

eman ta zabal zazu



Universidad
del País Vasco

Euskal Herriko
Unibertsitatea

Stereoselective Synthesis of Secondary and Tertiary Amines through Brønsted Base Assisted Mannich, Nitro-Mannich and α -Amination Reactions

DOCTORAL THESIS

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Ama, Aita... zuei esker eta zuentzat

ESKERRAK

Esta Tesis Doctoral ha sido realizada en el Departamento de Química Orgánica I de la Facultad de Química de Donostia, Universidad del País Vasco (UPV/EHU), bajo la dirección del Dr. Claudio Palomo Nicolau, a quien expreso mi gratitud por la oportunidad, dedicación y esfuerzo brindados, y la Dra. Rosa M^a López Álvarez, pilar fundamental de este trabajo, a quien estoy totalmente agradecido por todo su apoyo, tanto en lo profesional como en lo personal, por su dedicación y pasión con la que me ha enseñado todo lo aprendido y por toda la confianza depositada en mí desde el primer día. ¡¡Muchísimas gracias!!

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Labokideei, eskerrik asko guztiagatik!! Zuen laguntza, barreak, negarrak, bazkariak, karameloak, abestiak, dantzak, besarkadak, marmarrak, juergak, eztulak, oihuak... ez ditut inoiz ahaztuko. Zuek ezagutu eta bidelagun izatea, ibilbide honetako onena izan da!! Eskerrik asko benetan!!!

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Matte zaituztet!!

SUMMARY

Chiral amines, structures with a carbon stereocenter adjacent to an amino group, are widely present as pharmaceutical or agrochemical compounds as well as natural products. In addition, they are also employed as ligands or catalysts in organic synthesis.

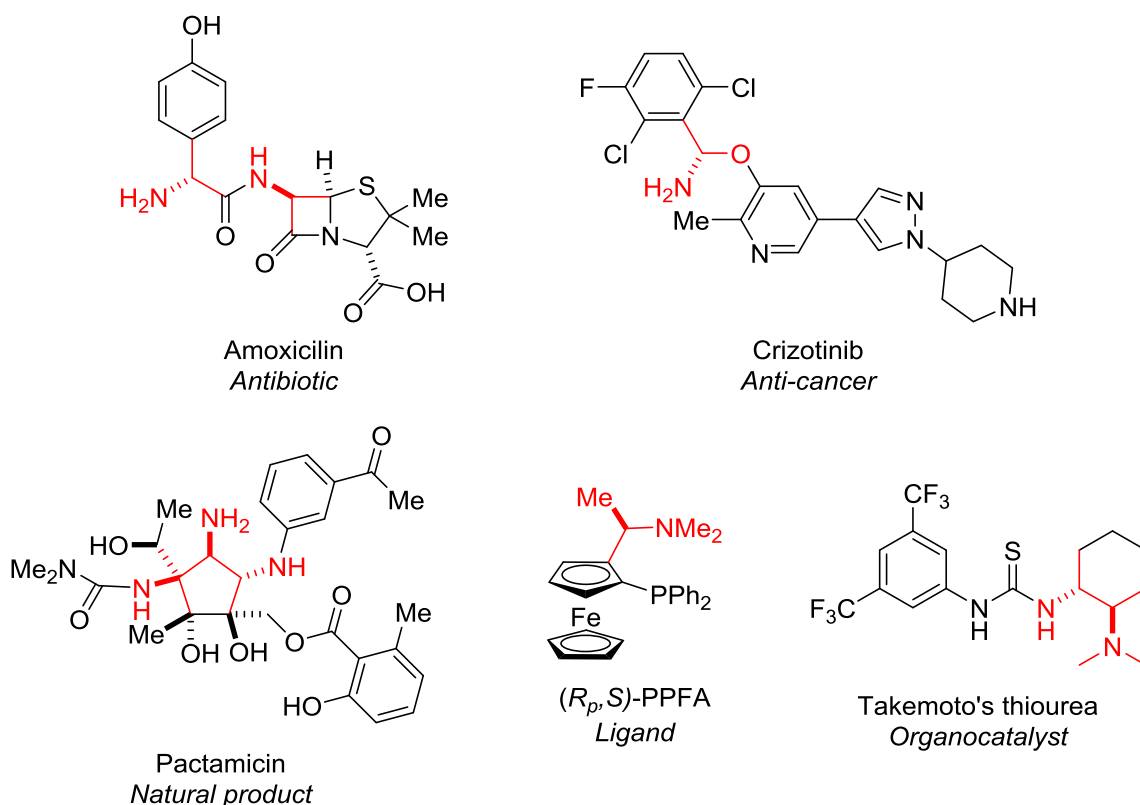
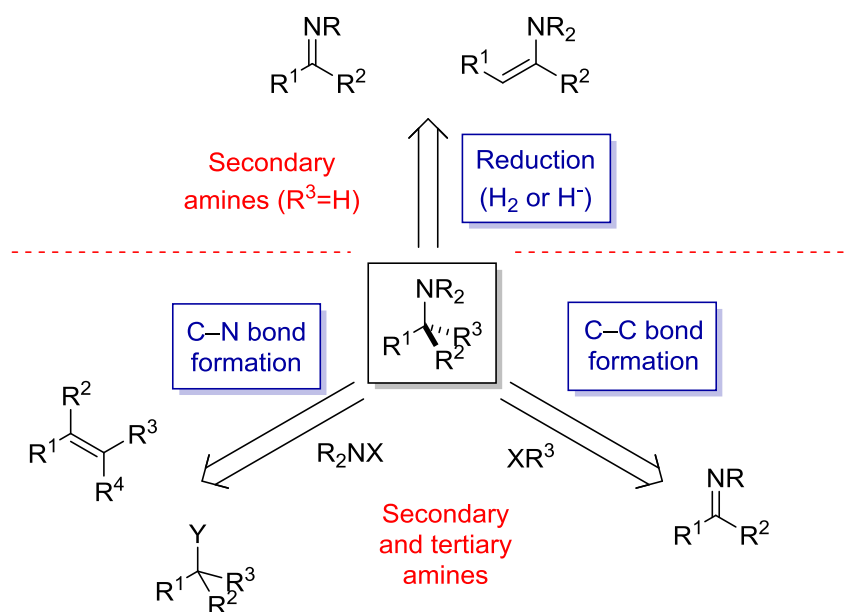


Figure 1. Representative examples of chiral amines as drugs, natural products, ligands and catalysts.

The interest of chiral amines has led to the development of several catalytic asymmetric methodologies for their synthesis during the last years. The main strategies are based, on the one hand, on reductive methods which provide exclusively secondary amines and, on the other hand, on C–C or C–N bond forming methodologies for the synthesis of secondary and tertiary amines (Scheme 1). Hydroamination and amination reactions are among the most popular approaches for C–N generation, whereas the stereoselective addition of carbon (pro)nucleophiles to azomethine groups is the one for C–C bond formations.

Summary

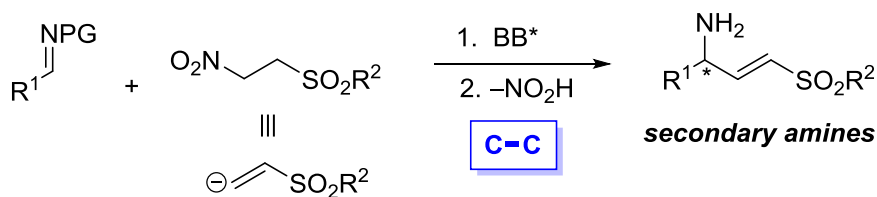


Scheme 1. Main strategies for chiral amine synthesis.

In this context, the main objective of this Ph. D. Thesis has been the development of new Brønsted base catalyzed methodologies for the synthesis of enantiomerically enriched secondary and tertiary amines of synthetic utility and with possible biological activity.

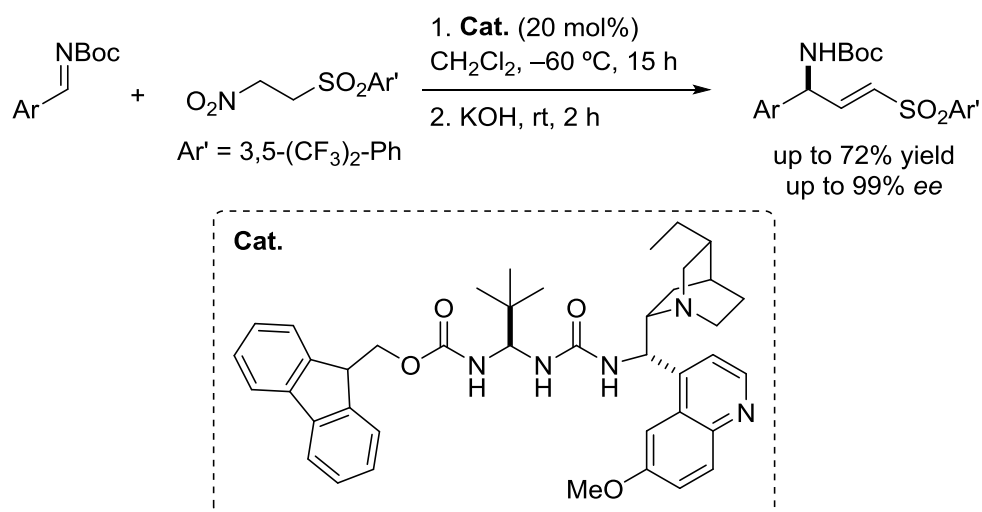
Many structures derived from enantiomerically pure γ -sulfonyl allyl amines have shown capacity to inhibit a wide variety of enzymatic processes. The structural requirements for an optimal enzyme-substrate recognition are still unknown and the elaboration of this type of structures could lead to the identification of more specific inhibitors or ones with better pharmacological properties. Nevertheless, there are practically no methodologies for their synthesis through catalytic enantioselective procedures. For that purpose, we envisioned that 2-nitroethyl sulfones could be employed as vinyl sulfone anion synthetic equivalents in chiral Brønsted base catalyzed nitro-Mannich type reactions to produce, after nitrous acid elimination, enantiomerically enriched secondary amines (Scheme 2). This approach would lead to the formation of the C–C bond and the new stereogenic center in a single step, which is a great advantage over the methodologies described to date.

Summary



Scheme 2. Synthetic plan for the enantioselective preparation of γ -sulfonyl allyl amines. *BB: chiral Brønsted base.

Based on this hypothesis, we have developed an enantioselective methodology for the nitro-Mannich reaction of 2-nitroethyl sulfones with *N*-Boc imines, catalyzed by a ureidopeptide-based bifunctional Brønsted base. The subsequent nitrous acid elimination affords the corresponding γ -sulfonyl allyl amines in variable yields and with generally excellent enantioselectivities (Scheme 3).



Scheme 3. Enantioselective synthesis of γ -sulfonyl allyl amines.

On the other hand, *ortho*-substituted pyridines are common fragments in chiral compounds with biological activity. In particular, α - and/or β -functionalized pyridines containing amino groups constitute a relevant family (Figure 2).

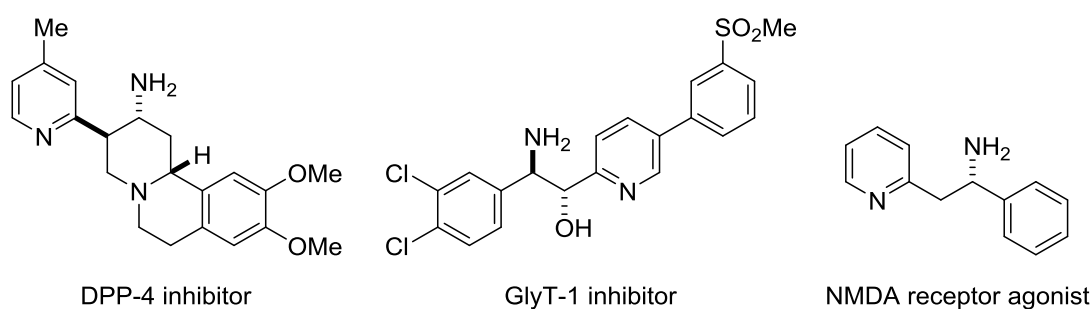
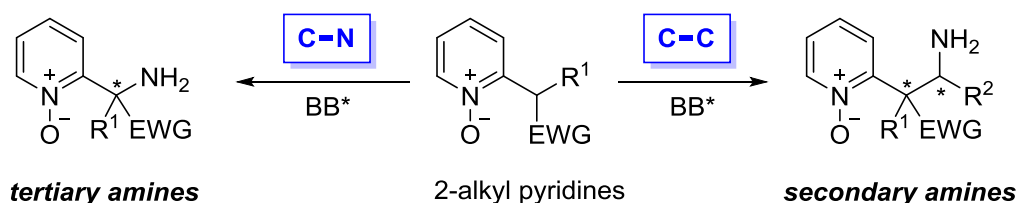


Figure 2. Representative examples of pyridines containing amino groups with biological activity.

Summary

In order to address the stereoselective synthesis of this type of chiral amines, we considered that 2-alkyl pyridines could be employed as pronucleophiles in chiral Brønsted base-catalyzed C–N and C–C bond forming reactions; in particular, the α -amination reaction for the preparation of tertiary amines and the Mannich-type reaction for the synthesis of secondary amines (Scheme 4).



Scheme 4. Synthetic plan for the stereoselective preparation of pyridine based amines. EWG: electron-withdrawing group.

To date, the main limitation of 2-alkyl azaarenes as pronucleophiles in catalytic asymmetric reactions is their low acidity, thus, generally stoichiometric amounts of base are required. On the other hand, no methodologies for the generation of tetrasubstituted stereogenic centers, which would afford chiral tertiary amines, have been described.

In order to enhance the low reactivity of 2-alkyl pyridines under basic conditions, we considered to employ 2-alkyl pyridine *N*-oxides as their synthetic equivalents. It is well known that the oxidation of the pyridine increases the acidity of the carbon at α position (Figure 3). Moreover, the *N*-oxide group could act as an additional coordinating site for the catalyst binding and provide more rigid transition states.

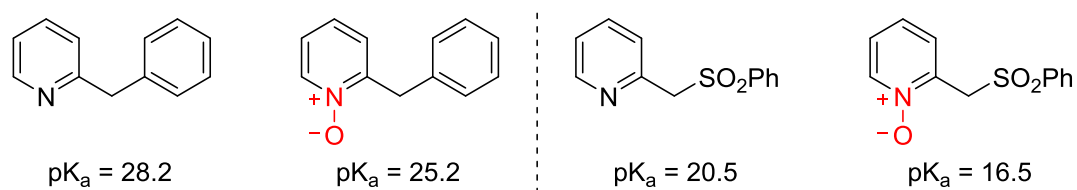
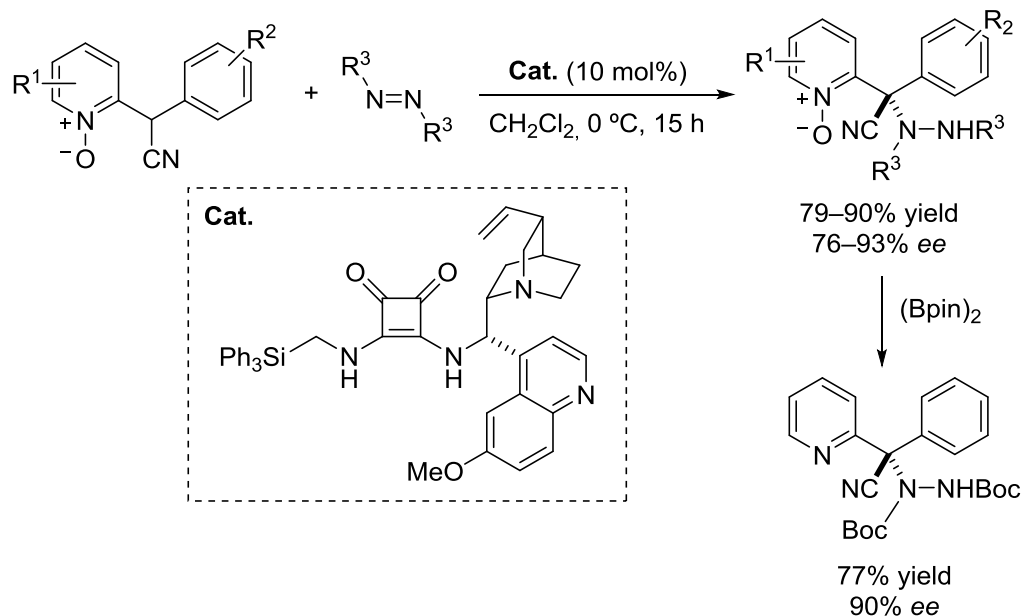


Figure 3. pK_a values for pyridine derivatives and their *N*-oxides.

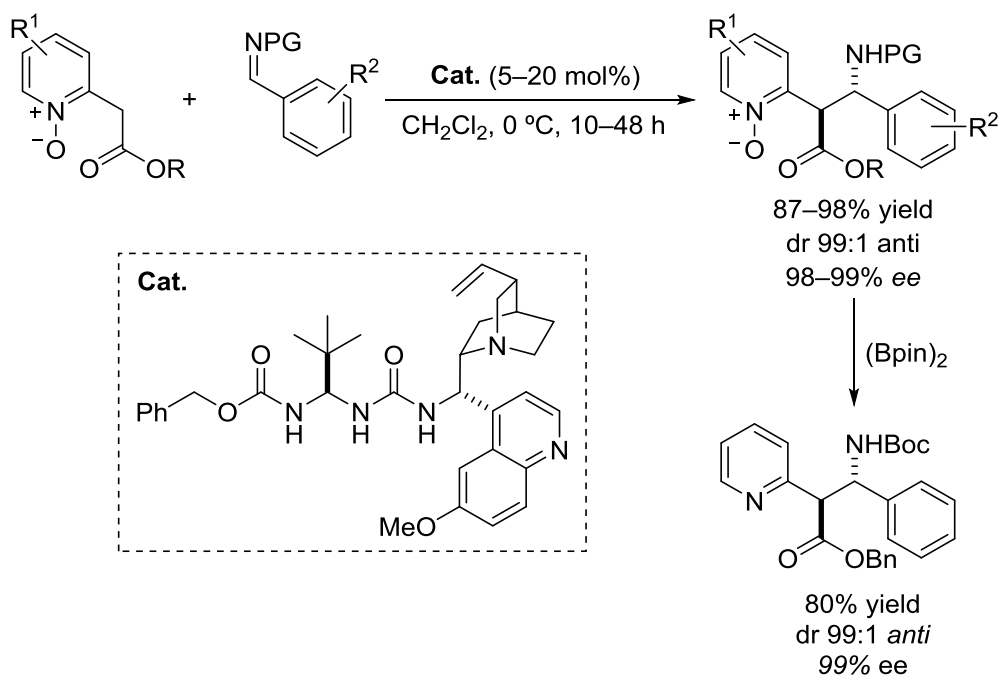
Hence, we have developed a methodology for the enantioselective synthesis of tertiary amines through α -amination of 2-cyanoalkyl pyridine *N*-oxides catalyzed by a novel squaramide-based Brønsted base bearing a bulky silyl group. The reduction of the adducts affords the corresponding enantiomerically enriched pyridine based tertiary amines (Scheme 5).

Summary



Scheme 5. Enantioselective synthesis of pyridine based tertiary amines (*JACS* **2016**, *138*, 3282–3285).

Likewise, we have developed a highly stereoselective Mannich-type reaction of 2-azaaryl acetate *N*-oxides with *N*-carbamoyl aldimines for the synthesis of pyridine based chiral secondary amines (Scheme 6). In this case, the ureidopeptide-based Brønsted base employed, not only provides excellent levels of asymmetric induction but is also able to preserve the configurational stability of the new generated tertiary stereocenters during the reaction.

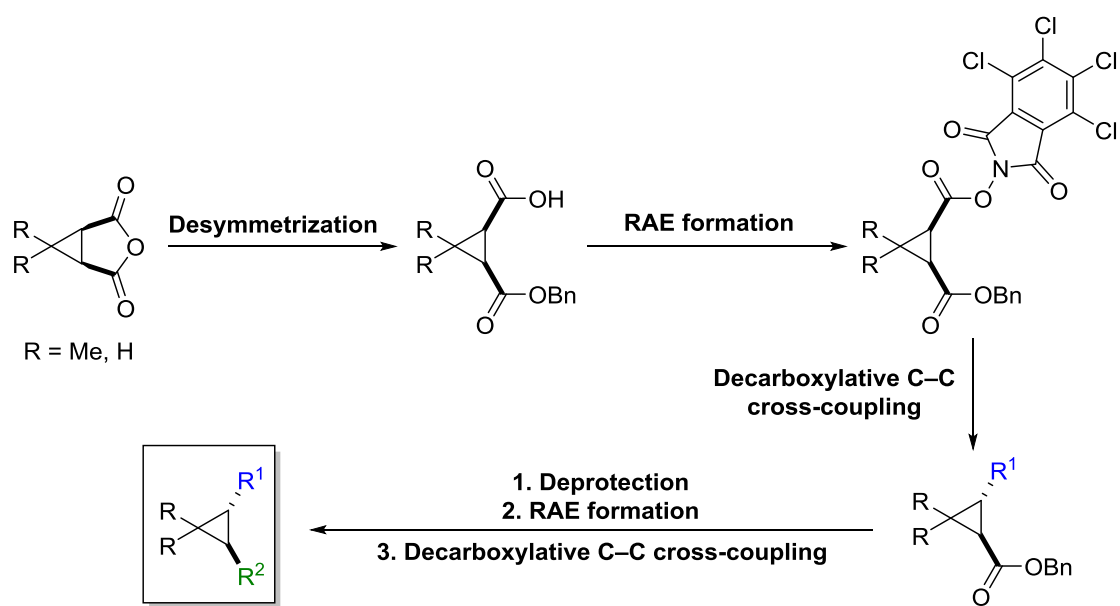


Scheme 6. Stereoselective synthesis of pyridine based secondary amines (*Chem. Eur. J.* **2017**, *23*, 13332–13336).

Summary

In both cases, the dual role of the *N*-oxide functionality as an activating and stereodirecting group has been proved since the parent 2-alkyl pyridines reacted sluggishly and with diminished stereoselectivities.

Finally, during a short stay at The Scripps Research Institute in La Jolla (California, USA), under the supervision of Prof. Baran, a synthetic strategy for the enantio- and diastereoselective modular preparation of *trans*-disubstituted cyclopropanes has been developed by the combination of the following reactions: i) desymmetrization of the caronic or 1,2-cyclopropanecarboxylic anhydride, ii) formation of the redox-active ester, iii) C–C cross-coupling, iv) hydrolysis, v) formation of the redox-active ester, and vi) subsequent C–C cross-coupling (Scheme 7).



Scheme 7. Synthetic plan for the modular and stereoselective preparation of *trans*-disubstituted cyclopropanes. RAE: redox-active ester.

For that purpose, the optimization of nickel catalyzed Negishi and Suzuki decarboxylative cross-coupling reactions has been carried out and the synthesis of a series of highly enantioenriched *trans*-disubstituted cyclopropanes has been successfully accomplished (Figure 4).

Summary

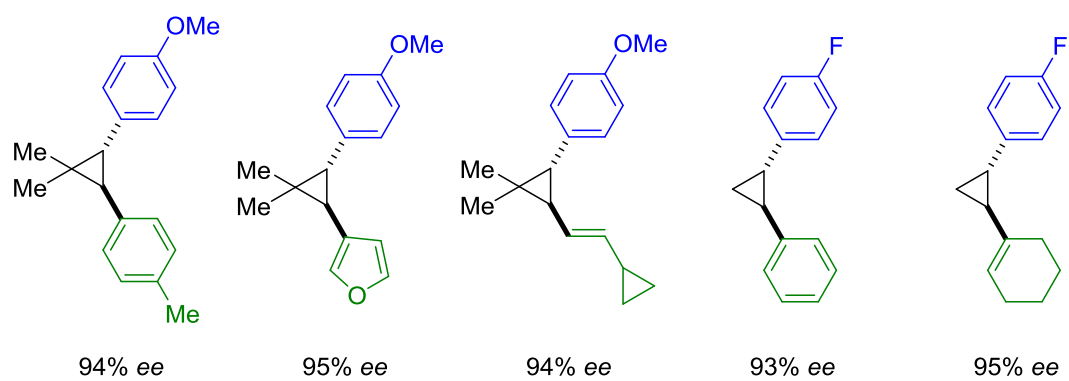


Figura 4. Synthesized *trans*-disubstituted cyclopropanes (*Nature* **2018**, *560*, 350–354).

RESUMEN

Las aminas quirales, por la presencia de un carbono estereogénico en la posición α , son estructuras muy frecuentes tanto en productos farmacéuticos y agroquímicos, como en productos naturales. Asimismo, también son ampliamente empleadas como ligandos y catalizadores en síntesis orgánica (Figura 1).

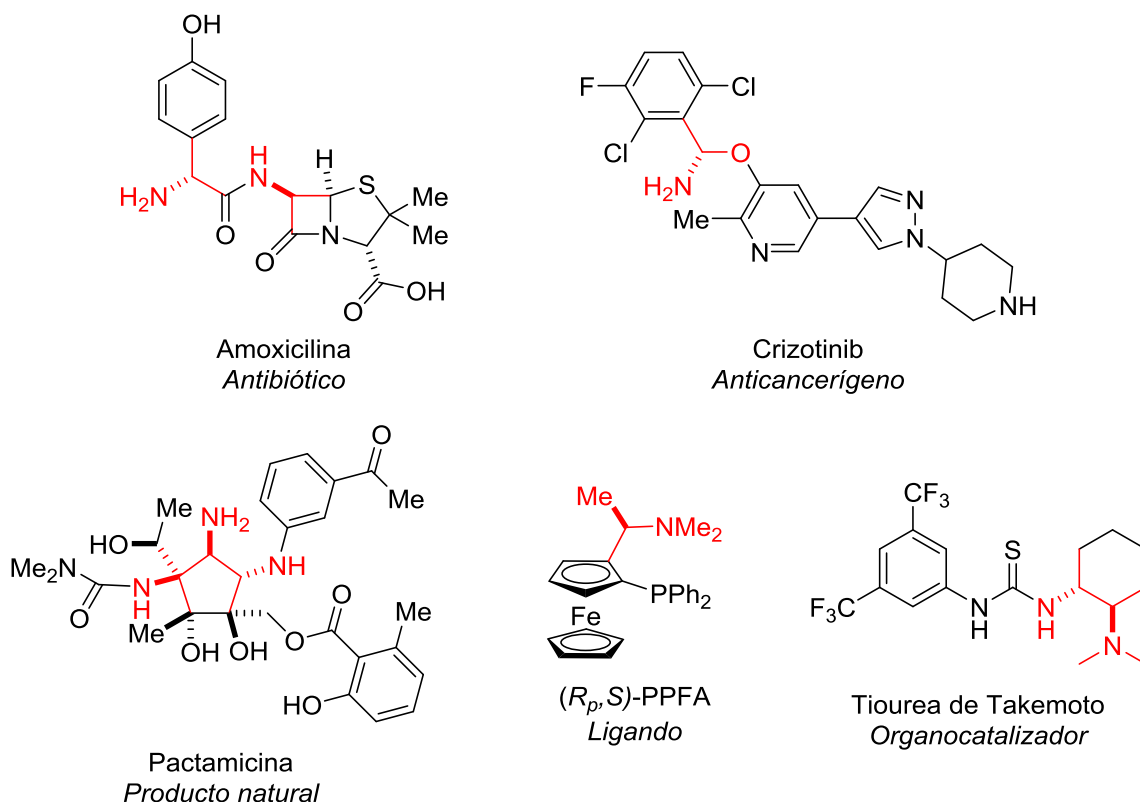
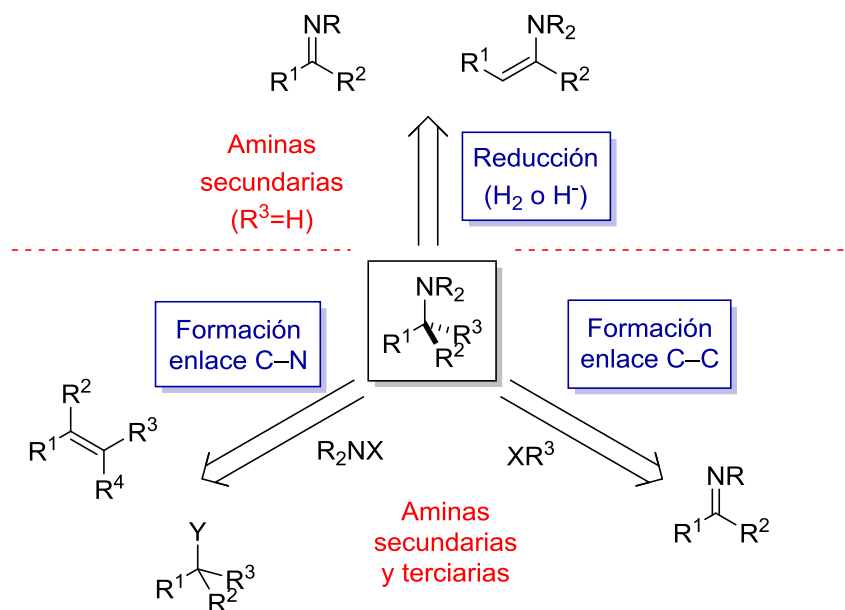


Figura 1. Ejemplos representativos de aminas quirales como fármacos, productos naturales, ligandos y catalizadores.

En los últimos años, el interés por estas estructuras ha motivado el desarrollo de un gran número de metodologías catalíticas y asimétricas. Las principales estrategias para la síntesis de este tipo de aminas quirales se centran, por un lado, en métodos reductores que conducen exclusivamente a la formación de aminas secundarias y, por otro lado, en metodologías de formación de enlaces C–C o C–N para la síntesis de aminas secundarias y terciarias (Esquema 1). Las reacciones de hidroaminación y aminación son las transformaciones más empleadas para la generación de enlaces C–N, mientras que la adición de (pro)nucleófilos carbonados a grupos azometino constituye la estrategia más relevante para la formación de enlaces C–C.

Resumen

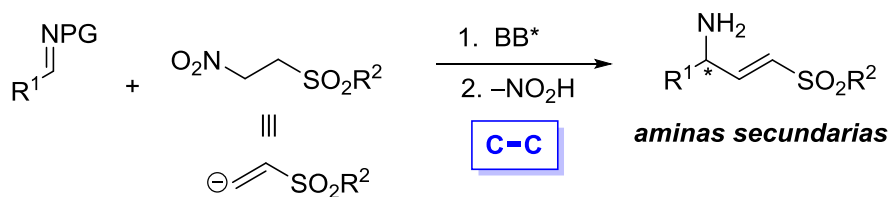


Esquema 1. Estrategias principales para la síntesis de aminas quirales.

En este contexto, el objetivo principal de esta Tesis Doctoral ha sido el desarrollo de nuevas metodologías de formación de enlaces C–C y C–N, catalizadas por bases de Brønsted quirales, para la síntesis de aminas secundarias y terciarias enantioméricamente enriquecidas con utilidad sintética y posible actividad biológica.

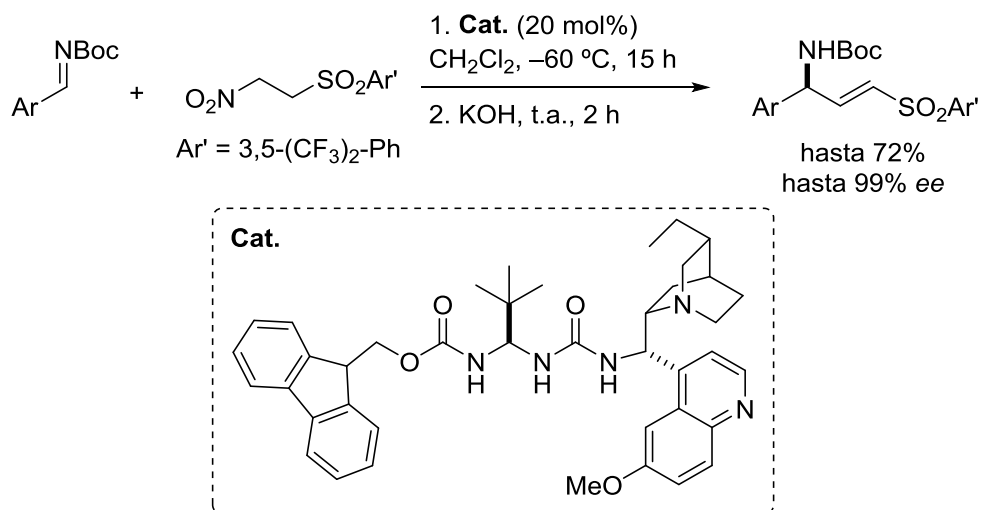
Varias estructuras derivadas de γ -sulfonil alil aminas enantioméricamente puras han demostrado tener capacidad para inhibir una amplia variedad de procesos enzimáticos. Los requisitos estructurales para un reconocimiento enzima–sustrato óptimo son aún desconocidos y la elaboración de este tipo de estructuras podría llevar a la identificación de inhibidores más específicos o con mejores propiedades farmacológicas. Sin embargo, no existen prácticamente metodologías que permitan su síntesis mediante procedimientos catalíticos y asimétricos. Con este propósito, consideramos que las 2-nitroetil sulfonas podrían emplearse como equivalentes sintéticos del anión vinil sulfona en reacciones de tipo nitro-Mannich catalizadas por bases de Brønsted quirales, para producir, tras la eliminación del ácido nitroso, aminas secundarias enantioméricamente enriquecidas (Esquema 2). Esta aproximación conduciría a la formación del enlace C–C y el nuevo centro estereogénico en una sola etapa, lo que supone una gran ventaja sobre las metodologías descritas hasta la fecha.

Resumen



Esquema 2. Plan sintético para la preparación enantioselectiva de γ -sulfonil alil aminas. BB*: base de Brønsted quiral.

Basada en esta hipótesis, ha sido posible desarrollar una metodología enantioselectiva para la reacción nitro-Mannich entre 2-nitroetil sulfonas y *N*-Boc iminas, catalizada por una base de Brønsted bifuncional de tipo ureidopeptídico. La posterior eliminación del ácido nitroso proporciona las γ -sulfonil alil aminas correspondientes con rendimientos variables y enantioselectividades generalmente excelentes (Esquema 3).



Esquema 3. Síntesis enantioselectiva de γ -sulfonil alil aminas.

Por otro lado, las piridinas *orto*-sustituidas son fragmentos muy comunes en compuestos quirales con actividad biológica. En particular, las piridinas α - y/o β -funcionalizadas que contienen grupos amino constituyen una familia importante (Figura 2).

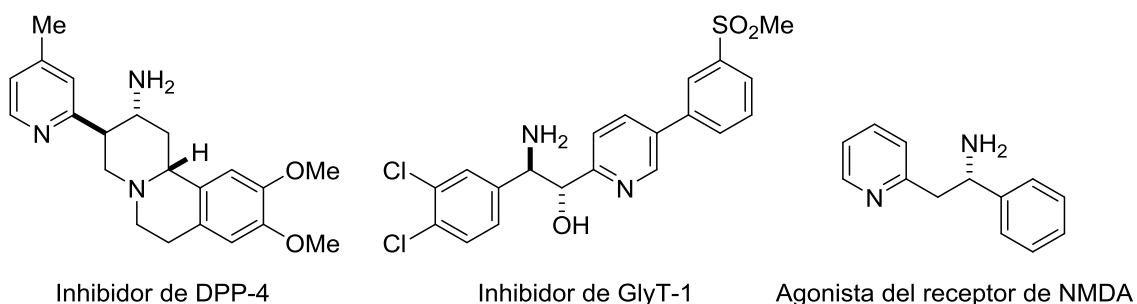
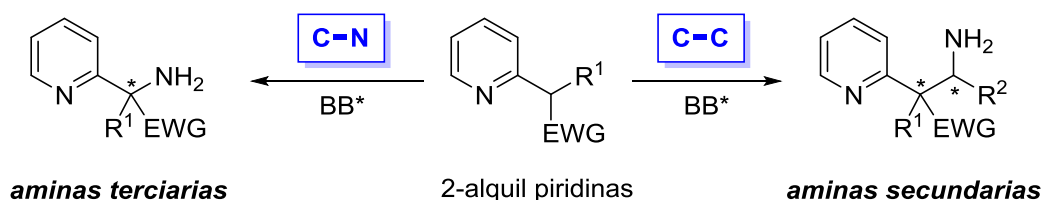


Figura 2. Ejemplos representativos de piridinas con actividad biológica que contienen grupos amino.

Resumen

Para abordar la síntesis estereoselectiva de este tipo de aminas quirales, consideramos factible el empleo de 2-alkil piridinas como pronucleófilos en reacciones de formación de enlaces C–N y C–C catalizadas por bases de Brønsted quirales; en concreto, la reacción de α -aminación para producir aminas terciarias y la reacción de tipo Mannich para la obtención de aminas secundarias (Esquema 4).



Esquema 4. Plan sintético para la síntesis estereoselectiva de aminas terciarias y secundarias. EWG: grupo electron-atractor.

Hasta la fecha, el empleo de 2-alkil azaarenos como pronucleófilos en reacciones catalíticas y asimétricas presenta como principal limitación su baja acidez, lo que generalmente requiere el empleo de cantidades estequiométricas de base. Por otro lado, no se han descrito métodos para la generación de centros estereogénicos tetrasustituidos que darían lugar a aminas terciarias quirales.

Con el objeto de aumentar la baja reactividad de las 2-alkil piridinas en condiciones básicas, se eligieron los *N*-óxidos de 2-alkil piridina como equivalentes sintéticos. Es conocido que la oxidación de la piridina produce un aumento de la acidez del carbono en la posición α (Figura 3). Además, el grupo *N*-óxido podría funcionar como un punto de anclaje adicional en la coordinación con el catalizador y, de este modo, proporcionar mayor rigidez a los estados de transición.

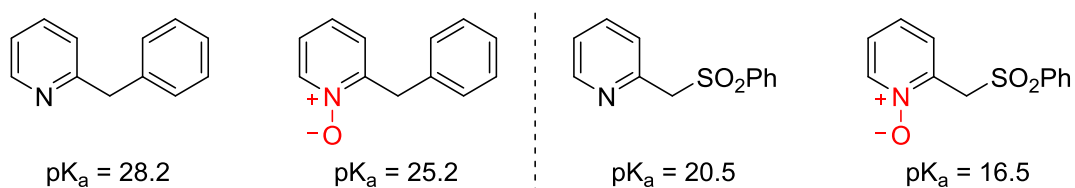
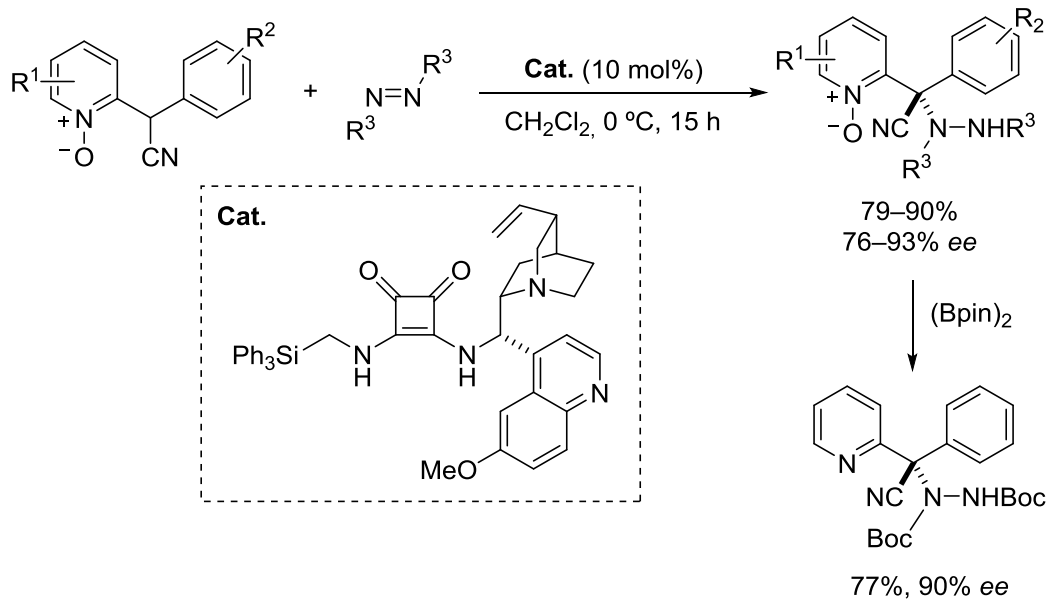


Figura 3. Valores de pK_a de derivados de piridina y sus correspondientes *N*-óxidos.

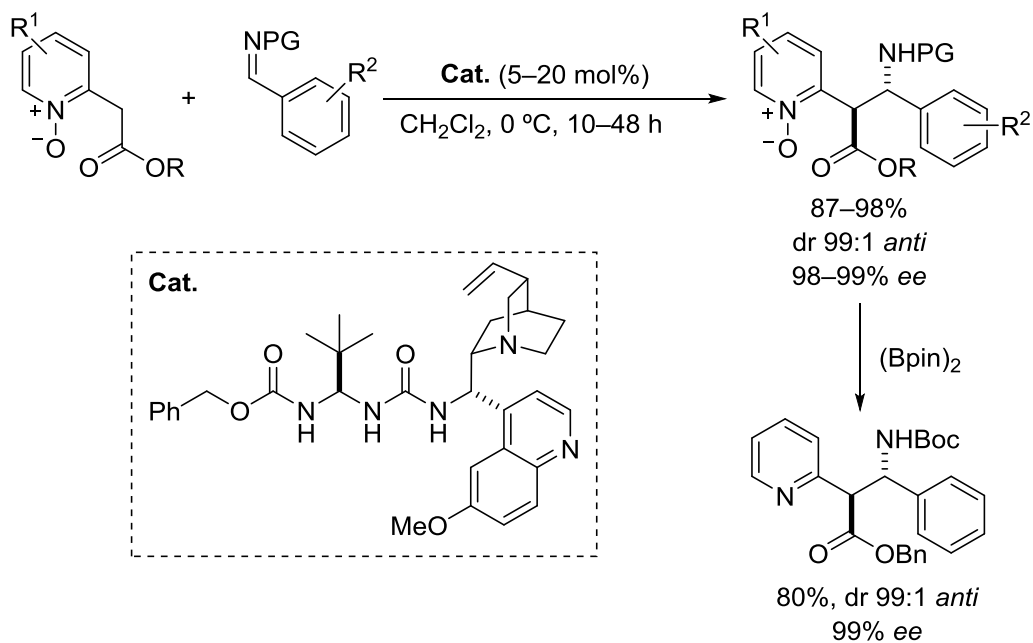
De este modo, se ha desarrollado una metodología que permite la síntesis enantioselectiva de aminas terciarias mediante la α -aminación de *N*-óxidos de 2-cianoalkil piridina promovida por una nueva base de Brønsted bifuncional de tipo escuaramida que contiene un grupo sililo voluminoso. La reducción de los aductos proporciona las correspondientes aminas terciarias de piridina altamente enantioenriquecidas (Esquema 5).

Resumen



Esquema 5. Síntesis enantioselectiva de aminas terciarias (*JACS* **2016**, *138*, 3282–3285).

De forma análoga, se ha desarrollado una reacción de tipo Mannich altamente estereoselectiva entre *N*-óxidos de acetato de 2-azaarilo y *N*-carbamoil aldiminas que proporciona aminas secundarias altamente enantioenriquecidas (Esquema 6). En este caso, la base de Brønsted de tipo ureidopeptídico empleada no solo proporciona excelentes niveles de inducción asimétrica, sino que es capaz de preservar la estabilidad configuracional de los estereocentros terciarios generados durante la reacción.

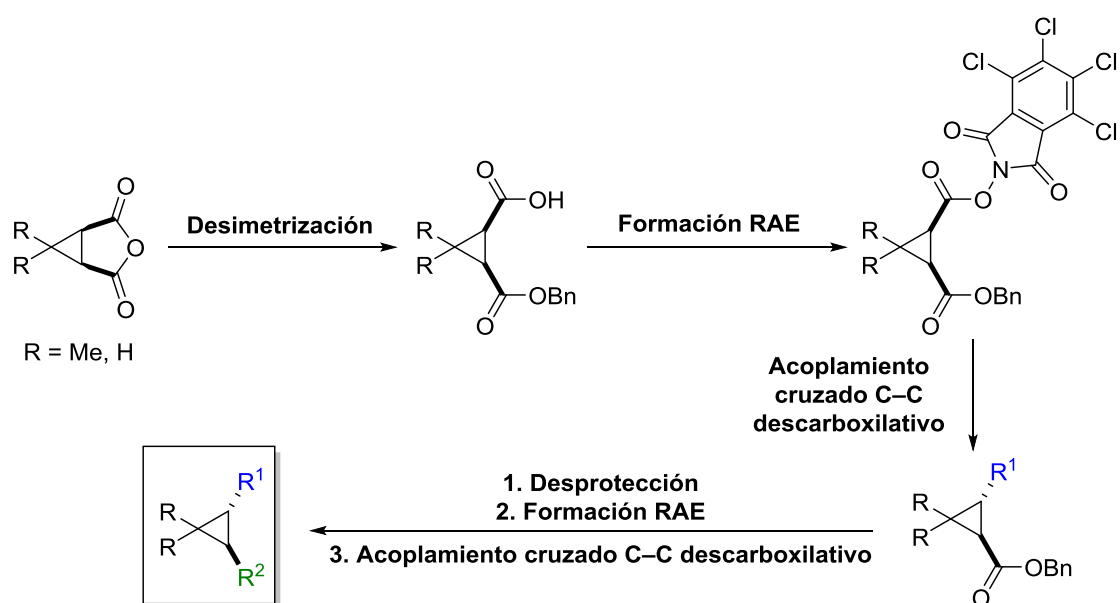


Esquema 6. Síntesis enantioselectiva de aminas secundarias (*Chem. Eur. J.* **2017**, *23*, 13332–13336).

Resumen

En ambos casos, el papel dual del *N*-óxido como grupo activante y estereodirector ha sido corroborado, puesto que, empleando las mismas condiciones de reacción, las 2-alquil piridinas análogas reaccionaron más lentamente y con enantioselectividades inferiores.

Finalmente, durante una estancia realizada en The Scripps Research Institute en La Jolla (California, USA), bajo la supervisión del Prof. Baran, se ha desarrollado una estrategia sintética para la preparación modular diastereo- y enantioselectiva de ciclopropanos *trans*-disustituidos mediante la combinación de las siguientes reacciones: i) desimetrización del anhídrido carónico o 1,2-ciclopropanodicarboxílico, ii) formación del éster redox-activo, iii) acoplamiento cruzado C–C, iv) desprotección, v) formación del éster redox-activo y vi) segundo acoplamiento cruzado C–C (Esquema 7).



Esquema 7. Plan sintético para la preparación modular y estereoselectiva de ciclopropanos *trans*-disustituidos. RAE: éster redox-activo.

Con este propósito, se ha llevado a cabo la optimización de reacciones de acoplamiento cruzado descarboxilativo de tipo Negishi y Suzuki catalizadas por níquel y se ha logrado la síntesis de una serie de ciclopropanos *trans*-disustituidos altamente enantioenriquecidos (Figura 4).

Resumen

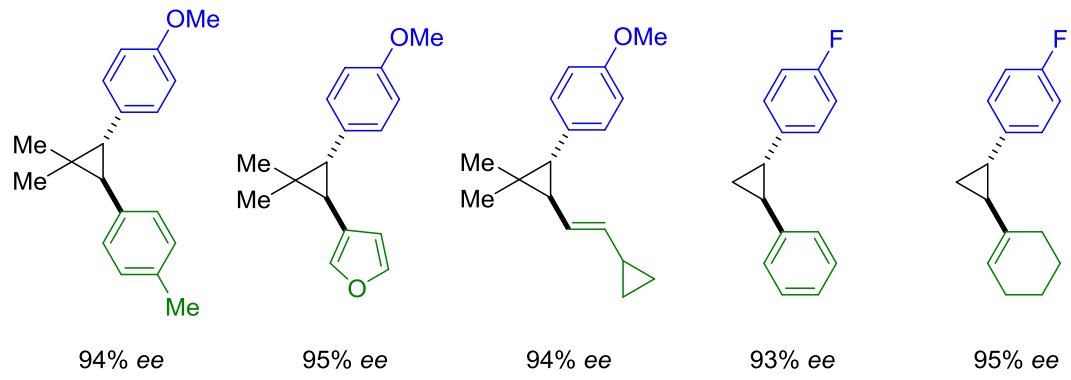


Figura 4. Ciclopropanos *trans*-disustituidos sintetizados (*Nature* **2018**, *560*, 350–354).

ABBREVIATIONS AND ACRONYMS

Standard abbreviations and acronyms have been used as recommended in “Guidelines for authors” (*J. Org. Chem.*, January 2015).

AA	Amino acid
Ac	Acetyl group
acac	Acetyl acetonate
APAQ	Acetyl-protected aminoethyl quinoline
Ar	Aryl group
B	Base
BB*	Chiral Brønsted base
BDPP	2,4-Bis(diphenylphosphino)pentane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEP	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl
Bn	Benzyl group
Boc	<i>tert</i> -Butyloxycarbonyl group
BPhen	Bathophenanthroline
Bu	Primary butyl group
calcd.	Calculated
Cat.	Catalyst
Cbz	Carboxybenzyl group
CNS	Central nervous system
conv.	Conversion
Cy	Cyclohexyl group
d	Days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
(DHQD) ₂ AQN	Hydroquinidine (anthraquinone-1,4-diyl) diether
(DHQD) ₂ PHAL	Hydroquinidine 1,4-phthalazinediyl diether

Abbreviations and acronyms

(DHQD) ₂ Pyr	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIC	<i>N,N'</i> -diisopropylcarbodiimide
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
<i>ee</i>	Enantiomeric excess
<i>ent</i>	Opposite enantiomer
Ent.	Entry
Et	Ethyl group
equiv.	Equivalent
EWG	Electron-withdrawing group
Fmoc	9-Fluorenylmethoxycarbonyl
GC	Gas chromatography
glyme	1,2-Dimethoxyethane
h	Hours
HMDS	Hexamethyl disilazane
HMPA	Hexamethyl phosphoramide
HPLC	High pressure liquid chromatography
<i>i</i> Pr	<i>iso</i> -Propyl group
L	Ligand
LC	Liquid chromatography
M	Metal
major.	Majority
Me	Methyl group
min	Minutes

Abbreviations and acronyms

minor.	Minority
MS	Molecular sieves or Mass spectrometry
Naph	Naphthyl
<i>n</i> -Bu	Primary butyl group
n.d.	Not determined or Not detected
NHPI	<i>N</i> -Hydroxyphthalimide
NMI	<i>N</i> -Methyl imidazole
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Ns	<i>para</i> -Nitrobenzenesulfonyl group
ox.	Oxidation
PG	Protecting group
Ph	Phenyl group
pin	Pinacol group
Piv	Pivaloyl group
PMP	<i>para</i> -methoxyphenyl group
PPFA	<i>N,N</i> -dimethyl-1-[2-(diphenylphosphino)-ferrocenyl]ethylamine
PTC	Phase transfer catalysis
pTLC	Preparative thin layer chromatography
<i>p</i> -Tol	<i>para</i> -Tolyl group
py	Pyridine
RAE	Redox-active ester
rt	Room temperature
SET	Single electron transfer
SFC	Supercritical fluid chromatography
T	Temperature
<i>t</i>	Time

Abbreviations and acronyms

<i>t</i> -Bu	<i>tert</i> -Butyl group
TCNHPI	Tetrachloro- <i>N</i> -hydroxyphthalimide
Tf	Trifluoromethanesulfonyl group
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMS	Trimethylsilyl group
Ts	<i>para</i> -Toluenesulfonyl group
TS	Transition state
UPLC	Ultra performance liquid chromatography
U.S. FDA	United States Food and Drug Administration

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1. INTRODUCTION

1.1. Chiral amines

1.1.1. General considerations

A vast majority of bioactive compounds, such as agrochemicals and active pharmaceutical ingredients, are amines or contain functional groups derived from amines. As an illustration, from 1086 unique small-molecule drugs approved by U.S. FDA in 2012, 910 (84%) contained at least one nitrogen atom, being 2.3 the average number of nitrogen atoms per drug.¹

During the past decades, the number of chiral and non-racemic amines that show biological activity has been increasing continuously. In fact, chiral amines are powerful pharmacophores for defining new pharmaceutical drugs due to their high density of structural information and inherent ability for hydrogen bonding.²

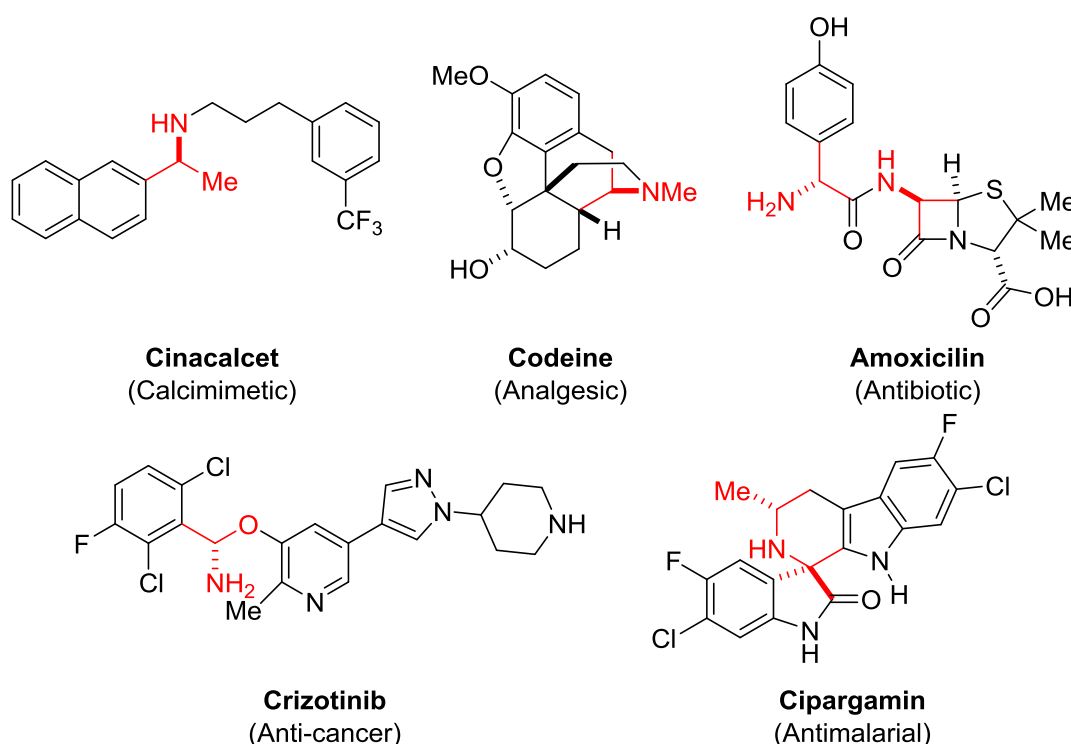


Figure 1. Examples of chiral amine-based pharmaceutical drugs.

¹ Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.

² a) *Chiral Amine Synthesis – Methods, Developments and Applications*; Nugent, T. C., Ed.; WILEY-VCH Verlag: Weinheim, 2010. b) *Stereoselective Formation of Amines*; Wang, C., Xiao, J., Eds.; Topics in Current Chemistry 343; Springer: Heidelberg, 2014.

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Figure 1 shows some examples of chiral amines used for the treatment of different diseases. Cinacalcet is used against hyperparathyroidism and hypercalcemia –high levels of calcium in the blood–.³ Codeine is an opioid used to treat severe pain,⁴ whereas amoxicillin is a penicillin antibiotic used against different types of infection caused by bacteria.⁵ In contrast, crizotinib is a cancer medication that interferes with the growth and spread of cancer cells in the body⁶ and cipargamin is an experimental synthetic antimalarial molecule.⁷

In addition, chiral amines can also be found in a wide variety of natural products (Figure 2). For instance, (–)-adaline acts as part of the defence system of the European ladybird, *Adalia bipunctata*, and has also been isolated from *Quadrifasciata* and *Patherina L.*⁸ The sesquiterpene aminobisabolene is an antimicrobial metabolite isolated from the tropical sponge, *Halichondria sp.*⁹ and the aminocyclopentitol pactamycin, which was isolated from *Streptomyces pactum var. pactum*, has recently displayed antitumor, antimicrobial, antiviral and antiprotozoal properties by acting as a universal inhibitor of translocation.¹⁰

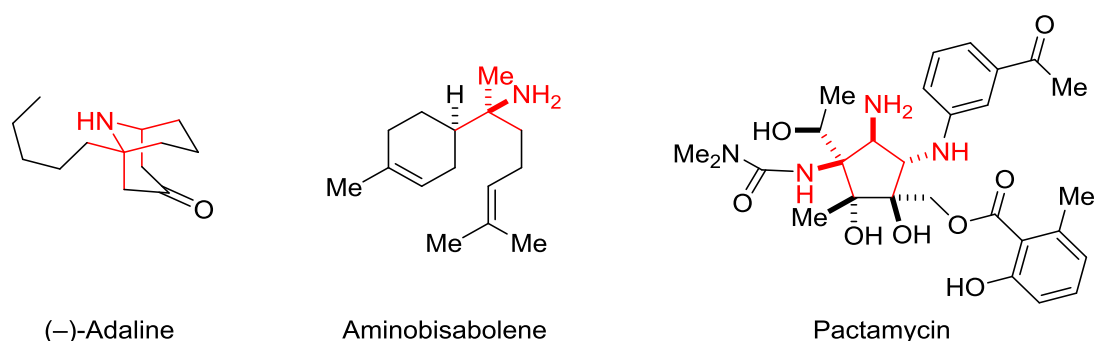


Figure 2. Examples of chiral amines found in nature.

³ <https://www.drugs.com/mtm/cinacalcet.html> (accessed May 3, 2018).

⁴ <https://www.drugs.com/codeine.html> (accessed May 3, 2018).

⁵ <https://www.drugs.com/amoxicillin.html> (accessed May 3, 2018).

⁶ <https://www.drugs.com/mtm/crizotinib.html> (accessed May 3, 2018).

⁷ Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Coher, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schimtt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T.; *Science* **2010**, *329*, 1175–1180.

⁸ Davison, E. C.; Holmes, A. B. *Tetrahedron Lett.* **1995**, *36*, 9047–9050.

⁹ Sullivan, B. W.; Faulkner, D. J.; Okamoto, K. T.; Chen, M. H. M.; Clardy, J. J. *Org. Chem.* **1986**, *51*, 5134–5136.

¹⁰ Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180–182.

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In this context, naturally occurring L- α -amino acids also constitute a very important type of chiral amines, which have an essential role as building blocks of oligopeptides and proteins.¹¹

Furthermore, chiral amines are also broadly used as chiral ligands or organocatalysts in asymmetric synthesis (Figure 3). For instance, chiral ferrocene P,N ligand PPFA was first developed by Hayashi and Kumada¹² and has been used in several metal catalyzed enantioselective transformations.¹³ Likewise, chiral acetyl-protected aminoethyl quinoline (APAQ) has been employed in enantioselective Pd catalyzed C(sp³)-H bond activations.¹⁴ On the other hand, diarylprolinol silyl ethers developed by Jørgensen and Hayashi¹⁵ and Takemoto's thiourea¹⁶ represent well-known organocatalysts used in asymmetric reactions.

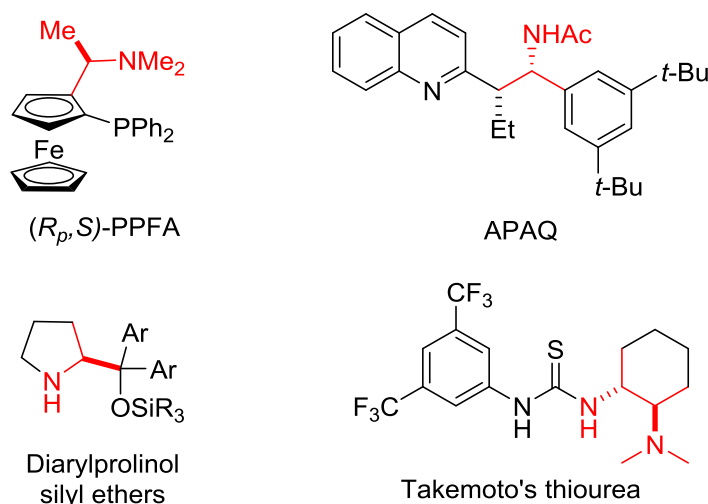


Figure 3. Examples of ligands and organocatalysts bearing chiral amines.

¹¹ α -Amino acid synthesis is a well-developed and extensively reviewed field that will not be discussed in the present thesis. For selected reviews, see: a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. b) Martens, J. *ChemCatChem* **2010**, *2*, 379–381. c) Luo, Y.-C.; Zhang, H.-H.; Wang, Y.; Xu, P.-F. *Acc. Chem. Res.* **2010**, *43*, 1317–1330. d) Jakubowska, A.; Kulig, K. *Curr. Org. Synth.* **2013**, *10*, 547–563. e) Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. *Amino Acids* **2013**, *45*, 1017–1033. f) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. *Amino Acids* **2014**, *46*, 2047–2073. For leading books on the topic, see: g) *Asymmetric Synthesis and Application of α -Amino Acids*; Soloshonok V. A., Izawa K., Eds.; ACS Symposium Series 1009; American Chemical Society: Washington, DC, 2009.

¹² Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138–1151.

¹³ a) Carroll, M. P.; Guiry, P. J. *Chem. Soc. Rev.* **2014**, *43*, 819–833. b) Han, J. W.; Tokunaga, N.; Hayashi, T. *Synlett* **2002**, 871–874. c) Standfest-Hauser, C.; Slugovc, C.; Mereiter, K.; Schmid, R.; Kirchner, K.; Xiao, L.; Weissensteiner, W. *J. Chem. Soc. Dalton Trans.* **2001**, 2989–2995. d) Xu, S.; Zhang, Z. M.; Xu, B.; Liu, B.; Liu, Y.; Zhang, J. *J. Am. Chem. Soc.* **2018**, *140*, 2272–2283.

¹⁴ Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y. Q.; Hong, X.; Yang, Y. F.; Liu, T.; Houk, K. N.; Yu, J. Q. *Science* **2016**, *353*, 1023–1027.

¹⁵ Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. *Chem. Soc. Rev.* **2017**, *46*, 1080–1102.

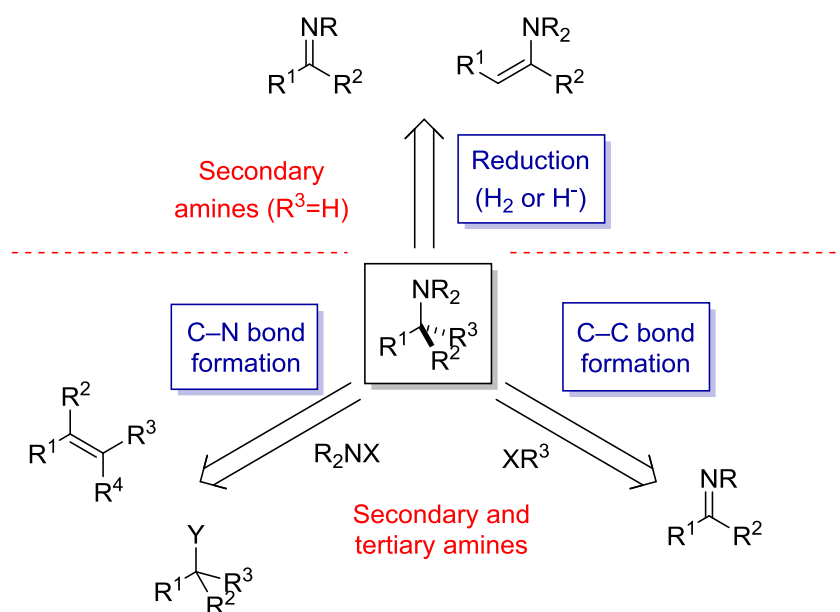
¹⁶ Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

These examples reveal the wide structural variety of synthetically interesting chiral amines, therefore standing their stereoselective preparation at the forefront of modern synthetic methodologies.

1.1.2. Stereoselective synthesis of chiral amines

A “chiral amine”, which is better described as an “ α -chiral amine”, is a structure bearing an amino group adjacent to a stereogenic carbon. In this context, two generic structural features of chiral amines are useful to point out: first, the nitrogen can be primary, secondary, tertiary or even quaternary (ammonium salt), and second, the α -stereogenic carbon, by necessity, can only be secondary or tertiary.^{2a}

The main strategies for chiral amine synthesis are summarized in Scheme 1. On the one hand, secondary amines are exclusively produced by stereoselective reduction of azomethine groups and enamines. On the other hand, secondary and tertiary amines can be prepared by the construction of C–N or C–C bonds. Hydroamination and amination reactions are among the most popular approaches for C–N bond generation, whereas the stereoselective addition of carbon (pro)nucleophiles to azomethine groups is the one for C–C bond formations.



Scheme 1. Main strategies for chiral amine synthesis.

Since the overall aim of this investigation, as explained later in detail, is focused on the preparation of enantiomerically pure secondary and tertiary amines through C–N and C–C bond formation, only the state of art for aminations and Mannich-type reactions is presented in the following sections. Concerning the asymmetric reduction of imines and

the enantioselective hydrogenation of enamines, the reader can be directed to several reviews on the topic.¹⁷

1.1.2.1. Enantioselective C–N bond formation

The enantioselective generation of new C–N bonds, through nucleophilic or electrophilic addition of nitrogen sources to carbon substrates, to afford optically pure α -chiral amines, is underexplored compared to reduction or C–C bond forming strategies. Nevertheless, significant advances have been made in this field during the past two decades.

1.1.2.1.1. Catalytic enantioselective hydroamination

The nucleophilic asymmetric addition of an amine N–H bond across an unsaturated carbon–carbon bond, the so-called hydroamination, provides a simple and highly atom-economical access to α -chiral amines.¹⁸ Alkyl linear amines are obtained by means of the intermolecular version of the reaction, whereas the intramolecular version affords *N*-heterocyclic compounds (Scheme 2). Currently, most studies involve the latter whilst, in general, the intermolecular hydroamination remains significantly less investigated.

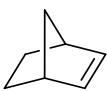
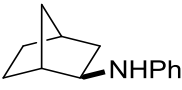
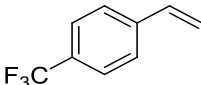
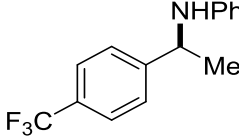

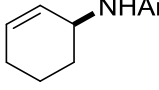
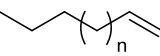
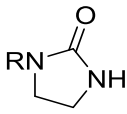
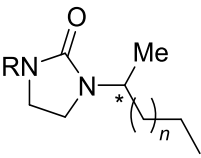

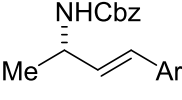
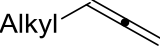
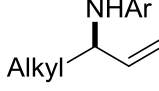
¹⁷ a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753–819. b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713–1760. For reviews and book chapters about asymmetric reduction of imines, see: c) Zhu, Q.-C.; Hutchins, R. O.; Hutchins, M. K. *Org. Prep. Proc. Int.* **1994**, *26*, 193–236. d) Rossi, S.; Benaglia, M.; Massolo, E.; Raimondi, L. *Catal. Sci. Technol.* **2014**, *4*, 2708–2723. e) Li, W.; Zhang, X. Asymmetric Hydrogenation of Imines. In *Stereoselective Formation of Amines*; Wang, C., Xiao, J., Eds.; Top. Curr. Chem. 343; Springer: Heidelberg, 2014; pp 103–144. For book chapters about enantioselective enamine hydrogenation, see: f) Zhou, Q.-L.; Xie, J.-H. Enantioselective Hydrogenation of Enamines with Monodentate Phosphorus Ligands. In *Chiral Amine Synthesis – Methods, Developments and Applications*; Nugent, T. C., Ed.; WILEY-VCH Verlag: Weinheim, 2010; pp 247–271. g) Hu, X.-P.; Zheng, Z. Bidentate Ligands for Enantioselective Enamide Reduction. In *Chiral Amine Synthesis – Methods, Developments and Applications*; Nugent, T. C., Ed.; WILEY-VCH Verlag: Weinheim, 2010; pp 273–298. h) Zhou Q.-L.; Xie, J.-H. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamides and Enamines. In *Stereoselective Formation of Amines*; Wang, C., Xiao, J., Eds.; Top. Curr. Chem. 343; Springer: Heidelberg, 2014; pp 75–102.

¹⁸ For book chapters on the topic, see: a) Reznichenko, A. L.; Hultsch, K. C. Asymmetric Hydroamination. In *Chiral Amine Synthesis – Methods, Developments and Applications*; Nugent, T. C., Ed.; WILEY-VCH Verlag: Weinheim, 2010; pp 299–339. b) Reznichenko, A. L.; Nawara-Hultsch, A. J.; Hultsch, K. C. Asymmetric Hydroamination. In *Stereoselective Formation of Amines*; Wang, C., Xiao, J., Eds.; Top. Curr. Chem. 343; Springer: Heidelberg, 2014; pp 75–102. c) Reznichenko, A. L.; Hultsch, K. C. Hydroamination of Alkenes. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2015; Vol. 88, pp 1–554.

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employing Ir-BINAP catalyst, albeit with low yield (22% yield, 95% *ee*).²⁴ Thereafter, some methodologies were developed for the intermolecular enantioselective hydroamination of alkenes,²⁵ allenes²⁶ and alkynes²⁷ (Table 1).

Table 1. Pioneering intermolecular asymmetric hydroaminations.

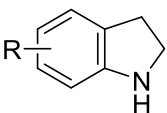
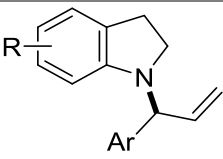
Ent.	Author	Unsaturated substrate	Amine	Catalytic system	Product
1	Togni 1997 ²⁴		PhNH ₂	Ir, BINAP	 22% yield 95% <i>ee</i>
2	Hartwig 2000 ^{25a}		PhNH ₂	Pd, BINAP	 80% yield, 81% <i>ee</i>
3	Hartwig 2001 ^{25b}		ArNH ₂	Pd, Troost ligand	 59–87% yield 86–95% <i>ee</i>
4	Widenhoefer 2009 ^{25c}			Au, MeOBIPHEP	 80–89% yield 71–78% <i>ee</i>
5	Widenhoefer 2012 ^{26a}		CbzNH ₂	Au, MeOBIPHEP	 42–97% yield 60–92% <i>ee</i>
6	Breit 2012 ^{26b}		ArNH ₂	Rh, JosiPhos	 43–99% yield 78–90% <i>ee</i>

²⁴ Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857–10858.

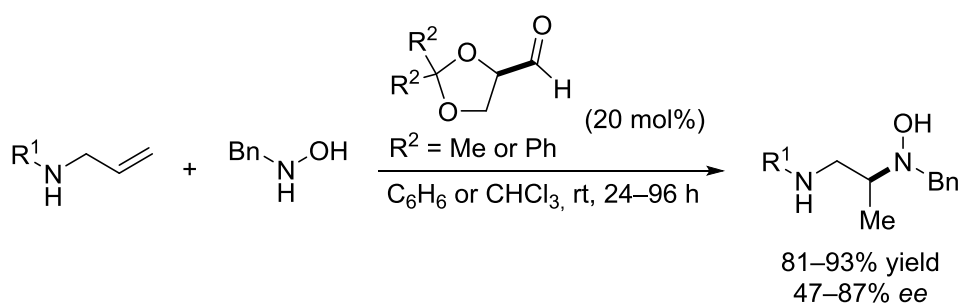
²⁵ For pioneering examples with alkenes, see: a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546–9547. b) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366–4367. c) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373.

²⁶ For pioneering examples with allenes, see: a) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5175–5178. b) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879.

²⁷ For the pioneering example with alkynes, see: Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392–8395.

Ent.	Author	Unsaturated substrate	Amine	Catalytic system	Product
7	Dong 2015 ²⁷	Ar—≡—Me		Rh, BDPP	 69–87% yield 77–94% ee

On the other hand, metal-free catalyzed enantioselective hydroaminations are rather limited and mainly consist of intramolecular transformations.²⁸ In 2011, Beauchemin and co-workers reported the only intermolecular organocatalytic enantioselective hydroamination so far, where a chiral aldehyde is used as a tethering precatalyst in order to enable, through temporary intramolecularity, the asymmetric synthesis of chiral vicinal diamines.²⁹



Scheme 4. Beauchemin's organocatalytic enantioselective intermolecular hydroamination.

1.1.2.1.2. Catalytic enantioselective allylic amination

The catalytic allylic amination, is the most explored nucleophilic amination reaction for the stereoselective generation of new C–N bonds.³⁰ In 1989, Hayashi, Ito and co-workers described the first asymmetric allylic amination of 1,3-symmetrically disubstituted

²⁸ a) Ackermann, L.; Althammer, A. *Synlett* **2008**, 995–998. b) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245–249. c) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747–6749. d) Lin, J.-S.; Yu, P.; Huang, L.; Zhang, P.; Tan, B.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 7847–7851.

²⁹ a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100–20103. b) Guimond, N.; Macdonald, M. J.; Lemieux, V.; Beauchemin, A. *J. Am. Chem. Soc.* **2012**, *134*, 16571–16577.

³⁰ For selected reviews on aminations *via* nucleophilic substitution, see: a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708. b) Grange, R. L.; Clizbe, E. A.; Evans, P. A. *Synthesis* **2016**, 2911–2968. For selected book chapters, see: c) Takemoto, Y.; Miyabe, H. C–N Bond Formation through Amination. In *Comprehensive Organometallic Chemistry III*; Elsevier, 2007; Vol. 10, pp 695–724. d) Takemoto, Y.; Miyabe, H. Asymmetric Carbon-Heteroatom Bond-Forming Reactions. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; John Wiley and Sons: Hoboken, NJ, 2010; pp 227–267.

substrates employing a ferrocenyldiphosphine-palladium complex (Table 2, entry 1).³¹ One year later, the same authors applied the same system to the regio- and enantioselective amination of terminal allylic substrates (entry 2).³²

In addition, other structures that also generate π -allylic intermediates have been employed in asymmetric aminations. For instance, palladium-catalyzed asymmetric cycloadditions of vinyloxirane³³ and vinylaziridine,³⁴ with heterocumulenes, were developed by the groups of Alper and Trost, respectively (Table 2, entries 3 and 4). Furthermore, the group of Trost reported the dynamic kinetic asymmetric allylic amination of racemic allene acetates through vinyl-allyl palladium intermediates (entry 5).³⁵ More recently, van Maarseveen and co-workers described the enantioselective copper-catalyzed substitution reaction of propargylic acetates with aryl amines (entry 6).³⁶

Table 2. Pioneering works in asymmetric nucleophilic amination.

Ent.	Author	Allylic substrate	Nitrogen source	Catalyst	Product
1	Hayashi, Ito 1989 ³¹		Ar-CH ₂ -NH ₂		 67–97% yield 73–97% ee
2	Hayashi, Ito 1990 ³²		BnNH ₂		 84% yield 84% ee
3	Alper 1997 ³³	 R = H, Me		Pd, TolBINAP	 60–98% yield 69–94% ee

³¹ Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301–6311.

³² a) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743–1746. For further examples with the same ligand, see: b) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471–7472.

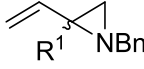
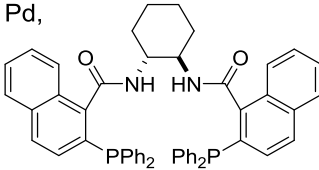
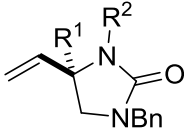
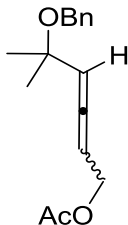
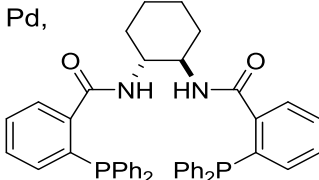
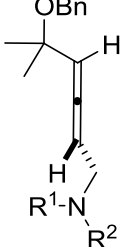
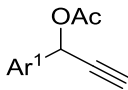
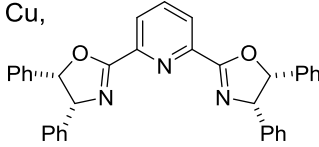
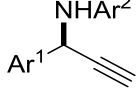
³³ Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709–3715.

³⁴ Trost, B. M.; Fandrlick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837.

³⁵ Trost, B. M.; Fandrlick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.

³⁶ Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777–3780.

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Ent.	Author	Allylic substrate	Nitrogen source	Catalyst	Product
4	Trost 2003 ³⁴	 R ¹ = H, Me	$R^2-N=C=O$ R ² = Ar, Bn	Pd, 	 60–99% yield 80–95% ee
5	Trost 2005 ³⁵		R^1-NH-R^2	Pd, 	 89–98% yield 89–95% ee
6	van Maarseven 2008 ³⁶		Ar ² NH ₂	Cu, 	 80–97% yield 74–88% ee

Alternatively, some organocatalytic methods have also been designed for the enantioselective allylic amination. Krische and co-workers reported the first regio- and enantioselective amination of Morita-Baylis-Hillman derived acetates with phthalimide, *via* nucleophilic phosphine catalysis, albeit only one example was reported with a moderate enantiomeric excess (Table 3, entry 1).³⁷ Subsequent to this work, other approaches involving related amino compounds were described,^{38,39} as shown in Table 3 (entries 2 and 3).

³⁷ Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337–1339.

³⁸ Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Chem. Eur. J.* **2011**, *17*, 13676–13679.

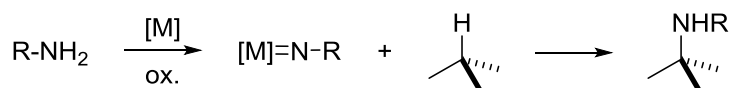
³⁹ Zhuang, M.; Du, H. *Org. Biomol. Chem.* **2014**, *12*, 4590–4593.

Table 3. Organocatalytic asymmetric nucleophilic aminations.

Ent.	Author	Allylic substrate	Nitrogen source	Catalyst	Product
1	Krische 2004 ³⁷				 80% yield 56% ee
2	Zhu, Cheng 2011 ³⁸				 53–86% yield 90–99% ee
3	Du 2014 ³⁹		TsNH ₂		 60–88% yield 62–86% ee

1.1.2.1.3. Catalytic enantioselective C–H amination

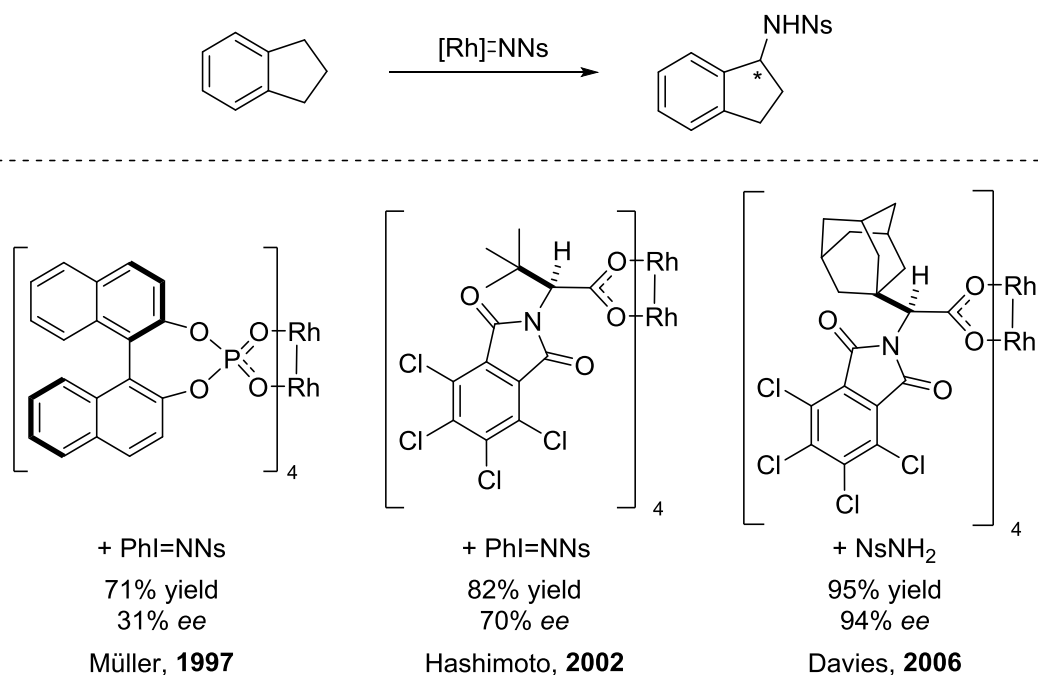
In the last two decades, C–H functionalization has emerged as a powerful tool for the synthesis of complex organic molecules. Particularly, metallonitrene chemistry allows the direct transformation of a C–H bond into a C–N bond. During the reaction, the amine binds to the metallic center forming a metallonitrene, which performs the insertion into a well-differentiated C–H bond –typically benzylic, allylic, tertiary or contiguous to a heteroatom– (Scheme 5).



Scheme 5. Metal-catalyzed C–H amination.

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In 1997, the group of Müller described the first enantioselective intermolecular C–H amination of indanes employing iminoiodane and a chiral dirhodium catalyst.⁴⁰ Thereafter, the groups of Hashimoto⁴¹ and Davies⁴² were able to improve the catalytic system, by using different chiral ligands and/or oxidants, and higher enantioselectivities were obtained (Scheme 6).



Scheme 6. Indan enantioselective C–H aminations.

Additionally, the groups of Katsuki⁴³ and Clark⁴⁴ reported the manganese- and copper-catalyzed enantioselective C–H amination of cyclohexene, respectively. Nevertheless, the corresponding cyclohexenyl amine was obtained in low to moderate yields and with moderate enantioselectivities (Scheme 7).

⁴⁰ Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087–1105.

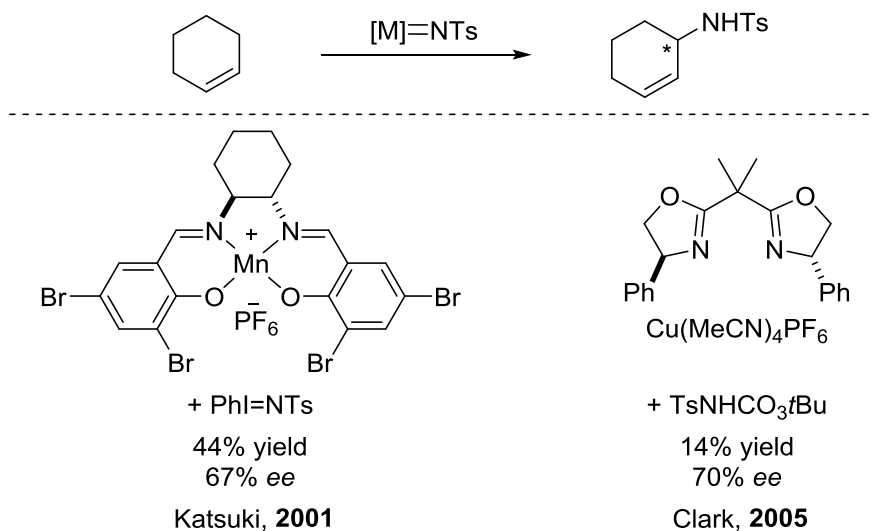
⁴¹ Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561–9564.

⁴² Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013–5016.

⁴³ Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339–3342.

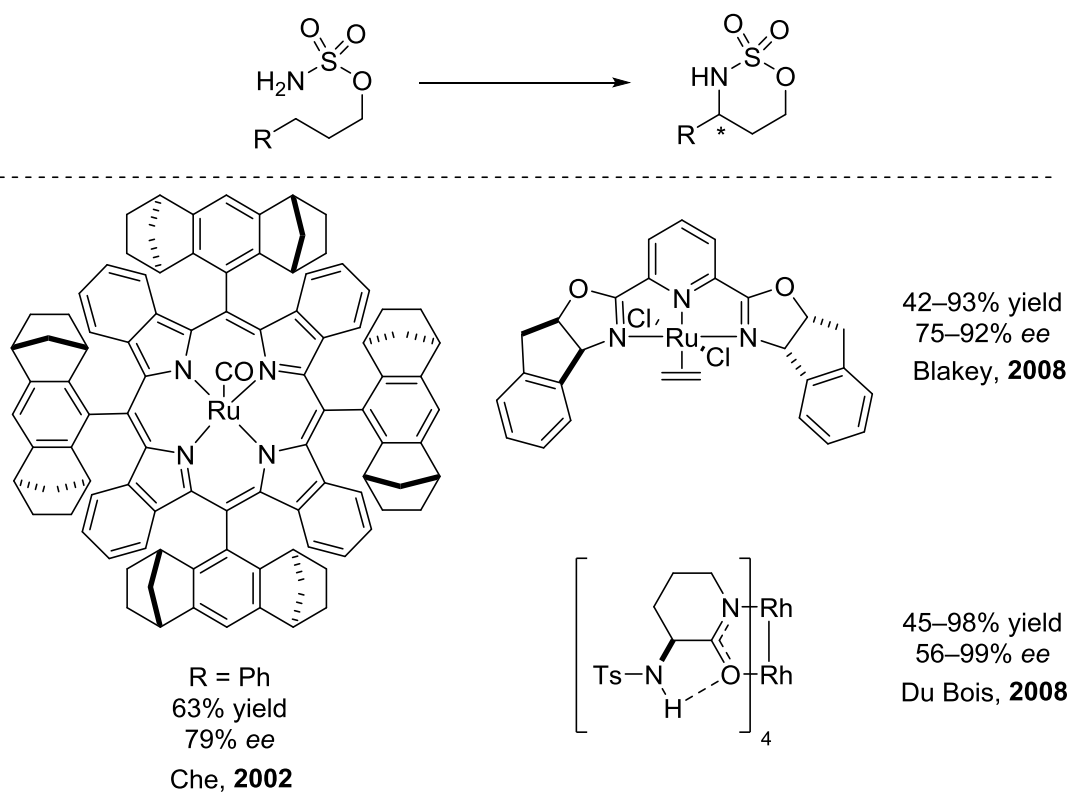
⁴⁴ Clark, J. S.; Roche, C. *Chem. Commun.* **2005**, 5175–5177.

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Scheme 7. Cyclohexene enantioselective C–H aminations.

Intramolecular enantioselective C–H aminations have also been developed. As a representative example, diverse catalytic systems performed satisfactorily for the asymmetric synthesis of 6-membered cyclic chiral sulfonamides (Scheme 8).⁴⁵



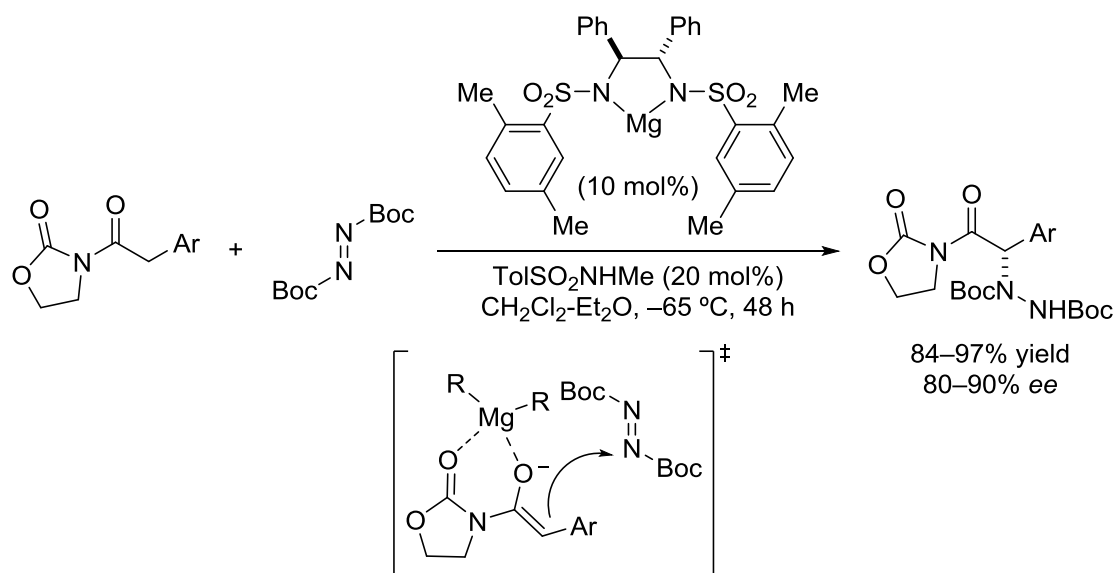
Scheme 8. Intramolecular enantioselective C–H amination.

⁴⁵ a) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3465–3468. b) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 6825–6828. c) Zalatan, D. N.; Du Bois, J. J. *Am. Chem. Soc.* **2008**, *130*, 9220–9221.

As illustrated, catalytic enantioselective C–H amination constitutes a new emerging field for the synthesis of α -chiral amines⁴⁶ still restricted to very specific substrates. Thus, the search for additional suitable structures and efficient catalytic systems represents the forthcoming steps in this field.

1.1.2.1.4. Catalytic enantioselective electrophilic amination

The catalytic asymmetric electrophilic amination has been established as a fruitful methodology for the construction of nitrogen-bearing tri- and tetrasubstituted carbon stereocenters. In 1997, Evans and co-workers documented the first enantioselective electrophilic amination of *N*-acyloxazolidinones with *tert*-butyl azodicarboxylate catalyzed by a chiral magnesium bis(sulfonamide) complex *via* Lewis acid activation (Scheme 9).⁴⁷ After this seminal work, several nucleophiles have been employed in metal-catalyzed reactions, particularly, α -carbonyl species.⁴⁸



Scheme 9. Evans' first enantioselective electrophilic amination.

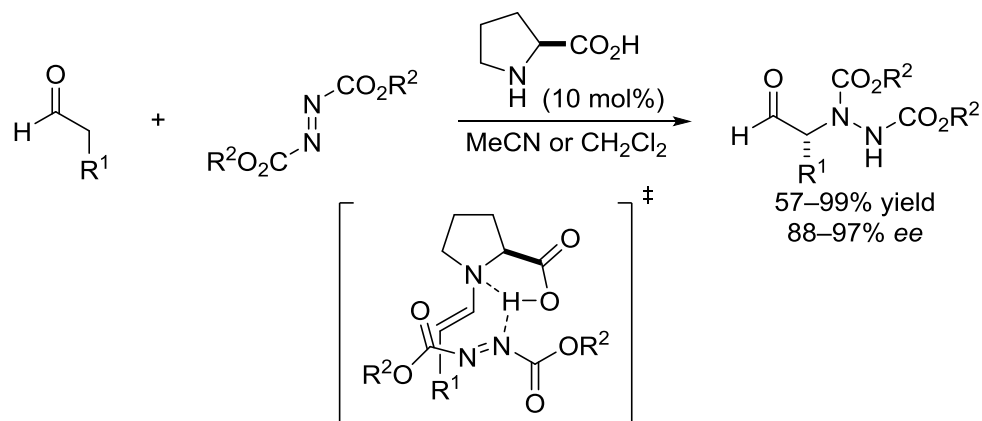
⁴⁶ For recent examples, see: a) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 9884–9887. b) Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 1739–1742. c) Höke, T.; Herdtweck, E.; Bach, T. *Chem. Commun* **2013**, *49*, 8009–8011. d) Wang, P. S.; Shen, M. L.; Wang, T. C.; Lin, H. C.; Gong, L. Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 16032–16036.

⁴⁷ Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452–6453.

⁴⁸ For examples with silyl enol ethers, see: a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598. 2-Ketoesters: b) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421. β -Keto phosphonate esters: c) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772–5773. Succinimides: d) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. **2007**, *129*, 11342–11343. α -Cyanoacetates: e) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158–2159. Ketones: f) Trost, B. M.; Tracy, J. S.; Saget, T. *Chem. Sci.* **2018**, *9*, 2975–2980.

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In addition, organocatalytic enantioselective electrophilic aminations have been extensively studied. The groups of List and Jørgensen, independently, reported the first proline-catalyzed amination of aldehydes in 2002 *via* a dual activation exerted by the catalyst (Scheme 10).⁴⁹



Scheme 10. Pioneer organocatalytic asymmetric electrophilic amination.

After these pioneering works *via* enamine catalysis, other organocatalytic activation modes have been applied in asymmetric amination reactions (Table 4).^{50–53}

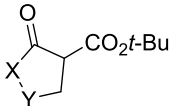
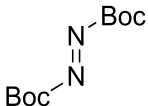
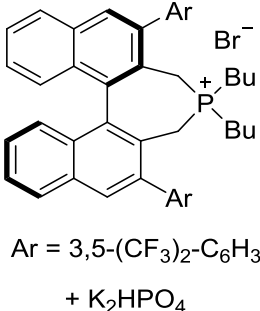
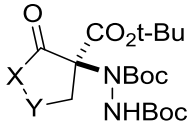
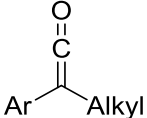
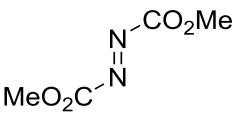
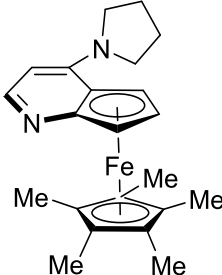
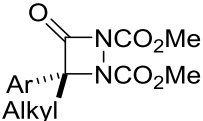
Table 4. Pioneering organocatalytic asymmetric electrophilic amination reactions.

Ent.	Author	Nucleophile	Electrophile	Catalyst	Product
1	Chen 2007 ⁵⁰				 39–77% yield 88–99% ee
2	Jørgensen 2004 ⁵¹				 84–99% yield 91–99% ee

⁴⁹ a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657. b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793.

⁵⁰ Liu, T. Y.; Cui, H. L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z. Q.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 3671–3674.

⁵¹ Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.

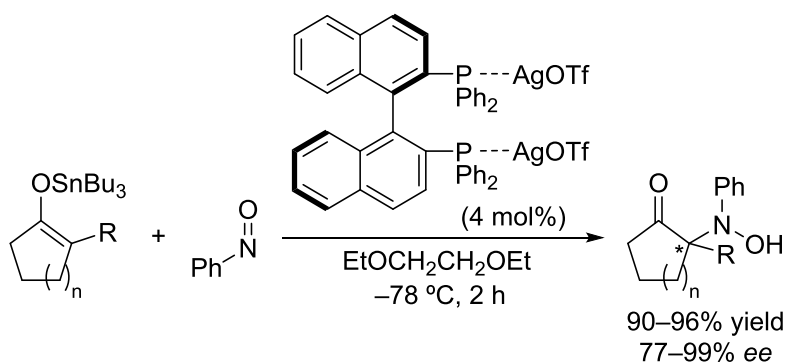
Ent.	Author	Nucleophile	Electrophile	Catalyst	Product
3	Maruoka 2008 ⁵²				 97–99% yield 89–92% ee
4	Fu 2008 ⁵³				 53–91% yield 67–96% ee

While electrophilic aminations have been developed with a wide variety of carbonyl derived pronucleophiles as shown in Table 4, the variety of aminating reagents is still quite limited. Azodicarboxylates are the most popular aminating reagents, due to their high reactivity and tunable level of steric hindrance, in spite of their low atom economy. In this context, nitroso compounds are another type of promising electrophilic amination reagents with high reactivity and higher atom-economy. Both nitrogen and oxygen atoms are highly reactive towards nucleophile attack, thus, chemoselective control is crucial to achieve productive α -aminations. In 2004, the group of Yamamoto described the first chemoselective and enantioselective amination employing nitrosobenzene, under metal catalysis, to afford the corresponding cyclic α -amino ketones in high yield and enantiomeric excess (Scheme 11).⁵⁴

⁵² He, R.; Wang, X. Hashimoto, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9466–9468.

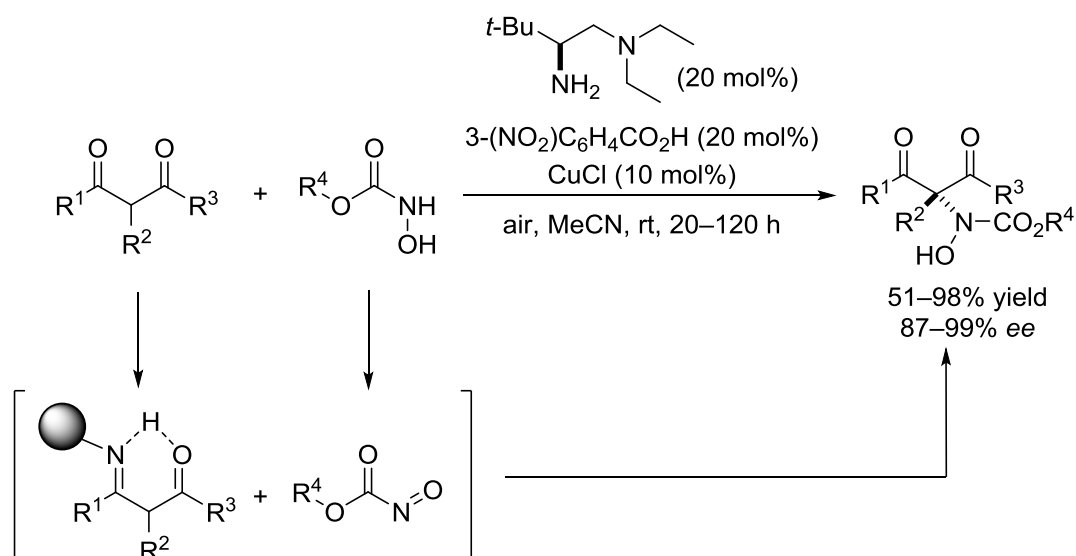
⁵³ Berlin, J. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 7048–7050.

⁵⁴ Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361.



Scheme 11. Yamamoto's pioneering enantioselective amination with nitrosobenzene.

Despite the progress made with nitroso aryl compounds,⁵⁵ a mild cleavage of the nitrogen–aryl bond, in the resulting products, remains unsolved. For that reason, the use of nitrocarbonyl compounds, formed *in situ* by oxidation of hydroxamic acid derivatives, is emerging as a promising alternative since the previous oxidation step for the formation of, sometimes toxic and unstable, nitroso compounds is avoided.⁵⁶ In this context, Luo and co-workers disclosed an appealing procedure for the asymmetric catalytic α -amination of β -keto carbonyls, using *N*-hydroxycarbamate, under primary amine catalysis and copper(I)-catalyzed aerobic oxidation (Scheme 12).⁵⁷



Scheme 12. Luo's enantioselective α -amination with *N*-hydroxycarbamate.

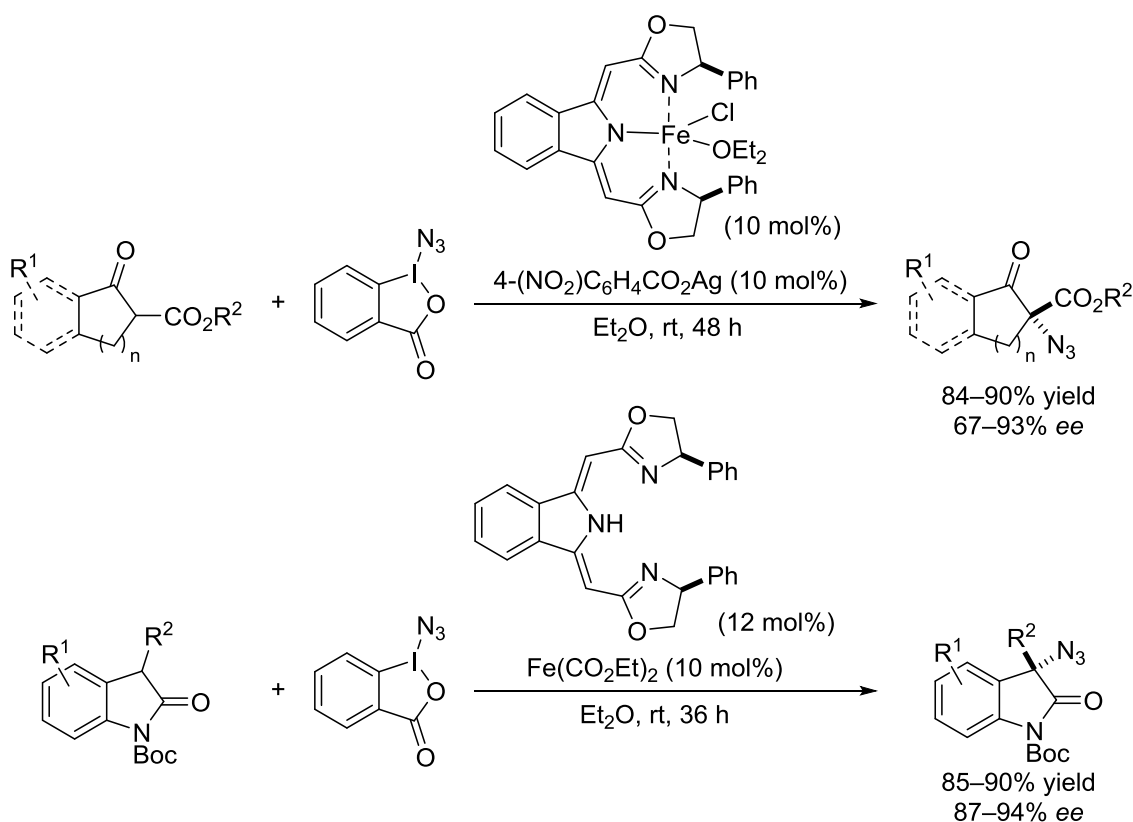
⁵⁵ For selected examples, see: a) Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q. *Chem. Commun.* **2006**, 429–431. b) López-Carretero, J.; Cid, M. B.; Poulsen, T. B.; Bella, M.; Ruano, J. L. G.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 7062–7065. c) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4684–4688. d) Companyó, X.; Valero, G.; Pineda, O.; Calvet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 431–439.

⁵⁶ For a review in the topic, see: Palmer, L. I.; Frazier, C. P.; Read de Alaniz, J. *Synthesis* **2014**, *46*, 269–280.

⁵⁷ Xu, C.; Zhang, L.; Luo, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 4149–4153.

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On the other hand, azido compounds are also attractive reagents for catalytic asymmetric amination, as demonstrated by the enantioselective iron-catalyzed azidation of β -keto esters developed by Gade and co-workers in 2013 (Scheme 13).⁵⁸



Scheme 13. Gade's enantioselective electrophilic azidation reactions.

As a conclusion, although significant advances have been made in catalytic enantioselective electrophilic amination reactions during the past two decades, there is still ample room for progress. The development of new aminating reagents to afford enantioenriched products with better atom- and step-economy is greatly important, as well as the search for new catalytic systems that could allow the activation of less reactive substrates such as esters, amides, nitriles and aromatic alkanes.

1.1.2.2. Enantioselective C–C bond formation

The enantioselective formation of carbon–carbon bonds by means of nucleophilic addition to imines and related C=N systems represents an effective strategy for the

⁵⁸ Deng, Q. H.; Bleith, T.; Wadepl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356–5359.

synthesis of α -chiral amines.⁵⁹ Imines are generally much less electrophilic than the corresponding aldehydes, a drawback that can often be overcome by employing Lewis or Brønsted acids and the introduction of activating electron-withdrawing groups at either one or both the nitrogen and the iminic carbon (Figure 4). On the other hand, imines derived from enolizable aldehydes have been barely employed due to their inherent instability and tendency to imine-enamine isomerization.⁶⁰

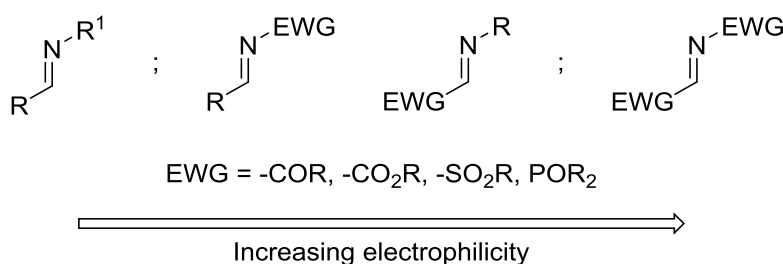
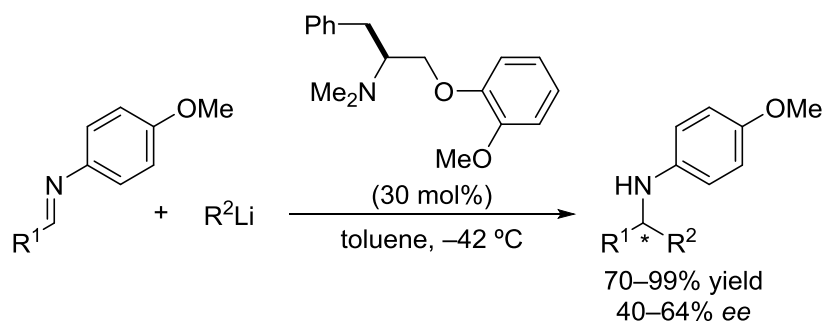


Figure 4. Reactivity of representative imines as electrophiles.

The group of Tomioka reported the first catalytic enantioselective alkylation of imines employing organolithium reagents and a chiral Lewis base organocatalyst (Scheme 14).⁶¹ Since then, most efforts have been addressed towards the development of catalytic and enantioselective versions for which the most representative examples are disclosed below.



Scheme 14. Tomioka's pioneering catalytic enantioselective alkylation of imines.

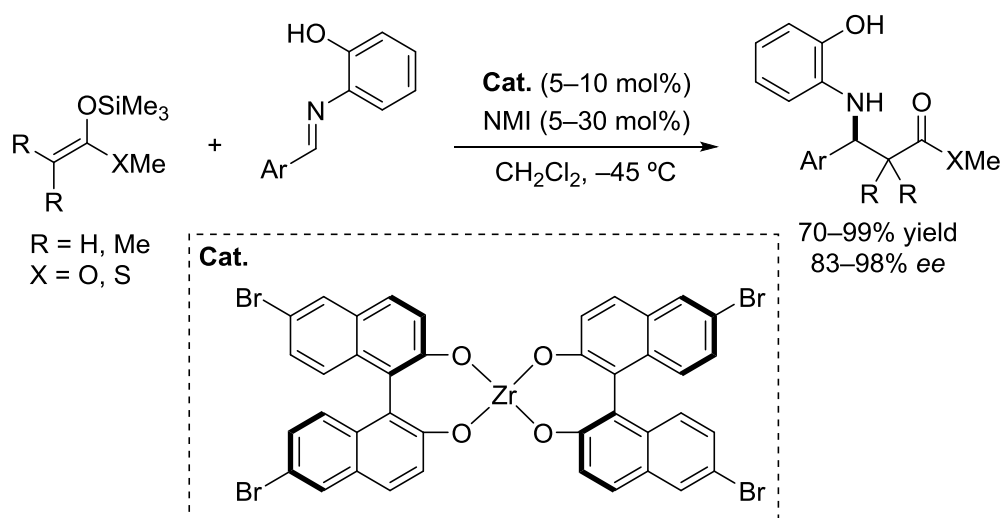
⁵⁹ For general reviews on the topic, see: a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094. b) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392. c) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

⁶⁰ For further information about aliphatic imine decomposition and isomerization, see: a) Katritzky, A. R.; Harris, P. A.; *Tetrahedron* **1990**, *46*, 987–996. b) Nolen, E. G.; Allocco, A.; Broody, A. M.; Zuppa, A. *Tetrahedron Lett.* **1991**, *32*, 73–74. c) Marson, C. M.; Fallah, A. *Chem. Commun.* **1998**, 83–84.

⁶¹ Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098.

- **Mannich reaction**

Among the different carbon nucleophilic species that have been employed in the asymmetric addition to imines, α -carbonyl moieties constitute the most used ones. The addition of these substrates to azomethine groups is named the Mannich reaction.⁶² The first catalytic enantioselective reaction of this type was described by Kobayashi and co-workers in 1997. High enantioselectivities were obtained in the addition of silyl enol ethers to aryl amines employing a chiral zirconium catalyst derived from BINOL (Scheme 15).⁶³

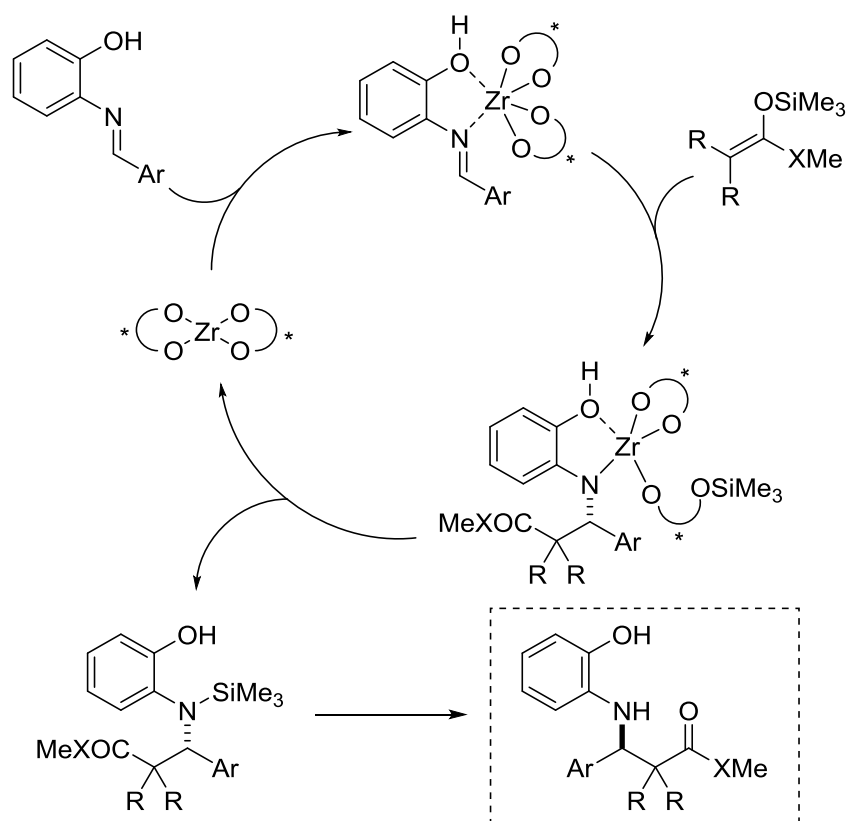


Scheme 15. Kobayashi's pioneering catalytic enantioselective Mannich reaction.

The authors assumed a catalytic cycle in which the catalyst coordinates the aldimine to produce an intermediate, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with the regeneration of the catalyst. Then, the final Mannich adduct is obtained after acidic treatment (Scheme 16).

⁶² For general reviews on asymmetric Mannich reaction, see: a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070. b) Syamala, M. *Org. Prep. Proced. Int.* **2009**, *41*, 1–68. c) Bhadury, P. S.; Song, B.-A. *Curr. Org. Chem.* **2010**, *14*, 1989–2006. d) Greco, S. J.; Lacerda, V.; Bezerra dos Santos, R. *Aldrichimica Acta* **2011**, *44*, 15–23. e) Xiao-Hua, C.; Hui, G.; Bing, X. *Eur. J. Chem.* **2012**, *3*, 258–266.

⁶³ Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154.



Scheme 16. Assumed catalytic cycle for Kobayashi's Mannich reaction.

This work inspired many subsequent catalytic non-direct examples in which either the metal center, the chiral ligands or the nature of the catalyst were modified.⁶⁴ A similar approach was employed by the group of Hoveyda and Snapper for the silver-catalyzed enantioselective indirect Mannich reaction of enol ethers with aryl, alkyl, alkenyl and alkynyl *N*-aryl imines.⁶⁵

In 1999, Shibasaki and co-workers described the first direct catalytic asymmetric Mannich reaction with ethyl and propyl phenyl ketones employing a lanthanum–lithium heterobimetallic chiral catalyst and an aminomethyl ether as a synthetic equivalent of $[\text{Et}_2\text{NCH}_2^+]$.⁶⁶ Based on this reaction, they reported in 2003 the zinc-catalyzed enantioselective *anti*⁶⁷ and *syn*⁶⁸ Mannich reactions of 2-hydroxy-1-(2-

⁶⁴ For examples on the use of metal catalysis, see: a) D. Ferraris, B. Young, T. Dudding, T. Lecta, *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549. b) A. Fuji, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458. c) S. Nakamura, H. Sano, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Tetrahedron Lett.* **2007**, *48*, 5565–5568. For an example on the use of organocatalysis, see: d) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; For an example on the use of ternary complex ligand, see: d) H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061.

⁶⁵ Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735.

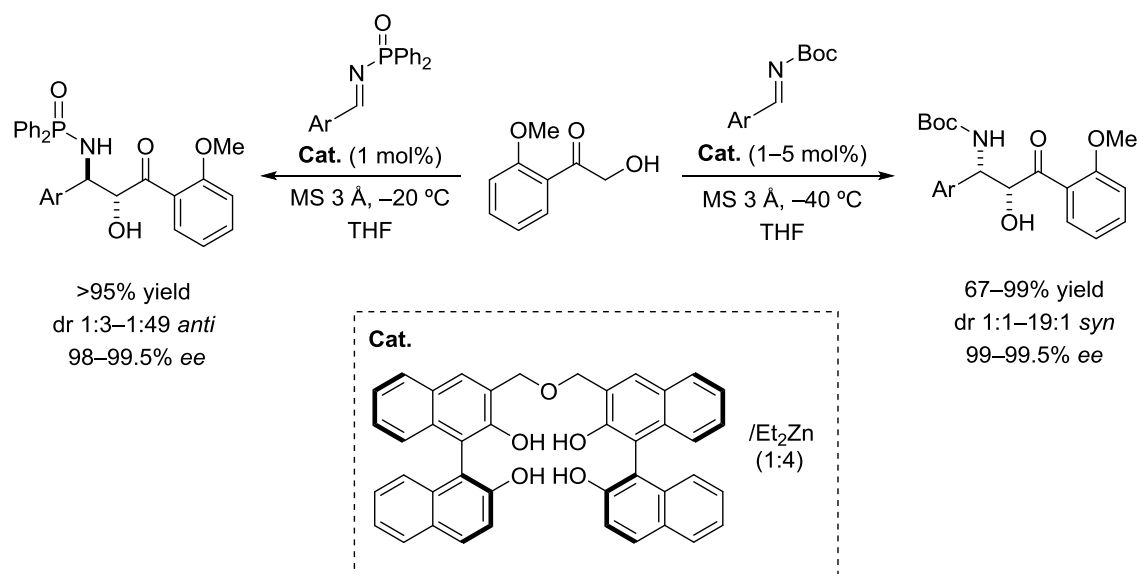
⁶⁶ Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307–310.

⁶⁷ Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713.

⁶⁸ Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339–5342.

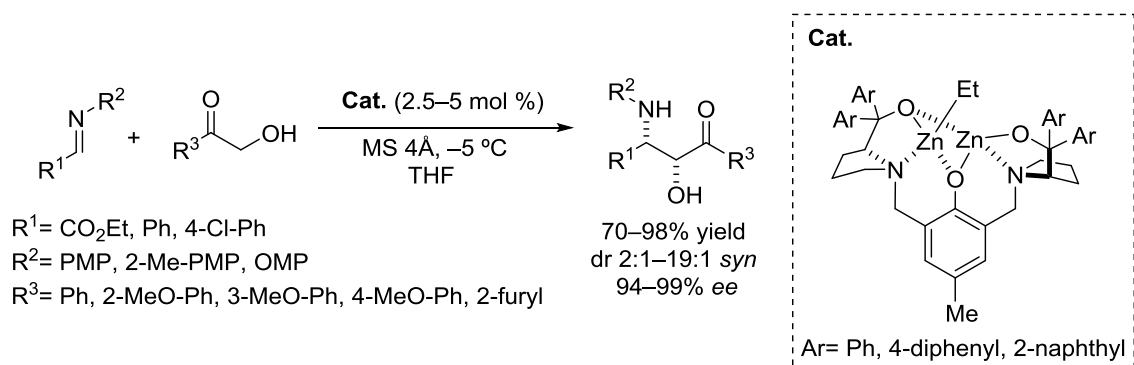
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methoxyphenyl)ethanone with *N*-phosphinoyl and *N*-Boc imines, respectively (Scheme 17).



Scheme 17. Shibasaki's stereoselective Mannich reactions with *N*-phosphinoyl and *N*-Boc imines.

Since then, several groups have worked in the search of suitable catalytic systems for the Mannich reaction with α -hydroxy ketones. For instance, Trost and co-workers introduced the use of chiral dinuclear Zn complexes in the reaction with *N*-methoxyphenyl imines as electrophiles (Scheme 18).⁶⁹ Likewise, under similar reaction conditions, switch to the *anti* Mannich adducts by using *N*-phosphinoyl imines was accomplished.⁷⁰



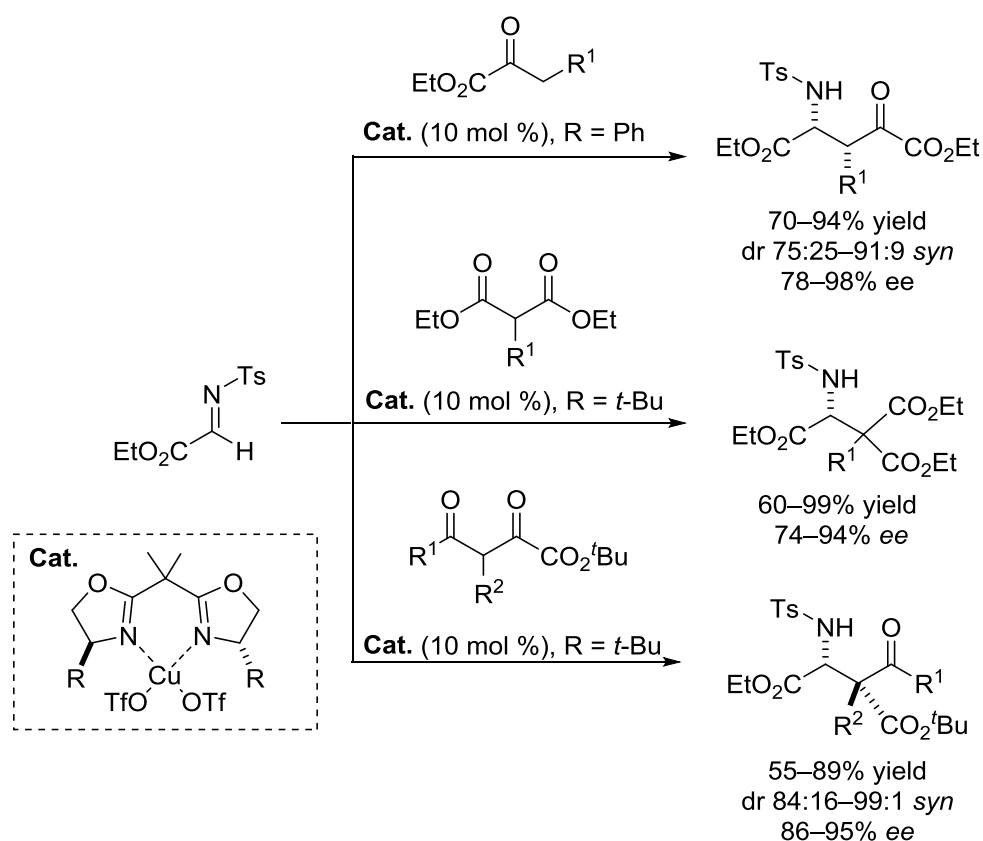
Scheme 18. Trost's zinc-catalyzed enantioselective *syn*-Mannich reaction.

On the other hand, in 2001, Jørgensen and co-workers disclosed the metal-catalyzed asymmetric Mannich reaction of ethyl *N*-tosyl α -iminoester and α -oxoesters promoted

⁶⁹ Trost, B. M.; Terrell, L. M. *J. Am. Chem. Soc.* **2003**, *125*, 338–339.

⁷⁰ Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779.

by a chiral Cu(II)–bis(oxazolidine) in a highly *syn*-diastereo- and enantioselective way.⁷¹ This methodology was later expanded to other activated carbonylic pronucleophiles, such as malonates and β -ketoesters.⁷² The latter allowed the construction of quaternary stereocenters for the first time through a metal-catalyzed Mannich reaction (Scheme 19). Nevertheless, while the system was versatile regarding the pronucleophile, it was limited to the use of highly activated *N*-tosyl iminoesters.⁷³



Scheme 19. Jørgensen's Cu-catalyzed enantioselective Mannich reactions with *N*-tosyl imines.

Thereafter, several groups have described metal-catalyzed direct Mannich reactions with a wide variety of pronucleophiles and *N*-protected imines.⁷⁴ Noteworthy, Kumagai, Shibasaki and co-workers and the group of Shimizu and Kanai have been able to address

⁷¹ Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997.

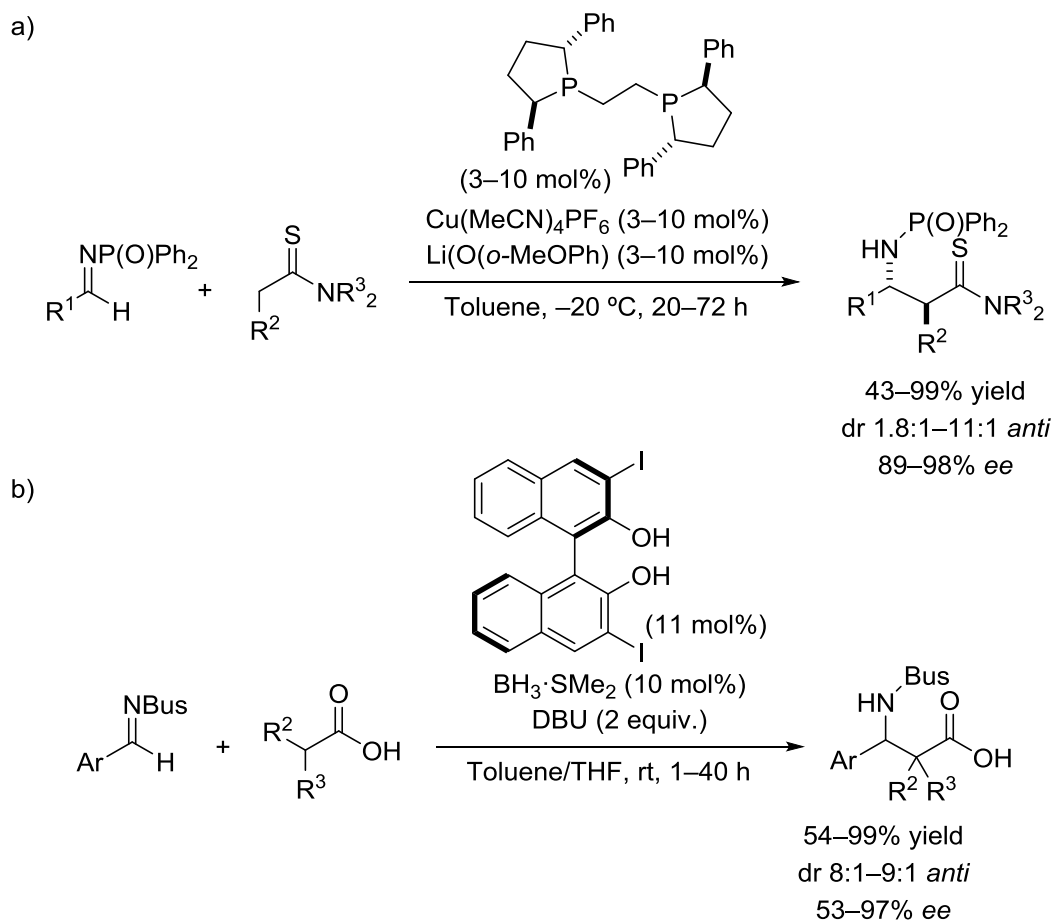
⁷² Marigo, M.; Kjaersgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359–2367.

⁷³ The procedure was later extended to a family of aryl and alkyl-substituted *N*-tosyl imines with variable results: Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583–2591.

⁷⁴ For selected examples, see: a) Hamashima, Y.; Samamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525–1529. b) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6847–6850. c) Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-L.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362–14363. d) Liang, G.; Tong, M.-C.; Tao, H.; Wang, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1851–1855. e) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823–3826. f) Poisson, T.; Tsubogo, T.; Yamashita, Y.; Kobayashi, S. *J. Org. Chem.* **2010**, *75*, 963–965. g) Hatano, M.; Horibe, T.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 56–57. g) Karimi, B.; Jafari, E.; Enders, D. *Chem. Eur. J.* **2013**, *19*, 10142–10145.

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Mannich reactions using more challenging pronucleophiles such as thioamides⁷⁵ and carboxylic acids,⁷⁶ respectively (Scheme 20).



Scheme 20. Asymmetric Mannich reactions with thioamides and carboxylic acids.

In 2000, List disclosed the first organocatalytic Mannich reaction using proline as the promoter. This three-component procedure afforded the corresponding *syn* Mannich adducts with good to excellent yields and stereoselectivities (Scheme 21a).⁷⁷ On the other hand, the same year, the group of Barbas III described the first *anti*-selective asymmetric Mannich reaction using chiral amine catalysis (Scheme 21b).⁷⁸ Subsequent

⁷⁵ Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 5026–5029.

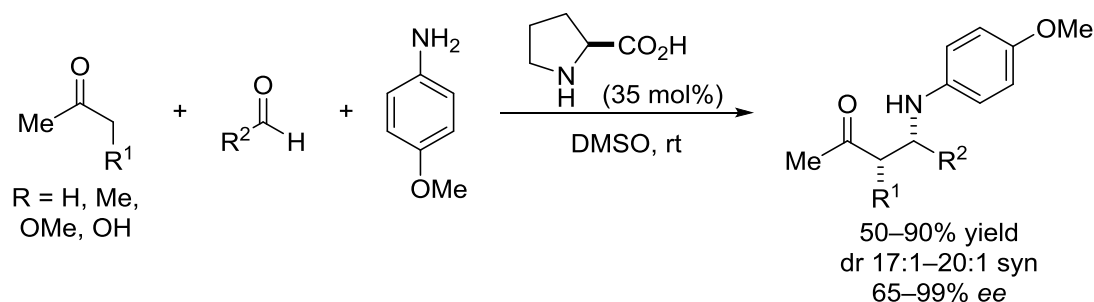
⁷⁶ Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075–7078.

⁷⁷ List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

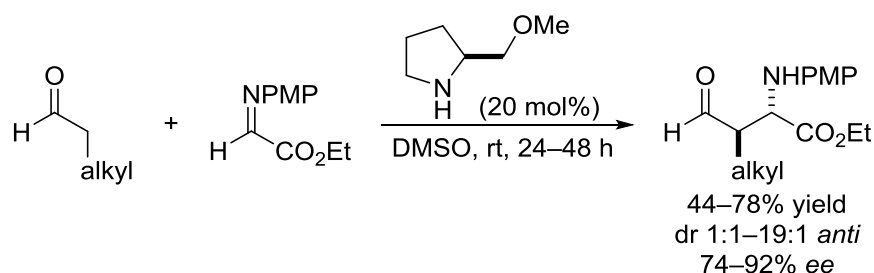
⁷⁸ Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749–7752.

to these works, many groups have exploited the ability of chiral secondary and primary amines to produce highly enantioenriched *syn*⁷⁹ and *anti*⁸⁰ Mannich adducts.

a) First organocatalytic enantioselective *syn*-Mannich reaction (List, **2000**).



b) First organocatalytic enantioselective *anti*-Mannich reaction (Barbas III, **2002**).



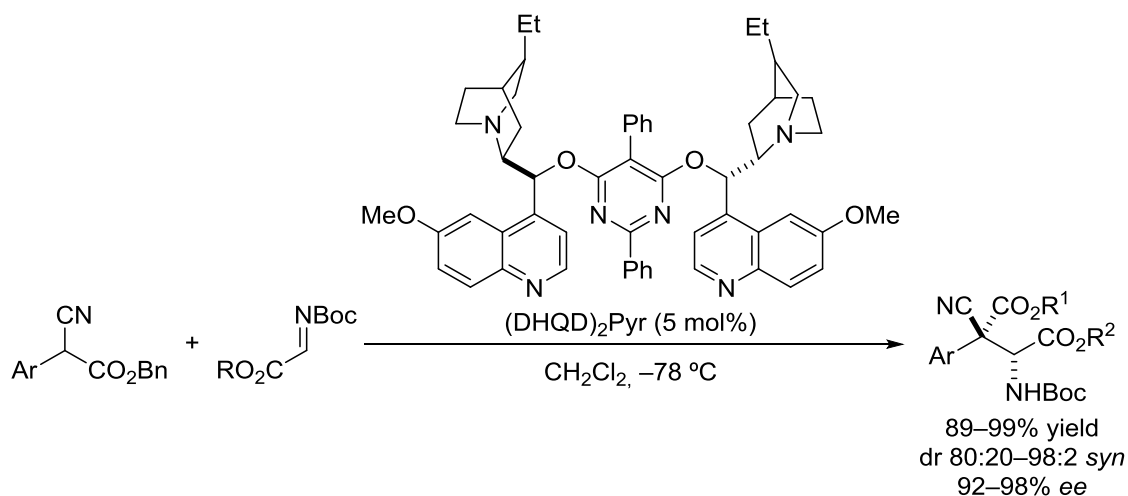
Scheme 21. Pioneering organocatalytic enantio- and diastereoselective Mannich reactions.

In 2005, Jørgensen and co-workers developed the first Brønsted base assisted asymmetric Mannich reaction. α -Aryl cyanoacetates were added to *N*-Boc iminoesters in a highly stereoselective manner *via* deprotonative activation with (DHQD)₂Pyr

⁷⁹ For selected *syn*-Mannich examples, see: a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833. b) Córdova, A.; Notz, W.; Zhong, G.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843. c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M. Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435–1439. d) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243–7246. e) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96. f) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 2246–2249. For primary amine-catalyzed *syn*-Mannich reactions, see: g) Ibrahim, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem. Eur. J.* **2005**, *11*, 7024–7029. h) Valero, G.; Balaguer, A.-N.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2008**, *48*, 6559–6562.

⁸⁰ For selected *anti*-Mannich examples with pyrrolidinic amines, see: a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jørgensen, K. A.; *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304. b) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041. c) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2008**, *130*, 875–886. d) Martín-Rapún, R.; Fan, X.; Sayalero, S.; Bahramnejad, M.; Cuevas, F.; Pericàs, M. A. *Chem. Eur. J.* **2011**, *17*, 8780–8783. e) Gómez-Bengoa, E.; Jiménez, J.; Lapuerta, I.; Mielgo, A.; Oiarbide, M.; Velilla, I.; Vera, S.; Palomo, C. *Chem. Sci.* **2012**, *3*, 2949–For non-pyrrolidinic amines, see: f) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409. g) Ramasatry, S. S. V.; Zhang, H. Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 228–289. h) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018–1020.

generating α -chiral aminoesters with an adjacent quaternary stereocenter (Scheme 22).⁸¹



Scheme 22. Jørgensen's pioneering Brønsted base-catalyzed asymmetric Mannich reaction.

Thereafter, many enantioselective Mannich procedures catalyzed by chiral Brønsted bases, in general bifunctional ones, have been developed (Figure 5). Deng's and Takemoto's groups described the enantioselective addition of *N*-Boc imines to malonates⁸² and β -keto esters,⁸³ respectively, whereas the groups of Lu⁸⁴ and Jiang⁸⁵ disclosed the reaction with α -fluorinated β -keto esters. In addition, Lambert and co-workers reported the highly diastereo- and enantioselective Mannich reaction of the less reactive glycinate to *N*-Boc imines.⁸⁶

⁸¹ Poulsen, T.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899.

⁸² Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049.

⁸³ Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis*, **2007**, *16*, 2571–2575.

⁸⁴ Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607.

⁸⁵ Pan, Y.; Zhao, Y.; Ma, T.; Yang, Y.; Liu, H.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2010**, *16*, 779–782.

⁸⁶ Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799–11802.

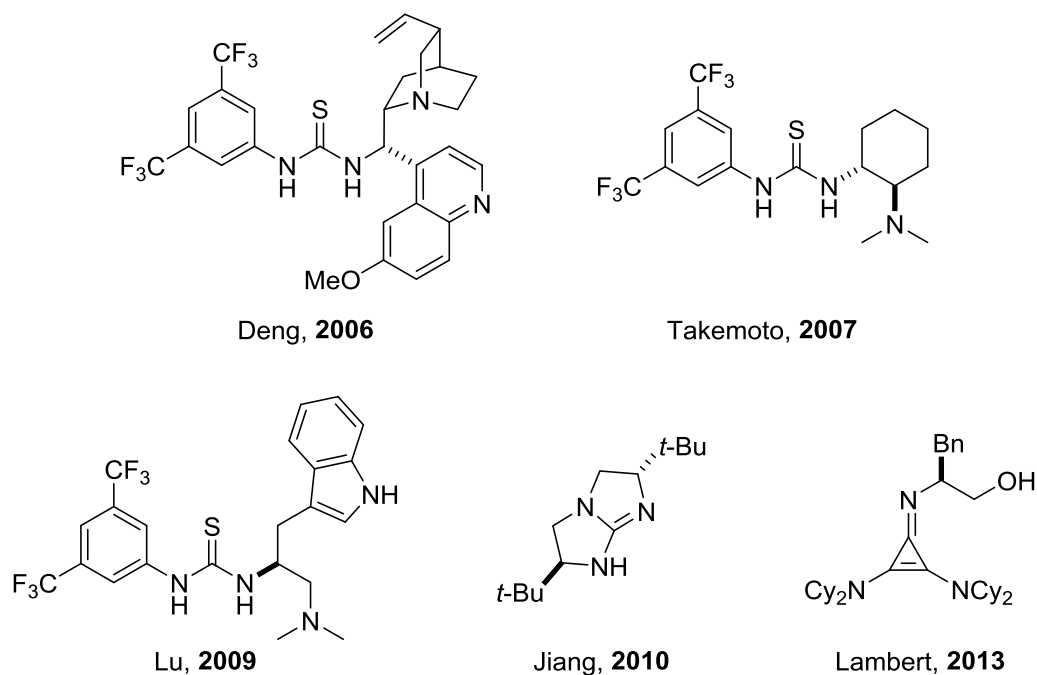
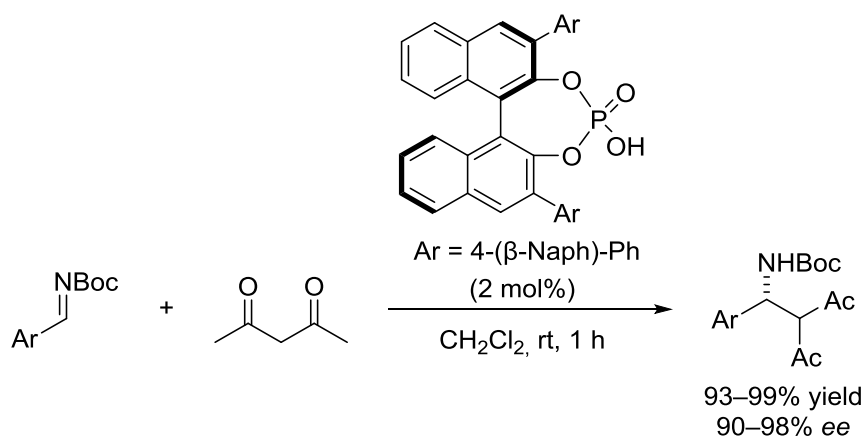


Figure 5. Representative Brønsted base catalysts for enantioselective Mannich reactions.

On the other hand, chiral Brønsted acids can also promote enantioselective Mannich reactions by protonating the imine and generating an iminium ion with an enantiopure counterion. In 2004, Terada and co-workers developed the first example of Brønsted acid-catalyzed asymmetric Mannich reaction employing a chiral phosphoric acid (Scheme 23).⁸⁷



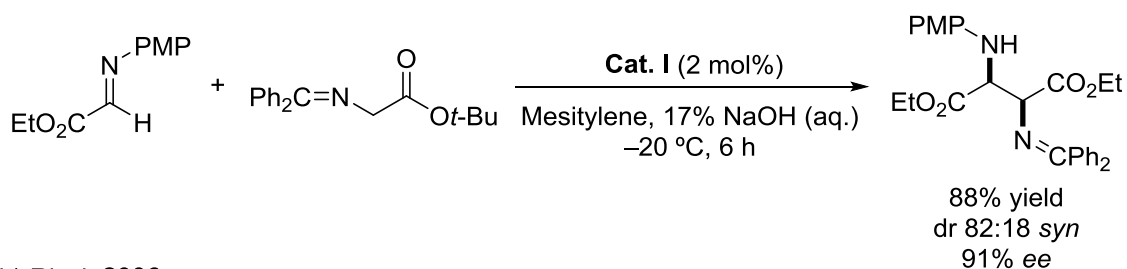
Scheme 23. Terada's pioneering Brønsted acid-catalyzed enantioselective Mannich reaction.

⁸⁷ a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. For more examples of Brønsted acid-catalyzed asymmetric Mannich reactions, see: b) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z.; *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791. c) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishitara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858–16860. d) Chen, Y.-Y.; Jiang, Y.-J.; Fan, Y.-S.; Sha, D.; Wang, G.; Zhang, G.; Zheng, L.; Zhang, S. *Tetrahedron: Asymmetry* **2012**, *23*, 904–909.

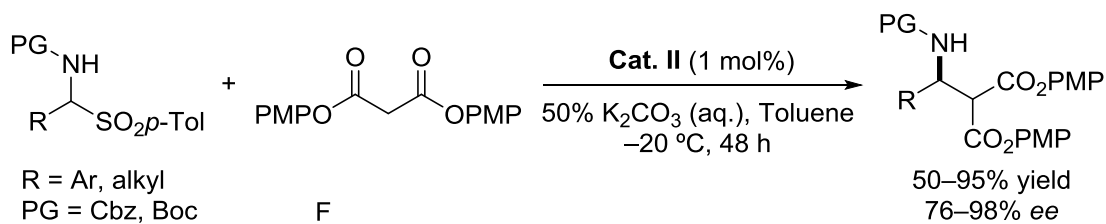
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The same year, Maruoka and co-workers described the first example of an asymmetric direct Mannich reaction under phase transfer conditions (Scheme 24a).⁸⁸ However, the first phase transfer catalyzed (PTC) enantioselective Mannich reaction, involving the *in situ* formation of *N*-Cbz and *N*-Boc imines, was developed by Ricci and co-workers in 2006. This example represents the first successful asymmetric direct-Mannich reaction with imines derived from enolizable aldehydes (Scheme 24b).⁸⁹ Since then, only one additional PTC Mannich approach has been reported, employing *tert*-butyl glycinate and *in situ* prepared aryl, alkyl, *E*-alkenyl and alkynyl *N*-Boc imines.⁹⁰

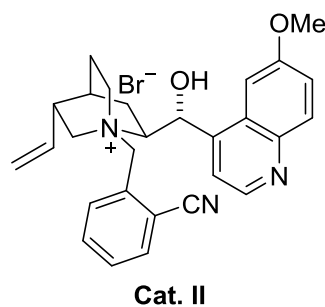
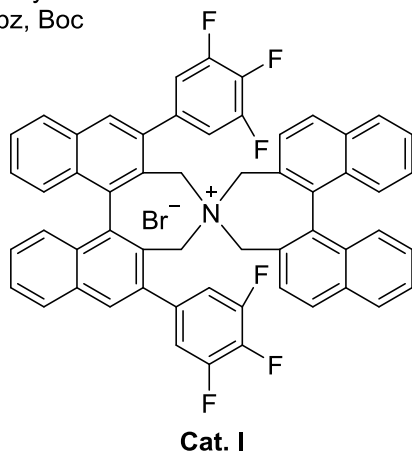
a) Maruoka, 2004



b) Ricci, 2006



R = Ar, alkyl
PG = Cbz, Boc



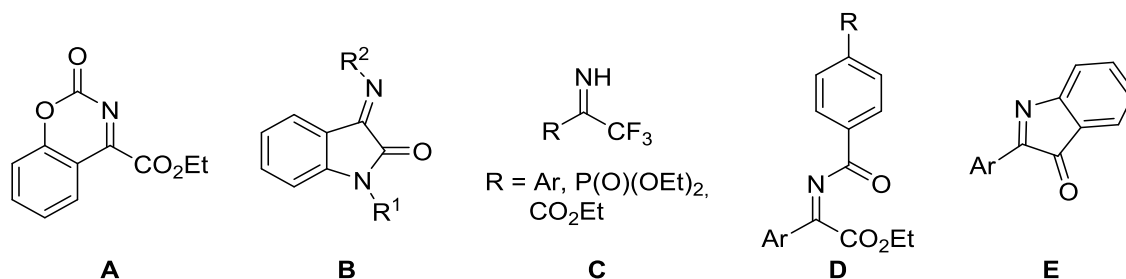
Scheme 24. Pioneering phase transfer catalyzed enantioselective Mannich reactions.

⁸⁸ a) Ooi, T.; Kameda, M.; Fujii, J.-I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397–2399. For a similar PTC approach, see: Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564–4567.

⁸⁹ Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043–2046.

⁹⁰ Kano, T.; Kobayashi, R.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 8471–8474.

Regarding the generation of tertiary amines, procedures are restricted to very particular active ketimines (Scheme 25).⁹¹ The group of Jørgensen was pioneer in using ketimines **A** in the zirconium-catalyzed enantioselective indirect Mannich reaction⁹² and the diastereo- and enantioselective direct Mannich reaction with aldehydes *via* enamine catalysis.⁹³ Isatin-derived scaffolds **B** are the most employed electrophiles of this type⁹⁴ whereas ketimines bearing an electron-withdrawing trifluoromethyl substituent **C** have also been employed in reactions with acetone⁹⁵ and diaryl diketones.⁹⁶ More recently, Terada and co-workers have reported a bis(guanidino)iminophosphorane-catalyzed asymmetric addition of thionolactones to iminoesters **D**⁹⁷ and Ma's group have developed a chiral phosphoric acid-catalyzed Mannich reaction of imines **E** with simple ketones.⁹⁸



Scheme 25. Ketimines in asymmetric Mannich reactions.

Importantly, Shibasaki and co-workers reported the use of simple *N*-phosphinoyl ketimines in the enantioselective indirect Mannich reaction⁹⁹ as well as in the enantio- and diastereoselective direct Mannich reaction with an α -isothiocyanate ester in which thioxoimidazolidines were afforded after cyclization of the Mannich adduct (Scheme

⁹¹ For a review on asymmetric addition to ketimines, see: Kumagai, N.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 503–517.

⁹² Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. A.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 6145–6154.

⁹³ Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476–4478.

⁹⁴ a) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512–2515. b) Tang, Z.; Shi, Y.; Mao, H.; Zhu, X.; Li, W.; Cheng, Y.; Zheng, W.-H.; Zhu, C. *Org. Biomol. Chem.* **2014**, *12*, 6085–6088. c) Engl, O. D.; Fritz, S. P.; Wennemers, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8193–8194. d) Dai, J.; Xiong, D.; Yuan, T.; Liu, J.; Chen, T.; Shao, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 12697–12701. e) Sawa, M.; Miyazaki, S.; Yonesaki, R.; Morimoto, H.; Ohshima, T. *Org. Lett.* **2018**, *20*, 5393–5397.

⁹⁵ a) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. *Tetrahedron: Asymmetry* **2008**, *19*, 761–764. b) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *Org. Lett.* **2011**, *13*, 1662–1665. c) Rassunaka, Y.; Yelenich, I. P.; Vlasenko, Y. G.; Onys'ko, P. P. *Tetrahedron: Asymmetry* **2014**, *25*, 1234–1238.

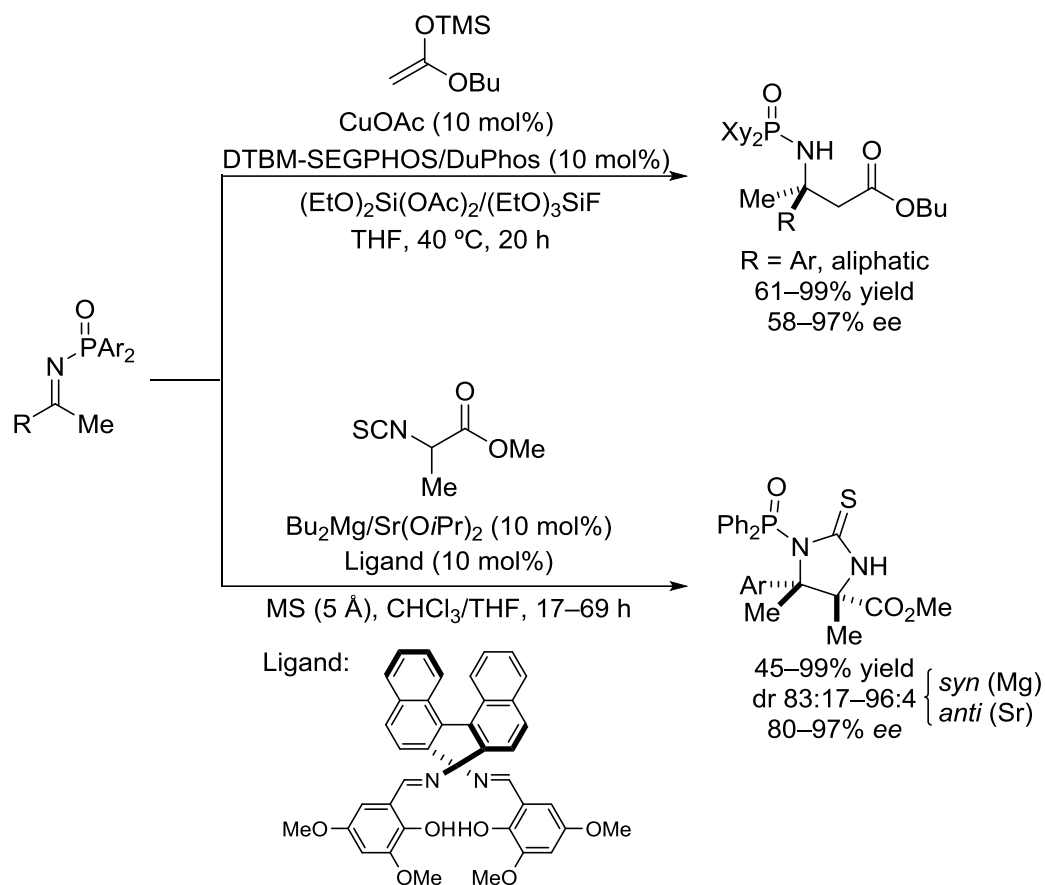
⁹⁶ Sawa, M.; Morisaki, K.; Kondo, Y.; Morimoto, H.; Ohshima, T. *Chem. Eur. J.* **2017**, *23*, 17022–17028.

⁹⁷ Takeda, T.; Kondoh, A.; Terada, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 4734–4737.

⁹⁸ Li, J. S.; Liu, Y.-J.; Li, S.; Ma, J.-A. *Chem. Commun.* **2018**, *54*, 9151–9154.

⁹⁹ a) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500–501. b) For an additional similar indirect example, see: Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147.

26).¹⁰⁰ Other groups have described the addition of isonitriles to *N*-phosphinoyl ketimines for the preparation of imidazolines¹⁰¹ but surprisingly, no direct Mannich reactions affording acyclic tertiary amines have been reported yet.



Scheme 26. Shibasaki's asymmetric Mannich reactions with *N*-phosphinoyl ketimines.

Despite the advances made in the catalytic asymmetric Mannich reaction, this transformation still presents some limitations such as the scarcity of methods for reactions with less activated pronucleophiles and/or imines derived from enolizable aldehydes.^{86,102} Moreover, as stated above, the generation of tertiary amines is restricted to the use of very particular active ketimines. Thus, the search for additional

¹⁰⁰ Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 4382–4385.

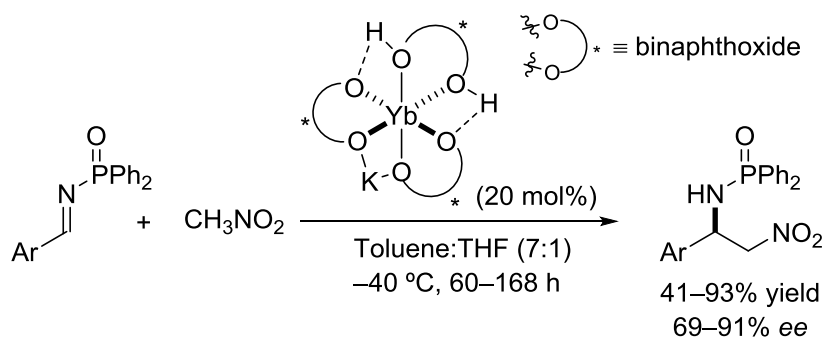
¹⁰¹ a) Nakamura, S.; Yamaji, R.; Iwanaga, M. *Chem. Commun.* **2016**, *52*, 7462–7465. b) de la Campa, R.; Yamagata, A. D. G.; Ortín, I.; Franchino, A.; Thompson, A. L.; Odell, B.; Dixon, D. J. *Chem. Commun.* **2016**, *52*, 10632–10635.

¹⁰² For examples of catalytic enantioselective Mannich reactions with aliphatic imines, see: a) Arai, T.; Moribatake, T.; Masu, H. *Chem. Eur. J.* **2015**, *21*, 10671–10675. b) Bae, H. Y.; Kim, M. J.; Sim, J. H.; Song, C. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 10825–10829. c) Echave, H.; Bastida, I.; López, R.; Palomo, C. *Chem. Eur. J.* **2018**, *24*, 11554–11558.

suitable substrates and more effective catalytic systems constitutes a challenge for next years.

- **Nitro-Mannich reaction**

Alternatively, there is a variant of the Mannich reaction which provides access to chiral diamines: the nitro-Mannich or aza-Henry reaction.¹⁰³ This transformation is based on the use of nitro alkanes as pronucleophiles in the addition to imines to produce β -nitro amines, which after reduction affords the mentioned diamines. In 1999, Shibasaki and co-workers described the first asymmetric nitro-Mannich reaction between nitromethane and *N*-phosphinoyl imines promoted by a heterobimetallic chiral complex of ytterbium and potassium, which works as a Lewis acid and a Brønsted base. The corresponding adducts were obtained with variable yields and enantioselectivities (Scheme 27).¹⁰⁴



Scheme 27. Shibasaki's pioneering metal-catalyzed asymmetric nitro-Mannich reaction.

A further improvement of the methodology with *N*-phosphinoyl imines was achieved employing an aluminium-lithium-binaphthoxide–potassium *tert*-butoxide complex (Figure 6) for the reaction with linear nitro alkanes to afford, for the first time, *anti* β -nitro amines with moderate to good diastereo- and enantioselectivities.¹⁰⁵ The same authors, also described, in 2007, the first and only metal-catalyzed *syn*-selective nitro-Mannich reaction of linear nitroalkanes to *N*-Boc imines employing a heterobimetallic samarium-copper complex,¹⁰⁶ which after further optimization of the catalytic system

¹⁰³ a) For a general review on nitro-Mannich reaction, see: Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887–2939. b) For a review on catalytic enantioselective nitro-Mannich reactions, see: Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401–2420.

¹⁰⁴ Yamada, K.-I.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506.

¹⁰⁵ a) Yamada, K.-I.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982. b) This procedure was also employed for the synthesis of bioactive compound CP-99994: Tsuritani, N.; Yamada, K.-I.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, *34*, 276–277.

¹⁰⁶ Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900–4901.

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was extended to *N*-Boc aliphatic imines with excellent yields and diastereo- and enantioselectivities.¹⁰⁷ Finally, in 2008, they designed a homodinuclear nickel catalyst for the asymmetric addition of nitro acetates to *N*-Boc imines for the preparation of α -quaternary *anti*- α,β -diamino acids.¹⁰⁸

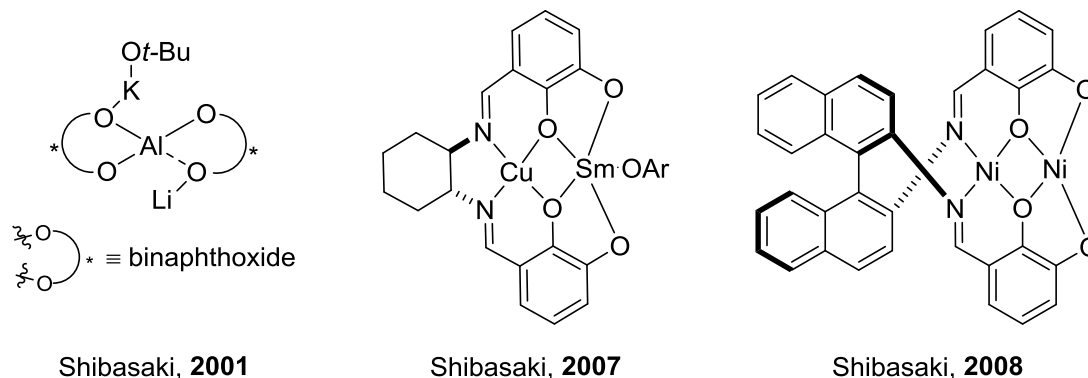


Figure 6. Metal catalysts employed in asymmetric nitro-Mannich reactions by Shibasaki's group.

Several groups have also developed metal-catalyzed asymmetric nitro-Mannich methodologies (Figure 7). For instance, in 2001, Jørgensen and co-workers described the direct¹⁰⁹ and indirect¹¹⁰ *anti*-selective nitro-Mannich reactions promoted by Cu(II)-bisoxazoline complexes with *N*-PMP iminoesters and linear nitroalkanes. The group of Anderson described, in 2005, a similar indirect approach where non-activated aromatic, heteroaromatic and aliphatic *N*-PMP imines were added for the first time to propyl nitronates with high yields and *anti*-stereoselectivities.¹¹¹ Thereafter, several metal based catalytic systems, such as zinc,¹¹² copper,¹¹³ cobalt¹¹³ and iron,¹¹⁴ have been reported.

¹⁰⁷ Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925–4934.

¹⁰⁸ Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171.

¹⁰⁹ Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2992–2995.

¹¹⁰ Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844.

¹¹¹ Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665–5670.

¹¹² a) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117–120. b) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023–2026.

¹¹³ Arai, T.; Matsumura, E. *Synlett* **2014**, *25*, 1776–1780.

¹¹⁴ Dudek, A.; Mlynarski, J. *J. Org. Chem.* **2017**, *82*, 11218–11224.

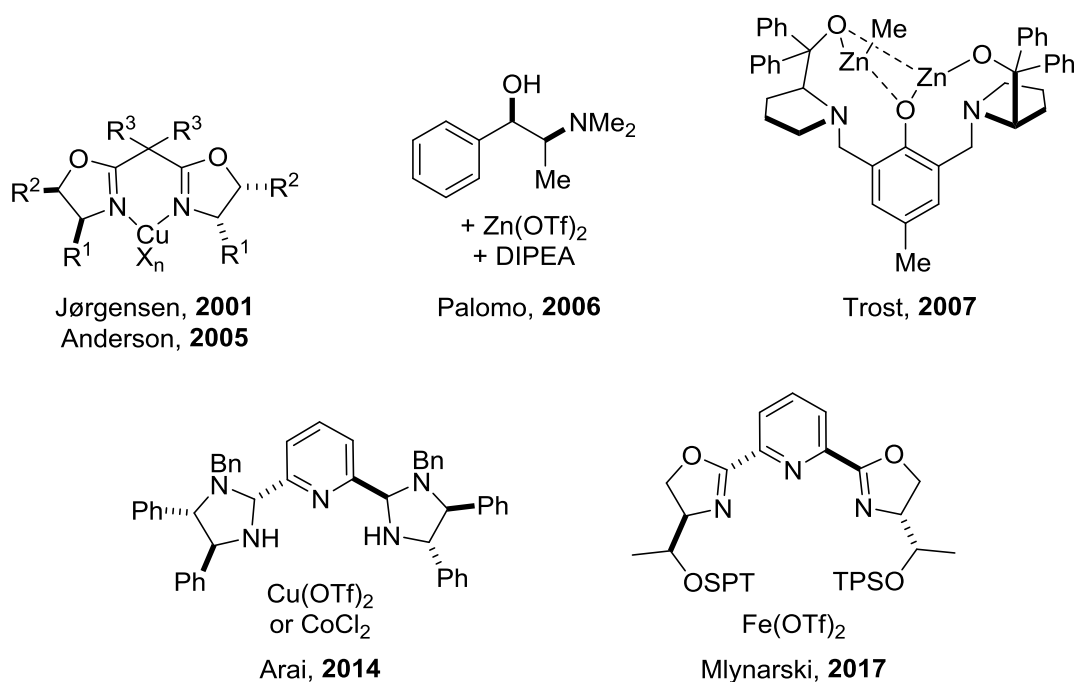


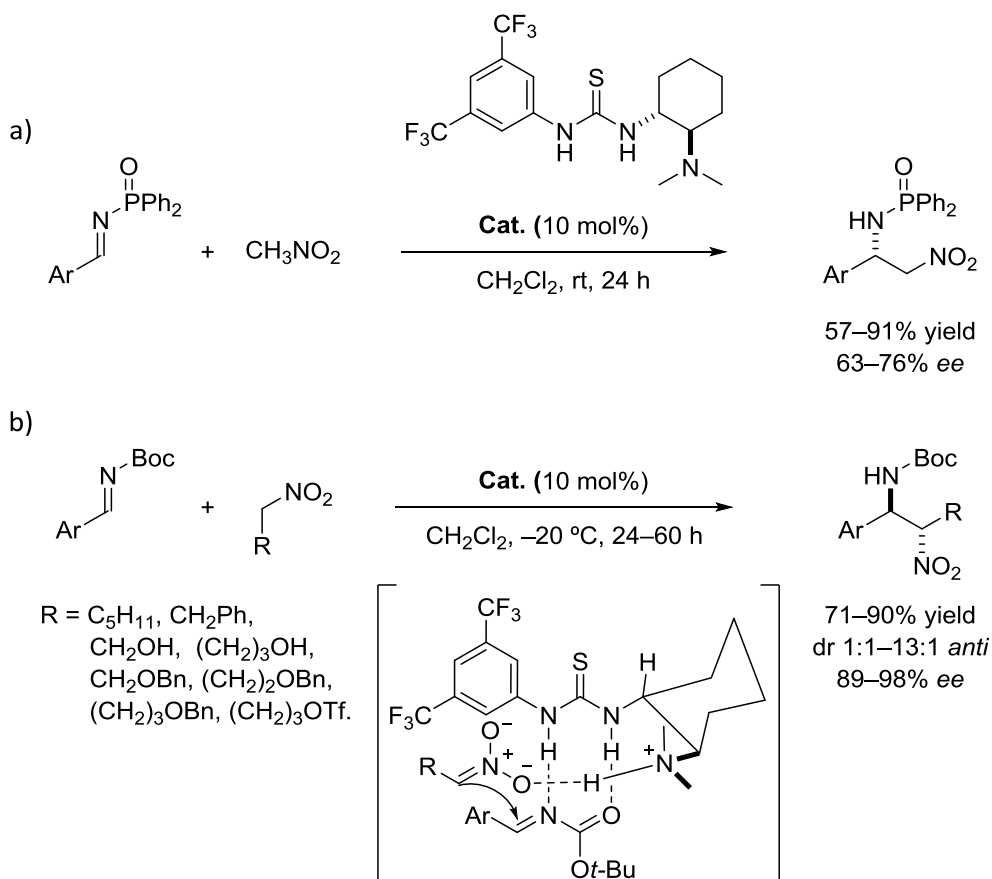
Figure 7. Representative metal catalysts in enantioselective nitro-Mannich reactions.

Regarding metal-free approaches, in 2004, Takemoto and co-workers described the first organocatalytic enantioselective nitro-Mannich procedure with *N*-phosphinoyl aromatic imines and nitromethane, under chiral Brønsted base catalysis, with good yields and moderate enantioselectivities (Scheme 28a).¹¹⁵ Further optimization of the method revealed that better stereocontrol could be achieved employing *N*-Boc imines instead (Scheme 28b). In order to explain the observed stereoselectivities, they suggested the formation of a trimolecular complex, in which the *N*-Boc imine is coordinated to the thiourea group through hydrogen-bonding interactions while the protonated amine approaches the nitronate to the imine inducing the attack to the less hindered face.¹¹⁶

¹¹⁵ Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627.

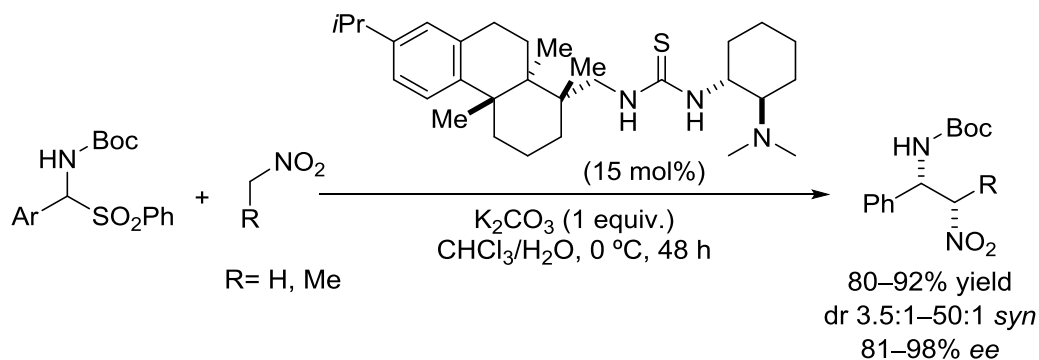
¹¹⁶ Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2005**, *12*, 466–476.

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Scheme 28. Takemoto's pioneering organocatalytic asymmetric nitro-Mannich reaction.

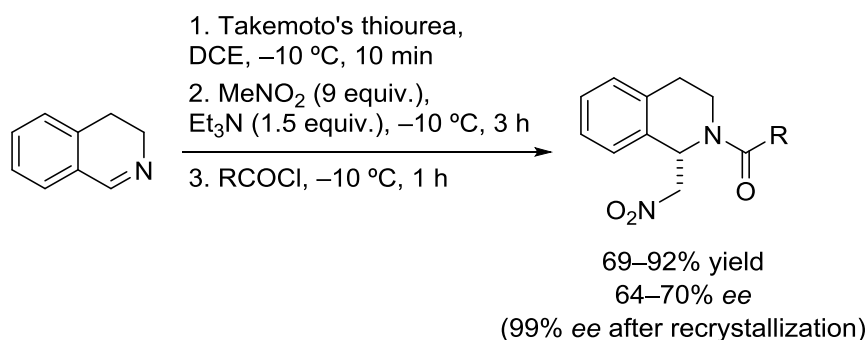
In 2009, Wang and co-workers described a Brønsted base catalyzed asymmetric nitro-Mannich procedure in which *N*-Boc imines were generated *in situ* employing 1 equivalent of potassium carbonate. The rosin-derived thiourea-Brønsted base promoted the addition of nitromethane and nitroethane with generally good yield and stereoselectivity (Scheme 29).¹¹⁷



Scheme 29. Wang's asymmetric nitro-Mannich reaction with *in situ* generated imines.

¹¹⁷ Jiang, X.; Zhang, Y.; Wu, L.; Zhang, G.; Liu, X.; Zhang, H.; Fu, D.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096–2100.

In 2012, the group of Todd reported the first catalytic enantioselective nitro-Mannich reaction with a non-activated cyclic imine employing Takemoto's thiourea. In this case, the nitro amine intermediate is trapped through acylation to produce the corresponding adducts with moderate enantioselectivities. Nevertheless, single recrystallization of the products provided the corresponding enantiopure compounds (Scheme 30).¹¹⁸



Scheme 30. Todd's asymmetric nitro-Mannich reaction with non-activated cyclic imines.

Furthermore, the catalytic nitro-Mannich reaction has been employed in the context of cascade processes with very high success.¹¹⁹

Other structurally diverse bifunctional Brønsted base organocatalysts have also been designed for the stereoselective nitro-Mannich reaction (Figure 8). In 2011, Johnston and co-workers reported the first highly diastereo- and enantioselective addition of aryl nitromethanes to *N*-Boc imines employing the pyrrolidine BisAMidine (PBAM) catalyst.¹²⁰ In 2014, Gong, Meggers and co-workers designed a very efficient iridium-templated chiral Brønsted base organocatalyst for the reaction of aryl or thiopenyl nitromethanes with *N*-Boc imines.¹²¹ In addition, Ooi and co-workers employed a chiral ammonium betaine catalyst for the same reaction with aryl nitromethanes. They proposed that the aryloxy basic moiety promotes the nitronate generation, which is stabilized by the quaternary amine *via* ionic interaction.¹²²

¹¹⁸ Amarasinghe, N. R.; Turner, P.; Todd, M. H. *Adv. Synth. Catal.* **2012**, *354*, 2954–2958.

¹¹⁹ For selected examples, see: a) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290–5293. b) Barber, D. M.; Āuriš, A.; Thompson, A. L.; Sanganee, H. J.; Dixon, D. J. *ACS Catal.* **2014**, *4*, 634–638. c) Hahn, R.; Jafari, E.; Raabe, G.; Enders, D. *Synthesis* **2015**, *47*, 472–480. d) Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2015**, *13*, 6825–6831.

¹²⁰ a) Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076–1079. For further applications of this reaction, see: b) Dobish, M. C.; Villalta, F.; Waterman, M. R.; Lepesheva, G. I.; Johnston, J. N. *Org. Lett.* **2012**, *14*, 6322–6325. c) Tsukanov, S. V.; Johnson, M. D.; May, S. A.; Rosemeyer, M.; Watkins, M. A.; Kolis, S. P.; Yates, M. H.; Johnston, J. N. *Org. Process Res. Dev.* **2016**, *20*, 215–226.

¹²¹ Ma, J.; Ding, X.; Hu, Y.; Huang, Y.; Gong, L.; Meggers, E. *Nat. Commun.* **2014**, *5*, 4531–4536.

¹²² a) Uraguchi, D.; Oyaizu, K.; Noguchi, H.; Ooi, T. *Chem. Asian J.* **2015**, *10*, 334–337. b) A similar catalytic system was employed for the asymmetric Mannich-type reaction with α -nitro esters: Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879.

Introduction

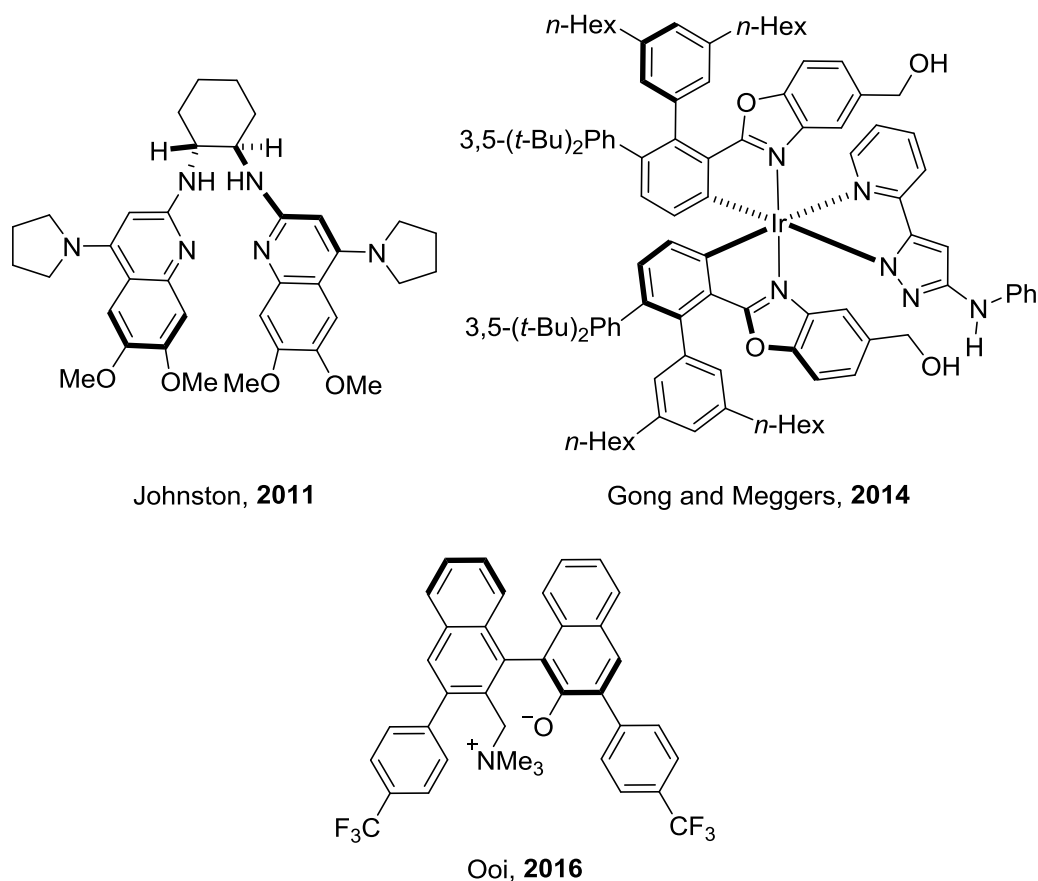


Figure 8. Structurally diverse bifunctional Brønsted bases in asymmetric nitro-Manich reactions.

Besides bifunctional Brønsted bases, purely hydrogen-bonding chiral catalysts have also been employed, along with external achiral bases, in asymmetric nitro-Mannich reactions (Figure 9).^{123–125} Although with catalysts such as those represented in Figure 8 good results have been obtained, the competitive racemic pathway promoted by the base alone constitutes the major problem of this approach.

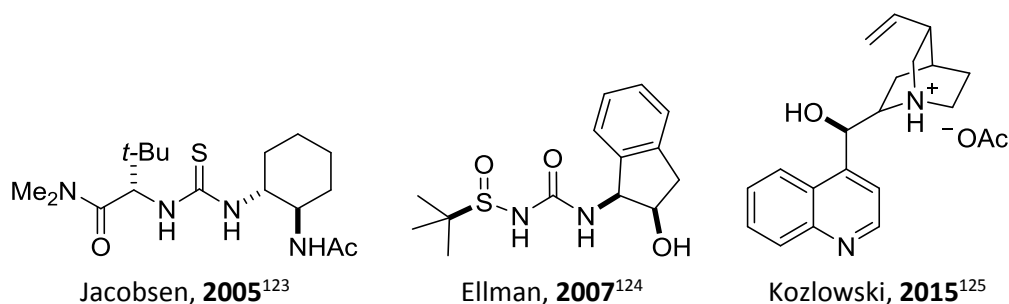


Figure 9. Representative H-bonding organocatalysts.

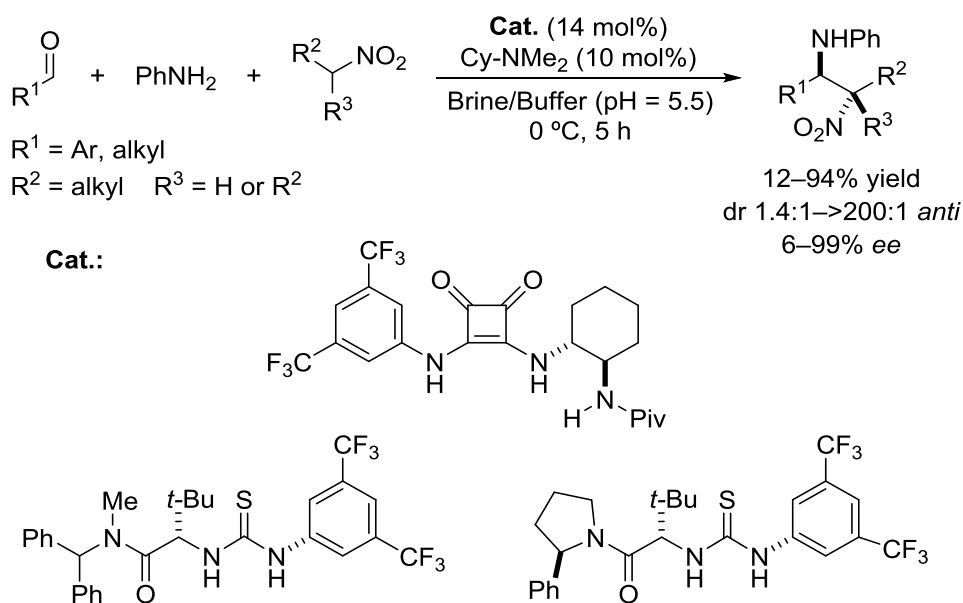
¹²³ Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.

¹²⁴ Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110–15111.

¹²⁵ Walvoord, R. R.; Kozlowski, M. C. *Tetrahedron Lett.* **2015**, *56*, 3070–3074.

Chapter 1

In 2013, the group of de Armas and García-Tellado described the water-compatible stereoselective multicomponent nitro-Mannich reaction. Aromatic and aliphatic *N*-phenyl imines were synthesized *in situ* and reacted with several nitroalkanes including symmetric tertiary nucleophiles, such as 2-nitropropane, nitrocyclopentane and nitrocyclohexane, employing a variety of squaramide- or thiourea-type H-bonding organocatalysts and substoichiometric amounts of *N,N*-dimethyl cyclohexylamine as Brønsted base. (Scheme 31).¹²⁶



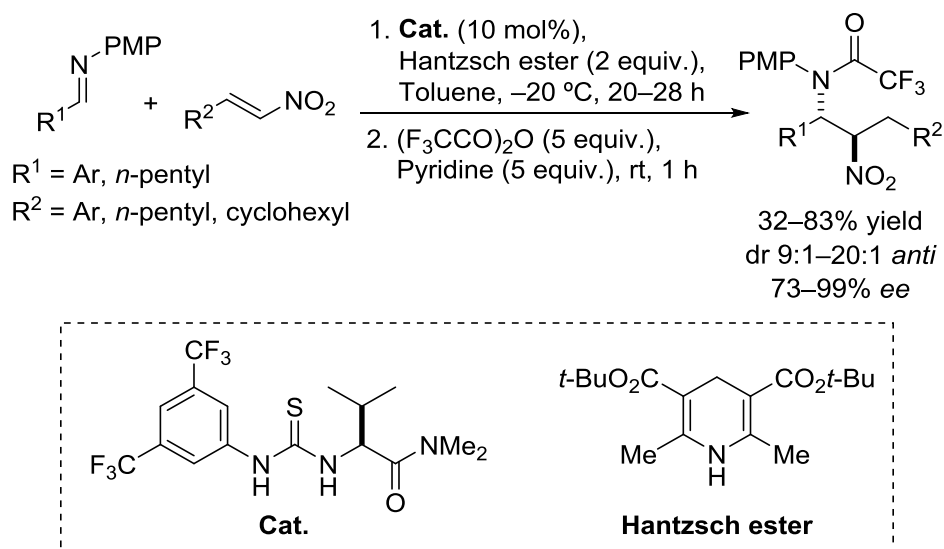
Scheme 31. Garcia-Delgado's water-compatible asymmetric multicomponent nitro-Mannich reaction.

Anderson and co-workers developed an interesting approach to β -nitro amines consisting of nitroolefin reduction, employing the Hantzsch ester, and subsequent nitronate addition to imines *via* hydrogen-bonding activation (Scheme 32).¹²⁷

¹²⁶ Cruz-Acosta, F.; De Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2013**, *19*, 16550–16554.

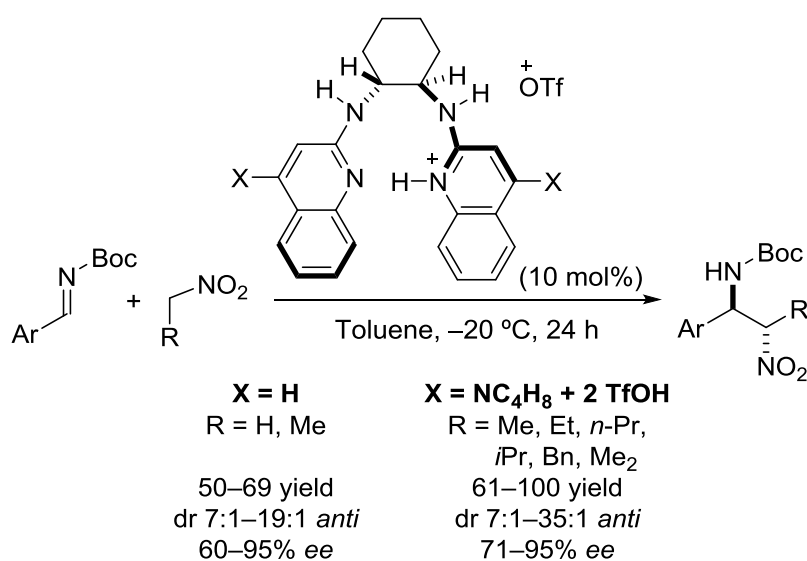
¹²⁷ a) Anderson, J. C.; Koovits, P. J. *Chem. Sci.* **2013**, *4*, 2897–2901. b) For the intramolecular version of the reaction, see: Anderson, J. C.; Barham, J. P.; Rundell, C. D. *Org. Lett.* **2015**, *17*, 4090–4093.

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Scheme 32. Anderson's asymmetric tandem reduction/nitro-Mannich reactions.

On the other hand, Johnston and co-workers reported, in 2004, the first stereoselective example of Brønsted acid catalyzed nitro-Mannich reaction. They designed a protonated version of the BisAMidine catalyst, able to promote the addition of nitroalkanes to *N*-Boc imines (Scheme 33).¹²⁸

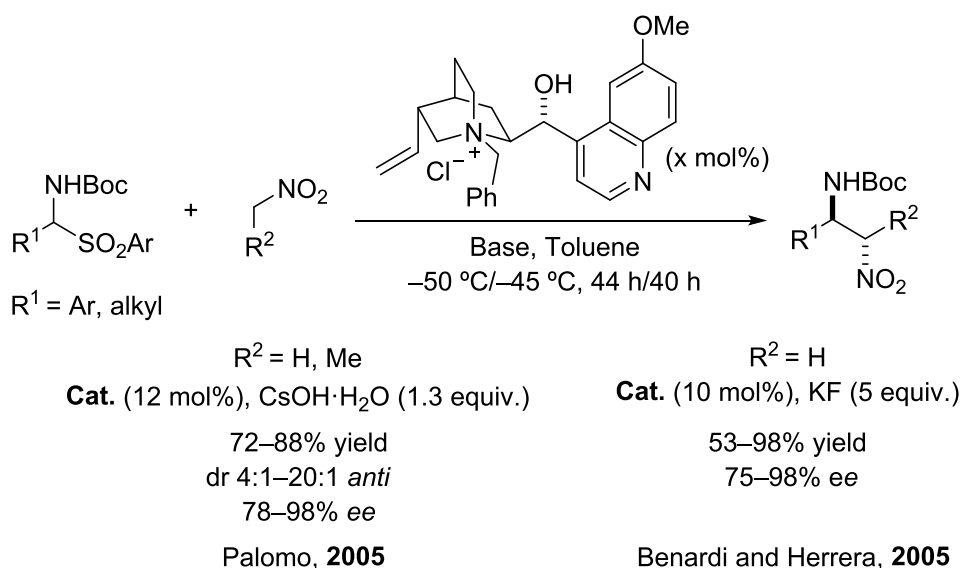


Scheme 33. Johnston's Brønsted acid-catalyzed asymmetric nitro-Mannich reaction.

Finally, the use of chiral organic salts, generally quaternary ammonium salts, in combination with inorganic bases in biphasic systems has also been effective for

¹²⁸ a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419. b) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880–2882. c) Schwieter, K. E.; Johnston, J. N. *ACS Catal.* **2015**, *5*, 6559–6562. d) Vara, B. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2016**, *138*, 13794–13797. For an example employing chiral phosphoric acid catalyst, see: e) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731–1734.

asymmetric nitro-Mannich procedures. Those basic reaction conditions are suitable for nitronate generation as well as to promote *in situ* formation of *N*-acyl or *N*-sulfonyl imines from the corresponding *N*-protected amino sulfones. This type of catalysis, moreover, allows the expansion of the methodology to imines coming from enolizable aldehydes. In fact, the first catalytic asymmetric nitro-Mannich procedure compatible with these imines was developed under phase transfer conditions. In 2005, our research group¹²⁹ and Herrera, Bernardi and co-workers,¹³⁰ concurrently, described the *N*-benzyl quininium chloride-catalyzed nitromethane addition to *N*-carbamoyl imines in phase transfer conditions. Both methodologies employed α -amido sulfones as starting material, providing the corresponding β -nitroamines with good yields and excellent stereoselectivities (Scheme 34).



Scheme 34. Pioneering phase transfer catalyzed asymmetric nitro-Mannich reactions.

After these pioneering works, other phase-transfer catalytic systems were developed for the asymmetric nitro-Mannich reaction (Figure 10).¹³¹⁻¹³⁴ All of them, in combination with inorganic salts, successfully allowed the use of aliphatic imines in the reaction.

¹²⁹ Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623.

¹³⁰ Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975–7978.

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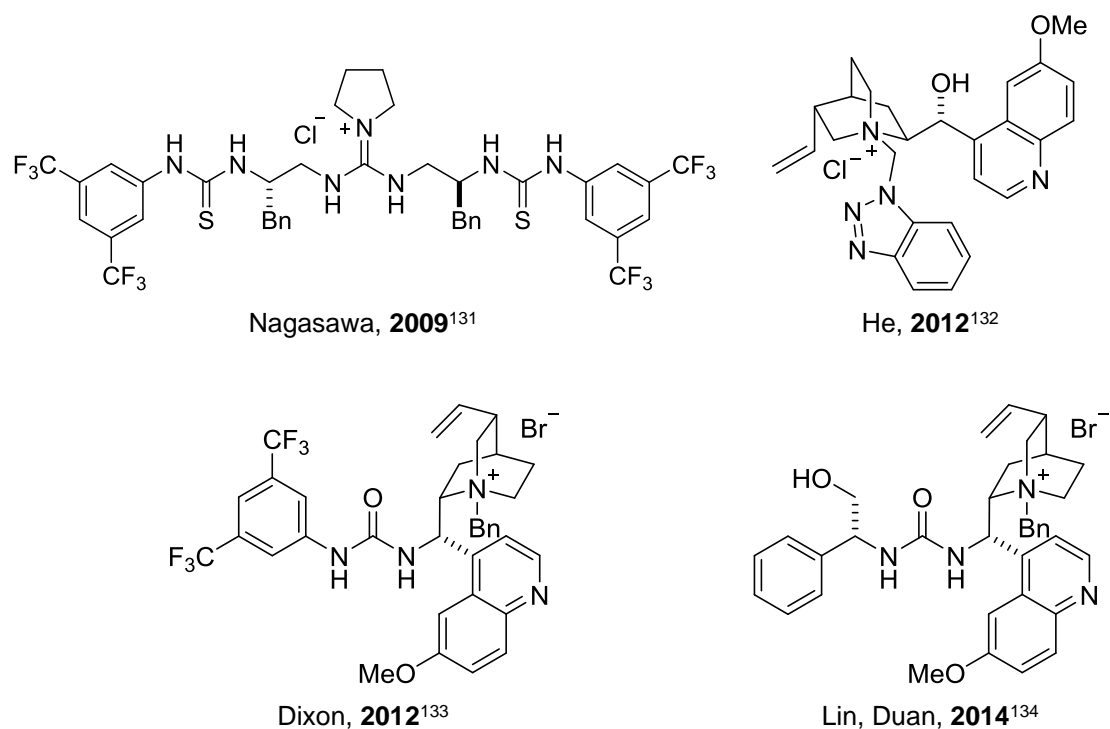


Figure 10. Phase transfer catalysts in asymmetric nitro-Mannich reactions.

Finally, the asymmetric synthesis of tertiary amines employing ketimines has been underexplored and the few examples described, mainly consist of the addition of nitromethane, nitroethane or (nitromethyl)benzene to particularly active isatin-derived ketimines.¹³⁵ In 2008, Feng and co-workers described the first enantioselective nitro-Mannich reaction with *N*-tosyl ketimines employing a chiral copper(I) catalyst (Figure 11). The reaction was very slow –generally required more than 10 days to go to completion– and moderate yields were obtained.¹³⁶ Later, Dixon and co-workers designed a bifunctional iminophosphorane organocatalyst for the reaction with *N*-phosphinoyl ketimines. The reactions were faster –24 to 96 hours to completion– and high yields and enantioselectivities were achieved.¹³⁷ More recently, the group of Lin

¹³¹ a) Takada, K.; Nagasawa, K. *Adv. Synth. Catal.* **2009**, *351*, 345–347. b) Huang, W.; Peng, C.; Guo, L.; Hu, R.; Han, B. *Synlett* **2011**, 2981–2984.

¹³² Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704–707.

¹³³ a) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492–2495. b) Clark, P. G. K.; Vieira, L. C. C.; Tallant, C.; Fedorov, O.; Singleton, D. C.; Rogers, C. M.; Monteiro, O. P.; Bennett, J. M.; Baronio, R.; Müller, S.; Daniels, D. L.; Méndez, J.; Knapp, S.; Brennan, P. E.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 6217–6221.

¹³⁴ Wang, B.; Liu, Y.; Sun, C.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *Org. Lett.* **2014**, *16*, 6432–6435.

¹³⁵ a) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768–2771. b) Liu, Y.; Liu, Y.; Wang, J.; Wei, Z.; Cao, J.; Liang, Y.; Lin, Y.; Duan, H. *Tetrahedron Lett.* **2017**, *58*, 2400–2403. c) Liu, Y.; Wang, J.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *New. J. Chem.* **2018**, *42*, 1608–1611.

¹³⁶ Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305–5308.

¹³⁷ Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

and Duan have reported a phase-transfer-catalyzed nitro-Mannich reaction of *N*-6-methyl-2-pyridylsulfonyl protected ketimines with nitromethane.¹³⁸

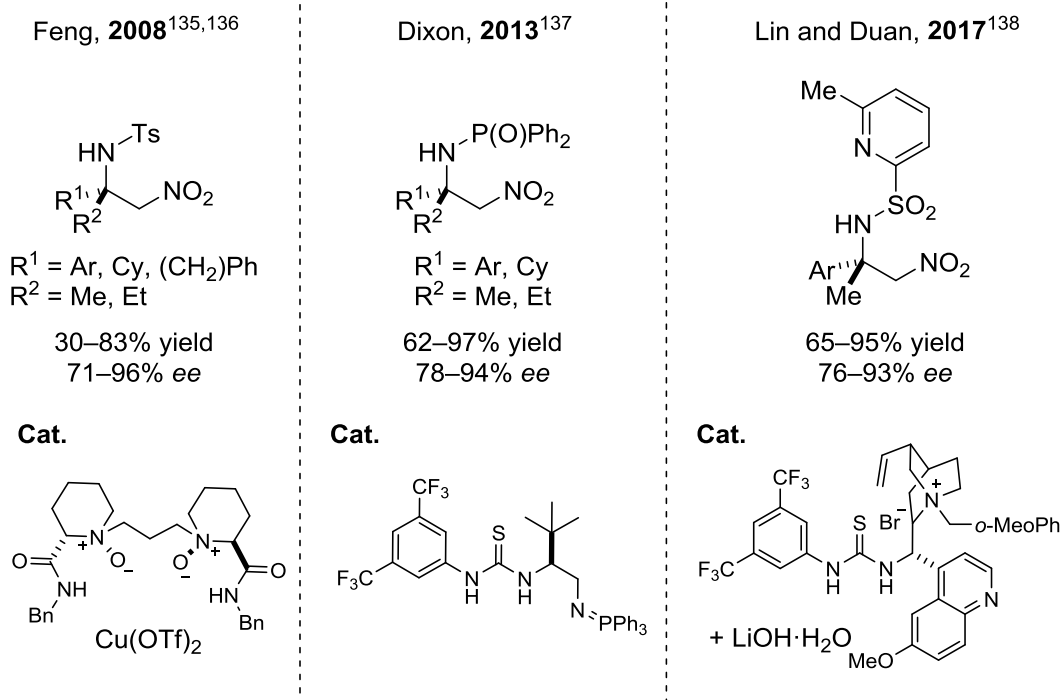


Figure 11. Enantioselective nitro-Mannich reactions with ketimines.

In conclusion, the nitro-Mannich reaction still presents some limitations for its application in the stereoselective synthesis of chiral amines. Regarding the azomethine component, imines derived from enolizable aldehydes have been scarcely explored, mainly under phase transfer conditions, and the use of ketimines to produce chiral tertiary amines is generally restricted to isatin-derived ketimines. With respect to the nucleophilic component, linear and non-functionalized nitroalkanes are used in most nitro-Mannich transformations.

Furthermore, the synthesis of α -chiral amines through nucleophilic asymmetric additions to imines is mainly limited to highly acidic pronucleophiles, such as α -carbonyl compounds in the Mannich reaction and nitroalkanes in the nitro-Mannich reaction. In consequence, the search of structurally different suitable pronucleophiles for their addition to azomethine scaffolds is also at the forefront of current research.

¹³⁸ Wang, B.; Xu, T.; Zhu, L.; Lan, Y.; Wang, J.; Lu, N.; Wei, Z.; Lin, Y.; Duan, H. *Org. Chem. Front.* **2017**, *4*, 1266–1271.

1.2. Objectives

As mentioned in the first section, the structural diversity of α -chiral amines and the arousing interest for their potential as therapeutic agents, chiral ligands and, in general, synthetically valuable molecules, prompt the development of new catalytic methodologies with enhanced efficiency, sustainability and production cost. In this context, the overall aim of this Ph. D. work consists of the development of new Brønsted base catalyzed methodologies for the synthesis of enantiomerically enriched amines of synthetic utility and with possible biological activity.

Chiral Brønsted base catalyzed transformations are a straightforward way to assembly simple starting materials into optically active functionalized fragments, since only proton transfer occurs between substrates and products.¹³⁹ Due to the intrinsic non-directional nature of the ionic interactions established with reactants, bifunctional Brønsted base catalysts, bearing hydrogen bond donor groups, have become much more suitable catalysts for asymmetric reactions. Among them, *Cinchona* alkaloids,¹⁴⁰ thiourea-¹¹⁵ and squaramide-based¹⁴¹ Brønsted bases are the most representative bifunctional organocatalysts (Figure 12).

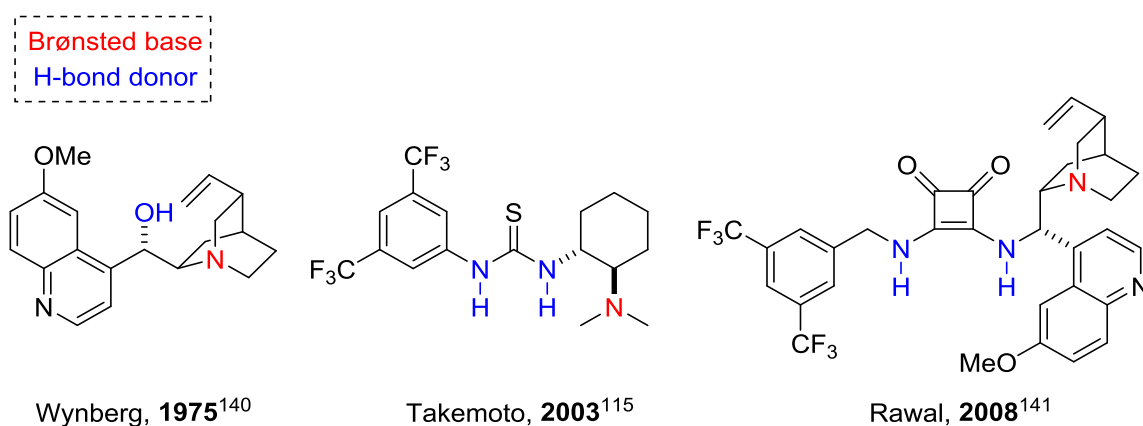


Figure 12. Most representative bifunctional Brønsted base organocatalysts.

¹³⁹ For selected reviews, see: a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. b) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145–200. c) Teng, B.; Lim, W. C.; Tan, C.-H. *Synlett* **2017**, *28*, 1272–1277. For a book chapter, see: d) Ting, A.; Schaus, S. E. *Brønsted Bases*. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Dalko, P. I., Ed. Wiley-VCH: Weinheim, 2013. Vol. 2, pp 343–363.

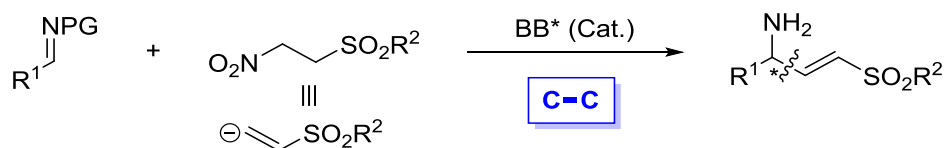
¹⁴⁰ Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057–4060.

¹⁴¹ Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.

In spite of the developments made based on these pioneering works,¹⁴² bifunctional Brønsted-base catalyzed reactions still show strong dependence on both substrate and catalyst structures. Thus, research on this field is centered on the design of more efficient and general organocatalysts able to activate less reactive pronucleophiles in a stereocontrolled manner. At the same time, the search for minimally modified pronucleophiles in order to enhance their reactivity and favor their interaction with the catalysts has attracted much attention.

In this context, this Ph. D. work will try to give evidence of the potential of Brønsted base catalyzed carbon–carbon and carbon–heteroatom bond forming reactions by properly setting subtle modifications in the reaction counterparts.

Many structures derived from enantiomerically pure γ -sulfonyl allyl amines have shown capacity to inhibit a wide variety of enzymatic processes. Nevertheless, the structural requirements for an optimal enzyme-substrate recognition are still unknown and the elaboration of this type of structures could lead to the identification of more specific inhibitors or ones with better pharmacological properties. Thus, the first objective of this work is the preparation of optically active γ -sulfonyl allyl amines by developing a Brønsted base catalyzed nitro-Mannich reaction with 2-nitroethyl sulfones as vinyl sulfone anion equivalents (Scheme 35).

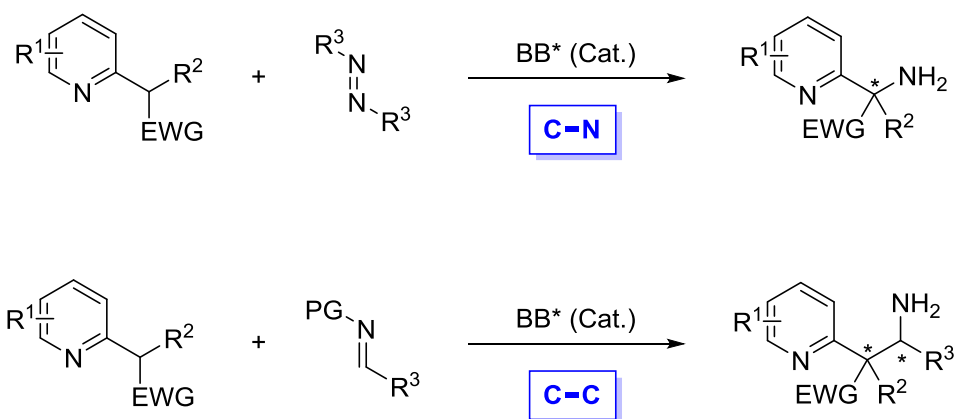


Scheme 35. Synthetic plan for the asymmetric preparation of γ -sulfonyl allyl amines.

On the other hand, *ortho*-substituted pyridines are common fragments in chiral compounds with biological activity. In particular, α - and/or β -functionalized pyridines containing amino groups constitute a relevant family. Thus, the second objective of the present thesis is to explore the potential of 2-alkyl pyridines as pronucleophiles in Brønsted base catalyzed α -aminations and Mannich type reactions to produce enantiomerically enriched tertiary and secondary amines, respectively (Scheme 36).

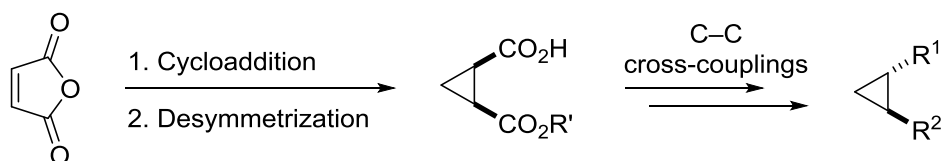
¹⁴² For selected reviews in bifunctional Brønsted base organocatalysis, see: a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. b) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. c) Lattanzi, A. *Chem. Commun.* **2009**, 1452–1463. d) Cucinotta, C.S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. *Chem. Eur. J.* **2009**, *15*, 7913–7921. e) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, *23*, 490–508. f) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

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Scheme 36. Synthetic plan for the asymmetric preparation of *ortho*-substituted pyridyl amines.

Finally, the results obtained during a short stay carried out at The Scripps Research Institute in La Jolla (California, USA), under the supervision of Prof. Baran are also included in this Ph.D. thesis. The main objective of the project consists of the preparation of a library of *trans*-disubstituted cyclopropanes through cycloaddition followed by desymmetrization and two consecutive cross coupling reactions (Scheme 37).



Scheme 37. Synthetic plan for the stereoselective modular preparation of *trans*-disubstituted cyclopropanes.

Challenges for each particular objective, working hypothesis and the state of the art along with the results obtained for each project will be presented in three different chapters:

- Chapter 2: Enantioselective synthesis of γ -sulfonyl allyl amines.
- Chapter 3: Stereoselective synthesis of pyridine based tertiary and secondary amines.
- Chapter 4: Stereoselective modular synthesis of *trans*-disubstituted cyclopropanes.

Chapter 2

Enantioselective synthesis of γ -sulfonyl allyl amines

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2. ENANTIOSELECTIVE SYNTHESIS OF γ -SULFONYL ALLYL AMINES

2.1. Introduction

2.1.1. γ -Sulfonyl allyl amines

Many structures derived from enantiomerically pure γ -sulfonyl allyl amines –also known as γ -amino vinyl sulfones– have shown capacity to act as cysteine protease inhibitors (Figure 13).¹⁴³

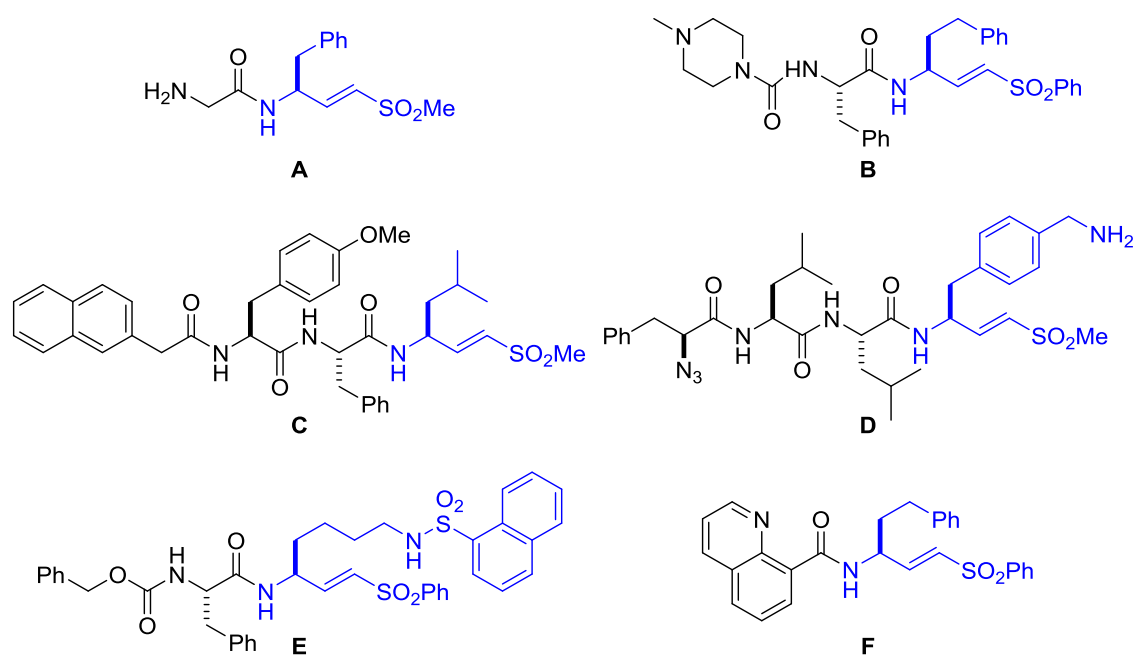
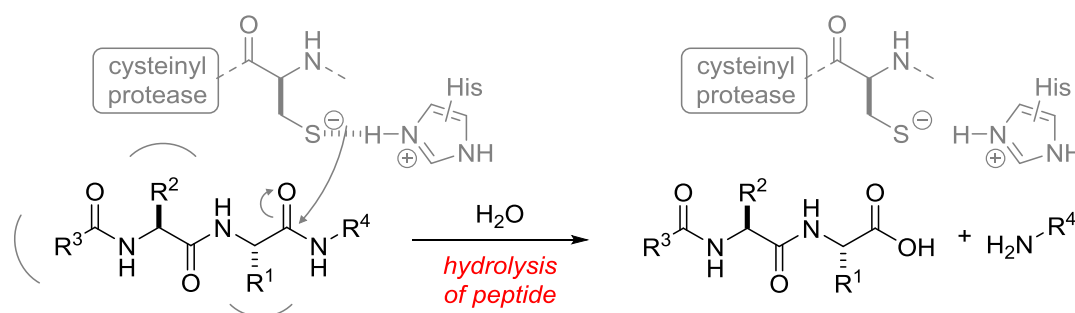


Figure 13. γ -Sulfonyl allyl amines with inhibitory activity.

¹⁴³ For a review about cysteine proteases and its inhibition, see: Lecaille, F.; Kaleta, J.; Brömme, D. *Chem. Rev.* **2002**, *102*, 4459–4488.

Structures **A**¹⁴⁴ and **B**¹⁴⁵ have exhibit activity against dipeptidyl aminopeptidase I (DPP-I) and cruzipain, respectively. Peptidyl vinyl sulfones **C**¹⁴⁶ and **D**¹⁴⁷ act as site-selective proteasome inhibitors; **C** is a β 5 specific inhibitor whilst compound **D** is active in trypsin-like sites. Additionally, γ -sulfonyl allyl amines **E**¹⁴⁸ and **F**¹⁴⁹ have recently shown activity as anti-trypanosomal agents to treat African trypanosomiasis –an African sleeping sickness caused by protozoan parasite *Trypanosoma brucei* transmitted by the tsetse fly.–

Cysteine proteases are proteolytic enzymes involved in the degradation of proteins, implicated in very diverse processes ranging from cardiovascular, neurological, respiratory, musculoskeletal, immunological, CNS and other disorders to cancer. Moreover, they are essential for the life cycle of several parasites such as falcipain –the causing agent of malaria– and rodhesain from *Trypanosoma brucei*. The activity of these cysteine proteases is based on a nucleophilic cysteine residue within the active site, which assists in the peptide bond hydrolysis (Scheme 38).^{148,150}



Scheme 38. Cysteine protease-based peptide hydrolysis.

Of the several types of compounds developed as cysteine protease inhibitors, most rely on covalent derivatization of the key cysteine residue. Among them, Michael-type

¹⁴⁴ Thompson, S. A.; Andrews, P. R.; Hanzlik, R. P. *J. Med. Chem.* **1986**, *29*, 104–111.

¹⁴⁵ Palmer, J. T.; Rasnik, D.; Klaus, J. L.; Brömme, D. *J. Med. Chem.* **1995**, *38*, 3193–3196.

¹⁴⁶ a) Screen, M.; Britton, M.; Downey, S. L.; Verdoes, M.; Voges, M. J.; Blom, A. E. M.; Geurink, P. P.; Risseuw, M. D. P.; Florea, B. I.; van der Linden, W. A.; Pletnev, A. A.; Overkleeft, H. S.; Kisselev, A. F. *J. Biol. Chem.* **2010**, *285*, 40125–40134. b) Verdoes, M.; Willems, L. I.; van der Linden, W. A.; Duivenvoorden, B. A.; van der Marel, G. A.; Florea, B. I.; Kisselev, A. F.; Overkleeft, H. S. *Org. Biomol. Chem.* **2010**, *8*, 2719–2727.

¹⁴⁷ Geurink, P. P.; van der Linden, W. A.; Mirabella, A. C.; Gallastegui, N.; de Briun, G.; Blom, A. E. M.; Voges, M. J.; Mock, E. D.; Florea, B. I.; van der Marel, G. A.; Driessen, C.; van der Stelt, M.; Groll, M.; Overkleeft, H. S.; Kisselev, A. F. *J. Med. Chem.* **2013**, *56*, 1262–1275.

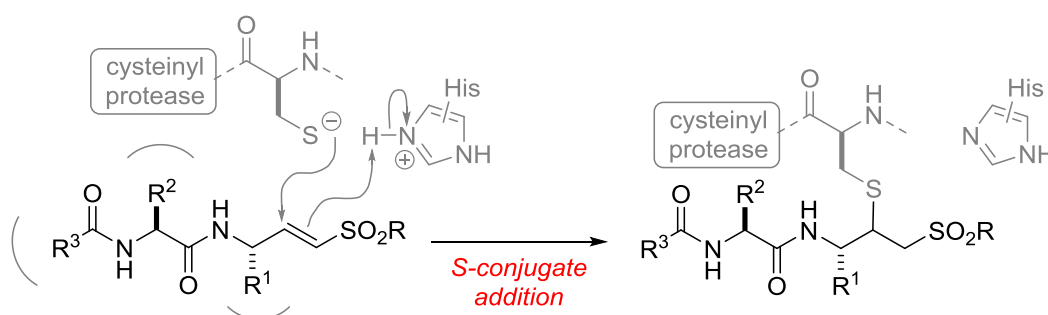
¹⁴⁸ Dunny, E. Doherty, W.; Evans, P.; Malthouse, J. P. G.; Nolan, D.; Knox, A. J. S. *J. Med. Chem.* **2013**, *56*, 6638–6650.

¹⁴⁹ Zhang, H.; Collins, J.; Nyamwihura, R.; Ware, S.; Kaiser, M.; Ogungbe, I. V. *Bioorg. Med. Chem.* **2018**, *28*, 1647–1651.

¹⁵⁰ Santos, M. M. M.; Moreira, R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1040–1050.

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acceptors have shown to be potent inhibiting agents due to the irreversible C–S bond formation (Scheme 39).^{148,150} In particular, the interest in γ -sulfonyl allyl amines principally relies on the absence of reactivity towards other proteases, such as serin- or metallo-proteases, and even other circulating nucleophiles such as glutathione. It is noteworthy the fact that inhibitors of enzymes from the same and related families have important structural differences.¹⁵¹ Since the structural requirements for an optimal enzyme-substrate recognition are still unknown, the elaboration of this type of structures could lead to the identification of more specific inhibitors or ones with better pharmacological properties.



Scheme 39. Mechanism of cysteine protease inhibition by γ -sulfonyl allyl amines.

Despite the interest for the preparation of structurally diverse γ -sulfonyl allyl amines, very few procedures have been reported for the synthesis of this type of compounds and most of them are based on olefination reactions of α -amino aldehydes derived from synthetic¹⁵² or naturally available amino acids.^{144–149,153} Enantioenriched γ -sulfonyl allyl amines have also been synthesized employing chiral auxiliaries. The group of Sato reported in 2003 the first diastereoselective allylation of imines employing a chiral *N*-protecting group, although only one example was reported with low yield (Scheme 40).¹⁵⁴

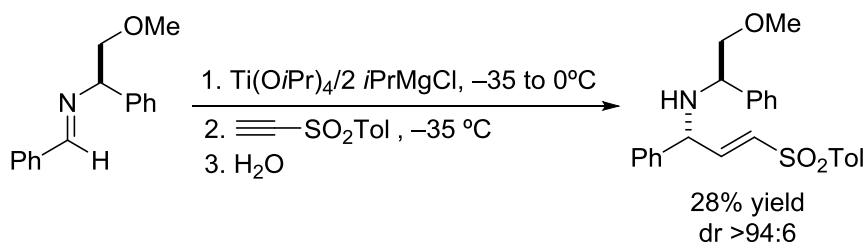
¹⁵¹ Simple achiral vinyl sulfones have also shown activity as sortase and tyrosine phosphatase inhibitors. a) Sortase inhibitor: Frankel, B. A.; Bentley, M.; Kruger, R. G.; McCafferty, D. G. *J. Am. Chem. Soc.*, **2004**, *126*, 3404–3405. b) Tyrosine phosphatase inhibitor: Liu, S.; Zhou, B.; Yang, H.; He, Y.; Jiang, Z.-X.; Kumar, S.; Wu, L.; Zhang, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 8251–8260.

