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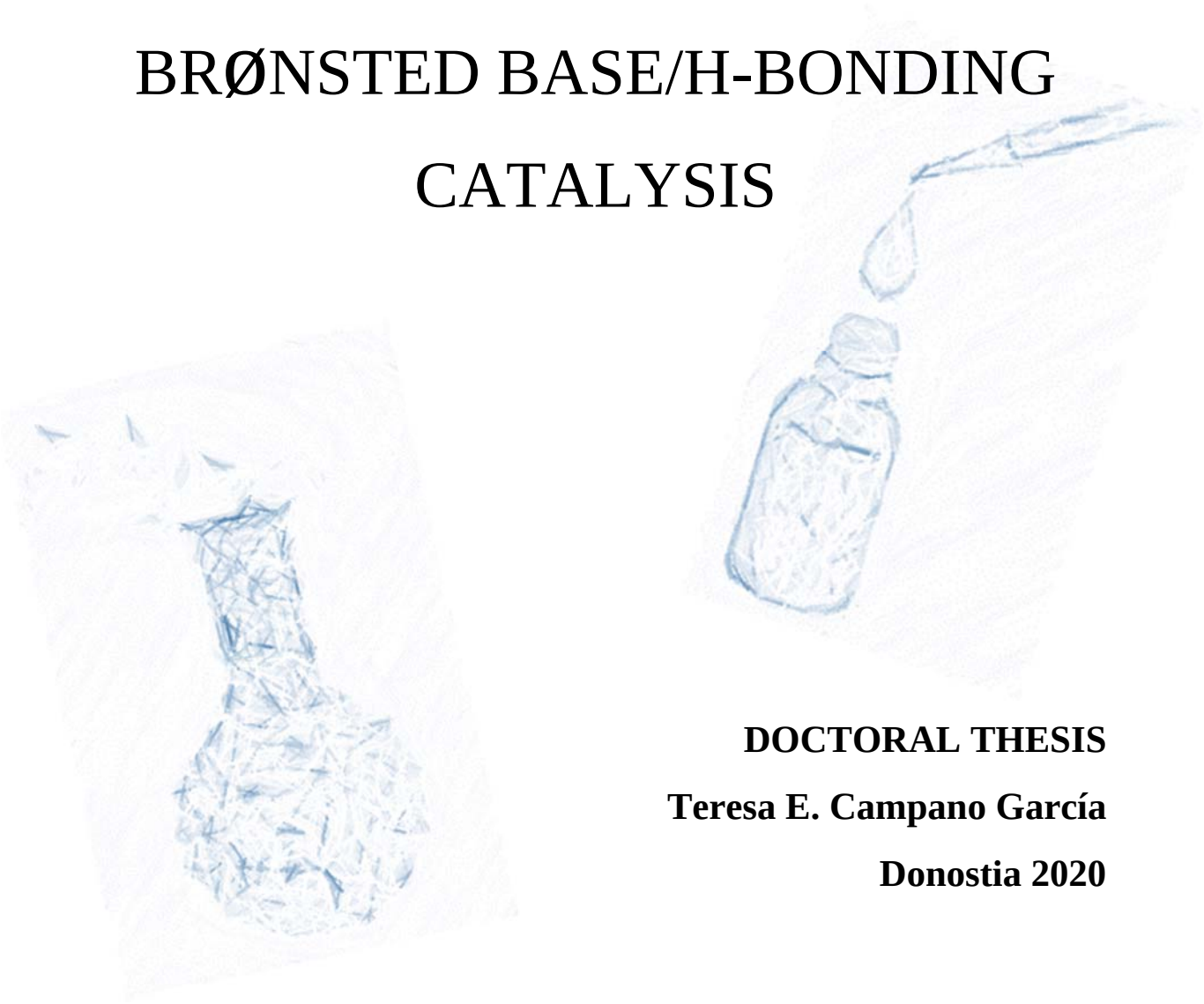
DIRECT ENANTIOSELECTIVE MICHAEL REACTIONS OF KETONES AND ALDEHYDES WITH NITROALKENES UNDER BRØNSTED BASE/H-BONDING CATALYSIS



DOCTORAL THESIS

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Summary

The development of catalytic methods for the proliferation of simple molecules through new C–C bond forming processes resulting in configurationally defined and functionally more complex structures represents a constant goal in the field of organic synthesis. Thus, direct protocols for the stereoselective α-functionalization of enolizable carbonyl compounds have been widely studied in the last years.

C–C bond forming reactions require an exquisite control of the intervening enolate geometry and the stereochemistry of the subsequent C-C bond formation in order to achieve enantiomerically pure compounds. In asymmetric catalysis, this task is usually performed by the catalyst by itself. Nevertheless, despite the progress in this field, a limitation is still the need of pronucleophiles with relatively high acidity; so 1,3-dicarbonyl compounds, related derivatives or nitroalkanes are generally the used substrates. Other less acidic carbonyl compounds such as simple ketones or aldehydes can just be employed as pronucleophiles in organocatalysis *via* enamine. Albeit, in the case of ketones, this activation mode is usually restricted to symmetrically substituted ones, owing to the difficulty in controlling the geometry and conformation of the enamine intermediate in the case of unsymmetrically substituted ketones, which therefore, involves the loss of stereoselectivity in the final adduct. An additional problem associated to aldehydes, in this context, is the complication for an effective control of enolate or enol side reactions, causing self-additions, Cannizzaro and/or Tishchenko disproportionations. Particularly, in the case of soft Brønsted base catalysis, the pK_a values of aldehydes (pK_a ~ 17) and ketones (pK_a ~ 22) makes their deprotonation difficult, which complicates their use as nucleophiles through this activation pathway.

Therefore, the aim of this PhD Thesis has been to explore the extension of Brønsted base catalysis under soft enolization conditions to ketones and aldehydes. For these investigations, the Michael addition to nitroolefins was selected due to the versatility of this transformation and to the presence of the nitro group, which acts as masked precursor of other several functional groups.

In order to increase the acidity of the α-carbon in acyl type substrates, three strategies are generally employed: (i) the use of carbonyl compounds with an electron withdrawing substituent at the α-carbon (Figure 1a), (ii) the use of carbonyl compounds with an electron withdrawing substituent adjacent to the carbonyl moiety (*ipso*-position,

Figure 1b) or (iii) the use of carbonyl compounds which incorporate a group enabling chelation with metals and/or through H-bonding (Figure 1c).

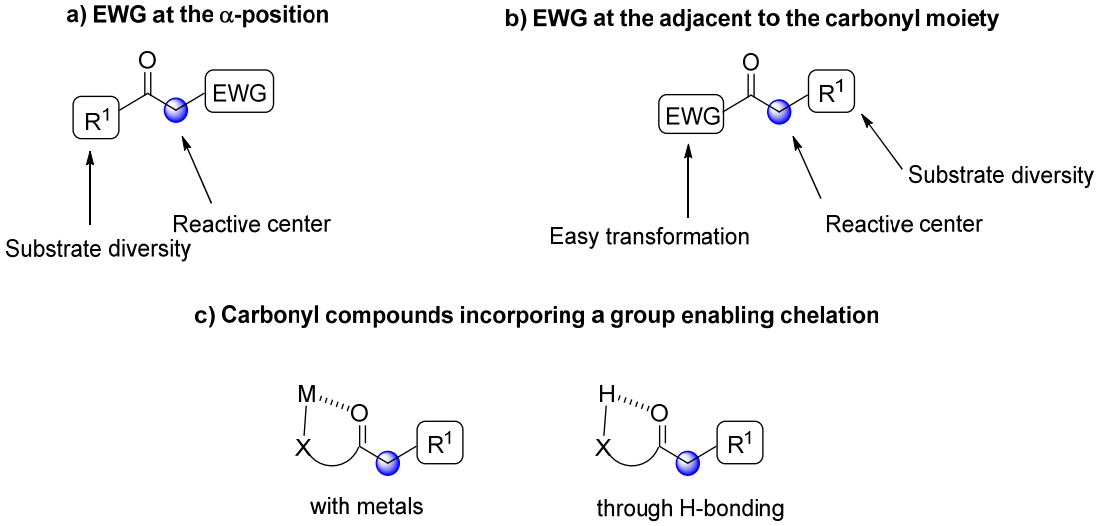


Figure 1. Strategies for increasing acidity of acyl-type substrates.

Following the third pathway, our laboratory reported the use of camphor-derived α'-oxy ketones and α'-hydroxy enones (Figure 2a and 2b respectively) in metal-catalyzed processes. Moreover, our group have also demonstrated that α'-hydroxy enones (Figure 2c) are effective substrates as Michael acceptor for diastereoselective cycloadditions and 1,4-conjugate additions promoted by metal-catalysis (*Chem. Soc. Rev.* **2012**, *41*, 4150–4164) as well as enantioselective Michael reactions promoted by organocatalysis (*J. Am. Chem. Soc.* **2014**, *136*, 17869–17881).

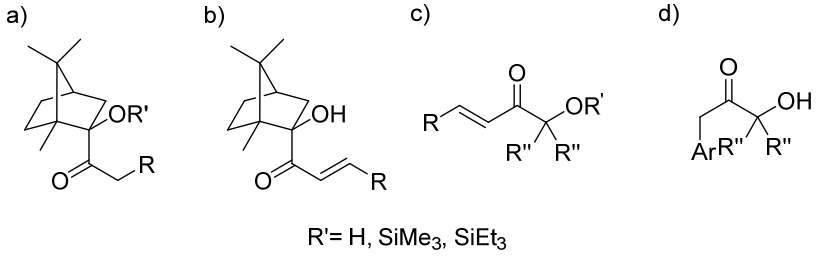
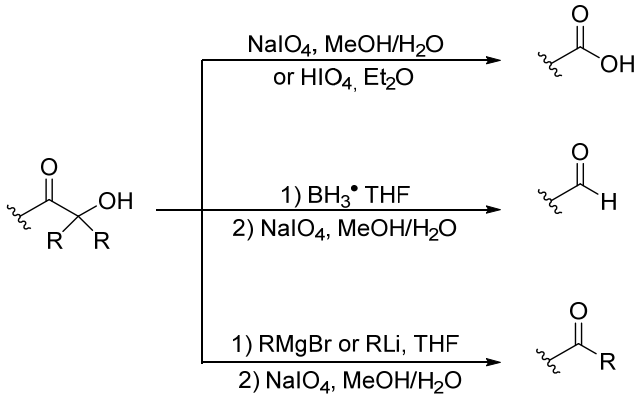


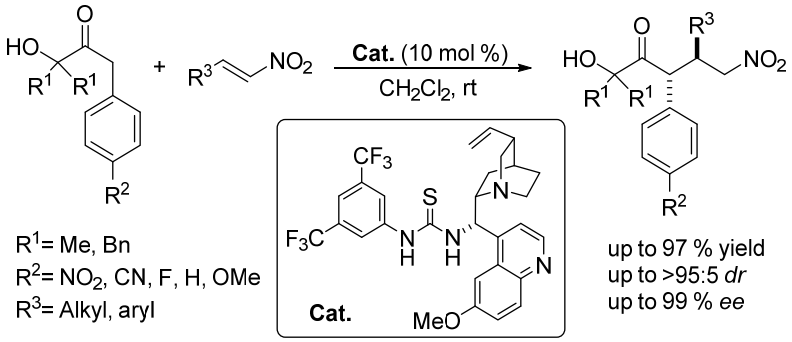
Figure 2. α'-Oxy ketone/enone templates.

In all these cases, the ketol moiety is significant for stereoselective control. Furthermore, in the final adducts it can be cleaved to provide functionalized carboxylic acids, ketones or aldehydes otherwise of difficult access (Scheme 1).



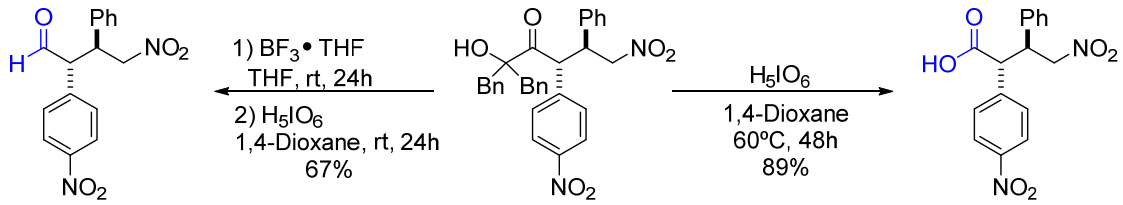
Scheme 1. Possible transformations of the α'-hydroxy ketone moiety.

Inspired by the good results obtained in these works, we considered that α-hydroxy ketones (Figure 2d) could also be efficient pronucleophiles for Brønsted base catalysis under soft enolization conditions. In fact, we demonstrate in the Chapter 2 of this PhD Thesis, that α-hydroxy ketones bearing an aryl group at the α'-carbon can be employed as Michael donors in Brønsted base-promoted addition reactions to nitroalkenes which lead to the reaction adducts with very high diastereo- and enantioselectivity (Scheme 2).



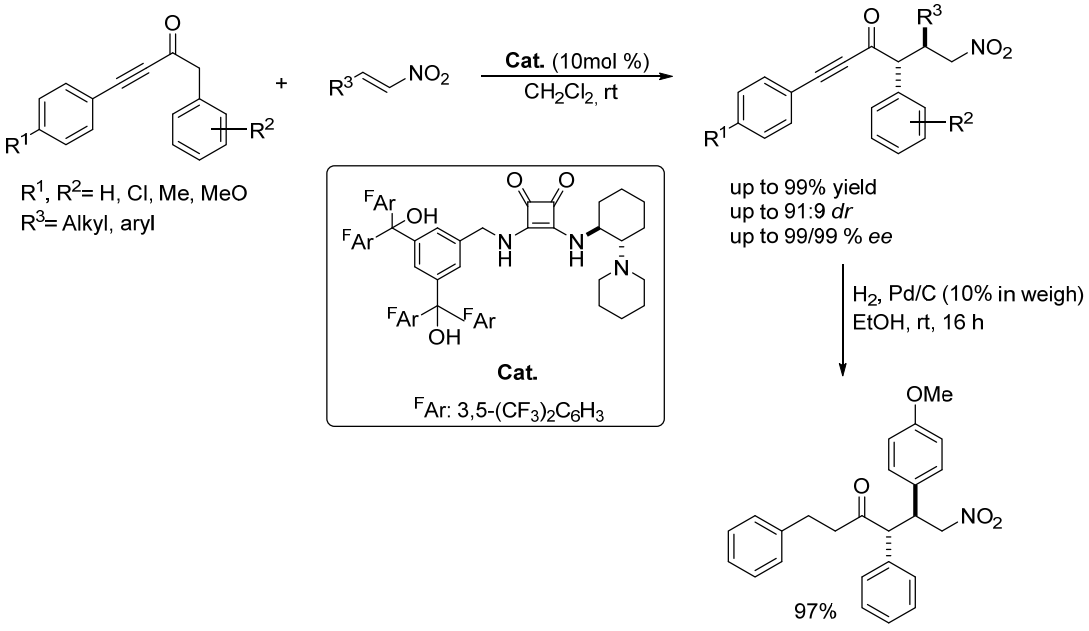
Scheme 2. Organocatalytic enantioselective Michael reaction of α-hydroxy ketones with nitroolefins.

As expected, the adducts coming from this reaction could be efficiently transformed through the oxidative cleavage of the ketol moiety into the corresponding aldehydes or carboxylic acids, whose direct α-functionalization is more challenging (Scheme 3).



Scheme 3. Oxidative cleavage in the Michael adducts to afford the corresponding aldehyde and carboxylic acid.

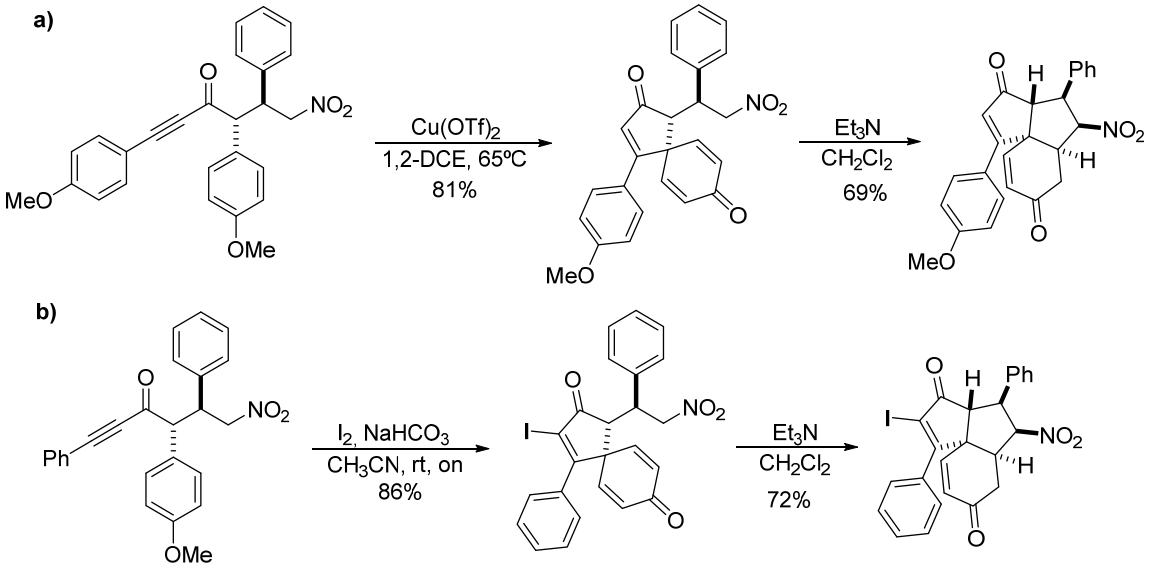
We also considered the evaluation of benzylic alkynyl ketones as substrates for Brønsted base catalysis to afford, after reduction of the corresponding adducts, α-substituted dialkyl ketones whose direct α-functionalization from the starting non-symmetrical dialkyl ketones is difficult owing to regioselectivity problems. In this way, in Chapter 3 of this PhD Thesis, the first conjugate addition of enolizable benzylic alkynyl ketones to nitroolefins assisted by Brønsted base catalyst in a highly selective fashion in which a stereogenic center at the α-position is created is described. Subsequent reduction of the alkyne moiety of these adducts affords the corresponding enantiopure non-symmetrical α-substituted dialkyl ketones in very good yields (Scheme 4).



Scheme 4. Enantioselective Michael addition of benzylic alkynyl ketones to nitroolefins promoted by a BB catalyst and reduction of the corresponding reaction adduct.

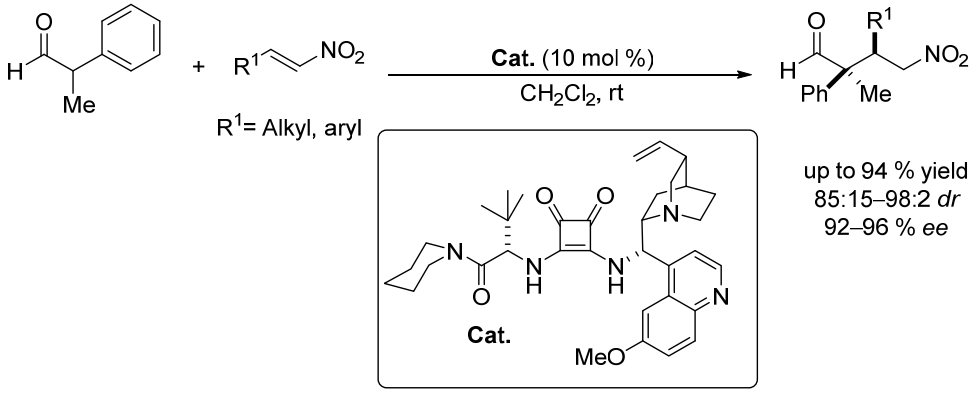
In addition, the versatility of the alkyne moiety allows the synthesis of other more complex structures. In this PhD Thesis, the transformation of the corresponding reactions adducts into enantiomerically pure spirocycles through an intramolecular *ipso*-cyclisation

is also described. The spirocycles are obtained in high yields and their subsequent treatment with base leads to tricyclic carbon structures (Scheme 5).



Scheme 5. Elaboration of adducts into carbocycles of intricate structure.

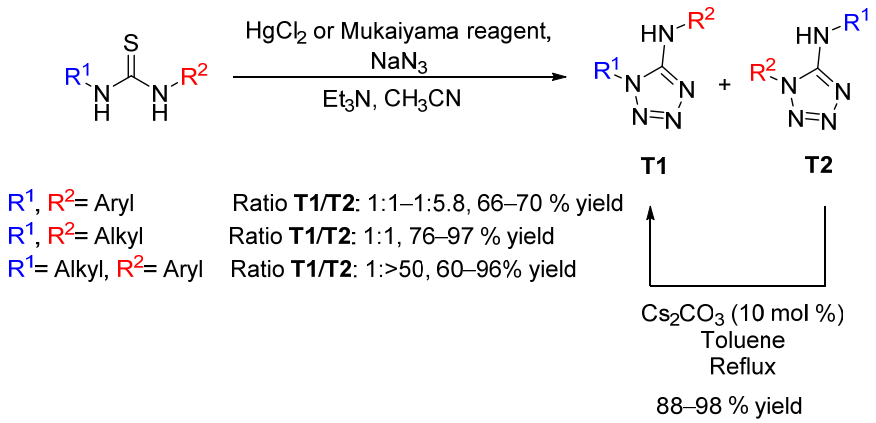
In Chapter 4 of this PhD Thesis, we set forth the results of the first asymmetric Brønsted base catalyzed conjugate addition of aldehydes to nitroolefins (Scheme 6). For this objective, arylacetaldehydes have been employed and a new family of amino acid derived squaramide-based bifunctional catalysts has been developed to afford the corresponding adducts with high diastereo- and enantioselectivity. These results show a similar diastereocontrol and higher enantiocontrol in comparison to previously reported protocols for this transformation *via* enamine activation.



Scheme 6. Organocatalytic enantioselective conjugate addition of 2-phenylpropanal to nitroalkenes.

Finally, in Chapter 5 the study and validation of a methodology for the synthesis of 1-substituted 5-aminotetrazoles is detailed (Scheme 6), which was carried out under the

supervision of Prof. Robert Batey at the University of Toronto (UofT). These aminotetrazoles are appealing due to their wide range of applications in coordination chemistry, material chemistry or pharmacological industry, so a straightforward approach for their synthesis is desirable.



Scheme 6. Synthesis of 1-substituted 5-substituted aminotetrazoles.

In the present process, the starting thiourea undergoes a desulfurizing reaction and a subsequent electrocyclization to obtain the tetrazole in high yield, although the regioselectivity is only controlled when starting from *N*-alkyl *N*'-aryl thioureas, which provide only the tetrazole regioisomer **T2**. Notwithstanding, in this case, the other regioisomer **T1** can be afforded by isomerization reaction of **T2** through rearrangement on heating in good yields.

Resumen

El desarrollo de métodos catalíticos para la síntesis de estructuras moleculares funcionalmente complejas y con configuración definida a partir de moléculas simples mediante la formación de nuevos enlaces C-C representa un objetivo constante en el campo de la síntesis química. De ahí, que el desarrollo de protocolos directos para la α-funcionalización estereoselectiva de compuestos carbonílicos enolizables haya sido ampliamente investigado en los últimos años.

Las reacciones de formación de enlaces C–C requieren un control exhaustivo de la geometría del enolato que interviene y de la estereoquímica en la formación del enlace C–C para lograr compuestos enantioméricamente puros. En catálisis asimétrica, esta tarea es normalmente desempeñada por el catalizador en sí mismo. Sin embargo, a pesar del progreso en este campo, una limitación todavía presente es la necesidad de pronucleófilos con una acidez relativamente alta, de forma que compuestos 1,3-dicarbonílicos, derivados o nitroalcanos son generalmente los sustratos usados. Otros compuestos carbonílicos menos ácidos, como cetonas simples o aldehídos, pueden ser sólo empleados como pronucleófilos en organocatálisis *vía* enamina. No obstante, en el caso de las cetonas, este modo de activación está normalmente restringido a las sustituidas simétricamente, debido a que las cetonas sustituidas asimétricamente presentan dificultad para controlar la geometría y la conformación del intermedio enamina, lo cual, por lo tanto, implica pérdida de estereoselectividad en el aducto final. Un problema adicional asociado a los aldehídos en este contexto es la complicación para efectuar un control efectivo de las reacciones laterales del enolato o enol que causan auto-adición, la reacción de Cannizzaro y/o la reacción de Tishchenko. Particularmente, en el caso de catálisis mediante bases de Brønsted, los relativamente altos valores de pK_a de los aldehídos (pK_a~ 17) y de las cetonas (pK_a~ 22) dificultan su desprotonación, lo cual obstaculiza su uso como nucleófilos en este modo de activación.

En este contexto el objetivo de la presente Tesis Doctoral ha sido explorar la extensión de la catálisis mediante bases de Brønsted bajo condiciones de enolización suaves a cetonas y aldehídos. Para este estudio se ha seleccionado la adición de Michael a nitroolefinas debido a la versatilidad de esta transformación y a la presencia del grupo nitro, que es precursor de otros varios grupos funcionales.

Con el fin de incrementar la acidez del carbono en α al carbonilo en sustratos tipo acilo, tres estrategias son generalmente empleadas: (i) el uso de compuestos carbonílicos

con un sustituyente atractor de electrones en el carbono en α (Figura 1a), (ii) el uso de compuestos carbonílicos con un sustituyente atractor de electrones directamente unido al grupo carbonilo (posición *ipso*, Figure 1b) o (iii) el uso de compuestos carbonílicos que incorporan un grupo capaz de quelación con metales y/o a través de enlaces de hidrógeno (Figura 1c).

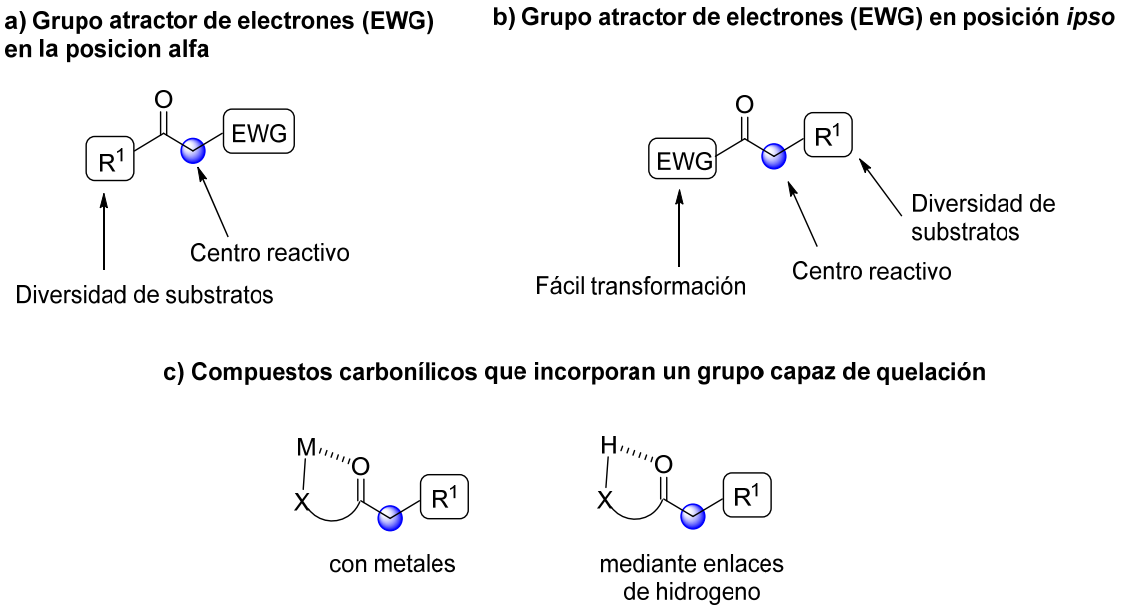


Figura 1. Estrategias para incrementar la acidez de los substratos tipo acilo.

Siguiendo la tercera estrategia, nuestro grupo de investigación ha descrito el uso de α'-oxicetonas y α'-hidroxienonas derivadas del alcanfor (Figura 2a y 2b respectivamente) en procesos catalizados por metales. Además, nuestro grupo ha demostrado también que las α'-oxienonas (Figura 2c) son sustratos eficientes para cicloadiciones diastereoselectivas y para adiciones conjugadas promovidas por catálisis metálica (*Chem. Soc. Rev.* **2012**, *41*, 4150–4164); así como para reacciones de Michael enantioselectivas promovidas por organocatalizadores (*J. Am. Chem. Soc.* **2014**, *136*, 17869–17881).

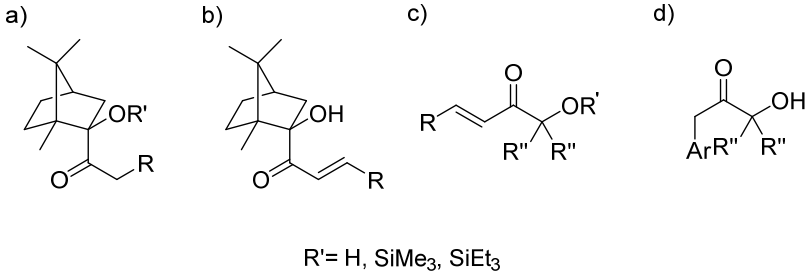
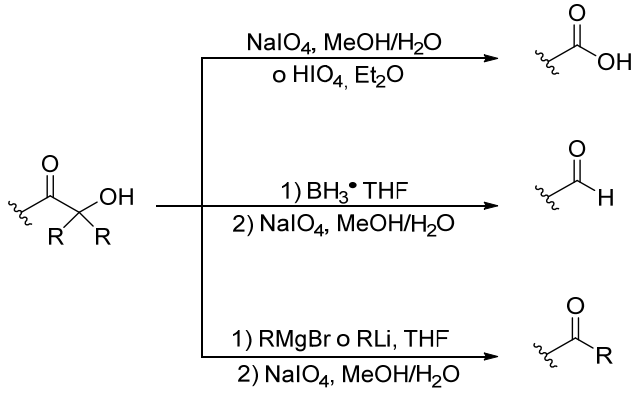


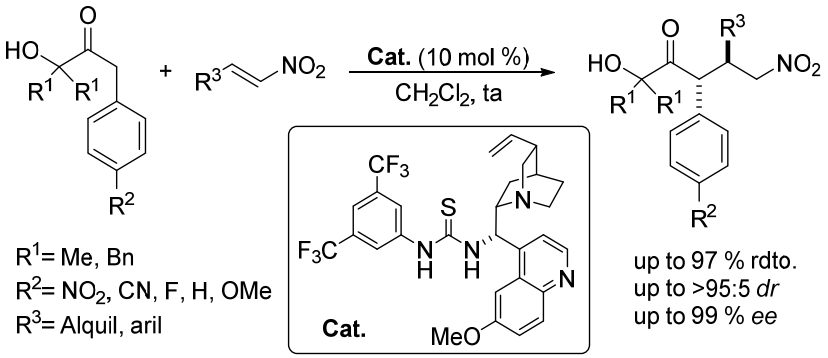
Figure 2. Plantillas de α'-oxicetonas/enonas.

En todos estos casos, la función aciloínica es significativa para el control de la estereoselectividad. Además, en los aductos finales, puede ser escindida para generar ácidos carboxílicos, cetonas o aldehídos funcionalizados, de difícil acceso por otras vías (Esquema 1).



Esquema 1. Posibles transformaciones de la función aciloínica.

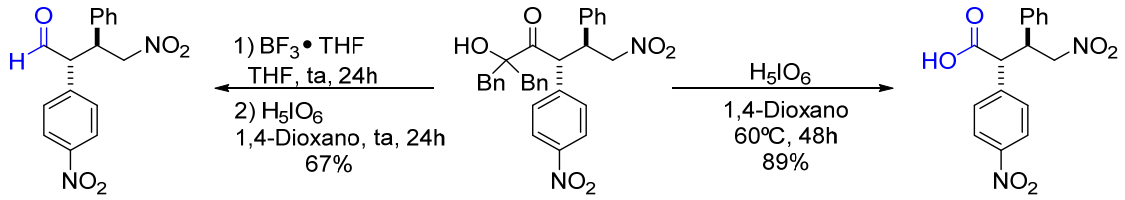
Inspirados por los buenos resultados obtenidos en estos trabajos, consideramos que las α-hidroxicetonas (Figura 2d) podrían también ser pronucleófilos eficientes para la catálisis mediante bases de Brønsted bajo condiciones suaves de enolización. De hecho, en el Capítulo 2 de esta Tesis Doctoral, demostramos que las α-oxicetonas portadoras de un grupo arilo en la posición alfa al carbonilo son dadores eficientes en reacciones de Michael con nitroalquenos promovidas por bases de Brønsted y generan los aductos de reacción con muy elevada diastereo- y enantioselectividad (Esquema 2).



Esquema 2. Reacción de Michael enantioselectiva y organocatalítica de α-hidroxicetonas con nitroolefinas.

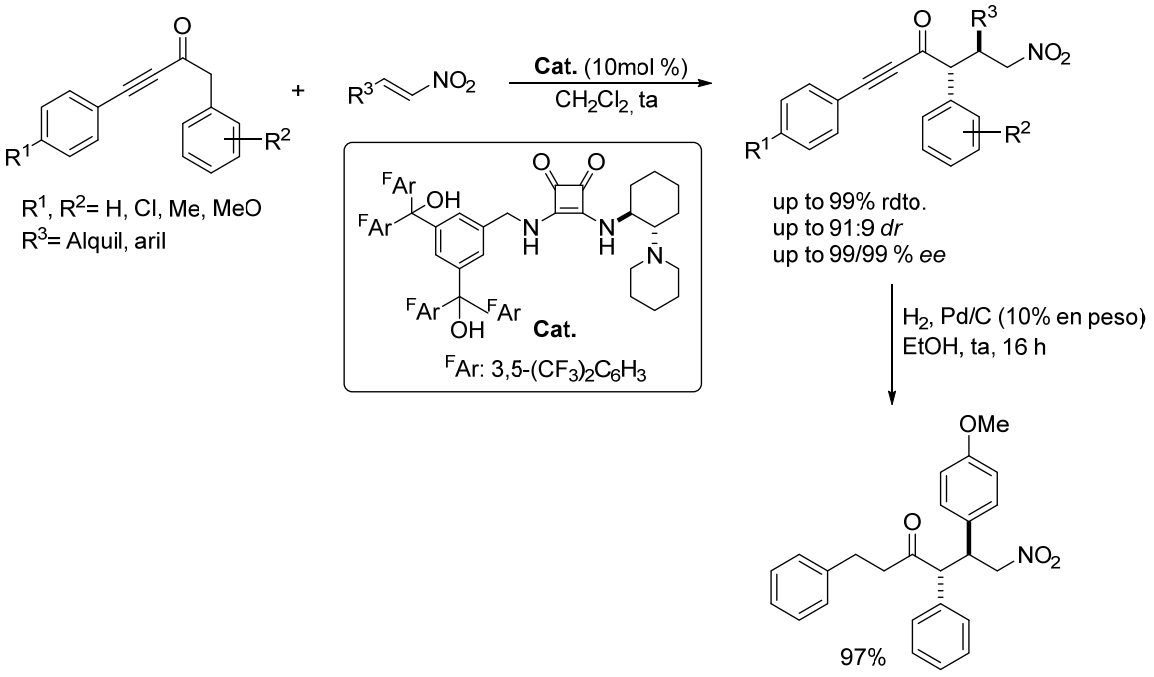
Como era de esperar, los aductos conseguidos en esta reacción pudieron ser efectivamente transformados a través de escisiones oxidativas de la fracción aciloínica en

los correspondientes aldehídos o ácidos carboxílicos, cuya directa α-funcionalización es más compleja (Esquema 3).



