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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

Iñaki Bastida Saiz

Donostia, 2018

Universidad del País Vasco Euskal Herriko Unibertsitatea

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CAMPUS DE EXCELENCIA INTERNACIONAL

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Dra. **Rosa Mª López Álvarez** con N.I.F. **02874081R** como Directora de la Tesis Doctoral: **Stereoselective Synthesis of Secondary and Tertiary Amines through Brønsted Base Assisted Mannich, Nitro-Mannich and α-Amination Reactions** realizada en el Programa de Doctorado **Química Sintética e Indusrial** por el Doctorando Don **Iñaki Bastida Saiz**, autorizo la presentación de la citada Tesis Doctoral, dado que reúne las condiciones necesarias para su defensa.

En Donostia, a 15 de octubre de 2018

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La Comisión Académica del Programa de Doctorado en **Química Sintética e Industrial** en reunión celebrada el día 16 de octubre de 2018,

ha acordado dar la conformidad a la presentación de la Tesis Doctoral titulada: **Stereoselective Synthesis of Secondary and Tertiary Amines through Brønsted Base Assisted Mannich, Nitro-Mannich and α-Amination Reactions** dirigida por los Dres. **Rosa Mª López Álvarez** y **Claudio Palomo Nicolau** y presentada por Don **Iñaki Bastida Saiz** adscrito al Departamento de **Química Orgánica I**.

En Leioa, a 16de octubre de 2018

LA RESPONSABLE DEL PROGRAMA DE DOCTORADO

Fdo.: Esther Lete Expósito

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El Consejo del Departamento de **Química Orgánica I**, en reunión celebrada el día 19 de octubre de 2018 ha acordado dar la conformidad a la admisión a trámite de presentación de la Tesis Doctoral titulada: **Stereoselective Synthesis of Secondary and Tertiary Amines through Brønsted Base Assisted Mannich, Nitro-Mannich and α-Amination Reactions** dirigida por los Dres. **Rosa Mª López Álvarez** y **Claudio Palomo Nicolau** y presentada por Don **Iñaki Bastida Saiz** ante este Departamento.

En Gasteiz, a 19 de octubre de 2018

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

DOCTORANDO: Don **Iñaki Bastida Saiz**

TITULO DE LA TESIS: **Stereoselective Synthesis of Secondary and Tertiary Amines through Brønsted Base Assisted Mannich, Nitro-Mannich and α-Amination Reactions**

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

unanimidad ó mayoría

SOBRESALIENTE / NOTABLE / APROBADO / NO APTO

Idioma/s de defensa (en caso de más de un idioma, especificar porcentaje defendido en cada idioma):

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Otros Idiomas (especificar cuál/cuales y porcentaje) _____

En _____a _____de _____de _____

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Dr/a: _____ Dr/a: _____

VOCAL 1º, VOCAL 2º, VOCAL 3º,

Fdo.: Fdo.: Fdo.:

Dr/a: _____Dr/a:_____Dr/a:_____

EL/LA DOCTORANDO/A,

Fdo.: _____

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

DOCTORAL THESIS

Iñaki Bastida Saiz

Donostia, 2018

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 Mª 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!!

I also want to thank Prof. Phil S. Baran and his group for giving me the opportunity to do a short but unforgettable stay in his laboratory at The Scripps Research Institute in La Jolla (California, USA) and participate in one of their research projects. Thank you very much for your kindness and hospitality.

La financiación de este trabajo ha provenido de una beca predoctoral del Gobierno Vasco, así como la ayuda para la realización de estancias predoctorales en centros distintos al de aplicación para el personal investigador en formación.

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!!!

Kuadrilako lagunei, lana dela eta, zuekin oso gutxitan egon arren, beti hor egoteagatik eta nahiz eta zuek ez konturatu, lanaren zama arintzen laguntzeagatik, eskerrik asko!!

Nire gurasoei, 27 urte hauetan eman didazuen guztiagatik. Tesi honen egileak zuek zarete!! Zuen maitasun, laguntza eta jakintzek ekarri naute honaino, eta zuen babesa une oro sentitzeak beldurrik gabe aurrera egitera bultzatu nau. Aneri, nigan, nik baino mila aldiz gehiago konfiatzeagatik. Jaio nintzen unetik nire alboan egoteagatik eta nire babeslerik onena izateagatik. Urkiri, gure familian hain gogor sartzeagatik eta lehen momentutik zure babesa eta animoak emateagatik. Marisa, Kepa, Amaia eta Jokini, zuen baldintzarik gabeko maitasun, animo eta babes guztiagatik. Eta azkenik, Maitaneri, nirekin bizitza konpartitzeagatik, momentu on zein txarrenetan beti hor egoteagatik, tesi honen bultzatzaile sutsuena izateagatik, egunero irribarre bat ateratzeagatik… azken finean, ZU izateagatik!!

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.

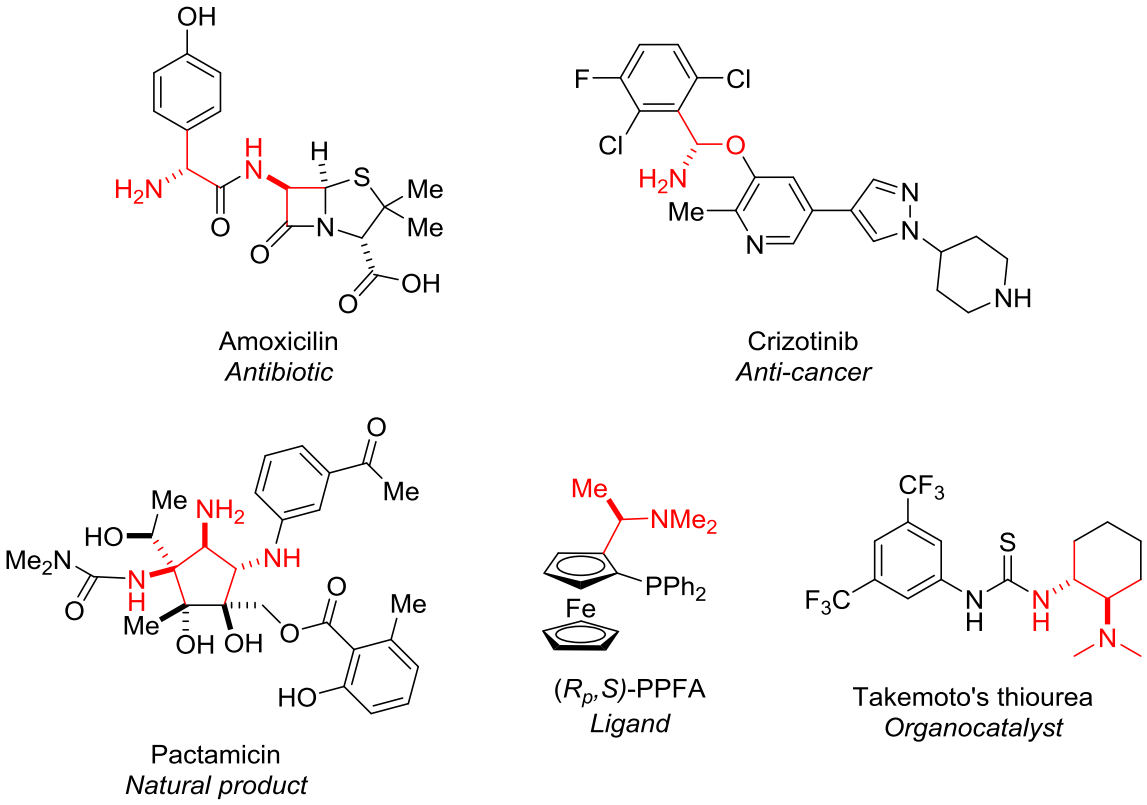
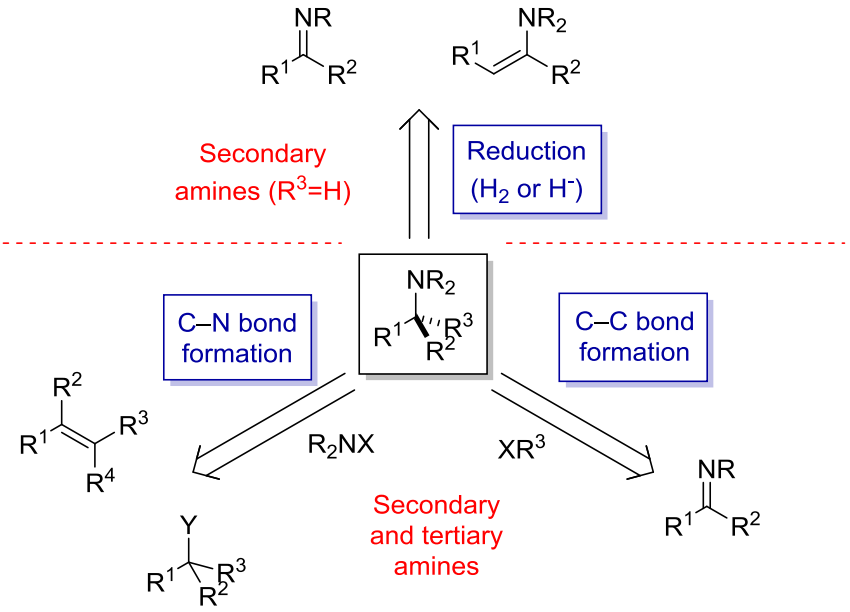


Figure 1. Representative examples of chiral amines as drugs, natural products, ligands and catalysts.

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.

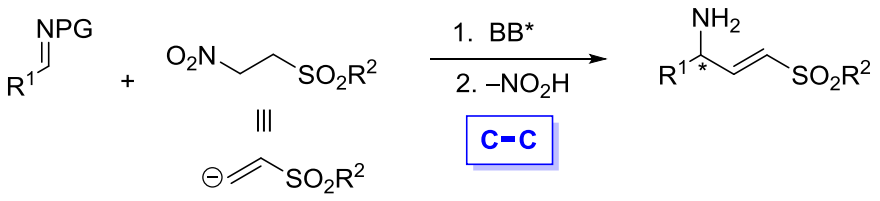
Summary



Scheme 1. Main strategies for chiral amine synthesis.

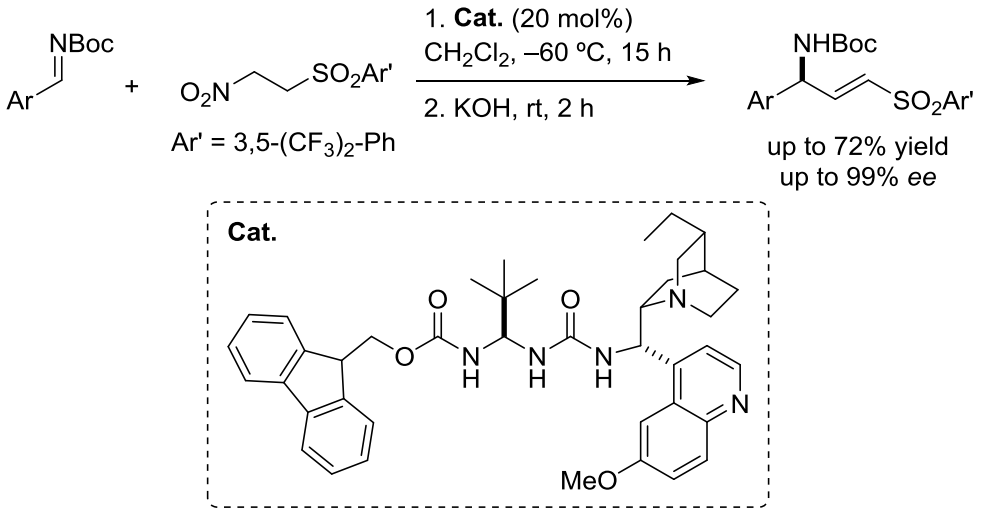
In this context, the main objective of this Ph. D. Thesis has been the development of new Brønsted base catalyzed methodologies for the synthesis of enantiomerically enriched secondary and tertiary amines of synthetic utility and with possible biological activity.

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 γ-sulfonyl allyl 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.



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).

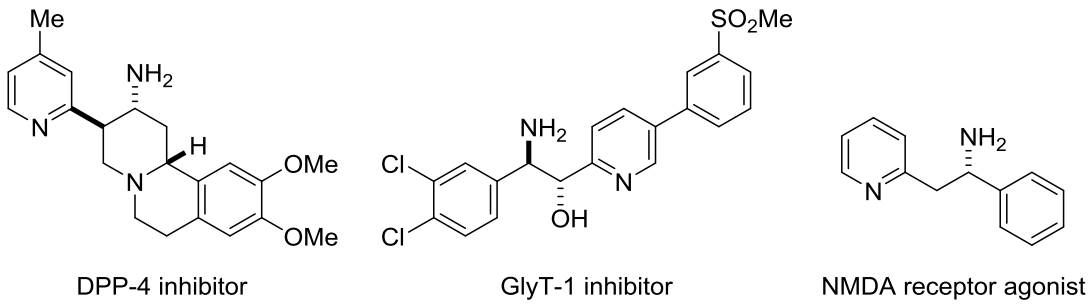
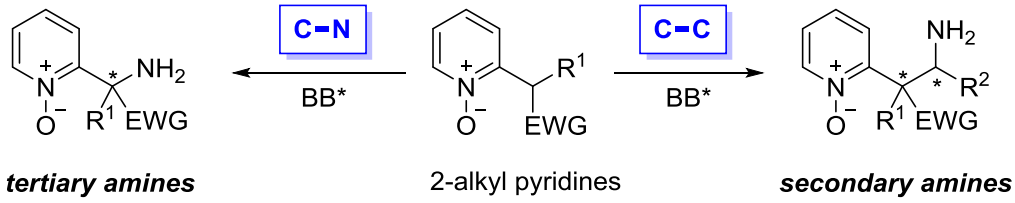


Figure 2. Representative examples of bioactive pyridines containing amino groups.

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 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 catalyst binding and provide more rigid transition states.

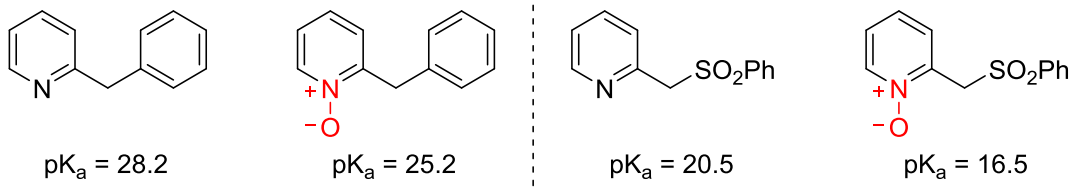
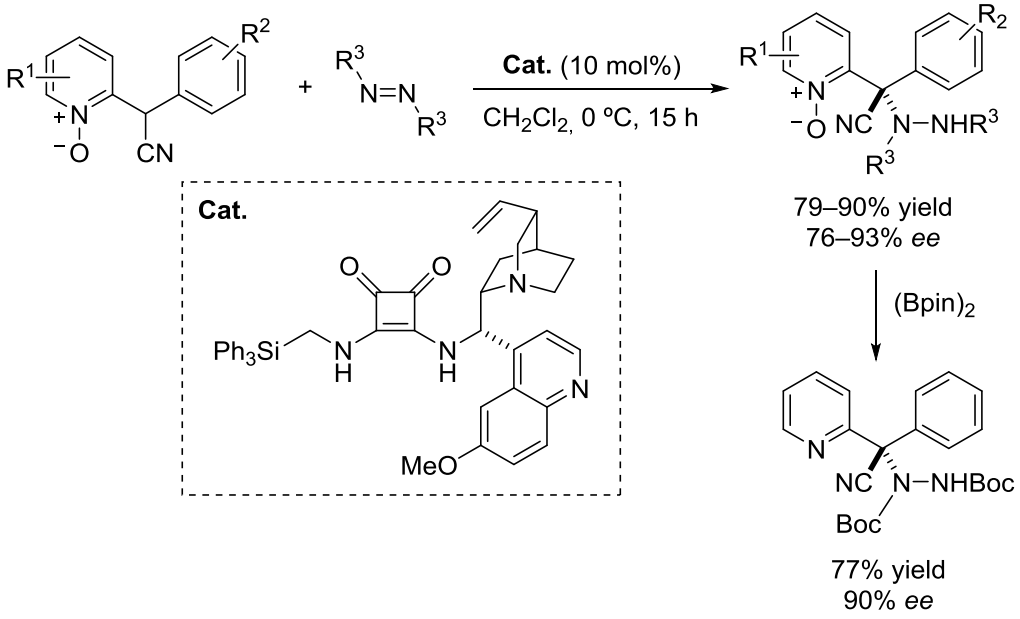


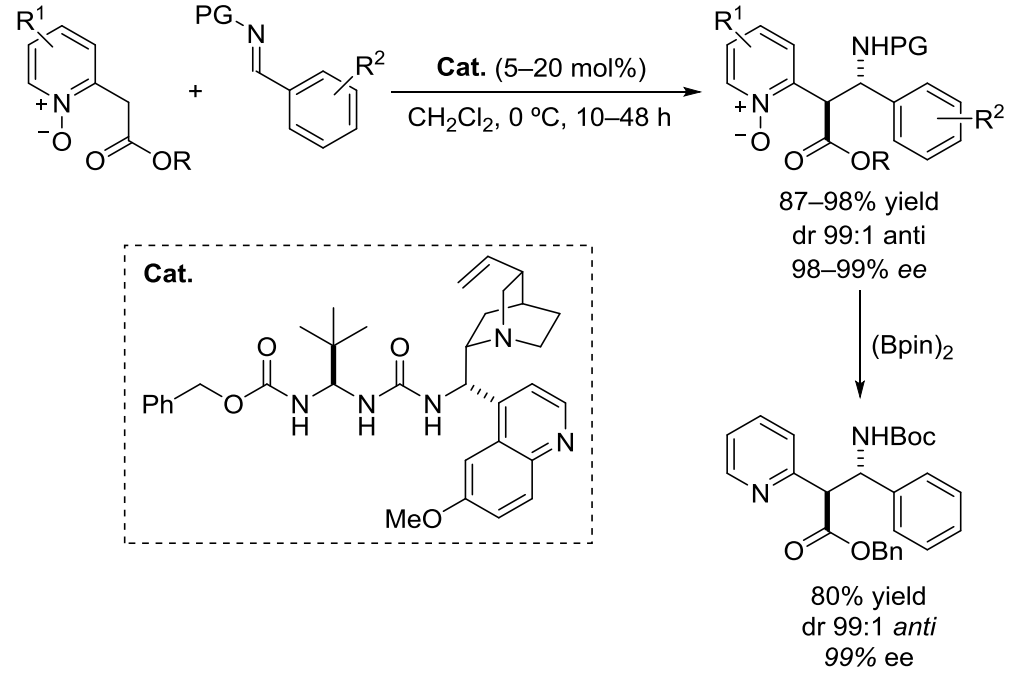
Figure 3. pK_a values for pyridine derivatives and their *N*-oxides.

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).



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

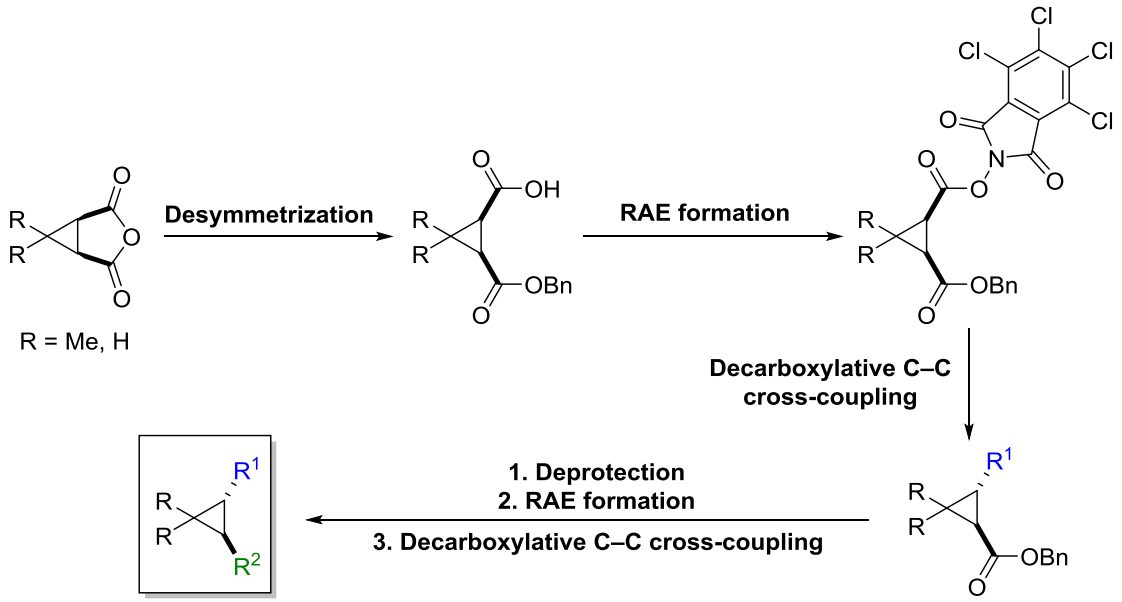
Likewise, we have developed a highly stereoselective Mannich-type reaction of 2-azaaryl acetate *N*-oxides with *N*-carbamoyl aldimines for the synthesis of pyridine based chiral secondary amines (Scheme 6). In this case, the ureidopeptide-based Brønsted base employed, not only provides excellent levels 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).

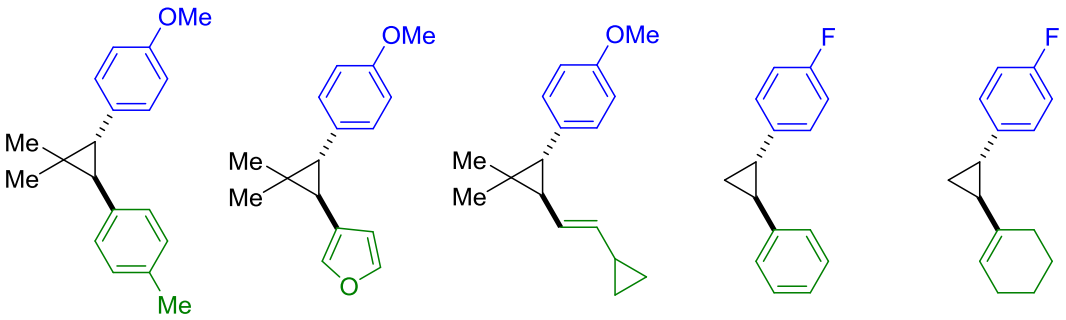
In both cases, the dual role of the *N*-oxide functionality as an activating and stereodirecting group has been proved since the parent 2-alkyl pyridines reacted sluggishly and with diminished stereoselectivities.

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).



94% *ee* 95% *ee* 94% *ee* 93% *ee* 95% *ee*

Figura 4. Synthetized *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).

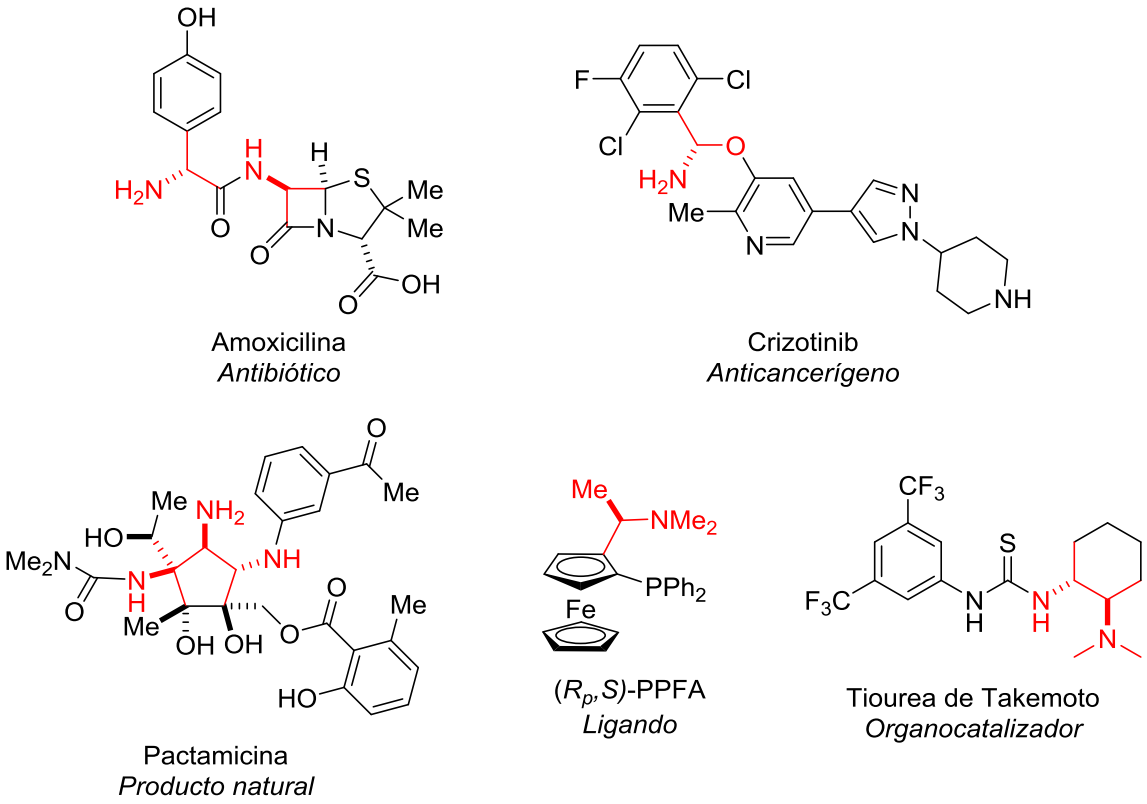
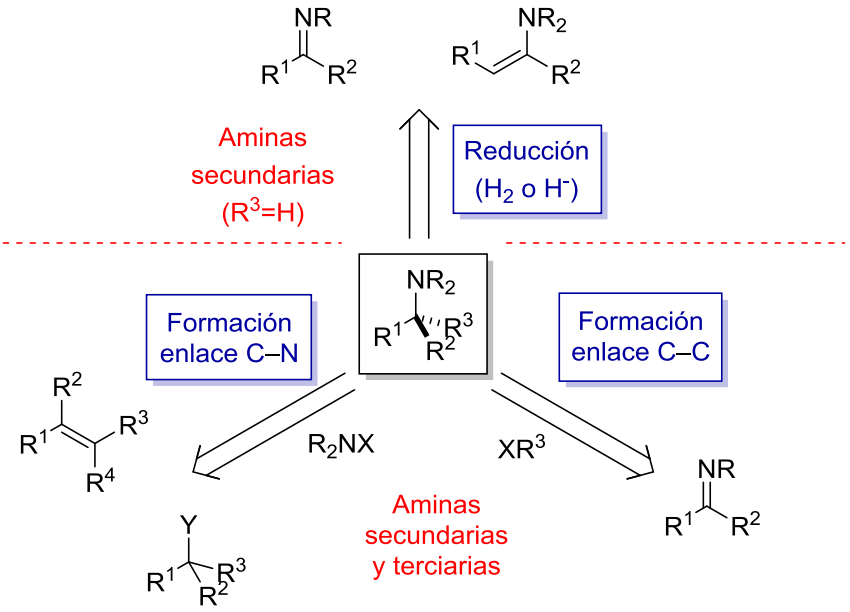


Figura 1. Ejemplos representativos de aminas quirales como fármacos, productos naturales, ligandos y catalizadores.

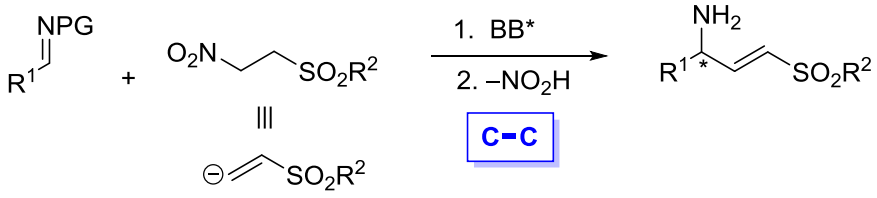
En los últimos años, el interés por estas estructuras ha motivado el desarrollo de un gran número de metodologías catalíticas y asimétricas. Las principales estrategias para la síntesis de este tipo de aminas quirales se centran, por un lado, en métodos reductores que conducen exclusivamente a la formación 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.



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

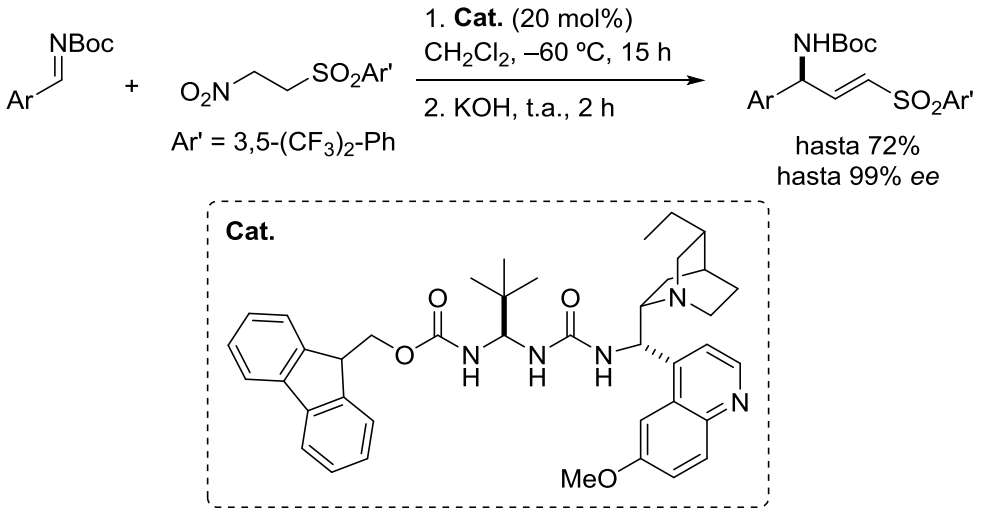
En este contexto, el objetivo principal de esta Tesis Doctoral ha sido el desarrollo de nuevas metodologías de formación de enlaces C–C y C–N, catalizadas por bases de Brønsted quirales, para la síntesis de aminas secundarias y terciarias enantioméricamente enriquecidas con utilidad sintética y posible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



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 bifunctional 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).

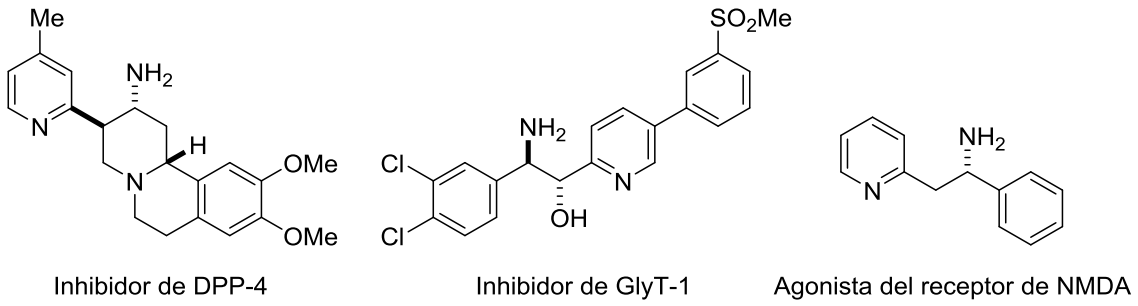
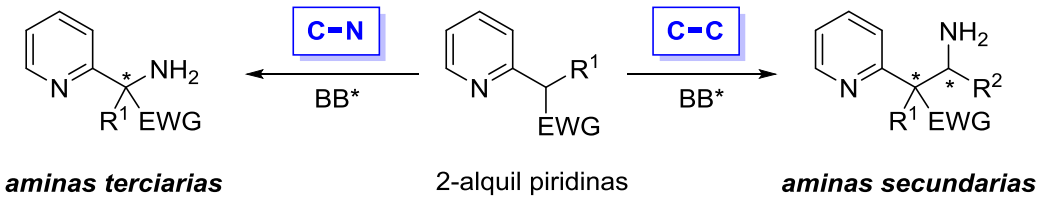


Figura 2. Ejemplos representativos de piridinas con actividad biológica que contienen grupos amino.

Para abordar la síntesis estereoselectiva de este tipo de aminas quirales, consideramos factible el empleo de 2-alquil 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-alquil 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 tetrasubstituidos que darían lugar a aminas terciarias quirales.

Con el objeto de aumentar la baja reactividad de las 2-alquil piridinas en condiciones básicas, se eligieron los *N*-óxidos de 2-alquil 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.

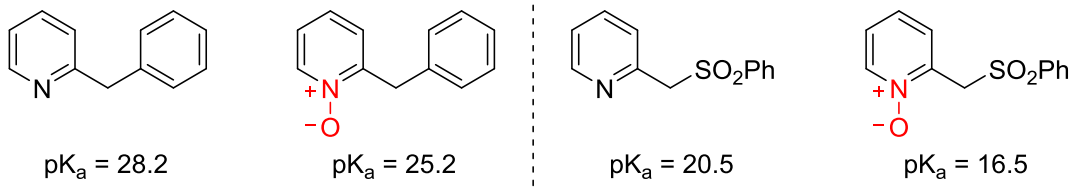
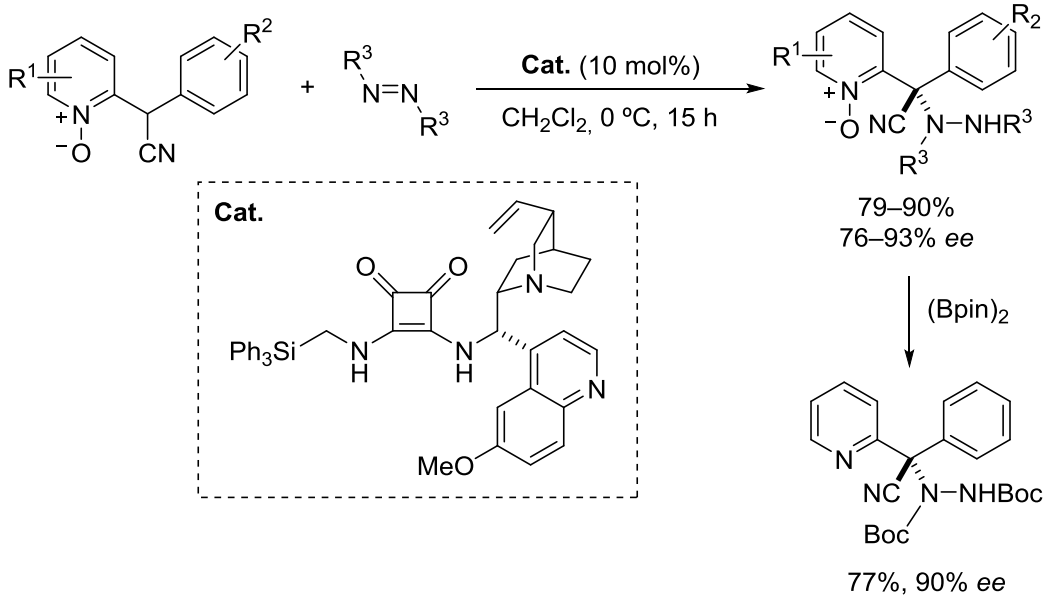


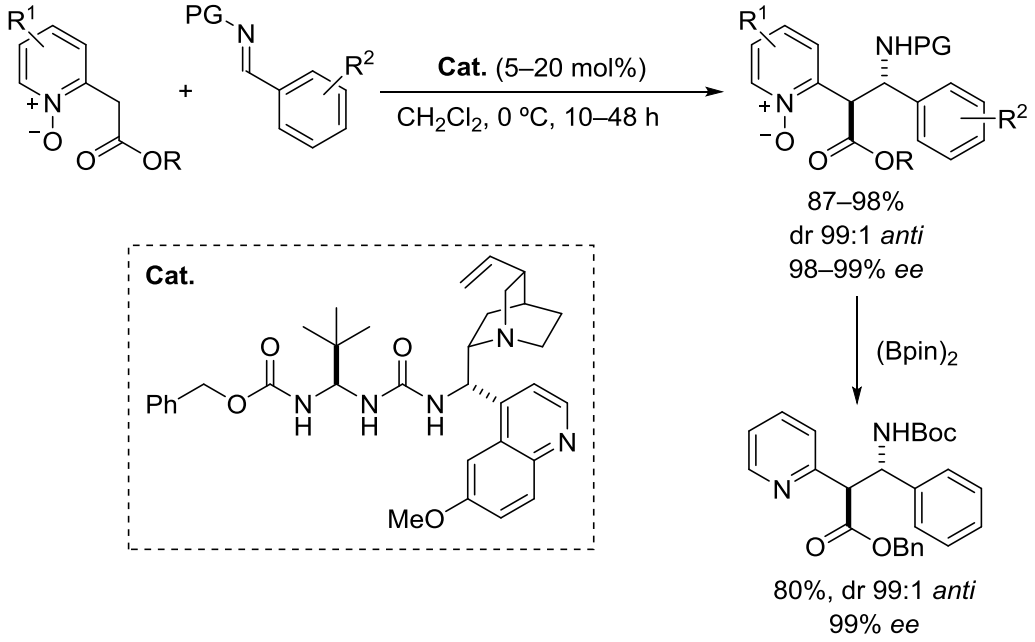
Figura 3. Valores de pK_a de derivados de piridina y sus correspondientes *N*-óxidos.

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-cianoalquil 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).



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

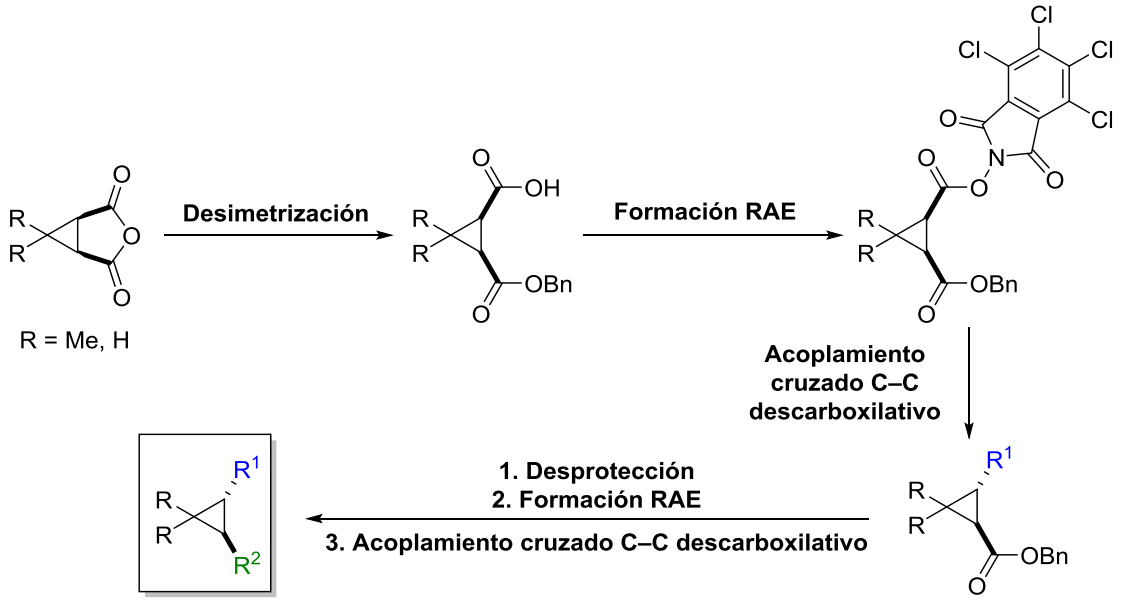
De forma análoga, se ha desarrollado una reacción de tipo Mannich altamente estereoselectiva entre *N*-óxidos de acetato de 2-azaarilo y *N*-carbamoil aldiminas que proporciona aminas secundarias altamente enantioenriquecidas (Esquema 6). En este caso, la base de Brønsted de tipo ureidopeptídico empleada 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).

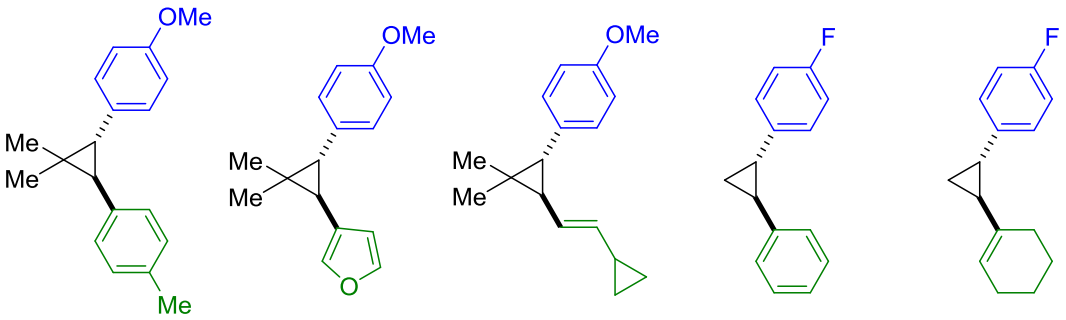
En ambos casos, el papel dual del *N*-óxido como grupo activante y estereodirector ha sido corroborado, puesto que, empleando las mismas condiciones de reacción, las 2-alquil piridinas análogas reaccionaron más lentamente y con enantioselectividades inferiores.

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*-disubstituidos altamente enantioenriquecidos (Figura 4).



94% *ee* 95% *ee* 94% *ee* 93% *ee* 95% *ee*

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	*tert*-Butyloxycarbonyl group
BPhen	Bathophenantroline
Bu	Primary butyl group
calcd.	Calculated
Cat.	Catalyst
Cbz	Carboxybenzyl group
conv.	Conversion
Cy	Cyclohexyl group
d	Day(s)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$(DHQD)_2AQN$	Hydroquinidine (anthraquinone-1,4-diyl) diether
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phtalazinediyl diether
$(DHQD)_2Pyr$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether

Abbreviations and acronyms

DIC	*N*,*N*′-diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
ent	Opposite enantiomer
Ent.	Entry
Et	Ethyl group
equiv.	Equivalent
EWG	Electron-withdrawing group
Fmoc	9-Fluorenylmethoxycarbonyl
GC	Gas chromatography
glyme	1,2-Dimethoxyethane
h	Hour(s)
HMDS	Hexamethyl disilazane
HMPA	Hexamethyl phophoramide
HPLC	High pressure liquid chromatography
*i*Pr	*iso*-Propyl group
L	Ligand
LC	Liquid chromatography
M	Metal
major.	Majority
Me	Methyl group
min	Minute(s)
minor.	Minority

Abbreviations and acronyms

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

Abbreviations and acronyms

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

INDEX

Chapter 1

Introduction

INDEX

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]

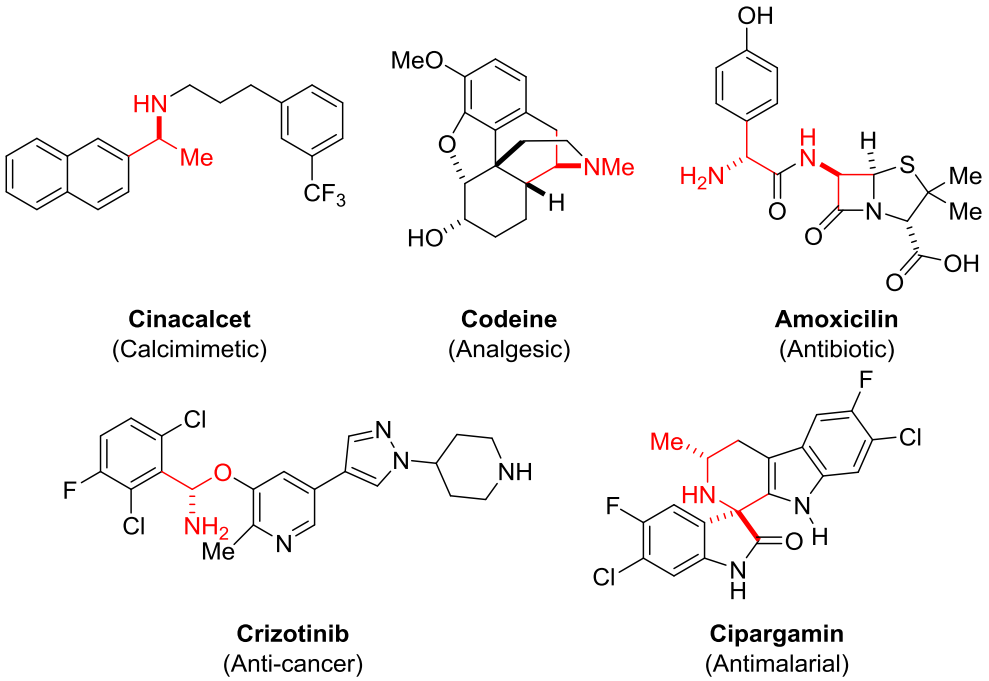


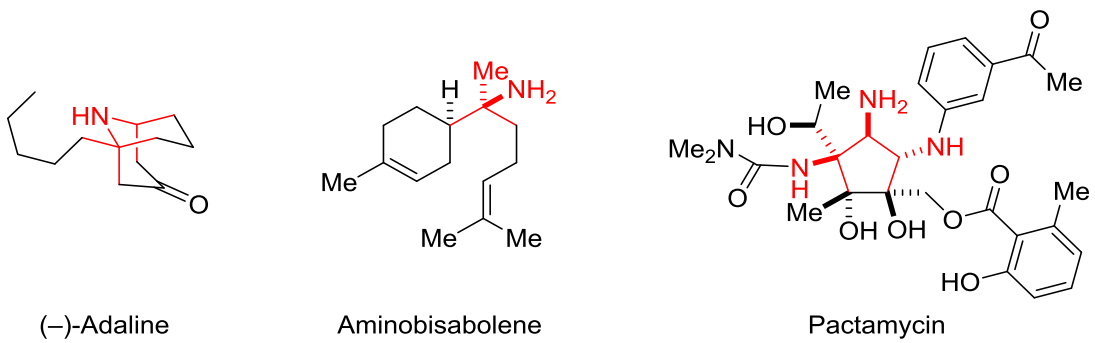
Figure 1. Examples of chiral amine-based pharmaceutical drugs.

[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.

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 body[6] 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 *Quadrimaculata* 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]



(–)-Adaline Aminobisabolene Pactamycin

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.

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 Kumada[12] and has been used in several metal catalyzed enantioselective transformations.[13] Likewise, chiral acetyl-protected aminoethyl quinoline (APAQ) has been employed in enantioselective Pd catalized C(sp^3)–H bond activations.[14] On the other hand, diarylprolinol silyl ethers developed by Jørgensen and Hayashi[15] and Takemoto's thiourea[16] represent well-known organocatalysts used in asymmetric reactions.

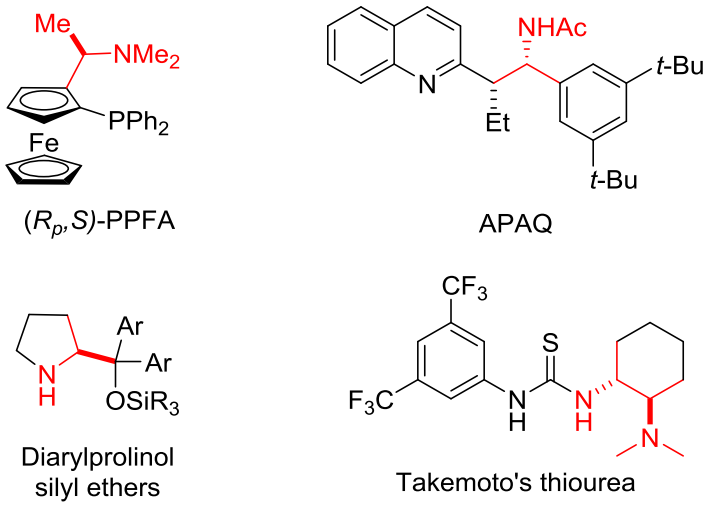


Figure 3. Examples of ligands and organocatalysts bearing chiral amines.

[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.

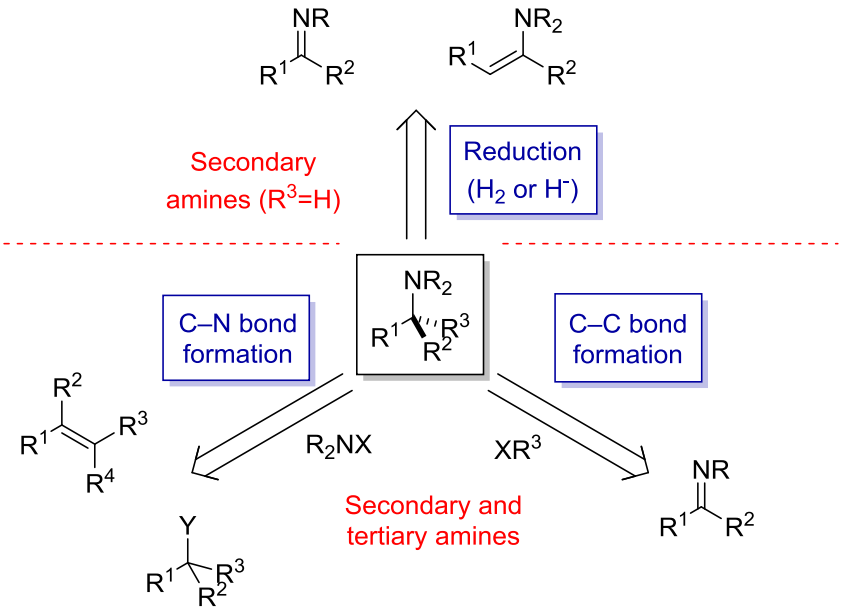
[16] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

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

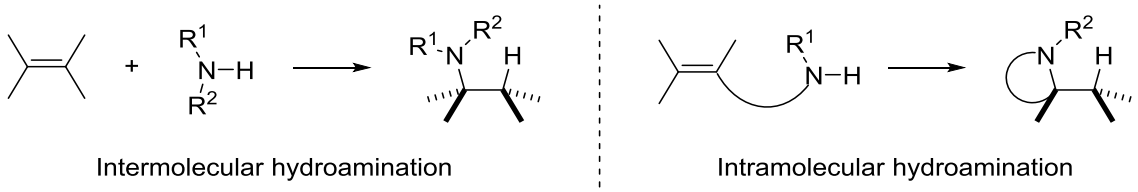
The enantioselective generation of new C–N bonds, through nucleophilic or electrophilic addition of nitrogen sources to carbon substrates, to afford optically pure α-chiral amines, is underexplored compared to reduction or C–C bond forming strategies. Nevertheless, significant advances have been made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

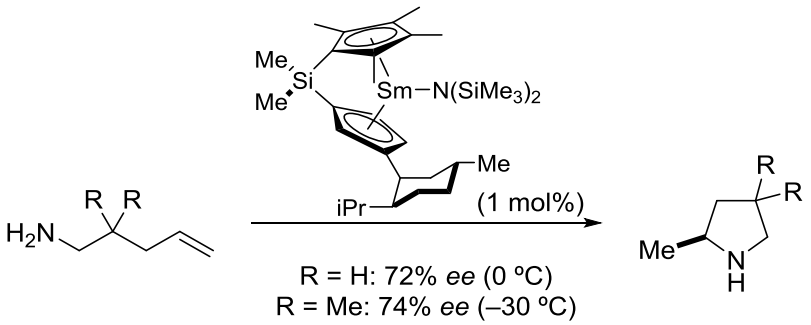
[17] a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753–819. b) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713–1760. For reviews and book chapters about asymmetric reduction of imines, see: c) Zhu, Q.-C.; Hutchins, R. O.; Hutchins, M. K. *Org. Prep. Proc. 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.; Hultzsch, 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-Hultzsch, A. J.; Hultzsch, 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.; Hultzsch, K. C. Hydroamination of Alkenes. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2015; Vol. 88, pp 1–554.



Scheme 2. Inter- and intramolecular hydroaminations.

In 1992, the group of Marks described the first enantioselective intramolecular hydroamination of terminal aminoalkenes assisted by a chiral lantanocene catalyst, which afforded 2-methyl pyrrolidines with moderate enantioselectivities (Scheme 3).[19] Since then, several metal-based catalytic systems were introduced for this reaction.[20] In addition, this intramolecular reaction was extended to other unsaturated substrates such as aminodienes,[21] aminoallenes[22] and aminoalkynes.[23]



Scheme 3. Marks' pioneering asymmetric intramolecular hydroamination.

As noted above, the enantioselective intermolecular hydroamination, has been less developed although it represents a high interesting and challenging approach towards the synthesis of chiral alkyl amines. An important difficulty to overcome, besides the negative entropy, is the competition between amines and alkenes for coordinating with the catalysts, since amines are usually much more chelating agents and could poison the catalytic center. The first intermolecular example was reported by the group of Togni in

[19] Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003–2005.

[20] a) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241–10254. b) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894–895. c) Horrillo Martínez, P.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221–2223. d) Zhang, X.; Emge, T. J.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2012**, *51*, 394–398. For a recent review in metal-catalyzed asymmetric hydroamination of alkenes, see: e) Michon, C.; Abadie, M.-A.; Medina, F.; Agbossou-Niedercorn, F. *J. Organomet. Chem.* **2017**, *847*, 13–27.

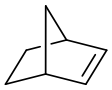
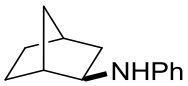
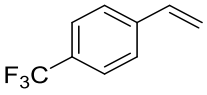
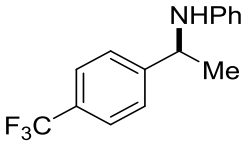
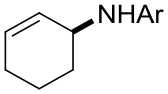
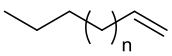
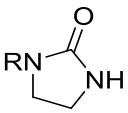
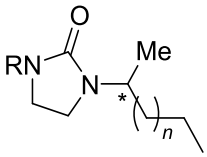
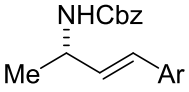
[21] Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878–15892.

[22] Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614–4620.

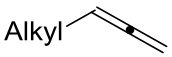
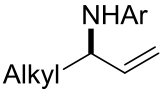
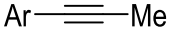
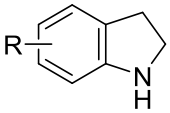
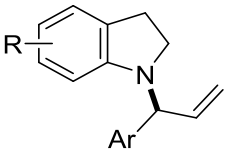
[23] Patil, N. T.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270–4279.

1997, in which norbornene was asymmetrically hydroaminated with phenylamine 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] allenes[26] and alkynes[27] (Table 1).

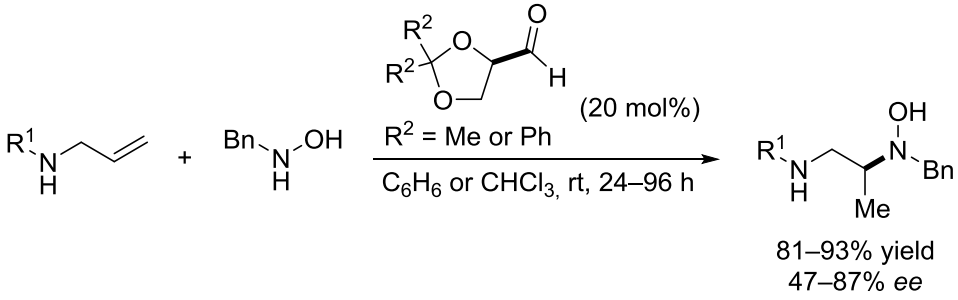
Table 1. Pioneering intermolecular asymmetric hydroaminations.

Ent.	Author	Unsaturated substrate	Amine	Catalytic system	Product
1	Togni **1997**[24]		$PhNH_2$	Ir, BINAP	 22% yield 95% *ee*
2	Hartwig **2000**[25a]		$PhNH_2$	Pd, BINAP	 80% yield, 81% *ee*
3	Hartwig **2001**[25b]		$ArNH_2$	Pd, Trost ligand	 59–87% yield 86–95% *ee*
4	Widenhoefer **2009**[25c]			Au, MeOBIPHEP	 80–89% yield 71–78% *ee*
5	Widenhoefer **2012**[26a]		$CbzNH_2$	Au, MeOBIPHEP	 42–97% yield 60–92% *ee*

[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
6	Breit **2012**[26b]		$ArNH_2$	Rh, JosiPhos	 43–99% yield 78–90% *ee*
7	Dong **2015**[27]			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.

[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.

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 substrates employing a ferrocenylphosphine-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 vinyloxirane[33] 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]

[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.

[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.

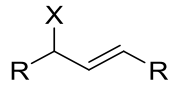
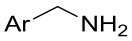
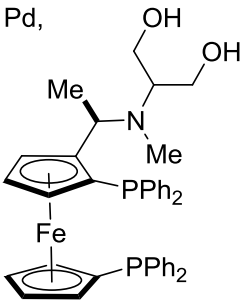
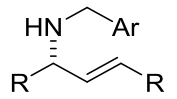
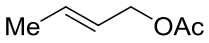
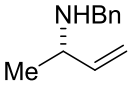
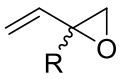
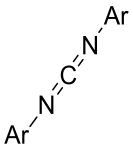
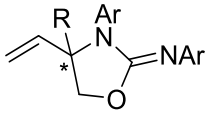
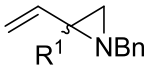
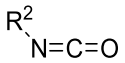
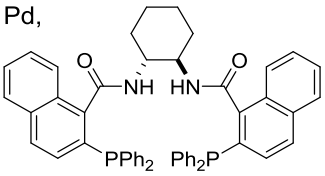
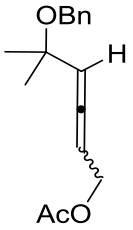
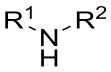
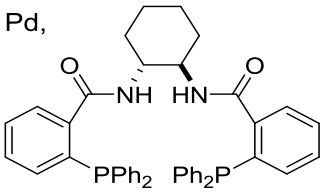
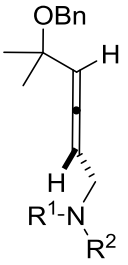
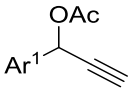
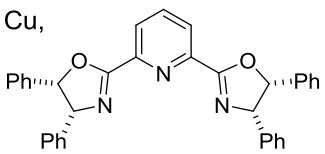
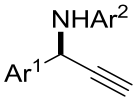
[33] Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709–3715.

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

[35] Trost, B. M.; Fandrick, 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.

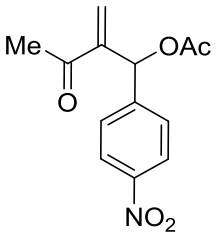
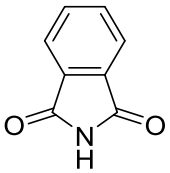
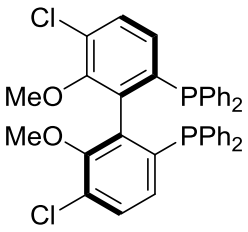
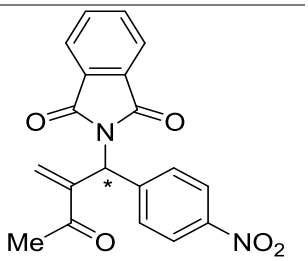
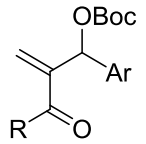
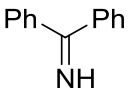
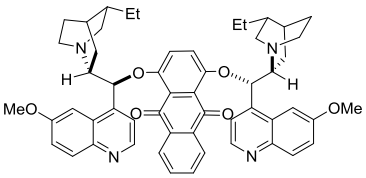
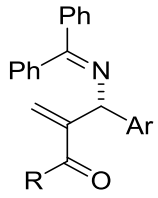
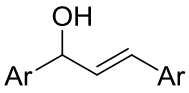
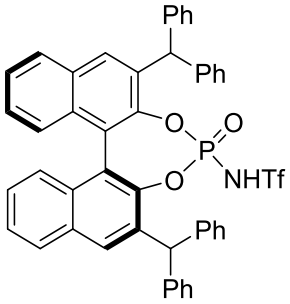
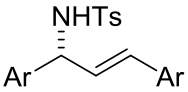
Table 2. Pioneering works in asymmetric nucleophilic amination.

Ent.	Author	Allylic substrate	Nitrogen source	Catalyst	Product
1	Hayashi, Ito **1989**[31]	 R = Ph, Me, *n*-Pr, *i*Pr X = OCO_2Et, $OP(O)Ph_2$			 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*
4	Trost **2003**[34]	 R^1 = H, Me	 R^2 = Ar, Bn	Pd, 	 60–99% yield 80–95% *ee*
5	Trost **2005**[35]			Pd, 	 89–98% yield 89–95% *ee*
6	van Maarseven **2008**[36]		Ar^2NH_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).

Table 3. Organocatalytic asymmetric nucleophilic aminations.

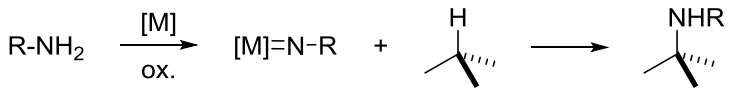
Ent.	Author	Allylic substrate	Nitrogen source	Catalyst	Product
1	Krische **2004**[37]				 80% yield 56% *ee*
2	Zhu, Cheng **2011**[38]	 R = Me, OR'			 53–86% yield 90–99% *ee*
3	Du **2014**[39]		$TsNH_2$		 60–88% yield 62–86% *ee*

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

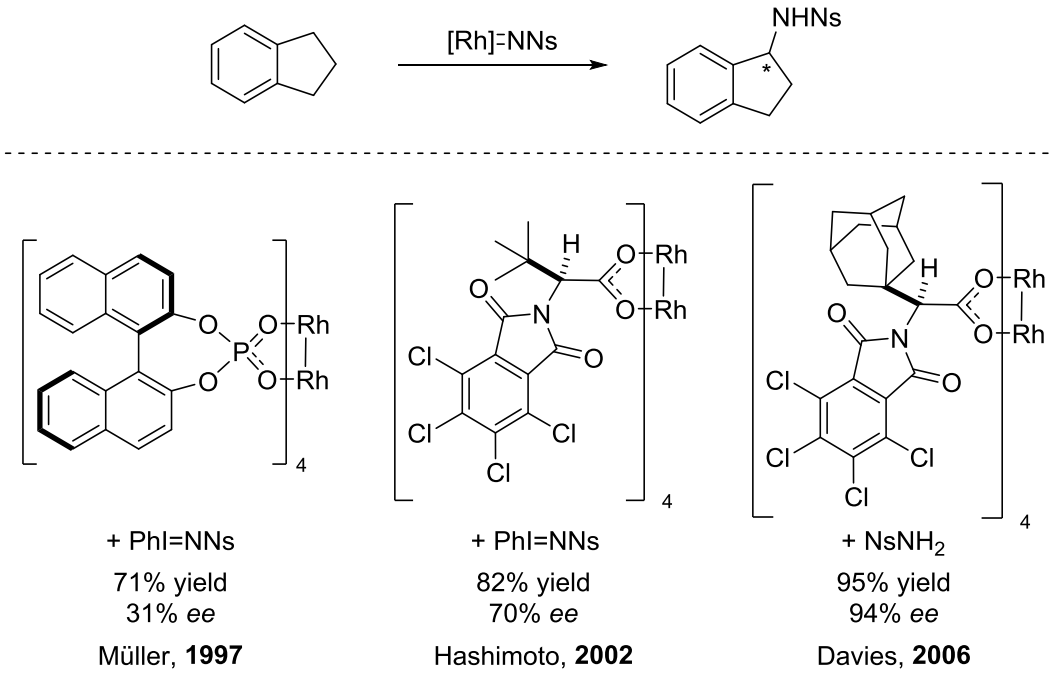
[37] Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337–1339.
[38] Lin, A.; Mao, H.; Zhu, X.; Ge, H.; Tan, R.; Zhu, C.; Cheng, Y. *Chem. Eur. J.* **2011**, *17*, 13676–13679.
[39] Zhuang, M.; Du, H. *Org. Biomol. Chem.* **2014**, *12*, 4590–4593.

a well-diferenciated C–H bond –tipically benzylic, allylic, tertiary or contiguous to a heteroatom– (Scheme 5).



Scheme 5. Metal-catalyzed C–H amination.

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 Hashimoto[41] and Davies[42] were able to improve the catalytic system, by using different chiral ligands and/or oxidants, and higher enantioselectivities were obtained (Scheme 6).

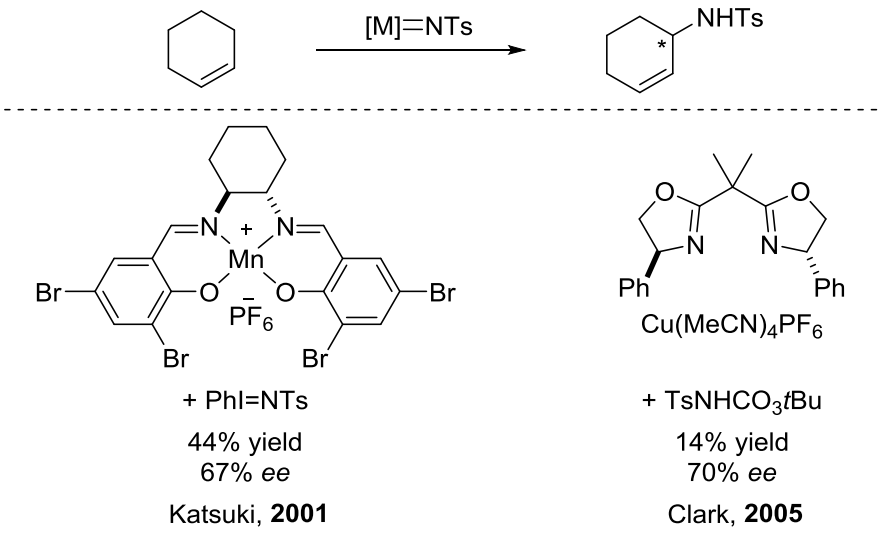


Scheme 6. Indan enantioselective C–H aminations.

Additionally, the groups of Katsuki[43] and Clark[44] reported the manganese- and copper-catalyzed enantioselective C–H amination of cyclohexene, respectively. Nevertheless,

[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.

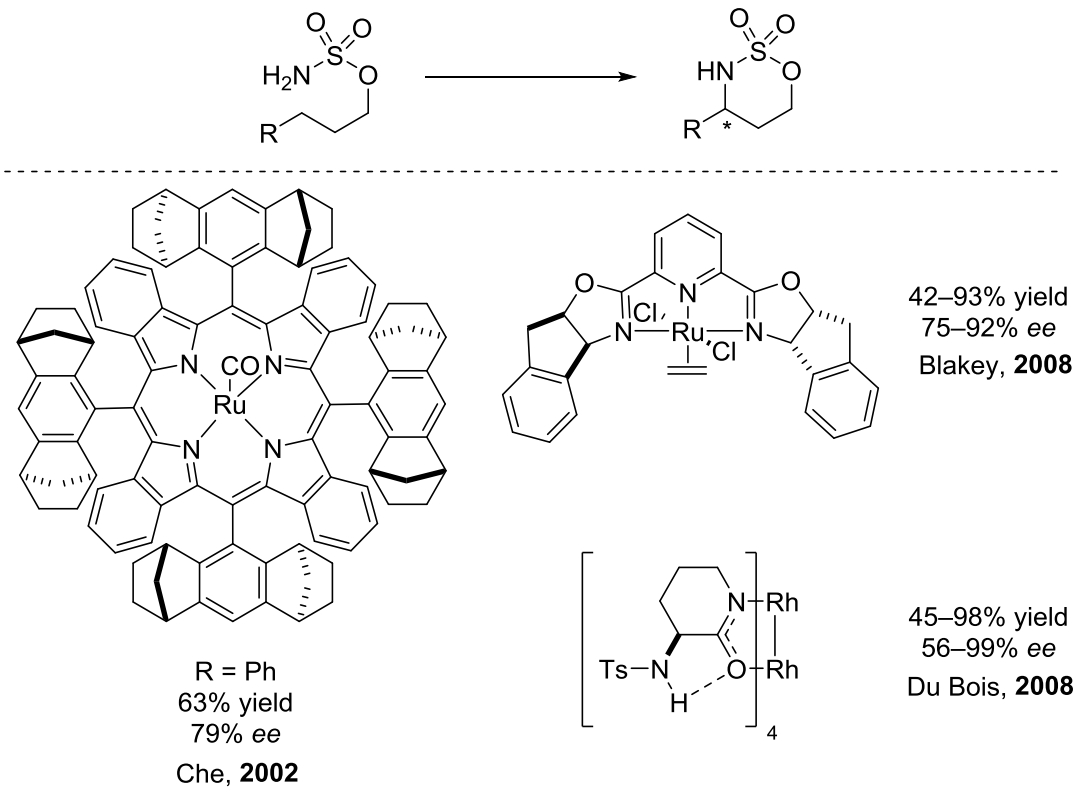
the corresponding cyclohexenyl amine was obtained in low to moderate yields and with moderate enantioselectivities (Scheme 7).



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]

[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.



Scheme 8. Intramolecular enantioselective C–H amination.

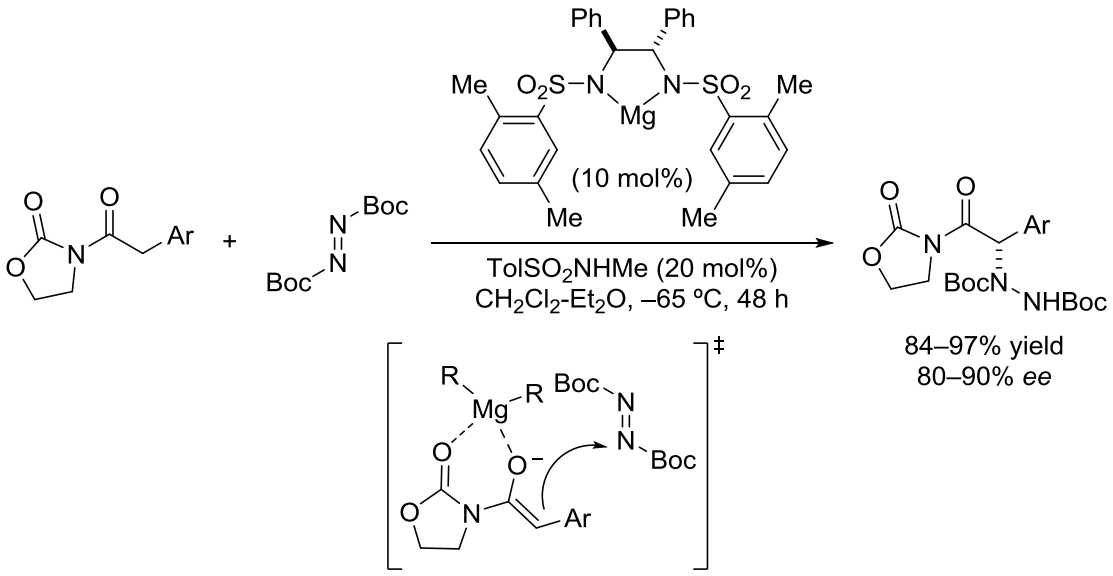
As illustrated, catalytic enantioselective C–H amination constitutes a new emerging field for the synthesis of α-chiral amines[46] still restricted to very specific substrates. Thus, the search for additional suitable structures and efficient catalytic systems represents the forthcoming steps in this field.

1.1.2.1.4. Catalytic enantioselective electrophilic amination

The catalytic asymmetric electrophilic amination has been stablished 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

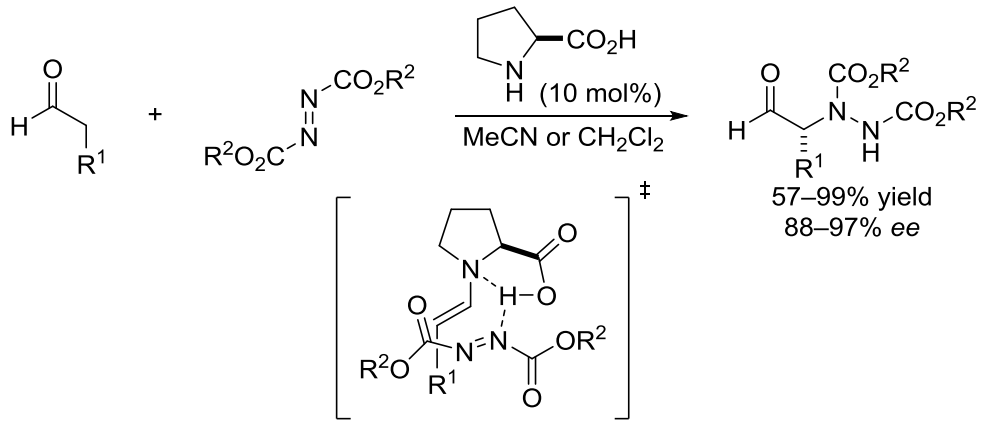
[46] For recent examples, see: a) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 9884–9887. b) Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 1739–1742. c) Höke, T.; Herdtweck, E.; Bach, T. *Chem. 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.

(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.

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]



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

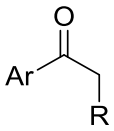
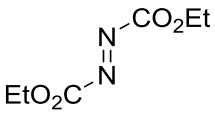
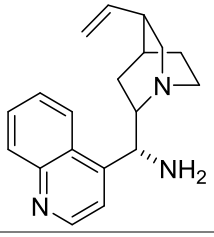
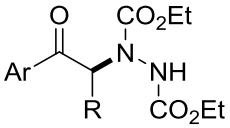
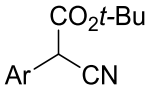
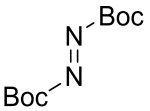
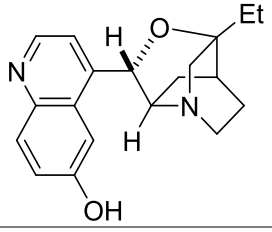
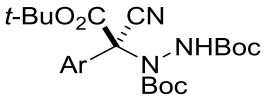
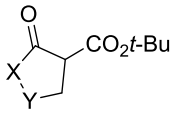
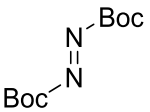
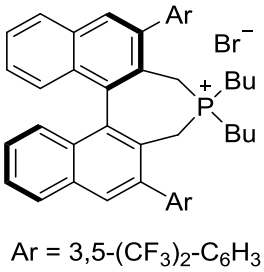
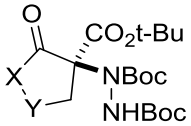
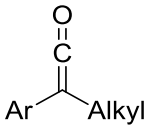
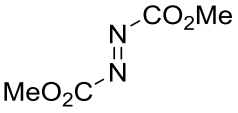
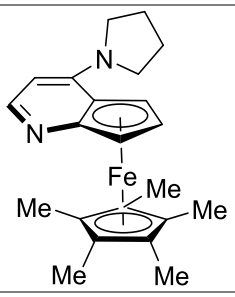
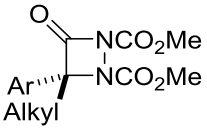
[48] For examples with silyl enol ethers, see: a) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598. 2-Ketoesters: b) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421. β-Keto phosphonate esters: c) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **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.

[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.

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]

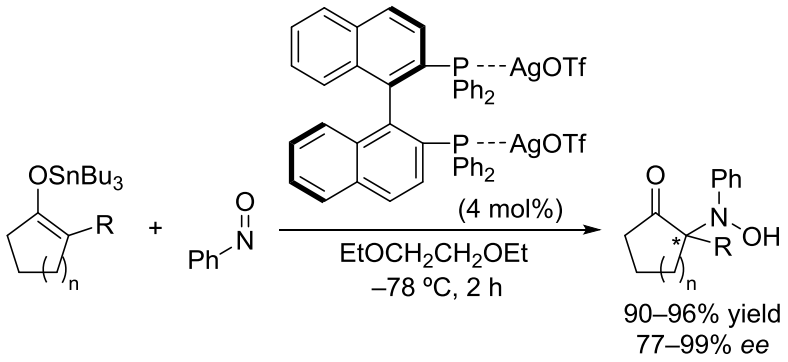
Table 4. Pioneering organocatalytic asymmetric electrophilic amination reactions.

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*
3	Maruoka **2008**[52]			 Ar = 3,5-$(CF_3)_2$-C_6H_3 + K_2HPO_4	 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

[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.
[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.

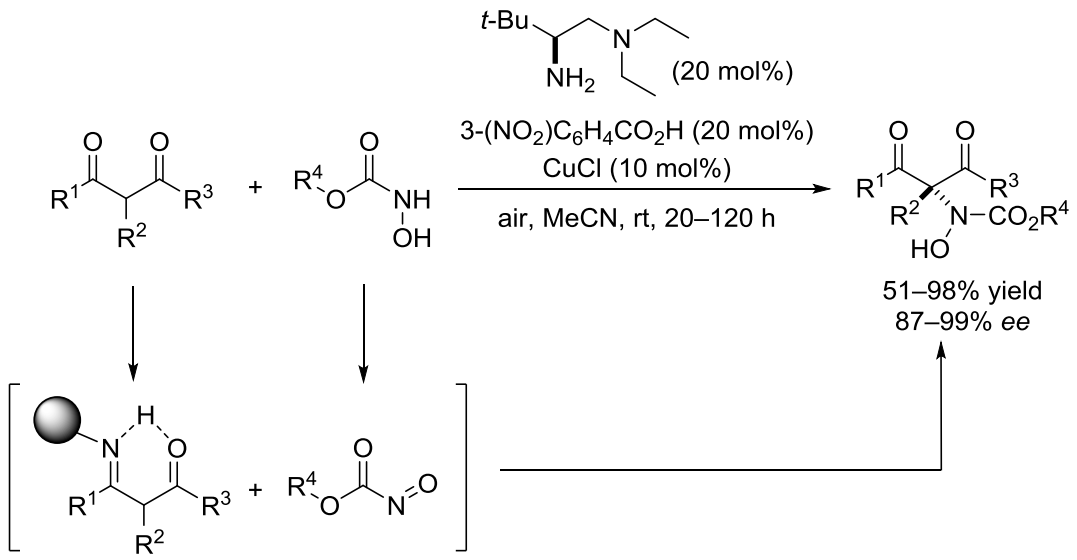
high reactivity and tunable level of steric hindrance, in spite of their low atom economy. In this context, nitroso compounds are another type of promising electrophilic amination reagents with high reactivity and higher atom-economy. Both nitrogen and oxygen atoms are highly reactive towards nucleophile attack, thus, chemoselective control is crutial 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]



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

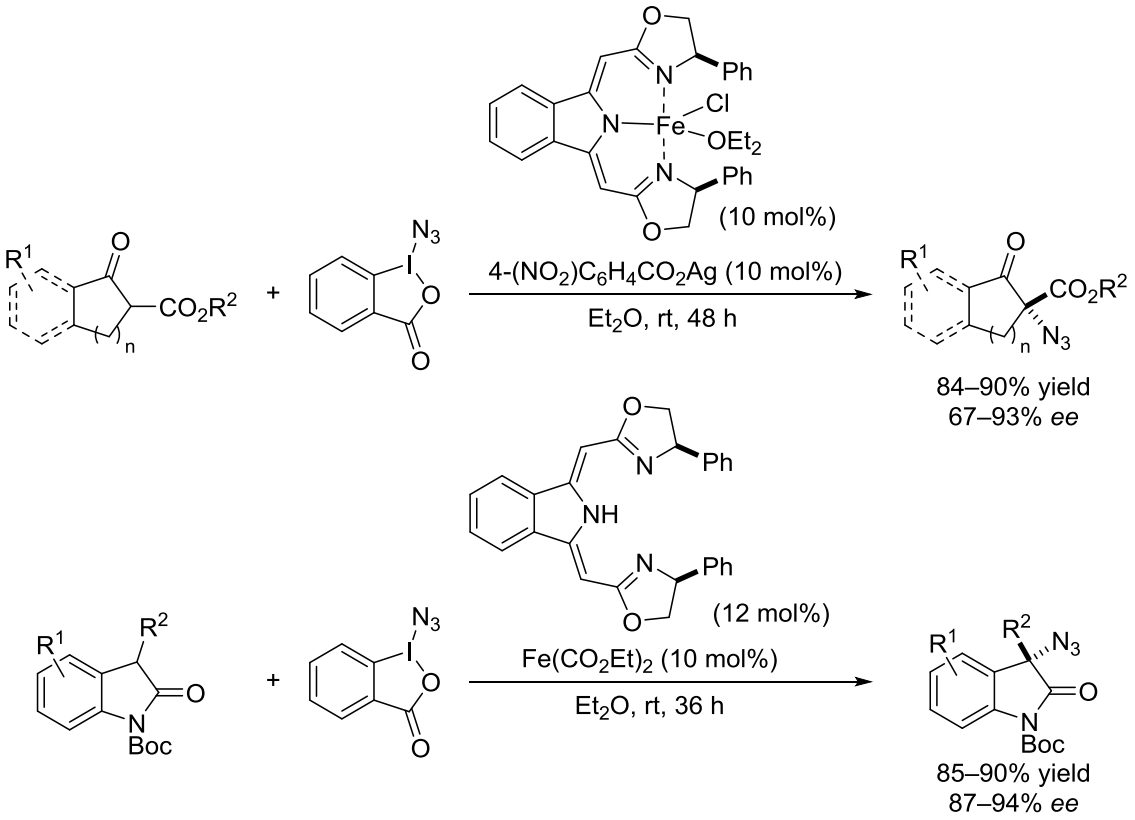
Despite the progress made with nitroso aryl compounds,[55] a mild cleavage of the nitrogen–aryl bond, in the resulting products, remains unsolved. For that reason, the use of nitrocarbonyl compounds, formed *in situ* by oxidation of hydroxamic acid derivatives, is emerging as a promising alternative 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]

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



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

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.

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

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 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] Likewise, examples employing ketimines for the synthesis of chiral tertiary amines are scarce.

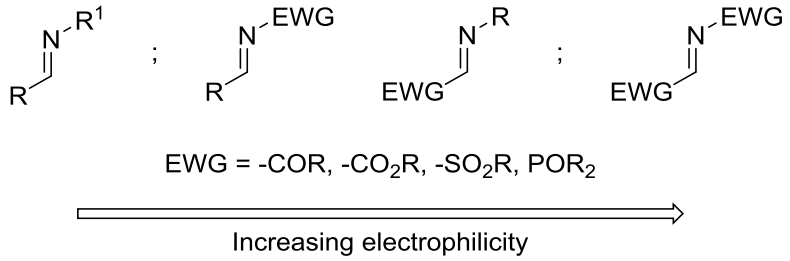


Figure 4. Reactivity of representative imines as electrophiles.

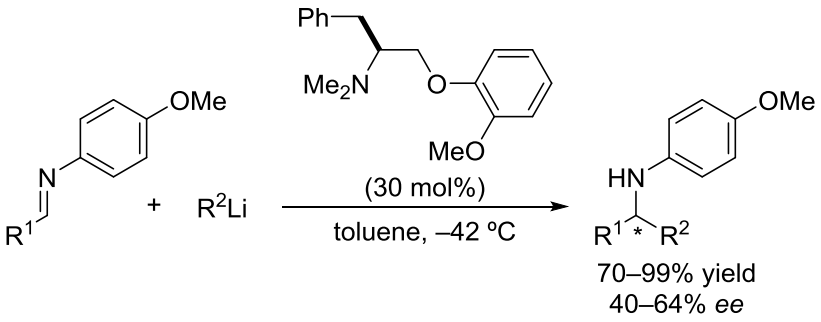
The group of Tomioka reported the first catalytic enantioselective alkylation of imines employing organolithium reagents and a chiral Lewis base organocatalyst (Scheme 14).[61] Since then, most efforts have been addressed towards the development of catalytic and enantioselective versions for which the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

---

[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.

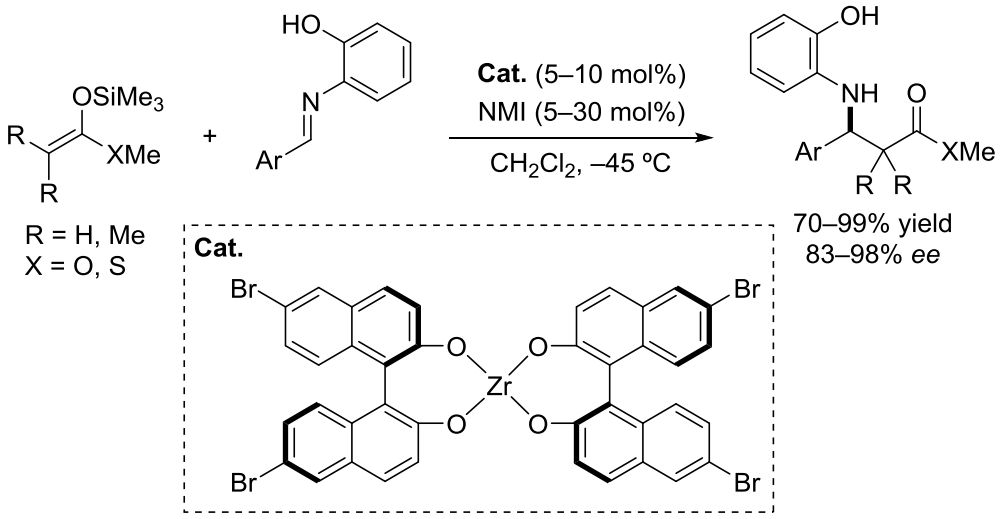
[61] Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098.



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

- **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]

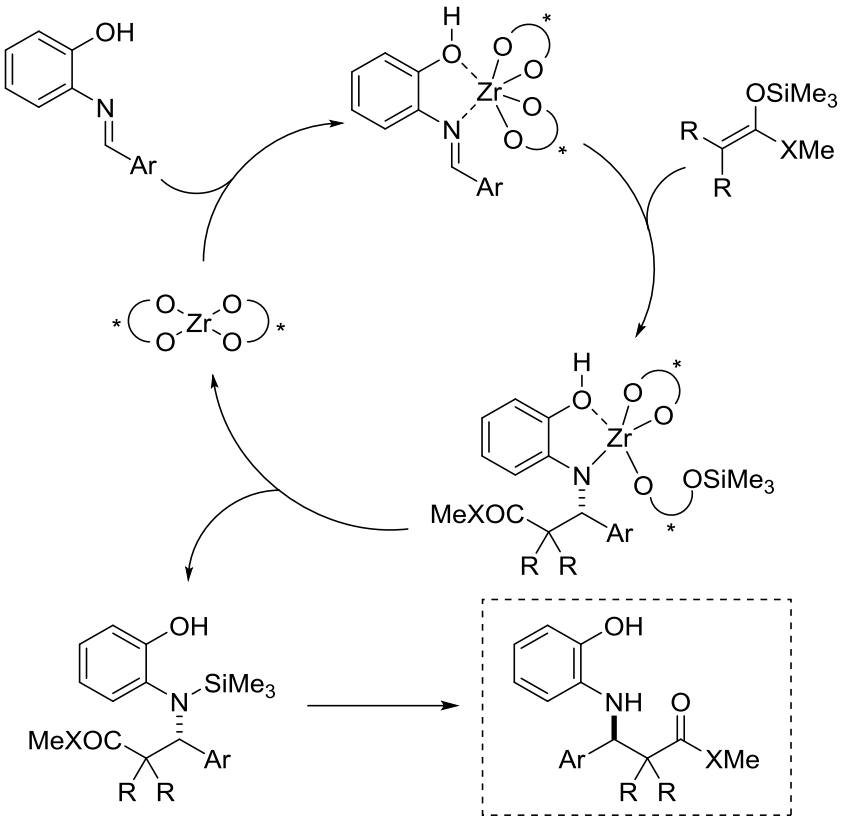


Scheme 15. Kobayashi's pioneering catalytic enantioselective Mannich reaction.

[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.

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).



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

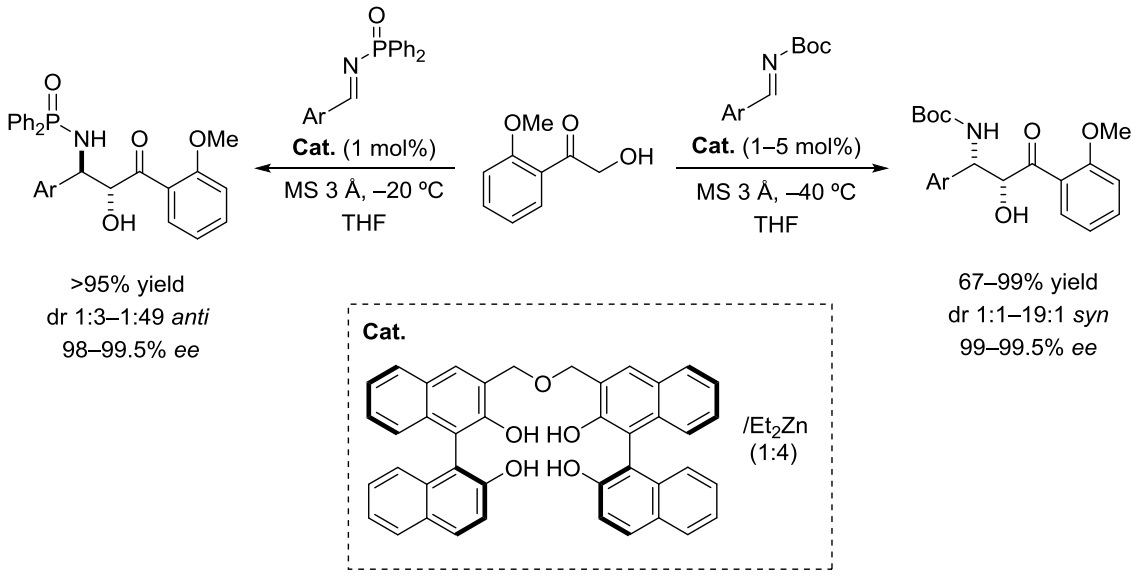
This work inspired many subsequent catalytic non-direct examples in which either the metal center, the chiral ligands or the nature of the catalyst were modified.[64] A similar approach was employed by the group of Hoveyda and Snapper for the silver-catalyzed enantioselective indirect Mannich reaction 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

[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.

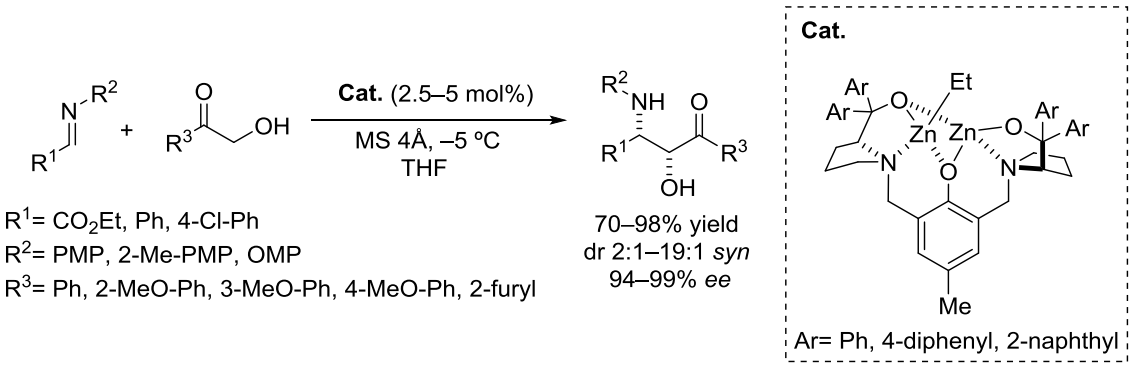
heterobimetallic chiral catalyst and an aminomethyl ether as a synthetic equivalent of [$Et_2NCH_2^+$].[66] Based on this reaction, they reported in 2003 the zinc-catalyzed enantioselective *anti*[67] and *syn*[68] Mannich reactions of 2-hydroxy-1-(2-methoxyphenyl)ethanone with *N*-phosphinoyl and *N*-Boc 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]

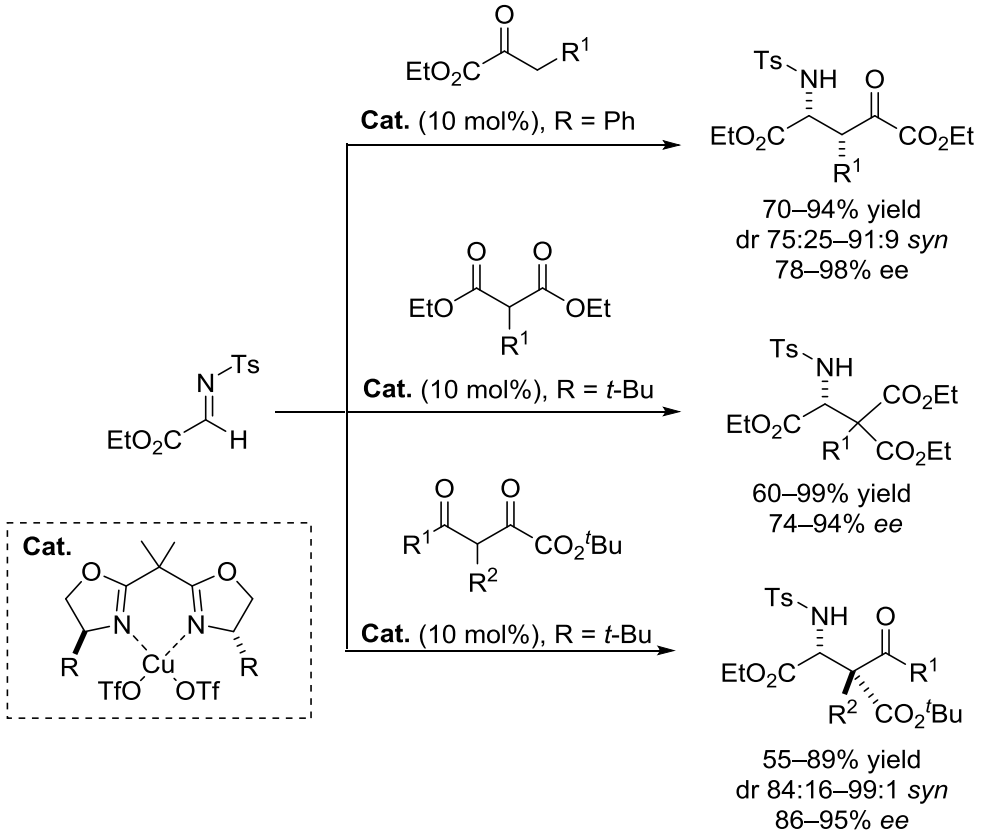
[66] Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 307–310.
[67] Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713.
[68] Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339–5342.
[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.



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 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]

[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.



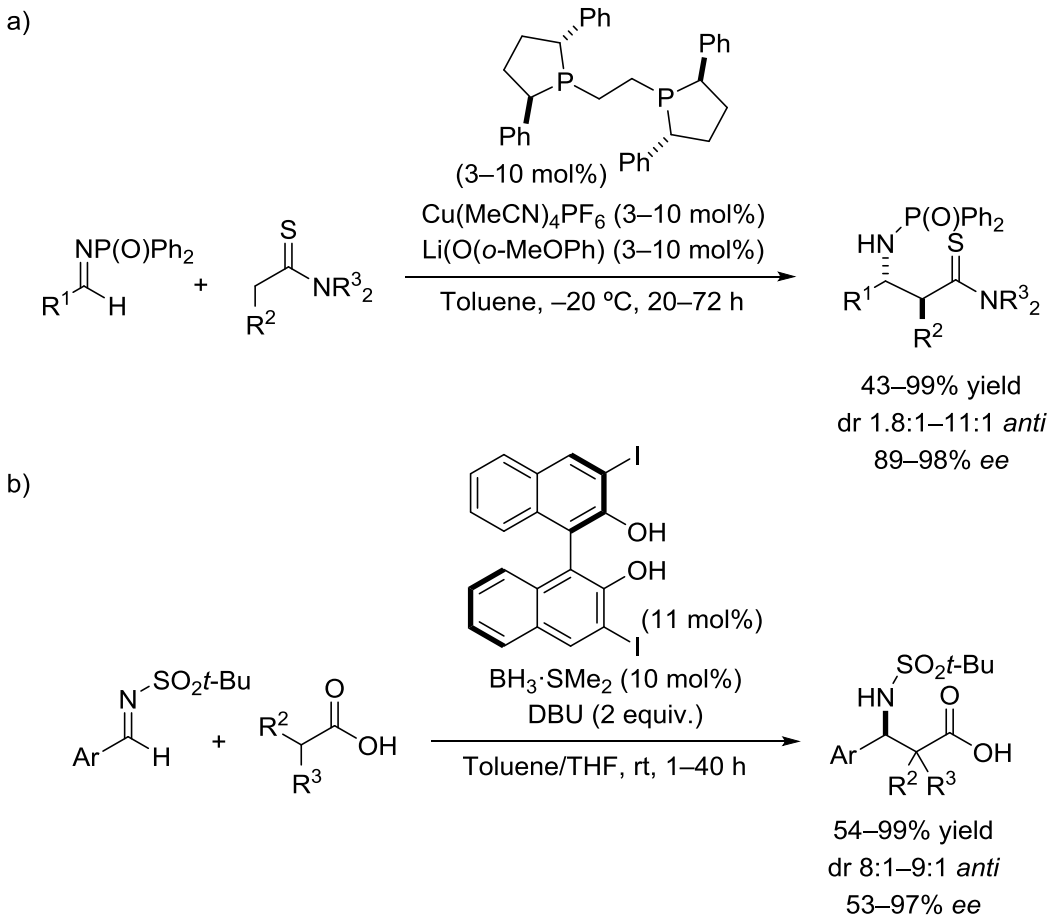
Scheme 19. Jørgensen's Cu-catalyzed enantioselective Mannich reactions with *N*-tosyl imines.

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 Mannich reactions using more challenging pronucleophiles such as thioamides[75] and carboxylic acids,[76] respectively (Scheme 20).

[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. f) 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.

[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.

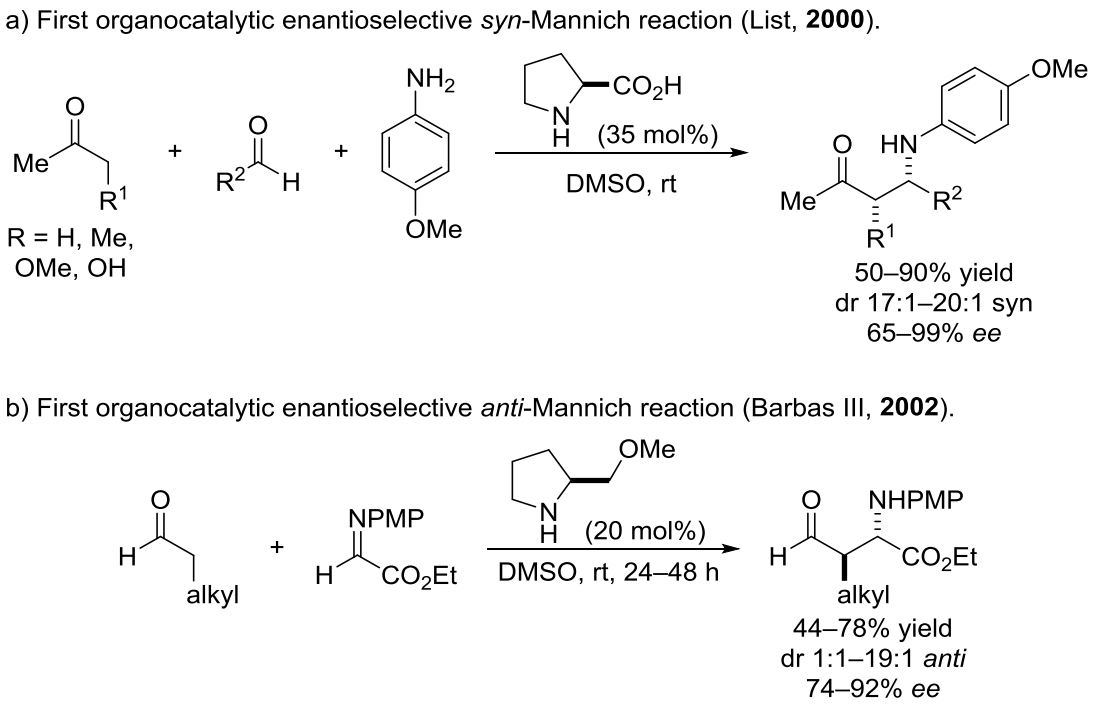


Scheme 20. Asymmetric Mannich reactions with thioamides and carboxylic acids.

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

[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.



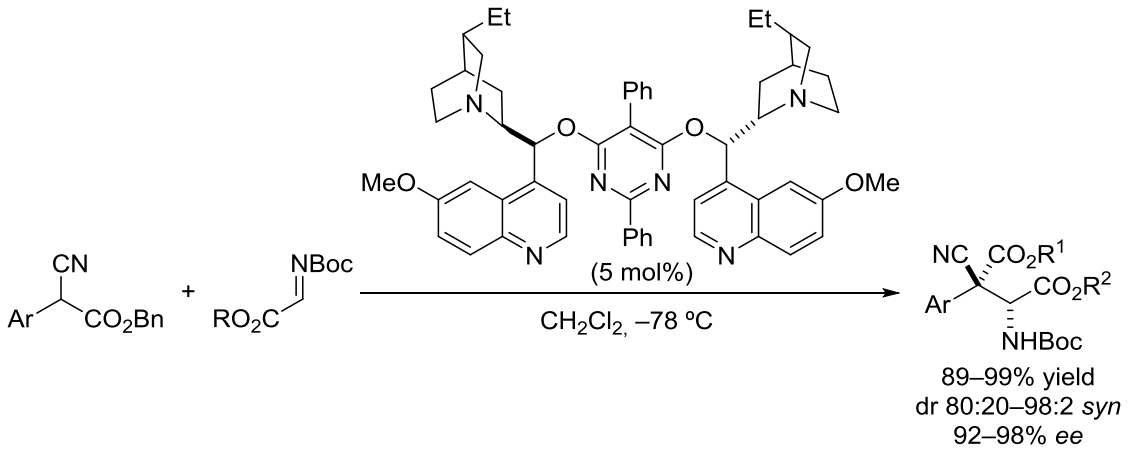
Scheme 21. Pioneering organocatalytic enantio- and diastereoselective Mannich reactions.

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) Ibrahem, 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 malonates[82] and β-keto esters,[83] respectively, to *N*-Boc imines, whereas the groups of Lu[84] and Jiang[85] 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 glycinates 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.

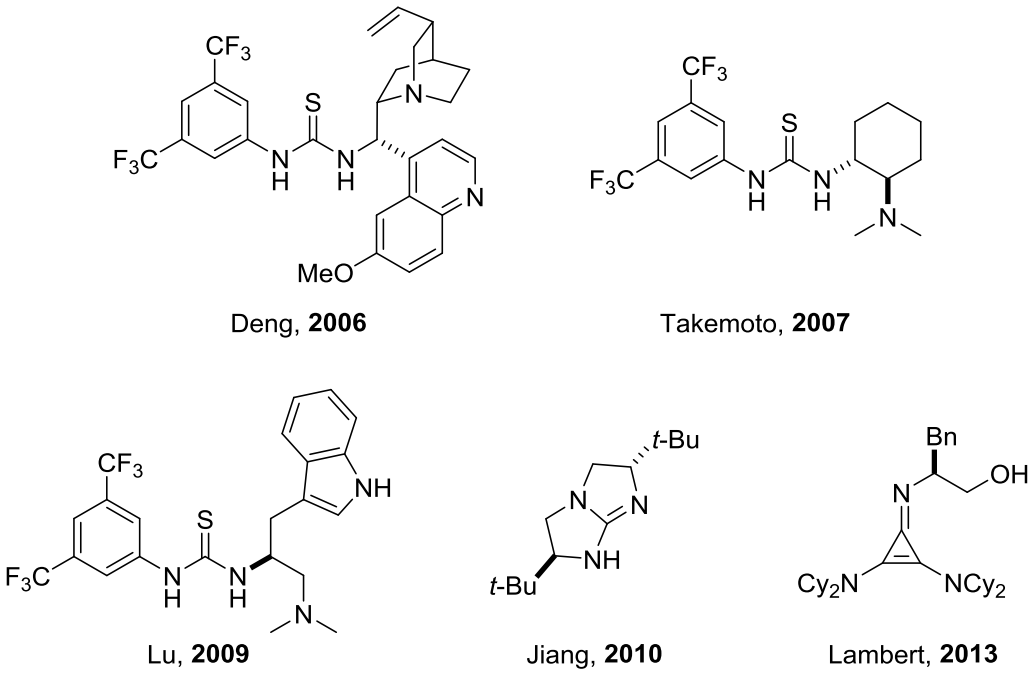
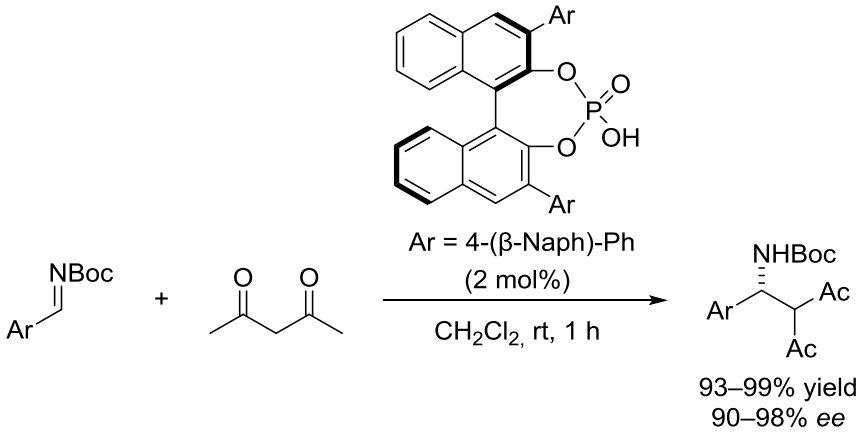


Figure 5. Representative Brønsted base catalysts for enantioselective Mannich reactions.

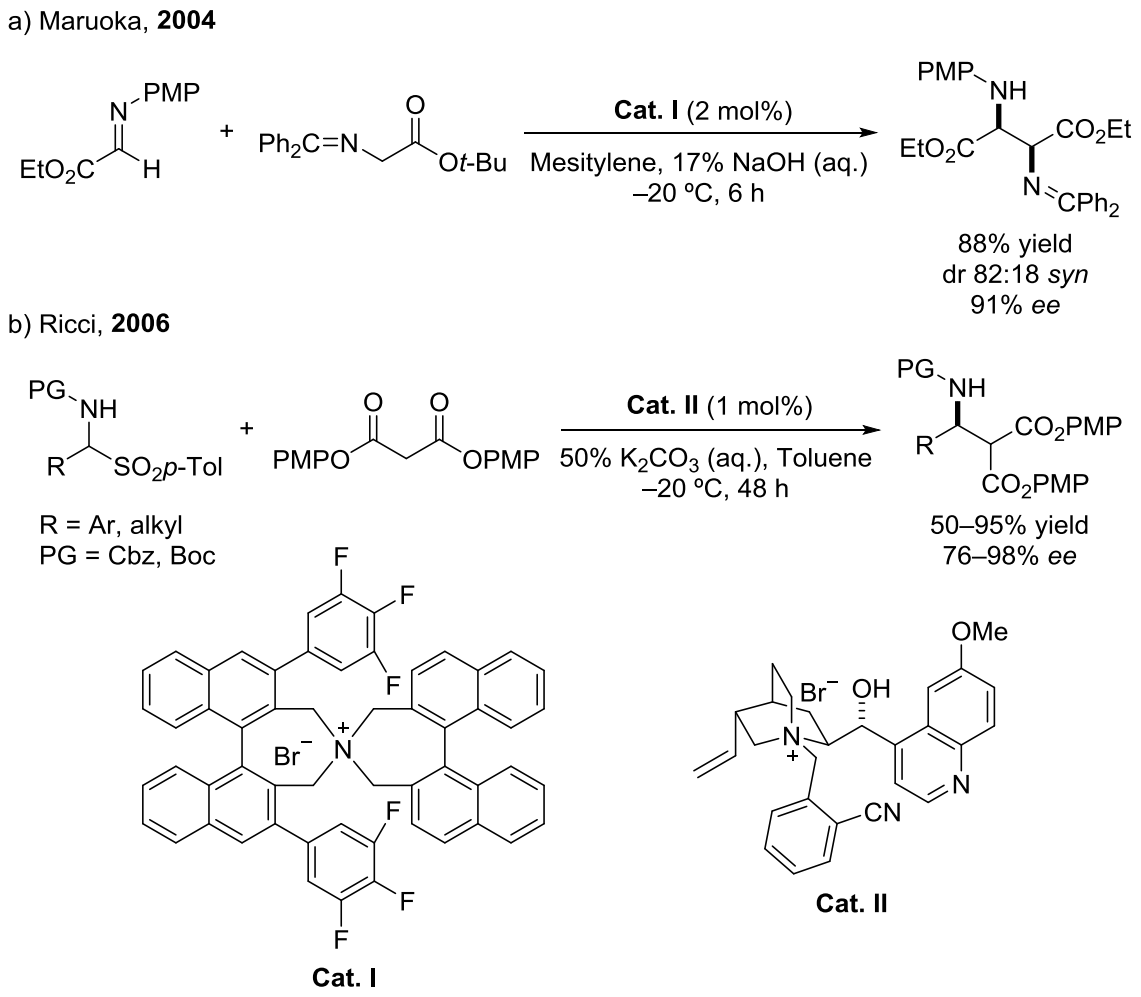
On the other hand, chiral Brønsted acids can also promote enantioselective Mannich reactions by protonating the imine and generating an iminium ion with an enantiopure counterion. In 2004, Terada and co-workers developed the first example of Brønsted acid-catalyzed asymmetric Mannich reaction employing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

The same year, Maruoka and co-workers described the first example of an asymmetric direct Mannich reaction under phase transfer conditions (PTC) (Scheme 24a),[88] whereas the first phase transfer catalyzed 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]



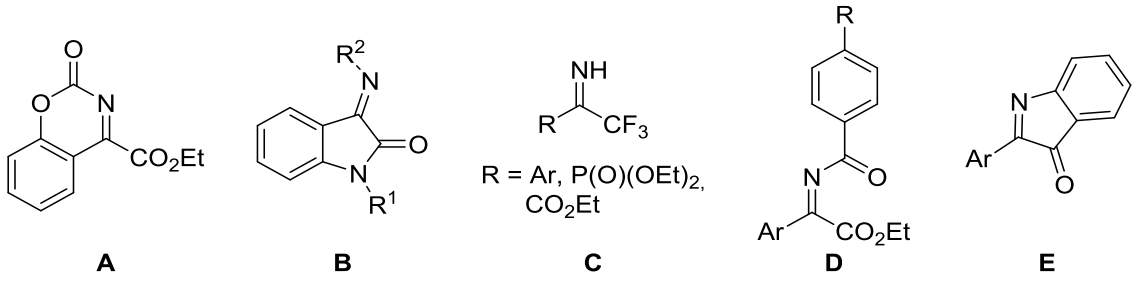
Scheme 24. Pioneering phase transfer catalyzed enantioselective Mannich reactions.

[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 ketimine **A** in the zirconium-catalyzed enantioselective indirect Mannich reaction[92] 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 type[94] whereas ketimines bearing an electron-withdrawing trifluoromethyl substituent **C** have also been employed in reactions with acetone[95] 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]

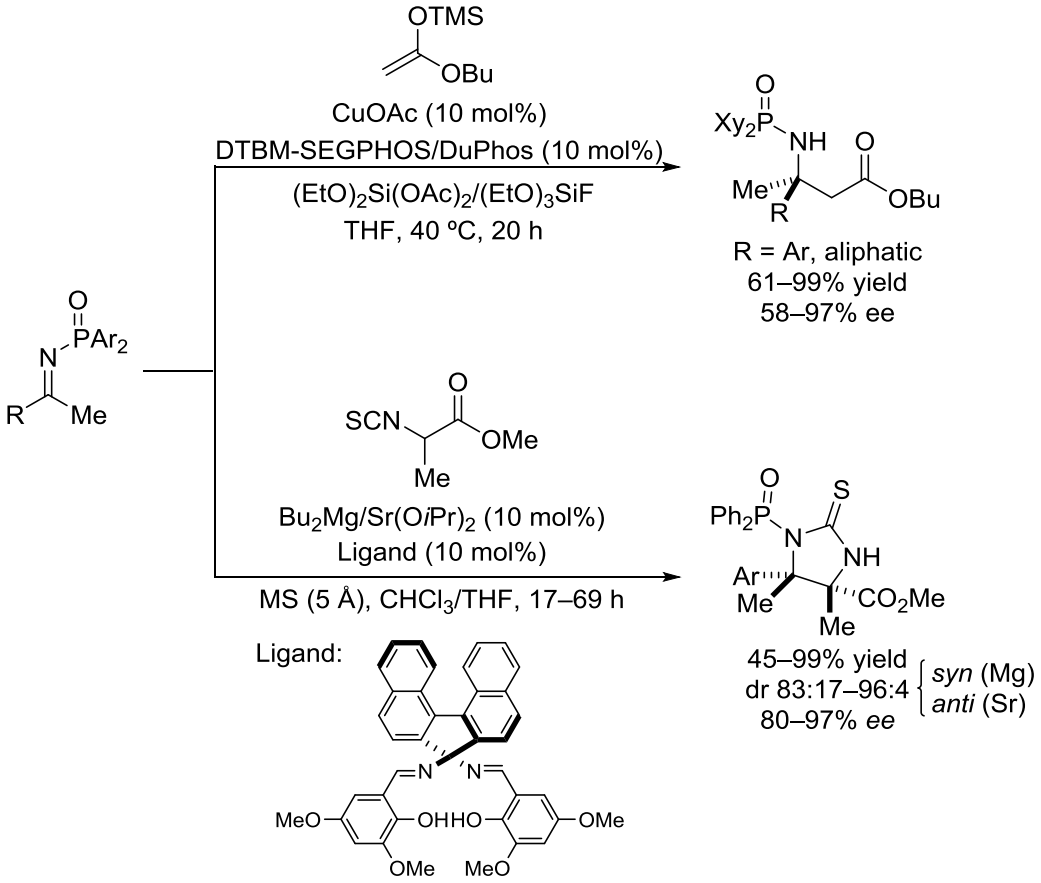


Scheme 25. Ketimines in asymmetric Mannich reactions.

Importantly, Shibasaki and co-workers reported the use of simple *N*-phosphinoyl ketimines in the enantioselective indirect Mannich reaction[99] as well as in the enantio- and diastereoselective direct Mannich reaction with an α-isothiocyanate ester in which

[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.

thioxoimidazolidines were afforded after cyclization of the Mannich adduct (Scheme 26).[100] Other groups have described the addition of isonitriles to *N*-phosphinoyl ketimines for the preparation of imidazolines[101] 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 enolyzable 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.

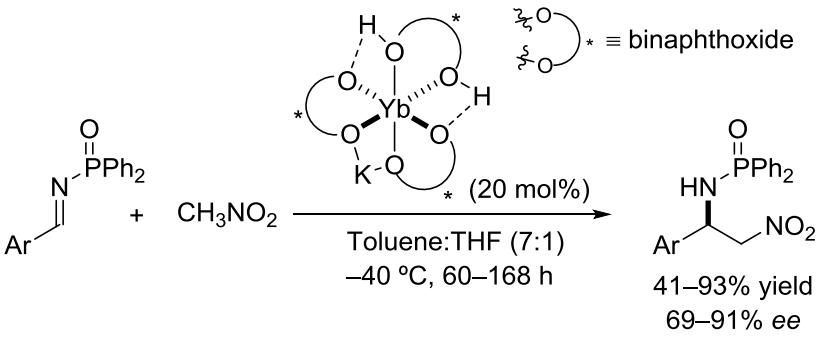
[101] a) Nakamura, S.; Yamaji, R.; Iwanaga, M. *Chem. Commun.* **2016**, *52*, 7462–7465. b) de la Campa, R.; Yamagata, A. D. G.; Ortín, I.; Franchino, A.; Thompson, A. L.; Odell, B.; Dixon, D. J. *Chem. Commun.* **2016**, *52*, 10632–10635.

[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 afford 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]

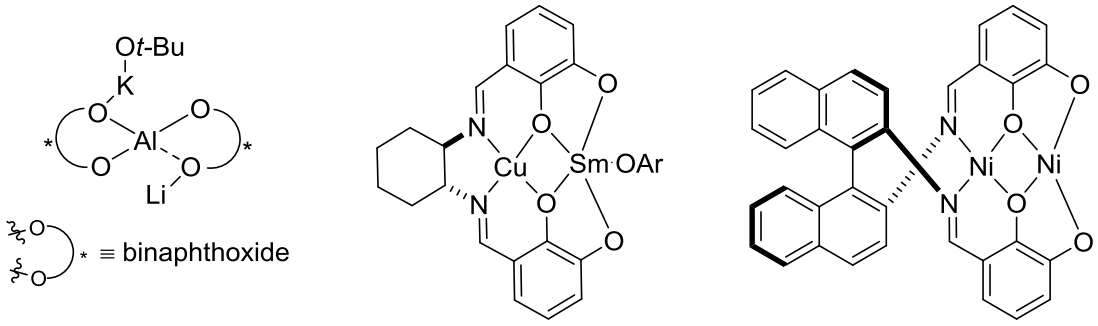


Scheme 27. Shibasaki's pioneering metal-catalyzed asymmetric nitro-Mannich reaction.

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.

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]



Shibasaki, **2001** Shibasaki, **2007** Shibasaki, **2008**

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 direct[109] and indirect[110] *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] cobalt[113] 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.

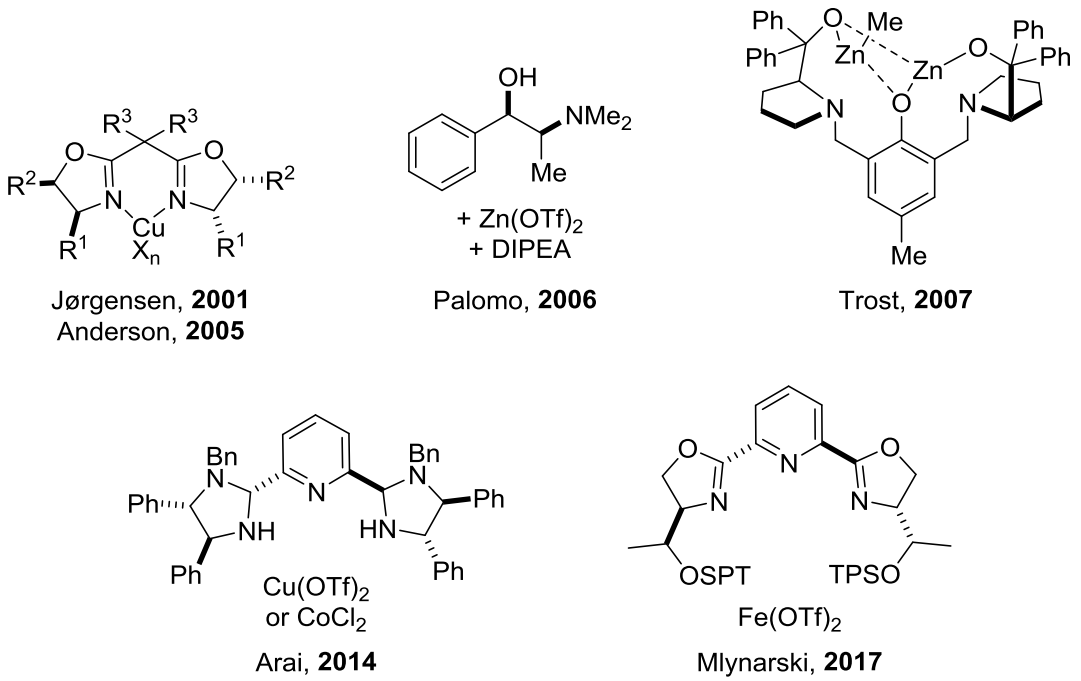
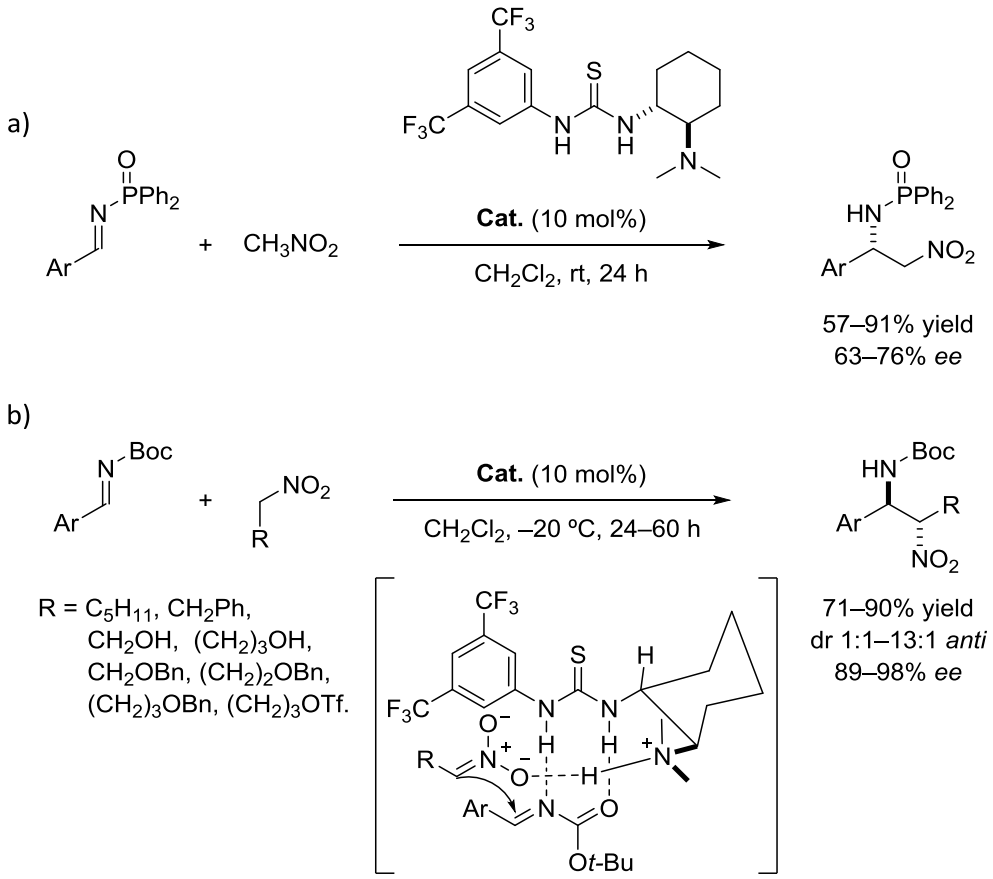


Figure 7. Representative metal based catalysts in enantioselective nitro-Mannich reactions.

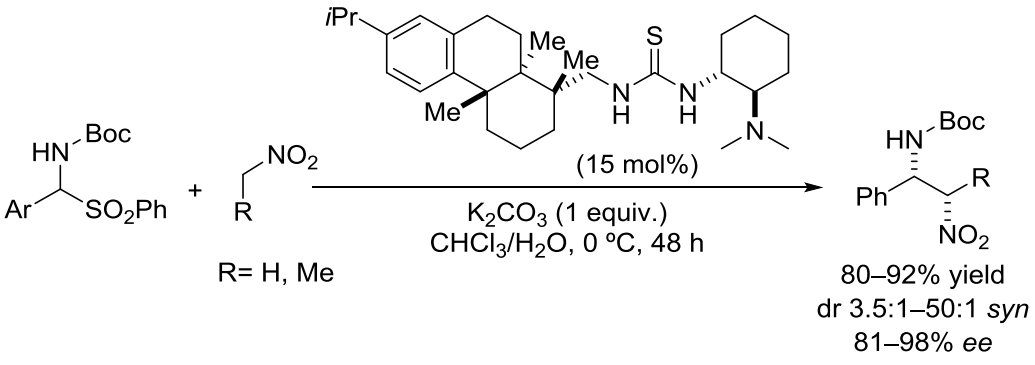
Regarding metal-free approaches, in 2004, Takemoto and co-workers described the first organocatalytic enantioselective nitro-Mannich procedure with *N*-phosphinoyl aromatic imines and nitromethane, under chiral Brønsted base catalysis, with good yields and moderate enantioselectivities (Scheme 28a).[115] 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.



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

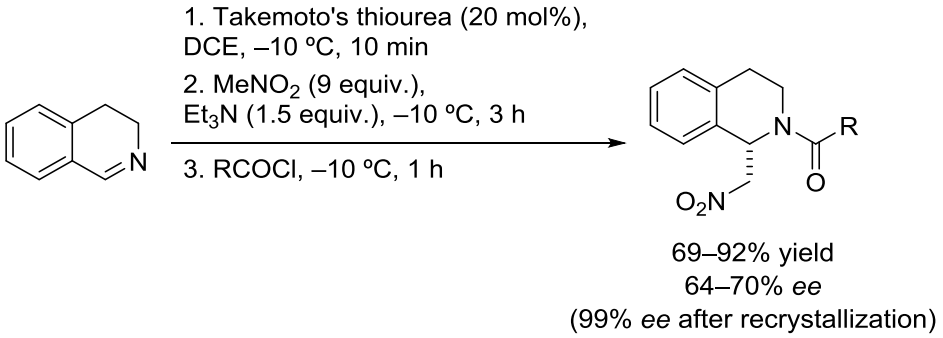
In 2009, Wang and co-workers described a Brønsted base catalyzed asymmetric nitro-Mannich procedure in which *N*-Boc imines were generated *in situ* employing 1 equivalent of potassium carbonate. The rosin-derived thiourea-Brønsted base promoted the addition of nitromethane and nitroethane with generally 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 interactions.[122]

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[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.; Ďuriš, 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.