¹⁵² de Bruin, G.; van Rooden, E. J.; Ward, D.; Wesseling, C.; van den Nieuwendijk, A. M. C. H.; van Boeckel, C. A. A.; Driessen, C.; Kisselev, A. F.; Florea, B. I.; van der Stelt, M.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2017**, 5921–5934.

¹⁵³ Kim, M.; Jeon, J.; Baek, J.; Choi, J.; Park, E. J.; Song, J.; Bang, H.; Suh, K. H.; Kim, Y. H.; Kim, J.; Kim, D.; Min, K. H.; Lee, K.-O. *Bull. Korean Chem. Soc.* **2014**, *35*, 345–346.

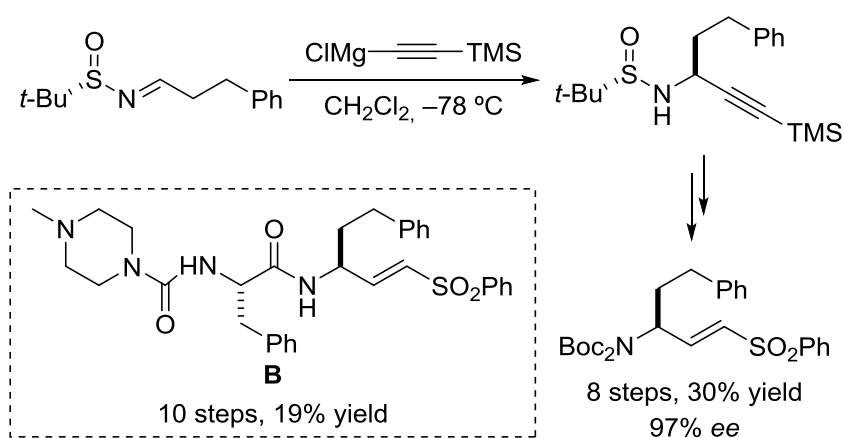
¹⁵⁴ Fukuhara, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2003**, *5*, 2145–2148.

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Scheme 40. Diastereoselective asymmetric synthesis of γ -sulfonyl allyl amines.

On the other hand, Love and co-workers have recently reported the total synthesis of compound **B**, performing, as the key stereoselective step, the alkylation of the chiral sulfinyl *N*-protected imine shown Scheme 41.¹⁵⁵



Scheme 41. Asymmetric synthesis of γ -sulfonyl allyl amines employing chiral sulfoxides .

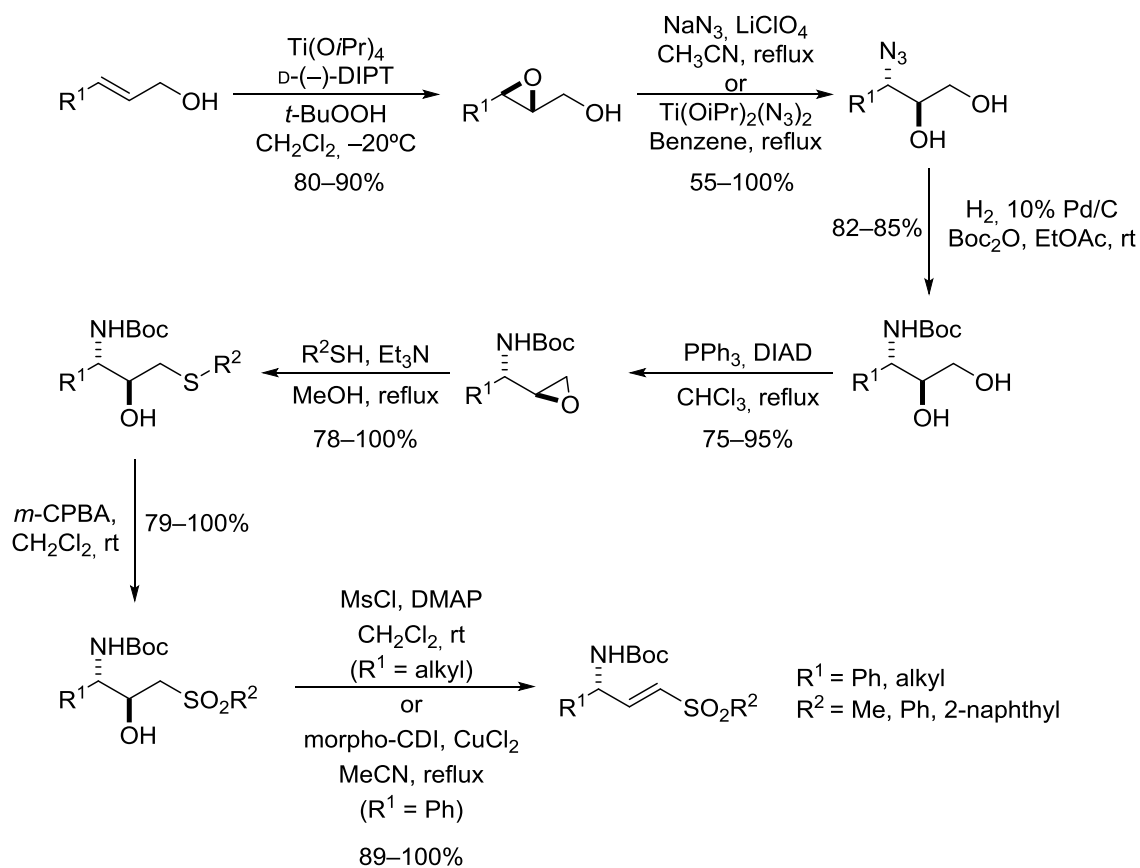
Nevertheless, to the best of our knowledge, only one procedure has been reported, to date, for the synthesis of enantioenriched γ -sulfonyl allyl amines based on a catalytic enantioselective strategy. In 2003, Moyano and co-workers reported the synthesis of such structures starting from 3-amino-1,2-alkanediols prepared from allylic alcohols,¹⁵⁶ being the key stereoselective step their asymmetric epoxidation described previously.¹⁵⁷ Additionally, this work is the only example in which amines with R^1 as an aromatic group have been produced in good yields (Scheme 42).

¹⁵⁵ Kiemele, E. R.; Wathier, M.; Bichler, P.; Love, J. A. *Org. Lett.* **2016**, *18*, 492–495.

¹⁵⁶ a) Picó, A.; Moyano, A.; Pericàs, M. A. *J. Org. Chem.* **2003**, *68*, 5075–5083. b) Moyano, A.; Pericàs, M. A.; Picó, A. Stereoselective Method of Preparing gamma-Amino Vinyl Sulphones. WO 2004101504 A1, 2004. For preparation of peptidyl aryl vinyl sulfones with this procedure, see: c) Mendieta, L.; Picó, A.; Tarragó, T.; Teixidó, M.; Castillo, M.; Rafecas, L.; Moyano, A.; Giralt, E. *ChemMedChem* **2010**, *5*, 1556–1567.

¹⁵⁷ a) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5187–5189. b) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931–6934. c) Martín, R.; Islas, G.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron*, **2001**, *57*, 6367–6374.

Enantioselective synthesis of γ -sulfonyl allyl amines



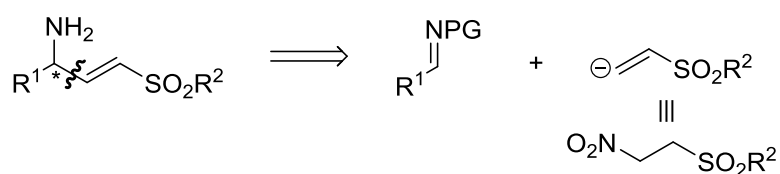
Scheme 42. Enantioselective synthesis of γ -sulfonyl allyl amines.

In view of the scarcity of methodologies described to prepare these type of potential protease inhibitors, in this chapter, we present our attempts to develop an alternative strategy which could provide γ -sulfonyl allyl amines in a more efficient way.

2.2. Working hypothesis and objectives

As mentioned in the introduction, it is relevant the fact that structurally diverse enantiopure γ -sulfonyl allyl amines show potential to act as irreversible protease inhibitors. Thus, a concise and general methodology for their preparation could facilitate the identification of novel inhibitors with improved activity.

Due to the experience of our group in the catalytic asymmetric C–C bond forming reactions, and more particularly in the nitro-Mannich reaction,¹⁵⁸ we considered that the base promoted addition of a synthetic equivalent of the vinyl sulfone anion to *N*-protected imines, followed by nitrous acid elimination, would represent a practical and short stereoselective route to γ -sulfonyl allyl amines. Both, the carbon–carbon bond and the new stereogenic center could be generated in a single operation, which is a clear advantage over traditional olefination methods (Scheme 43).



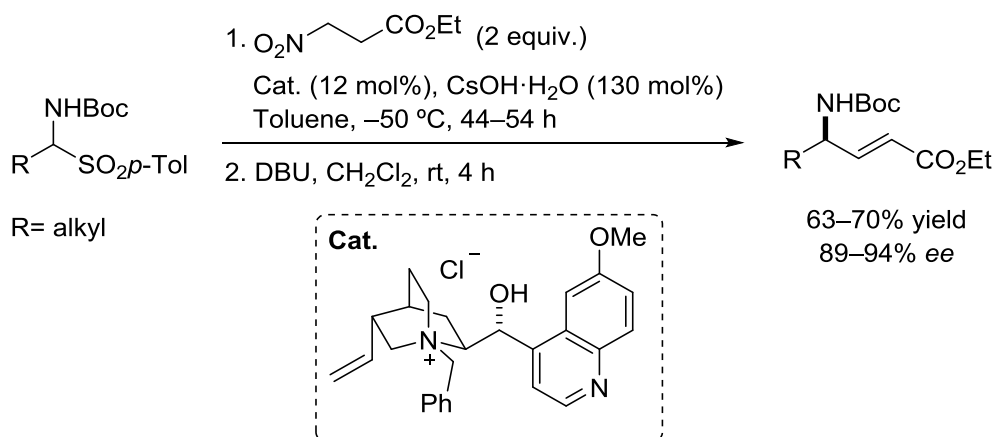
Scheme 43. Retrosynthetic analysis for the preparation of γ -sulfonyl allyl amines.

As previously disclosed, our group reported the preparation of highly enantioenriched α,β -unsaturated γ -amino esters under catalytic phase transfer conditions. This methodology represents a unique example of the use of 3-nitropropionates as β -acryloyl anion equivalents, through their organocatalytic asymmetric addition to *N*-Boc α -amino sulfones followed by basic treatment (Scheme 44).¹⁵⁹

¹⁵⁸ a) Ref. 112a, page 66. b) Ref. 129, page 73.

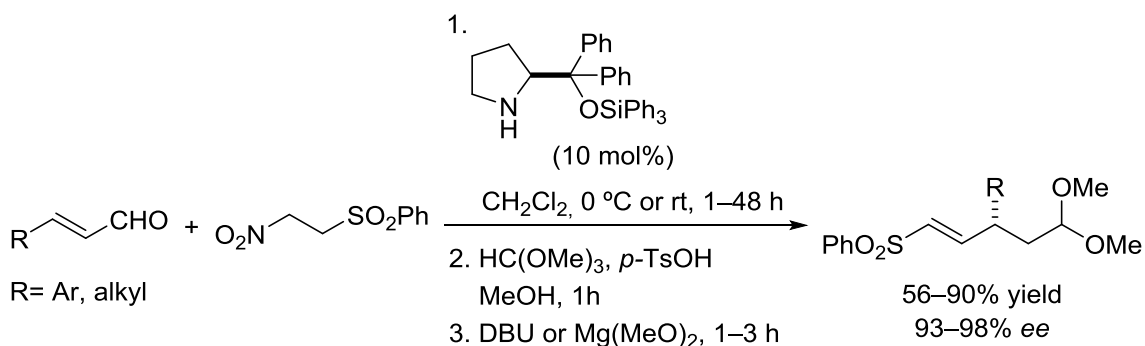
¹⁵⁹ Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966.

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Scheme 44. Enantioselective synthesis of α,β -unsaturated γ -amino esters.

In fact, this *umpolung* strategy for the olefination reaction was successfully applied later in Michael-type reactions employing 2-nitroethyl sulfones as vinyl sulfone anion equivalents.¹⁶⁰ In particular, the asymmetric Michael addition of 2-nitroethyl sulfones to α,β -unsaturated aldehydes, *via* iminium ion catalysis, followed by nitrous acid elimination, provided access to highly enantioenriched γ -substituted vinyl sulfones in a *one-pot* process (Scheme 45).

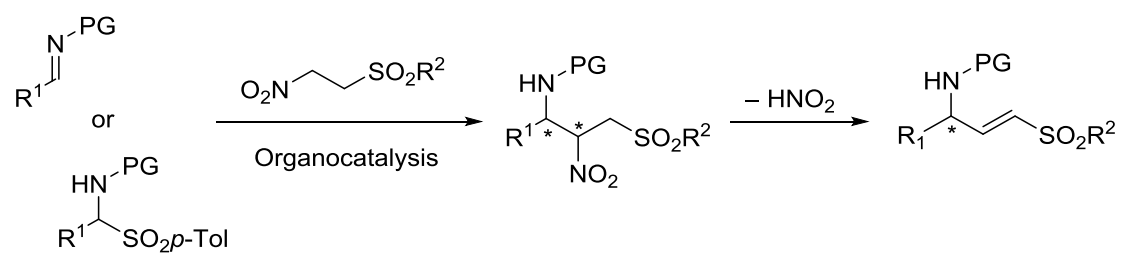


Scheme 45. Enantioselective synthesis of γ -substituted vinyl sulfones.

Encouraged by these results, we envisioned, as mentioned before, that the organocatalyzed asymmetric nitro-Mannich reaction with 2-nitroethyl sulfones followed by nitrous acid elimination could represent a general procedure for the synthesis of enantioenriched γ -sulfonyl allyl amines (Scheme 46). The present strategy would reduce significantly the number of synthetic steps required for the synthesis of this type of scaffolds, providing access to a wide variety of structures from economic achiral substrates.

¹⁶⁰ López, R.; Zalacain, M.; Palomo, C. *Chem. Eur. J.* **2011**, *17*, 2450–2457.

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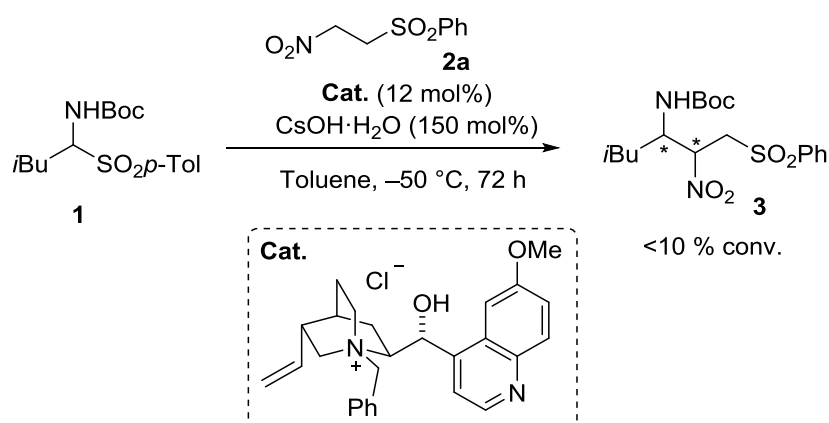


Scheme 46. Synthetic plan for the preparation of enantioenriched γ -sulfonyl allyl amines.

2.3. Results and discussion

2.3.1. Initial experiments

Several organocatalytic systems have shown their efficiency for the stereoselective addition of linear nitroalkanes to imines. However, protocols with functionalized nitroalkanes have been scarcely explored. Due to the structural similarities between 2-nitroethyl sulfones and ethyl 3-nitropropionates, it seemed appropriate to evaluate first their behavior in the phase transfer catalyzed nitro-Mannich reaction employing the optimal conditions established before for the analogous reaction (Scheme 44 in page 91).¹⁵⁹ Specifically, we studied the addition of 2-nitroethyl sulfone **2a** to α -amido sulfone **1**, in the presence of catalytic amounts of *N*-benzyl quininium chloride and suprapstoichiometric amounts of cesium hydroxide, in toluene at $-50\text{ }^{\circ}\text{C}$.¹⁶¹ Unfortunately, only traces of adduct **3** were detected after 72 hours (Scheme 47).



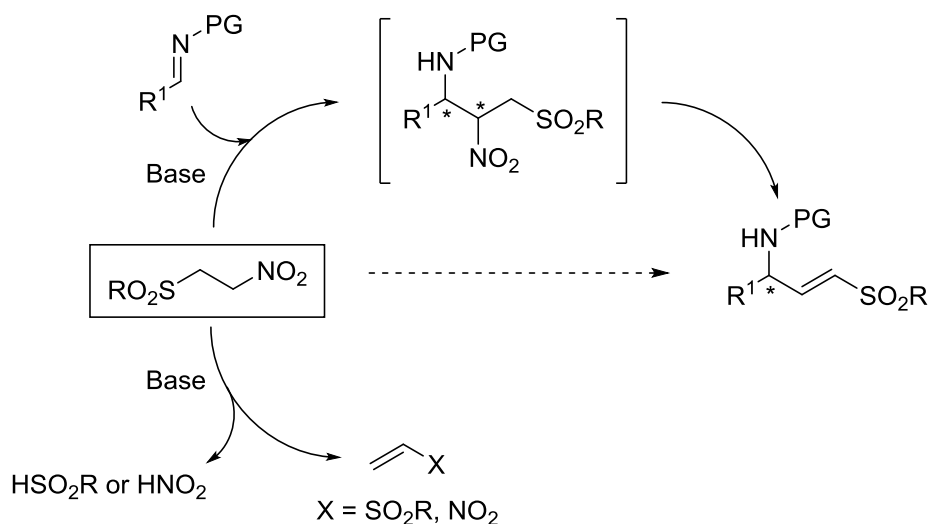
Scheme 47. Nitro-Mannich reaction of **1** and **2a** under phase transfer conditions.

Higher cesium hydroxide quantities –up to 3 equivalents– provided similar results whereas the use of other inorganic bases such as potassium carbonate or sodium bicarbonate led to total absence of reactivity. On the other hand, rise of reaction temperature up to $-10\text{ }^{\circ}\text{C}$ provided better transformations at the expense of the formation of complex mixtures. This low reactivity was attributed to a lower solubility of 2-nitroethyl sulfone **2a** in comparison with ethyl 3-nitropropionate.

In view of these results, we decided to explore the asymmetric nitro-Mannich reaction of *N*-Boc imines and 2-nitroethyl sulfones, under homogeneous conditions, employing

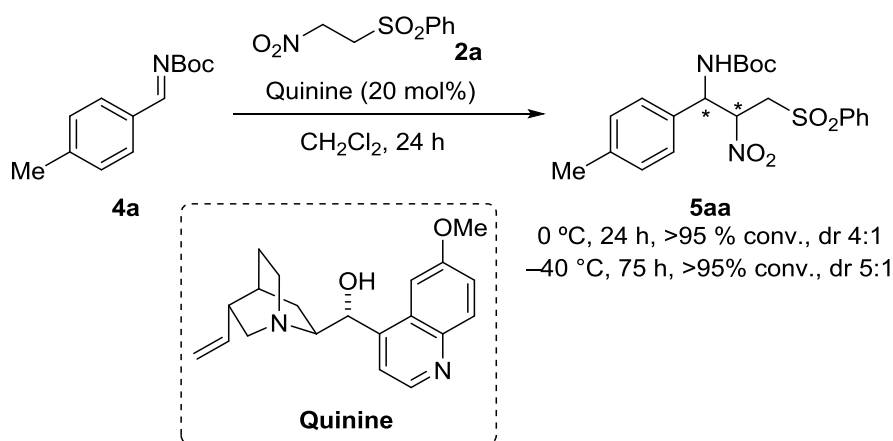
¹⁶¹ This part of the work was carried out by Dr. Maitane Zalacain: Zalacain, M. Reacción de Michael enantioselectiva de 2-nitroetil sulfonas. Ph.D. Thesis, University of the Basque Country, Donostia-San Sebastian, 2014.

chiral Brønsted base catalysis. One critical issue to address in this approach would be the tendency of such nitroalkanes to eliminate nitrous or sulphinic acid in the presence of base. Consequently, the chiral Brønsted base used in the reaction should promote the addition reaction –C–C bond formation– rather than the nitrous or sulfinic acid elimination in the starting pronucleophile (Scheme 48).



Scheme 48. Possible reaction pathways under Brønsted base catalysis.

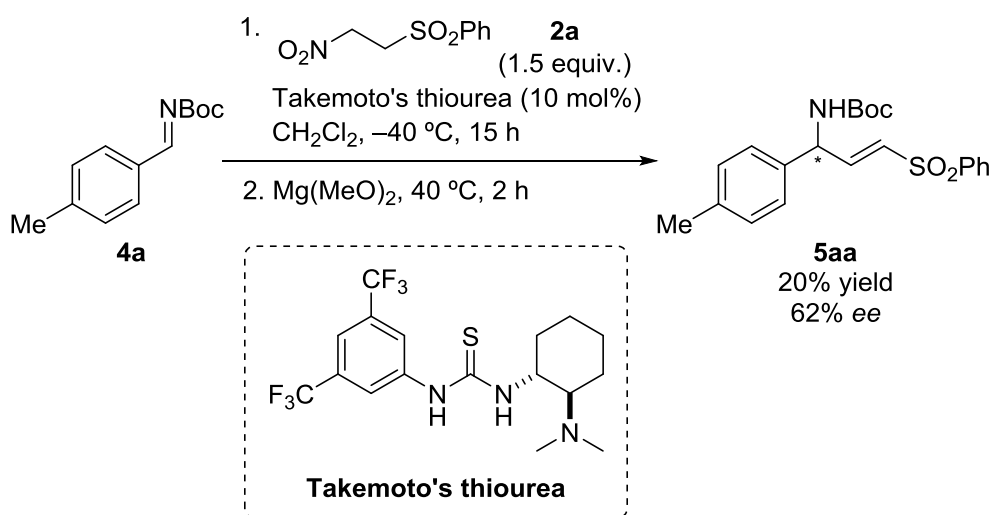
Preliminary assays with catalytic amounts of DBU, DABCO and triethylamine showed that nitrous acid elimination in the starting material competed with the addition reaction especially at temperatures above $-10\text{ }^{\circ}\text{C}$. Nevertheless, quinine-mediated nitro-Mannich addition of 2-nitroethyl sulfone **2a** to *N*-Boc imine **4a** worked satisfactorily at $0\text{ }^{\circ}\text{C}$ and the addition product **5aa** was obtained (Scheme 49).¹⁶¹



Scheme 49. Quinine-catalyzed addition of 2-nitroethyl sulfone **2a** to imine **4a**.

This result suggests that certain Brønsted bases may be compatible with the proposed reaction pathway and favor the new C–C bond formation instead of the elimination of

nitrous or sulfinic acid in the starting 2-nitroethyl sulfone. Further studies with chiral Brønsted bases showed that bases lacking hydrogen-bond donors, such as (DHQD)₂Pyr, (DHQD)₂AQN and (DHQD)₂PHAL, gave no reaction while bifunctional organocatalysts provided total transformations. Quinine, as previously shown, and cinchonine promoted complete transformation of **4a** into the corresponding adducts at $-40\text{ }^{\circ}\text{C}$ after 72 hours, whereas the reaction with Takemoto's thiourea only required 15 hours to completion. After elimination of nitrous acid by adding magnesium methoxide,¹⁶² the highest enantioselectivity was obtained with Takemoto's thiourea although the desired γ -sulfonyl allyl amine **5aa** was produced in low global yield (20%) (Scheme 50).¹⁶¹ The nitro-Mannich reaction proceeded to completion but the basic conditions, for the nitrous acid elimination, promoted retroaddition and the isomerization of the double bond to afford the corresponding achiral γ -sulfonyl vinyl amine.



Scheme 50. Takemoto's thiourea-catalyzed synthesis of γ -sulfonyl allyl amine **5aa**.

2.3.2. Optimization of nitrous acid elimination in the Mannich adducts

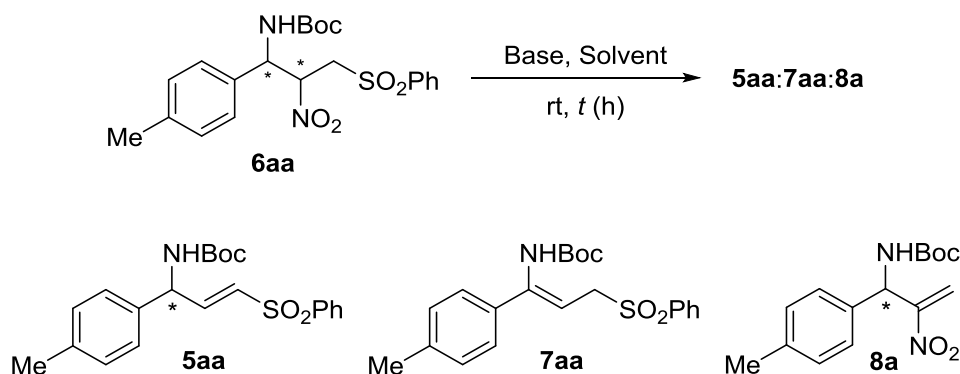
Nitro-Mannich adduct **5aa**, obtained by the addition of 2-nitroethyl sulfone **2a** to *N*-Boc imine **3a**, seemed to be more sensitive to basic conditions than the adducts produced in the reaction with ethyl 3-propionate (only aliphatic adducts were tested, see Scheme 44 in page 91)¹⁵⁹ and in the amine-catalyzed conjugate addition of 2-nitroethyl sulfones (see Scheme 45 in page 91).¹⁶⁰ Thus, we decided to focus on the optimization of the nitrous acid elimination. Several bases were tested, although the traditional organic ones were excluded from the study since previous experiments

¹⁶² Nitrous acid elimination under these conditions provided satisfactory results for the enantioselective Michael reaction with 2-nitroethyl sulfones (see Scheme 45 in page 76).

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already showed that they favored the isomerization of the double bond. Most representative results are depicted in Table 5.

Table 5. Optimization of nitrous acid elimination step.



Entry	Base	Equiv.	Solvent	t (h)	Conv. (%) ^b	5aa:7aa:8a ^b
1	Mg(MeO) ₂	2	MeOH	2	60	0:100:0
2 ^c	Mg(MeO) ₂	2	MeOH	2	>95	0:100:0
3	Mg	3	MeOH	1.5	>95	0:100:0
4 ^c	AcOK	5	CH ₂ Cl ₂	24	70	0:100:0
5	CsF	5	CH ₂ Cl ₂	5	>95	0:100:0
6	DMAP	2	CH ₂ Cl ₂	2	>95	0:100:0
7	CsOH·H ₂ O	2	CH ₂ Cl ₂	1.5	>95	61:39:0
8	Cs ₂ CO ₃ (0.2 M aq.)	4	CH ₂ Cl ₂	20	>95	0:0:100
9	K ₂ CO ₃	2	CH ₂ Cl ₂	24	60	0:0:100
10	<i>t</i> -BuOK	2	CH ₂ Cl ₂	2	>95	0:100:0
11	KOH	2	CH₂Cl₂	2	>95	100:0:0
12	Amberlyst A-21	1 mg/mmol	CH ₂ Cl ₂	48	N.R.	-
13	Basic silica gel	0.1 g/mmol	CH ₂ Cl ₂	24	N.R.	-

^a Reactions conducted on 0.5 mmol scale in 20 mL of the indicated solvent at room temperature.

^b Reaction conversion and **5aa:7aa:8a** ratio determined by ¹H NMR of the crude product. ^c Reactions carried out at 40 °C.

Isomerization of adduct **5aa** into **7aa** was observed with bases of different nature (entries 1–6). Cesium hydroxide monohydrate provided a mixture of desired adduct **5aa** and isomerized **7aa** (entry 7), which could not be improved decreasing neither reaction

time nor temperature. On the other hand, cesium or potassium carbonates induced sulfinic acid elimination to produce compound **8a** (entries 8 and 9). When potassium *tert*-butoxide was employed, the desired γ -sulfonyl allyl amine **5aa** was detected in initial assays but these results were later irreproducible, giving rise only to the isomerized product **7aa** (entry 10). We attributed the lack of reproducibility to the non-homogeneity of some commercial inorganic bases, which were usually stored under non-anhydrous conditions. Considering that hydroxide species could be present in the used potassium *tert*-butoxide, we carried out a last experiment employing potassium hydroxide. To our satisfaction, treatment of **6aa** with 2 equivalents of potassium hydroxide for 2 hours, in methylene chloride at room temperature, provided only the desired γ -sulfonyl allyl amine **5aa** (entry 11). As reaction time seemed to be crucial to avoid isomerization, the reactions were always monitored by IR spectroscopy and quenched when the NO₂ band (1560 cm⁻¹) disappeared. In addition, other basic agents such as resins and basic silica gel (entries 12 and 13) were assayed but no transformation was observed in any case regardless temperature or reaction time.

On the other hand, attempts to perform the *one-pot* nitro-Mannich and potassium hydroxide-promoted elimination reactions produced adduct **5aa** in low yield.

With these results in hand, we decided to proceed with the optimization of the asymmetric nitro-Mannich reaction step promoted by a chiral Brønsted base.

2.3.3. Catalyst screening for the asymmetric nitro-Mannich reaction

Encouraged by the results obtained using bifunctional Takemoto's thiourea (see Scheme 50 in page 95), we decided to explore the use of bifunctional Brønsted bases, particularly, ureidopeptide-type bifunctional catalysts developed by our group, which had previously demonstrated a great efficiency in conjugate additions.¹⁶³ Their design was inspired by observations made by the group of Zhong¹⁶⁴ and later corroborated by Schreiner and co-workers.¹⁶⁵ Based on exhaustive studies on NMR and IR spectroscopy, mass-spectrometry and DFT calculations, they suggested that the success of

¹⁶³ For pioneering ureidopeptide-type catalyst promoted asymmetric Michael reaction, see: a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851. For ureidopeptide-type catalyst promoted asymmetric Mannich reaction, see: b) Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526–6531. For ureidopeptide-type catalyst promoted asymmetric aldol reaction, see: c) Echave, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.

¹⁶⁴ Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682–2685.

¹⁶⁵ Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919–5927.

electronically deficient thioureas may be a consequence of the participation of three contiguous H-bond donors during the electrophile activation event: both N–H bonds in thiourea unit and the *ortho* C–H bond in the aryl group (Figure 14).

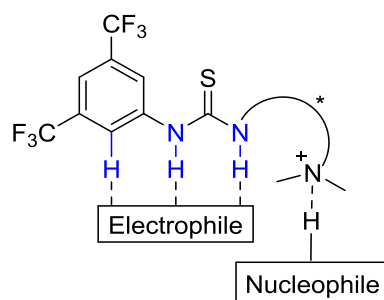


Figure 14. Activation mode proposal.

Based on these appreciations and given the efficacy of flexible synthetic peptides for the fine-tuning of reactivity and selectivity in several synthetic transformations,¹⁶⁶ our group developed a new class of organocatalysts, the so-called *ureidopeptide-based Brønsted base catalysts*. These compounds are distinguished by the presence of an *N,N*-diacyl aminal unit, in place of the bis(trifluoromethyl)-phenyl group, and a urea moiety as hydrogen bond donors, both in close proximity to an additional stereodirecting group. This type of structures closely resembles to ureidopeptides, which have been recognized for their ability to develop hydrogen bond interactions.¹⁶⁷ It was expected that replacement of the α -amino acid terminus in ureidopeptides by a group bearing a tertiary amine would result in novel bifunctional Brønsted base catalysts with several sites amenable for structural modification (Figure 15).

¹⁶⁶ Selected review: Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.

¹⁶⁷ a) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem. Eur. J.* **2000**, *6*, 2633–2643. b) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1893–1895. c) Myers, A. C.; Kowalski, J. A.; Lipton, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222. d) Sureshbabu, V. V; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705.

Enantioselective synthesis of γ -sulfonyl allyl amines

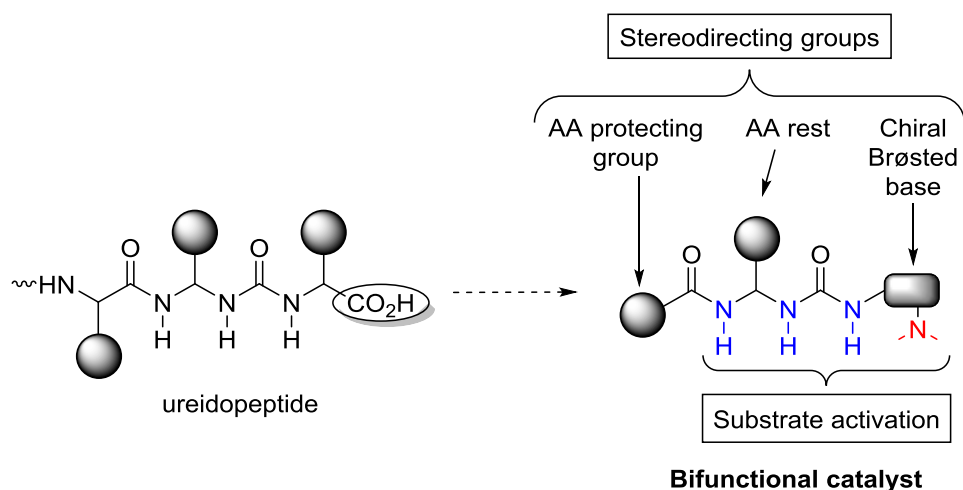
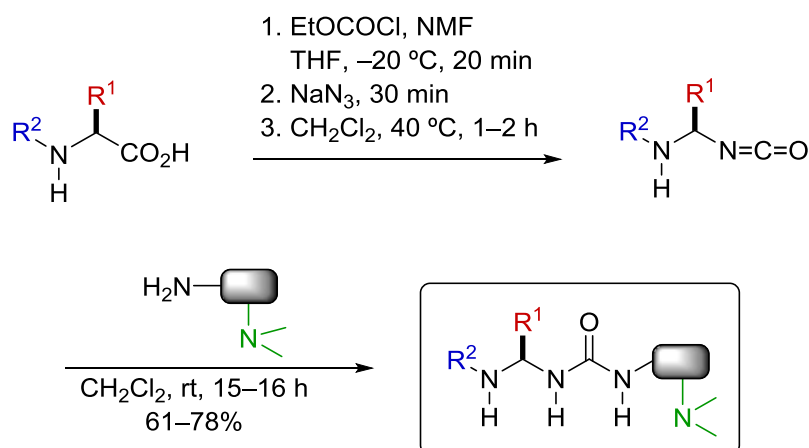


Figure 15. Design of ureidopeptide-based bifunctional Brønsted bases.

The first synthesis and subsequent optimization of these organocatalysts was conducted by Dr. Diosdado in our research group.¹⁶⁸ The proposed general synthetic sequence involves carbamate protection of the α -amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base (Scheme 51). Hence, from a synthetic point of view, these structures can be easily tuned in several sites facilitating the modulation of catalyst properties.



Scheme 51. Synthesis of ureidopeptide-based bifunctional Brønsted base catalysts.

Following the methodology described above, we synthesized a series of ureidopeptide-based organocatalysts (Figure 16) that were tested in the nitro-Mannich reaction of 2-nitroethyl sulfone **2a** with *N*-Boc imine **4a** (Table 6).

¹⁶⁸ Diosdado, S. Adición de Fosfonoacetatos, Malonatos y Sulfonilacetoneitrilos a Iminas. Desarrollo de Bases de Brønsted Bifuncionales, Ureidopéptido-Cinchona. Ph.D. Thesis, University of the Basque Country, Donostia-San Sebastian, 2014.

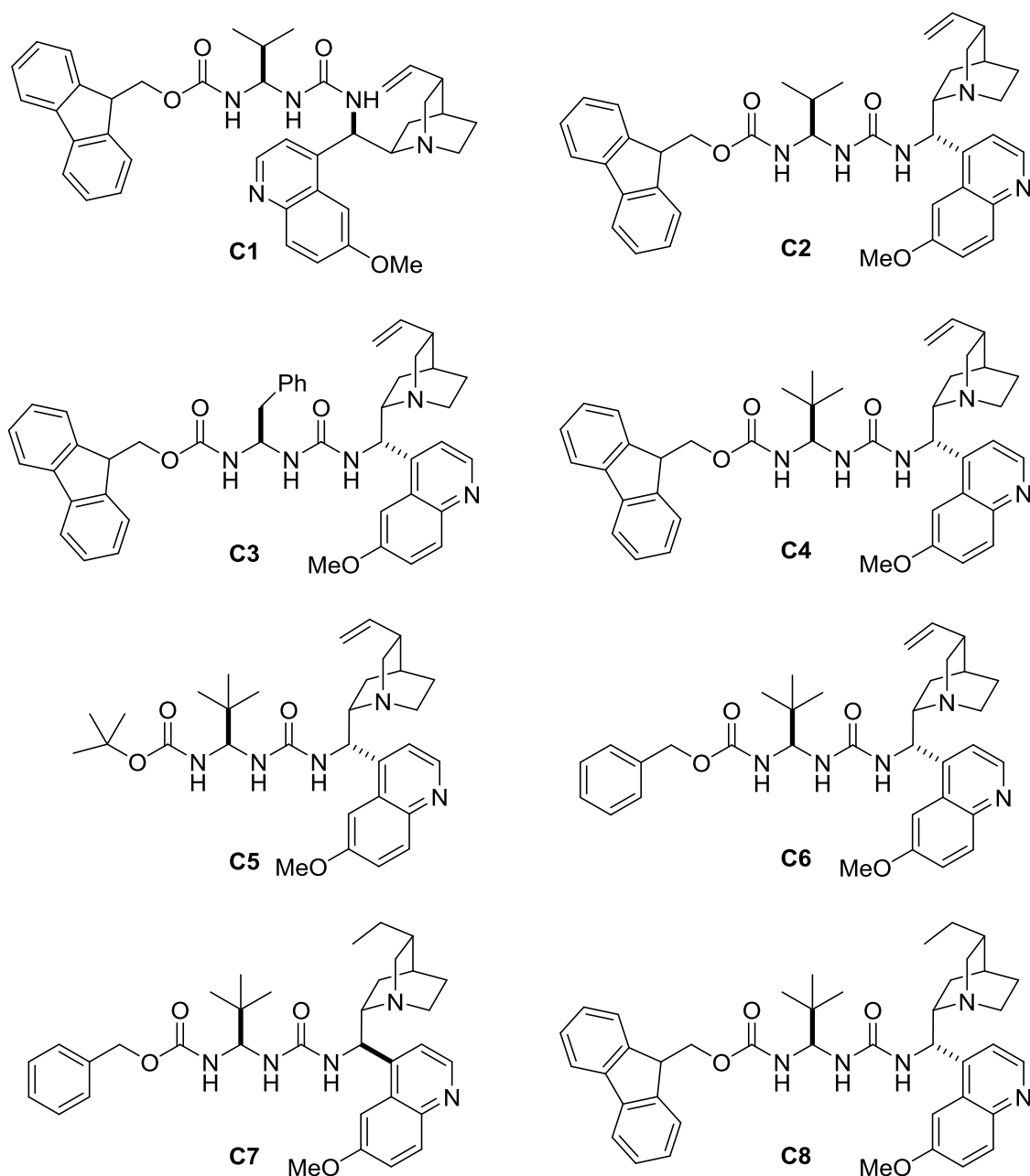


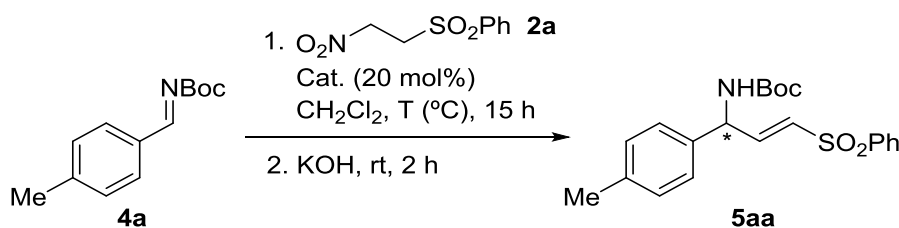
Figure 16. Bifunctional ureido-peptide-based Brønsted base organocatalysts.

Results in Table 6 show the high capacity of the synthesized catalysts **C1–C8** to promote the addition of 2-nitroethyl sulfone **2a** to imine **4a**. The transformation resulted complete with each catalyst after 15 hours at -40 or -60 °C. In addition, this study permitted the evaluation of the effect that each tunable group from the catalyst had in the asymmetric induction of the reaction. First, a higher enantiomeric excess was obtained with 9-*epi*-9-amino-9-deoxyquinine (catalyst **C2**, entry 2) than when employing 9-*epi*-9-amino-9-deoxyquinidine (catalyst **C1**, entry 1) as the Brønsted base fragment. Likewise, we observed that a higher volume of the aminor geminal group provided better enantioselectivity since the substitution of the *iso*-propyl and benzyl groups (catalysts

Enantioselective synthesis of γ -sulfonyl allyl amines

C2 and **C3**) with a bulkier *tert*-butyl group (catalyst **C4**) increased the enantiomeric excess of γ -sulfonyl allyl amine **5aa** up to 82 % (entries 2–4). On the other hand, the impact of the *N*-protecting group was tested, observing a drastic drop in the enantioselectivity when the Fmoc group was replaced by Boc or Cbz groups (catalysts **C4–C6**, entries 4–6). In addition, the convenient use of 9-*epi*-9-amino-9-deoxyquinine fragment was corroborated as the matched pair, since catalysts **C7** provided a lower enantiomeric excess (entry 7). Finally, the highest enantiomeric excess was obtained with catalyst **C8**, prepared from Fmoc-protected *L-tert*-leucine and 9-*epi*-9-amino-9-deoxyhydroquinine, at -60 °C (entry 8). Under these reaction conditions followed by nitrous acid elimination, compound **5aa** was obtained with 85% *ee*. The use of apolar solvents, such as toluene, decreased drastically the enantioselectivity of the reaction (entry 9).

Table 6. Catalyst screening for the asymmetric nitro-Mannich reaction of **2a** with **4a**.



Entry	Cat.	Solvent	T ($^\circ\text{C}$)	Conv. (%) ^b	<i>ee</i> (%) ^c
1	C1	CH_2Cl_2	-40	>95	13
2	C2	CH_2Cl_2	-40	>95	75
3	C3	CH_2Cl_2	-60	>95	70
4	C4	CH_2Cl_2	-40	>95	82
5	C5	CH_2Cl_2	-40	>95	20
6	C6	CH_2Cl_2	-40	>95	49
7	C7	CH_2Cl_2	-60	>95	42
8	C8	CH_2Cl_2	-60	>95	85^d
9	C8	Toluene	-60	>95	40

^a Reactions conducted on 0.5 mmol scale employing 1.5 equiv. of **2a**. ^b Conversion determined for addition step by ^1H NMR spectroscopy. ^c Enantiomeric excess of product **5aa** was determined by chiral HPLC on the reaction crude. ^d Diastereomeric ratio of addition product **6aa** was 4:1, determined by ^1H NMR spectroscopy on the reaction crude.

2.3.4. Evaluation of the sulfone group in 2-nitroethyl sulfones

As already mentioned, since reactivity and stereoselectivity in Brønsted base catalyzed reaction is promoted through non-covalent interactions, the stereochemical outcome shows strong dependence not only on catalyst but also on substrate structure. For this reason, we decide to evaluate the impact of the sulfone moiety in the stereoselectivity of the reaction and 2-nitroethyl sulfones **2b–2d** were synthesized following the same procedure as for **2a** (Figure 17).

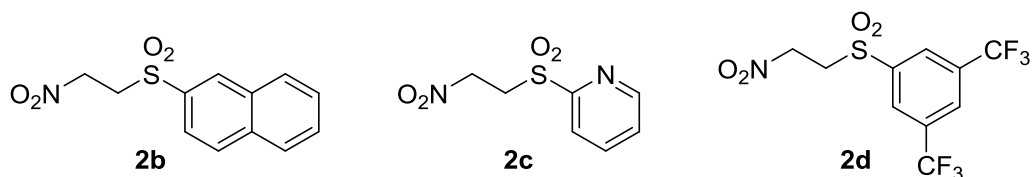
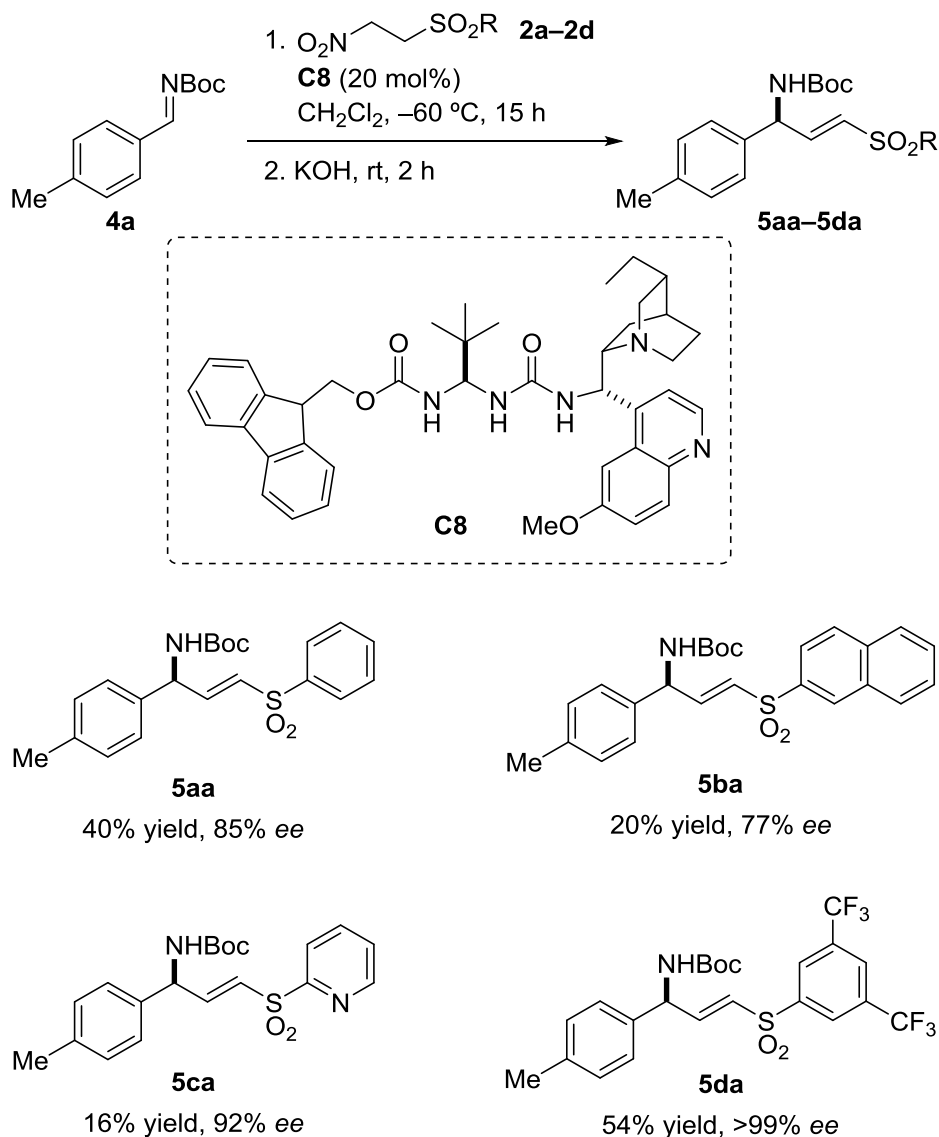


Figure 17. 2-Nitroethyl sulfones **2b–2d** employed in the study.

These 2-nitroethyl sulfones were tested in the nitro-Mannich reaction with *N*-Boc imine **4a**, in the presence of catalyst **C8**, under the optimized conditions. (Table 7). The substitution of the phenyl ring with a bulkier 2-naphthyl group decreased enantioselectivity, whereas the inclusion of nitrogen in the ring increased the enantiomeric excess up to 92%. Nevertheless, adduct **5ca** was isolated in very low yield due to the low efficiency of the elimination step. Surprisingly, 2-nitroethyl sulfone **2d**, bearing a 3,5-bis(trifluoromethyl)phenyl group, provided γ -sulfonyl allyl amine **5da** as only one detectable enantiomer in moderate yield after two steps.

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Table 7. Effect of sulfone substituents in the asymmetric nitro-Mannich reaction.



^a Reactions conducted on 0.5 mmol scale employing 1.5 equiv. of **2(a-d)**. ^b Yields refer to isolated adducts after 2 steps. ^c Enantiomeric excess was determined by chiral HPLC.

2.3.5. Reaction scope

A selection of N -Boc imines was evaluated in order to establish the generality of this asymmetric route to γ -sulfonyl allyl amines. As data in Table 8 show, catalyst **C8** promoted the addition reaction of **2d** within 15 hours at $-60\text{ }^\circ\text{C}$ to afford the corresponding enantioenriched amines in variable yields over two steps. The enantiomeric excesses were excellent for aryl N -Boc imines with electron-donating and electron-withdrawing groups, irrespective of their number. For example, the reaction with imines **4(a-c)**, **4e** and **4h** led to the corresponding products with 99% enantiomeric

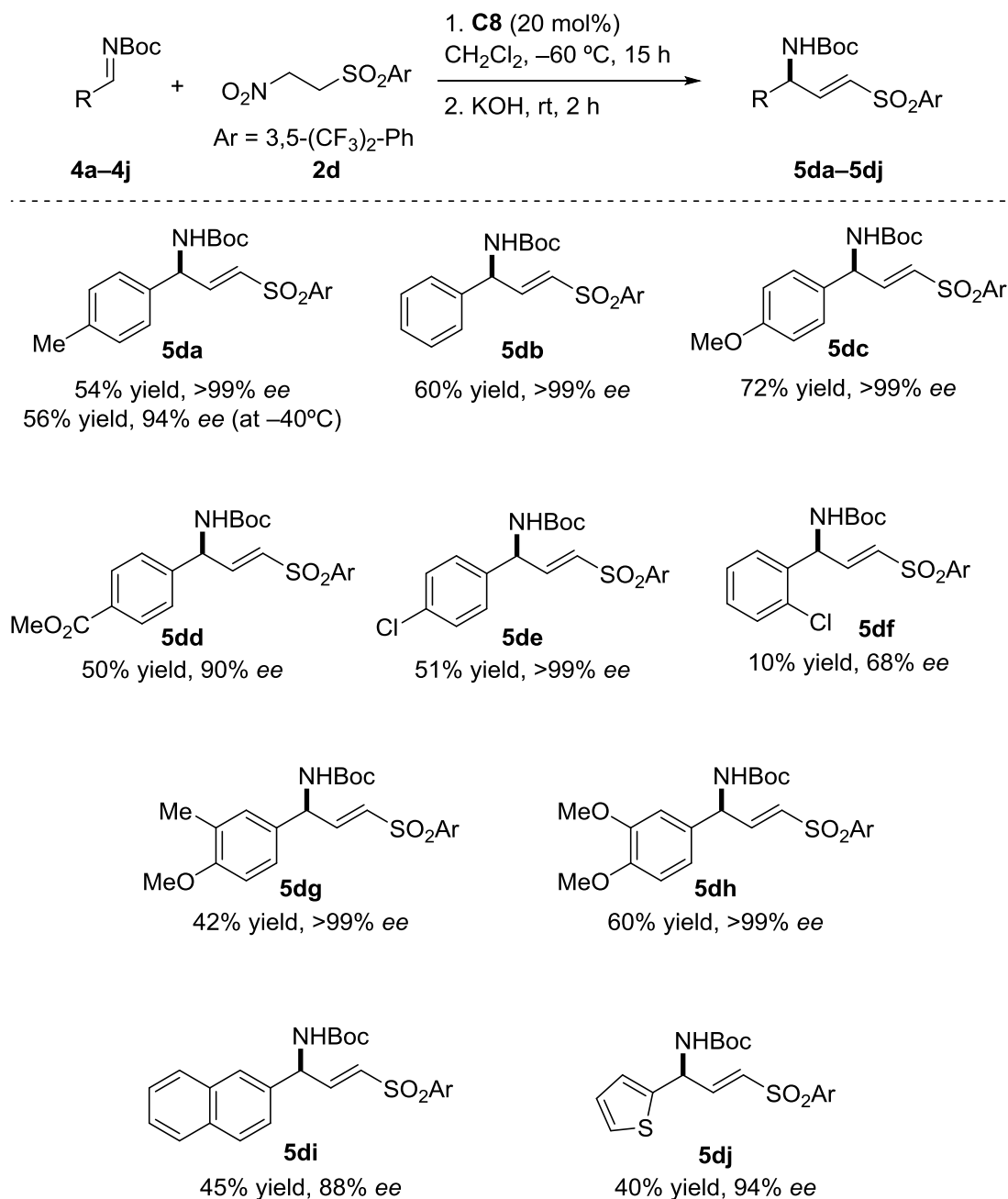
Chapter 2

excess. The method also worked well for imines with bulkier groups (**4i**) and heteroaromatic azomethines such as **4i**, to afford adducts with 88% and 94% *ee*, respectively.

Nevertheless, the overall yields were variable from moderate to low. In spite of having optimized the base promoted nitrous acid elimination step, we realized that during purification, the γ -sulfonyl allyl amines tended to isomerize into the corresponding achiral vinyl amines. All attempts to minimize the isomerization event during purification resulted fruitless and consequently, compounds **5dd**, **5dh** and **5dj** could not be completely characterized (only ^1H NMR and UPLC-MS analysis were conducted).

Enantioselective synthesis of γ -sulfonyl allyl amines

Table 8. *N*-Boc imine reaction scope.

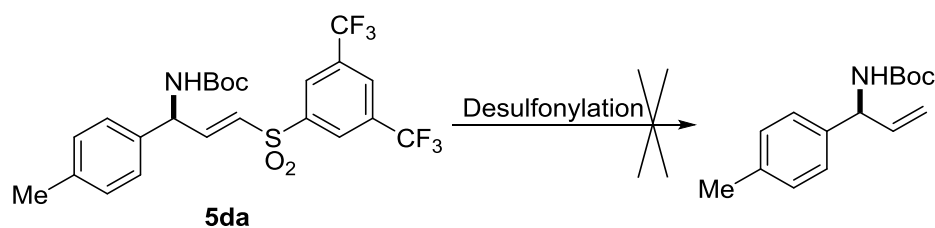


^a Reactions conducted on 0.5 mmol scale employing 1.5 equiv. of **2d**. ^b Yields refer to isolated adducts after 2 steps. ^c Enantiomeric excess was determined by chiral HPLC.

On the other hand, the nitro-Mannich reaction with *N*-Boc aliphatic imines was also investigated. Unfortunately, no addition reaction was observed neither employing pre-formed imines **4k–4m** (Scheme 52a) nor preparing them *in situ* from amido sulfone **9** in the presence of stoichiometric amounts of cesium carbonate (Scheme 52b). For the last case, the imine formation was confirmed since hydrocinnamaldehyde was obtained

Enantioselective synthesis of γ -sulfonyl allyl amines

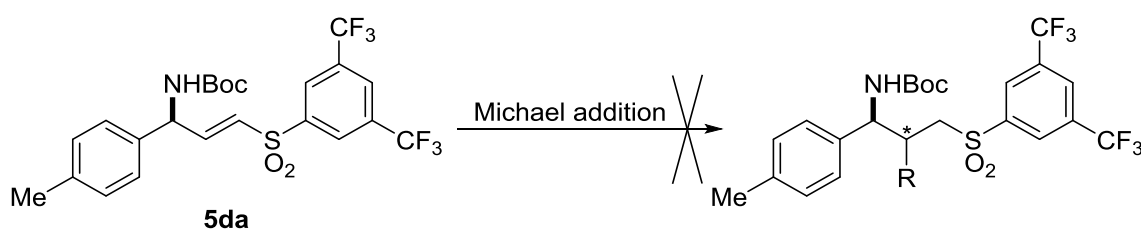
Table 9. Unsuccessful desulfonation of adduct **5da**.

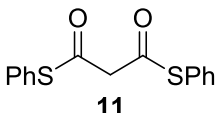


Entry	Reagent (equiv.)	Solvent	T (°C)	t (h)
1	Mg (15), TMSCl (0.5), DBE (0.5)	MeOH	rt	2 h
2	Na ₂ S ₂ O ₄ (4), NaHCO ₃ (12)	DMF:THF:H ₂ O (1:1:1)	50	2 h
3	Na(Hg) 5% (6)	MeOH	-20	4 h

On the other hand, attempts to employ the γ -sulfonyl allyl amines as Michael acceptors were also disappointing. The use of Grignard or organocuprate reagents did not promote the reaction at low temperature and only isomerization of the double bond was detected at higher temperatures. (Table 10, entries 1–3). Otherwise, since thiomalonate **11** was found to perform the Mannich reaction with *N*-Boc imines in absence of an external base,¹⁶⁸ we considered this pronucleophile as an alternative. Unfortunately, no reaction was observed in the stated conditions (entry 4) and further addition of 20 mol% of Et₃N resulted in adduct isomerization.

Table 10. Unsuccessful conjugate addition to adduct **5da**.

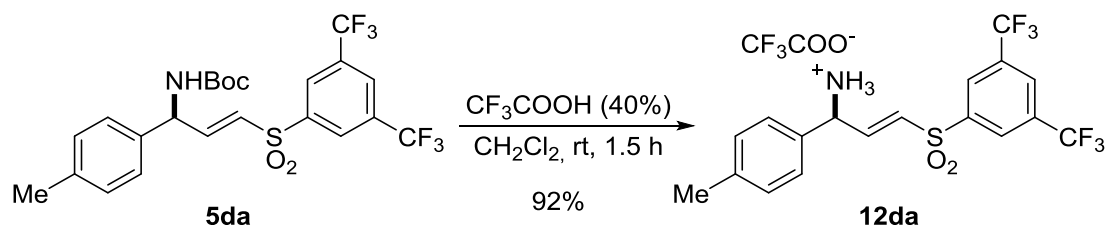


Entry	Reagent (equiv.)	Solvent	T (°C)	t (h)
1	MeMgBr (3)	THF	-40	48
2	Me ₂ CuLi (2)	Et ₂ O	0	48
3	<i>n</i> -Bu ₂ CuLi (2)	Et ₂ O	0	48
4	 (3)	CH ₂ Cl ₂	rt to 40	72

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Other chemical transformations such as iodocyclocarbamation¹⁶⁹ and photochemical substitutions,¹⁷⁰ previously described for vinyl sulfones lacking α -stereogenic centers, went also without success.

We were able only to produce the corresponding free secondary amines in excellent yield (Scheme 54).^{156c}



Scheme 54. Amine deprotection in final adduct **5da**.

In spite of the difficulties, mainly related to the purification and manipulation of the adducts, our initial hypothesis resulted correct and we have been able to develop a catalytic methodology for the synthesis of highly enantioenriched γ -sulfonyl allyl amines. Nevertheless, the inconvenients found out during the work made us focus on other projects that were being developed in parallel with greater success.

¹⁶⁹ Dell'Uomo, N.; Di Giovanni, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Liebigs Ann. Chem.* **1994**, 641–644.

¹⁷⁰ Amaoka, Y.; Nagamoto, M.; Watanabe, M.; Tao, K.; Kamijo, S.; Inoue, M. *Chem. Sci.* **2014**, 5, 4339–4345.

Chapter 3

**Stereoselective synthesis of pyridine based
tertiary and secondary amines**

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3. STEREOSELECTIVE SYNTHESIS OF PYRIDINE BASED TERTIARY AND SECONDARY AMINES

3.1. Pyridine based amines

3.1.1. General considerations

Nitrogen-containing heterocycles are one of the most significant structural components in pharmaceuticals.^{171,172} For instance, from 1086 unique small-molecule drugs approved by U.S. FDA in 2012, 640 (59%) contained at least one nitrogen heterocycle.¹⁷³ Moreover, from the top 6 prescribed drugs in the U.S. in 2016, 5 of them also incorporated this type of moiety (Figure 18).¹⁷⁴

¹⁷¹ For selected books about nitrogen-containing heterocycles, see: a) Royer, J., Ed. *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-VCH: Weinheim, 2009. b) Majumdar, K. C.; Chattopadhyay, S. K., Eds. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, 2011. c) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 3rd ed.; Wiley-VCH: Weinheim, 2012.

¹⁷² For a survey of the heterocyclic drugs approved by the U.S. FDA from 2000 to 2012, see: a) Wu, Y.-J. *Prog. Heterocycl. Chem.* **2012**, *24*, 1–53. For a study in anticancer activity of nitrogen-containing heterocyclic moieties, see: b) Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Shahar Yar, M. *Eur. J. Med.* **2017**, *125*, 143–149.

¹⁷³ Ref. 1, page 35.

¹⁷⁴ a) <https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster> (accessed Jul 26, 2018). b) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348–1349.

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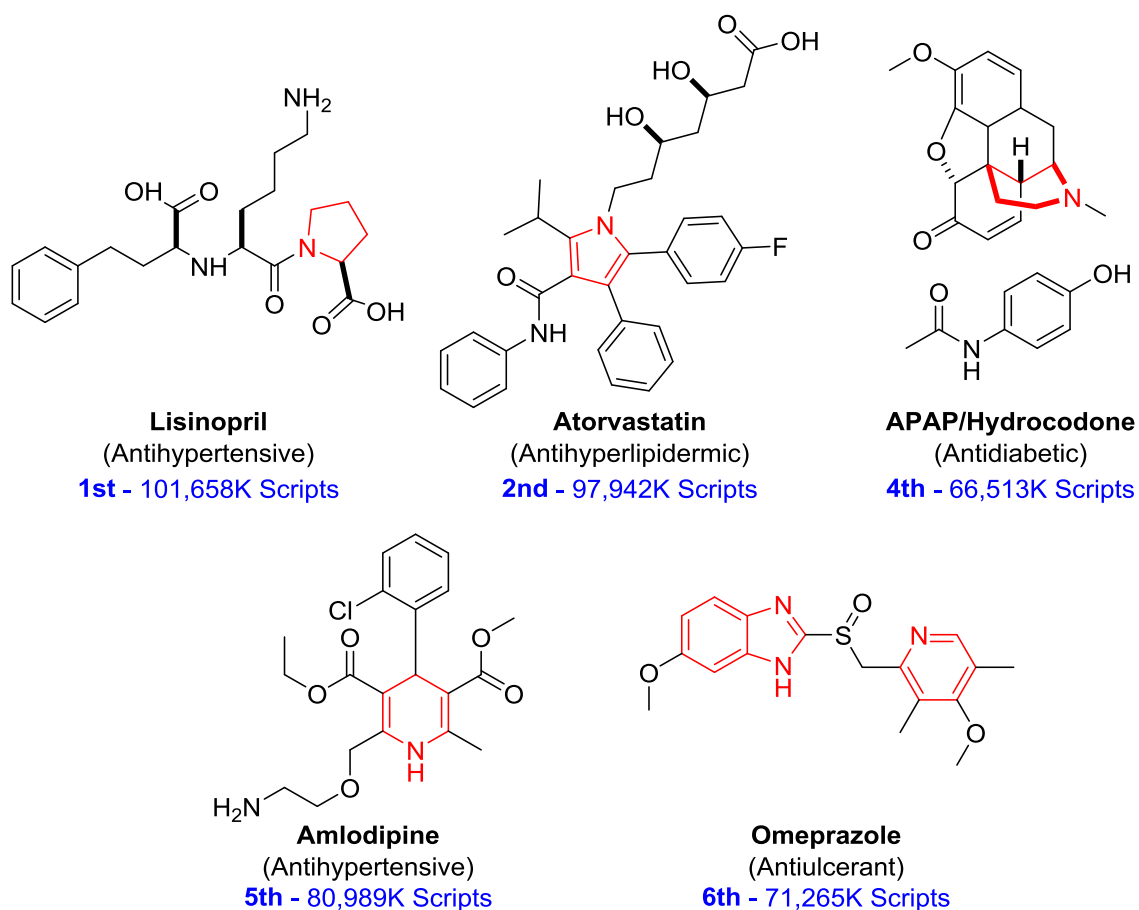
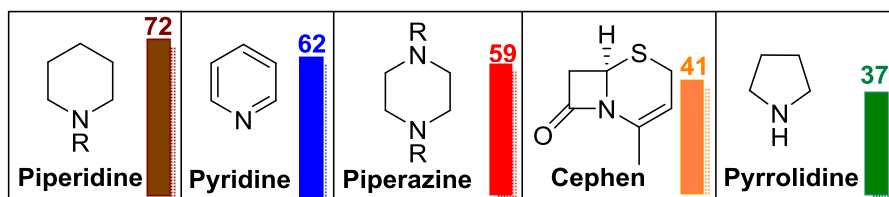


Figure 18. Top *N*-heterocycle-containing pharmaceuticals by prescriptions in 2016.

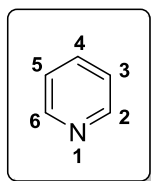
Among the nitrogen-containing heterocycles, pyridine represents the second most common moiety, appearing in 62 drugs (Figure 19a). In addition, C2-position results the preferred one for substitution with a frequency of 66% (Figure 19b).¹⁷³

a) Top five most frequent nitrogen heterocycles in U.S. FDA drugs.



b) Substituted pyridines frequency.

N-1	7/62
C-2	41/62
C-3	25/62
C-4	17/62
C-5	13/62
C-6	3/62



Mono-	51.6%
Di-	29.0%
Tri-	12.9%
Tetra-	4.9%
Penta-	1.6%

Figure 19. Most frequent *N*-heterocycles and substituted pyridines in U.S. FDA approved drugs (2012).

Stereoselective synthesis of pyridine based tertiary and secondary amines

Furthermore, C-2 or *ortho*-substituted pyridines are frequent structures in chiral molecules. Among them, chiral α -functionalized 2-pyridyl amines present interesting properties due to their high density of structural information. Figure 20 shows some examples of biologically active compounds¹⁷⁵ and chiral ligands¹⁷⁶ bearing this structural moiety, including some α -chiral amines.

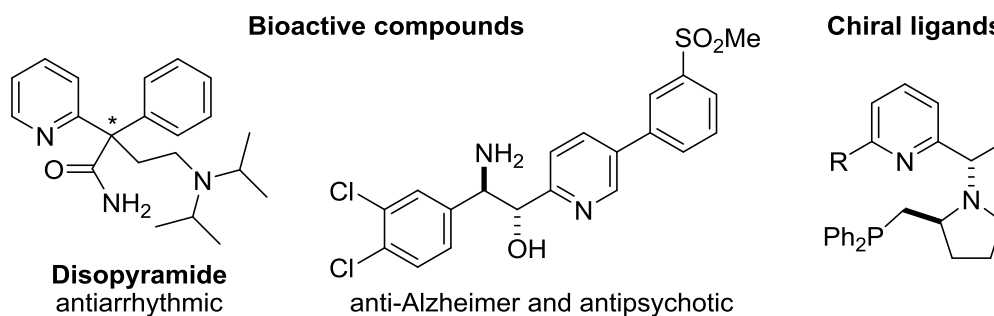


Figure 20. *Ortho*-substituted pyridines as bioactive compounds or chiral ligands.

3.1.2. Enantioselective synthesis of α -functionalized 2-pyridyl amines

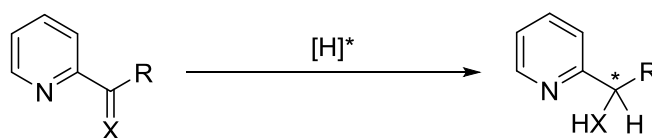
The synthesis of *ortho*-substituted chiral pyridine-containing building blocks has recently attracted much attention. Actually, there are three main catalytic approaches for the preparation of α -functionalized chiral 2-alkyl pyridines: the reduction of 2-pyridyl based carbonyls and olefins (Scheme 55a), the nucleophilic addition to 2-pyridyl carbonyls, azomethines and alkenes (Scheme 55b), and the use of 2-alkyl pyridines as pronucleophiles in nucleophilic additions (Scheme 55c).

¹⁷⁵ For information about disopyramide, see: a) Mokler, C. M.; van Arman, C. G. *J. Pharmacol. Exp. Ther.* **1962**, *136*, 114–124. b) <https://www.drugs.com/mtm/disopyramide.html> (accessed August 10, 2018). For information about the anti-Alzheimer and antipsychotic agent, see: Kolczewski, S.; Marty, H.-P.; Narquizian, R.; Pinard, E.; Stader, H. Preparation of cyclic amines or amino alcohols as therapeutic GlyT-1 inhibitors. US 20100210592 A1, 2010.

¹⁷⁶ Uenishi, J.; Hamada, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2999–3006.

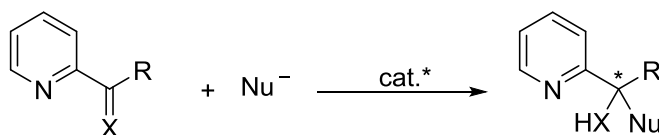
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a) Enantioselective reduction of 2-pyridyl based carbonyls and olefins



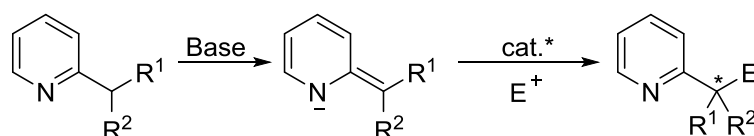
R ≠ H
X = O, R'

b) Nucleophilic addition to 2-pyridyl carbonyls, azomethine and alkenes



X = O, NR', R'

c) Nucleophilic addition of 2-alkyl pyridines to electrophiles



Scheme 55. Main approaches for the synthesis of α -functionalized chiral 2-alkylpyridines.

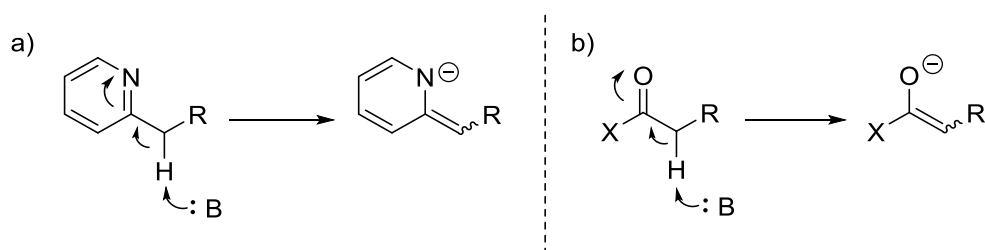
These three approaches constitute straightforward methodologies for the preparation of pyridine based tertiary and secondary amines, but all remain underexplored. For instance, whereas general enantioselective reductive methods have been described for ketones and olefins, only isolated examples of the use of ketimines has been reported with very low efficiency.¹⁷⁷ At the same time, regarding the use of 2-pyridyl imines as electrophiles, only few examples appear as particular cases of enantioselective nucleophilic additions to aromatic imines.¹⁷⁸ The third approach, towards the synthesis of pyridine based tertiary and secondary amines, constitutes the main objective of this chapter, therefore the state of the art for this particular strategy is presented.

¹⁷⁷ For selected examples, see: a) Malkov, A. V.; Vranková, K.; Stončius, S.; Kočovský, P. *J. Org. Chem. Soc.* **2009**, *74*, 5839–5849. b) Huang, K.; Merced, F. G.; Ortiz-Marciales, M.; Meléndez, H. J.; Correa, W.; De Jesús, M. *J. Org. Chem.* **2008**, *73*, 4017–4026. c) Adams, M. R.; Tien, C.-H.; McDonald, R.; Speed, A. W. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 16660–16663.

¹⁷⁸ For selected examples, see: a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627. b) Budragchaa, T.; Abraham, M.; Schöfberger, W.; Roller, A.; Widhalm, M. *Asym. Catal.* **2016**, *3*, 1–14. For catalytic asymmetric [2+3] cycloaddition with 2-pyridyl imines, see: c) Padilla, S.; Tejero, R.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2010**, *12*, 5608–5611. d) Pascual-Escudero, A.; González-Esguevillas, M.; Padilla, S.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2014**, *16*, 2228–2231. e) Takizawa, S.; Arteaga, F. A.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Asian J. Org. Chem.* **2014**, *3*, 412–415. f) Takizawa, S.; Kishi, K.; Abozeid, M. A.; Murai, K.; Fujioka, H.; Sasai, H. *Org. Biomol. Chem.* **2015**, *14*, 761–767.

- **2-Alkyl pyridines as pronucleophiles**

α -Deprotonation of 2-alkyl pyridines presents a remarkable parallelism with the enolization of carbonyl compounds since C=N moiety exhibits electron-withdrawing properties resembling those of the carbonyl group (Scheme 56).¹⁷⁹ Nevertheless, although the latter has been employed in many direct catalytic enantioselective bond forming reactions (Scheme 56b),¹⁸⁰ the use of 2-alkyl pyridines in analogous processes has been scarcely explored (Scheme 56a). The principal obstacle in the development of such reactions is the lower acidity of 2-alkyl pyridines compared to carbonyl compounds.



Scheme 56. α -Deprotonation of 2-alkyl pyridines and enolization of carbonyl compounds.

Despite this difficulty, several non-asymmetric methods have been reported for the α -functionalization of 2-alkyl pyridines employing transition-metal catalysis. Normally, harsh reaction conditions, such as suprastoichiometric amounts of strong bases, high reaction temperatures or microwave radiation were required.¹⁸¹ These issues have compromised the development of asymmetric versions of these reactions and only a few precedents concerning catalytic enantioselective approaches that employ 2-alkylazaarenes as pronucleophiles have been found in the literature.

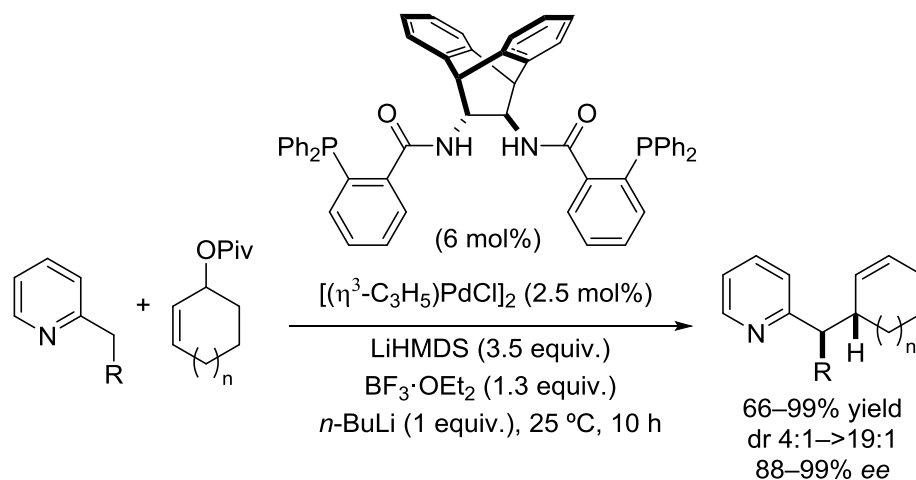
In 2009, the group of Trost described the palladium-catalyzed stereoselective allylation of 2-alkyl pyridines with excellent yields, diastereo- and enantioselectivities (Scheme

¹⁷⁹ For a perspective in the matter, see: Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831–845.

¹⁸⁰ For selected reviews in the matter, see: a) MacMillan, D. W. C.; Watson, A. J. B. α -Functionalization of Carbonyl Compounds. In *Science of Synthesis: Stereoselective Synthesis*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2011; Vol. 3, pp 675–745. b) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770. c) Hodgson, D. M.; Charlton, A. *Tetrahedron* **2014**, *70*, 2207–2236.

¹⁸¹ For selected examples, see: a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. b) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650–3651. c) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195–3200. d) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849–6855. e) Qian, B.; Shi, D.; Yang, L.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2146–2150. f) Liu, X.-J.; You, S.-L. *Angew. Chem. Int. Ed.* **2017**, *56*, 4002–4005. g) Suzuki, H.; Igarashi, R.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 4520–4524. h) Zhai, D.-D.; Zhang, X.-Y.; Liu, Y.-F.; Zheng, L.; Guan, B.-T. *Angew. Chem. Int. Ed.* **2018**, *57*, 1650–1653. i) Zhang, G.; Irrgang, T.; Dietel, T.; Kallmeier, F.; Kempe, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 9131–9135.

57). The reactive nucleophiles were generated by coordination to $\text{BF}_3 \cdot \text{OEt}_2$ followed by deprotonation with 3.5 equivalents of LiHMDS and 1 equivalent of *n*-BuLi.¹⁸²



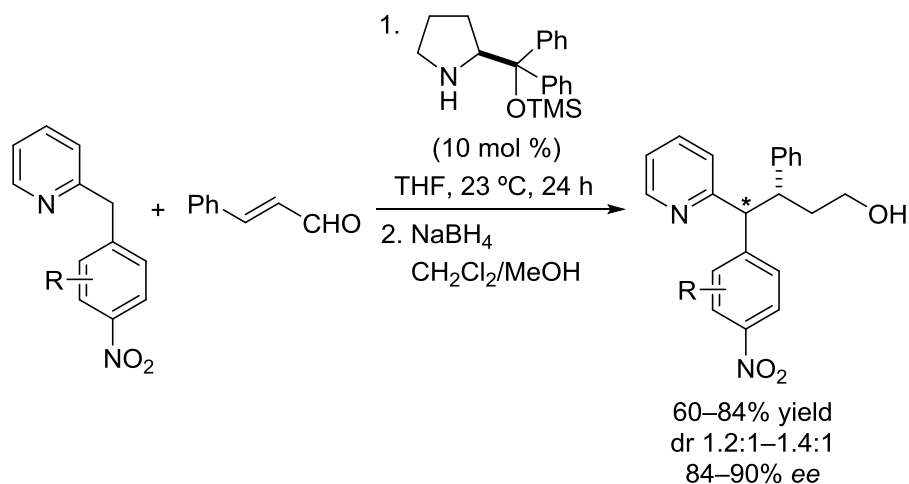
Scheme 57. Trost's asymmetric allylation of 2-alkyl pyridines.

Otherwise, the installation of an additional activating group into the substrate has become a successful strategy to overcome the low acidity of 2-alkyl pyridines. In 2011, Melchiorre and co-workers reported the enantioselective addition of nitrobenzyl pyridines to α,β -unsaturated aldehydes *via* iminium ion catalysis. In this process, the combination of the electron-withdrawing nitrophenyl and pyridine groups rendered the methylene at the benzylic position sufficiently acidic for the reaction to proceed, under mild conditions, and the corresponding adducts were obtained with good yields and excellent enantioselectivities, albeit with low diastereoselectivities (Scheme 58).¹⁸³

¹⁸² a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056–12057. See also: b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093. c) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. J. *J. Am. Chem. Soc.* **2011**, *133*, 12439–12441.

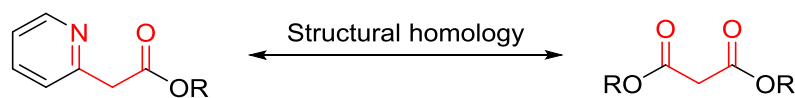
¹⁸³ Vera, S.; Liu, Y.; Marigo, M.; Escudero-Afán, E. C.; Melchiorre, P. *Synlett* **2011**, 489–494.

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Scheme 58. Melchiorre's asymmetric Michael addition of nitrobenzyl pyridine to enals.

The attachment of an extra activating group, such as an ester or amide group, to the α -carbon of the 2-alkyl pyridine, enhances the acidity to an extent that is almost comparable to that for 1,3-dicarbonyl compounds.

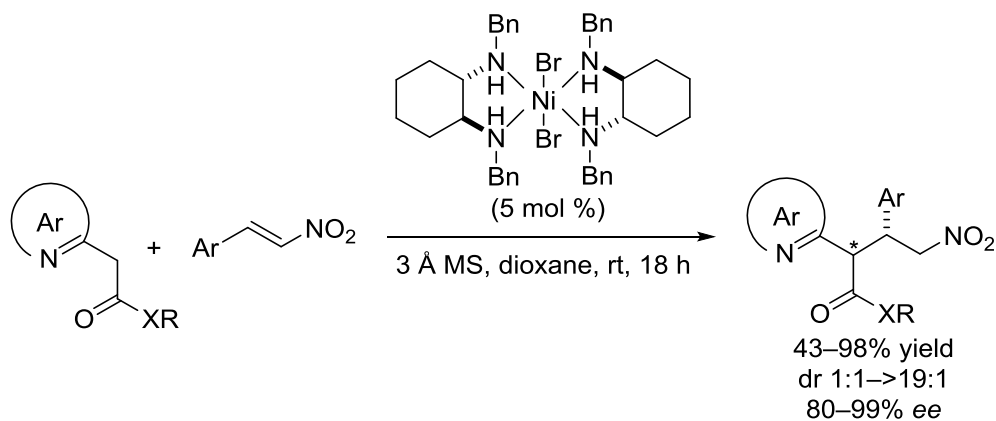


Scheme 59. Structural homology between 2-pyridyl acetates and 1,3-dicarbonyl compounds.

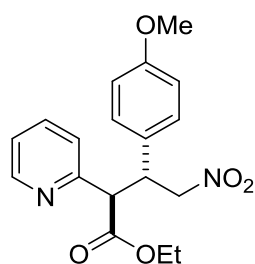
Following this principle, the group of Lam verified that certain 2-azaaryl acetates and acetamides, which had not previously been used in asymmetric catalysis, behaved as excellent pronucleophiles in Michael type additions to nitroalkenes, promoted by a chiral nickel (II) complex (Scheme 60).¹⁸⁴ This methodology was compatible with a wide variety of azarenes, such as pyridines, pyrazines, triazines, isoquinolines, quinazolines, benzotiazoles and benzisoxazoles, and represents the first general approach for the construction of highly enantioenriched α -substituted azaarenes.

¹⁸⁴ Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214–11218.

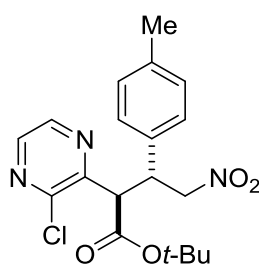
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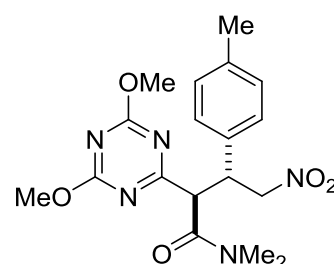
Representative examples:



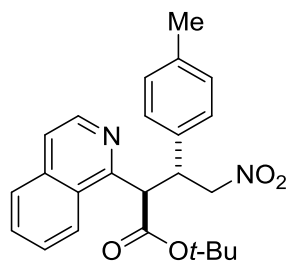
88%; dr 7.5:1; 80% ee



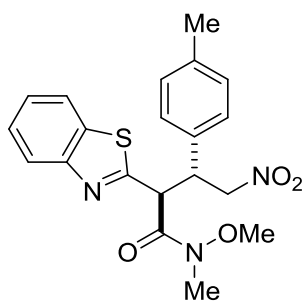
66%; dr 7:1; 94% ee



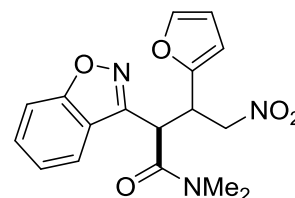
99%; dr 10:1; 93% ee



78%; dr 9:1; 99% ee



85%; dr >19:1; 96% ee



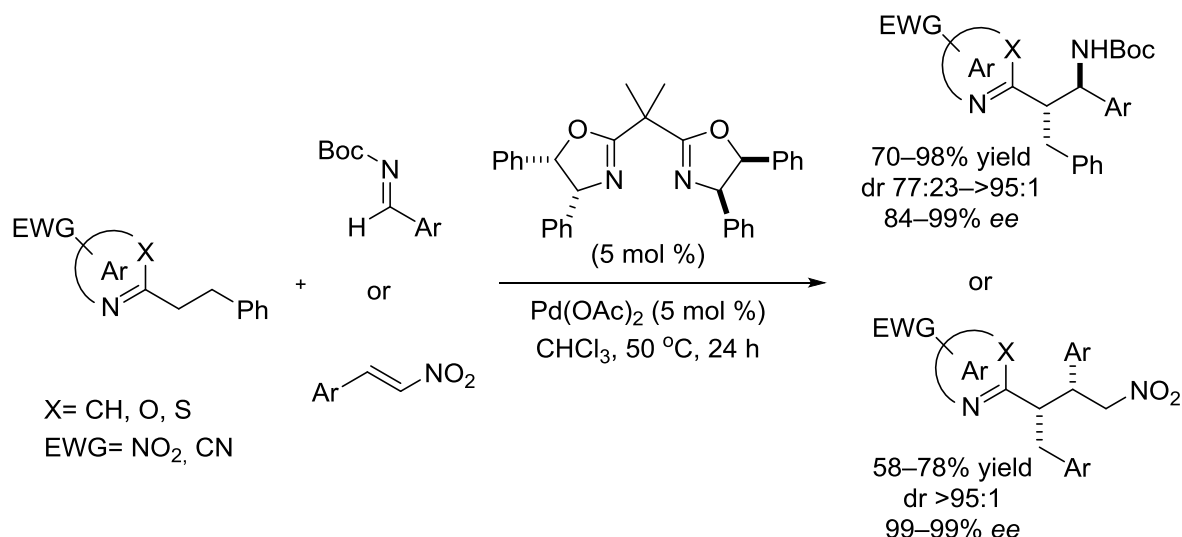
73%; dr 2:1; 88% ee

Scheme 60. Lam's enantioselective Michael reaction of 2-azaaryl acetates and acetamides.

The same group also developed a similar approach to increase the acidity of 2-alkyl azaarenes; the incorporation of an electron-withdrawing group into the azaarene ring. High levels of stereoselectivity were achieved in the reactions of these substituted 2-alkyl azaarenes with *N*-Boc imines and nitroalkenes promoted by a chiral Pd(II)-bis(oxazoline) complex (Scheme 61).¹⁸⁵ As far as we know, this is the only catalytic asymmetric methodology described, so far, for the synthesis of azaarene derived secondary amines based on the use of 2-alkyl azaarenes as pronucleophiles.

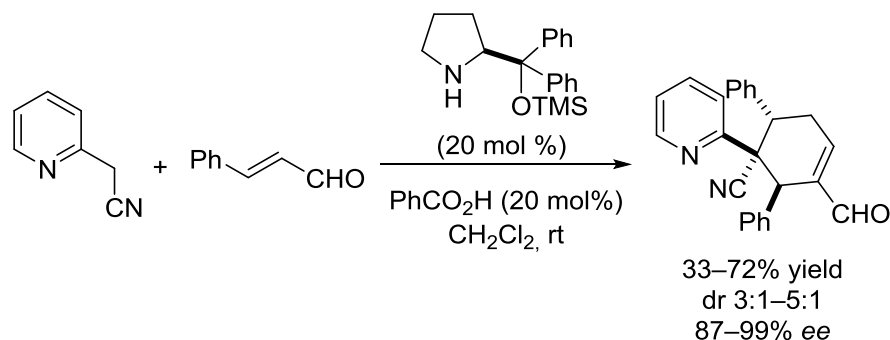
¹⁸⁵ Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196.

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Scheme 61. Lam's asymmetric addition of 2-alkyl azaarenes to *N*-Boc imines and nitroalkenes.

More recently, and after the work developed in this thesis, Rios and co-workers reported the stereoselective synthesis of 2-alkyl pyridine derivatives, bearing a quaternary stereocenter, through Michael/Michael/aldol cascade reactions employing 2-pyridyl acetonitrile as pronucleophile and iminium ion activation (Scheme 62).¹⁸⁶

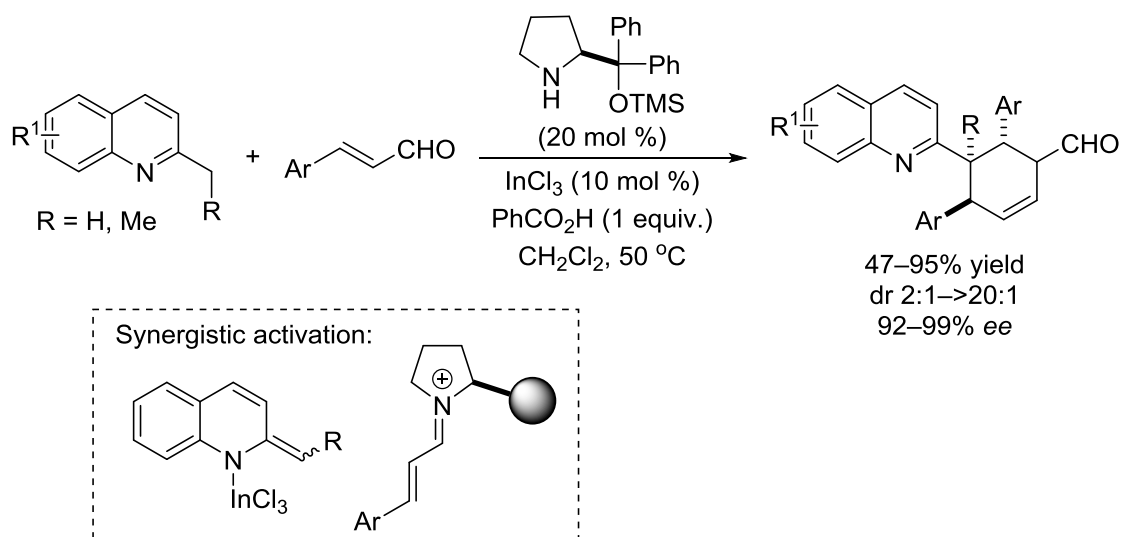


Scheme 62. Rios' asymmetric synthesis of 2-alkyl pyridine derivatives bearing a quaternary stereocenter *via* cascade reaction.

Meanwhile, Jørgensen and co-workers performed the analogous reaction employing unactivated alkyl quinolines through synergistic activation of the alkyl quinolone by InCl_3 , and the electrophile, by iminium ion catalysis (Scheme 63),¹⁸⁷ although no examples with 2-alkylpyridines were included.

¹⁸⁶ Meazza, M.; Potter, M.; Pitak, M. B.; Coles, S. J.; Mazzanti, A.; Rios, R. *Eur. J. Org. Chem.* **2017**, 719–725.

¹⁸⁷ Meazza, M.; Tur, F.; Hammer, N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2017**, 56, 1634–1638.

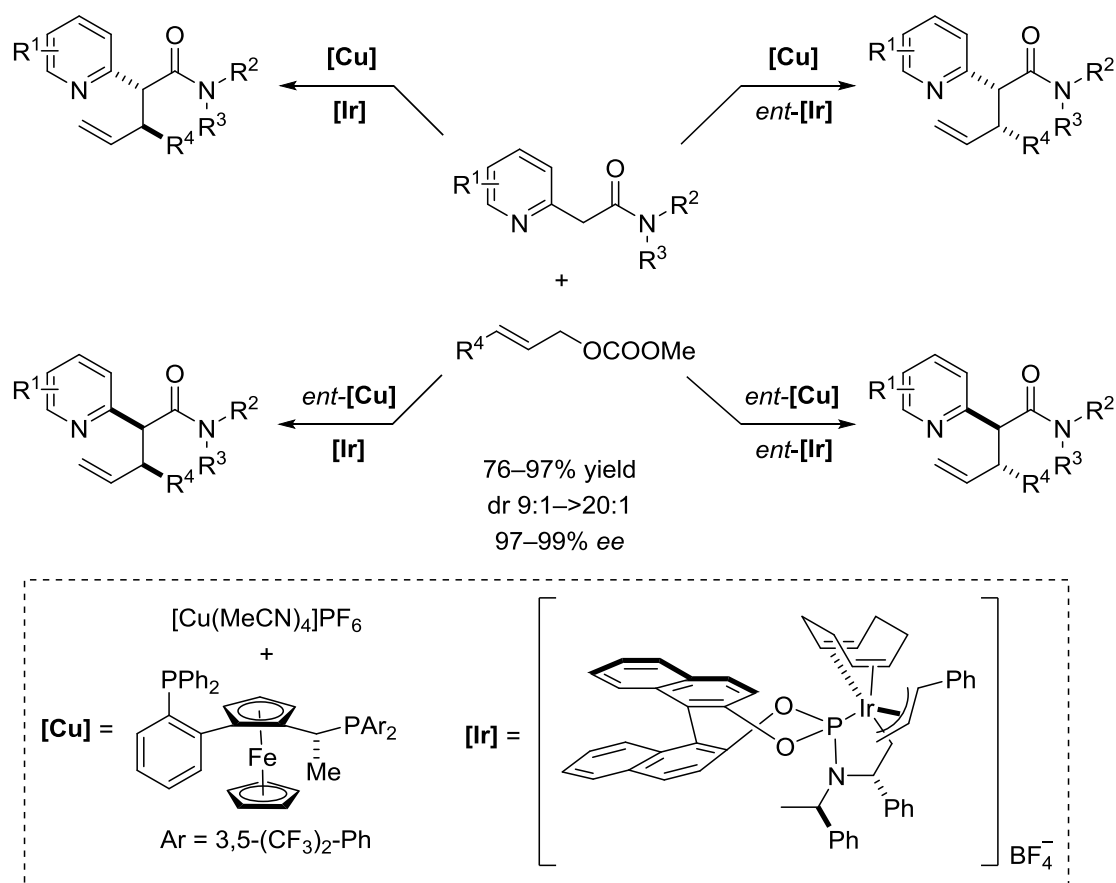


Scheme 63. Jørgensen's functionalization of alkyl quinolines

Finally, this year, Hartwig and co-workers reported the stereodivergent allylation of azaaryl acetamides and acetates employing a chiral metallacyclic iridium complex and a chiral bis-phosphine-ligated copper(I) complex, which individually controlled the configuration of the electrophilic and nucleophilic carbon atoms, respectively. Thus, by simple permutation of catalysts enantiomers, all four stereoisomers were synthesized with excellent diastereo- and enantioselectivity (Scheme 64).¹⁸⁸

¹⁸⁸ Jiang, X.; Boehm, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 1239–1242.

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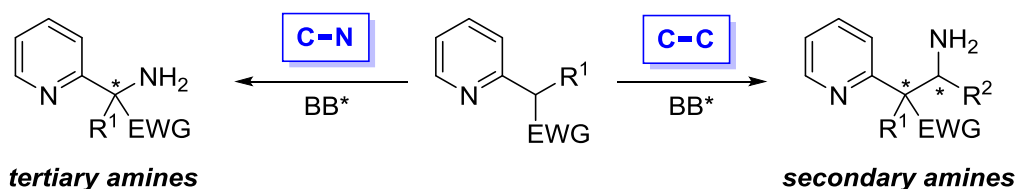
Reaction conditions: $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (2 mol%), Ligand (2.2 mol%), $[\text{Ir}]$ (1 mol%), DBU (2 mol%), THF, rt, 10 h

Scheme 64. Hartwig's stereodivergent allylation of 2-pyridyl acetamides.

In summary, precedents described above show that, although some examples of catalytic enantioselective addition of 2-alkyl pyridines to different electrophiles have been accomplished, the approach still presents numerous limitations. On the one hand, suprastoichiometric amounts of strong bases or substrate pre-activation with electron-withdrawing groups are required for the reaction to proceed. Likewise, the asymmetric generation of quaternary stereocenters remains almost unexplored and no examples for the stereoselective synthesis of pyridine based tertiary and secondary amines have been reported through C–N bond formation whereas only one example has been disclosed for the synthesis of azaarene based secondary amines through C–C bond formation under metal catalysis (Scheme 61, page 123).

3.2. Working hypothesis and objectives

Based on the experience of our research group in the development of Brønsted base catalyzed C–C and C–heteroatom bond forming reactions, we considered that 2-alkyl pyridines could be employed as pronucleophiles to address the stereoselective synthesis of pyridine based chiral tertiary and secondary amines through chiral Brønsted base-catalyzed C–N and C–C bond formation reactions, respectively (Scheme 65).



Scheme 65. Synthetic plan for the preparation of pyridine based tertiary and secondary amines.

Precedents described above reveal the main limitations that substrates of this type present: i) the low acidity of 2-alkylazaarenes, that requires the use of pre-activated substrates either in the azarene ring and/or the C α , ii) the lack of methods to address the generation of C α quaternary stereocentres and iii) the difficulties to maintain the configurational stability of tertiary stereocenters generated under basic conditions.

As mentioned in the general introduction, Brønsted base catalyzed transformations usually show a strong dependence on both substrate and catalyst structure. As a result, methodologies that imply modifications in the pronucleophile structures to enhance reactivity and improve stereoselectivity are of great interest. In this context, and following the atom economy principle,¹⁸⁹ we envisioned that 2-alkyl azaarene *N*-oxides could be perfect candidates to perform efficiently in chiral Brønsted base catalyzed C–N and C–C bond formation reaction.

The two key elements that make 2-alkyl azaarene *N*-oxides good candidates *a priori*, are their relatively high CH Brønsted acidity as compared to most alkylazaarenes (Figure 21)¹⁹⁰ and the presence of the N–O group as a potentially coordinating site for catalyst binding.¹⁹¹ Considering this, we could expect that bifunctional Brønsted bases might be

¹⁸⁹ a) Trost, B. M. *Science* **1991**, *254*, 1471–1471 b) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–381. c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.

¹⁹⁰ 2-Alkylpyridine *N*-oxides are more acidic than the parent 2-alkyl pyridines in about 3–4 pK_a units in DMSO: a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. b) http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf (accessed Aug 30, 2018).

¹⁹¹ Stereoselective methodologies with *N*-oxides: a) Landa, A.; Minkkilä, A.; Blay, G.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 3472–3483. b) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240–245. c) Holmquist, M.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Org. Lett.* **2014**, *16*, 1204–

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adequate for an effective α -deprotonation and subsequent stereoselective bond formation. As far as we know, azaarene *N*-oxides have not been investigated in the context of asymmetric functionalizations.

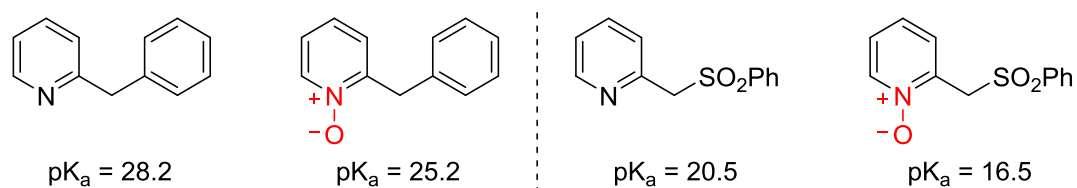
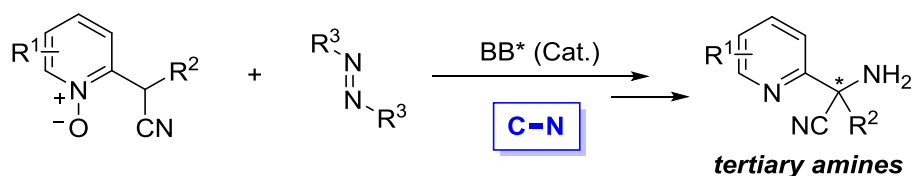


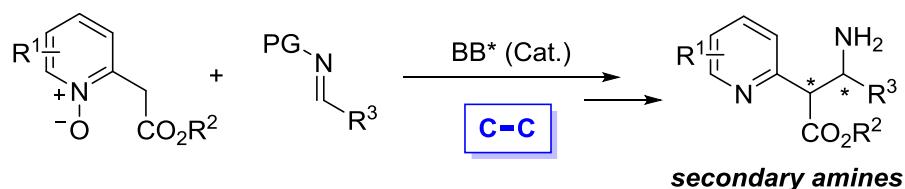
Figure 21. pK_a values of pyridine and pyridine *N*-oxide derivatives.

In consequence, we decided to address, as first objective, the stereoselective synthesis of pyridine based tertiary amines through Brønsted base-catalyzed stereoselective α -amination of 2-cyanoalkylazaarene *N*-oxides with azodicarboxylates (0).



Scheme 66. Synthetic plan for the enantioselective formation of pyridine based tertiary amines.

As a second objective, we envisioned that pyridine based α -chiral secondary amines might be prepared through Brønsted base-catalyzed stereoselective Mannich-type reaction of 2-azaaryl acetate *N*-oxides with *N*-protected aldimines (0).



Scheme 67. Synthetic plan for the enantioselective formation of pyridine based secondary amines.

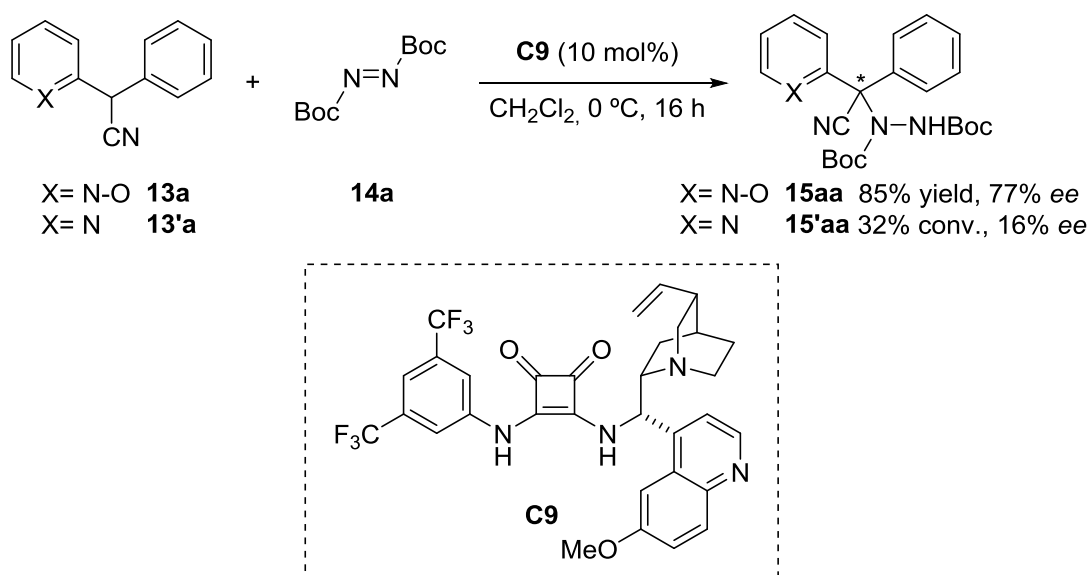
1207. For examples reported after the present work, see: d) Xu, Y.; Zhang, S.; Li, L.; Wang, Y.; Zha, Z.; Wang, Z. *Org. Chem. Front* **2018**, *5*, 376–379. e) He, F.; Chen, G.; Yang, J.; Liang, G.; Deng, P.; Xiong, Y.; Zhou, H. *RSC Adv.* **2018**, *8*, 9414–9422.

3.3. Results and discussion

3.3.1. Enantioselective α -amination of 2-(cyanomethyl)pyridine *N*-oxides with azodicarboxylates

3.3.1.1. Initial experiments and catalyst design.

In order to address our goal on the enantioselective synthesis of pyridine based tertiary amines, we first examined the addition of 2-(cyano(phenyl)methyl)pyridine *N*-oxide **13a** to di(*tert*-butyl) azodicarboxylate **14a** promoted by the bifunctional squaramide-type Brønsted base **C9**. Fortunately, the reaction went smoothly at 0 °C and total conversion was achieved in only 16 hours. Adduct **15aa** was obtained in 85% yield and 77% *ee* (Scheme 68). More gratifying was to find out that the reaction between the pyridine analogue **13'a** and **14a** went sluggish and with low asymmetric induction, thus confirming our initial hypothesis.



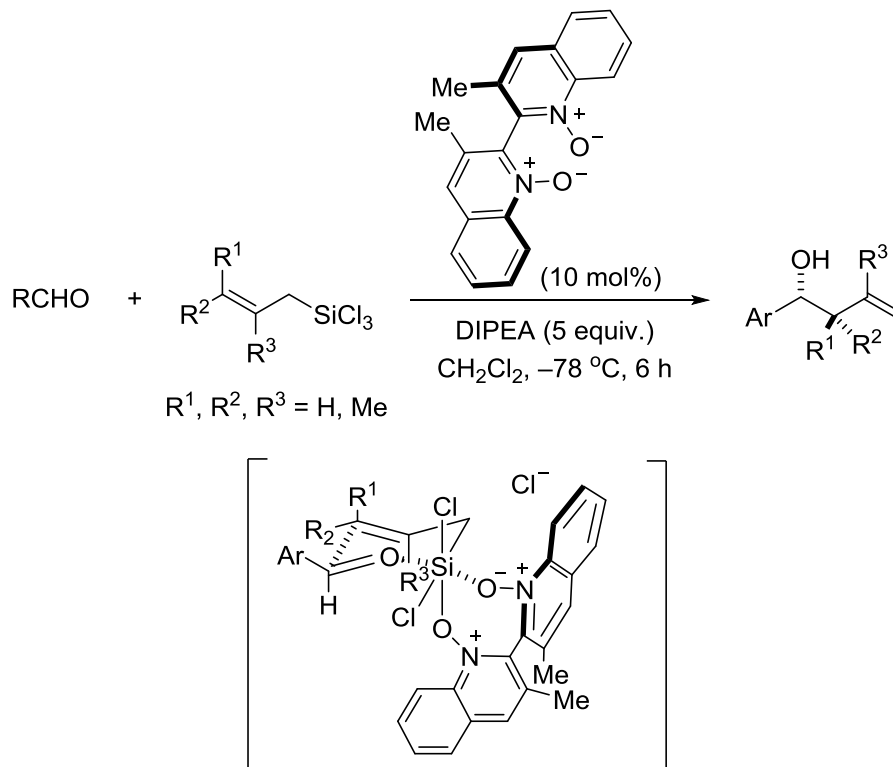
Scheme 68. Comparison of the reactivity of **13a** and **13'a** in the reaction with **14a** promoted by **C9**.

As mentioned before, the development of stereoselective Brønsted based catalyzed transformations is linked to the search of new modes of substrate activation and new catalyst design. Accordingly, with this promising result in hand, we decided to focus on a way to improve the enantiocontrol by designing new catalysts with additional sites for substrate activation.

For the new catalyst design, we were inspired by the work by Hashimoto and co-workers on the enantioselective allylation of aldehydes with allyltrichlorosilanes

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assisted by chiral azaarene *N*-oxide catalyst.¹⁹² The authors suggested that the allylation of aromatic and unsaturated aldehydes proceeded *via* a cyclic chair-like transition state model where the *N*-oxide groups of the catalyst are coordinated to the hypervalent silicon (Scheme 69).

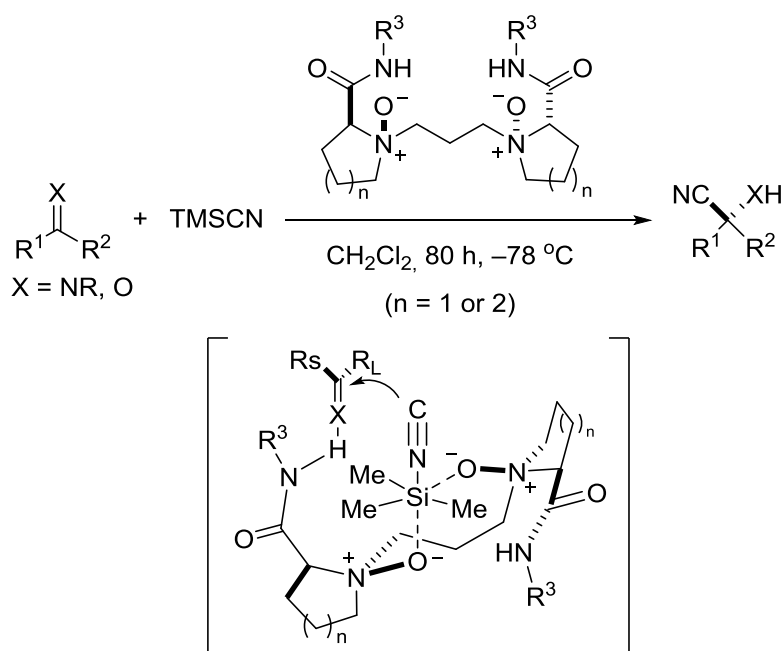


Scheme 69. Hashimoto's allylation with allyltrichlorosilanes catalyzed by chiral azaarene *N*-oxide.

In addition, Feng and co-workers, developed the enantioselective cyanation of carbonyl compounds and imines employing trimethylsilyl cyanide (TMSCN). The reactions were promoted by *L*-proline or *L*-piperidinamide based *N,N'*-dioxides, activating cooperatively both TMSCN and the electrophile. The possible mechanism consists of the generation of a hypervalent silicon intermediate from the bidentate *N,N'*-dioxide which enhances the nucleophilicity of the cyano group as well as the rigidity of the reaction environment. Consequently, the electrophile activated by hydrogen bonding by the nearby amide is attacked by the cyano group (Scheme 70).¹⁹³

¹⁹² a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420. For further works with similar activation models, see: b) Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353–354. c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235. d) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659–9668. e) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235–5248. f) Chen, J.; Captain, B.; Takenaka, N. *Org. Lett.* **2011**, *13*, 1654–1657.

¹⁹³ a) Wen, Y.; Huang, X.; Huang, J.; Xiong, Y.; Qin, B.; Feng, X. *Synlett* **2005**, 2445–2448. b) Huang, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X. *J. Org. Chem.* **2007**, *72*, 204–208. c) Qin, B.; Liu, X.; Shi, J.; Zheng, K.; Zhao, H.;



Scheme 70. Feng's cyanosilylation reaction catalyzed by *N,N'*-dioxides.

Taking these works into account and given the high chemical affinity of silicon for oxygen, we envisioned a multifunctional catalyst based on *N*-oxide–silicon interactions as a suitable candidate to carry out the reaction satisfactorily (Figure 22).

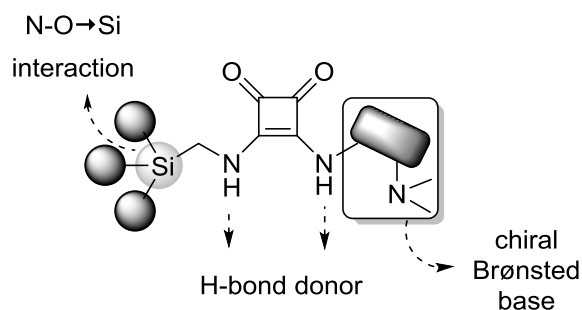


Figure 22. New design for the multifunctional squaramide-based Brønsted base catalyst.

The proposed general synthetic sequence for this type of catalysts is depicted in Scheme 71. Their preparation involved the amination of the corresponding (chloromethyl)silyl derivative in a two-step sequence; first, the corresponding azide was prepared by treatment of the alkyl chloride with NaN_3 in HMPA¹⁹⁴ and subsequent reduction with LiAlH_4 led to the corresponding amine.¹⁹⁵ The coupling with 3,4-

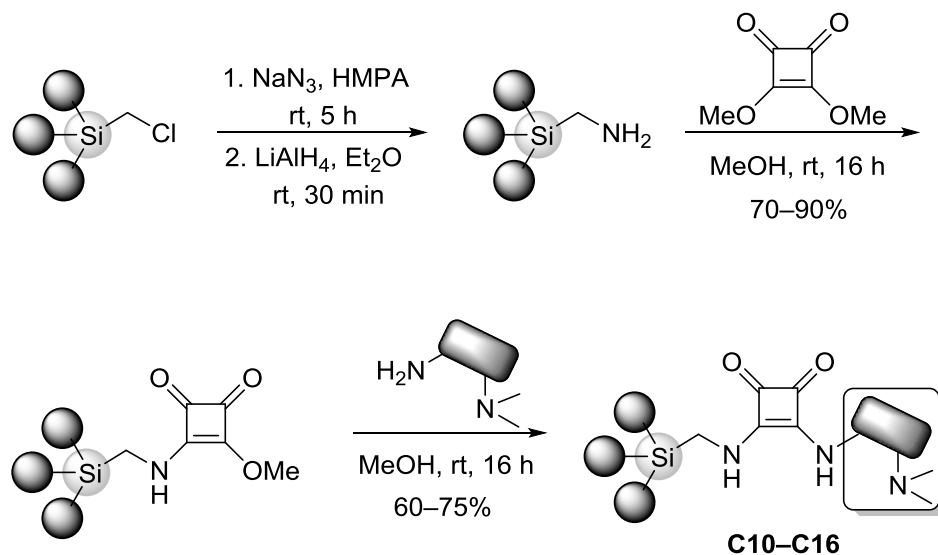
Feng, X. *J. Org. Chem.* **2007**, *72*, 2374–2378. For further examples employing proline-based *N*-oxides as chiral catalysts, see: d) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151–3154. For a review on chiral *N,N'*-dioxides as ligands and organocatalysts in catalytic asymmetric reactions, see: Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574–587.

¹⁹⁴ Otohiko, T.; Shuji, K.; Koyo, M. *Chem. Lett.* **1983**, *7*, 1131–1134.

¹⁹⁵ Lettelier, M.; McPhee, D. J.; Griller, D. *Synth. Commun.* **1988**, *18*, 1975–1978.

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dimethoxy-3-cyclobutadiene-1,2-diene and the amine was carried out at room temperature and, finally, the coupling of the second amino group, containing the corresponding chiral Brønsted base, was performed to produce the novel multifunctional squaramide-based Brønsted base catalysts.



Scheme 71. Synthesis of squaramide-based Brønsted base catalysts bearing a silicon group.

3.3.1.2. Catalyst screening

Following the methodology described above, we synthesized a series of silicon-containing squaramide-based Brønsted base catalysts (Figure 23) and we tested them in the reaction of 2-(cyano(phenyl)methyl)pyridine *N*-oxide **13a** with di(*tert*-butyl) azodicarboxylate **14a**.

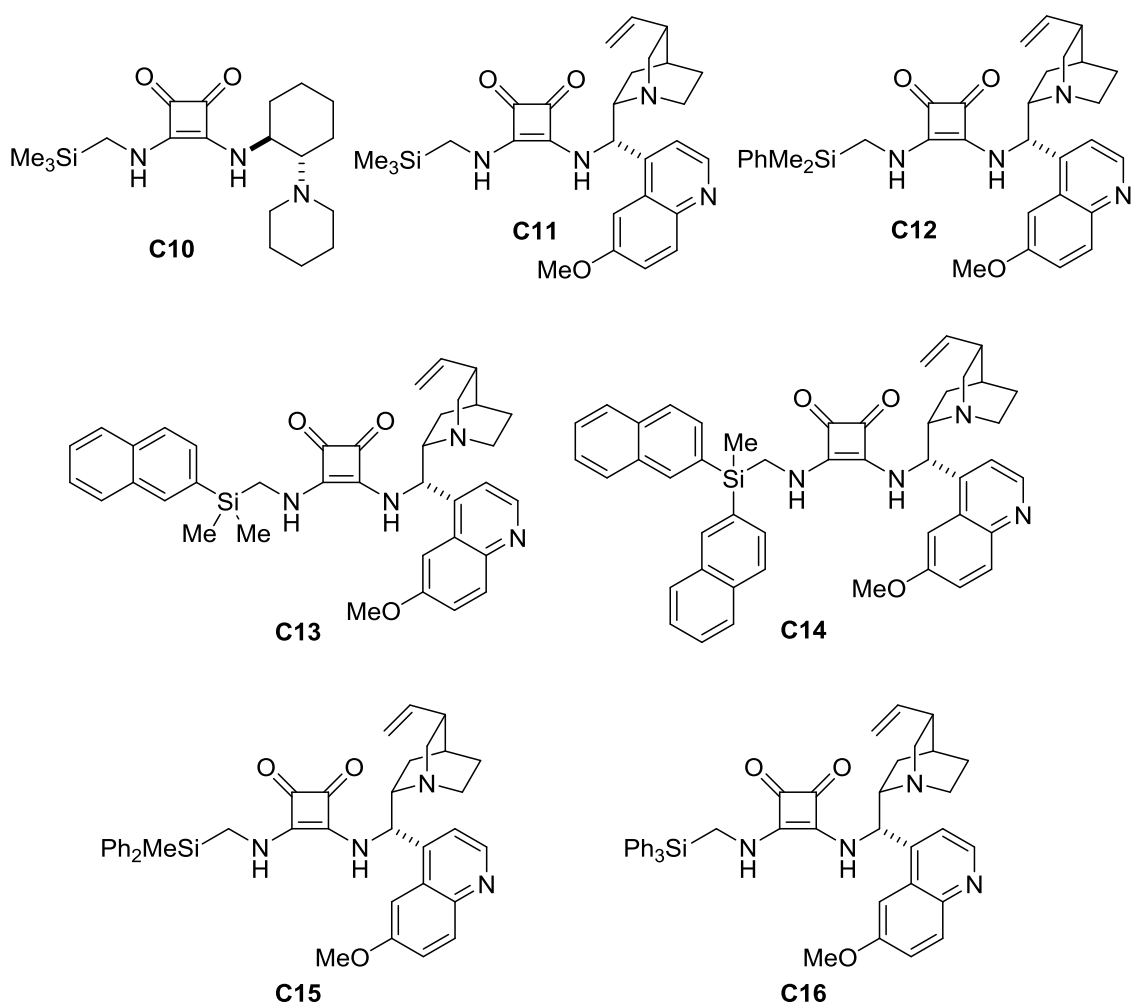


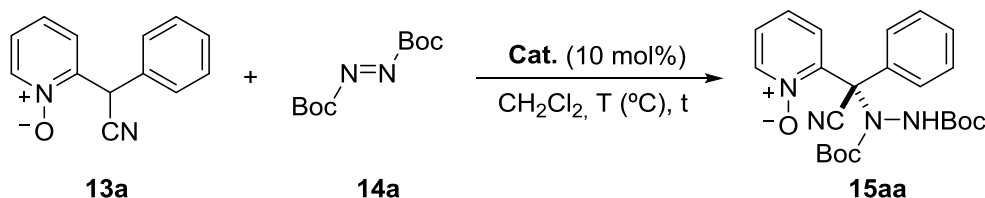
Figure 23. Silicon-containing squaramide-based Brønsted base catalysts.

Results obtained for each catalyst are shown in Table 6. The effect of the chiral Brønsted base moiety was first examined with catalysts **C10** and **C11** at room temperature. Catalyst **C10** bearing the 2-(piperidin-1-yl)cyclohexan-1-amine scaffold provided much lower enantioselectivity (38% *ee*, entry 1) than catalyst **C11** with the 9-amino-9-deoxy-9-epiquinine fragment (70% *ee*, entry 2). Consequently, the 9-amino-9-deoxy-9-epiquinine was maintained as the Brønsted base and variations on the silyl group were evaluated. First, the inclusion of a phenyl group –catalyst **C12**– induced a modest improvement in the enantioselectivity (72% *ee*, entry 3), which could not be increased at lower temperatures (entries 4 and 5). Replacement of the phenyl group by a 2-naphthyl moiety –catalyst **C13**– provided similar results (76% *ee*, entry 6) whereas the introduction of an additional 2-naphthyl group in the structure –catalyst **C14**– caused a significant drop in the asymmetric induction (57% *ee*, entry 7). Catalyst **C15** bearing two phenyl groups attached to the silyl atom provided a higher enantiomeric excess (81% *ee*, entry 8). On the other hand, increasing the concentration of the reactants, the enantioselectivity significantly decreased (48% *ee*, entry 9) while it was

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maintained with dilution (entry 10) and at lower temperatures (entry 10). Apolar solvents such as toluene produced the adduct **15aa** as a racemic mixture (entry 12). Finally, the reaction promoted by catalyst **C16**, bearing the triphenylsilyl group, in CH₂Cl₂ at 0 °C provided the best results in terms of stereocontrol (90% *ee*, entry 13).

Table 11. Catalyst screening for asymmetric α -amination of **13a** with **14a**.



Entry	Cat.	Solvent (mL)	T (°C)	t (h)	Yield (%)	<i>ee</i> (%) ^b
1	C10	CH ₂ Cl ₂	rt	15	80	38
2	C11	CH ₂ Cl ₂	rt	15	96	70
3	C12	CH ₂ Cl ₂	rt	15	78	72
4	C12	CH ₂ Cl ₂	-10	32	97	76
5	C12	CH ₂ Cl ₂	-40	56	96	75
6	C13	CH ₂ Cl ₂	0	40	92	76
7	C14	CH ₂ Cl ₂	0	15	99	57
8	C15	CH ₂ Cl ₂	0	15	90	81
9	C15	CH ₂ Cl ₂ (0.5)	0	15	92	48
10	C15	CH ₂ Cl ₂ (2)	0	15	93	81
11	C15	CH ₂ Cl ₂	-10	15	95	81
12	C15	Toluene	0	24	90	0
13	C16	CH₂Cl₂	0	15	88	90

^a Reactions were conducted on 0.2 mmol scale employing 1.5 equiv. of **14a** in 1 mL of CH₂Cl₂ (unless otherwise stated). ^b Enantiomeric excess of adduct **15aa** was determined by chiral HPLC.

3.3.1.3. Reaction scope

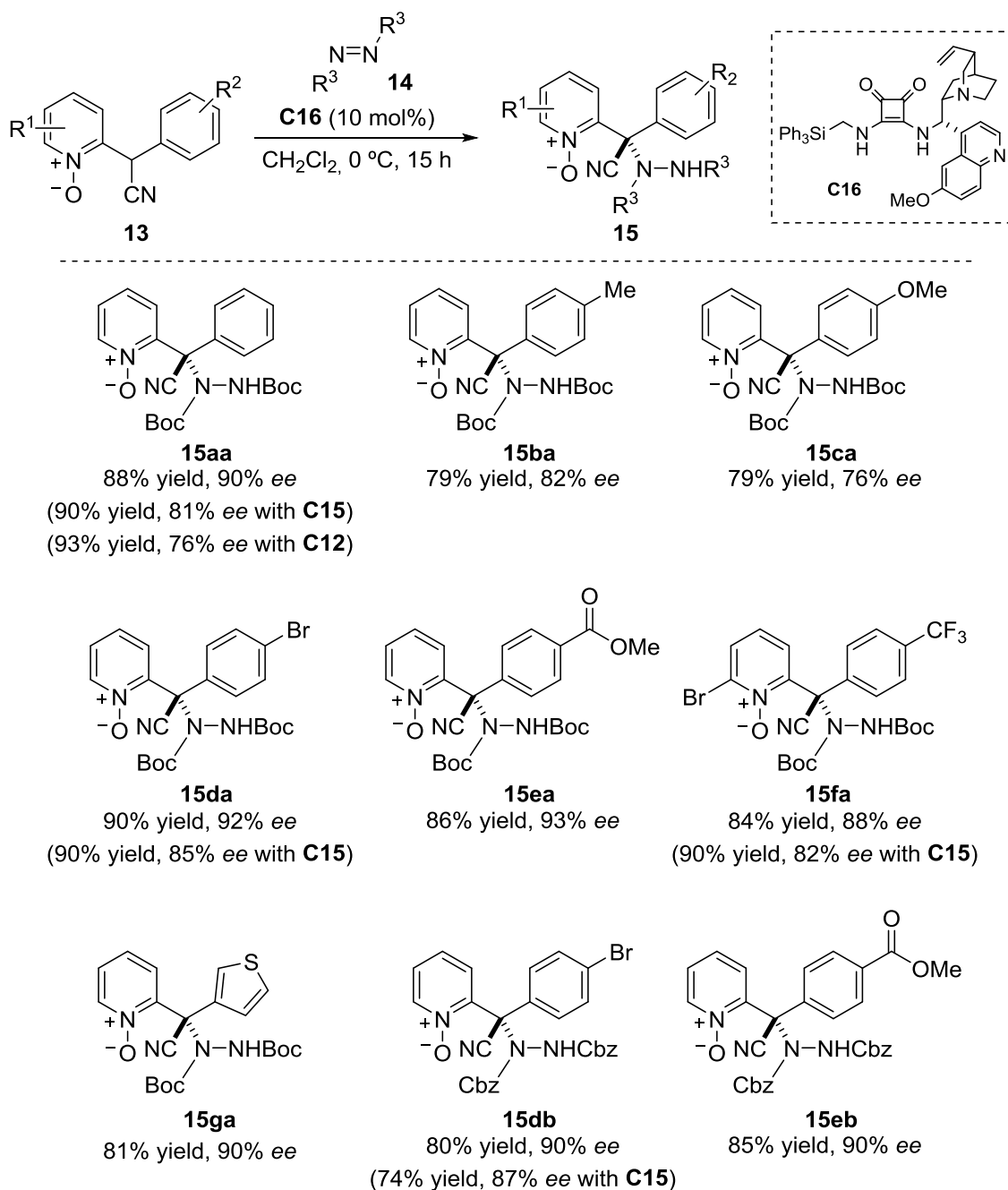
The scope of this α -amination process using either di-*tert*-butyl or dibenzyl azodicarboxylates (**14a** or **14b**), as aminating reagents, was investigated for a range of 2-cyanomethylpyridine *N*-oxides. As data collected in Table 12 show, reactions proceeded successfully to give adducts **15** with good yield and enantiomeric excess with

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catalyst **C16** providing the best results for all entries. A slight decrease in enantioselectivity was observed for nucleophiles containing electron-donating groups into the aromatic ring (**15ba** and **15ca**) whereas excellent yields and enantiomeric excesses were obtained with electron-withdrawing groups (**15da–15fa**) as well as with heteroaromatic rings (**15ga**). In addition, dibenzyl azodicarboxylate **14b** performed in a similar way providing adducts **15db** and **15eb** with excellent yield and enantioselectivity.

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Table 12. Enantioselective α -amination reaction scope.

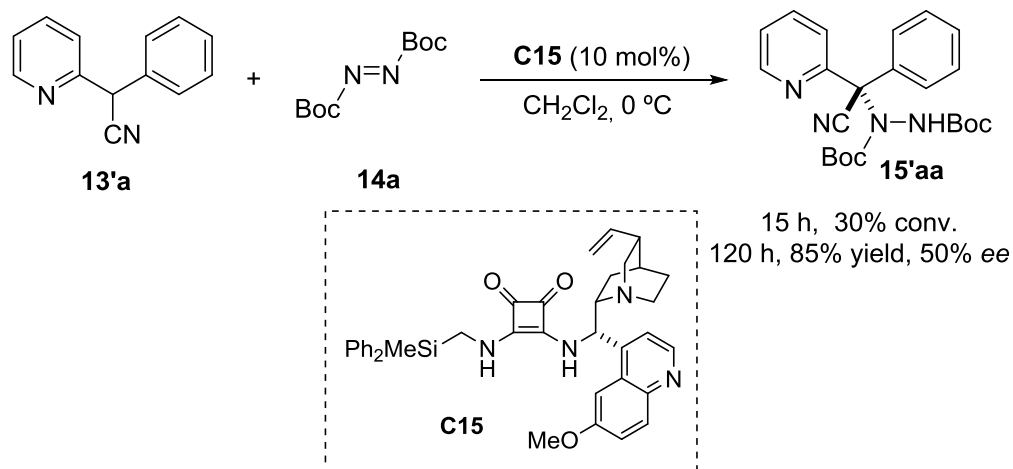


Reactions were conducted on 0.2 mmol scale employing 1.5 equiv. of **14** and 10 mol% of catalyst **C16** in 1 mL of CH_2Cl_2 (unless otherwise stated). Yields were determined for isolated products. Enantiomeric excess of adduct **15** was determined by chiral HPLC.

Once again, the parent pyridine **13'a** proved to be less efficient for this transformation (Scheme 72). The reaction of **13'a** and **14a** in the presence of 10 mol% catalyst **C15** proceeded to a limited extent of 30% conversion after 15 hours at $0\text{ }^\circ\text{C}$. After 120 hours,

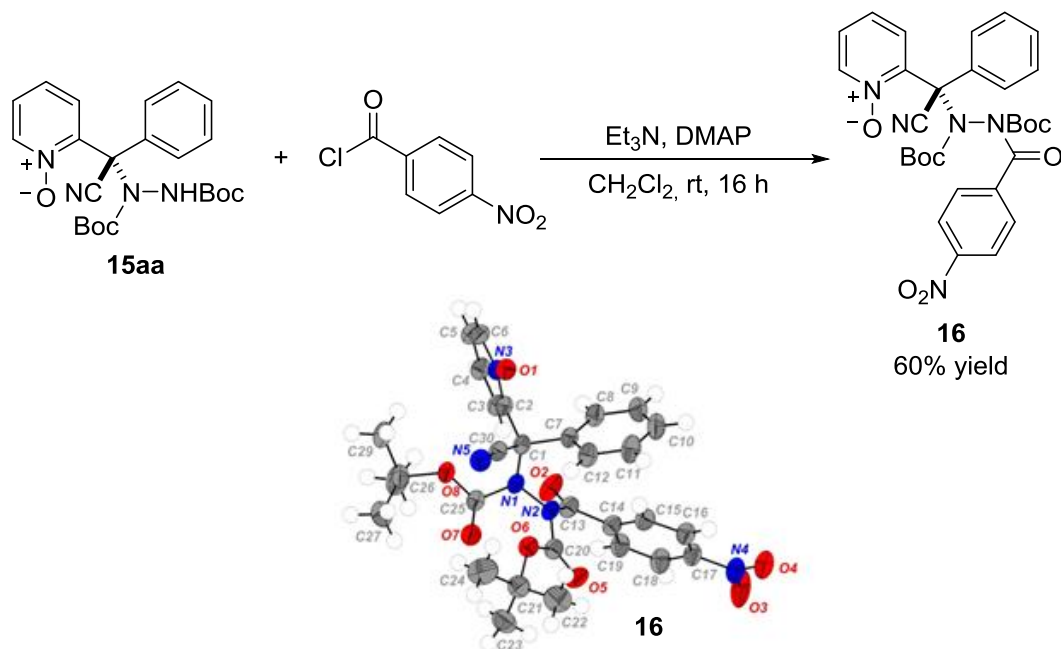
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complete transformation was observed and adduct **15'a** was obtained in 85% yield and with 50% *ee*.



Scheme 72. Effect of the *N*-oxide functionality.

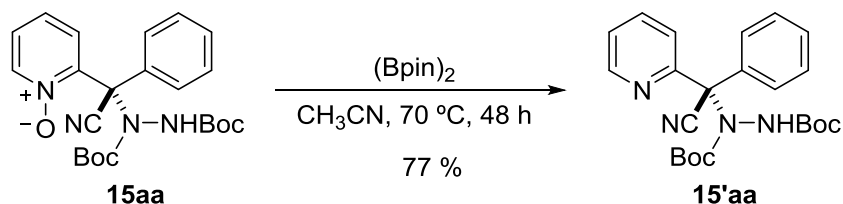
Transformation of the adduct **15aa** into the crystalline compound **16** allowed the determination of the absolute configuration by single-crystal X-ray analysis (Scheme 73). The configuration of the rest of adducts was established by assuming a uniform reaction mechanism.



Scheme 73. Determination of the absolute configuration.

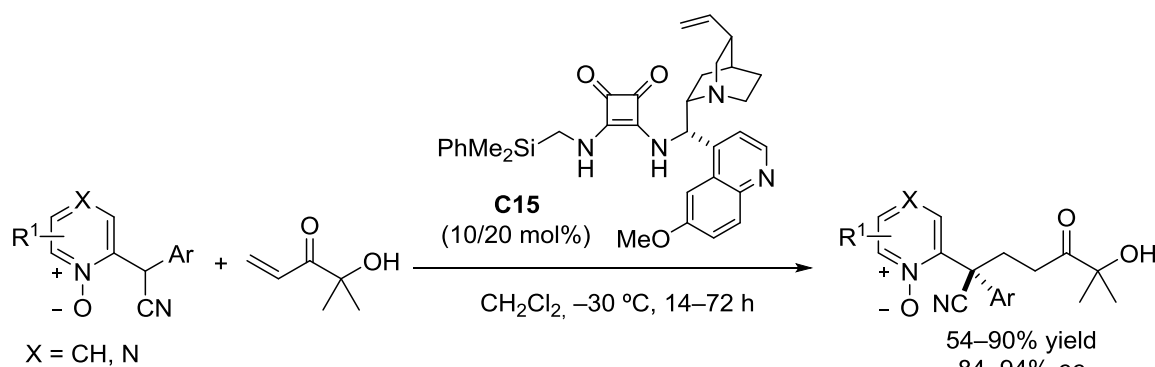
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To prove the utility of the *N*-oxide functionality as a temporary activating and stereodirecting group in the stereoselective synthesis of pyridine base tertiary amines, the reduction of the *N*-oxide group was accomplished in adduct **15aa** under mild conditions by treatment with (Bpin)₂.¹⁹⁶ In this way, the protected enantioenriched 2-pyridyl tertiary amine **15'aa** was synthesized in 77% yield (Scheme 74). The methodology described represents the first catalytic and enantioselective procedure for the synthesis of pyridine based tertiary amines by means of α -amination of 2-alkyl pyridines.



Scheme 74. Reduction of *N*-oxide group on adduct **15aa**.

In parallel, it was proven by Dr. Joseba Izquierdo that 2-cyanomethylazaarene *N*-oxides could also work as enabling substrates for conjugate additions to acrylate surrogates to afford elusive 2-*tert*-alkyl azaaryl adducts with high enantioselectivity (Scheme 75).¹⁹⁷



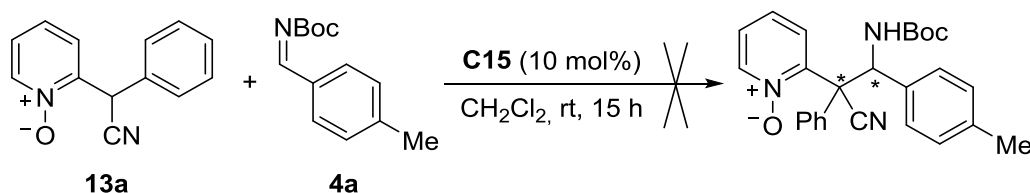
Scheme 75. Enantioselective conjugate addition of 2-(cyanomethyl)azaarene *N*-oxides to α -hydroxy enones.

¹⁹⁶ Procedure adapted from: Kokatla, H. P.; Thompson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. J. *Org. Chem.* **2011**, *76*, 7842–7848.

¹⁹⁷ Izquierdo, J. New Approach to Optically Active 2-*tert*-Alkyl Azaaryl Compounds and 5,5-Disubstituted Hydantoins. Ph.D. Thesis, University of the Basque Country, Donostia-San Sebastian, 2018.

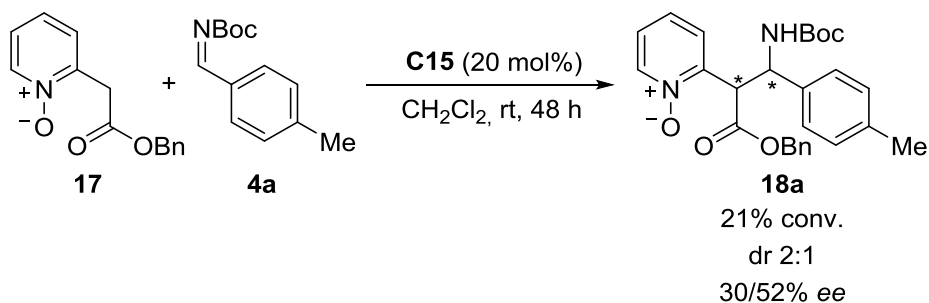
3.3.2. Enantioselective Mannich reaction of 2-azaaryl acetates with *N*-carbamoyl imines

With the satisfactory results obtained in the previous section, we decided to further extend the methodology for the stereoselective synthesis of pyridine based secondary amines with contiguous quaternary and tertiary stereocenters. For that purpose, we envisioned that the addition of 2-(cyanomethyl)pyridine *N*-oxides to *N*-Boc imines could be an attractive approach for their preparation. Therefore, the Mannich reaction of 2-(cyano(phenyl)methyl)pyridine *N*-oxide **13a** with *N*-Boc imine **4a** was investigated. Unfortunately, the reaction promoted by catalyst **C15** did not proceed at room temperature (Scheme 76), nor even when 0.5 equivalents of triethylamine were added.



Scheme 76. Unfruitful Mannich reaction of **6a** with *N*-Boc imine **3a**.

Since α -amination worked well for **13a**, we attributed the lack of conversion to steric reasons. At this point, we became also interested in the generation of configurationally labile stereocenters under Brønsted base catalysis, since their stability is easily compromised under proton transfer conditions. Therefore, we decide to investigate the Mannich reaction of 2-pyridyl acetate *N*-oxide **17** with *N*-Boc imine **4a**. The reaction promoted by **C15** provided adduct **18a** in very low conversion, after 48 hours at room temperature, low enantioselectivity and, as expected for tertiary stereocenters generated under Brønsted base catalysis, with low diastereoselectivity (Scheme 77).



Scheme 77. Mannich reaction of **17** with *N*-Boc imine **4a** catalyzed by **C15**.

Given the structural differences between pronucleophile **17** and **13a**, we decided to explore other catalytic systems that could result more appropriate for the reaction.

3.3.2.1. Catalyst screening

A variety of bifunctional Brønsted base catalysts was prepared and tested in the enantioselective Mannich reaction of 2-pyridyl acetate *N*-oxide **17** with *N*-Boc imine **4a** (Figure 24).

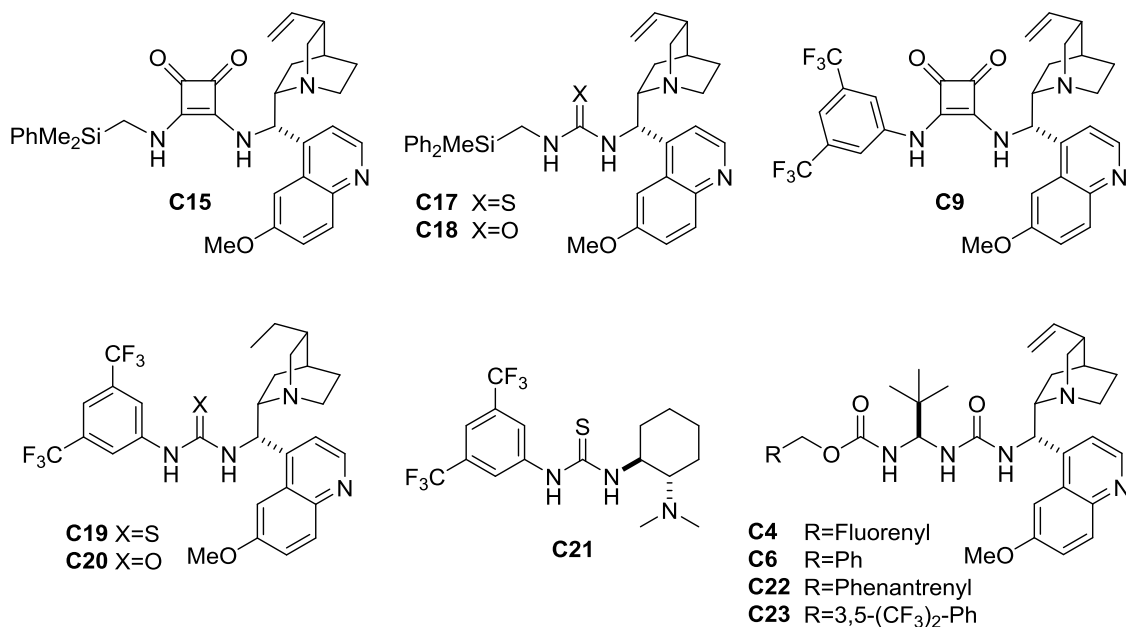
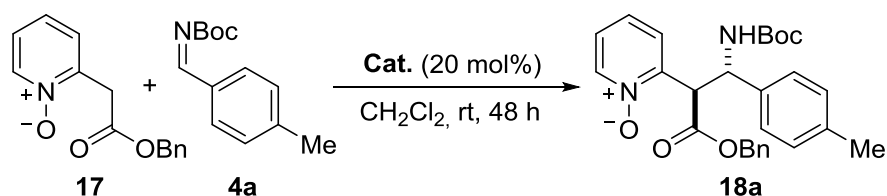


Figure 24. Catalyst library for the enantioselective Mannich reaction.

As data in Table 13 show, squaramide- and (thio)urea-based catalysts containing silyl groups –**C15**, **C17** and **C18**– afforded very poor results in terms of reactivity and stereoselectivity (entries 1–3) and similar results were achieved with conventional catalysts **C9**, **C19**, **C20** and **C21** (entries 4–7). In contrast, it was gratifying to observe that after 64 hours of stirring at room temperature, ureidopeptide-based Brønsted base catalysts –**C22**, **C4**, **C6** and **C23**– exhibited high (88%, entry 8) and complete conversion (entries 9-11). Most remarkably, the corresponding Mannich adduct **18a** was produced with high *anti:syn* ratio (5.7:1–9:1) and enantioselectivity (96-99% *ee*) regardless the nature of the R substituent in the catalyst. After some additional screening,¹⁹⁸ catalyst **C6** enabled the production of **18a** as the only detectable diastereomer in 99% *ee* (entry 12).

¹⁹⁸ Reactions performed in THF and toluene at 0 °C provided lower conversions with **C6** after 48 hours, although similar stereoselectivities were obtained. *N*-Tosyl imine afforded poor results with **C6** after 48 hours at 0 °C in methylene chloride –40% conv., dr 2.5:1 *anti*, 44/0% *ee*–.

Table 13. Catalyst screening for the enantioselective Mannich reaction of **17** with **4a**.

Entry	Cat.	T (°C)	t (h)	Conv. (%) ^b	dr (<i>anti:syn</i>) ^c	ee (%) ^d
1	C15	rt	64	21	2:1	30/52
2	C17	40	48	30	1:1	26/18
3	C18	rt	64	51	1.7:1	54/28
4	C9	40	48	20	0.9:1	4/53
5	C19	40	70	42	0.8:1	3/16
6	C20	40	48	36	0.7:1	50/74
7	C21	rt	140	60	0.6:1	17/79
8	C22	rt	64	88	6.7:1	99/99
9	C4	rt	64	>95	5.7:1	99/98
10	C6	rt	64	>95	9:1	96/94
11	C23	rt	64	>95	9:1	98/55
12^e	C6	0	48	>95	99:1	99

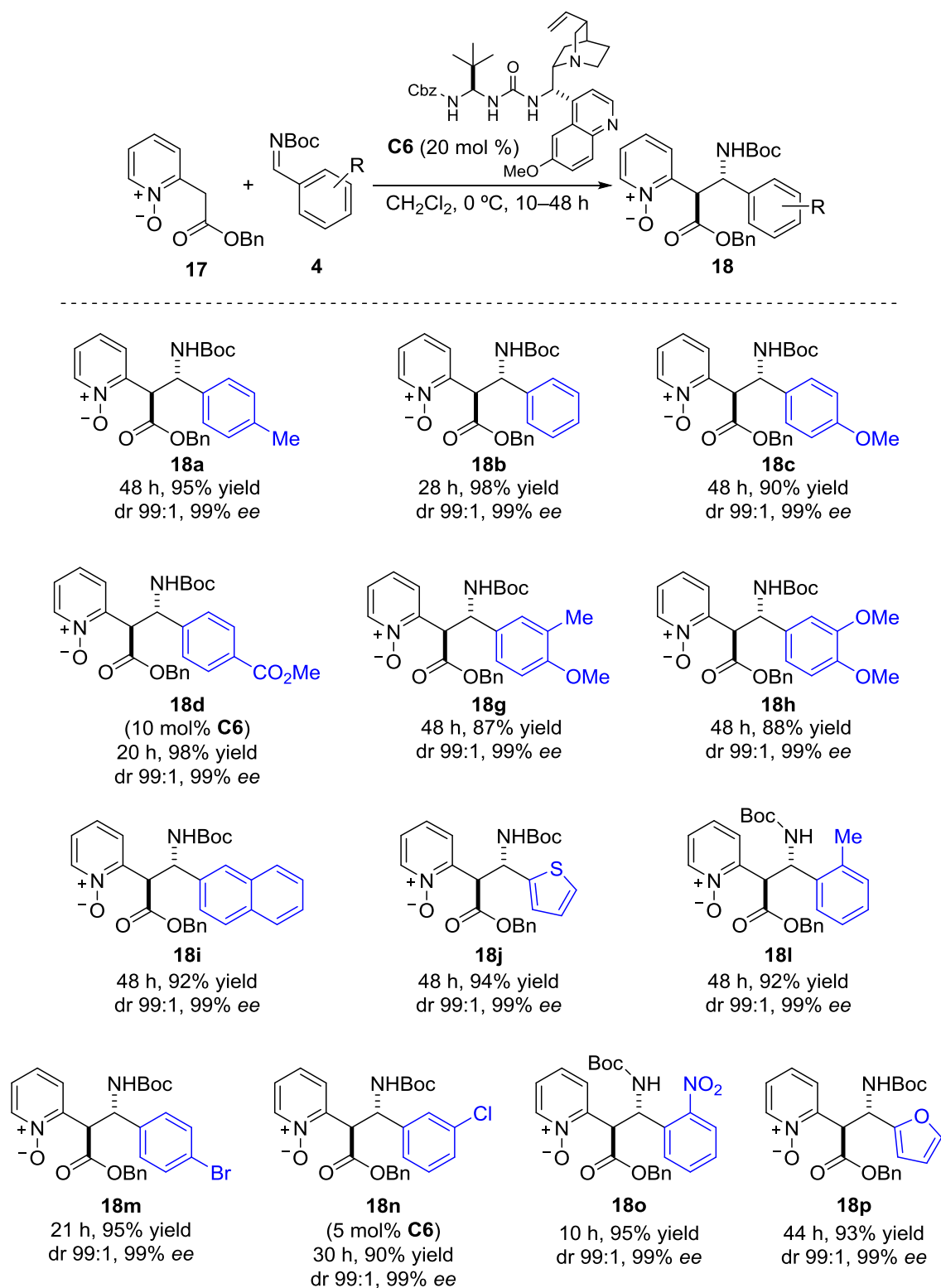
^a Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH₂Cl₂ (molar ratio of **17:4a**, 1:1.2). ^b Conversion determined by ¹H NMR. ^c Diastereomeric ratio determined by ¹H NMR of crude mixture and corroborated by chiral HPLC. ^d Enantiomeric excess determined by chiral HPLC. ^e Molar ratio of **17:4a**, 1:2.

3.3.2.2. Reaction scope

Next, we explored the generality of the optimized procedure for *N*-oxide **17** with a range of *N*-Boc imines under the action of catalyst **C6**. As data in Table 14 show, *N*-Boc imines **4** with either electron-donating or electron withdrawing groups at *ortho*, *meta* or *para* positions in the aromatic ring, and even heteroaromatic and disubstituted ones, were equally tolerated to produce the corresponding *anti* Mannich adducts **18(a–p)**, as sole diastereomers with excellent enantiomeric excess (99%). In this study, we employed 20 mol% of catalyst but it is worth mentioning that using 5–10 mol% of catalyst loading, the reactions proceeded equally well without compromising either stereoselectivity or chemical yield (adducts **18d** and **18n**).

Stereoselective synthesis of pyridine based tertiary and secondary amines

Table 14. Scope of *N*-Boc imines.



^a Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH_2Cl_2 (molar ratio of **17**:**4**, 1:2). ^b Diastereomeric ratio determined by ^1H NMR of crude mixture and corroborated by chiral HPLC. ^c Enantiomeric excess determined by chiral HPLC.

Crystallization of compound **18c** allowed the determination of the relative and absolute configuration by single-crystal X-ray analysis (Figure 25) and the configuration of the rest of adducts was established by assuming a uniform reaction mechanism.

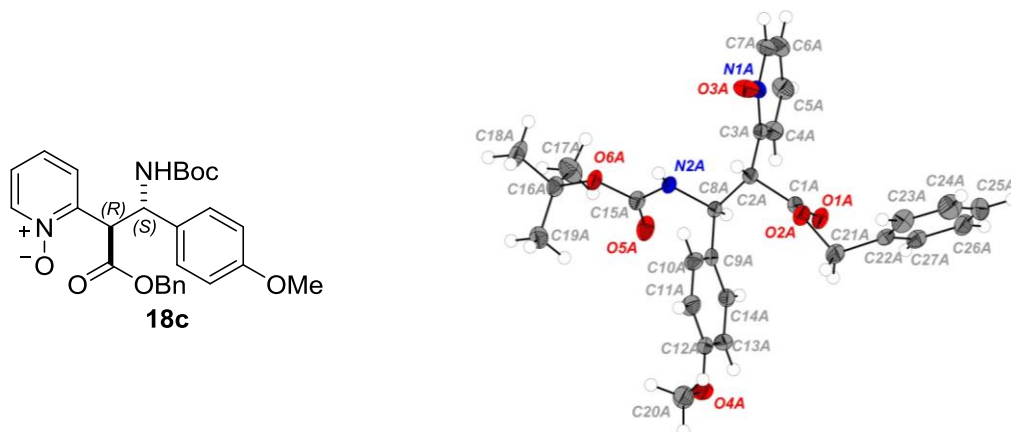
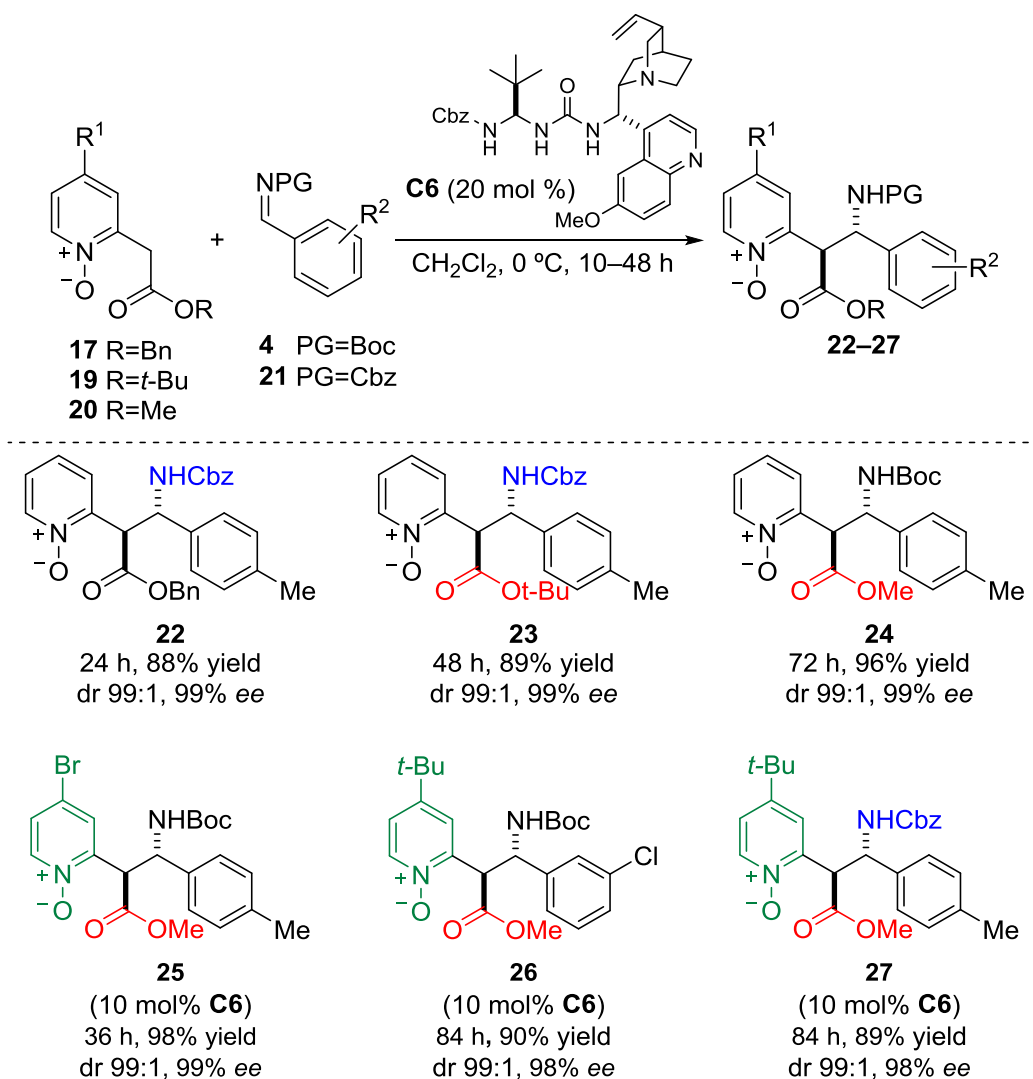


Figure 25. ORTEP diagram of compound **18c**.

Furthermore, the reaction with *N*-Cbz imine **21** produced the corresponding Mannich adduct **22** with identical level of stereocontrol and *tert*-butyl and methyl pyridyl *N*-oxide acetates **19** and **20a** were also compatible with the reaction conditions and produced the Mannich adducts **23** and **24**, respectively, with equal high stereoselectivity. This functional group compatibility represents an important advantage for subsequent adducts manipulations. Furthermore, the methodology was also suitable for substituted pyridyl *N*-oxide acetates such as **20b** and **20c**, which reacted with either *N*-Boc or *N*-Cbz imines using 10 mol% of catalyst **C6** to afford adducts **25**, **26** and **27** (Table 15).

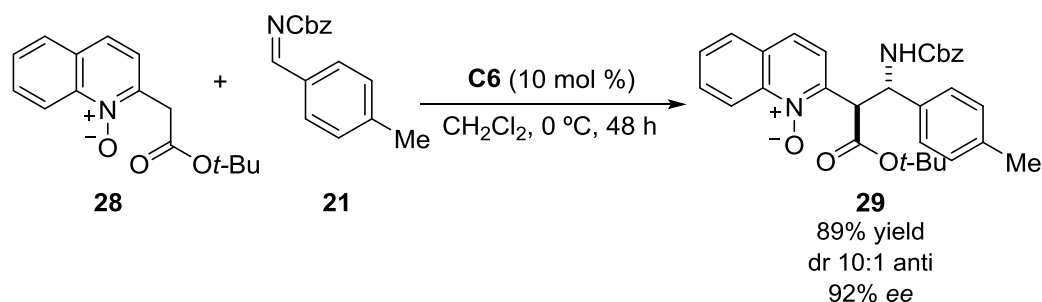
Stereoselective synthesis of pyridine based tertiary and secondary amines

Table 15. Further scope of the enantioselective Mannich reaction with 2-pyridyl acetate *N*-oxides.



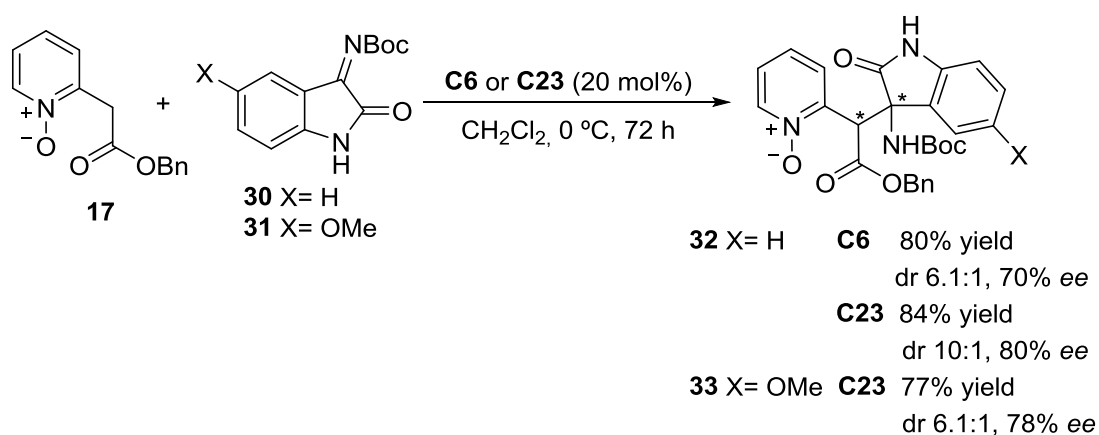
^a Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH₂Cl₂ (molar ratio of **17/19/20**:**4/21**, 1:2). ^b Diastereomeric ratio determined by ¹H NMR of crude mixture and corroborated by chiral HPLC. ^c Enantiomeric excess determined by chiral HPLC.

Moreover, quinoline *N*-oxide **28** performed well with *N*-Cbz imine **21** and 10 mol% of catalyst **C6** to afford the corresponding Mannich adduct **29**, albeit with slightly diminished diastereoselectivity (Scheme 78).



Scheme 78. Enantioselective Mannich reaction with quinoline *N*-oxide **28**.

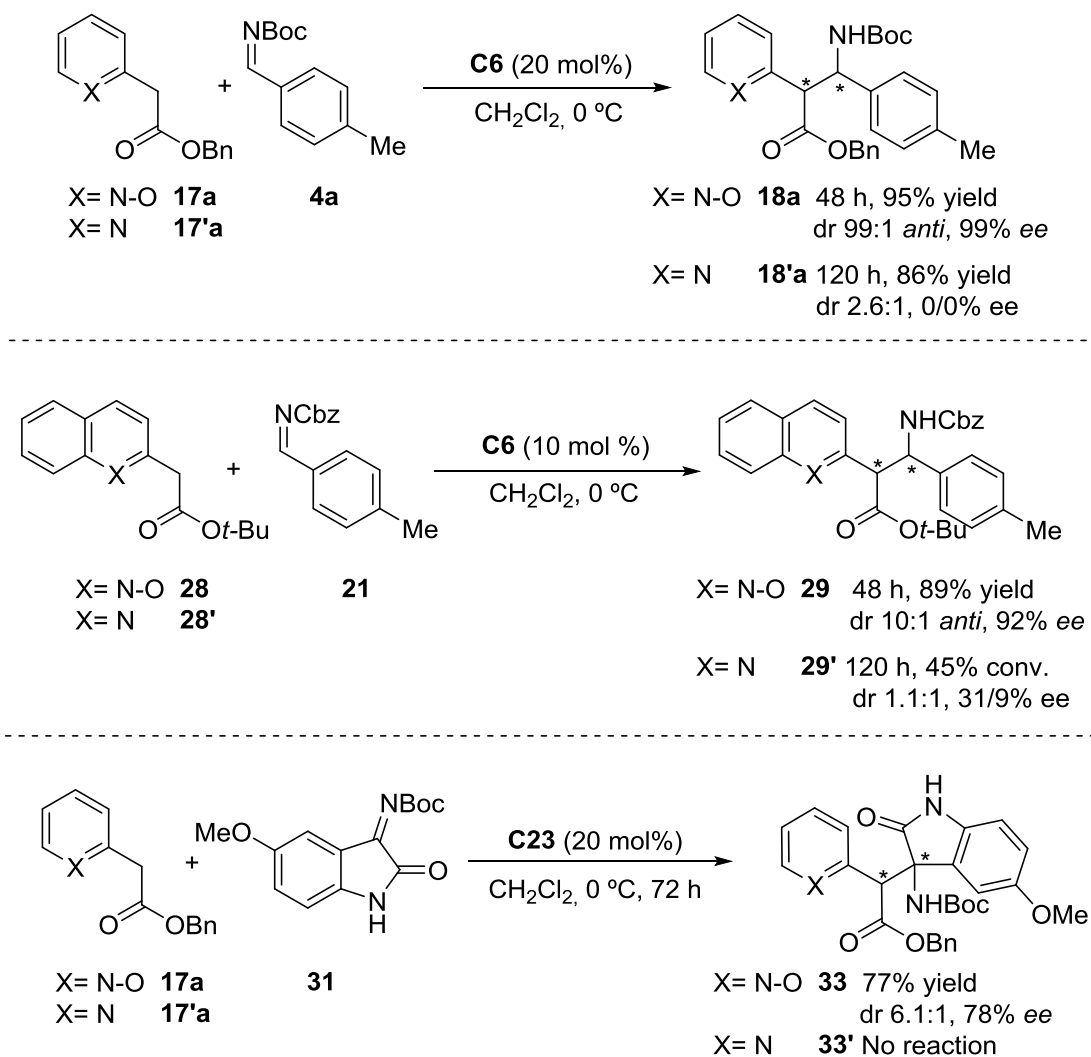
The suitability of this stereoselective Mannich reaction to generate quaternary stereogenic centers was briefly examined. 2-Pyridyl acetate *N*-oxide **17** reacted with *N*-Boc imine derived isatines **30** and **31** in the presence of either catalyst **C6** or **C23** to produce the corresponding Mannich adducts **32** and **33** in good yields, after 72 hours. In this case, catalyst **C23** improved the results obtained with **C6** and good diastereo- and enantioselectivities were achieved although they were not as good as those obtained for the reaction with aldimines **4** and **21** (Scheme 79).



Scheme 79. Mannich reaction with imine derived isatines **30** and **31**.

Finally, the role of the *N*-oxide functionality in the Mannich reactions described above was reexamined under the optimized reaction conditions (Scheme 80). Again, the presence of the *N*-oxide was essential to ensure reactivity and selectivity since reactions went much slower or did not proceed with the corresponding pyridine analogs and lower diastereo- and enantioselectivities were obtained. These results corroborate again the dual role of the *N*-oxide functionality as an activating and stereodirecting group.

Stereoselective synthesis of pyridine based tertiary and secondary amines



Scheme 80. Effect of the *N*-oxide functionality

3.3.2.3. Configurational stability of Mannich *anti* adducts

We were intrigued by the configurational stability of the *anti* adducts obtained in the reaction. It can be argued that the *anti* adducts obtained in the Mannich reaction are produced under kinetic control since their diastereomeric ratio and enantiomeric excess remained constant during the reaction progress despite the basic reaction conditions. For instance, upon complete transformation into the Mannich adduct **18a**, its configurational stability was maintained at 0 °C and slowly diminished at room temperature; after 96 hours the diastereomeric ratio turned to 7.3:1 (99% ee) (Figure 26). This stability of the *anti* adduct **18a**, could be explained by the difficulty of the catalyst to remove the remaining hydrogen at the exocyclic tertiary C α carbon. Less hindered and stronger bases, such as Et₃N, DBU, and even the analogous bifunctional

urea **C20** promoted epimerization at shorter reaction times at room temperature (Figure 26).

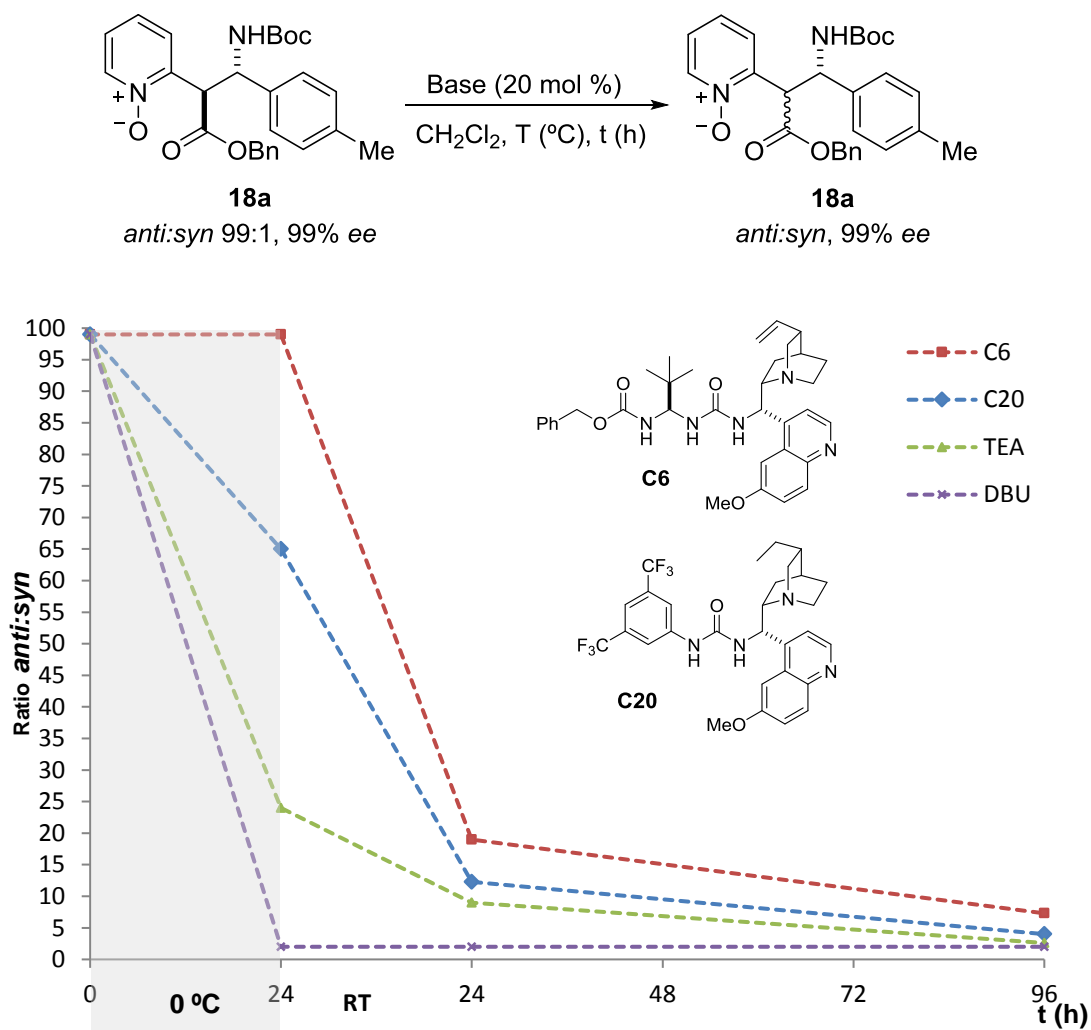


Figure 26. Effect of different Brønsted bases on the configurational stability of the *anti* adducts.

3.3.2.4. Reaction model proposal

The capacity of ureidopeptide-based catalyst **C6** to exclusively produce *anti-R,S*-configured Mannich adducts might be consistent with a tight transition state (TS) in which multiple hydrogen-bonding may be operating in unison, as depicted in Figure 27. In this way, the *Re* face of the enolate approaches the *Si* face of the *N*-protected imine to afford the corresponding *anti-R,S*-adducts.

Stereoselective synthesis of pyridine based tertiary and secondary amines

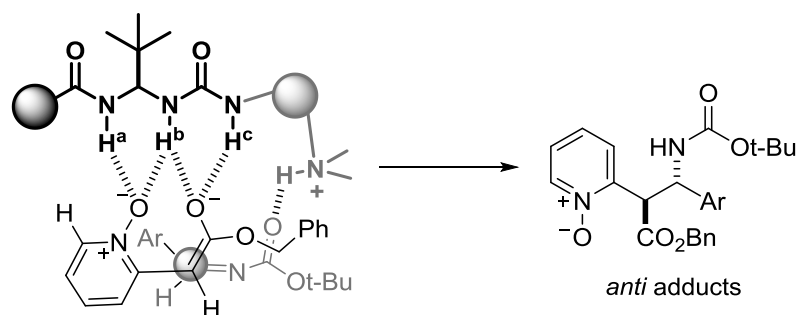


Figure 27. Plausible TS model for the enantioselective Mannich reaction.

This transition state proposal would be in accordance with the model proposed by Pápai and Soós, for bifunctional thiourea and squaramide-based organocatalysts, in which the deprotonated nucleophile binds to the H-bond network, while the protonated amine activates and orientates the electrophile (Figure 28).¹⁹⁹

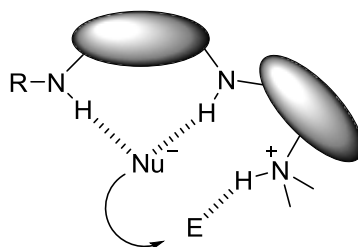


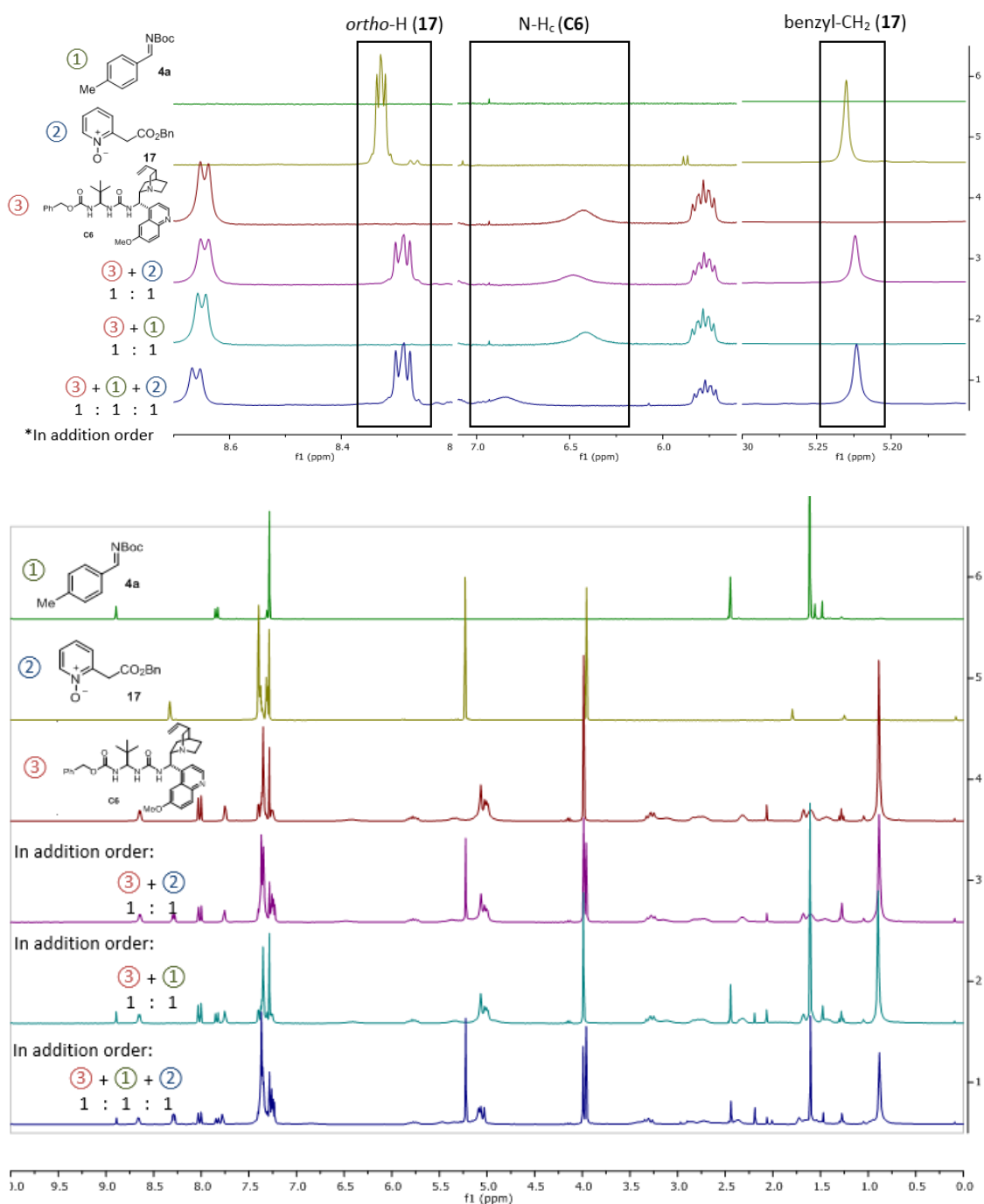
Figure 28. Pápai and Soós' transition state model.

An evidence in favor of the proposed model, wherein the three N–H of the catalyst are involved in hydrogen bonding, is the observation that chemical shifts of the ortho-H in the pyridine and the methylene of the benzyl group in **15** were affected ($\Delta\delta = +0.03$ and $+0.02$ ppm, respectively, in CDCl₃) by addition of 1 equivalent of **C6**, as well as the chemical shifts of the three N–H in the catalyst. Chemical shifts for H^a and H^b could not be exactly determined due to overlapping, whereas for H^c was determined as $\Delta\delta = +0.07$ ppm. On the other hand, N–H shifts remained unaffected by addition of *N*-Boc imine (Figure 29).²⁰⁰

¹⁹⁹ a) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160. b) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, T.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639.

²⁰⁰ All N–H's of the catalyst were unequivocally assigned based on COSY, HSQC and HMBC experiments.

Chapter 3



^1H NMR spectra of each of the following compounds in CDCl_3 (0.02 M) were recorded: (i) Pyridyl *N*-oxide acetate **17**, (ii) *N*-Boc imine **4a** and (iii) catalyst **C6**. Subsequently, ^1H NMR spectra of the following mixtures were recorded under the same conditions (0.02 M in CDCl_3): (iv) **C6/17** (1:1 mixture), (v) **C6/4a** (1:1 mixture) and (vi) **C6/17/4a** (1:1:1 mixture).

Figure 29. Expanded and full ^1H NMR (300 MHz) spectra of equimolar mixtures.

Stereoselective synthesis of pyridine based tertiary and secondary amines

Additionally, the ^1H NMR spectra of catalyst **C6** (0.02 M in CDCl_3) were recorded in the presence of increasing amounts of pyridyl *N*-oxide acetate **17** (increments of 0.25 equivalents until saturation) and the chemical shift of the N–H proton H_c was monitored and the interaction of N– H^c was corroborated (Figure 30).

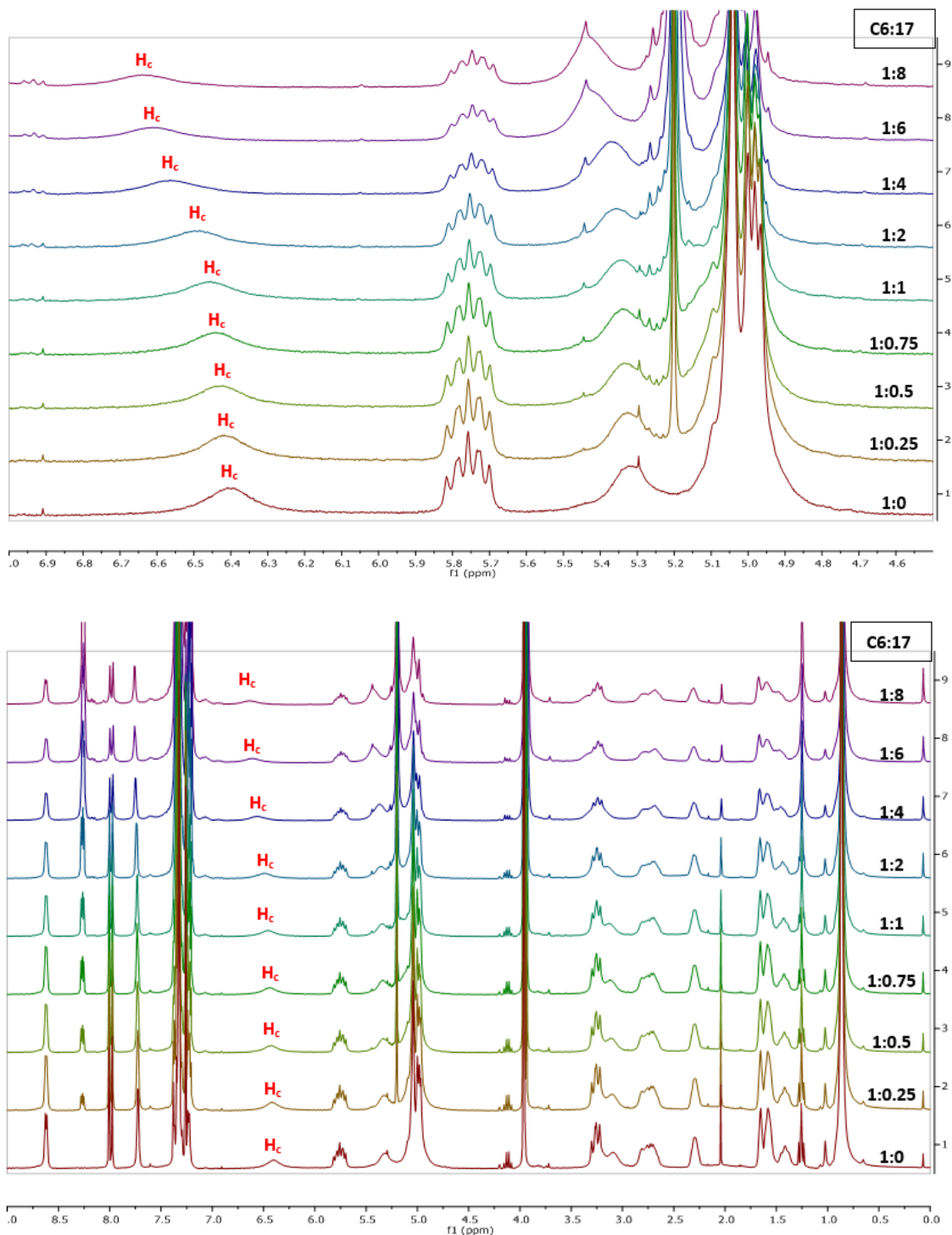
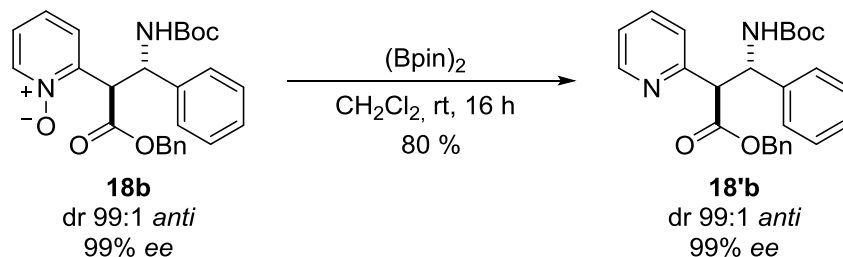


Figure 30. Expanded and full ^1H NMR (300 MHz) spectra of **C6** in presence of increasing amounts of **17**. To a 0.02M solution of catalyst **C6** in CDCl_3 , 0.25 equivalents of **17** were subsequently added until saturation.

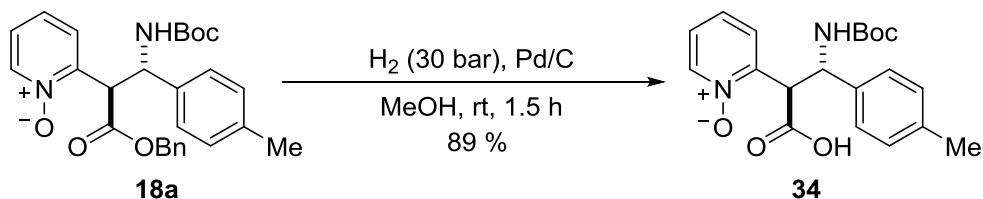
3.3.2.5. Elaboration of adducts

We explored the elaboration of Mannich adducts in order to evaluate the utility of the present reaction as an effective way to synthesize highly enantioenriched chiral pyridine based secondary amines. First, reduction of the *N*-oxide group on the Mannich adducts was accomplished; adduct **18b** was successfully reduced by treatment with $B(\text{pin})_2$ ¹⁹⁶ to afford the corresponding *N*-Boc protected secondary amine **18'b** in 80% isolated yield with unaltered diastereo- and enantioselectivity (Scheme 81).



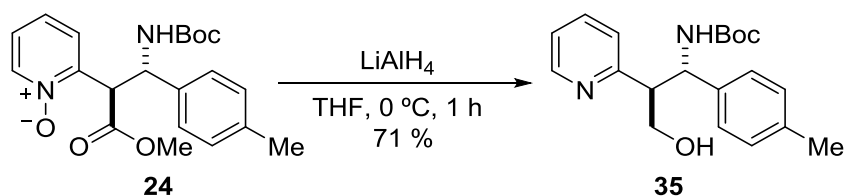
Scheme 81. Reduction of *N*-oxide group on adduct **18b**.

On the other hand, cleavage of the benzyl group on adduct **18a** by hydrogenation under 30 bar pressure for 1.5 hours afforded $\beta^{2,3}$ -amino acid **34** in very good yield (Scheme 82).



Scheme 82. Synthesis of $\beta^{2,3}$ -amino acid **34**.

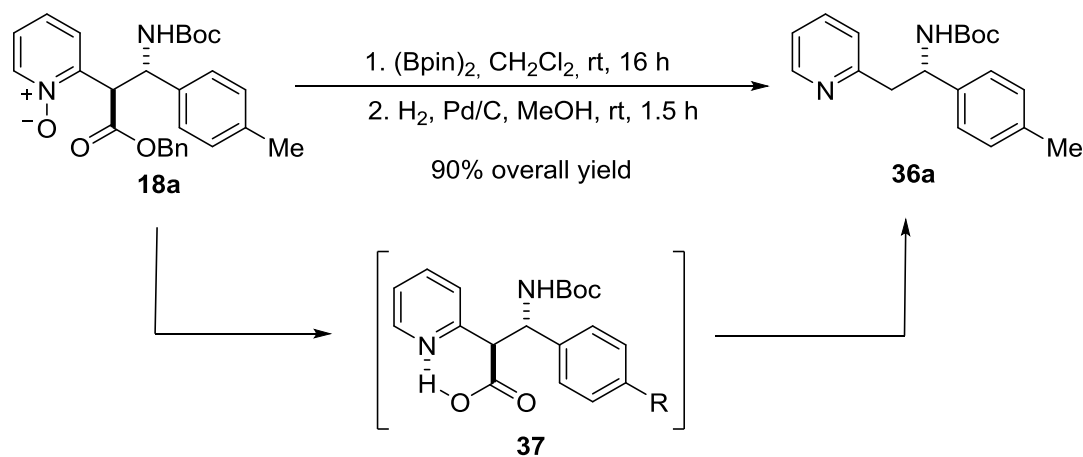
In addition, the treatment of compound **24** with lithium aluminium hydride resulted in simultaneous reduction of the ester and the *N*-oxide group to provide the corresponding amino alcohol **35** (Scheme 83).



Scheme 83. Synthesis of amino alcohol **35**.

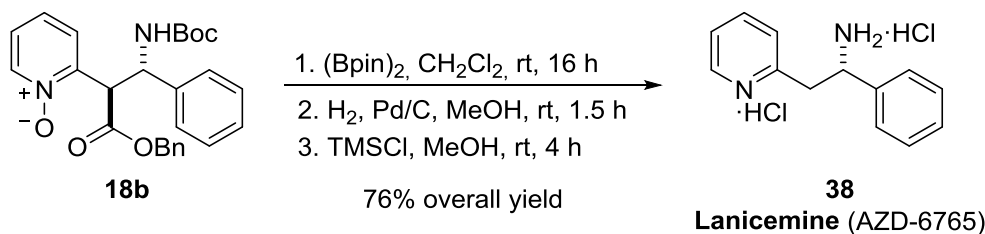
Stereoselective synthesis of pyridine based tertiary and secondary amines

Enantiopure benzyl amines²⁰¹ can also be obtained from the Mannich adducts through hydrogenation and subsequent *N*-oxide group reduction, a step that proceeds with concomitant *in situ* decarboxylation, probably through intermediate **37** assisted by the pyridine basic nitrogen atom.²⁰² Under the reaction conditions shown in Scheme 84, adduct **18a** led to benzylic amine **36a** in 90% overall yield.



Scheme 84. Synthesis of enantiopure benzyl amine **36a**.

Besides, adduct **18b** was easily transformed into Lanicemine (AZD-6765) **38** (Scheme 85), a potent low-trapping NMDA (*N*-methyl-D-aspartate) receptor agonist, usually prepared by resolutive methods.²⁰³



Scheme 85. Synthesis of Lanicemine (AZD-6765).

²⁰¹ For other enantioselective methods for the preparation of chiral benzyl amines, see: a) Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347. b) Zhu, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 4500–4503. c) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.

²⁰² a) Taylor, P. J. *J. Chem. Soc. Perkin Trans. 2* **1972**, 1077–1086. b) Button, R. G.; Taylor, P. J. *J. Chem. Soc. Perkin Trans. 2* **1973**, 557–567.

²⁰³ For further information about lanicemine, see: a) Griffith, R. C.; Murray, R. J.; Balestra, M. Preparation of enantiomeric 1-phenyl-2-(2-pyridinyl)ethylamine for the treatment of neurodegenerative disorders. WO 9320052 A1, 1993. b) Sanacora, G.; Smith, M. A.; Pathak, S.; Su, H.-L.; Boeijinga, P. H.; McCarthy, D. J.; Quirk, M. C. *Mol. Psychiatry* **2014**, *19*, 978–985. c) Sanacora, G.; Johnson, M. R.; Khan, A.; Atkinson, S. D.; Riesenber, R. R.; Schronen, J. P.; Burke, M. A.; Zajecka, J. M.; Barra, L.; Su, H.-L.; Posener, J. A.; Bui, K. H.; Quirk, M. C.; Piser, T. M.; Mathew, S. J.; Pathak, S. *Neuropsychopharmacology* **2017**, *42*, 844–853.

Chapter 4

**Stereoselective modular synthesis of *trans*-
disubstituted cyclopropanes**

INDEX

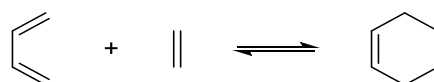
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4. STEREOSELECTIVE MODULAR SYNTHESIS OF *TRANS*-DISUBSTITUTED CYCLOPROPANES

4.1. Introduction

This part of the work has been carried out in the group of Prof. Phil S. Baran at The Scripps Research Institute in La Jolla (California, USA) during a 3-months internship. In this project, the enantioselective synthesis of *trans*-disubstituted cyclopropanes by combining cycloaddition and C–C cross-coupling reactions has been explored. The work has been carried out under the supervision of Dr. Tian Qin and Prof. Phil S. Baran.

Cycloaddition reactions are considered among the most powerful bond-forming reactions in organic synthesis because of their ability to form many bonds in one step and also for their potential in generating several stereogenic centers (Scheme 86). The reactions happen between two π -systems to form rings by breaking two π bonds and making two new σ bonds. They generally proceed through concerted pathways and follow precise rules for predicting stereo- and regiochemistry.²⁰⁴ Starting with specialized building blocks, that are designed to enable reaction to take place cleanly, this process rapidly generates complex ring systems with multiple stereocenters.



Scheme 86. Diels-Alder reaction, the most popular cycloaddition reaction.

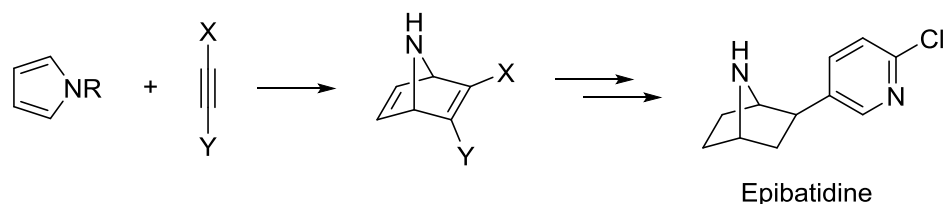
Cycloaddition reactions have featured in numerous total syntheses.²⁰⁵ As an illustration, epibatidine, valued for its pronounced analgesic properties, has been prepared by total synthesis more than 60 times, from which at least 31 have used cycloaddition chemistry as their key ring-constructing step. The vast majority of these approaches involve formation of the bridged pyrrolidine core, followed by stepwise, and often lengthy, pyridine incorporation (Scheme 87).²⁰⁶

²⁰⁴ Dinda, B. *Essentials of Pericyclic and Photochemical Reactions*; Lecture Notes in Chemistry 93; Springer: Switzerland, 2017.

²⁰⁵ Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.

²⁰⁶ Olivo, H. F.; Hemenway, M. *Org. Prep. Proced. Int.* **2002**, *34*, 1–25.

Chapter 4



Scheme 87. Synthesis of epibatidine.

On the other hand, transition metal catalyzed C–C cross-coupling reactions form one new sigma bond, between easily accessible building blocks, in a controllable manner (Scheme 88).²⁰⁷ Indeed, what C–C cross-coupling lacks in terms of complexity generation, it makes up for by its reliability and modularity.



Scheme 88. Cross-coupling reaction.

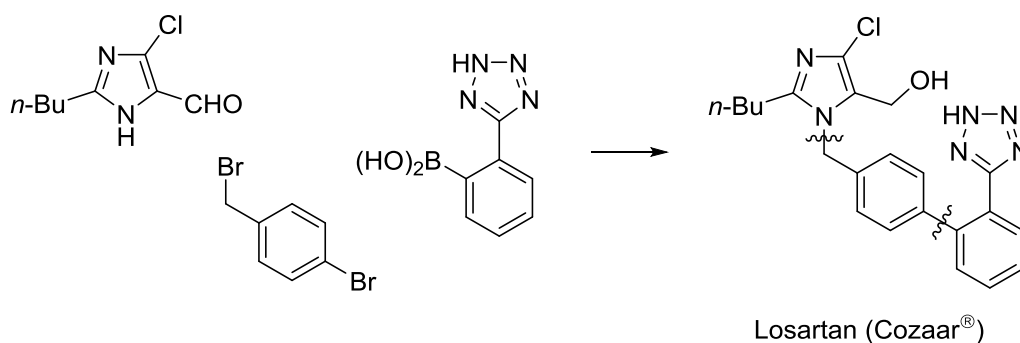
This strategy is one of the most recurrent methodologies for C–C bond forming reactions in the patent literature.²⁰⁸ For instance, the preparation of the commercial antihypertensive medicine Cozaar[®], considered as one of the first examples of a “blockbuster” drug, has employed C–C cross-coupling reactions –Ullman and Suzuki reactions– for the key bond formation, from its initial synthesis to its eventual manufacture (Scheme 89).²⁰⁹ This approach facilitated both a convergent assembly and a modularity that permitted the rapid exploration of hundreds of analogues.

²⁰⁷ de Meijere, A.; Bräse, S.; Oestreich, M. *Metal Catalyzed Cross-Coupling Reactions and More*; Wiley-VCH: New York, 2014.

²⁰⁸ Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem.* **2016**, *59*, 4385–4402.

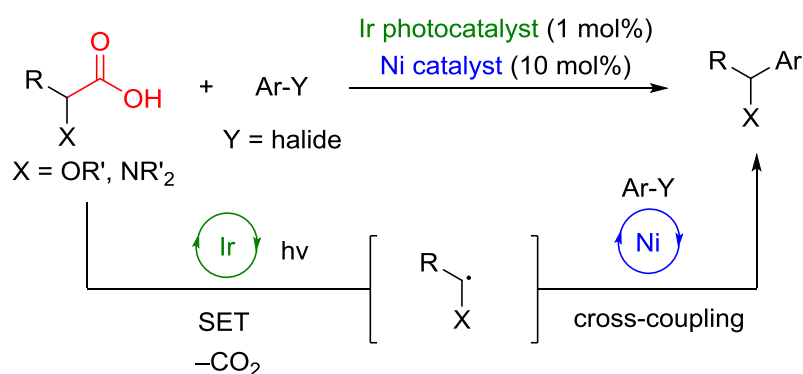
²⁰⁹ a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella III, J. B.; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525–2547. b) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 6391–6394. c) Dolitzky, B.-Z.; Nisnevich, G.; Ruchman, I.; Kaftanov, J. Processes for preparing losartan and losartan potassium. CA 2482857 A1, 2003.

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Scheme 89. Synthesis of Cozaar[®].

In this context, the group of Prof. Baran has recently developed novel C–C cross-coupling reactions that enable to couple simple alkyl carboxylic acids with a wide variety of reagents under nickel or iron catalysis. These transformations represent a great contribution into the C–C cross-coupling field, since previous methodologies were generally based on the use of alkyl halides.²¹⁰ The only example with alkyl carboxylic acids reported until then, by MacMillan and co-workers, was limited to α -nitrogen or oxygen substituted carboxylic acids and employed a combination of photocatalysis and metal catalysis. A carbon-centered radical was generated through an Ir-photomediated oxidation event whereas a Ni(0) catalyst promoted the cross-coupling reaction with aryl halide coupling partners (Scheme 90).²¹¹



Scheme 90. Cross-coupling with carboxylic acids merging photoredox with nickel catalysis.

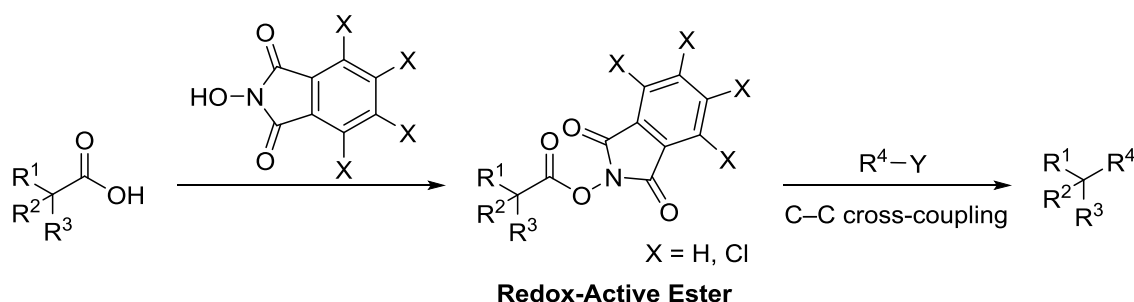
Alternatively, Baran's methodology is based on the activation of alkyl carboxylic acids with *N*-hydroxyphthalimide (NHPI) or tetrachloro-*N*-hydroxyphthalimide (TCNHPI) to form a redox-active ester (RAE) able to participate efficiently in Ni or Fe-catalyzed decarboxylative cross-coupling reactions with several coupling partners. In

²¹⁰ For reviews in the field, see: a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, *509*, 299–309.

²¹¹ Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; Macmillan, D. W. C. *Science* **2014**, *345*, 437–440.

consequence, a wide range of functionalities can be installed, such as aryl or heteroaryl systems,^{212,213} alkynyl,²¹⁴ alkenyl²¹⁵ and alkyl groups²¹⁶ (Table 16).

Table 16. C–C cross-coupling reactions developed by Baran and co-workers.



Reaction	R ⁴ -Y	C–C cross-coupling conditions	Product
Arylation (Negishi) ²¹²	(Het)Ar–ZnCl·LiCl (3 equiv.)	20 mol% NiCl ₂ ·glyme 40 mol% di- <i>t</i> -Bubipy THF:DMF (3:2) 25 °C, 16 h	
Arylation (Suzuki) ²¹³	 (3 equiv.)	10–20 mol% NiCl ₂ ·6H ₂ O 10–20 mol% di- <i>t</i> -Bubipy/BPhen Et ₃ N (10 equiv.) 1,4-dioxane:DMF (10:1) 75 °C, 12 h	
Alkynylation ²¹⁴	 (2.5 equiv.)	20 mol% NiCl ₂ ·6H ₂ O 20 mol% di-MeObipy THF:DMF (3:2) rt, 12 h	
	 (1.5 equiv.)	20 mol% FeBr ₂ ·H ₂ O NMP:THF (3:2) –15 °C, 15 min	

²¹² Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177.

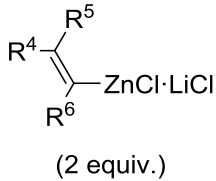
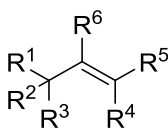
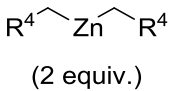
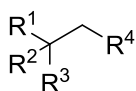
²¹³ Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9676–9679.

²¹⁴ Smith, J. M.; Qin, T.; Merchant, R. R.; Edwards, J. T.; Malins, L. R.; Liu, Z.; Che, G.; Shen, Z.; Shaw, S. A.; Eastgate, M. D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 11906–11910.

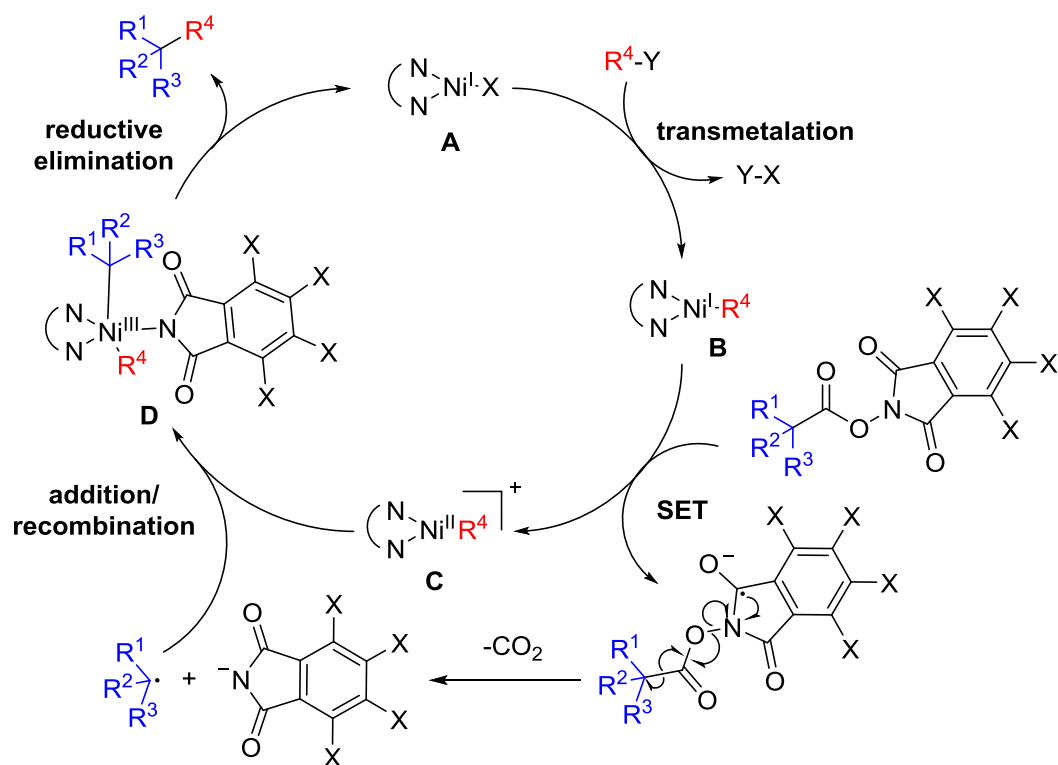
²¹⁵ Edwards, J. T.; Merchant, R. R.; McClymont, K. S.; Knouse, K. W.; Qin, T.; Malins, L. R.; Vokits, B.; Shaw, S. A.; Bao, D.-H.; Wei, F.-L.; Zhou, T.; Eastgate, M. D.; Baran, P. S. *Nature* **2017**, *545*, 213–218.

²¹⁶ Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science*, **2016**, *352*, 801–805.

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Reaction	R ⁴ -Y	C–C cross-coupling conditions	Product
Alkenylation ²¹⁵		10 mol% Ni(acac) ₂ ·xH ₂ O 10 mol% bipy THF:DMF (3:2) rt, 12 h	
Alkylation ²¹⁶		20 mol% NiCl ₂ ·glyme 40 mol% bipy/di- <i>t</i> -Bubipy THF:DMF (3:2) 25 °C, 8–14 h	

A possible reaction mechanism was postulated for the decarboxylative C–C cross-coupling reaction (Scheme 91). The authors proposed that Ni(I)-X complex **A** transmetalates with the coupling partner to produce Ni(I)-R⁴ complex **B**. Then, this complex acts as a reducing agent and deliver an electron into the redox-active ester, thus generating the radical anion of the activated ester with concomitant formation of [Ni(II)-R⁴]⁺ complex **C**. Fragmentation of the former, followed by extrusion of CO₂, generates the phthalimide anion and the desired radical species. At this point, recombination of the radical species and the phthalimide anion with [Ni(II)-R⁴]⁺ complex **C** renders the Ni(III) intermediate **D**, which upon reductive elimination affords the desired cross-coupling product and close the catalytic cycle.

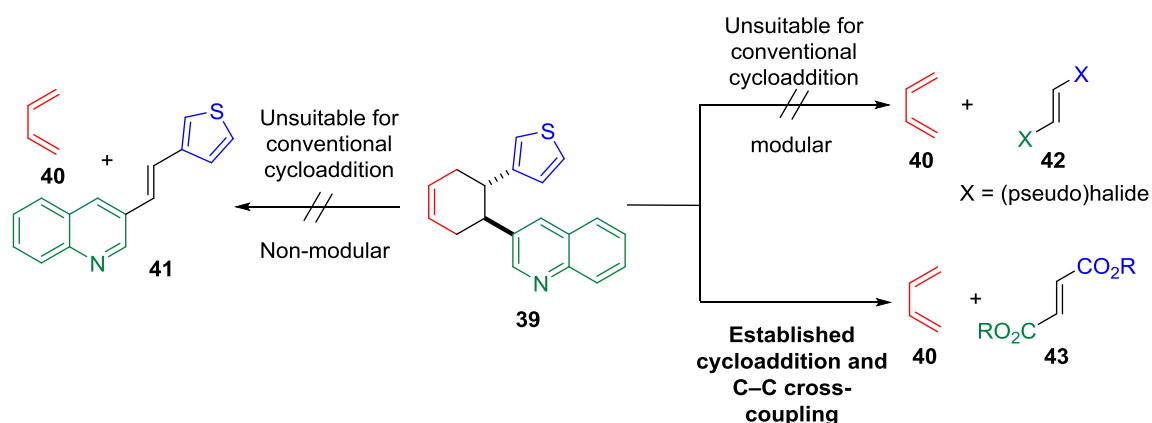


Scheme 91. Plausible mechanism for the decarboxylative C-C cross-coupling reaction.

4.2. Working hypothesis and objectives

In this work, we considered to combine the innate complexity generated by cycloaddition reactions with the simplicity and modularity of C–C cross-coupling reactions in order to achieve the rapid generation of challenging complex chemical structures.

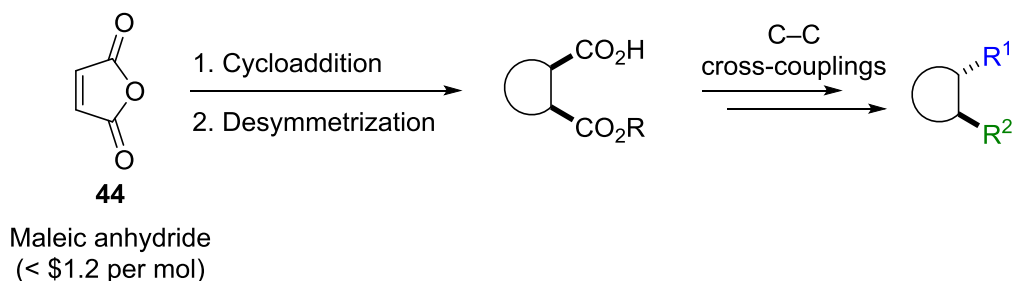
For instance, building block **39**, of hypothetical value in medicinal chemistry, represents the manifestation of this idea (Scheme 92). The Diels-Alder reaction of the relevant building blocks **40** and **41**, which are not electronically matched, is expected to not take place. But, even a workable enantioselective Diels-Alder reaction could be invented to achieve this transformation, the strategy would suffer from lack of modularity. In the same way, although the use of vicinal (pseudo)haloethylenes **42** could overcome the modularity issue through C-C cross-coupling reactions, the cycloaddition with **40** would not take place neither. We envisioned that the use of a vicinal (pseudo)haloethylene surrogate, such as **43**, would solve this problem since the electronics are favorable for the cycloaddition reaction, and the subsequent decarboxylative cross-coupling reactions have been widely explored in the group, as previously commented.



Scheme 92. Case study.

In order to address the stereoselective challenge in the overall process, we considered a combination of transformations (Scheme 93). First, we thought that maleic anhydride **44** could act as a surrogate of **43** in the C-C cross-coupling reactions, and take advantage of its inexpensive nature, ready participation in most cycloaddition reactions ([2+1], [2+2], [3+2], [4+2]), and its easy desymmetrization through chiral Lewis base-mediated alcoholysis. Thus, the sequence that we proposed for the enantioselective modular synthesis of *trans*-disubstituted cycles would involve five steps:

1. Cycloaddition to build the scaffold.
2. Desymmetrization to set the absolute configuration.
3. First decarboxylative cross-coupling.
4. Hydrolysis of the ester group.
5. Second decarboxylative cross-coupling.



Scheme 93. Synthetic plan.

In consequence, the total project would involve the development of a synthetic strategy for the modular preparation of structures bearing 6-, 5-, 4- and 3-membered rings. During my 3-months internship, I was involved in the enantioselective modular synthesis of *trans*-disubstituted cyclopropanes. Following this strategy, interesting 3-membered cyclic scaffolds, not affordable through conventional methodologies, could be produced. In general, the methodologies employed for their synthesis, to date, involve late-stage cyclopropanations of olefins which usually suffer from lack of enantiocontrol.²¹⁷

²¹⁷ For a review on asymmetric cyclopropanation reactions, see: Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, 46, 979–1029.

4.3. Results and discussion

For the particular case of cyclopropane construction, caronic anhydride **45** and 1,2-cyclopropanedicarboxylic anhydride **46** are commercially available compounds (Figure 31), thus the [2+1] cycloaddition reaction was not explored.

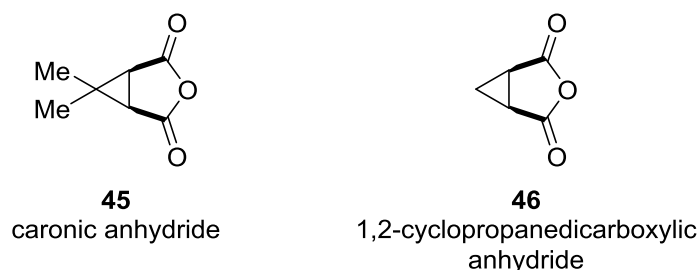
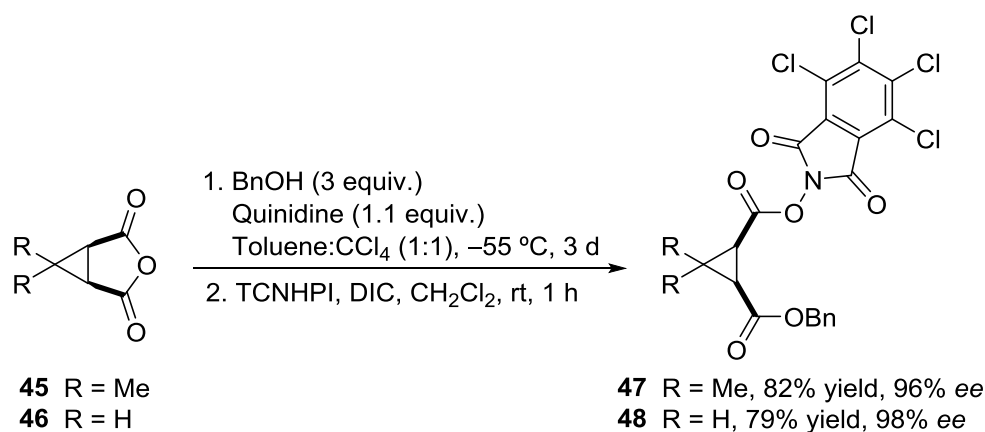


Figure 31. Starting materials.

4.3.1. Desymmetrization step

The desymmetrization of anhydrides **45** and **46** was conducted by quinidine-mediated alcoholysis with benzyl alcohol at low temperature.²¹⁸ Then, the corresponding free carboxylic acid was activated with tetrachloro-*N*-hydroxyphthalimide (TCNHPI). As a result, redox-active esters **47** and **48** were prepared in high yield and with excellent enantioselectivity (Scheme 94).