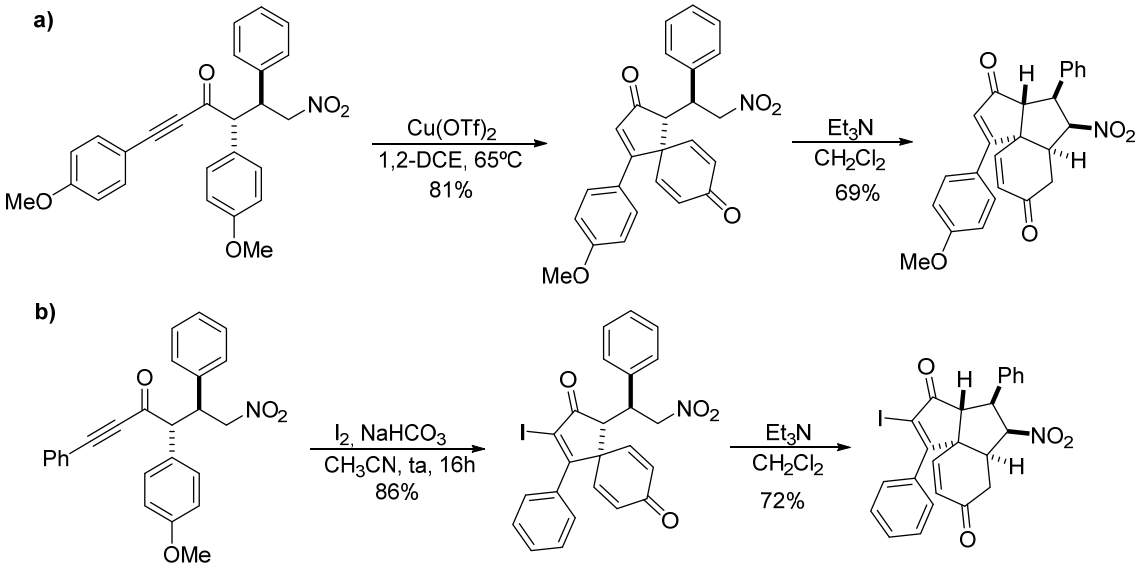
Scheme 3. Escisión oxidativa de los aductos de Michael para la obtención del correspondiente aldehído y ácido carboxílico.

Por otro lado, en la presente Tesis hemos también considerado la evaluación de bencil alquinil cetonas como sustratos para la catálisis mediante bases de Brønsted. En este caso la reducción de los correspondientes aductos de reacción generaría cetonas dialquílicas α-sustituidas, cuya directa α-funcionalización a partir de cetonas dialquílicas no simétricas es dificultosa debido a problemas de regioselectividad. De este modo, en el Capítulo 3 de esta Tesis Doctoral, se describe la primera adición conjugada de cetonas alquinil bencílicas a nitroolefinas promovida por catalizadores de tipo base de Brønsted de manera altamente selectiva y con la creación de un centro estereogénico en la posición alfa. Además, tras la consiguiente reducción del grupo alquinil de los aductos de Michael, se obtienen las correspondientes cetonas dialquílicas no simétricas α-sustituidas enantiopuras (Esquema 4).



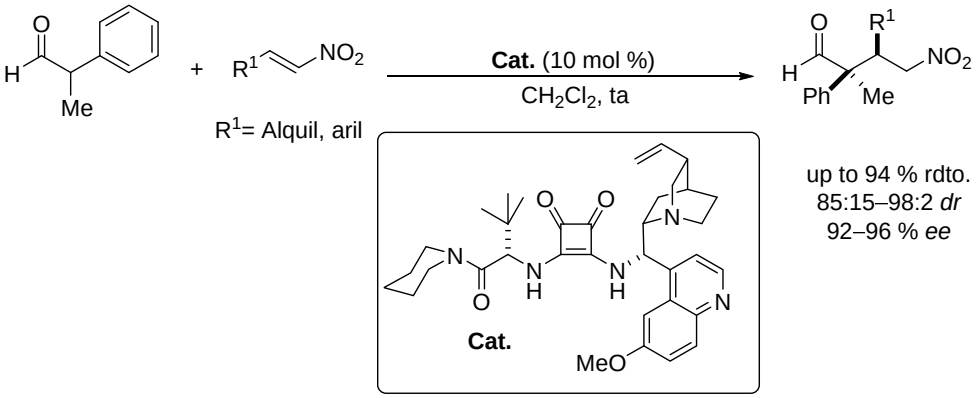
Esquema 4. Adición de Michael enantioselectiva de bencil alquinil cetonas a nitroolefinas promovida por un catalizador del tipo BB y reducción del correspondiente aducto de Michael.

Adicionalmente, la versatilidad del grupo alquino permite la síntesis de otras estructuras más complejas. En esta Tesis Doctoral se describe también la transformación de los correspondientes aductos de reacción en espirociclos enantioméricamente puros a través de una *ipso*-ciclación intramolecular. Los espirociclos se obtienen en altos rendimientos y su posterior tratamiento con base conduce a la formación de estructuras moleculares tricíclicas (Esquema 5).



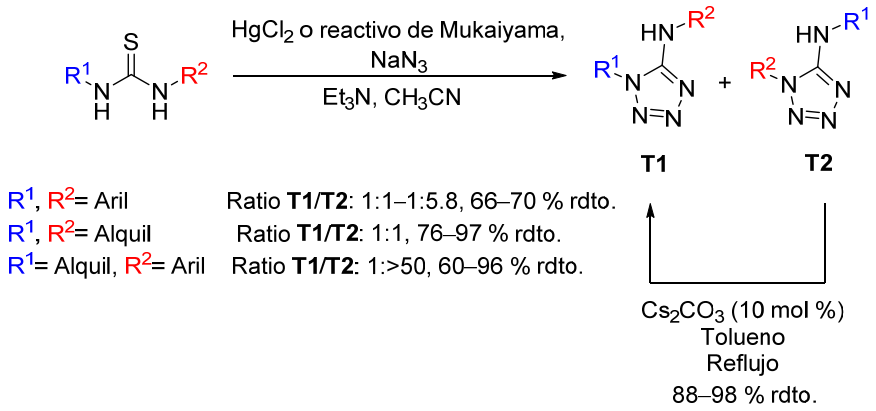
Esquema 5. Elaboración de los correspondientes aductos en carbociclos de estructuras complejas.

Por otra parte, en el Capítulo 4 de esta Tesis Doctoral se describen los resultados de la primera adición conjugada asimétrica catalizada por bases de Brønsted de aldehídos a nitroolefinas (Esquema 6). Para este objetivo, se han empleado aril acetaldehídos y se ha desarrollado una nueva familia de catalizadores bifuncionales de tipo escuaramida y derivados de aminoácidos. Los correspondientes aductos se obtienen con elevada diastereo- y enantioselectividad. Bajo estas condiciones los aductos de reacción se obtienen con un diastereocontrol similar y un mayor enantiocontrol que los protocolos previamente descritos en la bibliografía para esta transformación, los cuales transcurren *vía* enamina.



Esquema 6. Adición conjugada enantioselectiva y organocatalítica de 2-fenilpropanal a nitroalquenos.

Finalmente, en el Capitulo 5 se presenta el estudio y validación de una metodología para la síntesis de 5-aminotetrazoles 1-sustituidos (Esquema 6), que ha sido llevado a cabo bajo la supervisión del Prof. Robert Batey en la Universidad de Toronto (UofT) en Lash Miller Chemical Laboratories. Los 5-aminotetrazoles 1-sustituidos son compuestos atractivos debido a su amplio rango de aplicaciones en química de coordinación, en química de los materiales o en la industria farmacéutica, así que un procedimiento directo para su síntesis es deseable.



Esquema 6. Síntesis de 5-aminotetrazoles 1-sustituidos.

En el presente proceso, la tiourea de partida es sometida a una reacción de desulfurización y una posterior electrociclación lo que permite la obtención del tetrazol en alto rendimiento, aunque la regioselectividad es únicamente controlada cuando se parte de tioureas *N*-alquil *N*'-aril sustituidas, que proporcionan el tetrazol regioisómero **T2.** No obstante, en este caso, el otro regioisómero **T1** puede obtenerse mediante una reacción de isomerización de **T2** con buenos rendimientos a través de un reordenamiento térmico.

Abbreviations and Acronyms

Standard abbreviations and acronyms have been used as recommended in "Guidelines for authors" (*J. Org. Chem.,* January **2017**). Additionally, the following abbreviations and acronyms have been employed:

*	Chiral
Alk	Alkyl (group)
Ax	Auxiliary
B	Base
BB	Brønsted base
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binapthyl
Box	Bis(oxazoline)
Cat	Catalyst
Conv.	Conversion
DIC	N,N'-Diisopropylcarbodiimide
$(DHQ)_2PHAL$	Hydroquinine 1,4-phtalazinediyl diether
$(DHQ)_2Pyr$	Hydroquinine 2,5-diphenyl-4,6-pyridineyl ether
DiPamp	Ethane-1,2-diylbis[(2-methoxyphenyl) phenylphosphane
DIPEA	Diisopropylethylamine
DMP	Dess-Martin periodinane
DTs	Disubstituted tetrazoles
E	Electrophile
ee	Enantiomeric excess
EDCI	*N*-(3-Dimetilaminopropil)-*N*'-etilcarbodiimida

EWG	Electron-withdrawing group
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HOBt	Hydroxybenztriazole
Ln	Lanthanides
M	Metal
n.d.	Not determined
NMM	4-Methylmorpholine
n.o.	Not observed
PyBox	Pyridine-2,6-bis(oxazoline)
rac	Racemic
Ref.	Reference
STs	Substituted tetrazoles
TADDOL	$\alpha,\alpha,\alpha',\alpha'$-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

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CHAPTER 1.

Introduction

Introduction

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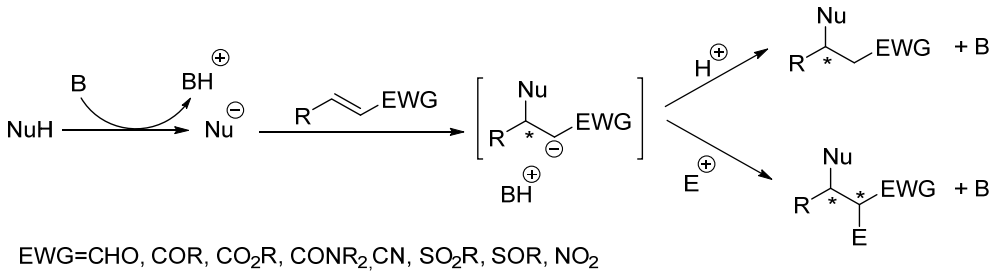
1. Introduction

1.1. The Michael reaction

"The way how this combination (of malonate ester with unsaturated acid ester) resulted was clearly known by Mr. Claisen and correctly described. Mr. Michael contributed to make the reaction remarkably practical by the use of sodium compounds of malonate and acetoacetate esters and to have substantially generalized".[1] That was the footnote by Ernest von Meyer, editor in 1887 at the Journal für Praktische Chemie (previous Advanced Synthesis & Catalysis), being the comment a valid arbitration for the dispute between Rainer Ludwig Claisen and Arthur Michael (Figure 1), over the authorship of the discovery of the novel addition reaction.[2] Then, the reaction was finally named the Michael reaction and nowadays constitutes one of the most versatile transformations in organic synthesis.

Figure 1. Arthur Michael

In general terms, the Michael reaction refers to a nucleophile, which previous deprotonation of its precursor NuH, adds to the β-carbon of an activated α,β-unsaturated acceptor producing a stabilized carbanion intermediate which can either be protonated or react with another electrophile to provide the final addition product (Scheme 1).



Scheme 1. General scheme for the Michael reaction.

[1] Michael, A. *J. Prakt. Chem.* **1887**, *36*, 113–114.
[2] Tokoroyama, T. *Eur. J. Org. Chem.* **2010**, 2009–2016.

During the years, a wide range of compounds has been employed as donors and acceptors spreading the utility of this transformation and demonstrating great generality.[3] Commonly, used nucleophiles are silyl enol ethers, and enolates of ketones, aldehydes, carboxylic acids or 1,3-dicarbonyl derivatives or related compounds. Nevertheless, there is an extensive variety of functional groups that have sufficient nucleophilicity to act as Michael donors, being non-enolate nucleophiles, for instance, selenium based compounds, amines, enamines, nitroalkanes, thiols or phosphines. These reactions involving heteroatom-centered nucleophiles are known as hetero-Michael.[4] The Michael acceptor possesses an electron withdrawing and resonance stabilizing activating group, which stabilizes the anionic intermediate. The most common acceptors are α,β-unsaturated carbonyl compounds such as aldehydes, ketones, esters, amides. Although thanks to the huge diversity of electron withdrawing activating groups, nitro, sulfonate, sulfoxide, phosphate or phosphonate derivatives have also been used. Moreover, the Michael reaction has also been showed as a versatility tool in tandem, domino or cascade reactions.[5]

An important aspect in the Michael reaction is that, besides the carbon-carbon bond, one or more stereogenic centers can be created, which means that if the stereochemistry of the reaction is efficiently controlled, it constitutes a synthetic methodology of great potential for the preparation of highly functionalized enantiomerically enriched compounds.

In this context, the general strategies developed for the synthesis of enantiomerically pure compounds (EPC)[6] have been classified into two major groups:

[3] For general reviews on Michael reactions, see: a) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, 42–53. g) Maharwald, R.; Scheffler, U. *Chem. Eur. J.* **2013**, *19*, 14346–14396. b) Reyes, E; Uria, U.; Vicario, J. L.; Carrillo, L. *Org. React.* **2016**, *90*, 1–898. For a reviews on Michael reactions assisted by metal catalysts, see: c) Matsunaga, S. *Comprehensive Chirality*, **2012**, *4*, 243–292. d) Hui, C.; Pu, F.; Xu, J. *Chem. Eur. J.* **2017**, *23*, 4023–4036. For more information on organocatalytic Michael reactions, see: e) Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions. A powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, **2010**, RSC Catalysis Series. f) Pellissier, H. *Current Organic Chemsitry*, **2018**, *22*, 323–344.

[4] For general hetero-Michael reactions, see: a) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065–2092. b) Heravi M. M.; Hajiabbasi, P. *Molecular diversity* **2014**, *18*, 411–439. c) Sanchez-Rosello, M.; Miro, J.; del Pozo, C. *Synthesis* **2017**, *49*, 2787–2802.

[5] For reviews of tandem/ domino/ cascade reactions, see: a) Bugaut, X.; Bonne, D.; Coquerel, Y.; Rodriguez, J.; Constantieux, T. *Current Organic Chemistry* **2013**, *17*, 1920–1928. b) Donner, C. D. *Tetrahedron* **2013**, *69*, 3747–3773. c) Nayak, S.; Panda, P.; Bhakta, S.; Mishra, S. K.; Mohapatra, S. *RSC Advances* **2016**, *6*, 96154–96175. d) Serrano-Molina, D.; Marin-Castro, A. M. *Synthesis* **2016**, *48*, 3459–3469.

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

"chiral pool"[7] and asymmetric synthesis.[8] In addition, when a racemic mixture is obtained, simple resolution,[9] kinetic resolution (KR)[10] or dynamic kinetic resolution (DKR)[11] can be used to obtain enantiomerically pure compounds.

In the field of asymmetric synthesis, the first reactions involving C-C bond formation made use of the chiral auxiliary approach,[12] in which the auxiliary is covalently bounded to one of the substrates, generally to the donor substrate, through amide bond,[13] imine[14] or hydrazone[15] formation. When the reaction is finished, the diastereomers are separated, if necessary, the auxiliary is cleaved under mild conditions to afford the enantiomerically pure compound and the free auxiliary is recovered for further use.

In spite of the high stereochemical control achieved through this methodology, the need for additional synthetic steps for the attachment/removal of the auxiliary and the requirement of stoichiometric quantities thereof turned into a limitation in these approaches. In consequence, asymmetric catalysis, in which the stereochemical outcome is controlled by substoichiometric amounts of chiral catalysts has emerged as an

[7] For general reviews on the strategy of chiral pool, see: a) Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III*, **2011**, Wiley-VCH, Weinheim. b) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. *Chem. Rev*. **2017**, *117*, 11753–11795.

[8] For more information on asymmetric synthesis: a) Gawley, R. e.; Aube, J. *Principles of Asymmetric Synthesis* 2nd Edition, **2012**, Pergamon Press, Oxford. b) Christmann, M.; Bräse, S. *Asymmetric Synthesis II: More Methods and Applications*, **2012**, Wiley-VHC, Weinheim, Germany.

[9] For a general review on the resolution of racemates, see: Synoradzki, L.; Bernaś, U.; Ruśkowski, P. *Org. Prep. Proced. Int.* **2008**, *40*, 163–200.

[10] For general reviews on kinetic resolution (KR), see: a) Todd, M. *Separation of Enantiomers: Synthetic Methods*, First Edition, **2014** Wiley-VCH Verlag GmbH & Co. b) Lorenz, H.; Seidel-Morgenstern, A. *Angew. Chem. Int. Ed*. **2014**, *53*, 1218–1250. c) De Risi, C.; Bortolini, O.; Di Carmine, G.; Ragno, D.; Masi, A. *Synthesis* **2019**, *51*, 1871–1891.

[11] For reviews on dynamic kinetic resolution (DKR), see: a) Ahmed, M.; Kelly, T.; Ghanem, A. *Tetrahedron* **2012**, *68*, 6781–6802. b) Li, P.; Hu, X.; Dong, X-Q.; Zhang, X. *Molecules* **2016**, *21*, 1327. c) Pellissier, H. *Tetrahedron*, **2016**, *72*, 3133–3150.

[12] For more information on chiral auxiliaries, see: a) Glorious, F.; Gnass, Y. *Synthesis* **2006**, *12*, 1899–1930. b) Gawley, R.E.; Aubé, J. *Principles of Asymmetric Synthesis*, **2012**, *5*, 245–334. c) Roos, G. *Key Chiral Auxiliary Applications*, **2014**, Academic Press, New York. For a general review on amino acids and their derivatives as stoichiometric auxiliaries, see: d) Studer, A. *Synthesis*, **1996**, *7*, 793–815.

[13] For the first example of the use of prolinol derivatives, see: a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236. For a general review on the use of oxazolidinones, see: b) Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Bevola, L.; Botta, B. *Current Organic Synthesis* **2007**, *4*, 81–135. For a general review on the use of Oppolzer's sultam, see: c) Oppolzer, *Pure Appl. Chem*. **1990**, *62*, 1241–1250. For a general review on the use of pseudoephedrine, see: d) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

[14] For the first example of the use of phenylalanine derivatives, see: Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3033.

[15] For a general review on the use of hydrazines, see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329.

alternative and attractive strategy with an exponential growth in the last decades since it constitutes a more direct and atom-economic approach.

The asymmetric catalytic methods have been divided into three main groups depending on the nature of the catalyst: biocatalysis (so called enzymatic catalysis),[16] metal catalysis,[17] in which chiral complexes of metallic species where the metal participates in the catalytic cycle are used; and organocatalysis,[18] in which organic molecules are the responsible of the stereoselective induction.

Although an extensive number of enzyme-catalyzed reactions have been reported,[16] Michael additions of this type are still a challenge, and limited examples are found in the literature,[19] probably due to the extremely high specificity of these biological catalysts towards the substrate structure. By contrast, metal catalysis and organocatalysis have emerged as attractive synthetic alternatives to synthesize enantiopure compounds.

1.2. Metal-catalyzed asymmetric reactions

Evidence of the importance of the metal catalysis was the award of the Nobel Prize in Chemistry in 2001 to Profs. W. S. Knowles, R. Noyori and K. B. Sharpless for their work in this field,[20] namely on metal catalyzed asymmetric hydrogenation and oxidation

[16] For more information on biocatalysis, see: a) Faber, K.; Fressner, W. Turner, N. J. *Science of Synthesis, Biocatalysis in Organic Synthesis,* **2015**, Thieme Chemistry. b) Miao, Y.; Rahimi, M.; Geertsema, E. M.; Poelarends, G. J. *Current Opinion in Chemical Biology*, **2015**, *25*, 115–123. c) Hönig, M.; Sondermann, P.; Turner, N. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 8942–8973.

[17] For general reviews on organometallic catalysis, see: a) Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H. *Chem. Soc. Rev.* **2015**, *44*, 433–448. b) Zhang, L.; Meggers, E. *Chem. Asian J.* **2017**, *12*, 2335–2342. c) Pellisser, H. *Adv. Synth. Catal.* **2019**, *361*, 1733–1755. d) Cao, W.; Feng, X.; Liu, X. *Org. Biomol. Chem.* **2019**, *17*, 6538–6550.

[18] For general reviews on organocatalysis, see: a) Dalko, P. I. *Enantioselective Organocatalysis*, **2007**, Wiley-VCH, Weinheim. b) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20618–20619. c) *Stereoselective Organocatalysis: Bond formation methodologies and activation modes*, Ed. Rios Torres, R., **2013**, John Wiley & Sons, Inc.; Hoboken, New Jersey. d) *Comprehensive enantioselective organocatalysis: Catalysts, Reactions and Applications*, Ed. Dalko, P. I. **2013**, Wiley-VCH Verlag GmbH & Co., Weinheim, Germany.

[19] For general reviews on biocatalysis for the Michael reaction, see: a) Geertsema, E. M; Poelarends, G. J. *Science of Synthesis, Biocatalysis in Organic Synthesis,* **2015**, *2*, 313–333. b) Garrabou, X.; Macdonald, D. S.; Wicky, B. I. M.; Hilvert, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 5288–5291.

[20] Ault, A. *J. Chem. Educ.* **2002**, *5*, 572–577. For the speech of receiving the Nobel Prize award by Prof. W. S. Knowles, see: b) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007. c) Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3–13. For the speech of receiving the Nobel Prize award by Prof. R. Noyori, see: d) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; e) R. Noyori, *Adv. Synth. Catal.* **2003**, *345*, 15–32. For the speech of receiving the Nobel Prize award by Prof. K. B. Sharpless, see: f) K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.

reactions (Figure 2). Knowles[21] and Noyori's[22] works were based on the catalytic enantiospecific hydrogenation of double bonds (Figure 2, a and b), and on the contrary, Sharpless[23] investigated the catalytic enantiospecific epoxidation and dihydroxylation of alkenes (Figure 2, c).

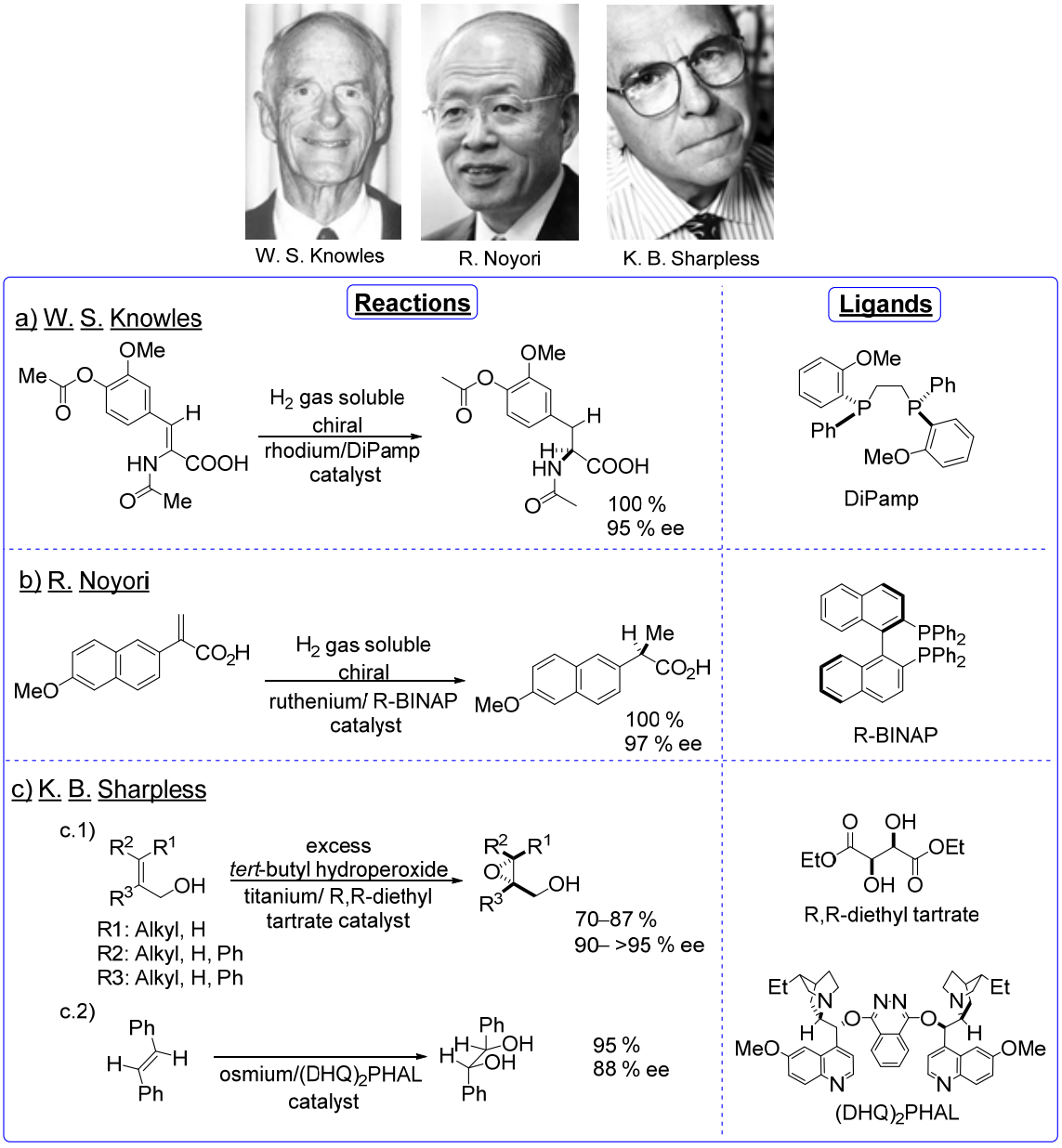


Figure 2. Winners of The Nobel Prize in Chemistry in 2001 and their representative works on metal catalyzed asymmetric reactions.

[21] For the first example: Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445–1446.

[22] For the first example: a) Miyashita, A.; Takya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245–1253. For a general review on BINAP: b) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev*. **2005**, *105*, 1801–1836. c) Ohkuma, T.; Kurono, N. *Privilege Chiral Ligands and Catalysis* **2011**, 1–53.

[23] For the first practical method for asymmetric epoxidation, see: a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. For the first effective example of asymmetric dihydroxylation, see: b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.

This catalysis type is based on metal complexes that incorporate chiral ligands which control the stereochemistry of the processes. Since these seminal works, different combinations of metals and chiral ligands have been reported to efficiently promote catalytic asymmetric organic transformations. Figure 3 sets out some representative chiral ligands employed for the generation of monometallic complex catalysts used in C–C bond forming reactions.[24]

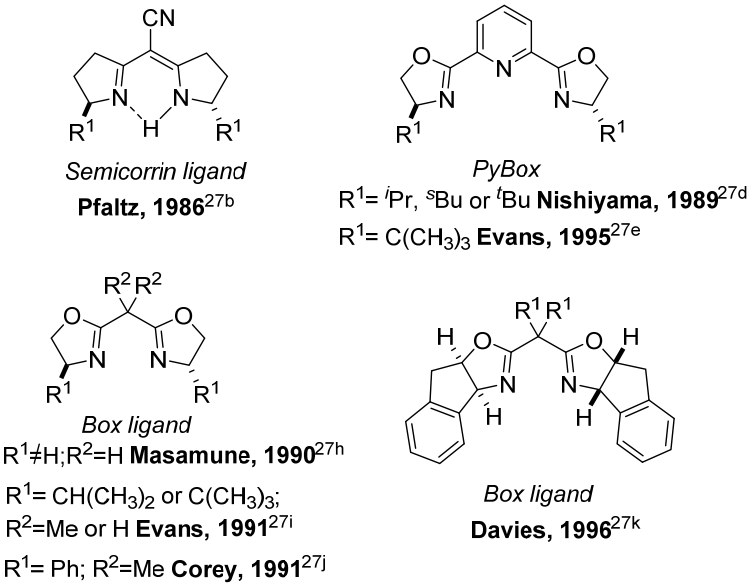


Figure 3. Some chiral ligands used for the formation of monometallic complexes to promote organic transformations.

The great breakthrough in this field occurred in 1997 when Shibasaki described the first aldol reaction promoted by a polymetallic complex.[25] These complexes incorporate two or more metal atoms within their structures and have contributed to a new concept

[24] For a general review on the use of semicorrin in asymmetric catalysis, see: a) Pfaltz, A. *J. Heterocyclic Chem.* **1999**, *36*, 1437–1451. For the first example of semicorrin in enantioselective catalysis, see: b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1005–1006. For a review on PyBox, see: c) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154. For the first example of PyBox ligand in asymmetric catalysis, see: d) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989,** *8*, 846–848. For the first example of PyBox ligand in *C-C* bond formation, see: e) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800. For general reviews on the use of chiral bis(oxazoline) (Box) ligands in asymmetric catalysis, see: f) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505–2550. g) Stanley, L. M.; Sibi, M. P. *Privilege Chiral Ligands and Catalysis* **2011**, 171–219. For the first example of Box ligand, see: h) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005–6008. For the first example of Box ligand in *C-C* bond formation, see: i) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726–728. j) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc*. **1991**, *113*, 728–729. For the first example of Box in two point-binding, see: k) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 1725–1726.

[25] a) Yamada, Y. M. A.; Yoshika, N.; Sasai, H. M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1871–1872. For more information, see: b) Shibasaki, M.; Matsunaga, S. *Privilege Chiral Ligands and Catalysis* **2011**, 295–332.

called bifunctional catalysis.[26] In these cases, one metal center activates the acceptor acting as a Lewis acid, and the heteroatoms bounded to the other metal work as Lewis/Brønsted base (Figure 4a). Therefore, nucleophile and electrophile can be simultaneously activated by two catalytic centers of the same catalyst. The most representative complex catalysts of this type are depicted in Figure 4b.[27]

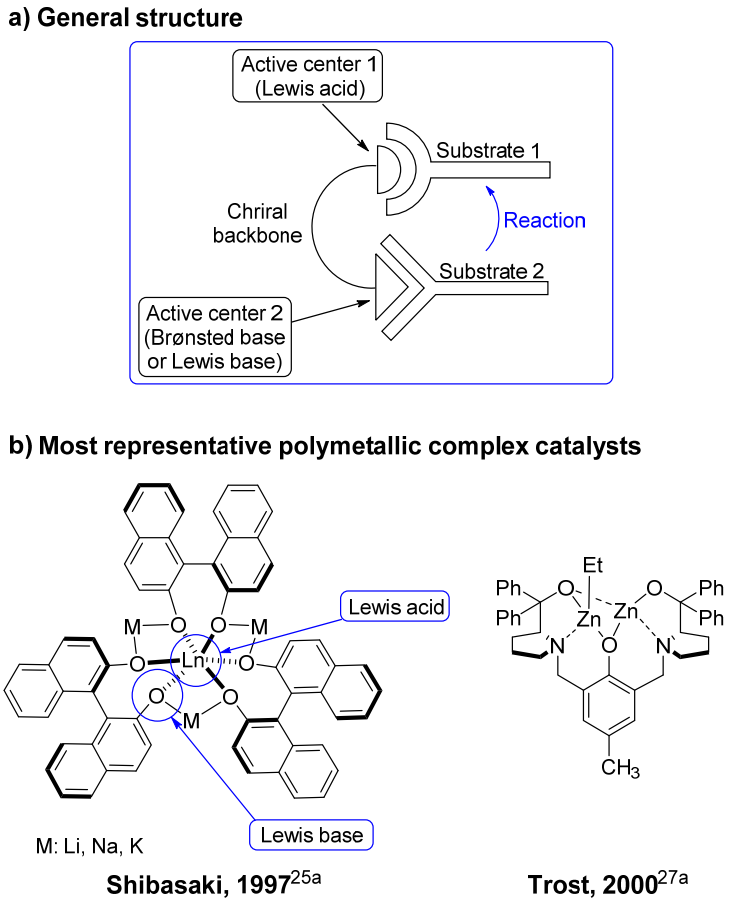


Figure 4. Characteristics and examples of the most representative polymetallic (hetero and homo) complex catalysts.

Despite the achievements with metal catalysts, this methodology has some limitations. Carbonyl compounds such as simple ketones, esters, nitriles or amides, which are less acidic, are usually restricted in this approach, because they have to be activated by strong bases and their corresponding conjugate acids generated during the reaction

[26] For reviews on metal-ligand bifunctional catalysis, see: a) Ikariya, T., Murata, K., & Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393–406. b) Ramasamy, B.; Ghosh, P. *Eur. J. Inorg. Chem.* **2016**, 1448–1465. c) Dub, P. A.; Gordon, J. C. *ACS Catal.* **2017**, *7*, 6635–6655.

[27] For the first example of the use of bis ProPhenol ligand, see: a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004. For a general review, see: b) Trost, B.; Hung, C.-I.; Mata, G. *Angew. Chem. Int. Ed.* **2019**, *58*, 2–24.

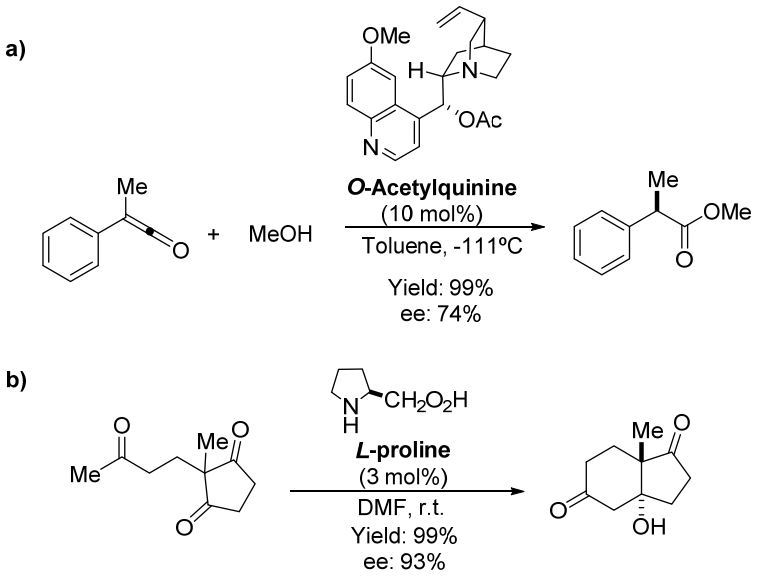
are unable to protonate the addition product. Therefore, a complementary synthetic route to achieve enantiomerically pure compounds came back with relevance in the last decades, organocatalysis.

1.3. Asymmetric organocatalysis

Asymmetric organocatalysis is based on the use of organic molecules, in other words, molecules composed of hydrogen, carbon, silicon, nitrogen, phosphorous, oxygen, sulphur, selenium, tellurium and/or halides. In certain cases, these organic compounds also incorporate in their structures some metal elements; however, these do not interact with the substrates in the catalytic process and in consequence are considered organocatalysts.[28]

The first use of an organic catalyst in an asymmetric reaction furnishing high levels of enantioselectivity was the addition of methanol to methyl phenyl ketene promoted by *O*-acetylquinine reported by Pracejus in 1960 (Scheme 2a).[29] This reaction set up the basis for the use of cinchona alkaloid-based catalysts in the realm of asymmetric organocatalysis. A decade later, two industrial research groups at Hoffmann-La Roche[30] and Schering[31] developed independently other relevant organocatalyzed reaction, the intramolecular aldol reaction promoted by proline, also known as Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 2b), in which the enamine catalytic cycle was described for the first time. Despite the results, in the 1980s and at the beginning of 1990s, organocatalysis was in hibernation excepting some odd publications. The renaissance came in the late 1990s, with organocatalysts such as ureas, thioureas[32] and amines, meaning an exponentially growth in this field until it is known nowadays.

[28] For representative examples, see: a) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007. b) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176–6177.
[29] Pracejus, H. *Justus Liebig Ann. Chem.* **1960**, *634*, 9.
[30] a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, **1971**. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1625.
[31] a) Eder, U.; Sauer, G.; Wiechert, R. German Patent DE 2014757, **1971**. b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497.
[32] a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306. b) Nakanishi, W. *Superbases for Organic Synthesis* **2009**, 273–293. c) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298–1310. d) Hof, K.; Lippert, M.; Schreiner, P. R. *Science of Synthesis, Asymmetric Organocatalysis* **2012**, *2*, 297–412. e) Inokuma, T.; Takemoto, Y. *Science of Synthesis, Asymmetric Organocatalysis* **2012**, *2*, 437–497. f) Takemoto, Y.; Inokuma, T. *Asymmetric Synthesis II* **2012**, 233–237. g) Zhang, Z.; Bao, Z.; Xing, H. *Org. Biomol. Chem.* **2014**, *12*, 3151–3162.



Scheme 2. a) First example of an organocatalyzed enantioselective reaction. **Pracejus, 1960**. b) The Hajos-Parrish-Eder-Sauer-Wiechert reaction, **1971.**

In the field of organocatalysis, an outlined classification[33] according to the interaction between the catalyst and the substrate is generally used. On this basis, two groups are considered: covalent and non-covalent catalysis.