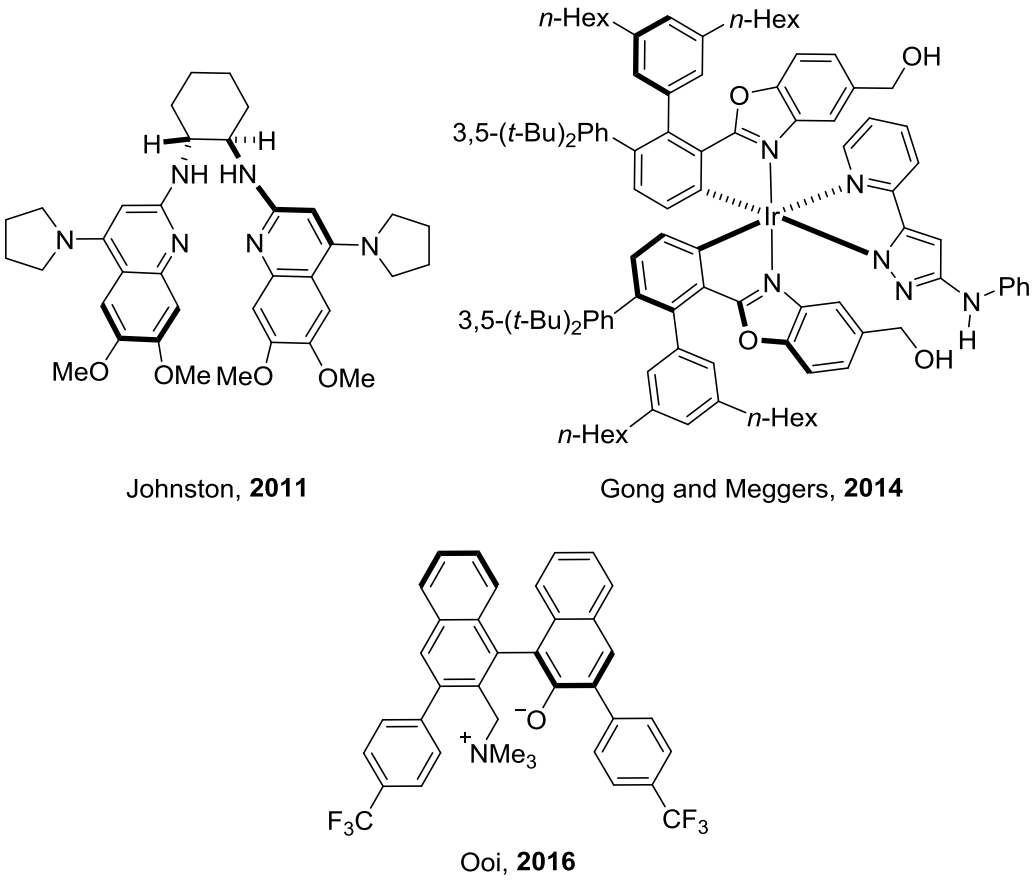


Figure 8. Structurally diverse bifunctional Brønsted bases in asymmetric nitro-Manich reactions.

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.

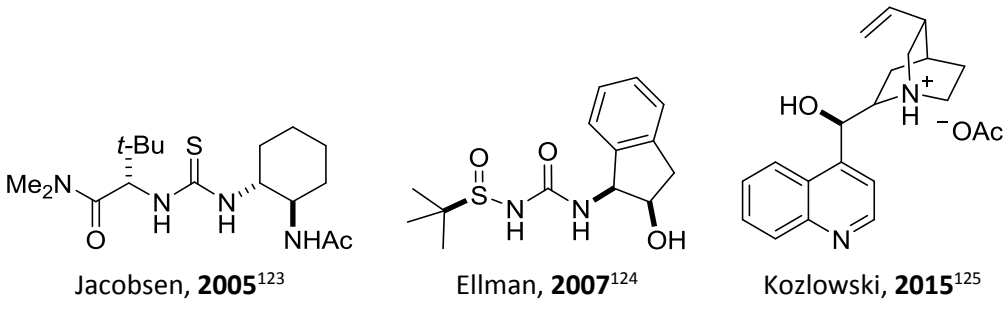
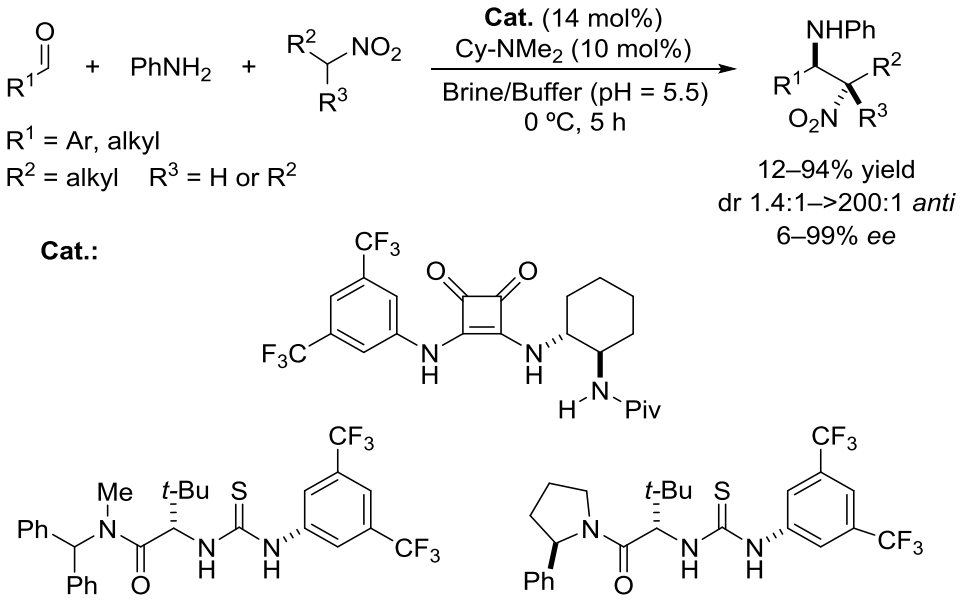


Figure 9. Representative hydrogen-bonding organocatalysts.

[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.

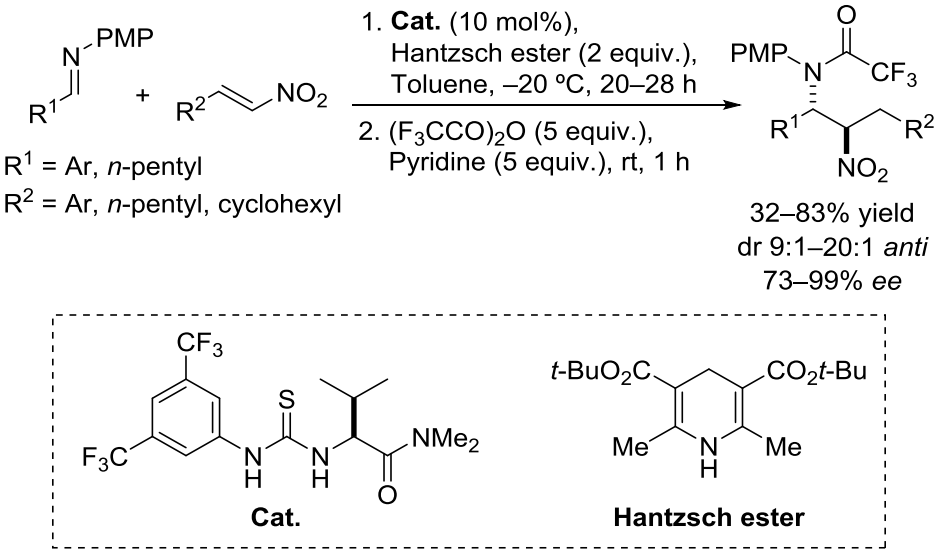
In 2013, the group of de Armas and García-Tellado described a water-compatible stereoselective multicomponent nitro-Mannich reaction. Aromatic and aliphatic *N*-phenyl imines were synthetized *in situ* and reacted with several nitroalkanes including symmetric tertiary nucleophiles, such as 2-nitropropane, 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.

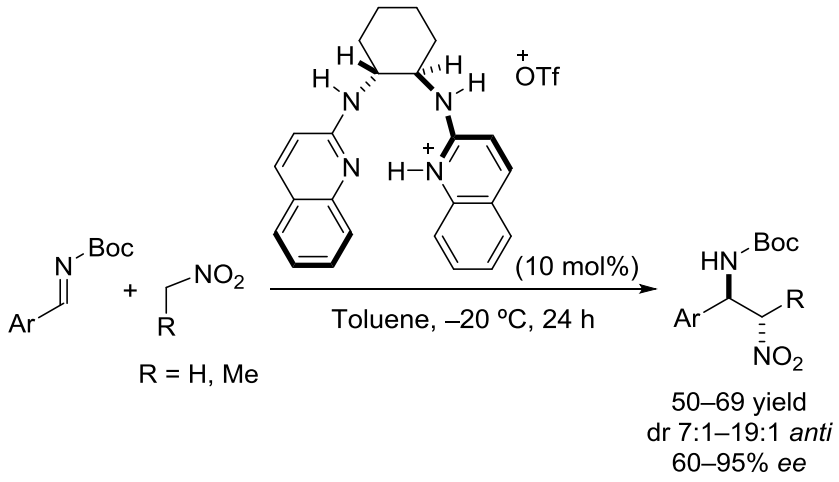
Anderson and co-workers developed an interesting approach towards β-nitro amines consisting of nitroolefin reduction, employing the Hantzsch ester, and subsequent nitronate addition to imines *via* hydrogen-bonding activation (Scheme 32).[127]

[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.



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.[128a] They designed a protonated version of the BisAMidine catalyst able to promote the addition of nitroalkanes to *N*-Boc imines (Scheme 33), which was further employed in similar transformations.[128] After that, the group of Rueping described a chiral phosphoric acid catalyzed enantioselective nitro-Mannich reaction.[129]

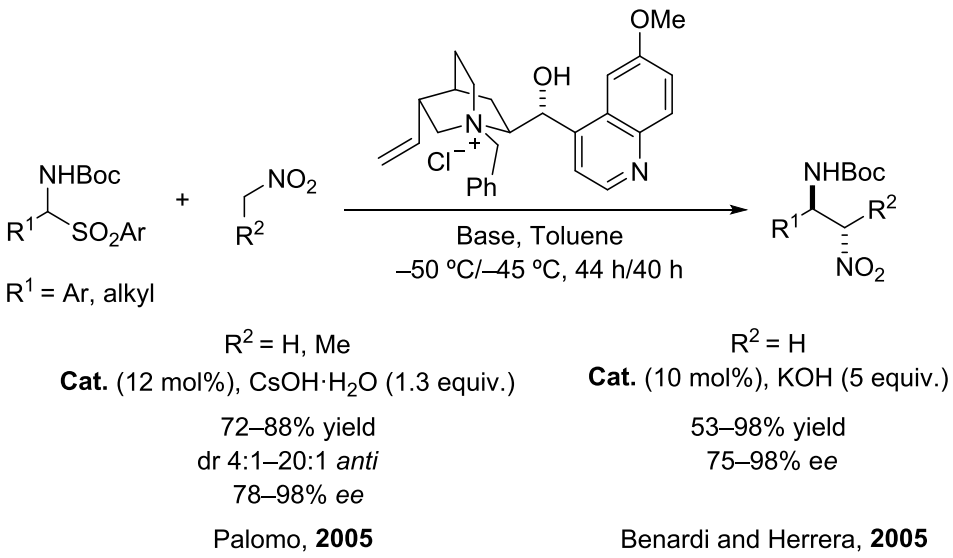


Scheme 33. Johnston's Brønsted acid-catalyzed asymmetric nitro-Mannich reaction.

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.
[129] 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 group[130] and Herrera, Bernardi and co-workers,[131] 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).[132-135] All of them, in combination with inorganic salts, successfully allowed the use of aliphatic imines in the reaction.

[130] Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623.
[131] Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44,* 7975–7978.

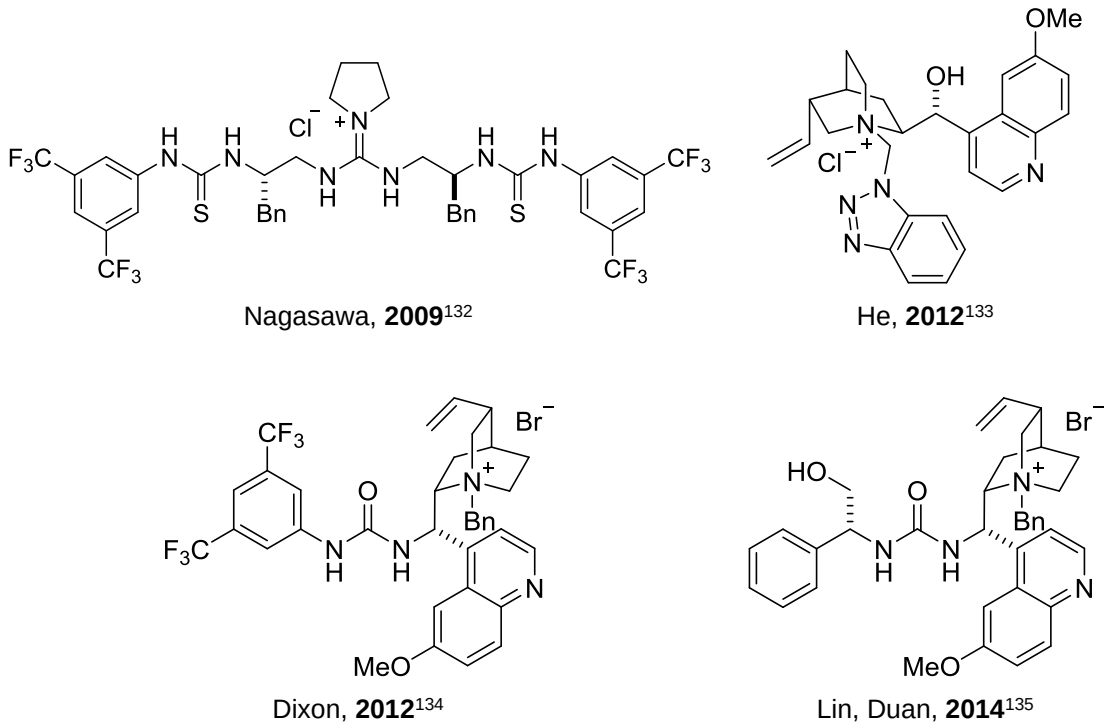


Figure 10. Phase transfer catalysts in asymmetric nitro-Mannich reactions.

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.[136] 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.[137] 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.[138] More recently, the group of Lin

[132] 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.
[133] Wei, Y.; He, W.; Liu, Y.; Liu, P.; Zhang, S. *Org. Lett.* **2012**, *14*, 704–707.
[134] 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.
[135] Wang, B.; Liu, Y.; Sun, C.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *Org. Lett.* **2014**, *16*, 6432–6435.
[136] 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.
[137] Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305–5308.
[138] Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351.

and Duan have reported a phase-tranfer-catalyzed nitro-Mannich reaction of *N*-6-methyl-2-pyridylsulfonyl protected ketimines with nitromethane.[139]

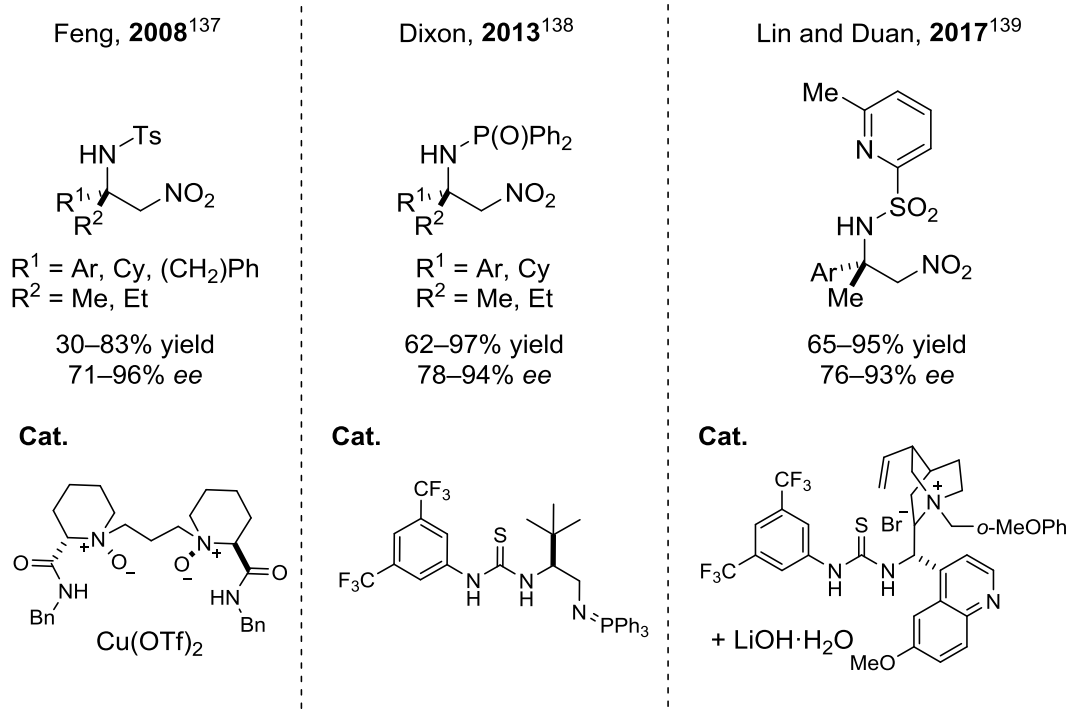


Figure 11. Enantioselective nitro-Mannich reactions with ketimines.

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.

[139] 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.[140] Due to the intrinsic non-directional nature of the ionic interactions stablished with reactants, bifunctional Brønsted base catalysts, bearing hydrogen bond donor groups, have become much more suitable catalysts for asymmetric reactions. Among them, *Cinchona* alkaloids,[141] thiourea-[115] and squaramide-based[142] Brønsted bases are the most representative bifunctional organocatalysts (Figure 12).

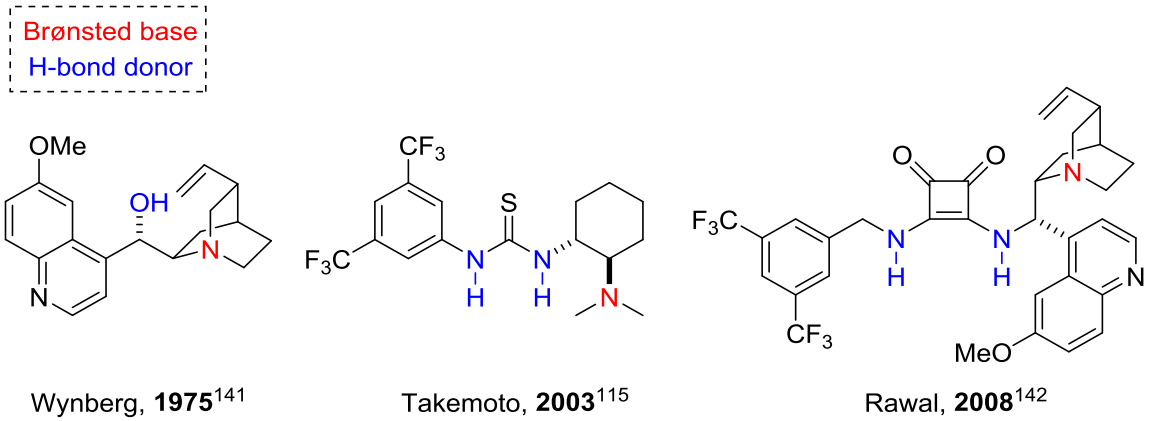


Figure 12. Most representative bifunctional Brønsted base organocatalysts.

[140] 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.

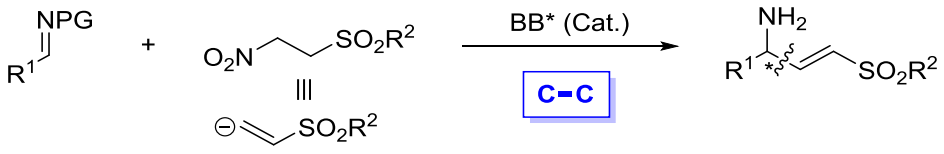
[141] Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057–4060.

[142] 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,[143] 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. 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.

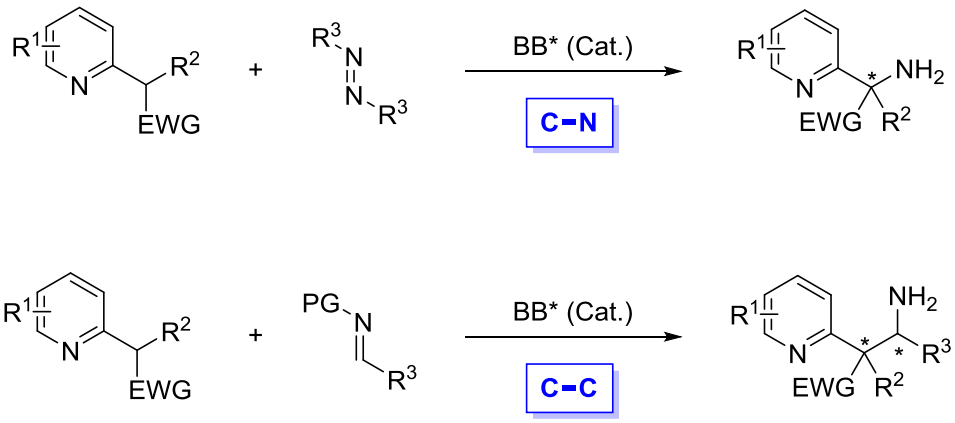
Many structures derived from enantiomerically pure γ-sulfonyl allyl amines have shown capacity to inhibit a wide variety of enzymatic processes. Nevertheless, the structural requirements for an optimal enzyme-substrate recognition are still unknown and the elaboration of this type of structures could 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.

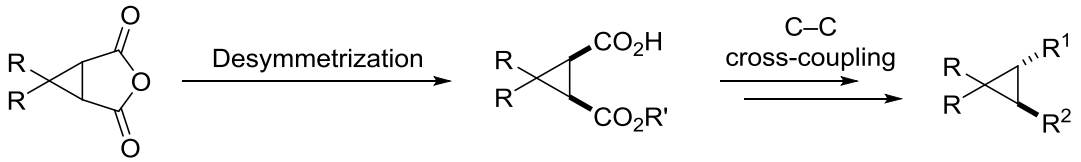
On the other hand, *ortho*-substituted pyridines are common fragments in chiral compounds with biological activity. In particular, α- and/or β-functionalized pyridines containing amino groups constitute a relevant family. Thus, the second objective of the present thesis is to explore the potential of 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).

[143] 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.



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 stereoselective modular preparation of *trans*-disubstituted cyclopropanes through the combination of the desymmetrization of *meso*-anhydrides and the C–C decarboxylative 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

INDEX

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).[144]

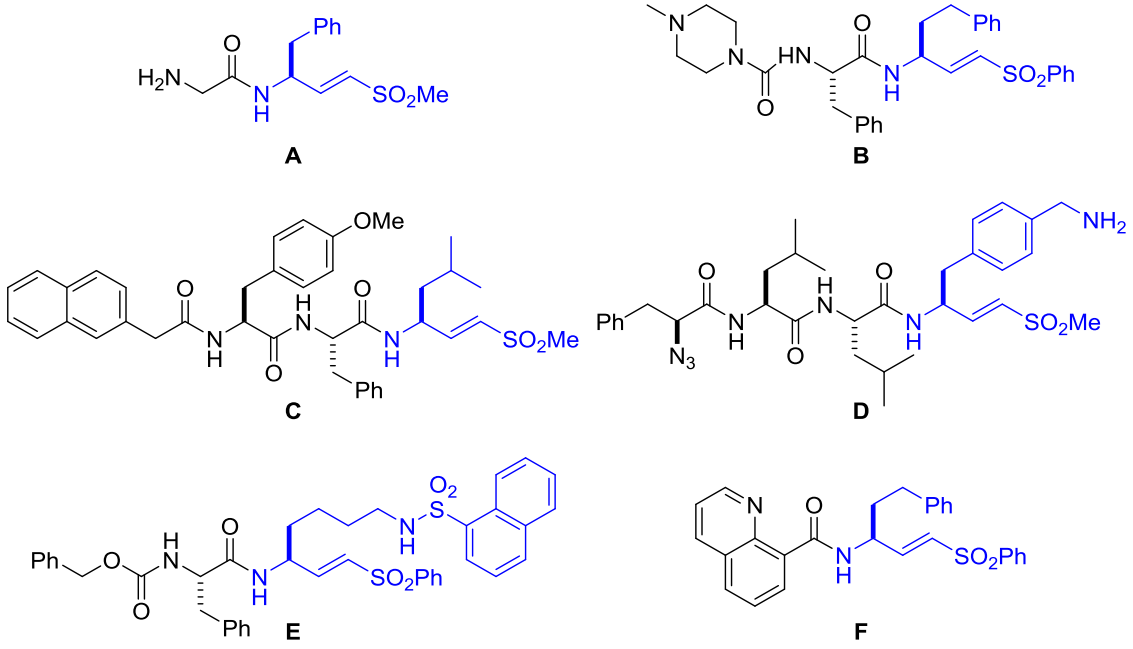
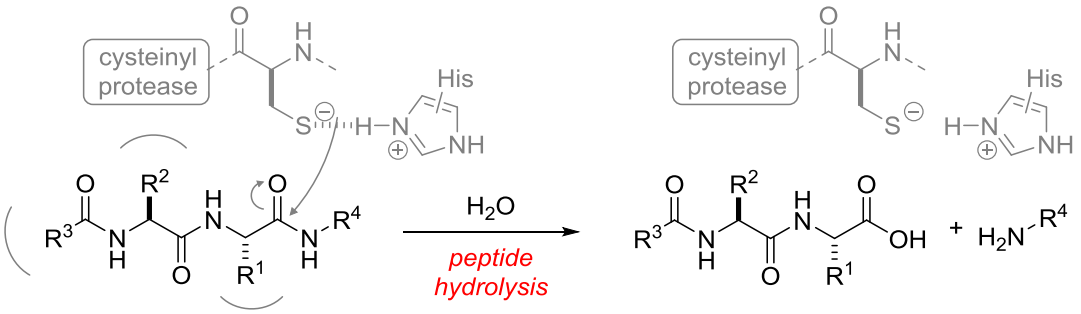


Figure 13. γ-Sulfonyl allyl amines with inhibitory activity.

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

Structures **A**[145] and **B**[146] have exhibited activity against dipeptidyl aminopeptidase I (DPP-I) and cruzipain, respectively. Peptidyl vinyl sulfones **C**[147] and **D**[148] act as site-selective proteasome inhibitors; **C** is a β5 specific inhibitor whilst compound **D** is active in trypsin-like sites. Additionally, γ-sulfonyl allyl amines **E**[149] and **F**[150] 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 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).[149,151]

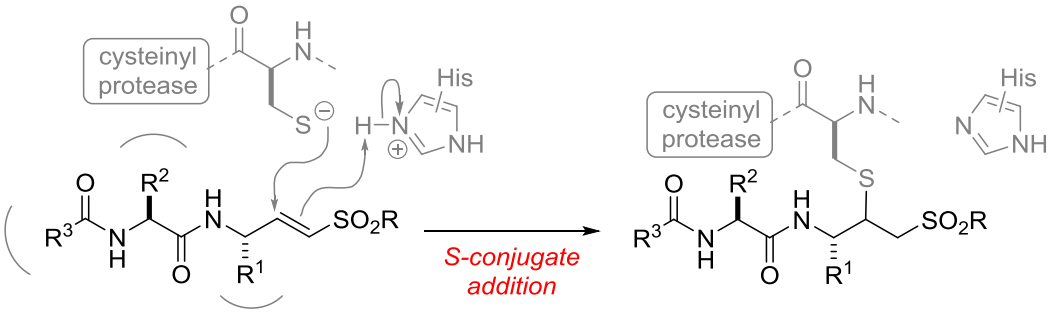


Scheme 38. Cysteine protease-based peptide hydrolysis.

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

[145] Thompson, S. A.; Andrews, P. R.; Hanzlik, R. P. *J. Med. Chem.* **1986**, *29*, 104–111.
[146] Palmer, J. T.; Rasnik, D.; Klaus, J. L.; Brömme, D. *J. Med. Chem.* **1995**, *38*, 3193–3196.
[147] a) Screen, M.; Britton, M.; Downey, S. L.; Verdoes, M.; Voges, M. J.; Blom, A. E. M.; Geurink, P. P.; Risseeuw, 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.
[148] 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.
[149] Dunny, E. Doherty, W.; Evans, P.; Malthouse, J. P. G.; Nolan, D.; Knox, A. J. S. *J. Med. Chem.* **2013**, *56*, 6638–6650.
[150] Zhang, H.; Collins, J.; Nyamwihura, R.; Ware, S.; Kaiser, M.; Ogungbe, I. V. *Bioorg. Med. Chem.* **2018**, *28*, 1647–1651.
[151] Santos, M. M. M.; Moreira, R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1040–1050.

acceptors have shown to be potent inhibiting agents due to the irreversible C–S bond formation (Scheme 39).[149,151,] In particular, the interest in γ-sulfonyl allyl amines principally relies on their selectivity, since they are inactive 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.[152] 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.

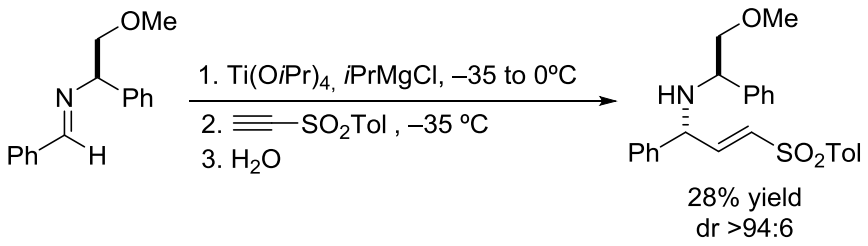
Despite the interest for the preparation of diverse γ-sulfonyl allyl amines, very few procedures have been reported for their synthesis and most of them are based on olefination reactions of α-amino aldehydes derived from synthetic[153] or naturally available amino acids.[145–150,154] Enantioenriched 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).[155]

[152] 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.

[153] 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.

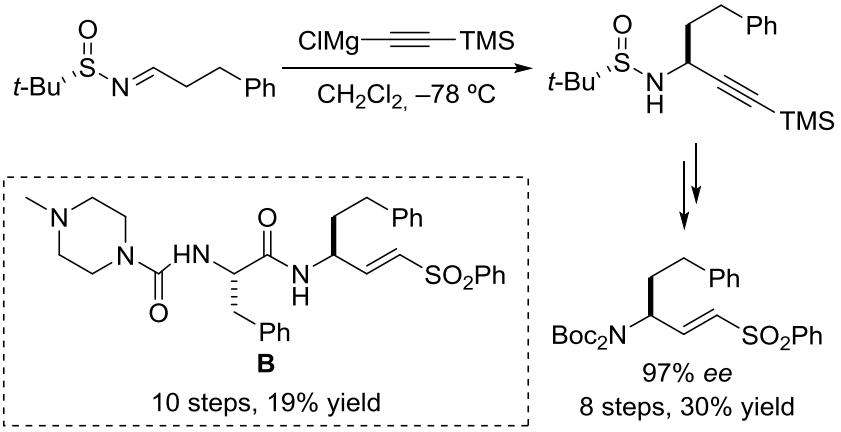
[154] Kim, M.; Jeon, J.; Baek, J.; Choi, J.; Park, E. J.; Song, J.; Bang, H.; Suh, K. H.; Kim, Y. H.; Kim, J.; Kim, D.; Min, K. H.; Lee, K.-O. *Bull. Korean Chem. Soc.* **2014**, *35*, 345–346.

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



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 alkynylation of the chiral sulfinyl *N*-protected imine shown in Scheme 41.[156]



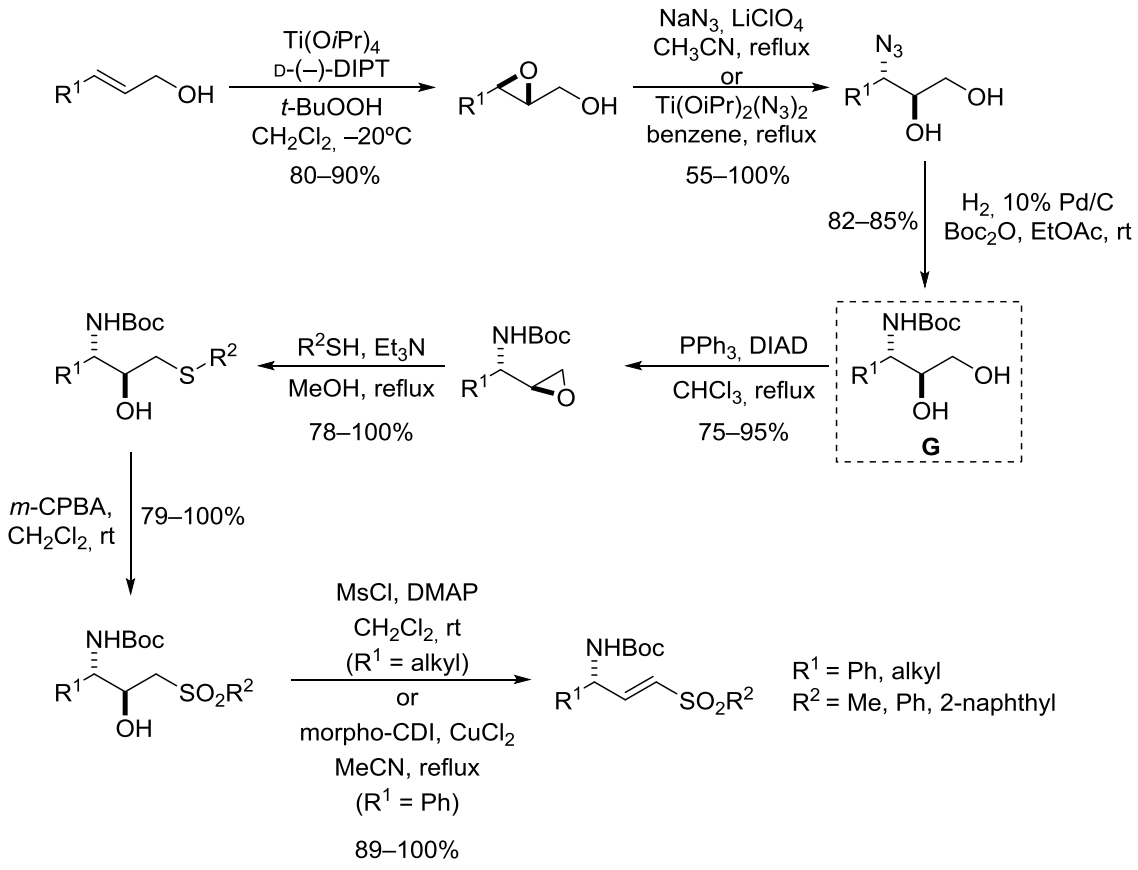
Scheme 41. Asymmetric synthesis of γ-sulfonyl allyl amines employing chiral sulfoxides .

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 **G** prepared from allylic alcohols,[157] being the key stereoselective step their asymmetric epoxidation described previously.[158] Additionally, this work is the only example in which an amine with an aromatic R^1 group has been synthetized (Scheme 42).

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

[157] 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.

[158] 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.



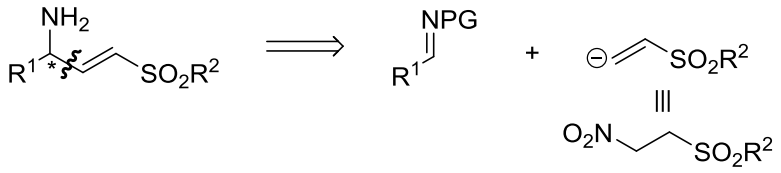
Scheme 42. Enantioselective synthesis of γ-sulfonyl allyl amines.

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.

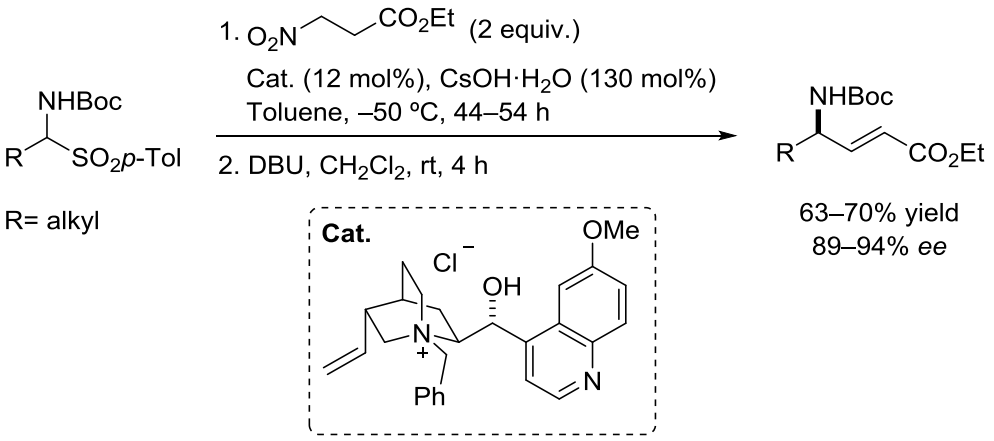
Due to the experience of our group in the catalytic asymmetric C–C bond forming reactions and, more particularly, in the nitro-Mannich reaction,[159] we considered that the base promoted addition of a synthetic equivalent of the vinyl sulfone anion to *N*-protected imines, followed by nitrous acid elimination, could 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.

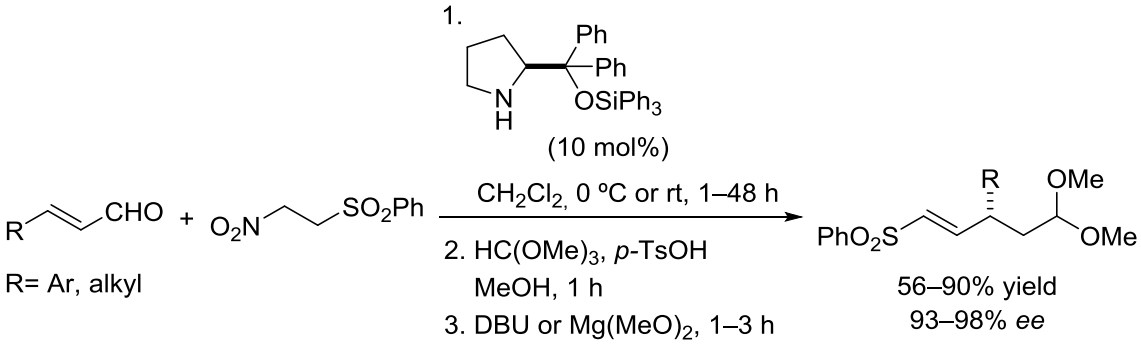
As previously disclosed, our group reported the preparation of highly enantioenriched α,β-unsaturated γ-amino esters under catalytic phase transfer conditions. This methodology represents a unique example of the use of 3-nitropropionates as acryloyl anion equivalents, through their organocatalytic asymmetric addition to *N*-Boc α-amino sulfones followed by basic treatment (Scheme 44).[160]

[159] a) Ref. 112a, page 37. b) Ref. 130, page 44.
[160] Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955–7966.



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

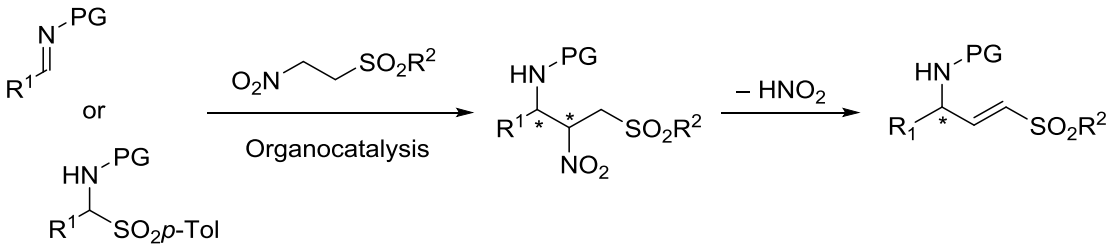
In fact, this *umpolung* strategy for the olefination reaction was successfully applied later in Michael-type reactions employing 2-nitroethyl sulfones as vinyl sulfone anion equivalents.[161] In particular, the asymmetric Michael addition of 2-nitroethyl sulfones to α,β-unsaturated aldehydes, *via* 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 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.

[161] a) López, R.; Zalacain, M.; Palomo, C. *Chem. Eur. J.* **2011**, *17*, 2450–2457. b) Gianelli, C.; López, R.; Puente, Á.; Zalacain, M.; Palomo, C. *Eur. J. Org. Chem.* **2012**, 2774–2779.

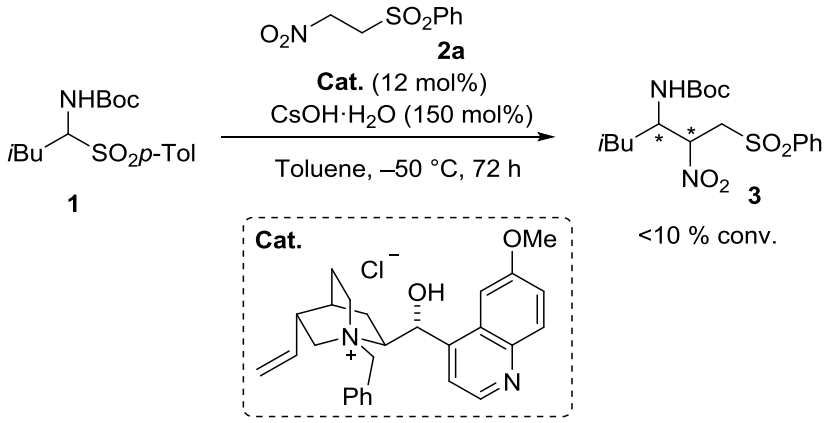


Scheme 46. Synthetic plan for the preparation of enantioenriched γ-sulfonyl allyl amines.

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 employing the optimal conditions established before for the analogous reaction (Scheme 44 in page 61).[160] 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 suprastoichiometric amounts of cesium hydroxide, in toluene at –50 °C.[162] Unfortunately, only traces of adduct **3** were detected after 72 hours (Scheme 47).



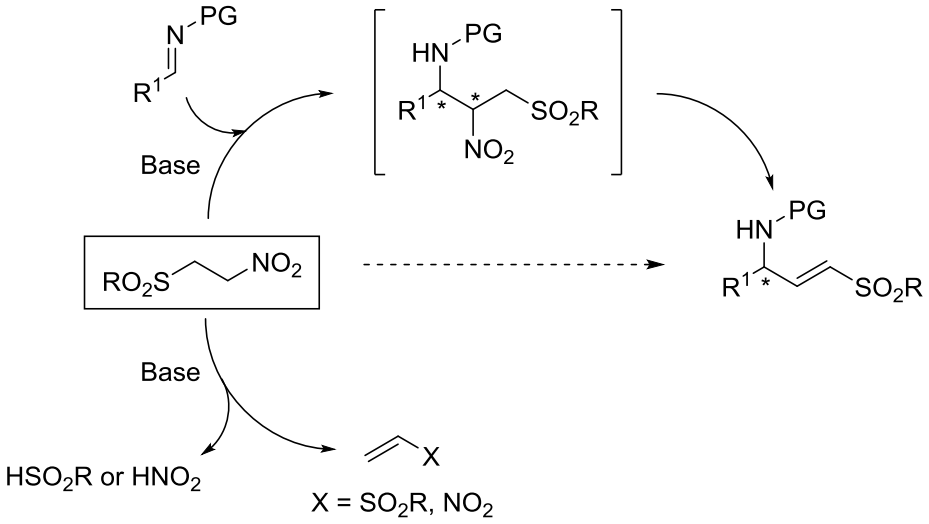
Scheme 47. Nitro-Mannich reaction of **1** and **2a** under phase transfer conditions.

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 °C provided better transformations at the expense of the formation of complex mixtures. This low reactivity was attributed to a lower solubility of the 2-nitroethyl sulfone **2a**, in toluene, 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

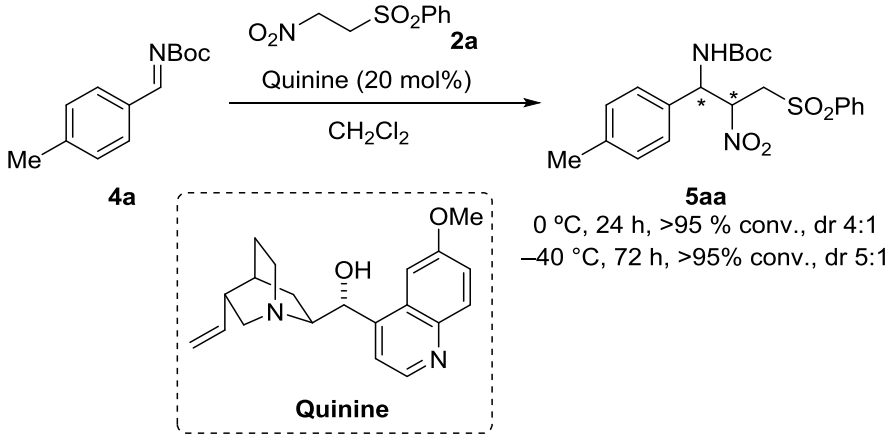
[162] This part of the work was carried out by Dr. Maitane Zalacain: Zalacain, M. Reacción de Michael enantioselectiva de 2-nitroetil sulfonas. Ph.D. Thesis, University of the Basque Country, Donostia-San Sebastian, 2014.

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.

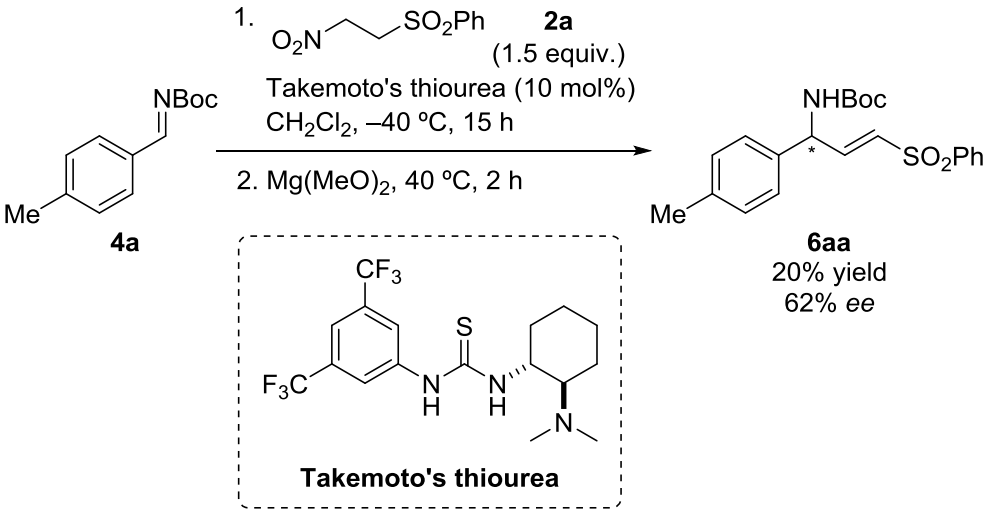
Preliminary assays with catalytic amounts of DBU, DABCO and triethylamine showed that nitrous acid elimination in the starting material competed with the addition reaction especially at temperatures above –10 °C. Nevertheless, quinine-mediated nitro-Mannich addition of 2-nitroethyl sulfone **2a** to *N*-Boc imine **4a** worked satisfactorily at 0 °C and the addition product **5aa** was obtained (Scheme 49).[162]



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 $(DHQD)_2PHAL$, did not promote the reaction while bifunctional organocatalysts provided total transformations. Quinine, as previously shown, and cinchonine promoted complete transformation of **4a** into the corresponding adduct **5aa** at –40 °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,[163] the highest enantioselectivity was obtained with Takemoto's thiourea although the desired γ-sulfonyl allyl amine **6aa** was produced in low global yield (20%) (Scheme 50).[162] 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 **6aa**.

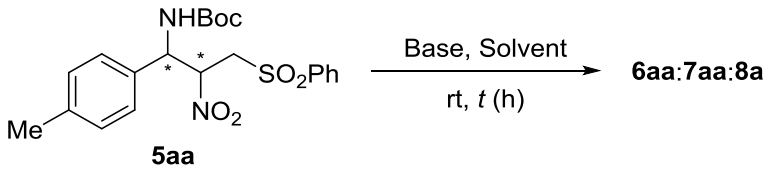
2.3.2. Optimization of nitrous acid elimination in the Mannich adducts

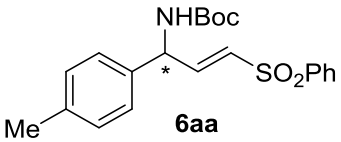
The nitro-Mannich adduct **6aa** seemed to be more sensitive to basic conditions than the adducts produced in the reaction with ethyl 3-propionate (only aliphatic adducts were tested, see Scheme 44 in page 61)[160] and in the amine-catalyzed conjugate addition of 2-nitroethyl sulfones (see Scheme 45 in page 61).[161] Thus, we decided to focus on the optimization of the nitrous acid elimination. Several bases were tested, although the common organic ones were excluded from the study since previous

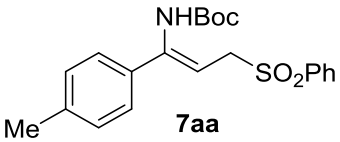
[163] Nitrous acid elimination under these conditions provided satisfactory results for the enantioselective Michael reaction with 2-nitroethyl sulfones (see Scheme 45 in page 61).

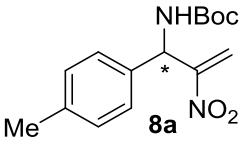
experiments already showed that they favored the isomerization of the double bond. Most representative results are depicted in Table 5.

Table 5. Optimization of the nitrous acid elimination step.









Entry	Base	Equiv.	Solvent	*t* (h)	Conv. (%)[b]	6aa: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_2Cl_2	24	70	0:100:0
5	CsF	5	CH_2Cl_2	5	>95	0:100:0
6	DMAP	2	CH_2Cl_2	2	>95	0:100:0
7	$CsOH·H_2O$	2	CH_2Cl_2	1.5	>95	61:39:0
8	Cs_2CO_3 (0.2 M aq.)	4	CH_2Cl_2	20	>95	0:0:100
9	K_2CO_3	2	CH_2Cl_2	24	60	0:0:100
10	*t*-BuOK	2	CH_2Cl_2	2	>95	0:100:0
11	**KOH**	**2**	**CH_2Cl_2**	**2**	**>95**	**100:0:0**
12	Amberlyst A-21	1 mg/mmol	CH_2Cl_2	48	N.R.	-
13	Basic silica gel	0.1 g/mmol	CH_2Cl_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 **6aa**:**7aa**:**8a** ratio determined by ^1H NMR of the crude product. [c] Reactions carried out at 40 °C.

Isomerization of adduct **6aa** into **7aa** was observed with bases of different nature (entries 1–6). Cesium hydroxide monohydrate provided a mixture of desired adduct **6aa** 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 **6aa** 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 **5aa** with 2 equivalents of potassium hydroxide for 2 hours, in methylene chloride at room temperature, provided only the desired γ-sulfonyl allyl amine **6aa** (entry 11). The key to success seemed to be the optimal combination of different features, such as the basicity and solubility of the base and the reaction time. In order to control the latter, the reactions were always monitorized by IR spectroscopy and quenched when the NO_2 band (1560 cm^{-1}) disappeared. On the other hand, other basic agents such as resins and basic silica gel (entries 12 and 13) were also assayed but no transformation was observed in any case regardless temperature or reaction time.

Attempts to perform the *one-pot* nitro-Mannich and potassium hydroxide-promoted elimination reactions produced adduct **6aa** in low yield.

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

2.3.3. Catalyst screening for the asymmetric nitro-Mannich reaction

Motivated by the results obtained using bifunctional Takemoto's thiourea (see Scheme 50 in page 65), we decided to explore the behavior of a particular type of bifunctional Brønsted bases, the ureidopeptide-type bifunctional catalysts developed by our group, which had previously demonstrated a great efficiency in conjugate additions.[164] Their design was inspired by observations made by the group of Zhong[165] and later

[164] 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.

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

corroborated by Schreiner and co-workers.[166] Based on exhaustive studies on NMR and IR spectroscopy, mass-spectrometry and DFT calculations, they suggested that the success of electronically deficient thioureas, as hydrogen bond donors, may be a consequence of the participation of three contiguous H-bond donor groups during the electrophile activation event: both N–H groups in the thiourea unit and the *ortho* C–H moiety in the aryl group (Figure 14).

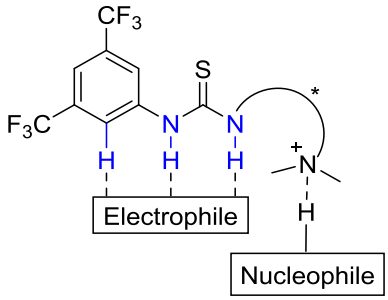


Figure 14. Activation mode proposal.

Based on these appreciations and given the efficacy of flexible synthetic peptides for the fine-tuning of reactivity and selectivity in several synthetic transformations,[167] 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 donor, 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 intermolecular hydrogen bond interactions.[168] 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] Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919–5927.
[167] Selected review: Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
[168] 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.

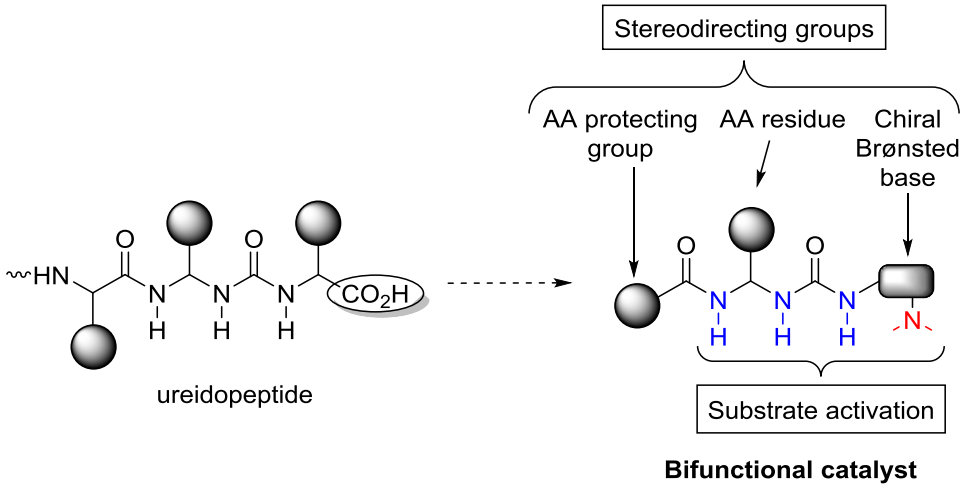
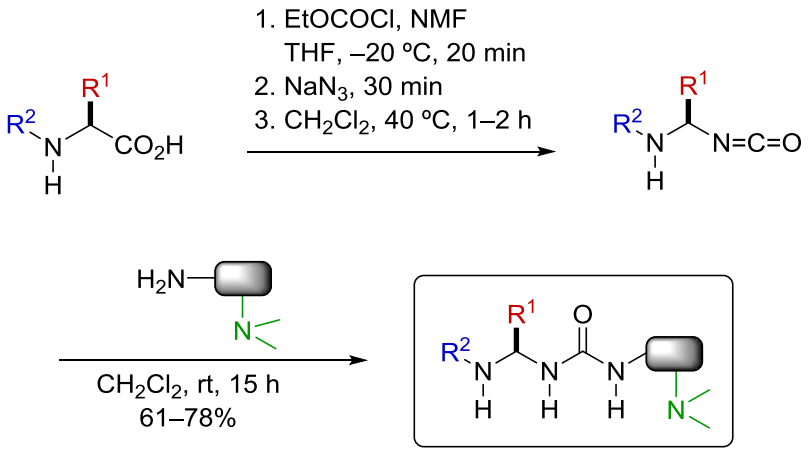


Figure 15. Design of ureidopeptide-based bifunctional Brønsted bases.

The first synthesis and subsequent optimization of these organocatalysts was conducted by Dr. Diosdado in our research group.[169] 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 synthetized 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).

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

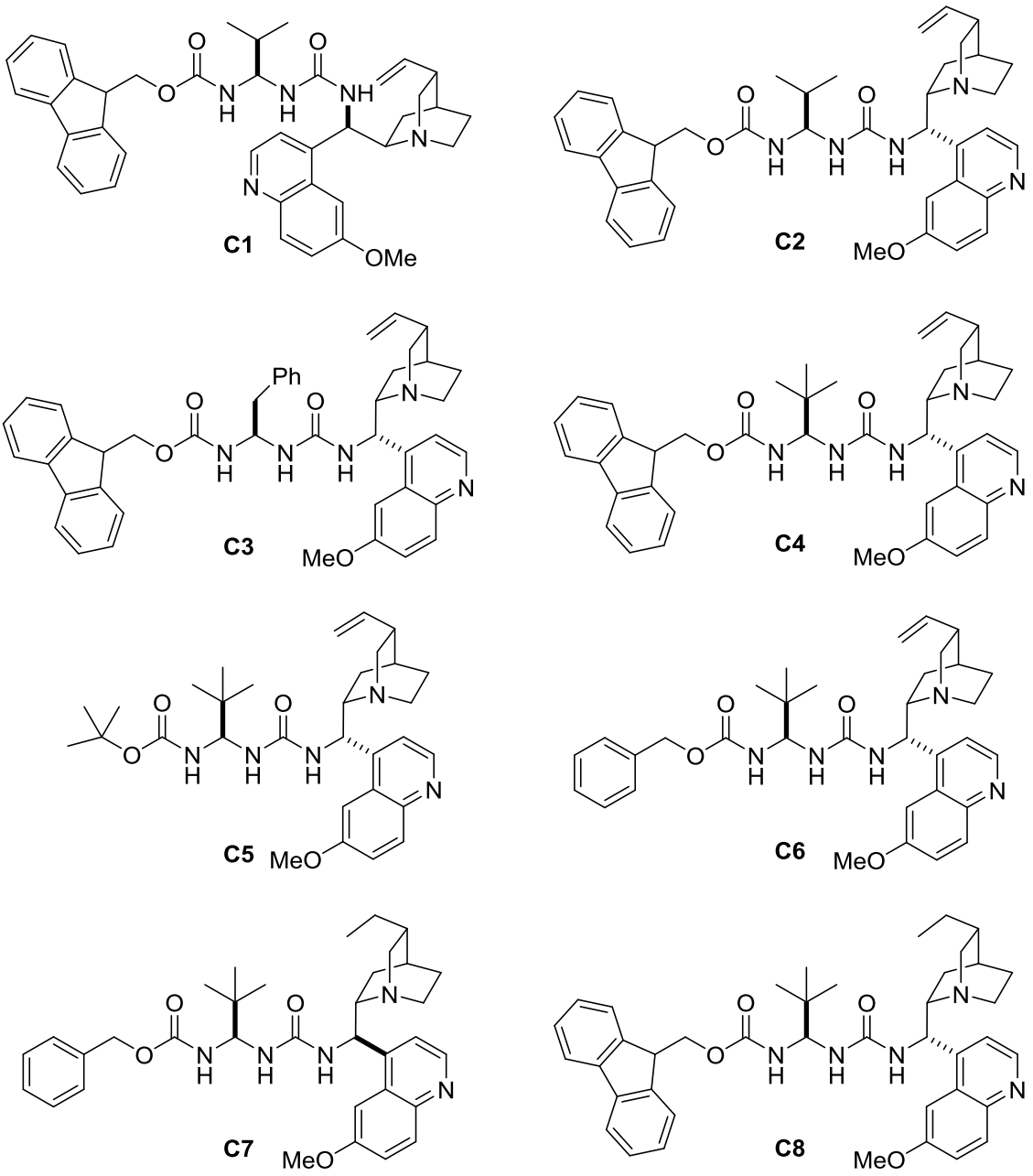
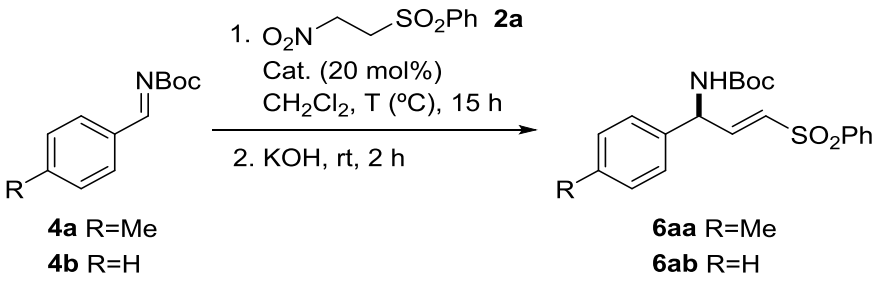


Figure 16. Bifunctional ureidopeptide-based Brønsted base organocatalysts.

Results in Table 6 show the high capacity of the synthetized 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 aminal geminal group provided better enantioselectivity since the substitution of the *iso*-propyl and benzyl groups (catalysts

C2 and **C3**) by a bulkier *tert*-butyl group (catalyst **C4**) increased the enantiomeric excess of γ-sulfonyl allyl amine **6aa** 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 **6aa** was obtained with 85% *ee*. The use of apolar solvents, such as toluene, drastically decreased the enantioselectivity of the reaction (entry 9). The optimized conditions applied to the reaction with imine **4b** afforded adduct **6ab** (entry 10), which allowed to determine the absolute configuration.[157a] A uniform mechanism was assumed for the subsequent reaction adducts.

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



4a R=Me
4b R=H

6aa R=Me
6ab R=H

Entry	Imine	Cat.	Solvent	T (°C)	Conv. (%)[b]	*ee* (%)[c]
1	**4a**	**C1**	CH_2Cl_2	–40	>95	13
2	**4a**	**C2**	CH_2Cl_2	–40	>95	75
3	**4a**	**C3**	CH_2Cl_2	–60	>95	70
4	**4a**	**C4**	CH_2Cl_2	–40	>95	82
5	**4a**	**C5**	CH_2Cl_2	–40	>95	20
6	**4a**	**C6**	CH_2Cl_2	–40	>95	49
7	**4a**	**C7**	CH_2Cl_2	–60	>95	42
8	**4a**	**C8**	**CH_2Cl_2**	**–60**	**>95 (42)[d]**	**85[e]**
9	**4a**	**C8**	Toluene	–60	>95	40
10	**4b**	**C8**	**CH_2Cl_2**	**–60**	**>95 (56)[d]**	**61**

[a] Reactions conducted on 0.5 mmol scale employing 1.5 equiv. of **2a**. [b] Conversion determined for the addition step by ^{1}H NMR spectroscopy. [c] Enantiomeric excess of product **6aa** was determined by chiral HPLC on the reaction crude. [d] Isolated yields indicated in parentheses. [e] Diastereomeric ratio of the addition product **5aa** was 4:1, determined by ^{1}H 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 synthetized following the same procedure as for **2a** (Figure 17)**.**

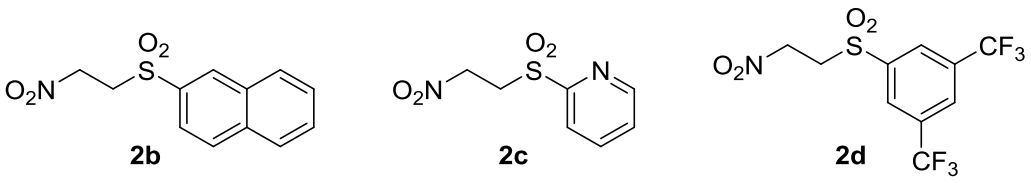
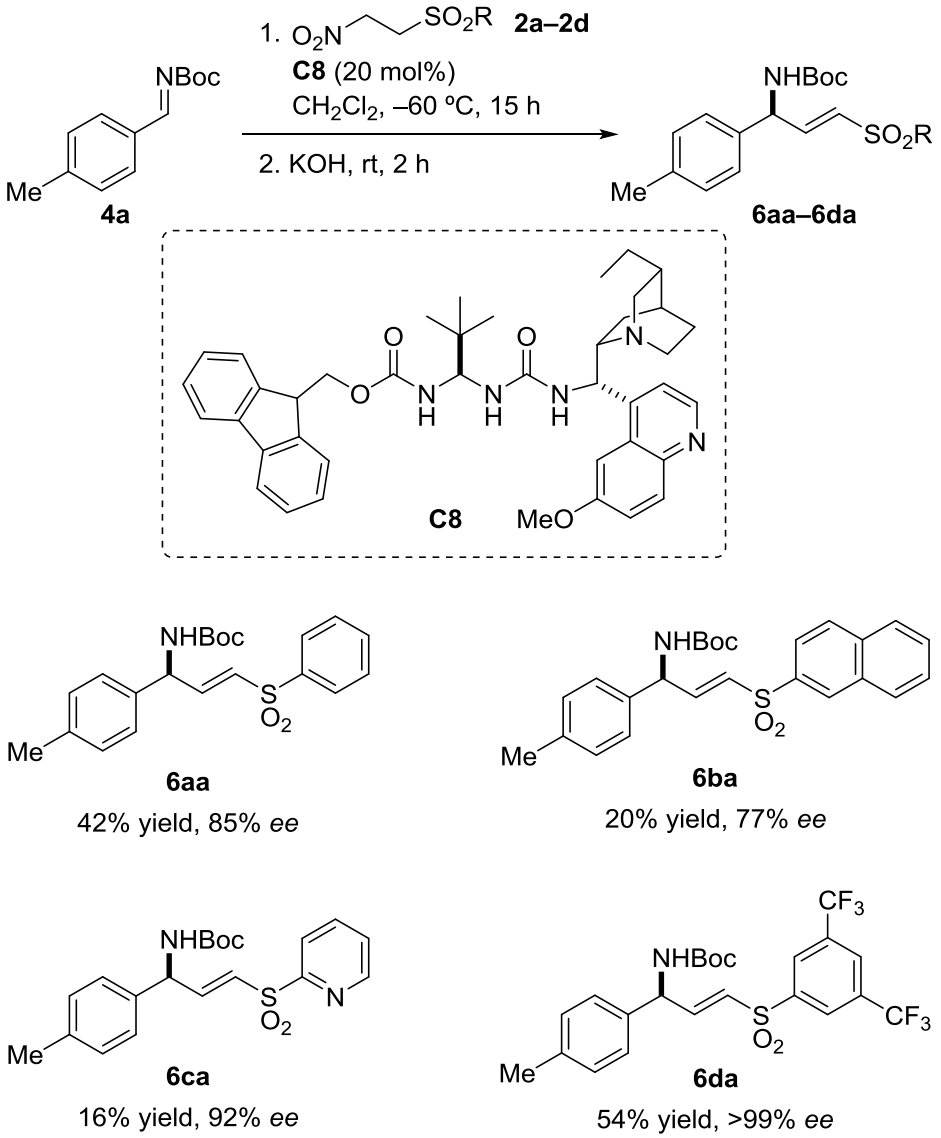


Figure 17. 2-Nitroethyl sulfones **2b–2d** employed in the study.

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 **6ca** 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 **6da** as only one detectable enantiomer in moderate yield after two steps. At this point, we do not have any experimental or theoretical evidence to explain this high asymmetric induction, although feasible π–π interactions between the electron-poor aromatic ring in **2d** and the electron-rich one in the quinine moiety in catalyst **C8** could be relevant.

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 **2a–2d**. [b] Yields refer to isolated adducts after 2 steps. [c] Enantiomeric excess was determined by chiral HPLC.

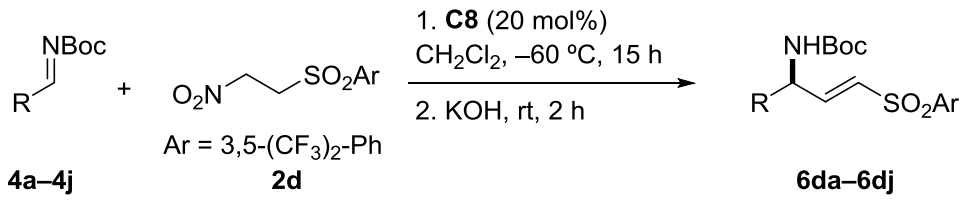
2.3.5. Reaction scope

A selection of *N*-Boc imines was evaluated in order to stablish 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 °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 **4a–4c**, **4e**, **4g** and **4h** led to the corresponding products with 99%

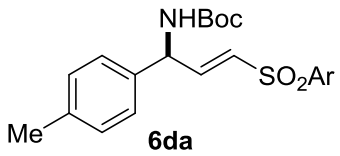
enantiomeric excess. The method also worked well for imines with bulkier groups (**4i**) and heteroaromatic azomethines such as **4i**, to afford adducts with 88% and 94% *ee*, respectively. Substituents at *ortho* position provided low yield and moderate enantiomeric excess (**6df**).

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 **6dd**, **6dh** and **6dj** could not be completely characterized (only ^{1}H NMR and UPLC-MS analysis were conducted).

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

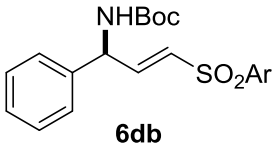


4a–4j **2d** **6da–6dj**



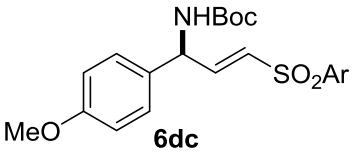
6da

54% yield, >99% *ee*
56% yield, 94% *ee* (at –40ºC)



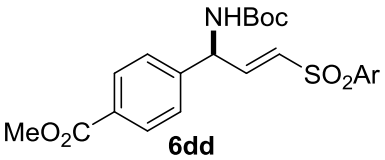
6db

60% yield, >99% *ee*



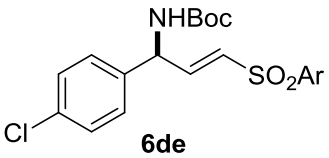
6dc

72% yield, >99% *ee*



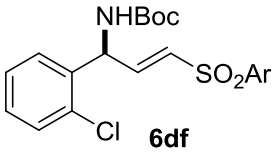
6dd

50% yield, 90% *ee*



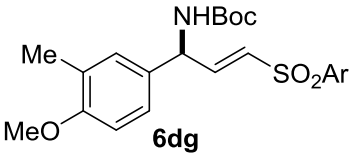
6de

51% yield, >99% *ee*



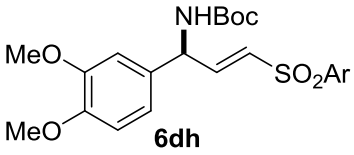
6df

10% yield, 68% *ee*



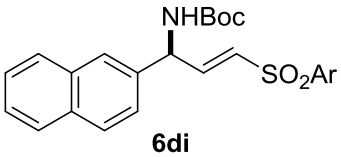
6dg

72% yield, >99% *ee*



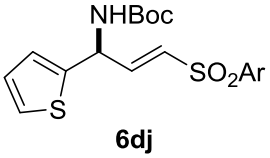
6dh

60% yield, >99% *ee*



6di

45% yield, 88% *ee*



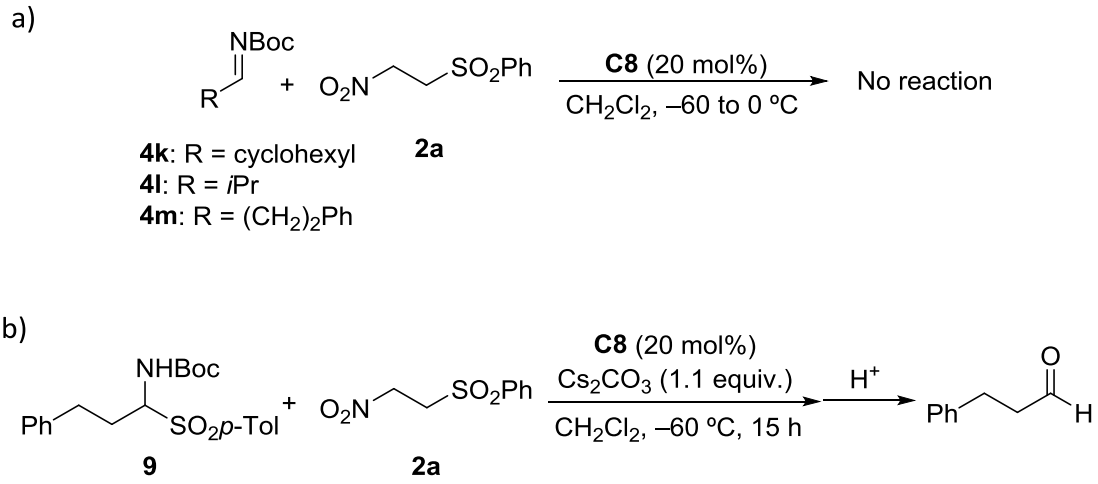
6dj

40% yield, 94% *ee*

[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.

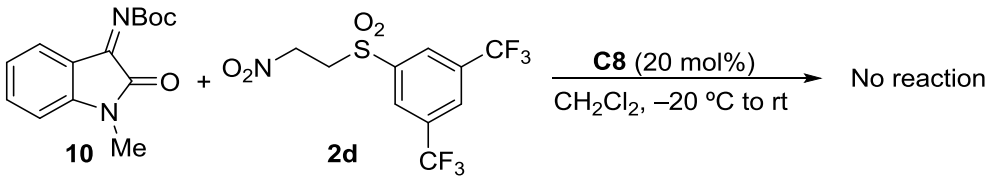
On the other hand, the nitro-Mannich reaction with *N*-Boc aliphatic imines was also investigated. Unfortunately, no addition reaction was observed neither employing pre-formed imines **4k–4m** (Scheme 52a) nor preparing them *in situ* from amido sulfone **9** in the presence of stoichiometric amounts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

after acid treatment. Additionally, the use of higher reaction temperatures resulted in nitrous acid elimination from 2-nitroethyl sulfone **2a**.



Scheme 52. Unsuccessful asymmetric nitro-Mannich reaction with aliphatic imines.

Moreover, attempts to promote the nitro-Mannich reaction of 2-nitroethyl sulfone **2d** with isatin-derived ketimine **10** were also fruitless.



Scheme 53. Unsuccessful asymmetric nitro-Mannich reaction with isatin-derived ketimine **10**.

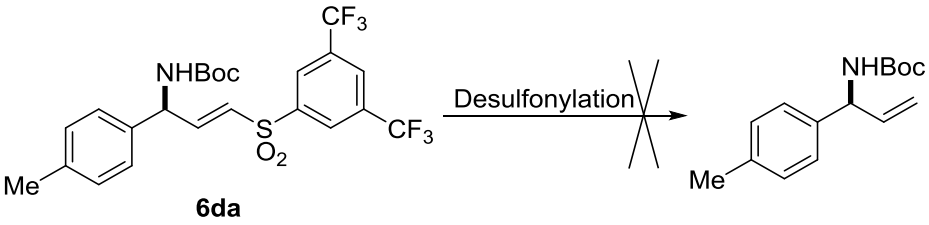
2.3.6. Elaboration of adducts

The fact that small γ-sulfonyl allyl amines are effective inhibitors of several proteases strongly supported our interest for developing this method but, at the same time, γ-sulfonyl allyl amines are interesting frameworks that could be easily transformed into enantiomerically enriched allylic amines or exploited as easily available chiral Michael acceptors.

For that purpose, the elimination of the sulfone group from the adducts was examined, first. To our disappointment, desulfonylation of adduct **6da**, employing standard conditions (magnesium, sodium hydrosulfite or sodium amalgam), did not produce the corresponding allyl amine. (Table 9). In all cases, the reactions resulted in messy crude mixtures, in which either isomerization and/or decomposition of adduct **6da** were

observed. This result confirms the difficulties related to the manipulation and elaboration of the γ-sulfonyl allyl amines, since researchers from our group were able, previously, to efficiently desulfonate the γ-substituted vinyl sulfones shown in Scheme 45 (page 61).[161b]

Table 9. Representative explored desulfonylation conditions.

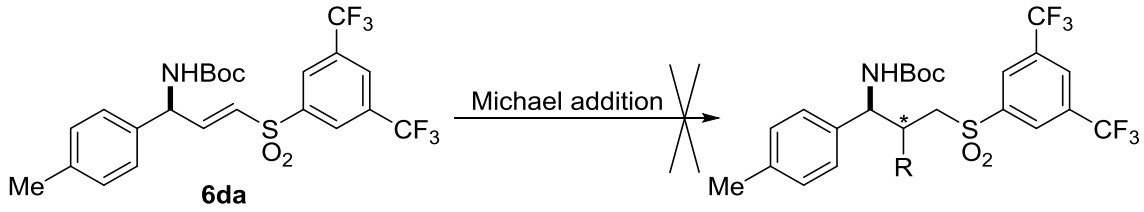


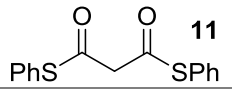
6da

Entry	Reagent (equiv.)	Solvent	T (°C)	t (h)
1	Mg (15), TMSCl (0.5), DBE (0.5)	MeOH	rt	2
2	$Na_2S_2O_4$ (4), $NaHCO_3$ (12)	DMF:THF:H_2O (1:1:1)	50	2
3	Na(Hg) 5% (6)	MeOH	–20	4

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,[169] 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 Et_3N resulted in adduct isomerization.

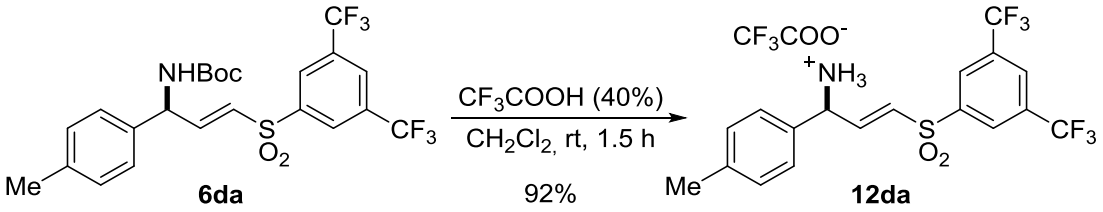
Table 10. Representative explored conjugate additions to adduct **6da**.



Entry	Reagent (equiv.)	Solvent	T (°C)	t (h)
1	MeMgBr (3)	THF	–40	48
2	Me_2CuLi (2)	Et_2O	0	48
3	*n*-Bu_2CuLi (2)	Et_2O	0	48
4	 **11** (3)	CH_2Cl_2	rt to 40	72

Other chemical transformations such as iodocyclocarbamation[170] and photochemical substitutions,[171] previously described for vinyl sulfones lacking α-stereogenic centers, were also unsuccessful.

We were able only to produce the corresponding free secondary amines in excellent yield (Scheme 54).[157c]



Scheme 54. Amine deprotection in final adduct **6da**.

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.

[170] Dell'Uomo, N.; Di Giovani, M. C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Liebigs Ann. Chem.* **1994**, 641–644.
[171] 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

INDEX

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.[172,173] For instance, from 1086 unique small-molecule drugs approved by U.S. FDA in 2012, 640 (59%) contained at least one nitrogen heterocycle.[174] Moreover, from the top 6 prescribed drugs in the U.S. in 2016, 5 of them also incorporated this type of moiety (Figure 18).[175]

[172] 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.

[173] 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.

[174] Ref. 1, page 5.

[175] 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.

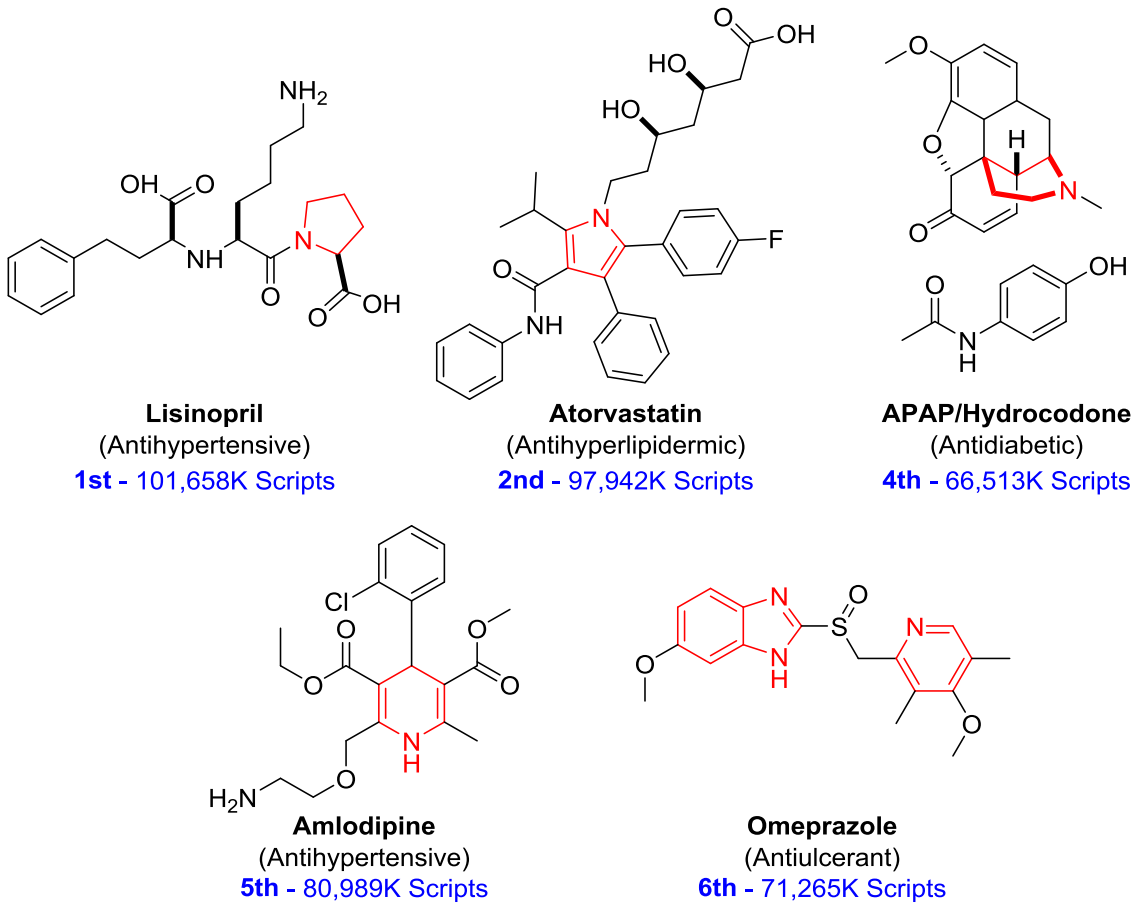


Figure 18. Top *N*-heterocycle-containing pharmaceuticals by prescriptions in 2016.

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).[174]

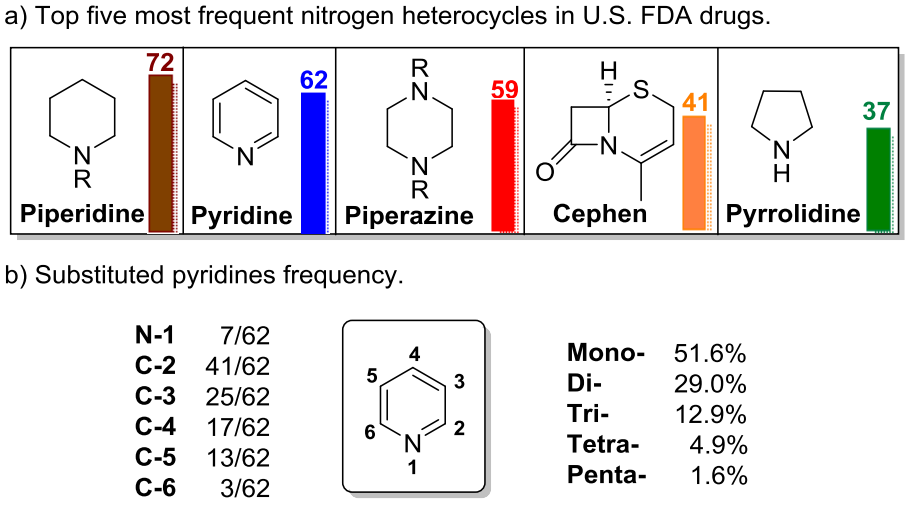


Figure 19. Most frequent *N*-heterocycles and substituted pyridines in U.S. FDA approved drugs (2012).

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 compounds[176] and chiral ligands[177] bearing this structural moiety, including some α-chiral amines.

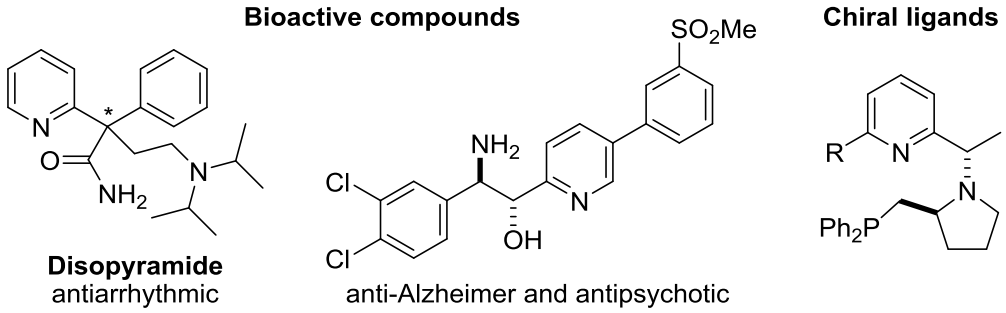


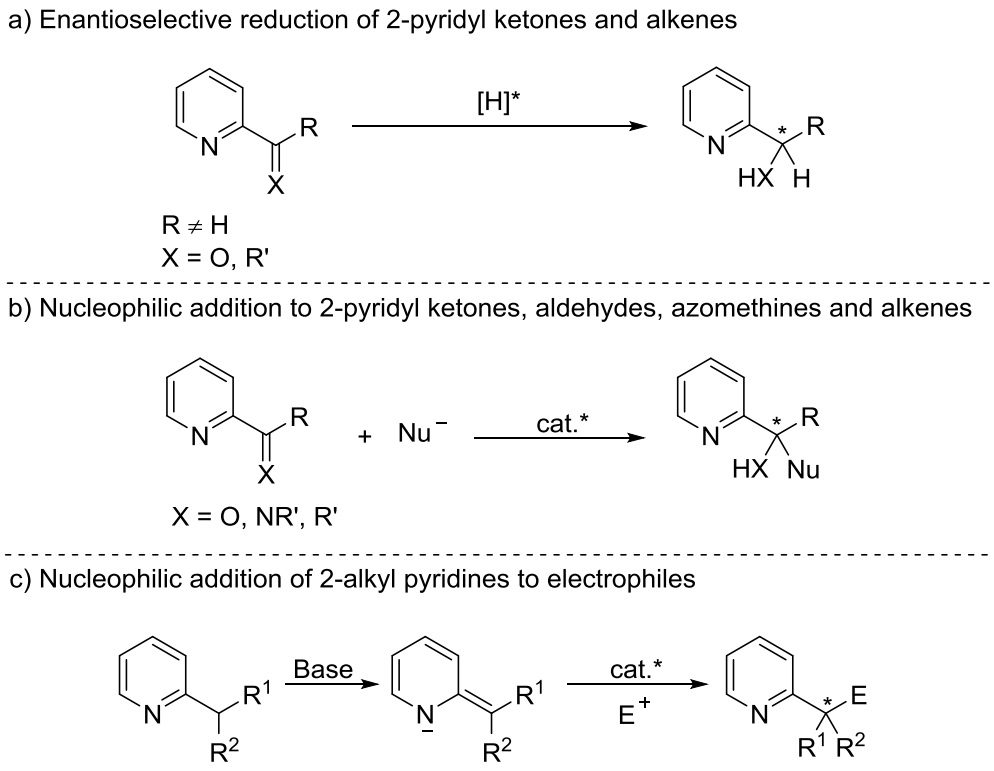
Figure 20. *Ortho*-substituted pyridines as bioactive compounds or chiral ligands.

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 chiral α-functionalized 2-alkyl pyridines: the reduction of 2-pyridyl ketones and alkenes (Scheme 55a), the nucleophilic addition to 2-pyridyl ketones, aldehydes, azomethines and alkenes (Scheme 55b), and the use of 2-alkyl pyridines as (pro)nucleophiles in nucleophilic additions (Scheme 55c).

[176] 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.

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



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

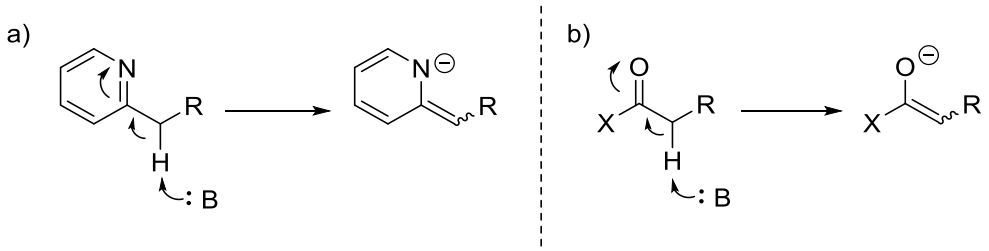
These three approaches constitute straightforward methodologies for the preparation of pyridine based tertiary and secondary amines, but all remain underexplored. For instance, whereas general enantioselective reductive methods have been described for ketones and alkenes, only isolated examples of the use of ketimines has been reported with very low efficiency.[178] 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.[179] 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.

[178] 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.

[179] 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 the C=N moiety exhibits electron-withdrawing properties resembling those of the carbonyl group (Scheme 56).[180] Nevertheless, although the latter has been employed in many direct catalytic enantioselective bond forming reactions (Scheme 56b),[181] 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.



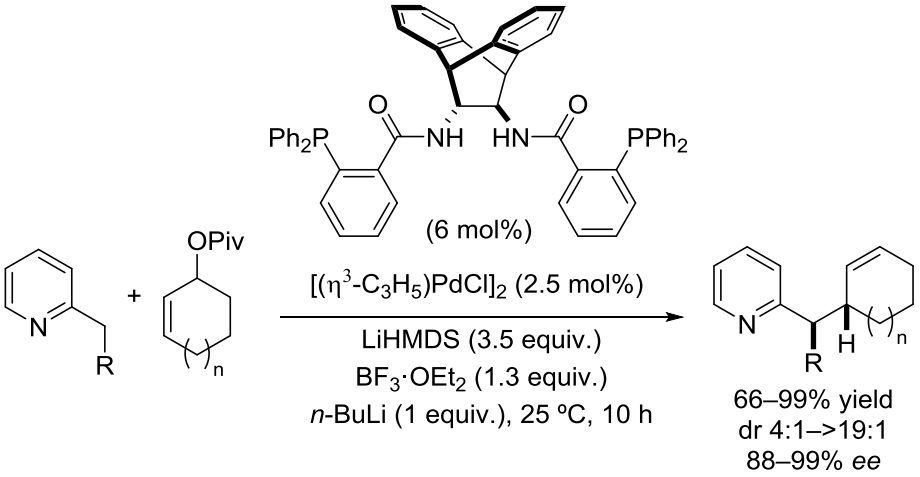
Scheme 56. α-Deprotonation of 2-alkyl pyridines and carbonyl compounds.

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.[182] 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

[180] For a perspective in the matter, see: Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831–845.
[181] 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.
[182] 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.

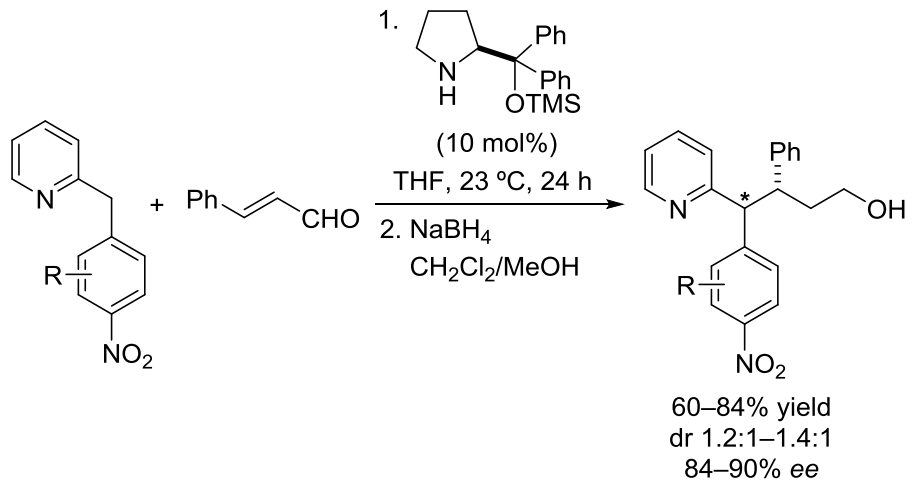
57). The reactive nucleophiles were generated by coordination to $BF_3{\cdot}OEt_2$ followed by deprotonation with 3.5 equivalents of LiHMDS and 1 equivalent of *n*-BuLi.[183]



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

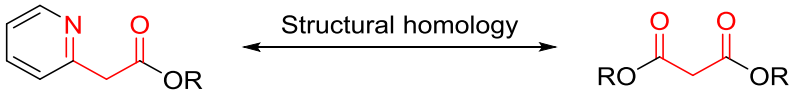
Otherwise, the installation of an additional activating group into the substrate has become a successful strategy to overcome the low acidity of 2-alkyl pyridines. In 2011, Melchiorre and co-workers reported the enantioselective addition of nitrobenzyl pyridines to α,β-unsaturated aldehydes *via* iminium 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 enatioselectivites, albeit with low diastereoselectivities (Scheme 58).[184]

[183] 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. Am. Chem. Soc.* **2011**, *133*, 12439–12441.
[184] Vera, S.; Liu, Y.; Marigo, M.; Escudero-Afán, E. C.; Melchiorre, P. *Synlett* **2011**, 489–494.



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

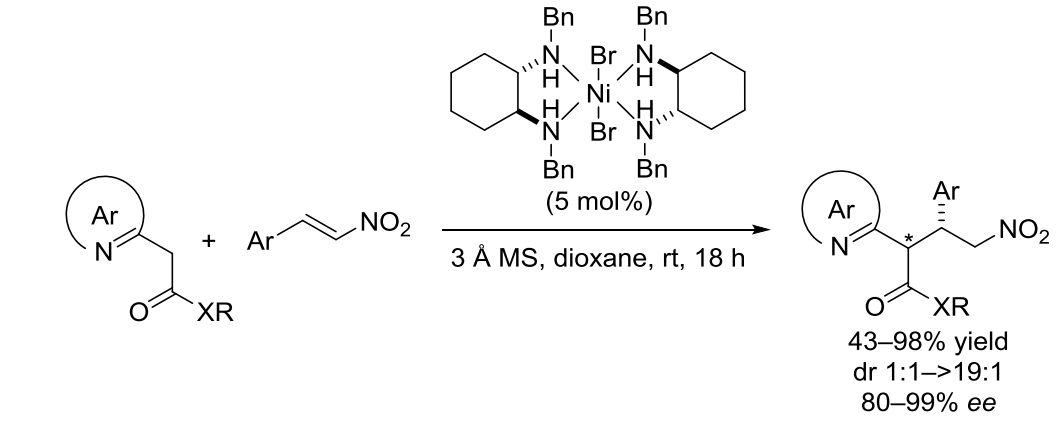
The attachment of an extra activating group, such as an ester or amide group, to the α-carbon of the 2-alkyl pyridine, enhances the acidity to an extent that is almost comparable to that for 1,3-dicarbonyl compounds.



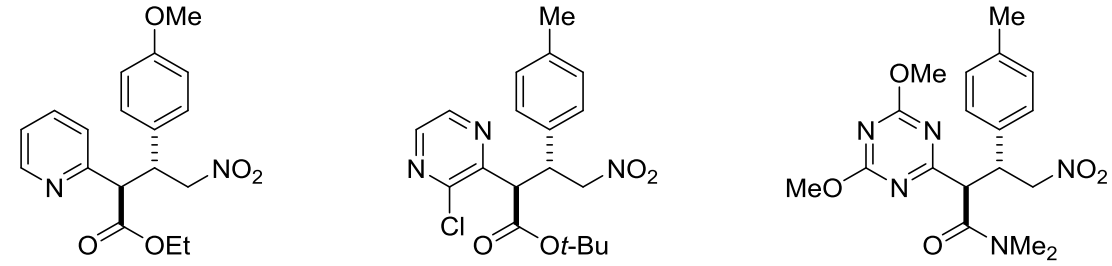
Scheme 59. Structural homology between 2-pyridyl acetates and 1,3-dicarbonyl compounds.

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).[185] 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.

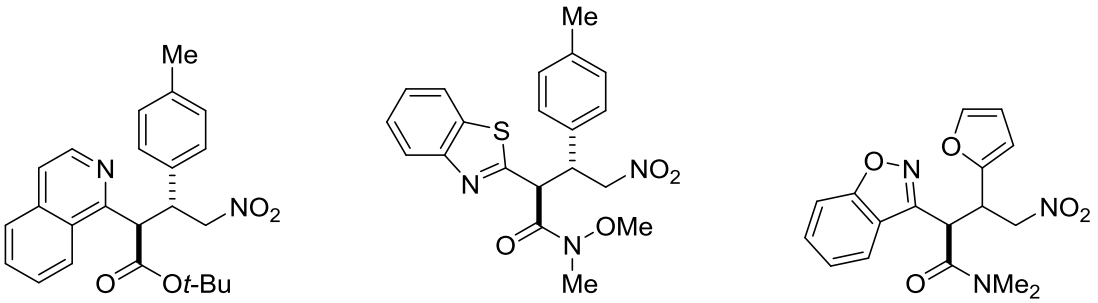
[185] Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214–11218.



Representative examples:



88%, dr 7.5:1, 80% *ee* | 66%, dr 7:1, 94% *ee* | 99%, dr 10:1, 93% *ee*

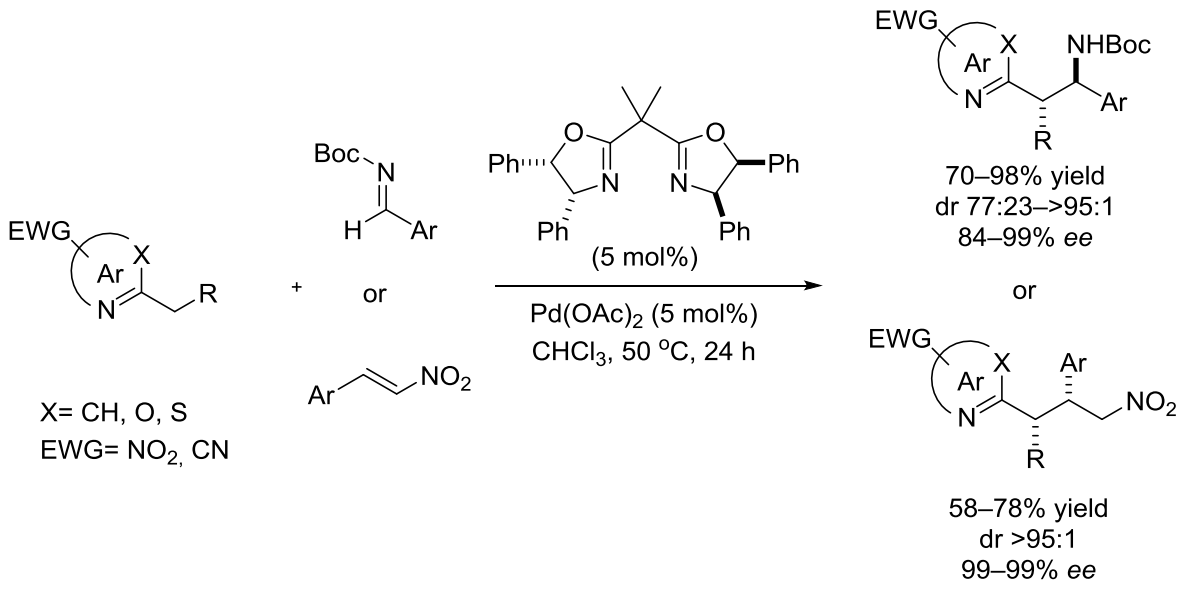


78%, dr 9:1, 99% *ee* | 85%, dr >19:1, 96% *ee* | 73%, dr 2:1, 88% *ee*

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

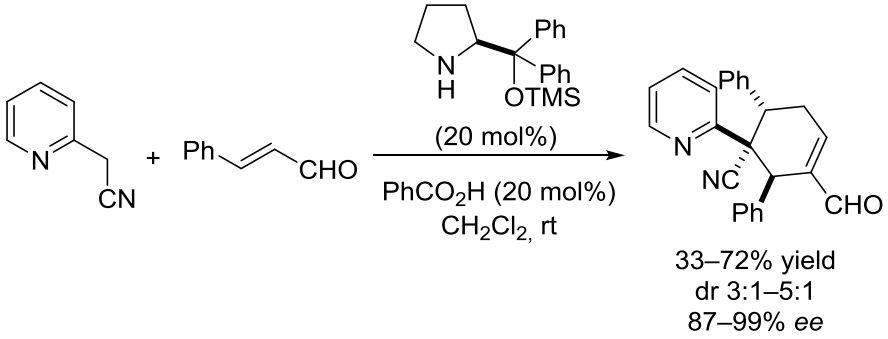
The same group also developed a similar approach to increase the acidity of 2-alkyl azaarenes; the incorporation of an electron-withdrawing group into the azaarene ring. High levels of stereoselectivity were achieved in the reactions of these substituted 2-alkyl azaarenes with *N*-Boc imines and nitroalkenes promoted by a chiral Pd(II)-bis(oxazoline) complex (Scheme 61).[186] 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 azarenes as pronuclephiles.

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



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

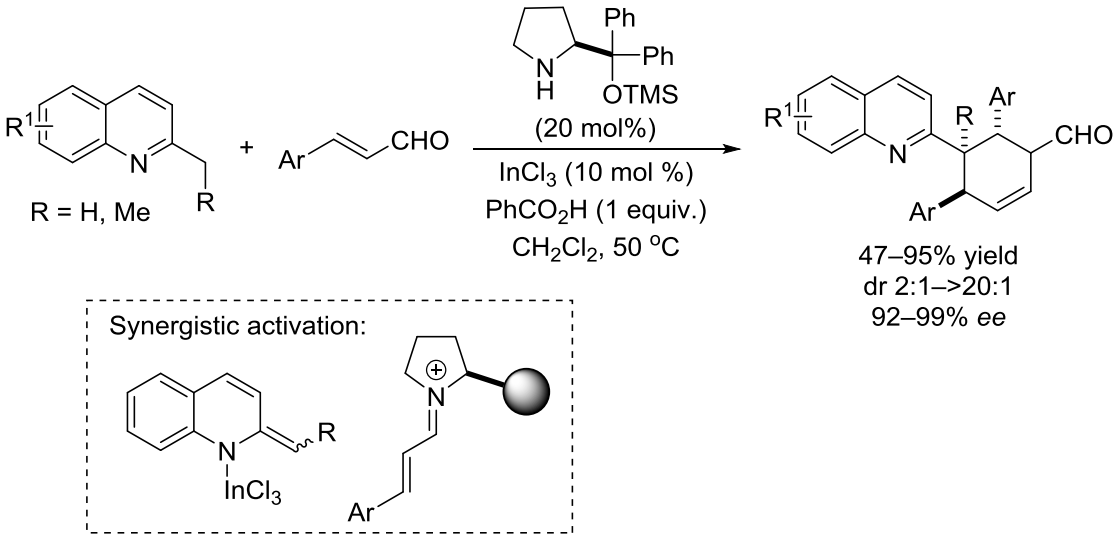
More recently, and after the work developed in this thesis, Rios and co-workers reported the stereoselective synthesis of 2-alkyl pyridine derivatives, bearing a quaternary stereocenter, through Michael/Michael/aldol cascade reactions employing 2-pyridyl acetonitrile as pronucleophile and iminium ion activation (Scheme 62).[187]



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),[188] although no examples with 2-alkylpyridines were included.

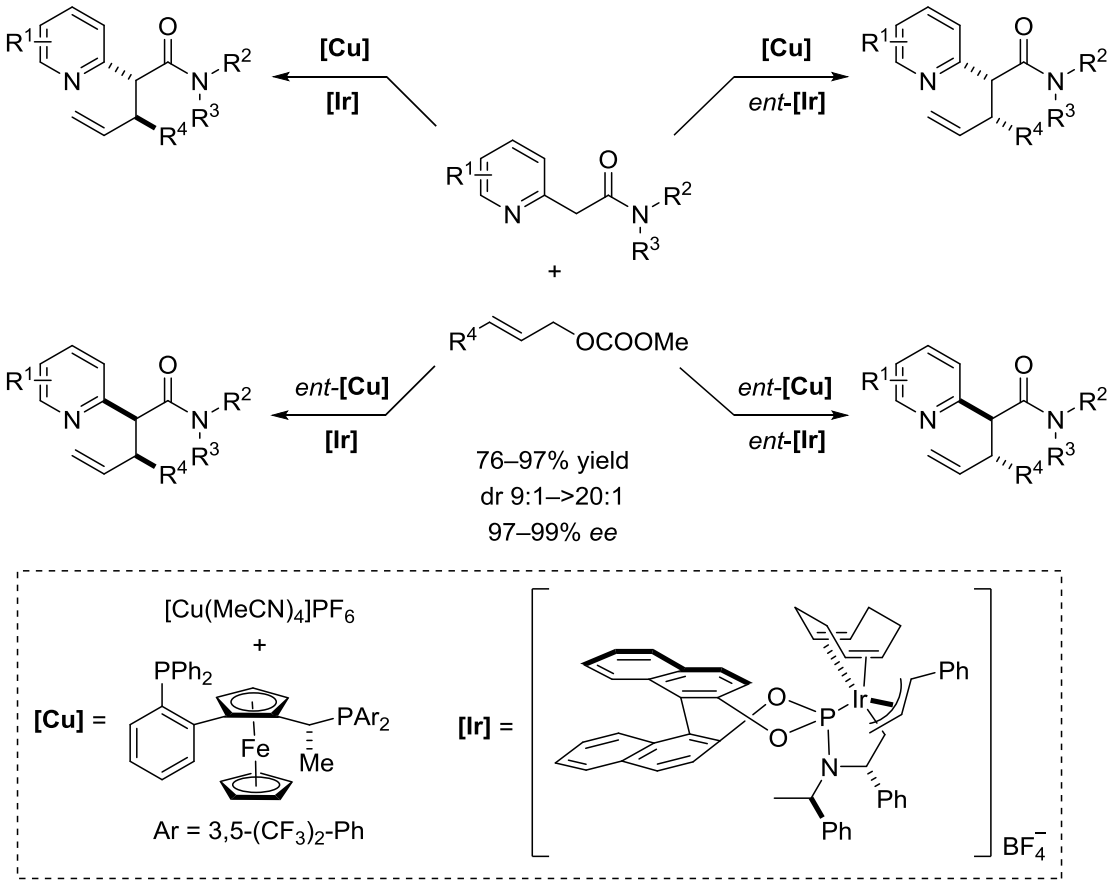
[187] Meazza, M.; Potter, M.; Pitak, M. B.; Coles, S. J.; Mazzanti, A.; Rios, R. *Eur. J. Org. Chem.* **2017**, 719–725.
[188] Meazza, M.; Tur, F.; Hammer, N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 1634–1638.



Scheme 63. Jørgensen's functionalization of alkyl quinolines

Finally, Hartwig and co-workers have reported, very recently, 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).[189]

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



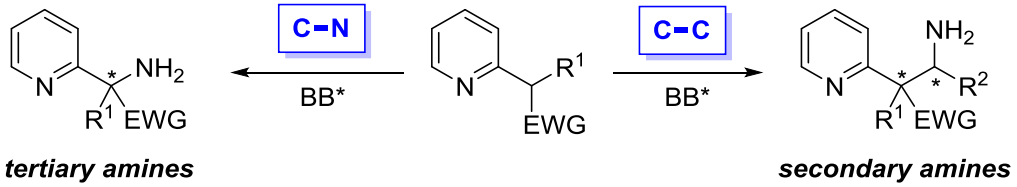
Reaction conditions: $[Cu(MeCN)_4]PF_6$ (2 mol%), Ligand (2.2 mol%), [Ir] (1 mol%), DBU (2 mol%), THF, rt, 10 h

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

In summary, precedents described 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 93).

3.2. Working hypothesis and objectives

Based on the experience of our research group in the development of Brønsted base catalyzed 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 forming 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 Cα, ii) the lack of methods to address the generation of Cα 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 structure to enhance reactivity and improve stereoselectivity are of great interest. In this context, and following the atom economy principle,[190] we envisioned that 2-alkyl azaarene *N*-oxides could be perfect 2-alkyl azaarene surrogates 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 enhanced CH Brønsted acidity as compared to most alkylazaarenes (Figure 21)[191] and the potential role of the N–O group as a coordinating site for catalyst binding.[192] Considering both aspects, we could expect that chiral bifunctional Brønsted

[190] 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.

[191] 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).

[192] 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.*

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

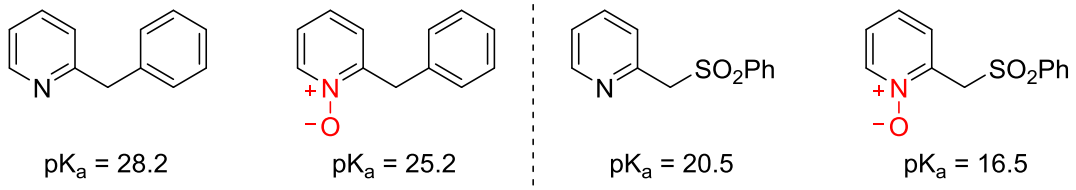
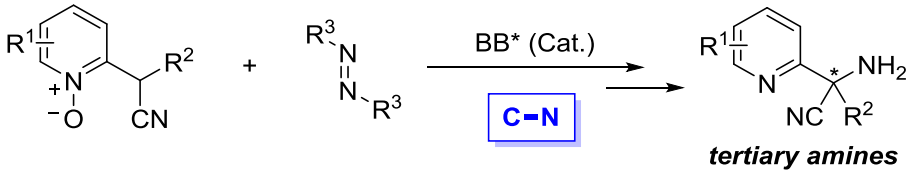


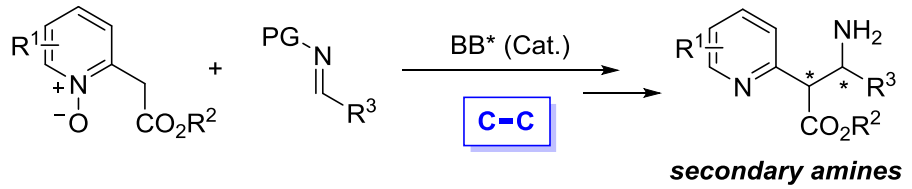
Figure 21. pK_a values of pyridine and pyridine *N*-oxide derivatives.

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 (Scheme 66).



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 (Scheme 67).



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

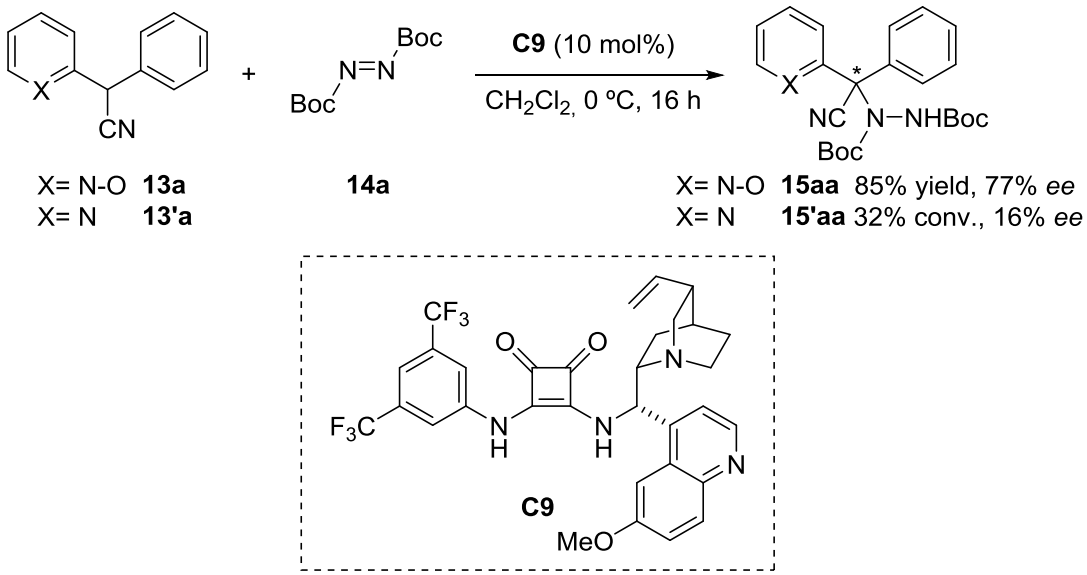
Chem. **2007**, *72*, 240–245. c) Holmquist, M.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Org. Lett.* **2014**, *16*, 1204–1207. For examples reported after the present work, see: d) Xu, Y.; Zhang, S.; Li, L.; Wang, Y.; Zha, Z.; Wang, Z. *Org. Chem. Front* **2018**, *5*, 376–379. e) He, F.; Chen, G.; Yang, 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 adddition 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 gratifiying 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.

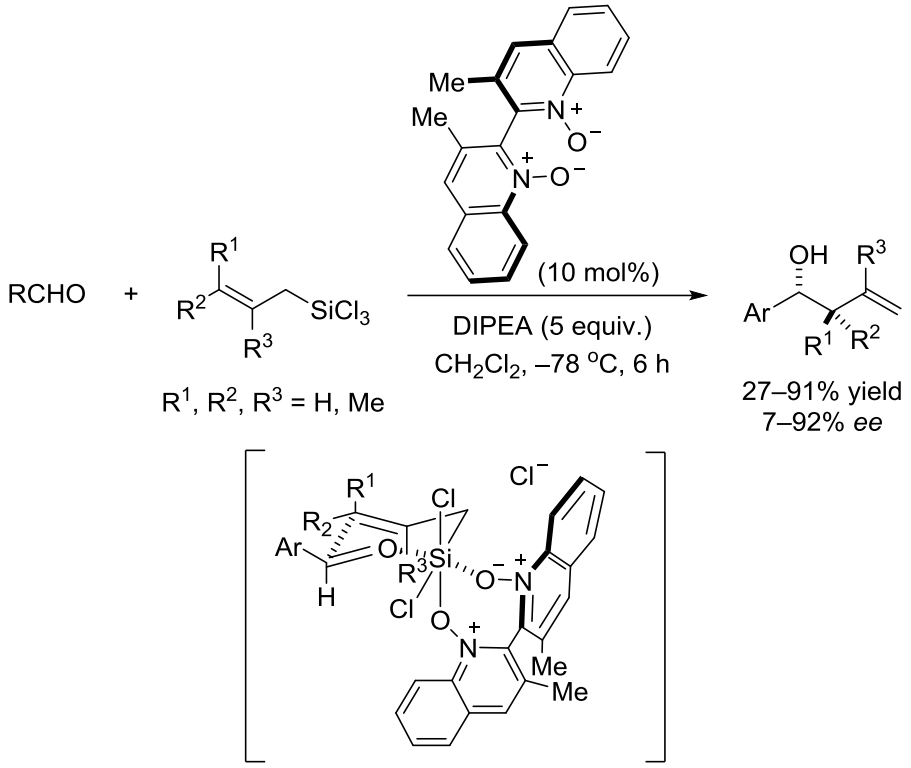


Scheme 68. Comparison of the reactivity of **13a** and **13'a** in the reaction with **14a** promoted by **C9**.

As mention before, the development of steroselective 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 interaction.

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

assisted by the chiral azaarene *N*-oxide catalyst shown in Scheme 69.[193] The authors suggested that the allylation of aromatic and unsaturated aldehydes proceeded *via* a cyclic chair-like transition state model in which the *N*-oxide groups of the catalyst were coordinated to the hypervalent silicon.



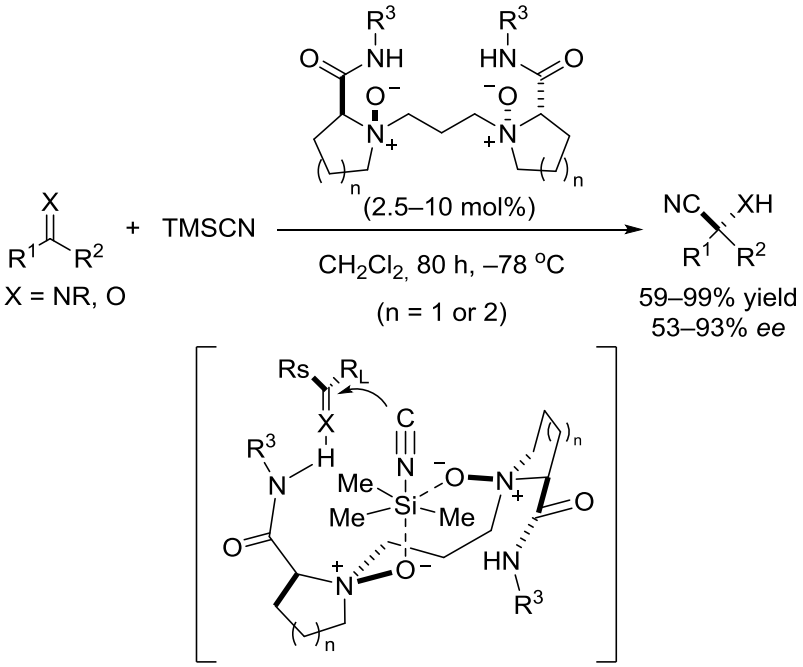
Scheme 69. Hashimoto's allylation with allyltrichorosilanes catalyzed by chiral azaarene *N*-oxide.

In addition, Feng and co-workers, developed the enantioselective cyanation of carbonyl compounds and imines employing trimethylsilyl cyanide (TMSCN) (Scheme 70).[194] The reactions were promoted by L-proline or L-piperidinamide based *N*,*N*'-dioxides, which cooperatively activated both the TMSCN and the electrophile. A plausible mechanism may consist of the generation of a hypervalent silicon

[193] 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.

[194] 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.; 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.

intermediate, from the bidentate *N*,*N*'-dioxide, which enhances the nucleophility of the cyano group as well as the rigidity of the transition state.



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

Based on these works and given the high chemical affinity of silicon for oxygen, we designed a multifunctional catalyst that, besides the chiral Brønsted base fragment and the hydrogen bond donor groups, contains a silicon residue that could account for extra *N*-oxide–silicon interactions and/or steric ones (Figure 22).

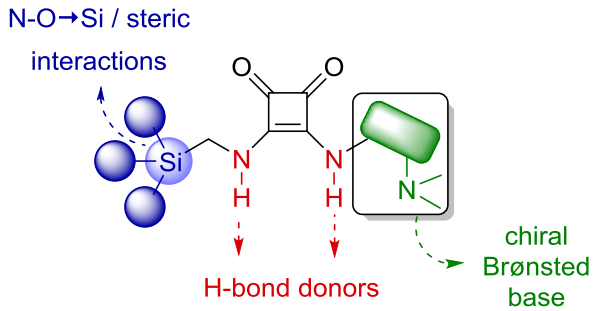
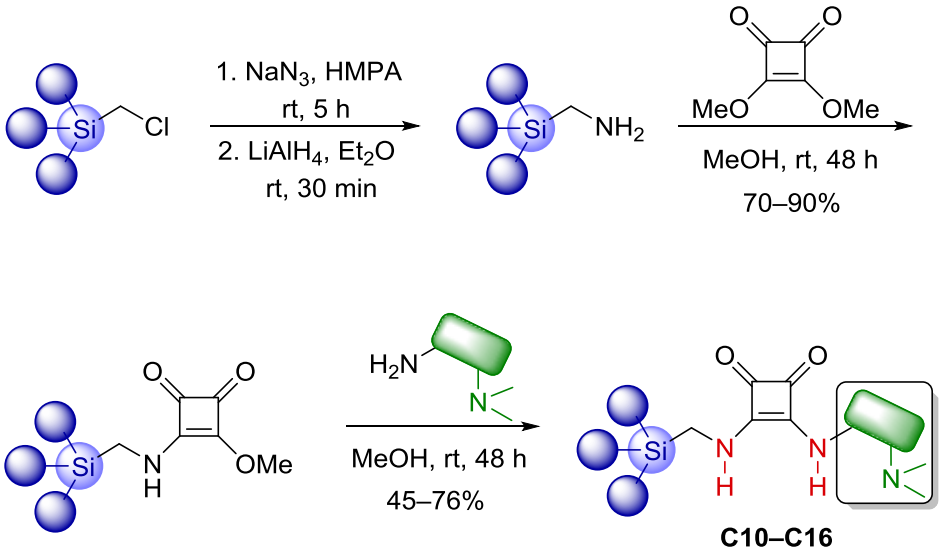


Figure 22. New design for the multifunctional squaramide-based Brønsted base catalyst.

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 HMPA[195] and subsequent reduction with $LiAlH_4$ led to the corresponding amine.[196] The coupling of 3,4-dimethoxy-3-cyclobutadiene-1,2-diene with the amine was carried out at room temperature and, finally, the coupling with 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, we synthetized 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**.

[195] Otohiko, T.; Shuji, K.; Koyo, M. *Chem. Lett.* **1983**, *7*, 1131–1134.
[196] Lettelier, M.; McPhee, D. J.; Griller, D. *Synth. Commun.* **1988**, *18*, 1975–1978.

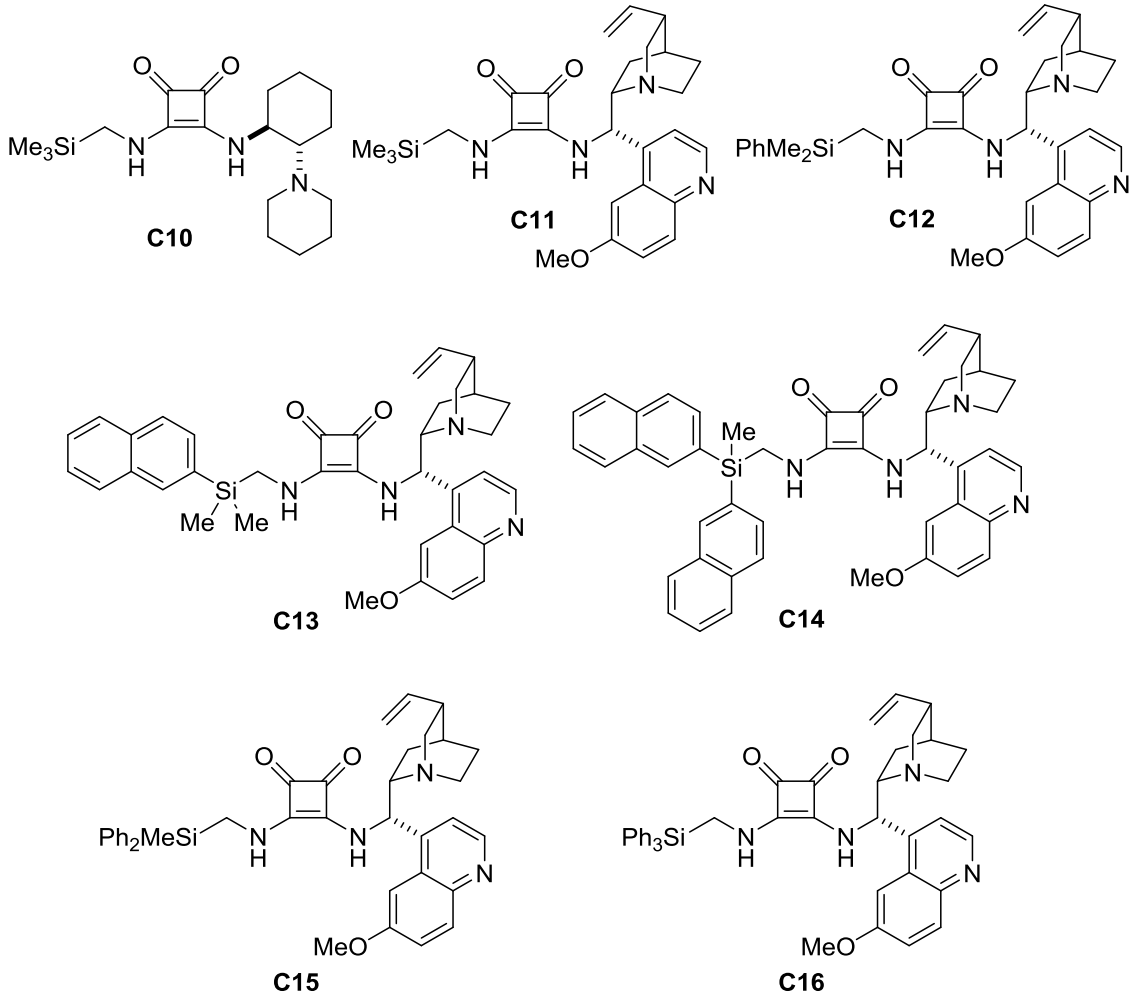
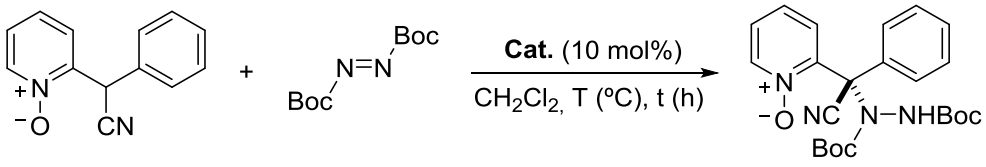


Figure 23. Silicon-containing squaramide-based Brønsted base catalysts.

Results obtained for each catalyst are shown in Table 11. 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 similar 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, by increasing the concentration of the reactants, the enantioselectivity significantly decreased (48% *ee*, entry 9) while it was maintained with dilution (entry 10)

and at lower temperatures (entry 11). Apolar solvents such as toluene produced the adduct **15aa** as a racemic mixture (entry 12). Finally, it turned out that the reaction promoted by catalyst **C16**, bearing the triphenylsilyl group, in CH_2Cl_2 at 0 °C provided the best results in terms of stereocontrol (90% *ee*, entry 13). This catalyst **C16** was selected to proceed with the α-amination studies.

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



13a **14a** **15aa**

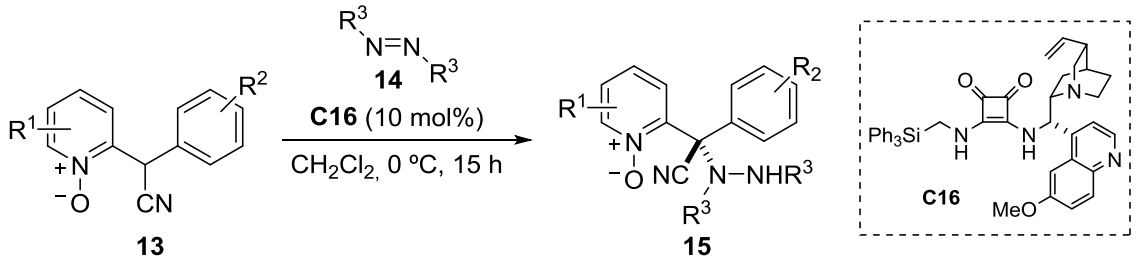
Entry	Cat.	T (°C)	t (h)	Yield (%)	*ee* (%)[b]
1	**C10**	rt	15	80	38
2	**C11**	rt	15	96	70
3	**C12**	rt	15	78	72
4	**C12**	–10	32	97	76
5	**C12**	–40	56	96	75
6	**C13**	0	15	92	76
7	**C14**	0	15	99	57
8	**C15**	0	15	90	81
9[c]	**C15**	0	15	92	48
10[d]	**C15**	0	15	93	81
11	**C15**	–10	15	95	81
12[e]	**C15**	0	24	90	0
13	**C16**	**0**	**15**	**88**	**90**

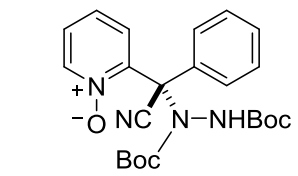
[a] Reactions were conducted on 0.2 mmol scale employing 1.5 equiv. of **14a** in 1 mL of CH_2Cl_2 (unless otherwise stated). [b] Enantiomeric excess of adduct **15aa** was determined by chiral HPLC. [c] Reaction conducted in 0.5 mL of CH_2Cl_2. [d] Reaction conducted in 2 mL of CH_2Cl_2. [e] Reaction conducted in 1 mL of toluene.