Scheme 94. Desymmetrization of anhydrides **45** and **46**.

²¹⁸ Procedure adapted from: Bolm, C.; Schiffrs, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry*, **2003**, *14*, 3455–3467.

4.3.2. Decarboxylative cross-coupling reactions

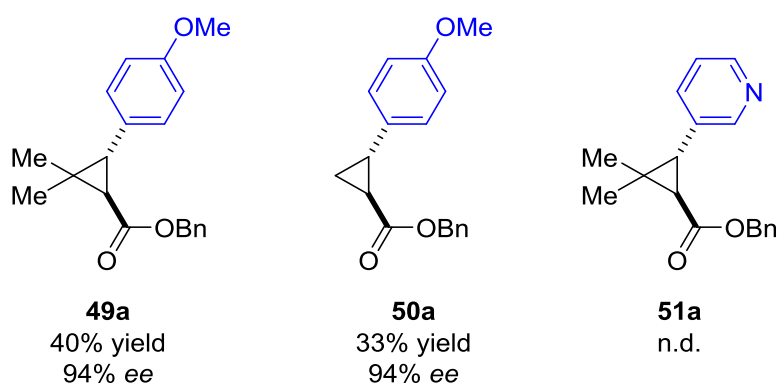
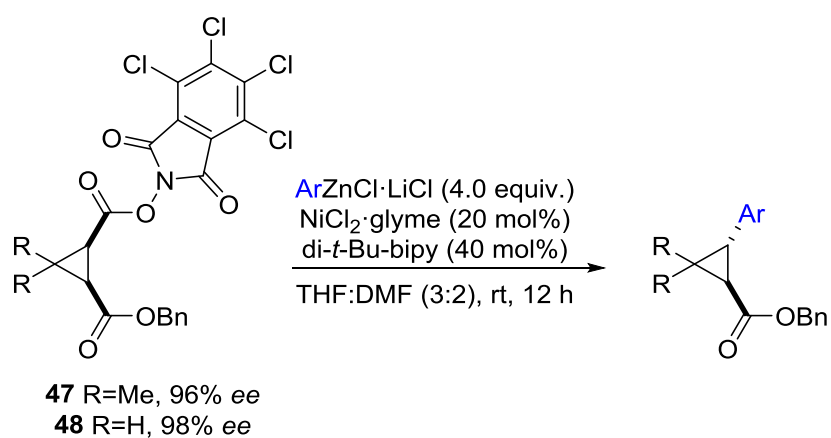
Next, the decarboxylative cross-coupling reaction, employing different coupling partners and conditions, was studied for redox-active esters **47** and **48**.

4.3.2.1. Negishi cross-coupling reactions

4.3.2.1.1. Negishi arylation

First, the nickel-catalyzed Negishi arylation reaction was explored employing similar conditions to those developed previously in the group for the same reaction (Table 17).²¹² Unfortunately, aryl adducts **49a** and **50a** were obtained in low yields and product **51a** was not even detected. Furthermore, large amounts of the decarboxylated product were observed, indicating that hydrogen abstraction from the solvent was occurring as side-reaction, which was not observed in cross-couplings with larger carbocycles carried out by other colleagues in the group.

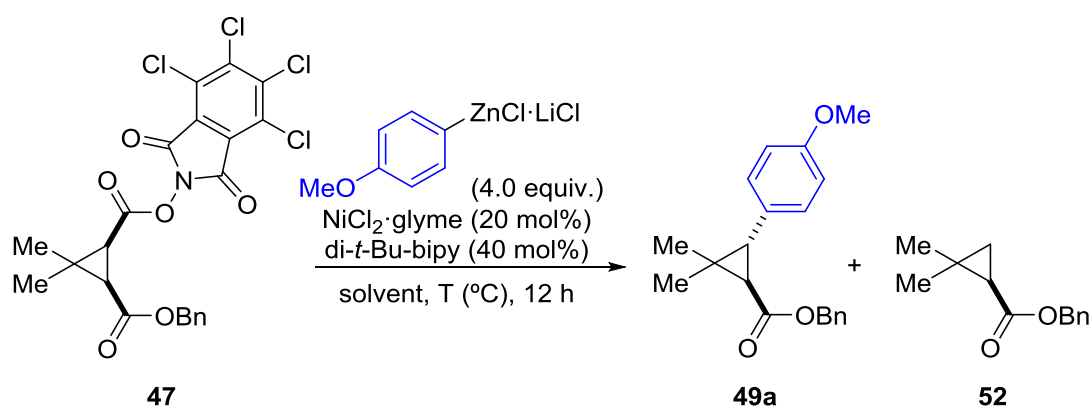
Table 17. Preliminary experiments for Negishi arylation.



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Then, we decided to evaluate the arylation reaction of **47** in other solvents to minimize the H-abstraction side-reaction (Table 18). First, we observed that the reaction temperature had an irrelevant effect (compare entries 1 and 2), whereas a remarkable solvent-dependence was confirmed. Different solvent systems provided significant variations in the **49a**:**52** ratio and in the reaction yield. Among all the solvents screened, acetonitrile afforded the best results, since the production of **52** was almost completely suppressed (entry 10). Nevertheless, the presence of DMF in the solvent system was required to obtain high yields. Hence, MeCN:DMF (3:2) resulted to be the optimal solvent system for the Negishi arylation with cyclopropanes, affording product **49a** in 56% isolated yield (entry 6).

Table 18. Optimization of the Negishi arylation reaction.



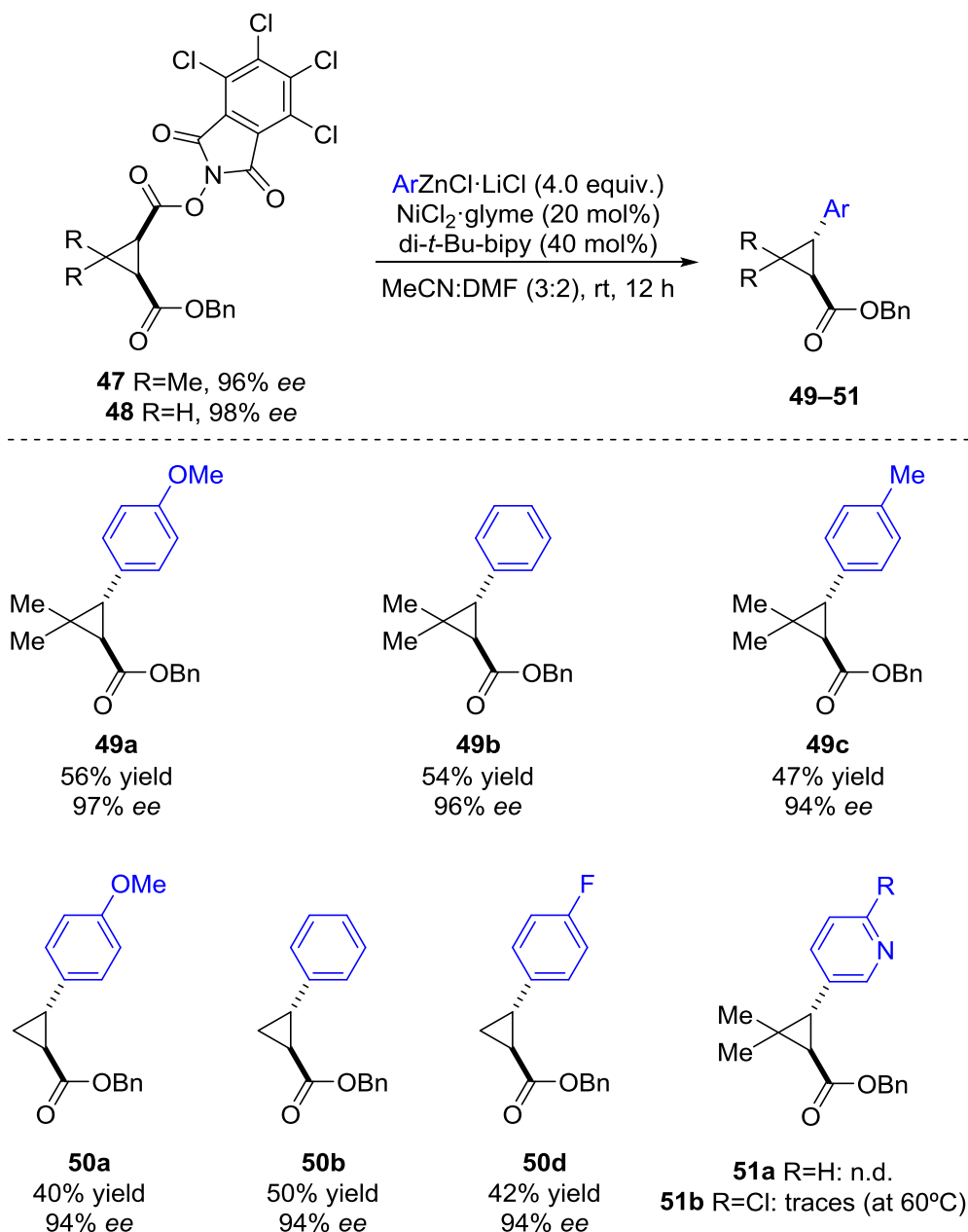
Entry	Solvent system	T (°C)	49a : 52 ^b	Yield ^c
1	THF:DMF (3:2)	rt	64:36	45 (40)
2	THF:DMF (3:2)	60	62:38	45
3	DMF	rt	71:29	52
4	dioxane:DMF (3:2)	rt	66:34	50
5	toluene:DMF (3:2)	rt	76:24	54
6	MeCN:DMF (3:2)	rt	91:9	60 (56)
7	Et ₂ O:DMF (3:2)	rt	73:27	56
8	CH ₂ Cl ₂ :DMF (3:2)	rt	78:22	42
9	CHCl ₃ :DMF (3:2)	rt	46:54	18
10	MeCN	rt	92:8	19

^a Reactions were carried out on 0.1 mmol scale in 2 mL of solvent. ^b **49a**:**52** ratio determined by GC/MS. ^c Yield determined on crude mixture by GC/MS. Isolated yields indicated in parentheses.

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With these optimal conditions in hand, the scope of the transformation was then explored (Table 19). Acceptable yields were obtained in the reactions with both electron-rich and electron-poor aryl groups for redox-active esters **47** and **48**, being the use of heteroaryl groups an exception; compounds **51a** and **51b** were not detected under these reaction conditions. On the other hand, the reactions were completely *trans*-diastereoselective and no significant decrease of the optical purity in adducts **49–50** was observed.

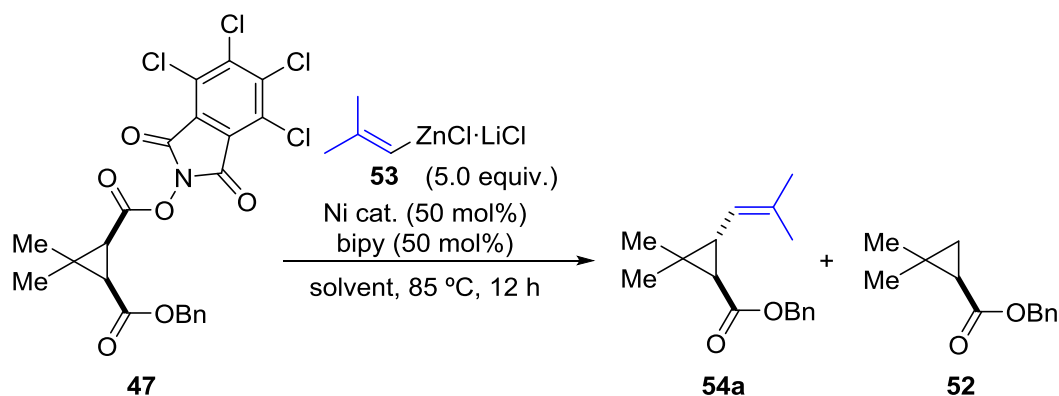
Table 19. Negishi arylation scope.



4.3.2.1.2. Negishi alkenylation

For the study of the nickel-catalyzed Negishi alkenylation reaction, we focused on the search of the most appropriate Ni source and solvent system since, in a previous study, different ligands and reaction temperatures had been already screened.²¹⁵ The alkenylation reaction of **47** with the organozinc reagent **53** was studied and, as data in Table 20 show, among all nickel sources tested, Ni(acac)₂·H₂O provided the best results. Again, the solvent system MeCN:DMF afforded the highest **54a**:**52** ratio and yield (entry 5). On the other hand, previous deoxygenation of the solvent or the absence of light had meaningless impact in the reaction outcome (entries 9 and 10).

Table 20. Optimization of Negishi alkenylation.

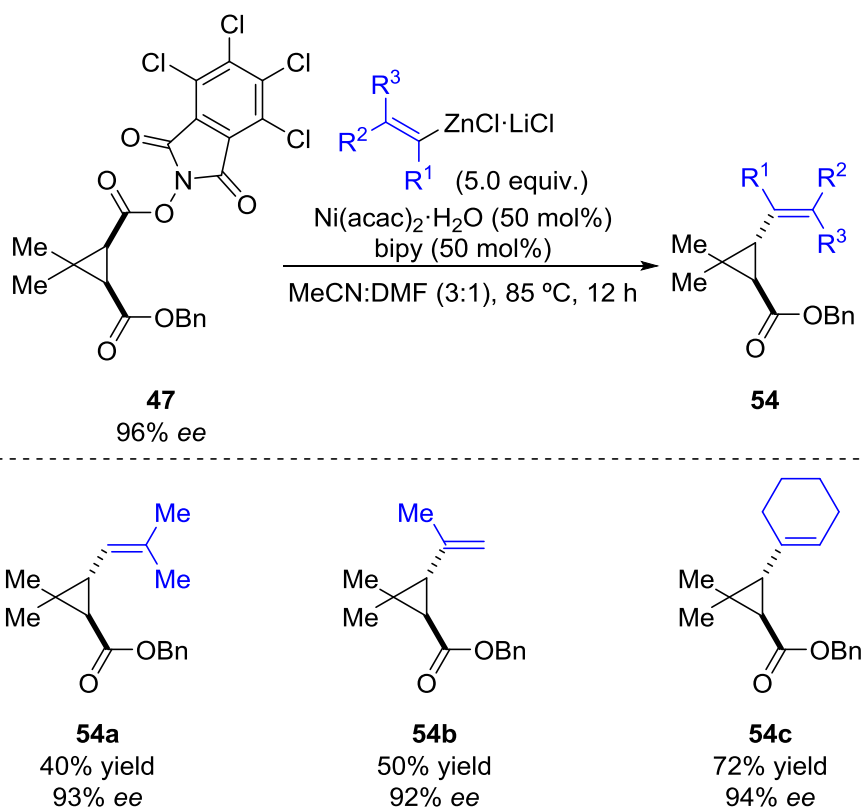


Entry	Ni source	Solvent system	54a : 52 ^b	Yield ^c
1	Ni(acac) ₂ ·H ₂ O	DMF	55:45	36 (35)
2	NiCl ₂ ·glyme	DMF	20:80	17
3	NiBr ₂ ·glyme	DMF	68:32	14
4	NiCl ₂ ·6H ₂ O	DMF	69:31	33 (30)
5	Ni(acac)₂·H₂O	MeCN:DMF (3:1)	82:18	42 (40)
6	Ni(acac) ₂ ·H ₂ O	toluene:DMF (3:1)	63:37	27 (25)
7	NiCl ₂ ·6H ₂ O	MeCN:DMF (3:1)	78:22	24
8	Ni(ClO ₄) ₂ ·H ₂ O	MeCN:DMF (3:1)	75:25	29
9 ^d	Ni(acac) ₂ ·H ₂ O	MeCN:DMF (3:1)	86:14	32
10 ^e	Ni(acac) ₂ ·H ₂ O	MeCN:DMF (3:1)	89:11	31

^a Reactions were carried out on 0.1 mmol scale in 3.5 mL of solvent. ^b **54a**:**52** ratio determined by GC/MS. ^c Yield determined on crude mixture by GC/MS. Isolated yields indicated in parentheses. ^d MeCN was previously purged. ^e Reaction carried out in absence of light.

The reaction with redox-active ester **47** was performed in the presence of several alkenylzinc reagents and the corresponding adducts **54(a-c)** were produced as only one detectable diastereoisomer and with almost unaltered enantiomeric excess (Table 21).

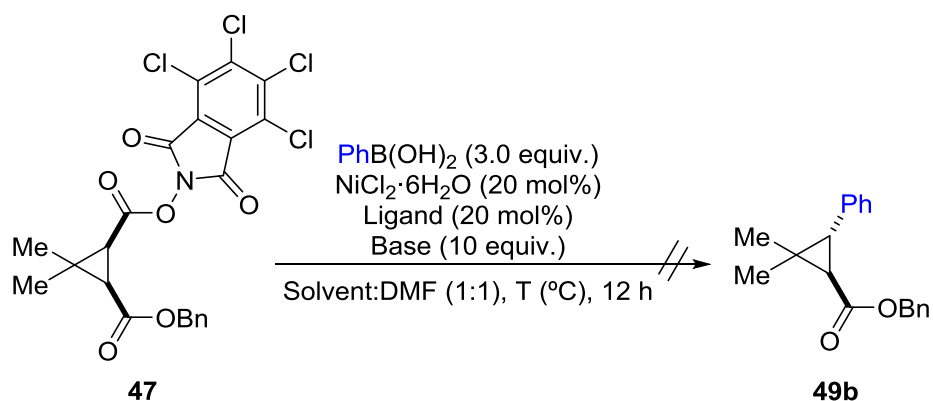
Table 21. Negishi alkenylation scope.



4.3.2.2. Suzuki cross-coupling reactions

The reaction of the redox-active ester **47** with phenylboronic acid, employing similar conditions to that reported previously by the group²¹³ did not produce the corresponding *trans*-disubstituted cyclopropane **49b**. Furthermore, the evaluation of other ligands, bases and solvent systems resulted ineffective. (Scheme 95).

Stereoselective modular synthesis of *trans*-disubstituted cyclopropanes



Ligands: di-*t*-Bubipy, bipy, Bphen

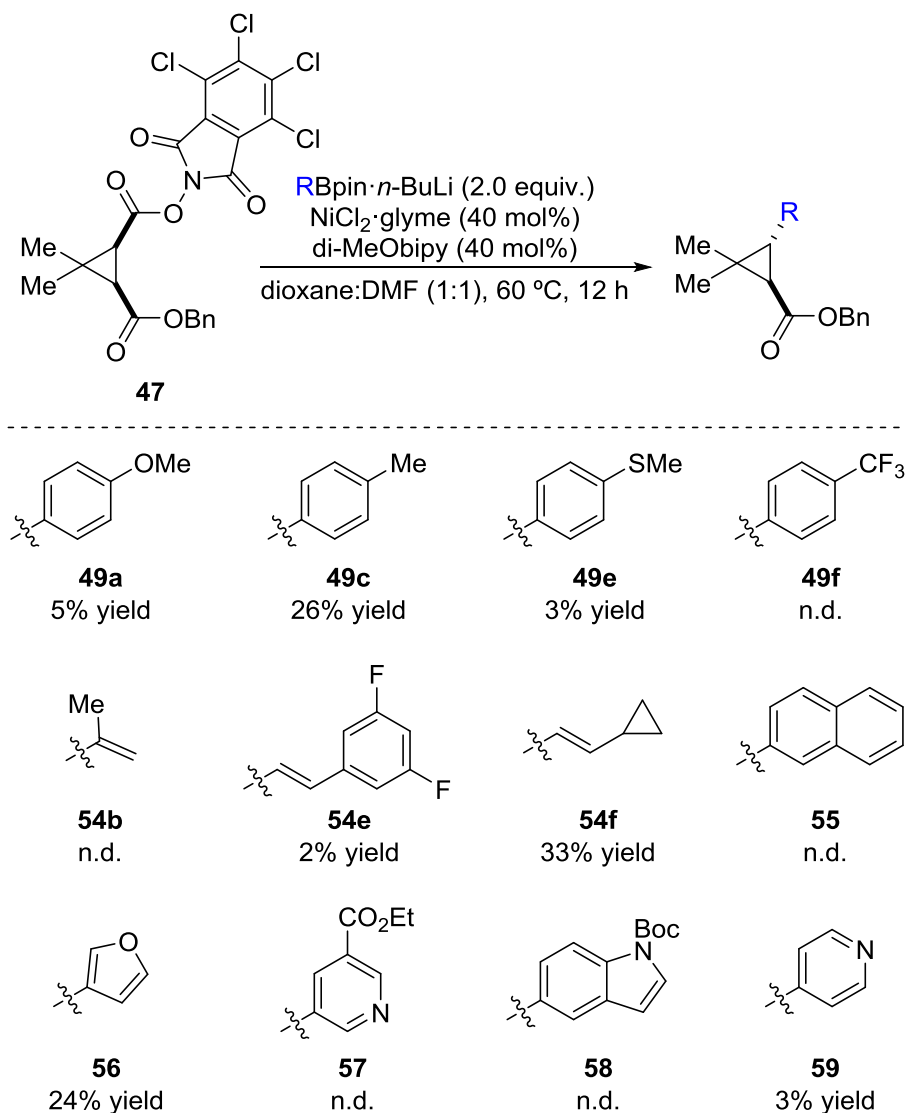
Bases: Et_3N , DIPEA, K_2CO_3 , *t*-BuOK

Solvents: dioxane, DMF, toluene, MeCN, *t*-BuOH

T (°C): 75 and 85 °C

Scheme 95. Preliminary experiments for the Suzuki cross-coupling reaction.

On the other hand, the Suzuki cross-coupling employing aryl, heteroaryl and alkenyl pinacol boronate esters showed to be highly substrate-dependent (Table 22).

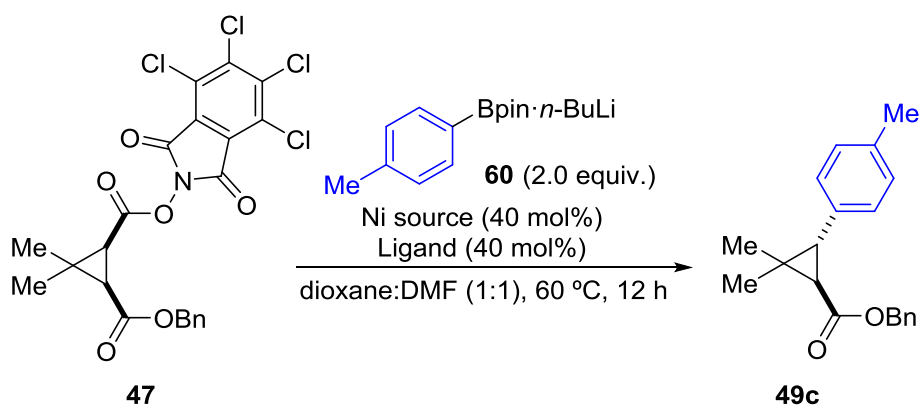
Table 22. Preliminary experiments for Suzuki cross-coupling with pinacol boronate esters.

Yields determined on crude mixtures by GC/MS. n.d. = not detected.

Thus, a further optimization of the reaction conditions was carried out for adducts **49c**, **54f** and **56** to improve the moderate yields obtained. First, the effect of the nickel source and the ligand was evaluated for the reaction of redox-active ester **47** with pinacol boronate ester **60** (Table 23). Unfortunately, the previous result could not be improved employing neither different nickel sources nor ligands. Moreover, the use of stoichiometric amounts of nickel and ligand afforded product **49c** in lower yield than when catalytic amounts were used (entries 1 and 8). Likewise, maintaining $\text{NiCl}_2 \cdot \text{glyme}$ and di-MeObipy as the catalytic system, variations in the stoichiometry of the reagents, the use of additives ($\text{MgBr}_2 \cdot \text{OEt}_2$, LiBr and ZnCl_2) or different solvents were also detrimental.

Stereoselective modular synthesis of *trans*-disubstituted cyclopropanes

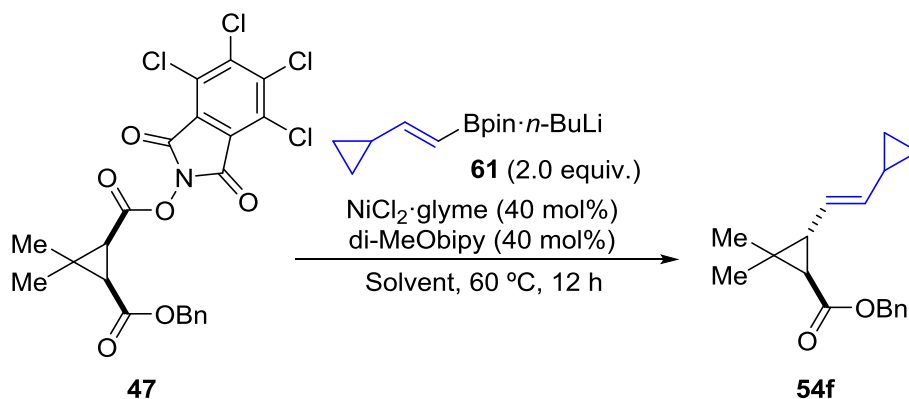
Table 23. Ni source and ligand screening for the Suzuki cross-coupling reaction with **62**.



Entry	Ni source	Ligand	Yield ^b
1	NiCl ₂ ·glyme	di-Meobipy	26
2	NiBr ₂ ·glyme	di-Meobipy	10
3	Ni(acac) ₂ ·H ₂ O	di-Meobipy	0
4	NiCl ₂ ·6H ₂ O	di-Meobipy	0
5	NiCl ₂ ·glyme	di- <i>t</i> -Bubipy	24
6	NiCl ₂ ·glyme	bipy	16
7	NiCl ₂ ·glyme	Bphen	10
8	NiCl ₂ ·glyme ^c	di-Meobipy ^c	11

^a Reactions were carried out on 0.1 mmol scale in 2 mL of solvent. ^b Yield determined on crude mixture by GC/MS. ^c 100 mol% of NiCl₂·glyme and di-Meobipy was used.

Meanwhile, we also studied the reaction of the redox-active ester **47** with (*trans*)-2-cyclopropylvinylboronic acid pinacol ester **61** (Table 24) and we found that the highest yield for adduct **54f** was produced in the presence of 40 mol% of the catalytic system in a toluene:DMF solvent mixture (entry 6).

Table 24. Optimization of the Suzuki cross-coupling reaction with **63**.

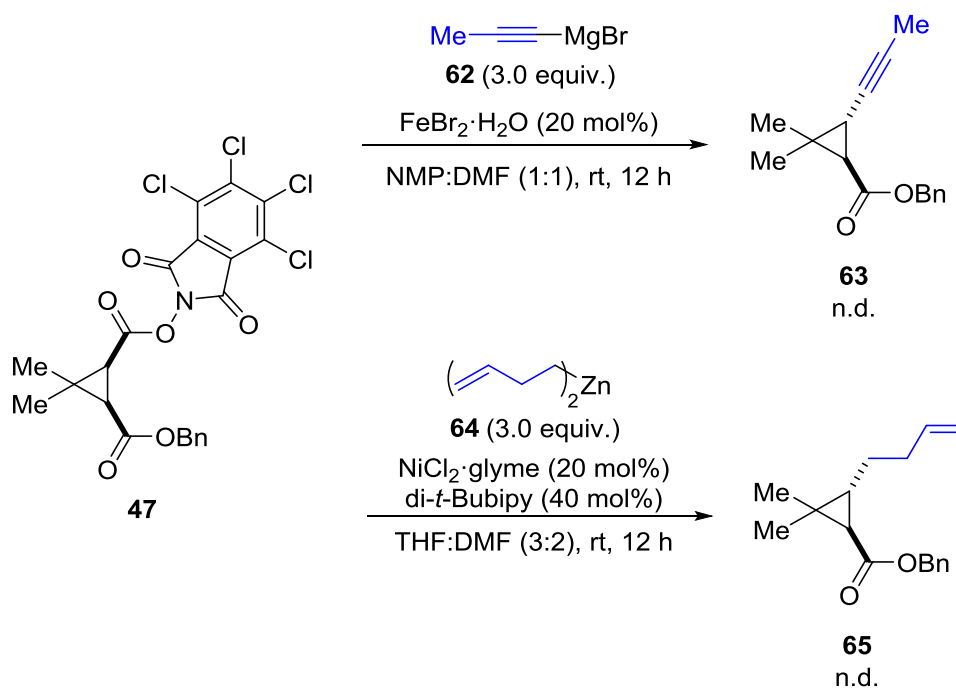
Entry	[Ni+L] (mol%)	Solvent	Yield ^b
1	40	dioxane:DMF (1:1)	33
2	20	dioxane:DMF (1:1)	14
3	60	dioxane:DMF (1:1)	44
4	40	dioxane:DMF (1:2) ^c	20
5	40	THF:DMF (1:1)	26
6	40	toluene:DMF (1:1)	56(55)
7	40	MeCN:DMF (1:1)	0

^a Reactions were carried out on 0.1 mmol scale in 2 mL of solvent. ^b Yield determined on crude mixture by GC/MS. Isolated yield indicated in parentheses. ^c Reaction conducted in 3 mL of solvent.

4.3.2.3. Unsuccessful cross-coupling reactions

Other cross-coupling reaction types were explored with no success. For instance, the iron-catalyzed alkylation of redox-active ester **47** with the Grignard reagent **62** and the nickel-promoted alkylation of **47** with the dialkylzinc reagent **64** did not afford the desired products (Scheme 96).^{214,216}

Stereoselective modular synthesis of *trans*-disubstituted cyclopropanes



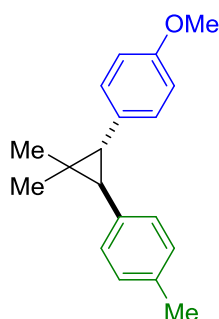
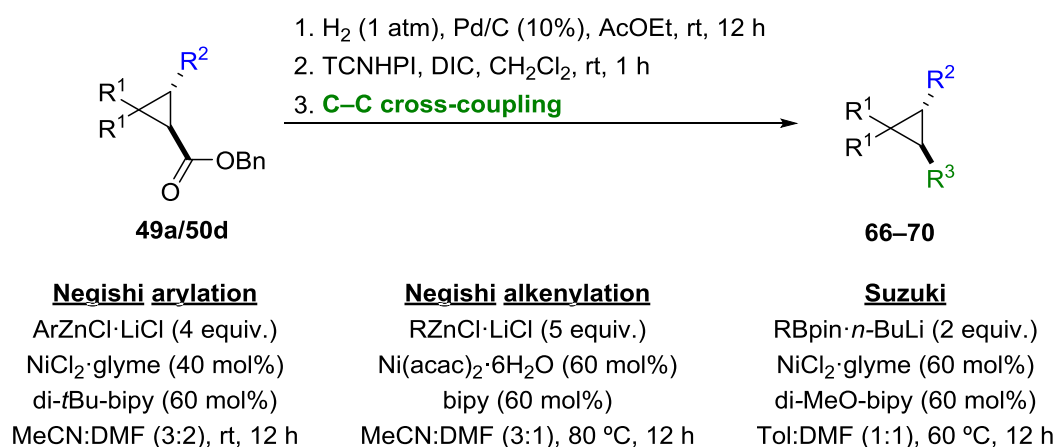
Scheme 96. Unsuccessful cross-coupling reactions.

4.3.3. Synthesis of *trans*-disubstituted cyclopropanes

Finally, with the above adducts in hand, completion of the synthesis of *trans*-disubstituted cyclopropanes **66–70** was carried out. To this end, products **49a** and **50d** were debenzylated *via* Pd-catalyzed hydrogenation and activated with tetrachloro-*N*-hydroxyphthalimide. Then, the resulting redox-active esters were subjected to further cross-coupling with the corresponding organozinc or organoboron compounds under the conditions shown in Table 25. In these cases, slightly higher catalytic charges were employed in order to increase the reaction yields. Accordingly, *trans*-disubstituted cyclopropanes **66–70** were successfully synthesized in acceptable yields and with excellent enantiomeric excesses (Table 25).

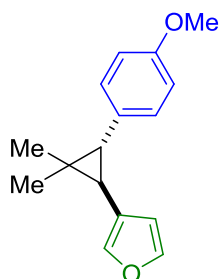
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Table 25. Synthesis of *trans*- α,β -disubstituted cyclopropanes **66–70**.



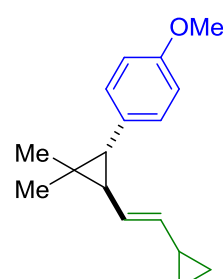
66

Suzuki: 55% yield, 94% ee
Negishi (20 mol%): 36% yield
Negishi (40 mol%): 40% yield



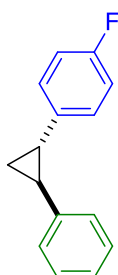
67

Suzuki: 54% yield, 95% ee



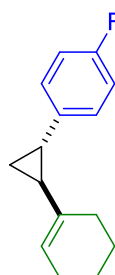
68

Suzuki: 64% yield, 94% ee



69

Negishi: 62% yield, 93% ee



70

Negishi: 44% yield, 95% ee

This strategy has also been employed by other co-workers in the group for the enantioselective modular synthesis of *trans*- α,β -disubstituted 4-, 5- and 6-membered rings, which has efficiently allowed the preparation of a great library of interesting structures.²¹⁹

²¹⁹ Chen, T.-G.; Barton, L. M.; Lin, Y.; Tsien, J.; Kossler, D.; Bastida, I.; Asai, S.; Bi, C.; Chen, J. S.; Shan, M.; Fang, H.; Fang, F. G.; Choi, H.-W.; Hawkins, L.; Qin, T.; Baran, P. S. *Nature* **2018**, *560*, 350–354.

Chapter 5

Conclusions

5. CONCLUSIONS

Three new Brønsted base catalyzed methodologies have been developed for the synthesis of enantiomerically enriched secondary and tertiary amines.

First, the ureidopeptide-based Brønsted base catalyzed enantioselective nitro-Mannich reaction with *N*-Boc imines and 2-nitroethyl sulfones, as synthetic equivalents of vinyl sulfone anions, followed by nitrous acid elimination, afforded γ -sulfonyl allyl amines in variable yields and with generally excellent enantioselectivities.

Second, the enantioselective α -amination of 2-cyanoalkylpyridine *N*-oxides with azodicarboxylates has been described for the synthesis of pyridine based α -chiral tertiary amines. The *N*-oxide functionality plays a strategic role as a removable activating and stereodirecting group, in conjunction with a newly designed multifunctional squaramide-based Brønsted base catalyst bearing a bulky silyl group.

Third, the ureidopeptide-based Brønsted base catalyzed highly stereoselective Mannich-type reaction of 2-azaaryl acetate *N*-oxides with *N*-carbamoyle aldimines has been developed for the synthesis of pyridine based chiral secondary amines. The *N*-oxide functionality and the ureidopeptide-based Brønsted base, able to preserve the configurational stability of the final adducts, are the key elements for the efficient preparation of pyridine based β -amino esters in high yield and with excellent diastereo- and enantioselectivity.

Finally, a synthetic strategy for the stereoselective modular preparation of *trans*-disubstituted cyclopropanes has been developed, which consists of [2+1] cycloaddition with maleic anhydride, desymmetrization of the corresponding *meso*-anhydrides and two subsequent nickel catalyzed decarboxylative C–C cross-coupling reactions.

Chapter 6

Experimental section

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6. EXPERIMENTAL SECTION

6.1. Materials and general techniques

6.1.1. General experimental

All non-aqueous reactions were performed using oven-dried glassware and were magnetically stirred unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

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

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

Organic solvents were evaporated under reduced pressure using rotavapors Büchi R-110, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (≈ 0.5 mmHg) was employed. IKA RV8 rotary evaporators equipped with a dry ice condenser were employed for the work in chapter 4.

6.1.2. Reagents and solvents

Reagents were purchased from different commercial suppliers (Sigma-Aldrich, Acros, Alfa Aesar, Fluka, TCI, Merck, Fluorochem, etc.), stored as specified by the manufacturer and used without previous purification unless otherwise stated. Imines **4** and **21**²²⁰ and *N*-Boc isatin ketimines **30** and **31**²²¹ were synthesized following described procedures. Azodicarboxylates **14** were purchased from Sigma-Aldrich, stored at -30 °C and used without previous purification. $\text{NiCl}_2 \cdot \text{glyme}$ and $\text{Ni}(\text{acac})_2 \cdot x\text{H}_2\text{O}$ were purchased from Strem, bipyridine ligands (2,2'-bipyridine, 4,4'-di-*tert*-butylbipyridine and 4,4'-di-OMe-

²²⁰ Wang, W.; van Gemmeren, M.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 13592–13595. b) Mbofana, C. T.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 3285–3292.

²²¹ Holmquist, M.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Cat.* **2015**, *357*, 3857–3862.

bipyridine) were purchased from Sigma-Aldrich and bathophenanthroline was purchased from Combi-Blocks.

Triethylamine, DBU, DIPA and DIPEA were purified by distillation. Liquid aldehydes were purified by distillation before usage and stored in the fridge at $-30\text{ }^{\circ}\text{C}$ under nitrogen.

When anhydrous solvents were required, they were dried following established procedures.²²² Dichloromethane was dried over CaH_2 , and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 \AA , basic, Sigma-Aldrich) columns. For the work in chapter 4, tetrahydrofuran (THF), *N,N*-dimethylformamide (DMF), toluene, acetonitrile (CH_3CN), and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through an activated alumina column. *N*-Methyl-2-pyrrolidone (NMP) (anhydrous, 99.5%) and carbon tetrachloride (CCl_4) (anhydrous, $\geq 99.5\%$) were purchased from Sigma-Aldrich and used without further purification.

6.1.3. Chromatography

Reactions were monitored by ^1H NMR, GC/MS, LC/MS or thin layer chromatography (TLC) using Merck silica gel (60F-254) plates and visualized by fluorescence quenching under UV light, Fisher Bioblock lamp VL-4LC, $\lambda = 254$ and 365 nm . A solution of potassium permanganate or phosphomolybdic acid and heat were employed as developing agents.

Purification of reaction products was carried out by flash column chromatography using ROCC silica gel 60 ($40\text{-}63\text{ }\mu\text{m}$, $230\text{-}400$ mesh). Preparative thin layer chromatography (pTLC) was performed on Merck silica plates (60F-254).

Non-acid silica gel was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 hours and subsequent evaporation of water in an oven at $80\text{ }^{\circ}\text{C}$ for 72 hours.

6.1.4. Melting points

Melting points were determined in open capillaries on a Stuart SHP3 or Fisher-Johns 12-144 melting point apparatus and a microscope and were uncorrected.

²²² Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals*, 6th ed.; Butterworth-Heinemann: Oxford, U.K., 2009.

6.1.5. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported.

6.1.6. NMR spectra

NMR spectra were recorded on Bruker AV-300, AV-400, AV-500, AMX-400, DRX-500 and DRX-600 instruments and are calibrated using residual undeuterated solvent (CHCl_3 at 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR; CH_3OH at 3.31 ppm ^1H NMR, 49.0 ppm ^{13}C NMR). ^{19}F NMR spectra were recorded using fluorobenzene ($\delta -113.15$ ppm) as internal standard. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

MestReNova Mnova 11.0 program was used to process and edit the registered spectra.

6.1.7. Mass spectra

Mass spectra were recorded on a UPLC-DAD-QTOF spectrometer (Ultra High Performance Liquid Chromatograph-Mass spectrometer; Waters UPLC ACQUITY, Waters PDA Detector, Waters Synapt G2). Mass-spectrometry analyses were performed in the General Research Service (SGIKer) of the University of the Basque Country (EHU-UPV) for chapters 2 and 3. For chapter 4, high-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD-ESI-QTOF mass spectrometer.

6.1.8. Determination of enantiomeric excesses

Enantiomeric excesses in chapters 2 and 3 were determined using analytical high performance liquid chromatography (HPLC) performed on Waters-600E (equipped with 2996 and 2998 photodiode array UV detector) employing Daicel columns (4.6 x 250 mm, 5 μm particle size). Enantiomeric excesses in chapter 4 were determined using supercritical fluid chromatography (SFC) performed on Waters UPC2 SFC (equipped with a photodiode array detector) employing Daicel columns (4.6 x 250 mm, 3 μm particle size) under isocratic conditions at 30 °C.

6.1.9. Optical rotations

Optical rotations were recorded using a Jasco P-2000 or a Rudolph Research Analytical Autopol III automatic polarimeter; specific rotations (SR) ($[\alpha]_D^{25}$) are reported in 10^{-1}

$\text{deg}\cdot\text{cm}^2\cdot\text{g}^{-1}$; concentrations (c) are quoted in g/100 mL; λ_{D} refers to the D-line of sodium (589 nm); temperatures (T) are given in Celsius degrees ($^{\circ}\text{C}$).

6.1.10. X-Ray diffraction analysis

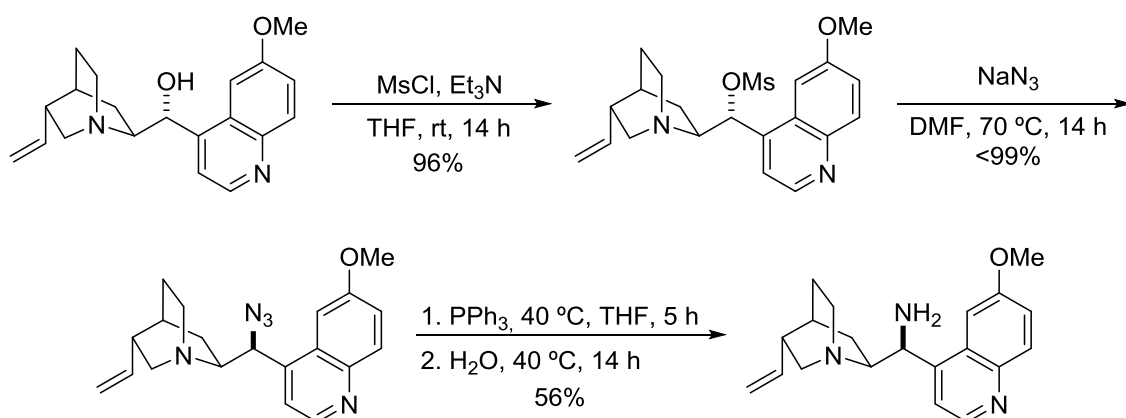
X-ray diffraction analysis experiments were conducted in the General Research Service (SGIKer) of the University of the Basque Country (EHU-UPV) using diffractometers for monocrystals.

6.2. Synthesis of catalysts

Catalysts **C9**,²²³ **C19**²²⁴ and **C20**²²⁵ were prepared following reported procedures and Takemoto's thiourea **C21** was purchased from Strem Chemicals.

6.2.1. Preparation of chiral amines

6.2.1.1. Preparation of *Cinchona* alkaloid derived amines



1st step:²²⁶ A mixture of the corresponding *Cinchona* alkaloid (1 equiv., 100 mmol) and triethylamine (3.6 equiv., 360 mmol, 50.0 mL) in dry THF (500 mL) was cooled to 0 °C and then methanesulfonyl chloride (1.8 equiv., 180 mmol, 13.9 mL) was added dropwise. The mixture was stirred at room temperature for 14 hours. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in CH₂Cl₂ (60 mL) and washed with water (40 mL) and saturated NaHCO₃ (2 x 40 mL). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum to afford the crude product (96% yield) which was used in the next step without further purification.

2nd step:²²⁷ The crude of the corresponding mesylated *Cinchone* (1 equiv., 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and sodium azide (2 equiv., 96 mmol, 6.2 g) was added portionwise. The mixture was stirred at 70 °C for 16 hours and after this time the reaction mixture was quenched with water (80 mL) and

²²³ Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450–5453.

²²⁴ Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

²²⁵ Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis* **2011**, *12*, 1880–1886.

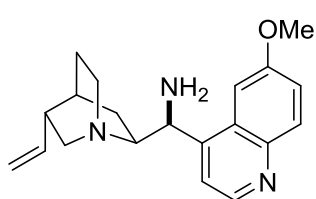
²²⁶ Adapted from: Zielińska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis* **2006**, *7*, 1176–1182.

²²⁷ Adapted from: Sundermeier, U.; Döbler, C.; Mehlretter, G. M.; Baumann, W.; Beller, M. *Chirality* **2003**, *15*, 127–134.

diluted with ethyl acetate (150 mL). The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over MgSO₄, filtered and evaporated under reduced pressure to afford the crude azide in quantitative yield, which was used in the next step without further purification.

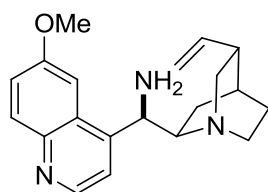
3rd step:²²⁷ The crude azide product was dissolved in dry THF (250 mL) and PPh₃ (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (≈5 hours). Then H₂O (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂ (150 mL). HCl 6M (250 mL) was added and the aqueous phase was extracted and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with CH₂Cl₂ (3 x 150 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the corresponding 9-amino-9-deoxy-9-epicinchone.

9-Amino-9-deoxy-9-epiquinine²²⁸



9-Amino-9-deoxy-epiquinine was synthesized following the general procedure employing quinine as starting material. Yield: 9.06 g (56%). Brown viscous oil. $[\alpha]_D^{25} = +80$ (c=1.1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

9-Amino-9-deoxy-9-epiquinidine^{228b,229}



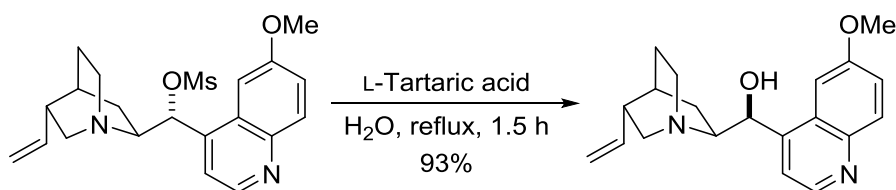
9-Amino-9-deoxy-epiquinidine was synthesized following the general procedure employing quinidine as starting material. Yield: 8.25 g (51%). Brown viscous oil. $[\alpha]_D^{22} = +69$ (c=2.5, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (d, *J* = 4.3 Hz, 1H), 7.64–8.14 (m, 2H), 7.55 (d, *J* = 4.6 Hz, 1H), 7.35 (m, 1H), 5.79–5.87 (m, 1H), 5.09 (m, 2H), 4.67 (d, *J* = 9.9 Hz, 1H), 3.97 (s, 3H), 2.79–3.01 (m, 5H), 2.28 (m, 1H), 2.16 (s, 2H), 1.46–1.56 (m, 3H), 1.14–1.32 (m, 1H), 0.78–0.96 (m, 1H).

²²⁸ Physical and spectroscopic data were coincident with the previously reported: a) Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702. b) He, W.; Liu, P.; Zhang, B. L.; Sun, X. L.; Zhang, S. Y. *Appl. Organometal. Chem.* **2006**, *20*, 328–334.

²²⁹ Physical and spectroscopic data were coincident with the previously reported: Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119–2133.

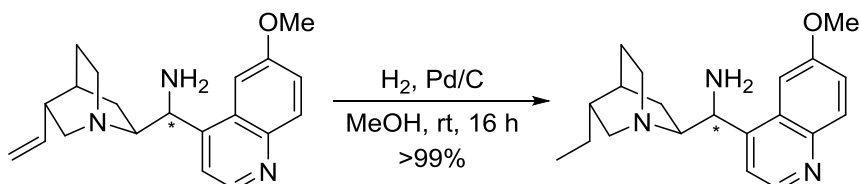
Experimental section

6.2.1.2. Preparation of 9-epiquinine²³⁰



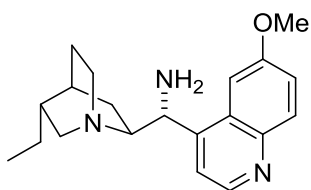
A solution of mesylated quinine (1 equiv., 30 mmol, 12.1 g) and L-tartaric acid (1.1 equiv., 33 mmol, 5.0 g) in H₂O (140 mL) was stirred at reflux for 1.5 hours. Then, the reaction mixture was cooled to room temperature and a saturated solution of NaHCO₃ (200 mL) was added and it was extracted with CH₂Cl₂ (3 x 150 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to afford 9-epiquinine. Yield: 9.08 g (93%). Brown solid. [α]_D²⁴ = +25.8 (c=1.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.73 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.65 (d, *J* = 2.7 Hz, 1H), 7.43–7.34 (m, 2H), 5.83–5.67 (m, 1H), 5.07–4.92 (m, 3H), 3.94 (s, 3H), 3.34–3.03 (m, 3H), 2.88–2.72 (m, 2H), 2.33 (m, *J* = 9.6, 6.7, 5.3, 3.7, 1.5 Hz, 1H), 1.72 (ddd, *J* = 4.2, 3.2, 2.2 Hz, 4H), 1.67–1.56 (m, 2H), 1.47 (dddd, *J* = 13.6, 9.6, 4.0, 2.0 Hz, 1H), 0.96 (ddt, *J* = 13.6, 7.9, 1.8 Hz, 1H).

6.2.1.3. Preparation of 9-amino-9-deoxyhydroquinines



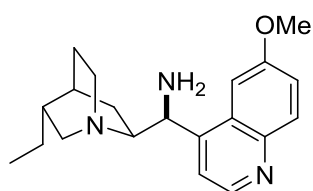
To a solution of 9-amino(9-deoxy)quinine (10 mmol, 3.23 g) in MeOH (40 mL) at inert atmosphere, Pd/C (10% w/w, 323 mg) was added. It was subjected to H₂ atmosphere at room temperature for 16 hours. Then, the reaction mixture was filtered through celite and concentrated under reduced pressure to afford the corresponding saturated 9-amino-9-deoxy-hydroquinine.

²³⁰ Adapted from: Braje, W. M.; Holzgreffe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2085–2087.

9-Amino-9-deoxyhydroquinine

9-Amino-9-deoxyhydroquinine was prepared following the general procedure for the preparation of chiral amines (see page 193) and subsequent hydrogenation employing 9-epiquinine. Overall yield: 8.10 g (50%). Brown viscous oil. $[\alpha]_D^{23} = -57.7$ ($c=0.3$, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.72

(d, $J = 4.6$ Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.46–7.24 (m, 3H), 4.58 (d, $J = 9.1$ Hz, 1H), 3.94 (s, 3H), 3.16 (q, $J = 8.8$ Hz, 1H), 3.08–2.82 (m, 2H), 2.58–2.44 (m, 1H), 2.39–2.30 (m, 1H), 2.06 (tdd, $J = 12.3, 5.6, 3.3$ Hz, 1H), 1.83 (dq, $J = 4.0, 2.0$ Hz, 1H), 1.71–1.56 (m, 2H), 1.54–1.29 (m, 5H), 0.96–0.74 (m, 3H).

9-Amino-9-deoxy-9-epihydroquinine

9-Amino-9-deoxy-9-epihydroquinine was prepared following the general procedure for the hydrogenation employing 9-amino-9-deoxy-9-epiquinine. Yield: 3.24 g (>99%). Brown viscous oil. $[\alpha]_D^{25} = +56$ ($c=1$, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3)

δ 8.75 (d, $J = 4.3$ Hz, 1H), 7.64–8.14 (m, 2H), 7.55 (d, $J = 4.6$ Hz, 1H), 7.35 (m, 1H), 5.79–5.87 (m, 1H), 5.09 (m, 2H), 4.67 (d, $J = 9.9$ Hz, 1H), 3.97 (s, 3H), 2.79–3.01 (m, 5H), 2.28 (m, 1H), 2.16 (s, 2H), 1.46–1.56 (m, 3H), 1.14–1.32 (m, 1H), 0.78–0.96 (m, 1H).

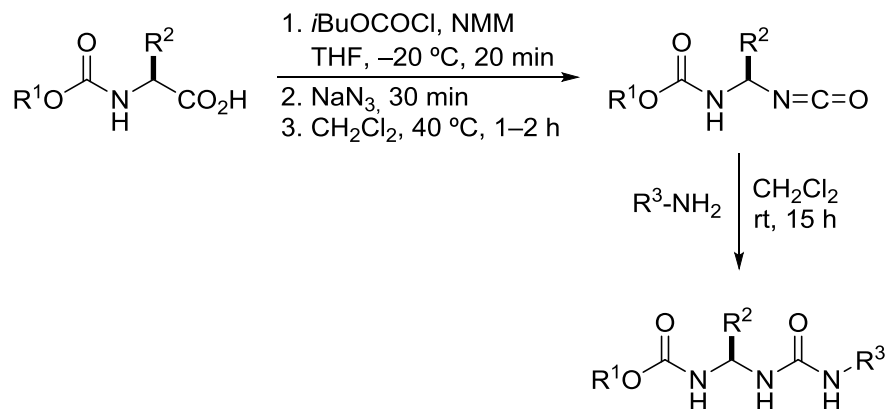
6.2.1.4. Preparation of (1S,2S)-2-(piperidin-1-yl)cyclohexanamine²³¹

To a mixture of (1S,2S)-cyclohexane-1,2-diamine (1 equiv., 10 mmol, 1.14 g) and $\text{NaBH}(\text{OAc})_3$ (4 equiv., 40 mmol, 8.50 g) in 1,2-dichloroethane (60 mL), glutaraldehyde (1.04 equiv., 50% w/w in H_2O , 10.4 mmol, 1.9 mL) was added dropwise at room temperature and stirred for 3 hours. The mixture was quenched with NaOH 6M solution (30 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure to give (1S,2S)-2-(piperidin-1-yl)cyclohexanamine which was used in next step without further purification. Yellow oil. Yield: 1.62 g (89%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.87–2.68 (m, 1H), 2.67–2.49 (m, 3H), 2.41–2.19 (m, 2H), 2.16–1.92 (m, 2H), 1.88–1.34 (m, 8H), 1.31–0.97 (m, 4H).

²³¹ Adapted from: Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

6.2.2. Synthesis of ureidopeptide-based Brønsted base catalysts

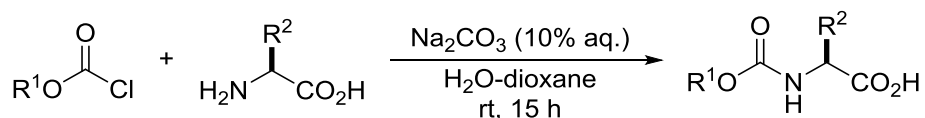
Ureidopeptide-based Brønsted base catalysts were prepared according to the following general scheme:



6.2.2.1. Preparation of *N*-carbamate protected α -amino acids

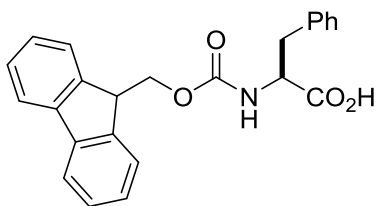
The amino acids *N*-(9-fluorenylmethoxycarbonyl)-*L*-valine (Fmoc-Val-OH) and *N*-tert-butoxycarbonyl-*L*-*tert*-leucine (Boc-Tle-OH) were bought from Fluka.

6.2.2.1.1. Procedure A using chloroformates²³²

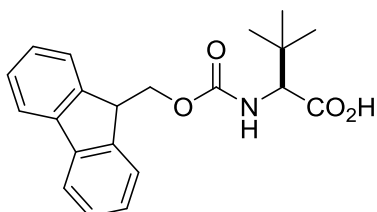


To a stirred solution of the corresponding amino acid (1 equiv., 10 mmol) in 10% aqueous Na_2CO_3 (25 mL) and dioxane (10 mL), a solution of the corresponding chloroformate (1 equiv., 10 mmol) in dioxane (30 mL) was slowly added at 0 °C. The mixture was stirred in an ice bath for 1 hour, then allowed to warm to room temperature and stirred at the same temperature for 15 hours. After that, the mixture was poured into water (100 mL) and washed with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure to afford the corresponding *N*-protected amino acid, which was used in the next step without further purification.

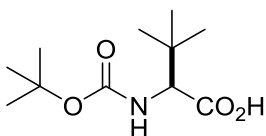
²³² Adapted from: Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron* **1991**, *47*, 2389–2400.

***N*-(((9H-Fluoren-9-yl)methoxy)carbonyl)-L-phenylalanine**

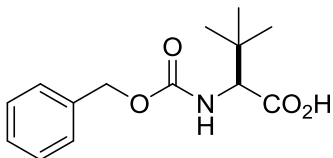
The title compound was prepared from (9H-fluoren-9-yl)methyl chloroformate and L-phenylalanine according to the general procedure A. Yield: 3.60 g (93%). White foam. ^1H NMR (300 MHz, CDCl_3) δ 7.87 (d, 2H), 7.71 (d, 1H), 7.64 (t, 2H), 7.40 (t, 2H), 7.33 – 7.19 (m, 8H), 4.20 – 4.16 (m, 4H), 3.10-3.06 (m, 1H), 2.90-2.84 (m, 1H) ^1H NMR (300 MHz, CD_3OD) δ 7.78 (d, $J = 7.5$, 2H), 7.68 (d, $J = 6.7$, 2H), 7.39 (t, $J = 7.5$, 2H), 7.33 – 7.18 (m, 7H), 4.50 (s, 2H), 4.39 – 4.33 (m, 2H), 4.23 (t, $J = 6.9$, 1H), 4.05 (brs, 1H), 3.04 (s, 1H).

***N*-(((9H-Fluoren-9-yl)methoxy)carbonyl)-L-tert-leucine**

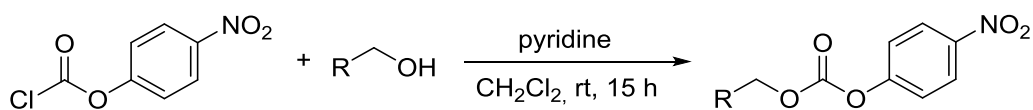
The title compound was prepared from (9H-fluoren-9-yl)methyl chloroformate and L-tert-leucine according to the general procedure A. Yield: 3.39 g (95%). White foam. ^1H NMR (300 MHz, CD_3OD) δ 7.78 (d, $J = 7.5$, 2H), 7.68 (d, $J = 6.7$, 2H), 7.39 (t, $J = 7.5$, 2H), 7.30 (dt, $J = 7.5$, 1.0, 2H), 4.50 (s, 2H), 4.39 – 4.33 (m, 2H), 4.23 (t, $J = 6.9$, 1H), 4.05 (brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

***N*-(*tert*-butoxycarbonyl)-L-tert-leucine**

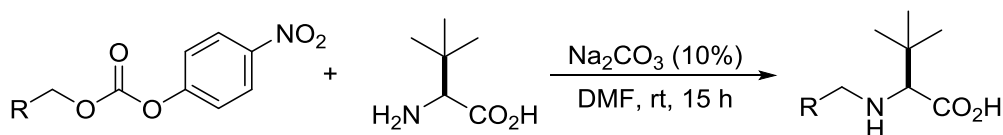
The title compound was prepared from *tert*-butyl chloroformate and L-tert-leucine according to the general procedure A. White foam. Yield: 2.29 g (99%). ^1H NMR (300 MHz, CDCl_3) δ 5.07 (d, $J = 8.5$, 1H), 4.18 – 4.07 (m, 1H), 1.45 (s, 9H), 1.02 (s, 9H).

***N*-(Carboxybenzyl)-L-tert-leucine**

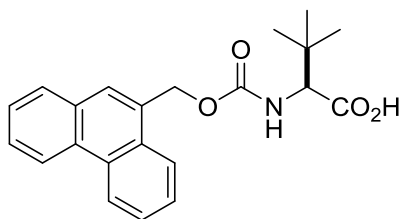
The title compound was prepared from benzyl chloroformate and L-tert-leucine according to the general procedure A. Yield: 2.38 g (91%). White foam. ^1H NMR (300 MHz, CDCl_3) δ 7.35 (m, 5H), 5.33 (d, $J = 9.6$, 1H), 5.12 (s, 2H), 4.21 (d, $J = 9.5$, 1H), 1.02 (s, 9H).

6.2.2.1.2. Procedure B using 4-nitrophenyl carbonates²³³

1st step: To a stirred solution of *p*-nitrophenylchloroformate (1.1 equiv., 11 mmol, 2.2 g) in CH₂Cl₂ (13.6 mL) was added pyridine (1.1 equiv., 11 mmol, 0.9 mL). The formed white slurry was cooled to 0 °C, and the corresponding alcohol (1 equiv., 10 mmol) was added in several portions to keep the temperature at 0 °C. After complete addition, the yellow mixture was allowed to warm to room temperature and stirred for 15 hours. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and subsequently washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL), dried with MgSO₄ and concentrated under reduced pressure. The residue was used in the next step without further purification.



2nd step: To a stirred solution of *L*-*tert*-leucine (1 equiv., 10 mmol, 1.31 g) in 10% aqueous Na₂CO₃ (26 mL) and *N*-dimethylformamide (10 mL), the solution of the corresponding 4-nitrophenyl carbonate (1 equiv., 10 mmol) in *N*-dimethylformamide (30 mL) was slowly added at 0 °C. The mixture was stirred in an ice bath for 1 hour, then allowed to warm to room temperature and stirred at the same temperature for 15 hours. After that, the mixture was poured into H₂O (100 mL) and washed with Et₂O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hex/EtOAc, 80:20) to afford the corresponding *N*-protected-*L*-*tert*-leucine.

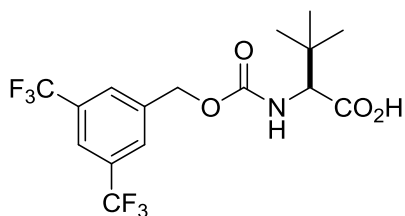
(S)-3,3-Dimethyl-2-(((phenanthren-9-ylmethoxy)carbonyl)amino)butanoic acid

The title compound was prepared from phenanthren-9-ylmethanol and *L*-*tert*-leucine according to the general procedure B. Yield: 2.74 g (75%). White foam. ¹H NMR (300 MHz, CDCl₃) δ 8.73 (d, *J* = 7.5, 1H), 8.66 (d, *J* = 8.0, 1H), 8.07 (d, *J* = 7.0, 1H), 7.88 (d, *J* = 7.5, 1H),

²³³ Adapted from: Lan, P.; Porco, J. A. Jr.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660–669.

7.81 (s, 1H), 7.61 (dd, $J = 18.5, 10.7$, 4H), 5.63 (q, $J = 12.4$, 2H), 5.37 (d, $J = 9.4$, 1H), 4.26 (d, $J = 9.5$, 1H), 1.02 (s, 9H).

(S)-2-((((3,5-Bis(trifluoromethyl)benzyl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid



The title compound was prepared from 3,5-bis(trifluoromethyl)benzyl alcohol and L-tert-leucine according to the general procedure B. Yield: 3.25 g (81%). White foam. ^1H NMR (300 MHz, CDCl_3) δ 7.83 (s, 1H), 7.30 (s, 2H), 5.33 (d, $J = 9.6$, 1H), 5.12 (s, 2H),

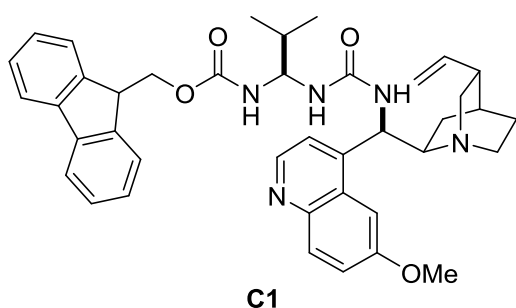
4.21 (d, $J = 9.5$, 1H), 1.02 (s, 9H).

6.2.2.2. Preparation of ureidopeptide-based catalysts

To a cooled solution of the corresponding *N*-protected α -amino acid (1 equiv., 5 mmol) in dry THF (20 mL), isobutyl chloroformate (1 equiv., 5 mmol, 0.65 mL) and *N*-methylmorpholine (1 equiv., 5 mmol, 0.6 mL) were added at $-20\text{ }^\circ\text{C}$ and the mixture was stirred for 20 minutes. Then, a suspension of NaN_3 (1.5 equiv., 7.5 mmol, 0.48 g in 5 mL of H_2O) was added and the reaction mixture was stirred at the same temperature. After 30 minutes, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with water (15 mL). The organic phase was dried over MgSO_4 , and concentrated *in vacuo* to give a yellow oil, which was redissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at $40\text{ }^\circ\text{C}$ under nitrogen atmosphere for 1–2 hours. The reaction was monitored by infrared analysis until disappearance of the azide band ($\lambda = 2140\text{ cm}^{-1}$) –isocyanate band is observed ($\lambda = 2240\text{ cm}^{-1}$)–. After completion, the corresponding amine was added (0.7 equiv., 3.5 mmol) and the reaction mixture was stirred at room temperature for 15 hours. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (CH_2Cl_2 – $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 80:20) or by non-acid silica gel (Hex/EtOAc, 80:20 to 0:100) to afford the desired catalysts **C1–C8**, **C22** and **C23**.

Experimental section

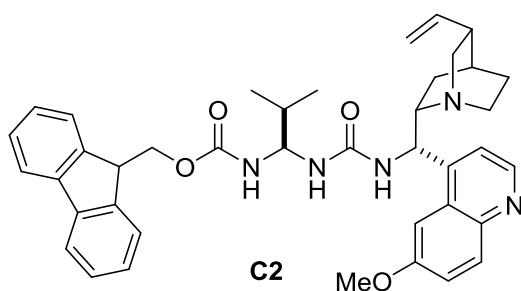
(9H-Fluoren-9-yl)methyl ((S)-1-(3-((R)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C1)



The title compound was prepared from *N*-Fmoc-L-Val-OH and 9-amino-9-deoxy-9-epiquinidine. Yield: 1.69 g (73%). White solid. m. p.= 115–127 °C. $[\alpha]_D^{25} = +104.8$ ($c = 0.86$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.71 (d, $J = 4.5$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 7.80 (d, $J = 7.4$ Hz, 2H), 7.66 (s, 1H), 7.58 (s, 2H), 7.46–

7.38 (m, 4H), 7.35–7.30 (m, 3H), 6.47–6.26 (brs, 1H), 6.00–5.81 (m, 1H), 5.68–5.49 (m, 2H), 5.10 (d, $J = 11.8$ Hz, 3H), 4.67–4.54 (m, 1H), 4.53–4.42 (m, 1H), 4.38–4.27 (m, 1H), 4.22 (t, $J = 6.6$ Hz, 1H), 3.97 (s, 3H), 2.94–2.83 (m, 6H), 2.31–2.18 (m, 1H), 1.64 (s, 1H), 1.64–1.42 (m, 2H), 1.36–1.22 (m, 1H), 0.98–0.89 (m, 2H), 1.87–0.77 (m, 5H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.7, 155.9, 147.6, 144.8, 143.9, 143.8, 141.3, 141.3, 140.4, 131.7, 127.7, 127.1, 125.1, 125.0, 121.9, 120.0, 114.7, 101.5, 66.8, 65.4, 55.5, 49.2, 47.2, 47.0, 39.2, 32.0, 27.4, 26.6, 25.3, 18.7, 18.6. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{40}\text{H}_{46}\text{N}_5\text{O}_4$: 660.3550; found: 660.3559.

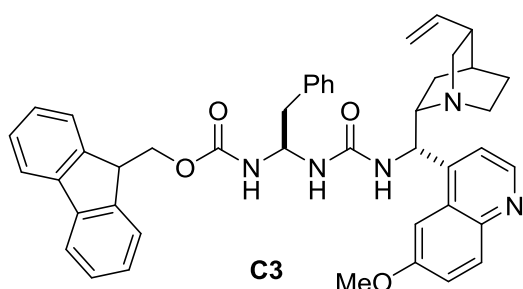
(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C2)



The title compound was prepared from *N*-Fmoc-L-Val-OH and 9-amino-9-deoxy-9-epiquinine. Yield: 1.76 g (76%). White solid. m. p.= 129–140 °C. $[\alpha]_D^{25} = -35.8$ ($c = 1.1$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.66 (d, $J = 3.8$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 7.86–7.69 (m, 3H), 7.79–7.73 (m, 2H), 7.49–7.20

(m, 7H), 6.47–6.28 (bs, 1H), 5.79–5.68 (m, 2H), 5.65–5.46 (bs, 1H), 5.40–5.19 (m, 1H), 5.03–4.95 (m, 2H), 4.80–4.57 (m, 1H), 4.48–4.26 (m, 2H), 4.19–4.15 (m, 1H), 3.96 (s, 3H), 3.28–3.20 (m, 2H), 3.17–3.02 (m, 1H), 2.75–2.70 (m, 2H), 2.60–2.54 (m, 1H), 2.38–2.22 (m, 1H), 1.66–1.58 (m, 3H), 1.53–1.35 (m, 1H), 0.87 (s, 7H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.8, 157.4, 156.1, 147.5, 145.7, 144.7, 143.9, 143.7, 141.2, 131.6, 128.4, 127.7, 127.0, 125.0, 121.5, 119.9, 114.6, 102.0, 66.7, 65.1, 60.1, 55.8, 55.6, 47.1, 40.9, 39.4, 31.9, 27.7, 27.4, 26.1, 18.7, 18.5. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{40}\text{H}_{46}\text{N}_5\text{O}_4$: 660.3550; found: 660.3557.

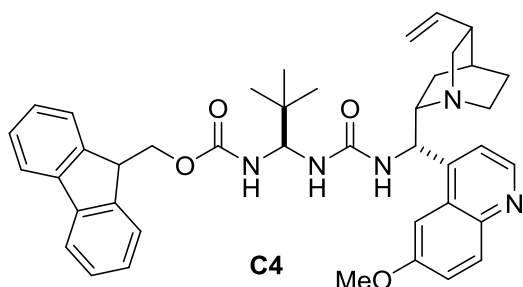
(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-phenylethyl)carbamate (C3)



The title compound was prepared from *N*-Fmoc-L-Phe-OH and 9-amino-9-deoxy-9-epiquinine. Yield: 1.66 g (67%). White solid. m. p.= 135–146 °C. $[\alpha]_D^{25} = -12.1$ (c= 1, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 8.72 (d, J= 4.5, 1H), 8.03 (d, J= 9.2, 1H), 7.79 (d, J= 7.5, 2H), 7.69 (d, J= 2.5, 1H), 7.57–7.52 (m, 2H),

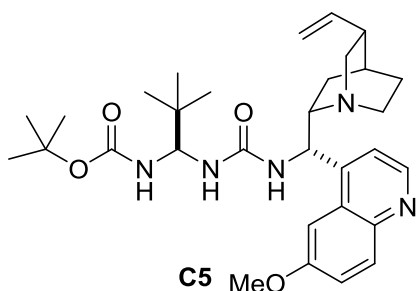
7.48–7.39 (m, 3H), 7.38–7.33 (m, 4H), 7.26–7.23 (m, 4H), 7.14 (s, 2H), 6.08 (bs, 1H), 5.82–5.66 (m, 2H), 5.16 (bs, 2H), 5.03–4.96 (m, 3H), 4.41–4.33 (m, 2H), 4.22–4.12 (m, 1H), 3.97 (s, 3H), 3.27–3.04 (m, 5H) 2.77 – 2.68 (m, 2H), 2.34–2.27 (m, 1H), 1.69–1.62 (m, 1H), 1.45–1.36 (m, 1H), 1.00–0.93 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 157.8, 156.9, 155.7, 147.5, 144.8, 143.9, 143.8, 141.3, 141.2, 136.8, 131.7, 129.3, 128.5, 127.7, 127.1, 126.7, 125.0, 121.5, 120.0, 114.6, 102.0, 66.6, 60.8, 60.1, 55.7, 55.6, 47.1, 40.8, 40.2, 39.4, 27.8, 27.3, 26.01. UPLC (DAD-QTOF [M+H]⁺) calcd for C₄₄H₄₆N₅O₄ 708.3550; found 708.3560.

(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C4)

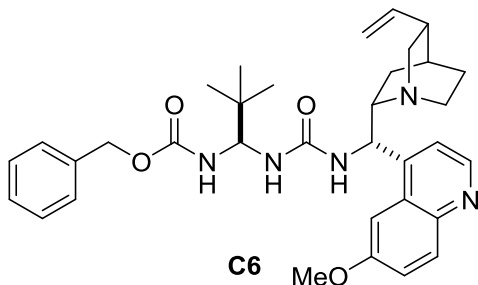


The title compound was prepared from *N*-Fmoc-L-Tle-OH and 9-amino-9-deoxy-9-epiquinine. Yield: 1.67 g (71%). White solid. m. p.= 130–139 °C. $[\alpha]_D^{25} = -16.2$ (c= 1, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 8.63 (d, J= 4.4 Hz, 1H), 8.01 (d, J= 9.2 Hz, 1H), 7.83–7.72 (m, 3H), 7.62–7.55 (m, 2H), 7.47–7.31

(m, 7H), 6.41–6.26 (bs, 1H), 5.84–5.69 (m, 1H), 5.40–5.25 (m, 1H), 5.09–5.05 (bs, 1H), 5.07–4.95 (m, 3H), 4.47–4.41 (m, 1H), 4.35–4.30 (m, 1H), 4.26–4.11 (m, 1H), 3.97 (s, 3H), 3.32–3.24 (m, 2H), 3.17–3.02 (m, 1H), 2.81–2.69 (m, 2H), 2.36–2.25 (m, 1H), 1.66–1.57 (m, 3H), 1.48–1.38 (m, 1H), 0.92 (s, 10H). ¹³C NMR (75 MHz, CDCl₃) δ 158.2, 157.8, 156.8, 147.9, 146.3, 145.1, 144.3, 144.1, 141.8, 141.7, 132.00, 128.9, 128.1, 127.5, 125.5, 122.0, 120.4, 114.9, 102.5, 67.4, 67.1, 60.8, 56.8, 56.3, 56.0, 47.6, 41.4, 39.9, 35.8, 28.3, 27.9, 26.5, 25.8. UPLC (DAD-QTOF [M+H]⁺) calcd for C₄₁H₄₇N₅O₄ 674.3726; found 674.3726.

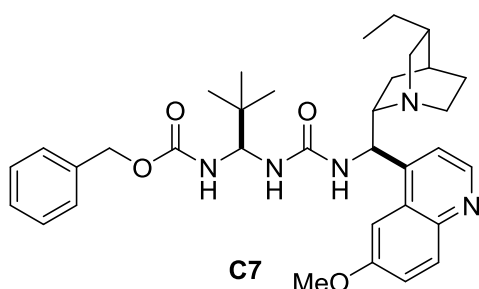
***tert*-Butyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C5)**

The title compound was prepared from *N*-Boc-*L*-Tle-OH and 9-amino-9-deoxy-9-epiquinine. Yield: 1.50 g (78%). White solid. m. p.= 118–130 °C. $[\alpha]_D^{25} = -26.7$ ($c = 1$, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3) δ 8.73 (d, $J = 4.6$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H), 7.79 (d, $J = 2.5$ Hz, 1H), 7.39 (dd, $J = 3.5, 8.4$ Hz, 2H), 6.62–6.43 (bs, 1H), 5.86–5.74 (m, 1H), 5.46–5.33 (m, 1H), 5.07–5.07 (m, 1H), 5.04–4.95 (m, 2H), 4.93–4.90 (m, 2H), 4.87–4.79 (bs, 1H), 4.01 (s, 3H), 3.38–3.21 (m, 2H), 3.18–3.08 (m, 1H), 2.89–2.69 (m, 2H), 2.37–2.28 (m, 1H), 1.69–1.66 (m, 1H), 1.66–1.57 (m, 2H), 1.42 (s, 10H), 0.91 (s, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ 157.8, 157.5, 156.0, 147.5, 146.2, 144.8, 141.6, 131.5, 128.7, 121.7, 119.1, 114.4, 102.1, 80.1, 66.2, 60.5, 56.0, 55.7, 41.1, 39.7, 35.3, 28.3, 28.0, 27.6, 26.2, 25.4. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{31}\text{H}_{46}\text{N}_5\text{O}_4$ 552.3550; found 552.3559.

Benzyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C6)

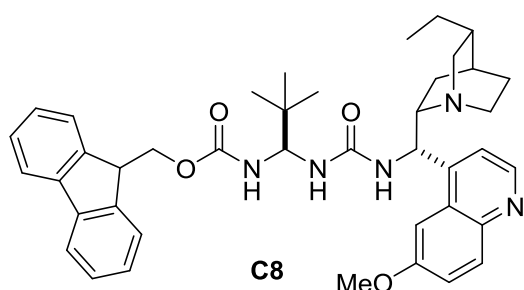
The title compound was prepared from *N*-Cbz-*L*-Tle-OH and 9-amino-9-deoxy-9-epiquinine. Yield: 1.48 g (72%). White solid. m. p.= 101–126 °C. $[\alpha]_D^{25} = -29.8$ ($c = 1$, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3) δ 8.62 (d, $J = 4.3$ Hz, 1H), 8.01 (d, $J = 9.2$ Hz, 1H), 7.74 (d, $J = 2.6$ Hz, 1H), 7.39 (d, $J = 2.7$ Hz, 1H), 7.36 (d, $J = 7.0$ Hz, 5H), 7.22 (d, $J = 4.4$ Hz, 1H), 6.48–6.35 (bs, 1H), 5.84–5.73 (m, 1H), 5.32–5.29 (m, 1H), 5.20 (d, $J = 9.4$ Hz, 1H), 5.08–5.05 (m, 2H), 5.04–4.95 (m, 3H), 3.97 (s, 3H), 3.30–3.23 (m, 2H), 3.12–2.99 (m, 1H), 2.80–2.70 (m, 2H), 2.34–2.27 (s, 1H), 1.68–1.64 (m, 2H), 1.62–1.56 (m, 1H), 1.45–1.38 (m, 1H), 0.82 (s, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.2, 157.8, 156.8, 148.0, 146.5, 145.1, 141.9, 136.6, 132.6, 132.0, 129.0, 128.7, 128.6, 122.0, 119.6, 114.8, 102.5, 67.4, 67.5, 60.8, 57.0, 56.4, 56.1, 41.4, 40.0, 35.8, 28.4, 27.9, 26.5, 25.7. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{34}\text{H}_{44}\text{N}_5\text{O}_4$ 586.3399; found 586.3393.

Benzyl ((S)-1-(3-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C7)



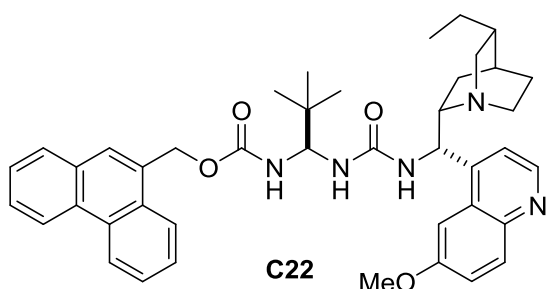
The title compound was prepared from *N*-Cbz-L-Tle-OH and 9-amino-9-deoxyhydroquinine. Yield: 1.18 g (65%). White solid. m. p.= 105–134 °C. $[\alpha]_D^{24} = +59.4$ ($c = 1.1$, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.66 (d, $J = 4.5$ Hz, 1H), 7.93 (d, $J = 9.2$ Hz, 1H), 7.70 (d, $J = 2.8$ Hz, 1H), 7.49–7.14 (m, 7H), 6.42 (s, 1H), 5.72 (t, $J = 9.9$ Hz, 1H), 5.31 (d, $J = 9.9$ Hz, 1H), 5.25–5.01 (m, 3H), 4.71 (t, $J = 9.6$ Hz, 1H), 3.93 (s, 3H), 3.40–3.31 (m, 1H), 3.10–2.83 (m, 2H), 2.55–2.33 (m, 2H), 1.97–1.82 (m, 1H), 1.80–1.63 (m, 2H), 1.57–1.30 (m, 5H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.81 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.74, 154.55, 147.90, 147.38, 144.64, 140.88, 140.56, 140.41, 131.51, 127.93, 121.84, 121.60, 120.95, 120.52, 116.30, 114.99, 114.81, 114.49, 102.19, 102.03, 55.56, 55.04, 53.85, 49.58, 47.90, 39.77, 30.57, 29.78, 28.87, 27.30. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{34}\text{H}_{46}\text{N}_5\text{O}_4$ 588.3550; found 588.3549.

(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C8)



The title compound was prepared from *N*-Fmoc-L-Tle-OH and 9-amino-9-deoxy-9-epihydroquinine. Yield: 1.44 g (61%). White solid. m. p.= 135–149 °C. $[\alpha]_D^{24} = -29.8$ ($c = 1$, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.61 (d, $J = 4.5$ Hz, 1H), 7.97 (d, $J = 9.2$ Hz, 1H), 7.81–7.69 (m, 3H), 7.62–7.49 (m, 2H), 7.44–7.27 (m, 7H), 6.28 (s, 1H), 5.27 (d, $J = 15.7$ Hz, 1H), 5.01 (s, 2H), 4.85 (s, 1H), 4.41 (dd, $J = 10.6$, 7.1 Hz, 1H), 4.30 (dd, $J = 10.6$, 6.7 Hz, 1H), 4.17 (t, $J = 6.8$ Hz, 1H), 3.94 (s, 3H), 3.22 (dd, $J = 13.6$, 9.9 Hz, 1H), 3.01 (s, 1H), 2.78–2.60 (m, 1H), 2.45 (d, $J = 13.7$ Hz, 1H), 1.60 (d, $J = 12.1$ Hz, 5H), 1.52–1.37 (m, 2H), 1.09–0.95 (m, 1H), 0.89 (s, 9H), 0.79 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.93, 157.44, 156.42, 147.68, 144.90, 143.97, 141.46, 131.76, 127.89, 127.20, 125.11, 121.80, 120.15, 102.15, 66.69, 66.00, 57.78, 55.78, 47.32, 41.18, 37.47, 35.63, 28.75, 27.65, 26.12, 25.60, 25.36, 15.43, 12.15. UPLC (DAD-QTOF $[\text{M}+\text{H}]^+$) calcd for $\text{C}_{41}\text{H}_{50}\text{N}_5\text{O}_4$ 696.3863; found 676.3876.

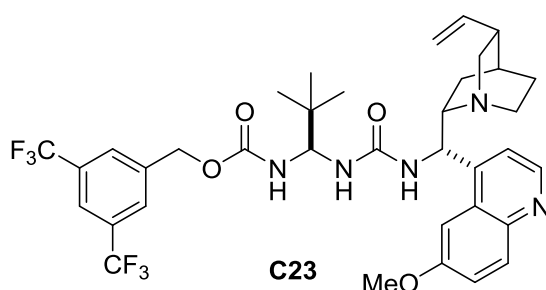
Phenanthren-9-ylmethyl ((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C22)



The title compound was prepared from (S)-3,3-dimethyl-2-(((phenanthren-9-ylmethoxy)carbonyl)amino)butanoic acid and 9-amino-9-deoxy-9-hydroepiquinine. Yield: 1.66 g, (69%). Yellow solid. m. p. = 152–159 °C. $[\alpha]_D^{25} = 8.7$ (c=1, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 8.66 (dd, J = 21.2,

8.1, 2H), 8.53 (s, 1H), 8.05 – 7.49 (m, 9H), 7.37 – 7.31 (m, 1H), 7.21 (s, 1H), 6.35 (s, 1H), 5.55 (t, J = 10.6, 2H), 5.11 (dd, J = 28.1, 15.1, 4H), 3.93 (s, 3H), 3.24 – 3.06 (m, 2H), 2.99 (s, 1H), 2.56 (s, 1H), 2.42 (d, J = 11.1, 1H), 2.21 (s, 1H), 1.36 (dd, J = 58.1, 27.4, 7H), 0.92 – 0.72 (m, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 157.9, 157.6, 156.7, 147.7, 146.5, 144.9, 131.8, 131.5, 131.2, 129.2, 126.8, 125.3, 124.2, 121.8, 119.4, 102.3, 66.7, 60.6, 59.6, 57.8, 55.8, 41.1, 37.5, 35.6, 28.8, 27.6, 25.9, 25.4, 21.2, 14.4, 12.2. UPLC (DAD-QTOF [M+H]⁺) calcd for C₄₂H₅₀N₅O₄ 688.3863, found 688.3863.

3,5-Bis(trifluoromethyl)benzyl ((S)-1-(3-((S)-((6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C23)



The title compound was prepared from (S)-2-(((3,5-(CF₃)₂-benzyloxy)carbonyl-amino)-3,3-dimethylbutanoic acid and 9-amino-9-deoxy-9-epiquinine. Yield: 2.3 g (65%). White solid. m. p. = 125–131 °C. $[\alpha]_D^{24} = -9.5$ (c = 1.00, CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 8.58 (d, J = 4.5 Hz, 1H), 7.94 (d, J =

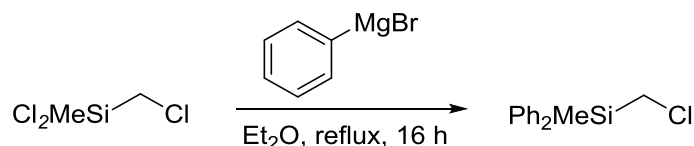
9.2 Hz, 1H), 7.85 – 7.61 (m, 4H), 7.30 (dd, J = 9.2, 2.6 Hz, 1H), 7.25 (d, J = 4.4 Hz, 1H), 6.46 (s, 1H), 5.91 – 5.54 (m, 3H), 5.13 (d, J = 13.3 Hz, 2H), 5.08 – 4.81 (m, 3H), 3.89 (s, 3H), 3.38 – 3.01 (m, 3H), 2.68 (d, J = 16.8 Hz, 2H), 2.25 (h, J = 5.3, 4.7 Hz, 1H), 1.70 – 1.28 (m, 4H), 0.76 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 158.0, 157.6, 155.7, 147.4, 145.9, 144.7, 141.0, 139.3, 131.78 (q, J = 35.7 Hz), 131.5, 128.5, 127.6, 125.0, 121.7, 121.4, 119.2, 114.8, 102.2, 66.7, 64.9, 60.2, 55.8, 55.7, 41.0, 39.3, 35.5, 27.6, 27.4, 27.2, 26.1, 25.3. UPLC-DAD-QTOF: C₃₆H₄₁N₅O₄F₆ [M+H]⁺ calcd.: 722.3136, found: 722.3138.

6.2.3. Synthesis of squaramide-based Brønsted base catalysts

6.2.3.1. Preparation of (chloromethyl)silyl derivatives²³⁴

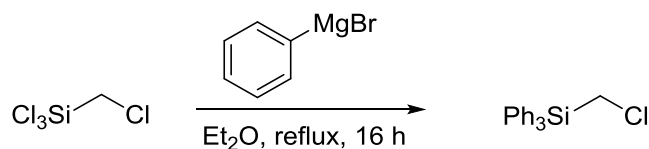
(Chloromethyl)dimethyl(phenyl)silane was purchased from Sigma-Aldrich.

(Chloromethyl)(methyl)diphenylsilane



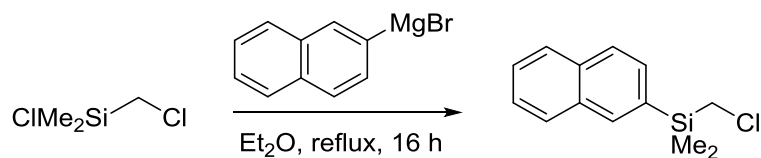
To a solution of dichloro(chloromethyl)methylsilane (1 equiv., 60 mmol, 7.62 mL) in anhydrous diethyl ether (30 mL), phenylmagnesium bromide (3.0 M in ether) (2 equiv., 120 mmol, 40 mL) was added dropwise at room temperature and the reaction mixture was refluxed for 16 hours. Then, the mixture was cooled to 0 °C, saturated solution of NH₄Cl (20 mL) was added and it was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford the title compound. Yield: 8.22 g (55 %). Colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.64 – 7.52 (m, 4H), 7.49 – 7.32 (m, 6H), 3.26 (s, 2H), 0.72 (s, 3H).

(Chloromethyl)triphenylsilane

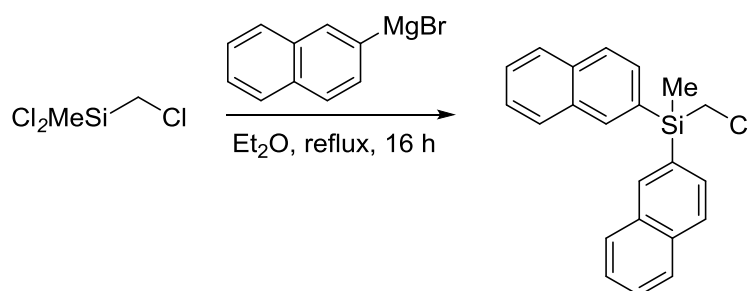


The title compound was prepared according to the procedure shown above from trichloro(chloromethyl)silane (1 equiv., 10 mmol, 1.25 mL) and phenylmagnesium bromide (3.0 M in ether) (3 equiv., 30 mmol, 10 mL). The crude material was purified by crystallization on methanol. The crystals were washed with petroleum ether to afford the title compound. Yield: 1.40 g (45 %). White solid. m. p. 110–113 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.68 – 7.52 (m, 6H), 7.53 – 7.29 (m, 9H), 3.53 (s, 2H).

²³⁴ Procedures adapted from: a) Larson, G. L.; Prieto, J. A.; Ortiz, E. *Tetrahedron*, **1988**, *44*, 3781-3790. b) Allen, J. M.; Aprahamian, S. L.; Sans, E. A.; Shechter, H. *J. Org. Chem.*, **2002**, *67*, 3561.

(Chloromethyl)dimethyl(naphthalen-2-yl)silane

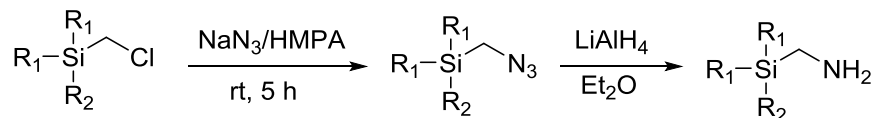
To a solution of chloro(chloromethyl)dimethylsilane (1 equiv., 20 mmol, 2.63 mL) in anhydrous diethyl ether (15 mL), 2-naphthylmagnesium bromide (0.5 M in THF) (1.4 equiv., 28 mmol, 56 mL) was added dropwise at room temperature and the reaction mixture was refluxed for 16 hours. Then, the mixture was cooled to 0 °C, saturated solution of NH_4Cl (20 mL) was added and it was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford the title compound. Yield: 2.34 g (50 %). Colorless liquid. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.04 (s, 1H), 7.86 – 7.45 (m, 6H), 3.02 (s, 2H), 0.50 (s, 6H).

(Chloromethyl)(methyl)di(naphthalen-2-yl)silane

To a solution of dichloro(chloromethyl)methylsilane (1 equiv., 20 mmol, 2.54 mL) in anhydrous diethyl ether (15 mL), 2-naphthylmagnesium bromide (0.5 M in ether) (2.4 equiv., 48 mmol, 96 mL) was added dropwise at room temperature and the reaction mixture was refluxed for 16 hours. Then, the mixture was cooled to 0 °C, saturated solution of NH_4Cl (20 mL) was added and it was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over MgSO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford the title compound. Yield: 4.17 g (61 %). Colorless liquid. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.02 (s, 2H), 7.80 – 7.42 (m, 12H), 3.07 (s, 2H), 0.56 (s, 3H).

6.2.3.2. Preparation of aminomethyl silanes²³⁵

(Trimethylsilyl)methylamine was purchased Fluka. The other aminomethyl silanes were prepared following the general procedure:



1st step: To a solution of the corresponding chloromethyl silane (20.0 mmol) in HMPA (10 mL) was added sodium azide (1.43 g, 22 mmol) and the reaction mixture was stirred for 5 hours at room temperature. Then, the mixture was poured into H₂O (30 mL) and extracted with hexane (3 x 30 mL). The combined extracts were washed with saturated solution of NH₄Cl, dried over MgSO₄ and concentrated under reduced pressure. The residue was used in the next step without further purification.

2nd step: To a suspension of LiAlH₄ (1 equiv., 10.0 mmol) in dry Et₂O (10 mL) was slowly added at 0 °C a solution of the corresponding azide (10.0 mmol) in dry diethyl ether (5 mL). The mixture was stirred in an ice bath for 10 min and then stirred at room temperature until liberation of nitrogen ceased (30 min). The reaction was quenched with 1 mL of NH₄OH 1 % aqueous solution. The mixture was filtered through celite, the filtered was dried over MgSO₄ and solvent was evaporated under reduced pressure. The residue was used in the next step without further purification.

(Dimethyl(phenyl)silyl)methanamine

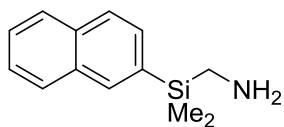
$\text{PhMe}_2\text{Si-CH}_2\text{-NH}_2$ The title compound was prepared according to the general procedure. Yield: 2.97 g (90 %) Colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.57-7.53 (m, 2H), 7.38-7.36 (m, 3H), 2.40 (s, 2H), 0.33 (s, 6H).

(Methyldiphenylsilyl)methanamine

$\text{Ph}_2\text{MeSi-CH}_2\text{-NH}_2$ The title compound was prepared according to the general procedure. Yield: 3.68 g (81 %). Colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.55 (m, 4H), 7.41-7.34 (m, 6H), 2.72 (s, 2H), 0.63 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 135.4, 134.5, 133.9, 129.4, 129.2, 127.8, 127.6, 29.1, -5.7. UPLC-DAD-QTOF: C₁₄H₁₈NSi [M+H]⁺ calcd.: 228.1209, found: 228.1197.

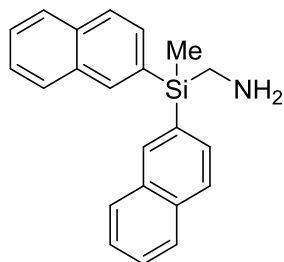
²³⁵ Adapted from: Lettelier, M.; McPhee, D. J.; Griller, D. *Synthetic Commun.* **1988**, 18, 1975.

(Dimethyl(naphthalen-2-yl)silyl)methanamine



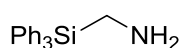
The title compound was prepared according to the general procedure. Yield: 3.68 g (80 %). Colorless liquid. ^1H NMR (300 MHz, CDCl_3) δ 8.04 (s, 1H), 7.87-7.81 (m, 3H), 7.63-7.60 (m, 1H), 7.51-7.48 (m, 2H), 2.49 (s, 2H), 0.42 (s, 6H).

(Methyl(naphthalen-2-yl)silyl)methanamine



The title compound was prepared according to the general procedure. Yield: 3.68 g (80 %). Colorless liquid. ^1H NMR (300 MHz, CDCl_3) δ 8.01 (s, 2H), 7.86-7.78 (m, 6H), 7.64-7.59 (m, 2H), 7.53-7.45 (m, 4H), 2.51 (s, 2H), 0.40 (s, 3H).

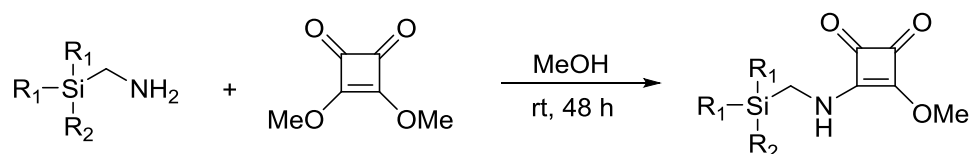
(Methyldiphenylsilyl)methanamine



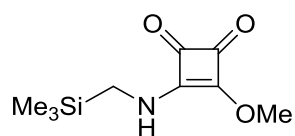
The title compound was prepared according to the general procedure. Yield: 4.85 g (84 %). Colorless liquid. ^1H NMR (300 MHz, CDCl_3) δ 7.66 – 7.54 (m, 6H), 7.54 – 7.31 (m, 9H), 3.04 (s, 2H).

6.2.3.3. Preparation of squaramide-type catalysts

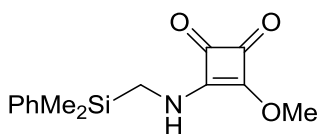
1st STEP:



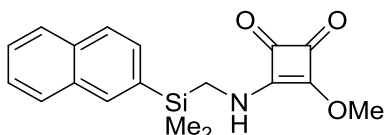
To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (0.71 g, 5.0 mmol) in 10 mL MeOH was added the corresponding (aminomethyl)silane. The reaction mixture was stirred for 48 hours at room temperature and white precipitate was generated. The reaction product was filtered and the filtration residue was washed with Et_2O to give the corresponding monosubstituted secondary amine.

3-Methoxy-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione

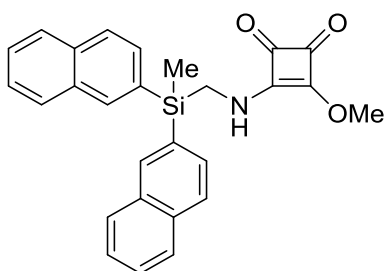
The title compound was prepared according to the general procedure. Yield: 0.884 g (83 %). White solid. m. p. 119–122 °C. IR (ν/cm^{-1}): 3205, 3014, 2969, 2948, 2357, 1790, 1692, 1576, 1493, 1366, 1228, 862, 584. ^1H NMR (300 MHz, CDCl_3) δ 5.68 (s, 1H), 4.40 (s, 3H), 3.02 – 2.96 (m, 2H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 189.4, 182.1, 176.9, 172.1, 60.1, 35.8, –3.42. UPLC-DAD-QTOF: $\text{C}_9\text{H}_{16}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 214.0899, found: 214.0892.

3-((Dimethyl(phenyl)silyl)methylamino)-4-methoxycyclobut-3-ene-1,2-dione

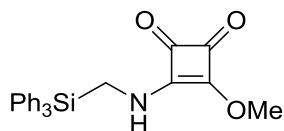
The title compound was prepared according to the general procedure. Yield: 0.963 g (70 %). White solid. m. p. 117–120 °C. IR (ν/cm^{-1}): 3247, 3135, 3046, 2968, 2359, 1799, 1691, 1586, 1357, 1229, 1112, 1051, 980, 934, 807, 697, 587, 467. ^1H NMR (300 MHz, CDCl_3) δ 7.53 – 7.48 (m, 2H), 7.42 – 7.35 (m, 3H), 6.20 (s, 1H), 4.32 (s, 3H), 3.22 – 3.15 (m, 2H), 0.40 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ : 189.5, 182.6, 177.4, 172.5, 134.9, 133.9, 130.2, 128.4, 60.5, 35.6, –4.6. UPLC-DAD-QTOF: $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 276.1056, found: 276.1058.

3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione

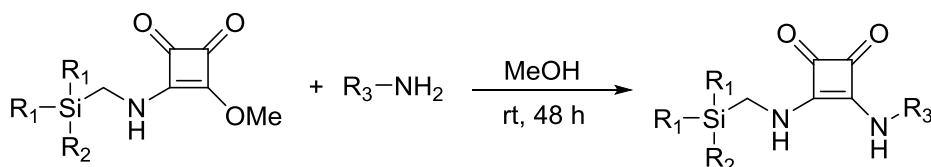
The title compound was prepared according to the general procedure. Yield: 1.14 g (70 %). White solid. m. p. 140–144 °C. IR (ν/cm^{-1}): 3277, 3065, 3001, 2939, 2904, 1803, 1696, 1622, 1495, 1396, 1275, 1109, 918, 848, 779, 725, 580, 459. ^1H NMR (300 MHz, CDCl_3) δ 8.00 (s, 1H), 7.86 – 7.81 (m, 3H), 7.55 – 7.49 (m, 3H), 6.63 (s, 1H), 4.23 (s, 3H), 3.21 (d, $J = 6\text{Hz}$, 1H), 0.48 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ 189.7, 182.3, 177.3, 172.2, 135.0, 134.1, 132.9, 129.5, 128.2, 127.9, 127.6, 127.0, 126.4, 60.4, 35.6, –4.5. UPLC-DAD-QTOF: $\text{C}_{18}\text{H}_{20}\text{NO}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 326.1212, found: 326.1212.

3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione

The title compound was prepared according to the general procedure. Yield: 1.56 g (72 %). White solid. m. p. 150–153 °C. IR (ν/cm^{-1}): 3240, 3046, 1801, 1699, 1605, 1497, 1461, 1396, 1362, 1085, 857, 758, 475. ^1H NMR (300 MHz, CDCl_3) δ 8.12 (s, 2H), 8.00 – 7.77 (m, 6H), 7.77 – 7.41 (m, 6H), 6.76 (brs, 1H), 4.17 (s, 3H), 3.62 (m, 6.3 Hz, 2H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 189.3, 182.2, 177.2, 172.2, 136.1, 134.2, 132.9, 130.6, 130.1, 128.2, 127.8, 127.7, 127.2, 126.4, 60.3, 34.3, –5.4. UPLC-DAD-QTOF: $\text{C}_{27}\text{H}_{23}\text{NO}_3\text{Si}$ [$\text{M}+\text{H}$] $^+$ calcd.: 438,1520, found: 438,1523.

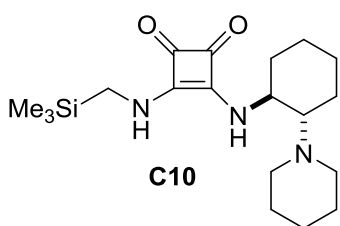
3-Methoxy-4-(triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione

The title compound was prepared according to the general procedure. Yield: 1.70 g (85 %). White solid. m. p. 167-171°C. IR (ν/cm^{-1}): 3254, 3046, 1801, 1702, 1601, 1426, 1360, 1111, 698, 505. ^1H NMR (300 MHz, CDCl_3) δ 7.63 – 7.35 (m, 15H), 5.32 (s, 1H), 4.28 (s, 3H), 3.76 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 188.9, 182.9, 177.6, 172.9, 136.0, 135.7, 130.8, 128.7, 60.5, 27.8. UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{21}\text{NO}_3\text{Si}$ [$\text{M}+\text{H}$] $^+$ calcd.: 400.1363, found: 400.1360.

2nd STEP:

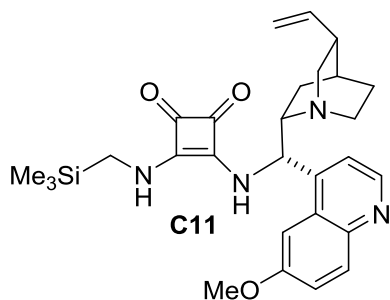
To a solution of monosubstituted squarate (1.5 mmol) in 6 mL MeOH was added the corresponding cinchona-base chiral amine (3.0 mmol) and the reaction mixture was stirred for 48 hours at room temperature. The reaction product was obtained after flash column chromatography on basic silica gel (eluting with ethyl acetate) to afford the desired catalysts **C10–C15**.

3-(((1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C10)



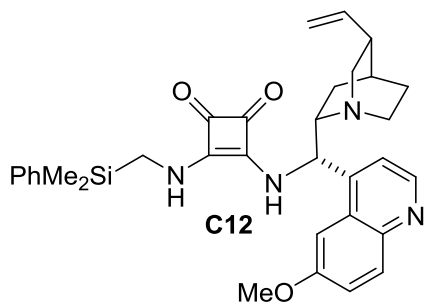
The title compound **C10** was prepared according to the general procedure. Yield: 0.247 g (45 %). m. p. 239–242 °C. $[\alpha]_{\text{D}}^{25} = +42.1$ ($c = 0.25$, DMSO). IR (ν/cm^{-1}): 3160, 3014, 2929, 2851, 1791, 1633, 1551, 1462, 1365, 1216, 846, 762. $^1\text{H NMR}$ (300 MHz, DMSO) δ 7.10 (s, 1H), 3.82 (s, 1H), 3.21 – 3.08 (m, 2H), 2.63 – 2.47 (m, 2H), 2.30 – 2.20 (m, 2H), 2.04 – 1.99 (m, 1H), 1.83 – 1.63 (m, 2H), 1.41 – 1.14 (m, 8H), 0.06 (s, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 182.3, 181.6, 168.1, 167.6, 68.4, 53.8, 49.3, 34.4, 26.4, 24.9, 24.6, 24.6, 23.8, –3.1. UPLC-DAD-QTOF: $\text{C}_{19}\text{H}_{34}\text{N}_3\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 364.2420, found: 276.2409.

3-(((*S*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C11)



The title compound **C11** was prepared according to the general procedure. Yield: 0.514 mg (68 %). White solid. m. p. 209–213 °C. $[\alpha]_{\text{D}}^{25} = -102.6$ ($c = 0.25$, CH_2Cl_2). IR (ν/cm^{-1}): 3203, 3014, 2936, 2871, 1788, 1636, 1545, 1455, 1366, 1232, 1037, 842. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.66 (d, $J = 4.5$ Hz, 1H), 8.06 – 8.02 (d, $J = 9.2$ Hz, 1H), 7.84 (s, 1H), 7.56 (d, $J = 3$ Hz, 1H), 7.40 (dd, $J = 3, 3$ Hz, 1H), 5.85 – 5.73 (m, 1H), 5.01 – 4.91 (m, 2H), 3.92 (s, 3H), 3.51 – 3.06 (m, 6H), 2.78 – 2.68 (m, 2H), 2.24 (brs, 1H), 1.62 – 1.42 (m, 4H), 0.78 – 0.72 (m, 1H), 0.02 (s, 3H), –0.06 (s, 6H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 183.5, 181.8, 181.7, 168.0, 167.7, 158.7, 147.9, 144.9, 141.5, 132.0, 128.0, 122.3, 114.8, 101.9, 56.1, 41.0, 39.7, 36.0, 35.9, 29.8, 28.0, 27.7, 26.2, –2.9. UPLC-DAD-QTOF: $\text{C}_{28}\text{H}_{37}\text{N}_4\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 505.2635, found: 505.2597.

3-(((Dimethyl(phenyl)silyl)methyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C12)

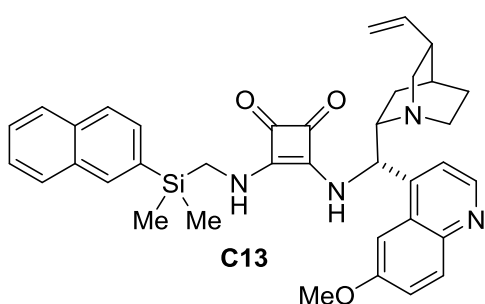


The title compound **C12** was prepared according to the general procedure. Yield: 0.594 g (70 %). White solid. m. p. 221–224 °C. $[\alpha]_{\text{D}}^{25} = -106.0$ ($c = 0.25$, CH_2Cl_2). IR (ν/cm^{-1}): 3183, 3047, 2919, 2862, 1788, 1631, 1542, 1455, 1399, 1232, 1032, 838, 711, 469. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.62 (d, $J = 3.4$ Hz, 1H), 8.01 (d, $J = 9.2$ Hz, 1H), 7.77 (s, 1H), 7.42 – 7.38 (m,

Experimental section

2H), 7.35 – 7.32 (m, 2H), 7.22 – 7.19 (m, 3H), 5.80 – 5.68 (m, 1H), 5.02 – 4.94 (m, 2H), 3.93 (s, 3H), 3.45–7.39 (m, 2H), 3.29 – 3.12 (m, 3H), 2.77 – 2.67 (m, 2H), 2.29 (s, 1H), 1.68 – 1.61 (m, 3H), 1.50 – 1.42 (m, 1H), 0.83 – 0.77 (m, 1H), 0.19 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 183.4, 181.0, 168.3, 167.2, 158.8, 147.7, 145.0, 140.9, 135.5, 133.8, 132.0, 129.9, 128.1, 122.6, 115.2, 101.8, 56.2, 41.0, 39.4, 35.1, 27.5, 26.1, –4.5. UPLC-DAD-QTOF: C₃₃H₃₉N₄O₃Si [M+H]⁺ calcd.: 567.2791, found: 567.2800.

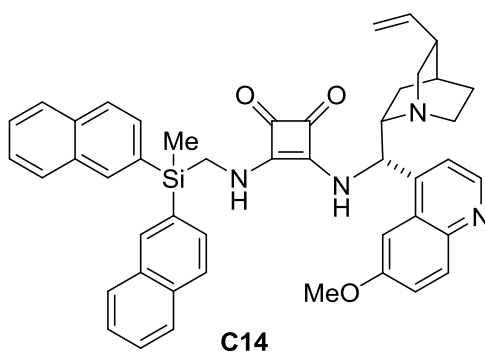
3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl))((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C13)



The title compound was **C13** prepared according to the general procedure. Yield: 0.693 g (75 %). White solid. m. p. 229–232 °C. [α]_D²⁵ = –109.5 (c = 0.5, CH₂Cl₂). IR (v/cm⁻¹): 3227, 2937, 2862, 1790, 1637, 1567, 1544, 1264, 1086, 1038, 817. ¹H NMR (300 MHz, CDCl₃) δ 8.54 (s, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.84 (s, 1H), 7.75 – 7.70 (m, 4H),

7.43 – 7.35 (m, 5H), 5.78 – 5.65 (m, 1H), 4.98 – 4.89 (m, 2H), 3.89 (s, 3H), 3.31 – 3.06 (m, 5H), 2.71 – 2.61 (m, 2H), 2.25 – 2.19 (m, 1H), 1.62 – 1.52 (m, 3H), 1.41 – 1.32 (m, 1H), 0.77 – 0.70 (m, 1H), 0.20 – 0.18 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 184.0, 182.8, 167.7, 159.2, 148.1, 145.5, 141.9, 135.3, 134.5, 133.3, 132.5, 130.0, 128.5, 128.3, 128.0, 127.4, 126.8, 122.9, 115.2, 102.2, 56.5, 41.3, 40.1, 35.2, 28.4, 28.0, 26.7, –4.0. UPLC-DAD-QTOF: C₃₇H₄₁N₄O₃Si [M+H]⁺ calcd.: 617.2948, found: 617.2961.

3-(((S)-(6-methoxyquinolin-4-yl))((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((methyl-di(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione (C14)

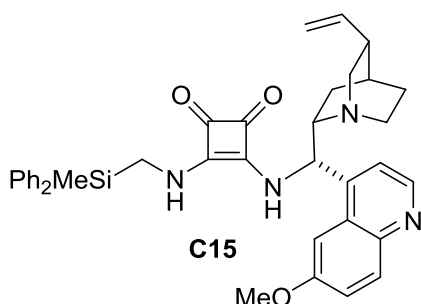


The title compound was **C14** prepared according to the general procedure. Yield: 0.830 g (76 %). White solid. m. p. 245–252 °C. [α]_D²⁵ = –124.6 (c = 0.7, CH₂Cl₂). IR (v/cm⁻¹): 3230, 3048, 2939, 1792, 1584, 1535, 1457, 1241, 1086, 908, 854, 730, 475. ¹H NMR (300 MHz, CDCl₃) δ 8.47 (s, 1H), 8.00 – 7.88 (m, 3H), 7.87 – 7.59 (m, 8H), 7.55 – 7.35 (m, 6H), 7.31

(dd, J = 9.2, 2.5 Hz, 1H), 5.64 (dt, J = 18.4, 9.7 Hz, 1H), 5.02 – 4.81 (m, 2H), 3.88 (s, 3H), 3.76 (d, J = 16.0 Hz, 1H), 3.50 (s, 1H), 3.16 (d, J = 42.3 Hz, 3H), 2.61 (s, 2H), 2.22 (s, 1H),

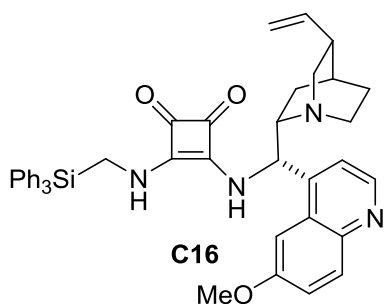
1.35 (s, 1H), 0.72 (dd, $J = 13.5, 7.4$ Hz, 1H), 0.55 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 183.3, 181.5, 167.8, 167.5, 158.6, 147.5, 144.6, 140.7, 135.9, 135.2, 134.0, 132.8, 131.6, 131.1, 131.0, 130.2, 128.1, 128.1, 127.7, 127.5, 126.9, 126.2, 122.5, 115.0, 101.7, 60.0, 56.0, 55.6, 53.3, 40.7, 39.1, 33.7, 27.4, 25.8, -5.5. UPLC-DAD-QTOF: $\text{C}_{46}\text{H}_{44}\text{N}_4\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 729.3255, found: 729.3251.

3-((S)-(6-Methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((methyl-diphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C15)



The title compound **C15** was prepared according to the general procedure. Yield: 0.560 g (60 %). m. p. 152–156 °C. $[\alpha]_{\text{D}}^{23} = -105.3$ ($c = 1.0$, CH_2Cl_2). IR (v/cm^{-1}): 3193, 2929, 2859, 1788, 1628, 1547, 1456, 1230, 1114, 803, 760, 730, 700, 489. ^1H NMR (300 MHz, CDCl_3) δ 8.49 (d, $J = 5.1$ Hz, 1H), 8.00 (d, $J = 9.2$ Hz, 1H), 7.79 (s, 1H), 7.48 – 6.97 (m, 12H), 5.75 (ddd, $J = 17.6, 10.9, 7.6$ Hz, 1H), 5.08 – 4.80 (m, 2H), 3.89 (s, 3H), 3.43 (ddd, $J = 32.6, 16.8, 9.5$ Hz, 4H), 3.15 (dd, $J = 13.8, 10.0$ Hz, 1H), 2.68 (dq, $J = 14.9, 7.5, 6.1$ Hz, 2H), 2.15 (s, 2H), 1.73 – 1.18 (m, 4H), 0.86 – 0.65 (m, 1H), 0.44 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 183.6, 181.9, 167.8, 158.7, 147.6, 144.9, 141.6, 134.6, 133.6, 133.5, 131.9, 130.1, 128.2, 128.2, 122.5, 114.7, 101.9, 56.1, 40.9, 39.7, 33.7, 28.0, 27.7, 26.3, -5.7. UPLC-DAD-QTOF: $\text{C}_{38}\text{H}_{41}\text{N}_4\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 629.2948, found: 629.2956.

3-((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methylamino)-4-((triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C16)

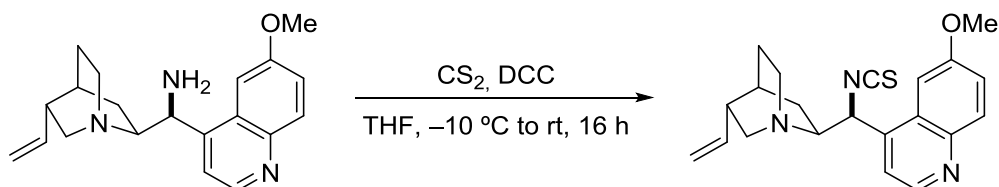


The title compound **C16** was prepared according to the general procedure. Yield: 0.688 g (67 %). White solid. m. p. 252–256 °C. $[\alpha]_{\text{D}}^{23} = -58.9$ ($c = 1.0$, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3) δ 8.40 (s, 1H), 7.96 (d, $J = 9.2$ Hz, 1H), 7.77 (s, 1H), 7.61 – 7.08 (m, 19H), 5.71 (dt, $J = 17.4, 9.3$ Hz, 1H), 5.03 – 4.83 (m, 2H), 3.90 (s, 3H), 3.72 (td, $J = 20.5, 20.0, 10.0$ Hz, 3H), 3.36 – 3.01 (m, 3H), 2.63 (dt, $J = 14.6, 7.5$ Hz, 2H), 2.23 (dt, $J = 10.8, 6.3$ Hz, 1H), 1.72 – 1.28 (m, 4H), 0.72 (q, $J = 7.6, 6.5$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 183.6, 182.0, 167.9, 167.8, 158.7, 147.4, 144.9, 141.5, 135.9, 135.7, 135.4, 131.8, 130.3, 128.4, 128.3, 128.2, 128.0, 122.7, 114.7, 101.9, 56.2, 40.8, 39.6, 32.6, 28.0, 27.8, 27.7, 26.4. UPLC-DAD-QTOF: $\text{C}_{43}\text{H}_{43}\text{N}_4\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ calcd.: 691.3104, found: 691.3129.

6.2.4. Synthesis of thiourea- or urea-based Brønsted base catalysts

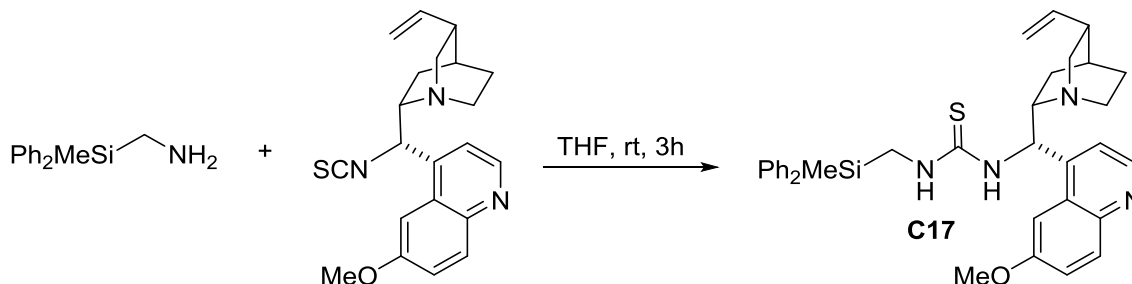
6.2.4.1. Preparation of silyl-thiourea type catalyst C17

6.2.4.1.1. Synthesis of 9-deoxy-9-epiquinine isocyanate derivative



To a solution of 9-amino-9-deoxy-9-epiquinine (1 equiv., 1 mmol, 0.323 g) in anhydrous THF (1 mL) at $-10\text{ }^{\circ}\text{C}$, carbon disulfide (6 equiv., 6 mmol, 0.36 mL) and DCC (1 equiv., 1 mmol, 0.206 g) were successively added. The reaction mixture was slowly warmed to room temperature in 3 hours and then, it was stirred at the same temperature for 16 hours. After that, the mixture was concentrated under reduced pressure and purified by flash chromatography column in silica gel (CH_2Cl_2 :MeOH, 97:3 to 90:10). Yield: 0.329 g (90 %). Yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 8.77 (d, $J = 4.5$ Hz, 1H), 8.07 (d, $J = 9.2$ Hz, 1H), 7.49 – 7.32 (m, 3H), 5.72 (ddd, $J = 17.1, 10.4, 6.6$ Hz, 1H), 5.30 (d, $J = 10.0$ Hz, 1H), 5.14 – 5.03 (m, 2H), 3.98 (s, 3H), 3.65 (dd, $J = 13.7, 10.2$ Hz, 1H), 3.47 – 3.23 (m, 3H), 3.08 (dt, $J = 13.5, 2.9$ Hz, 1H), 2.58 (s, 1H), 2.02 (s, 1H), 1.88 – 1.72 (m, 3H), 1.38 (dd, $J = 13.5, 8.9$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 164.16, 157.86, 147.72, 144.46, 141.92, 138.54, 131.81, 127.18, 121.46, 119.86, 116.76, 101.48, 66.56, 65.69, 57.19, 55.81, 46.23, 38.73, 27.65, 26.19, 25.42. UPLC-DAD-QTOF: $\text{C}_{21}\text{H}_{24}\text{NOS}$ $[\text{M}+\text{H}]^+$ calcd.: 366.1640, found: 366.1644.

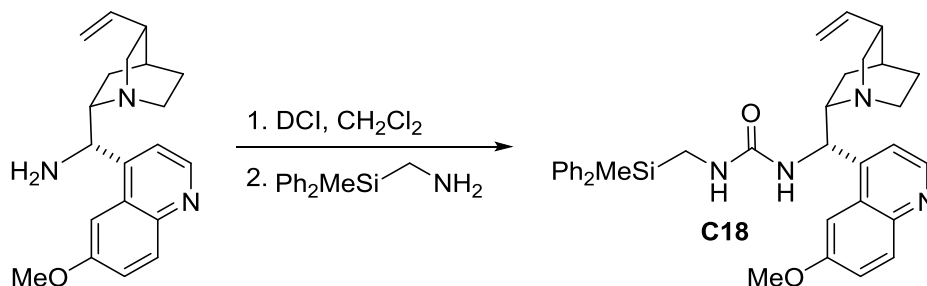
6.2.4.1.2. Synthesis of silyl-thiourea catalyst C17



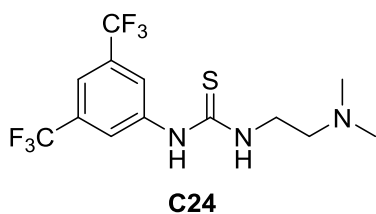
(Methyldiphenylsilyl)methanamine (1 equiv., 1.4 mmol, 0.32 g) was added to a solution of 9-isocyanate-9-deoxy-9-epiquinine (1 equiv., 1.4 mmol, 0.51 g) in anhydrous THF (2 mL) and the mixture was stirred at room temperature for 3 hours. After that, the mixture

was concentrated under reduced pressure and purified by flash chromatography column in silica gel (CH₂Cl₂:MeOH, 90:10) to afford catalyst **C17**. Yield: 0.746 g (90 %). White solid. m. p. 136–145 °C. [α]_D²³ = –106.7 (c = 1.0, CH₂Cl₂). IR (v/cm⁻¹): 2932, 1620, 1508, 1422, 1227, 1113, 1029, 910, 818, 730, 699, 483. ¹H NMR (300 MHz, CDCl₃) δ 8.57 (s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.65 – 7.51 (m, 2H), 7.44 – 7.28 (m, 12H), 6.03 (s, 1H), 5.71 – 5.52 (m, 1H), 5.00 – 4.84 (m, 2H), 3.91 (s, 3H), 3.44 (s, 2H), 3.24 – 2.85 (m, 4H), 2.72 – 2.53 (m, 2H), 2.24 (s, 1H), 1.70 – 1.46 (m, 3H), 1.27 (td, *J* = 12.4, 10.4, 3.7 Hz, 1H), 0.95 – 0.81 (m, 1H), 0.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 183.68, 158.00, 147.60, 144.87, 141.11, 134.56, 134.51, 134.10, 131.98, 129.78, 128.29, 128.23, 127.93, 122.09, 114.79, 101.88, 60.77, 55.77, 55.59, 40.78, 39.48, 33.43, 31.00, 27.87, 27.40, 25.89, –5.31. UPLC-DAD-QTOF: C₃₅H₄₁N₄OSSi [M+H]⁺ calcd.: 593.2770, found: 593.2776.

6.2.4.2. Preparation of silyl-urea type catalyst **C18**



To a solution of *N,N'*-carbonyldiimidazole (1.1 equiv., 1.1 mmol, 0.178 g) in anhydrous CH₂Cl₂ (1 mL), a solution of 9-amino-9-deoxy-9-epiquinine (1.0 equiv., 1.0 mmol, 0.323 g) in CH₂Cl₂ (1 mL) was added at room temperature. The reaction was monitored by TLC and once the reaction was finished –30 minutes approx.–, (methyldiphenylsilyl)methanamine (1 equiv., 1.4 mmol, 0.23 g) was added and stirred at room temperature for 16 hours. After that, the mixture was concentrated under reduced pressure and purified by flash chromatography column in silica gel (CH₂Cl₂:MeOH, 90:10) to afford catalyst **C18**. Yield, 0.346 g (60 %). White solid. m. p. 129–135 °C. [α]_D²³ = –36.3 (c = 1.0, CH₂Cl₂). IR (v/cm⁻¹): 2931, 1621, 1546, 1508, 1427, 1228, 1113, 1028, 910, 821, 730, 699, 484. ¹H NMR (300 MHz, CDCl₃) δ 8.66 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 2.8 Hz, 1H), 7.46 – 7.22 (m, 12H), 5.86 (s, 1H), 5.77 – 5.60 (m, 1H), 5.04 (s, 1H), 5.02 – 4.87 (m, 2H), 4.23 (t, *J* = 5.5 Hz, 1H), 3.93 (s, 3H), 3.25 – 2.91 (m, 5H), 2.74 – 2.56 (m, 2H), 2.33 – 2.20 (m, 1H), 1.70 – 1.52 (m, 3H), 1.41 – 1.26 (m, 1H), 1.00 – 0.85 (m, 1H), 0.44 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 159.09, 157.84, 147.65, 144.92, 141.35, 134.60, 134.47, 134.11, 131.86, 129.90, 128.20, 127.95, 121.77, 119.89, 114.67, 101.99, 60.22, 55.97, 55.71, 40.86, 39.63, 28.01, 27.49, 26.11, –5.26. UPLC-DAD-QTOF: C₃₅H₄₁N₄O₂Si [M+H]⁺ calcd.: 577.2999, found: 577.3004.

6.2.4.3. Preparation of achiral thiourea catalyst **C24**²³⁶

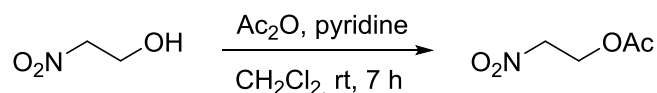
To a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (0.91 mL, 5 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL), *N,N*-dimethylethylenediamine (0.55 mL, 5 mmol, 1 equiv.) was added. The mixture was stirred at room temperature for 2 hours and then, the solvent was eliminated under reduced pressure to afford catalyst **C24**. Yield: 1.76 g (98%). White solid. ^1H RMN (300 MHz, $\text{MeOD-}d_4$) δ 8.15 (s, 2H), 7.58 (s, 1H), 3.79 – 3.56 (m, 2H), 2.56 (t, $J=6.3$ Hz, 2H), 2.27 (s, 6H). ^{13}C RMN (75 MHz, $\text{MeOD-}d_4$) δ 182.8, 143.2, 132.7 (q, $J=33.2$ Hz), 126.5, 123.6, 117.8, 58.6, 45.5, 43.0. Spectroscopic data were coincident with the previously reported.²³⁶

²³⁶ Procedure adapted from: a) Pratt, R. C.; Lohmeijer, B. G.; Long, D. A.; Lundberg, P. N.; Dove, A. P.; Li, H. B.; Wade, C. G.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules*, **2006**, *39*, 7863. b) Opalka, S. M.; Steinbacher, J. L.; Lambiris, B. A.; McQuade, D. T. *J. Org. Chem.* **2011**, *76*, 6503-6571.

6.3. Experimental section for Chapter 2

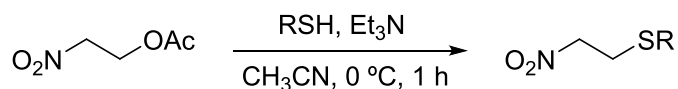
6.3.1. Preparation of 2-nitroethyl sulfones²³⁷

1st STEP:



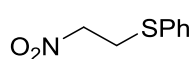
A solution of 2-nitroethanol (1.0 equiv., 50 mmol, 3.5 mL), pyridine (1.0 equiv., 50 mmol, 4.0 mL) and acetic anhydride (1.0 equiv., 50 mmol, 4.7 mL) in CH₂Cl₂ (80 mL) was stirred under nitrogen atmosphere at room temperature in the dark. After 7 hours, the reaction mixture was poured into 1M HCl (80 mL). The organic solvent was removed under reduced pressure and the aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed under reduced pressure to afford pure 2-nitroethyl acetate. Yield: 6.0 g (91%). Brown oil. ¹H NMR (300 MHz, CDCl₃) δ 4.60 (s, 4H), 2.08 (s, 3H).

2nd STEP:



To a solution of 2-nitroethyl acetate (1.0 equiv., 15 mmol, 1.99 g) and the corresponding thiol (1.0 equiv., 15 mmol) in acetonitrile (40 mL), a solution of Et₃N (1.1 equiv., 16.5 mmol, 2.20 mL) in CH₃CN (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 hour and then poured into 1M HCl (20 mL). The organic solvent was eliminated under reduced pressure and the aqueous phase was extracted with hexane (3 x 30 mL). The organic layer was washed with H₂O (100 mL), dried over MgSO₄ and the removal of the solvent under reduced pressure afforded the corresponding thioether, which was used in the following step without further purification.

(2-Nitroethyl)(phenyl)sulfane



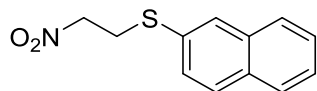
The title compound was prepared from thiophenol following the general procedure. Yield: 2.55 g (93%). Yellow oil. ¹H NMR (300 MHz,

²³⁷ Procedure adapted from: Mukhina, E. S.; Pavlova, Z. F.; Nekrasova, G. V.; Lipina, E. S.; Perekalin, V. V. *Russ. J. Org. (Chem. Zhurnal Organicheskoi Khimii)* **1990**, 26, 2285-2290.

Experimental section

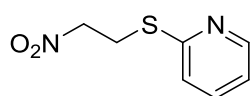
CDCl₃) δ 7.47 – 7.40 (m, 2H), 7.39 – 7.27 (m, 3H), 4.50 (t, J = 7.2 Hz, 2H), 3.44 (t, J = 7.2 Hz, 2H).

Naphthalen-2-yl(2-nitroethyl)sulfane



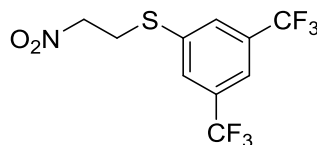
The title compound was prepared from 2-naphthalenethiol following the general procedure. Yield: 2.70 g (77%). White solid. ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, J = 1.6 Hz, 1H), 7.88 – 7.74 (m, 3H), 7.59 – 7.44 (m, 3H), 4.54 (t, J = 6.8 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H).

2-((2-Nitroethyl)thio)pyridine



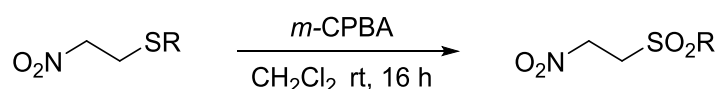
The title compound was prepared from 2-mercaptopyridine following the general procedure. Yield: 2.45 g (89%). Yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 8.11 – 8.02 (m, 1H), 7.90 – 7.72 (m, 2H), 7.01 (ddd, J = 6.9, 4.7, 2.0 Hz, 1H), 4.48 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H).

(3,5-Bis(trifluoromethyl)phenyl)(2-nitroethyl)sulfane

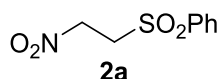


The title compound was prepared from 3,5-bis(trifluoromethyl)benzenethiol following the general procedure. Yield: 4.26 g (89%). Yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.81 (s, 2H), 7.77 (s, 1H), 4.58 (t, J = 6.8 Hz, 2H), 3.58 (t, J = 6.8 Hz, 2H).

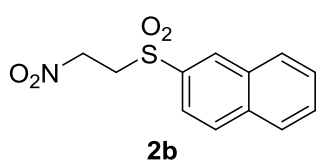
3rd STEP:



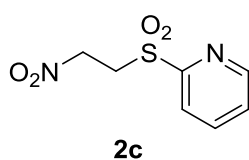
To a solution of the corresponding thioether (1.0 equiv., 10 mmol) in CH₂Cl₂ (100 mL), *m*-CPBA (2.0 equiv, 20 mmol, 6.4 g (70%)) was added in portions and the resulting solution was stirred overnight at room temperature. The reaction mixture was then cooled to 0°C and treated with 10% aqueous Na₂SO₃ (80 mL) for 15 minutes. The aqueous layer was separated and the organic phase was successively washed with a saturated NaHCO₃ solution (80 mL) and brine (80 mL), dried over MgSO₄ and the solvent was removed under reduced pressure to afford the corresponding pure 2-nitroethyl sulfone.

((2-Nitroethyl)sulfonyl)benzene (2a)

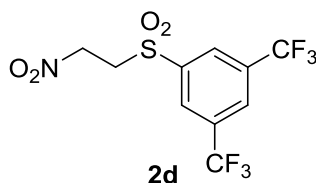
The title compound **2a** was prepared from (2-nitroethyl)(phenyl)sulfane according to the general procedure. Yield: 2.00 g (93%). White solid. m. p.= 99–101 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.95 – 7.91 (m, 2H), 7.78 – 7.67 (m, 1H), 7.66 – 7.57 (m, 2H), 4.74 (t, *J*= 7.0 Hz, 2H), 3.81 (t, *J*= 7.0 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 138.2, 134.9, 129.9, 128.2, 68.2, 52.5. Elem. Anal. calcd for C₈H₉NO₄S (215.23): C, 44.64; H, 4.21; N, 6.51. Found: C, 44.71; H, 4.21; N, 6.34.

2-((2-Nitroethyl)sulfonyl)naphthalene (2b)

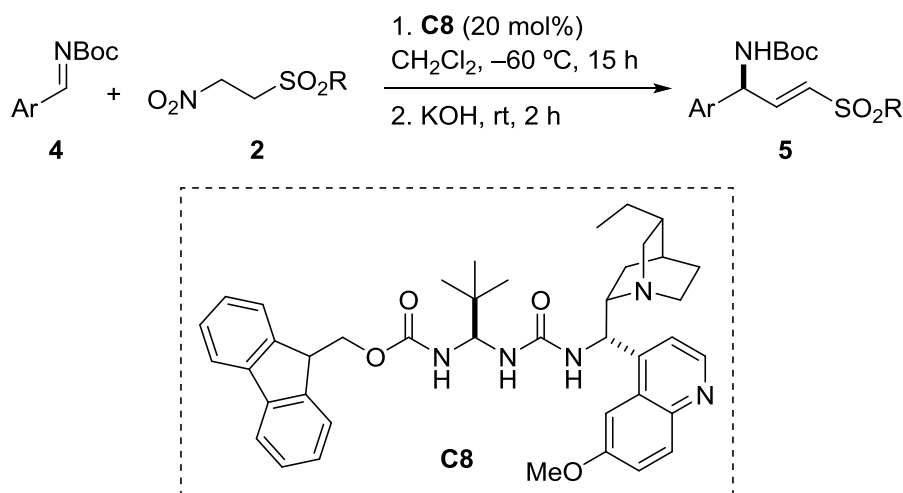
The title compound **2b** was prepared from naphthalen-2-yl(2-nitroethyl)sulfane according to the general procedure. Yield: 2.23 g (84%). White solid. m. p.= 135–137 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.55 – 8.48 (m, 1H), 8.12 – 7.81 (m, 4H), 7.80 – 7.50 (m, 2H), 4.78 (d, *J*= 7.3 Hz, 2H), 3.89 (t, *J*= 7.3 Hz, 2H). ¹³C NMR (75 MHz, CD₂Cl₂) δ 136.20, 135.47, 132.69, 130.83, 130.72, 130.38, 130.04, 128.61, 122.72, 68.78, 52.90. UPLC-DAD-QTOF: C₁₂H₁₁NO₄S [M+H]⁺ calcd.: 266.0482, found: 266.0479.

2-((2-Nitroethyl)sulfonyl)pyridine (2c)

The title compound **2c** was prepared from 2-((2-nitroethyl)thio)pyridine according to the general procedure. Yield: 1.56 g (72%). Yellow solid. m. p.= 116–120 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.74 – 8.62 (m, 1H), 8.07 – 7.90 (m, 2H), 7.58 (ddd, *J*= 6.9, 4.7, 2.0 Hz, 1H), 4.87 (t, *J*= 6.8 Hz, 2H), 4.06 (t, *J*= 6.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 150.3, 138.7, 128.2, 122.0, 68.3, 48.7. UPLC-DAD-QTOF: C₇H₉N₂O₄S [M+H]⁺ calcd.: 217.0286, found: 217.0283; C₇H₈N₂O₄SNa [M+Na]⁺ calcd.: 239.0104, found: 217.0102.

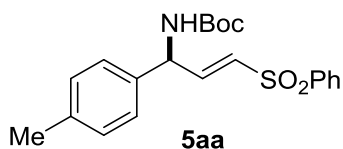
1-((2-Nitroethyl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (2d)

The title compound **2d** was prepared from (3,5-bis(trifluoromethyl)phenyl)(2-nitroethyl)sulfane according to the general procedure. Yield: 3.06 g (87%). White solid. m. p.= 138–140 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.43 (s, 2H), 8.26 (s, 1H), 4.90 (t, *J*= 6.6 Hz, 2H), 3.94 (t, *J*= 6.6 Hz, 2H). ¹³C NMR (75 MHz, CD₂Cl₂) δ 141.77, 134.00 (q, *J*= 34.9 Hz), 129.34, 129.03, 124.71, 68.22, 53.08. UPLC-DAD-QTOF: C₁₀H₇F₆NO₄S [M+H]⁺ calcd.: 352.0073, found: 352.0075.

6.3.2. Enantioselective synthesis of γ -sulfonyl allyl amines

To a solution of the corresponding *N*-Boc imine **4** (1.0 equiv., 0.5 mmol) and catalyst **C8** (0.20 equiv., 0.1 mmol, 0.067 g) in CH_2Cl_2 (5 mL), was added the 2-nitroethyl sulfone **2** (1.5 equiv., 0.75 mmol) at $-60\text{ }^\circ\text{C}$. The reaction mixture was stirred for 15 hours, then quenched with HCl 1 M (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. Impurities were removed by trituration with Et_2O . Then, the nitro-Mannich adduct was dissolved in dichloromethane (20 mL, from a commercial bottle) and KOH (2.0 equiv., 1 mmol, 0.056 g) was added and stirred at room temperature. The reaction was monitored by IR, observing the disappearance of the band at 1560 cm^{-1} in 1–2 hours. The reaction mixture was quenched with HCl 1 M (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over MgSO_4 and concentrated under reduced pressure to give the crude product. The corresponding products were purified²³⁸ by trituration in Et_2O or flash column chromatography (hexane:ethyl acetate) to afford the corresponding γ -sulfonyl allyl amines **5**.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing achiral catalyst **C23**.

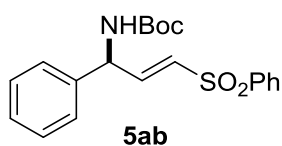
***tert*-Butyl (*S,E*)-(3-(phenylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5aa**)**

The title compound **5aa** was prepared from 2-nitroethyl sulfone **2a** and *N*-Boc imine **4a** following the general procedure. Yield: 0.081 g (42%). White solid. m. p.= 120–123 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} = -64.2$ ($c = 0.05$, CH_2Cl_2). $^1\text{H NMR}$ (300 MHz,

²³⁸ Some adducts decomposed during isolation and purification procedures.

CDCl₃) δ 7.88 (d, J = 7.2 Hz, 2H), 7.65 – 7.49 (m, 2H), 7.20 – 7.05 (m, 5H), 6.49 (dd, J = 15.0, 1.7 Hz, 1H), 5.41 (s, 1H), 4.86 (d, J = 7.3 Hz, 1H), 2.34 (s, 3H), 1.38 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 154.8, 145.8, 140.5, 138.7, 135.2, 133.6, 131.2, 130.1, 129.5, 127.9, 127.3, 80.6, 55.1, 28.4, 21.3. UPLC-DAD-QTOF: C₂₁H₂₆NO₄S [M+H]⁺ calcd.: 388.1577, found: 388.1574. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 0.50 mL/min, λ = 230 nm) t_R (major.) = 41.5 min, t_R (minor.) = 54.3 min. 85% *ee*.

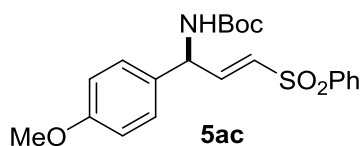
***tert*-Butyl (*S,E*)-(1-phenyl-3-(phenylsulfonyl)allyl)carbamate (**5ab**)**



The title compound **5ab** was prepared from 2-nitroethyl sulfone **2a** and *N*-Boc imine **4b** following the general procedure. Yield: 0.105 g (56%). White solid. m. p. = 131–135 °C. $[\alpha]_D^{25} = -46.9$ ($c = 2.5$, CHCl₃) ($[\alpha]_D^{23} = +31.5$ ($c = 1.04$, CHCl₃) for *R*-enantiomer).²³⁹

¹H NMR (300 MHz, CDCl₃) δ 7.96 – 7.83 (m, 2H), 7.67 – 7.59 (m, 1H), 7.55 (ddt, $J = 8.4, 6.7, 1.4$ Hz, 2H), 7.36 (dtd, $J = 7.0, 5.2, 2.3$ Hz, 3H), 7.25 – 7.19 (m, 2H), 7.11 (dd, $J = 15.0, 4.8$ Hz, 1H), 6.50 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.47 (s, 1H), 4.84 (s, 1H), 1.39 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 154.8, 145.6, 140.4, 138.2, 133.7, 131.4, 129.7, 129.6, 129.5, 128.9, 127.9, 127.4, 77.4, 55.6, 28.4. UPLC-DAD-QTOF: C₂₀H₂₄NO₄S [M+H]⁺ calcd.: 374.1421, found: 374.1419. Chiral HPLC (Chiralpak IA; 90:10 hexane:*i*PrOH; 0.50 mL/min, λ = 230 nm) t_R (major.) = 35.8 min, t_R (minor.) = 43.2 min. 61% *ee*.

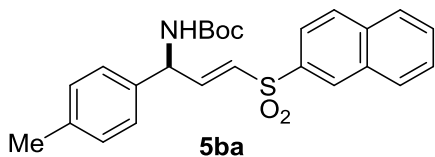
***tert*-Butyl (*S,E*)-(1-(4-methoxyphenyl)-3-(phenylsulfonyl)allyl)carbamate (**5ac**)**



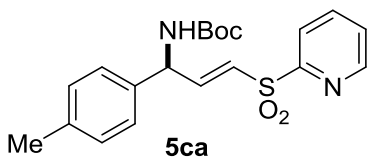
The title compound **5ac** was prepared from 2-nitroethyl sulfone **2a** and *N*-Boc imine **4c** following the general procedure. Yield: 0.042 g (56%). White solid. m. p. = 115–119 °C. $[\alpha]_D^{24} = -16.0$ ($c = 0.5$, CHCl₃). ¹H NMR (300 MHz,

CDCl₃) δ 7.97 – 7.82 (m, 2H), 7.71 – 7.45 (m, 3H), 7.13 (d, $J = 8.7$ Hz, 2H), 7.11 – 7.04 (m, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.48 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.40 (s, 1H), 4.88 (s, 1H), 3.79 (s, 3H), 1.49 – 1.29 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 159.9, 154.8, 145.9, 140.5, 133.7, 131.0, 130.2, 129.5, 128.7, 127.9, 114.7, 80.6, 55.5, 54.7, 28.4. UPLC-DAD-QTOF: C₂₁H₂₆NO₅S [M+H]⁺ calcd.: 404.1526, found: 404.1529. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (major.) = 35.5 min, t_R (minor.) = 50.8 min. 77% *ee*.

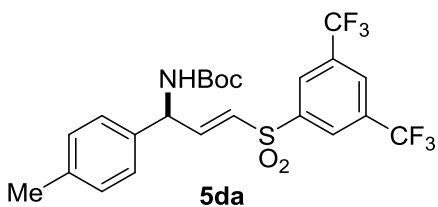
²³⁹ Ref. 156a, page 88.

***tert*-Butyl (*S,E*)-(3-(naphthalen-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5ba**)**

The title compound **5ba** was prepared from 2-nitroethyl sulfone **2b** and *N*-Boc imine **4a** following the general procedure. Yield: 0.044 g (20%). White solid. m. p.= 160–162 °C. $[\alpha]_D^{25} = -33.7$ ($c = 0.8$, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.49 (d, $J = 1.8$ Hz, 1H), 8.03 – 7.95 (m, 2H), 7.95 – 7.89 (m, 1H), 7.81 (dd, $J = 8.7, 1.9$ Hz, 1H), 7.72 – 7.57 (m, 2H), 7.21 – 7.06 (m, 5H), 6.53 (dd, $J = 15.1, 1.8$ Hz, 1H), 5.44 (s, 1H), 4.83 (s, 1H), 2.34 (s, 3H), 1.36 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 154.7, 145.9, 138.6, 137.1, 135.3, 135.1, 132.4, 131.0, 130.0, 129.8, 129.5, 129.5, 129.4, 128.1, 127.8, 127.2, 122.6, 80.5, 55.0, 28.3, 21.2. UPLC-DAD-QTOF: $\text{C}_{25}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ calcd.: 438.1734, found: 438.1730. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 0.50 mL/min, $\lambda = 230$ nm) t_R (major.) = 59.5 min, t_R (minor.) = 66.2 min. 77% *ee*.

***tert*-Butyl (*S,E*)-(3-(pyridin-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5ca**)**

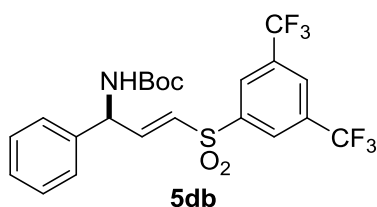
The title compound **5ca** was prepared from 2-nitroethyl sulfone **2c** and *N*-Boc imine **4a** following the general procedure. Yield: 0.031 g (16%). White solid. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.90 – 8.66 (m, 1H), 8.21 – 7.90 (m, 2H), 7.71 – 7.47 (m, 1H), 7.42 – 7.02 (m, 5H), 6.79 (dd, $J = 15.1, 1.9$ Hz, 1H), 5.52 (s, 1H), 4.98 (d, $J = 8.3$ Hz, 1H), 2.36 (s, 3H), 1.42 (s, 9H). UPLC-DAD-QTOF: $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4\text{SNa}$ $[\text{M}+\text{H}]^+$ calcd.: 411.1349, found: 411.1358. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 210$ nm) t_R (major.) = 25.0 min, t_R (minor.) = 31.5 min. 92% *ee*.

***tert*-Butyl (*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5da**)**

The title compound **5da** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4a** following the general procedure. Yield: 0.141 g (54%). White solid. m. p.= 149–152 °C. $[\alpha]_D^{25} = -8.9$ ($c = 0.28$, CHCl_3). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.40 – 8.29 (m, 2H), 8.12 (dd, $J = 2.0, 1.1$ Hz, 1H), 7.25 (dd, $J = 15.0, 4.9$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 6.52 (dd, $J = 15.0, 1.7$ Hz, 1H), 5.41 (s, 1H), 4.85 (s, 1H), 2.35 (s, 3H), 1.38 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 154.8, 149.6, 143.6, 139.2, 134.4, 133.5 (q, $J = 35.4, 33.7$ Hz), 130.3, 129.2, 128.2, 127.4, 124.4, 120.8, 80.9, 55.6, 28.4, 21.3. UPLC-DAD-QTOF: $\text{C}_{23}\text{H}_{24}\text{NO}_4\text{SF}_6$ $[\text{M}+\text{H}]^+$ calcd.: 524.1330, found: 524.1332. Chiral HPLC

(Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 28.1 min, t_R (minor.) = 36.4 min. >99% *ee*.

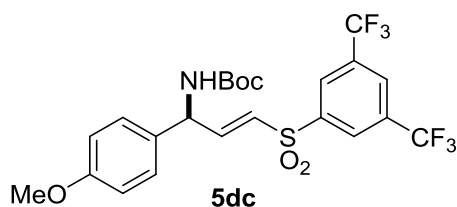
***tert*-Butyl (*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-phenylallyl)carbamate (5db)**



The title compound **5db** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4b** following the general procedure. Yield: 0.153 g (60%). White solid. m. p.= 131–135 °C. $[\alpha]_D^{24} = -32.0$ ($c=1$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 8.34 (d, $J = 1.9$ Hz, 2H), 8.12 (d, $J = 2.0$ Hz, 1H),

7.45 – 7.18 (m, 6H), 6.53 (dd, $J = 15.0, 1.7$ Hz, 1H), 5.46 (s, 1H), 4.87 (s, 1H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.8, 149.3, 143.4, 137.4, 133.4 (q, $J = 34.9$ Hz), 129.6, 129.3, 129.1, 128.2, 127.4, 125.2, 120.1, 81.0, 55.7, 28.3. UPLC-DAD-QTOF: $\text{C}_{22}\text{H}_{21}\text{NO}_4\text{SF}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd.: 532.0993, found: 532.1001. Chiral HPLC (Chiralpak IC; 99:1 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 60.5 min, t_R (minor.) = 73.1 min. >99% *ee*.

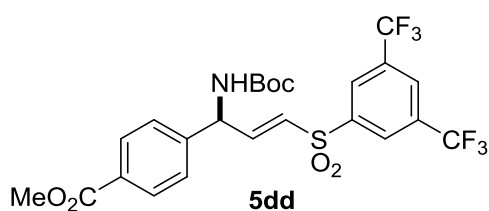
***tert*-Butyl (*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)allyl)carbamate (5dc)**



The title compound **5dc** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4c** following the general procedure. Yield: 0.194 g (72%). White solid. m. p.= 139–142 °C. $[\alpha]_D^{24} = -39.6$ ($c=1$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 8.34 (d, $J = 1.6$ Hz, 2H),

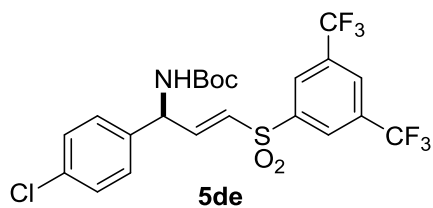
8.12 (s, 1H), 7.25 (dd, $J = 14.9, 4.9$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.51 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.39 (s, 1H), 4.82 (s, 1H), 3.81 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 160.1, 154.7, 149.6, 143.5, 133.4 (q, $J = 34.7$ Hz), 128.9, 128.7, 128.2, 127.2, 124.3, 120.7, 114.9, 80.8, 55.5, 55.2, 28.3. UPLC-DAD-QTOF: $\text{C}_{23}\text{H}_{24}\text{NO}_5\text{SF}_6$ $[\text{M}+\text{H}]^+$ calcd.: 540.1279, found: 540.1277. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 40.9 min, t_R (minor.) = 49.8 min. >99% *ee*.

Methyl **(S,E)-4-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-((tert-butoxycarbonyl)amino)allyl)benzoate (5dd)**



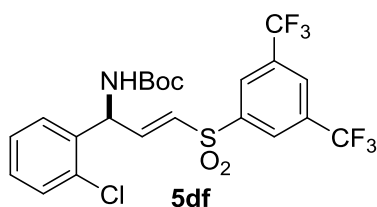
The title compound **5dd** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4d** following the general procedure. Yield: 0.142 g (50%). White solid. ^1H NMR (300 MHz, CDCl_3) δ 8.35 (s, 2H), 8.13 (s, 1H), 8.06 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.26 (dd, $J = 15.0, 5.0$ Hz, 1H), 6.53 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.53 (s, 1H), 4.90 (s, 1H), 3.94 (s, 3H), 1.39 (s, 9H). UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{23}\text{NO}_6\text{SF}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ calcd.: 590.1048, found: 590.1051. Chiral HPLC (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_{R} (minor.) = 34.0 min, t_{R} (major.) = 38.1 min. 90% *ee*.

tert-Butyl **(S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-chlorophenyl)allyl)carbamate (5de)**



The title compound **5de** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4e** following the general procedure. Yield: 0.138 g (51%). White solid. ^1H NMR (300 MHz, CDCl_3) δ 8.34 (s, 2H), 8.13 (s, 1H), 7.36 (dd, $J = 8.5, 2.0$ Hz, 2H), 7.25 – 7.21 (m, 1H), 7.18 (dd, $J = 8.5, 2.0$ Hz, 2H), 6.52 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.46 (d, $J = 7.1$ Hz, 1H), 4.89 (d, $J = 7.4$ Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.6, 148.4, 143.3, 136.0, 135.1, 133.5 (q, $J = 34.8$ Hz), 129.9, 129.8, 128.7, 128.2, 127.4, 124.3, 120.7, 81.2, 55.0, 28.3. UPLC-DAD-QTOF: $\text{C}_{22}\text{H}_{20}\text{NO}_4\text{SF}_6\text{ClNa}$ $[\text{M}+\text{Na}]^+$ calcd.: 566.0603, found: 566.0601. Chiral HPLC (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_{R} (major.) = 16.6 min, t_{R} (minor.) = 19.2 min. >99% *ee*.

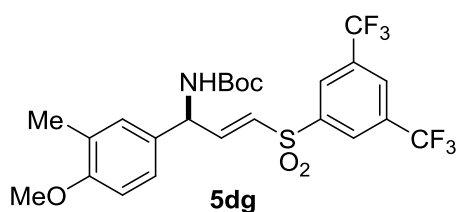
tert-Butyl **(S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(2-chlorophenyl)allyl)carbamate (5df)**



The title compound **5df** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4f** following the general procedure. Yield: 0.027 g (10%). White solid. ^1H NMR (300 MHz, CDCl_3) δ 8.36 (d, $J = 1.5$ Hz, 2H), 8.15 (s, 1H), 7.46 – 7.26 (m, 4H), 6.53 (d, $J = 15.1$ Hz, 1H), 5.96 – 5.79 (m, 1H), 5.22 (d, $J = 8.1$ Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.7, 148.6, 143.3, 135.3, 133.4 (q, $J = 34.6$ Hz), 130.8, 130.4, 129.8, 129.3, 128.2, 127.9, 127.3, 124.3, 120.7, 81.1, 53.7, 28.3. UPLC-DAD-QTOF: $\text{C}_{22}\text{H}_{21}\text{NO}_4\text{SF}_6\text{Cl}$ $[\text{M}+\text{H}]^+$ calcd.: 544.0779,

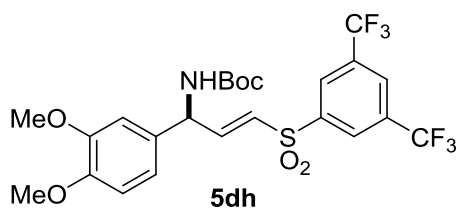
found: 544.0783 Chiral HPLC (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 29.2 min, t_R (major.) = 47.7 min. 68% *ee*.

***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxy-3-methylphenyl)allyl)carbamate (5dg)**

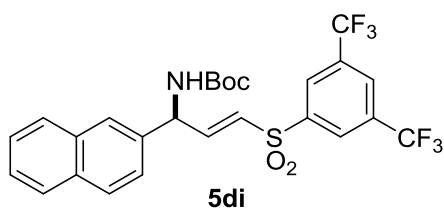


The title compound **5dg** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4g** following the general procedure. Yield: 0.194 g (72%). White solid. m. p. = 144–149 °C. $[\alpha]_D^{24} = -42.6$ (c=1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.35 (s, 2H), 8.11 (s, 1H), 7.21 (dd, $J = 15.0, 4.9$ Hz, 1H), 7.04 – 6.95 (m, 2H), 6.80 (d, $J = 8.2$ Hz, 1H), 6.51 (dd, $J = 15.0, 1.7$ Hz, 1H), 5.34 (brs, 1H), 4.79 (brs, 1H), 3.83 (s, 3H), 2.20 (s, 3H), 1.38 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 158.3, 154.7, 149.9, 143.7, 142.2, 133.4 (q, $J = 34.9$ Hz), 129.7, 128.8, 128.2, 127.2, 126.0, 124.3, 120.7, 110.6, 80.8, 55.6, 31.1, 28.3, 16.4. UPLC-DAD-QTOF: C₂₄H₂₆NO₄SF₆ [M+H]⁺ calcd.: 554.1436, found: 554.1439. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 32.1 min, t_R (minor.) = 38.5 min. >99% *ee*.

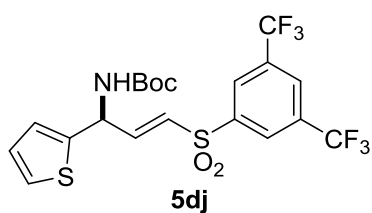
***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(3,4-dimethoxyphenyl)allyl)carbamate (5dh)**



The title compound **5dh** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4h** following the general procedure. Yield: 0.170 g (60%). White solid. m. p. = 147–151 °C. $[\alpha]_D^{24} = -40.3$ (c=1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.35 (s, 2H), 8.12 (s, 1H), 7.27 (dd, $J = 15.0, 4.8$ Hz, 1H), 6.90 – 6.81 (m, 1H), 6.80 – 6.70 (m, 2H), 6.52 (dd, $J = 15.0, 1.8$ Hz, 1H), 5.38 (s, 1H), 4.82 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.39 (s, 9H). UPLC-DAD-QTOF: C₂₄H₂₆NO₆SF₆ [M+H]⁺ calcd.: 570.1385, found: 570.1389. Chiral HPLC (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 15.1 min, t_R (major.) = 17.2 min. >99% *ee*.

tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(naphthalen-2-yl)allyl carbamate (5di)

The title compound **5di** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4i** following the general procedure. Yield: 0.126 g (45%). White solid. m. p. = 121–124 °C. $[\alpha]_D^{23} = -39.4$ (c=1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.36 (s, 2H), 8.13 (s, 1H), 7.82 (ddd, *J* = 13.5, 7.3, 3.9 Hz, 3H), 7.68 (s, 1H), 7.53 (dt, *J* = 6.2, 3.4 Hz, 2H), 7.37 (dd, *J* = 15.0, 4.8 Hz, 1H), 7.31 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.60 (dd, *J* = 15.0, 1.6 Hz, 1H), 5.64 (brs, 1H), 5.13 (brs, 1H), 1.40 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 149.0, 143.3, 134.6, 133.2 (q, *J* = 34.6 Hz), 133.2, 133.1, 129.5, 128.0, 127.9, 127.7, 127.1, 126.8, 126.4, 124.5, 124.1, 120.5, 80.8, 55.6, 28.1. UPLC-DAD-QTOF: C₂₆H₂₄NO₄SF₆ [M+H]⁺ calcd.: 560.1330, found: 560.1334. Chiral HPLC (Chiralpak AD-H; 99:1 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) *t*_R (minor.) = 41.7 min, *t*_R (major.) = 60.5 min. 88% *ee*.

tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(thiophen-2-yl)allyl carbamate (5dj)

The title compound **5dj** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4j** following the general procedure. Yield: 0.103 g (40%). White solid. ¹H NMR (300 MHz, CDCl₃) δ 8.35 (s, 2H), 8.13 (s, 1H), 7.34 – 7.30 (m, 1H), 7.26 (d, *J* = 5.0 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.58 (dd, *J* = 15.0, 1.7 Hz, 1H), 5.74 (s, 1H), 4.90 (s, 1H), 1.40 (s, 9H). UPLC-DAD-QTOF: C₂₀H₂₀NO₄S₂F₆ [M+H]⁺ calcd.: 516.0738, found: 516.0737. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) *t*_R (major.) = 24.5 min, *t*_R (minor.) = 31.1 min. 94% *ee*.

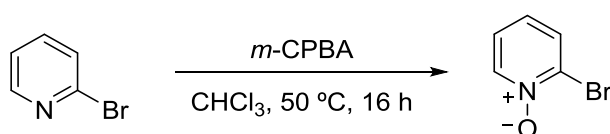
6.4. Experimental section for Chapter 3

6.4.1. Enantioselective α -amination of 2-(cyanomethyl)pyridine *N*-oxides with azodicarboxylates

6.4.1.1. Preparation of 2-(cyanomethyl)pyridine *N*-oxides

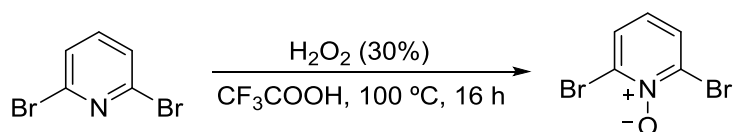
6.4.1.1.1. Oxidation of 2-bromo pyridines

6.4.1.1.1.1. Synthesis of 2-bromopyridine *N*-oxide²⁴⁰



To a solution of 2-bromopyridine (1 equiv., 10 mmol, 1.58 g) in CHCl_3 (20 mL), *m*-CPBA (1.4 equiv., 14 mmol, 4.35 g (70% w/w)) was added and the resulting mixture was stirred at 50 °C for 16 hours. The organic layer was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (Hexane:AcOEt, 50:50 to 0:100) to afford pure 2-bromopyridine *N*-oxide. Yield: 4.15 g (80%). Grey oil. IR (ν/cm^{-1}): 3096, 3035, 1697, 1589, 1541, 1411, 1251, 1121, 1065, 1037, 838, 762, 674, 565, 519, 446. ^1H NMR (300 MHz, CDCl_3) δ 8.40 – 8.38 (m, 1H), 7.68 – 7.64 (m, 1H), 7.28 – 7.22 (m, 1H), 7.14 – 7.08 (m, 1H).

6.4.1.1.1.2. Synthesis of 2,6-dibromopyridine *N*-oxide²⁴¹



To an ice-cold solution of 2,6-dibromopyridine (1 equiv., 10 mmol, 2.37 g) in trifluoroacetic acid (12 mL) was added drop-wise an aqueous solution of H_2O_2 (30 %) (0.33 mL/mmol, 3.3 mL). The reaction mixture was stirred at 100 °C for 16 hours and then cooled to rt, poured into 50 mL of water and the precipitate was filtered. The solid

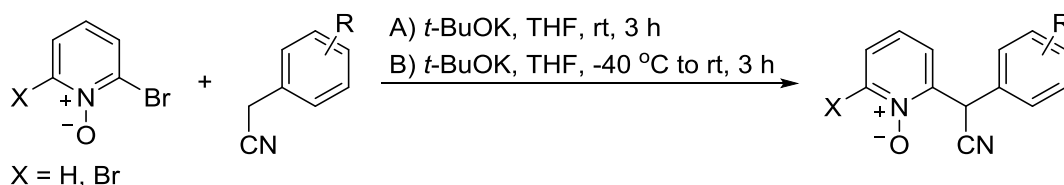
²⁴⁰ Adapted from: Brasse, M.; Cámpora, J.; Palma, P.; Álvarez, E. *Organometallics* **2008**, *27*, 4711–4723.

²⁴¹ Adapted from: Palmer, J. T.; Luniss, C. J.; Offermann, D. A.; Axford, L. C.; Blair, M.; Mitchell, D.; Palmer, M.; Steele, C.; Atherall, F.; Watson, D.; Haydon, D.; Czaplowski, L.; Davies, D.; Collins, I.; Tyndall, E. M.; Andrau, L.; Pitt, G. R. W. Bacteria topoisomerase II inhibiting 2-ethylcarbamoylamino-1,3-benzothiazol-5-yls. WO 2012045124, 2012.

Experimental section

obtained was the starting material. The filtrate was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with 0.5 M K_2CO_3 solution (3 x 20 mL). The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure to afford 2,6-dibromopyridine *N*-oxide. Yield: 2.10 g (84%). White solid. m. p.= 180–183 °C. IR (v/cm^{-1}): 3090, 3034, 1696, 1554, 1403, 1268, 1125, 1066, 1032, 808, 743, 660, 567, 528, 444. ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, $J = 9$ Hz, 2H), 6.93 (t, $J = 6, 9$ Hz, 1H).

6.4.1.1.2. Synthesis of 2-(cyanomethyl)pyridine *N*-oxides 13(a–f)



GENERAL PROCEDURE A

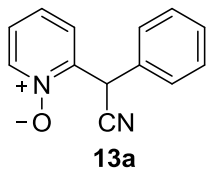
To a solution of potassium *tert*-butoxide (2 equiv., 6 mmol, 0.673 g) in dry THF (10 mL) at room temperature, the corresponding 2-arylacetonitrile (1.5 equiv., 4.5 mmol) was added and the resulting mixture was stirred for 45 minutes at the same temperature. Afterwards, the corresponding 2-bromopyridine *N*-oxide (1 equiv., 3 mmol) was added as a solution in dry THF (5 mL) and the mixture was stirred for additional 3 hours at the same temperature. The reaction mixture was quenched with H_2O and diluted with CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over MgSO_4 and concentrated to afford the crude product which was purified by flash column chromatography on silica gel.

GENERAL PROCEDURE B

To a solution of potassium *tert*-butoxide (2 equiv., 6 mmol, 0.673 g) in dry THF (10 mL) at -40 °C, the corresponding 2-arylacetonitrile (1.5 equiv.) was added and the resulting mixture was stirred for 45 minutes at the same temperature. A solution of the corresponding 2-bromopyridine *N*-oxide (1 equiv., 3 mmol) in dry THF (5 mL) was added and the mixture was stirred for additional 3 hours at -40 °C and then allowed to warm to room temperature over 30 minutes. The reaction mixture was quenched with H_2O and diluted with CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over MgSO_4 and concentrated to afford the crude product which was purified by flash column chromatography on silica gel.

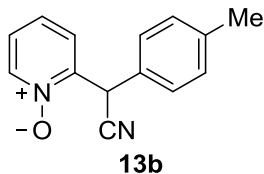
Note: Pyridine *N*-oxides **13(a–f)** decompose over time and should be stored in a refrigerator (at $-30\text{ }^{\circ}\text{C}$ they are stable for several months).

2-(Cyano(phenyl)methyl)pyridine *N*-oxide (**13a**)



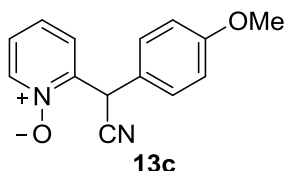
The title compound **13a** was prepared from 2-bromopyridine *N*-oxide and 2-phenylacetonitrile according to general procedure A. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.567 g (90 %). Yellow solid. m. p.= $112\text{--}115\text{ }^{\circ}\text{C}$. IR (v/cm^{-1}): 3110, 3052, 2894, 2246, 1489, 1438, 1246, 884, 794, 696. ^1H NMR (300 MHz, CDCl_3) δ 8.29 – 8.27 (m, 1H), 7.52 – 7.28 (m, 8H), 6.11 (s, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 146.2, 139.6, 132.0, 129.3, 12.9, 128.1, 125.8, 125.7, 125.4, 117.5, 36.8. UPLC-DAD-QTOF: $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ calcd.: 211.0871, found: 211.0863.

2-(Cyano(*p*-tolyl)methyl)pyridine *N*-oxide (**13b**)



The title compound **13b** was prepared from 2-bromopyridine *N*-oxide and 2-(*p*-tolyl)acetonitrile according to general procedure A. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.565 g (84%). Yellow solid. m. p.= $96\text{--}99\text{ }^{\circ}\text{C}$. IR (v/cm^{-1}): 3082, 3042, 3013, 2909, 2247, 1687, 1513, 1488, 1429, 1279, 1242, 837, 798, 765, 705. ^1H NMR (300 MHz, CDCl_3) δ 8.26 – 8.23 (m, 1H), 7.43 – 7.33 (m, 3H), 7.27 – 7.24 (m, 2H), 7.20 – 7.17 (m, 2H), 6.03 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 146.5, 139.6, 138.9, 130.0, 129.0, 128.1, 125.8, 125.6, 125.4, 117.7, 36.5, 21.1. UPLC-DAD-QTOF: $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ calcd.: 225.1028, found: 225.1046.

2-(Cyano(4-methoxyphenyl)methyl)pyridine *N*-oxide (**13c**)

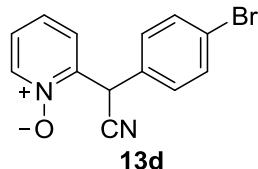


The title compound **13c** was prepared from 2-bromopyridine *N*-oxide and 2-(4-methoxyphenyl)acetonitrile according to general procedure A. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.511 mg (71%). Red oil. IR (v/cm^{-1}): 3110, 3071, 3013, 2934, 2837, 2245, 1607, 1583, 1509, 1429, 1365, 1178, 1027, 830, 762. ^1H NMR (300 MHz, CDCl_3) δ 8.21 – 8.19 (m, 1H), 7.38 – 7.33 (m, 3H), 7.23 – 7.20 (m, 2H), 6.87 – 6.84 (m, 2H), 5.95 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 159.8, 146.3, 139.5, 129.3, 125.8, 125.5, 125.1,

Experimental section

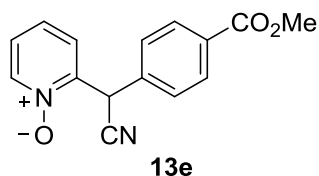
123.7, 117.7, 114.6, 55.3, 36.1. UPLC-DAD-QTOF: $C_{14}H_{13}N_2O_2$ $[M+H]^+$ calcd.: 241.0977, found: 241.0974.

2-((4-Bromophenyl)(cyano)methyl)pyridine *N*-oxide (**13d**)



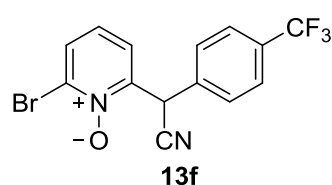
The title compound **13d** was prepared from 2-bromopyridine *N*-oxide and 2-(4-bromophenyl)acetonitrile according to general procedure A. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.760 g (88 %). Red oil. IR (ν/cm^{-1}): 3112, 3078, 3050, 3023, 2896, 2247, 1692, 1587, 1484, 1428, 1404, 1237, 1047, 1010, 824, 782, 729, 625. 1H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.24 (m, 1H), 7.53 – 7.50 (m, 3H), 7.39 – 7.39 (m, 2H), 7.32 – 7.29 (m, 2H), 6.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 139.8, 132.6, 131.2, 129.9, 125.3, 123.3, 117.3, 36.6. UPLC-DAD-QTOF: $C_{13}H_{10}N_2OBr$ $[M+H]^+$ calcd.: 288.9977, found: 288.9973.

2-(Cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (**13e**)



The title compound **13e** was prepared from 2-bromopyridine *N*-oxide and methyl 4-(cyanomethyl)benzoate according to general procedure B. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.643 g (80 %). Red oil. IR (ν/cm^{-1}): 3111, 3080, 3013, 2926, 2245, 1710, 1620, 1590, 1469, 1240, 1113, 1054, 840, 631. 1H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 8.06 – 8.02 (m, 2H), 7.58 – 7.49 (m, 3H), 7.32 – 7.29 (m, 2H), 6.16 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 145.7, 139.8, 136.9, 130.9, 130.6, 128.3, 126.1, 126.0, 125.5, 117.2, 52.4, 36.9. UPLC-DAD-QTOF: $C_{15}H_{13}N_2O_3$ $[M+H]^+$ calcd.: 269.0926, found: 269.0923.

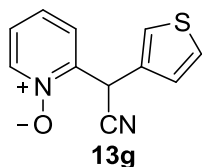
2-Bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine *N*-oxide (**13f**)



The title compound **13f** was prepared from 2,6-dibromopyridine *N*-oxide and 2-(4-(trifluoromethyl)phenyl)acetonitrile according to general procedure B. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 70:30 to 0:100). Yield: 0.897 g (84%). Red solid. m. p. = 92–96 °C. IR (ν/cm^{-1}): 3086, 3043, 2984, 2893, 2248, 1691, 1618, 1576, 1556, 1462, 1378, 1322, 1240, 1163, 1113, 1066, 857, 844, 783. 1H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.55 (m, 6H), 7.18 (t, J = 8.1 Hz, 1H), 6.12 (s, 1H). ^{13}C NMR (75

MHz, CDCl₃) δ 146.9, 135.7, 133.9, 133.0, 128.9, 126.4, 126.4, 125.5, 124.1, 117.0, 38.0. UPLC-DAD-QTOF: C₁₄H₉N₂OF₃Br [M+H]⁺ calcd.: 356.9850, found: 356.9843.

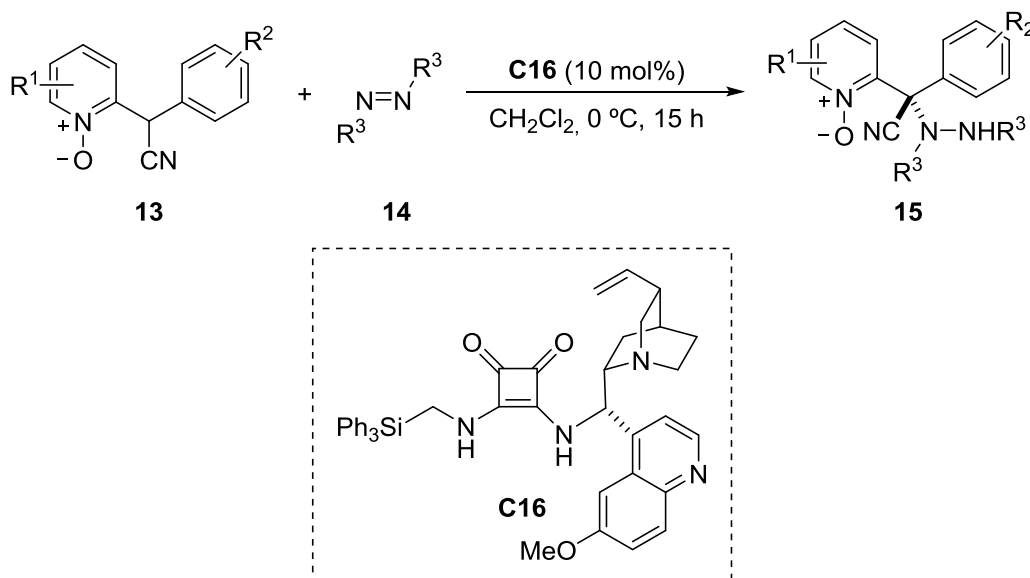
2-(Cyano(thiophen-3-yl)methyl)pyridine 1-oxide (**13g**)



The title compound **13g** was prepared from 2-bromopyridine *N*-oxide and 2-(thiophen-3-yl)acetonitrile according to general procedure B. The crude material was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 50:50 to 0:100). Yield: 0.383 g (60%).

Red oil. IR (v/cm⁻¹): 3114, 3083, 2890, 2240, 1711, 1604, 1483, 1427, 1272, 1237, 1142, 943, 837, 762, 621. ¹H NMR (300 MHz, CDCl₃) δ 8.30 – 8.28 (m, 1H), 7.51 – 7.50 (m, 1H), 7.45 – 7.42 (m, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.26 (m, 2H), 7.15 – 7.13 (m, 1H), 6.18 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 145.8, 139.6, 131.5, 127.6, 126.7, 126.0, 125.8, 125.2, 124.6, 117.3, 32.5. UPLC-DAD-QTOF: C₁₁H₉N₂OS [M+H]⁺ calcd.: 217.0436, found: 217.0428.

6.4.1.2. General procedure for the enantioselective α -amination



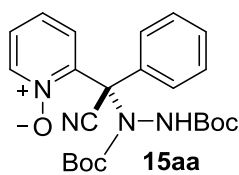
To a solution of the corresponding pyridine *N*-oxide **13** (1 equiv., 0.2 mmol) in methylene chloride (1 mL), catalyst **C16** (0.1 equiv, 0.02 mmol, 0.014 g) and the corresponding azodicarboxylate **14** (1.5 equiv., 0.3 mmol) were added at 0 °C. The resulting mixture was stirred for 15 hours at the same temperature. Then, the reaction mixture was quenched with HCl 0.1 M (7 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The residues were purified by flash column chromatography on silica gel

Experimental section

(Hex:EtOAc 80:20 to 0:100) to afford the expected adducts. In general, these compounds were detected as a 1:1 mixture of rotamers by ^1H NMR analysis (in $\text{DMSO-}d_6$ at 70°C).

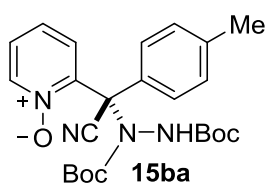
Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing DBU as a chiral Brønsted base.

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(phenyl)methyl)pyridine *N*-oxide (15aa)



The title compound **15aa** was prepared from 2-(cyano(phenyl)methyl)pyridine *N*-oxide **13a** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.078 g (88 %). White foam. $[\alpha]_D^{22} = +41.3$ ($c = 1.96$, CH_2Cl_2). IR (v/cm^{-1}): 3330, 2977, 2931, 2251, 1717, 1604, 1428, 1366, 1245, 1149, 1051, 912, 839, 729. ^1H NMR (500 MHz, 70°C , $\text{DMSO-}d_6$) δ 8.26 (d, $J = 6.1$ Hz, 1H) (rotamer A), 8.18 (d, $J = 6.1$ Hz, 1H) (rotamer B), 7.59 – 7.30 (m, 8H), 1.37 (s, 9H), 1.26 (brs, 9H). ^{13}C NMR (126 MHz, 70°C , $\text{DMSO-}d_6$) δ 154.5, 153.7, 152.2, 152.0, 145.2, 144.7, 139.6, 139.1, 132.5, 131.8, 128.3, 128.3, 127.9, 127.8, 127.4, 127.4, 126.0, 125.7, 125.5, 124.1, 123.7, 115.1, 114.7, 82.2, 82.1, 79.5, 66.67, 66.4, 27.4, 27.4, 27.1. UPLC-DAD-QTOF: $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 441.2138, found: 441.2141. Elem. Anal. calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_5$ (440.50): C, 62.71; H, 6.41; N, 12.72. Found: C, 62.47; H, 6.35; N, 12.99. Chiral HPLC (Chiralpak IC; 60:40 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 8.1 min, t_R (major.) = 10.4 min. 90% *ee*.

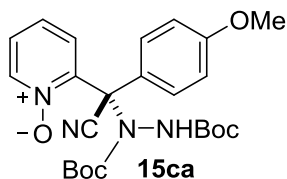
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(*p*-tolyl)methyl)pyridine *N*-oxide (15ba)



The title compound **15ba** was prepared from 2-(cyano(*p*-tolyl)methyl)pyridine *N*-oxide **13b** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.072 g (79%). White foam. $[\alpha]_D^{23} = +50.9$ ($c = 1.01$, CH_2Cl_2). IR (v/cm^{-1}): 3174, 2976, 2930, 2252, 1716, 1607, 1428, 1365, 1248, 1150, 1050, 1025, 1008, 765. ^1H NMR (500 MHz, 70°C , $\text{DMSO-}d_6$) δ 8.25 (brs, 1H) (rotamer A), 8.17 (d, $J = 6.3$ Hz, 1H) (rotamer B), 7.58 – 7.44 (m, 3H), 7.25 (d, $J = 7.7$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.15 (dd, $J = 11.6, 8.1$ Hz, 2H), 2.30 (s, 3H) (rotamer A), 2.30 (s, 3H) (rotamer B), 1.45 – 1.32 (s, 9H), 1.29 (brs, 9H). ^{13}C NMR (126 MHz, 70°C , $\text{DMSO-}d_6$) δ 155.3, 154.3, 153.9, 152.6, 145.5, 145.0, 140.0, 139.8, 139.5, 138.6, 138.4, 129.5, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 126.6, 126.4, 126.2, 125.4, 125.1, 124.9, 124.8, 124.6, 124.3, 116.4, 115.2, 82.9,

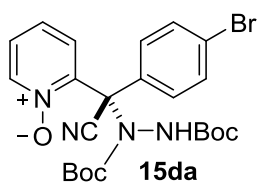
82.4, 80.7, 80.5, 79.7, 79.6, 66.9, 66.2, 27.8, 27.8, 27.6, 20.6. UPLC-DAD-QTOF: $C_{24}H_{31}N_4O_5$ $[M+H]^+$ calcd.: 455.2294, found: 455.2297. Chiral HPLC (Chiralpak IA; 80:20 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 21.8 min, t_R (major.) = 48.7 min. 82% *ee*.

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-methoxyphenyl)methyl)pyridine *N*-oxide (15ca)



The title compound **15ca** was prepared from 2-(cyano(4-methoxy)methyl)pyridine *N*-oxide **13c** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.074 g (79%). White foam. $[\alpha]_D^{23} = +47.0$ ($c = 1.02$, CH_2Cl_2). IR (ν/cm^{-1}): 3325, 2976, 2932, 2839, 2233, 1720, 1607, 1512, 1429, 1367, 1253, 1152, 1031, 841, 766. 1H NMR (500 MHz, $70^\circ C$, $DMSO-d_6$) δ 8.25 (brs, 1H) (rotamer A), 8.18 (d, $J = 6.1$ Hz, 1H) (rotamer B), 7.49 (m, 3H), 7.26 (m, 2H), 6.90 (m, 2H), 3.77 (s, 3H) (rotamer A), 3.76 (s, 3H) (rotamer B), 1.36 (s, 9H), 1.31 (brs, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 153.8, 152.3, 152.1, 145.5, 139.7, 139.2, 129.4, 126.0, 125.7, 125.3, 124.2, 123.8, 123.6, 115.3, 115.0, 113.2, 113.2, 82.2, 82.0, 79.3, 66.1, 65.9, 54.9, 27.5, 27.5, 27.2, 27.2. UPLC-DAD-QTOF: $C_{24}H_{31}N_4O_6$ $[M+H]^+$ calcd.: 471.2244, found: 471.2247. Chiral HPLC (Chiralpak IA; 80:20 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 28.3 min, t_R (major.) = 65.7 min. 76% *ee*.

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine 1-oxide (15da)

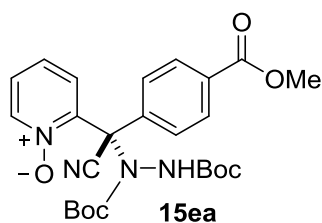


The title compound **15da** was prepared from 2-((4-bromophenyl)(cyano)methyl)pyridine 1-oxide **13d** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.094 g (90%). White foam. $[\alpha]_D^{23} = +18.0$ ($c = 1.00$, CH_2Cl_2). IR (ν/cm^{-1}): 3307, 2976, 2931, 2239, 1717, 1587, 1366, 1245, 1147, 1010, 763, 734. 1H NMR (500 MHz, $70^\circ C$, $DMSO-d_6$) δ 8.27 (d, $J = 6.0$ Hz, 1H) (rotamer A), 8.21 (d, $J = 6.2$ Hz, 1H) (rotamer B), 7.67 – 7.43 (m, 5H), 7.31 (d, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 8.3$ Hz, 1H), 1.37 (s, 9H), 1.28 (brs, 9H). ^{13}C NMR (126 MHz, $70^\circ C$, $DMSO-d_6$) δ 154.7, 153.9, 152.2, 152.0, 144.7, 144.2, 139.7, 139.3, 132.1, 131.4, 130.5, 130.0, 129.8, 126.3, 126.1, 125.5, 125.1, 124.4, 124.1, 122.0, 114.9, 114.3, 82.6, 82.4, 79.5, 66.2, 65.9, 27.5, 27.4, 27.2, 27.2. UPLC-DAD-QTOF: $C_{23}H_{27}N_4O_5Br$ $[M+H]^+$ calcd.: 519.1243, found: 519.1255. Elem. Anal. calcd for $C_{23}H_{27}N_4O_5Br$ (519.40): C, 53.19; H, 5.24; N, 10.79. Found: C, 52.92; H,

Experimental section

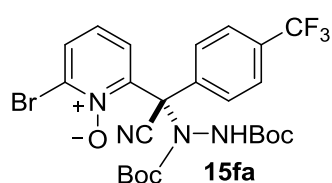
5.16; N, 10.10. Chiral HPLC (Chiralpak IA; 90:10 hexane:EtOH; 1.00 mL/min, $\lambda = 210$ nm) t_R (minor.) = 26.8 min, t_R (major.) = 56.6 min. 92% *ee*.

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15ea)



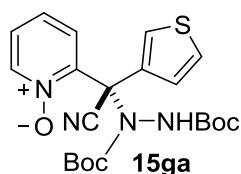
The title compound **15ea** was prepared from 2-(cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide **13e** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.085 g (86%). White foam. $[\alpha]_D^{23} = +20.1$ ($c = 1.79$, CH_2Cl_2). IR (ν/cm^{-1}): 3309, 2976, 2931, 2870, 2288, 1719, 1609, 1367, 1277, 1248, 1150, 1112, 764. ^1H NMR (500 MHz, 70 °C, $\text{DMSO}-d_6$) δ 8.27 (brs, 1H) (rotamer A), 8.21 (d, $J = 6.3$ Hz, 1H) (rotamer B), 7.92 (t, $J = 9.0$ Hz, 2H), 7.65 – 7.42 (m, 5H), 3.87 (s, 3H), 1.38 (s, 9H), 1.26 (brs, 9H). ^{13}C NMR (126 MHz, 70 °C, $\text{DMSO}-d_6$) δ 165.2, 152.2, 152.0, 144.6, 139.7, 139.3, 136.8, 130.0, 128.3, 128.1, 126.4, 126.2, 125.7, 125.2, 124.5, 124.2, 114.9, 114.3, 82.6, 82.5, 79.6, 66.0, 51.7, 27.5, 27.4, 27.2. UPLC-DAD-QTOF: $\text{C}_{25}\text{H}_{31}\text{N}_4\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 499.2193, found: 499.2196. Chiral HPLC (Chiralpak IA; 60:40 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 13.9 min, t_R (major.) = 23.0 min. 93% *ee*.

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(trifluoromethyl)phenyl)methyl)-6-bromopyridine *N*-oxide (15fa)



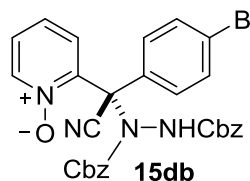
The title compound **15fa** was prepared from 2-bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine *N*-oxide **13f** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.099 g (84 %). White foam. $[\alpha]_D^{23} = +42.3$ ($c = 1.98$, CH_2Cl_2). IR (ν/cm^{-1}): 3323, 2978, 2932, 2296, 1719, 1618, 1367, 1323, 1244, 1122, 1068, 844, 733, 702. ^1H NMR (300 MHz, 70 °C, $\text{DMSO}-d_6$) δ 8.05 (dt, $J = 8.3$, 2.0 Hz, 1H), 7.73 (d, $J = 8.3$ Hz, 2H), 7.55 (m, 4H), 1.40 (s, 9H) (rotamer B), 1.38 (s, 9H) (rotamer A), 1.28 (brs, 9H). ^{13}C NMR (75 MHz, DMSO) δ 154.6, 153.7, 152.1, 152.0, 145.9, 145.6, 136.3, 136.0, 132.7, 132.2, 130.9, 130.7, 129.3 (q, $J = 31.8$ Hz), 128.8, 128.6, 125.2, 125.0, 124.7, 124.2, 121.6, 114.6, 113.9, 82.9, 82.7, 79.7, 66.8, 66.5, 27.4, 27.3, 27.2. UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{27}\text{BrF}_3\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 587.1117, found: 587.1119. Chiral HPLC (Chiralpak IA; 95:5 hexane:EtOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 35.7 min, t_R (major.) = 91.0 min. 88% *ee*.

(S)-2-((1,2-bis(tert-butoxycarbonyl)hydrazinyl)(cyano)(thiophen-3-yl)methyl)pyridine N-oxide (15ga)



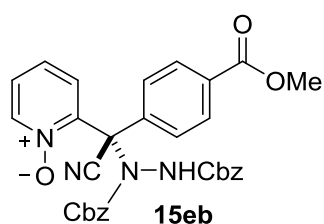
The title compound **15ga** was prepared from 2-(cyano(thiophen-3-yl)methyl)pyridine *N*-oxide **13g** and di-*tert*-butyl azodicarboxylate **14a** according to the general procedure. Yield: 0.072 g (81%). White foam. $[\alpha]_{\text{D}}^{23} = +49.3$ ($c = 0.88$, CH_2Cl_2). IR (v/cm^{-1}): 3198, 2976, 2931, 2244, 1719, 1586, 1429, 1367, 1249, 1152, 771. ^1H NMR (300 MHz, CDCl_3) δ 8.34 (d, $J = 5.9$ Hz, 1H), 8.17 (d, $J = 6.1$, 1H) (minor), 8.00 (brs, 1H), 7.59 (d, $J = 5.3$ Hz, 1H), 7.46 – 7.15 (m, 4H), 6.99 (dd, $J = 8.3$, 2.1 Hz, 1H), 1.38 (s, 9H) (minor), 1.35 (s, 9H) (minor), 1.33 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 155.4, 152.4, 145.3, 140.5, 140.0, 136.5, 128.0, 127.5, 127.2, 126.8, 126.7, 126.4, 126.1, 125.9, 125.7, 125.4, 116.3, 84.0, 81.7, 81.2, 64.3, 28.1, 28.0. UPLC-DAD-QTOF: $\text{C}_{21}\text{H}_{27}\text{N}_4\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$ calcd.: 447.1702, found: 447.1707. Chiral HPLC (Chiralpak IA; 70:30 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_{R} (minor.) = 15.1 min, t_{R} (major.) = 23.8 min. 90% *ee*.

(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine N-oxide (15db)



The title compound **15db** was prepared from 2-((4-bromophenyl)(cyano)methyl)pyridine *N*-oxide **13d** and dibenzyl azodicarboxylate **14b** according to the general procedure. Yield: 0.094 g (80%). White foam. $[\alpha]_{\text{D}}^{23} = +47.1$ ($c = 1.02$, CH_2Cl_2). IR (v/cm^{-1}): 3330, 2976, 2931, 2250, 1716, 1604, 1365, 1244, 1147, 755, 732, 695. ^1H NMR (500 MHz, 70 °C, $\text{DMSO}-d_6$) δ 8.26 (d, $J = 6.4$ Hz, 1H) (rotamer A), 8.19 (d, $J = 6.4$ Hz, 1H) (rotamer B), 7.78 – 6.88 (m, 17H), 5.19 (s, 2H), 5.08 – 4.91 (m, 2H). ^{13}C NMR (126 MHz, 70 °C, $\text{DMSO}-d_6$) δ 153.4, 153.3, 143.7, 143.5, 139.7, 139.3, 135.5, 134.9, 131.4, 130.9, 130.6, 129.8, 129.7, 127.8, 127.5, 127.4, 127.0, 126.4, 126.1, 125.3, 124.9, 124.4, 124.1, 122.3, 114.4, 113.9, 78.1, 67.9, 67.8, 66.1. UPLC-DAD-QTOF: $\text{C}_{29}\text{H}_{24}\text{BrN}_4\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 587.0930, found: 587.0948. Elem. Anal. calcd for $\text{C}_{29}\text{H}_{23}\text{BrN}_4\text{O}_5$ (586.08): C, 59.30; H, 3.95; N, 9.54. Found: C, 59.37; H, 3.87; N, 9.41. Chiral HPLC (Chiralpak IA; 60:40 hexane:EtOH; 0.80 mL/min, $\lambda = 210$ nm) t_{R} (minor.) = 17.3 min, t_{R} (major.) = 27.6 min. 90% *ee*.

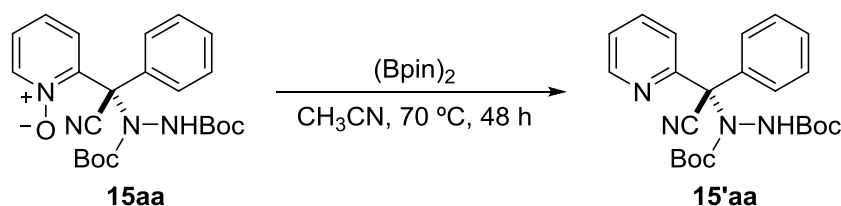
(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine N-oxide (15eb)



The title compound **15eb** was prepared from 2-(cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine N-oxide **13e** and dibenzyl azodicarboxylate **14b** according to the general procedure. Yield: 0.096 g (85%). White foam. $[\alpha]_D^{23} = +13.7$ ($c = 1.39$, CH_2Cl_2). IR (ν/cm^{-1}): 3301, 2951, 2236, 1721, 1609, 1430, 1278, 1111, 733, 697. ^1H NMR (500 MHz, 70°C , $\text{DMSO}-d_6$) δ 8.26 (d, $J = 6.4$ Hz, 1H) (rotamer A), 8.19 (d, $J = 6.3$ Hz, 1H) (rotamer B), 7.87 (d, $J = 8.2$ Hz, 2H), 7.46 (m, 6H), 7.38 – 7.21 (m, 7H), 7.15 (bs, 1H), 5.19 (m, 2H), 4.98 (m, 2H), 3.94 – 3.79 (m, 3H). ^{13}C NMR (126 MHz, 70°C , $\text{DMSO}-d_6$) δ 165.1, 153.4, 153.3, 143.6, 143.4, 139.7, 139.2, 136.6, 136.2, 135.4, 134.9, 130.1, 128.4, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4, 127.0, 126.5, 126.2, 125.4, 125.0, 124.5, 124.2, 114.4, 113.8, 67.9, 67.9, 66.0, 51.5. UPLC-DAD-QTOF: $\text{C}_{31}\text{H}_{27}\text{BrN}_4\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 567.1880, found: 567.1876. Elem. Anal. calcd for $\text{C}_{31}\text{H}_{26}\text{N}_4\text{O}_7$ (566.57): C, 65.72; H, 4.63; N, 9.89. Found: C, 65.53; H, 4.67; N, 9.34. Chiral HPLC (Chiralpak IA; 70:30 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 52.3 min, t_R (major.) = 63.2 min. 90% *ee*.

6.4.1.3. Elaboration of adducts

6.4.1.3.1. Reduction of N-oxide group on adduct **15aa**²⁴²

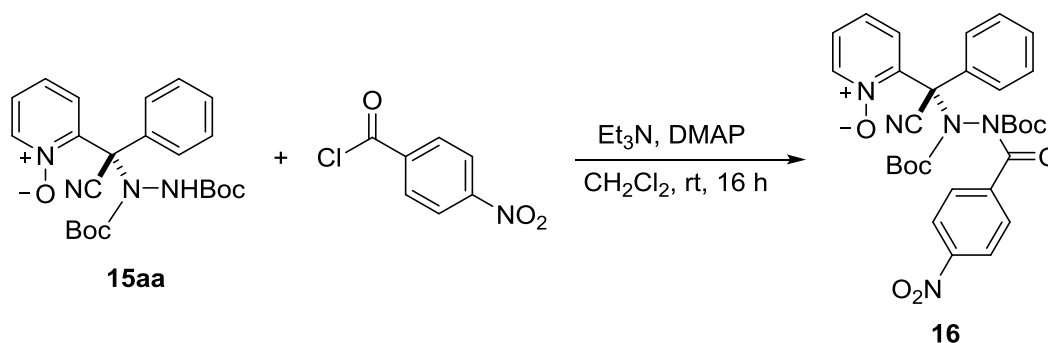


A solution of adduct **15aa** (0.440 g, 1 mmol, 1 equiv.) in acetonitrile (10 mL) was stirred in an oven-dried reaction vial, bis(pinacolato)diboron ((pinB)₂) (0.762 g, 3 mmol, 3 equiv.) was added and the mixture was stirred at 70°C for 24 h. Afterwards 3 equiv. more of (pinB)₂ were added and the reaction stirred at 70°C for additional 24 hours. Then, ethylenediamine (8 mL, 120 mmol, 120 equiv.) was added to the mixture, and the stirring was continued for 1 hour at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was

²⁴² Procedure adapted from: Kokatla, H. P.; Thompson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. J. *Org. Chem.* **2011**, *76*, 7842–7848.

dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80/20 to 50/50) to give the desired compound as a colourless oil. Yield: 0.327 g (77 %). $[\alpha]_{\text{D}}^{25} = +22.6$ ($c = 1.00$, CH_2Cl_2). IR (v/cm^{-1}): 2977, 2931, 2252, 1720, 1451, 1367, 1244, 1149, 912, 729, 697. ^1H NMR (300 MHz, CDCl_3) δ 8.72 – 8.54 (m, 1H), 7.81 (td, $J = 7.7, 1.8$ Hz, 1H), 7.65 (dd, $J = 23.5, 7.0$ Hz, 1H), 7.50 – 7.31 (m, 5H), 6.65 (s, 1H), 1.45 – 1.18 (m, 18H). UPLC-DAD-QTOF: $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ calcd.: 425.2183, found: 425.2179.

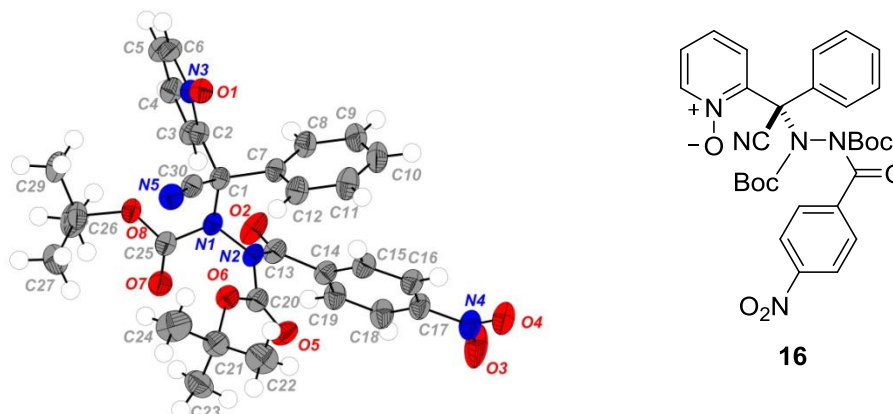
6.4.1.3.2. Acylation of adduct **15aa**.²⁴³ Determination of the absolute configuration.



To a solution of **15aa** (1 equiv., 0.30 mmol, 0.130 g) in CH_2Cl_2 (4 mL), Et_3N (16 equiv., 4.8 mmol, 0.67 mL) and 4-dimethylaminopyridine (DMAP) (0.1 equiv., 0.03 mmol, 0.037 g) were added at 0 °C. After stirring the reaction mixture at room temperature for 16 hours, CH_2Cl_2 was evaporated under reduce pressure. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc 50:50 to 20:80) to give the desired compound as a white solid. The solid was recrystallized in a benzene/hexane mixture; Yield: 106 mg (60%). White solid. m. p.= 163–165 °C. IR (v/cm^{-1}): 2976, 2922, 2851, 2273, 1759, 1730, 1520, 1427, 1346, 1304, 1259, 1134, 838, 779, 756. $[\alpha]_{\text{D}}^{25} = +143.0$ ($c = 1.1$, 90% *ee*, CH_2Cl_2). ^1H NMR (300 MHz, CDCl_3) δ 8.70 – 8.51 (m, 1H), 8.52 – 8.24 (m, 1H), 8.24 – 7.92 (m, 3H), 7.79 – 7.57 (m, 1H), 7.57 – 7.21 (m, 4H), 7.15 – 6.82 (m, 1H), 6.82 – 6.57 (m, 1H), 6.57 – 6.26 (m, 1H), 1.59 – 1.37 (m, 18H). UPLC-DAD-QTOF: $\text{C}_{30}\text{H}_{32}\text{N}_5\text{O}_8$ $[\text{M}+\text{H}]^+$ calcd.: 590.2251, found: 590.2255.

Compound **16** was synthesized for X-Ray analysis purpose. CCDC 1453241 contains the supplementary crystallographic data for its structural analysis. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/deposit/>.

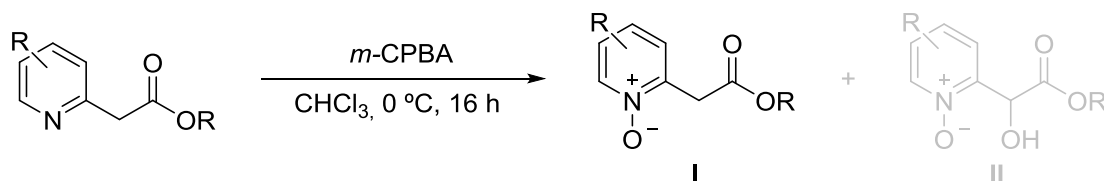
²⁴³ Procedure adapted from: Ji, C.-B.; Liu, Y.-L.; Zhao, X.-L.; Guo, Y.-L.; Wang, H.-Y.; Zhou, J. *Org. Biomol. Chem.* **2012**, *10*, 1158.



6.4.2. Enantioselective Mannich reaction of 2-azaaryl *N*-oxides to *N*-Boc imines

6.4.2.1. Preparation of pronucleophiles

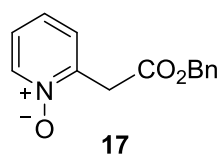
6.4.2.1.1. Synthesis of pyridyl *N*-oxide acetates **17**, **19** and **20**



To a solution of the corresponding pyridyl acetate (5.5 mmol, 1.1 equiv) in CHCl_3 (20 mL), *m*-CPBA (75 %) (1.15 g, 5 mmol, 1.0 equiv.) was added at 0 °C and the resulting mixture was stirred at the same temperature for 16 hours. Solvent was removed under reduce pressure and the corresponding *N*-oxide was purified by flash column chromatography on silica gel (CH_2Cl_2 :MeOH, 98:2).

Note: The oxidation reaction gives the α -hydroxyl compound as a side product.

2-(2-(Benzyloxy)-2-oxoethyl)pyridine *N*-oxide (**17**)

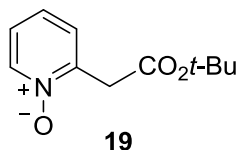


The title compound **17** was prepared according to the general procedure using benzyl 2-(pyridin-2-yl)acetate²⁴⁴ (5% of **II** was obtained). Yield: 0.81 g (66%). White solid. m. p. = 101 – 104 °C. IR

²⁴⁴ Prepared following the reported procedure: Sahoo, B.; Hopkinson, M. N.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 15545–15549.

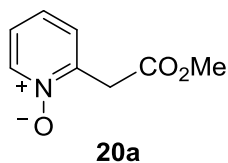
(ν/cm^{-1}): 3062, 1733, 1493, 1439, 1252, 1160, 994, 753, 699. ^1H NMR (300 MHz, CDCl_3) δ 8.29 – 8.22 (m, 1H), 7.39 – 7.28 (m, 6H), 7.26 – 7.17 (m, 2H), 5.20 (s, 2H), 3.93 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.42, 145.49, 139.29, 135.65, 128.53, 128.23, 128.17, 127.20, 125.38, 124.93, 77.58, 77.16, 76.74, 66.97, 36.95. UPLC-DAD-QTOF: $\text{C}_{14}\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$ calcd.: 244.0979, found: 244.0974.

2-(2-(*tert*-Butoxy)-2-oxoethyl)pyridine *N*-oxide (19)



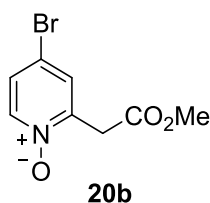
The title compound **19** was prepared according to the general procedure using *tert*-butyl 2-(pyridin-2-yl)acetate²⁴⁴ (10% of **II** was obtained). Yield: 0.59 g (56%). White solid. m. p. = 49 – 52 °C. IR (ν/cm^{-1}): 2977, 1725, 1491, 1438, 1367, 1344, 1247, 1146, 766, 731. ^1H NMR (300 MHz, CDCl_3) δ 8.32 – 8.19 (m, 1H), 7.36 – 7.27 (m, 1H), 7.27 – 7.11 (m, 2H), 3.79 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.7, 146.1, 139.3, 127.1, 125.3, 124.6, 81.6, 38.0, 28.0. UPLC-DAD-QTOF: $\text{C}_{11}\text{H}_{16}\text{NO}_3$ $[\text{M}+\text{H}]^+$ calcd.: 210.1130, found: 210.1127.

2-(2-Methoxy-2-oxoethyl)pyridine *N*-oxide (20a)

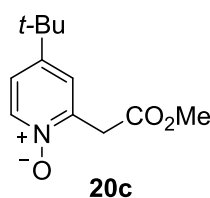


The title compound **20a** was prepared according to the general procedure using methyl 2-(pyridin-2-yl)acetate²⁴⁵ (50% of **II** was obtained). Yield: 0.33 g (40%). White solid. m. p. = 88 – 93 °C. IR (ν/cm^{-1}): 2953, 1731, 1492, 1436, 1348, 1220, 1166, 1001, 771, 681, 562, 488. ^1H NMR (300 MHz, CDCl_3) δ 8.34 – 8.25 (m, 1H), 7.41 – 7.32 (m, 1H), 7.28 – 7.23 (m, 2H), 3.91 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.0, 145.5, 139.3, 127.2, 125.6, 124.9, 52.3, 36.8. UPLC-DAD-QTOF: $\text{C}_8\text{H}_{10}\text{NO}_3$ $[\text{M}+\text{H}]^+$ calcd.: 168.0661, found: 168.0664.

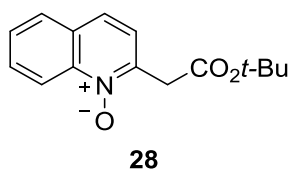
²⁴⁵ Prepared following the reported procedure: Nacsá, E. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2015**, *137*, 10246–10253.

4-Bromo-2-(2-methoxy-2-oxoethyl)pyridine N-oxide (20b)

The title compound **20b** was prepared according to the general procedure using methyl 2-(4-bromopyridin-2-yl)acetate²⁴⁶ (30% of **II** was obtained). Yield: 0.55 g (45%). White solid. m. p. = 93 – 97 °C. IR (v/cm⁻¹): 3047, 2952, 1734, 1461, 1425, 1339, 1248, 1164, 1003, 821, 730, 649, 547, 494. ¹H NMR (300 MHz, CDCl₃) δ 8.09 (d, *J* = 6.9 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.35 (dd, *J* = 6.9, 2.8 Hz, 1H), 3.72 (s, 2H), 3.42 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 168.5, 146.8, 140.1, 130.2, 128.2, 118.6, 52.6, 36.6. UPLC-DAD-QTOF: C₈H₈NO₃Br [M+H]⁺ calcd.: 245.9766, found: 245.9769.

4-(tert-Butyl)-2-(2-methoxy-2-oxoethyl)pyridine N-oxide (20c)

The title compound **20c** was prepared according to the general procedure using methyl 2-(4-(*tert*-butyl)pyridin-2-yl)acetate²⁴⁶ (20% of **II** was obtained). Yield: 0.61 g (55%). Colorless oil. IR (v/cm⁻¹): 2955, 1739, 1438, 1245, 773. ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 2.8 Hz, 1H), 7.18 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.85 (s, 2H), 3.70 (s, 3H), 1.27 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 150.5, 144.5, 138.6, 124.2, 122.1, 52.4, 37.1, 34.6, 30.6. UPLC-DAD-QTOF: C₁₂H₁₈NO₃ [M+H]⁺ calcd.: 244.1287, found: 244.1293.

6.4.2.1.2. Synthesis of 2-(2-(tert-butoxy)-2-oxoethyl)quinoline N-oxide (28)²⁴⁷

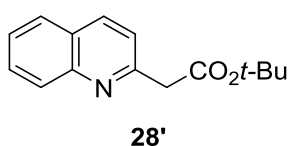
To a solution of *tert*-butyl acetate (2.7 mL, 20 mmol, 2.0 equiv.) in *t*-BuNH₂ (25 mL) at -15 °C, *n*-BuLi (2.5 M in hexane) (10 mL, 25 mmol, 2.5 equiv.) was added. After 10 minutes stirring at the same temperature, quinoline *N*-oxide (1.45 g, 10 mmol, 1.0 equiv.) was added and reaction mixture was allowed to warm to room temperature. After 4 hours, the reaction was quenched with HCl 2M (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over MgSO₄ and solvent was removed under reduced pressure. The residue was purified by flash column

²⁴⁶ Prepared following the reported procedure: Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. *Org. Lett.* **2014**, *16*, 3336–3339.

²⁴⁷ Procedure adapted from: Hamana, M.; Genji, I.; Saeki, S. *Heterocycles* **1982**, *17*, 177–181.

chromatography on silica gel (AcOEt, 100%) to afford pure compound **28**. Yield: 0.80 g (31%). Brown solid. m. p. = 88–92 °C. IR (ν/cm^{-1}): 2978, 2235, 1726, 1339, 1220, 1148, 907, 724, 644, 562. ^1H NMR (300 MHz, CDCl_3) δ 8.54 (dd, J = 8.7, 1.2 Hz, 1H), 7.60 (dd, J = 8.1, 1.3 Hz, 1H), 7.50 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.18 (d, J = 8.6 Hz, 1H), 3.87 (s, 2H), 1.33 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.5, 142.1, 141.0, 129.8, 129.3, 127.8, 127.8, 124.5, 122.7, 119.2, 81.2, 38.6, 27.8. UPLC-DAD-QTOF: $\text{C}_{15}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$ calcd.: 260.1287, found: 260.1286.