1.3.1. Covalent catalysis

In covalent catalysis, the activation of the substrate occurs through formation of a covalent bond between the catalyst and the substrate itself, which must be reversible, allowing the catalyst to be detached from the final product. This protocol reminds to chiral auxiliaries; however, in covalent organocatalysis, as the name implies, substoichiometric amounts are employed. Some of the most representative catalysts responsible of this kind of activation, among others,[34] are chiral amines, which set up a subgroup, so known as aminocatalysis.[35] In this case, regarding the reactive species generated by the interaction between the carbonyl compound and the catalyst, different activation modes have been

[33] a) Langenbeck, W. *Die organischen Ktalysatoren und ihre Bziehungen zu den Fermenten (Organic Catalysts and Their Relations with Enzymes)*, 2nd., Springer, Berlin **1949**. For a more recent classification, see: b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138–5175. For an alternative classification based on the acidic/base reactivity of the catalysts, see: c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

[34] Other catalysis types have also been reported, such as nucleophilic catalysis, which involves the use of *N*-heterocyclic carbenes, some tertiary amines and analogous, alkyl pyridines, trialkylphosphines and trialkyl amines.

[35] For general reviews on aminocatalysis, see: a) List, B. *Synlett*, **2001**, *11*, 1675–1686. b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 358–368. c) Matos Paz, B.; Hao, J.; Jørgensen, K. A. *Chem. Eur. J.* **2015**, *21*, 1846–1853. d) Lv, J.; Zhang, Q.; Cai, M.; Han, Y.; Luo, S. *Chem. Asian J.* **2018**, *13*, 740–753.

developed, based on HOMO activation, via enamine,[36] dienamine,[37] trienamine[38] and tetraenamine[39] intermediates; LUMO activation, via iminium-ion intermediates[40] and SOMO activation, via radical intermediates[41] (Figure 5).

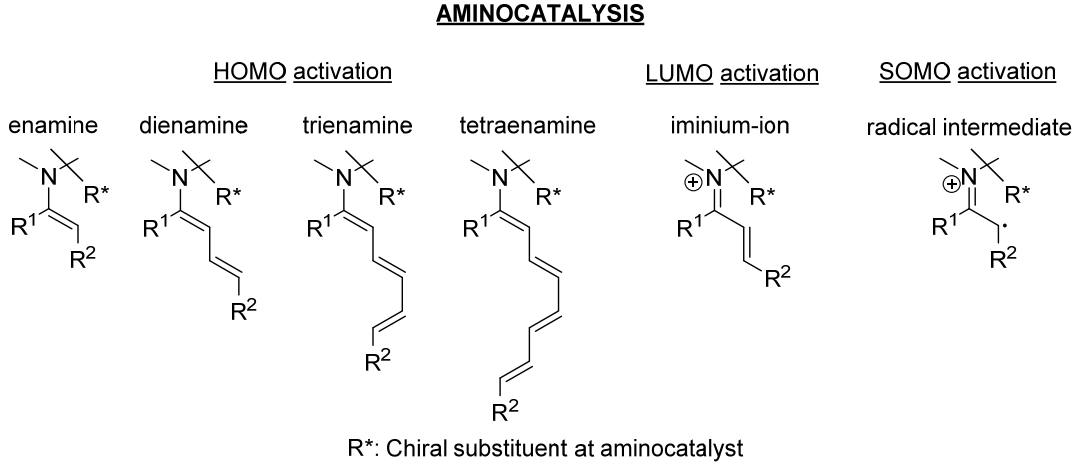


Figure 5. Reactive intermediates according to the activation modes in aminocatalysis.

In all these reactions, the stereoselectivity is induced by the aminocatalyst either by steric interactions or through H-bonding. On the subject of this latter activation mode, the "bifunctional catalysis" concept arisen for the metal catalysts[26] was later brought for the organocatalysis.[42]

[36] For more information on enamine catalysis, see: a) List, B. *Science of Synthesis, Asymmetric Organocatalysis I*, **2012**, *1*, 35–269, Thieme. b) Murphy, J. J.; Mattia, S.; Melchiorre, P. *Lewis Base Catalysis in Organic Synthesis*, **2016**, *17*, 857–902, Wiley-VCH Verlag, GmbH & Co. KGaA.

[37] For general reviews on dienamine catalysis, see: a) Bertelsen, S.; Marigo, M.; Brandes, S.; Diér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980. b) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865–887. C) Marcos, V.; Aleman, J. *Chem. Soc. Rev*. **2016**, *45*, 6812–6832.

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

[39] For general reviews on tetraenamine catalysis, see: a) Stiller, J.; Poulsen, H.; Cruz, D. C.; Dourado, J.; Davis, R. L.; Jørgensen, *Chem. Sci.* **2014**, *5*, 2052–2056. b) Zhou, Q.-Q.; Xiao, Y.-C-; Yuan, X.; Chen, Y.-C. *Asian J. Org. Chem.* **2014**, *3*, 545–549.

[40] For general reviews on iminium catalysis, see: a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79–87. b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416–5470. C) Bartoli, G.; Melchorre, P. *Synlett* **2008**, *12*, 1759–1779. d) Brazier, J. b.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281–347. e) List, B. *Science of Synthesis, Asymmetric Organocatalysis I*, **2012**, *1*, 309–437, Thieme.

[41] For general reviews on SOMO catalysis, see: a) Young, H.-Y.; Hung, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005. b) Bertelsen, S.; Nielsen, M.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356–7359. c) Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1360–1363. d) MacMillan, D. W. C.; Rendler, S. *Asymmetric Synthesis II* **2012**, 87–94.

[42] For reviews on bifunctional organocatalysts, see: a) Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 6145–6158. b) Bhadury, P. S.; Song, B-A.; Yang, S.; Hu, D-Y.; Xue, W. *Current Organic Synthesis* **2009**, *6*, 380–399. c) Quintavalla, A.; Cerisoli, L.; Montroni, E. *Current Organocatalysis*, **2014**, *1*, 107–171. d) Najera, C.; Miguel Sansano, J.; Gómez-Bengoa, E. *Pure App. Chem.* **2016**, *88*, 561–578.

Figure 6 shows some of the most representative aminocatalysts. In 2000, the understanding of enamine activation through the proline-catalyzed enantioselective intermolecular aldol reaction reported by List[43] and iminium activation through amine catalyzed Diels-Alder reaction by MacMillan[44] triggered a development in proline derivatives and their use in aminocatalysis. Pyrrolidine-based chiral amines are the most commonly used secondary amines (Figure 6a), which facilitate stereocontrol[45] through the presence of either bulky groups or substituents in their structure which participate in H-bonding interactions. For instance, the tripeptide developed by Wennemers,[46] which works through H-bonding interactions, exhibits high catalytic activity, attaining optimal results with low catalyst loading (1 mol %). Several primary amine based catalysts have also been studied, such as simple amino acids[47] and analogues,[48] thiourea based catalysts[49] or natural cinchonine derivatives (Figure 6b).[50]

[43] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[44] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[45] For the first examples of reactions promoted by *O*-trialkylsilyl α,α-diarylprolinol catalysts, see: a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215. b) Marigo, M.; Wabnitz, T.C; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797. For a summary of diarylprolinol ethers, see: c) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880. d) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922–948. For the first examples of reactions promoted by by *O*-trialkylsilyl α,α-dialkylprolinol catalysts, see: e) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.
[46] For the first example of aldol reaction promoted by peptides, see: a) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett*. **2005**, *7*, 1101–1103. For the first examples of Michael addition of aldehydes promoted by peptides, see: to nitroalkenes: b) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1871–1874. To nitroethene: c) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc*. **2008**, *130*, 5610–5611.
[47] For selected examples, see: a) Bassan A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7828–7032. b) Córdova, A.; Ibrahem, I.; Casas, J.; Sundén, H.; Engqvist, M; Reyes, E. *Eur. Chem. J*. **2005**, *11*, 4772–4784. c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 288–289.
[48] Ishihara K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505.
[49] For a general review on bifunctional primary amine-thioureas in organocatalysis, see: a) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051–7071. For a pioneering example, see: b) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826–832. For a pioneering example of amino acid/thiourea based catalysts, see: c) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7170. d) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451–1453.
[50] For pioneering examples, see: a) Xie, J.-W.; Chen, W.; Li, R.;Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C-; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389– 392. b) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L. S.; Chen, Y.-C. *Org. Biomol. Chem.*, **2007**, *5*, 816–817. c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri L.; Melchiorre, P. *Org. Lett.*, **2007**,*9*, 1403–1405. For a general review, see: d) Duan, J.; Li, P. *Catal. Sci. Technol.* **2014**, *4* , 311–320.

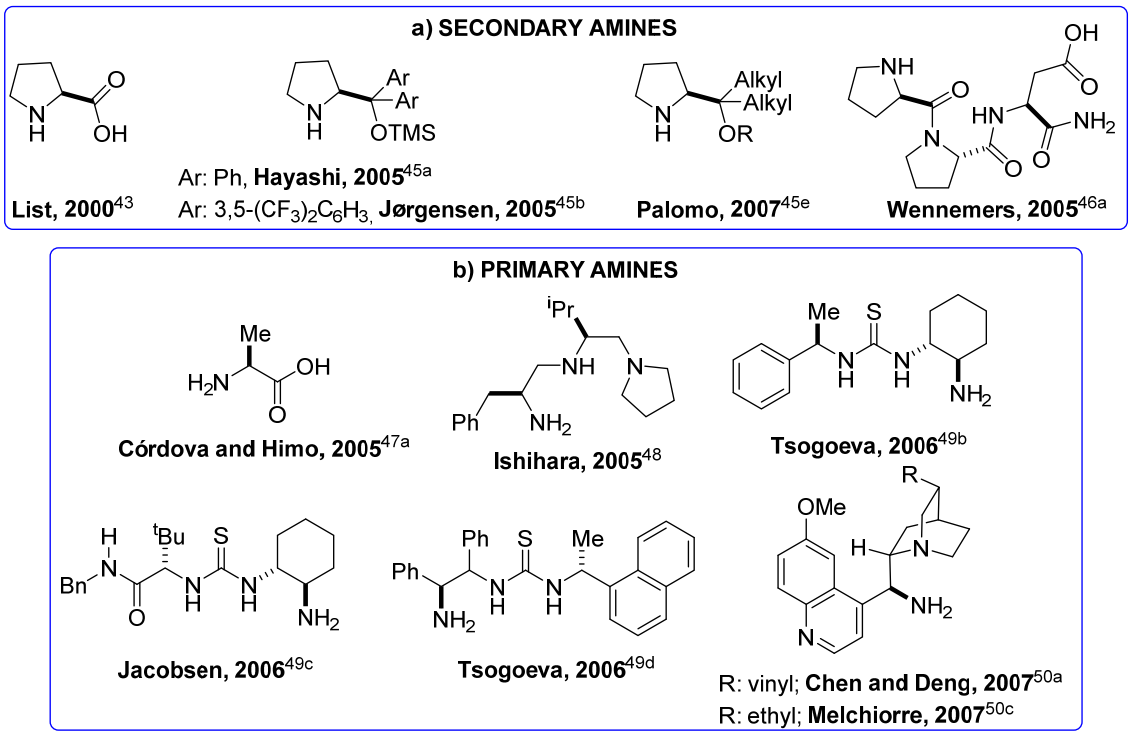


Figure 6. Most representative primary and secondary aminocatalysts for covalent catalysis.

The Michael reaction promoted by secondary amine catalysts via enamine formation has been deeply investigated for aldehydes as Michael donors. But, unfortunately, its use for ketones has been limited mainly due to the difficulty in controlling the geometry and conformation of the enamine intermediate. To overcome this problem, symmetrically substituted ketones are employed, for instance cyclohexanone or acetone. Nevertheless, for unsymmetrically substituted ketones, the solution is the use of primary amines, since the condensation of ketones and primary amines is sterically more feasible and the geometric control is easier. Aminocatalysts also promoete Michael reactions with α,β-unsaturated aldehydes and ketones as Michael acceptors. In this case, the reaction proceeds through iminium ion activation, albeit, this approach presents some disadvantages. For instance, the need for the pro-nucleophile to show high acidity to be deprotonated in the neutral or slightly acidic media, where the reaction is performed. Therefore, the Michael donors via iminium activation are mostly limited to 1,3-dicarbonyl compounds or nitroalkanes. In addition, other important drawback of Michael reactions working through this strategy is the high catalyst loading usually required, which complicates the scaling up of these reactions.

1.3.2. Non-covalent catalysis

In an organocatalytic asymmetric reaction, the catalysts can also interact with the substrates through non covalent interactions such as H-bonding or ion pairing. Based on these weak interactions catalysis can be classified into three categories: phase-transfer catalysis,[51] H-bonding mediated catalysis[52] and chiral Brønsted bases promoted catalysis.[53]

1.3.2.1. Phase-transfer catalysis (PTC)

In this case, the nucleophile and the electrophile are in immiscible phases and the activation mode of the reaction occurs through the formation of an organic chiral ion-paired intermediate (Cat^+ Nu^-) between the catalyst and an anionic nucleophile. The reaction mechanism is initiated by the deprotonation of the nucleophile in the interface by an enough strong base for that, and which at the same time is compatible with water. Aqueous metal hydroxides or carbonates are the most used bases for this purpose. Exchange of the cation by a chiral counterion catalyst produces a new ion-paired intermediate (Cat^+ Nu^-), which is more soluble in organic solvents, facilitating, in this way, the reaction to occur in the organic phase. In addition, this chiral counterion is the responsible of the stereocontrol of the reaction. Figure 7 shows the mechanism of PTC exemplified for the Michael reaction.

[51] For general reviews on phase-transfer catalysis, see: a) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266. b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. c) Maruoka, K. *Asymmetric Transfer Catalysis*, **2008**, Wiley-VCH. d) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *526*, 4312–4348.

[52] For general reviews on H-bonding catalysis, see: a) Doye, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. b) Akiyama, Y. *Chem. Rev*. **2007**, *107*, 5744–5758. c) Yu, X.; Wang, W. *Chem. Asian J*. **2008**, *3*, 516–532. d) Zhang, Z.; Scheriner, P. R. *Chem. Soc. Rev*. **2009**, *38*, 1187–1198. e) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*, **2009**, Wiley-VCH, Weinheim, Alemania. f) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, 1–22. g) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633–2646.

[53] For general reviews on Brønsted base catalysis, see: a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T.; *Chem. Rev.* **2003**, *103*, 2985–3012. b) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595. c) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638. d) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. e) Tiang, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145–200.

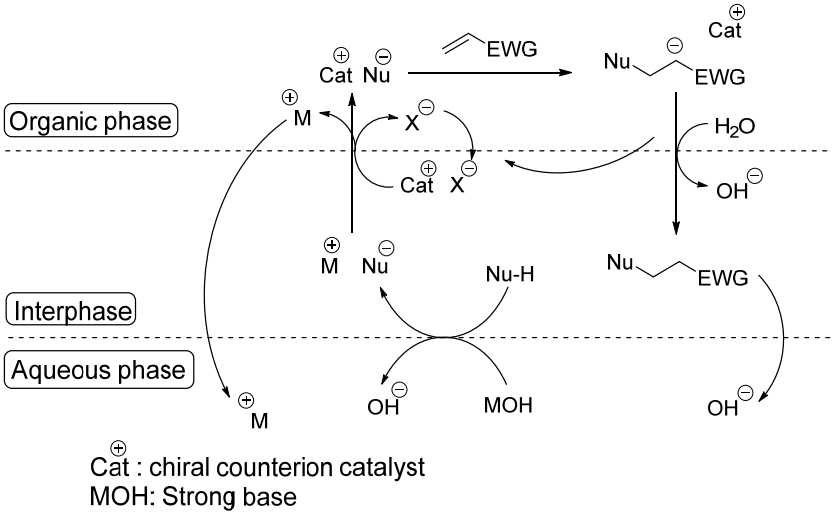


Figure 7. General mechanism of a conjugate addition operation under PTC.

The most representative catalysts for phase-transfer catalysis are generally chiral quaternary ammonium salts,[54] chiral phosphonium salts[55] or chiral crown ethers[56] (Figure 8).

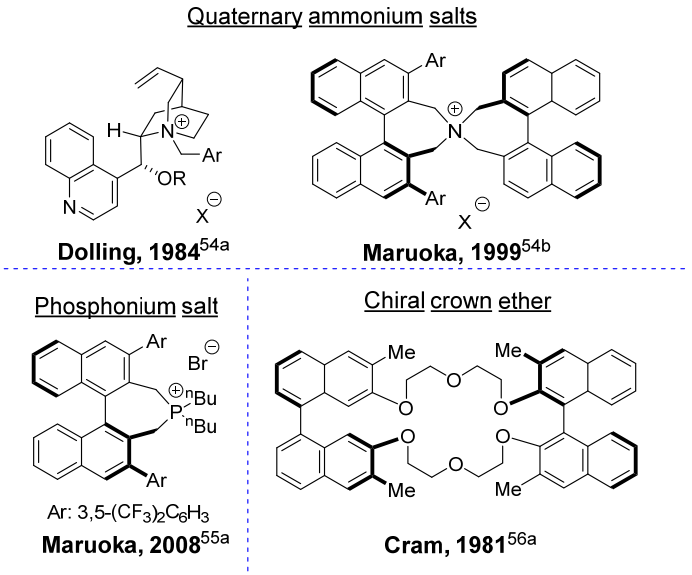


Figure 8. Representative catalysts used in PTC.

[54] For the pioneering study on the use of cinchone based quaternary ammonium salts, see: a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1984**, *106*, 446–447. For the first example of a binaphthyl based quaternary ammonium salt, see: b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

[55] For the first example of the use of quaternary phosphonium salts in phase transfer catalysis, see: a) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9466–9468. For general reviews on quaternary phosphonium salts in organocatalysis, see: b) Enders, D.; Nguyen, T. V. *Org. Biomol. Chem.* **2012**, *10*, 5327–5331. c) Liu, S.; Kumatabara, Y.; Shirakawa, S. *Green Chem.* **2016**, *18*, 331–341.

[56] For the first example of the use of chiral crown ethers in asymmetric catalysis, see: a) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625–628. For a review on asymmetric phase transfer reactions catalyzed by chiral crown ethers, see: b) Bakó, P.; Keglevich, G.; Rapi, Z. *Letters in Organic Chemistry*, **2010**, *7*, 645–656. For the speech of receiving the Nobel Prize award by Donald J. Cram, see: c) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020.

In the Michael reaction, this methodology is limited to *N*-protected α-amino esters (usually glycinate-benzophenone imines), active methylene compounds or nitroalkanes as Michael donors, due to the acidity needed to undergo deprotonation by the compatible bases with water.

1.3.2.2. Hydrogen bonding catalysis

The organocatalysts that participate in this activation mode have been usually developed as hydrogen bond or proton donor compounds. The mechanism is similar to the activation of electrophiles by metal Lewis acid catalysts, where electronic density is removed from the electrophile (LUMO-lowering effect). In addition, the stereochemical control of the reaction is exerted by the chiral structure of the organocatalyst. Therefore, an important aspect to consider is the design of the catalyst, which apart from incorporating functional groups that enable the engagement in one or multiple H-bonds and a chiral functionalization, they can also promote other secondary interactions with the nucleophile. This is the bifunctional catalysis[26] concept mentioned before. In this way, it is possible to overcome the limitation that this methodology suffers owing to the weak nature of the hydrogen bonds, which provides a weak enthalpic binding between the Brønsted acid catalyst and the electrophile. Examples of that are the bifunctional diol, (thio)urea or squaramide derived Brønsted base catalysts presented later (Brønsted base/H-bonding catalysis section).

Another representative catalyst of this type of activation is phosphoric acid (Figure 9), which contains a Brønsted acid and a chiral backbone.[57] In these cases, the strongly acidic OH group from the phosphoric acid enables to activate the electrophile through the formation of an H-bond or protonation. As mechanistic studies demonstrate, slight changes in the structure of the catalyst, for example introducing substituents with different electronic properties, address to an H-bonding or ion-pairing activation mode;[58] however, in some cases no conclusive data have been provided for this assumption.[59] Furthermore, in this structure, the P=O moiety interacts with the nucleophile and the BINOL scaffold is the chiral backbone, responsible of the facial control in the conjugate addition.

[57] For a review on asymmetric BINOL-phosphate derived Brønsted acid catalysts, see: a) Terada, M. *Chem. Commun.* **2008**, 4097–4112. b) Parmar, D.; Surgiono, E.; Rja, S.; Rueping, M. *Chem. Rev*. **2014**, *114*, 9047–9153. c) Monaco, M. R.; Pupo, G.; List, B. *Synlett* **2016**, *27*, 1027–1040.

[58] Fleischmann, M.; Drettwan, D.; Sugiono, E.; Rueping, M.; Gschwind, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6364–6369.

[59] A selected example in which no conclusive data about the H-bonded complex or ion-paring activation mode is provided, see: Saito, K.; Moriya, Y.; Akiyama, T. *Org. Lett.* **2015**, *17*, 3202–3205.

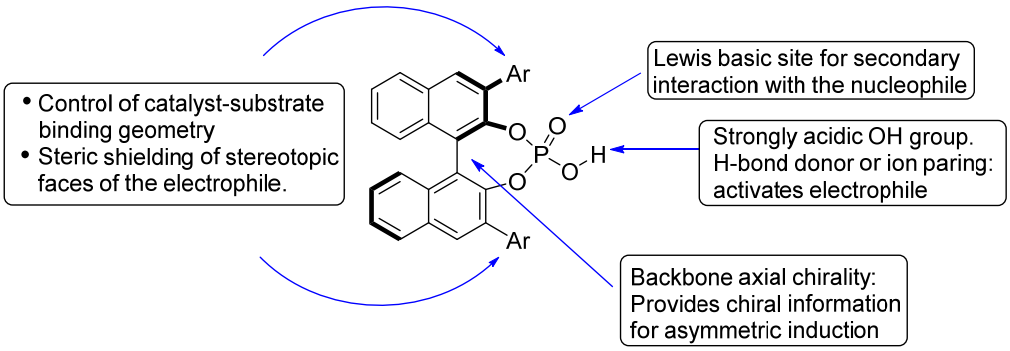
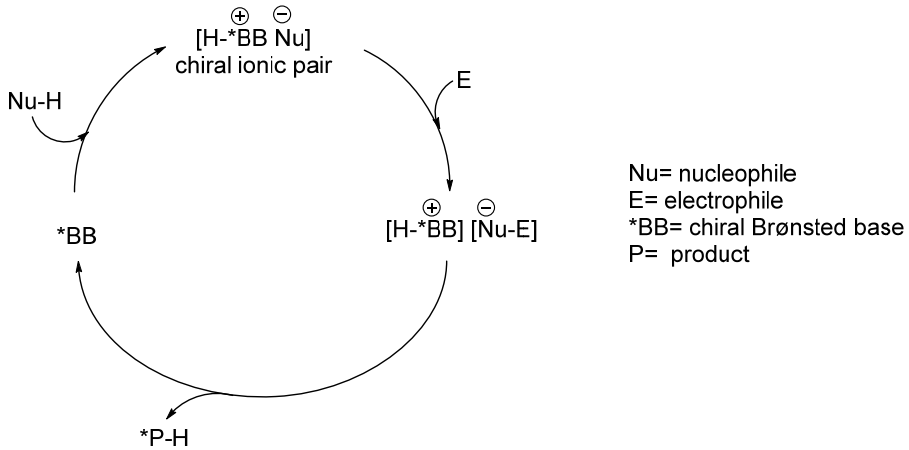


Figure 9. Relevant aspects of the design of chiral phosphoric acids as H-donor catalysts.

In conjugate additions, these catalysts activate the Michael acceptor, specifically α,β-unsaturated carbonyl compounds or nitroolefins, through H-bonding interactions. Nevertheless, the presence of strong acid catalysts means a disadvantage for this protocol, since a selective activation of different functionalities is required in order to reach conformationally rigid intermediates and well-defined transition states for obtaining enantioenriched compounds.

1.3.2.3. Chiral Brønsted base catalysis

The stereochemistry in an asymmetric reaction can also be controlled by a chiral base, which activates the pronucleophile. Although in homogeneous solution, the activation mode of the reaction is similar to phase transfer catalysis. A chiral Brønsted base (*BB) is able to accept a hydrogen (or proton) from an acid or pronucleophile, being this proton transfer the key activation step of this transformation. Afterwards, a new bond is created in the coupling between the reactants through the formation of a chiral ionic pair. In the last step, the product and the Brønsted base are liberated and the latter is free to initiate a new catalytic cycle (Scheme 3).



Scheme 3. Catalytic cycle promoted by chiral Brønsted bases.

Chiral Brønsted base catalysts have been developed and employed in several enantioselective transformations, namely, 1,2- and 1,4-additions to acyl and α,β-unsaturated acyl systems, respectively. For the design of these catalysts, different nitrogen-containing functionalities have been employed such as tertiary amines, guanidines, amidines and imidazoles (Figure 10).

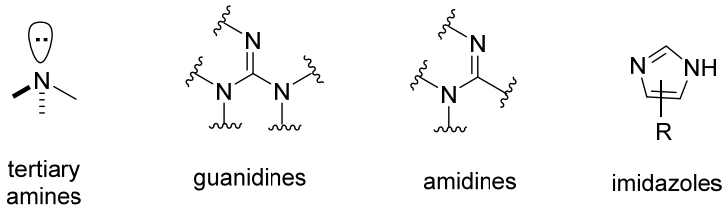
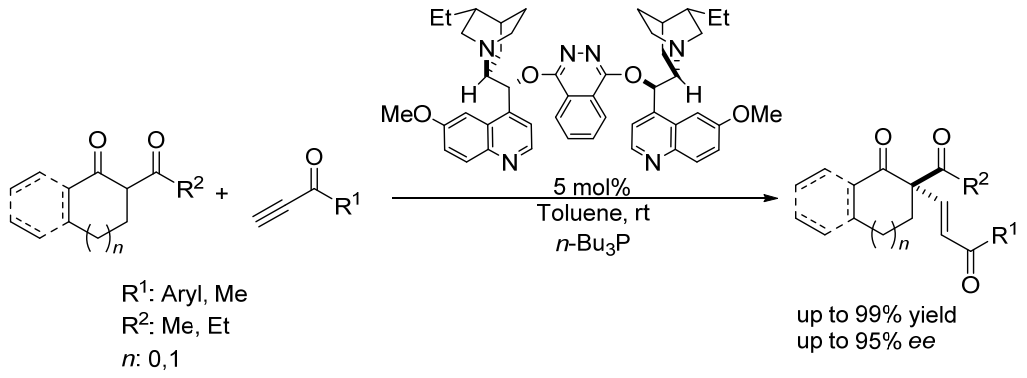


Figure 10. Basic core functions of chiral BB catalysts.

In the case of the Michael reaction, to the best of our knowledge, all cases reported refers to the use of dimeric cinchona alkaloid-derivatives.[60] A representative example reported by Jørgensen in 2004 is the first Michael addition of β-dicarbonyl compounds to alkynones (Scheme 4),[61] which is promoted by $(DHQ)_2PHAL$. The initial reaction leads to *E*/*Z*-enone mixtures of approximately 1:1 ratio and high values of enantiomeric excess for both adducts. Additionally, in the presence of silica gel the reaction mainly provides the *Z*-adduct (*Z*/*E*>98:2), while the addition of a catalytic amount of Bu_3P (10 mol %) yields mostly the *E*-adduct (*E*/*Z*>98:2), without affecting the yield or the enantioselectivity.



Scheme 4. First Michael addition of β-dicarbonyl compounds to alkynones catalyzed by chiral Brønsted base catalyst. **Jørgensen, 2004**.

[60] For selected examples of the use of Brønsted base catalysts in the Michael reaction, see: a) Xue, D.; Chen, Y.-C.; Wang, Q.-W.; Cun, L.-Y.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293–5296. b) Poulsen, T. B.; Bell, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2006**, *4*, 63–70. c) Nielsen, M.; Zhuang, W.; Jørgensen, K. A. *Tetrahedron* **2007**, *63*, 5849–5854. d) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205–2208. f) Yao, W.; Pan, L.; Wu, Y.; Ma, C. *Org. Lett.* **2010**, *12*, 2422–2425. e) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. *Beilstein J. Org. Chem.* **2012**, *8*, 1360–1365.

[61] a) Bella, M; Jørensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673.

As a consequence of the intrinsic nondirectional nature of electrostatic interactions in ion pairing complexes, the sense of stereoinduction exerted from the chiral catalyst is difficult to predict. In order to overcome this issue, sites with hydrogen-bond donor ability are included in the structure of the catalyst, generating a bifunctional organocatalyst. In this way, the BB of the organocatalyst activates the nucleophile through deprotonation generating an additional H-bond donor site (BBH^+). In this scenario, both, the activated nucleophile (Nu^-) and the electrophile can coordinate to the catalyst through these H-bond donor sites in different modes (see section 1.3), anchoring them in a more rigid transition state by which higher degree of stereochemical order can be achieved.

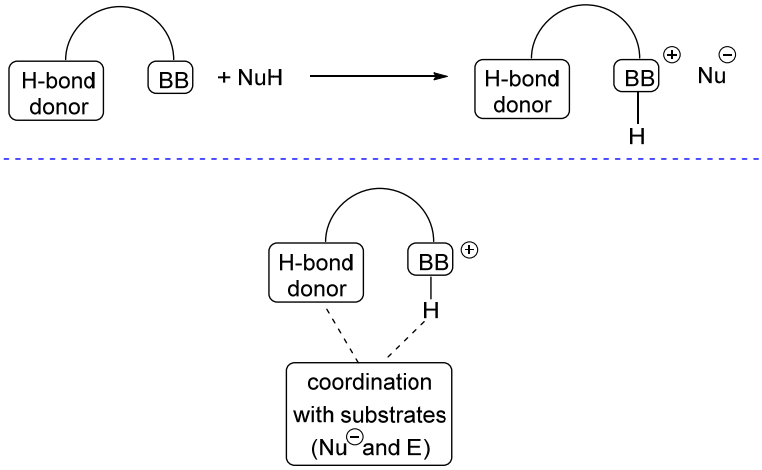


Figure 11. Activation mode of a bifunctional Brønsted base/H-donor catalyst.

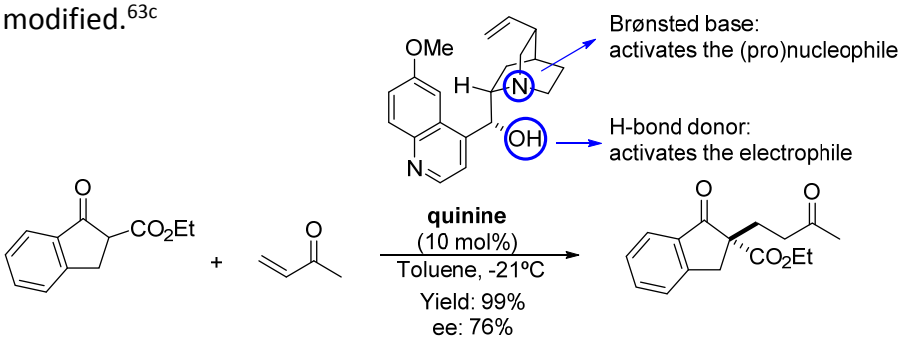
1.4. Brønsted Base/H-bonding catalysis

The previously cited first effective organocatalytic asymmetric reaction, which was promoted by *O*-acetylquinine (Scheme 2a),[29] set out the basis for the study of cinchona alkaloid-based catalysts in other reactions. The first use of an organic catalyst in an asymmetric Michael reaction appeared in 1973 and was reported by Lảngström and Bergeson.[62] Their studies consisted on the conjugate addition of β-keto esters to acrolein using 2-hydroxymethylquinuclidine as catalyst, albeit the authors were not able to determine the enantioselectivity. Two years later, Wynberg and Helder reported the use of a cinchona alkaloid (quinine) as a chiral catalyst for the Michael reaction of cyclic α-ketoesters and methyl vinyl ketone, demonstrating for the first time that an organic molecule could achieve asymmetric induction in this transformation (Scheme 5).[63]

[62] Lảngström, B.; Bergeson, G. *Acta Chem. Scand*. **1973**, *27*, 3118.

[63] For the first work published on asymmetric induction in a Michael reaction promoted by an organic catalyst, see: a) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057–4060. For later work see: b)

Moreover, the authors observed a bifunctional behaviour in the natural cinchona alkaloid, where the –OH group activates the methyl vinyl ketone through a H-bonding interaction and the quinuclidine basic moiety activates the 1,3-dicarbonyl pronucleophile. Despite the moderate enantioselectivities obtained (76% *ee*), these early studies revealed the significance of the –OH group, since its participation in the activation of the electrophile facilitates the orientation of the substrates for stereoselectivity control, providing better results, regarding activity and selectivity, than using cinchona alkaloid catalysts with the –OH group modified.[63c]



Scheme 5. Bifunctional behaviour as H-bond donor and Brønsted base of cinchona alkaloide catalysts. **Wynberg, 1975.**

The natural cinchona alkaloid and their derivatives (Figure 12) are highly regarded due to their usefulness as bifunctional Brønsted base/H-bonding catalysts in a great variety of important enantioselective transformations.[64]

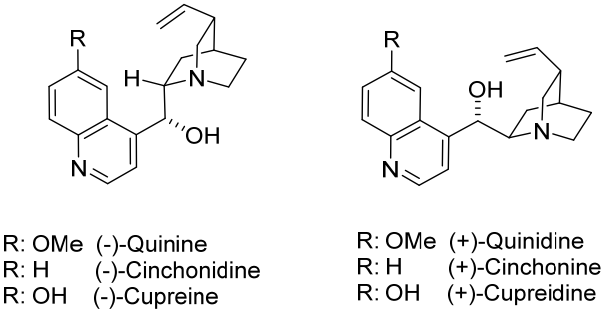


Figure 12. Cinchona alkaloid derivatives used as bifunctional organocatalysts.

Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238–2244. For a review, see: c) Wynberg, H. *Top. Sterochem*. **1986**, *16*, 87–129.

[64] For general reviews on cinchona alkaloid derivatives in asymmetric catalysis, see: a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *8*, 1229–1279. b) Marcelli, T. Marcelli, T. *Organocatalysis: Cinchona catalysts. Wiley Interdisciplinary Reviews: Computational Molecular Science*, **2011**, *1*, 142–152. c) Ager, D. *Comprehensive Chirality*, **2012**, *3.9*, 223–247. d) Singh, G.; Yeboah, E. *Reports in Organic Chemistry*, **2016**, *6*, 47–75. For reviews on cupreines and cupreidines as organocatalysts, see: e) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504. f) Bryant, L. A.; Fanelli, R.; Cobb, A. J. A. *Beilstein J. Org. Chem.* **2016**, *12*, 429–443.

Other Brønsted base/H-bonding bifunctional catalysts have been designed through modular structures such as urea, thiourea, squaramide and sulfonamide (Figure 13a). These backbones contain amine moieties as H-bond donor groups and a chiral Brønsted base that activates the nucleophile by deprotonation, providing an additional anchoring point and facilitating reaction stereocontrol. In addition, an electron-withdrawing substituent (R) is usually incorporated in the structure to increase the H-bonding activity, such as an aryl substituent that contains non basic electron-releasing groups, for example CF_3.

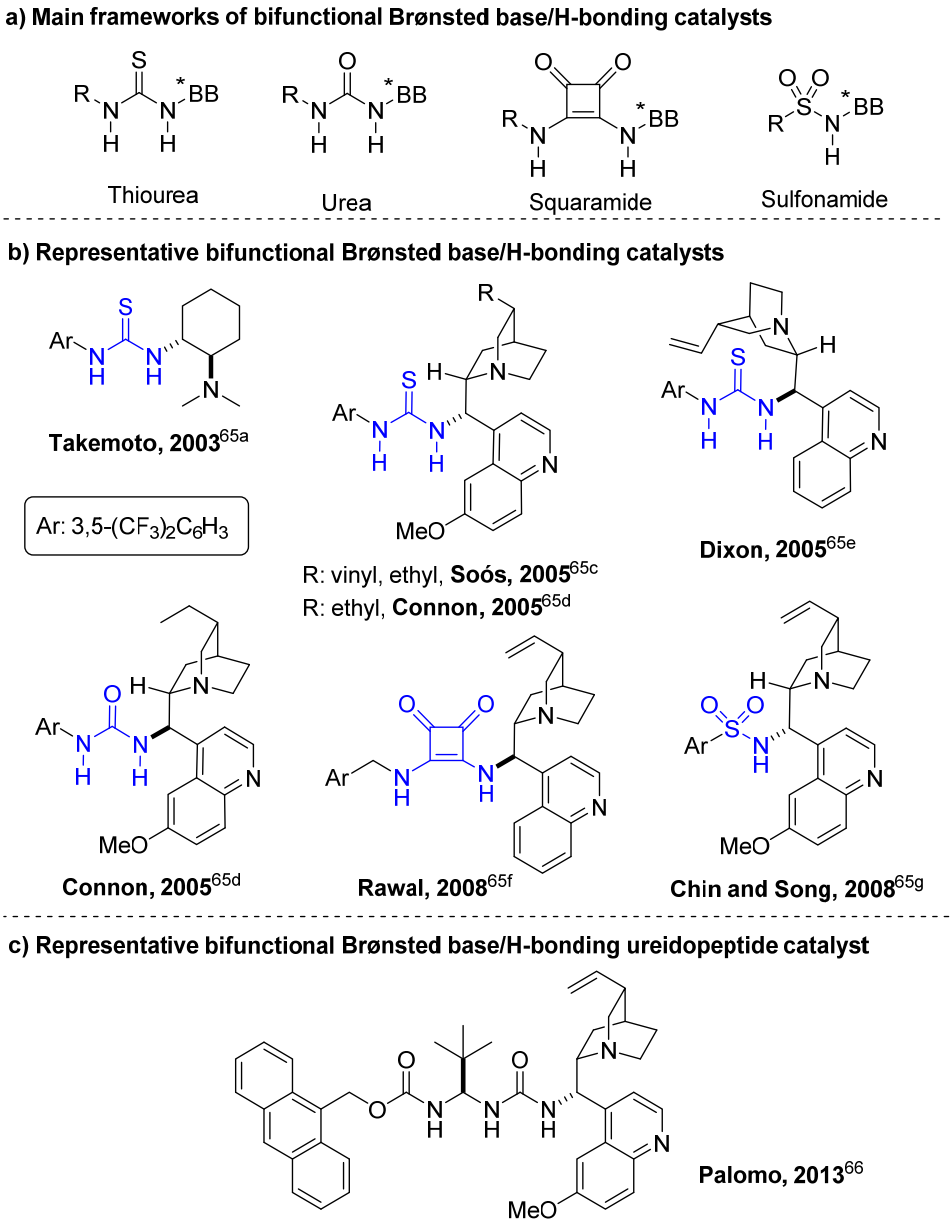


Figure 13. Structural features and representative examples of Brønsted base/H-bonding catalysts.

