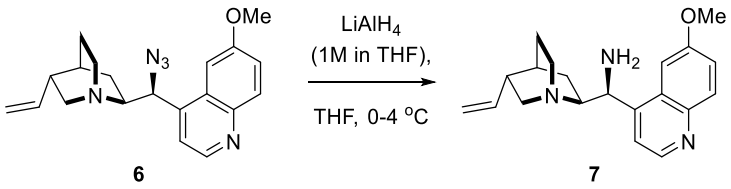
R_f: 0.6 (9/1 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 4.4 Hz, 1H), 8.43 (d, *J* = 9.2 Hz), 7.46 (bs, 1H), 7.42 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.33 (d, *J* = 4.4 Hz, 1H), 5.75 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.04-4.91 (m, 3H), 3.97 (s, 3H), 3.43-3.26 (m, 2H), 3.26-3.13 (m, 1H), 2.98-2.88 (m, 1H), 2.88-2.78 (m, 1H), 2.36-2.23 (m, 1H), 1.78-1.67 (m, 1H), 1.63-1.49 (m, 2H), 1.45-1.33 (m, 1H), 0.76 (dd, *J* = 13.6, 7.6 Hz, 1H).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 350.43.

Found: $[M+H^+]$: 350.1.

Preparation of 2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (7)



Crude compound **6** was dissolved in anhydrous THF (7.5 ml) in a 3-necked 25 ml round bottom flask under argon atmosphere. The mixture was magnetically stirred and cooled down in a water-ice bath so that the internal temperature was 0-4 °C. When the temperature was stabilized, lithium aluminium hydride solution in THF (1M) (0.94 ml, 0.94 mmol) was added slowly via syringe through a rubber septum. Upon addition the colour of the reaction mixture turns first to orange and then to red. Gas evolution was observed. The reaction was stirred at 0 °C for 4 hours. When the reaction was complete, ethyl acetate (2.5 ml) was added slowly to quench the reaction while stirring at 0-4 °C. An aqueous solution of NH_3 (0.5 M) (6 ml) was then added dropwise. The aqueous and the organic layers were separated and the organic phase was retained. The aqueous layer was further extracted with ethyl acetate (2×2 ml); all of the organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford crude **7** (430 mg) as a yellow oil. The crude **7** was submitted to the next reaction without any further purification.

Data for **7**:

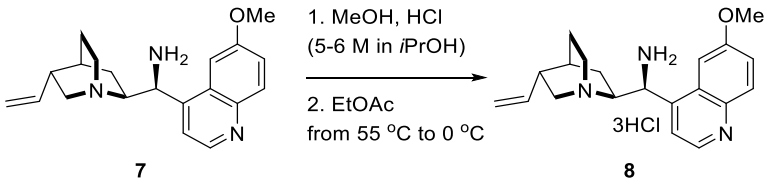
R_f: 0.2 (9/1 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.66 (bs, 1H), 7.48-7.41 (m, 1H), 7.38 (dd, *J* = 9.6, 2.8 Hz, 1H), 5.8 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1H), 5.07-4.87 (m, 2H), 4.7-4.48 (m, 1H), 3.96 (s, 3H), 3.27 (dd, *J* = 14, 10.4 Hz, 1H), 3.23-3.13 (m, 1H), 3.13-3.00 (m, 1H), 2.87-2.64 (m, 2H), 2.35-2.23 (m, 1H), 2.23-1.93 (m, 2H), 1.64-1.6 (m, 1H), 1.59-1.52 (m, 2H), 1.47-1.37 (m, 1H), 0.76 (dd, *J* = 13.6, 7.6 Hz, 1H).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 324.44.

Found: $[M+H^+]$: 323.1.

Preparation of 2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine three hydrochloride (8)



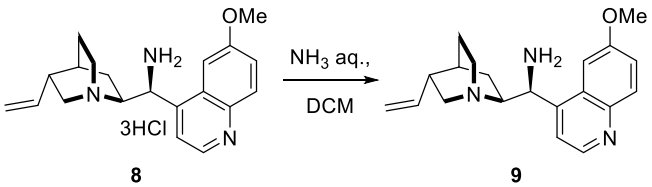
The crude compound **7** was dissolved in anhydrous methanol (11 ml) and the mixture was heated to 55 °C. Hydrogen chloride solution in 2-propanol (5-6 M) (0.67 ml) was added *via* a syringe and the colour of the solution turned to red. The mixture was stirred at 55 °C for one hour and then allowed to reach room temperature while stirring observing the formation of a light white precipitate. Ethyl acetate (1.5 ml) was then added and the mixture was stirred one hour in an ice bath. The solid was filtered, washed with a methanol/ethyl acetate 1/1 mixture, and dried under vacuum. The product **8** was obtained as a white solid (240 mg, 36% yield relative to starting quinine (**4**)) and it was used for the next reaction.

Data for **8**:

^{1}H NMR (500 MHz, D_2O): δ 8.9 (d, *J* = 6 Hz, 1H), 8.15 (d, *J* = 9.5 Hz, 1H), 8.02 (d, *J* = 6 Hz, 1H), 7.8 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.7 (m, 1H), 5.77 (ddd, *J* = 17.5, 11, 6.5 Hz, 1H), 5.42 (d, *J* = 11 Hz, 1H), 5.16-5.09 (m, 2H), 4.16 (m, 1H), 3.99 (s, 3H), 3.9-3.8 (m, 1H), 3.71 (dd, *J* = 13.5, 11 Hz, 1H), 3.46-3.31 (m, 2H), 2.86-2.77 (m, 1H), 2.02-1.89 (m, 3H), 1.82-1.72 (m, 1H), 1.08-1.00 (m, 1H).

MS (ESI, 5600eV): Calcd.: $[M^+]$: 323.44.
Found: $[M^+]$: 323.00.

Preparation of 2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (9)

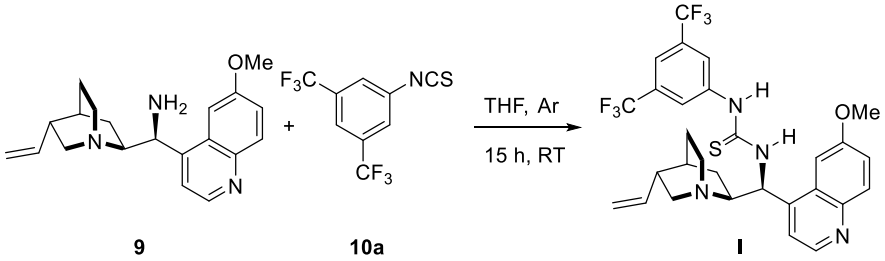


The trihydrochloride **8** (240 mg, 0.55 mmol) was suspended in dichloromethane (1.6 ml). 5 M aqueous solution of NH_3 (1.2 ml, 6 mmol) was slowly added while stirring. After 5 minutes, the biphasic mixture was transferred to a separating funnel, the organic layer was retained and the aqueous layer was washed with dichloromethane (2×1.2ml). The organic solutions were

recombined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield the product **9** (169 mg, 95%) as a yellow oil.

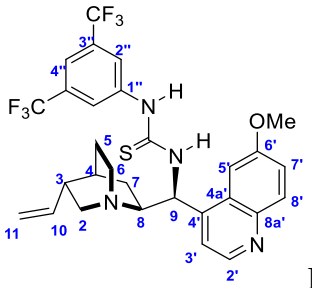
Data for **9**: data of compound **9** have been collected above, under preparation of compound **7**.

Preparation of catalyst I



9 **10a** **I**

Working at room temperature, a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) (105.3 µl, 0.57 mmol) in 0.9 ml of anhydrous THF was slowly added to a solution of 2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (**9**) (169 mg, 0.52 mmol) in anhydrous THF (4 ml). The mixture was stirred overnight, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 90/10 as eluent, to yield catalyst **I** as yellow solid (262 mg, 84%).



Data for catalyst **I**: yellow solid.

R_f: 0.37 (95/5 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.67–8.5 (m, 1H, H-2′), 8.07-7.93 (m, 1H, H-8′), 7.83 (bs, 2H, H-2″), 7.67 (bs, 1H, H-4″), 7.59 (bs, 1H, H-5′), 7.38 (dd, *J* = 9 Hz, 1H, H-7′), 7.23-7.09 (m, 1H, H-3′), 5.92 (bs, 1H, H-9), 5.69 (m, 1H, H-10), 5.15-4.89 (m, 2H, H-11), 3.97 (s, 3H, OMe), 3.53-3.25 (m, 2H, H-6, H-8), 3.24-3.1 (m, 1H, H-2), 2.92-2.65 (m, 2H, H-2, H-6), 2.36 (bs, 1H, H-3), 1.8-1.53 (m, 3H, H-4, H-5), 1.49-1.34 (m, 1H, H-7), 0.93 (bs, 1H, H-7), two N-H protons could not be observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 180.77 (1C, C=S), 158.11 (1C, C-6′), 147.29 (1C, C-2′), 146.44 (1C, C-4′), 144.58 (1C, C-8a′), 140.4 (1C, C-1″), 140.06 (1C, C-10), 132.46 (q, *J* = 32.2 Hz, 2C, C-3″), 131.52 (1C, C-8′), 128.02 (1C, C-4a′), 123.57 (1C, C-7′), 122.9 (q, *J* =

274.3 Hz, 2C, CF_3), 122.09 (C-2″), 122.76 (2C, C-3′), 118.72 (1C, C-4″), 115.16 (1C, C-11), 102.12 (1C, C-5′), 60.97 (1C, C-8), 55.79 (1C, OMe), 54.79 (1C, C-2), 54.46 (1C, C-9), 41.42 (1C, C-6), 38.9 (1C, C-3), 27.38 (1C, C-4), 27.05 (1C, C-5), 25.67 (1C, C-7).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 595.6.

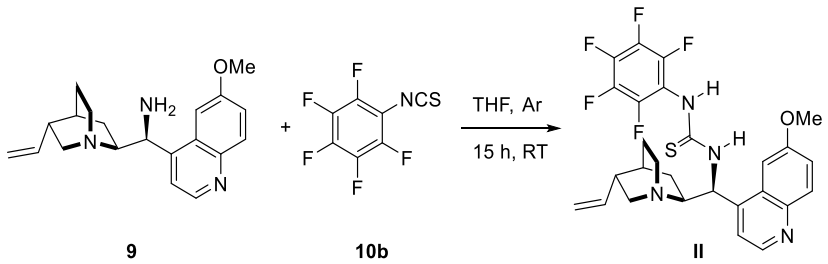
Found: $[M+H^+]$: 595.3.

Opt. Rot.: $[\alpha]_D^{25}$ -72.18 (*c* 0.5, $CHCl_3$).

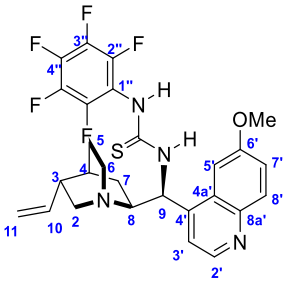
3.5.2.3.2 Preparation, analytical and spectroscopic data of catalyst II

2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (**9**) was prepared according to procedures decribed above, and their spectral data perfectly matched those reported in literature.[109a]

Preparation of catalyst II



Working at room temperature, a solution of pentafluorophenyl isothiocyanate (**10b**) (54 µl, 0.37 mmol) in 0.6 ml of anhydrous THF was slowly added to a solution of 2-((*S*)-amino(6-methoxyquinolin-4-yl)methyl)-8-vinylquinuclidine (**9**) (109 mg, 0.34 mmol) in anhydrous THF (2.5 ml). The mixture was stirred overnight, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 90/10 as eluent, to yield catalyst **II** as white solid (63 mg, 34%).



Data for catalyst **II**: white solid.

R_f: 0.42 (95/5 CH_2Cl_2/MeOH).

m.p.: 118-121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H, H-2′), 8.05 (d, *J* = 9.5 Hz, 1H, H-8′), 7.63-7.45 (m, 1H, H-5′), 7.42 (d, *J* = 9.0 Hz, 1H, H-7′), 7.34 (d, *J* = 4.5 Hz, 1H, H-3′), 5.92-5.55 (bs, 2H, H-9, H-10), 5.07 (d, *J* = 14.0 Hz, 2H, H-11), 3.98 (s, 3H, OMe), 3.68-3.44 (bs, 1H, H-8), 3.43-3.29 (bs, 1H, H-6), 3.22 (dd, *J* = 13.5, 10.5 Hz, 1H, H-2), 3.13-2.92 (bs, 1H, H-2), 2.85-2.74 (m, 1H, H-6), 2.48-2.35 (bs, 1H, H-3), 1.84-1.61 (m, 3H, H-5, H-4), 1.56-1.39 (m, 1H, H-7), 1.05-0.79 (bs, 1H, H-7), two N-H protons could not be observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 183.32 (1C, C=S), 158.31 (1C, C-6′), 147.39 (1C, C-2′), 144.8 (2C, C-F), 142.66 (1C, C-8a′), 141.3 (1C, C-4′), 139.31 (2C, C-10, C-1″), 138.79 (m, 1C, C-F), 136.79 (m, 2C, C-F), 131.84 (1C, C-8′), 127.77 (1C, C-4a′), 122.2 (2C, C-7′, C-3′), 115.82 (1C, C-11), 101.76 (1C, C-5′), 61.13 (1C, C-8), 57.82 (1C, C-9), 55.75 (1C, OMe), 54.41 (1C, C-2), 41.14 (1C, C-6), 38.28 (1C, C-3), 26.91 (1C, C-4), 26.51 (1C, C-5), 25.12 (1C, C-7).

IR (cm^{-1}, NaCl): 3206, 2946, 1727, 1621, 1588, 1510, 1474, 1433, 1343, 1297, 1264, 1228, 1137, 1084, 1028, 991, 918, 853, 738, 681.

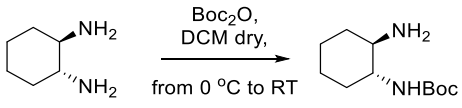
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 549.5.
Found: $[M+H^+]$: 549.1.

Opt. Rot.: $[\alpha]_D^{25}$ -63.35 (*c* 0.7, $CHCl_3$).

3.5.2.3.3 Preparation, analytical and spectroscopic data of catalyst III

Catalyst **III** was prepared according to reported procedures, and its spectral data perfectly matched those reported in literature.[110]

Preparation of *tert*-butyl (1*R*,2*R*)-2-aminocyclohexylcarbamate (14)



13 **14**

Working under Argon atmosphere, a solution of di-*tert*-butyl dicarbonate (1593 mg, 7.29 mmol) in dry DCM (20 ml) was added dropwise to a solution of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (**13**) (2500 mg, 21.89 mmol) in dry DCM (65 ml) over a period of 30 min at 0 °C. The reaction mixture was warmed to RT and left under stirring for 24 hrs. Water

[110] a) L. Yu, P. Li, *Tetrahedron Lett.* **2014**, *55*, 3697; b) N.-R. Amarasinghe, P. Turner, M.-H. Todd, *Adv. Synth. Catal.* 2012, *354*, 2954; c) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*. 2003, *125*, 12672; d) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* 2005, *127*, 119.

(10 ml) and DCM (10 ml) were added to dissolve the white precipitate formed. The organic phase was separated and concentrated under reduced pressure. The residue was taken-up with diethyl ether (20 ml) and water (30 ml). HCl (4M) was used to acidify the mixture to pH 5, and the aqueous layer was collected. The pH of the aqueous layer was brought to pH= 11 with NaOH (4M) and extracted with ethyl acetate (5 × 50 ml). The organic phases were collected, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to yield crude **14** (1515 mg, 97%) as white solid.

Data for **14**:

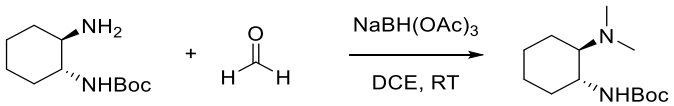
R_f: 0.2 (95/5 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, DMSO-*d6*): δ 6.61 (d, *J* = 8 Hz, 1H), 2.92-2.8 (m, 1H), 2.29 (dt, *J* = 10.5, 10.5, 4 Hz, 1H), 1.8-1.67 (m, 2H), 1.62-1.51 (m, 2H), 1.36 (s, 9H), 1.21-0.92 (m, 4H).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 215.3.

Found: $[M+H^+]$: 215.4.

Preparation of *tert*-butyl (1*R*,2*R*)-2-(dimethylamino)cyclohexylcarbamate (16)



14 **15** **16**

To a solution of *tert*-butyl (1*R*,2*R*)-2-aminocyclohexylcarbamate (**14**) (1515 mg, 7.07 mmol) in DCE (108 ml) was added formaldehyde **15** as an aqueous solution 36.5%-38% (1.15 ml, 15.55 mmol) and the mixture was stirred at RT for 15 minutes. Solid $NaBH(OAc)_3$ (3446 mg, 16.26 mmol) was added and the resulting mixture was stirred at RT for 6 hours. Then an aqueous solution of $NaHCO_3$ was added to adjust the pH at about 7 and stirring was continued for 15 minutes. The layers were separated and the aqueous phase was extracted with DCM (3 × 100 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo.* The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 90/10 as eluent affording compound **16** (1200 mg, 70%) as a yellow oil.

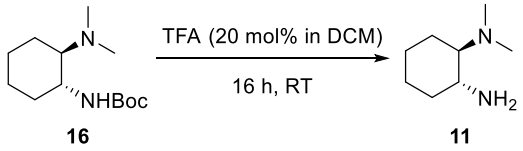
Data for **16**:

R_f: 0.26 (95/5 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.34 (s, 1H), 3.29-3.18 (m, 1H), 2.47-2.38 (m, 1H), 2.27 (s, 7H), 1.9-1.76 (m, 2H), 1.7-1.63 (m, 1H), 1.45 (s, 9H), 1.36-1.13 (m, 3H), 1.13-1.02 (m, 1H).

MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 243.35.
Found: [M+H$^+$]: 243.5.

Preparation of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (11)



To a solution of *tert*-butyl ((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)carbamate (**16**) (1200 mg, 4.95 mmol) was added trifluoroacetic acid (67mL, 20% in DCM). The reaction mixture was stirred at RT for 16 hours. Solvents were removed under reduced pressure, pH was adjusted to 10 with 2 N NaOH and the mixture was extracted with DCM (3 × 25 mL). The combined organic phases were washed with brine (20 mL) dried over anhydrous Na_2SO4 and the solvent was removed *in vacuo* yielding crude **11** (704 mg, 99%) as a yellow oil.

Data for **11**:

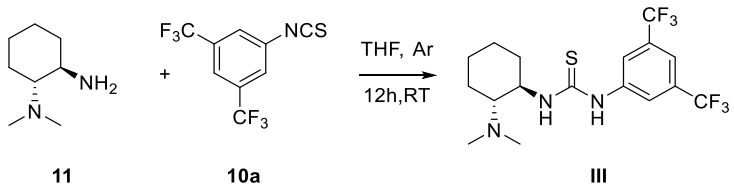
R_f: 0.15 (9/1 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (td, *J* = 10.4, 10.4, 4.4 Hz, 1H, H-2), 2.19 (s, 6H, $N(CH_3)_2$), 2.04-1.84 (m, 4H, H-1, H-3, NH_2), 1.79-1.54 (m, 3H, H-4, H-5, H-6), 1.27-0.96 (m, 4H, H-3, H-4, H-5, H-6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 69.51 (C-1), 51.44 (C-2), 40.21 (2C, Me), 34.85 (C-3), 25.56 (1C), 25.06 (1C), 20.71 (1C).

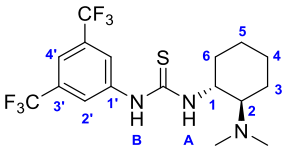
MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 143.24.
Found: [M+H$^+$]: 142.9.

Preparation of catalyst III



Working at room temperature, a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) (300 µl, 1.64 mmol) in 2 ml of anhydrous THF was slowly added to a solution of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) (234 mg, 1.64 mmol) in anhydrous THF (10 ml). The mixture was stirred for 16 hours, and the solvent was removed *in vacuo*. The

crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 95/5 as eluent to yield catalyst **III** (325 mg, 48%) as a white solid.



Data for catalyst **III**: white solid.

R_f: 0.36 (90/10 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.06 (s, 1H, N-H_B), 8.22 (s, 1H, N-H_A), 8.16 (s, 2H, H-2′), 7.66 (s, 1H, H-4′), 4.12 (s, 1H), 2.54 (bs, 1H), 2.37-2.08 (m, 7H), 1.9-1.8 (m, 1H), 1.77-1.7 (m, 1H), 1.67-1.58 (m, 1H), 1.27-1.08 (m, 4H).

^{13}C NMR (126 MHz, DMSO- *d6*): δ 179.22 (1C, C=S), 142.36 (1C, C-1′), 130.79 (q, *J* = 32.5 Hz, 2C, C-3′), 123.69 (q, *J* = 273.42 Hz, 2C, CF_3), 121.46 (2C, C-2′), 115.91 (1C, C-4′), 65.58 (1C), 55.35 (1C), 40.22 (2C, NMe_2), 32.07 (1C), 24.95 (1C), 24.89 (1C), 21.72 (1C).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 414.42.

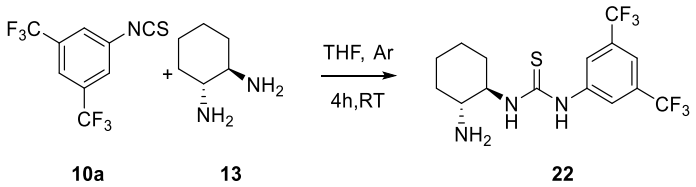
Found: $[M+H^+]$: 414.4.

Opt. Rot.: $[\alpha]_D^{20}$ -19.06 (*c* 1.035, $CHCl_3$).

3.5.2.3.4 Preparation, analytical and spectroscopic data of catalyst IV

1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-aminocyclohexyl)thiourea (**22**) was prepared according to known procedures.[111]

Preparation of 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-aminocyclohexyl)thiourea (22)



10a **13** **22**

Working at room temperature, a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) (304 µl, 1.66 mmol) in 2.5 ml of anhydrous THF was slowly added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**13**) (227 mg, 1.99 mmol) in anhydrous THF (12.5 ml). The mixture was stirred for 4 hours, and the solvent was removed *in vacuo*. The

[111] Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang, L. He, *Org. Lett.* **2013**, *15*, 6090.

crude compound was purified by flash chromatography on silica gel using AcOEt/MeOH 80/20 as eluent to yield compound **22** as yellow solid (305 mg, 47%).

Data for **22**: yellow solid.

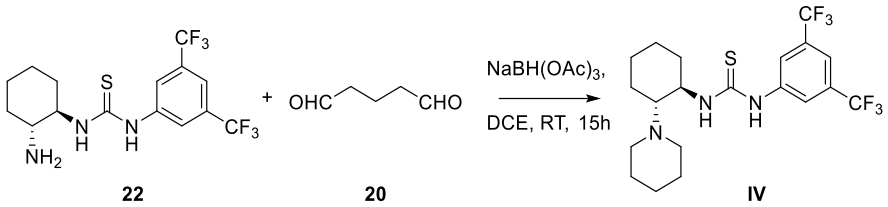
R_f: 0.5 (80/20 AcOEt/MeOH).

^{1}H NMR (500 MHz, CD_3OD): δ 8.19 (s, 2H, Ar-H), 7.63 (s, 1H, Ar-H), 4.4-4.16 (bs, 1H, C-H), 2.72-2.56 (m, 1H, C-H), 2.16-2.06 (m, 1H, C-H), 2.05-1.97 (m, 1H, C-H), 1.85-1.7 (m, 2H, C-H), 1.48-1.18 (m, 4H, C-H), N-H protons not be observed.

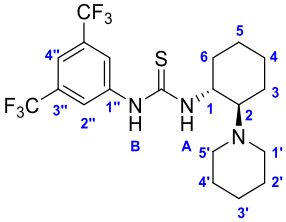
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 386.37.

Found: $[M+H^+]$: 386.4.

Preparation of catalyst IV



Aqueous glutaraldehyde (**20**) (50%, 141 µl, 0.79 mmol) was added dropwise into a mixture of $NaBH(OAc)_3$ (676 mg, 3.16 mmol) and compound **22** (305 mg, 0.79 mmol) in 1,2-dichloroethane (10 mL) at room temperature. The resulting mixture was stirred at room temperature for 15 hours, and then quenched with aqueous NaOH (10%, 3 ml). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3×3 ml). The combined organic layers were washed with brine (3 ml), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using AcOEt/MeOH 90/10 as eluent to yield catalyst **IV** as white solid (77 mg, 21%).



Data for catalyst **IV**: white solid.

R_f: 0.44 (80/20 AcOEt/MeOH).

m.p.: 115-118 °C.

^{1}H NMR (500 MHz, DMSO-*d6*): δ 10.07 (s, 1H, N-H_B), 8.19 (s, 2H, H-2″), 7.99 (s, 1H, N-H_A), 7.69 (s, 1H, H-4″), 4.25-4.06 (bs, 1H, H-1), 2.76-2.53 (bs, 2H, CH_2), 2.47-2.39 (bs, 1H, H-2), 2.37-2.21 (bs, 2H, CH_2), 2.2-2.07 (bs, 1H, H-6), 1.92-1.79 (bs, 1H, H-3), 1.77-1.68 (bs, 1H, H-4), 1.66-1.59 (bs, 1H, H-5), 1.57-1.26 (m, 6H, $3CH_2$), 1.25-0.97 (m, 4H, H-3, H-4, H-5, H-6).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 2H, H-2″), 7.71 (s, 1H, H-4″), 3.76-3.64 (m, 1H, H-1), 2.8-2.54 (m, 3H), 2.43-2.22 (m, 3H), 1.96-1.88 (m, 1H), 1.87-1.8 (m, 1H), 1.78-1.7 (m, 1H), 1.47-1.09 (m, 11H), one N-H proton not be observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 181.44 (1C, C=S), 136.68 (1C, C-1″), 132.68 (q, J = 31.62 Hz, 2C, C-3″), 124.53 (2C, C-2″), 122.88 (q, J = 273.67 Hz, 2C, CF_3), 119.05 (1C, C-4″), 68.86 (1C, C-2), 56.21 (1C, C-1), 49.59 (1C), 32.58 (1C), 26.2 (2C), 25.19 (1C), 24.42 (2C), 24.12 (1C), 23.42 (1C).

IR (cm^{-1}, NaCl): 3238, 2936, 2859, 2808, 1620, 1535, 1470, 1383, 1278, 1177, 1135, 1035, 1007, 968, 886, 848, 739, 702, 681.

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 454.49.
Found: $[M+H^+]$: 454.5.

Opt. Rot.: $[\alpha]_D^{25}$ -16.48 (*c* 0.42, $CHCl_3$).

3.5.2.3.5 Preparation, analytical and spectroscopic data of catalyst V

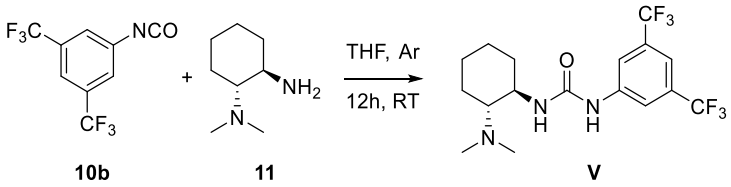
Catalyst **V** was prepared according to known procedures, and their spectral data perfectly matched those reported in literature.[110,112]

Preparation of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (11)

(1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) was prepared according to procedures decribed above, and their spectral data perfectly matched those reported in literature.[110b]

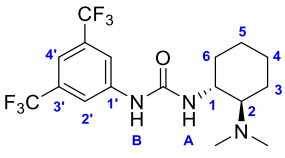
[112] A. Berkessel, S. Mukherjee, T. N. Müller, F. Cleemann, K. Roland, M. Brandeburg, J.-M. Neudörfl, J. Lex, *Org. Biomol. Chem.* **2006**, *4*, 4319.

Preparation of catalyst V



10b **11** **V**

Working at room temperature, a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (**10b**) (136.5 µl, 0.79 mmol) in 2 ml of anhydrous THF was slowly added to a solution of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) (112.4 mg, 0.79 mmol) in anhydrous THF (5 ml). The mixture was stirred for 16 hours, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 95/5 as eluent to yield catalyst **V** (176 mg, 55%) as a white solid.



Data for catalyst **V**: white solid.

R_f: 0.31 (90/10 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H, N-H_B), 7.8 (s, 2H, H-2′), 7.4 (s, 1H, H-4′), 5.72 (s, 1H, N-H_A), 3.56-3.48 (m, 1H), 2.44-2.35 (m, 1H), 2.35-2.27 (s, 7H), 1.93-1.81 (m, 2H), 1.75-1.68 (m, 1H), 1.37-1.1 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.45 (1C, C=O), 140.92 (1C, C-1′), 132.00 (q, J = 33.26 Hz, 2C, C-3′), 123.18 (q, J = 273.42 Hz, 2C, CF_3), 118.44 (1C, C-2′), 118.41 (1C, C-2′), 115.37 (m, 1C, C-4′), 67.37 (1C), 51.78 (1C), 40.11 (2C, NMe_2), 33.68 (1C), 25.02 (1C), 24.62 (1C), 21.52 (1C).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 398.37.
Found: $[M+H^+]$: 398.4.

Opt. Rot.: $[\alpha]_D^{25}$ -10.9 (*c* 0.93, $CHCl_3$).

3.5.2.3.6 Preparation, analytical and spectroscopic data of catalyst VI

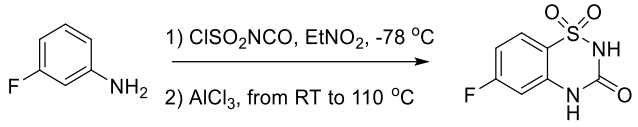
Catalyst **VI** was prepared according to reported procedures, and its spectral data perfectly matched those reported in literature.[110b,113]

[113] a) T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470; b) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 11114.

Preparation of (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (11)

(1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) was prepared according to procedures decribed above, and their spectral data perfectly matched those reported in literature.[110b]

Preparation of 6-fluoro-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one-1,1-dioxide (18)



17 **18**

A solution of 3-fluoroaniline (**17**) (1.08 ml, 11.2 mmol) in nitroethane (7 ml) was added dropwise, over a period of 5 minutes, to a solution of chlorosulfonyl isocyanate (1.17 ml, 13.4 mmol) in nitroethane (17 ml) maintained at -78 °C. . The resulting mixture was stirred and warmed to RT. When the temperature reached 25 °C, the pink solution was stirred for another 30 minutes. Then aluminium chloride (2g, 1.34 mmol) was added to the pink solution and the mixture was stirred at 110 °C for 30 minutes. Then the reaction mixture was poured into ice water and the resulting brown precipitate was washed with water and dried under vacuum to yield crude **18** (1.34 g, 55%) as brown solid.

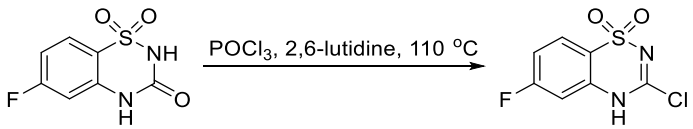
Data for **18**:

^{1}H NMR (500 MHz, CD_3OD): δ 7.85 (ddd, *J* = 7.5, 5.5, 1.5 Hz, 1H), 7.1-7.04 (m, 1H), 6.96-6.91 (m, 1H).

^{13}C NMR (126 MHz, CD_3OD): δ 165.48 (d, *J* = 252 Hz, C-6), 150.91 (C=O), 137.55 (d, *J* = 12 Hz), 119.55 (d, *J* = 2.9 Hz), 124.91 (d, *J* = 10.9 Hz), 110.93 (d, *J* = 23.9 Hz), 103.37 (d, *J* = 27 Hz).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 217.18.
Found: $[M+H^+]$: 217.0.

Preparation of 3-chloro-6-fluoro-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (12)



18 **12**

To a mixture of crude compound **18** (1.32 g, 6.1 mmol) and $POCl_3$ (8.53 ml, 91.5 mmol) was added 2,6-lutidine (0.71 ml, 6.1 mmol) at RT. The mixture was then heated at 110 °C and kept under stirring for 12 hours. Then the reaction mixture was cooled to 0 °C and cold water was added dropwise over a period of 1 hour. The brown precipitate was washed with water, dissolved in methanol and the solvent was removed *in vacuo* to yield crude **12** (936 mg, 65%) as brown solid.

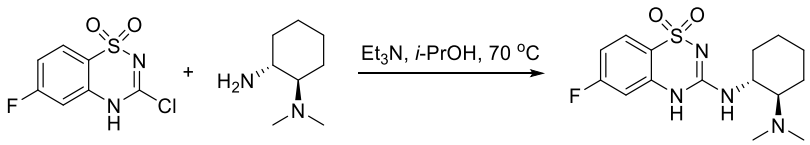
Data for **12**:

^{1}H NMR (500 MHz, CD_3OD): δ 7.93 (dd, *J* = 9, 5.5 Hz, 1H, H-8), 7.28 (td, *J* = 8.5, 8.5, 2 Hz, 1H, H-7), 7.02 (dd, *J* = 9.5, 2 Hz, 1H, H-5).

^{13}C NMR (126 MHz, CD_3OD): δ 164.8 (d, *J* = 253.7 Hz, C-6), 145.93 (C-3), 136.7 (d, *J* = 12 Hz, 1C), 126.8 (d, *J* = 10.7 Hz, C-8), 118 (d, *J* = 3.15 Hz, 1C), 114.9 (d, *J* = 23.8 Hz, C-7), 103.7 (d, *J* = 27.2 Hz, C-5).

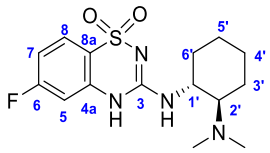
MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 235.63.
Found: [M+H$^+$]: 235.3.

Preparation of catalyst VI



12 **11** **VI**

To a mixture of 3-chloro-6-fluoro-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (**12**) (464.56 mg, 1.98 mmol) and (1*R*,2*R*)-*N*,*N*-dimethylcyclohexane-1,2-diamine (**11**) (281.63 mg, 1.98 mmol) in *i*-PrOH (5.5 ml) was added triethylamine (331 µl, 2.37 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 5 hours when TLC indicated the reaction was complete. The reaction mixture was concentrated *in vacuo* and the crude compound was purified by flash chromatography on silica gel using AcOEt/MeOH/Et3N (80/20/1 as eluent to yield catalyst **VI** (359 mg, 53%) as a yellow solid.



Data for catalyst **VI**: yellow solid.

R_f: 0.34 (80/20/1 AcOEt/MeOH/Et_3N).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (t, *J* = 7, 7 Hz, 1H, H-8), 6.93 (t, *J* = 8.5, 8.5 Hz, 1H, H-7), 6.57 (d, *J* = 8 Hz, 1H, H-5), 3.54-3.42 (m, 1H, H-1′), 2.62-2.34 (m, 7H, H-2′, NMe_2), 2.31-2.21 (m, 1H, H-6′), 1.99-1.91 (m, 1H, H-3′), 1.9-1.82 (m, 1H, H-4′), 1.79-1.71 (m, 1H, H-5′), 1.35-1.16 (m, 4H, H-3′, H-4′, H-5′, H-6′), two N-H protons could not be observed.

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.6 (d, J = 253.1 Hz, 1C, C-6), 152.2 (1C, C-3), 138.4 (d, *J* = 8.8 Hz, 1C), 126.3 (d, *J* = 9.5 Hz, 1C, C-8), 118.6 (d, *J* = 19.2 Hz, 1C), 111.8 (d, *J* = 22.6 Hz, 1C, C-7), 103.6 (d, *J* = 21.4 Hz, 1C, C-5), 67.23 (1C, C-2′), 52.83 (1C, C-1′), 40.2 (2C, NMe_2), 32.9 (1C, C-6′), 24.5 (1C), 24.3 (1C), 22.1 (1C, C-3′).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 341.41.

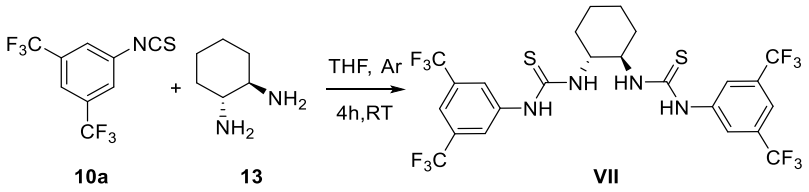
Found: $[M+H^+]$: 341.4.

Opt. Rot.: $[\alpha]_D^{23}$ +16.57 (*c* 0.99, $CHCl_3$).

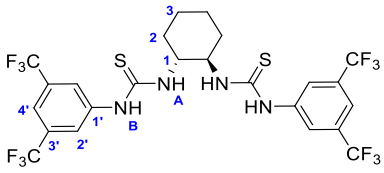
3.5.2.3.7 Preparation, analytical and spectroscopic data of catalyst VII

Catalyst **VII** was prepared according to reported procedures, and its spectral data perfectly matched those reported in literature.[114]

Preparation of catalyst VII



Working at room temperature, a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**10a**) (304 µl, 1.66 mmol) in 2.5 ml of anhydrous THF was slowly added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane (**13**) (227 mg, 1.99 mmol) in anhydrous THF (12.5 ml). The mixture was stirred for 4 hours, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using AcOEt/MeOH 80/20 as eluent to yield catalyst **VII** as a white solid (250 mg, 23%).



Data for catalyst **VII**: white solid.

[114] Y. Sohtone, N. Takemura, R. Takagi, Y. Hashimoto, K. Nagasawa, *Tetrahedron* **2008**, *64*, 9423.

R_f: 0.5 (80/20 AcOEt/MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (bs, 2H, N-H_B), 7.8 (s, 4H, H-2′), 7.7 (s, 2H, H-4′), 6.97 (bs, 2H, N-H_A), 4.39 (s, 2H, H-1), 2.2 (s, 2H), 1.82 (s, 2H), 1.36 (s, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 180.42 (2C, C=S), 138.5 (2C, C-1′), 132.8 (q, J = 34.39 Hz, 4C, C-3′), 124.05 (4C, C-2′), 122.67 (q, J = 273.79 Hz, 4C, CF_3), 119.7 (2C, C-4′), 59.45 (2C), 31.71 (2C), 24.36 (2C).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 657.55.

Found: $[M+H^+]$: 657.1.

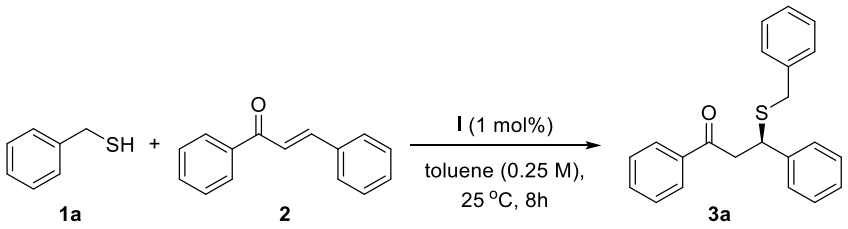
Opt. Rot.: $[\alpha]_D^{25}$ +74.58 (*c* 1.0, $CHCl_3$).

3.5.3 Preparation of sulfa-Michael adducts

Racemic products **3a-3c** were prepared using Et_3N as the sole amine catalyst.

Representative Procedure

3.5.3.1 Preparation of 3-(*R*)-(benzylthio)-1,3-diphenylpropan-1-one (3a)



To a solution of *trans*-chalcone (**2**) (237.4 mg, 1.14 mmol) and catalyst **I** (6.8 mg, 0.0114 mmol) in anhydrous toluene (4.6 ml), benzyl mercaptan (**1a**) (167.3 µl, 1.425 mmol) was added dropwise. The mixture was stirred at room temperature for 8 hours, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/Petroleum ether 50/50 as eluent, to yield compound **3a** as a white solid (379 mg, >99%, 67.8% *ee*).

Data for (3*R*)-**3a**: white solid.

R_f: 0.43 (50/50 CH_2Cl_2/Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.8 (m, 2H, Ar-H), 7.55-7.48 (m, 1H, Ar-H), 7.43-7.35 (m, 4H, Ar-H), 7.33-7.26 (m, 4H, Ar-H), 7.23-7.18 (m, 4H, Ar-H), 4.44 (t, J = 6.8, 6.8 Hz, 1H, H-3), 3.58-3.42 (m, 4H, H-2, S-CH_2-Ph).

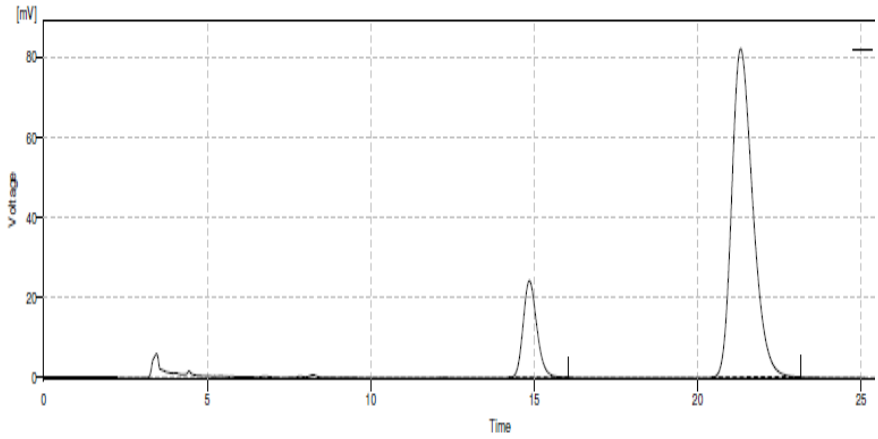
^{13}C NMR (126 MHz, $CDCl_3$): δ 196.72 (1C, C=O), 141.76 (1C), 137.87 (1C), 136.73 (1C), 133.15 (1C), 128.92 (2C), 128.56 (2C), 128.52 (2C), 128.43 (2C), 128.07 (2C), 128.05 (2C), 127.3 (1C), 126.97 (1C), 45.28 (1C), 44.19 (1C, C-3), 35.9 (1C).

MS (ESI, 5600eV): Calcd.: $[M+Na^+]$: 355.44.

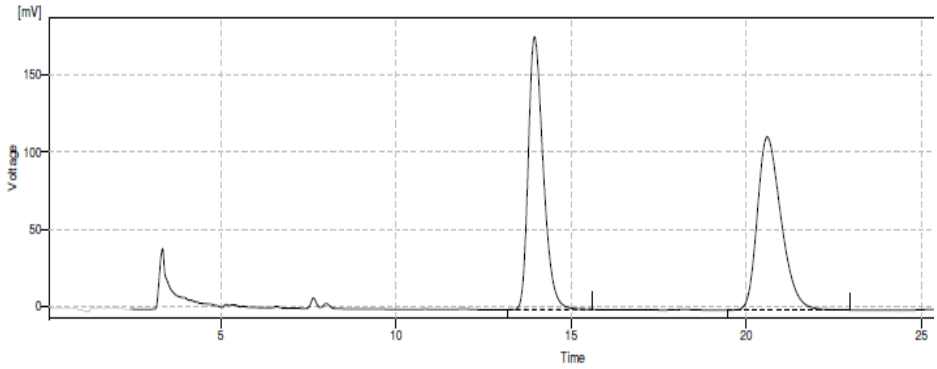
Found: $[M+Na^+]$: 355.1.

Opt. Rot.: $[\alpha]_D^{25}$ +98.41 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Lux 5μ cellulose III, hexane/*i*PrOH = 80/20, 1 ml/min, 254 nm.

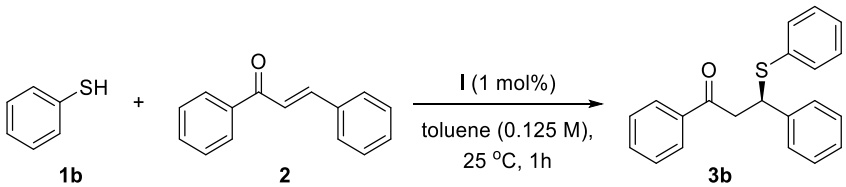


	Rt (min)	Area (%)
Minor	14.857	16.1
Major	21.317	83.9



	Rt (min)	Area (%)
Minor	13.953	49.3
Major	20.6	49.6

3.5.3.2 Preparation of 3-(*R*)-1,3-diphenyl-3-(phenylthio)propan-1-one (3b)



1b **2** **3b**

To a solution of *trans*-chalcone (**2**) (237.4 mg, 1.14 mmol) and catalyst **I** (6.8 mg, 0.0114 mmol) in anhydrous toluene (9.2 ml), thiophenol (**1b**) (146.3 μl, 1.425 mmol) was added dropwise. The mixture was stirred at room temperature for 1 hour, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel

using CH_2Cl_2/Petroleum ether 50/50 as eluent to yield compound **3b** as a white solid (345 mg, 95%, 57% *ee*).

Data for (3*R*)-**3b**: white solid.

R_f: 0.46 (50/50 CH_2Cl_2/Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (m, 1H, Ar-H), 7.86 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.53 (m, 1H, Ar-H), 7.42 (m, 2H, Ar-H), 7.3 (m, 5H, Ar-H), 7.19 (m, 5H, Ar-H), 4.94 (dd, *J* = 8.0, 6.0 Hz, 1H, H-3), 3.66 (m, *J* = 17.2, 8.4 Hz, 1H, H-2), 3.56 (m, *J* = 17.2, 6 Hz, 1H, H-2).

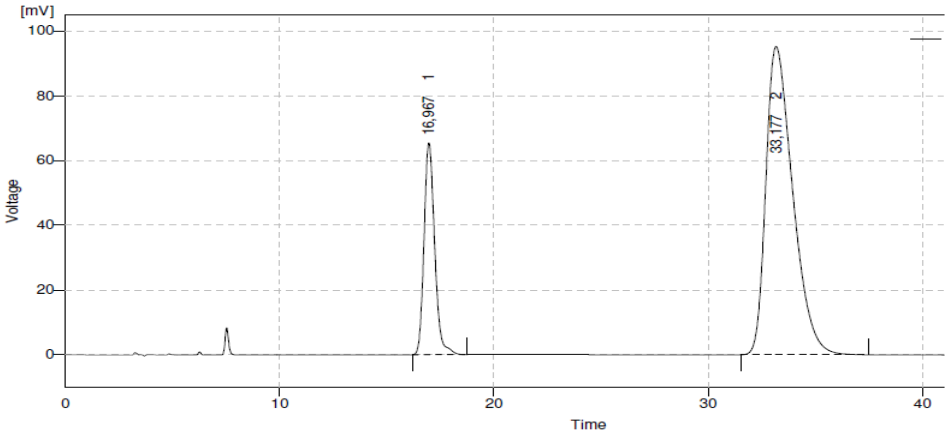
^{13}C NMR (126 MHz, $CDCl_3$): δ 196.96 (1C, C=O), 141.18 (1C), 136.73 (1C), 134.24 (1C), 133.23 (1C), 132.75 (2C), 128.84 (2C), 128.6 (2C), 128.44 (2C), 128.05 (2C), 127.79 (2C), 127.52 (1C), 127.35 (1C), 48.23 (1C, C-3), 44.7 (1C, C-2).

MS (ESI, 5600eV): Calcd.: $[M+Na^+]$: 341.41.

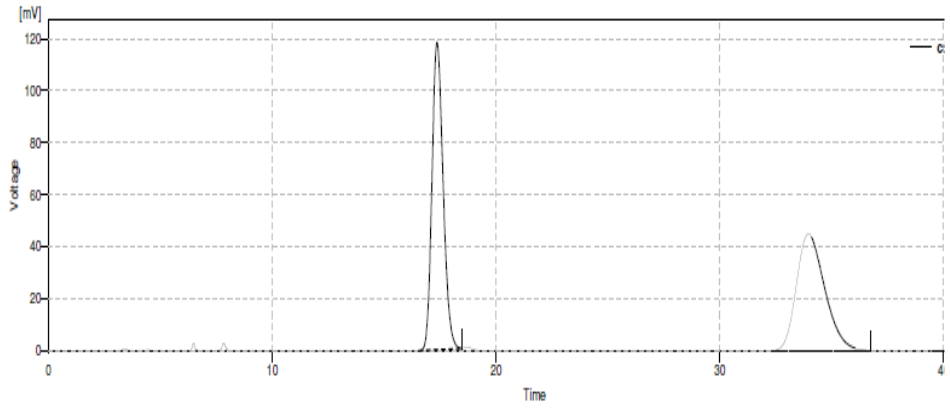
Found: $[M+Na^+]$: 341.0.

Opt. Rot.: $[\alpha]_D^{20}$ +56.47 (*c* 1.02, CH_2Cl_2).

Chiral HPLC: Lux 5µ cellulose III, hexane/*i*PrOH = 80/20, 1 ml/min, 254 nm.

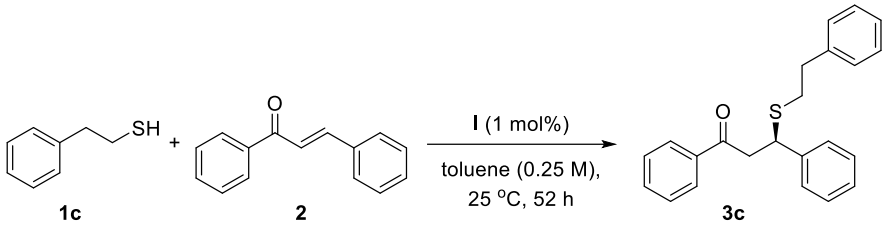


	Rt (min)	Area (%)
Minor	16.967	21
Major	33.177	78



	Rt (min)	Area (%)
Minor	17.363	51.1
Major	33.96	48.9

3.5.3.3 Preparation of 3-(*R*)-1,3-diphenyl-3-(phenethylthio)propan-1-one (3c)



To a solution of *trans*-chalcone (**2**) (237.4 mg, 1.14 mmol) and catalyst **I** (6.8 mg, 0.0114 mmol) in anhydrous toluene (4.6 ml), 2-phenylethanethiol (**1c**) (190.87 µl, 1.425 mmol) was added dropwise. The mixture was stirred at room temperature for 52 hours, and the solvent was removed *in vacuo*. The crude compound was purified by flash chromatography on silica gel using CH_2Cl_2/Petroleum ether 50/50 as eluent to yield compound **3c** as a white solid (372 mg, 94%, 40% *ee*).

Data for (3*R*)-**3c**: white solid.

R_f: 0.36 (50/50 CH_2Cl_2/Petroleum ether).

m.p.: 80-83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94–7.88 (m, 2H, Ar-H), 7.59-7.52 (m, 1H, Ar-H), 7.48-7.4 (m, 4H, Ar-H), 7.35-7.29 (m, 2H, Ar-H), 7.26-7.15 (m, 4H, Ar-H), 7.11-7.05 (m, 2H, Ar-H), 4.61 (m, *J* = 7.0, 7.0 Hz, 1H, H-3), 3.6-3.49 (m, 2H, H-2), 2.87-2.7 (m, 2H, S-CH_2CH_2-Ph), 2.66-2.52 (m, 2H, S-CH_2CH_2-Ph).

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.8 (1C, C=O), 142.02 (1C), 140.45 (1C), 136.77 (1C), 133.22 (1C), 128.6 (2C), 128.56 (2C), 128.45 (2C), 128.37 (2C), 128.09 (2C), 127.91 (2C), 127.32 (1C), 126.25 (1C), 45.4 (1C, C-2), 44.46 (1C, C-3), 35.93 (1C), 32.93 (1C).

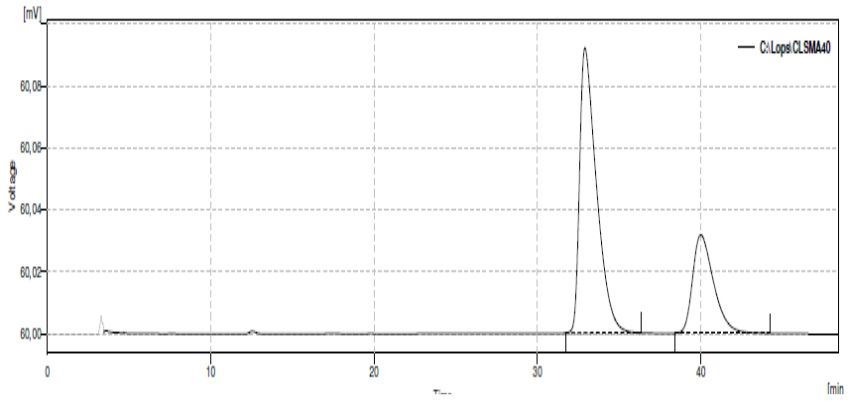
IR (cm^{-1}, NaCl): 3027, 1682, 1596, 1494, 1365, 1228, 980, 750, 694, 643, 545.

MS (ESI, 5600eV): Calcd.: $[M+Na^+]$: 369.47.