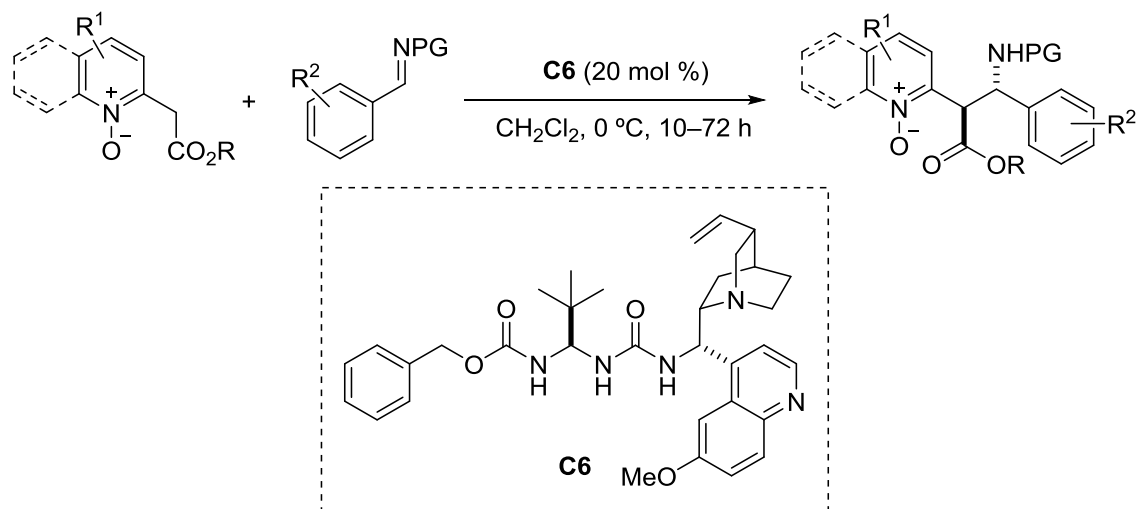
6.4.2.1.3. Synthesis of *tert*-butyl 2-(quinolin-2-yl)acetate (**28'**)



To a solution of **28** (1 equiv., 1 mmol, 0.259 g) in CH_2Cl_2 (9 mL), bis(pinacolato)diboron (3 equiv., 3 mmol, 0.762 g) was added and the reaction mixture was stirred at room temperature for 16 hours. Then, ethylenediamine (120 equiv., 120 mmol, 8 mL) was added to the mixture, and the stirring was continued for 1 hour at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Hexane:EtOAc, 90:10). Yield: 0.181 g (75%). ^1H NMR (300 MHz, CDCl_3) δ 8.12 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 8.0, 1.4 Hz, 1H), 7.70 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 3.96 (s, 2H), 1.46 (s, 8H). Physical and spectroscopic data were coincident with the previously reported.²⁴⁸

²⁴⁸ Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920.

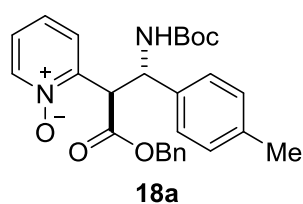
6.4.2.2. General procedure for the enantioselective Mannich reaction of pyridyl *N*-oxide acetate with *N*-protected imines



To a solution of the corresponding azaaryl *N*-oxide acetate (1 equiv., 0.12 mmol) and catalyst **C6** (0.2 equiv., 0.024 mmol, 0.014 g), unless otherwise stated, in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C, the corresponding *N*-protected imine (2 equiv., 0.24 mmol) was added. The resulting solution was stirred at the same temperature until complete disappearance of *N*-oxide and then poured into a flash column chromatography (Hexane:EtOAc, 50:50 to 0:100) to afford the corresponding pure Mannich adducts.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing DBU as a chiral Brønsted base.

2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-oxo-3-phenoxylpropan-2-yl)pyridine *N*-oxide (**18a**)

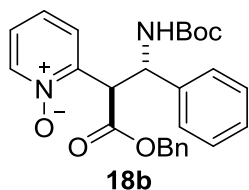


The title compound **18a** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4a** at 1 mmol scale. Reaction time: 48 hours. Yield: 0.46 g (95%). White solid. m. p.= 42–45 °C. $[\alpha]_{\text{D}}^{25} = -46.1$ ($c = 0.55$, CHCl_3). IR (ν/cm^{-1}): 2973, 1706, 1514, 1434, 1365, 1286, 1250, 1164, 764, 697.

^1H NMR (300 MHz, CDCl_3) δ 8.32 (dd, $J = 4.7, 3.1$ Hz, 1H), 7.46 (dd, $J = 6.1, 4.0$ Hz, 1H), 7.39 – 7.17 (m, 6H), 7.14 – 6.96 (m, 4H), 6.83 (d, $J = 8.3$ Hz, 1H), 5.37 (t, $J = 9.2$ Hz, 1H), 5.16 (d, $J = 10.0$ Hz, 1H), 5.06 – 4.92 (m, 2H), 2.33 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 155.4, 147.2, 139.5, 137.6, 137.4, 135.1, 129.3, 128.4, 128.2, 128.1, 127.0, 126.5, 126.4, 124.5, 79.2, 67.1, 57.5, 51.1, 28.3, 21.2. UPLC-DAD-QTOF: $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 463.2233, found: 463.2241. Chiral HPLC (Chiralpack IC; 50:50

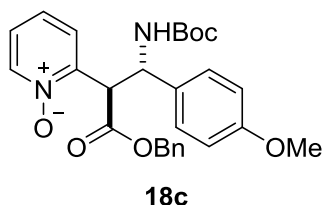
Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 10.1$ min (*anti*, major.), 11.4 min (*anti*, minor.), 14.0 min (*syn*), 23.7 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)pyridine *N*-oxide (18b)



The title compound **18b** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4b**. Reaction time: 28 hours. Yield: 0.053 g (98%). White solid. m. p.= 170–172 °C. $[\alpha]_D^{25} = -12.2$ ($c = 2.5$, CHCl_3). IR (ν/cm^{-1}): 2974, 1704, 1495, 1434, 1365, 1250, 1165, 982, 698. ^1H NMR (300 MHz, CDCl_3) δ 8.36 – 8.28 (m, 1H), 7.48 – 7.34 (m, 3H), 7.33 – 7.16 (m, 8H), 7.13 – 6.98 (m, 2H), 6.90 (d, $J = 7.9$ Hz, 1H), 5.41 (t, $J = 9.0$ Hz, 1H), 5.07 (d, $J = 40.3$ Hz, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.10, 155.45, 147.17, 140.70, 139.64, 135.15, 128.72, 128.52, 128.30, 128.20, 127.91, 127.16, 126.63, 126.40, 125.00, 79.35, 67.28, 58.07, 51.23, 28.37. UPLC-DAD-QTOF: $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 449.2076 found: 449.2082. Chiral HPLC (Chiralpak IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 15.6$ min (*anti*, major.), 17.0 min (*anti*, minor.), 31.9 min (both *syn* enantiomers). dr 99:1; 99% *ee*.

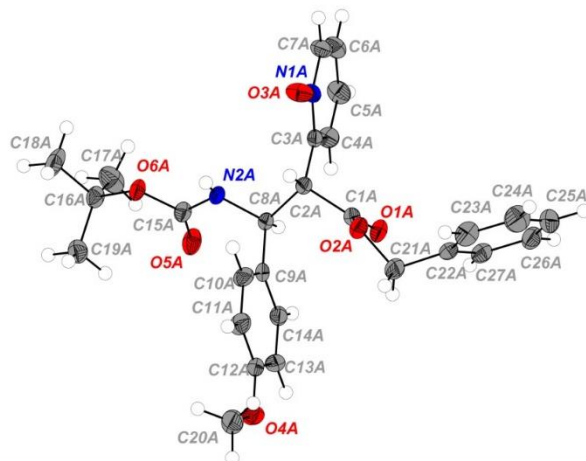
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18c)



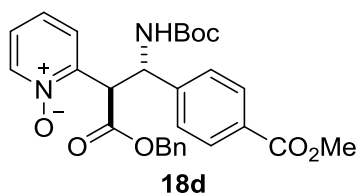
The title compound **18c** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4c**. Reaction time: 48 hours. Yield: 0.052 g (90%). White solid. m. p.= 40–43 °C. $[\alpha]_D^{25} = -67.26$ ($c = 2$, CH_2Cl_2). IR (ν/cm^{-1}): 2973, 1705, 1512, 1433, 1246, 1165, 1031, 767. ^1H NMR (300 MHz, CDCl_3) δ 8.31 (dd, $J = 4.7, 3.1$ Hz, 1H), 7.46 (t, $J = 5.0$ Hz, 1H), 7.38 – 7.14 (m, 6H), 7.10 – 7.01 (m, 2H), 6.81 (d, $J = 8.7$ Hz, 3H), 5.33 (t, $J = 9.2$ Hz, 1H), 5.15 (d, $J = 10.1$ Hz, 1H), 5.00 (q, $J = 12.3$ Hz, 2H), 3.78 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 159.2, 155.4, 147.2, 139.6, 135.1, 132.8, 128.4, 128.3, 128.2, 128.1, 126.4, 124.9, 114.0, 79.2, 67.1, 57.4, 55.3, 51.1, 28.3. UPLC-DAD-QTOF: $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd.: 479.2182, found: 479.2187. Chiral HPLC (Chiralpak AD-H; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 270$ nm) $t_R = 16.0$ min (*anti*, major.), 30.2 min (*anti*, minor.), 68.0 min (*syn*), 111.0 min (*syn*). dr 99:1; 99% *ee*.

Experimental section

CCDC 1559084 contains the supplementary crystallographic data for the structural analysis of **18c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/deposit/>.

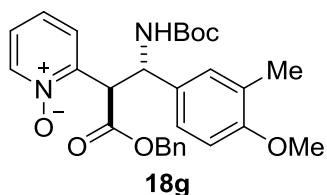


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18d**)



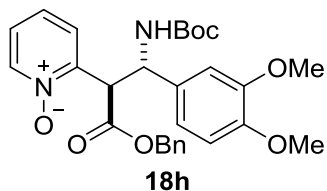
The title compound **18d** was prepared according to the general procedure employing *N*-oxide **17**, *N*-Boc imine **4d** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). Reaction time: 20 hours. Yield: 0.059 g (98%). White solid. m. p.= 68–70 °C. $[\alpha]_D^{25} = -27.0$ ($c = 2.5$, CH_2Cl_2). IR (ν/cm^{-1}): 2972, 1717, 1490, 1434, 1278, 1164, 1104, 1018, 764, 698. ^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, $J = 6.1, 1.6$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H), 7.34 – 7.12 (m, 6H), 7.12 – 6.94 (m, 2H), 5.42 (t, $J = 8.4$ Hz, 1H), 5.09 – 4.87 (m, 3H), 3.90 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.6, 166.8, 155.5, 146.8, 145.8, 139.7, 135.0, 130.0, 129.8, 129.6, 128.5, 128.3, 128.2, 127.2, 126.7, 125.2, 79.5, 67.4, 57.7, 52.1, 51.2, 28.3. UPLC-DAD-QTOF: $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 507.2131, found: 507.2141. Chiral HPLC (Chiralpack IC; 70:30 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 30.2$ min (*anti*, minor.), 31.6 min (*anti*, major.), 42.7 min (*syn*), 58.0 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18g)



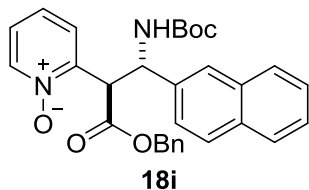
The title compound **18g** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4g**. Reaction time: 48 hours. Yield: 0.51 g (87%). White solid. m. p.= 58–61 °C. $[\alpha]_D^{24} = -37.3$ ($c = 0.58$, CH_2Cl_2). IR (v/cm^{-1}): 2966, 2924, 2853, 1728, 1705, 1503, 1253, 1163, 1029, 766. ^1H NMR (300 MHz, CDCl_3) δ 8.35 – 8.24 (m, 1H), 7.53 – 7.41 (m, 1H), 7.27 – 7.20 (m, 5H), 7.17 (d, $J = 7.0$ Hz, 2H), 7.08 – 6.94 (m, 2H), 6.75 – 6.65 (m, 1H), 6.44 (d, $J = 6.6$ Hz, 1H), 5.28 (t, $J = 9.3$ Hz, 1H), 5.22 – 5.10 (m, 1H), 5.03 (d, $J = 12.3$ Hz, 1H), 4.93 (d, $J = 12.3$ Hz, 1H), 3.80 (s, 3H), 2.17 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.3, 157.5, 155.3, 147.4, 139.6, 135.2, 132.2, 129.4, 128.4, 128.3, 126.9, 126.5, 125.7, 124.9, 109.9, 79.3, 67.2, 57.6, 55.4, 51.0, 28.4, 16.4. UPLC-DAD-QTOF: $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd.: 493.2339, found: 493.2345. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 14.0$ min (*anti*, minor.), 16.8 min (*syn*), 17.8 min (*anti*, major.), 27.7 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18h)



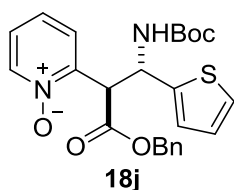
The title compound **18h** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4h**. Reaction time: 48 hours. Yield: 0.54 g (88%). White solid. m. p.= 55–59 °C. $[\alpha]_D^{24} = -45.0$ ($c = 0.79$, CH_2Cl_2). IR (v/cm^{-1}) = 2969, 2930, 1728, 1706, 1515, 1257, 1162, 1026, 765. ^1H NMR (300 MHz, CDCl_3) δ 8.36 – 8.25 (m, 1H), 7.40 (dd, $J = 6.7, 3.4$ Hz, 1H), 7.30 – 7.18 (m, 5H), 7.11 – 7.00 (m, 2H), 6.93 (dd, $J = 8.3, 2.0$ Hz, 1H), 6.86 (d, $J = 2.1$ Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 1H), 6.72 (brs, 1H), 5.32 (t, $J = 9.0$ Hz, 1H), 5.14 – 5.01 (m, 2H), 4.96 (d, $J = 12.3$ Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 155.4, 149.1, 148.6, 147.2, 139.6, 135.2, 133.3, 128.5, 128.3, 128.1, 126.7, 126.5, 125.0, 119.4, 111.2, 110.1, 79.3, 67.3, 57.9, 56.0, 56.0, 51.2, 28.4. UPLC-DAD-QTOF: $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 509.2288 found: 509.2299. Chiral HPLC (Chiralpack IC; 70:30 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 21.3$ min (*anti*, major.), 23.1 min (*anti*, minor.), 32.1 min (*syn*), 46.2 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18i)



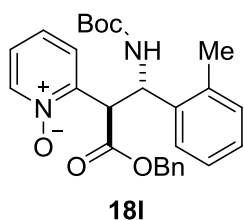
The title compound **18i** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4i**. Reaction time: 48 hours. Yield: 0.055 g (92%). White solid. m. p.= 83–87 °C. $[\alpha]_D^{24} = -69.5$ ($c = 0.88$, CH_2Cl_2). IR (v/cm^{-1}) = 2974, 2929, 1703, 1490, 1433, 1365, 1250, 1163, 1050, 1019, 984, 858, 765, 746, 697, 479. ^1H NMR (300 MHz, CDCl_3) δ 8.39 – 8.26 (m, 1H), 7.87 – 7.72 (m, 4H), 7.54 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.51 – 7.37 (m, 3H), 7.25 – 7.16 (m, 2H), 7.16 – 7.10 (m, 1H), 7.05 (t, $J = 7.5$ Hz, 2H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 7.5$ Hz, 2H), 5.55 (t, $J = 8.9$ Hz, 1H), 5.24 (d, $J = 9.9$ Hz, 1H), 4.98 (d, $J = 12.4$ Hz, 1H), 4.91 (d, $J = 12.3$ Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.1, 155.5, 147.1, 139.6, 138.0, 134.9, 133.3, 133.2, 128.7, 128.3, 128.3, 128.2, 128.0, 127.7, 126.6, 126.5, 126.4, 126.2, 126.1, 125.0, 124.9, 79.4, 67.3, 58.2, 51.1, 28.4. UPLC-DAD-QTOF: $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 499.2233, found: 499.2237. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 9.2$ min (*anti*, minor.), 10.4 min (*anti*, major.), 12.1 min (*syn*), 15.4 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)pyridine *N*-oxide (18j)



The title compound **18j** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4j**. Reaction time: 48 hours. Yield: 0.051 g (94%). Yellow solid. m. p = 49–53 °C. $[\alpha]_D^{24} = -21.4$ ($c = 0.85$, CH_2Cl_2). IR (v/cm^{-1}): 2975, 2928, 1706, 1489, 1433, 1365, 1251, 1163, 766, 734, 698. ^1H NMR (300 MHz, CDCl_3) δ 8.34 – 8.25 (m, 1H), 7.38 – 7.22 (m, 4H), 7.24 – 7.09 (m, 5H), 6.99 (d, $J = 3.6$ Hz, 1H), 6.87 (dd, $J = 5.0, 3.5$ Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 5.70 (t, $J = 8.7$ Hz, 1H), 5.17 – 4.99 (m, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.9, 155.4, 146.8, 144.7, 139.7, 135.2, 128.6, 128.4, 128.3, 126.9, 126.6, 126.4, 125.2, 125.0, 124.7, 79.6, 67.5, 53.3, 51.8, 28.3. UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$ calcd.: 455.1641, found: 455.1645. Chiral HPLC (Chiralpack IC; 80:20 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 32.7$ min (*anti*, minor.), 34.8 min (*anti*, major.), 69.0 min (*syn*), 89.2 min (*syn*). dr 99:1; 99% *ee*.

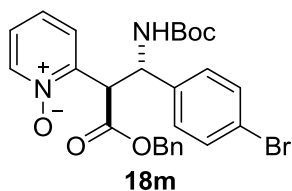
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(*o*-tolyl)propan-2-yl)pyridine *N*-oxide (18l)



The title compound **18l** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4l**. Reaction time: 48 hours. Yield: 0.051 g (92%). White solid. m. p.= 61–63 °C. $[\alpha]_D^{25} = -62.3$ ($c = 2$, CH_2Cl_2). IR (ν/cm^{-1}): 2973, 1702, 1492, 1433, 1365, 1287, 1250, 1164, 1045, 729, 697. $^1\text{H NMR}$ (300 MHz, CDCl_3)

δ 8.37 – 8.28 (m, 1H), 7.50 – 7.39 (m, 2H), 7.30 – 7.09 (m, 8H), 7.07 – 6.93 (m, 2H), 6.49 (d, $J = 8.7$ Hz, 1H), 5.70 (t, $J = 9.4$ Hz, 1H), 5.31 (d, $J = 4.3$ Hz, 1H), 5.00 (q, 2H), 2.50 (s, 3H), 1.24 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 169.2, 155.3, 147.3, 139.5, 138.9, 136.0, 135.2, 130.8, 128.5, 128.2, 128.1, 127.7, 126.6, 126.5, 126.47, 126.2, 124.9, 79.2, 67.2, 53.5, 50.0, 28.3, 19.5. UPLC-DAD-QTOF: $\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 463.2233, found: 463.2247. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 12.2$ min (*anti*, major.), 13.7 min (*anti*, minor.), 16.7 min (*syn*), 31.9 min (*syn*). dr 99:1; 99% *ee*.

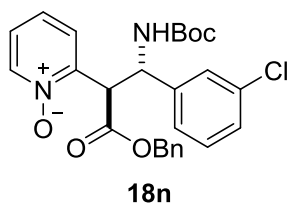
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(4-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-1-oxopropan-2-yl)pyridine *N*-oxide (18m)



The title compound **18m** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4m**. Reaction time: 21 hours. Yield: 0.060 g (95%). White solid. m. p.= 44–46 °C. $[\alpha]_D^{25} = -17.5$ ($c = 3.0$, CH_3Cl_3). IR (ν/cm^{-1}): 2974, 1705, 1488, 1434, 1365, 1283, 1250, 1165, 1010, 765. $^1\text{H NMR}$ (300 MHz, CDCl_3)

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.35 – 8.24 (m, 1H), 7.55 – 6.89 (m, 13H), 5.31 (t, $J = 8.9$ Hz, 1H), 5.11 – 4.88 (m, 3H), 1.26 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 168.9, 155.4, 146.9, 139.8, 139.6, 134.9, 131.7, 128.9, 128.5, 128.4, 128.2, 126.6, 126.5, 125.1, 121.8, 79.5, 67.4, 57.4, 51.0, 28.3. UPLC-DAD-QTOF: $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_5\text{Br}$ $[\text{M}+\text{H}]^+$ calcd.: 527.1182, found: 527.1183. Chiral HPLC (Chiralpack IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 12.1$ min (*anti*, major.), 13.4 min (*anti*, minor.), 15.0 min (*syn*), 22.4 min (*syn*). dr 99:1; 99% *ee*.

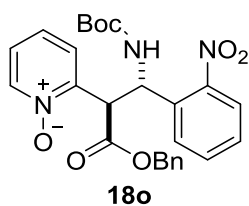
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18n)



The title compound **18n** was prepared according to the general procedure employing *N*-oxide **17**, *N*-Boc imine **4n** and catalyst **C6** (0.05 equiv., 0.006 mmol, 0.004 g). Reaction time: 30 hours. Yield: 0.104 g (90%). White solid. m. p.= 51–53°C. $[\alpha]_{\text{D}}^{25} = -58.9$ ($c = 1.45$, CH_2Cl_2). IR (v/cm^{-1}): 2974, 1706, 1490, 1434, 1365,

1250, 1164, 767, 697. ^1H NMR (300 MHz, CDCl_3) δ 8.42 – 8.23 (m, 1H), 7.59 – 6.91 (m, 12H), 5.36 (t, $J = 8.6$ Hz, 1H), 5.23 – 4.83 (m, 3H), 1.28 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.7, 155.5, 146.8, 142.9, 139.7, 135.0, 134.5, 129.9, 128.5, 128.4, 128.3, 128.2, 128.1, 127.3, 126.7, 125.4, 125.2, 79.5, 67.4, 57.6, 51.2, 28.3. UPLC-DAD-QTOF: $\text{C}_{26}\text{H}_{28}\text{ClN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 483.1687, found: 483.1691. Chiral HPLC (Chiralpak IC; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_{\text{R}} = 25.5$ min (*anti*, major.), 27.0 min (*anti*, minor.), 43.5 min (*syn*), 48.1 min (*syn*). dr 99:1; 99% *ee*.

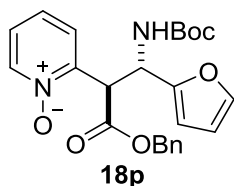
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(2-nitrophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18o)



The title compound **18o** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4o**. Reaction time: 10 hours. Yield: 0.056 g (95%). Yellow solid. m. p.= 170–173 °C. $[\alpha]_{\text{D}}^{25} = 28.8$ ($c = 0.63$, CH_2Cl_2). IR (v/cm^{-1}): 2975, 1706, 1525,

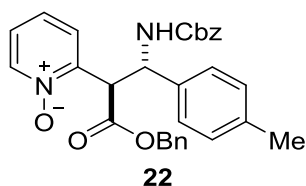
1437, 1364, 1249, 1166, 1052, 746. ^1H NMR (300 MHz, CDCl_3) δ 8.29 (d, $J = 6.5$, 1.2 Hz, 1H), 8.08 (brs, 1H), 7.92 (d, $J = 7.9$ Hz, 1H), 7.44 – 7.19 (m, 9H), 7.11 (t, $J = 7.7$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.11 (t, $J = 5.9$ Hz, 1H), 5.23 (d, $J = 12.4$ Hz, 1H), 5.14 (d, $J = 12.5$ Hz, 1H), 4.80 (d, $J = 6.2$ Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 167.4, 155.7, 148.2, 146.5, 139.8, 136.5, 135.4, 129.4, 129.0, 128.5, 128.1, 128.1, 126.6, 125.5, 125.0, 79.4, 67.4, 53.5, 51.8, 28.3. UPLC-DAD-QTOF: $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 494.1927, found: 494.1941. Chiral HPLC (Chiralpak IA; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_{\text{R}} = 14.0$ min (*anti*, minor.), 17.4 min (*anti*, major.), 32.3 min (*syn*), 48.8 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18p)



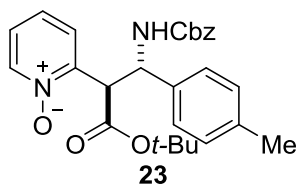
The title compound **18p** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4p**. Reaction time: 44 hours. Yield: 0.049 g (93%). White solid. m. p = 52–55 °C. $[\alpha]_D^{25} = -34.74$ ($c = 1.75$, CH_2Cl_2). IR (v/cm^{-1}): 2969, 1707, 1498, 1434, 1366, 1255, 1165, 1022, 874, 768. ^1H NMR (300 MHz, CDCl_3) δ 8.30 (dd, $J = 5.0, 2.7$ Hz, 1H), 7.56 – 7.43 (m, 1H), 7.38 (s, 1H), 7.33 – 7.27 (m, 3H), 7.26 – 7.12 (m, 4H), 6.51 – 6.33 (m, 2H), 5.42 (t, $J = 9.5$ Hz, 1H), 5.21 – 5.02 (m, 4H), 1.28 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.3, 155.4, 147.0, 143.3, 140.0, 139.6, 135.1, 128.5, 128.4, 128.3, 126.3, 125.3, 125.2, 125.0, 109.1, 79.4, 67.4, 50.2, 49.4, 28.3. UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd.: 439.1869, found: 439.1878. Chiral HPLC (Chiralpak IC; 80:20 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 26.0$ min (*anti*, major.), 27.1 min (*anti*, minor.), 43.6 min (*syn*), 48.4 min (*syn*). dr 99:1; 99% *ee*.

2-((2*R*,3*S*)-1-(Benzyloxy)-3-(((benzyloxy)carbonyl)amino)-1-oxo-3-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (22)



The title compound **22** was prepared according to the general procedure employing *N*-oxide **17** and *N*-Cbz imine **21**. Reaction time: 24 hours. Yield: 0.052 g (88%). White solid. m. p = 50–53 °C. $[\alpha]_D^{25} = -21.7$ ($c = 1.5$, CH_2Cl_2). IR (v/cm^{-1}): 3030, 1721, 1514, 1433, 1258, 1174, 1042, 764, 697. ^1H NMR (300 MHz, CDCl_3) δ 8.34 – 8.13 (m, 1H), 7.50 – 6.84 (m, 17H), 5.35 (t, $J = 8.6$ Hz, 1H), 5.11 – 4.82 (m, 5H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.0, 156.0, 147.1, 139.7, 137.7, 137.4, 136.8, 135.1, 129.4, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.1, 126.7, 126.4, 125.0, 67.3, 66.4, 58.6, 51.2, 21.3. UPLC-DAD-QTOF: $\text{C}_{30}\text{H}_{29}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 497.2076, found: 497.2072. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 21.5$ min (*anti*, minor.), 24.3 min (*anti*, major.), 31.0 min (*syn*), 41.3 min (*syn*). dr 99:1; 99% *ee*.

2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (23)

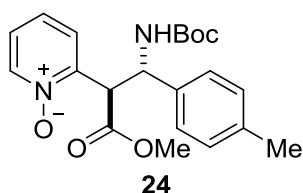


The title compound **23** was prepared according to the general procedure employing *N*-oxide **19** and *N*-Cbz imine **21**. Reaction time: 48 hours. Yield: 0.049 g (89 %). White solid. m. p. = 63–65 °C. $[\alpha]_D^{25} = -58.4$ ($c = 0.43$, CH_2Cl_2). IR (v/cm^{-1}): 2972, 1716, 1646, 1540, 1433, 1255, 1152, 1027, 736. ^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, $J = 6.5$ Hz,

Experimental section

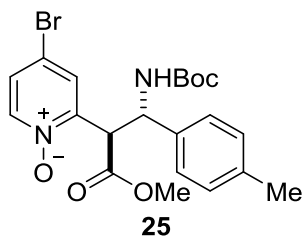
1H), 7.69 (d, $J = 7.7$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.40 – 6.92 (m, 10H), 5.32 – 5.20 (m, 1H), 5.08 – 4.79 (m, 3H), 2.31 (s, 3H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 168.0, 155.9, 147.8, 139.6, 137.5, 136.8, 129.1, 128.3, 128.0, 127.8, 127.4, 126.7, 126.1, 124.7, 82.2, 66.3, 58.7, 51.6, 27.7, 21.2. UPLC-DAD-QTOF: $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd.: 463.2233, found: 463.2240. Chiral HPLC (Chiralpak IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_{\text{R}} = 18.7$ min (*anti*, major.), 30.9 min (*anti*, minor.), 35.1 min (*syn*), 44.9 min (*syn*). dr 99:1; 99% *ee*.

2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (24)



The title compound **24** was prepared according to the general procedure employing *N*-oxide **20a** and *N*-Boc imine **4a**. Reaction time: 72 hours. Yield: 0.045 g (96 %). White solid. m. p. = 126–130 °C. $[\alpha]_{\text{D}}^{25} = -64.0$ ($c = 1.00$, CH_2Cl_2). IR (v/cm^{-1}): 2975, 1734, 1705, 1513, 1489, 1432, 1365, 1250, 1165, 1051, 1020, 995, 768. ^1H NMR (300 MHz, CDCl_3) δ 8.28 (dd, $J = 4.9, 2.8$ Hz, 1H), 7.39 (dd, $J = 6.3, 3.7$ Hz, 1H), 7.32 – 7.15 (m, 4H), 7.10 (d, $J = 7.9$ Hz, 2H), 6.70 (d, $J = 8.2$ Hz, 1H), 5.35 (t, $J = 9.0$ Hz, 1H), 5.02 (d, $J = 9.5$ Hz, 1H), 3.54 (s, 3H), 2.30 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.8, 155.4, 147.3, 139.6, 137.7, 137.5, 129.3, 126.9, 126.6, 126.4, 124.9, 79.2, 57.4, 52.5, 51.2, 28.3, 21.2. UPLC-DAD-QTOF: $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 387.1920, found: 387.1929. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_{\text{R}} = 12.6$ min (*anti*, minor.), 15.0 min (*anti*, major.), 20.9 min (*syn*), 22.8 min (*syn*). dr 99:1; 99% *ee*.

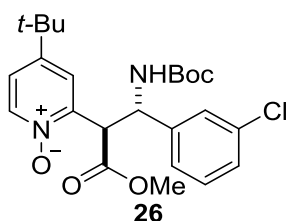
4-Bromo-2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (25)



The title compound **25** was prepared according to the general procedure employing *N*-oxide **20b** and *N*-Boc imine **21** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). Reaction time: 36 hours. Yield: 0.055 g (98 %). White solid. m. p. = 85–89 °C. $[\alpha]_{\text{D}}^{25} = -28.4$ ($c = 1.75$, CH_2Cl_2). IR (v/cm^{-1}): 2974, 2248, 1731, 1701, 1513, 1458, 1410, 1365, 1247, 1162, 729, 650. ^1H NMR (300 MHz, CDCl_3) δ 8.12 (d, $J = 6.9$ Hz, 1H), 7.64 (d, $J = 2.8$ Hz, 1H), 7.33 (dd, $J = 6.9, 2.8$ Hz, 1H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 7.9$ Hz, 2H), 6.43 (d, $J = 8.6$ Hz, 1H), 5.32 (t, $J = 9.4$ Hz, 1H), 5.00 (d, $J = 9.9$ Hz, 1H), 3.52 (s, 3H), 2.31 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.4, 155.3, 148.5, 140.1, 137.8, 137.3, 129.4, 128.1, 126.9, 126.2, 119.7, 79.6, 57.1, 52.6,

51.1, 28.3, 21.3. UPLC-DAD-QTOF: $C_{21}H_{26}N_2O_5Br$ $[M+H]^+$ calcd.: 465.1025, found: 465.1030. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 8.3$ min (*anti*, minor.), 10.3 min (*anti*, major.), 12.5 min (*syn*), 15.6 min (*syn*). dr 99:1; 99% *ee*.

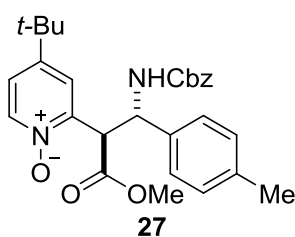
2-((1S,2R)-1-((*tert*-Butoxycarbonyl)amino)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (26)



The title compound **26** was prepared according to the general procedure employing *N*-oxide **20c** and *N*-Boc imine **4m** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). Reaction time: 84 hours. Yield: 0.050 g (90 %). White solid. m. p. = 77–80 °C. $[\alpha]_D^{24} = -49.7$ ($c = 0.73$, CH_2Cl_2). IR (ν/cm^{-1}): 2966, 2926, 2248, 1734,

1705, 1480, 1365, 1282, 1244, 1165, 732. 1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, $J = 6.8$ Hz, 1H), 7.54 (brs, 1H), 7.27 – 7.20 (m, 5H), 6.95 (brs, 1H), 5.44 (t, $J = 7.1$ Hz, 1H), 4.53 (brs, 1H), 3.66 (s, 3H), 1.34 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 155.9, 152.1, 145.5, 143.3, 139.1, 134.6, 130.0, 127.9, 127.1, 125.1, 124.7, 122.5, 79.5, 57.6, 52.7, 34.8, 30.4, 29.8, 28.4. UPLC-DAD-QTOF: $C_{24}H_{32}N_2O_5Cl$ $[M+H]^+$ calcd.: 463.2020, found: 463.2000. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 7.5$ min (*anti*, minor.), 10.8 min (*anti*, major.), 13.4 min (*syn*), 19.3 min (*syn*). dr 99:1; 98% *ee*.

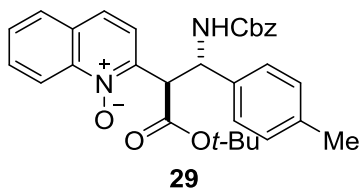
2-((1S,2R)-1-(((Benzyloxy)carbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (27)



The title compound **27** was prepared according to the general procedure employing *N*-oxide **20c** and *N*-Boc imine **21** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). Reaction time: 84 hours. Yield: 0.051 g (89 %). White solid. m. p. = 75–79 °C. $[\alpha]_D^{24} = -21.7$ ($c = 0.19$, CH_2Cl_2). IR (ν/cm^{-1}): 3030, 2959, 2924, 2852,

1715, 1514, 1482, 1434, 1246, 1049, 698. 1H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, $J = 6.9$ Hz, 1H), 7.39 – 7.34 (m, 1H), 7.25 (s, 4H), 7.17 (td, $J = 5.6, 5.1, 3.0$ Hz, 3H), 7.08 (d, $J = 7.9$ Hz, 2H), 7.00 (brs, 1H), 5.44 (t, $J = 7.4$ Hz, 1H), 5.04 – 4.86 (m, 2H), 4.67 (s, 1H), 3.61 (s, 3H), 2.29 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 156.3, 152.2, 145.9, 139.0, 138.6, 137.5, 133.0, 129.4, 128.4, 128.0, 127.9, 126.8, 122.3, 66.4, 58.4, 52.6, 30.4, 30.4, 29.9, 21.2. UPLC-DAD-QTOF: $C_{28}H_{32}N_2O_5$ $[M+H]^+$ calcd.: 477.2389, found: 477.2398. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 14.0$ min (*anti*, minor.), 28.0 min (*syn*), 40.2 min (*anti*, major.), 80.4 min (*syn*). dr 99:1; 98% *ee*.

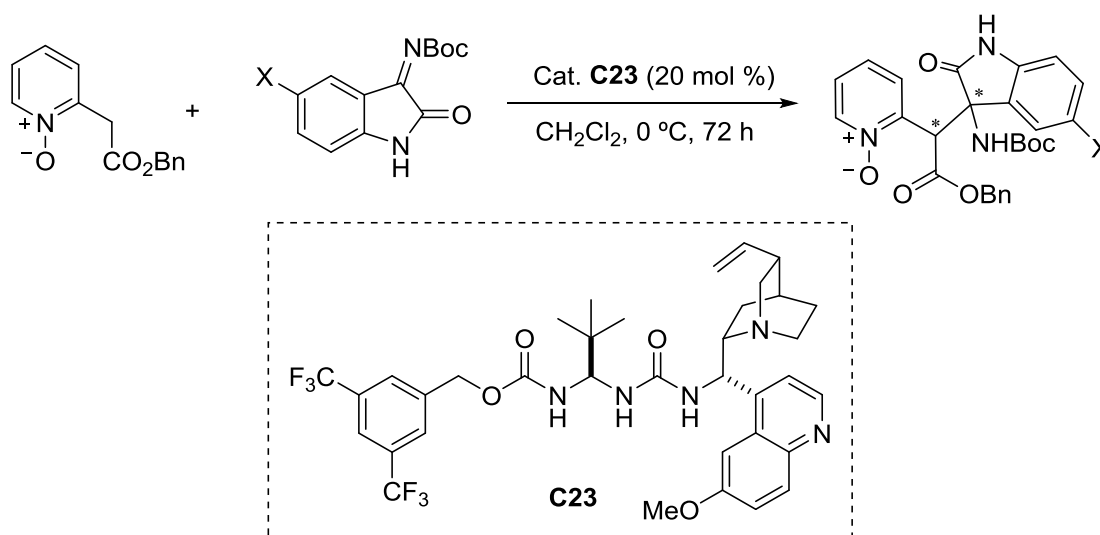
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)quinoline *N*-oxide (29**)**



The title compound **29** was prepared according to the general procedure employing *N*-oxide **28** and *N*-Boc imine **21** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). Reaction time: 48 hours. Yield: 0.051 g (89 %). Yellow oil.

$[\alpha]_D^{24} = -22.9$ ($c = 1.96$, CH_2Cl_2). IR (v/cm^{-1}): 3030, 2976, 1717, 1514, 1327, 1282, 1241, 1046, 736, 697. $^1\text{H NMR}$ (300 MHz, CDCl_3) $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.82 (d, $J = 8.8$ Hz, 1H), 7.97 – 7.76 (m, 2H), 7.76 – 7.62 (m, 2H), 7.57 (d, $J = 8.8$ Hz, 1H), 7.44 – 7.31 (m, 5H), 7.25 – 7.08 (m, 4H), 7.08 – 6.94 (m, 1H), 5.53 – 5.16 (m, 2H), 4.87 (d, $J = 12.5$ Hz, 1H), 4.80 (d, $J = 12.5$ Hz, 1H), 2.35 (s, 3H), 1.26 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 168.2, 156.0, 144.6, 141.5, 137.7, 137.6, 130.9, 129.6, 129.2, 129.1, 128.7, 128.6, 128.3, 128.2, 127.7, 127.6, 127.4, 126.4, 121.3, 120.2, 82.4, 66.2, 59.2, 52.3, 27.8, 21.3. UPLC-DAD-QTOF: $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ calcd.: 513.2389, found: 513.2393. Chiral HPLC (Chiralpak IC; 70:30 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_{\text{R}} = 8.6$ min (*anti*, minor.), 11.9 min (*syn*, minor.), 13.0 min (*anti*, major.), 16.2 min (*syn*, major.). dr 10:1; 92% ee.

6.4.2.3. General procedure for the Mannich reaction of pyridyl acetate *N*-oxide with *N*-Boc isatin ketimines

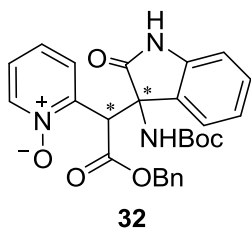


To a solution of pyridyl acetate *N*-oxide **17** (1 equiv., 0.12 mmol, 0.029 g) and catalyst **C23** (0.2 equiv., 0.024 mmol, 0.017 g) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C, the corresponding *N*-Boc isatin ketimine (0.36 mmol, 3 equiv.) was added. The resulting solution was stirred at the same temperature for 72 hours and then poured into a flash

column chromatography (Hexane:EtOAc, 50:50 to 0:100) to afford the corresponding pure Mannich adducts.

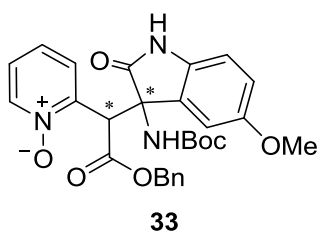
Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing DBU as a chiral Brønsted base.

2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (32)



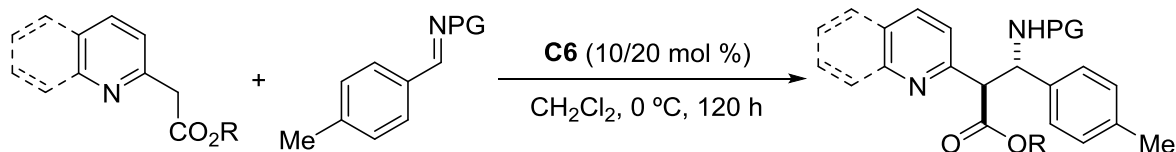
The title compound **32** was prepared according to the general procedure employing ketimine **30**. Yield: 0.047 g (84 %). Yellow solid. m. p. = 108–113 °C. $[\alpha]_D^{24} = +43.5$ ($c = 0.45$, CH_2Cl_2). IR (v/cm^{-1}): 2963, 2926, 1741, 1716, 1619, 1473, 1257, 1157, 751. ^1H NMR (300 MHz, CDCl_3) δ 8.64 (s, 1H), 8.42 – 8.27 (m, 1H), 8.01 (s, 1H), 7.72 – 7.57 (m, 1H), 7.42 (d, $J = 7.3$ Hz, 1H), 7.31 – 7.14 (m, 6H), 7.04 – 6.94 (m, 3H), 6.76 (d, $J = 7.7$ Hz, 1H), 5.76 (s, 1H), 4.81 – 4.69 (m, 2H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 167.3, 154.0, 143.4, 141.7, 140.0, 134.5, 129.7, 129.4, 128.6, 128.5, 128.4, 126.8, 125.7, 123.4, 122.5, 121.9, 110.0, 80.1, 67.6, 64.2, 49.5, 28.3. UPLC-DAD-QTOF: $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_6$ $[\text{M}+\text{H}]^+$ calcd.: 490.1978, found: 490.1985. Chiral HPLC (Chiralpak IC + Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 28.9$ min (diast. A, major.), 36.1 min (diast. B, minor.), 37.8 min (diast. A, minor.), 41.8 min (diast. B, major). dr 10:1; 80% *ee*.

2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-5-methoxy-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (33)



The title compound **33** was prepared according to the general procedure employing ketimine **31**. Yield: 0.048 g (77 %). Yellow solid. m. p. = 118–122 °C. $[\alpha]_D^{24} = +44.2$ ($c = 1.28$, CH_2Cl_2). IR (v/cm^{-1}): 2976, 1712, 1489, 1215, 1161, 733. ^1H NMR (300 MHz, CDCl_3) δ 8.67 (s, 1H), 8.47 – 8.29 (m, 1H), 7.96 (d, $J = 8.6$ Hz, 1H), 7.72 (dd, $J = 6.3, 3.8$ Hz, 1H), 7.27 (dddd, $J = 12.9, 10.6, 6.0, 3.2$ Hz, 6H), 7.10 – 6.89 (m, 2H), 6.73 (qd, $J = 8.5, 2.1$ Hz, 2H), 5.76 (s, 1H), 4.91 – 4.63 (m, 2H), 3.73 (d, $J = 1.7$ Hz, 3H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 167.2, 155.9, 154.0, 143.3, 140.0, 134.9, 134.5, 128.6, 128.6, 128.4, 126.9, 125.7, 115.3, 114.2, 110.6, 109.5, 80.3, 67.6, 64.7, 55.9, 49.4, 28.3. UPLC-DAD-QTOF: $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_7$ $[\text{M}+\text{H}]^+$ calcd.: 520.2084, found: 520.2087. Chiral HPLC (Chiralpak IC; 80:20 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 43.1$ min (diast. A, major.), 62.6 min (diast. B, minor.), 66.4 min (diast. A, minor.), 73.7 min (diast. B, major). dr 6.1:1; 78% *ee*.

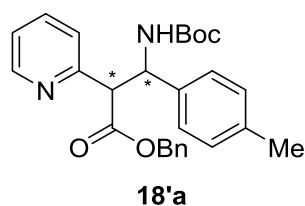
6.4.2.4. General procedure for the Mannich reaction of azaaryl acetates with *N*-protected imines



To a solution of the corresponding azaaryl acetate (0.12 mmol, 1 equiv.) and catalyst **C6** in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C, the corresponding *N*-protected imine (0.24 mmol, 2 equiv.) was added and stirred at the same temperature for 120 hours and then poured into a flash column chromatography (Hexane:EtOAc, 70:30) to afford the corresponding pure Mannich adducts.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing DBU as a chiral Brønsted base.

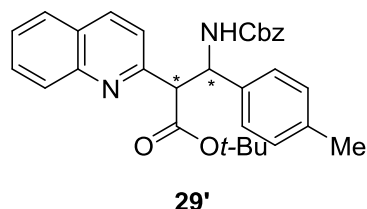
Benzyl 3-((*tert*-butoxycarbonyl)amino)-2-(pyridin-2-yl)-3-(*p*-tolyl)propanoate (**18'a**)



The title compound **18'a** was prepared according to the general procedure employing benzyl 2-(pyridin-2-yl)acetate **17'**, *N*-Boc imine **4a** and catalyst **C6** (0.2 equiv., 0.024 mmol, 0.014 g). Reaction time: 120 hours. Purification with flash column chromatography (Hexane:EtOAc, 90:10). Yield: 0.046 g

(86 %). Colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.85 (d, J = 8.1 Hz, 1H), 7.64 – 6.86 (m, 13H), 5.30 – 4.98 (m, 2H), 4.25 (m, 1H), 3.97 (m, 1H), 2.46 (s, 3H), 1.63 (s, 9H). Chiral HPLC (Chiralpak IC; 50:50 Hexane:*i*PrOH; 0.5 mL/min, λ = 210 nm) t_{R} = 10.9 min (*anti*), 12.7 min (*anti*), 19.1 min (*syn*), 24.1 min (*syn*). dr 2.6:1; 0/0% *ee*.

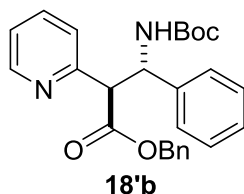
tert-Butyl 3-(((benzyloxy)carbonyl)amino)-2-(quinolin-2-yl)-3-(*p*-tolyl)propanoate (**29'**)



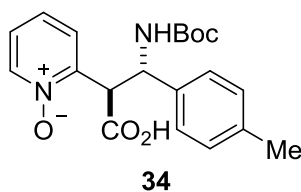
The title compound **29'** was prepared according to the general procedure employing *tert*-butyl 2-(quinolin-2-yl)acetate, *N*-Cbz imine **21** and catalyst **C6** (0.1 equiv., 0.012 mmol, 0.007 g). After 120 hours, the reaction conversion was 45 %. Chiral HPLC (Chiralpak IC; 80:20

Hexane:*i*PrOH; 0.5 mL/min, λ = 210 nm) t_{R} = 13.4 min (diast. A, minor.), 18.5 min (diast. A, major.), 26.6 min (diast. B, major.), 30.0 min (diast. B, minor.). dr 1.1:1; 31/9% *ee*.

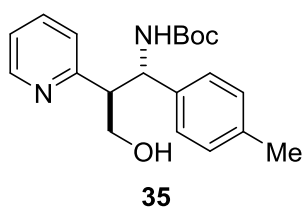
6.4.2.5. Elaboration of adducts

6.4.2.5.1. Reduction of the *N*-oxide group to afford **18'b**

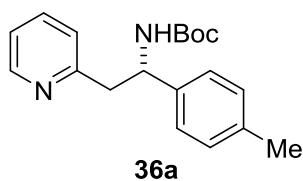
To a solution of adduct **18b** (1 equiv., 0.25 mmol, 0.114 g) in CH₂Cl₂ (3 mL) was added bis(pinacolato)diboron (3 equiv., 0.75 mmol, 0.190 g) and the reaction mixture was stirred at room temperature for 16 hours. Then, the solution was concentrated under reduced pressure and poured into a neutral aluminium oxide flash column chromatography (Hexane:EtOAc, 80:20) to afford the corresponding Mannich adduct which was further purified by grinding with a mixture of solvents (Hexane:MeOH:, 95:5) to produce pure **18'b**. Yield: 0.087 g (80%). White solid. m. p = 117–120 °C. $[\alpha]_D^{24} = -22.8$ (c = 0.5, CH₂Cl₂). IR (v/cm⁻¹): 2975, 1711, 1591, 1497, 1365, 1288, 1164, 753, 699. ¹H NMR (300 MHz, CDCl₃) δ 8.56 (d, *J* = 5.0, 1.8 Hz, 1H), 7.51 (td, *J* = 7.7, 1.9 Hz, 1H), 7.34 – 6.96 (m, 12H), 6.38 (s, 1H), 5.53 (s, 1H), 5.13 – 4.90 (m, 2H), 4.19 (d, *J* = 7.1 Hz, 1H), 1.27 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 170.4, 155.7, 155.2, 149.2, 140.9, 136.8, 135.6, 128.5, 128.4, 128.2, 128.1, 127.4, 126.8, 124.5, 122.8, 79.4, 67.0, 58.9, 56.4, 28.4. UPLC-DAD-QTOF: C₂₆H₂₉N₂O₄ [M+H]⁺ calcd.: 433.2049, found: 433.2124. Chiral HPLC (Chiralpak IC; 80:20 Hexane:Isopropanol; 0.5 mL/min, λ = 210 nm) t_R = 16.6 min (*anti*, minor.), 19 min (*anti*, major.), 39.5 min (*syn*), 42.2 min (*syn*). dr 99:1; 99% *ee*.

6.4.2.5.2. Synthesis of β^{2,3}-amino acid **34**

To a solution of adduct **18a** (1 equiv., 0.25 mmol, 0.115 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.0115 g, 10 % w/w.) was added and the reaction mixture was stirred under H₂ pressure (30 bar) at room temperature for 1.5 hours. Then, the solution was filtrated and concentrated under reduced pressure to give the deprotected carboxylic acid **34**. Yield: 0.087 g (89%). White solid. m. p = 72–77 °C. $[\alpha]_D^{24} = -2.4$ (c = 1.94, CH₂Cl₂). IR (v/cm⁻¹): 2975, 2927, 1700, 1512, 1365, 1249, 1165, 1018, 768. ¹H NMR (300 MHz, MeOD) δ 8.38 (d, *J* = 4.9 Hz, 1H), 7.62 – 7.31 (m, 3H), 7.24 (q, *J* = 6.5, 5.4 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.40 (d, *J* = 9.1 Hz, 1H), 4.88 (d, *J* = 9.6 Hz, 1H), 2.29 (s, 3H), 1.28 (s, 9H). ¹³C NMR (75 MHz, MeOD) δ 157.3, 149.5, 140.8, 138.3, 130.3, 130.0, 128.2, 127.3, 126.5, 125.6, 123.2, 80.2, 57.4, 54.1, 28.6, 21.1. UPLC-DAD-QTOF: C₂₀H₂₄N₂O₅ [M+H]⁺ calcd.: 373.1763, found: 373.1771; [M+Na]⁺ calcd.: 395.1583, found: 395.1581.

6.4.2.5.3. Synthesis of amino alcohol **35**

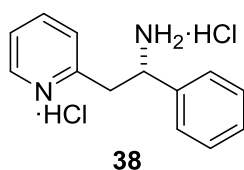
To a solution of adduct **24** (1 equiv., 0.25 mmol, 0.097 g) in THF (2.5 mL), lithium aluminium hydride (0.190 g, 0.75 mmol, 3 equiv.) was added at 0 °C. The reaction mixture was stirred at that temperature for 1 hour. The reaction mixture was then quenched with water (2 mL) and NaOH (20 %) (3 mL) and extracted with CH₂Cl₂ (3 x 7 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Hexane:EtOAc, 90:10 to 70:30) to give compound **35**. Yield: 0.061 g (71%). White solid. m. p = 81–86 °C. $[\alpha]_D^{25} = -39.2$ (c = 0.14, CH₂Cl₂). IR (v/cm⁻¹): 3342, 3007, 2975, 2925, 2867, 1693, 1594, 1503, 1365, 1252, 1168, 1053. ¹H NMR (300 MHz, CDCl₃) δ 8.53 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 7.12 (t, *J* = 6.3 Hz, 1H), 7.00 (s, 4H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.49 (brs, 1H), 5.30 (brs, 1H), 3.98 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.82 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.39 (brs, 1H), 3.32 (brs, 1H), 2.26 (s, 3H), 1.42 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 160.9, 150.0, 139.3, 137.5, 137.4, 130.0, 127.4, 126.2, 123.1, 111.1, 80.7, 65.2, 55.4, 55.1, 29.5, 22.1. UPLC-DAD-QTOF: C₂₀H₂₇N₂O₃ [M+H]⁺ calcd.: 343.2022, found: 343.2042.

6.4.2.5.4. Synthesis of benzyl amine **36a**

To a solution of adduct **18a** (1 equiv., 0.25 mmol, 0.115 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.0115 g, 10 % w/w.) was added and the reaction mixture was stirred under H₂ pressure (30 bar) at room temperature for 1.5 hours. Then, the solution was filtrated and concentrated under reduced pressure to give the deprotected carboxylic acid as white foam. The acid was dissolved in CH₂Cl₂ (3 mL) and bis(pinacolato)diboron (3 equiv., 0.75 mmol, 0.190 g) was added. The reaction mixture was stirred at room temperature for 16 hours. Then, ethylenediamine (2 mL, 30 mmol, 120 equiv.) was added to the mixture, and the stirring was continued for 1 hour at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Hexane:EtOAc, 90:10 to 80:20) to give compound **36a**. Yield: 0.070 g (90%). White solid. m. p = 121–124 °C. $[\alpha]_D^{25} = -28.7$ (c = 1.2, CH₂Cl₂). IR

(ν/cm^{-1}): 3006, 2974, 2924, 2867, 1695, 1511, 1364, 1247, 1164, 1018, 810, 751, 541. ^1H NMR (300 MHz, CDCl_3) δ 8.53 (dd, $J = 5.2, 1.7$ Hz, 1H), 7.51 (td, $J = 7.7, 1.9$ Hz, 1H), 7.17 – 7.00 (m, 4H), 6.97 (dd, $J = 7.8, 1.4$ Hz, 1H), 5.88 (brs, 1H), 5.03 (brs, 1H), 3.26 (dd, $J = 13.6, 5.2$ Hz, 1H), 3.11 (dd, $J = 13.9, 7.9$ Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.4, 155.3, 149.2, 136.6, 136.4, 129.1, 126.2, 124.1, 121.7, 79.3, 54.8, 44.9, 28.4, 21.2. UPLC-DAD-QTOF: $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ calcd.: 313.1916, found: 313.1929.

6.4.2.5.5. Synthesis of Lanicemine (AZD6765) dihydrochloride (**38**)

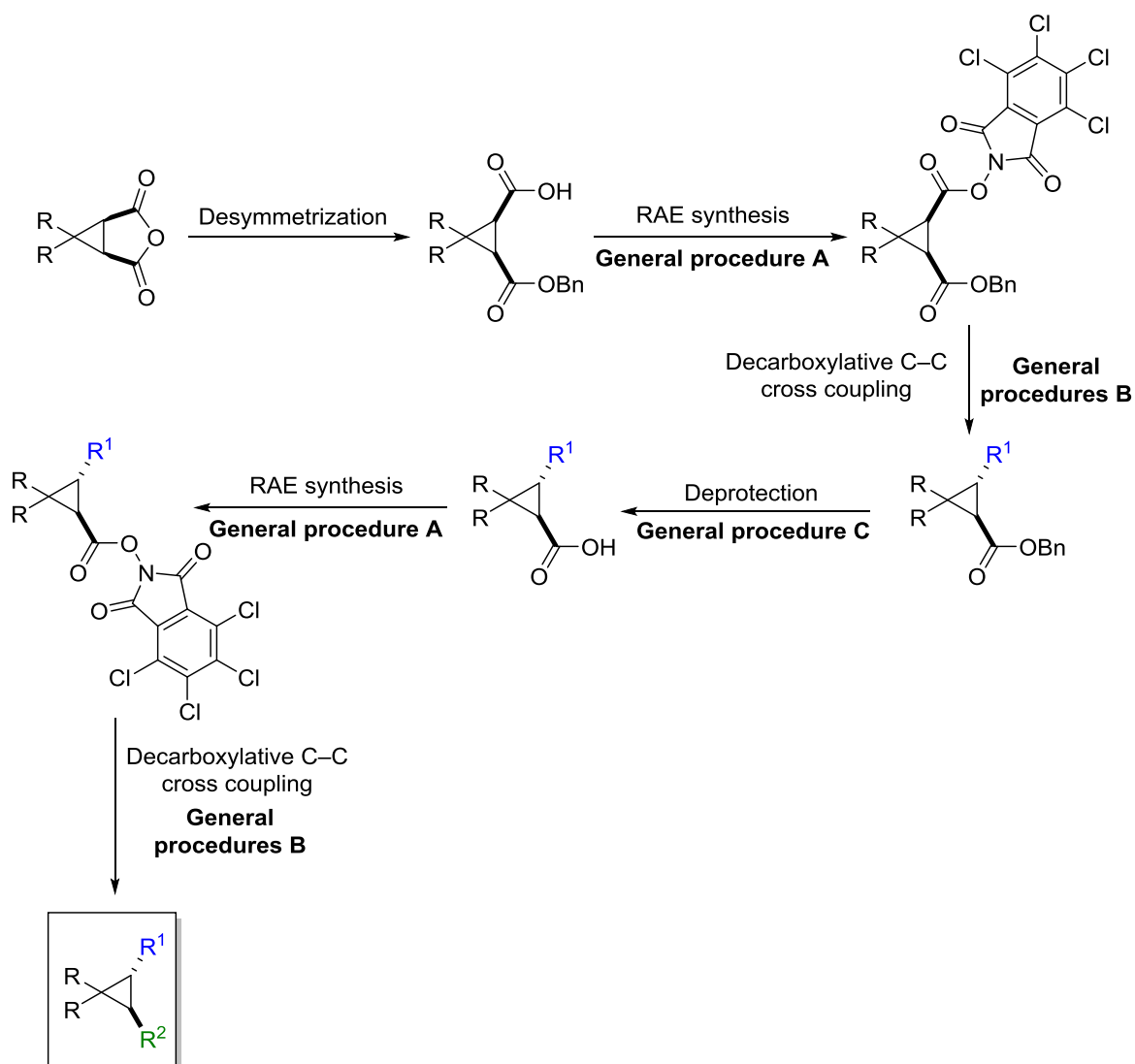


To a solution of adduct **18b** (1 equiv., 0.25 mmol, 0.115 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.0115 g, 10 % w/w.) was added and the reaction mixture was stirred under H_2 pressure (30 bar) at room temperature for 1.5 hours. Then, the solution was filtrated and concentrated under reduced pressure to give the deprotected carboxylic acid as white foam. The acid was dissolved in CH_2Cl_2 (3 mL) and bis(pinacolato)diboron (3 equiv., 0.75 mmol, 0.190 g) was added. The reaction mixture was stirred at room temperature for 16 hours. Then, ethylenediamine (120 equiv., 30 mmol, 2 mL) was added to the mixture, and the stirring was continued for 1 hour at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (Hexane:EtOAc, 90:10 to 80:20) to give compound **36b**. This compound was redissolved in MeOH (10 mL) and TMSCl (0.64 mL, 5.0 mmol, 20.0 equiv.) was added at room temperature. After 4 hours, the reaction mixture was concentrated under reduced pressure. THF (3 mL) was added and a white solid precipitated. Centrifugation and solvent elimination gave pure lanicemine dihydrochloride (**38**). Overall yield: 0.052 g (76%). White solid. ^1H NMR (300 MHz, $\text{MeOD}-d_4$) δ 8.74 (dd, $J = 5.7, 0.9$ Hz, 1H), 8.43 (td, $J = 7.9, 1.7$ Hz, 1H), 8.00 – 7.80 (m, 2H), 7.47 (dtt, $J = 6.2, 3.7, 1.9$ Hz, 5H), 4.95 (dd, $J = 9.5, 6.3$ Hz, 1H), 3.94 (dd, $J = 14.4, 6.3$ Hz, 1H), 3.72 (dd, $J = 14.4, 9.6$ Hz, 1H). Physical and spectroscopic data were coincident with the previously reported.²⁴⁹

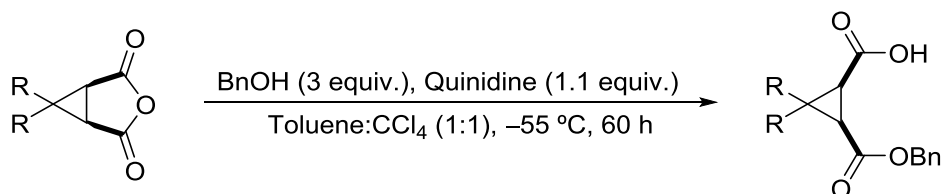
²⁴⁹ Ref. 203a, page 151.

6.5. Experimental section for Chapter 4

Products in chapter 4 were synthesized following this general synthetic pathway:



6.5.1. Desymmetrization of *meso*-anhydrides²⁵⁰

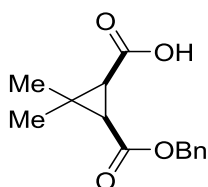


Benzyl alcohol (3.0 equiv., 45.0 mmol, 4.66 mL) was added dropwise to a stirred suspension of the corresponding anhydride (1.0 equiv., 15.0 mmol) and quinidine (1.1

²⁵⁰ Ref. 218, page 165.

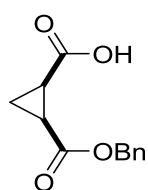
equiv., 16.5 mmol, 5.35 g) in a 1:1 mixture of toluene and tetrachloromethane (75 mL) at $-55\text{ }^{\circ}\text{C}$ under argon. The reaction mixture was stirred at this temperature for 60 hours. During this period, the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuo to dryness, and the resulting residue was then dissolved in Et_2O (40 mL). The solution was washed with 2 M HCl (3 x 15 mL), followed by extraction of the aqueous phase with Et_2O (5 x 20 mL) and the combined organic layers extracted with saturated solution of sodium carbonate (5 x 25 mL). The resulting aqueous phase was washed with Et_2O (1 x 40 mL) in order to remove traces of benzyl alcohol, acidified with concentrated HCl, extracted with methylene chloride (5 x 30 mL) and the organic layer was dried over MgSO_4 , filtered, and concentrated providing the corresponding hemiester.

(1S,3R)-3-((Benzyloxy)carbonyl)-2,2-dimethylcyclopropane-1-carboxylic acid



The title compound was prepared according to the general procedure employing caronic acid **45**. Yield: 3.5 g (94 %). Colorless oil. $[\alpha]_{\text{D}}^{20} = -2.2$ ($c = 1.04$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.52 – 7.41 (m, 5H), 5.28 (AB-system, 2H), 2.13 (d, $J = 8.7$ Hz, 1H), 2.09 (d, $J = 8.7$ Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 172.7, 171.7, 135.3, 128.8, 128.6, 67.6, 33.8, 33.0, 28.4, 27.9, 15.4. Spectroscopic data matched with literature.²⁵⁰

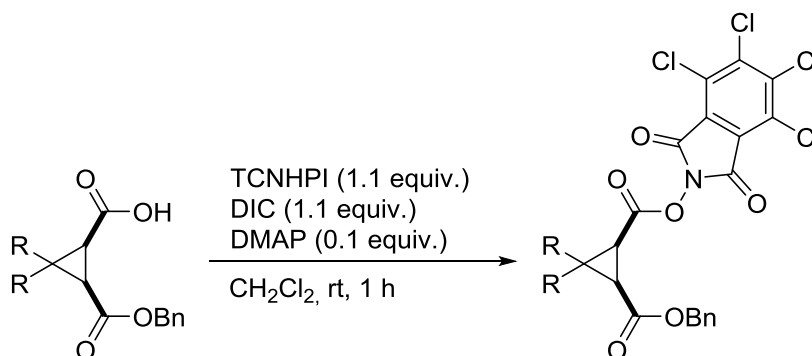
(1R,2S)-2-((Benzyloxy)carbonyl)cyclopropane-1-carboxylic acid



The title compound was prepared according to the general procedure employing 3-oxabicyclo[3.1.0]hexane-2,4-dione **46**. Yield: 3.0 g (92 %). Colorless oil. $[\alpha]_{\text{D}}^{20} = -5.2$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.52 (brs, 1H), 7.40 – 7.28 (m, 5H), 5.13 (AB-system, 2H), 2.23 – 2.14 (m, 1H), 2.13 – 2.05 (m, 1H), 1.73 (td, $J = 6.8, 5.1$ Hz, 1H), 1.34 (td, $J = 8.4, 5.1$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 175.9, 169.9, 135.6, 128.7, 128.5, 128.5, 67.3, 22.6, 21.5, 12.7. Spectroscopic data matched with literature.²⁵¹

²⁵¹ Jnoff, E.; Albrecht, C.; Barker, J. J.; Barker, O.; Beaumont, E.; Bromidge, S.; Brookfield, F.; Brooks, M.; Bubert, C.; Ceska, T.; Corden, V.; Dawson, G.; Duclos, S.; Fryatt, T.; Genicot, C.; Jigorel, E.; Kwong, J.; Maghames, R.; Mushi, I.; Pike, R.; Sands, Z. A.; Smith, M. A.; Stimson, C. C.; Courade, J.-P. *ChemMedChem* **2014**, *9*, 699–705.

6.5.2. Synthesis of redox-active esters (General procedure A)



Redox-active esters were prepared according to the previously reported procedure.²⁵² The corresponding carboxylic acid (1.0 equiv.) was dissolved in methylene chloride (0.1 – 0.2 M) and *N*-hydroxytetrachlorophthalimide (1.1 equiv.), DIC (1.1 equiv.) and DMAP (0.1 equiv.) were added. The mixture was stirred vigorously at room temperature for 1 hour. After completion of reaction, the mixture was filtered over silica gel and rinsed with additional CH_2Cl_2 . The solvent was removed under reduced pressure, and purification by crystallization in Et_2O afforded the desired pure TCNHPI redox-active ester.

6.5.3. Decarboxylative cross-coupling reactions

6.5.3.1. Ni catalyzed Negishi reactions

Preparation of organozinc reagents

Mg insertion for the preparation of non-commercial Grignard reagents (10 mmol scale):

LiCl (1.25 equiv., 12.5 mmol, 0.530 g) was flame-dried under vacuum. After cooling, the flask was placed under Ar atmosphere, and Mg turnings (2.5 equiv., 25 mmol, 0.608 g) were added. In a separate flask under Ar atmosphere, a solution of the corresponding aryl or alkenyl bromide (1.0 equiv., 10 mmol) in THF (8 mL) was prepared. A small amount of THF (ca. 2 mL) was added to the flask containing LiCl and Mg, followed by dropwise addition of 1,2-dibromoethane (0.1 equiv., 0.09 mL). Vigorous bubbling occurred. If vigorous bubbling did not occur, the mixture was gently heated with a heat gun until effervescence ensued. At this time, the solution of alkenyl bromide in THF was added dropwise, and the mixture was periodically heated with a heat gun. Upon

²⁵² Ref. 212, page 160.

complete addition, the mixture was placed in an oil bath (ca. 70 – 80 °C) and refluxed for 1 hour. The Grignard reagent was titrated with I₂ before use (see below). Typical concentrations were between 0.4 M and 0.8 M.

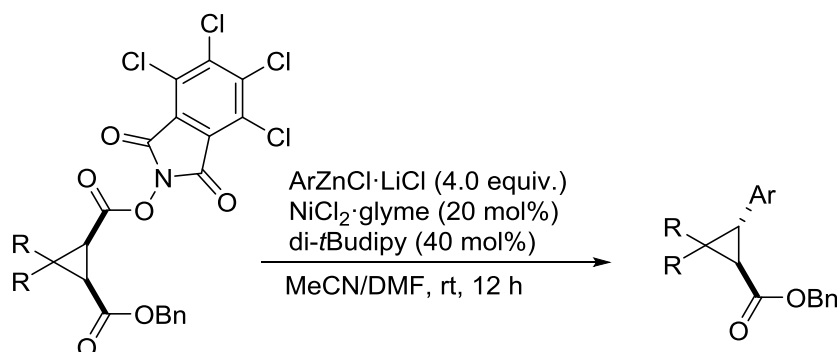
Transmetalation with ZnCl₂ (5 mmol scale):

ZnCl₂ (1.0 equiv., 5 mmol, 0.680 g) (and LiCl (1.0 equiv., 5 mmol, 0.212 g) for commercial Grignard reagents) was flame-dried under vacuum. Upon cooling, the flask was placed under Ar atmosphere. Anhydrous THF (5 mL) was added, and the mixture was stirred vigorously until all ZnCl₂ dissolved. At this time, the Grignard reagent (1 equiv., 5 mmol) was added slowly to the ZnCl₂ solution and the solution was stirred for 15 minutes. Then, the organozinc reagent solution in THF was concentrated under reduced pressure under argon atmosphere, anhydrous MeCN was added and stirred for 5 minutes. The organozinc reagent was titrated with I₂ see below before its use. Typical concentrations were between 0.35 M and 0.25 M.

Titration of arylzinc reagents:

I₂ (approximately 1.0 equiv., 0.1 mmol, 0.025 g) was quickly added to the culture tube. THF (anhydrous, 1.0 mL) was added, and the mixture was stirred for 5 min to give a dark brown solution. A 1.00 mL syringe was filled with the corresponding RZnCl·LiCl, and the solution was added dropwise via the syringe. Over the course of the titration the color changed from dark brown to light brown to yellow to clear, indicating complete consumption of I₂. The concentration of the RZnCl·LiCl solution was then calculated.

6.5.3.1.1. Negishi arylation (General procedure B1)



Preparation of the nickel/ligand solution:

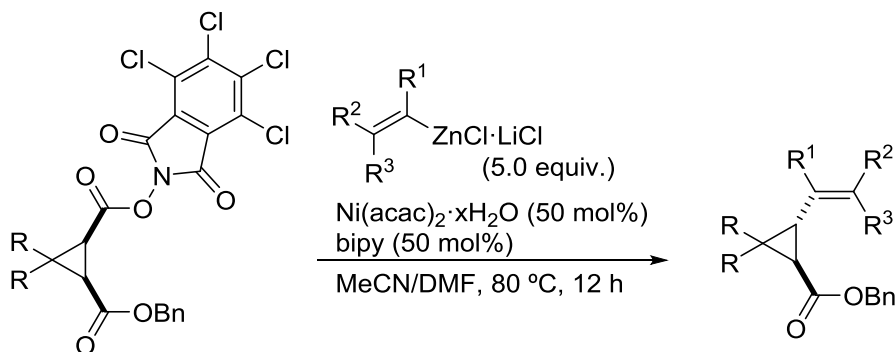
A culture tube was charged with NiCl₂·glyme (0.25 mmol, 0.055 g) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.5 mmol, 0.134 g) under argon atmosphere. Anhydrous DMF (10

mL) was added and the homogeneous solution was stirred at room temperature for 15 minutes before use.

Procedure for 0.1 mmol scale:

A culture tube was charged with the corresponding TCNHPI redox-active ester (1.0 equiv., 0.1 mmol) and a stir bar. The tube was then evacuated and backfilled with argon from a balloon. Nickel/ligand solution (0.8 mL) was added and stirred at room temperature for 5 minutes. After that, a solution of the corresponding arylzinc reagent (4.0 equiv.) was added in one portion and stirred at room temperature for 12 hours. After the reaction completion, Et₂O (2 mL) was added, quenched with 1 M HCl (1 mL), washed with brine (2 x 1 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography or preparative TLC (pTLC) to yield the pure compound.

6.5.3.1.2. Negishi alkenylation (General procedure B2)



Preparation nickel/ligand solution:

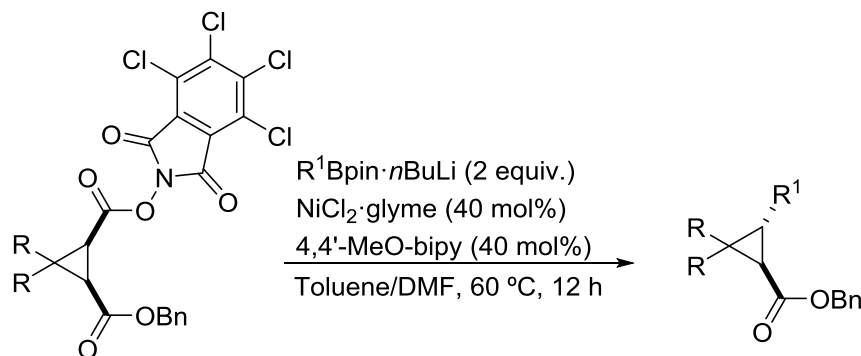
A culture tube was charged with Ni(acac)₂·xH₂O (0.5 mmol, 0.148 g) and 2,2'-bipyridine (0.5 mmol, 0.078 g) under argon atmosphere. Anhydrous DMF (10 mL) was added and the homogeneous solution was stirred at room temperature for 15 minutes before use.

Procedure for 0.1 mmol scale:

A culture tube was charged with the corresponding TCNHPI redox-active ester (1.0 equiv., 0.1 mmol) and a stir bar. The tube was then evacuated and backfilled with argon from a balloon. Nickel/ligand solution (1.0 mL) was added and stirred at room temperature for 5 minutes. After that, a solution of the corresponding alkenylzinc reagent (5.0 equiv.) was added in one portion and stirred at 80 °C for 12 hours. After the reaction completion, Et₂O (2 mL) was added, quenched with 1 M HCl (1 mL), washed with brine (2 x 1 mL), dried with MgSO₄, filtered, and concentrated under reduced

pressure. The crude product was purified by preparative TLC (pTLC) to yield the pure compound.

6.5.3.2. Suzuki coupling (General procedure B3)



Preparation of the nickel/ligand solution:

A culture tube was charged with $\text{NiCl}_2\cdot\text{glyme}$ (0.4 mmol, 0.088 g) and 4,4'-dimethoxy-2,2'-bipyridine (0.4 mmol, 0.087 g), under argon atmosphere. Anhydrous DMF (10 mL) was added and the homogeneous solution was stirred at room temperature for 15 minutes before use.

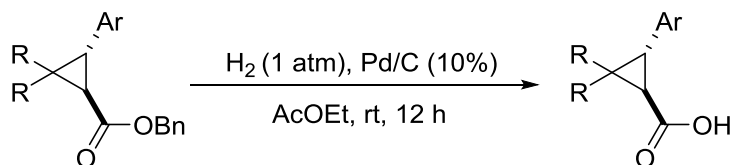
Preparation of $R^1\text{Bpin}\cdot n\text{BuLi}$ solution:

A flame-dried culture tube was charged with the corresponding $R^1\text{Bpin}$ (0.3 mmol) under argon atmosphere and anhydrous toluene (1.5 mL) was added. A 2.5 M solution of $n\text{-BuLi}$ in hexane (0.3 mmol, 0.12 mL) was added at 0 °C and the resulting mixture was stirred at room temperature for 15 minutes.

Procedure for 0.1 mmol scale:

A culture tube was charged with the corresponding TCNHPI redox-active ester (1.0 equiv., 0.1 mmol) and a stir bar. The tube was then evacuated and backfilled with argon from a balloon. Nickel/ligand solution (1.0 mL) was added and stirred at room temperature for 5 minutes. After that, the corresponding $R^1\text{Bpin}\cdot n\text{BuLi}$ solution (2 equiv., 0.2 mmol, 1.0 mL) was added in one portion and stirred at 60 °C for 12 hours. After the reaction completion, Et_2O (2 mL) was added, quenched with 1 M HCl (1 mL), washed with brine (2 x 1 mL), dried with MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (pTLC) to yield the pure compound.

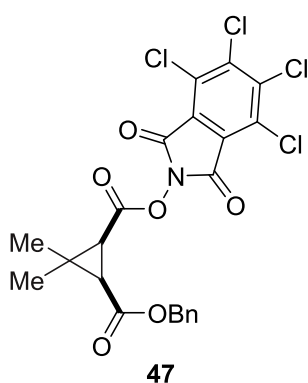
6.5.4. Deprotection of benzyl esters (General procedure C)



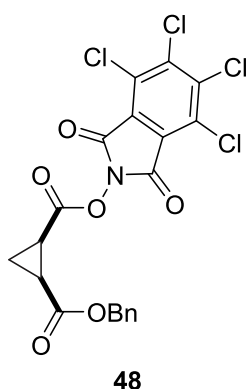
The corresponding benzylic ester (1.0 mmol) was dissolved in AcOEt (2.0 mL) in argon atmosphere. Pd on carbon (10 %) was added and the flask was evacuated and backfilled with H₂ (g) with a balloon three times. The reaction was stirred under H₂ atmosphere at room temperature for 12 hours. After that, the reaction mixture was filtrated over celite and solvent was evaporated under reduced pressure to afford the corresponding deprotected carboxylic acid.

Characterization of compounds

1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) (1R,2S)-3,3-dimethylcyclopropane-1,2-dicarboxylate (47)

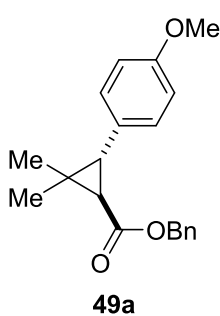


The title compound **47** was prepared on a 10.0 mmol scale according to general procedure A employing (1*S*,3*R*)-3-((benzyloxy)carbonyl)-2,2-dimethylcyclopropane-1-carboxylic acid. Yield: 4.4 g (83 %). Yellow solid. m.p. = 115–117 °C. $[\alpha]_D^{20} = +3.7$ ($c = 1.00$, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.26 (m, 5H), 5.17 – 5.10 (m, 2H), 2.24 (d, $J = 9.3$ Hz, 1H), 2.18 (d, $J = 9.3$ Hz, 1H), 1.47 (s, 3H), 1.33 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.3, 165.1, 157.5, 141.0, 135.6, 130.5, 128.7, 128.6, 128.4, 124.8, 67.1, 34.1, 28.6, 27.8, 27.8, 15.3. HRMS (ESI-TOF): calcd for C₂₂H₁₆Cl₄NO₆ [M+H]⁺: 529.9726, found: 529.9725. Chiral SFC (Daicel IB; 40% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 238$ nm). t_R (major) = 4.14 min, t_R (minor) = 5.84 min. 96% ee.

1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) (1R,2S)-cyclopropane-1,2-dicarboxylate (48)

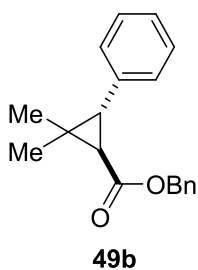
The title compound **48** was prepared on a 10.0 mmol scale according to general procedure A employing (1R,2S)-2-((benzyloxy)carbonyl)cyclopropane-1-carboxylic acid. Yield: 4.0 g (80 %). Yellow solid. m.p. = 137–140 °C. $[\alpha]_D^{20} = -66.4$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.48 – 7.27 (m, 5H), 5.25 – 5.15 (m, 2H), 2.45 – 2.35 (m, 2H), 2.00 – 1.89 (m, 1H), 1.57 – 1.47 (m, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 168.1, 165.9, 157.3, 141.1, 135.6, 130.6, 128.8, 128.7, 128.5, 124.8, 67.7, 23.5, 18.4, 12.9. HRMS (ESI-TOF): calcd for $\text{C}_{20}\text{H}_{12}\text{Cl}_4\text{NO}_6$ $[\text{M}+\text{H}]^+$: 501.9413, found: 501.9413.

Chiral SFC (Daicel IA; 40% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 238$ nm). t_R (minor) = 8.91 min, t_R (major) = 10.59 min, 96% *ee*.

Benzyl (1R,3R)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (49a)

The title compound **49a** was prepared on a 2.0 mmol scale according to general procedure B1 employing **47** and the arylzinc reagent derived from 4-bromoanisole. Purification by flash column chromatography with gradient elution (4:1 hexane: CH_2Cl_2 to 1:1 hexane: CH_2Cl_2). Yield: 0.292 g (47 %). Yellow oil. $[\alpha]_D^{20} = +16.2$ ($c = 0.65$, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.45 – 7.30 (m, 5H), 7.12 – 7.04 (m, 2H), 6.86 – 6.78 (m, 2H), 5.17 (AB-system, 2H), 3.79 (s, 3H),

2.67 (d, $J = 5.8$ Hz, 1H), 1.95 (d, $J = 5.8$ Hz, 1H), 1.37 (s, 3H), 0.92 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 173.4, 140.1, 136.1, 128.7, 128.6, 128.4, 128.3, 126.7, 126.3, 66.7, 26.5, 24.3, 17.4. HRMS (ESI-TOF): calcd for $\text{C}_{20}\text{H}_{23}\text{O}_3$ $[\text{M}+\text{H}]^+$: 311.1642, found: 311.1646. Chiral SFC (Daicel IG; 30% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 226$ nm). t_R (minor) = 1.64 min, t_R (major) = 1.94 min, 94% *ee*.

Benzyl (1R,3R)-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (49b)

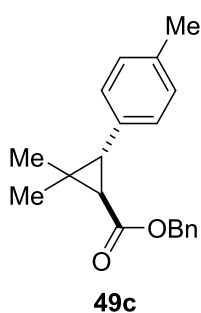
The title compound **49b** was prepared according to general procedure B1 employing **47** and the arylzinc reagent derived from phenylmagnesium bromide. Purification by pTLC (7:3 hexane: CH_2Cl_2). Yield: 0.015 g (56 %). Colorless oil. $[\alpha]_D^{20} = +23.6$ ($c = 0.40$, CHCl_3). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.43 – 7.32 (m, 5H), 7.28 (dd, $J = 8.2, 6.8$ Hz, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.14 (m, 2H), 5.19 (d, $J = 12.5$ Hz, 1H),

5.17 (d, $J = 12.3$ Hz, 1H), 2.74 (d, $J = 5.8$ Hz, 1H), 2.03 (d, $J = 5.8$ Hz, 1H), 1.39 (s, 3H), 0.93

Experimental section

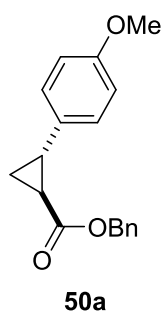
(s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 172.3, 137.4, 136.3, 128.9, 128.7, 128.4, 128.3, 128.3, 126.5, 66.5, 37.9, 31.7, 29.8, 22.1, 20.9. HRMS (ESI-TOF): calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$: 281.1536, found: 281.1539. Chiral SFC (Daicel IG; 5% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_{R} (minor) = 2.63 min, t_{R} (major) = 2.94 min, 96% *ee*.

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropane-1-carboxylate (49c)

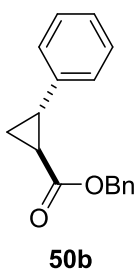


The title compound **49c** was prepared according to general procedure B1 employing **47** and the arylzinc reagent derived from 4-bromotoluene. Purification by pTLC (1:1 hexane: CH_2Cl_2). Yield: 0.016 g (54 %). Yellow oil. $[\alpha]_{\text{D}}^{20}$ = +6.4 (c = 0.10, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ 7.41 – 7.32 (m, 5H), 7.09 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 5.18 (d, J = 12.3 Hz, 1H), 5.16 (dd, J = 33.7, 12.3 Hz, 1H), 2.69 (d, J = 5.9 Hz, 1H), 2.31 (s, 3H), 1.98 (d, J = 5.8 Hz, 1H), 1.38 (d, J = 2.0 Hz, 3H), 0.92 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 172.5, 136.4, 136.1, 134.3, 129.0, 128.8, 128.7, 128.4, 128.3, 66.5, 37.6, 31.7, 29.7, 22.1, 21.2, 20.9. HRMS (ESI-TOF): calcd for $\text{C}_{20}\text{H}_{23}\text{O}_2$ $[\text{M}+\text{H}]^+$: 295.1693, found: 295.1696. Chiral SFC (Daicel IC; 5% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_{R} (minor) = 1.59 min, t_{R} (major) = 1.72 min, 94% *ee*.

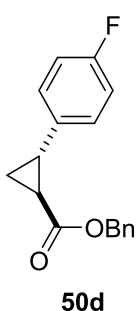
Benzyl (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (50a)



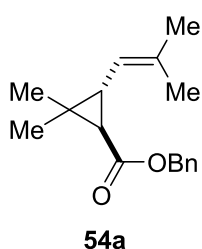
The title compound **50a** was prepared according to general procedure B1 employing **48** and the arylzinc reagent derived from 4-bromoanisole. Purification by pTLC (1:1 hexane: CH_2Cl_2). Yield: 0.011 g (40 %). Yellow oil. $[\alpha]_{\text{D}}^{20}$ = +101.5 (c = 0.27, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ 7.39 – 7.35 (m, 4H), 7.35 – 7.31 (m, 1H), 7.05 – 7.00 (m, 2H), 6.84 – 6.79 (m, 2H), 5.17 (d, J = 12.3 Hz, 1H), 5.14 (d, J = 12.3 Hz, 1H), 3.78 (s, 3H), 2.52 (ddd, J = 9.2, 6.6, 4.1 Hz, 1H), 1.89 (ddd, J = 8.3, 5.2, 4.1 Hz, 1H), 1.59 (ddd, J = 9.2, 5.2, 4.6 Hz, 3H), 1.28 (ddd, J = 8.4, 6.6, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.6, 158.6, 136.2, 132.1, 128.8, 128.5, 128.4, 127.6, 114.2, 66.8, 55.6, 26.1, 24.1, 17.2. HRMS (ESI-TOF): calcd for $\text{C}_{18}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 283.1329, found: 383.1335. Chiral SFC (Daicel IG; 35% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 231 nm). t_{R} (minor) = 2.57 min, t_{R} (major) = 3.19 min, 94% *ee*.

Benzyl (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylate (50b)

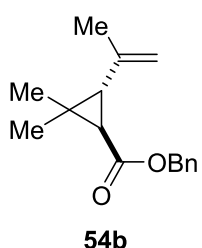
The title compound **50b** was prepared according to general procedure B1 employing **48** and the arylzinc reagent derived from phenylmagnesium bromide. Purification by pTLC (1:1 hexane:CH₂Cl₂). Yield: 0.013 g (50 %). Colorless oil. $[\alpha]_D^{20} = +168.2$ ($c = 0.75$, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.30 (m, 5H), 7.32 – 7.24 (m, 2H), 7.25 – 7.17 (m, 1H), 7.14 – 7.07 (m, 2H), 5.18 (d, $J = 15.0$ Hz, 1H), 5.15 (d, $J = 15.0$ Hz, 1H), 2.57 (ddd, $J = 9.2, 6.6, 4.2$ Hz, 1H), 1.98 (ddd, $J = 8.4, 5.3, 4.1$ Hz, 1H), 1.64 (ddd, $J = 9.2, 5.3, 4.6$ Hz, 1H), 1.35 (ddd, $J = 8.4, 6.5, 4.5$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 173.4, 140.1, 136.1, 128.7, 128.6, 128.4, 128.3, 126.7, 126.3, 66.7, 26.5, 24.3, 17.4. HRMS (ESI-TOF): calcd for C₁₇H₁₇O₂ [M+H]⁺: 253.1223, found: 253.1219. Chiral SFC (Daicel IBN; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.51 min, t_R (major) = 2.65 min, 94% *ee*.

Benzyl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (50d)

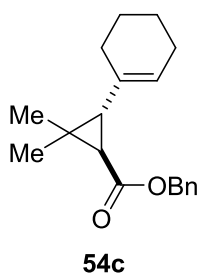
The title compound **50d** was prepared on a 2.0 mmol scale according to general procedure B1 employing **48** and the arylzinc reagent derived from 4-bromofluorobenzene. Purification by flash column chromatography with gradient elution (4:1 hexane:CH₂Cl₂ to 3:2 hexane:CH₂Cl₂). Yield: 0.227 g (42 %). Yellow oil. $[\alpha]_D^{20} = +161.6$ ($c = 0.19$, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ 7.40 – 7.30 (m, 5H), 7.08 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 5.17 (d, $J = 12.3$ Hz, 1H), 5.14 (d, $J = 12.3$ Hz, 1H), 2.54 (ddd, $J = 9.3, 6.6, 4.2$ Hz, 1H), 1.91 (ddd, $J = 8.5, 5.3, 4.2$ Hz, 1H), 1.62 (dt, $J = 9.2, 5.0$ Hz, 1H), 1.29 (ddd, $J = 8.5, 6.5, 4.6$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 173.3, 161.8 (d, $J = 244.6$ Hz), 136.0, 135.7 (d, $J = 3.3$ Hz), 128.7, 128.4, 128.4, 127.9 (d, $J = 7.7$ Hz), 115.55 (d, $J = 21.5$ Hz), 66.8, 25.8, 24.1, 17.2. ¹⁹F NMR (376 MHz, CDCl₃) δ -116.3. GC/MS (EI): m/z (%) 270 (1%), 225 (5%), 133 (14%), 91 (100%). Chiral SFC (Daicel IG; 15% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.04 min, t_R (major) = 2.37 min, 94% *ee*.

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (54a)

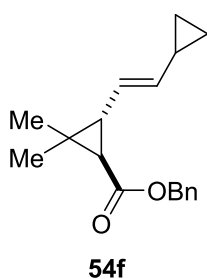
The title compound **54a** was prepared according to general procedure B2 employing **47** and the arylzinc reagent derived from 2-methyl-1-propenylmagnesium bromide. Purification by pTLC (7:3 hexane:CH₂Cl₂). Yield: 0.010 g (40 %). Yellow oil. $[\alpha]_{\text{D}}^{20} = -9.5$ ($c = 0.48$, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ 7.39 – 7.35 (m, 4H), 7.35 – 7.31 (m, 1H), 7.05 – 7.00 (m, 2H), 6.84 – 6.79 (m, 2H), 5.17 (d, $J = 12.3$ Hz, 1H), 5.14 (d, $J = 12.3$ Hz, 1H), 3.78 (s, 3H), 2.52 (ddd, $J = 9.2, 6.6, 4.1$ Hz, 1H), 1.89 (ddd, $J = 8.3, 5.2, 4.1$ Hz, 1H), 1.59 (ddd, $J = 9.2, 5.2, 4.6$ Hz, 3H), 1.28 (ddd, $J = 8.4, 6.6, 4.5$ Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 172.6, 136.5, 135.7, 128.7, 128.3, 128.2, 121.2, 66.3, 34.9, 33.1, 29.0, 25.7, 22.3, 20.6, 18.6. HRMS (ESI-TOF): calcd for C₁₇H₂₃O₂ [M+H]⁺: 259.1693, found: 259.1692. Chiral SFC (Daicel IG; 3% MeOH / CO₂ (2.8 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_{R} (minor) = 2.51 min, t_{R} (major) = 2.80 min, 93% *ee*.

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(prop-1-en-2-yl)cyclopropane-1-carboxylate (54b)

The title compound **54b** was prepared according to general procedure B2 employing **47** and the arylzinc reagent derived from isopropenylmagnesium bromide. Purification by pTLC (7:3 hexane:CH₂Cl₂). Yield: 0.013 g (55 %). Yellow oil. $[\alpha]_{\text{D}}^{20} = +10.2$ ($c = 0.55$, CHCl₃). ¹H NMR (600 MHz, CDCl₃) δ 7.42 – 7.29 (m, 5H), 5.16 – 5.10 (m, 2H), 4.85 (h, $J = 1.5$ Hz, 1H), 4.63 (td, $J = 1.7, 0.9$ Hz, 1H), 2.00 (d, $J = 5.9$ Hz, 1H), 1.77 (dt, $J = 1.6, 0.8$ Hz, 3H), 1.73 (d, $J = 5.9$ Hz, 1H), 1.29 (s, 3H), 1.06 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 172.3, 141.7, 136.4, 128.7, 128.4, 128.3, 111.5, 66.4, 39.7, 31.1, 28.9, 23.8, 20.8, 20.6. HRMS (ESI-TOF): calcd for C₁₆H₂₁O₂⁺ [M+H]⁺: 245.1536; found: 245.1537. Chiral SFC (Daicel IG; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_{R} (minor) = 1.71 min, t_{R} (major) = 1.95 min, 92% *ee*.

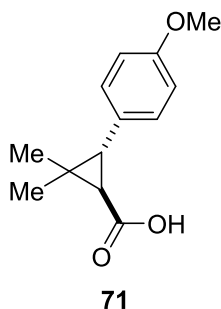
Benzyl (1*R*,3*R*)-3-(cyclohex-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylate (54c)

The title compound **54c** was prepared according to general procedure B2 employing **47** and the arylzinc reagent derived from 1-bromocyclohexene.²⁵³ Purification by pTLC (7:3 hexane:CH₂Cl₂). Yield: 0.022 g (72 %). Yellow oil. $[\alpha]_{\text{D}}^{20} = +26.7$ ($c = 0.33$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.28 (m, 5H), 5.28 (dd, $J = 15.2, 8.2$ Hz, 1H), 5.16 – 5.09 (m, 2H), 2.06 – 1.99 (m, 1H), 1.68 – 1.55 (m, 1H), 1.54 (d, $J = 5.3$ Hz, 1H), 1.46 – 1.28 (m, 2H), 1.28 (s, 1H), 1.25 (s, 3H), 1.16 (d, $J = 1.8$ Hz, 3H), 0.72 – 0.64 (m, 2H), 0.34 (dddd, $J = 6.7, 5.2, 3.3, 1.4$ Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 172.6, 136.5, 133.9, 128.7, 128.3, 128.2, 122.9, 66.3, 40.0, 30.2, 29.9, 28.8, 25.2, 23.0, 22.6, 20.9, 20.8. HRMS (ESI-TOF): calcd for C₁₉H₂₅O₂⁺ [M+H]⁺: 285.1849; found: 285.1852. Chiral SFC (Daicel IA; 3% ⁱPrOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_{R} (minor) = 2.29 min, t_{R} (major) = 2.45 min, 94% *ee*.

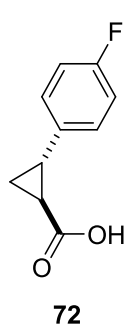
Benzyl (1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropane-1-carboxylate (54f)

The title compound **54f** was prepared according to general procedure B3 employing **47** and (trans)-2-cyclopropylvinylboronic acid pinacol ester. Purification by pTLC (7:3 hexane:CH₂Cl₂). Yield: 0.022 g (55 %). Yellow oil. $[\alpha]_{\text{D}}^{20} = -7.8$ ($c = 0.51$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.28 (m, 5H), 5.28 (dd, $J = 15.2, 8.2$ Hz, 1H), 5.13 (dd, $J = 14.8, 8.7$ Hz, 1H), 5.12 (d, $J = 8.0$ Hz, 1H), 5.08 (d, $J = 12.4$ Hz, 1H), 2.02 (dd, $J = 8.2, 5.3$ Hz, 1H), 1.54 (d, $J = 5.3$ Hz, 1H), 1.44 – 1.32 (m, 1H), 1.25 (s, 3H), 1.15 (s, 3H), 0.71 – 0.65 (m, 2H), 0.34 (dtd, $J = 6.7, 3.6, 1.1$ Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 172.2, 136.8, 136.4, 128.7, 128.4, 128.3, 124.4, 77.5, 77.2, 76.8, 66.3, 36.5, 34.0, 29.0, 22.1, 20.5, 14.0, 6.8, 6.7. HRMS (ESI-TOF): calcd for C₁₈H₂₃O₂⁺ [M+H]⁺: 271.1693; found: 271.1693. Chiral SFC (Daicel IG; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_{R} (minor) = 1.87 min, t_{R} (major) = 2.27 min, 95% *ee*.

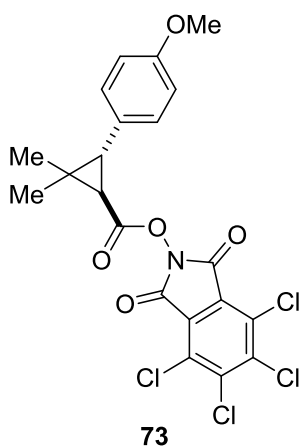
²⁵³ Prepared following the procedure in: Likhite, N.; Ramasamy, S.; Tendulkar, S.; Sathasivam, S.; Luzung, M.; Zhu, Y.; Strotman, N.; Nye, J.; Ortiz, A.; Kiau, S.; Eastgate, M. D.; Vaidyanathan, R. *Org. Process Res. Dev.* **2016**, *20*, 977–981.

(1*R*,3*R*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylic acid (71)

The title compound **71** was prepared according to general procedure C employing **49a**. Yield: 0.220 g (99 %). Colorless oil. $[\alpha]_D^{20} = +9.8$ ($c = 0.56$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.14 – 7.03 (m, 2H), 6.88 – 6.79 (m, 2H), 3.79 (s, 3H), 2.69 (d, $J = 5.7$ Hz, 1H), 1.89 (d, $J = 5.8$ Hz, 1H), 1.42 (s, 3H), 0.95 (s, 3H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 179.2, 158.3, 129.8, 129.1, 113.7, 55.3, 37.8, 31.8, 30.6, 22.2, 20.7.

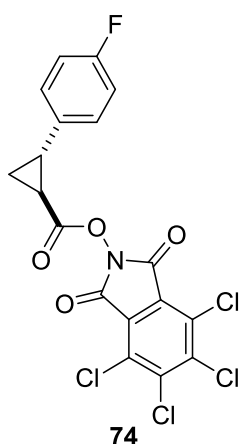
(1*S*,2*S*)-2-(4-Fluorophenyl)cyclopropane-1-carboxylic acid (72)

The title compound **72** was prepared according to general procedure C employing **50d**. Yield: 0.180 g (99 %). Colorless oil. $[\alpha]_D^{20} = +9.8$ ($c = 0.56$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.08 (ddt, $J = 8.2, 5.2, 2.5$ Hz, 2H), 7.01 – 6.94 (m, 2H), 2.59 (ddd, $J = 9.3, 6.7, 4.1$ Hz, 1H), 1.85 (ddd, $J = 8.4, 5.2, 4.1$ Hz, 1H), 1.71 – 1.60 (m, 1H), 1.36 (ddd, $J = 8.4, 6.7, 4.7$ Hz, 1H). $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 178.5, 161.87 (d, $J = 245.0$ Hz), 135.25 (d, $J = 2.8$ Hz), 128.06 (d, $J = 8.2$ Hz), 115.54 (d, $J = 21.4$ Hz) 26.5, 23.7, 17.5. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -116.0.

**4,5,6,7-Tetrachloro-1,3-dioxoisindolin-2-yl
dimethylcyclopropane-1-carboxylate (73)****(1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-**

The title compound **73** was prepared on a 1.0 mmol scale according to general procedure A employing carboxylic acid **71**. Yield: 0.45 g (90 %). Yellow solid. m.p. = 170–173 °C. $[\alpha]_D^{24} = +57.5$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.17 – 7.09 (m, 2H), 6.91 – 6.82 (m, 2H), 3.81 (s, 3H), 2.82 (d, $J = 5.7$ Hz, 1H), 2.18 (d, $J = 5.7$ Hz, 1H), 1.44 (s, 3H), 1.06 (s, 3H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 172.2, 136.8, 136.4, 128.7, 128.4, 128.3, 124.4, 66.4, 36.5, 34.0, 29.0, 22.1, 20.5, 14.0, 6.8, 6.7. HRMS (ESI-TOF): calcd for $\text{C}_{21}\text{H}_{16}\text{Cl}_4\text{NO}_5$ $[\text{M}+\text{H}]^+$: 501.9777, found: 501.9776.

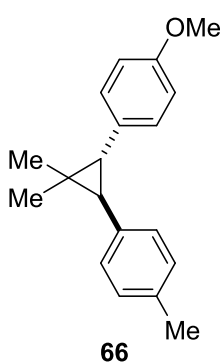
4,5,6,7-Tetrachloro-1,3-dioxoisindolin-2-yl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (74**)**



The title compound **74** was prepared on a 1.0 mmol scale according to general procedure A employing carboxylic acid **72**. Yield: 0.42 g (91 %). Yellow solid. m.p. = 148–150 °C. $[\alpha]_D^{23} = +97.6$ ($c = 1.00$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.20 – 7.14 (m, 2H), 7.07 – 7.01 (m, 2H), 2.80 (ddd, $J = 9.4, 6.9, 4.1$ Hz, 1H), 2.18 (ddd, $J = 8.4, 5.2, 4.1$ Hz, 1H), 1.85 (dt, $J = 9.4, 5.2$ Hz, 1H), 1.65 (ddd, $J = 8.5, 7.0, 5.1$ Hz, 1H). $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 169.3, 162.15 (d, $J = 246.0$ Hz), 157.7, 141.2, 133.96 (d, $J = 3.1$ Hz), 130.7, 128.30 (d, $J = 7.9$ Hz), 124.8, 115.76 (d, $J = 21.7$ Hz), 28.1, 20.9, 18.4. $^{19}\text{F NMR}$ (376 MHz, CDCl_3): δ –115.1. HRMS (ESI-TOF): calcd for $\text{C}_{18}\text{H}_8\text{FNNaO}_4$ $[\text{M}+\text{Na}]^+$:

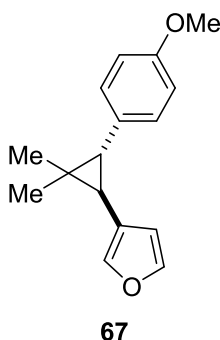
483.9084, found: 483.9079.

1-((1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropyl)-4-methoxybenzene (66**)**



The title compound **66** was prepared according to general procedure B3 from redox-active ester **73** and *p*-toluenboronic acid pinacol ester employing $\text{NiCl}_2 \cdot \text{glyme}$ (60 mol%) and 4,4'-dimethoxy-2,2'-bipyridine (60 mol%). Purification by pTLC (7:3 hexane: CH_2Cl_2). Yield: 0.015 g (55 %). Yellow oil. $[\alpha]_D^{20} = +38.0$ ($c = 0.30$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.21 – 7.18 (m, 2H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.11 (d, $J = 7.9$ Hz, 2H), 6.87 – 6.83 (m, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 2.29 (d, $J = 6.0$ Hz, 1H), 2.26 (d, $J = 6.2$ Hz, 1H), 0.96 (s, 6H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 158.0, 136.9, 135.4, 132.0, 130.2, 129.1, 128.9, 113.6, 77.5, 77.2, 76.8, 55.4, 34.3, 33.6, 25.5, 22.5, 22.4, 21.2. GC/MS (EI): m/z (%) 266 (75%), 251 (100%), 159 (33%), 143 (38%). Chiral SFC (Daicel IA; 10% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 229$ nm). t_R (minor) = 1.38 min, t_R (major) = 2.13 min, 94% ee.

1-((1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl)furan (67**)**

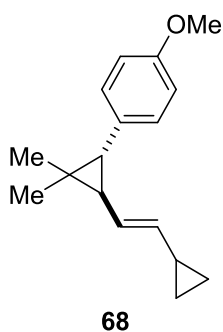


The title compound **67** was prepared according to general procedure B3 from redox-active ester **73** and 3-furanboronic acid pinacol ester employing $\text{NiCl}_2 \cdot \text{glyme}$ (60 mol%) and 4,4'-dimethoxy-2,2'-bipyridine (60 mol%). Purification by pTLC (7:3 hexane: CH_2Cl_2). Yield: 0.013 g (54 %). Yellow oil. $[\alpha]_D^{20} = +16.0$ ($c = 0.30$, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36 (t, $J = 1.7$ Hz, 1H), 7.28 (dd, $J = 1.7, 0.9$ Hz, 1H), 7.21 – 7.10 (m, 2H), 6.89 – 6.79 (m, 2H), 6.31 (dd, $J = 1.8, 0.9$ Hz, 1H), 3.80

Experimental section

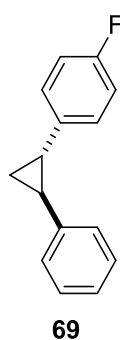
(s, 3H), 2.06 (d, $J = 5.8$ Hz, 1H), 1.94 (d, $J = 6.0$ Hz, 1H), 1.06 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.0, 142.6, 140.1, 131.6, 130.0, 124.1, 113.6, 112.1, 77.5, 77.2, 76.8, 55.4, 34.7, 24.9, 24.7, 22.3, 22.0. GC/MS (EI): m/z (%) 242 (50%), 227 (100%), 199 (40%), 121 (60%). Chiral SFC (Daicel IG; 7% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 226$ nm). t_R (minor) = 1.50 min, t_R (major) = 2.38 min, 95% *ee*.

1-((1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropyl)-4-methoxybenzene (68)

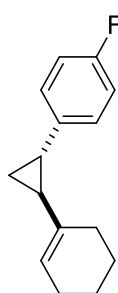


The title compound **68** was prepared according to general procedure B3 from redox-active ester **73** and (trans)-2-cyclopropylvinylboronic acid pinacol ester employing $\text{NiCl}_2\cdot\text{glyme}$ (60 mol%) and 4,4'-dimethoxy-2,2'-bipyridine (60 mol%). Purification by pTLC (7:3 hexane: CH_2Cl_2). Yield: 0.016 g (64 %). Yellow oil. $[\alpha]_D^{20} = +90.3$ ($c = 0.36$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.08 (d, $J = 8.8$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 5.44 (dd, $J = 15.2, 8.2$ Hz, 1H), 5.15 (dd, $J = 15.2, 8.6$ Hz, 1H), 3.78 (s, 3H), 1.80 (d, $J = 5.7$ Hz, 1H), 1.60 (dd, $J = 8.2, 5.6$ Hz, 1H), 1.41 (dtd, $J = 13.2, 8.4, 4.8$ Hz, 1H), 1.20 (s, 3H), 0.82 (s, 3H), 0.74 – 0.60 (m, 2H), 0.41 – 0.29 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 157.8, 134.4, 132.0, 130.0, 127.4, 113.5, 55.4, 36.2, 32.7, 24.9, 22.5, 22.1, 14.0, 6.8, 6.7. HRMS (ESI-TOF): calcd for $\text{C}_{17}\text{H}_{23}\text{O}^+$ $[\text{M}+\text{H}]^+$: 243.1743; found: 243.1743. Chiral SFC (Daicel IA; 2% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 220$ nm). t_R (minor) = 1.47 min, t_R (major) = 1.76 min, 94% *ee*.

1-Fluoro-4-((1*S*,2*S*)-2-phenylcyclopropyl)benzene (69)



The title compound **69** was prepared according to general procedure B1 from redox-active ester **74** and the arylzinc derived from phenylmagnesium bromide employing $\text{NiCl}_2\cdot\text{glyme}$ (40 mol%) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (40 mol%). Purification by pTLC (9:1 hexane: CH_2Cl_2). Yield: 0.013 g (62 %). Yellow oil. $[\alpha]_D^{20} = +125.5$ ($c = 0.44$, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.27 (m, 2H), 7.23 – 7.16 (m, 1H), 7.16 – 7.07 (m, 4H), 7.02 – 6.94 (m, 2H), 2.13 (dddd, $J = 19.0, 8.7, 6.0, 4.6$ Hz, 2H), 1.42 (dddd, $J = 16.2, 8.7, 6.0, 5.3$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.4 (d, $J = 243.7$ Hz), 142.5, 138.2 (d, $J = 3.3$ Hz), 128.6, 127.4 (d, $J = 7.8$ Hz), 126.0, 125.9, 115.3 (d, $J = 21.4$ Hz), 27.9, 27.4, 18.2. ^{19}F NMR (376 MHz, CDCl_3) δ -117.7. GC/MS (EI): m/z (%) 197 (40%), 133 (35%), 115 (49%). Chiral SFC (Daicel IA; 10% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; $\lambda = 226$ nm). t_R (major) = 1.30 min, t_R (minor) = 1.43 min, 93% *ee*.

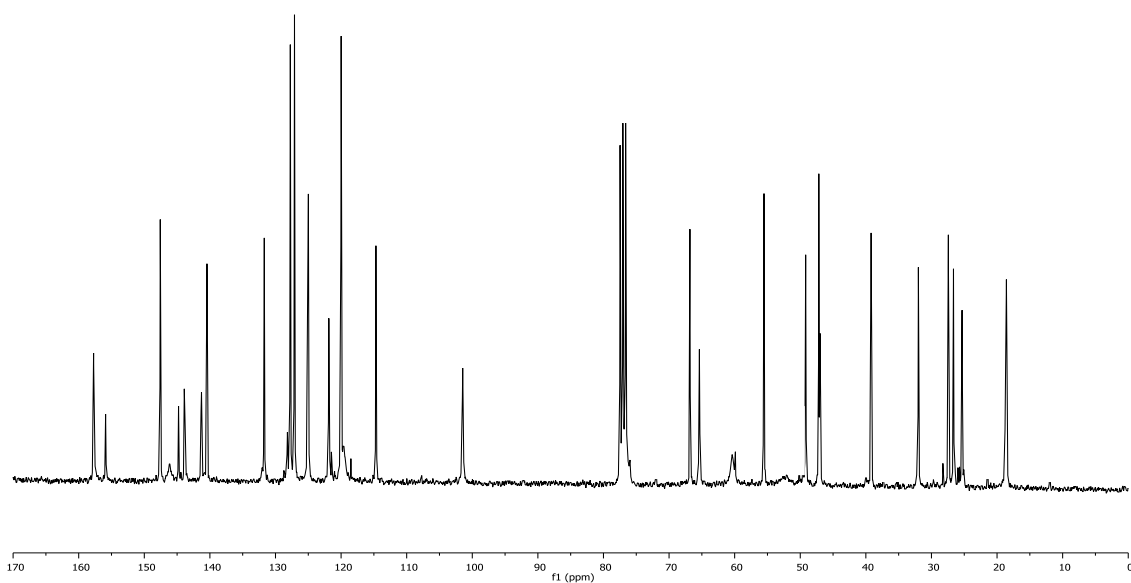
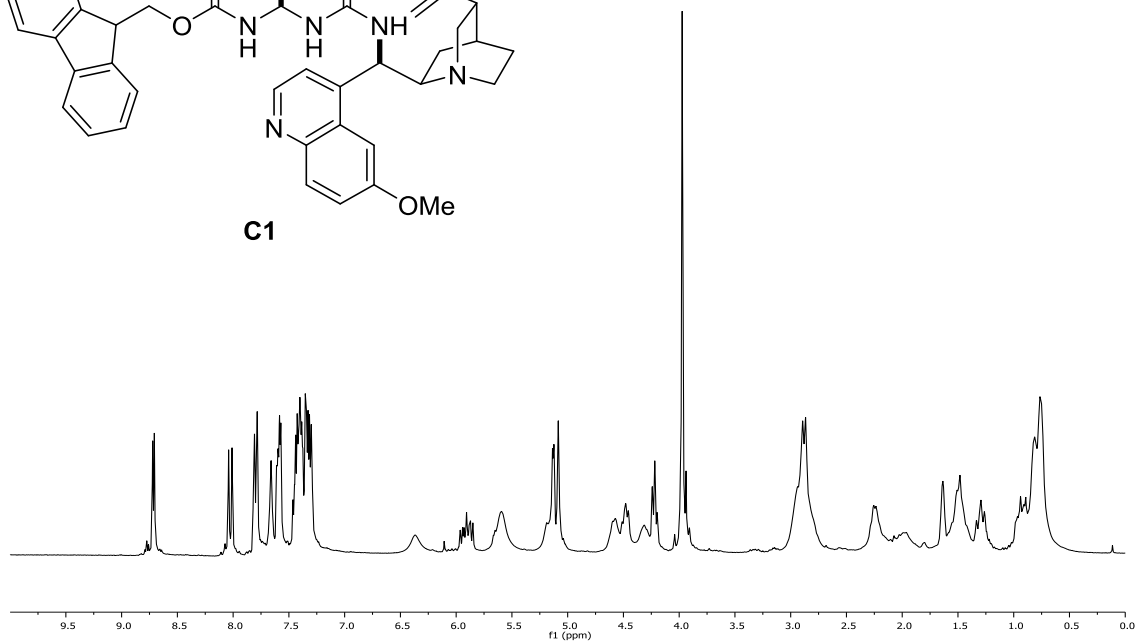
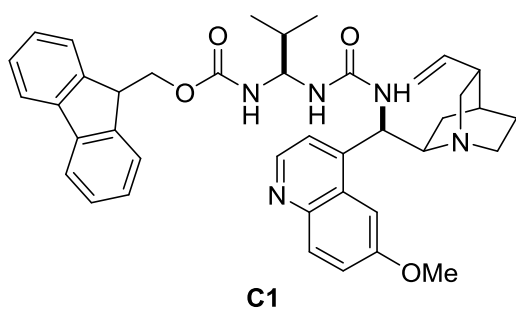
1-((1S,2S)-2-(Cyclohex-1-en-1-yl)cyclopropyl)-4-fluorobenzene (70)

The title compound **70** was prepared according to general procedure B2 from redox-active ester **74** and the alkenylzinc derived from 1-bromocyclohexene²⁵³ employing Ni(acac)₂·xH₂O (60 mol%) and 2,2'-bipyridine (60 mol%). Purification by pTLC (9:1 hexane:CH₂Cl₂). Yield: 0.010 g (44 %). Yellow oil. $[\alpha]_D^{20} = +61.3$ (c = 0.38, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.07 – 7.00 (m, 2H), 6.97 – 6.90 (m, 2H), 5.49 (ddq, J = 3.9, 2.5, 1.3 Hz, 1H), 2.04 – 1.98 (m, 2H), 1.94 – 1.90 (m, 2H), 1.88 (dt, J = 8.7, 5.1 Hz, 1H), 1.64 (qd, J = 6.2, 3.4 Hz, 2H), 1.57 (ddd, J = 7.2, 5.7, 3.0 Hz, 2H), 1.51 (dd, J = 9.2, 5.1 Hz, 1H), 1.16 (ddd, J = 8.7, 6.1, 4.9 Hz, 1H), 0.94 (dt, J = 8.8, 5.2 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 161.2 (d, J = 243.2 Hz), 139.1 (d, J = 3.3 Hz), 137.1, 127.3 (d, J = 7.7 Hz), 120.6, 115.1 (d, J = 21.4 Hz), 30.1, 27.1, 25.3, 23.0, 22.8, 22.5, 14.2. ¹⁹F NMR (376 MHz, CDCl₃) δ -118.3. HRMS (ESI-TOF): calcd for C₁₅H₁₈F⁺ [M+H]⁺: 217.1387; found: 217.1384. Chiral SFC (Daicel IG; 2% *i*PrOH / CO₂ (3.3 mL/min), 1600 psi backpressure; λ = 229 nm). *t*_R (major) = 2.24 min, *t*_R (minor) = 2.46 min, 95% *ee*.

6.6. NMR spectra

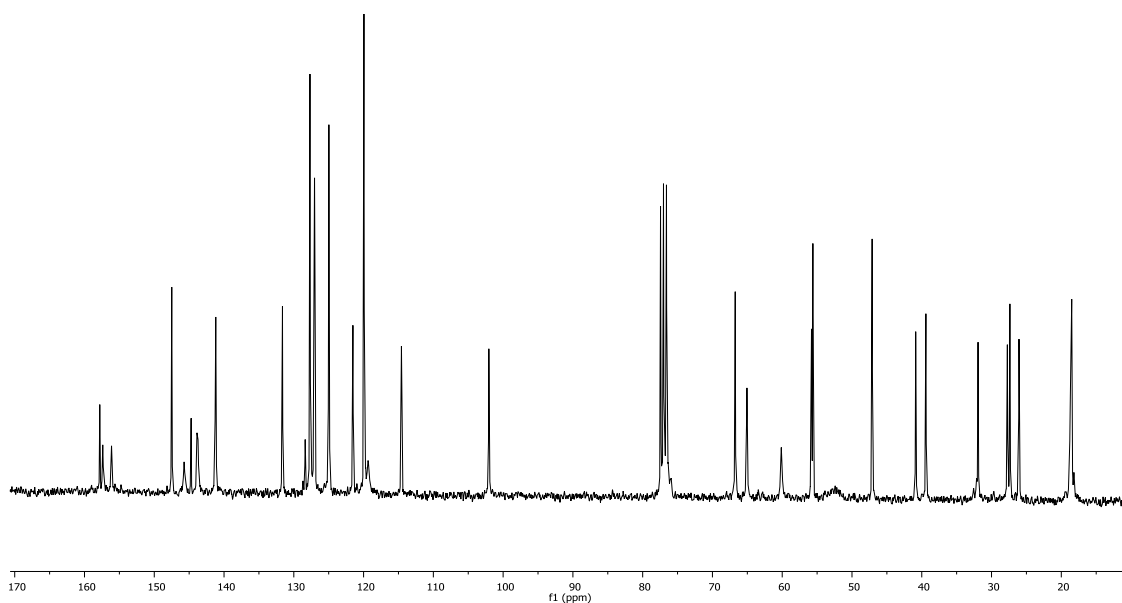
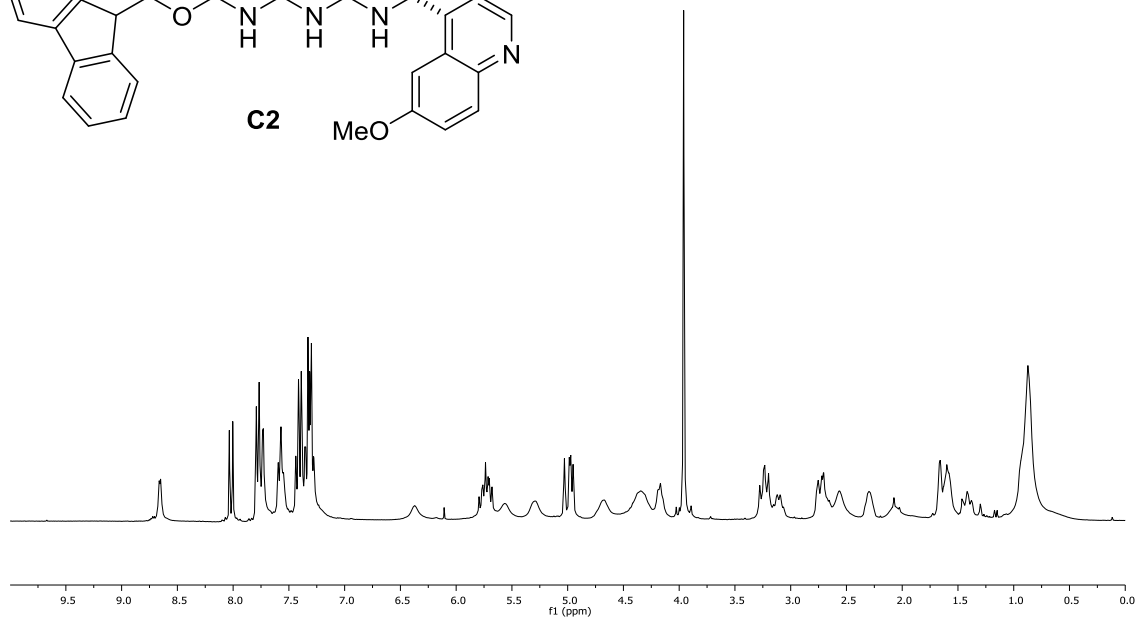
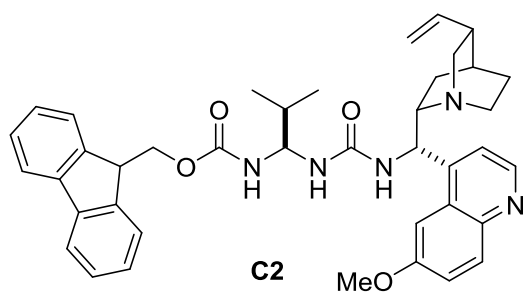
6.6.1. Catalysts

(9H-Fluoren-9-yl)methyl ((S)-1-(3-((R)-6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C1)

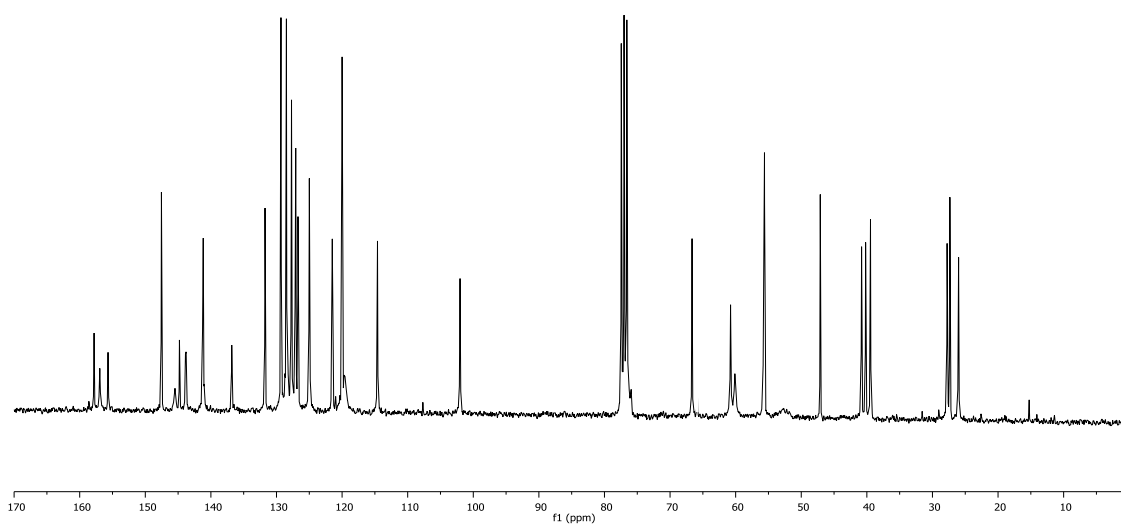
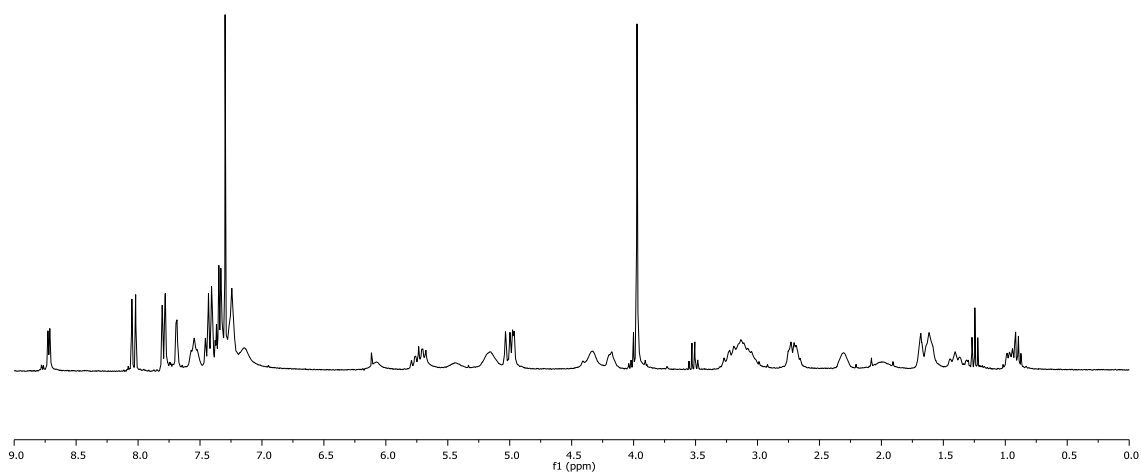
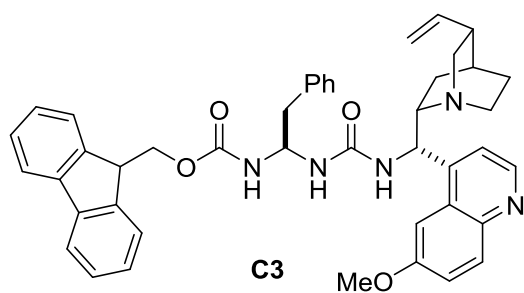


Experimental section

(9H-Fluoren-9-yl)methyl **((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C2)**

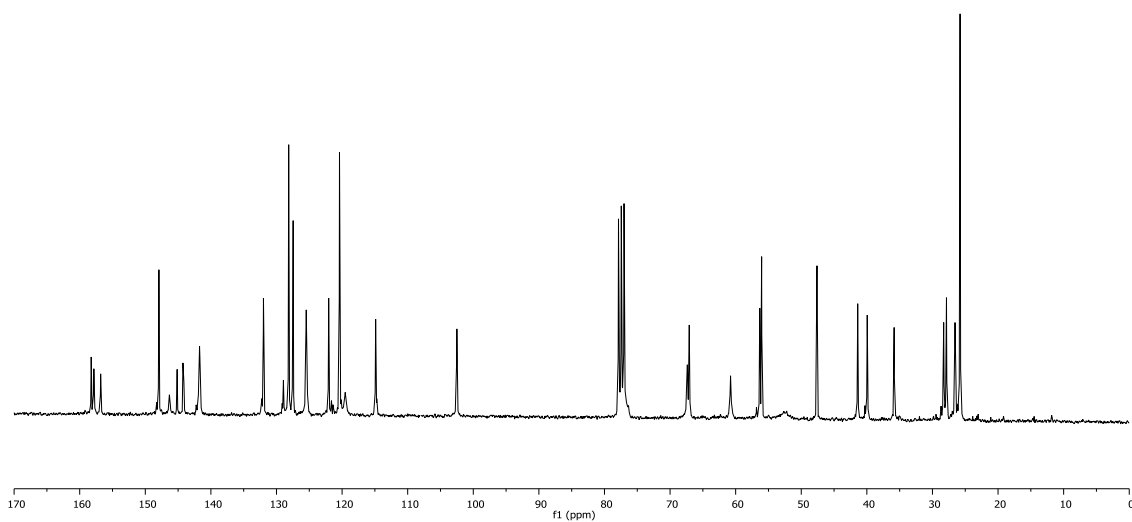
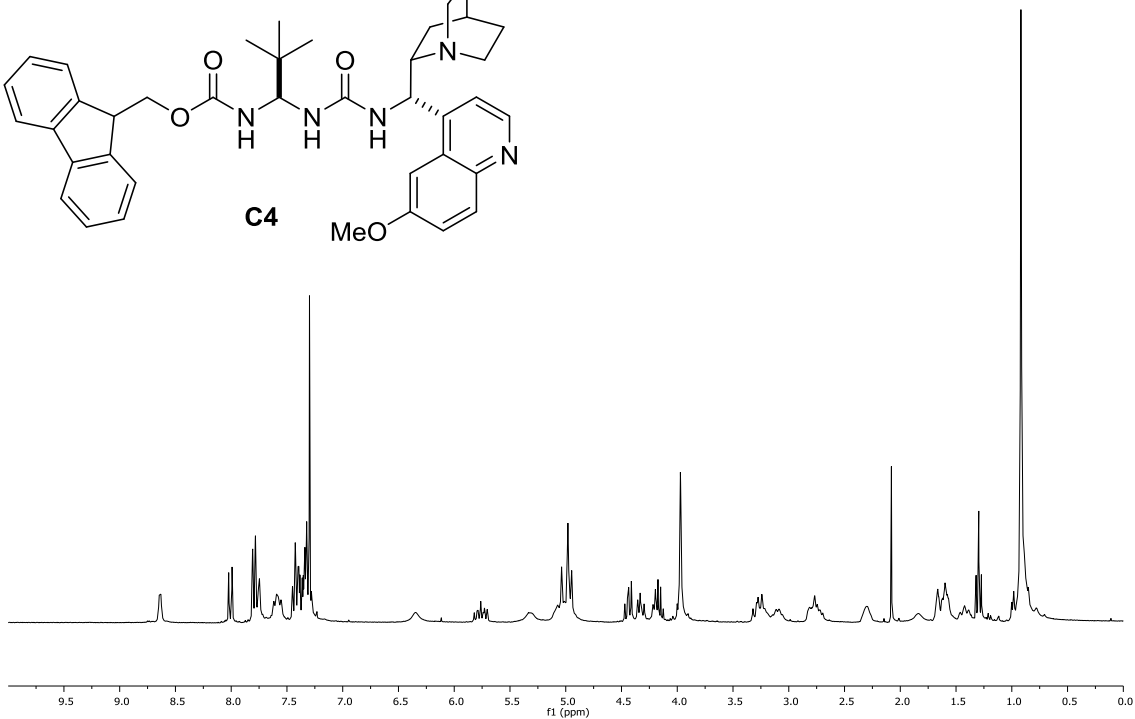
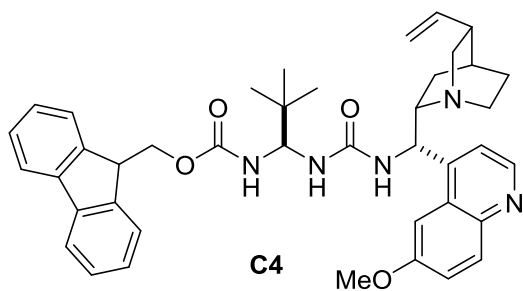


(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-phenylethyl)carbamate (C3)



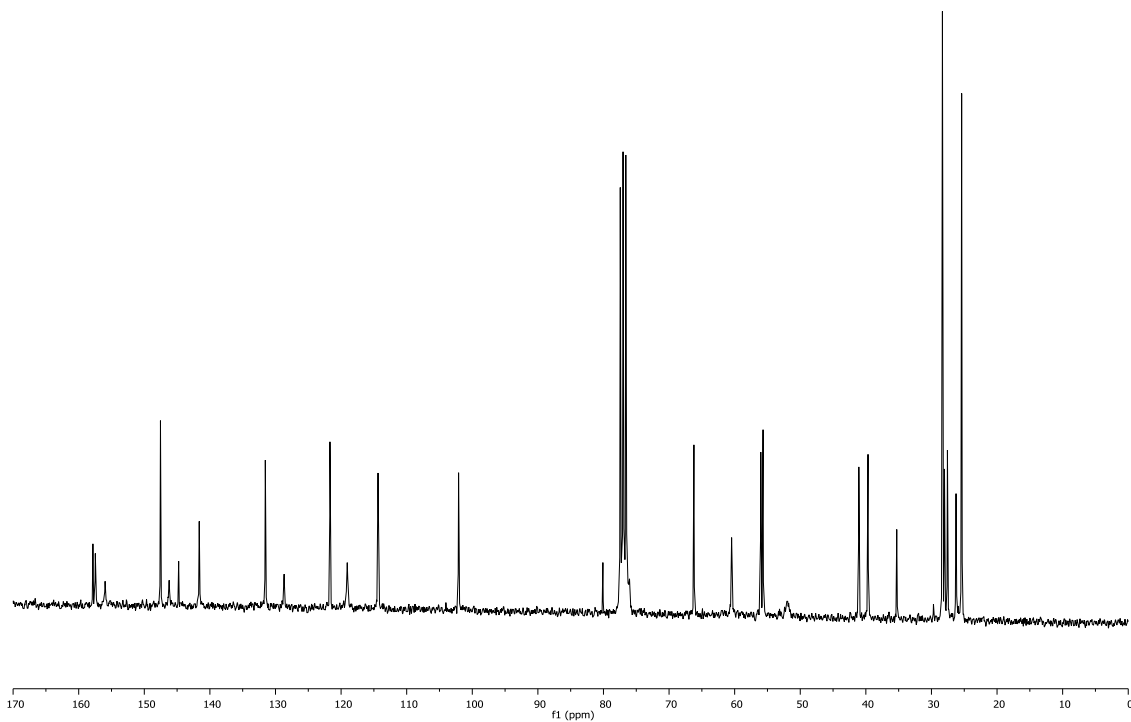
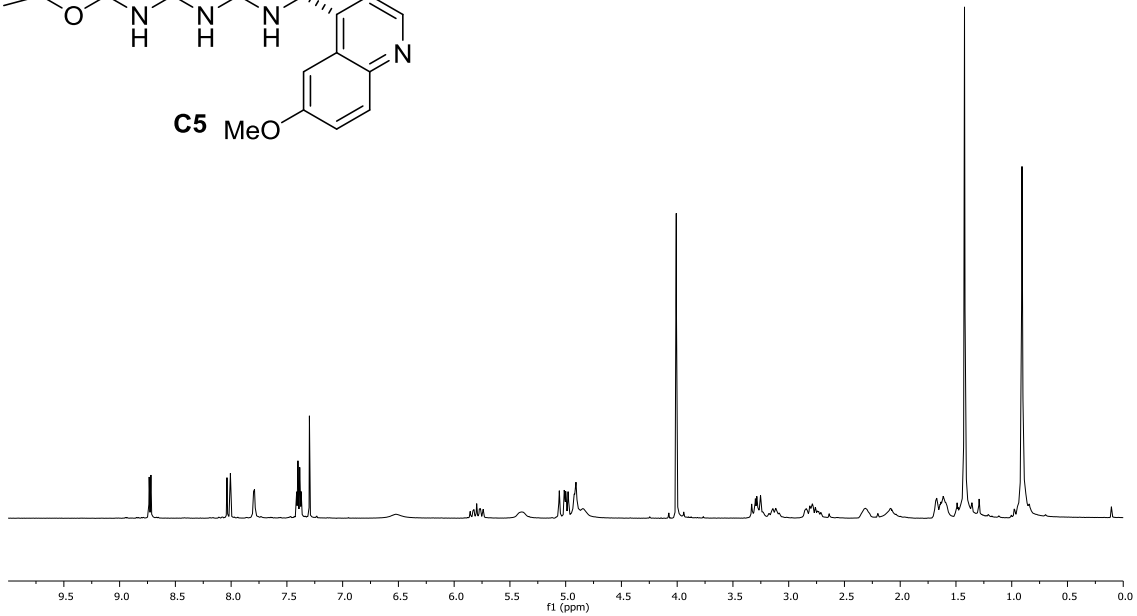
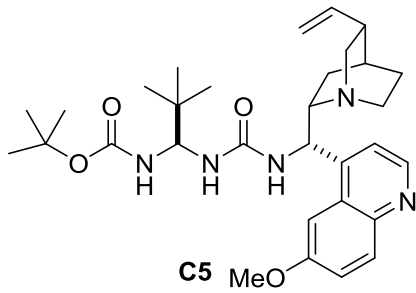
Experimental section

(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-1-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C4)



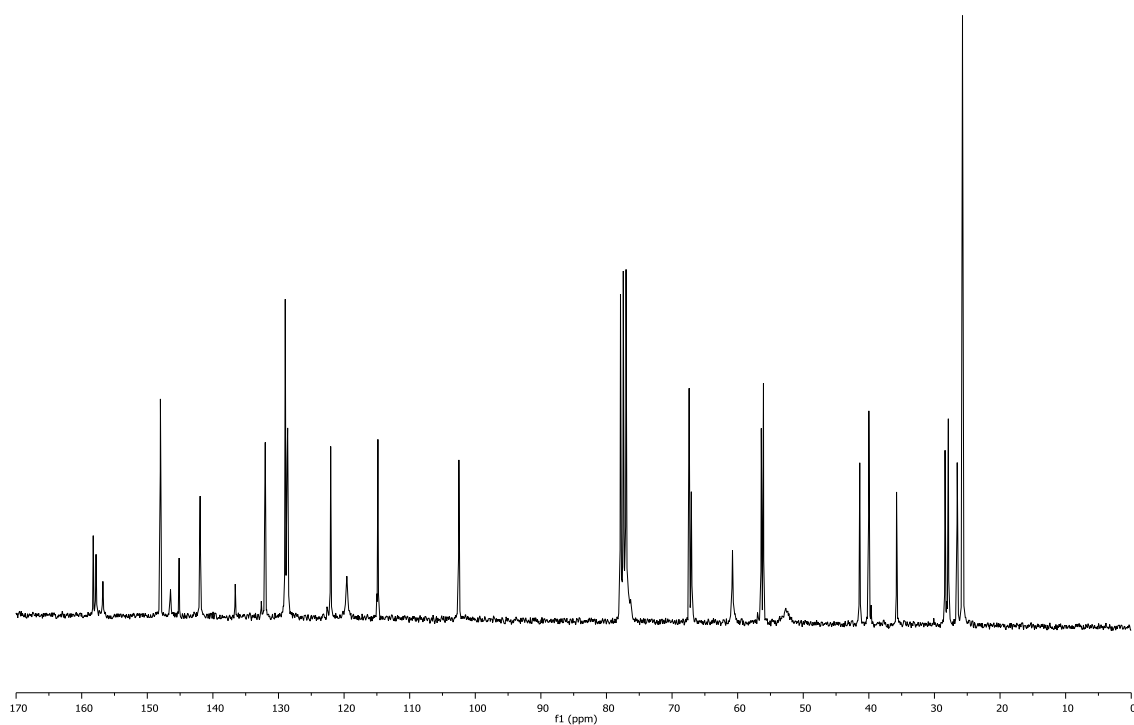
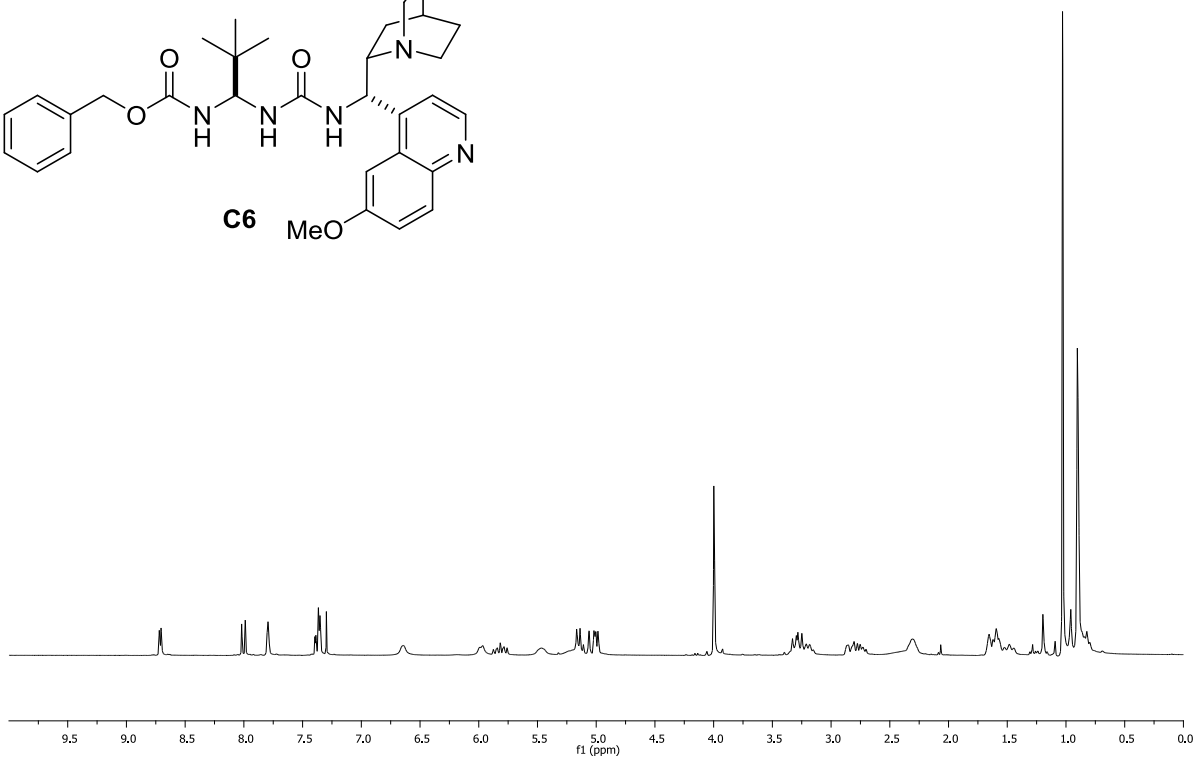
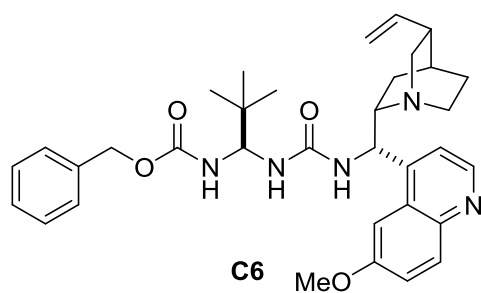
Chapter 6

***tert*-Butyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C5)**



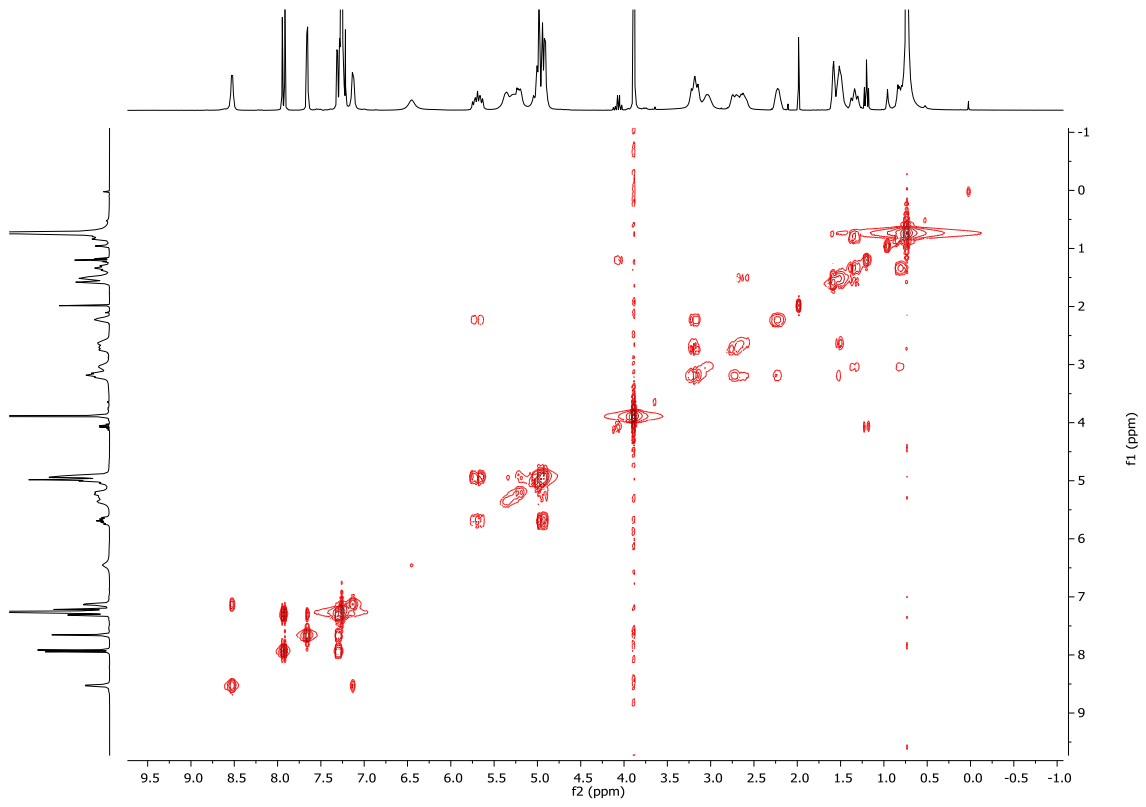
Experimental section

Benzyl ((S)-1-(3-((S)-1-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C6)

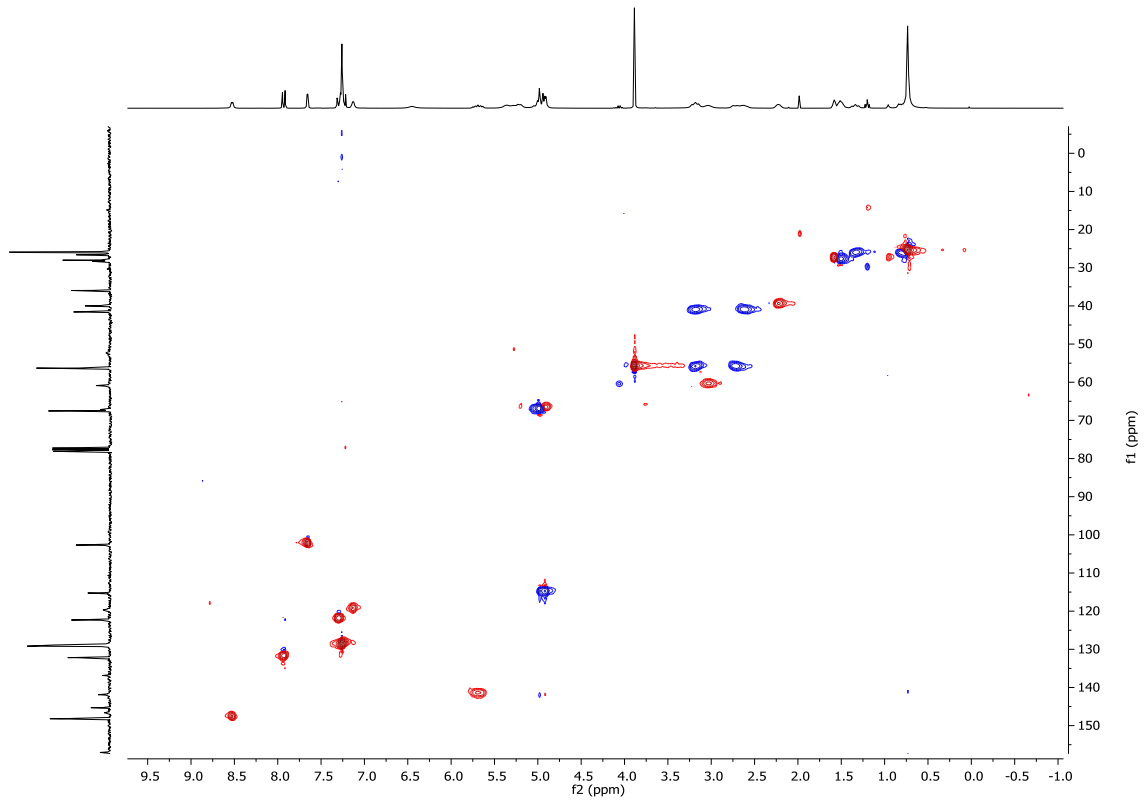


Chapter 6

COSY:

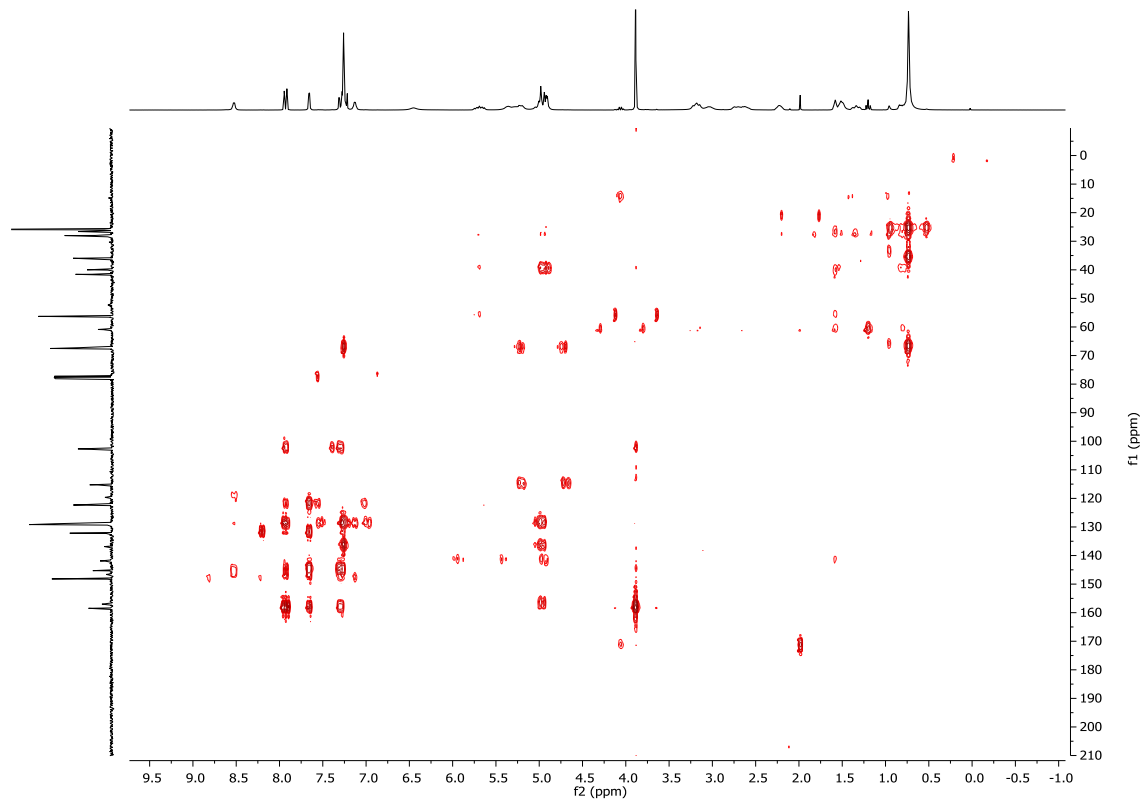


HSQC:

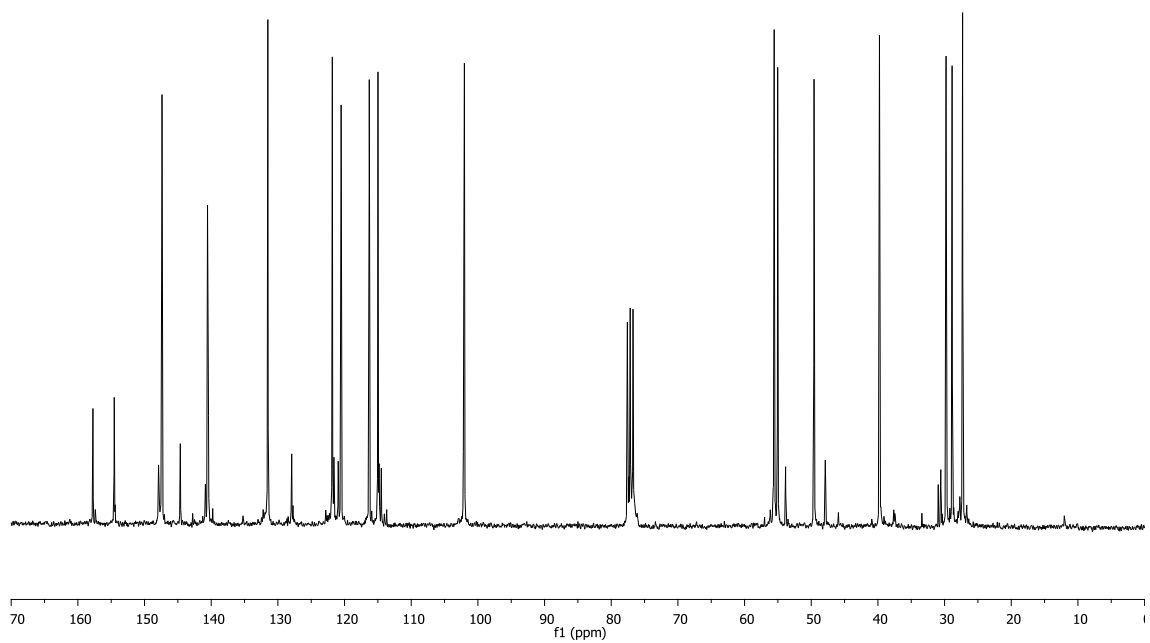
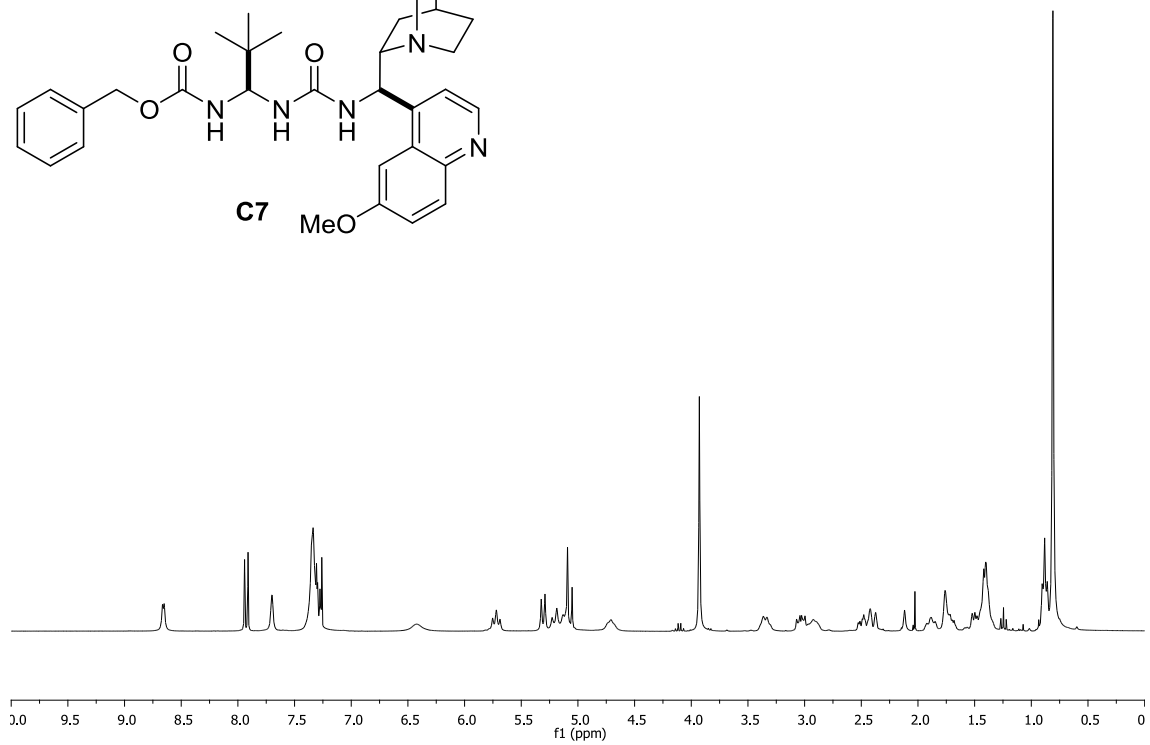
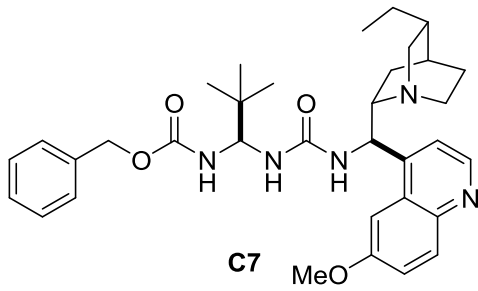


Experimental section

HMBC:

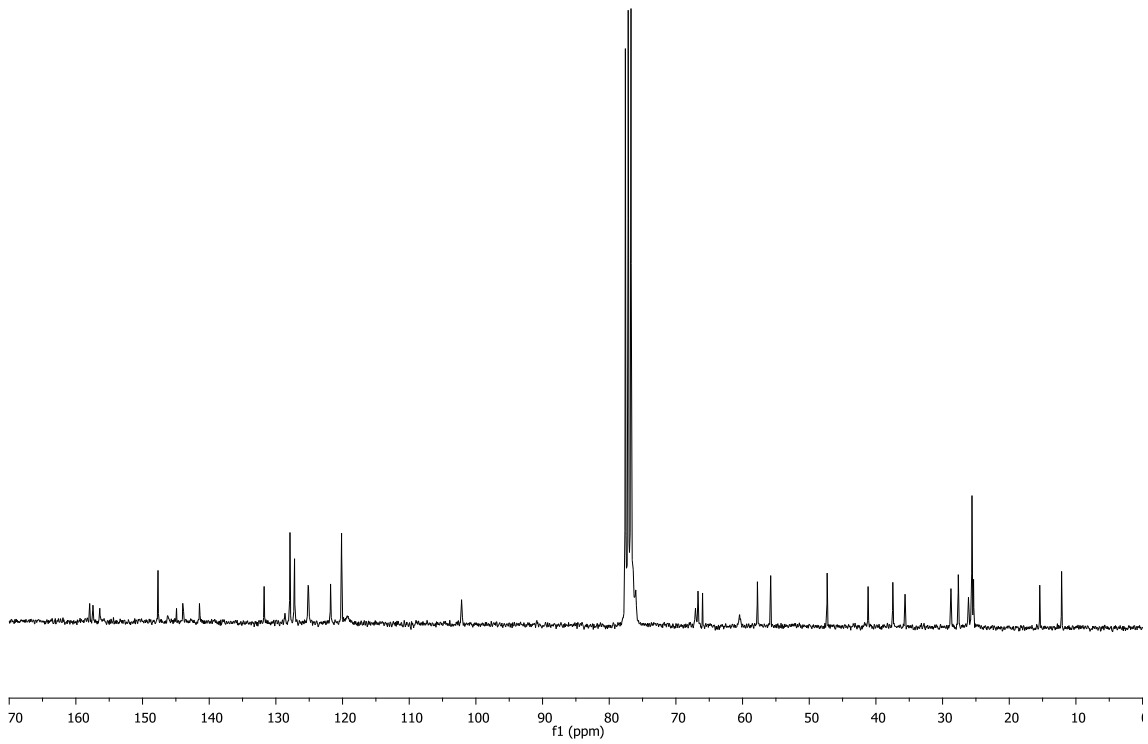
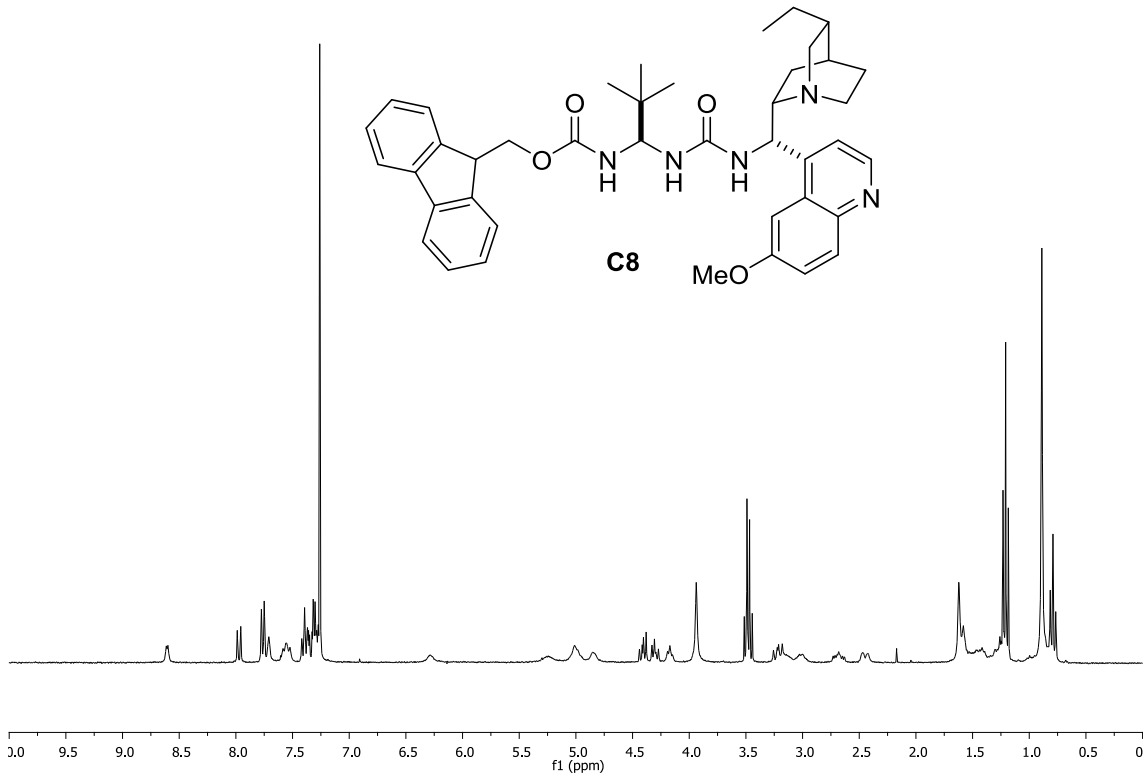


Benzyl ((S)-1-(3-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C7)

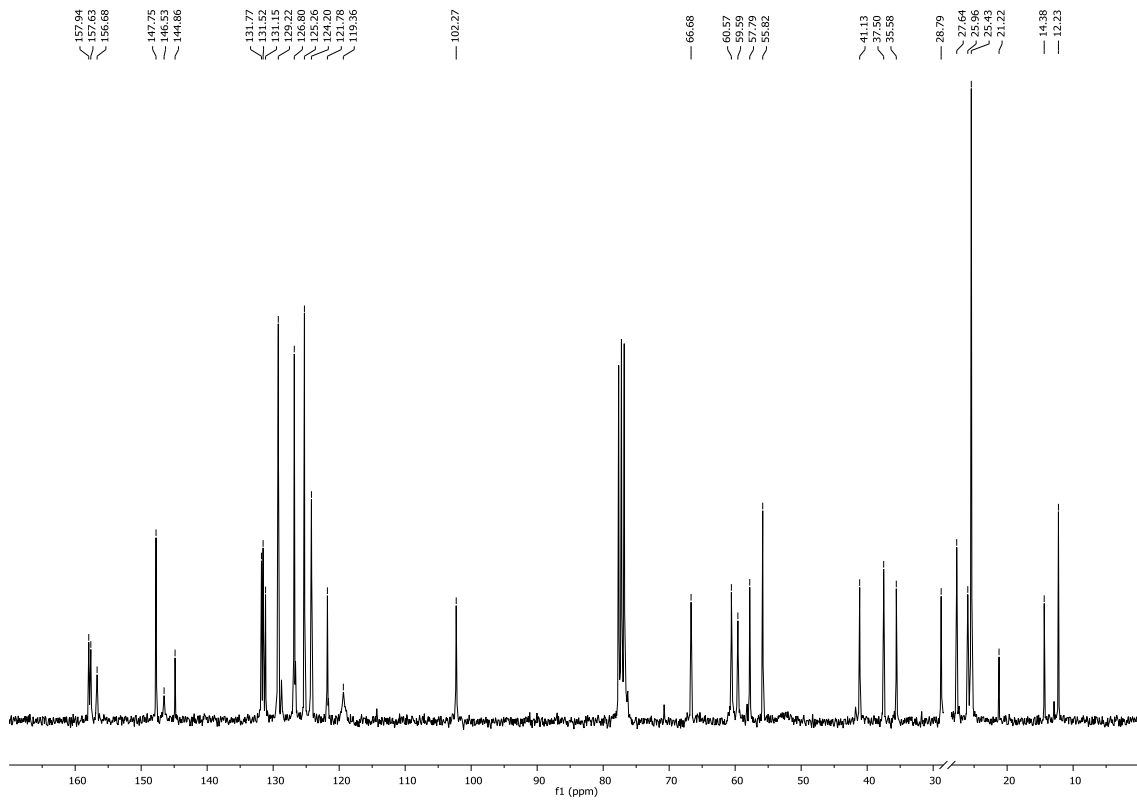
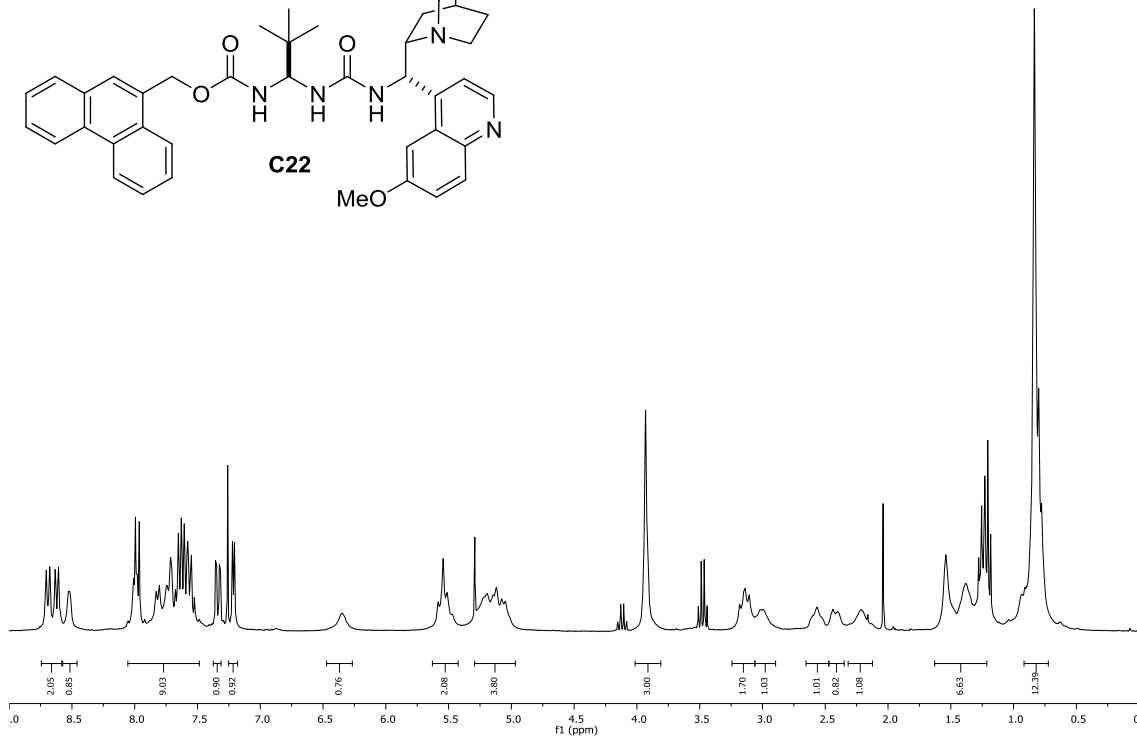
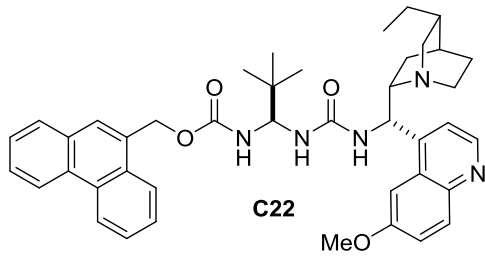


Experimental section

(9H-Fluoren-9-yl)methyl ((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C8)

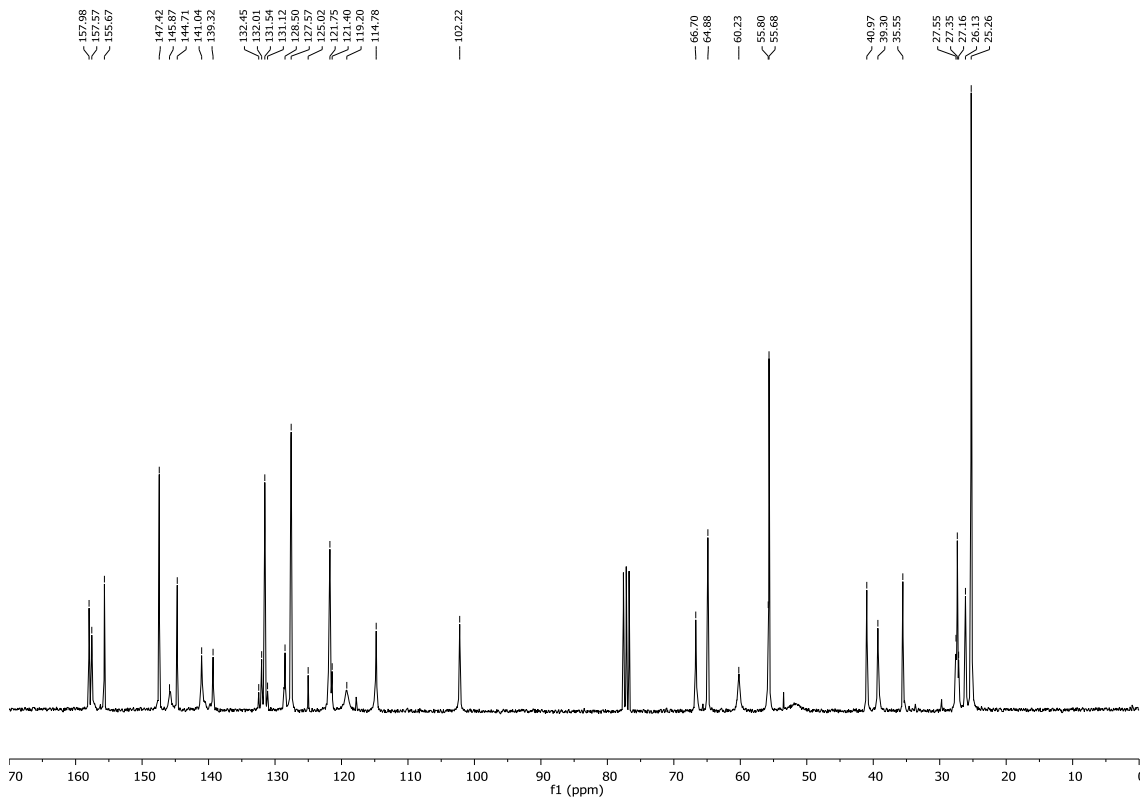
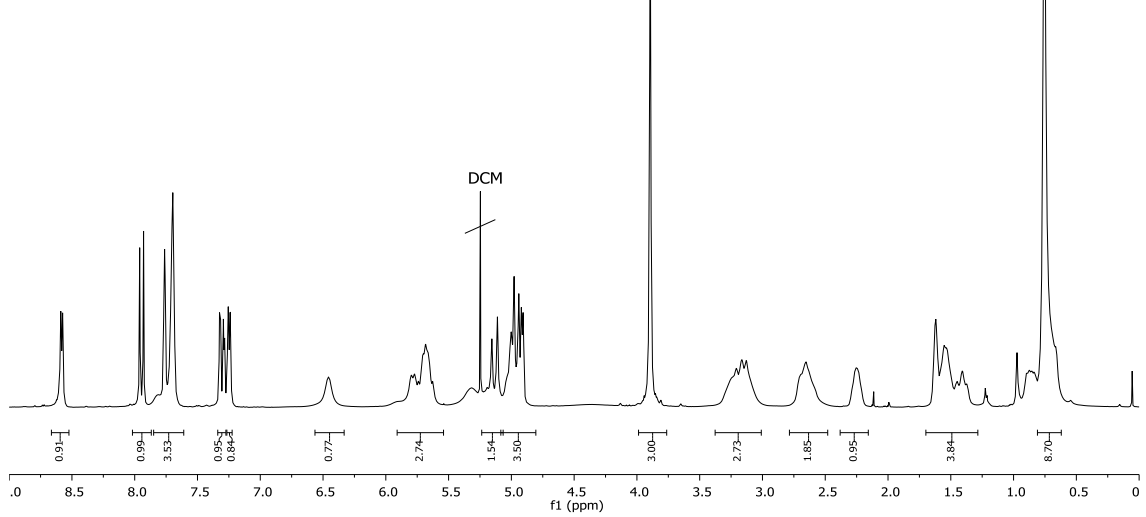
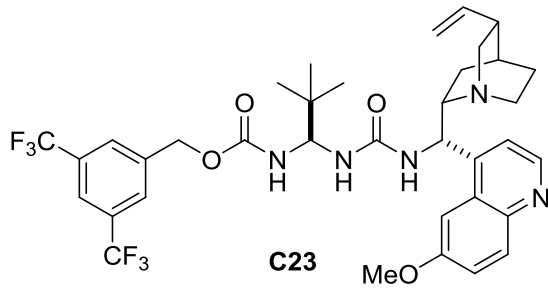


Phenanthren-9-ylmethyl **((S)-1-(3-((S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C22)**

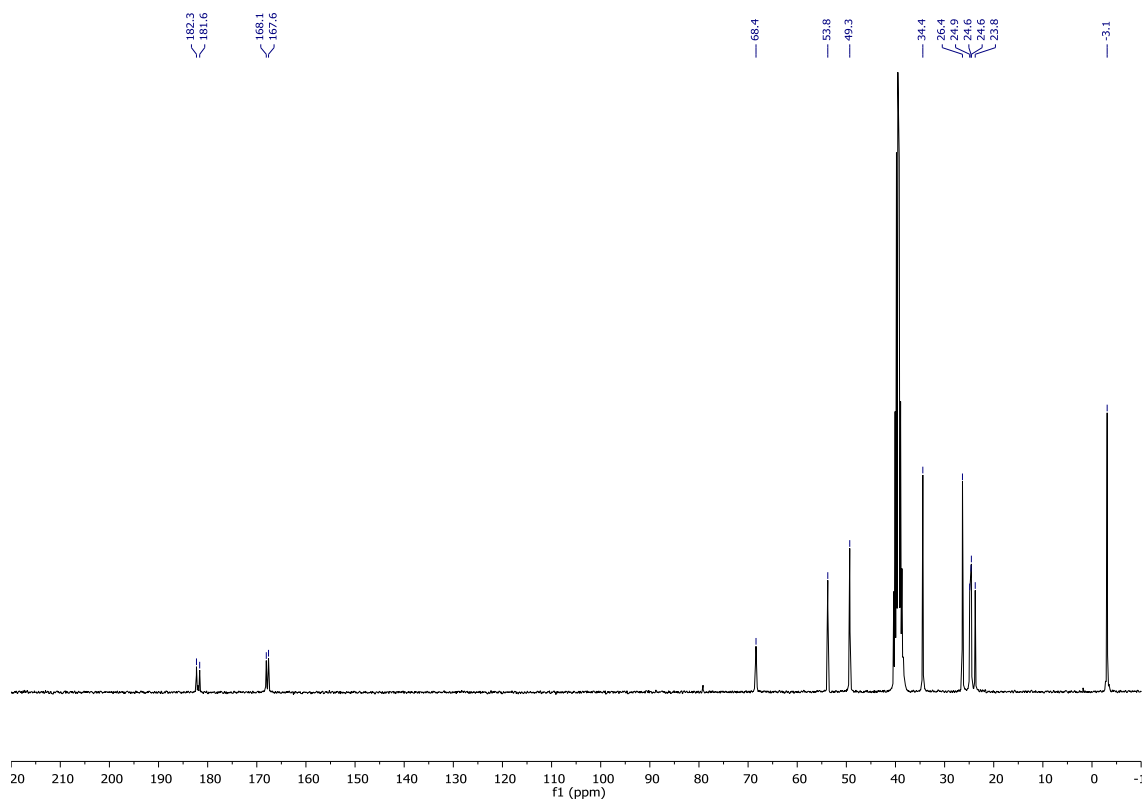
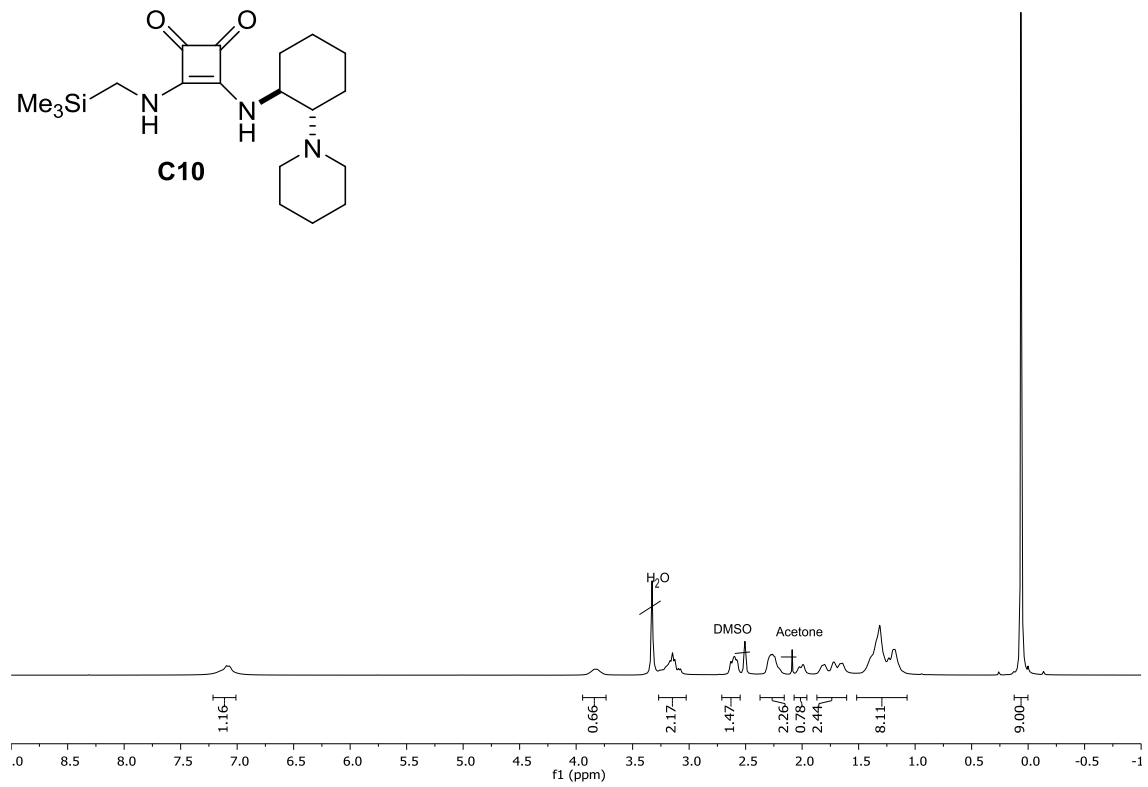
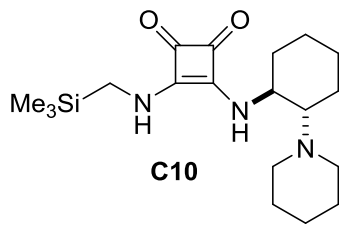


Experimental section

3,5-Bis(trifluoromethyl)benzyl ((S)-1-(3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C23)

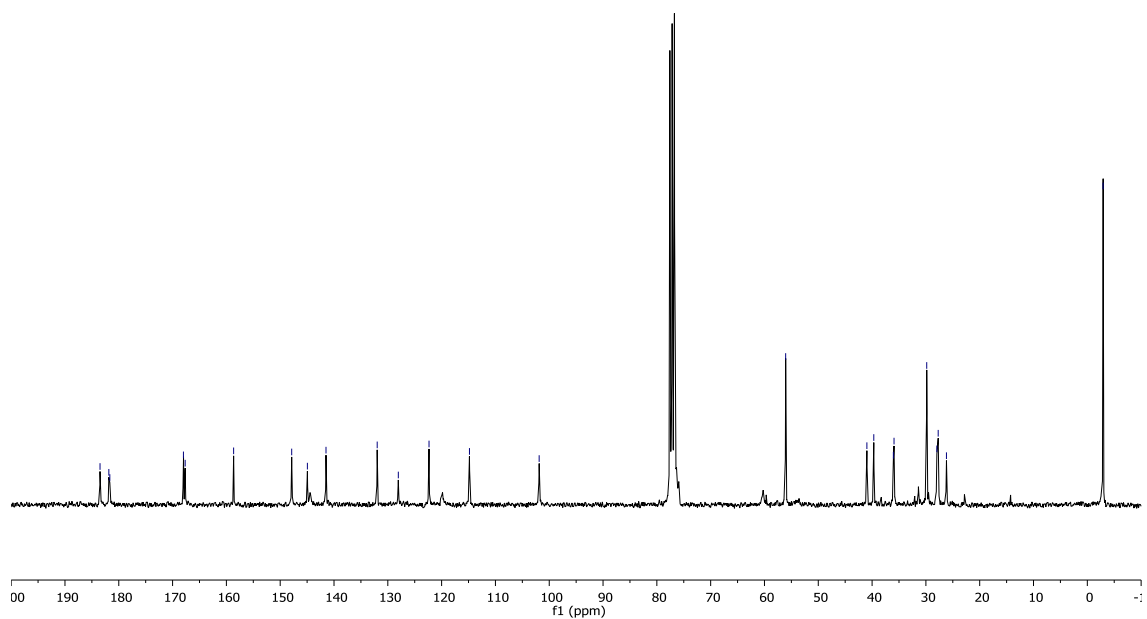
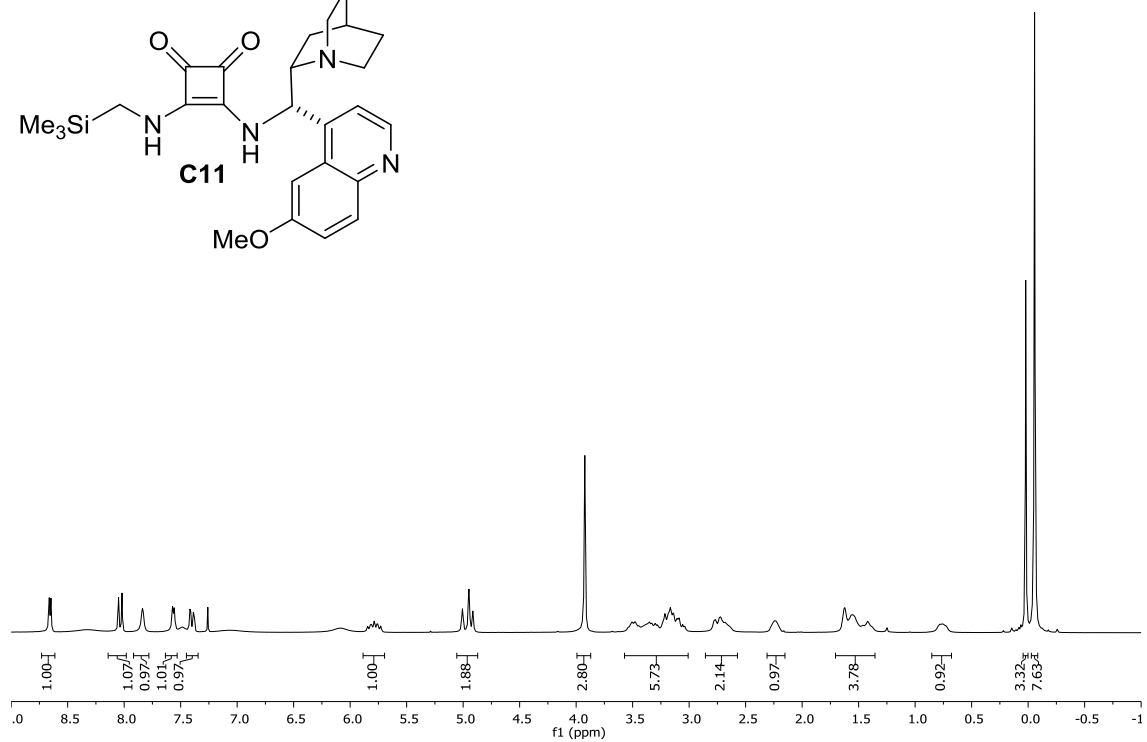
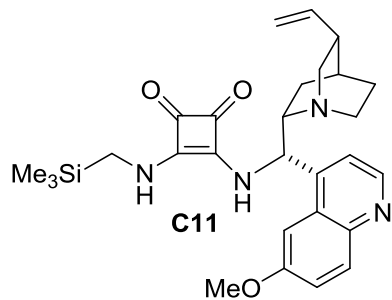


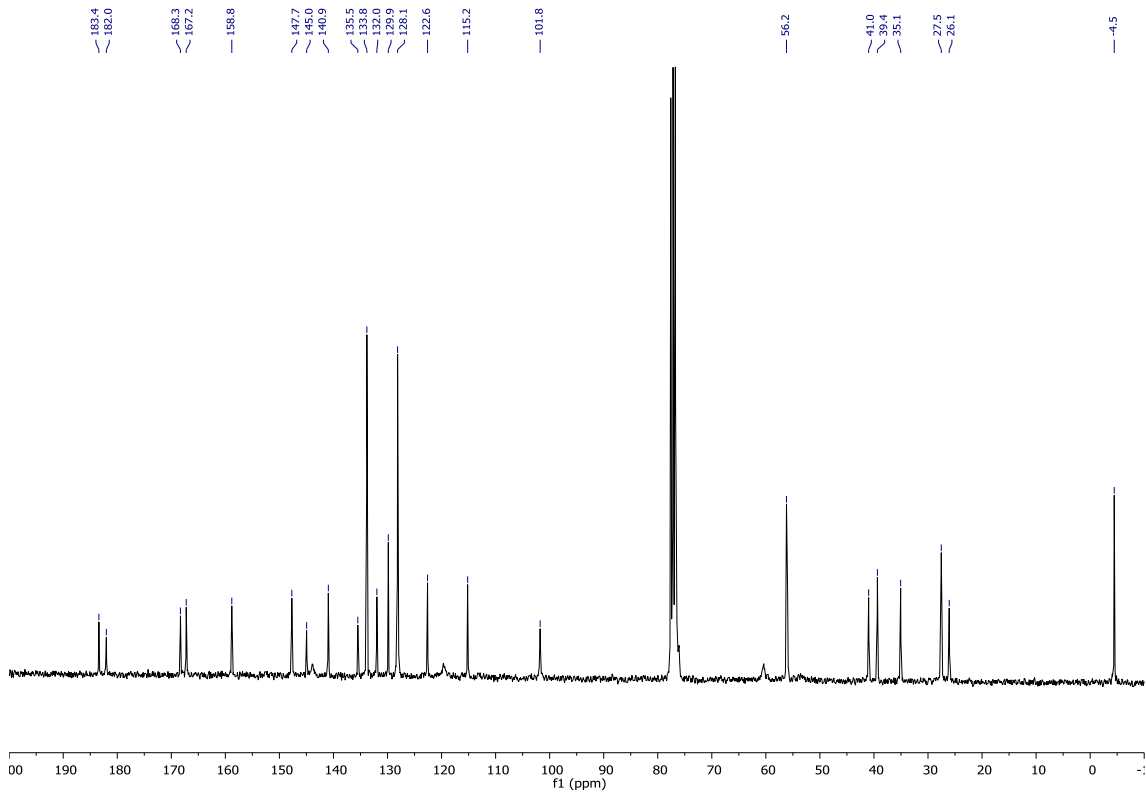
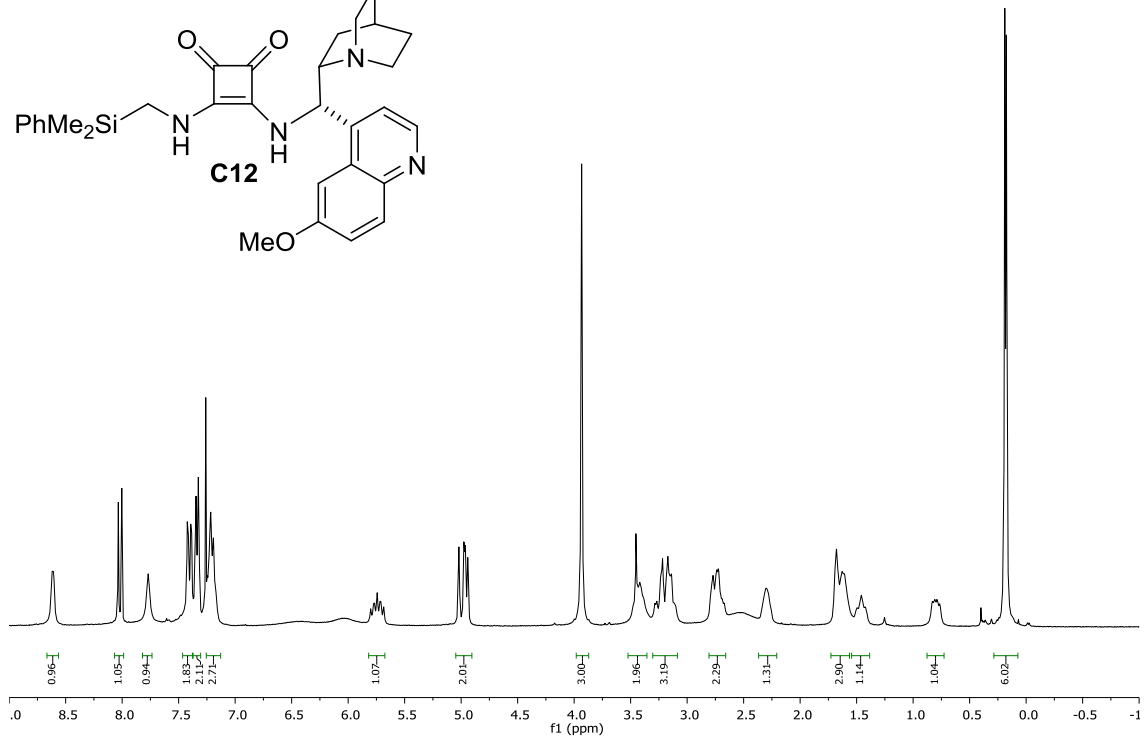
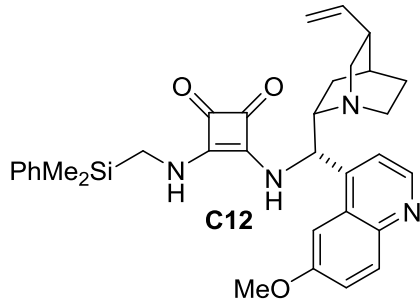
3-(((1S,2S)-2-(Piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C10)



Experimental section

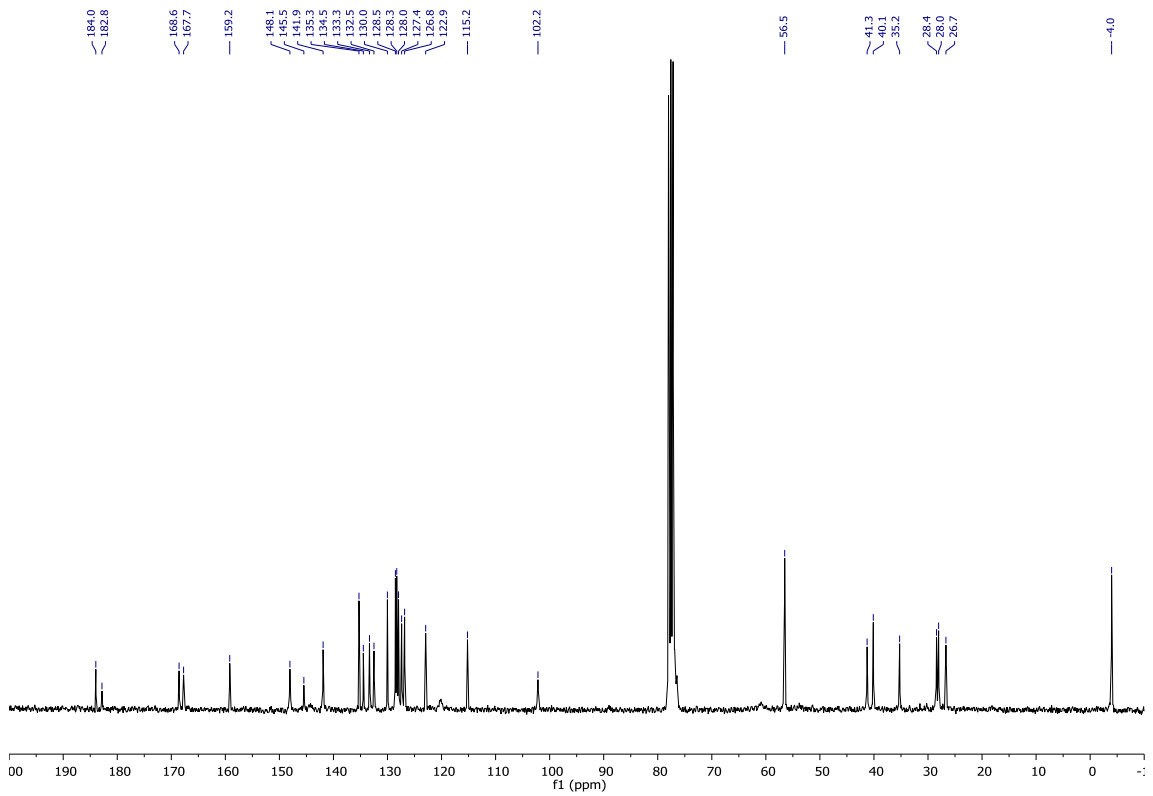
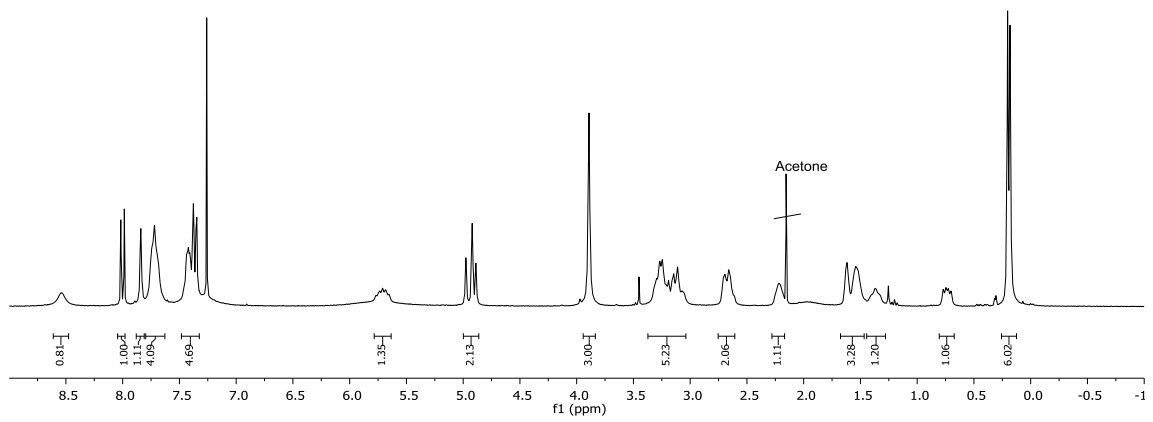
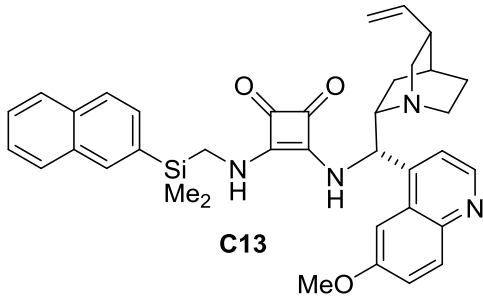
3-((S)-(6-Methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C11)



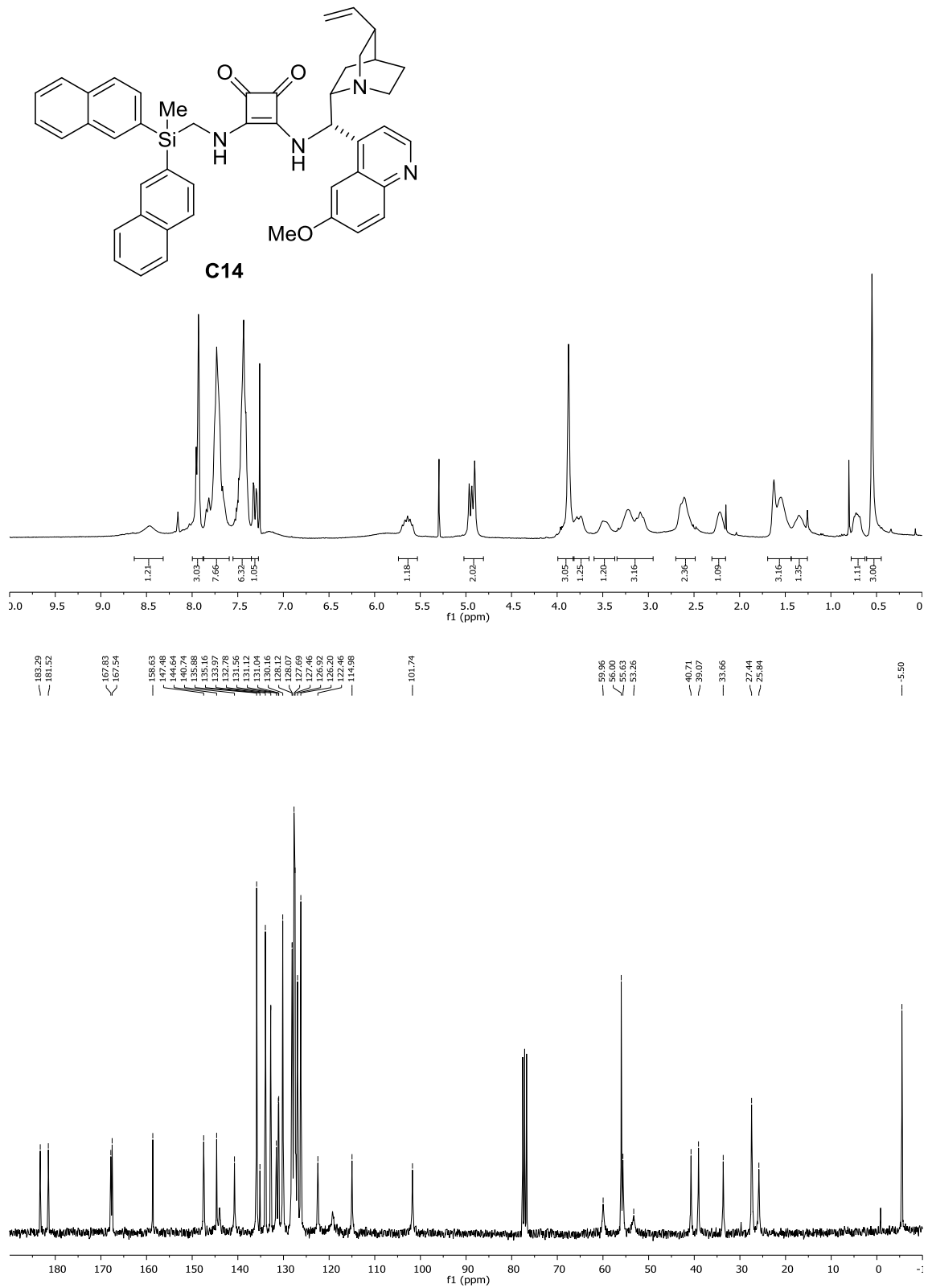
3-((Dimethyl(phenyl)silyl)methylamino)-4-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C12)

Experimental section

3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C13)

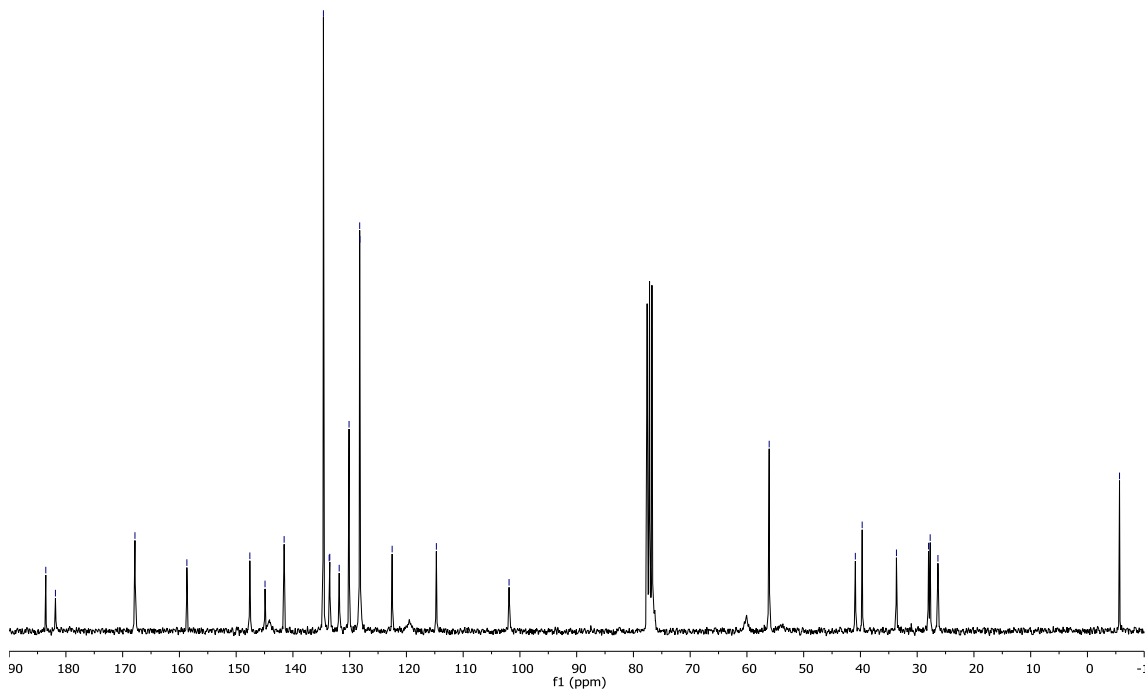
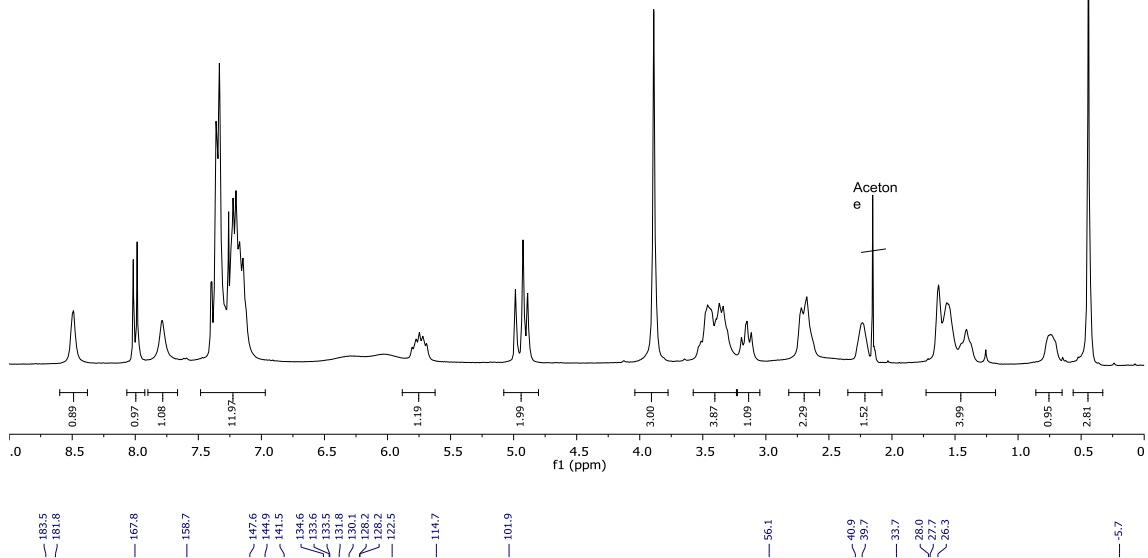
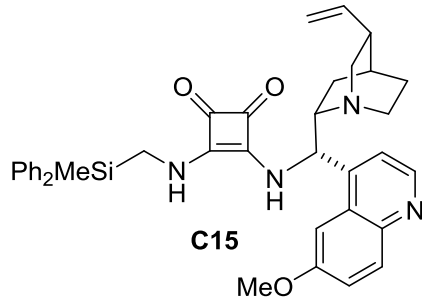


3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((methyl-di(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione (C14)

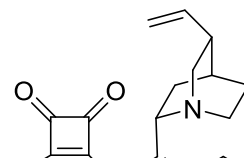


Experimental section

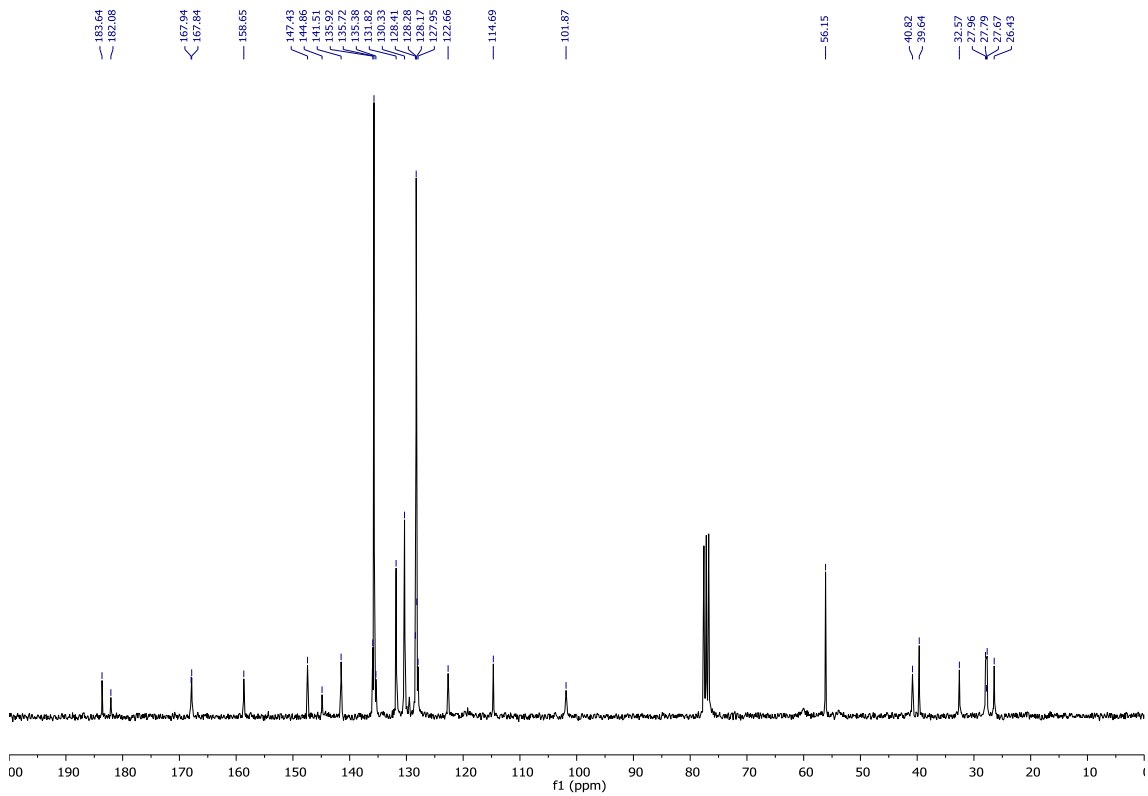
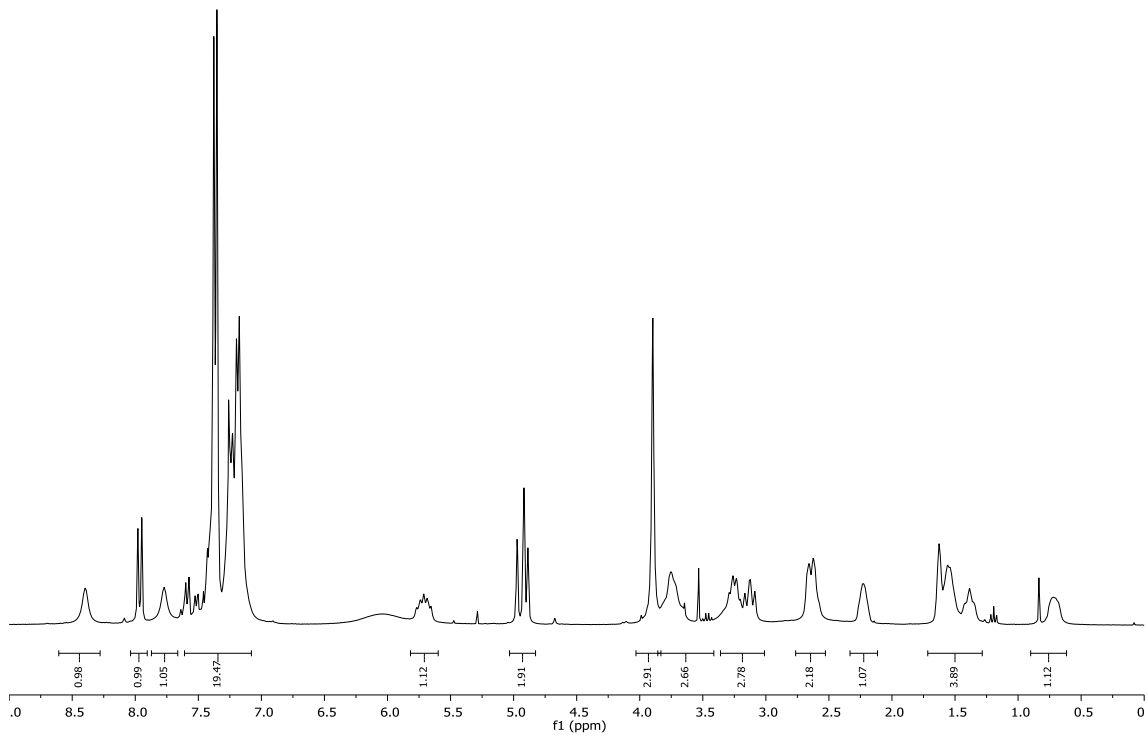
3-((S)-(6-Methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((methyl-diphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C15)



3-((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methylamino)-4-((triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C16)