Figure 13b shows the most representative catalysts with this structure.[65] In addition to these frameworks, our group developed a new family of bifunctional BB/H-bonding catalysis, the ureidopeptides,[66] which contain three hydrogen donor sites (Figure 13c).

The study on the use of bifunctional BBs incorporating the thiourea moiety in the Michael addition of α-substituted β-ketoesters to nitroolefins[65a] reported by Takemoto in 2003, which afforded the Michael adducts in excellent yields (up to 94%), enantioselectivities (up to 95%) and diastereoselectivities (up to 96:4), meant a breakthrough in organocatalysis. Thus, in 2005, Soós,[65c] Connon[65d] and Dixon[65e] independently reported the first effective use of (thio)urea-cinchona alkaloid catalysts, particularly in the case of the Michael addition. These catalysts consisted of a cinchona alkaloid structural backbone whose hydroxyl group at C9 had been substituted by an aryl(thio)urea moiety (Figure 13b).[67]

Other "privileged" chiral structures[68] have also been integrated in this type of (thio)urea catalysts. In 2005, Wang *et al.* published the use of a new bifunctional binaphtyl-derived amino thiourea catalyst (Figure 14a) in Michael additions of 1,3-diketones to nitroalkenes with high enantioselectivities.[69] Afterwards, this catalyst was also reported to be efficient at the particularly difficult conjugate addition of nitroalkanes to nitroalkenes.[70] Brønsted base/H-bonding catalysts involving TADDOL and thiourea moieties (Figure 14b) have also been synthetized; however, to our best knowledge, there

[65] For the first examples of the use of a Brønsted base incorporating a thiourea moiety, see: a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673. b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125. For the first examples of the use of a cinchona alkaloid-based catalyst incorporating a thiourea moiety, see: c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969. d) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370. e) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481–4483. For the first examples of the use of a cinchona alkaloid-based catalyst incorporating a squaramide moiety, see: f) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417. For the first examples of the use of a cinchona alkaloid-based catalyst incorporating a sulfonamide moiety, see: g) Oh, S.-H.; Rho, H.-S.; Lee, W. J.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 7872–7875.

[66] For the first example of the use of an ureidopeptide catalyst in asymmetric reactions, see: Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[67] For reviews on thiourea catalysts derived from diamines with C2-symmetry, see: a) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593–601. For reviews on cinchona-based thiourea organocatalysts, see: b) Connon, S. J. *Chem. Commun.* **2008**, *44*, 2499–2510. c) Xi, Y.; Shi, X. *Chem. Commun.* **2013**, *49*, 8583–8585. d) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

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

[69] Wang, J.; Li, H.; Duand, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713–4716.

[70] Rabalakos, K.; Wulff, W. D. *J. Am. Chem. Soc*. **2008**, *130*, 13524–13525.

is an only study on their application as asymmetric organocatalysts, concretely, in the Friedel-Crafts alkylation of indole[71] with low yields and levels of enantioselectivity.

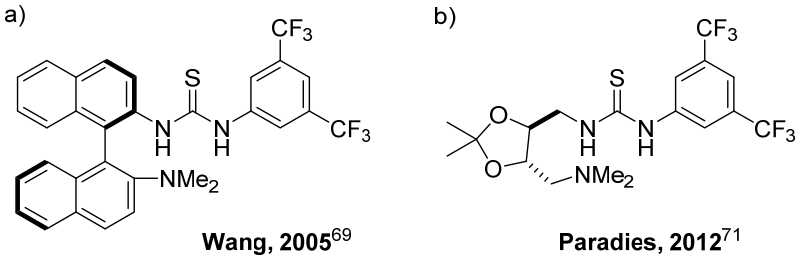


Figure 14. Bifunctional Brønsted base/H-bonding catalysts incorporating binaphtyl or TADDOL.

The mechanism of these thiourea-catalyzed Michael additions has been the subject of several studies, in which four main possible activation modes have been proposed (Figure 15). Nonetheless, slight modifications in the structure either of the substrates or of the catalyst, for instance, in the chiral scaffold at the catalyst could affect the reaction mechanism and hence the stereoselectivity of the Michael adducts, so each reaction must be studied in a particular fashion.

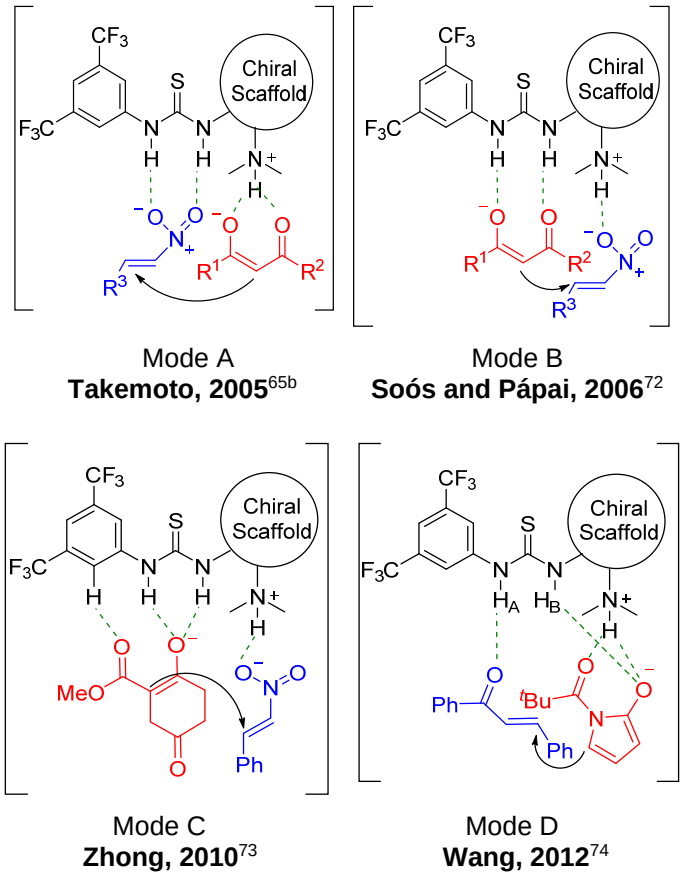


Figure 15. Activation modes proposed for bifunctional thiourea-catalyzed asymmetric Michael additions.

[71] Paradies, J.; Lauber, M.; Fröhlich, R. *Synthesis*, **2012**, *44*, 3209–3215.

Based on ^{1}H NMR studies, Takemoto and coworkers proposed Mode A (Figure 15) for the Michael addition of diethyl malonate to *trans*-β-nitrostyrene,[65b] in which the acidic α-carbon of the nucleophile is deprotonated by the tertiary amine of the catalyst; then, the protonated amine coordinates to the enolate nucleophile while the thiourea moiety links to the electrophile. In contrast, one year later, Soós and Pápai *et al.* reported Mode B for the same reaction by using 2,4-pentadione as the nucleophile (Figure 15),[72] based on DFT calculations of the relative energies of pre-reaction complexes, in which the thiourea moiety links to the nucleophile and the protonated amine coordinates to the electrophile. In 2010, supported by ^{1}H NMR and DFT studies on the relative energies of the different transition states for the reaction of methyl 2,5-dioxocyclohexane-1-carboxylate to the same nitroolefin that previous ones, Zhong reported Mode C (Figure 15),[73] similar to Mode B. Although, in this case, the proposed transition state also incorporates the formation of a hydrogen bond between the ester group of the nucleophile and the *ortho* hydrogen atom from the phenyl group of the catalyst. Finally, by locating competing transition states in the addition of α,β-unsaturated γ-butyrolactams to chalcone, Wang and coworkers proposed Mode D (Figure 15),[74] in which the nucleophile is simultaneously coordinated to the protonated amine and the N-H_B of the thiourea moiety while the other N-H_A coordinates to the electrophile.

In 2008, a new family of cinchona alkaloid-based catalysts involving a squaramide moiety (Figure 13b) was developed.[65f] Since this pioneering report from Rawal's group, chiral amino-squaramides have emerged as an effective tool in organocatalysis,[75] with remarkable applications in domino and tandem processes.[76] It is interesting to note that the enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkenes in the presence of this family of catalysts can also proceed in brine, with dramatic acceleration compared to that in organic solvents owing to the hydrophobic effect.[77]

Comparing the squaramide catalyst to its thiourea counterpart, there are some differences that affect the catalyzed reaction outcome. i) Duality, squaramides contain two hydrogen-bond donors (N–H) and two carbonyl acceptors (C=O), making possible

[72] Hamza, A.; Schubert, G.; Soós, t.; Papai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.
[73] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682–2685.
[74] Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813–9825.
[75] For an overview on squaramides as organocatalysts, see: a) Aleman, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899. b) Storer, I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. c) Han, X.; Zhou, H.-B.; Dong, C. *Chem. Rec*. **2016**, *16*, 897–906. d) Zhao, B.-L.; Li, J.-H.; Du, D.-M. *Chem. Rec.* **2017**, *17*, 994–1018.
[76] For a review on squaramide-catalyzed domino and tandem reactions, see: Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 254–281.
[77] Bae, H. Y.; Some, S.; Oh, J. S.; Lee, Y. S.; Song, C.E. *Chem. Commun*. **2011**, *47*, 9621–9623.

three H-bonding patterns (Figure 16, i).[78] ii) Both are structurally rigid, but the relative distance and spacing between the two N–H groups in the bisamides of a squaramide is approximately one third larger than that in a thiourea and the squaramide structure induces a convergent orientation of the N–H groups, canting each by approximately 6° (Figure 16, ii). These data were calculated by Takemoto[65b] and Rawal[65f] in their respective works. The H-bond angle in the squaramide unit may give rise to the greater linearity in hydrogen bonding (for some substrates) providing different binding properties in the transition state. iii) Finally, in both, thioureas and squaramides the lone pair on the nitrogen atom is delocalized, thereby restricting the rotation of the C–N bond. Regardless, the delocalization in squaramides can occur through the cyclobutenedione system (Figure 16, iii), as a result, the N-H acidity of the squaramide is higher compared to thiourea analogous (pK_a values of squaramides are lower than their thiourea analogous, 0.13–1.97 pK_a gap units).[79] This difference between the N-H acidity provides stronger hydrogen bonds for squaramides, explaining their higher activity, even at relatively low squaramide catalyst loading.

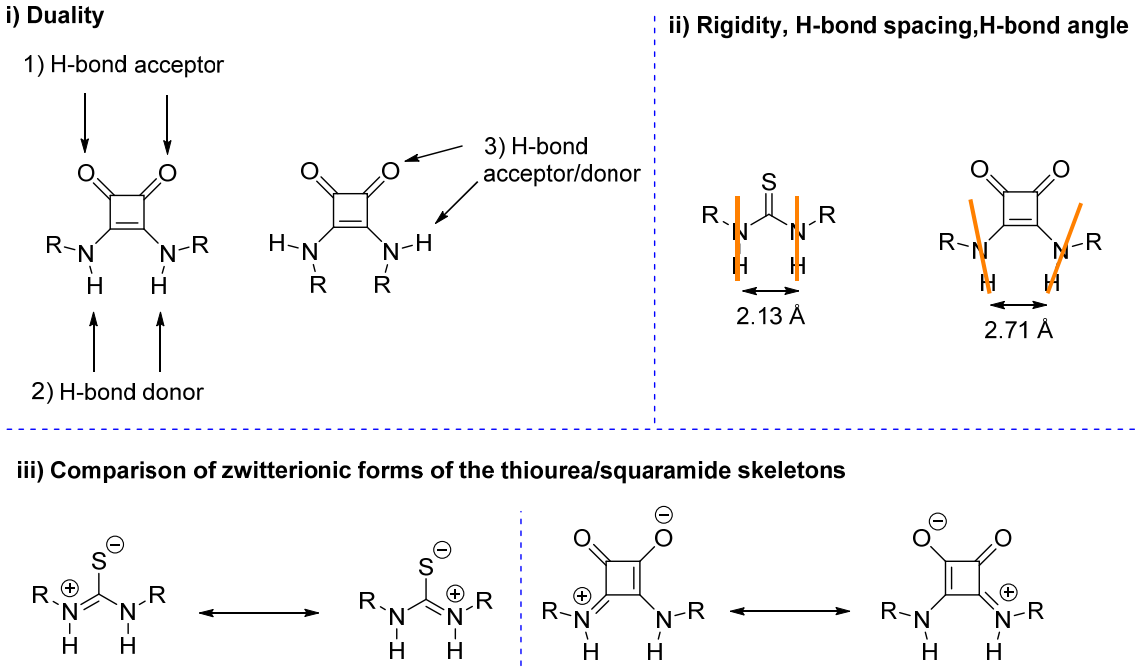


Figure 16. Structural differences between thiourea and squaramide units.

The examination of the catalytic activity of cinchona squaramide catalysts in the Michael addition of nitroalkanes to enones by DFT calculations by Yang and Du[80] in 2010

[78] a) Tomàs, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deyá, P. M.; Ballester, P.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394–9401. b) Davis, A. P.; Draper, S. M.; Dunne, G.; Ashton, P. *Chem. Commun.* **1999**, 2265–2266.
[79] Ni, X.; Li, X.; Wang, Z.; Cheng, J. P. *Org. Lett.* **2014**, *16*, 1786–1789.
[80] Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450–5453.

and most recent theoretical studies by Soós and Pápai suggest that their mode of activation is closely related to bifunctional thiourea catalysts.[81,82]

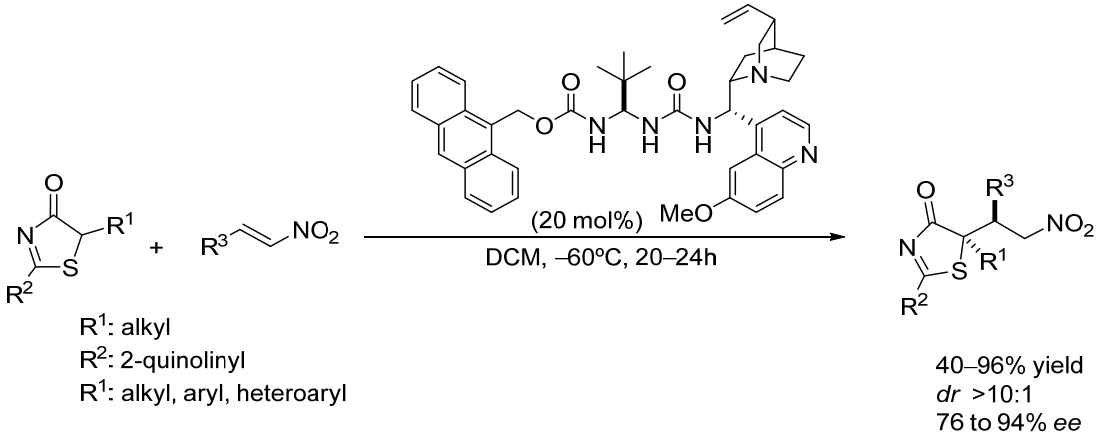
Despite (thio)urea- and squaramide based organocatalysts have provided excellent enantioselectivities in many cases, some of the reported methods suffer from several drawbacks such as a limited combination of nucleophile and electrophile type, the need for a large excess of substrates and reaction times up to weeks in some cases. In addition, these catalysts can auto-associate, forming hydrogen-bonded aggregates, under concentrated reaction conditions or low temperatures,[83] because of their bifunctional nature, bearing both acidic and basic moieties[84,85] Consequently, reactivity and enantioselectivity decrease being the self-association a noteworthy issue in the efficiency of bifunctional acid-base catalysts. Furthermore, thiourea groups tend to degrade under thermal conditions.[86]

In 2008, Song and coworkers introduced a bifunctional cinchona-based sulfonamide catalyst (Figure 13b), for the desymmetrization of cyclic *meso*-anhydrides.[65g] The catalytic activity, enantioselectivity and/or diastereoselectivity in the reactions assisted by pyrrolidine sulfonamide catalyst were the result of the acidic[87] and sterically bulky properties of the sulfonamide moiety. Hence, the incorporation of *N*-sulfonamides into the quinidine structural scaffold turned out in a bifunctional organocatalyst with the possibility of engaging hydrogen bonds between the acidic hydrogen of the *N*-sulfonamide and the electrophile, and simultaneously, the quinuclidine group would be able to activate the nucleophile as a Brønsted base.[88] Furthermore, this sulfonamide catalyst only possesses a single hydrogen-bonding donor, that despite being more acidic than in thioureas, makes it less prone to dimerize solving the (thio)ureas and squaramides catalysts' issue. However, so far, the reactions using sulfonamide based catalysts is limited

[81] Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**, *20*, 5631–5639.
[82] For a recent overview on the mechanism in cinchona thiourea- and squaramide-catalyzed asymmetric Michael additions of nitroalkanes to enones, see: Grayson, M. N. *J. Org. Chem.* **2017**, *82*, 4396–4401.
[83] Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208–1210.
[84] For a detailed NMR study confirming that thiourea-based catalysts are in equilibrium between the self-associated dimeric and monomeric forms in solution state, see: a) Tarkanyi, G.; Kiraly, P.; Varga, S.; Vakuya, B.; Soós, T. *Chem. Eur. J.* **2008**, *14*, 6078–6086. b) Kiraly, P.; Soós, T.; Varga, S.; Vakulya, B.; Tarkanyi, G. *Magn. Reson. Chem*. **2010**, *48*, 13–19.
[85] X-Ray cristal structure of Rawal's catalyst shows that it exixts as a hydrogen-bonded aggregate in the solid state, see: ref. 65f, page 25. b) Portell, A.; Barbas, r.; Braga, D.; Polito, M.; Puigjaner, C.; Prohens, R. *CyrstEngComm*, **2009**, *11*, 52–54.
[86] It was reported that hydroquinine-based thioureas are thermally unstable: Ref. 65c, page 25.
[87] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
[88] Reiter, C.; López-Molina, S.; Schmid, B.; Neiss, C.; Görling, A.; Tsogoevva, S. B. *ChemCatChem* **2014**, *6*, 1324–1332.

to desymmetrization of cyclic anhydrides, enantioselective decarboxylative aldol reaction of MAHTs with aldehydes and Michael additions with nitroolefins.[89]

In 2013, our group developed a new effective type of bifunctional Brønsted base/H-bonding catalysts, which involve an ureidopeptide unit with three H-bond donor sites and three modifiable parts (Figure 13c).[90] The first use of this catalyst family in the Michael addition of 5*H*-thiazol-4-ones to nitroolefins led to good yields and high diastereo- and enantioselectivity (Scheme 6);[66] later its application in Mannich[90b-c] and aldol[90d-e] reactions has also been reported showing the generality of these bifunctional catalysts in asymmetric organocatalysis.



Scheme 6. First example of Michael reaction assisted by an ureidopeptide-based Brønsted base bifunctional catalyst. **Palomo, 2013**.

Furthermore, other representative family of compounds that have also been employed as Brønsted base/H-bonding catalysts are chiral guanidines.[91] Regarding how the guanidine group is incorporated into a ring framework, guanidine catalysts are structurally classified into acyclic, monocyclic or bicyclic guanidines. Their bifunctional behaviour is owing to their strong Brønsted base character enabling deprotonation of the

[89] For a general review on the use of bifunctional cinchona-based sulfonamide catalysts in asymmetric organocatalysis, see: Bae, H. Y.; Song, C. E. *Bull. Korean Chem. Soc.* **2014**, *35*, 1590–1600.

[90] For the Michael reaction, see: a) ref.66, page 25. For the Mannich reaction, see: b) Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526–6531. c) Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 13332–13336. For the aldol reaction, see: d) Lapuerta, I.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2016**, *22*, 7229–7237. e) Etxabe, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.

[91] For more information on guanidine-catalyzed reactions, see: a) Nagasawa, K.; Sohtome, Y. *Science of Synthesis, Asymmetric Organocatalysis* **2012**, *2*, 1–40. b) Terada, M. *Asymmetric Synthesis II: More methods and applications* **2012**, *34*, 273–278. c) Selig, P. *Guanidines as Reagents and Catalysts I, Topics in Heterocyclic Chemistry*, **2017**, Springer Cham. d) Hosoya, K.; Odagi, M.; Nagasawa, K. *Tetrahedron Lett*. **2018**, *59*, 687–696. e) Dong, S.; Feng, X.; Liu, X. *Chem. Soc. Rev.*, **2018**, *47*, 8525–8540.

pronucleophile and providing, therefore, sites for multiple H-bonding interactions with the enolate nucleophile and the electrophile concomitantly (Figure 17).

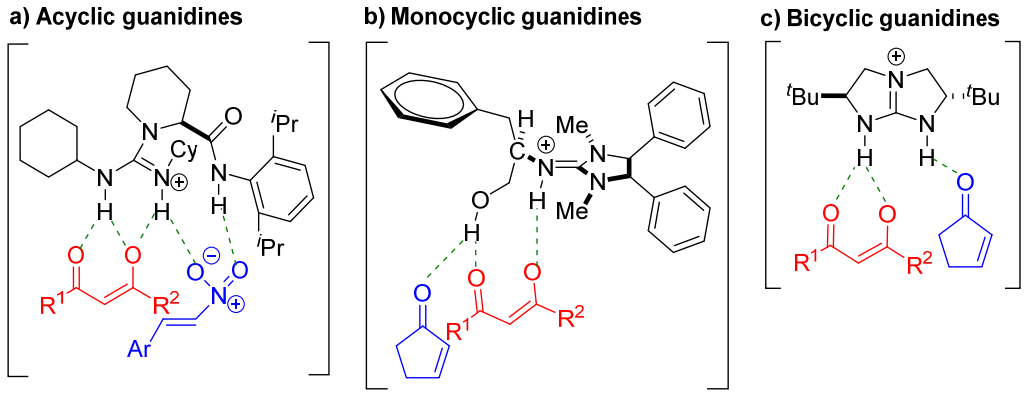


Figure 17. Examples of bifunctional Brønsted base/H-bonding activation of guanidines in Michael reactions.

To conclude, despite chiral Brønsted bases mediated asymmetric catalysis has been successfully employed generally in 1,2- and 1,4- addition reactions, most of the methods are restricted to relatively acidic pronucleophiles, meaning, easily enolizable nucleophiles, such as active methylenes (1,3-diketones, β-keto esters, β-cyano esters, malonates, malononitriles), nitroalkanes and thiophenols. Moreover, most of these asymmetric reactions to date lead to the formation of a single stereogenic center or provide two consecutive new stereogenic centers with variable diastereoselectivity.

1.5. Limitations and objectives

As it has been mentioned, in asymmetric catalysis promoted by Brønsted bases a key aspect is the pK_a value of the pronucleophiles in relation with that of the BB employed. The pK_a values of the tertiary amines used as catalysts in the direct methods lie between 11 and 21 (Figure 18a shows pK_a values for some BB catalysts in DMSO);[79,92] thus, on the average, BB catalysts require pronucleophiles with pK_a values of 16–20.[93] Therefore, the prefereable substrates are enolizable 1,3-dicarbonyl compounds, which exhibit a low pK_a value (Figure 18b) and have been widely used in this type of catalysis. However, ketones

[92] a) Li, X.; Deng, H.; Zhang, B.; Li, J.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 450–455. b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724–1727. c) Ho, J.; Zwicker, V. E.; Yuen, K. K. Y.; Jolliffe, K. A. *J. Org. Chem.* **2017**, *82*, 10732–10736.

[93] a) Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591. b) Guang, J.; Rout, S.; Bihani, M.; Larson, A. J.; Arman, H. D.; Zhao, J. C.-G. *Org. Lett.* **2016**, *18*, 2648–2651.

and aldehydes are in the borderline with pK_a values around 17, which means more difficulty for their activation and esters are the most challenging ones.[94]

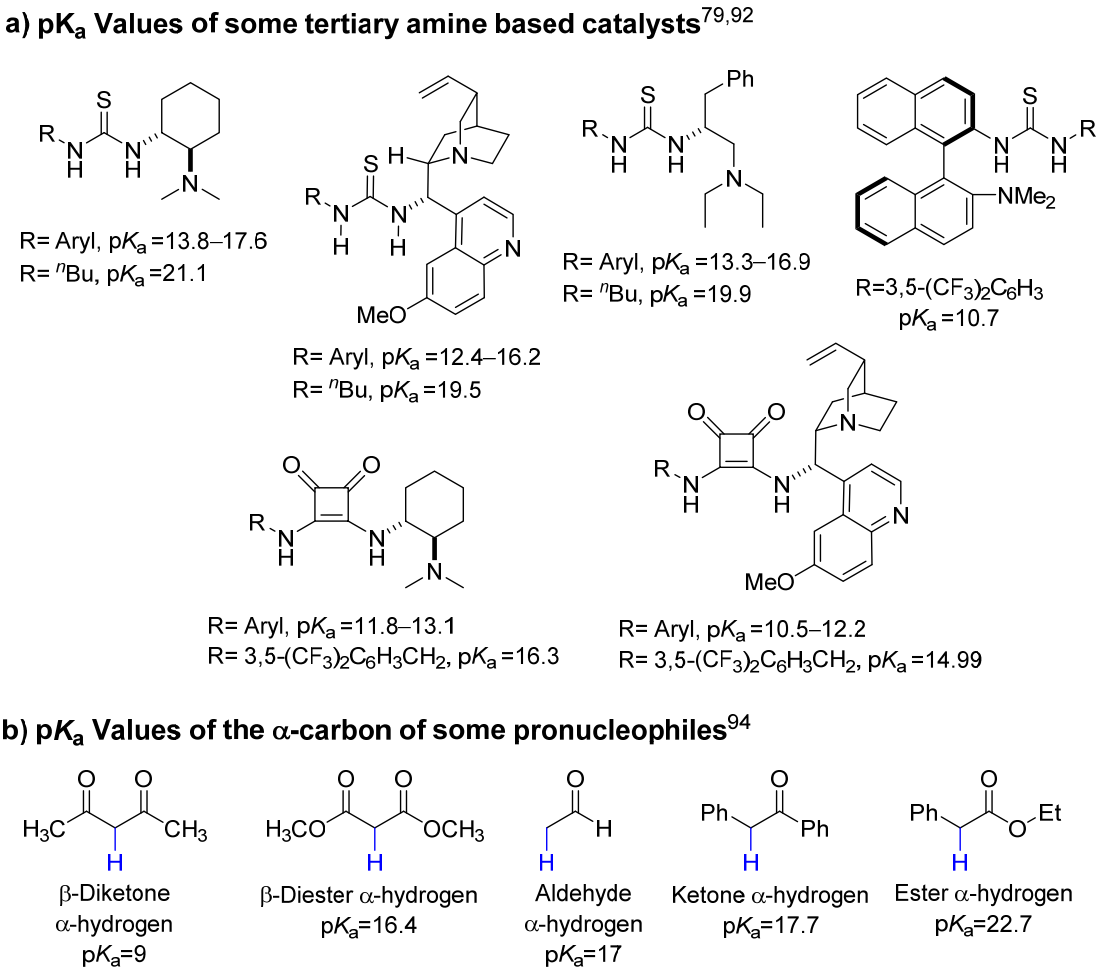
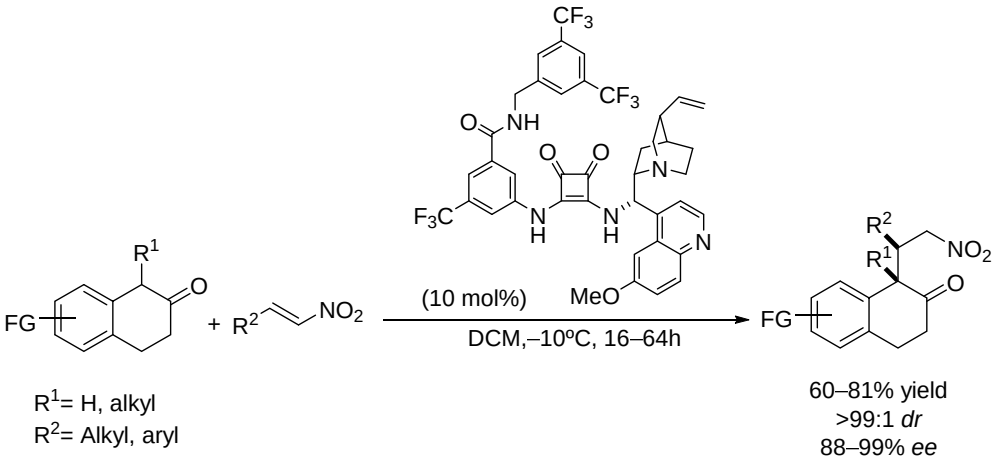


Figure 18. a) pK_a Values of representative tertiary amine based catalysts. b) pK_a Values of the α-carbon of some pronucleophiles.

In particular, in Michael reactions, the direct α-functionalization of aldehydes and ketones has been mostly catalyzed through enamine activation by chiral primary and secondary amines. Nonetheless, scarce examples are found in the literature in Michael reactions assisted by Brønsted base/H-bonding catalysis for ketones, which, in order to activate the removal of the α-proton by electronic tuning, bear an EWG at the α-position or activating equivalents. In this context, our group reported in 2017 the Michael addition of α-monosubstituted β-tetralones to nitroalkenes catalyzed by a squaramide-cinchona

[94] For a webpage of Bordwell pK_a values (acidities in DMSO) of different compounds, see: http://www.chem.wisc.edu/areas/reich/pkatable/index.htm.

Brønsted base organocatalyst providing the corresponding products in good yield and excellent diastereo- and enantioselectivity (Scheme 7).[95]



Scheme 7. Asymmetric organocatalyzed Michael addition of β-tetralones to nitroolefins. **Palomo, 2017**.

In contrast, for aldehydes the conjugate addition promoted by Brønsted base catalysts remains elusive. Likely, this is due in part to the relatively low acidity of the α-carbon and additionally to the difficulty in controlling the side reactions owing to the inherent high reactivity of the carbon atom in that oxidation state (i.e. self-condensation).

To sum up, the direct α-functionalization of aldehydes and ketones promoted by Brønsted base/H-bonding catalysis is still challenging. Thus, the general aim of this Doctoral Thesis has been to study the Michael addition of benzylic ketones and arylacetaldehydes assisted by Brønsted base/H-bonding catalysis.

In this respect, among all the Michael acceptors, nitroalkenes have turned out to be very attractive compounds,[96] because of the presence of the nitro group, which is the strongest known electron withdrawing group.[97] In addition, its ability to undergo a wide range of functional group transformations makes it a masked precursor of many useful functionalities (Figure 19).[98] For instance, it can be converted into a carbonyl group

[95] Urruzuno, I.; Mugica, O.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 2059–2063.

[96] For reviews on Michael additions to nitroalkenes, see: a) Somanathan, R.; Chavez, D.; Servin, F. A.; Romero, J.A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; Anaya, D. P. C.; González, J. *Curr. Org. Chem.* **2012**, *16*, 2440–2461. b) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627–2648. c) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gómez, C.; Guillena, G.; Pastor, I. M.; Ramón, D. J. *Molecules* **2017**, *22*, 895. For a theoretical evaluation of the Michael acceptor ability of conjugated nitroalkenes, see: d) Rai, V.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2006**, 4693–4703.

[97] Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia*, **1979**, *33*, 1–18.

[98] For more information on nitro compounds, see: a) Iyer, S. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, VCH, Weinheim, **1990**. b) Ono, N. *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

through the Nef reaction[99] or using Cr(II) compounds,[100] into a carboxylic acid under Mioskowski conditions,[101] or into primary amines[102] or hydroxyl amines by reduction.[103] Processes such as nucleophilic displacement[104] or the conversion into nitrile oxide[105] are also possible transformations (Figure 19).

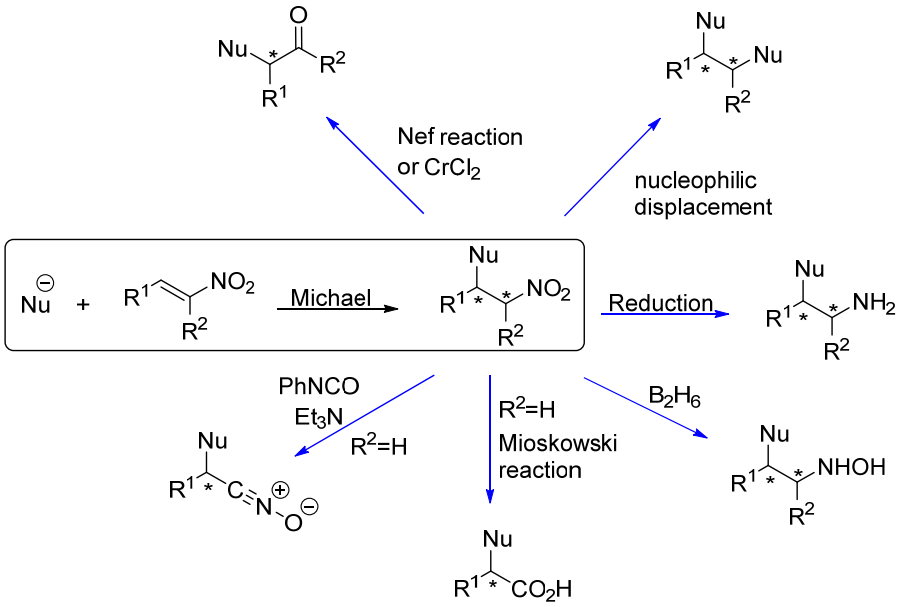


Figure 19. Possible transformation of the nitro group.

In this context, α-hydroxy α'-aryl ketones were selected for their study as pronucleophiles in the Michael reaction with nitroolefins assisted by bifunctional Brønsted base catalysts (Scheme 8). The α-hydroxy ketone framework is probable in 1,4-chelate conformation which facilitates the intramolecular hydrogen bonding and consequently, increases the acidity of the α'-carbon which is the only position for enolization. Furthermore, we envisioned that an aryl substituent at the α'-carbon in the ketone would induce a stabilization in the formed enolate intermediate by charge delocalization through the aromatic ring.

[99] a) Nef, J. U. *Justus Liebigs Ann. Chem*. **1894**, *280*, 263–291. b) Pinnick, H. W. *Org. React.* **1990**, *38*, 655–792. c) Ballini, R.; Petrini, M *Tetrahedron*, **2004**, *60*, 1017–1047. d) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357*, 2371–2402.

[100] Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 3777–3778.

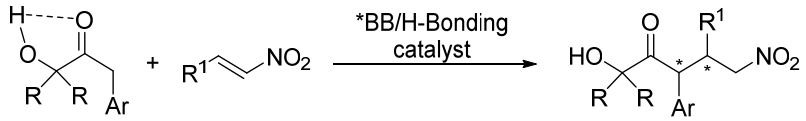
[101] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234–235.

[102] a) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733–5734. b) Larock, R. C. *Comprehensive Organic Transformations*, VCH, New York, **1989**, 411–415. c) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609. d) Göksu, H.; Sert, H.; Kilbas, B.; Sen, F. *Curr. Org. Chem*. **2017**, *21*, 794–820.

[103] Feuer, H.; Bartlett, R. S.; Vincent, B. F. Jr.; Anderson, R. S. *J. Org. Chem*. **1965**, *30*, 2880–2882.