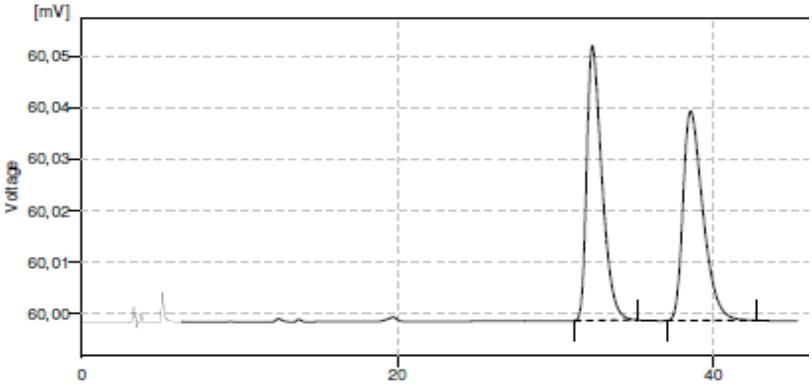
Found: $[M+Na^+]$: 369.4.

Opt. Rot.: $[\alpha]_D^{25}$ +42.67 (*c* 1.0, $CHCl_3$).

Chiral HPLC: Lux 5µ cellulose III, hexane/*i*PrOH = 95/5, 1 ml/min, 254 nm.

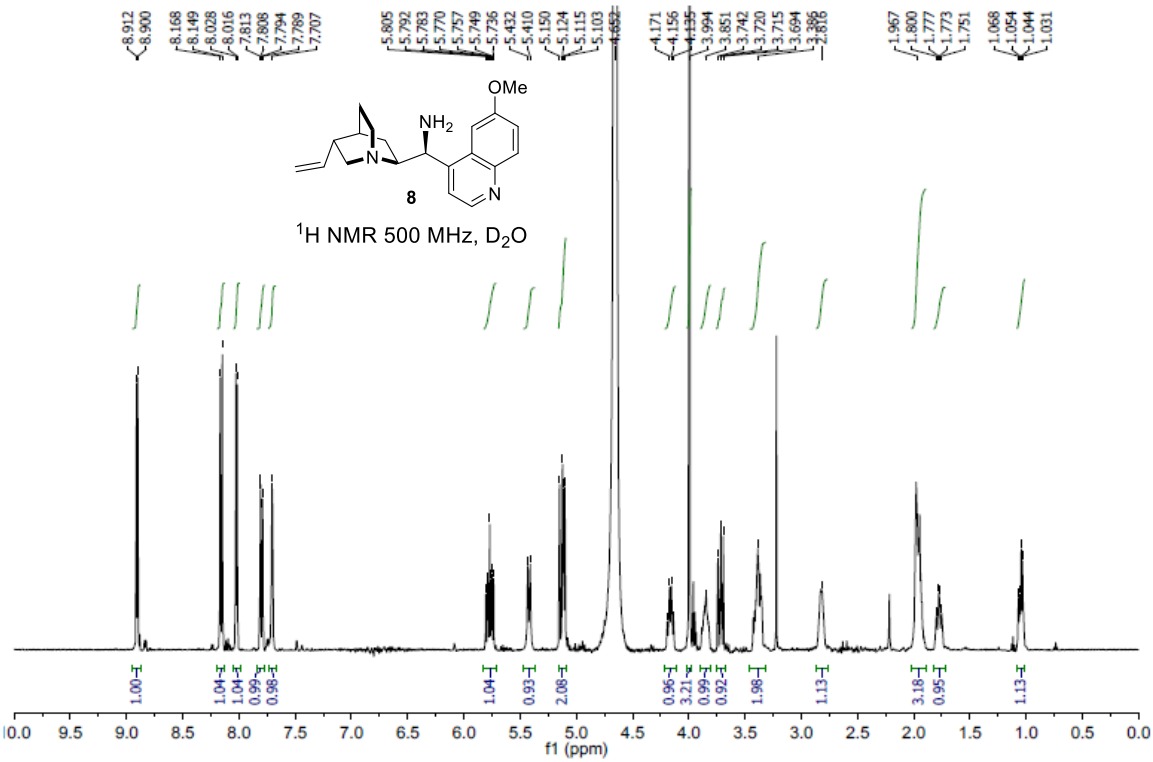


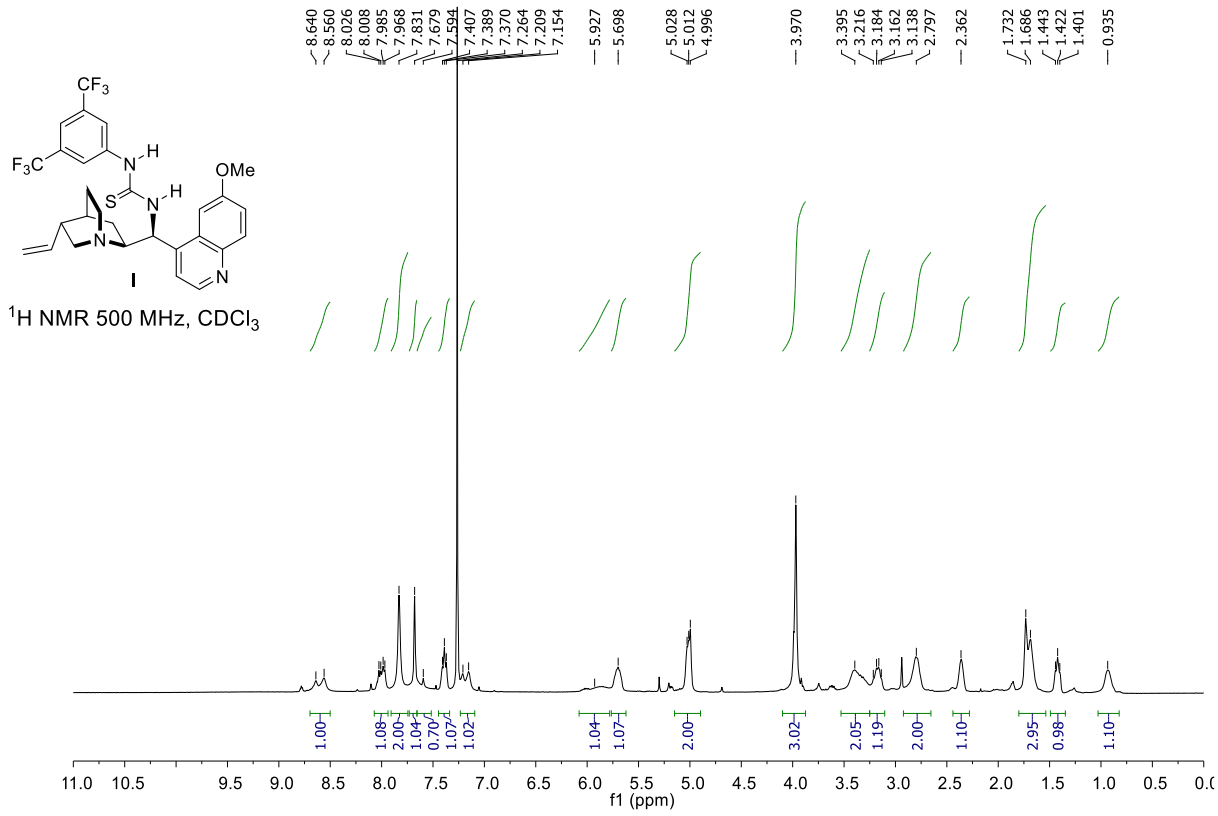
	Rt (min)	Area (%)
Major	32.913	70
Minor	40.007	30

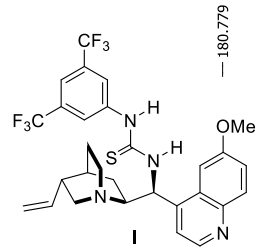


	Rt (min)	Area (%)
Major	32.353	49.9
Minor	38.577	50.1

3.5.4 ^{1}H NMR, ^{13}C NMR spectra of representive compounds

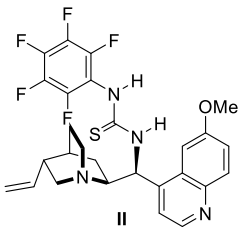






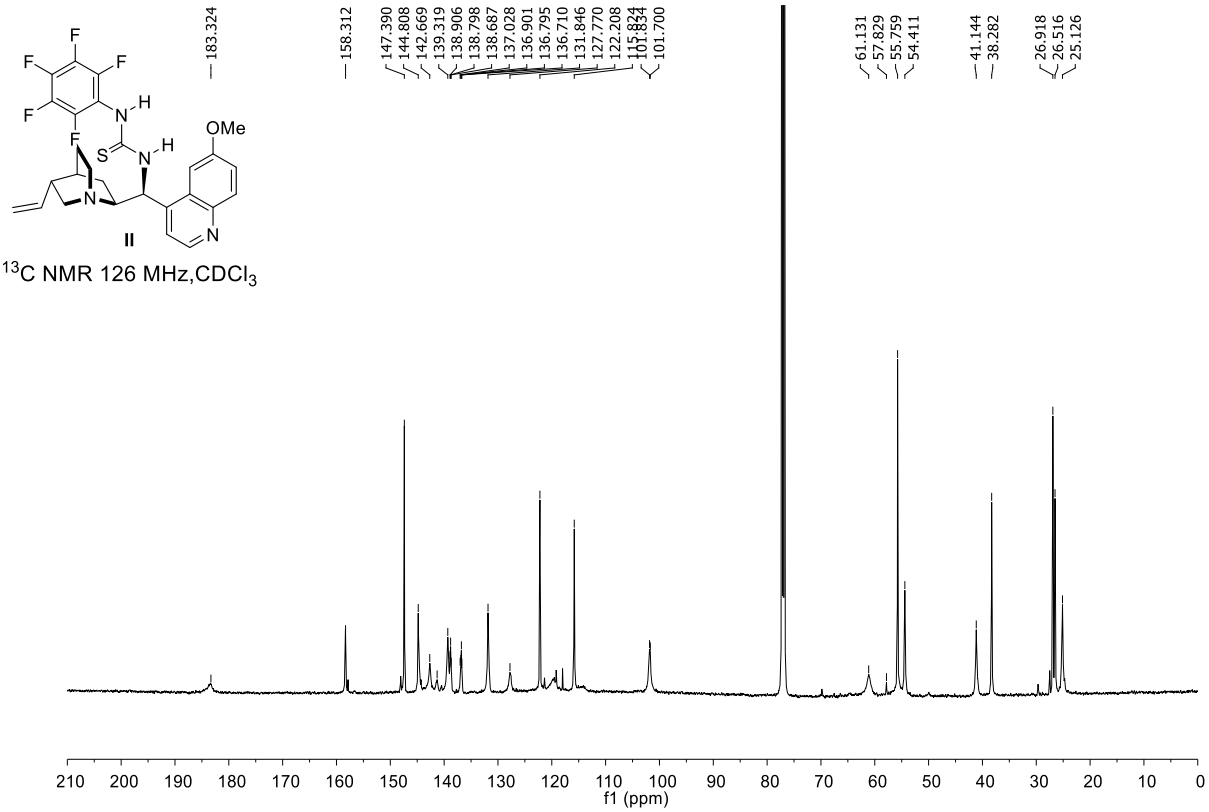
I

^{13}C NMR 126 MHz, $CDCl_3$



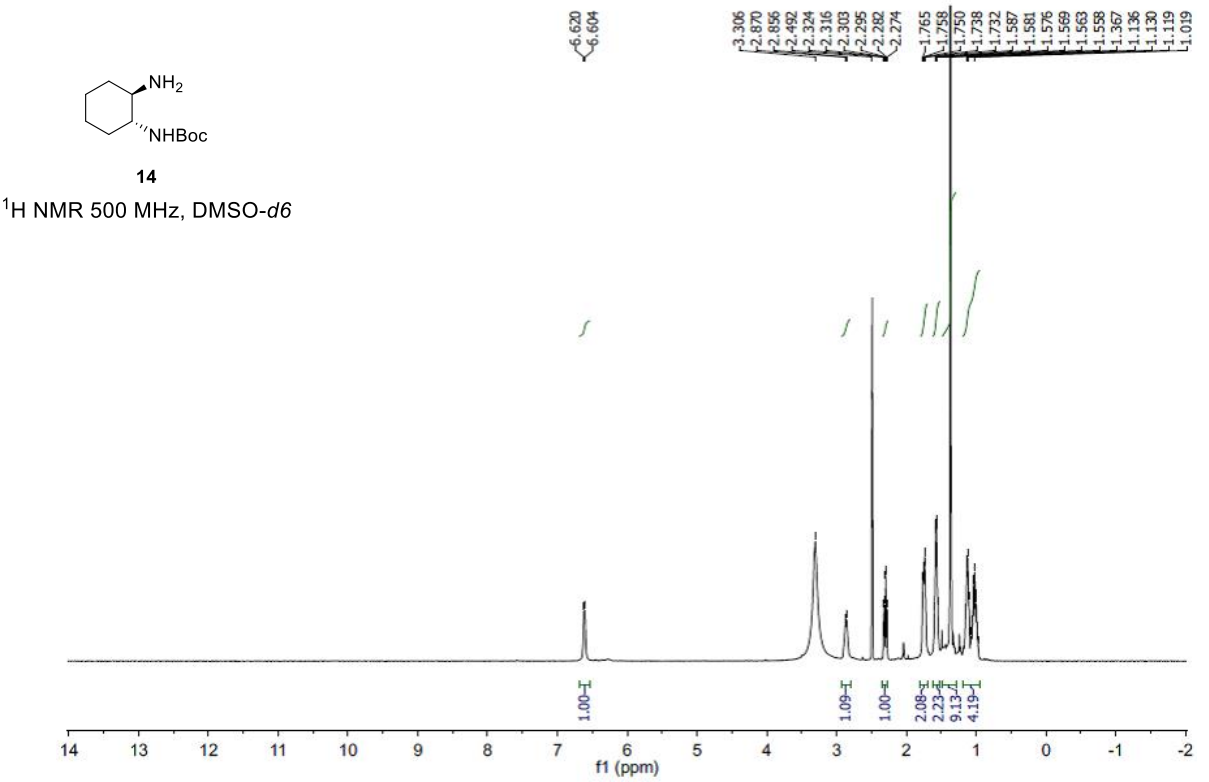
II

^{1}H NMR 500 MHz,$CDCl_3$



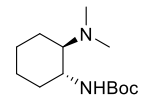
II

^{13}C NMR 126 MHz,$CDCl_3$



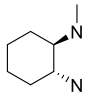
14

^{1}H NMR 500 MHz, DMSO-*d6*



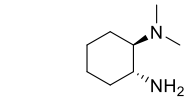
16

^{1}H NMR 500 MHz, $CDCl_3$



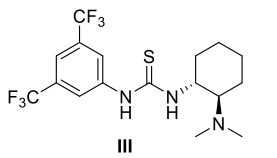
11

^{1}H NMR 400 MHz, $CDCl_3$



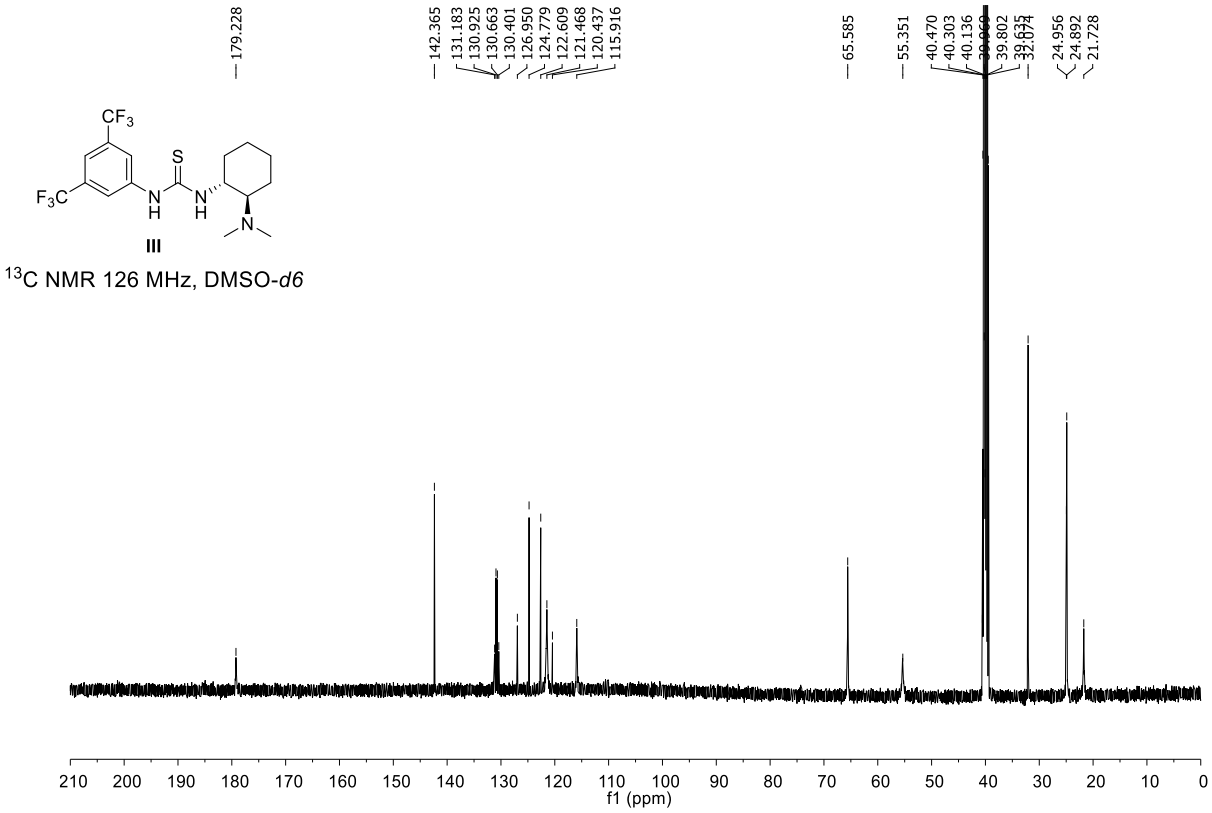
11

^{13}C NMR 126 MHz, $CDCl_3$

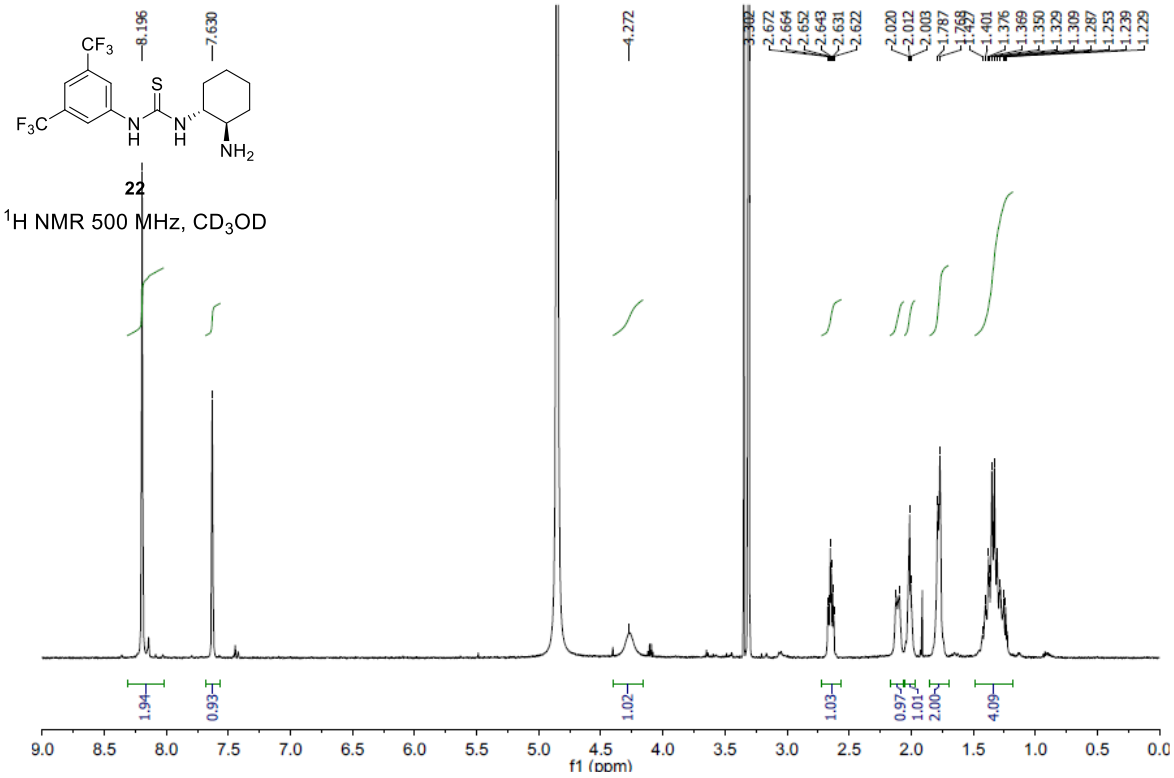


III

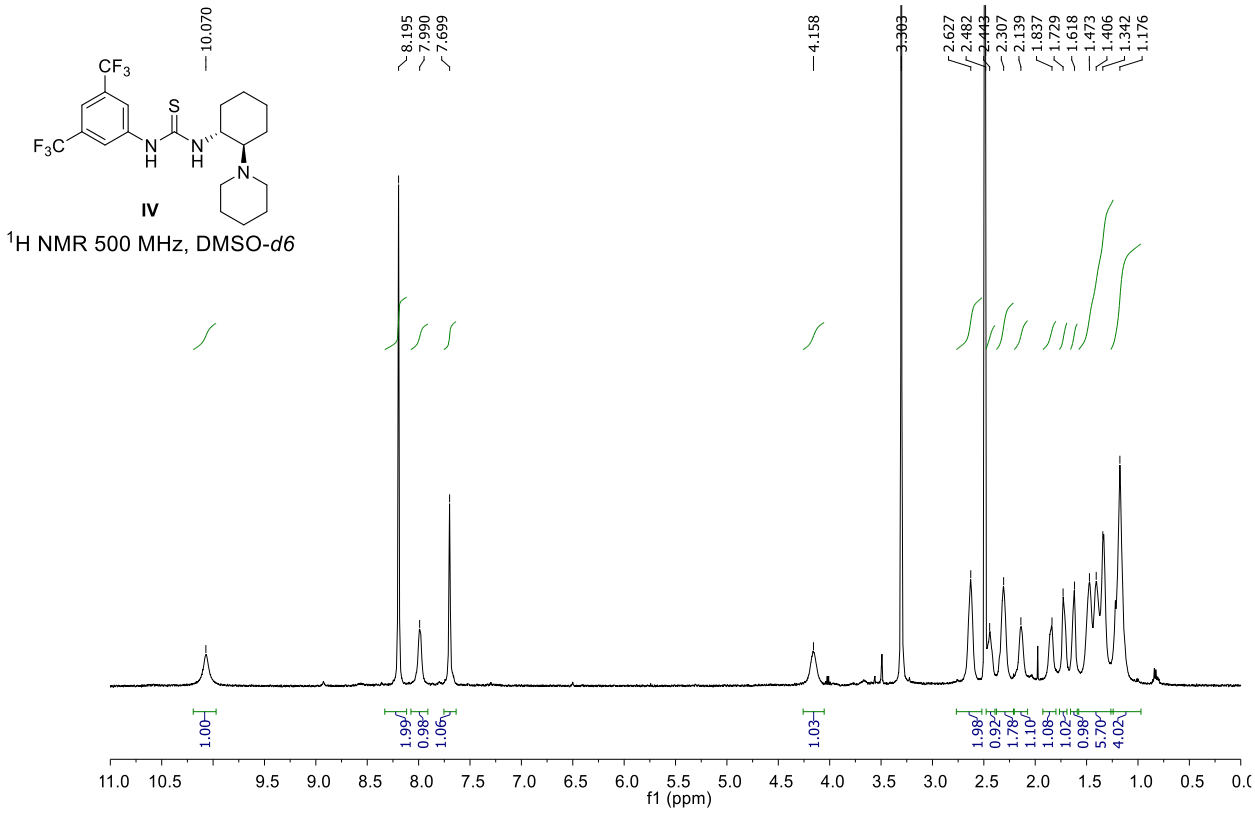
^{1}H NMR 500 MHz, DMSO-*d6*

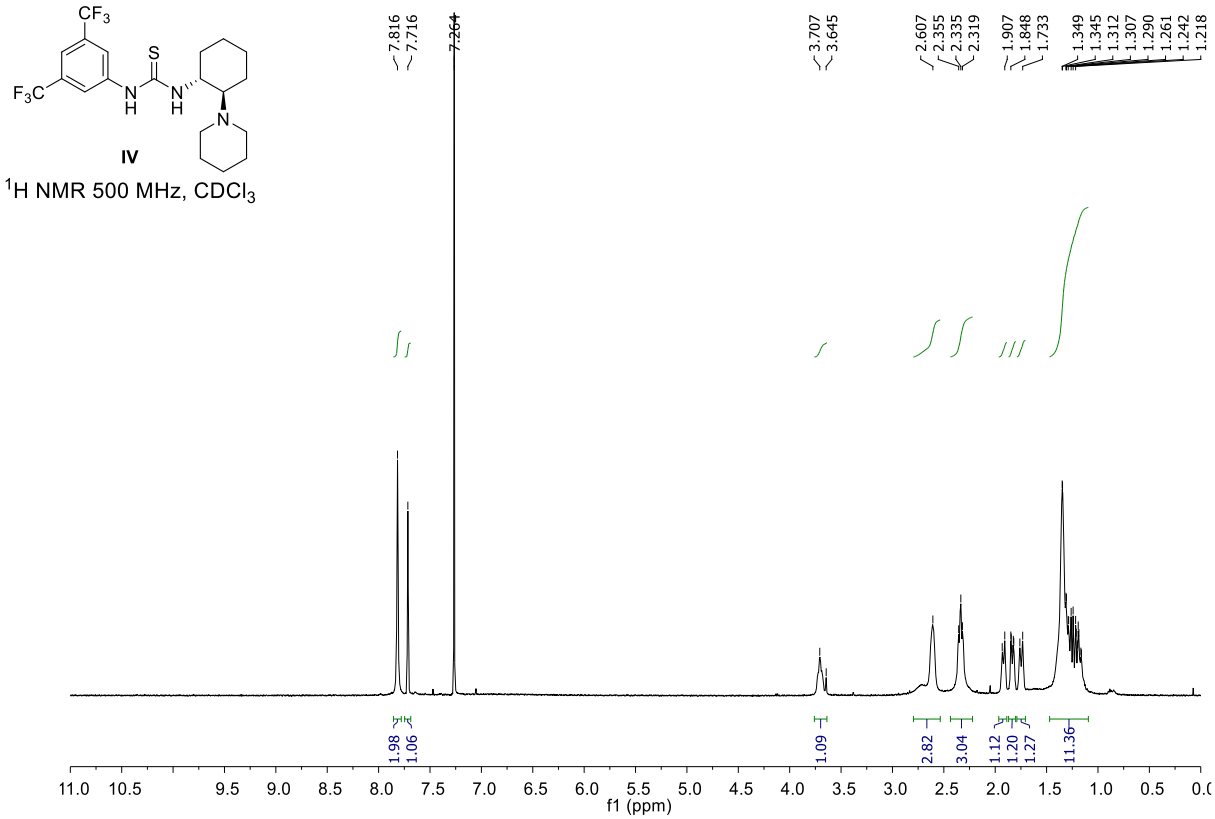


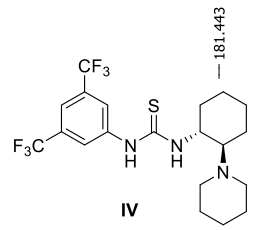
^{13}C NMR 126 MHz, DMSO-*d6*



^{1}H NMR 500 MHz, CD_3OD

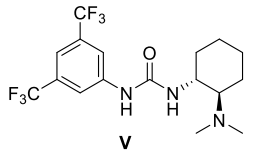

IV
^{1}H NMR 500 MHz, DMSO-*d6*
10.070
8.195
7.990
7.699
4.158
3.303
2.627
2.482
2.443
2.307
2.139
1.837
1.729
1.618
1.473
1.406
1.342
1.176
f1 (ppm)


IV
^{1}H NMR 500 MHz, CDCl$_3$
7.816
7.716
7.264
3.707
3.645
2.607
2.355
2.335
2.319
1.907
1.848
1.733
1.349
1.345
1.312
1.307
1.290
1.261
1.242
1.218
f1 (ppm)



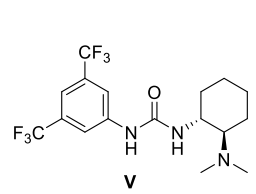
IV

^{13}C NMR 126 MHz, $CDCl_3$



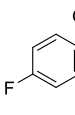
V

^{1}H NMR 500 MHz, $CDCl_3$



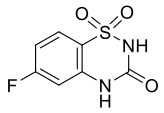
V

^{13}C NMR 126 MHz, $CDCl_3$



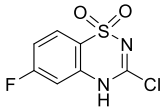
18

^{1}H NMR 500 MHz, CD_3OD



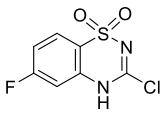
18

^{13}C NMR 126 MHz, CD_3OD



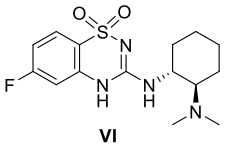
12

^{1}H NMR 500 MHz, CD_3OD



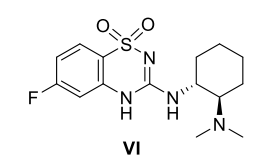
12

^{13}C NMR 126 MHz, CD_3OD



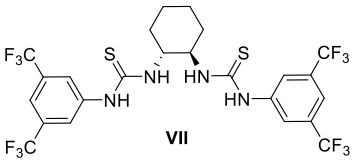
VI

^{1}H NMR 500 MHz, $CDCl_3$



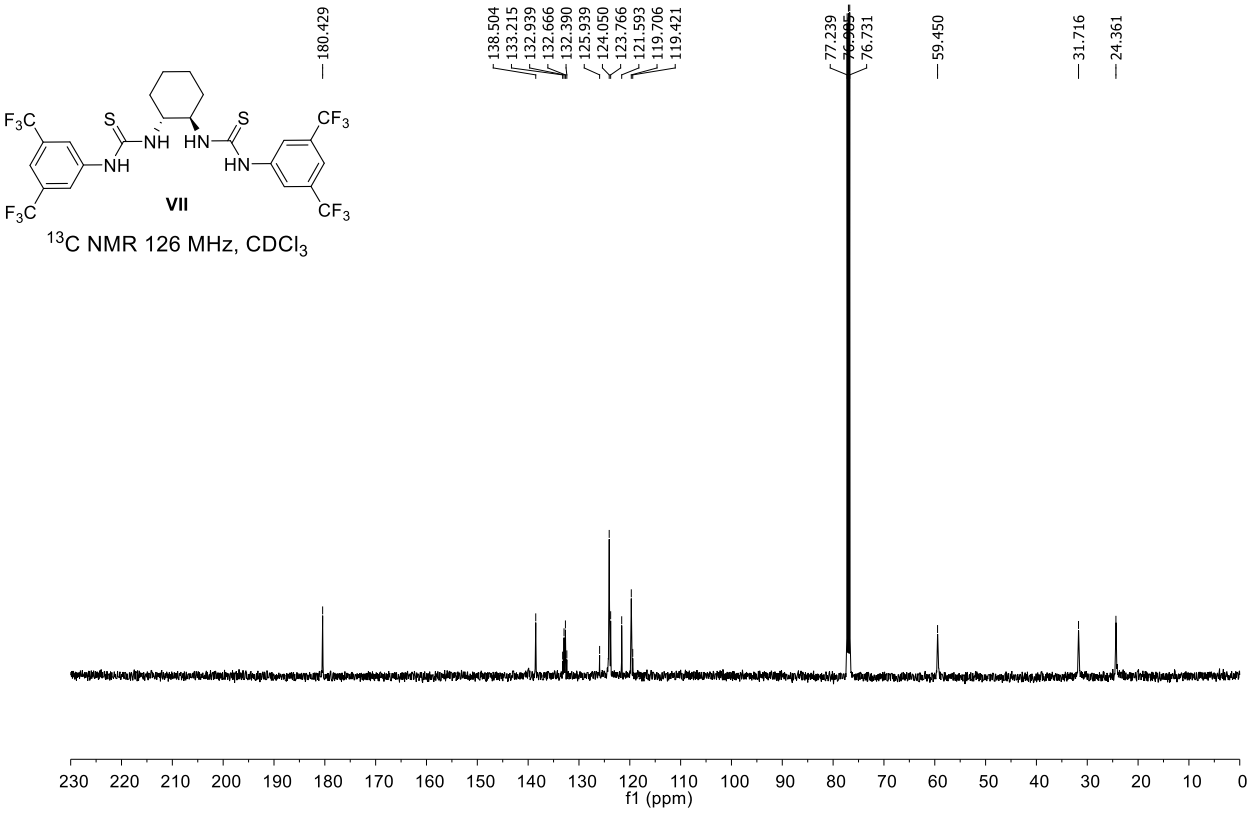
VI

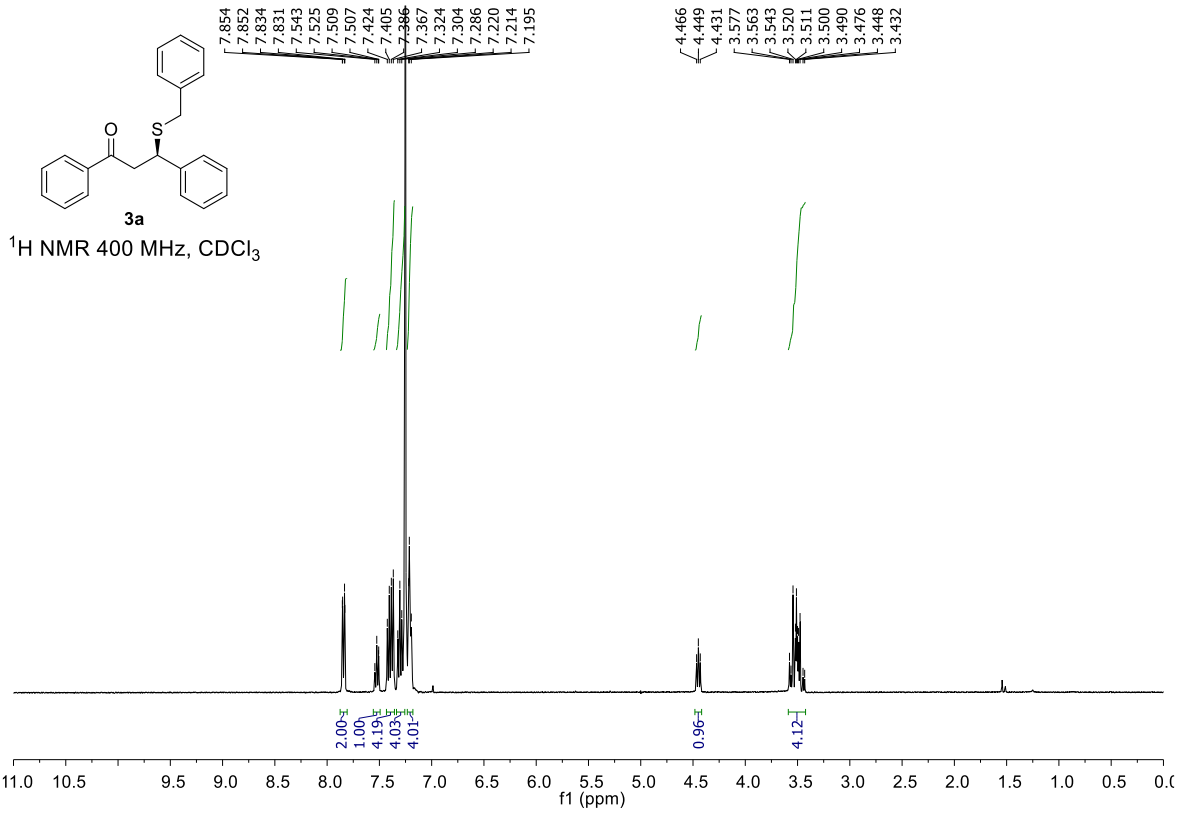
^{13}C NMR 126 MHz, $CDCl_3$

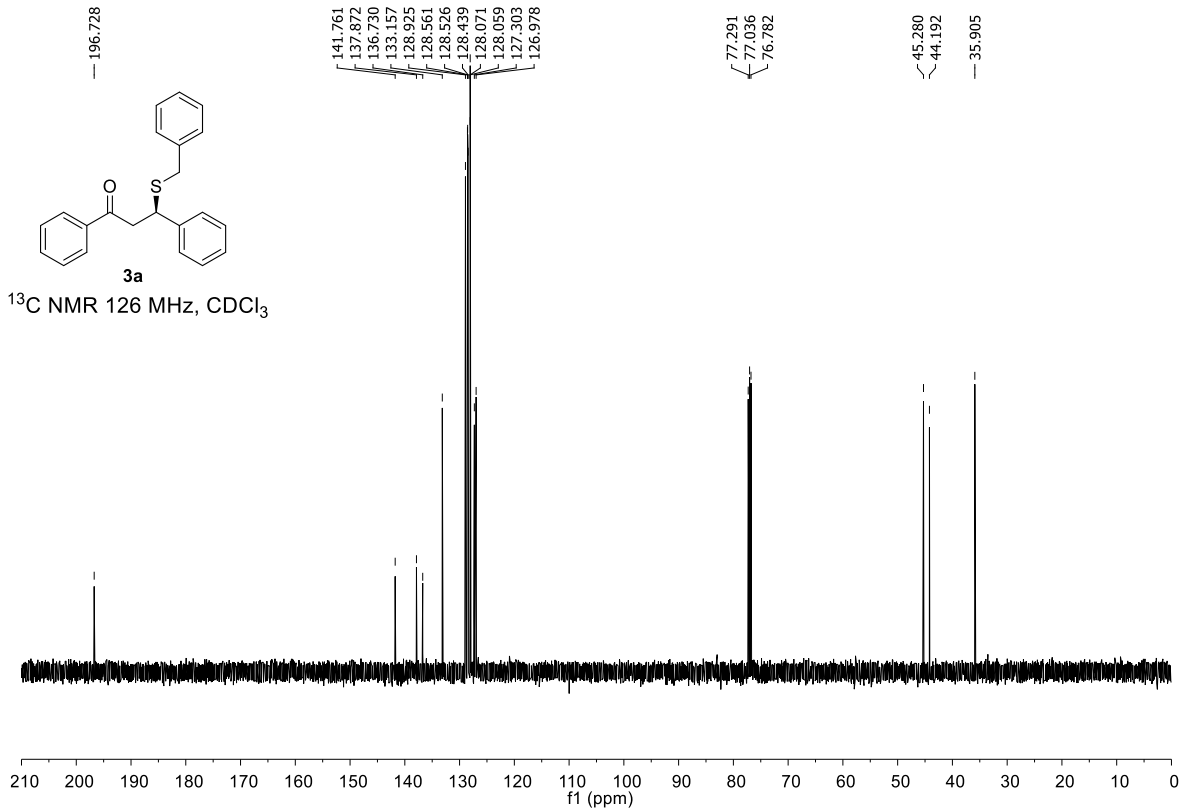


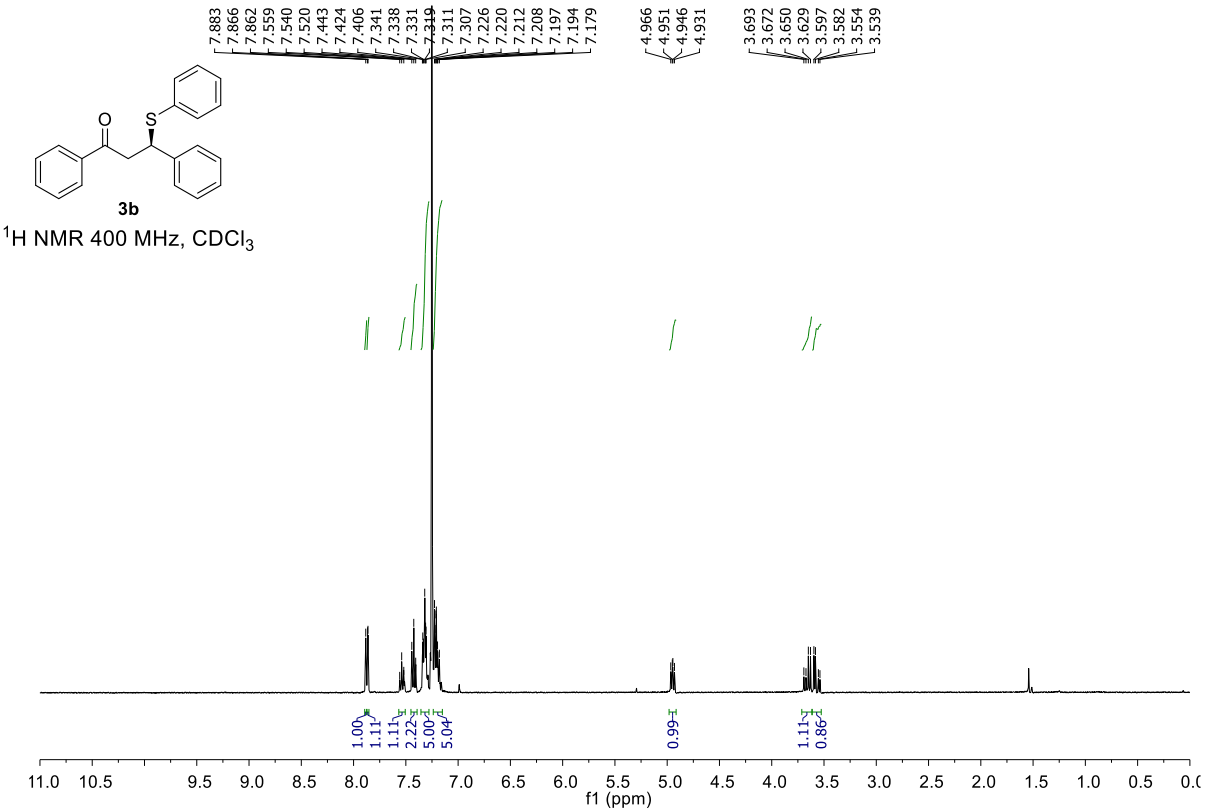
VII

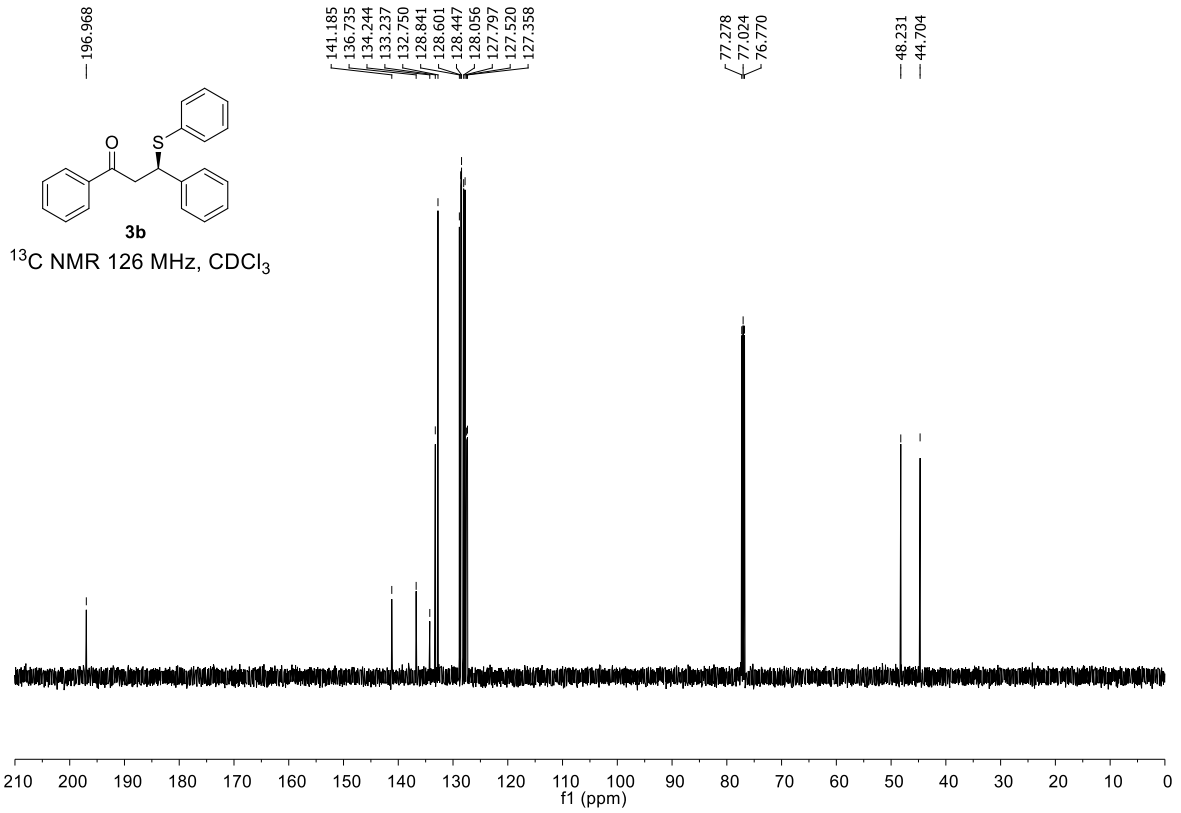
^{1}H NMR 500 MHz, $CDCl_3$

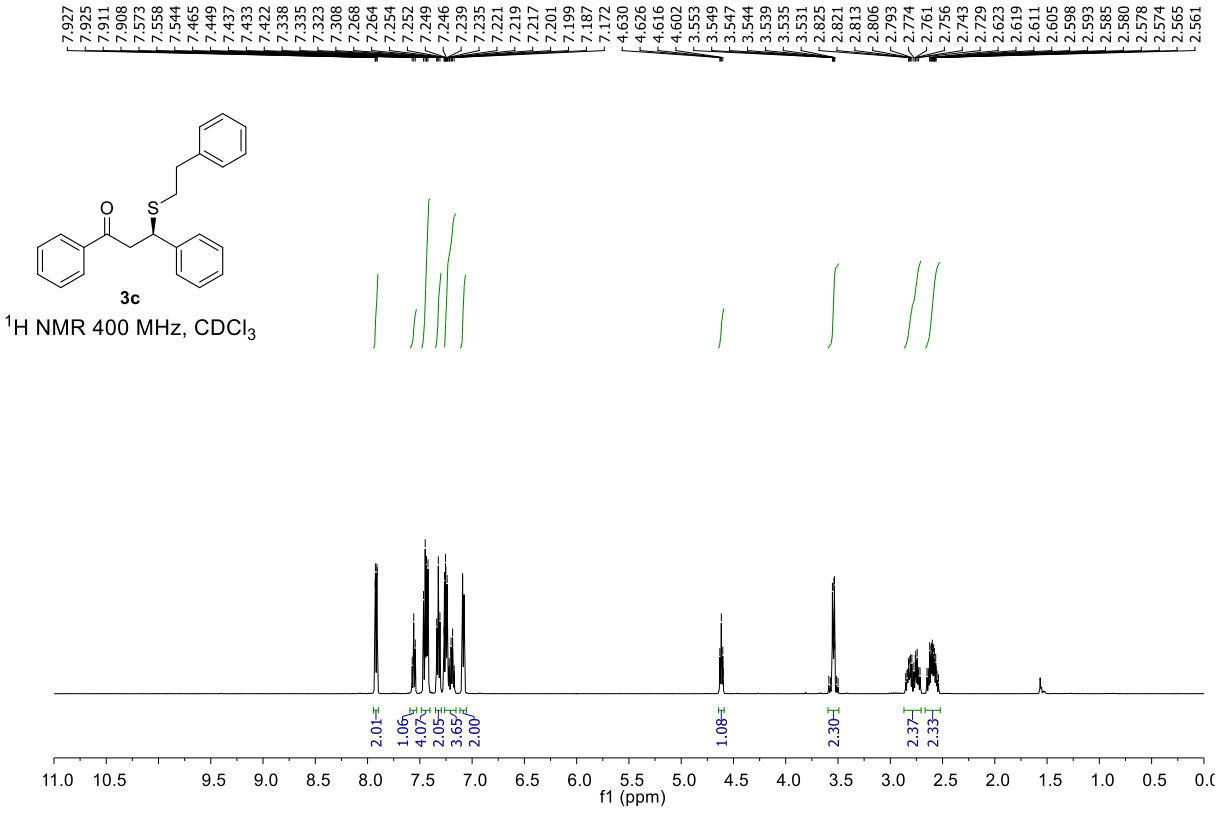

180.429
138.504
133.215
132.939
132.666
132.390
125.939
124.050
123.766
121.593
119.706
119.421
77.239
76.985
76.731
59.450
31.716
24.361
F3C
CF3
S
NH
HN
NH
HN
F3C
CF3
VII
13C NMR 126 MHz, CDCl3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

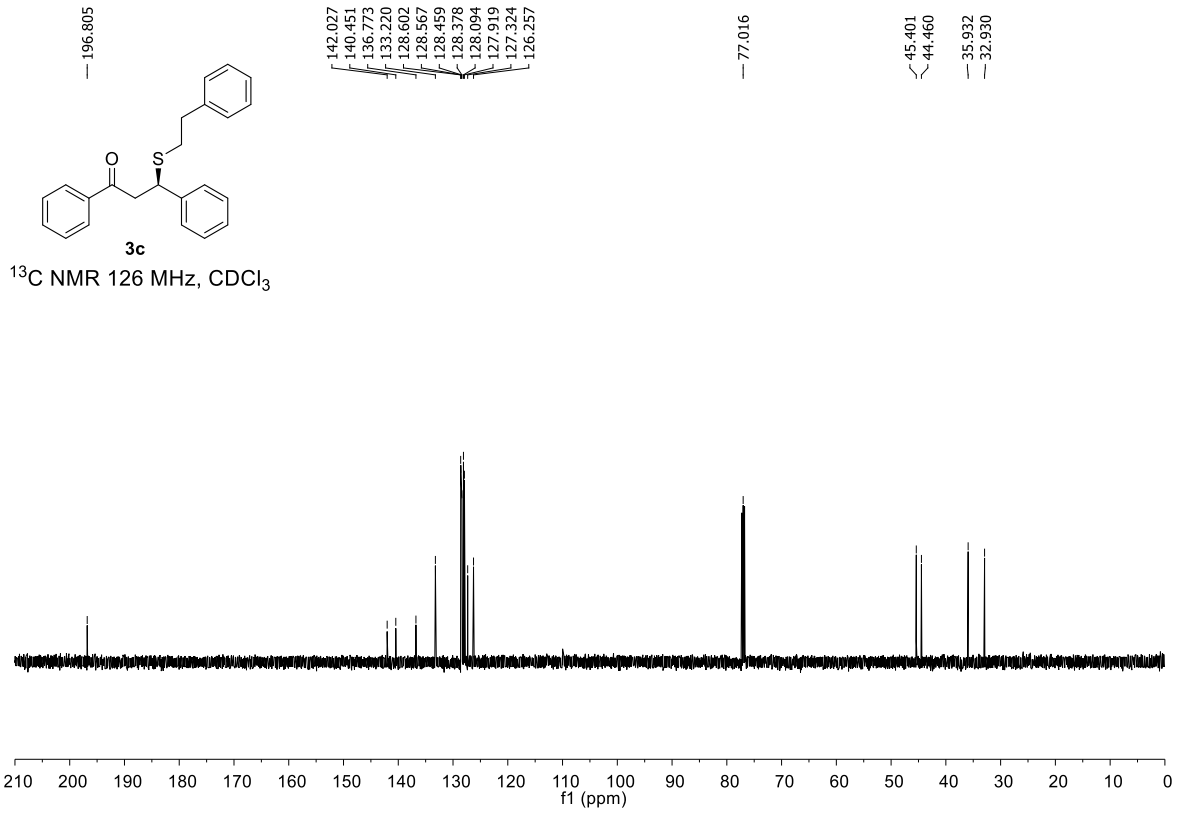

7.854
7.852
7.834
7.831
7.543
7.525
7.509
7.507
7.424
7.405
7.386
7.367
7.324
7.304
7.286
7.220
7.214
7.195
4.466
4.449
4.431
3.577
3.563
3.543
3.520
3.511
3.500
3.490
3.476
3.448
3.432
O
S
3a
1H NMR 400 MHz, CDCl3
2.00
1.00
4.19
4.03
4.01
0.96
4.12
11.0 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


196.728
141.761
137.872
136.730
133.157
128.925
128.561
128.526
128.439
128.071
128.059
127.303
126.978
77.291
77.036
76.782
45.280
44.192
35.905
O
S
3a
13C NMR 126 MHz, CDCl3
f1 (ppm)


7.883
7.866
7.862
7.559
7.540
7.520
7.443
7.424
7.406
7.341
7.338
7.331
7.319
7.311
7.307
7.226
7.220
7.212
7.208
7.197
7.194
7.179
4.966
4.951
4.946
4.931
3.693
3.672
3.650
3.629
3.597
3.582
3.554
3.539
O
S
3b
1H NMR 400 MHz, CDCl3
1.00
1.11
1.11
2.22
5.00
5.04
0.99
1.11
0.86
f1 (ppm)


196.968
141.185
136.735
134.244
133.237
132.750
128.841
128.601
128.447
128.056
127.797
127.520
127.358
77.278
77.024
76.770
48.231
44.704
O
S
3b
13C NMR 126 MHz, CDCl3
f1 (ppm)


7.927
7.925
7.911
7.908
7.573
7.558
7.544
7.465
7.449
7.437
7.433
7.422
7.338
7.335
7.323
7.308
7.268
7.264
7.254
7.252
7.249
7.246
7.239
7.235
7.221
7.219
7.217
7.201
7.199
7.187
7.172
4.630
4.626
4.616
4.602
3.553
3.549
3.547
3.544
3.539
3.535
3.531
2.825
2.821
2.813
2.806
2.793
2.774
2.761
2.756
2.743
2.729
2.623
2.619
2.611
2.605
2.598
2.593
2.585
2.580
2.578
2.574
2.565
2.561
O
S
3c
1H NMR 400 MHz, CDCl3
2.01
1.06
4.07
2.05
3.65
2.00
1.08
2.30
2.37
2.33
f1 (ppm)


196.805
142.027
140.451
136.773
133.220
128.602
128.567
128.459
128.378
128.094
127.919
127.324
126.257
77.016
45.401
44.460
35.932
32.930
O
S
3c
13C NMR 126 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter 4: Epoxide forming reactions

4.1 Introduction

Catalytic stereoselective epoxidations of carbon-carbon double bonds are powerful reactions for the generation of optically active epoxides, which are common structures in pharmaceutical compounds, as well as important intermediates in fine chemicals or API, Figure 4.1.[115]

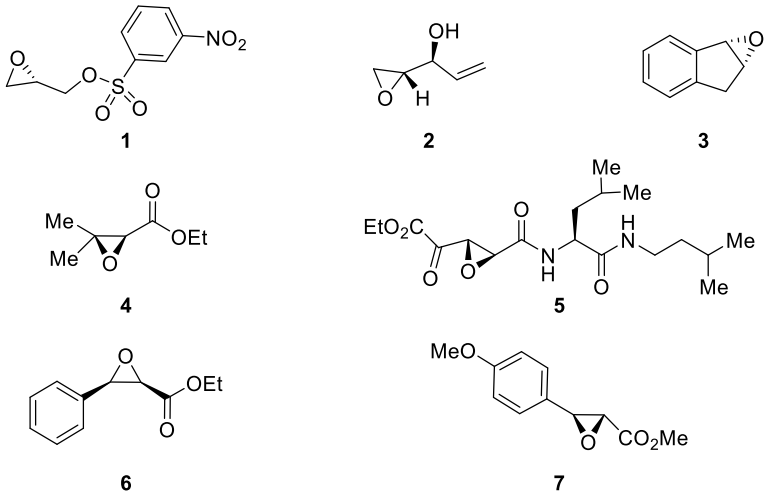


Figure 4.1 Epoxides as building blocks for the synthesis of chiral drugs.