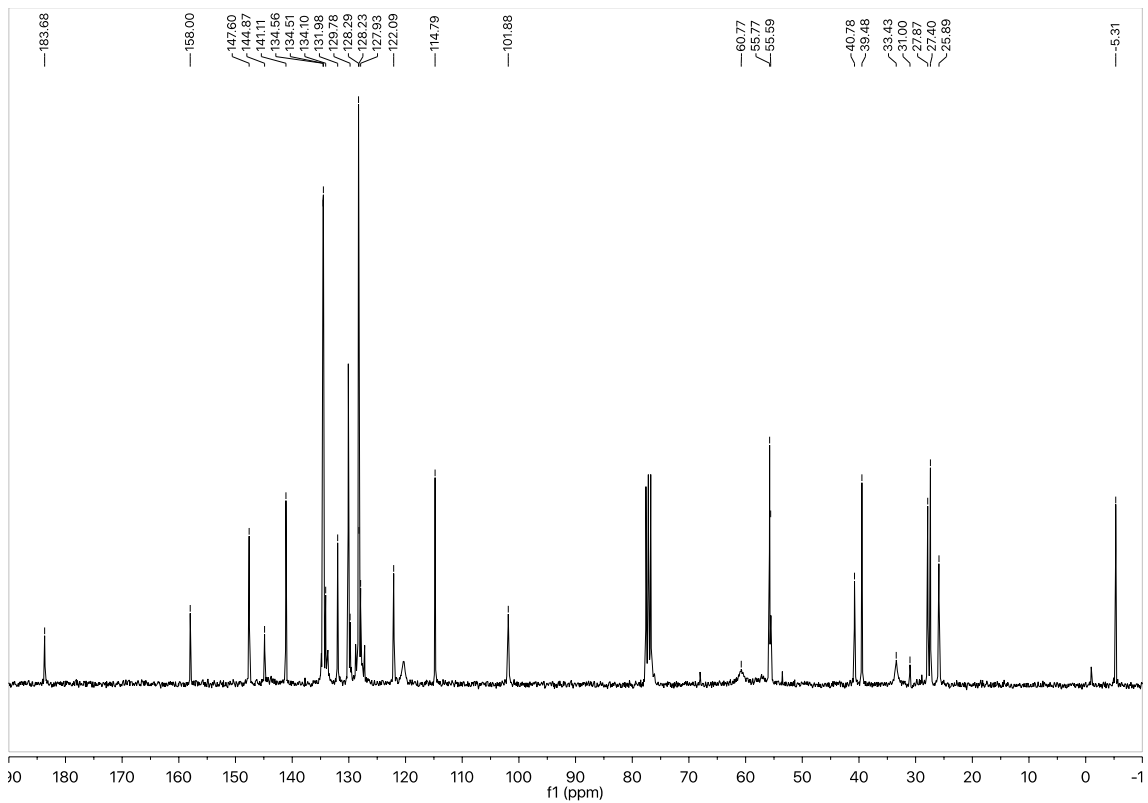
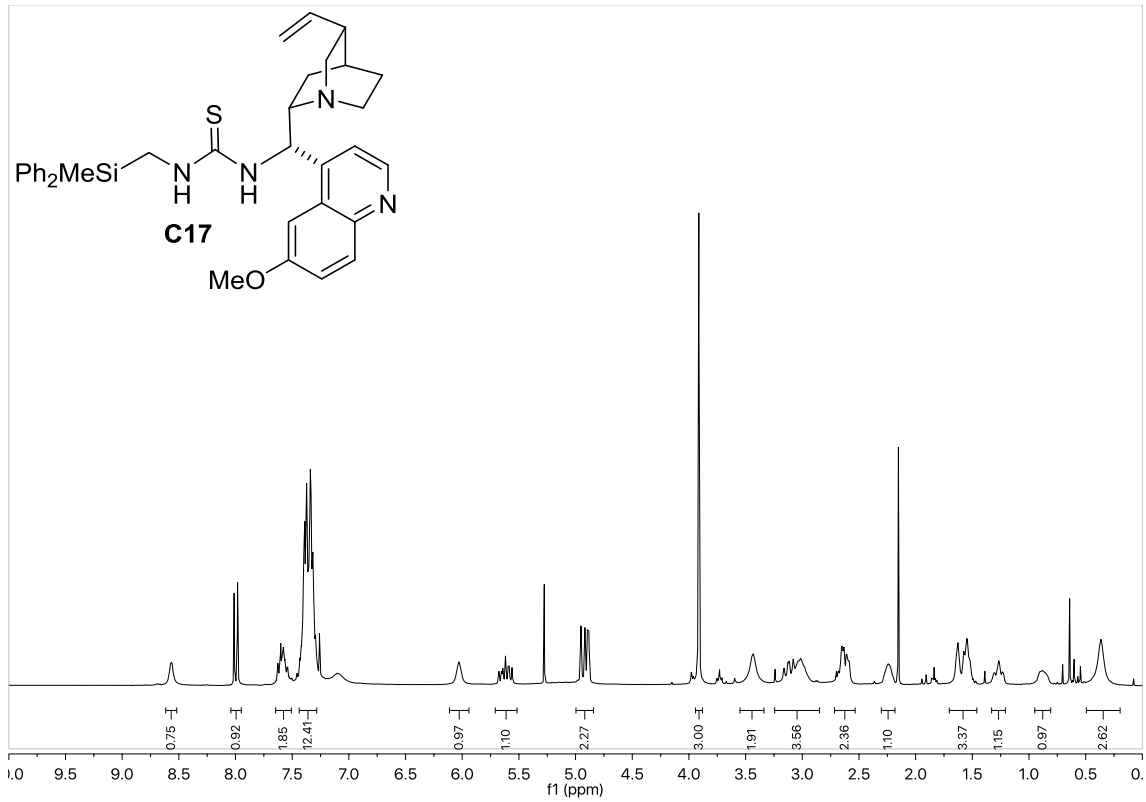


Chapter 6

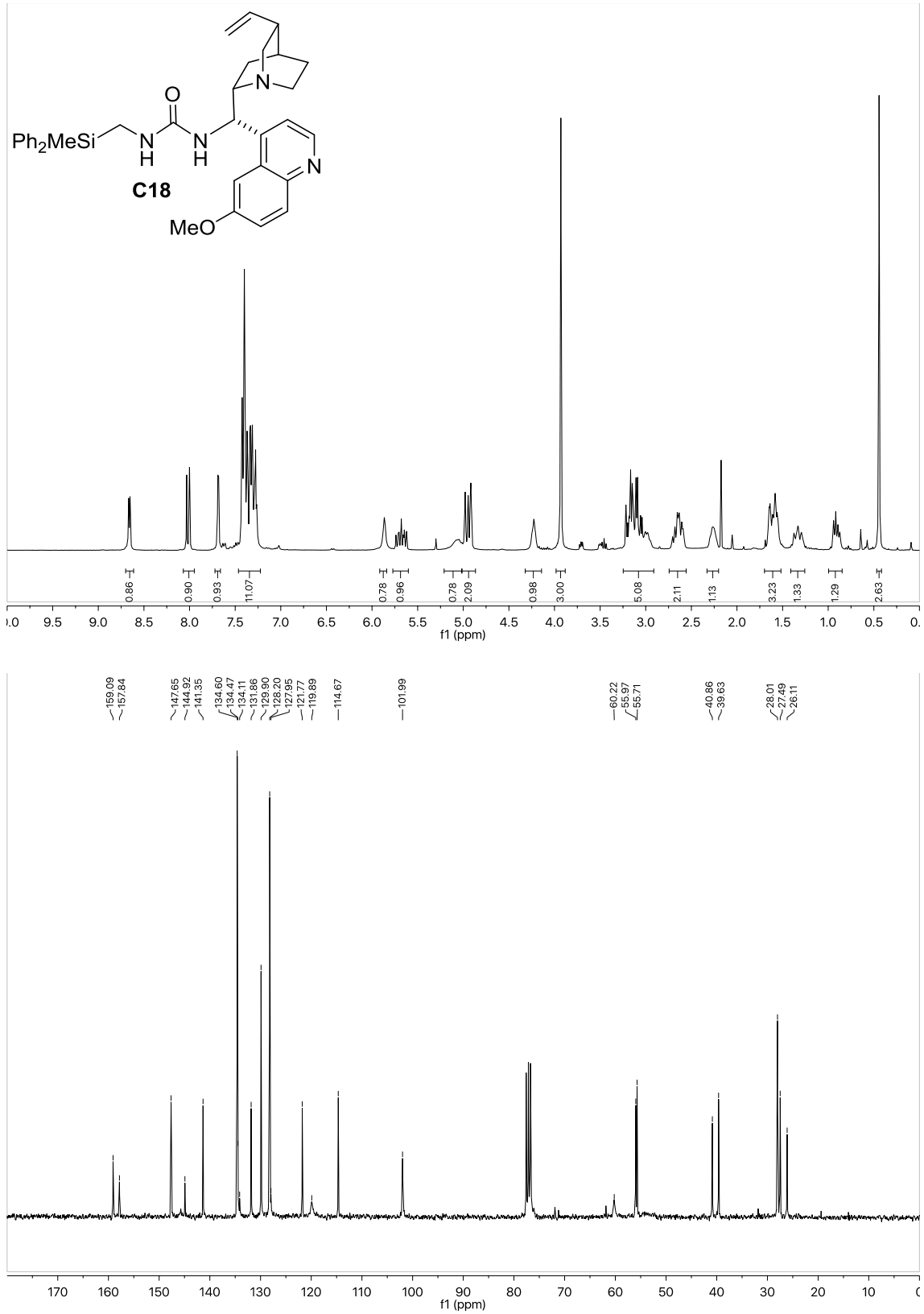


Experimental section

1-((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-3-((methyl-diphenylsilyl)methyl)thiourea (C17)

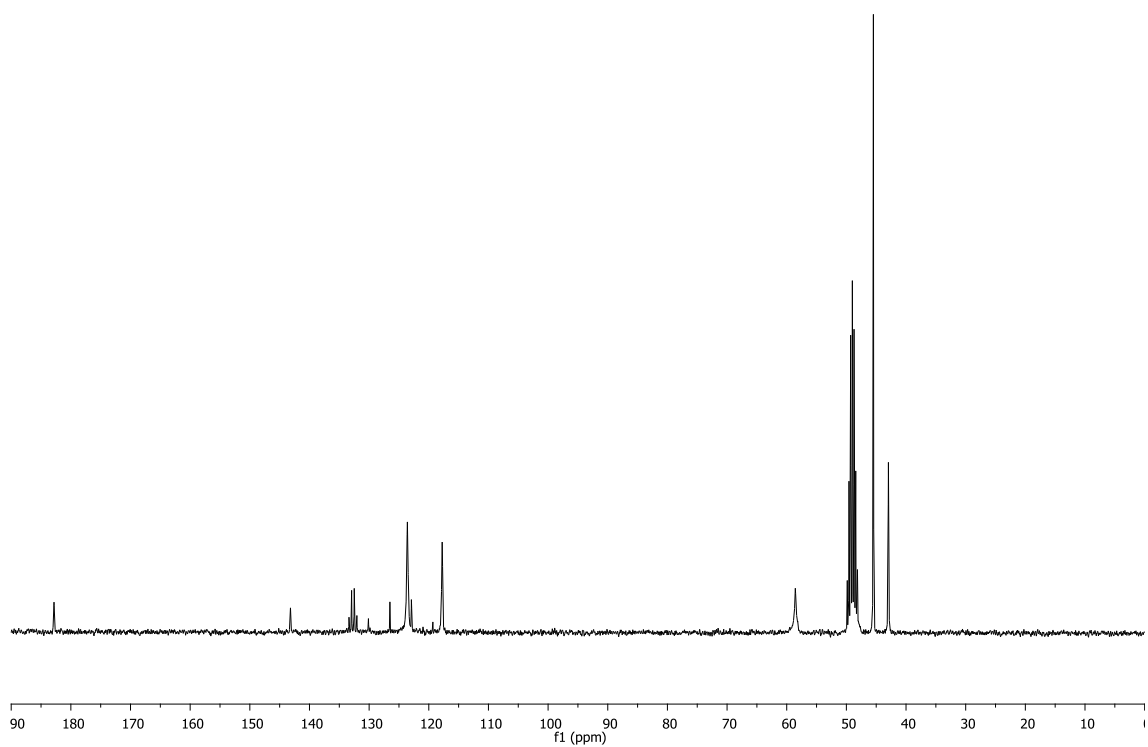
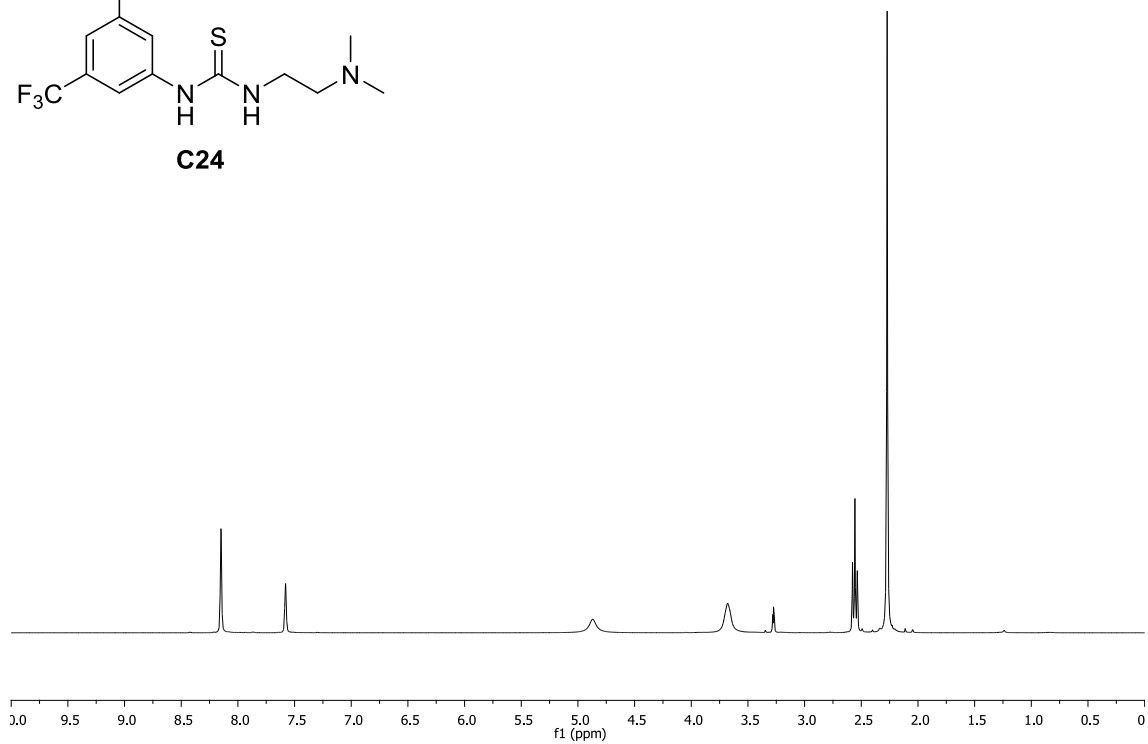
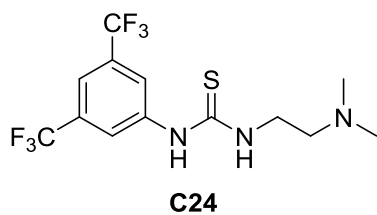


1-((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-3-((methyl-diphenylsilyl)methyl)urea (C18)

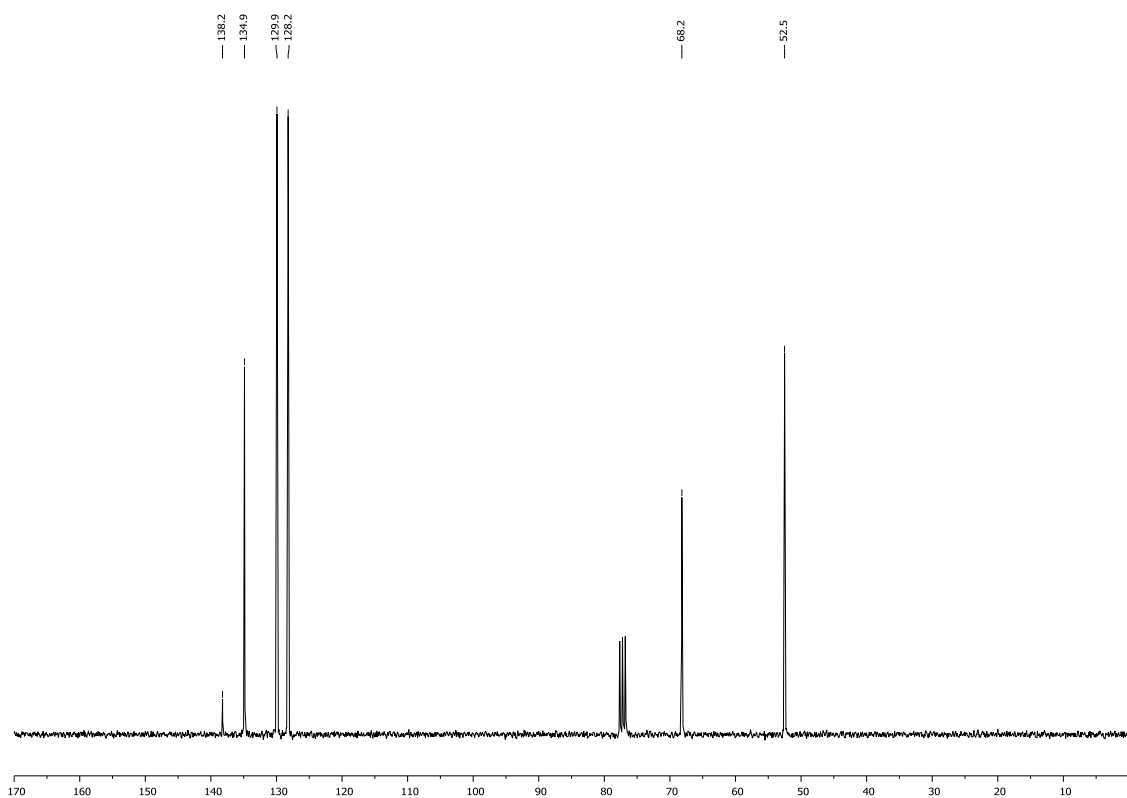
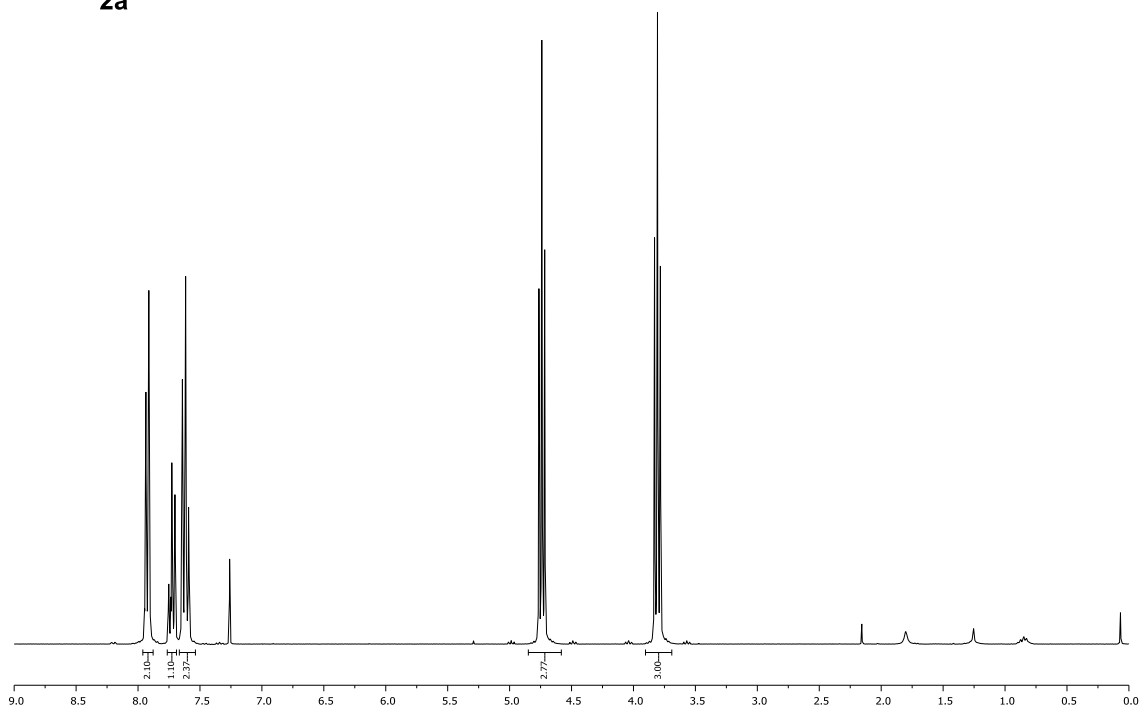
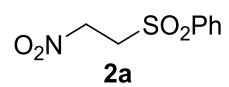


Experimental section

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea (C24)

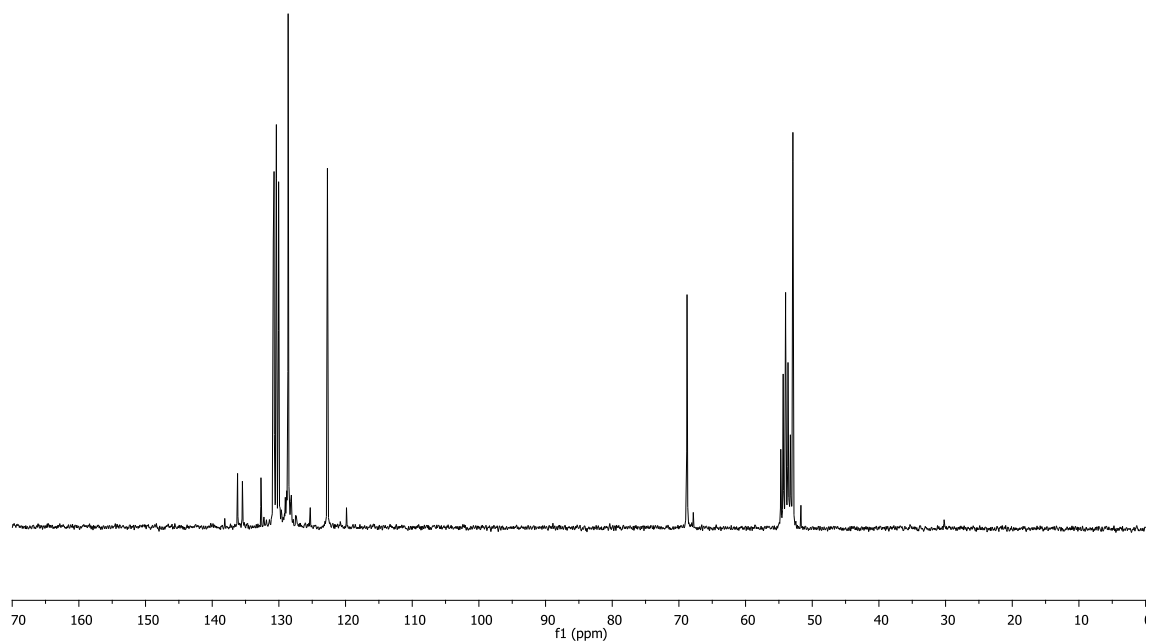
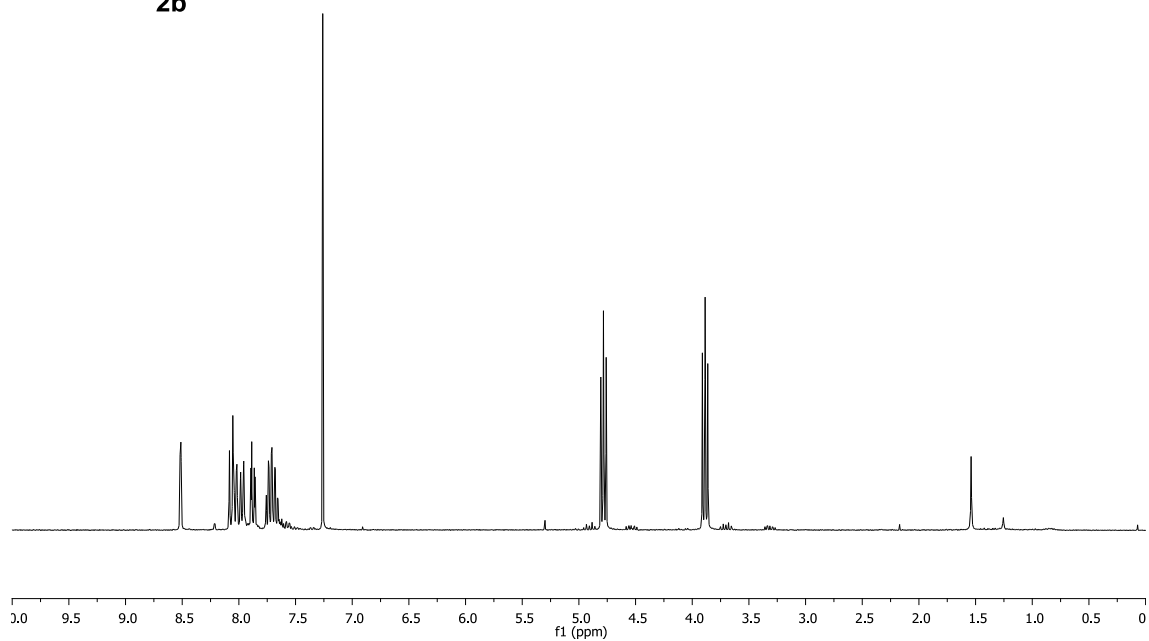
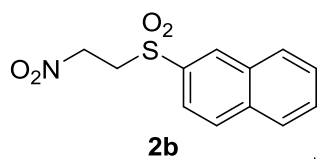


6.6.2. NMR spectra for Chapter 2

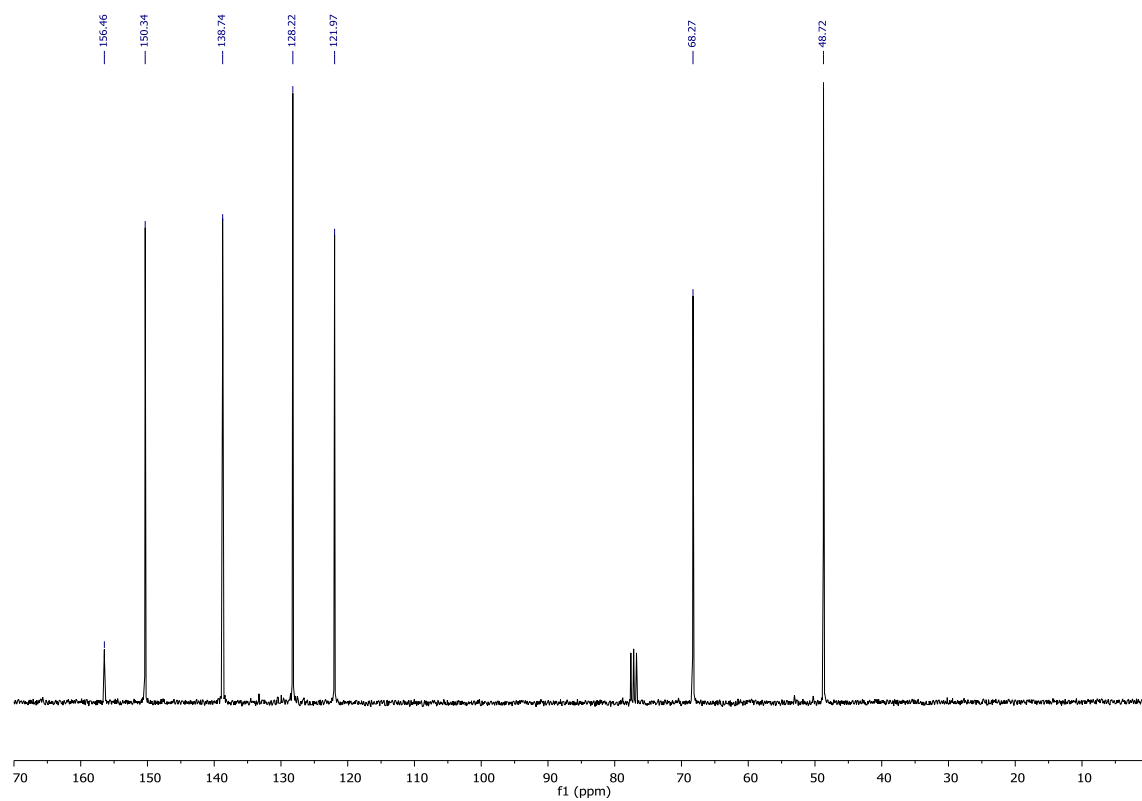
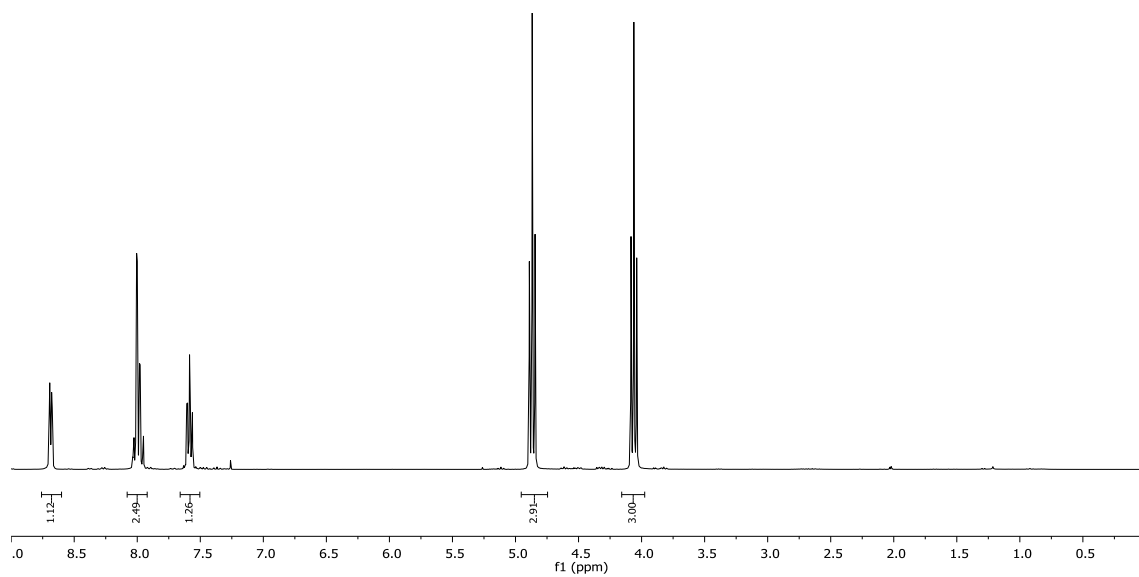
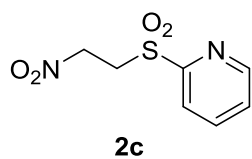
((2-Nitroethyl)sulfonyl)benzene (2a)

Experimental section

2-((2-Nitroethyl)sulfonyl)naphthalene (2b)

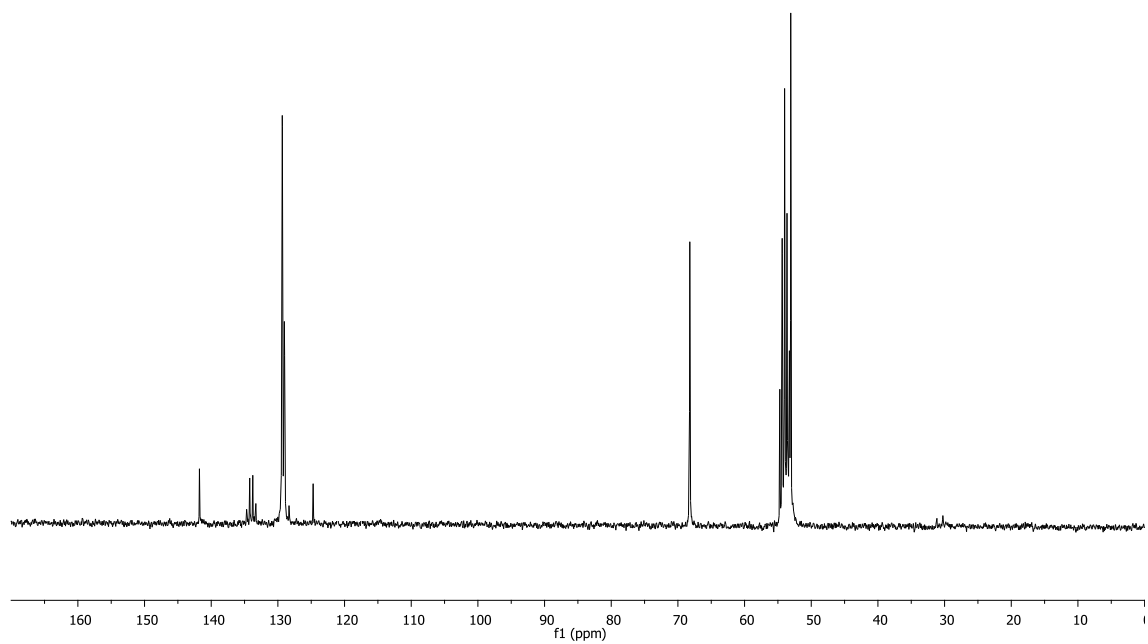
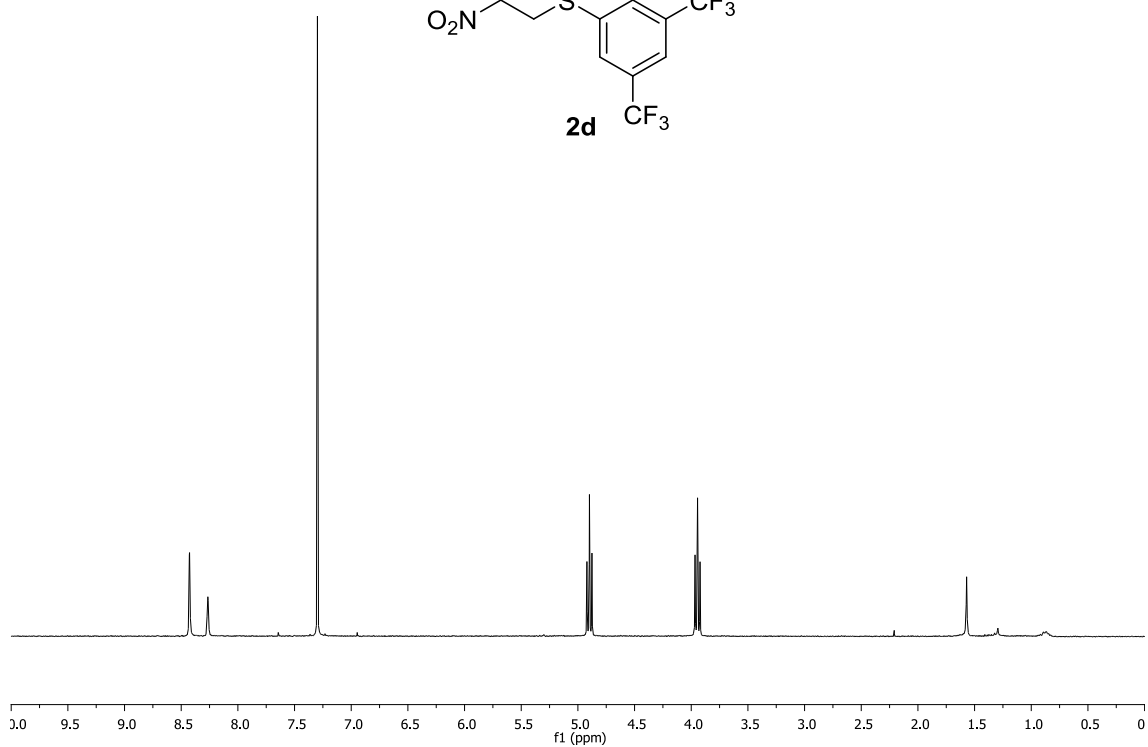
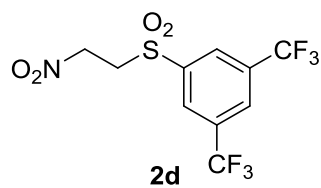


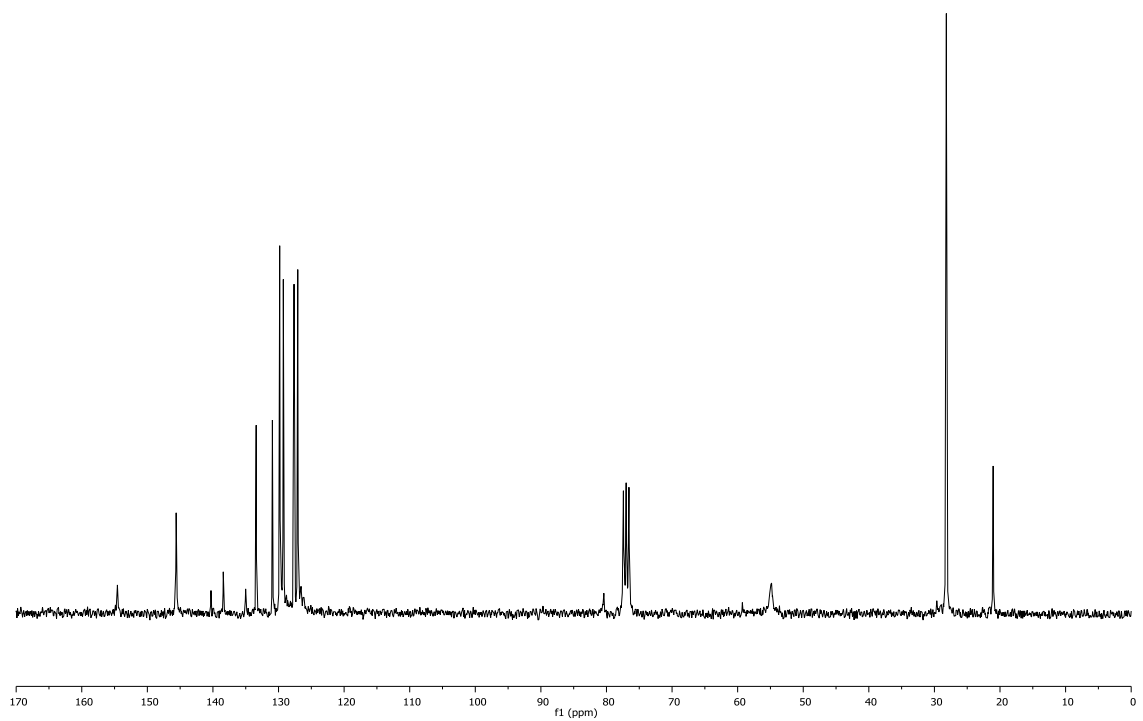
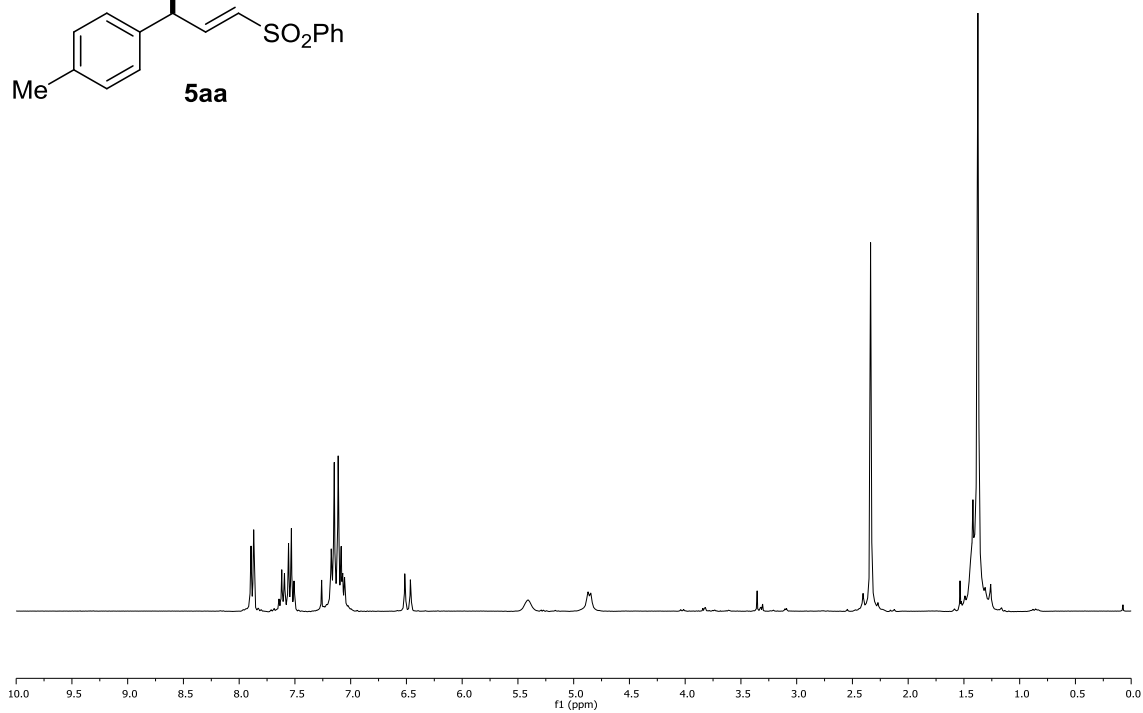
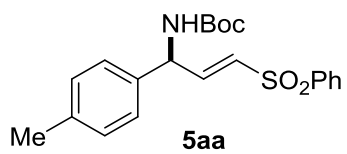
2-((2-Nitroethyl)sulfonyl)pyridine (2c)



Experimental section

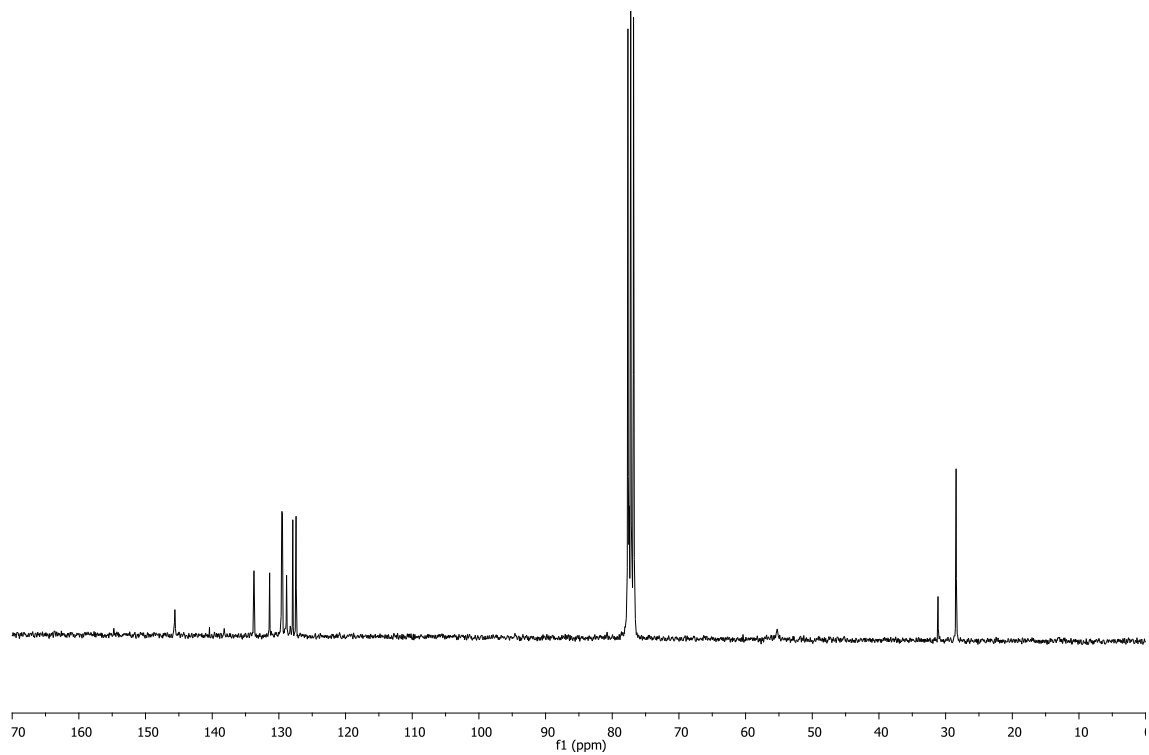
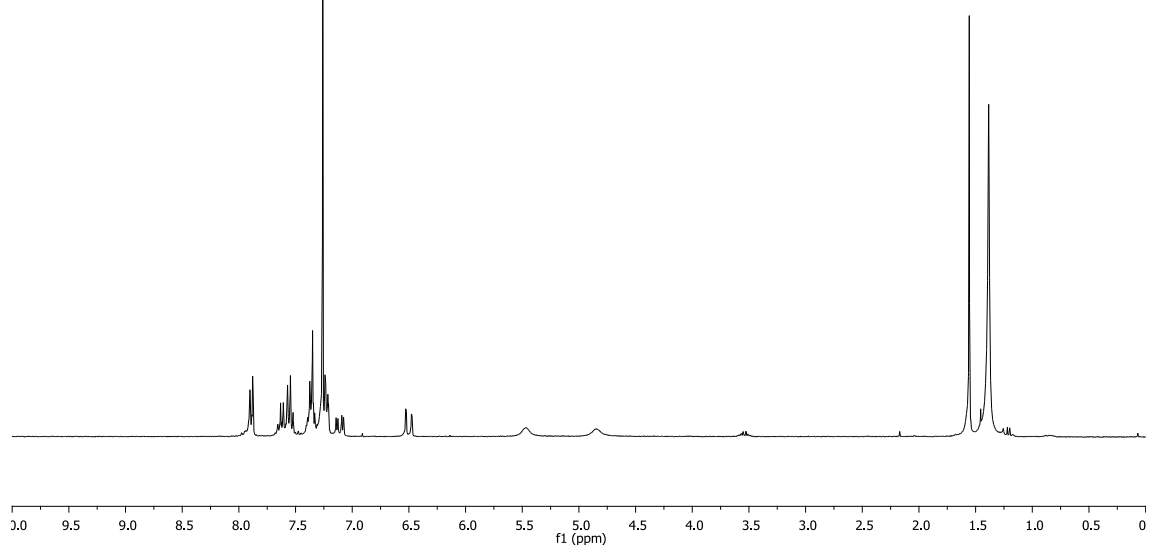
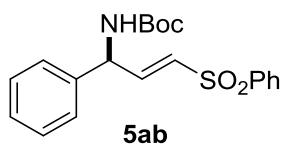
1-((2-Nitroethyl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (2d)

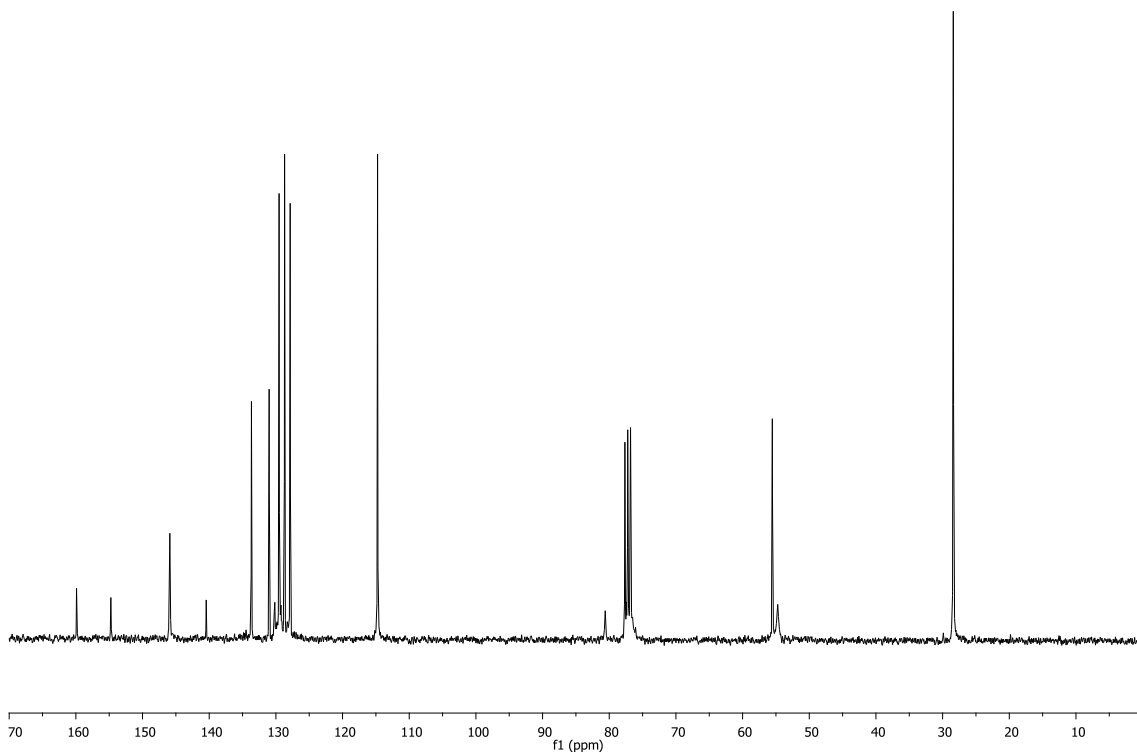
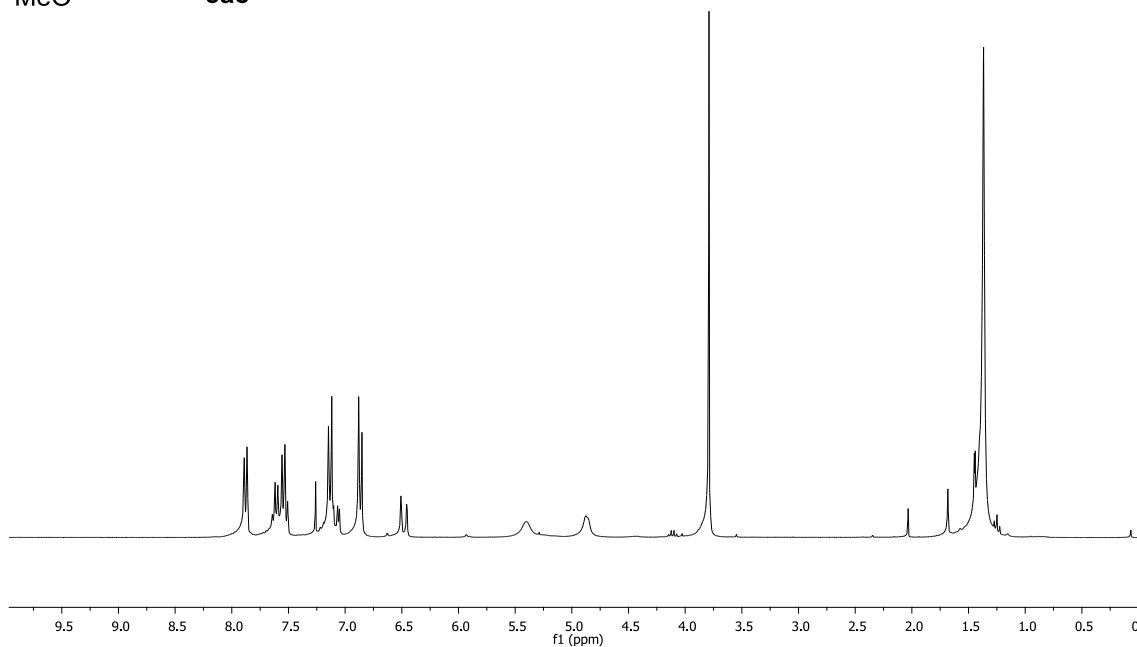
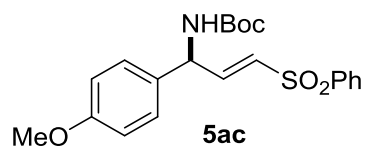


***tert*-Butyl (*S,E*)-(3-(phenylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (5aa)**

Experimental section

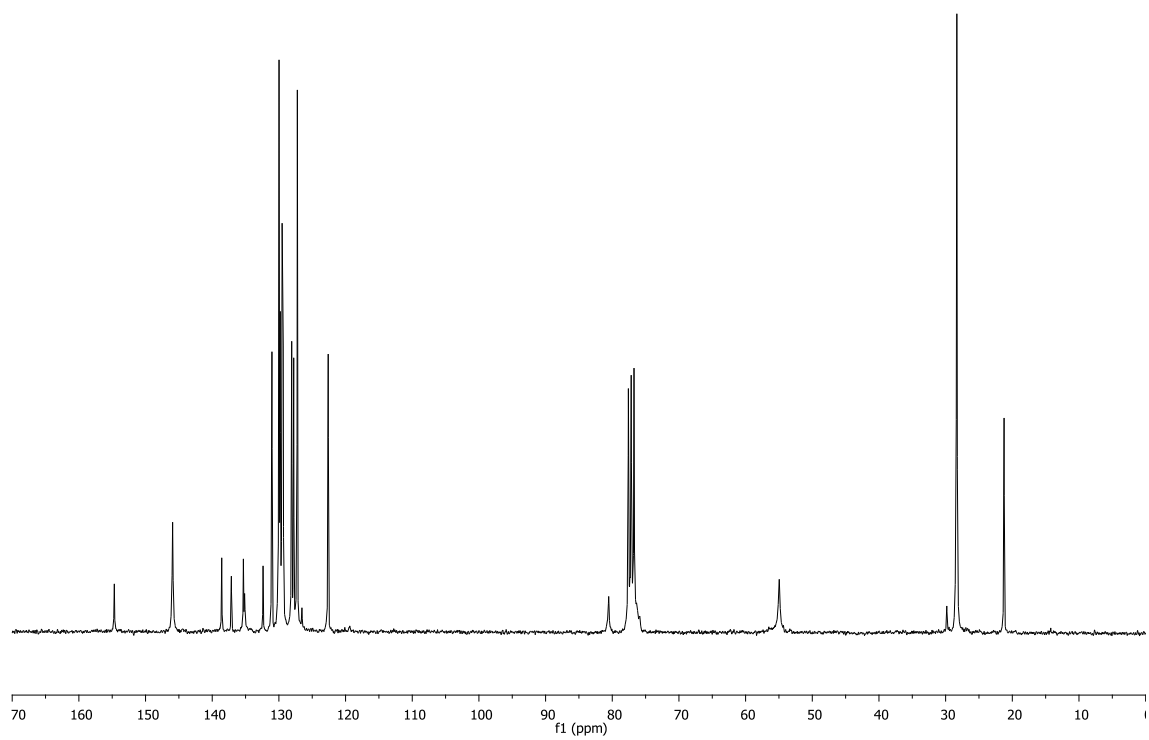
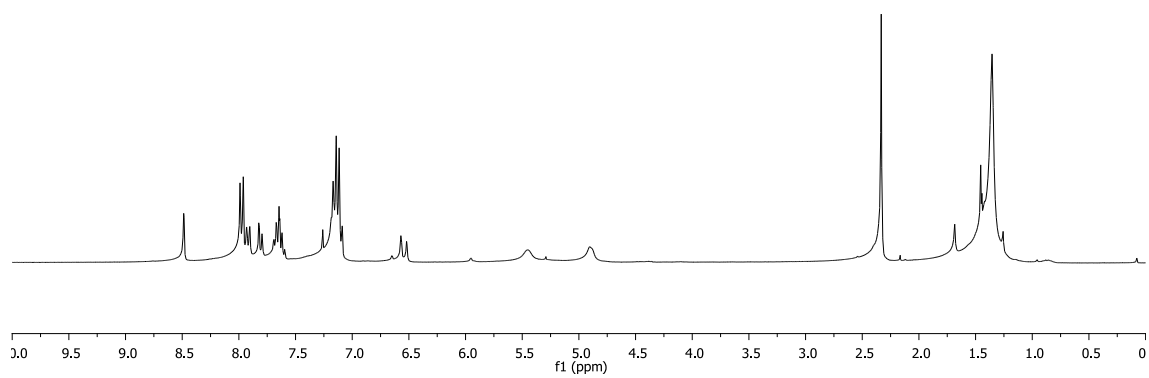
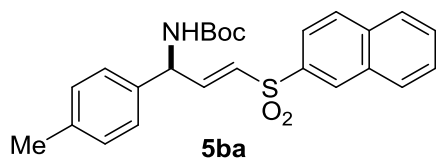
***tert*-Butyl (*S,E*)-(1-phenyl-3-(phenylsulfonyl)allyl)carbamate (**5ab**)**

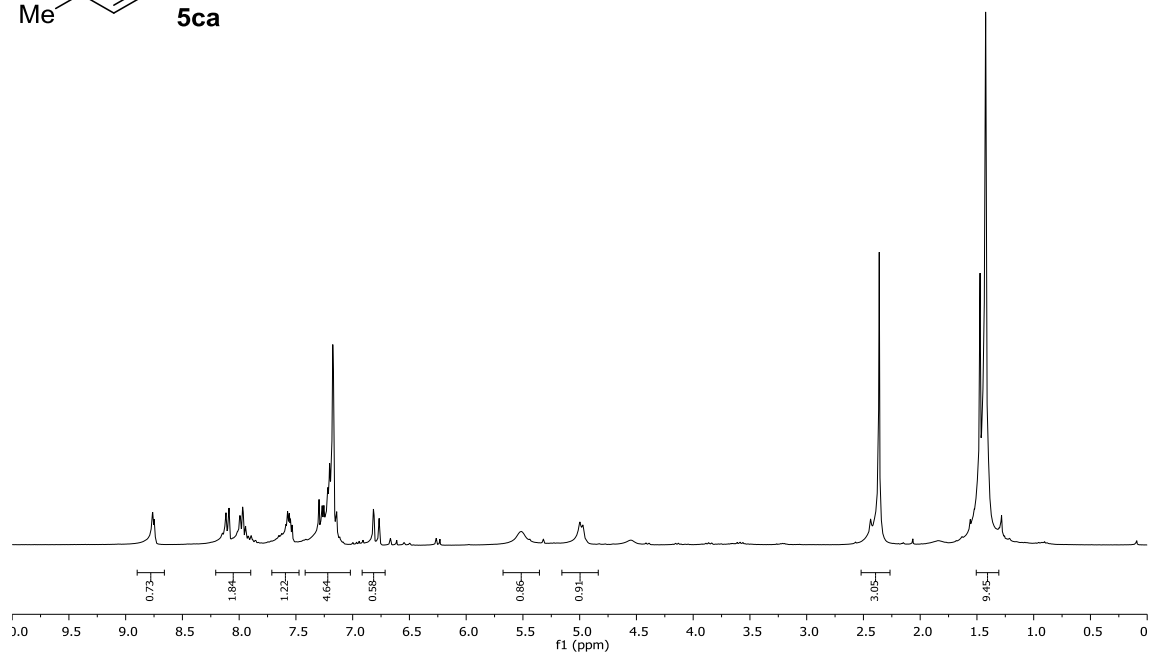
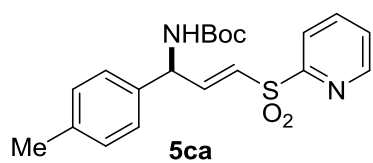


***tert*-Butyl (*S,E*)-(1-(4-methoxyphenyl)-3-(phenylsulfonyl)allyl)carbamate (**5ac**)**

Experimental section

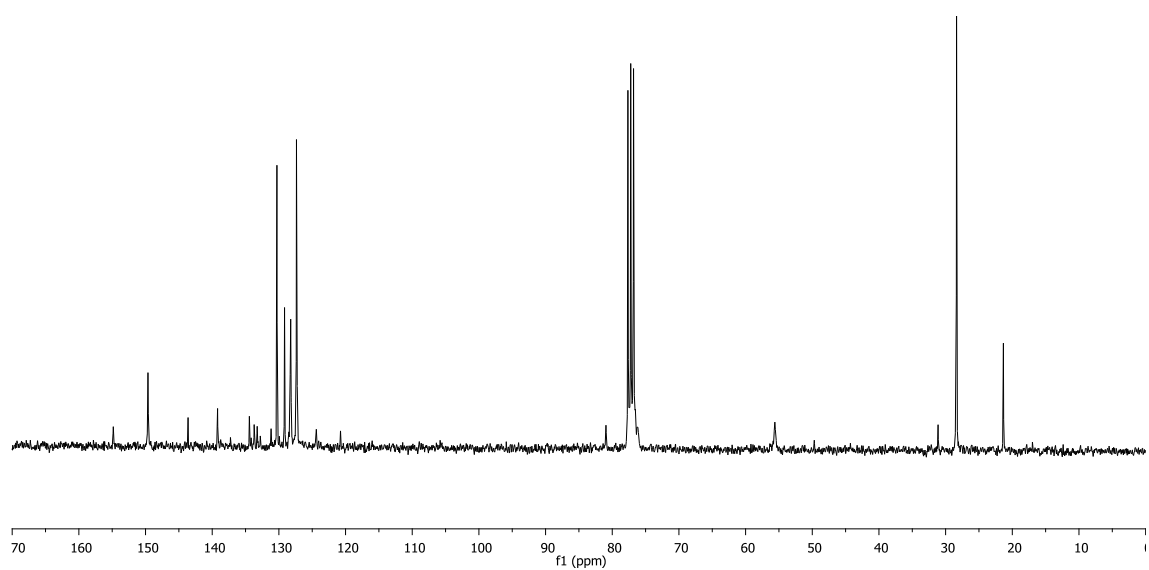
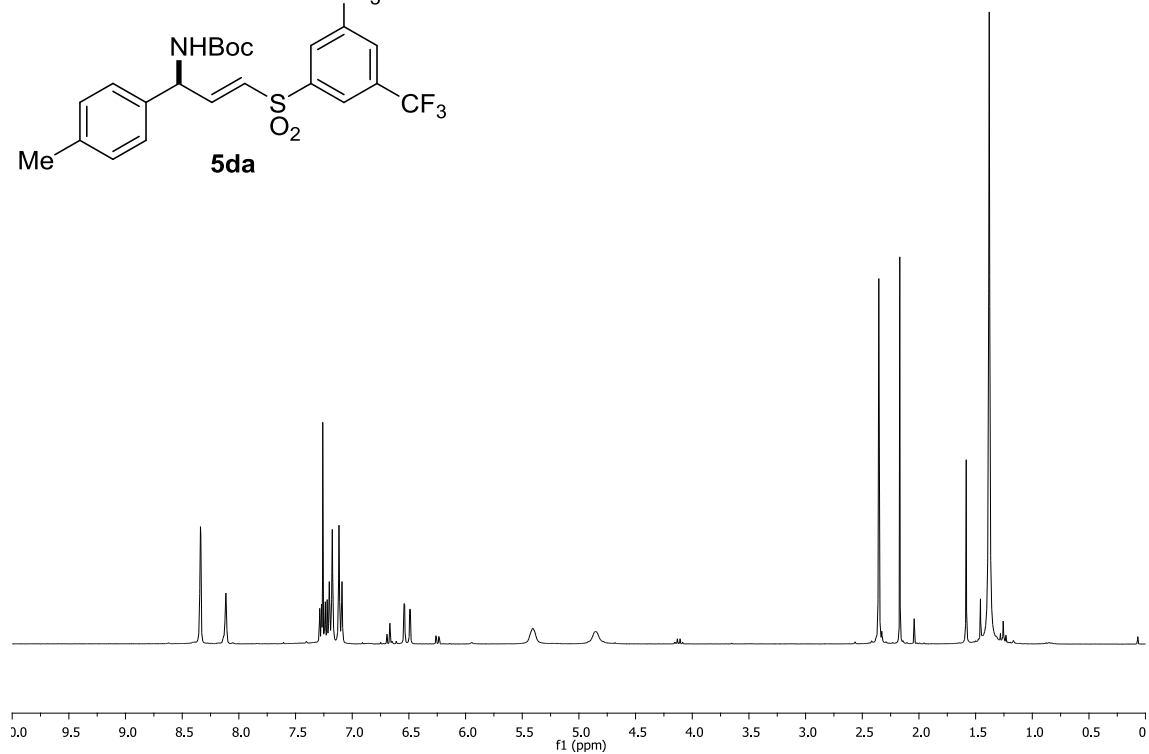
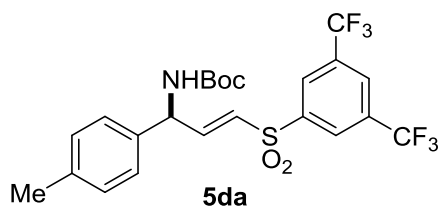
***tert*-Butyl (*S,E*)-(3-(naphthalen-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5ba**)**



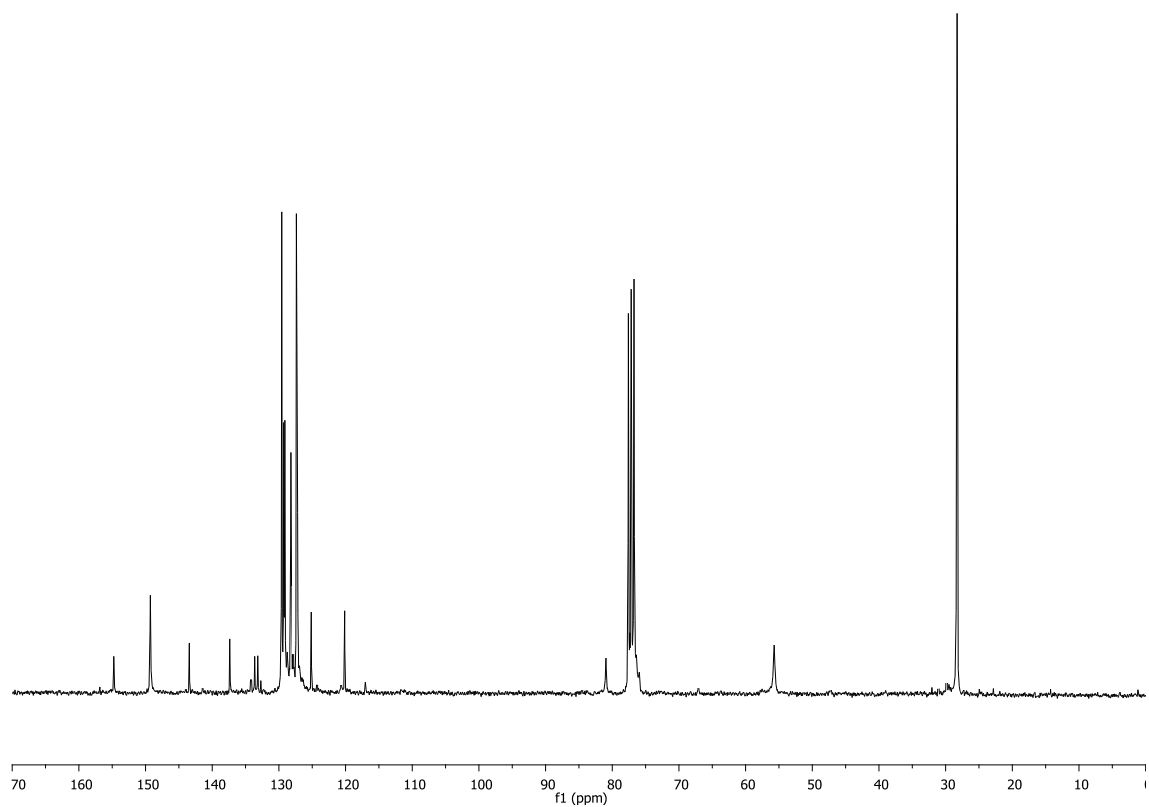
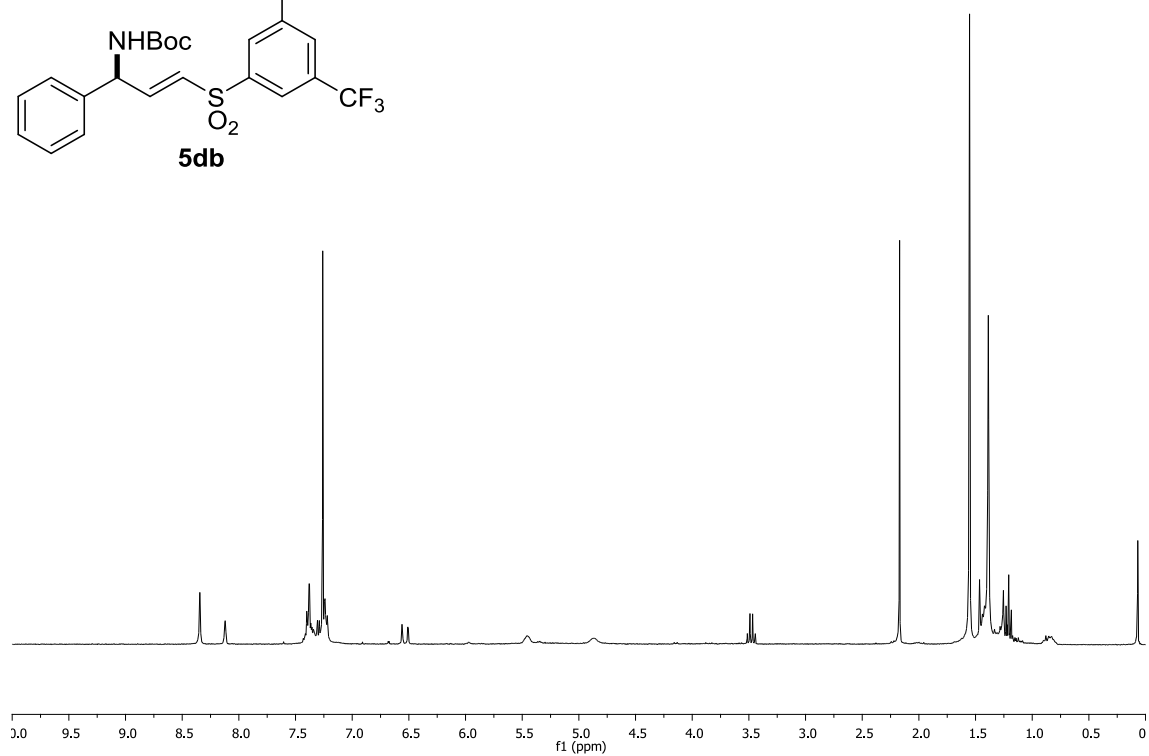
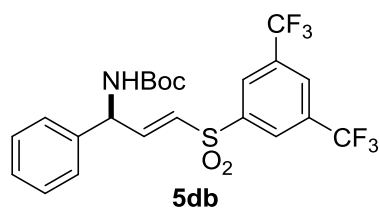
***tert*-Butyl (*S,E*)-(3-(pyridin-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5ca**)**

Experimental section

tert-Butyl
(*S,E*)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(*p*-
tolyl)allyl)carbamate (**5da**)

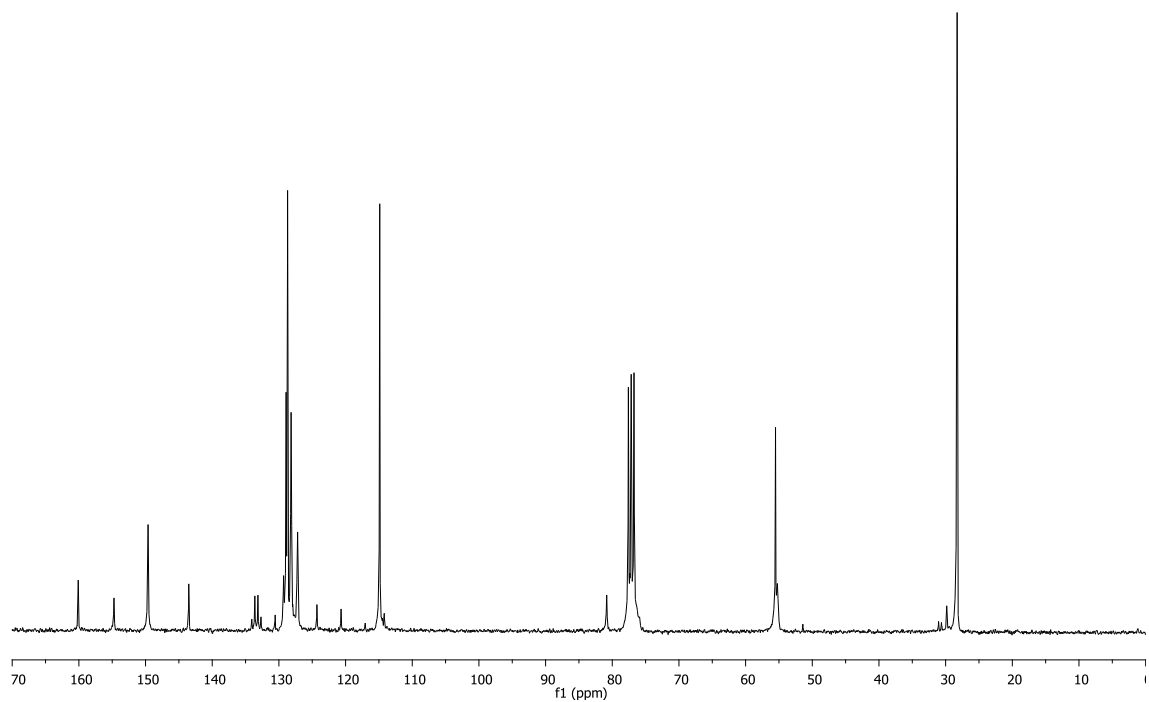
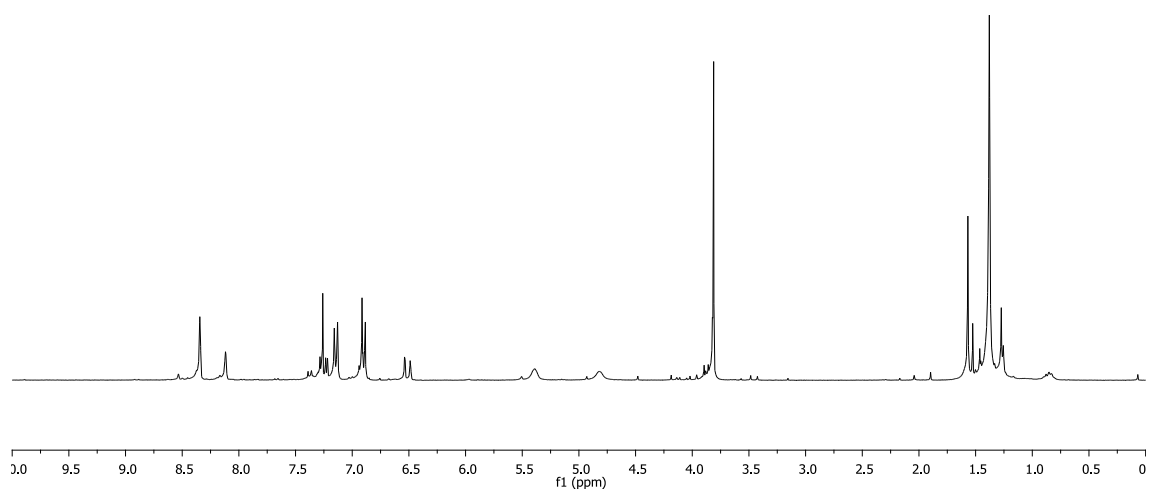
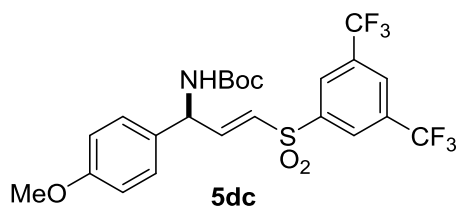


***tert*-Butyl (*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-phenylallyl)carbamate (5db)**

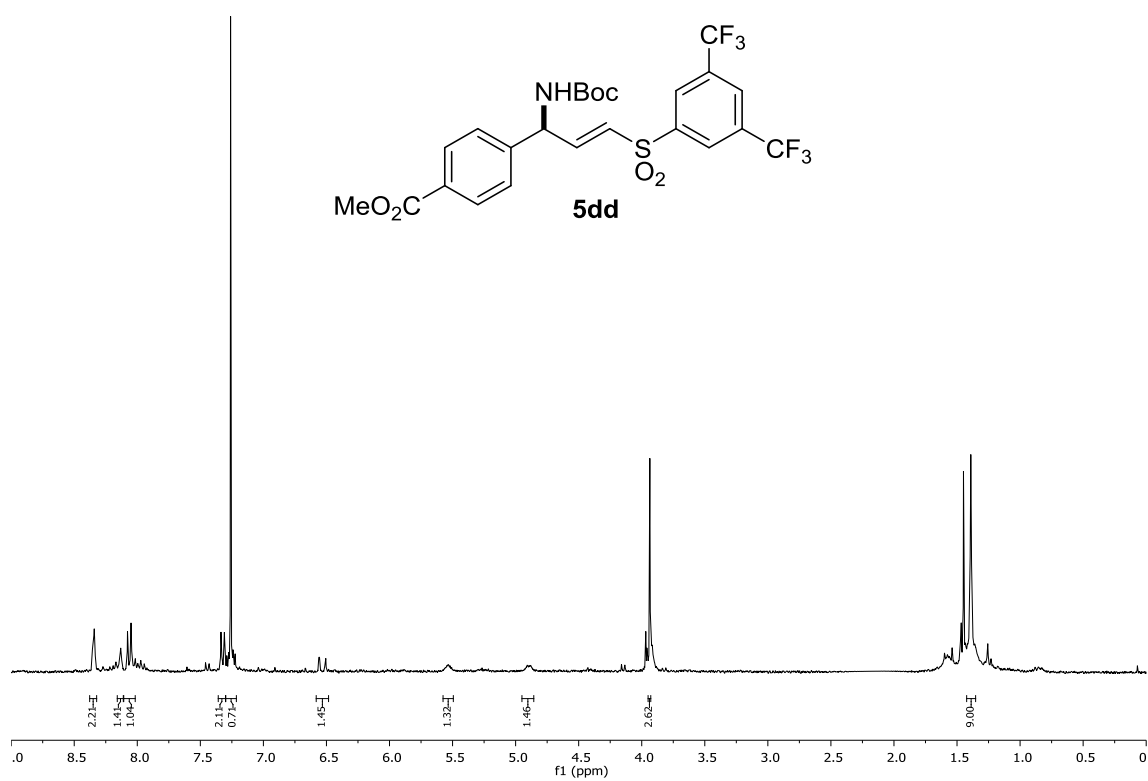


Experimental section

tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)allyl carbamate (5dc)



Methyl (S,E)-4-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-((tert-butoxycarbonyl)amino)allyl)benzoate (5dd)

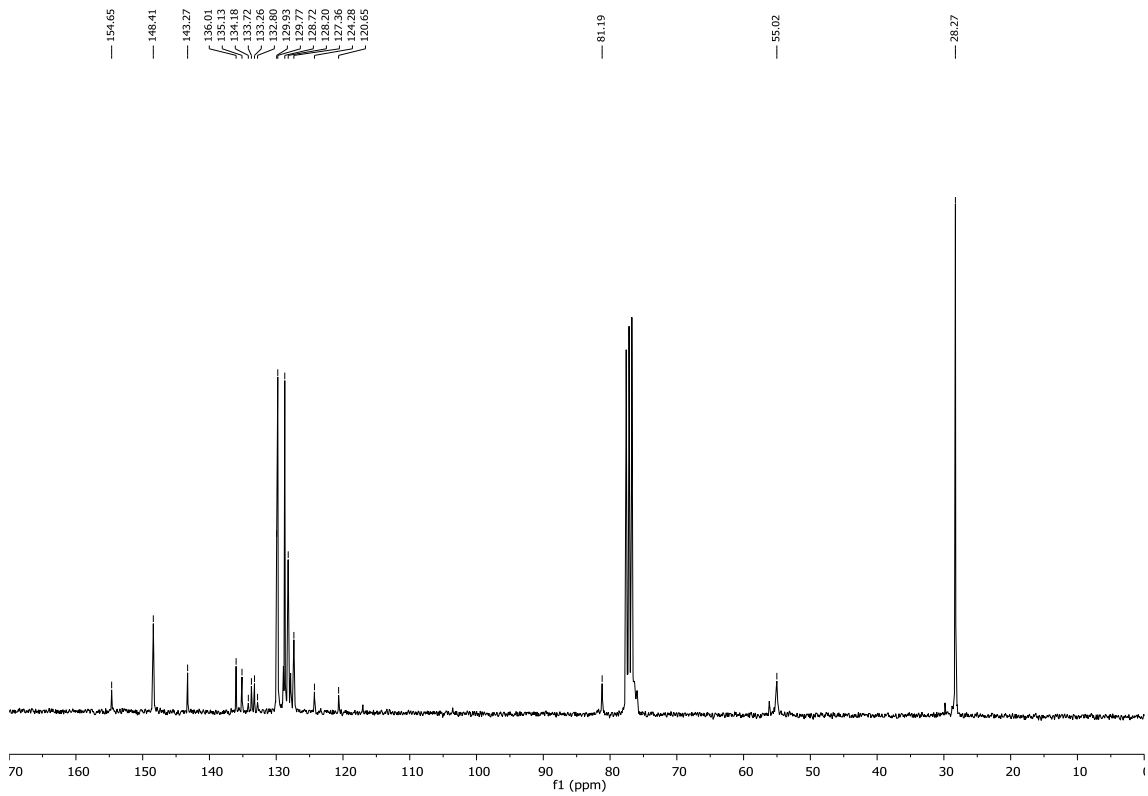
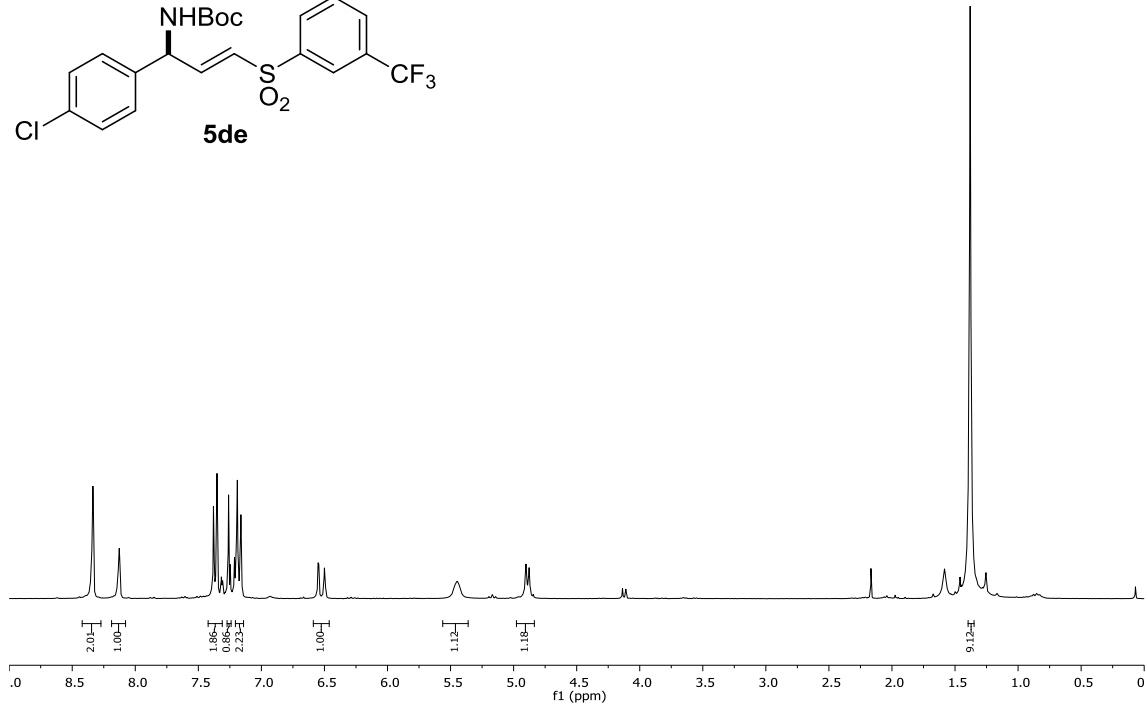
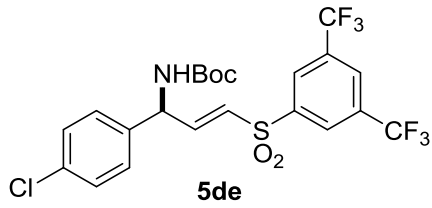


Experimental section

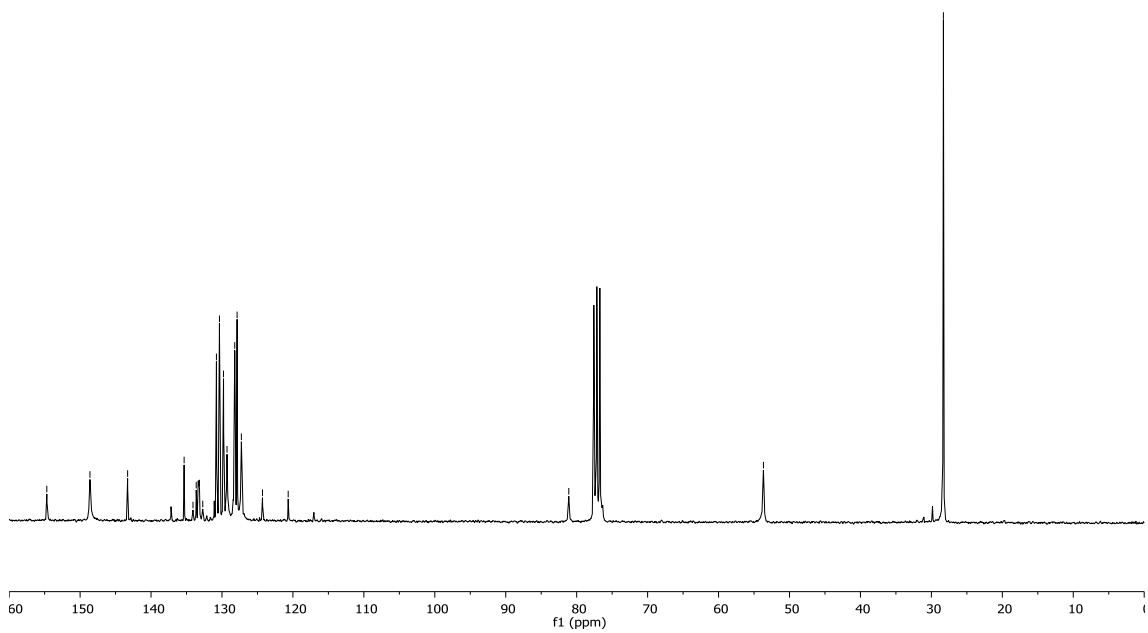
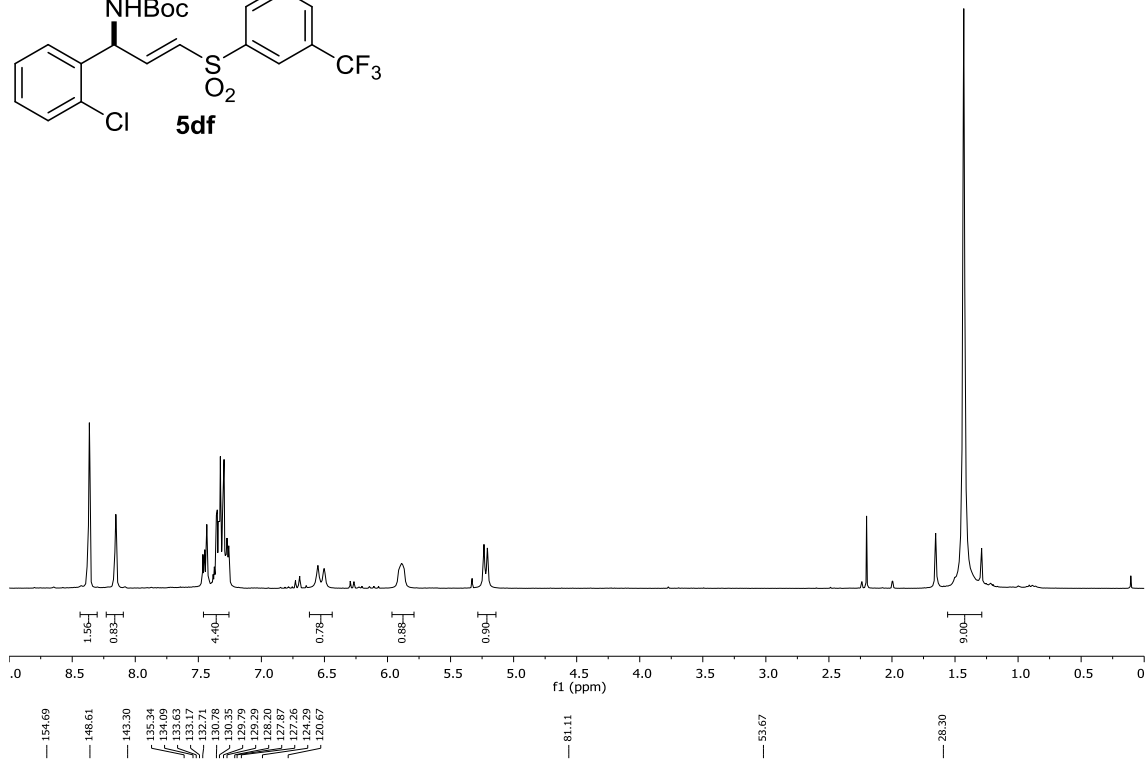
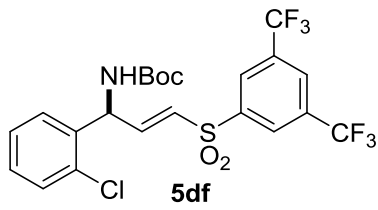
tert-Butyl

(*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-

chlorophenyl)allyl)carbamate (**5de**)

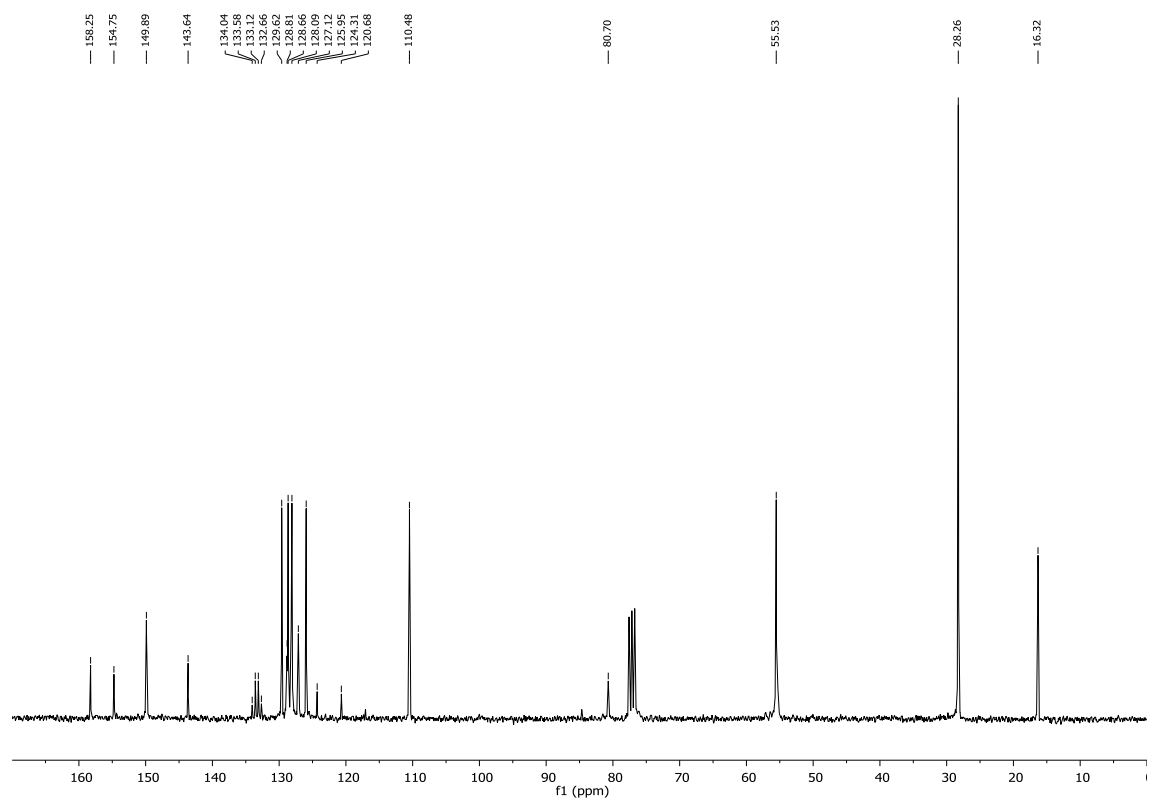
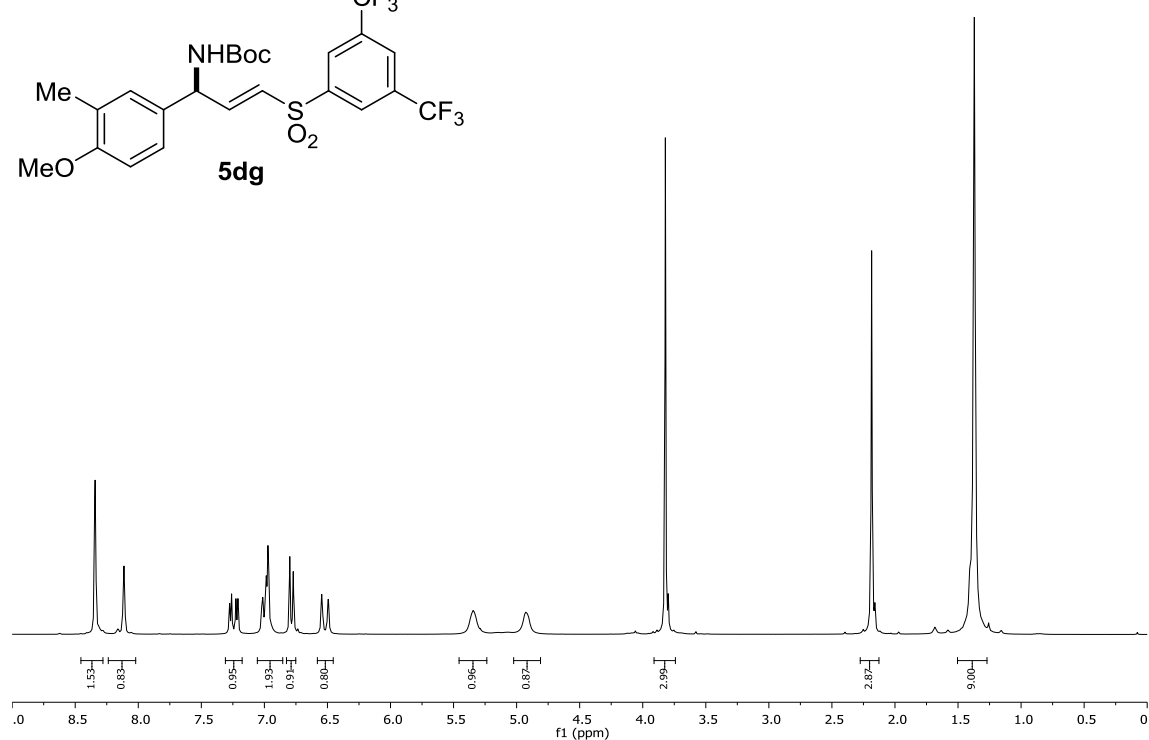
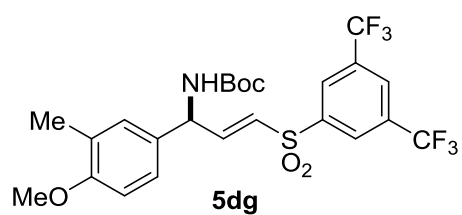


tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(2-chlorophenyl)allyl carbamate (5df)

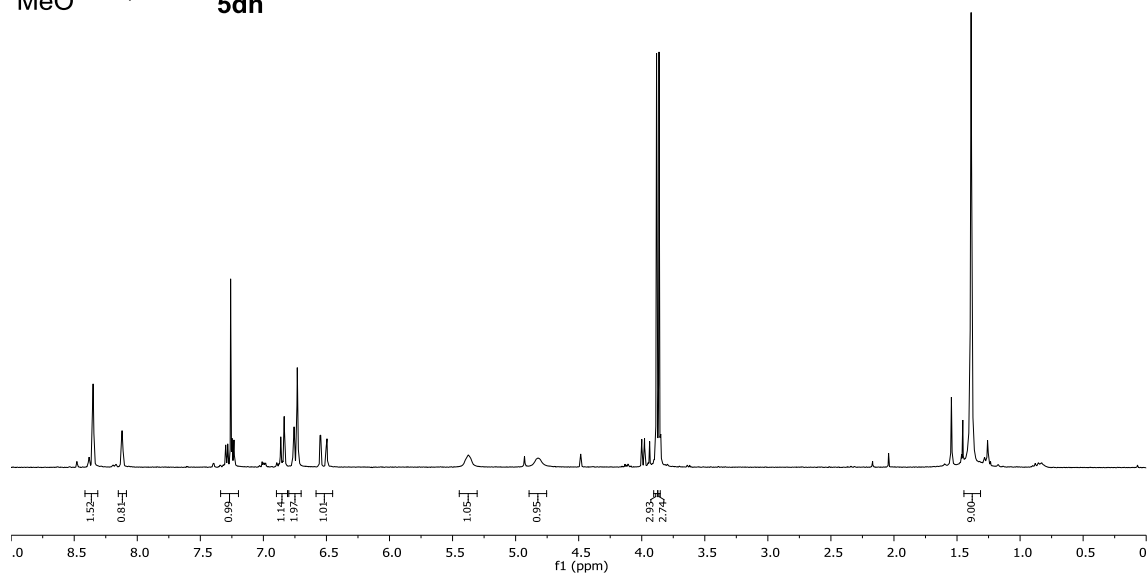
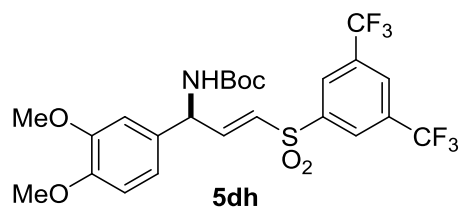


Experimental section

***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxy-3-methylphenyl)allyl carbamate (5dg)**

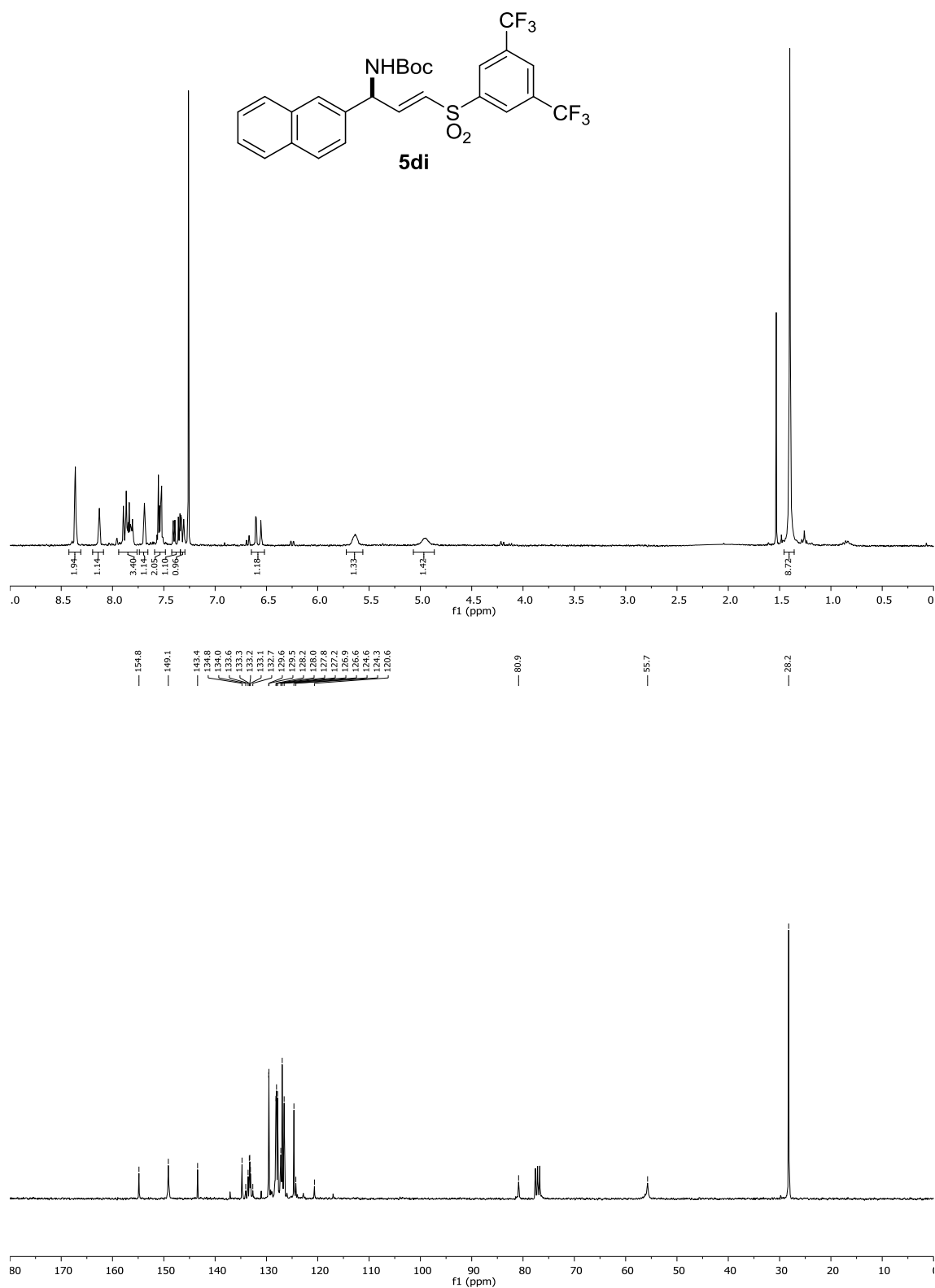


tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(3,4-dimethoxyphenyl)allyl carbamate (5dh)

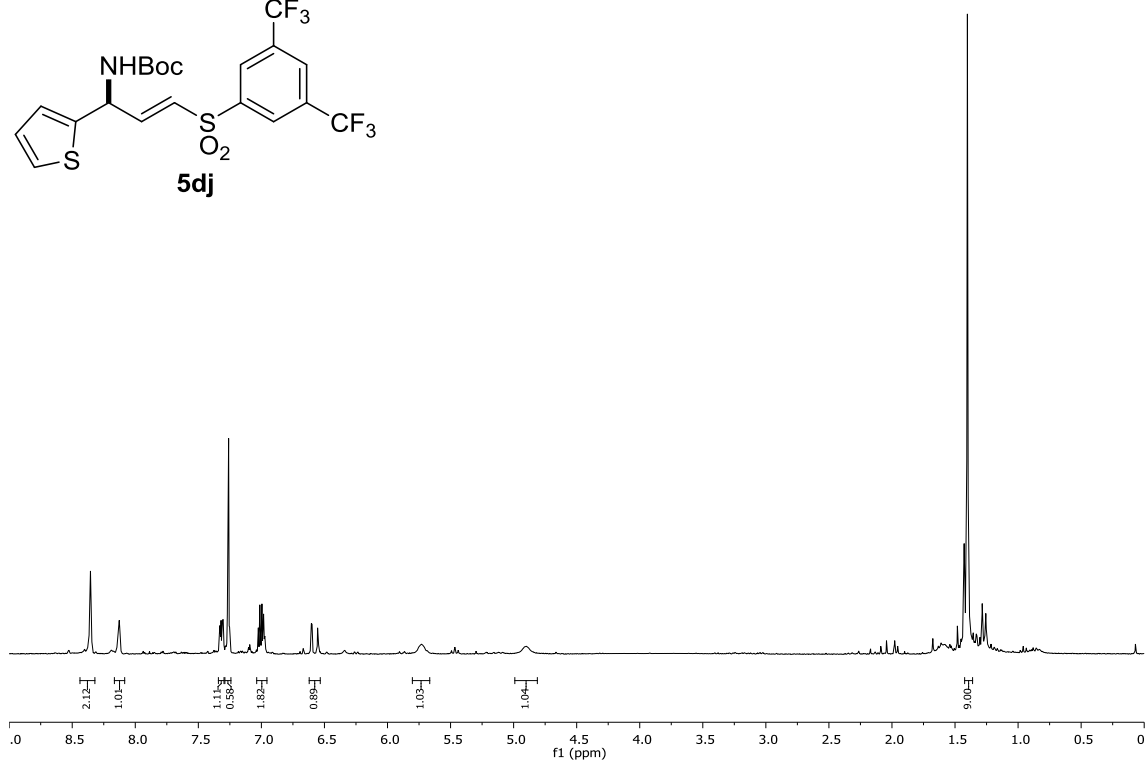
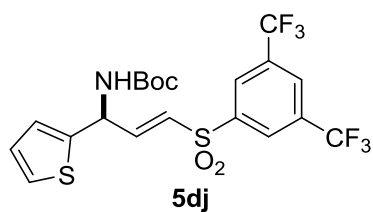


Experimental section

***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(naphthalen-2-yl)allyl carbamate (5di)**

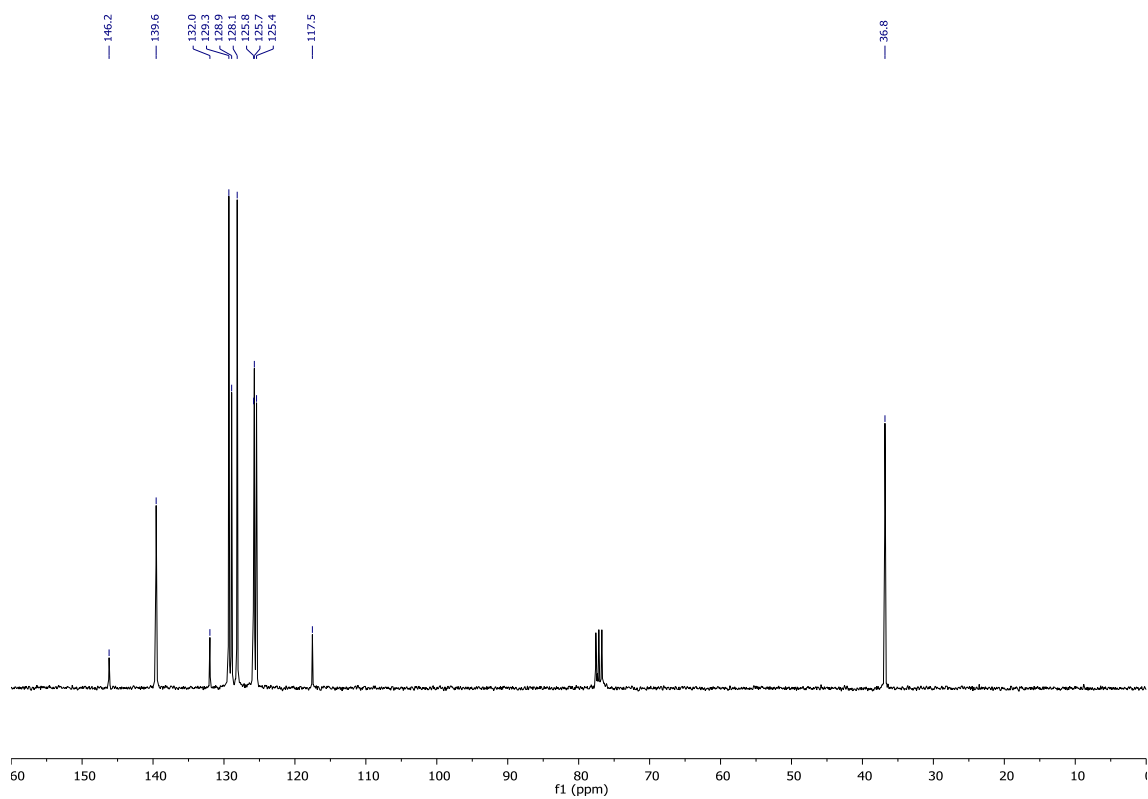
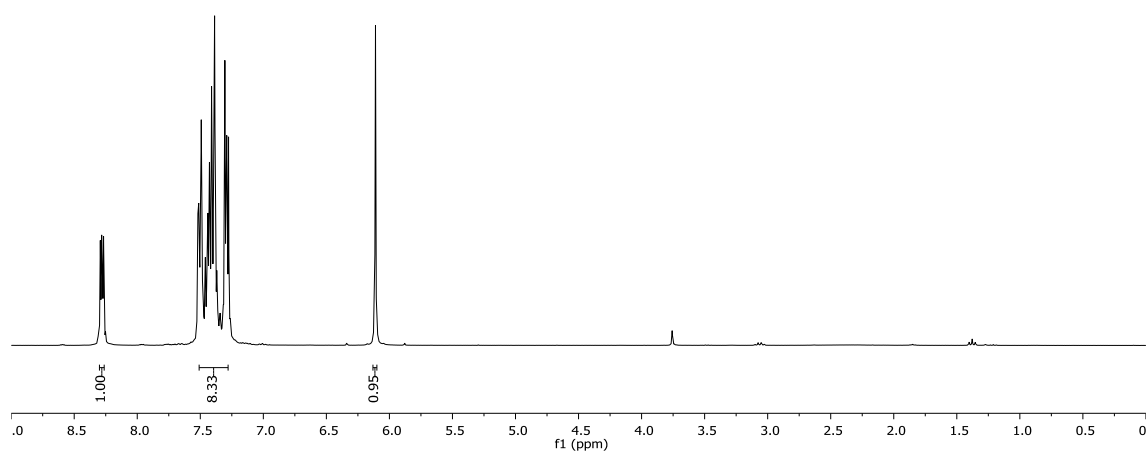
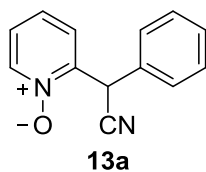


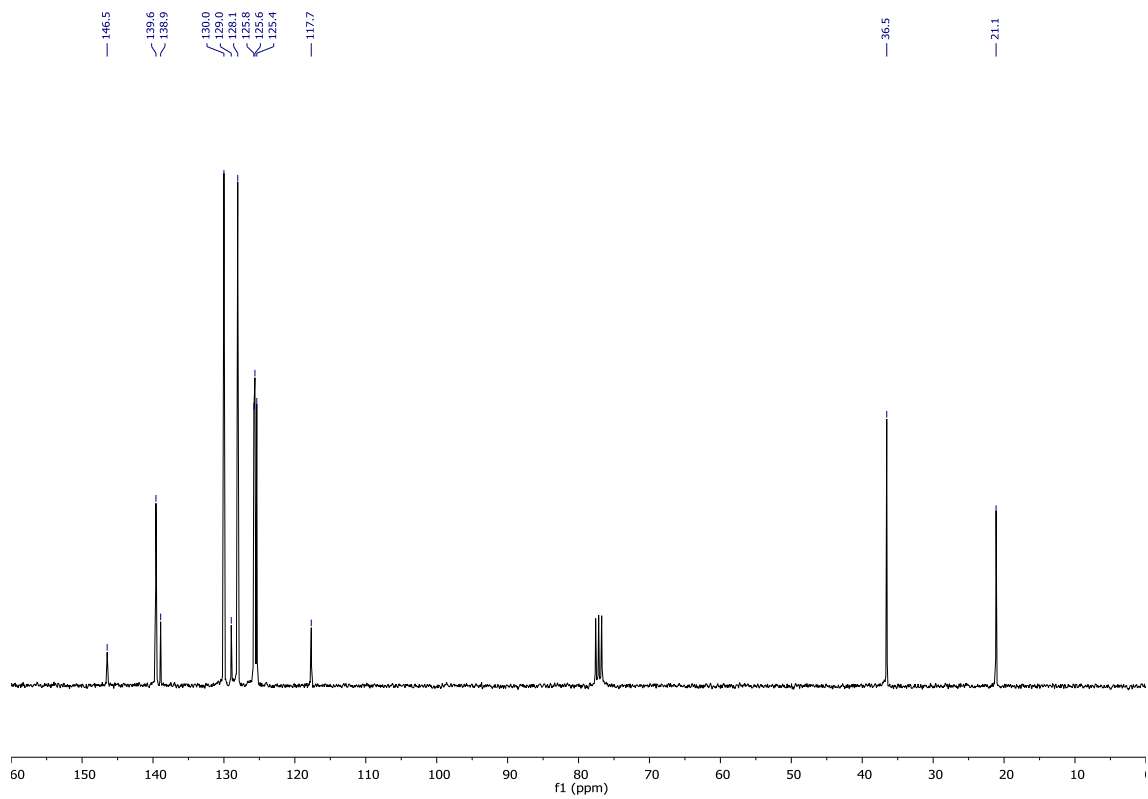
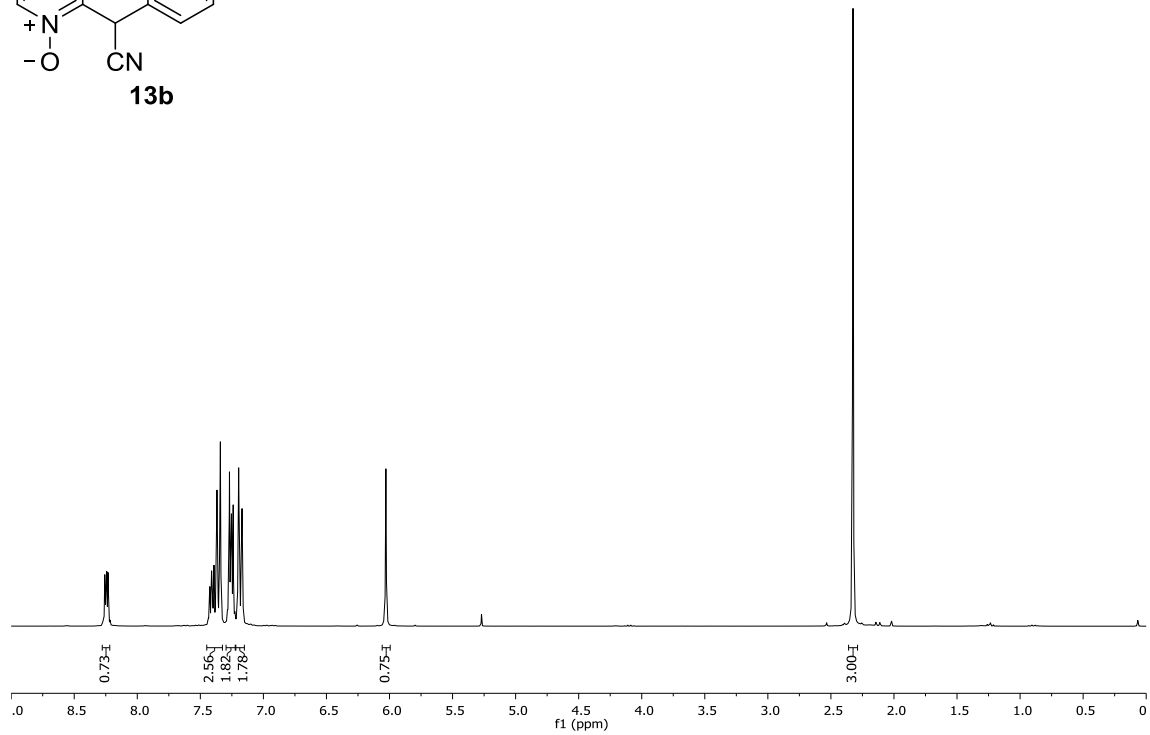
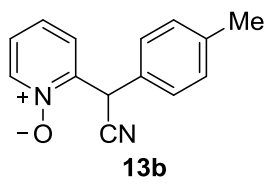
***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(thiophen-2-yl)allyl carbamate (5dj)**



6.6.3. NMR spectra for Chapter 3

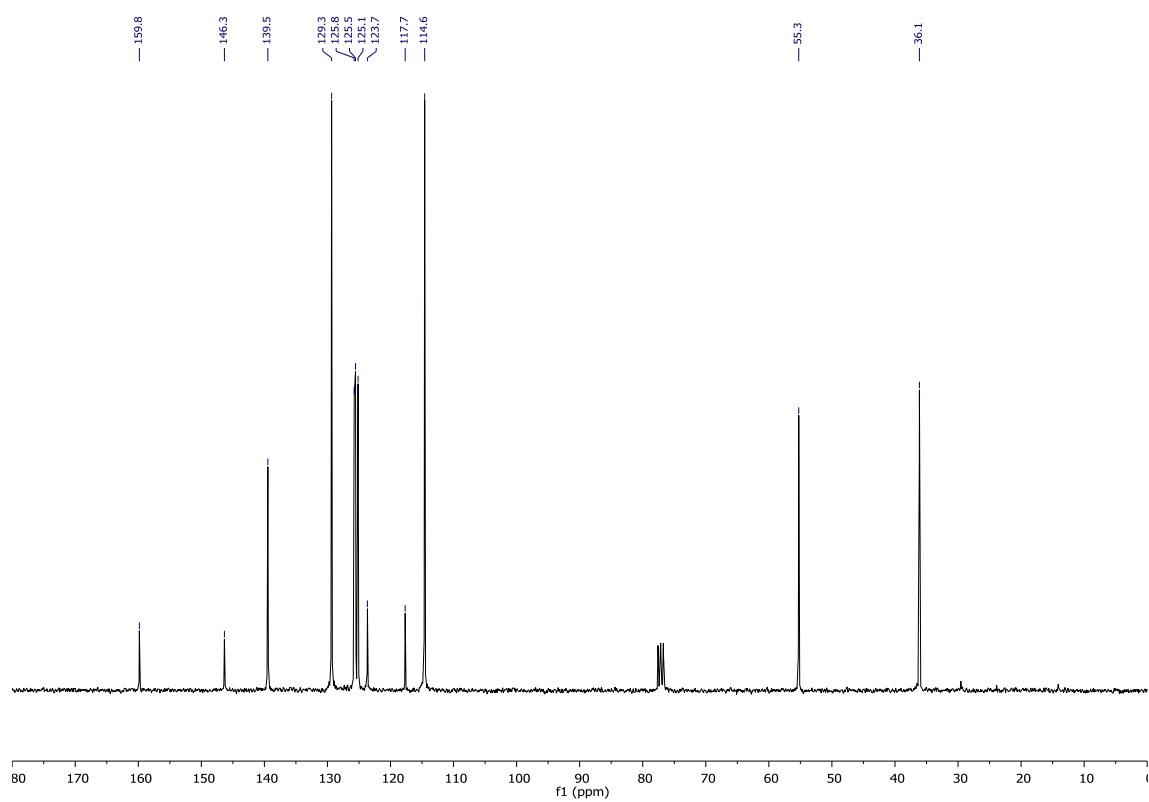
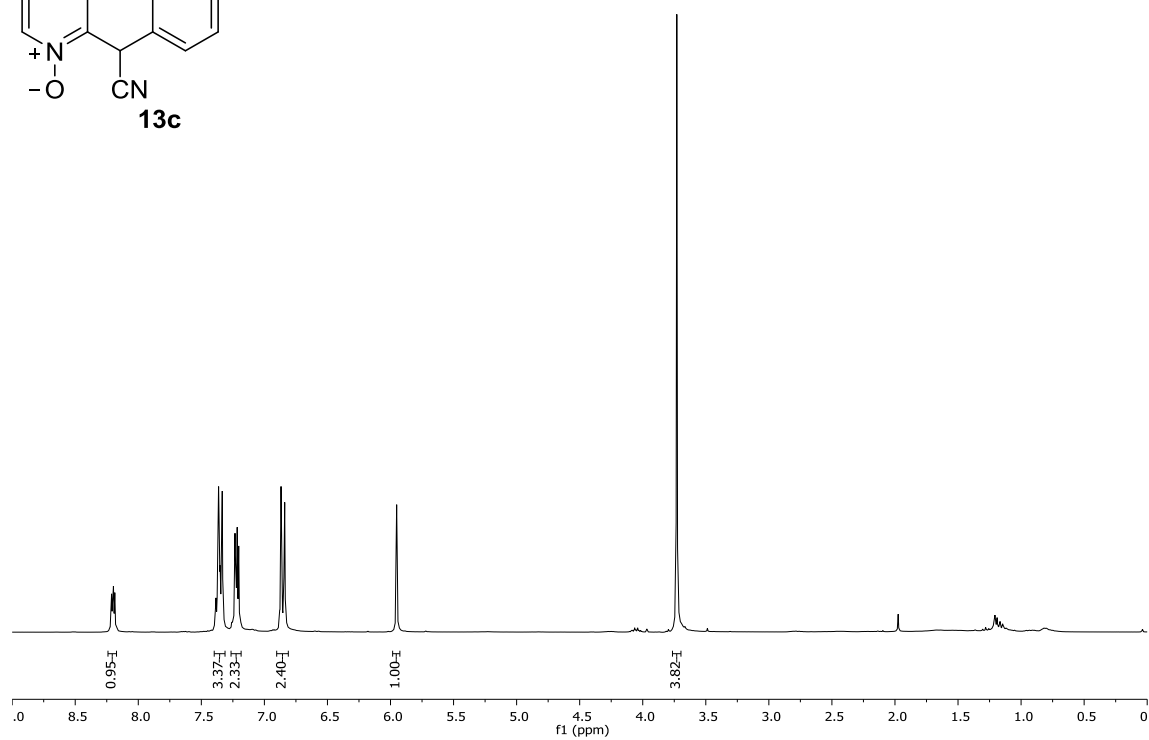
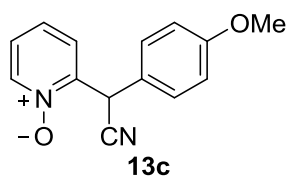
2-(Cyano(phenyl)methyl)pyridine *N*-oxide (13a)

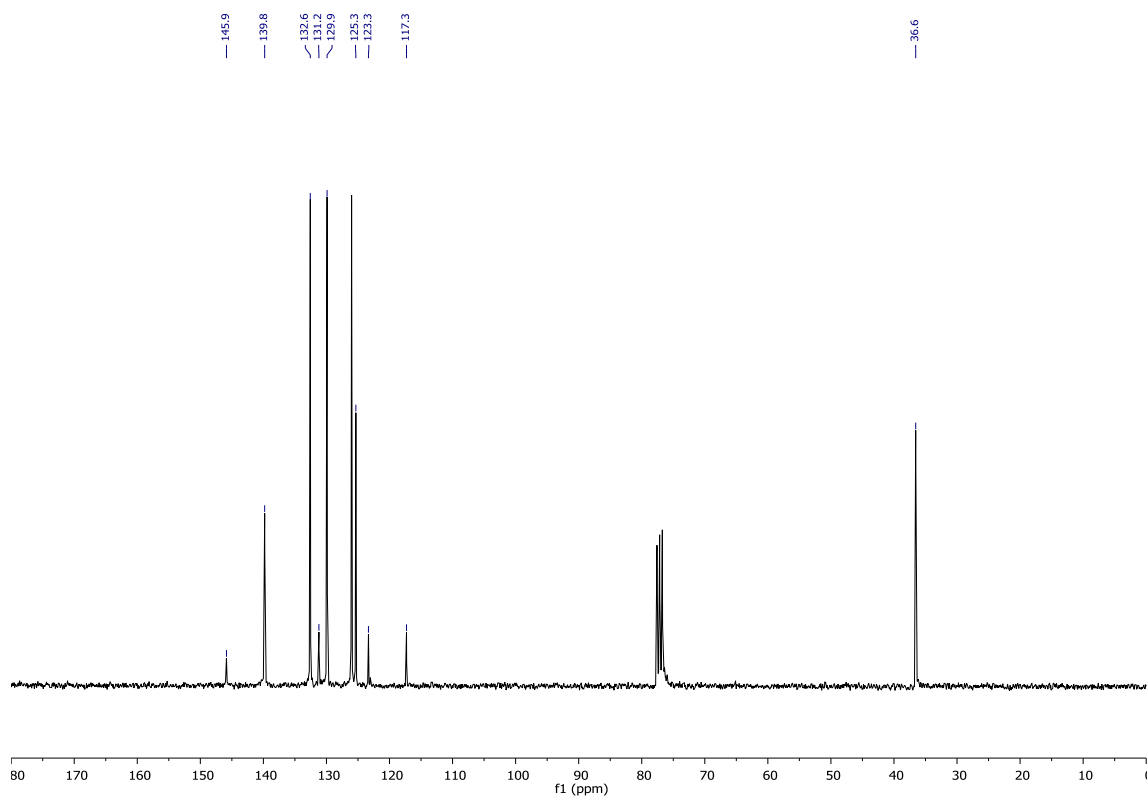
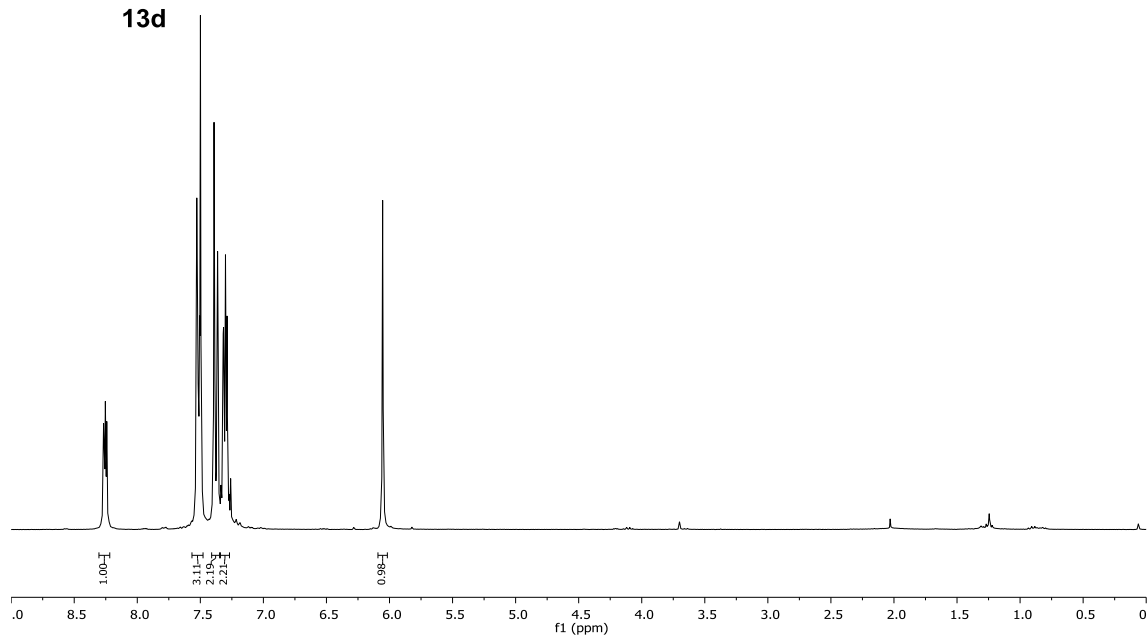
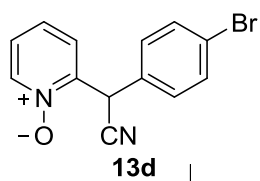


2-(Cyano(*p*-tolyl)methyl)pyridine *N*-oxide (13b)

Experimental section

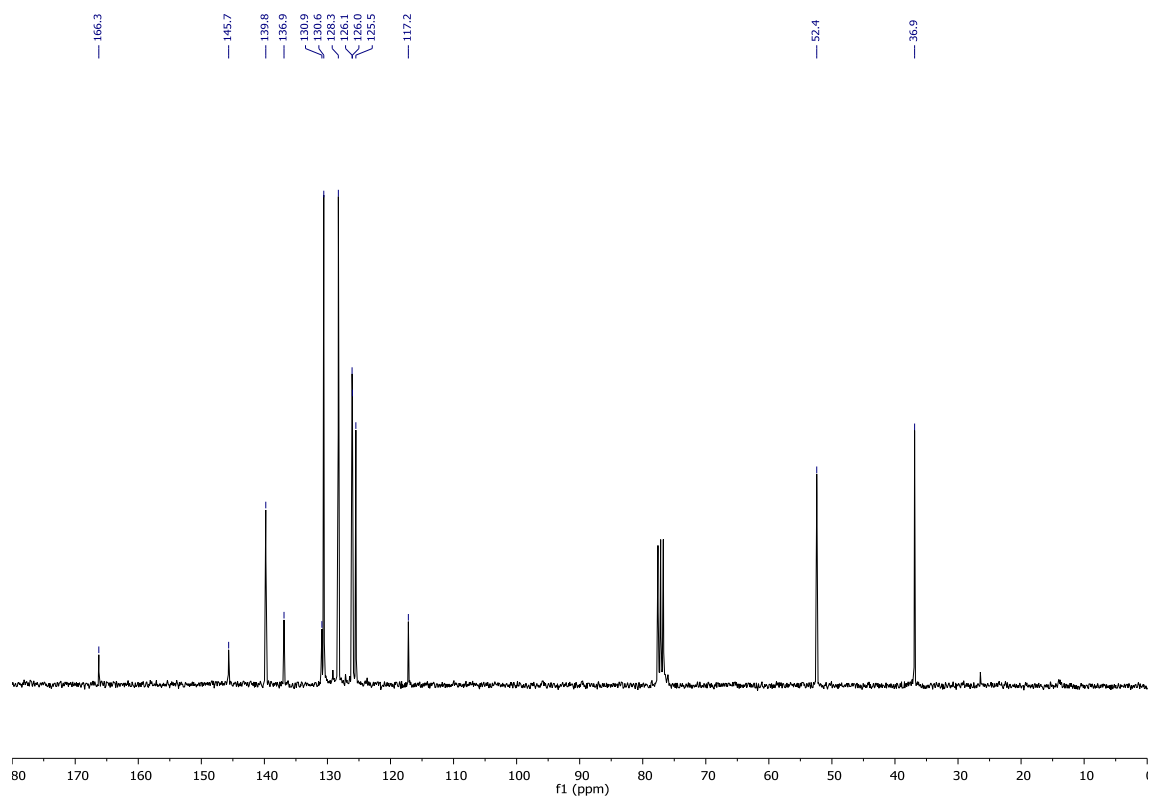
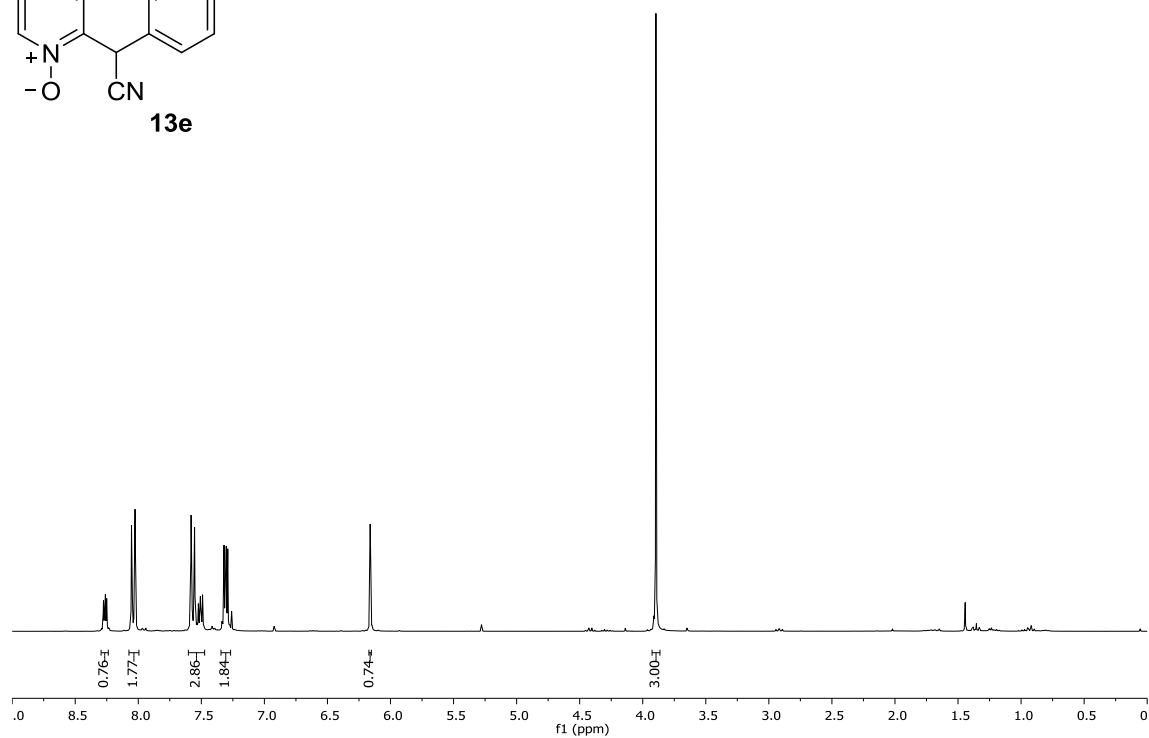
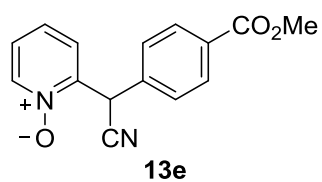
2-(Cyano(4-methoxyphenyl)methyl)pyridine *N*-oxide (13c)

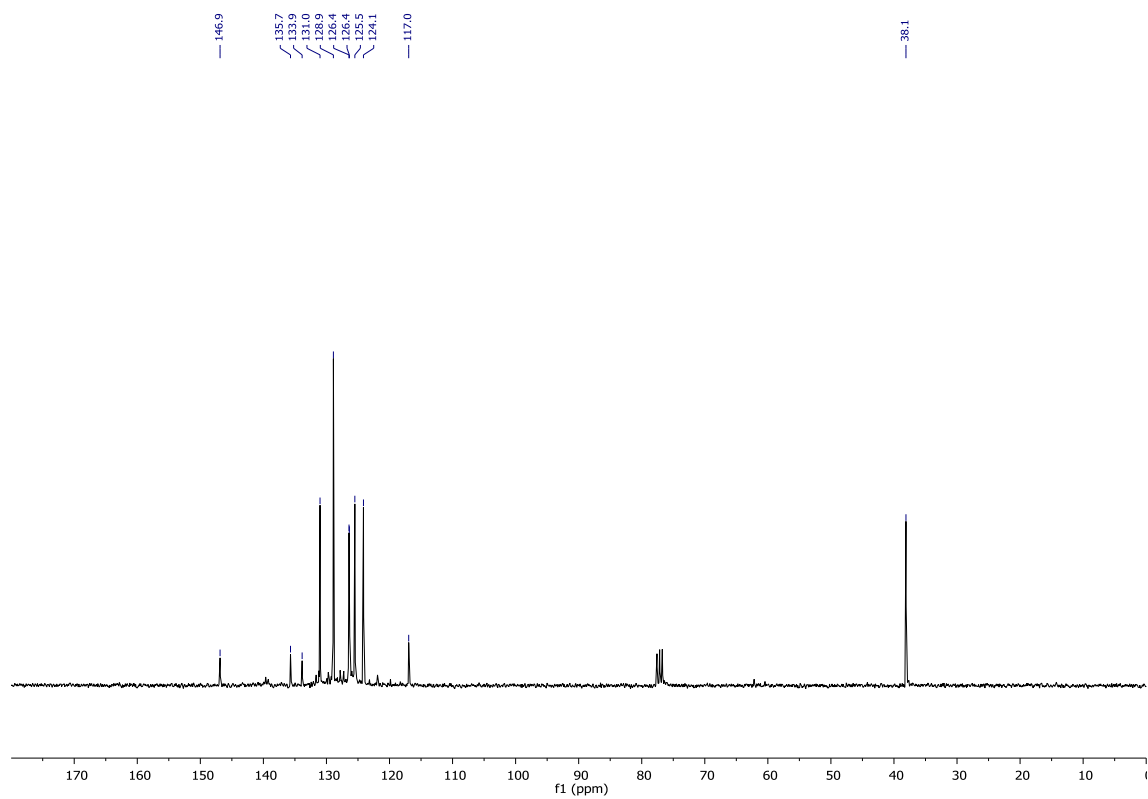
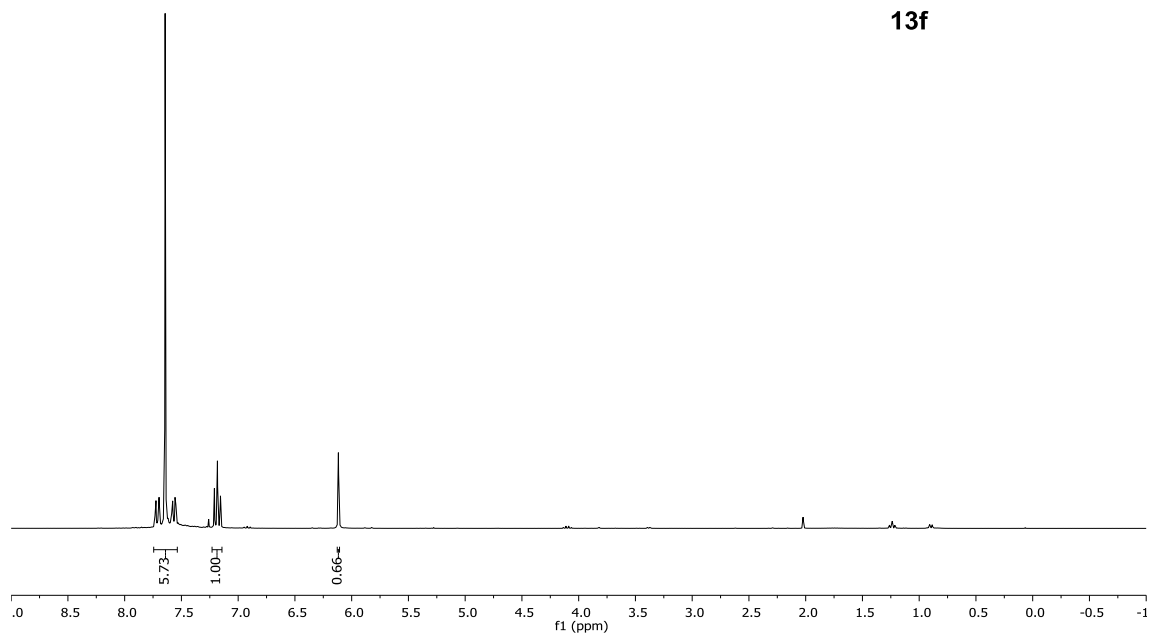
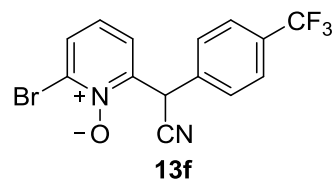


2-((4-Bromophenyl)(cyano)methyl)pyridine *N*-oxide (13d)

Experimental section

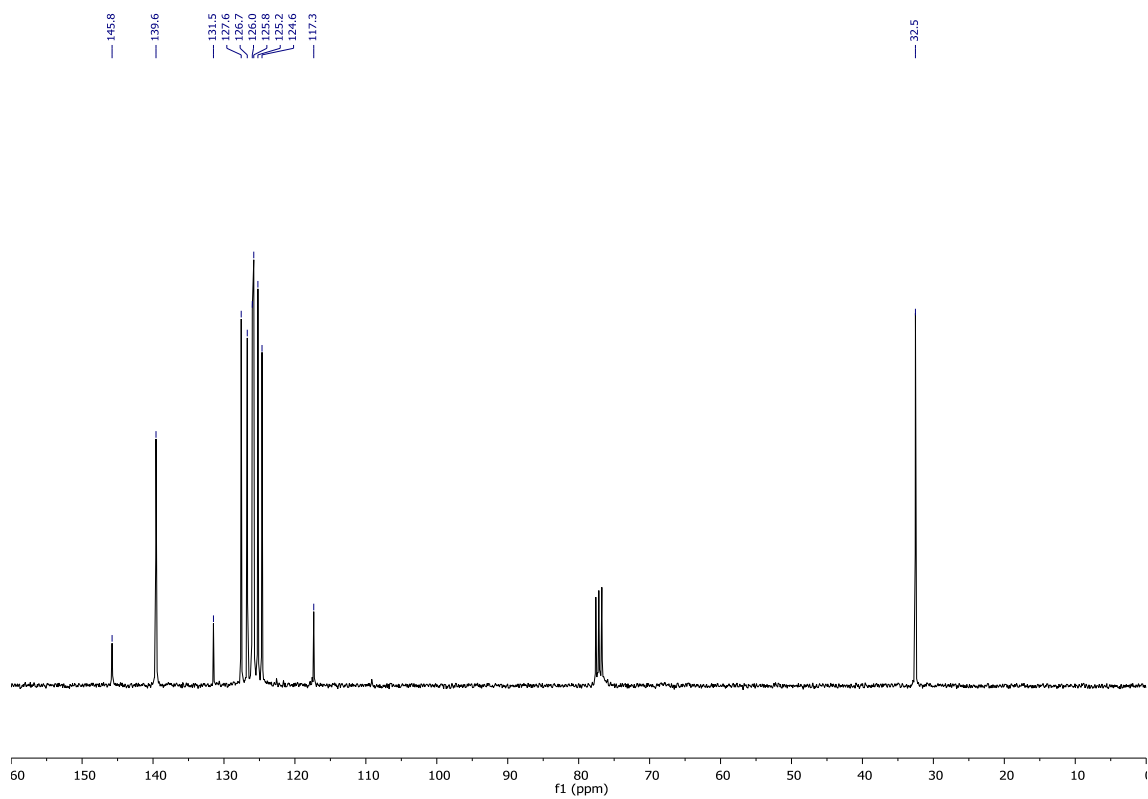
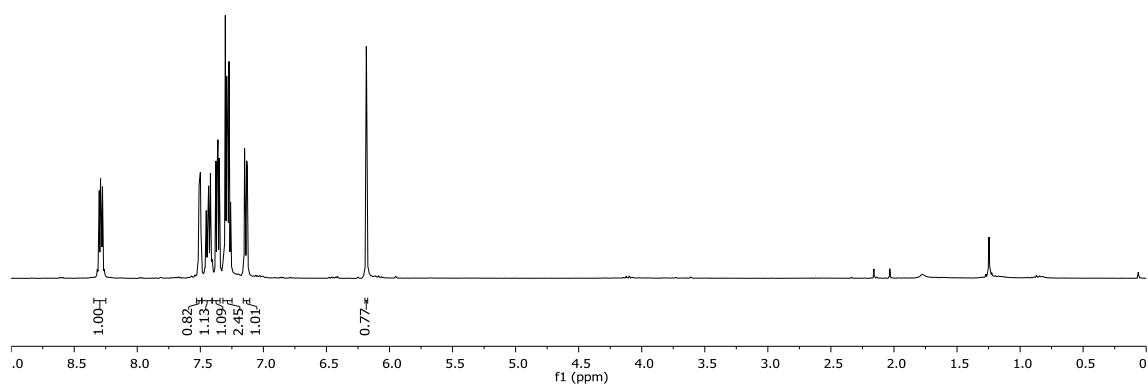
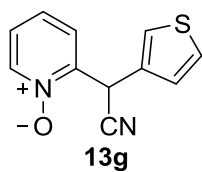
2-(Cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (13e)

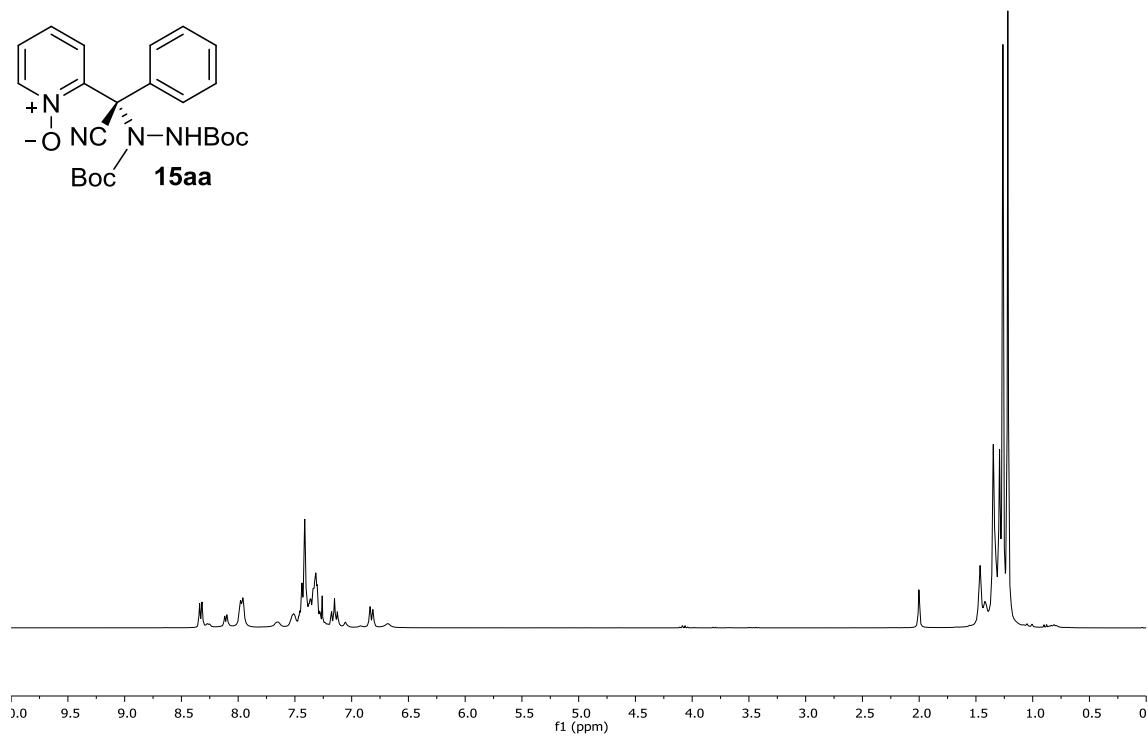
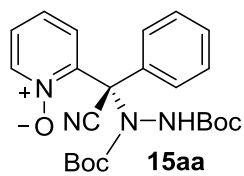
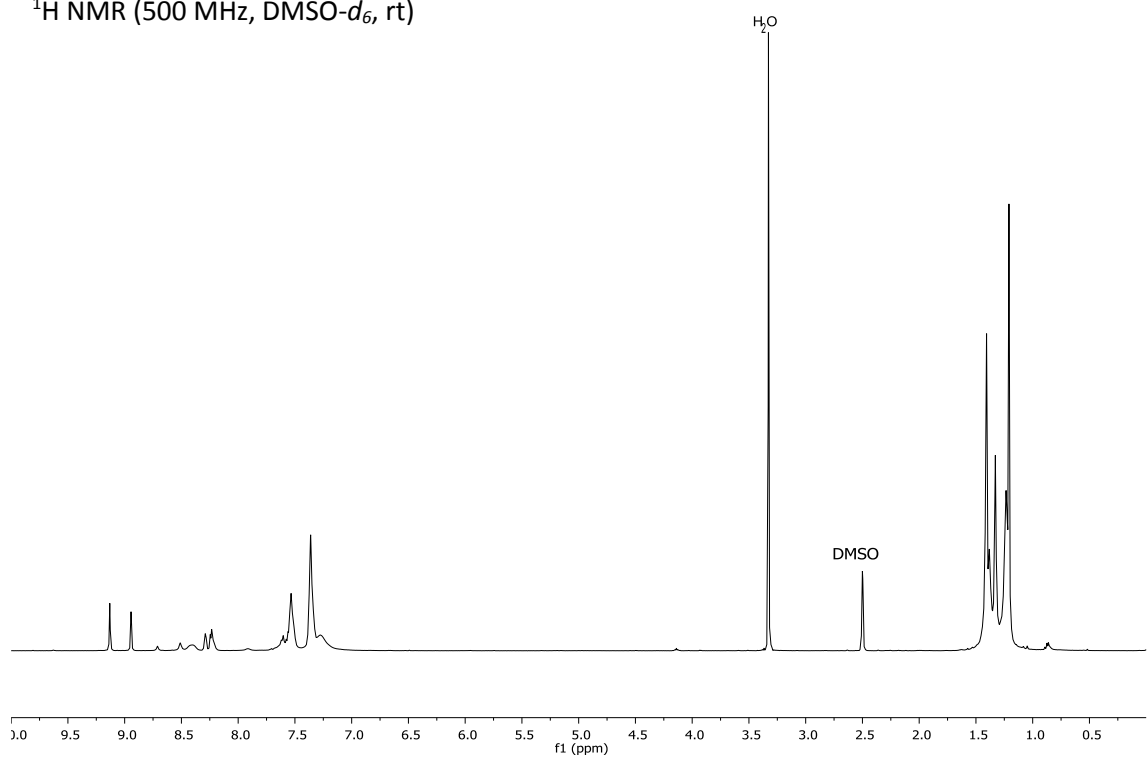


2-Bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine *N*-oxide (13f)

Experimental section

2-(Cyano(thiophen-3-yl)methyl)pyridine 1-oxide (13g)

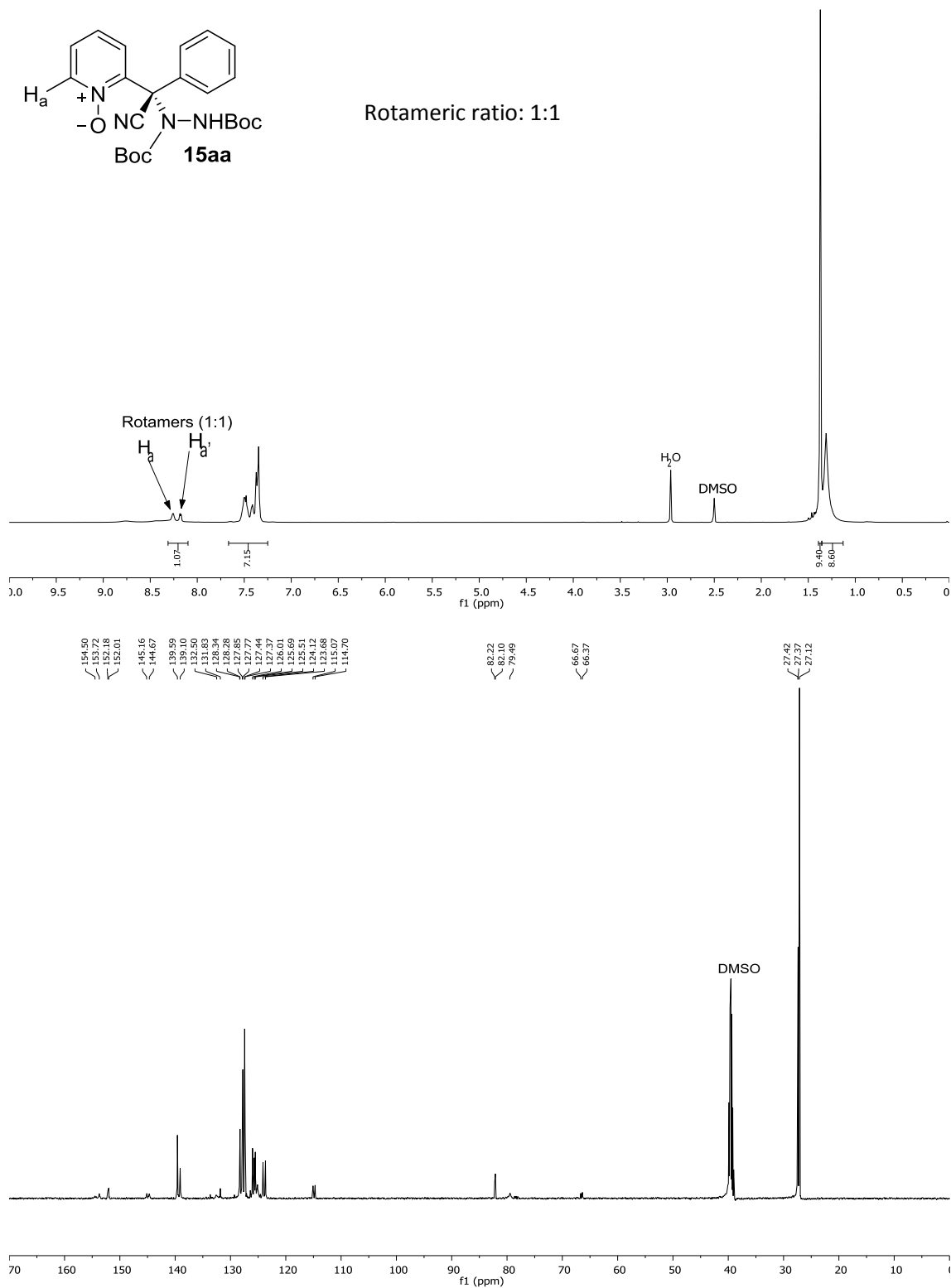


(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(phenyl)methyl)pyridine *N*-oxide (15aa)¹H NMR (300 MHz, CDCl₃, rt)¹H NMR (500 MHz, DMSO-*d*₆, rt)

Experimental section

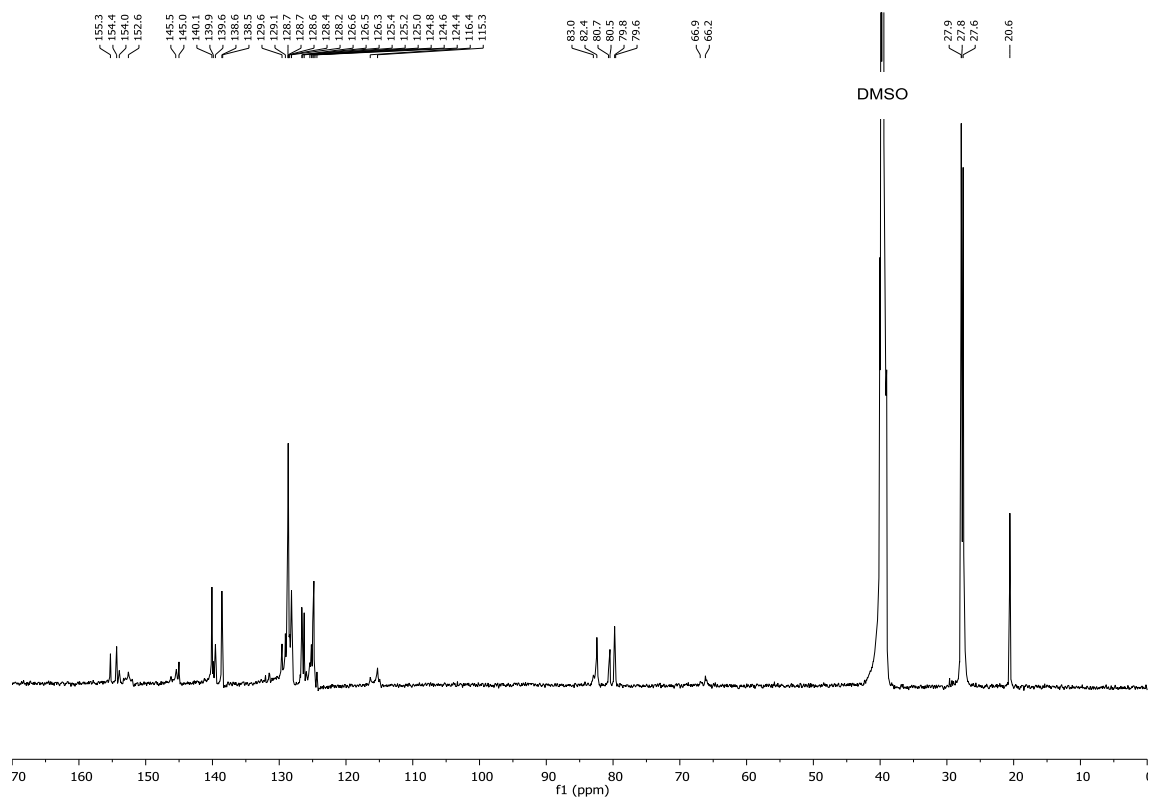
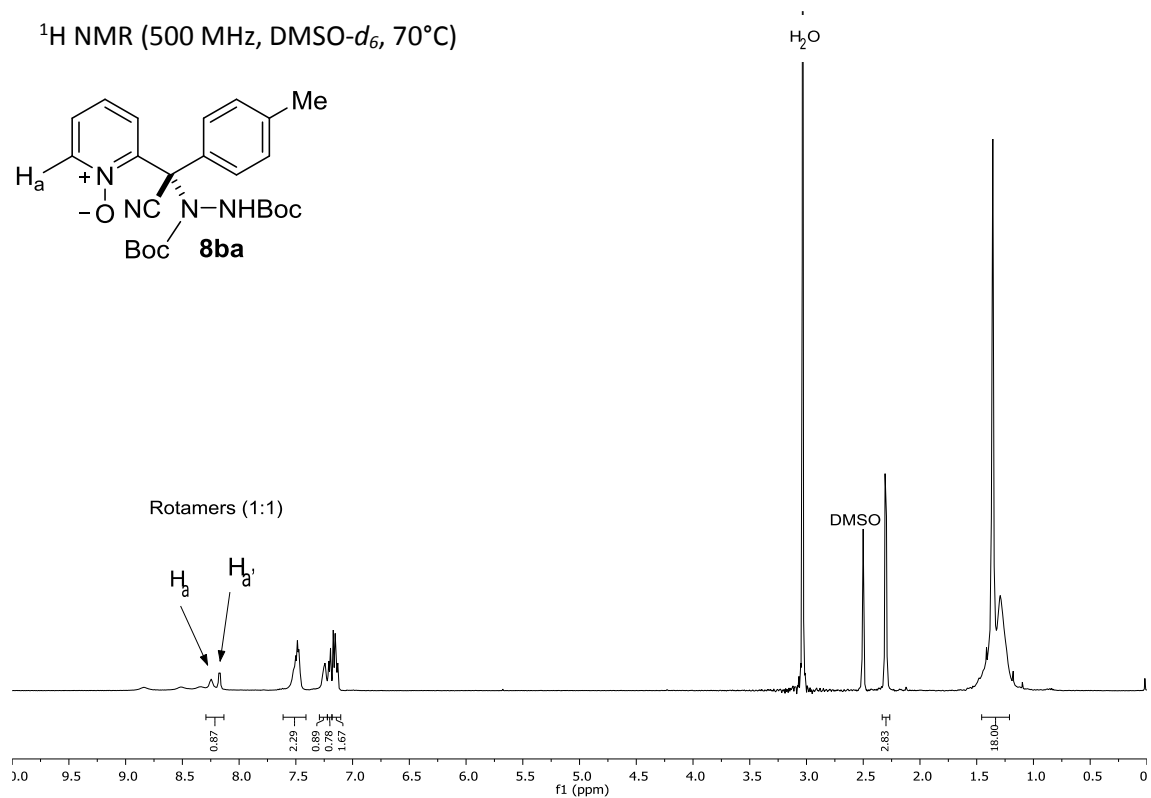
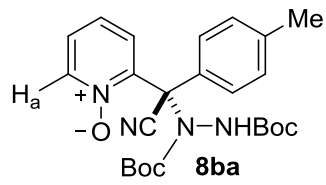
^1H NMR experiments in CDCl_3 (at room temperature and at 55°C) and $\text{DMSO-}d_6$ (at room temperature) showed a mixture of rotamers **15aa**, whose ratio could not be determined. A simpler ^1H NMR was obtained in $\text{DMSO-}d_6$ at 70°C , in which a 1:1 mixture of rotamers was observed.

^1H NMR (500 MHz, $\text{DMSO-}d_6$, 70°C)



(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(*p*-tolyl)methyl)pyridine N-oxide (15ba)

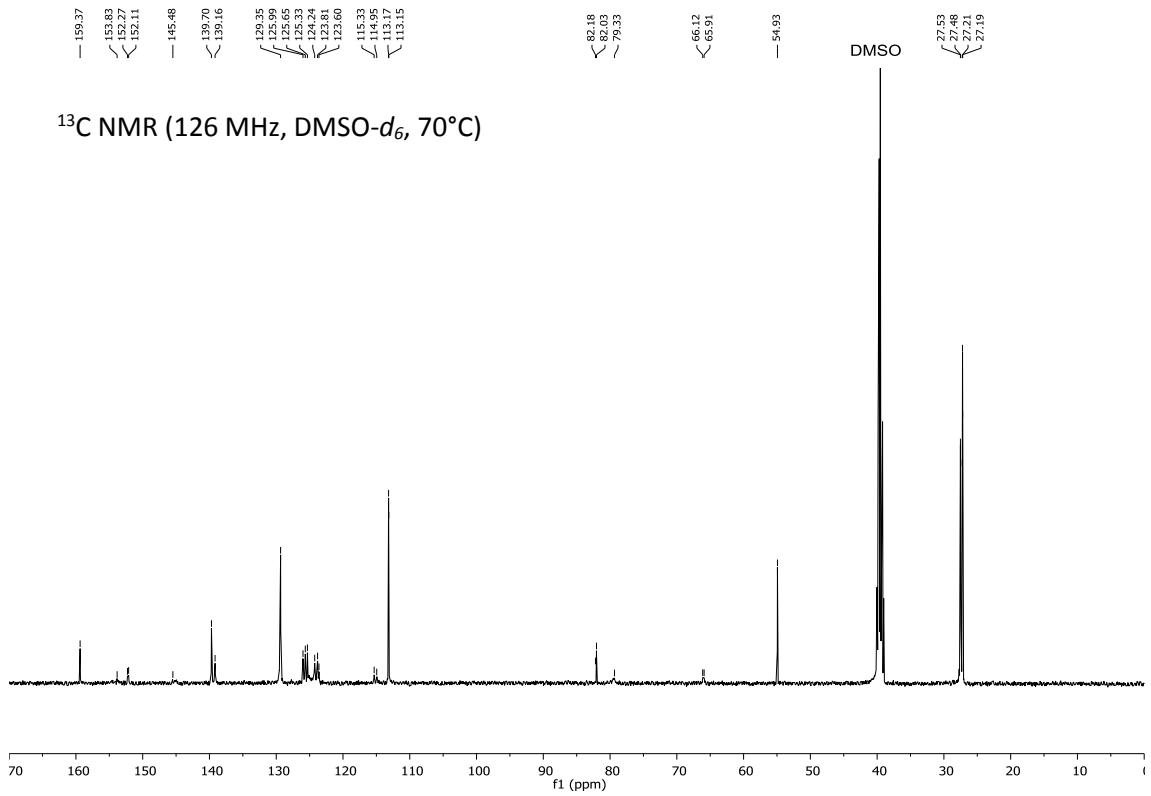
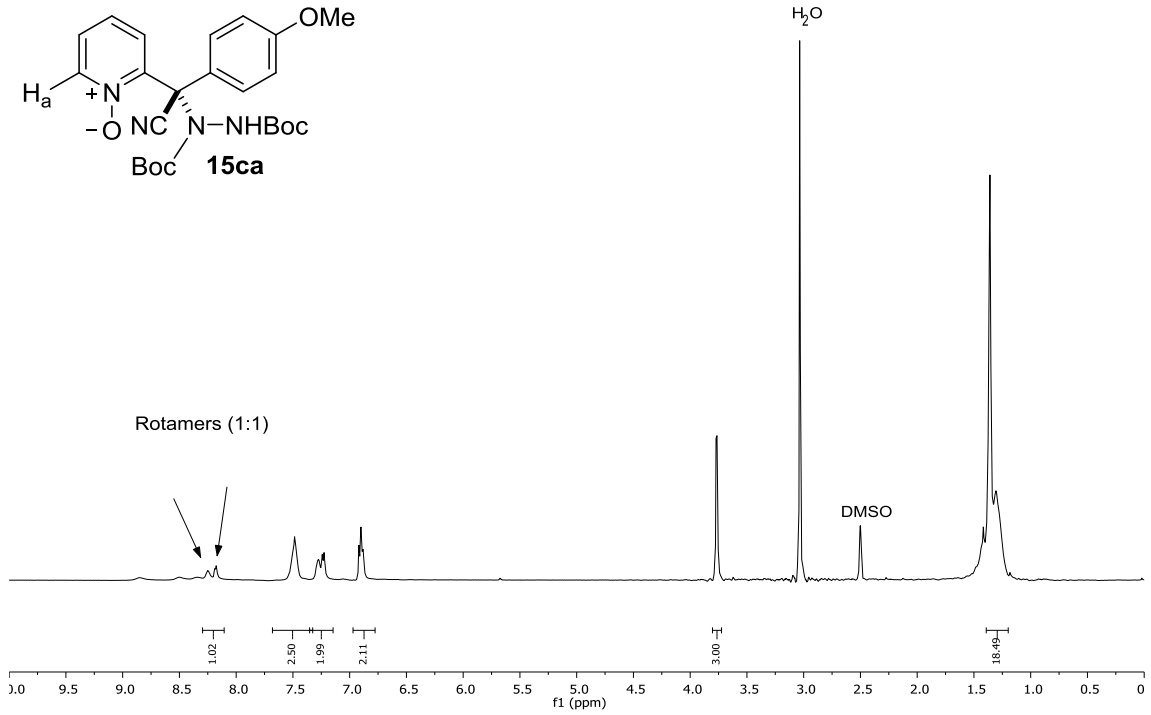
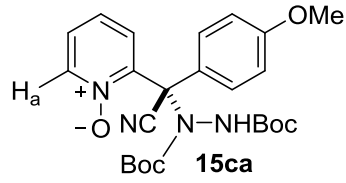
^1H NMR (500 MHz, $\text{DMSO-}d_6$, 70°C)



Experimental section

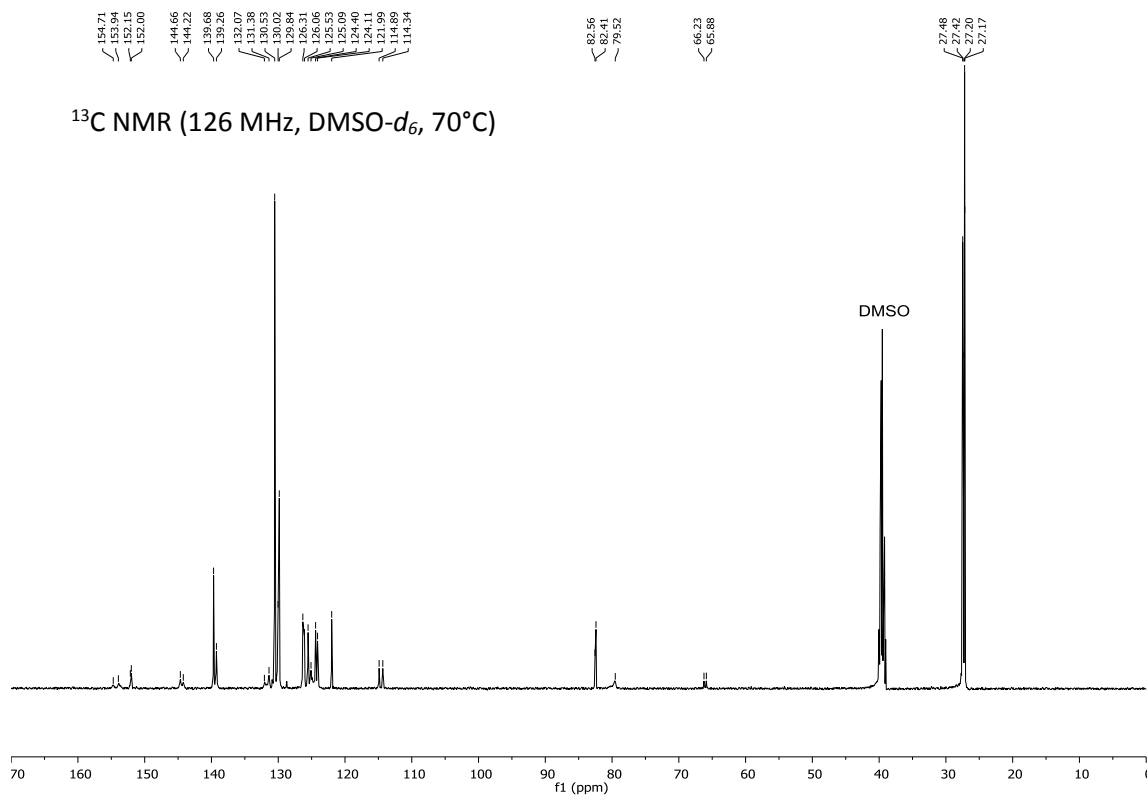
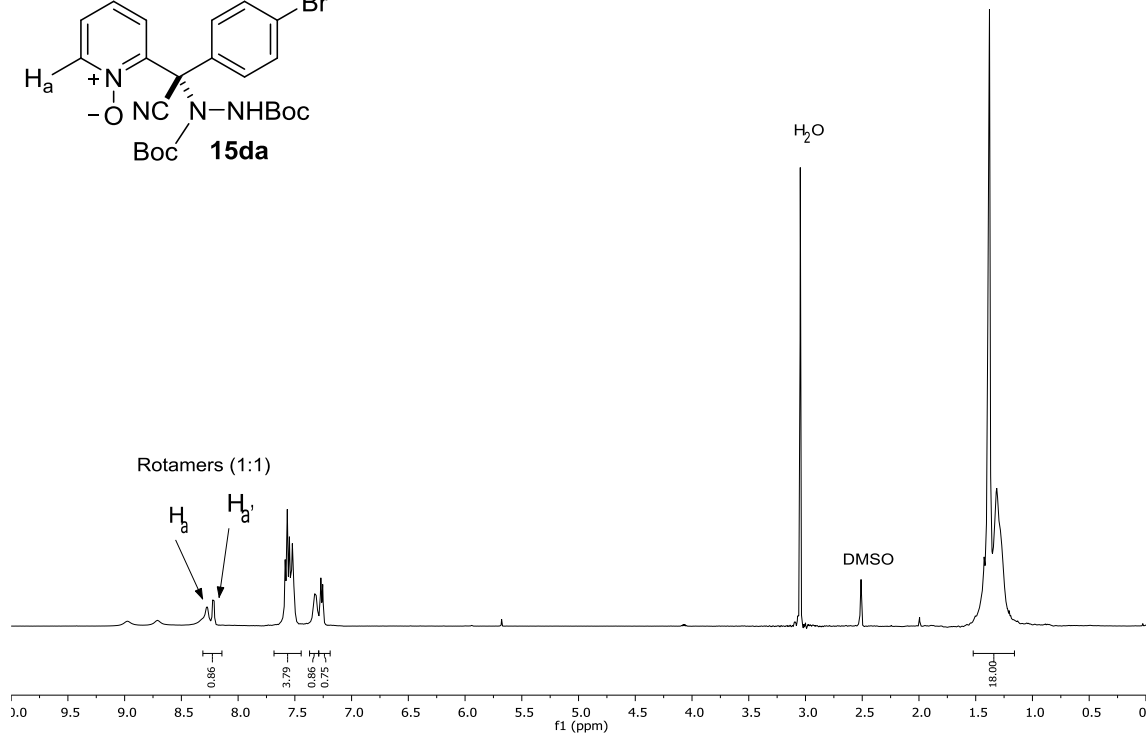
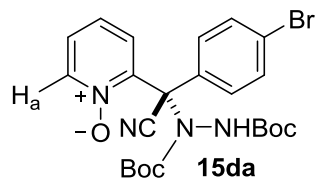
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-methoxyphenyl)methyl)pyridine *N*-oxide (15ca)

¹H NMR (500 MHz, DMSO-*d*₆, 70°C)



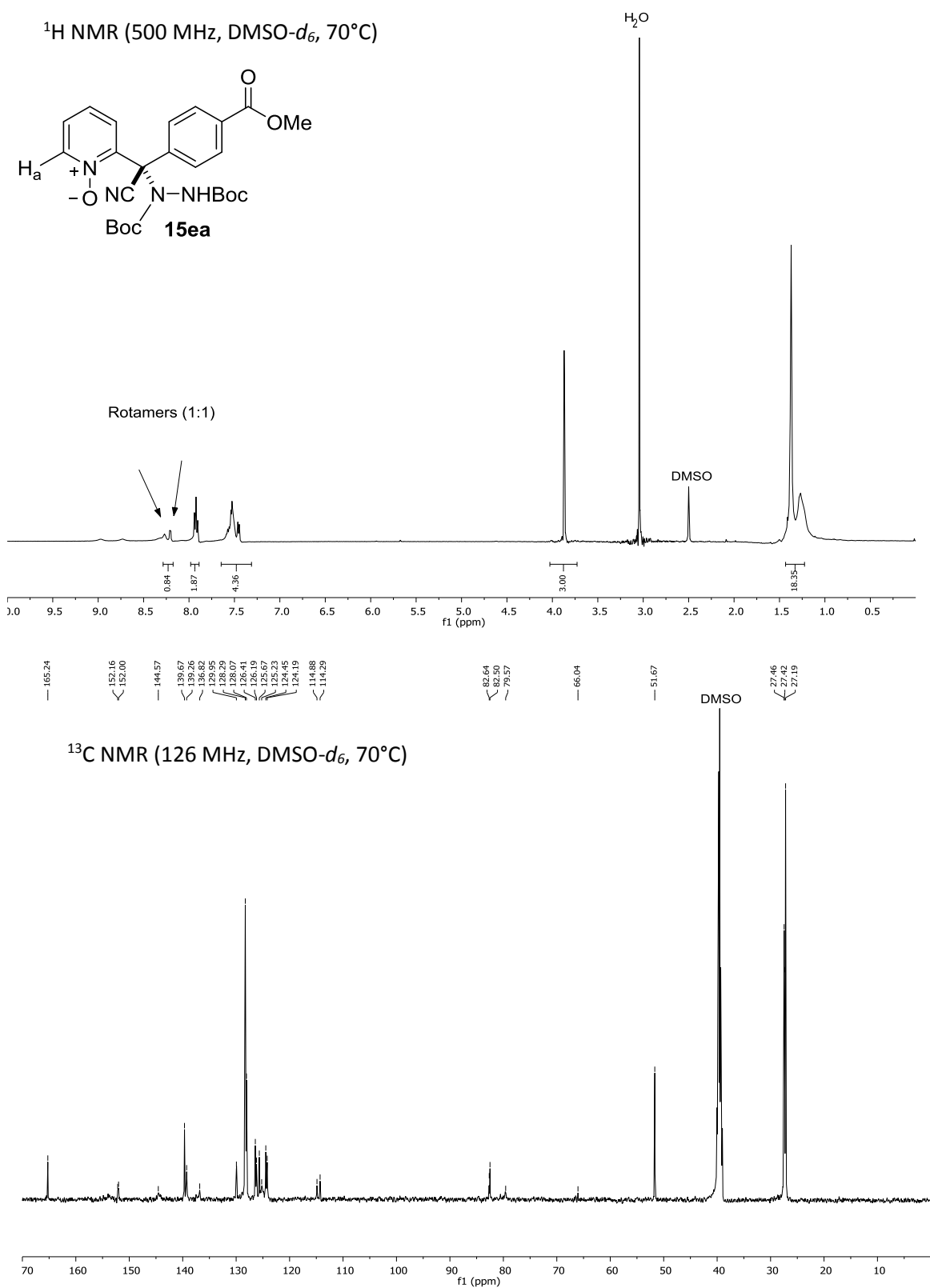
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine 1-oxide (15da)

^1H NMR (500 MHz, $\text{DMSO-}d_6$, 70°C)

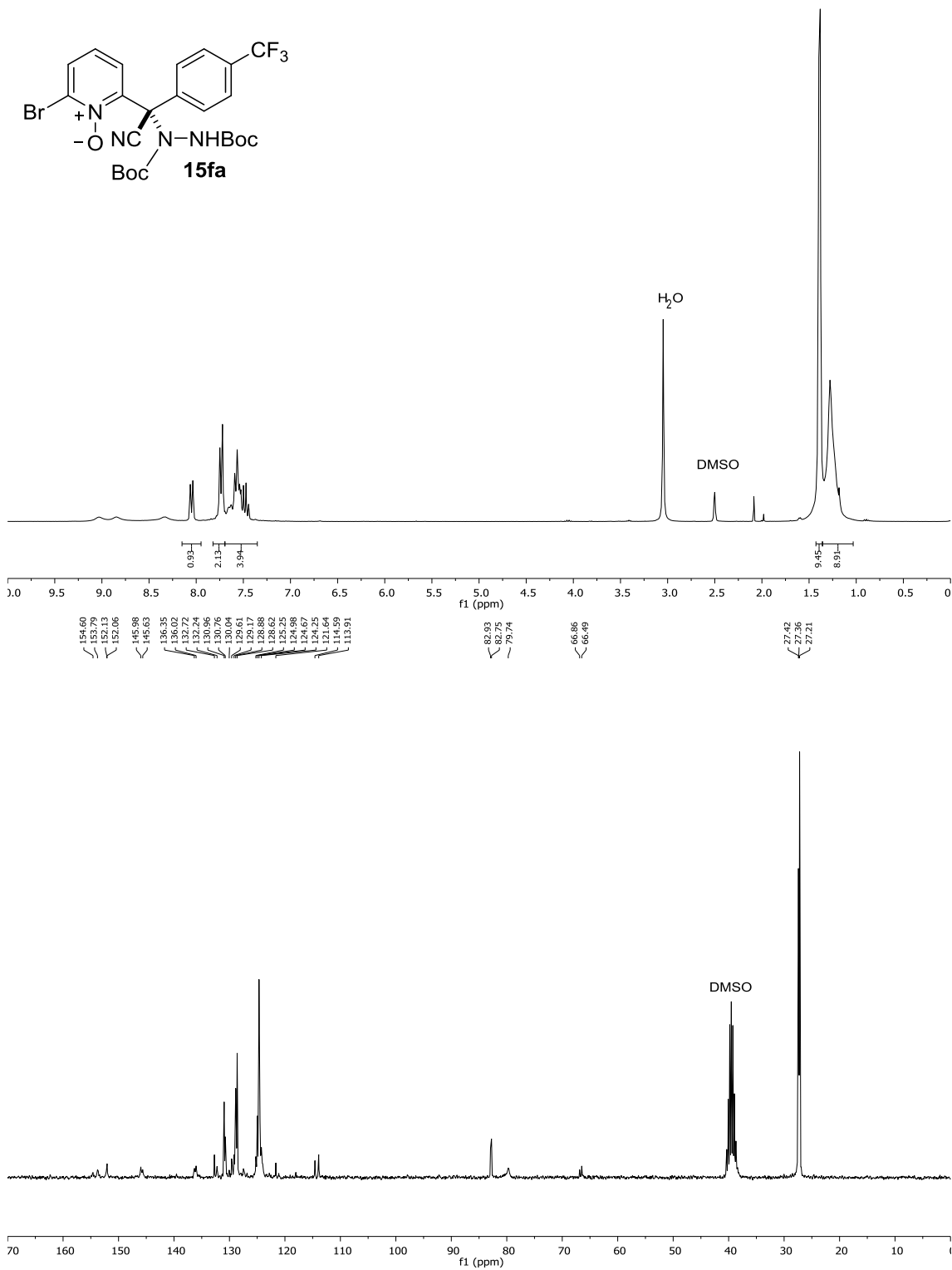


Experimental section

(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15ea)

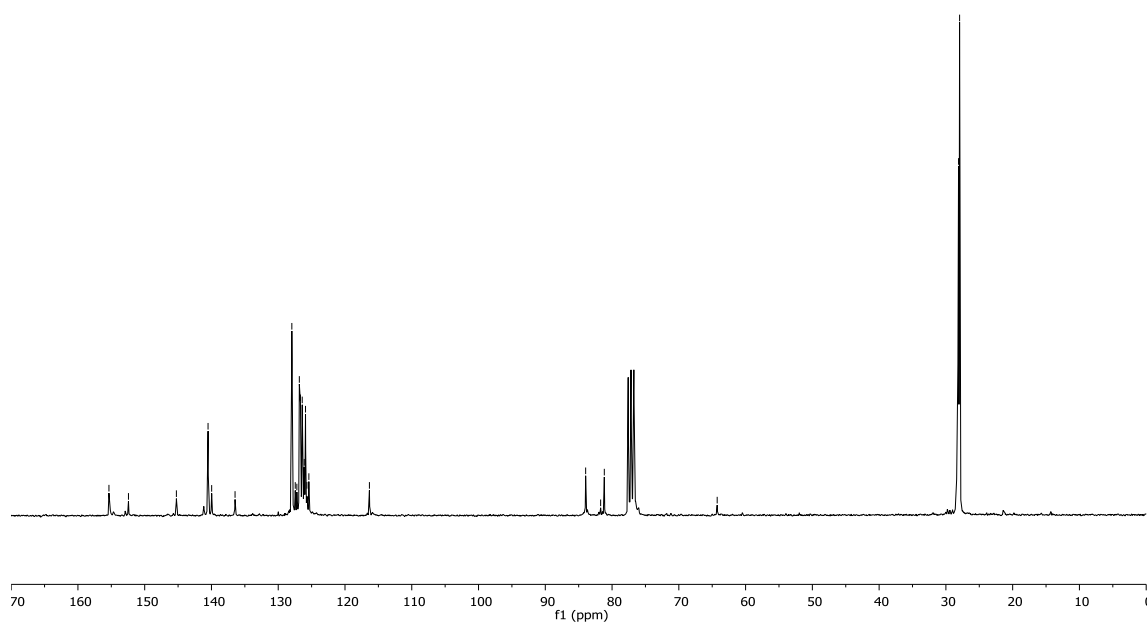
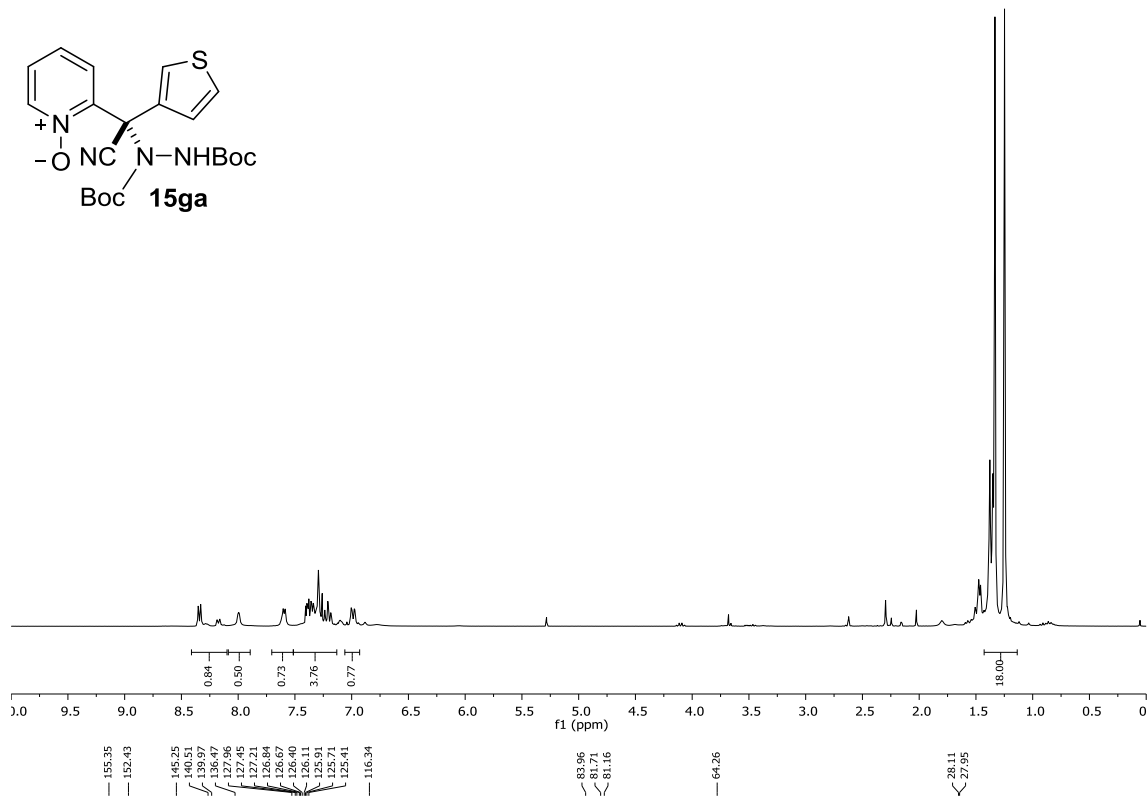
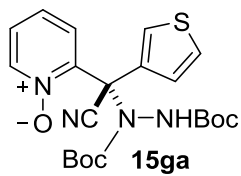


(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(trifluoromethyl)phenyl)methyl)-6-bromopyridine *N*-oxide (15fa)

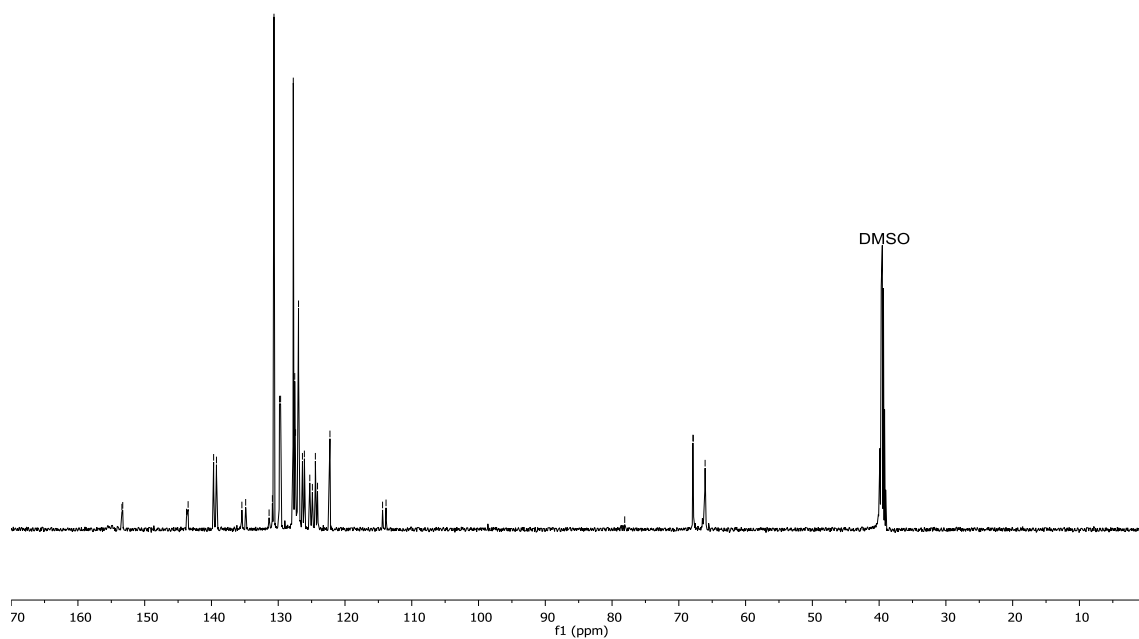
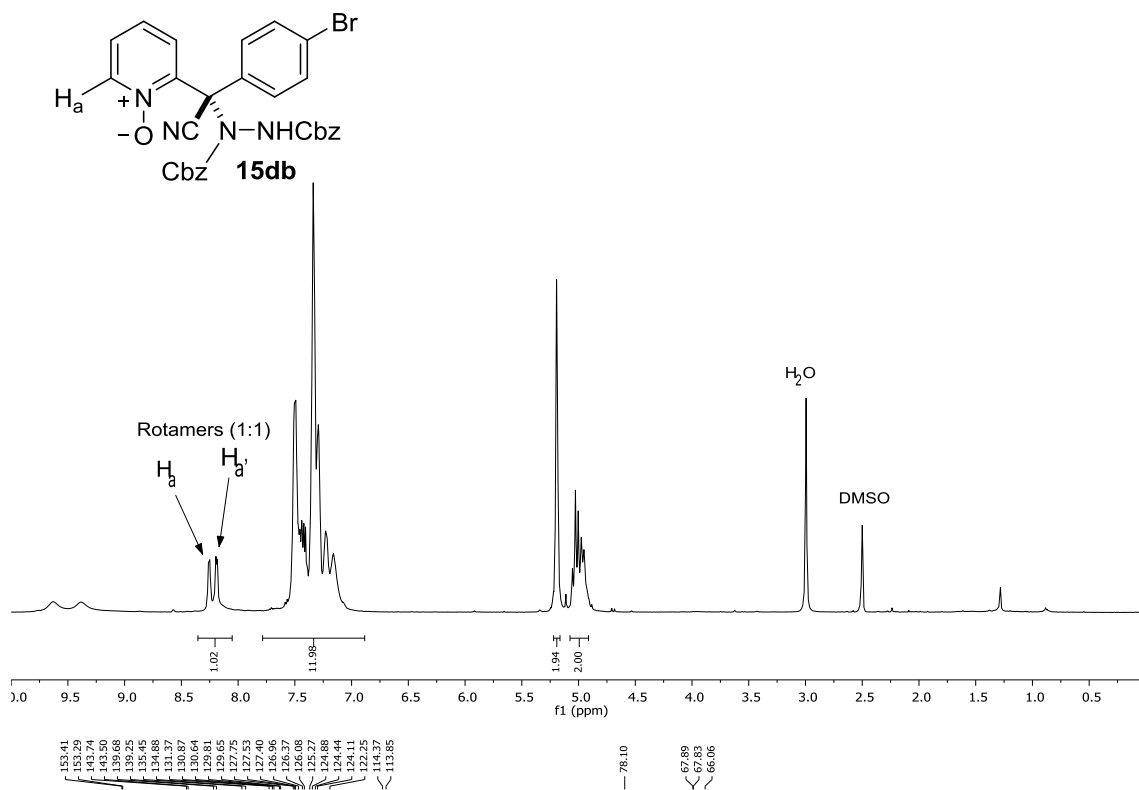


Experimental section

**(S)-2-((1,2-bis(tert-butoxycarbonyl)hydrazinyl)(cyano)(thiophen-3-yl)methyl)pyridine
N-oxide (15ga)**

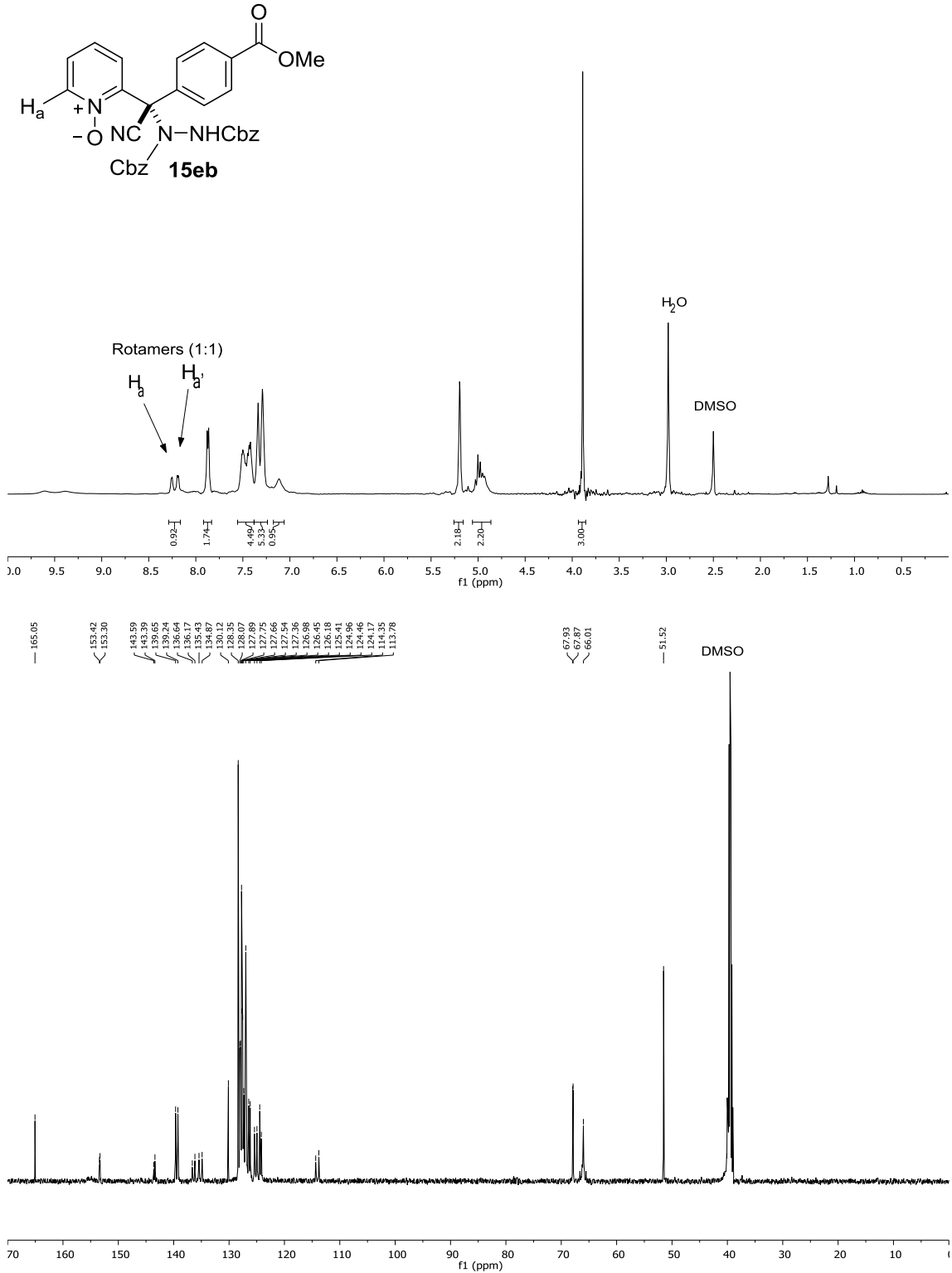


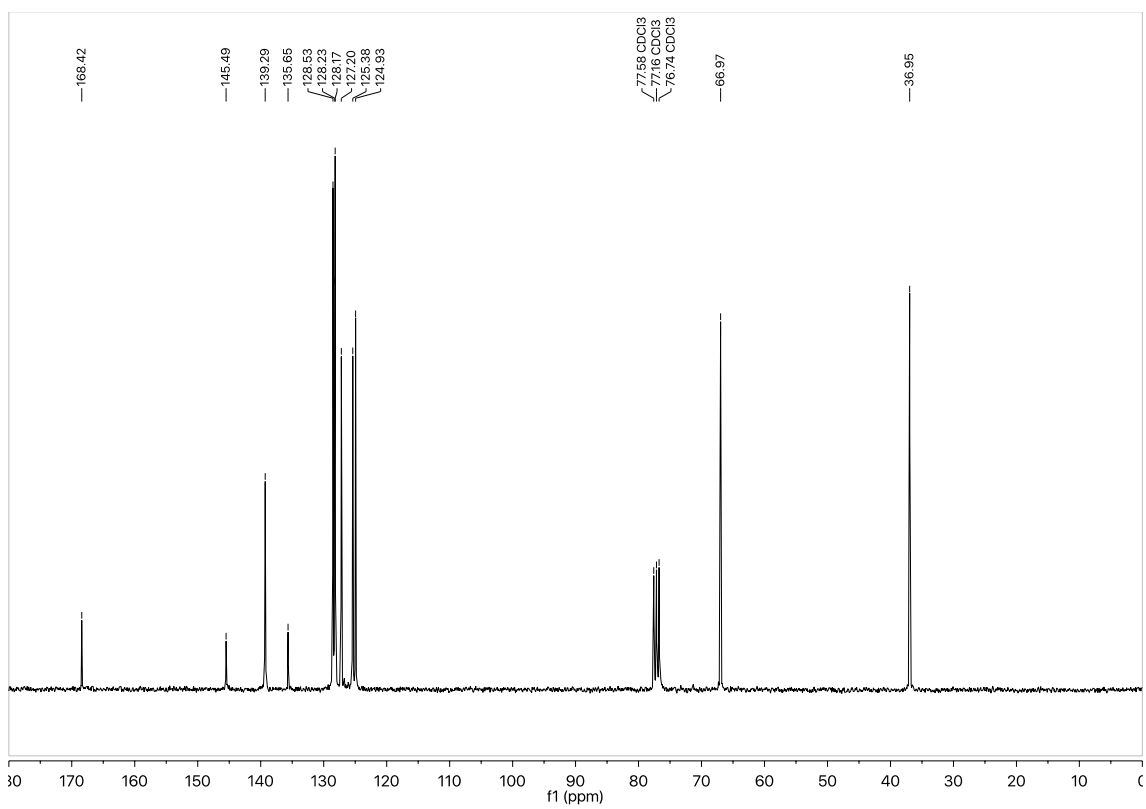
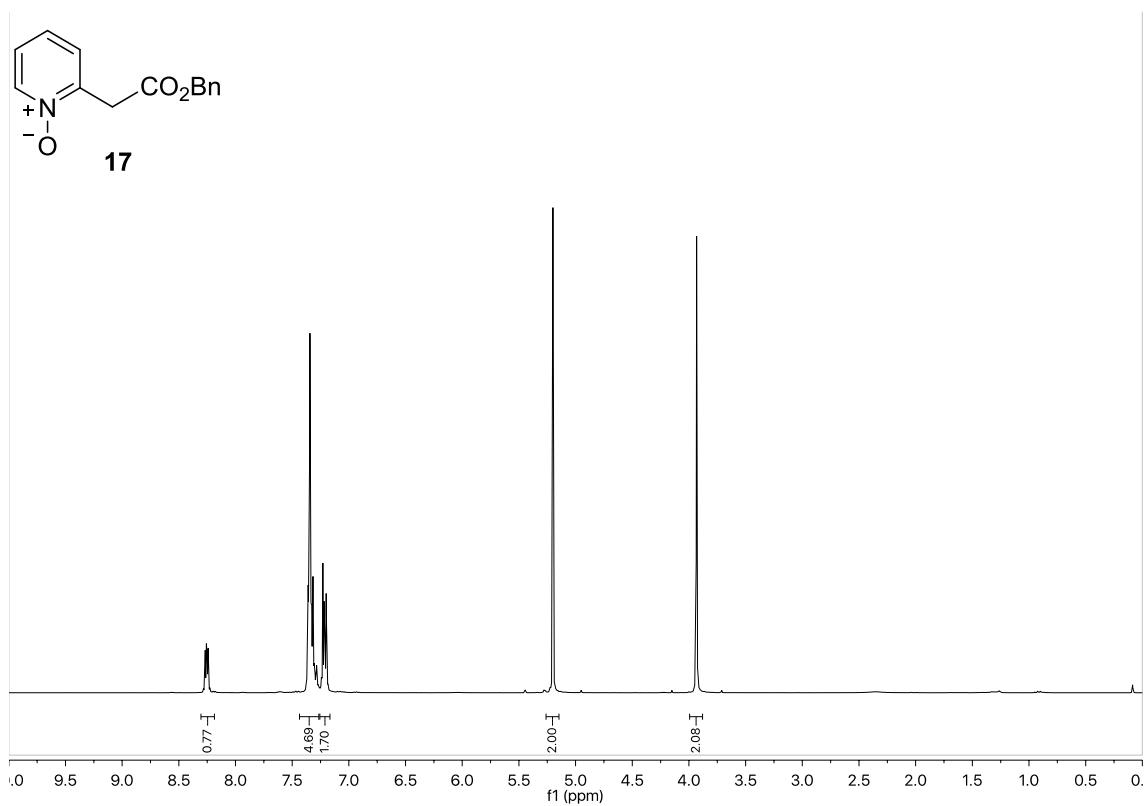
(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine N-oxide (15db)



Experimental section

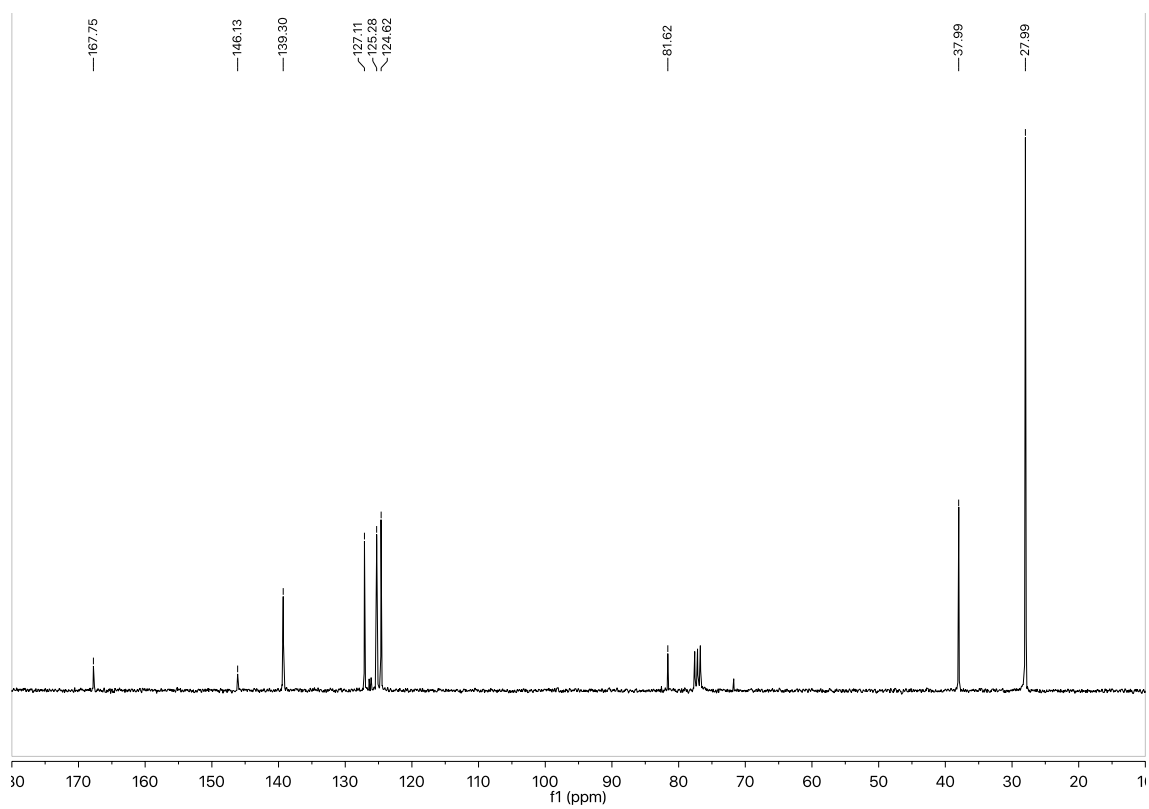
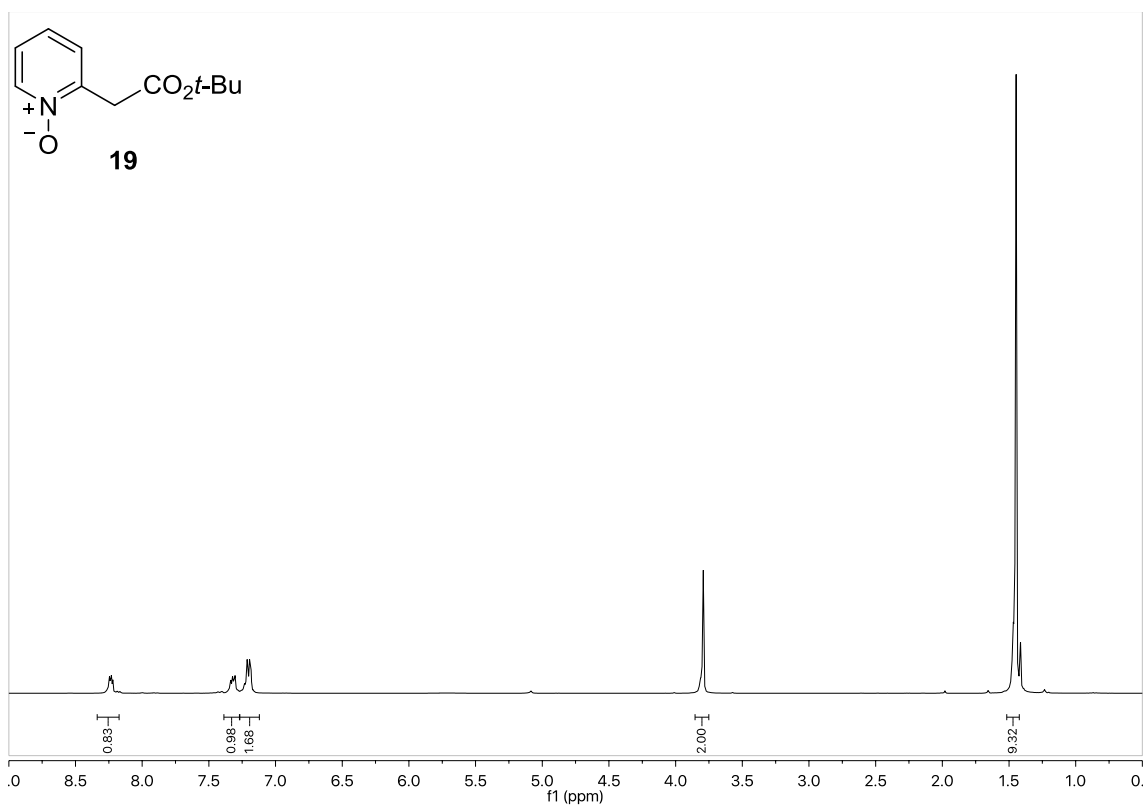
(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine N-oxide (15eb)

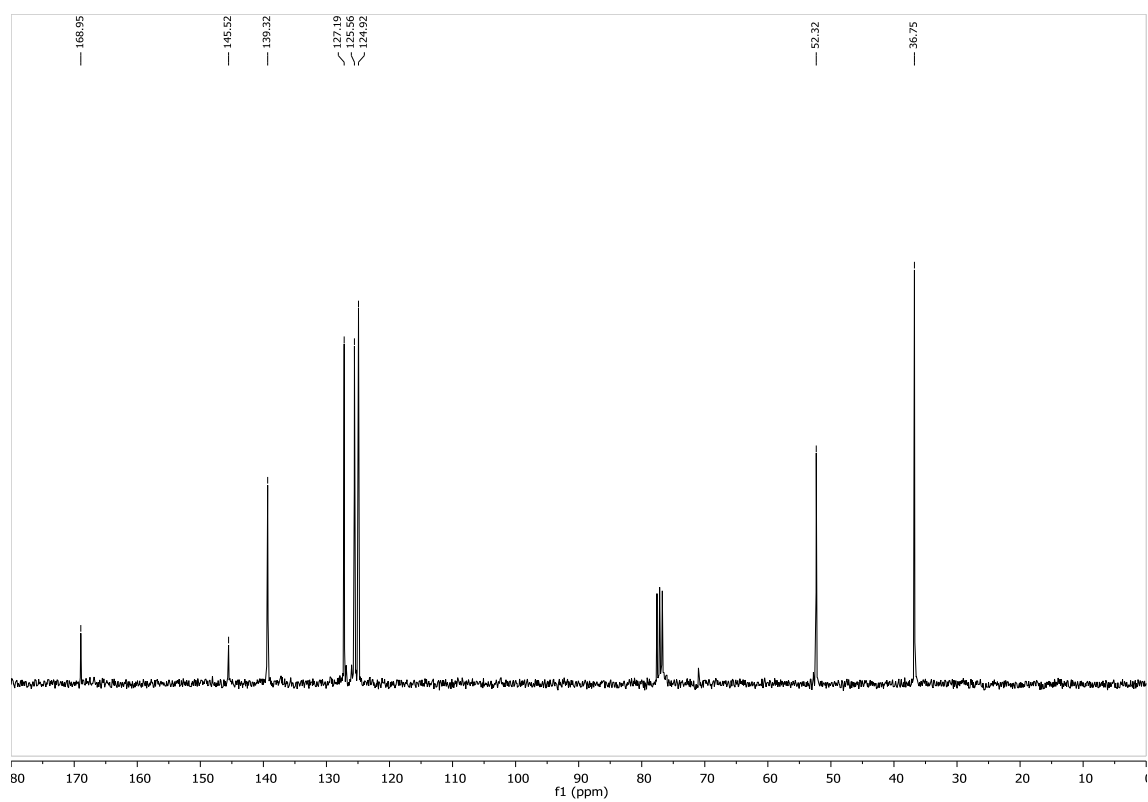
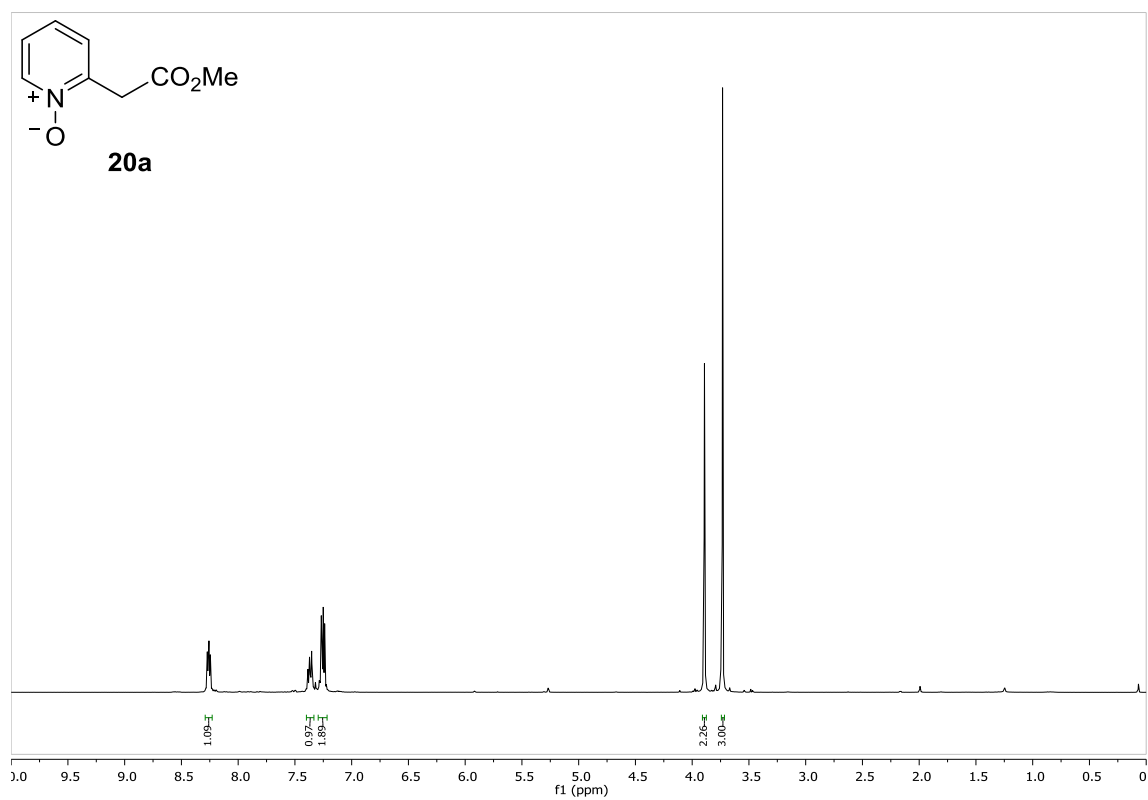