3.3.1.3. Reaction scope

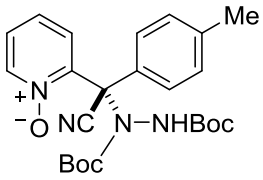
The scope of this α-amination process, using either di-*tert*-butyl or dibenzyl azodicarboxylates (**14a** or **14b**) as aminating reagents, was investigated for a range of 2-cyanomethylpyridine *N*-oxides. As data collected in Table 12 show, reactions proceeded successfully to afford adducts **15** with good yield and enantiomeric excess with 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**). Good yields and enantiomeric excesses were obtained with electron-withdrawing groups (**15da–15fa**) as well as with heteroaromatic rings (**15ga**). The result obtained for adduct **15fa** confirms the compatibility of the methodology with *N*-oxides of substituted pyridines. Furthermore, dibenzyl azodicarboxylate **14b** performed in a similar way providing adducts **15db** and **15eb** with excellent yield and enantioselectivity.

Table 12. Enantioselective α-amination reaction scope.

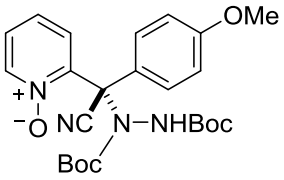




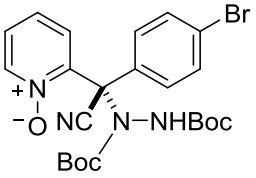
15aa
88% yield, 90% *ee*
(90% yield, 81% *ee* with **C15**)
(93% yield, 76% *ee* with **C12**)



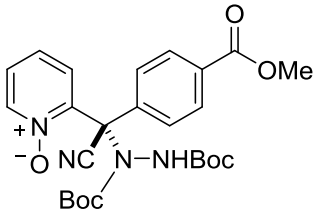
15ba
79% yield, 82% *ee*



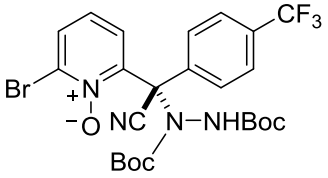
15ca
79% yield, 76% *ee*



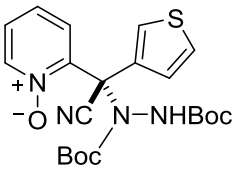
15da
90% yield, 92% *ee*
(90% yield, 85% *ee* with **C15**)



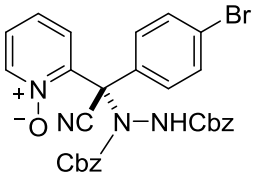
15ea
86% yield, 93% *ee*



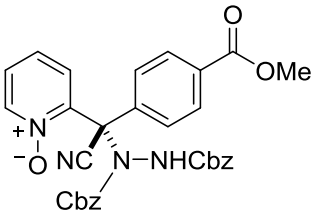
15fa
84% yield, 88% *ee*
(90% yield, 82% *ee* with **C15**)



15ga
81% yield, 90% *ee*



15db
80% yield, 90% *ee*
(74% yield, 87% *ee* with **C15**)

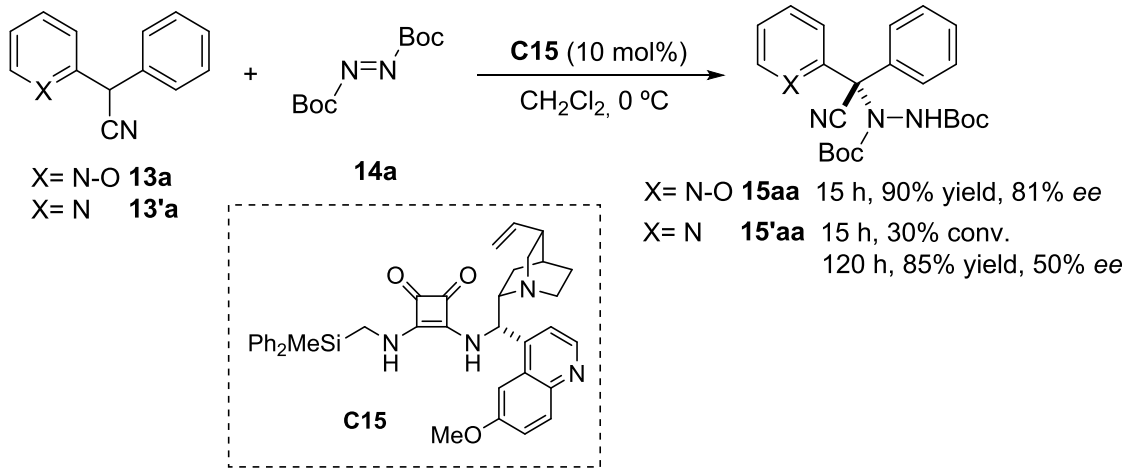


15eb
85% yield, 90% *ee*

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.

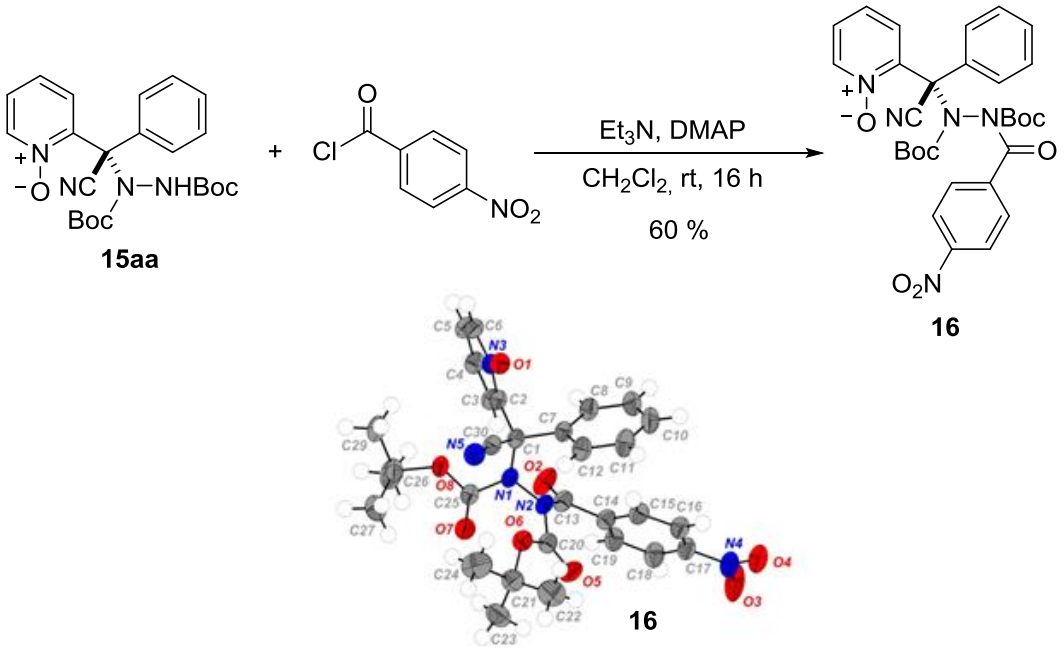
Once again, the parent pyridine **13'a** proved to be less efficient for this transformation under the optimized conditions (Scheme 72). The reaction of **13'a** and **14a** in the presence of 10 mol% catalyst **C15** proceeded to a limited extent of 30% conversion after

15 hours at 0 °C. After 120 hours, complete transformation was observed and adduct **15'aa** was obtained in 85% yield and with 50% *ee*.



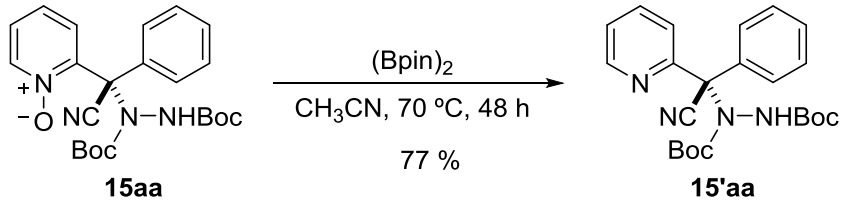
Scheme 72. Effect of the *N*-oxide functionality.

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 stablished by assuming a uniform reaction mechanism.



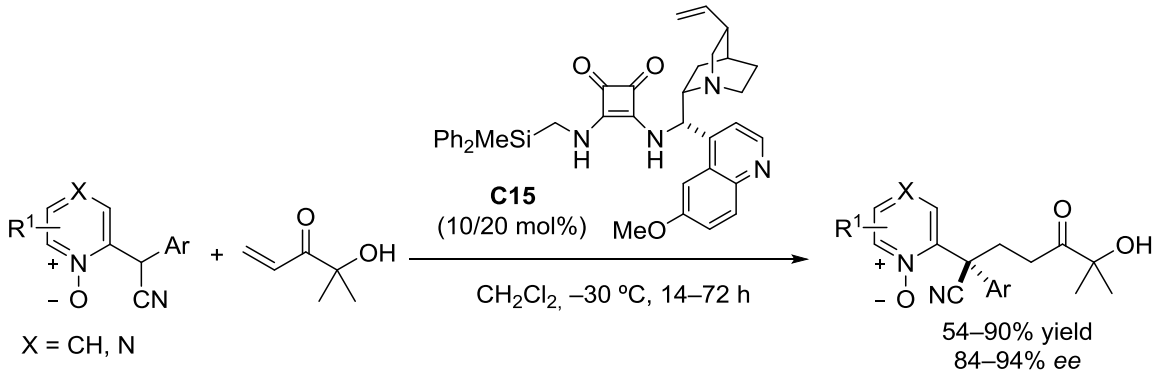
Scheme 73. Determination of the absolute configuration.

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 $(Bpin)_2$.[197] In this way, the protected enantioenriched 2-pyridyl tertiary amine **15'aa** was synthetized 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 to this work, 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).[198]



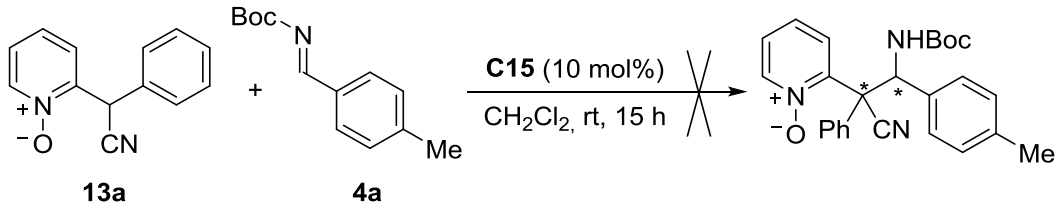
Scheme 75. Enantioselective conjugate addition of 2-(cyanomethyl)azaarene *N*-oxides to α-hydroxy enones.

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

[198] 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.

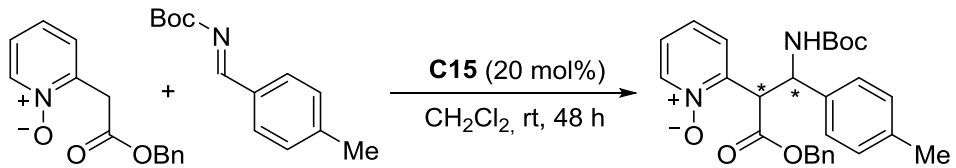
3.3.2. Enantioselective Mannich reaction of 2-azaaryl acetates with *N*-carbamoyl imines

With the satisfactory results obtained in the previous section, we decided to further extend the positive effect of the *N*-oxide group 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. Unfructuous Mannich reaction of **13a** with *N*-Boc imine **4a**.

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 sterocenters under Brønsted base catalysis, since their stability is easily compromised under proton transfer conditions. We decide to investigate the Mannich reaction of 2-pyridyl acetate *N*-oxide **17** with *N*-Boc imine **4a** (Scheme 77). 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 sterocenters generated under Brønsted base catalysis, with low diasteroselectivity.



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

Given the structural differences between pronucleophiles **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).

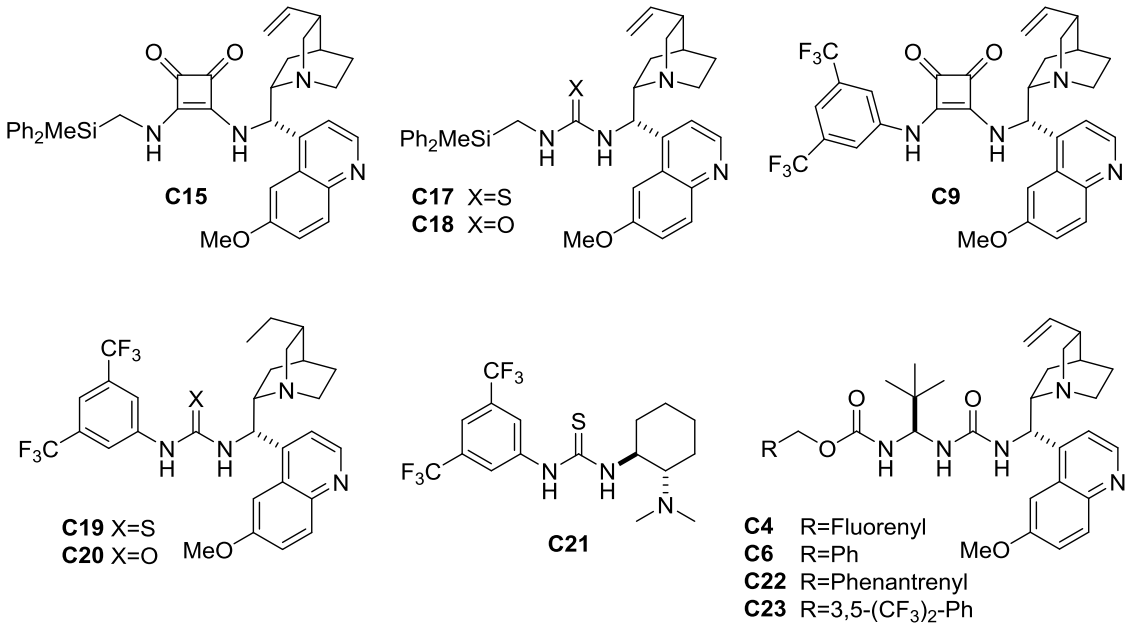


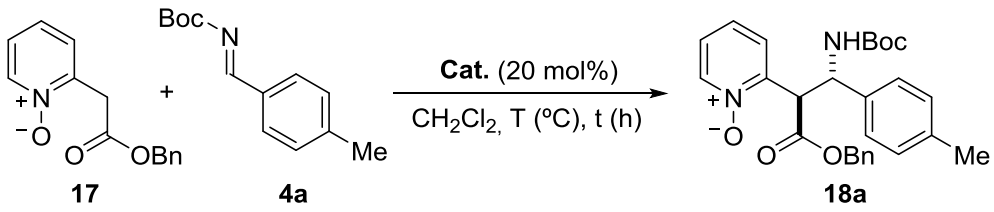
Figure 24. Catalysts studied in the enantioselective Mannich reaction.

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,[199] catalyst

[199] 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*–.

C6 enabled the production of **18a** as the only detectable diastereomer in 99% *ee* (entry 12).

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



17 **4a** **18a**

Entry	Cat.	T (°C)	t (h)	Conv. (%)[b]	dr (*anti*:*syn*)[c]	*ee* (%)[d]
1	**C15**	rt	48	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**

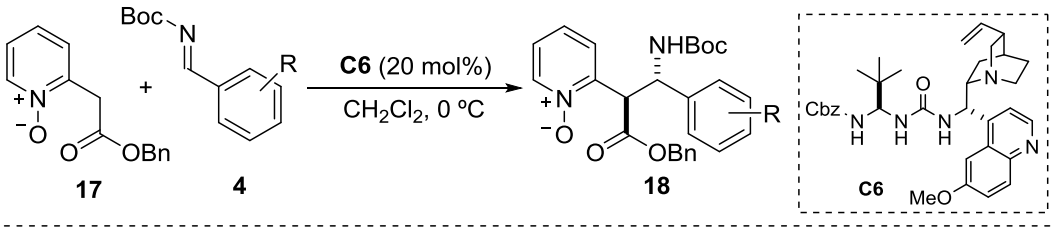
[a] Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH_2Cl_2 (molar ratio of **17**:**4a**, 1:1.2). [b] Conversion determined by ^{1}H NMR. [c] Diastereomeric ratio determined by ^{1}H NMR of crude mixture and corroborated by chiral HPLC. [d] Enantiomeric excess determined by chiral HPLC. [e] Molar ratio of **17**:**4a**, 1:2.

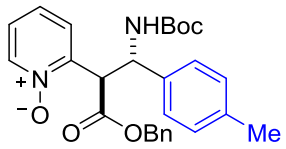
3.3.2.2. Reaction scope

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 **18a–18p**, as sole diastereomers with excellent enantiomeric excess (99%). In this study, we

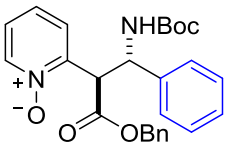
employed 20 mol% of catalyst but it is worth mentioning that using 5–10 mol% of catalyst loading, the reactions proceeded equally well without compromising either stereoselectivity or chemical yield (adducts **18d** and **18n**).

Table 14. *N*-Boc imine scope.

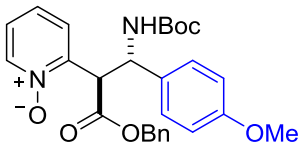




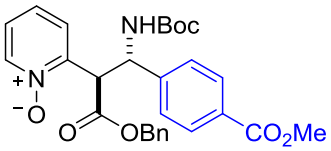
18a
1 mmol scale
48 h, 95% yield
dr 99:1, 99% *ee*



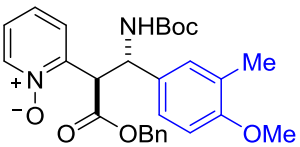
18b
28 h, 98% yield
dr 99:1, 99% *ee*



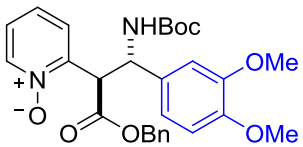
18c
48 h, 90% yield
dr 99:1, 99% *ee*



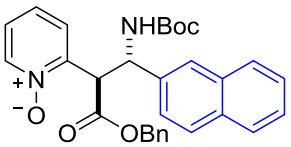
18d
(10 mol% **C6**)
20 h, 98% yield
dr 99:1, 99% *ee*



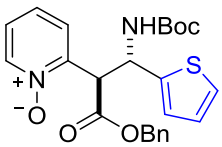
18g
48 h, 87% yield
dr 99:1, 99% *ee*



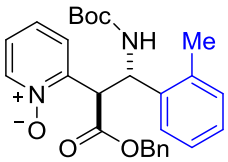
18h
48 h, 88% yield
dr 99:1, 99% *ee*



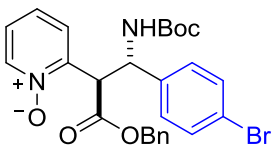
18i
48 h, 92% yield
dr 99:1, 99% *ee*



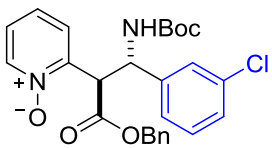
18j
48 h, 94% yield
dr 99:1, 99% *ee*



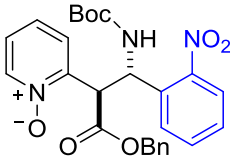
18l
48 h, 92% yield
dr 99:1, 99% *ee*



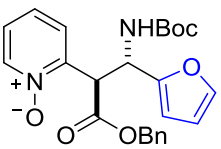
18m
21 h, 95% yield
dr 99:1, 99% *ee*



18n
(5 mol% **C6**)
30 h, 90% yield
dr 99:1, 99% *ee*



18o
10 h, 95% yield
dr 99:1, 99% *ee*



18p
44 h, 93% yield
dr 99:1, 99% *ee*

[a] Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH_2Cl_2 (molar ratio of **17**:**4**, 1:2), unless otherwise stated.[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 stablished by assuming a uniform reaction mechanism.

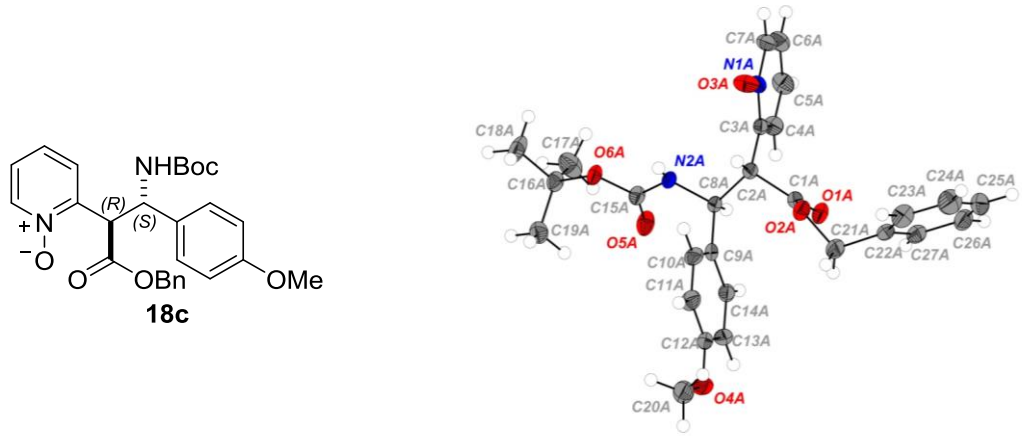
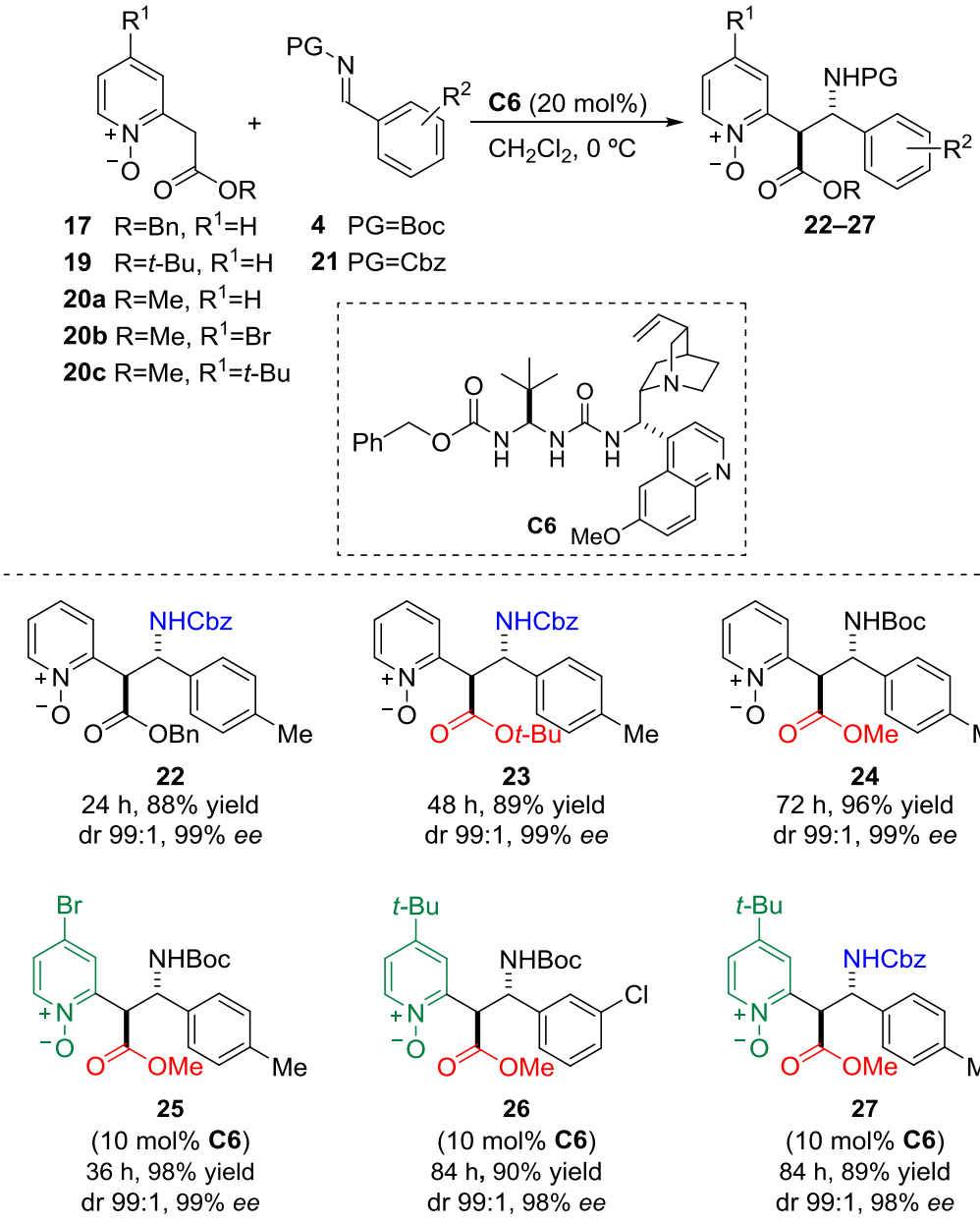


Figure 25. ORTEP diagram of compound **18c**.

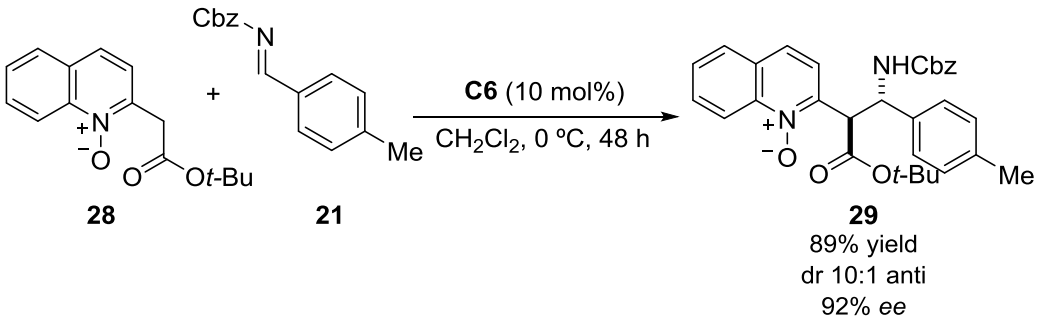
Furthermore, the reaction of benzyl pyridyl *N*-oxide acetate **17** with *N*-Cbz imine **21** produced the corresponding Mannich adduct **22** with identical level of stereocontrol (Table 15). Likewise, *tert*-butyl and methyl pyridyl *N*-oxide acetates **19** and **20a** were also compatible with the 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 adduct 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** with excellent yields and stereoselectivities.

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



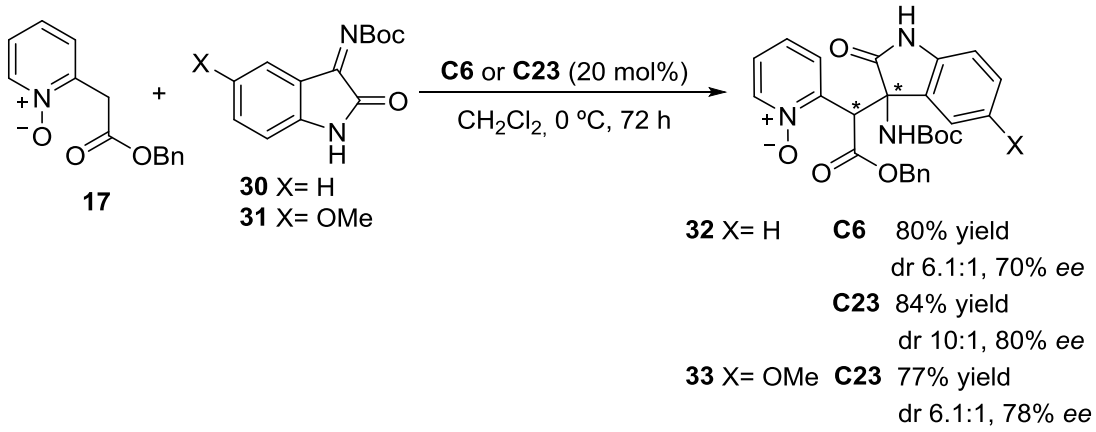
[a] Reactions conducted on a 0.12 mmol scale in 0.5 mL of CH_2Cl_2 (molar ratio of **17/19/20**:**4/21**, 1:2).[b] Diastereomeric ratio determined by ^1H NMR of crude mixture and corroborated by chiral HPLC. [c] Enantiomeric excess determined by chiral HPLC.

Moreover, quinoline *N*-oxide **28** performed well in the reaction with *N*-Cbz imine **21** promoted by catalyst **C6** to afford the corresponding Mannich adduct **29**, albeit with a slightly diminished diastereoselectivity (Scheme 78).



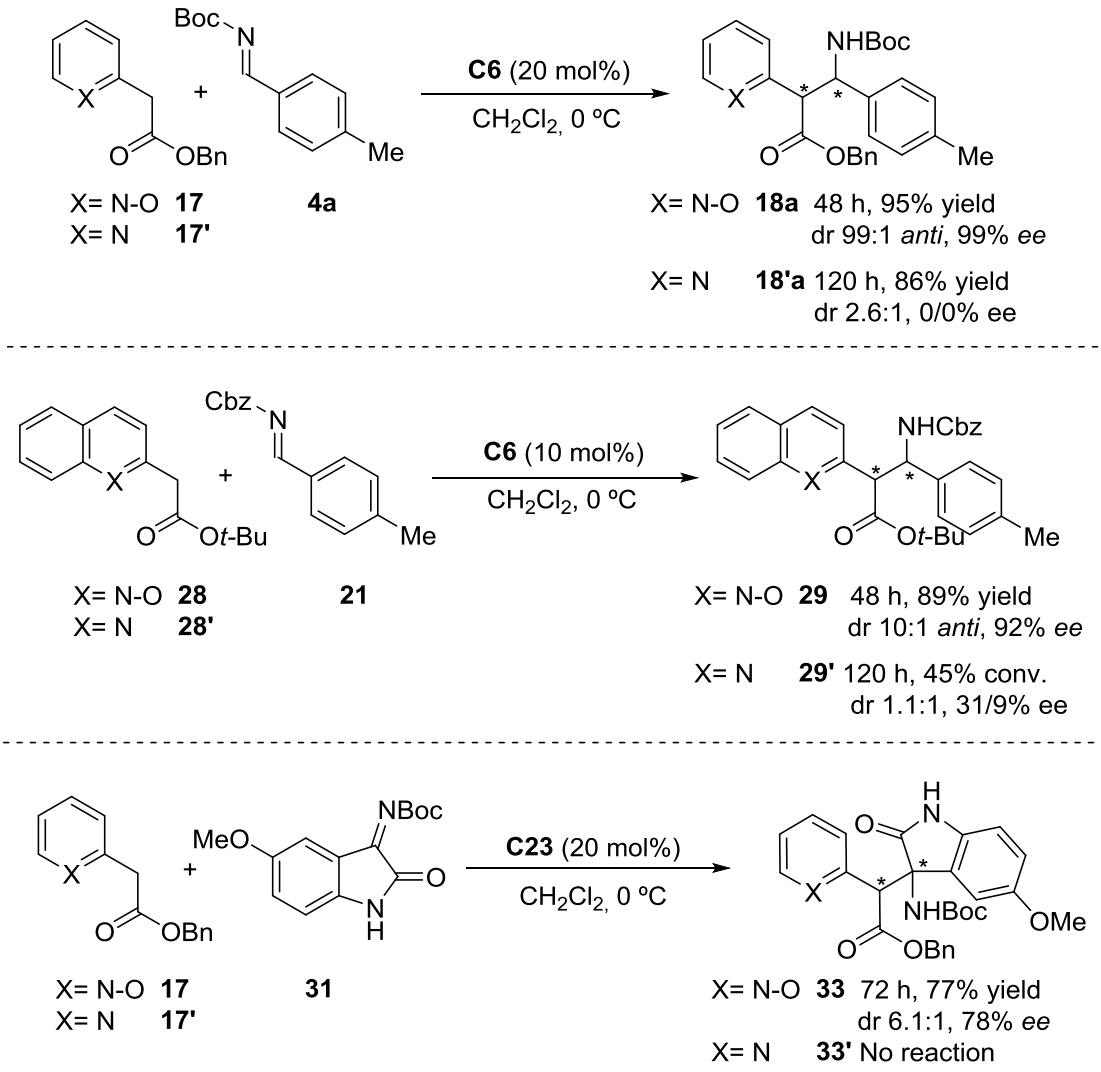
Scheme 78. Enantioselective Mannich reaction with quinoline *N*-oxide **28**.

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 (Scheme 79). 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. 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). 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 sterodirecting group.



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

3.3.2.3. Configurational stability of the Mannich adducts

We were intringued by the configurational stability of the 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* for both diastereomers) (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 Cα carbon. Less hindered and stronger bases, such as Et_3N, DBU, and even the analogous bifunctional urea **C20** promoted epimerization at shorter reaction times at room

temperature (Figure 26) to reach the termodinamic equilibrium (dr 2:1 *anti*:*syn*, 99% *ee* for both diastereomers).

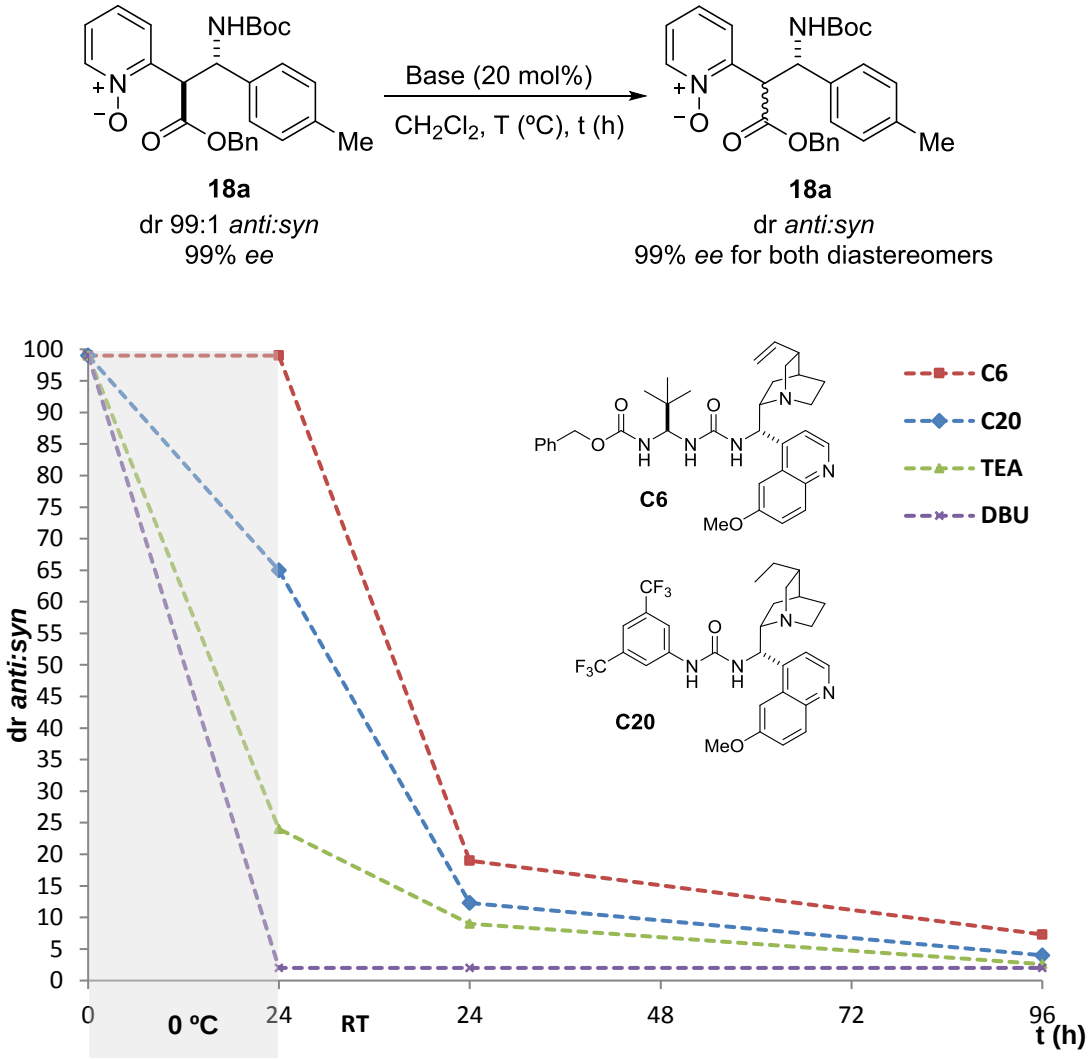


Figure 26. Effect of different Brønsted bases on the configurational stability of the *anti* adducts.

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 reaction model in which multiple hydrogen-bonding may be operating in unison, as depicted in Figure 27. In this way, the *Re* face of the enolate could approach the *Si* face of the *N*-protected imine to afford the corresponding *anti*-*R*,*S*-adducts.

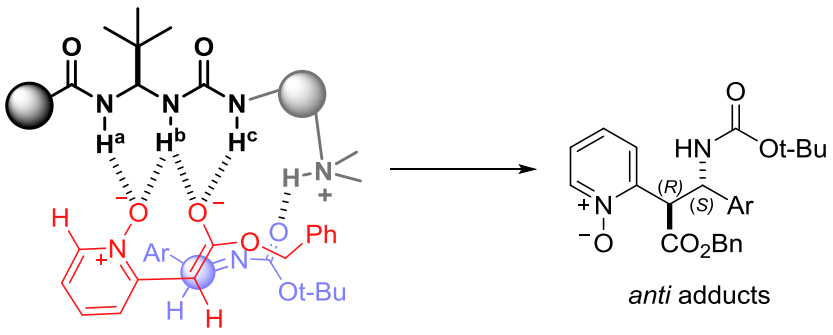


Figure 27. Plausible reaction model.

This 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).[200]

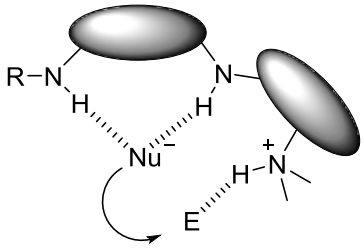


Figure 28. Pápai and Soós' transition state model.

An evidence in favor of this model was found by carrying out ^{1}H NMR studies, since variations of the chemical shifts for selected protons in the 2-pyridyl acetate *N*-oxide **17** were observed in the presence of catalyst **C6**. We recorded the ^{1}H NMR spectra for the pronucleophile **17**, imine **4a** and catalyst **C6** in $CDCl_3$ (0.02 M) at room temperature, separately, and then, the spectra of equimolecular mixtures of **17:C6**, **4a:C6** and **17:4a:C6** in $CDCl_3$ (0.02 M) at room temperature (Figure 29 and Figure 30).

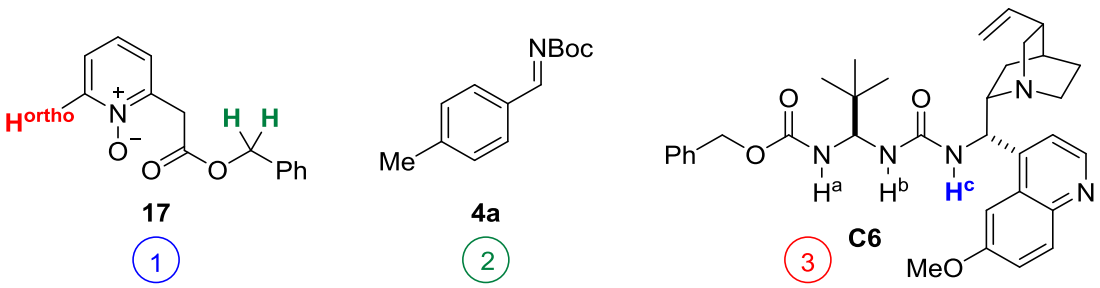


Figure 29. Substrates employed in the study.

[200] 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.

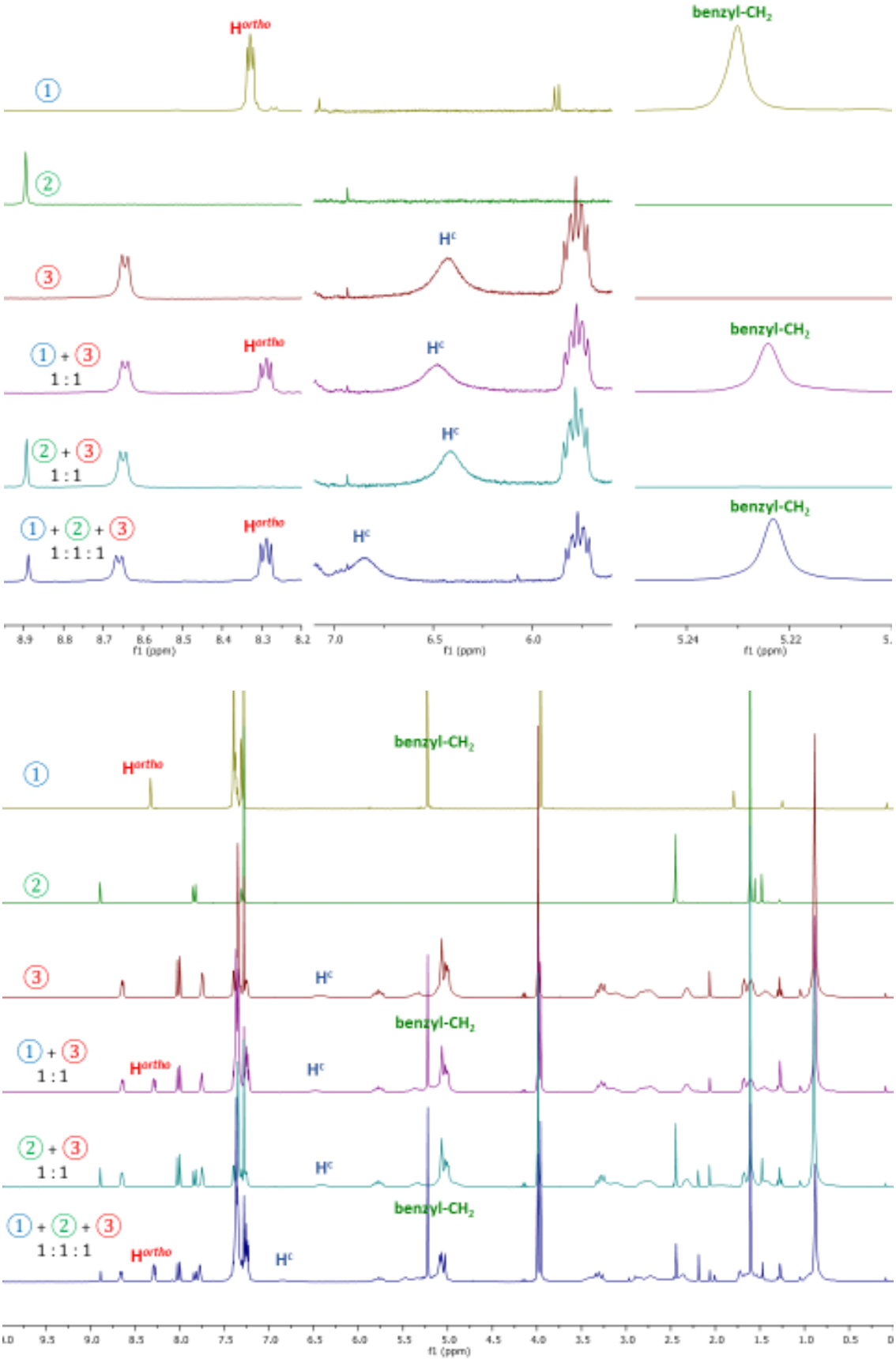


Figure 30. Expanded and full ^{1}H NMR (300 MHz) spectra of equimolecular mixtures.

As data in Table 16 show, upfield shiftings for the *ortho*-H in the pyridine and the benzyl group in **17** were observed (Δδ = –0.04 and –0.02 ppm, respectively) in the presence of catalyst **C6** and in the presence of both catalyst **C6** and imine **4a**. In contrast, no variation in chemical shifts for imine **4a** was detected under the same conditions. More importantly, the chemical shifts of the three N–H in the catalyst were only affected in the presence of the pronucleophile **17**. Variations for H^a and H^b could not be exactly determined due to overlapping, but that for H^c was determined as Δδ = +0.07 ppm (Figure 30).[201]

Table 16. ^{1}H NMR chemical shift variations.

Compound or mixture	H^{ortho}		benzyl-CH_2		N–H^c	
	δ (ppm)	Δδ (ppm)	δ (ppm)	Δδ (ppm)	δ (ppm)	Δδ (ppm)
17	8.33	-	5.24	-	-	-
4a	-	-	-	-	-	-
C6	-	-	-	-	6.42	-
C6 + 17	8.29	–0.04	5.22	–0.02	6.49	+0.07
C6 + 4a	-	-	-	-	6.42	0
C6 + 17 + 4a	8.29	–0.04	5.22	–0.02	6.85	+0.43

Additionally, in an independent study, ^{1}H NMR titration of catalyst **C6** was conducted with increasing amounts of 2-pyridyl acetate *N*-oxide **17** (increments of 0.25 equivalents until saturation) (Figure 31). The chemical shift of the N–H proton H^c was monitored and a possible interaction with the pronucleophile was detected, since downfield shifting was observed.

These observations could support our proposed model in which the deprotonated nucleophile binds to the H-bond network, while the protonated amine activates and orientates the electrophile (Figure 27). Nevertheless, more experimental and theoretical evidences would be required to strongly support this model.

[201] The three N–H groups of the catalyst were unequivocally assigned based on COSY, HSQC and HMBC experiments (see pages 250–252).

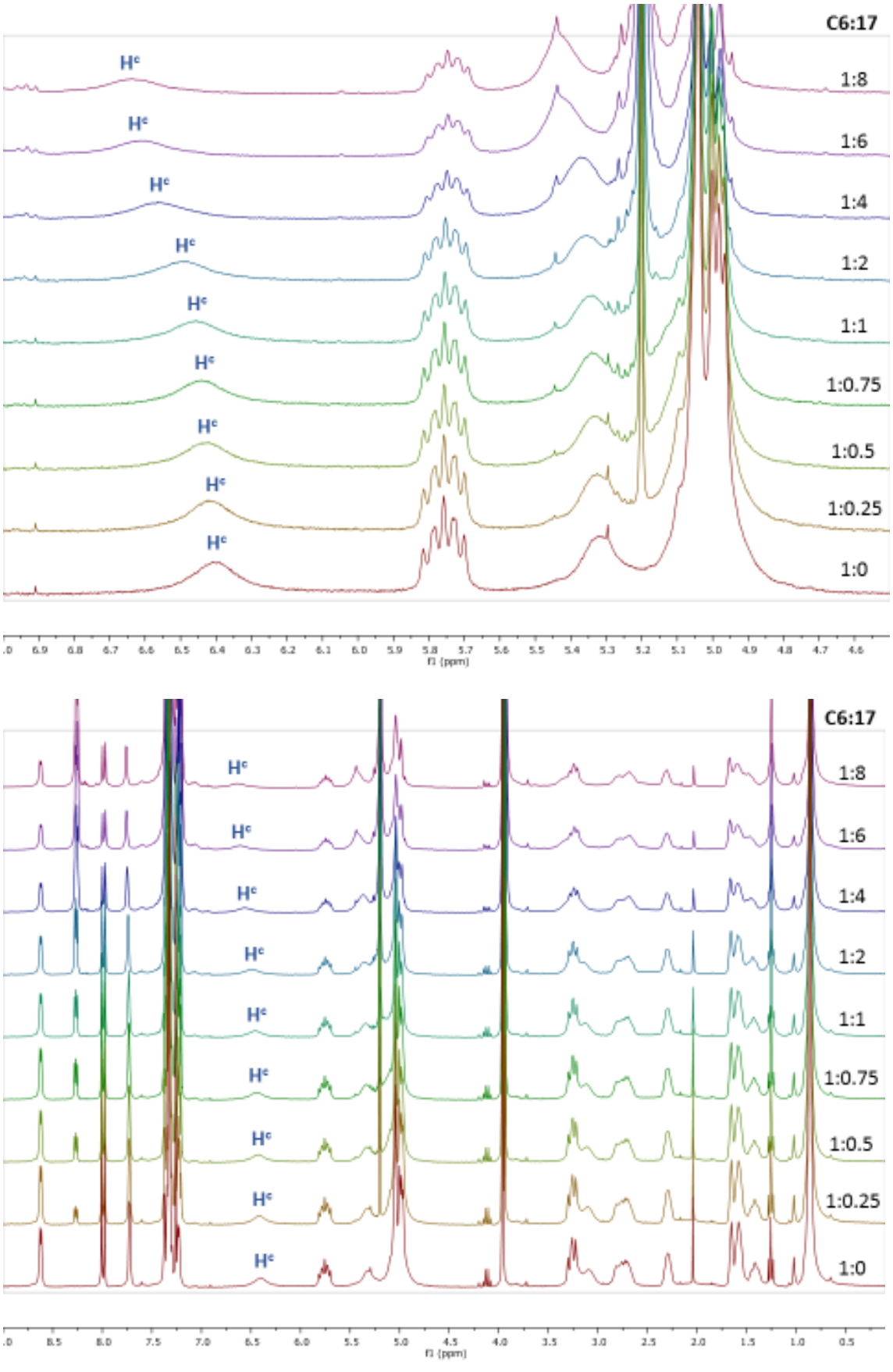
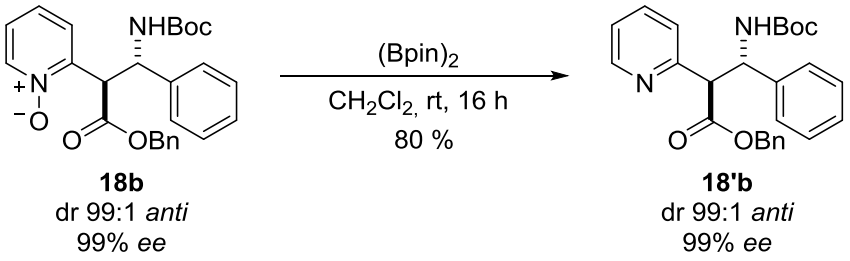


Figure 31. Expanded and full ^{1}H NMR (300 MHz) spectra of catalyst **C6** (0.02 M in $CDCl_3$ at rt) upon the addition of increasing amounts of 2-pyridyl acetate *N*-oxide **17**.

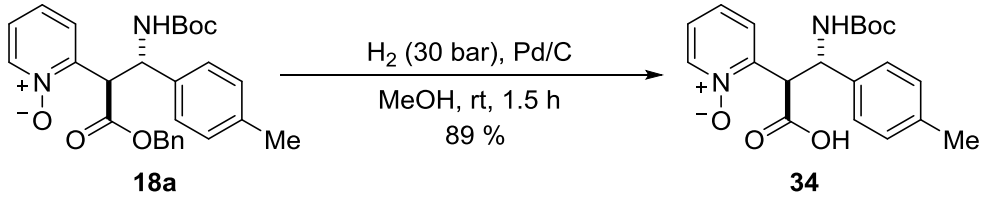
3.3.2.5. Elaboration of adducts

We explored the elaboration of the Mannich adducts in order to evaluate the utility of the present reaction as an effective way to synthetize 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 $B(pin)_2$[197] to afford the corresponding *N*-Boc protected secondary amine **18'b** in 80% isolated yield with unaltered diastereo- and enantioselectivity (Scheme 81).



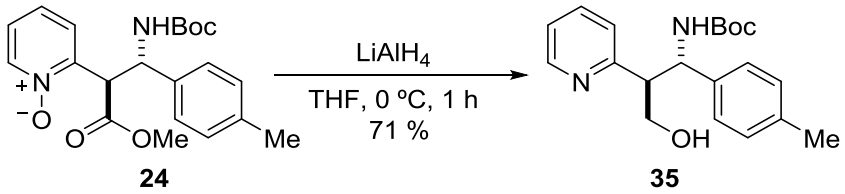
Scheme 81. Reduction of *N*-oxide group on adduct **18b**.

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



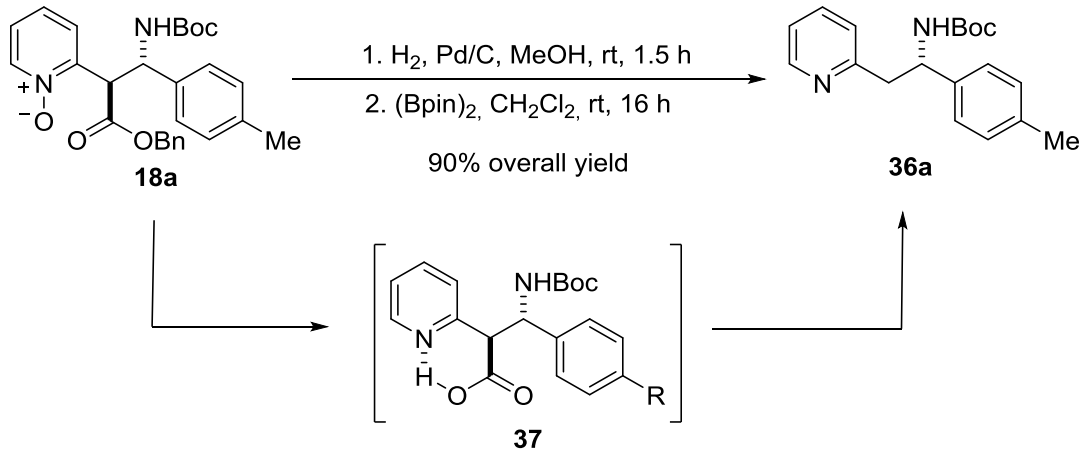
Scheme 82. Synthesis of $\beta^{2,3}$-amino acid **34**.

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).



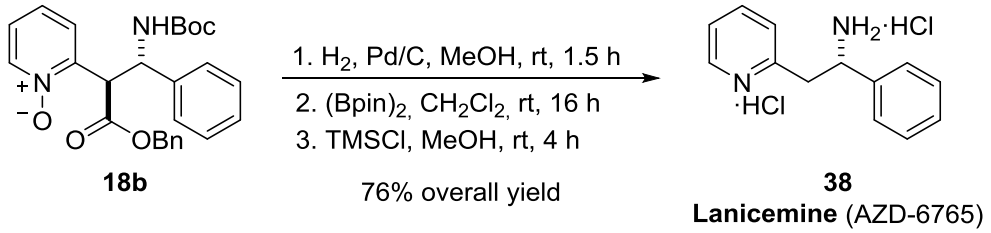
Scheme 83. Synthesis of amino alcohol **35**.

Enantiopure benzyl amines[202] 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.[203] 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**.

Following this methodology, 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.[204]



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

[202] 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.

[203] 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.

[204] 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.; Riesenberg, 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

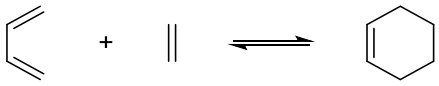
INDEX

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.

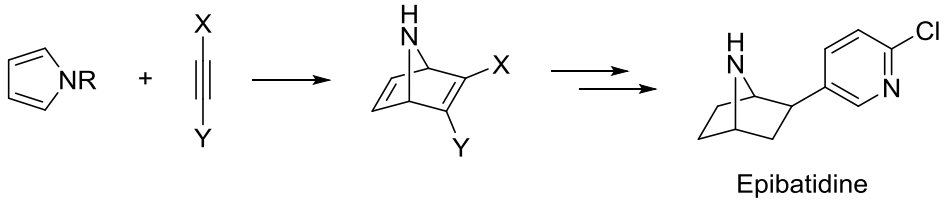
Cycloaddition reactions are considered among the most powerful bond-forming reactions in organic synthesis because of their ability to form many bonds in one step and also for their potential in generating several stereogenic centers (Scheme 86). The reactions happen between two π-systems to form rings 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.[205] 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.

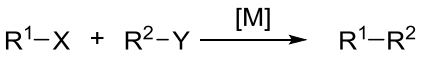
Cycloaddition reactions have featured in numerous total syntheses.[206] As an illustration, epibatidine, valued for its pronounced analgesic properties, has been prepared by total synthesis more than 60 times, from which at least 31 have used cycloaddition chemistry as their key ring-constructing step. The vast majority of these approaches involve formation of the bridged pyrrolidine core, followed by stepwise, and often lengthy, pyridine incorporation (Scheme 87).[207]

[205] Dinda, B. *Essentials of Pericyclic and Photochemical Reactions;* Lecture Notes in Chemistry 93; Springer: Switzerland, 2017.
[206] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.
[207] Olivo, H. F.; Hemenway, M. *Org. Prep. Proced. Int.* **2002**, *34*, 1–25.



Scheme 87. Synthesis of epibatidine.

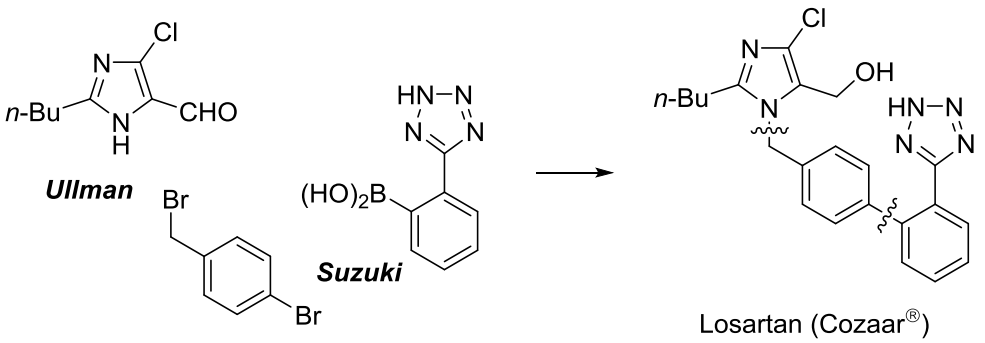
On the other hand, transition metal catalyzed C–C cross-coupling reactions form one new sigma bond, between easily accessible building blocks, in a controllable manner (Scheme 88).[208] Indeed, what C–C cross-coupling lacks in terms of complexity generation, it makes up for by its reliability and modularity.



Scheme 88. Cross-coupling reaction.

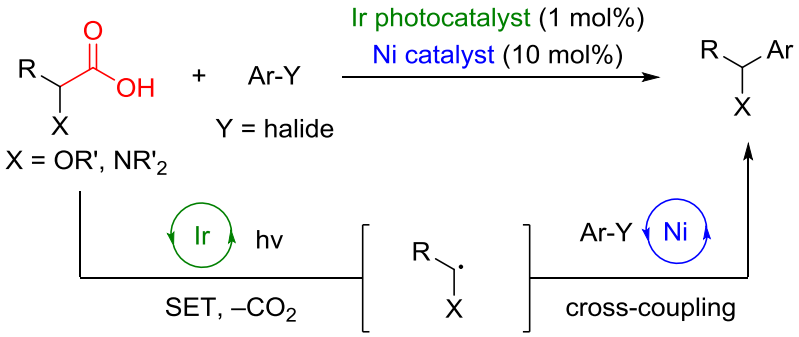
This strategy is one of the most recurrent methodologies for C–C bond forming reactions in the patent literature.[209] For instance, the preparation of the commercial antihypertensive medicine Cozaar®, considered as one of the first examples of a "blockbuster" drug, has employed C–C cross-coupling reactions –Ullman and Suzuki reactions– for the key bond formation, from its initial synthesis to its eventual manufacture (Scheme 89).[210] This approach facilitated both a convergent assembly and a modularity that permitted the rapid exploration of hundreds of analogues.

[208] de Meijere, A.; Bräse, S.; Oestreich, M. *Metal Catalyzed Cross-Coupling Reactions and More*; Wiley-VCH: New York, 2014.
[209] Schneider, N.; Lowe, D. M.; Sayle, R. A.; Tarselli, M. A.; Landrum, G. A. *J. Med. Chem.* **2016**, *59*, 4385–4402.
[210] 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.



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.[211] 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.[212] The only previous example with alkyl carboxylic acids had been reported by MacMillan and co-workers and was limited to α-nitrogen or oxygen substituted carboxylic acids. 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).[213]



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

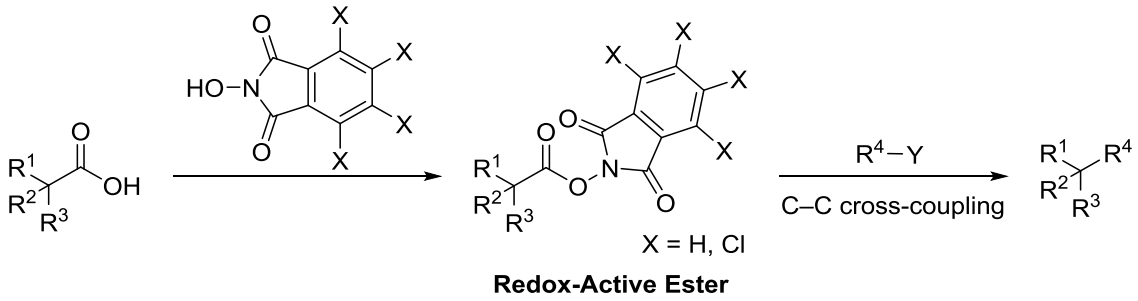
[211] a) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177. b) Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9676–9679. c) 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. d) 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. e) 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.

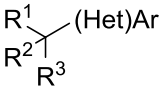
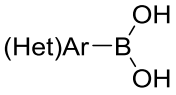
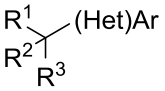
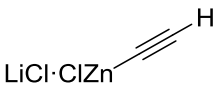
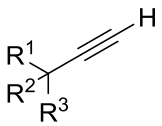
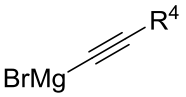
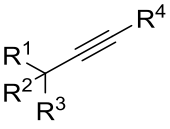
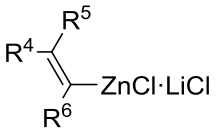
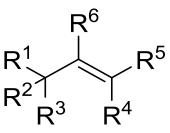
[212] For reviews in the field, see: a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature*, **2014**, *509*, 299–309.

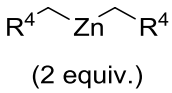
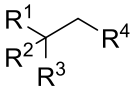
[213] Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; Macmillan, D. W. C. *Science* **2014**, *345*, 437–440.

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 consequence, a wide range of functionalities can be installed, such as aryl or heteroaryl systems,[211a,b] alkynyl,[211c] alkenyl[211d] and alkyl groups[211e] (Table 17).

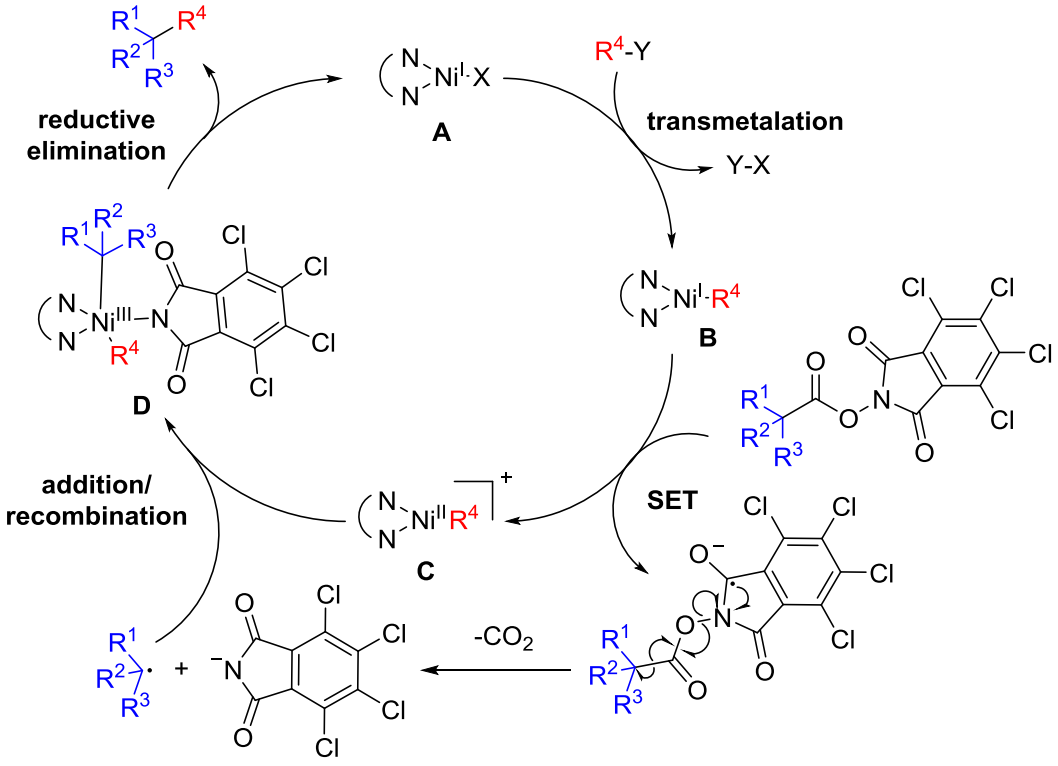
Table 17. C–C cross-coupling reactions developed by Baran and co-workers.



Reaction	R^4-Y	C–C cross-coupling conditions	Product
Arylation (Negishi)[211a]	(Het)Ar–ZnCl·LiCl (3 equiv.)	20 mol% $NiCl_2$·glyme 40 mol% di-*t*-Bubipy THF:DMF (3:2) 25 °C, 16 h	
Arylation (Suzuki)[211b]	 (3 equiv.)	10–20 mol% $NiCl_2·6H_2O$ 10–20 mol% di-*t*-Bubipy/BPhen Et_3N (10 equiv.) 1,4-dioxane:DMF (10:1) 75 °C, 12 h	
Alkynylation[211c]	 (2.5 equiv.)	20 mol% $NiCl_2·6H_2O$ 20 mol% di-MeObipy THF:DMF (3:2) rt, 12 h	
	 (1.5 equiv.)	20 mol% $FeBr_2·H_2O$ NMP:THF (3:2) –15 °C, 15 min	
Alkenylation[211d]	 (2 equiv.)	10 mol% $Ni(acac)_2·xH_2O$ 10 mol% bipy THF:DMF (3:2) rt, 12 h	

Reaction	R^4-Y	C–C cross-coupling conditions	Product
Alkylation[211e]	 (2 equiv.)	20 mol% $NiCl_2$·glyme 40 mol% bipy/di-*t*-Bubipy THF:DMF (3:2) 25 °C, 8–14 h	

A plausible reaction mechanism was postulated for the nickel-catalyzed decarboxylative C–C cross-coupling reactions (Scheme 91). The authors proposed that Ni(I)-X complex **A** transmetalates with the coupling partner to produce Ni(I)-R^4 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)-R^4]$^+$ complex **C**. Fragmentation of the former, followed by extrusion of CO_2, generates the phtalimide anion and the desired radical species. At this point, recombination of the radical species and the phthalimide anion with [Ni(II)-R^4]$^+$ complex **C** renders the Ni(III) intermediate **D**, which upon reductive elimination affords the desired cross-coupling product and close the catalytic cycle.

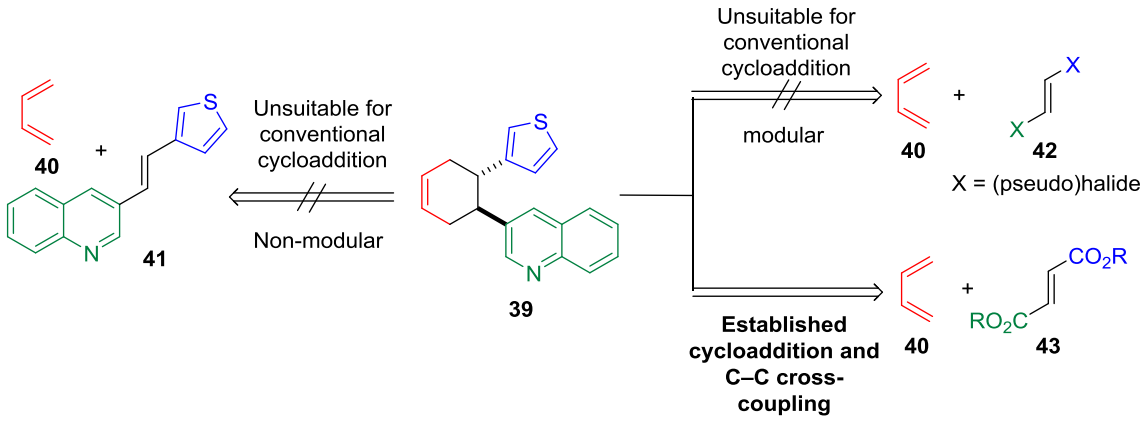


Scheme 91. Plausible mechanism for the nickel-catalyzed decarboxylative C–C cross-coupling reaction.

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.

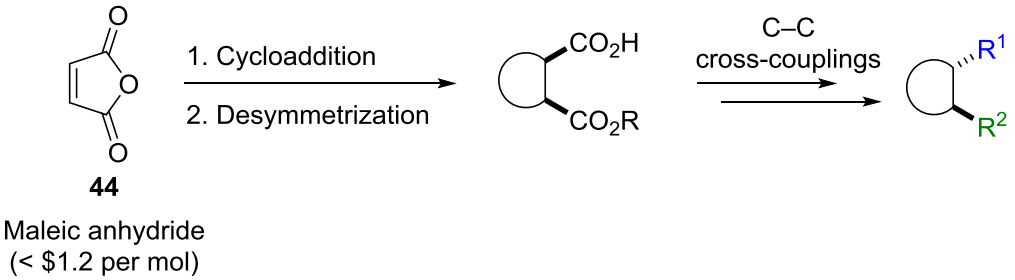
For instance, building block **39**, of hypothetical value in medicinal chemistry, represents the manifestation of this idea (Scheme 92). The Diels-Alder reaction of the relevant building blocks **40** and **41**, which are not electronically matched, is expected to not take place. In addition, even if 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.[214]

[214] 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 32), thus the [2+1] cycloaddition reaction was not explored.

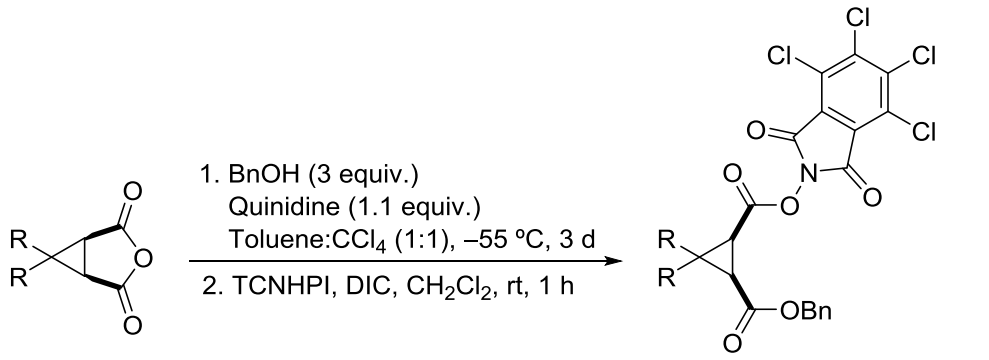
45
caronic anhydride

46
1,2-cyclopropanedicarboxylic anhydride

Figure 32. Starting materials.

4.3.1. Desymmetrization step

The desymmetrization of anhydrides **45** and **46** was conducted by quinidine-mediated alcoholisis with benzyl alcohol at low temperature.[215] 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).



45 R = Me
46 R = H

47 R = Me, 78% yield, 96% *ee*
48 R = H, 74% yield, 96% *ee*

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

[215] Procedure adapted from: Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry*, **2003**, *14*, 3455–3467.

4.3.2. Decarboxylative cross-coupling reactions

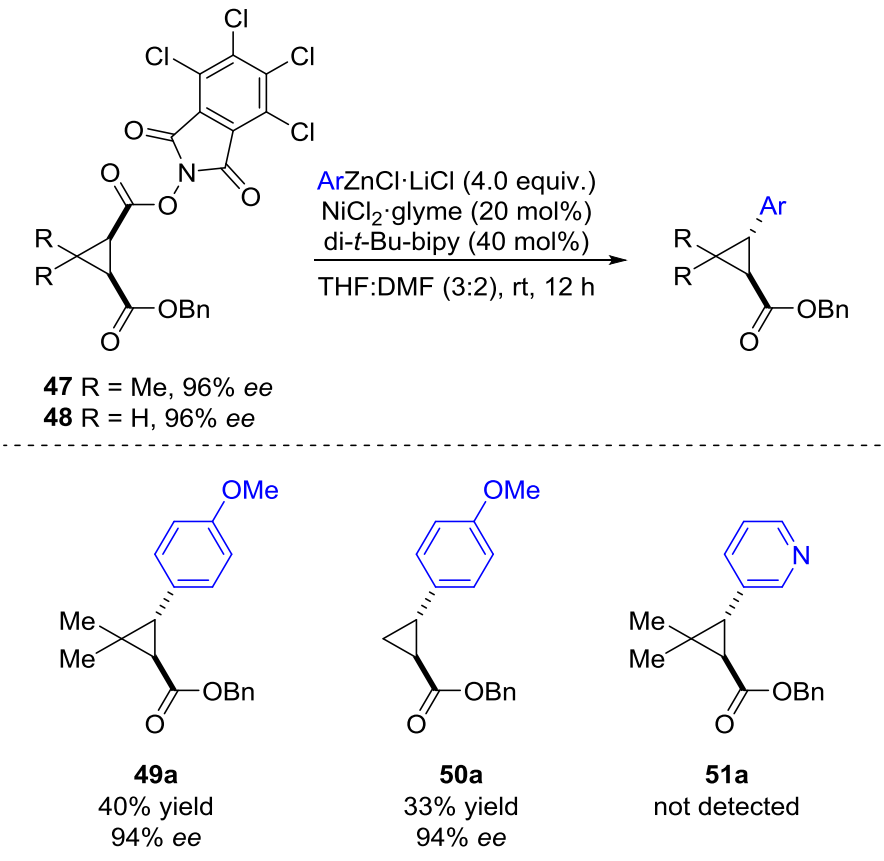
Next, the decarboxylative cross-coupling reaction, employing different coupling partners and conditions, was studied for redox-active esters **47** and **48.**

4.3.2.1. Negishi cross-coupling reactions

4.3.2.1.1. Negishi arylation

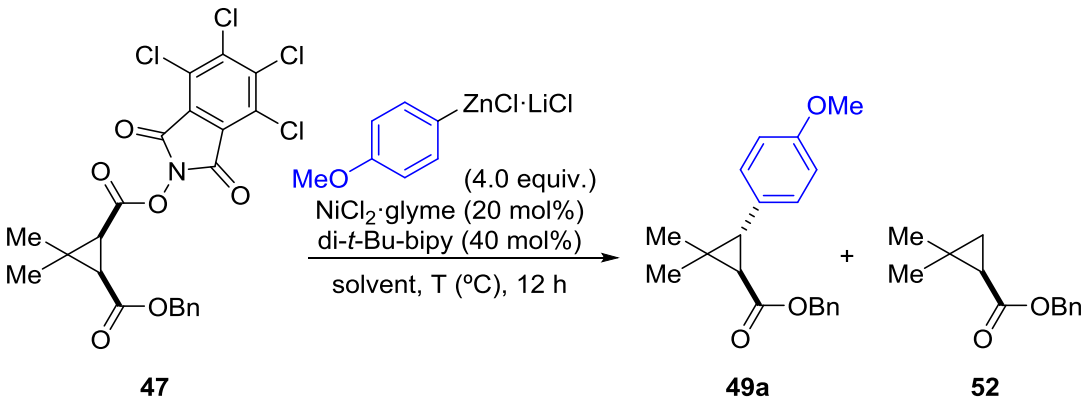
First, the nickel-catalyzed Negishi arylation reaction was explored employing similar conditions to those developed previously in the group for the same reaction (Table 18).[211a] Unfortunately, aryl adducts **49a** and **50a** were obtained in low yields and product **51a** was not even detected. Furthermore, 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 18. Preliminary experiments for Negishi arylation.



Then, we decided to evaluate the arylation reaction of **47** in other solvents to minimize the H-abstraction side-reaction (Table 19). 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 19. Optimization of the Negishi arylation reaction.



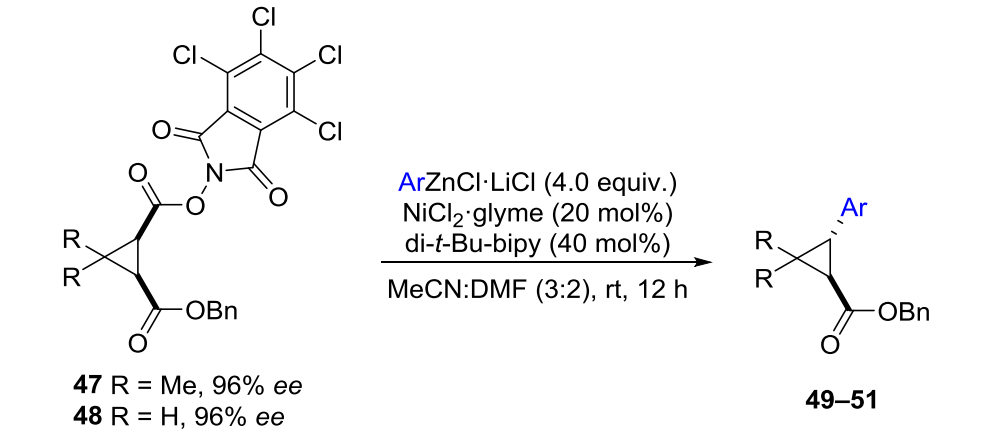
47 **49a** **52**

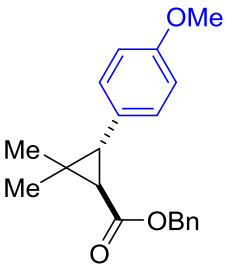
Entry	Solvent system	T (°C)	49a:52[b]	Yield[c]
1	THF:DMF (3:2)	rt	64:36	45 (40)
2	THF:DMF (3:2)	60	62:38	45
3	DMF	rt	71:29	52
4	dioxane:DMF (3:2)	rt	66:34	50
5	toluene:DMF (3:2)	rt	76:24	54
6	**MeCN:DMF (3:2)**	**rt**	**91:9**	**60 (56)**
7	Et_2O:DMF (3:2)	rt	73:27	56
8	CH_2Cl_2:DMF (3:2)	rt	78:22	42
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 in parentheses.

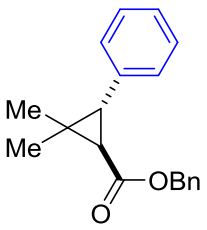
With these optimal conditions in hand, the scope of the transformation was then explored (Table 20). Acceptable yields were obtained in the reactions with both electron-rich and electron-poor aryl groups for redox-active esters **47** and **48**, being the use of heteroaryl groups an exception; compounds **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 20. Negishi arylation scope.

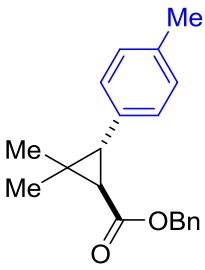




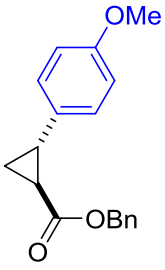
49a
56% yield
94% *ee*



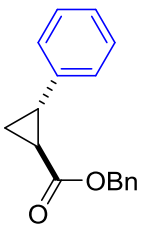
49b
54% yield
97% *ee*



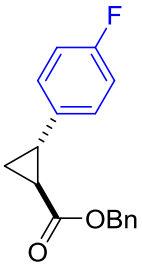
49c
47% yield
96% *ee*



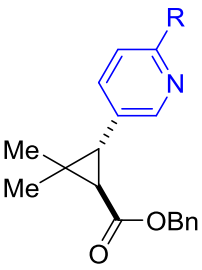
50a
40% yield
94% *ee*



50b
50% yield
94% *ee*



50d
42% yield
94% *ee*

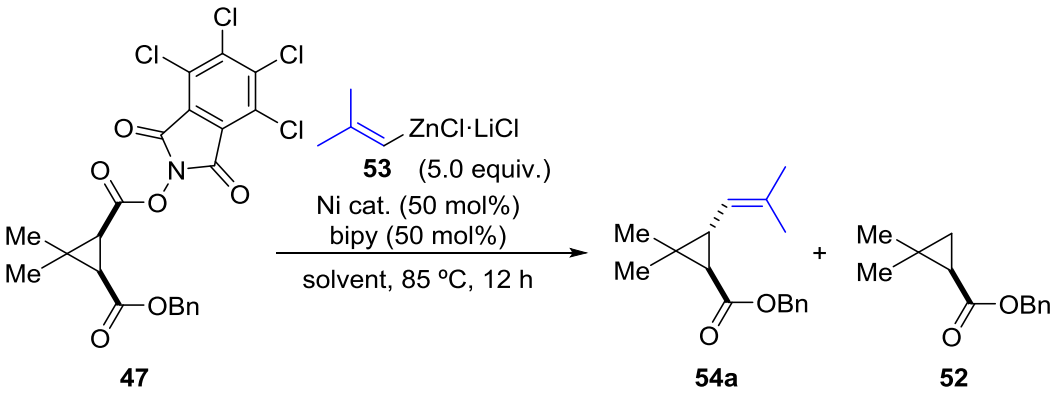


51a R=H: not detected
51b R=Cl: traces (at 60ºC)

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.[211d] The alkenylation reaction of **47** with the organozinc reagent **53** was studied and, as data in Table 21 show, among all nickel sources tested, $Ni(acac)_2 \cdot H_2O$ 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 deoxigenation of the solvent or the absence of light had meaningless impact in the reaction outcome (entries 9 and 10).

Table 21. Optimization of Negishi alkenylation.

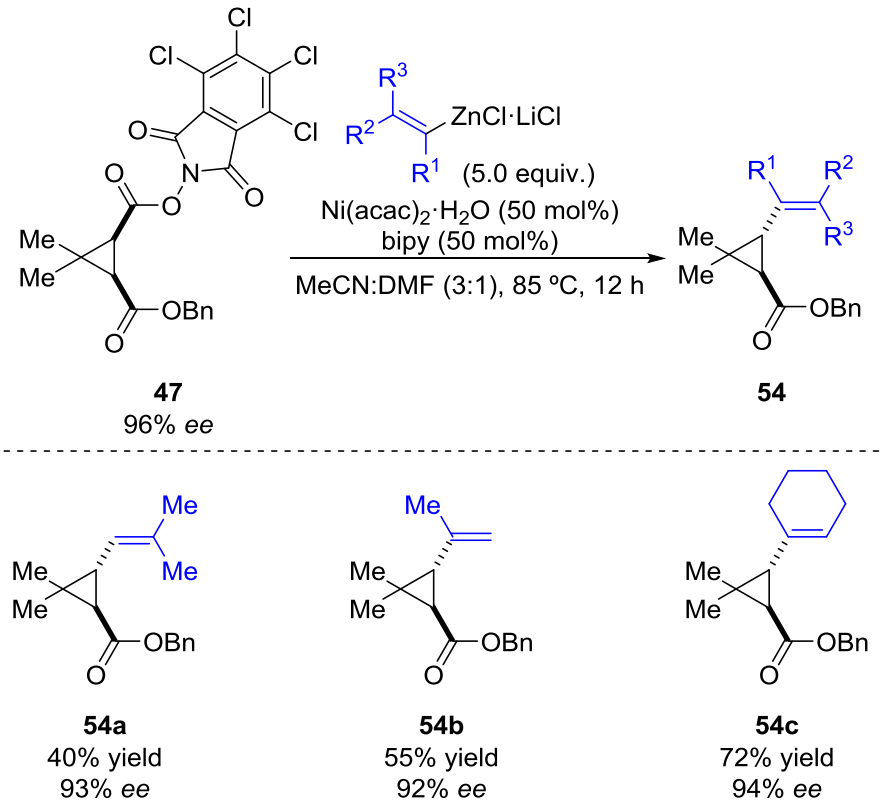


Entry	Ni source	Solvent system	54a:52[b]	Yield[c]
1	$Ni(acac)_2 \cdot H_2O$	DMF	55:45	36 (35)
2	$NiCl_2$·glyme	DMF	20:80	17
3	$NiBr_2$·glyme	DMF	68:32	14
4	$NiCl_2 \cdot 6H_2O$	DMF	69:31	33 (30)
5	**$Ni(acac)_2 \cdot H_2O$**	**MeCN:DMF (3:1)**	**82:18**	**42 (40)**
6	$Ni(acac)_2 \cdot H_2O$	toluene:DMF (3:1)	63:37	27 (25)
7	$NiCl_2 \cdot 6H_2O$	MeCN:DMF (3:1)	78:22	24
8	$Ni(ClO_4)_2 \cdot H_2O$	MeCN:DMF (3:1)	75:25	29
9[d]	$Ni(acac)_2 \cdot H_2O$	MeCN:DMF (3:1)	86:14	32
10[e]	$Ni(acac)_2 \cdot H_2O$	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 in parentheses. [d] MeCN was previously purged. [e] Reaction carried out in absence of light.

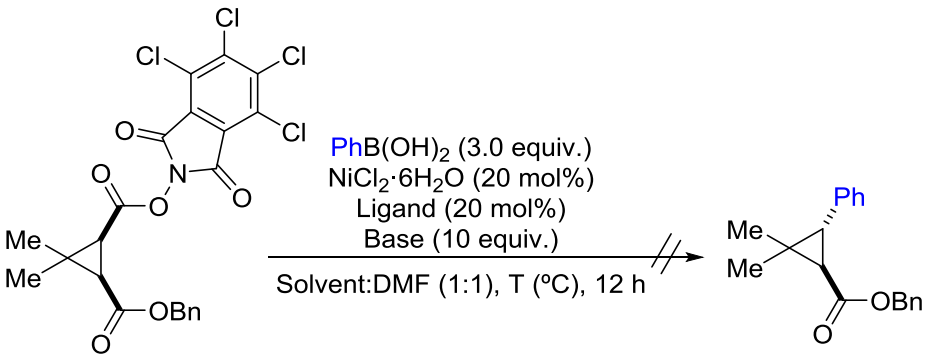
The reaction with the redox-active ester **47** was performed in the presence of several alkenylzinc reagents and the corresponding adducts **54a–54c** were produced as only one detectable diasteroisomer and with almost unaltered enantiomeric excess (Table 22).

Table 22. 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 group[211b] did not produce the corresponding *trans*-disubstituted cyclopronane **49b**. Furthermore, the evaluation of other ligands, bases and solvent systems resulted ineffective (Scheme 95).



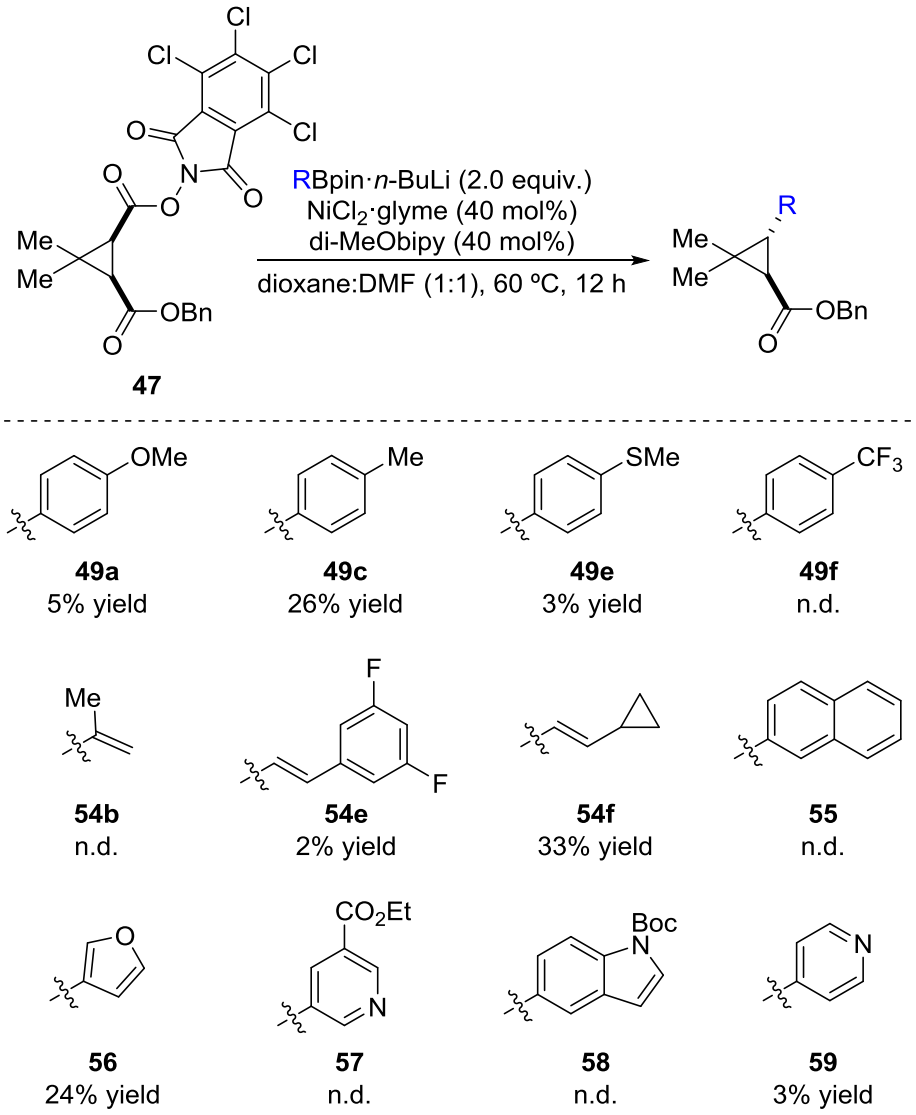
47 **49b**

Ligands: di-*t*-Bubipy, bipy, Bphen
Bases: Et_3N, DIPEA, K_2CO_3, *t*-BuOK
Solvents: dioxane, DMF, toluene, MeCN, *t*-BuOH
T (ºC): 75 and 85 ºC

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 23).

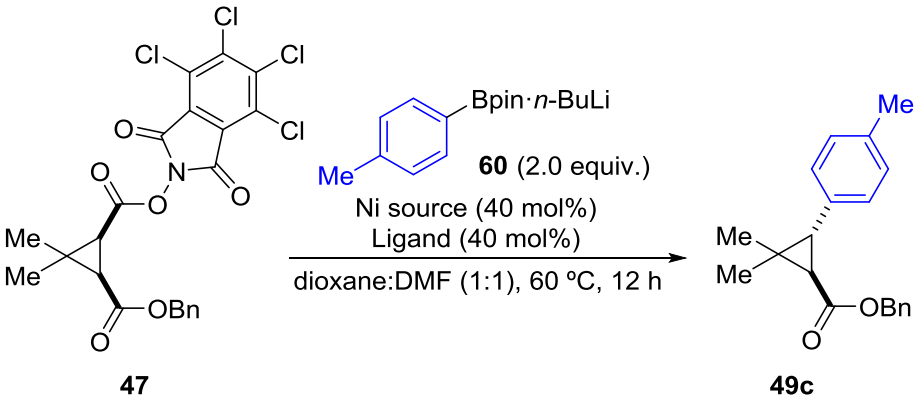
Table 23. Preliminary experiments for Suzuki cross-coupling with pinacol boronate esters.



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 24). 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 $NiCl_2$·glyme and di-Meobipy as the catalytic system, variations in the stoichiometry of the reagents, the use of additives ($MgBr_2$·OEt_2, LiBr and $ZnCl_2$) or different solvents were also detrimental.

Table 24. Ni source and ligand screening for the Suzuki cross-coupling reaction with **62.**

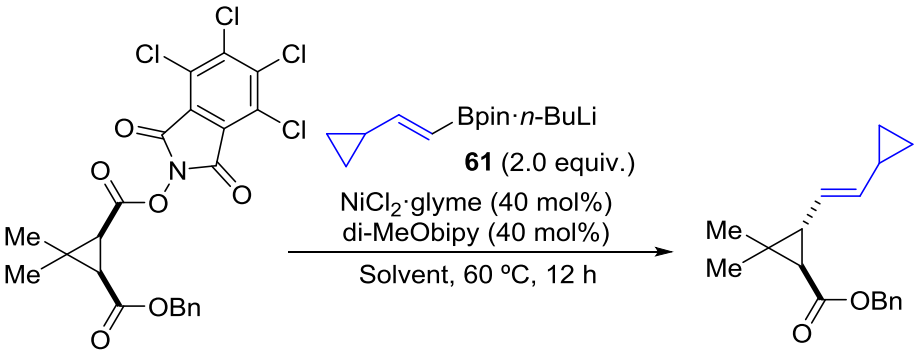


Entry	Ni source	Ligand	Yield[b]
1	**$NiCl_2$·glyme**	**di-Meobipy**	**26**
2	$NiBr_2$·glyme	di-Meobipy	10
3	$Ni(acac)_2·H_2O$	di-Meobipy	0
4	$NiCl_2·6H_2O$	di-Meobipy	0
5	$NiCl_2$·glyme	di-*t*-Bubipy	24
6	$NiCl_2$·glyme	bipy	16
7	$NiCl_2$·glyme	Bphen	10
8	$NiCl_2$·glyme[c]	di-Meobipy[c]	11

[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 $NiCl_2$·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 25) 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 25. Optimization of the Suzuki cross-coupling reaction with **63.**



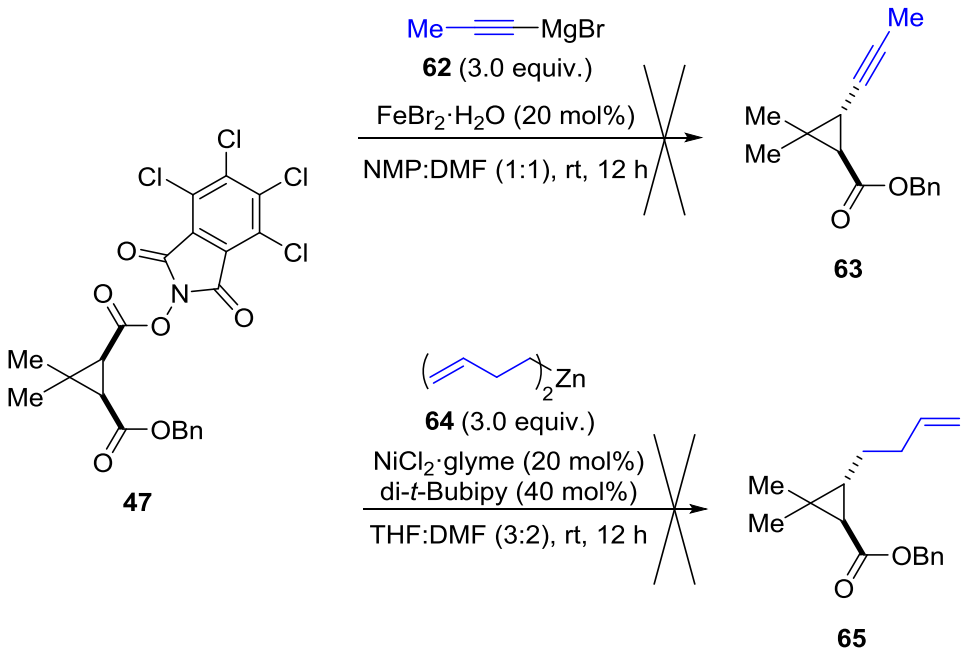
47 **54f**

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)** **95% *ee***
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 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 alkynylation[211c] of the redox-active ester **47** with the Grignard reagent **62** and the nickel-promoted alkylation[211e] of **47** with the dialkylzinc reagent **64** did not afford the desired products (Scheme 96).

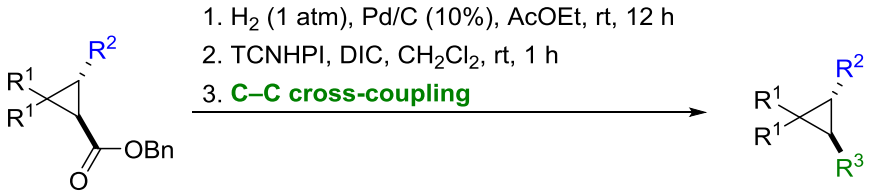


Scheme 96. Unsuccessful cross-coupling reactions.

4.3.3. Synthesis of *trans*-disubstituted cyclopropanes

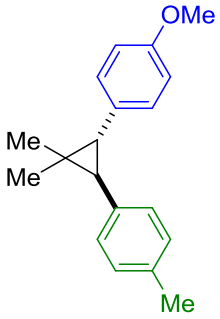
Finally, with the above adducts in hand, completion of the synthesis of *trans*-disubstituted cyclopropanes **66–70** was carried out. To this end, products **49a** and **50d** were debenzylated *via* Pd-catalyzed hydrogenation and activated with tetrachloro-*N*-hydroxyphthalimide. Then, the resulting redox-active esters were subjected to further cross-coupling with the corresponding organozinc or organoboron compounds under the conditions shown in Table 26. In these cases, slightly higher catalytic charges were employed in order to increase the reaction yields. Accordingly, *trans*-disubstituted cyclopropanes **66–70** were successfully synthetized in acceptable yields and with excellent enantiomeric excesses (Table 26).

Table 26. Synthesis of *trans*-α,β-disubstituted cyclopropanes **66–70**.



49a/50d **66–70**

Negishi arylation	**Negishi alkenylation**	**Suzuki**
ArZnCl·LiCl (4 equiv.)	RZnCl·LiCl (5 equiv.)	RBpin·*n*-BuLi (2 equiv.)
$NiCl_2$·glyme (40 mol%)	$Ni(acac)_2·6H_2O$ (60 mol%)	$NiCl_2$·glyme (60 mol%)
di-*t*Bu-bipy (60 mol%)	bipy (60 mol%)	di-MeO-bipy (60 mol%)
MeCN:DMF (3:2), rt, 12 h	MeCN:DMF (3:1), 80 ºC, 12 h	Tol:DMF (1:1), 60 ºC, 12 h

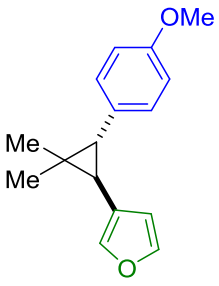


66

Suzuki: 55% yield, 94% *ee*

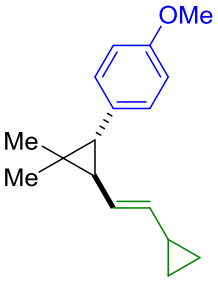
Negishi (20 mol%): 36% yield

Negishi (40 mol%): 40% yield



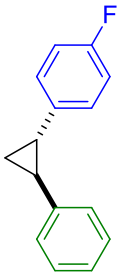
67

Suzuki: 54% yield, 95% *ee*



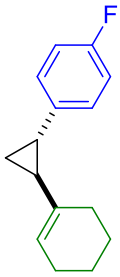
68

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.[216]

[216] 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*-carbamoyl 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 the desymmetrization of *meso*-anhydrides and two subsequent nickel catalyzed decarboxylative C–C cross-coupling reactions.

Chapter 6

Experimental section

INDEX

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**[217] and *N*-Boc isatin ketimines **30** and **31**[218] were synthesized following described procedures. Azodicarboxylates **14** were purchased from Sigma-Aldrich, stored at –30 °C and used without previous purification. $NiCl_2$·glyme and $Ni(acac)_2 \cdot xH_2O$ were purchased from Strem, bipyridine ligands (2,2'-bipyridine, 4,4'-di-*tert*-butylbipyridine and 4,4'-di-OMe-

[217] 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.
[218] 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 °C under nitrogen.

When anhydrous solvents were required, they were dried following established procedures.[219] Dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. For the work in chapter 4, etrahydrofuran (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, ≥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, Ficher Bioblock lamp VL-4LC, λ= 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 (40-63 μm, 230-400 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 °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.

[219] 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 (δ –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) ($[\alpha]_D^T$) are reported in 10^{-1}

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

6.1.10. X-Ray diffraction analysis

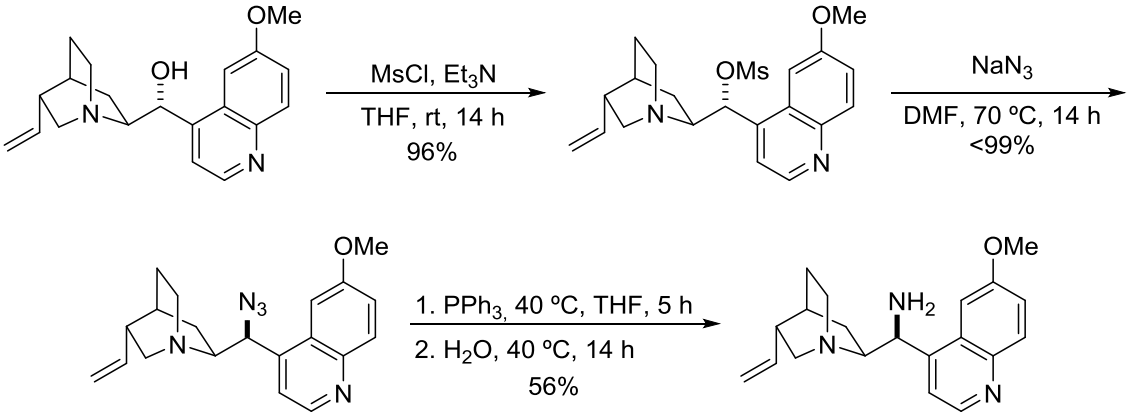
X-ray diffraction analysis experiments were conducted in the General Research Service (SGIKer) of the University of the Basque Country (EHU-UPV) using difractometers for monocrystals.

6.2. Synthesis of catalysts

Catalysts **C9**,[220] **C19**[221] and **C20**[222] 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:[223] 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 CH_2Cl_2 (60 mL) and washed with water (40 mL) and saturated $NaHCO_3$ (2 x 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the crude product (96% yield) which was used in the next step without further purification.

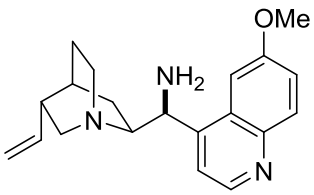
2nd step:[224] The crude of the corresponding mesylated *Cinchone* (1 equiv., 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and sodium azide (2 equiv., 96 mmol, 6.2 g) was added portionwise. The mixture was stirred at 70 °C for 16 hours and after this time the reaction mixture was quenched with water (80 mL) and

[220] Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450–5453.
[221] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett*. **2005***, 7*, 1967–1969.
[222] Greenaway, K.; Dambruoso, P.; Ferrali, A.; Hazelwood, A. J.; Sladojevich, F.; Dixon, D. J. *Synthesis* **2011**, *12*, 1880–1886.
[223] Adapted from: Zielińska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis* **2006**, *7*, 1176–1182.
[224] Adapted from: Sundermeier, U.; Döbler, C.; Mehltretter, 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 $MgSO_4$, filtered and evaporated under reduced pressure to afford the crude azide in quantitative yield, which was used in the next step without further purification.

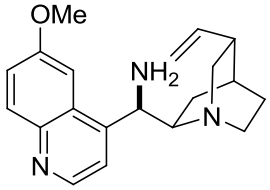
3rd step:[224] The crude azide product was dissolved in dry THF (250 mL) and PPh_3 (1 equiv., 48 mmol, 12.6 g) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (≈5 hours). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (150 mL). HCl 6M (250 mL) was added and the aqueous phase was extracted and washed with dichloromethane (2 × 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 CH_2Cl_2 (3 × 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the corresponding 9-amino-9-deoxy-9-*epicinchone.*

9-Amino-9-deoxy-9-*epi*quinine[225]



9-Amino-9-deoxy-*epi*quinine was synthetized following the general procedure employing quinine as starting material. Yield: 9.06 g (56%). Brown viscous oil. $[\alpha]_D^{25}$= +80 (c=1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J*= 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J*= 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

9-Amino-9-deoxy-9-*epi*quinidine[225b,226]

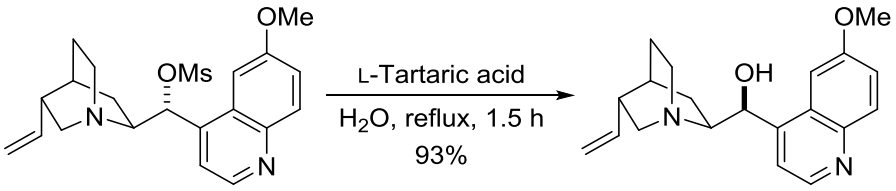


9-Amino-9-deoxy-*epi*quinidine was synthetized following the general procedure employing quinidine as starting material. Yield: 8.25 g (51%). Brown viscous oil. $[\alpha]_D^{22}$= +69 (c=2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J*= 4.3 Hz, 1H), 7.64–8.14 (m, 2H), 7.55 (d, *J*= 4.6 Hz, 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).

[225] 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.

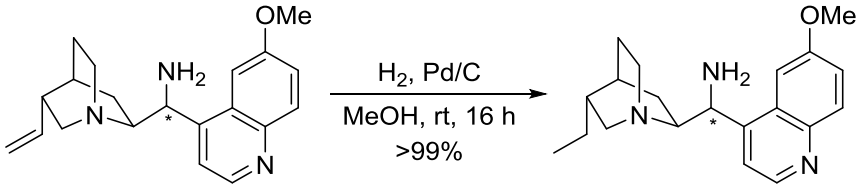
[226] Physical and spectroscopic data were coincident with the previously reported: Brunner, H.; Schmidt, P. *Eur. J. Org. Chem*. **2000**, 2119–2133.

6.2.1.2. Preparation of 9-*epi*quinine[227]



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 H_2O (140 mL) was stirred at reflux for 1.5 hours. Then, the reaction mixture was cooled to room temperature and a saturated solution of $NaHCO_3$ (200 mL) was added and it was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-*epi*quinine. Yield: 9.08 g (93%). Brown solid. $[\alpha]_D^{24}$= +25.8 (c=1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 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).

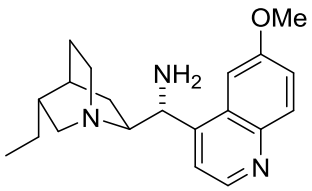
6.2.1.3. Preparation of 9-amino-9-deoxyhydroquinines



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 H_2 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.

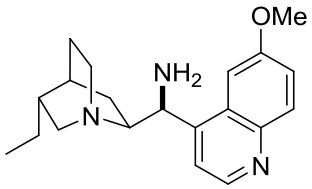
[227] Adapted from: Braje, W. M.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2085–2087.

9-Amino-9-deoxyhydroquinine



9-Amino-9-deoxyhydroquinine was prepared following the general procedure for the preparation of chiral amines (see page 163) 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}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-*epi*hydroquinine



9-Amino-9-deoxy-9-*epi*hydroquinine 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}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).

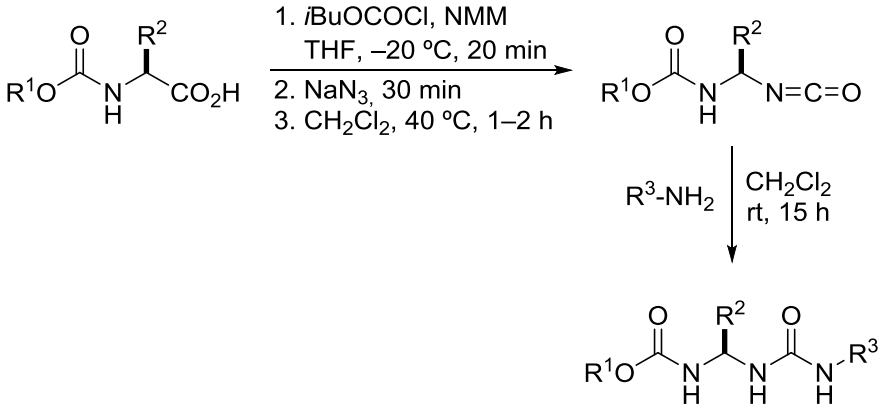
6.2.1.4. Preparation of (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine[228]

To a mixture of (1*S*,2*S*)-cyclohexane-1,2-diamine (1 equiv., 10 mmol, 1.14 g) and $NaBH(OAc)_3$ (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 6 M 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 (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexanamine which was used in next step without further purification. Yellow oil. Yield: 1.62 g (89%). ^{1}H NMR (300 MHz, CDCl3) 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).

[228] 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

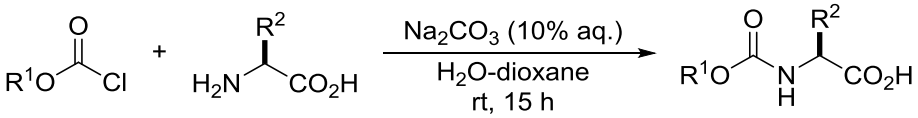
Ureidopeptide-based Brønsted base catalysts were prepared according to the following general scheme:



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

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

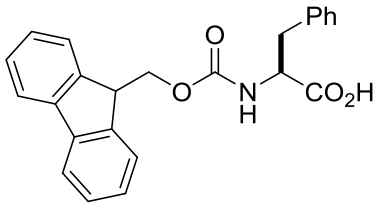
6.2.2.1.1. Procedure A using chloroformates[229]



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.

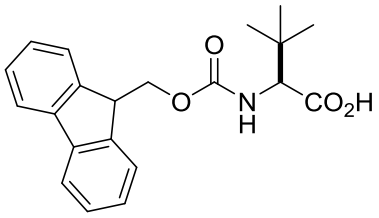
[229] Adapted from: Bain, J. D.; Wacker, D. A.; Kuo, E. E.; Chamberlin, A. R. *Tetrahedron* **1991**, *47*, 2389–2400.

_N_-(((9H-Fluoren-9-yl)methoxy)carbonyl)-L-phenylalanine



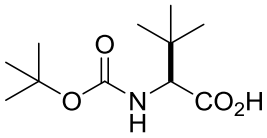
The title compound was prepared from (9H-fluoren-9-yl)methyl chloroformate and L-phenylalanine according to the general procedure A. Yield: 3.60 g (93%). White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 2H), 7.71 (d, 1H), 7.64 (t, 2H), 7.40 (t, 2H), 7.33 – 7.19 (m, 8H), 4.20 – 4.16 (m, 4H), 3.10-3.06 (m, 1H), 2.90-2.84 (m, 1H) ^{1}H 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



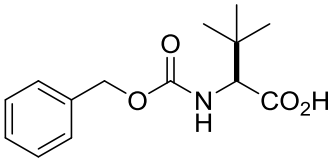
The title compound was prepared from (9H-fluoren-9-yl)methyl chloroformate and L-tert-leucine according to the general procedure A. Yield: 3.39 g (95%). White foam. ^{1}H NMR (300 MHz, CD_3OD) δ 7.78 (d, J = 7.5, 2H), 7.68 (d, J = 6.7, 2H), 7.39 (t, J = 7.5, 2H), 7.30 (dt, J = 7.5, 1.0, 2H), 4.50 (s,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



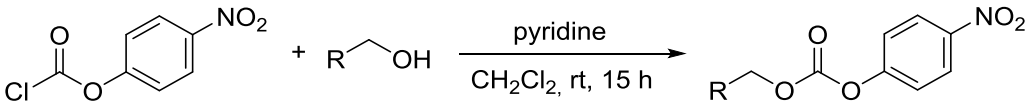
The title compound was prepared from *tert*-butyl chloroformate and L-tert-leucine according to the general procedure A. White foam. Yield: 2.29 g (99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 8.5, 1H), 4.18 – 4.07 (m, 1H), 1.45 (s, 9H), 1.02 (s, 9H).

_N_-(Carboxybenzyl)-L-tert-leucine

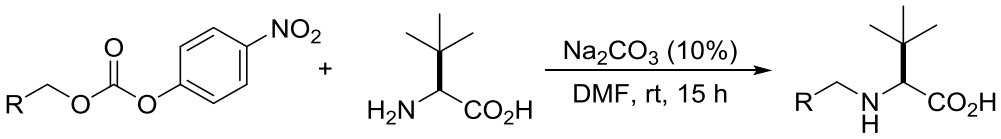


The title compound was prepared from benzyl chloroformate and L-tert-leucine according to the general procedure A. Yield: 2.38 g (91%). White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.33 (d, J = 9.6, 1H), 5.12 (s, 2H), 4.21 (d, J = 9.5, 1H), 1.02 (s, 9H).

6.2.2.1.2. Procedure B using 4-nitrophenyl carbonates[230]

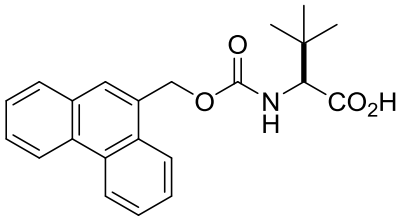


1st step: To a stirred solution of *p*-nitrophenylchloroformate (1.1 equiv., 11 mmol, 2.2 g) in CH_2Cl_2 (13.6 mL) was added pyridine (1.1 equiv., 11 mmol, 0.9 mL). The formed white slurry was cooled to 0 °C, and the corresponding alcohol (1 equiv., 10 mmol) was added in several portions to keep the 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 CH_2Cl_2 (40 mL) and subsequently washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL), dried with $MgSO_4$ 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 Na_2CO_3 (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 H_2O (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. 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

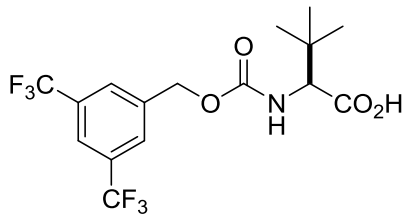


The title compound was prepared from phenanthren-9-ylmethanol and L-tert-leucine according to the general procedure B. Yield: 2.74 g (75%). White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 7.5, 1H), 8.66 (d, J = 8.0, 1H), 8.07 (d, J = 7.0, 1H), 7.88 (d, J = 7.5, 1H),

[230] 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

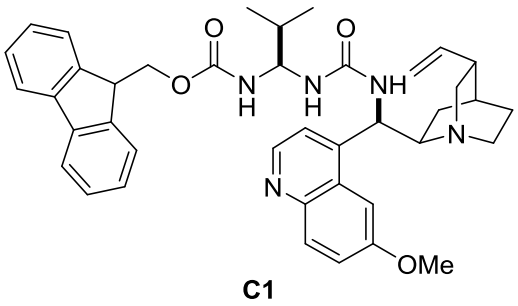


The title compound was prepared from 3,5-bis(trifluoromethyl)benzyl alcohol and L-tert-leucine according to the general procedure B. Yield: 3.25 g (81%). White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.30 (s, 2H), 5.33 (d, J = 9.6, 1H), 5.12 (s, 2H), 4.21 (d, J = 9.5, 1H), 1.02 (s, 9H).

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 °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 °C under nitrogen atmosphere for 1–2 hours. The reaction was monitored by infrared analysis until disappearance of the azide band (λ = 2140 cm^{-1}) –isocyanate band is observed (λ = 2240 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–CH_2Cl_2/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**.

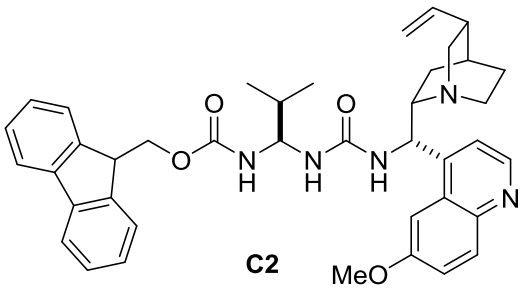
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C1)



C1

The title compound was prepared from *N*-Fmoc-L-Val-OH and 9-amino-9-deoxy-9-*epi*quinidine. Yield: 1.69 g (73%). White solid. m. p.= 115–127 °C. $[\alpha]_D^{25}$= +104.8 (c= 0.86, CH_2Cl_2). ^{1}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}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 $[M+H]^+$) calcd for $C_{40}H_{46}N_5O_4$: 660.3550; found: 660.3559.

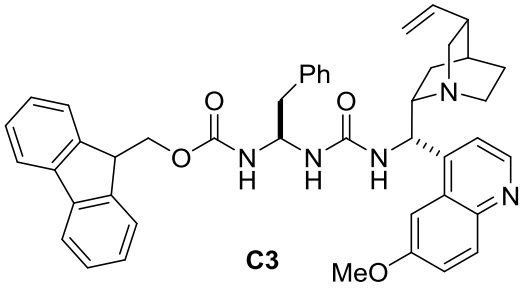
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C2)



C2

The title compound was prepared from *N*-Fmoc-L-Val-OH and 9-amino-9-deoxy-9-*epi*quinine. Yield: 1.76 g (76%). White solid. m. p.= 129–140 °C. $[\alpha]_D^{25}$= –35.8 (c= 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, *J*= 3.8 Hz, 1H), 8.02 (d, *J*= 9.2 Hz, 1H), 7.86–7.69 (m, 3H), 7.79–7.73 (m, 2H), 7.49–7.20 (m, 7H), 6.47–6.28 (bs, 1H), 5.79–5.68 (m, 2H), 5.65–5.46 (bs, 1H), 5.40–5.19 (m, 1H), 5.03–4.95 (m, 2H), 4.80–4.57 (m, 1H), 4.48–4.26 (m, 2H), 4.19–4.15 (m, 1H), 3.96 (s, 3H), 3.28–3.20 (m, 2H), 3.17–3.02 (m, 1H), 2.75–2.70 (m, 2H), 2.60–2.54 (m, 1H), 2.38–2.22 (m, 1H), 1.66–1.58 (m, 3H), 1.53–1.35 (m, 1H), 0.87 (s, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 157.4, 156.1, 147.5, 145.7, 144.7, 143.9, 143.7, 141.2, 131.6, 128.4, 127.7, 127.0, 125.0, 121.5, 119.9, 114.6, 102.0, 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 $[M+H]^+$) calcd for $C_{40}H_{46}N_5O_4$: 660.3550; found: 660.3557.

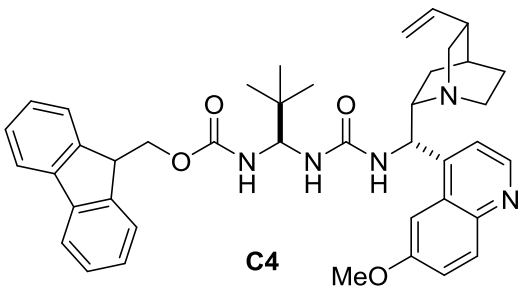
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-phenylethyl)carbamate (C3)



C3

The title compound was prepared from *N*-Fmoc-L-Phe-OH and 9-amino-9-deoxy-9-*epi*quinine. Yield: 1.66 g (67%). White solid. m. p.= 135–146 °C. $[\alpha]_D^{25}$= –12.1 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.9, 155.7, 147.5, 144.8, 143.9, 143.8, 141.3, 141.2, 136.8, 131.7, 129.3, 128.5, 127.7, 127.1, 126.7, 125.0, 121.5, 120.0, 114.6, 102.0, 66.6, 60.8, 60.1, 55.7, 55.6, 47.1, 40.8, 40.2, 39.4, 27.8, 27.3, 26.01. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{44}H_{46}N_5O_4$ 708.3550; found 708.3560.

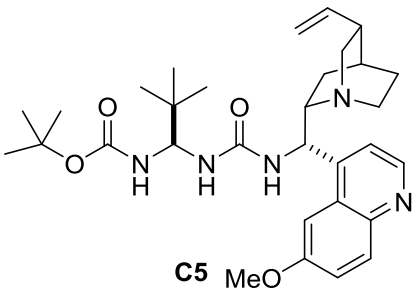
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C4)



C4

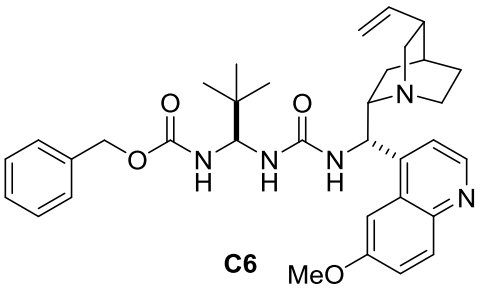
The title compound was prepared from *N*-Fmoc-L-Tle-OH and 9-amino-9-deoxy-9-*epi*quinine. Yield: 1.67 g (71%). White solid. m. p.= 130–139 °C. $[\alpha]_D^{25}$= –16.2 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (d, *J*= 4.4 Hz, 1H), 8.01 (d, *J*= 9.2 Hz, 1H), 7.83–7.72 (m, 3H), 7.62–7.55 (m, 2H), 7.47–7.31 (m, 7H), 6.41–6.26 (bs, 1H), 5.84–5.69 (m, 1H), 5.40–5.25 (m, 1H), 5.09–5.05 (bs, 1H), 5.07–4.95 (m, 3H), 4.47–4.41 (m, 1H), 4.35– 4.30 (m, 1H), 4.26–4.11 (m, 1H), 3.97 (s, 3H), 3.32–3.24 (m, 2H), 3.17–3.02 (m, 1H), 2.81–2.69 (m, 2H), 2.36–2.25 (m, 1H), 1.66–157 (m, 3H), 1.48–1.38 (m, 1H), 0.92 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 157.8, 156.8, 147.9, 146.3, 145.1, 144.3, 144.1, 141.8, 141.7, 132.00, 128.9, 128.1, 127.5, 125.5, 122.0, 120.4, 114.9, 102.5, 67.4, 67.1, 60.8, 56.8, 56.3, 56.0, 47.6, 41.4, 39.9, 35.8, 28.3, 27.9, 26.5, 25.8. UPLC (DAD-QTOF $[M+H]^+$) calcd for $C_{41}H_{47}N_5O_4$ 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)



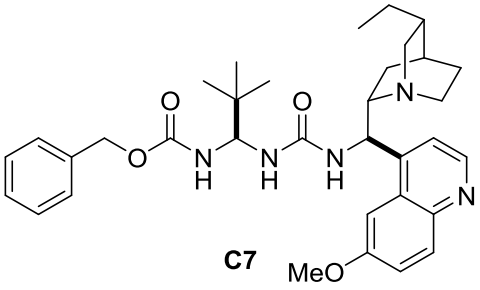
The title compound was prepared from *N*-Boc-L-Tle-OH and 9-amino-9-deoxy-9-*epi*quinine. Yield: 1.50 g (78%). White solid. m. p.= 118–130 °C. $[\alpha]_D^{25}$= –26.7 (c= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, *J*= 4.6 Hz, 1H), 8.02 (d, *J*= 9.2 Hz, 1H), 7.79 (d, *J*= 2.5 Hz, 1H), 7.39 (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 $[M+H]^+$) calcd for $C_{31}H_{46}N_5O_4$ 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-*epi*quinine. Yield: 1.48 g (72%). White solid. m. p.= 101–126 °C. $[\alpha]_D^{25}$= –29.8 (c= 1, CH_2Cl_2). ^{1}H 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 $[M+H]^+$) calcd for $C_{34}H_{44}N_5O_4$ 586.3399; found 586.3393.

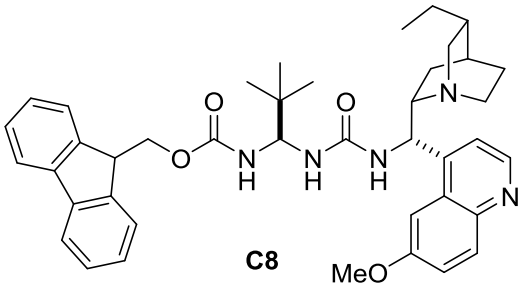
Benzyl ((*S*)-1-(3-((*R*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C7)



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}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}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 $[M+H]^+$) calcd for $C_{34}H_{46}N_5O_4$ 588.3550; found 588.3549.

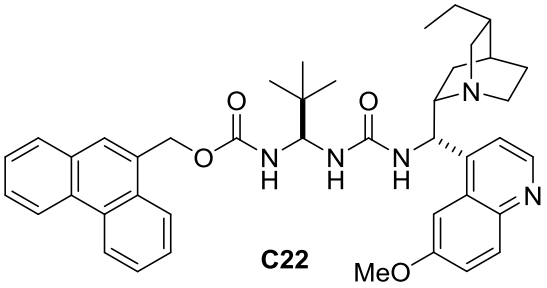
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C8)



C8

The title compound was prepared from *N*-Fmoc-L-Tle-OH and 9-amino-9-deoxy-9-*epi*hydroquinine. Yield: 1.44 g (61%). White solid. m. p.= 135–149 °C. $[\alpha]_D^{24}$= –29.8 (c= 1, $CHCl_3$). ^{1}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}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 $[M+H]^+$) calcd for $C_{41}H_{50}N_5O_4$ 696.3863; found 676.3876.

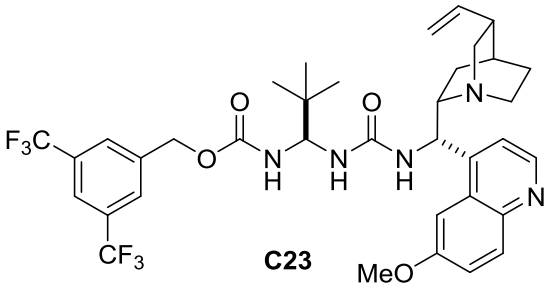
Phenanthren-9-ylmethyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C22)



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-hydro*epi*quinine. Yield: 1.66 g, (69%). Yellow solid. m. p.= 152–159 °C. $[\alpha]_D^{25}$ = 8.7 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{42}H_{50}N_5O_4$ 688.3863, found 688.3863.

3,5-Bis(trifluoromethyl)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 (C23)



C23

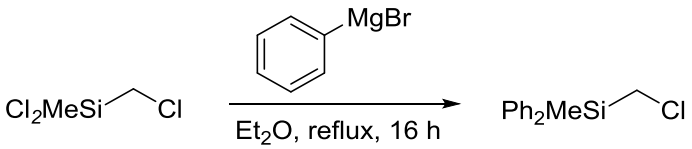
The title compound was prepared from (*S*)-2-((((3,5-$(CF_3)_2$-benzyloxycarbonyl-amino-3,3-dimethylbutanoic acid and 9-amino-9-deoxy-9-*epi*quinine. Yield: 2.3 g (65%). White solid. m. p. = 125–131 °C. $[\alpha]_D^{24}$ = –9.5 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.5 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{36}H_{41}N_5O_4F_6$ $[M+H]^+$ calcd.: 722.3136, found: 722.3138.

6.2.3. Synthesis of squaramide-based Brønsted base catalysts

6.2.3.1. Preparation of (chloromethyl)silyl derivatives[231]

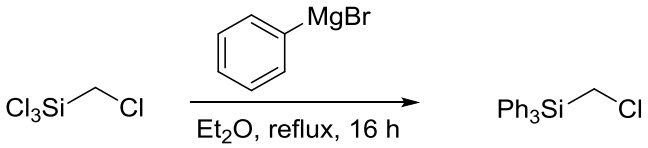
(Chloromethyl)dimethyl(phenyl)silane was purchased from Sigma-Aldrich.

(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 ^{o}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 concentred 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. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 4H), 7.49 – 7.32 (m, 6H), 3.26 (s, 2H), 0.72 (s, 3H).