The epoxide functionality, is for example, featured in Loxistatin **5**, the synthetic analog of E-64, a potent, irreversible cysteine protease inhibitor isolated from *Aspergillus japonicus*.[116] From the perspective of a synthetic chemist, the three-membered ring system makes epoxides valuable reagents for nucleophilic ring-opening reactions;[117] for example epoxide **6** is a precursor of the side chain of Taxol[118] and epoxide **7** is a key intermediate for the synthesis of Diltiazem.[48-50]

Sharpless and Katsuki pioneered the field of asymmetric epoxidation with the stereoselective epoxidation of allylic alcohol **8** using (+) or (-)-diethyl tartrate (DET), titanium tetraisopropoxide, and *tert*-butyl hydroperoxide, Scheme 4.1.[119] The reaction is catalyzed by Ti(O*i*Pr)$_4$, which binds the hydroperoxide, the allylic alcohol group, and the asymmetric tartrate ligand *via* oxygen atoms.

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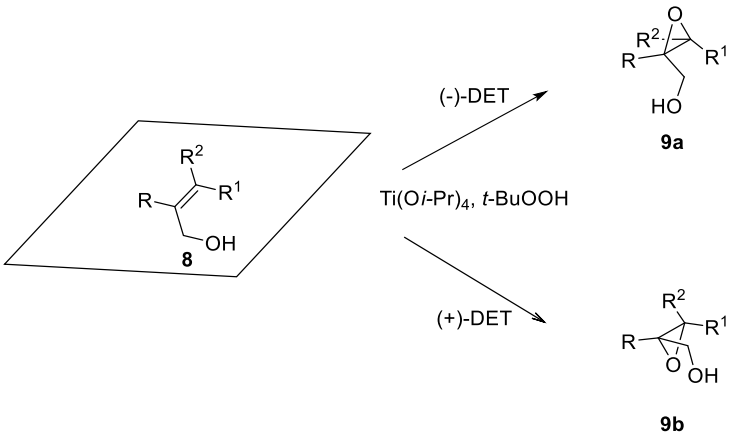
[115] a) Davis, R. L.; Stiller, D. J.; Naicker, T.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 2; b) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 788; c) a) P. Crotti, M. Pineschi in *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[116] Lygo, B.; Gardiner, S. D.; To, D. C. M. *Synlett* **2006**, 2063.
[117] a) Vilotijevic, I.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250; b) Sharpless, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[118] Bourzat, J.-D.; Commercon, A. WO 9209589, **1991**.
[119] a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; b) Katsuki, T.; Sharpless, K. B.US 4471130, **1984**.

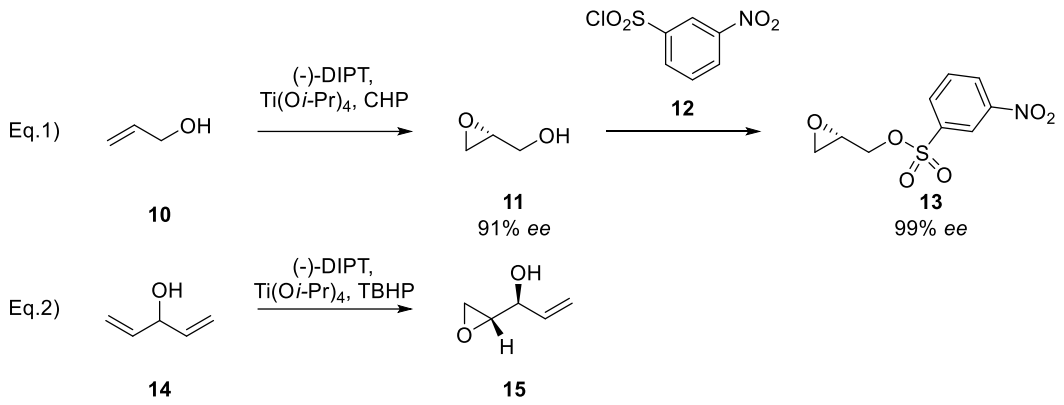


Scheme 4.1 Sharpless epoxidation reaction.

In 1986, the same author discovered that upon the addition of molecular sieves to the reaction mixture only catalytic amounts (5–10 mol%) of the titanium tartrate complex were required expanding the scope for industrial application.[120]

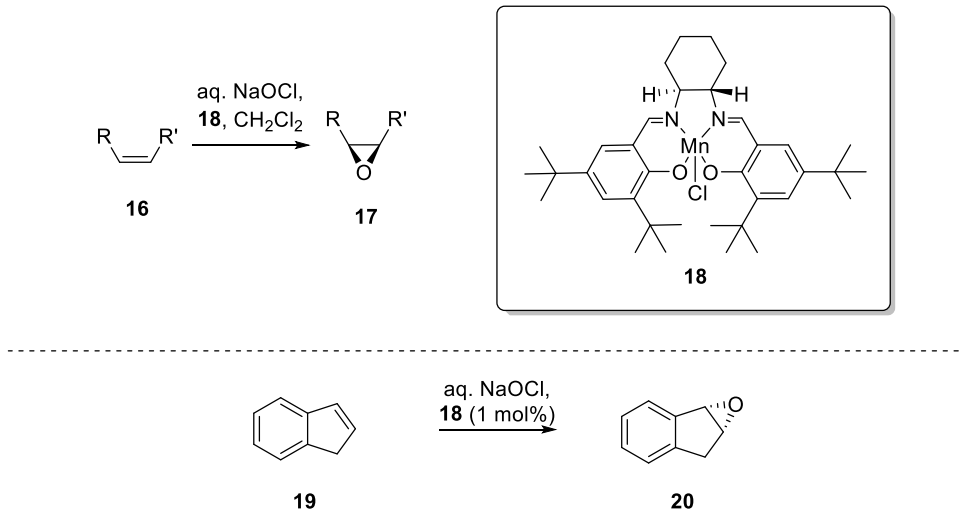
Arco Chemical developed the first Sharpless epoxidations on an industrial scale.[121] The oxidation of allyl alcohol (**10**) in the presence of cumene hydroperoxide (CHP) as oxygen-atom donor provided the (*R*)-glycidol (**11)** with 91% *ee,* Scheme 4.2, eq. 1. The isolation of the product was performed by derivatization as *m*-nitrobenzene sulfonate **13** that was obtained after crystallization with >99% *ee*, Scheme 4.2, eq. 1.[122] Enantiomerically pure compounds **11** and **13** are used as intermediates in the synthesis of cidofovir and indinavir.[123] (2*S*,3*R*)-1,2-Epoxy-4-penten-3-ol (**15**), an intermediate in the synthesis of the immunosuppressant FK-506, can be synthesized by the Sharpless epoxidation of divinylmethanol **14**, Scheme 4.2, Eq. 2.[123]

[120] a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922; b) Gao, Y.; R. M. Hanson, Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am Chem. Soc.* **1987**, *109*, 5765; c) Hanson, R. M.; Ko, S. Y.; Sharpless, K. B. US 4900847, **1986**.
[121] a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710; b) Dougherty, W.; Liotta, F.; Mondimore, D.; Shum, W. *Tetrahedron Lett.* **1990**, *31*, 4389.
[122] a) Kasai, N.; Suzuki, T.; Furukawa, Y. *J. Mol. Catal. B* **1998**, *4*, 237; b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5 765; c) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.
[123] Kleemann, A.; Engel, J. *Pharmaceutical Substances*, 4th ed., Thieme, Stuttgart, **2001**.



Scheme 4.2 Some examples of industrial application of the Sharpless epoxidation.

In 1990, Jacobsen and Katsuki developed an efficient catalytic systems based on manganese/salen complexes that allowed to the stereoselective epoxidation of alkenes in the presence of a stoichiometric quantity of hypochlorite as oxidizing agent, Scheme 4.3.[124]

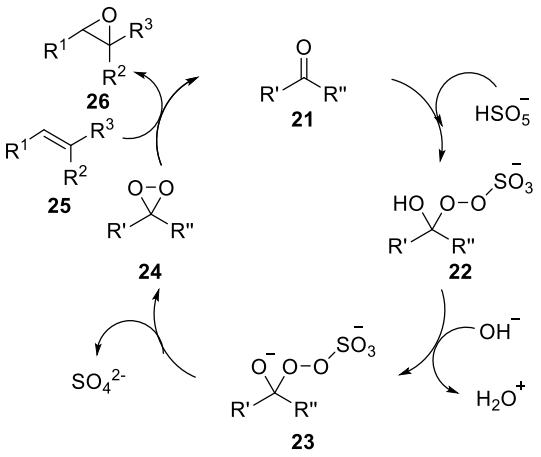


Scheme 4.3 Jacobsen- Katsuki stereoselective epoxidation.

Reactions of *cis* alkenes in the presence of 1 mol% of the catalyst afford epoxides with >98% *ee*. Epoxidations of *trans*, tetra-substituted, and terminal alkenes give both low yields and stereoselectivities. The company ChiRex applied this methodology on a multiton scale for the epoxidation of indene (**19**) to (1*S*,2*R*)-indene oxide (**20**) with catalytic amounts of manganese/salen complex **18**. Compound (1*S*,2*R*)-**20** is an intermediate in the synthesis of an HIV-protease inhibitors.[123]

[124] a) Zhang, W.; Leobach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

In 1996, Shi and co-workers developed the stereoselective synthesis of epoxides from various alkenes using the fructose-derived organocatalyst **28**, Scheme 4.5, with potassium peroxomonosulfate (oxone) as the primary oxidant source, Scheme 4.4.[125] This stereoselective epoxidation is mediated by dioxiranes **24**, which are formed *in situ* from the chiral ketone **21** and oxone, which facilitates the oxygen transfer from catalyst **28** to the alkene **25**. The ketone functionality is regenerated upon epoxidation, allowing the chiral catalyst to enter another epoxidation cycle. A high pH value was required to suppress a competing Baeyer–Villiger oxidation occurring during the formation of intermediate **22**. Since oxone tends to decompose at higher pH levels, reactions are carried out in buffered solution, or biphasic mixtures in the presence of phase transfer catalysts. However, it was demonstrated that an increase in pH to 10.5 allowed lower catalyst loading (20–30 mol%) providing the desired epoxides in higher yield and stereoselectivity.[126]

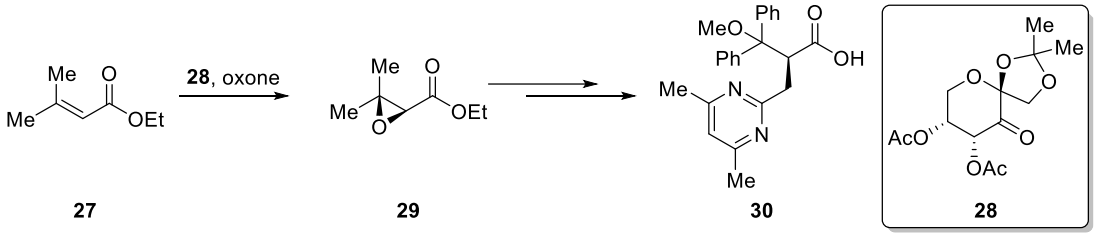


Scheme 4.4 Mechanism of the Shi epoxidation.

Over the last few years more efforts have been devoted to improve this methodology[127] and it was also applied for the synthesis of complex optically active compounds.[128] For example, the synthesis of (+)-ambrisentan **30**, used for the treatment of pulmonary arterial hypertension, was realized in four steps with 53% overall yield and 99% *ee* on 100 gram

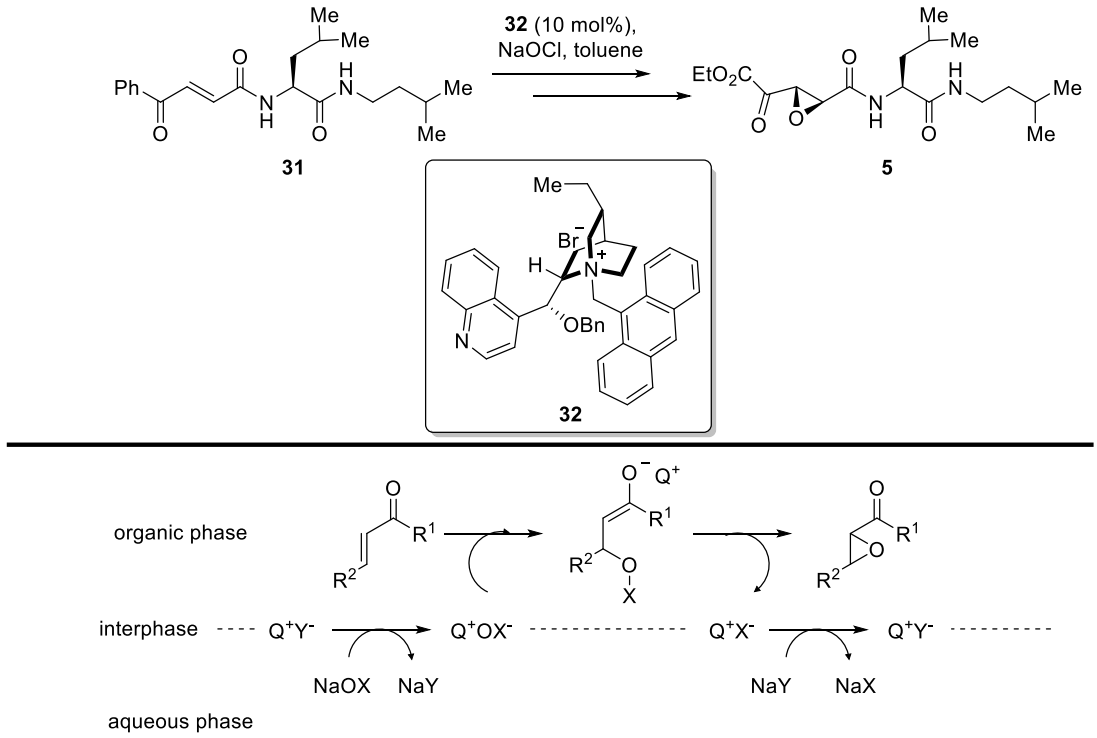
[125] a) Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806; b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.*, **1997**, *119*, 11224.
[126] Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.
[127] Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.
[128] a) Magolan, J.; Coster, M. J. *J. Org. Chem.* **2009**, *74*, 5083; b) Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965; c) Tong, R. B.; Boone, M. A.; McDonald, F. E. *J. Org. Chem.* **2009**, *74*, 8407; d) Yang, Y. R.; Lai, Z.W.; Shen, L. A.; Huang, J. Z.; Wu, X. D.; Yin, J. L.; Wei, K. *Org. Lett.* **2010**, *12*, 3430.

scale, Scheme 4.5.[129] The chiral epoxide intermediate was prepared in the presence of catalyst **28**.



Scheme 4.5 Synthesis of (+)-ambrisentan.

Stereoselective phase-transfer catalysis (PTC) has been successfully applied to the asymmetric epoxidation of electron-deficient alkenes, specifically *α,β*-unsaturated ketones.[130] This reaction proceeds through a biphasic Weitz–Scheffer-type mechanism where the quaternary ammonium salt serves to bring the nucleophilic epoxidizing agent across the interface and direct its approach to the alkene, Scheme 4.6.



Scheme 4.6 Stereoselective epoxidation of carbon-carbon double bonds by chiral PTCs.

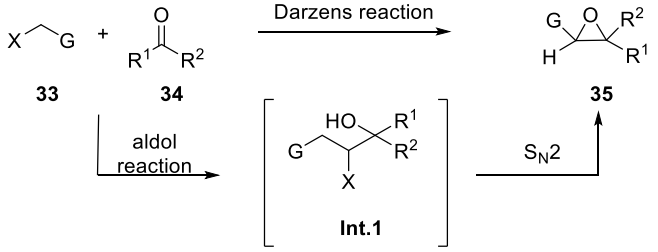
[129] Peng, X.; Li, P.; Shi, Y. *J. Org. Chem.* **2012**, *77*, 701.
[130] a) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222 ; b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312.

The potential of these catalytic reactions was applied in the total synthesis of Loxistatin **5**, Scheme 4.6.[131] In particular, the epoxidation of compound **31** occurs with the nucleophilic addition of NaOCl to the α,β-unsaturated ketone and subsequently, formation of the oxirane ring by an S_N2-type reaction on the oxygen atom providing to the desired product **5**.

[131] Lygo, B.; Gardiner, S. D.; To, D. C. M. *Synlett* **2006**, 2063.

4.2 The Darzens reaction

A valuable alternative method to olefin epoxidations is the Darzens condensation, Scheme 4.7.[132] The Darzens reaction is a condensation between the α-halo compound **33** and the carbonyl compound **34** in the presence of a base.



33 **34** **35**

Scheme 4.7 Darzens condensation for the synthesis of α,β-epoxycarbonyl compounds.

The Darzens reaction is a two-step reaction. The first step is an aldol-type reaction with the formation of the α-halo-β-hydroxyl compound **Int.1**, while the second step is an intramolecular S_N2 reaction giving the desired epoxide **35**.

Since two stereogenic centers are established in the Darzens reaction, determined by the steric requirements of the transition state of the aldol step,[133] a number of efforts have been devoted to develop efficient stereoselective Darzens condensations. The stereocontrol in the epoxide formation was induced by using chiral auxiliaries[134] or chiral catalysts, Figure 4.2.[135]

[132] a) Darzens, G. *Compt. Rend*. **1911**, *151*, 883; b) Bakó, P.; Rapi, Z.; Keglevich, G. *Curr. Org. Chem.* **2014**, *11*, 361.
[133] Yliniemelä, A.; Brunov, G.; Flügge, J.; Teleman, O. *J. Org. Chem.* **1996**, *61*, 6723.
[134] a) Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojima, S.; Ohkata, K. *J. Chem. Soc*.,Perkin Trans. *1*, **1998**; b) Schwartz, A.; Madan, P.; Mohacsi, E.; O'Brien, J.; Todaro, L.; Coffen, D. *J. Org. Chem.* **1992**, *57*, 851; c) Pridgen, L.; Abdel-Magid, A.; Lantos, I.; Shilcrat, S.; Eggleston, D. *J. Org. Chem*. **1993**, *58*, 5107; d) Aggarwal, V.; Charmant, J.; Fuentes, D.; Harvey, J.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C. *J. Am. Chem. Soc.* **2006**, *128*, 2105.
[135] a) Watanabe, S.-I.; Hasebe, R.; Ouchi, J.; Nagasawa, H.; Kataoka, T. *Tetrahedron Lett.* **2010**, *51*, 5778; b) He, L.; Liu, W.-J.; Ren, L.; Lei, T.; Gong, L.-Z. *Adv. Synth. Catal.* **2010**, *352*, 1123; c) Arai, S.; Tokumaru, K.; Aoyama, Y. *Tetrahedron Lett*. **2004**, *45*, 1845; d) Bakó, P.; Rapi, Z.; Keglevich, G.; Szöllösy, A.; Drahos, L.; Botyánszki, A.; Holczbauer, T. *Tetrahedron: Asymmetry*, **2012**, *23*, 489; e) Achard, T.R.J.; Belokon, Y.N.; Ilnyin, M.; Moskalenko, M.; North, M.; Pizzato, F. *Tetrahedron Lett*. **2007**, *48*, 2965.

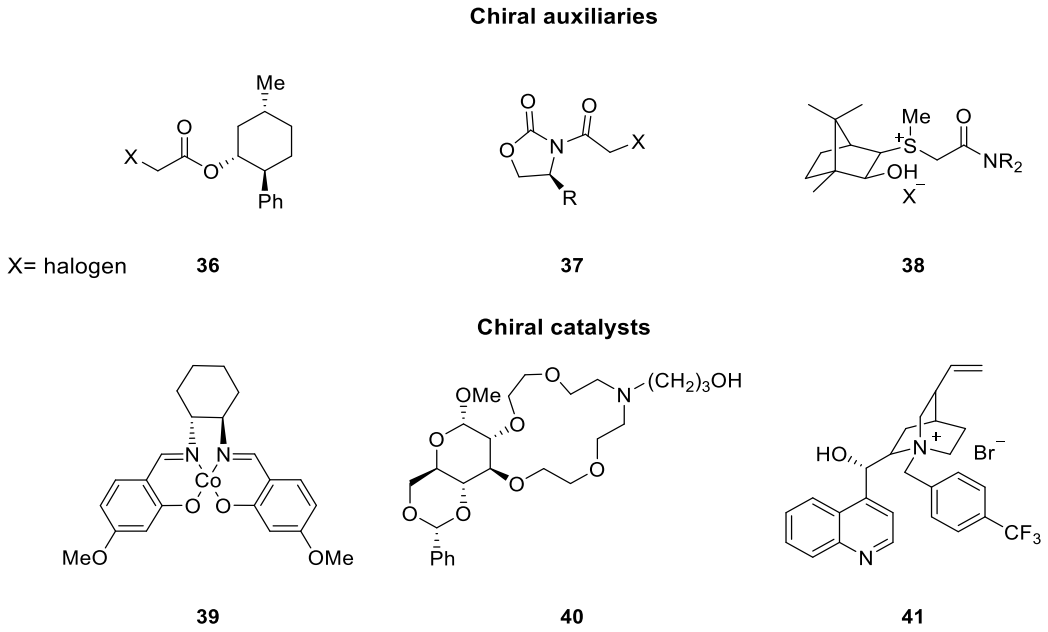
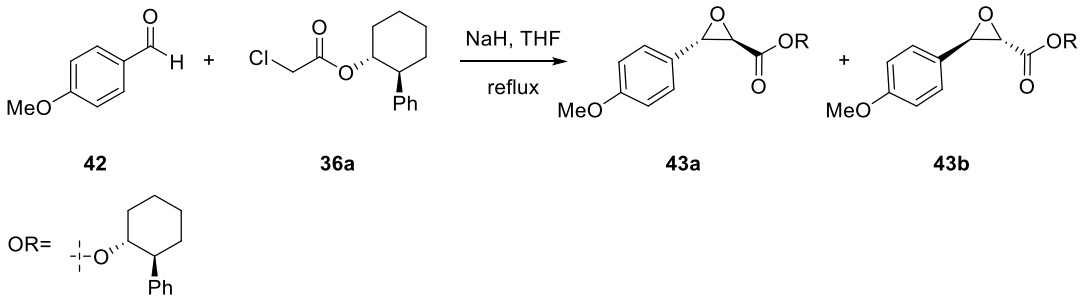


Figure 4.2 Examples of chiral auxiliaries and catalysts used in stereoselective Darzens reactions.

4.2.1 Reactions in the presence of a chiral auxiliary

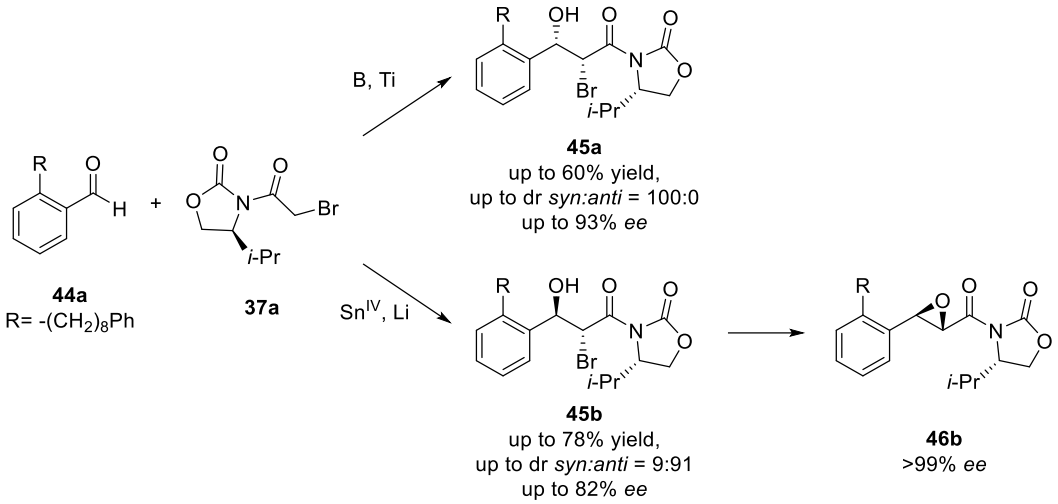
In 1992, Schwartz and co-workers screened different auxiliaries for the synthesis of epoxide **43a**, a key intermediate for the synthesis of Diltiazem, Scheme 4.8.[134b] None of the auxiliaries screened induced asymmetry leading to acceptable levels of enantiomeric excess. However, (1*R*,2*S*)-2-phenylcyclohexanol (**36a**) afforded a diastereomeric pair of glycidic esters, **43a** and **43b**, possessing marked differences in solubility. Direct crystallization of the crude product mixture provided ready access to **43a**, the required isomer, in 54% yield as a stereochemically pure entity.



Scheme 4.8 Use of enantiopure alcohol derivatives as chiral auxiliaries in the Darzens condensations.

In 1993, Pridgen and co-workers studied the aldol reaction between the enantiopure *N*-(haloacetyl)-2 oxazolidinone **37a** with aromatic aldehydes **44** inducing the reaction to yield predominantly *anti*-adducts, *e.g.* **45b**, Scheme 4.9.[134c] It was found that the steric and stereo-

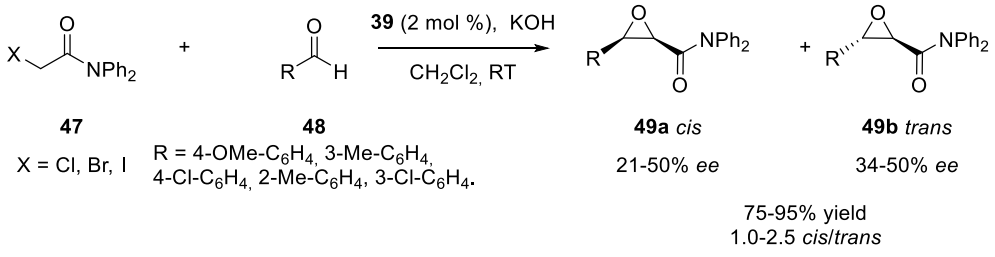
electronic properties of the aldehydes **44**, as well as its chelating ability with the enolate counterions, are crucial in determining which of its enantiotopic faces reacts. Metal enolates, such as those derived from Sn^{IV} and Li^{+}, are postulated to react through a three-point coordination transition state yielding mainly the *anti*-adduct, *e.g.* **45b**, while boron and Ti^{IV} enolates are shown to react *via* non-coordinated transition states to yield *syn*-adduct, *e.g.* **45a**. Successively the *anti*-halohydrin **45b** was stereospecifically converted to the *trans*-epoxy amide **46b** with >99% *ee*.



Scheme 4.9 Use of a chiral oxazolidinone as auxiliary in the Darzens condensations.

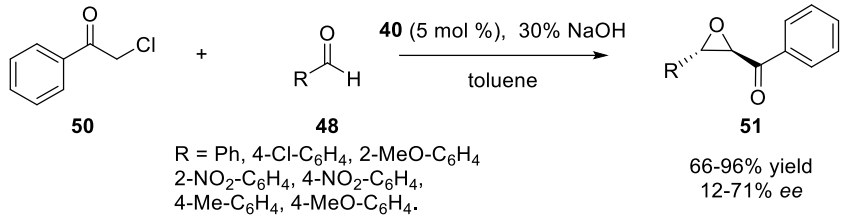
4.2.2 Stereoselective catalytic reactions

North *et al*. have developed metal(salen)complexes derived from (*R*,*R*)-diaminocyclohexane, *e.g.* catalyst **39**, Figure 4.2.[135e] The Darzens reactions between *α*-haloamides **47** and aldehydes **48** were performed in the presence of salen catalyst **39**, Scheme 4.10. The reactions, in the presence of 2 mol% of **39** in dichloromethane and at room temperature, give the epoxide **49** with up to 95% yield, and *cis*/*trans* diastereomeric ratios up to 1.0/2.5 and *ee* up to 50%.



Scheme 4.10 Use of salen catalyst **39** in asymmetric Darzens reactions.

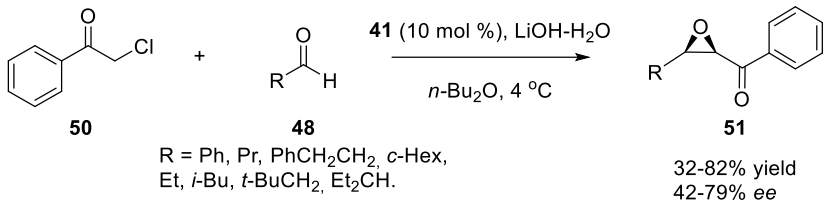
Bakó and Töke developed chiral crown ethers from monosaccharides, *e.g.* **40**, Figure 4.2, and used them as phase transfer catalysts in stereoselective reactions.[136] Catalyst **40** proved to be an efficient catalyst in the reaction between phenacyl chloride **50** and aromatic aldehydes **48** in a liquid-liquid (toluene-NaOH 30%) two phase system, Scheme 4.11. The *trans*-epoxyketones **51** were obtained with yield up to 96% and *ee* up to 71%.[135d]



Scheme 4.11 Use of chiral crown ether **40** in stereoselective Darzens reactions.

Arai-Shioiri and co-workers used a chiral phase transfer catalyst derived from *Cinchonine*, *N*-(4-trifluoromethylbenzyl)cinchonium bromide **41**, Figure 4.2, proving to be an effective catalyst in stereoselective Darzens reactions.[135c]

The reaction of chloroacetophenone **50** with different aldehydes **48** proceeded smoothly in the presence of 10 mol% of catalyst **41** and LiOH monohydrate in dibutyl ether at 4 °C to give the corresponding *trans*-epoxides **51** with moderate to high *ee* and yields under mild conditions, Scheme 4.12.



Scheme 4.12 Use of quaternary ammonium salt **41** in asymmetric Darzens reactions.

The field of stereoselective Darzens reactions is only at the beginning. A lot of efforts will be required to find experimental procedures which lead to products with high chemical yield and stereoselection.

[136] Bakó, P.; Keglevich, G.; Rapi, Z. *Lett. Org. Chem.* **2010**, *7*, 645.

Chapter 5: Darzens reaction

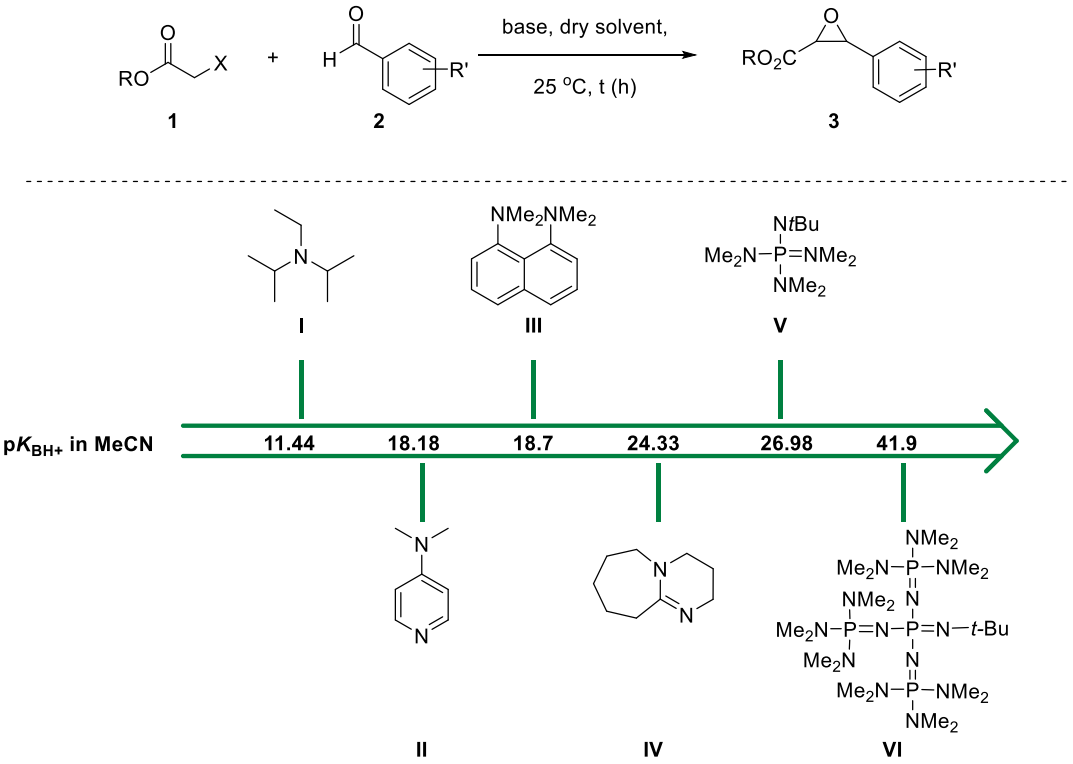
5.1 Object of study

Darzens reaction represents an interesting procedure for the preparation of multifunctional intermediates in the synthesis of fine chemicals or API, that has witnessed in the recent years a sustained development.[132] Their scope and synthetic significance have enlarged with the inclusion of *α*-haloamides[135c,137] and nitriles,[138] *α*-haloketones[139] and *α*-halosulfones[140] or ammonium ylides[141] as the pro-nucleophile components. Moreover, aza-Darzens reactions have been also developed using imines instead of aldehydes or ketones.[142] Lewis acid catalysed Darzens reactions have been reported for *α*-diazoacetamides[143] and *N*-heterocyclic carbenes have also been used as catalysts for the preparation of *α,β*-epoxy ketones from aldehydes and *in situ* generated *α*-bromoacetophenones.[144] However, in their base promoted version, these reactions are most commonly run in the presence of strong anionic bases such as alkali metal hydroxides or alkoxides, sodium amide, LDA, LiHMDS or *n*-butyllithium,[145] very often with pre-formation of the reactive ester enolate anion. In the case of *α*-chloroketones and *α*-chloroamides, the use of phase transfer agents in association with aqueous metal hydroxides, has now become a paradigm and has enabled the preparation of *α,β*-epoxy carbonyl compounds in moderate-to-excellent yields and stereoselectivity.[146] This notwithstanding, the yields of *α,β*-epoxy esters as the products of Darzens reactions run under basic conditions are low to moderate only. As far as *α*-haloesters are concerned, evidence exist that under these conditions the corresponding *trans*-epoxy esters are particularly susceptible to hydrolysis,[147] even in the case of *tert*-butyl esters[148] providing a possible explanation for the low yields generally observed, or the exclusive *cis* selectivity documented in some cases.[144] In addition, in the reactions promoted by metal alkoxides, *α*-chlorocinnamate[149] esters byproducts were reported and the formation of *α*-chloro-*β*-lactones

[137] Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 833.
[138] Wang, Z.; Xu, L.; Mu, Z.; Xia, C.; Wang, H. *J. Mol. Cat. A Chemical* **2004**, *218*, 157.
[139] a) Liu, Y.; Provencher, B. A.; Bartelson, K. J.; Deng, L. *Chem. Sci.* **2011**, *2*, 1301; b) Bakó, P.; Rapi, Z.; Keglevich, G.; Szabó, T.; Sóti, P. L.; Vígh, T.; Grűn, A.; Holczbauer, T. *Tetrahedron Lett.* **2011**, *52*, 1473; c) Rapi, Z.; Szabó, T.; Keglevich, G.; Szöllősy, Á, Drahos, L.; Bakó, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1189; d) Rapi, Z.; Bakó, P.; Keglevich, G.; Szöllősy, Á, Drahos, L.; Botyánszki, A.; Holczbauer, T. *Tetrahedron: Asymmetry* **2012**, *23*, 489.
[140] a) Ku, J.-M.; Yoo, M.-S.; Park, H.-G.; Jew, S.-S.; Jeong, B.-S. *Tetrahedron Lett.* **1998**, *39*, 8299; b) Ku, J.-M.; Yoo, M.-S.; Park, H.-g.; Jew, S.-s. Jeong, B.-S. *Tetrahedron* **2007**, *63*, 8099; c) Arai, S.; Shioiri, T. *Tetrahdron* **2002**, *58*, 1407; d) Latorre, A.; RodrÍguez, S.; Gonzaléz, F. V.; Florea, B. I.; Overkleeft, H. S. *J. Org. Chem.* **2015**, *80*, 7752.
[141] a) Waser, M.; Herchl, R.; Müller, N. *Chem. Commun.* **2011**, *47*, 2170; b) Pichler, M.; Novacek, J.; Robiette, R.; Poscher, V.; Himmelsbach, M.; Monkowius, U.; Müller, N.; Waser, M. *Org. Biomol. Chem.* **2014**, *13*, 2092.
[142] Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911.
[143] Liu,W.-J.; Lv, B.-D.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2009**, *48*, 6503.
[144] Reddi, R. N.; Prasad, P. K.; Sudalai, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 14150.
[145] Takahashi, T.; Muraoka, M.; Capo, M.; Koga, K. *Chem. Pharm. Bull.* **1995**, *43*, 1821.
[146] Herchl, R.; Waser, M. *Tetrahedron* **2014**, 70, 1935.
[147] Kimura, C.; Kashiwaya, K.; Murai, K.; Katada, H. *Ind. Eng. Chem. Prod. Res. Dev.* **1983**, *22*, 118.
[148] Jonczyk, A.; Zomerfeld, T. *Tetrahedron Lett.* **2003**, *44*, 2359.
[149] Field, L.; Carlile, C. G. *J. Org. Chem.* **1961**, *26*, 3170.

was even dominant in the case of the Darzens condensation involving phenyl esters of α-chlorocarboxylic acids promoted by lithium *N*-cyclohexyl-*N*-isopropylamide.[150]

To the best of our knowledge, there are no examples of Darzens reaction involving uncharged organobase. Prompted by this information, we surveyed the activity of readily available organobases **I-VI** with different pK_{BH}^{+} [151] to promote the Darzens condensation between α-halo esters **1** and aromatic aldehydes **2**, Scheme 5.1.



Scheme 5.1 Evaluation of uncharged organobases in the Darzens reactions between α-halo esters **1** and aromatic aldehydes **2** studied in this research project.

[150] Wedler, C.; Kunath, A.; Schick, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2028.
[151] Kaljurand, I.; Kütt, A.; Sooväli, L.; Rodima, T.; Mäemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

5.2 Results and discussion

5.2.1 Organobases screening

In our study, we selected the commercially available organobases **I-VI**, Figure 5.1, for the epoxide formation between methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**), Table 5.1. The reactions were performed in the presence of 1.0 eq. of 4-bromobenzaldehyde (**2a**), 1.5 eq. of methyl chloroacetate (**1a**), 1.5 eq. of organobases **I-IV** in dry THF at 25 °C.

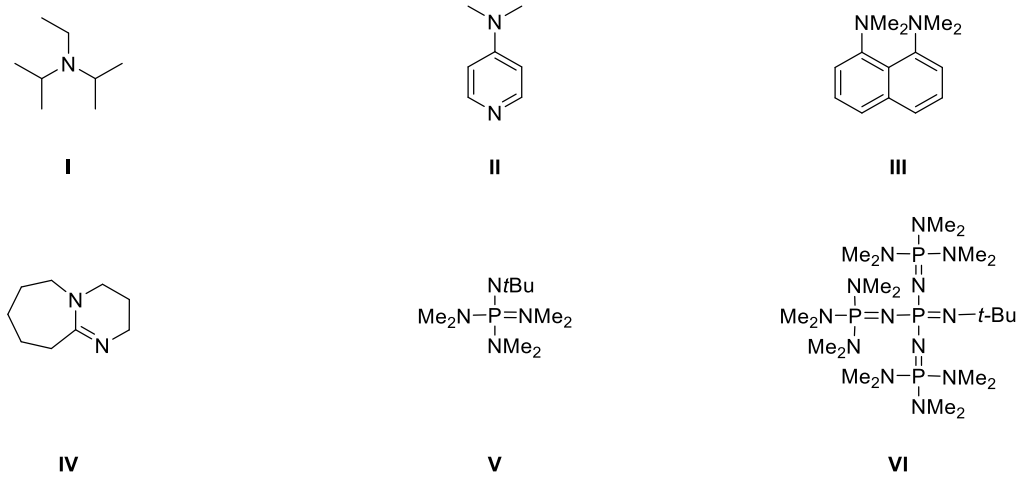


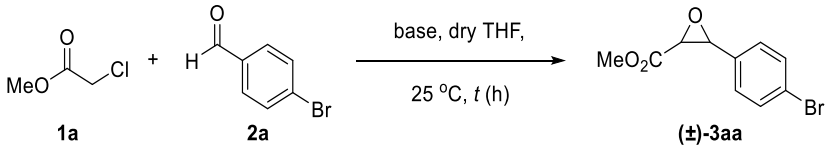
Figure 5.1 Uncharged organobases **I-VI** used in this study.

Darzens reaction did not proceed in the presence of bases **I-IV**, Table 5.1, entries 1-4. While the reaction mixture did not show by-products with Hünig's base (**I**) and Proton-Sponge® (**III**), different types of chemical reactions were observed in the presence of DMAP (**II**) and DBU (**IV**), Scheme 5.2. In particular, the nucleophilic addition of DMAP (**II**) to methyl chloroacetate (**1a**) gave the salt **4**, Scheme 5.2, eq.1. With DBU (**IV**), considered a strong neutral organic base (with a pK_{BH^+} value of 24.33 in acetonitrile),[152] the reaction showed a complex mixture. Three products were obtained, Scheme 5.2, eq.2, : tricyclic compound **5**, derived from the domino reaction of DBU (**II)** with methyl chloroacetate (**1a**), by-product **(±)-6** obtained *via* aldol reaction between compound **5** and 4-bromobenzaldehyde (**2a**) and the compound **(*Z*)-7** obtained from compound **6** after water elimination.

These preliminary experiments show that the nucleophilicity and basicity properties of bases **I-IV** are not sufficient to develop a Darzens condensation.

[152] a) B. Nand, G. Khanna; A. Chaudhary; A. Lumb, J. M. Khurana, *Curr. Org. Chem.* **2015**, *19*, 790; b) Trofimov, B. A.; Shemyakina, O. A.; Mal'kina, A. G.; Stepanov, A. V.; Volostnykh, O. G.; Ushakov, I. A.; Vashchenko, A. V. *Eur. J. Org. Chem.* **2016**, 5465.

Table 5.1 Survey of bases to promote the Darzens reaction of methyl chloroacetate (**1a**) with 4-bromobenzaldehyde (**2a**).[a]



1a **2a** **(±)-3aa**

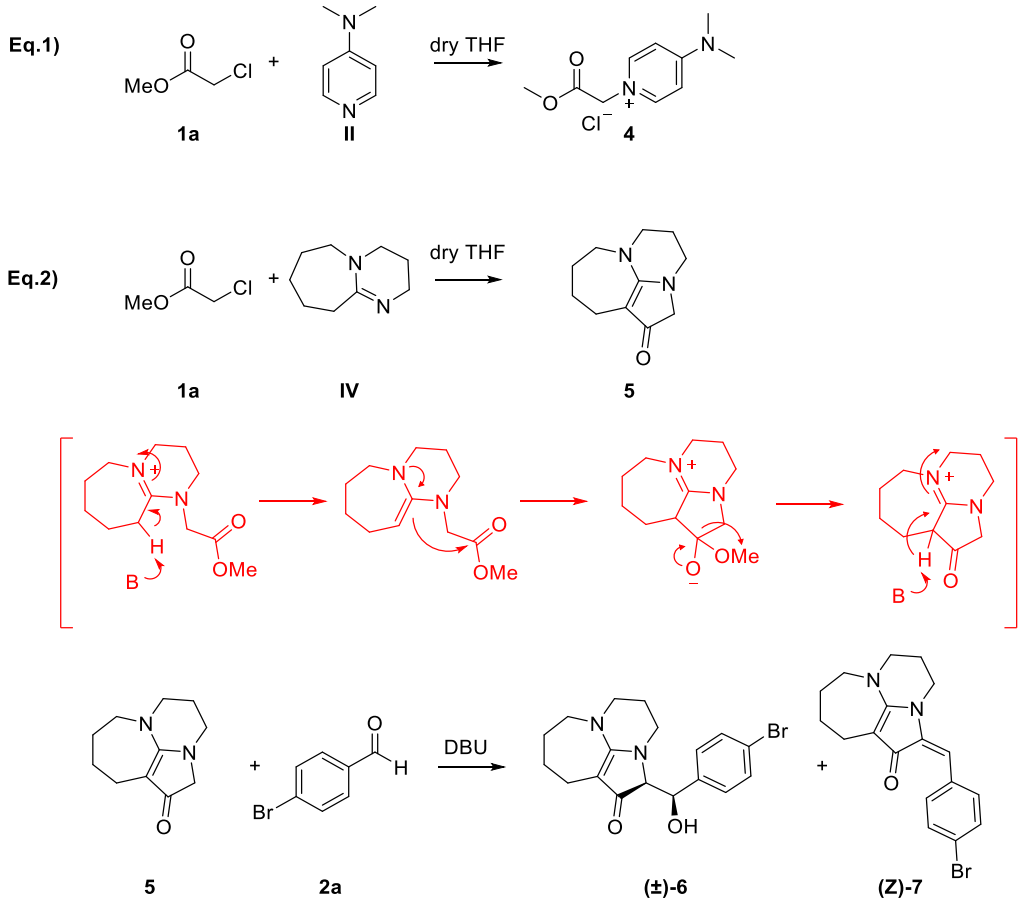
entry	base	*t* (h)[b]	yield (%)[c,d]	d.r. (*cis*/*trans*)[d,e]
1	**I**	-	-	-
2	**II**	-	-	-
3	**III**	-	-	-
4	**IV**	-	-	-
5	**V**	24	83	1/0.94
6	**VI**	24	57	1/0.85

[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.5 mmol scale using 1.5:1:1.5 **1a/2a/I-VI** molar ratio in 2 mL of dry THF at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2 experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Within the broader category of Brønsted bases, polyaminophosphazenes represent a family of extremely strong, non-ionic Brønsted bases (superbases) with pK_{BH^+} values up to about 42 as determined in acetonitrile.[153] The particular ability of phosphazene bases to produce highly reactive anions together with their low nucleophilicity and inertness towards electrophilic components enables reactions of very weak C-H acidic substrates via deprotonation in excellent yields. Their high solubility in organic solvents of low polarity such as hexane, toluene, or THF generates new alternatives to run base-promoted processes in

[153] a) Schwesinger, R.; Schlemper, H. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1167; b) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E.-M.; Peters, K.; Schnering, H. G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1361; c) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Heinz W. Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H.G.; Wake, L. *Liebigs Ann.* **1996**, 1055; d) Kaupmees, K.; Trummal, A.; Leito, I. *Croat. Chem. Acta* **2014**, *87*, 385; e) Kaljurand, I.; Saame, J.; Rodima, T.; Koppel, I.; Koppel, I. A.; Kögel, J. F.; Sundermeyer, J.; Köhn, U.; Coles, M. P.; Leito, I. *J. Phys. Chem. A* **2016**, *120*, 2591.

organic media.[154] We surmised that the basicity of phosphazene might offer advantages in the development of a Darzens condensation.



Scheme 5.2 Chemical reactions observed in presence of DMAP (**II**), Eq.1 and DBU (**IV**), Eq.2. In red is reported the suggested mechanism for the formation of tricyclic compound **5** and the reaction of the latter compound with the 4-bromobenzaldheyde **2a**.

Accordingly, we used the two readily available phosphazene bases P$_1$-*t*-Bu **V** (pK_{BH^+} = 26.98)[155] and P$_4$-*t*-Bu **VI** (pK_{BH^+} = 41.9),[156] Figure 5.1, for the possible epoxide formation between methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**) in dry THF at 25 °C, Table 5.1, entries 5-6. By using P$_1$-*t*-Bu **V** the desired epoxide **3aa** was obtained in 83% yield with a d.r. *cis*/*trans* of 1/0.94, Table 5.1, entry 5. The Darzens condensation was also performed with the stronger phosphazene base, P$_4$-*t*-Bu **VI**. In this case the reaction gave the desired product **3aa** in 57% yield with a d.r. *cis*/*trans* of 1/0.85, Table 5.1, entry 6; using P$_4$-*t*-Bu **VI** rather

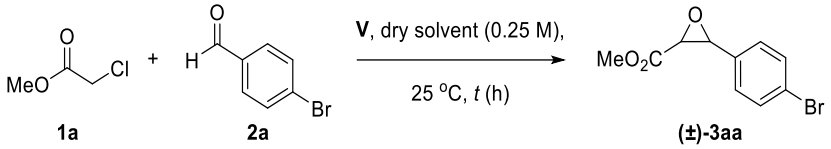
[154] *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*; Ishikawa, T., Ed.; John Wiley & Sons, Ltd: Chichester, UK, **2009**.
[155] a) Kondoh, A.; Aoki, T.; Terada, M. *Org. Lett.* **2014**, *16*, 3528; b) Caldwell, N.; Jamieson, C.; Simpson, I.; Tuttle, T. *Org. Lett.* **2013**, *15*, 2506.
[156] a) Kondoh, A.; Ando, K.; Terada, M. *Chem. Commun.* **2013**, *49*, 10254; b) Araki, Y.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. *Org. Biomol. Chem.* **2011**, *9*, 78.

than P_1-*t*-Bu **V** resulted in a relatively complex composition of the crude mixture with formation of unidentified by-products likely because of its higher basicity.

5.2.2 Optimization of the reaction conditions

The reaction conditions were initially optimized for the Darzens reaction between methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**) in the presence of P_1-*t*-Bu **V**, Table 5.2. To this end, the effect of various solvents was examined.

Table 5.2 Optimization of the reaction conditions for the Darzens reaction between methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**): effect of the solvent.[a]



entry	solvent	*t* (h)[b]	yield (%)[c,d]	d.r. (*cis*/*trans*)[d,e]
1	dry THF	24	83	1/0.94
2	dry CH_2Cl_2	16	90	1/0.85
3	dry toluene	48	66	0.88/1
4	dry MeCN	6	92	1/0.9
5[f]	dry MeCN	10	86	0.9/1

[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.5 mmol scale using 1.5:1:1.5 **1a**/**2a**/**V** molar ratio in 2 mL of solvent at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2 experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture. [f] Darzens reactions were carried out at -25 °C.