2-(2-(Benzyloxy)-2-oxoethyl)pyridine *N*-oxide (17)

Experimental section

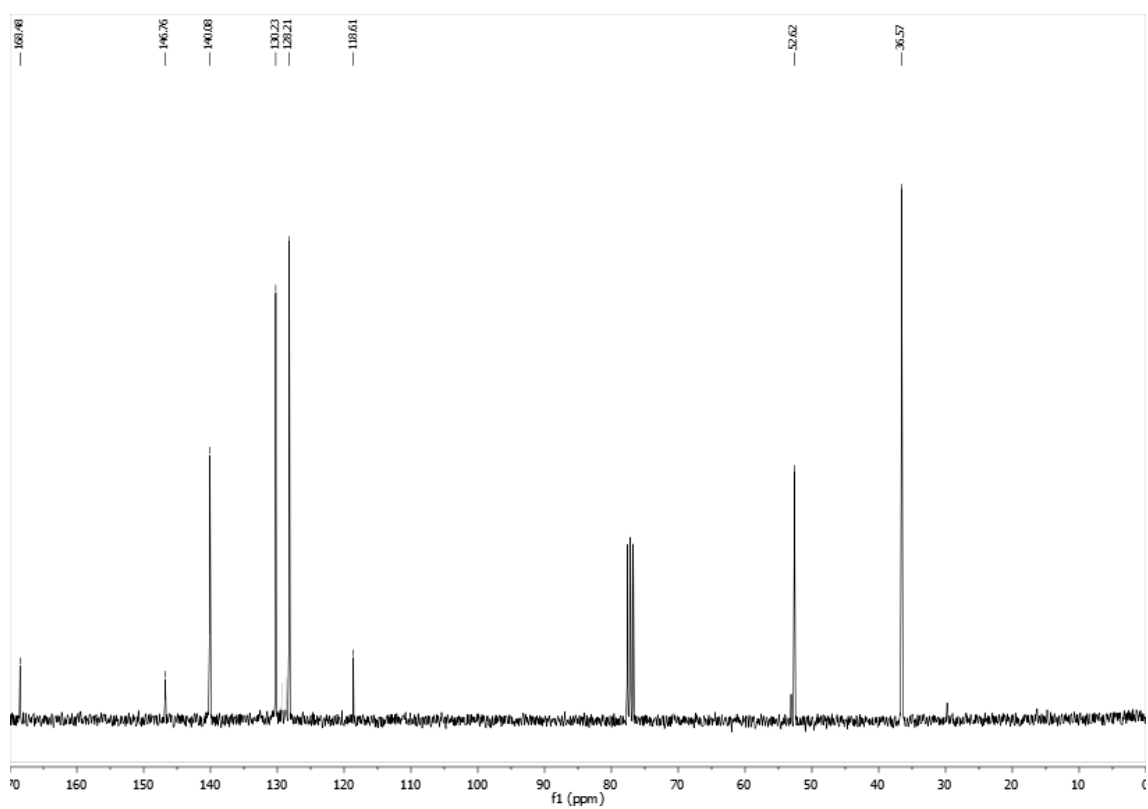
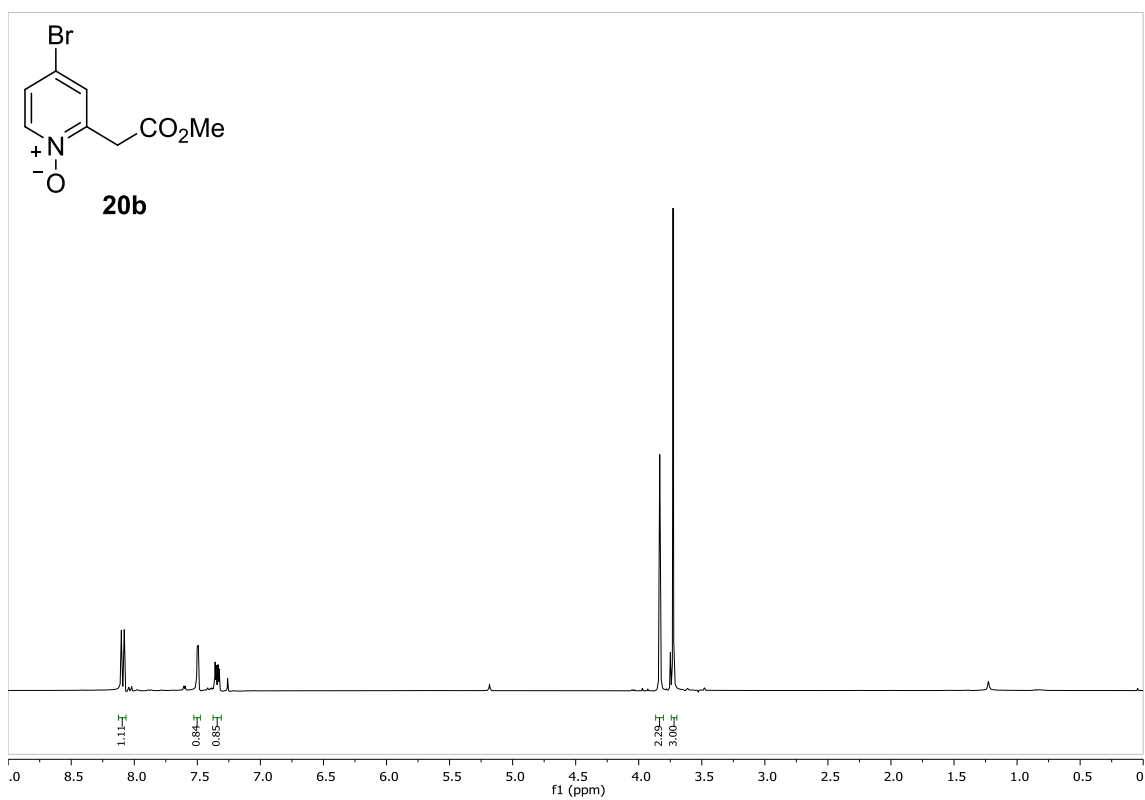
2-(2-(*tert*-Butoxy)-2-oxoethyl)pyridine *N*-oxide (19)

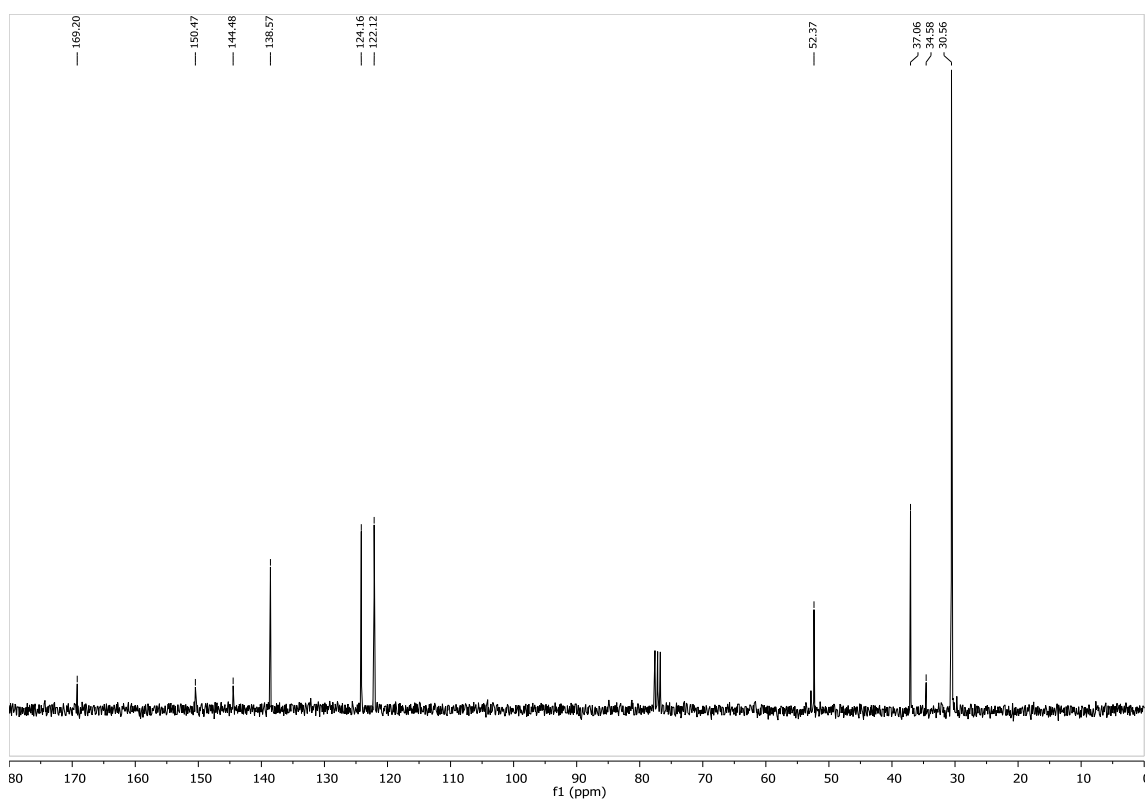
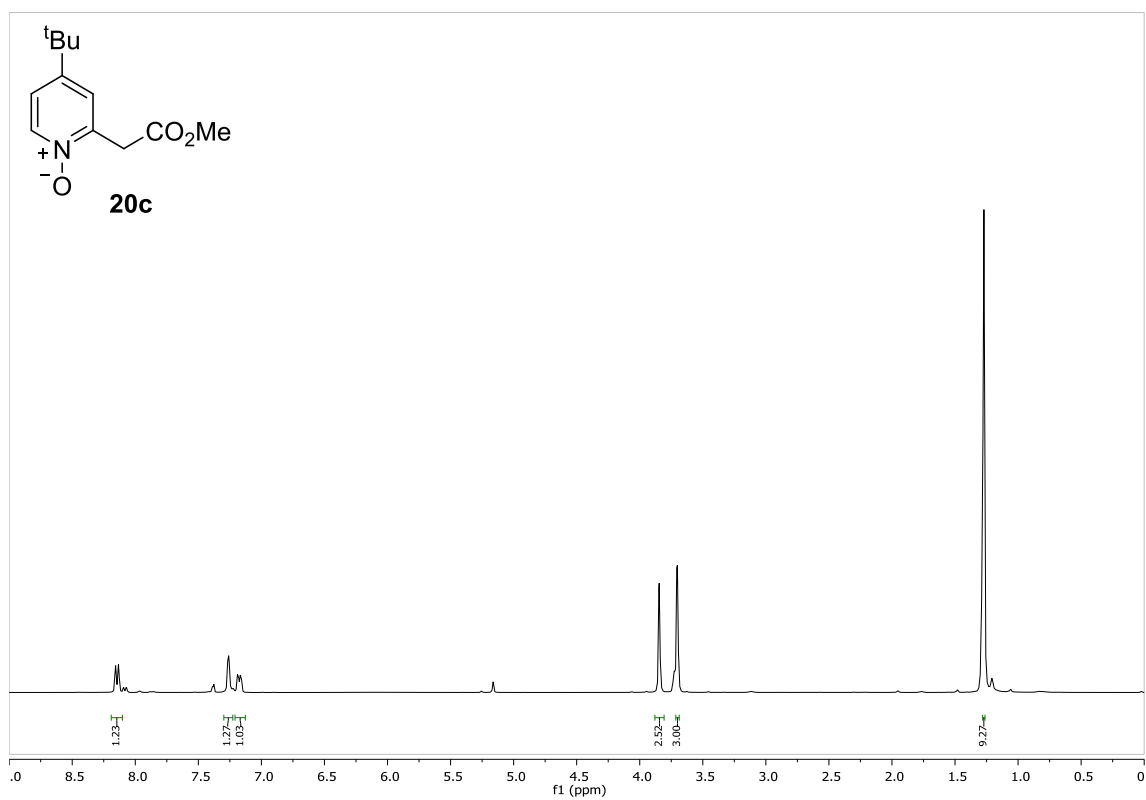


2-(2-Methoxy-2-oxoethyl)pyridine *N*-oxide (20a)

Experimental section

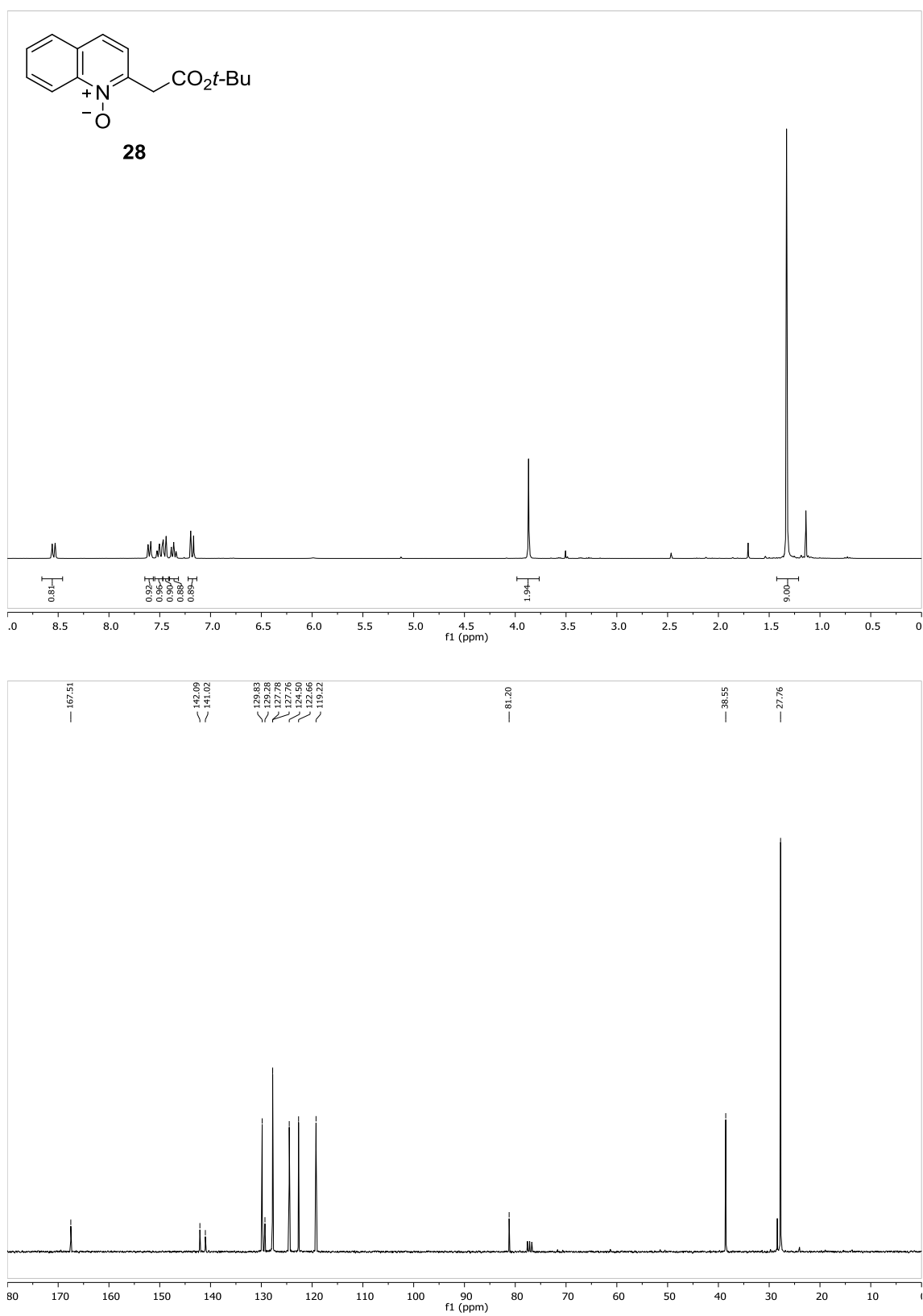
4-Bromo-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20b)

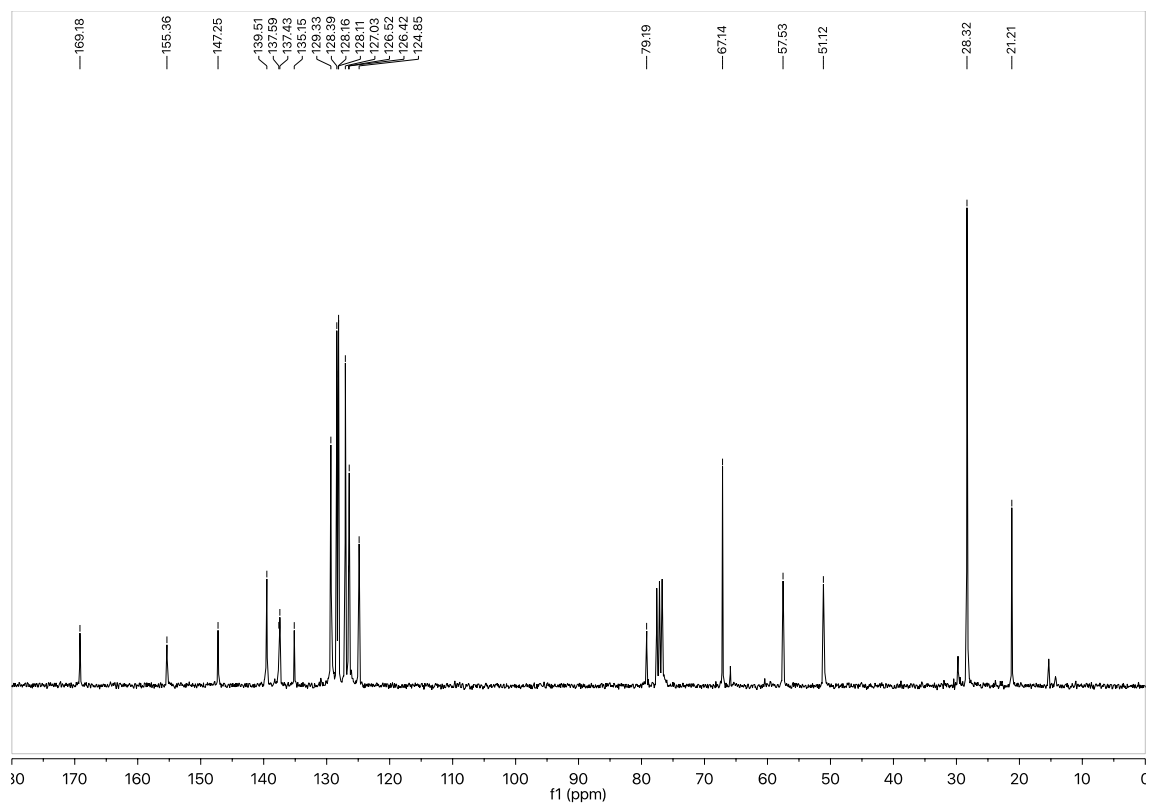
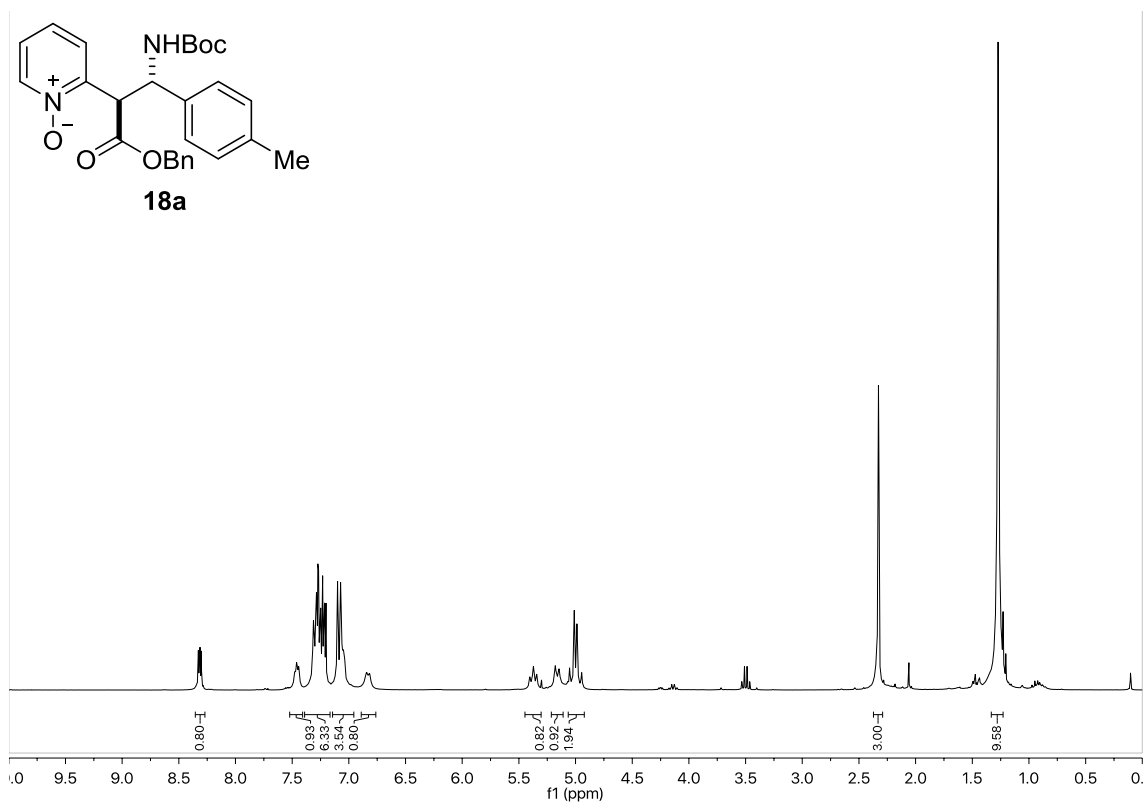


4-(*tert*-Butyl)-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20c)

Experimental section

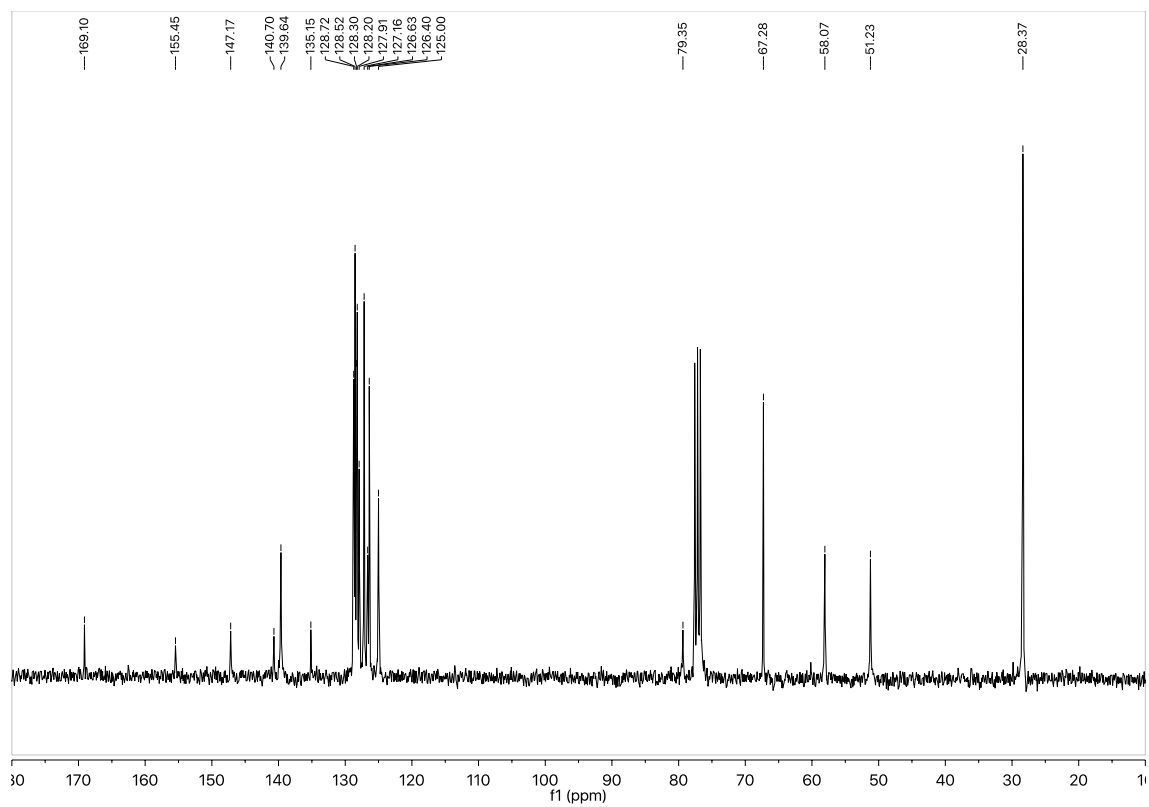
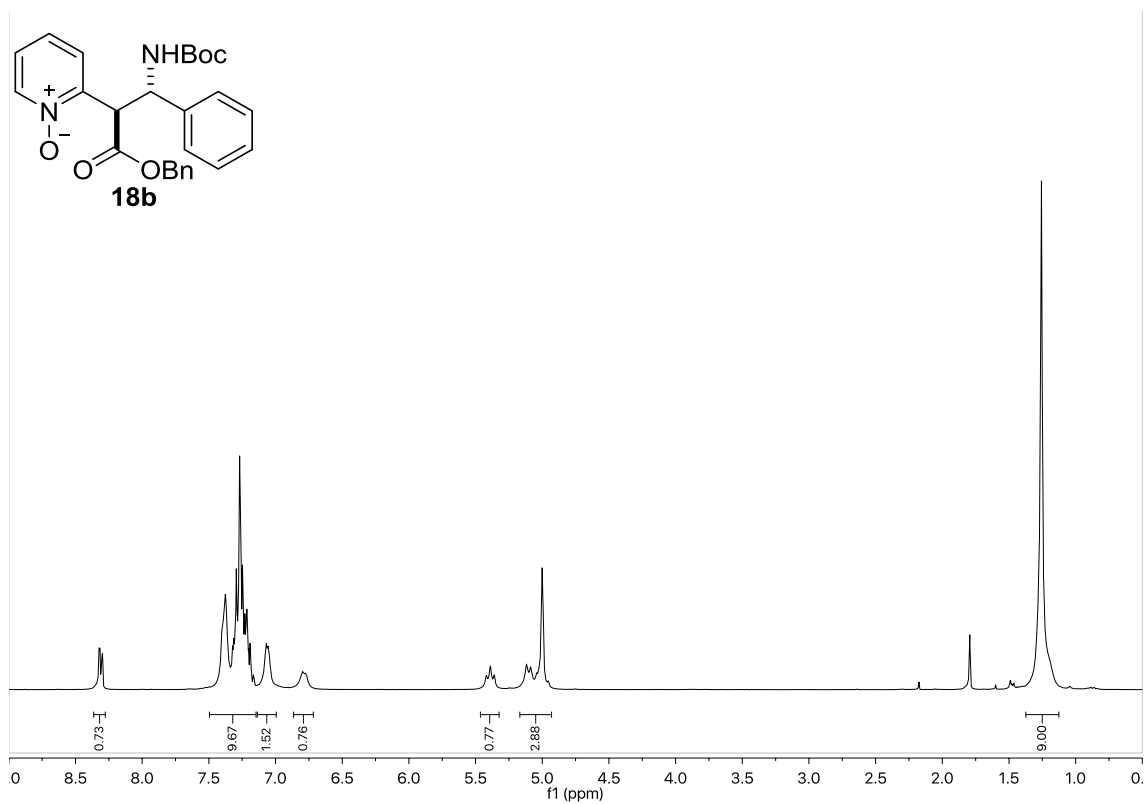
2-(2-(*tert*-Butoxy)-2-oxoethyl)quinoline *N*-oxide (28)

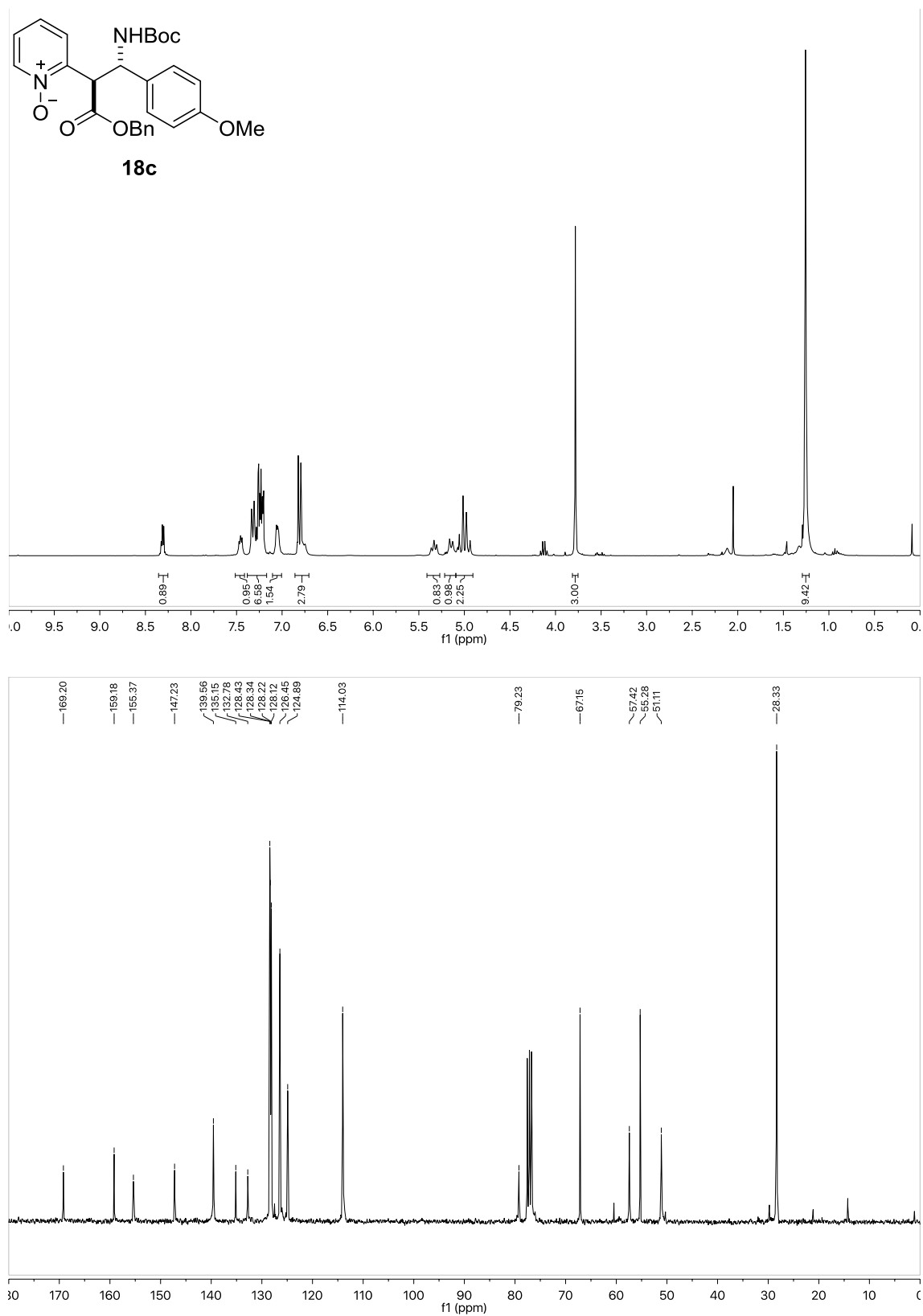


2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-oxo-3-phenoxy-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (18a)

Experimental section

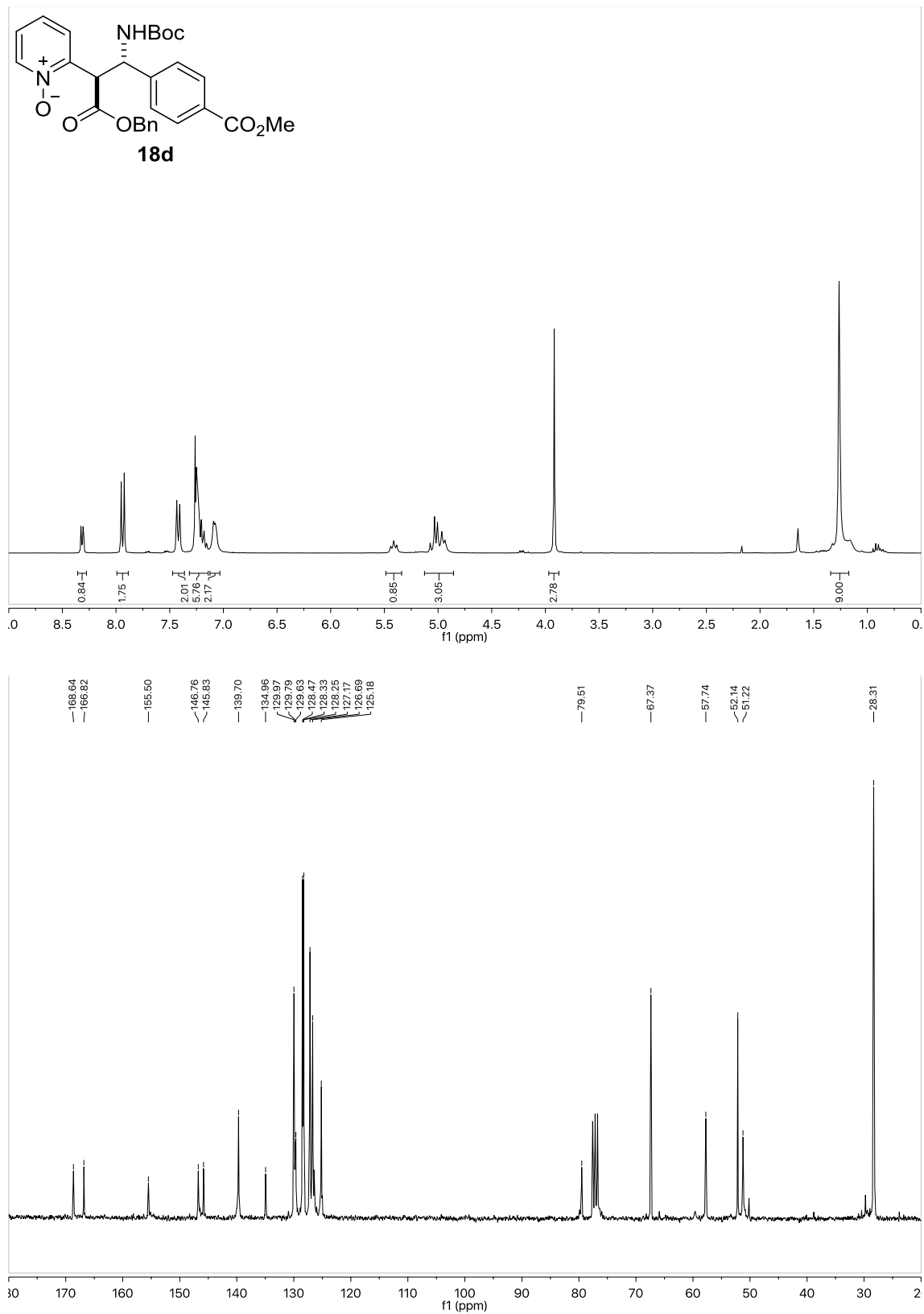
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)pyridine *N*-oxide (18b)

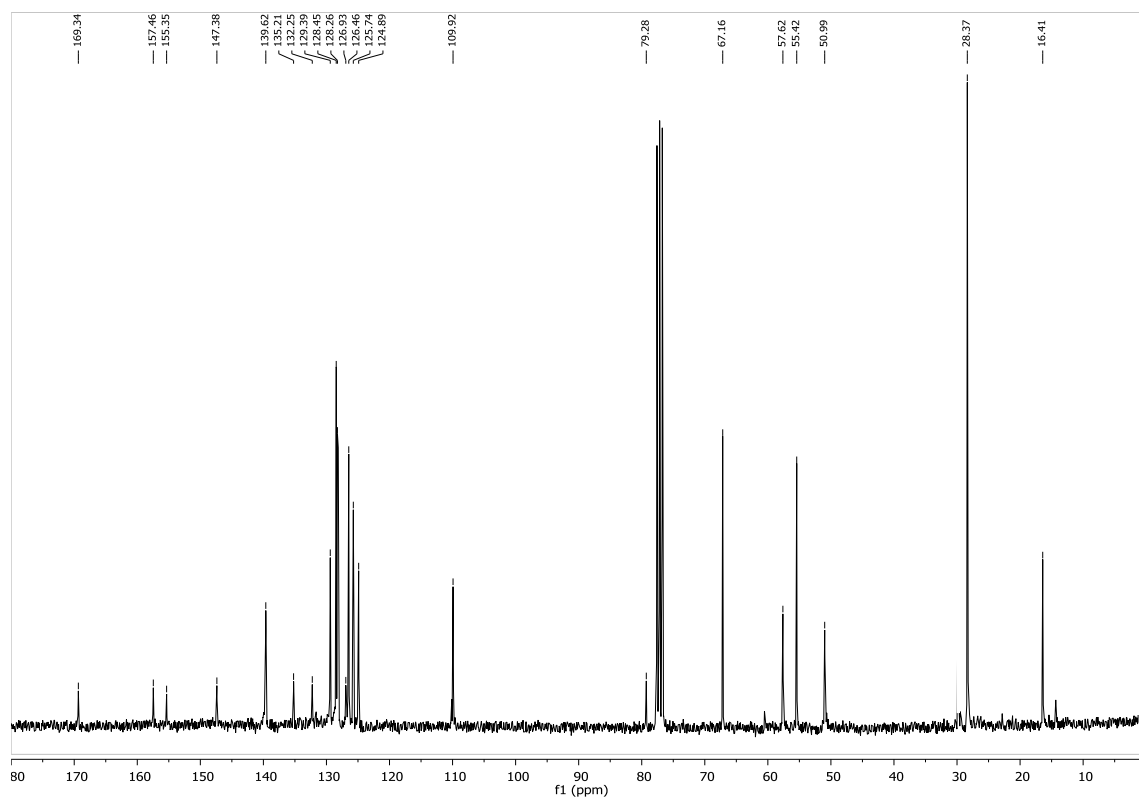
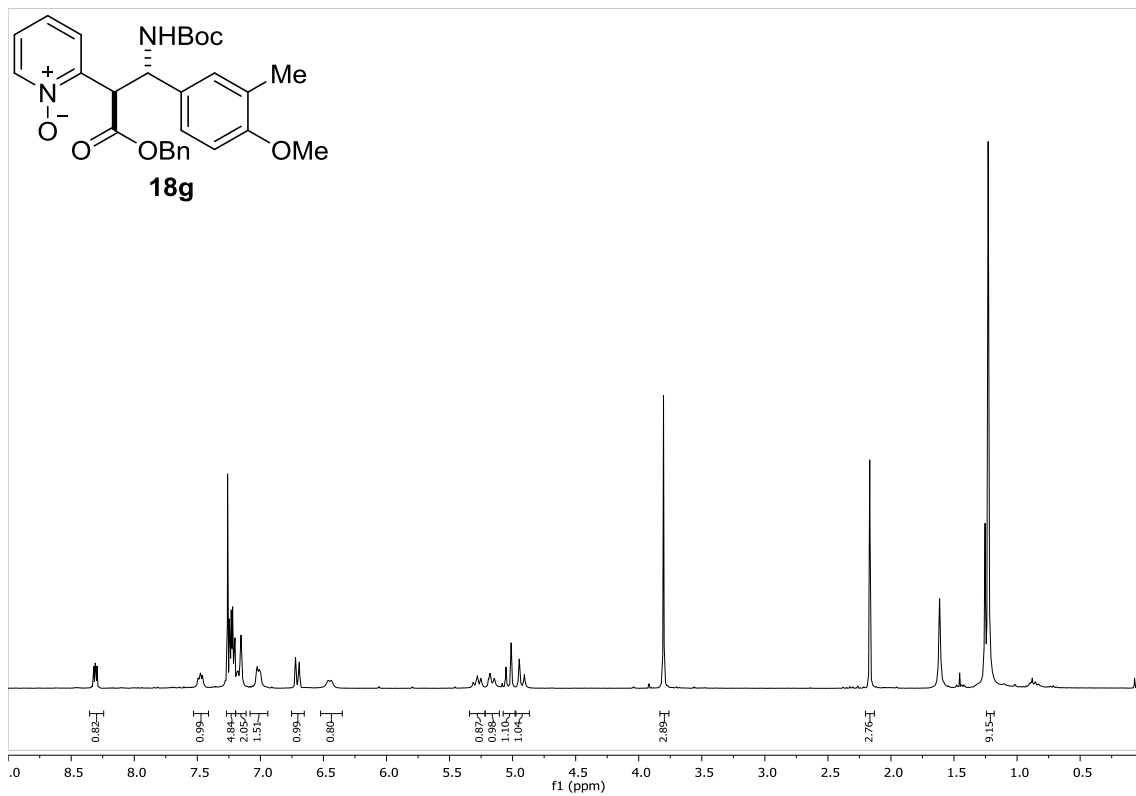


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18c)

Experimental section

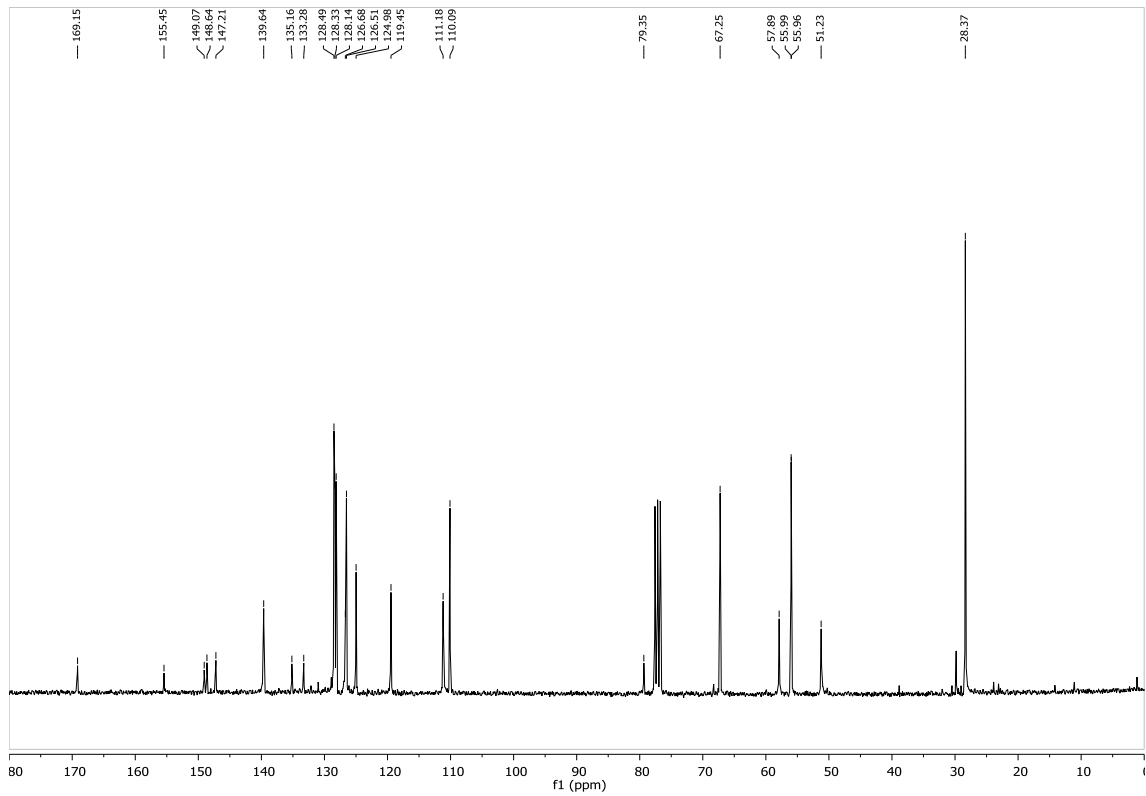
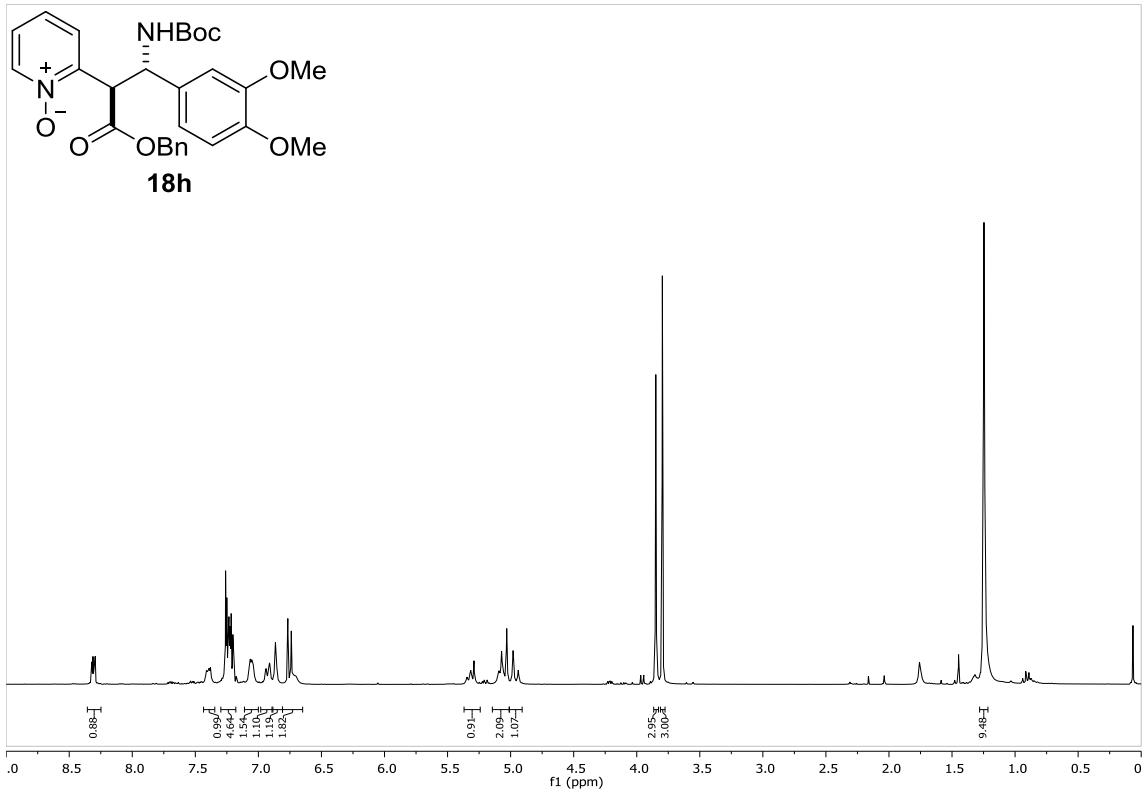
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18d)



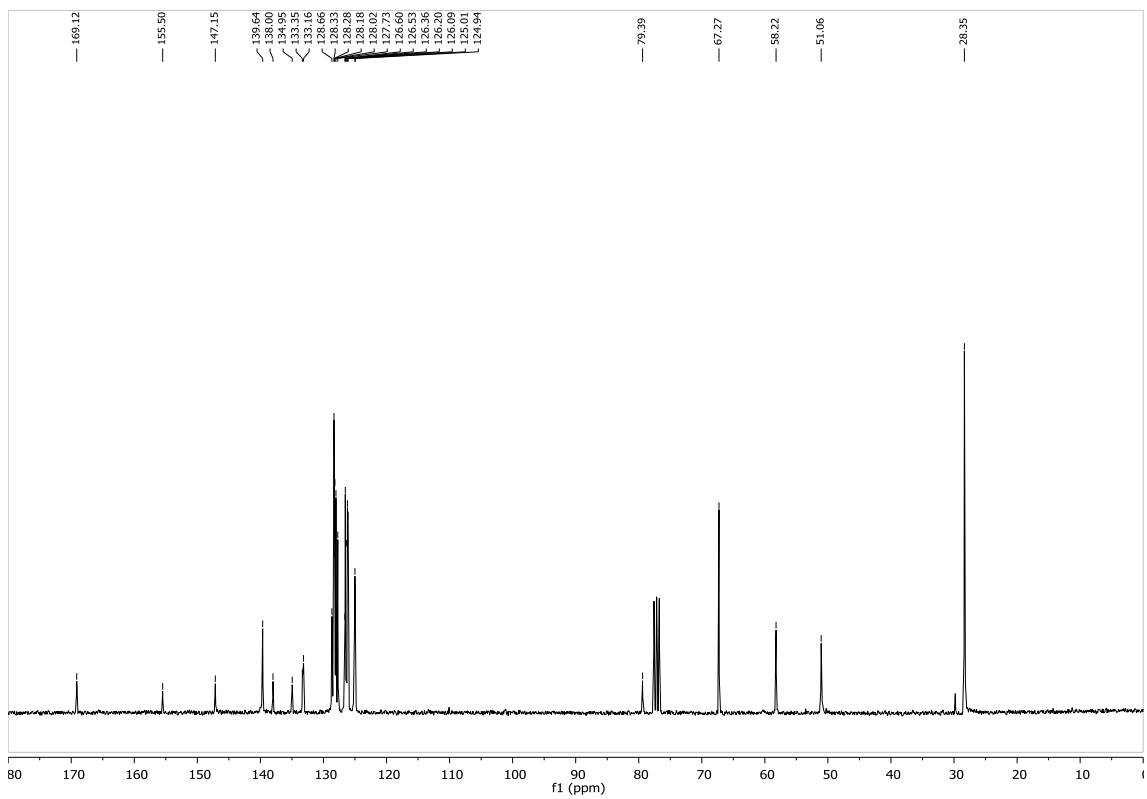
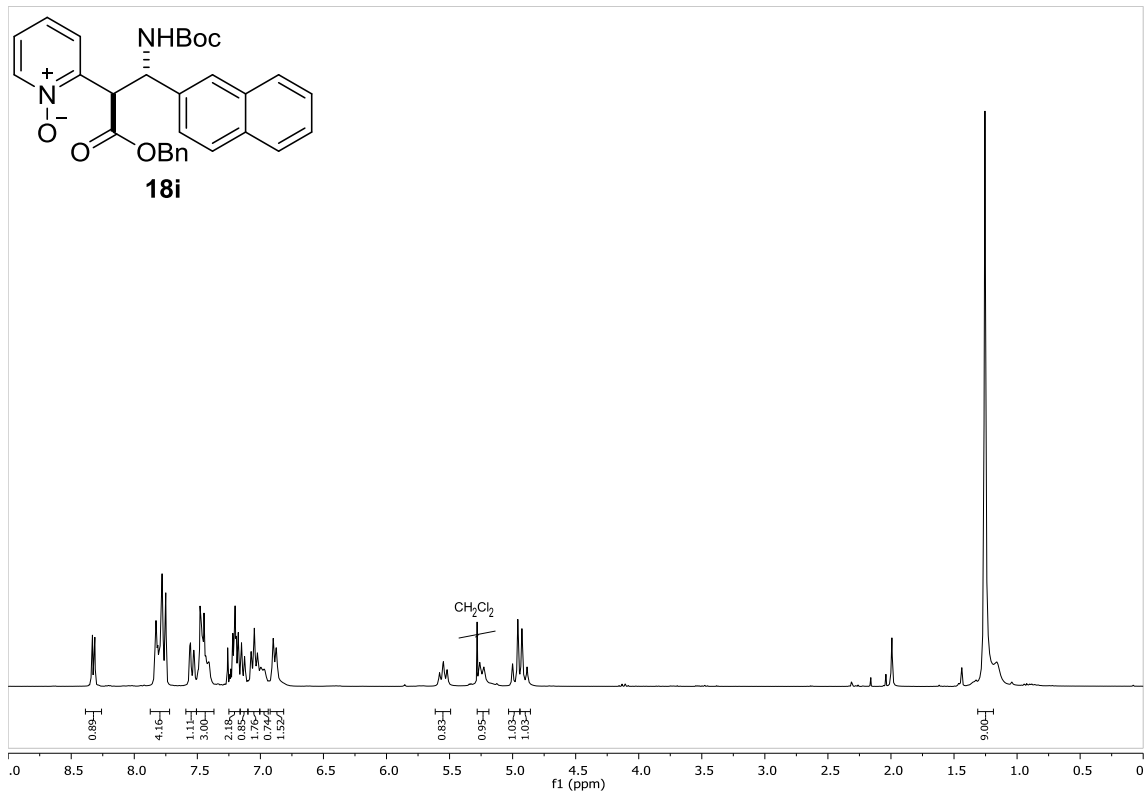
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18g)

Experimental section

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18h)

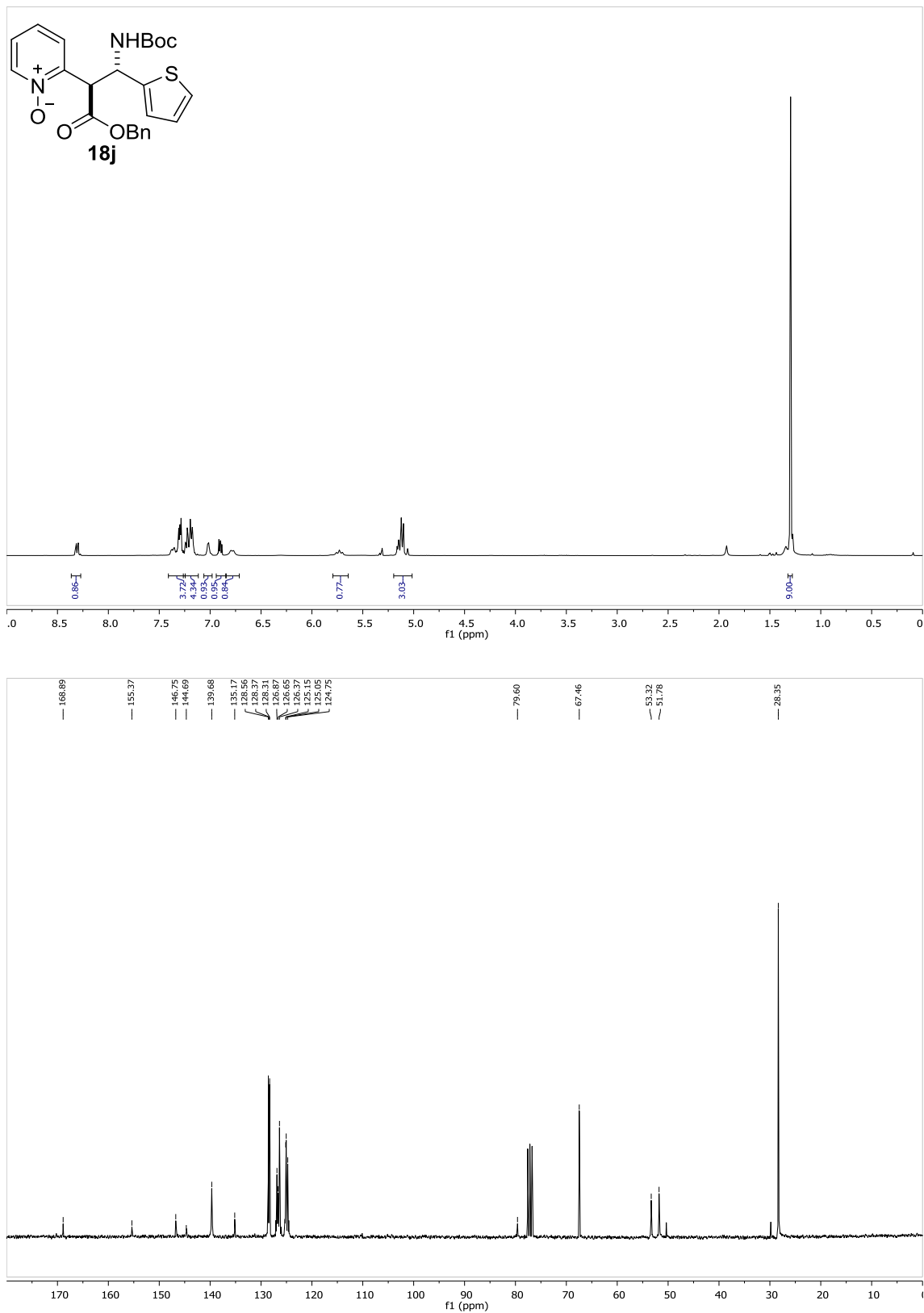


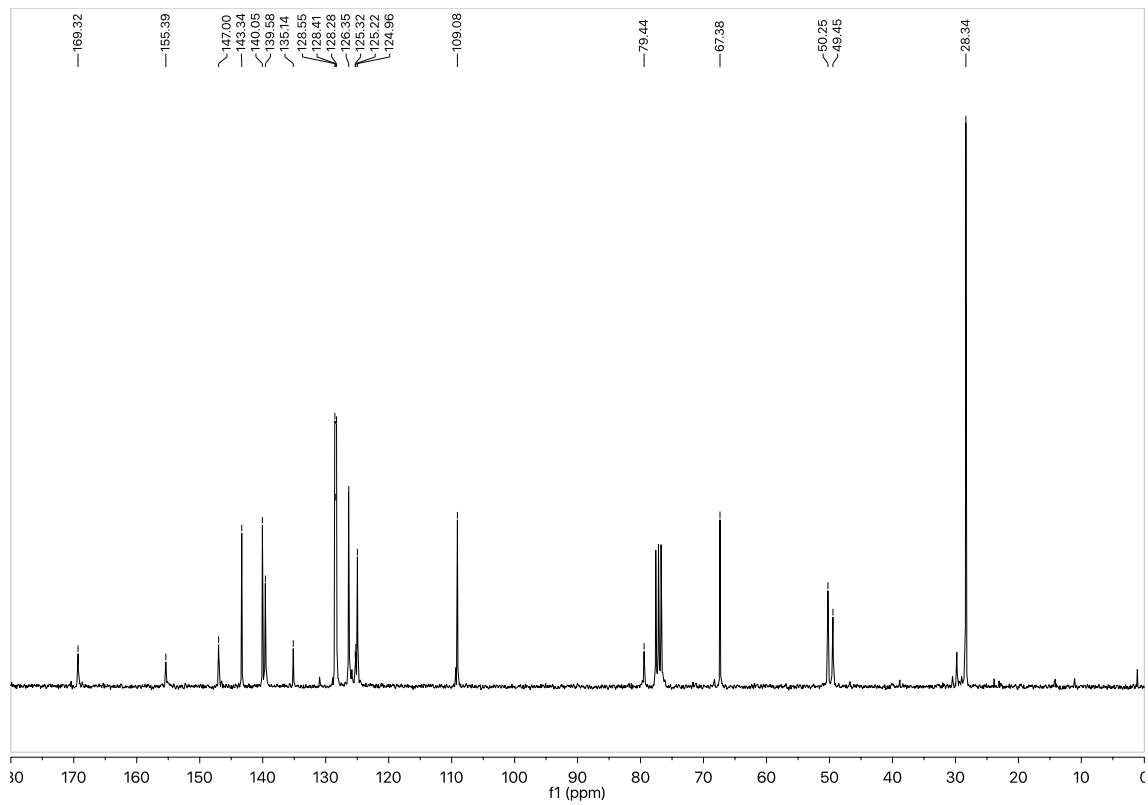
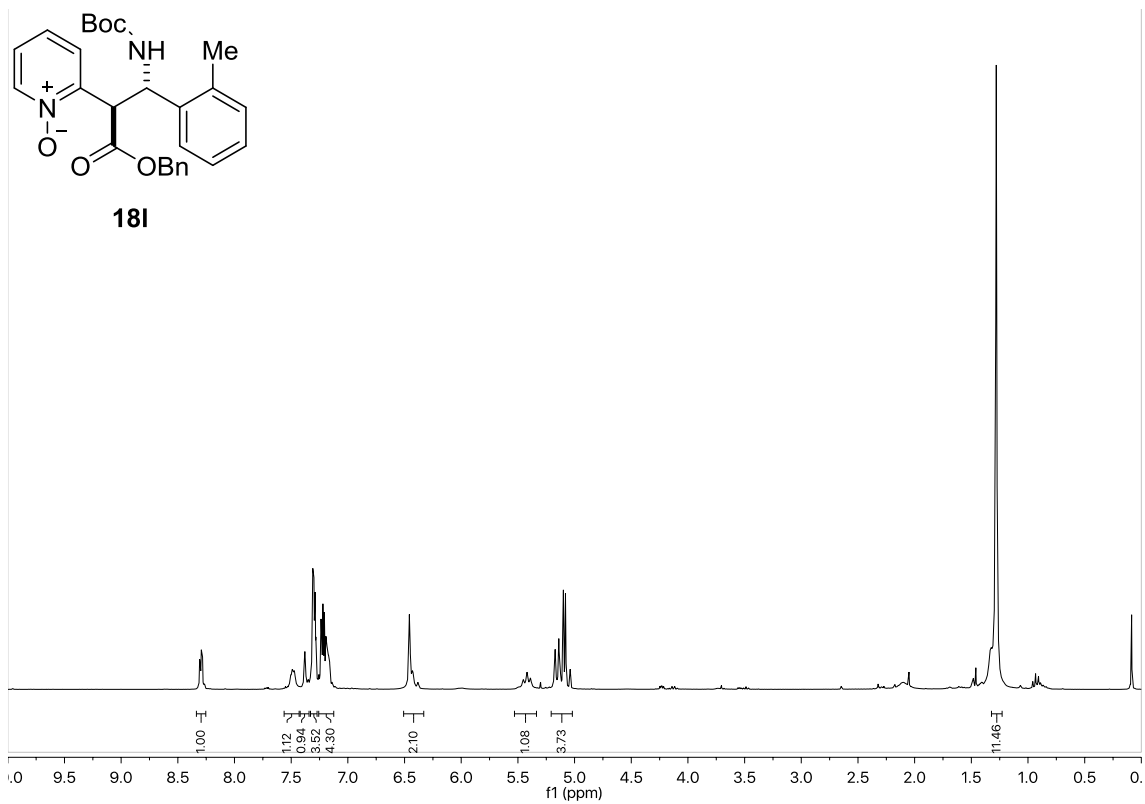
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18i)



Experimental section

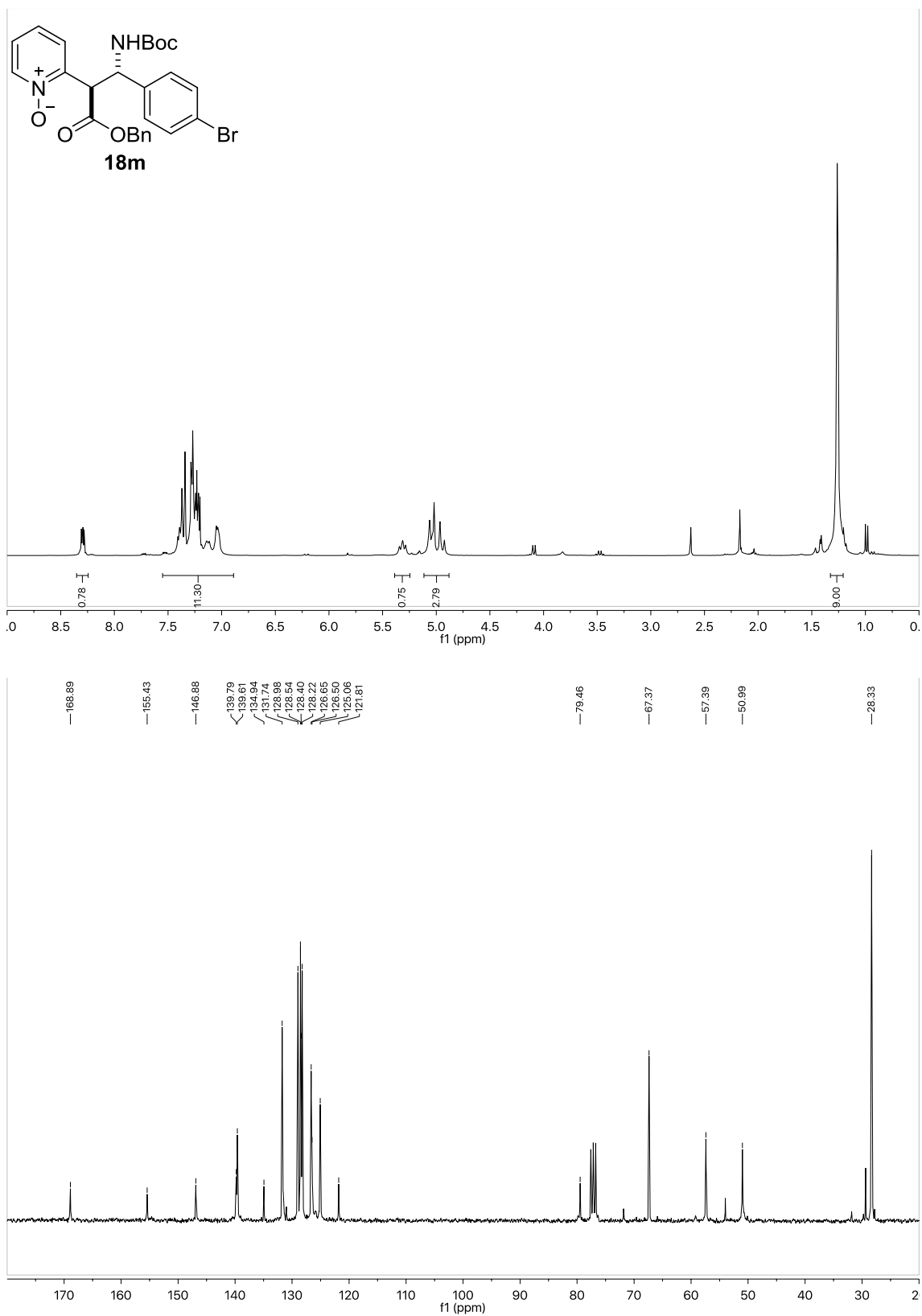
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)pyridine *N*-oxide (18j)

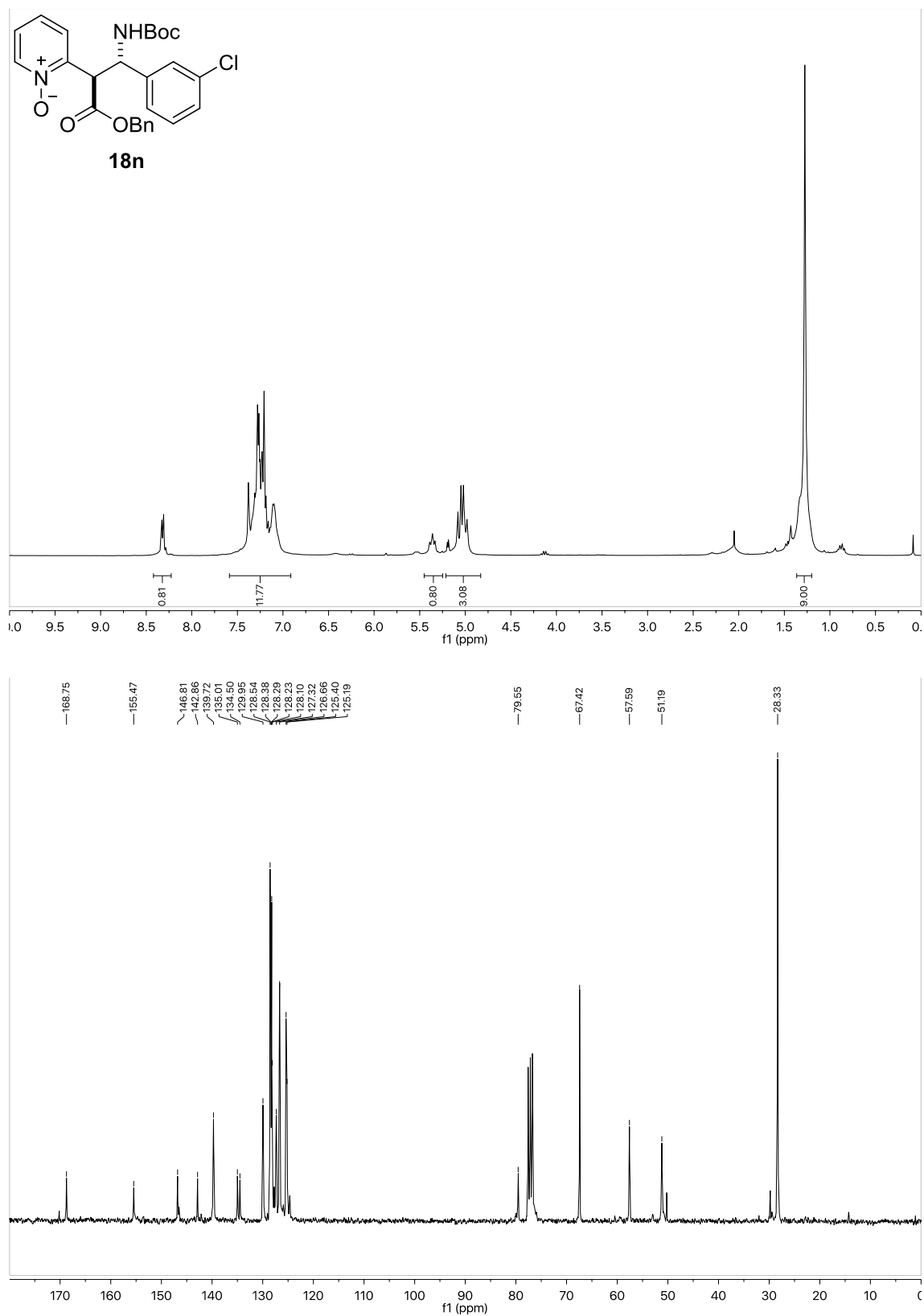


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(*o*-tolyl)propan-2-yl)pyridine *N*-oxide (18I)

Experimental section

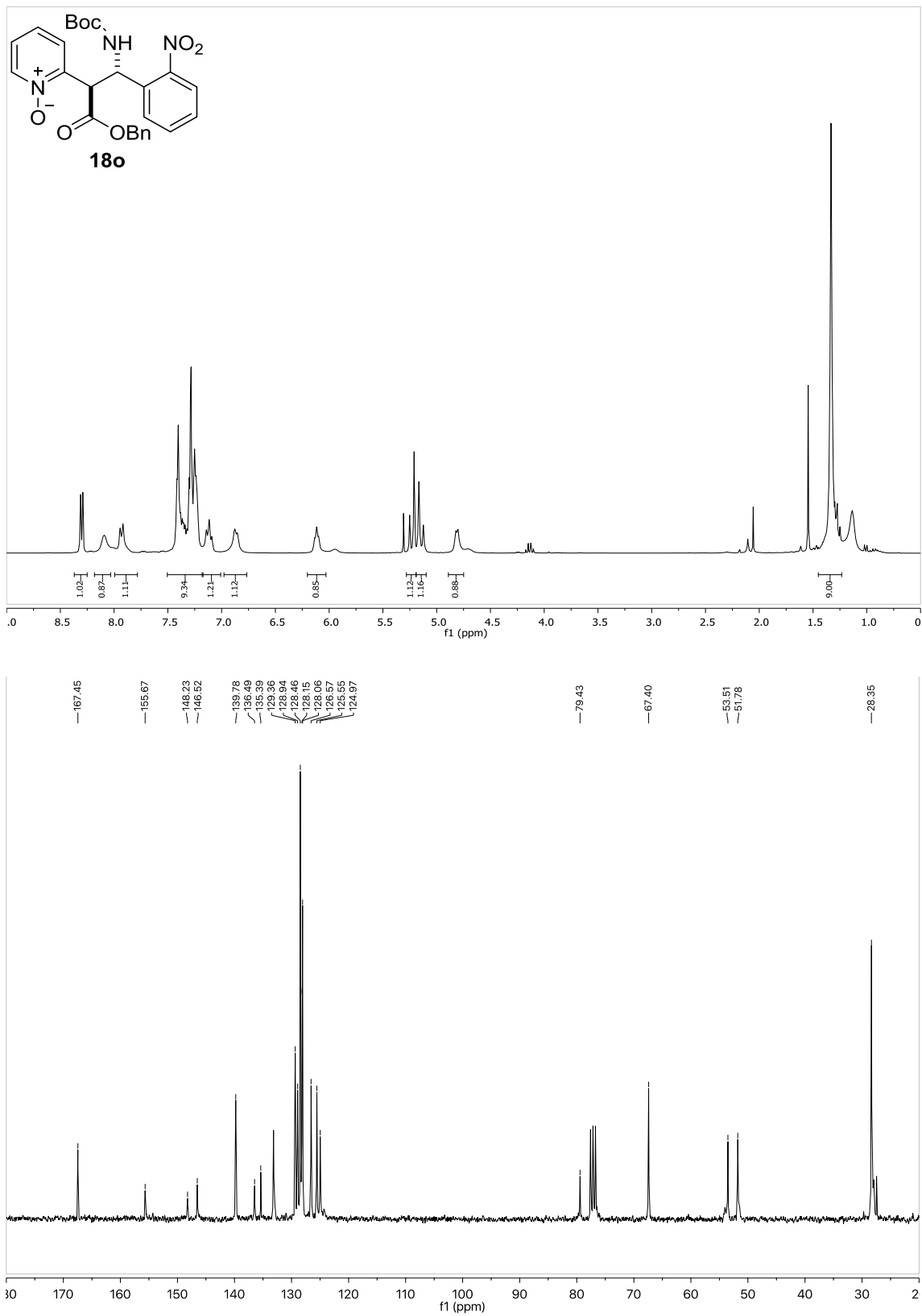
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(4-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-1-oxopropan-2-yl)pyridine *N*-oxide (18m)

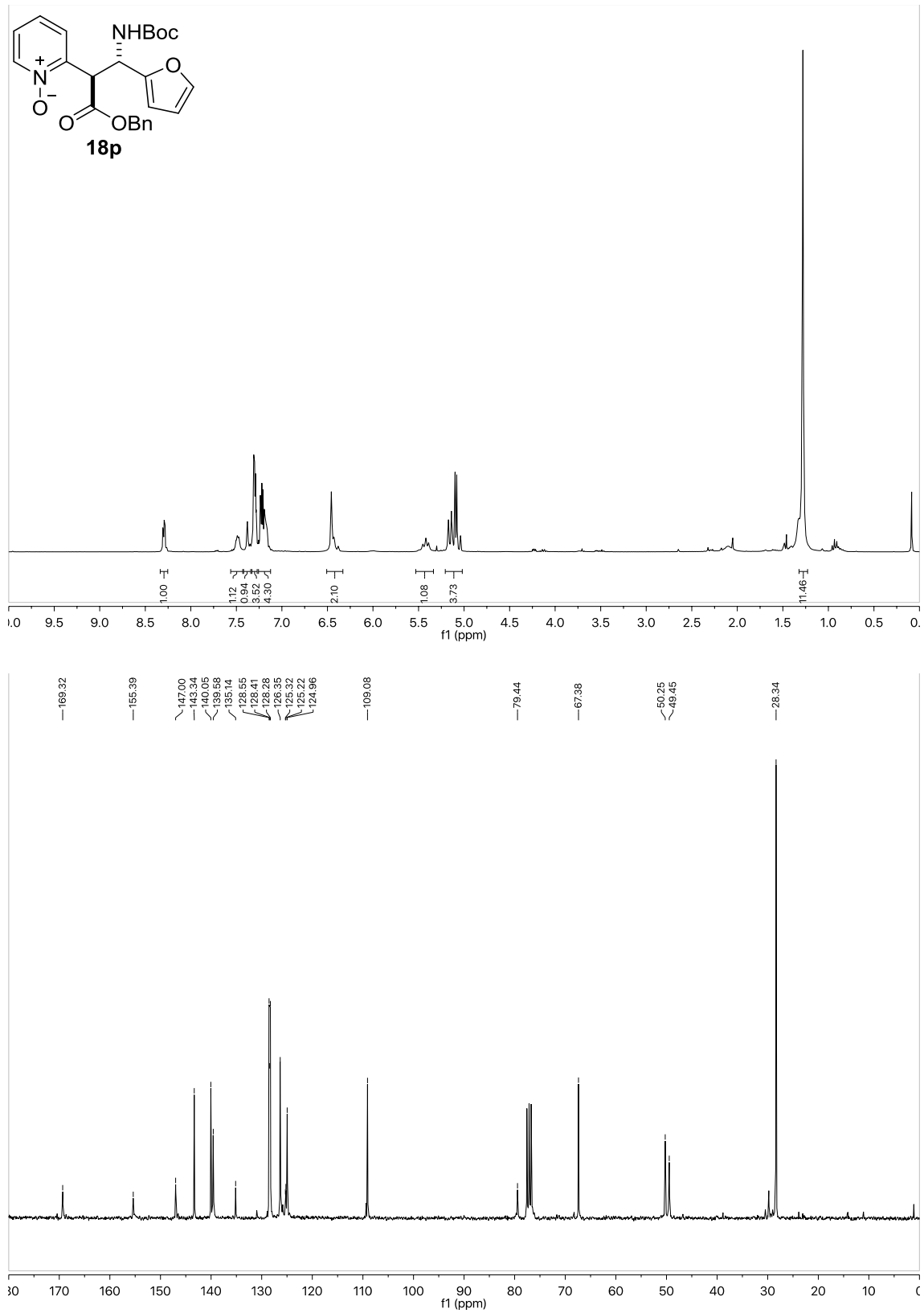


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18n)

Experimental section

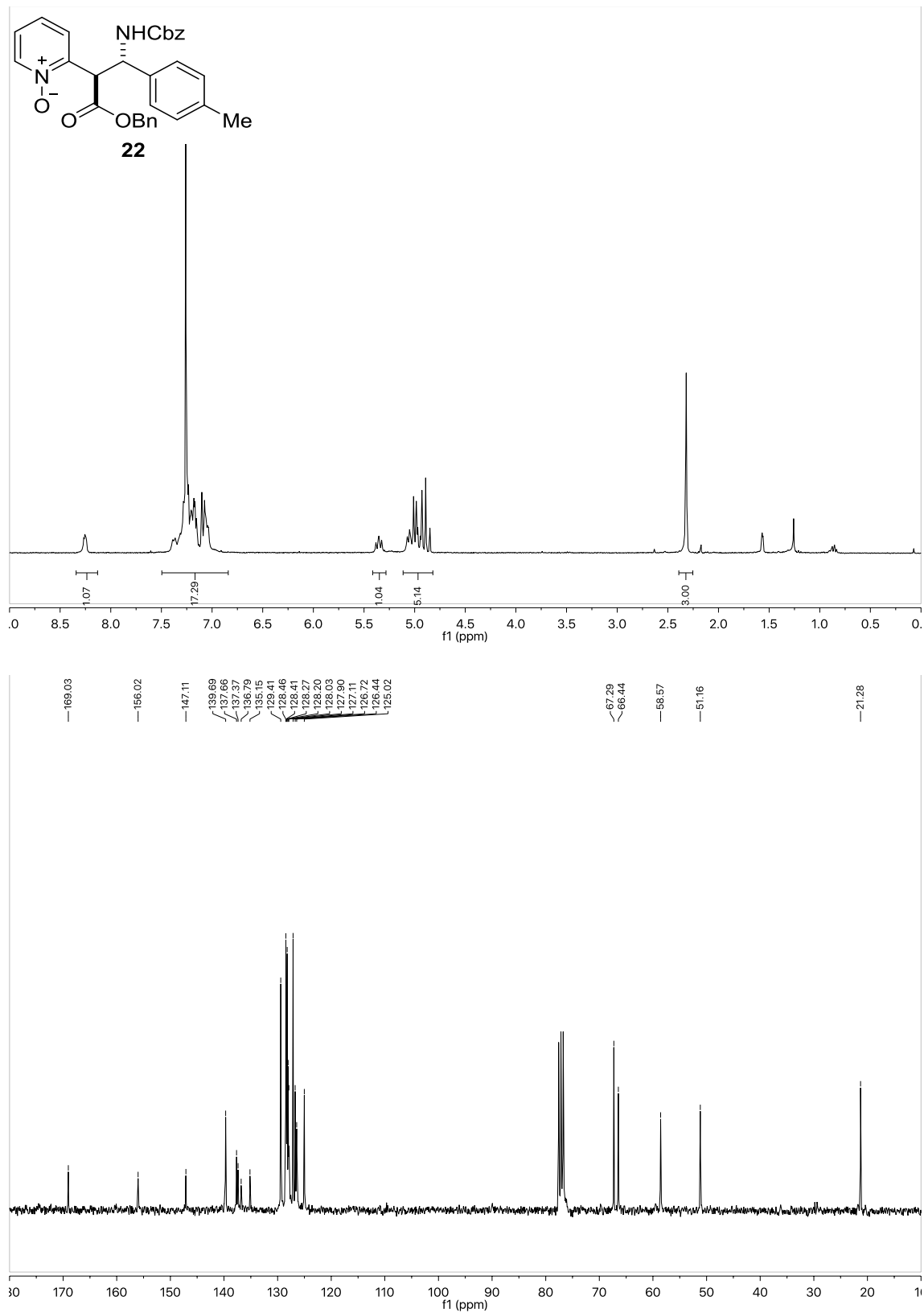
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(2-nitrophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18o)



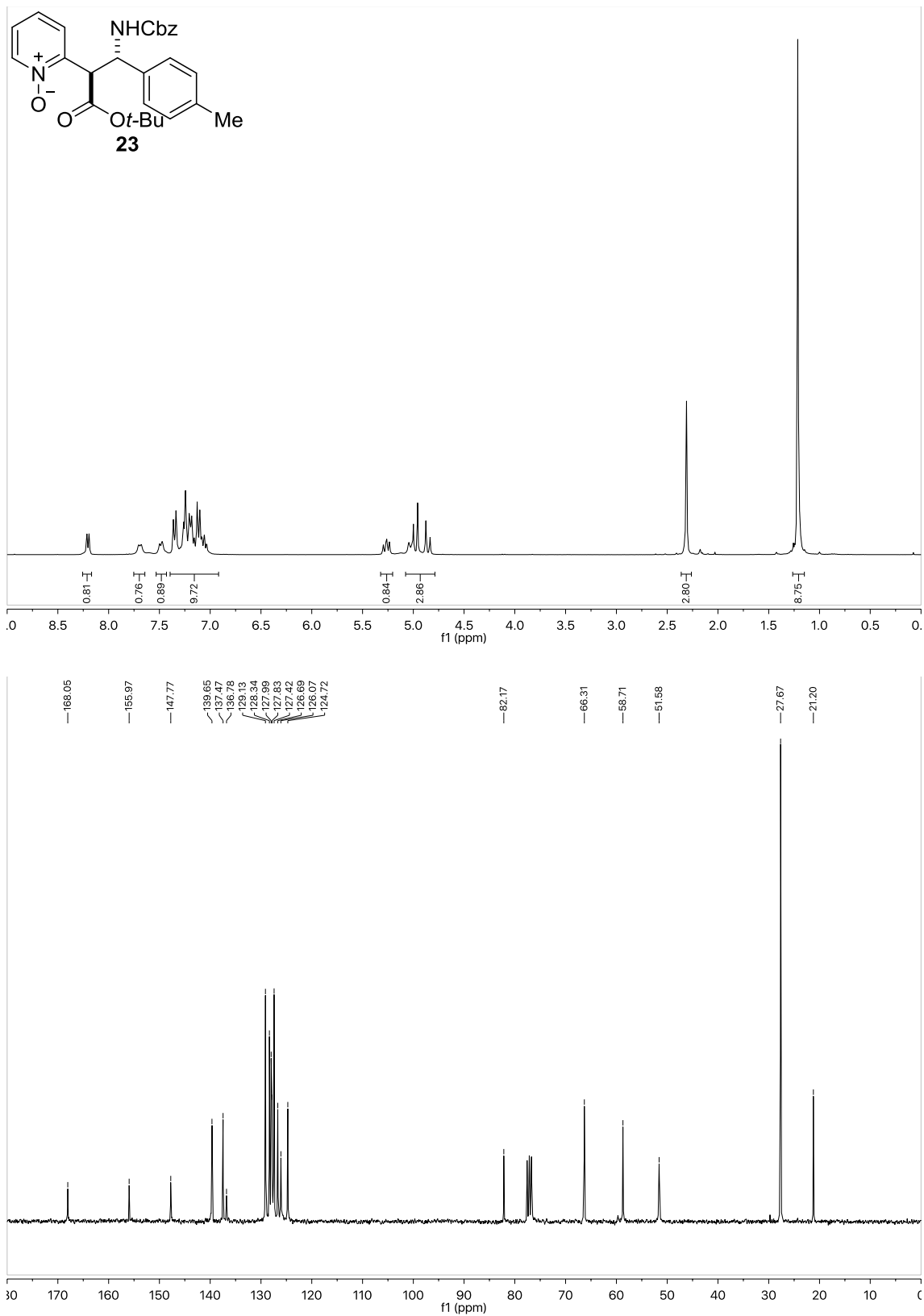
2-((2R,3S)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18p)

Experimental section

2-((2*R*,3*S*)-1-(Benzyloxy)-3-(((benzyloxy)carbonyl)amino)-1-oxo-3-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (22)

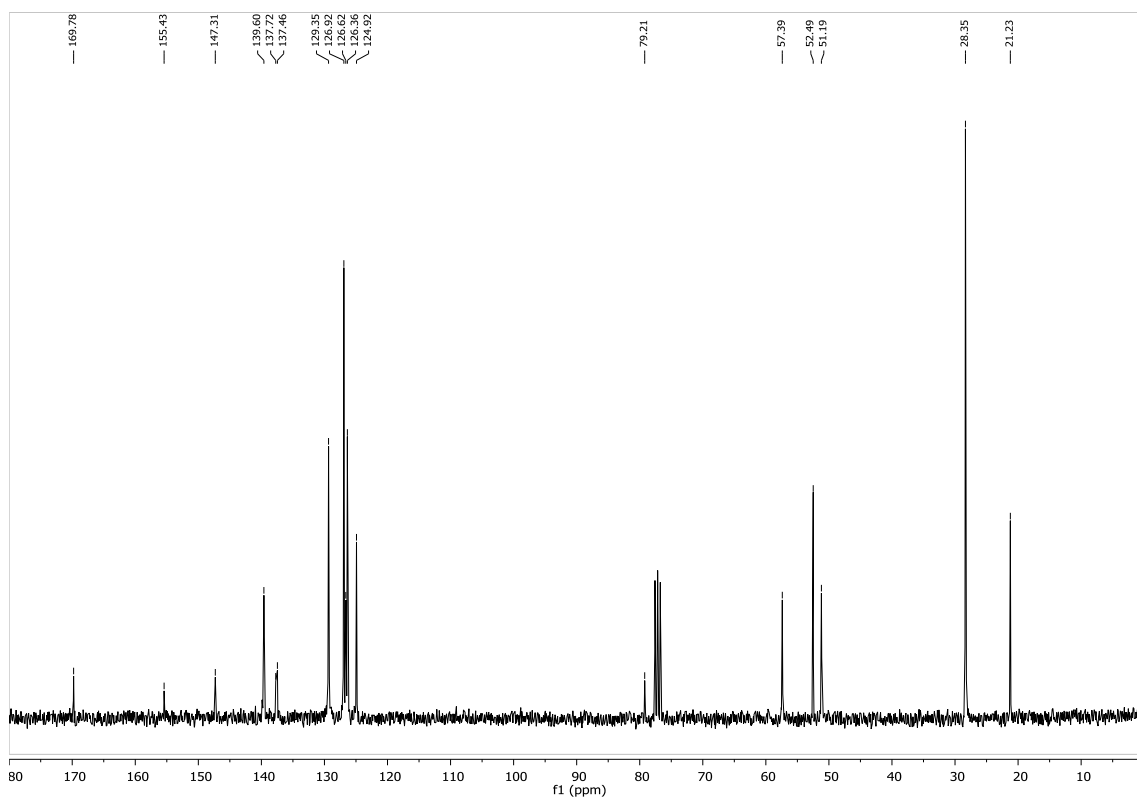
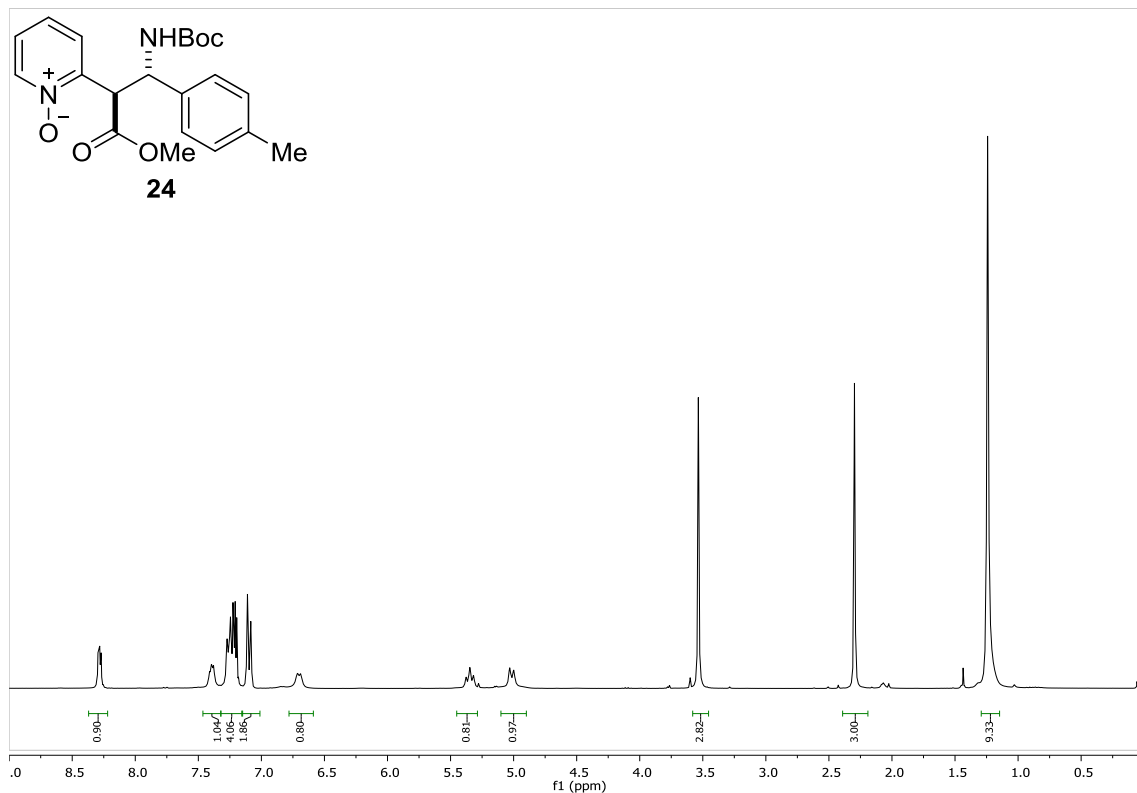


2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (23)



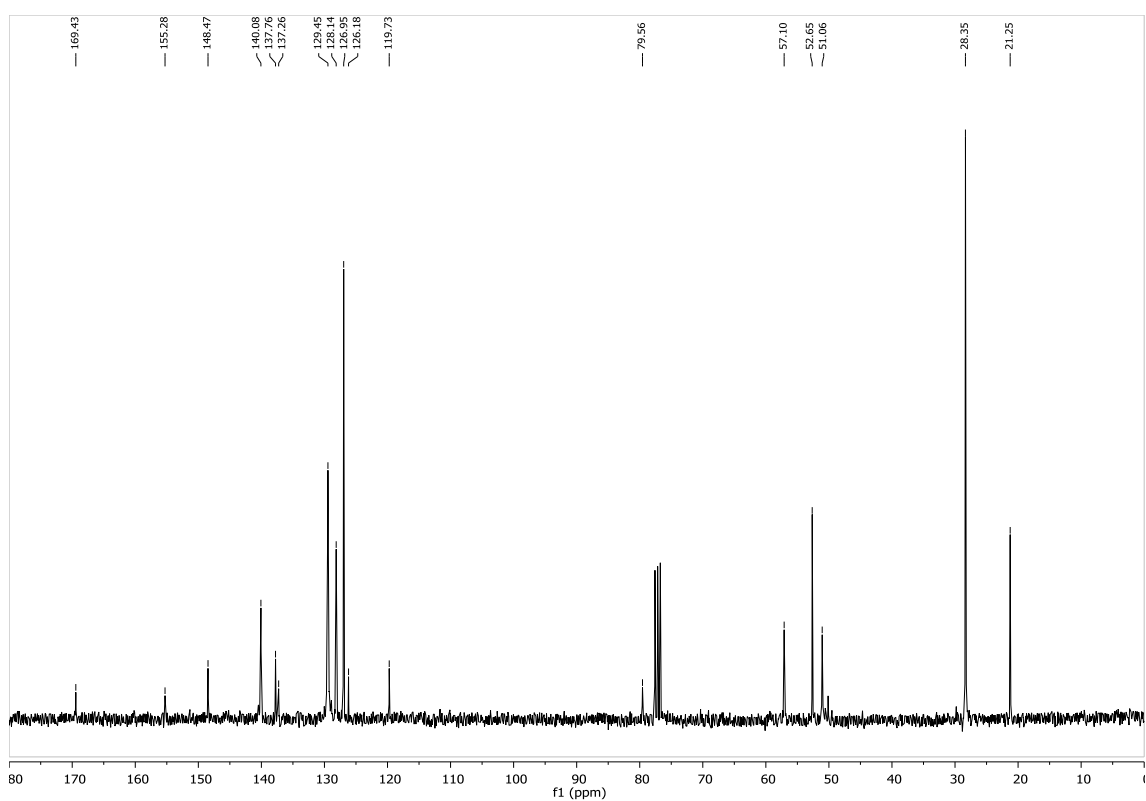
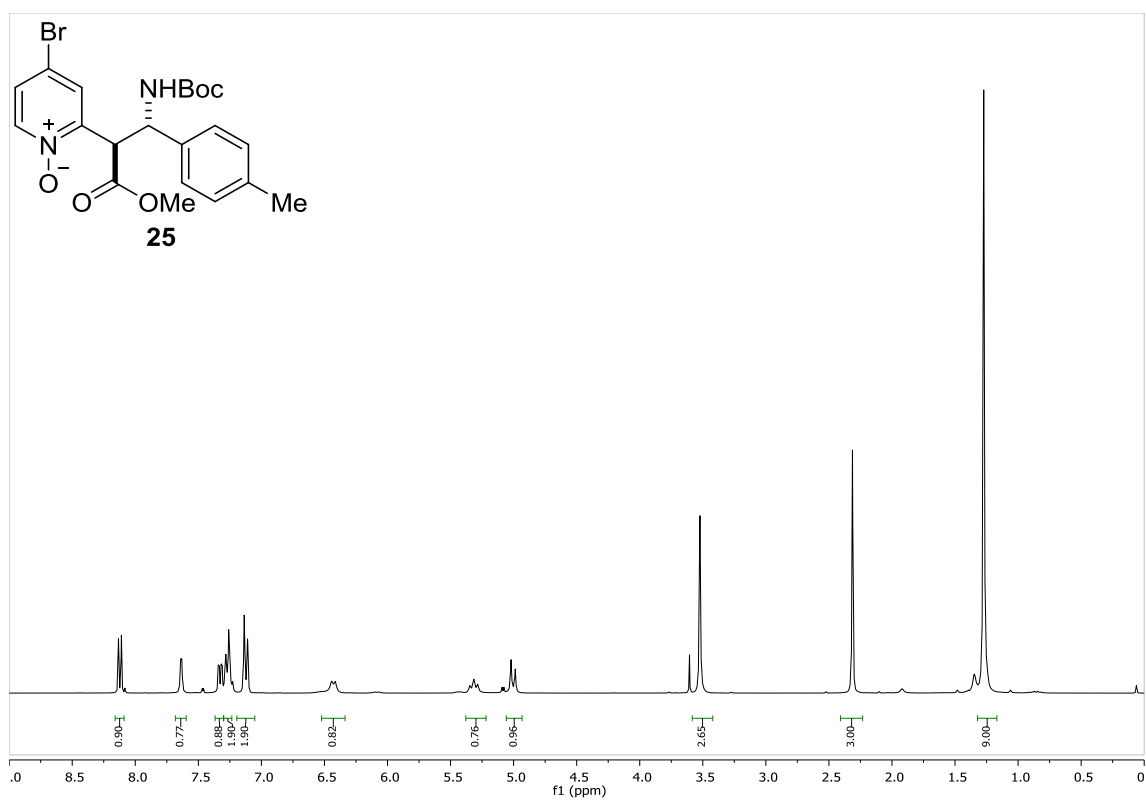
Experimental section

2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (24)



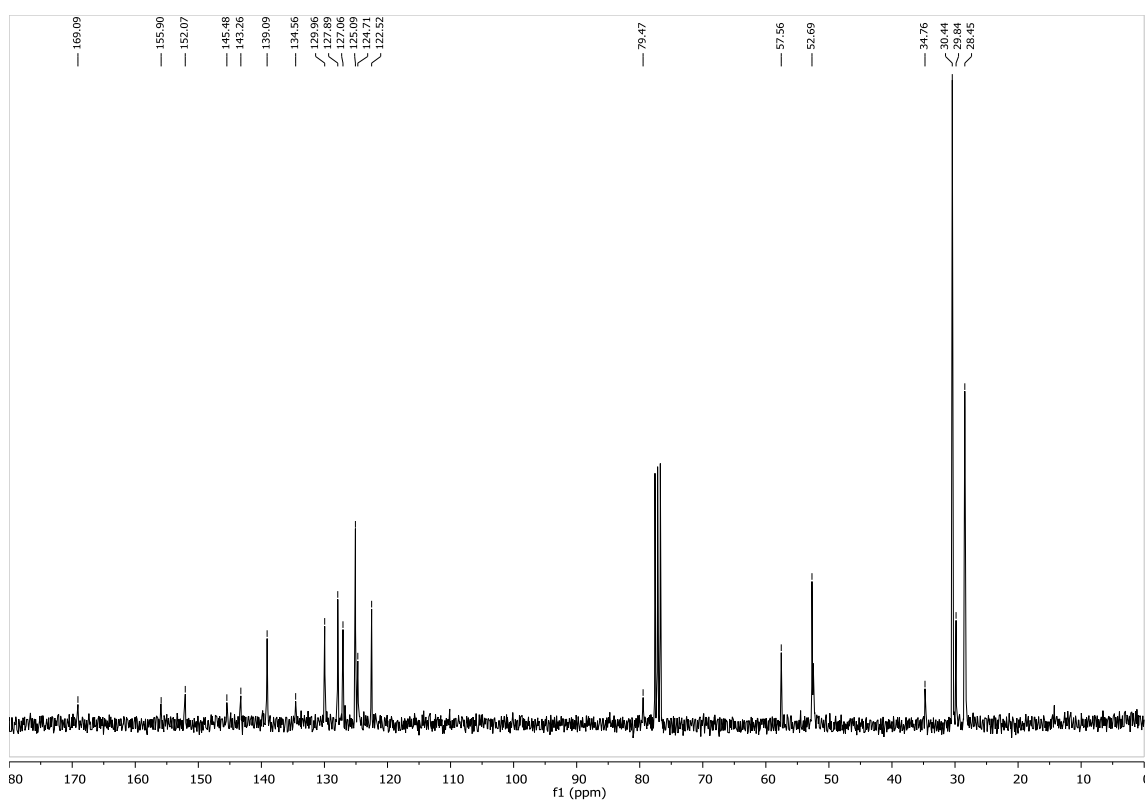
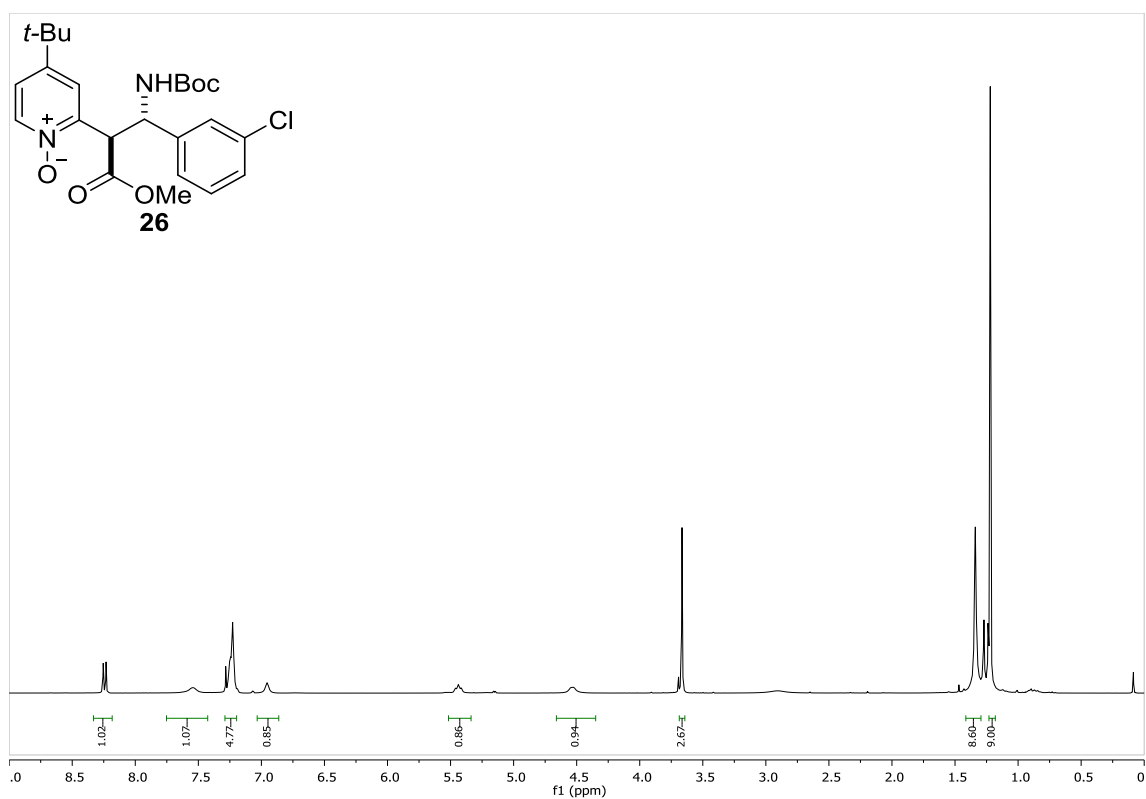
4-Bromo-2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (25)

Chapter 6



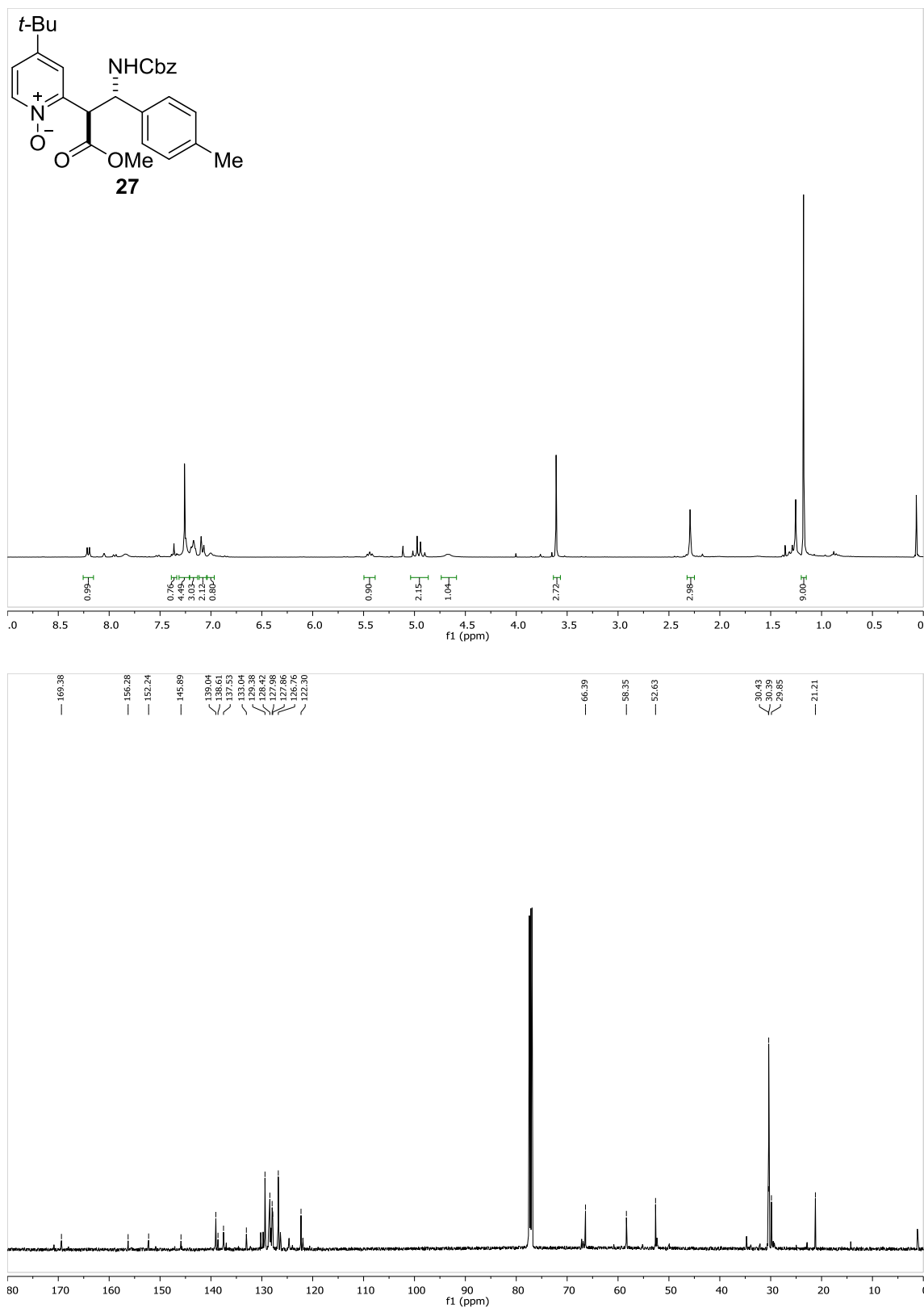
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (26**)**

Experimental section



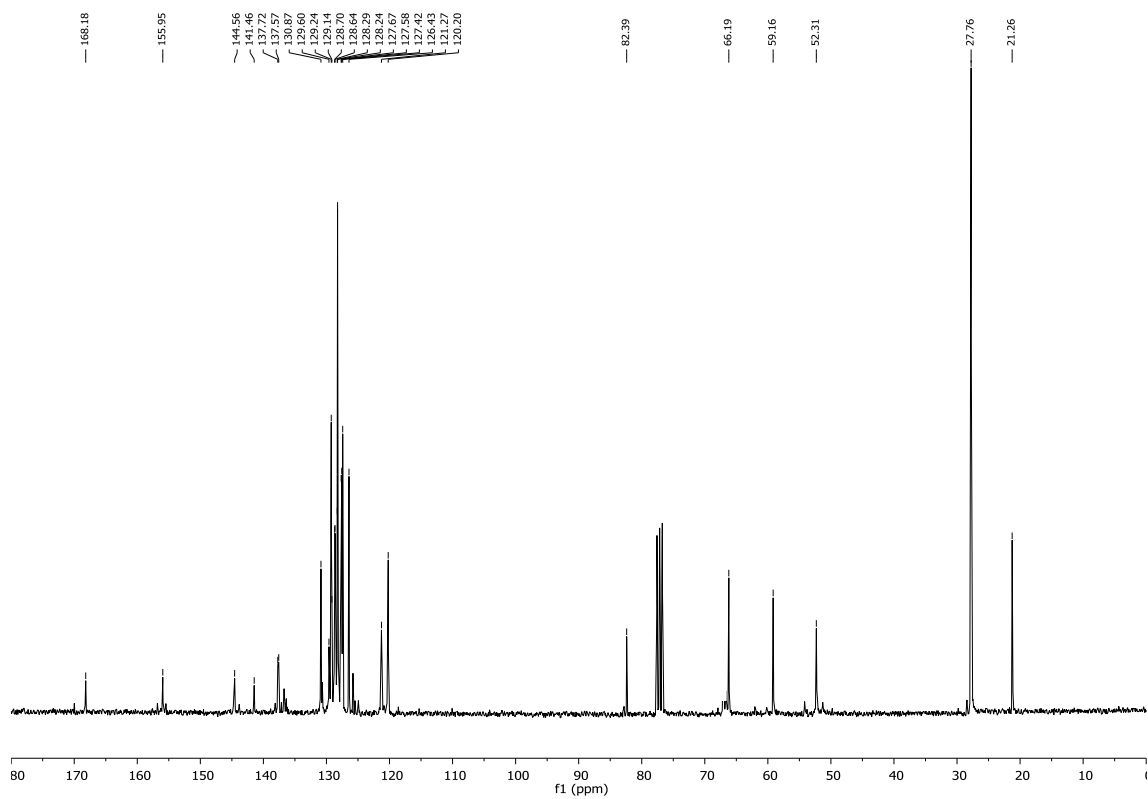
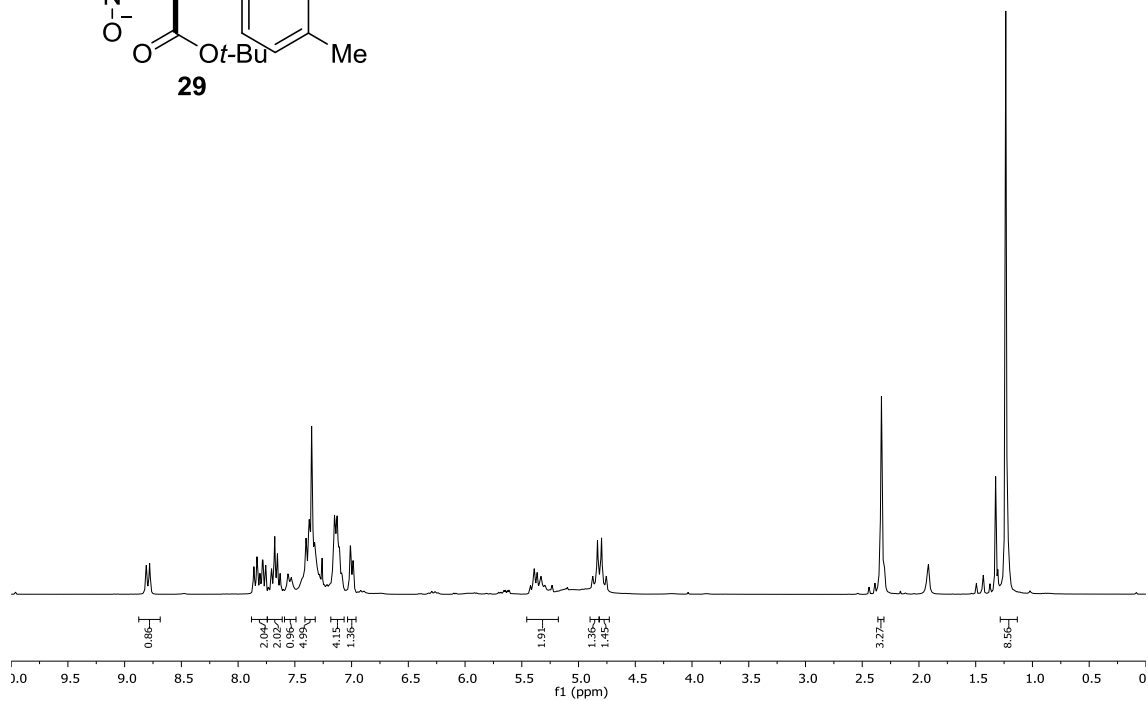
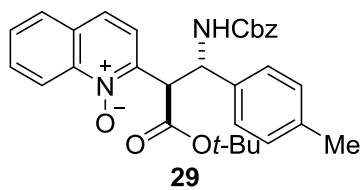
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (27**)**

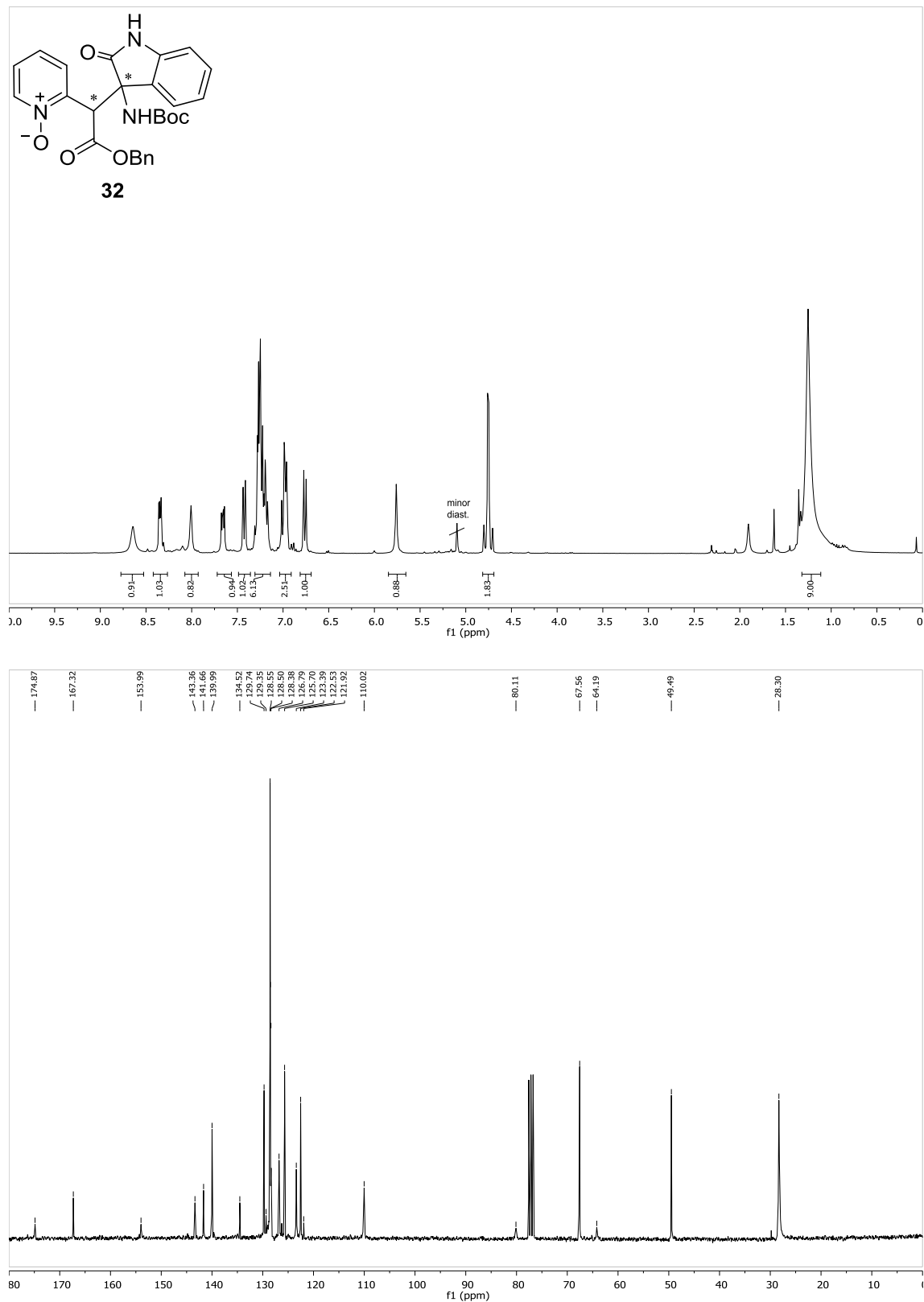
Chapter 6



Experimental section

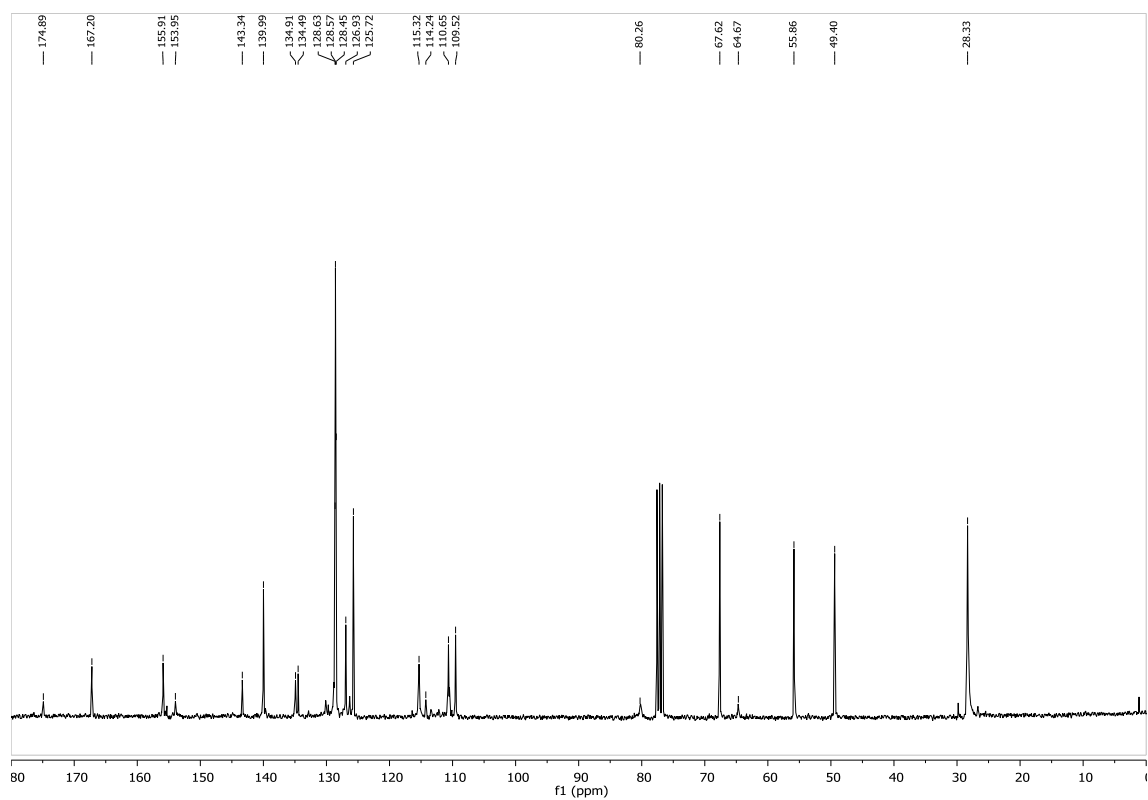
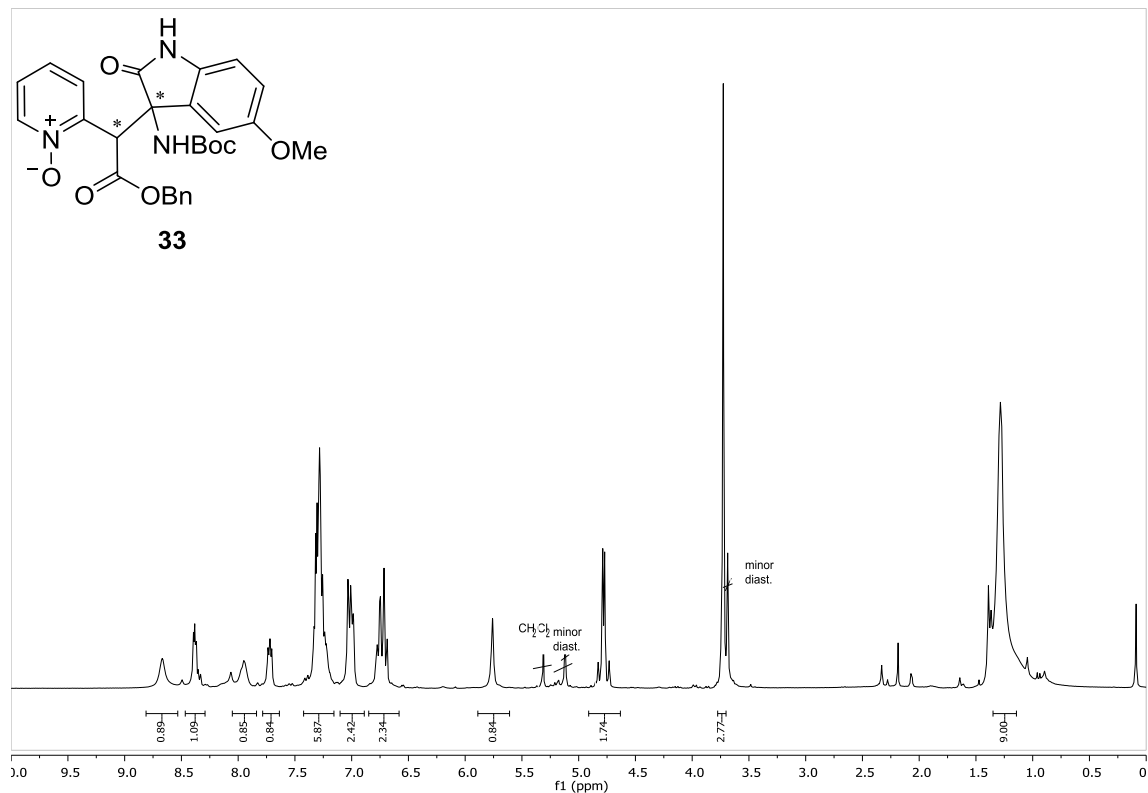
2-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)quinoline *N*-oxide (29)

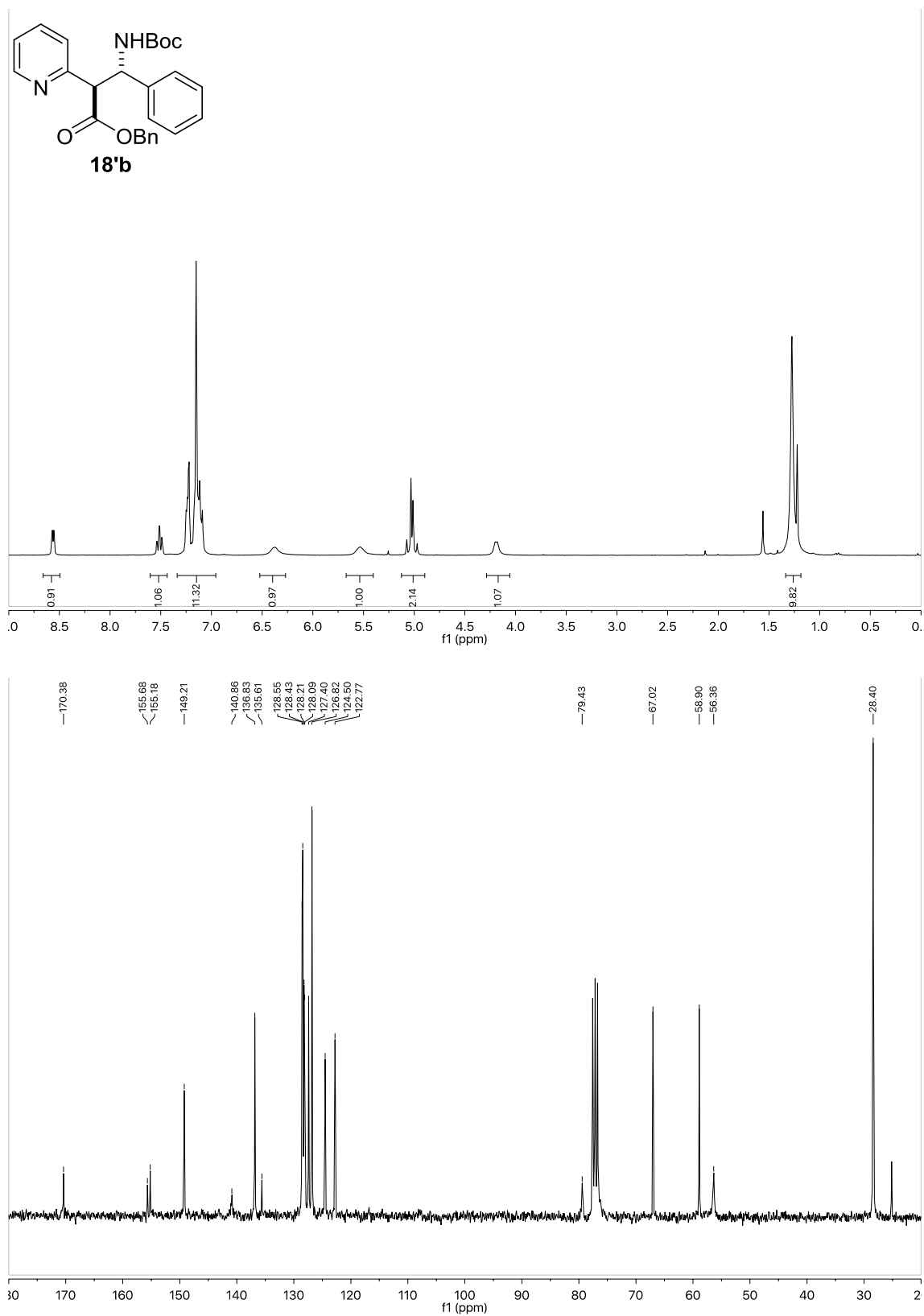


2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (32)

Experimental section

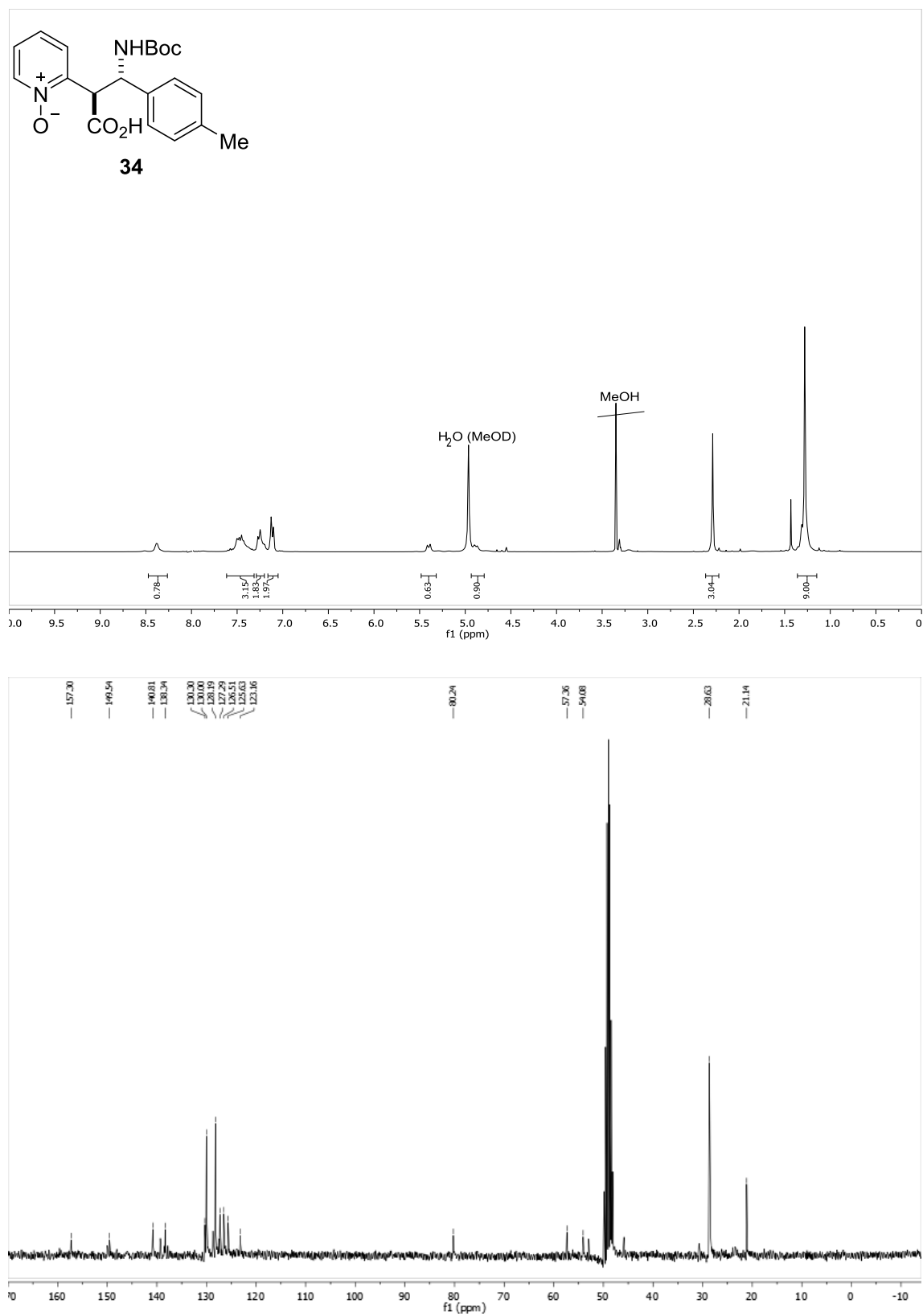
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-5-methoxy-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (33)

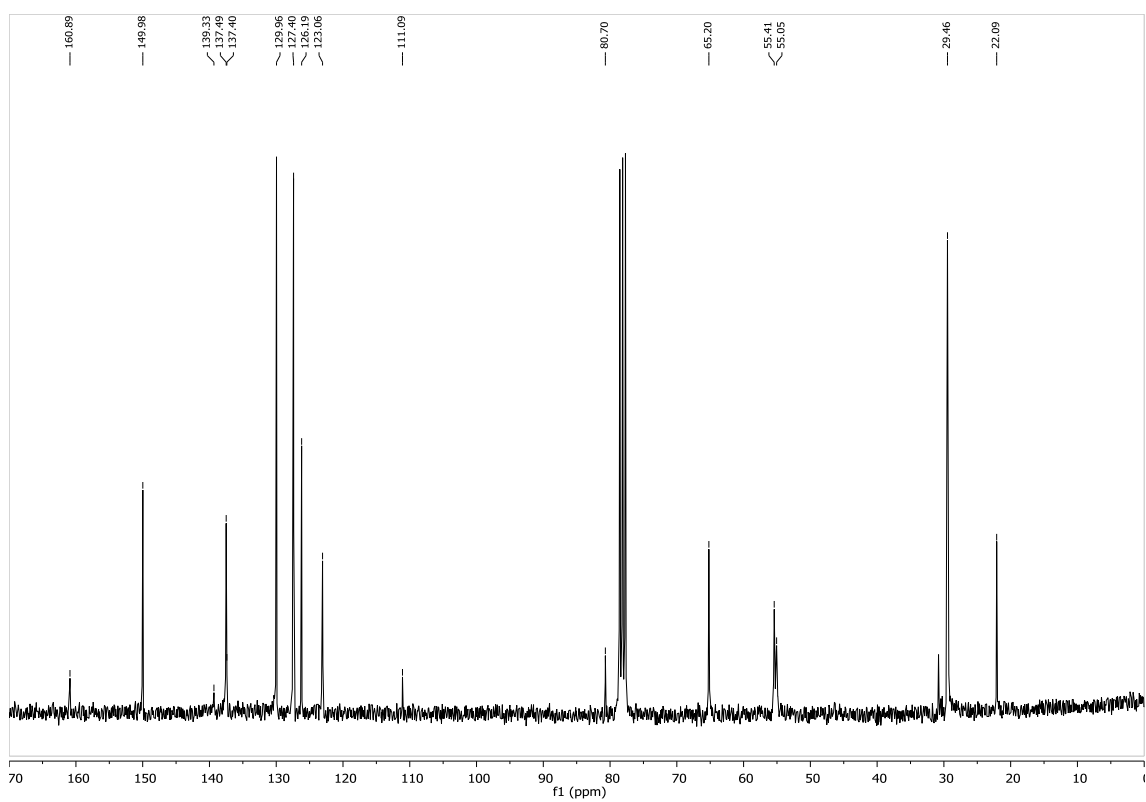
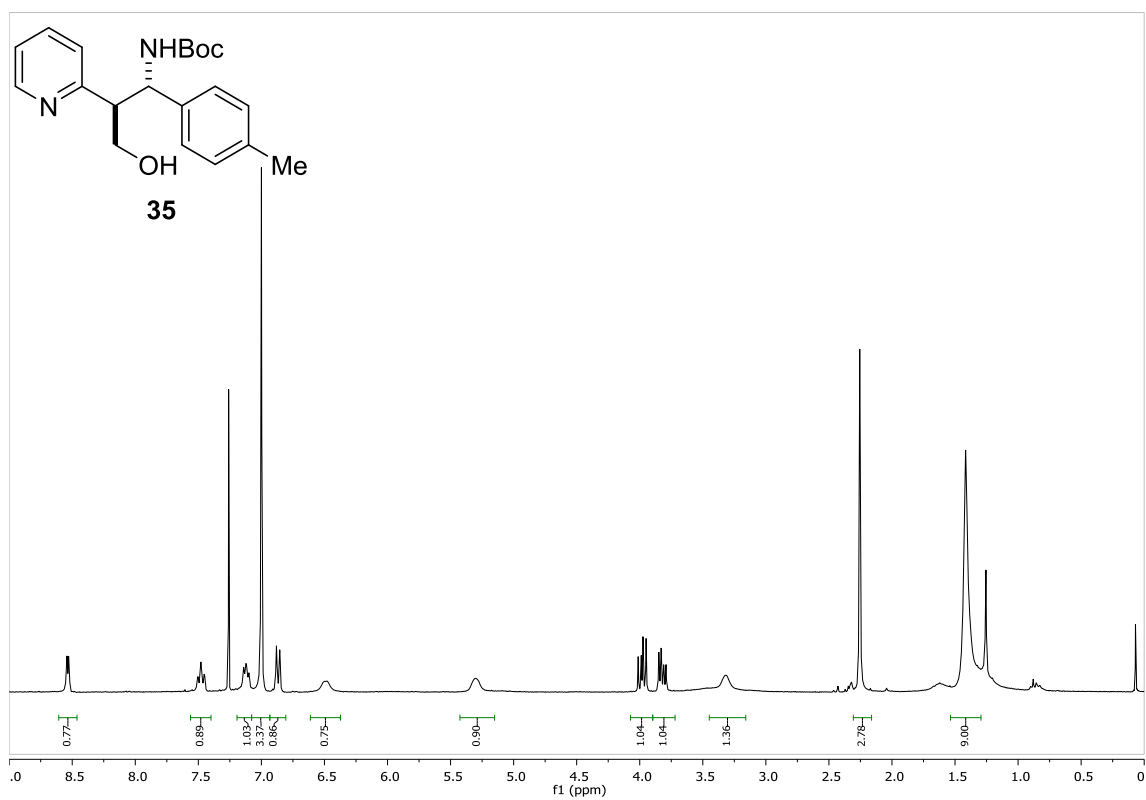


Benzyl (2*R*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-phenyl-2-(pyridin-2-yl)propanoate (18'b)

Experimental section

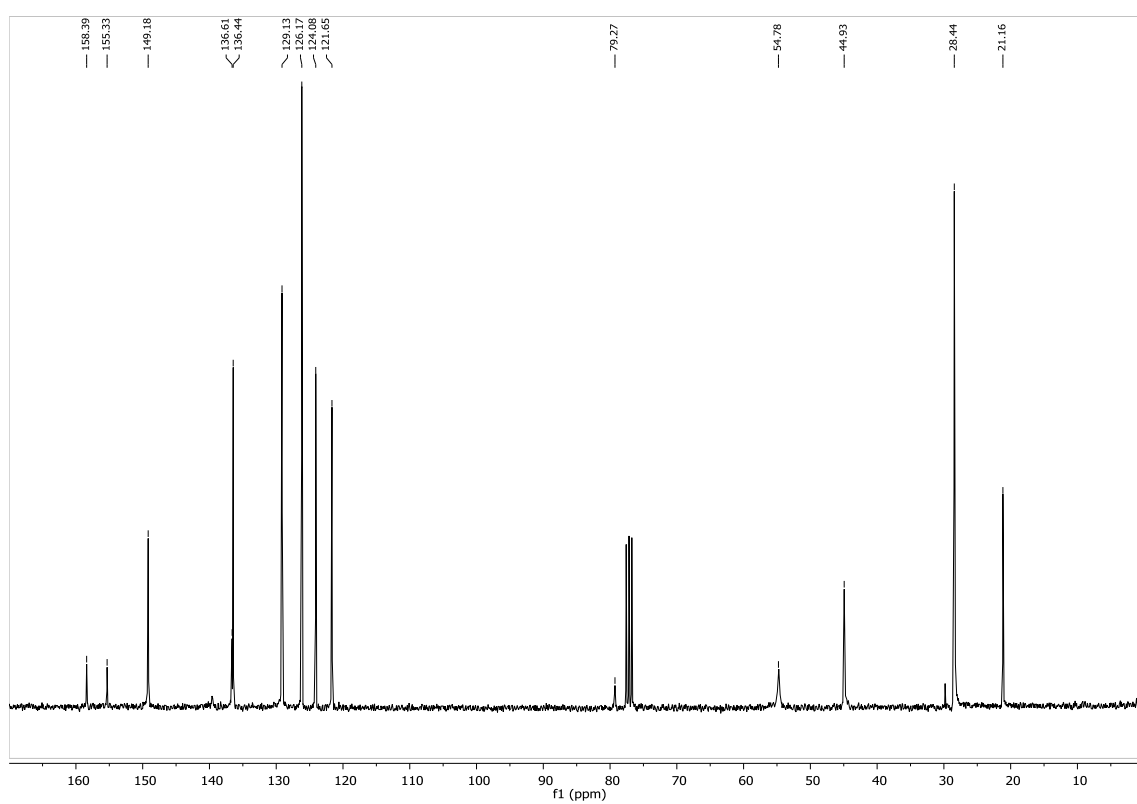
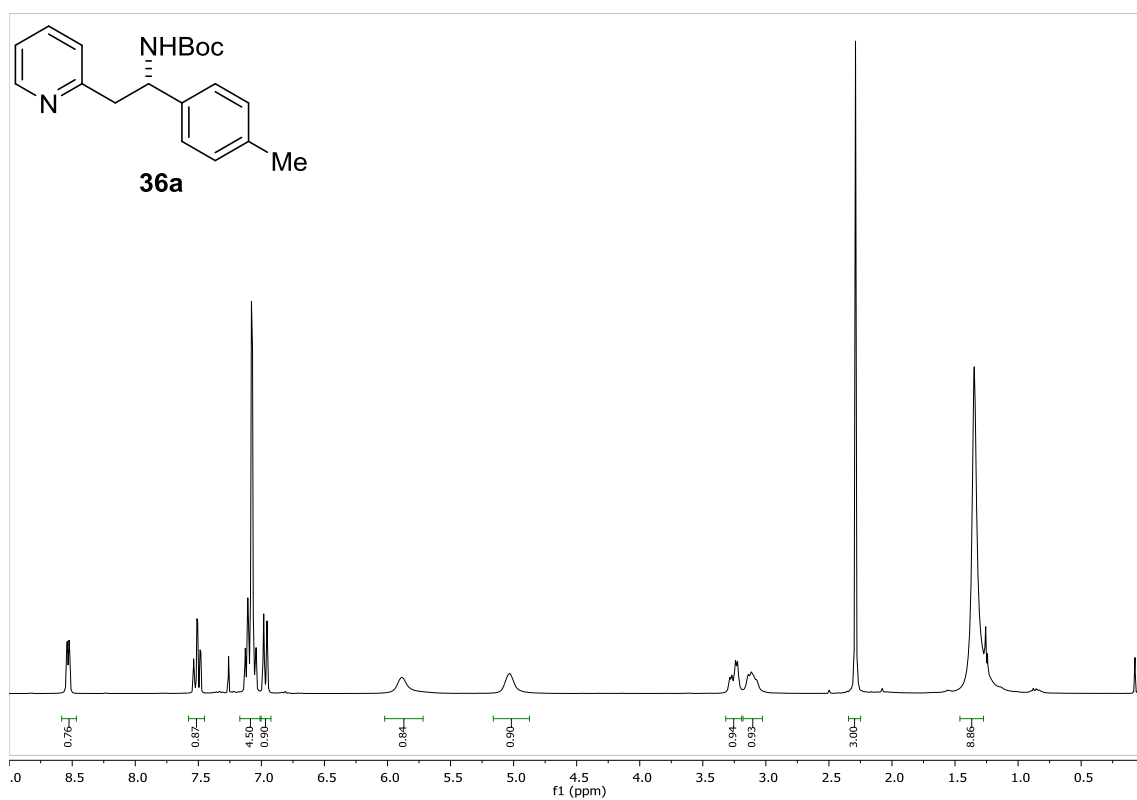
2-((1*R*,2*S*)-2-((*tert*-butoxycarbonyl)amino)-1-carboxy-2-(*p*-tolyl)ethyl)pyridine *N*-oxide (34)



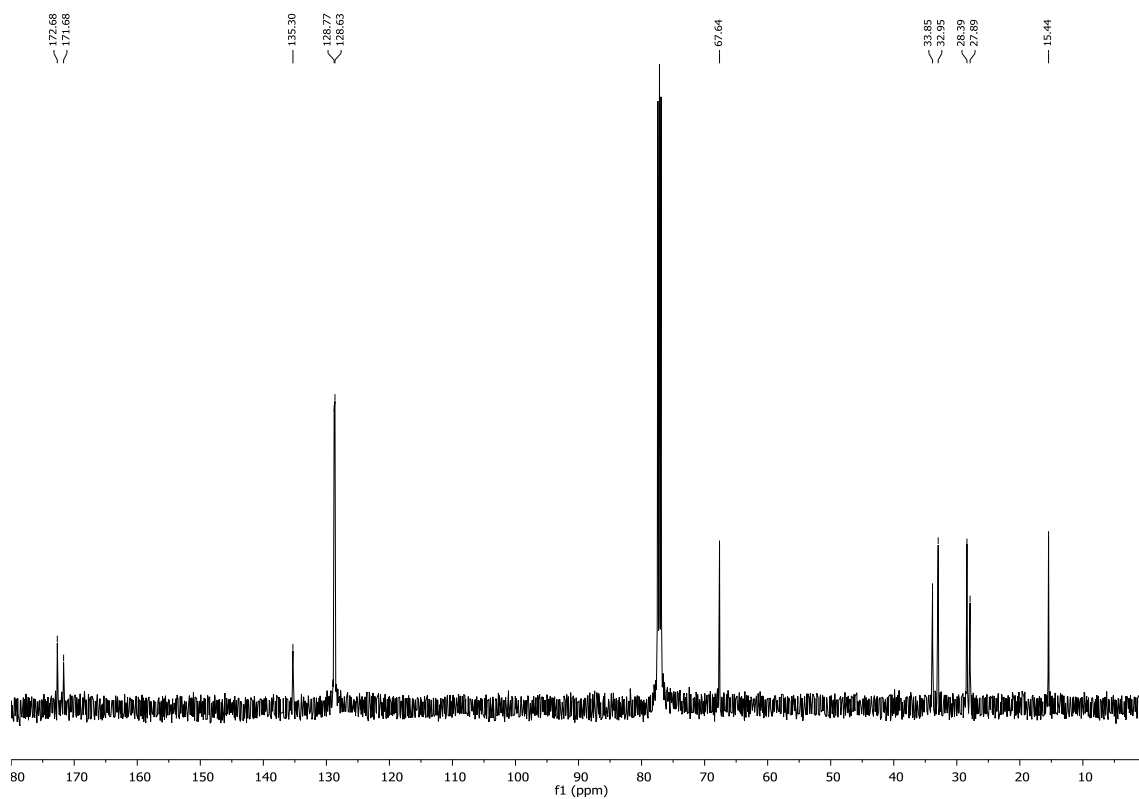
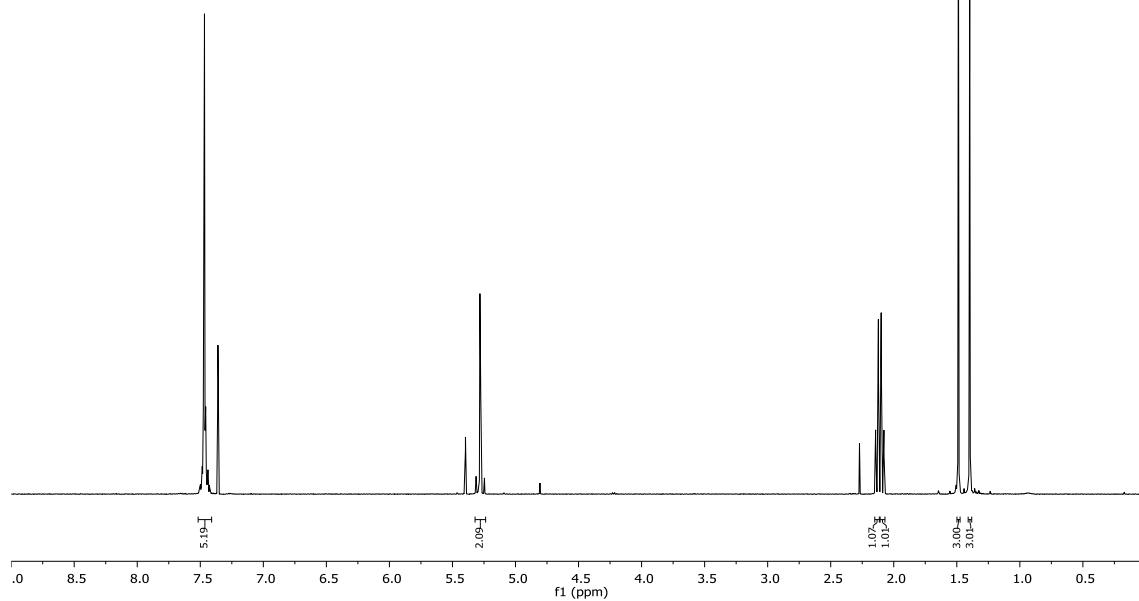
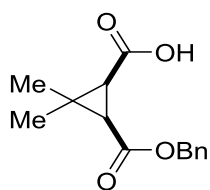
***tert*-Butyl ((1*S*,2*R*)-3-hydroxy-2-(pyridin-2-yl)-1-(*p*-tolyl)propyl)carbamate (35)**

Experimental section

tert-butyl (*S*)-(2-(pyridin-2-yl)-1-(*p*-tolyl)ethyl)carbamate (**36a**)

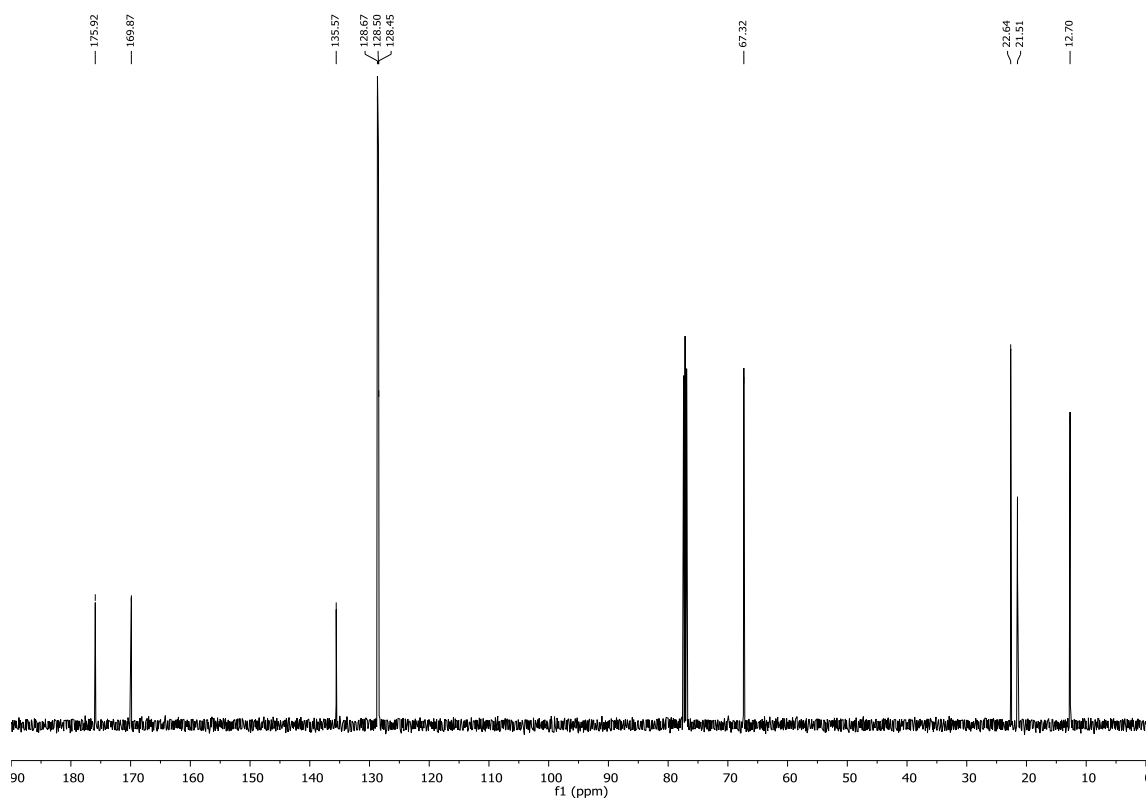
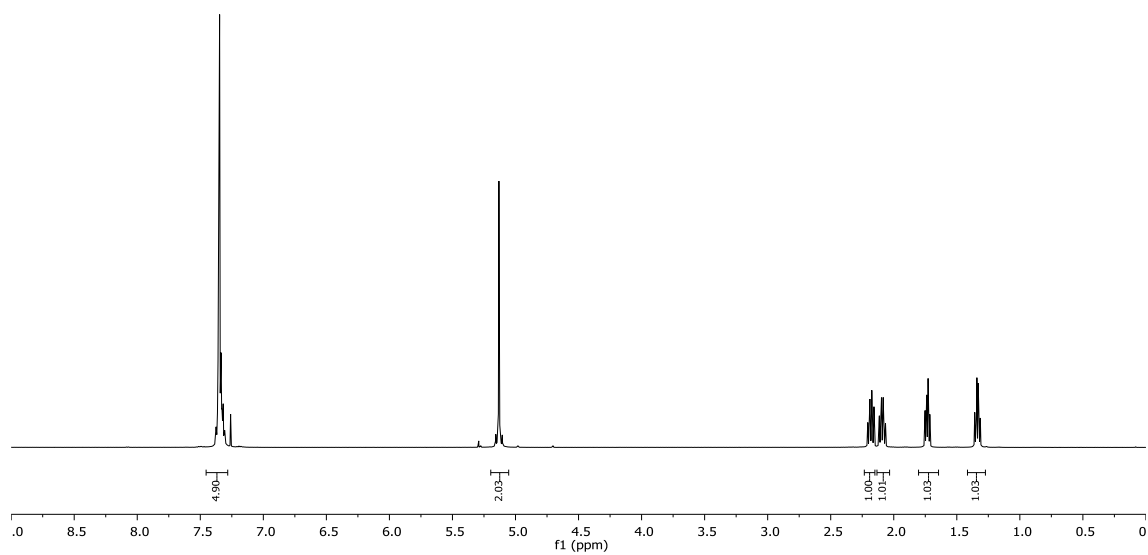
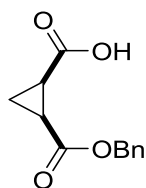


6.6.4. NMR spectra for Chapter 4

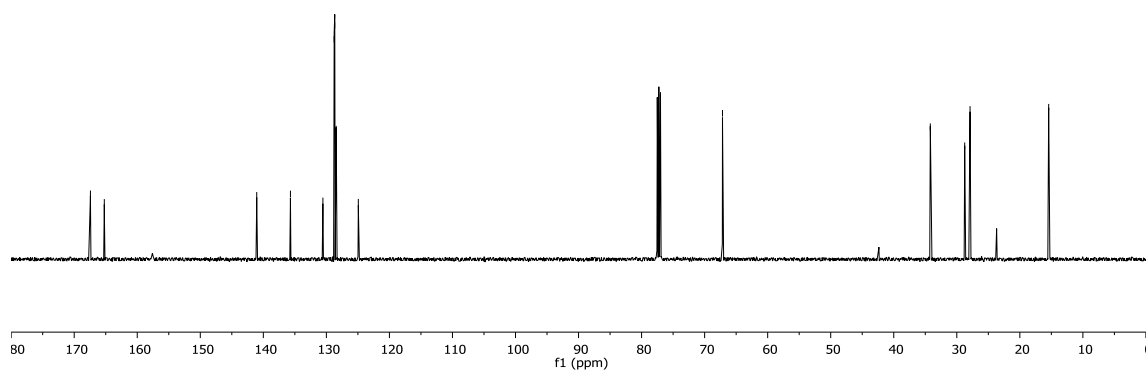
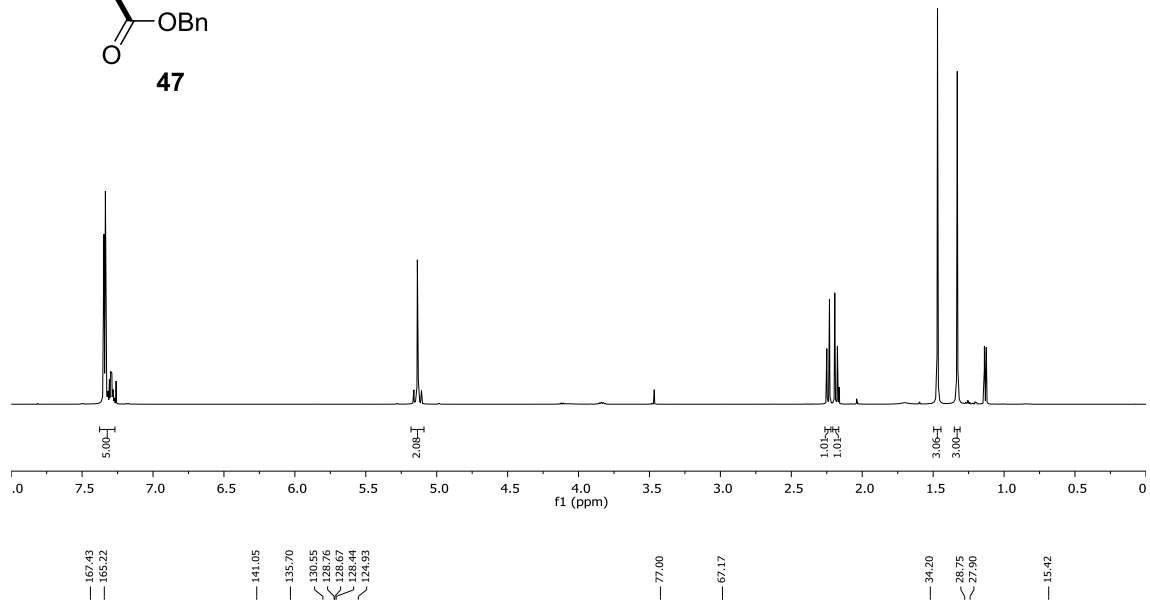
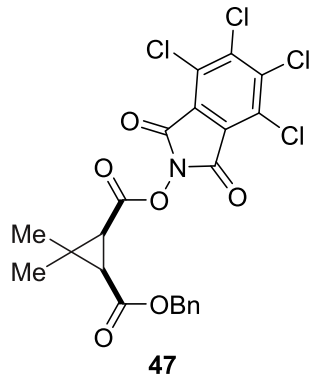
(1*S*,3*R*)-3-((Benzyloxy)carbonyl)-2,2-dimethylcyclopropane-1-carboxylic acid

Experimental section

(1*R*,2*S*)-2-((Benzyloxy)carbonyl)cyclopropane-1-carboxylic acid

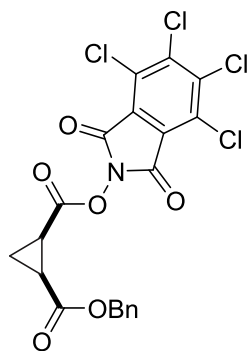


1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) dimethylcyclopropane-1,2-dicarboxylate (47)

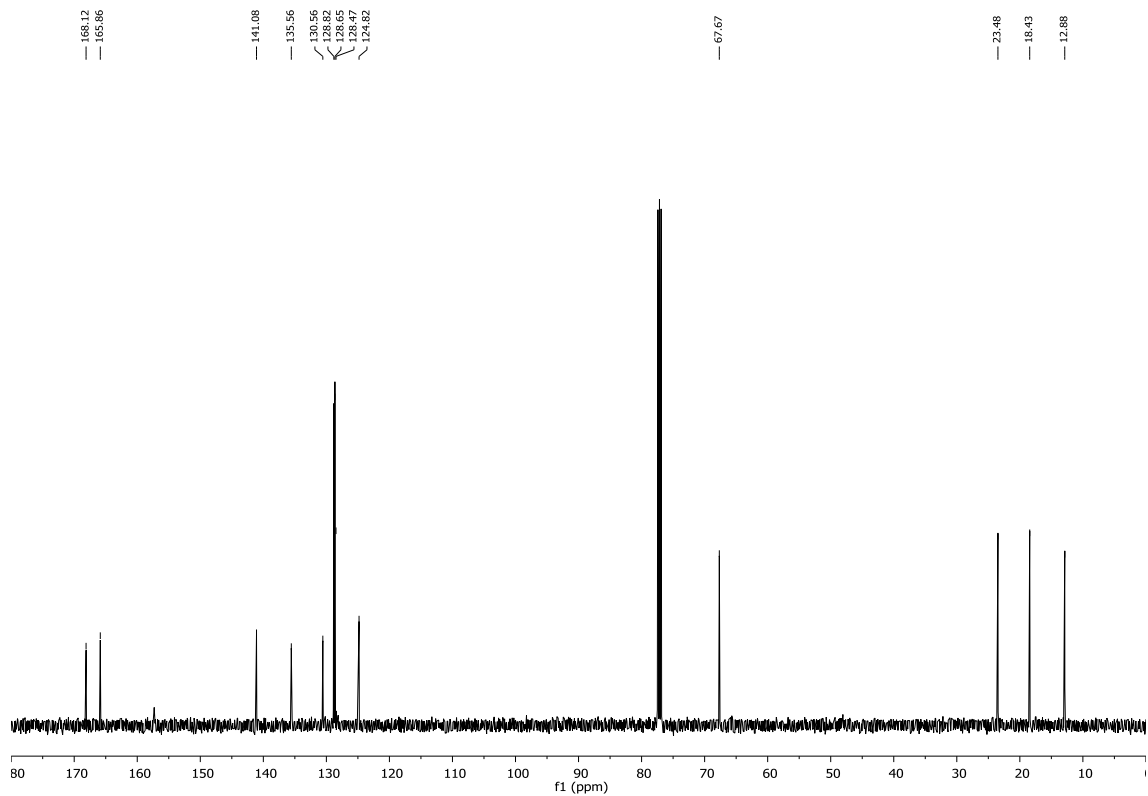
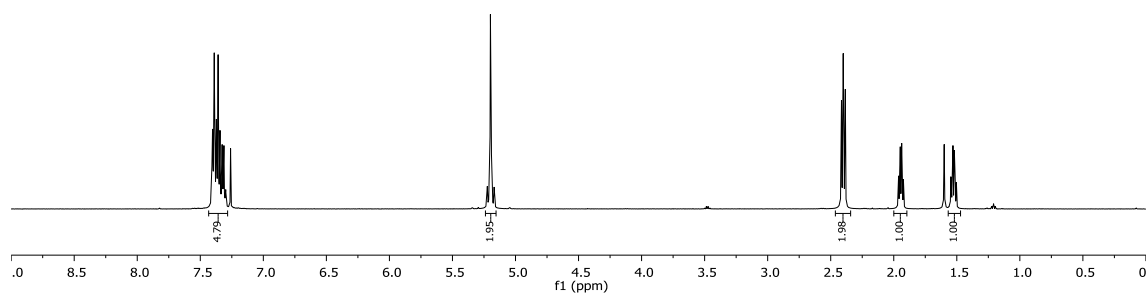


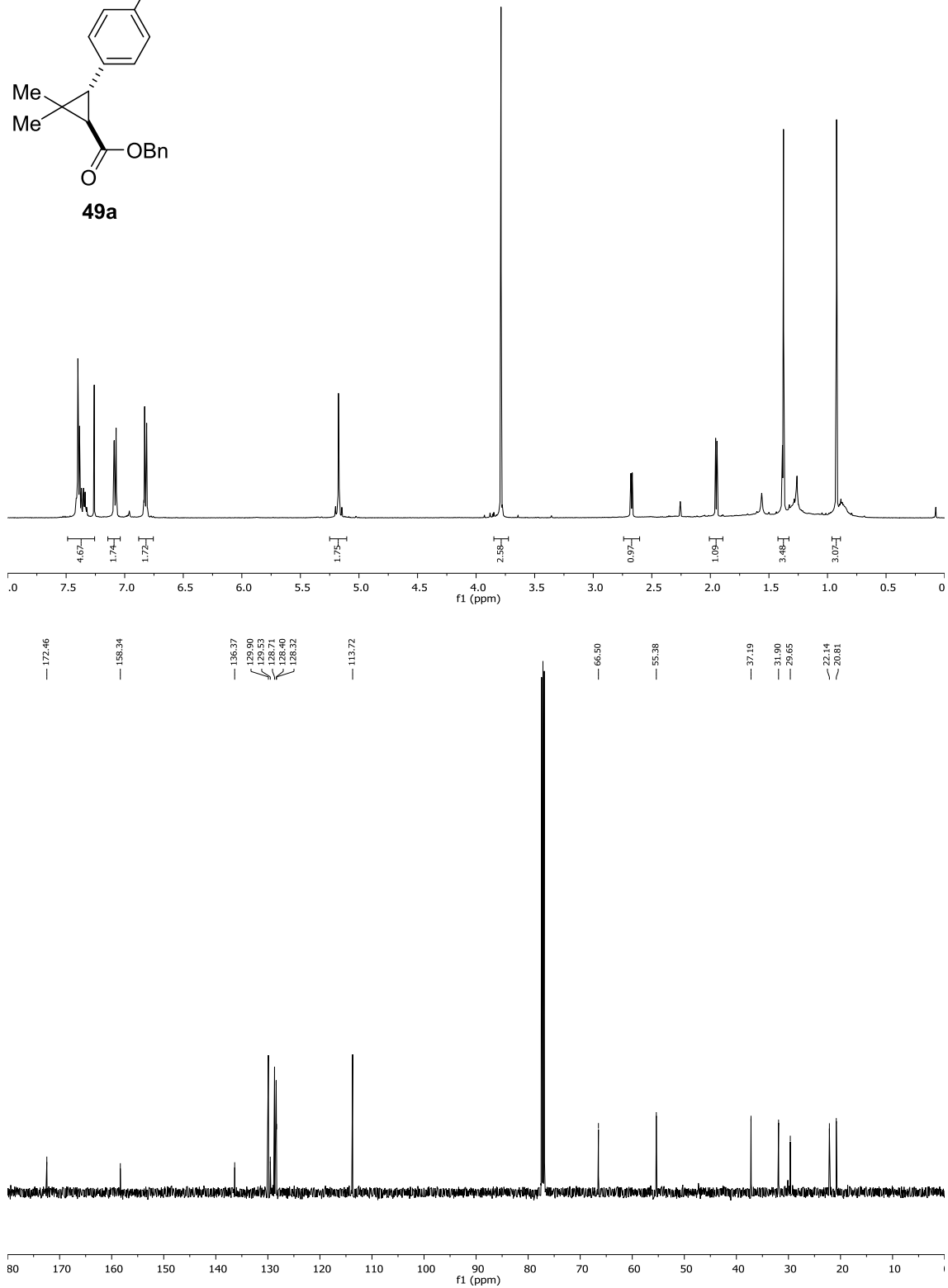
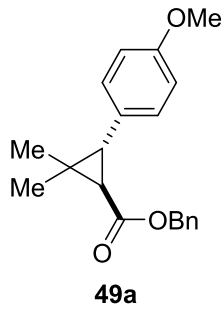
Experimental section

1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) (1*R*,2*S*)-cyclopropane-1,2-dicarboxylate (**48**)



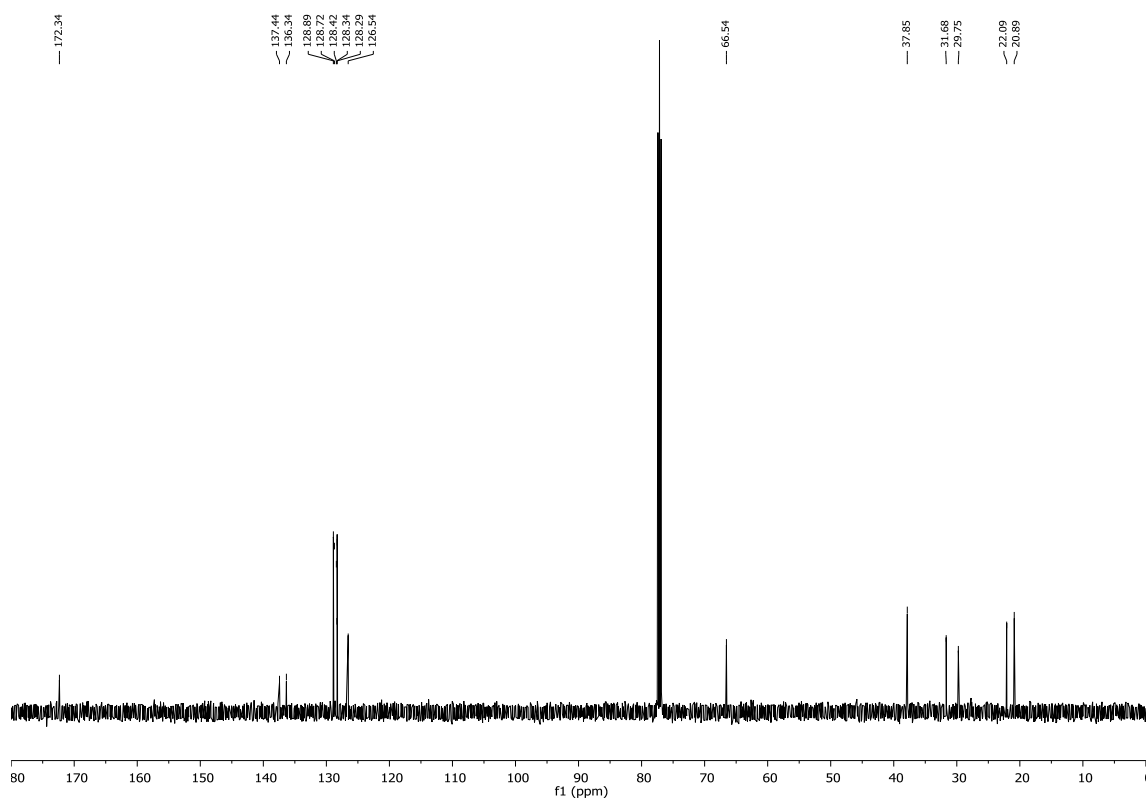
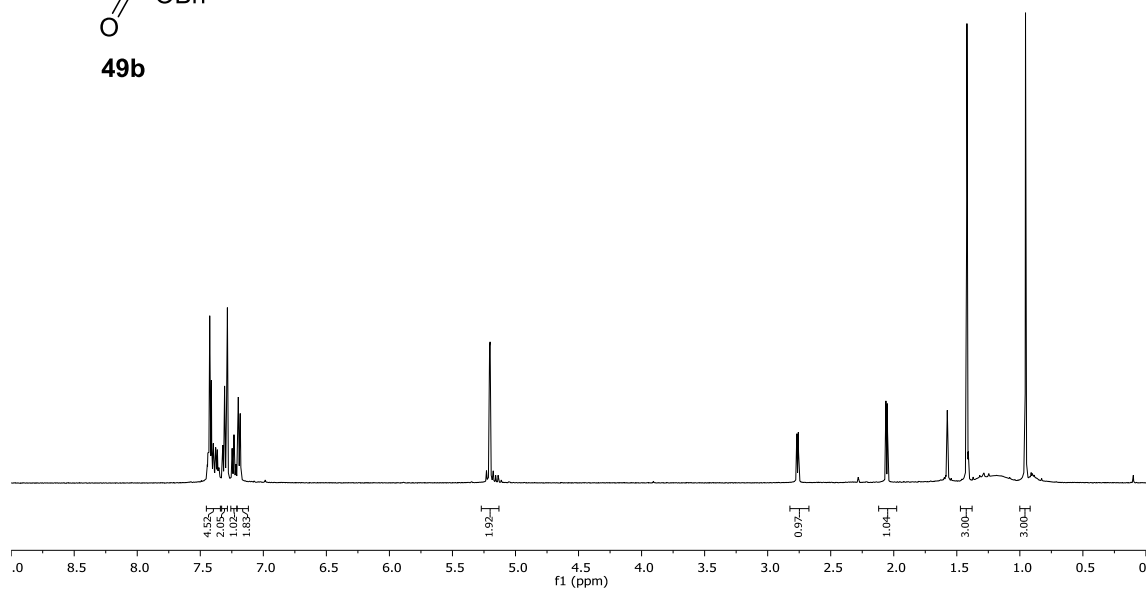
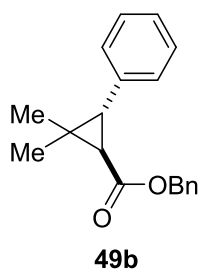
48

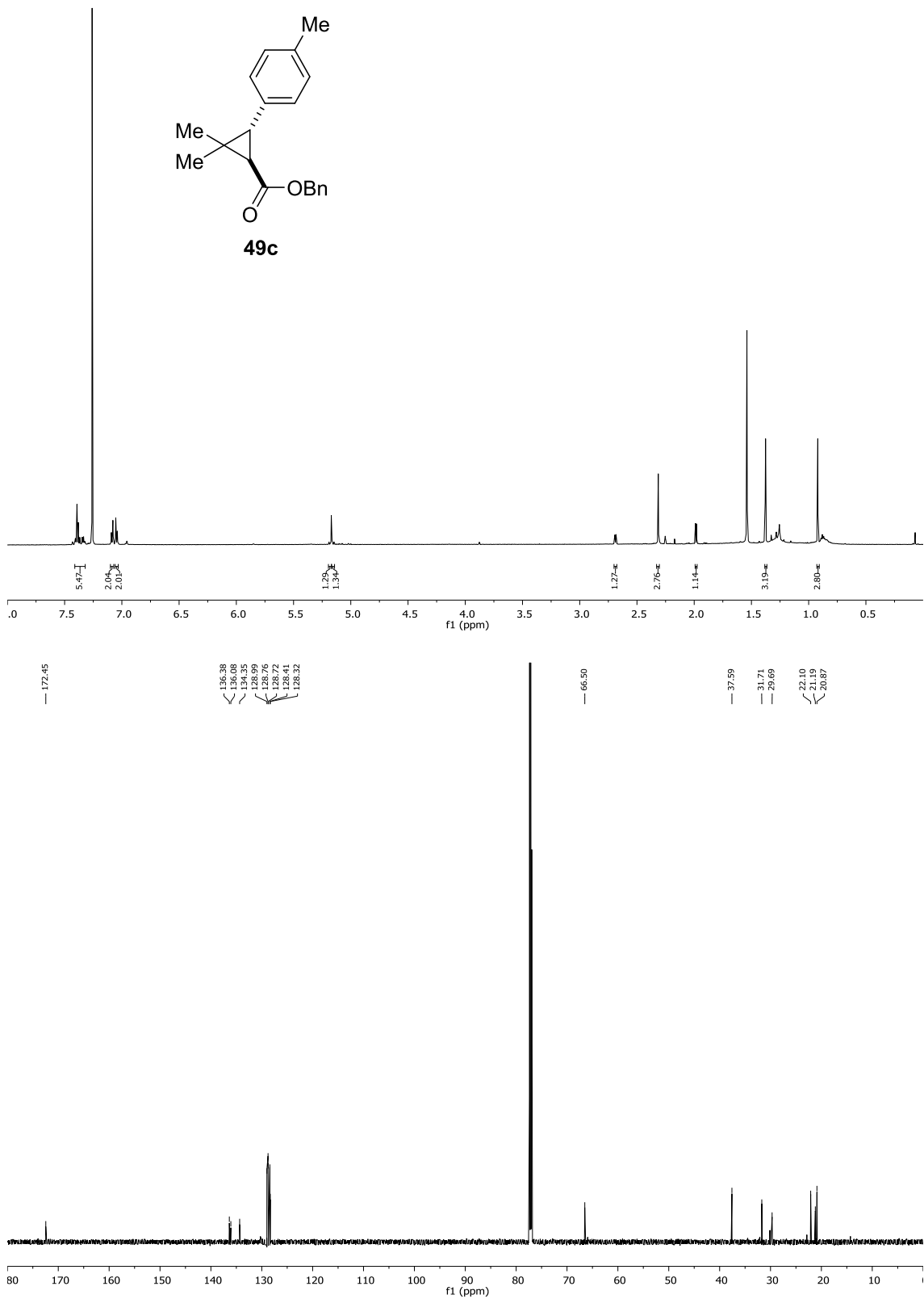


Benzyl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (49a)

Experimental section

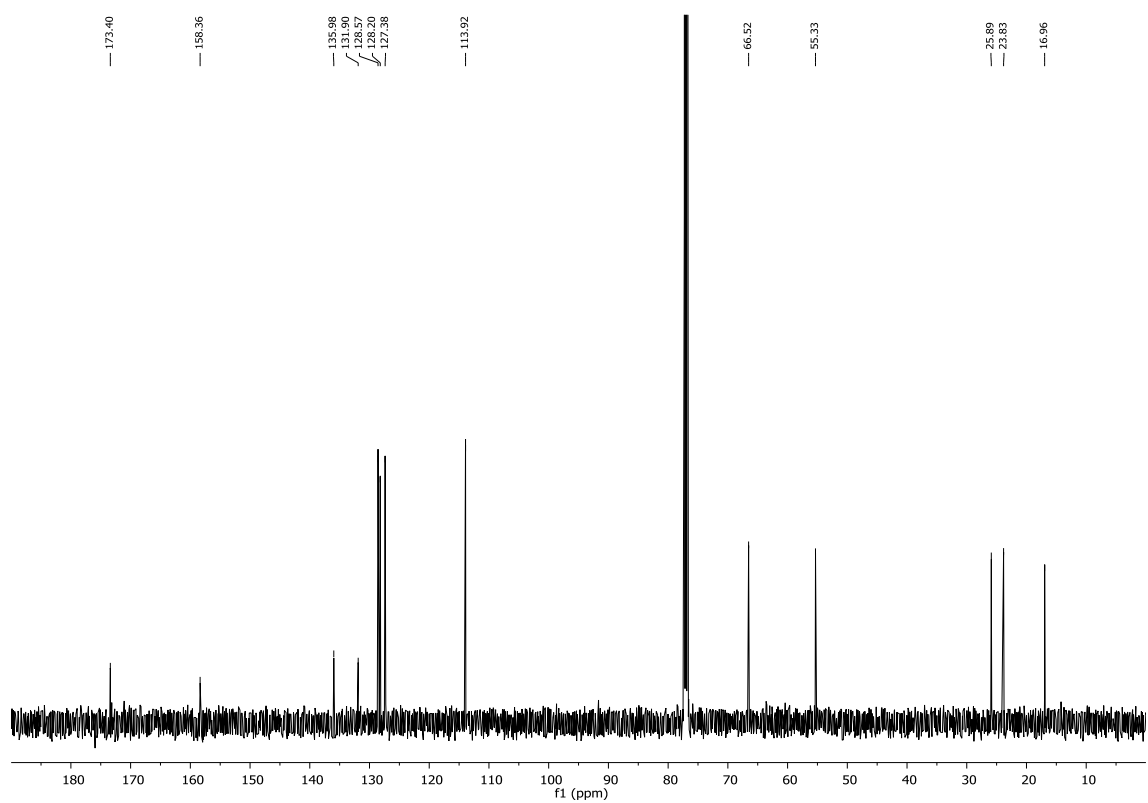
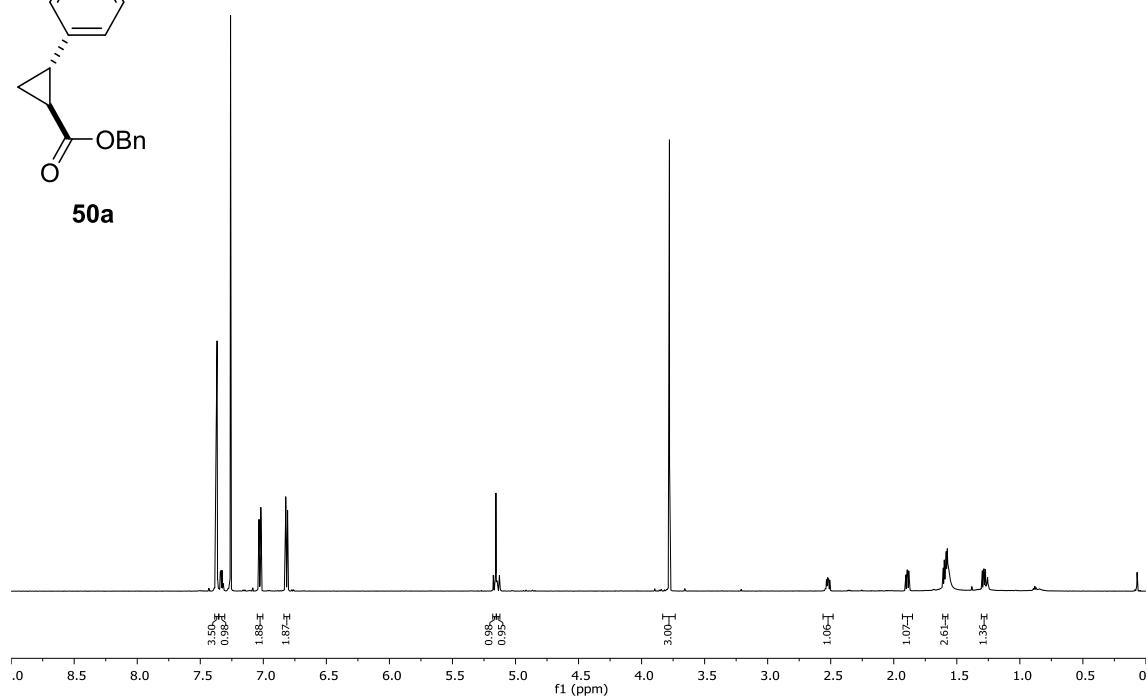
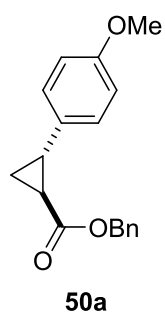
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (**49b**)

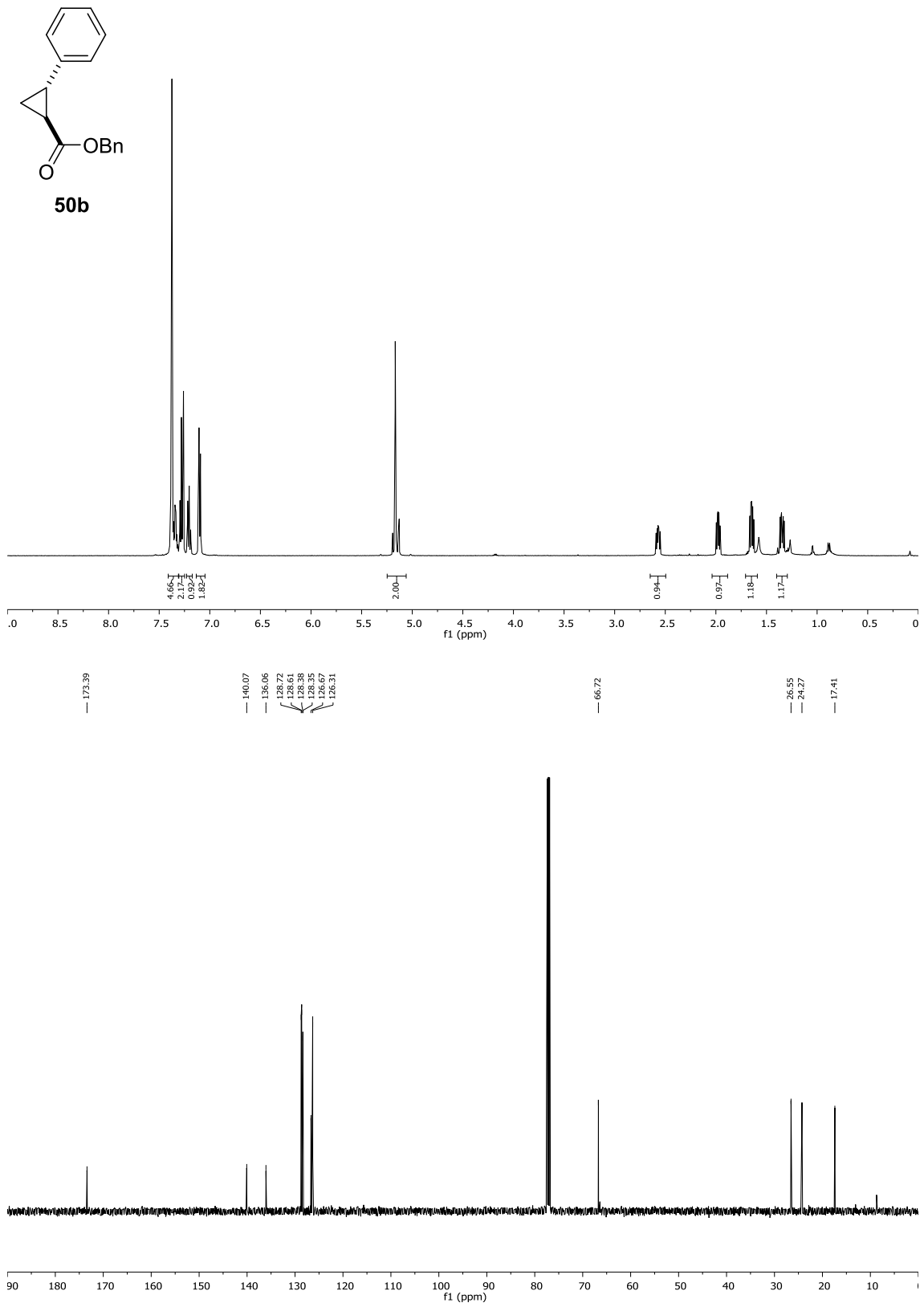


Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropane-1-carboxylate (49c)

Experimental section

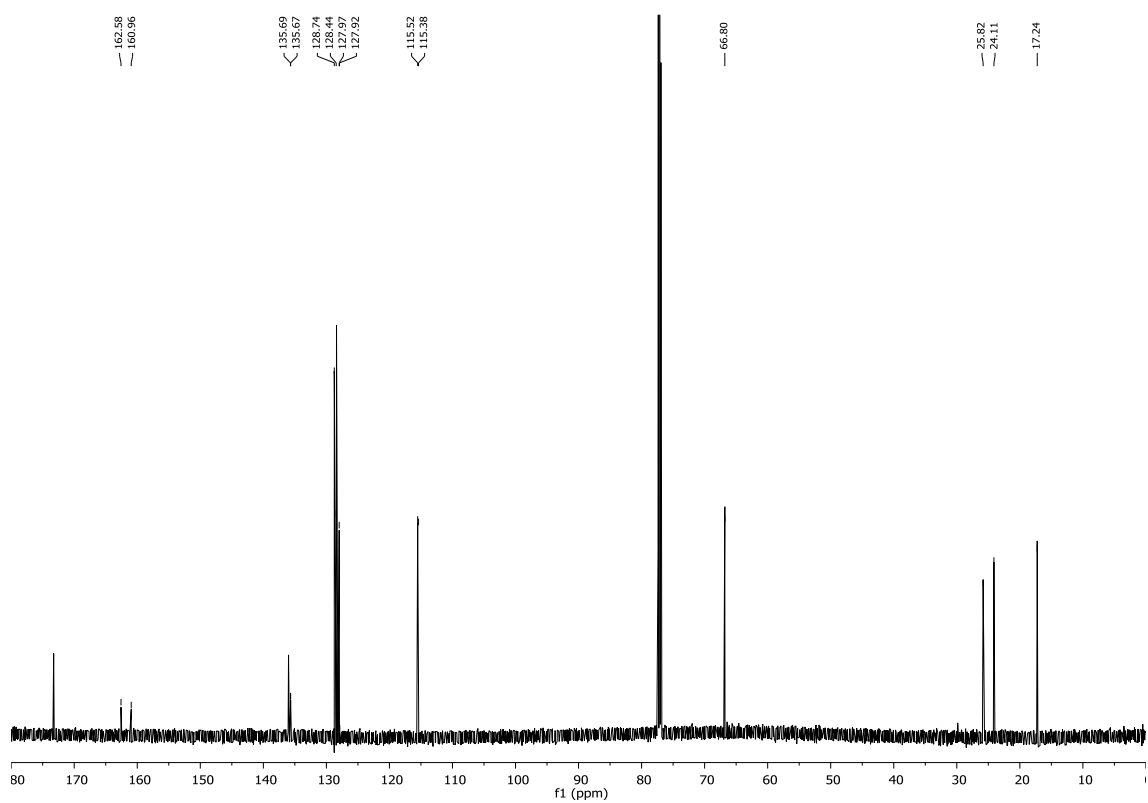
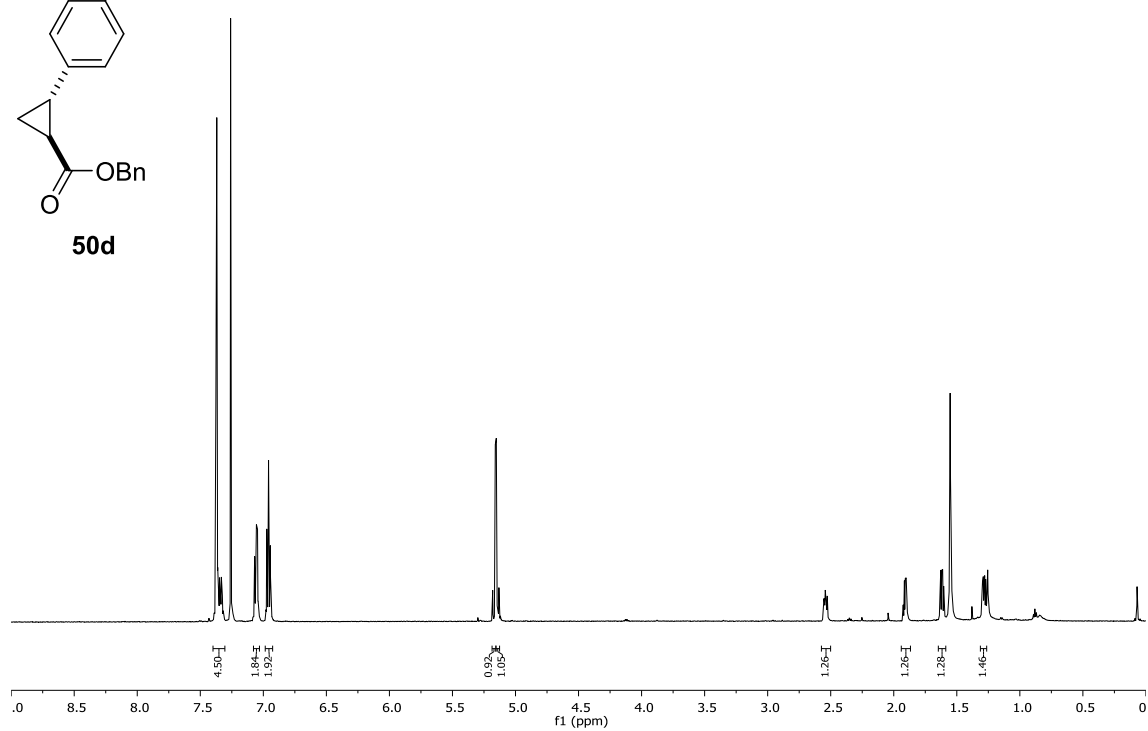
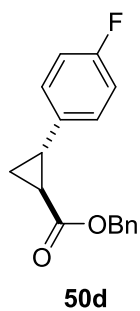
Benzyl (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (50a)



Benzyl (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylate (**50b**)

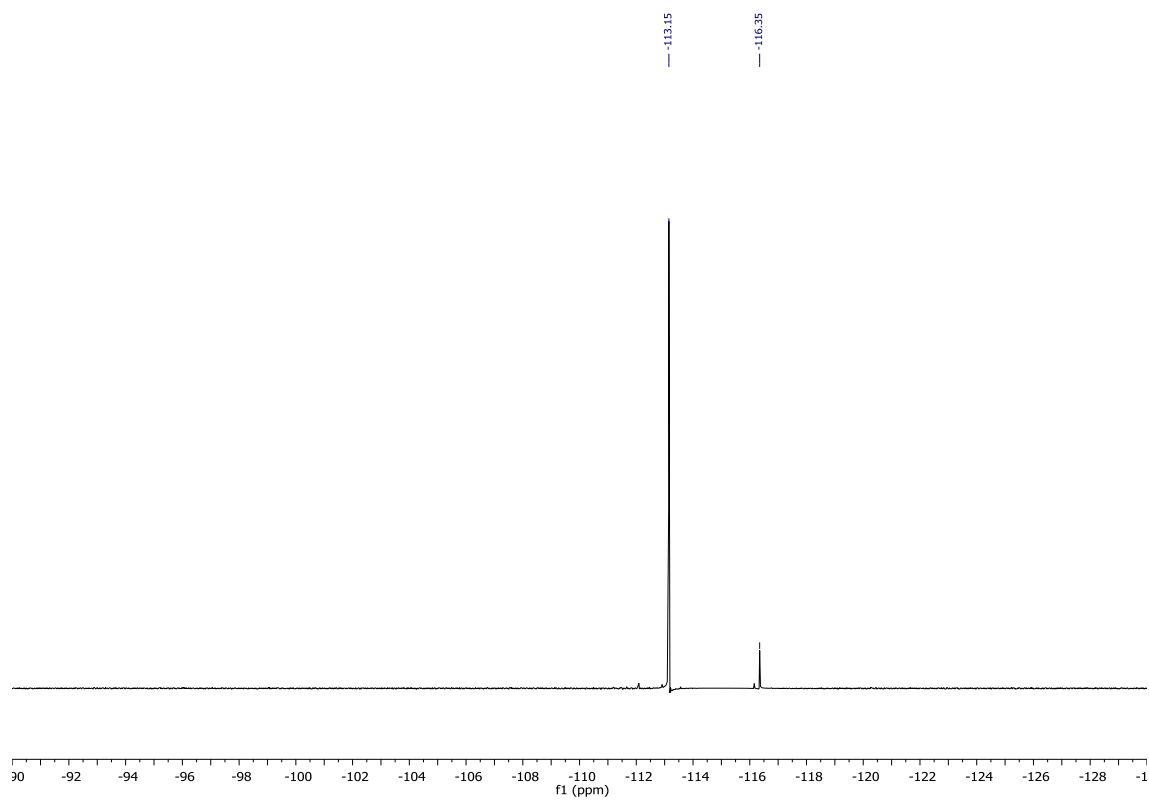
Experimental section

Benzyl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (**50d**)



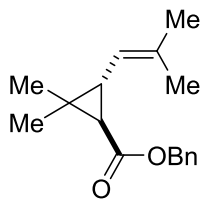
Chapter 6

^{19}F NMR:

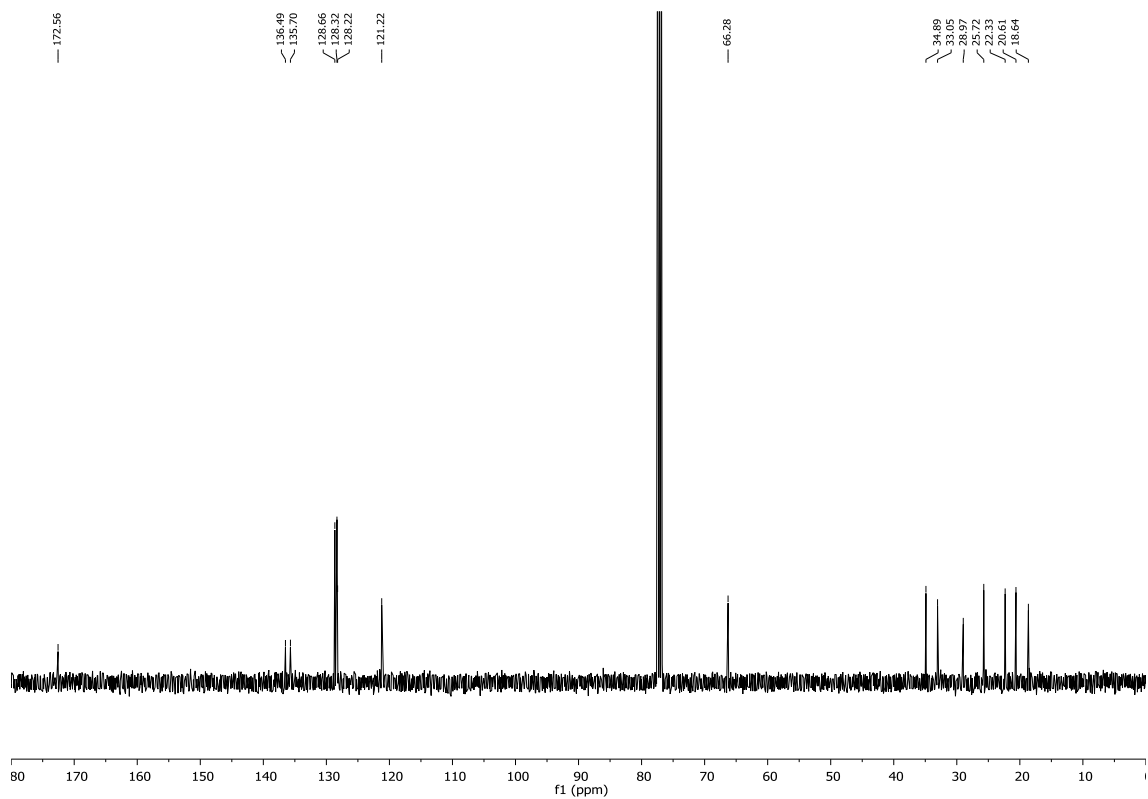
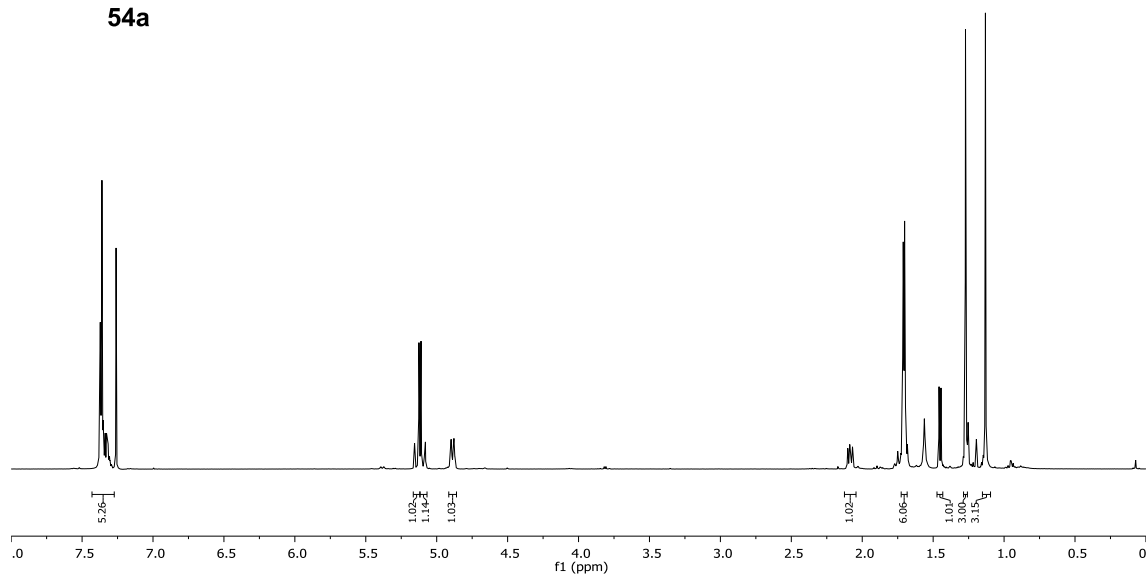


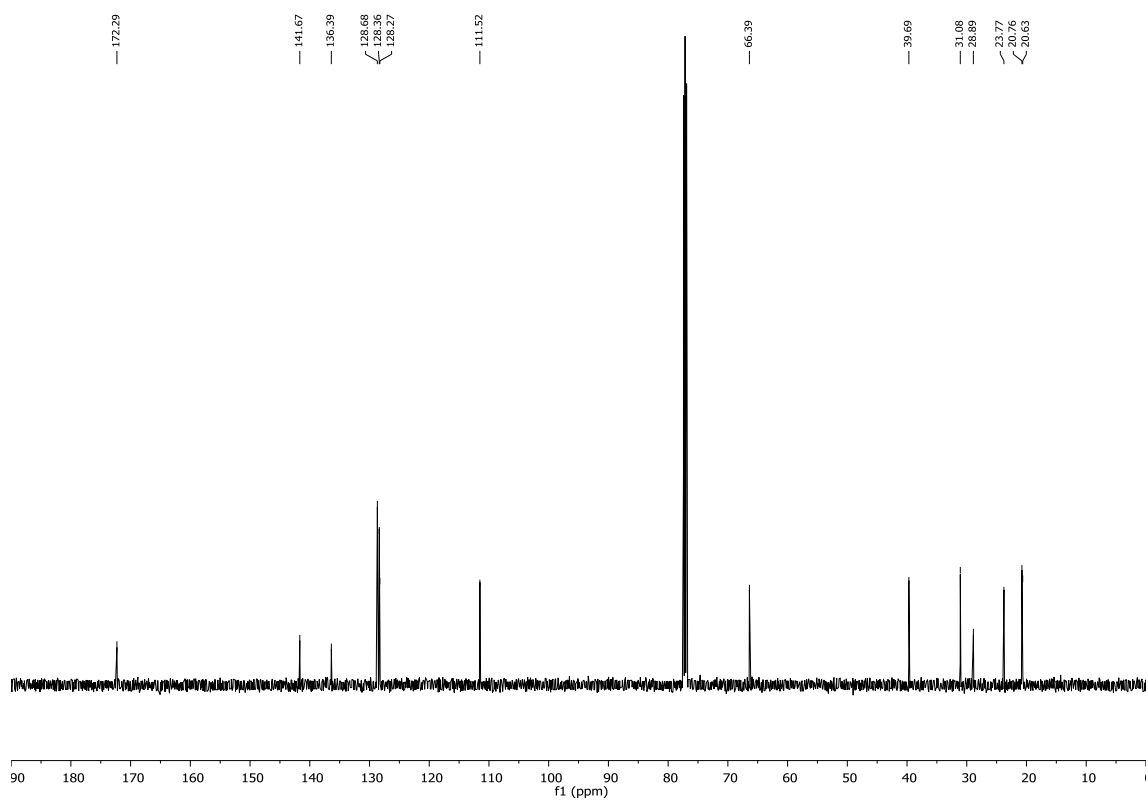
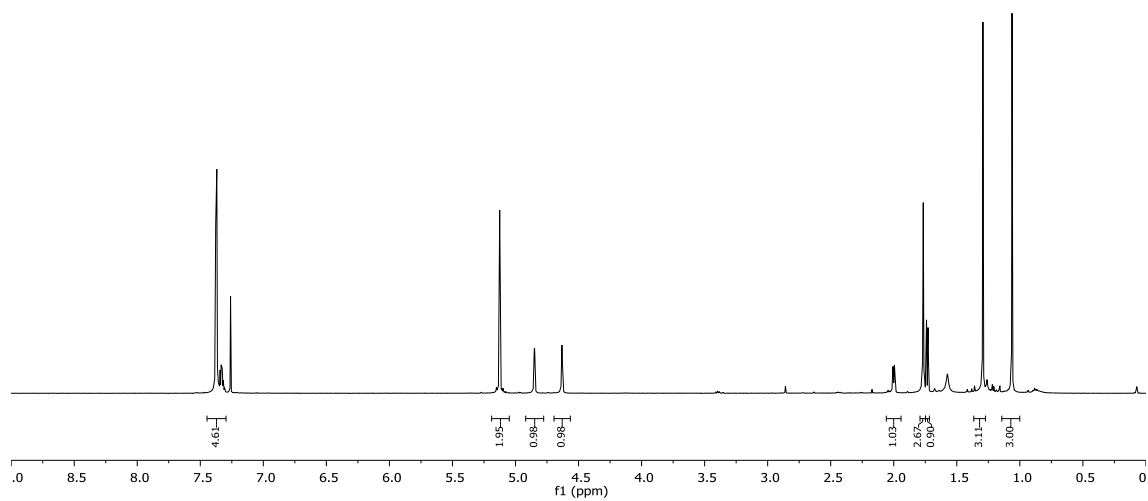
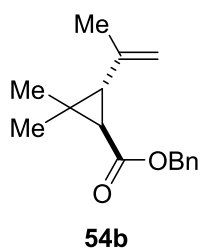
Experimental section

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (54a)



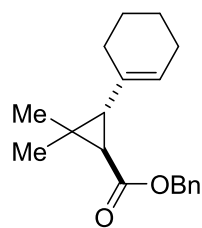
54a



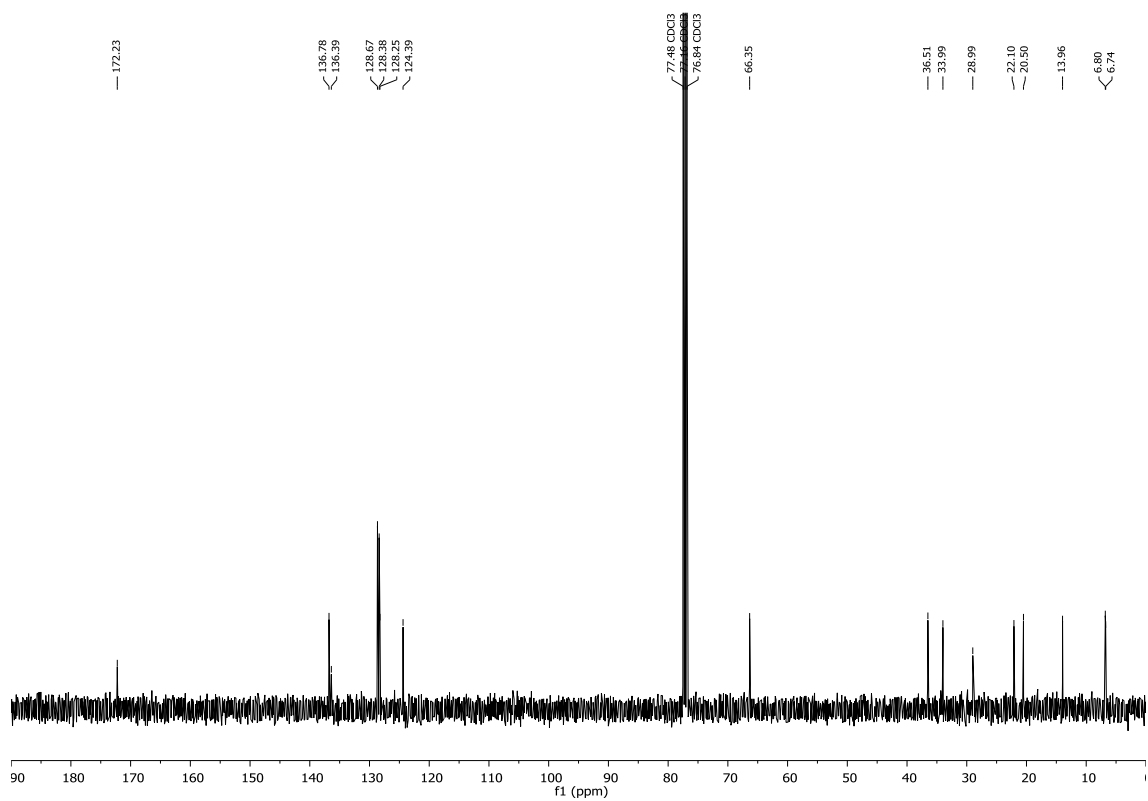
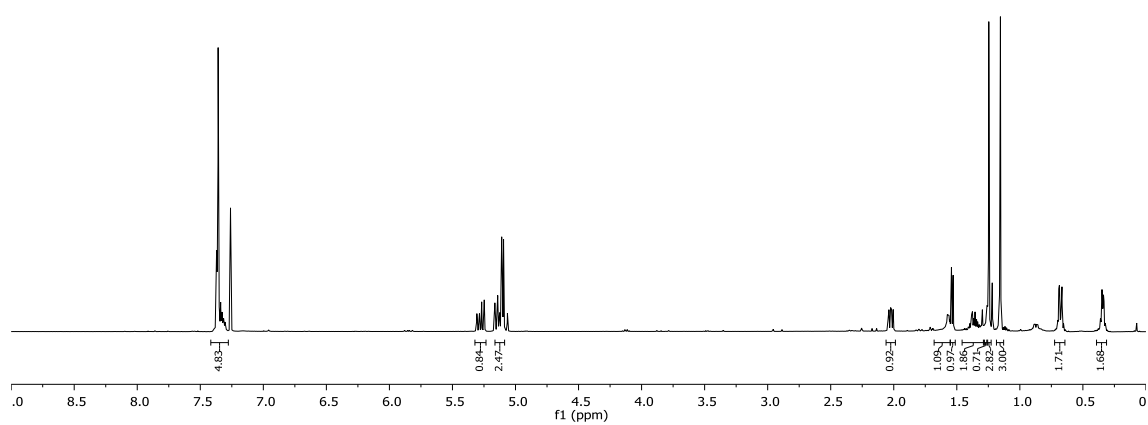
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(prop-1-en-2-yl)cyclopropane-1-carboxylate (**54b**)