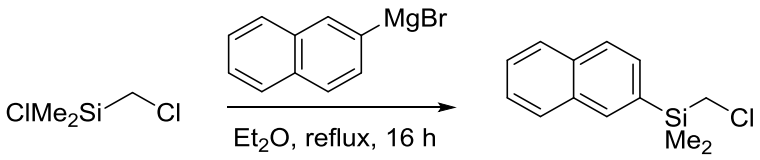
(Chloromethyl)triphenylsilane



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 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.52 (m, 6H), 7.53 – 7.29 (m, 9H), 3.53 (s, 2H).

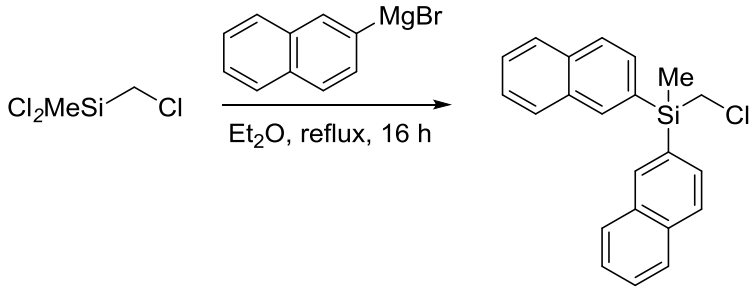
[231] Procedures adapted from: a) Larson, G. L.; Prieto, J. A.; Ortiz, E. *Tetrahedron*, **1988**, *44*, 3781-3790. b) Allen, J. M.; Aprahamian, S. L.; Sans, E. A.; Shechter, H. *J. Org. Chem.*, **2002**, *67*, 3561.

(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 concentred 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}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).

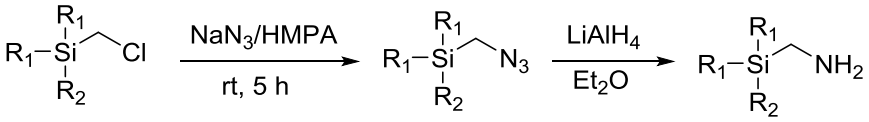
(Chloromethyl)(methyl)di(naphthalen-2-yl)silane



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 concentred 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}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 silanes[232]

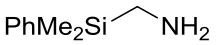
(Trimethylsilyl)methylamine was purchased Fluka. The other aminomethyl silanes were prepared following the general procedure:



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 H_2O (30 mL) and extracted with hexane (3 x 30 mL). The combined extracts were washed with saturated solution of NH_4Cl, dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

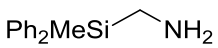
2nd step: To a suspension of $LiAlH_4$ (1 equiv., 10.0 mmol) in dry Et_2O (10 mL) was slowly added at 0 °C a solution of the corresponding azide (10.0 mmol) in dry diethyl ether (5 ml). The mixture was stirred in an ice bath for 10 min and then stirred at room temperature until liberation of nitrogen ceased (30 min). The, the reaction was quenched with 1 mL of NH_4OH 1 % aqueous solution. The mixture was filtered through celite, the filtered was dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The residue was used in the next step without further purification.

(Dimethyl(phenyl)silyl)methanamine



The title compound was prepared according to the general procedure from (chloromethyl)dimethyl(phenyl)silane. Yield: 2.97 g (90 %) Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.38 – 7.36 (m, 3H), 2.40 (s, 2H), 0.33 (s, 6H).

(Methyldiphenylsilyl)methanamine

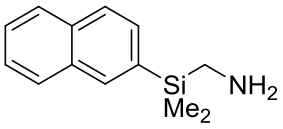


The title compound was prepared according to the general procedure from (chloromethyl)(methyl)diphenylsilane. Yield: 3.68 g (81 %). Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 4H), 7.41 – 7.34 (m, 6H), 2.72 (s, 2H), 0.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 134.5, 133.9, 129.4,

[232] Adapted from: Lettelier, M.; McPhee, D. J.; Griller, D. *Synth. Commun*. **1988**, 18, 1975.

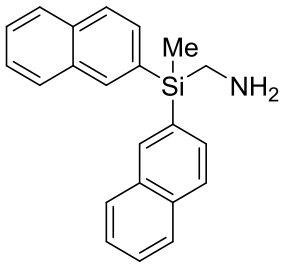
129.2, 127.8, 127.6, 29.1, –5.7. UPLC-DAD-QTOF: $C_{14}H_{18}NSi$ $[M+H]^+$ calcd.: 228.1209, found: 228.1197.

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



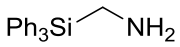
The title compound was prepared according to the general procedure from (chloromethyl)dimethyl(naphthalen-2-yl)silane. Yield: 3.68 g (80 %). Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.87 – 7.81 (m, 3H), 7.63 – 7.60 (m, 1H), 7.51 – 7.48 (m, 2H), 2.49 (s, 2H), 0.42 (s, 6H).

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



The title compound was prepared according to the general procedure from (chloromethyl)(methyl)di(naphthalen-2-yl)silane. Yield: 3.68 g (80 %). Colorless liquid. ^{1}H 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).

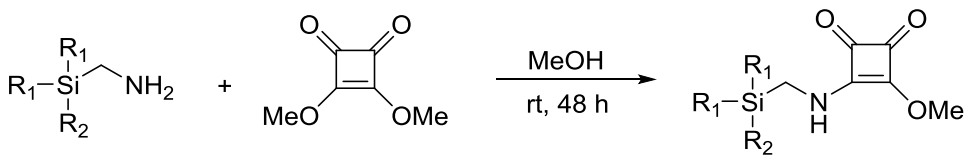
(Triphenylsilyl)methanamine



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

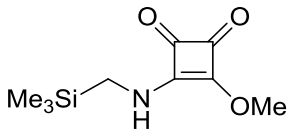
6.2.3.3. Preparation of squaramide-type catalysts

1st STEP:



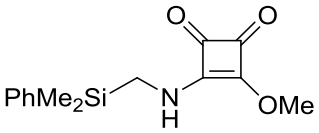
To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (0.71 g, 5.0 mmol) in 10 mL MeOH was added the corresponding (aminomethyl)silane. The reaction mixture was stirred for 48 hours at room temperature and white precipitate was generated. The reaction product was filtered and the filtration residue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

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



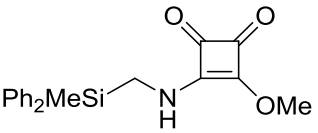
The title compound was prepared according to the general procedure from (trimethylsilyl)methylamine. Yield: 0.88 g (83 %). White solid. m. p. 119–122 °C. IR (v/cm^{-1}): 3205, 3014, 2969, 2948, 2357, 1790, 1692, 1576, 1493, 1366, 1228, 862, 584. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (s, 1H), 4.40 (s, 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: $C_9H_{16}NO_3Si$ [M+H]+ calcd.: 214.0899, found: 214.0892.

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



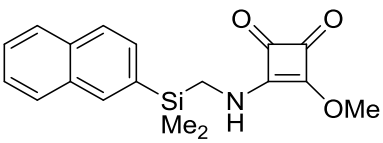
The title compound was prepared according to the general procedure from (dimethyl(phenyl)silyl)methanamine. Yield: 0.96 g (70 %). White solid. m. p. 117–120 °C. IR (v/cm^{-1}): 3247, 3135, 3046, 2968, 2359, 1799, 1691, 1586, 1357, 1229, 1112, 1051, 980, 934, 807, 697, 587, 467. ^{1}H NMR (300 MHz, $CDCl_3$) 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: $C_{14}H_{18}NO_3Si$ $[M+H]^+$ calcd.: 276.1056, found: 276.1058.

3-Methoxy-4-(((methyldiphenylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione



The title compound was prepared according to the general procedure from (methyldiphenylsilyl)methanamine. Yield: 1.63 g (90 %). White solid. m. p. 148–152 °C. IR (v/cm^{-1}): 3247, 3051, 2968, 2898, 2359, 1810, 1691, 1643, 1536, 1463, 1354, 1062, 933, 854, 816, 745, 648, 483. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.37 (m, 10H), 5.86 (s, 1H, NH), 4.30 (s, 3H), 3.49 – 3.46 (m, 2H), 0.67 (s, 3H). UPLC-DAD-QTOF: $C_{19}H_{20}NO_3Si$ $[M+H]^+$ calcd.: 338.1212, found: 338.1218.

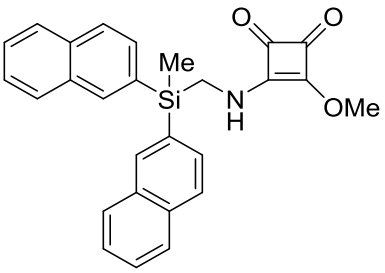
3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



The title compound was prepared according to the general procedure from (dimethyl(naphthalen-2-yl)silyl)methanamine. Yield: 1.14 g (70 %). White solid. m. p. 140–144 °C. IR (v/cm^{-1}): 3277, 3065, 3001, 2939, 2904, 1803, 1696, 1622, 1495, 1396, 1275, 1109, 918, 848, 779, 725, 580, 459. ^{1}H 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),

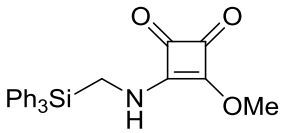
4.23 (s, 3H), 3.21 (d, *J* = 6Hz, 1H), 0.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 182.3, 177.3, 172.2, 135.0, 134.1, 132.9, 129.5, 128.2, 127.9, 127.6, 127.0, 126.4, 60.4, 35.6, –4.5. UPLC-DAD-QTOF: $C_{18}H_{20}NO_3Si$ $[M+H]^+$ calcd.: 326.1212, found: 326.1212.

3-Methoxy-4-(((methyldi(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione



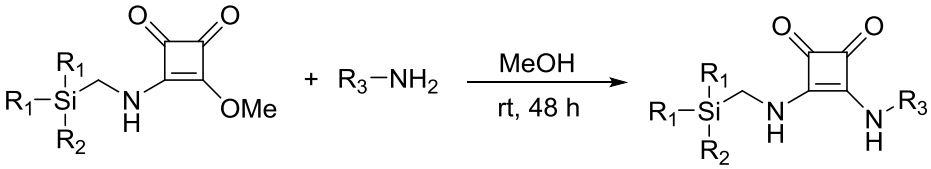
The title compound was prepared according to the general procedure from (methyldi(naphthalen-2-yl)silyl)methanamine. Yield: 1.56 g (72 %). White solid. m. p. 150–153 °C. IR (ν/cm^{-1}): 3240, 3046, 1801, 1699, 1605, 1497, 1461, 1396, 1362, 1085, 857, 758, 475. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 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: $C_{27}H_{23}NO_3Si$ $[M+H]^+$ calcd.: 438,1520, found: 438,1523.

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



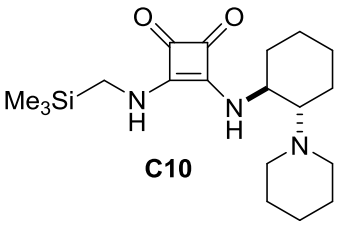
The title compound was prepared according to the general procedure from (triphenylsilyl)methanamine. Yield: 1.70 g (85 %). White solid. m. p. 167-171°C. IR (ν/cm^{-1}): 3254, 3046, 1801, 1702, 1601, 1426, 1360, 1111, 698, 505. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.35 (m, 15H), 5.32 (s, 1H), 4.28 (s, 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: $C_{24}H_{21}NO_3Si$ $[M+H]^+$ 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**.

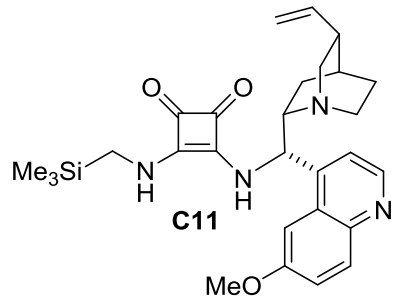
3-(((1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C10)



C10

The title compound **C10** was prepared according to the general procedure from 3-methoxy-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine. Yield: 0.25 g (45 %). m. p. 239–242 °C. $[\alpha]_D^{25}$= +42.1 (c = 0.25, DMSO)**.** IR (ν/cm^{-1}): 3160, 3014, 2929, 2851, 1791, 1633, 1551, 1462, 1365, 1216, 846, 762. ^{1}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}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: $C_{19}H_{34}N_3O_2Si$ $[M+H]^+$ calcd.: 364.2420, found: 276.2409.

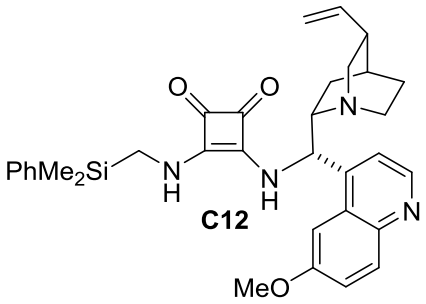
3-((*S*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C11)



C11

The title compound **C11** was prepared according to the general procedure from 3-methoxy-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.51 mg (68 %). White solid. m. p. 209–213 °C. $[\alpha]_D^{25}$= –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}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}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: $C_{28}H_{37}N_4O_3Si$ $[M+H]^+$ calcd.: 505.2635, found: 505.2597.

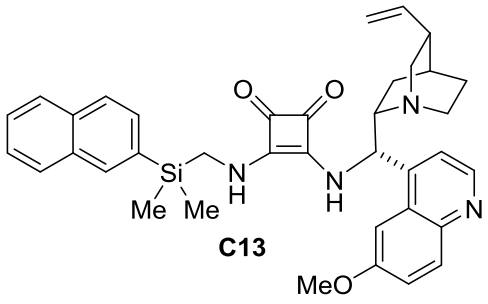
3-((Dimethyl(phenyl)silyl)methylamino)-4-((*S*)-(6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C12)



C12

The title compound **C12** was prepared according to the general procedure from 3-((dimethyl(phenyl)silyl)methylamino)-4-methoxycyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.59 g (70 %). White solid. m. p. 221–224 °C. $[\alpha]_D^{25}$= –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}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, 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{33}H_{39}N_4O_3Si$ $[M+H]^+$ calcd.: 567.2791, found: 567.2800.

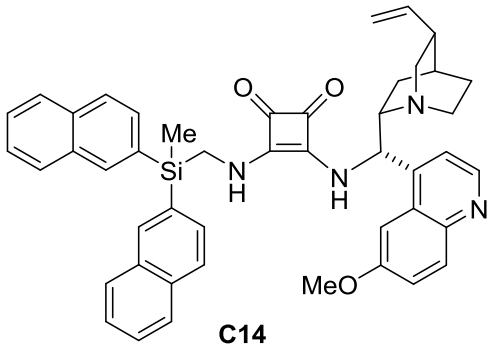
3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C13)



C13

The title compound was **C13** prepared according to the general procedure from 3-(((dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.69 g (75 %). White solid. m. p. 229–232 °C. $[\alpha]_D^{25}$= –109.5 (c = 0.5, CH_2Cl_2). IR (ν/cm^{-1}): 3227, 2937, 2862, 1790, 1637, 1567, 1544, 1264, 1086, 1038, 817. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{37}H_{41}N_4O_3Si$ $[M+H]^+$ calcd.: 617.2948, found: 617.2961.

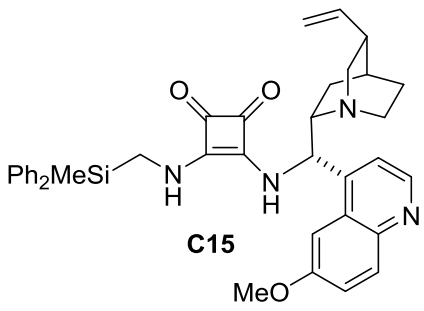
3-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((methyldi(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione (C14)



C14

The title compound was **C14** prepared according to the general procedure from 3-methoxy-4-(((methyldi(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.83 g (76 %). White solid. m. p. 245–252 °C. $[\alpha]_D^{25}$= –124.6 (c = 0.7, CH_2Cl_2). IR (ν/cm^{-1}): 3230, 3048, 2939, 1792, 1584, 1535, 1457, 1241, 1086, 908, 854, 730, 475. ^{1}H NMR (300 MHz, $CDCl_3$) 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: $C_{46}H_{44}N_4O_3Si$ $[M+H]^+$ calcd.: 729.3255, found: 729.3251.

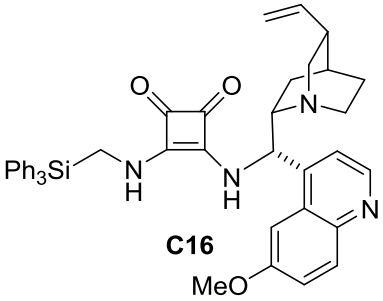
3-((*S*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)-4-((methyldiphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C15)



C15

The title compound **C15** was prepared according to the general procedure from 3-methoxy-4-(((methyldiphenylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.56 g (60 %). m. p. 152–156 °C. $[\alpha]_D^{23}$= –105.3 (c = 1. 0, CH_2Cl_2). IR (ν/cm^{-1}): 3193, 2929, 2859, 1788, 1628, 1547, 1456, 1230, 1114, 803, 760, 730, 700, 489. ^{1}H 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: $C_{38}H_{41}N_4O_3Si$ $[M+H]^+$ calcd.: 629.2948, found: 629.2956.

3-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methylamino)-4-((triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C16)

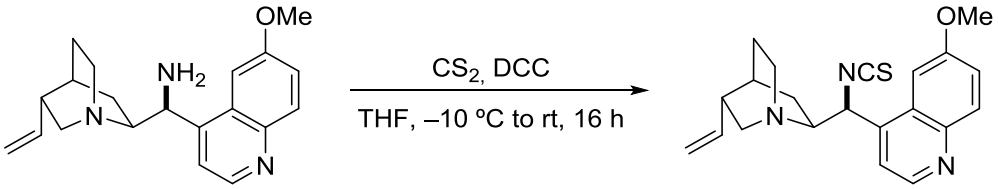


The title compound **C16** was prepared according to the general procedure from 3-methoxy-4-(triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione and 9-amino-9-deoxy-9-*epi*quinine. Yield: 0.69 g (67 %). White solid. m. p. 252–256 °C. $[\alpha]_D^{23}$= –58.9 (c = 1. 0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) 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: $C_{43}H_{43}N_4O_3Si$ $[M+H]^+$ 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

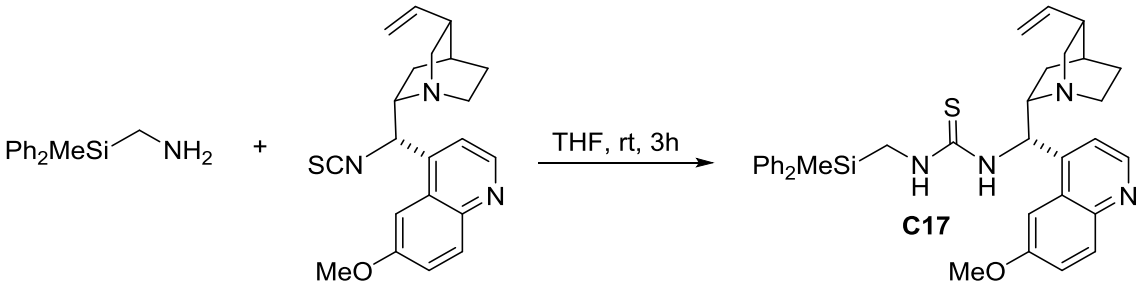
6.2.4.1.1. Synthesis of 9-deoxy-9-*epi*quinine isocyanate derivative



To a solution of 9-amino-9-deoxy-9-*epi*quinine (1 equiv., 1 mmol, 0.32 g) in anhydrous THF (1 mL) at –10 °C, carbon disulfide (6 equiv., 6 mmol, 0.36 mL) and DCC (1 equiv., 1 mmol, 0.21 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: 0.33 g (90 %). Yellow solid. ^{1}H 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,

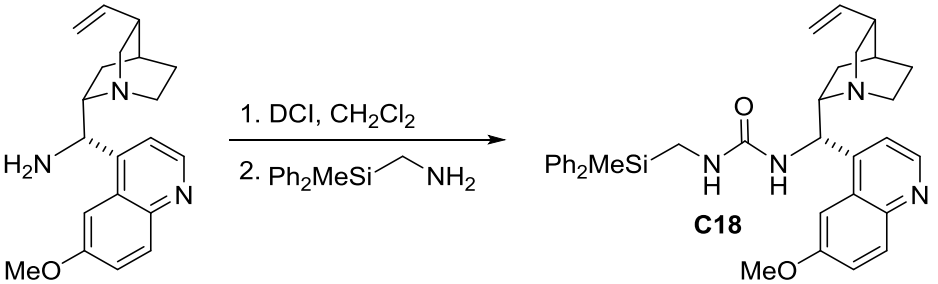
8.9 Hz, 1H).[13]C NMR (75 MHz, $CDCl_3$) δ 164.16, 157.86, 147.72, 144.46, 141.92, 138.54, 131.81, 127.18, 121.46, 119.86, 116.76, 101.48, 66.56, 65.69, 57.19, 55.81, 46.23, 38.73, 27.65, 26.19, 25.42. UPLC-DAD-QTOF: $C_{21}H_{24}NOS$ $[M+H]^+$ calcd.: 366.1640, found: 366.1644.

6.2.4.1.2. Synthesis of silyl-thiourea catalyst C17



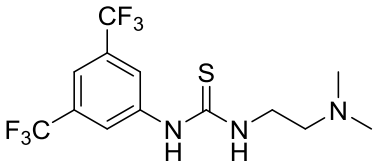
(Methyldiphenylsilyl)methanamine (1 equiv., 1.4 mmol, 0.32 g) was added to a solution of 9-isocyanate-9-deoxy-9-*epi*quinine (1 equiv., 1.4 mmol, 0.51 g) in anhydrous THF (2 mL) and the mixture was stirred at room temperature for 3 hours. After that, the mixture was concentrated under reduced pressure and purified by flash chromatography column in silica gel (CH_2Cl_2:MeOH, 90:10) to afford catalyst **C17**. Yield: 0.75 g (90 %). White solid. m. p. 136–145 °C. $[\alpha]_D^{23}$= –106.7 (c = 1. 0, CH_2Cl_2). IR (ν/cm^{-1}): 2932, 1620, 1508, 1422, 1227, 1113, 1029, 910, 818, 730, 699, 483. ^{1}H NMR (300 MHz, $CDCl_3$) 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).[13]C NMR (75 MHz, $CDCl_3$) 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: $C_{35}H_{41}N_4OSSi$ $[M+H]^+$ 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, 0.18 g) in anhydrous CH_2Cl_2 (1 mL), a solution of 9-amino-9-deoxy-9-*epi*quinine (1.0 equiv., 1.0 mmol, 0.32 g) in CH_2Cl_2 (1 mL) was added at room temperature. The reaction was monitorized by TLC and once the reaction was finished –30 minutes aprox.–, (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 (CH_2Cl_2:MeOH, 90:10) to afford catalyst **C18**. Yield: 0.346 g (60 %). White solid. m. p. 129–135 °C. $[\alpha]_D^{23}$= –36.3 (c = 1. 0, CH_2Cl_2). IR (ν/cm^{-1}): 2931, 1621, 1546, 1508, 1427, 1228, 1113, 1028, 910, 821, 730, 699, 484. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{35}H_{41}N_4O_2Si$ $[M+H]^+$ calcd.: 577.2999, found: 577.3004.

6.2.4.3. Preparation of achiral thiourea catalyst C24[233]



C24

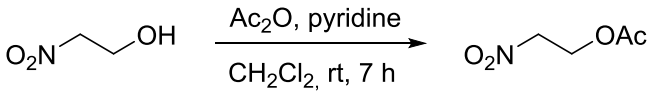
To a solution of 3,5-bis(trifluoromethyl)phenyl isocianate (0.91 mL, 5 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (5 mL), *N,N*-dimethylelthylenediamine (0.55 mL, 5 mmol, 1 equiv.) was added. The mixture was stirred at room temperature for 2 hours and then, the solvent was eliminated under reduced pressure to afford catalyst **C24**. Yield: 1.76 g (98%). White solid. ^{1}H RMN (300 MHz, 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, 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.[233]

[233] 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

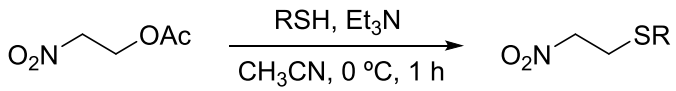
6.3.1. Preparation of 2-nitroethyl sulfones[234]

1st STEP:



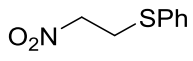
A solution of 2-nitroethanol (1.0 equiv., 50 mmol, 3.5 mL), pyridine (1.0 equiv., 50 mmol, 4.0 mL) and acetic anhydride (1.0 equiv., 50 mmol, 4.7 mL) in CH_2Cl_2 (80 mL) was stirred under nitrogen atmosphere at room temperature in the dark. After 7 hours, the reaction mixture was poured into 1M HCl (80 mL). The organic solvent was removed under reduced pressure and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford pure 2-nitroethyl acetate. Yield: 6.0 g (91%). Brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) 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 Et_3N (1.1 equiv., 16.5 mmol, 2.20 mL) in CH_3CN (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 H_2O (100 mL), dried over $MgSO_4$ 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

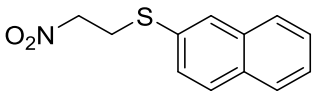


The title compound was prepared from thiophenol following the general procedure. Yield: 2.55 g (93%). Yellow oil. ^{1}H NMR (300 MHz,

[234] 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.

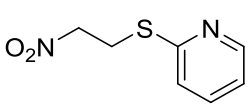
$CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.39 – 7.27 (m, 3H), 4.50 (t, *J*= 7.2 Hz, 2H), 3.44 (t, *J*= 7.2 Hz, 2H).

Naphthalen-2-yl(2-nitroethyl)sulfane



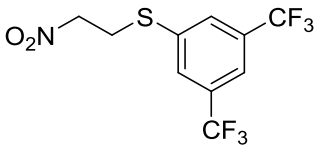
The title compound was prepared from 2-naphthalenethiol following the general procedure. Yield: 2.70 g (77%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J*= 1.6 Hz, 1H), 7.88 – 7.74 (m, 3H), 7.59 – 7.44 (m, 3H), 4.54 (t, *J*= 6.8 Hz, 2H), 3.53 (t, *J*= 6.8 Hz, 2H).

2-((2-Nitroethyl)thio)pyridine



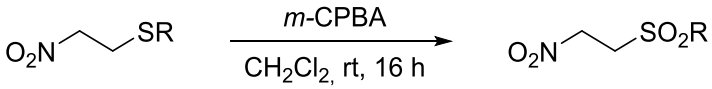
The title compound was prepared from 2-mercaptopyridine following the general procedure. Yield: 2.45 g (89%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 1H), 7.90 – 7.72 (m, 2H), 7.01 (ddd, *J* = 6.9, 4.7, 2.0 Hz, 1H), 4.48 (t, *J* = 6.8 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 2H).

(3,5-Bis(trifluoromethyl)phenyl)(2-nitroethyl)sulfane



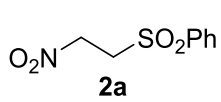
The title compound was prepared from 3,5-bis(trifluoromethyl)benzenethiol following the general procedure. Yield: 4.26 g (89%). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.77 (s, 1H), 4.58 (t, *J*= 6.8 Hz, 2H), 3.58 (t, *J*= 6.8 Hz, 2H).

3rd STEP:



To a solution of the corresponding thioether (1.0 equiv., 10 mmol) in CH_2Cl_2 (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 Na_2SO_3 (80 mL) for 15 minutes. The aqueous layer was separated and the organic phase was successively washed with a saturated $NaHCO_3$ solution (80 mL) and brine (80 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford the corresponding pure 2-nitroethyl sulfone.

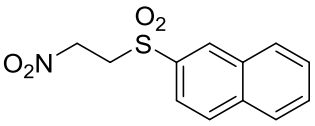
((2-Nitroethyl)sulfonyl)benzene (2a)



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. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 134.9, 129.9, 128.2, 68.2, 52.5. Elem. Anal. calcd for $C_8H_9NO_4S$ (215.23): C, 44.64; H, 4.21; N, 6.51. Found: C, 44.71; H, 4.21; N, 6.34.

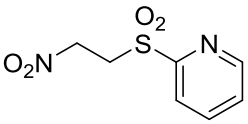
2-((2-Nitroethyl)sulfonyl)naphthalene (2b)



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. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, CD_2Cl_2) 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: $C_{12}H_{11}NO_4S$ $[M+H]^+$ calcd.: 266.0482, found: 266.0479.

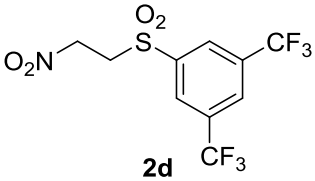
2-((2-Nitroethyl)sulfonyl)pyridine (2c)



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. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 150.3, 138.7, 128.2, 122.0, 68.3, 48.7. UPLC-DAD-QTOF: $C_7H_9N_2O_4S$ $[M+H]^+$ calcd.: 217.0286, found: 217.0283; $C_7H_8N_2O_4SNa$ $[M+Na]^+$ calcd.: 239.0104, found: 217.0102.

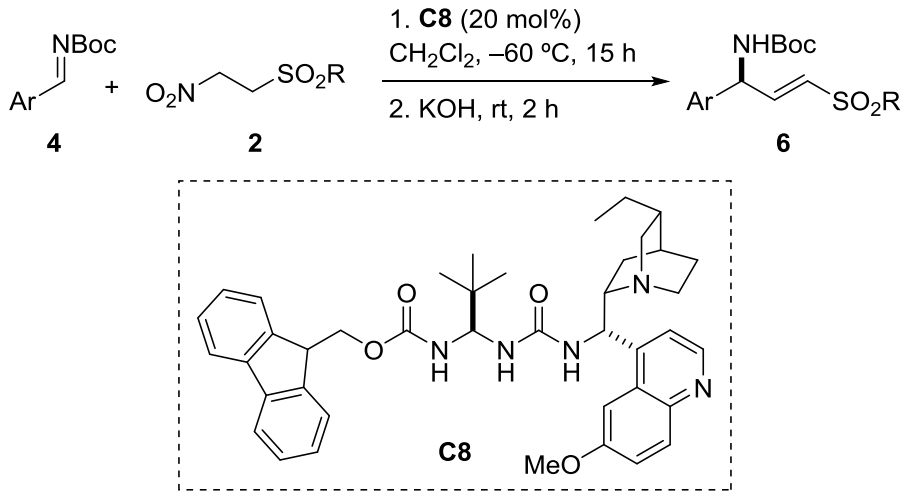
1-((2-Nitroethyl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (2d)



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. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 141.77, 134.00 (q, J= 34.9 Hz), 129.34, 129.03, 124.71, 68.22, 53.08. UPLC-DAD-QTOF: $C_{10}H_7F_6NO_4S$ $[M+H]^+$ calcd.: 352.0073, found: 352.0075.

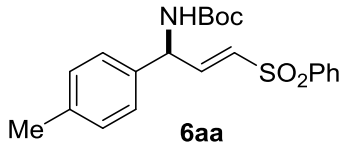
6.3.2. Enantioselective synthesis of γ-sulfonyl allyl amines



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 °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 moniterized by IR, observing the disappearence 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 purified[235] by trituration in Et_2O or flash column chromatography (hexane:ethyl acetate) to afford the corresponding γ-sulfonyl allyl amines **6**.

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing achiral catalyst **C24**.

***tert*-Butyl (*S*,*E*)-(3-(phenylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (6aa)**



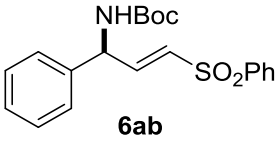
6aa

The title compound **6aa** 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 °C. $[\alpha]_D^{25}$= –64.2 (c= 0.05, CH_2Cl_2). ^1H NMR (300 MHz,

[235] Some adducts decomposed during isolation and purification procedures.

$CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{21}H_{26}NO_4S$ $[M+H]^+$ 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*.

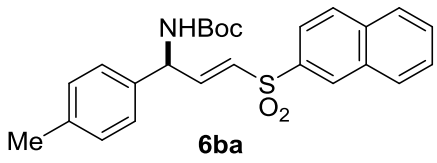
tert-Butyl (*S*,*E*)-(1-phenyl-3-(phenylsulfonyl)allyl)carbamate (6ab)



6ab

The title compound **6ab** 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, $CHCl_3$) ($[\alpha]_D^{23}$= +31.5 (c= 1.04, $CHCl_3$) for *R*-enantiomer).[236] ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{20}H_{24}NO_4S$ $[M+H]^+$ 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*)-(3-(naphthalen-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (6ba)

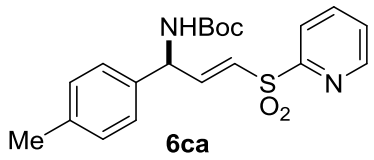


6ba

The title compound **6ba** 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}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}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: $C_{25}H_{28}NO_4S$ $[M+H]^+$ calcd.: 438.1734, found: 438.1730. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 0.50 mL/min, λ = 230 nm) t_R (major.) = 59.5 min, t_R (minor.) = 66.2 min. 77% *ee*.

[236] Ref. 157a, page 58.

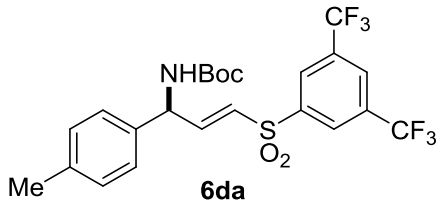
tert-Butyl (_S_,_E_)-(3-(pyridin-2-ylsulfonyl)-1-(_p_-tolyl)allyl)carbamate (6ca)



6ca

The title compound **6ca** was prepared from 2-nitroethyl sulfone **2c** and *N*-Boc imine **4a** following the general procedure. Yield: 0.031 g (16%). White solid. ^{1}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: $C_{20}H_{24}N_2O_4SNa$ $[M+H]^+$ calcd.: 411.1349, found: 411.1358. Chiral HPLC (Chiralpak AD-H; 90:10 hexane:*i*PrOH; 1.00 mL/min, λ = 210 nm) t_R (major.) = 25.0 min, t_R (minor.) = 31.5 min. 92% *ee*.

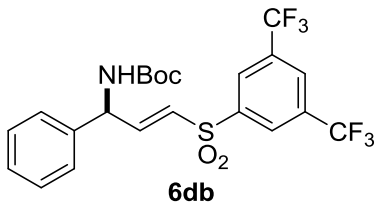
tert-Butyl (_S_,_E_)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(_p_-tolyl)allyl)carbamate (6da)



6da

The title compound **6da** 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}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}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: $C_{23}H_{24}NO_4SF_6$ $[M+H]^+$ calcd.: 524.1330, found: 524.1332. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 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 (6db)

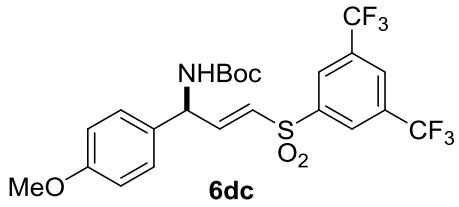


6db

The title compound **6db** 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, $CHCl_3$). ^{1}H 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: $C_{22}H_{21}NO_4SF_6Na$ $[M+Na]^+$ calcd.: 532.0993, found: 532.1001. Chiral HPLC (Chiralpak IC; 99:1

hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (major.) = 60.5 min, t_R (minor.) = 73.1 min. >99% *ee*.

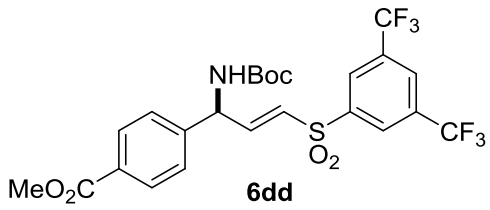
tert-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)allyl)carbamate (6dc)



6dc

The title compound **6dc** 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, $CHCl_3$). ^{1}H 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: $C_{23}H_{24}NO_5SF_6$ $[M+H]^+$ calcd.: 540.1279, found: 540.1277. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (major.) = 40.9 min, t_R (minor.) = 49.8 min. >99% *ee*.

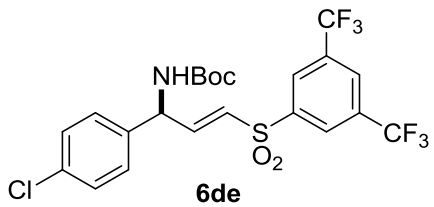
Methyl (*S*,*E*)-4-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-((tert-butoxycarbonyl)amino)allyl)benzoate (6dd)



6dd

The title compound **6dd** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4d** following the general procedure. Yield: 0.142 g (50%). White solid. ^{1}H 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: $C_{24}H_{23}NO_6SF_6Na$ $[M+Na]^+$ calcd.: 590.1048, found: 590.1051. Chiral HPLC (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, λ = 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 (6de)

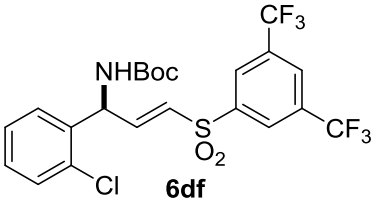


6de

The title compound **6de** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4e** following the general procedure. Yield: 0.138 g (51%). White solid. ^{1}H 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: $C_{22}H_{20}NO_4SF_6ClNa$ $[M+Na]^+$ calcd.: 566.0603, found: 566.0601. Chiral HPLC (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (major.) = 16.6 min, t_R (minor.) = 19.2 min. >99% *ee*.

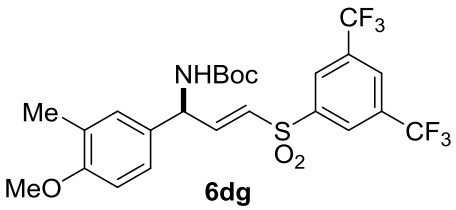
tert-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(2-chlorophenyl)allyl)carbamate (6df)



6df

The title compound **6df** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4f** following the general procedure. Yield: 0.027 g (10%). White solid. ^{1}H 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: $C_{22}H_{21}NO_4SF_6Cl$ $[M+H]^+$ calcd.: 544.0779, found: 544.0783 Chiral HPLC (Chiralpak AD-H; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (minor.) = 29.2 min, t_R (major.) = 47.7 min. 68% *ee*.

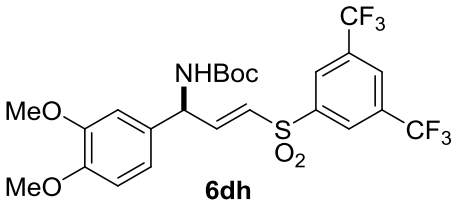
tert-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxy-3-methylphenyl)allyl)carbamate (6dg)



6dg

The title compound **6dg** 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, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{24}H_{26}NO_4SF_6$ $[M+H]^+$ calcd.: 554.1436, found: 554.1439. Chiral HPLC (Chiralpak IC; 98:2 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (major.) = 32.1 min, t_R (minor.) = 38.5 min. >99% *ee*.

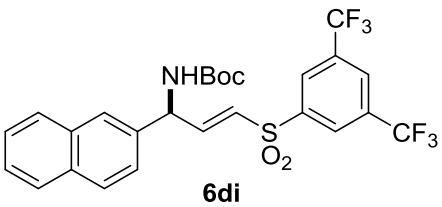
tert-Butyl (_S_,_E_)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(3,4-dimethoxyphenyl)allyl)carbamate (6dh)



6dh

The title compound **6dh** 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, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 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: $C_{24}H_{26}NO_6SF_6$ $[M+H]^+$ calcd.: 570.1385, found: 570.1389. Chiral HPLC (Chiralpak IC; 95:5 hexane:*i*PrOH; 1.00 mL/min, λ = 230 nm) t_R (minor.) = 15.1 min, t_R (major.) = 17.2 min. >99% *ee*.

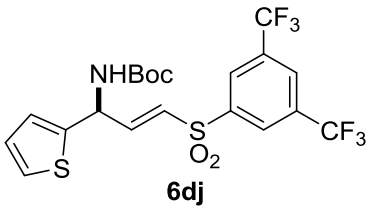
tert-Butyl (_S_,_E_)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(naphthalen-2-yl)allyl)carbamate (6di)



6di

The title compound **6di** 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, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{26}H_{24}NO_4SF_6$ $[M+H]^+$ 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 (6dj)

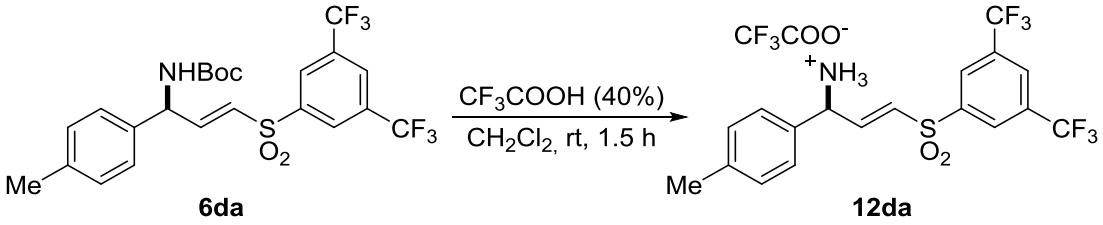


6dj

The title compound **6dj** was prepared from 2-nitroethyl sulfone **2d** and *N*-Boc imine **4j** following the general procedure. Yield: 0.103 g (40%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) 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:

$C_{20}H_{20}NO_4S_2F_6$ $[M+H]^+$ 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*.

6.3.3. Amine deprotection in adduct 6da[237]



A solution of CF_3COOH (40% v/v in CH_2Cl_2) was added to adduct **6da** (1.0 equiv., 0.1 mmol, 0.052 g) and the mixture was stirred for 1.5 hours at room temperature. After that, the white suspension was concentrated under reduced pressure to afford the corresponding free γ-sulfonyl allyl amine **12da**. Yield: 0.054 g (92%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 2H), 8.22 (brs, 3H), 8.13 (s, 1H), 7.35 (dd, *J* = 15.3, 5.4 Hz, 1H), 7.24 – 7.14 (m, 4H), 6.78 (d, *J* = 15.3 Hz, 1H), 5.13 (d, *J* = 5.4 Hz, 1H), 2.35 (s, 3H).

[237] Procedure adapted from ref. 157c in page 58.

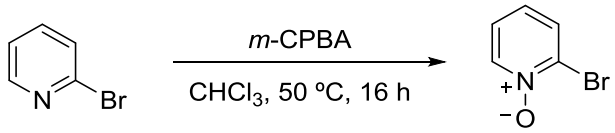
6.4. Experimental section for Chapter 3

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

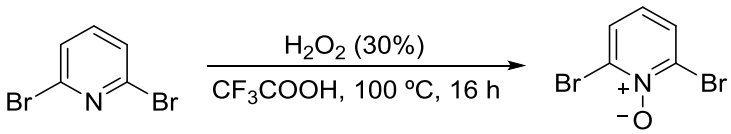
6.4.1.1.1. Oxidation of 2-bromo pyridines

6.4.1.1.1.1. Synthesis of 2-bromopyridine *N*-oxide[238]



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 ºC 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 (v/cm^{-1}): 3096, 3035, 1697, 1589, 1541, 1411, 1251, 1121, 1065, 1037, 838, 762, 674, 565, 519, 446. ^{1}H 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*-oxide[239]

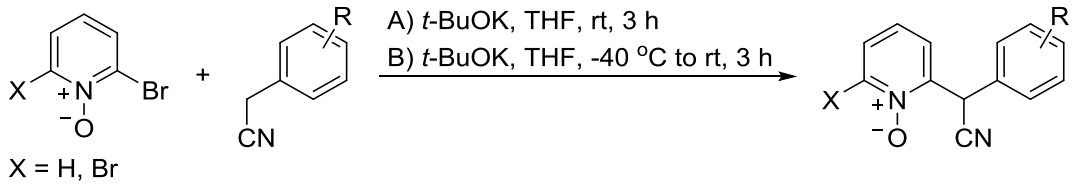


To an ice-cold solution of 2,6-dibromopyridine (1 equiv., 10 mmol, 2.37 g) in trifluoroacetic acid (12 mL) was added drop-wise an aqueous solution of H_2O_2 (30 %) (0.33 mL/mmol, 3.3 mL). The reaction mixture was stirred at 100 ºC for 16 hours and then cooled to rt, poured into 50 mL of water and the precipitate was filtered. The solid

[238] Adapted from: Brasse, M.; Cámpora, J.; Palma, P.; Álvarez, E. *Organometallics* **2008**, *27*, 4711–4723.
[239] 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.; Czaplewski, 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.

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. ^{1}H 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 13a–13f



GENERAL PROCEDURE A

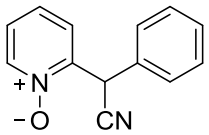
To a solution of potassium *tert*-butoxide (2 equiv., 6 mmol, 0.67 g) in dry THF (10 mL) at room temperature, the corresponding 2-arylacetonitrile (1.5 equiv., 4.5 mmol) was added and the resulting mixture was stirred for 45 minutes at the same temperature. Afterwards, the corresponding 2-bromopyridine *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, 0.67 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 **13a–13g** decompose over time and should be stored in a refrigerator (at –30 °C they are stable for several months).

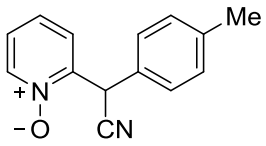
2-(Cyano(phenyl)methyl)pyridine *N*-oxide (13a)



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: 0.57 g (90 %). Yellow solid. m. p.= 112–115 °C. IR (ν/cm^{-1}): 3110, 3052, 2894, 2246, 1489, 1438, 1246, 884, 794, 696. ^{1}H 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: $C_{13}H_{11}N_2O_3$ $[M+H]^+$ calcd.: 211.0871, found: 211.0863.

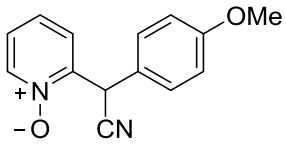
2-(Cyano(*p*-tolyl)methyl)pyridine *N*-oxide (13b)



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: 0.57 g (84%). Yellow solid. m. p.= 96–99 °C. IR (ν/cm^{-1}): 3082, 3042, 3013, 2909, 2247, 1687, 1513, 1488, 1429, 1279, 1242, 837, 798, 765, 705. ^{1}H NMR (300 MHz, CDCl3) 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, CDCl3) 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: $C_{14}H_{13}N_2O$ $[M+H]^+$ calcd.: 225.1028, found: 225.1046.

2-(Cyano(4-methoxyphenyl)methyl)pyridine *N*-oxide (13c)

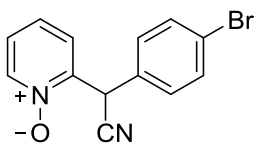


13c

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: 0.051 g (71%). Red oil. IR (ν/cm^{-1}): 3110, 3071, 3013, 2934, 2837, 2245, 1607, 1583, 1509, 1429, 1365, 1178, 1027, 830, 762. ^{1}H 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,

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.

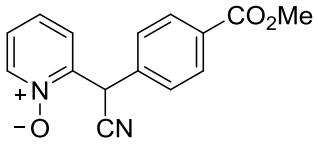
2-((4-Bromophenyl)(cyano)methyl)pyridine *N*-oxide (13d)



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: 0.76 g (88 %). Red oil. IR (v/cm^{-1}): 3112, 3078, 3050, 3023, 2896, 2247, 1692, 1587, 1484, 1428, 1404, 1237, 1047, 1010, 824, 782, 729, 625. ^{1}H 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.

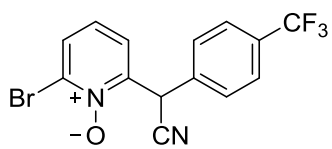
2-(Cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (13e)



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: 0.64 g (80 %). Red oil. IR (v/cm^{-1}): 3111, 3080, 3013, 2926, 2245, 1710, 1620, 1590, 1469, 1240, 1113, 1054, 840, 631. ^{1}H 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)

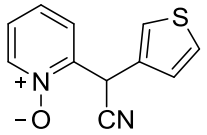


13f

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: 0.90 g (84%). Red solid. m. p.= 92–96 °C. IR (v/cm^{-1}): 3086, 3043, 2984, 2893, 2248, 1691, 1618, 1576, 1556, 1462, 1378, 1322, 1240, 1163, 1113, 1066, 857, 844, 783. ^{1}H 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

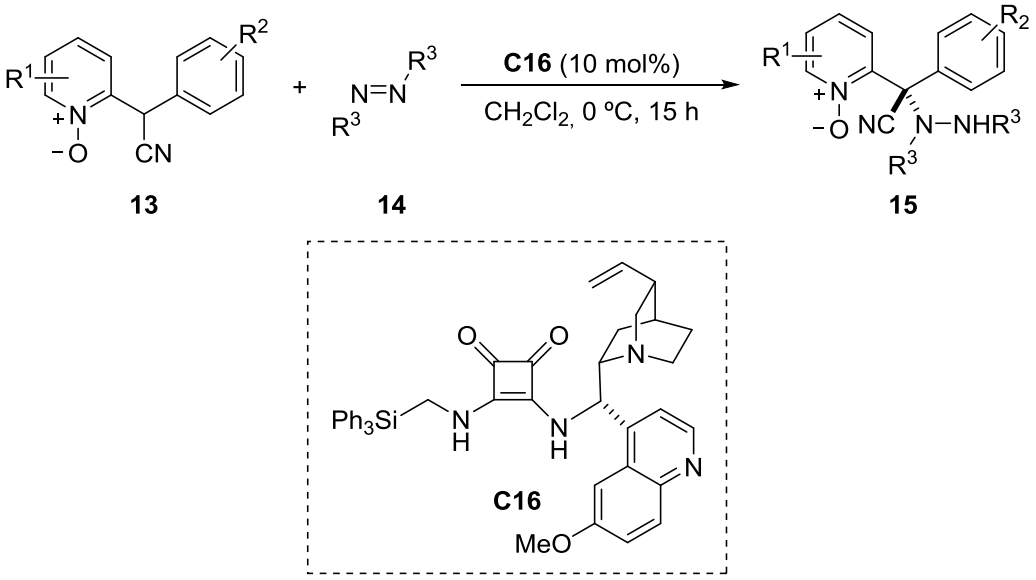
MHz, $CDCl_3$) δ 146.9, 135.7, 133.9, 133.0, 128.9, 126.4, 126.4, 125.5, 124.1, 117.0, 38.0. UPLC-DAD-QTOF: $C_{14}H_9N_2OF_3Br$ $[M+H]^+$ calcd.: 356.9850, found: 356.9843.

2-(Cyano(thiophen-3-yl)methyl)pyridine *N*-oxide (13g)


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: 0.38 g (60%). Red oil. IR (ν/cm^{-1}): 3114, 3083, 2890, 2240, 1711, 1604, 1483, 1427, 1272, 1237, 1142, 943, 837, 762, 621. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{11}H_9N_2OS$ $[M+H]^+$ calcd.: 217.0436, found: 217.0428.

6.4.1.2. General procedure for the enantioselective α-amination

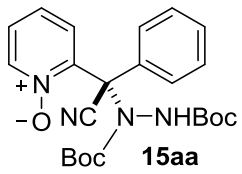


To a solution of the corresponding pyridine *N*-oxide **13** (1 equiv., 0.2 mmol) in CH_2Cl_2 (1 mL), catalyst **C16** (0.1 equiv, 0.02 mmol, 0.014 g) and the corresponding azodicarboxylate **14** (1.5 equiv., 0.3 mmol) were added at 0 ºC. The resulting mixture was stirred for 15 hours at the same temperature. Then, the reaction mixture was quenched with HCl 0.1 M (7 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by flash column chromatography on silica gel (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 ^{1}H NMR analysis (in DMSO-*d*$_6$ at 70 °C).

Racemic adducts for the determination of the enantiomeric excesses were prepared following the general procedure employing DBU as aquiral Brønsted base.

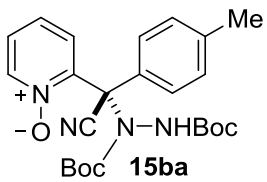
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(phenyl)methyl)pyridine *N*-oxide (15aa)



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 (ν/cm^{-1}): 3330, 2977, 2931, 2251, 1717, 1604, 1428, 1366, 1245, 1149, 1051, 912, 839, 729. ^{1}H NMR (500 MHz, 70 °C, 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, 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: $C_{23}H_{28}N_4O_5$ $[M+H]^+$ calcd.: 441.2138, found: 441.2141. Elem. Anal. calcd for $C_{23}H_{28}N_4O_5$ (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, λ = 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)

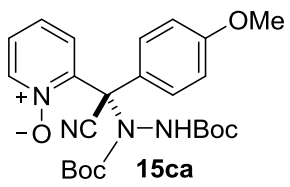


15ba

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 (ν/cm^{-1}): 3174, 2976, 2930, 2252, 1716, 1607, 1428, 1365, 1248, 1150, 1050, 1025, 1008, 765. ^{1}H NMR (500 MHz, 70 °C, 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, 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, λ = 210 nm) t_R (minor.) = 21.8 min, t_R (major.) = 48.7 min. 82% *ee*.

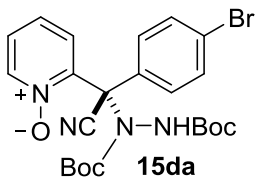
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-methoxyphenyl)methyl)pyridine *N*-oxide (15ca)



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. ^{1}H NMR (500 MHz, 70°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, λ = 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 *N*-oxide (15da)

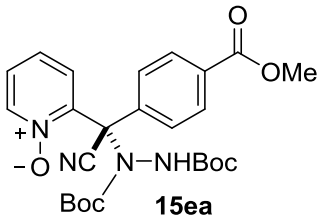


15da

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. ^{1}H NMR (500 MHz, 70 °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°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,

5.16; N, 10.10. Chiral HPLC (Chiralpak IA; 90:10 hexane:EtOH; 1.00 mL/min, λ = 210 nm) t_R (minor.) = 26.8 min, t_R (major.) = 56.6 min. 92% *ee*.

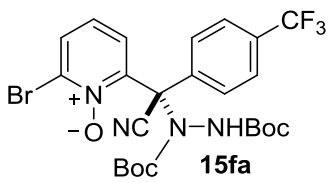
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15ea)



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. ^{1}H NMR (500 MHz, 70 °C, 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, 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: $C_{25}H_{31}N_4O_7$ $[M+H]^+$ calcd.: 499.2193, found: 499.2196. Chiral HPLC (Chiralpak IA; 60:40 hexane:EtOH; 0.50 mL/min, λ = 210 nm) t_R (minor.) = 13.9 min, t_R (major.) = 23.0 min. 93% *ee*.

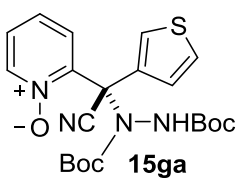
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(trifluoromethyl)phenyl)methyl)-6-bromopyridine *N*-oxide (15fa)



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. ^{1}H NMR (300 MHz, rt, 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, rt, DMSO-d_6) 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: $C_{24}H_{27}BrF_3N_4O_5$ $[M+H]^+$ calcd.: 587.1117, found: 587.1119. Chiral HPLC (Chiralpak IA; 95:5 hexane:EtOH; 1.00 mL/min, λ = 230 nm) t_R (minor.) = 35.7 min, t_R (major.) = 91.0 min. 88% *ee*.

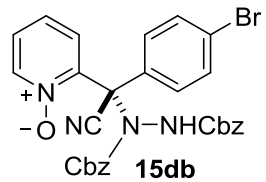
(*S*)-2-((1,2-bis(tert-butoxycarbonyl)hydrazinyl)(cyano)(thiophen-3-yl)methyl)pyridine *N*-oxide (15ga)



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. $[\alpha]_D^{23}$= +49.3 (*c* = 0.88, CH_2Cl_2). IR (ν/cm^{-1}): 3198, 2976, 2931, 2244, 1719, 1586, 1429, 1367, 1249, 1152, 771. ^{1}H 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: $C_{21}H_{27}N_4O_5S$ $[M+H]^+$ calcd.: 447.1702, found: 447.1707. Chiral HPLC (Chiralpak IA; 70:30 hexane:EtOH; 0.50 mL/min, λ = 210 nm) t_R (minor.) = 15.1 min, t_R (major.) = 23.8 min. 90% *ee*.

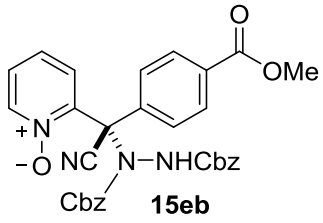
(*S*)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine *N*-oxide (15db)



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. $[\alpha]_D^{23}$= +47.1 (*c* = 1.02, CH_2Cl_2). IR (ν/cm^{-1}): 3330, 2976, 2931, 2250, 1716, 1604, 1365, 1244, 1147, 755, 732, 695. ^{1}H NMR (500 MHz, 70 °C, 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, 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: $C_{29}H_{24}BrN_4O_5$ $[M+H]^+$ calcd.: 587.0930, found: 587.0948. Elem. Anal. calcd for $C_{29}H_{23}BrN_4O_5$ (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, λ = 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)

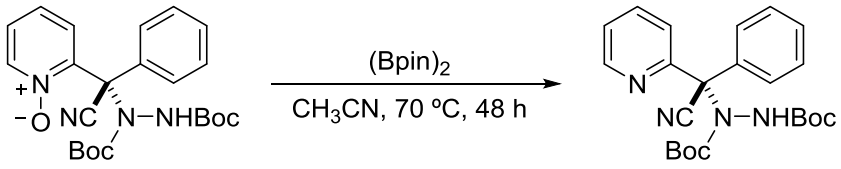


15eb

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 (v/cm^{-1}): 3301, 2951, 2236, 1721, 1609, 1430, 1278, 1111, 733, 697. ^{1}H NMR (500 MHz, 70°C, 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, 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: $C_{31}H_{27}BrN_4O_7$ $[M+H]^+$ calcd.: 567.1880, found: 567.1876. Elem. Anal. calcd for $C_{31}H_{26}N_4O_7$ (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, λ = 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[240]



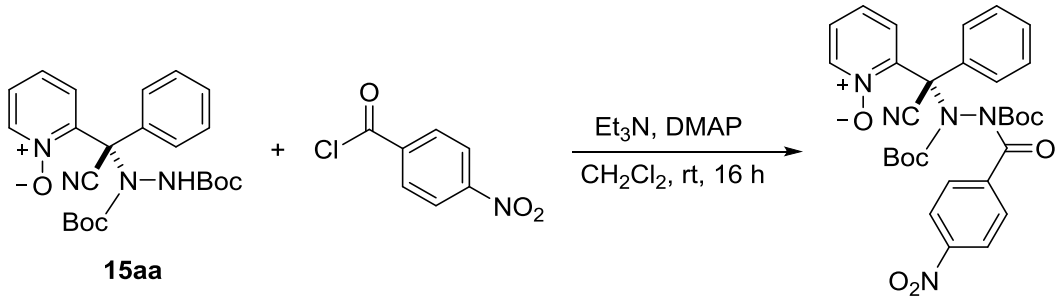
15aa **15'aa**

A solution of adduct **15aa** (0.44 g, 1 mmol, 1 equiv.) in acetonitrile (10 mL) was stirred in an oven-dried reaction vial, bis(pinacolato)diboron ($(pinB)_2$) (0.76 g, 3 mmol, 3 equiv.) was added and the mixture was stirred at 70 ºC for 24 h. Afterwards 3 equiv. more of $(pinB)_2$ were added and the reaction stirred at 70 ºC 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

[240] 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: 0.33 g (77 %). $[\alpha]_D^{25}$= +22.6 (*c* = 1.00, CH_2Cl_2)**.** IR (ν/cm^{-1}): 2977, 2931, 2252, 1720, 1451, 1367, 1244, 1149, 912, 729, 697. ^{1}H 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: $C_{23}H_{29}N_4O_4$ $[M+H]^+$ calcd.: 425.2183, found: 425.2179.

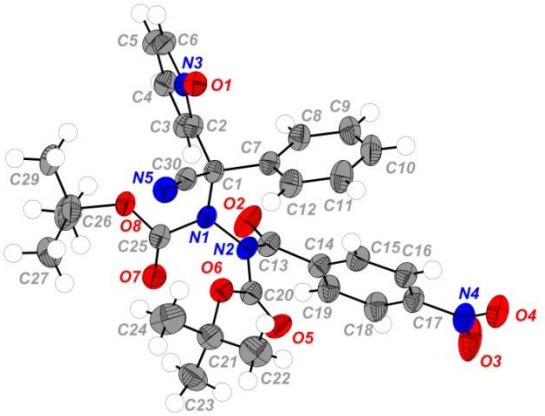
6.4.1.3.2. Acylation of adduct 15aa.[241] Determination of the absolute configuration.

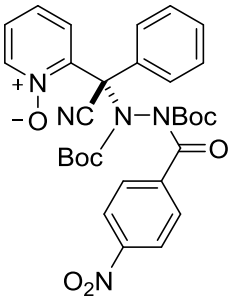


To a solution of **15aa** (1 equiv., 0.30 mmol, 0.13 g) in CH_2Cl_2 (4 mL), Et_3N (16 equiv., 4.8 mmol, 0.67 mL) and 4-dimethylaminopyridine (DMAP) (0.1 equiv., 0.03 mmol, 0.037 g) were added at 0 °C. After stirring the reaction mixture at room temperature for 16 hours, CH_2Cl_2 was evaporated under 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: 0.11 g (60%). White solid. m. p.= 163–165 °C. IR (ν/cm^{-1}): 2976, 2922, 2851, 2273, 1759, 1730, 1520, 1427, 1346, 1304, 1259, 1134, 838, 779, 756. $[\alpha]_D^{25}$= +143.0 (*c* = 1.1, 90% *ee*, CH_2Cl_2). ^{1}H 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: $C_{30}H_{32}N_5O_8$ $[M+H]^+$ calcd.: 590.2251, found: 590.2255.

Compound **16** was synthetized 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/.

[241] 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.



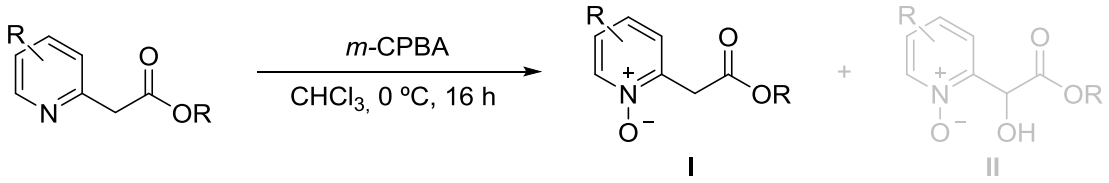


16

6.4.2. Enantioselective Mannich reaction of 2-azaaryl *N*-oxides to *N*-Boc imines

6.4.2.1. Preparation of pronucleophiles

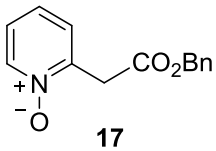
6.4.2.1.1. Synthesis of pyridyl *N*-oxide acetates 17, 19 and 20



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)



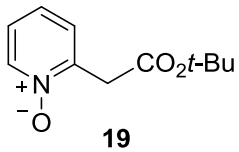
17

The title compound **17** was prepared according to the general procedure using benzyl 2-(pyridin-2-yl)acetate[242] (5% of **II** was obtained). Yield: 0.81 g (66%). White solid. m. p. = 101 – 104 °C. IR

[242] 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. ^{1}H 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: $C_{14}H_{14}NO_3$ $[M+H]^+$ calcd.: 244.0979, found: 244.0974.

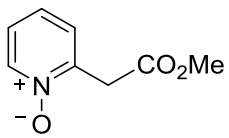
2-(2-(*tert*-Butoxy)-2-oxoethyl)pyridine *N*-oxide (19)



19

The title compound **19** was prepared according to the general procedure using *tert*-butyl 2-(pyridin-2-yl)acetate[242] (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. ^{1}H 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: $C_{11}H_{16}NO_3$ $[M+H]^+$ calcd.: 210.1130, found: 210.1127.

2-(2-Methoxy-2-oxoethyl)pyridine *N*-oxide (20a)

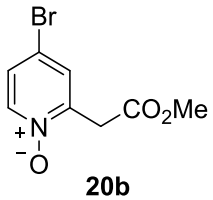


20a

The title compound **20a** was prepared according to the general procedure using methyl 2-(pyridin-2-yl)acetate[243] (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. ^{1}H 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: $C_8H_{10}NO_3$ $[M+H]^+$ calcd.: 168.0661, found: 168.0664.

[243] Prepared following the reported procedure: Nacsa, E. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2015**, *137*, 10246–10253.

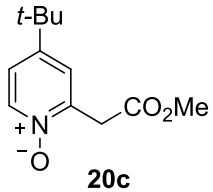
4-Bromo-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20b)



20b

The title compound **20b** was prepared according to the general procedure using methyl 2-(4-bromopyridin-2-yl)acetate[244] (30% of **II** was obtained). Yield: 0.55 g (45%). White solid. m. p. = 93 – 97 °C. IR (ν/cm^{-1}): 3047, 2952, 1734, 1461, 1425, 1339, 1248, 1164, 1003, 821, 730, 649, 547, 494. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 146.8, 140.1, 130.2, 128.2, 118.6, 52.6, 36.6. UPLC-DAD-QTOF: $C_8H_8NO_3Br$ $[M+H]^+$ calcd.: 245.9766, found: 245.9769.

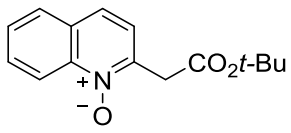
4-(*tert*-Butyl)-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20c)



20c

The title compound **20c** was prepared according to the general procedure using methyl 2-(4-(*tert*-butyl)pyridin-2-yl)acetate[244] (20% of **II** was obtained). Yield: 0.61 g (55%). Colorless oil. IR (ν/cm^{-1}): 2955, 1739, 1438, 1245, 773. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 150.5, 144.5, 138.6, 124.2, 122.1, 52.4, 37.1, 34.6, 30.6. UPLC-DAD-QTOF: $C_{12}H_{18}NO_3$ $[M+H]^+$ calcd.: 244.1287, found: 244.1293.

6.4.2.1.2. Synthesis of 2-(2-(*tert*-butoxy)-2-oxoethyl)quinoline *N*-oxide (28)[245]



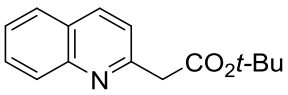
28

To a solution of *tert*-butyl acetate (2.7 mL, 20 mmol, 2.0 equiv.) in *t*-$BuNH_2$ (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 $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by flash column

[244] Prepared following the reported procedure: Londregan, A. T.; Burford, K.; Conn, E. L.; Hesp, K. D. *Org. Lett.* **2014**, *16*, 3336–3339.
[245] 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. ^{1}H 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: $C_{15}H_{17}NO_3$ $[M+H]^+$ calcd.: 260.1287, found: 260.1286.

6.4.2.1.3. Synthesis of *tert*-butyl 2-(quinolin-2-yl)acetate (28')

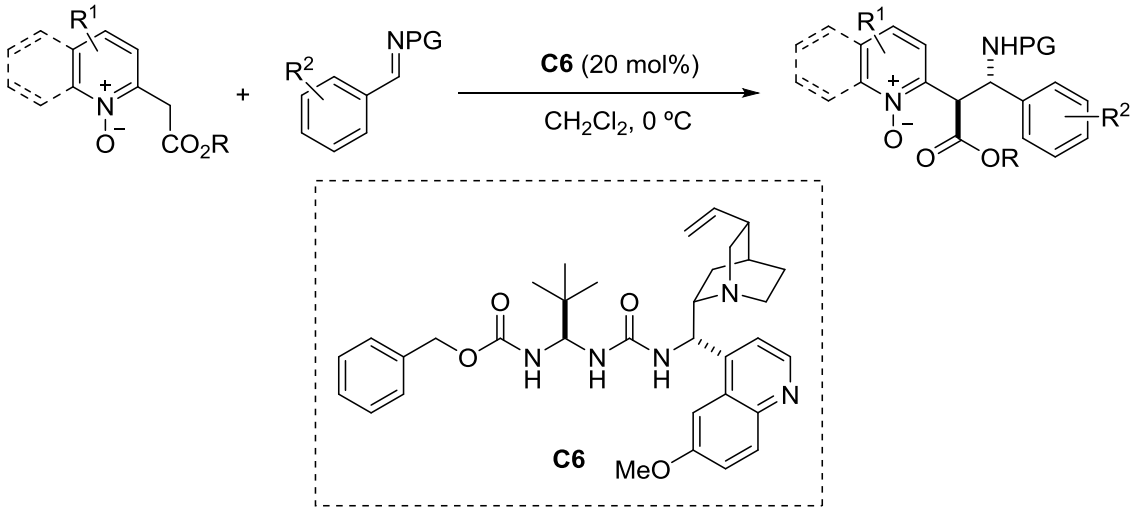


28'

To a solution of **28** (1 equiv., 1 mmol, 0.26 g) in CH_2Cl_2 (9 mL), bis(pinacolato)diboron (3 equiv., 3 mmol, 0.76 g) was added and the reaction mixture was stirred at room temperature for 16 hours. Then, ethylendiamine (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: 0.18 g (75%). ^{1}H 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.[246]

[246] Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916–920.

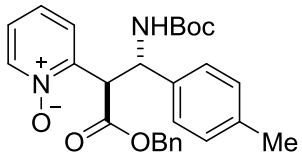
6.4.2.2. General procedure for the enantioselective Mannich reaction of pyridyl *N*-oxide acetate with *N*-protected imines



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) 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 aquiral Brønsted base.

2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-oxo-3-phenoxy-1-(*p*-tolyl)propan-2yl)pyridine *N*-oxide (18a)

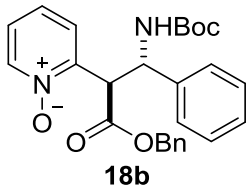


18a

The title compound **18a** was prepared on 1 mmol scale according to the general procedure employing *N*-oxide **17** and *N*-Boc imine **4a**. Reaction time: 48 hours. Yield: 0.46 g (95%). White solid. m. p.= 42–45 °C. $[\alpha]_D^{25}$= –46.1 (c = 0.55, $CHCl_3$). IR (ν/cm^{-1}): 2973, 1706, 1514, 1434, 1365, 1286, 1250, 1164, 764, 697. ^{1}H 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: $C_{27}H_{31}N_2O_5$ $[M+H]^+$ calcd.: 463.2233, found: 463.2241. Chiral HPLC (Chiralpack IC; 50:50

Hexane:Ethanol; 0.7 mL/min, λ = 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.*

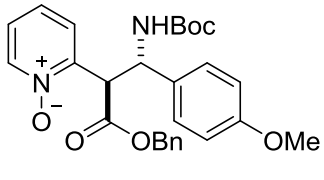
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)pyridine *N*-oxide (18b)



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. ^{1}H 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: $C_{26}H_{29}N_2O_5$ $[M+H]^+$ calcd.: 449.2076 found: 449.2082. Chiral HPLC (Chiralpack IC; 60:40 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

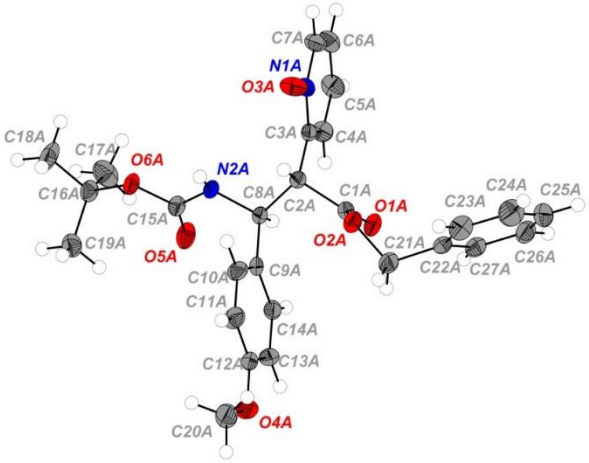
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18c)



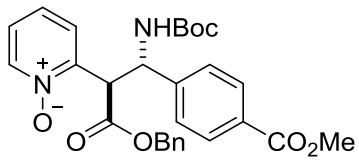
18c

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. ^{1}H 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: $C_{27}H_{31}N_2O_6$ $[M+H]^+$ calcd.: 479.2182, found: 479.2187. Chiral HPLC (Chiralpak AD-H; 20:80 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

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/.



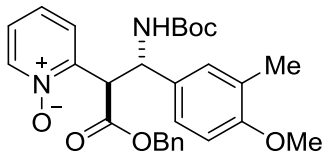
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18d)



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 (v/cm^{-1}): 2972, 1717, 1490, 1434, 1278, 1164, 1104, 1018, 764, 698. ^{1}H 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: $C_{28}H_{31}N_2O_7$ $[M+H]^+$ calcd.: 507.2131, found: 507.2141. Chiral HPLC (Chiralpack IC; 70:30 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

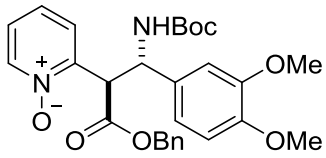
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18g)



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: 0.051 g (87%). White solid. m. p.= 58–61 °C. $[\alpha]_D^{24}$ = –37.3 (c = 0.58, CH_2Cl_2). IR (ν/cm^{-1}): 2966, 2924, 2853, 1728, 1705, 1503, 1253, 1163, 1029, 766. ^{1}H 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: $C_{28}H_{32}N_2O_6$ $[M+H]^+$ calcd.: 493.2339, found: 493.2345. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

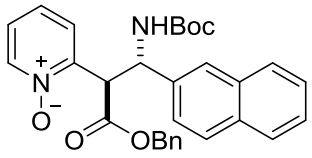
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18h)



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: 0.054 g (88%). White solid. m. p.= 55–59 °C. $[\alpha]_D^{24}$ = –45.0 (c = 0.79, CH_2Cl_2). IR (ν/cm^{-1}) = 2969, 2930, 1728, 1706, 1515, 1257, 1162, 1026, 765. ^{1}H 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: $C_{28}H_{32}N_2O_7$ $[M+H]^+$ calcd.: 509.2288 found: 509.2299. Chiral HPLC (Chiralpack IC; 70:30 Hexane:Ethanol; 0.7 mL/min, λ = 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.*

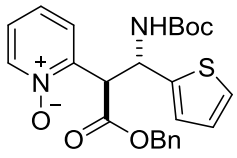
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18i)



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 (ν/cm^{-1}) = 2974, 2929, 1703, 1490, 1433, 1365, 1250, 1163, 1050, 1019, 984, 858, 765, 746, 697, 479. ^{1}H 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: $C_{30}H_{30}N_2O_5$ $[M+H]^+$ calcd.: 499.2233, found: 499.2237. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.7 mL/min, λ = 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.*

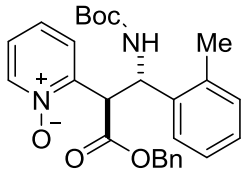
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)pyridine *N*-oxide (18j)



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 (ν/cm^{-1}): 2975, 2928, 1706, 1489, 1433, 1365, 1251, 1163, 766, 734, 698. ^{1}H 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: $C_{24}H_{26}N_2O_5S$ $[M+H]^+$ calcd.: 455.1641, found: 455.1645. Chiral HPLC (Chiralpack IC; 80:20 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

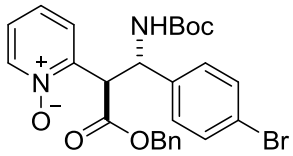
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(o-tolyl)propan-2-yl)pyridine *N*-oxide (18l)



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 (v/cm^{-1}): 2973, 1702, 1492, 1433, 1365, 1287, 1250, 1164, 1045, 729, 697. ^{1}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}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: $C_{27}H_{31}N_2O_5$ $[M+H]^+$ calcd.: 463.2233, found: 463.2247. Chiral HPLC (Chiralpack IC; 50:50 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

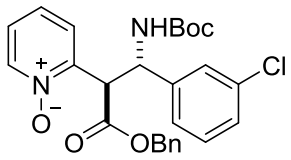
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(4-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-1-oxopropan-2-yl)pyridine *N*-oxide (18m)



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 (v/cm^{-1}): 2974, 1705, 1488, 1434, 1365, 1283, 1250, 1165, 1010, 765. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}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}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: $C_{26}H_{28}N_2O_5Br$ $[M+H]^+$ calcd.: 527.1182, found: 527.1183. Chiral HPLC (Chiralpack IC; 60:40 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

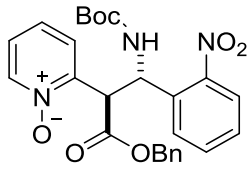
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18n)



18n

The title compound **18n** was prepared on 0.24 mmol scale according to the general procedure employing *N*-oxide **17**, *N*-Boc imine **4n** and catalyst **C6** (0.05 equiv., 0.012 mmol, 0.007 g). Reaction time: 30 hours. Yield: 0.104 g (90%). White solid. m. p.= 51–53°C. $[\alpha]_D^{25}$ = –58.9 (c = 1.45, CH_2Cl_2). IR (v/cm^{-1}): 2974, 1706, 1490, 1434, 1365, 1250, 1164, 767, 697. ^{1}H 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: $C_{26}H_{28}Cl\ N_2O_5$ $[M+H]^+$ calcd.: 483.1687, found: 483.1691. Chiral HPLC (Chiralpak IC; 20:80 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

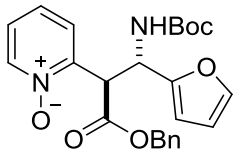
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(2-nitrophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18o)



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. $[\alpha]_D^{25}$ = 28.8 (c = 0.63, CH_2Cl_2). IR (v/cm^{-1}): 2975, 1706, 1525, 1437, 1364, 1249, 1166, 1052, 746. ^{1}H 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: $C_{26}H_{28}N_3O_7$ $[M+H]^+$ calcd.: 494.1927, found: 494.1941. Chiral HPLC (Chiralpack IA; 20:80 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

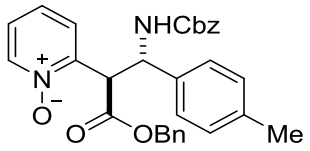
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18p)



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 (ν/cm^{-1}): 2969, 1707, 1498, 1434, 1366, 1255, 1165, 1022, 874, 768. ^{1}H 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: $C_{24}H_{27}N_2O_6$ $[M+H]^+$ calcd.: 439.1869, found: 439.1878. Chiral HPLC (Chiralpack IC; 80:20 Hexane:Ethanol; 0.5 mL/min, λ = 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.*

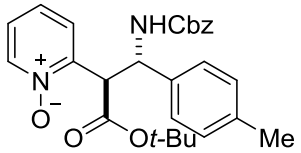
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(((benzyloxy)carbonyl)amino)-1-oxo-3-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (22)



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 (ν/cm^{-1}): 3030, 1721, 1514, 1433, 1258, 1174, 1042, 764, 697. ^{1}H 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: $C_{30}H_{29}N_2O_5$ $[M+H]^+$ calcd.: 497.2076, found: 497.2072. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, λ = 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)

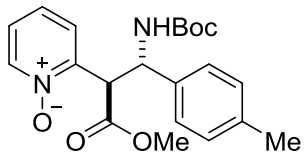


23

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 (ν/cm^{-1}): 2972, 1716, 1646, 1540, 1433, 1255, 1152, 1027, 736. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.5 Hz,

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: $C_{24}H_{27}N_2O_6$ $[M+H]^+$ calcd.: 463.2233, found: 463.2240. Chiral HPLC (Chiralpak IC; 60:40 Hexane:Ethanol; 0.5 mL/min, λ = 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*.

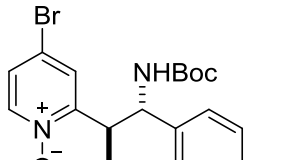
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (24)



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. $[\alpha]_D^{25}$ = – 64.0 (c = 1.00, CH_2Cl_2). IR (ν/cm^{-1}): 2975, 1734, 1705, 1513, 1489, 1432, 1365, 1250, 1165, 1051, 1020, 995, 768. ^{1}H 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: $C_{21}H_{27}N_2O_5$ $[M+H]^+$ calcd.: 387.1920, found: 387.1929. Chiral HPLC (Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, λ = 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*.

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)

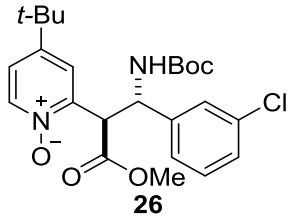


25

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. $[\alpha]_D^{25}$ = – 28.4 (c = 1.75, CH_2Cl_2). IR (ν/cm^{-1}): 2974, 2248, 1731, 1701, 1513, 1458, 1410, 1365, 1247, 1162, 729, 650. ^{1}H 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, λ = 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*.

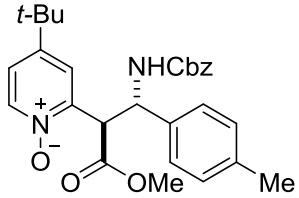
2-((1S,2R)-1-((*tert*-Butoxycarbonyl)amino)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (26)



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. ^{1}H 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, λ = 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*.

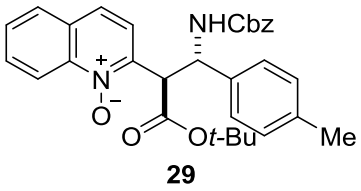
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (27)



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. ^{1}H 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, λ = 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*.

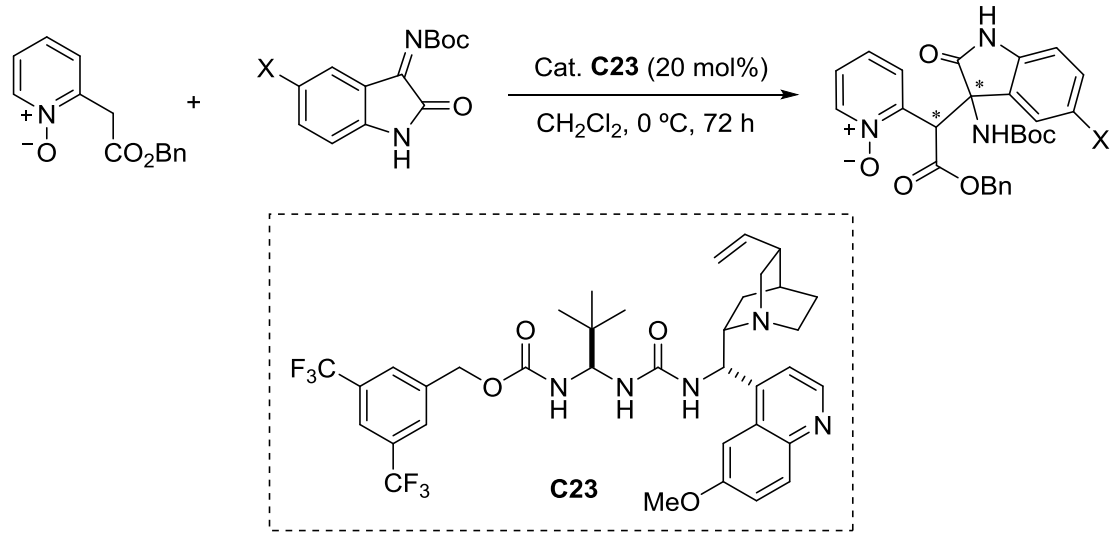
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)quinoline *N*-oxide (29)



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 (ν/cm^{-1}): 3030, 2976, 1717, 1514, 1327, 1282, 1241, 1046, 736, 697. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}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}C NMR (75 MHz, $CDCl_3$) ^{13}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: $C_{31}H_{32}N_2O_5$ $[M+H]^+$ calcd.: 513.2389, found: 513.2393. Chiral HPLC (Chiralpak IC; 70:30 Hexane:Ethanol; 0.7 mL/min, λ = 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*.

6.4.2.3. General procedure for the Mannich reaction of pyridyl acetate *N*-oxide with *N*-Boc isatin ketimines

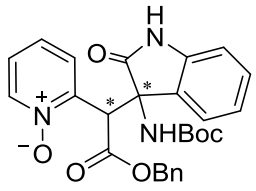


To a solution of pyridyl acetate *N*-oxide **17** (1 equiv., 0.12 mmol, 0.029 g) and catalyst **C23** (0.2 equiv., 0.024 mmol, 0.017 g) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C, the corresponding *N*-Boc isatin ketimine (0.36 mmol, 3 equiv.) was added. The resulting solution was stirred at the same temperature 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 aquiral Brønsted base.

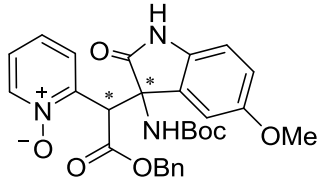
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (32)



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 (ν/cm^{-1}): 2963, 2926, 1741, 1716, 1619, 1473, 1257, 1157, 751. ^{1}H 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: $C_{27}H_{27}N_3O_6$ $[M+H]^+$ calcd.: 490.1978, found: 490.1985. Chiral HPLC (Chiralpak IC + Chiralpak IC; 50:50 Hexane:Ethanol; 0.5 mL/min, λ = 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*.

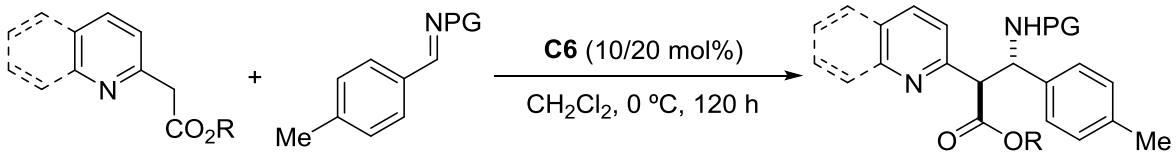
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-5-methoxy-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (33)



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 (ν/cm^{-1}): 2976, 1712, 1489, 1215, 1161, 733. ^{1}H 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: $C_{28}H_{29}N_3O_7$ $[M+H]^+$ calcd.: 520.2084, found: 520.2087. Chiral HPLC (Chiralpak IC; 80:20 Hexane:Ethanol; 0.7 mL/min, λ = 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*.

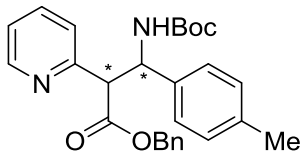
6.4.2.4. General procedure for the Mannich reaction of azaaryl acetates with *N*-protected imines



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 aquiral Brønsted base.

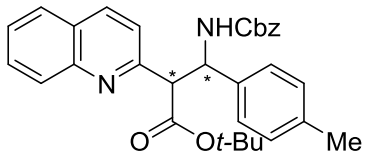
Benzyl 3-((*tert*-butoxycarbonyl)amino)-2-(pyridin-2-yl)-3-(*p*-tolyl)propanoate (18'a)



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. ^{1}H 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')**

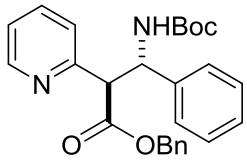


29'

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

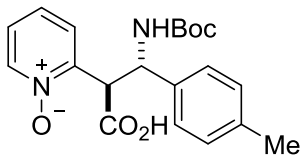
6.4.2.5.1. Reduction of the *N*-oxide group to afford 18'b



18'b

To a solution of adduct **18b** (1 equiv., 0.25 mmol, 0.12 g) in CH_2Cl_2 (3 mL) was added bis(pinacolato)diboron (3 equiv., 0.75 mmol, 0.19 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, CH_2Cl_2). IR (ν/cm^{-1}): 2975, 1711, 1591, 1497, 1365, 1288, 1164, 753, 699. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{26}H_{29}N_2O_4$ $[M+H]^+$ 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*.

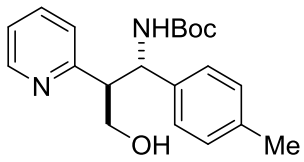
6.4.2.5.2. Synthesis of β^{2,3}-amino acid 34



34

To a solution of adduct **18a** (1 equiv., 0.25 mmol, 0.12 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.012 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 **34**. Yield: 0.087 g (89%). White solid. m. p = 72–77 °C. $[\alpha]_D^{24}$ = –2.4 (c = 1.94, CH_2Cl_2). IR (ν/cm^{-1}): 2975, 2927, 1700, 1512, 1365, 1249, 1165, 1018, 768. ^{1}H 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). ^{13}C 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: $C_{20}H_{24}N_2O_5$ $[M+H]^+$ calcd.: 373.1763, found: 373.1771; $[M+Na]^+$ calcd.: 395.1583, found: 395.1581.

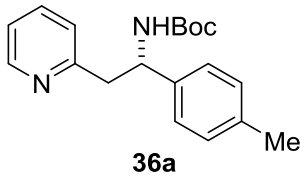
6.4.2.5.3. Synthesis of amino alcohol 35



35

To a solution of adduct **24** (1 equiv., 0.25 mmol, 0.097 g) in THF (2.5 mL), lithium aluminium hydride (0.19 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 CH_2Cl_2 (3 x 7 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 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, CH_2Cl_2). IR (ν/cm^{-1}): 3342, 3007, 2975, 2925, 2867, 1693, 1594, 1503, 1365, 1252, 1168, 1053. ^{1}H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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: $C_{20}H_{27}N_2O_3$ $[M+H]^+$ calcd.: 343.2022, found: 343.2042.

6.4.2.5.4. Synthesis of benzyl amine 36a

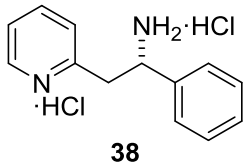


36a

To a solution of adduct **18a** (1 equiv., 0.25 mmol, 0.12 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.012 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, 0.19 g) was added. The reaction mixture was stirred at room temperature for 16 hours. Then, ethylendiamine (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 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 **36a**. Yield: 0.070 g (90%). White solid. m. p = 121–124 °C. $[\alpha]_D^{25}$ = –28.7 (c = 1.2, CH_2Cl_2). IR

(ν/cm^{-1}): 3006, 2974, 2924, 2867, 1695, 1511, 1364, 1247, 1164, 1018, 810, 751, 541. ^{1}H 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: $C_{19}H_{25}N_2O_2$ $[M+H]^+$ calcd.: 313.1916, found: 313.1929.

6.4.2.5.5. Synthesis of Lanicemine (AZD6765) dihydrochoride (38)



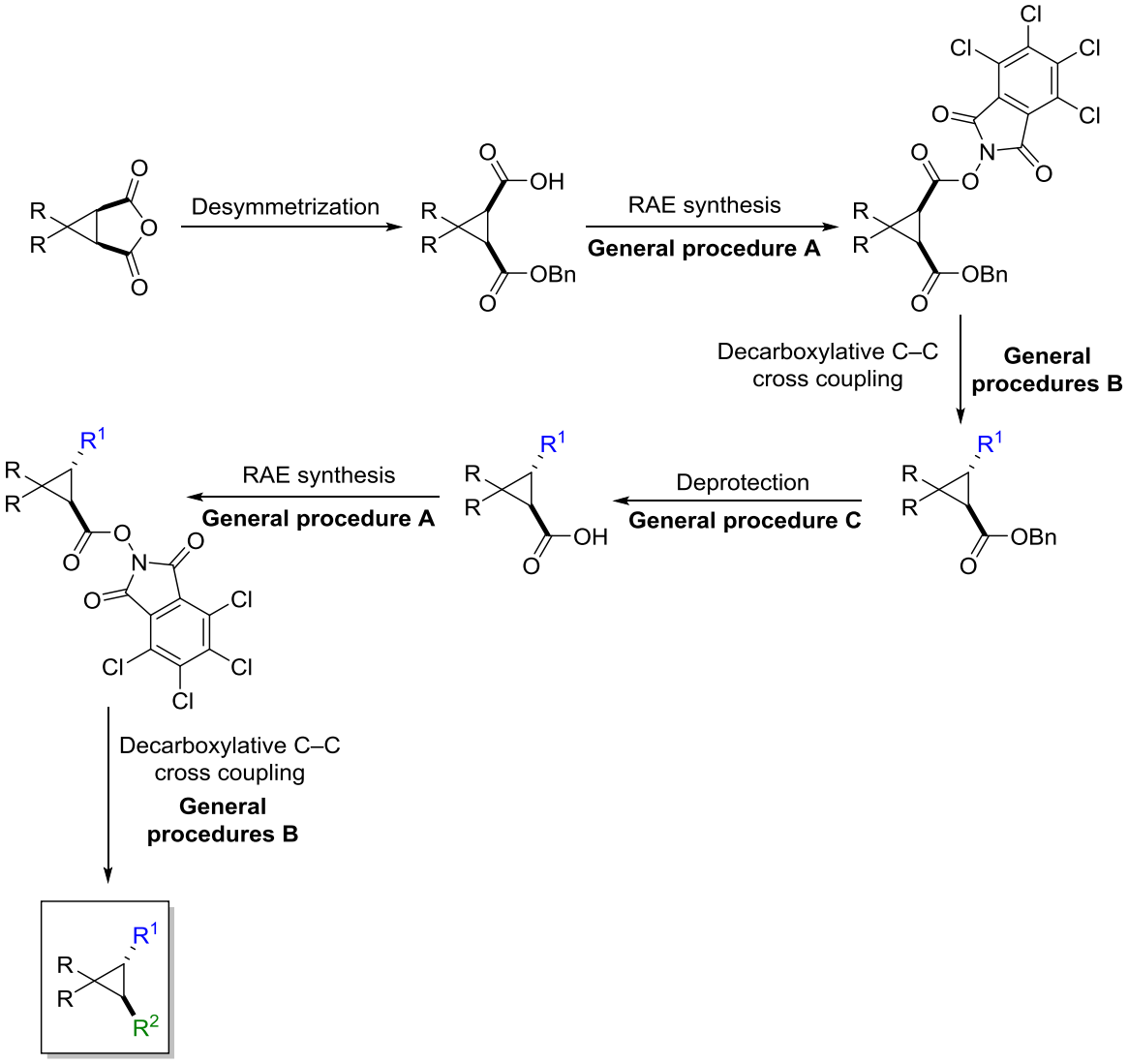
38

To a solution of adduct **18b** (1 equiv., 0.25 mmol, 0.12 g) in MeOH (3 mL) palladium on carbon (Pd/C) (0.012 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, ethylendiamine (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. ^{1}H NMR (300 MHz, 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.[247]

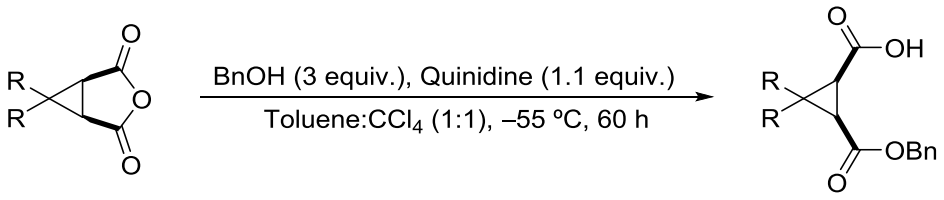
[247] Ref. 204a, page 122.

6.5. Experimental section for Chapter 4

Products in chapter 4 were synthetized following this general synthetic pathway:



6.5.1. Desymmetrization of *meso*-anhydrides[248]

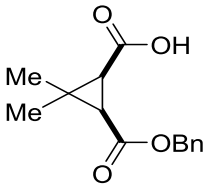


Benzyl alcohol (3.0 equiv., 45.0 mmol, 4.66 mL) was added dropwise to a stirred suspension of the corresponding anhydride (1.0 equiv., 15.0 mmol) and quinidine (1.1

[248] Ref. 215, page 136.

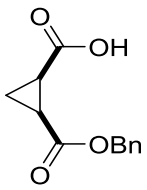
equiv., 16.5 mmol, 5.35 g) in a 1:1 mixture of toluene and tetrachloromethane (75 mL) at –55 °C under argon. The reaction mixture was stirred at this temperature for 60 hours. During this period, the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuo to 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.

(1*S*,3*R*)-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. $[\alpha]_D^{20}$ = –2.2 (c = 1.04, $CHCl_3$). ^{1}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}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.[248]

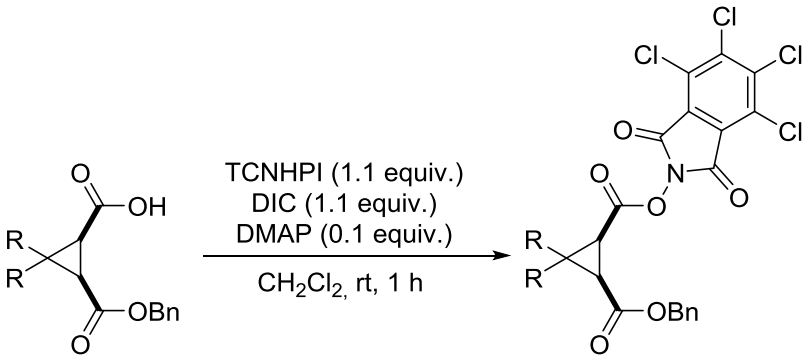
(1*R*,2*S*)-2-((Benzyloxy)carbonyl)cyclopropane-1-carboxylic acid



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. $[\alpha]_D^{20}$ = –5.2 (c = 1.00, $CHCl_3$). ^{1}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}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.[249]

[249] 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.[250] 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-comercial Grignard reagents (10 mmol scale):

LiCl (1.25 equiv., 12.5 mmol, 0.53 g) was flame-dried under vacuum. After cooling, the flask was placed under Ar atmosphere, and Mg turnings (2.5 equiv., 25 mmol, 0.61 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 complete addition, the mixture was placed in an oil bath (approximately 70 – 80 °C) and

[250] Ref. 211, page 131.

refluxed for 1 hour. The Grignard reagent was titrated with I_2 before use (see below). Typical concentrations were between 0.4 M and 0.8 M.

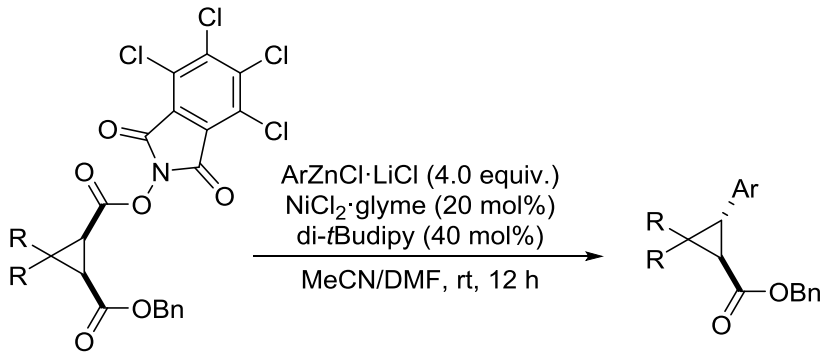
Transmetallation with $ZnCl_2$ (5 mmol scale):

$ZnCl_2$ (1.0 equiv., 5 mmol, 0.68 g) (and LiCl (1.0 equiv., 5 mmol, 0.21 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 $ZnCl_2$ dissolved. At this time, the Grignard reagent (1 equiv., 5 mmol) was added slowly to the $ZnCl_2$ 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 I_2 see below before its use. Optimal concentrations for the reactions to proceed successfully were between 0.35 M and 0.25 M for arylation reaction (arylzinc reagents) and between 0.25 M and 0.15 M for alkenylation reaction (alkenylzinc reagents).

Titration of arylzinc reagents:

I_2 (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 I_2. The concentration of the RZnCl·LiCl solution was then calculated.

6.5.3.1.1. Negishi arylation (General procedure B1)



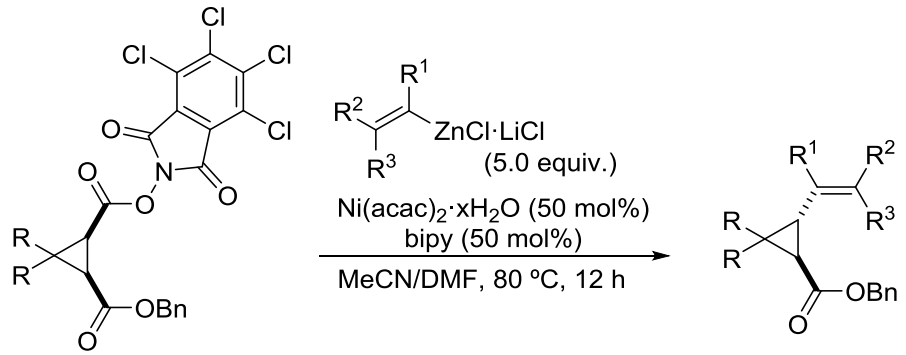
Preparation of the nickel/ligand solution:

A culture tube was charged with $NiCl_2$·glyme (0.25 mmol, 0.055 g) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.5 mmol, 0.13 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., 0.4 mmol) was added in one portion, the mixture was adjusted to a final approximate volume of 2 mL with MeCN and stirred at room temperature 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 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:

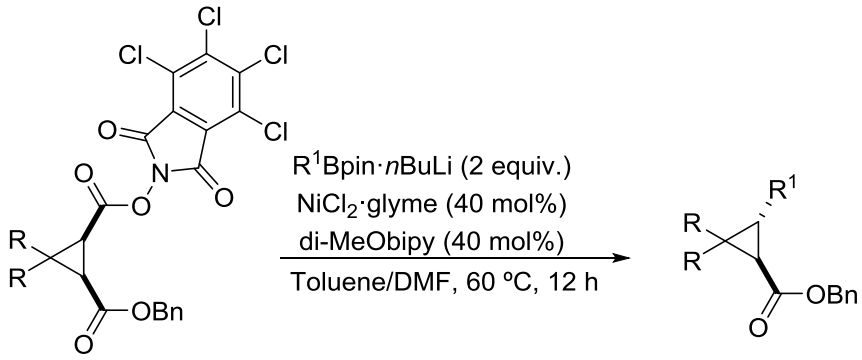
A culture tube was charged with $Ni(acac)_2$·xH_2O (0.5 mmol, 0.15 g) and 2,2'-bipyridine (0.5 mmol, 0.078 g) under argon atmosphere. Anhydrous DMF (10 mL) was added and the homogeneous solution was stirred at room temperature for 15 minutes before use.

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., 0.5 mmol) was added in one portion, the mixture was adjusted to a final approximate volume of 3.5 mL with MeCN and stirred at 80 °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.

6.5.3.2. Suzuki coupling (General procedure B3)



Preparation of the nickel/ligand solution:

A culture tube was charged with $NiCl_2$·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^1Bpin·*n*BuLi solution:

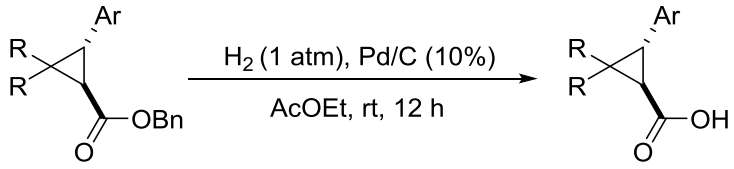
A flame-dried culture tube was charged with the corresponding R^1Bpin (0.3 mmol) under argon atmosphere and anhydrous toluene (1.5 mL) was added. A 2.5 M solution of *n*-BuLi in hexane (0.3 mmol, 0.12 mL) was added at 0 °C and the resulting mixture was stirred at room temperature for 15 minutes.

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^1Bpin·*n*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.

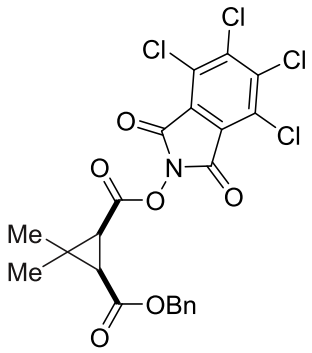
6.5.4. Deprotection of benzyl esters (General procedure C)



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 H_2 (g) with a balloon three times. The reaction was stirred under H_2 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.

Caracterization of compounds

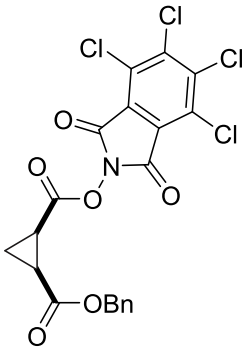
1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (1*R*,2*S*)-3,3-dimethylcyclopropane-1,2-dicarboxylate (47)



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, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{22}H_{16}Cl_4NO_6$ $[M+H]^+$: 529.9726, found: 529.9725. Chiral SFC (Daicel IB; 40% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 238 nm). t_R (major) = 4.14 min, t_R (minor) = 5.84 min. 96% *ee*.

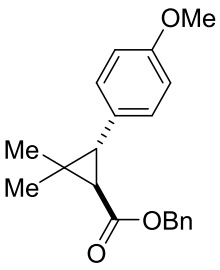
1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (1*R*,2*S*)-cyclopropane-1,2-dicarboxylate (48)



48

The title compound **48** was prepared on a 10.0 mmol scale according to general procedure A employing (1*R*,2*S*)-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}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}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 $C_{20}H_{12}Cl_4NO_6$ $[M+H]^+$: 501.9413, found: 501.9413. Chiral SFC (Daicel IA; 40% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 238 nm). t_R (minor) = 8.91 min, t_R (major) = 10.59 min. 96% *ee*.

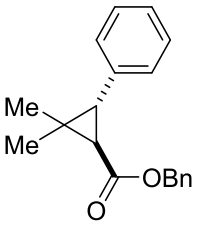
Benzyl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (49a)



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: 0.347 g (56 %). Yellow oil. $[\alpha]_D^{20}$ = +16.2 (c = 0.65, $CHCl_3$). ^{1}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}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 $C_{20}H_{23}O_3$ $[M+H]^+$: 311.1642, found: 311.1646. Chiral SFC (Daicel IG; 30% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 226 nm). t_R (minor) = 1.64 min, t_R (major) = 1.94 min. 94% *ee*.

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (49b)

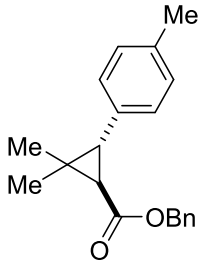


49b

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 (54 %). Colorless oil. $[\alpha]_D^{20}$ = +23.6 (c = 0.40, $CHCl_3$). ^{1}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

(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 $C_{19}H_{21}O_2$ $[M+H]^+$: 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. 97% *ee*.

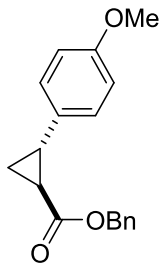
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropane-1-carboxylate (49c)



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: 0.014 g (47 %). Yellow oil. $[\alpha]_D^{20}$ = +6.4 (c = 0.10, $CHCl_3$). ^{1}H 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 $C_{20}H_{23}O_2$ $[M+H]^+$: 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. 96% *ee*.

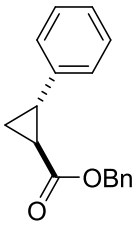
Benzyl (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (50a)



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. $[\alpha]_D^{20}$ = +101.5 (c = 0.27, $CHCl_3$). ^{1}H 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 $C_{18}H_{19}O_3$ $[M+H]^+$: 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*.

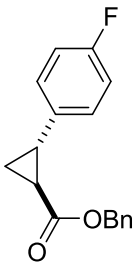
Benzyl (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylate (50b)



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:CH_2Cl_2). Yield: 0.013 g (50 %). Colorless oil. $[\alpha]_D^{20}$ = +168.2 (c = 0.75, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}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 $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223, found: 253.1219. Chiral SFC (Daicel IBN; 5% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 2.51 min, t_R (major) = 2.65 min. 94% *ee*.

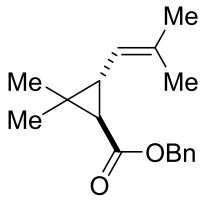
Benzyl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (50d)



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:CH_2Cl_2 to 3:2 hexane:CH_2Cl_2). Yield: 0.227 g (42 %). Yellow oil. $[\alpha]_D^{20}$ = +161.6 (c = 0.19, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) 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).^{13}C NMR (126 MHz, $CDCl_3$) 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.3. GC/MS (EI): m/z (%) 270 (1%), 225 (5%), 133 (14%), 91 (100%). Chiral SFC (Daicel IG; 15% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 2.04 min, t_R (major) = 2.37 min. 94% *ee*.

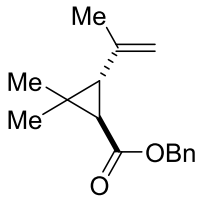
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (54a)



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:CH_2Cl_2). Yield: 0.010 g (40 %). Yellow oil. $[\alpha]_D^{20}$ = –9.5 (c = 0.48, $CHCl_3$). ^{1}H 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 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 $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1693, found: 259.1692. Chiral SFC (Daicel IG; 3% MeOH / CO_2 (2.8 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 2.51 min, t_R (major) = 2.80 min. 93% *ee*.

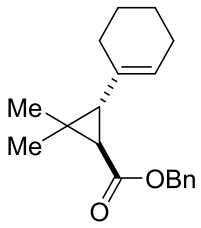
Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(prop-1-en-2-yl)cyclopropane-1-carboxylate (54b)



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:CH_2Cl_2). Yield: 0.013 g (55 %). Yellow oil. $[\alpha]_D^{20}$ = +10.2 (c = 0.55, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{16}H_{21}O_2^+$ $[M+H]^+$: 245.1536; found: 245.1537. Chiral SFC (Daicel IG; 5% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 1.71 min, t_R (major) = 1.95 min. 92% *ee*.

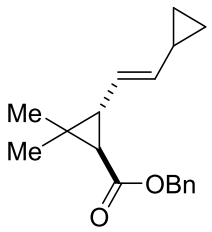
Benzyl (1*R*,3*R*)-3-(cyclohex-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylate (54c)



54c

The title compound **54c** was prepared according to general procedure B2 employing **47** and the arylzinc reagent derived from 1-bromocyclohexene.[251] Purification by pTLC (7:3 hexane:CH_2Cl_2). Yield: 0.022 g (72 %). Yellow oil. $[\alpha]_D^{20}$ = +26.7 (c = 0.33, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.4 Hz, 4H), 7.35 – 7.29 (m, 1H), 5.38 (tt, *J* = 3.9, 1.8 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 2.01 – 1.96 (m, 2H), 1.94 (dd, *J* = 5.7, 2.0 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.69 (d, *J* = 5.8 Hz, 1H), 1.65 – 1.58 (m, 3H), 1.53 – 1.48 (m, 1H), 1.27 (s, 3H), 1.26 – 1.25 (m, 1H), 1.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) 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 $C_{19}H_{25}O_2^+$ $[M+H]^+$: 285.1849; found: 285.1852. Chiral SFC (Daicel IA; 3% ^{i}PrOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 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)

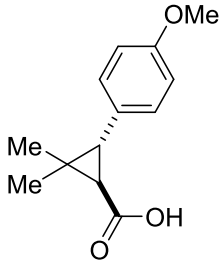


54f

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:CH_2Cl_2). Yield: 0.022 g (55 %). Yellow oil. $[\alpha]_D^{20}$ = –7.8 (c = 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $C_{18}H_{23}O_2^+$ $[M+H]^+$: 271.1693; found: 271.1693. Chiral SFC (Daicel IG; 5% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 214 nm). t_R (minor) = 1.87 min, t_R (major) = 2.27 min. 95% *ee*.

[251] 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.

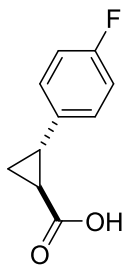
(1*R*,3*R*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylic acid (71)



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}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}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.

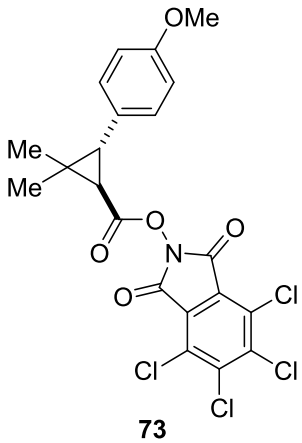
(1*S*,2*S*)-2-(4-Fluorophenyl)cyclopropane-1-carboxylic acid (72)



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, CHCl3). ^{1}H NMR (400 MHz, CDCl3) 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}C NMR (151 MHz, CDCl3) 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}F NMR (376 MHz, CDCl3) δ -116.0.

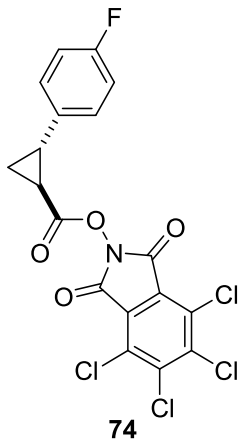
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (73)



73

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}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}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 $C_{21}H_{16}Cl_4NO_5$ $[M+H]^+$: 501.9777, found: 501.9776.

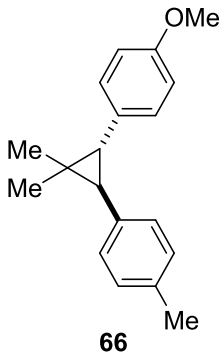
4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (74)



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}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}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}F NMR (376 MHz, $CDCl_3$): δ –115.1. HRMS (ESI-TOF): calcd for $C_{18}H_8FNNaO_4$ $[M+Na]^+$: 483.9084, found: 483.9079.

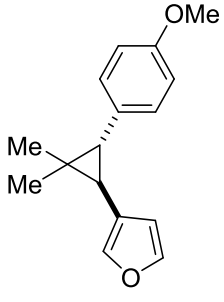
1-((1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropyl)-4-methoxybenzene (66)



66

The title compound **66** was prepared according to general procedure B3 from redox-active ester **73** and *p*-toluenboronic acid pinacol ester employing $NiCl_2$·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}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}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; λ = 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)

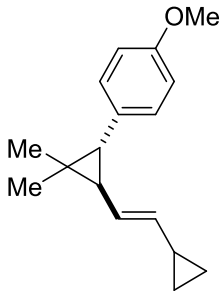


67

The title compound **67** was prepared according to general procedure B3 from redox-active ester **73** and 3-furanboronic acid pinacol ester employing $NiCl_2$·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}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

(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; λ = 226 nm). t_R (minor) = 1.50 min, t_R (major) = 2.38 min. 95% *ee.*

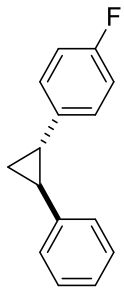
1-((1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropyl)-4-methoxybenzene (68)



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 $NiCl_2$·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, $CHCl_3$). ^{1}H 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 $C_{17}H_{23}O^+$ $[M+H]^+$: 243.1743; found: 243.1743. Chiral SFC (Daicel IA; 2% MeOH / CO_2 (4 mL/min), 1600 psi backpressure; λ = 220 nm). t_R (minor) = 1.47 min, t_R (major) = 1.76 min. 94% *ee*.

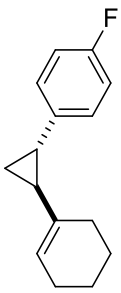
1-Fluoro-4-((1*S*,2*S*)-2-phenylcyclopropyl)benzene (69)



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 $NiCl_2$·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, $CHCl_3$). ^{1}H 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; λ = 226 nm). t_R (major) = 1.30 min, t_R (minor) = 1.43 min. 93% *ee*.

1-((1*S*,2*S*)-2-(Cyclohex-1-en-1-yl)cyclopropyl)-4-fluorobenzene (70)



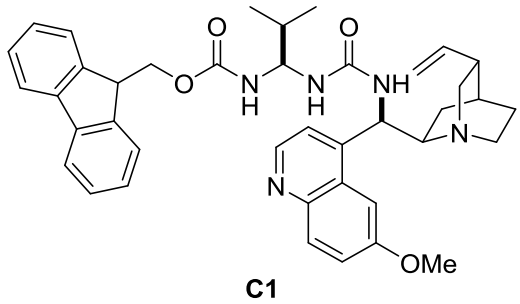
70

The title compound **70** was prepared according to general procedure B2 from redox-active ester **74** and the alkenylzinc derived from 1-bromocyclohexene[251] employing $Ni(acac)_2 \cdot xH_2O$ (60 mol%) and 2,2'-bipyridine (60 mol%). Purification by pTLC (9:1 hexane:CH_2Cl_2). Yield: 0.010 g (44 %). Yellow oil. $[\alpha]_D^{20}$ = +61.3 (c = 0.38, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (151 MHz, $CDCl_3$) 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. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.3. HRMS (ESI-TOF): calcd for $C_{15}H_{18}F^+$ $[M+H]^+$: 217.1387; found: 217.1384. Chiral SFC (Daicel IG; 2% *i*PrOH / CO_2 (3.3 mL/min), 1600 psi backpressure; λ = 229 nm). t_R (major) = 2.24 min, t_R (minor) = 2.46 min. 95% *ee*.