The polar aprotic solvent acetonitrile (MeCN) was optimal, resulting in complete consumption of the starting material in 6 hours at room temperature and a 92% product yield, Table 5.2, entry 4. Comparatively, the use of slightly less polar dichloromethane (CH_2Cl_2) provided a similar outcome to that of MeCN in terms of product yield, Table 5.2, entry 2. Meanwhile, the use of toluene resulted in a slower reaction rate, extended reactions times, and poor overall product yield, Table 5.2, entry 3.

By lowering the temperature to -25 °C in acetonitrile, we observed a slight decrease in the chemical yield, prolonged reaction time while the diastereoselectivity was not affected, Table 5.2, entry 5.

Afterwards, investigations of the stereochemical outcome were performed. In 1998, Schwesinger and co-workers had developed a stereoselective alkylation of the Schiff base of glycine *t*-butyl ester in the presence of phosphazenes bases in conjunction with chiral quaternary ammonium salts.[157] Prompted by this information, we surveyed the activity of three chiral quaternary ammonium salts **A-C**, Figure 5.2, in the Darzens condensation between methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**) in dry MeCN at 25 °C, Table 5.3.

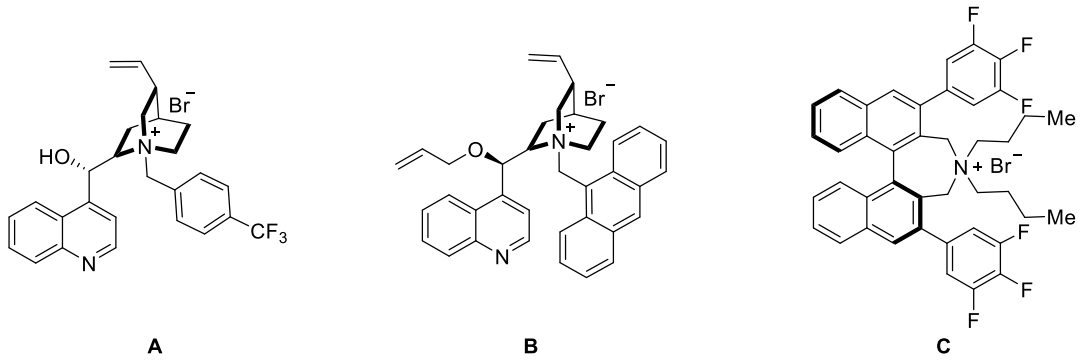
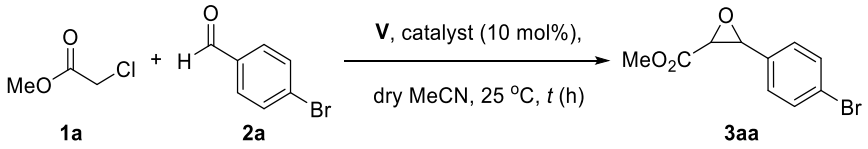


Figure 5.2 Chiral quaternary ammonium salts **A-C** used in this study.

The catalysts were selected to include the ammonium salts **A** and **B**, derived from the *Cinchona* alkaloids, and Maruoka catalyst **C**.[158] Investigations displayed that the reactions in the presence of 10 mol% of catalysts **A-C** provided the desired epoxide **3aa** without effects on the stereoselectivity.

[157] O`Donnell, M.J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775.
[158] a) Jew, S.; Park, H. *Chem. Commun.* **2009**, *46*, 7090; b) Ooi, T.; Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K. *Tetrahedron: Asymmetry* **2006**, *17*, 603.

Table 5.3 Darzens reaction of methyl chloroacetate (**1a**) and 4-bromobenzaldehyde (**2a**) in the presence of phosphazene P_1-*t*-Bu **V** and chiral quaternary ammonium salts **A-C**.[a]



1a **2a** **3aa**

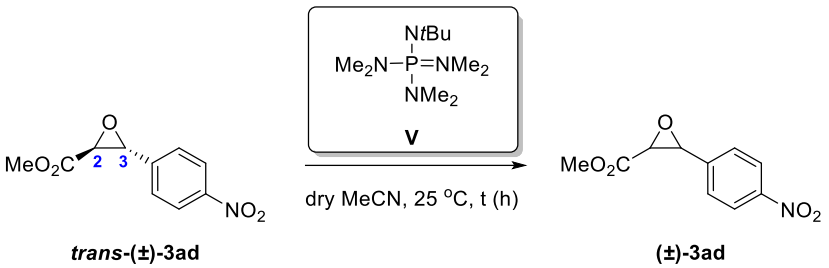
entry	catalyst	*t* (h)[b]	yield (%)[c,d]	d.r. (*cis*/*trans*)[d,e]	*ee* (%)[f]
1	**A**	2	91	0.7/1	racemic
2	**B**	16	87	1/0.77	racemic
3	**C**	3	98	1/0.9	racemic

[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.5 mmol scale using 1.5:1:1.5 **1a**/**2a**/**V** molar ratio and 10 mol% of catalyst in 2 mL of dry MeCN at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2 experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture. [f] Determined by chiral HPLC analysis using a Chiralpak IA column.

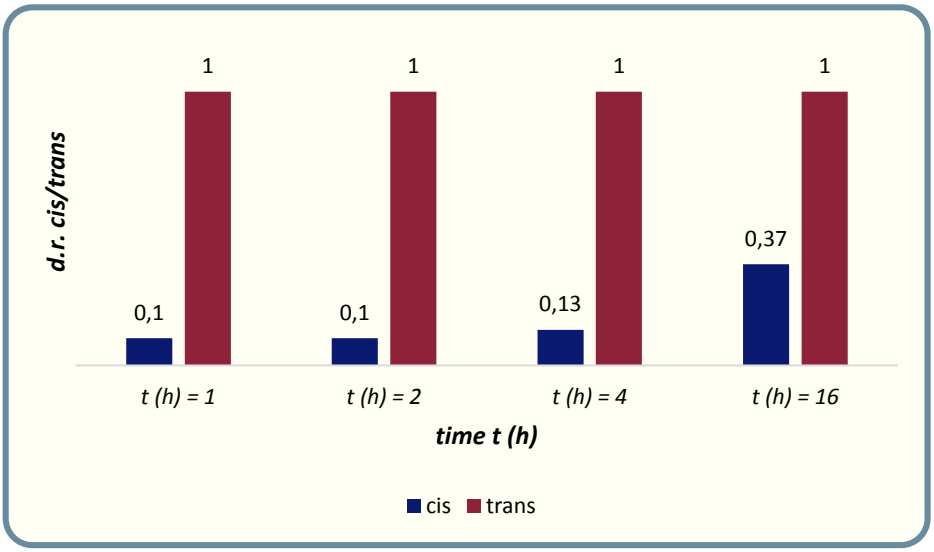
The low diastereoselectivity observed could be due to the high basicity of P_1-*t*-Bu **V** and the relatively high acidity expected for the C-H proton in position 2 of epoxide **3**. In order to characterize the system we tested the stability of *trans*-epoxide **3ad** in the presence of P_1-*t*-Bu **V**, Table 5.4. For this study *trans*-epoxide **3ad** and base **V** were co-dissolved in acetonitrile with the same concentration used in the Darzens reactions and, after given time intervals, the reaction mixture was analysed by ^{1}H NMR. The analysis revealed that *trans*-epoxide **3ad** did not undergo any epimerization. The lowest d.r. observed after 16 hours was due to the epoxide degradation.

Overall, the best conditions required the use of 1.5 eq. of base **V**, dry MeCN as solvent and a 0.25 M concentration of reagents with a reaction temperature of 25 °C.

Table 5.4 Stability of *trans*-epoxide **3ad** in the presence of P_1-*t*-Bu **V**.



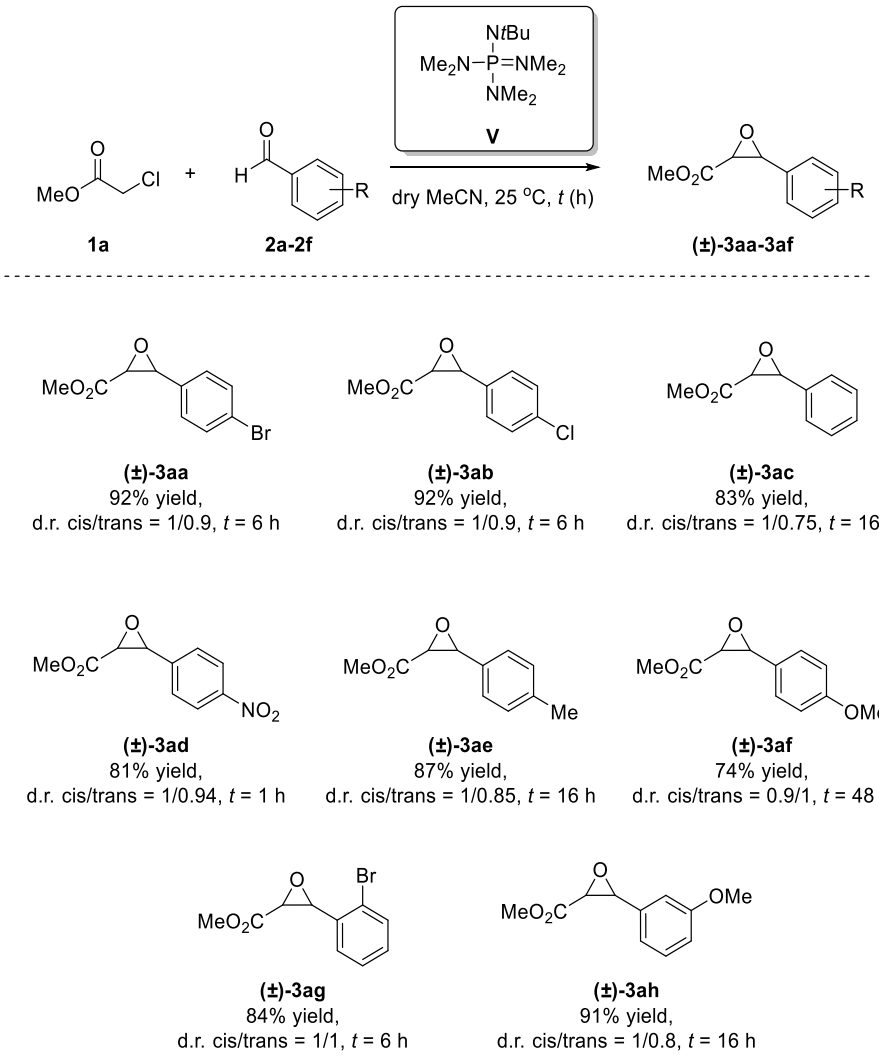
***trans*-(±)-3ad** **(±)-3ad**



5.2.3 Screening of aldehydes

With the optimised conditions, a screening of aldehydes carrying different substituents at the *para*, *meta* and *ortho* position was performed using methyl choloroacetate **1a** as the pro-nucleophile component, Scheme 5.3.

4-chlorobenzaldehyde (**2b**) was comparable in reactivity to 4-bromobenzaldehyde (**2a**), resulting in 92% isolated yield with a d.r. *cis*/*trans* of 1/0.9. The reaction of benzaldehyde (**2c**) was more sluggish, affording product **3ac** in 83% yield only after 16 hours. With the electron-withdrawing 4-nitro **2d** the epoxide was obtained with 81% yield while with the electron-donating 4-methyl **2e** and 4-methoxy groups **2f** the *α,β*-epoxycarbonyl compounds were obtained with 87% and 74% yield, respectively and a prolonged reaction time was required for the completion of the process. The presence of the bromo substituent at the *ortho* position of aldehyde **2g** provided the desired epoxide **3ag** in 84% yield with a d.r. *cis/trans* of 1/1 suggesting that the steric hindrance at the 2' position was not required to improve the diastereoselectivity of the Darzens reaction. By replacing the methoxy group from the *para* to the *meta* position, the reaction gave the desired product **3ah** in better yield (91%) and a shorter reaction time (16 hours).

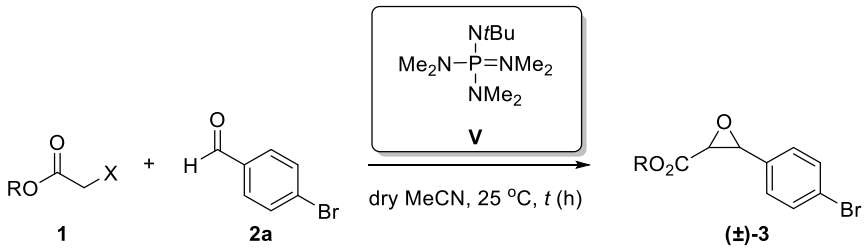


Scheme 5.3 Darzens reaction of methyl chloroacetate (**1a**) and aromatic aldehydes **2a**-**2h** in the presence of phosphazene P_1-*t*-Bu **V**. Unless otherwise stated, all Darzens reactions were carried out on a 0.5 mmol scale using 1.5:1:1.5 **1a**/**2a**/**V** molar ratio in 2 mL of dry MeCN at 25 °C. The reported yields are those of the isolated products with an average of 2 experiments. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The origin of the adducts can be derived by the formula abbreviation **3xy**: the first letter identifies the α-halo ester, while the second letter identifies the aldehyde. *t* (h) = reaction time.

5.2.4 Effect of changing the halogen and/or the alkoxy group of esters

Afterward, we examined the effect of changing the halide and/or the alkoxy group of esters **1** on the yield and reaction time. As in the previous cases, the reactions were performed in the presence of P_1-*t*-Bu **V** and 4-bromobenzaldehyde (**2a**) in dry MeCN at 25 °C, Table 5.5. In this regard, esters carrying the chloride leaving group provide faster reaction with respect to the corresponding *α*-bromoesters, Table 5.5, entry 1 *vs* enty 2; entry 3 *vs* entry 4; consistently with the expected higher acidity of the C-H protons of **1a** respect to **1b** and **1c** respect to **1d**. The change of the alcoholic group of the ester display that the steric hindrance of *tert*-butyl group slighty improved the diastereoselectivity of the Darzens reaction (d.r. *cis*/*trans* = 1/0.7), Table 5.5, entries 3 and 4.

Table 5.5 Darzens reaction of α-halo ester **1** and 4-bromobenzaldehyde (**2a**) in the presence of phosphazene P_1-*t*-Bu **V**.[a]

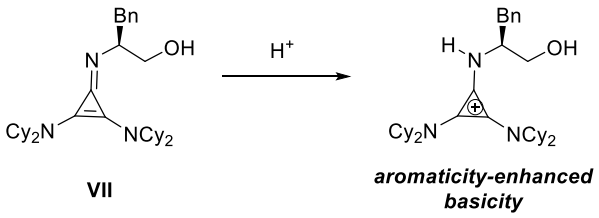


entry	R	X	*α*-halo ester	*t* (h)[b]	yield (%)[c,d]	d.r. (*cis*/*trans*)[d,e]
1	Me	Cl	**1a**	6	92	1/0.9
2	Me	Br	**1b**	16	85	1/0.9
3	*t*-Bu	Cl	**1c**	16	92	1/0.7
4	*t*-Bu	Br	**1d**	36	84	1/0.7

[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.5 mmol scale using 1.5:1:1.5 **1/2a/V** molar ratio in 2 mL of dry MeCN at 25 °C. [b] Reaction time. [c] Yield of isolated product after column chromatography. [d] Average of 2 experiments. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture.

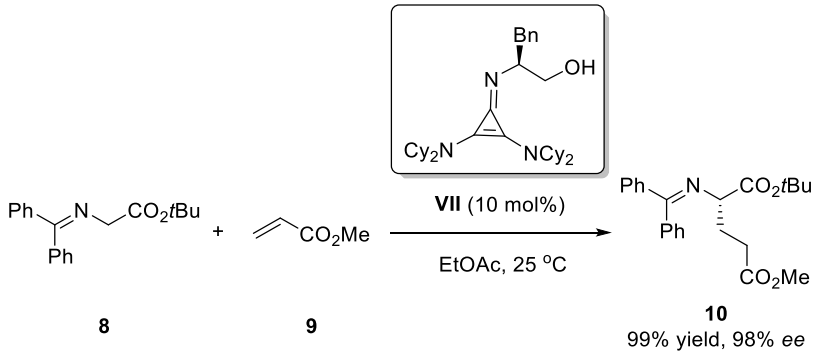
5.2.5 Chiral cyclopropenimine as organobase for Darzens reaction

Although phosphazenes potentially have great utility, both the problems of their stability and difficulties of their preparation make the identification of new superbases an important goal. To this end, Lambert and co-workers have developed the 2,3 bis(dialkylamino)cyclopropenimines, *e.g.* organobase **VII**, Scheme 5.4; as a highly effective platform for chiral Brønsted base catalyst and with a pK_{BH+} = 26.9 similar to that of P_1-*t*-Bu **V**.[159]



Scheme 5.4 Chiral cyclopropenimine **VII**.

The signature feature of the cyclopropenimine scaffold is the presence of a latent cyclopropenium ion, which is revealed upon protonation of the imino nitrogen, Scheme 5.4, the 2π-electron cyclopropenium ion provides substantial aromatic resonance stabilization to the conjugate acid of the cyclopropenimine.[160] The same authors demonstrated that the chiral 2,3-bis(dialkylamino)cyclopropenimine **VII** catalyzes the rapid Michael reaction of glycine imine **8** to the methyl ester of acrylic acid with high levels of stereoselectivity, Scheme 5.5.[159a]

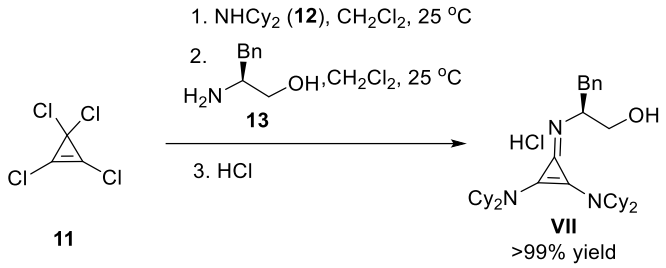


Scheme 5.5 Michael addition Brønsted base catalysed with chiral cyclopropenimine **VII**.

[159] a) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552; b) Bandar, J. S.; Barthelme, A.; Mazori, A. Y.; Lambert, T. H. *Chem. Sci.* **2015**, *6*, 1537; c) Nacsa, E. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2015**, *137*, 10246.
[160] Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371.

Prompted by this information and with the aim to develop an organocatalytic Darzens reaction, we studied the epoxide formation in the presence of chiral cyclopropenimine **VII**.

At the outset of study, the cyclopropenimine hydrochloride salt **VII** was synthesized following a procedure reported in the literature,[159a] Scheme 5.6. Catalyst **VII** was obtained by coupling dicyclohexylamine (**12**) and (*S*)-2-amino-3-phenylpropan-1-ol (**13**) with tetrachlorocyclopropene (**11**). Then, the mixture was washed with 1.0 M HCl and concentrated under vacuum to yield salt **VII** in >99% yield.



Scheme 5.6 Synthesis of catalyst **VII**.

Subsequently, preliminary investigations for the Darzens reaction between readily available *tert*-butyl chloroacetate (**1c**) and 4-bromobenzaldehyde (**2a**) in the presence of a stoichiometric quantity of cyclopropenimine **VII** were investigated, Table 5.6. The reactions were carried out on a 0.25 mmol scale using 1.5:1:1.5 **1c**/**2a**/**VII** molar ratio in 1 mL of solvent at 25 °C. The reaction performed in the presence of free base[161] **VII** in dry CH_3CN provided the desired epoxide **3ca** in 34% yield with 1/0.85 d.r. *cis*/*trans*, Table 5.6, entry 1. By replacing dry CH_3CN with dry ethyl acetate, the Darzens reaction did not proceed, Table 5.6, entry 2.

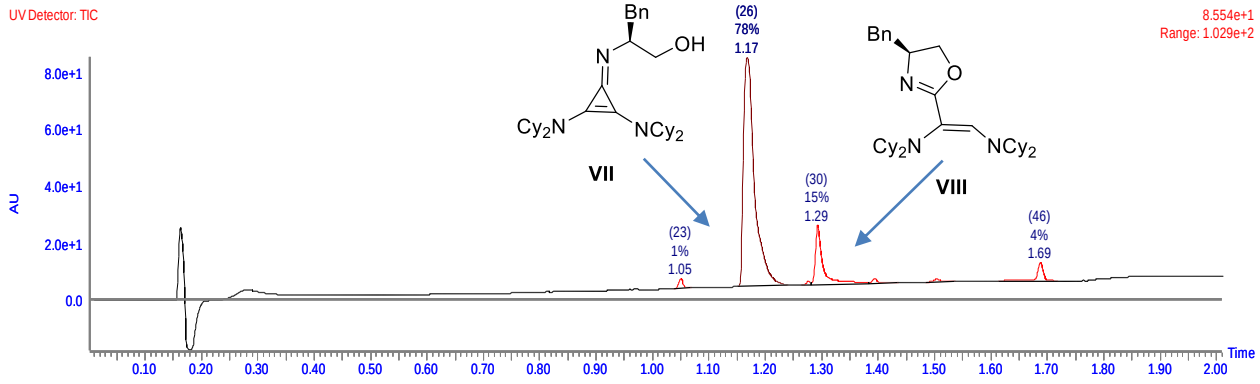
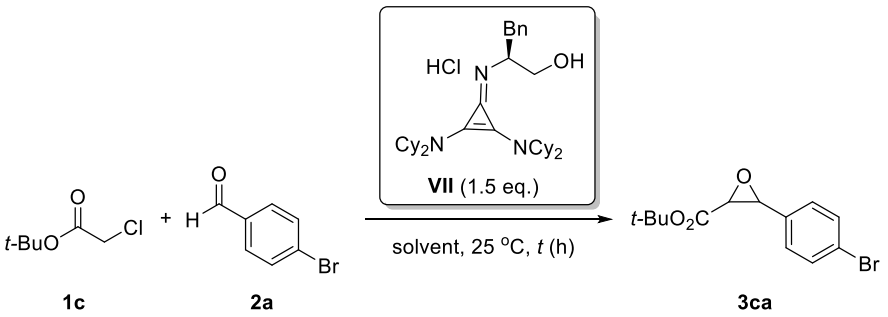


Figure 5.3 UPLC analysis of chiral cyclopropenimine **VII**.

[161] The cyclopropenimine free base was generated by dissolving the salt in CH_2Cl_2 and the resulting solution was washed with NaOH 1M. Then, the organic layer was dried and concentrated in vacuum; see reference 159b.

Although the reaction was observed using free base **VII**, Lambert and co-workers have noticed a slow but appreciable decrease in the efficiency of catalyst **VII** when it was stored in its free base form, while the hydrochloride salt **VII** is essentially indefinitely stable.[159b] UPLC analysis revealed that the free base **VII** undergoes rearrangement to oxazoline **VIII**, Figure 5.3. On this basis, we screened some biphasic reaction conditions in the presence of cyclopropenimine salt **VII**, Table 5.6, entries 3-4. By using CH_2Cl_2/KOH aq. 50%, the Darzens reaction provided the epoxide **3ca** in 21% yield with 1/0.6 d.r. cis/trans, Table 5.6, entry 3; by using toluene/KOH aq. 50% the reaction gave lower chemical yield and diastereoselectivity, Table 5.6, entry 4.

Table 5.6 Darzens reaction of *tert*-butyl chlorocetate (**1c**) and 4-bromobenzaldehyde (**2a**) in the presence of stoichiometric cyclopropenimine **VII** or its hydrochloride salt.[a]



entry	solvent	*t* (h)[b]	conv. (%)[c,d]	yield (%)[d,e]	d.r. (*cis*/*trans*)[d,f]	*ee* (%)[g]
1[h]	dry CH_3CN	16	44	34	1/0.85	racemate
2[h]	dry EtOAc	24	-	-	-	-
3[i]	CH_2Cl_2/KOH aq. 50%[m]	16	33	21	1/0.6[l]	racemate
4[i]	toluene/KOH aq. 50%[m]	16	28	17	1/0.8[l]	racemate

[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.25 mmol scale using 1.5:1:1.5 **1c/2a/VII** molar ratio in 1 mL of solvent at 25 °C. [b] Reaction time. [c] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Average of 2 experiments. [e] Yield of isolated product after column chromatography. [f] Determined by ^{1}H NMR analysis of the crude reaction mixture. [g] Determined by chiral HPLC analysis. [h] Free base of catalyst **VII** was used. [i] The reaction without catalyst **VII** did not provide compound **3ca**. [l] d.r. were determined by ^{1}H NMR analysis of the purified compound **3ca**. [m] 2.0 eq. of KOH aq. 50% were used.

We hypothesized that the strong basicity of cyclopropenimine **VII** might offer advantages in terms of reactivity and reaction scope for Brønsted base catalyzed Darzens

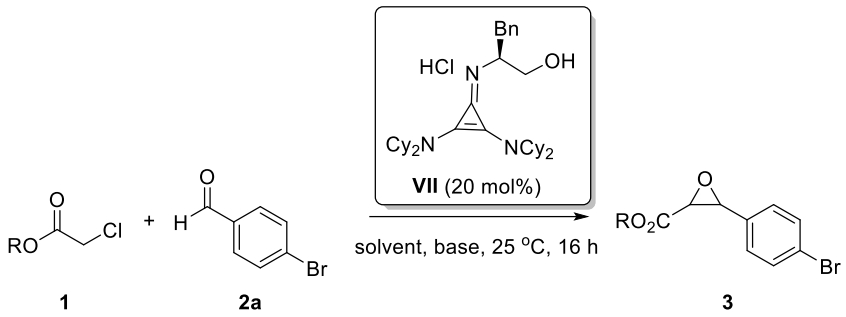
condensation. To test this hypothesis, we screened different reaction conditions in the presence of 4-bromobenzaldehyde (**2a**) and 20 mol% of organobase **VII**, Table 5.7.

The reaction performed in CH_2Cl_2/KOH aq. 50% provided the epoxide **3** in 17% conversion, Table 5.7, entry 1. By replacing dichloromethane with toluene, the Darzens reaction did not proceed, Table 5.7, entries 2-3. With the addition of 10 mol% of tetrabutylammonium bromide (TBAB), the reaction provided racemic mixture of epoxide **3** with good conversion, moderate yield and with a 1/0.3 d.r. cis/trans, Table 5.7, entries 4-5. However, the same reaction without catalyst **VII** provided similar results.

Among different conditions screened, the reaction performed in CH_3CN in the presence of 2.0 eq. of potassium carbonate and 20 mol% of catalyst **VII** gave the desired compound **3** in 36% yield with 1/0.7 d.r. cis/trans, Table 5.7, entry 11. Under the same conditions but using THF instead of acetonitrile, the Darzens reaction did not proceed, Table 5.7, entry 12. By replacing potassium carbonate with caesium carbonate, the reaction provided lower chemical conversion with similar results in the presence or in absence of catalyst **VII**, Table 5.7, entry 13. The reaction in the presence of methyl chloroacetate (**1a**) gave lower chemical conversion probably due to the hydrolysis of methyl ester under basic conditions, Table 5.7, entry 14. By using 4.0 eq. of potassium carbonate, the epoxide **3** was obtained in moderate chemical conversion, 60% yield with 1/0.7 d.r. *cis*/*trans*, Table 5.7, entry 15. By increasing the catalyst loading from 20 mol% to 30 mol%, the epoxide **3** was obtained in 67% yield with 1/0.7 d.r. *cis*/*trans*, Table 5.7, entry 16. The addition of 10 mol% of chiral quaternary ammonium salts **A-C** did not improve the stereoselectivity, Table 5.7, entry 17.

Overall, the best reaction conditions required the use of 30 mol% of catalyst **VII**, 4.0 eq. of potassium carbonate, acetonitrile as solvent and a reaction temperature of 25 °C, Table 5.7, entry 16.

Table 5.7 Development of Darzens reaction in the presence of catalytic loading of organobase **VII**.[a]



entry	R	solvent	base	conv. (%)[b,c]	yield (%)[c,d]	d.r. (cis/trans)[e]	*ee* (%)[f]
1	*t*-Bu	CH_2Cl_2	KOH 50 % aq.	17	-	-	-
2	*t*-Bu	toluene	KOH 50 % aq.	-	-	-	-
3[g]	*t*-Bu	toluene	KOH 50 % aq.	-	-	-	-
4[h]	*t*-Bu	CH_2Cl_2	KOH 50 % aq.	95 (76)[h,i]	78 (72)[h,i]	1/0.3[j]	racemate
5[h]	*t*-Bu	toluene	KOH 50 % aq.	99 (85)[h,i]	70 (58)[h,i]	1/0.3[j]	racemate
6[h]	*t*-Bu	toluene	NaOH 1M	-	-	-	-
7	*t*-Bu	CH_2Cl_2	K_2CO_3	-	-	-	-
8	*t*-Bu	CH_2Cl_2	pyridine	-	-	-	-
9	*t*-Bu	toluene	Cs_2CO_3	-	-	-	-
10	*t*-Bu	toluene	$LiOH·H_2O$	-	-	-	-
11	*t*-Bu	CH_3CN	K_2CO_3	49	36	1/0.7	racemate
12	*t*-Bu	THF	K_2CO_3	-	-	-	-
13	*t*-Bu	CH_3CN	Cs_2CO_3	14 (18)[i]	-	-	-
14	Me	CH_3CN	K_2CO_3	16	-	-	-
15[k]	*t*-Bu	CH_3CN	K_2CO_3	85	60	1/0.7	racemate
16[k,l]	*t*-Bu	CH_3CN	K_2CO_3	93	67	1/0.7	racemate
17[k,l,m]	*t*-Bu	CH_3CN	K_2CO_3	93	67	1/0.7	racemate
18	Me	CH_3CN	**III**	-	-	-	-
19	Me	CH_3CN	**I**	-	-	-	-
20	Me	CH_2Cl_2	**III**	-	-	-	-
21	Me	CH_2Cl_2	**I**	-	-	-	-

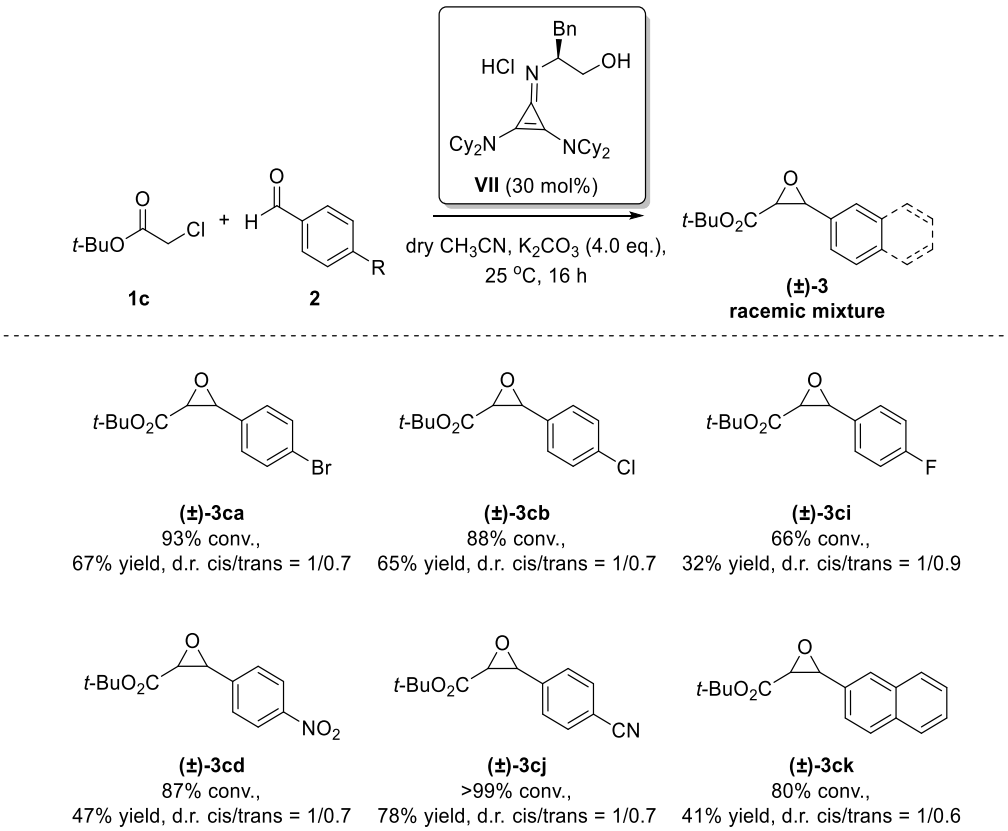
[a] Unless otherwise stated, all Darzens reactions were carried out on a 0.25 mmol scale using 1.5:1:2 **1**/**2a**/base molar ratio and 20 mol% of catalyst **VII** in 1 mL of solvent at 25 °C. The reaction without catalyst **VII** did not provide compound **3**. [b] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Average of 2 experiments. [d] Yield of isolated product after column chromatography. [e] Determined by ^{1}H NMR analysis of the crude reaction mixture. [f] Determined by chiral HPLC analysis. [g] Reaction was performed in microwave at 100 °C. [h] 10 mol% of TBAB was added. [i] Reaction performed without catalyst **VII**. [j] The same values were obtained for the reactions without catalyst **VII**. [k] 4.0 eq. of K_2CO_3 were used. [l] 30 mol% of catalyst **VII** were used. [m] 10 mol% of catalysts **A-C** were added.

With these optimised conditions, we analysed the performance of catalyst **VII** in the presence of various aldehydes, Scheme 5.7.

With halogens as substituents at *para* position, the epoxides were obtained from low (*p*-fluoro **2i**, 32% yield) to moderate yield (*p*-chloro derivative **2b**, 65% yield) and up to 1/0.9

d.r. *cis*/*trans*, Scheme 5.7. The use of 4-nitro-functionalized aldehyde **2d** provided the desired compound **(±)-3cd** with 47% yield and 1/0.7 d.r. *cis*/*trans*. With the 4-cyanobenzaldehyde (**2j**), the reaction showed a full conversion affording the epoxide **(±)-3cj** with 78% yield and 1/0.7 d.r. *cis*/*trans*. With 2-naphthaldehyde (**2k**), the epoxide **(±)-3ck** was obtained with 41% yield and 1/0.6 d.r. *cis*/*trans*.

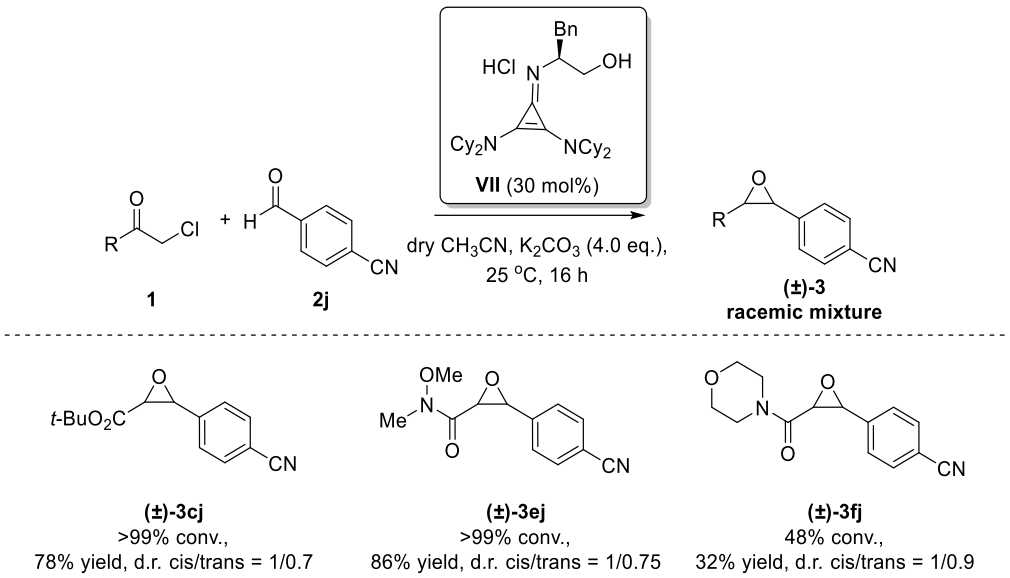
Overall, the best result was achieved with 4-cyanobenzaldehyde (**2j**) which was selected as model aldehyde for the screening of different *α*-halo carbonyl compounds **1**, Scheme 5.8.



Scheme 5.7 Darzens reaction of *tert*-butyl chlorocetate (**1c)** and aromatic aldehydes **2** in the presence of catalytic organobase **VII**. Unless otherwise stated, all Darzens reactions were carried out on a 0.25 mmol scale using 1.5:1:4 **1c**/**2**/K_2CO_3 molar ratio in 1 mL of dry MeCN at 25 °C. The reaction without catalyst **VII** did not provide compound **3**. The reported conversion were determined by ^{1}H NMR analysis of the crude reaction mixture. The reported yields are those of the isolated products with an average of 2 experiments. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by chiral HPLC. The origin of the adducts can be derived by the formula abbreviation **3xy**: the first letter identifies the *α*-halo ester, while the second letter identifies the aldehyde.

The reactions were performed in the presence of 30 mol% of catalyst **VII**, 4.0 eq. of potassium carbonate, 1.5 eq. of *α*-halo carbonyl compounds **1** and 1.0 eq. of 4-cyanobenzaldehyde (**2j**) in dry MeCN at 25 °C. With 2-chloro-*N*-methoxy-*N*-methylacetamide (**1e**), the reaction showed a full conversion affording the epoxide **(±)-3ej**

with 86% yield and 1/0.75 d.r. *cis*/*trans*. While, with 4-(chloroacetyl)morpholine (**1f**), the reaction afforded compound **(±)-3fj** with 48% yield and 1/0.9 d.r. *cis*/*trans*.



Scheme 5.8 Darzens reaction of *α*-halo carbonyl compounds **1** and 4-cyanobenzaldehyde (**2j**) in the presence of catalytic organobase **VII**. Unless otherwise stated, all Darzens reactions were carried out on a 0.25 mmol scale using 1.5:1:4 **1/2j/**K_2CO_3 molar ratio in 1 mL of dry MeCN at 25 °C. The reaction without catalyst **VII** did not provide compound **3**. The reported conversion were determined by ^{1}H NMR analysis of the crude reaction mixture. The reported yields are those of the isolated products with an average of 2 experiments. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by chiral HPLC. The origin of the adducts can be derived by the formula abbreviation **3xy**: the first letter identifies the *α*-halo ester, while the second letter identifies the aldehyde.

Finally, Darzens condensation with *α*-halo carbonyl compounds **1g-1i**, Figure 5.4, showed complex crude reaction mixtures with formation of unidentified by-products.

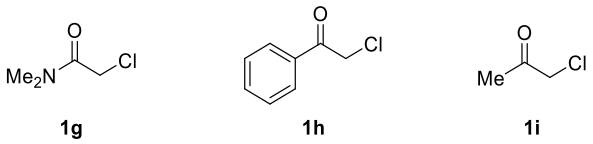
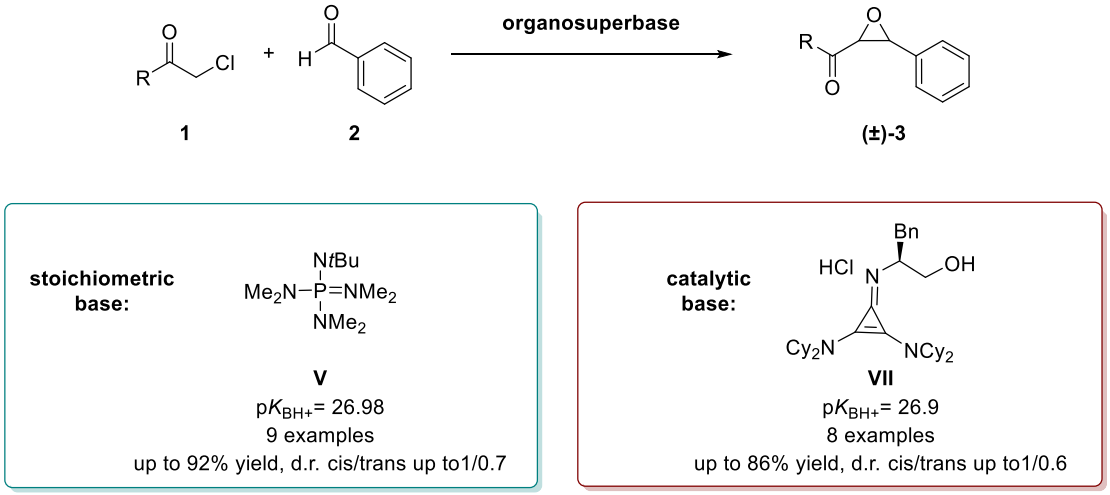


Figure 5.4 Other *α*-halo compounds **1** tested in the Darzens reaction.

5.3 Conclusion

In this study, the suitability of 'organosuperbases' in the synthesis of *α,β*-epoxycarbonyl compounds was assessed, Scheme 5.9. The reaction proceeds under mild conditions, in the presence of stoichiometric quantity of phosphazene P_1-*t*-Bu **V** to give the corresponding *cis*- and *trans*-epoxides **3** in good yield up to 92% and short reaction times.



Scheme 5.9 Darzens condensation developed in the presence of 'organosuperbases' **V** and **VII**.

Although phosphazenes have great utility, both the problems of their stability and difficulties of their preparation make the identification of new superbases an important goal. To this end, cyclopropenimine **VII**, with a pK_{BH}^{+} similar to that of P_1-*t*-Bu **V**, was tested. By using a stoichiometric quantity of 'superbase' **VII**, the epoxide **3** was obtained with up to 34% yield and 1/0.85 d.r. cis/trans. By using a catalytic amount of 'superbase' **VII** (30 mol%), the *α,β*-epoxycarbonyl compounds **3** were obtained with up to 86% yield and 1/0.6 d.r. *cis*/*trans*; proving to be tolerant to both variations in the structure and electronic properties of the aromatic aldehydes and *α*-halo carbonyl compounds used.

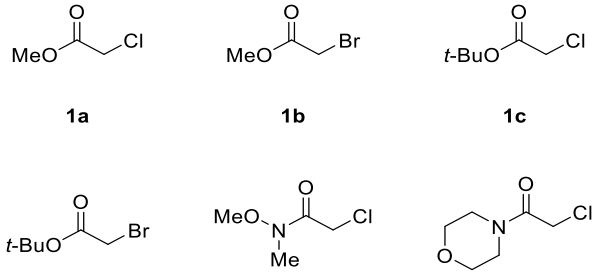
5.4 Experimental procedure

5.4.1 General experimental

Unless otherwise noted, all reactions were performed in oven-dried or flame-dried glassware. Air-sensitive reagents and solutions were transferred *via* a syringe and were introduced into the apparatus through rubber septa. All reagents were purchased from Sigma-Aldrich Co. LLC. or Alfa Aesar GmbH and used as such. All solvents were purchased from Sigma-Aldrich Co. LLC or Alfa Aesar GmbH. Dry dichloromethane, dry acetonitrile, dry ethyl acetate, dry THF, toluene (ACS grade) were used as such. Solvents for chromatography and filtration including ethyl acetate, dichloromethane, petroleum ether and methanol were used as received; hexane and 2-propanol were HPLC grade. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates with visualization under short-wavelenght UV light. Additionally, spots were visualized by dipping the plates into aqueous potassium permanganate (aqueous H_2SO_4 solution of potassium permanganate) or ninhydrin reagent (*n*-butanol solution of ninhydrin and acetic acid) followed by heating. Flash column chromatography was performed using Biotage® SNAP Cartridges KP-Sil 10g, Biotage apparatus and the indicated solvent mixtures. Analytical chiral HPLC analysis were carried out using the indicated columns, solvents and conditions. ^{1}H NMR spectra were recorded at 400 MHz (Bruker UltraShield™ 400 MHz). ^{13}C NMR spectra were recorded at 100 MHz (Bruker 400 MHz). The proton chemical shifts were referenced to the residual non deuterated solvent (δ = 7.26 for $CDCl_3$; δ = 2.49 for DMSO-d_6). Chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), m (multiplet), and b (broad). Coupling constants, *J*, are quoted in Hertz. ^{1}H and ^{13}C NMR assignments were supported by 2D experiments (gCOSY, gHSQC, ROESY sequences). ESI-mass spectra were recorded on Acquity™ Ultra Performance LC apparatus and are reported as (*m/z*): a) column: Acquity UPLC CSH C18 column (50mm x 2.1 mm i.d. 1.7 μm particle size) at 40°C; b) solvents: A = 0.1% v/v solution of HCOOH in water B = 0.1% v/v solution of HCOOH in acetonitrile; c) gradient: from 3% to 99.9% of solvent B; d) flow rate: 1 ml/min; e) acquisition stop time: 2.0 min.

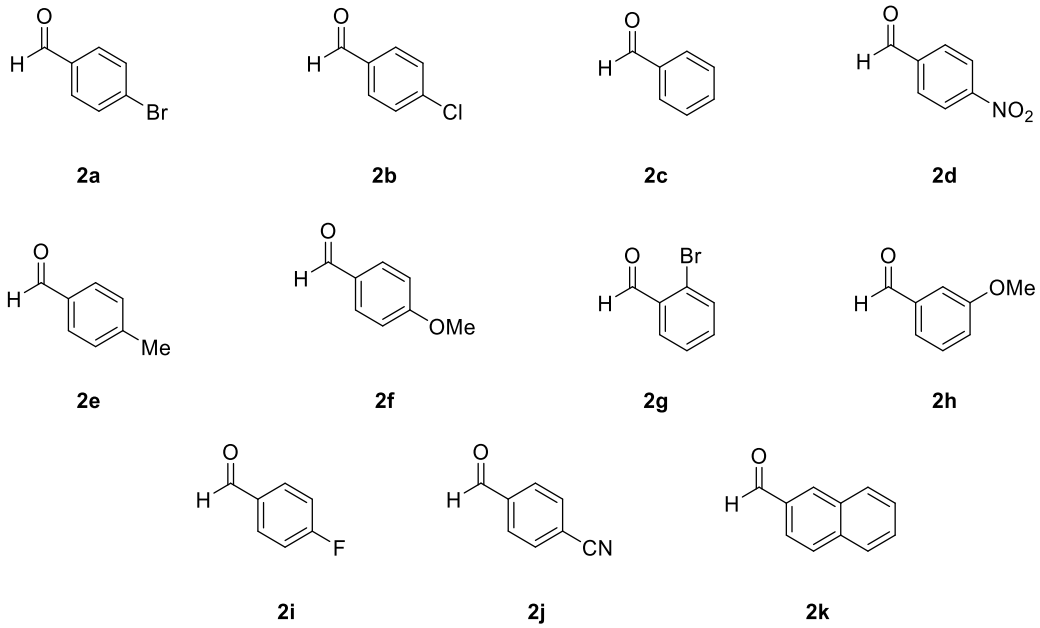
5.4.2 Starting materials

5.4.2.1 *α*-halo esters and *α*-halo amides



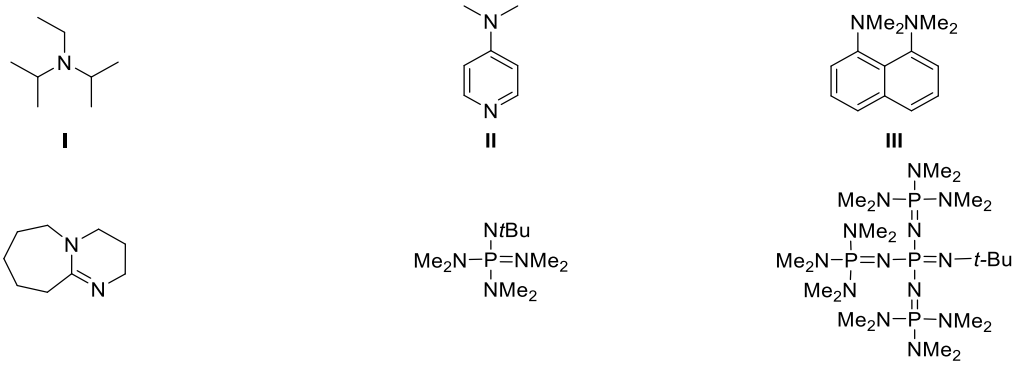
All compounds **1a-1f** were commercially available, and were used as such without further purifications.

5.4.2.2 Aldehydes



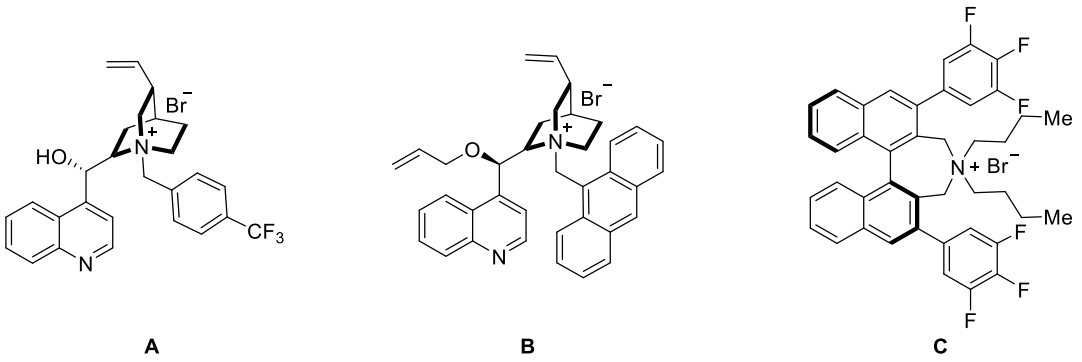
All compounds **2a-2k** were commercially available, and were used as such without further purifications.

5.4.2.3 Bases



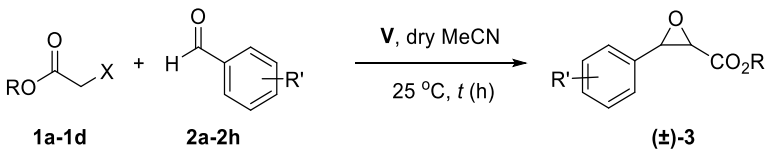
All compounds **I-VI** were commercially available, and were used as such without further purifications.

5.4.2.4. Chiral quaternary ammonium salt catalysts



All compounds **A-C** were commercially available, and were used as such without further purifications.

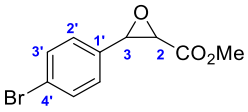
5.4.3 Preparation of compounds (±)-3 in the presence of P_1-*t*-Bu V



To a solution of aldehyde **2a-2h** (0.5 mmol, 1.0 equiv) and *α*-halo ester **1a-1d** (0.75 mmol, 1.5 equiv) in anhydrous acetonitrile (2 ml) was added P_1-*t*-Bu **V** (187 µL, 0.75 mmol) at 25 °C. The resulting mixture was stirred at 25 °C. The reaction mixture was concentrated in *vacuo* to yield crude compound. The crude material was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate 90/10 as eluent to yield compound **(±)-3**.

Characterization data of compounds (±)-3

The designation of each compound follows this scheme: **3xx** where the first letter refers to the parent halo ester/amide while the second letter refers to the parent aldehyde.



Data for **(±)-3aa** (92% yield, d.r. *cis*/*trans* = 1/0.9, colourless oil):

R_f: 0.35 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.5 Hz, 2H, H-3′), 7.17 (d, *J* = 8.5 Hz, 2H, H-2′), 4.07 (d, *J* = 1.3 Hz, 1H, H-3), 3.84 (s, 3H, Me), 3.47 (d, *J* = 1.5 Hz, 1H, H-2).[162]

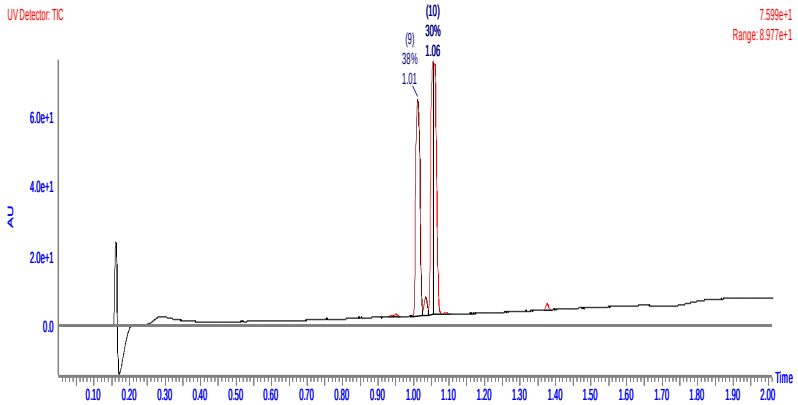
Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.5 Hz, 2H, H-3′), 7.3 (d, *J* = 8.3 Hz, 2H, H-2′), 4.21 (d, *J* = 4.5 Hz, 1H, H-3), 3.84-3.83 (m, 1H, H-2), 3.58 (s, 3H, Me).

Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.29 (1C, C=O), 134.01 (1C, C-1′), 131.89 (2C, C-3′), 127.43 (2C, C-2′), 123.08 (1C, C-4′), 57.37 (1C, C-3), 56.58 (1C, C-2), 52.66 (1C, Me).[162]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.71 (1C, C=O), 131.85 (1C, C-1′), 131.28 (2C, C-3′), 128.38 (2C, C-2′), 122.68 (1C, C-4′), 57.01 (1C, C-3), 55.67 (1C, C-2), 52.15 (1C, Me).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 258.08.
Found: $[M+H^+]$: 258.8.