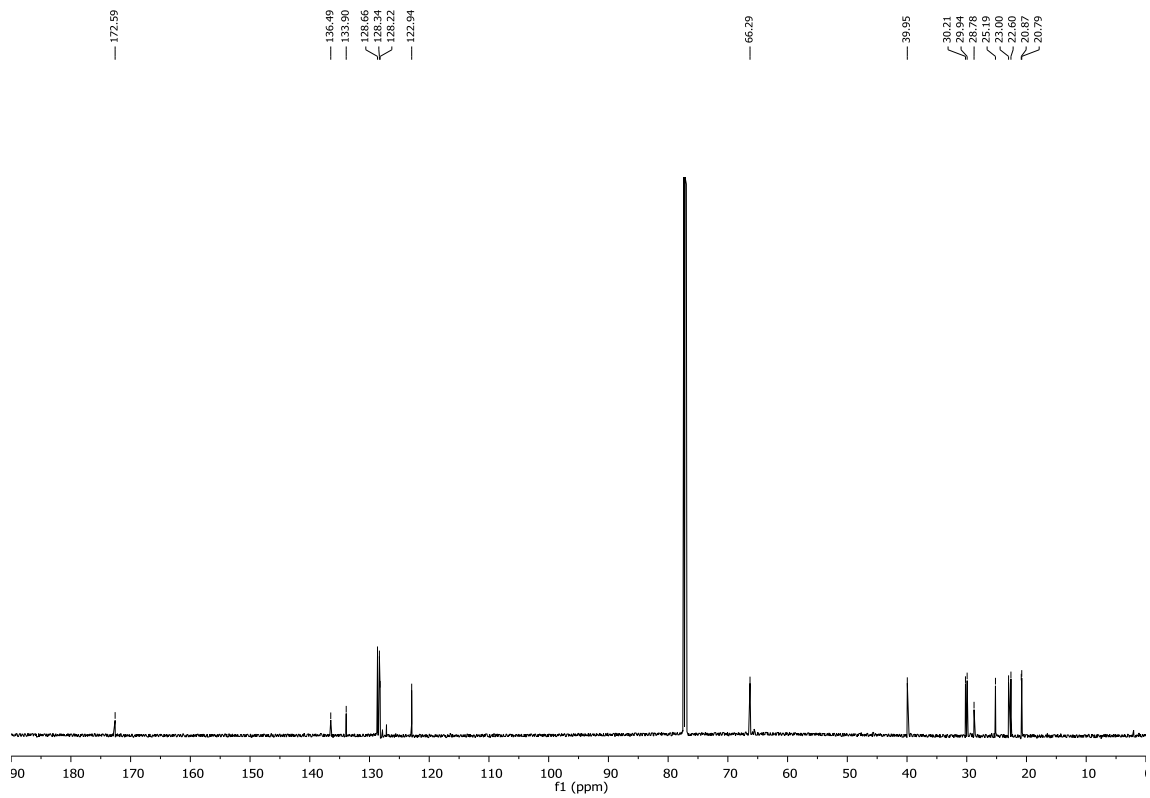
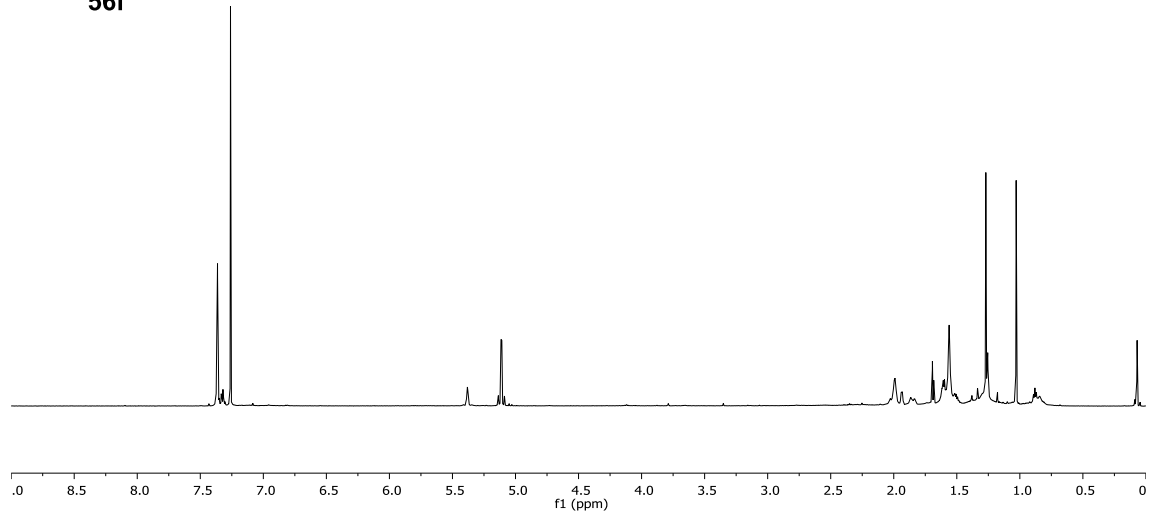
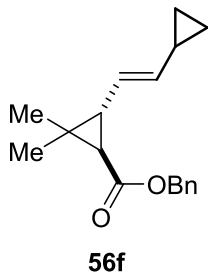
Experimental section

Benzyl (1*R*,3*R*)-3-(cyclohex-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylate (54c)



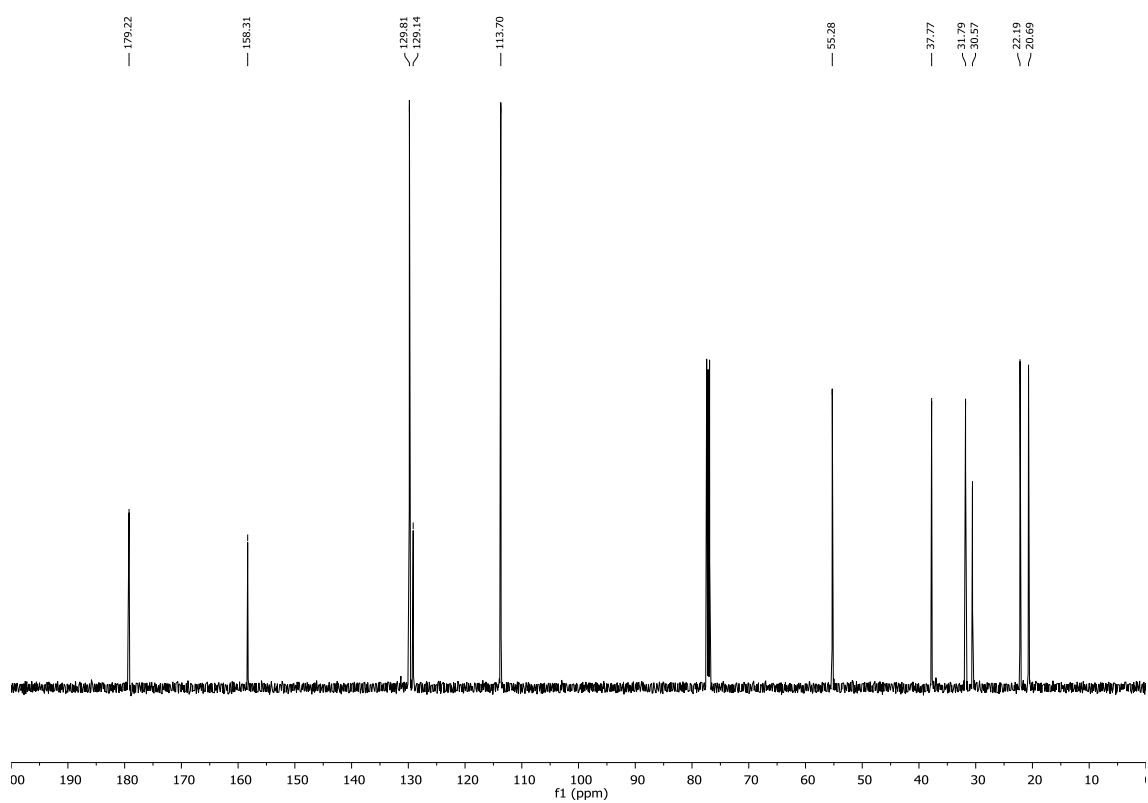
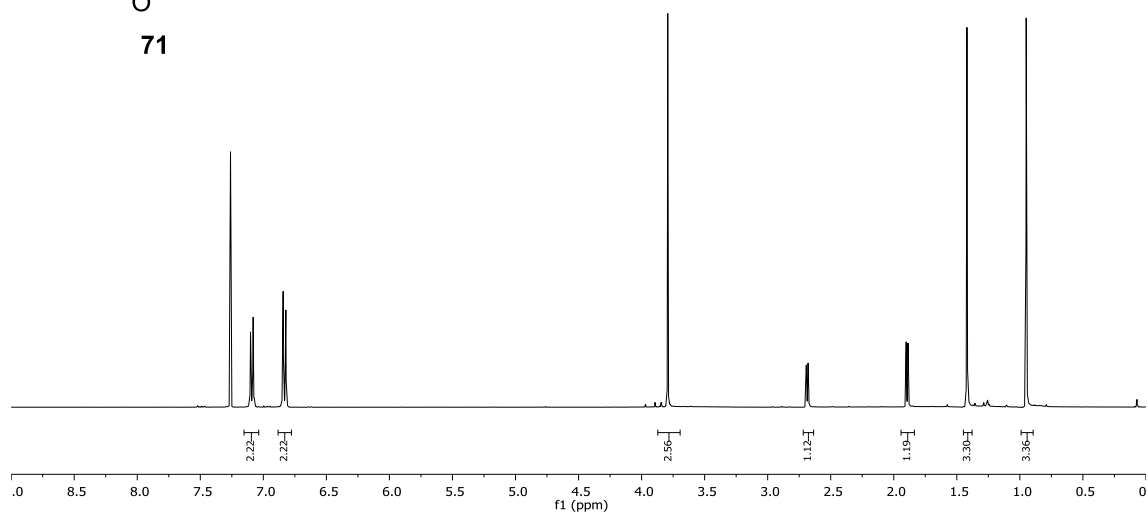
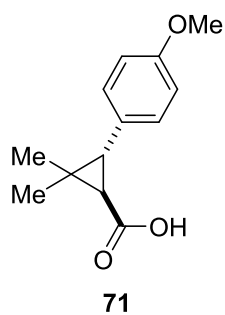
54c

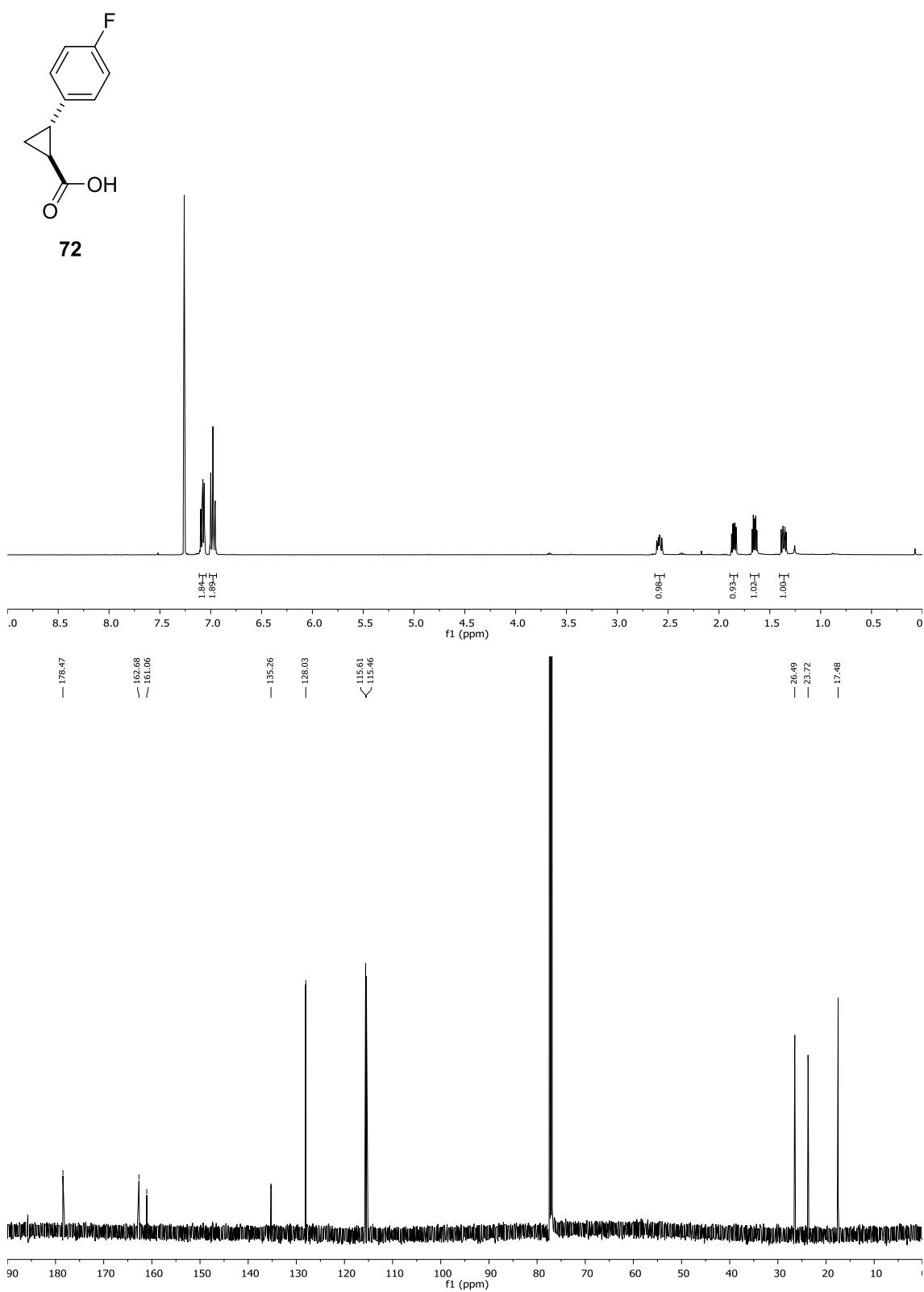


Benzyl (1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropane-1-carboxylate (54f)

Experimental section

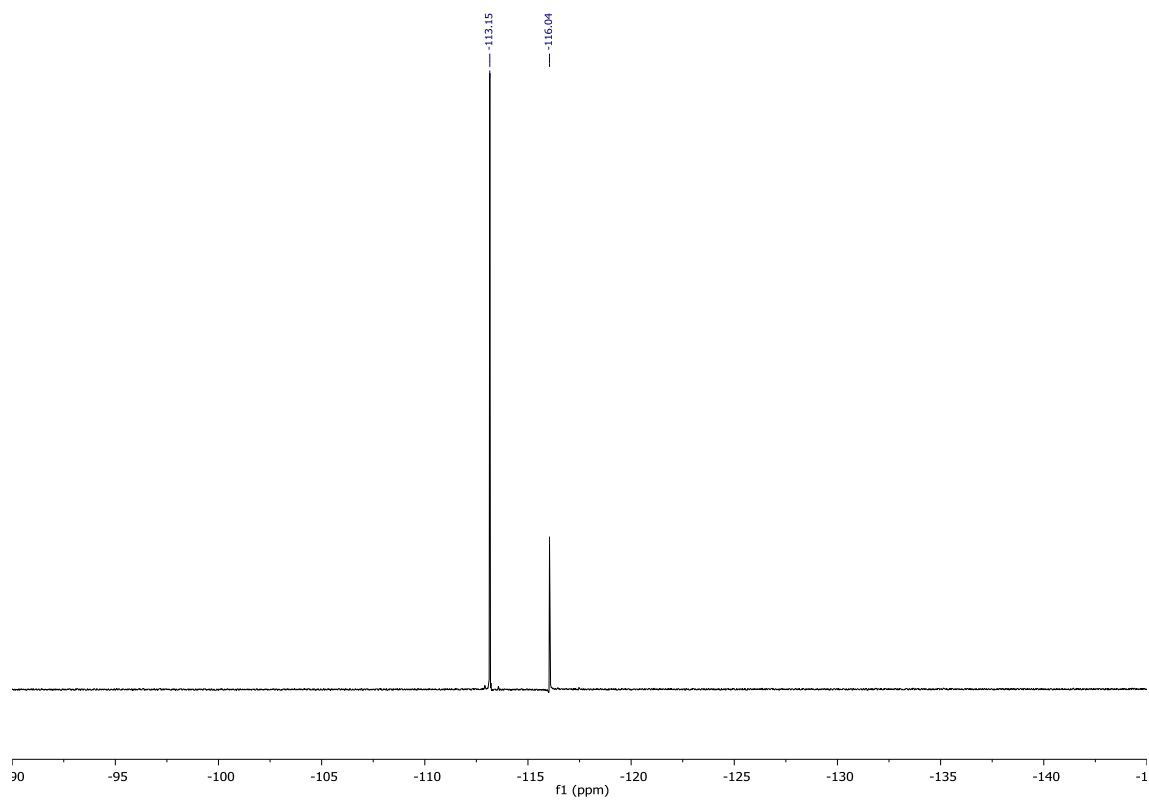
(1*R*,3*R*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylic acid (71)



(1*S*,2*S*)-2-(4-Fluorophenyl)cyclopropane-1-carboxylic acid (72)

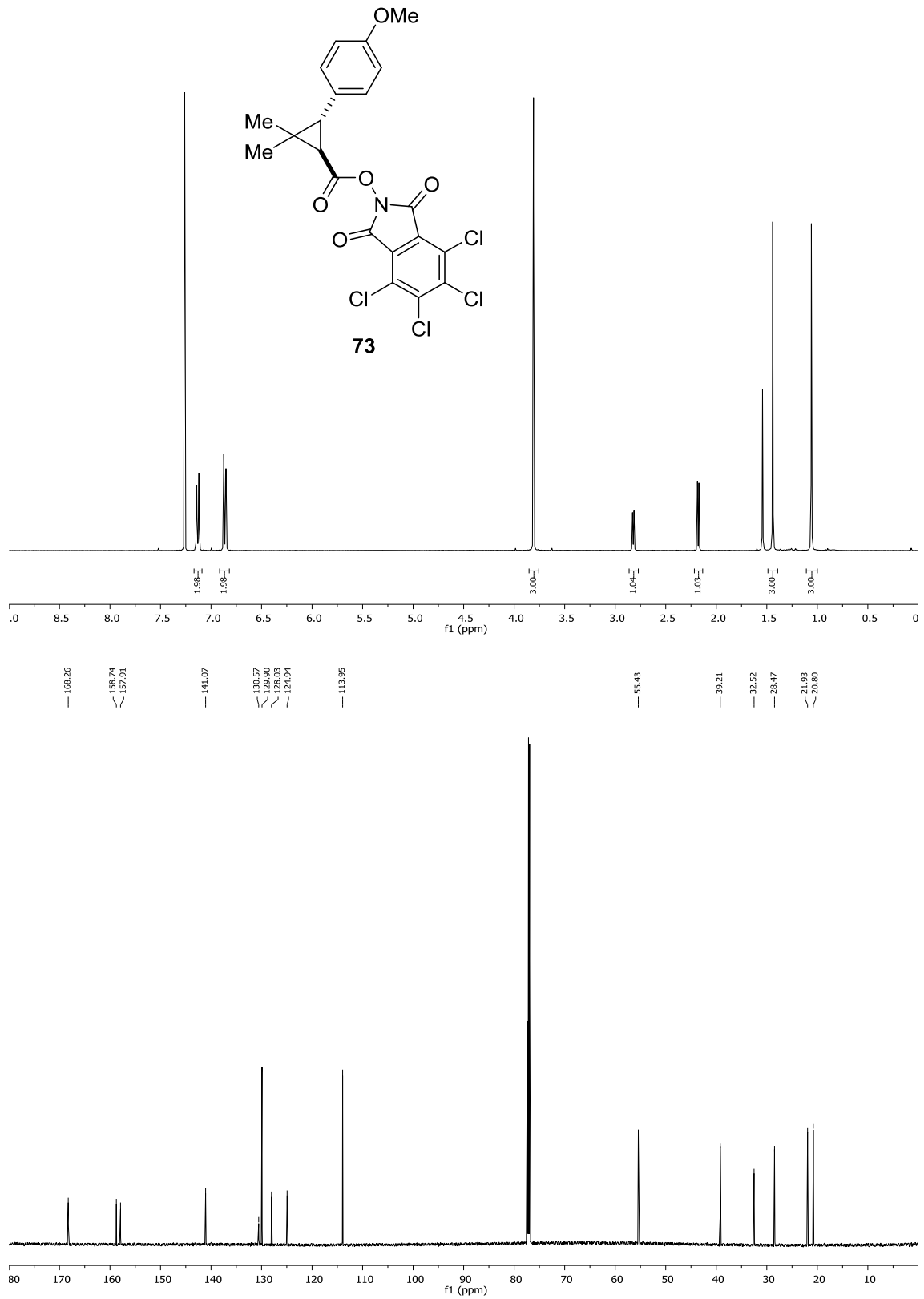
Experimental section

^{19}F NMR:



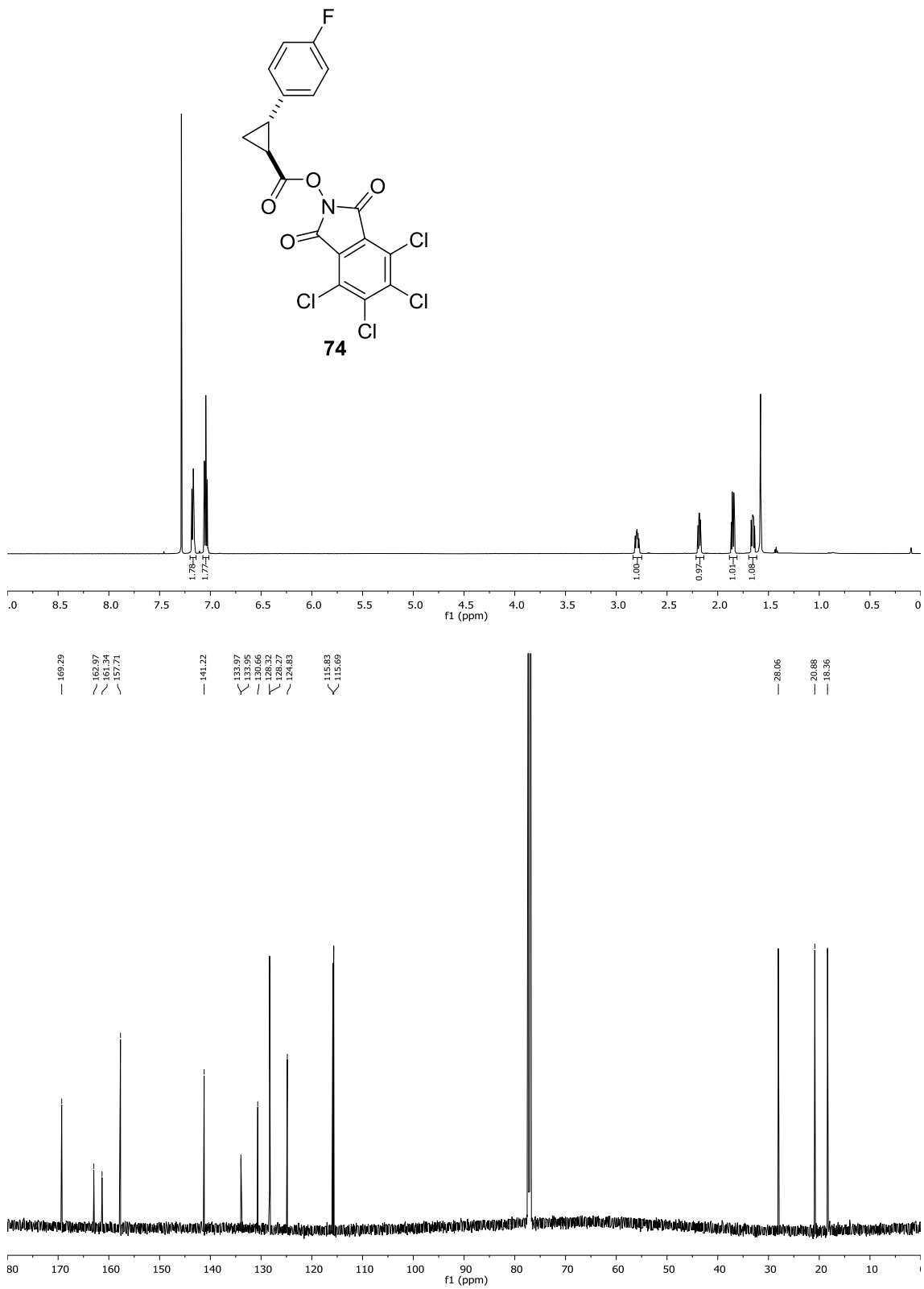
**4,5,6,7-Tetrachloro-1,3-dioxisoindolin-2-yl
dimethylcyclopropane-1-carboxylate (73)**

(1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-



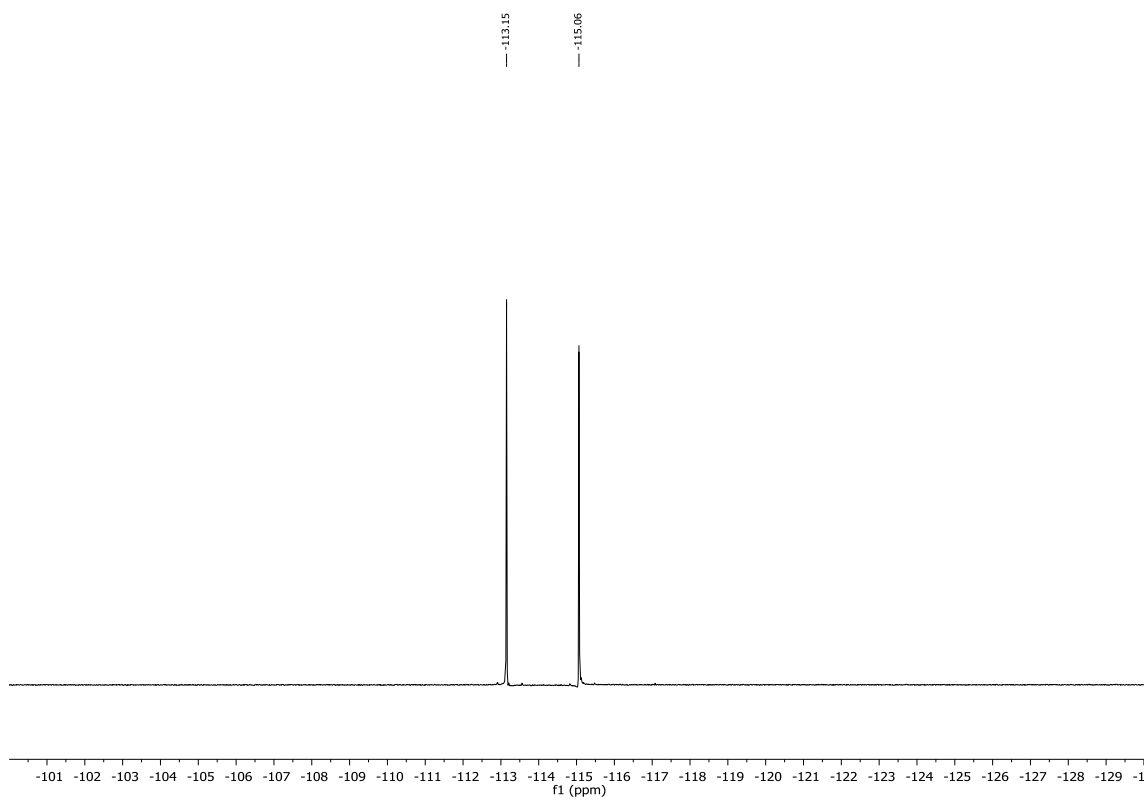
Experimental section

4,5,6,7-Tetrachloro-1,3-dioxisoindolin-2-yl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (74)



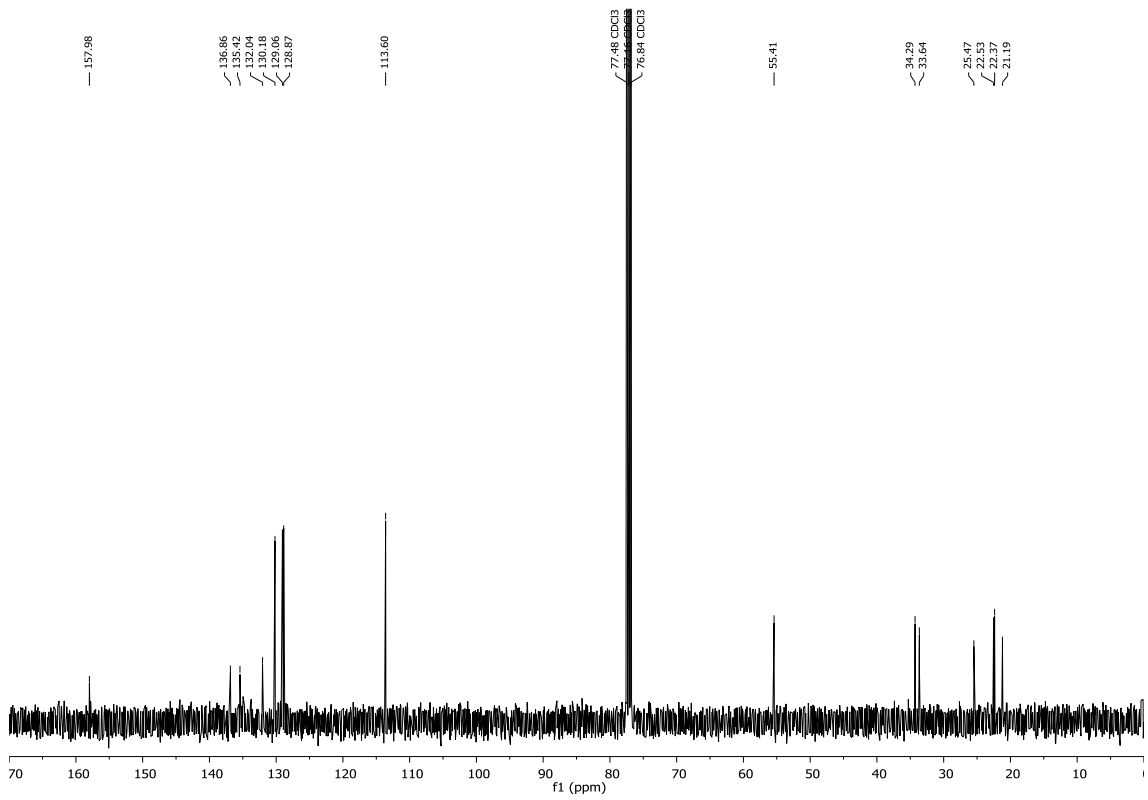
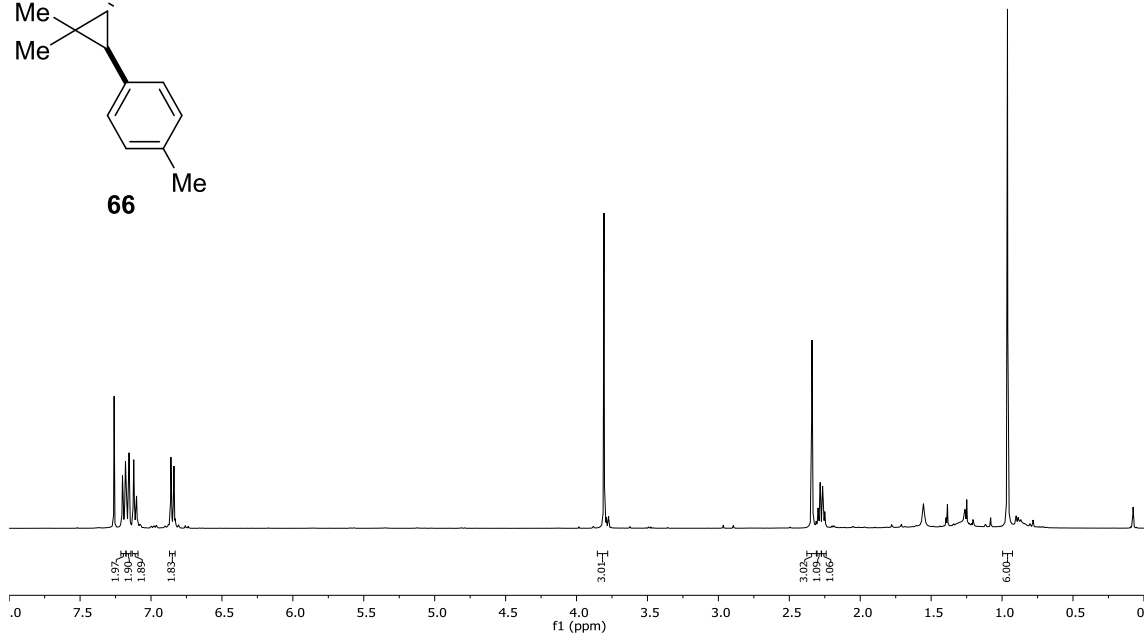
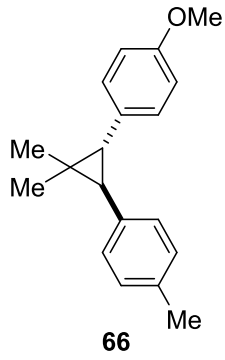
Chapter 6

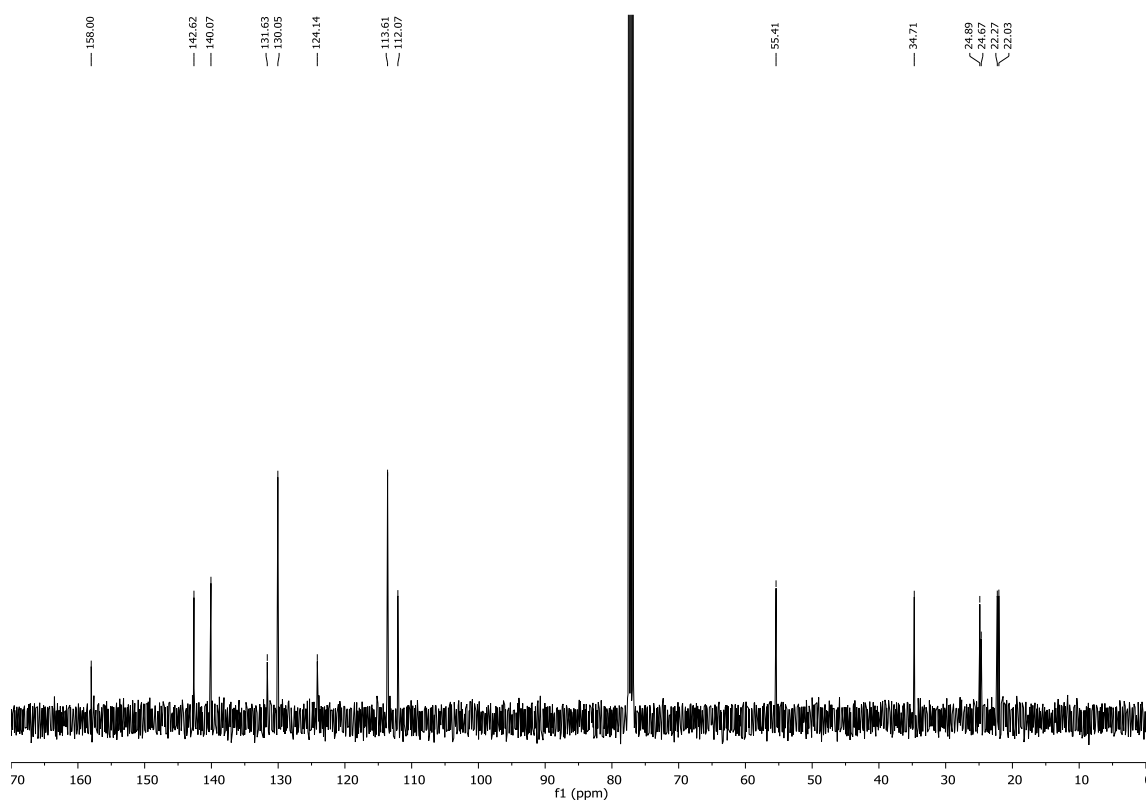
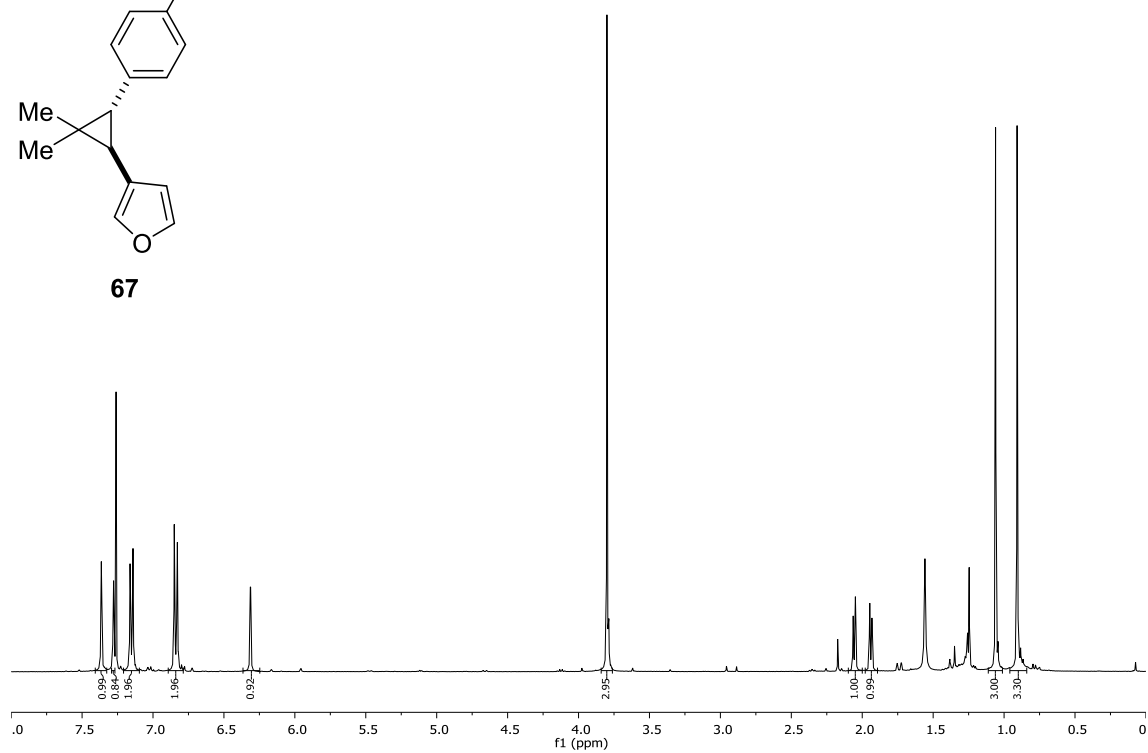
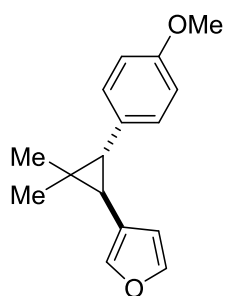
^{19}F NMR:



Experimental section

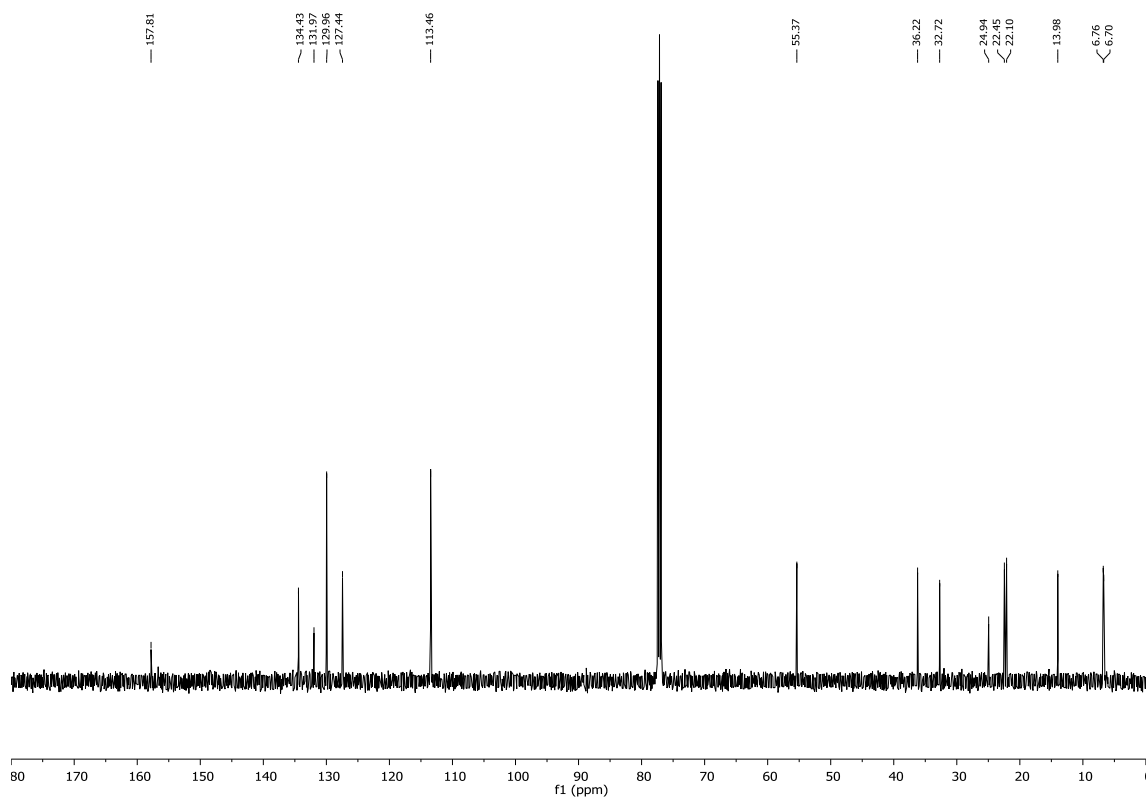
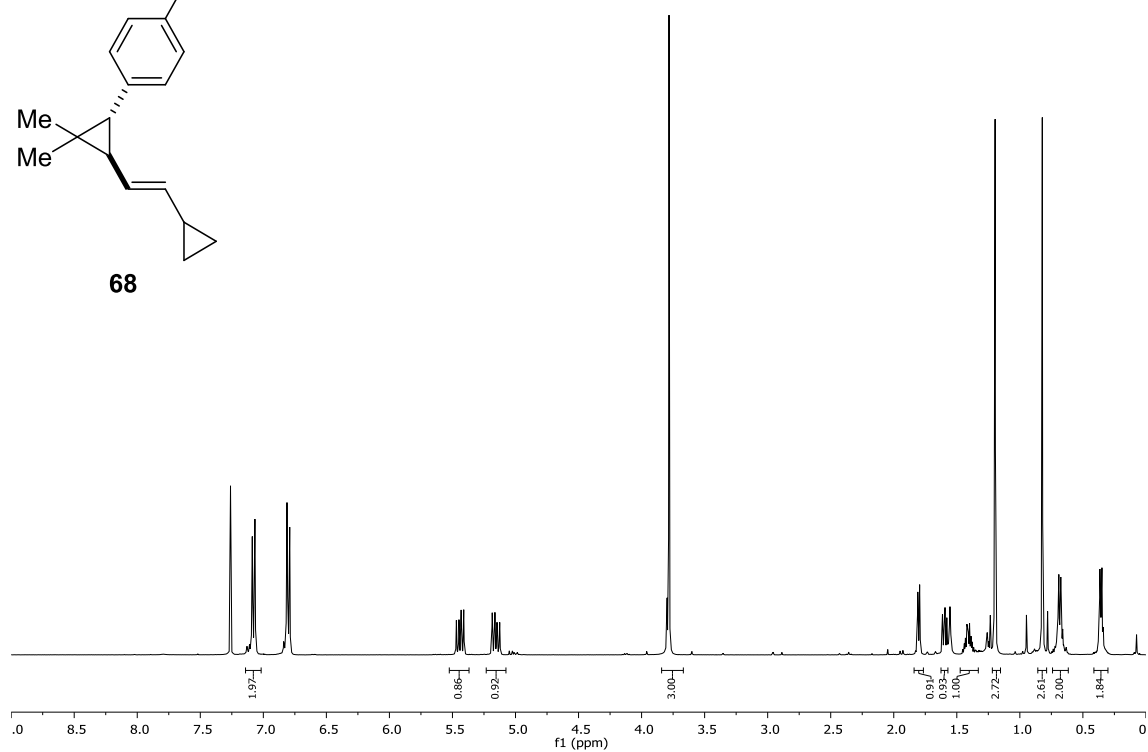
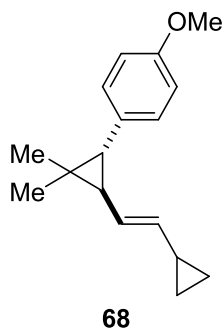
1-((1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropyl)-4-methoxybenzene (**66**)



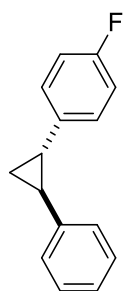
1-((1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl)furan (67)

Experimental section

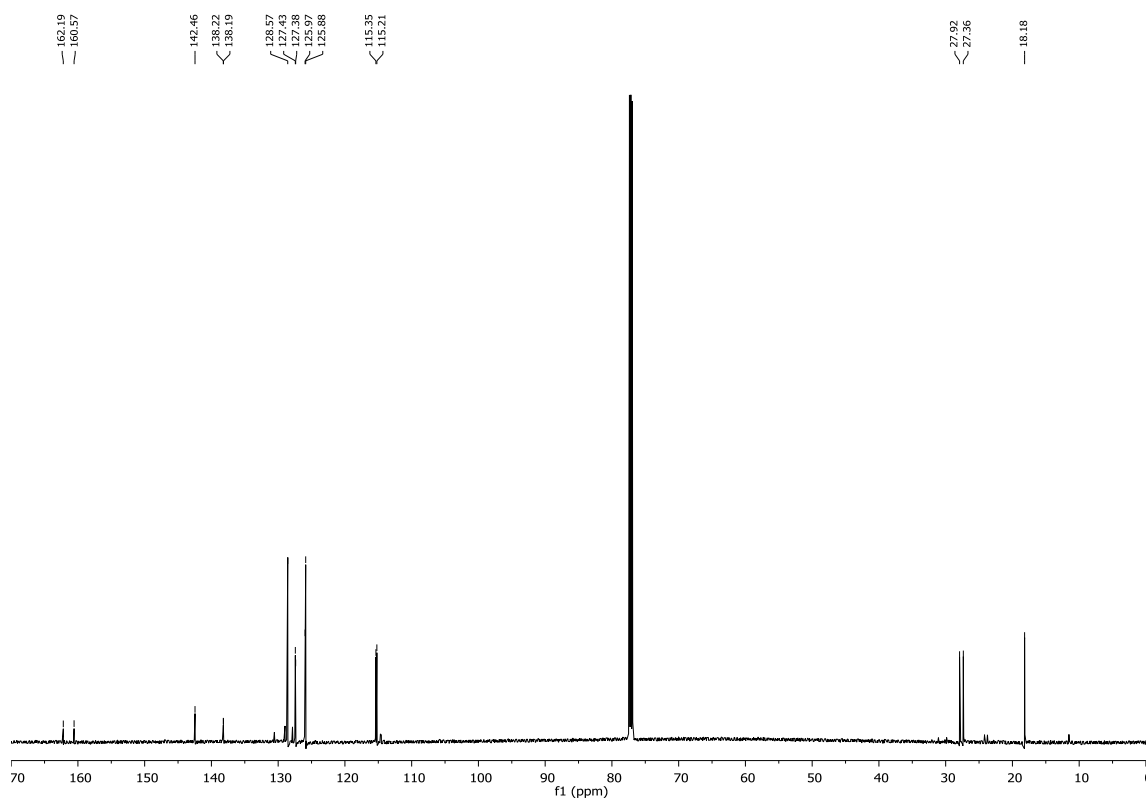
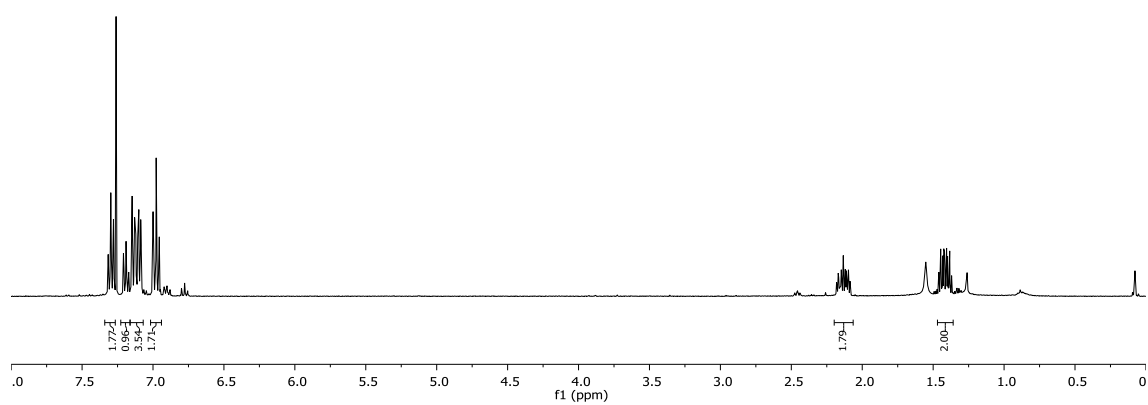
1-((1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropyl)-4-methoxybenzene (68)



1-Fluoro-4-((1S,2S)-2-phenylcyclopropyl)benzene (69)

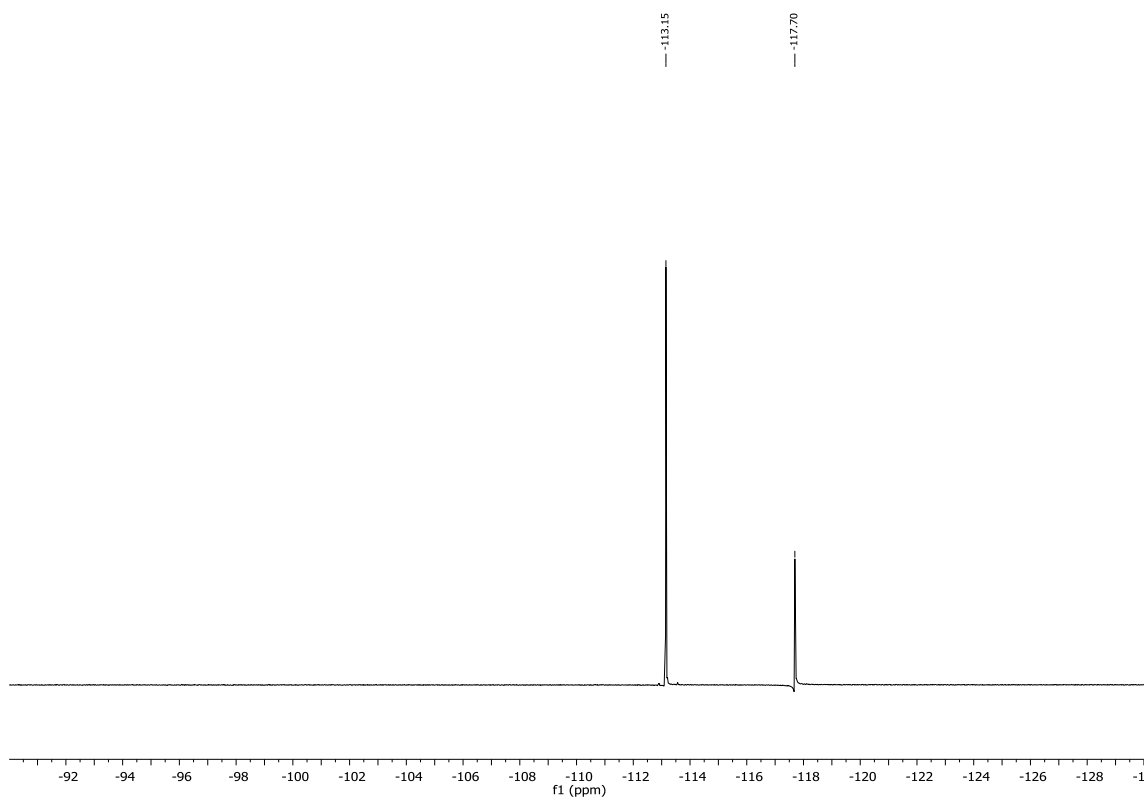


69

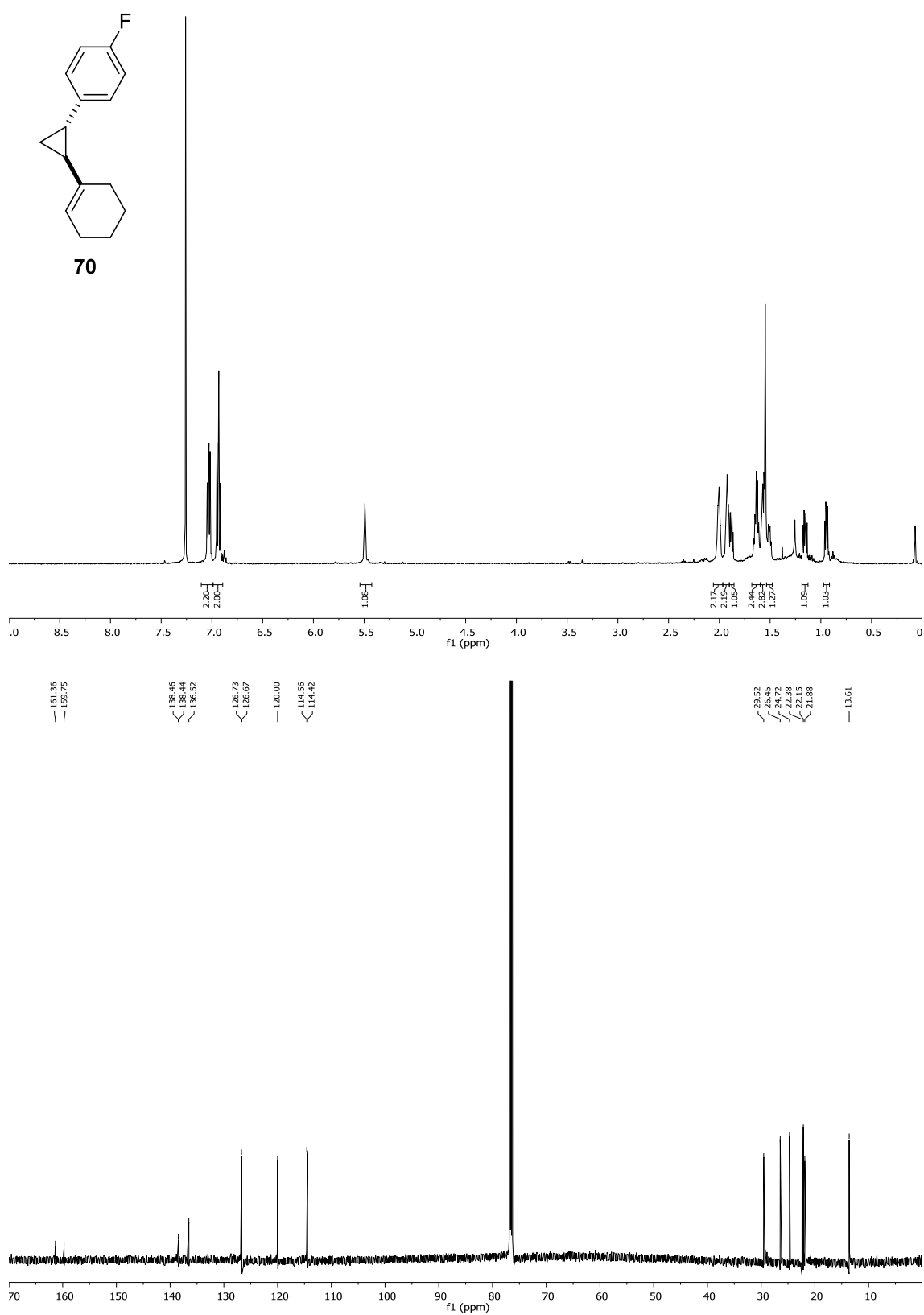


Experimental section

^{19}F NMR:

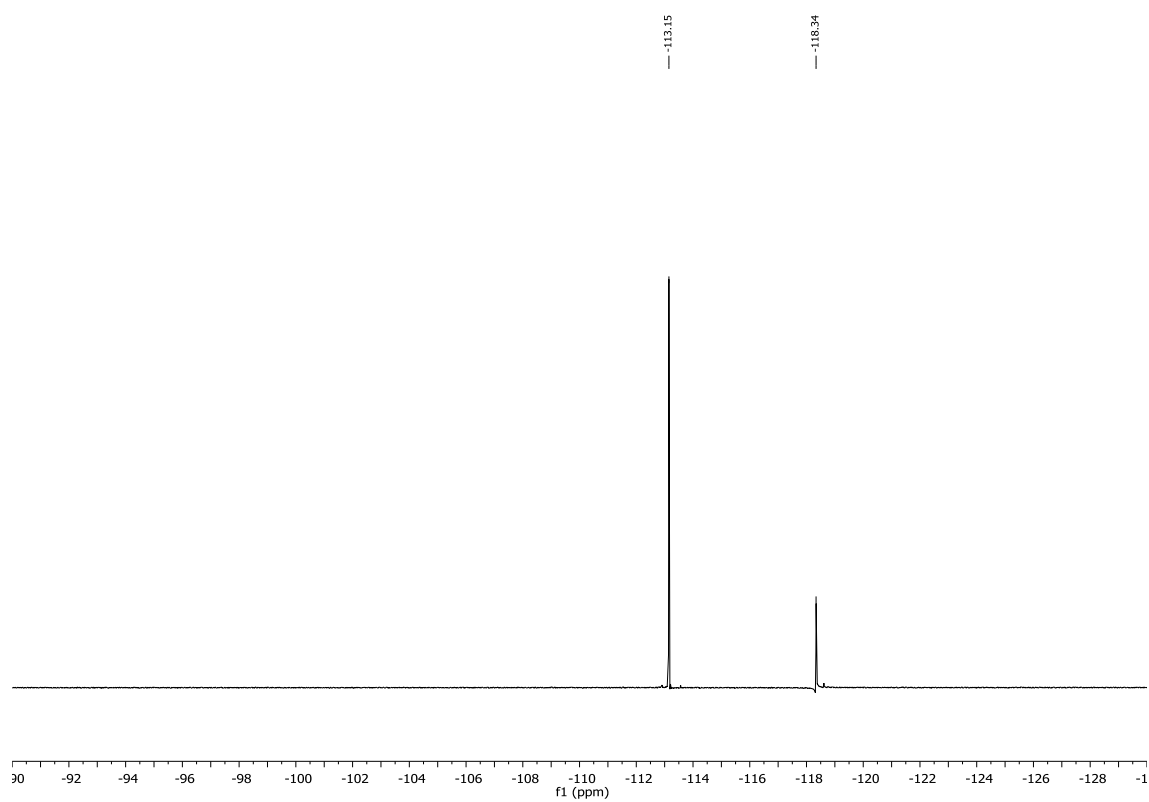


1-((1S,2S)-2-(Cyclohex-1-en-1-yl)cyclopropyl)-4-fluorobenzene (70)



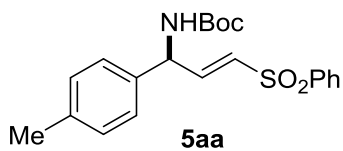
Experimental section

^{19}F NMR:

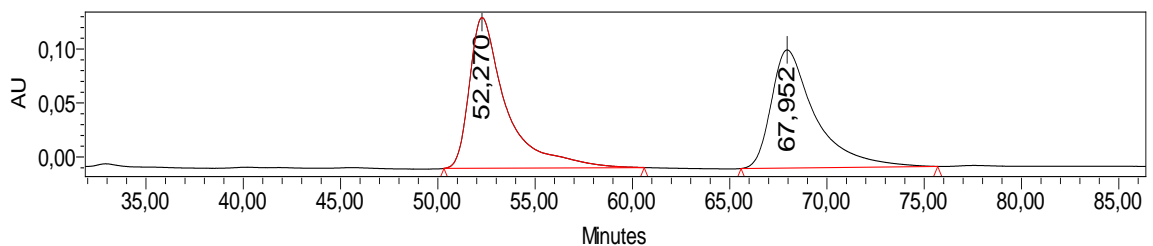


6.7. Determination of enantiomeric excesses

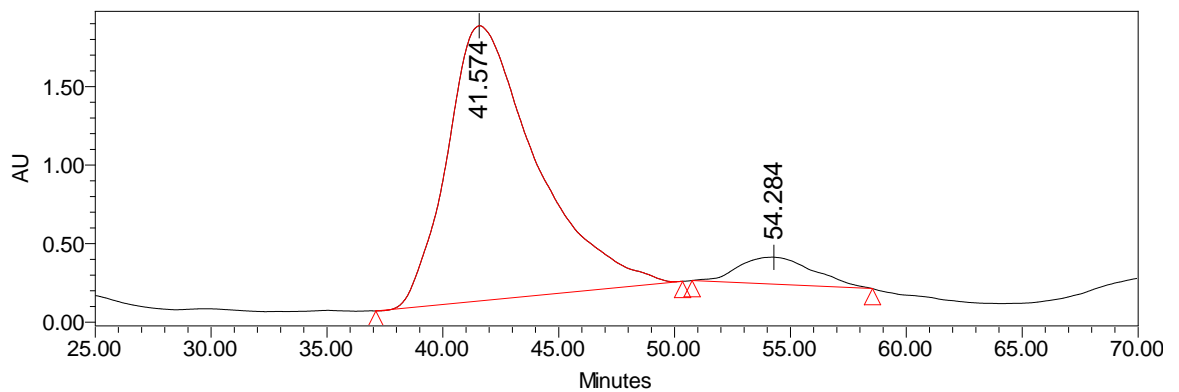
6.7.1. HPLC Chromatograms for Chapter 2

tert-Butyl (*S,E*)-(3-(phenylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5aa**)

The enantiomeric purity of compound **5aa** was determined by chiral HPLC analysis (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 0.50 mL/min, $\lambda = 230$ nm) t_R (major.) = 41.5 min, t_R (minor.) = 54.3 min. 85% *ee*.



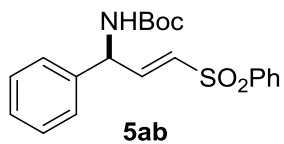
	Retention Time	% Area
1	52.270	51.83
2	67.952	48.17



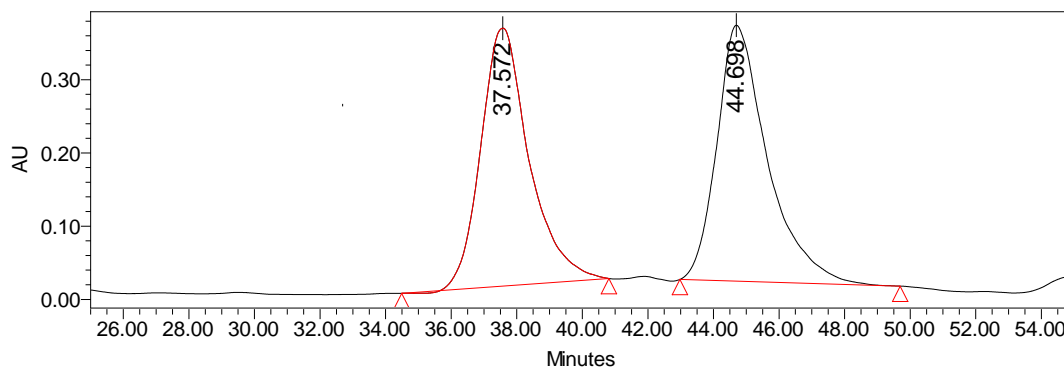
	Retention Time	% Area
1	41.574	92.39
2	54.284	7.61

Experimental section

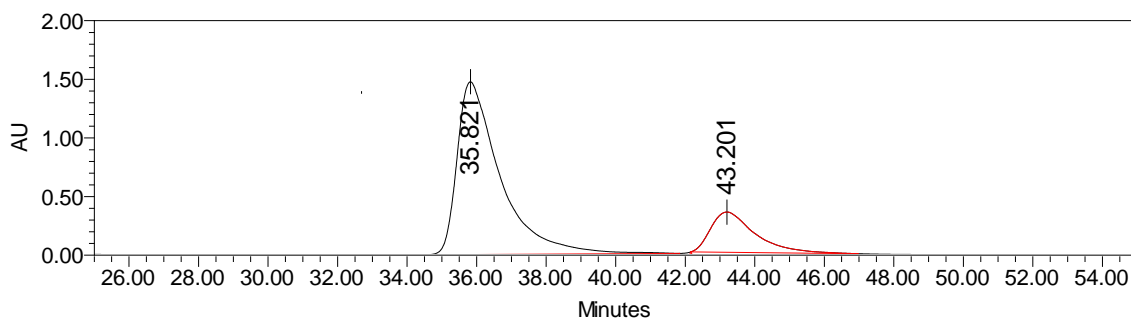
tert-Butyl (*S,E*)-(1-phenyl-3-(phenylsulfonyl)allyl)carbamate (**5ab**)



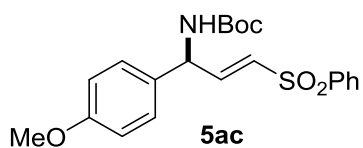
The enantiomeric purity of compound **5ab** was determined by chiral HPLC analysis (Chiralpak IA; 90:10 hexane:*i*PrOH; 0.50 mL/min, $\lambda = 230$ nm) t_R (major.) = 35.8 min, t_R (minor.) = 43.2 min. 61% *ee*.



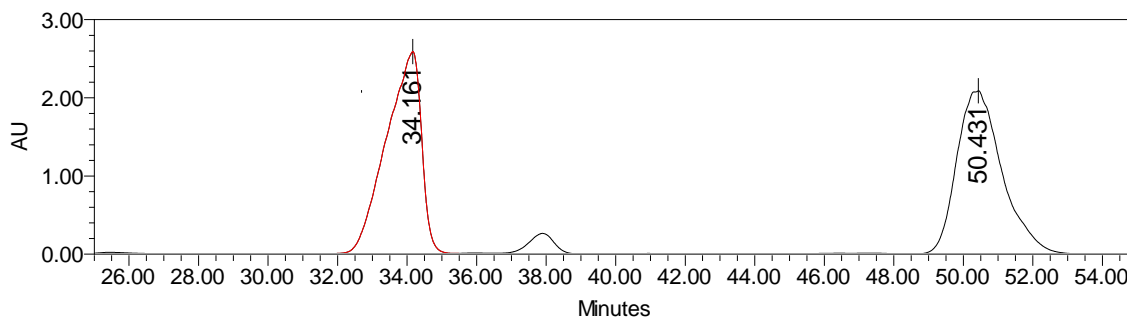
	Retention Time	% Area
1	37.572	49.12
2	44.698	50.88



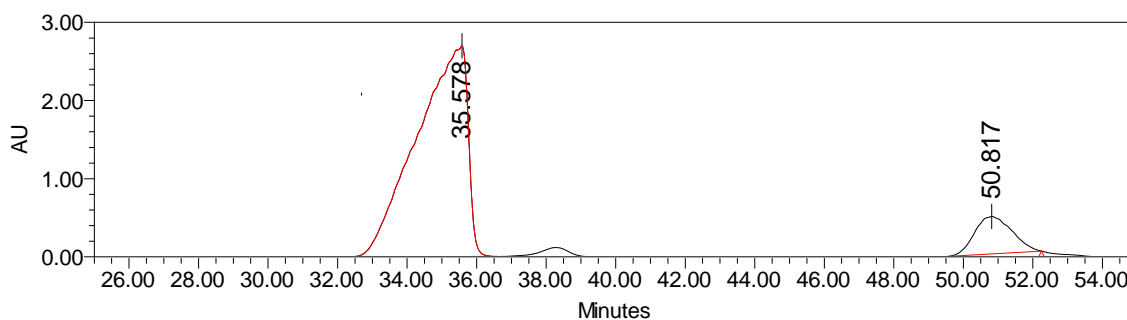
	Retention Time	% Area
1	35.821	80.74
2	43.201	19.26

***tert*-Butyl (*S,E*)-(1-(4-methoxyphenyl)-3-(phenylsulfonyl)allyl)carbamate (**5ac**)**

The enantiomeric purity of compound **5ac** was determined by chiral HPLC analysis (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 35.5 min, t_R (minor.) = 50.8 min. 77% *ee*.



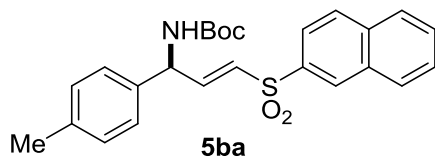
	Retention Time	% Area
1	34.161	49.01
2	50.431	50.99



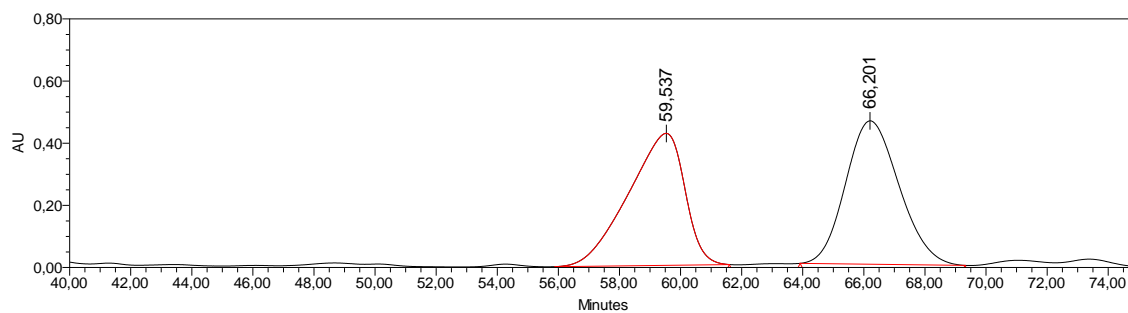
	Retention Time	% Area
1	35.578	88.42
2	50.817	11.58

Experimental section

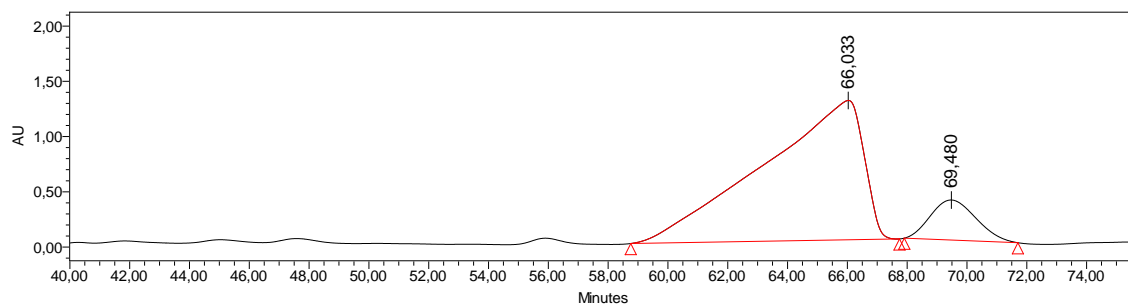
tert-Butyl (*S,E*)-(3-(naphthalen-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (**5ba**)



The enantiomeric purity of compound **5ba** was determined by chiral HPLC analysis (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 0.50 mL/min, $\lambda = 230$ nm) t_R (major.) = 59.5 min, t_R (minor.) = 66.2 min. 77% *ee*.

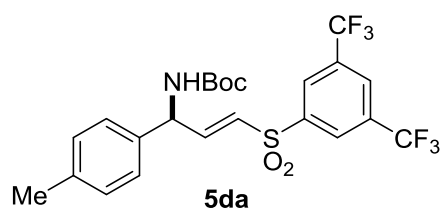


	Retention Time	% Area
1	59,537	49,24
2	66,201	50,76

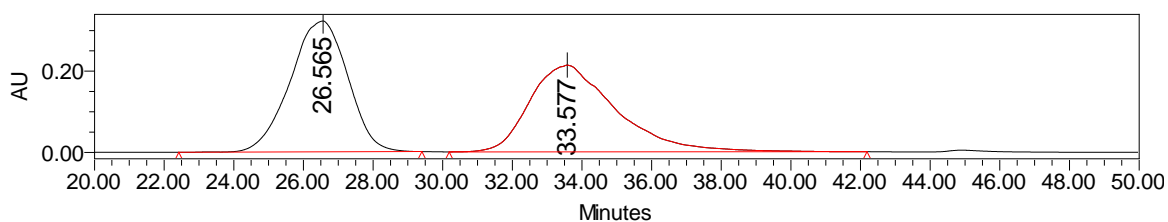


	Retention Time	% Area
1	66,033	88,47
2	69,480	11,53

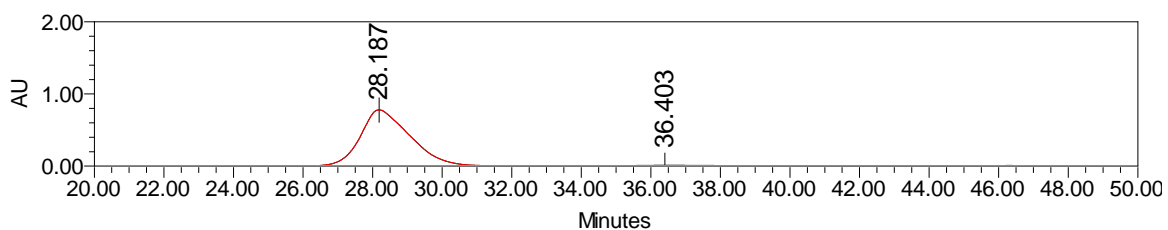
***tert*-Butyl
 (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(*p*-
 tolyl)allyl)carbamate (5da)**



The enantiomeric purity of compound **5da** was determined by chiral HPLC analysis (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 28.1 min, t_R (minor.) = 36.4 min. >99% *ee*.



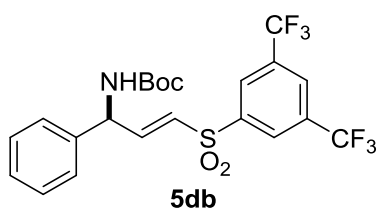
	Retention Time	% Area
1	26.565	50.28
2	33.577	49.72



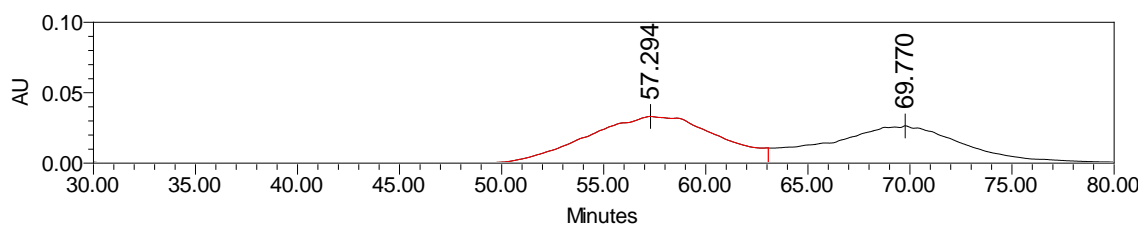
	Retention Time	% Area
1	28.187	99.96
2	36.403	0.04

Experimental section

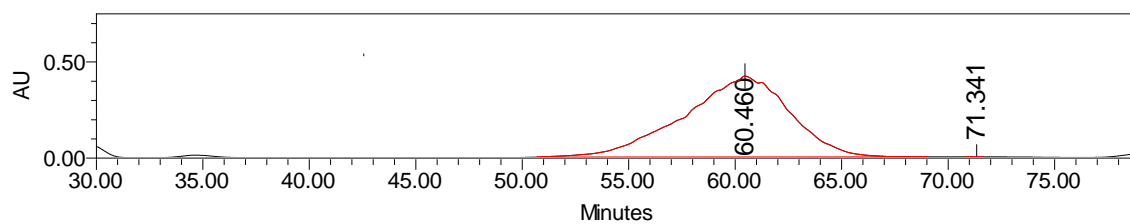
tert-Butyl (*S,E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-phenylallyl)carbamate (**5db**)



The enantiomeric purity of compound **5db** was determined by chiral HPLC analysis (Chiralpak IC; 99:1 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 60.5 min, t_R (minor.) = 73.1 min. >99% *ee*.

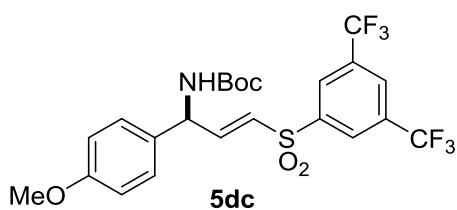


	Retention Time	% Area
1	57.294	53.90
2	69.770	46.10

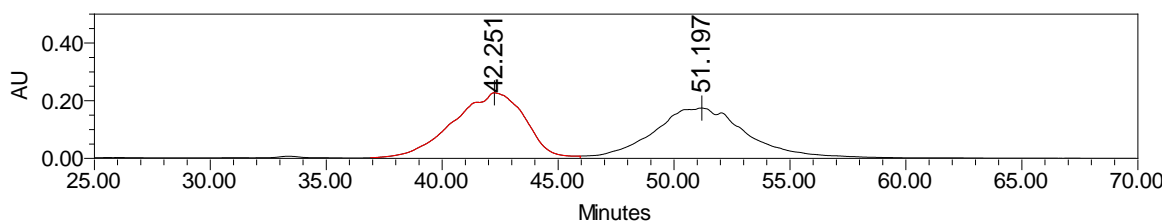


	Retention Time	% Area
1	60.460	100.00
2	71.341	0.00

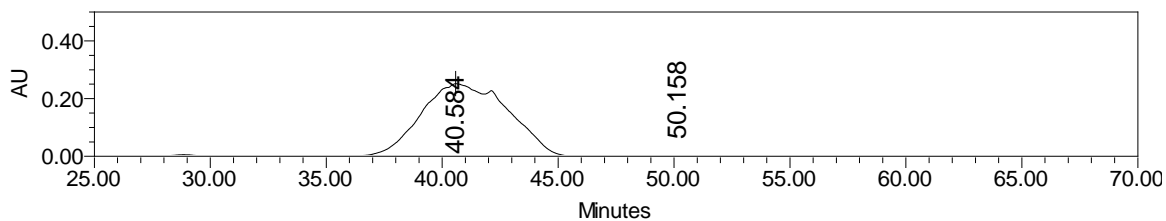
tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)allyl carbamate (5dc)



The enantiomeric purity of compound **5dc** was determined by chiral HPLC analysis (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 40.9 min, t_R (minor.) = 49.8 min. >99% *ee*.



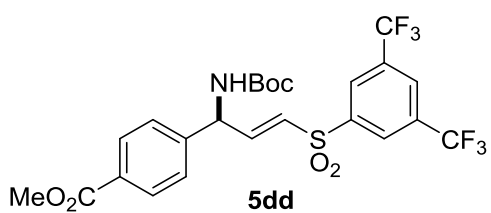
	Retention Time	% Area
1	42.251	50.46
2	51.197	49.54



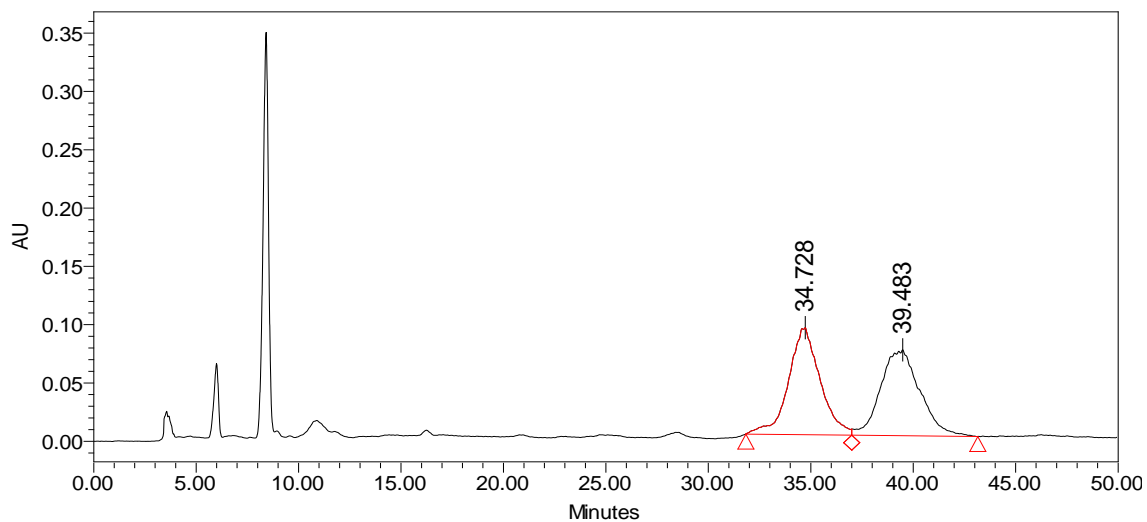
	Retention Time	% Area
1	40.584	99.77
2	50.158	0.23

Experimental section

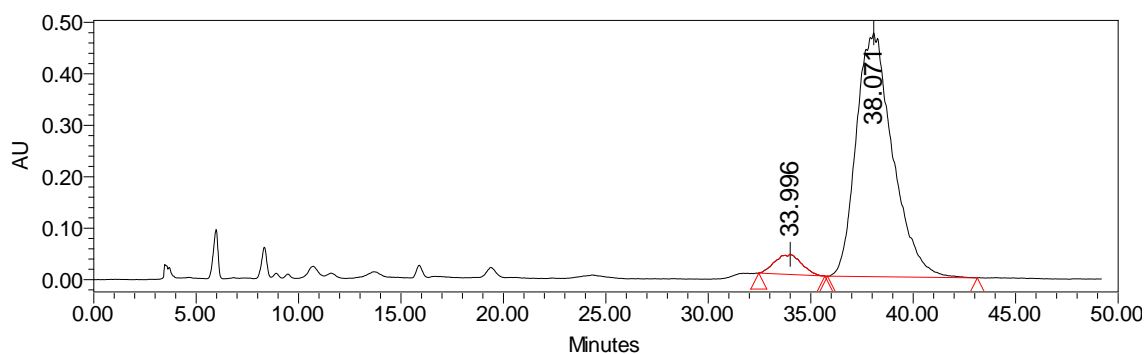
Methyl **(S,E)-4-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-((tert-butoxycarbonyl)amino)allyl)benzoate (5dd)**



The enantiomeric purity of compound **5dd** was determined by chiral HPLC analysis (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 34.0 min, t_R (major.) = 38.1 min. 90% *ee*.

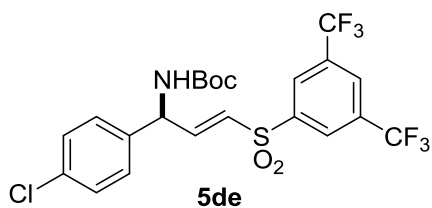


	Retention Time	% Area
1	34.728	50.04
2	39.483	49.96

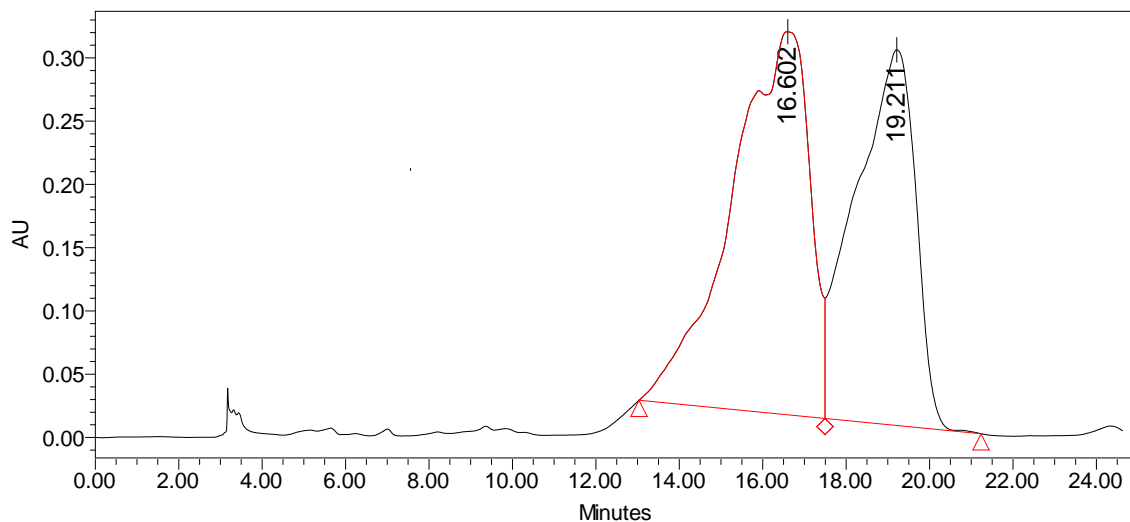


	Retention Time	% Area
1	33.996	5.36
2	38.071	94.64

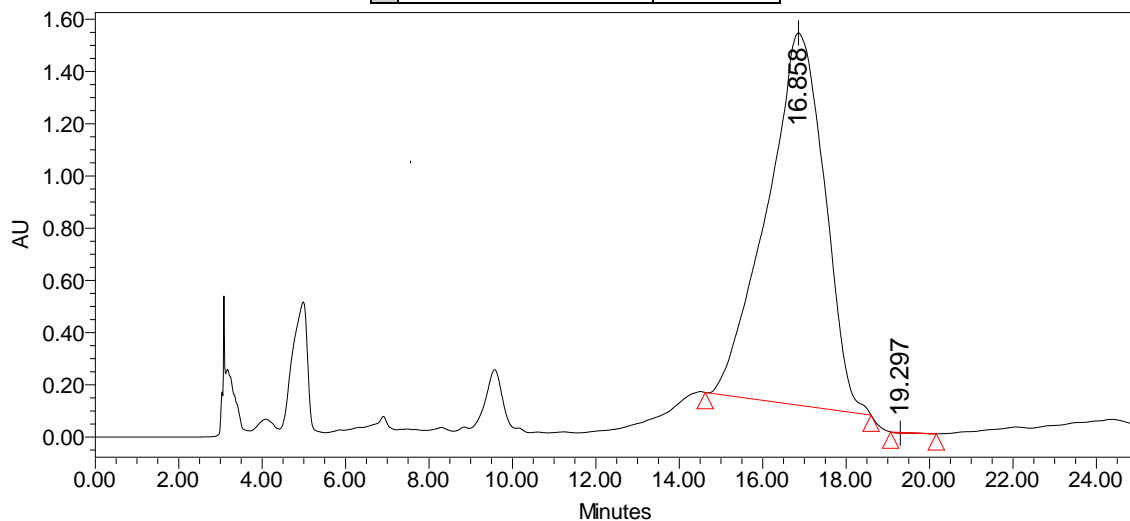
tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-chlorophenyl)allyl carbamate (5de)



The enantiomeric purity of compound **5de** was determined by chiral HPLC analysis (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 16.6 min, t_R (minor.) = 19.2 min. >99% *ee*.



	Retention Time	% Area
1	16.602	51.92
2	19.211	48.08

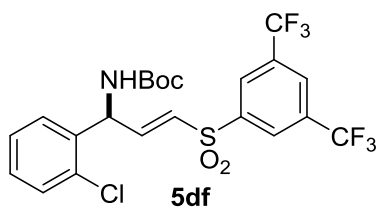


	Retention Time	% Area
1	16.858	99.94
2	19.297	0.06

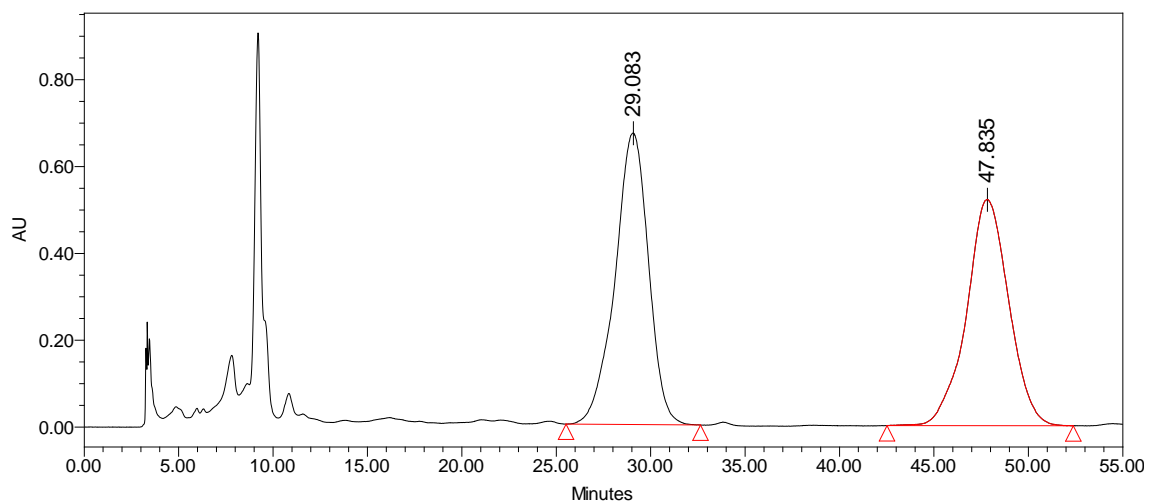
Experimental section

tert-Butyl

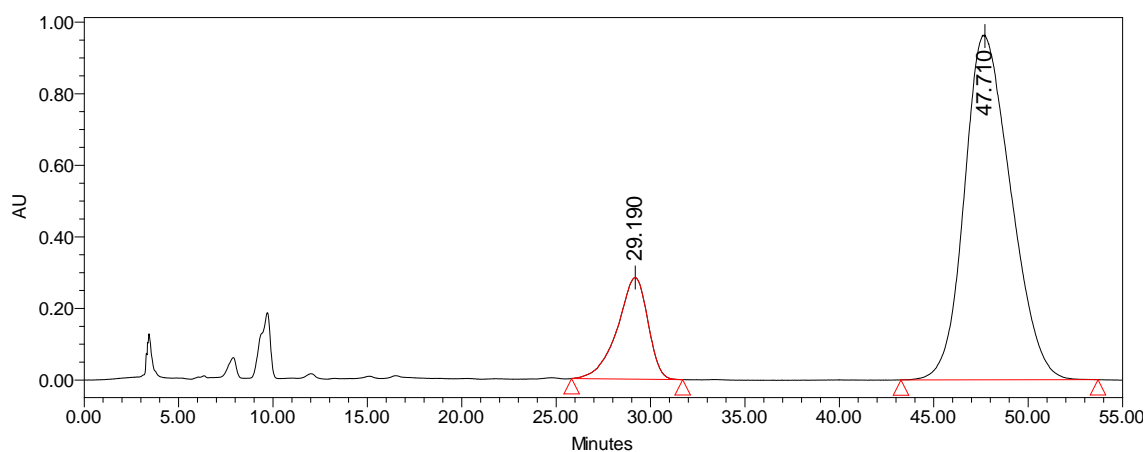
(*S,E*)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(2-chlorophenyl)allyl)carbamate (5df**)**



The enantiomeric purity of compound **5df** was determined by chiral HPLC analysis (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 29.2 min, t_R (major.) = 47.7 min. 68% *ee*.

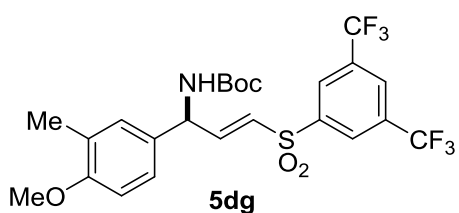


	Retention Time	% Area
1	29.083	50.49
2	47.835	49.51

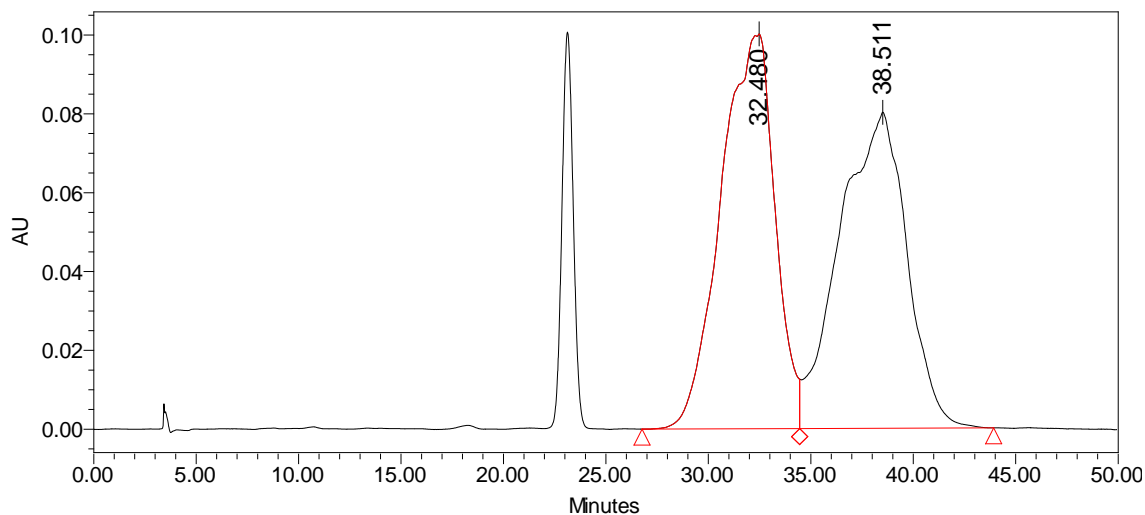


	Retention Time	% Area
1	29.190	16.26
2	47.710	83.74

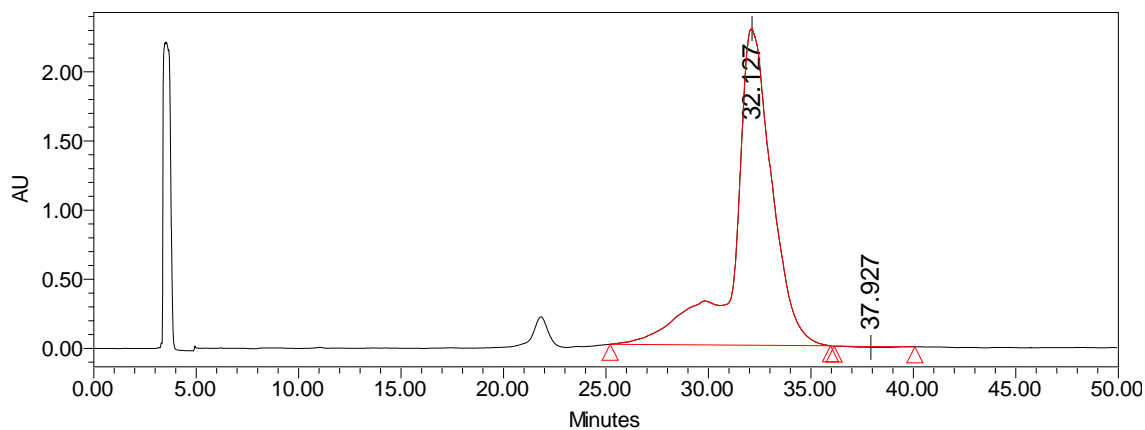
tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxy-3-methylphenyl)allyl carbamate (5dg)



The enantiomeric purity of compound **5dg** was determined by chiral HPLC analysis (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 32.1 min, t_R (minor.) = 38.5 min. >99% *ee*.



	Retention Time	% Area
1	32.480	50.07
2	38.511	49.93

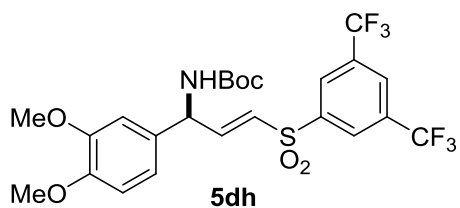


	Retention Time	% Area
1	32.127	99.72
2	37.927	0.28

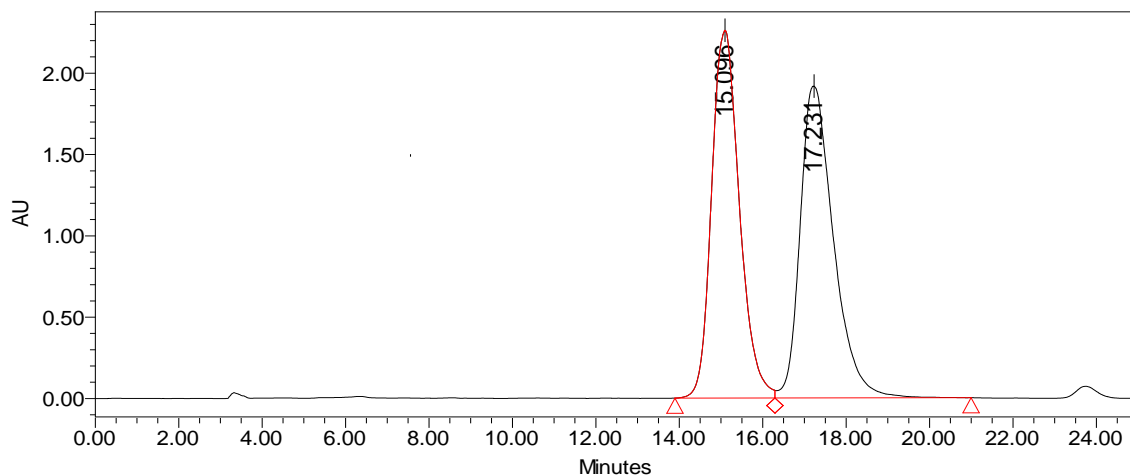
Experimental section

tert-Butyl

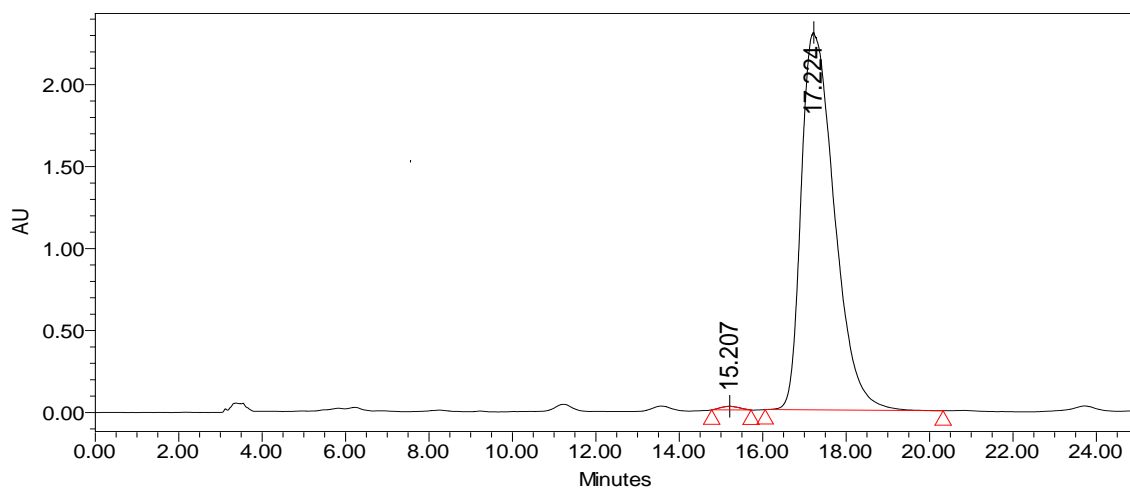
(*S,E*)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(3,4-dimethoxyphenyl)allyl)carbamate (5dh**)**



The enantiomeric purity of compound **5dh** was determined by chiral HPLC analysis (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 15.1 min, t_R (major.) = 17.2 min. >99% *ee*.

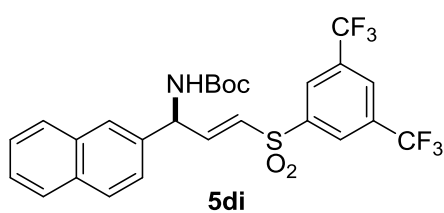


	Retention Time	% Area
1	15.096	49.58
2	17.231	50.42

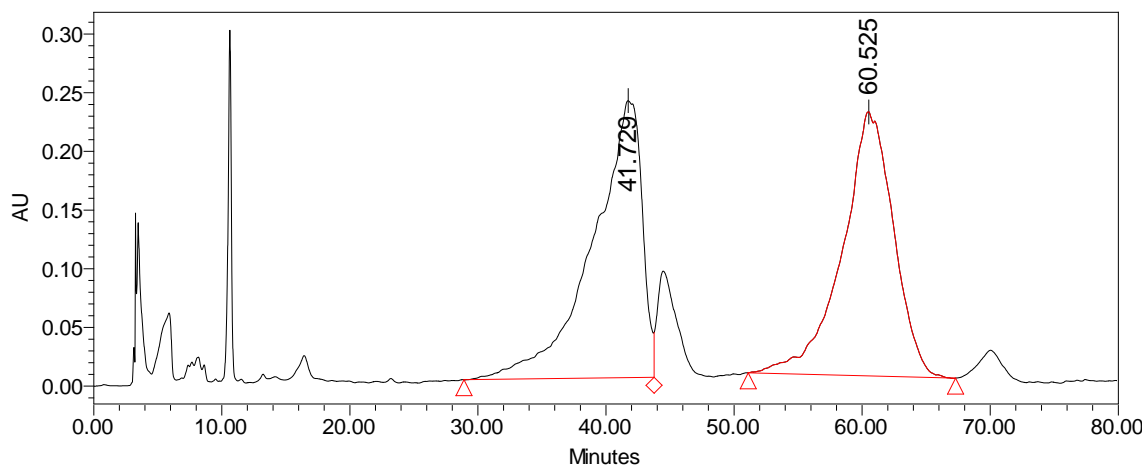


	Retention Time	% Area
1	15.207	0.39
2	17.224	99.61

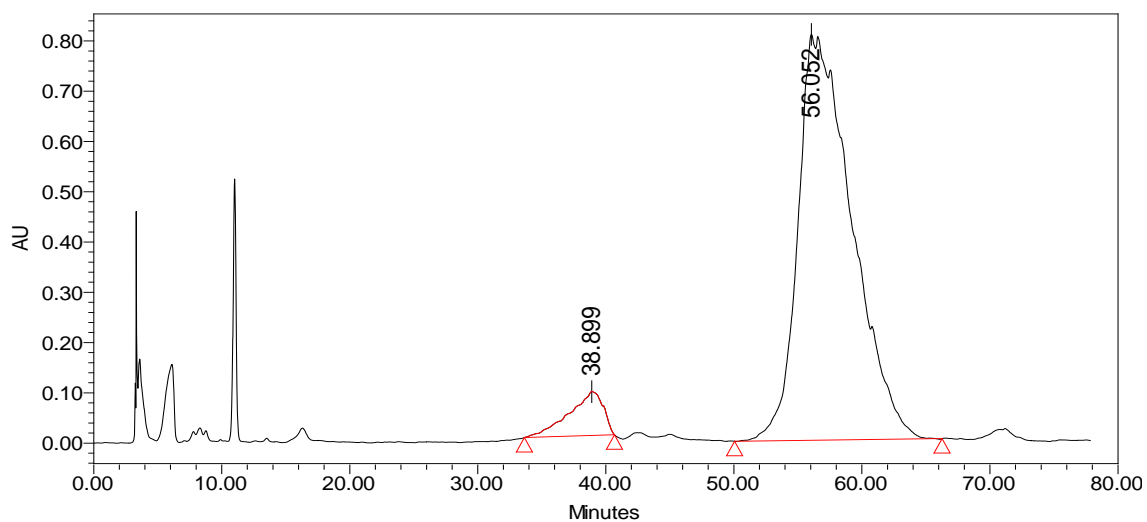
***tert*-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(naphthalen-2-yl)allyl carbamate (5di)**



The enantiomeric purity of compound **5di** was determined by chiral HPLC analysis (Chiralpak AD-H; 99:1 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 41.7 min, t_R (major.) = 60.5 min. 88% *ee*.



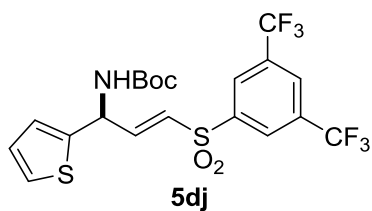
	Retention Time	% Area
1	41.729	50.18
2	60.525	49.82



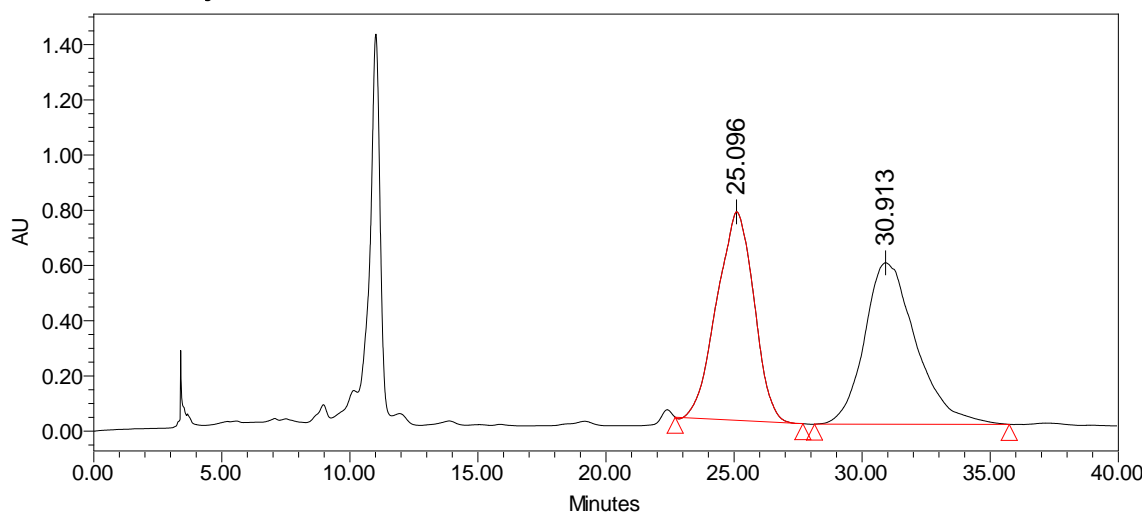
	Retention Time	% Area
1	38.899	6.39
2	56.052	93.61

Experimental section

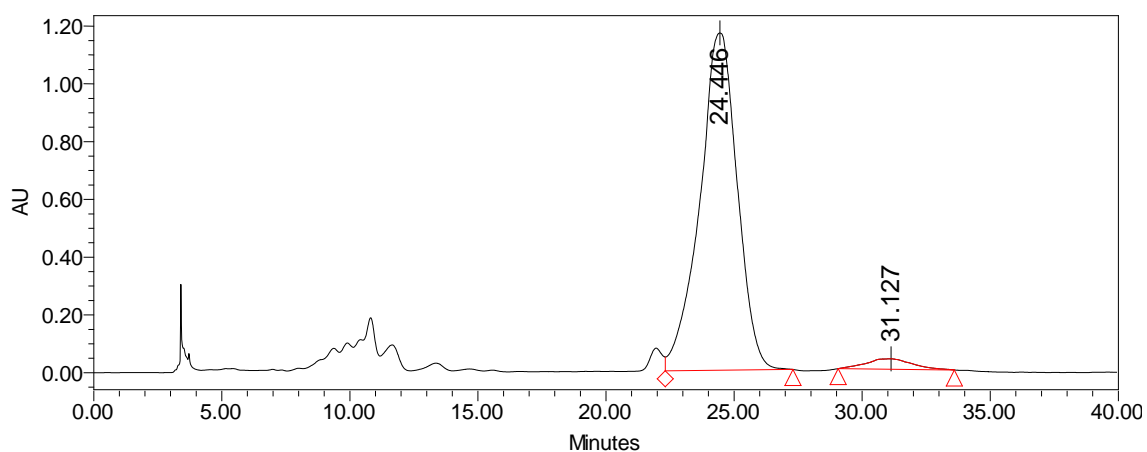
tert-Butyl (S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(thiophen-2-yl)allyl carbamate (**5dj**)



The enantiomeric purity of compound **5dj** was determined by chiral HPLC analysis (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (major.) = 24.5 min, t_R (minor.) = 31.1 min. 94% *ee*.



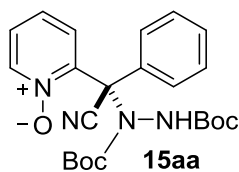
	Retention Time	% Area
1	25.096	48.29
2	30.913	51.71



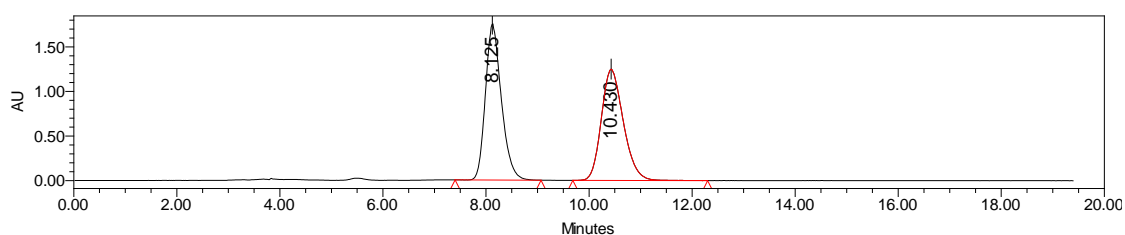
	Retention Time	% Area
1	24.446	96.34
2	31.127	3.66

6.7.2. HPLC Chromatograms for Chapter 3

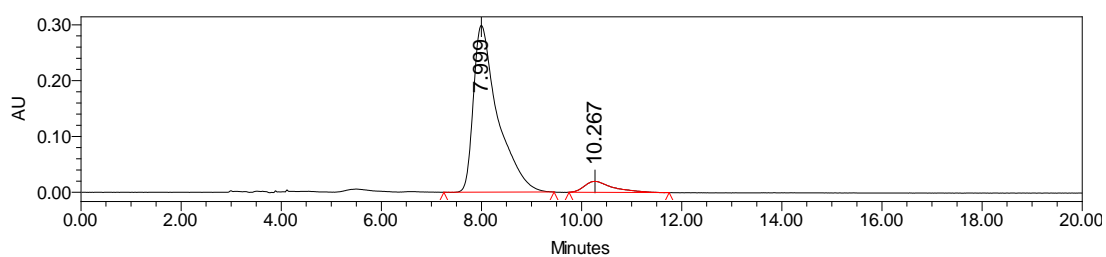
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(phenyl)methyl)pyridine *N*-oxide (15aa)



The enantiomeric purity of compound **15aa** was determined by chiral HPLC analysis (Chiralpak IC; 60:40 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 8.1 min, t_R (major.) = 10.4 min. 90% *ee*.



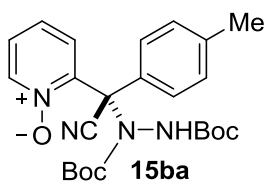
	Retention Time	% Area
1	8.125	50.46
2	10.430	49.54



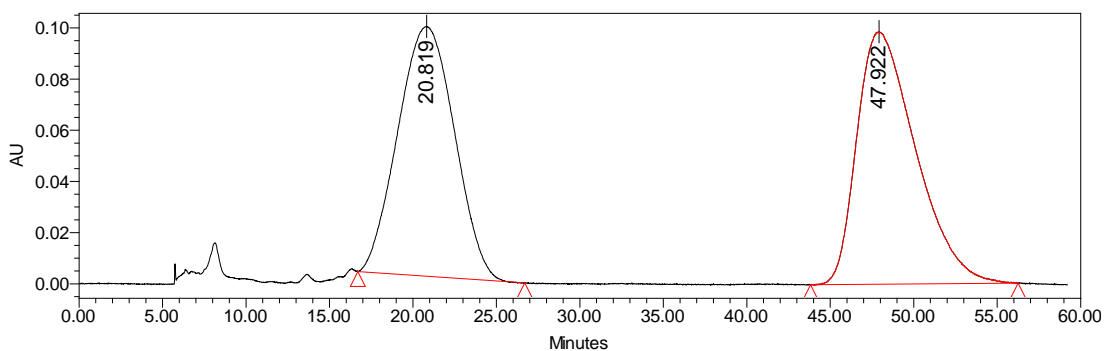
	Retention Time	% Area
1	7.999	94.67
2	10.267	5.33

Experimental section

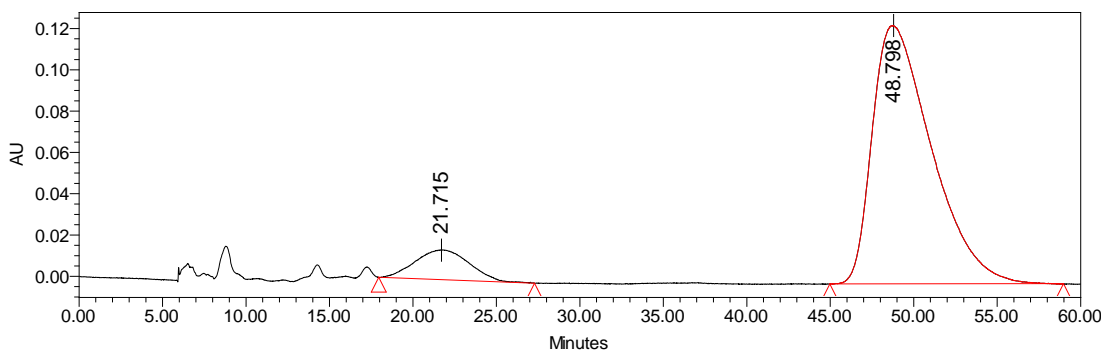
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(*p*-tolyl)methyl)pyridine *N*-oxide (**15ba**)



The enantiomeric purity of compound **15ba** was determined by chiral HPLC analysis (Chiralpak IA; 80:20 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 21.8 min, t_R (major.) = 48.7 min. 82% ee.

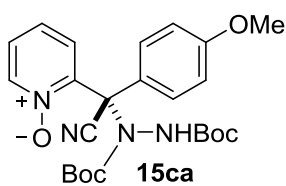


	Retention Time	% Area
1	20.819	48.64
2	47.922	51.36

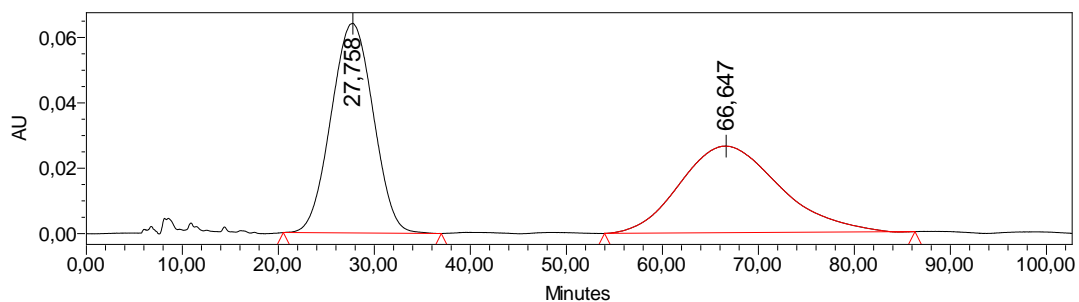


	Retention Time	% Area
1	21.715	8.92
2	48.798	91.08

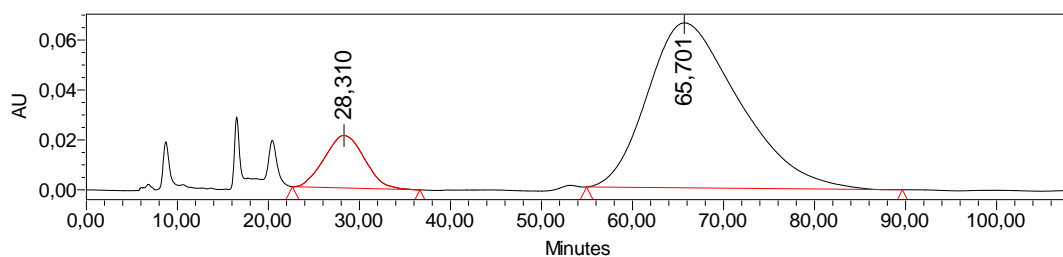
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-methoxyphenyl)methyl)pyridine *N*-oxide (15ca)



The enantiomeric purity of compound **15ca** was determined by chiral HPLC analysis (Chiralpak IA; 80:20 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 28.3 min, t_R (major.) = 65.7 min. 76% *ee*.



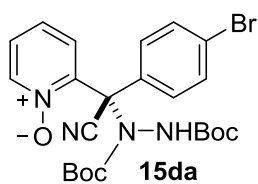
	Retention Time	% Area
1	27.748	50.31
2	66.646	49.69



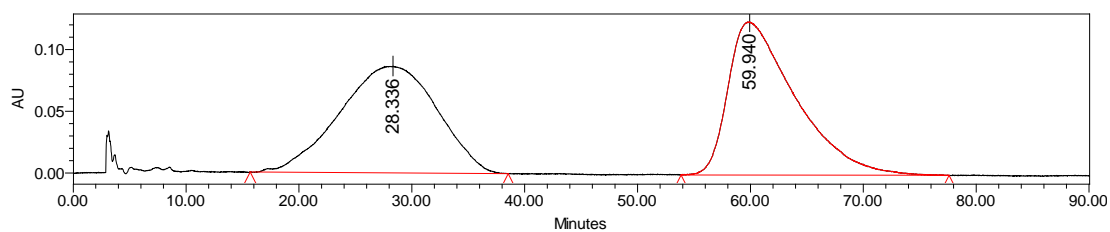
	Retention Time	% Area
1	28,347	11,91
2	65,686	88,09

Experimental section

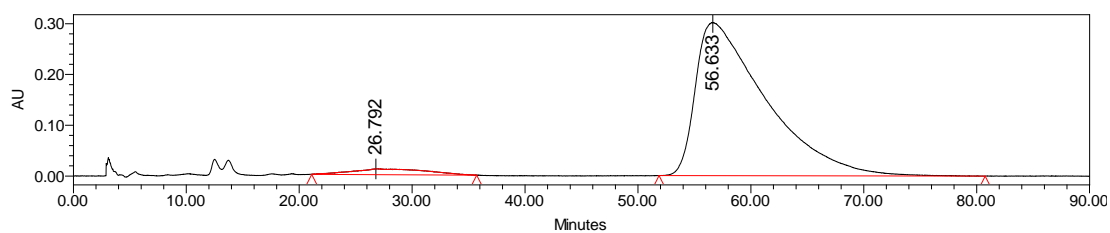
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine 1-oxide (15da)



The enantiomeric purity of compound **15da** was determined by chiral HPLC analysis (Chiralpak IA; 90:10 hexane:EtOH; 1.00 mL/min, $\lambda = 210$ nm) t_R (minor.) = 26.8 min, t_R (major.) = 56.6 min. 92% *ee*.

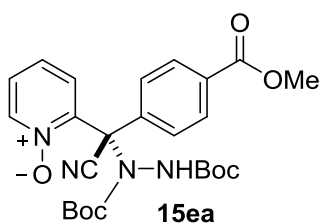


	Retention Time	% Area
1	28.336	50.27
2	59.940	49.73

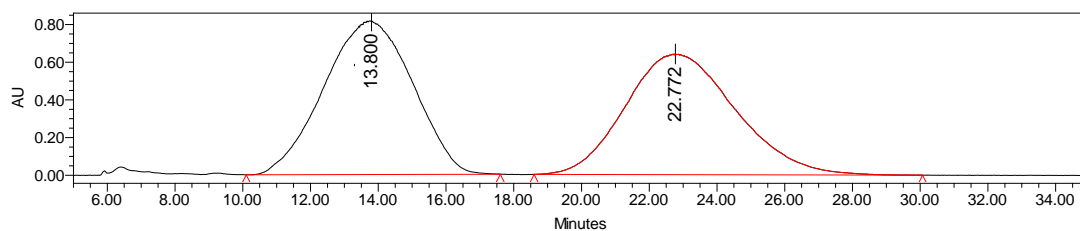


	Retention Time	% Area
1	26.792	3.93
2	56.633	96.07

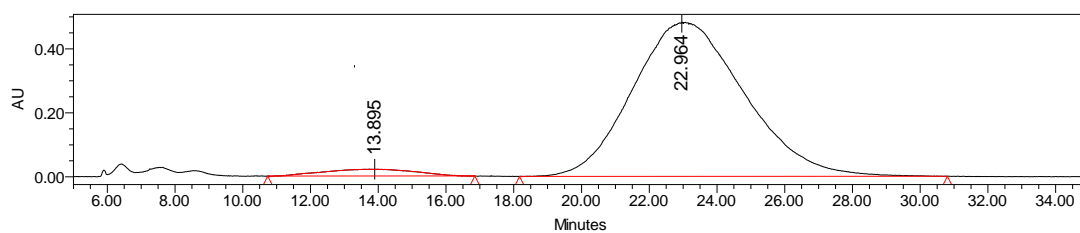
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15ea)



The enantiomeric purity of compound **15ea** was determined by chiral HPLC analysis (Chiralpak IA; 60:40 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 13.9 min, t_R (major.) = 23.0 min. 93% *ee*.



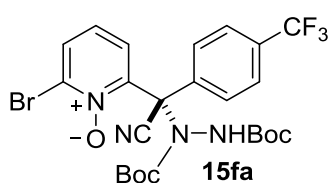
	Retention Time	% Area
1	13.800	50.70
2	22.772	49.30



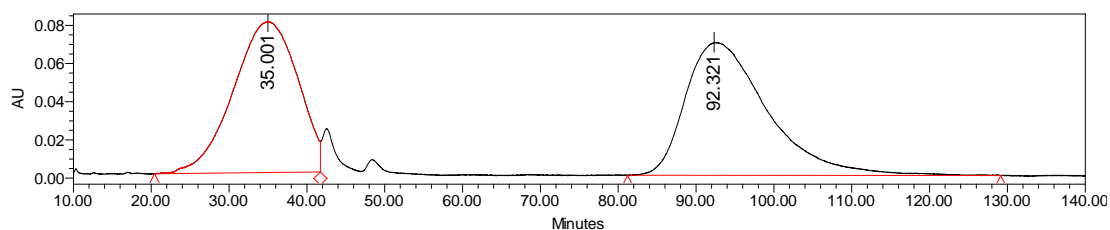
	Retention Time	% Area
1	13.895	3.46
2	22.964	96.54

Experimental section

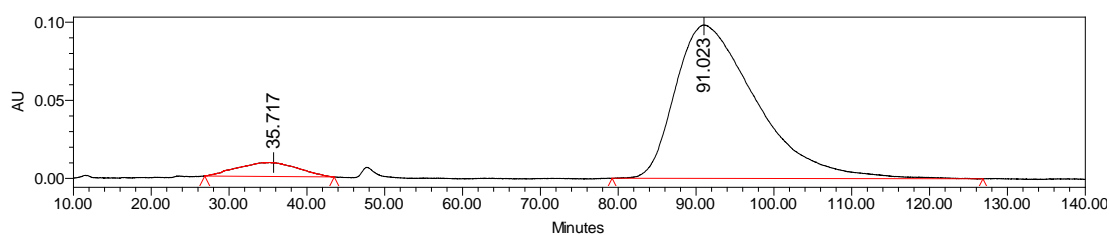
(S)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(trifluoromethyl)phenyl)methyl)-6-bromopyridine *N*-oxide (**15fa**)



The enantiomeric purity of compound **15fa** was determined by chiral HPLC analysis (Chiralpak IA; 95:5 hexane:EtOH; 1.00 mL/min, $\lambda = 230$ nm) t_R (minor.) = 35.7 min, t_R (major.) = 91.0 min. 88% ee.

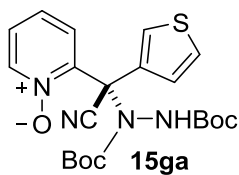


	Retention Time	% Area
1	35.001	47.20
2	92.321	52.80

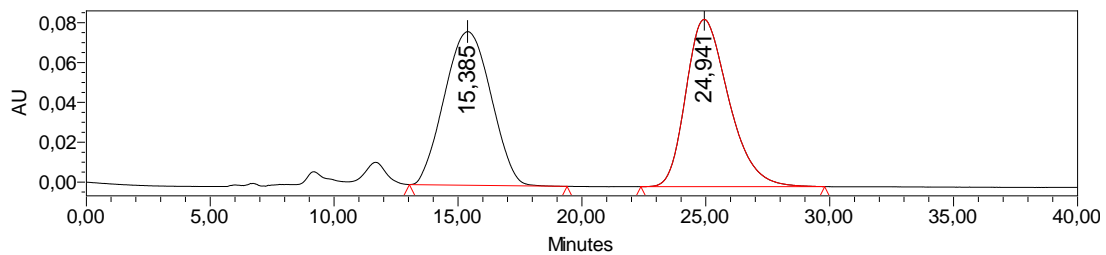


	Retention Time	% Area
1	35.717	6.36
2	91.023	93.64

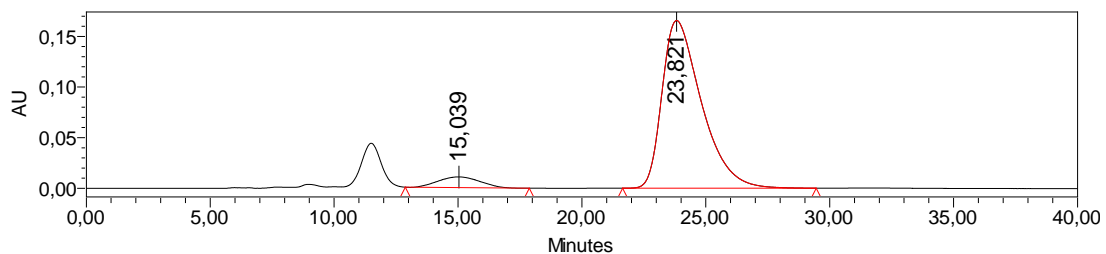
**(S)-2-((1,2-bis(tert-butoxycarbonyl)hydrazinyl)(cyano)(thiophen-3-yl)methyl)pyridine
N-oxide (15ga)**



The enantiomeric purity of compound **15ga** was determined by chiral HPLC analysis (Chiralpak IA; 70:30 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 15.1 min, t_R (major.) = 23.8 min. 90% *ee*.



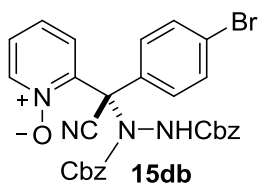
	Retention Time	% Area
1	15.385	50,46
2	24.941	49,54



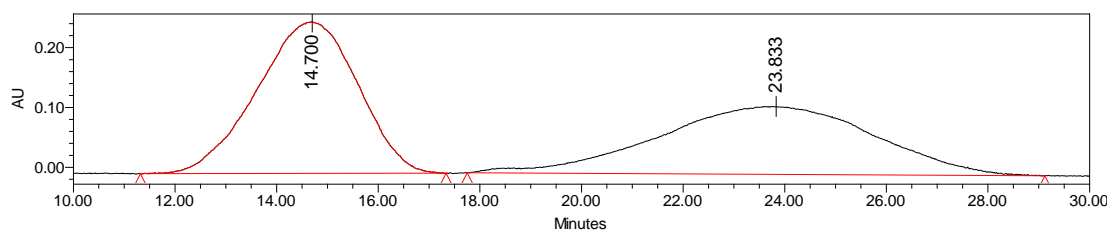
	Retention Time	% Area
1	15.039	5,43
2	23.821	94,57

Experimental section

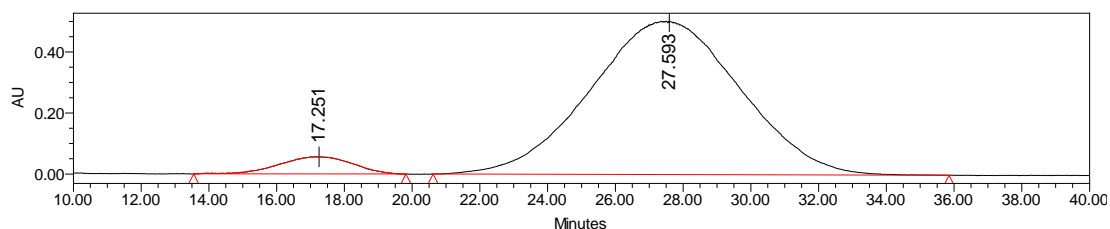
(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine N-oxide (**15db**)



The enantiomeric purity of compound **15db** was determined by chiral HPLC analysis (Chiralpak IA; 60:40 hexane:EtOH; 0.80 mL/min, $\lambda = 210$ nm) t_R (minor.) = 17.3 min, t_R (major.) = 27.6 min. 90% ee.

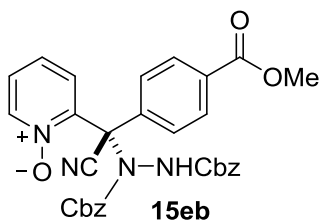


	Retention Time	% Area
1	14.700	51.01
2	23.833	48.99

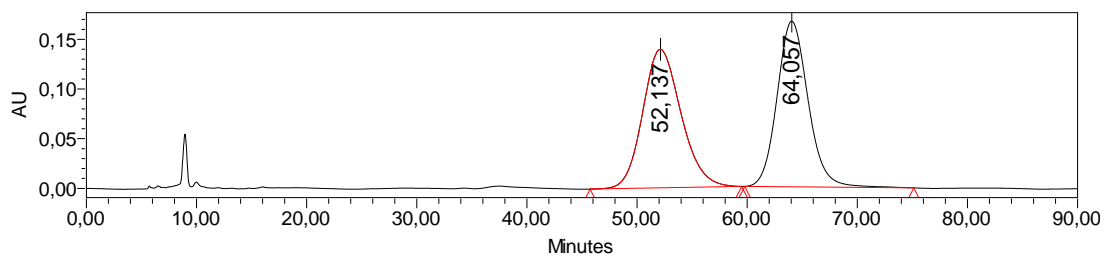


	Retention Time	% Area
1	17.251	5.19
2	27.593	94.81

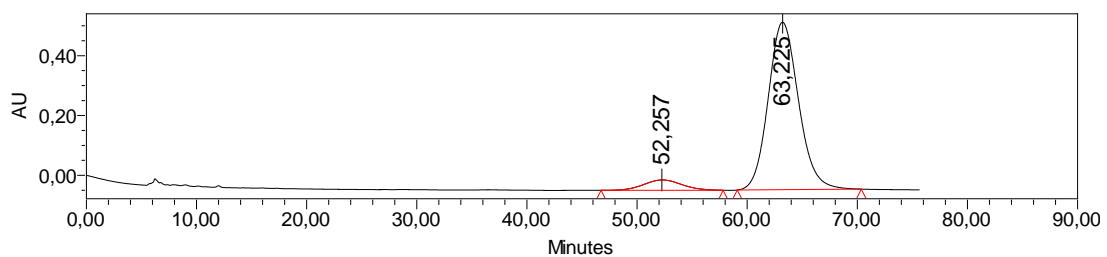
(S)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine N-oxide (15eb)



The enantiomeric purity of compound **15eb** was determined by chiral HPLC analysis (Chiralpak IA; 70:30 hexane:EtOH; 0.50 mL/min, $\lambda = 210$ nm) t_R (minor.) = 52.3 min, t_R (major.) = 63.2 min. 90% *ee*.



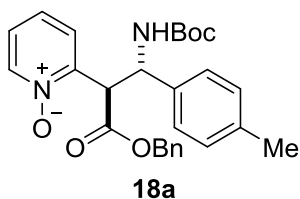
	Retention Time	% Area
1	52.137	50.72
2	64.057	49.28



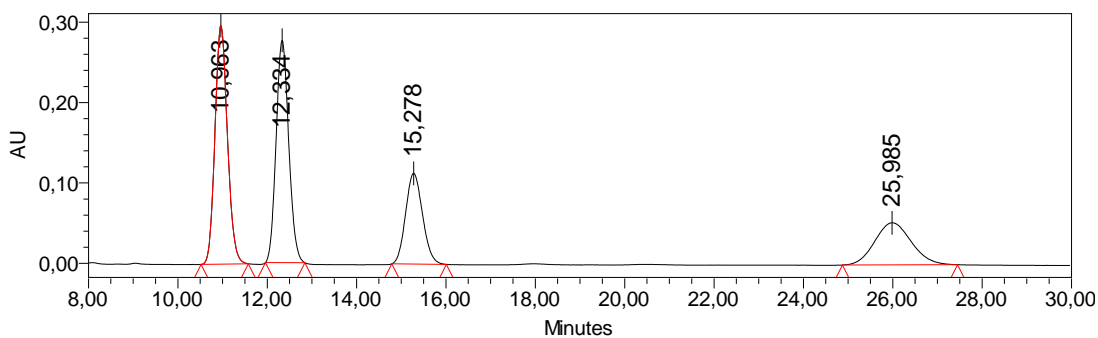
	Retention Time	% Area
1	52.257	5.43
2	63.225	94.57

Experimental section

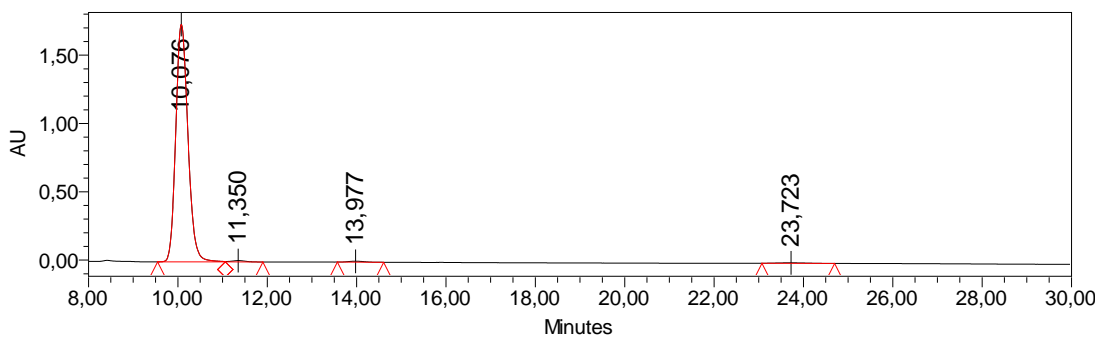
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-oxo-3-phenoxy-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (**18a**)



The enantiomeric purity of compound **18a** was determined by chiral HPLC analysis (Chiralpack IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 10.1$ min (*anti*, major.), 11.4 min (*anti*, minor.), 14.0 min (*syn*), 23.7 min (*syn*). dr 99:1; 99% *ee*.

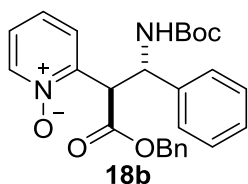


Retention Time	% Area
10.963	33.59
12.334	31.64
15.278	17.32
25.985	17.45

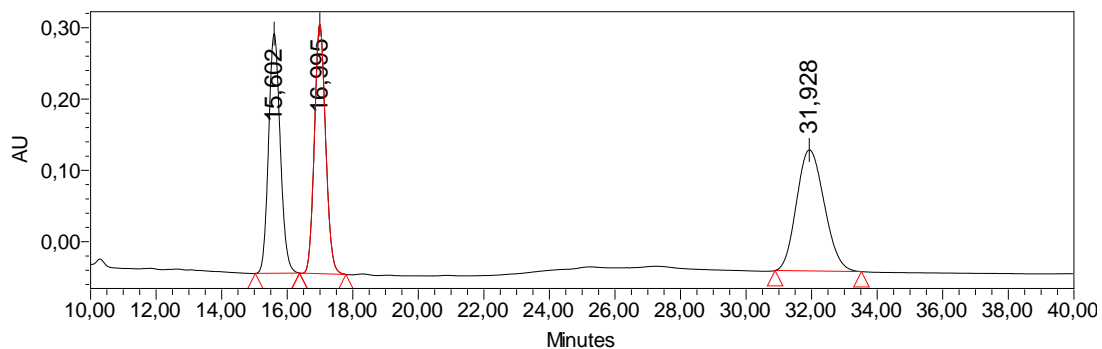


Retention Time	% Area
10.076	98.33
11.350	0.65
13.977	0.51
23.723	0.51

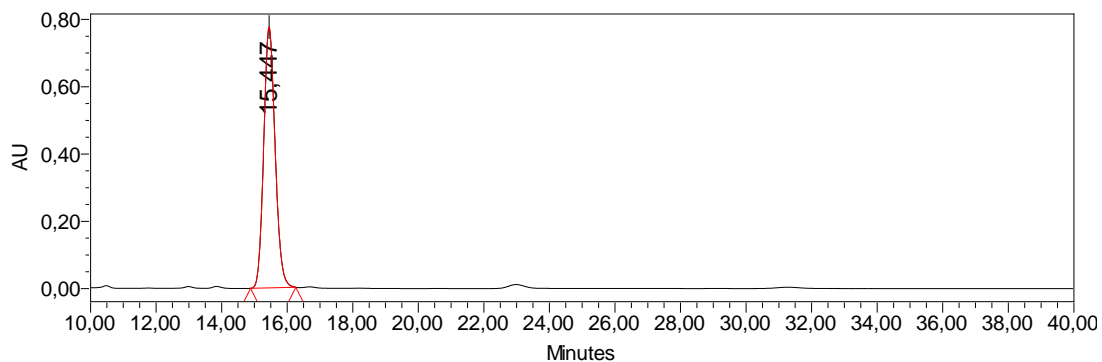
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)pyridine *N*-oxide (18b**)**



The enantiomeric purity of compound **18b** was determined by chiral HPLC analysis (Chiralpack IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 15.6$ min (*anti*, major.), 17.0 min (*anti*, minor.), 31.9 min (both *syn* enantiomers). dr 99:1; 99% *ee*.



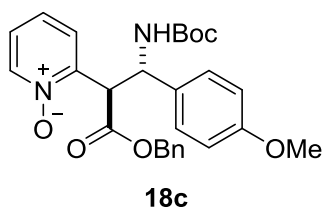
Retention Time	% Area
15.602	31.22
16.995	31.20
31.928	37.58



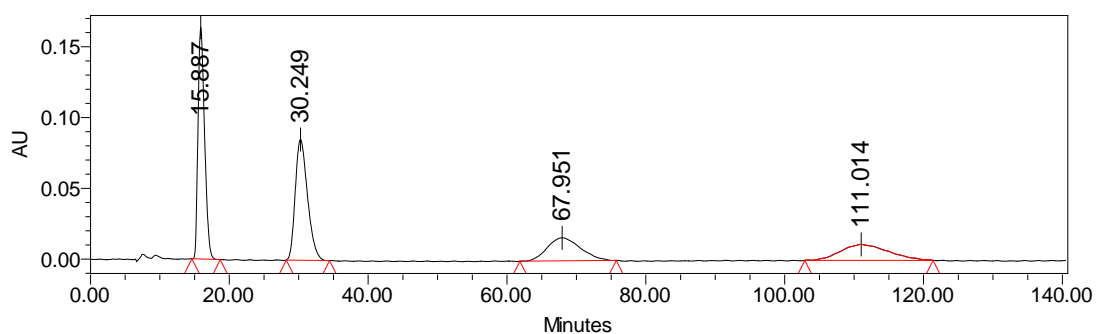
Retention Time	% Area
15.447	100.00

Experimental section

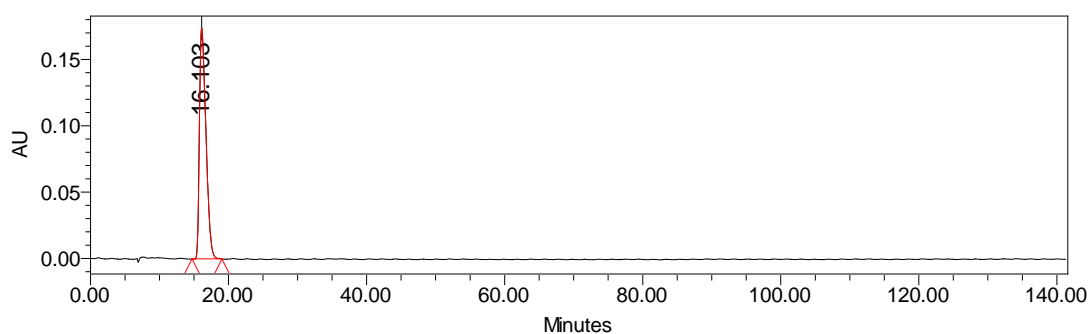
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18c**)



The enantiomeric purity of compound **18c** was determined by chiral HPLC analysis (Chiralpak AD-H; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 270$ nm) $t_R = 16.0$ min (*anti*, major.), 30.2 min (*anti*, minor.), 68.0 min (*syn*), 111.0 min (*syn*). dr 99:1; 99% *ee*.

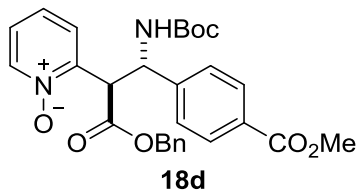


Retention Time	% Area
15.887	33.60
30.249	32.67
67.951	16.84
111.014	16.90



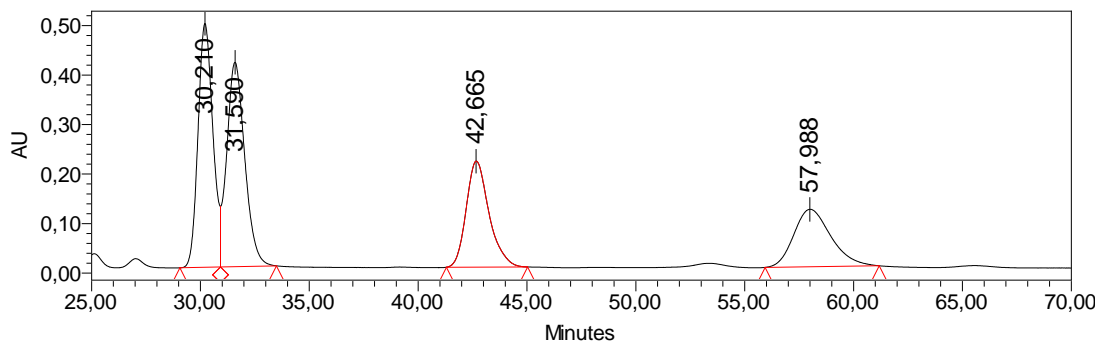
Retention Time	% Area
16.103	100.00

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18d)

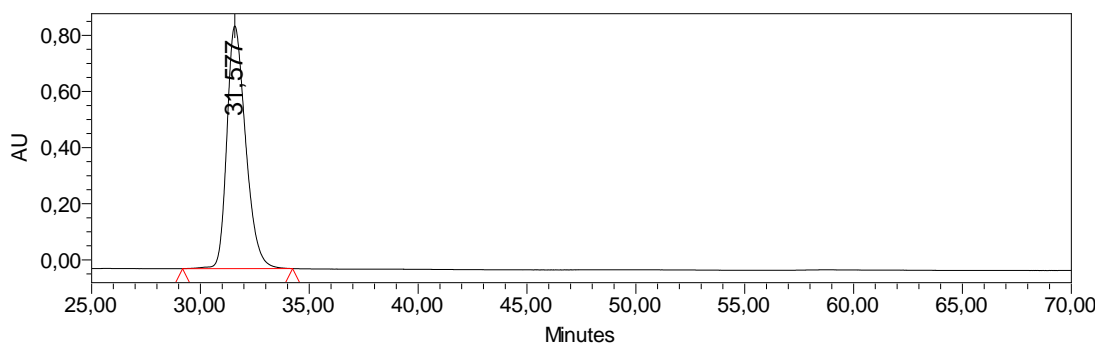


The enantiomeric purity of compound **18d** was determined by chiral HPLC analysis (Chiralpack IC; 70:30 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 30.2$ min (*anti*, minor.), 31.6 min (*anti*, major.), 42.7 min (*syn*), 58.0

min (*syn*). dr 99:1; 99% *ee*.



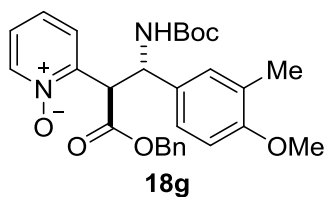
Retention Time	% Area
30.210	30.56
31.590	31.05
42.665	20.43
57.988	17.96



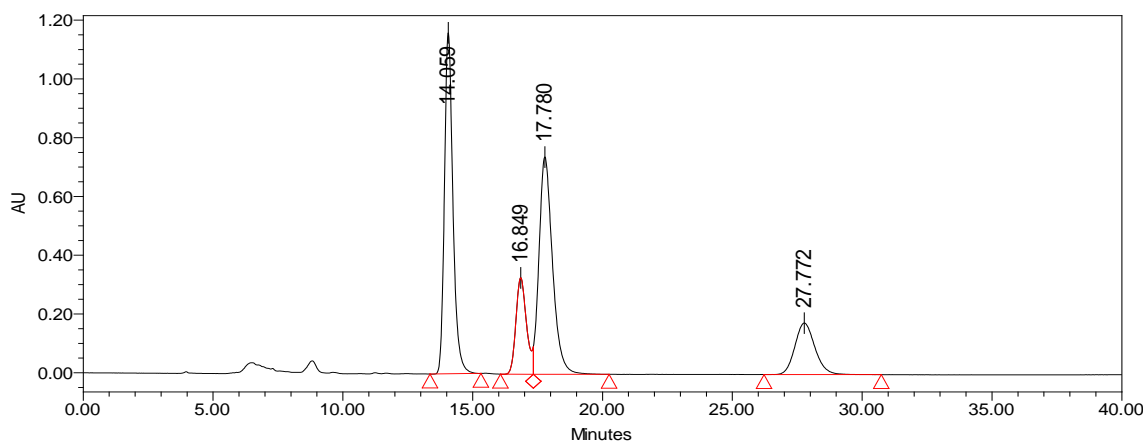
Retention Time	% Area
31.577	100.00

Experimental section

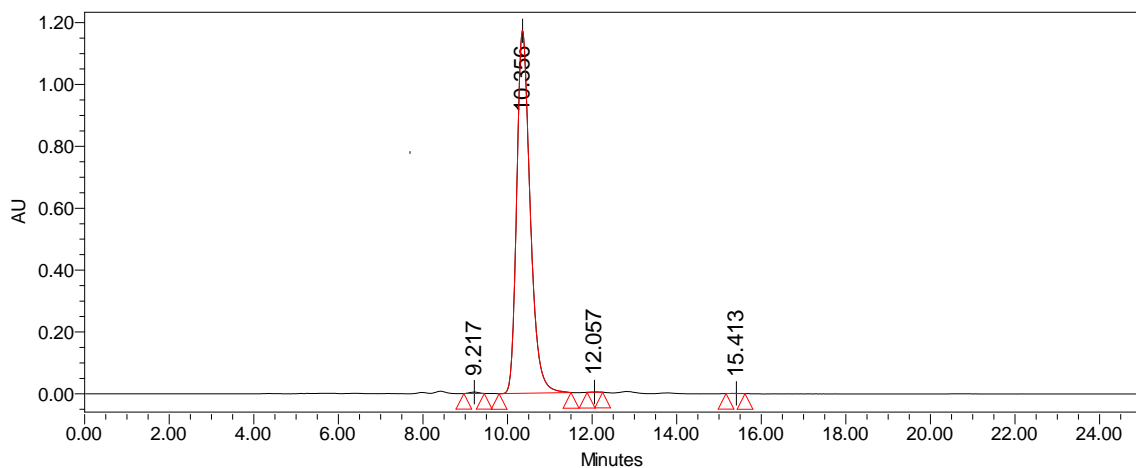
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18g**)



The enantiomeric purity of compound **18g** was determined by chiral HPLC analysis (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 14.0$ min (*anti*, minor.), 16.8 min (*syn*), 17.8 min (*anti*, major.), 27.7 min (*syn*). dr 99:1; 99% *ee*.

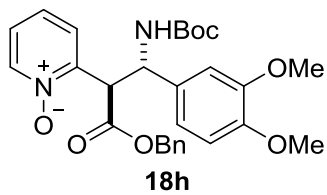


Retention Time	% Area
14.059	36.74
16.849	13.03
17.780	37.14
27.772	13.09

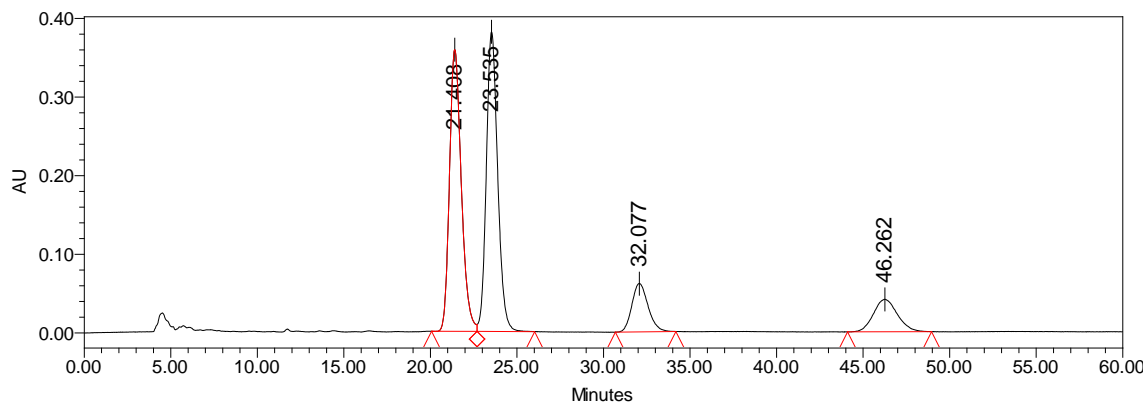


Retention Time	% Area
13.979	0.30
16.771	0.02
17.766	99.59
27.743	0.09

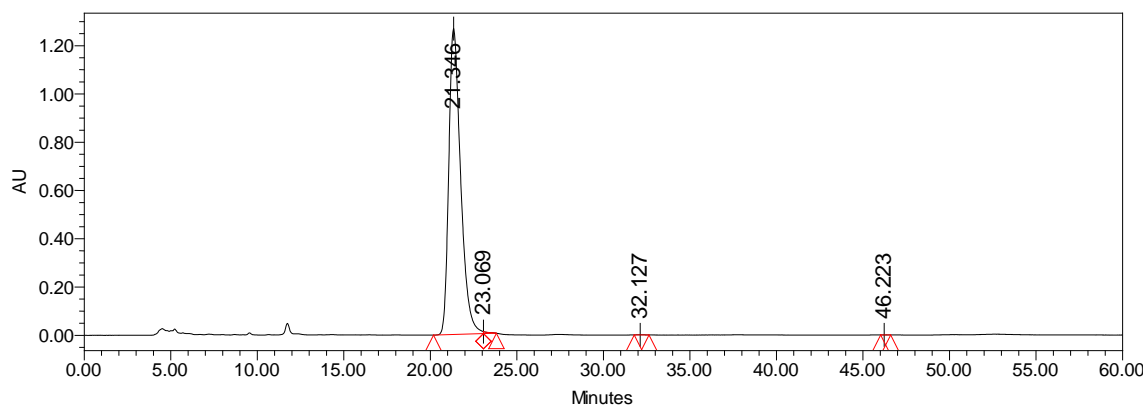
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18h)



The enantiomeric purity of compound **18h** was determined by chiral HPLC analysis (Chiralpack IC; 70:30 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 21.3$ min (*anti*, major.), 23.1 min (*anti*, minor.), 32.1 min (*syn*), 46.2 min (*syn*). dr 99:1; 99% *ee*.



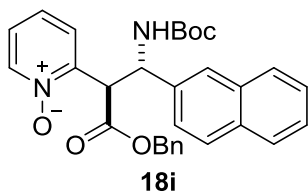
Retention Time	% Area
21.408	40.11
23.535	41.04
32.077	9.49
46.262	9.36



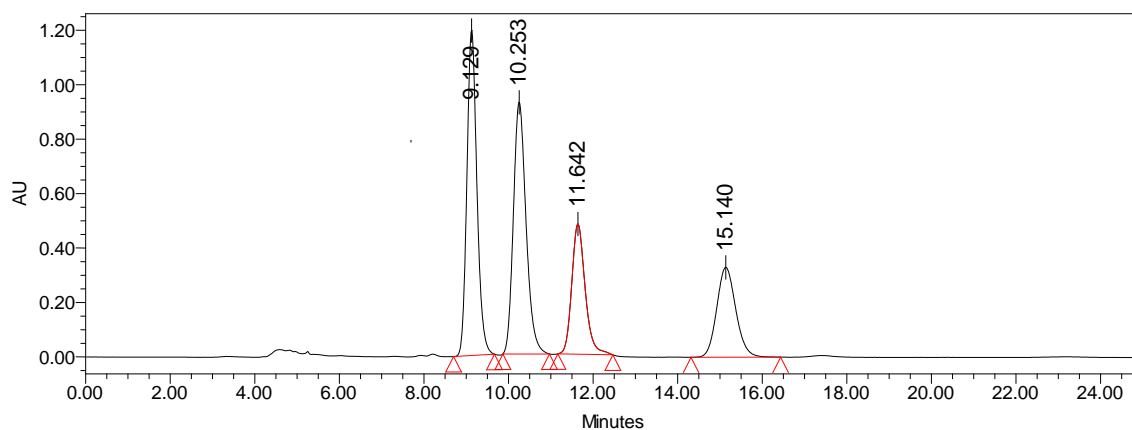
Retention Time	% Area
21.346	99.69
23.069	0.28
32.127	0.03
46.223	0.01

Experimental section

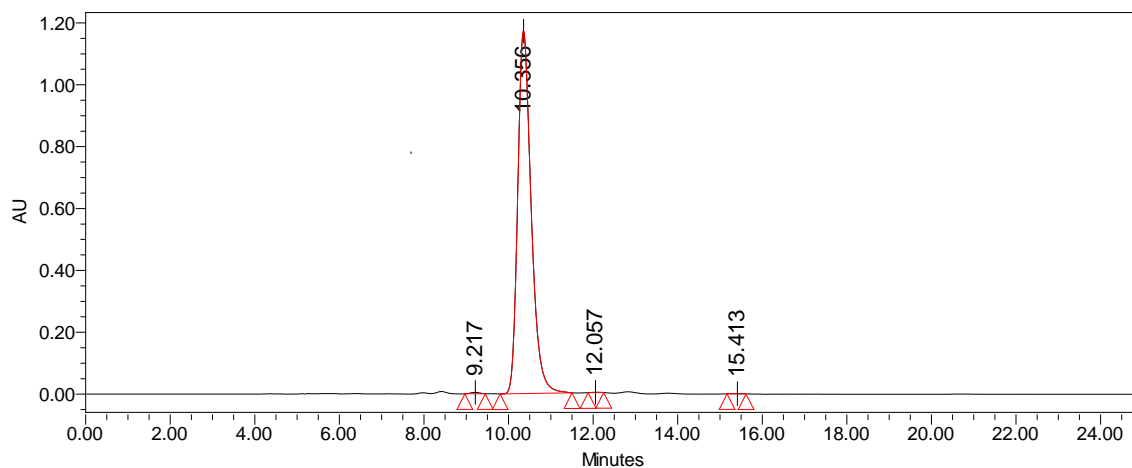
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18i**)



The enantiomeric purity of compound **18i** was determined by chiral HPLC analysis (Chiralpack IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 9.2$ min (*anti*, minor.), 10.4 min (*anti*, major.), 12.1 min (*syn*), 15.4 min (*syn*). dr 99:1; 99% *ee*.

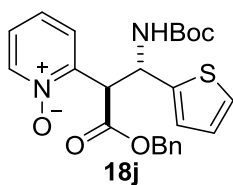


Retention Time	% Area
9.129	32.85
10.253	32.27
11.642	17.60
15.140	17.28

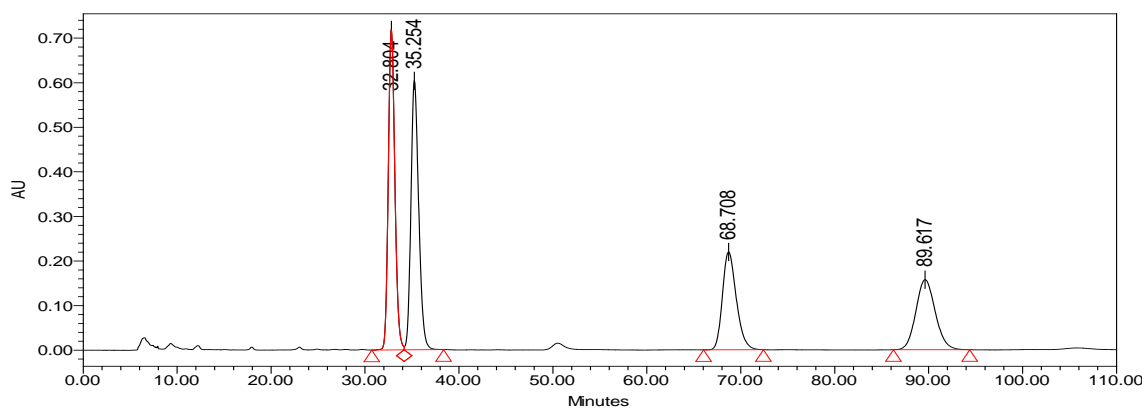


Retention Time	% Area
9.217	0.26
10.356	99.65
12.057	0.06
15.413	0.03

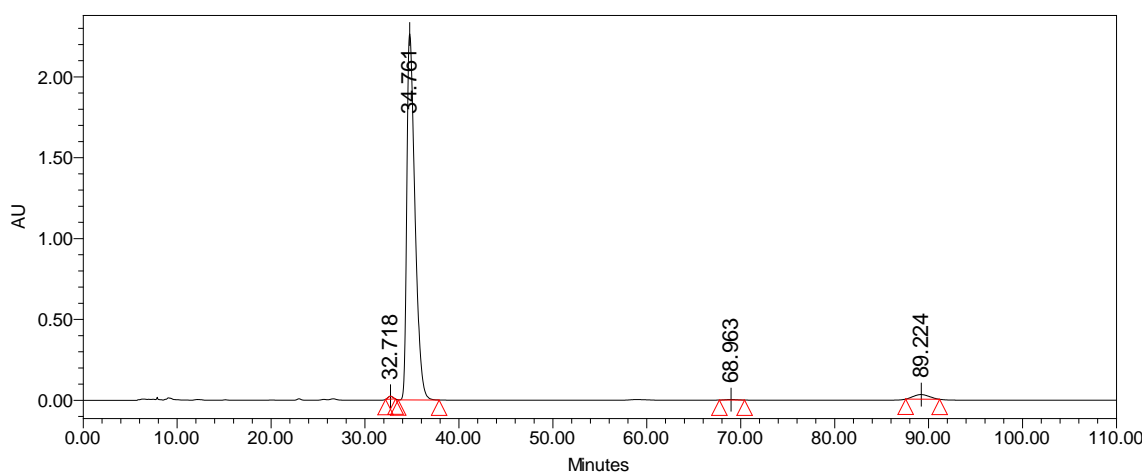
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)pyridine *N*-oxide (18j**)**



The enantiomeric purity of compound **18j** was determined by chiral HPLC analysis (Chiralpack IC; 80:20 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 32.7$ min (*anti*, minor.), 34.8 min (*anti*, major.), 69.0 min (*syn*), 89.2 min (*syn*). dr 99:1; 99% *ee*.



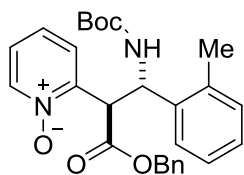
Retention Time	% Area
32.804	30.37
35.254	30.34
68.708	19.64
89.617	19.66



Retention Time	% Area
32.718	0.48
34.761	96.94
68.963	0.19
89.224	2.39

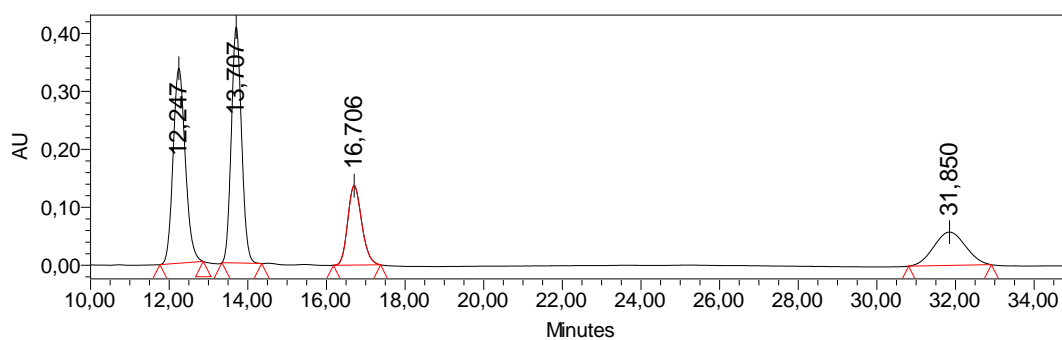
Experimental section

2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(*o*-tolyl)propan-2-yl)pyridine *N*-oxide (**18I**)

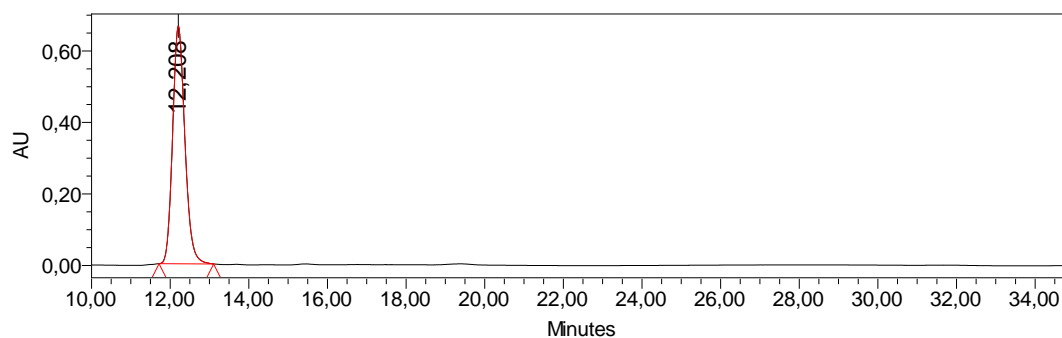


18I

The enantiomeric purity of compound **18I** was determined by chiral HPLC analysis (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 12.2$ min (*anti*, major.), 13.7 min (*anti*, minor.), 16.7 min (*syn*), 31.9 min (*syn*). dr 99:1; 99% *ee*.

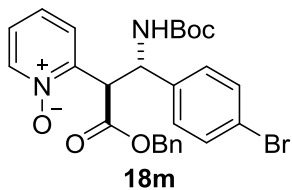


Retention Time	% Area
12.247	34.18
13.707	34.61
16.706	15.96
31.850	15.25

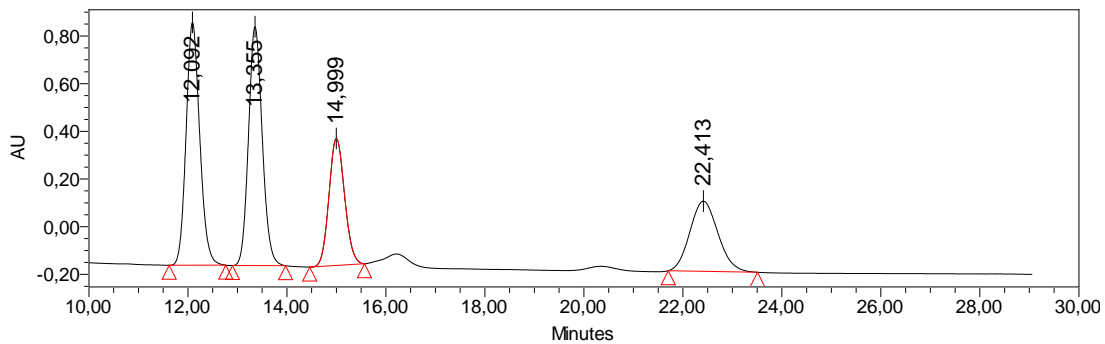


Retention Time	% Area
12.208	100.00

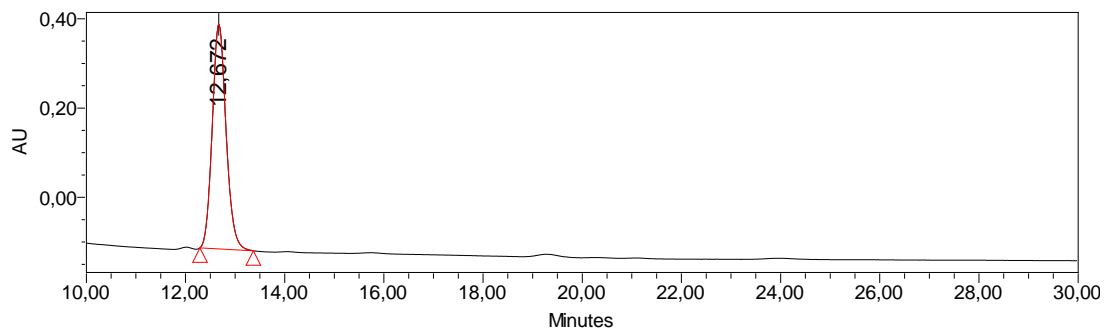
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(4-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-1-oxopropan-2-yl)pyridine *N*-oxide (18*m*)



The enantiomeric purity of compound **18*m*** was determined by chiral HPLC analysis (Chiralpack IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 12.1$ min (*anti*, major.), 13.4 min (*anti*, minor.), 15.0 min (*syn*), 22.4 min (*syn*). dr 99:1; 99% *ee*.



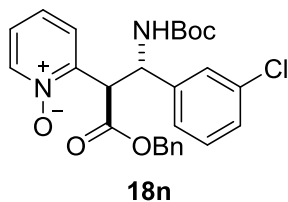
Retention Time	% Area
12.092	31.40
13.355	31.10
14.999	18.79
22.413	18.71



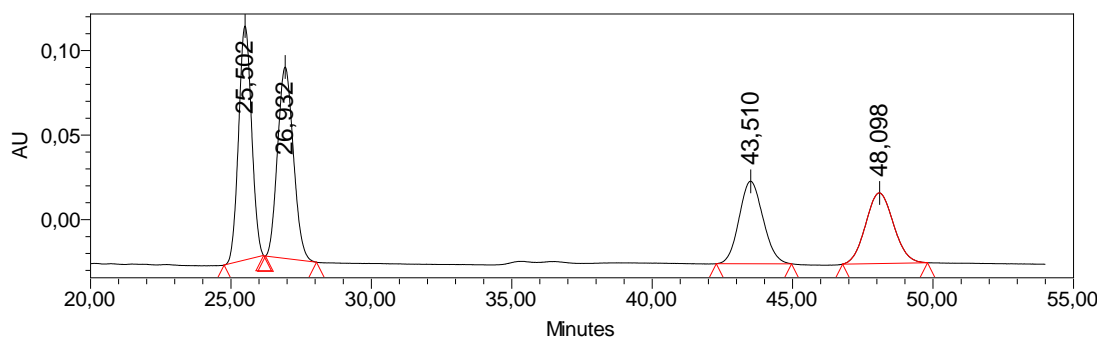
Retention Time	% Area
12.672	100.00

Experimental section

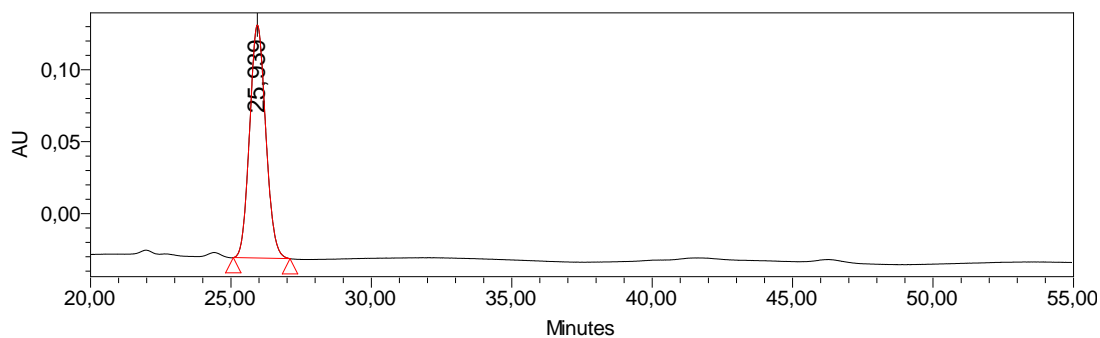
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18n**)



The enantiomeric purity of compound **18n** was determined by chiral HPLC analysis (Chiralpak IC; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 25.5$ min (*anti*, major.), 27.0 min (*anti*, minor.), 43.5 min (*syn*), 48.1 min (*syn*). dr 99:1; 99% *ee*.

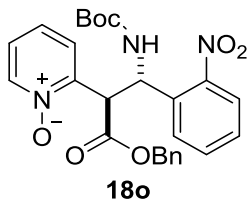


Retention Time	% Area
25.502	30.31
26.932	30.24
43.510	19.75
48.098	19.71

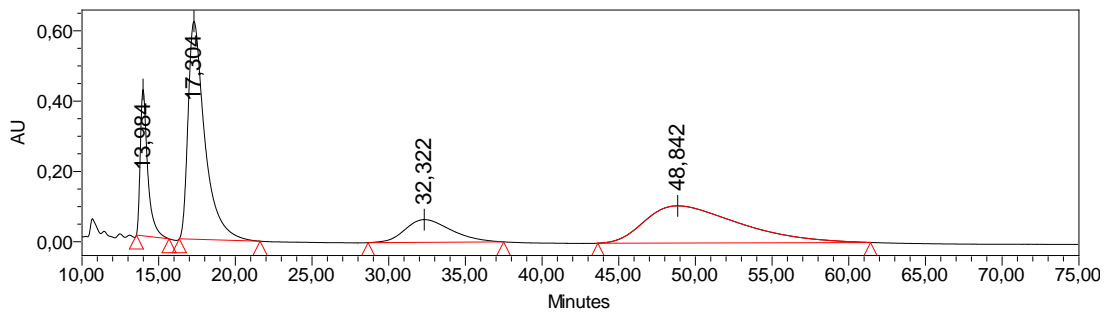


Retention Time	% Area
25.939	100.00

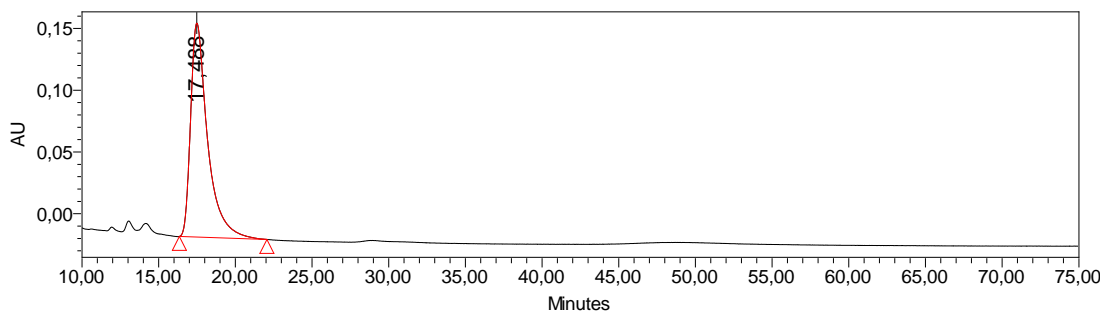
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(2-nitrophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18o**)**



The enantiomeric purity of compound **18o** was determined by chiral HPLC analysis (Chiralpack IA; 20:80 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 14.0$ min (*anti*, minor.), 17.4 min (*anti*, major.), 32.3 min (*syn*), 48.8 min (*syn*). dr 99:1; 99% *ee*.



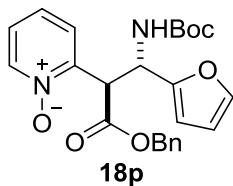
Retention Time	% Area
13.984	11.66
17.304	39.23
32.322	11.33
48.842	37.78



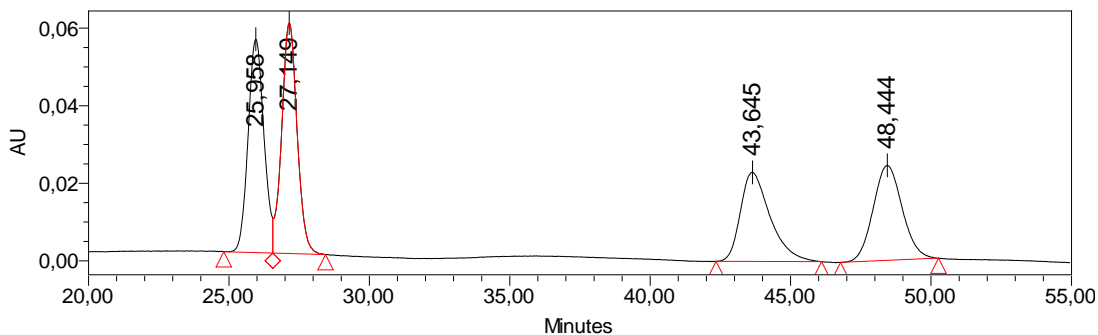
Retention Time	% Area
17.488	100.00

Experimental section

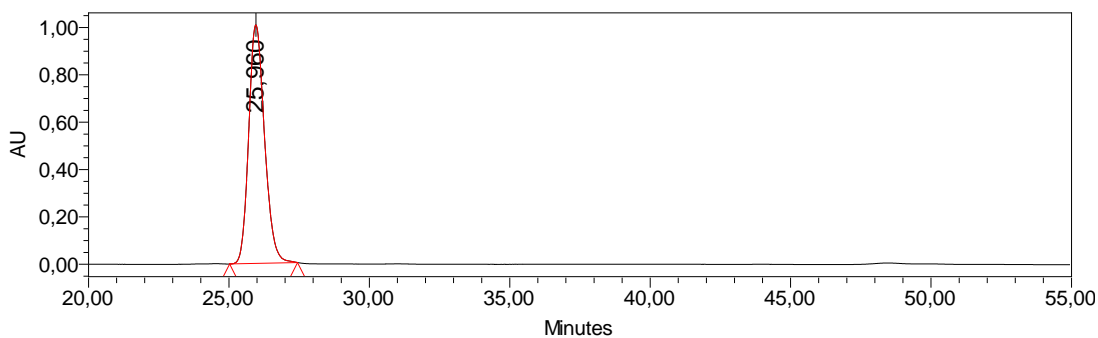
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (**18p**)



The enantiomeric purity of compound **18p** was determined by chiral HPLC analysis (Chiralpack IC; 80:20 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 26.0$ min (*anti*, major.), 27.1 min (*anti*, minor.), 43.6 min (*syn*), 48.4 min (*syn*). dr 99:1; 99% *ee*.

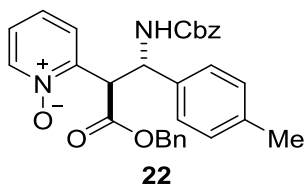


Retention Time	% Area
25.958	27.32
27.149	28.88
43.645	21.46
48.444	22.34

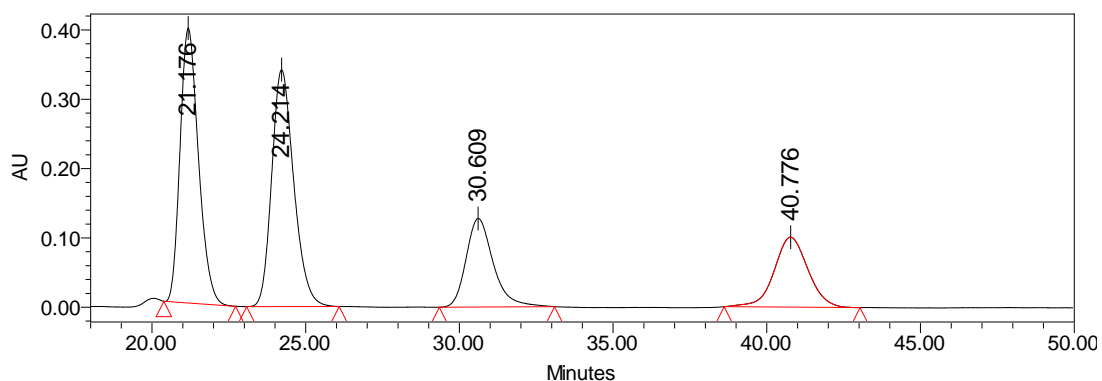


Retention Time	% Area
25.960	100.00

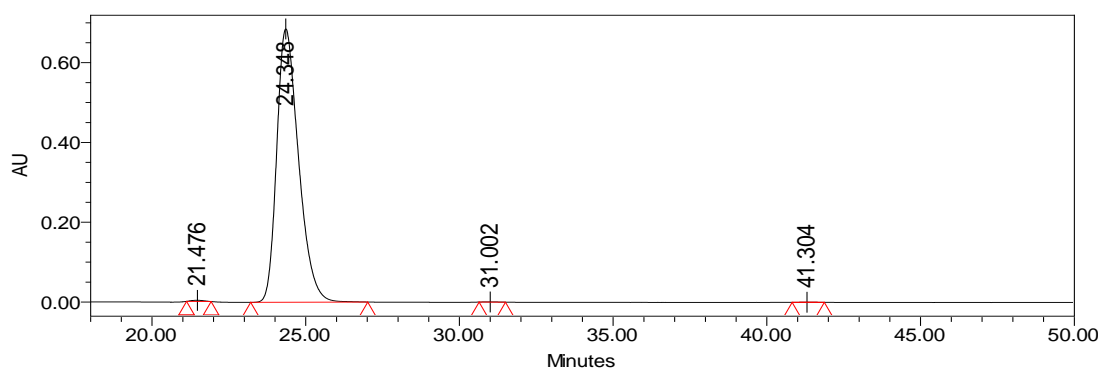
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(((benzyloxy)carbonyl)amino)-1-oxo-3-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (22**)**



The enantiomeric purity of compound **22** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 21.5$ min (*anti*, minor.), 24.3 min (*anti*, major.), 31.0 min (*syn*), 41.3 min (*syn*). dr 99:1; 99% *ee*.



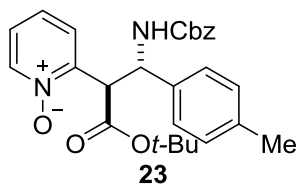
Retention Time	% Area
21.176	33.58
24.214	34.69
30.609	16.01
40.776	15.72



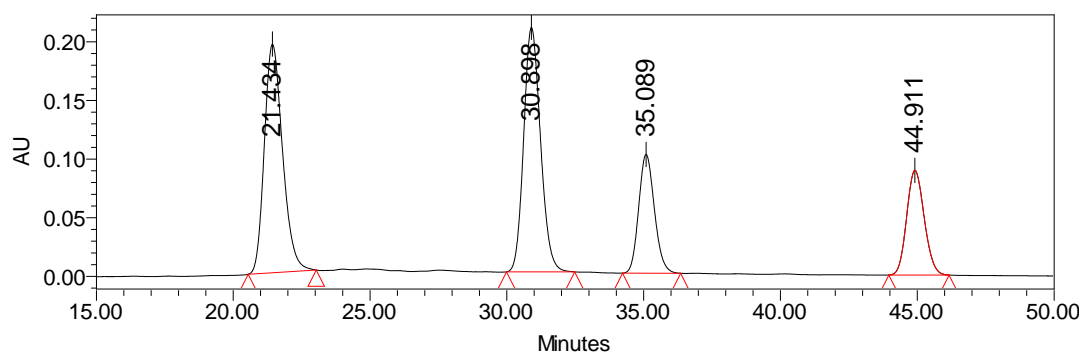
Retention Time	% Area
21.476	0.25
24.348	99.68
31.002	0.05
41.304	0.02

Experimental section

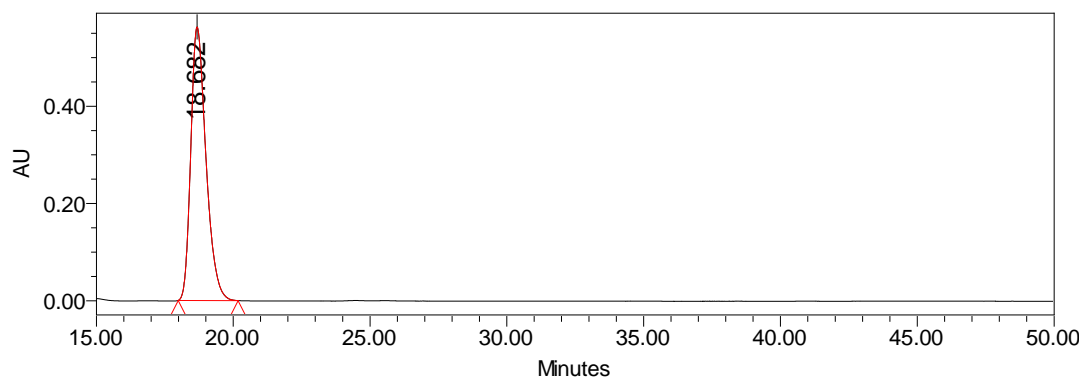
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (**23**)



The enantiomeric purity of compound **23** was determined by chiral HPLC analysis (Chiralpak IC; 60:40 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 18.7$ min (*anti*, major.), 30.9 min (*anti*, minor.), 35.1 min (*syn*), 44.9 min (*syn*). dr 99:1; 99% ee.

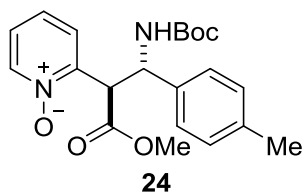


Retention Time	% Area
21.434	34.79
30.898	34.31
35.089	15.60
44.911	15.31

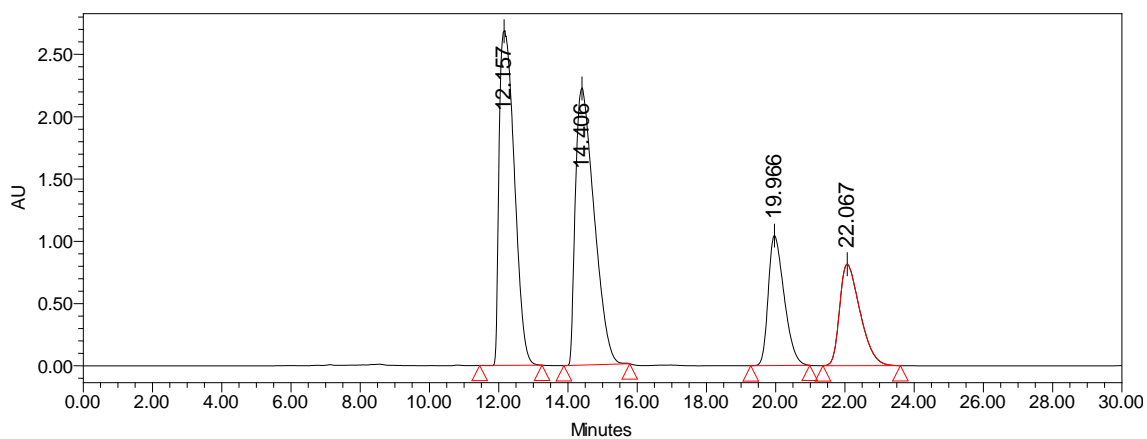


Retention Time	% Area
18.682	100.00

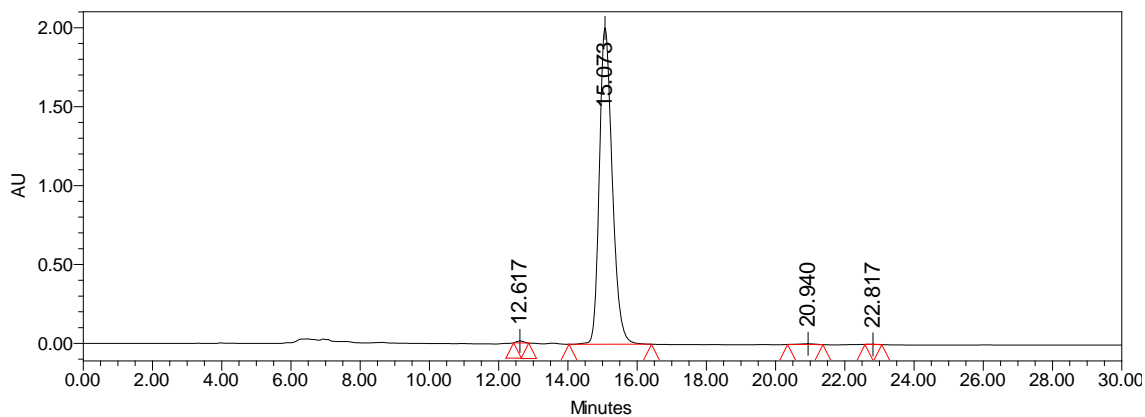
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (24)



The enantiomeric purity of compound **24** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 12.6$ min (*anti*, minor.), 15.0 min (*anti*, major.), 20.9 min (*syn*), 22.8 min (*syn*). dr 99:1; 99% ee.



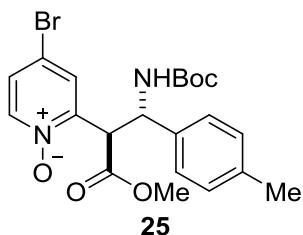
Retention Time	% Area
12.157	35.39
14.406	35.86
19.966	14.34
22.067	14.41



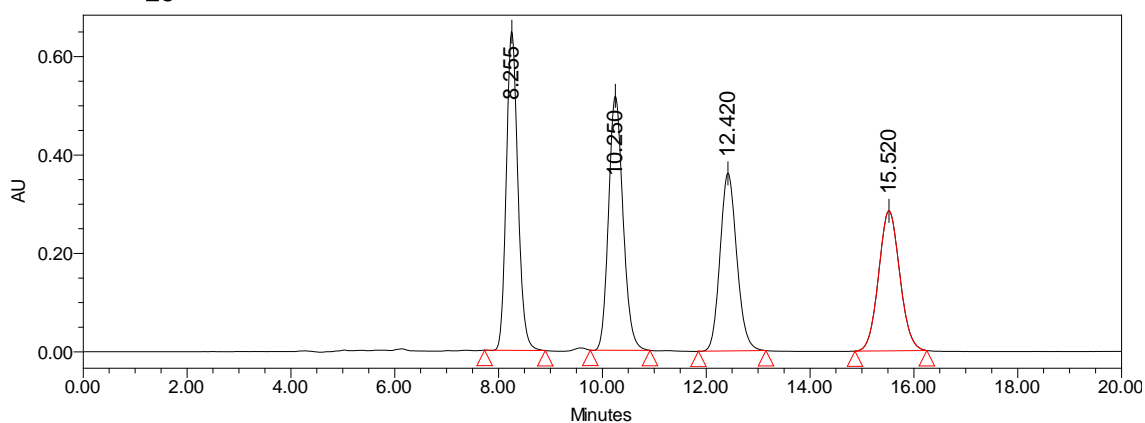
Retention Time	% Area
12.617	0.33
15.073	99.30
20.940	0.33
22.817	0.04

Experimental section

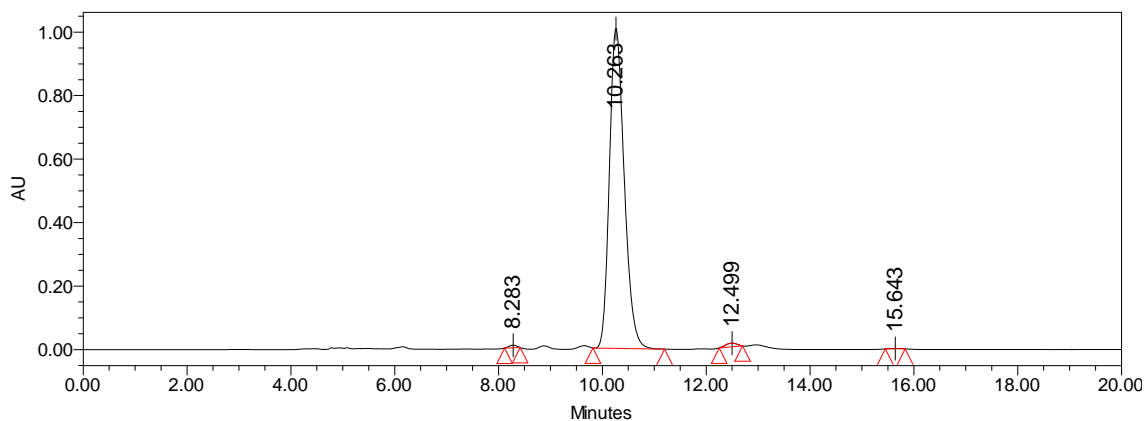
4-Bromo-2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (**25**)



The enantiomeric purity of compound **25** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 8.3$ min (*anti*, minor.), 10.3 min (*anti*, major.), 12.5 min (*syn*), 15.6 min (*syn*). dr 99:1; 99% *ee*.

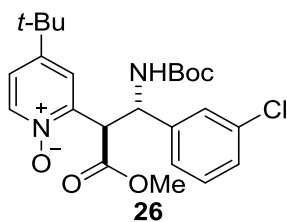


Retention Time	% Area
8.255	27.80
10.250	27.79
12.420	22.24
15.521	22.17

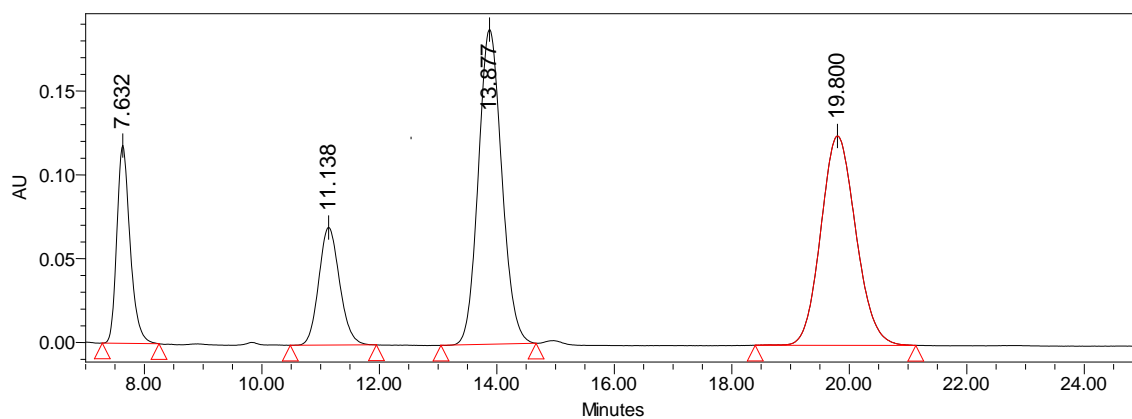


Retention Time	% Area
8.283	0.42
10.263	98.59
12.499	0.88
15.643	0.11

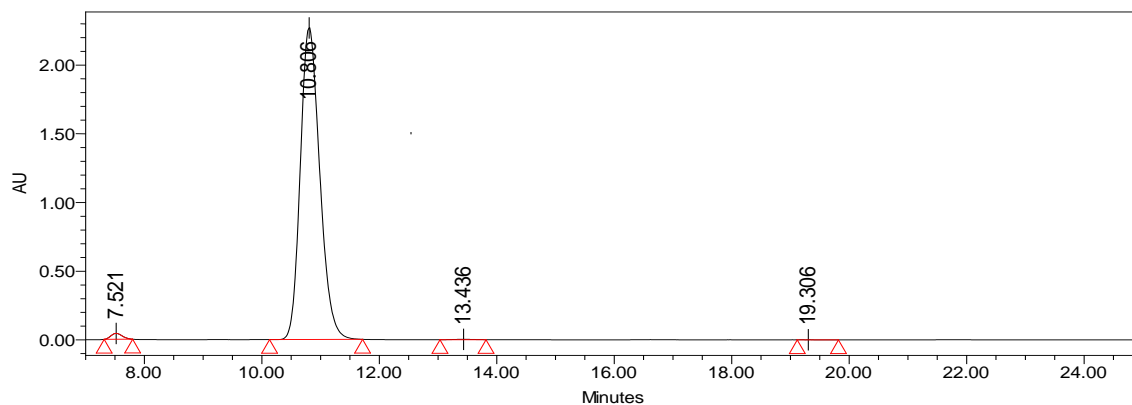
2-((1S,2R)-1-((*tert*-Butoxycarbonyl)amino)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (26)



The enantiomeric purity of compound **26** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 7.5$ min (*anti*, minor.), 10.8 min (*anti*, major.), 13.4 min (*syn*), 19.3 min (*syn*). dr 99:1; 98% *ee*.



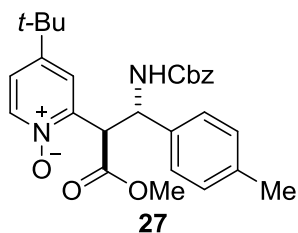
Retention Time	% Area
7.632	13.22
11.138	12.40
13.877	37.32
19.800	37.06



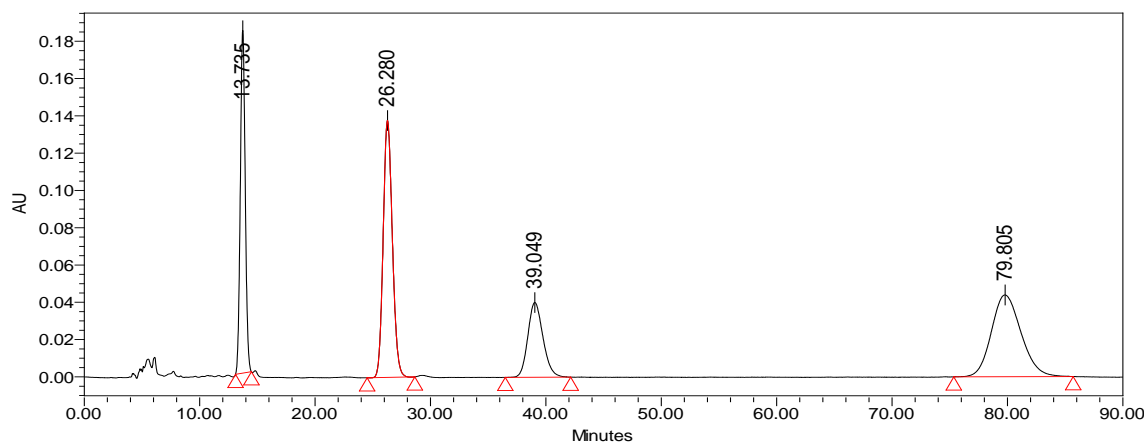
Retention Time	% Area
7.521	1.10
10.806	98.77
13.436	0.13
19.306	0.00

Experimental section

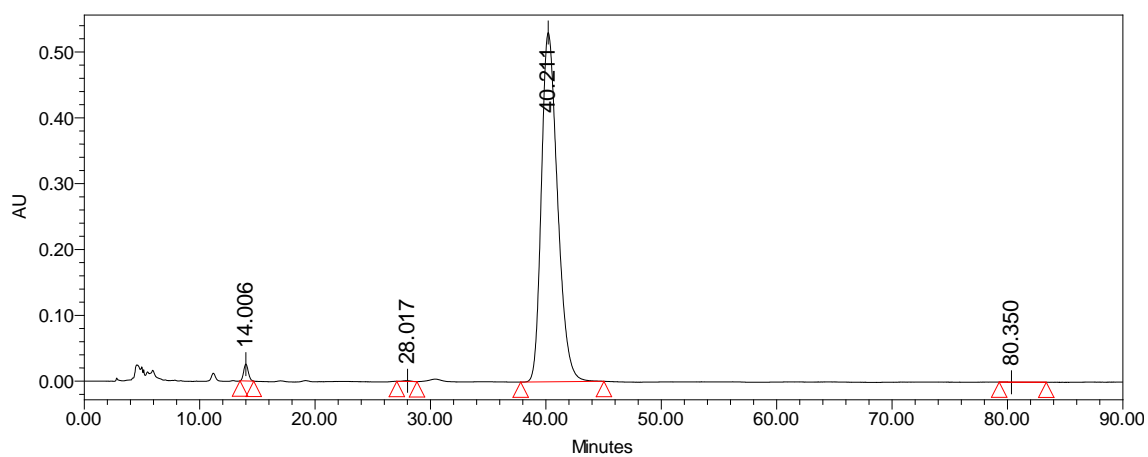
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (**27**)



The enantiomeric purity of compound **27** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 14.0$ min (*anti*, minor.), 28.0 min (*syn*), 40.2 min (*anti*, major.), 80.4 min (*syn*). dr 99:1; 98% *ee*.

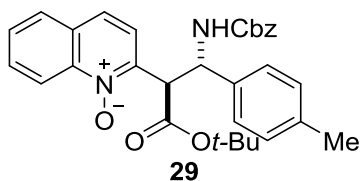


Retention Time	% Area
13.735	19.02
26.280	31.10
39.049	18.01
79.805	31.87

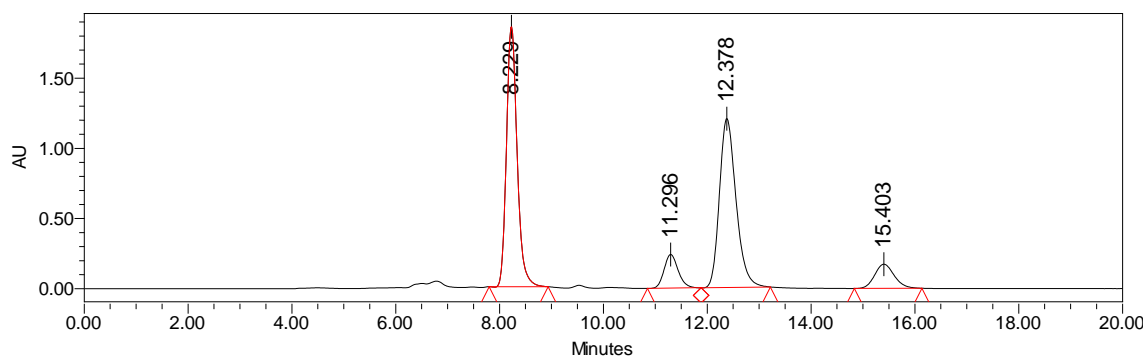


Retention Time	% Area
14.006	1.37
28.017	0.10
40.211	98.51
80.350	0.02

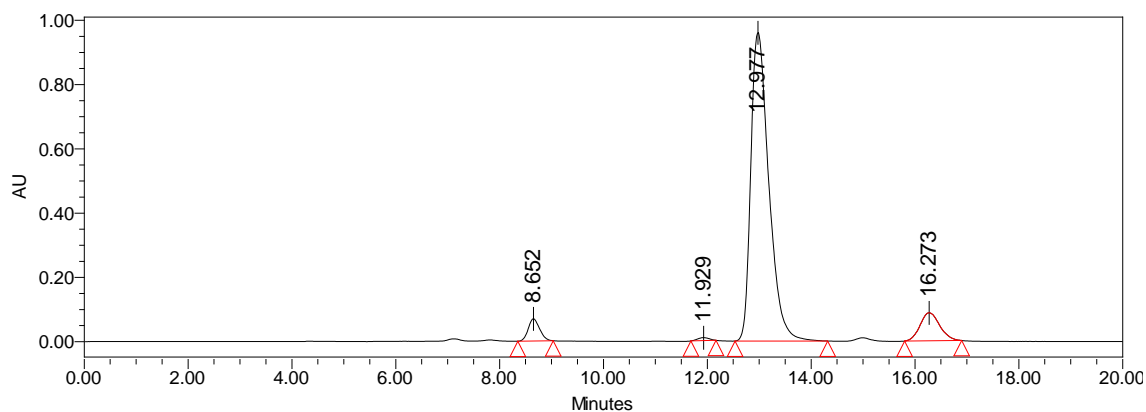
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)quinoline *N*-oxide (29**)**



The enantiomeric purity of compound **29** was determined by chiral HPLC analysis (Chiralpak IC; 70:30 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 8.6$ min (*anti*, minor.), 11.9 min (*syn*, minor.), 13.0 min (*anti*, major.), 16.2 min (*syn*, major.). dr 10:1; 92% *ee*.



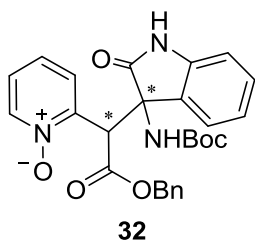
Retention Time	% Area
8.229	42.55
11.296	7.27
12.378	42.93
15.403	7.25



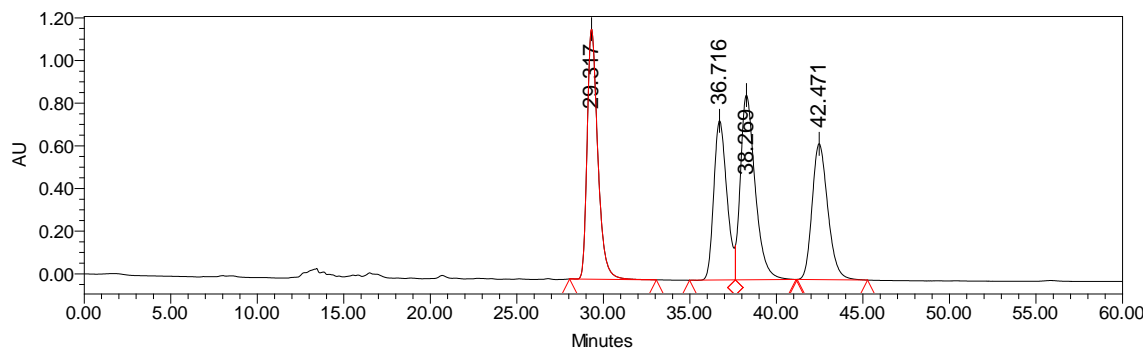
Retention Time	% Area
8.652	3.95
11.929	0.55
12.977	86.88
16.273	8.62

Experimental section

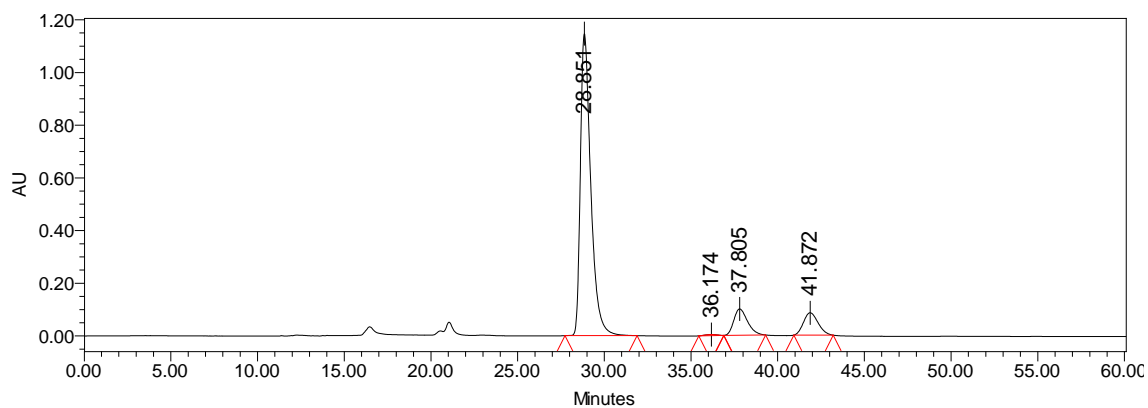
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (**32**)



The enantiomeric purity of compound **32** was determined by chiral HPLC analysis (Chiralpak IC + Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 28.9$ min (diast. A, major.), 36.1 min (diast. B, minor.), 37.8 min (diast. A, minor.), 41.8 min (diast. B, major). dr 10:1; 80% *ee*.

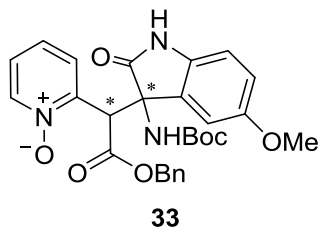


Retention Time	% Area
29.317	27.72
36.716	21.78
38.269	28.28
42.471	22.23

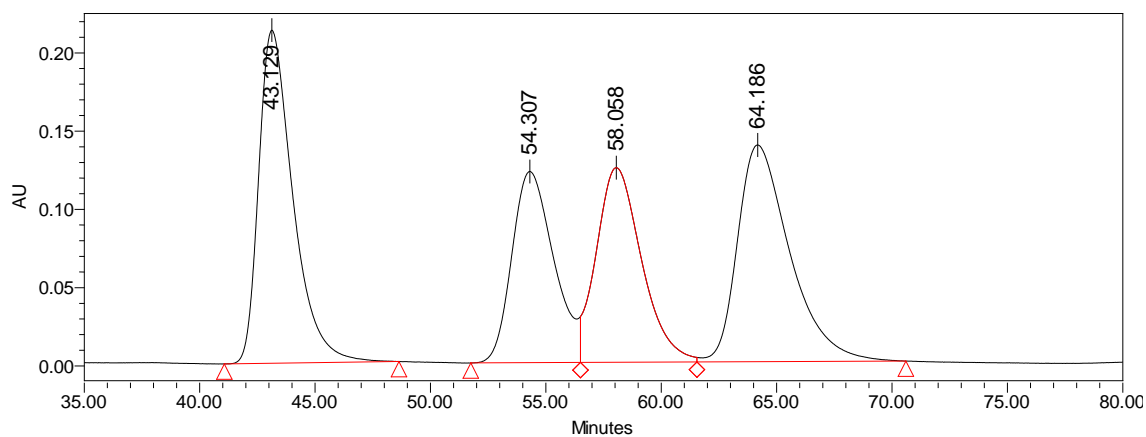


Retention Time	% Area
28.851	81.76
36.174	0.34
37.805	9.40
41.872	8.50

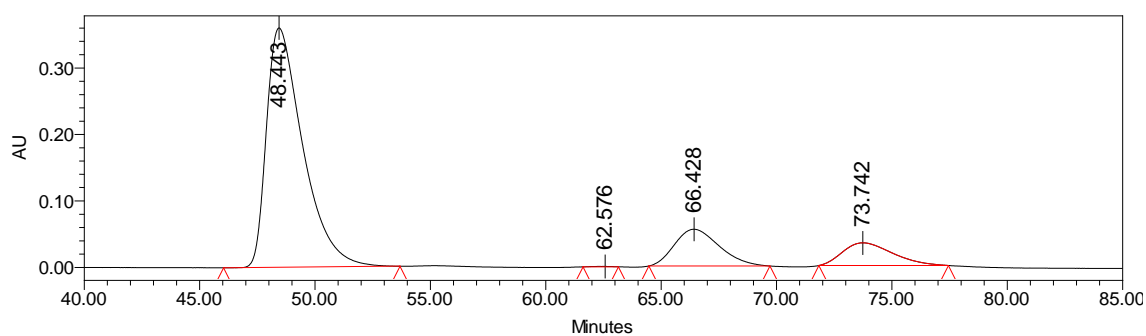
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-5-methoxy-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (33)



The enantiomeric purity of compound **33** was determined by chiral HPLC analysis (Chiralpak IC; 80:20 Hexane:Ethanol; 0.7 mL/min, $\lambda = 210$ nm) $t_R = 43.1$ min (diast. A, major.), 62.6 min (diast. B, minor.), 66.4 min (diast. A, minor.), 73.7 min (diast. B, major). dr 6.1:1; 78% *ee*.