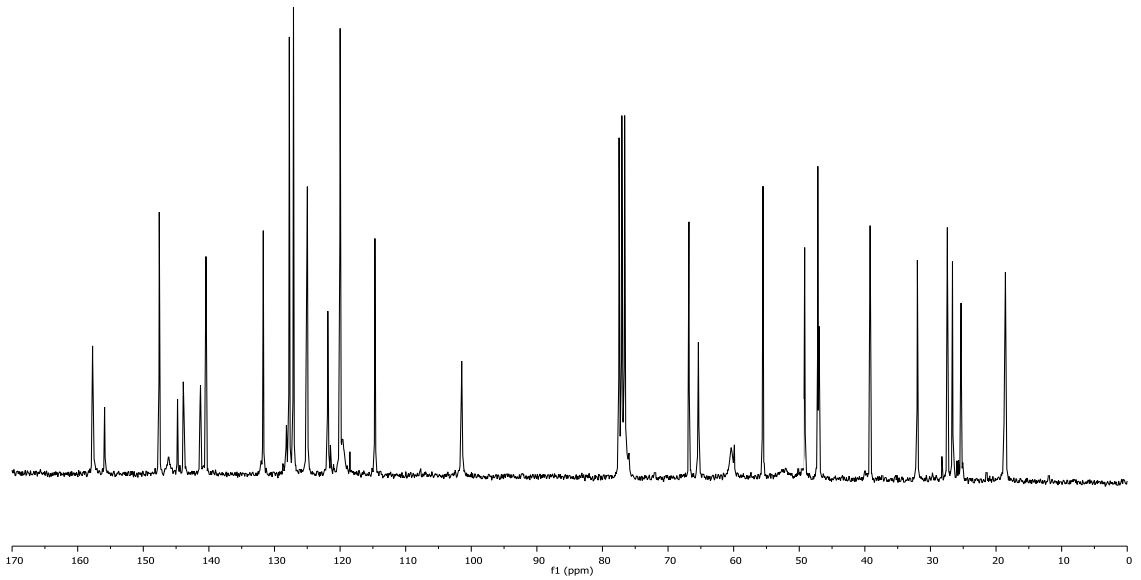
6.6. NMR spectra

6.6.1. Catalysts

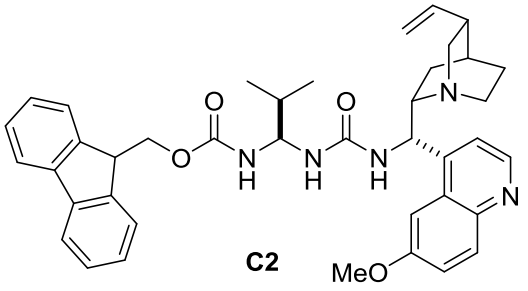
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*R*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C1)



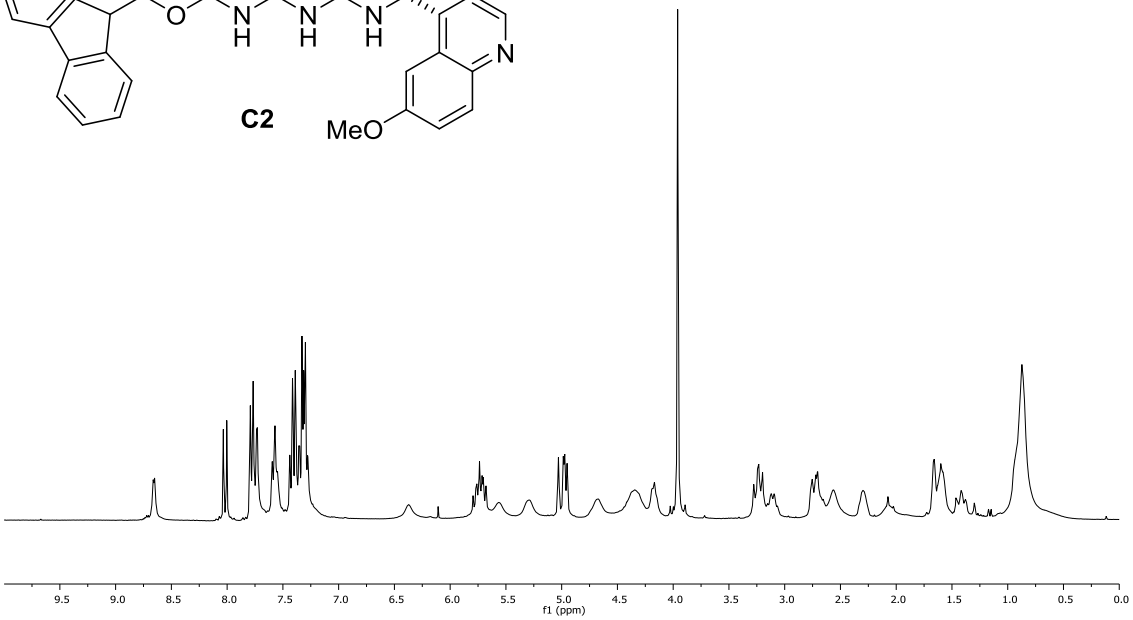
C1

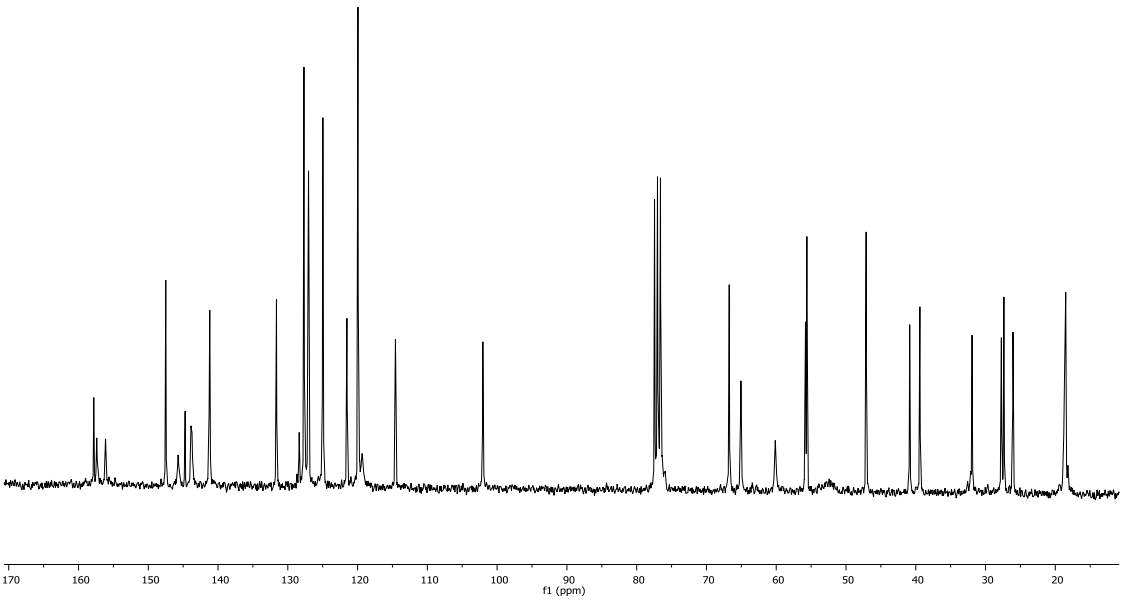


(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-methylpropyl)carbamate (C2)

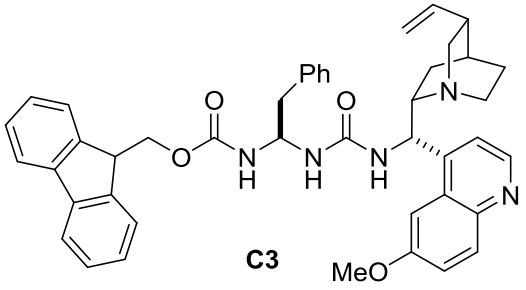


C2

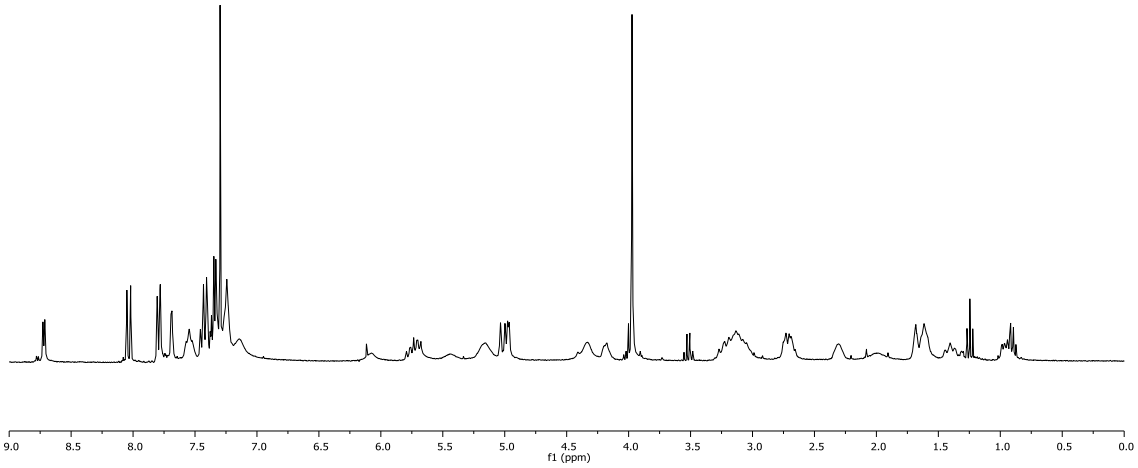


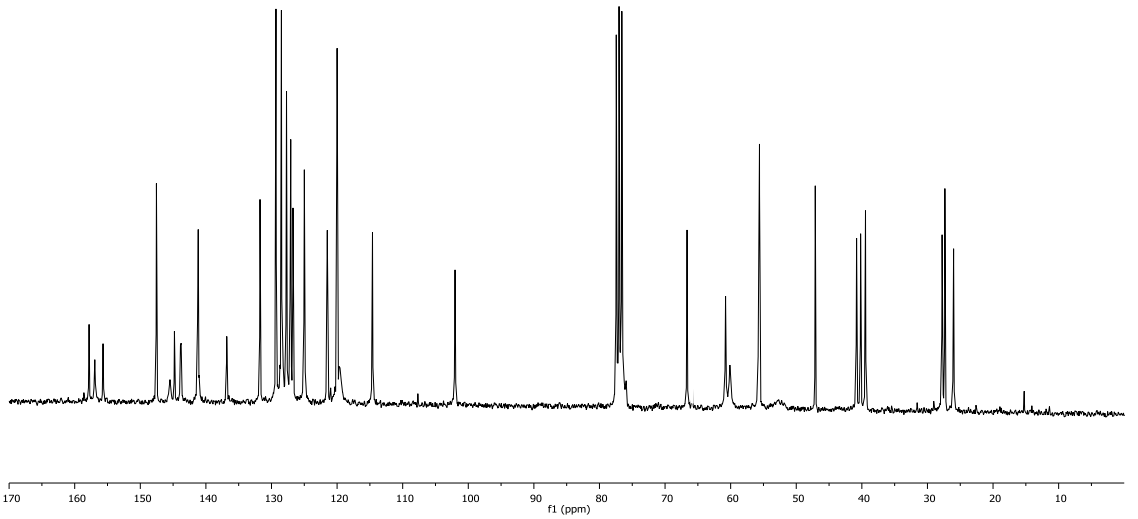


(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2-phenylethyl)carbamate (C3)

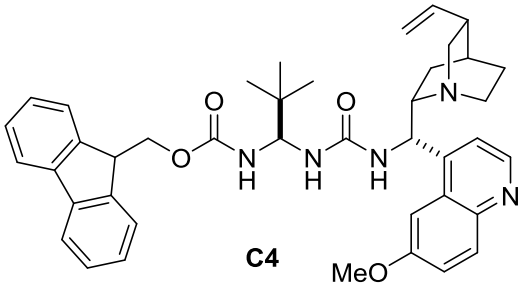


C3

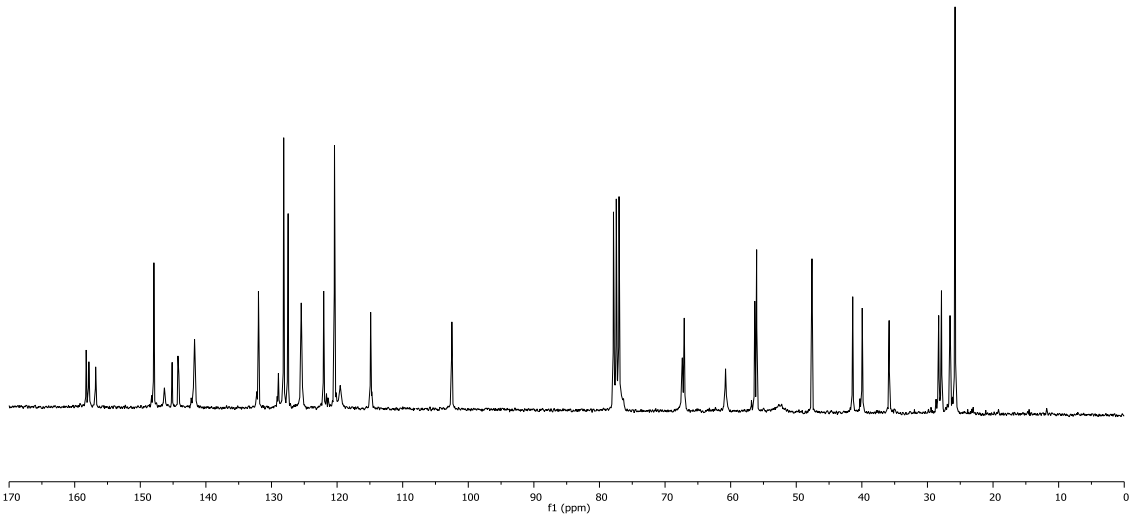




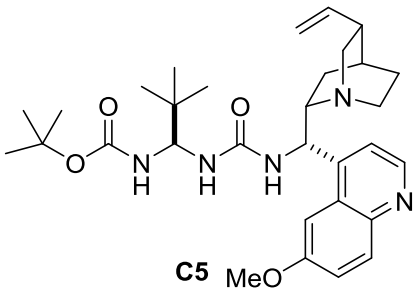
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C4)

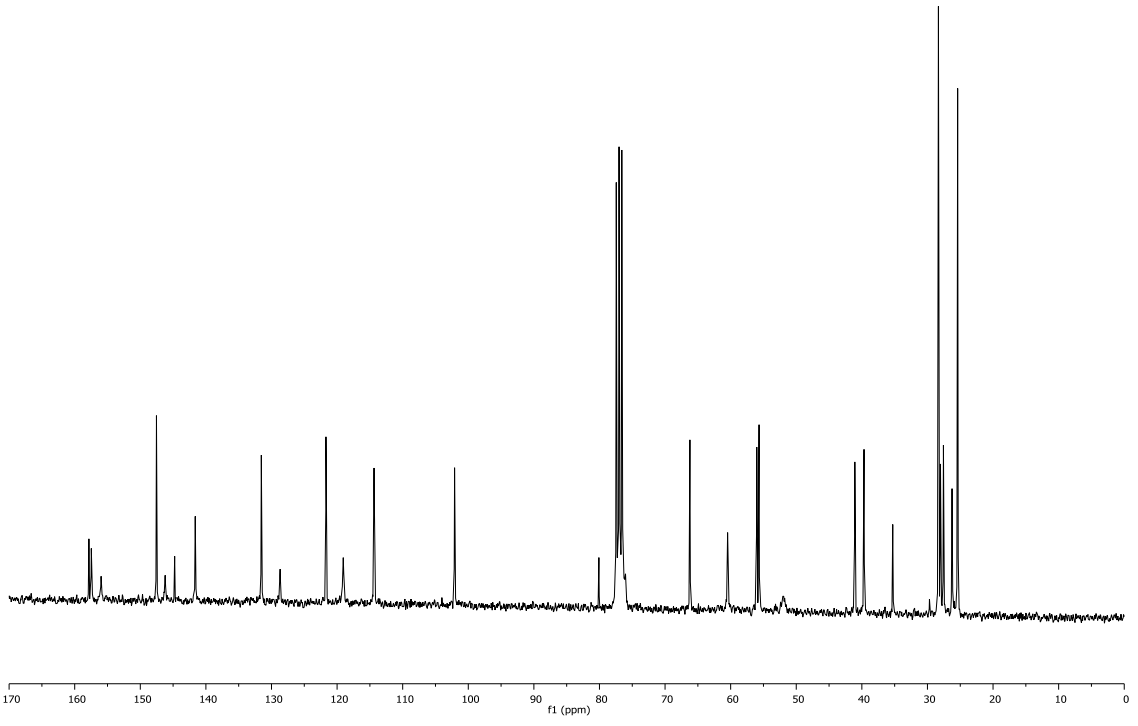


C4

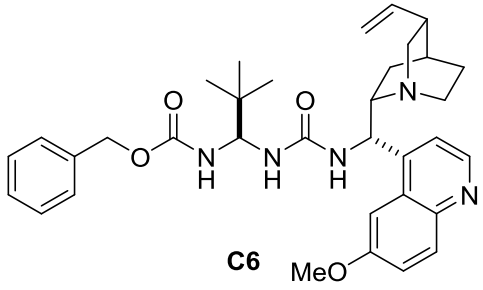


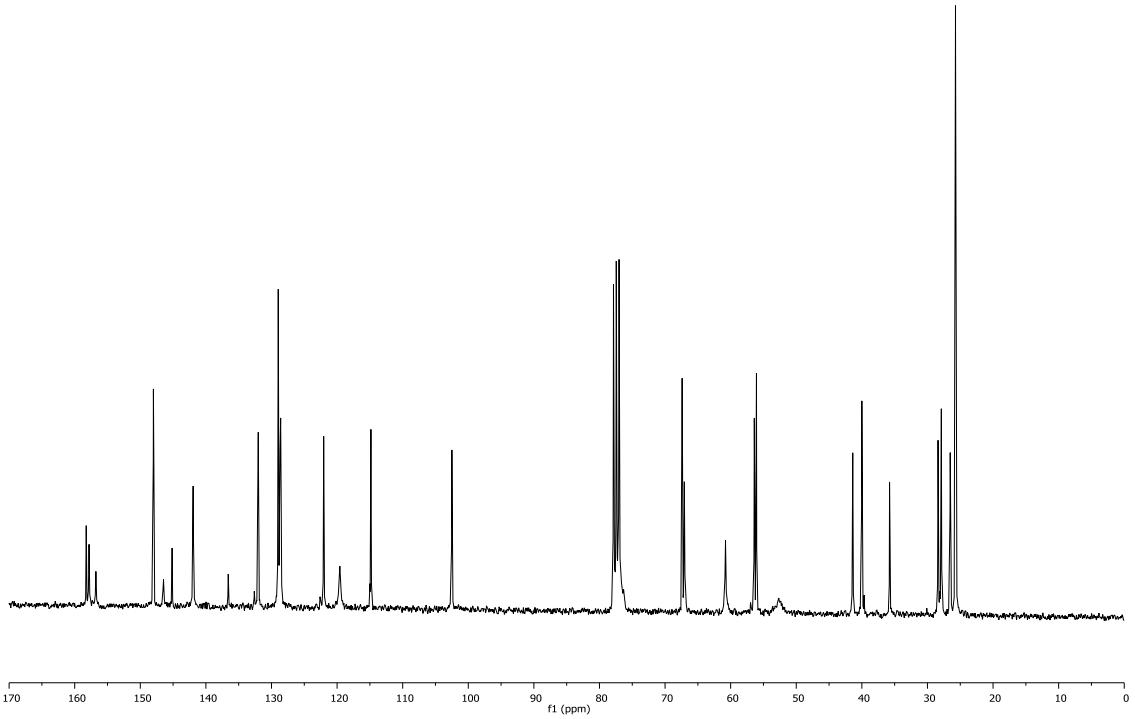
***tert*-Butyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C5)**



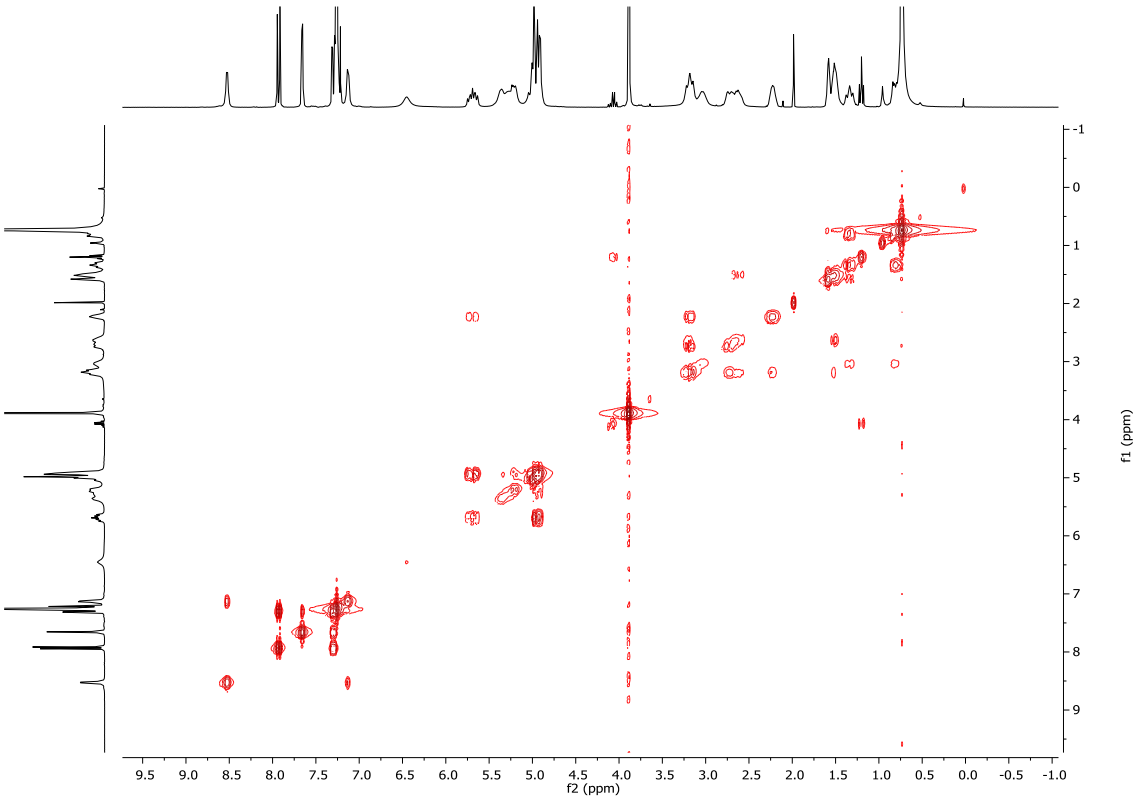


Benzyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C6)

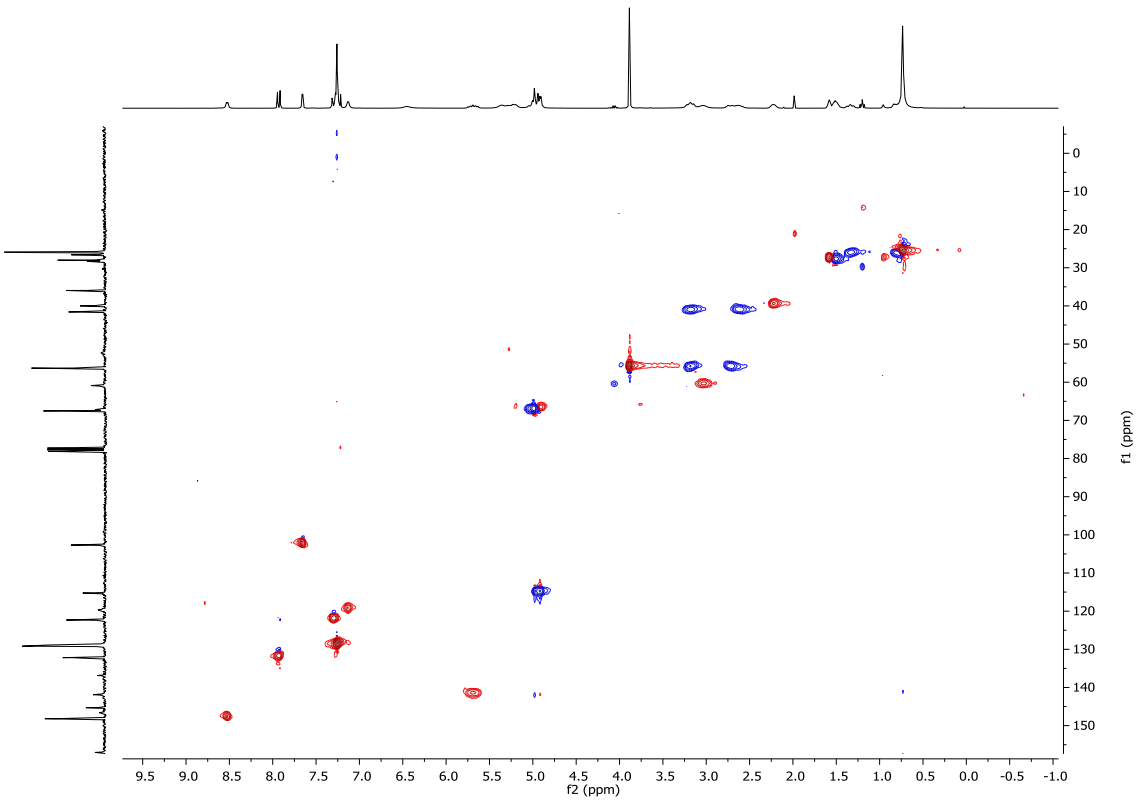




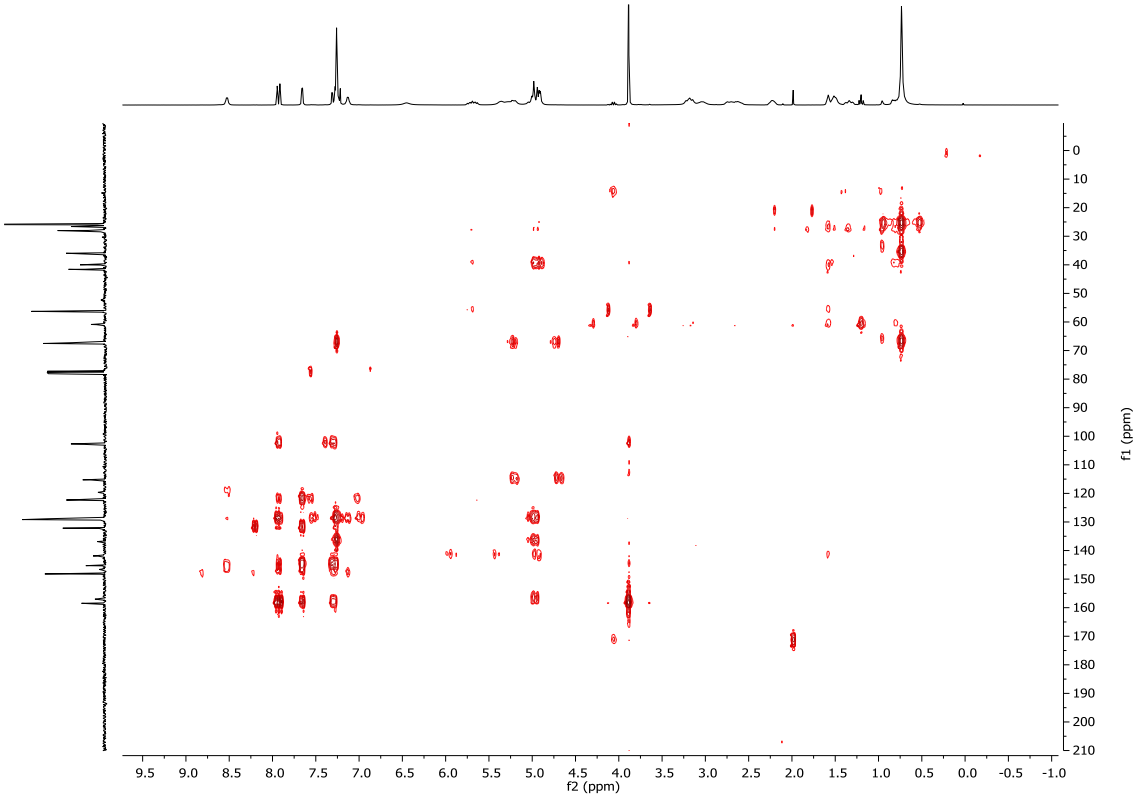
COSY:



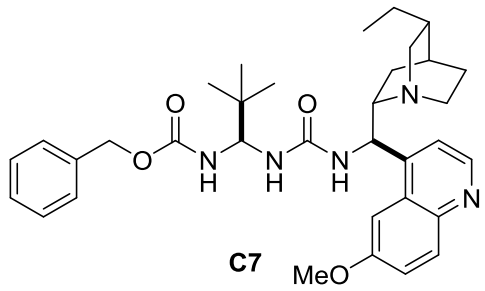
HSQC:



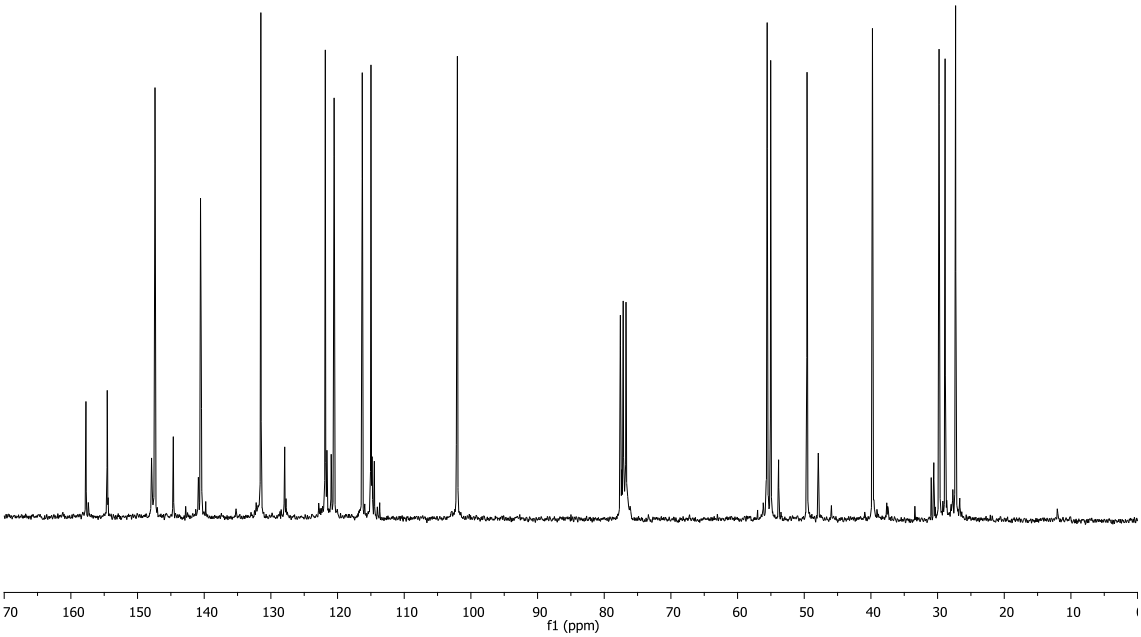
HMBC:



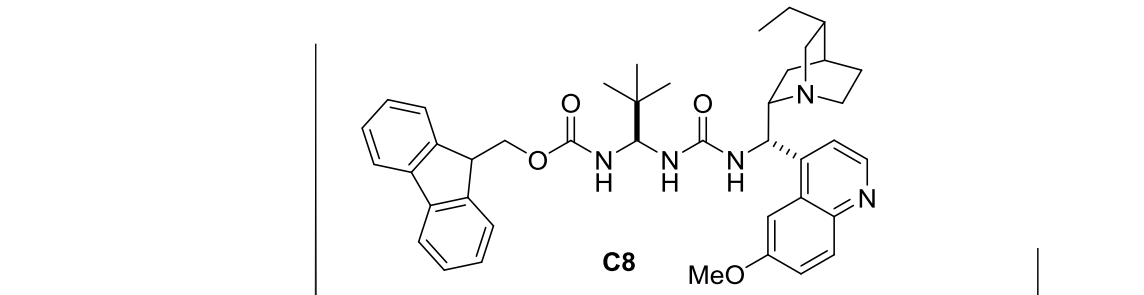
Benzyl ((*S*)-1-(3-((*R*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C7)



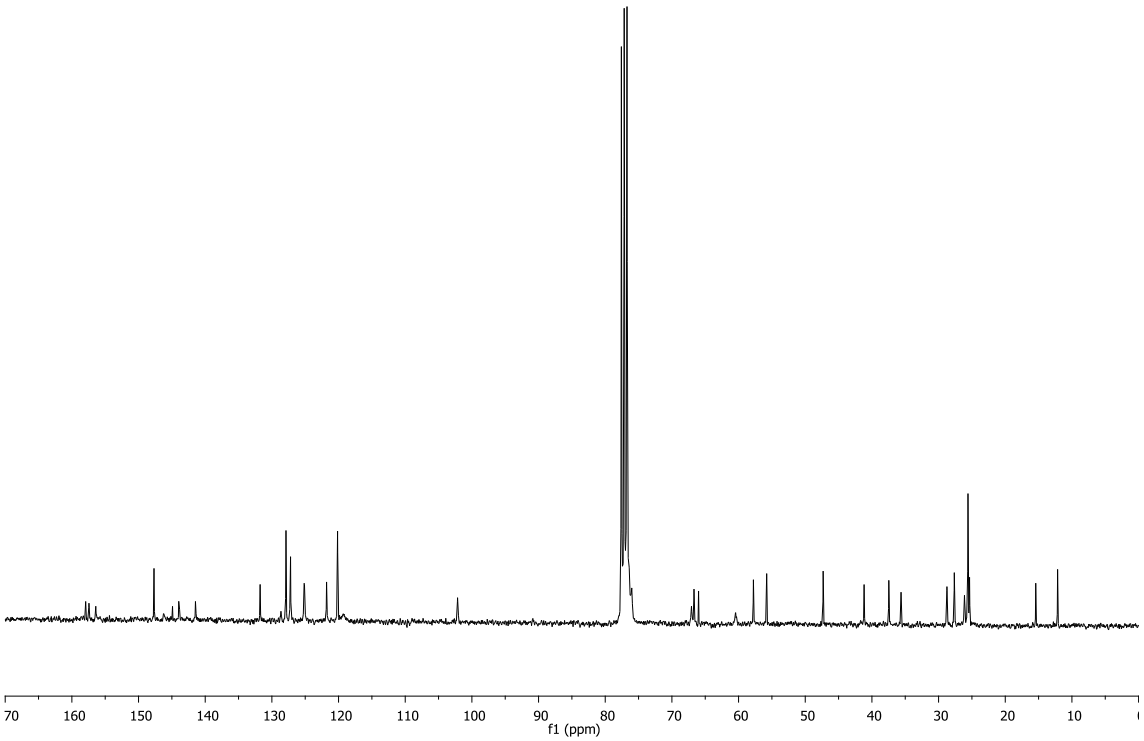
C7



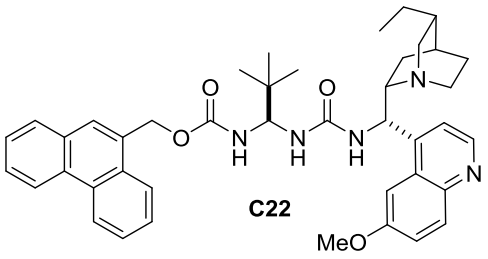
(9H-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C8)



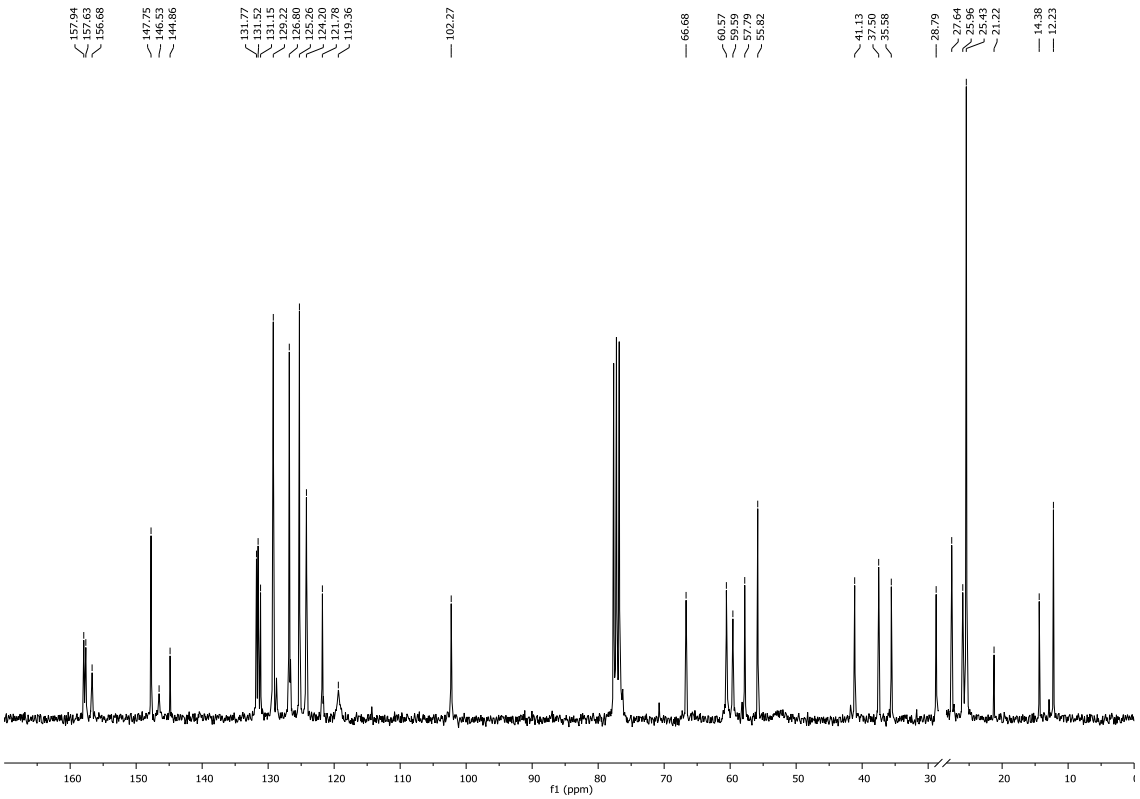
C8



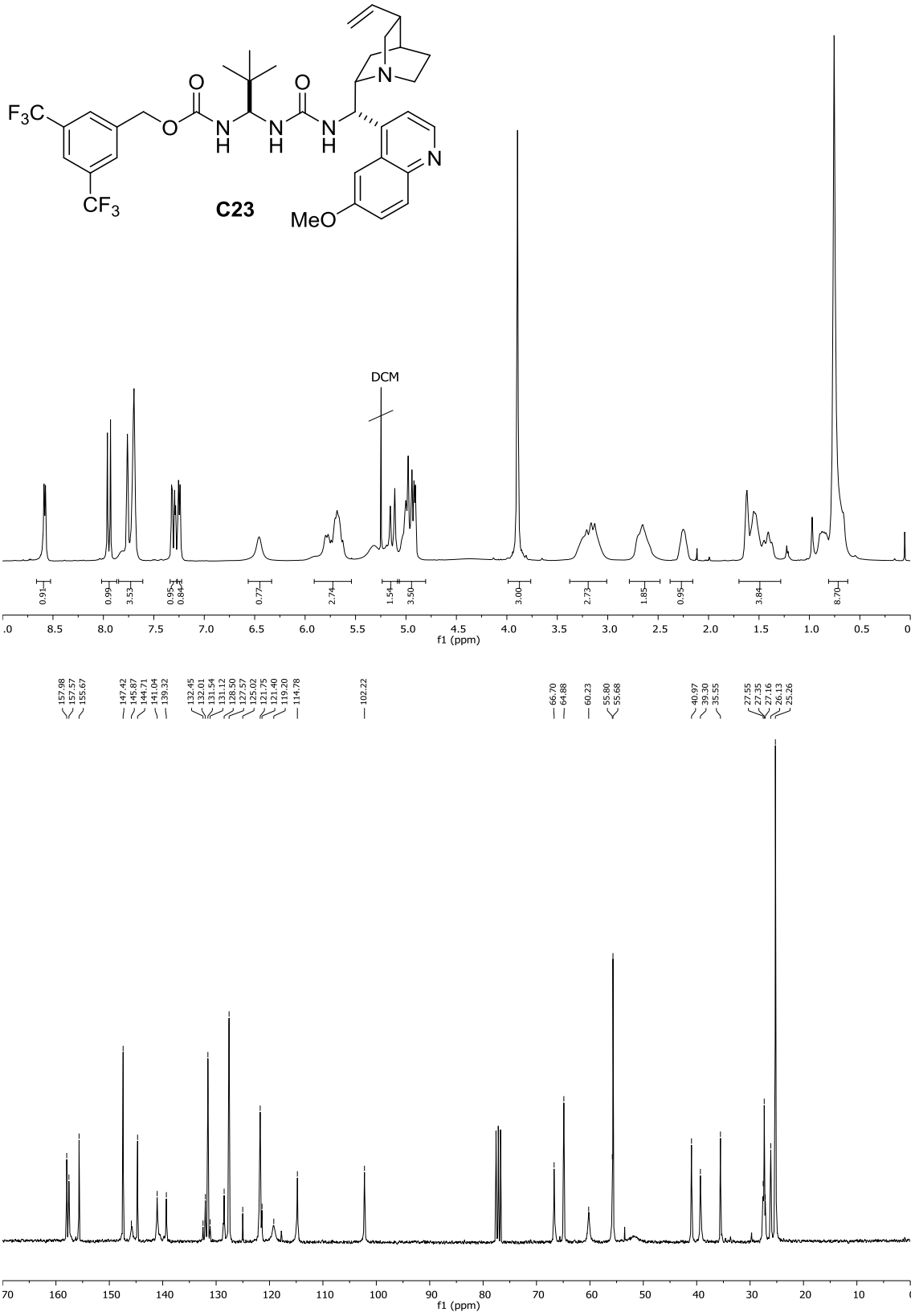
Phenanthren-9-ylmethyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C22)



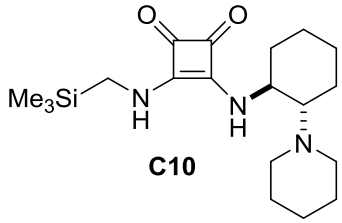
C22



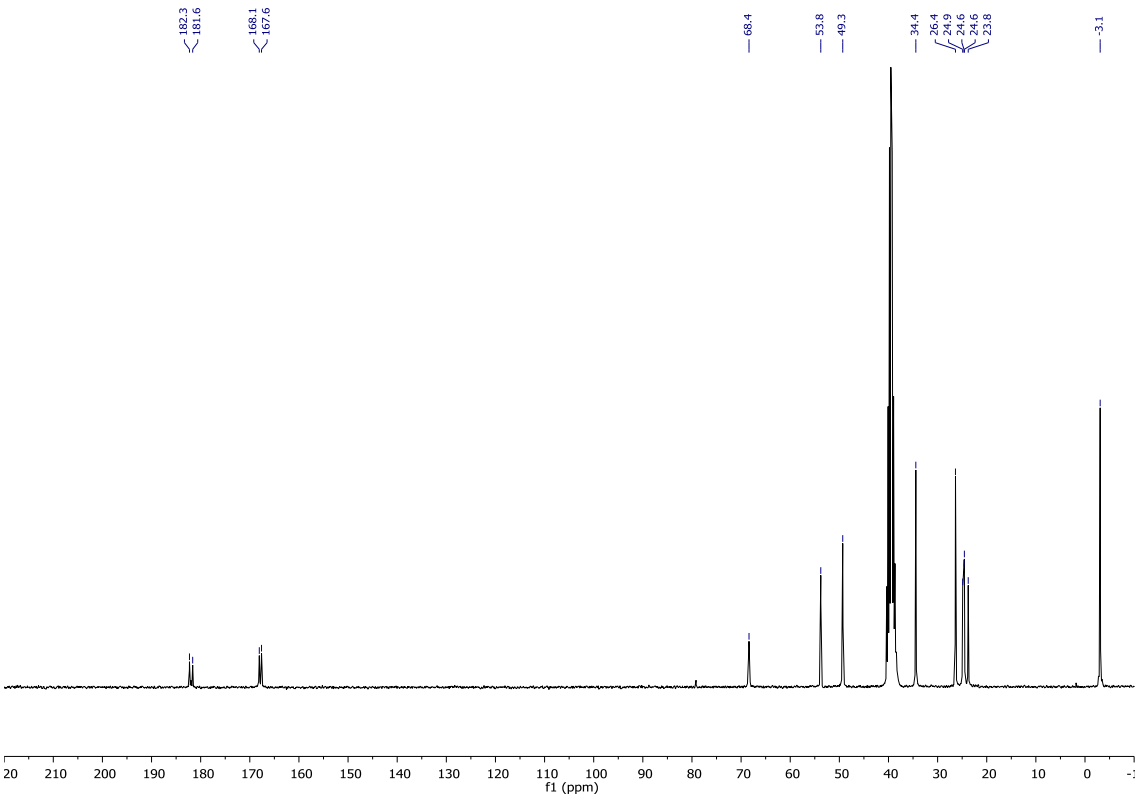
3,5-Bis(trifluoromethyl)benzyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C23)



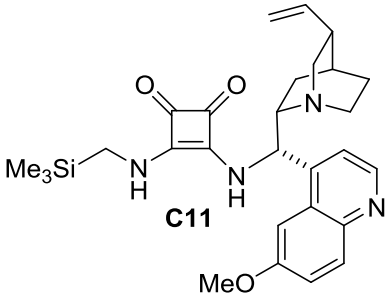
3-(((1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C10)



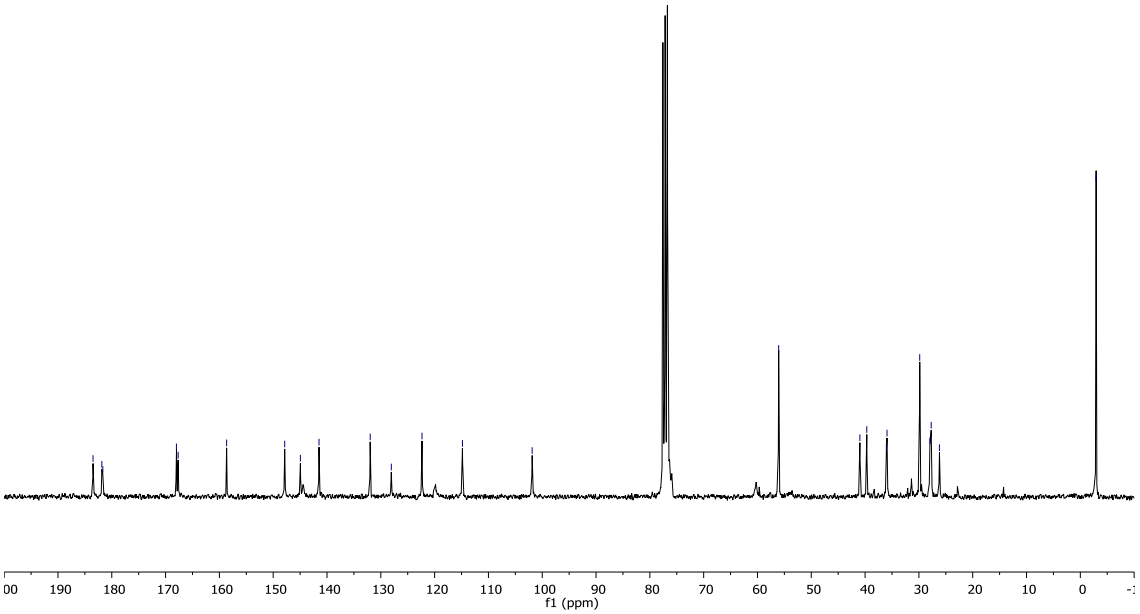
C10



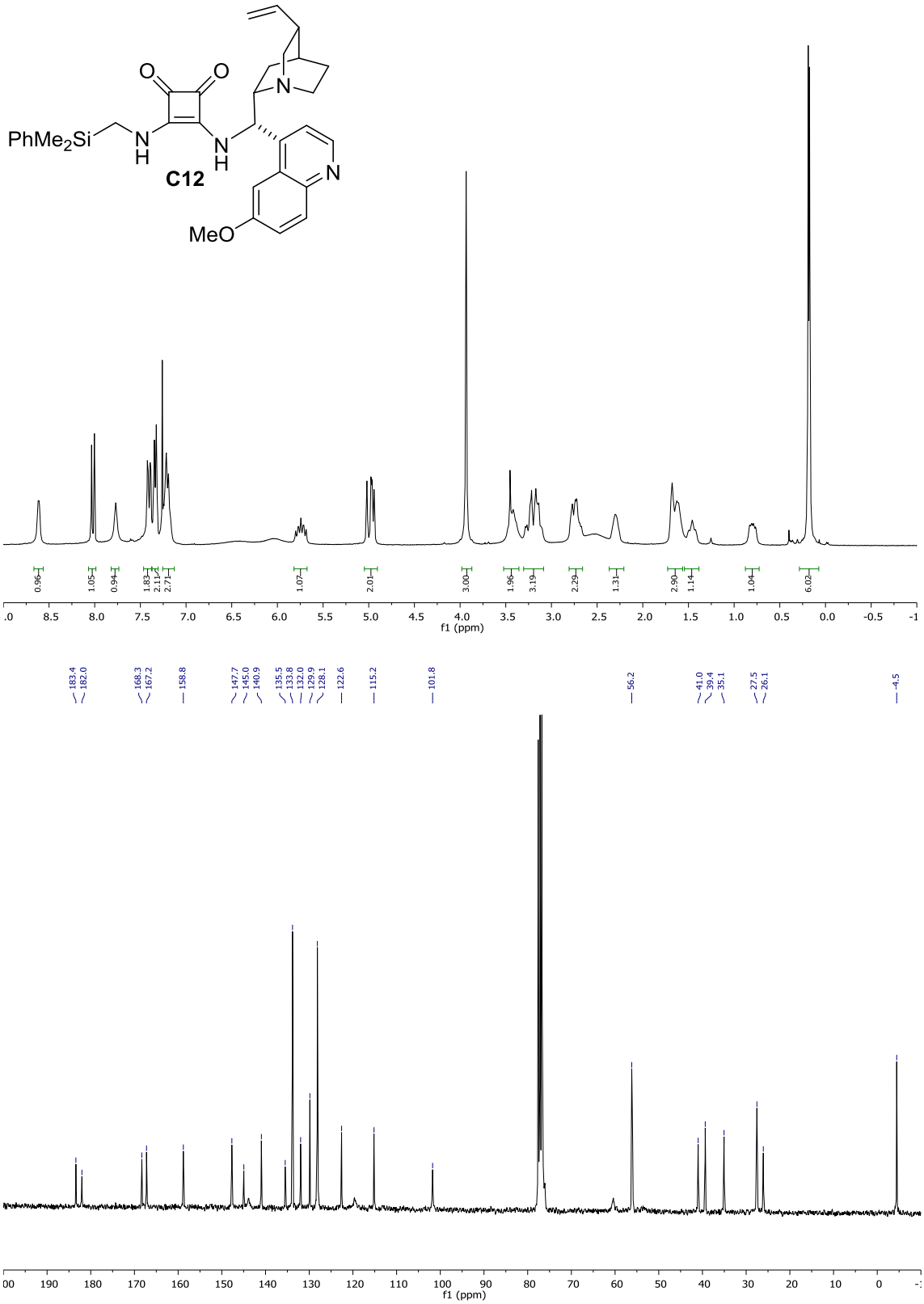
3-((*S*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C11)



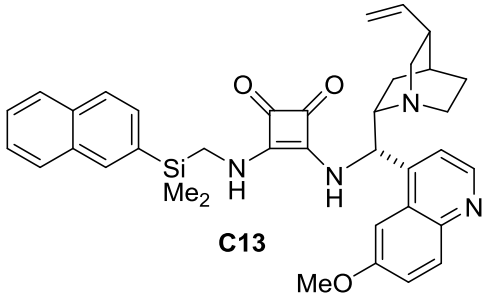
C11



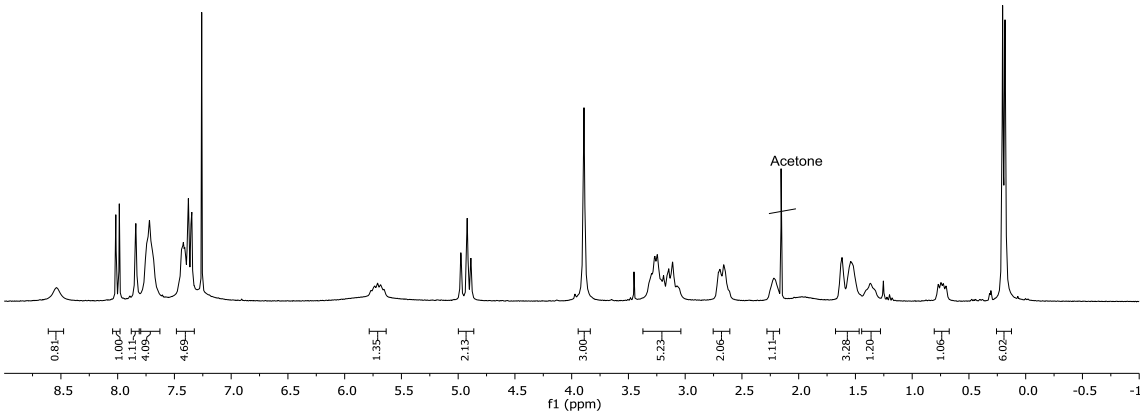
3-((Dimethyl(phenyl)silyl)methylamino)-4-((*S*)-(6-methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C12)

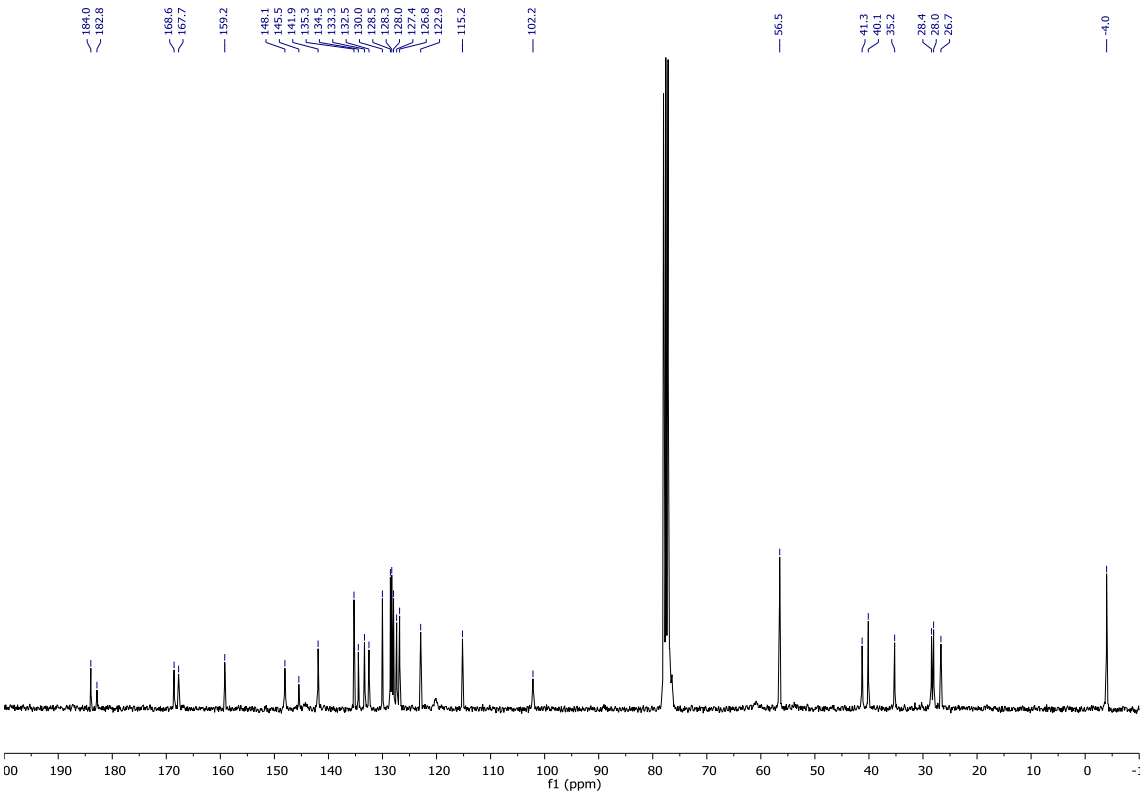


3-(((Dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C13)

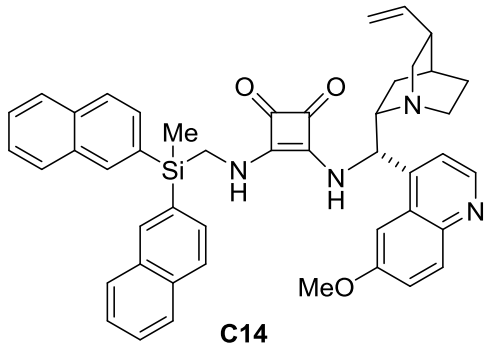


C13

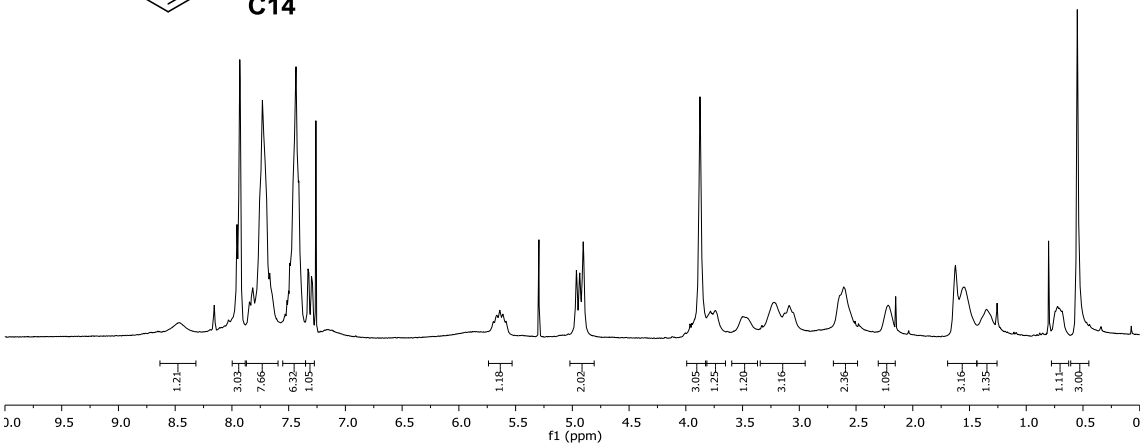


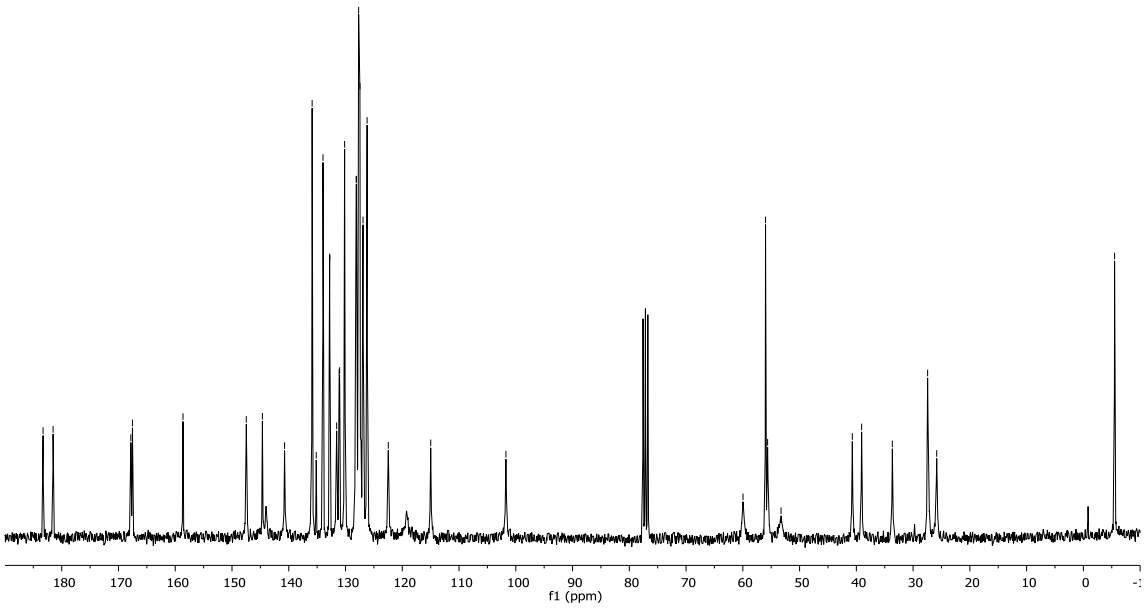


3-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((methyldi(naphthalen-2-yl)silyl)methyl)amino)cyclobut-3-ene-1,2-dione (C14)

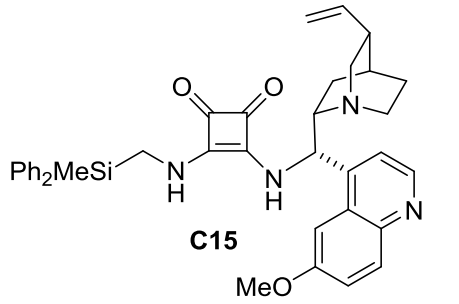


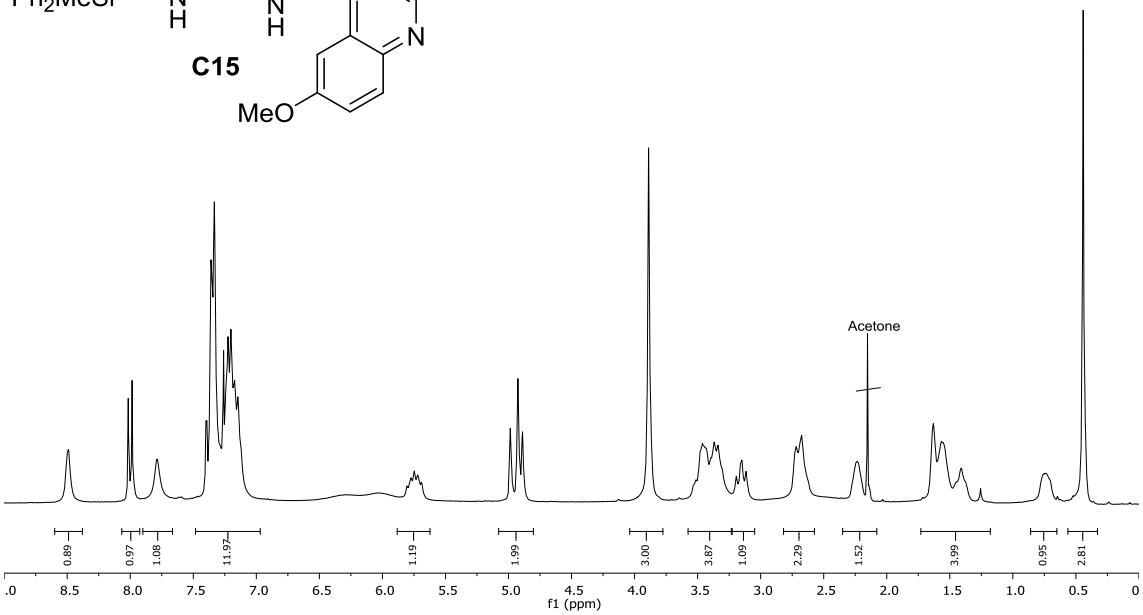
C14

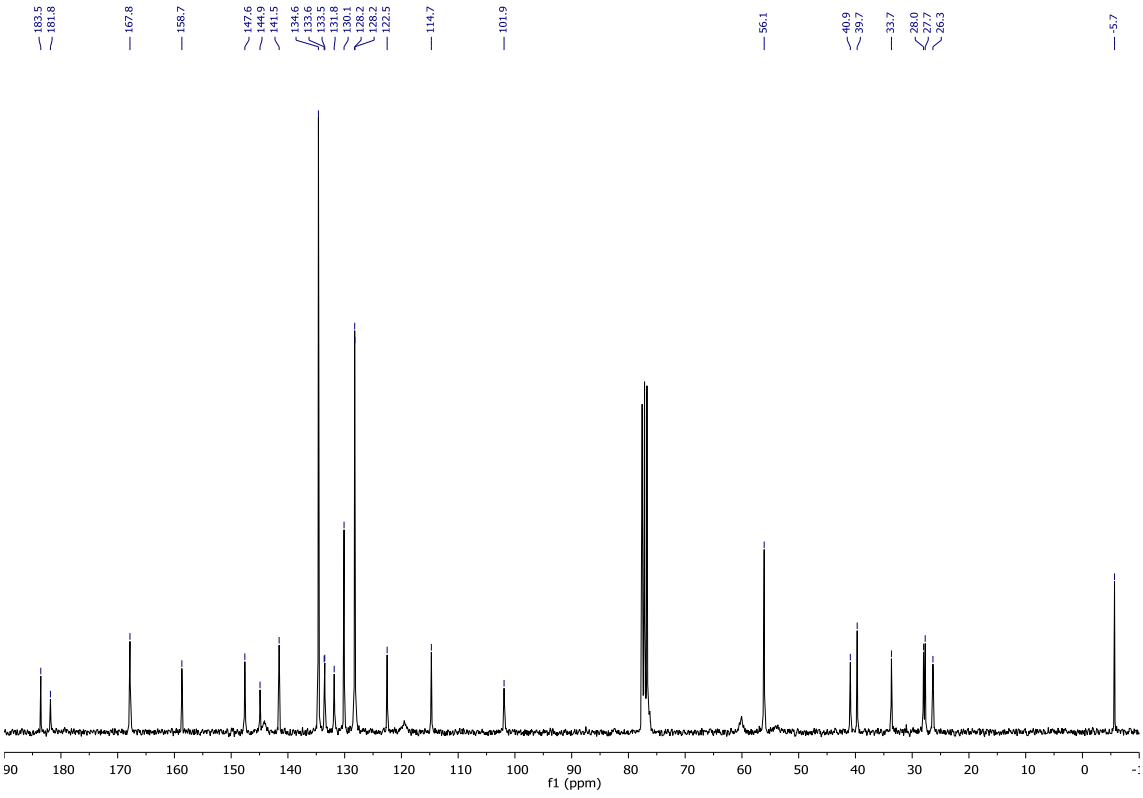




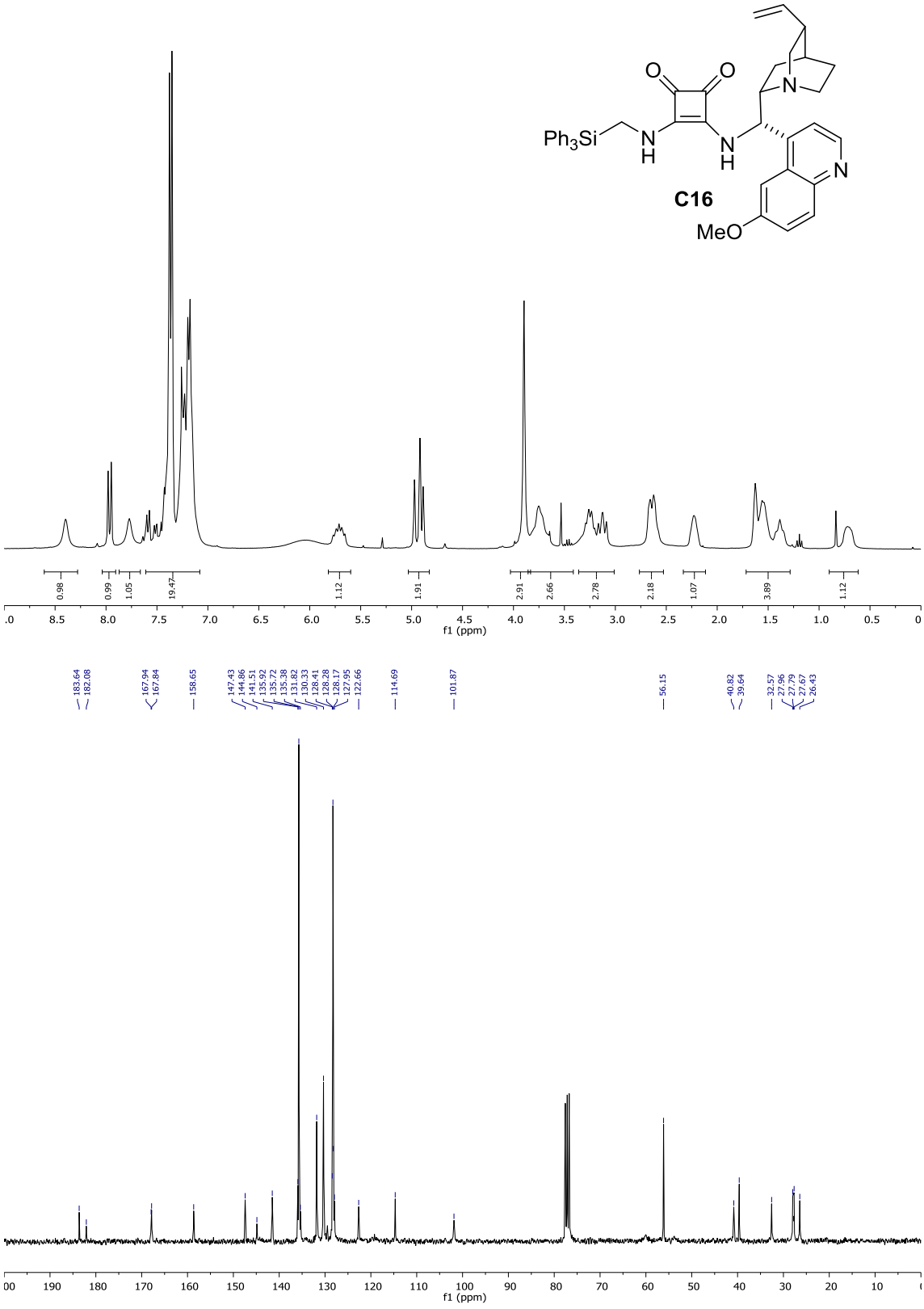
3-((*S*)-(6-Methoxyquinolin-4-yl)((2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl)methylamino)-4-((methyldiphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C15)



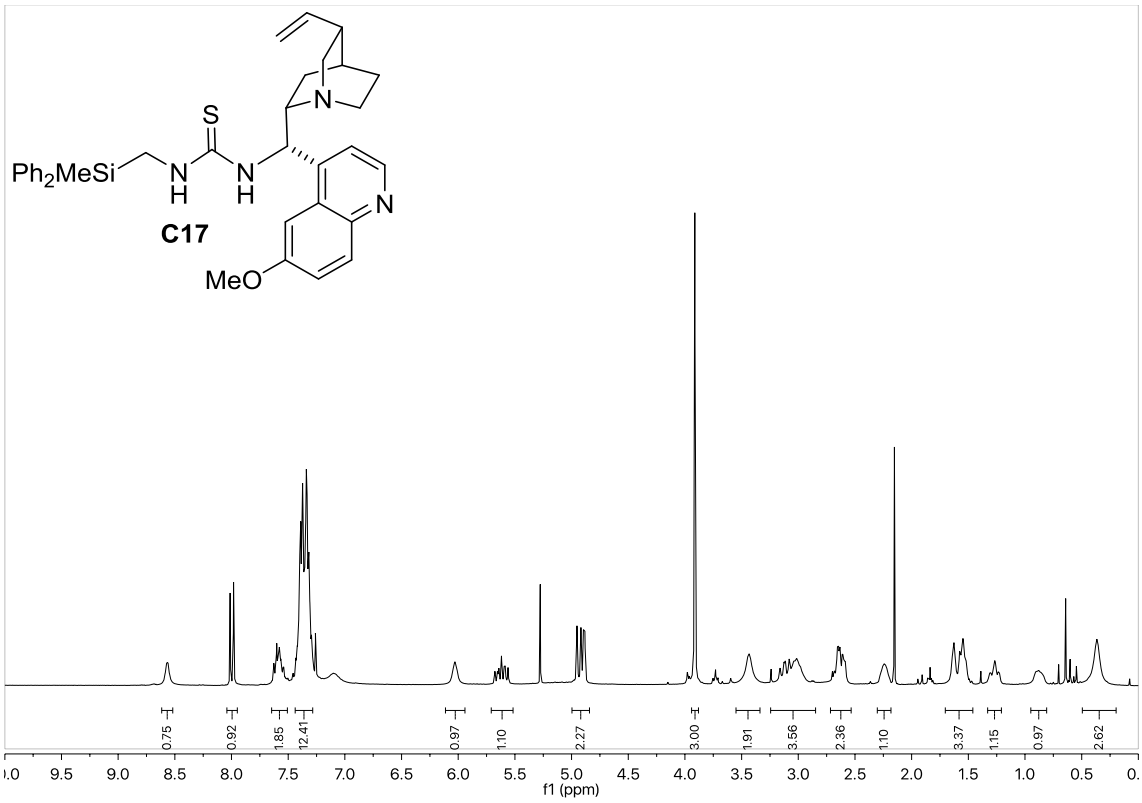


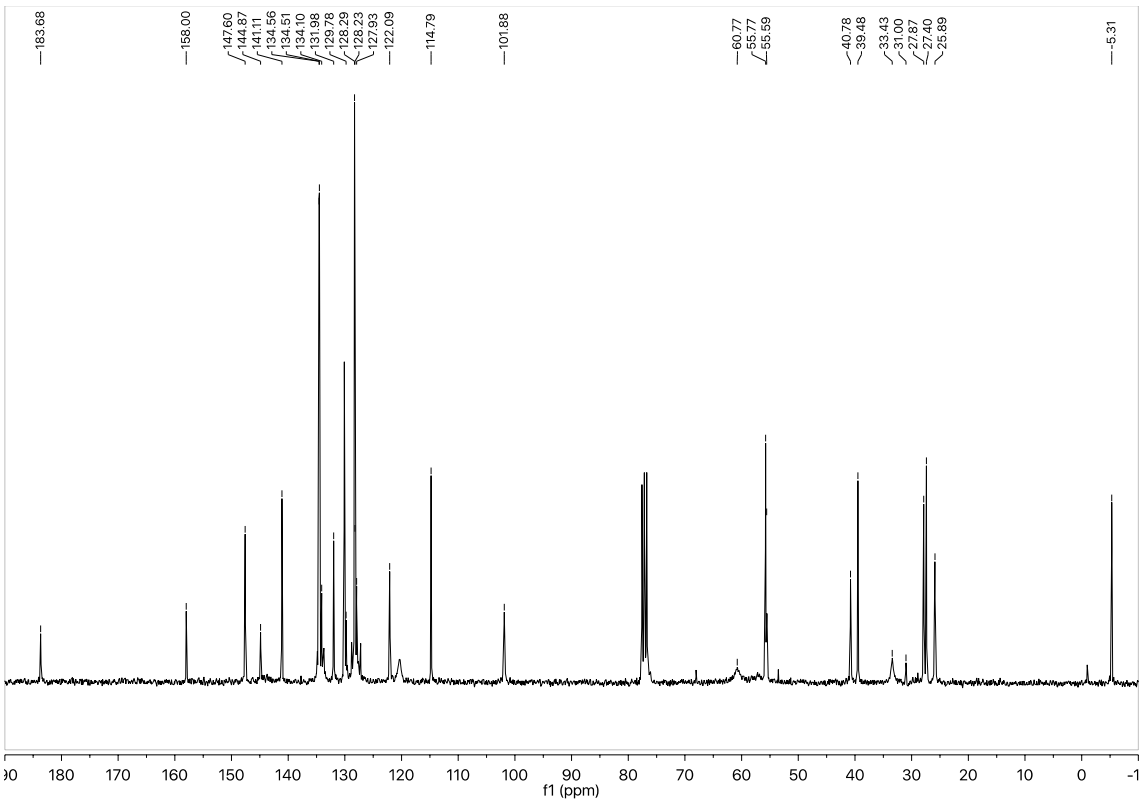


3-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methylamino)-4-((triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C16)

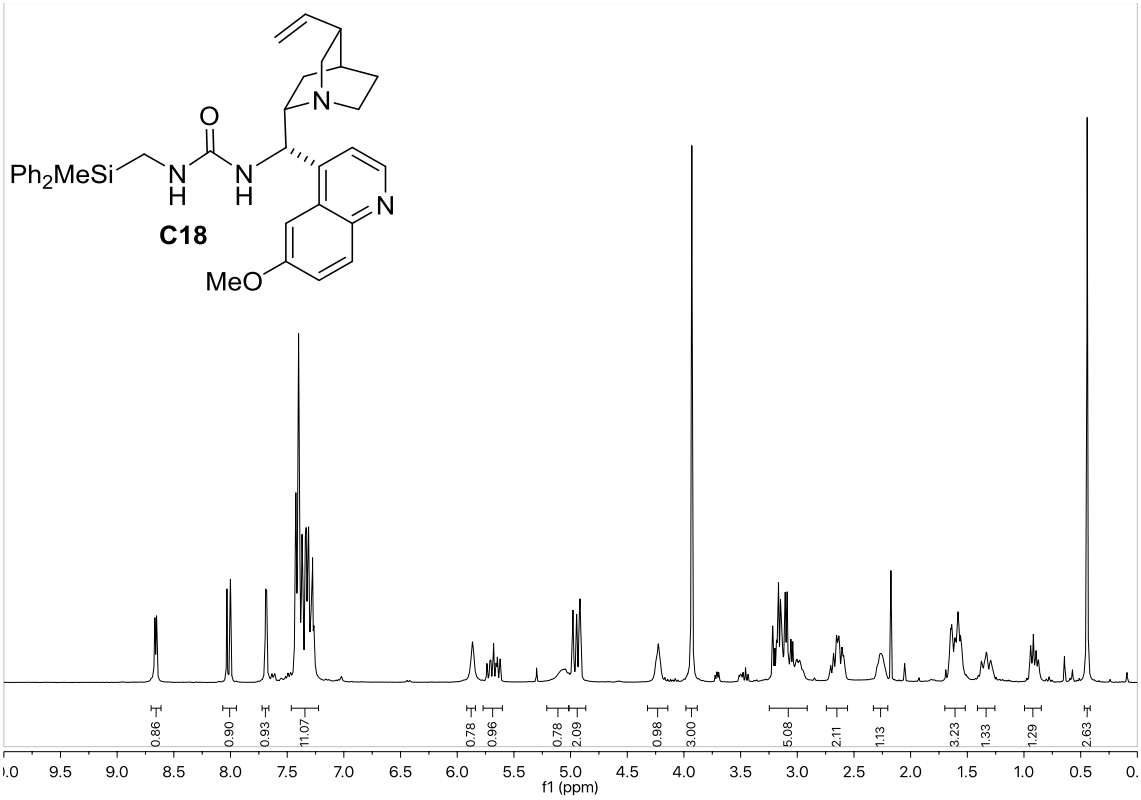


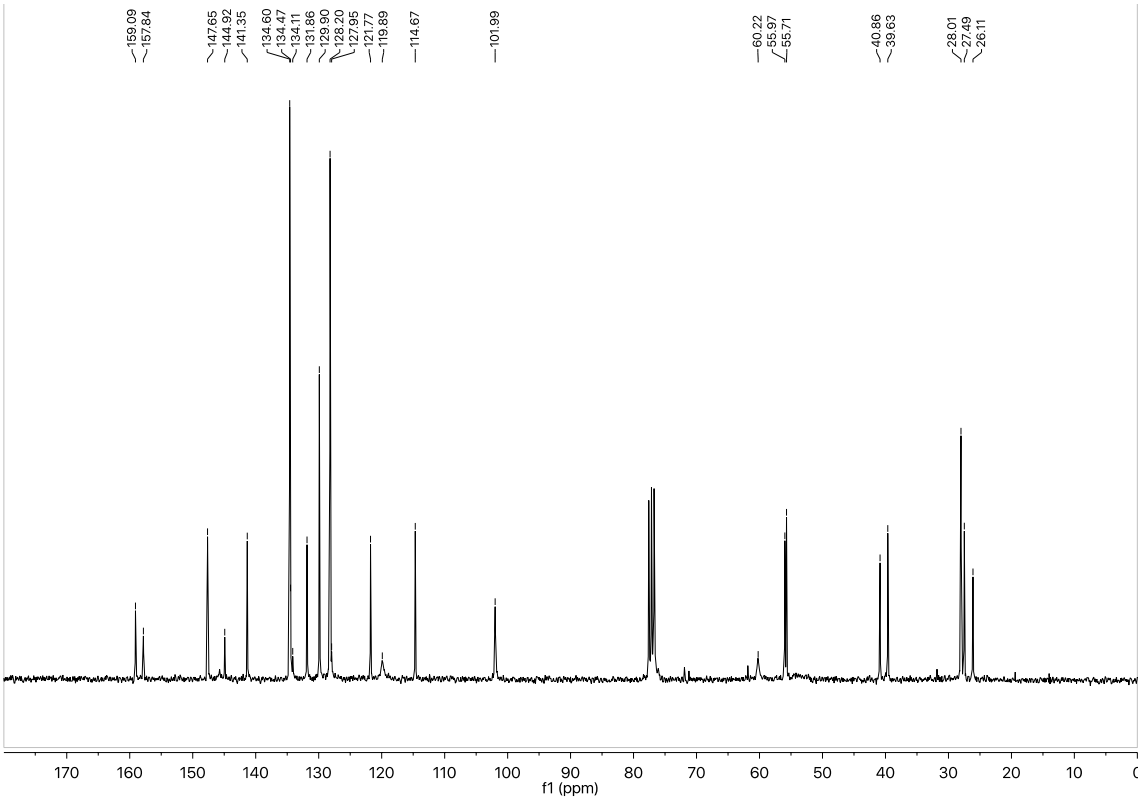
1-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-3-((methyldiphenylsilyl)methyl)thiourea (C17)



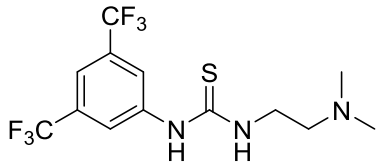


1-((*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)-3-((methyldiphenylsilyl)methyl)urea (C18)

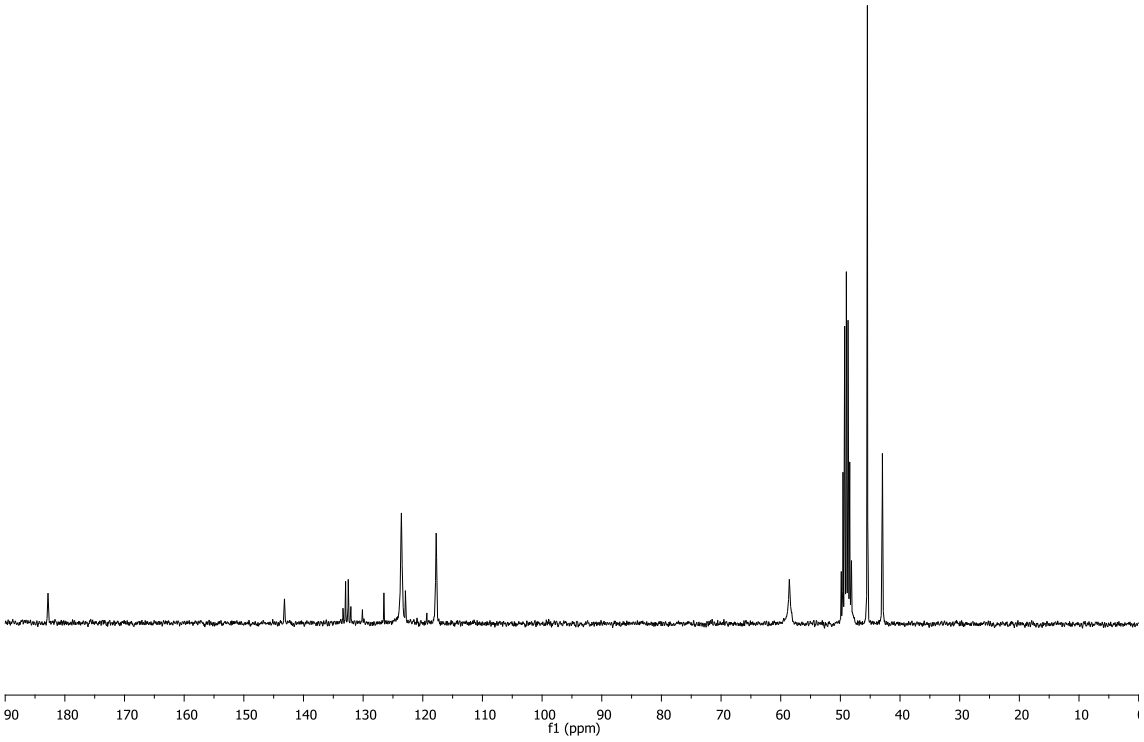




1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-(dimethylamino)ethyl)thiourea (C24)

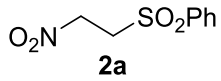


C24

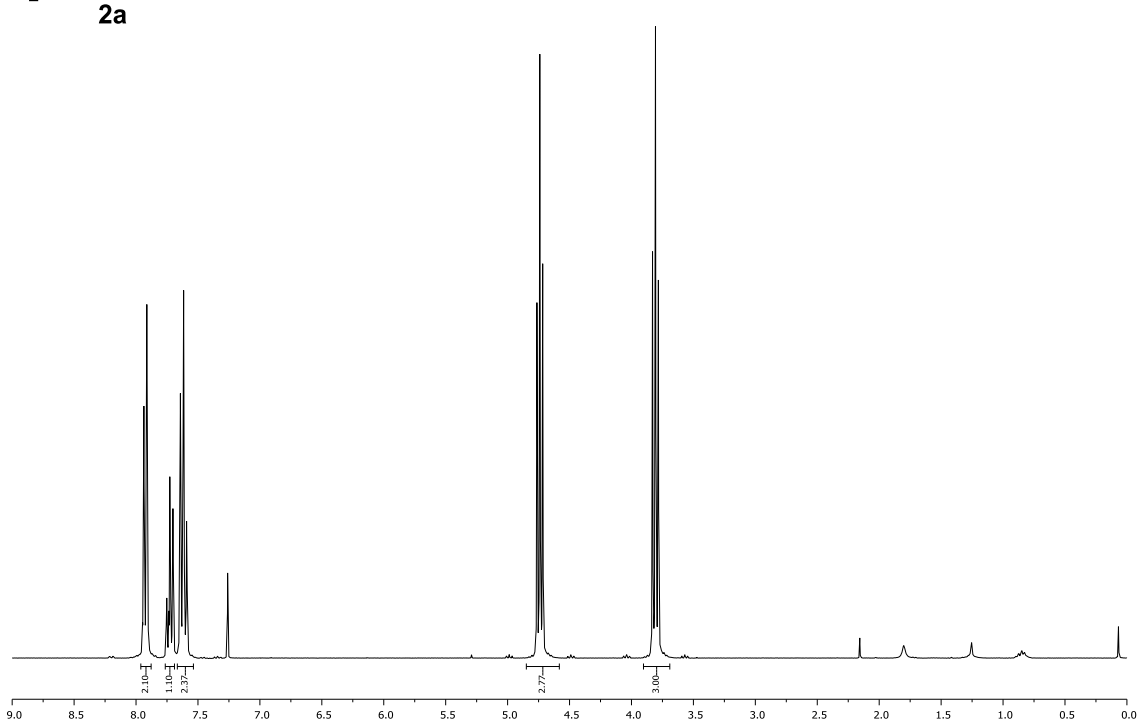


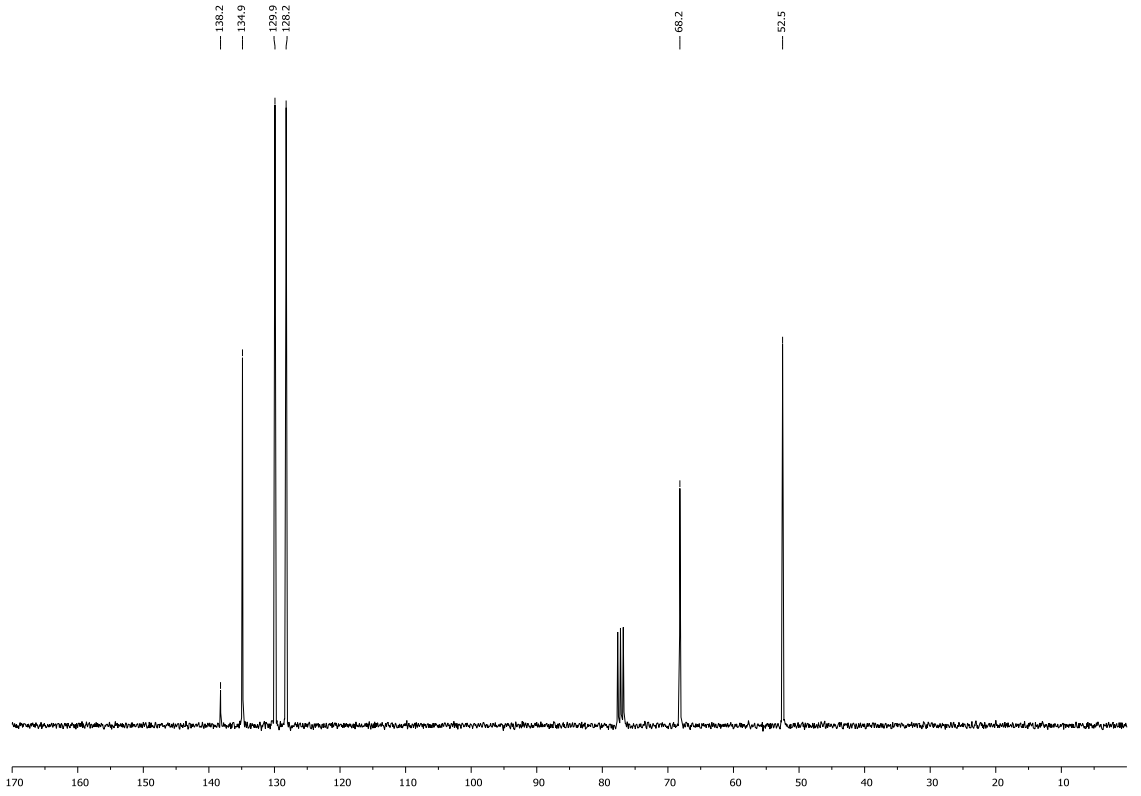
6.6.2. NMR spectra for Chapter 2

((2-Nitroethyl)sulfonyl)benzene (2a)

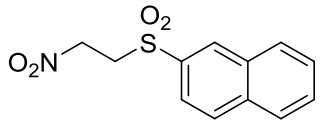


2a

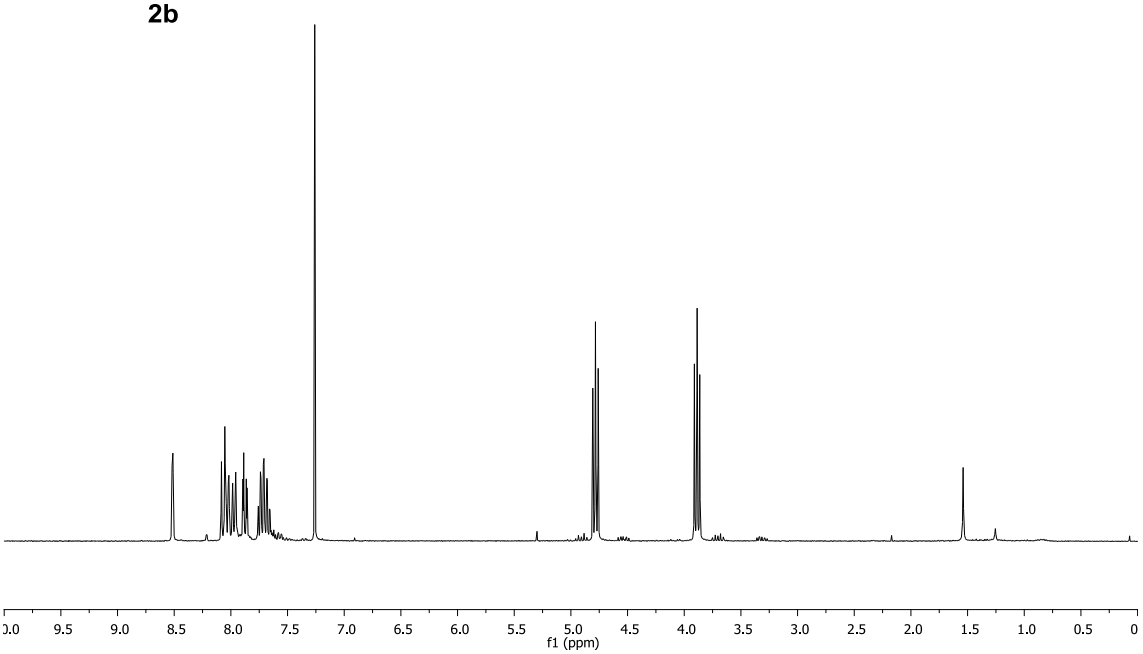


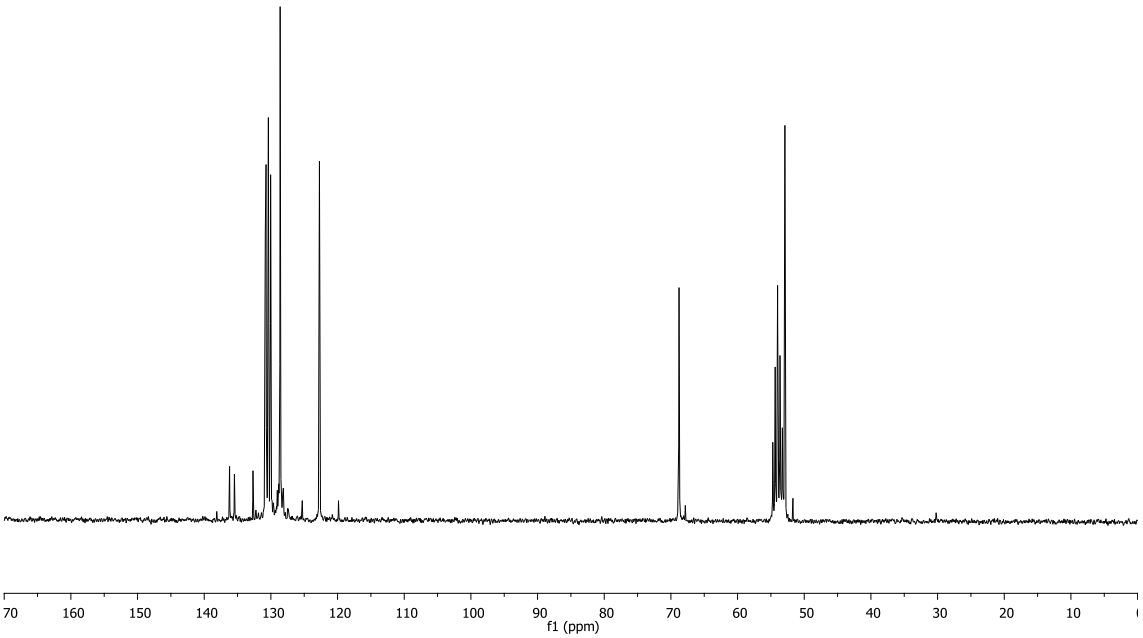


2-((2-Nitroethyl)sulfonyl)naphthalene (2b)

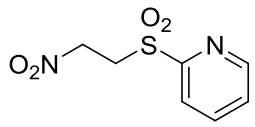


2b

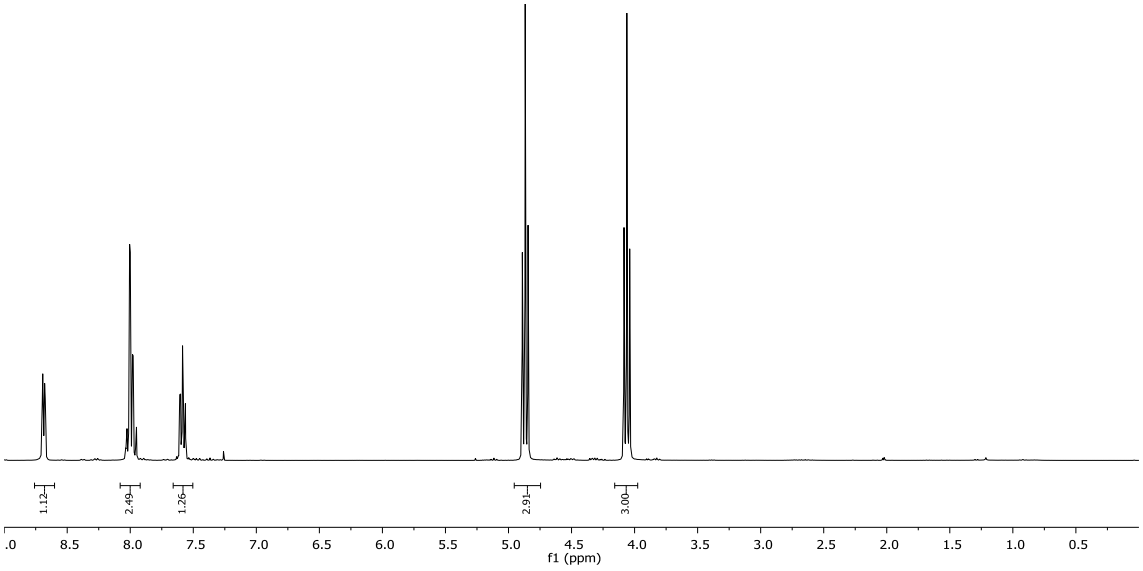


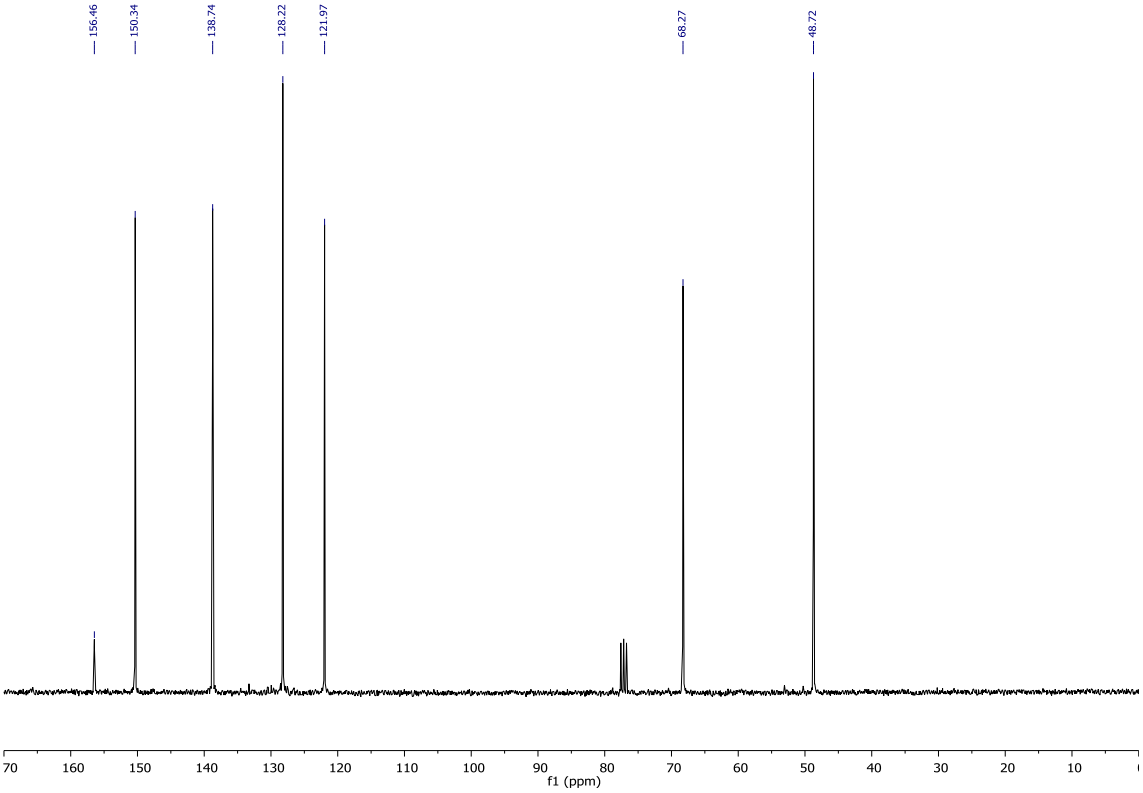


2-((2-Nitroethyl)sulfonyl)pyridine (2c)

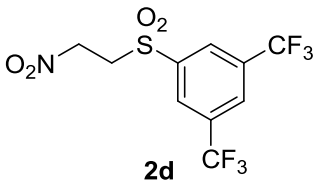


2c

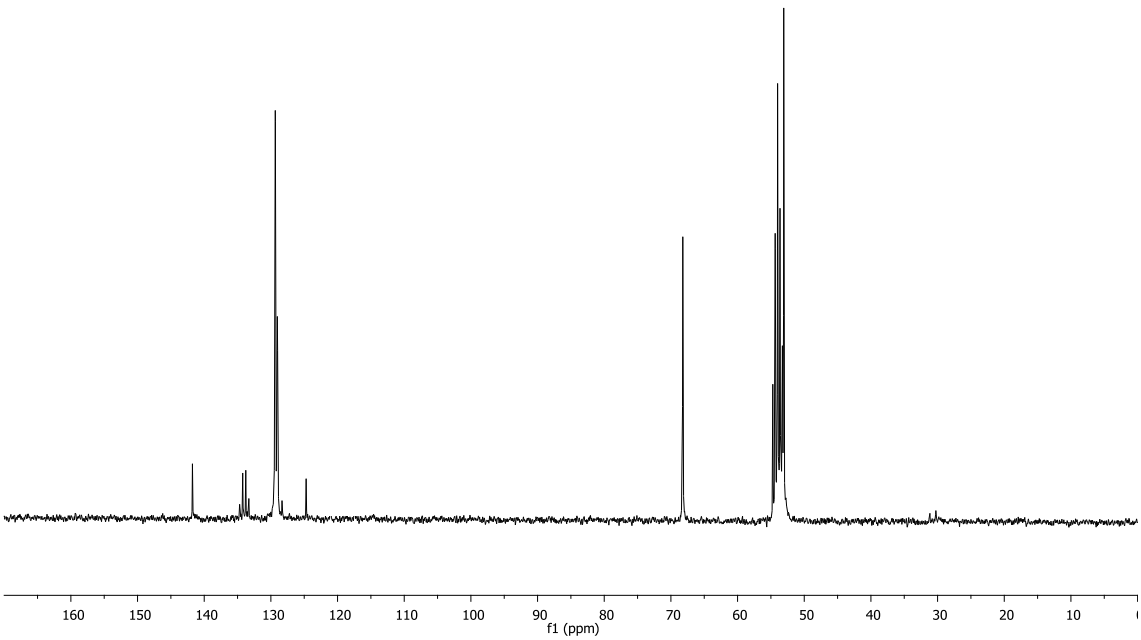




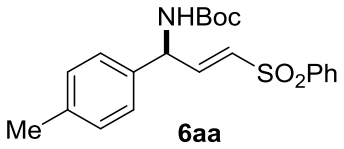
1-((2-Nitroethyl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (2d)



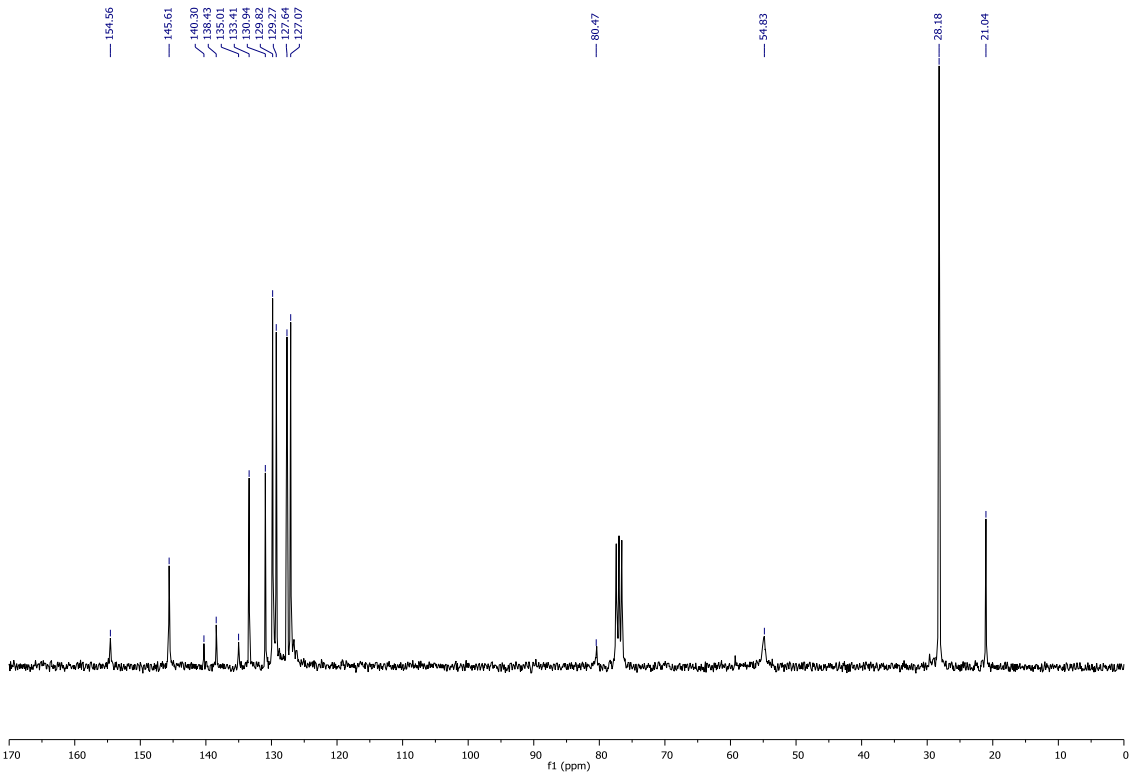
2d



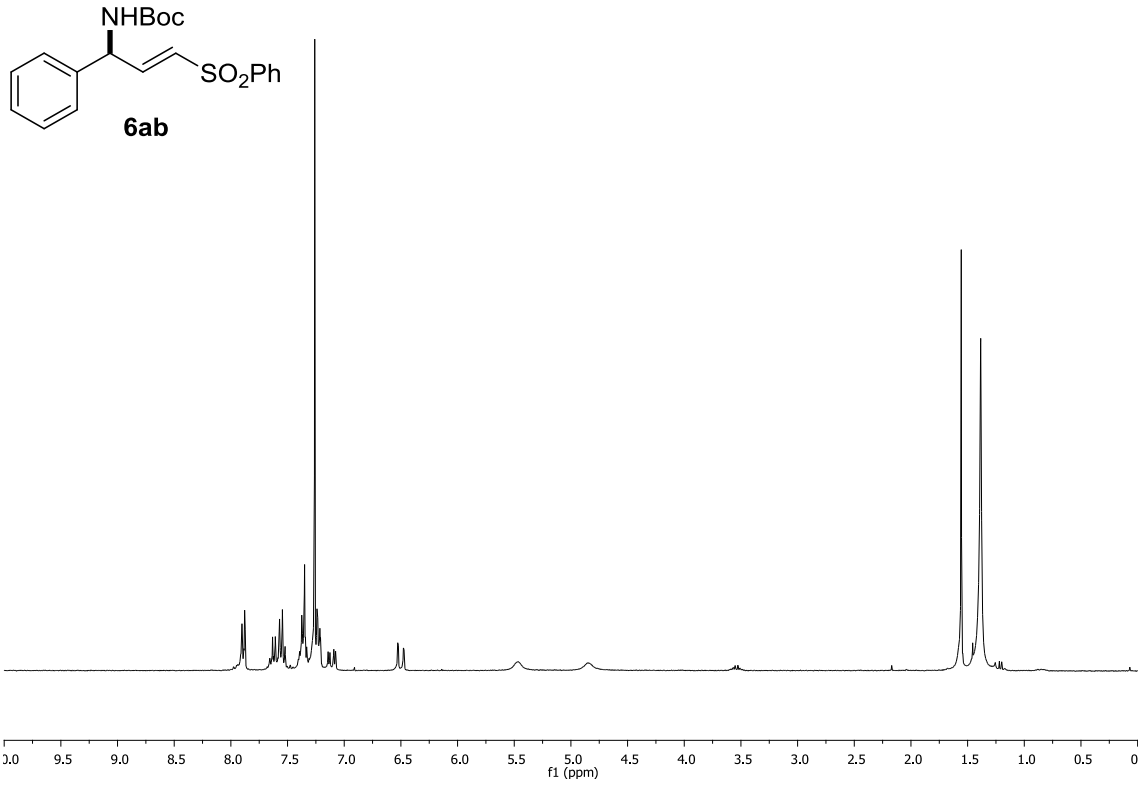
tert-Butyl (*S*,*E*)-(3-(phenylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (6aa)

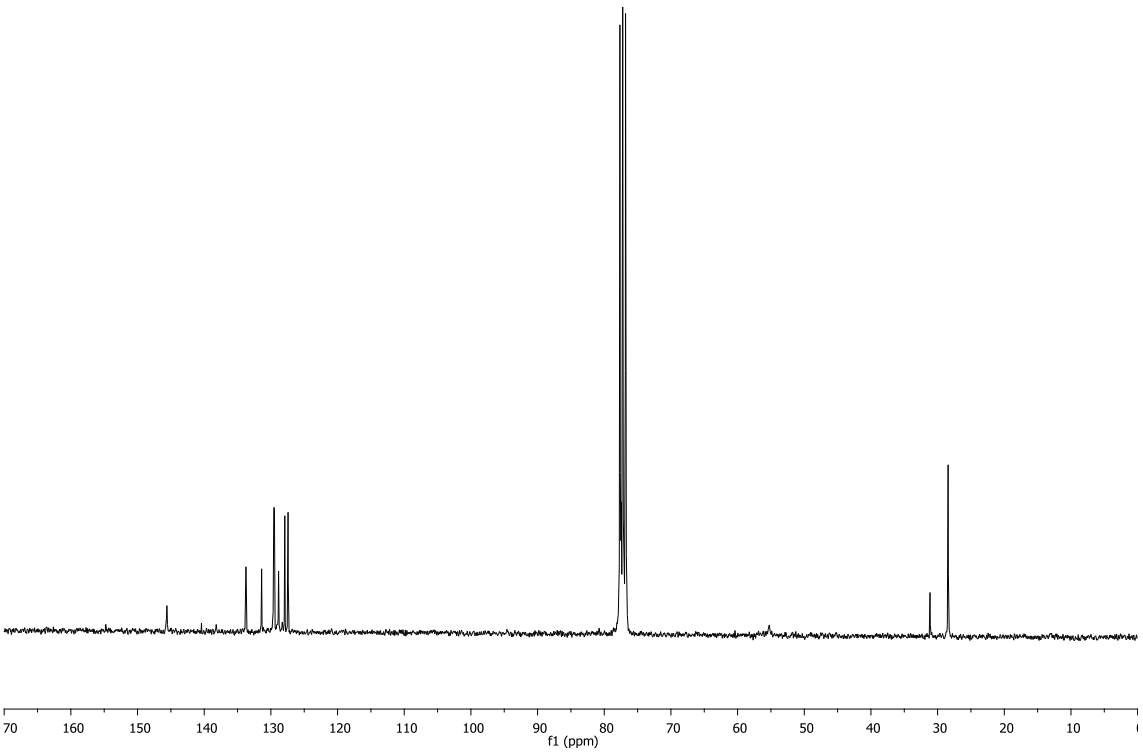


6aa

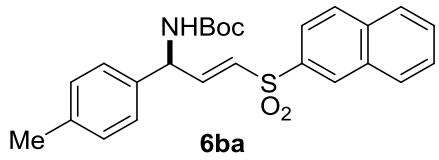


tert-Butyl (_S_,_E_)-(1-phenyl-3-(phenylsulfonyl)allyl)carbamate (6ab)

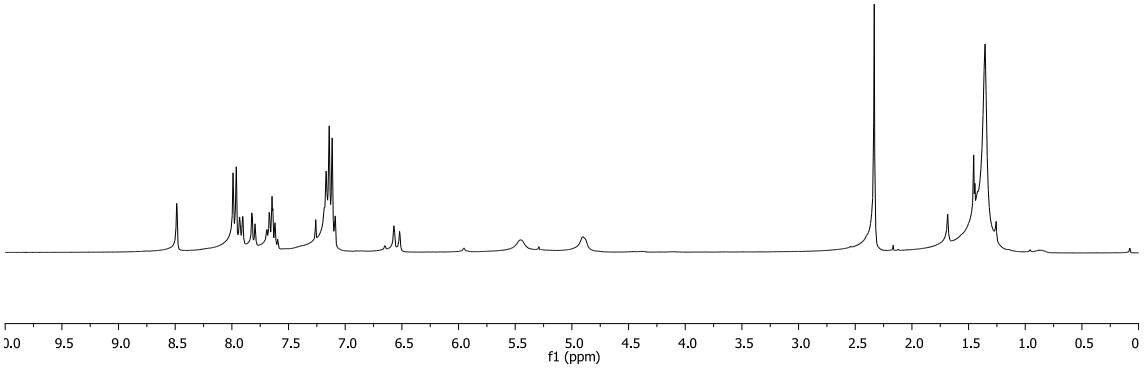


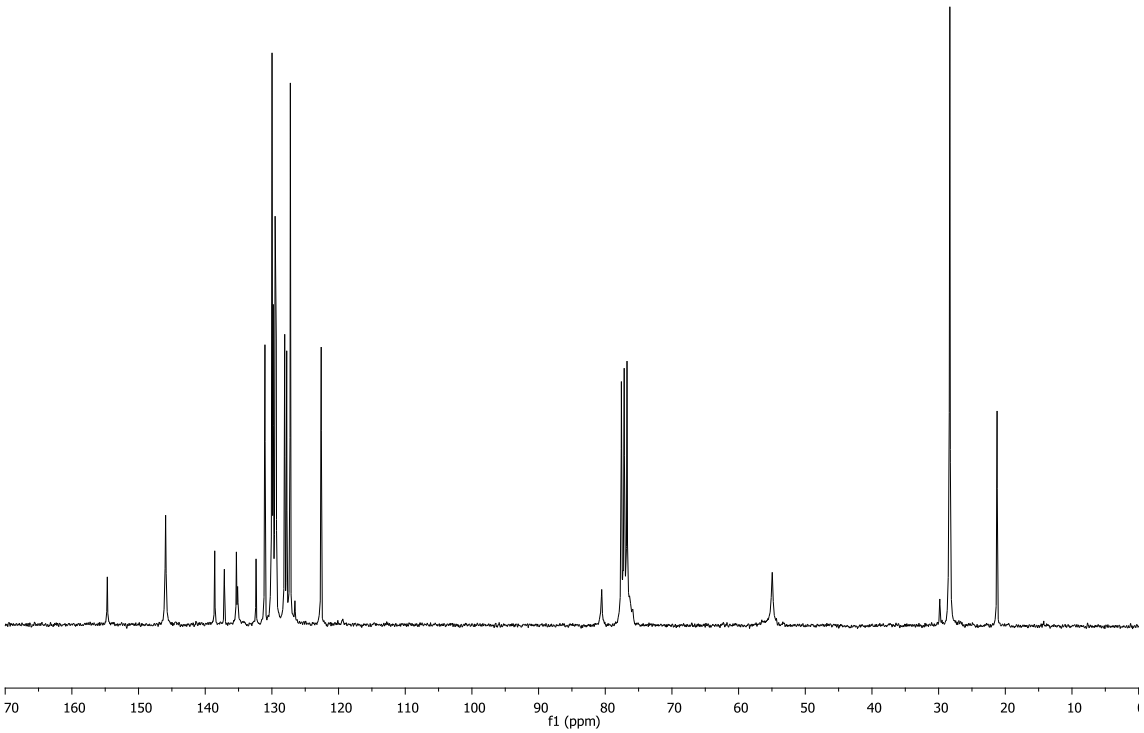


tert-Butyl (_S_,_E_)-(3-(naphthalen-2-ylsulfonyl)-1-(_p_-tolyl)allyl)carbamate (6ba)

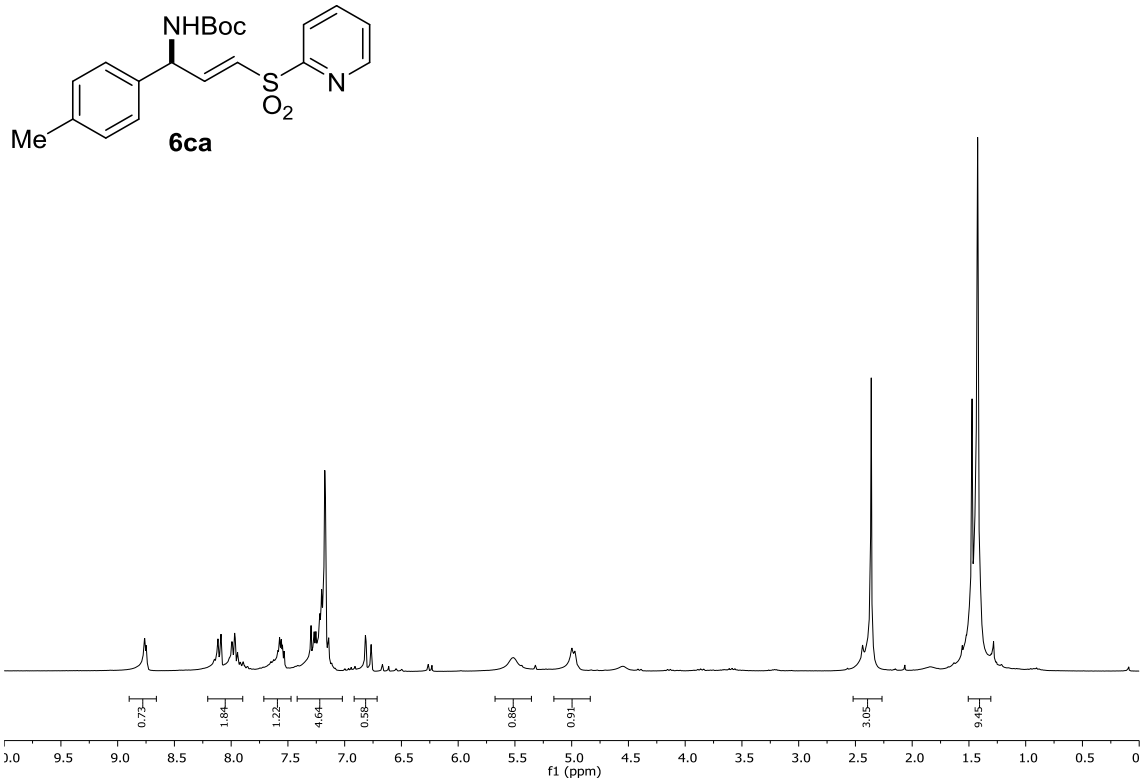


6ba

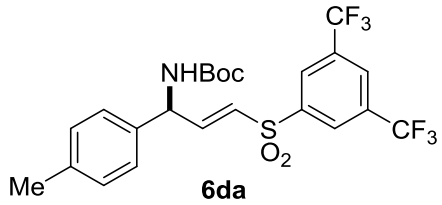




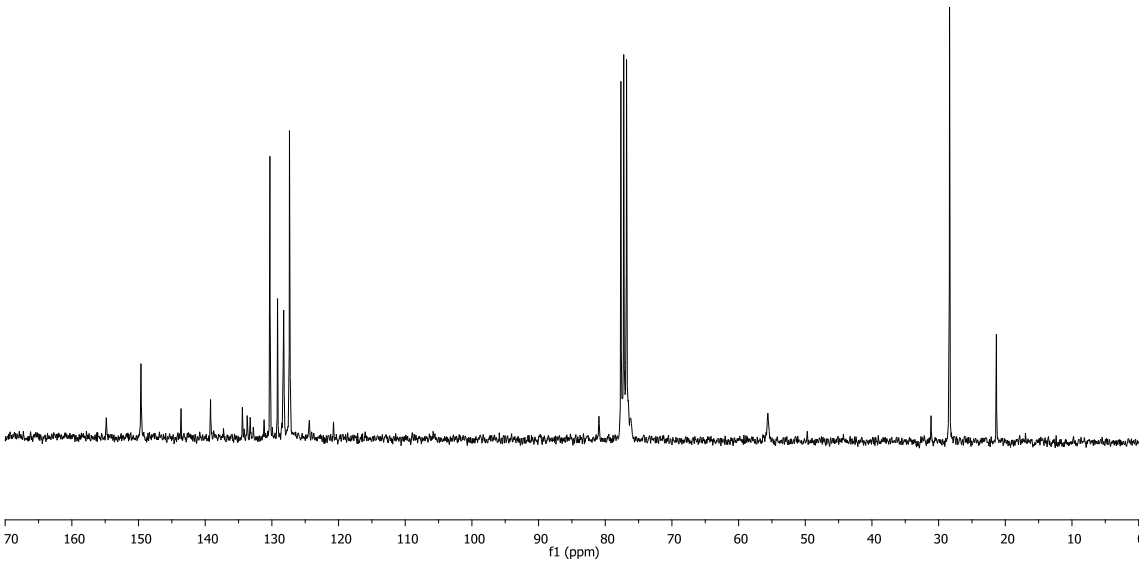
***tert*-Butyl (*S*,*E*)-(3-(pyridin-2-ylsulfonyl)-1-(*p*-tolyl)allyl)carbamate (6ca)**



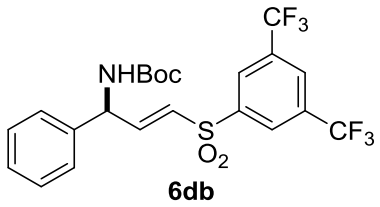
tert-Butyl (_S_,_E_)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(_p_-tolyl)allyl)carbamate (6da)



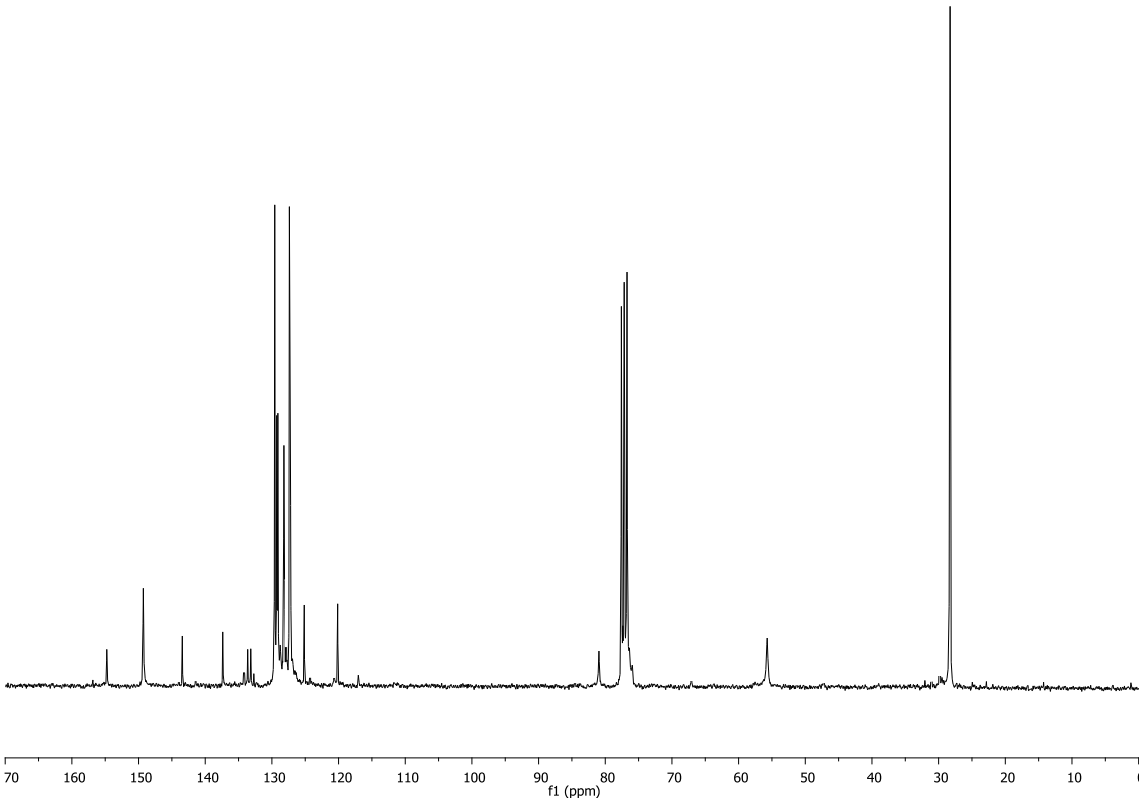
6da



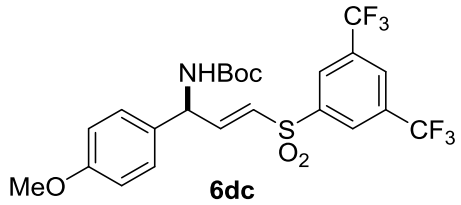
***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-phenylallyl)carbamate (6db)**



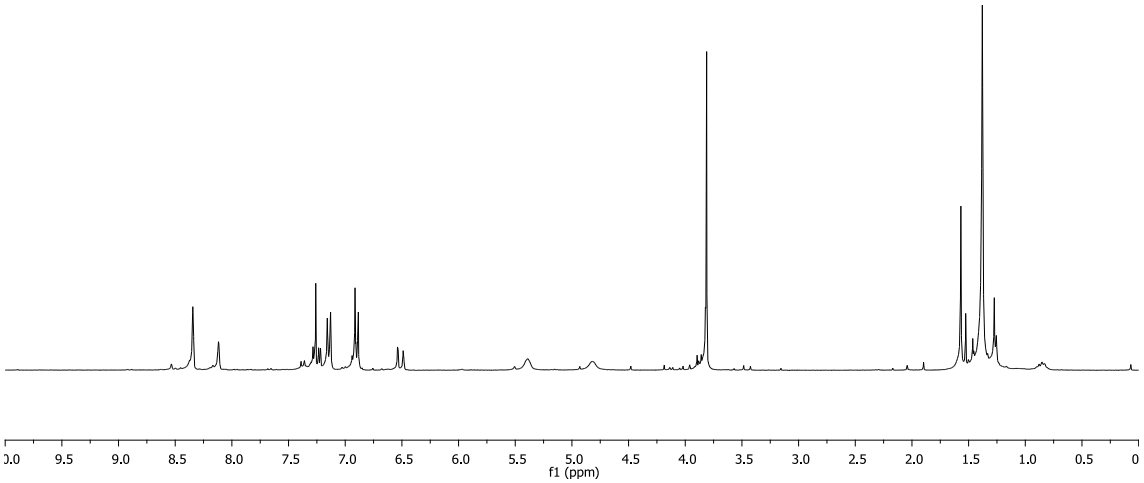
6db

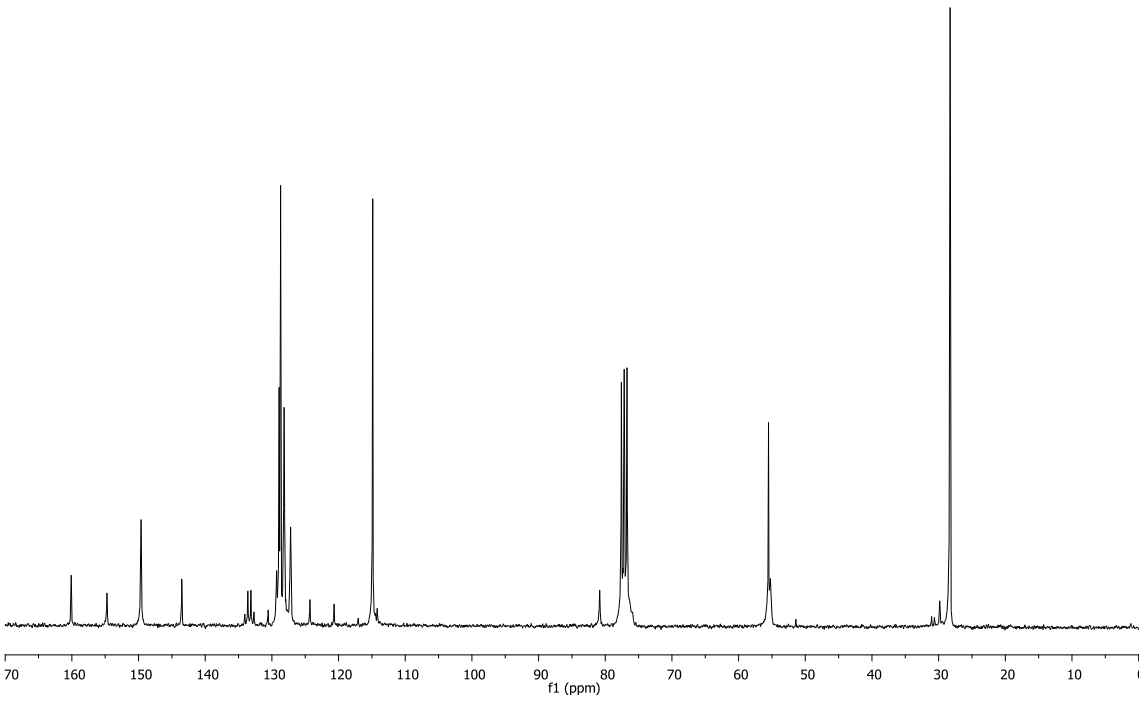


***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxyphenyl)allyl)carbamate (6dc)**

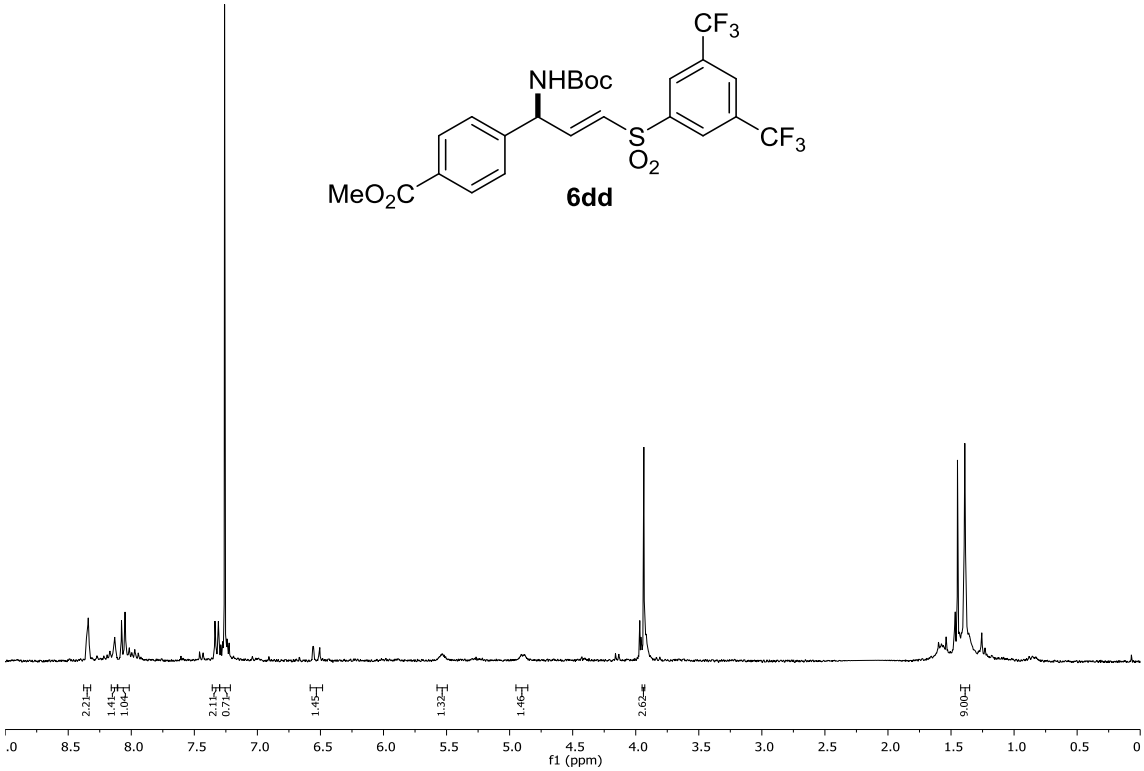


6dc

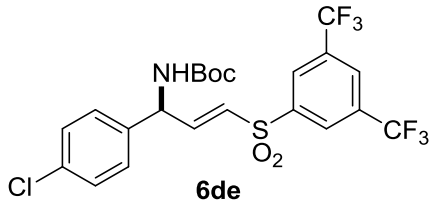




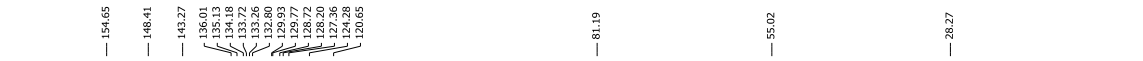
Methyl (*S*,*E*)-4-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-((tert-butoxycarbonyl)amino)allyl)benzoate (6dd)