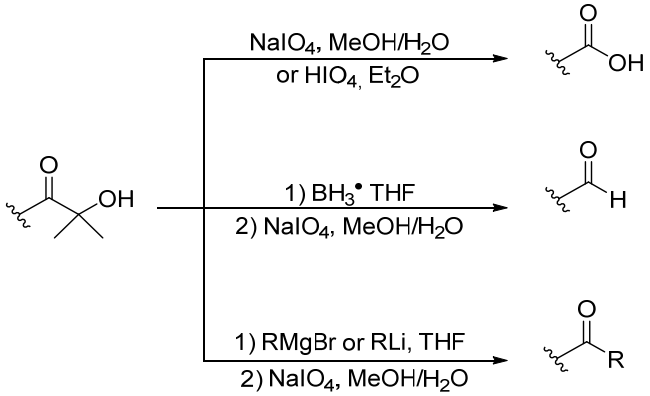
[104] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423–434.

[105] Mukayama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.



Scheme 8. Proposed stereoselective Michael addition of α'-hydroxy ketones to nitroolefins promoted by Brønsted base/H-bonding catalysis.

Additionally, an interesting aspect of this moiety is that the resulting Michael adducts can be converted under smooth conditions, as previously shown in our group,[106] into some organic functionalities such as carboxylic acids, aldehydes and ketones (Scheme 9) whose α-functionalization is more problematic.

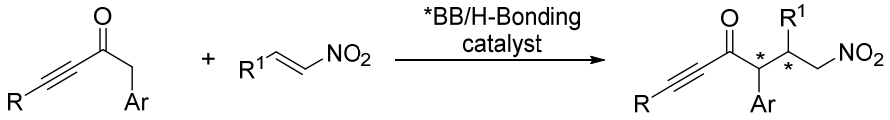


Scheme 9. Possible transformations of the α-hydroxy ketone moiety.

All the results concerning the use of α-hydroxy ketones as pronucleophiles as well as the transformations of the resulting adducts are collected in Chapter 2.

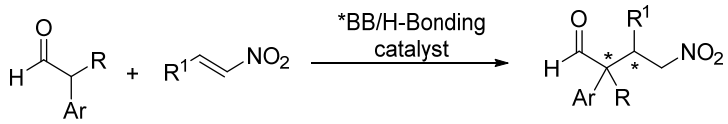
In this line of thought, we also envisaged that a ketone bearing an acetylene group (α,β-ynones) would increase the acidity of the α'-carbon and restrict the enolate formation in only this site. In addition, a phenyl group in the α'-carbon could stabilize the enolate intermediate. Therefore, these benzylic alkynyl ketones could be also suitable substrates for their reaction with nitroolefins in the presence of bifunctional Brønsted bases/H-bonding catalysts (Scheme 10). Moreover, the combination of the carbon-carbon triple bond and the carbonyl function would give access to a wide variety of transformations in order to build complex structures. The results of this proposal are presented in Chapter 3.

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



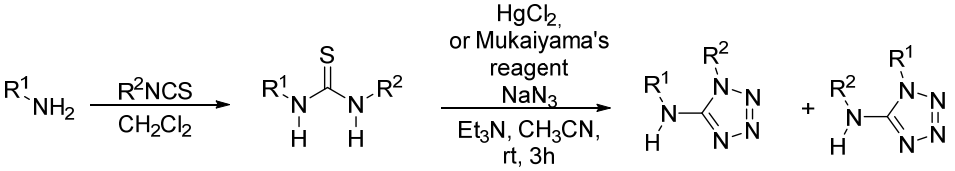
Scheme 10. Proposed stereoselective Michael addition of benzylic alkynyl ketones to nitroolefins promoted by Brønsted base/H-bonding catalysis.

In addition, the last part of this Doctoral Thesis has focused on the study of the Michael addition of α-branched arylacetaldehydes to nitroolefins promoted by Brønsted base/H-bonding catalysis, field that remains entirely unexplored. For that and similar to the previous proposals, we envisioned that an aryl substituent at the α-carbon of the aldehyde could provide the necessary acidity to this carbon and stabilize the enolate intermediate in order to be activated by a bifunctional Brønsted base catalyst (Scheme 11). The results of this investigation are described in Chapter 4.



Scheme 11. Proposed stereoselective Michael addition of arylacetaldehydes to nitroolefins promoted by Brønsted base/H-bonding catalysis.

Finally, a short stay was carried out under the supervision of Prof. Robert Batey in the Lash Miller Chemical Labs at the University of Toronto (UofT) in Canada. The research project was focused on the preparation of 1-substituted-5-amino substituted tetrazoles from the non symmetric thioureas in the presence of stoichiometric amounts of mercury chloride or the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) and sodium azide (Scheme 12). The corresponding results are presented in Chapter 5.



Scheme 12. Synthesis of 1-substituted-5-aminotetrazles from non symmetric thioureas.

CHAPTER 2.

α-Hydroxy α'-aryl ketones as Michael donors

α-Hydroxy α'-aryl ketones as Michael donors

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2. α-Hydroxy α'-aryl ketones as Michael donors

2.1 Introduction

As mentioned in the previous chapter, one of the goals of this Thesis has been to investigate the efficiency of α-hydroxy ketones as nucleophiles in enolate-mediated organocatalytic enantioselective Michael reactions with nitroolefins.

This purpose has its origin in the need to create direct protocols for the α-functionalization of acyl-type substrates, which are highly useful for synthetic chemistry. Nevertheless, as disclosed before, the diminished carbon acidity of aldehydes, ketones and carboxylic acid derivatives has led to a minor development of methods for the α-functionalization of these carbonyl compounds. To solve this problem, three general alternatives have been developed: (i) the use of carbonyl compounds bearing electron withdrawing groups at the α-position (Figure 20a), (ii) the use of carbonyl compounds bearing an electron withdrawing substituent adjacent to the carbonyl moiety (*ipso*-position, Figure 20b) and (iii) the use of carbonyl compounds which incorporate a group enabling chelation with metals and/or through H-bonding (Figure 20c). In these cases, the enolization of the resulting carbonyl compound in which are included these modifications would be facilitated due to the decrease of the pK_a of the α-carbon.

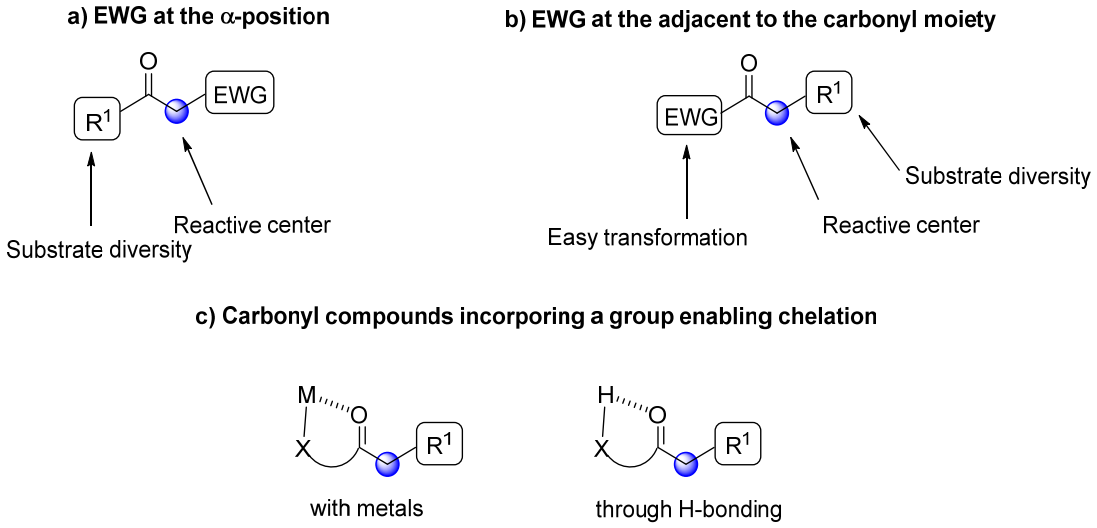


Figure 20. General characteristics of activated ester surrogates.

These frameworks have been successfully employed in asymmetric C-C bond forming reactions promoted by metal catalysis and organocatalysis. For instance, the use

of α-cyanoacetates,[107] as exemplification of an electron withdrawing group in the α-position of a carbonyl compound, is widely extended. However, few examples are found in the literature of asymmetric reactions through noncovalent activation of reactive ester equivalents, which involve the use of pyrazoleamides,[108] acyl phophonates,[109] acyl silanes,[110] thioesters,[93,111] or cyclic anhydrides.[112] Particularly, there are scarce examples of Michael reactions of these enolizable carbonyl compounds with nitroolefins promoted by Brønsted base/H-bonding catalysis,[108a,109a-b,110,111f,113] which are depicted in Figure 21.

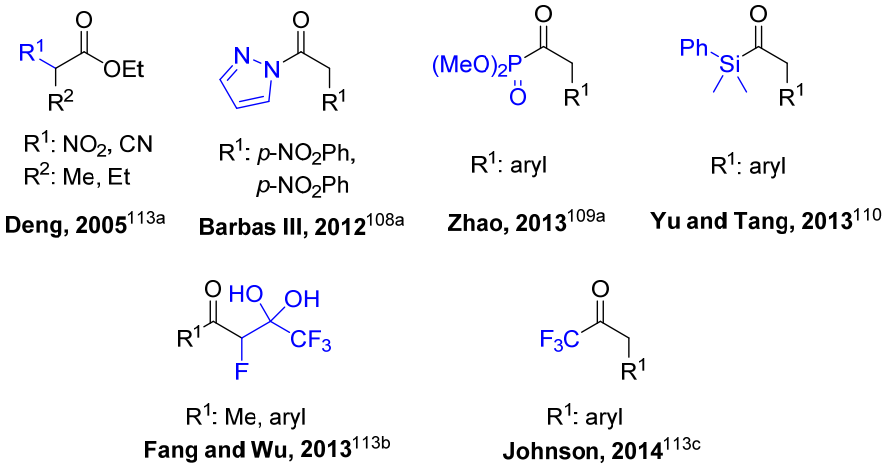


Figure 21. Representative acyclic ester/amide surrogates employed in Michael reactions to nitroolefins.

[107] For reviews on organocatalytic in enantioselective α-functionalization of α-cyanoacetates, see: a) Jautza, S.; Peters, R. *Synthesis* **2010**, 365–388. b) Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261–3288.

[108] a) Tan, B.; Hernández-Torres, G.; Barbás III, C. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 5381–5385. b) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *J. Org. Chem.* **2014**, *79*, 4332–4339.

[109] a) Guang, J.; Zhao, J. C.-G. *Tetrahedron Lett.* **2013**, *54*, 5703–5706; b) Zhang, M. L.; Chen, L.; You, Y.; Wang, Z.-H; Yue, D.-F.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *Tetrahedron* **2016**, *72*, 2677–2682. c) Zhang, M. L.; Wu, Z. J.; Zhao, J.-Q.; Luo, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2016**, *18*, 5110–5113.

[110] Wu, L.; Li, G.; Fu, Q.; Yu, L.; Tang, Z. *Org. Biomol. Chem.* **2013**, 11, 443–447.

[111] a) Kohler, M.C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett*. **2010**, *12*, 3376–3379. b) Guang, J.; Larson, A. J.; Zhao, J. C. G. *Adv. Synth. Catal.* **2015**, *357*, 523–529. For β,γ-unsaturated (thio)esters, see: c) Wang, J. Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 2382–2386. For a particular example of the use of malonic acid half-thioesters as acetate equivalents, see: d) Lubkoll, J.; Wennemers, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844. e) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Perez-Herrera, R.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037–1040. For a review on organocatalytic enantioselective reactions based on half-thioesters, see: f) Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394–405.

[112] Cornaggia, C.; Manoni, F.; Torrente, E.; Tallon, S.; Connon, S. *J. Org. Lett.* **2012**, *14*, 1850–1853.

[113] For the use of electron withdrawing groups at the α-position to carbonyl compounds, see: a) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108. b) Saidalimu, I.; Fang, X.; Lv, W.; Yang, X.; He, X.; Zhang, J.; Wu, F. *Adv. Synth. Catal.* **2013**, *355*, 857–863. For trifluoromethyl ketones, see: c) Corbett, M. T.; Xu, Q.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 2362–2365.

On the other hand, work in this laboratory has demonstrated that α-hydroxy enones[114] (Figure 22) show ability for a bidentate coordination with the catalyst and the readily cleavable *C-C* ketol/diol system to provide the corresponding carboxylic acid, aldehyde or ketone under suitable conditions. Therefore, we reasoned that α-hydroxy ketones would show similar characteristics and could be suitable Michael donors in organocatalytic reactions.

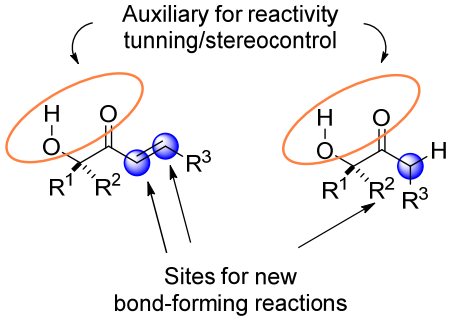
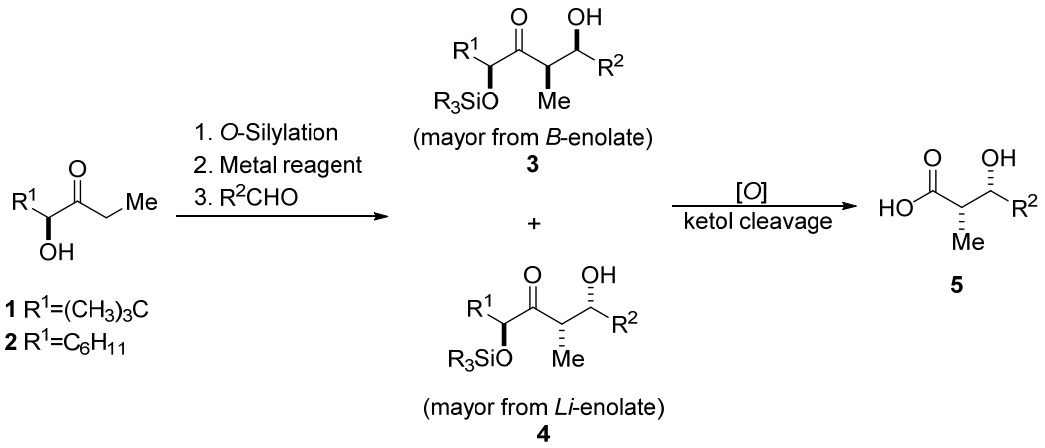


Figure 22. General depiction of the α-hydroxy ketone/enone template.

2.1.1 α-Hydroxy ketones as carboxylic acid surrogates

Early 80's, the groups of Heathcock[115] and Masamune[116] independently described the first use of α-hydroxy ketones as carboxylic acid surrogates in asymmetric synthesis for aldol reactions via boron and lithium enolates. Upon an enolization/α'-functionalization sequence the corresponding *syn*-aldols **3** and **4** of complementary configuration were produced with excellent yields. Subsequently, an oxidative ketol scission provided the α-modified carboxylic acids **5** (Scheme 13).

[114] Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev*. **2012**, *41*, 4150–4164.
[115] a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Shon, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079. b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J. ; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300. c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499–2506.
[116] a) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl*. **1980**, *19*, 557–558. b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568. c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521–5523.



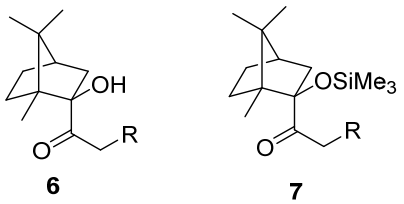
Scheme 13. Asymmetric aldol reaction with chiral hydroxy ketones *via* boron and lithium enolates. **Heathcock, 1991 and Masamune, 1982**.

Afterwards, effective aldol reactions with α- and β-oxy alkyl ketones with applications in the synthesis of natural products such as polyketides[117] and Diels-Alder cycloaddition reactions with α'-hydroxy enones[118] were also reported by Paterson and Masamune groups respectively.

Inspired by these precedents, our laboratory designed the camphor-derived α-oxy ketones **6**/**7**[119] (Figure 23) for the acetate aldol reaction, which provides a high level of diastereofacial control not only in that transformation, but also in Mannich reactions,[120] carbonyl α-alkylation reactions,[121] conjugate additions to nitroalkenes[122] and Darzens reactions.[123] Thus, these applications show the generality of this scaffold in the context of C-C bond forming processes. In addition, it is noteworthy that after ketol cleavage, the

[117] Paterson, I.; Cowden, C. J.; Wallace, D. J. in *Modern Carbonyl Chemistry*, ed. J. Otera, Wiley-VCH, Weinheim, **2000**, 249–297.
[118] a) Choy, W.; Reed III, L. A.; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137–1139. b) Masamune, S.; Reed III, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441–4444.
[119] a) Palomo, C. Gónzalez, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 180–182. b) Palomo, C.; Oiarbide, M.; Aizpurua, J. M.; González, A.; García, J. M.; Landa, C.; Odriozola, I.; Linden, A. *J. Org. Chem.* **1999**, *64*, 8193–8200. c) Palomo C.; Oiarbide, M.; Gómez-Bengoa, E.; Mielgo, A.; González-Rego, M. C.; García, J. M. González, A.; Odriozola, J. M.; Bañuelos, P. Linden A. *ARKIVOC*, **2005**, *vi*, 377–392.
[120] a) Palomo, C.; Oiarbide, M.; González-Rego, M. C.; Sharma, A. K.; García, J. M.; González, A.; Landa, C.; Linden, A. *Angew. Chem. Int. Ed*. **2000**, *39*, 1063–1065. b) Palomo, C.; Oiarbide, M.; Landa, A.; González-Rego, M. C.; Garcia, J. M.; González, A.; Odriozola, J. M.; Martín-Pastor, M.; Linden, A. *J. Am. Chem. Soc*. **2002**, *124*, 8637–8643.
[121] Palomo, C.; Oiarbide, M.; Mielgo, A.; González, A.; García, J. M.; Landa, C.; Lecumberri, A.; Linden, A. *Org. Lett*. **2001**, *3*, 3249–3252.
[122] Palomo, C. Aizpurua, J. M.; Oiarbide, M.; García, J. M.; Gónzalez, A; Odriozola, I.; Linden, A. *Tetrahedron Lett.* **2001**, *42*, 4829–4831.
[123] Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. J. *Org. Chem*. **2000**, *65*, 9007–9012.

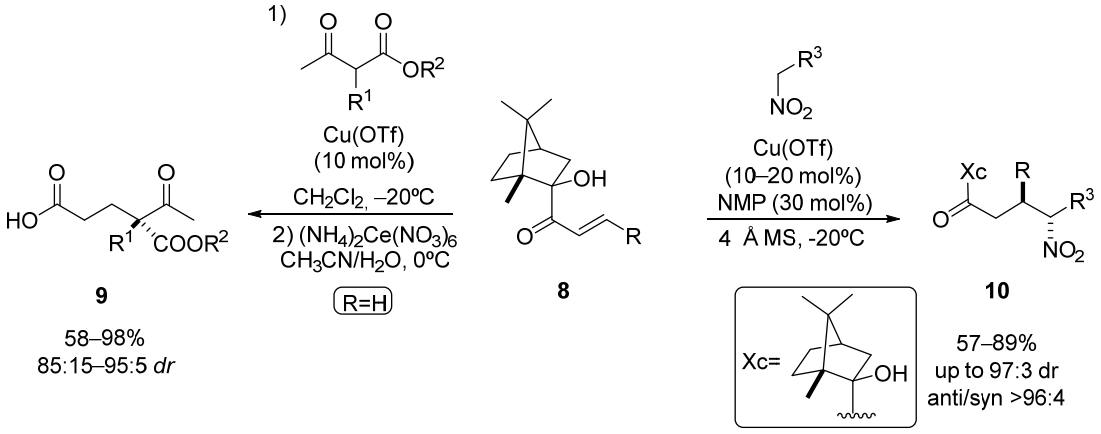
camphor auxiliary is recovered, being possible its reuse as source of stereochemical information.



6 **7**

Figure 23. Camphor-derived α-oxy ketones **6**/**7**. **Palomo, 1998**.

Thereafter, our group also developed the camphor-derived α'-hydroxy enone **8** as a chiral surrogate of acrylate, which participates efficiently in diastereoselective reactions such as Diels-Alder[124] and 1,3-dipolar cycloadditions,[125] and Michael additions of α-substituted β-keto esters[126] and nitroalkanes[127] (Scheme 14).



Scheme 14. Michael reactions described by our group with camphor-derived α'-hydroxy enone **8**.

In this line, our group also extended this strategy to enantioselective versions by exploring achiral hydroxy enones **11** in various metal catalyzed asymmetric reactions.[114] Thus, under optimized conditions, cycloadditions[128] and 1,4-conjugate additions of

[124] a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288–10289. b) Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J. *J. Org. Chem.* **2010**, *75*, 1458–1473.

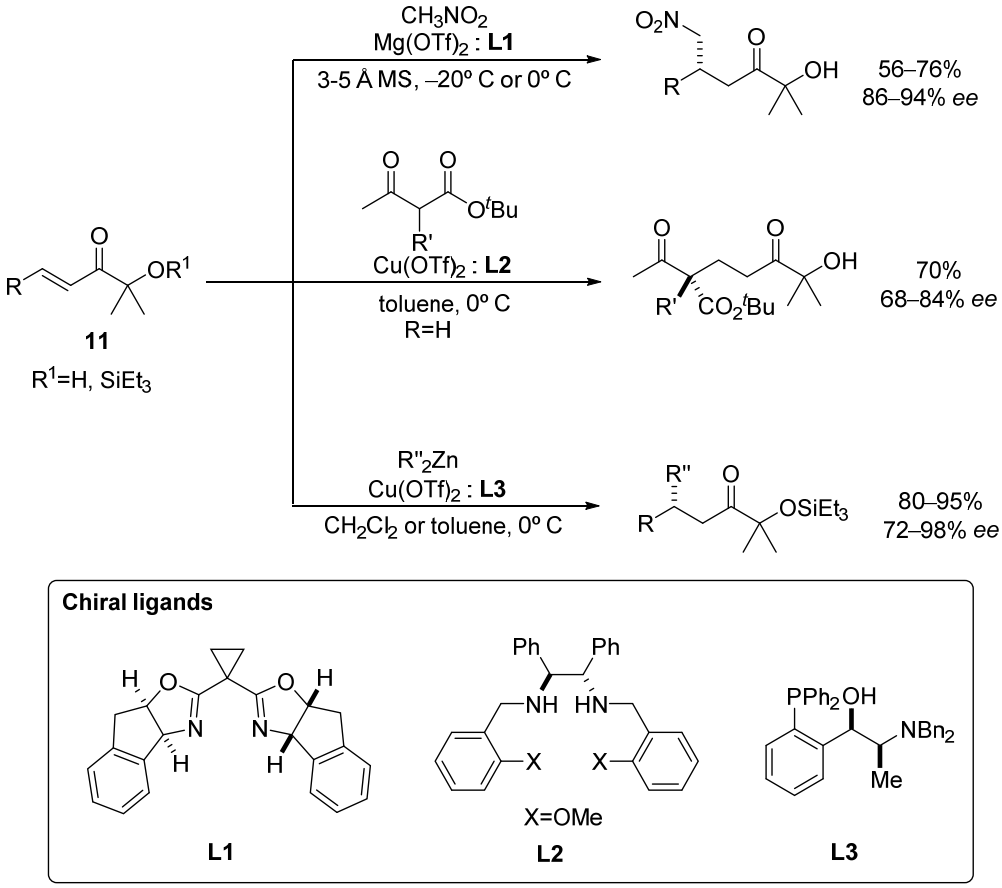
[125] Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 6187–6190.

[126] Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A. *Org. Lett.* **2008**, *10*, 2637–2640.

[127] García, J. M.; Maestro, M. A.; Oiarbide, M.; Odriozola, J. M.; Razkin, J.; Palomo, C. *Org. Lett.* **2009**, *11*, 3826–3829.

[128] For cooper promoted Diels-Alder, see: a) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc*. **2003**, *125*, 13942–13943. For cooper promoted nitrone-alkene 1,3-dipolar cycloadditions, see: b) ref. 125, page 45.

carbamates,[129] pyrroles/indoles (Friedel-Crafts),[130] nitroalkanes,[131] β-ketoesters and dialkyl zinc[132] proceeded efficiently to provide the corresponding adducts with very good stereoselectivity (Scheme 15).



Scheme 15. Metal-catalyzed asymmetric Michael reactions using α'-hydroxy enones **11** as Michael acceptors.

In this respect, the stereochemical outcome of the corresponding reactions indicates that the coordination between the α'-hydroxy enone and metals or Brønsted acids in the transition state is quite effective.[133] α'-Hydroxy enones are potentially

[129] Palomo, C.; Oiarbide, M; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189.

[130] a) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc*. **2005**, *127*, 4154–4155. For an efficient Friedel-Crafts alkylation of indoles with β-aryl α'-hydroxy enones, see: b) Yang, L.; Zhu, Q.; Guo, S.; Quian, B.; Xia, C.; Huang, H. *Chem. Eur. J.* **2010**, *16*, 1638–1645.

[131] Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161–1164.

[132] García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C. *Chem. Eur. J.* **2008**, *14*, 8768–8771.

[133] It has been reported that in the presence of metals or Brønsted acids the intramolecular oxa-Michael cyclisation of α'-hydroxy enones is a side reaction under forcing conditions, see: a) Bradley, J. P.; Jarvis, T. C.; Johnson, C. D.; Mc Donnell, P. D.; Weatherstone, T. A. P. *Tetrahedron Lett.* **1983**, *24*, 2851–2854. b) Hong, Y. M.; Shen, Z. L.; Hu, X. Q.; Mo, W. M.; He, X. F.; Hu, B. X.; Sun, N. *ARKIVOC*, **2009**, *xiv*, 146–155.

bidentate compounds, whose most probable 1,4-chelated conformation is highly planar with both C–O bonds eclipsed and favoring intramolecular hydrogen bonding.[134] Therefore, α-hydroxy enones can generate 1,4-metal binding (Figure 24a) or 1,4-proton binding (Figure 24b) chelates which facilitate reaction stereocontrol. On this basis, in 2014, our group extended the scope of these achiral α'-hydroxy enones to organocatalytic transformations. It was envisioned that reactions initiated by a proton-transfer event, such as bifunctional Brønsted base-promoted Michael reactions could be influenced by the H-bonding ability of the ketol moiety in α'-hydroxy enones (Figure 24c). Thus, in the transition state, α'-hydroxy enones could act through their two anchor points as H-bond donor/acceptor (DA model, Figure 24c) or acceptor/acceptor (AA model, Figure 24c) partner, an interesting design element that was lacking in previous described enoyl templates.

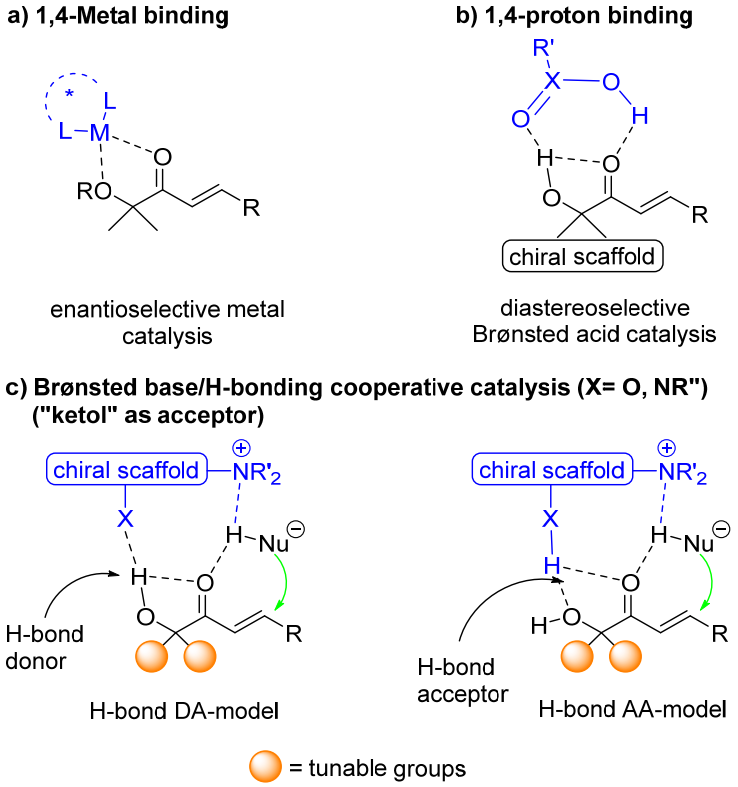
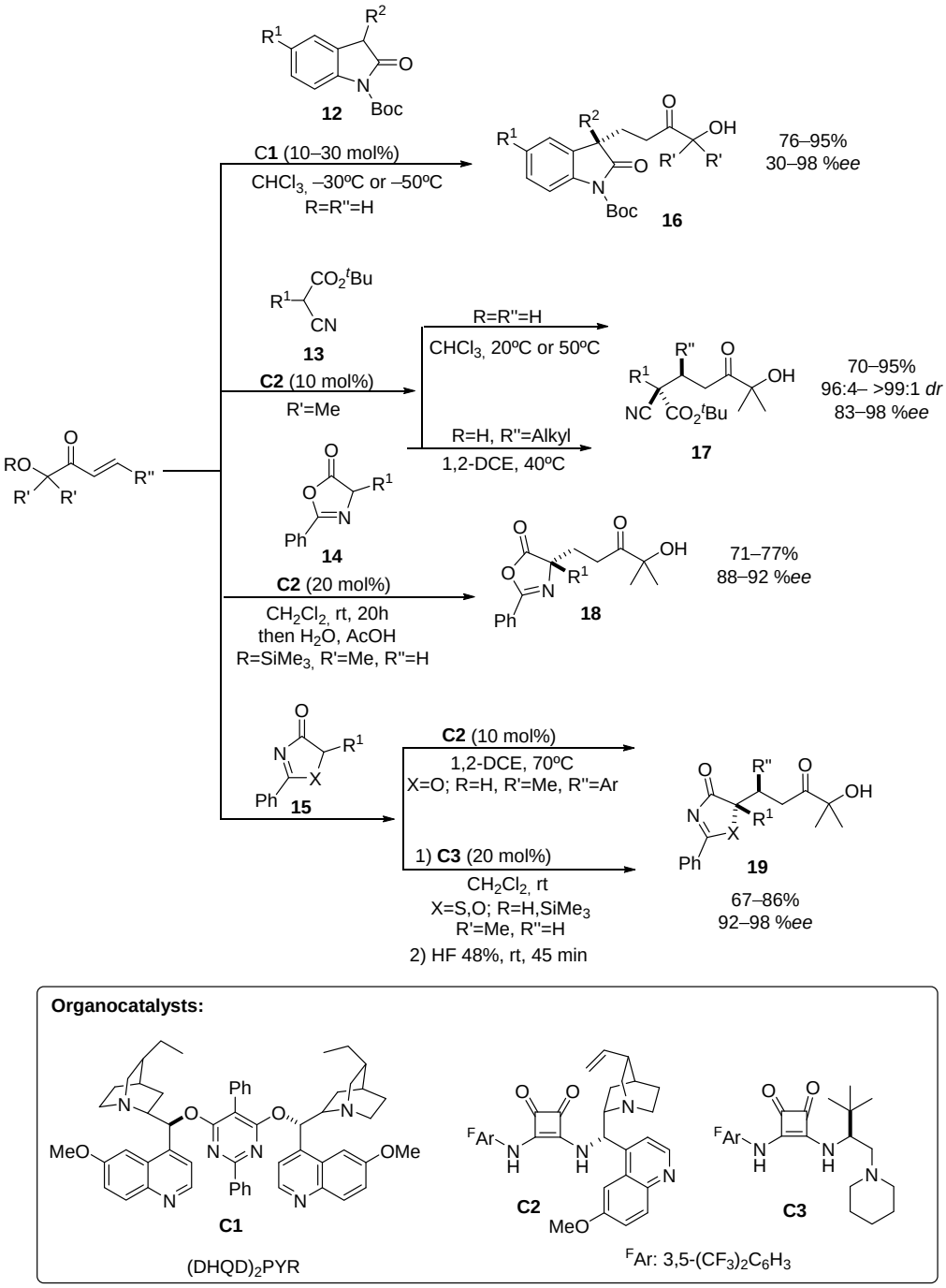


Figure 24. Two point binding α'-hydroxy enone templates for asymmetric catalysis.

[134] For spectroscopic proofs of intramolecular H-bonding in α-hydroxy ketones, see: a) Joris, L; Schleyer, P.; von, R. *J. Am. Chem. Soc.* **1968**, *90*, 4599–4611. b) Cho, T.; Kida, I.; Ninomiya, J.; Ikawa, S.-I. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 103–107.

This research work developed by our group showed the first efficient use of α'-hydroxy enones as Michael acceptors in organocatalytic processes.[106] The reactions were carried out between various types of hitherto challenging prostereogenic *C*-nucleophiles such as oxindoles **12**, cyanoacetates **13**, oxazolones **14**, thiazolones or azlactones **15** achieving high levels of reactivity and stereoselectivity (Scheme 16).



Scheme 16. Brønsted base catalyzed enantioselective Michael reactions of α'-hydroxy enones. **Palomo, 2014.**

To understand the distinct behaviour that α-oxy enones exhibit in these reactions in comparation to ordinary enones, computational studies were carried out for the reaction of α-hydroxy enone with cyanoacetates by our group.[135] The results revealed that, among several possible H-bond combinations for the nucleophile-catalyst-electrophile complex, the most plausible structure (Figure 25) is one in which the squaramide group interacts with the α-hydroxy enone (electrophile activation) and the protonated quinuclidine interacts with the cyanoacetate anion (nucleophile activation).

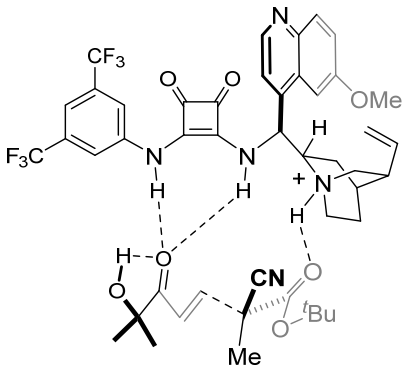
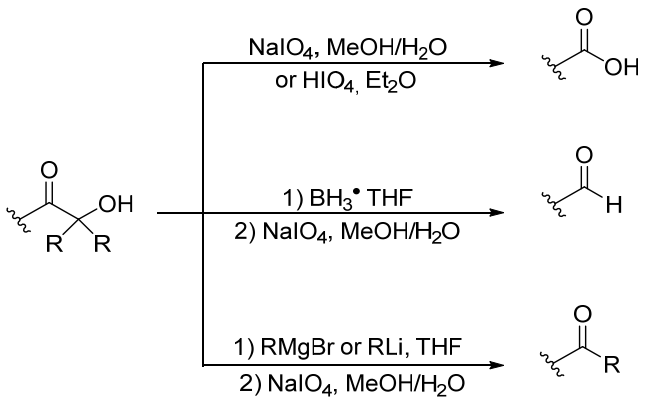


Figure 25. Preferred transition state for the reaction of α-hydroxy enone with cyanoacetates promoted by BB catalysis.

Furthermore, another interesting aspect developed in this research with these achiral/chiral substrates is that the resulting α-oxy ketone adducts can smoothly be converted into the corresponding aldehyde, ketone or carboxylic acid derivatives through simple elaboration of the ketol unit, giving access to a variety of enantioenriched densely functionalized building blocks (Scheme 17). In every case, the corresponding ketone is formed, which could be recovered and reused for the preparation of the required starting hydroxy ketone. Particularly, if R=CH_3, acetone is formed as the only organic side product which is not recovered, but it is of practical interest in terms of product isolation.

[135] All calculations were performed with Gaussian 09, Revision D.01: Frisch, M. J. et al. *Gaussian 09, revision D.01*; Gaussian, Inc., Wallingford, CT, 2013. The geometries of the stationary points wer optimidez by using DFT with the B3LYP functional and 6-311++G** basis set in a dichloromethane solvent system.