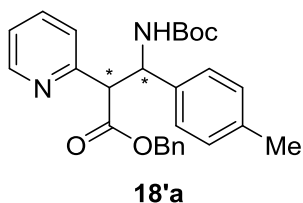
Retention Time	% Area
43.129	28.81
54.307	21.16
58.058	21.40
64.186	28.63



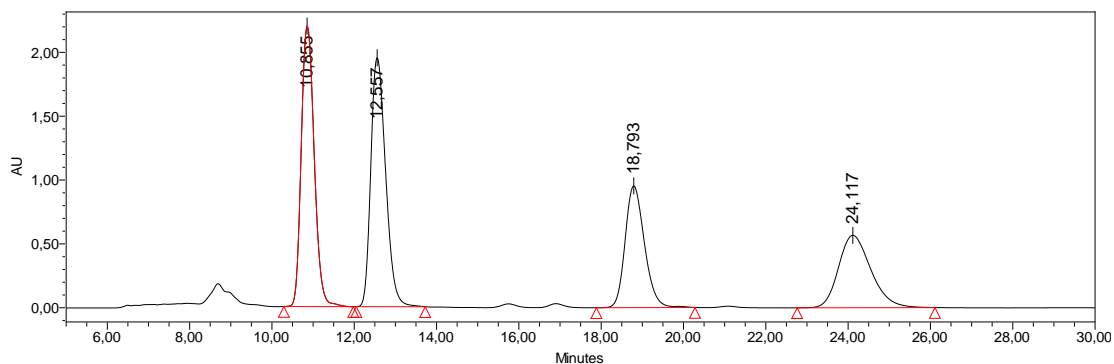
Retention Time	% Area
48.443	75.78
62.576	0.06
66.428	14.31
73.742	9.85

Experimental section

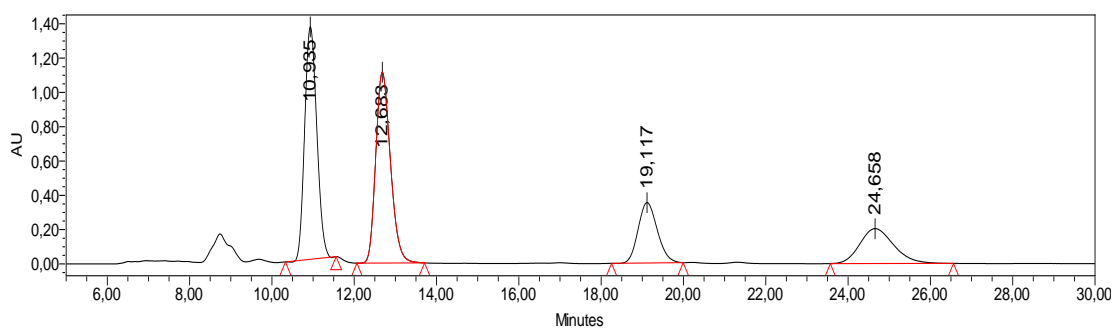
Benzyl 3-((*tert*-butoxycarbonyl)amino)-2-(pyridin-2-yl)-3-(*p*-tolyl)propanoate (**18'a**)



The enantiomeric purity of compound **18'a** was determined by chiral HPLC analysis (Chiralpak IC; 50:50 Hexane:*i*PrOH; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 10.9$ min (*anti*), 12.7 min (*anti*), 19.1 min (*syn*), 24.1 min (*syn*). dr 2.6:1; 0/0% *ee*.

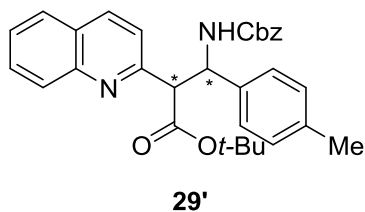


Retention Time	% Area
10.855	30.29
12.557	30.71
18.793	19.56
24.117	19.44



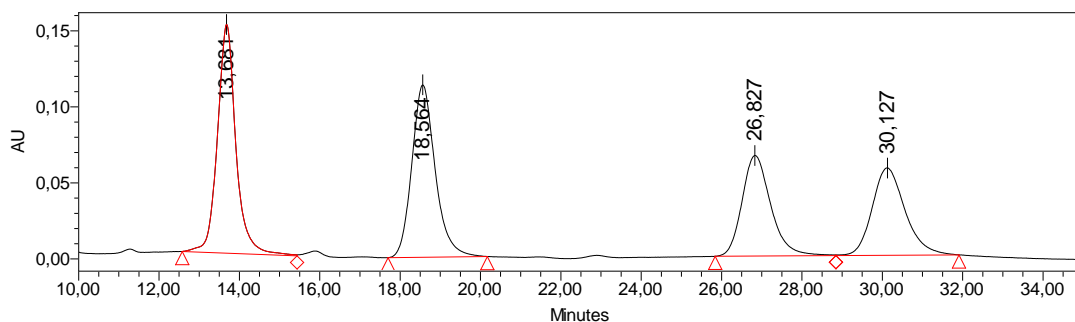
Retention Time	% Area
10.935	35.73
12.683	35.27
19.117	14.40
24.658	14.60

tert-Butyl 3-(((benzyloxy)carbonyl)amino)-2-(quinolin-2-yl)-3-(*p*-tolyl)propanoate (29')

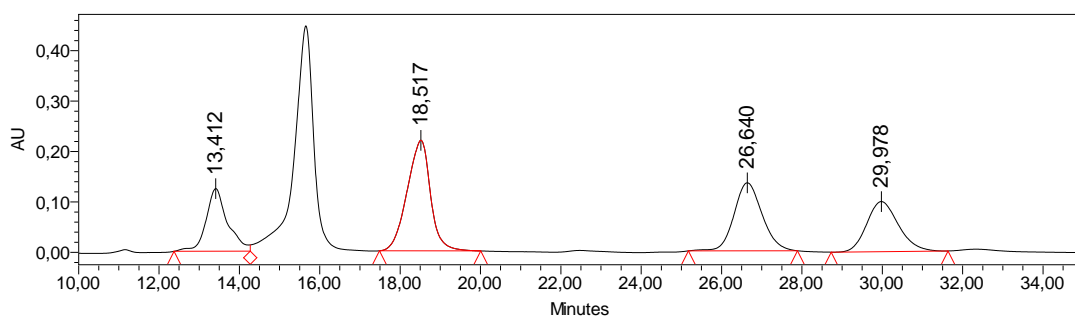


The enantiomeric purity of compound **29'** was determined by chiral HPLC analysis (Chiralpak IC; 80:20 Hexane:*i*PrOH; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 13.4$ min (diast. A, minor.), 18.5 min (diast. A, major.), 26.6 min (diast. B, major.), 30.0 min (diast. B, minor.). dr 1.1:1; 31/9% *ee*.

31/9% *ee*.



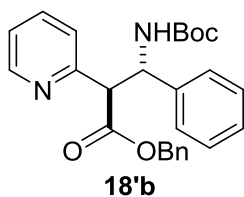
Retention Time	% Area
13.681	30.13
18.564	28.75
26.827	20.62
30.127	20.51



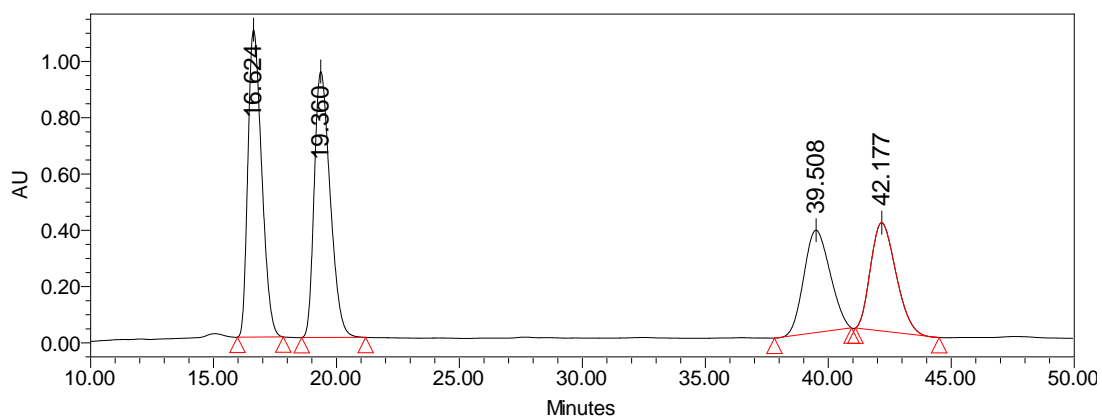
Retention Time	% Area
13.412	18.12
18.517	34.70
26.640	25.78
29.978	21.39

Experimental section

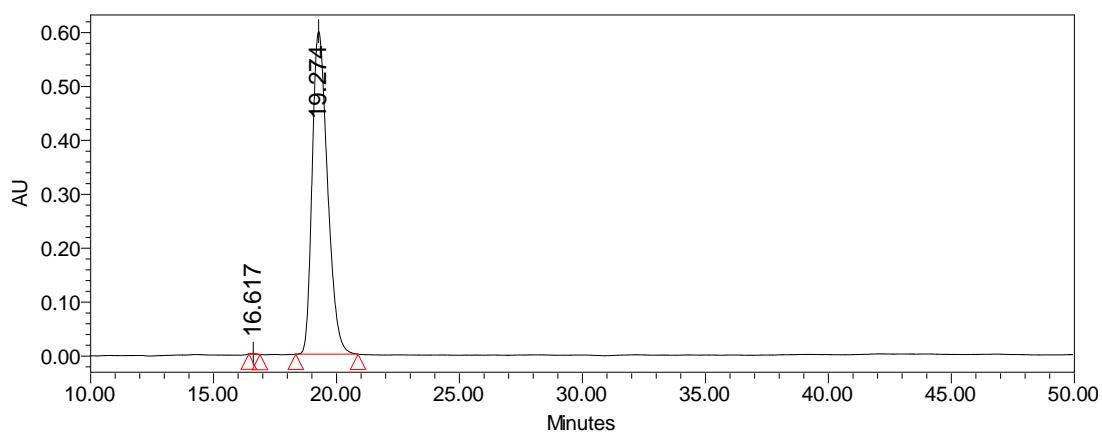
Benzyl (2*R*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-phenyl-2-(pyridin-2-yl)propanoate (18'*b*)



The enantiomeric purity of compound **18'*b*** was determined by chiral HPLC analysis (Chiralpak IC; 80:20 Hexane:Isopropanol; 0.5 mL/min, $\lambda = 210$ nm) $t_R = 16.6$ min (*anti*, minor.), 19 min (*anti*, major.), 39.5 min (*syn*), 42.2 min (*syn*). dr 99:1; 99% *ee*.



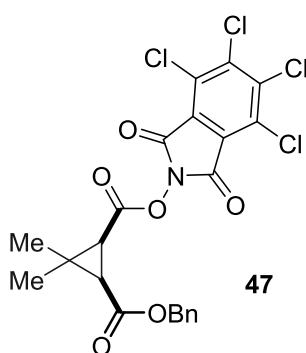
Retention Time	% Area
16.624	30.26
19.360	30.23
39.508	19.56
42.177	19.95



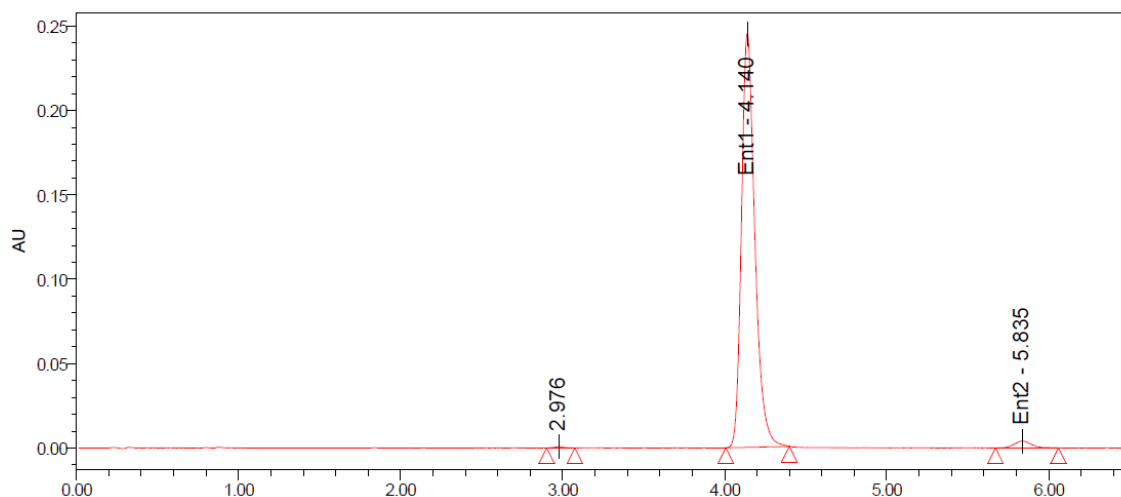
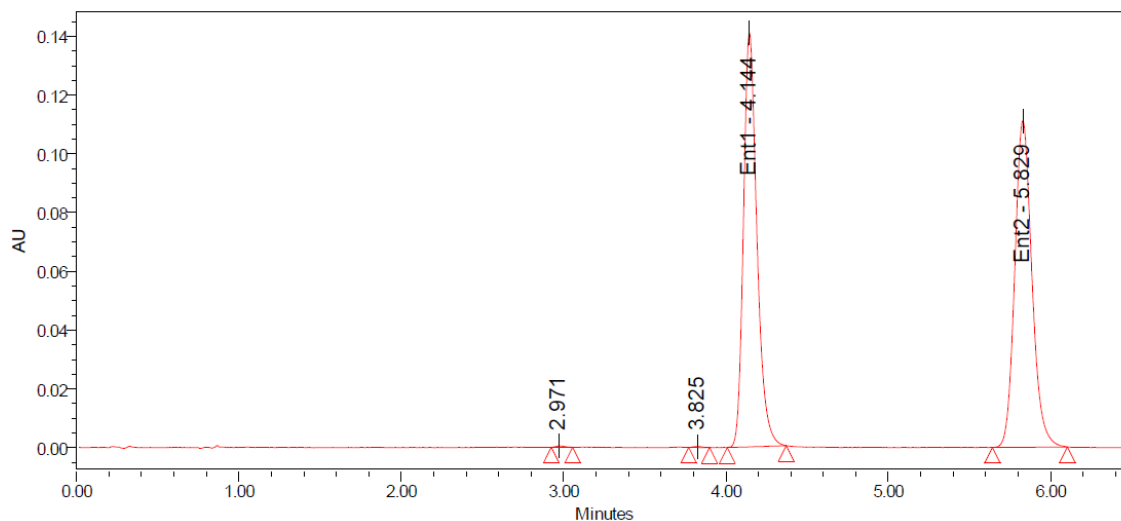
Retention Time	% Area
16.617	0.05
19.274	99.95

6.7.3. SFC Chromatograms for Chapter 4

1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) (1*R*,2*S*)-3,3-dimethylcyclopropane-1,2-dicarboxylate (**47**)



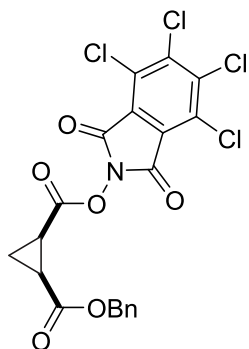
The enantiopurity of compound **47** was determined by chiral SFC analysis (Daicel IB; 40% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 238$ nm). t_R (major) = 4.14 min, t_R (minor) = 5.84 min. 96% ee.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	47.rac	49.70	50.30	-0.59	1001432	1013351
2	47	2.10	97.90	-95.81	59016	2757971

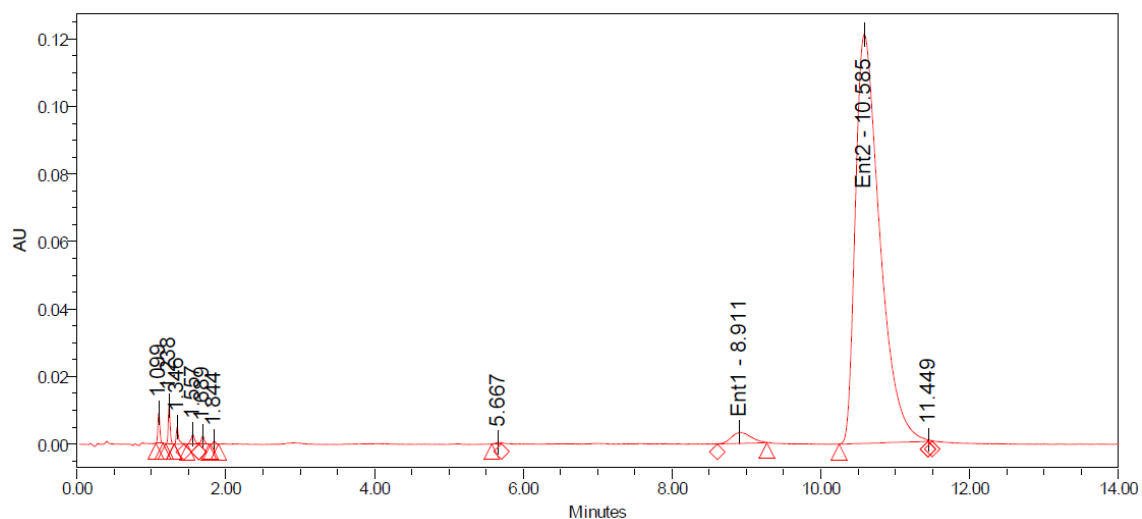
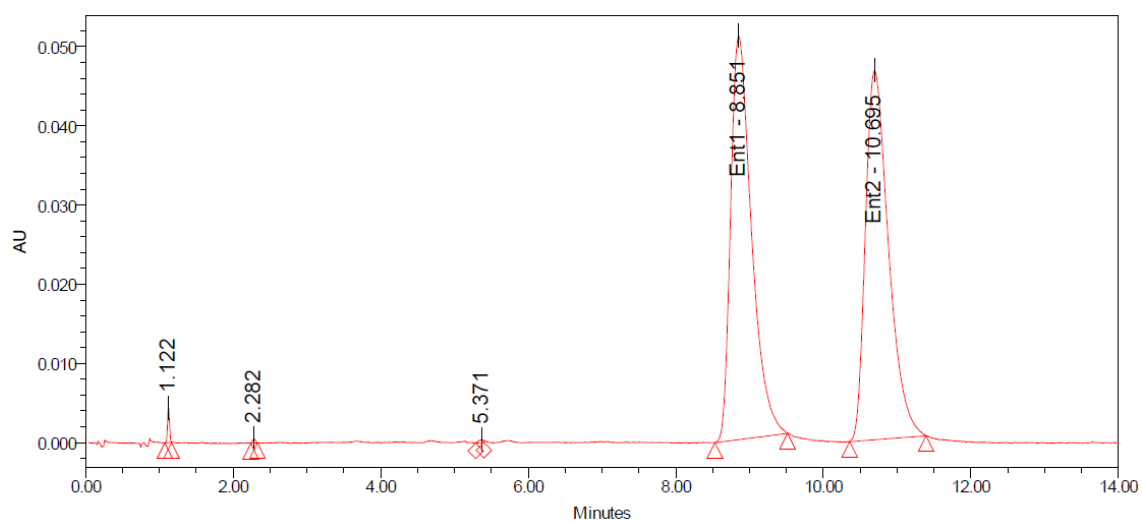
Experimental section

1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl) (1*R*,2*S*)-cyclopropane-1,2-dicarboxylate (**48**)

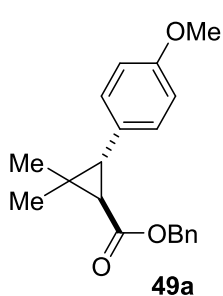


48

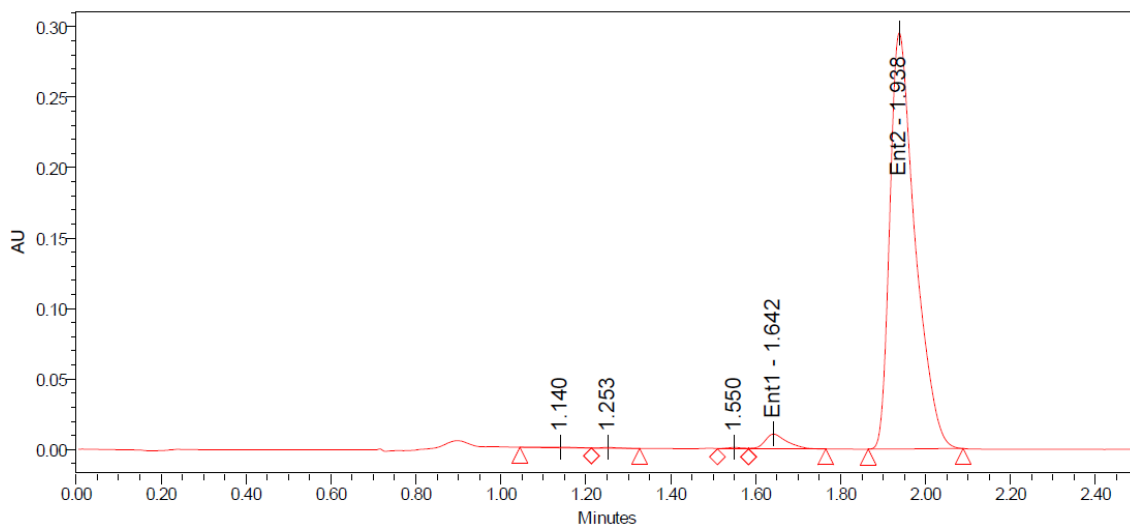
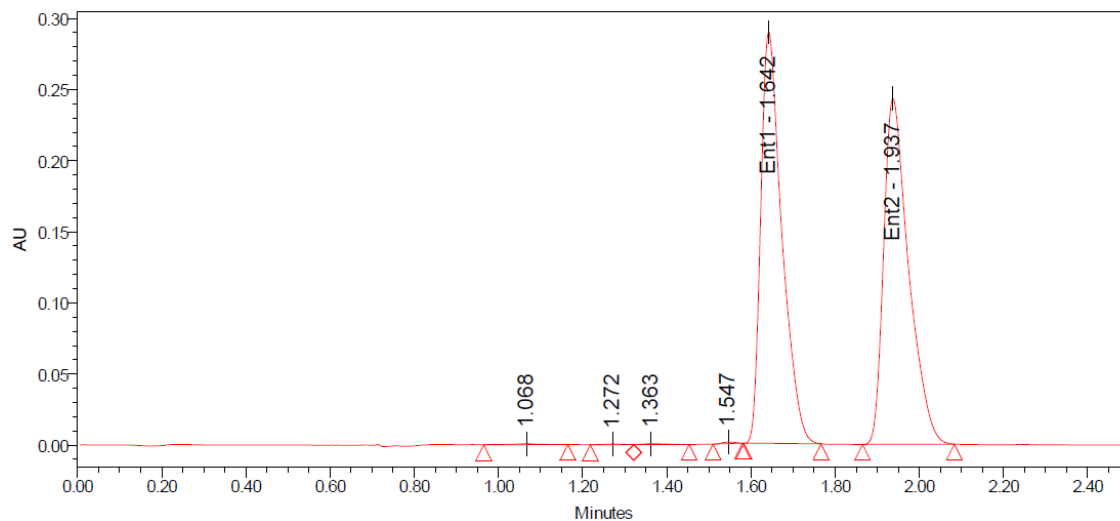
The enantiopurity of compound **48** was determined by chiral SFC analysis (Daicel IA; 40% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 238$ nm). t_R (minor) = 8.91 min, t_R (major) = 10.59 min, 96% ee.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	48.rac	49.81	50.19	-0.37	810298	816337
2	48	97.93	2.07	95.87	1409889	29746

Benzyl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (49a)


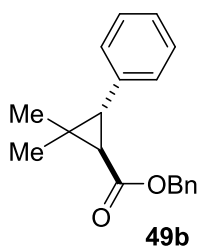
The enantiopurity of compound **49a** was determined by chiral SFC analysis (Daicel IG; 30% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; λ = 226 nm). t_R (minor) = 1.64 min, t_R (major) = 1.94 min, 94% ee.



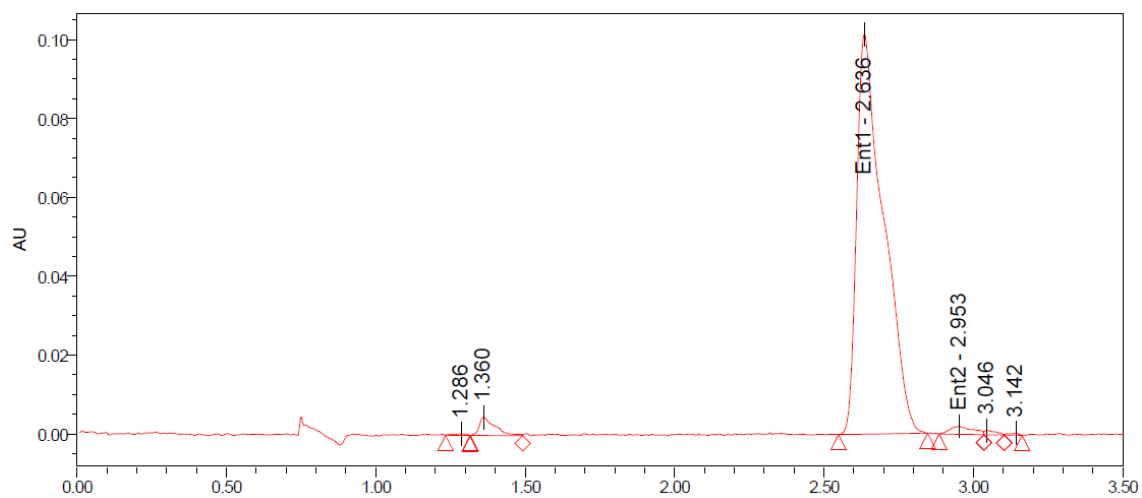
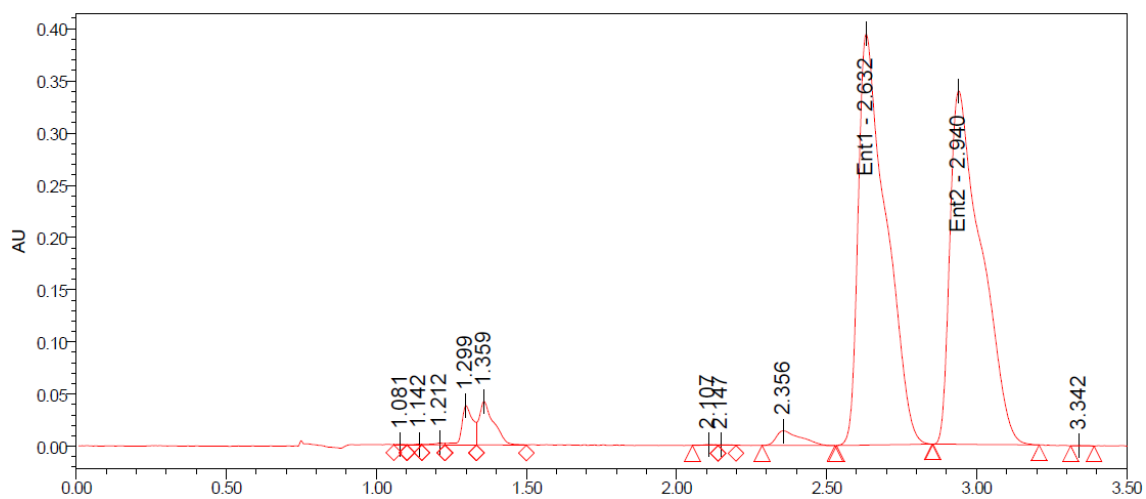
	Compound	ent1	ent2	ee	Ent1	Ent2
1	49a.rac	50.08	49.92	0.16	1004427	1001168
2	49a	3.02	96.98	-93.96	37897	1216276

Experimental section

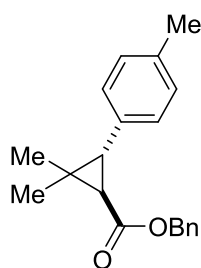
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (**49b**)



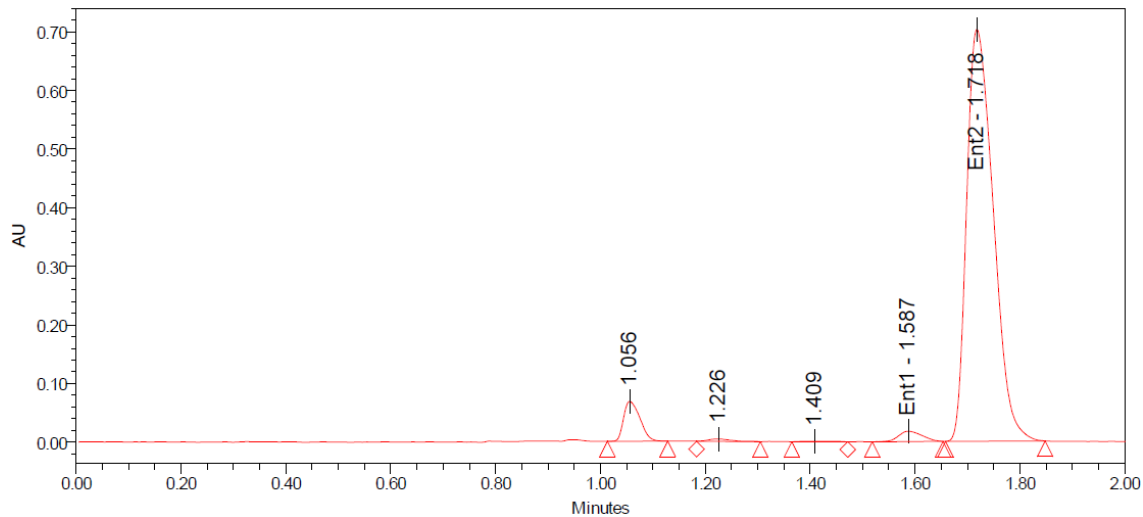
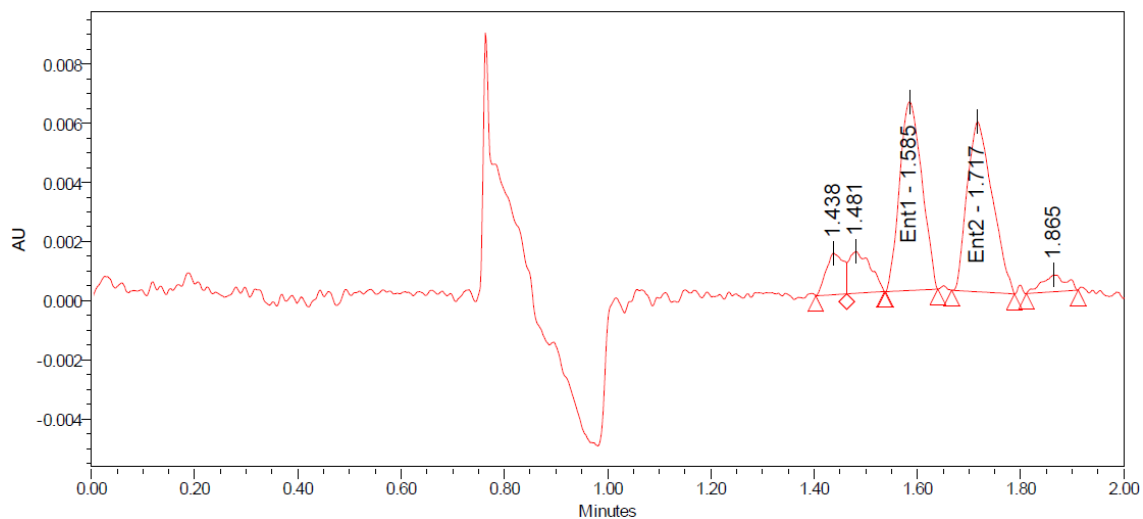
The enantiopurity of compound **49b** was determined by chiral SFC analysis (Daicel IG; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.63 min, t_R (major) = 2.94 min, 96% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	49b.rac	50.81	49.19	1.63	2535829	2454532
2	49b	98.31	1.69	96.62	631958	10873

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropane-1-carboxylate (49c)
**49c**

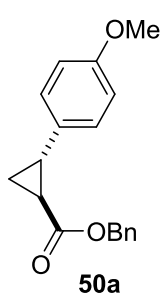
The enantiopurity of compound **49c** was determined by chiral SFC analysis (Daicel IC; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 1.59 min, t_R (major) = 1.72 min, 94% *ee*.



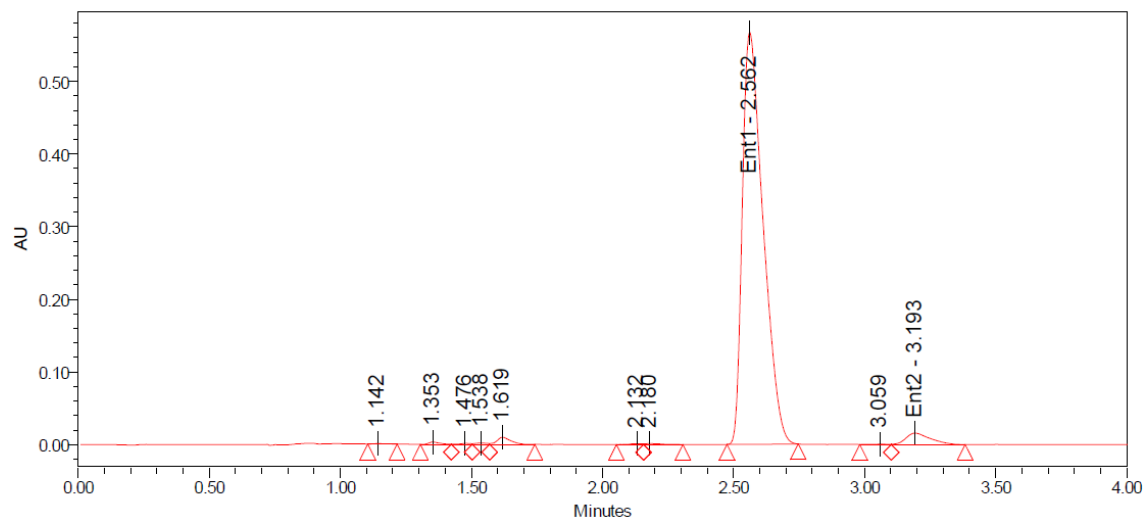
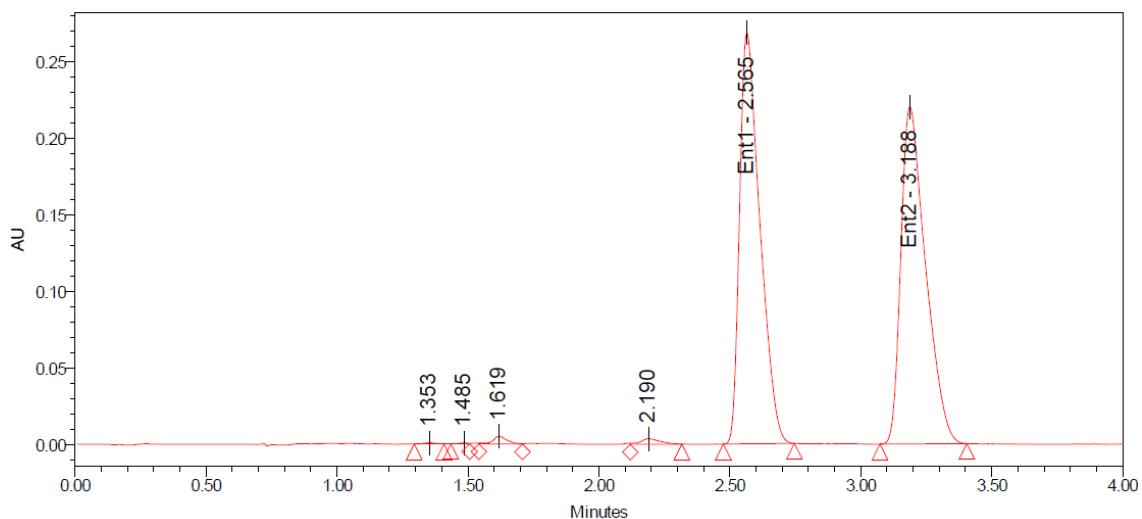
	Compound	ent1	ent2	ee	Ent1	Ent2
1	49c.rac	49.48	50.52	-1.03	19158	19557
2	49c	2.17	97.83	-95.66	55005	2478703

Experimental section

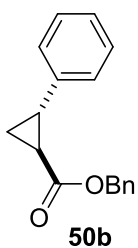
Benzyl (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (**50a**)



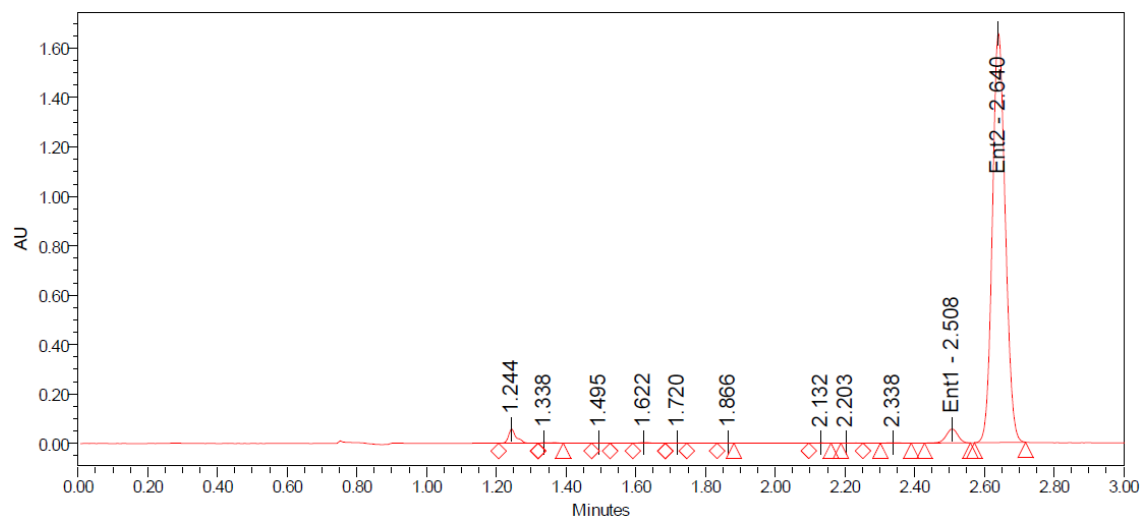
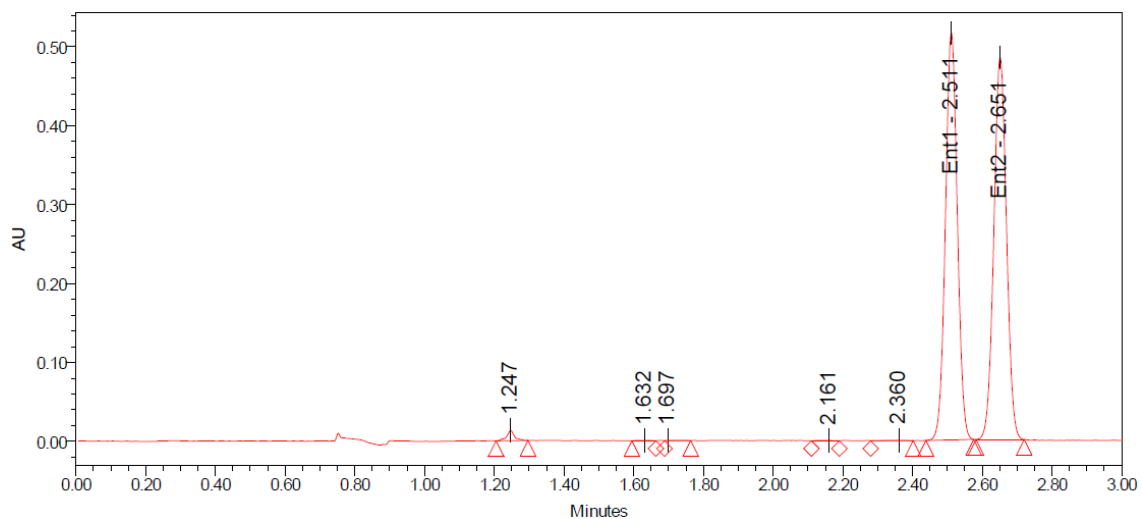
The enantiopurity of compound **50a** was determined by chiral SFCa analysis (Daicel IG; 35% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 231$ nm). t_R (minor) = 2.57 min, t_R (major) = 3.19 min, 94% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	50a.rac	50.03	49.97	0.06	1441439	1439750
2	50a	96.83	3.17	93.65	3113934	102106

Benzyl (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylate (50b)

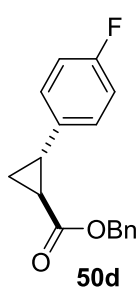
The enantiopurity of compound **50b** was determined by chiral SFC analysis (Daicel IBN; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.51 min, t_R (major) = 2.65 min, 94% *ee*.



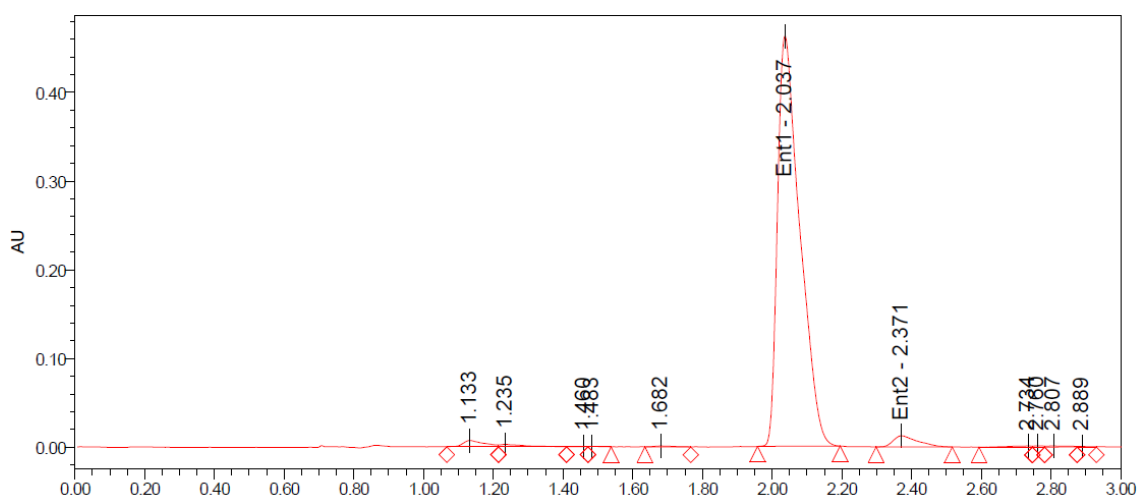
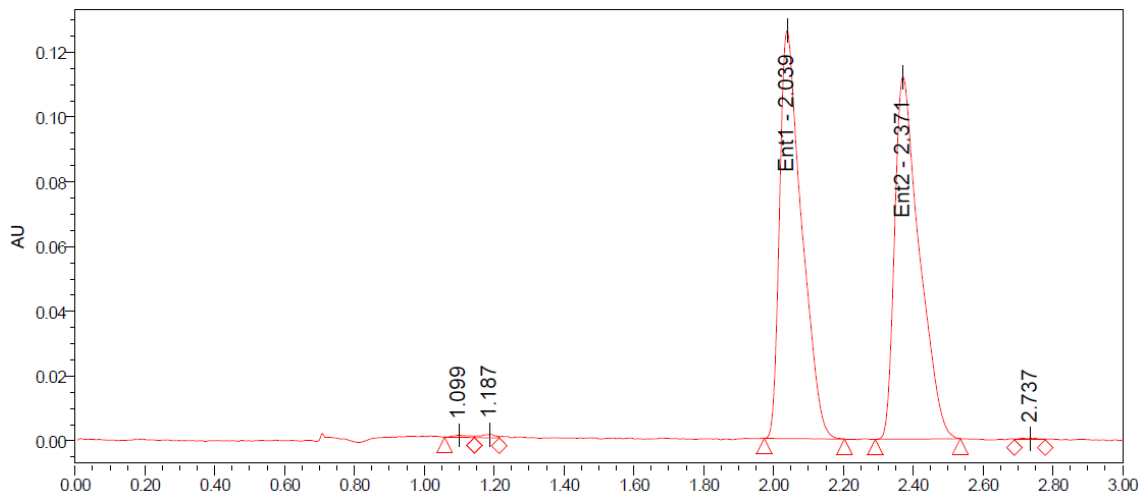
	Compound	ent1	ent2	ee	Ent1	Ent2
1	50b.rac	50.03	49.97	0.06	1220379	1218859
2	50b	2.98	97.02	-94.03	131289	4267884

Experimental section

Benzyl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (**50d**)

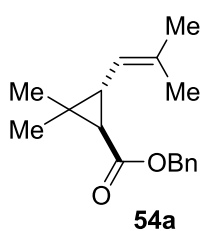


The enantiopurity of compound **50d** was determined by chiral SFC analysis (Daicel IG; 15% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.04 min, t_R (major) = 2.37 min, 94% *ee*.

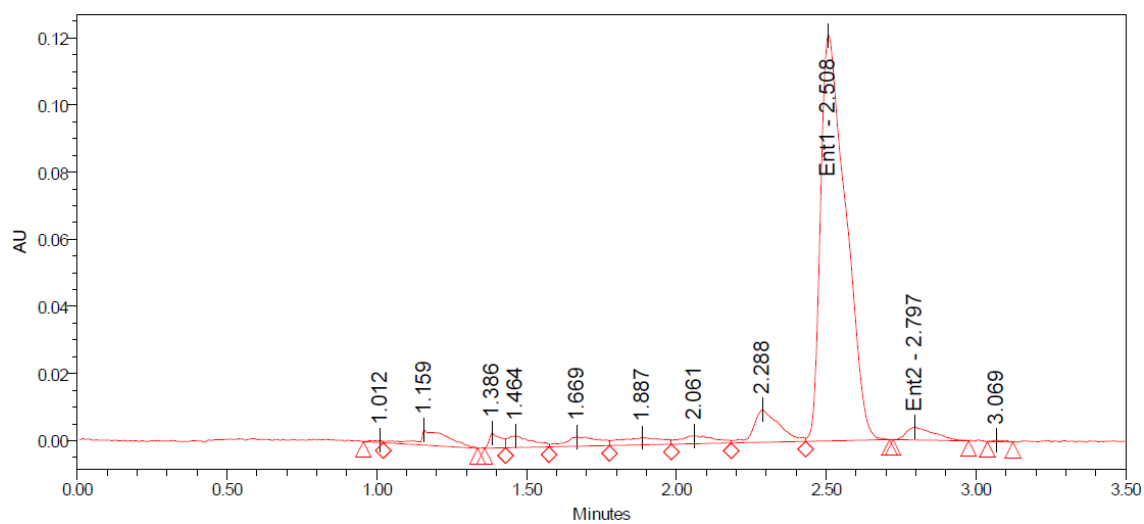
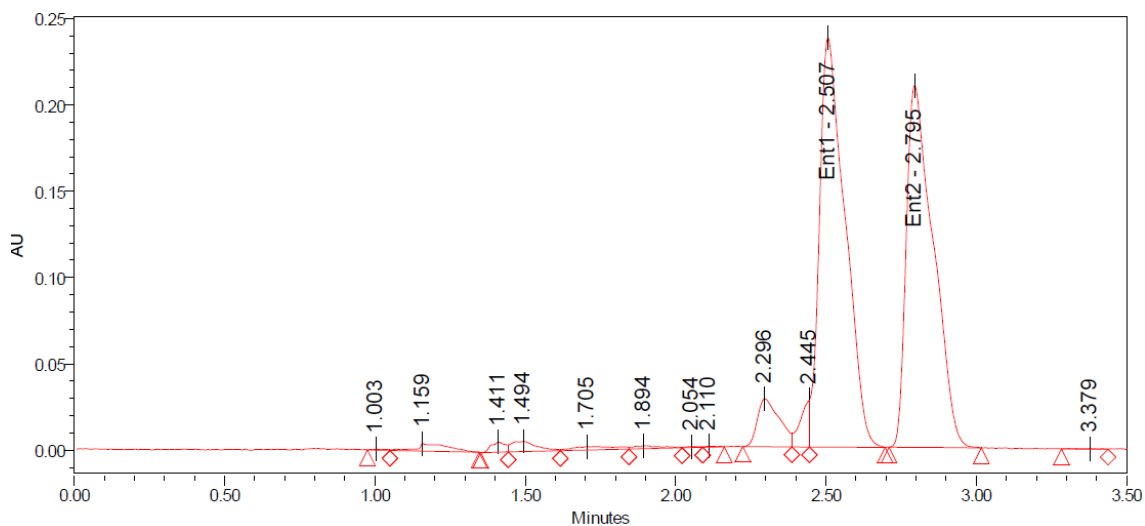


	Compound	ent1	ent2	ee	Ent1	Ent2
1	50d.rac	50.11	49.89	0.21	550860	548550
2	50d	97.09	2.91	94.19	2050447	61378

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (54a)



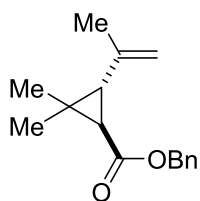
The enantiopurity of compound **54a** was determined by chiral SFC analysis (Daicel IG; 3% MeOH / CO₂ (2.8 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.51 min, t_R (major) = 2.80 min, 93% ee.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	54a.rac	51.77	48.23	3.54	1404027	1308039
2	54a	96.66	3.34	93.32	704365	24339

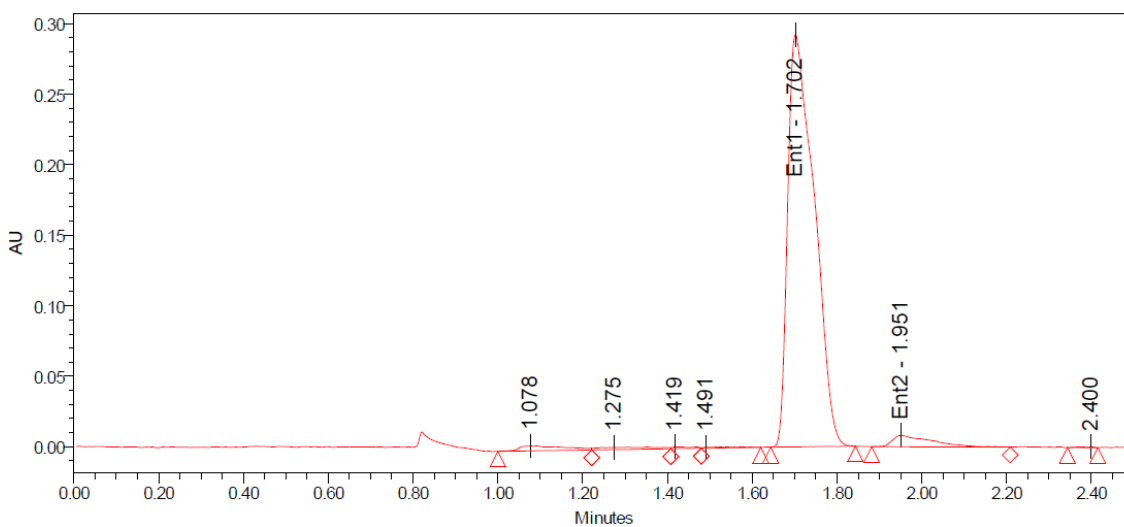
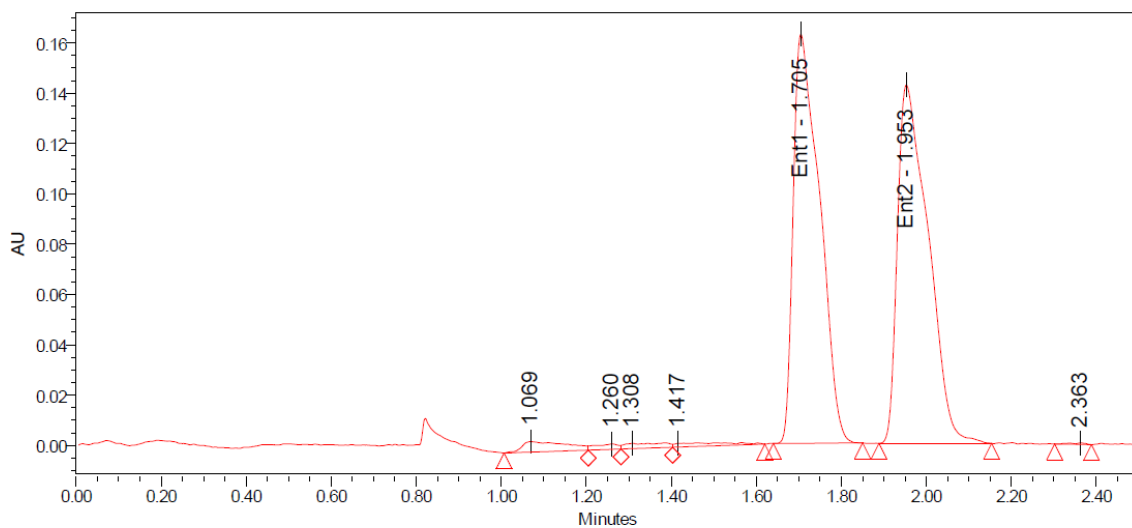
Experimental section

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(prop-1-en-2-yl)cyclopropane-1-carboxylate (**54b**)

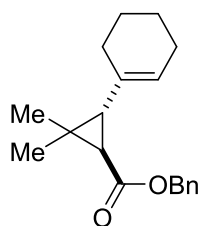


54b

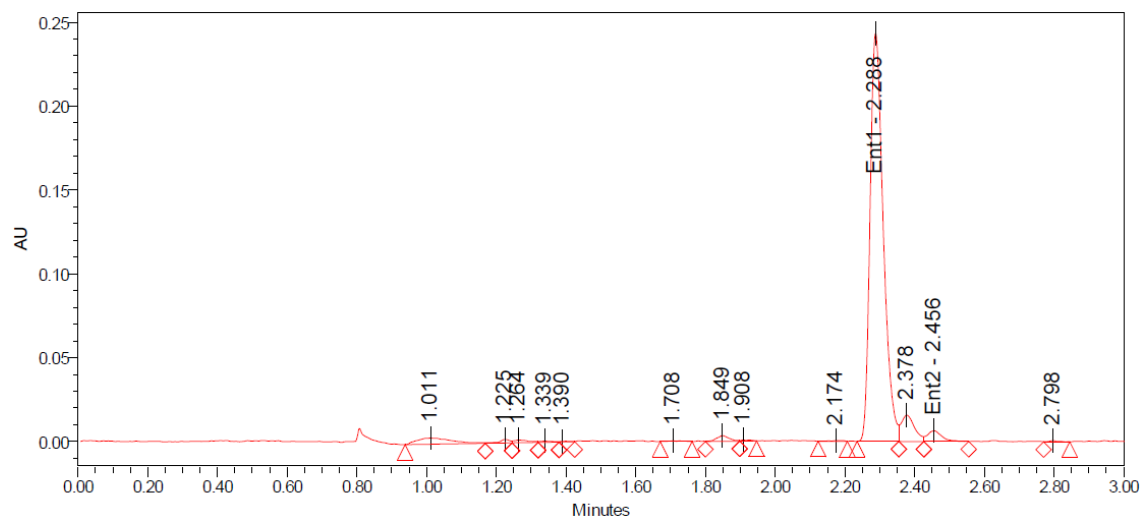
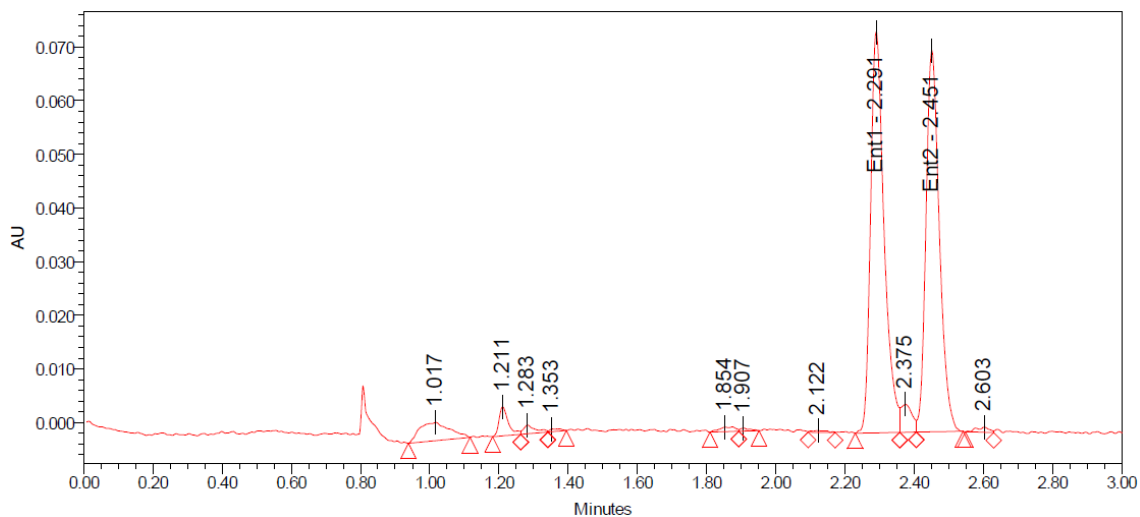
The enantiopurity of compound **54b** was determined by chiral SFC analysis (Daicel IG; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 1.71 min, t_R (major) = 1.95 min, 92% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	54b.rac	49.56	50.44	-0.88	698704	711163
2	54b	96.06	3.94	92.13	1264765	51816

Benzyl (1*R*,3*R*)-3-(cyclohex-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylate (54c)
**54c**

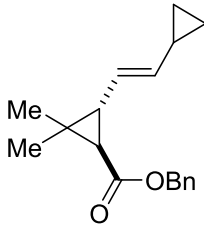
The enantiopurity of compound **54c** was determined by chiral SFC analysis (Daicel IA; 3% *i*PrOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 214$ nm). t_R (minor) = 2.29 min, t_R (major) = 2.45 min, 94% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	54c.rac	51.46	48.54	2.92	203210	191684
2	54c	97.24	2.76	94.47	639907	18195

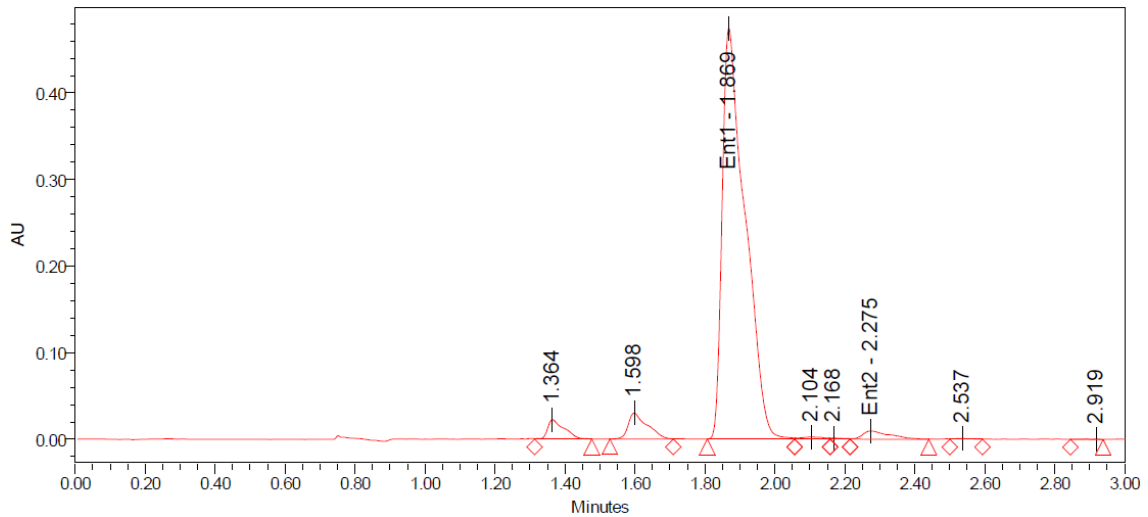
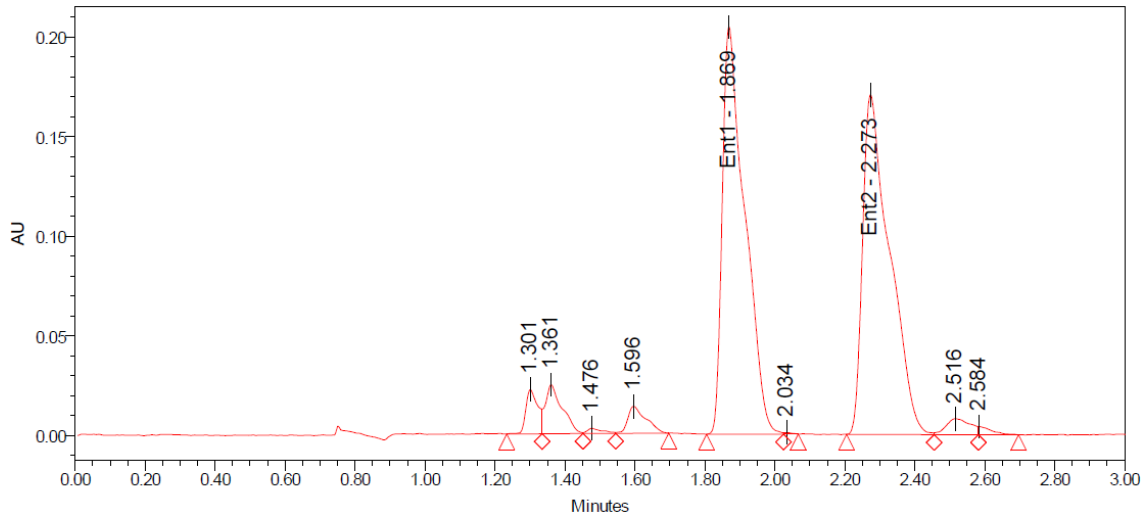
Experimental section

Benzyl (1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropane-1-carboxylate (54f)

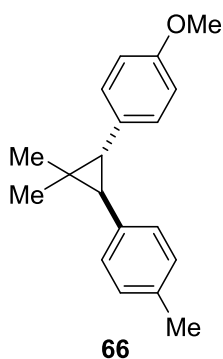


54f

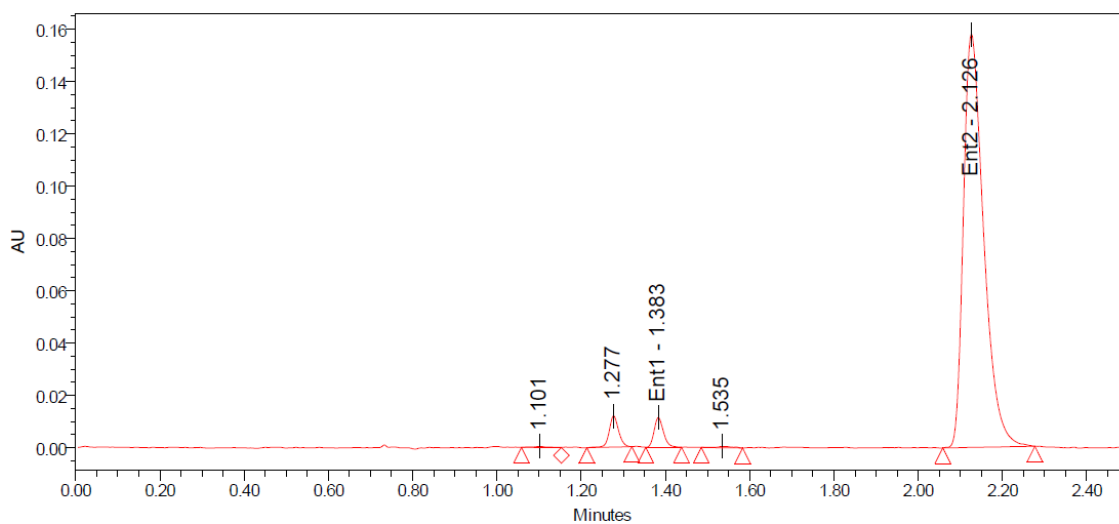
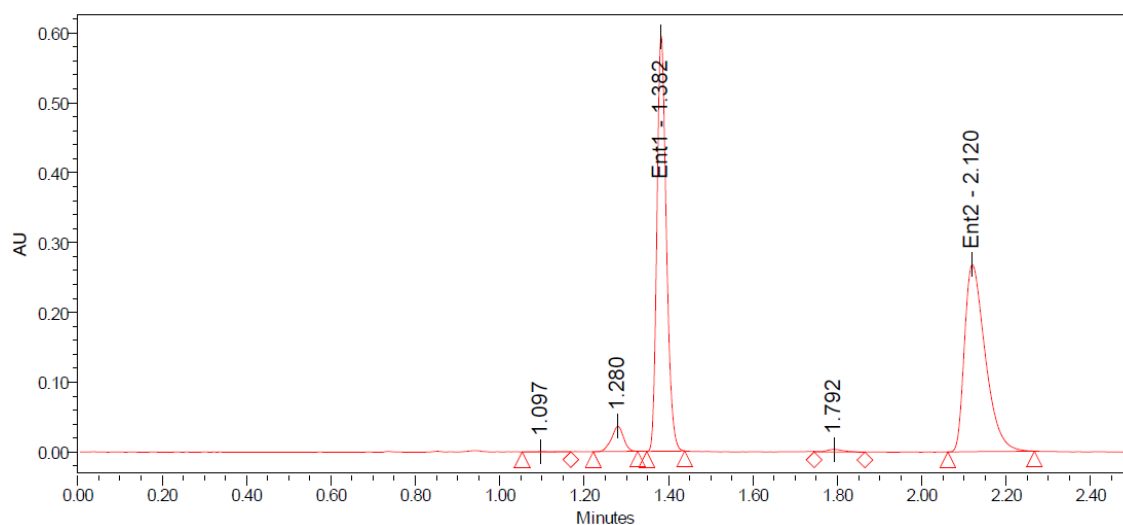
The enantiopurity of compound **54f** was determined by chiral SFC analysis (Daicel IG; 5% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 1.87 min, t_R (major) = 2.27 min, 95% ee.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	54f.rac	49.99	50.01	-0.02	914357	914778
2	54f	97.69	2.31	95.38	2147962	50815

1-((1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropyl)-4-methoxybenzene (**66**)

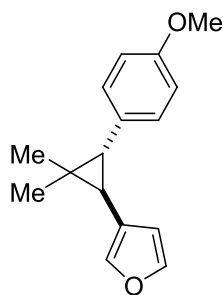
The enantiopurity of compound **66** was determined by chiral SFC analysis (Daicel IA; 10% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; $\lambda = 229$ nm). t_R (minor) = 1.38 min, t_R (major) = 2.13 min, 94% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	66.rac	50.13	49.87	0.25	920447	915827
2	66	3.18	96.82	-93.64	17343	527747

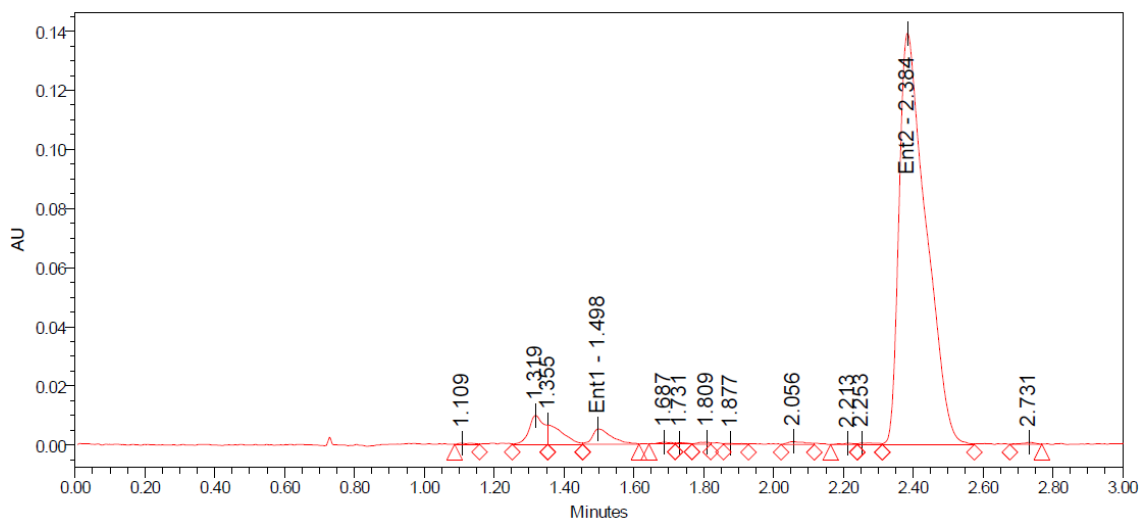
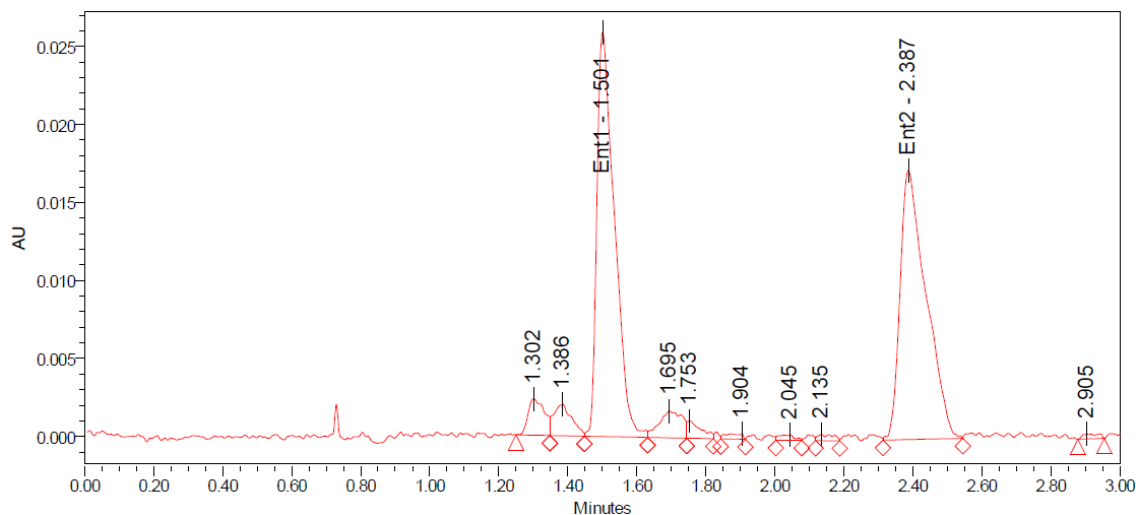
Experimental section

1-((1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl)furan (**67**)



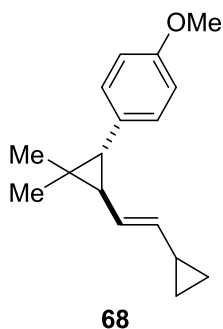
67

The enantiopurity of compound **67** was determined by chiral SFC analysis (Daicel IG; 7% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; λ = 226 nm). *t_R* (minor) = 1.50 min, *t_R* (major) = 2.38 min, 95% *ee*.

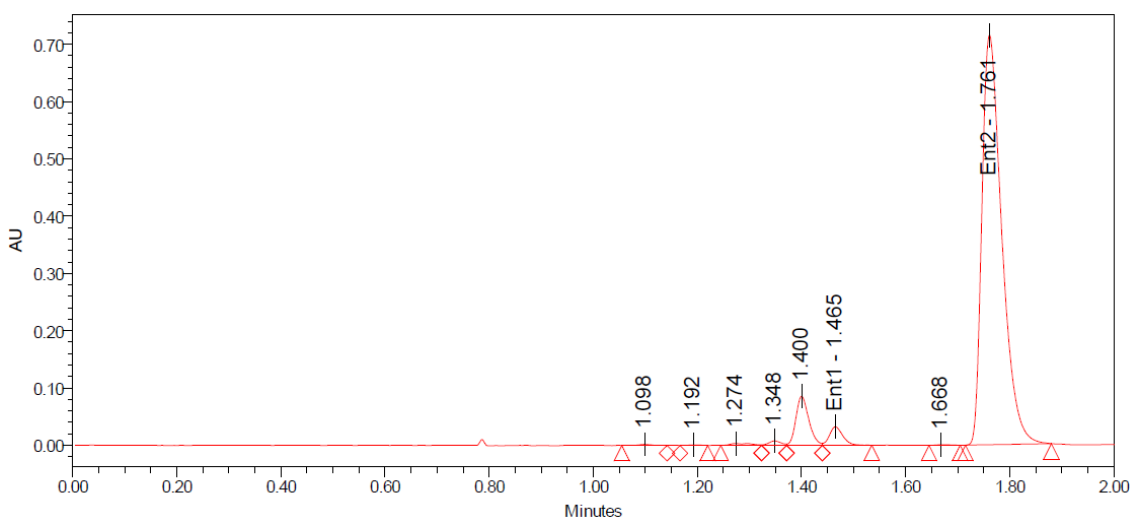
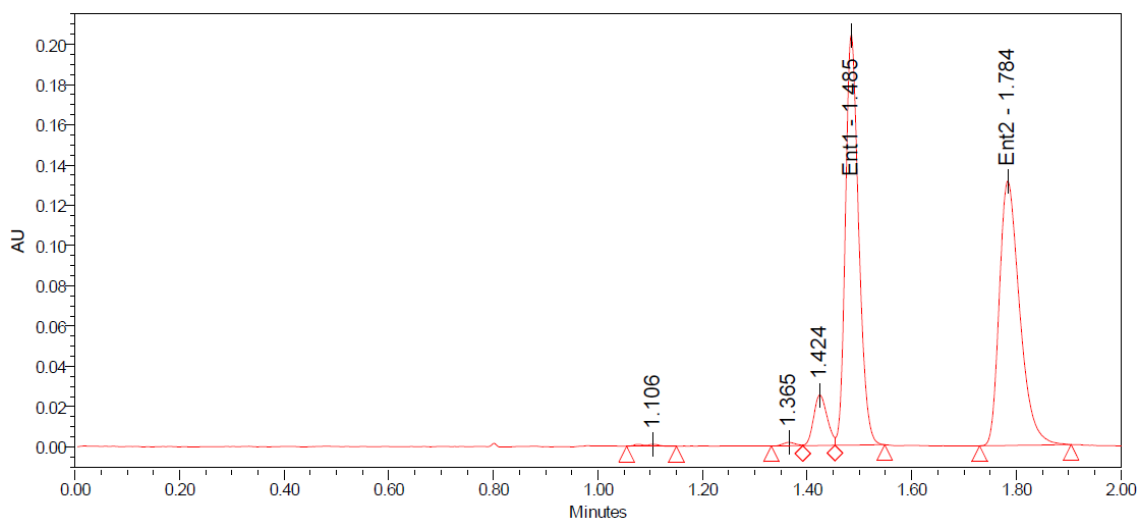


	Compound	ent1	ent2	ee	Ent1	Ent2
1	67.rac	50.31	49.69	0.62	91426	90292
2	67	2.59	97.41	-94.83	19676	741098

1-((1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropyl)-4-methoxybenzene (68)



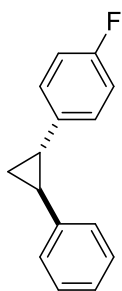
The enantiopurity of compound **68** was determined by chiral SFC analysis (Daicel IA; 2% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; λ = 220 nm). *t_R* (minor) = 1.47 min, *t_R* (major) = 1.76 min, 94% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	68.rac	50.29	49.71	0.58	359064	354917
2	68	2.92	97.08	-94.16	56993	1895962

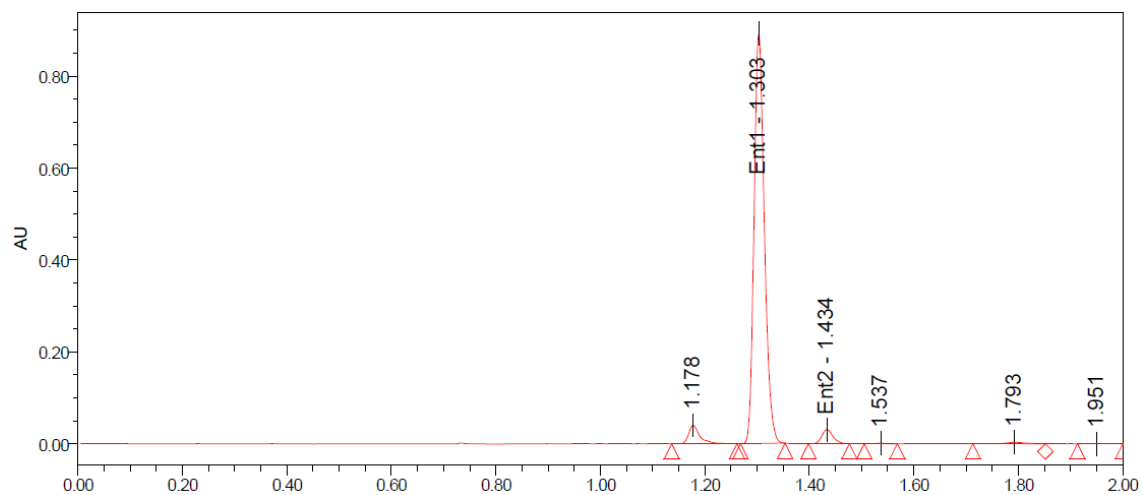
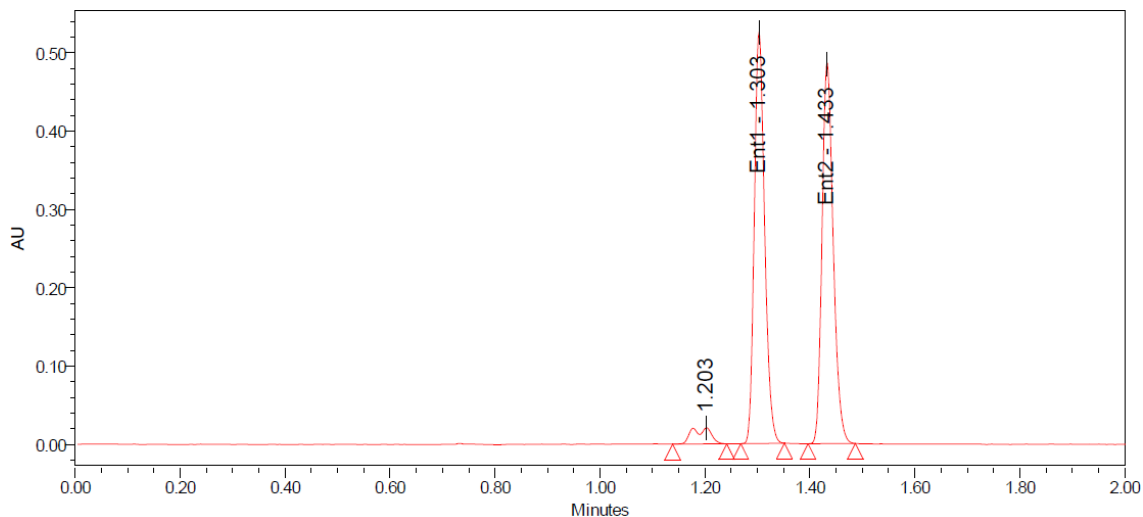
Experimental section

1-Fluoro-4-((1*S*,2*S*)-2-phenylcyclopropyl)benzene (**69**)

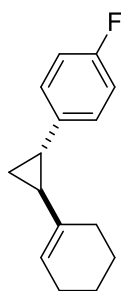


The enantiopurity of compound **69** was determined by chiral SFC analysis (Daicel IA; 10% MeOH / CO₂ (4 mL/min), 1600 psi backpressure; λ = 226 nm).
 t_R (major) = 1.30 min, t_R (minor) = 1.43 min, 93% *ee*.

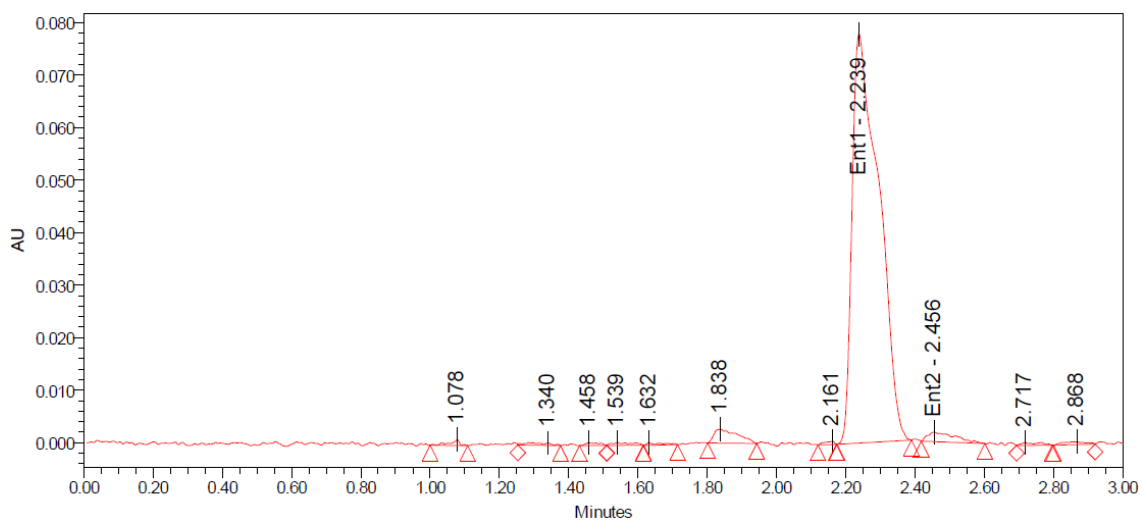
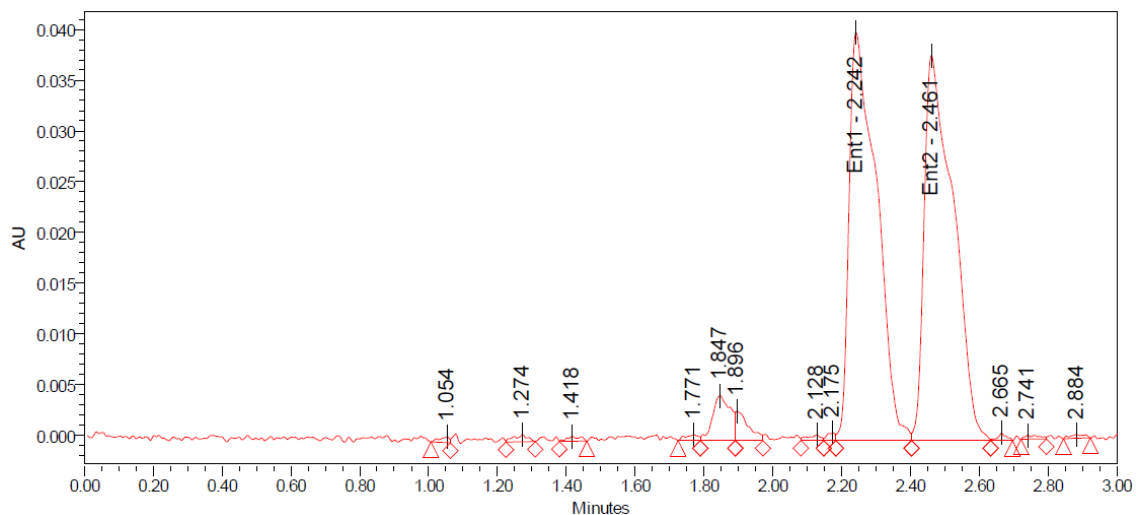
69



	Compound	ent1	ent2	ee	Ent1	Ent2
1	69.rac	49.93	50.07	-0.14	717813	719807
2	69	96.49	3.51	92.97	1223765	44579

1-((1*S*,2*S*)-2-(Cyclohex-1-en-1-yl)cyclopropyl)-4-fluorobenzene (**70**)**70**

The enantiopurity of compound **70** was determined by chiral SFC analysis (Daicel IG; 2% *i*PrOH / CO₂ (3.3 mL/min), 1600 psi backpressure; $\lambda = 229$ nm). t_R (major) = 2.24 min, t_R (minor) = 2.46 min, 95% *ee*.



	Compound	ent1	ent2	ee	Ent1	Ent2
1	70.rac	50.01	49.99	0.02	222078	222011
2	70	97.61	2.39	95.22	416652	10208

Publications

Base-Catalyzed Asymmetric α -Functionalization of 2-(Cyanomethyl)azaarene *N*-Oxides Leading to Quaternary Stereocenters

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S Supporting Information

ABSTRACT: A simple, new strategy for the direct asymmetric α -functionalization of 2-alkyl azaarenes is described. Specifically, a Brønsted base catalyzed conjugate addition of substituted 2-cyanomethylpyridine (and pyrazine) *N*-oxides to acrylate equivalents to afford hitherto elusive 2-*tert*-alkyl azaaryl adducts with high enantioselectivity (up to 94% *ee*) is realized. Extension of the method to the α -amination reaction by using azodicarboxylate esters as electrophiles is also demonstrated. Key for success is the *N*-oxide functionality of substrates that acts as a removable activating and stereodirecting group. A bifunctional Brønsted base catalyst bearing a squaramide with an attached bulky silyl group is also disclosed.

Ortho-substituted pyridines, and more generally azaarenes, are widespread structural motifs,¹ with the congeners that are chiral by virtue of an α -stereogenic *o*-substituent constituting a relevant subset. Several catalytic approaches have recently been reported for the enantioselective synthesis of such chiral units via α -deprotonation of the corresponding 2-alkylazaarene (Figure 1a).² With simple 2-alkylazaarenes (R: H, alkyl, etc.), substrate activation requires a (super)stoichiometric strong base (LiHMDS),³ thus compromising practicality. Milder conditions have been developed for the α -functionalization of preactivated

substrates, i.e. those with electron-withdrawing substituents (EWG) in either the azaarene ring (*p*-nitroazaarenes, polyheteroarenes) or the *C* α (α -ester, amide, electron-deficient aryl) or both (strategy 2).^{4,5} In these cases, α -stereogenic 2-substituted azaarenes can be produced with high enantioselectivities by means of a chiral Pd(II),^{4a} Ni(II),^{4b} or amine⁵ catalyst and no base, or only a catalytic weak base, being added. However, none of these methods address the generation of a quaternary α -stereocenter,⁶ an issue of general importance in organic synthesis,⁷ and of particular significance to the present context given the interest in 1,1-diaryl quaternary compounds as potential pharmacophores.⁸ Here we describe an enantioselective α -functionalization of *o*-substituted azaarenes that is complementary to the known procedures in several aspects: (i) successfully affords hitherto elusive all-carbon quaternary stereocenters, (ii) relies on a Brønsted base activation strategy using newly designed chiral bifunctional organocatalysts, and (iii) uses azaarene *N*-oxides, more specifically substituted 2-cyanomethyl azaarene *N*-oxides,⁹ as enabling substrates (Figure 1b).

Two key elements that make 2-cyanomethyl azaarene *N*-oxides perfect substrate candidates *a priori* are their relatively high CH Brønsted acidity as compared to most alkylazaarenes¹⁰ and the presence of the N \rightarrow O group as a potentially coordinating site for catalyst binding.¹¹ Considering this, one might expect that bifunctional chiral Brønsted bases¹² would suffice for an effective α -deprotonation and subsequent stereoselective bond formation. As far as we know azaarene *N*-oxides have not been investigated within the context of asymmetric C(sp³)-H functionalizations.^{13,14}

At the outset, we studied the behavior of 2-cyanoalkylpyridine **1** under Brønsted base catalysis conditions and selected as a reaction partner enone **2**, an acrylate surrogate well suited for organocatalytic conjugate additions.¹⁵ As data in Scheme 1 show, the reactions in the presence of typical cinchona-based bifunctional Brønsted base catalysts **C1–C3**¹⁶ were sluggish, with low conversion after an extended reaction time (96 h) at room temperature and poor enantioselectivity. The reactivity increased substantially when the corresponding *N*-oxide¹⁷ **4a** was employed instead (Scheme 2). Thus, conversions of ~70% were reached after 2 days at ambient temperature, almost complete at 40 °C, but with yet suboptimal enantioselectivity (75% *ee* with **C3**). After some additional screening,¹⁸ we tested the new

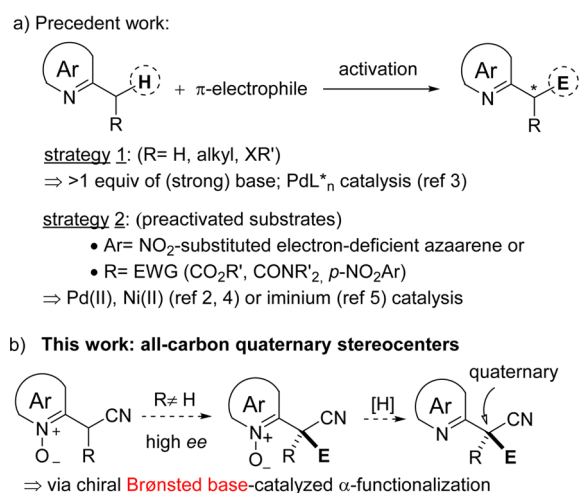
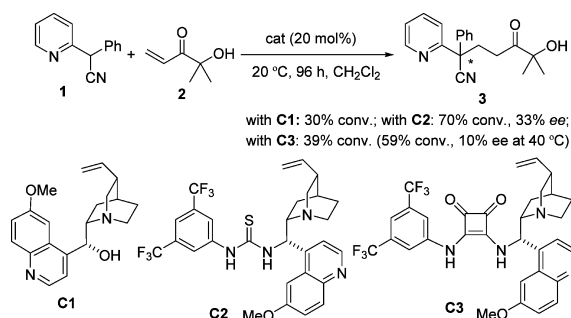


Figure 1. Enantioselective routes to *o*-substituted azaarenes.

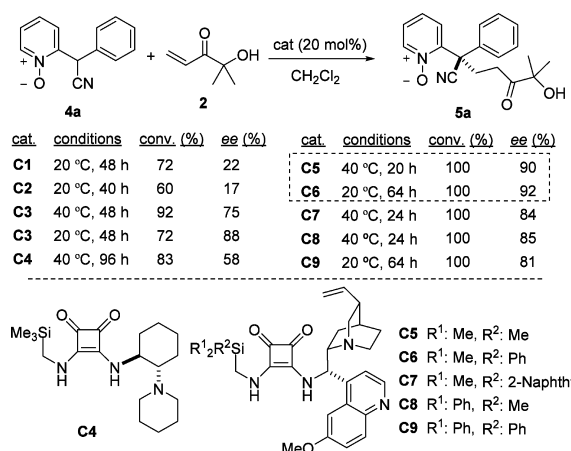
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Scheme 1. Difficulties in the Brønsted Base Catalyzed Reaction of 2-Cyanomethylpyridine 1



Scheme 2. Catalyst Screening for the Reaction of 2-Cyanomethylpyridine *N*-Oxide 4a and Enone 2

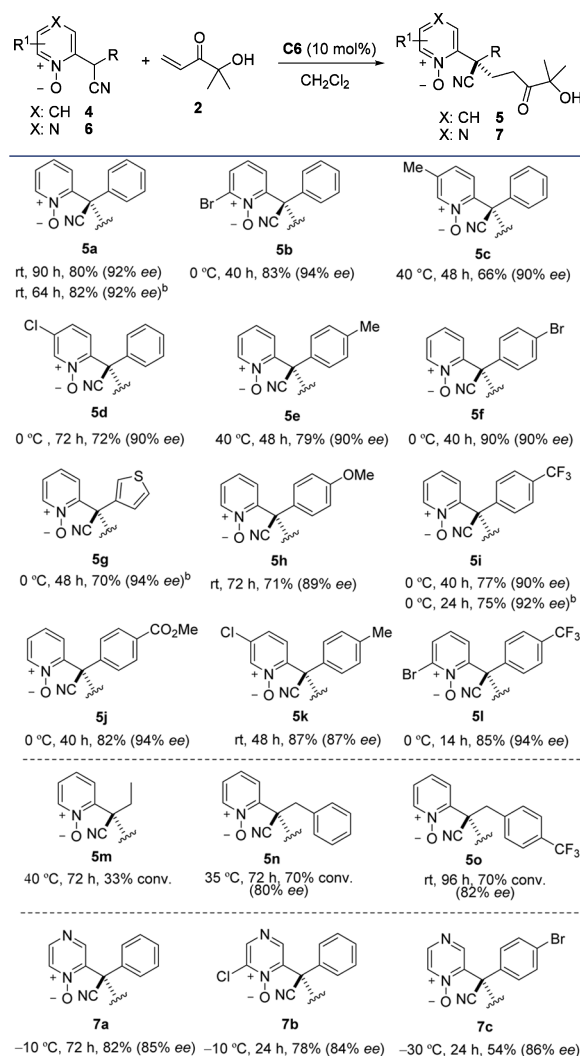


squaramide catalysts¹⁹ **C4**–**C9**, which show as a novel feature a R₄Si site that might play a steric function or even participate in some specific *N*–O → Si interaction.²⁰ Gratifyingly, we observed that while catalyst **C4** performed poorly, the reaction between **4a** and **2** catalyzed by **C5** and **C6** led to the highest selectivity (90% and 92% ee, respectively) in dichloromethane at temperatures in the range 20–40 °C.

Catalyst **C6** was thus selected to explore the scope of the reaction with a range of 2-cyanomethylazaarene *N*-oxides (Table 1). It was found that under these conditions the reaction tolerated well pyridine *N*-oxides **4** with both electron-releasing and -withdrawing groups attached at different positions of the pyridine ring. Similarly, substrates bearing both electron-rich and -poor aryl substituents at *Cα* were equally effective in providing the corresponding addition adducts **5** in generally very good yield and high enantioselectivity. Nonetheless, the method was less tolerant with the corresponding α -alkyl substituted 2-(cyanomethyl)azaarene *N*-oxides **4** (R = alkyl, products **5m**–**o**). Then it was proven that variation of the azaarene system did not apparently affect the reaction course, as the corresponding 2-cyanomethylpyrazines **6** added efficiently to **2** to afford the quaternary 1,1'-diaryls **7a**–**c** in good yields. In these latter cases somewhat lower enantioselectivity was obtained, although they were still acceptable considering the challenge posed by these types of targets.⁹

It was subsequently proven that these 2-cyanomethylpyridine *N*-oxides may also work as enabling substrates for stereoselective α -heterofunctionalization reactions under conditions similar to those mentioned above. For example, the pyridine *N*-oxide **4a** reacted with di(*tert*-butyl) azodicarboxylate **8** in the presence of

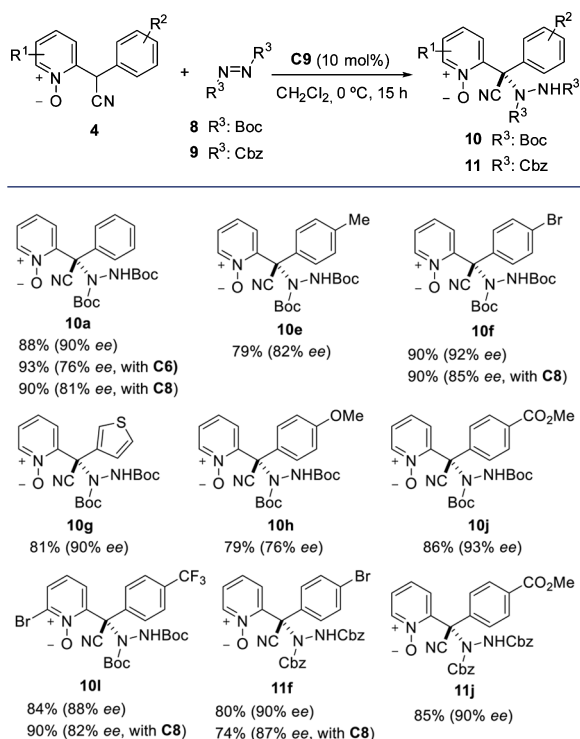
Table 1. Scope of the Reaction of α -Substituted 2-(Cyanomethyl)azaarene *N*-Oxides with **2** Catalyzed by **C6**^a



^aReactions conducted on a 0.2 mmol scale in 1 mL of CH₂Cl₂ (molar ratio of **4** or **6**/2/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase. ^b20 mol % **C6** was used.

10 mol % **C8** to afford α -aminated adduct **10a** in 90% isolated yield and 81% ee. The same reaction using catalyst **C9** led to product with 90% ee. The scope of this α -amination process using either di(*tert*-butyl) or dibenzyl azodicarboxylate **8** or **9** as the amination reagent was briefly investigated for a range of 2-cyanoalkylpyridine *N*-oxides. As data collected in Table 2 show, reactions proceeded successfully to give products **10** and **11** in good yields and ee's, with catalyst **C9** providing the best results for most of the entries. Once again, the parent pyridine **1** proved to be less efficient for these transformations. For instance, the reaction of **1** and di(*tert*-butyl) azodicarboxylate **8** in the presence of 10 mol % catalyst **C8** proceeded to a limited extent of 30% conversion after 15 h at 0 °C.

The detailed mechanism of these catalytic transformations as well as the precise role played by each element involved remains unclear. However, data in Figure 2 indicate that the *N*-oxide group and its *ortho*-relationship to the cyanoalkyl substituent are key for optimal reaction outcome.²¹ As a general trend, for the three positional isomers *ortho*, *meta*, and *para*, the corresponding pyridine *N*-oxide was more reactive than the parent pyridine in

Table 2. α -Amination Reaction of 4^a

^aReactions conducted on a 0.2 mmol scale in 1 mL of CH₂Cl₂ at 0 °C (molar ratio of 4/8 or 9/catalyst 1:1.5:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase.

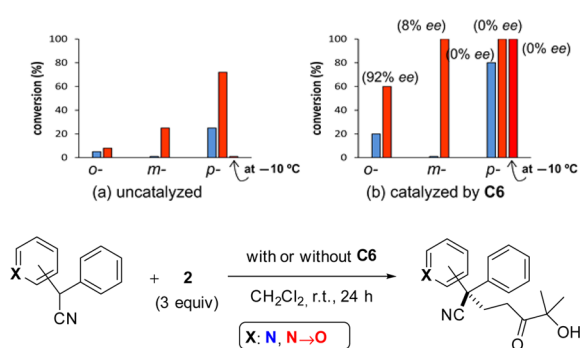
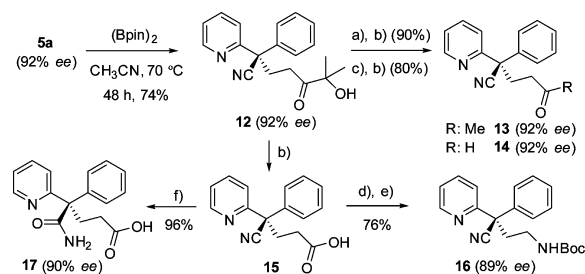


Figure 2. Conversion after 24 h for the reactions of **2** with *o*-, *m*-, and *p*-substituted cyanoalkylpyridines and pyridine *N*-oxides.

both the catalyzed and uncatalyzed reactions. In fact, among the six experiments involving cyanoalkylpyridines, only that using *p*-cyanoalkylpyridine in the presence of **C6** provided practical conversion after 24 h, leading to a racemic product. Equally important is the position of the *N*-oxide group relative to the cyanoalkyl substituent on the ring. Among the three cyanoalkylpyridine *N*-oxides, the *meta* and *para* isomers proved to be inherently more reactive than the *ortho* isomer, also in the presence of catalyst **C6**, although both led to essentially a racemic product. In contrast, the *ortho* isomer led to 92% *ee*.

Adducts obtained from these catalytic transformations can be modified in several ways. For instance, reduction of the *N*-oxide group on adduct **5a** by treatment with (Bpin)₂ afforded pyridine **12** in 74% isolated yield and unaltered enantioselectivity (92% *ee*, Scheme 3). Furthermore, elaboration of the ketol moiety in adducts by applying well established protocols allows

Scheme 3. Elaboration of **5a** into Quaternary 1,1'-Diaryls^a

^aReagents and conditions: (a) MeMgBr, 0 °C, 6 h; (b) NaO₄, MeOH/H₂O, rt, 1 h; (c) BH₃·THF, THF, 0 °C, 2 h, then MeOH; (d) Et₃N, DPPA, toluene, 80 °C, 2 h; (e) ^tBuOH, 50 °C, 16 h; (f) H₂SO₄ (conc.), rt, overnight.

the corresponding ketone (**13**), aldehyde (**14**), or carboxylic acid (**15**) product to be furnished from a common single intermediate and with formation of acetone as the only organic waste. These results are of particular interest in that the direct conjugate addition of azaarene *N*-oxide **4** to simple enones, i.e. methyl vinyl ketone, or unsaturated esters, i.e. methyl acrylate, did not work under the present catalytic conditions. In addition, the reaction of **4** with acrolein afforded the corresponding 1,4-addition adduct, but with a poor 15% *ee*. Another illustration of the synthetic versatility of adducts is shown by transformation of the nitrile carboxylic acid **15** into the protected amine **16** and amide **17**, respectively. On the other hand, the configuration of adducts **5a** and **10a** was established by single crystal X-ray analysis,²³ and for the remaining adducts it was assigned by assuming a uniform reaction mechanism.

In summary, a mild and highly enantioselective carbo- and hetero- α -functionalization of 2-cyanomethylazaarene *N*-oxides is developed as the first direct and asymmetric entry to α -quaternary alkylazaarenes. The *N*-oxide group plays a strategic role as a removable activating and stereodirecting element in conjunction with newly designed bifunctional squaramide-Brønsted base catalysts bearing a bulky silyl group. While the specific role played by the silyl group during catalysis is not clear yet,²⁴ its easy variation makes this new subclass of squaramides very attractive for further asymmetric transformations under proton transfer conditions. Work to address these issues is currently underway in our laboratory.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13385.

Crystallographic data for **5a** (CIF)

Crystallographic data for a **10a** derivative (CIF)

Experimental details, NMR spectra, HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Pyridine is the second (near the first) most commonly used nitrogen heterocycle among all U.S. FDA approved pharmaceuticals, with the pyridine C2-position being the preferred position for substitution. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274.
- (2) Perspective: Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831–845.
- (3) (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093. (b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056–12057. (c) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439–12441. Also, see: (d) Hamana, H.; Sugawara, T. *Chem. Lett.* **1984**, *13*, 1591–1594.
- (4) (a) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196. (b) Fallan, C.; Lam, H. W. *Chem. - Eur. J.* **2012**, *18*, 11214–11218.
- (5) (a) Vera, S.; Liu, Y. K.; Marigo, M.; Escudero-Adan, E. C.; Melchiorre, P. *Synlett* **2011**, *2011*, 489–494. (b) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem. - Eur. J.* **2013**, *19*, 9147–9150. (c) Meazza, M.; Ceban, V.; Pitak, M. B.; Coles, S. J.; Ríos, R. *Chem. - Eur. J.* **2014**, *20*, 16853–16857. For related reactions involving 2-alkylarenes, see: (d) Cid, M. B.; Duce, S.; Morales, S.; Rodrigo, E.; García-Ruano, J. L. *Org. Lett.* **2010**, *12*, 3586–3589. (e) Duce, S.; Jorge, M.; Alonso, I.; García-Ruano, J. L.; Cid, M. B. *Eur. J. Org. Chem.* **2013**, *2013*, 7067–7075. (f) Dell'Amico, L.; Companyó, X.; Naicker, T.; Bräuer, T. M.; Jørgensen, K. A. *Eur. J. Org. Chem.* **2013**, *2013*, 5262–5265.
- (6) Recent catalytic approaches to nonracemic chiral azaarenes that, however, do not address the synthesis of the α -quaternary congeners: (Reductive coupling of 2-alkenyl azaarenes with ketones) (a) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428–8431. (Stereospecific coupling of *sec*-organoboronic esters with azaaryl-lithium) (b) Lloveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958–10961. (Reductive cross-coupling between heteroaryl iodides and α -chloronitriles) (c) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480–10483.
- (7) (a) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751. (b) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, *2013*, 2745–2759. (c) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295–7306. (d) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623. (e) Bella, M.; Gasperi, T. *Synthesis* **2009**, *2009*, 1583–1614. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *2007*, 5969–5994. (g) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (h) *Quaternary Stereocenters*; Christoffers, J.; Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (i) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367.
- (8) Ameen, D.; Snape, T. J. *MedChemComm* **2013**, *4*, 893–907.
- (9) For challenges associated with α -cyanoalkylations, see: López, R.; Palomo, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 13170–13184.
- (10) 2-Alkylpyridine *N*-oxides are more acidic than the parent 2-alkylpyridines by about 3–4 pK_a units in DMSO: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. (b) <http://www.chem.wisc.edu/areas/reich/pkatable/>.
- (11) (a) Karayannis, N. M. *Coord. Chem. Rev.* **1973**, *11*, 93–159. (b) Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574–587. (c) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29–36. (d) Landa, A.; Minkkilä, A.; Blay, G.; Jørgensen, K. A. *Chem. - Eur. J.* **2006**, *12*, 3472–3483.
- (12) Reviews on Brønsted base catalysis: (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. (b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Maruoka, K., Ed.; Thieme: Stuttgart, 2012.
- (c) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2009**, *291*, 145–200.
- (13) Use of pyridine *N*-oxides has been mainly directed to the activation of the pyridine core. See: (a) Yan, G.; Borah, A. J.; Yang, M. *Adv. Synth. Catal.* **2014**, *356*, 2375–2394. (b) Wang, Y.; Zhang, L. *Synthesis* **2015**, *47*, 289–305. (c) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642–2713.
- (14) For an *N*-oxide assisted α C(sp³)-trifluoromethylation of (mainly) *o*-methyl pyridines, see: (a) Kuninobu, Y.; Nagase, M.; Kanai, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10263–10266. For palladium-catalyzed α -arylation of 2-methyl azine *N*-oxides, see: (b) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. (c) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164.
- (15) For a review on the use of α' -hydroxy enones in asymmetric synthesis, see: (a) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150–4164. For a recent example: (b) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.
- (16) Reviews on cinchona-based catalysts: (a) Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725–1762. (b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *2010*, 1229–1279. (c) *Cinchona Alkaloids in Synthesis and Catalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, 2009.
- (17) The substrates were easily prepared through a two-step sequence starting from commercial 2-halopyridines. For details, see the [Supporting Information](#) (SI).
- (18) When using monofunctional Brønsted bases such as (DHQD)₂PYR and (DHQD)₂PHAL, no reaction was observed.
- (19) For reviews on squaramide catalysis, see: (a) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2011**, *17*, 6890–6899. (c) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281. For pioneering work on squaramides, see: (d) Malerich, J. P.; Hagihara, K.; Rawal, V. R. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. (e) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153–156.
- (20) *N*-Oxide/silicon interactions have been previously proposed in reactions involving chiral azaarene *N*-oxide catalysts and silicon-containing substrates; see: (a) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235–5248. (b) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420. (c) Chen, J.; Captain, B.; Takenaka, N. *Org. Lett.* **2011**, *13*, 1654–1657. (d) Reference 11b.
- (21) Unlike the *meta* and *para* isomers, the ¹H NMR spectrum of the *ortho* isomer shows significant changes when recorded in the absence or the presence of 1 mol equiv of C6, respectively. For details, see the SI.
- (22) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842–7848.
- (23) CCDC-1437384 (compound 5a) and CCDC-1453241 (*p*-nitrobenzoyl amide of 10a) contain the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. See the SI for details.
- (24) In a preliminary prospect, these Brønsted bases proved to be efficient catalysts in reactions involving C-nucleophiles other than azaarene *N*-oxides. For example, the reaction of *tert*-butyl phenylcyanoacetate with 2 promoted by C6 led to the corresponding Michael addition product with 94% *ee*. See the SI for details.

Heterocycle Synthesis

Strategy for Stereoselective Metal-free α -Functionalization of 2-Azaaryl Acetates with *N*-Boc IminesIñaki Bastida, Marcos San Segundo, Rosa López, and Claudio Palomo^{*[a]}

Abstract: We report the first diastereo- and enantioselective formal Mannich reaction of 2-pyridyl acetates which gives rise to α - and β -functionalized 2-substituted pyridines. Key for success is the previous azaarene *N*-oxide formation enabling α -carbon deprotonation by a mild bifunctional Brønsted base and subsequent reaction with *N*-Boc imines under almost perfect stereocontrol.

ortho-Substituted pyridines are common fragments in chiral compounds with biological activity.^[1] In particular, α - and/or β -functionalized 2-substituted pyridines containing amino groups in the β -position constitute a relevant family (Figure 1).^[2] A practical synthesis of these structural motifs is

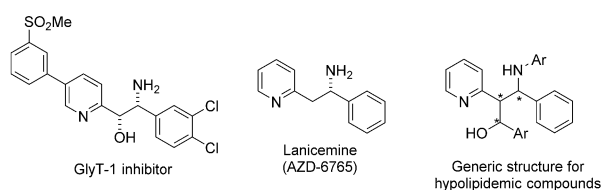


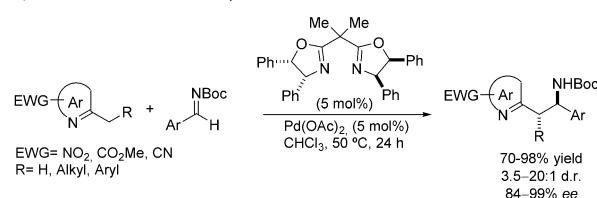
Figure 1. Drug candidates for the treatment of schizophrenia (Gly-T1 inhibitor), neurodegenerative (lanicemine) and lipid metabolism disorders.

the addition of 2-alkylazaarene anions to imines, the Mannich-like reaction.^[3] Although several methods relying on metal catalyzed approaches have been reported,^[4] they have some limitations. Firstly, the majority of the methods reported until now are racemic. Secondly, 2-methylazaarenes, for example, 2-methyl pyridines are the substrates of choice to generate a single stereocenter, and finally, high temperatures are needed for reaction success, a condition that may cause subsequent C–N elimination.^[4e,f]

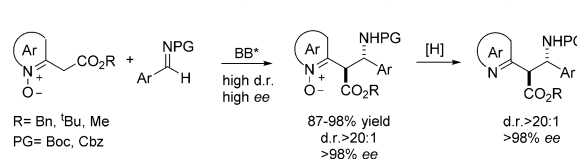
In these methods the metal generally coordinates with the nitrogen atom of the azaarene ring thus facilitating α -carbon deprotonation of the 2-alkyl substituent using a Brønsted base,

typically a tertiary amine base. However, the development of an enantioselective variant of these approaches becomes complicated by competitive metal/amine base self-quenching. Not surprisingly, there is only one example that documents the asymmetric synthesis of this kind of motif. The group of Lam^[5] reported that high levels of stereoselectivity may be achieved in the reaction of 2-alkyl azaarenes with *N*-Boc imines promoted by a chiral Pd^{II}-bis(oxazoline) complex without the need of

a) Precedent work: metal catalysis/electron deficient azaarenes



b) **This work:** Brønsted base catalysis/broad scope/high stereoselectivity control



Scheme 1. Enantioselective Mannich-like reactions of 2-alkylazaarenes.

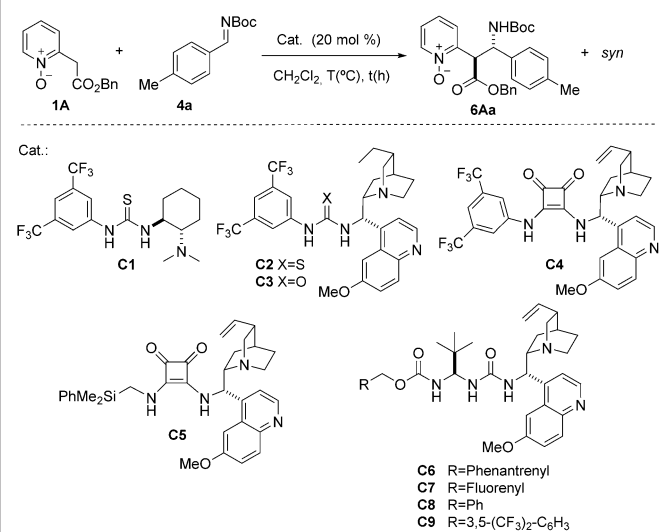
a tertiary amine base (Scheme 1a). However, although in this approach the acetate counterion appears to act as base, the incorporation of an electron withdrawing group (EWG) into the azaarene ring is required to facilitate the generation of the chiral azaallylmetal species.^[6] To date, only a few methods to control reactivity and stereoselectivity in reactions involving 2-alkyl azaarenes for example, 2-alkyl pyridines and quinolines have been accomplished through different approaches.^[7] Recently, we have reported the enantioselective α -functionalization of (cyanomethyl)azaarene *N*-oxides to generate quaternary stereogenic centers with high enantioselectivity.^[8] In this approach, the *N*-oxide functionality plays a dual role. On the one hand, it facilitates deprotonation at the exocyclic azaarene α -carbon side chain, and on the other hand, it acts as a powerful temporary stereodirecting group. Herein we report further utility of this hitherto unknown property of the *N*-oxide functionality^[9,10] by documenting the first catalytic highly diastereo- and enantioselective Mannich reaction of azaaryl *N*-oxide acetates (Scheme 1b).

To establish the feasibility of the proposal the reaction of pyridyl *N*-oxide acetate **1A** with *N*-Boc imine **2a** in the pres-

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Table 1. Catalyst screening for the Mannich reaction of **1A** and *N*-Boc imine **4a**.^[a]



Entry	Cat.	T [°C], t [h] ^[b]	Conv. [%] ^[c,d]	<i>anti</i> : <i>syn</i>	<i>ee</i> [%] ^[e]
1	C1	RT, 140	60	0.6:1	17/79
2	C2	40, 70	42	0.8:1	3/16
3	C3	40, 40	28	0.7:1	50/74
4	C4	40, 48	20	0.9:1	4/53
5	C5	RT, 48	21	2:1	30/52
6	C6	RT, 64	88	6.7:1	99/99
7	C7	RT, 64	> 95	5.7:1	99/98
8	C8	RT, 64	> 95	9:1	96/94
9	C9	RT, 64	> 95	9:1	98/55
10	C8	0, 48 ^[f]	> 95	> 20:1	99

[a] Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH₂Cl₂ (molar ratio of **1A**:**4a**, 1:1.2). [b] Determined by ¹H NMR. [c] Determined by ¹H NMR and corroborated by HPLC. [d] Configuration for the *syn* isomer not determined. [e] for both diastereomers determined by chiral HPLC. [f] Molar ratio of **1A**:**4a**, 1:2.

ence of several benchmark Brønsted base catalysts^[11] was examined first. The results (Table 1) soon revealed that not only the *N*-oxide group, but also the Brønsted base were critical for success. For example, using chiral thiourea tertiary amines **C1**,^[12] and **C2**,^[13] the urea catalyst **C3**^[13] and squaramides **C4**^[14] and **C5**,^[8] low transformations were observed even when the reactions were carried out for extended reaction time or at 40 °C (entries 1–5). These catalysts exerted low asymmetric inductions, especially in terms of *anti*:*syn* diastereoselectivity, which was clearly negligible. In particular, catalyst **C5**, which efficiently promoted the α -functionalization of 2-(cyanomethyl)azaarene *N*-oxides, performed very poorly in the current Mannich reaction (entry 5). Next we examined catalysts **C6–9**,^[15] which display three consecutive hydrogen bond donors and would thus provide an additional site for hydrogen-bond-accepting substrate recognition.^[16] It was gratifying to observe that after 64 hours of stirring at room temperature, these catalysts exhibited high (88%, entry 6) and complete conversion (entries 7–9). Most remarkably, the corresponding Mannich adduct **3a** was produced with high *anti*:*syn* ratio (5.7:1–> 9:1) and enantioselectivity (96–99% *ee*) regardless the nature of

the R substituent in the catalyst. After some additional screening,^[17] catalyst **C8** enabled the production of **3a** as the only detectable diastereomer in 99% *ee* (entry 10).

Importantly, this result provides new insight on the versatility of ureido-peptide-based bifunctional Brønsted bases to promote reactions under mild proton transfer conditions and, for the first time, their utility for construction of configurationally labile tertiary stereocenters.^[15]

Next, we explored the generality of the optimized procedure for *N*-oxide **1A** with a range of *N*-Boc imines under the action of catalyst **C8**. As the data in Table 2 show, *N*-Boc imines **4** with either electron-donating or electron-withdrawing groups at the *ortho*, *meta* or *para* positions on the aromatic ring, as well as heteroaromatic groups, were equally tolerated to produce the corresponding Mannich adducts **6Aa–m** as sole diastereomers with excellent enantiomeric excess (99%).

In this study we employed 20 mol% of catalyst but it is important to note that using 5–10 mol% of catalyst loading the reactions proceeded equally well without compromising either selectivity or chemical yield (Table 2, adducts **6Af** and **6Ag**). The relative and absolute configuration of the *anti* enantiomer were determined by X-ray crystallographic analysis of **6Ad**.^[18] Additionally, the reaction with *N*-Cbz (benzyloxycarbonyl) imine **5a** produced the corresponding Mannich adduct **7Aa** with an identical level of stereocontrol, and the *tert*-butyl and methyl pyridyl *N*-oxide acetates **2A** and **3A** were also compatible with the reaction conditions and produced the Mannich adducts **8Aa** and **9Aa**, respectively, with equal high stereoselectivity. This functional group compatibility represents an important advantage for subsequent adduct manipulations. Furthermore, the methodology was also suitable for substituted pyridyl *N*-oxides such as **3B** and **3C** which reacted with either *N*-Boc or *N*-Cbz imines using 10 mol% of catalyst **C8** to afford adducts **9Ba**, **9Cf** and **10Ca**.

The importance of the *N*-oxide functionality in these reactions was clearly illustrated from the reaction of **11** with **4a** (Scheme 1a), which proceeded sluggishly and with poor stereoselectivity to give **12** essentially in racemic form. On the other hand, other azaaryl *N*-oxide acetates such as **13** performed well to produce the corresponding Mannich adduct **14**, albeit with slightly diminished diastereoselectivity (Scheme 2b). Again, the presence of the *N*-oxide functionality was essential to ensure reactivity and selectivity (Scheme 2b) as illustrated from the reaction of quinoyl acetate **15** with imine **5a**.

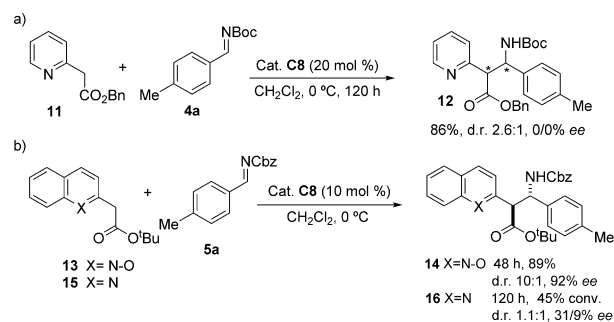
It can be argued that the *anti* adducts obtained in the Mannich reaction are produced under kinetic control, since their diastereomeric ratio and enantiomeric excess remained constant during the reaction progress despite the basic reaction conditions. For instance, upon complete transformation into the Mannich adduct **6Aa**, its configurational stability was maintained at 0 °C and slowly diminished at room temperature; after 96 hours the diastereomeric ratio turned to 7.3:1 (99% *ee*) (Figure 2). This stability of the *anti* adduct **6Aa**, could be explained by the difficulty of the catalyst to remove the remaining hydrogen from the exocyclic tertiary α -carbon. Less-hindered and stronger bases, such as Et₃N, DBU (1,8-diazabicy-

Table 2. Scope for the catalytic Mannich reaction of pyridyl *N*-oxide acetates.^[a]

<p>1 R¹=Bn 2 R¹=^tBu 3 R¹=Me</p> <p>A R=H, B R=Br, C R=^tBu</p>	<p>4 PG=Boc 5 PG=Cbz</p>	<p>6 R¹=Bn, PG=Boc 7 R¹=Bn, PG=Cbz 8 R¹=^tBu, PG=Cbz 9 R¹=Me, PG=Boc 10 R¹=Me, PG=Cbz</p>																		
<table border="0"> <tr> <td> 6Aa: 48 h, 93% (1 mmol scale) d.r.>20:1, 99% ee 7Aa: 24 h, 88%, d.r.>20:1, 99% ee </td> <td> 6Ab: 48 h, 92% d.r.>20:1, 99% ee </td> <td> 6Ac: 28 h, 98% d.r.>20:1, 99% ee </td> </tr> <tr> <td> 6Ad: 48 h, 90% d.r.>20:1, 99% ee </td> <td> 6Ae: 21 h, 95% d.r.>20:1, 99% ee </td> <td> 6Af: 30 h, 90% (5 mol% C8) d.r.>20:1, 99% ee </td> </tr> <tr> <td> 6Ag: 20 h, 98% (10 mol% C8) d.r.>20:1, 99% ee </td> <td> 6Ah: 10 h, 95% d.r.>20:1, 99% ee </td> <td> 6Ai: 44 h, 93% d.r.>20:1, 99% ee </td> </tr> <tr> <td> 6Aj: 48 h, 94% d.r.>20:1, 99% ee </td> <td> 6Ak: 48 h, 92% d.r.>20:1, 99% ee </td> <td> 6Al: 48 h, 87% d.r.>20:1, 99% ee </td> </tr> <tr> <td> 6Am: 48 h, 88% d.r.>20:1, 99% ee </td> <td> 8Aa: 48 h, 89% d.r.>20:1, 99% ee </td> <td> 9Aa: 72 h, 96% d.r.>20:1, 99% ee </td> </tr> <tr> <td> 9Ba: 36 h, 98% (10 mol% C8) d.r.>20:1, 99% ee </td> <td> 9Cf: 84 h, 90% (10 mol% C8) d.r.>20:1, 98% ee </td> <td> 10Ca: 84 h, 89% (10 mol% C8) d.r.>20:1, 99% ee </td> </tr> </table>			 6Aa: 48 h, 93% (1 mmol scale) d.r.>20:1, 99% ee 7Aa: 24 h, 88%, d.r.>20:1, 99% ee	 6Ab: 48 h, 92% d.r.>20:1, 99% ee	 6Ac: 28 h, 98% d.r.>20:1, 99% ee	 6Ad: 48 h, 90% d.r.>20:1, 99% ee	 6Ae: 21 h, 95% d.r.>20:1, 99% ee	 6Af: 30 h, 90% (5 mol% C8) d.r.>20:1, 99% ee	 6Ag: 20 h, 98% (10 mol% C8) d.r.>20:1, 99% ee	 6Ah: 10 h, 95% d.r.>20:1, 99% ee	 6Ai: 44 h, 93% d.r.>20:1, 99% ee	 6Aj: 48 h, 94% d.r.>20:1, 99% ee	 6Ak: 48 h, 92% d.r.>20:1, 99% ee	 6Al: 48 h, 87% d.r.>20:1, 99% ee	 6Am: 48 h, 88% d.r.>20:1, 99% ee	 8Aa: 48 h, 89% d.r.>20:1, 99% ee	 9Aa: 72 h, 96% d.r.>20:1, 99% ee	 9Ba: 36 h, 98% (10 mol% C8) d.r.>20:1, 99% ee	 9Cf: 84 h, 90% (10 mol% C8) d.r.>20:1, 98% ee	 10Ca: 84 h, 89% (10 mol% C8) d.r.>20:1, 99% ee
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 6Aj: 48 h, 94% d.r.>20:1, 99% ee	 6Ak: 48 h, 92% d.r.>20:1, 99% ee	 6Al: 48 h, 87% d.r.>20:1, 99% ee																		
 6Am: 48 h, 88% d.r.>20:1, 99% ee	 8Aa: 48 h, 89% d.r.>20:1, 99% ee	 9Aa: 72 h, 96% d.r.>20:1, 99% ee																		
 9Ba: 36 h, 98% (10 mol% C8) d.r.>20:1, 99% ee	 9Cf: 84 h, 90% (10 mol% C8) d.r.>20:1, 98% ee	 10Ca: 84 h, 89% (10 mol% C8) d.r.>20:1, 99% ee																		
<p>[a] Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH₂Cl₂ (molar ratio of 1–3:4/5, 1:2). [b] d.r. Determined by ¹H NMR and corroborated by HPLC. [c] ee Determined by chiral HPLC.</p>																				

clo[5.4.0]undec-7-ene), and even the analogous bifunctional urea **C3** promoted epimerization at shorter reaction times at room temperature (Figure 2).

Taking into account the diastereo- and enantioselectivity observed, the capacity of the ureido-peptide-based catalyst to exclusively produce *anti*-configured adducts could be consistent with a tight transition state (TS), in which multiple hydrogen bonding interactions may be operating in unison, such as in the model depicted in Figure 3 for adducts **6A**.^[19]



Scheme 2. Effect of the *N*-oxide group on reactivity and stereoselectivity in the Mannich reaction of a) pyridyl acetate **11** b) quinoline acetates **13** and **15**.

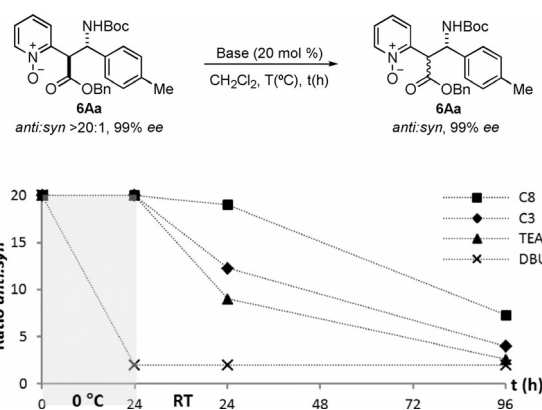


Figure 2. Effect of the Brønsted base on the configurational stability of the *anti* adduct.

The excellent stereoselectivity displayed by the catalytic system provides a quick access to α - and/or β -functionalized 2-substituted azaarenes (Scheme 3). For instance, reduction of the *N*-oxide group in adduct **6Ac** by treatment with (Bpin)₂^[20]

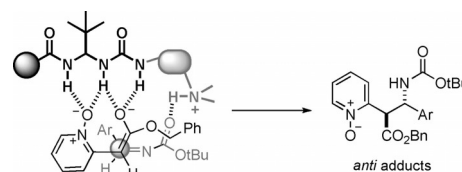
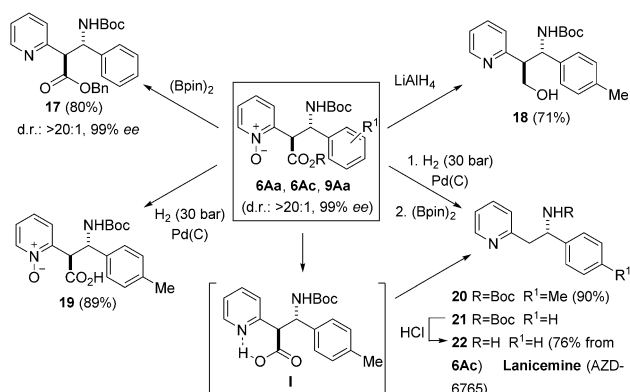


Figure 3. Proposed model that might account for the observed preference for *anti* adduct formation.

afforded the corresponding pyridine derivative **17** in 80% isolated yield with remarkable unaltered diastereoselectivity (d.r. >20:1). Simple elaborations of the ester moiety, in adduct **6Aa** and **9Aa**, brought into the corresponding aminoalcohol **18** and $\beta^{2,3}$ -amino acid **19**, respectively.

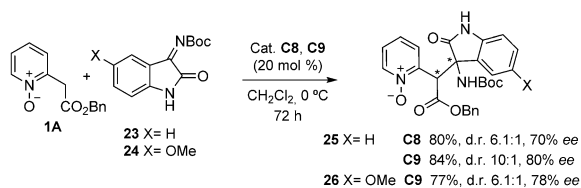
Furthermore, enantiopure benzylic amines^[21] can also be easily obtained from the Mannich adducts through hydrogenation and subsequent *N*-oxide group reduction step that proceeds with concomitant *in situ* decarboxylation, probably through intermediate **I** assisted by the pyridine nitrogen atom.^[22] For instance, **6Aa** led to the benzylic amine **20** in



Scheme 3. Elaboration of Mannich adducts and synthesis of Lanicemine utilizing developed methodology.

90% overall yield and, most importantly, adduct **6Ac** was easily transformed into Lanicemine (AZD-6765), which is a potent low-trapping NMDA (*N*-methyl-D-aspartate) receptor agonist,^[2b–e] usually prepared by resolutive methods^[2b] (Scheme 3).

Eventually, the suitability of this highly stereoselective Mannich reaction to generate quaternary stereogenic centers was briefly examined (Scheme 4). For example, the pyridyl *N*-oxide



Scheme 4. Mannich reaction with imine derived isatines.

acetate **1A** reacted with *N*-Boc imine derived isatines **23** and **24** in the presence of either catalyst **C8** or **C9** to produce the corresponding Mannich adducts in good yield and selectivity. Although it seems that the stereochemical outcome of the reaction may be improved, what is once again significant is the essential lack of reactivity observed in the reaction of **24** with the parent 2-pyridyl acetate **11** to generate the corresponding quaternary stereocenter.^[17]

In summary, we report the first direct catalytic formal Mannich reaction of 2-pyridyl acetates to produce β -amino esters with very high diastereo- and enantioselectivity. This realization was feasible thanks to an emergent strategy for exocyclic α -carbon functionalization that employs the azaarene *N*-oxide functionality as a powerful activating and stereodirecting group.^[9] We also demonstrated that, in contrast to other known parent catalysts, ureidopeptide-based Brønsted bases not only provide excellent levels of asymmetric induction but also are able to preserve the configurational stability of the azaarene adducts during reaction. From these results, it may be anticipated that this new strategy will find future applications in the field of azaarene chemistry.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: azaarenes · Mannich reaction · *N*-oxides · organocatalysis · β -amino pyridines

- [1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
- [2] Gly-T1 inhibitor: a) S. Kolzowski, H.-P. Marty, R. Narquizian, E. Pinard, H. Stalder, US 20100210592 A1, August 19, 2010. Lanicemine; b) R. Griffith, R. J. Murray, M. Balestra, AU705419B2, May 20, 1999; c) C. A. Zarate, D. Mathews, L. Ibrahim, J. F. Chaves, C. Marquardt, I. Ukoh, L. Jolkovsky, N. E. Brutsche, M. A. Smith, *Biol. Psychiatry* **2013**, *74*, 257–264; d) G. Sanacora, M. A. Smith, S. Pathak, H.-L. Su, P. H. Boeijinga, D. J. McCarthy, M. C. Quirk, *Mol. Psychiatry* **2014**, *19*, 978–985; e) D. Downey, A. Dutta, S. McKie, G. R. Dawson, C. T. Dourish, K. Craig, M. A. Smith, D. J. McCarthy, C. J. Harmer, G. M. Goodwin, S. Williams, J. F. W. Deakin, *Eur. Neuropharmacol.* **2016**, *26*, 994–1003; Hypolipidemic compounds: f) H. Glombik, A. Enhsen, W. Kramer, K.-H. Baringhaus, US 005874451A, February 23, 1999.
- [3] For selected reviews on the topic, see: a) J. Verkade, L. Van Hermert, P. Quaedflieg, F. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41; b) R. Gómez-Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940–1948; c) B. Karimi, D. Enders, J. Ehsan, *Synthesis* **2013**, *45*, 2769–2812.
- [4] a) B. Qiang, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2010**, *132*, 3650–3651; b) Q. Qiang, S. Guo, C. Xia, H. Huang, *Adv. Synth. Catal.* **2010**, *352*, 3195–3200; c) M. Rueping, N. Tolstoluzhsky, *Org. Lett.* **2011**, *13*, 1095–1097; d) H. Komai, T. Yoshino, S. Matsnaga, M. Kanai, *Synthesis* **2012**, *44*, 2185–2194; e) B. Qian, P. Xie, Y. Xie, H. Huang, *Org. Lett.* **2011**, *13*, 2580–2583; f) Y. Yau, K. Xu, Y. Fang, Z. Wang, *J. Org. Chem.* **2011**, *76*, 6849–6855.
- [5] D. Best, S. Kujawa, H. W. Lam, *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196.
- [6] For further uses of this strategy, see: D. Best, H. W. Lam, *J. Org. Chem.* **2014**, *79*, 831–845.
- [7] Michael reactions: metal based allylic alkylations: a) B. M. Trost, D. A. Thaisrivongs, J. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 12439–12441. Michael addition under Iminium catalysis: b) M. Meazza, F. Tur, N. Hammer, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2017**, *56*, 1634–1638; *Angew. Chem.* **2017**, *129*, 1656–1660; Aldol addition under bifunctional base catalysis: c) X. Bai, G. Zeng, T. Shao, Z. Jiang, *Angew. Chem. Int. Ed.* **2017**, *56*, 3684–3688; *Angew. Chem.* **2017**, *129*, 3738–3742.
- [8] J. Izquierdo, A. Landa, I. Bastida, R. López, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2016**, *138*, 3282–3285.
- [9] To date the *N*-oxide functionality has commonly been employed to activate and functionalize the azaarene ring. See: a) G. Yan, A. J. Borah, M. Yang, *Adv. Synth. Catal.* **2014**, *356*, 2375–2394; b) Y. Wang, L. Zhang, *Synthesis* **2015**, *47*, 289–305; c) J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Rev.* **2012**, *112*, 2642–2713.
- [10] For an *N*-oxide-assisted α -C(sp³) trifluoromethylation of (mainly) 2-methyl pyridines, see: a) Y. Kuninobu, M. Nagase, M. Kanai, *Angew. Chem. Int. Ed.* **2015**, *54*, 10263–10266; *Angew. Chem.* **2015**, *127*, 10401–10404; For palladium-catalyzed α -arylation of 2-methyl azine *N*-oxides, see: b) L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267.

- [11] a) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis* (Ed.: K. Maruoka), Thieme: Stuttgart, **2012**; c) A. Ting, J. M. Gross, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145–200.
- [12] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
- [13] a) S. M. McCooney, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; *Angew. Chem.* **2005**, *117*, 6525–6528; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; c) B. Vakulya, S. Varga, A. Csampai, T. Sois, *Org. Lett.* **2005**, *7*, 1967–1969; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606.
- [14] a) W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450–5453; b) L. Dai, S.-X. Wang, F.-E. Chen, *Adv. Synth. Catal.* **2010**, *352*, 2137–2141. For pioneering work on squaramides, see: c) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
- [15] a) S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851; *Angew. Chem.* **2013**, *125*, 12062–12067; b) S. Diosdado, R. López, C. Palomo, *Chem. Eur. J.* **2014**, *20*, 6526–6531; c) H. Echave, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368; *Angew. Chem.* **2016**, *128*, 3425–3429.
- [16] For catalysts bearing multiple hydrogen bond donors, see: a) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197; b) R. Kenny, F. Liu, *Eur. J. Org. Chem.* **2015**, 5304–5319.
- [17] See Supporting information.
- [18] CCDC 1559084 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See the Supporting Information for details.
- [19] Although still premature, we have proposed, on the basis of ¹H NMR data, a plausible TS model, in which the three N–H bonds in the catalyst are involved in hydrogen bonding (see Supporting Information for details).
- [20] H. P. Kokatla, P. F. Thomson, S. Bae, V. R. Doddi, M. K. Lakshman, *J. Org. Chem.* **2011**, *76*, 7842–7848.
- [21] a) L. Chu, X.-C. Wang, C. E. Moore, A. L. Rheingold, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 16344–16347; b) Y. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 4500–4503; c) Z. Zuo, H. Cong, W. Li, J. Choi, G.-C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.
- [22] a) P. J. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1972**, 1077–1086; b) R. G. Button, P. J. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1973**, 557–567.

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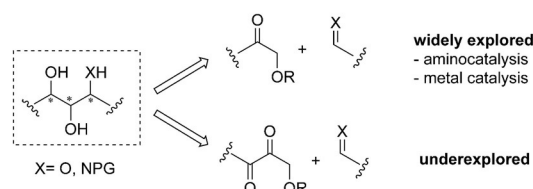
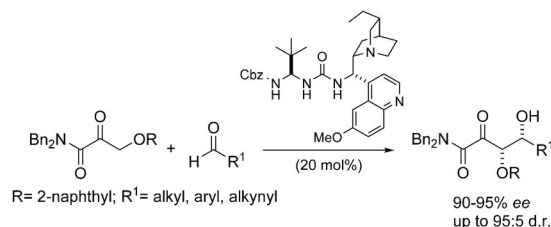
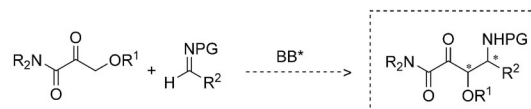
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Bifunctional Brønsted Base Catalyzed Mannich Reaction of β -Alkoxy α -Keto Amides: Stereocontrolled Entry to Functionalized Amino DiolsHaizea Echave, Iñaki Bastida, Rosa López, and Claudio Palomo^{*[a]}

Abstract: The potential of β -alkoxy α -keto amides as pronucleophiles in the enantioselective Mannich type reaction with *p*-nosyl imines is presented. The proper combination of β -alkoxy α -keto amides and a squaramide-based Brønsted base catalyst produced highly enantioenriched Mannich adducts, which may be transformed into functionalized amino diols.

A common feature of enantiopure compounds possessing therapeutic potential, is their dense functionalization containing numerous and frequently contiguous stereogenic centers, with linear polyols^[1] and amino polyols^[2] being some of the most frequent fragments contained in this class of molecules. α -Hydroxyketones are traditionally the pronucleophiles of choice in direct asymmetric and catalytic aldol^[3] and Mannich^[4] reactions to assemble 1,2-diols and 1,2-amino alcohols, which, after subsequent stereoselective reduction of the ketone moiety, afford the corresponding enantioenriched fragments with three contiguous stereogenic centers. In contrast, β -hydroxy-1,2-dicarbonyl compounds that present extra reactive centers and offer the opportunity for the construction of highly functionalized moieties have been much less explored (Scheme 1 a). The inherent high reactivity of the dicarbonyl function against nucleophilic 1,2-additions has hampered their use as pronucleophiles^[5] until recently, when progress in selective activation modes has made it possible to enhance their nucleophilic character towards cross-condensation instead of self-condensation.^[6] Most examples employ piruvates and belong to the Michael type reaction, for which metallo- and organocatalytic approaches have been described,^[7] whereas the aldol^[8] and Mannich-type reactions^[9] have been scarcely examined. Trying to fill this gap, we have recently described the first direct enantioselective cross-aldol reaction of β -alkoxy α -keto amides with aldehydes catalyzed by a bifunctional Brønsted

a) Direct catalytic aldol and Mannich reactions towards polyols and amino polyols

b) Previous work: BB^{*} catalyzed cross-aldol reaction (ref. 10)c) This work: BB^{*} catalyzed Mannich reaction

Scheme 1. Polyols and amino polyols construction by direct catalytic aldol and Mannich reactions.

base (Scheme 1 b).^[10] We now document the first direct Mannich-type reaction of these β -alkoxy α -keto amides, which further proves their utility as efficient pronucleophile partners and provides a route to highly versatile enantioenriched amino polyols.

One problem associated with adducts from aldol and Mannich reactions with α -keto esters is their high tendency to cyclize and produce isotetronic acids and pyrrolones, respectively, which would result in the loss of one of the stereogenic centers generated during the reaction.^[8,9d,e]

Initially, we evaluated the reaction of α -keto amides **1 a** and **1 b** with different N-protected imines in the presence of several bifunctional Brønsted base catalysts (Table 1). The experiments soon revealed nosyl^[11] protected imines to be the most suitable azometines for this Mannich reaction. Nevertheless, to our disappointment, ureido-peptide-based Brønsted base catalysts, which were the most effective in promoting the parent stereoselective aldol reaction,^[10] displayed poor control over the reaction selectivity; the addition of either α -ketoamide **1 a** or **1 b** to nosyl imines, promoted by catalysts **C1** and **C2**, afforded the corresponding Mannich adducts in generally good conversion and high diastereoselectivity but poor enantioselectivities

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Table 1. Nitrogen-protecting group in imine and catalyst screening for the Mannich reaction of α -keto amides.^[a-d]

Cat.:

Ent	α -keto/Imine	Cat	T [°C], t [h]	Conv [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	1a/2	C1	0, 72	0	–	–
2	1a/3	C1	0, 72	0	–	–
3	1a/4	C1	–20, 120	80	85:15	34
4	1a/5	C1	–20, 120	0	–	–
5	1a/6	C1	–20, 15	71	82:18	28
6	1a/7a	C1	–20, 15	>95	94:6	30
7	1b/7a	C2	–20, 17	>95	93:7	30
8	1b/7a	C2	–60, 45	90	99:1	40
9	1a/7a	C3	–20, 15	>95	94:4	–48
10	1a/7a	C4	–20, 15	>95	95:5	–48
11	1a/7a	C5	–20, 15	>95	94:6	88
12	1a/7a	C6	–20, 15	>95	87:13	64
13	1a/7a	C7	–20, 15	>95	95:5	92
14	1a/7a	C8	–20, 15	>95	97:3	92
15	1a/7a	C9	–20, 15	>95	90:10	80

[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of CH₂Cl₂ (mol ratio of α -keto amide/imine, 1:1.5). [b] Determined by ¹H NMR. [c] Determined by ¹H NMR and corroborated by HPLC. [d] ee of the major diastereomer determined by chiral HPLC.

regardless of the reaction temperature (Table 1, entries 5–8). Likewise, the thiourea catalysts **C3**^[12] and **C4**^[13] provided poor enantiocontrol in the reaction of **1a** with imine **7a** (entries 9, 10). However, cyclization of the Mannich adducts was not observed under the described reaction conditions. We were gratified to find out that squaramide based *Cinchona* bases^[14] (catalysts **C5–C9**) provided high conversions and higher stereoselectivities, being the best result achieved with catalyst **C8**, which produced the Mannich adduct **10a** with a 97:3 diastereomeric ratio and 92% ee for the major diastereomer (entry 14).

The influence of solvent and temperature was evaluated using catalyst **C8** and, among the solvents, chloroform gave the best results in the presence of molecular sieves; adduct **10a** was obtained with 99:1 diastereomeric ratio and 92% ee at –20 °C.^[15]

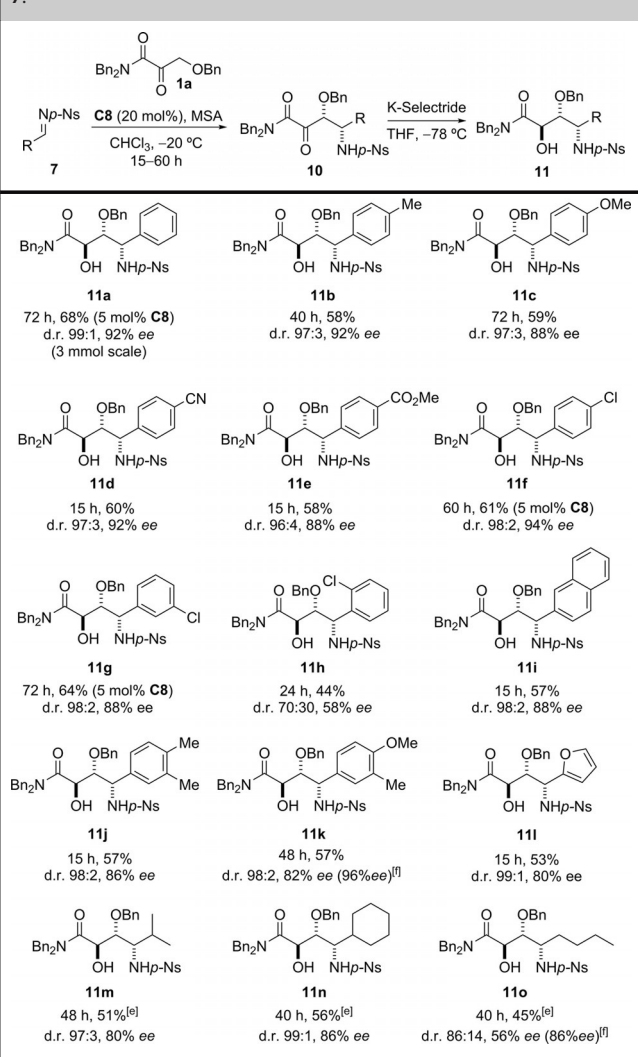
It is also worth noting that catalysts **C6–C9** belong to a new modular subfamily of squaramides, which, by simply fine-tuning the carboxamide function, offers several options for better catalyst/substrate recognition compared with common catalysts such as **C5**.^[16]

Having optimized the reaction conditions, we examined the scope of the transformation with respect to the azomethine group. A representative selection of *N-p*-nosyl imines was subjected to treatment with **1a** to afford Mannich adducts **10** in generally good diastereo- and enantioselectivities.

Again, and most importantly, in none of these reactions was formation of cyclized product observed, thus enabling subsequent carbonyl reduction to produce amino diols in a concise and simple way. The reduction step performed on the crude reaction adducts **10** using K-Selectride provided *anti,syn*-amino diols **11** (Table 2) in reasonably good yields upon isolation after the two steps and with essentially complete stereoselectivity, whereas the opposite *syn,syn*- isomers could be obtained using Et₃B/NaBH₄ (vide infra). The absolute configuration was determined for compound **11a** by single-crystal X-ray structure analysis and that of the remaining adducts was established by assuming a uniform reaction mechanism.^[17] As data in Table 2 show, *N-p*-nosyl protected imines with electron-donating or -withdrawing substituents were equally competent reaction partners, apparently irrespective of the *p*- or *m*-substitution pattern for adducts monosubstituted (**11a–g**) and disubstituted (**11i–k**) in the aromatic ring, producing enantiomeric excesses generally above 90%. Heteroaromatic imine such as **7l** also produced the corresponding adduct **11l** with excellent diastereoselectivity and high enantioselectivity. Nevertheless, *o*-substitution considerably affected both diastereo- and enantioselectivity of the reaction (adduct **11h**). On the other hand, reactions performed at 3 mmol scale showed no detrimental effect on the stereochemical outcome (adduct **11a**). In addition, when catalyst loading was lowered to 5 mol%, the reaction occurred with identical levels of selectivity although longer reaction times were required (adducts **11a**, **11f**, and **11g**). We also studied the Mannich reaction between α -keto amide **1a** and a representative selection of *p*-nosyl *N*-protected imines derived from aliphatic aldehydes. Imines derived from α -branched alkyl aldehydes produced the corresponding adducts **11m** and **11n** in high enantiomeric excesses and excellent diastereomeric ratios, whereas the lower asymmetric induction exerted in the reaction^[13] with linear imine **7o** could be mitigated by recrystallization of the corresponding *anti,syn* adduct **11o**.

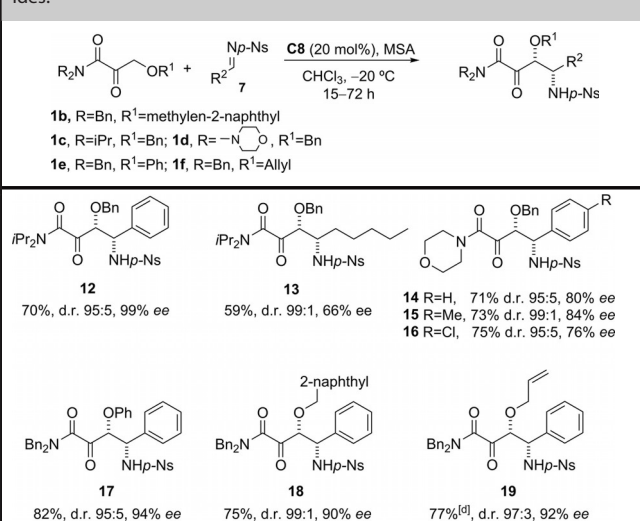
To further test the efficacy of this protocol, differently substituted α -keto amides were subjected to Mannich reaction under the previous conditions. Satisfactorily, variations on the substitution of both the amide and alkoxy moieties (R and R¹, respectively), were compatible with the methodology and, as data in Table 3 show, results were consistently good. Diisopropyl α -keto amide **1c** reacted with both aromatic and aliphatic *p*-nosyl *N*-protected imines to produce the corresponding Mannich adducts **12** and **13** with high diastereoselectivity, albeit with moderate enantioselectivity for the aliphatic adduct **13**. Interestingly, the methodology resulted also compatible

Table 2. Mannich reaction scope of **1a** with different *N-p*-nosyl imines **7** [a–d]

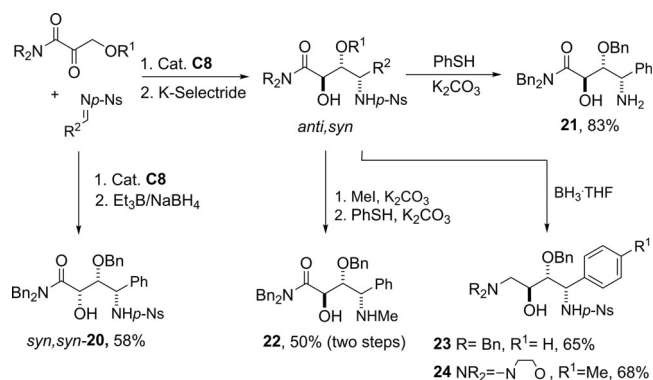


[a] Reactions conducted on a 0.15 mmol scale in 1.5 mL of CHCl₃ (mol ratio of **1a**/**7**, 1:1.5 for aromatic imines; 1:3 for aliphatic imines). [b] Yield of the isolated *anti,syn* adduct **11** after Mannich reaction and stereoselective reduction. [c] *Syn,anti* ratio determined by ¹H NMR spectroscopy and corroborated by HPLC for the Mannich adducts **10** before reduction. [d] The *ee* value of the major diastereomer (*syn* Mannich adduct), before reduction, was determined by chiral-phase HPLC. [e] Mannich reaction carried out at 0 °C. [f] Determined after recrystallization of the corresponding *anti,syn* adduct.

Table 3. Mannich reaction scope with different β-alkoxy α-keto amides. [a–c]



[a] Reactions conducted on a 0.15 mmol scale in 1.5 mL of CHCl₃ (mol ratio of **1**/**7**, 1:1.5 for aromatic imines; 1:3 for aliphatic imines). Yield of the *syn* adduct after purification. [b] *Syn,anti* ratio determined by ¹H NMR spectroscopy and corroborated by HPLC. [c] The *ee* value of the major diastereomer (*syn* Mannich adduct) was determined by chiral-phase HPLC. [d] Reaction carried out at -40 °C.



Scheme 2. Elaboration of Mannich adducts into enantioenriched amino diols.

with morpholine derived α-keto amide **1d** to produce the enantioenriched adducts **14–16**. Likewise, modification in the nature of the alkoxy moiety did not substantially affect either reactivity or selectivity (adducts **17–19**), confirming the high versatility of the method.

As noted above, the stereochemical outcome of the stereoselective reduction of the Mannich adducts, promoted by K-Selectride, could be inverted (Scheme 2) to efficiently produce, under treatment with Et₃B/NaBH₄, a 12:88 mixture of *anti,syn*:*syn,syn* diastereoisomers from which the major *syn,syn* adduct **20** was isolated in 58% yield. On the other hand, the cleavage of the *p*-nosyl protecting group was efficiently pro-

moted in the presence of thiophenol and potassium carbonate, to afford the corresponding amino diol **21** in high yield.^[18] An interesting feature of nosyl protected amines is that they can be easily transformed in secondary amines through alkylation followed by deprotection.^[19] Methylation of adduct **11a**, and subsequent *p*-nosyl cleavage, produced the corresponding secondary amine **22** in 50% overall yield. This approach highlights the structural versatility of the catalytic Mannich reaction displayed, because the nosyl group allows access to either primary or secondary amines. Also, the reduction of the amide group, carried out using the borane tetrahydrofuran complex^[20] produced diamines **23** and **24** in good yields.

The diastereo- and enantioselectivity observed might be consistent with a reaction model in which the *Re* face of the *Z*

enolate approaches the *Re* face of the *N*-protected imine (Figure 1). For this model, we propose that the deprotonated nucleophile binds to the H-bond network, and the protonated amine activates the electrophile while orienting its approach

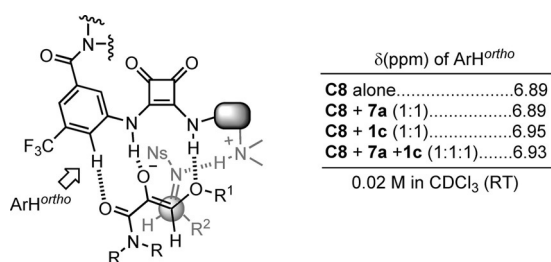


Figure 1. Plausible reaction model and selected ¹H NMR.

during reaction.^[21] As evidence in favor of this assumption, we found that the chemical shift of the *ortho*-ArH in **C8** is affected^[22] ($\Delta\delta = +0.06$ ppm) by addition of 1 equivalent of α -keto amide **1c**, whereas it remains unaffected by addition of the imine **7a**. Furthermore, the singlet corresponding to the protons at the enolizable position in **1c** splits into two peaks upon addition of **C8**. This effect suggests catalyst **C8** and the α -keto amide interact strongly, so that the homotopic protons in the achiral substrate become heterotopic and distinguishable in the substrate–catalyst complex.

In summary, we report the first direct catalytic formal Mannich reaction of β -alkoxy α -keto amides with *p*-nosyl *N*-protected imines that provides a quick entry for construction of amino diols. The newly developed squaramide-based Brønsted base catalyst employed promoted the transient generation of α -keto amide enolates, regardless of the substitution pattern at both the amide and alkoxy moieties, which reacted with either aromatic and aliphatic imines in a highly stereoselective fashion. The resulting Mannich adducts upon reduction produced highly enantioenriched linear *anti,syn*- and *syn,syn*-amino diols containing three contiguous stereogenic centers in an unprecedented way.

Experimental Section

To a cooled solution of the corresponding α -keto amide **1** (1 equiv, 0.15 mmol) squaramide-based catalyst **C8** (0.02 equiv, 0.03 mmol) and molecular sieves (pellets, 3 Å, 0.1 g) in CHCl₃ (1.5 mL) was added the corresponding imine **7** (1.5 equiv for aromatic imines; 3 equiv for aliphatic imines) at the indicated temperature. The resulting solution was stirred at the same temperature until complete disappearance of **1**. The reaction mixture was quenched with HCl 0.1 M (5 mL), the organic layer was washed with HCl 0.1 M (3 × 5 mL), dried over MgSO₄, filtered, and concentrated in vacuo to afford the corresponding crude Mannich adduct. To a cooled solution of the corresponding crude Mannich adduct in THF (1.5 mL) was added K-Selectride (1 M THF, 3–4 equiv) at -78°C . After stirring for 2 h, phosphate buffer pH 7 (0.5 mL) and EtOH (1.0 mL) were successively added, followed by H₂O₂ (30%, 0.8 mL) five minutes later. The reaction temperature was allowed to rise to room temperature and the mixture was stirred for ten additional minutes.

Then, it was diluted with EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), the organic layers were combined, dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (Hex/EtOAc) to afford the corresponding pure *anti,syn* compounds.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • Brønsted bases • Mannich reaction • organocatalysis • synthetic reactions

- a) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, *Phytochemistry* **2001**, *56*, 265–295; b) Y. Nishimura, *J. Antibiot.* **2009**, *62*, 407–423; c) D. S. Alonzi, T. D. Butters, *Chimia* **2011**, *65*, 35–39; d) S. Pal, S. G. Dumbre, *Synlett* **2016**, *27*, 2799–2802.
- For selected examples on the synthesis of aminopolyol structures with therapeutic potential, see: a) T. Ayad, Y. Génisson, M. Baltas, *Org. Biomol. Chem.* **2005**, *3*, 2626–2631; b) A. Banchet-Cadeddu, E. Hénon, M. Dauchez, J.-H. Renault, F. Monneaux, A. Haudrechy, *Org. Biomol. Chem.* **2011**, *9*, 3080–3104; c) E. D. D. Calder, A. M. Zaed, A. Sutherland, *J. Org. Chem.* **2013**, *78*, 7223–7233.
- For selected examples using metal catalysis, see: a) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Oshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467; b) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368; c) N. Kumagai, S. Matsunaga, N. Yoshikawa, M. Shibasaki, *Org. Lett.* **2001**, *3*, 1539–1542; d) N. Yoshikawa, M. Shibasaki, *Tetrahedron* **2001**, *57*, 2569–2579; e) N. Yoshikawa, T. Suzuki, M. Shibasaki, *J. Org. Chem.* **2002**, *67*, 2556–2565; f) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; g) B. M. Trost, D. J. Michaelis, M. I. Truica, *Org. Lett.* **2013**, *15*, 4516–4519. h) For pioneering works using organocatalysis, see (*anti*): W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; i) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; j) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154; *Angew. Chem.* **2004**, *116*, 2204–2206; k) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210–1212; *Angew. Chem.* **2005**, *117*, 1235–1238; l) J. T. Suri, R. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1383–1385; m) T. Kano, R. Sakamoto, K. Maruoka, *Org. Lett.* **2014**, *16*, 944–947; n) for (*syn*), see: S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288–289; o) N. Utsumi, M. Imai, F. Tanaka, S. S. V. Ramasastry, C. F. Barbas III, *Org. Lett.* **2007**, *9*, 3445–3448; p) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812–816; q) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2007**, *46*, 5572–5575; *Angew. Chem.* **2007**, *119*, 5668–5671.
- For selected examples using metal catalysis, see: a) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339; b) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713; c) S. Matsunaga, T. Yoshida, H. Morimoto, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777–8785; d) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*,

- 3470–3474; *Angew. Chem.* **2005**, *117*, 3536–3540; e) B. M. Trost, J. Jaratjaroonphong, V. Reutrakul, *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779; f) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368; *Angew. Chem.* **2005**, *117*, 4439–4442; g) D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527; *Angew. Chem.* **2012**, *124*, 7641–7645; h) B. Sun, R. Pluta, N. Kumagai, M. Shibasaki, *Org. Lett.* **2018**, *20*, 526–529. i) For selected examples using organocatalysis, see: B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; j) W. Notz, S.-I. Watanabe, N. S. Chowdari, G. Zhong, J. M. Betancort, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131–1140; k) See ref. 3n; l) L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018–1020; m) C. Wu, X. Fu, S. Li, *Tetrahedron: Asymmetry* **2011**, *22*, 1063–1073; n) C. Ayats, A. H. Henseler, E. Dibello, M. A. Pericàs, *ACS Catal.* **2014**, *4*, 3027–3033; o) B. Westermann, C. Neuhaus, *Angew. Chem. Int. Ed.* **2005**, *44*, 4077–4079; *Angew. Chem.* **2005**, *117*, 4145–4147; p) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083; *Angew. Chem.* **2005**, *117*, 4147–4151; q) I. Ibrahim, W. Zou, Y. Xu, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 211–222; r) Q. Guo, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 508–511.
- [5] 1,2-Dicarbonyl compounds, such as pyruvic acid and phosphoenolpyruvate, are employed as C3 donor units in aldolase promoted biosynthesis: a) M. F. Utter, D. B. Keech, *J. Biol. Chem.* **1963**, *238*, 2603–2608; b) D. Voet, J. G. Voet, *Biochemistry, 3rd ed.*, Wiley, New York, **2004**.
- [6] For reviews on asymmetric transformations of 1,2-dicarbonyl compounds as pronucleophiles, see: a) W. Raimondi, D. Bonne, J. Rodriguez, *Chem. Commun.* **2012**, *48*, 6763–6775; b) W. Raimondi, D. Bonne, J. Rodriguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 40–42; *Angew. Chem.* **2012**, *124*, 40–42. c) For a review on the chemistry of α -oxoesters, see: B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2015**, *115*, 151–264.
- [7] For selected examples with nitroalkenes, see (Metallo-catalytic approaches): a) A. Nakamura, S. Leetard, D. Hashizume, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4036–4037; b) A. Nakamura, S. Leetard, R. Shimizu, Y. Hamashima, M. Sodeoka, *Tetrahedron: Asymmetry* **2010**, *21*, 1682–1687; c) Y. Xu, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2010**, *12*, 3246–3249; d) D. Shi, Y. Xie, H. Zhou, C. Xia, H. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 1248–1251; *Angew. Chem.* **2012**, *124*, 1274–1277; e) H. Ouchi, A. Ashina, T. Asakawa, M. Inai, Y. Hamashima, T. Kan, *Org. Lett.* **2014**, *16*, 1980–1983; f) Q. Liang, J. He, B. Ni, *Tetrahedron: Asymmetry* **2014**, *25*, 1146–1149; g) X. Chen, H. Zhou, H. Huang, *Chin. J. Catal.* **2015**, *36*, 57–67. h) For organocatalytic approaches, see: O. Baslé, W. Raimondi, M. M. S. Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246–5249; i) W. Raimondi, M. del Mar Sanchez Duque, S. Gouedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne, J. Rodriguez, *Synthesis* **2013**, *45*, 1659–1666; j) W. Raimondi, O. Baslé, T. Constantieux, D. Bonne, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 563–568; k) M. Rueping, A. Kuenkel, R. Fröhlich, *Chem. Eur. J.* **2010**, *16*, 4173–4176; l) D. Ding, C.-G. Zhao, Q. Guo, H. Arman, *Tetrahedron* **2010**, *66*, 4423–4427; m) Y. Liu, Y. Wang, H. Song, Z. Zhou, C. Tang, *Adv. Synth. Catal.* **2013**, *355*, 2544–2549. n) For selected examples with α,β -unsaturated carbonyl compounds, see: M. Rueping, E. Sugiono, E. Merino, *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049; *Angew. Chem.* **2008**, *120*, 3089–3092; o) M. Rueping, A. Kuenkel, F. Tato, J. W. Bats, *Angew. Chem. Int. Ed.* **2009**, *48*, 3699–3702; *Angew. Chem.* **2009**, *121*, 3754–3757; p) Y. Gao, Q. Ren, Q.-S. Ang, J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 3691–3697; q) A. Lefranc, L. Guénée, A. Alexakis, *Org. Lett.* **2013**, *15*, 2172–2175.
- [8] For pyruvate cross-aldol reactions with highly reactive carbonyl compounds, see: a) N. Gathergood, K. Juhl, T. B. Poulsen, K. Thorndrup, K. A. Jørgensen, *Org. Biomol. Chem.* **2004**, *2*, 1077–1085; b) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986; *Angew. Chem.* **2004**, *116*, 2017–2020. c) For enamine-based cross-aldol reaction between α -ketoacids and aromatic aldehydes, see: B. Zhang, Z. Jiang, X. Zhou, S. Lu, J. Li, Y. Liu, C. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 13159–13162; *Angew. Chem.* **2012**, *124*, 13336–13339; d) V. Liautard, D. Jardel, C. Davies, M. Berlande, T. Buffeteau, D. Cavagnat, F. Robert, J.-M. Vicent, Y. Landais, *Chem. Eur. J.* **2013**, *19*, 14532–14539. e) For diastereoselective pyruvate cross-aldol reactions, see: O. El-Sepelgy, J. Mlynarski, *Adv. Synth. Catal.* **2013**, *355*, 281–286; f) M. A. Molenda, S. Bäs, J. Mlynarski, *Eur. J. Org. Chem.* **2016**, 4394–4403.
- [9] For metal-catalyzed Mannich reactions of 1,2-dicarbonyl compounds, see (α -keto esters and *N*-tosyl- α -imino ester): a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; *Angew. Chem.* **2001**, *113*, 3083–3085. b) For α -keto anilides and *N*-sulfonyl imines, see: G. Lu, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 6847–6850; *Angew. Chem.* **2008**, *120*, 6953–6956; c) Y. Xu, G. Lu, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3353–3356; *Angew. Chem.* **2009**, *121*, 3403–3406. d) For organocatalyzed Mannich reactions of α -keto esters and imines, leading to cyclized products, see: W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu, C. Li, *Chem. Eur. J.* **2014**, *20*, 8545–8550; e) X. del Corte, A. Maestro, J. Vicario, E. M. de Marigorta, F. Palacios, *Org. Lett.* **2018**, *20*, 317–320.
- [10] H. Echave, R. López, C. Palomo, *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368; *Angew. Chem.* **2016**, *128*, 3425–3429.
- [11] T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353–359.
- [12] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
- [13] a) S. M. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; *Angew. Chem.* **2005**, *117*, 6525–6528; b) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; c) B. Vakulya, S. Varga, A. Csampa, T. Sois, *Org. Lett.* **2005**, *7*, 1967–1969; d) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606.
- [14] For pioneering work on squaramides, see: a) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156; *Angew. Chem.* **2010**, *122*, 157–160.
- [15] Molecular sieves (3 Å) prevented *p*-nosyl *N*-protected imine decomposition especially in reactions that required long reaction times. For solvent and temperature screening, see the Supporting Information.
- [16] a) E. Badiola, I. Olaizola, A. Vazquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185–8189; b) I. Urruzuno, O. Mugica, M. Oiarbide, C. Palomo, *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063; *Angew. Chem.* **2017**, *129*, 2091–2095.
- [17] CCDC 1590297 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [18] N. Kato, T. Shirai, Y. Yamamoto, *Chem. Eur. J.* **2016**, *22*, 7739–7742.
- [19] Selected examples on the use of nosyl group for the selective alkylation of amines: a) See ref. 11; b) F. Cardullo, D. Donati, V. Fusillo, G. Merlo, A. Paio, M. Salaris, A. Solinas, M. Taddei, *J. Comb. Chem.* **2006**, *8*, 834–840. c) For a recent example on alkylation of *N*-sulfonyl imines, see: J. N. Naoum, K. Chandra, D. Shemesh, R. B. Gerber, C. Gilon, M. Hurevich, *Beilstein J. Org. Chem.* **2017**, *13*, 806–816.
- [20] B. Ramalingam, M. Neuburger, A. Pfaltz, *Synthesis* **2007**, 572–582.
- [21] a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160; b) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631–5639.
- [22] a) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682–2685; b) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919–5927.

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Building C(sp³)-rich complexity by combining cycloaddition and C–C cross-coupling reactions

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Prized for their ability to rapidly generate chemical complexity by building new ring systems and stereocentres¹, cycloaddition reactions have featured in numerous total syntheses² and are a key component in the education of chemistry students³. Similarly, carbon–carbon (C–C) cross-coupling methods are integral to synthesis because of their programmability, modularity and reliability⁴. Within the area of drug discovery, an overreliance on cross-coupling has led to a disproportionate representation of flat architectures that are rich in carbon atoms with orbitals hybridized in an sp² manner⁵. Despite the ability of cycloadditions to introduce multiple carbon sp³ centres in a single step, they are less used⁶. This is probably because of their lack of modularity, stemming from the idiosyncratic steric and electronic rules for each specific type of cycloaddition. Here we demonstrate a strategy for combining the optimal features of these two chemical transformations into one simple sequence, to enable the modular, enantioselective, scalable and programmable preparation of useful building blocks, natural products and lead scaffolds for drug discovery.

Retrosynthetic chemical analysis is built upon the strategic identification of the reactions (transforms) that offer the greatest potential to simplify target preparation (the ‘T-goal’)³. To this end, the capacity of cycloadditions to generate complex ring systems and multiple bonds with precise stereochemical control is unmatched. By contrast, C–C cross-couplings such as Heck, Suzuki and Negishi reactions are capable of making only one bond at a time (most often between flat sp² systems)⁴, yet are the most used C–C bond forming methods in the patent literature⁷. To understand this phenomenon, it is worthwhile to compare the features of these two diverse reaction classes (Fig. 1a). Cycloadditions form two new sigma bonds, generally through concerted pathways that follow precise rules for predicting stereo- and regiochemistry. Starting with specialized building blocks that are designed to enable the reaction to take place cleanly, this process rapidly accesses complexity⁸. On the other hand, C–C cross-couplings form one new sigma bond between easily accessible building blocks, using a transition-metal catalyst to reliably and controllably produce new connections. What C–C cross-coupling lacks in terms of complexity generation, it makes up for in terms of sheer reliability and modularity.

These distinct features are illustrated by the syntheses of the alkaloid epibatidine (**1**)⁹ and the commercial antihypertensive medicine Cozaar (**2**)¹⁰ (Fig. 1a). Epibatidine, coveted for its pronounced analgesic properties, has been prepared by total synthesis more than 60 times (see Supplementary Information for a complete listing). Of these syntheses, at least 31 have used cycloaddition chemistry as their key ring-constructing step. The vast majority of these approaches involve formation of the bridged pyrrolidine core, followed by stepwise, and often lengthy, pyridine incorporation. Meanwhile, medicinal agent **2**, bereft of any stereogenic centres or topological complexity, was heralded as one of the first examples of a ‘blockbuster’ drug. Both its discovery and its eventual manufacture used C–C cross-couplings (Ullmann and Suzuki reactions) for the key bond cleavage^{11,12}.

This facilitated both a convergent assembly and a modularity that permitted the rapid exploration of hundreds of analogues.

Here, we sought to combine the innate complexity generation of cycloaddition with the simplicity and modularity of C–C coupling. When applied to structures such as **1**, this strategy will permit the rapid generation of analogues, and when applied to medicinal programs such as **2**, it will allow for the rapid exploration of otherwise challenging complex chemical space.

Building block **3**, of hypothetical value in medicinal chemistry, represents the manifestation of this idea (Fig. 1b). Although its structure would seem to suggest that it could be formed through a Diels–Alder reaction, the relevant synthetic building blocks, structures **4** and **5**, are not electronically matched and therefore one would expect no reaction to take place. Even if a workable enantioselective Diels–Alder reaction could be invented to achieve this transform, the strategy would suffer from a lack of modularity. In order to solve this problem, one could envisage using a hypothetical vicinal dihaloethylene (**6**) in place of **5**, with a fumarate-type dienophile such as **7** serving as a viable synthetic equivalent. The favourable matched electronics of the dienophile should allow for a facile Diels–Alder reaction and subsequent radical cross-coupling (RCC).

To address the enantioselectivity challenge, a combination of transforms was proposed (Fig. 1c). Maleic anhydride was chosen as a surrogate for the hypothetical chiral (pseudo)dihalide **6** given its inexpensive nature, ready participation in most cycloaddition modes ([2+1], [2+2], [3+2], [4+2]), and known desymmetrization through chiral Lewis-base-mediated alcoholysis. Our sequence for generating complexity in a modular fashion involves five simple steps: first, cycloaddition to build a scaffold; second, desymmetrization to set absolute stereochemistry; third, RCC to install a new C–C bond; fourth, hydrolysis; and fifth, RCC to forge another new C–C bond. The known versatility of RCC enables a range of functionalities to be installed, from aryl¹³ and heteroaryl¹⁴ systems to alkenes¹⁵, alkynes¹⁶ and alkyl groups¹⁷. We describe here the preparation of more than 80 synthetic examples and multiple applications, covering a range of natural products (including the synthesis of **1**) and real-world examples from industrial settings.

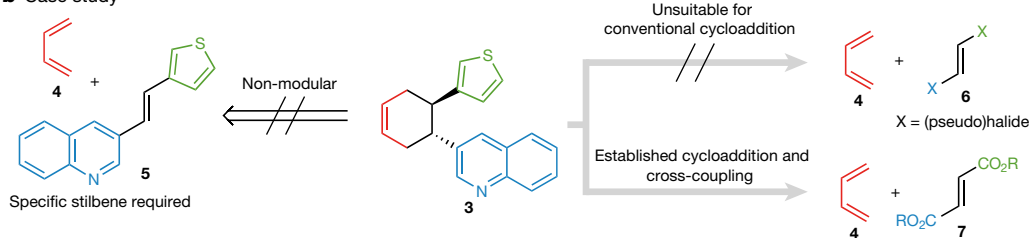
Studies commenced with Diels–Alder [4+2] cycloaddition (Fig. 2a), by which a large variety of enantiomerically enriched scaffolds could be produced in a simple modular fashion. First, scaffolds **A**₁–**A**₆ (**A**₂ being a Diels–Alder adduct and all others being derived from Diels–Alder/hydrogenation) were desymmetrized using Deng’s conditions, with either quinine or quinidine used as the Lewis base to deliver mixed acids/esters in excellent enantioselectivity¹⁸. Next, the mono-acid substrate was subjected to successive Negishi^{13,15–17} and Suzuki¹⁴ type RCC reactions, depending on starting-material availability or individual preferences. In this manner, some of the most simple and inexpensive Diels–Alder adducts known (**A**₁ costs US\$38.54 per mol and **A**₂ is US\$9.52 per mol) can be transformed into enantioenriched products (**11**–**63**) of high value. Indeed, none of these products can at present be prepared using a Diels–Alder reaction (racemic or enantioenriched),

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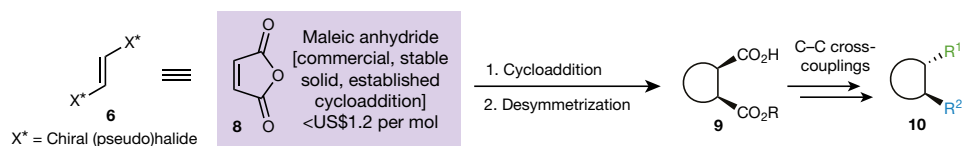
a Cycloaddition and C–C cross-coupling

<p>Cycloadditions Epibatidine 1</p>	Concerted/ pericyclic (substrate controlled)	2	Sterics/ electronics	Multiple rings/ complex architecture	Boutique building blocks
	Mechanism	New bonds formed	Predictability	Complexity	Starting material availability
<p>C–C cross couplings Losartan (Cozaar) 2</p>	Transition metal-mediated (ligand controlled)	1	Easily programmed coupling partners	Single C–C bond	Ubiquitous
Combining the best strategic assets of powerful transforms					

b Case study



c Maleic anhydride as chiral dihalide surrogate



because in most cases the reaction would require both an electron-rich diene and an electron-rich dienophile and therefore is electronically unfavoured. Furthermore, controlling the chemoselectivity when there are multiple alkenes present in the dienophile is challenging using traditional Diels–Alder chemistry; however, with our method, diverse alkenes and alkynes can be easily installed post-cyclization, with excellent isomeric and geometrical purity (accessing **12**, **15**, **19**, **21**, **25** and **31**). Typically, scaffolds derived from Diels–Alder adducts **A**₁–**A**₆ have a clear retrosynthetic signature, wherein the electron-withdrawing groups on the dienophile have been homologated, alkylated, or degraded. Therefore, our approach allows access to the previously unexplored chemical space of electron-rich, chiral, 1,2-disubstituted Diels–Alder scaffolds. Using the tactical combination outlined above, a virtually limitless array of substituents is now easily accessed, including halogenated arenes, Lewis-basic heterocycles, α,β -unsaturated carbonyl groups, cyclopropanes, cyclobutanes, sulfur moieties, and alkenes. In the case of *exo* and *endo* isomers **A**₄ and **A**₅ (both commercially available), the sequences converged to an identical product using the same coupling partners (**27** could be prepared from **A**₄ or **A**₅).

As shown in Fig. 2b–d, the strategy outlined above could also be applied to [3+2], [2+2] and [2+1] cycloadditions. The vast scope observed with Diels–Alder chemistry was also seen in these cases, accessing substituents such as substituted olefins, terminal alkynes, homoallyl groups, and heterocycles. Pyrrolidine-containing systems could be derived from simple building blocks **B**₁ and **B**₂ (accessed through dipolar cycloaddition)¹⁹ to furnish **64**–**82** with high enantiomeric excess. Quick access to pyrrolidine-containing drug scaffolds is useful: historically these have been extremely relevant to medicinal chemists, with around 40 pharmaceuticals containing this motif²⁰. As with the Diels–Alder adducts, none of these structures has been accessed before. Therefore, our approach serves as a modular entry to chiral variants of these coveted scaffolds.

In a similar vein, enantioenriched cyclopentenes were easily produced from palladium-catalysed, trimethylenemethane-based, formal [3+2] cycloaddition adduct **B**₃²¹. Such structures are highly challenging

Fig. 1 | Combining the logic of cycloaddition and C–C cross-coupling. a, Comparison of cycloaddition and C–C cross-coupling. Bu, butyl; R–X, electrophile; R'–M, nucleophile. b, Case study: retrosynthetic analysis of enantiopure building block **3**. This building block could in theory be formed through a Diels–Alder reaction, but the structures that would be used for this, **4** and **5**, are not electronically matched and no reaction would occur; moreover, the strategy would not result in any modularity. Instead a hypothetical vicinal dihaloethylene (**6**) could be used; however, this is unsuitable for conventional cycloaddition. **7** is a viable synthetic equivalent. c, Maleic anhydride can be used as an available and modular chiral dihalide surrogate.

to access in any other way. Scaffolds **C**₁ and **C**₂, representing entry to [2+2]-derived systems, could be similarly processed. Modular access to enantioenriched cyclobutanes is important and useful given the strict electronic requirements for photochemical cycloaddition and the documented challenge in achieving general asymmetric induction²². Access to 1,2-disubstituted cyclobutanes (**83**–**86**, derived from **C**₁) compares favourably with photochemical approaches to such systems that frequently give inseparable racemic mixtures of regiomers and diastereomers. Furthermore, access to tetrasubstituted, chiral cyclobutanes is highly useful, as multiple families of dimeric and pseudodimeric cyclobutane natural products contain such structural motifs²³. Structures such as **87**, which would be otherwise extremely difficult to access through conventional photochemistry, can be easily prepared in enantioenriched manner from maleic anhydride heterodimerization adducts such as **C**₂. Finally, the strategy outlined above when applied to [2+1] cycloadditions using scaffolds **D**₁ and **D**₂ is a major departure from the common retrosynthetic logic normally applied to such structures. Conventional approaches, usually involving late-stage cyclopropanation of an olefin, suffer from lack of enantiocontrol in the absence of directing groups or specialized carbenoid donors and complex catalysts²⁴. Structures **94** and **95** (**D**₂-derived) are particularly illustrative of this fact: it would be extremely challenging to access either of these in an enantioselective fashion with current synthetic technology (cyclopropanation or C–C cross-coupling). As testament to the power of this strategy to access diverse libraries, we synthesized an additional 48 enantioenriched compounds in a similar manner (see Extended Data Figs. 1 and 2 for details).

To further demonstrate the potential of this approach to simplify synthesis, we present six applications in the total synthesis of natural products and in both early- and late-stage medicinal chemistry programs (Fig. 3a–f). As mentioned above, alkaloid **1** has been a popular target of both academic and industrial scientists. Through the application of cycloaddition and cross-coupling, the native carboxylate required for the Diels–Alder reaction can be used directly to produce epibatidine (**1**) in five steps (for optimization and in-depth analysis of previous approaches, see Supplementary Information) with a 38% gram-scale overall yield

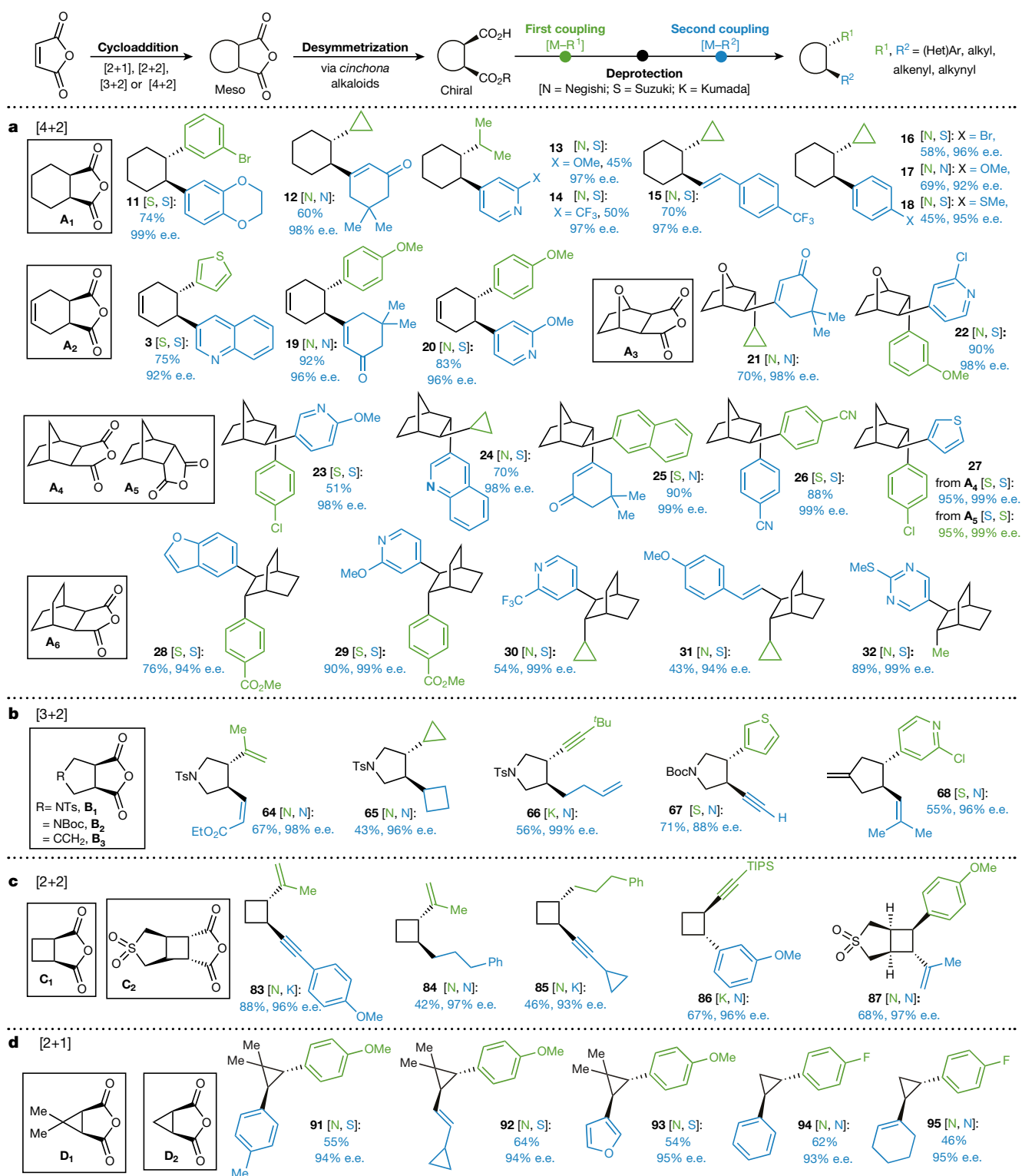


Fig. 2 Substrate scope of combining cycloaddition and C–C cross-coupling. **a–d**, The cycloaddition component is shown in black, the first cross-coupling in green and the second cross-coupling in blue. The yield and enantiomeric excess (e.e.) refer to the second cross-coupling. Besides compound **89** (diastereomeric ratio (d.r.), see Extended Data Fig. 2), excellent diastereoselectivity (d.r. greater than 10/1) was observed in all

cross-couplings. See Extended Data Figs. 1 and 2 for complete substrate scope and Supplementary Information for synthetic details. X-ray structure data are available for compounds **11**, **19**, **23**, **25**, **28**, **65** and **C₂**. N, Negishi cross-coupling; S, Suzuki cross-coupling; K, Kumada cross-coupling; Boc, *tert*-butyloxycarbonyl; TIPS, triisopropylsilyl; Ts, tosyl.

(Fig. 3a). It is worth noting that the key decarboxylative cross-coupling takes place with 95% isolated yield (gram-scale, 72% yield).

Saphris (asenapine, **102**; Fig. 3b), an antipsychotic approved by the US Food and Drug Administration (FDA), is currently marketed as a racemic mixture (although the (+)-isomer has superior

pharmacokinetic properties)²⁵. This near-symmetric molecule has been challenging to prepare enantioselectively, as the two aromatic systems differ only in one chlorine substituent. It is therefore hard to envisage a cycloaddition that could be rendered enantioselective for the preparation of **102**, and only one enantioselective approach has been reported

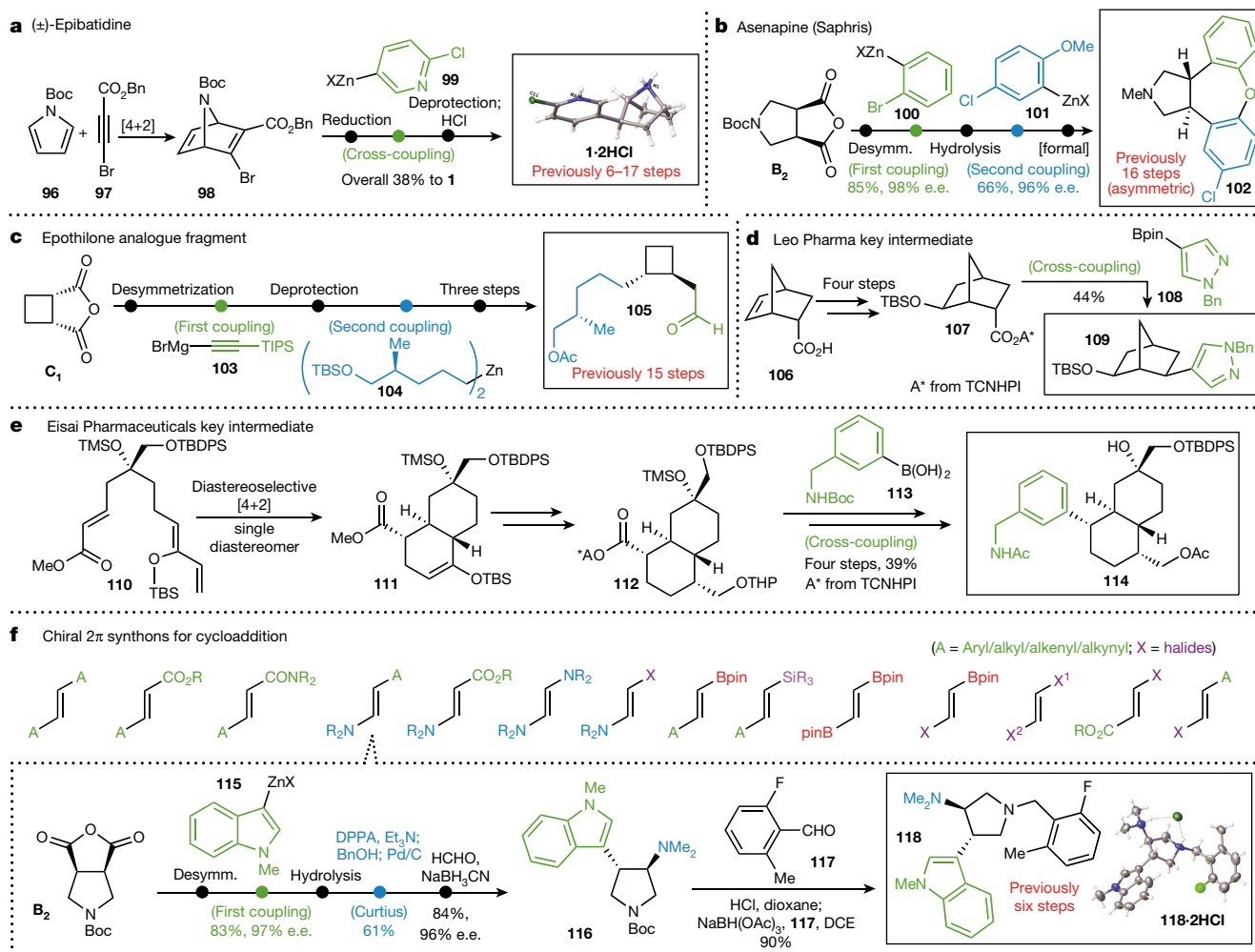


Fig. 3 | Applications of combining cycloaddition and C–C cross-coupling. **a**, Gram-scale synthesis of (±)-epibatidine. **b**, Asymmetric synthesis of asenapine (Saphris). **c**, Modular synthesis of intermediate **105**, a fragment used in the synthesis of a cyclobutyl-containing analogue of epothilone. **d**, Synthesis of a Leo Pharma key intermediate. **e**, Synthesis of an Eisai Pharmaceuticals key intermediate. **f**, New chiral 2π synthons for cycloaddition: application to the modular asymmetric synthesis of an inhibitor of the EED protein. Excellent diastereoselectivity

(d.r. greater than 10/1) was observed in all cross-couplings. See Supplementary Information for full synthetic details and schemes. X-ray structure data are available for compounds **1-2HCl**, **107** and **118-2HCl**. Boc, *tert*-butyloxycarbonyl; Pin, pinacol group; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TCNHPI, tetrachloro-*N*-hydroxyphthalimide; THP, tetrahydropyran; TIPS, triisopropylsilyl; TMS, trimethylsilyl.

in 16 steps²⁶. However, **102** can be prepared in formally six steps, with complete enantiocontrol, from **B₂**, through a strategy that could also be used to make an array of near-symmetric analogues.

Epothilone—a famous natural product that inhibits the dynamics of cellular microtubules and inspired the FDA-approved medicine Ixabepilone²⁷—has been the subject of numerous synthetic studies and analogue campaigns²⁸. Intermediate **105** (Fig. 3c) has been used during Nicolaou's synthesis of a cyclobutyl-containing analogue of epothilone, but required 15 steps (24% overall yield) to be prepared in enantioenriched form from **C₁**, via enzymatic desymmetrization and a series of carefully choreographed homologations²⁸. Using the same starting material, **C₁**, we have prepared intermediate **105** in only eight steps, through sequential desymmetrization, RCC with alkyne **103**, hydrolysis, RCC with alkyl zinc **104**, protecting-group exchange, and finally hydroboration/oxidation.

Differentially substituted norbornene rings have been shown to be useful phenyl bioisosteres in medicinal chemistry; however, their broad implementation is hindered by a lack of methods for their rapid modular construction (unlike the construction of aryl systems)²⁹. In collaboration with Leo Pharma, we prepared a key target for an ongoing program (**109**; Fig. 3d) from Diels–Alder adduct **106** via alkene hydration and RCC with the pyrazole-boronic ester **108** in 44% yield. It is

worth noting that this is, to our knowledge, the first report of a RCC reaction using a bis(pinacolato)diboron (Bpin) derivative rather than a boronic acid. This advance was achieved using an *in situ* prepared ate complex, prepared by adding one equivalent of *n*-BuLi relative to the aryl-Bpin donor³⁰. We also used this modification of our Suzuki–RCC protocol to prepare cyclopropanes **91**, **92** and **93**.

Finally, an ongoing program at Eisai Pharmaceuticals necessitated the preparation of complex scaffold **114** (Fig. 3e), wherein the key structure–activity relationship to be explored resided at the aryl (green) portion of the molecule. This is a particularly powerful application of the strategy outlined herein, because a carboxylate—needed to achieve the diastereoselective Diels–Alder reaction to construct the decalin framework—served as a gateway for the exploration of chemical space at the desired position. Thus, an asymmetric Diels–Alder reaction using Corey's oxazaborolidine³¹ catalyst, followed by functional group manipulations (see Supplementary Information), led to intermediate **112**, which could be cross-coupled with boronic acid **113** in a particularly challenging context to deliver **114** and enable biological follow-up.

The strategy outlined here could be useful for more than just forging C–C linkages through cross-coupling. The incorporation of classic nucleophilic functionalization (in ketone synthesis) and decarboxylative functionalization (in the Hunsdiecker reaction and in Curtius

and Wolff rearrangements) of intermediate adducts opens up innumerable possibilities for diversification, rendering access to previously inaccessible building blocks (Fig. 3f). As an example, we used a chiral 2π enamine synthon to prepare **118**, an inhibitor of the embryonic ectoderm development (EED) protein ($K_i = 4$ nM), which was previously prepared by AbbVie³² through a non-modular, racemic [3+2] approach in 1.9% overall yield. Our approach began with intermediate *meso* scaffold **B**₂ and used RCC followed by Curtius rearrangement, yielding optically pure **118** in 13% overall yield.

The advance that we have described is largely strategic in nature, and thus the underlying limitations are tied mainly to individual parameters of a particular cycloaddition and ensuing RCC reactions. That said, *cis*-1,2-disubstituted products are not currently accessible unless downstream isomerization reactions are pursued, which need to be evaluated on a case-by-case basis. Although ligand-controlled RCC reactions might eventually address this issue, in its present form this platform for modular molecular assembly holds great promise for accessing new areas of chemical space. The combination of classic cycloaddition chemistry with newly emerging radical C–C coupling offers a powerful way to repurpose the most classic skeleton-building reactions of organic synthesis, to simplify the enantioselective preparation of building blocks, natural products and medicines.

Data availability

Metrical parameters for the structures of **11**, **19**, **23**, **25**, **28**, **44**, **45**, **49**, **65**, **C2**, **107**, **1-2HCl** and **118-2HCl** are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference numbers 1837572, 1837575, 1837577, 1837578, 1837579, 1937573, 1837574, 1937576, 1821880, 1821878, 1821879, 1825177 and 1838237, respectively. Data are available from the corresponding author on reasonable request.

Online content

Any Methods, including any statements of data availability and Nature Research reporting summaries, along with any additional references and Source Data files, are available in the online version of the paper at <https://doi.org/10.1038/s41586-018-0391-9>

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- Fleming, I. *Pericyclic Reactions* (Oxford Univ. Press, Oxford, 2015).
- Nicolaou, K. C., Snyder, S. A., Montagnon, T. & Vassilikogiannakis, G. The Diels–Alder reaction in total synthesis. *Angew. Chem. Int. Ed.* **41**, 1668–1698 (2002).
- Corey, E. J. & Cheng, X. M. *The Logic of Chemical Synthesis* (Wiley, New York, 1989).
- de Meijere, A., Bräse, S. & Oestreich, M. *Metal Catalyzed Cross-Coupling Reactions and More* (Wiley-VCH, New York, 2014).
- Lovering, F., Bikker, J. & Humblet, C. Escape from Flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752–6756 (2009).
- Brown, D. G. & Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? *J. Med. Chem.* **59**, 4443–4458 (2016).
- Schneider, N., Lowe, D. M., Sayle, R. A., Tarselli, M. A. & Landrum, G. A. Big data from pharmaceutical patents: a computational analysis of medicinal chemists' bread and butter. *J. Med. Chem.* **59**, 4385–4402 (2016).
- Fleming, I. *Frontier Orbitals and Organic Chemical Reactions* (Wiley, New York, 1991).
- Olivo, H. F. & Hemenway, M. S. Recent syntheses of epibatidine. A review. *Org. Prep. Proced. Int.* **34**, 1–25 (2002).
- Carini, D. J. et al. Nonpeptide angiotensin II receptor antagonists: the discovery of a series of *N*-(biphenylmethyl)imidazoles as potent, orally active antihypertensives. *J. Med. Chem.* **34**, 2525–2547 (1991).
- Dolitzky, B.-Z., Nisnevich, G., Ruchman, I. & Kaftanov, J. Processes for preparing losartan and losartan potassium. Canadian patent CA2482857A1 (2003).
- Larsen, R. D. et al. Efficient synthesis of losartan, a nonpeptide angiotensin II receptor antagonist. *J. Org. Chem.* **59**, 6391–6394 (1994).
- Cornella, J. et al. Practical Ni-catalyzed aryl–alkyl cross-coupling of secondary redox-active esters. *J. Am. Chem. Soc.* **138**, 2174–2177 (2016).
- Wang, J. et al. Nickel-catalyzed cross-coupling of redox-active esters with boronic acids. *Angew. Chem. Int. Ed.* **55**, 9676–9679 (2016).
- Edwards, J. T. et al. Decarboxylative alkenylation. *Nature* **545**, 213–218 (2017).
- Smith, J. M. et al. Decarboxylative alkylation. *Angew. Chem. Int. Ed.* **56**, 11906–11910 (2017).
- Qin, T. et al. A general alkyl–alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **352**, 801–805 (2016).
- Chen, Y., Tian, S.-K. & Deng, L. A highly enantioselective catalytic desymmetrization of cyclic anhydrides with modified cinchona alkaloids. *J. Am. Chem. Soc.* **122**, 9542–9543 (2000).
- Padwa, A. & Dent, W. Use of *N*-[(trimethylsilyl)methyl]amino ethers as capped azomethine ylide equivalents. *J. Org. Chem.* **52**, 235–244 (1987).
- Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).
- Trost, B. M. & Chan, D. M. T. Palladium-mediated cycloaddition approach to cyclopentanoids. Introduction and initial studies. *J. Am. Chem. Soc.* **105**, 2315–2325 (1983).
- Poplata, S., Tröster, A., Zou, Y.-Q. & Bach, T. Recent advances in the synthesis of cyclobutanes by olefin [2 + 2] photocycloaddition reactions. *Chem. Rev.* **116**, 9748–9815 (2016).
- Fan, Y.-Y., Gao, X.-H. & Yue, J.-M. Attractive natural products with strained cyclopropane and/or cyclobutane ring systems. *Sci. China Chem.* **59**, 1126–1141 (2016).
- Bartoli, G., Bencivenni, G. & Dalpozzo, R. Asymmetric cyclopropanation reactions. *Synthesis* **46**, 979–1029 (2014).
- Committee for Medicinal Products for Human Use (CHMP) assessment report EMA/CHMP/58301/1/2010 (2010).
- Anugui, R. R., Mainkar, P. S., Sridhar, B. & Chandrasekhar, S. The Ireland–Claisen rearrangement strategy towards the synthesis of the schizophrenia drug, (+)-asenapine. *Org. Biomol. Chem.* **14**, 1332–1337 (2016).
- Trivedi, M., Budihardjo, I., Loureiro, K., Reid, T. R. & Ma, J. D. Epothilones: a novel class of microtubule-stabilizing drugs for the treatment of cancer. *Future Oncol.* **4**, 483–500 (2008).
- Nicolaou, K. C. et al. Chemical synthesis and biological evaluation of *cis*- and *trans*-12,13-cyclopropyl and 12,13-cyclobutyl epothilones and related pyridine side chain analogues. *J. Am. Chem. Soc.* **123**, 9313–9323 (2001).
- Myers, M. R. et al. Potent quinoxaline-based inhibitors of PDGF receptor tyrosine kinase activity. Part 1: SAR exploration and effective bioisosteric replacement of a phenyl substituent. *Bioorg. Med. Chem. Lett.* **13**, 3091–3095 (2003).
- Hatakeyama, T. et al. Iron-catalyzed Suzuki–Miyaura coupling of alkyl halides. *J. Am. Chem. Soc.* **132**, 10674–10676 (2010).
- Corey, E. J., Shibata, T. & Lee, T. W. Asymmetric Diels–Alder reactions catalyzed by a triflic acid activated chiral oxazaborolidine. *J. Am. Chem. Soc.* **124**, 3808–3809 (2002).
- He, Y. et al. The EED protein–protein interaction inhibitor A-395 inactivates the PRC2 complex. *Nat. Chem. Biol.* **13**, 389–395 (2017); erratum **13**, 922 (2017).

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Author contributions T.-G.C., T.Q. and P.S.B. conceived the work. T.-G.C., L.M.B., Y.L., J.T., D.K., I.B., S.A., C.B., J.S.C., M.S., H.F., F.G.F., H.-W.C., L.H., T.Q. and P.S.B. designed the experiments and analysed the data. T.-G.C., L.M.B., Y.L., J.T., D.K., I.B., S.A. and C.B. performed the experiments. M.S., H.F., F.G.F., H.-W.C. and L.H. performed the experiments described in Fig. 3f. P.S.B. wrote the manuscript. T.-G.C., L.M.B., Y.L., J.T., D.K., I.B., S.A., C.B., J.S.C. and T.Q. assisted in writing and editing the manuscript.

Competing interests M.S., H.F., F.G.F., H.-W.C. and L.H. are employees of Eisai Inc. This work was part-funded by Leo Pharma.

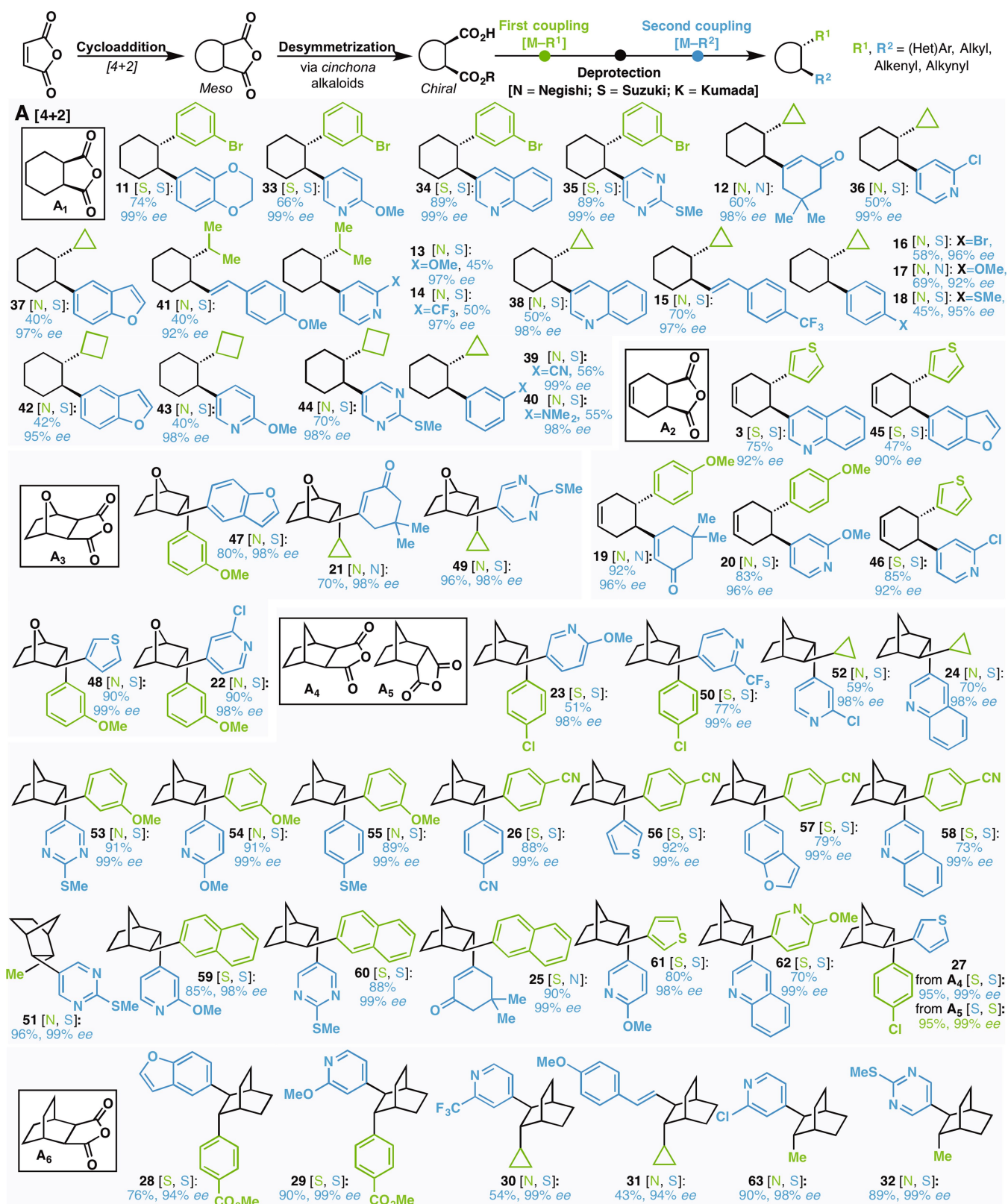
Additional information

Extended data is available for this paper at <https://doi.org/10.1038/s41586-018-0391-9>.

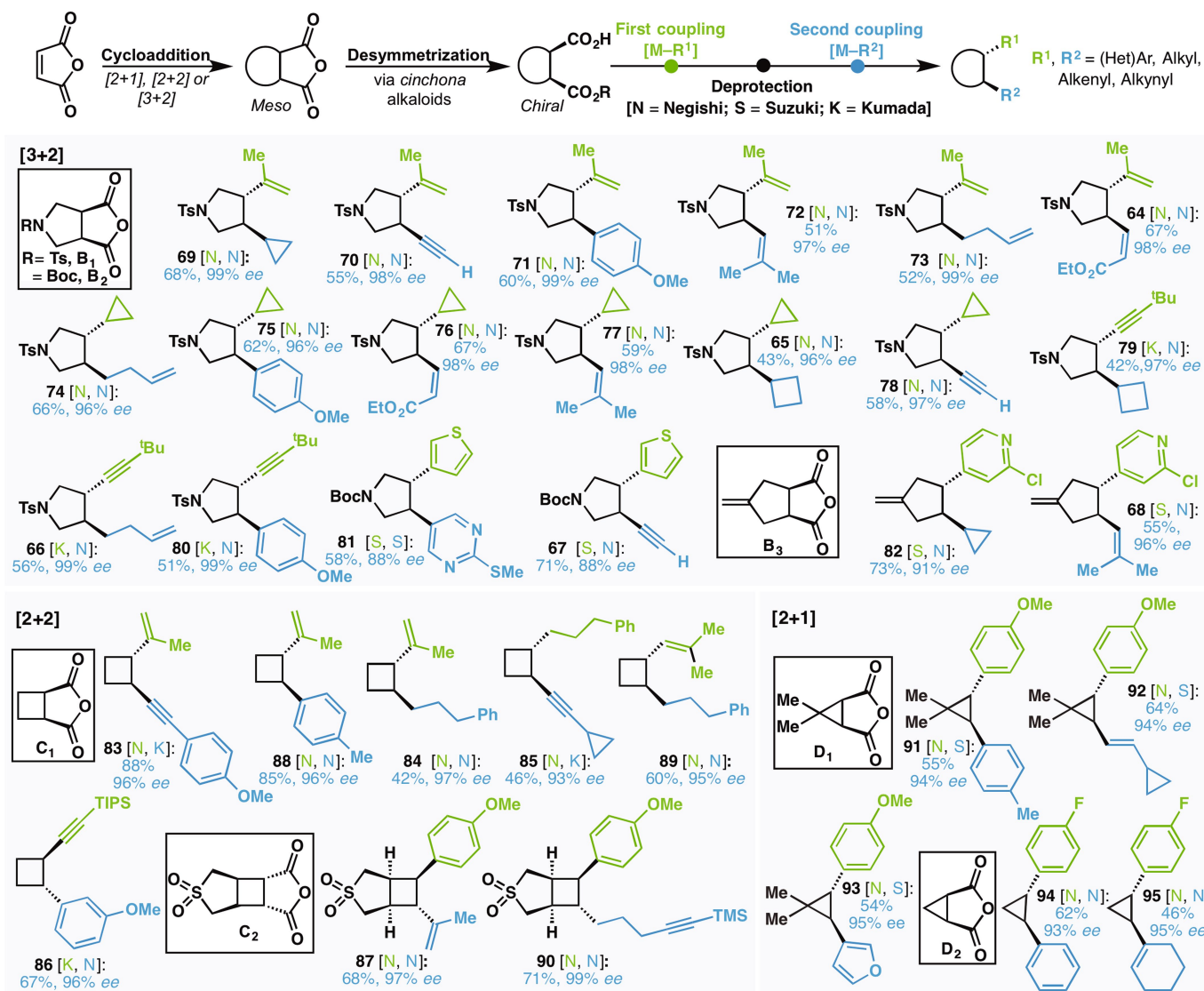
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Extended Data Fig. 1 | Complete substrate scope of [4+2] cycloadditions/cross-couplings. See Supplementary Information for synthetic details. R¹, R² = (Het)Aryl, alkyl, alkenyl, alkynyl. X-ray structure data are available for compounds 11, 19, 23, 25, 28, 44, 45 and 49.



Extended Data Fig. 2 | Complete substrate scope of [3+2], [2+2] and [2+1] sections. See Supplementary Information for synthetic details. R¹, R² = (Het)Aryl, alkyl, alkenyl, alkynyl. X-ray structure data are available for compounds C₂ and 65.