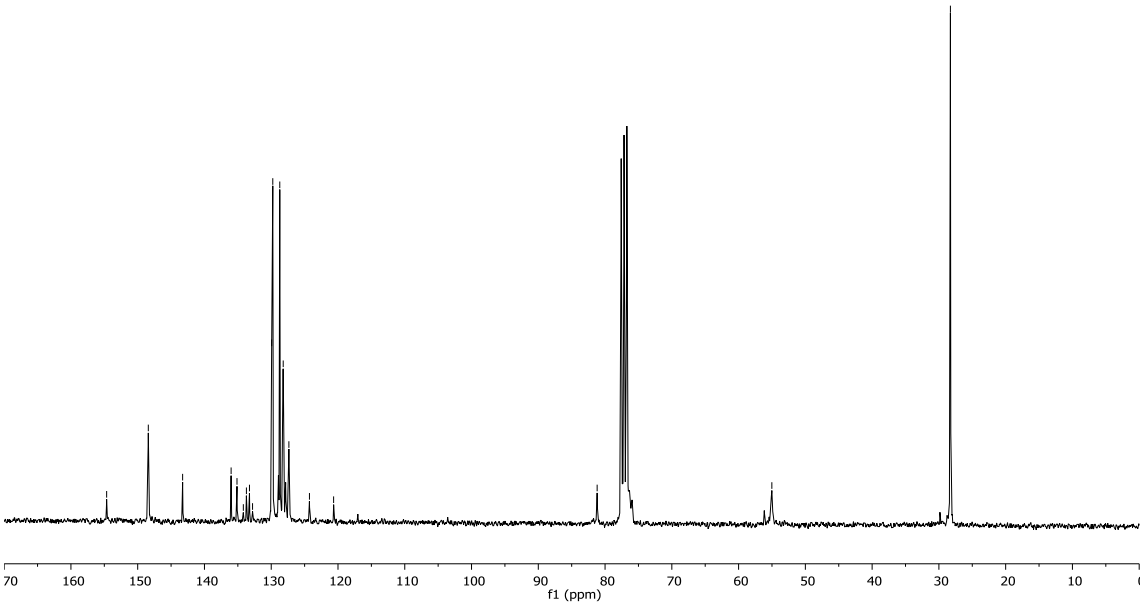


***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-chlorophenyl)allyl)carbamate (6de)**

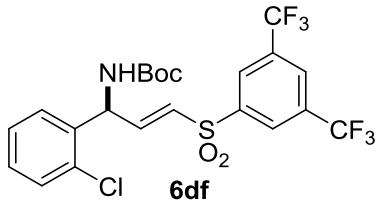


6de



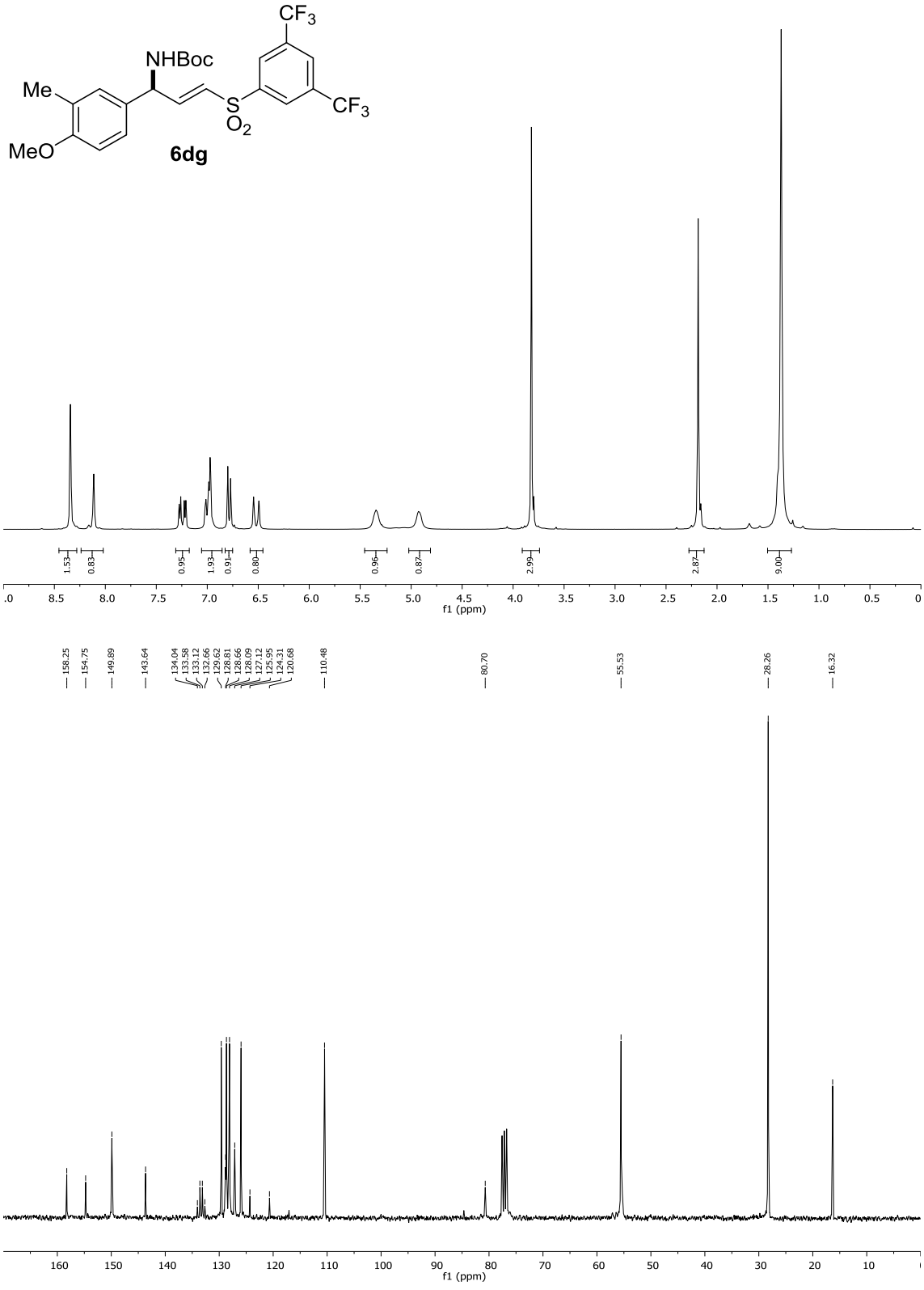


***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(2-chlorophenyl)allyl)carbamate (6df)**

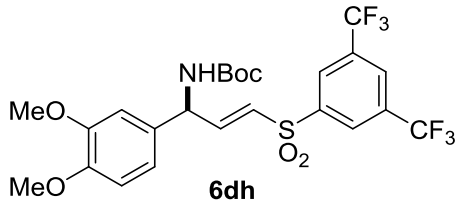


6df

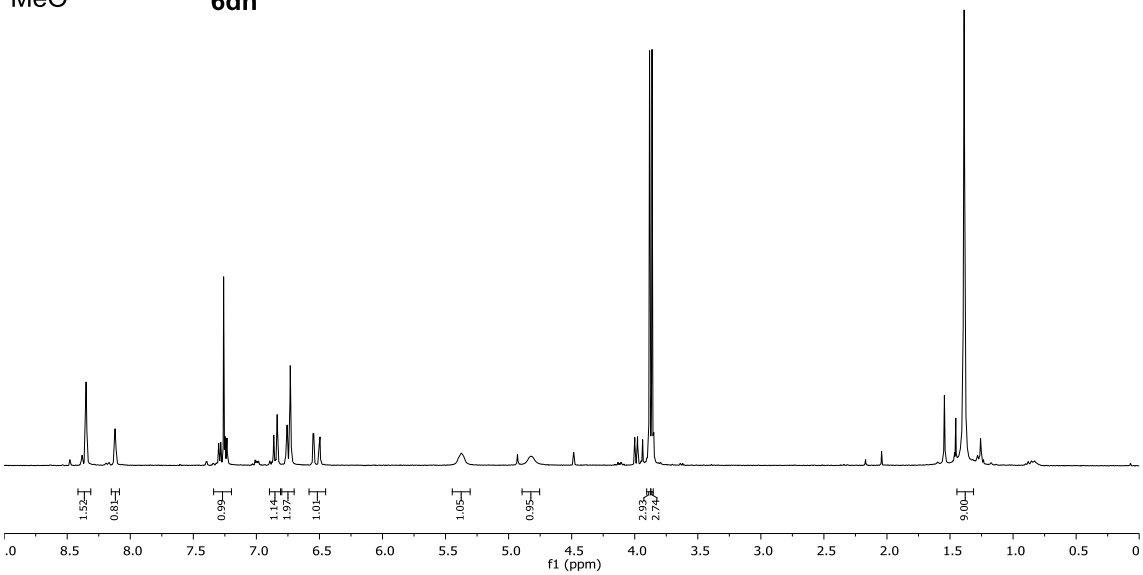
***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(4-methoxy-3-methylphenyl)allyl)carbamate (6dg)**



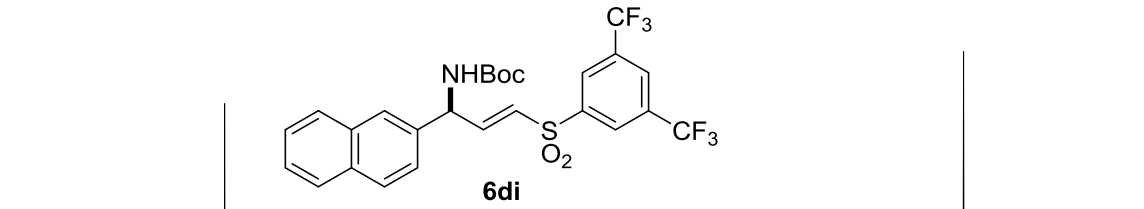
***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(3,4-dimethoxyphenyl)allyl)carbamate (6dh)**



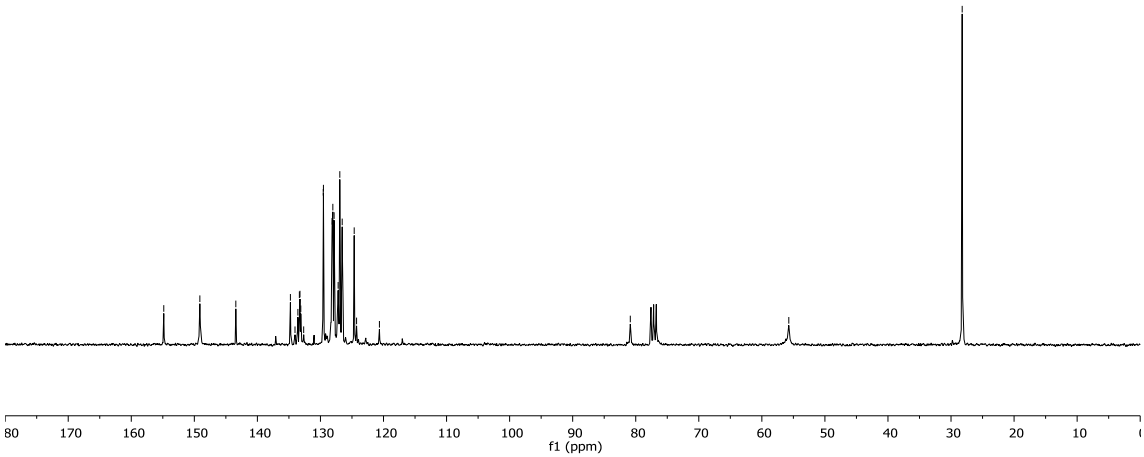
6dh



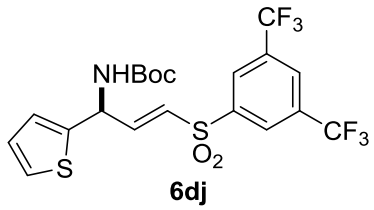
***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(naphthalen-2-yl)allyl)carbamate (6di)**



6di

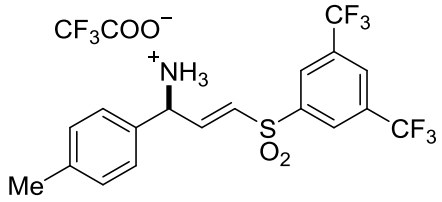


***tert*-Butyl (*S*,*E*)-(3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(thiophen-2-yl)allyl)carbamate (6dj)**

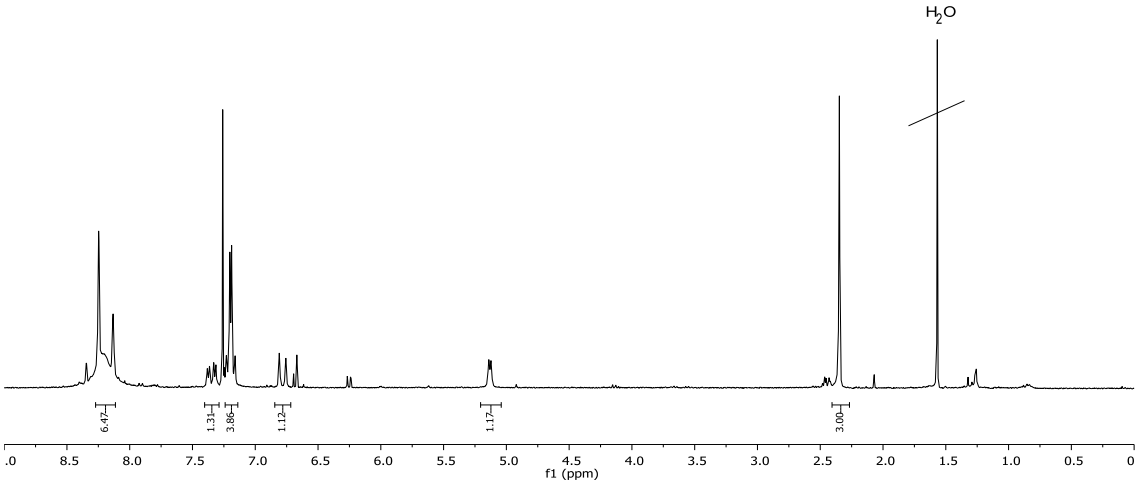


6dj

(S,E)-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-1-(p-tolyl)prop-2-en-1-aminium 2,2,2-trifluoroacetate (12da)

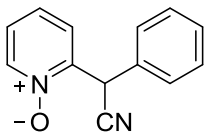


12da

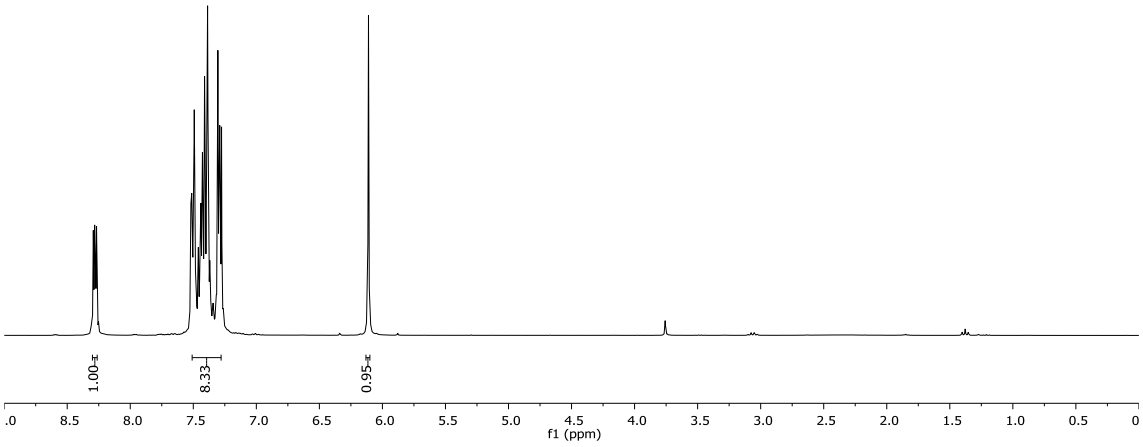


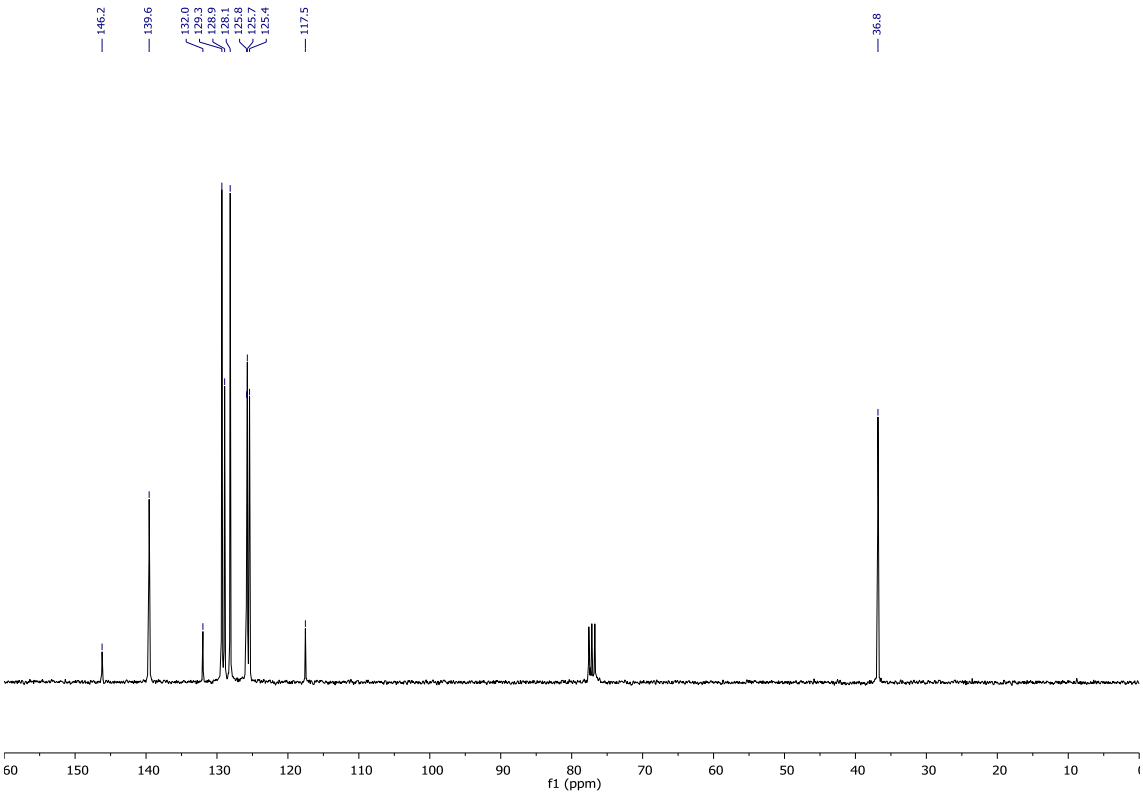
6.6.3. NMR spectra for Chapter 3

2-(Cyano(phenyl)methyl)pyridine *N*-oxide (13a)

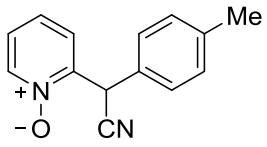


13a

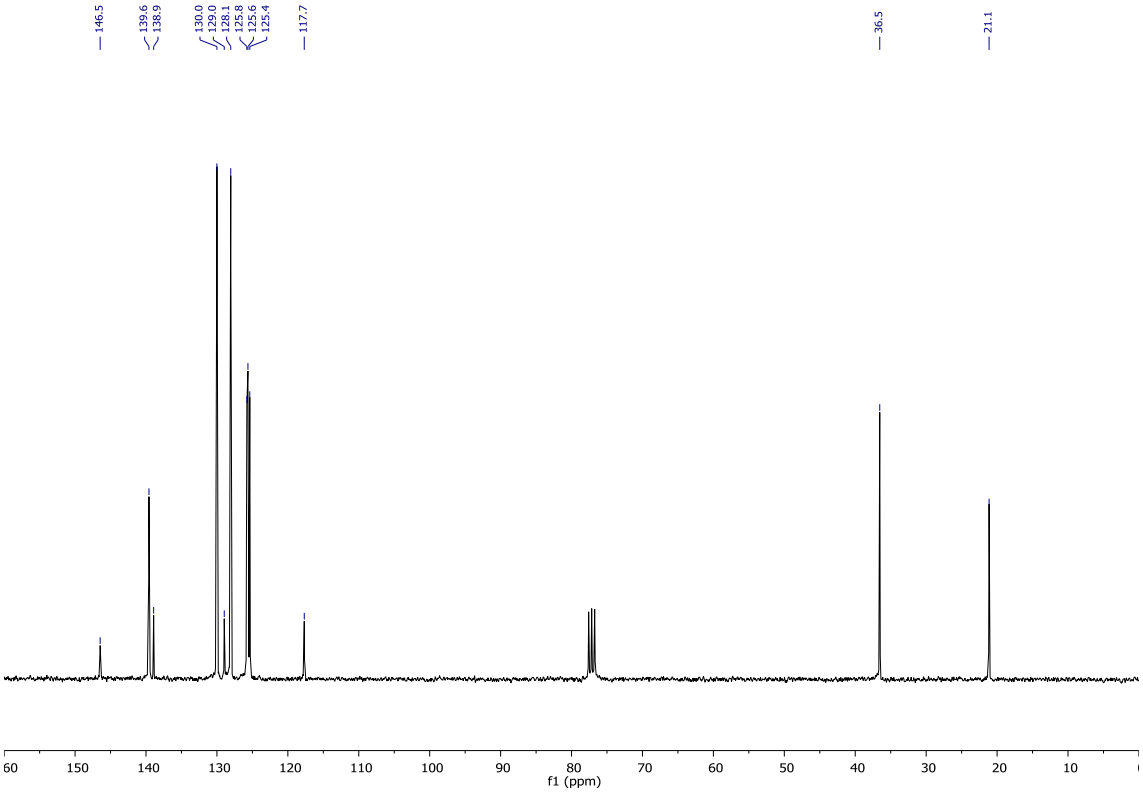




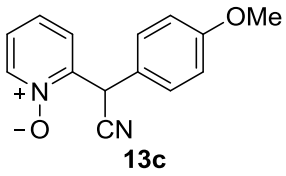
2-(Cyano(*p*-tolyl)methyl)pyridine *N*-oxide (13b)



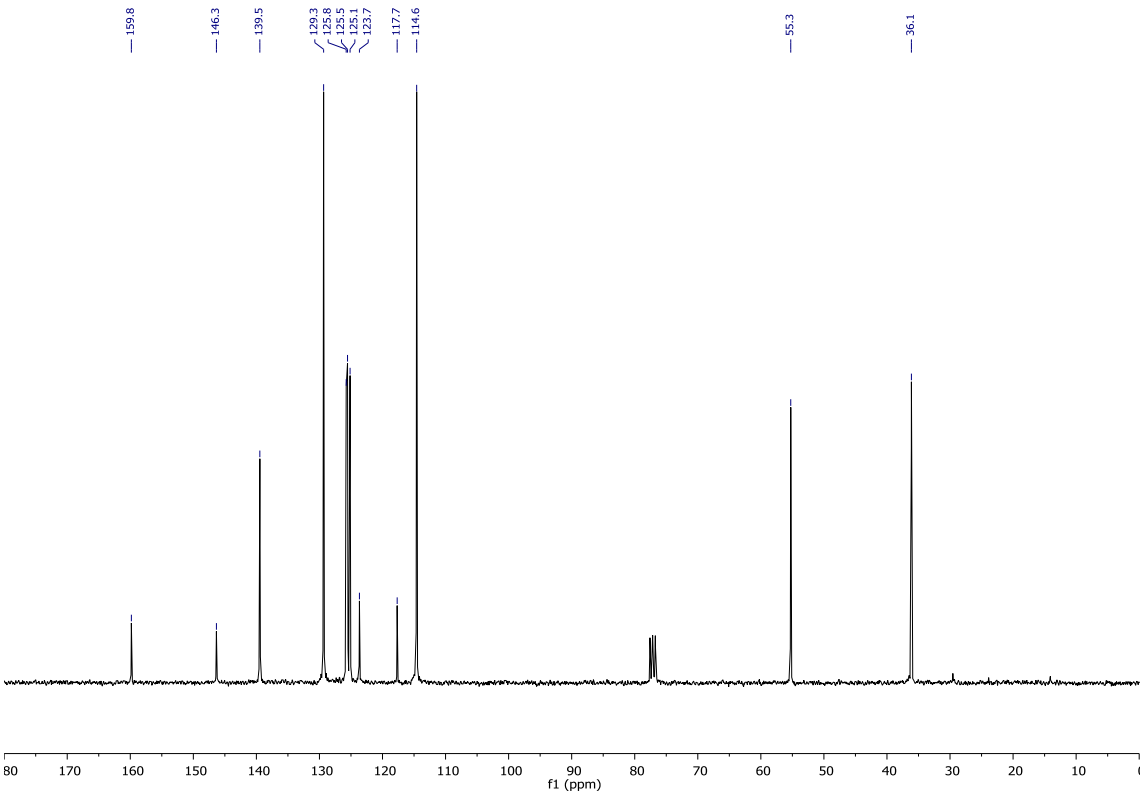
13b



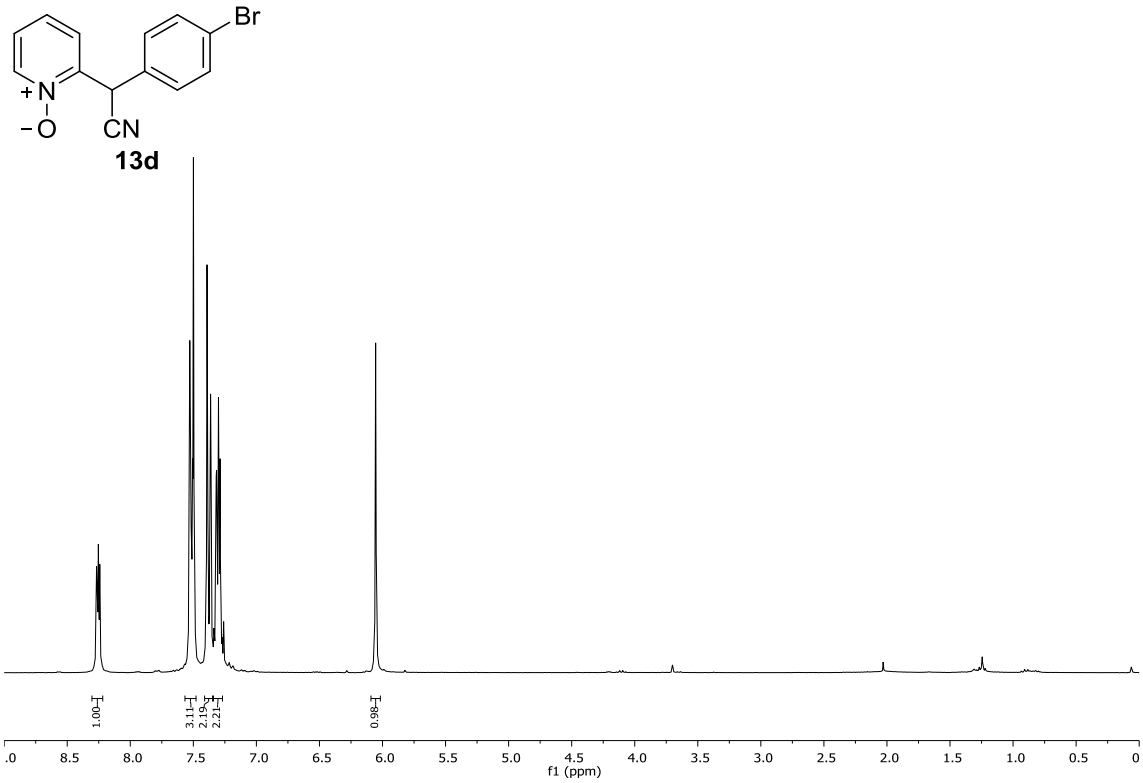
2-(Cyano(4-methoxyphenyl)methyl)pyridine *N*-oxide (13c)

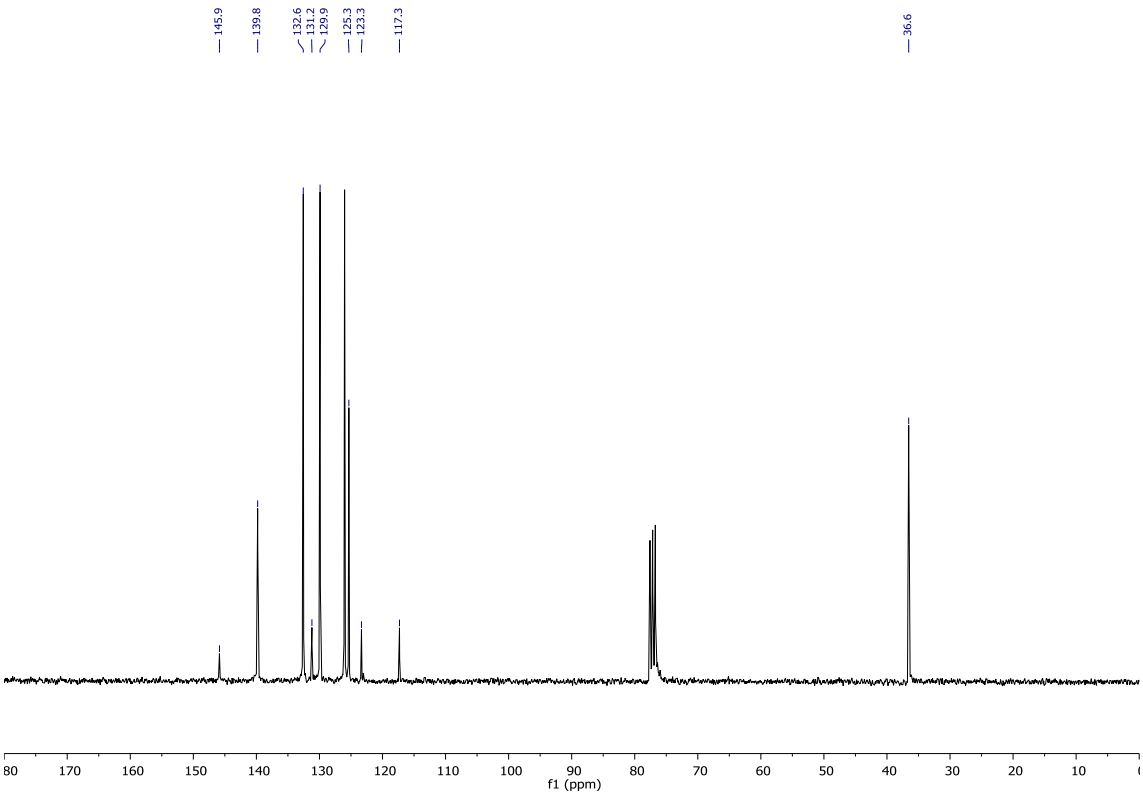


13c

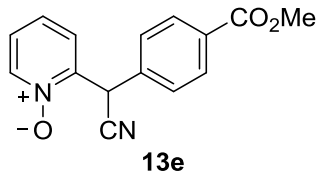


2-((4-Bromophenyl)(cyano)methyl)pyridine *N*-oxide (13d)

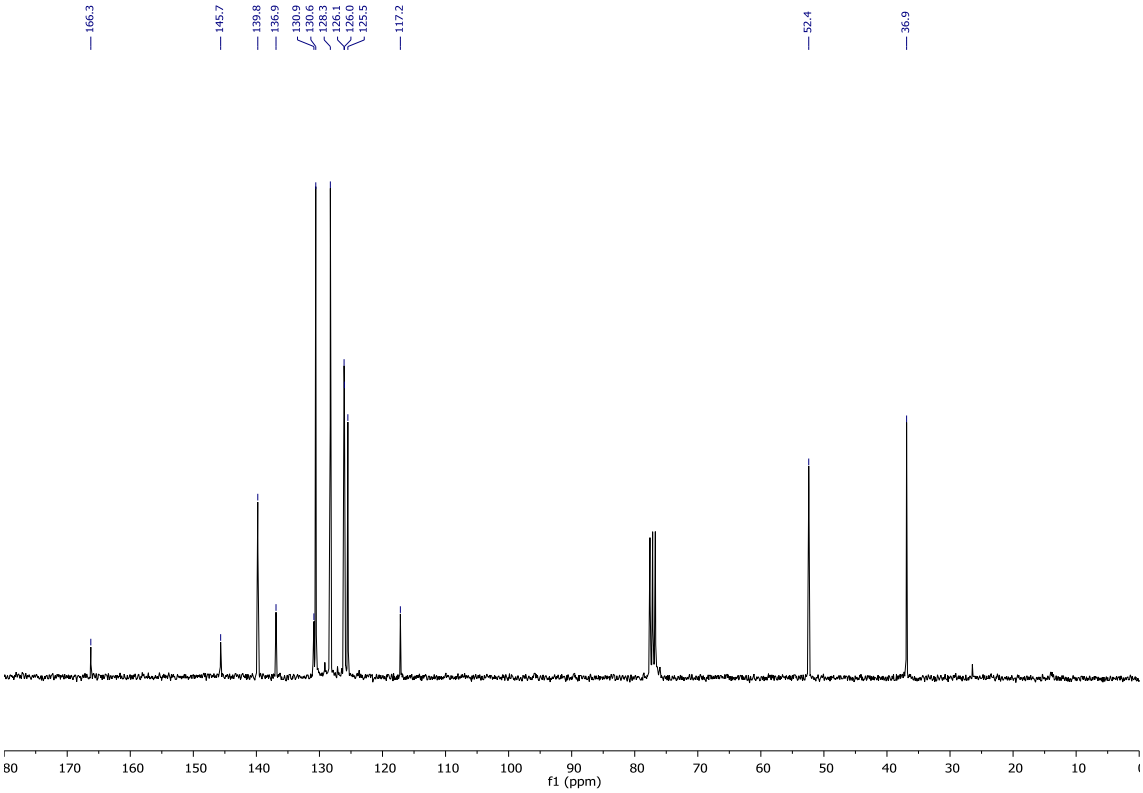




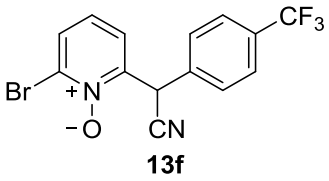
2-(Cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (13e)



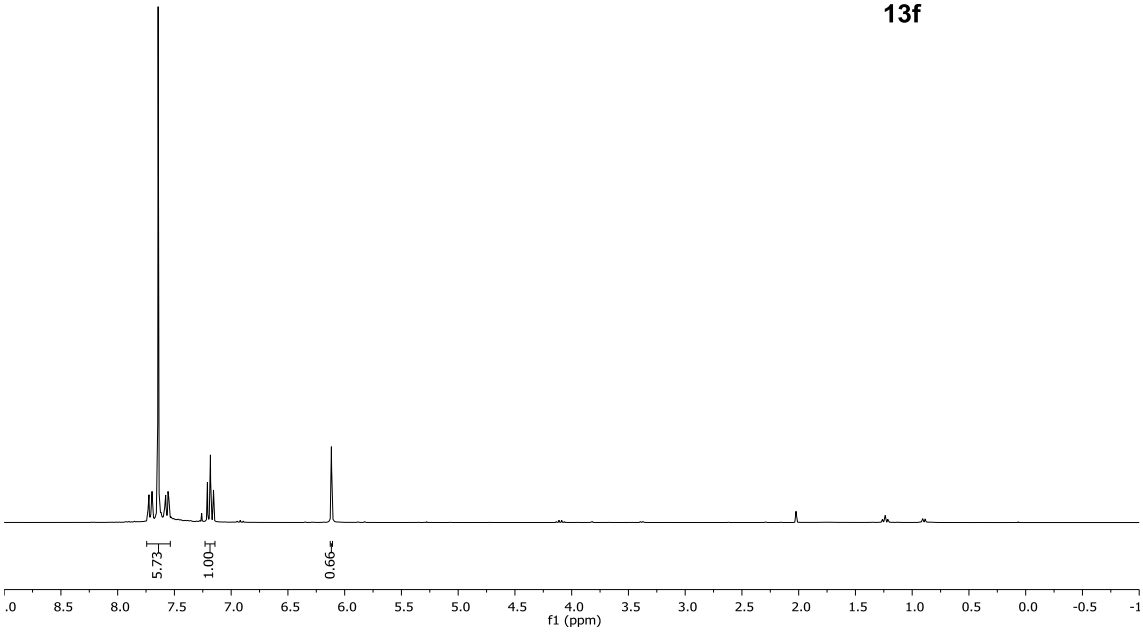
13e

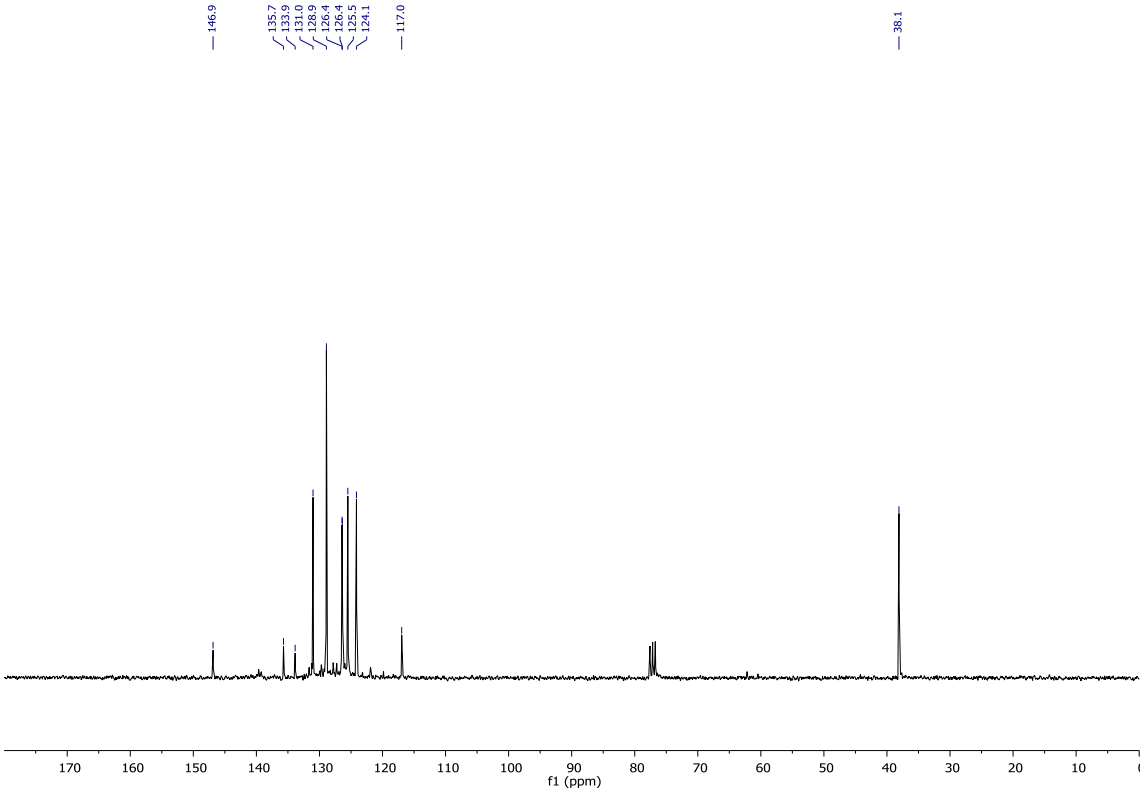


2-Bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine *N*-oxide (13f)

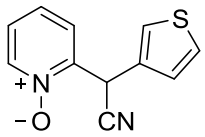


13f

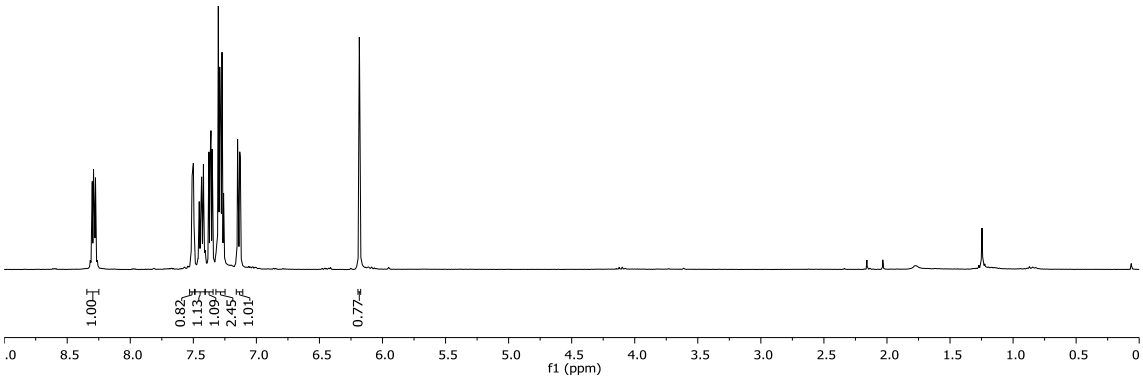


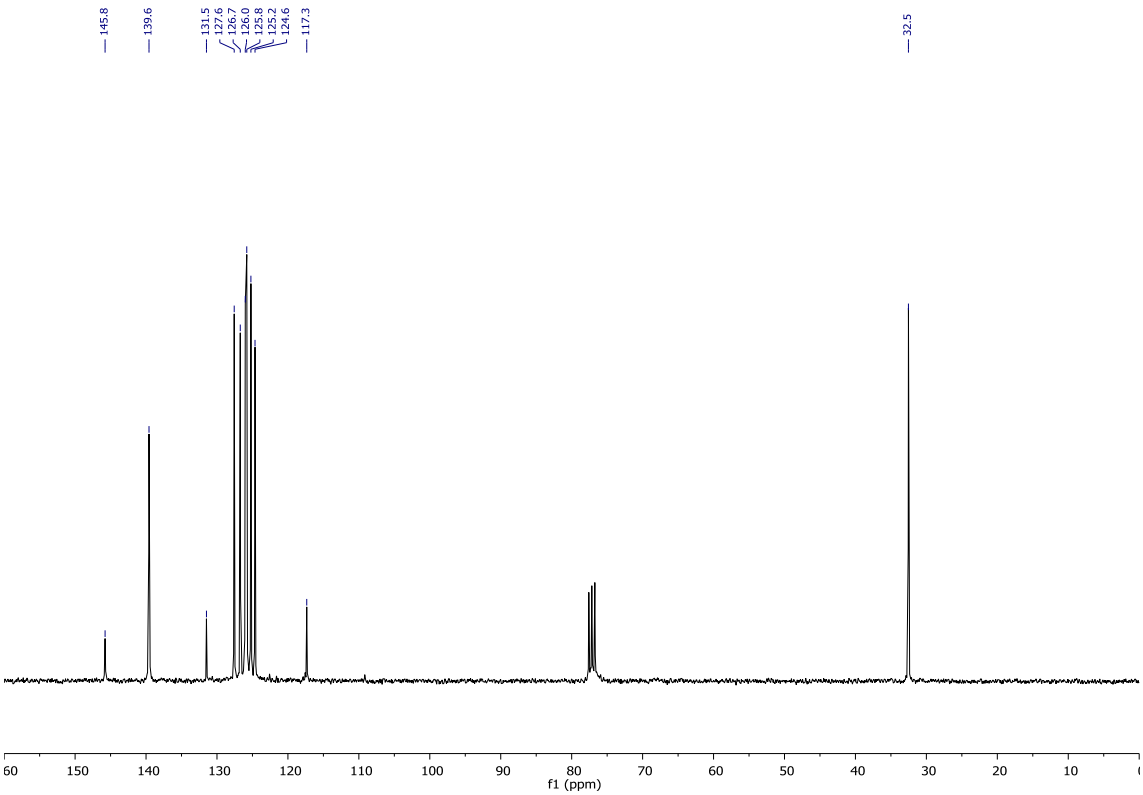


2-(Cyano(thiophen-3-yl)methyl)pyridine *N*-oxide (13g)



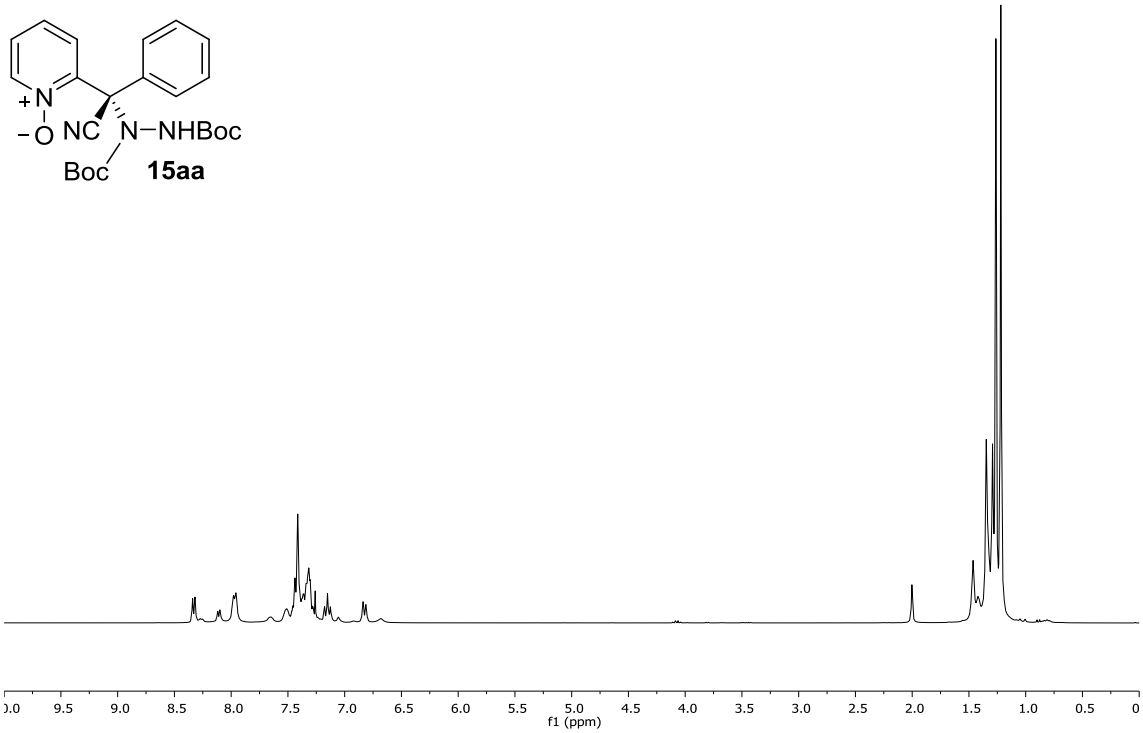
13g



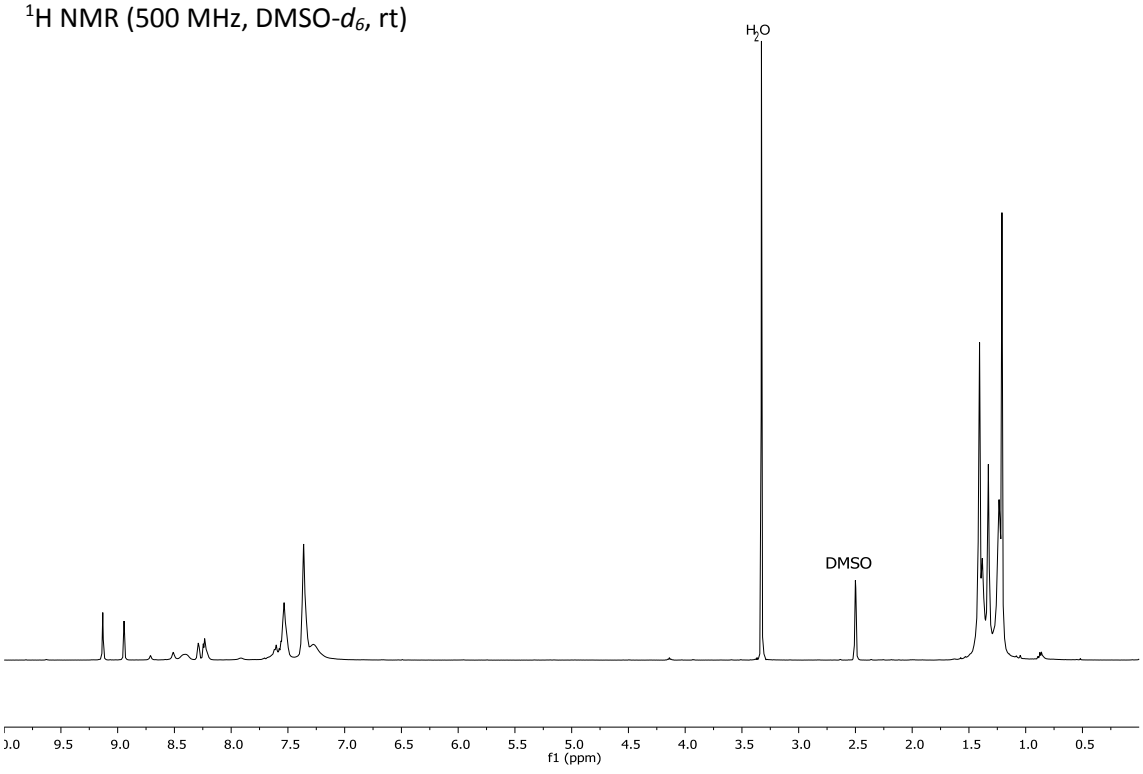


(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(phenyl)methyl)pyridine *N*-oxide (15aa)

^{1}H NMR (300 MHz, $CDCl_3$, rt)

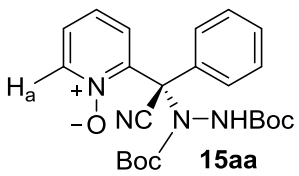


^{1}H NMR (500 MHz, DMSO-d_6, rt)



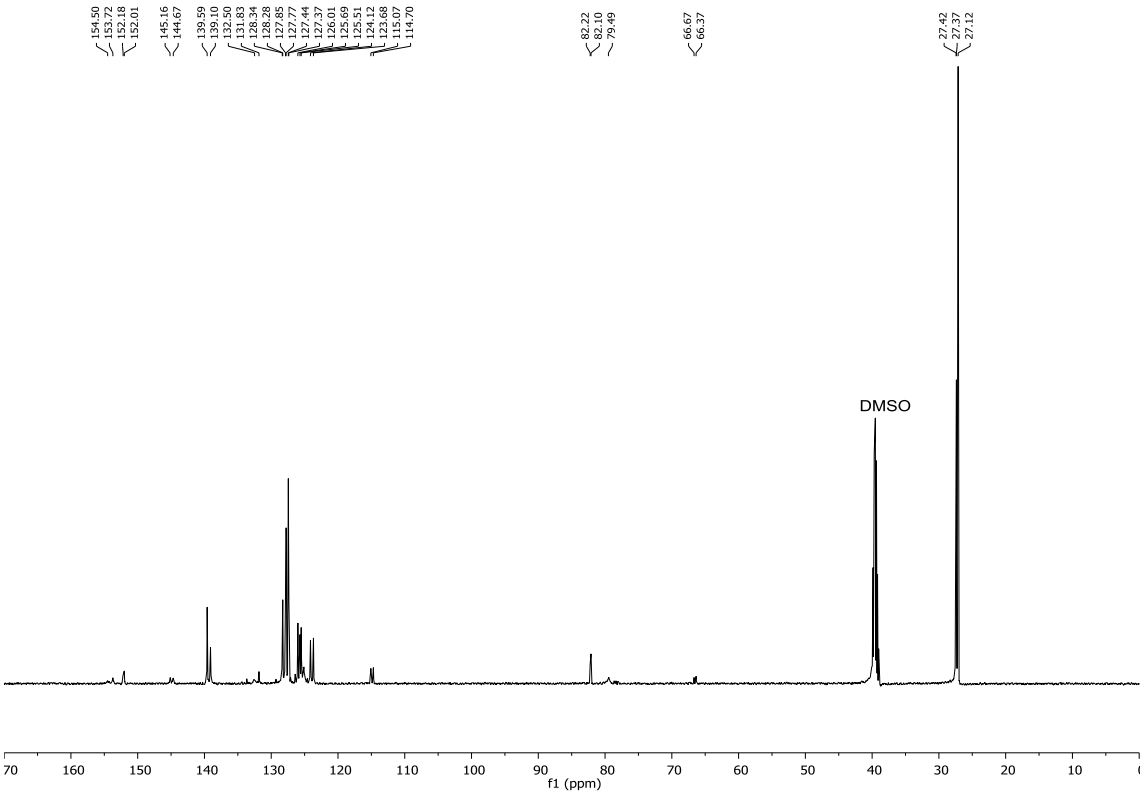
^{1}H NMR experiments in $CDCl_3$ (at room temperature and at 55°C) and DMSO-d_6 (at room temperature) showed a mixture of rotamers **15aa**, whose ratio could not be determined. A simpler ^{1}H NMR was obtained in DMSO-d_6 at 70°C, in which a 1:1 mixture of rotamers was observed.

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)



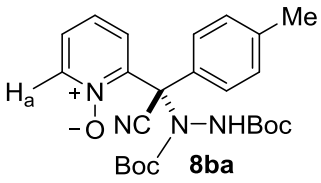
15aa

Rotameric ratio: 1:1

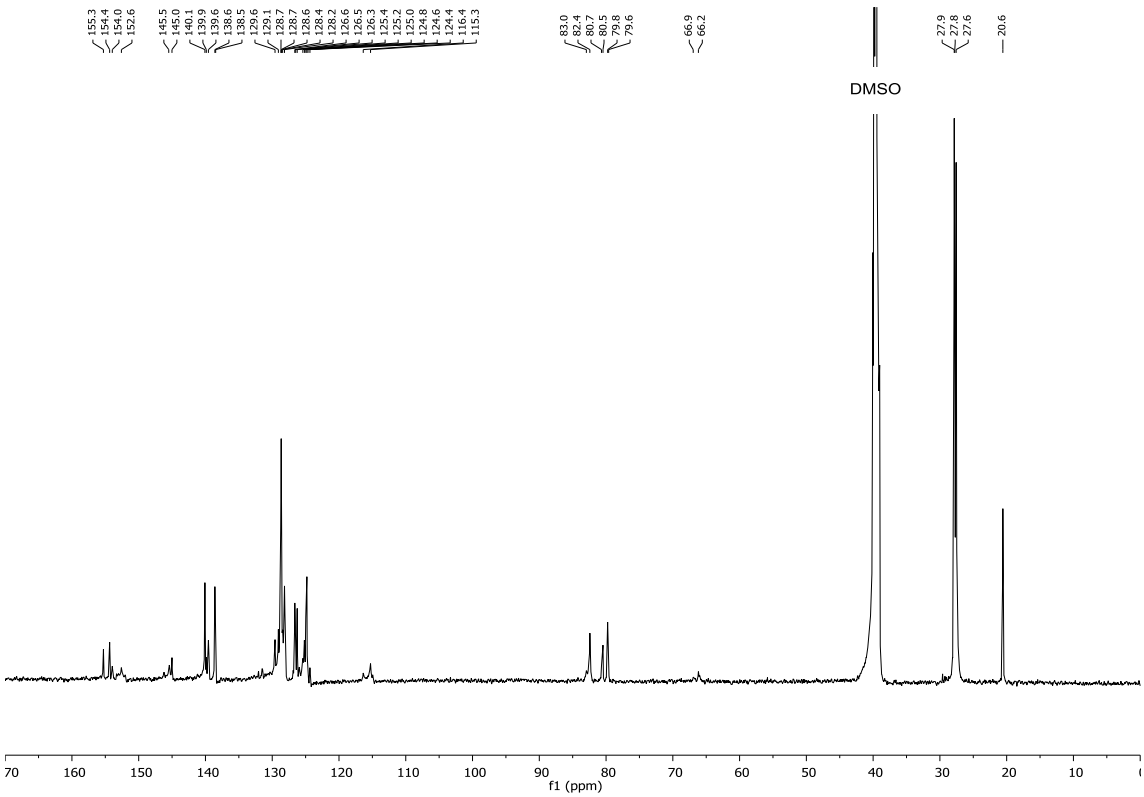


(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(*p*-tolyl)methyl)pyridine *N*-oxide (15ba)

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)

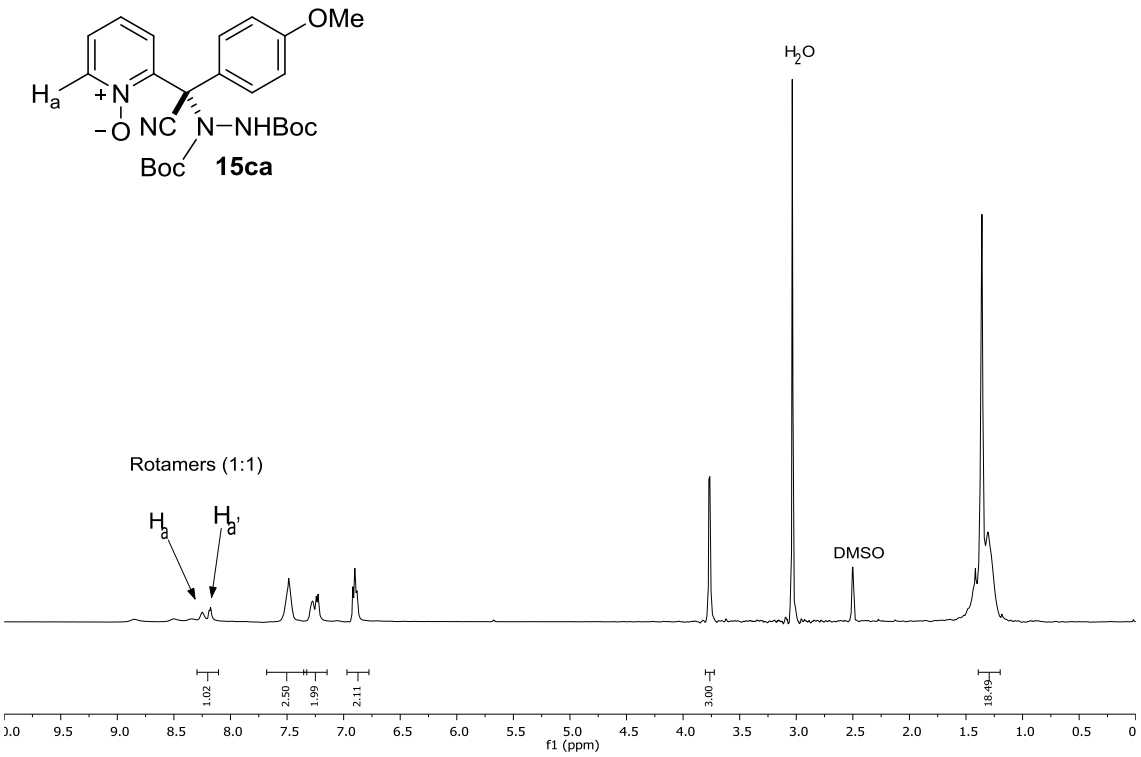


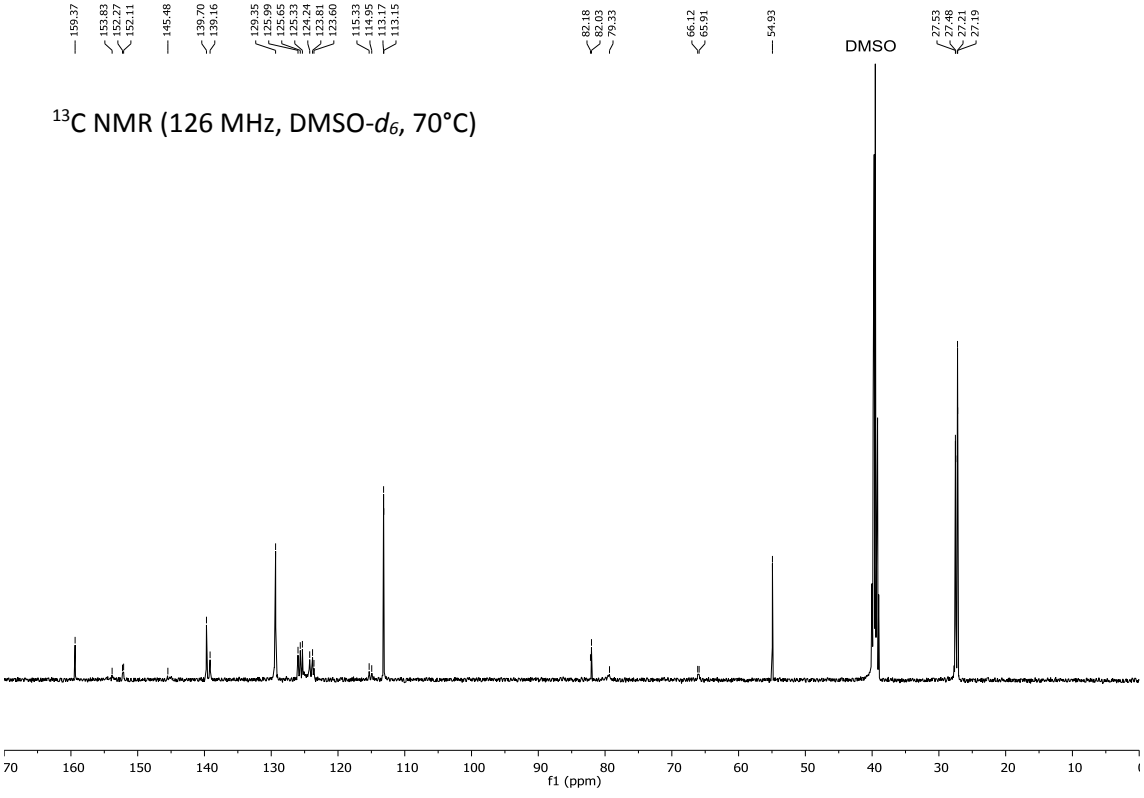
8ba



(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-methoxyphenyl)methyl)pyridine *N*-oxide (15ca)

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)

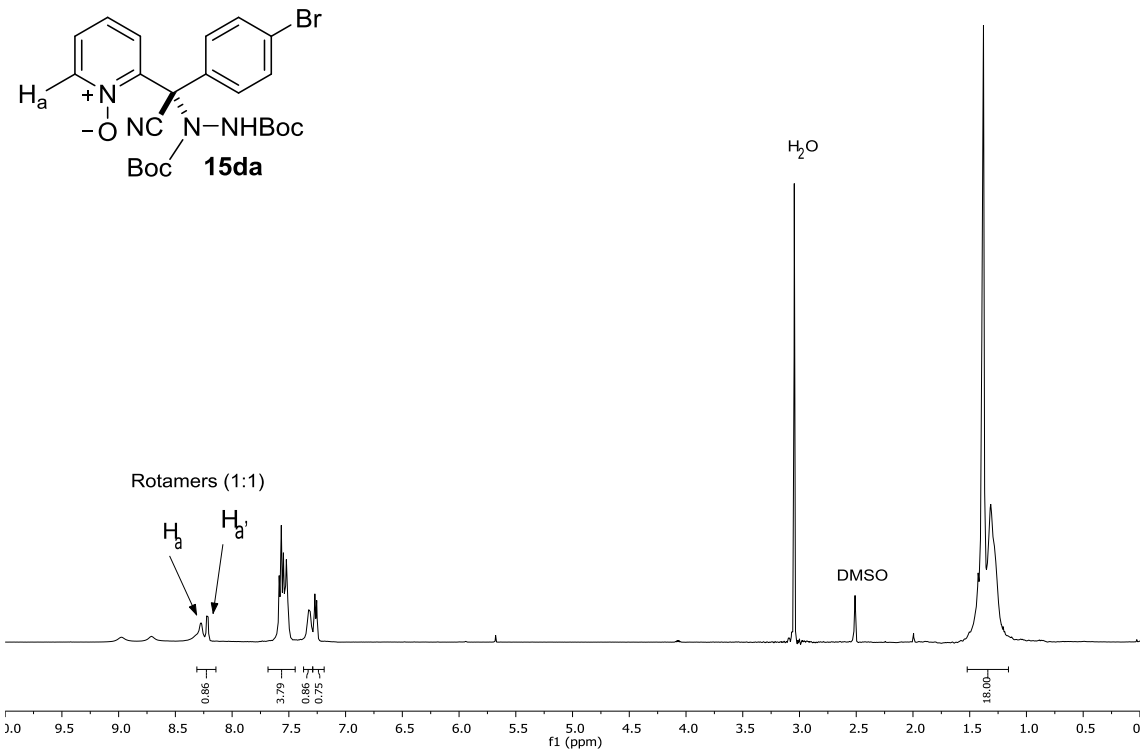


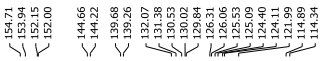


^{13}C NMR (126 MHz, DMSO-d_6, 70°C)

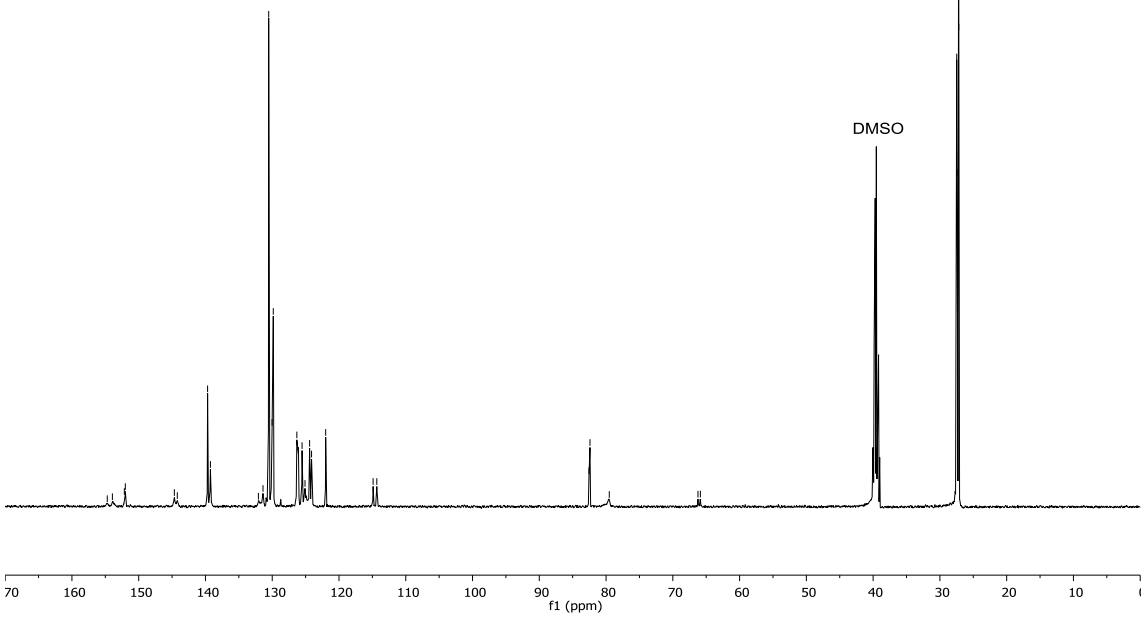
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine *N*-oxide (15da)

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)



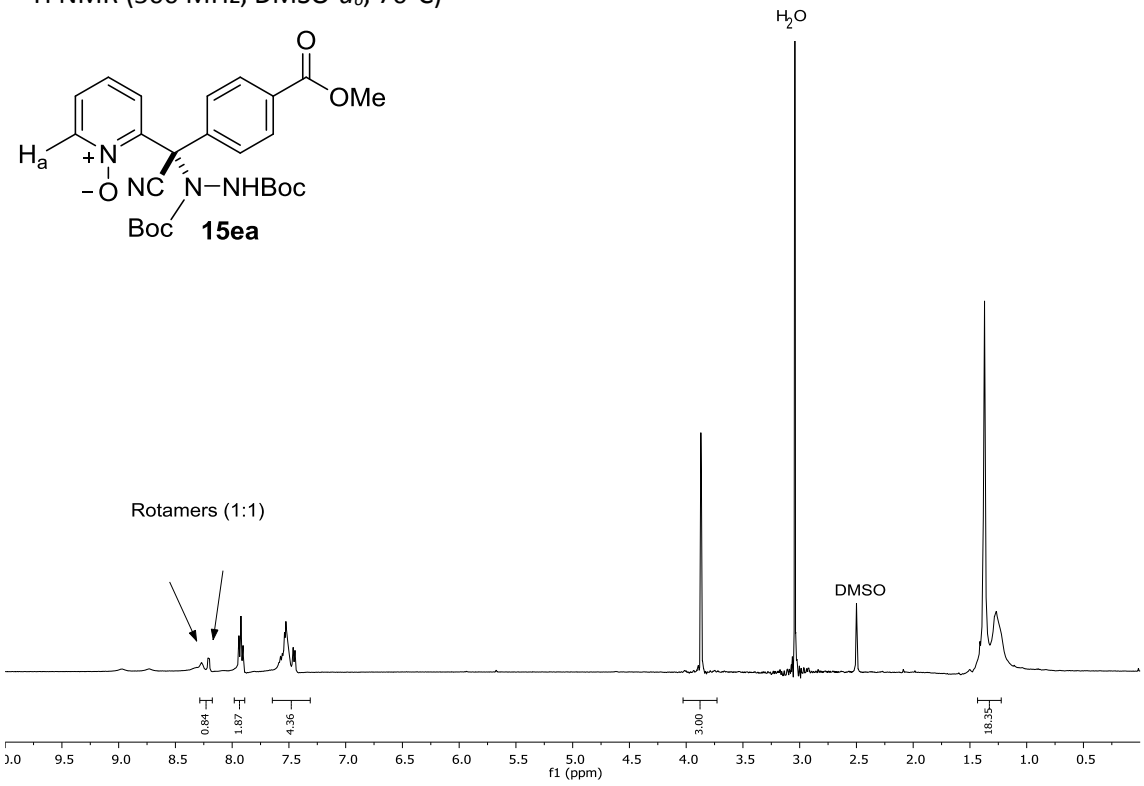


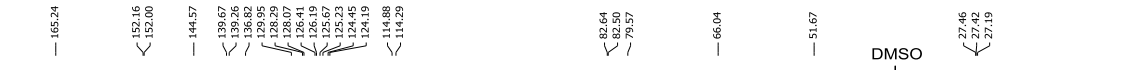
^{13}C NMR (126 MHz, DMSO-d_6, 70°C)



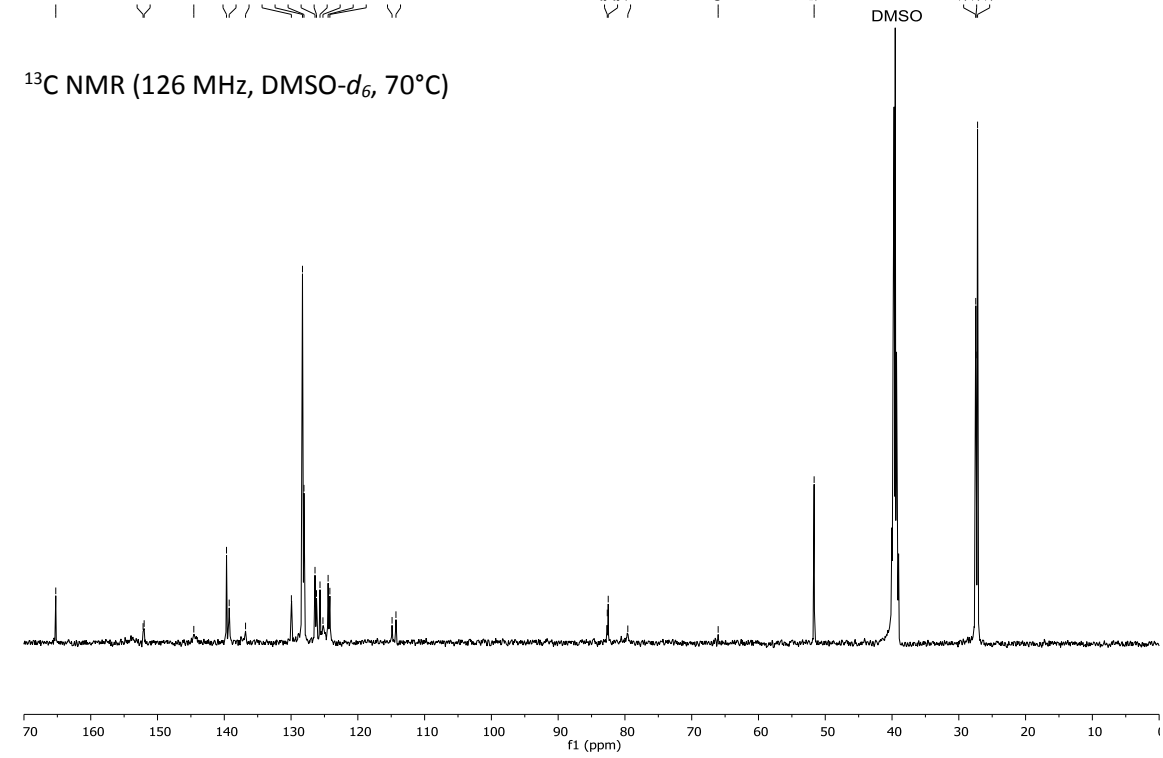
(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15ea)

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)



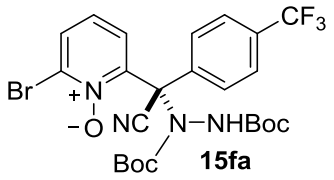


^{13}C NMR (126 MHz, DMSO-d_6, 70°C)

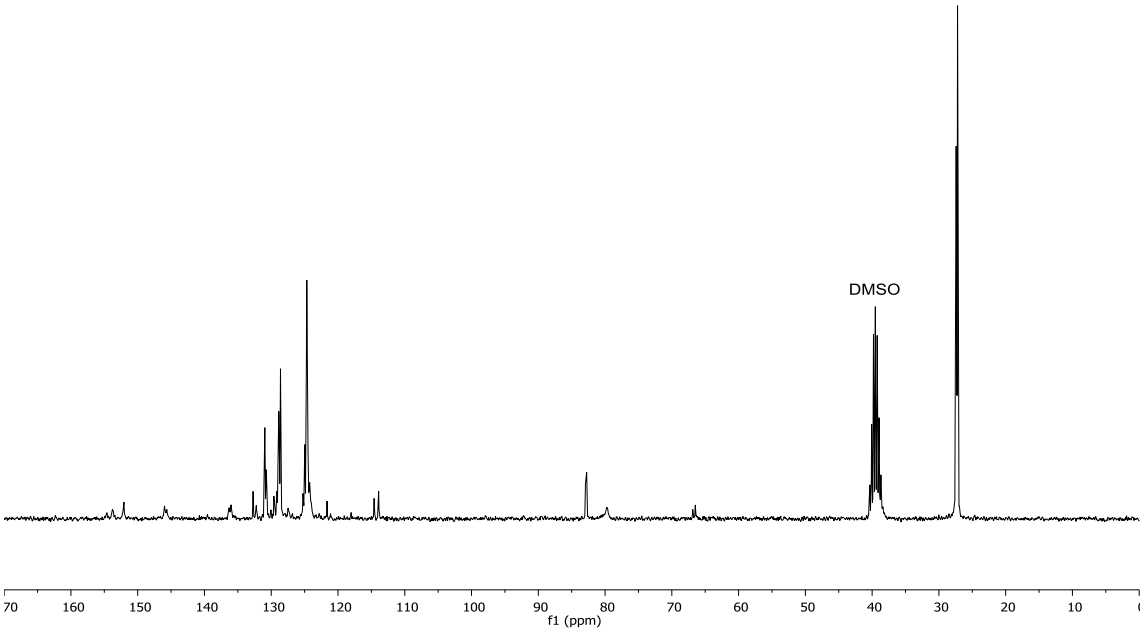


(*S*)-2-((1,2-bis(*tert*-butoxycarbonyl)hydrazinyl)(cyano)(4-(trifluoromethyl)phenyl)methyl)-6-bromopyridine *N*-oxide (15fa)

^{1}H NMR (300 MHz, DMSO-d_6, rt)

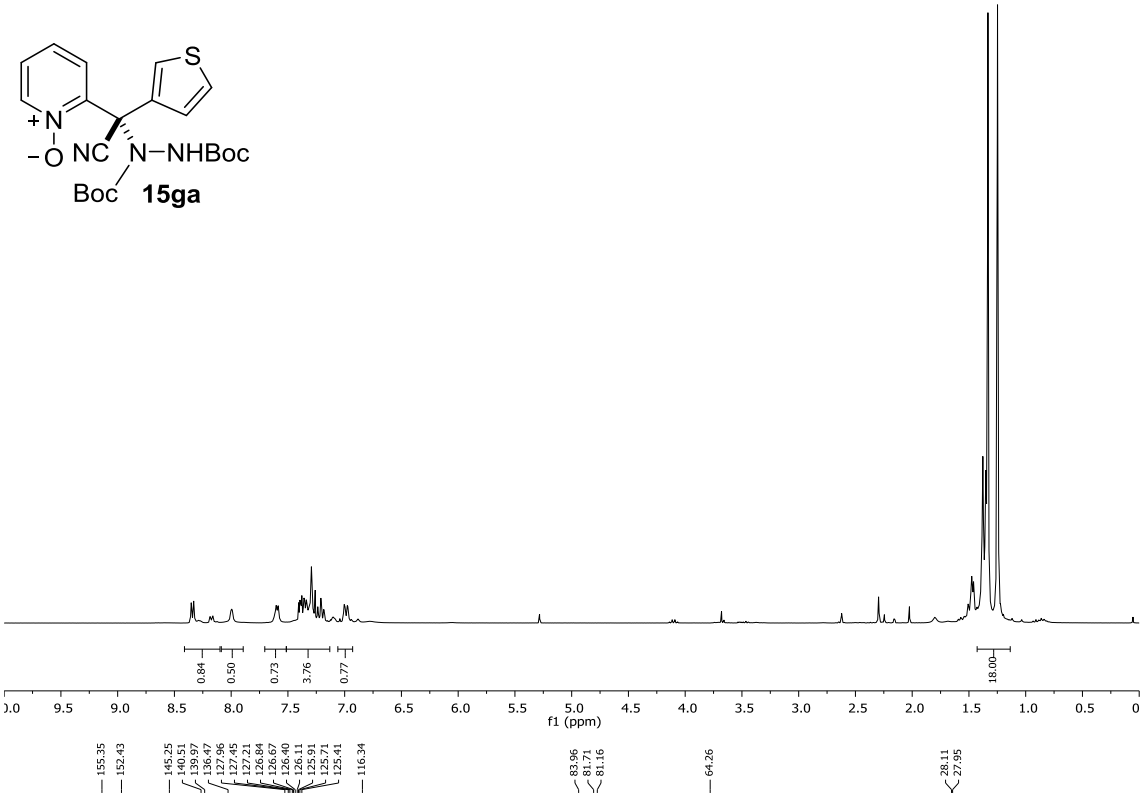


^{13}C NMR (75 MHz, DMSO-d_6, rt)

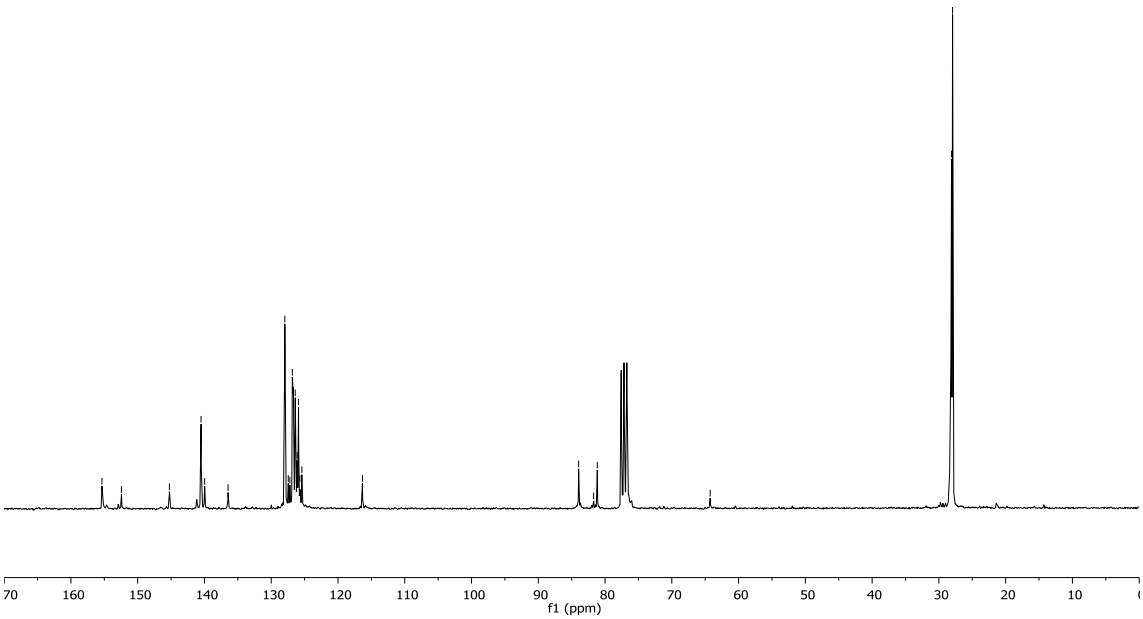


(*S*)-2-((1,2-bis(tert-butoxycarbonyl)hydrazinyl)(cyano)(thiophen-3-yl)methyl)pyridine *N*-oxide (15ga)

^{1}H NMR (300 MHz, $CDCl_3$, rt)

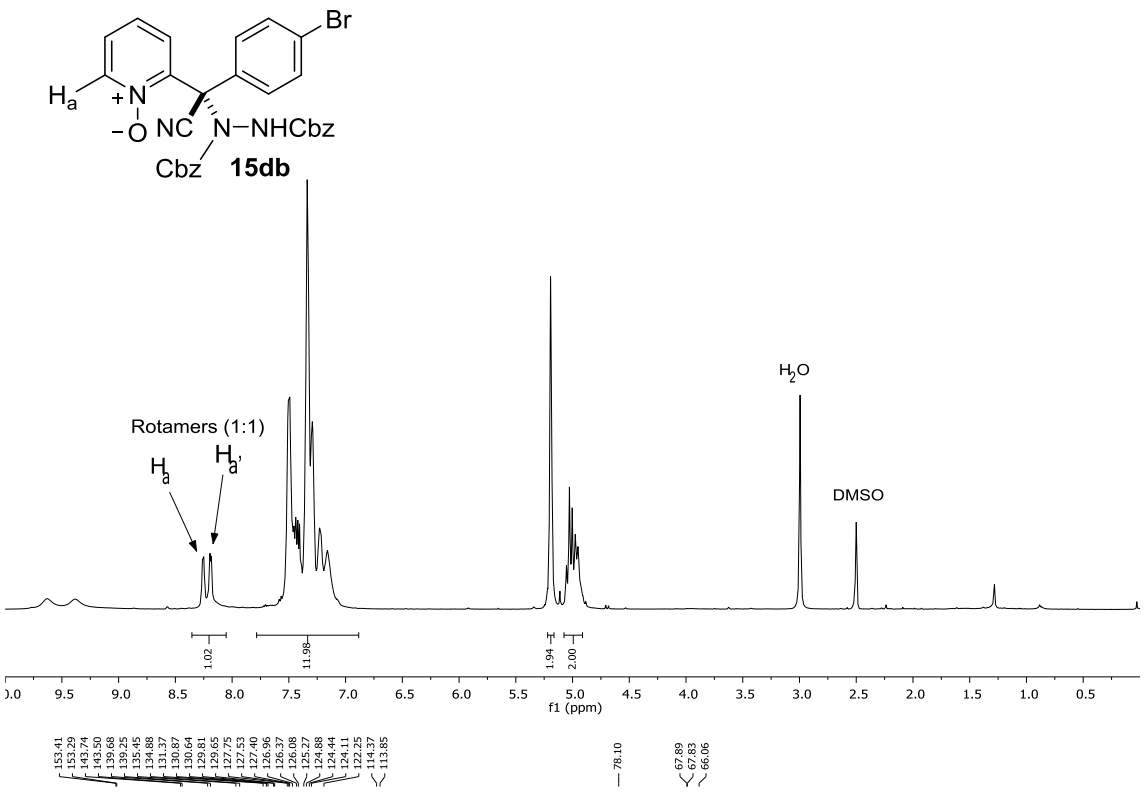


^{13}C NMR (75 MHz, $CDCl_3$, rt)

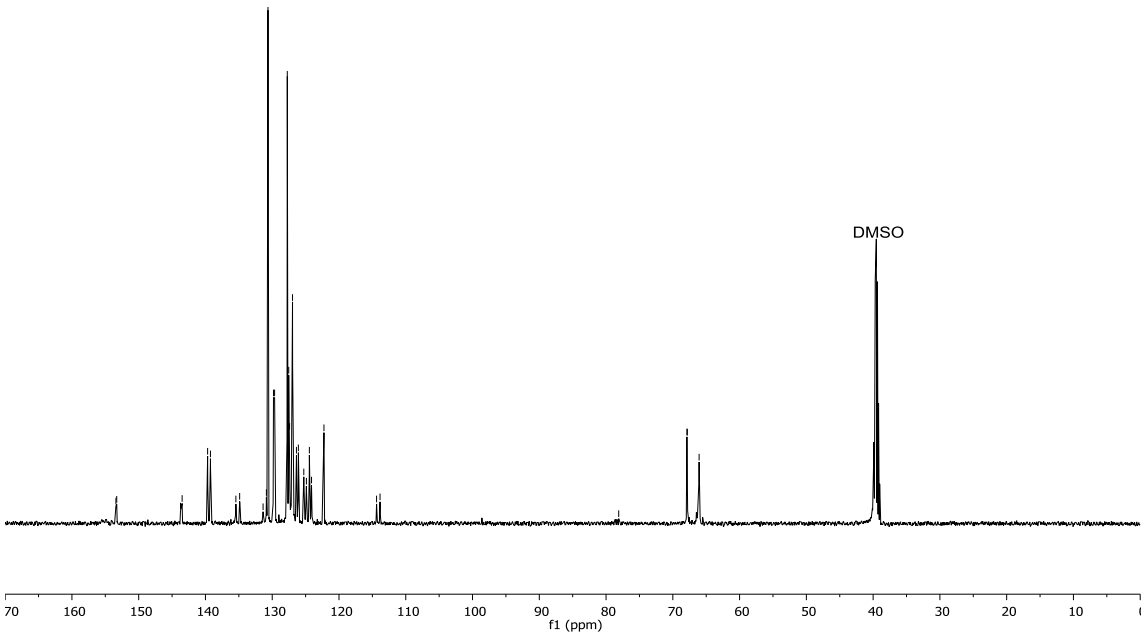


(*S*)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(4-bromophenyl)(cyano)methyl)pyridine *N*-oxide (15db)

^{1}H NMR (500 MHz, DMSO-d_6, 70°C)

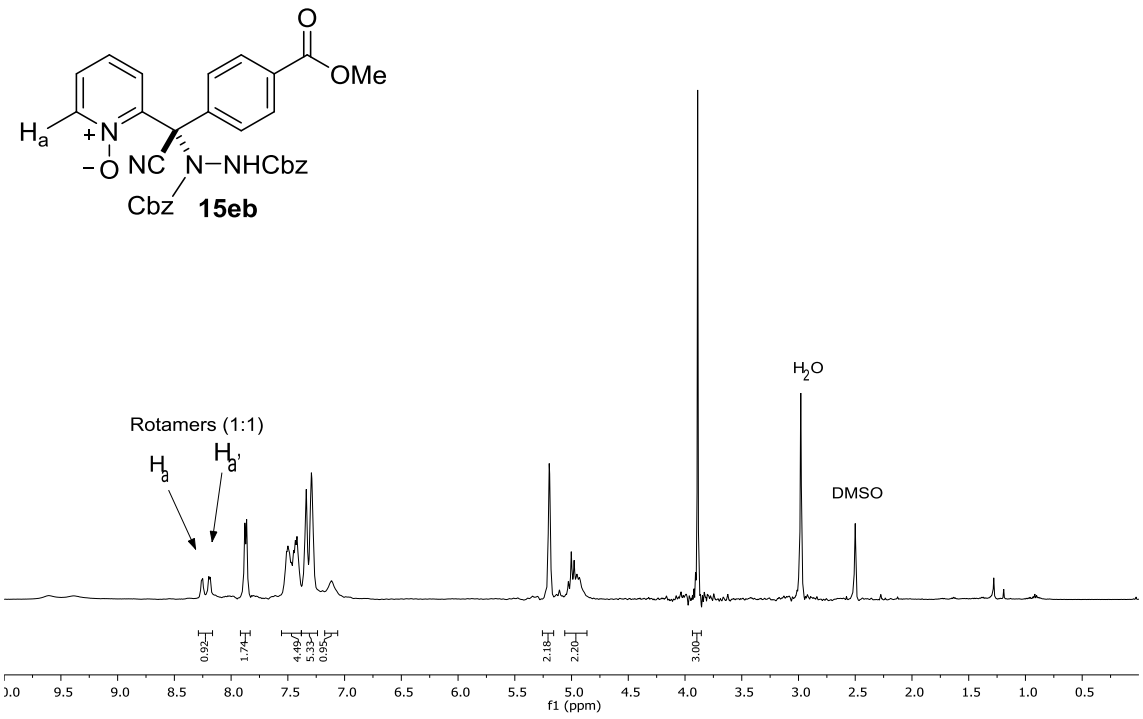


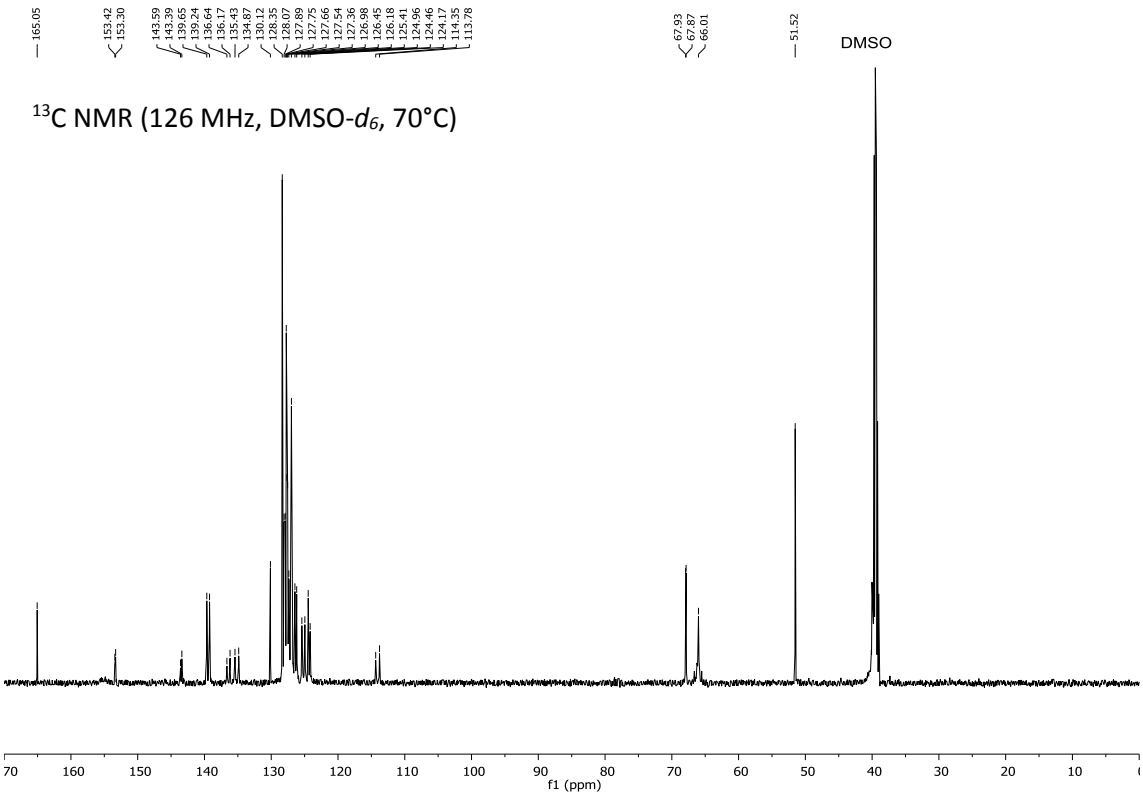
^{13}C NMR (126 MHz, DMSO-d_6, 70°C)



(*S*)-2-((1,2-bis((benzyloxy)carbonyl)hydrazinyl)(cyano)(4-(methoxycarbonyl)phenyl)methyl)pyridine *N*-oxide (15eb)

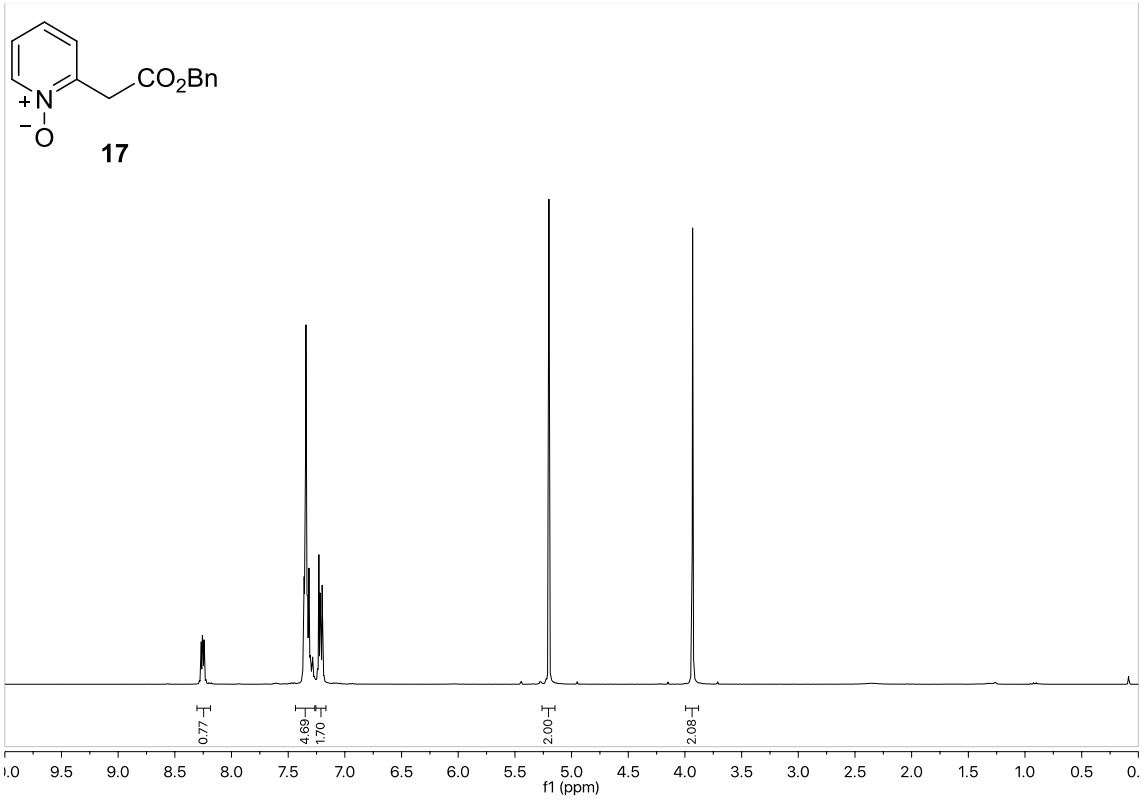
^{1}H NMR (500 MHz, DMSO-d_6, 70°C)

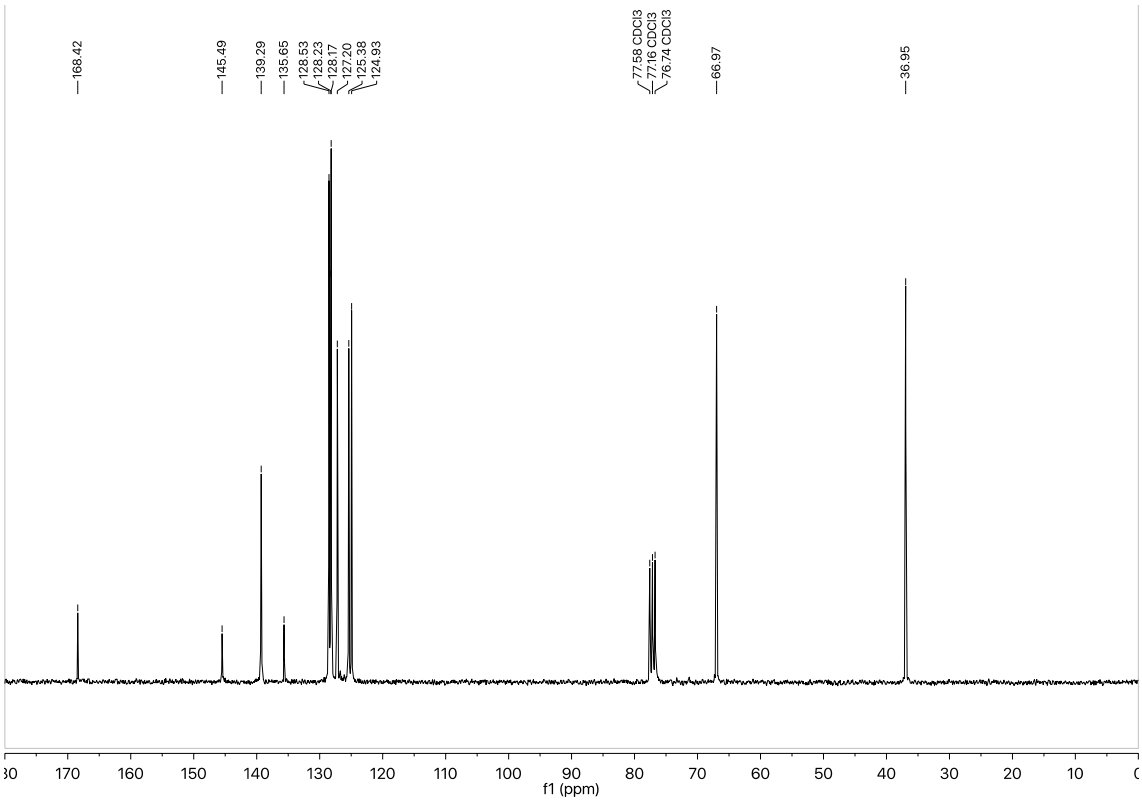




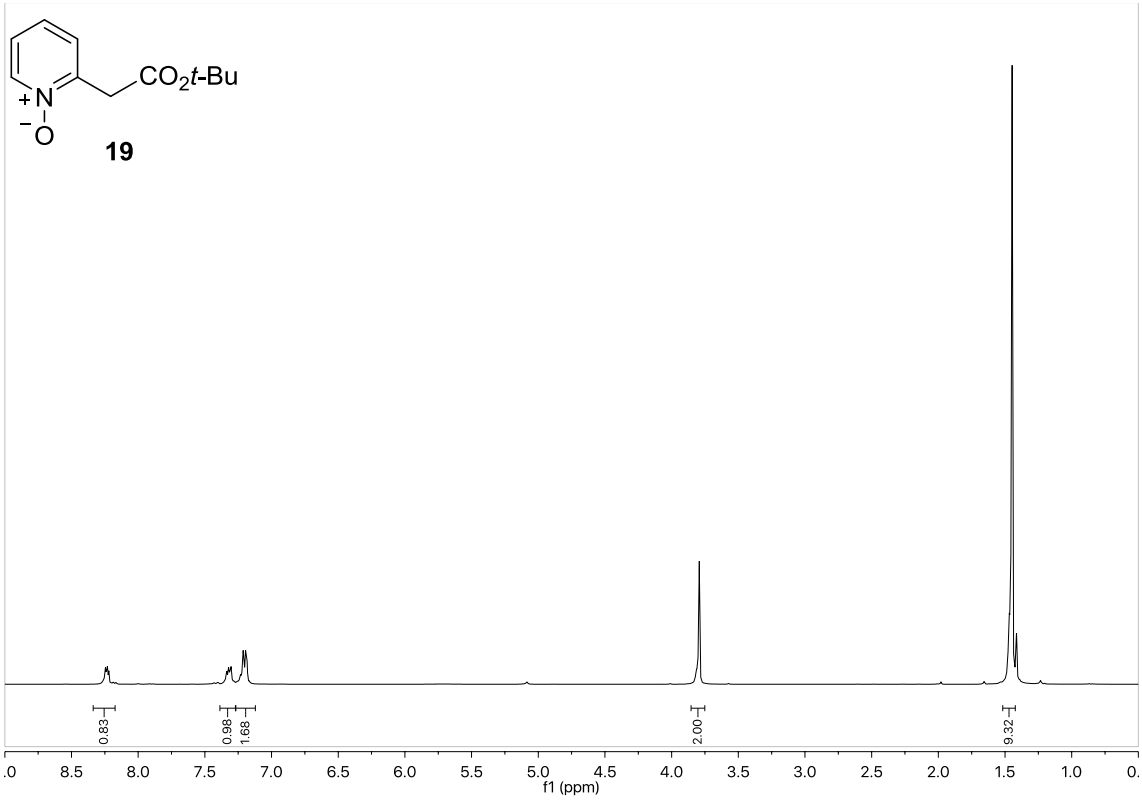
^{13}C NMR (126 MHz, DMSO-d_6, 70°C)

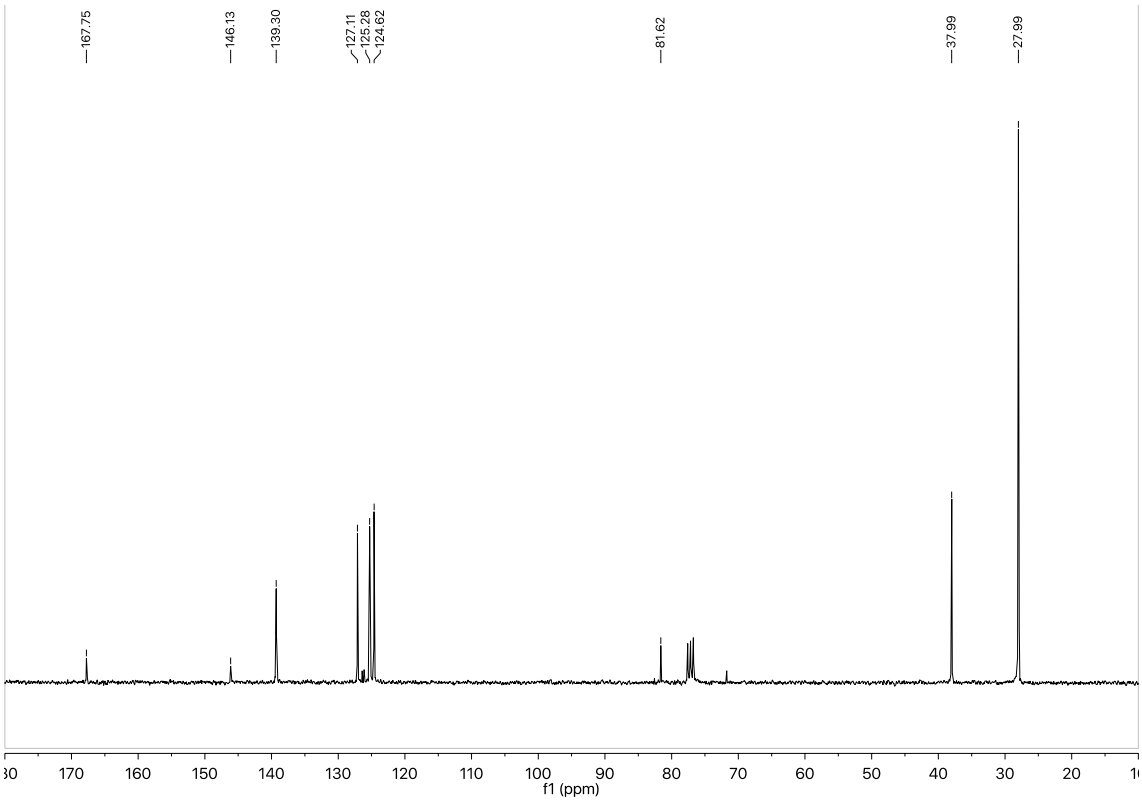
2-(2-(Benzyloxy)-2-oxoethyl)pyridine *N*-oxide (17)



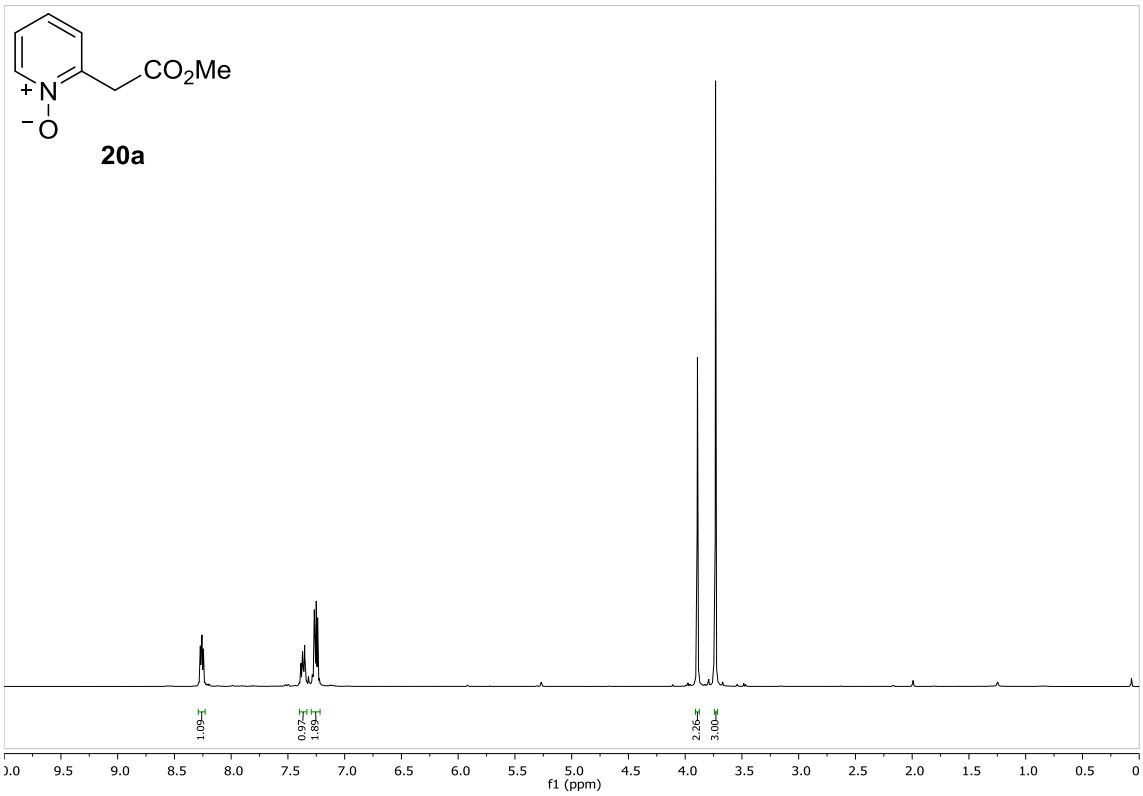


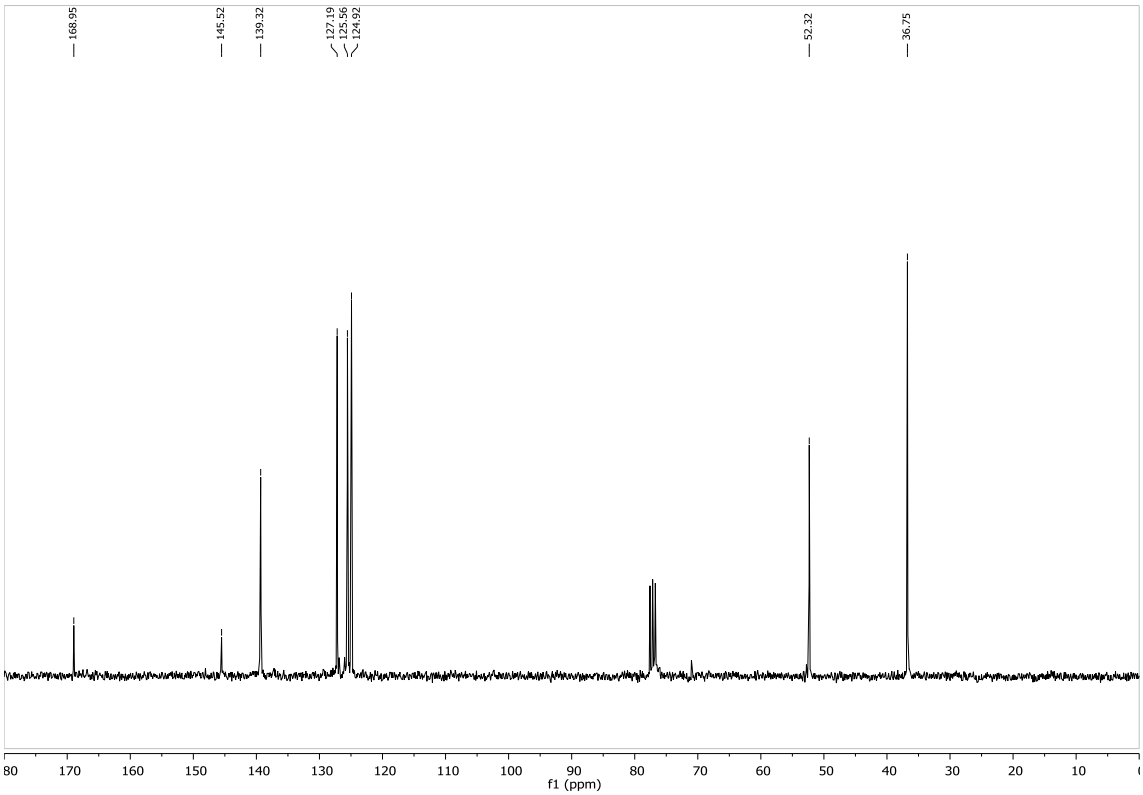
2-(2-(*tert*-Butoxy)-2-oxoethyl)pyridine *N*-oxide (19)



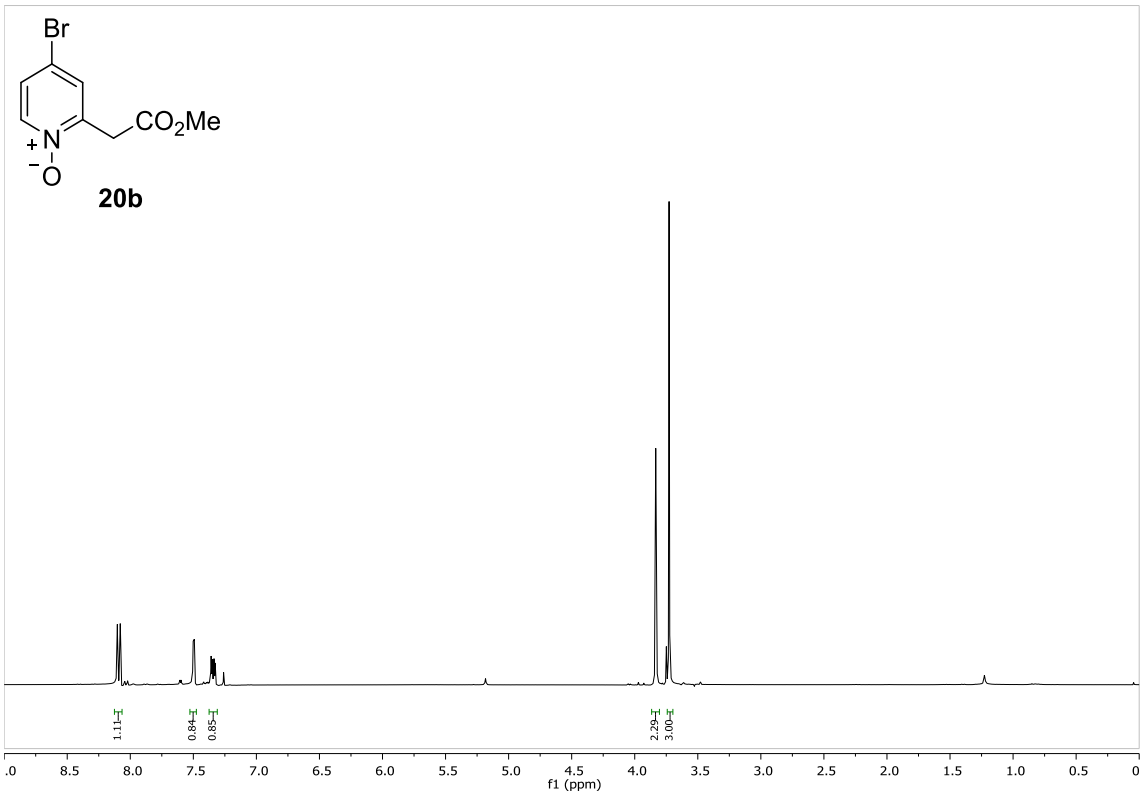


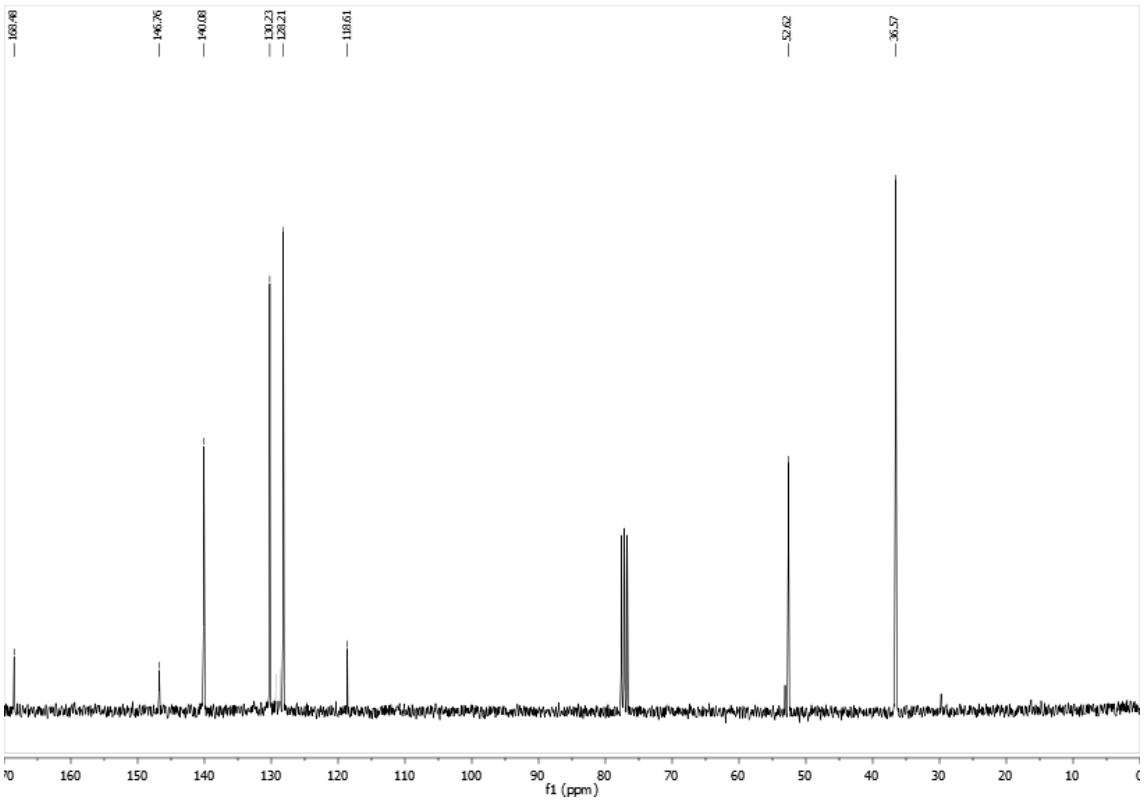
2-(2-Methoxy-2-oxoethyl)pyridine *N*-oxide (20a)



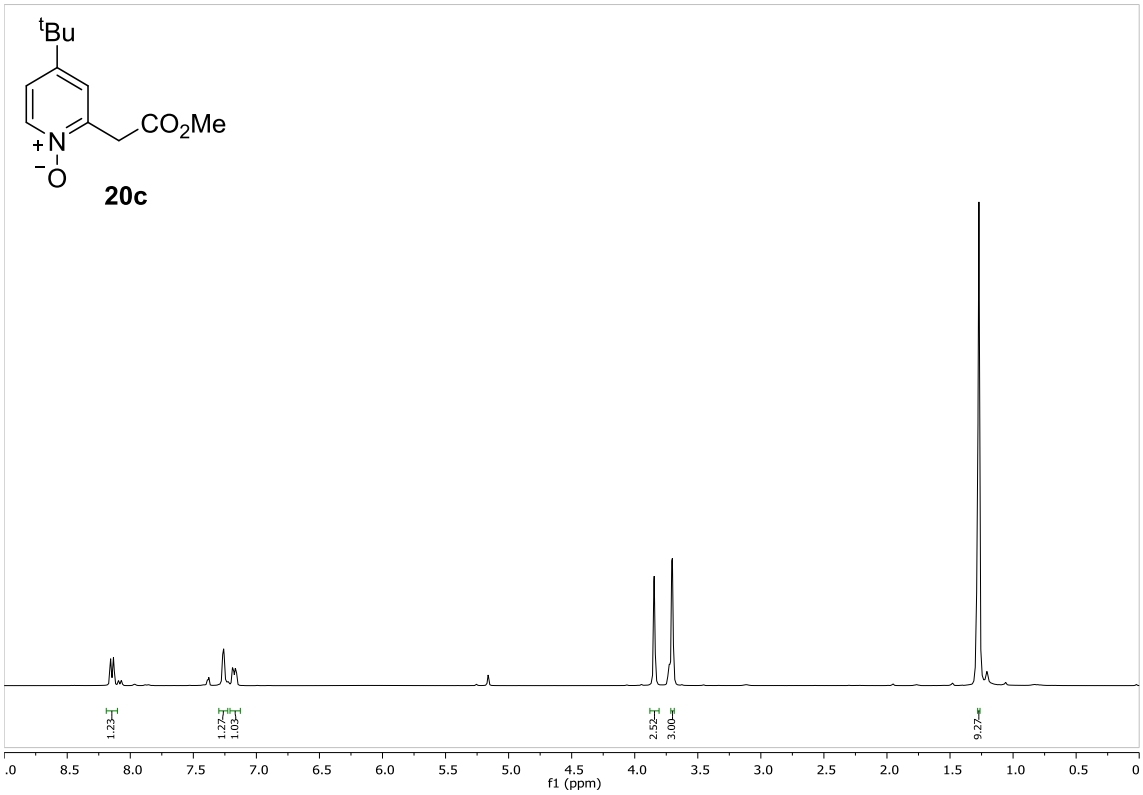


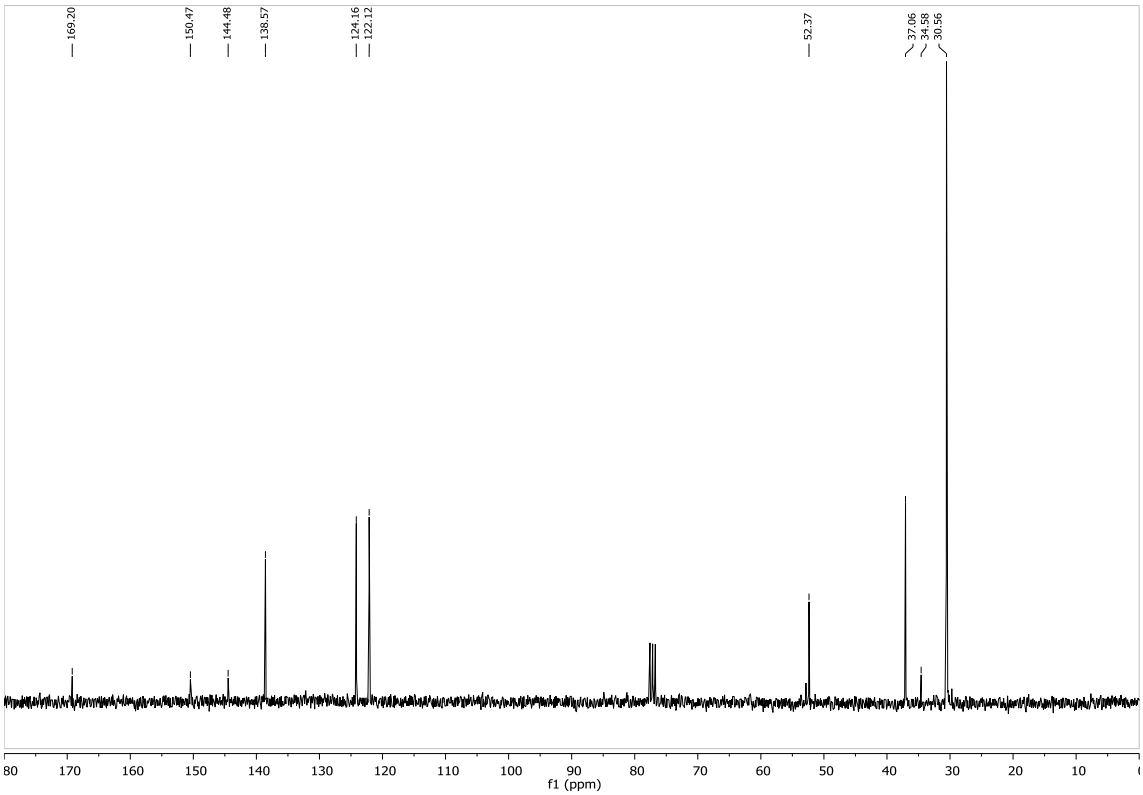
4-Bromo-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20b)



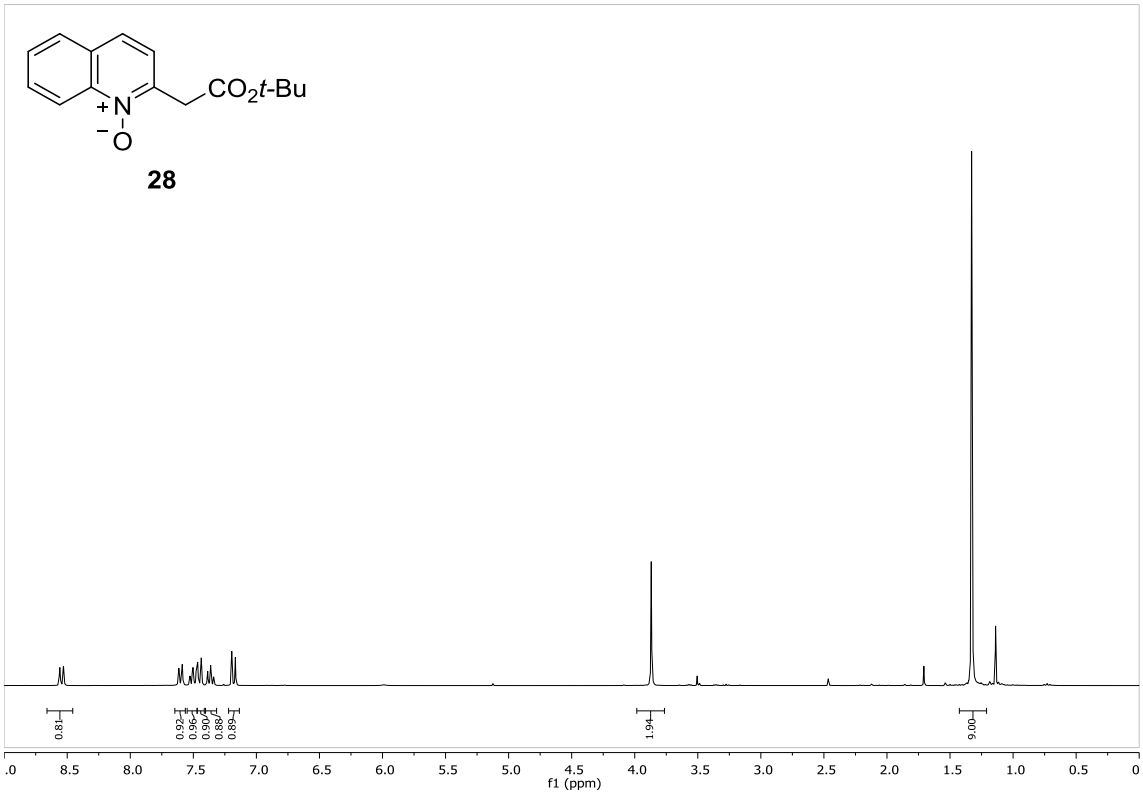


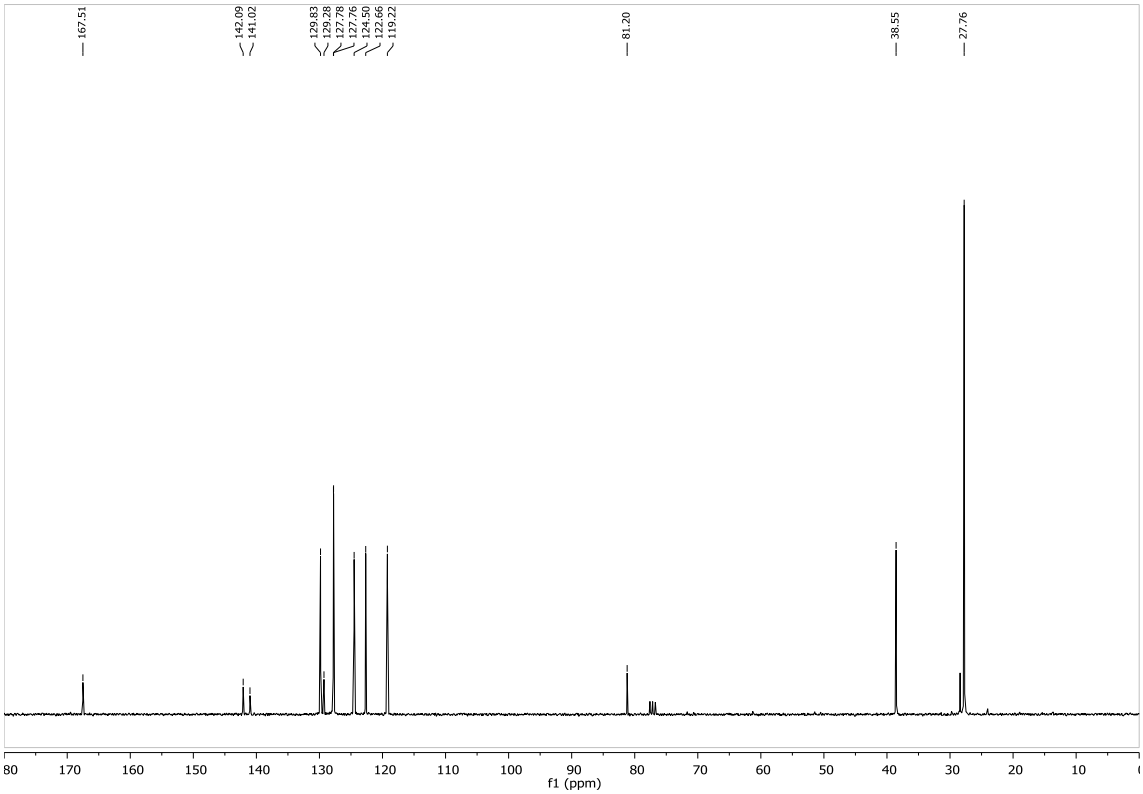
4-(*tert*-Butyl)-2-(2-methoxy-2-oxoethyl)pyridine *N*-oxide (20c)



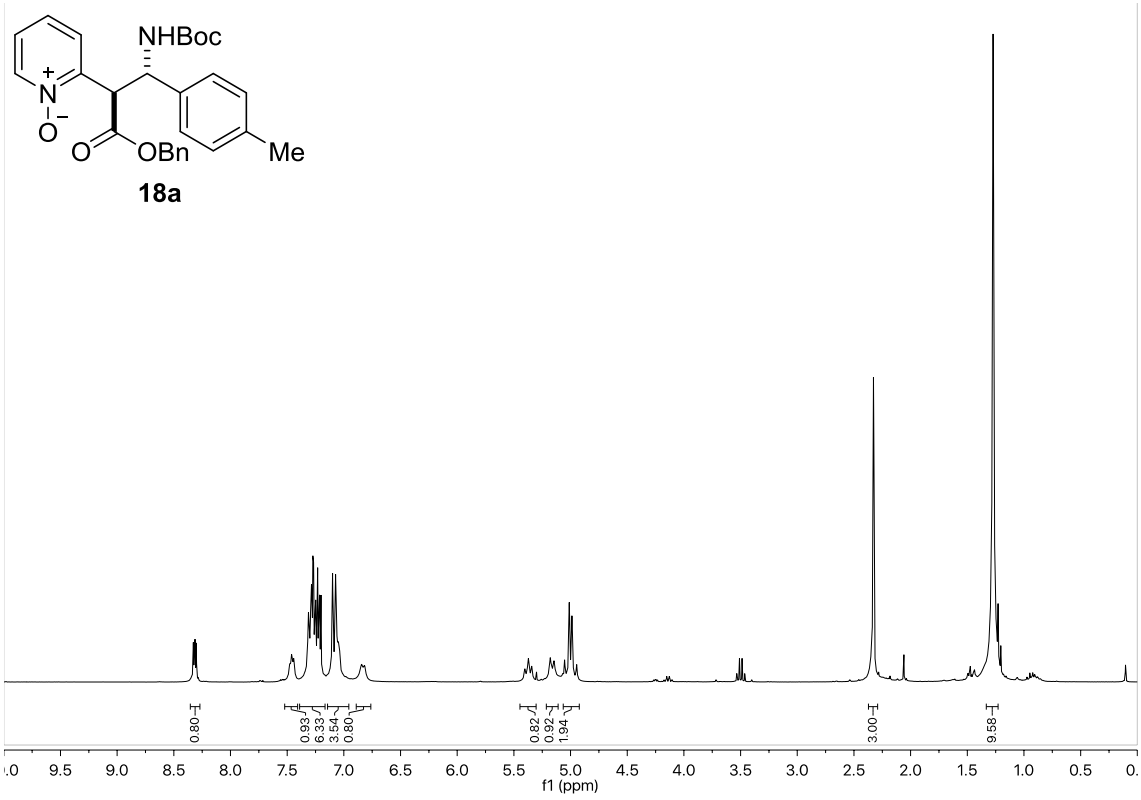


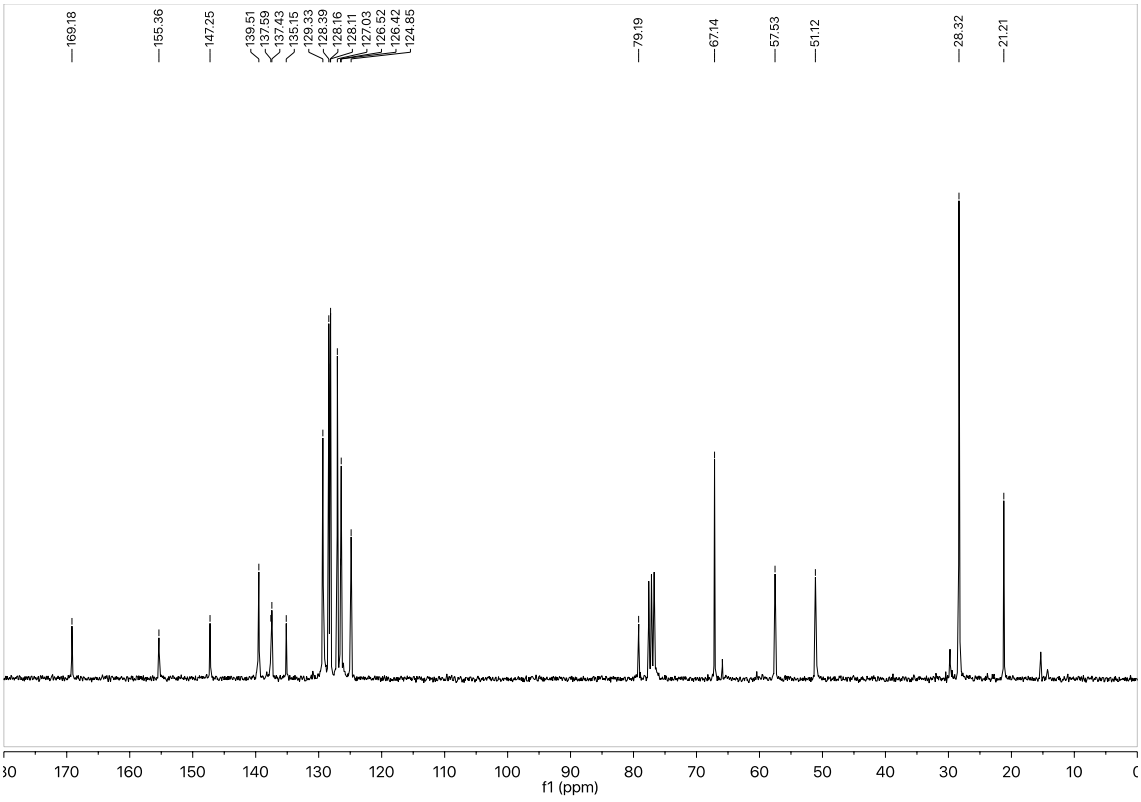
2-(2-(*tert*-Butoxy)-2-oxoethyl)quinoline *N*-oxide (28)