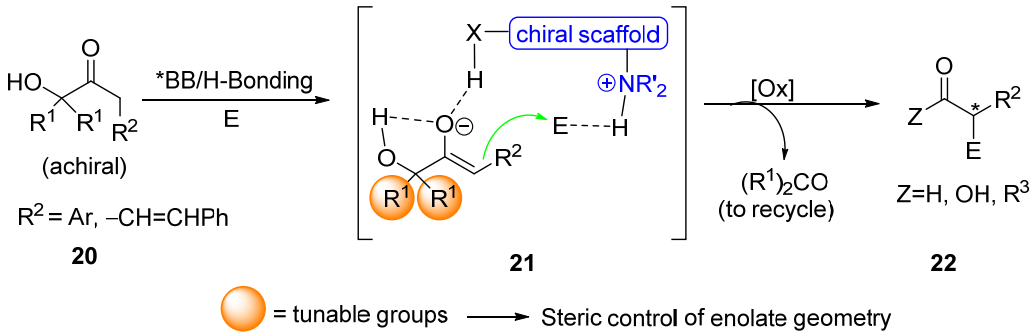
Scheme 17. Possible transformations of the α'-hydroxy ketone moiety.

2.2 Objectives

The previous precedents show that α'-hydroxy enones are very efficient ester/aldehyde equivalents in diastereoselective reactions and enantioselective metal and Brønsted base catalyzed Michael reactions. Additionally, it is worth mentioning the smooth accessibility to carboxylic acid derivatives, aldehydes or ketones through the oxidative cleavage of the ketol moiety. However, and despite its potential and practicality, to the best of our knowledge, no direct version of α-hydroxy ketones as ester or aldehyde donor equivalents in asymmetric organocatalysis had been reported.[136]

On the basis of these studies and the combination of the H-bonding ability with the bidentate feature of α-hydroxy ketones, one of the goals of this Thesis, as previously said, has been to investigate the efficiency of these substrates as Michael donors in Brønsted base-promoted addition reactions. Thus, we hypothesized that substrate **20** with the appropriate R^2 substituents could be activated by a bifunctional tertiary amine/hydrogen-bond donor catalyst, as in transition state **21**, in a similar mode to the transition state previously proposed for α-oxy enones[106] (Figure 25). In this way, substrate **20** would react with a suitable π-electrophilic reaction partner and lastly, undergo a ketol scission, providing enantioenriched α-branched carboxylic acids and derivatives of type **22** (Scheme 18).

[136] For an example on diasteroselective Michael reactions of methyl ketone with nitroolefins, see: a) ref. 122, page 44. For an example of a *p*-anisyl ketone acting as an ester donor equivalent in organocatalyzed Mannich reactions, see: b) Guo, Q.; Zhao, J. C.-G. *Org. Lett.* **2013**, *15*, 508–511.



Scheme 18. Hypothesis for α-hydroxy ketones as donor carboxylic acid equivalents in Brønsted base/H-bonding catalyzed Michael reactions.

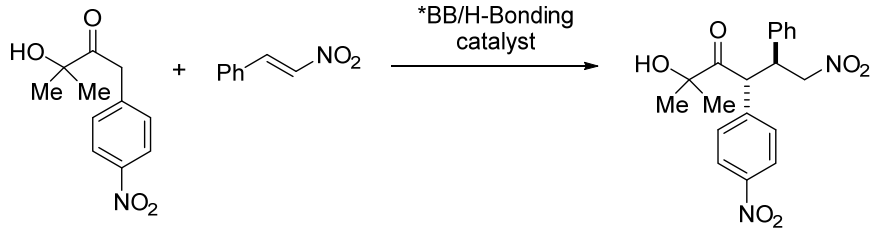
2.3 Results and discussion

2.3.1 Catalyst screening

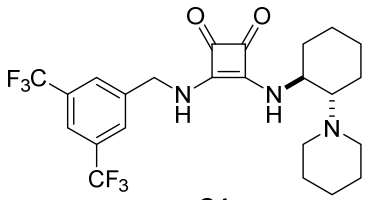
To evaluate the above assumption, we elected nitroolefins as the electrophilic reaction partners for the study. As it has been mentioned in the introduction, nitro compounds are versatile intermediates that can act as masked precursors to many useful functionalities and can be activated by several catalysts.

Accordingly, the reaction between α-hydroxy ketone **23A** and nitrostyrene **24a** was taken as a model to find the optimal catalyst for the α-alkylation of these ketones (Table 1).

Table 1. Catalyst screening for the Michael addition of α-hydroxy ketone **23A** to nitroolefin **24a**.[a]

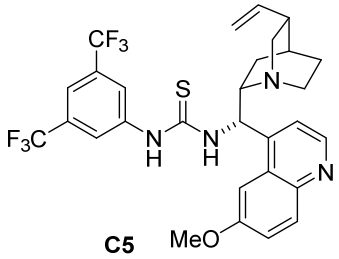


23A **24a** **25Aa**



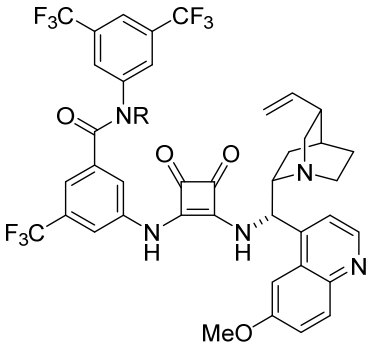
C4

rt, 72h, 96%, >95:5 *dr*, 69% *ee*

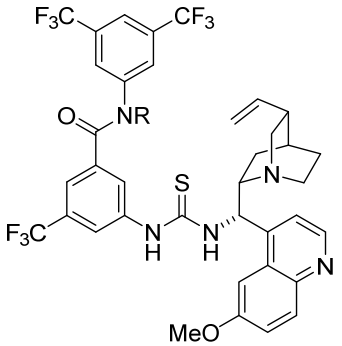


C5

rt, 5h, 97%, >95:5 *dr*, 72% *ee*
–20ºC, 72h, cuant., >95:5 *dr*, 80% *ee*[b]
–40ºC, 48h, cuant., >95:5 *dr*, 80% *ee*[b]



C6, R=H rt, 24h, 80%, >95:5 *dr*, 30% *ee*
C7, R=Bn rt, 24h, 80%, >95:5 *dr*, 24% *ee*



C8, R=H –20ºC, 16h, 96%, 90:10 *dr*, 82% *ee*
C9, R=Me –20ºC, 16h, 95%, >95:5 *dr*, 82% *ee*
C10, R=Bn –20ºC, 16h, 94%, >95:5 *dr*, 67% *ee*

[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:2:0.1 molar ratio of **23A**/**25a**/catalyst). Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [b] Reaction carried out by Dr. Iurre Olaizola.

Initially, classical squaramide-based catalyst **C4** and thiourea-based catalyst **C5** were evaluated. Catalyst **C4**, bearing piperidinyl cyclohexylamine as Brønsted base led to adduct **25Aa** with excellent diastereoselectivity although moderate enantioselectivity. With Soós' catalyst **C5**, the Michael adduct was obtained with high diastereoselectivity (>95:5 *dr*) and good enantioselectivity, which increased slightly when the temperature was lowered (at –20°C or –40°C, 80% *ee* and at room temperature, 72 % *ee*). Then, we considered that a major control of the stereochemistry could be exerted either through the incorporation of an additional H-bonding site in the catalyst (i.e. squaramide based

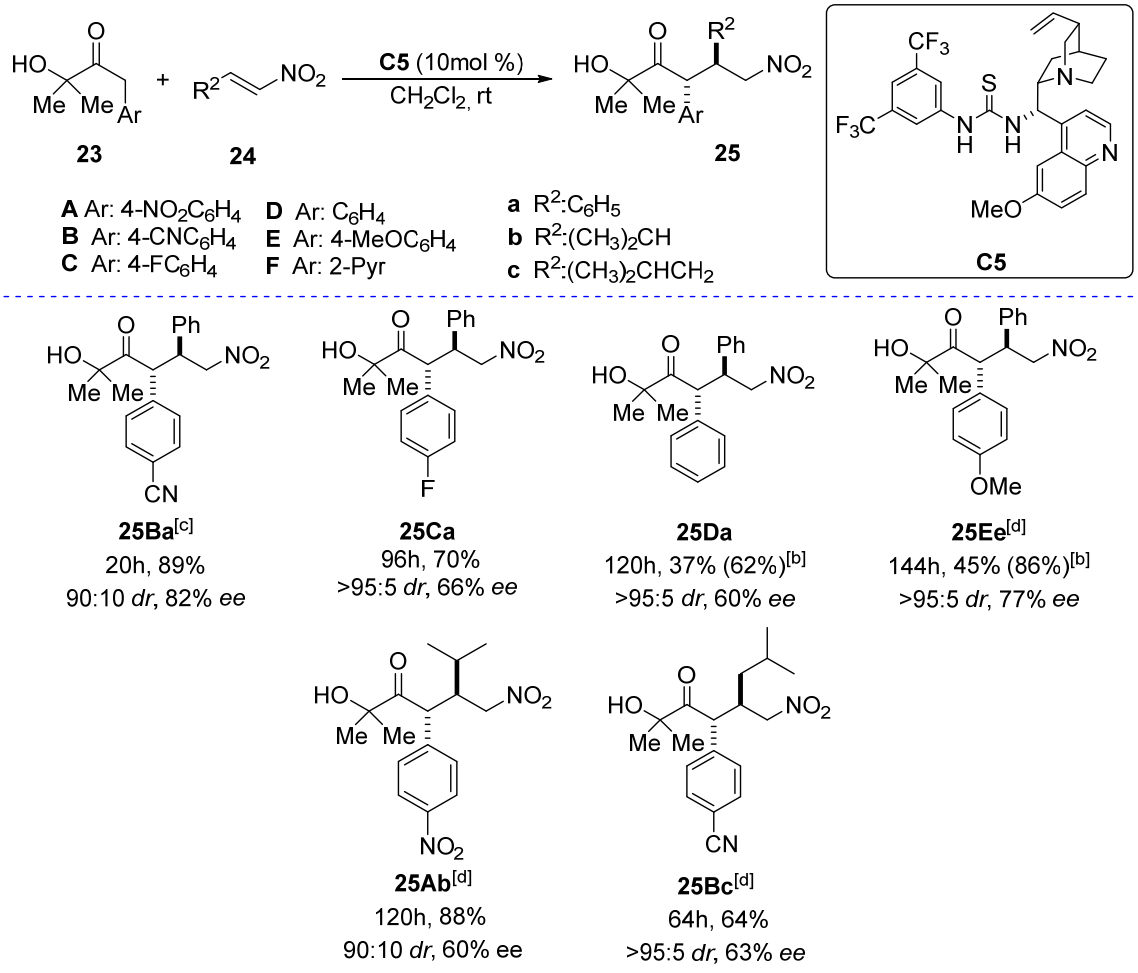
catalyst **C6**, developed previously in our group,[137] and thiourea-based catalyst **C8** or through steric hindrance, for example, *N*-methyl catalyst **C9** and *N*-benzyl catalyst **C7**, and **C10.** Cinchona alkaloids-squaramide base catalysts **C6** and **C7**, which incorporate an amide group on the squaramide *N*-aryl group, did not provide high enantioselectivity despite the good diastereocontrol. When the reaction was performed at −20°C and in the presence of **C8** and **C9**, product **25Aa** was obtained with a slight rise in the enantioselectivity (82 % *ee*), but in the first case a little loss in the diastereoselectivity was observed. Catalyst **C10** at −20°C led to a reduction in the enantiocontrol (67 % *ee*) compared with its homologous **C8** and **C9**. Therefore, **C5** and **C9** provided the best results and in the view that they are similar, **C5** was chosen for the reaction of α-hydroxy ketones with different nitroolefins due to the simplicity regarding its synthesis.

2.3.2 Reaction scope

The reaction scope was then explored with respect to the substitution at the α-phenyl ring in ketone **23** in the presence of catalyst **C5**. The Michael addition of α-hydroxy ketones **23A-23E** to nitrostyrene **24a** and aliphatic nitroalkenes **24b-24c** was conducted at room temperature in dichloromethane (Table 2). The procedure involved the use of 1.2 or 3.0 equivalents of nitroolefins **24a-24c** and 10 mol % of catalyst **C5** and after verifying that the reaction was finished (NMR monitoring), the reaction mixture was submitted to flash column chromatography on silica gel eluting with hexane/EtOAc mixtures.

[137] Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.

Table 2. Scope of the reaction regarding the α-hydroxy ketone.[a]



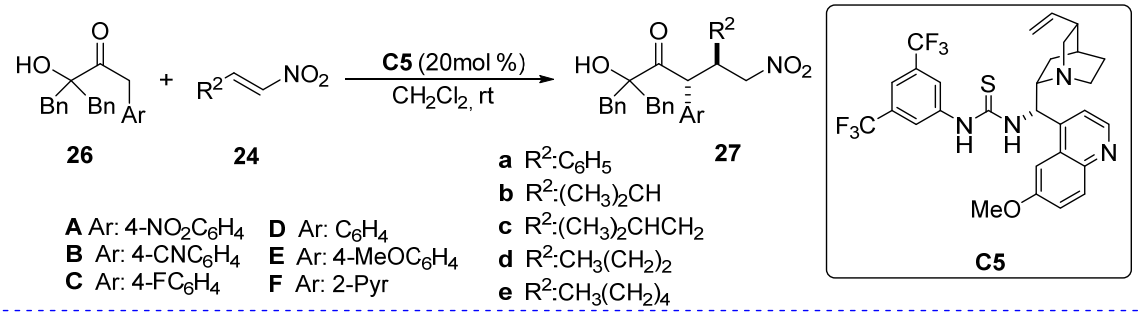
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:3:0.2 molar ratio of ketone **23**/**24**/**C5**) at room temperature, unless otherwise stated. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [b] Yield in parenthesis based on recovered starting material. [c] 1.2 equivalents of nitroolefin **24a**. [d] 20 mol % of catalyst **C5** was used.

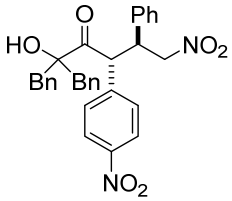
Initially, ketones such as α'-(*p*-cyanophenyl)-α-hydroxy ketone **23B** (Ar: 4-CNC_6H_4) and the *p*-fluorophenyl analogue **23C** (Ar: 4-FC_6H_4), which carry electron-poor substituents at the α'-phenyl ring were employed. In both cases, the reaction with β-nitrostyrene **24a** led to the corresponding adducts **25Ba** and **25Ca** in high disastereoselectivity and moderate enantioselectivity (**25Ba**: 90:10 *dr*, 82 % *ee* and **25Ca**: >95:5 *dr*, 66 % *ee*). When ketone **23D**, unsubstituted at the α'-phenyl group, was reacted with **24a**, lower reactivity was observed, although similar stereoselectivity outcome was achieved for adduct **25Da**. For the reaction of ketone **23E**, which bears an electron-donating group at the α'-pheny ring (Ar: 4-$MeOC_6H_3$), with **24a**, adduct **25Ee** was obtained

with high diastereoselectivity (>95:5) and 77 % enantiomeric excess, but after 144 hours the conversion of the reaction was uncompleted. Moreover, the reaction also tolerates β-aliphatic nitroolefins as demonstrated by the reaction of **23A** with **24b** and **23B** with **24c**, which afford adducts **25Ab** and **25Bc** with high diastereoselectivity although in moderate enantioselectivity (**25Ab**: 90:10 *dr*, 60 % *ee* and **25Bc**: >95:5 *dr*, 63 % *ee*).

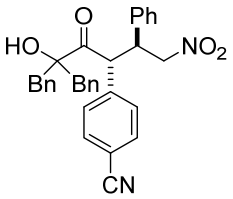
Furthermore, the Michael addition of α,α-dibenzyl ketones **26A-26F** to nitrostyrene and alkyl substituted nitroalkenes was also explored (Table 3)**.** Ketones **26A, 26B** and **26C** bearing electron-withdrawing substituents at the α'-phenyl as well as unsubstituted α'-phenyl ketone **26D** reacted with nitrostyrene **24a** to provide adducts **27Aa, 27Ba**, **27Ca** and **27Da** practically as a single isomer (>95:5 *dr* for all of them and 99%, 99%, 96 % and 99 % *ee* respectively). Remarkably, even the less reactive alkyl-substituted nitroalkenes afforded the corresponding addition adducts **27Ab**, **27Ad**, **27Ae** and **27Bc** with excellent stereoselectivity (90:10 – >95:5 *dr*, 96 – 99 % *ee*), although the reaction with the branched alkyl substituted nitroalkenes, **24b** and **24c**, run slower and the conversion was uncompleted. The comparison of the results from the experiments performed with α,α-dimethyl ketols **23A**-**23D** and the bulkier α,α-dibenzyl congeners **26B**-**26D** shows the influence of the ketol R group: the latter required longer reaction times but attained adducts with considerably better diastereo- (*dr* ≥ 95:5) and enantioselectivities (96–99% *ee*).

Table 3. Scope of the reaction regarding the α-hydroxy ketone.[a]

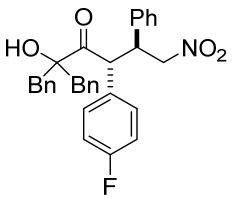




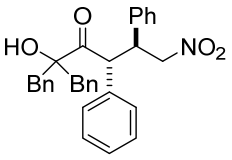
27Aa[c]
24h, 99%
>95:5 *dr*, 99% *ee*



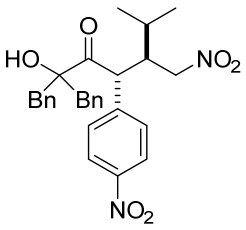
27Ba[c]
96h, 70%
>95:5 *dr*, 99% *ee*



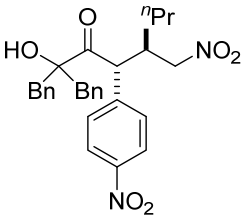
27Ca
96h, 49% (96%)[b]
>95:5 *dr*, 96% *ee*



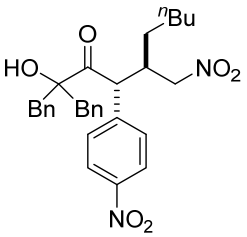
27Da[d]
96h, 46% (92%)[b]
>95:5 *dr*, 96% *ee*



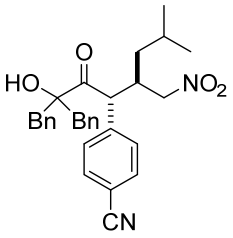
27Ab
120h, 45% (75%)[b]
90:10 *dr*, 97% ee



27Ad
44h, 76%
>95:5 *dr*, 99% *ee*



27Ae
72h, 75%
>95:5 *dr*, 96% *ee*



27Bc
64h, 36% (90%)[b]
>95:5 *dr*, 99% *ee*

[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:3:0.2 molar ratio of ketone **26**/**24**/**C5**) at room temperature, unless otherwise stated. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [b] Yield in parenthesis based on recovered starting material. [c] 1.2 equivalents of nitroolefin **24a** and 10 mol % of catalysts **C5** were used. [d] 10 mol % of catalyst **C5** was used. [e] Enantiomeric excess (*ee*) in parenthesis refers to the minor diastereomer.

The relative and absolute configuration of the above adducts was established by a single crystal X-ray analysis of compound **27Af**[138] (Figure 26) and by assuming a uniform reaction mechanism.

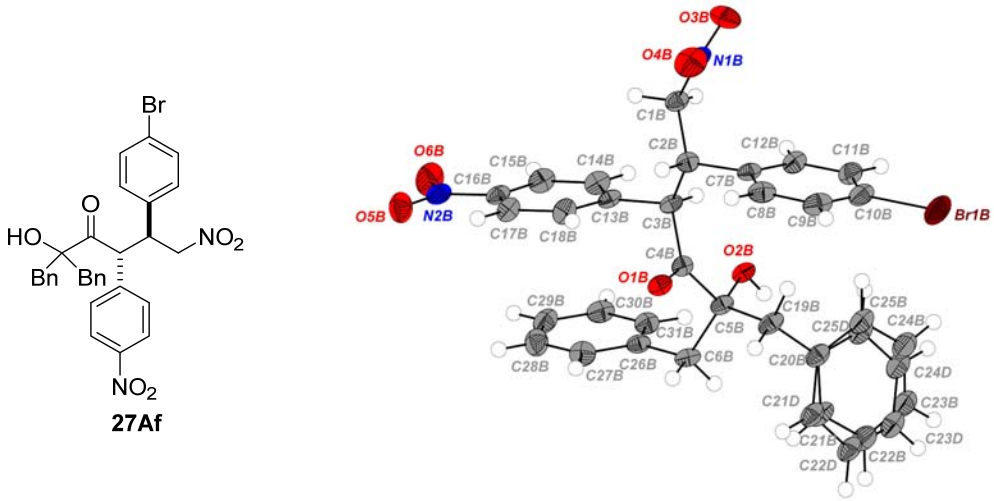
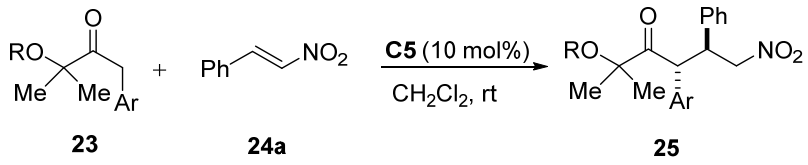


Figure 26. ORTEP diagram of compound **27Af**.

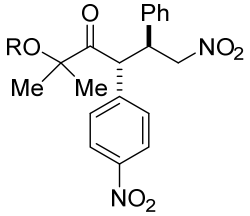
On the other hand, the comparison of the reaction conversions with nitrostyrene **24a** between α-hydroxy α'-phenyl ketone **23A** and its silyloxy analogue **23A'** as well as between substrate **23B** and its silyloxy equivalent **23B'** (Table 4) indicates that the free hydroxyl group plays an active role. For instance, in the case of the addition of **23A** to **24a**, the reaction, which was run in a NMR tube with $CDCl_3$ as solvent, was completed after 8 h, while when the reaction was performed with its silyloxy analogue **23A'**, the conversion was 74 % after 72 hours. Likewise, the reaction of **23B** with **24a** was completed after 20h, while under the same conditions the reaction with substrate **23B'** progressed much slower, with around 35% conversion reached after 70 hours.

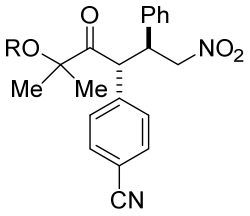
[138] Compound **27Af** was obtained by Dr. Olaizola from this laboratory using this same procedure.

Table 4. Comparing α-hydroxy- vs α-silyloxy-ketones.



A Ar: 4-$NO_2C_6H_4$; R: H **A'** Ar: 4-$NO_2C_6H_4$; R: $SiMe_3$
B Ar: 4-CNC_6H_4; R: H **B'** Ar: 4-CNC_6H_4; R: $SiMe_3$





R: H **25Aa**[a] 8h 95 % conv.[b]

R: $SiMe_3$ **25A'a**[a] 20h 50 % conv. 72h 74 % conv.

R: H **25Ba** 20h >95 % conv.

R: $SiMe_3$ **25B'a** 20h 23 % conv. 70h 35 % conv.

[a] Reactions carried out by Dr. Olaizola. [b] Reaction conduced in $CDCl_3$ (3 mL/mmol) and run in a NMR tube.

A plausible explantion of the configuration of the adducts in these reactions can be provided by the transition state model B shown in Figure 27 (Soós and Pápai model),[81,139] although more studies would be required for a better understanding. Notwithstanding, as a result of the observed reaction outcome it can be certainly assumed that the coordination of the hydroxy group is decisive for reactivity and stereoselectivity.

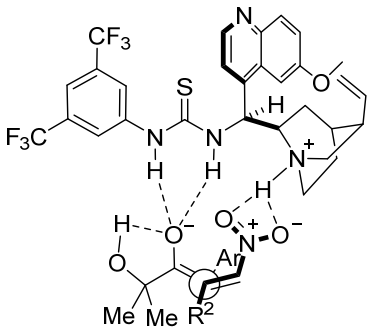
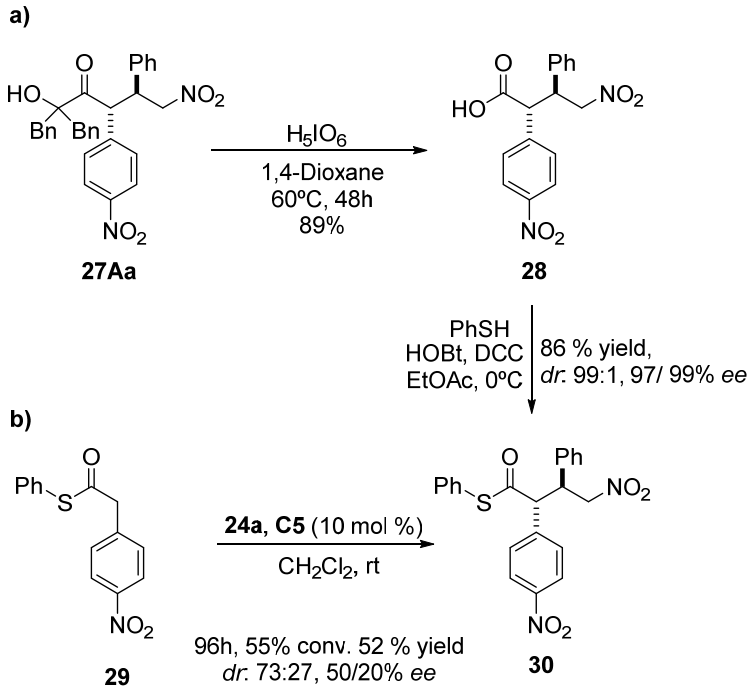


Figure 27. Proposed transition-state model B for the reaction of ketones **26** with nitroolefins **24**.

[139] Grayson, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 9041–9044.

2.3.3 Elaborations of the adducts

As disclosed before, an interesting aspect of the α-hydroxy ketones is that they can give easy access to the challenging enantioenriched α-branched carboxylic acid and aldehyde products through smoothly oxidative ketol cleavage in the first case and by carbonyl reduction and subsequent diol cleavage in the second one. Thus, treatment of adduct **27Aa** with H_5IO_6 in dioxane at 60 °C led to arylacetic acid[140] **28** in 89% yield (Scheme 19a) along with dibenzyl ketone as the only organic byproduct, which could be recovered and reused.[141] Besides, compound **28** can be transformed into the corresponding thioester **30** through the reaction with PhSH. In this manner, the lack of reactivity and selectivity observed in our preliminary studies for α-functionalization of thioesters (Scheme 19b) are solved.



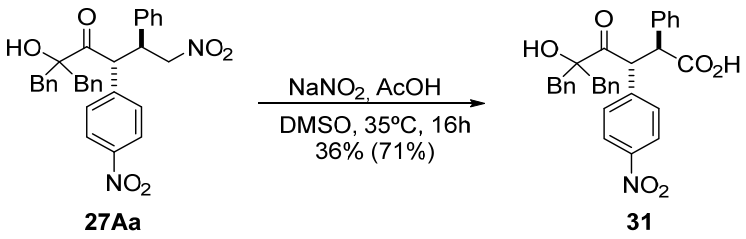
Scheme 19. Transformation of adduct **27Aa** to arylacetic acid **28** and subsequently to thioester **30**.

Moreover, the oxidation of the C–NO_2 group in adduct **27Aa** under Mioskowski conditions[101] resulted without modifying the ketol moiety in carboxylic acid **31** (Scheme 20). After 16 hours, the first oxidation run was incomplete and compound **31** was obtained

[140] For interest in aryl acetic acids, see: Feng, Y.-S.; Wu, W.; Xu, Z.-Q; Li, Y.; Li, M.; Xu, H.-J. *Tetrahedron* **2012**, *68*, 2113–2120, and references therein.

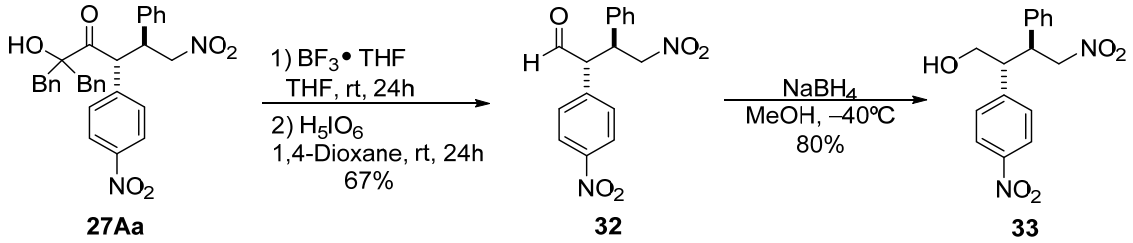
[141] This is in contrast with the sole example described in ref. 136b, page 50, in which oxidative cleavage of the C–C bond led to the formation of *p*-methoxy-phenol as non-reusable waste.

in 36 % yield. The recovered unreacted starting material was again oxidized to provide the final compound in a combined yield of 71 %.



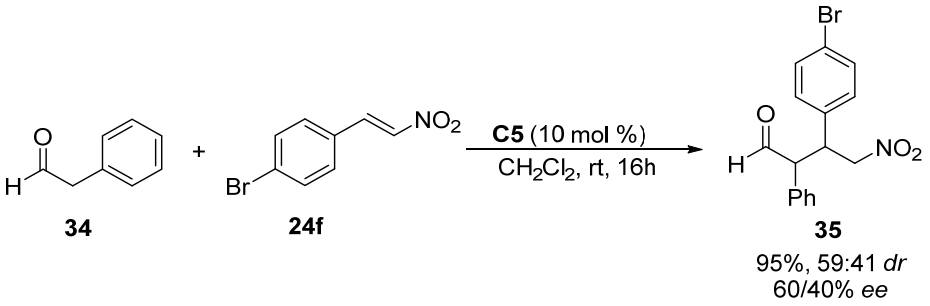
Scheme 20. Oxidation of adduct **27Aa** under Mioskowski conditions to deliver carboxylic acid derivative **31**.

Furthermore, another transformation was the reduction with borane of the ketol carbonyl in **27Aa**, and subsequent treatment with H_5IO_6 in dioxane, which provided aldehyde **32** in 67% yield (Scheme 21). It is worth mentioning that no epimerization at Cα was observed in the reaction. In addition, reduction of the obtained aldehyde **32** by treatment with $NaBH_4$ led to alcohol **33** in 80% yield and likewise, without signs of epimerization.



Scheme 21. Sequential reduction of the ketol carbonyl in **27Aa** and aldehyde **32** to afford alcohol **33**.

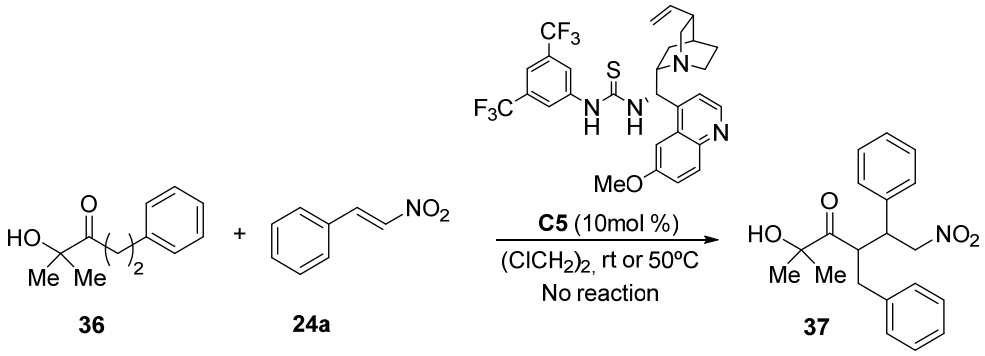
The importance of this approach is again illustrated from the enantioselective α-functionalization of aldehydes, which remains challenging. For instance, in a control experiment, the addition of simple benzyl aldehyde **34** to nitroolefin **24f** afforded the corresponding aldehyde **35** in almost equimolar mixture of epimers and with *ee* values of 60/40% (Scheme 22).



Scheme 22. Unsatisfactory enantioselective addition of phenylacetaldehyde **34** to nitroolefin **24f.**

2.3.4 Extension to β',γ'-unsaturated alkenyl α-hydroxy ketones

Given the good results regarding reactivity and stereoselectivity achieved in the Michael addition of α-hydroxy α'-aryl ketones to nitroolefins promoted by Brønsted base/H-bonding catalysts, in particular by arylthiourea-cinchona alkaloid catalyst **C5**, we also investigated this approach for α-hydroxy ketones with less α'-carbon acidity, such as **36**. Unfortunately, substrate **36** remained intact in the conjugate addition to nitroolefin **24a** in the presence of **C5** after 24 h at room temperature or even at 50 °C (Scheme 23).



Scheme 23. Control experiments with α-hydroxy ketone **36**.

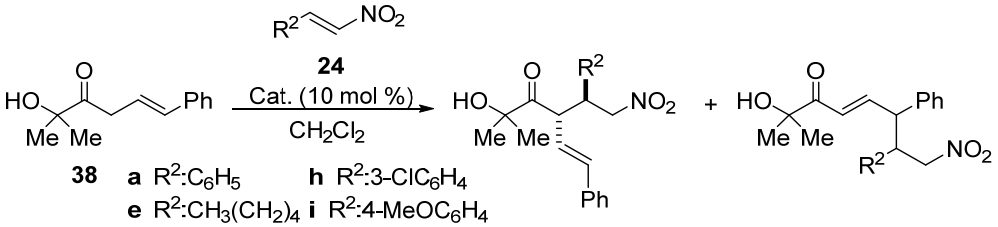
Simultaneously, our group was working on controlling the α/γ-reactivity of vinylogous ketone enolates promoted by Brønsted base catalysis,[142] and the β',γ'-unsaturated ketols were found to be suitable substrates for the Michael addition with nitroolefins reacting with high regio- and stereoselectivity. Therefore, we envisioned that β',γ'-unsaturated α-hydroxy ketones could be also competent substrates for this reaction and the ketol scission would make possible to synthesize the corresponding carboxylic

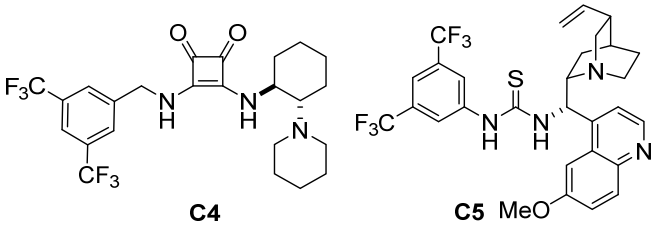
[142] Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 8860–8864.

acids or aldehydes. In addition, a simple hydrogenation of the C=C bond of the resulting adducts could give access to α-functionalizated less acidic ketones similar to **37**.

Based on that, β',γ'-unsaturated *gem*-dimethyl ketone **38** was examined in the Michael reaction with nitroolefins **24** in the presence of two Brønsted base/H-bonding catalysts under different conditions, squaramide based **C4** and thiourea based **C5** (Table 5). Firstly, the reaction of substrate **38** with β-aryl-substituted nitroalkenes **24a** and **24g-i** was examined using catalyst **C5**. In these cases, the catalyst did not take enough control in the α- versus γ-regioselectivity (61:39–86:14 ratio α/γ) in the reaction neither with nitrostyrene **24a** (Table 5, entries 1–3) nor with nitrostyrenes **24g-l** carrying electron withdrawing substituents at the aryl group (Table 5, entries 7–9, 11, 13–14). A clear influence of the reaction temperature was also observed and the best results were attained at −20 °C; however, when the reaction was carried out either at room temperature or at −40 °C a significant decrease in stereoselectivity was detected. Gratifyingly, when the reaction with β-aryl-substituted nitroalkenes was performed in the presence of **C4** at room temperature, adducts **39** were obtained as essentially a single diastereomer and excellent enantiomeric excesses (Table 5, entries 4, 10, 12 and 15). Additionally, for the aliphatic nitroalkene **24e** (Table 5, entries 5 and 6), the reaction afforded a single isomer **39e** in the presence of **C4** (>98:2 ratio α/γ, 98% *ee*) or **C5** (>98:2 ratio α/γ, 96% *ee*), although the first one showed to be more active.