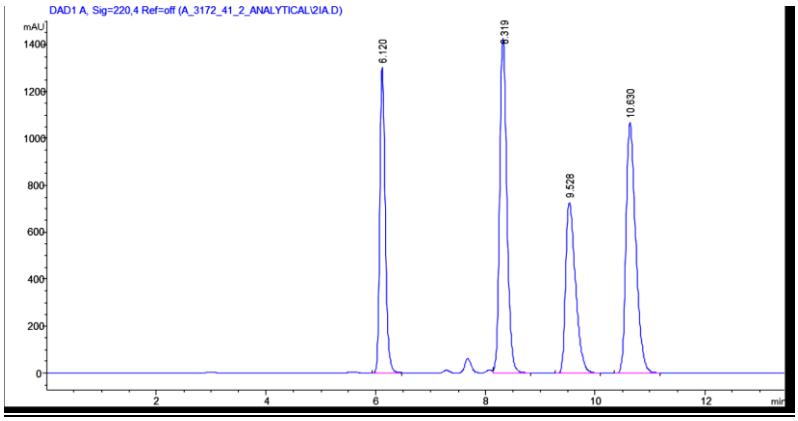
Ultra Performance LC analysis:



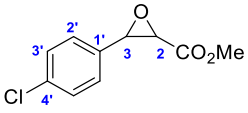
	Rt (min)	Area (%)
3aa′	1.01	38
3aa″	1.06	60

[162] Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474.

Chiral HPLC: Chiralpak IA (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 85/15, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3aa	6.1	20.3
3aa	8.3	29.5
3aa	9.5	20.5
3aa	10.6	29.7



Data for **(±)-3ab** (92% yield, d.r. *cis*/*trans* = 1/0.9, colourless oil):

R_f: 0.36 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 2 H, H-3′), 7.25 (d, *J* = 8.3 Hz, 2H, H-2′), 4.1 (d, *J* = 1.0 Hz, 1H, H-3), 3.85 (s, 3H, Me), 3.49 (d, *J* = 1.5 Hz, 1H, H-2).[162]

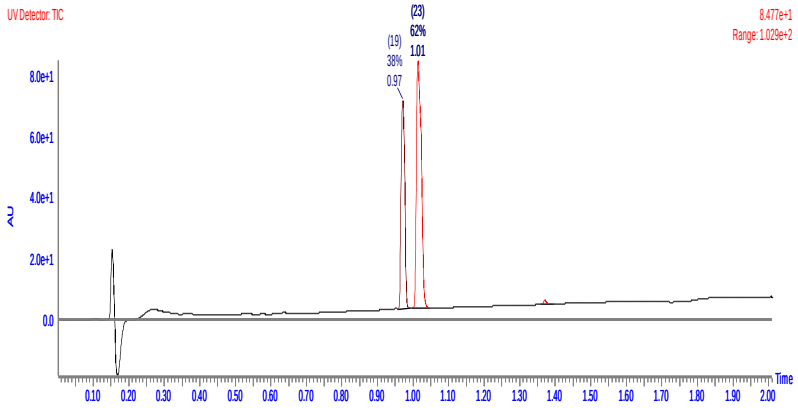
Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 4 H, H-2′ and H-3′), 4.24 (d, *J* = 4.5 Hz, 1H, H-3), 3.85-3.79 (m, 1H, H-2), 3.6 (s, 3H, Me).

Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.32 (1C, C=O), 134.97 (1C), 133.47 (1C), 128.95 (2C, C-3′), 127.15 (2C, C-2′), 57.32 (1C, C-3), 56.62 (1C, C-2), 52.66 (1C, Me).[162]

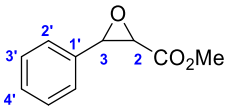
Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.74 (1C, C=O), 134.5 (1C), 131.32 (1C), 128.35 (2C), 128.08 (2C), 56.96 (1C, C-3), 55.73 (1C, C-2), 52.14 (1C, Me).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 213.63.
Found: $[M+H^+]$: 212.99.

Ultra Performance LC analysis:



	Rt (min)	Area (%)
3ab′	0.97	38
3ab″	1.01	62



Data for **(±)-3ac** (83% yield, d.r. *cis*/*trans* = 1/0.75, colourless oil):

R_f: 0.33 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5 H), 4.11 (d, *J* = 1.5 Hz, 1H, H-3), 3.84 (s, 3H, Me), 3.53 (d, *J* = 1.8 Hz, 1H, H-2).[163]

Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.29 (m, 5 H), 4.27 (d, *J* = 4.5 Hz, 1H, H-3), 3.89-3.81 (m, 1H, H-2), 3.56 (s, 3H, Me).[164]

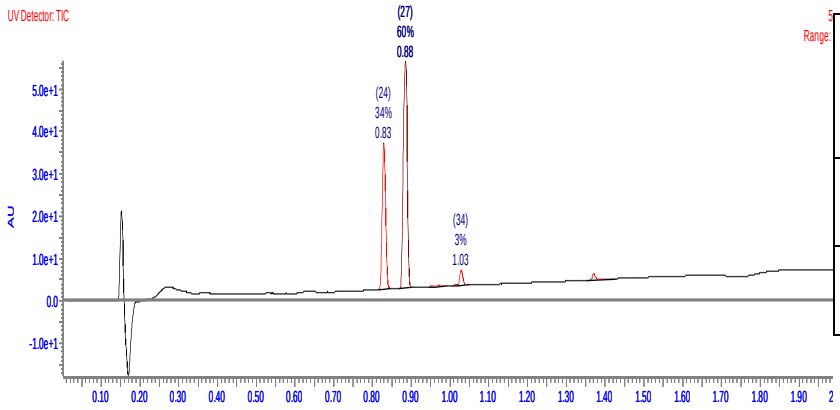
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.63 (1C, C=O), 134.92 (1C), 129.03 (1C), 128.68 (2C), 125.82 (2C), 57.98 (1C, C-3), 56.64 (1C, C-2), 52.58 (1C, Me).[163]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.02 (1C, C=O), 132.83 (1C), 128.51(1C), 128.08 (2C), 126.61 (2C), 57.52 (1C, C-3), 55.8 (1C, C-2), 52.00 (1C, Me).[164]

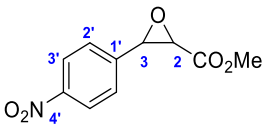
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 179.18.
Found: $[M+H^+]$: 179.00.

[163] Prévost, S.; Gauthier, S.; Cano de Andrade, M. C.; Mordant, C.; Touati, A. R.; Lesot, P.; Savignac, P.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron: Asymmetry* **2010**, *21*, 1436.
[164] Hoover, T. R.; Groeper, J. A.; Parrott, R. W.; Chandrashekar, S. P.; Finefield, J. M.; Dominguez, A.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1831.

Ultra Performance LC analysis:



	Rt (min)	Area (%)
3ac′	0.83	34
3ac″	0.88	60



Data for **(±)-3ad** (81% yield, d.r. *cis*/*trans* = 1/0.94, white solid):

R_f: 0.35 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.0 Hz, 2H, H-3'), 7.49 (d, *J* = 8.0 Hz, 2H, H-2'), 4.22 (d, *J* = 1.8 Hz, 1H, H-3), 3.86 (s, 3H, Me), 3.51 (d, *J* = 1.8 Hz, 1H, H-2).[165]

Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.0 Hz, 2H, H-3'), 7.63 (d, *J* = 8.0 Hz, 2H, H-2'), 4.35 (d, *J* = 4.5 Hz, 1H, H-3), 3.92 (d, *J* = 4.8 Hz, 1H, H-2), 3.58 (s, 3H, Me).

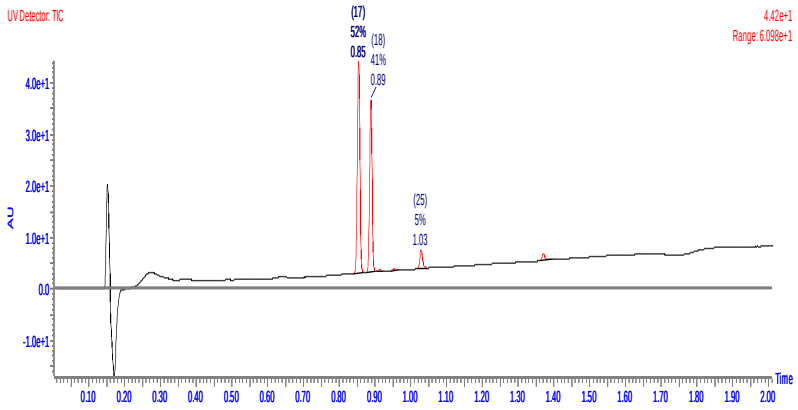
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.71 (1C, C=O), 148.38 (1C, C-4'), 142.13 (1C, C-1'), 126.65 (2C, C-2'), 123.97 (2C, C-3'), 56.82 (1C, C-3), 56.74 (1C, C-2), 52.85 (1C, Me).[165]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.24 (1C, C=O), 148.1 (1C, C-4'), 139.92 (1C, C-1'), 127.79 (2C, C-2'), 123.29 (2C, C-3'), 56.63 (1C, C-3), 55.64 (1C, C-2), 52.31 (1C, Me).

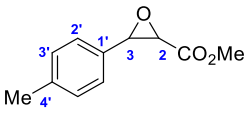
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 224.18.
Found: $[M+H^+]$: 224.18.

[165] Xuan, Y.-N.; Lin, H.-S.; Yan, M. *Org. Biomol. Chem.* **2013**, *11*, 1815.

Ultra Performance LC analysis:



	Rt (min)	Area (%)
3ad′	0.85	52
3ad′′	0.89	41



Data for **(±)-3ae** (87% yield, d.r. *cis*/*trans* = 1/0.85, colourless oil):

R_f: 0.36 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.14 (m, 4H), 4.07 (d, *J* = 1.5 Hz, 1H, H-3), 3.83 (s, 3H, OMe), 3.52 (d, *J* = 1.5 Hz, 1H, H-2), 2.34 (s, 3H, Me).[166]

Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.14 (m, 4H), 4.23 (d, *J* = 4.5 Hz, 1H, H-3), 3.86-3.8 (s, 1H, H-2), 3.58 (s, 3H, OMe), 2.36 (s, 3H, Me).

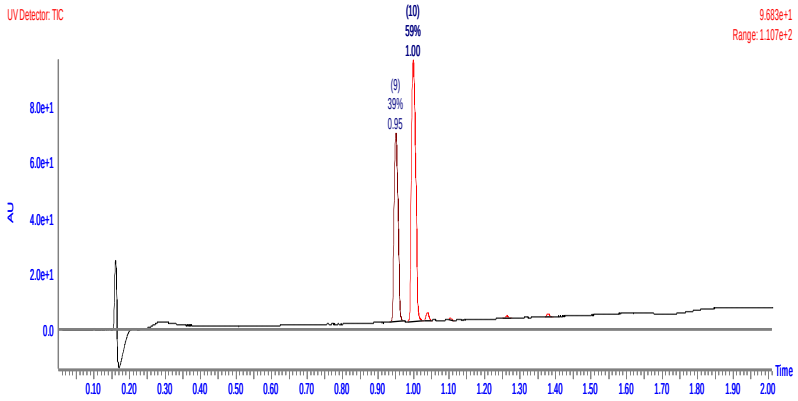
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.77 (1C, C=O), 139.00 (1C, C-4′), 131.87 (1C, C-1′), 129.37 (2C, C-3′), 125.79 (2C, C-2′), 58.03 (1C, C-3), 56.58 (1C, C-2), 52.54 (1C, OMe), 21.22 (1C, Me).[166]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.13 (1C, C=O), 138.31(1C, C-4′), 129.8 (1C, C-1′), 128.8 (2C, C-3′), 126.53 (2C, C-2′), 57.58 (1C, C-3), 55.87 (1C, C-2), 52.01 (1C, OMe), 21.22 (1C, Me).

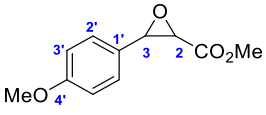
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 193.21.
Found: $[M+H^+]$: 193.07.

Ultra Performance LC analysis:

[166] Wilcke, D.; Bach, T. *Org. Biomol. Chem.* **2012**, *10*, 6498.



	Rt (min)	Area (%)
3ae′	0.95	39
3ae″	1.0	59



Data for **(±)-3af** (74% yield, d.r. *cis*/*trans* = 0.9/1, white solid):

R_f: 0.4 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H, H-2'), 6,92 (d, *J* = 8.8 Hz, 2H, H-3'), 4.07 (d, *J* = 1.5 Hz, 1H, H-3), 3.87-3.78 (m, 6H), 3.53 (d, *J* = 1.8 Hz, 1H, H-2).[167]

Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.5 Hz, 2H, H-2'), 6.89 (d, *J* = 8.8 Hz, 2H, H-3'), 4.23 (d, *J* = 4.3 Hz, 1H, H-3), 3.87-3.78 (m, 4H), 3.6 (s, 3H).[168]

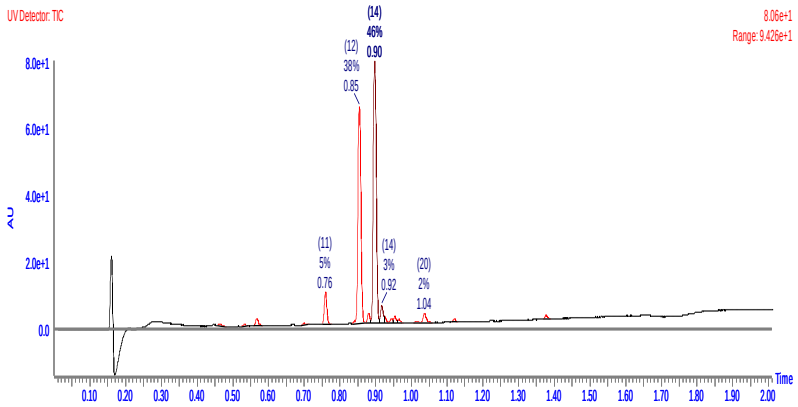
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.82 (1C, C=O), 160.3 (1C, C-4'), 127.21 (2C, C-2'), 126.76 (1C, C-1'), 114.16 (2C, C-3'), 57.96 (1C, C-3), 56.55 (1C, C-2), 55.35 (1C, Me), 52.56 (1C, Me).[167]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (1C, C=O), 159.79 (1C, C-4'), 127.93 (2C, C-2'), 124.76 (1C, C-1'), 113.57 (2C, C-3'), 57.44 (1C, C-3), 55.97 (1C, C-2), 55.24 (1C, Me), 52.05 (1C, Me).[168]

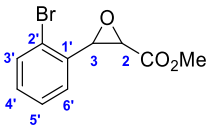
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 209.00.
Found: $[M+H^+]$: 209.14.

Ultra Performance LC analysis:

[167] Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, *68*, 974.
[168] Wilcke, D.; Bach, T. *Org. Biomol. Chem.* **2012**, *10*, 6498.



	Rt (min)	Area (%)
3af′	0.85	38
3af″	0.9	46



Data for **(±)-3ag** (84% yield, d.r. *cis*/*trans* = 1/1, colourless oil):

R_f: 0.34 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.61-7.56 (m, 1H), 7.39-7.31 (m, 1H), 7.27-7.18 (m, 2H), 4.39 (d, *J* = 1.3 Hz, 1H, H-3), 3.87 (s, 3H, Me), 3.38 (d, *J* = 1.5 Hz, 1H, H-2).[169]

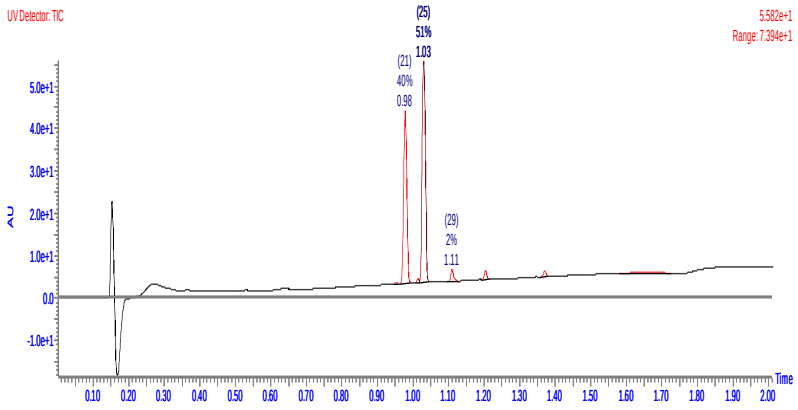
Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.56-7.49 (m, 2H), 7.39-7.31 (m, 1H), 7.27-7.18 (m, 1H), 4.35 (d, *J* = 4.8 Hz, 1H, H-3), 3.93 (d, *J* = 4.5 Hz, 1H, H-2), 3.56 (s, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.29 (1C, C=O), 166.81 (1C, C=O), 134.76 (1C), 132.64 (1C), 132.48 (1C), 131.92 (1C), 130.03 (1C), 129.82 (1C), 129.07 (1C), 127.71 (1C), 126.91 (1C), 126.35 (1C), 122.69 (1C), 122.05 (1C), 57.92 (1C, C-3, *cis*), 57.73 (1C, C-3, *trans*), 55.97 (1C, C-2, *trans*), 54.93 (1C, C-2, *cis*), 52.71 (1C, Me, *trans*), 52.13 (1C, Me, *cis*).

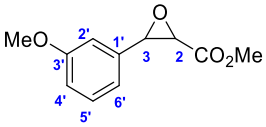
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 258.08.
Found: $[M+H^+]$: 258.92.

Ultra Performance LC analysis:

[169] Roscales, S.; Csákÿ, A. G. *Chem. Commun.* **2014**, *50*, 454.



	Rt (min)	Area (%)
3ag′	0.98	40
3ag′′	1.03	51



Data for **(±)-3ah** (91% yield, d.r. *cis*/*trans* = 1/0.8, colourless oil):

R_f: 0.36 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.32–7.29 (m, 1H), 6.93-6.83 (m, 2H), 6.82-6.79 (m, 1H), 4.09 (d, *J* = 1.5 Hz, 1H, H-3), 3.84 (s, 3H, Me), 3.82 (s, 3H, Me), 3.5 (d, *J* = 1.8 Hz, 1H, H-2).[170]

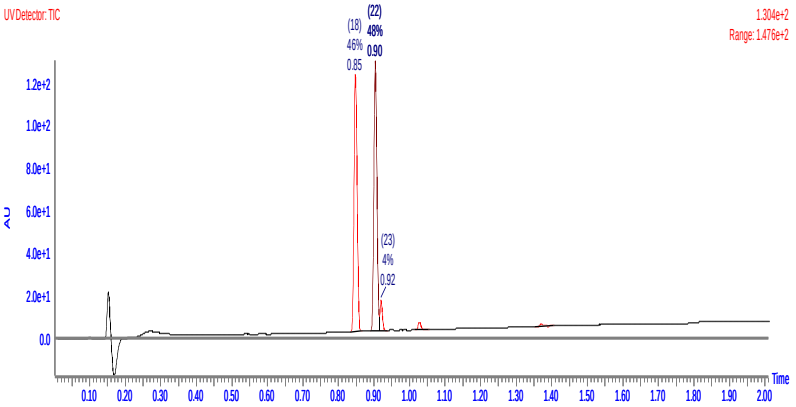
Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.27-7.22 (m, 1H), 7.03-6.96 (2H), 6.93-6.83 (m, 1H), 4.24 (d, *J* = 4.5 Hz, 1H, H-3), 3.88-3.83 (m, 1H, H-2), 3.82 (s, 3H, Me), 3.59 (s, 3H, Me).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.58 (1C, C=O), 166.95 (1C, C=O), 160.00 (1C, C-3'), 159.46 (1C, C-3'), 136.54 (1C, C-1'), 134.39 (1C, C-1'), 129.77 (1C), 129.18 (1C), 119.00 (1C), 118.25 (1C), 114.77 (1C), 114.66 (1C), 111.63 (1C), 110.89 (1C), 57.89 (1C, C-3, *trans*), 57.48 (1C, C-3, *cis*), 56.56 (1C, C-2, *trans*), 55.85 (1C, C-2, *cis*), 55.3 (1C, Me), 55.25 (1C, Me), 52.58 (1C, Me, *trans*), 52.06 (1C, Me, *cis*).

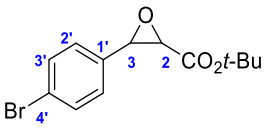
MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 209.21.
Found: $[M+H^+]$: 209.16.

Ultra Performance LC analysis:

[170] Imashiro, R.; Seki, M. *J. Org. Chem.* **2004**, *69*, 4216.



	Rt (min)	Area (%)
3ah′	0.85	46
3ah′′	0.90	48



Data for **(±)-3ca** (92% yield, d.r. *cis*/*trans* = 1/0.7, white solid):

R_f: 0.36 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.5 (d, *J* = 8.0 Hz, 2H, H-3'), 7.18 (d, *J* = 8.3 Hz, 2H, H-2'), 3.99 (m, 1H, H-3), 3.36 (d, *J* = 1.5 Hz, 1H, H-2), 1.54 (s, 9H).

Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.0 Hz, 2H, H-3'), 7.31 (d, *J* = 8.5 Hz, 2H, H-2'), 4.17 (d, *J* = 4.5 Hz, 1H, H-3), 3.72 (d, *J* = 4.5 Hz, 1H, H-2), 1.23 (s, 9H).[171]

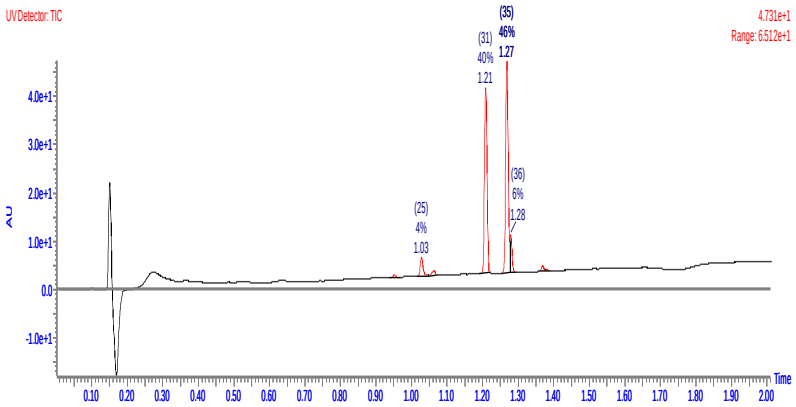
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.86 (1C, C=O), 134.44 (1C, C-1'), 131.78 (2C, C-3′), 127.5 (2C, C-2'), 122.86 (1C, C-4'), 82.9 (1C, *C*H(CH_3)$_3$), 57.39 (1C, C-2), 57.01 (1C, C-3), 28.00 (3C, CH(*C*H_3)$_3$).

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.45 (1C, C=O), 132.32 (1C, C-1'), 131.04 (2C, C-3′), 128.5 (2C, C-2'), 122.3 (1C, C-4'), 82.63 (1C, *C*H(CH_3)$_3$), 56.56 (1C, C-3), 55.89 (1C, C-2), 27.74 (3C, CH(*C*H_3)$_3$).

MS (ESI, 5600eV): Calcd.: [M+H^+]: 300.16.
Found: [M+H^+]: 300.86.

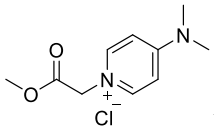
Ultra Performance LC analysis:

[171] Sharifi, A.; Abaee, M. S.; Mirzaei, M.; Salimi, R. *JICS* **2008**, *5*, 135.



	Rt (min)	Area (%)
3ca′	1.21	40
3ca″	1.27	46

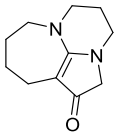
5.4.4 Analytical and spectroscopic data of compounds 4-7



Data for **4**: (white solid)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J*= 8.0 Hz, 2H), 6.88 (d, *J*= 7.5 Hz, 2H), 5.71 (s, 2H), 3.79 (s, 3H), 3.27 (s, 6H).

MS (ESI, 5600eV): Calcd.: $[M^+Cl^-]$: 230.69.
Found: $[M^+]$: 195.1.



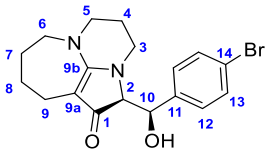
Data for **5**: (yellow solid)

R_f: 0.27 (90/10 CH_2Cl_2/MeOH).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.67 (s, 2H), 3.32 (t, *J*= 5.5, 6.0 Hz, 2H), 3.27 (t, *J*= 5.5, 6.0 Hz, 2H), 3.21 (t, *J*= 5.5, 6.0 Hz, 2H), 2.4 (t, *J*= 5.5, 6.0 Hz, 2H), 2.08 (qt, *J*= 6.0, 6.0, 6.0, 6.0 Hz, 2H), 1.86 (qt, *J*= 6.0, 6.0, 6.0, 6.0 Hz, 2H), 1.69 (qt, *J*= 6.5, 6.0, 6.5, 6.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 188.21 (1C), 169.37 (1C), 95.8 (1C), 57.75 (1C), 53.67 (1C), 48.69 (1C), 41.84 (1C), 28.72 (1C), 25.74 (1C), 22.13 (1C), 20.77 (1C).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 193.26.
Found: $[M+H^+]$: 193.0.



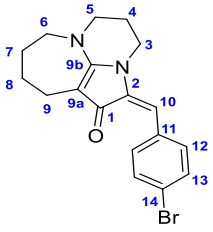
Data for **(±)-6**: (yellow solid)

R_f: 0.32 (95/5 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J*= 8.5 Hz, 2H, H-13), 7.18 (d, *J*= 8.5 Hz, 2H, H-12), 6.52 (bs, 1H, OH), 5.1 (d, *J*= 5.5 Hz, 1H, H-10), 3.93 (d, *J*= 5.5 Hz, 1H, H-2), 3.39 (ddd, *J*= 13.6, 9.8, 3.3 Hz, 1H, H-6), 3.28-3.01 (m, 5H, H-3, H-5, H-6), 2.43-2.3 (m, 1H, H-9), 2.27-2.14 (m, 1H. H-9), 2.05-1.85 (m, 2H, H-4), 1.84-1.66 (m, 2H), 1.52-1.37 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 188.68 (1C, C-1), 169.29 (1C, 9b), 139.41 (1C, C-11), 130.64 (2C, C-13), 128.4 (2C, C-12), 121.35 (1C, C-14), 96.77 (1C, 9a), 72.59 (1C, C-10), 66.3 (1C, C-2), 52.95 (1C, C-6), 48.22 (1C), 40.40 (1C), 28.05 (1C), 25.14 (1C), 21.86 (1C, C-4), 19.84 (1C, C-9).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 378.28.
Found: $[M+H^+]$: 378.97.



Data for **7**: (yellow solid)

R_f: 0.34 (95/5 CH_2Cl_2/MeOH).

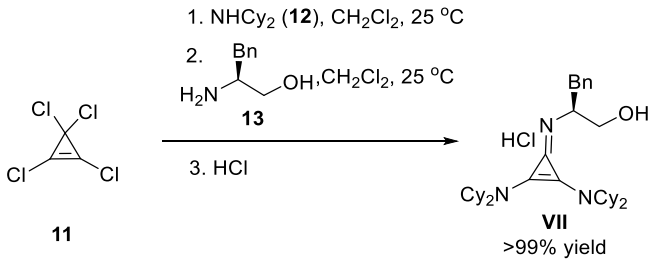
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J*= 8.3 Hz, 2H, H-13), 7.19 (d, *J*= 8.3 Hz, 2H, H-12), 6.71 (s, 1H, H-10), 3.5-3.43 (m, 2H, H-6), 3.36 (t, *J*= 5.7 Hz, 2H, H-5), 3.17 (t, *J*= 6.0 Hz, 2H, H-3), 2.57-2.49 (m, 2H, H-9), 1.88-2.03 (m, 4H, H-4, H-7), 1.78 (q, *J*= 6.21 Hz, 2H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 180.11 (1C, C-1), 165.44 (1C, C-9b), 138.52 (1C, C-2), 134.43 (1C, C-14), 131.23 (2C), 131.12 (2C), 121.10 (1C, C-11), 106.96 (1C, C-10), 95.63 (1C, 9a), 54.61 (1C, C-6), 48.92 (1C, C-5), 42.56 (1C, C-3), 28.63 (1C, C-7), 25.92 (1C, C-8), 22.49 (1C, C-4), 21.07 (1C, C-9).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 360.26.
Found: $[M+H^+]$: 360.9.

5.4.5 Preparation, analytical and spectroscopic data of catalyst VII

Catalyst **VII** was prepared according to reported procedures, and its spectral data perfectly matched those reported in literature.[172]



Dicyclohexylamine (**12**) (33.5 ml, 168.66 mmol) was slowly added to a solution of tetrachlorocyclopropene (**11**) (5g, 28.11 mmol) in CH_2Cl_2 (280 ml) in a 1L round bottom flask. A white precipitate was formed. The reaction mixture was stirred for 4 hours at 25 °C. Next, (*S*)-2-amino-3-phenylpropan-1-ol (**13**) (4.67 g, 30.92 mmol) was added in one portion and the reaction mixture was stirred for an additional 10 hours. The crude reaction mixture was filtered through a celite plug, then washed with 1.0 M HCl (3 x 130 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield pure cyclopropenimine hydrochloride salt **VII** (16.3 g, >99% yield) as yellow solid.

Data for **VII** (>99% yield, yellow solid):

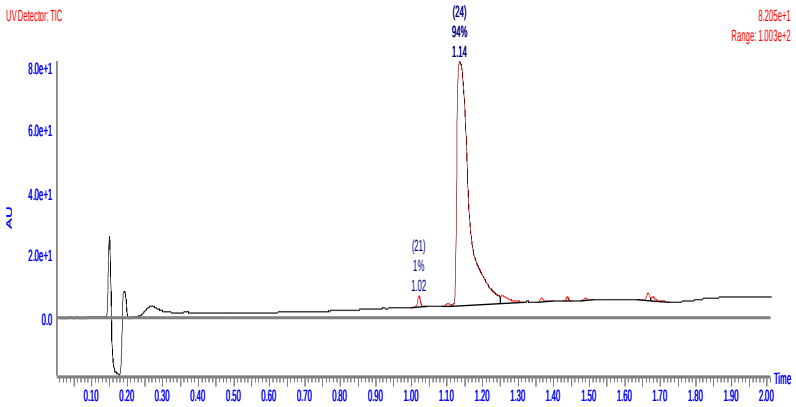
^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.78 (d, *J* = 9.5 Hz, 1H, N*H*), 7.25-7.12 (m, 5H, Ar*H*), 5.2 (bs, 1H, -O*H*), 4.05-3.78 (m, 3H, NC*H*BnC*H*$_2$OH), 3.27 (ddd, *J* = 11.9, 8.4, 3.8 Hz, 4H, NCy*H*), 3.16-3.00 (m, 2H, -C*H*$_2$Ph), 1.98-1.00 (m, 40H, Cy*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.43 (1C, C=N), 129.52 (2C, Ar), 128.24 (2C, Ar), 126.33 (1C, Ar), 117.41 (Cq), 114.83 (Cq), 64.08 (1C, NCHBn*C*H$_2$OH), 61.9 (1C, N*C*HBnCH$_2$OH), 59.43 (4C, -NCy), 38.61 (1C, -*C*H$_2$Ph), 32.41 (4C, Cy), 32.24 (4C, Cy), 25.73 (4C, Cy), 25.67 (4C, Cy), 24.68 (4C, Cy).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 546.85.
Found: $[M+H^+]$: 546.28.

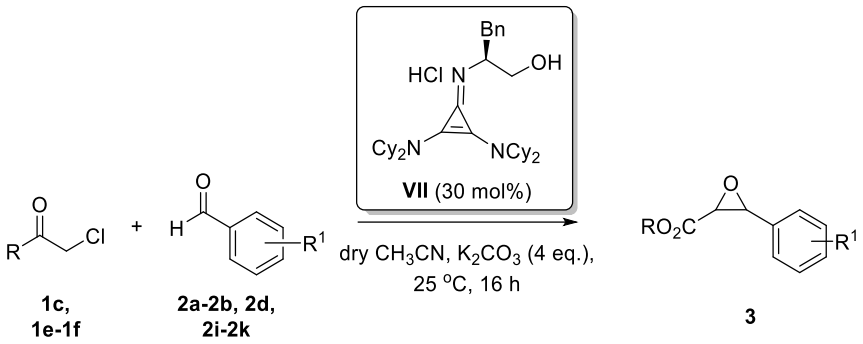
Ultra Performance LC analysis:

[172] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799.

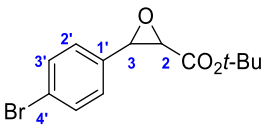


	Rt (min)	Area (%)
VII	1.14	94

5.4.6 Preparation of compounds (±)-3 in the presence of catalyst VII



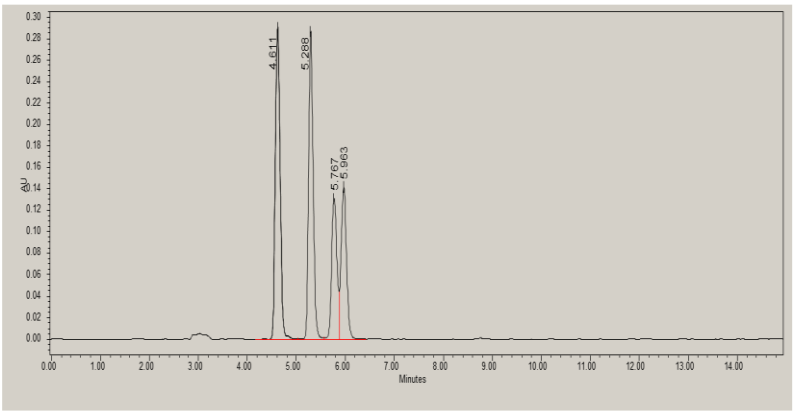
To a solution of aldehyde **2** (0.25 mmol, 1.0 equiv.) and *α*-halo carbonyl compound **1** (0.375 mmol, 1.5 equiv.) in anhydrous acetonitrile (1 ml) were added catalyst **VII** (43 mg, 0.075 mmol) and K_2CO_3 (138 mg, 1.0 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 16 hours. Then, a saturated aqueous solution of ammonium chloride (1 ml) was added. The resulting mixture was extracted with CH_2Cl_2 (3×2 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield crude compound. The crude compound was purified by flash chromatography on silica gel using cyclohexane/ethyl acetate 90/10 as eluent to yield compound **3**.



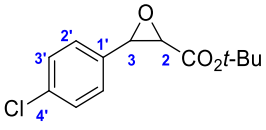
Data for **(±)-3ca** (67% yield, d.r. *cis*/*trans* = 1/0.7, white solid):

Data of compound **(±)-3ca** have been reported above.

Chiral HPLC: Chiralpak IA (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 85/15, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3ca	4.6	33.8
3ca	5.2	31.2
3ca	5.7	16.7
3ca	5.9	18.3



Data for **(±)-3cb** (65% yield, d.r. *cis*/*trans* = 1/0.7, white solid):

R_f: 0.36 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.43-7.2 (m, 4H), 4.02 (d, *J* = 1.5 Hz, 1H, H-3), 3.38 (d, *J* = 1.8 Hz, 1H, H-2), 1.57 (s, 9H, *t*-Bu).[173]

Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.43-7.2 (m, 4H), 4.21 (d, *J* = 4.8 Hz, 1H, H-3), 3.74 (d, *J* = 4.8 Hz, 1H, H-2), 1.24 (s, 9H, *t*-Bu).[173]

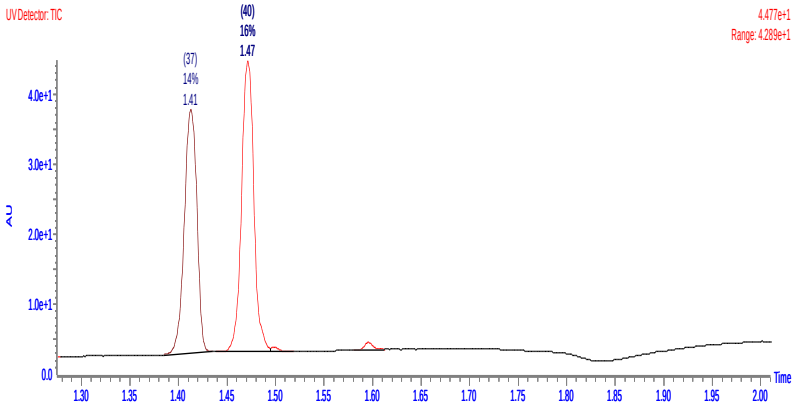
Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.91 (1C, C=O), 134.75 (1C, Cq), 133.9 (1C, Cq) 128.84 (2C, C-3′), 127.22 (2C, C-2'), 82.9 (1C, $C(CH_3)_3$), 57.44 (1C, C-2), 56.97 (1C, C-3), 28.00 (3C, $CH(CH_3)_3$).

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.48 (1C, C=O), 134.17 (1C, Cq), 131.78 (1C, Cq) 128.19 (2C, C-3′), 128.1 (2C, C-2'), 82.61 (1C, $C(CH_3)_3$), 56.51 (1C, C-2), 55.96 (1C, C-3), 27.73 (3C, $CH(CH_3)_3$).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 255.71.
Found: $[M+H^+]$: 255.02.

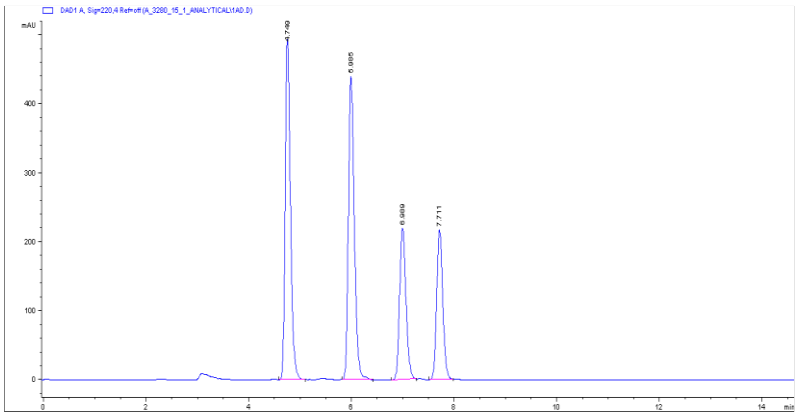
[173] Kowalkowska, A.; Jończyk, A. *Org. Process Res. Dev.* **2010**, *14*, 728.

Ultra Performance LC analysis:

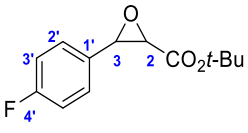


	Rt (min)	Area (%)
3cb′	1.41	14
3cb″	1.47	16

Chiral HPLC: Chiralpak IA (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 90/10, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3cb	4.7	32.9
3cb	5.9	132.7
3cb	7.0	17.6
3cb	7.7	16.8



Data for **(±)-3ci** (32% yield, d.r. *cis*/*trans* = 1/0.9, white solid):

R_f: 0.32 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.31–7.22 (m, 2H, H-2'), 7.09-7,01 (m, 2H, H-3'), 4.01 (d, *J* = 1.3 Hz, 1H, H-3), 3.37 (d, *J* = 1.5 Hz, 1H, H-2), 1.52 (s, 9H).[174]

Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.44–7.36 (m, 2H, H-2'), 7.09-7,01 (m, 2H, H-3'), 4.2 (d, *J* = 4.5 Hz, 1H, H-3), 3.7 (d, *J* = 4.5 Hz, 1H, H-2), 1.22 (s, 9H).

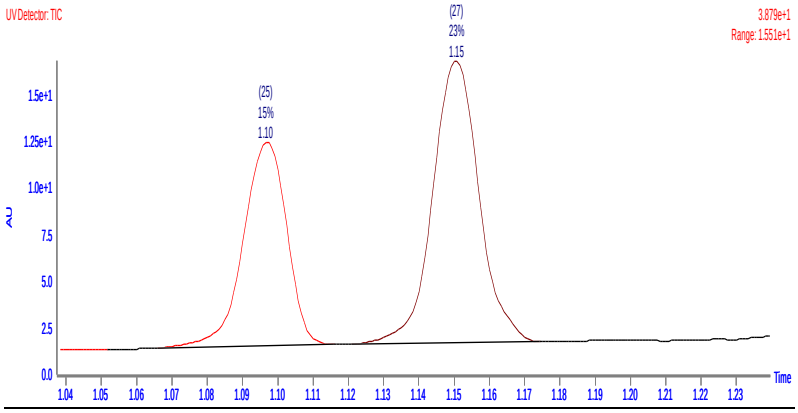
[174] Tanaka, A.; Kagawa, T. EP 1127885, **2001**.

Trans ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.03 (1C, C=O), 163.08 (d, *J* = 245 Hz, C-4'), 131.1 (d, *J* = 2 Hz, C-1'), 127.6 (d, *J* = 8 Hz, C-2'), 115.65 (d, *J* = 21 Hz, C-3'), 82.82 (1C, *C*$(CH_3)_3$), 57.41 (1C, C-2), 57.05 (1C, C-3), 28.00 (3C, CH(*C*$H_3)_3$).[174]

Cis ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (1C, C=O), 162.7 (d, *J* = 245 Hz, C-4'), 129.01 (d, *J* = 3 Hz, C-1'), 128.5 (d, *J* = 8 Hz, C-2'), 114.89 (d, *J* = 22 Hz, C-3'), 82.51 (1C, *C*$(CH_3)_3$), 56.53 (1C, C-2), 55.98 (1C, C-3), 27.71 (3C, CH(*C*$H_3)_3$).

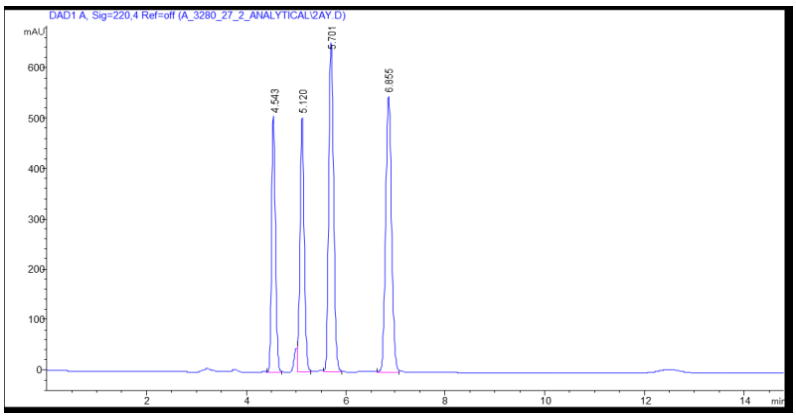
MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 239.25.
Found: [M+H$^+$]: 238.95.

Ultra Performance LC analysis:

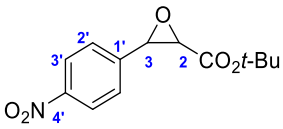


	Rt (min)	Area (%)
6ci′	1.1	15
6ci″	1.15	23

Chiral HPLC: Chiralpak AY-H (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 85/15, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
6ci	4.5	18.6
6ci	5.1	20.5
6ci	5.7	29.9
6ci	6.8	31.0



Data for **(±)-3cd** (47% yield, d.r. *cis*/*trans* = 1/0.7, white solid):

R_f: 0.29 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 8.27–8.17 (m, 2H, H-3'), 7.50 (d, *J* = 8.5 Hz, 2H, H-2'), 4.13 (d, *J* = 1.3 Hz, 1H, H-3), 3.39 (d, *J* = 1.3 Hz, 1H, H-2), 1.54 (s, 9H).

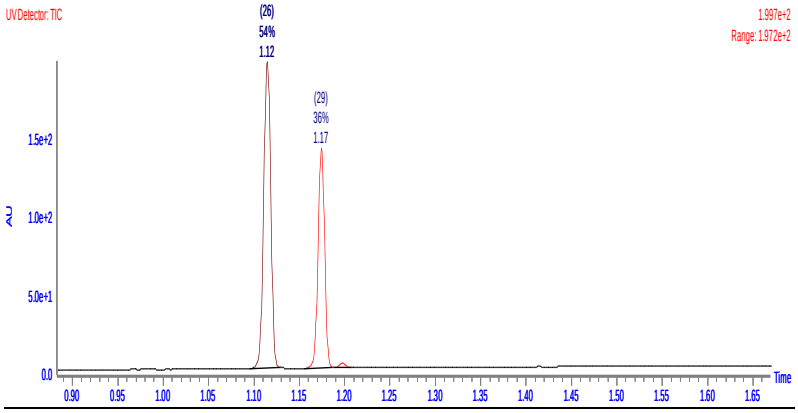
Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 8.27–8.17 (m, 2H, H-3'), 7.62 (d, *J* = 8.5 Hz, 2H, H-2'), 4.3 (d, *J* = 4.5 Hz, 1H, H-3), 3.8 (d, *J* = 4.5 Hz, 1H, H-2), 1.22 (s, 9H).[175]

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.28 (1C, C=O), 164.91 (1C, C=O), 142.64 (1C), 140.48 (1C), 130.47 (1C), 127.87 (1C, C-2', *cis*), 126.7 (1C, C-2', *trans*), 124.31 (1C), 123.89 (1C, C-3', *trans*), 123.11 (1C, C-3', *cis*), 83.36 (1C), 83.04 (1C), 57.7 (1C, *trans*), 56.42 (1C, *trans*), 56.25 (1C, *cis*), 55.96 (1C, *cis*), 27.98 (3C, $CH(CH_3)_3$, *trans*), 27.75 (3C, $CH(CH_3)_3$, *cis*).[175]

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 266.26.

Found: $[M+H^+]$: 266.04.

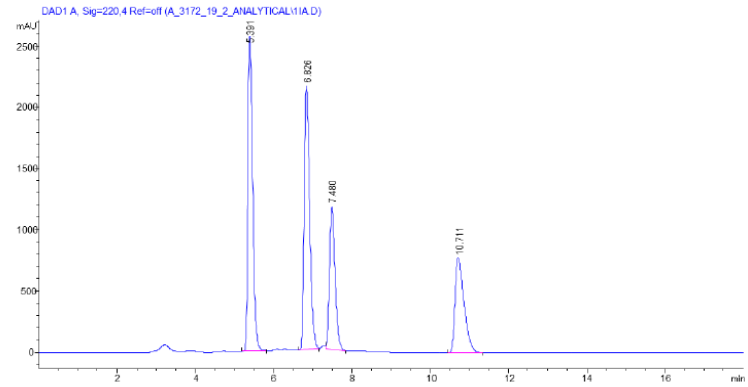
Ultra Performance LC analysis:



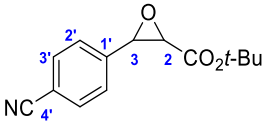
	Rt (min)	Area (%)
3cd′	1.12	54
3cd″	1.17	36

Chiral HPLC: Chiralpak IA (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 70/30, 1 ml/min, 220 nm.

[175] Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 833.



	Rt (min)	Area (%)
3cd	5.3	32
3cd	6.8	32.3
3cd	7.4	17.2
3cd	10.7	18.5



Data for **(±)-3cj** (78% yield, d.r. *cis*/*trans* = 1/0.7, white solid):

R_f: 0.35 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.71–7.63 (m, 2H, H-3'), 7.42 (d, *J* = 8.0 Hz, 2H, H-2'), 4.09 (d, *J* = 1.3 Hz, 1H, H-3), 3.37 (d, *J* = 1.5 Hz, 1H, H-2), 1.56 (s, 9H).[176]

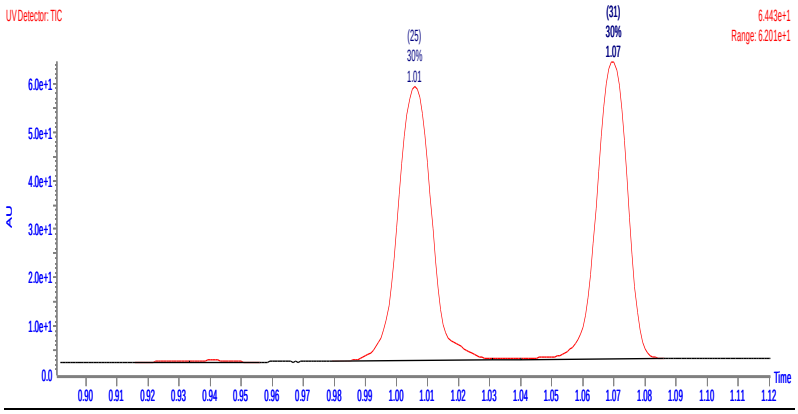
Cis ^{1}H NMR (400 M MHz, $CDCl_3$): δ 7.71–7.63 (m, 2H, H-3'), 7.56 (d, *J* = 8.0 Hz, 2H, H-2'), 4.25 (d, *J* = 4.8 Hz, 1H, H-3), 3.78 (d, *J* = 4.8 Hz, 1H, H-2), 1.21 (s, 9H).[176]

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.38 (1C, C=O), 165.00 (1C, C=O), 140.74 (1C), 138.58 (1C), 132.43 (2C), 131.69 (2C), 127.65 (2C, C-2', *cis*), 126.53 (2C, C-2', *trans*), 118.52 (1C), 118.36 (1C), 112.71 (1C), 112.19 (1C), 83.28 (1C), 82.96 (1C), 57.65 (1C, C-3, *trans*), 56.61 (1C, C-2, *trans*), 56.34 (1C, C-3, *cis*), 55.93 (1C, C-2, *cis*), 27.98 (3C, $CH(CH_3)_3$, *trans*), 27.71 (3C, $CH(CH_3)_3$, *cis*).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 246.27
Found: $[M+H^+]$: 245.99

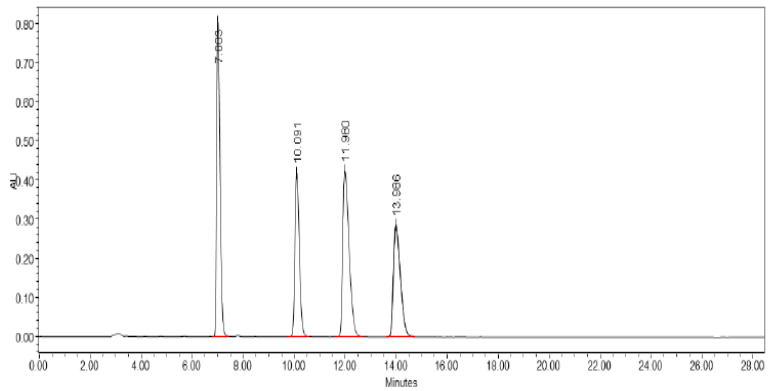
Ultra Performance LC analysis:

[176] Kowalkowska, A.; Jonczyk, A. *Org. Process Res. Dev.* **2010**, *14*, 728.

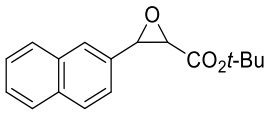


	Rt (min)	Area (%)
3cj′	1.01	30
3cj″	1.07	30

Chiral HPLC: Chiralpak IA (25 × 0.46 cm), 5 µm, *n*-hexane/EtOH = 85/15, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3cj	7.0	29.4
3cj	11.9	28.8
3cj	10.1	20.5
3cj	13.9	21.3



Data for **(±)-3ck** (41% yield, d.r. *cis*/*trans* = 1/0.6, white solid):

R_f: 0.25 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.32 (m, 7H, Ar), 4.2 (d, *J* = 1.3 Hz, 1H), 3.54 (d, *J* = 1.3 Hz, 1H), 1.54 (s, 9H).

Cis ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.32 (m, 7H, Ar), 4.39 (d, *J* = 4.5 Hz, 1H), 3.8 (d, *J* = 4.8 Hz, 1H), 1.12 (s, 9H).

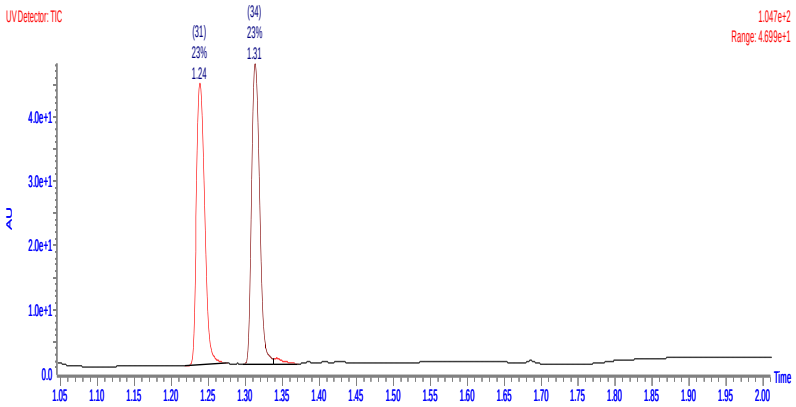
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.23 (1C, C=O, trans), 165.84 (1C, C=O, cis), 133.57 (1C), 133.2 (1C), 133.04 (1C), 132.73 (1C), 130.72 (1C), 128.57 (1C), 127.96 (1C), 127.85 (1C), 127.8 (1C), 127.73 (1C), 127.64 (1C), 126.56 (1C), 126.47 (1C), 126.28 (1C), 126.17 (1C),

126.08 (1C), 125.96 (1C), 124.24 (1C), 122.59 (1C), 82.77 (1C, *C*H(CH$_3$)$_3$, *trans*), 82.43 (1C, *C*H(CH$_3$)$_3$, *cis*), 57.92 (1C, *trans*), 57.51 (1C, *trans*), 57.31 (1C, *cis*), 56.24 (1C, *cis*), 28.03 (1C, CH(*C*H$_3$)$_3$, *trans*), 27.64 1C, (CH(*C*H$_3$)$_3$, *cis*).

MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 271.32.

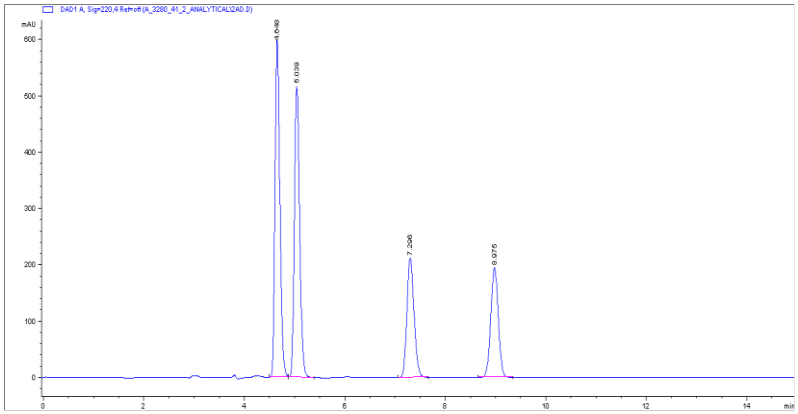
Found: [M+H$^+$]: 271.04.

Ultra Performance LC analysis:

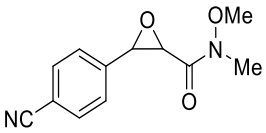


	Rt (min)	Area (%)
3ck′	1.24	23
3ck″	1.31	23

Chiral HPLC: Chiralpak AD-H (25 x 0.46 cm) 5 µm, *n*-hexane/EtOH = 80/20, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3ck	4.6	34
3ck	5.0	31.5
3ck	7.3	17.5
3ck	8.9	17



Data for **(±)-3ej** (86% yield, d.r. *cis*/*trans* = 1/0.75, white solid):

R_f: 0.23 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.6 (d, *J* = 8.3 Hz, 2H), 4.22 (d, *J* = 1.3 Hz, 1H), 4.11 (d, *J* = 1.5 Hz, 1H), 3.69 (s, 3H, Me), 3.18 (s, 3H, Me).

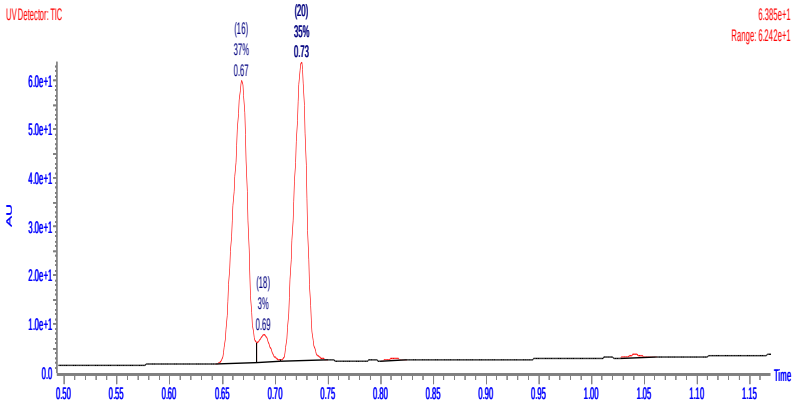
Cis ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 4.52 (d, *J* = 5 Hz, 1H), 4.35 (bs, 1H), 3.57 (bs, 3H, Me), 2.91 (bs, 3H, Me).

^{13}C NMR (100 MHz, DMSO-*d6*): δ 166.53 (1C, C=O), 165.83 (1C, C=O), 141.91 (1C), 140.34 (1C), 132.97 (2C, *trans*), 132.39 (2C, *cis*), 128.11 (2C, *cis*), 127.59 (2C, *trans*), 119.08 (1C), 119.06 (1C), 111.8 (1C), 111.37 (1C), 62.36 (1C), 62.11 (1C), 57.72 (1C, *cis*), 56.47 (1C, *cis*), 56.27 (1C, *trans*), 56.13 (1C, *trans*), 32.58 (1C), 32.35 (1C).

MS (ESI, 5600eV): Calcd.: [M+H$^+$]: 233.23.

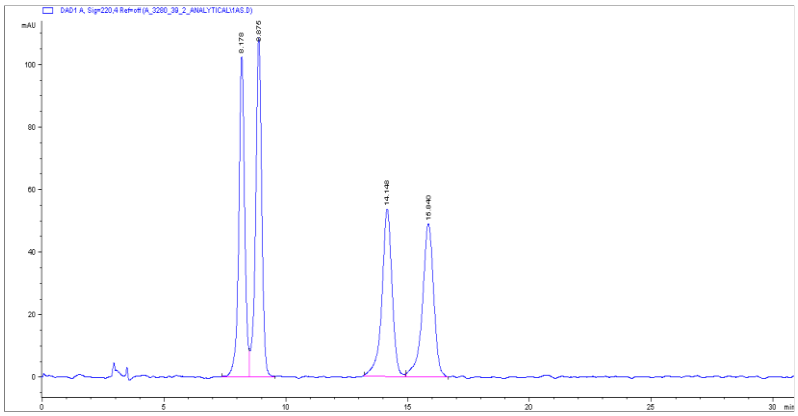
Found: [M+H$^+$]: 232.96.

Ultra Performance LC analysis:

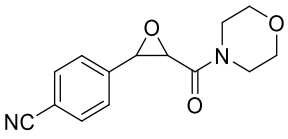


	Rt (min)	Area (%)
3ej′	0.67	37
3ej″	0.73	35

Chiral HPLC: Chiralpak AS-H (25 x 0.46 cm) 5 µm, *n*-hexane/ethanol 70/30, 1 ml/min, 220 nm.



	Rt (min)	Area (%)
3ej	8.1	25.6
3ej	8.8	28.1
3ej	14.1	23.2
3ej	15.8	23.1



Data for **(±)-3fj** (32% yield, d.r. *cis*/*trans* = 1/0.9, white solid):

R_f: 0.15 (18/2 Cyclohexane/AcOEt).

Trans ^{1}H NMR (400 MHz, DMSO-*d6*): 7.87 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 4.47 (d, *J* = 4.8 Hz, 1H), 4.24 (d, *J* = 4.8 Hz, 1H), 3.67-2.68 (m, 8H).

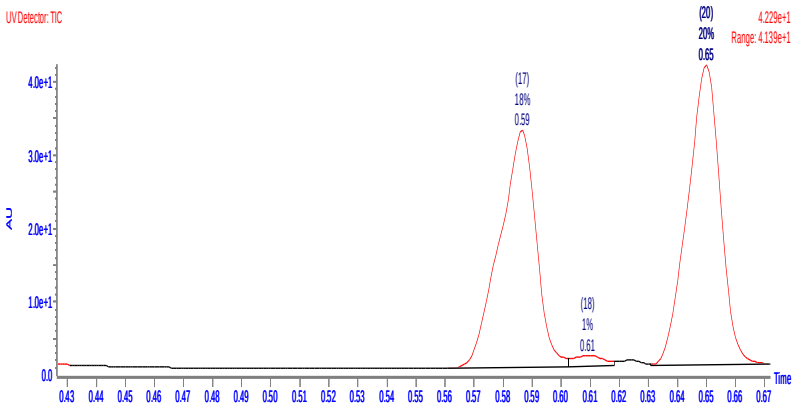
Cis ^{1}H NMR (400 MHz, DMSO-*d6*): 7.84 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 4.21 (d, *J* = 1.8 Hz, 1H), 4.17 (d, *J* = 1.8 Hz, 1 H), 3.67-2.68 (m, 8H).

^{13}C NMR (100 MHz, DMSO-*d6*): δ 164.85 (1C, C=O), 163.16 (1C, C=O), 142.02 (1C), 140.62 (1C), 132.89 (2C), 132.5 (2C), 127.71 (2C), 127.65 (2C), 119.1 (1C), 119.08 (1C), 111.7 (1C), 111.42 (1C), 66.53 (1C), 66.5 (1C), 66.39 (1C), 66.37 (1C), 58.32 (1C, *cis*), 56.8 (1C, *trans*), 56.58 (1C, *cis*), 56.31 (1C, *trans*), 45.4 (1C), 44.88 (1C), 42.44 (1C), 41.62 (1C).

MS (ESI, 5600eV): Calcd.: $[M+H^+]$: 259.27.

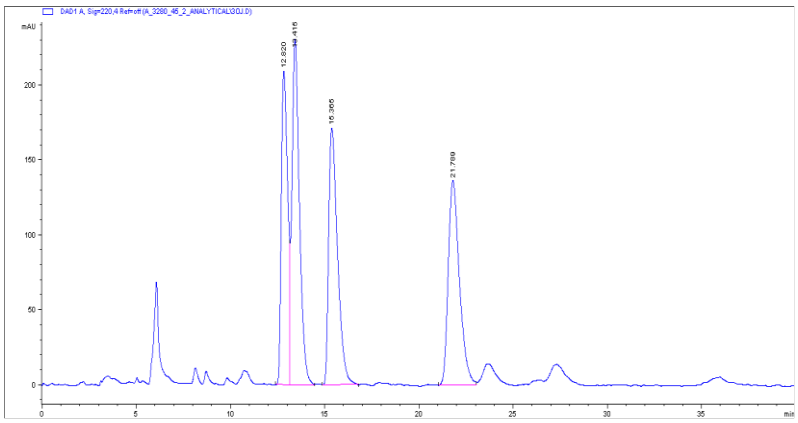
Found: $[M+H^+]$: 259.08.

Ultra Performance LC analysis:



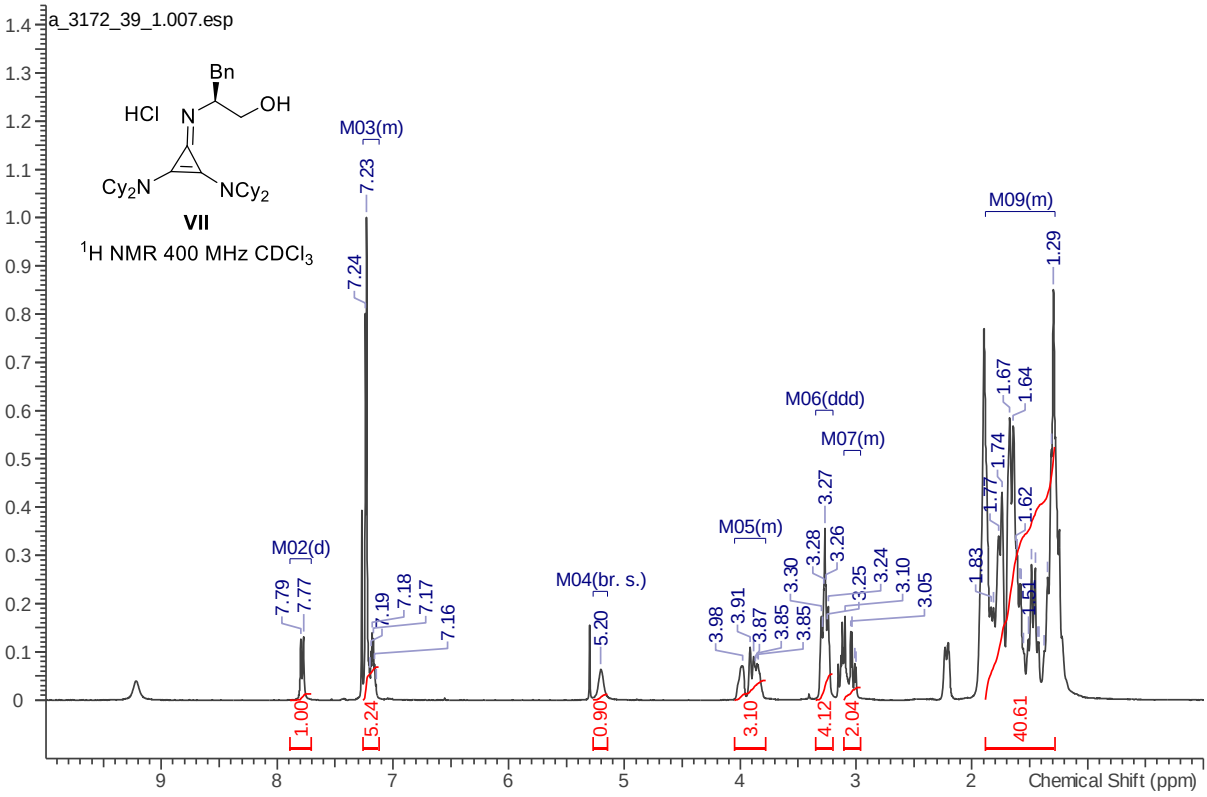
	Rt (min)	Area (%)
3fj′	0.59	18
3fj″	0.65	20

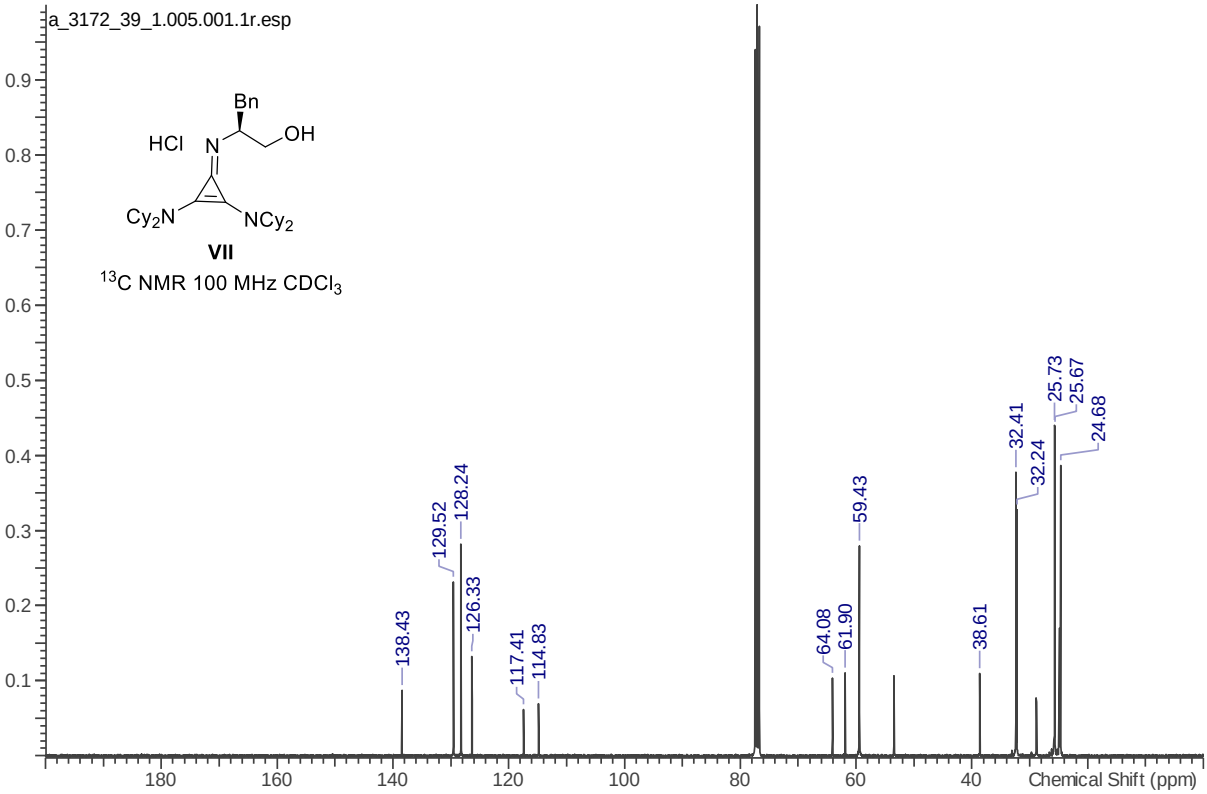
Chiral HPLC: Chiralcel OJ-H (25 x 0.46 cm) 5 µm *n*-hexane/ethanol 60/40, 1 ml/min, 220 nm.

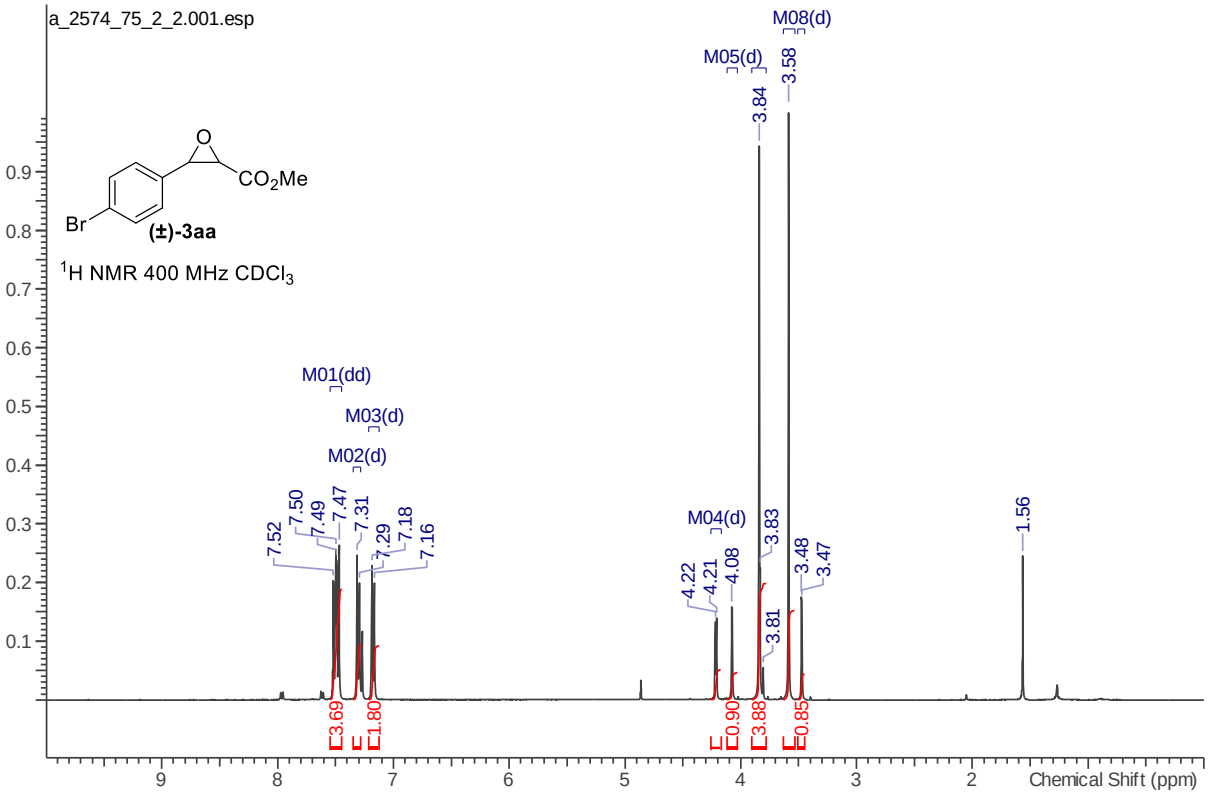


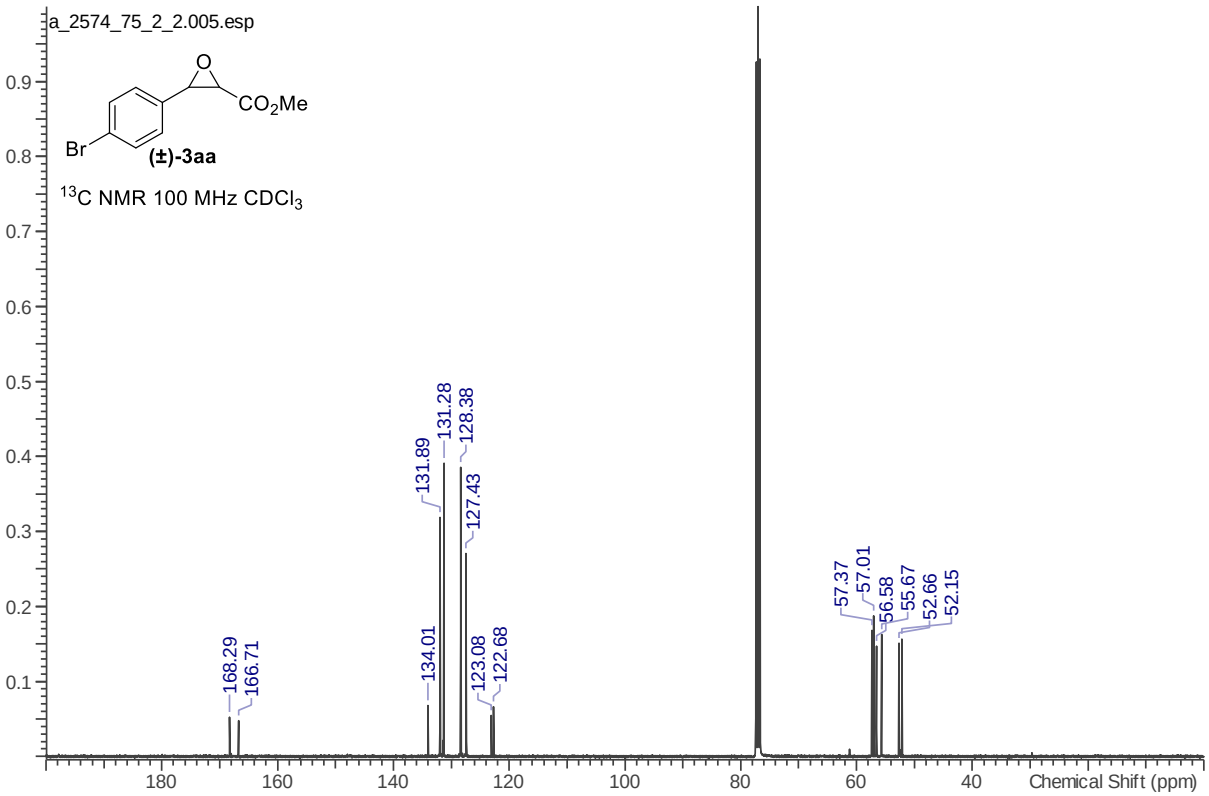
	Rt (min)	Area (%)
3fj	12.8	22
3fj	13.4	28
3fj	15.3	25
3fj	21.7	25

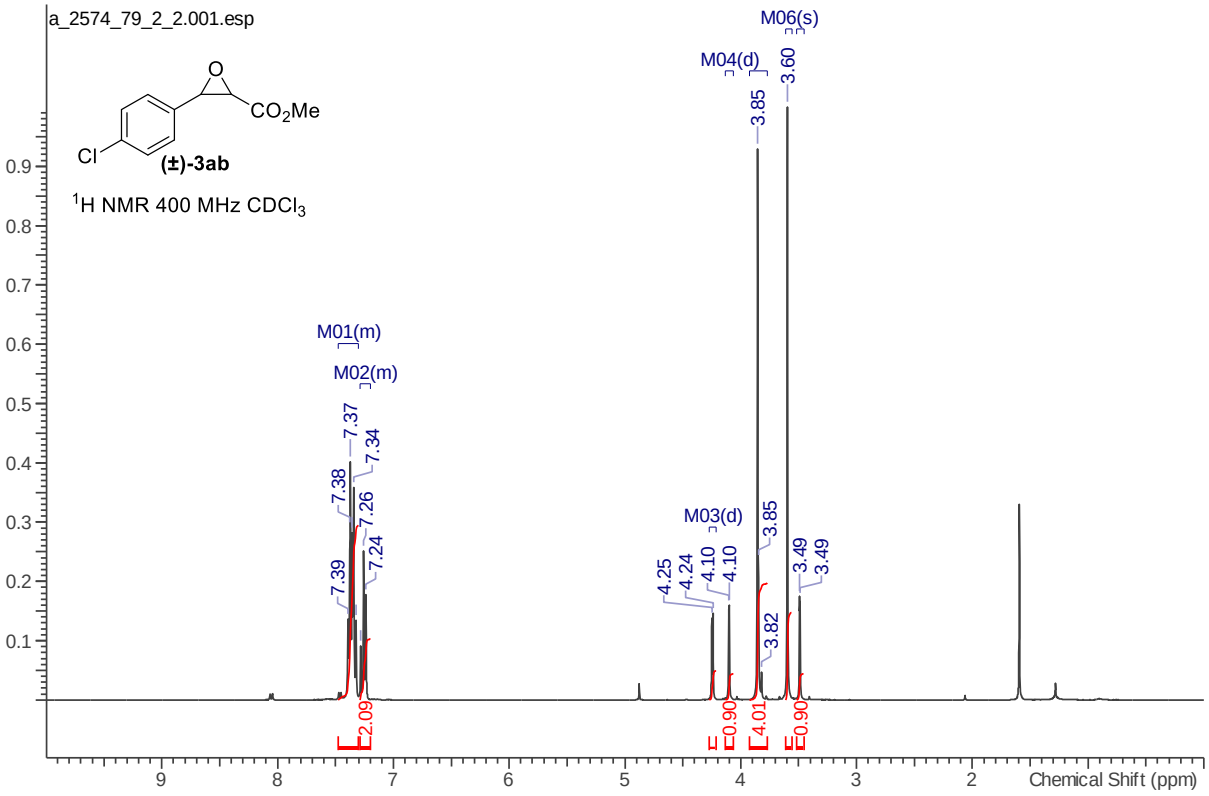
5.4.7 ^{1}H NMR, ^{13}C NMR spectra of representative compounds

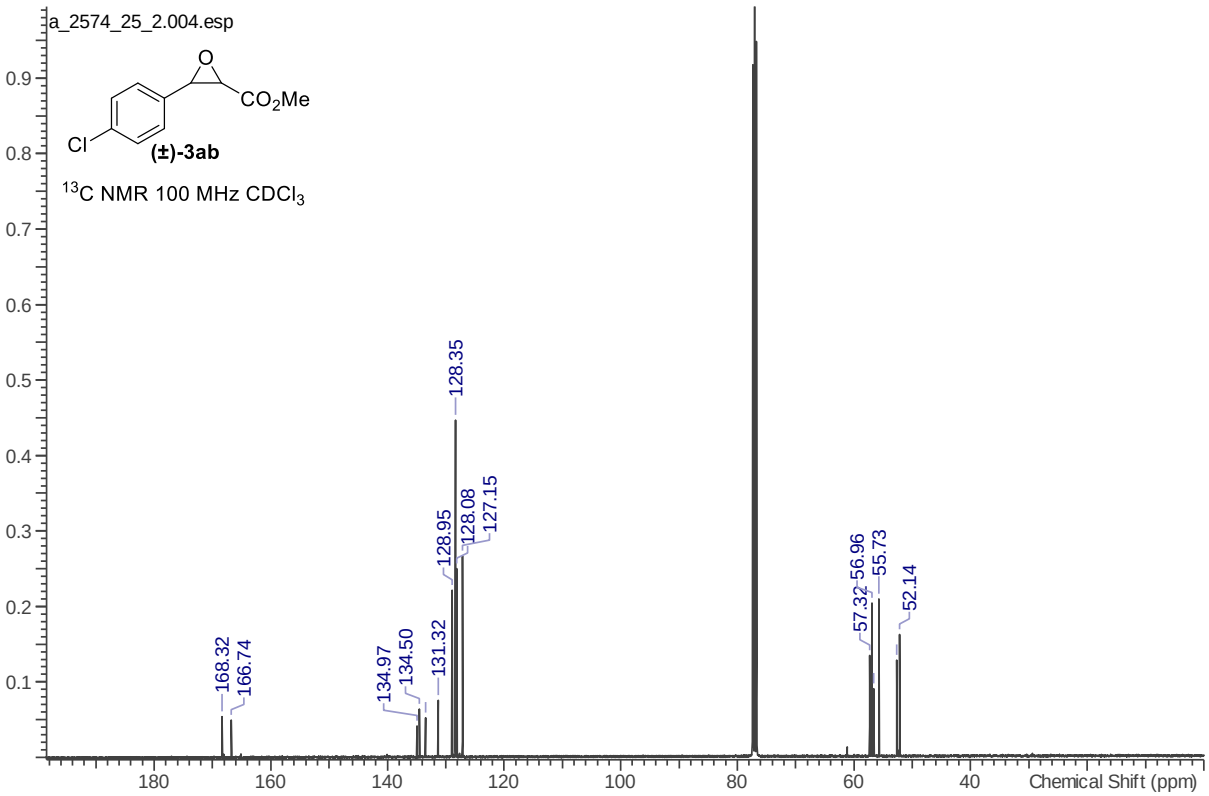


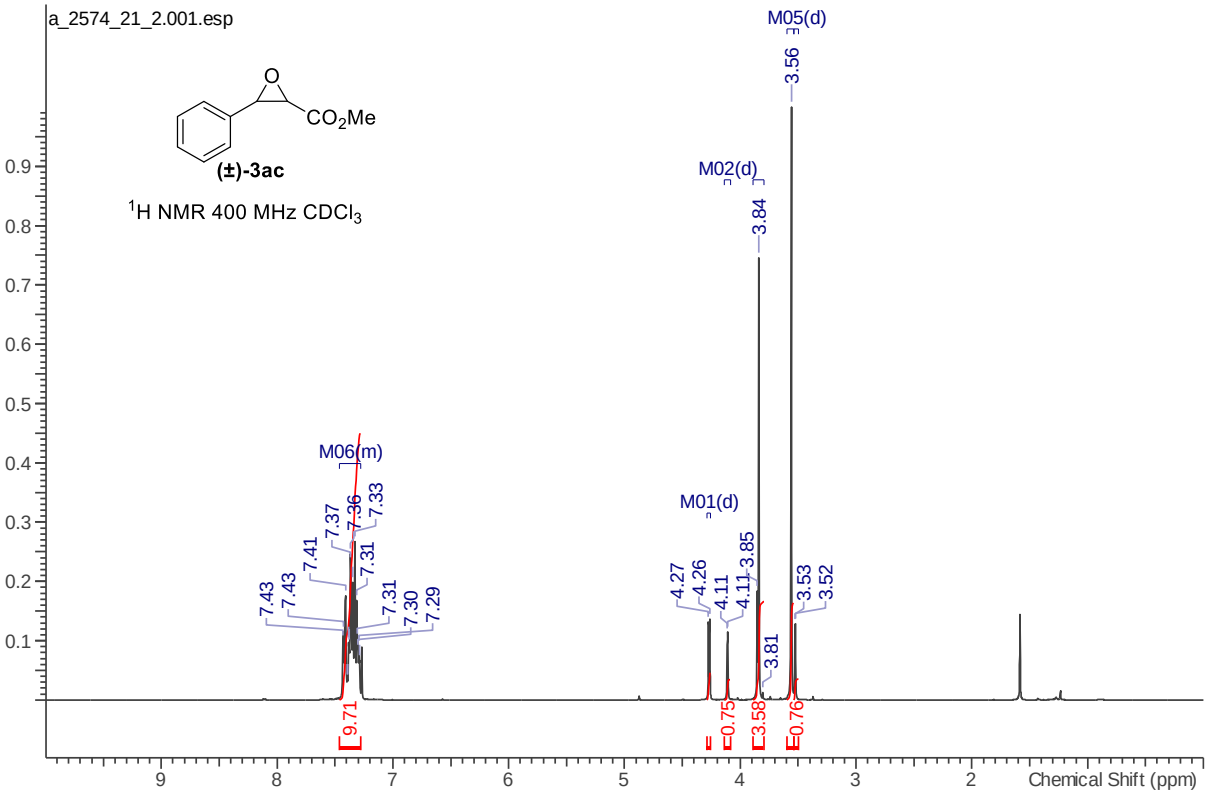


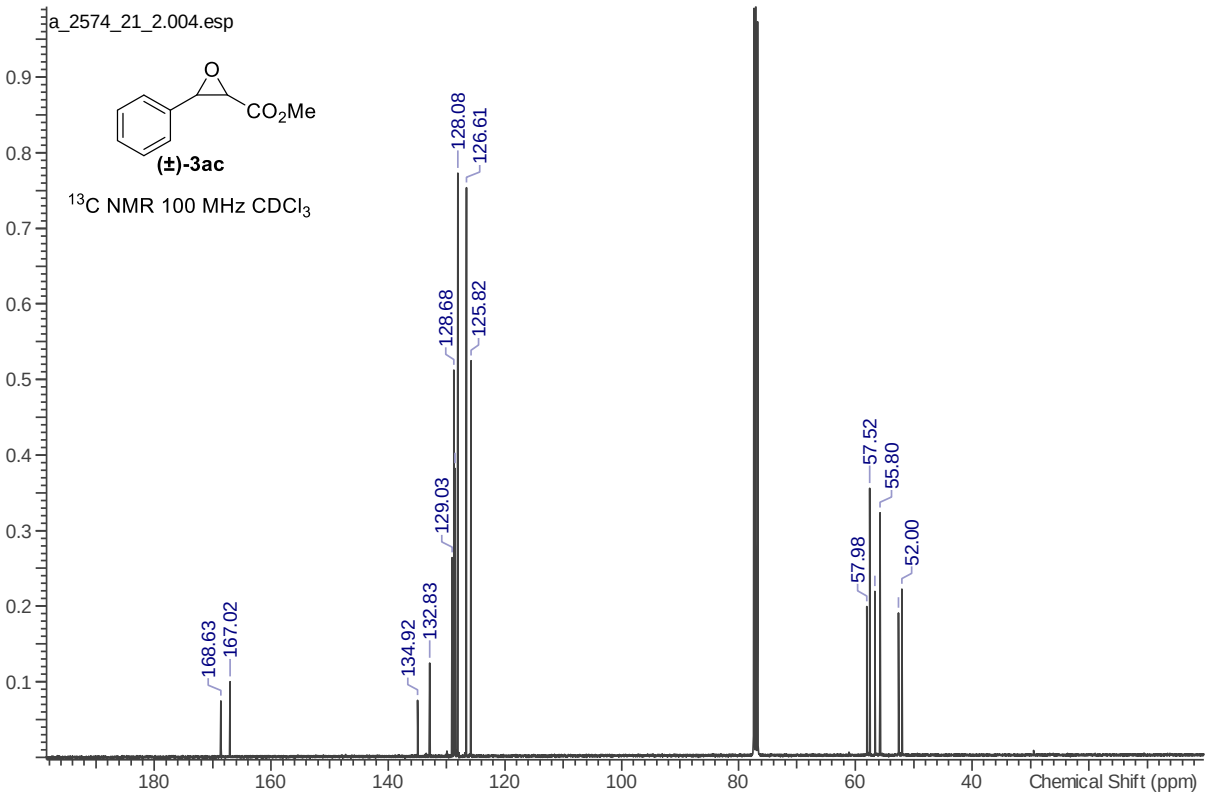

a_2574_75_2_2.001.esp
O
CO2Me
Br
(±)-3aa
1H NMR 400 MHz CDCl3
M08(d)
M05(d)
3.58
3.84
M01(dd)
M03(d)
M02(d)
7.52
7.50
7.49
7.47
7.31
7.29
7.18
7.16
M04(d)
3.83
4.22
4.21
4.08
3.48
3.47
3.81
1.56
3.69
1.80
0.90
3.88
0.85
Chemical Shift (ppm)

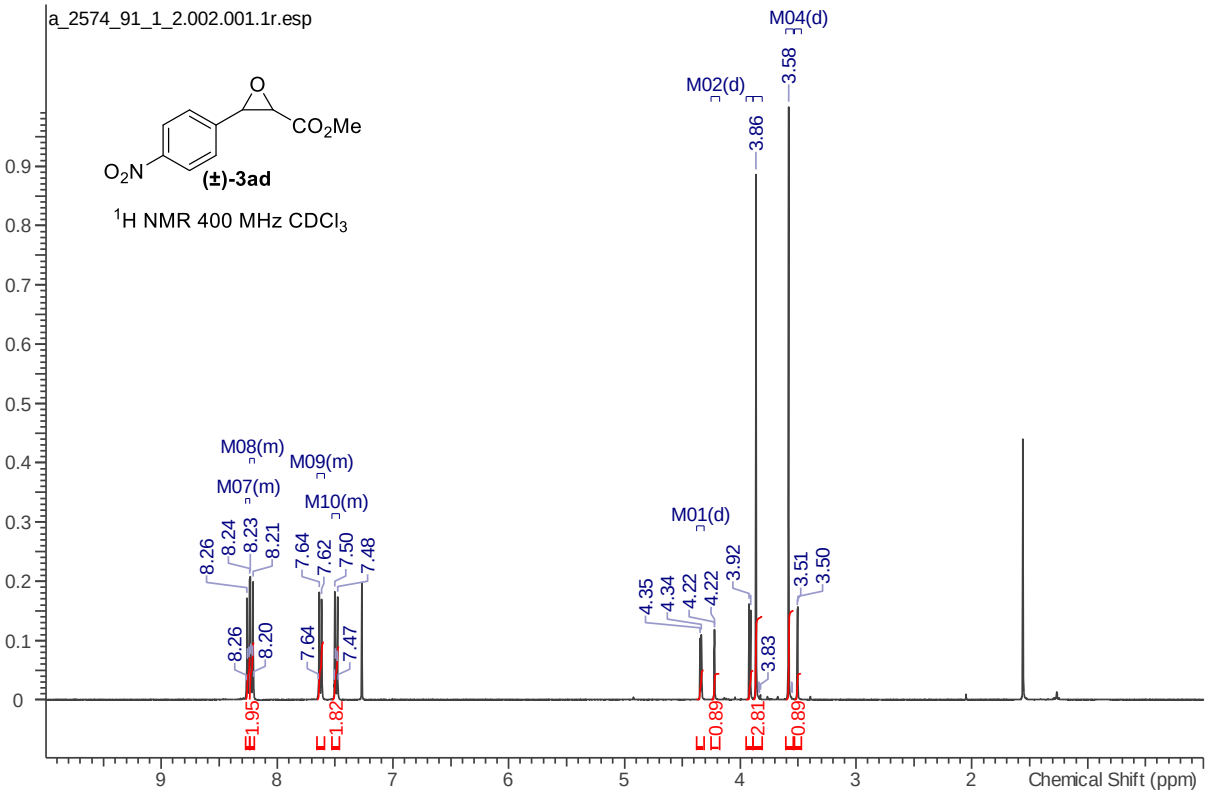

a_2574_75_2_2.005.esp
O
CO2Me
Br
(±)-3aa
13C NMR 100 MHz CDCl3
131.89
131.28
128.38
127.43
134.01
123.08
122.68
168.29
166.71
57.37
57.01
56.58
55.67
52.66
52.15
Chemical Shift (ppm)

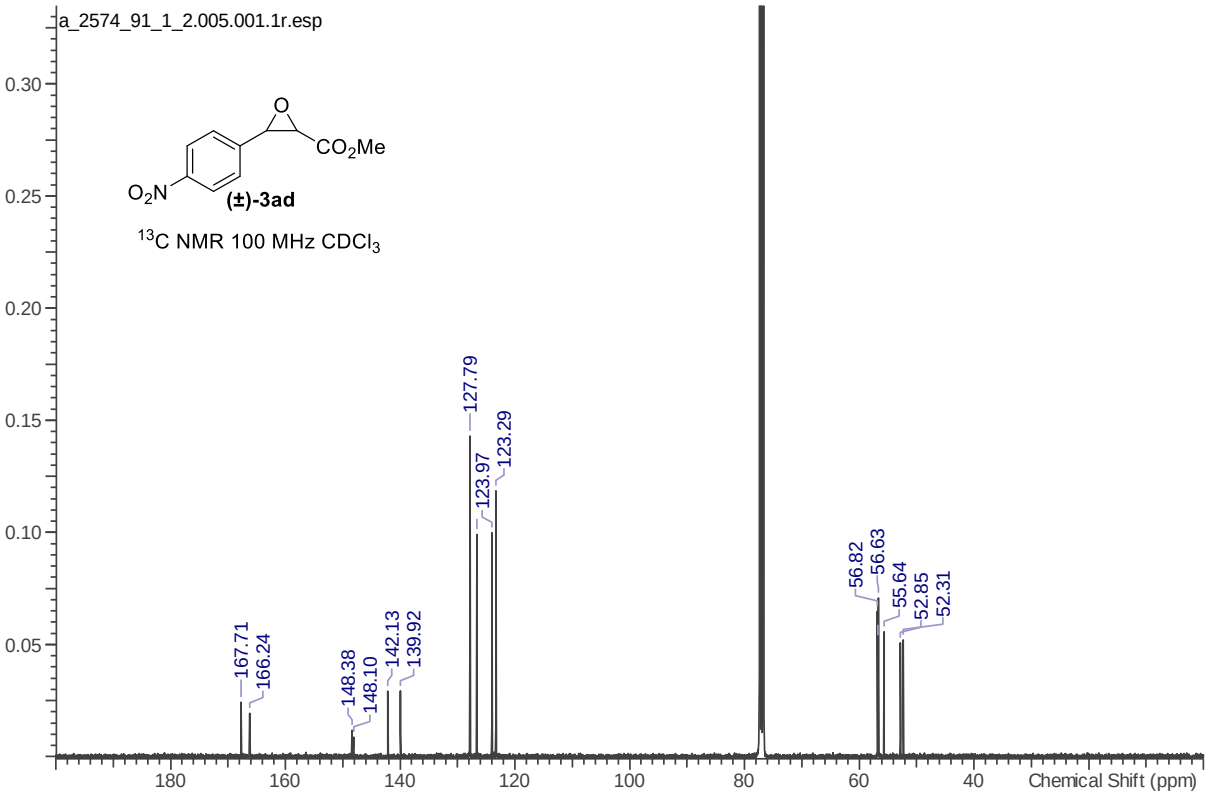

a_2574_79_2_2.001.esp
O
CO2Me
Cl
(±)-3ab
1H NMR 400 MHz CDCl3
M06(s)
M04(d)
3.60
3.85
M01(m)
M02(m)
7.37
7.34
7.38
7.26
7.24
7.39
M03(d)
3.85
4.25
4.24
4.10
4.10
3.49
3.49
3.82
2.09
0.90
4.01
0.90
Chemical Shift (ppm)

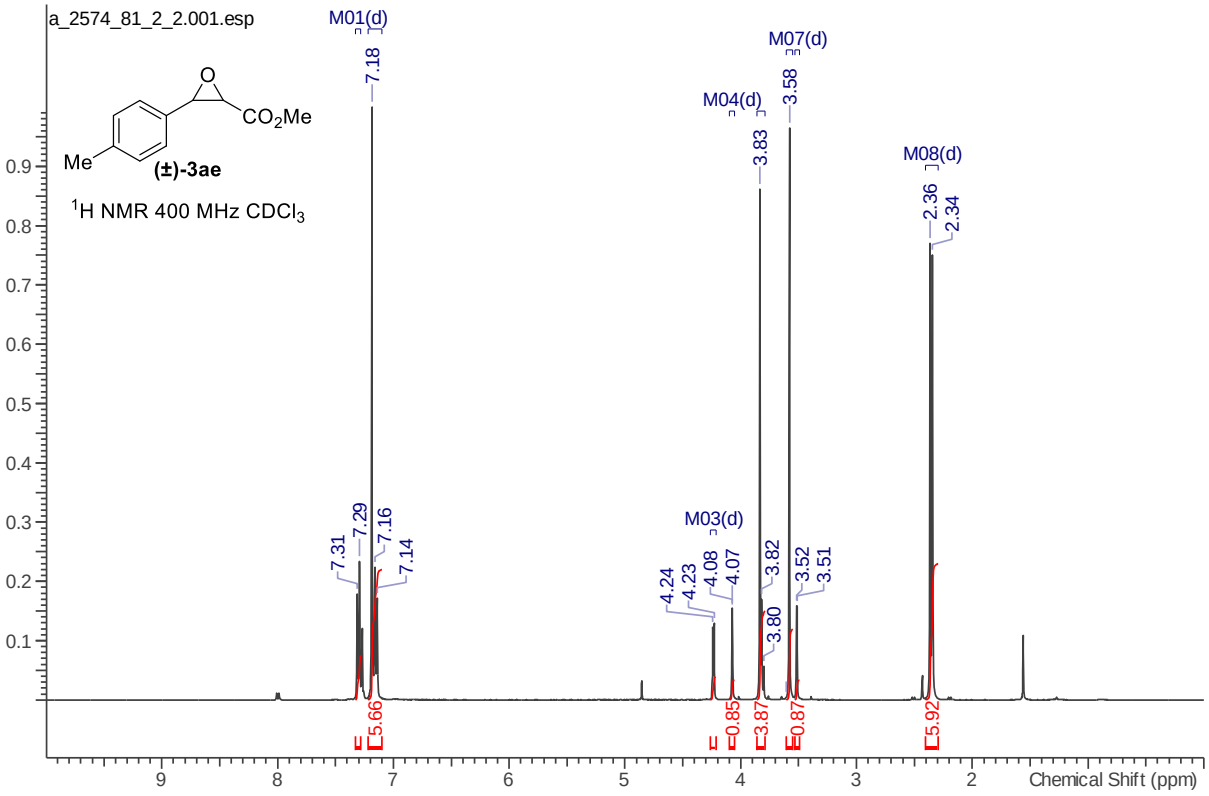

a_2574_25_2.004.esp
O
CO2Me
Cl
(±)-3ab
13C NMR 100 MHz CDCl3
168.32
166.74
134.97
134.50
131.32
128.95
128.35
128.08
127.15
57.32
56.96
55.73
52.14
Chemical Shift (ppm)

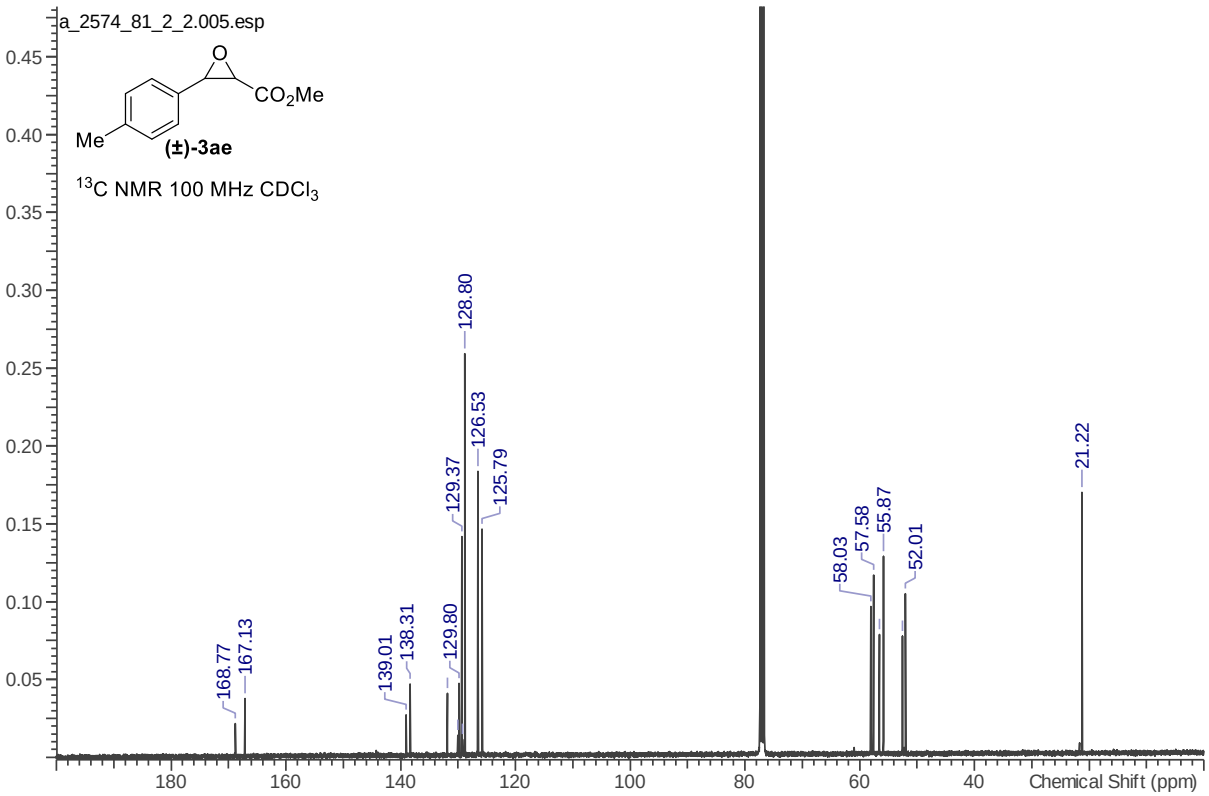

a_2574_21_2.001.esp
CO2Me
(±)-3ac
1H NMR 400 MHz CDCl3
M05(d)
M02(d)
M06(m)
M01(d)
3.56
3.84
7.43
7.43
7.41
7.37
7.36
7.33
7.31
7.31
7.30
7.29
4.27
4.26
4.11
4.11
3.85
3.81
3.53
3.52
9.71
0.75
3.58
0.76
Chemical Shift (ppm)

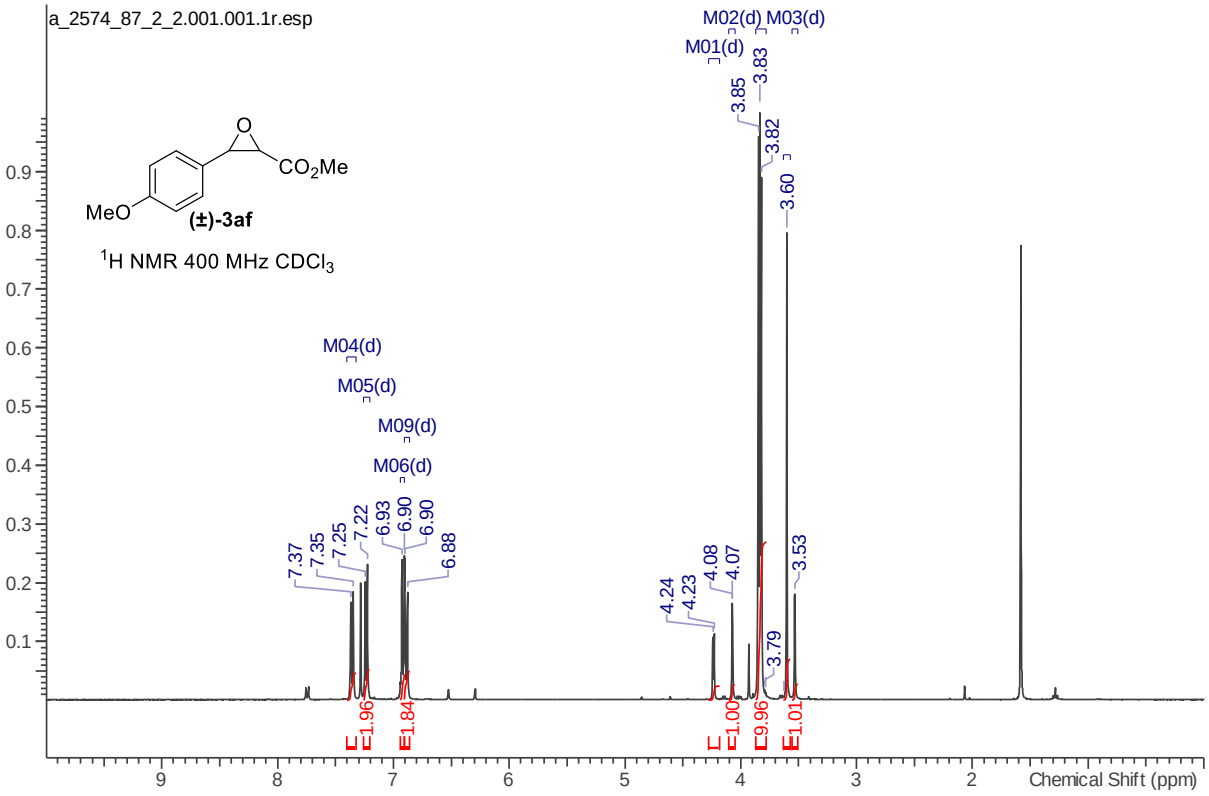

a_2574_21_2.004.esp
CO2Me
(±)-3ac
13C NMR 100 MHz CDCl3
128.08
126.61
128.68
125.82
129.03
132.83
134.92
168.63
167.02
57.52
55.80
57.98
52.00
Chemical Shift (ppm)