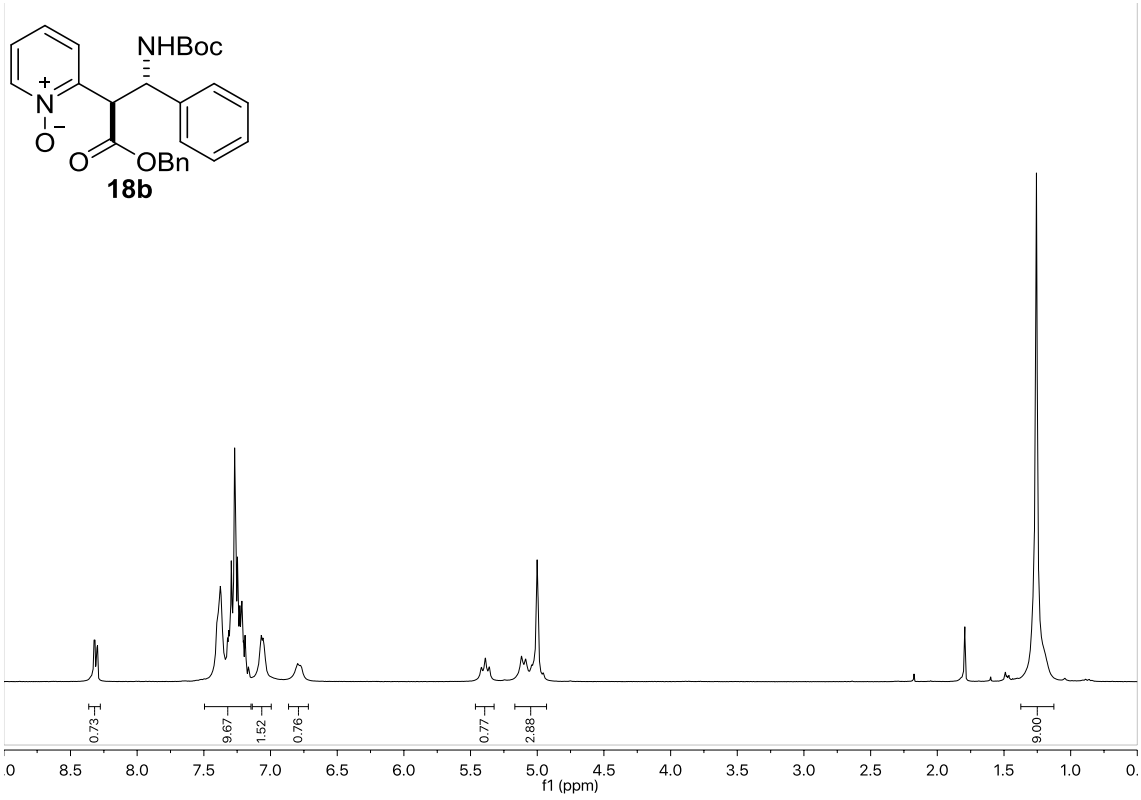


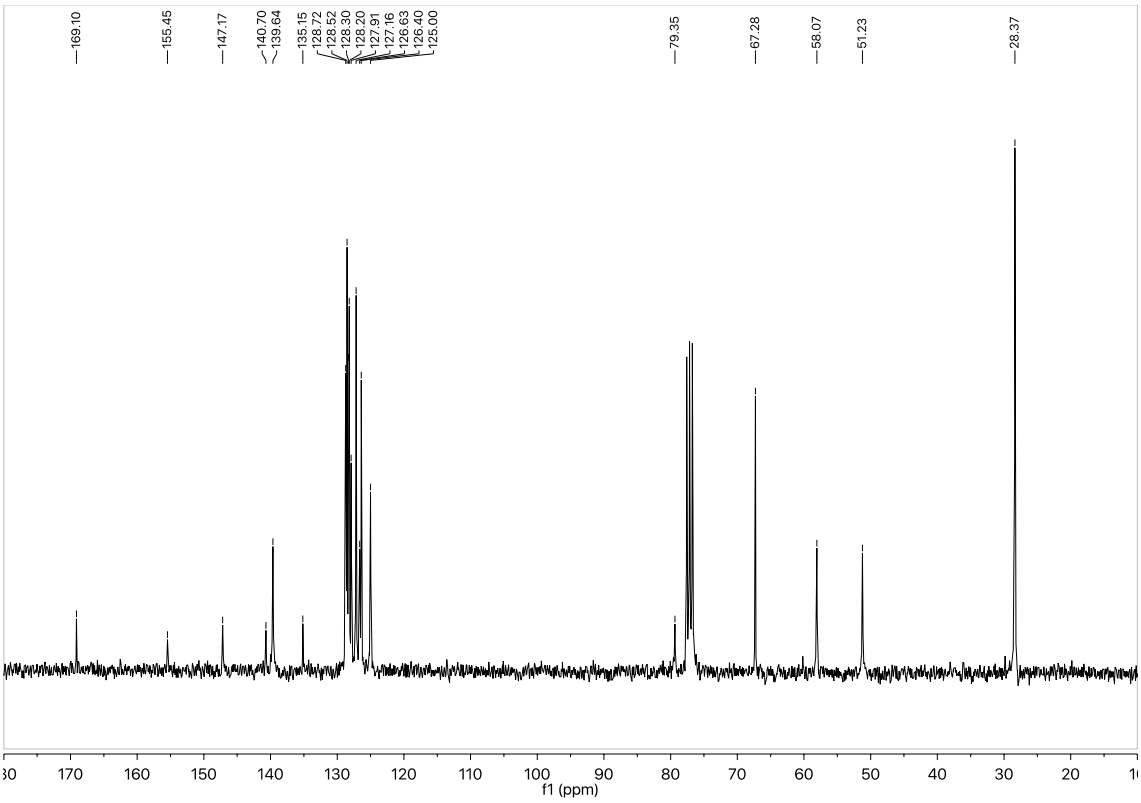
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-oxo-3-phenoxy-1-(*p*-tolyl)propan-2yl)pyridine *N*-oxide (18a)



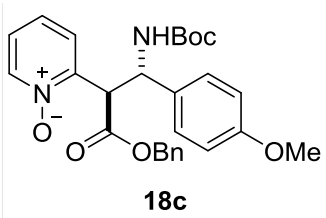


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)pyridine *N*-oxide (18b)

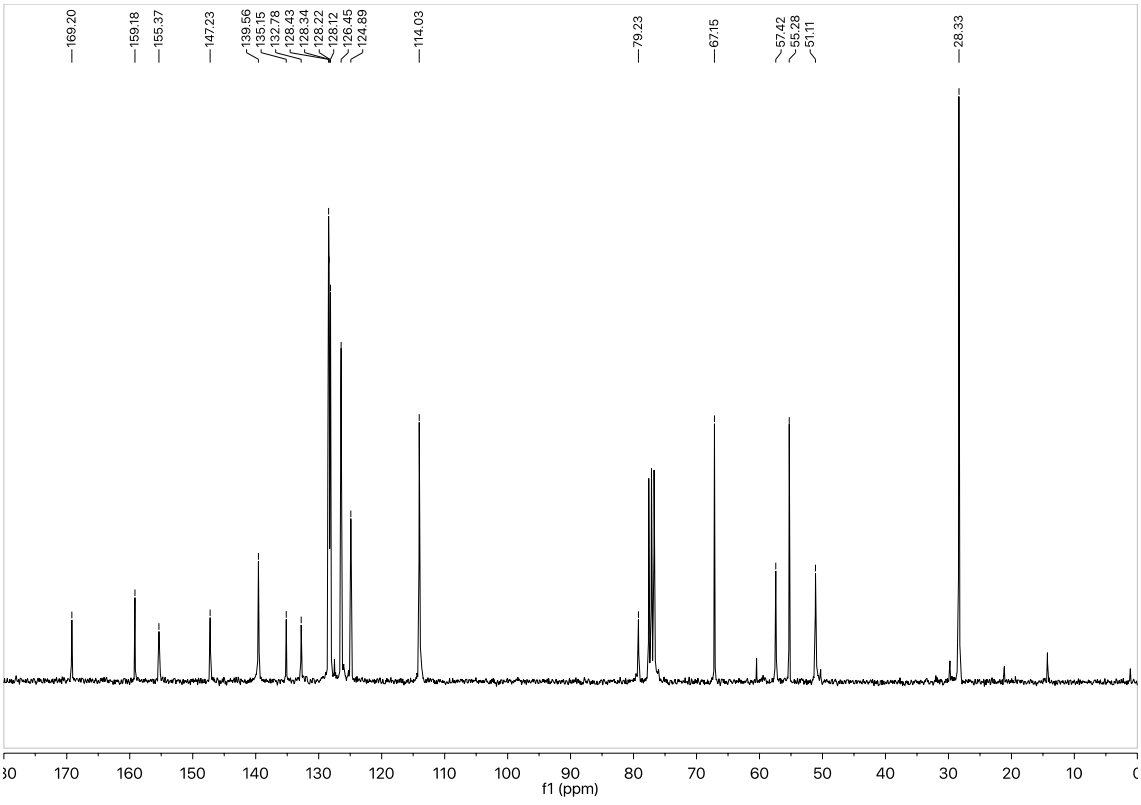




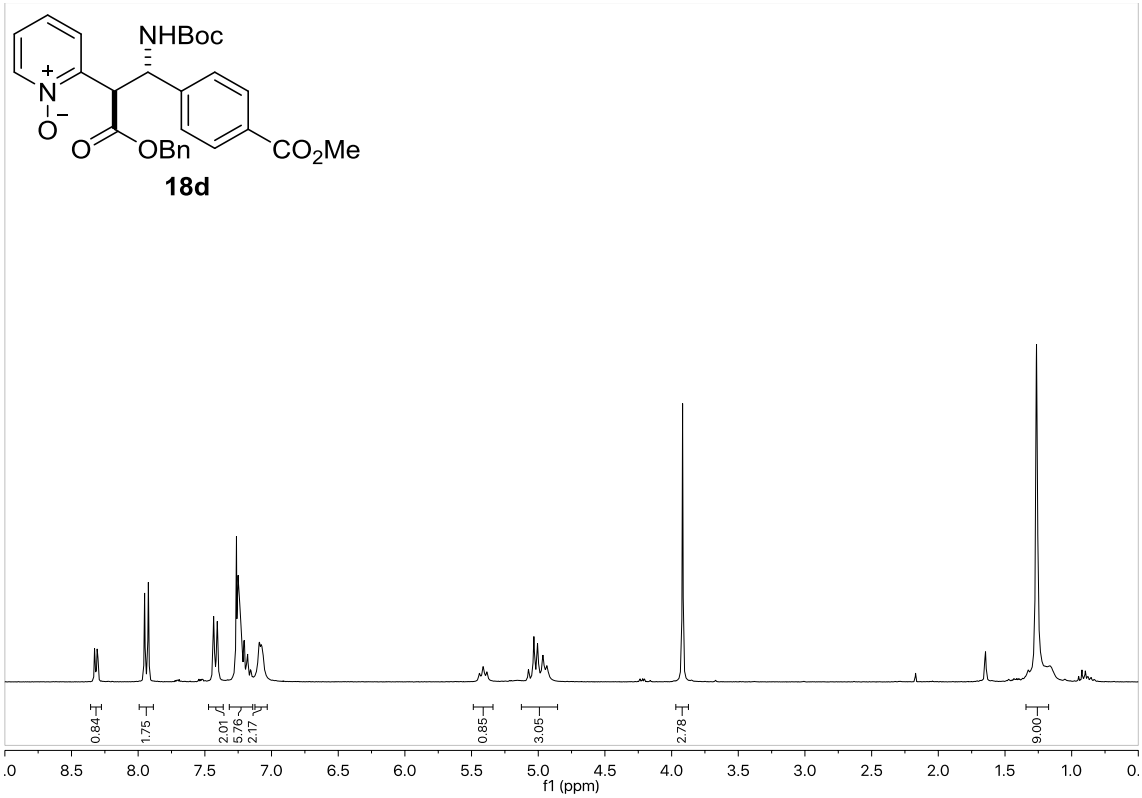
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18c)

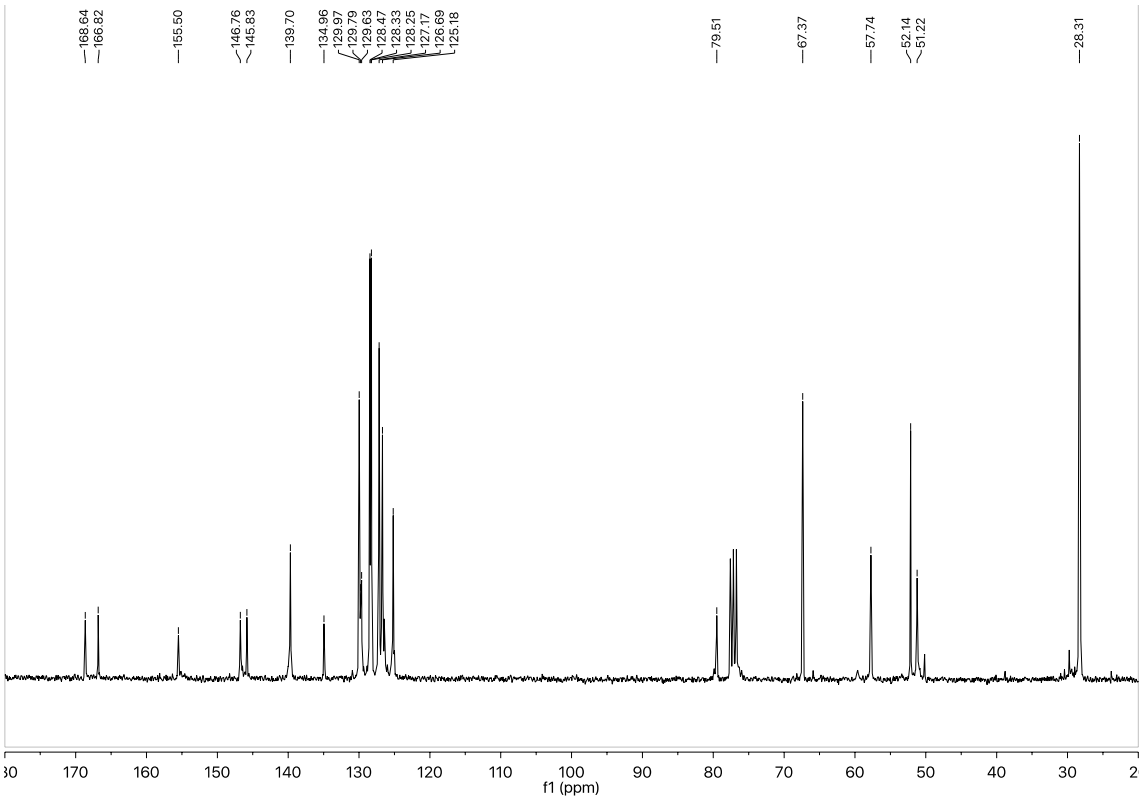


18c

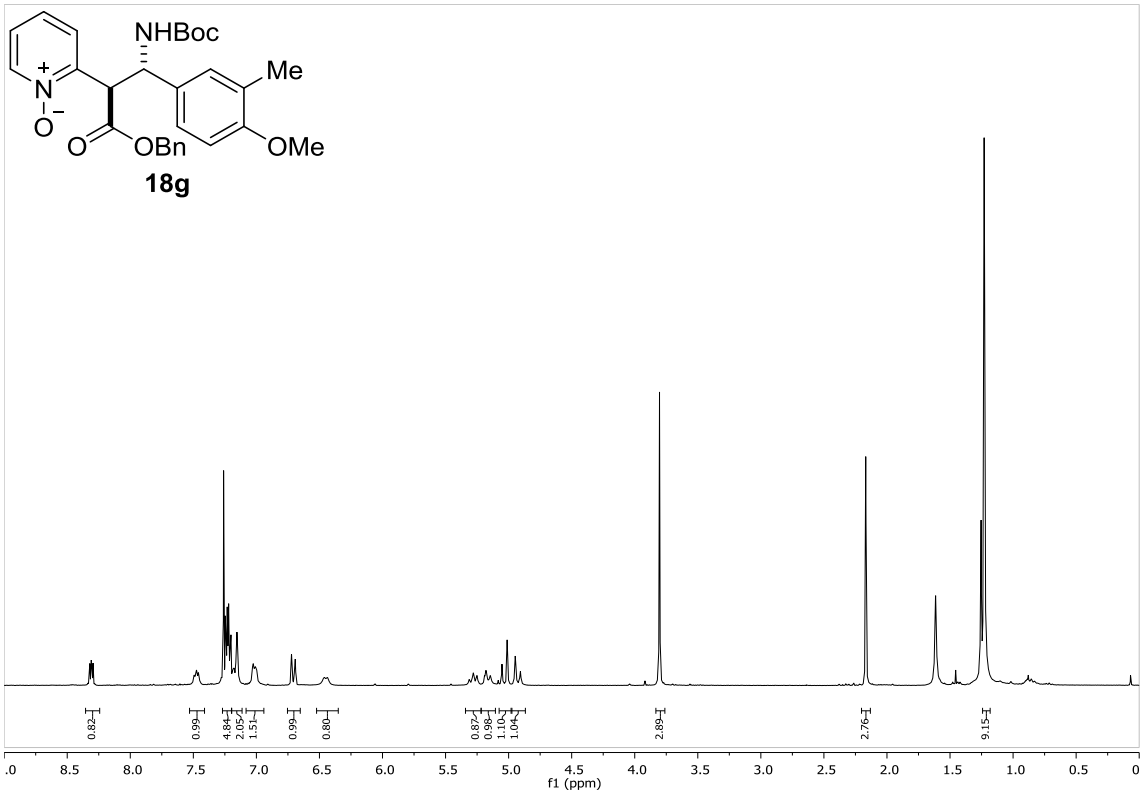


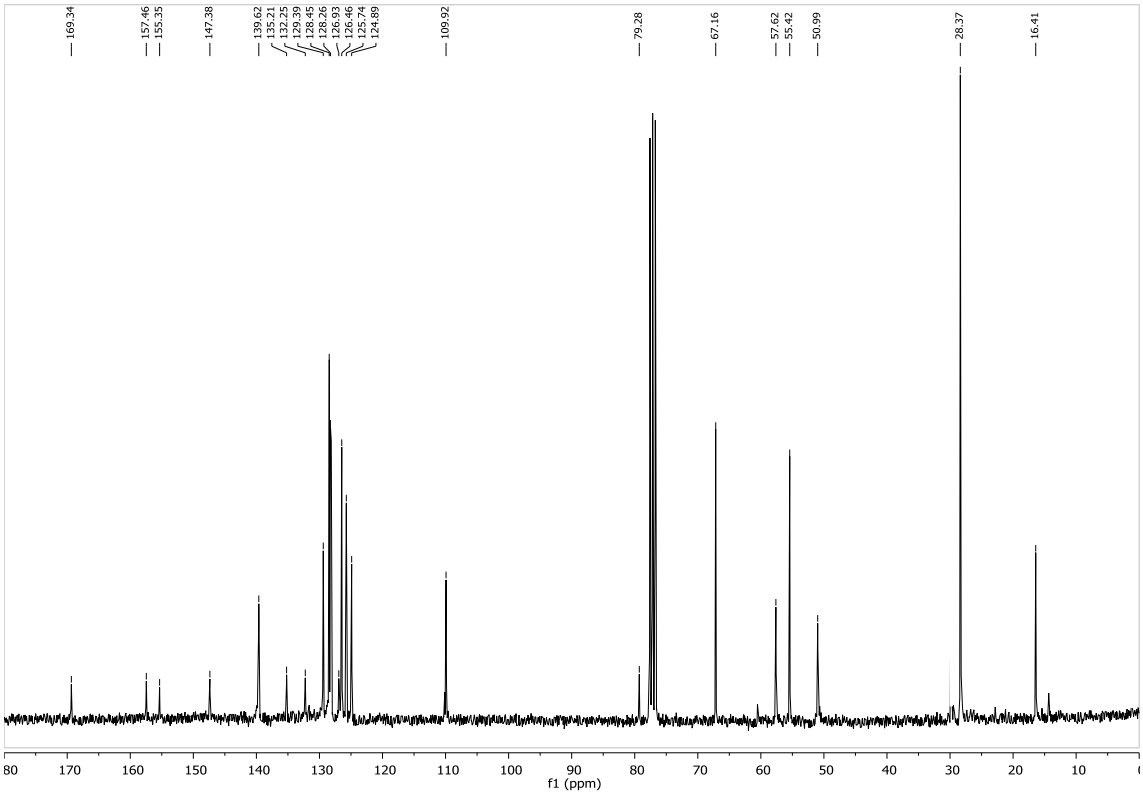
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-(methoxycarbonyl)phenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18d)



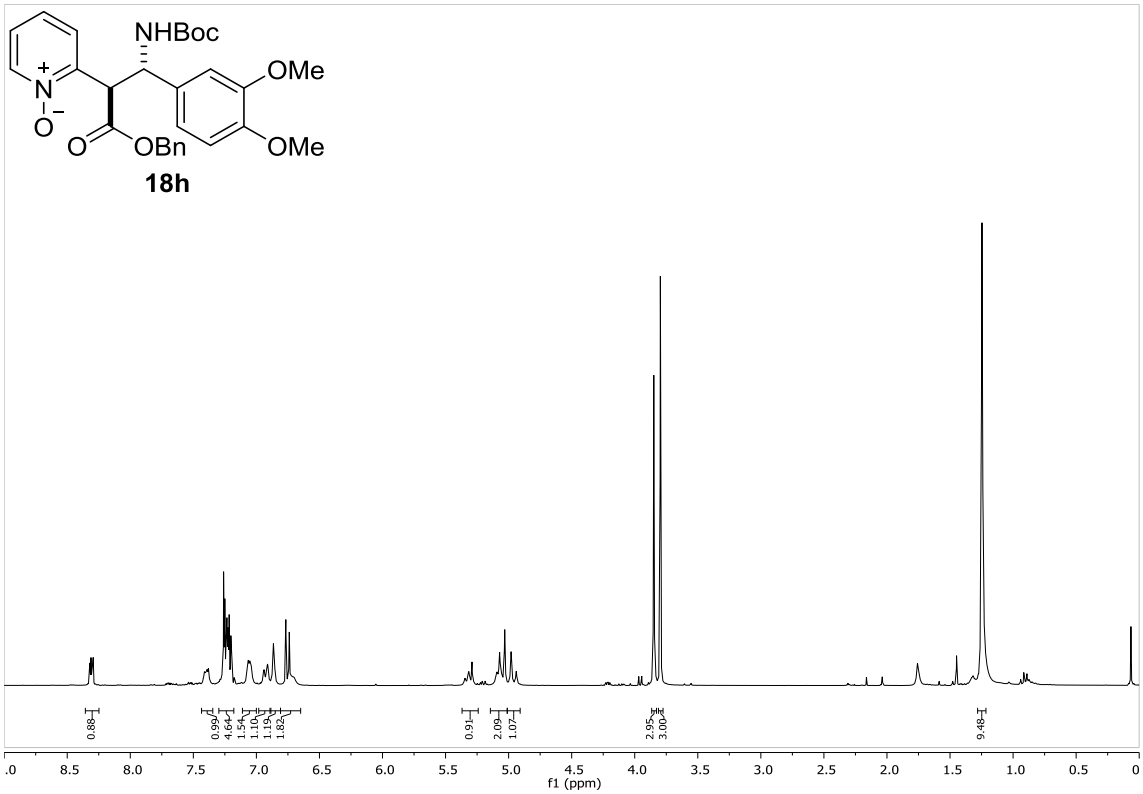


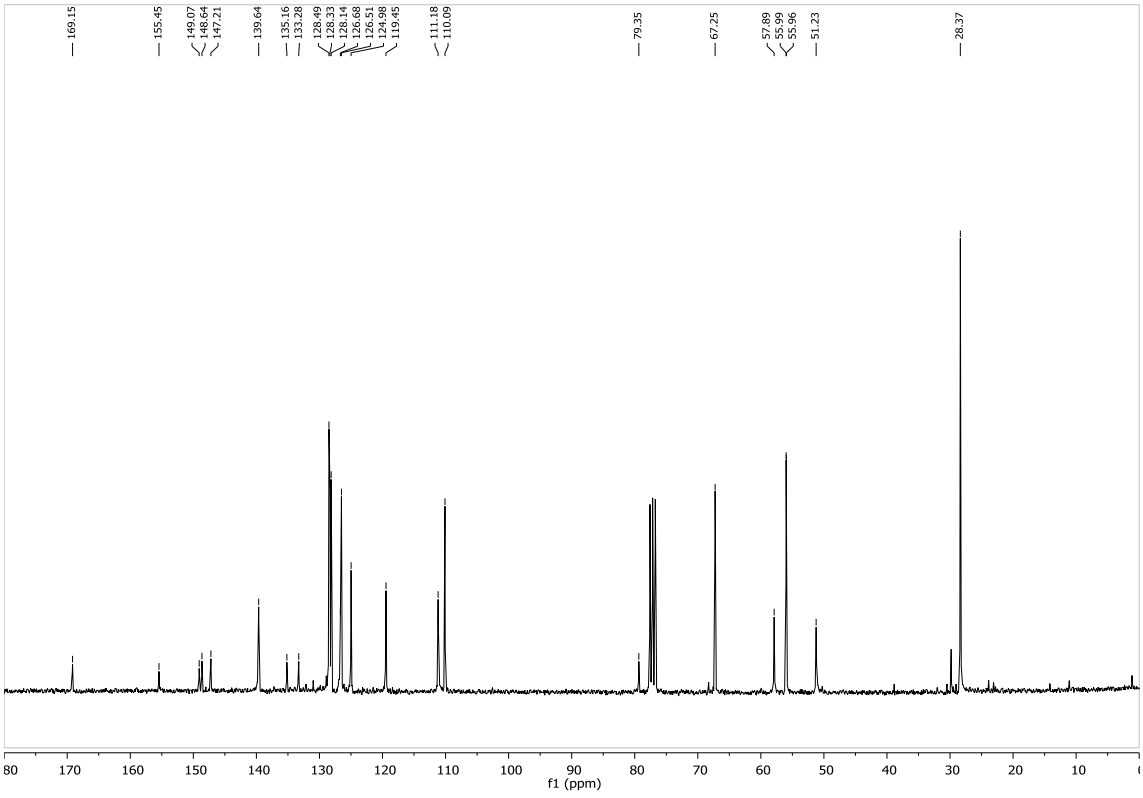
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(4-methoxy-3-methylphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18g)



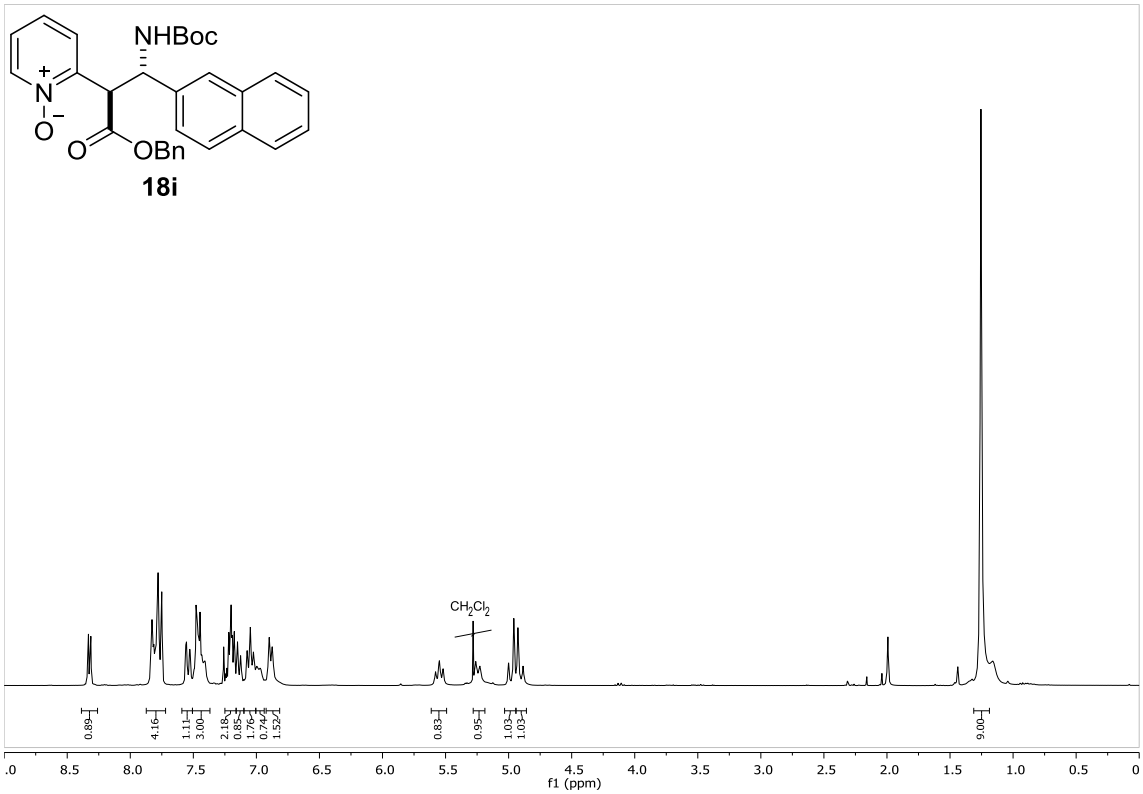


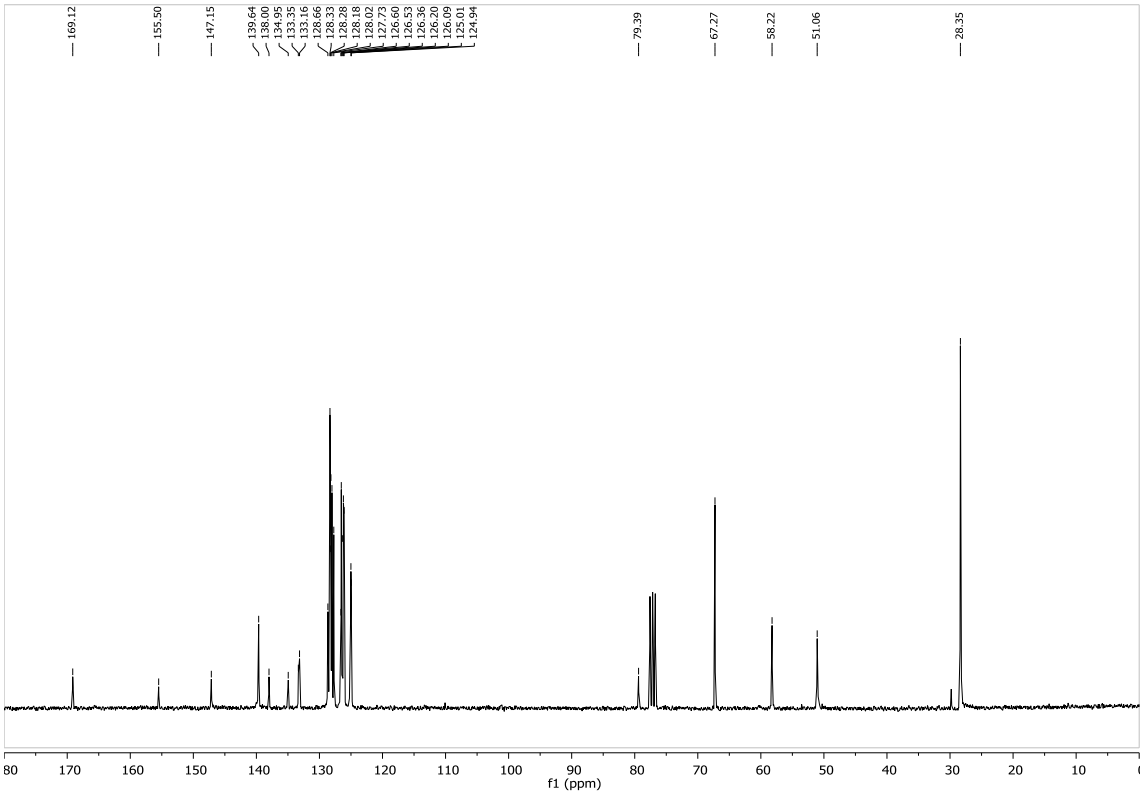
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3,4-dimethoxyphenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18h)



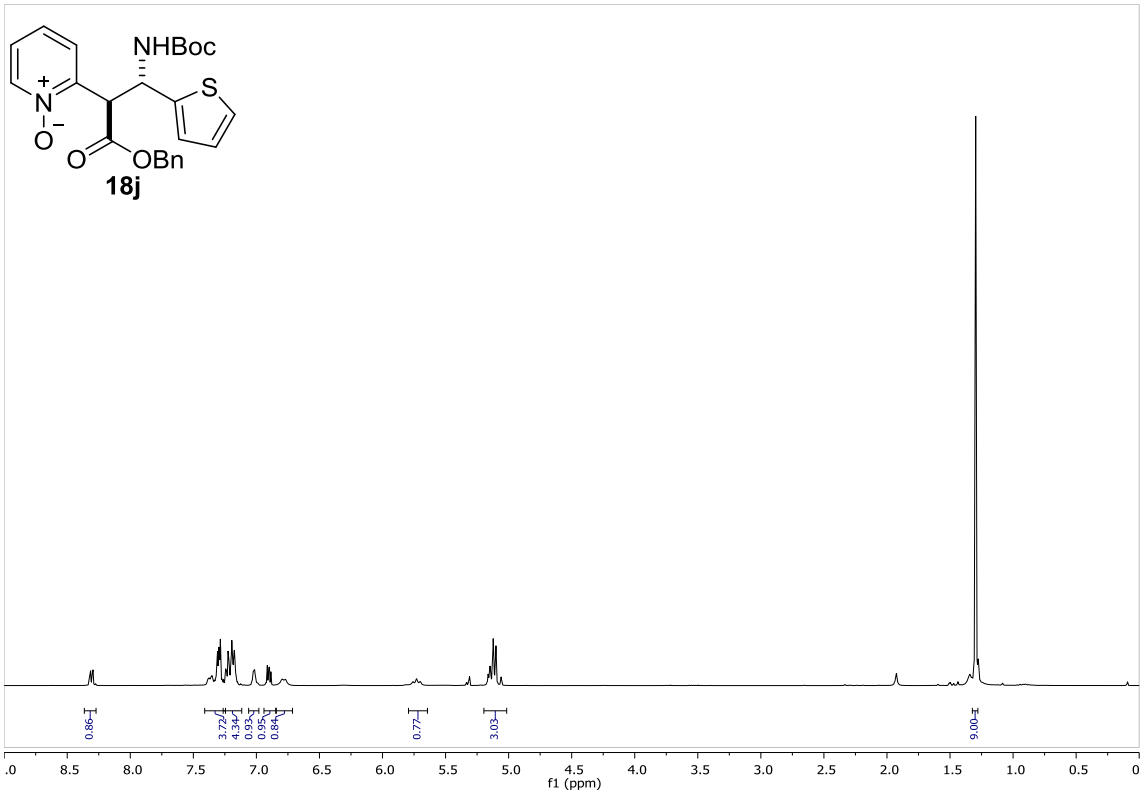


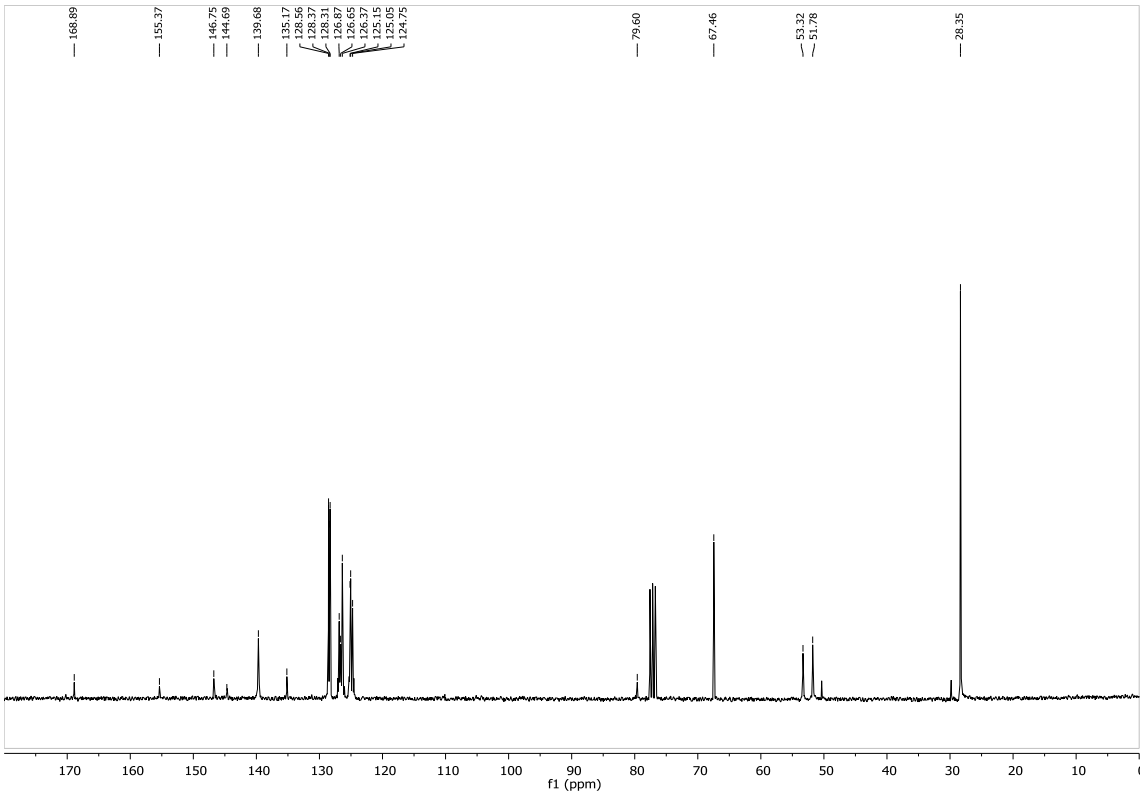
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18i)



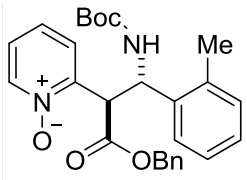


2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)pyridine *N*-oxide (18j)

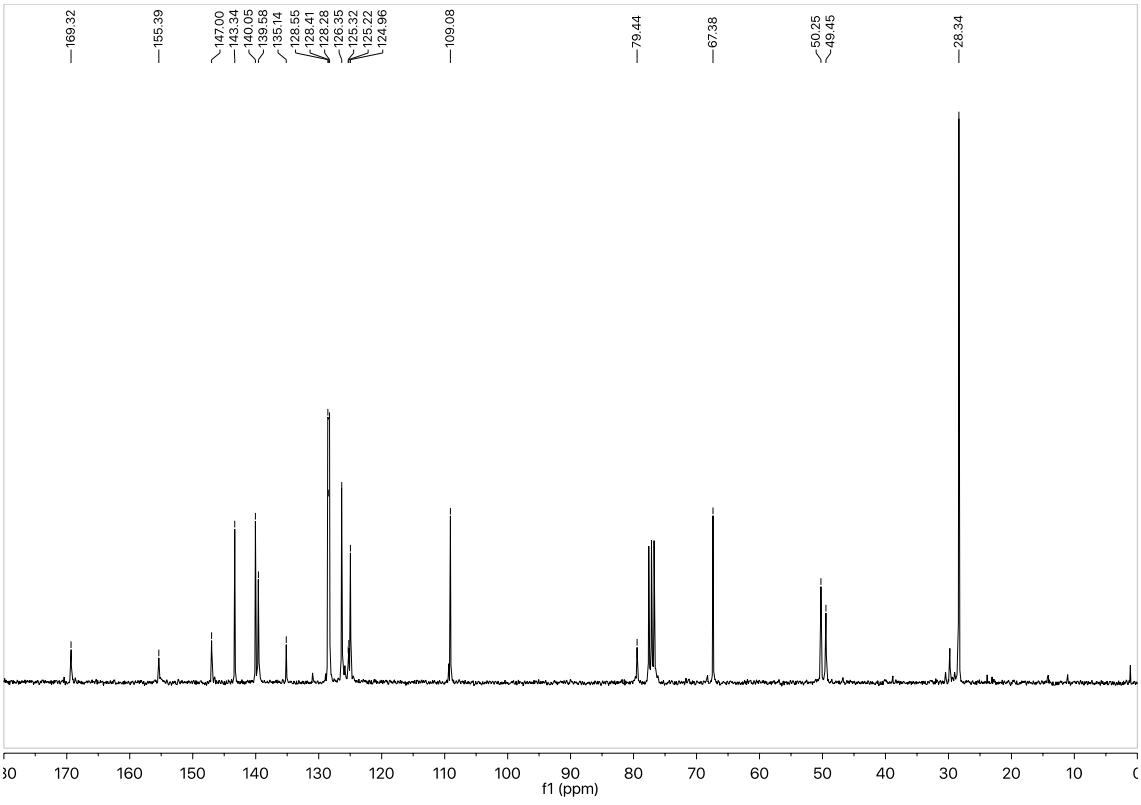




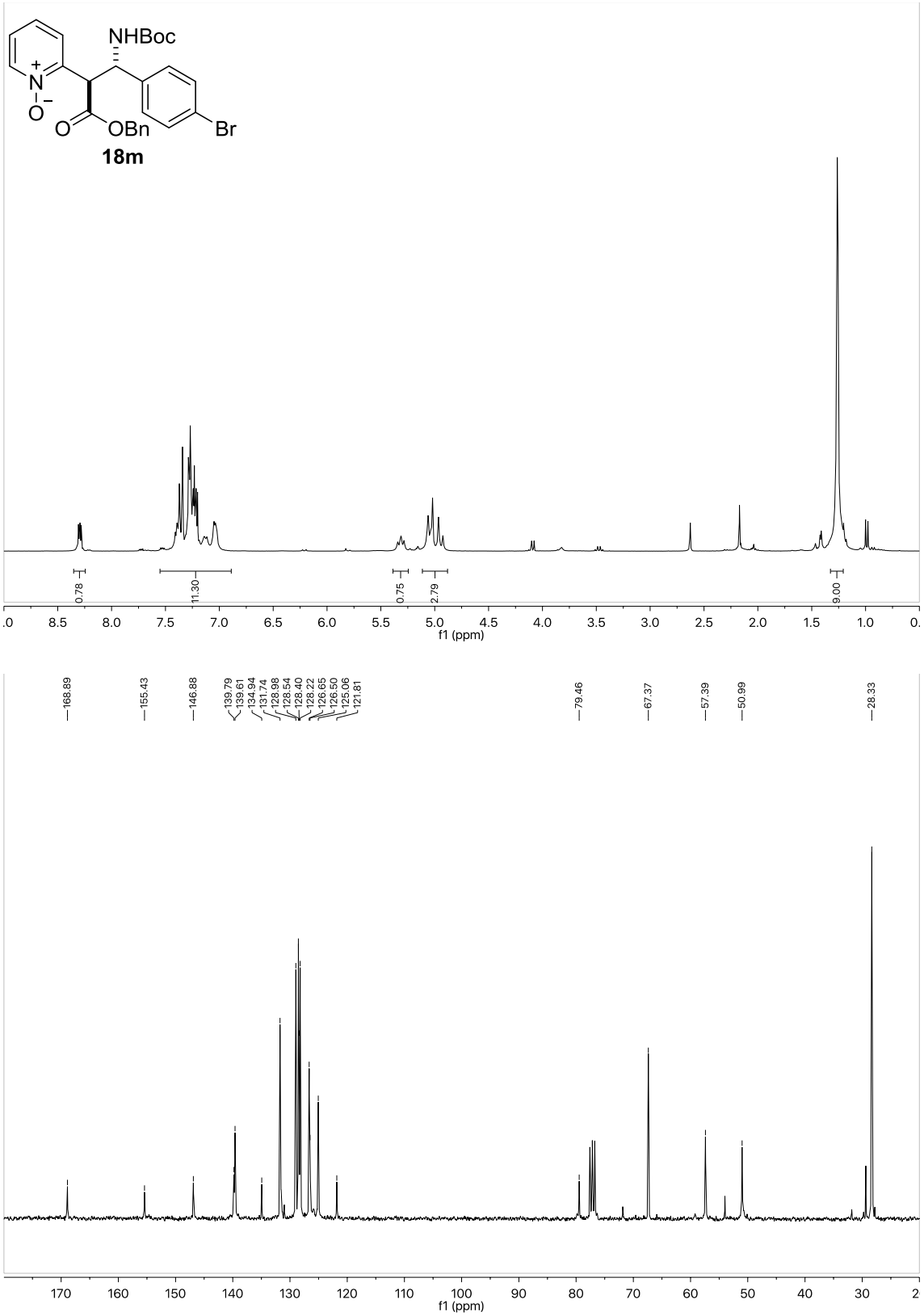
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-1-oxo-3-(o-tolyl)propan-2-yl)pyridine *N*-oxide (18l)



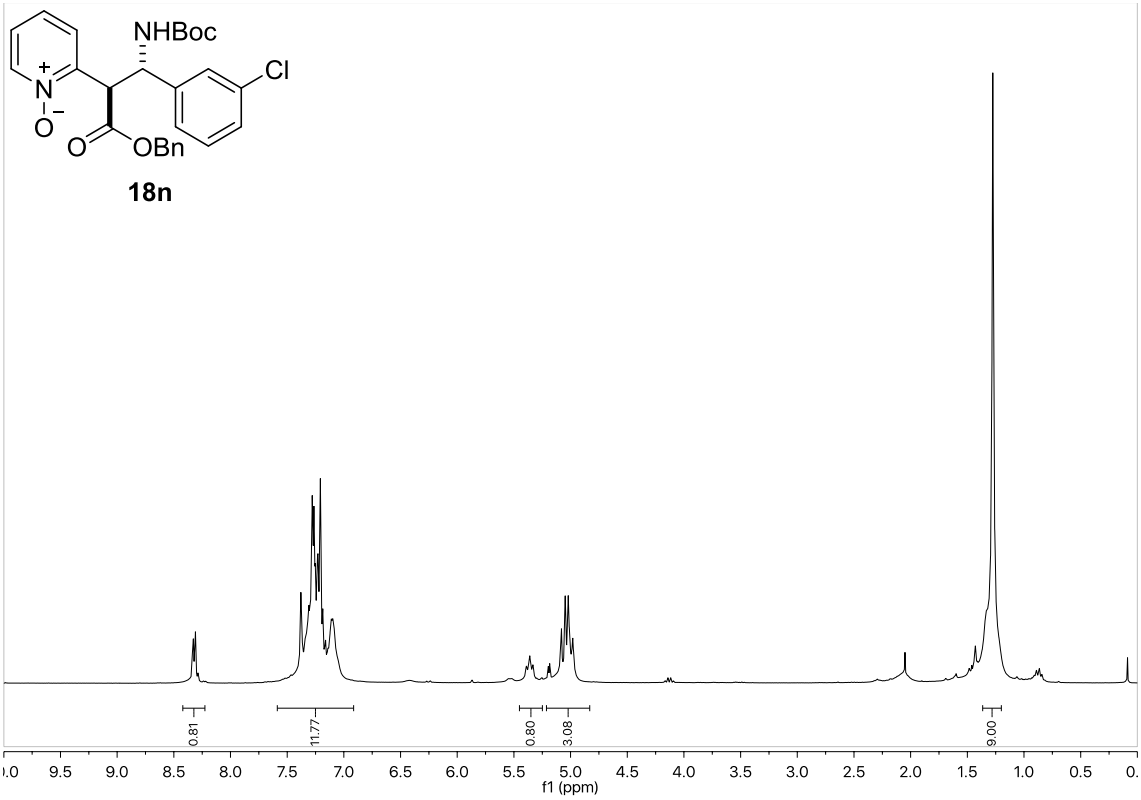
18l

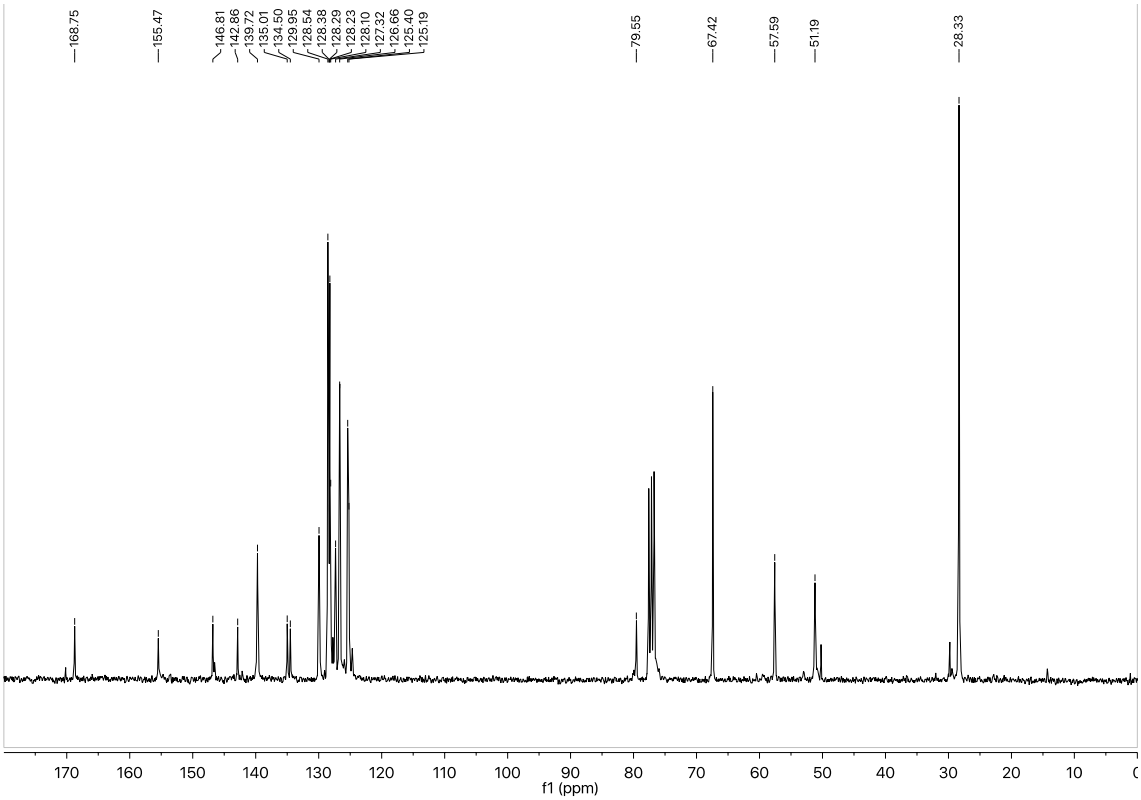


2-((2*R*,3*S*)-1-(Benzyloxy)-3-(4-bromophenyl)-3-((*tert*-butoxycarbonyl)amino)-1-oxopropan-2-yl)pyridine *N*-oxide (18m)

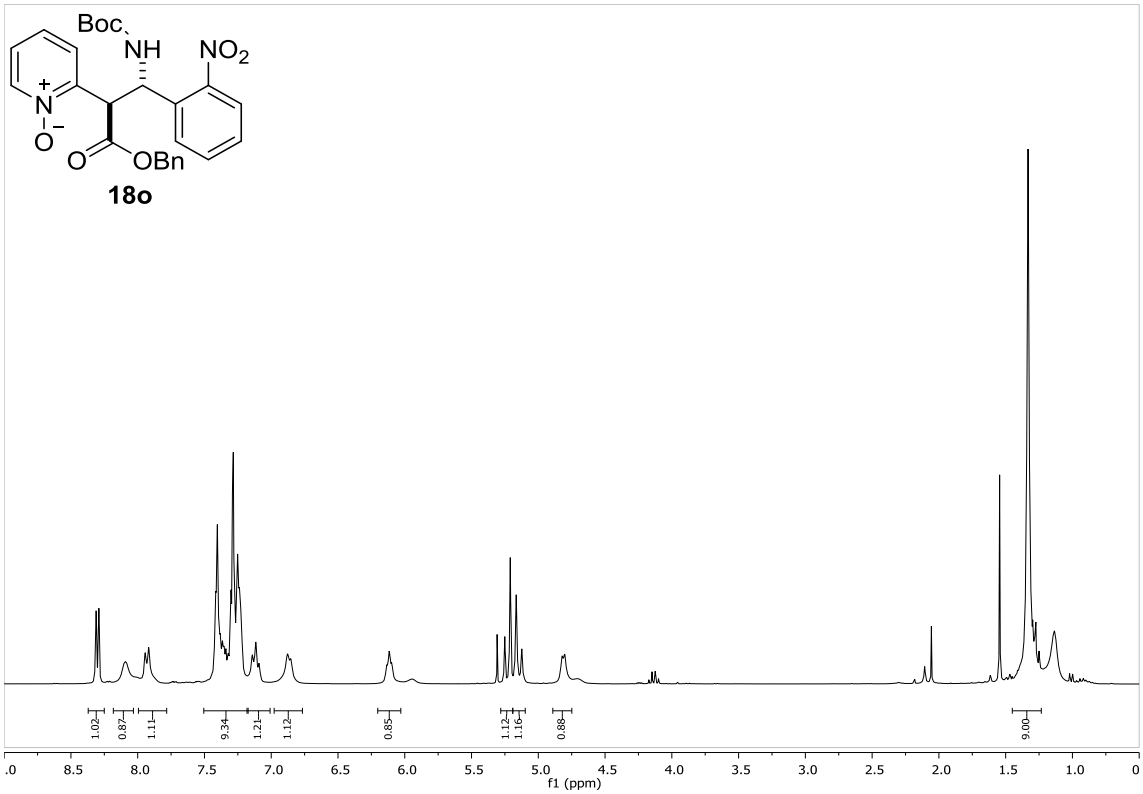


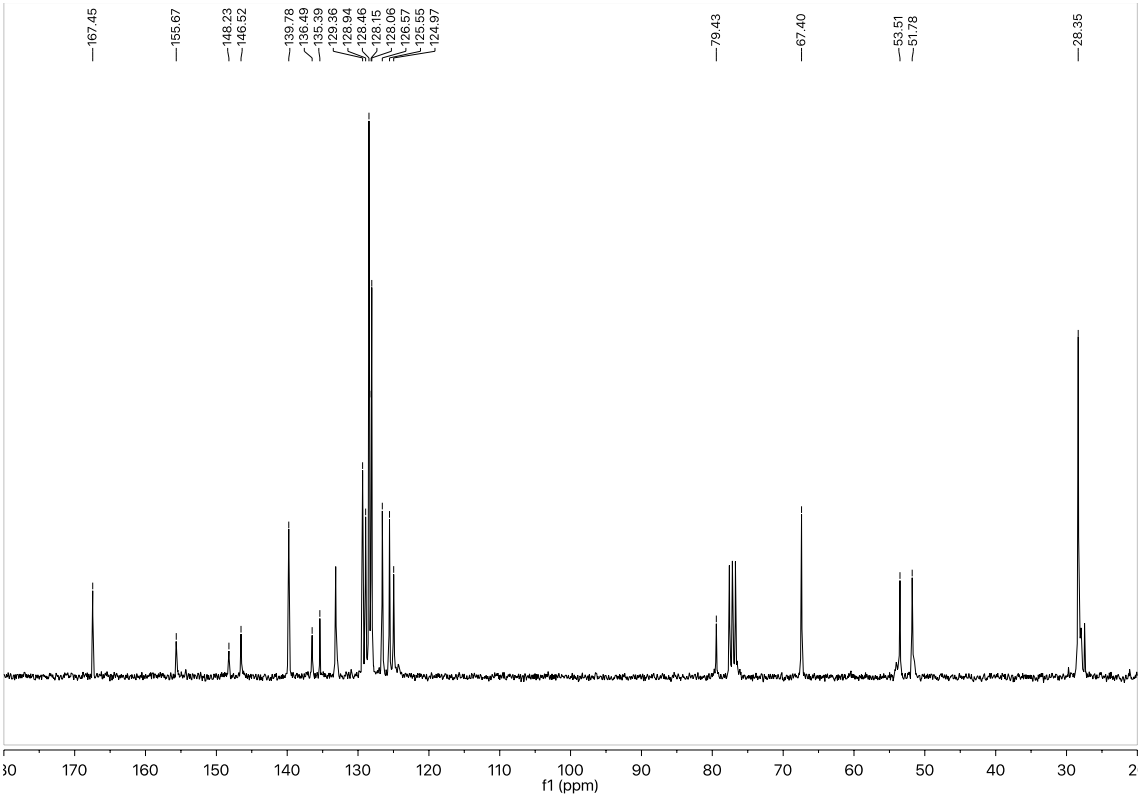
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(3-chlorophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18n)



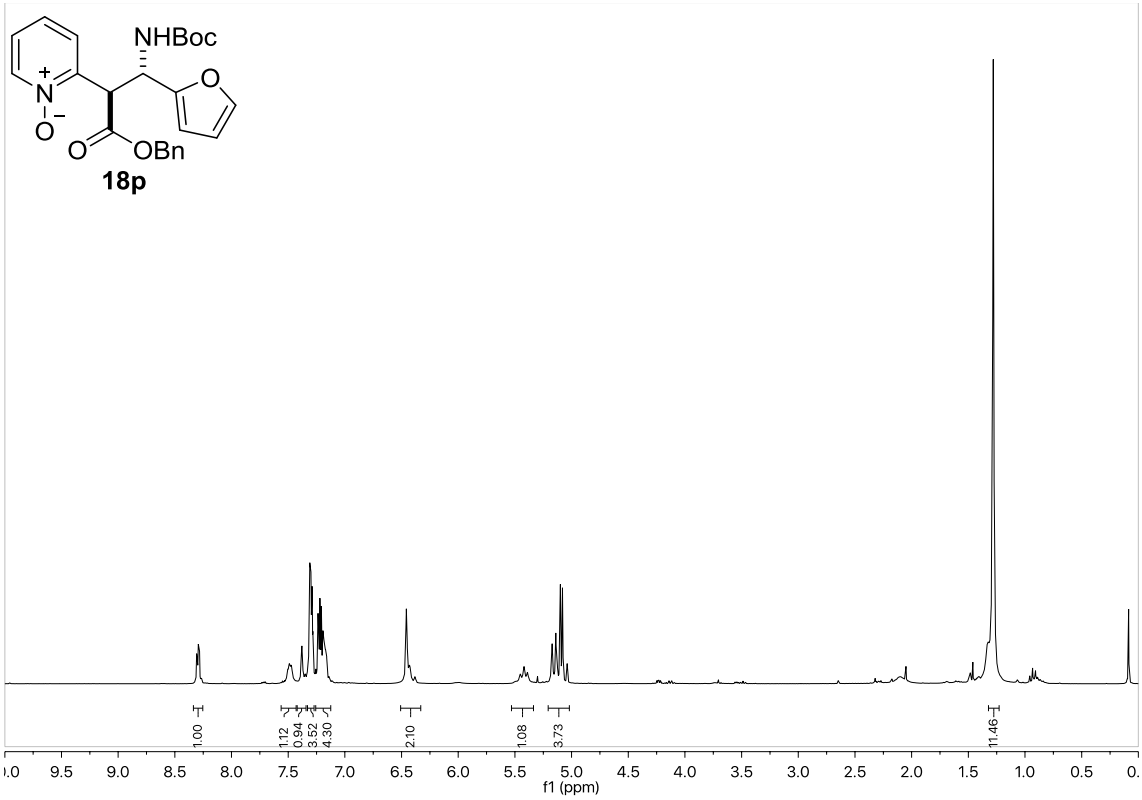


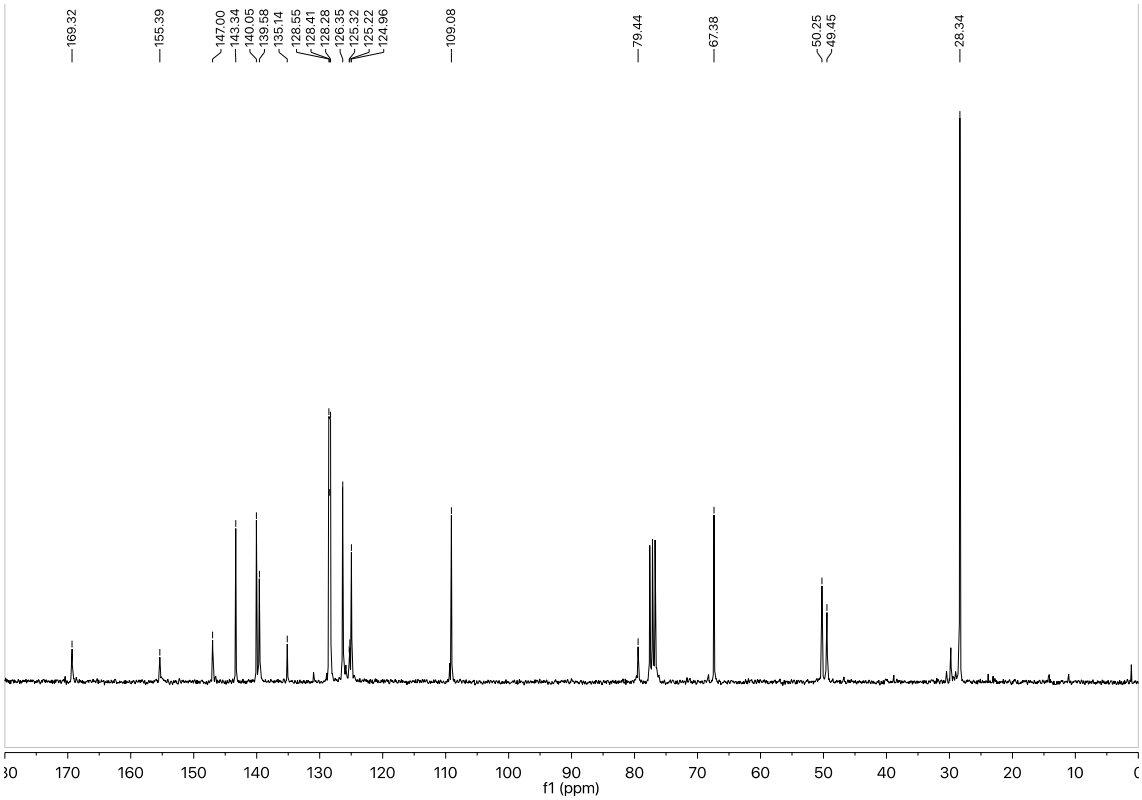
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(2-nitrophenyl)-1-oxopropan-2-yl)pyridine *N*-oxide (18o)



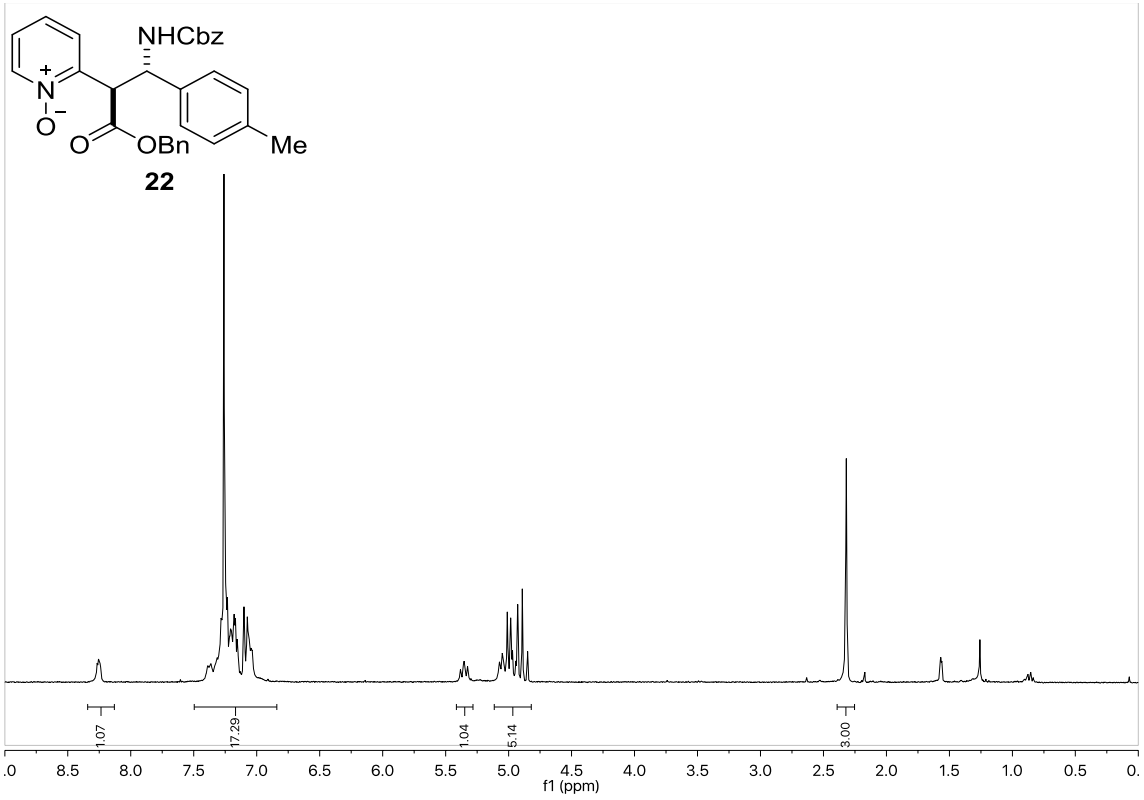


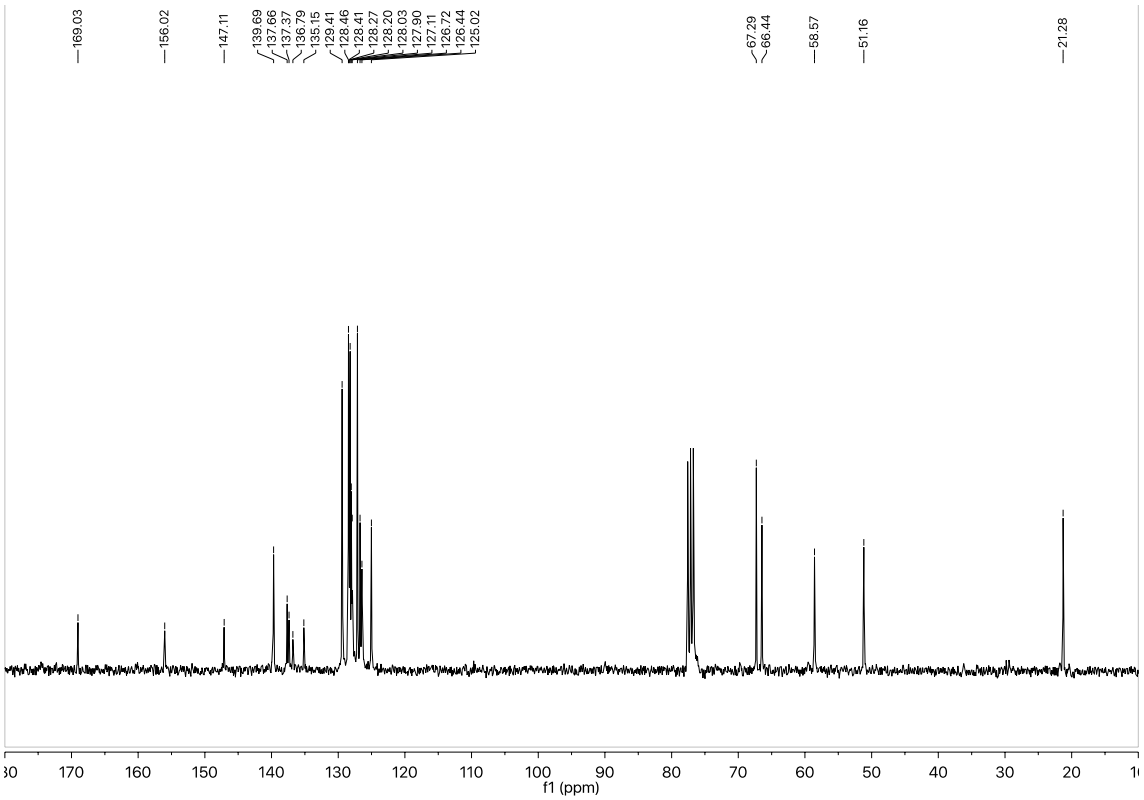
2-((2*R*,3*S*)-1-(Benzyloxy)-3-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-1-oxopropan-2-yl)pyridine *N*-oxide (18p)



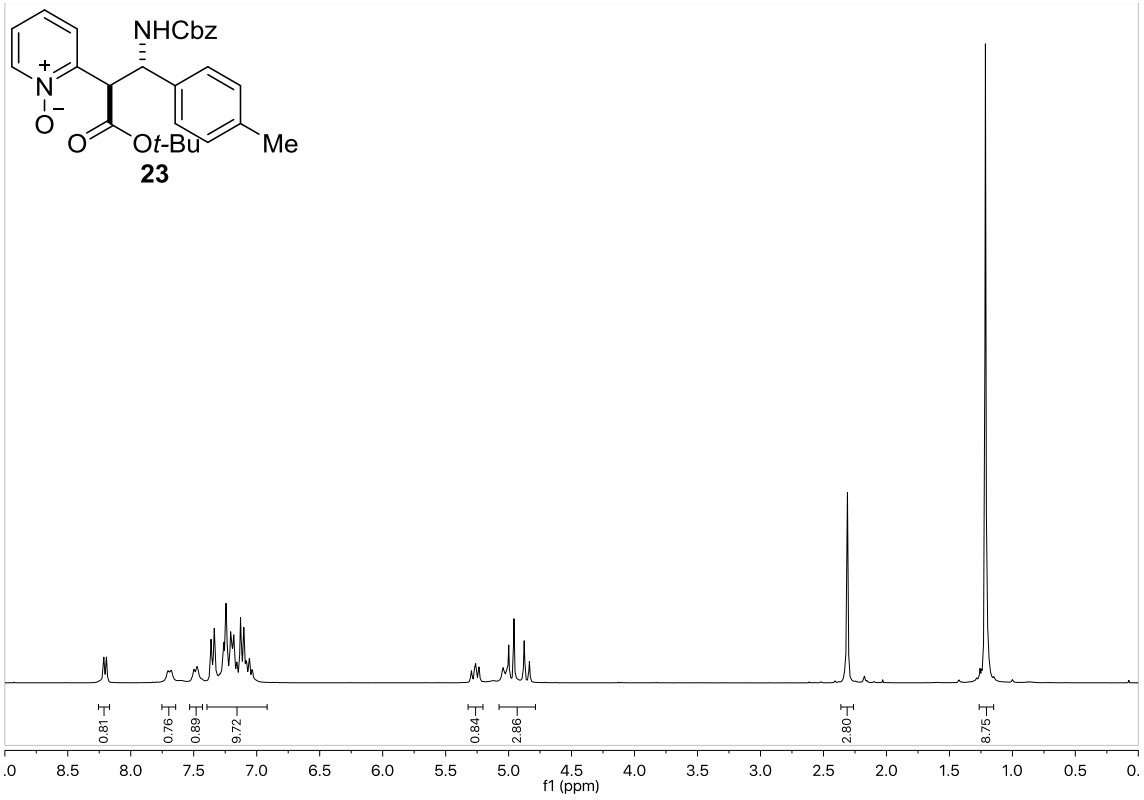


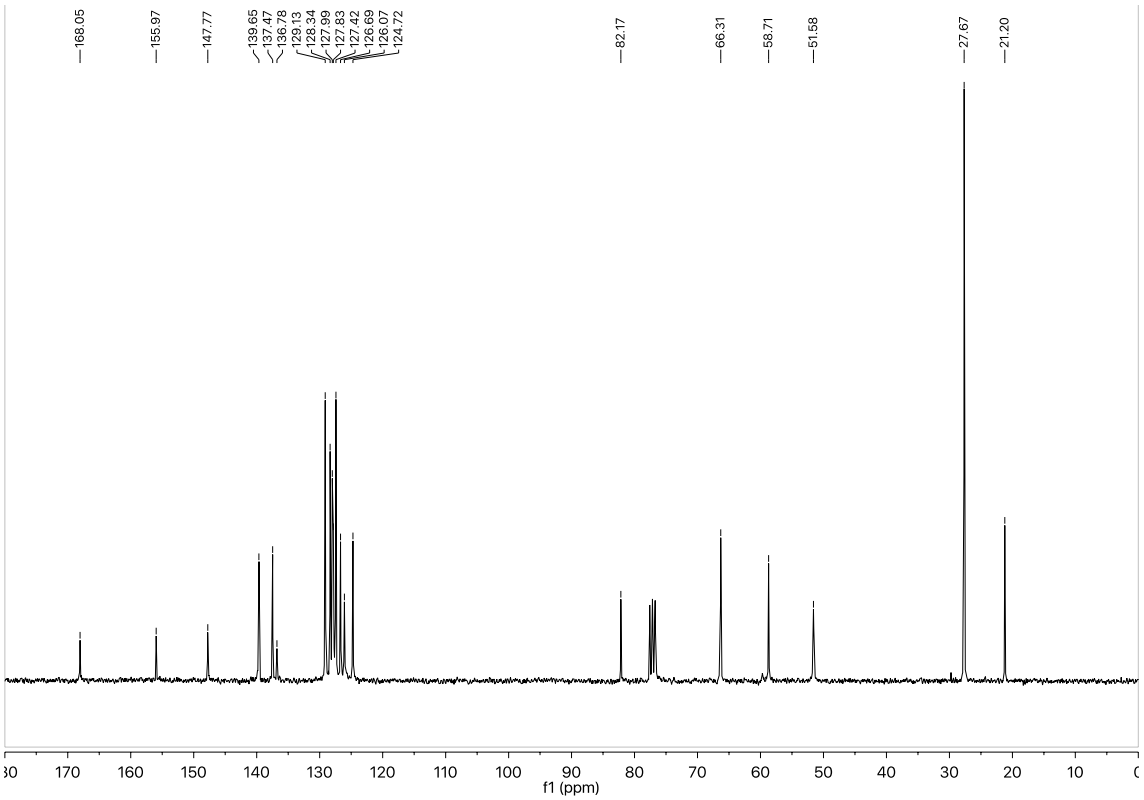
2-((2*R*,3*S*)-1-(Benzyloxy)-3-(((benzyloxy)carbonyl)amino)-1-oxo-3-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (22)



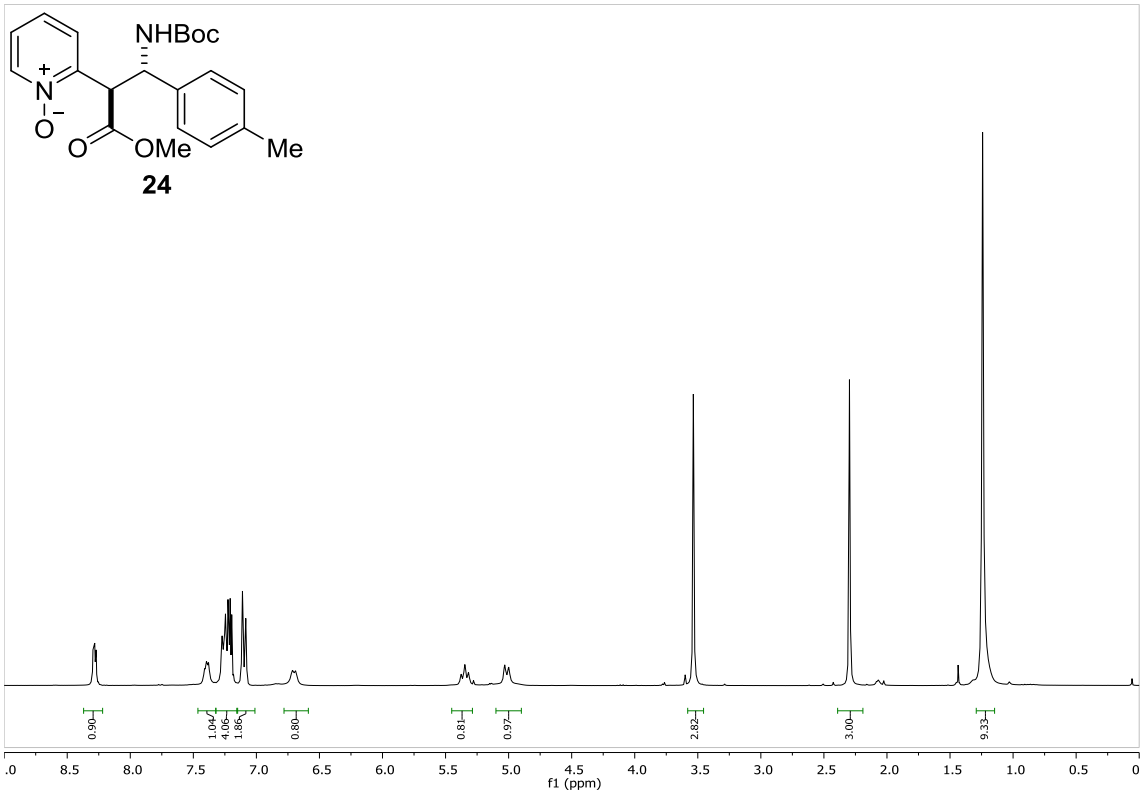


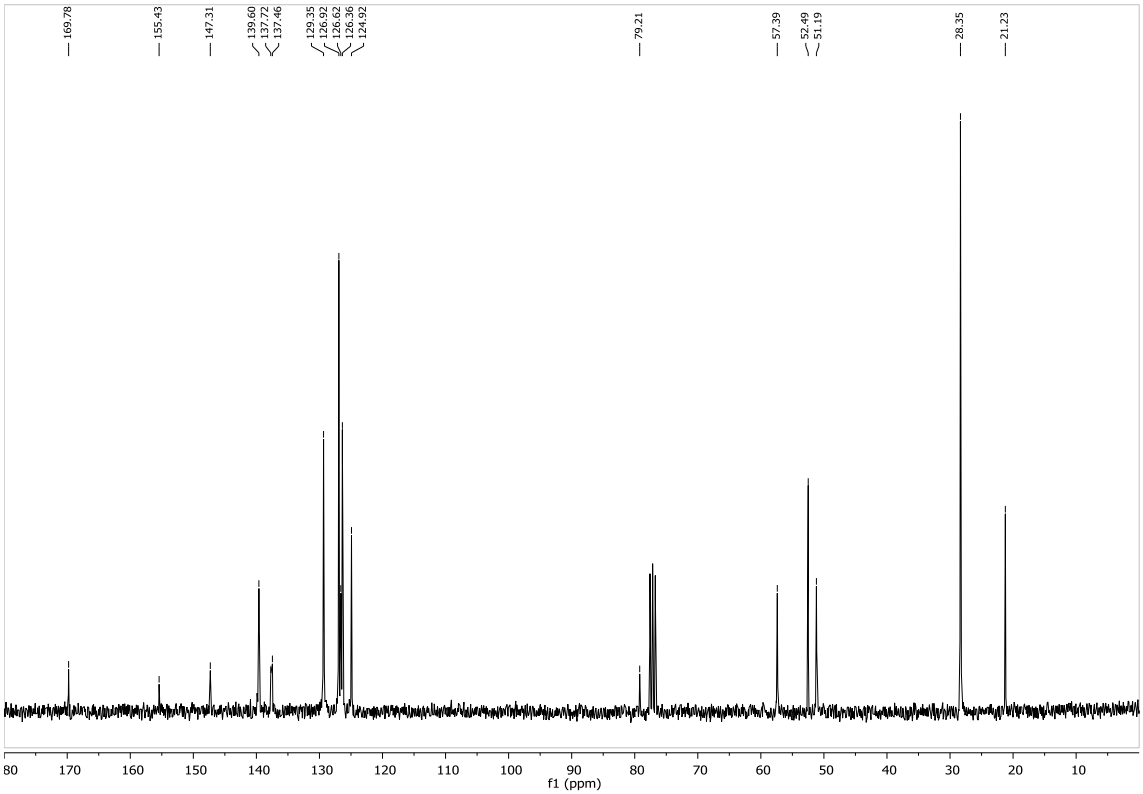
2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (23)



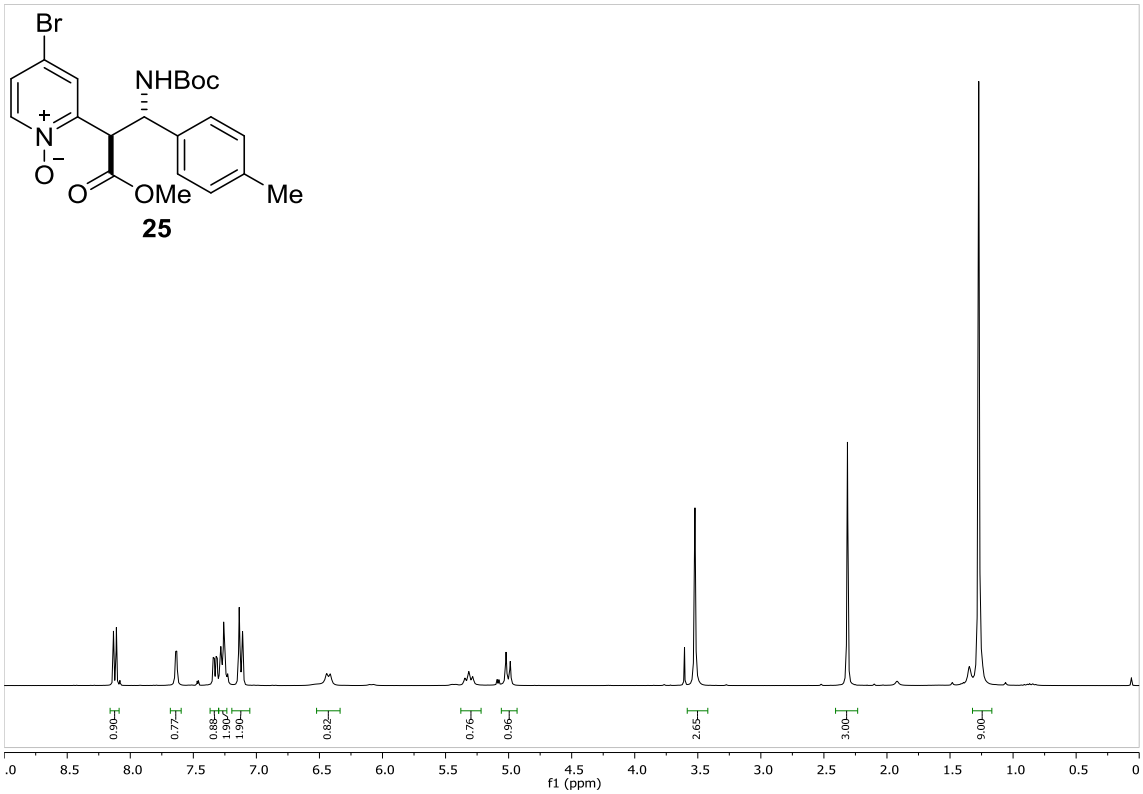


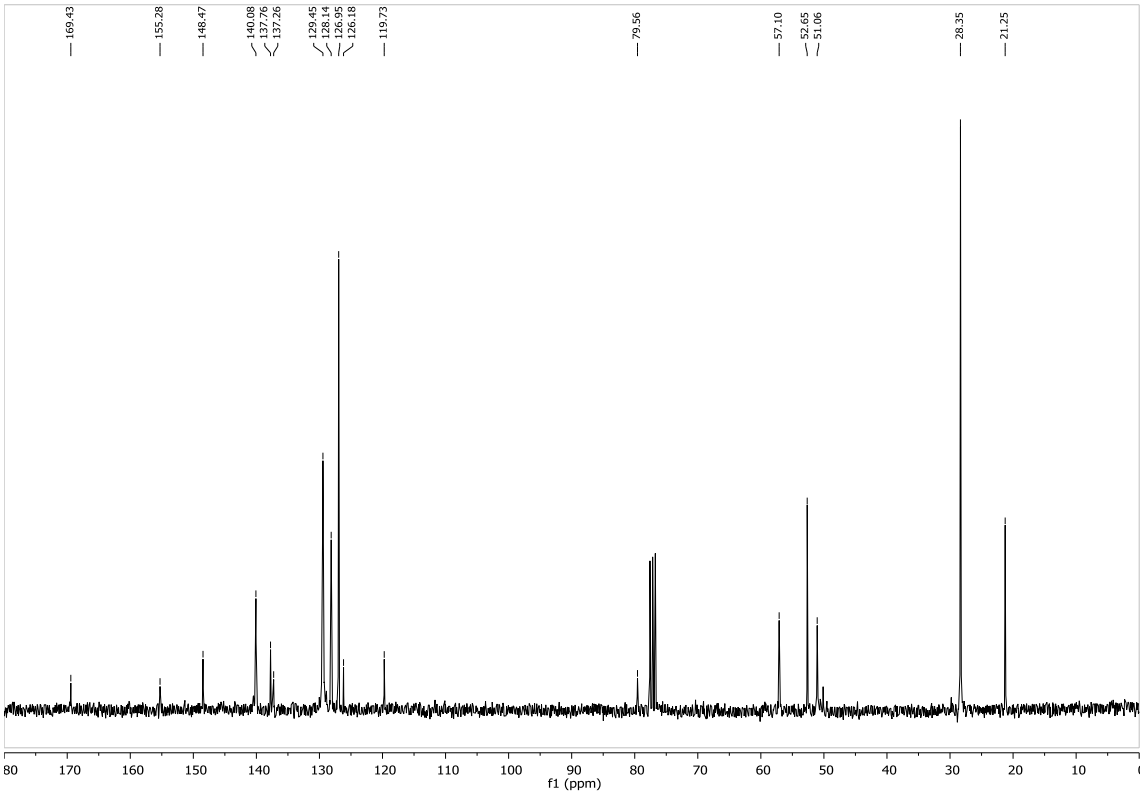
2-((1*S*,2*R*)-1-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (24)



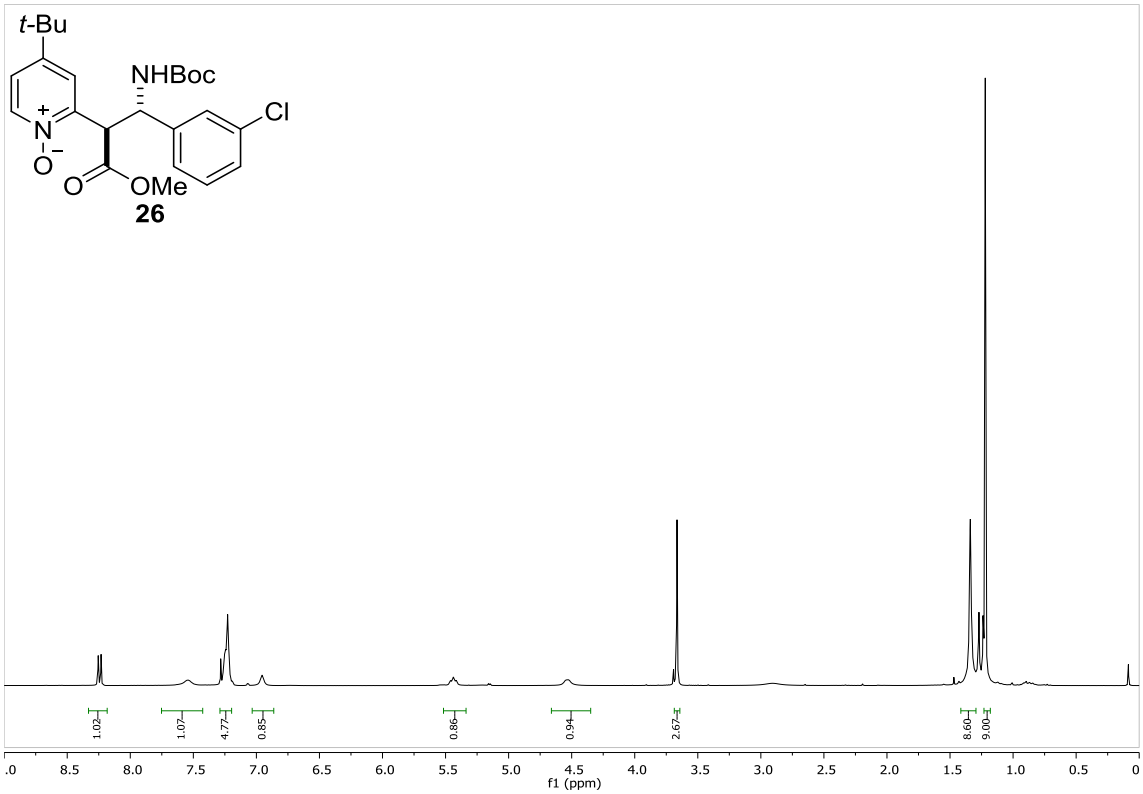


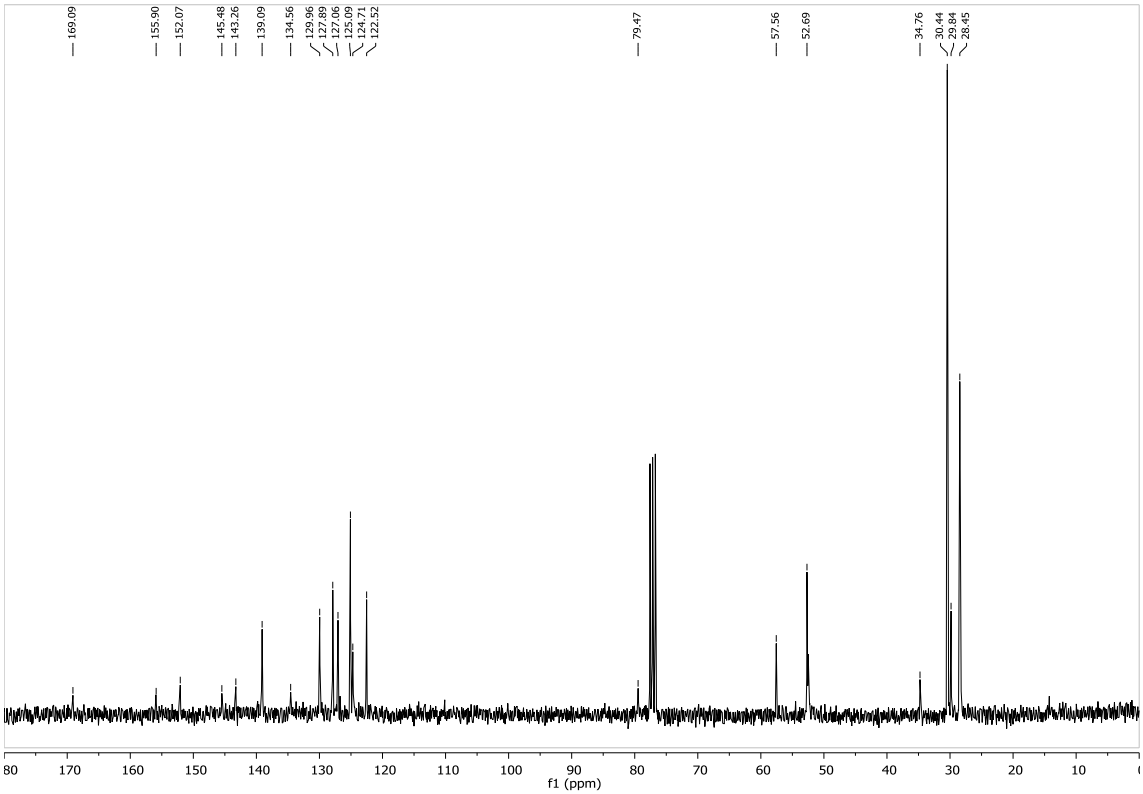
4-Bromo-2-((1*S*,2*R*)-1-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)pyridine *N*-oxide (25)



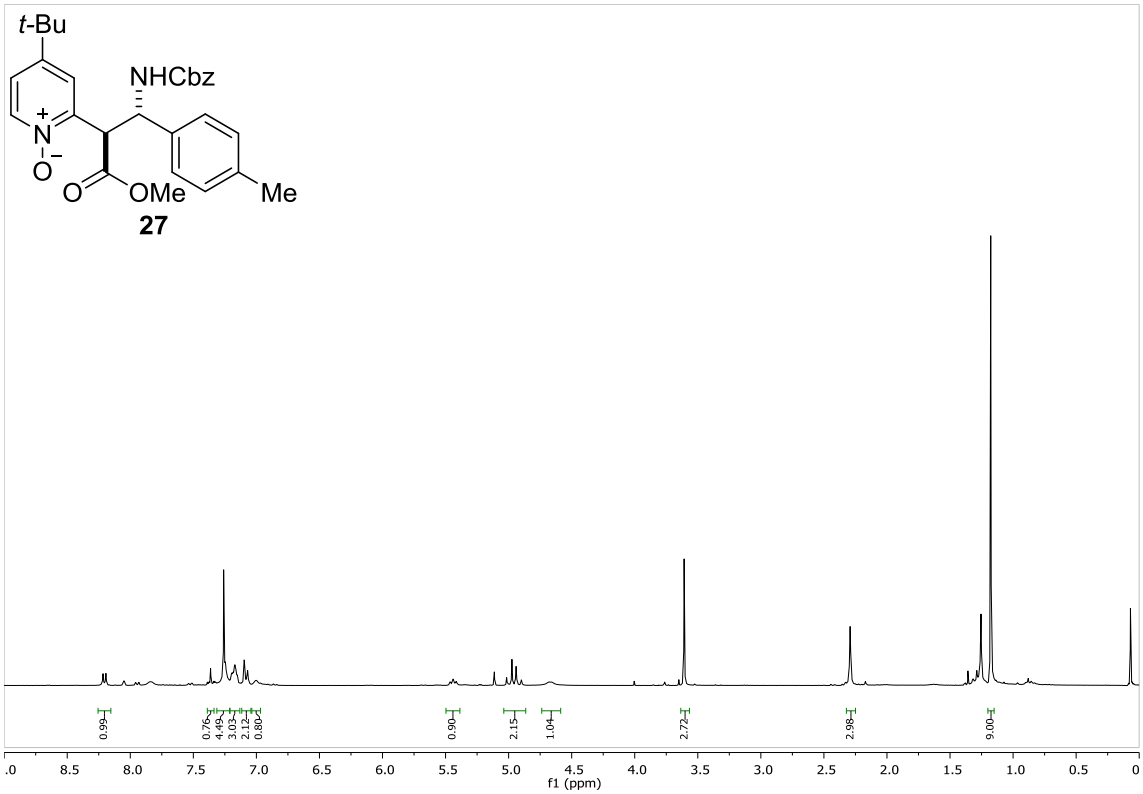


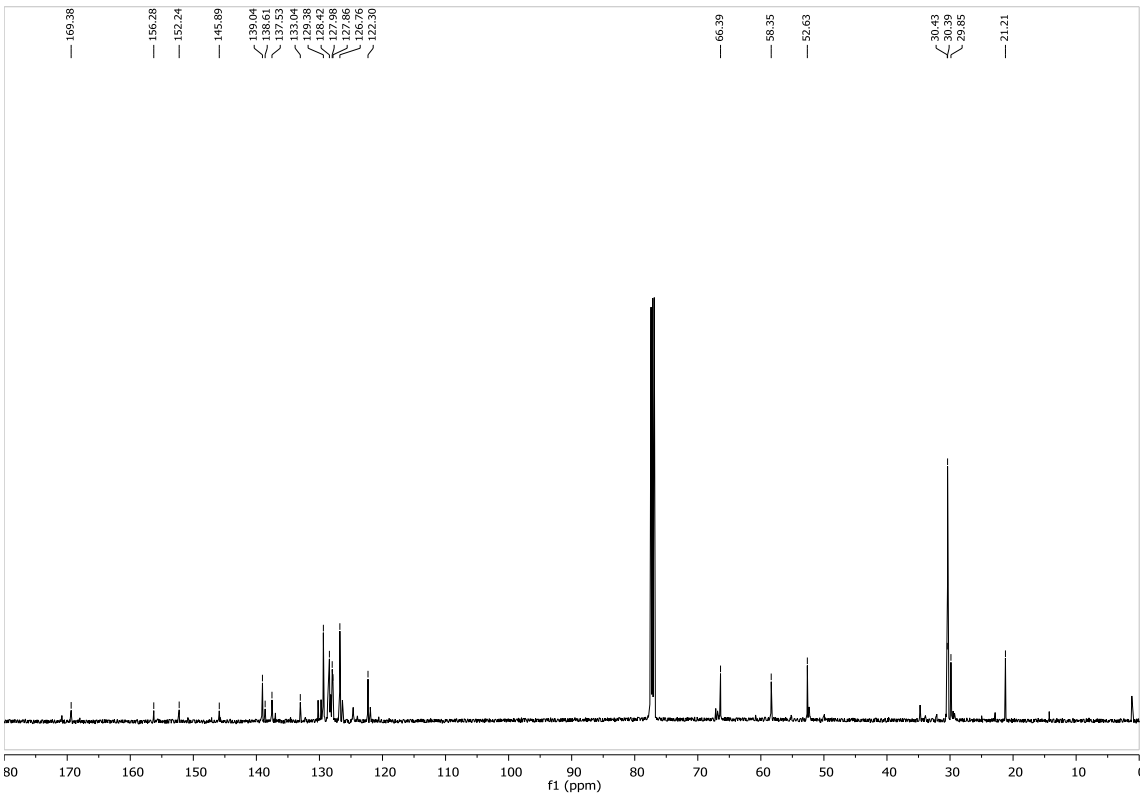
2-((1S,2R)-1-((*tert*-Butoxycarbonyl)amino)-1-(3-chlorophenyl)-3-methoxy-3-oxopropan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (26)



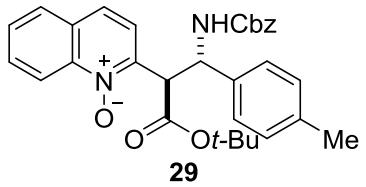


2-((1*S*,2*R*)-1-(((Benzyloxy)carbonyl)amino)-3-methoxy-3-oxo-1-(*p*-tolyl)propan-2-yl)-4-(*tert*-butyl)pyridine *N*-oxide (27)

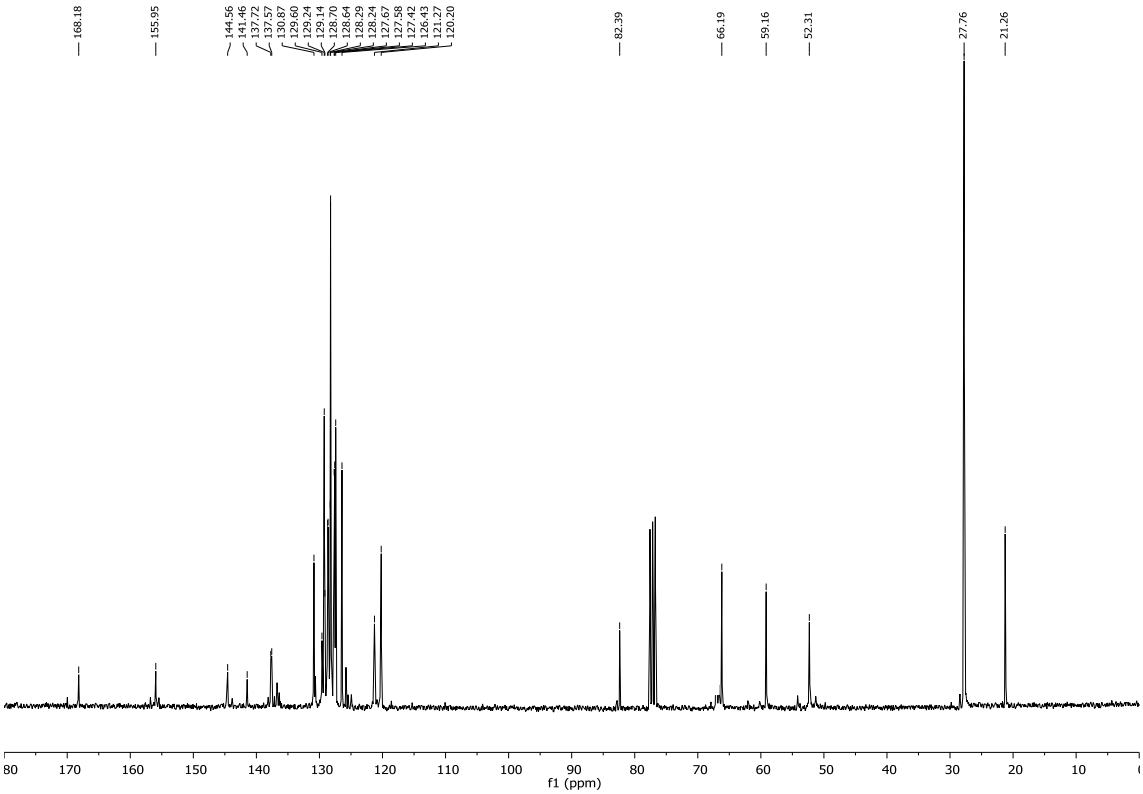




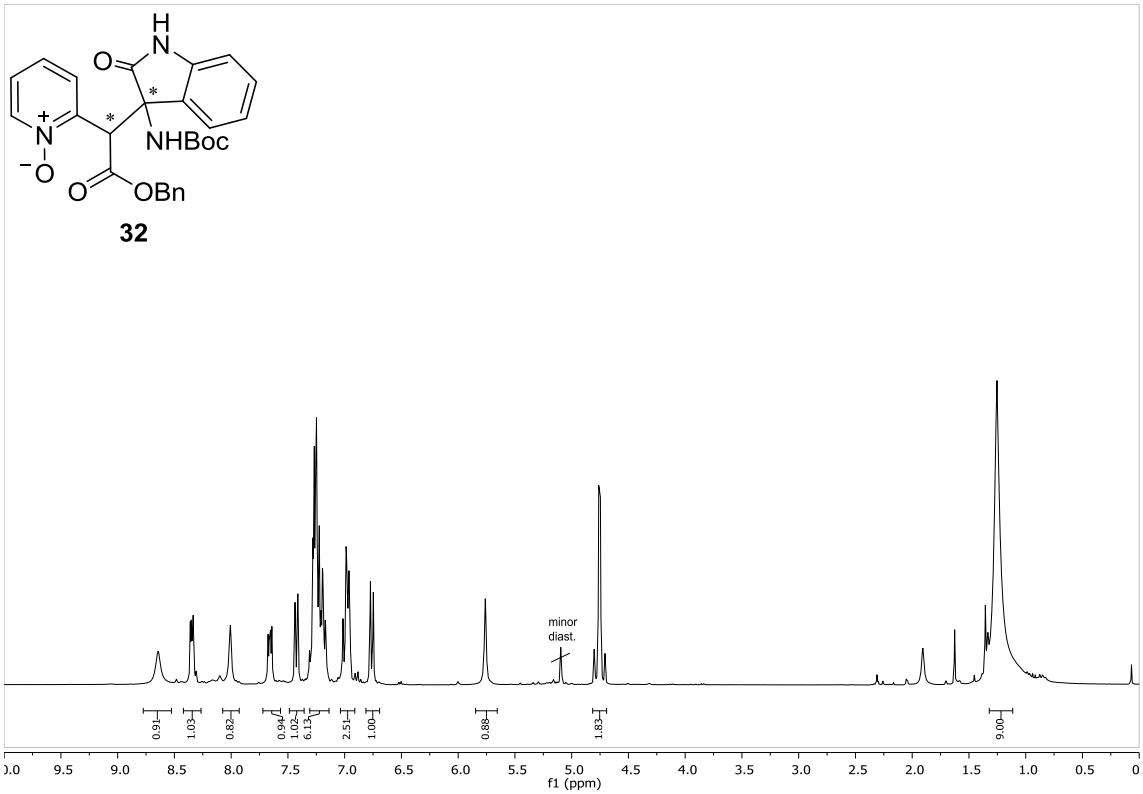
2-((1*S*,2*R*)-1-(((benzyloxy)carbonyl)amino)-3-(*tert*-butoxy)-3-oxo-1-(*p*-tolyl)propan-2-yl)quinoline *N*-oxide (29)



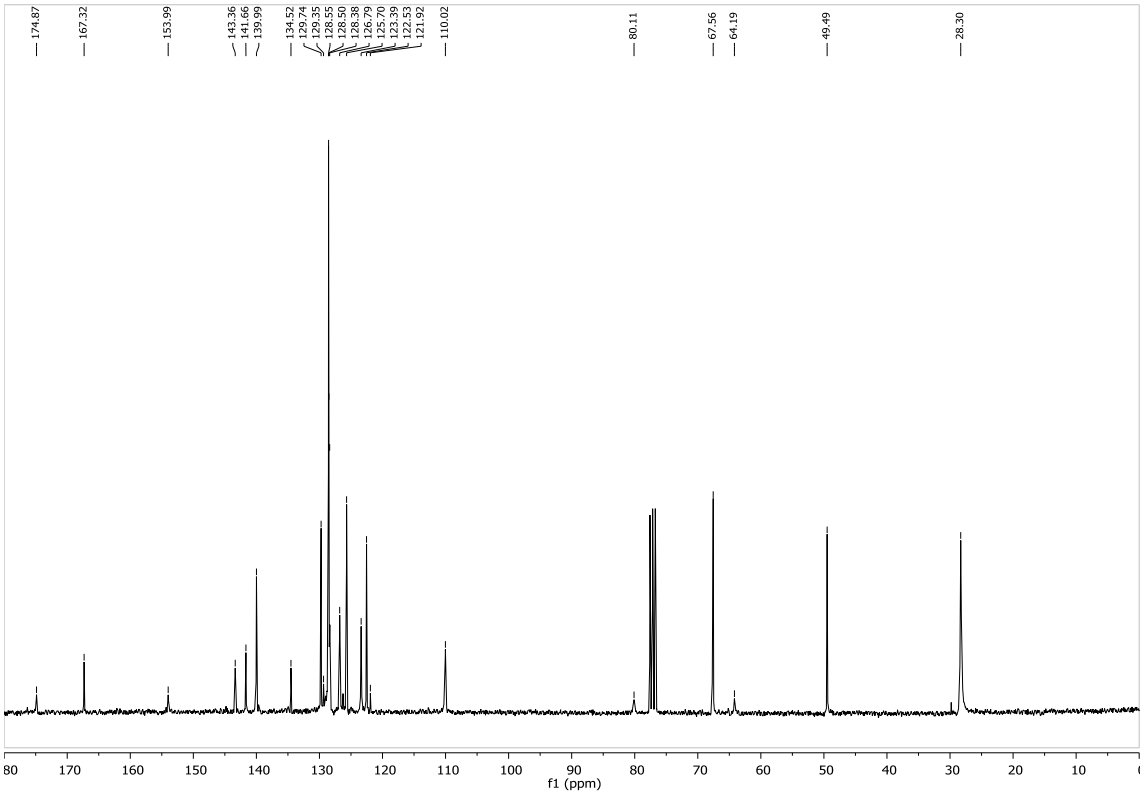
29



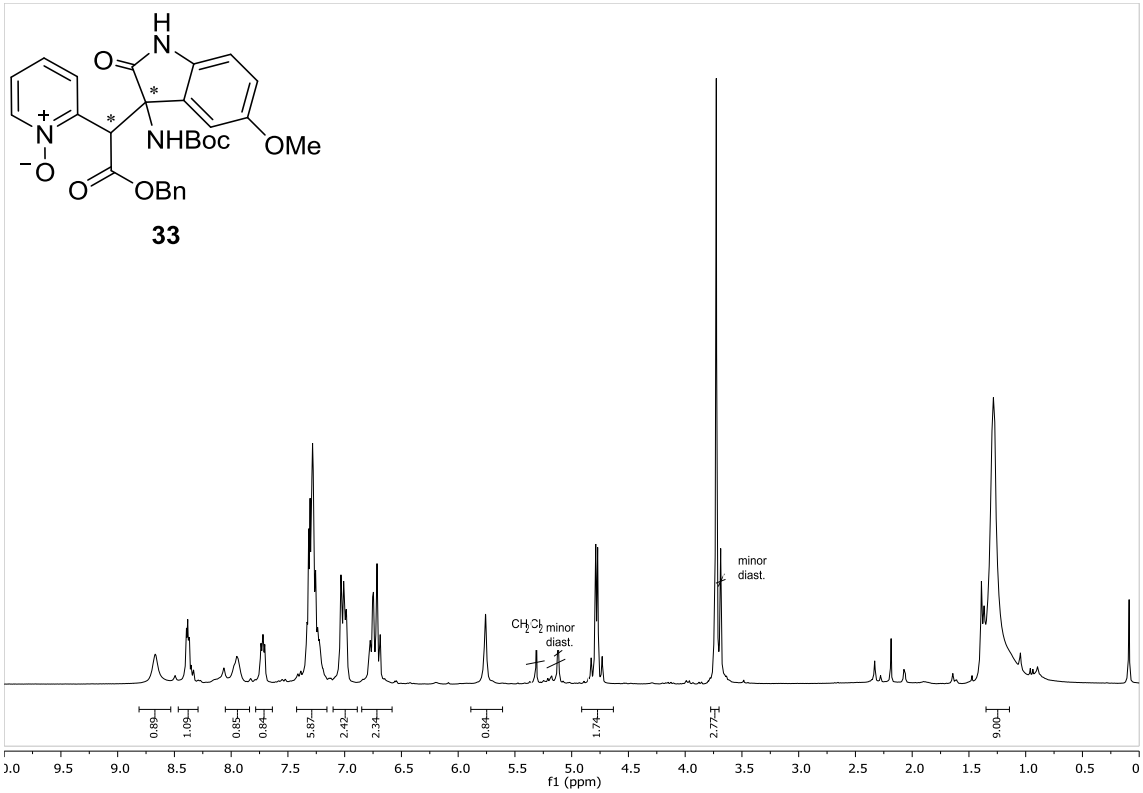
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (32)



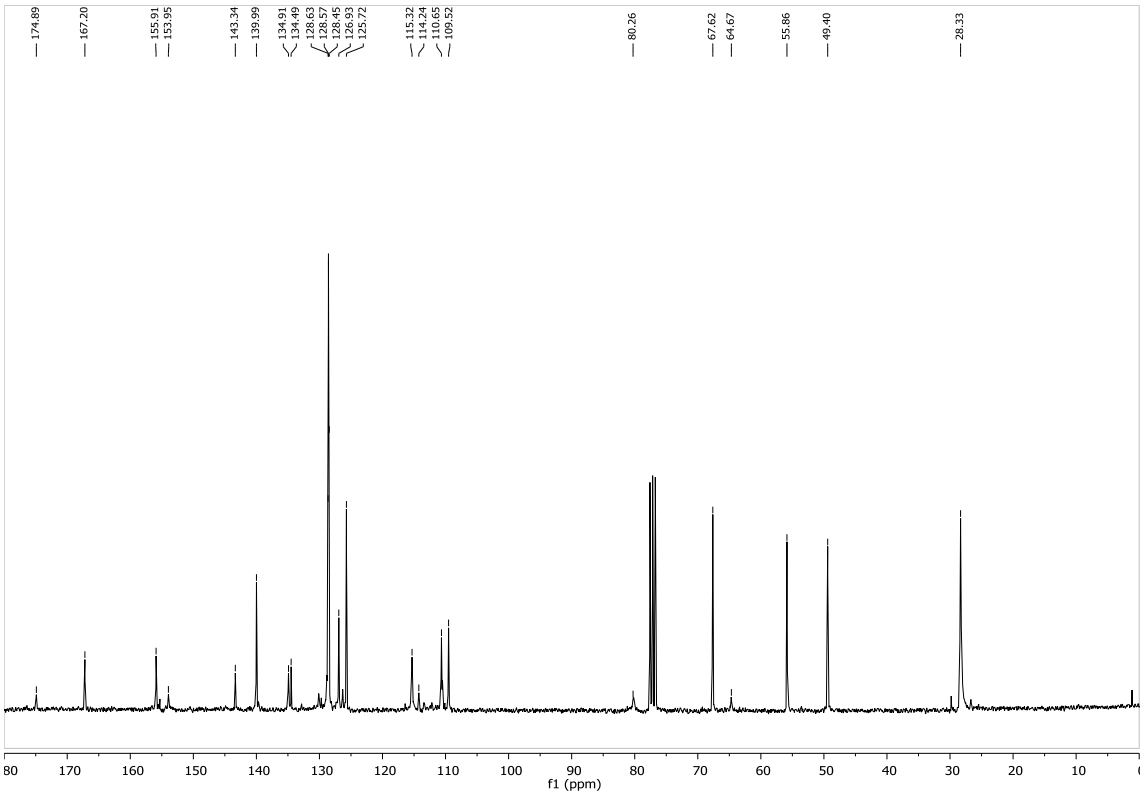
32



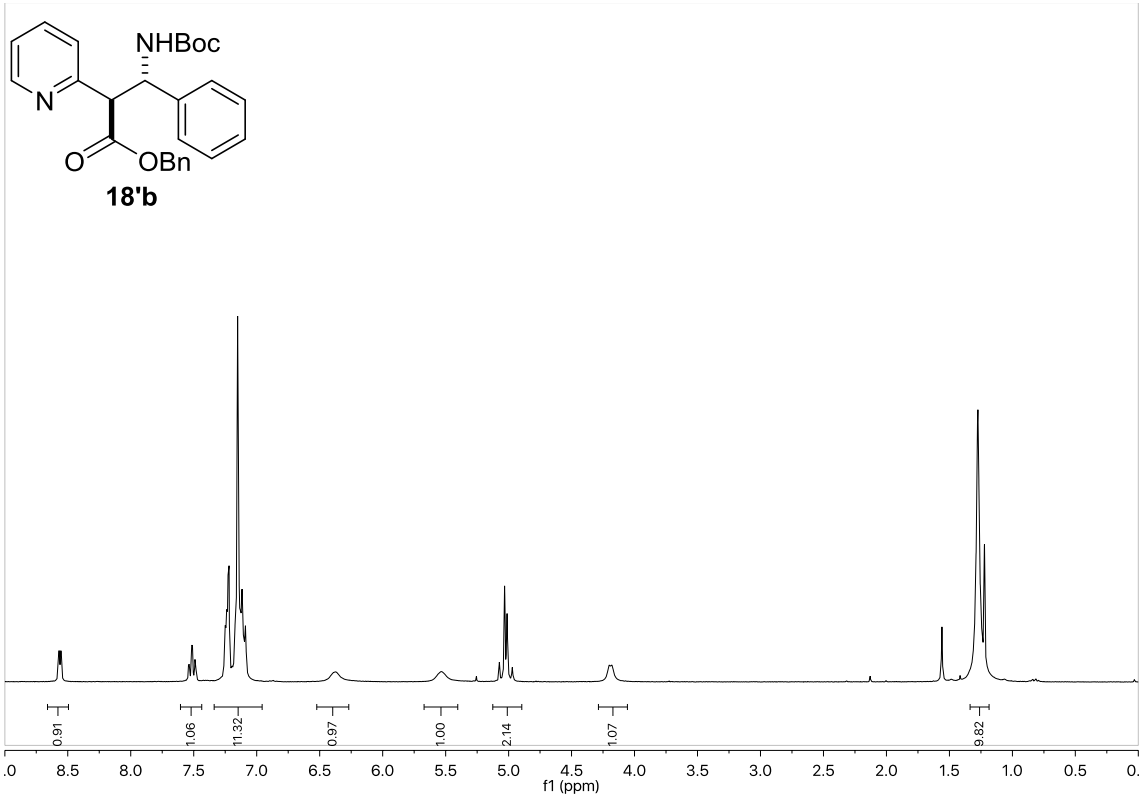
2-(2-(Benzyloxy)-1-(3-((*tert*-butoxycarbonyl)amino)-5-methoxy-2-oxoindolin-3-yl)-2-oxoethyl)pyridine *N*-oxide (33)

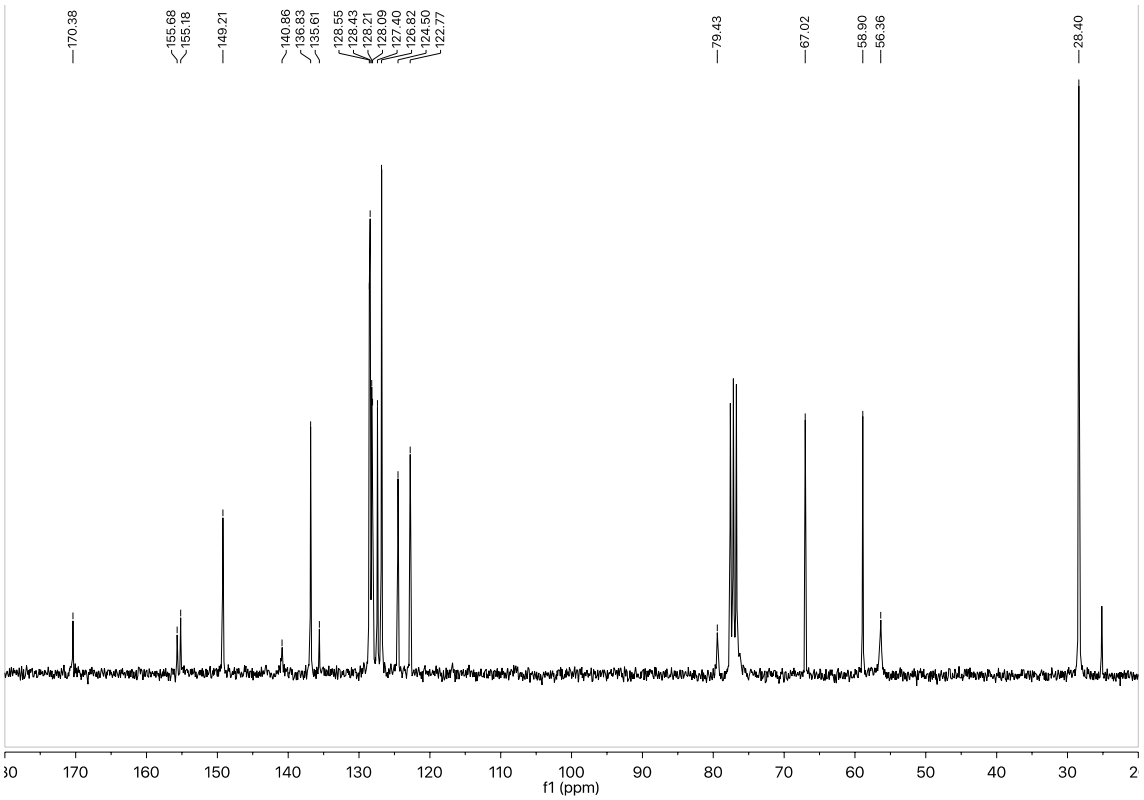


33

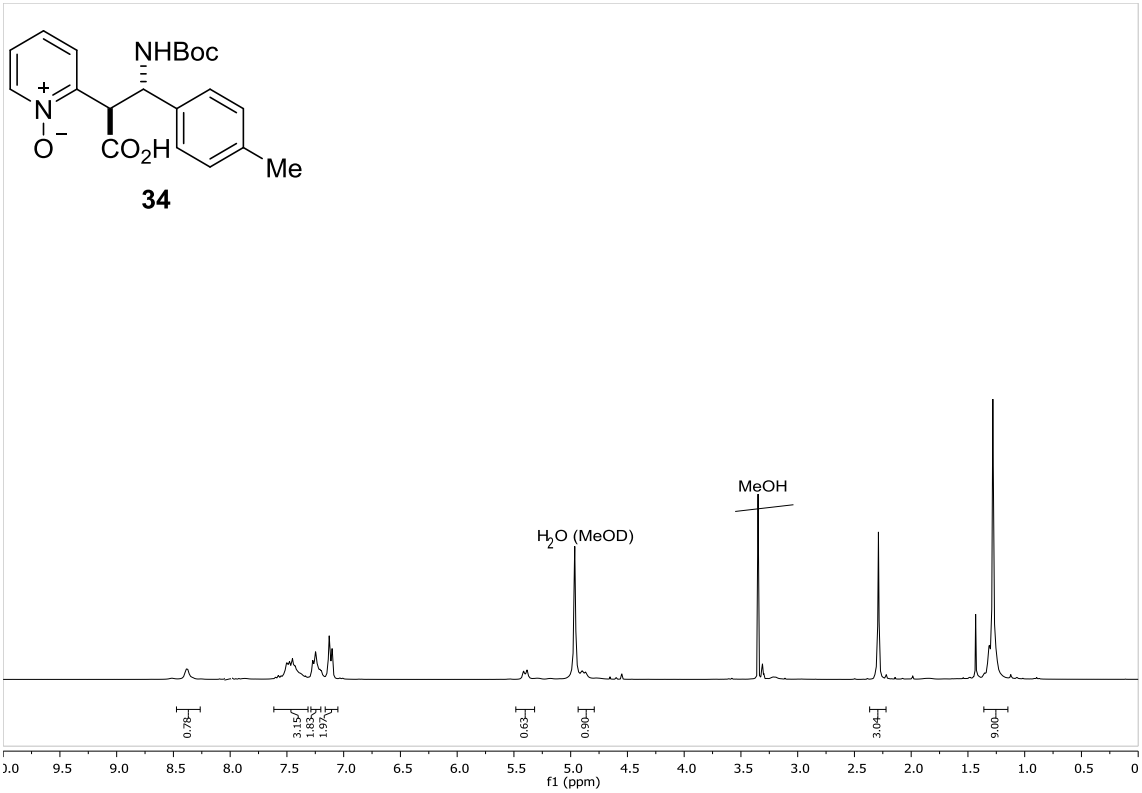


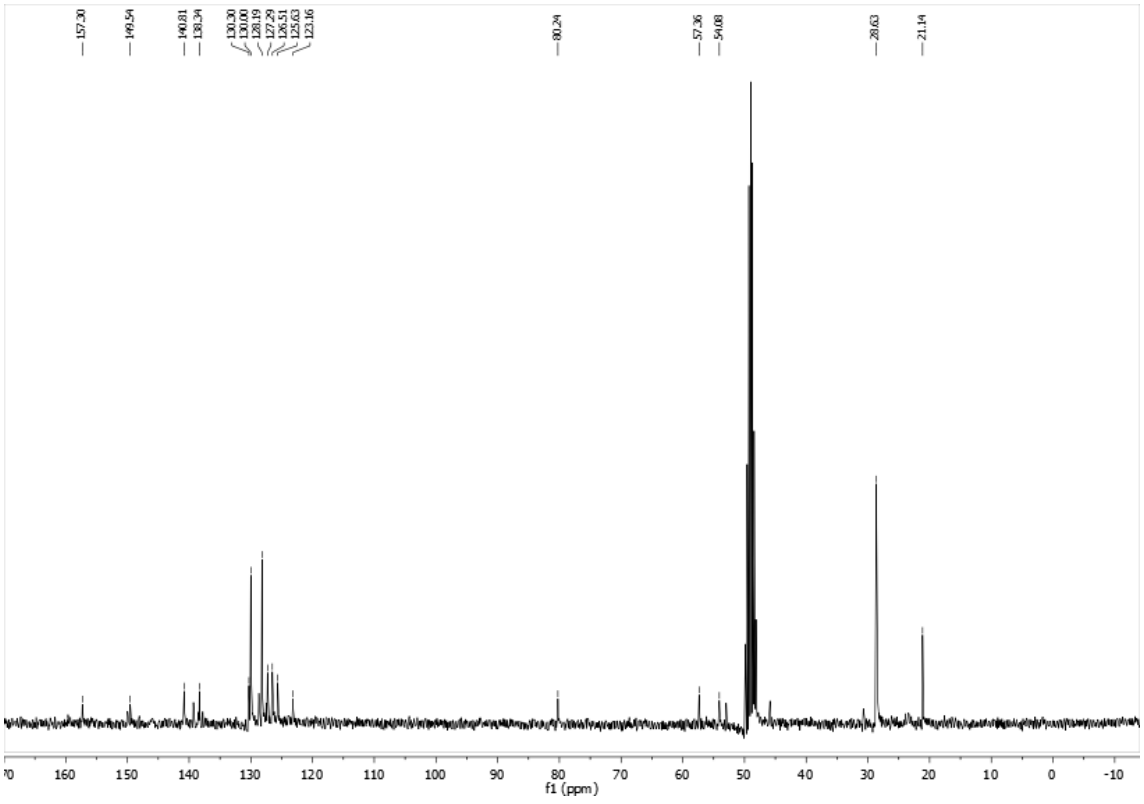
Benzyl (2*R*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-3-phenyl-2-(pyridin-2-yl)propanoate (18'b)