Table 5. β',γ'-unsaturated α-hydroxy α,α-dimethyl ketone **38** as ester donor equivalent.[a]

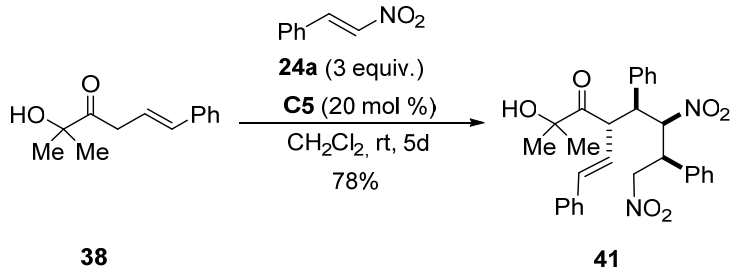




Entry	Product	Cat.	T [°C]	T [h]	Ratio α/γ	Yield [%][b]	*ee*[c]
1[d]	**39a/40a**		rt	14	71:29	42	88
2[d]		**C5**	0	16	81:19	45	84
3			–10	20	86:14	68	95
4		**C4**	rt	2.5	>98:2	85	94
5	**39e/40e**	**C5**	rt	70	>98:2	36[e]	96
6		**C4**	rt	14	>98:2	94	98
7	**39g/40g**		–10	14	68:32	60	83 (66)[f]
8		**C5**	–20	16	69:31	64	88
9			–40	14	63:37	55	87
10		**C4**	rt	2.5	>98:2	82	95
11	**39h/40h**	**C5**	–20	16	61:39	57	81 (71)[f]
12		**C4**	rt	3	>98:2	95	94
13	**39i/40i**	**C5**	–20	16	96:4	77	87
14			–40	16	83:17	70	88
15		**C4**	rt	2.5	>98:2	75	96

[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.3 mL; 1.5:1:0.1 molar ratio of **38**/**24**/**C5** and 1:1.1:0.05 molar ratio of **38**/**24**/**C4**). Diastereomeric ratio (*dr*) for the product **39** was >95:5 % in all entries and was determined by ^{1}NMR spectroscopy analysis of the crude sample. [b] Yields of products **39** isolated after chromatography. [c] Enantiomeric excess (*ee*) for product **39**, which were determined by chiral HPLC analysis. [d] 1:2:0.01 molar ratio of **38**/**24a**/**C5**. [e] Conversion 47%. [f] *ee* in parenthesis refers to product **40**. Adducts **40g** and **40h** were obtained as a mixture of diastereomers (*dr*: 93:7) and a single diastereomer respectively.

In addition, when higher amount of **24a** (3 equivalents) was employed in the conjugate addition of **38** in the presence of catalyst **C5**, tandem product **41** was isolated in a 78 % yield (Scheme 24).

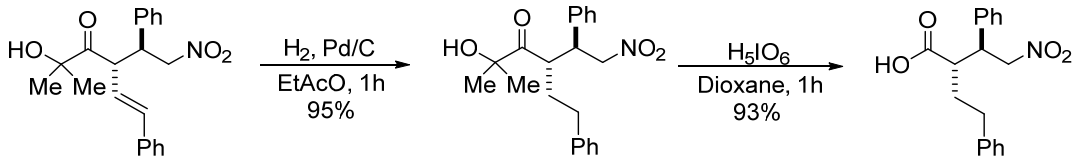


38 **41**

Scheme 24. Conjugate addition of **38** to excess of **24a** assisted by **C5**.

2.3.4.1 Elaboration of adducts

As mentioned before, the reduction of the C=C double bond and subsequent ketol scission in the resulting adducts from β',γ'-unsaturated α-hydroxy ketones is an easy approach to access α-substituted carboxilyc acids with the less acid α-carbon. Therefore, the Michael adduct **39a** was transformed by hydrogenation with H_2, Pd/C into compound **42** and the oxidative cleavage of this latter led to carboxylic acid **43** in high yield (Scheme 25).



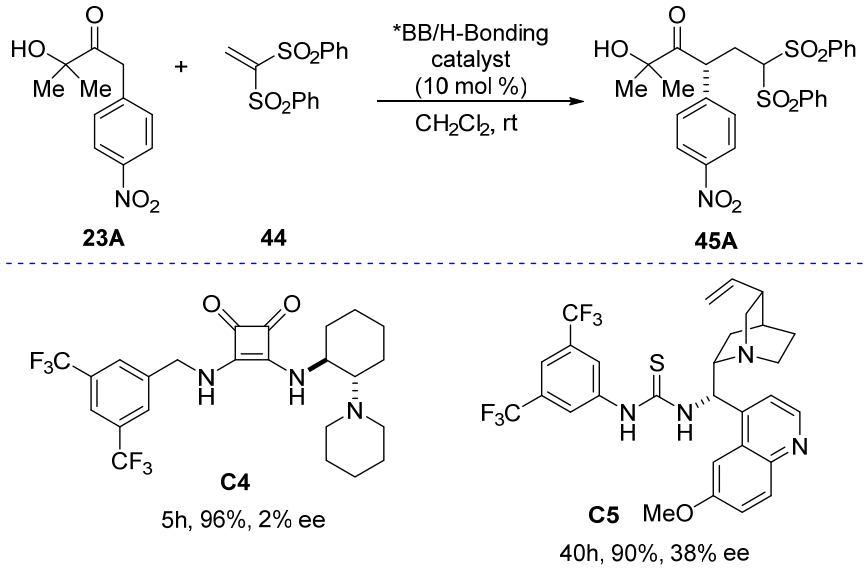
39a **42** **43**

Scheme 25. Elaborations of adduct **39a**.

2.3.5 Additional experiments

In order to find other suitable Michael acceptors, vinyl sulfone **44** was explored in the reaction with α-hydroxy ketone **23A** in the presence of catalyst **C4** and **C5** (Table 6). In spite of the high reactivity, useful levels of enantioselectivity were not achieved, so a future study will be needed.

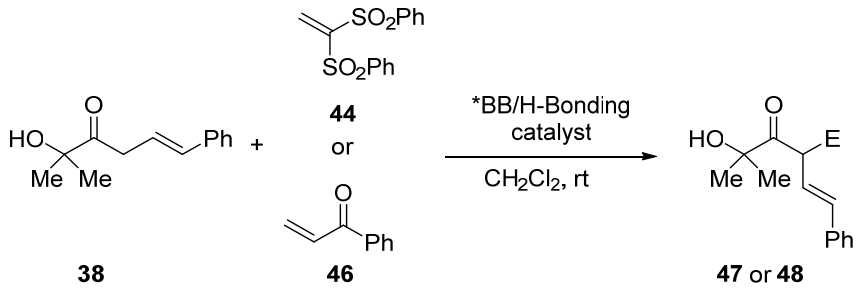
Table 6. Additional experiments of the Michael reaction of α-hydroxy ketone **23A** with vinyl sulfone **44.**[a]

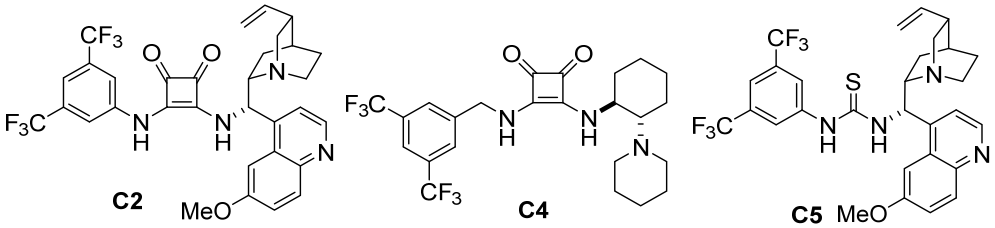


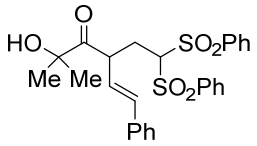
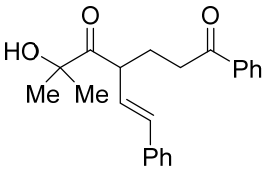
[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.3 mL; 1:3:0.1 molar ratio of **23A**/**44**/**Cat**). The enantiomeric excess (*ee*) was determined by chiral HPLC analysis after silica gel flash column chromatography.

In other experiment carried out with β',γ'-unsaturated α-hydroxy ketone **38** and vinyl sulfone **44** (Table 7, entry 1), the reaction proceeded to completion, but the resulting adduct showed again low enantioselectivity. The reaction was also tested with phenyl vinyl ketone **46** as Michael acceptor (Table 7, entries 2–4), but the reactivity was unsatisfactory with conversion no higher than 20 %.

Table 7. Additional experiments of the Michael reaction of β',γ'-unsaturated α-hydroxy ketone **38** with vinyl sulfone **44** or phenyl vinyl ketone **46.**





Entry	Electrophile	Product	Cat.	t [h]	Conv. [%]	Yield [%]	*ee*[b] [%]
1	**44**	 **47**	**C2**	5	100	n.d.	17
2	**46**	 **48**	**C2**	16	<1	--	--
3			**C4**	16	20	--	--
4			**C5**	30	<1	--	--

[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.3 mL; 1:3:0.1 molar ratio of **38**/**44** or **46**/**Cat**). [b] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis of the crude sample. n.d.: not determined.

To sum up, enolizable α-hydroxy α,α-disubstituted ketones have shown to be suitable Michael donors in the enantioselective conjugate addition to β-alkyl or aryl substituted nitroalkenes under bifunctional Brønsted bases/H-bonding catalysis to afford adducts with very high diastereo- and enantioselectivity. Elaboration of the resulting adducts through oxidative ketol cleavage has also demonstrated that these substrates are efficient ester and aldehyde donor equivalents to achieve enantioenriched α-functionalized carboxylic acid and aldehyde products.

CHAPTER 3.

Benzylic alkynyl ketones as Michael donors

Benzylic alkynyl ketones as Michael donors

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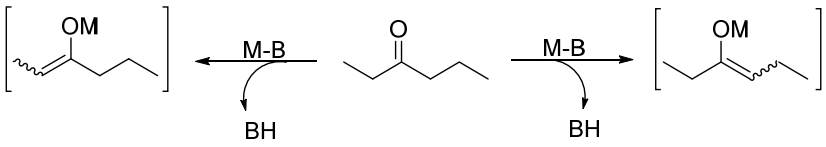
3. Benzylic alkynyl ketones as Michael donors

3.1 Introduction

The most straightforward strategy for the preparation of α-chiral ketones, aldehydes or carboxylic acids is the direct α-functionalization of the corresponding carbonyl compounds. However, as it has been disclosed before, in spite of the significant progress in processes for C-C bond formation, the low acidity of the α-carbon in these compounds limits the development of these methodologies. In the previous chapter, in order to solve the issue related to acidity, we proposed α-hydroxy α'-aryl ketones as liable pronucleophiles for Brønsted base mediated activation in Michael reactions with nitroolefins, whose reaction products give access to chiral modified α-aldehydes or carboxylic acids through oxidative diol and ketol cleavage respectively.

Apart from the need of increasing the acidity of the carbon adjacent to the carbonyl moiety, other problem to be tackled in the α-functionalization of carbonyl compounds is regioselectivity. When unsymmetrical acyclic ketones are not functionalized in proximity to the carbonyl group, the reactions through enol or enolate intermediates do not proceed with chemo-, regio- and stereoselectivity because the enolization process is not controlled (Scheme 26).[143]

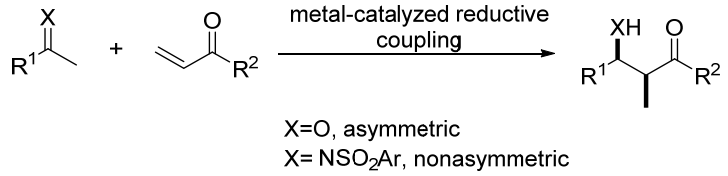


Scheme 26. Enolization process for non-functionalized unsymmetrical acyclic ketones can ensue at both sides and it is not controlled.

A feasible strategy to attain regiodefined α-functionalized acyclic dialkyl ketones has been the use of α,β-unsaturated ketones in metal-catalyzed reductive couplings *via*

[143] For a conjugate addition of non symmetric acyclic ketone via enamine, see: ref. 49c and 49d, page 17.

hydrogenation (Scheme 27),[144] and although effective, it is generally only applied to vinyl ketone.[145]



Scheme 27. Possible approach to generate regiodefined acyclic dialkyl ketones through reductive coupling with vinyl ketones via metal-catalysis.

Since acetylene group can also act as alkane equivalent, the direct α-functionalization of an ynone followed by hydrogenolysis has been shown to be an alternative route to generate α-functionalized acyclic dialkyl ketones. In this context, an alkyne, on the one hand, prevents the enolization on that side of the ketone and on the other hand, can be subsequently hydrogenated to obtain the corresponding alkane (Figure 28).

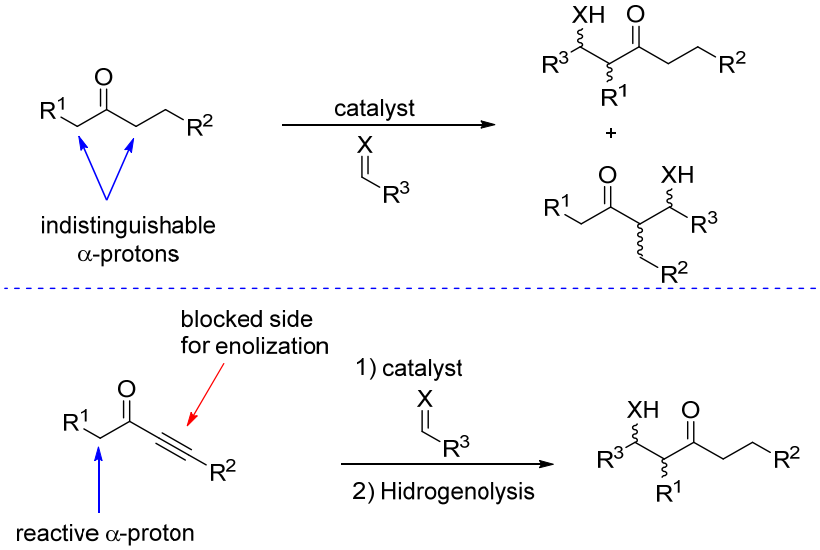


Figure 28. Acetylene group blocks a side of the ketone as donor.

Moreover, from a synthetic point of view, beyond the hydrogenation of the alkyne moiety, the reactivity and versatility of alkynes allow structural proliferation and diversification. For instance, ynones are appealing precursors to chiral propargylic

[144] For selected reviews on aldol, Michael and Mannich reactions, see: a) Nishyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137. Aldol reactions: b) Han, S.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, 2669–2669. c) Garner, S. A.; Han, S.-B.; Krische, M. J. *Metal-Catalyzed Reductive Aldol Coupling. In Modern Reduction Methods*; Andersson, P. G.; Munslow, I. J. Eds.; Wiley-VCH: Weinheim, Germany **2008**, 387–417.

[145] For selected examples on aldol reactions, see: a) Bee, C; Han, S.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747. For Mannich reactions: b) Garner, S. A.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 5843–5846.

alcohols[146] and various heterocycles.[147] In addition, alkynyl ketones are also very attractive templates for the construction of many complex natural products.[148] Therefore, ynones possessing a stereogenic α-center are highly desirability for later transformations.

Nevertheless, the implementation of methodologies of direct asymmetric catalysis progresses very slowly due to the drawbacks that these substrates present; mainly, their tendency to act as Michael acceptors rather than donors[149] and the difficulty to control the enolate *E*/*Z* geometry and low facial discrimination that acetylene group induces since it is linear and small.

Despite these problems, direct asymmetric reactions in which enolizable ynones act as donors have been reported; for instance, through metal catalyzed aldol[148b-c,150] and Mannich[151] reactions and enamine mediated aldol reactions.[152] In addition, catalytic

[146] a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938–10939. b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

[147] Selected examples, for pyrroles: a) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277–4278. b) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074–2075. For furans: c) Jeevanandam, A.; Narkunan, K.; Ling, Y.-C. *J. Org. Chem.* **2001**, *66*, 6014–6020. d) Kel'i, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95–98. For furanones: e) Van den Hoven, B. G.; Ali, B. E.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4131–4137. For pyrazoles: f) Wang, X.-J.; Tan, J.; Zhang, L. *Org. Lett.* **2000**, *2*, 3107–3109. g) Kirkham, J. D.; Edeson, S. J.; Stokes, S.; Harrity, J. P. *Org. Lett.* **2012**, *14*, 5354–5357. For isoxazoles: h) Hojo, M.; Tomita, K.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 485–488. For pyrimidines: i) Karpov, A. S.; Muller, T. J. J. *Org. Lett.* **2003**, *5*, 3451–3454. For flavones: j) Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11*, 3210–3213. For quinolones: k) Arcadi, A.; Mrinelli, F.; Rossi, E. *Tetrahedron* **1999**, *55*, 13233–13250.

[148] Selected examples, for cyathane diterpenes: a) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett*. **2001**, *3*, 2105–2108. For fostriecin: b) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc*. **2005**, *127*, 3666–3667. c) Maki, K.; Motoki, R.; Fujii, K.; Kanai, M.; Kobayashi, T.; Tamura, S.; Shibasaki, M. *J. Am. Chem. Soc*. **2005**, *127*, 17111–17117. For oxcillatioxin D: d) Nokura, Y.; Araki, Y.; Nakazaki, A.; Nishikawa, T. *Org. Lett.* **2017**, *19*, 5992–5995. For azaspiracides: e) Zhang, Z.; Ding, Y.; Xu, J.; Chen, Y.; Forsyth, C. J. *Org. Lett.* **2013**, *15*, 2338–2341. f) Kenton, N. T.; Adu-Ampratwum, D.; Okumu, A. A.; Zhang, ZZ.; Chen, Y.; Nguyen, S.; Xu, J.; Ding, Y.; McCarron, P.; Kilcoyne, J.; Wilkins, F. A. L.; Miles, C. O.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 810–813.

[149] For reviews on ynones in synthesis, see: a) Salvio, R.; Moliterno, M.; Bella, M. *Asian J. Org. Chem.* **2014**, *3*, 340–351. b) Fraile, A.; Parra, A.; Tortosa, M.; Alemán, J. *Tetrahedron* **2014**, *70*, 9145−9173. c) Abbiati, G.; Arcadi, A.; Marinelli, F.; Rossi, E. *Synthesis* **2014**, *46*, 687−721. d) Rulev, A. Y.; Romanow, A. R. *RSC Adv.* **2016**, *6*, 1984−1998. e) Whittaker, R. E.; Dermenci, A.; Dong, G. *Synthesis*, **2016**, *48*, 161−183. f) Nájera, C.; Sydnes, L. K.; Yus, M. *Chem. Rev.* **2019**, *119*, 11110–11244.

[150] For aldol reaction with ynones as donors promoted by bifunctional metal catalysts, see: a) Fujiii, K.; Maki, M.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733–736. b) Trost, B. M.; Fetters, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660–2661. c) Shi, S. L.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3932–3935.

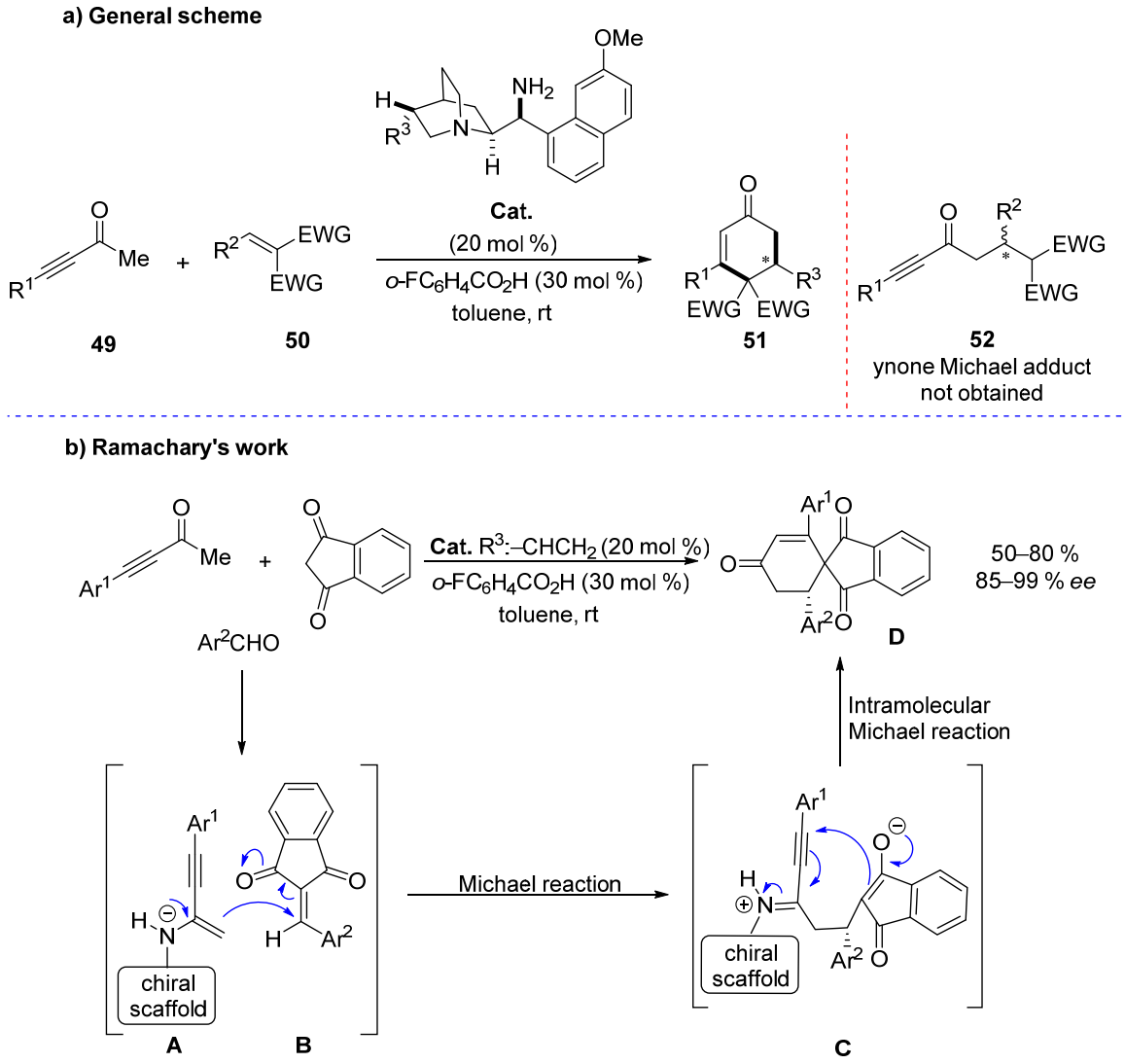
[151] For Mannich reactions with ynones as donors assisted by bifunctional metal catalysts, see: a) Shi, S.-L.; Wei, X.-F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019–17022. b) Trost, B. M.; Hung, C. I. *J. Am. Chem. Soc.* **2015**, *137*, 15940–15946.

[152] For aldol reactions with ynones as donors promoted by enamine activation, see: a) Silva, F.; Reiter, M.; Mills-Webb, R. Sawicki, M.; Klär, D.; Bensel, N.; Wagner, A.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 8390–8394. b) Silva, F.; Sawicki, M.; Gouverner, V. *Org. Lett.* **2006**, *8*, 5417–5419. c) Kang, G.; Jiang, J.; Liu, H.; Wu, H. *J. Braz. Chem. Soc.* **2012**, *23*, 5–10.

asymmetric conjugate additions of methyl ynones to highly activated Michael acceptors through aminocatalysis have also been investigated (Scheme 28a).[153] Although the utilization of highly active Michael acceptors **50** facilitates this reaction, this strategy do not lead to ynone Michael adducts **52**; instead, a subsequent intramolecular Michael addition occurs, giving place to a reflexive-Michael reaction, and the cyclized products **51** are obtained in good yields with high enantioselectivities. Scheme 28b shows as example the Ramachary's work, in which an efficient organocascade asymmetric reflexive-Michael reaction takes place through *in situ* formation of 2-aminobuta-1,3-enynes **A** and the activated Michael acceptor, 2-arylidene-indan-1,3-diones **B** by using sequential iminium-enamine-iminium activation. Then, conjugate addition of **A** to **B** leads to ynone iminium intermediate **C**, which undergoes intramolecular Michael reaction generating spirocyclic cyclohexane **D**. These reactions demonstrate the tendency of α,β-ynones to act as Michael acceptors since the intramolecular Michael addition cannot be avoided.[154] Besides, the use of two strong electron-withdrawing groups for activating the Michael acceptor and facilitating the addition significantly limits the reaction scope.

[153] a) Ramachary, D. B.; Venkaiah, C.; Krishna, P. M. *Chem. Commun.* **2012**, *48*, 2252–2254. b) Ramachary, D. B.; Venkaiah, C.; Madhavachary, R. *Org. Lett.* **2013**, *15*, 3042–3045.

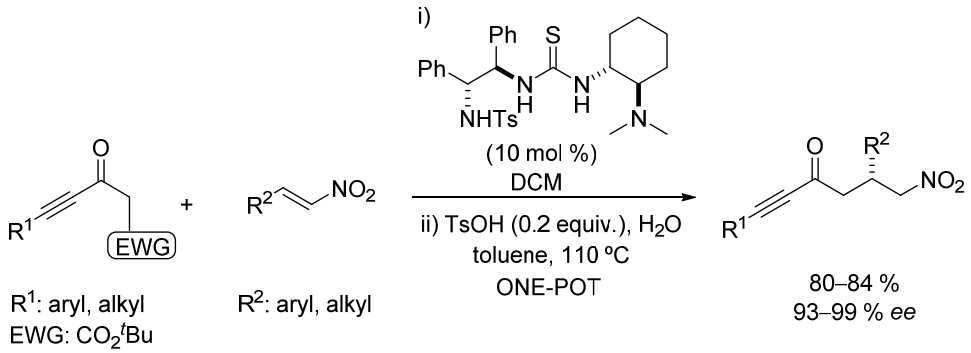
[154] For an example on domino cyclisation (Mannich reaction-Michael reaction) of cyclic *N*-sulfimines with ynones, see: Liu, Y.; Kang, T.-R.; Liu, Q.-Z.; Chen, L.-M.; Wang, Y.-C.; Liu, J.; Xie, Y.-M.; Yang, J.-L.; He, L. *Org. Lett.* **2013**, *15*, 6090–6093.



Scheme 28. a) Catalytic asymmetric conjugate addition reactions of methyl ynones **49** with highly activated Michael acceptors **50** through amino catalysis. b) Example of a reflexive Michael reaction. **Ramachary**, **2012**.

As it is well known, Brønsted base catalysis is a supplementary strategy to metal and aminocatalytic activation and it arouses great interest, since this methodology entails an ideal atom economy and BB catalysts tolerate several functional groups. Nevertheless, to the best of our knowledge, only one report on α-addition of enolizable ynones has been reported (Scheme 29).[155] This work, carried out by Peng, Wang and Shao in 2016, represents an alternative strategy to reverse the reactivity of ynones from Michael acceptors to donors and miss the double Michael addition.

[155] Liu, W.; Zou, L.; Fu, B.; Wang, X.; Wang, K.; Sun, Z.; Peng, F.; Wang, W.; Shao, Z. J. *Org. Chem.* **2016**, *81*, 8296–8305.

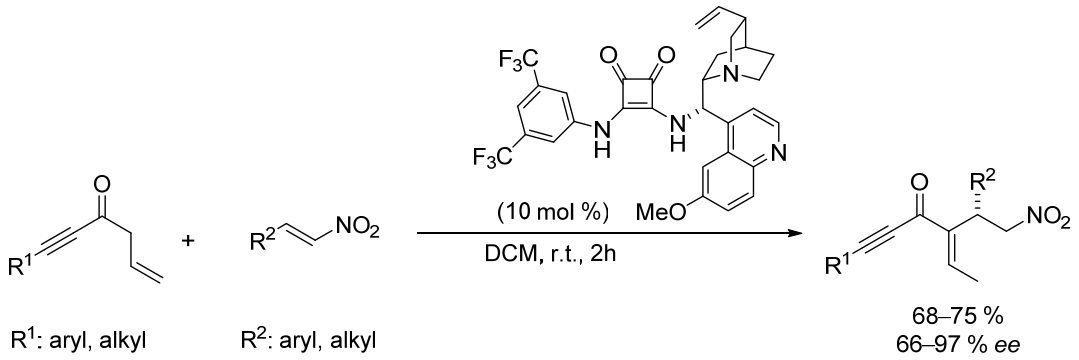


Scheme 29. First use of ynones as Michael donors in catalytic asymmetric Michael reaction with nitroolefins. **Peng**, **Wang and Shao**, **2016**.

The preliminary control studies between 4-phenyl-3-butyn-2-one and *trans*-β-nitrostyrene in the presence of chiral Brønsted base/H-bonding-based catalysts performed by Peng, Wang and Shao[155] showed that the functional pK_a barrier of this kind of catalysts compromises the efficiency with less acidic carbon pronucleophiles and that non activated Michael acceptors are unable to afford the desired Michael adduct. Therefore, they proposed the incorporation of a traceless directing group,[156] as $CO_2{}^t$Bu, to increase the nucleophilicity of ynones. In addition to enhancing the reactivity of the reaction, the $CO_2{}^t$Bu group interacts with the catalyst, which induces the obtaining of the final products with excellent enantioselectivity; however, the final decarboxylation produced the loss of the α-chiral center.

One year later, our group reported a study on organocatalytic enantioselective Michael reaction of vinylogous ketones with nitroolefins,[142] in which allyl ynones demonstrated to be a suitable subset of allyl ketones for BB catalysis (Scheme 30). The allyl group activates the ynone for reacting with nitroolefins *via* Brønsted base/H-bonding catalysis and although the Michael adducts are obtained in moderate yields with high enantio and α/γ-selectivity, the α-stereocenter is missed because the C=C double bond in the reaction adducts isomerizes spontaneously to the most stable α,β-position.

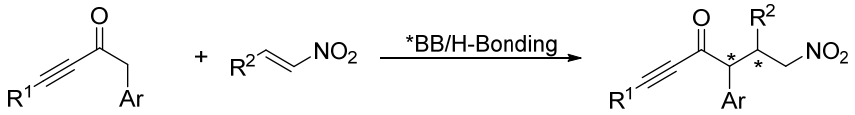
[156] For a review on removable directing groups in organic synthesis and catalysis, see: Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494.



Scheme 30. Michael addition of allyl ynones as subset of allyl ketones through Brønsted base/H-bonding catalysis. **Palomo and Oiarbide**, **2017**.

3.2 Objectives

Although the above precedents show an effective approach for the α-functionalization of ynones with nitroalkenes through Brønsted base/H-bonding catalysis wherein a single new stereocenter is generated in the final adduct and the subsequent undesired intramolecular Michael reaction is avoided, the creation of a stereogenic center at α-position of the ynone Michael adduct reminds elusive. For that reason, and keeping in mind the previous results of this Thesis work (Chapter 2),[157] where it was demonstrated that benzyl ketones are appropriate substrates for bifunctional Brønsted base mediated catalysis, we envisioned that benzyl ynones could be competent pronucleophiles for the Michael addition to nitroolefins through Brønsted base/H-bonding activation (Scheme 10).



Scheme 31. Proposed stereoselective Michael addition of benzyl ynones to nitroolefins catalyzed by bifunctional Brønsted bases.

3.3 Results and discussion

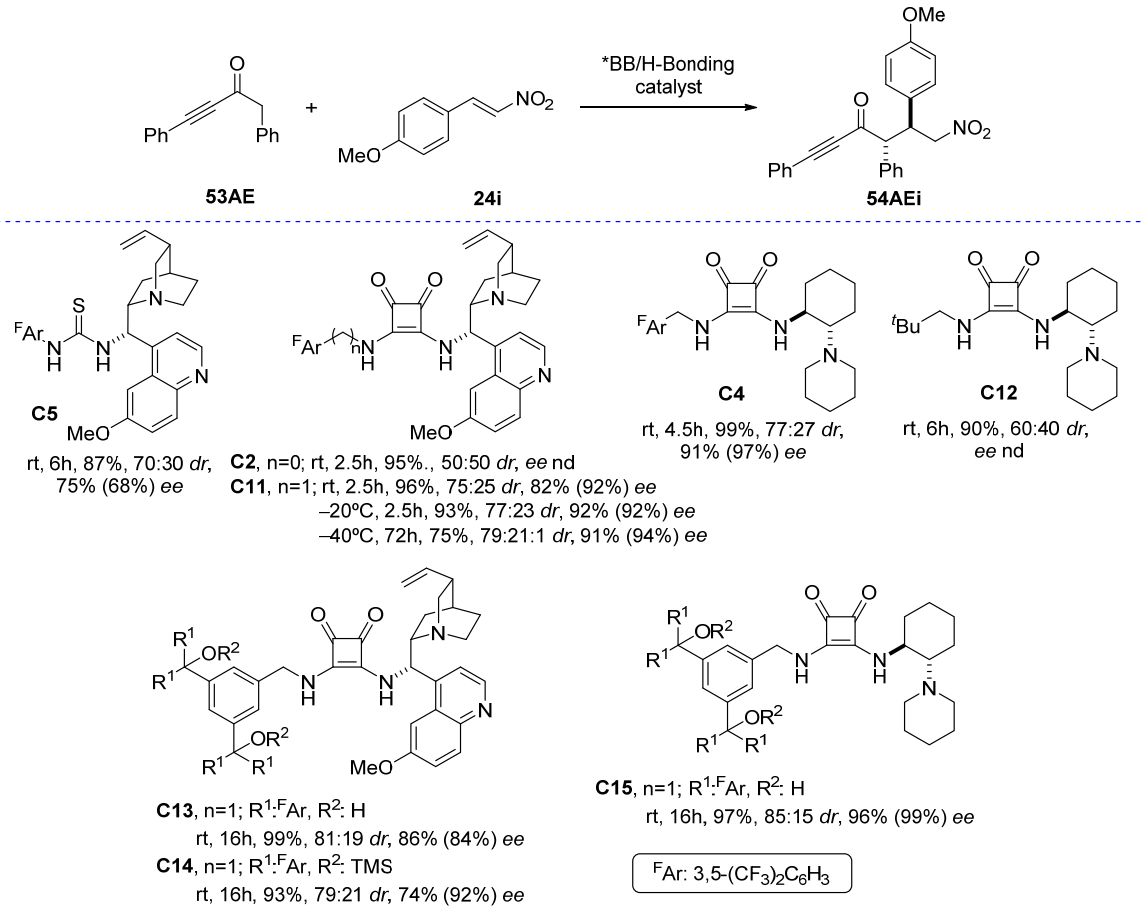
3.3.1 Catalyst screening

In order to check the viability of our proposal and find out the best reaction conditions, 1,4-diphenylbut-3-yn-2-one **53AE** was selected to react with (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **24i** in the presence of different Brønsted base/H-bonding catalysts

[157] Olaizola, I.; Campano T. E.; Iriarte, I.; Vera, S.; Mielgo, A.; García, J. M.; Odriozola, J. M.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2018**, *24*, 3893–3901.

(Table 8). Initially, classical cinchona alkaloid-based thiourea **C5** and squaramides **C2** and **C11** were synthetized and evaluated, but the diastereoselectivity was not higher than 79:21, albeit, high enantioselectivity was observed in the presence of squaramide catalysts **C11**. In addition, the reaction in the presence of **C11** was tested at different temperatures, but the adduct **54AEi** was obtained with similar stereoselectivity outcome in all of them.

Table 8. Catalyst screening for the Michael addition of benzyl ynone **53AE** to nitrostyrene **24i**.[a]



[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:1.2:0.1 molar ratio of **53AE**/**24i**/catalyst). Combined yield of diastereomers isolated after chromatography. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis of the crude sample. The enantiomeric excess in parenthesis refers to the minor diastereomer.

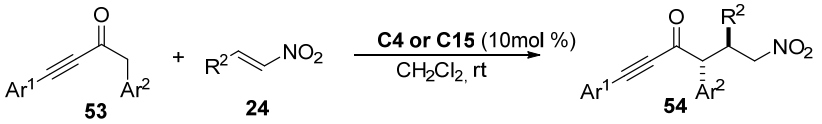
Then, variation of the Brønsted base in the squaramide catalysts **C11** was considered since it provided the best result. The cyclohexanamine derived **C4**, in comparison to its analogous **C11**, afforded at room temperature a slight improvement in the diastereo- and enantioselectivity (77:23 *dr*, 91/97 % *ee*). In contrast, catalyst **C12** led to the final product with worse diastereoselectivity (60:40 *dr*). Afterwards, the influence

of the incorporation of bulky substituents in the aromatic ring was investigated, since the increase of the steric congestion around the squarate might be favourable for enantiocontrol. In this context, catalysts **C13** and **C14** were synthetized. In the presence of **C13**, Michael adduct **53AEi** was obtained with a slight improvement in the diastereoselectivity (81:19 *dr*). The silylation of the hydroxy groups at **C13** provided catalyst **C14**, which did not enhance the reaction stereocontrol (79:21 *dr*, 74/92 % *ee*). Again, the remplacement of cinchona alkaloid by the 2-(piperidin-1-yl)ciclohexanamine was considered and catalyst **C15** was synthetized and tested, which afforded the Michael adduct with higher diastereoselectivity (85:15 *dr*) and enantioselectivity (96/99 % *ee*) than the before checked ones. These results reveal **C15** as the best catalyst and demonstrate that steric effects alone may not suffice to explain its salient performance.