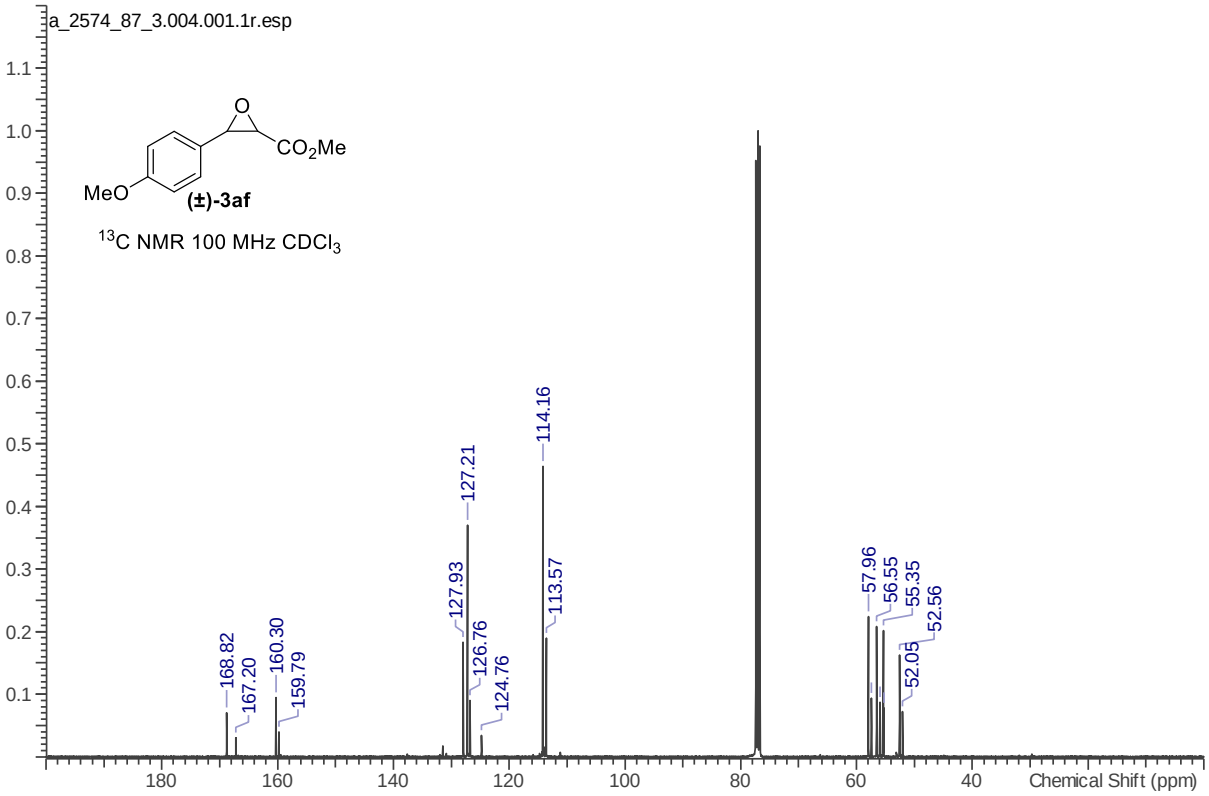

a_2574_91_1_2.002.001.1r.esp
O
CO2Me
O2N
(±)-3ad
1H NMR 400 MHz CDCl3
M04(d)
M02(d)
M08(m)
M09(m)
M07(m)
M10(m)
M01(d)
3.58
3.86
8.26
8.24
8.23
8.21
7.64
7.62
7.50
7.48
3.92
4.35
4.34
4.22
4.22
3.51
3.50
8.26
8.20
7.64
7.47
3.83
1.95
1.82
0.89
2.81
0.89
Chemical Shift (ppm)

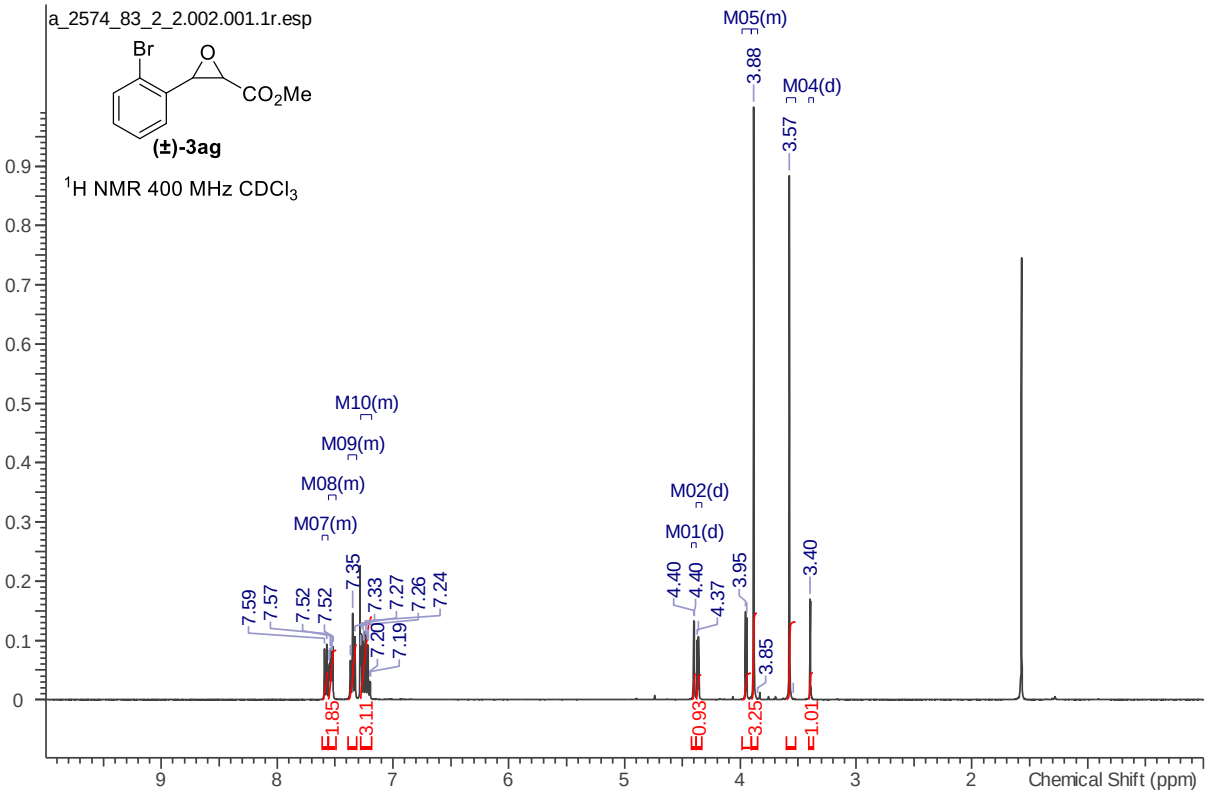

a_2574_91_1_2.005.001.1r.esp
O
CO2Me
O2N
(±)-3ad
13C NMR 100 MHz CDCl3
127.79
123.97
123.29
167.71
166.24
148.38
148.10
142.13
139.92
56.82
56.63
55.64
52.85
52.31
Chemical Shift (ppm)

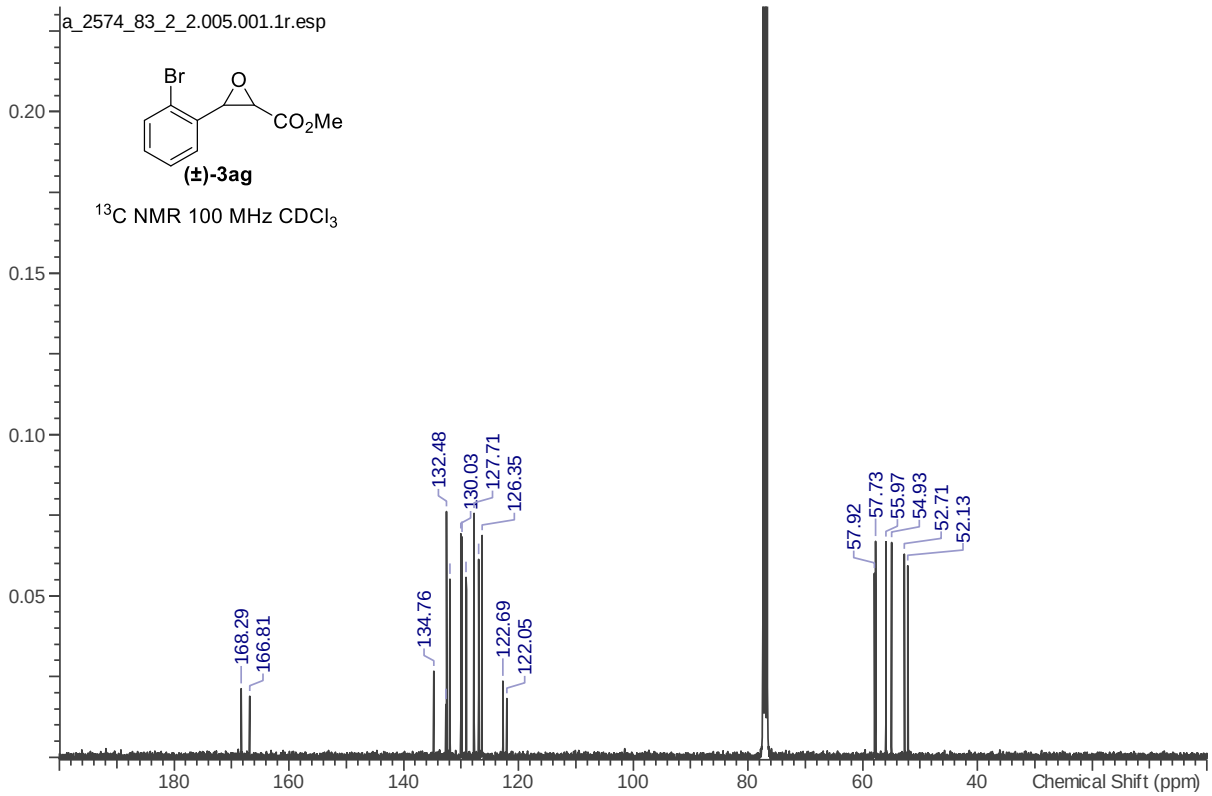

a_2574_81_2_2.001.esp
M01(d)
7.18
M07(d)
3.58
M04(d)
3.83
M08(d)
2.36
2.34
M03(d)
7.31
7.29
7.16
7.14
4.24
4.23
4.08
4.07
3.82
3.80
3.52
3.51
5.66
0.85
3.87
0.87
5.92
O
CO2Me
Me
(±)-3ae
1H NMR 400 MHz CDCl3
Chemical Shift (ppm)

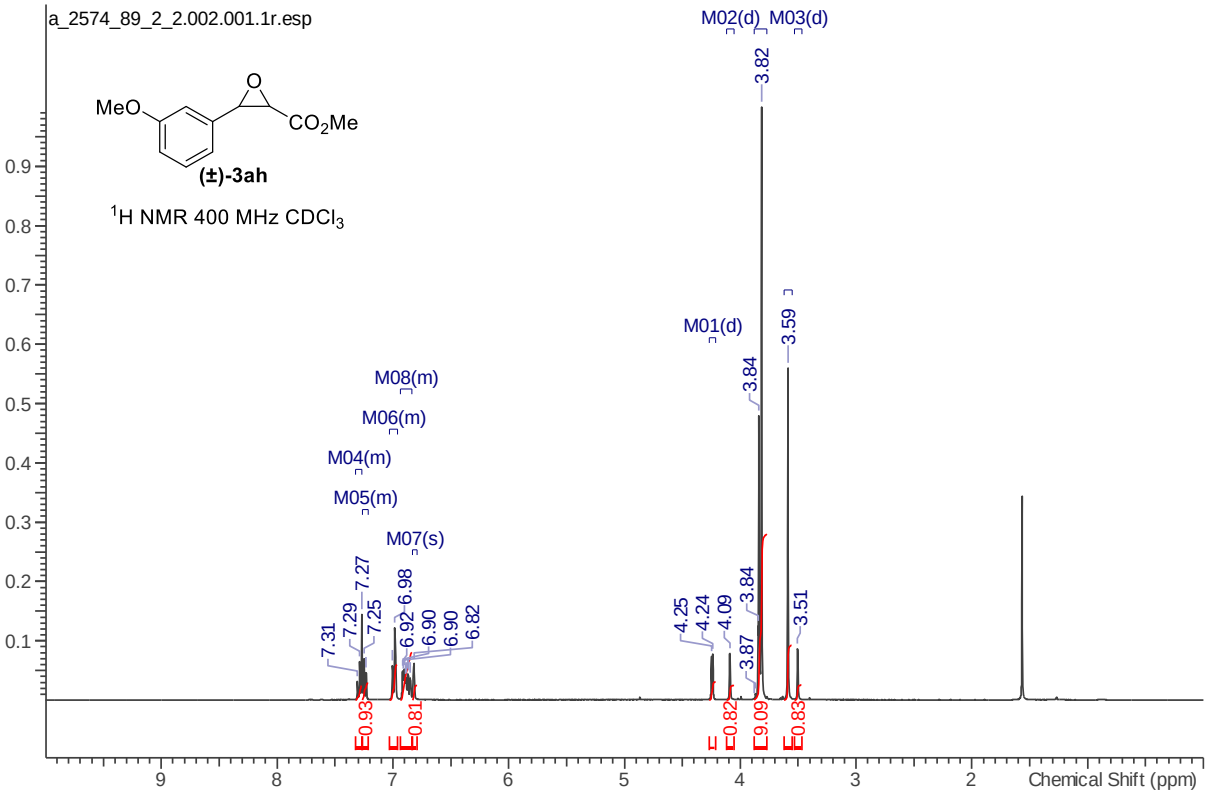

a_2574_81_2_2.005.esp
O
CO2Me
Me
(±)-3ae
13C NMR 100 MHz CDCl3
168.77
167.13
139.01
138.31
129.80
129.37
128.80
126.53
125.79
58.03
57.58
55.87
52.01
21.22
Chemical Shift (ppm)

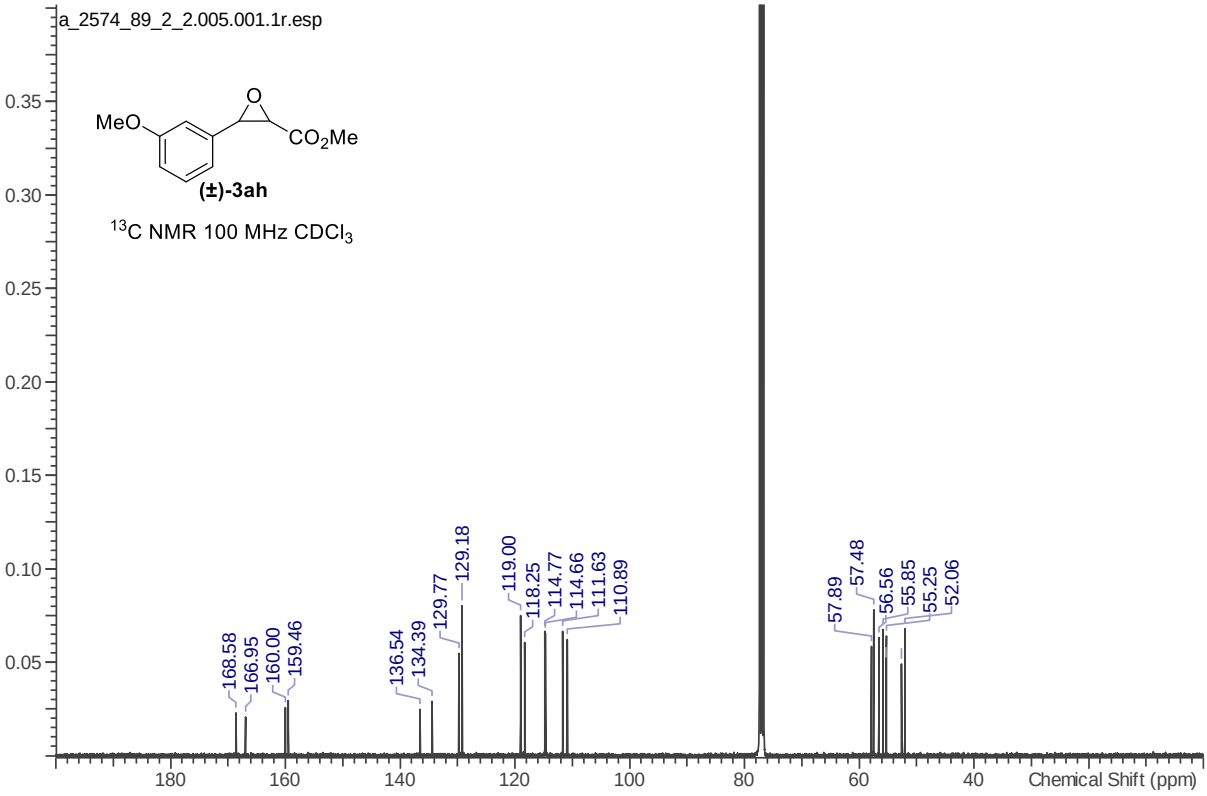

a_2574_87_2_2.001.001.1r.esp
MeO
CO2Me
(±)-3af
1H NMR 400 MHz CDCl3
M02(d) M03(d)
M01(d)
3.85
3.83
3.82
3.60
M04(d)
M05(d)
M09(d)
M06(d)
7.37
7.35
7.25
7.22
6.93
6.90
6.90
6.88
4.24
4.23
4.08
4.07
3.79
3.53
1.96
1.84
1.00
9.96
1.01
Chemical Shift (ppm)

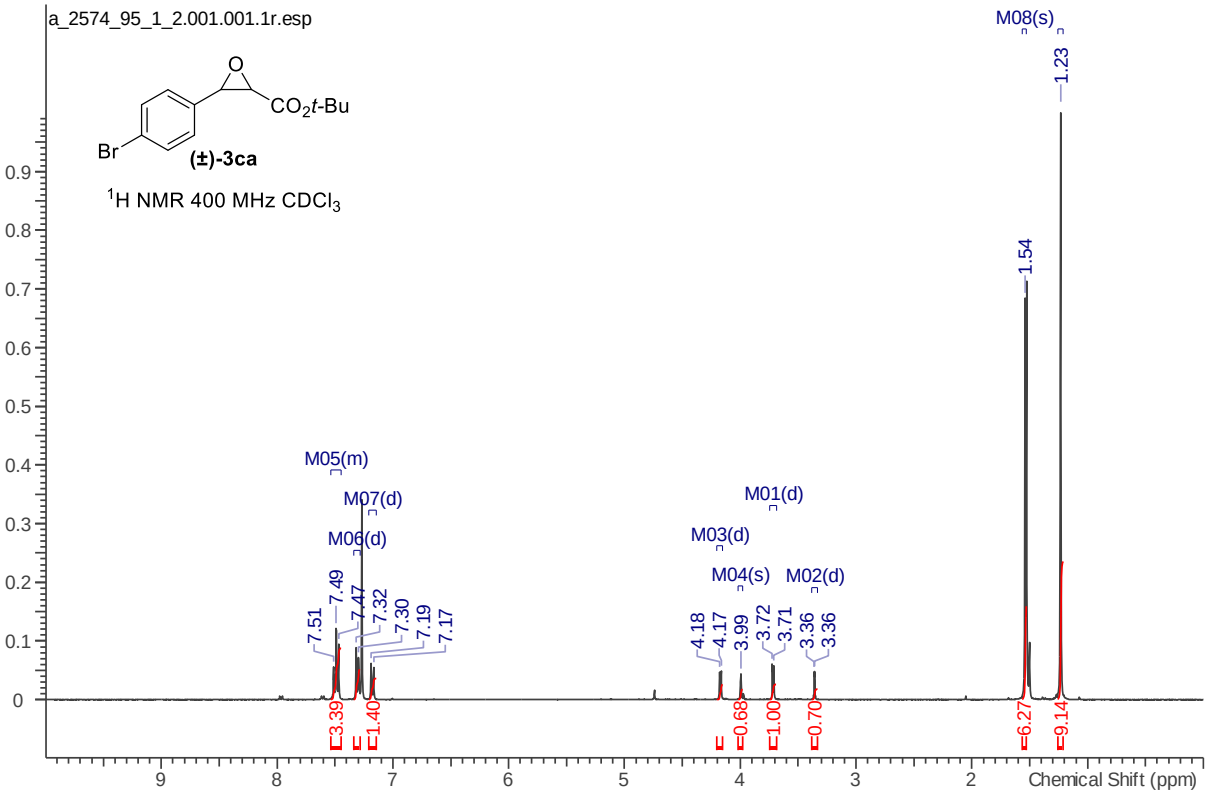

a_2574_87_3.004.001.1r.esp
MeO
CO2Me
(±)-3af
13C NMR 100 MHz CDCl3
168.82
167.20
160.30
159.79
127.93
127.21
126.76
124.76
114.16
113.57
57.96
56.55
55.35
52.56
52.05
Chemical Shift (ppm)

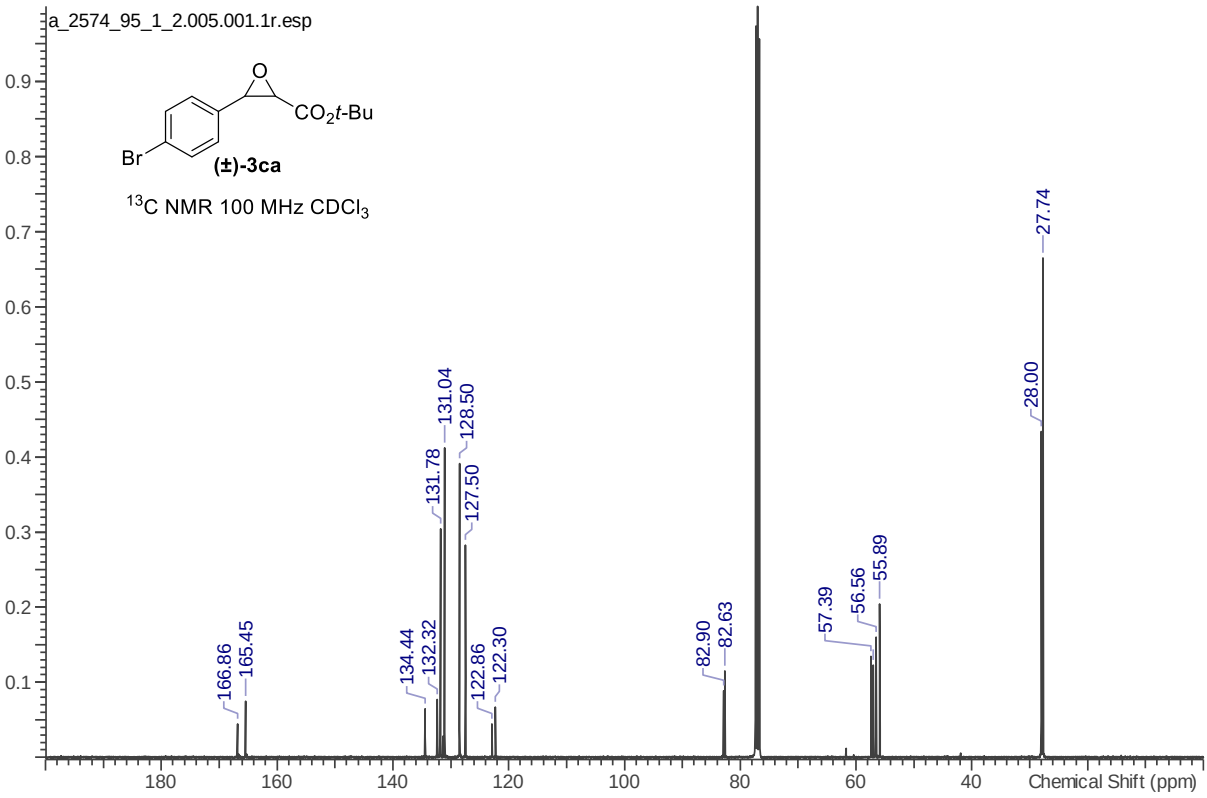

a_2574_83_2_2.002.001.1r.esp
Br
O
CO2Me
(±)-3ag
1H NMR 400 MHz CDCl3
M05(m)
3.88
M04(d)
3.57
M10(m)
M09(m)
M08(m)
M07(m)
M02(d)
M01(d)
7.59
7.57
7.52
7.52
7.35
7.33
7.27
7.26
7.24
7.20
7.19
4.40
4.40
4.37
3.95
3.85
3.40
1.85
3.11
0.93
3.25
1.01
Chemical Shift (ppm)

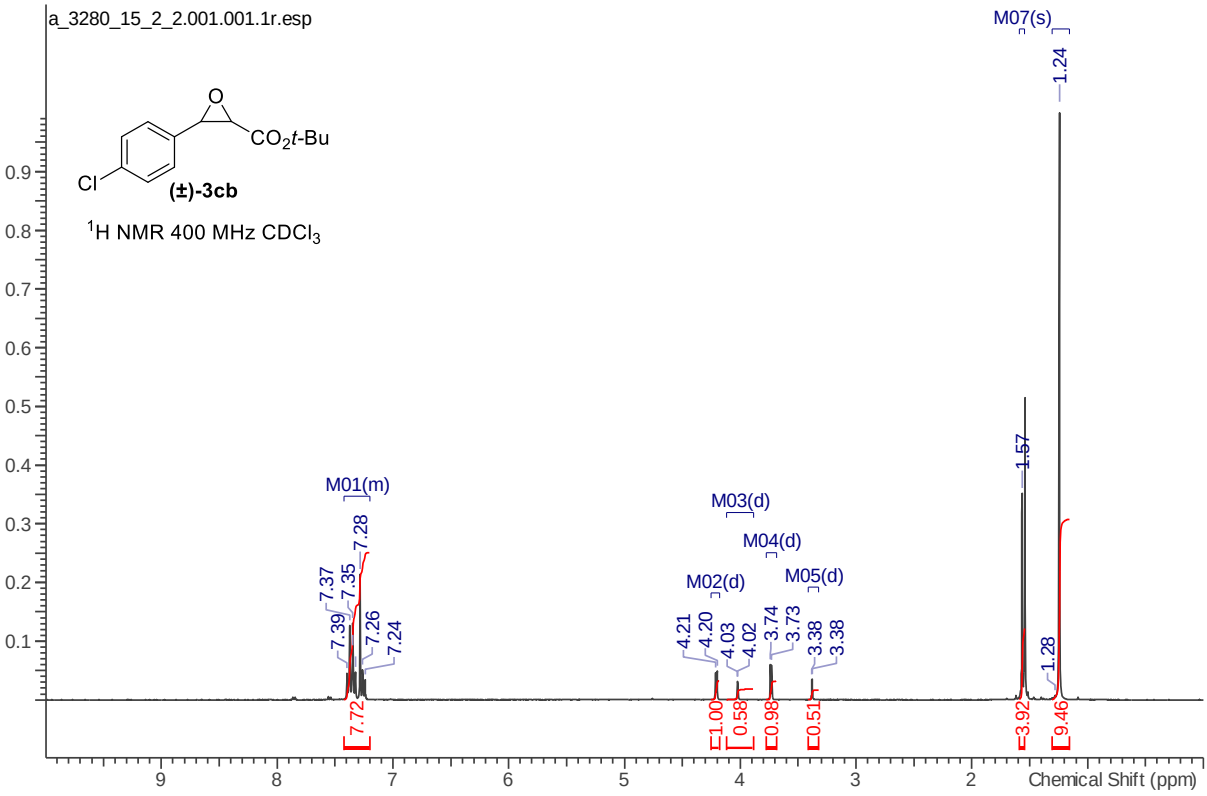

a_2574_83_2_2.005.001.1r.esp
Br
O
CO2Me
(±)-3ag
13C NMR 100 MHz CDCl3
168.29
166.81
134.76
132.48
130.03
127.71
126.35
122.69
122.05
57.92
57.73
55.97
54.93
52.71
52.13
Chemical Shift (ppm)

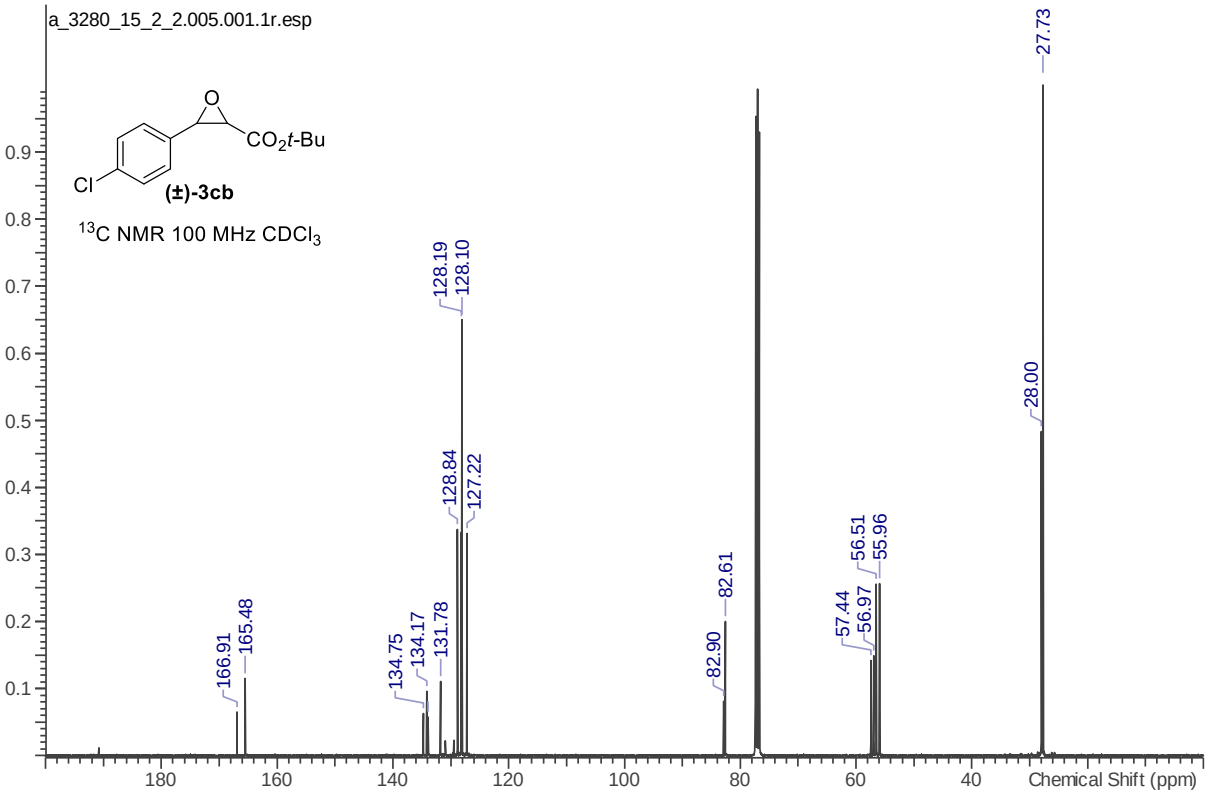

a_2574_89_2_2.002.001.1r.esp
MeO
CO2Me
(±)-3ah
1H NMR 400 MHz CDCl3
M02(d) M03(d)
3.82
M01(d)
3.59
3.84
M08(m)
M06(m)
M04(m)
M05(m)
M07(s)
7.27
7.31
7.29
7.25
6.98
6.92
6.90
6.90
6.82
4.25
4.24
4.09
3.84
3.87
3.51
0.93
0.81
0.82
9.09
0.83
Chemical Shift (ppm)

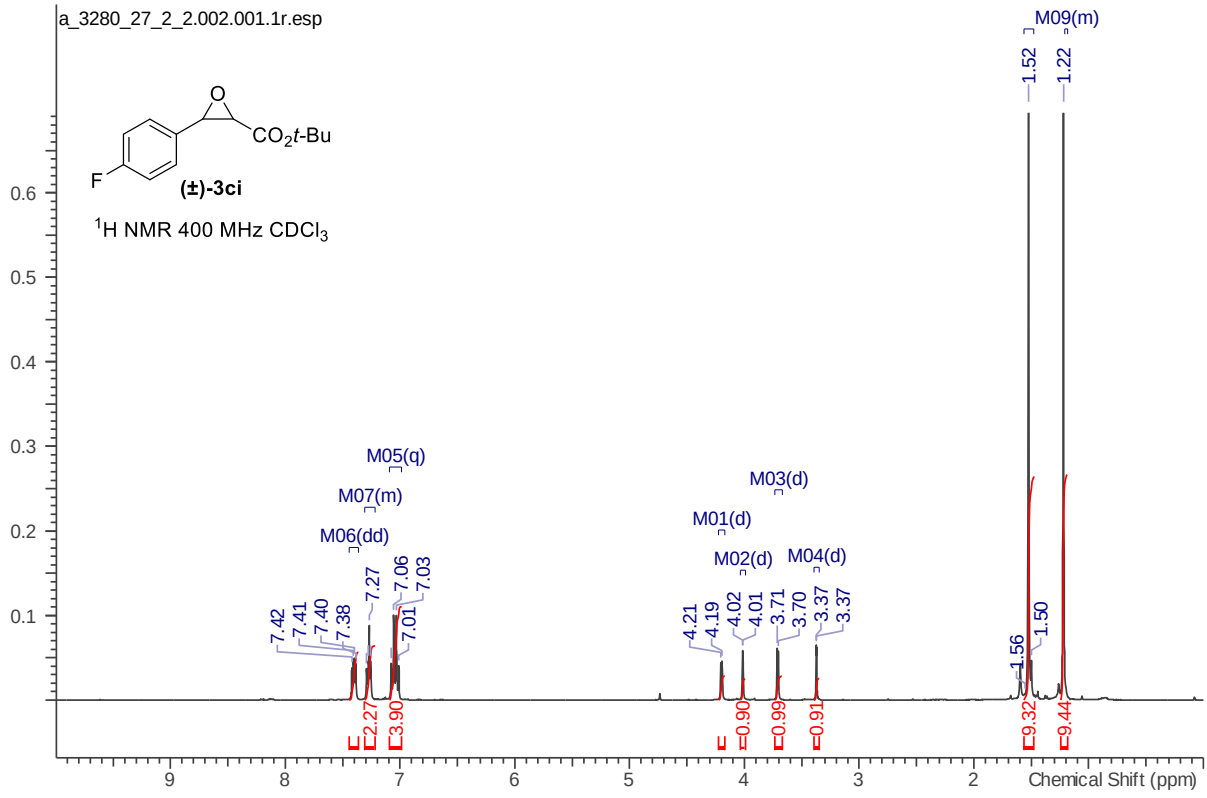

a_2574_89_2_2.005.001.1r.esp
MeO
CO2Me
(±)-3ah
13C NMR 100 MHz CDCl3
168.58
166.95
160.00
159.46
136.54
134.39
129.77
129.18
119.00
118.25
114.77
114.66
111.63
110.89
57.89
57.48
56.56
55.85
55.25
52.06
Chemical Shift (ppm)

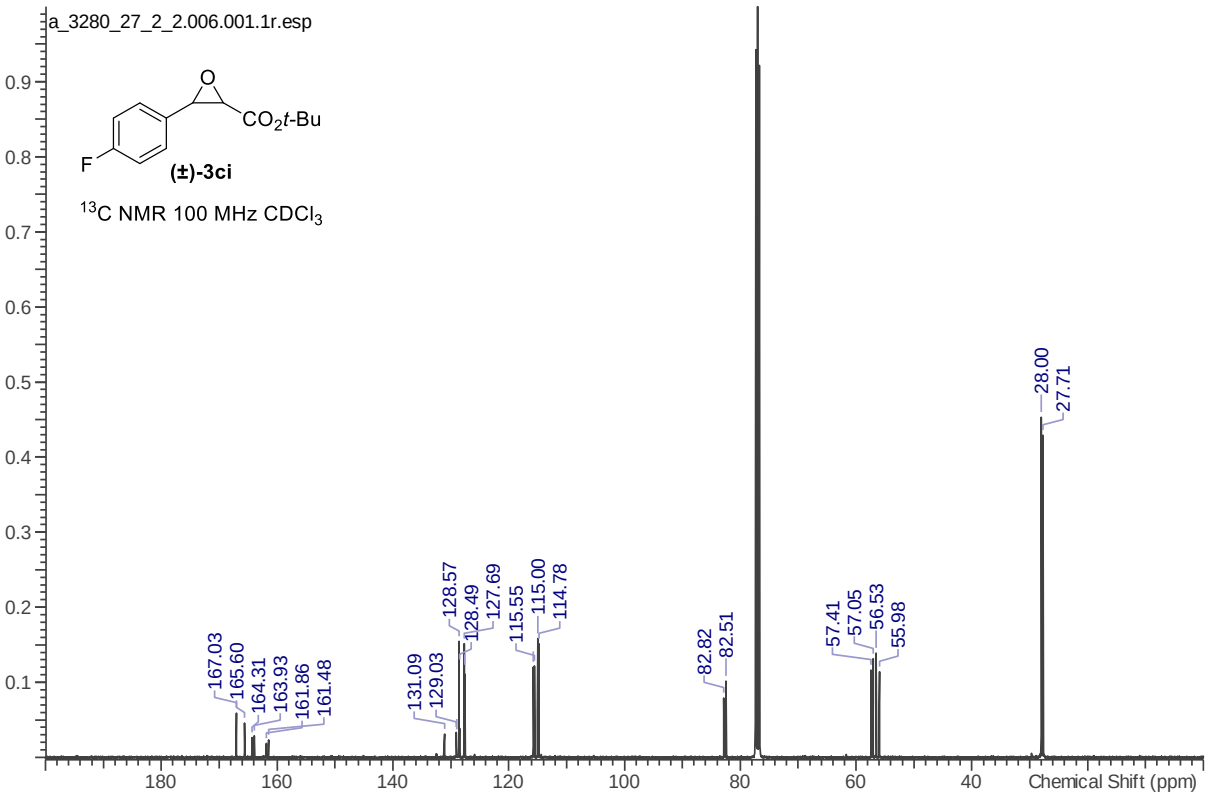

a_2574_95_1_2.001.001.1r.esp
O
CO2t-Bu
Br
(±)-3ca
1H NMR 400 MHz CDCl3
M08(s)
1.23
1.54
M05(m)
M07(d)
M06(d)
M01(d)
M03(d)
M04(s)
M02(d)
7.51
7.49
7.47
7.32
7.30
7.19
7.17
4.18
4.17
3.99
3.72
3.71
3.36
3.36
3.39
1.40
0.68
1.00
0.70
6.27
9.14
Chemical Shift (ppm)

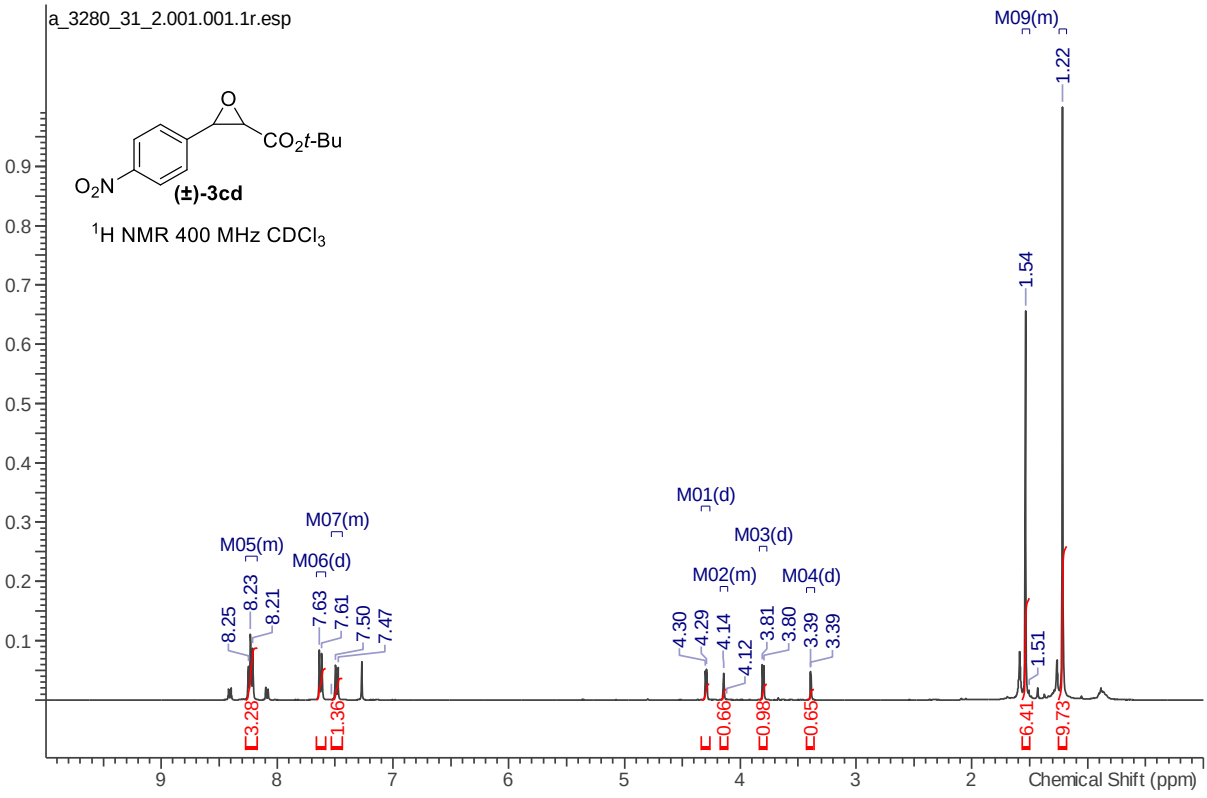

a_2574_95_1_2.005.001.1r.esp
O
CO2t-Bu
Br
(±)-3ca
13C NMR 100 MHz CDCl3
27.74
28.00
131.04
128.50
131.78
127.50
166.86
165.45
134.44
132.32
122.86
122.30
82.90
82.63
57.39
56.56
55.89
Chemical Shift (ppm)

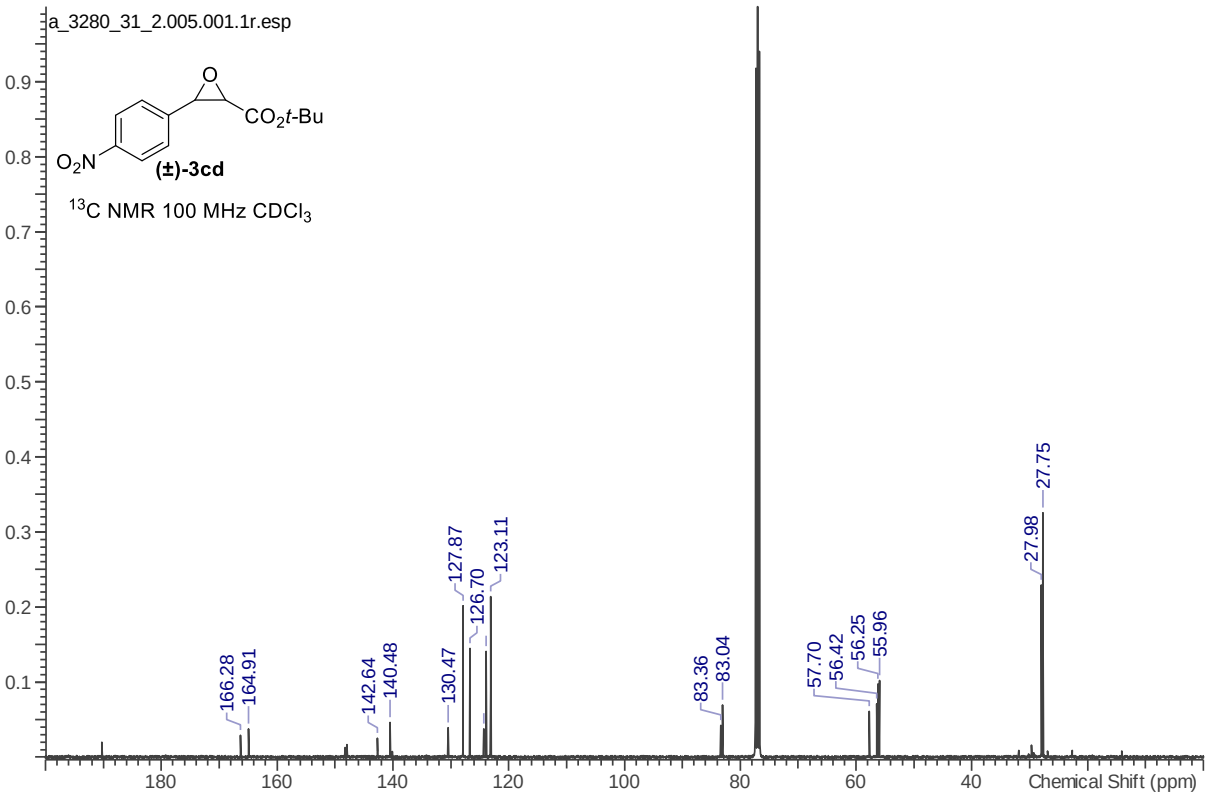

a_3280_15_2_2.001.001.1r.esp
O
CO2t-Bu
Cl
(±)-3cb
1H NMR 400 MHz CDCl3
M07(s)
1.24
M01(m)
7.28
7.37
7.35
7.39
7.26
7.24
M03(d)
M04(d)
M02(d)
M05(d)
4.21
4.20
4.03
4.02
3.74
3.73
3.38
3.38
1.57
1.28
7.72
1.00
0.58
0.98
0.51
3.92
9.46
Chemical Shift (ppm)

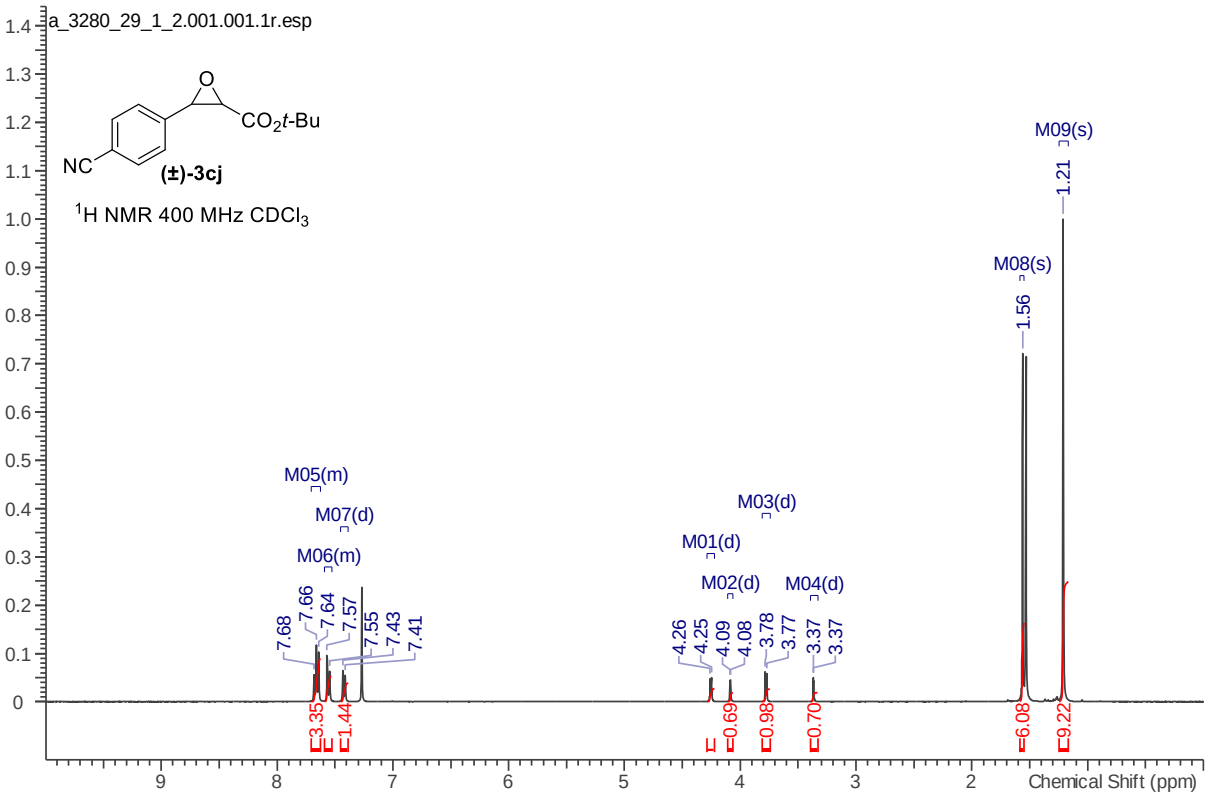

a_3280_15_2_2.005.001.1r.esp
O
CO2t-Bu
Cl
(±)-3cb
13C NMR 100 MHz CDCl3
27.73
28.00
128.19
128.10
128.84
127.22
166.91
165.48
134.75
134.17
131.78
82.90
82.61
57.44
56.97
56.51
55.96
Chemical Shift (ppm)

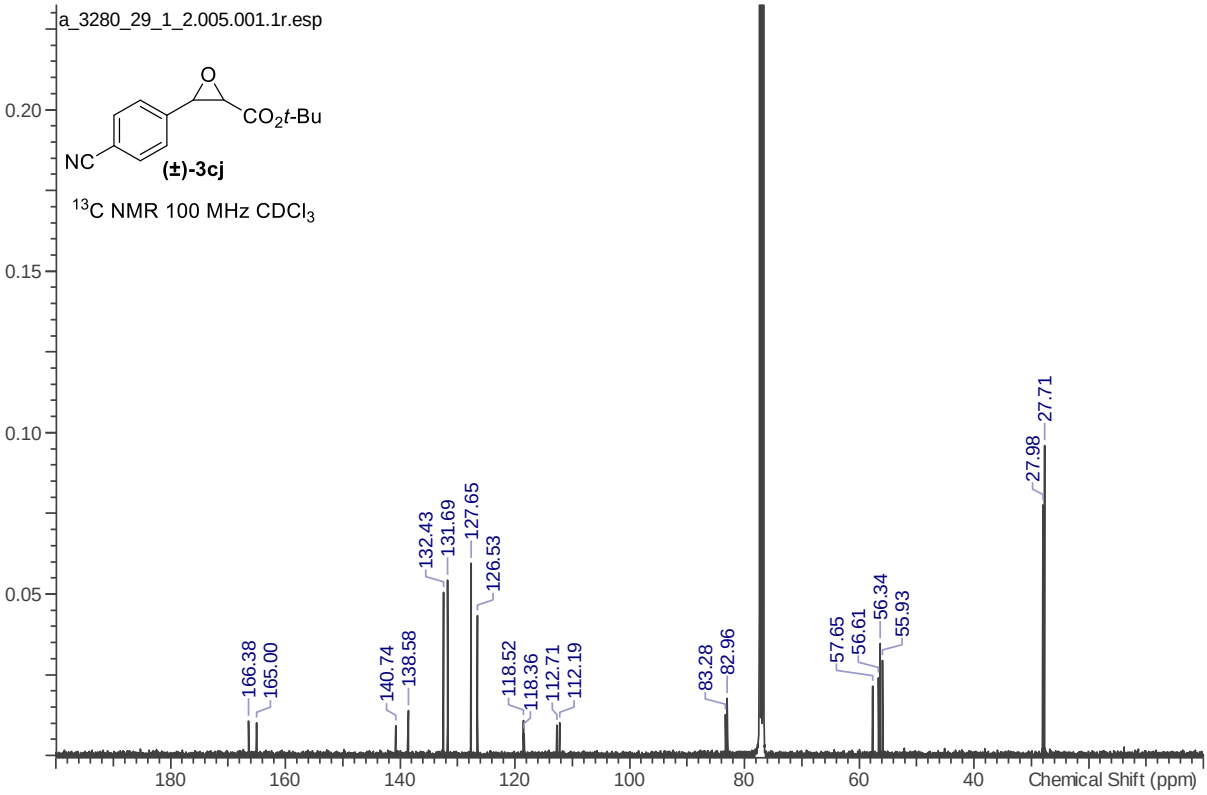

a_3280_27_2_2.002.001.1r.esp
O
CO2t-Bu
F
(±)-3ci
1H NMR 400 MHz CDCl3
M09(m)
1.52
1.22
M05(q)
M07(m)
M06(dd)
M03(d)
M01(d)
M02(d)
M04(d)
7.42
7.41
7.40
7.38
7.27
7.06
7.03
7.01
4.21
4.19
4.02
4.01
3.71
3.70
3.37
3.37
1.56
1.50
2.27
3.90
0.90
0.99
0.91
9.32
9.44
Chemical Shift (ppm)