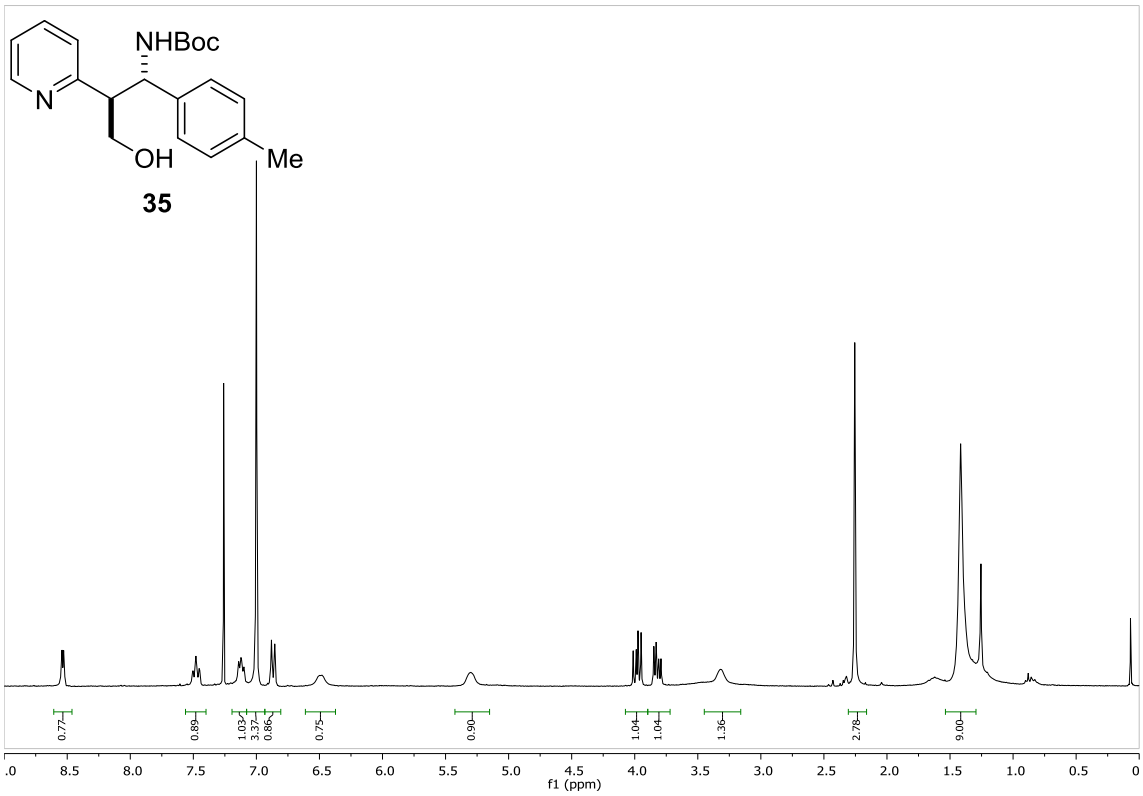


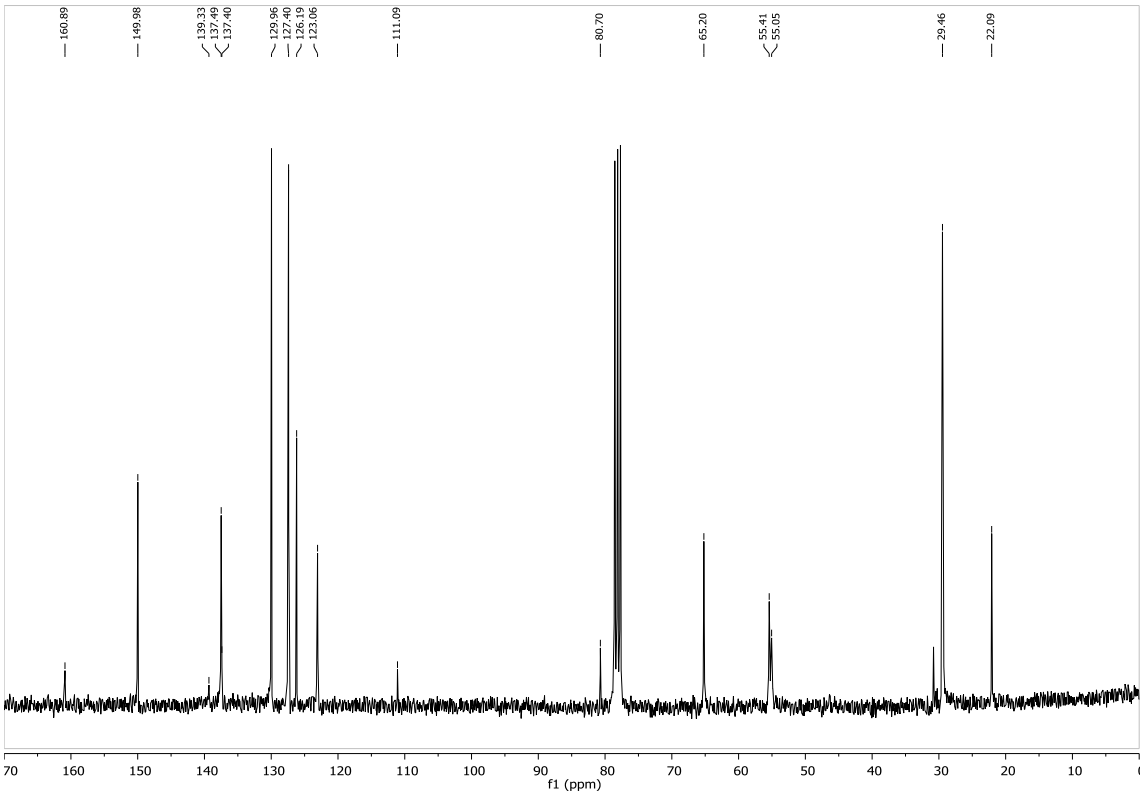
2-((1*R*,2*S*)-2-((*tert*-butoxycarbonyl)amino)-1-carboxy-2-(p-tolyl)ethyl)pyridine *N*-oxide (34)



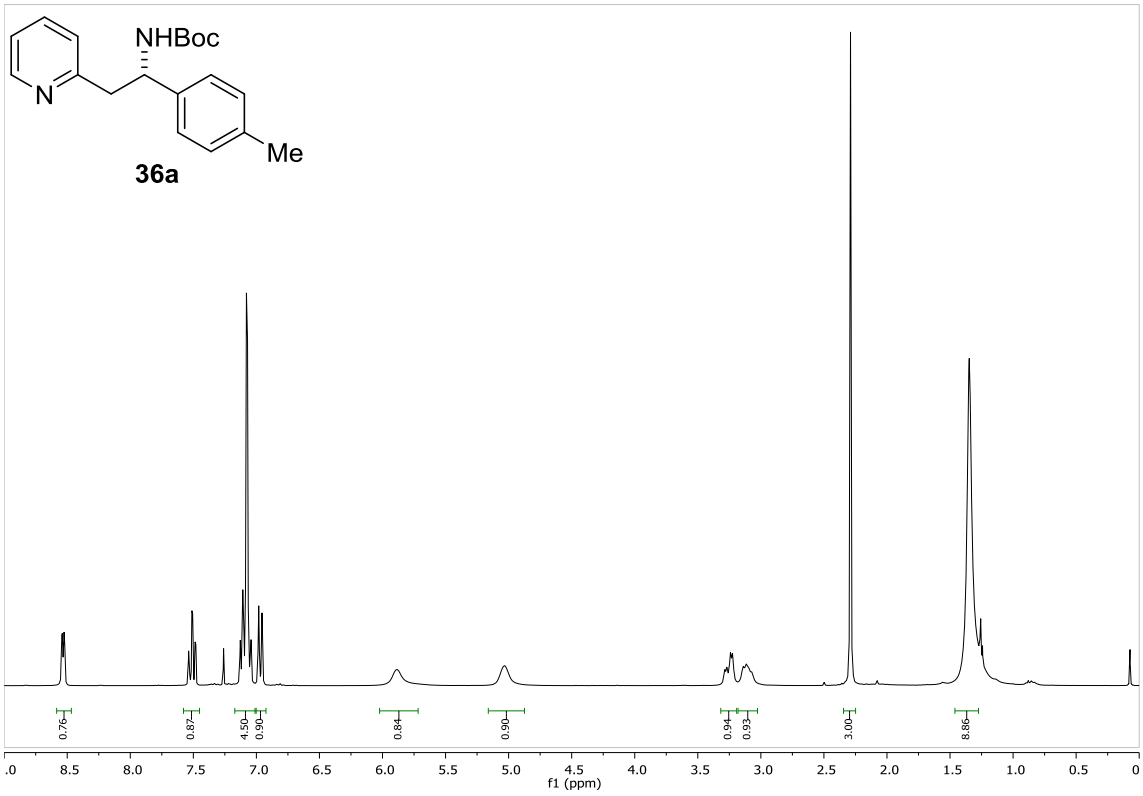


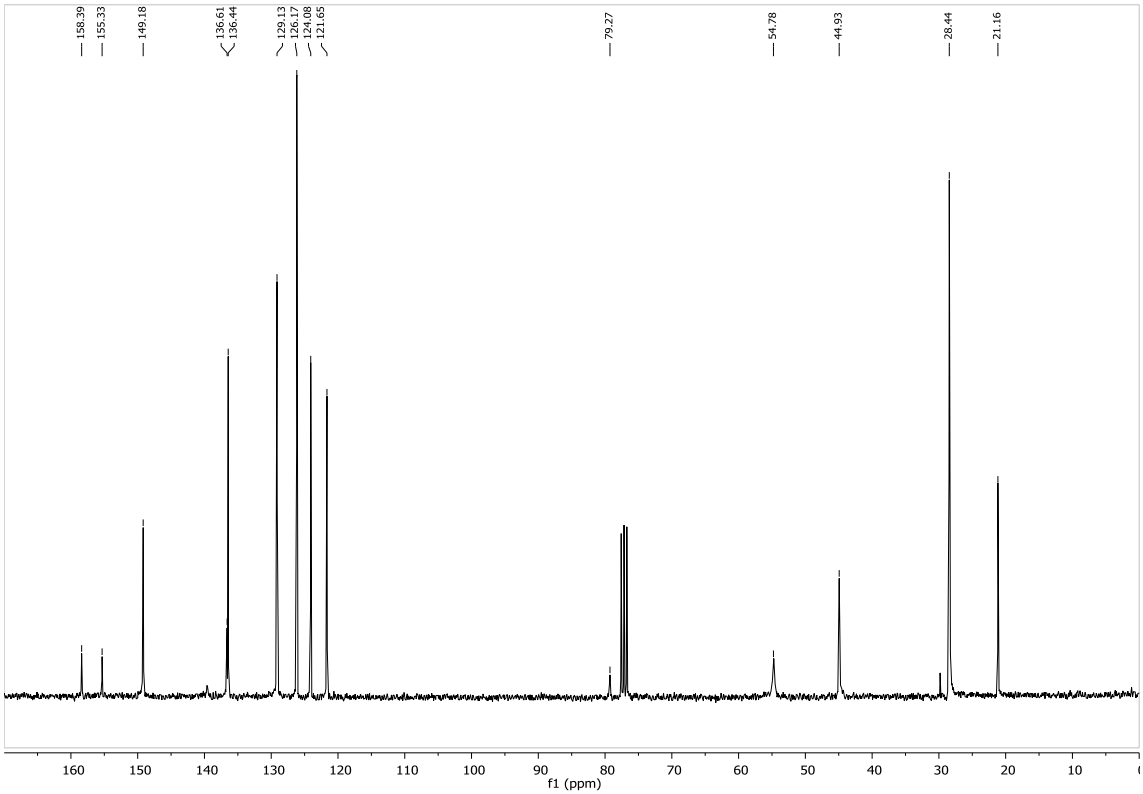
tert-Butyl ((1_S_,2_R_)-3-hydroxy-2-(pyridin-2-yl)-1-(_p_-tolyl)propyl)carbamate (35)





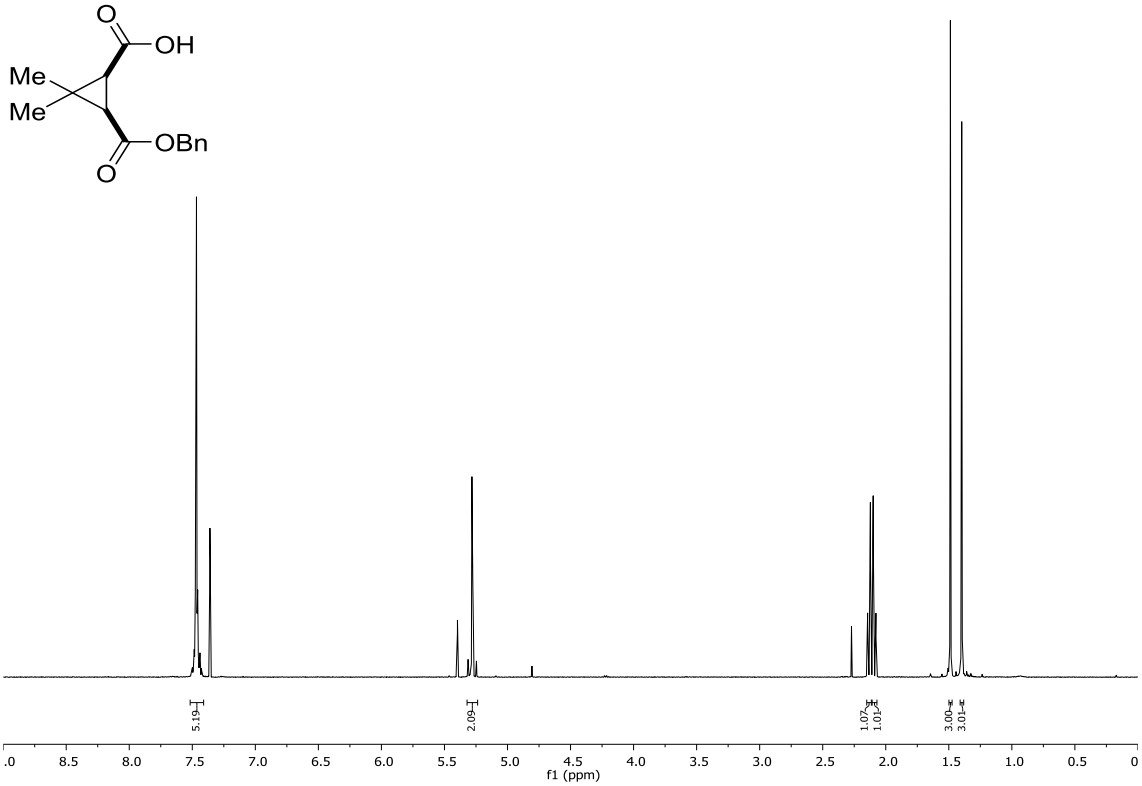
tert-butyl (_S_)-(2-(pyridin-2-yl)-1-(_p_-tolyl)ethyl)carbamate (36a)

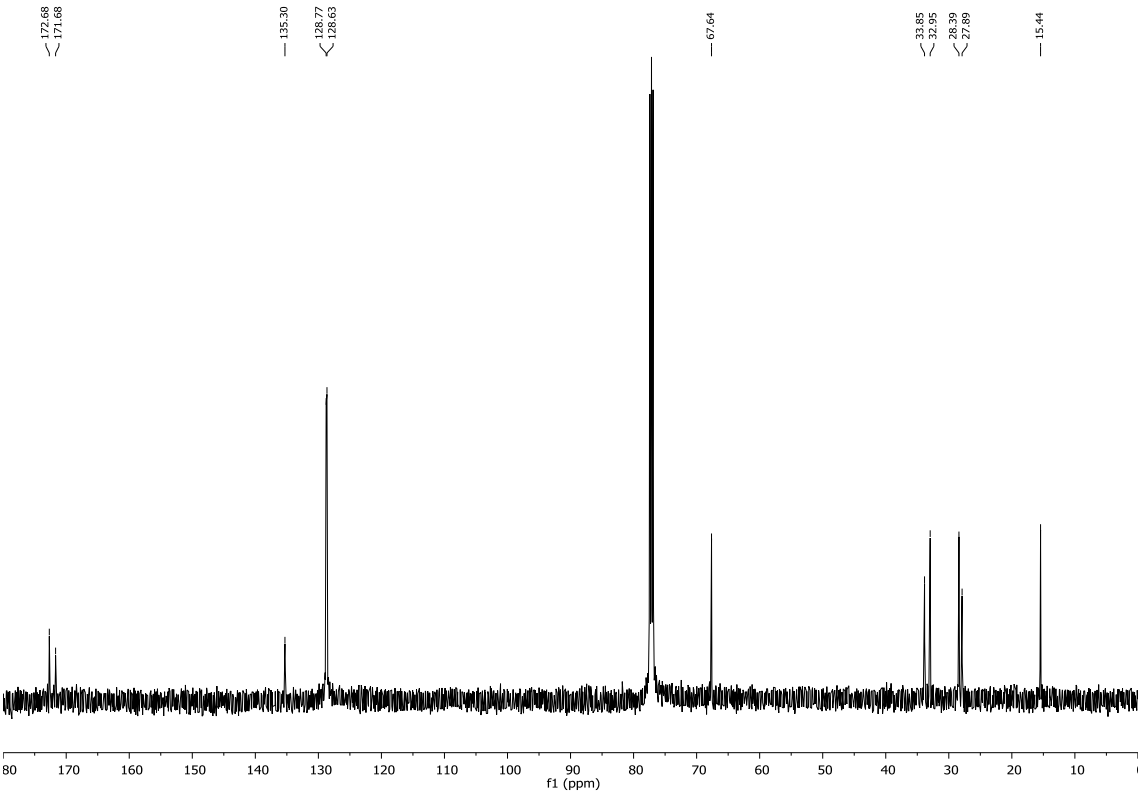




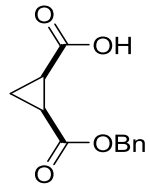
6.6.4. NMR spectra for Chapter 4

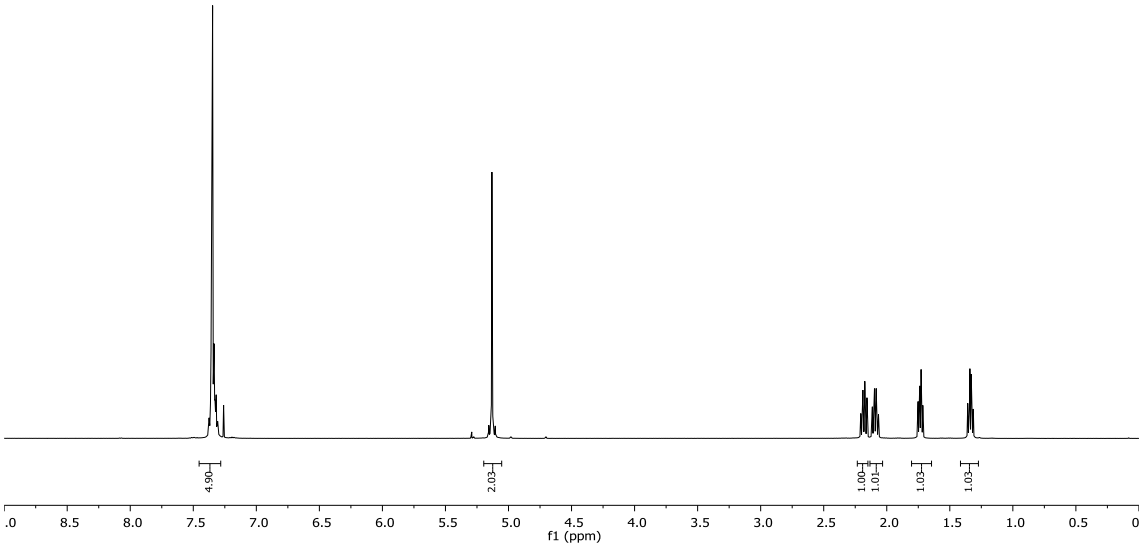
(1*S*,3*R*)-3-((Benzyloxy)carbonyl)-2,2-dimethylcyclopropane-1-carboxylic acid

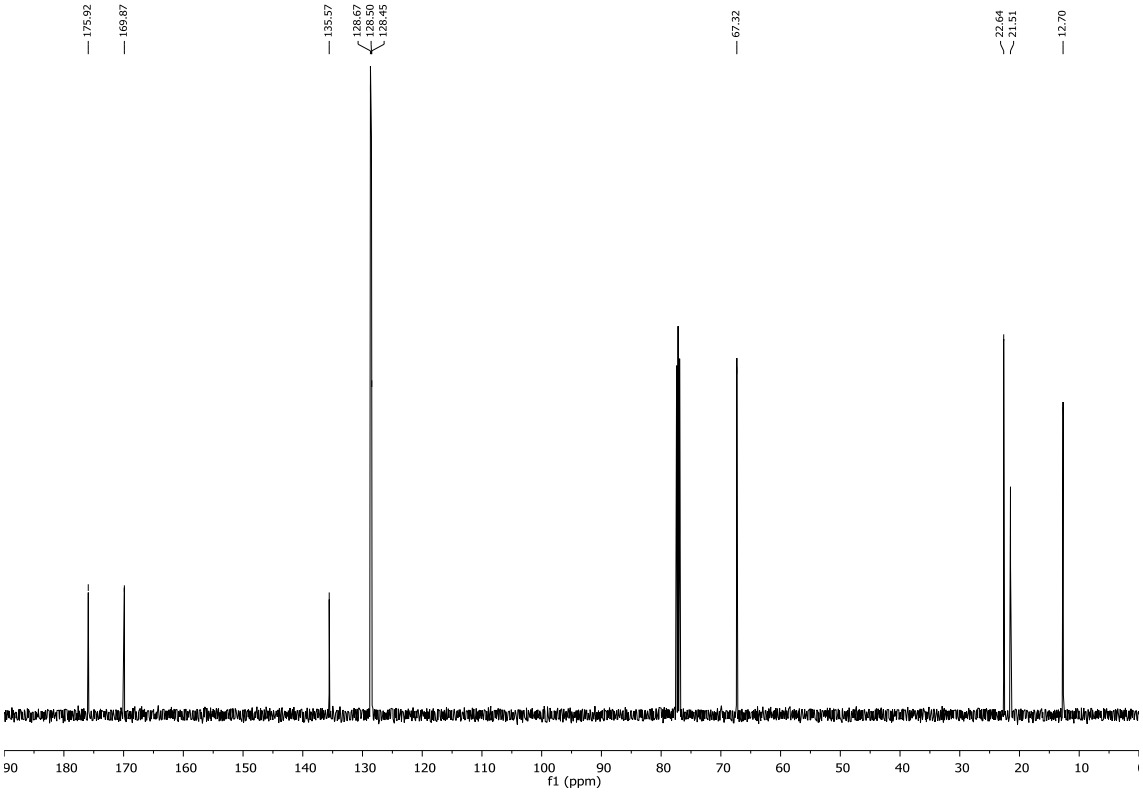




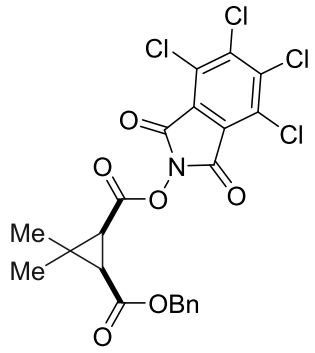
(1*R*,2*S*)-2-((Benzyloxy)carbonyl)cyclopropane-1-carboxylic acid



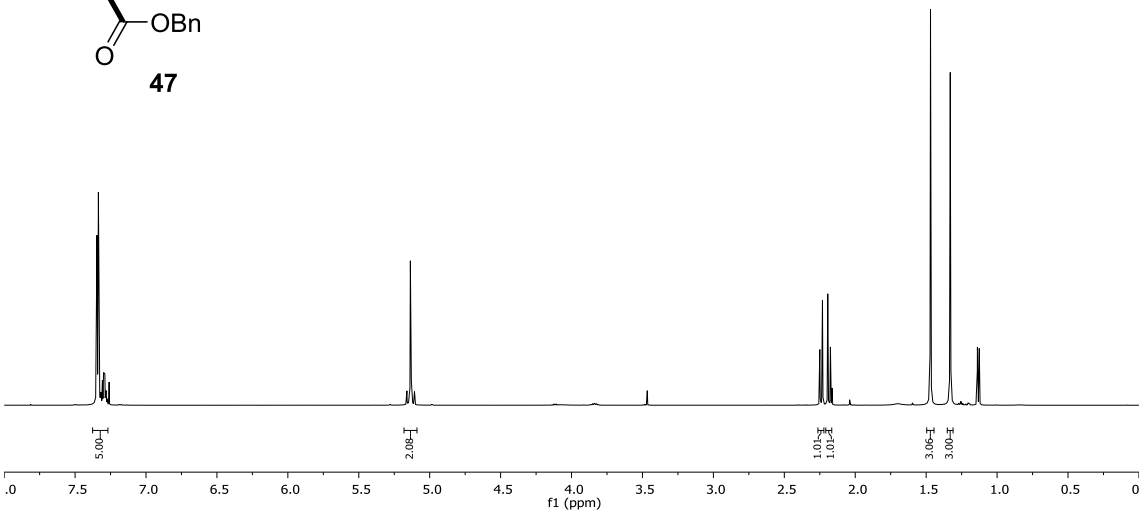


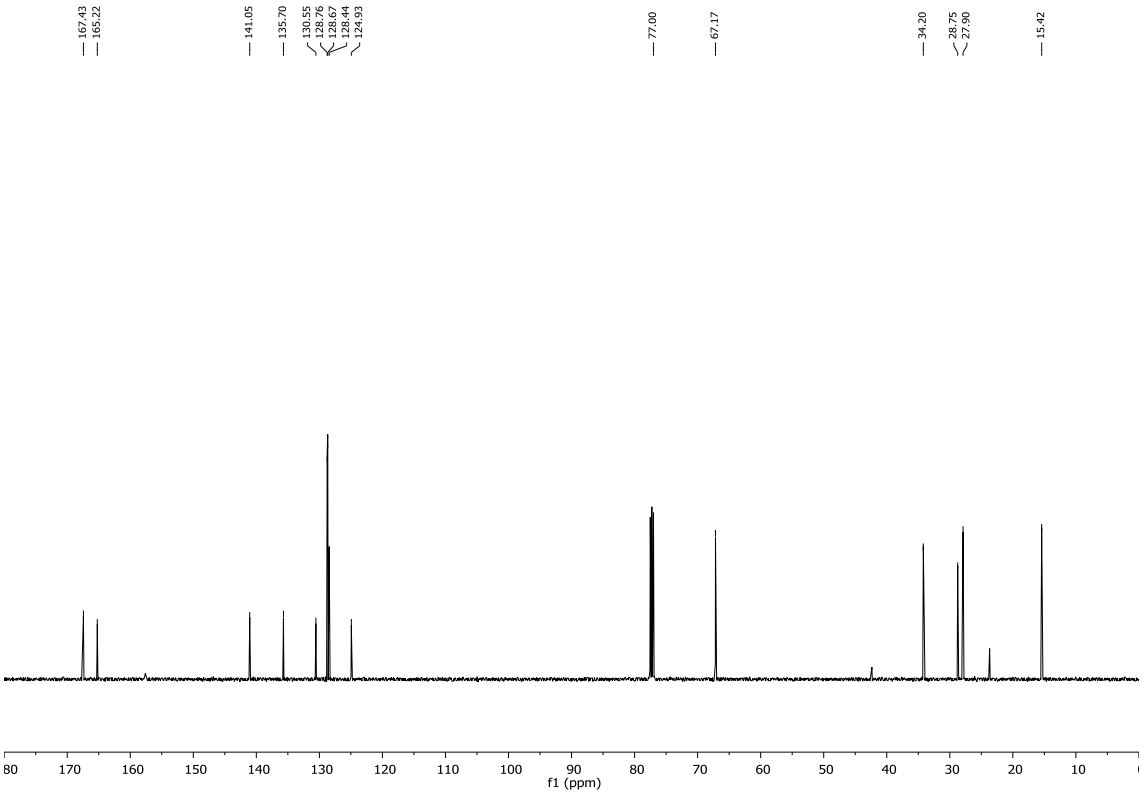


1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (1*R*,2*S*)-3,3-dimethylcyclopropane-1,2-dicarboxylate (47)

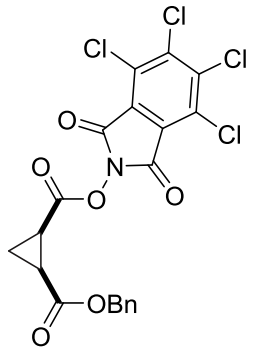


47

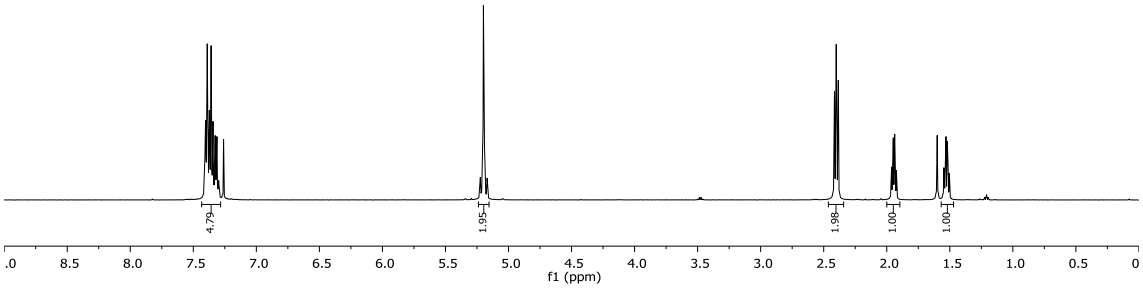


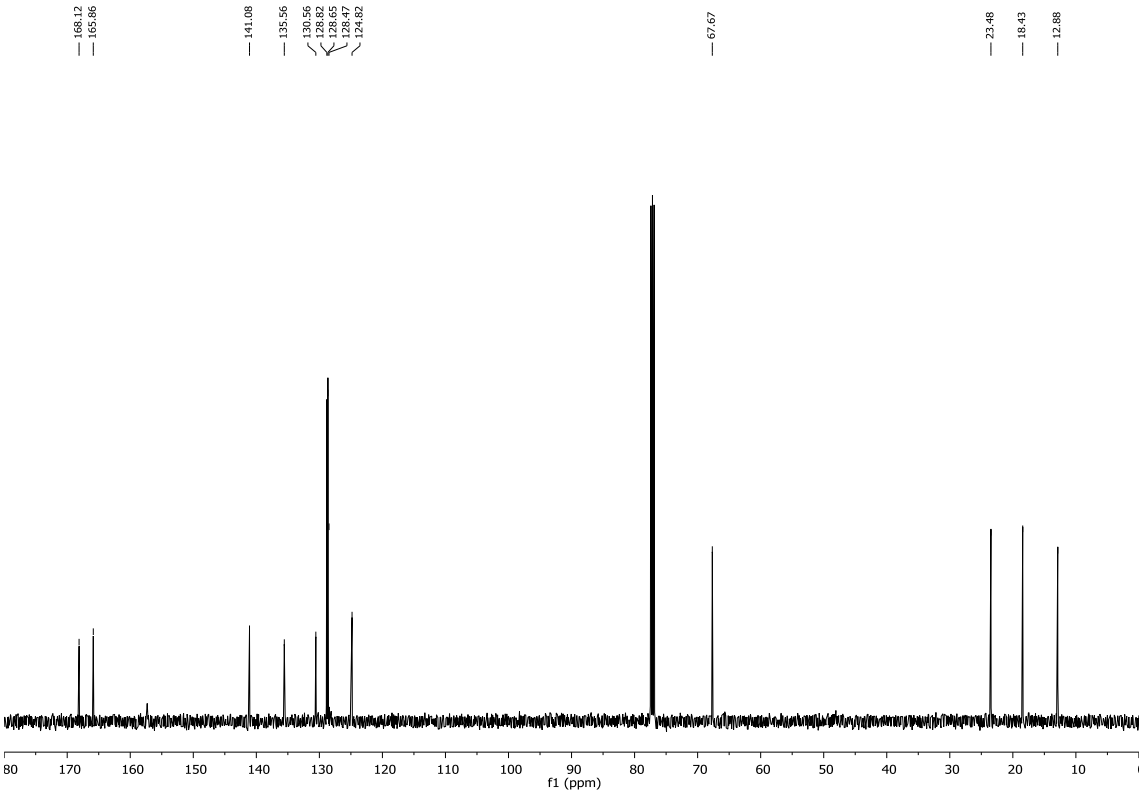


1-Benzyl 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (1*R*,2*S*)-cyclopropane-1,2-dicarboxylate (48)

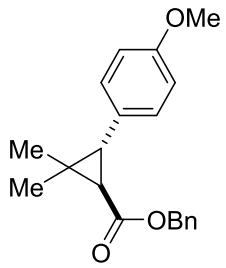


48

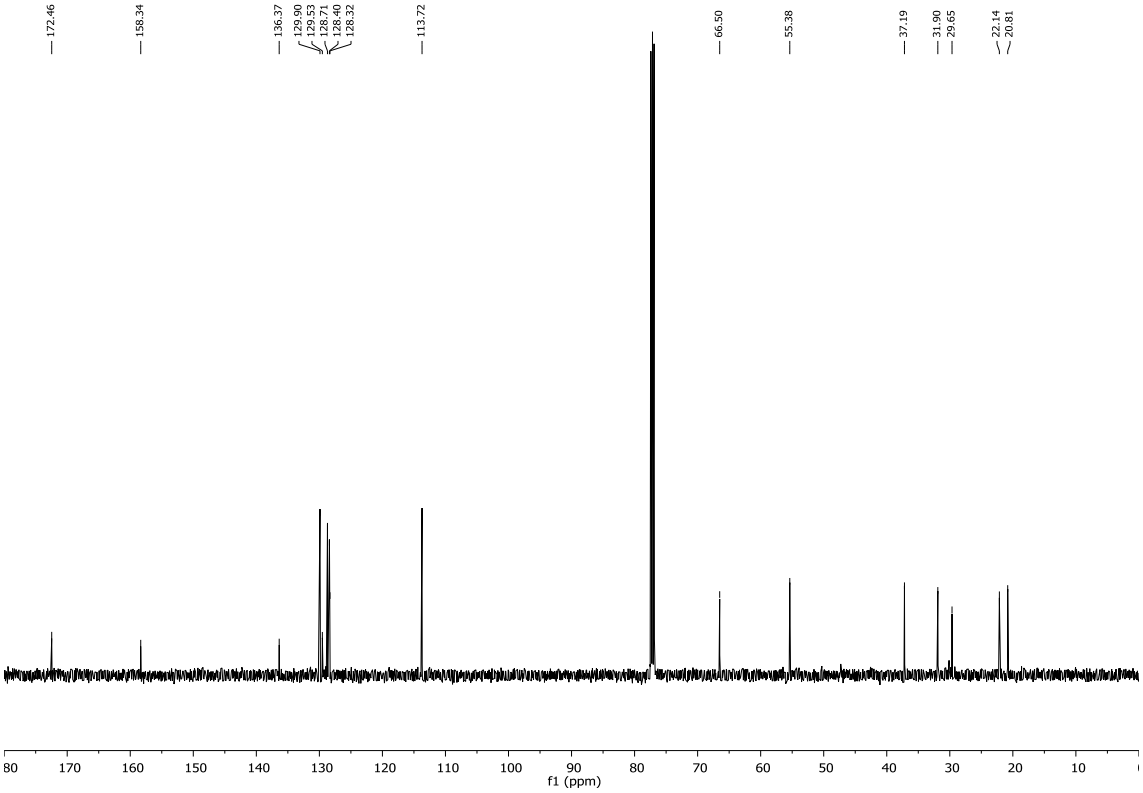




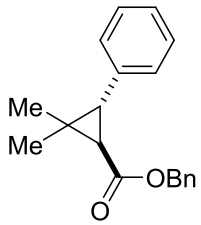
Benzyl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (49a)



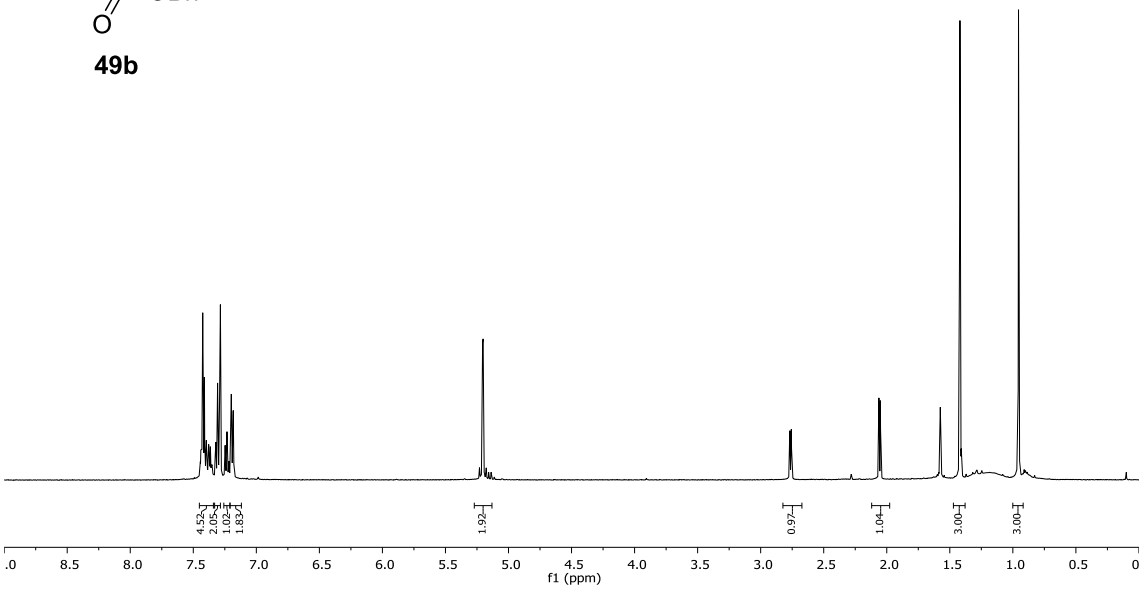
49a

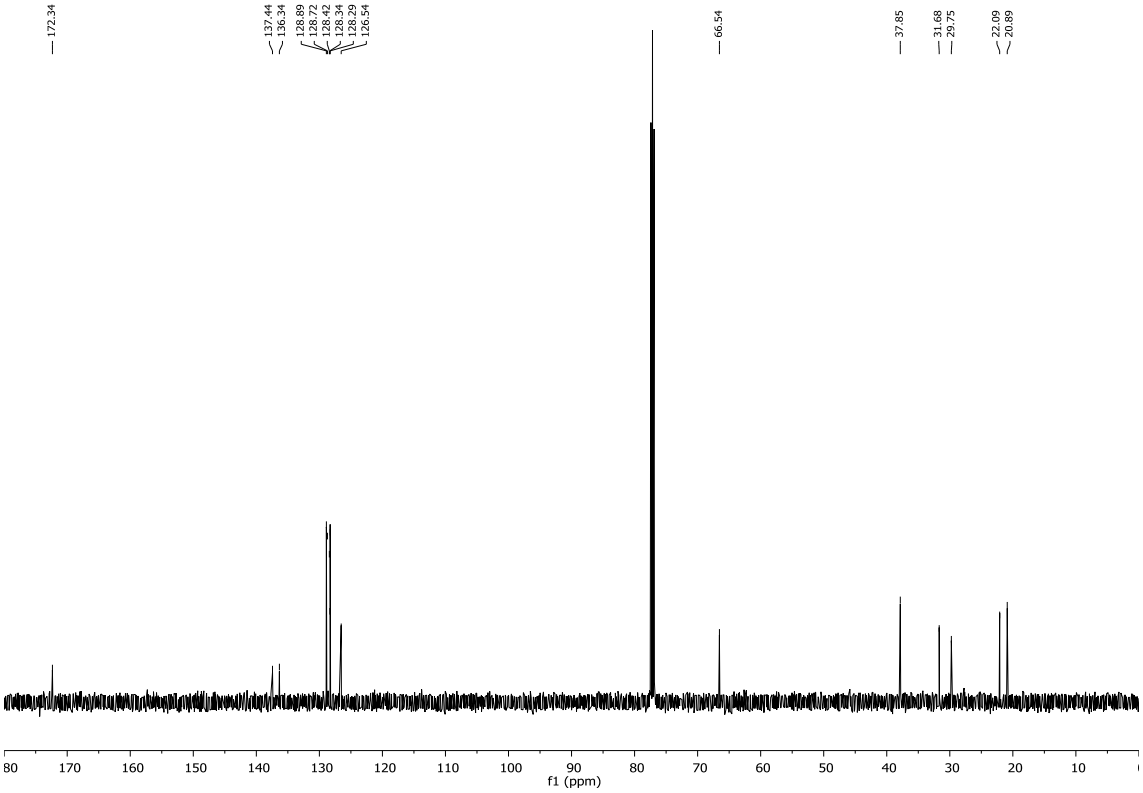


Benzyl (1*R*,3*R*)-2,2-dimethyl-3-phenylcyclopropane-1-carboxylate (49b)

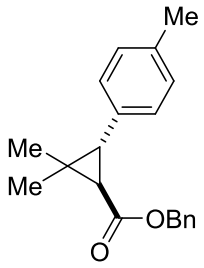


49b

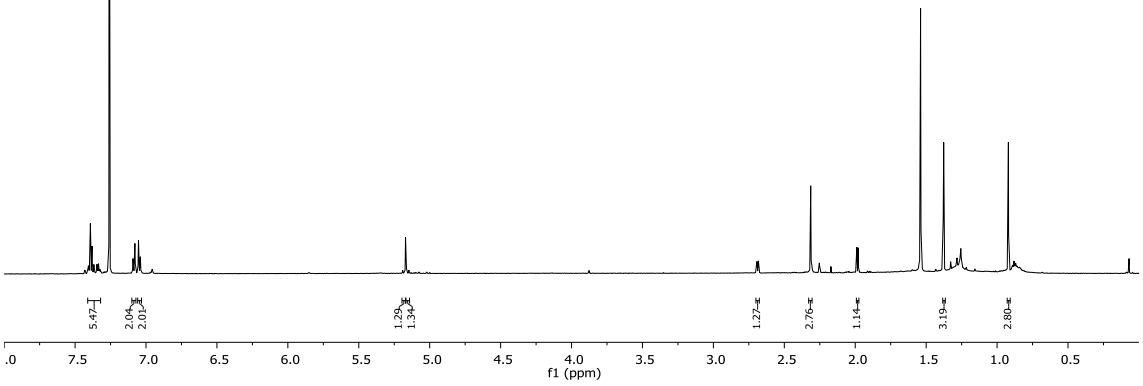


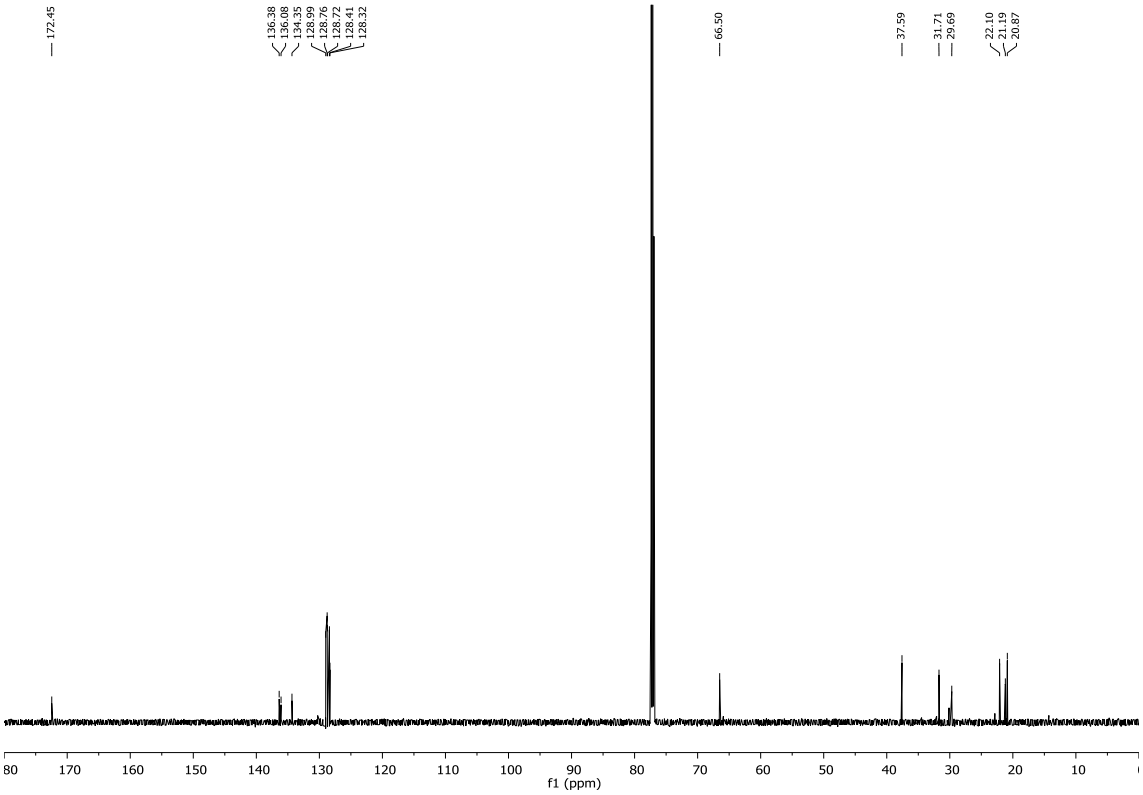


Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropane-1-carboxylate (49c)

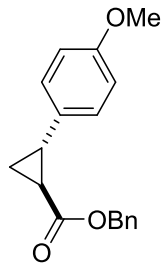


49c

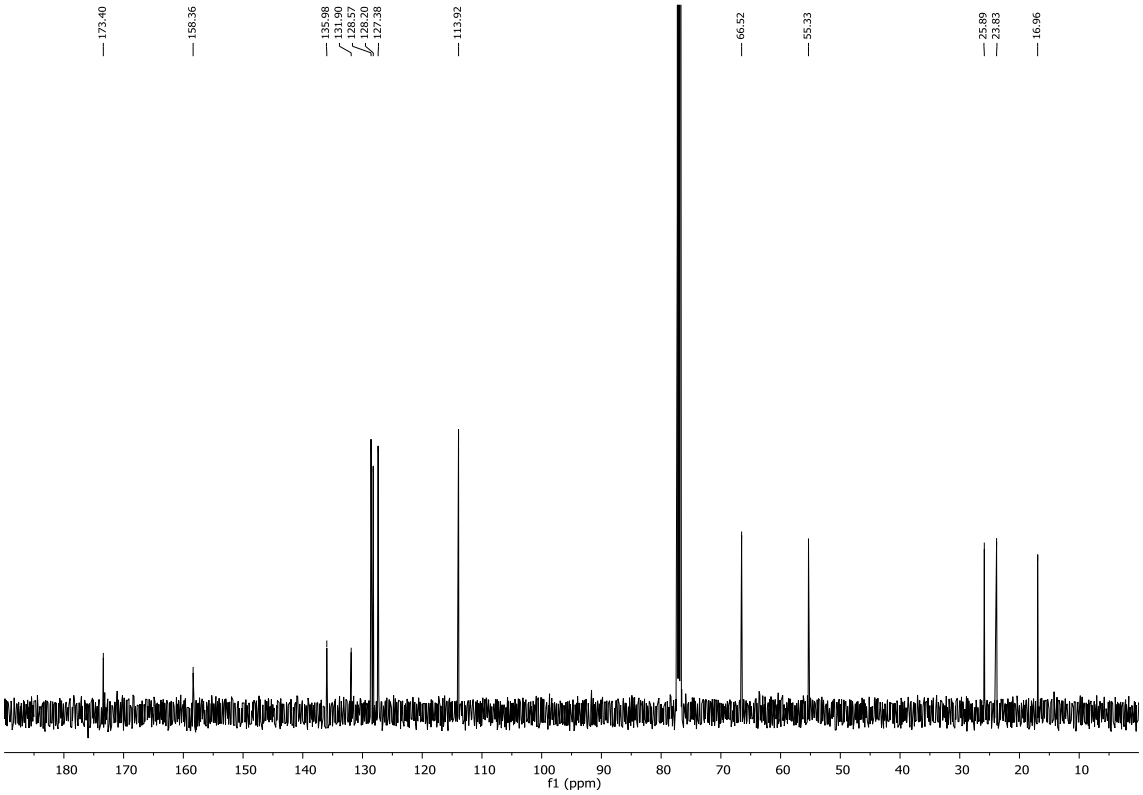




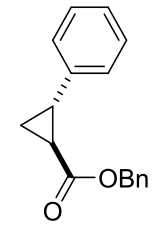
Benzyl (1*S*,2*S*)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (50a)



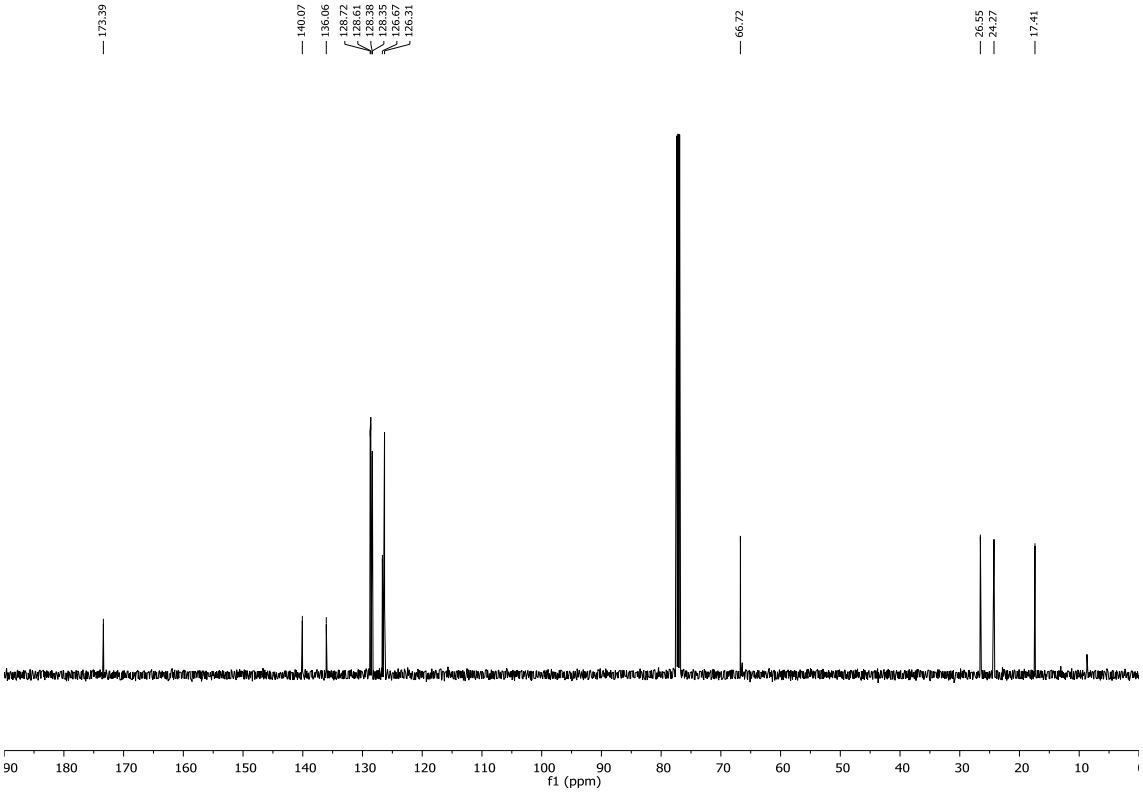
50a



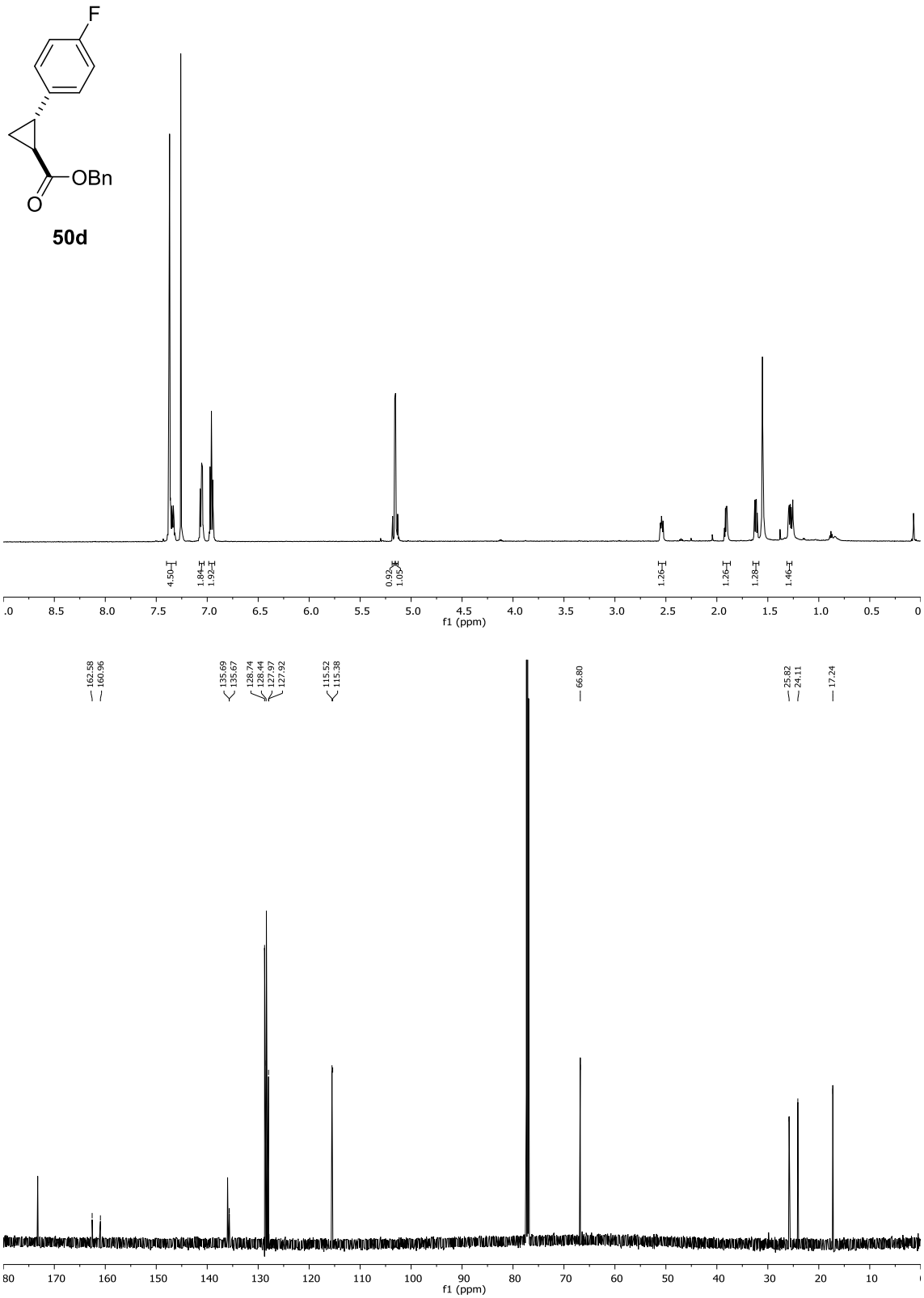
Benzyl (1*S*,2*S*)-2-phenylcyclopropane-1-carboxylate (50b)



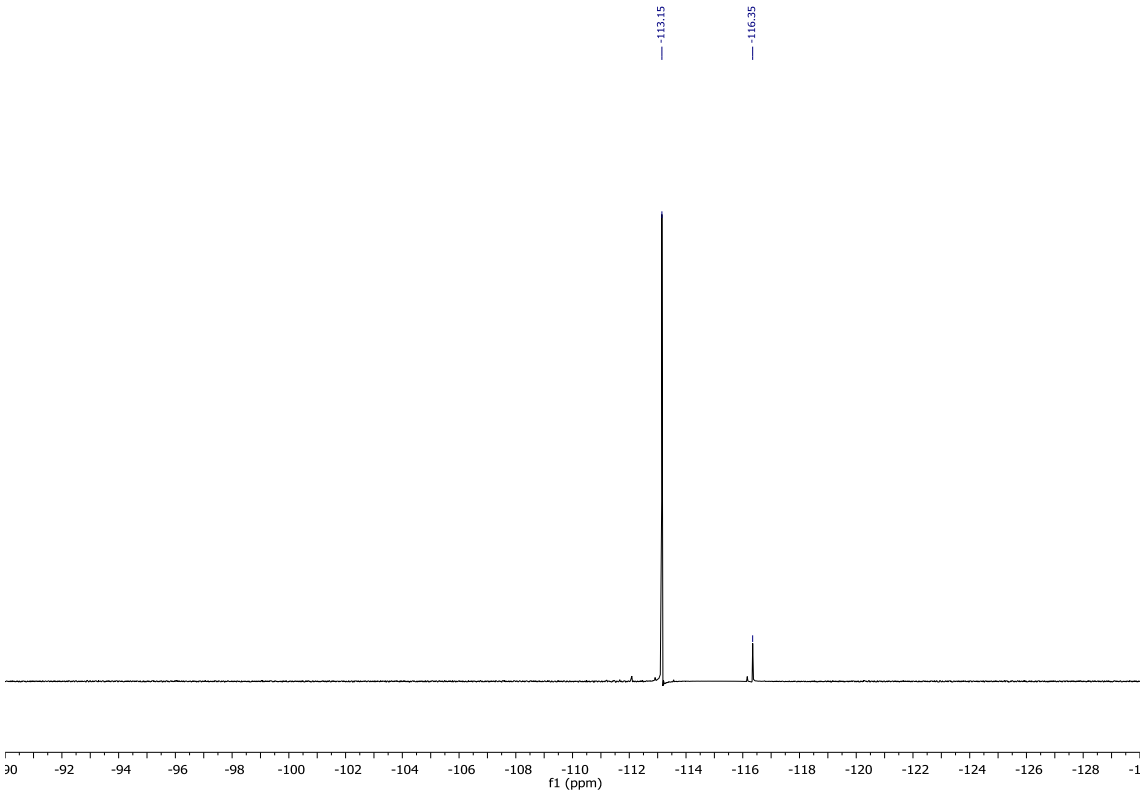
50b



Benzyl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (50d)



^{19}F NMR:


-113.15
-116.35
-92
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-98
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-104
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-108
-110
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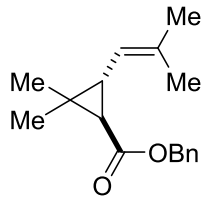
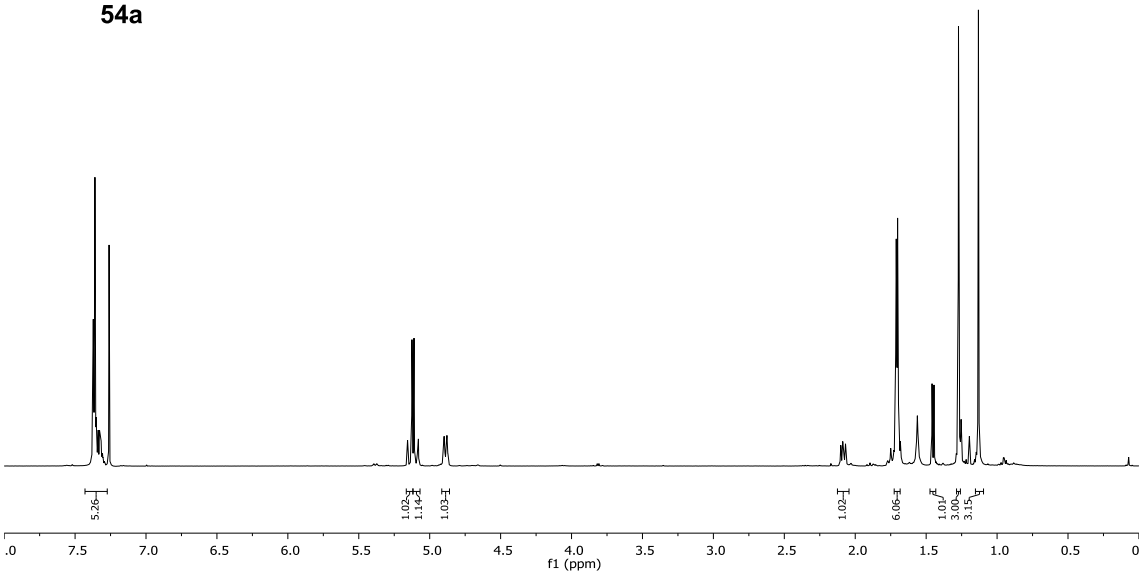
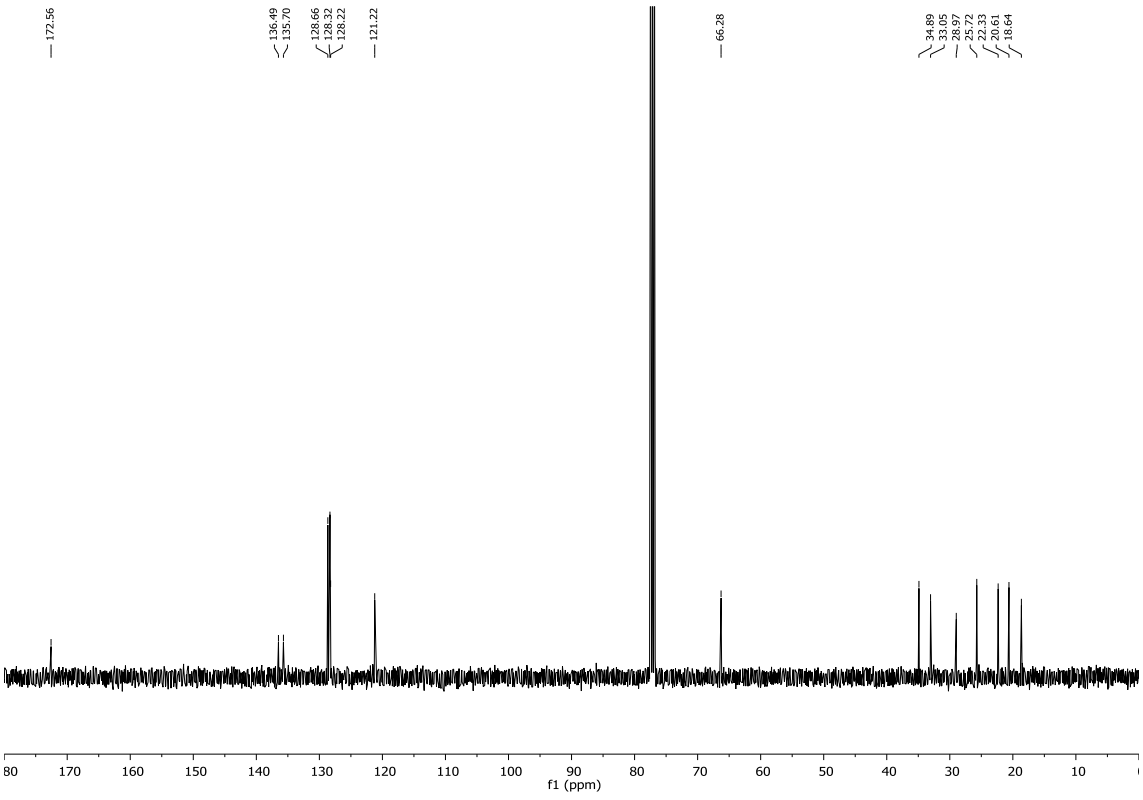
-114
-116
-118
-120
-122
-124
-126
-128
f1 (ppm)

Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate (54a)

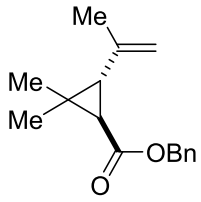


54a

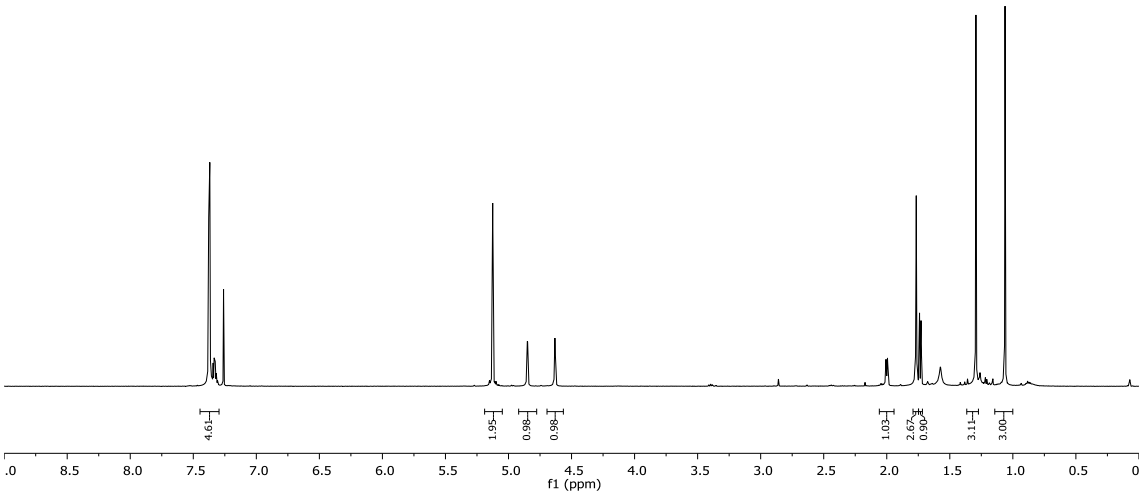


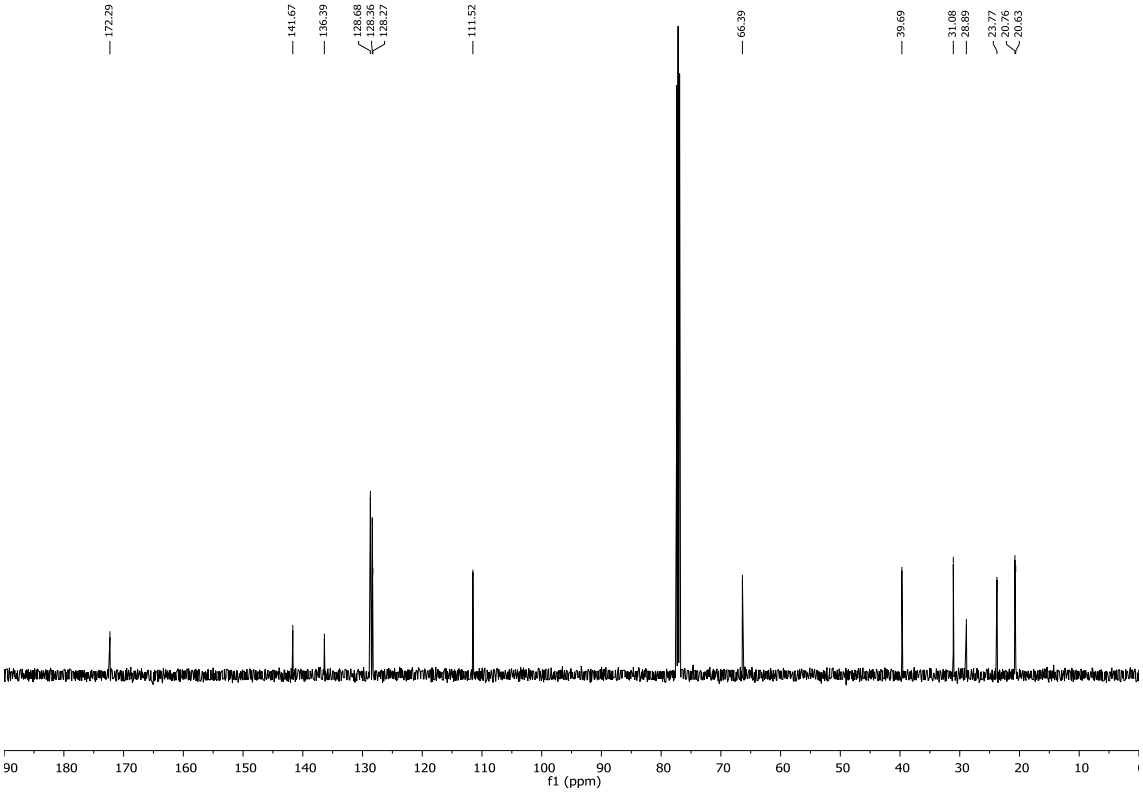


Benzyl (1*R*,3*R*)-2,2-dimethyl-3-(prop-1-en-2-yl)cyclopropane-1-carboxylate (54b)

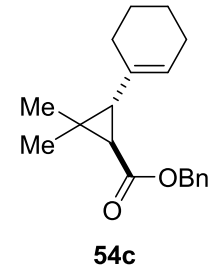


54b

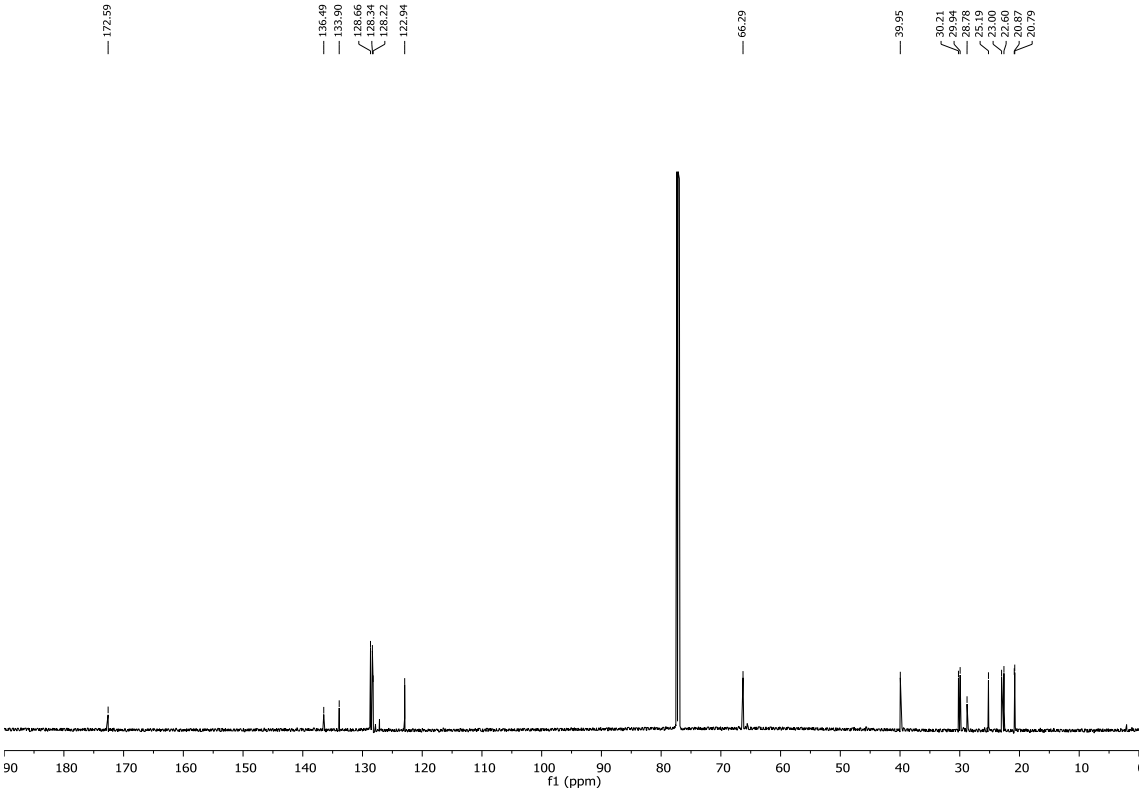




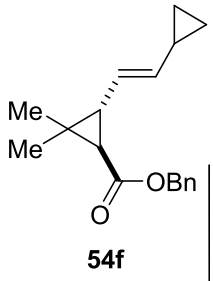
Benzyl (1*R*,3*R*)-3-(cyclohex-1-en-1-yl)-2,2-dimethylcyclopropane-1-carboxylate (54c)



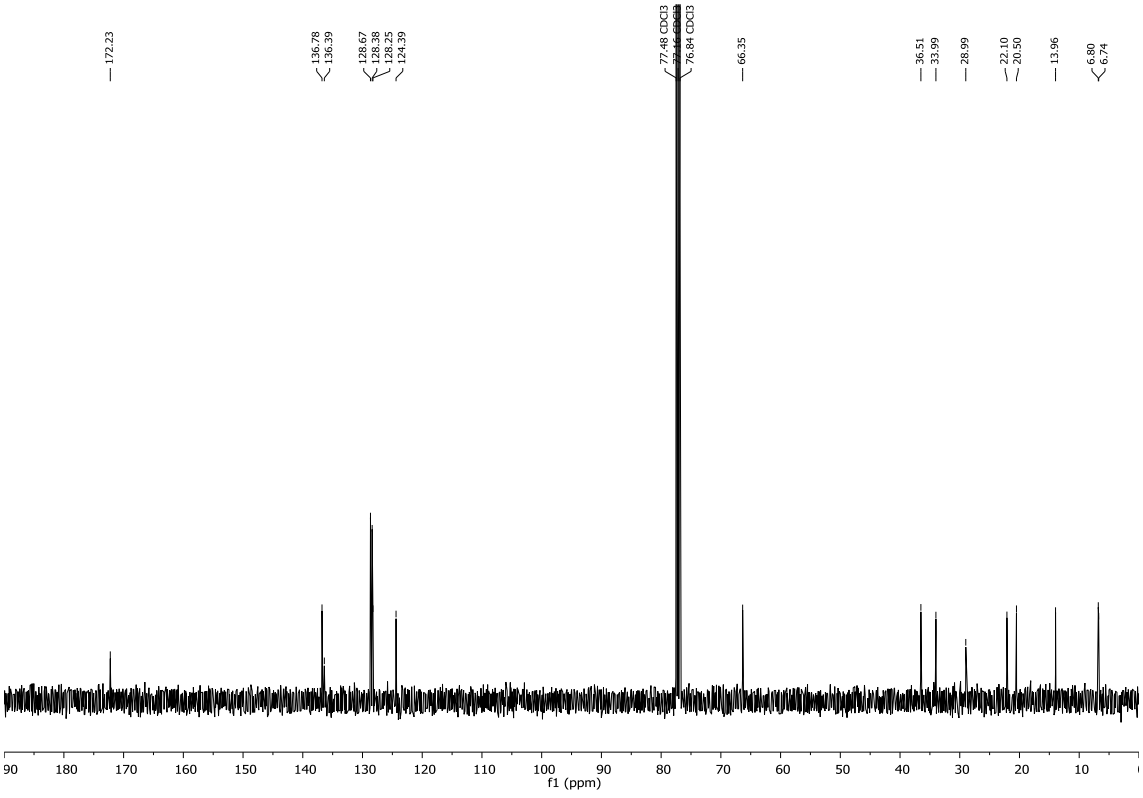
54c



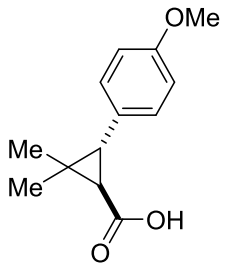
Benzyl (1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropane-1-carboxylate (54f)



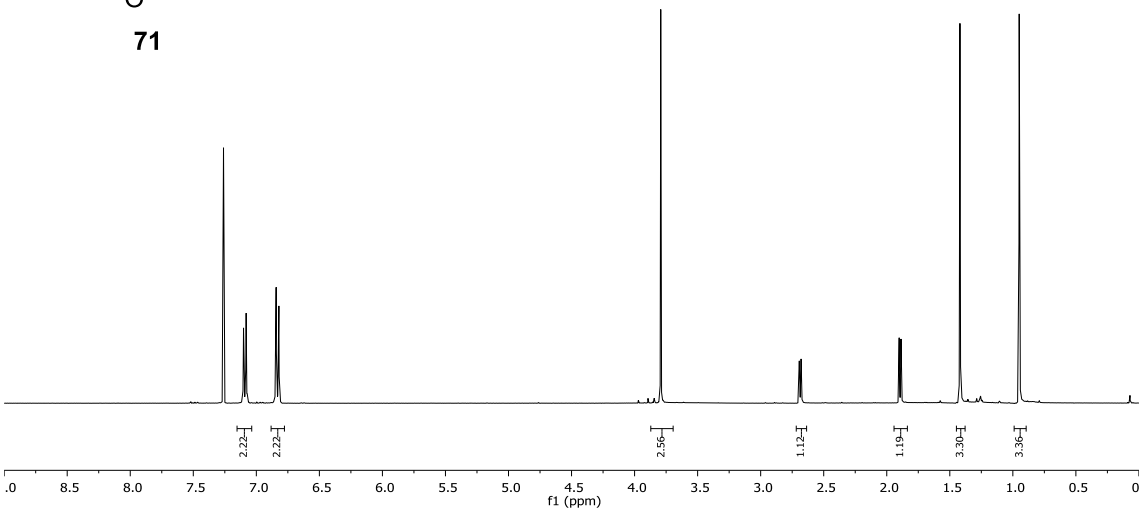
54f

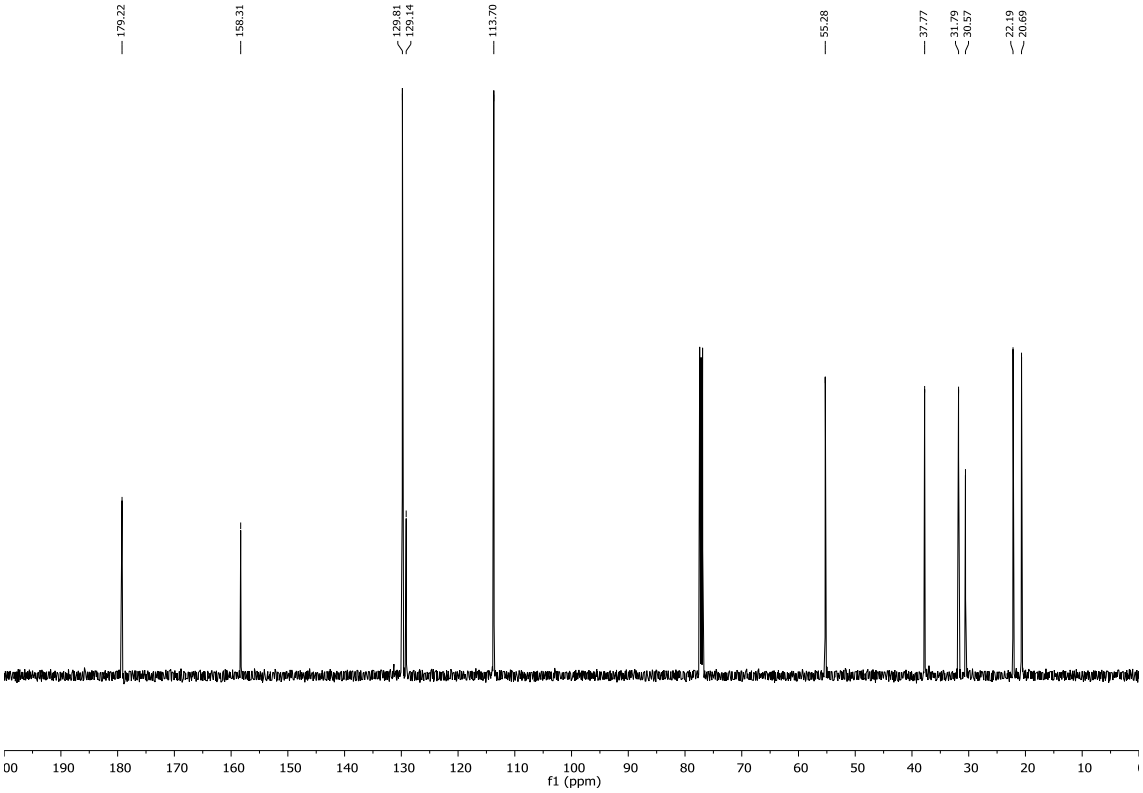


(1*R*,3*R*)-3-(4-Methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylic acid (71)

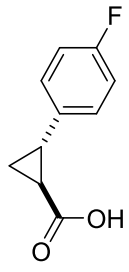


71

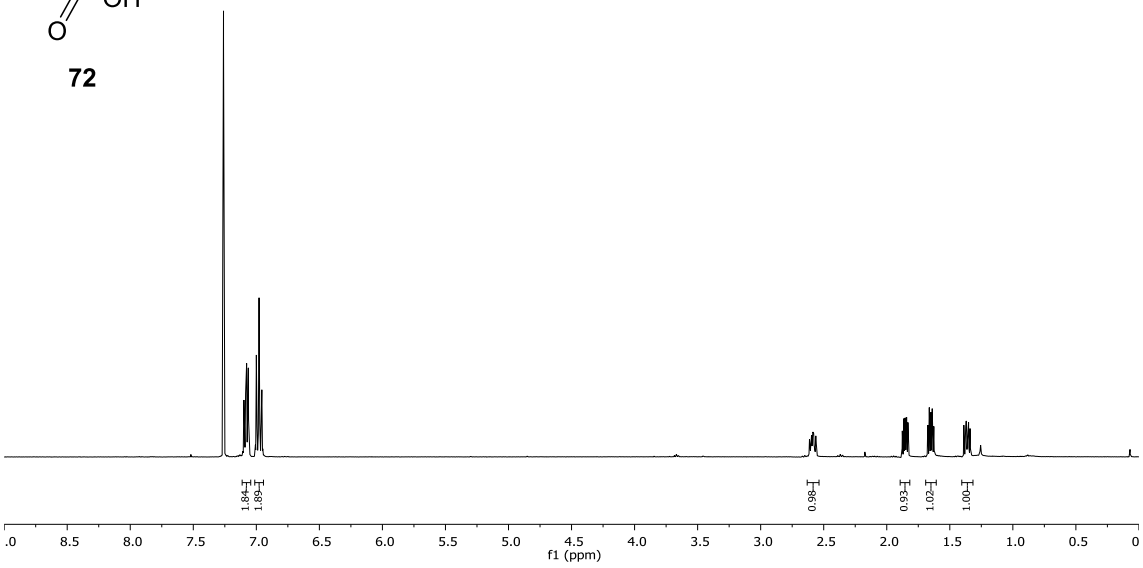


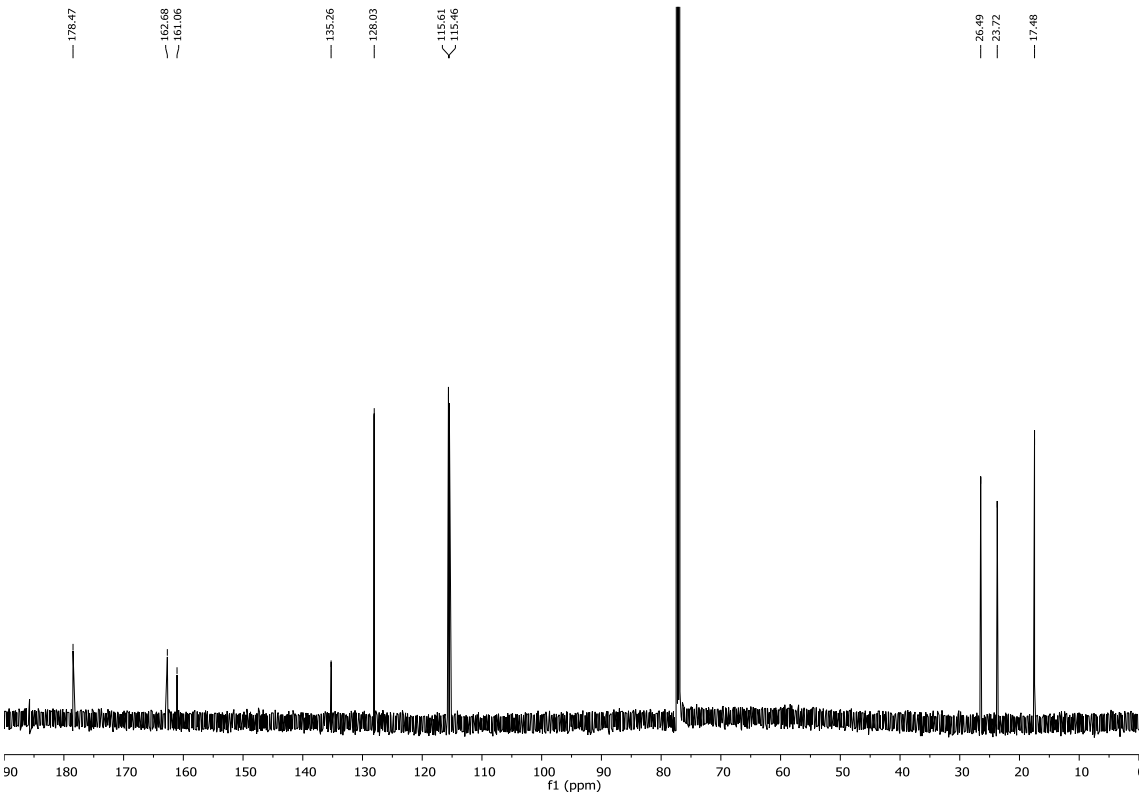


(1*S*,2*S*)-2-(4-Fluorophenyl)cyclopropane-1-carboxylic acid (72)

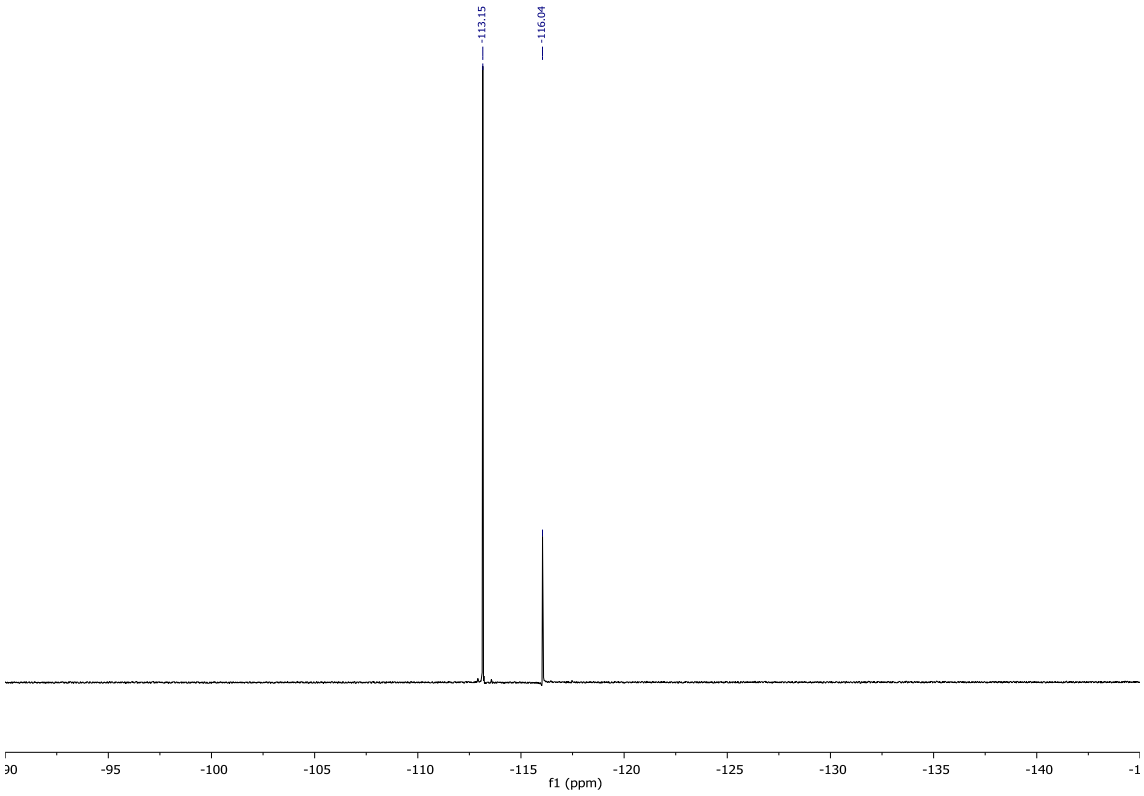


72

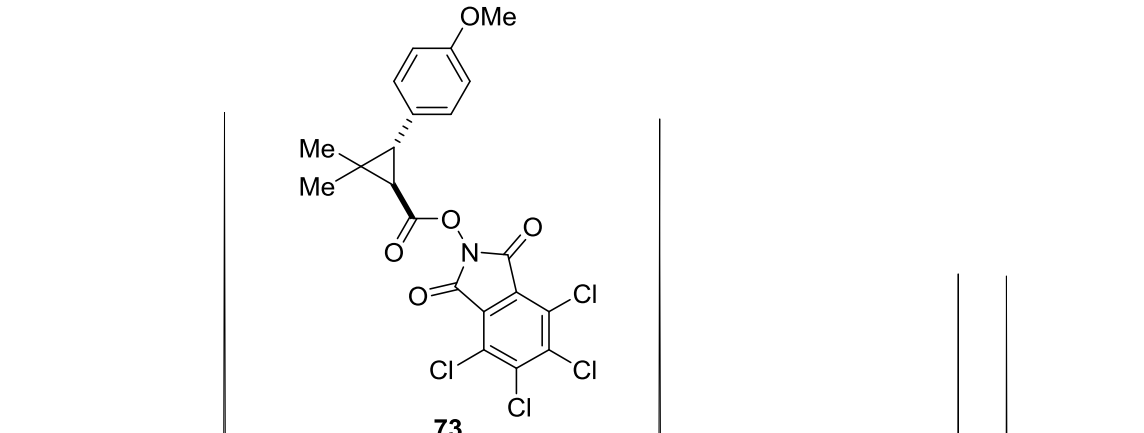




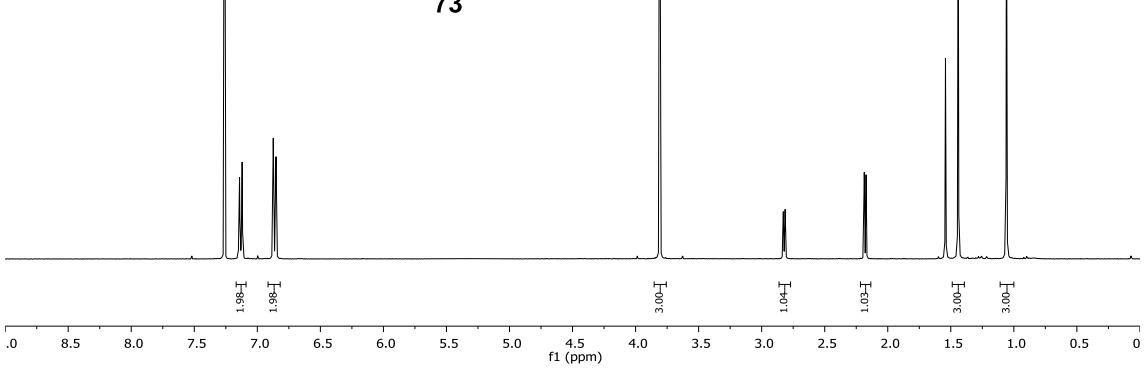
^{19}F NMR:

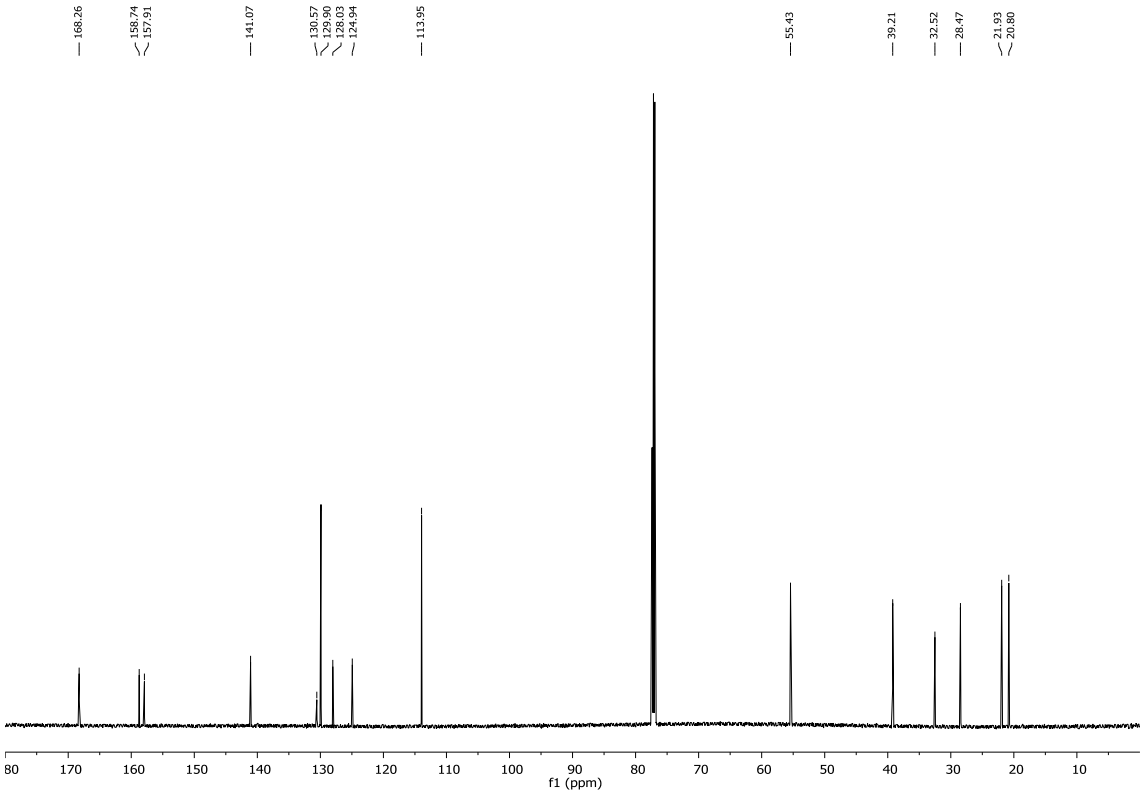


4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl (1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropane-1-carboxylate (73)

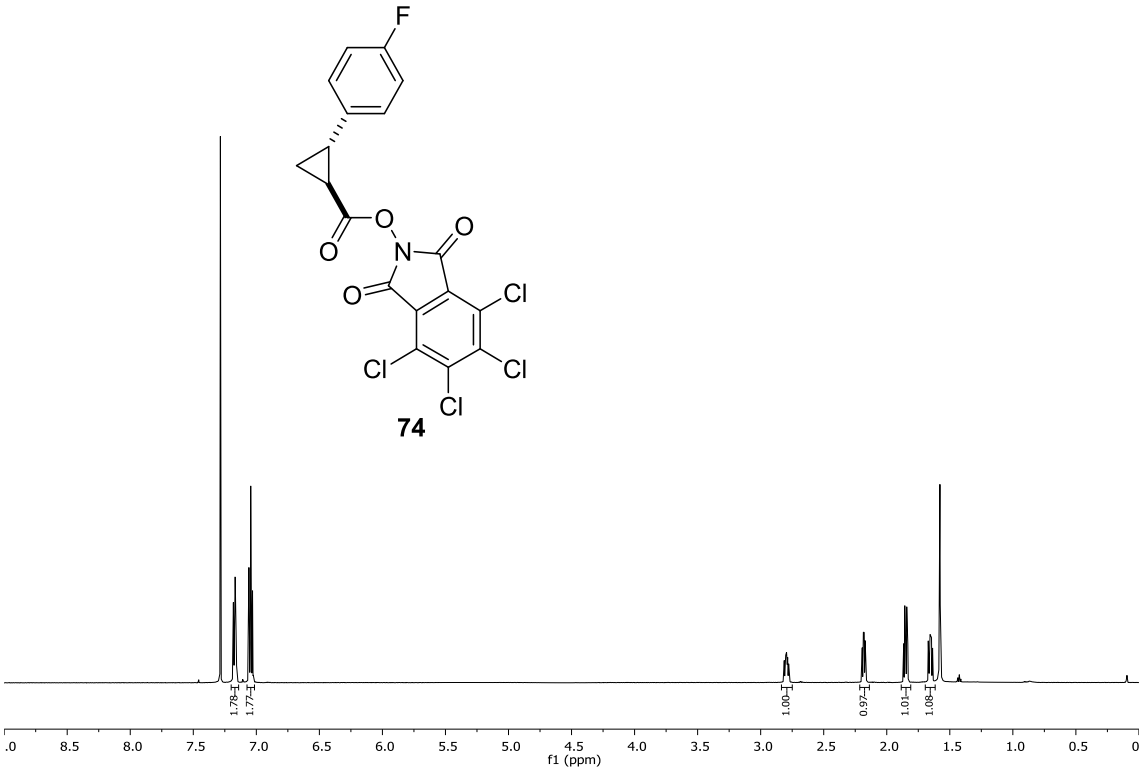


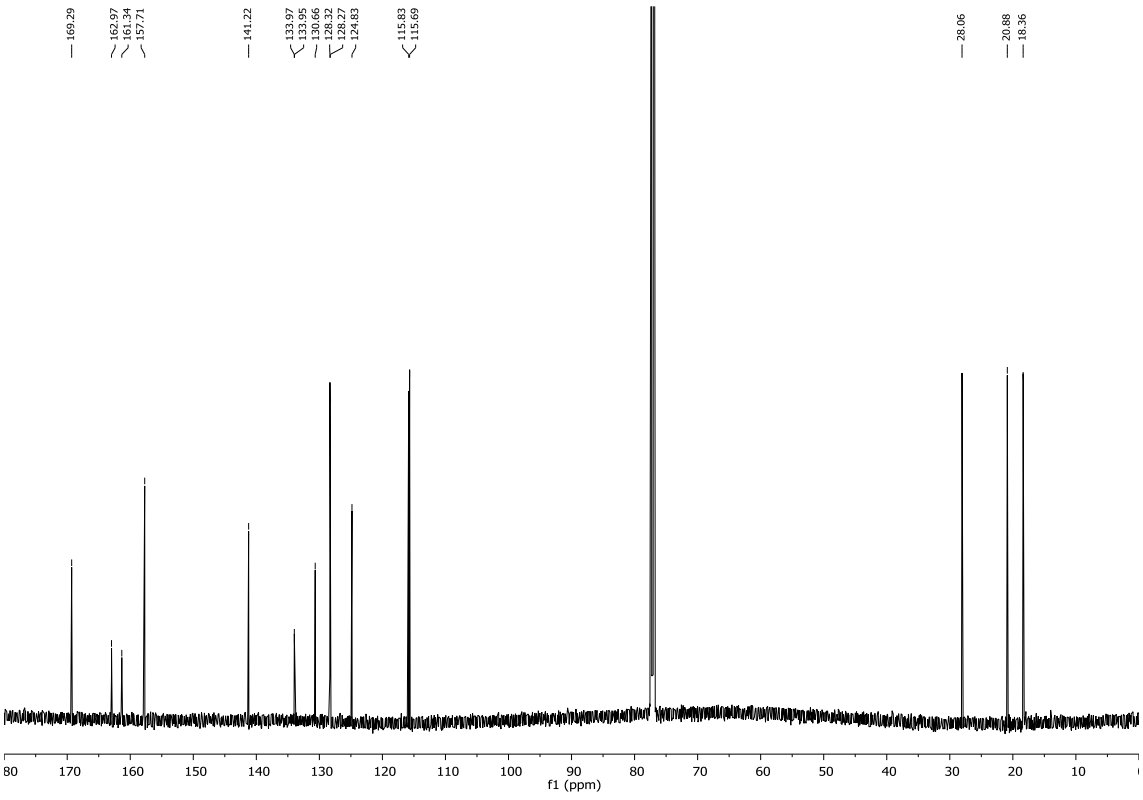
73



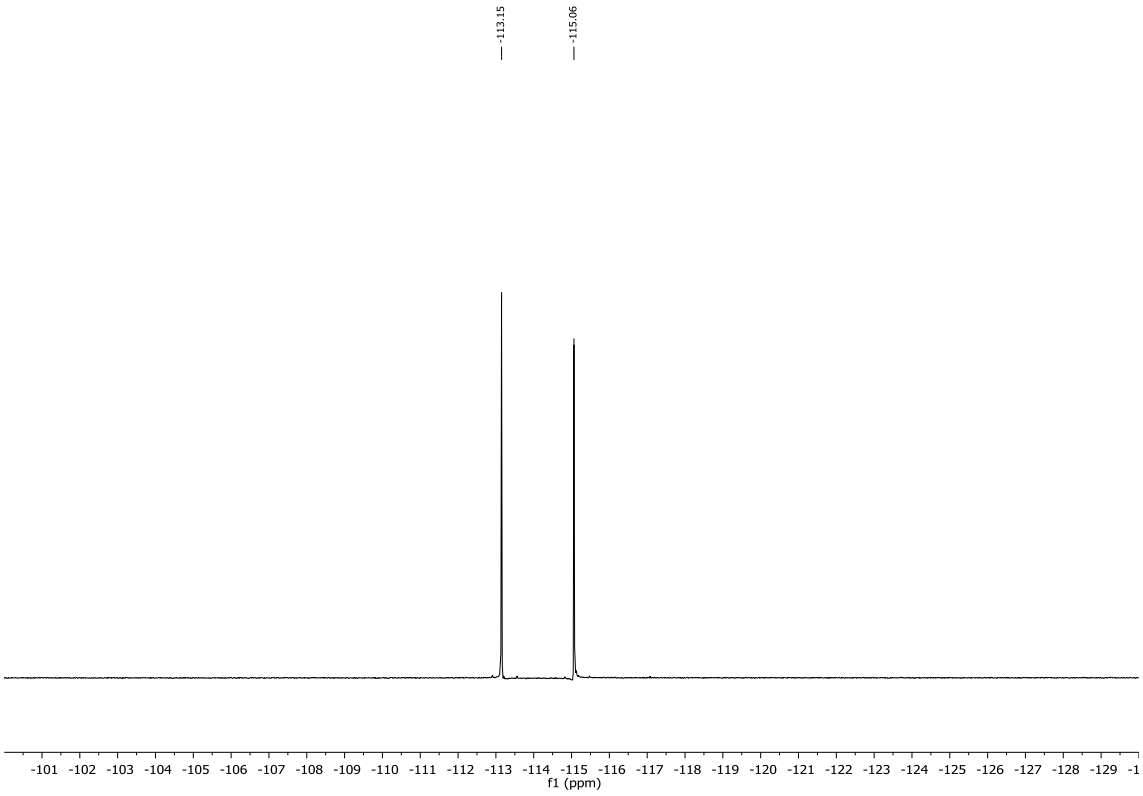


4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl (1*S*,2*S*)-2-(4-fluorophenyl)cyclopropane-1-carboxylate (74)





^{19}F NMR: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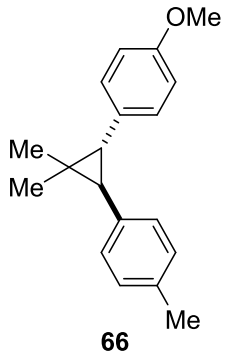
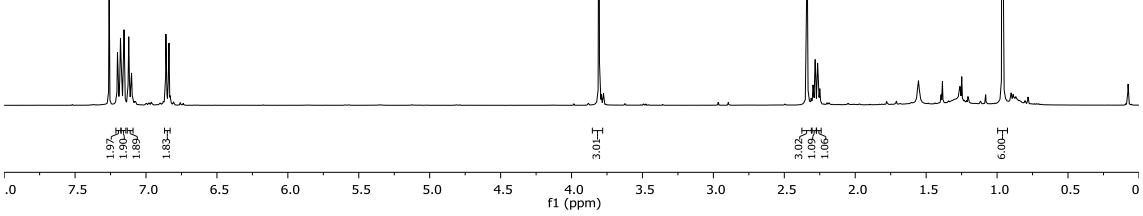
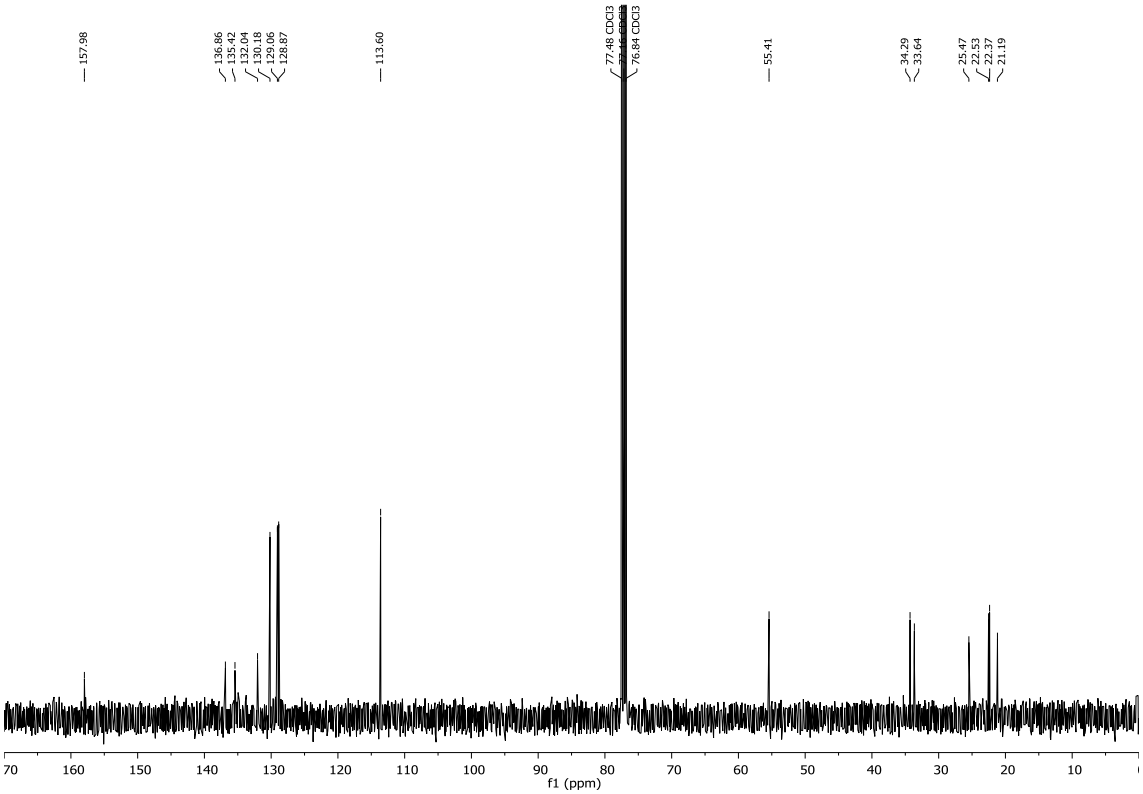
-115.06
-101 -102 -103 -104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128 -129 -1
f1 (ppm)

1-((1*R*,3*R*)-2,2-dimethyl-3-(*p*-tolyl)cyclopropyl)-4-methoxybenzene (66)

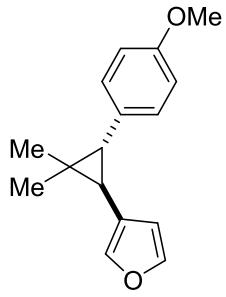


66

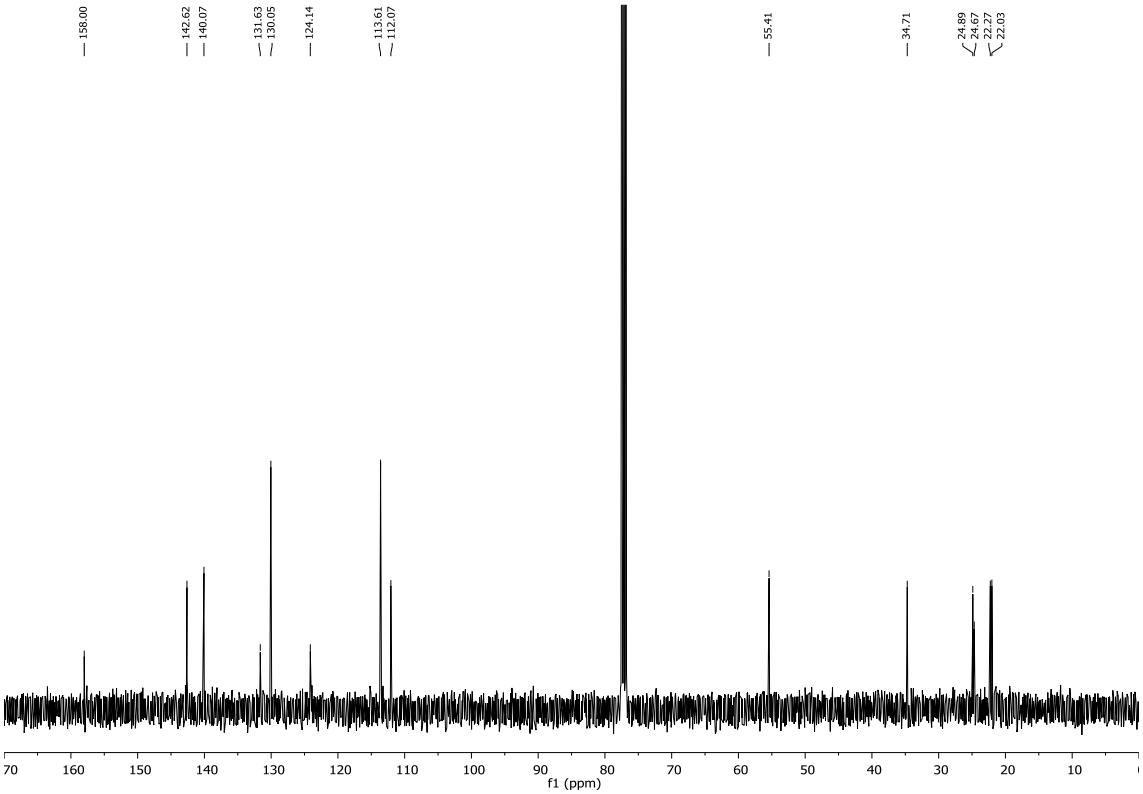




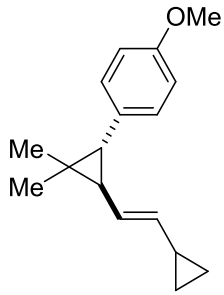
1-((1*R*,3*R*)-3-(4-methoxyphenyl)-2,2-dimethylcyclopropyl)furan (67)



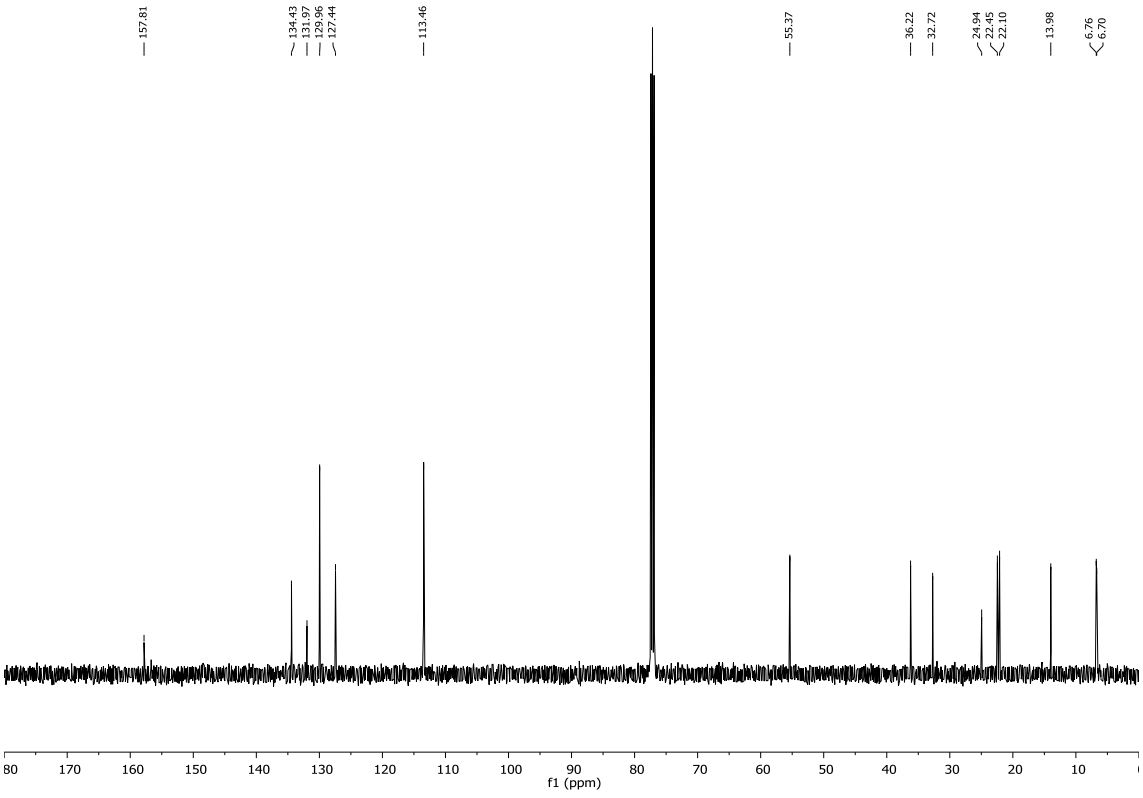
67



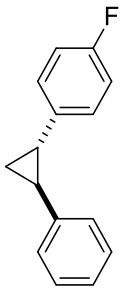
1-((1*R*,3*R*)-3-((*E*)-2-cyclopropylvinyl)-2,2-dimethylcyclopropyl)-4-methoxybenzene (68)



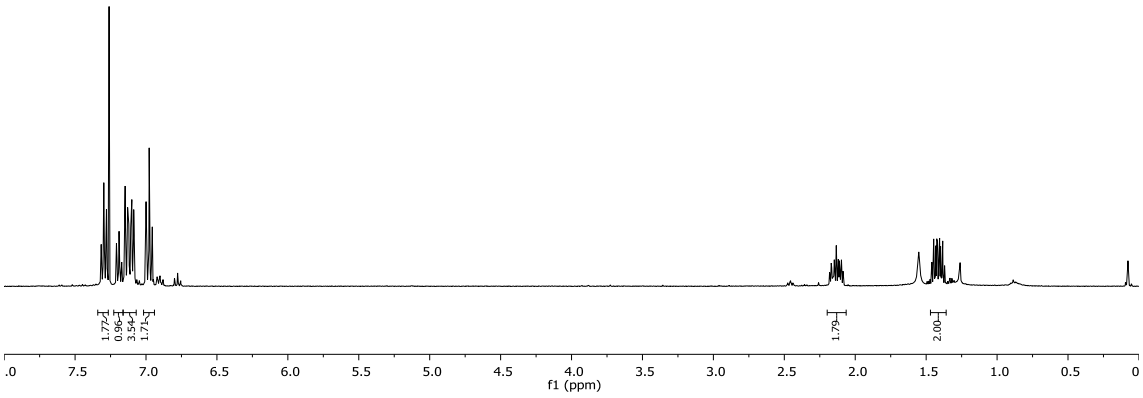
68

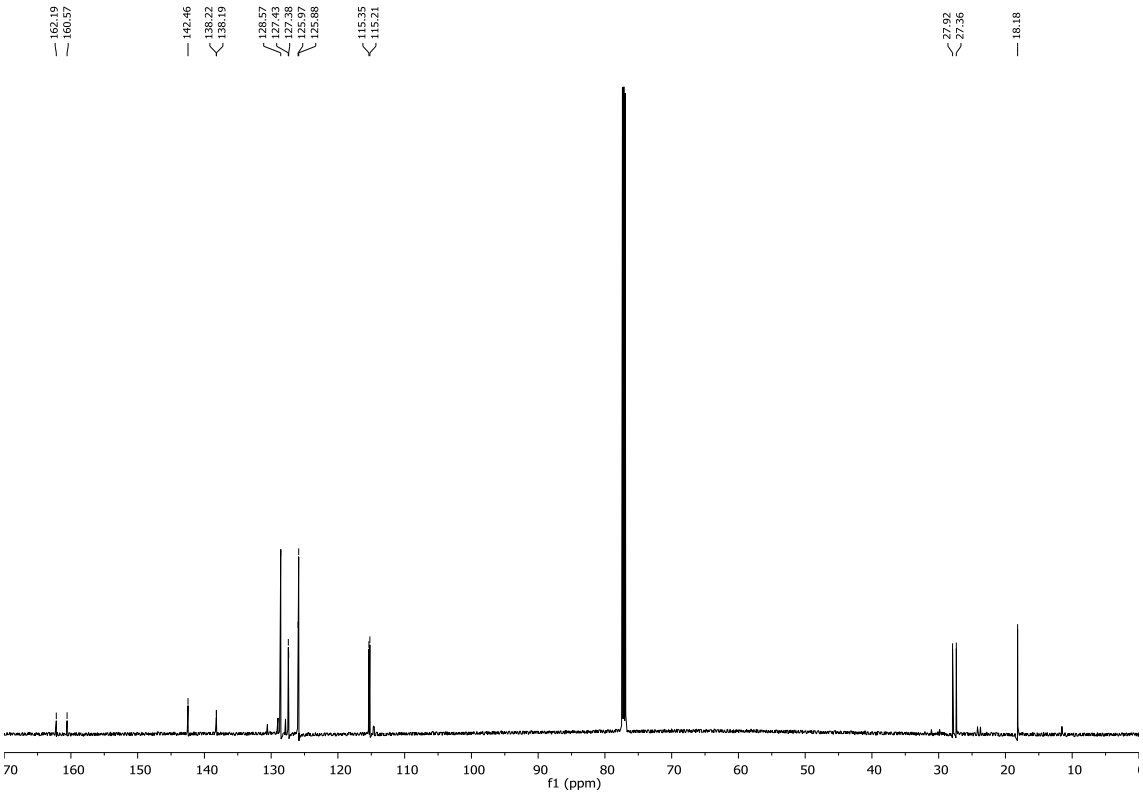


1-Fluoro-4-((1*S*,2*S*)-2-phenylcyclopropyl)benzene (69)

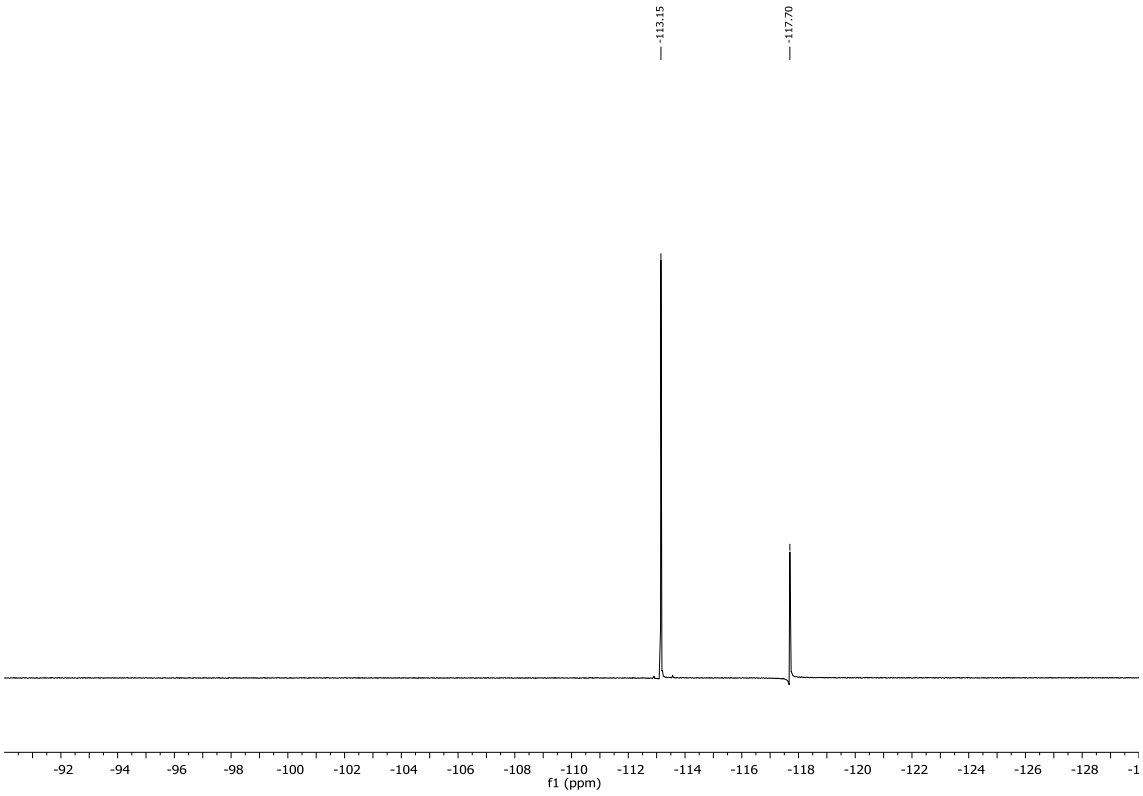


69





^{19}F NMR:


-113.15
-117.70
-92
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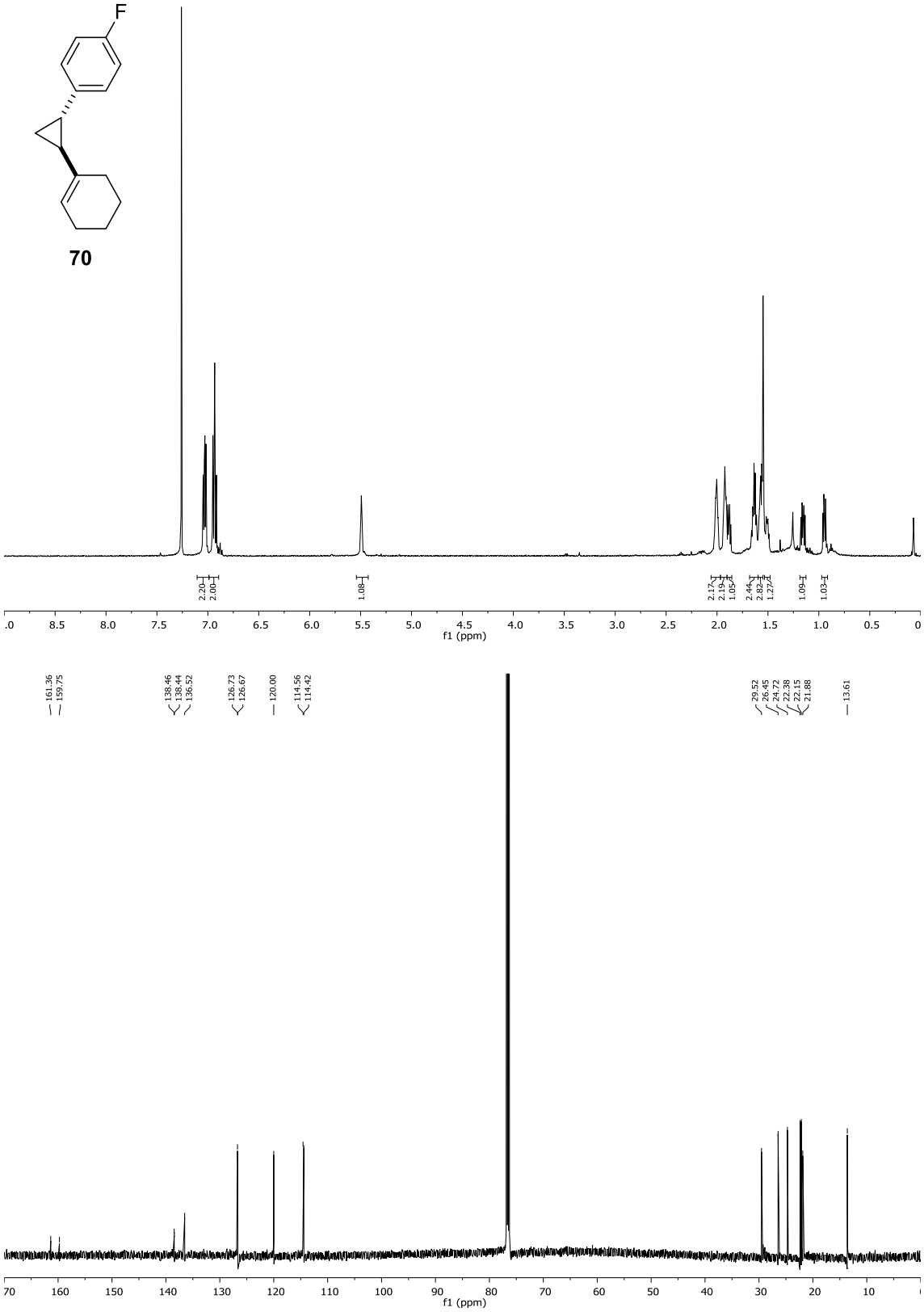
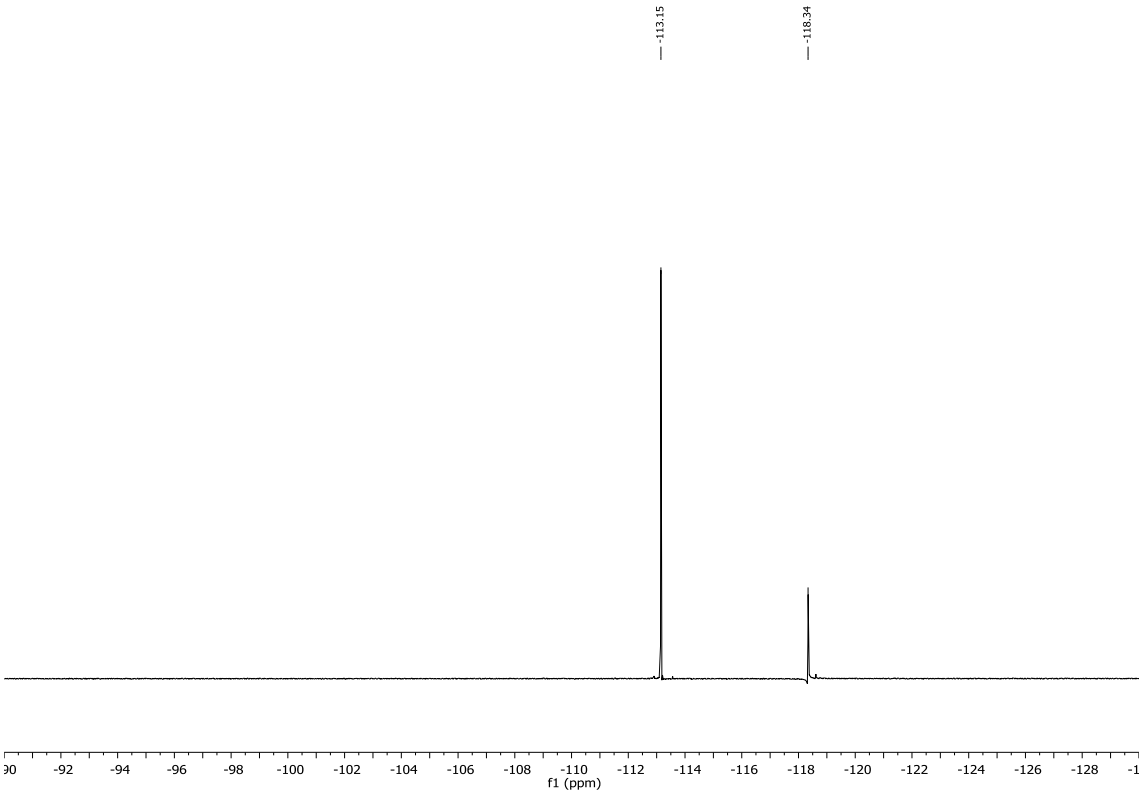
-98
-100
-102
-104
-106
-108
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
f1 (ppm)

1-((1*S*,2*S*)-2-(Cyclohex-1-en-1-yl)cyclopropyl)-4-fluorobenzene (70)



^{19}F NMR:


-113.15
-118.34
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-94
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-98
-100
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-104
-106
-108
-110
-112
-114
-116
-118
-120
-122
-124
-126
-128
f1 (ppm)