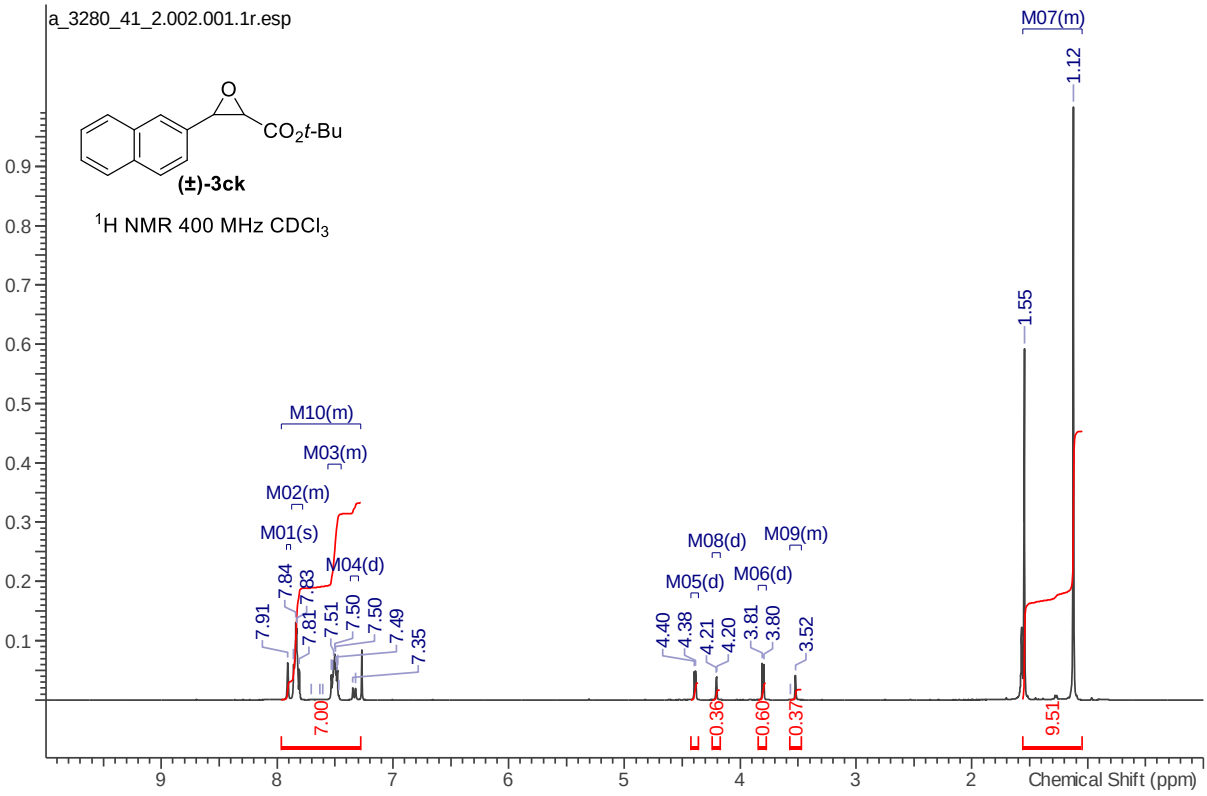

a_3280_27_2_2.006.001.1r.esp
O
CO2t-Bu
F
(±)-3ci
13C NMR 100 MHz CDCl3
167.03
165.60
164.31
163.93
161.86
161.48
131.09
129.03
128.57
128.49
127.69
115.55
115.00
114.78
82.82
82.51
57.41
57.05
56.53
55.98
28.00
27.71
Chemical Shift (ppm)

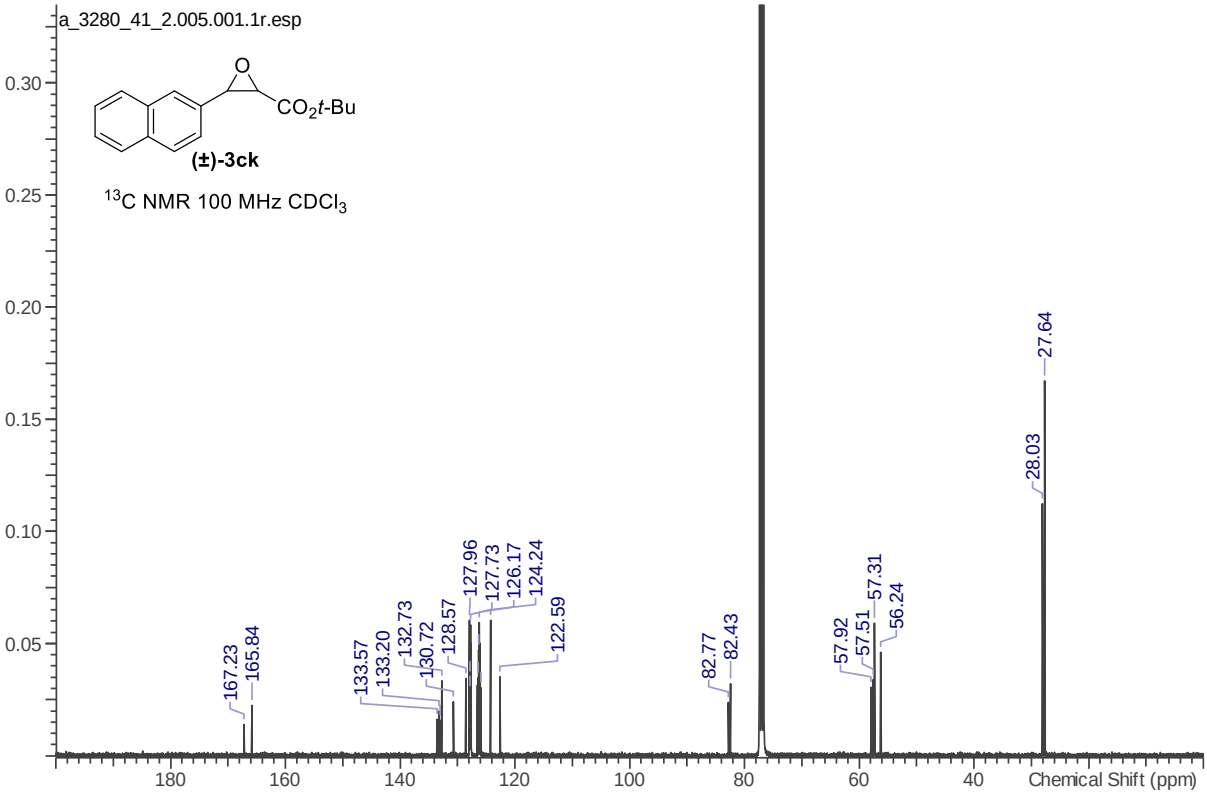

a_3280_31_2.001.001.1r.esp
O
CO2t-Bu
O2N
(±)-3cd
1H NMR 400 MHz CDCl3
M09(m)
1.22
1.54
M01(d)
M03(d)
M07(m)
M05(m)
M06(d)
M02(m)
M04(d)
8.25
8.23
8.21
7.63
7.61
7.50
7.47
4.30
4.29
4.14
4.12
3.81
3.80
3.39
3.39
1.51
3.28
1.36
0.66
0.98
0.65
6.41
9.73
Chemical Shift (ppm)

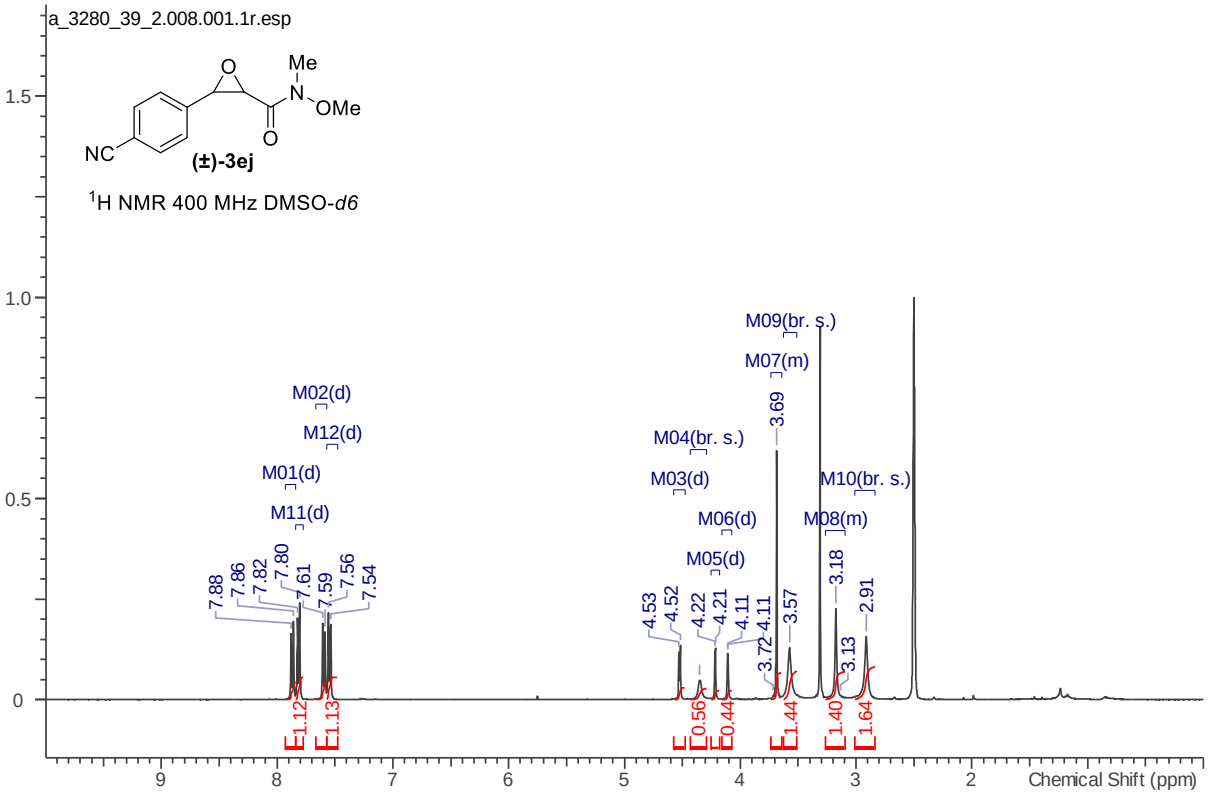

a_3280_31_2.005.001.1r.esp
O
CO2t-Bu
O2N
(±)-3cd
13C NMR 100 MHz CDCl3
166.28
164.91
142.64
140.48
130.47
127.87
126.70
123.11
83.36
83.04
57.70
56.42
56.25
55.96
27.98
27.75
Chemical Shift (ppm)

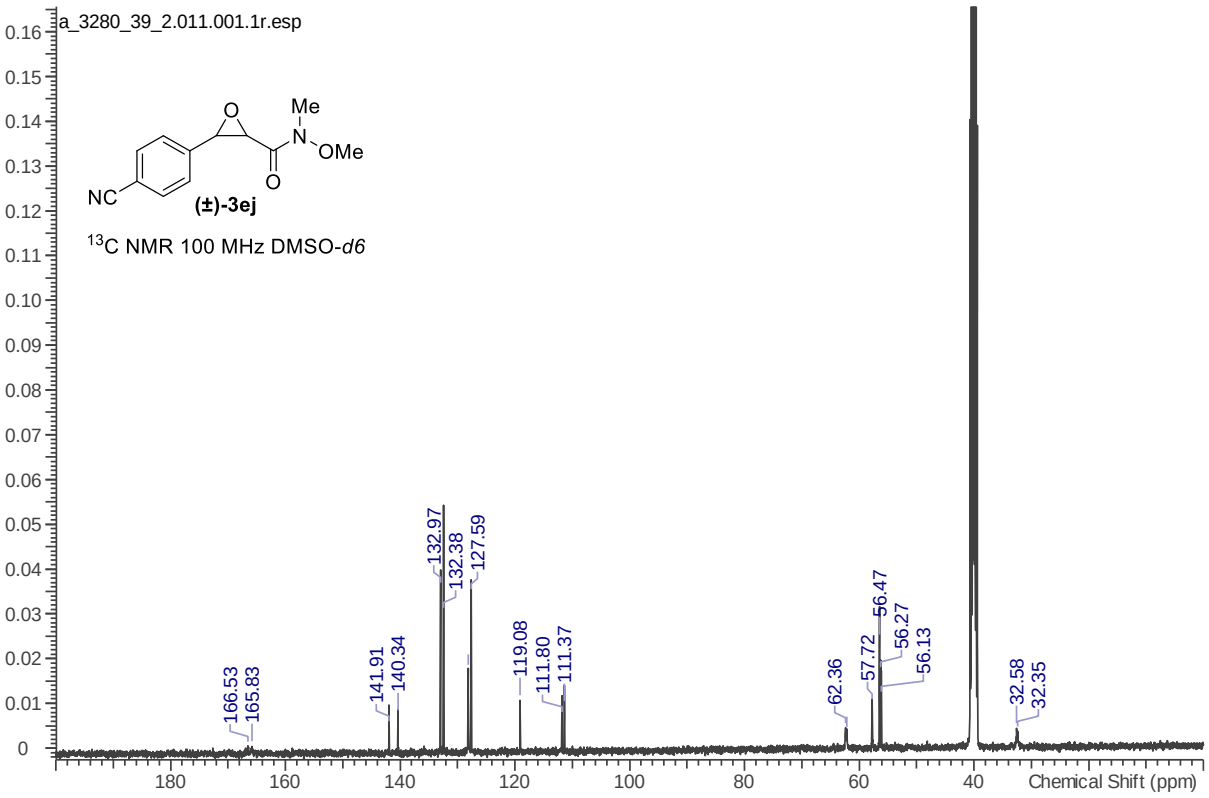

a_3280_29_1_2.001.001.1r.esp
O
CO2t-Bu
NC
(±)-3cj
1H NMR 400 MHz CDCl3
M09(s)
1.21
M08(s)
1.56
M05(m)
M07(d)
M06(m)
M03(d)
M01(d)
M02(d)
M04(d)
7.68
7.66
7.64
7.57
7.55
7.43
7.41
4.26
4.25
4.09
4.08
3.78
3.77
3.37
3.37
3.35
1.44
0.69
0.98
0.70
6.08
9.22
Chemical Shift (ppm)

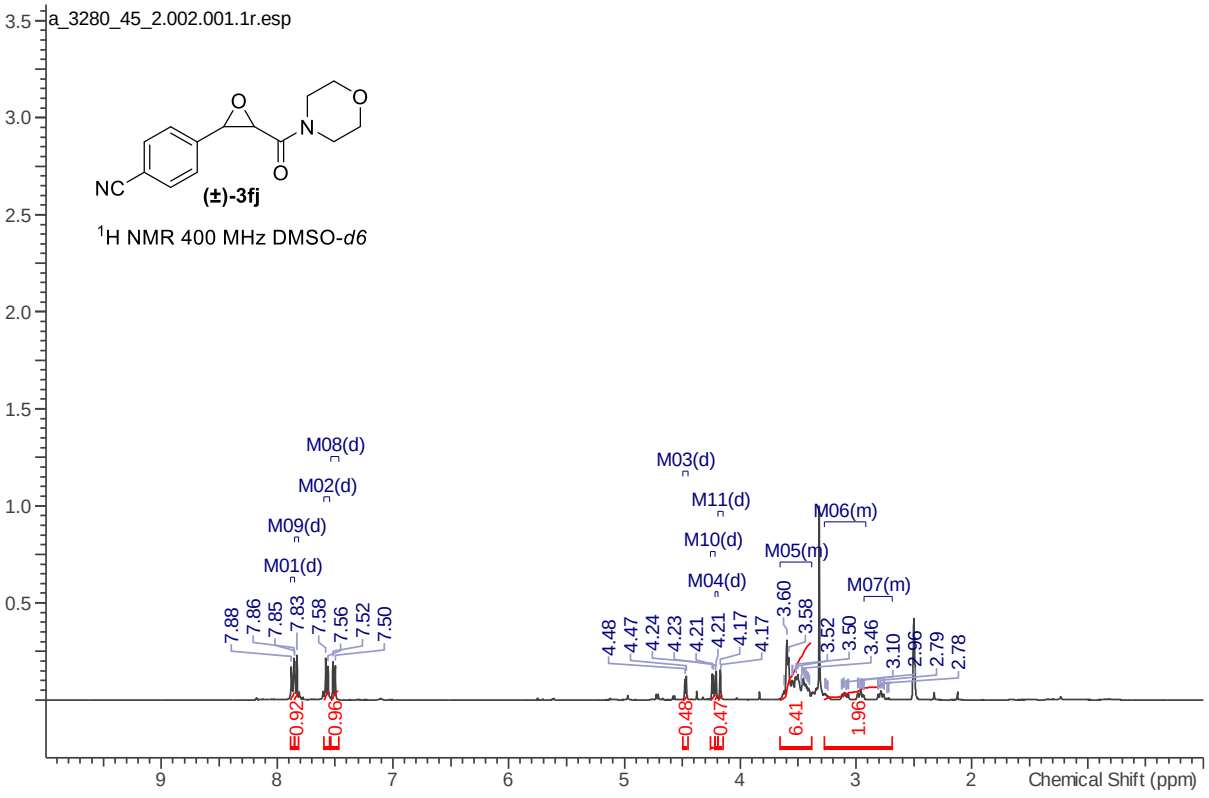

a_3280_29_1_2.005.001.1r.esp
O
CO2t-Bu
NC
(±)-3cj
13C NMR 100 MHz CDCl3
27.71
27.98
166.38
165.00
140.74
138.58
132.43
131.69
127.65
126.53
118.52
118.36
112.71
112.19
83.28
82.96
57.65
56.61
56.34
55.93
Chemical Shift (ppm)

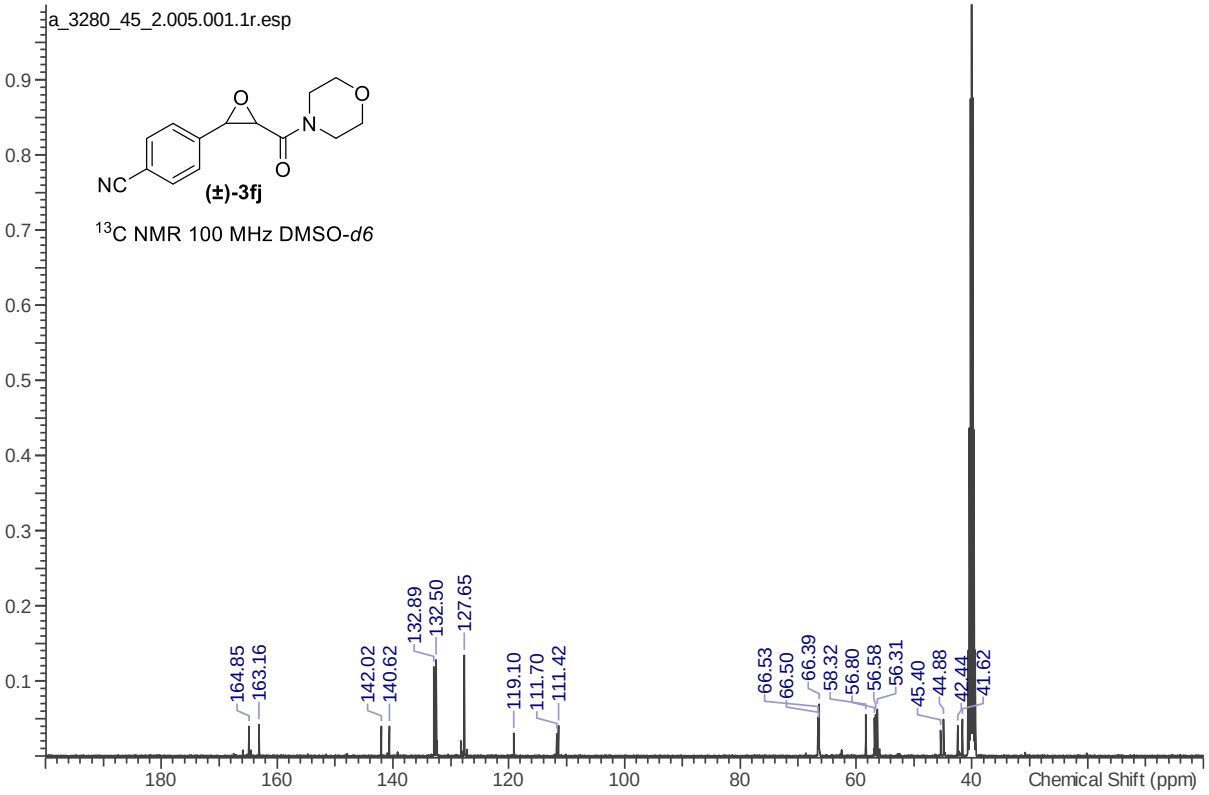

a_3280_41_2.002.001.1r.esp
O
CO2t-Bu
(±)-3ck
1H NMR 400 MHz CDCl3
M07(m)
1.12
1.55
M10(m)
M03(m)
M02(m)
M01(s)
M04(d)
M08(d)
M09(m)
M05(d)
M06(d)
7.91
7.84
7.83
7.81
7.51
7.50
7.50
7.49
7.35
4.40
4.38
4.21
4.20
3.81
3.80
3.52
7.00
0.36
0.60
0.37
9.51
Chemical Shift (ppm)

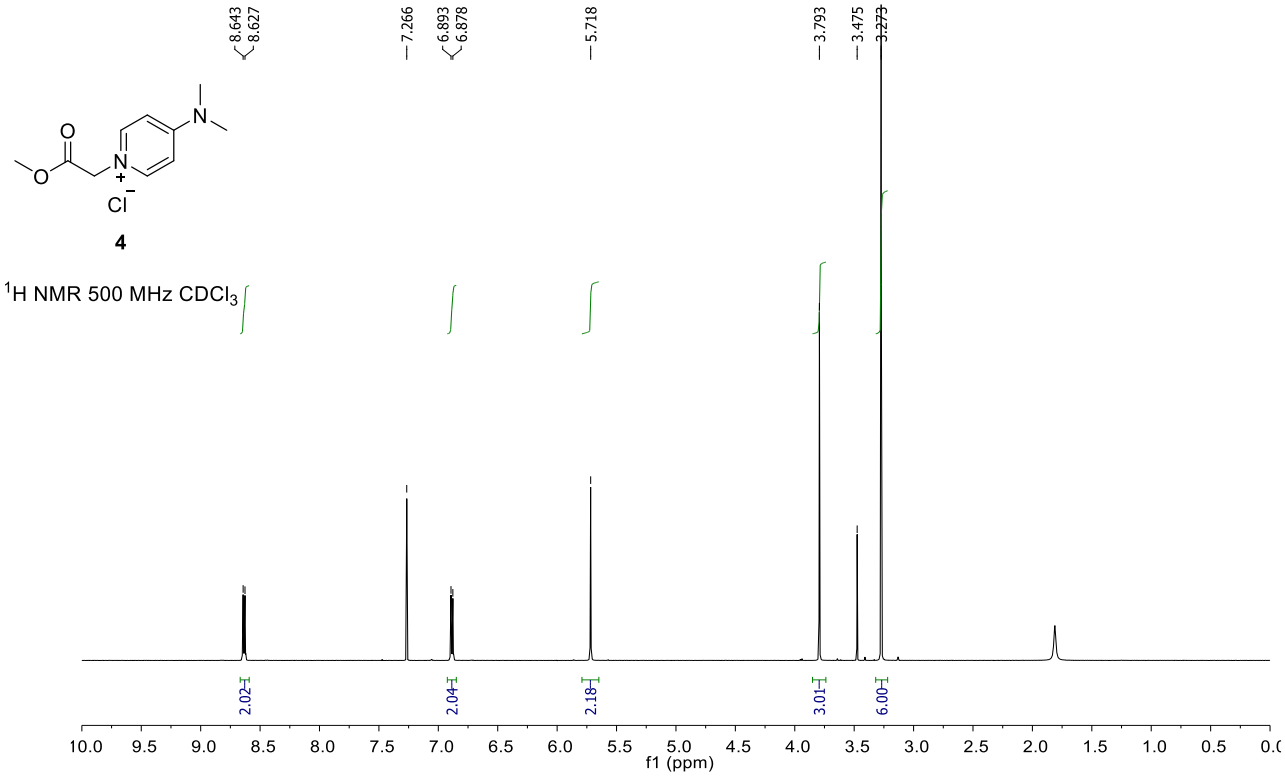

a_3280_41_2.005.001.1r.esp
O
CO2t-Bu
(±)-3ck
13C NMR 100 MHz CDCl3
27.64
28.03
167.23
165.84
133.57
133.20
132.73
130.72
128.57
127.96
127.73
126.17
124.24
122.59
82.77
82.43
57.92
57.51
57.31
56.24
Chemical Shift (ppm)


a_3280_39_2.008.001.1r.esp
(±)-3ej
^{1}H NMR 400 MHz DMSO-*d6*
M09(br. s.)
M07(m)
M02(d)
M12(d)
M04(br. s.)
M01(d)
M03(d)
M10(br. s.)
M11(d)
M06(d)
M08(m)
M05(d)
Chemical Shift (ppm)


a_3280_39_2.011.001.1r.esp
(±)-3ej
^{13}C NMR 100 MHz DMSO-*d6*
Chemical Shift (ppm)

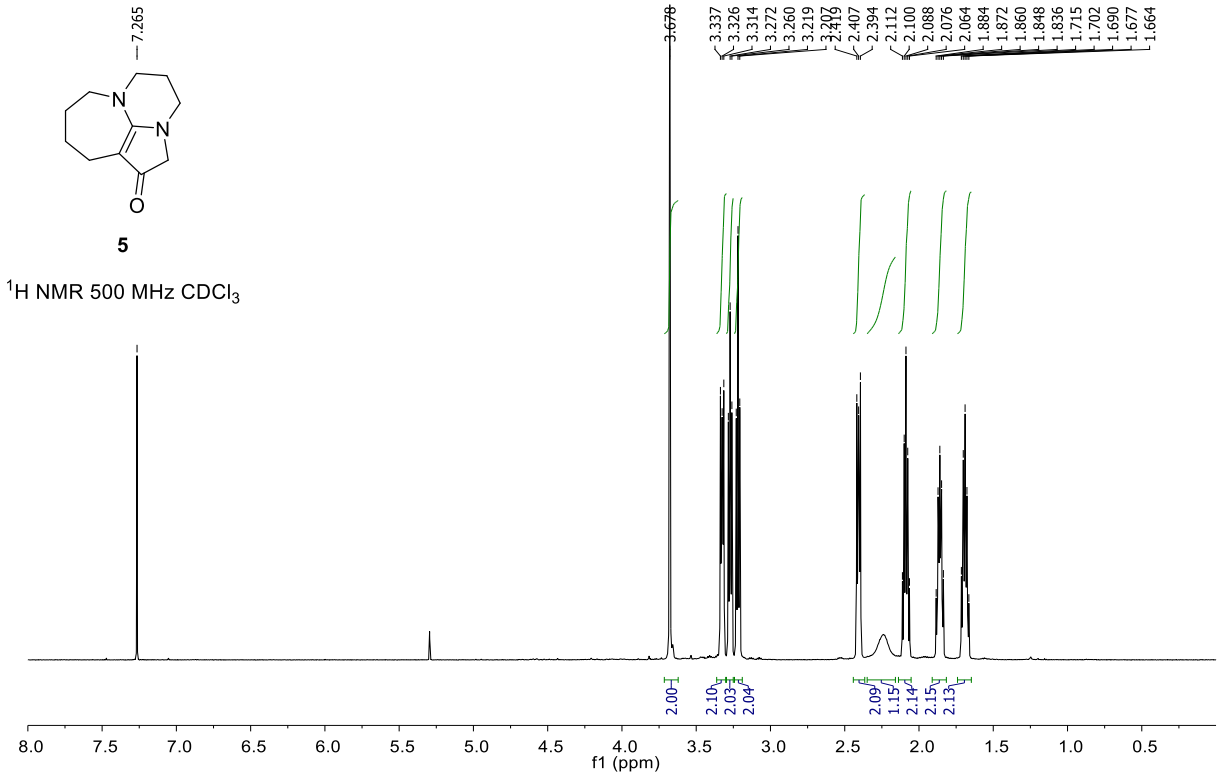

a_3280_45_2.002.001.1r.esp
NC
(±)-3fj
1H NMR 400 MHz DMSO-d6
M08(d)
M02(d)
M09(d)
M01(d)
M03(d)
M11(d)
M10(d)
M04(d)
M06(m)
M05(m)
M07(m)
7.88
7.86
7.85
7.83
7.58
7.56
7.52
7.50
4.48
4.47
4.24
4.23
4.21
4.21
4.17
3.60
3.58
3.52
3.50
3.46
3.10
2.96
2.79
2.78
0.92
0.96
0.48
0.47
6.41
1.96
Chemical Shift (ppm)


a_3280_45_2.005.001.1r.esp
NC
(±)-3fj
13C NMR 100 MHz DMSO-d6
164.85
163.16
142.02
140.62
132.89
132.50
127.65
119.10
111.70
111.42
66.53
66.50
66.39
58.32
56.80
56.58
56.31
45.40
44.88
42.44
41.62
Chemical Shift (ppm)



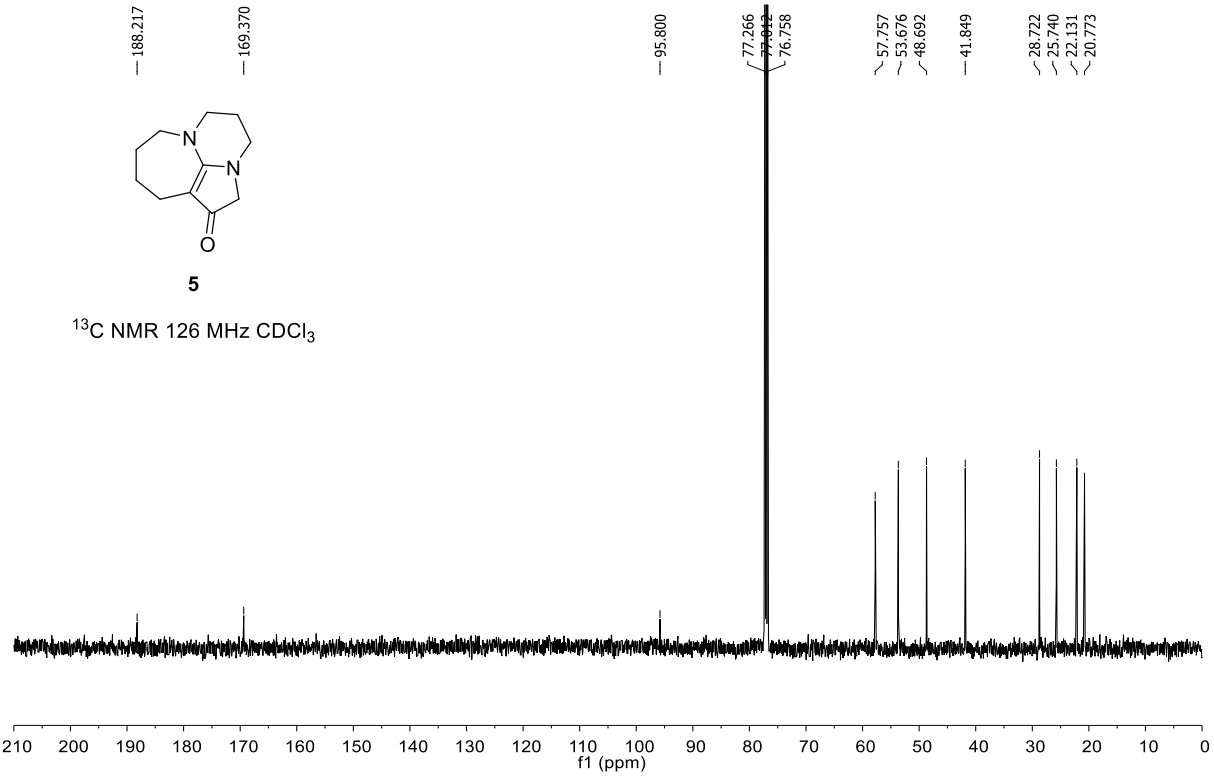
4

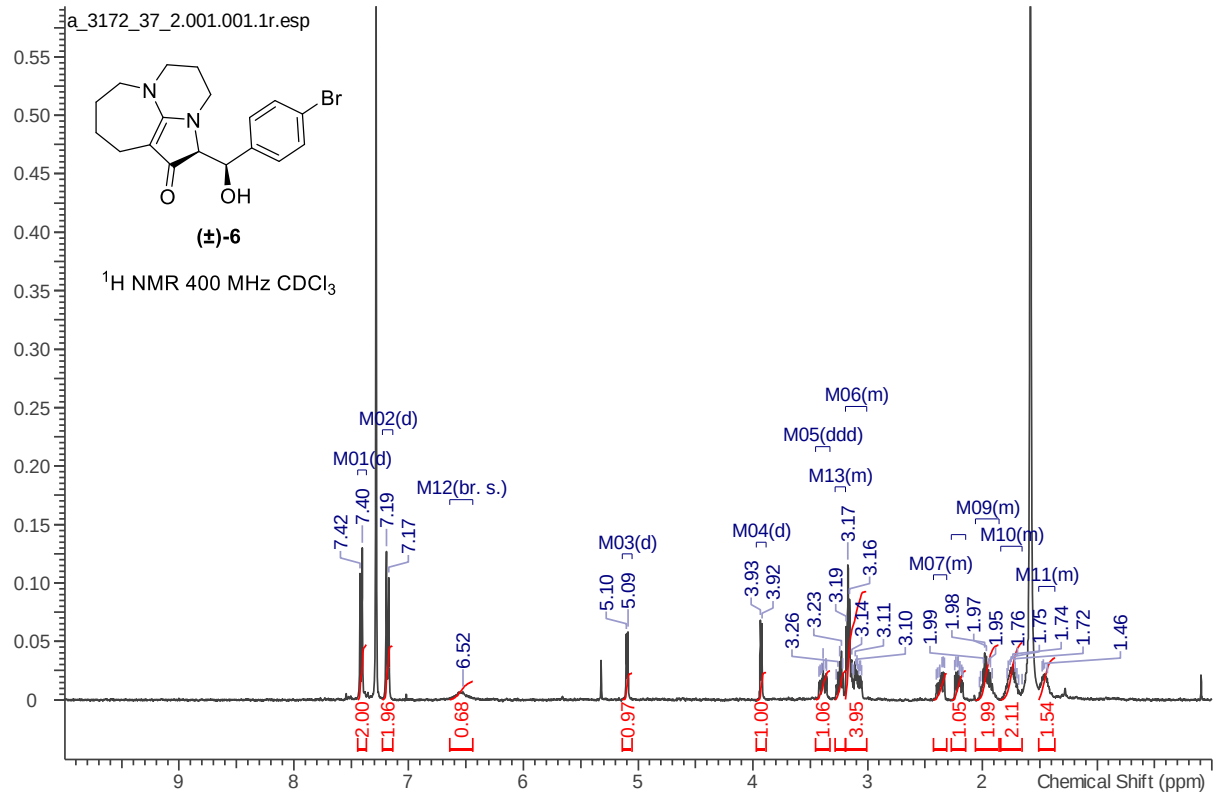
^{1}H NMR 500 MHz $CDCl_3$

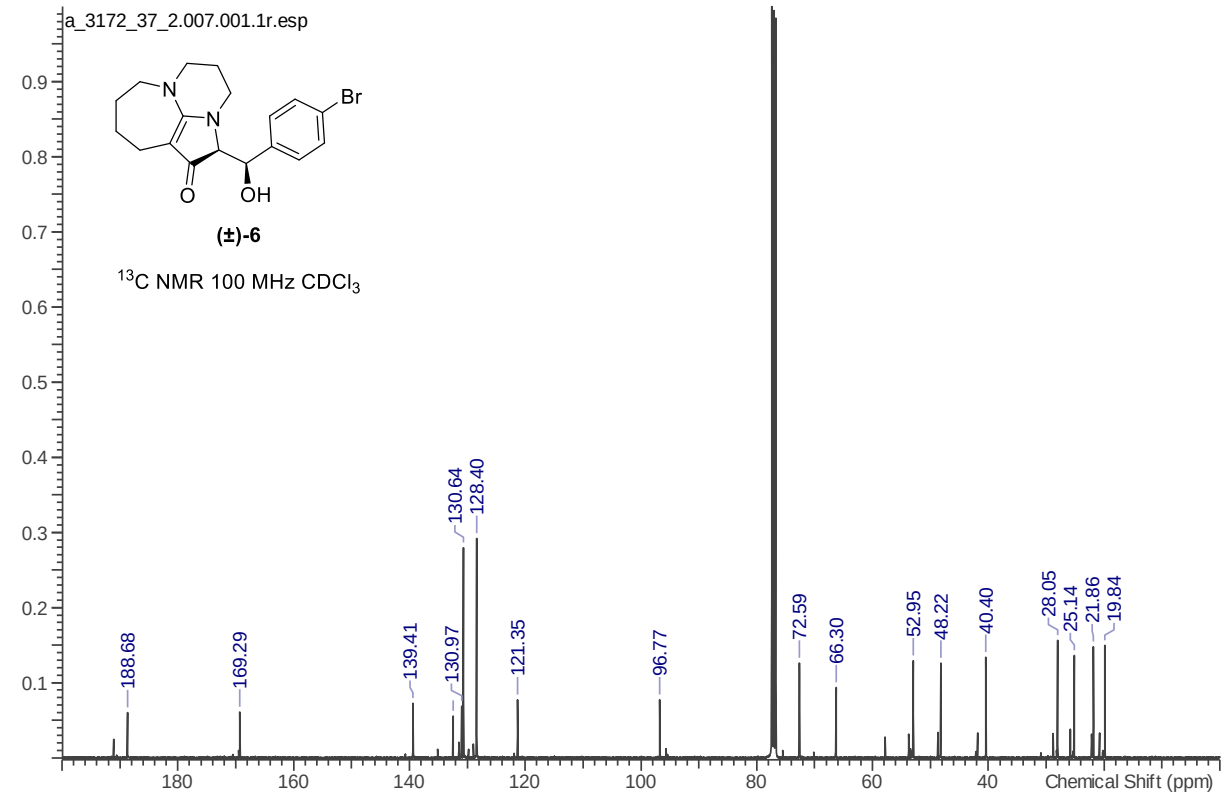


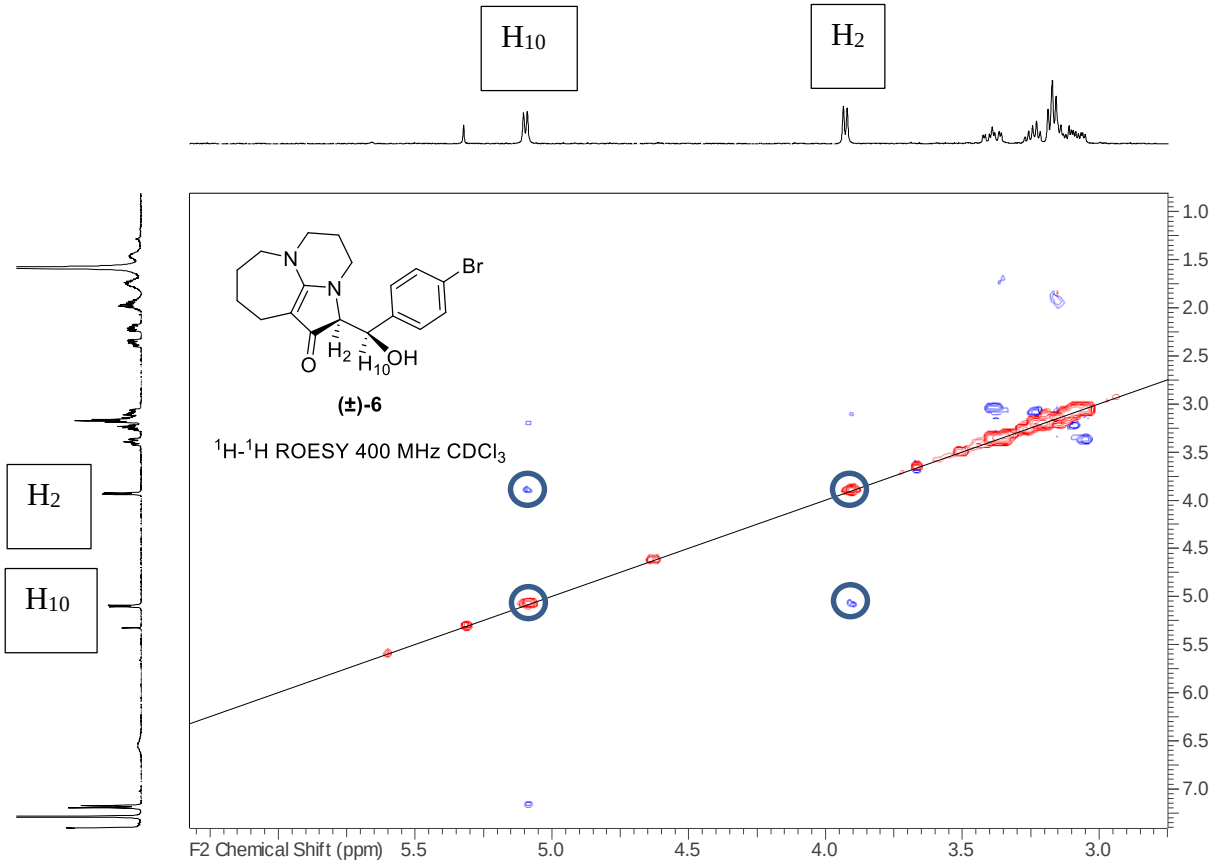
5

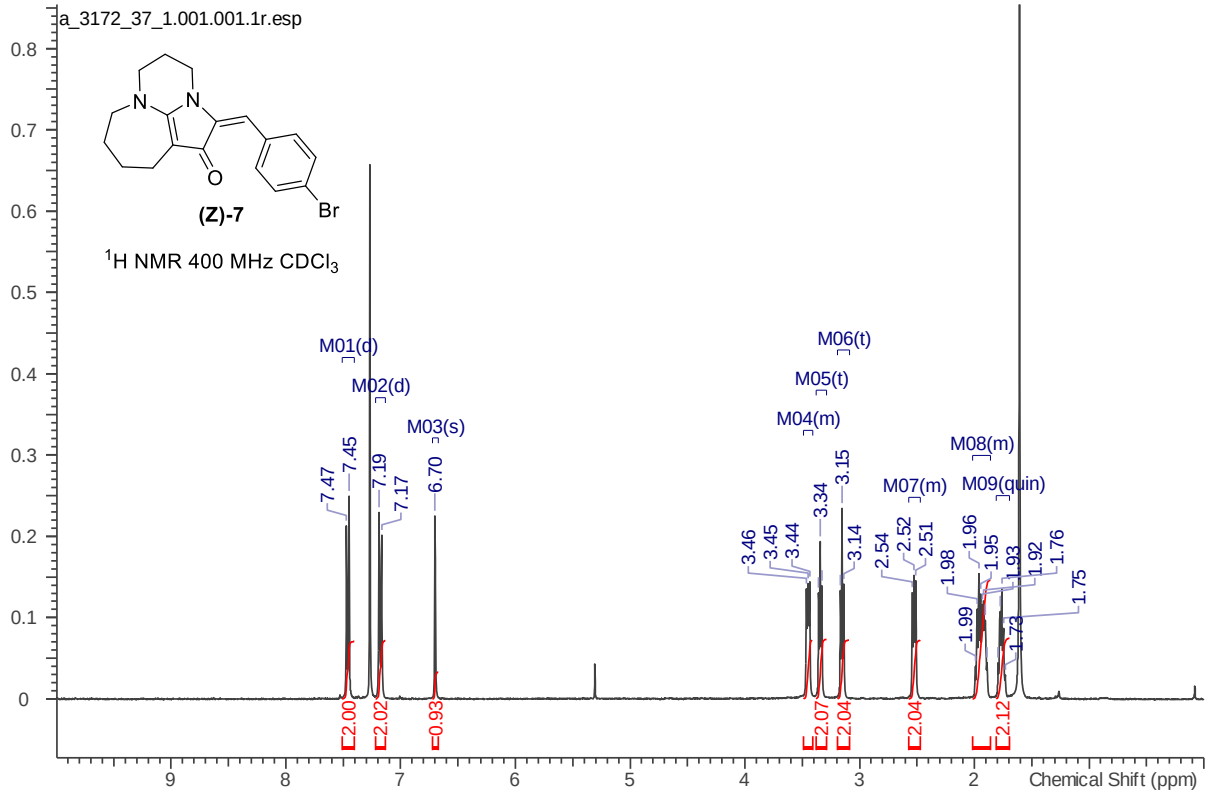
^{1}H NMR 500 MHz $CDCl_3$

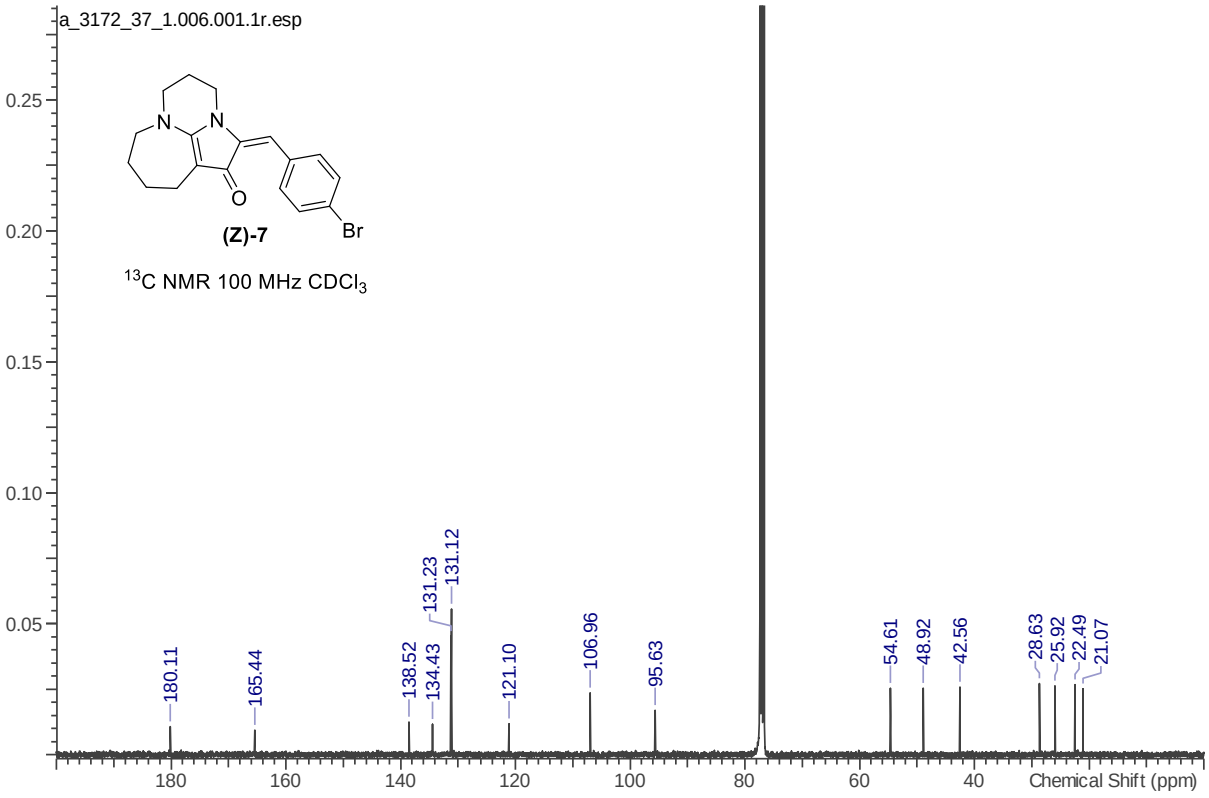

188.217
169.370
95.800
77.266
77.042
76.758
57.757
53.676
48.692
41.849
28.722
25.740
22.131
20.773
N
N
O
5
^{13}C NMR 126 MHz $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

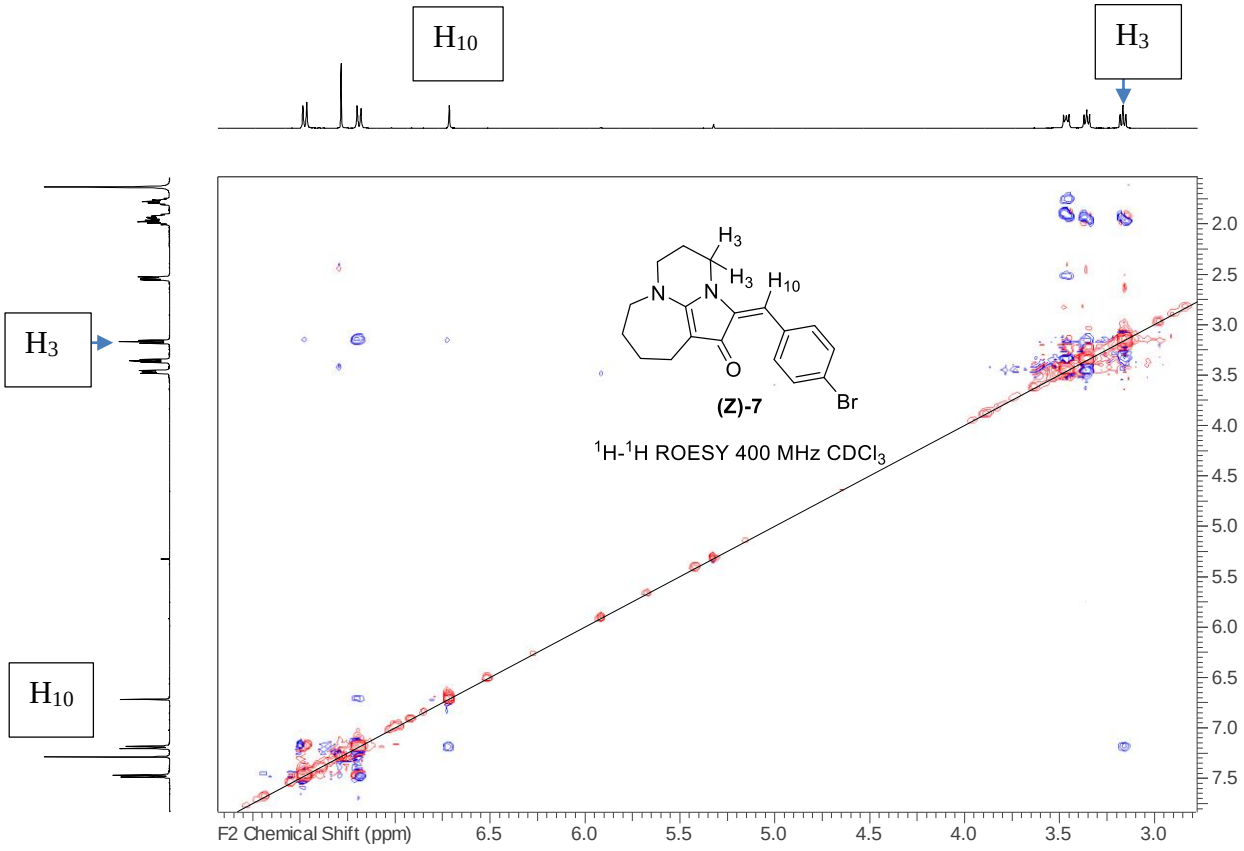

a_3172_37_2.001.001.1r.esp
N
N
Br
O
OH
(±)-6
^{1}H NMR 400 MHz $CDCl_3$
M01(d)
M02(d)
M03(d)
M04(d)
M05(ddd)
M06(m)
M07(m)
M09(m)
M10(m)
M11(m)
M12(br. s.)
M13(m)
7.42
7.40
7.19
7.17
6.52
5.10
5.09
3.93
3.92
3.26
3.23
3.19
3.17
3.16
3.14
3.11
3.10
1.99
1.98
1.97
1.95
1.76
1.75
1.74
1.72
1.46
2.00
1.96
0.68
0.97
1.00
1.06
3.95
1.05
1.99
2.11
1.54
Chemical Shift (ppm)


a_3172_37_2.007.001.1r.esp
Br
N
N
O
OH
(±)-6
^{13}C NMR 100 MHz $CDCl_3$
188.68
169.29
139.41
130.97
130.64
128.40
121.35
96.77
72.59
66.30
52.95
48.22
40.40
28.05
25.14
21.86
19.84
Chemical Shift (ppm)


H10
H2
Br
N
N
O
H2
H10
OH
(±)-6
^{1}H-^{1}H ROESY 400 MHz $CDCl_3$
H2
H10
F2 Chemical Shift (ppm)


a_3172_37_1.001.001.1r.esp
(Z)-7
^{1}H NMR 400 MHz $CDCl_3$
M01(d)
M02(d)
M03(s)
M04(m)
M05(t)
M06(t)
M07(m)
M08(m)
M09(quin)
7.47
7.45
7.19
7.17
6.70
3.46
3.45
3.44
3.34
3.15
3.14
2.54
2.52
2.51
1.98
1.96
1.95
1.93
1.92
1.76
1.75
1.99
1.73
2.00
2.02
0.93
2.07
2.04
2.04
2.12
Chemical Shift (ppm)


a_3172_37_1.006.001.1r.esp
(Z)-7
^{13}C NMR 100 MHz $CDCl_3$
180.11
165.44
138.52
134.43
131.23
131.12
121.10
106.96
95.63
54.61
48.92
42.56
28.63
25.92
22.49
21.07
Chemical Shift (ppm)


H10
H3
H3
H10
H3
H3
H10
N
N
O
Br
(Z)-7
1H-1H ROESY 400 MHz CDCl3
F2 Chemical Shift (ppm)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5