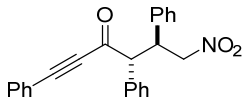
3.3.2 Reaction scope

Taking into account the catalyst screening results, **C15** was choosen to explore the reaction scope. As standard reaction conditions, the ynone **53** was dissolved in CH_2Cl_2 (0.3 M) and 1.2 equivalents of nitroolefin **24** and 10 mol % of **C15** were added (some examples were also carried out in the presence of **C4**) and the reaction mixture was stirred at room temperature (TLC monitoring). Table 9 shows the results of the reaction of benzyl ynones incorporating variations at the benzylic site with different nitroalkenes. The reactions was first performed with 1,4-diphenylbut-3-yn-2-one (**53AE**) and different nitroolefins and it should be noted that in the case of β-alkyl substituted nitroalkenes **24c** and **24e** the Michael adducts were obtained in moderate yield (up to 71%) and diastereoselectivity (up to 2.8:1 *dr*) and nearly perfect enantioselectivity (up to 94/98% *ee*). Afterwards, ynones bearing electron-poor and –rich substituents at the *ortho* and *para* positions of the aromatic ring Ar^2 (**53AF–53AJ**) also reacted with nitrostyrenes (**24a**, **24f** and **24j**) in the presence of **C4** and **C15** to afford the corresponding adducts with moderate to high diastereoselectivity (76:24–91:9 *dr*) and excellent enantioselectivity (84–99% *ee*). In all cases, the comparison of the stereoselectivity outcome from **C4** and **C15** reveals that the latter was a more efficient catalyst for this reaction.

Table 9. Reaction scope for the Michael addition of different benzyl ynones **53** to nitrostyrene **24** in the presence of catalyst **C4** and **C15**.[a]

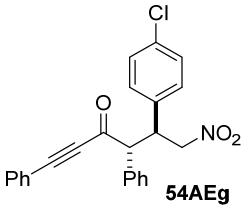


A Ar^1: C_6H_5 **E** Ar^2: C_6H_5 **I** Ar^2: 4-ClC_6H_4 **i** R^2: 4-$MeOC_6H_4$ **f** R^2: 4-BrC_6H_4
B Ar^1: 4-MeC_6H_4 **F** Ar^2: 4-MeC_6H_4 **J** Ar^2: 3-ClC_6H_4 **a** R^2: C_6H_5 **c** R^2: $(CH_3)_2CHCH_2$
C Ar^1: 4-ClC_6H_4 **G** Ar^2: 3-MeC_6H_4 **g** R^2: 4-ClC_6H_4 **e** R^2: $CH_3(CH_2)_4$
D Ar^1: 4-$MeOC_6H_4$ **H** Ar^2: 4-$MeOC_6H_4$ **j** R^2: 4-MeC_6H_4



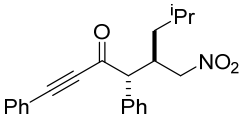
54AEa

C4, 3h 80%,
dr 85:15, 93% ee (98% ee)
C15, 4h 86%,
dr 83:17, 96% ee (99% ee)



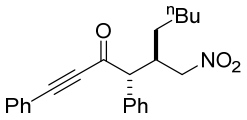
54AEg

C4, 3h 99%,
dr 77:23, 94% ee (98% ee)
C15, 6h 93%,
dr 84:16, 99% ee (99% ee)



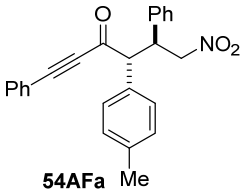
54AEc

C15, 144h 71%, dr 72:28,
94% ee (98% ee)



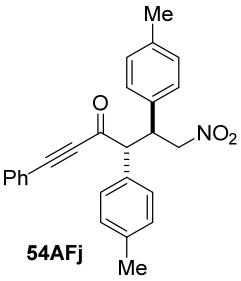
54AEe

C15, 144h 68%, dr 74:26,
94% ee (88% ee)



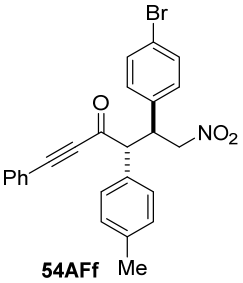
54AFa

C4, 3h 85%,
dr 76:24, 90% ee (99% ee)
C15, 16h, 90%,
dr 83:17, 84% ee (99% ee)



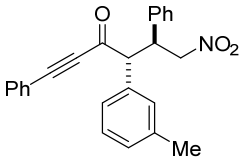
54AFj

C15, 16h 90%,
dr 83:17, 96% ee (98% ee)



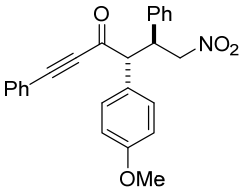
54AFf

C4, 4h 89%,
dr 72:28, 94% ee (98% ee)
C15, 16h, 90%,
dr 87:13, 96% ee (99% ee)



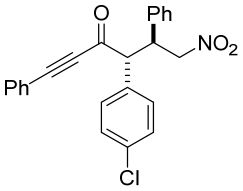
54AGa

C15, 16h 96%,
dr 86:14, 94% ee (99% ee)



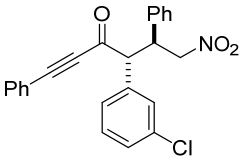
54AHa

C15, 16h 96%,
dr 80:20, 96% ee (99% ee)



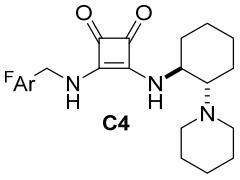
54AIa

C4, 5h 41%,
dr 89:11, 98% ee (92% ee)
C15, 16h 30%,
dr 91:9, 98% ee (99% ee)

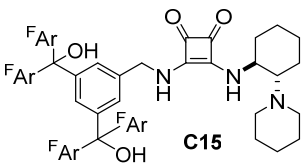


54AJa

C15, 16h 88%,
dr 86:14, 95% ee (99% ee)



C4



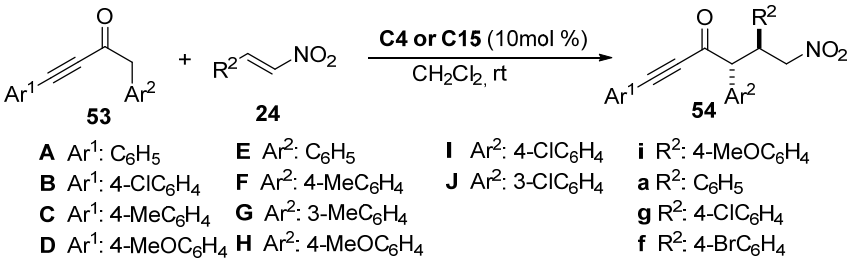
C15

^{F}Ar: 3,5-$(CF_3)_2C_6H_3$

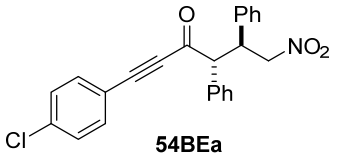
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:1.2:0.1 molar ratio of **53**/**24**/catalyst). Combined yield of diastereomers isolated after chromatography. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis of the crude sample. The enantiomeric excess in parenthesis refers to the minor diastereomer.

Table 10 shows the adducts obtained when alkynyl ketones **53B-D** incorporating electron donating and withdrawing substituents at the aromatic ring of the acetylenic side (Ar^1) were reacted with β-aryl substituted nitroalkenes in the presence of **C4** and **C15**. The stereoselectivity was controlled in all the cases, so the reactions provided the Michael adducts with good diastereoselectivity (73:27–89:11 *dr*) and nearly perfect enantioselectivity (90–99 % *ee*), independently of the substitution pattern of each reaction component.

Table 10. Reaction scope for the Michael addition of different acetylenic benzyl ynones **53** to nitrostyrene **24** in the presence of catalyst **C4** and **C15**.[a]

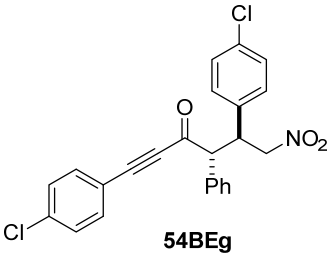


A Ar^1: C_6H_5 **B** Ar^1: 4-ClC_6H_4 **C** Ar^1: 4-MeC_6H_4 **D** Ar^1: 4-$MeOC_6H_4$
E Ar^2: C_6H_5 **F** Ar^2: 4-MeC_6H_4 **G** Ar^2: 3-MeC_6H_4 **H** Ar^2: 4-$MeOC_6H_4$
I Ar^2: 4-ClC_6H_4 **J** Ar^2: 3-ClC_6H_4
i R^2: 4-$MeOC_6H_4$ **a** R^2: C_6H_5 **g** R^2: 4-ClC_6H_4 **f** R^2: 4-BrC_6H_4



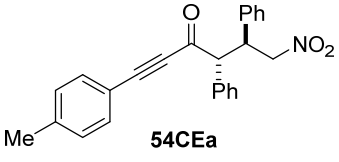
54BEa

C4, 16h 77%, dr 73:27, 90% ee (98% ee)
C15, 16h 87%, dr 75:25, 96% ee (99% ee)



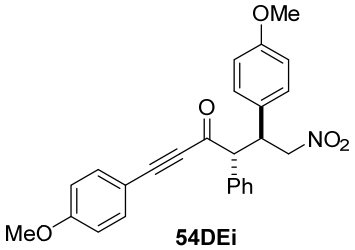
54BEg

C4, 16h 77%, dr 77:23, 90% ee (98% ee)
C15, 16h, 90%, dr 82:18, 92% ee (99% ee)



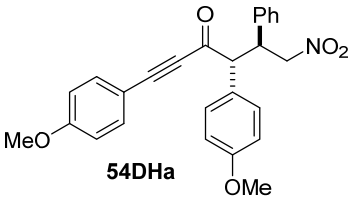
54CEa

C15, 16h 87%, dr 80:20, 96% ee (ee nd)



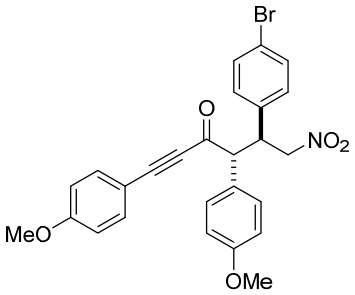
54DEi

C15, 16h 86%, dr 87:13, 94% ee (99% ee)



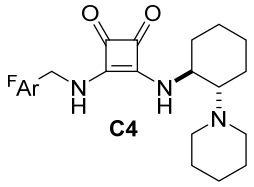
54DHa

C15, 16h 96%, dr 89:11, 98% ee (99% ee)

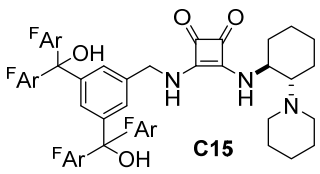


54DHf

C15, 16h 82%, dr 87:13 96% ee (99% ee)



C4



C15

^{F}Ar: 3,5-$(CF_3)_2C_6H_3$

[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:1.2:0.1 molar ratio of **53**/**24**/catalyst). Combined yield of diastereomers isolated after chromatography. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis of the crude sample and which are in parenthesis refers to minor diastereomer.

The absolute configuration of adduct **54AEi** was established by single-crystal X-ray structure analysis (Figure 29) and for the remaining adducts **54** was assumed by analogy on the basis of a uniform reaction mechanism.

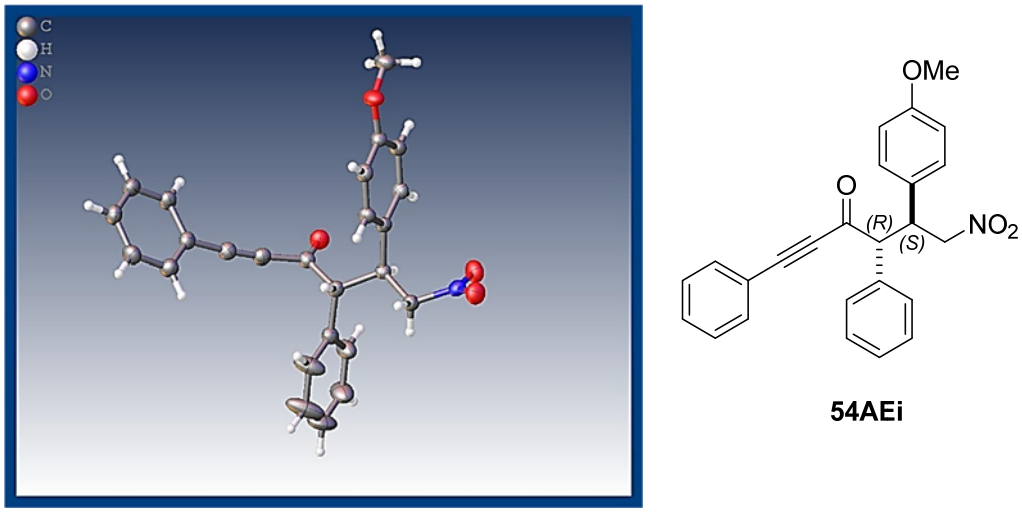
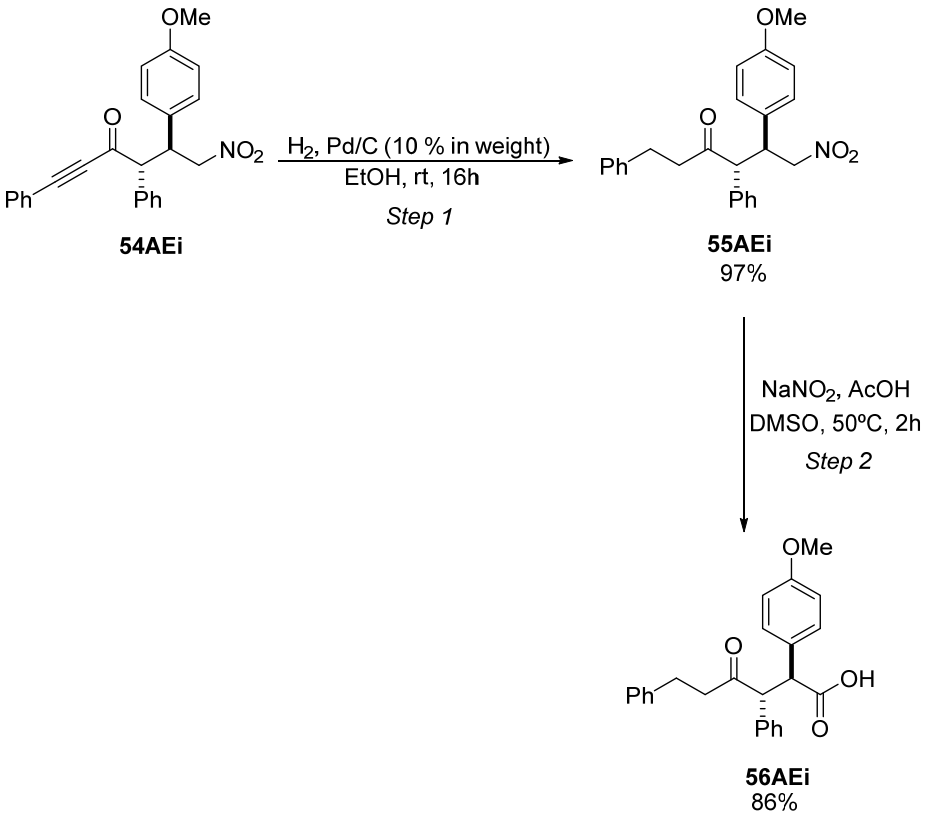


Figure 29. Results of the single-crystal X-ray structure analysis of adduct **54AEi**.

3.3.3 Elaboration of adducts

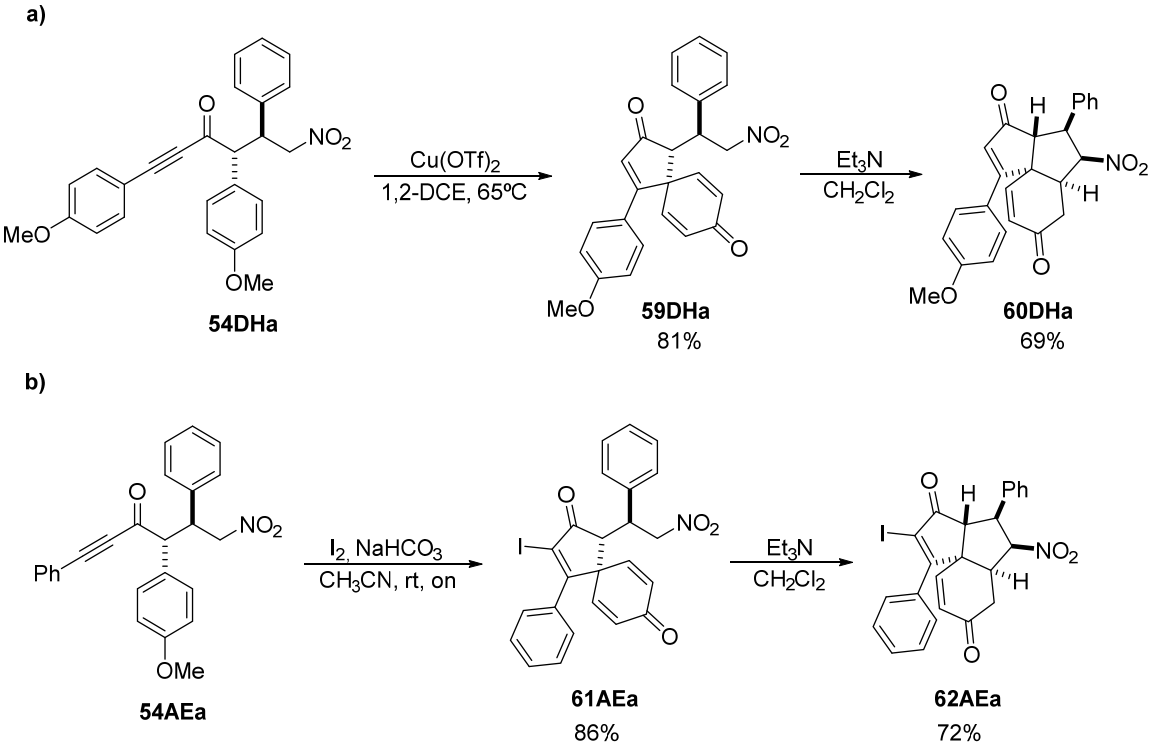
As mentioned before, the alkyne group is appealing since its reactivity facilitates skeletal diversification. For instance, reduction of adduct **54AEi** provides dissymmetric alkyl alkyl ketone product **55AEi** with two tertiary stereocenters at α and β positions in 97 % yield (Scheme 32, step 1), which is still not accessible from α-alkylation of the corresponding phenethyl ketone. Moreover, in these molecules the nitro group can be transform into a carboxylic acid function upon Nef reaction[99] following Mioskowski[101] conditions. For instance, oxidation of compound **55AEi** led to carboxylic acid derivative **56AEi** in 86 % yield (Scheme 32, step 2).



Scheme 32. Reduction of adduct **54AEi** to α-branched alkyl alkyl ketone **55AEa** and oxidation of that to carboxylic acid derivative **56AEi**.

Furthermore, the alkyne group also serves for the synthesis of other more complex structures. For instance, Cu^{II} can activate the alkyne group towards nucleophilic attack and then, the ynones can be converted into spirocyclic dienones through an intramolecular *ipso*-cyclisation.[158] Scheme 33a shows the cyclisation of anisole-substituted ynone **54DHa** under $Cu(OTf)_2$ mediated conditions to afford spyrocycle **59DHa** in 81 % yield. Nevertheless, a limitation of this approach is the requirement of electron-donating groups on the alkyne terminus. This issue might be addressed by using I_2 through an iodonium ion-induced electrophilic intramolecular *ipso*-cyclisation.[159] For example, ynone **54EAa** under these reaction conditions led to spyrocycle **61AEa** in 86 % yield (Scheme 33b). Additionally, spirocycles **59DHa** and **61AEa** were converted upon treatment with base into compounds **60DHb** and **62AEa**, which display a tricyclic carbon core. The configuration of compounds **60DHb** and **62AEa** was established by NOE and NOESY experiments.[160]

[158] Clare, A. K.; Liddon, J. T.R.; Curhbertson, J. D.; Taylor, R. J. K.; Unsworth, W. P. *Org. Biomol. Chem.* **2017**, *15*, 233–245.
[159] Zhang, X.; Larock, R. C. J. *Am. Chem. Soc.* **2005**, *127*, 12230–12231.
[160] For more details, see experimental section, Chapter 7.



Scheme 33. Elaboration of adducts **54DHa** and **54AEa** into carbocycles of intricate structure.

In summary, ketones bearing an alkyne and benzyl group have been appropriate pronucleophiles for conjugate additions to nitroalkenes in the presence of Brønsted base/squaramide bifunctional catalysts, affording the Michael adducts with high regio-, diastereo- and enantioselectivity, thus, complementing the few existing direct approaches for the α-functionalization of ynones. Moreover, the versatility of the acetylene group has given access to α-functionalizated dialkyl ketones and other enantioenriched complex structures such as intricate trycyclic carbon skeletons.

CHAPTER 4.

Arylacetaldehydes as Michael donors

Arylacetaldehydes as Michael donors

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4. Arylacetaldehydes as Michael donors

4.1 Introduction

The inherent features of aldehydes have hampered their α-functionalization throughout years, owing to the difficulty for their activation and the high reactivity of the *ipso*-carbon atom in this oxidation state, which complicates control of enolate or enol side reactions. In addition to these issues, the reaction enantiocontrol is also a matter that increases the complexity of the α-functionalization of aldehydes.

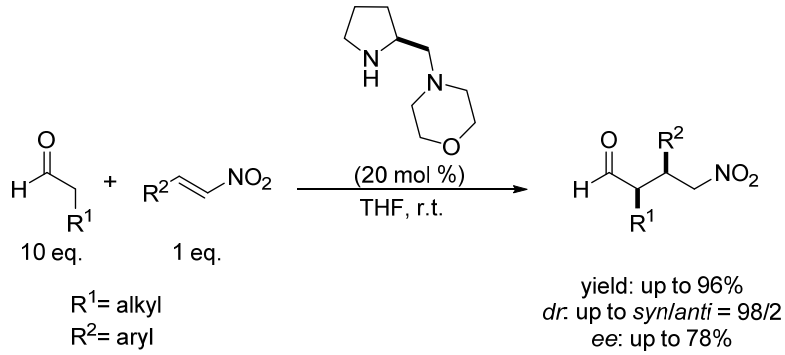
Aminocatalysis has provided solutions to this challenge, developing several approaches for the enantioselective α-functionalization of aldehydes as outlined below. However, in spite of the great development of Brønsted base catalysis under soft enolization conditions, its application in the α-functionalization of aldehydes has not been reported, as far as we know; probably due to the previously mentioned problems. In light of the results of the previous chapters, we wondered if this type of catalysis could also be extended to aldehydes. In this chapter, we report our results on the exploration of this strategy in the conjugate addition of aldehydes to nitroalkenes.

As previously mentioned, a plethora of examples of the α-functionalization of unmodified aldehydes through Michael additions promoted by chiral primary and secondary amines as catalysts *via* enamine[3] have been reported to provide mainly *syn*-products.[161] Consequently, a wide variety of electron-deficient olefins have been employed as acceptors, among which, nitroalkenes have been the most frequently used,[96] due to, as it was disclosed in the introduction, their high electrophilicity and the presence of the nitro functionality that can easily be transformed into other interesting functional groups.[98] In addition, γ-nitroaldehydes are precursors of γ-aminobutyric acid analogues

[161] To the best of our knowledge, only four examples leading to the *anti*-isomers, which employ linear aldehydes through enamine activation, have been reported: By generating the *Z*-enamine, see: a) Uehara, H.; Barbas, C. F. III *Angew. Chem. Int. Ed.* **2009**, *48*, 9848–9852. By using a *Z*-nitroolefin in combination with an *E*-enamine, see: b) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4656–4660. By inducing a different approach of the *E*-nitroalkene to the *E*-enamine, see: c) Kano, T.; Sugimoto, H.; Tokuda, O.; Maruoka, K. *Chem. Commun.* **2013**, *49*, 7028–7030. By generation of the s-*cis* enamine, see: d) Shnitzer, T.; Budinská, A.; Wennemers, H. *Nature Catalysis*, **2020**, *3*, 143–147. For a report on a computational design and prediction based on transition state energies of conjugate addition of aldehydes to nitroalkenes, see: e) Yang, H.; Wong, M. W. *J. Org. Chem.* **2011**, *76*, 7399–7405.

(GABAs), which show pharmacological activities[162] such as antidepressant, anticonvulsant or anxiolytic, and are employed in the treatment of neurodegenerative disorders.[163]

In 2001, Barbas III reported the first enantioselective Michael addition of naked aldehyde donors catalyzed by chiral amines through enamine activation (Scheme 34).[164] In this case, pyrrolidine base catalysts were employed leading to *syn*-Michael adducts in up to 96% yield, with a diastereoselective ratio up to 98/2 (*syn*/*anti*) and up to 78% *ee.*



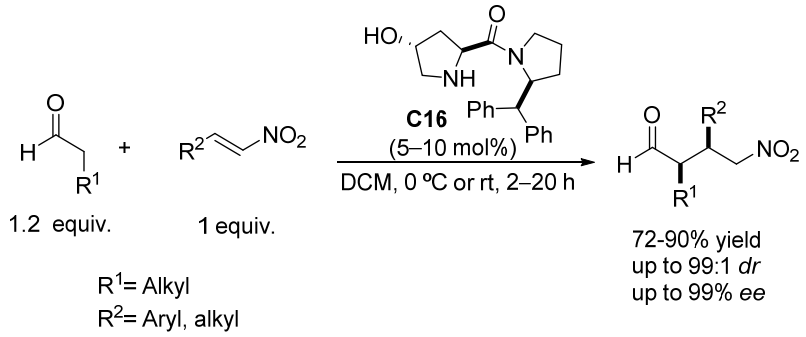
Scheme 34. First direct catalytic enantio- and diastereoselective Michael additions of unmodified aldehydes to nitroolefins promoted by a pyrrolidine based catalyst. **Barbas III, 2001**.

In this line, it has been shown that a slight change in the catalyst structure allowed to improve the catalytic activity, so the use of bipyrrolidines[165] provide moderate stereoselectivity and the most representative catalysts, diphenylprolinol silyl ether[45b] or a pyrrolidine-sulfonamide,[166] developed by Hayashi and Wang respectively, attain the corresponding adducts with high diastereo- and enantioselectivities.

Nonetheless, the need of a large excess of the aldehyde substrate, generally 10 equivalents, was a limitation for this type of reactions. Besides, the reactions with β-alkyl-substituted nitroalkenes produced adducts in moderate yields or essentially no enantioselectivity. In 2006, our research group reported the conjugate addition of alkyl aldehydes to aryl and alkyl substituted nitroalkenes lowering the amount of the Michael donor to 1.2 equivalents in the presence of the *trans*-4-hydroxyprolylamide **C16**, reaching excellent yields and *syn*-stereoselectivity (Scheme 35).[167] This catalyst controls the

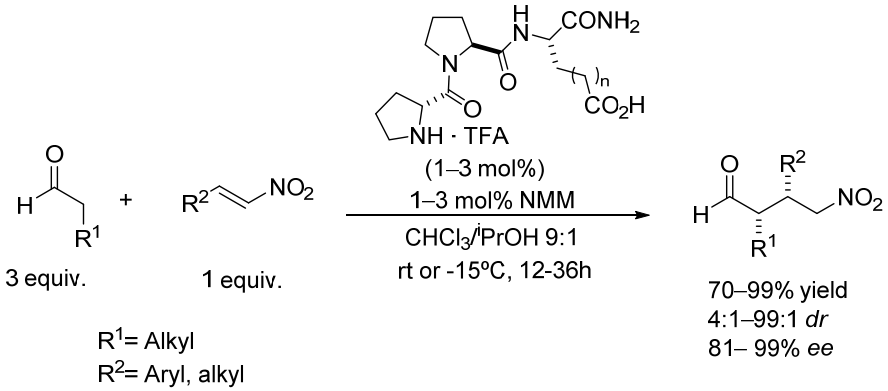
[162] a) R. Ballini, *Stud. Nat. Prod. Chem*. **1997**, *19*, 117–184. b) Andresen, H.; Aydin, B. E.; Mueller, A.; Iwersen-Bergmann, S. *Drug Test. Anal.* **2011**, *3*, 560–568. c) Aboul-Enein, M. N.; El-Azzouny, A. A.; Saleh, O. A.; Maklad, Y. A. *Mini Rev. Med. Chem.* **2012**, *12*, 671–700.
[163] Gajcy, K.; Lochynski, S.; Librowski, T. *Curr. Med. Chem.* **2010**, *17*, 2338–2347.
[164] Betancort, J. M.; Barbas III, C. F. *Org. Lett*. **2001**, *3*, 3737–3740.
[165] a) Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611–3614. b) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901–7904. c) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147–1168.
[166] Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371.
[167] Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 5984–5987.

enamine geometry through a bulky substituent at the 2 position of the pyrrolidine skeleton, and the hydrogen-bond donor (–OH group) at the 4 position activates the acceptor and directs its approach from the less hindered enamine face.



Scheme 35. Enantioselective Michael reaction of aldehydes with nitroolefins using a hydroxyproline derived catalyst. **Palomo, 2006**.

A great contribution in the field came from Wennemers' group. A similar catalyst design incorporating two proline amino acids together with a third amino acid (H-D-Pro-Pro-Asp-NH_2) was developed. The use of this tripeptide catalyst in the Michael addition of alkyl aldehydes to aryl and alkyl substituted nitroalkenes leads to the *syn*-adducts with high yields and enantioselectivities (Scheme 36).[46b] A remarkable fact in this reaction was the use of small loadings of the catalyst (1-3 mol %), the first example with this low catalyst loading until that moment. Since then, other peptides have also been used to promote the Michael reaction of aldehydes to nitroolefins with similar results.[46c,168]



Scheme 36. Enantioselective Michael addition of aldehydes to nitroalkenes catalyzed by a tripeptide. **Wennemers, 2008**.

[168] For selected examples see: a) Wiesner, M.; Neuburger, M. Wennemers, H. *Chem. Eur. J.* **2009**, *15*, 10103–10109. b) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6–7. c) Kastl, R.; Arakawa, Y.; Duschmale, J.; Wiesner, M.; Wennemers, H. *Chimia* **2013**, *67*, 279–282. d) De la Torre, A. F.; Rivera, D. G.; Ferreira, M. A. B.; Correa, A. G.; Paixao, M. W. *J. Org. Chem.* **2013**, *78*, 10221–10232. e) Cortes-Clerget, M.; Gager, O.; Monteil, M.; Pirat, J.-L.; Migianu-Griffoni, E.; Deschamp, J.; Lecouve, M. *Adv. Synth. Catal.* **2016**, *358*, 34–40.

Chiral secondary amine catalysts have been used in most of the asymmetric conjugate additions of aldehydes to nitroolefins,[169,170] however, chiral primary amines also play an important role. Secondary amines react with carbonyl compounds to generate enamines more readily than primary amines do. Nevertheless, primary amines can generate enamines more readily in the case of sterically hindered carbonyl compounds. As a result, they have been successfully used in asymmetric Michael reactions of α-branched aldehydes with nitroalkenes, despite the drawbacks that α-branched aldehydes suffer; for instance, the difficulty for the condensation of the amino catalyst with an α-branched aldehyde due to the steric hindrance around the carbonyl moiety,[171] and lower reactivity of the resulting enamine.[172] In addition, a possible inhibition of the catalytic cycle can be produced owing to the irreversible formation of intermediates generated because of the absence of a proton at the α-position.[173] Added to that, the enamine formation from a-branched aldehydes can lead to a *Z*/*E* mixtures which affect tostereoslectivity. As solution, isobutyraldehyde or cyclic aldehydes have been selected to react with nitroalkenes assisted by primary amino catalysts, generally involving hydrogen-bond donors,[174] but the reaction scope goes on limited.

For the formation of enantioenriched γ-nitroaldehydes bearing quaternary stereocenters through the addition of unsymmetrically α,α-disubstituted aldehydes to nitroolefins, to the best of our knowledge, only five contributions, which involve the use

[169] For selected examples catalyzed by proline derivatives, see: a) Reyes, E. Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135–6138. b) An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Synthesis* **2013**, *45*, 1612–1623. c) Yu, H.; Liu, M.; Han, S. *Tetrahedron* **2014**, *70*, 8380–8384. For a triple cascade organocatalytic reaction (Michael-Michael-aldol sequence) see: d) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature*, **2006**, *441*, 861–863. For selected examples catalyzed by prolinamides derivatives, see: e) Wang, Y.; Lin, J.; Wei, K. *Tetrahedron Asymmetry* **2014**, *25*, 1599–1604. f) Wang, Y.; Ji, S.; Wei, K.; Lin, J. *RSC Adv.* **2014**, *4*, 30850–30856. g) Wang, Y.; Li, D.; Lin, J.; Wei, K. *RSC Adv.* **2015**, *5*, 5863–5874. For selected examples catalyzed by pyrrolidine derivatives, see: h) Kumar, T. P. *Tetrahedron Asymmetry* **2014**, *25*, 1286–1291. i) Hu, X.; Wei, Y.-F.; Wu, N.; Jiang, Z.; Liu, C.; Luo, R.-S. *Tetrahedron Asymmetry* **2016**, *27*, 420–427. j) Kumar, T. P.; Abdul Sattar, M.; Prasad, S. S.; Haribabu, K.; Reddy, C. S. *Tetrahedron Asymmetry* **2017**, *28*, 401–409.

[170] For selected examples of Michael reactions of aldehyde with nitroalkenes in water as reaction medium, see: a) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548. b) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50–51. For selected examples of Michael additions of aldehydes to nitroolefins promoted by polymer supported catalysts, see: c) Varela, M. c.; Dixon, S. M.; Lam, K. S.; Schore, N. E. *Tetrahedron*, **2008**, *64*, 10087–10090. d) Alza, E.; Pericás, M. A. *Adv. Synth. Catal.*, **2009**, *351*, 3051–3056. e) Arakawa, y.; Wiesner, M.; Wennemers, H. *Adv. Synth. Catal.*, **2011**, *353*, 1201–1206. . f) Keller, M.; Perrier, A.; Linhardt, R.; Travers, L.; Wittmann, S.; Caminade, A.-M.; Majoral, J.-P.; Reiser, O.; Ouali, A. *Adv. Synth. Catal.* **2013**, *355*, 1748–1754. g) Sagamanova, I.; Rodríguez-Escrich, C.; Molnár, I. G.; Sayalero, S.; Gilmour, R.; Pericás, M. A. *ACS Catal.* **2015**, *5*, 6241–6248.

[171] Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14*, 536–539.

[172] Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209–2218.

[173] Burés, J.; Armstrong, a.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741–6750.

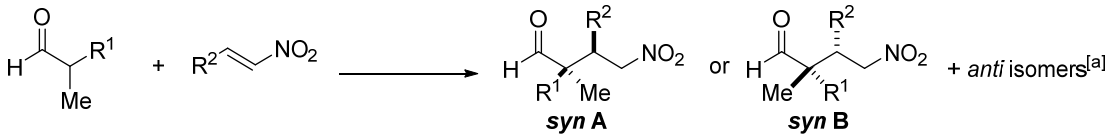
[174] For general reviews on asymmetric organocatalytic functionalization of α,α-disubstituted aldehydes, see: a) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron*, **2014**, *70*, 2491–2513. b) Martínez-Guillén, J. R.; Flores-Ferrándiz, J.; Gómez, C.; Gómez-Bengoa, E.; Chinchilla, R. *Molecules*, **2018**, *23*, 141.

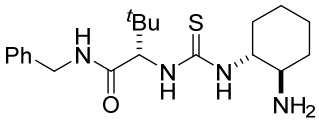
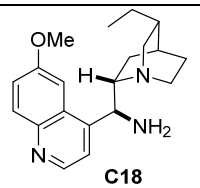
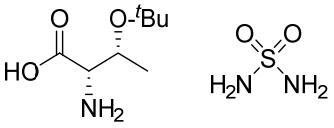
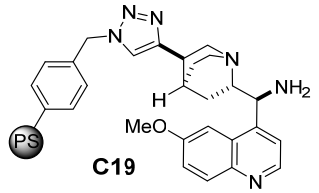
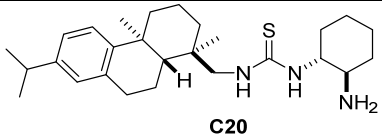
of primary amines as catalysts, have reported efficient protocols (Table 11),[175] since the first report on this reaction by Barbas III in the presence of a proline based catalyst, which attained moderate stereoselectivity.[176] Besides, it should be mentioned, that all these examples provide the *syn*-products. For α-alkyl α-methyl aldehydes (R^1=alkyl), in all cases, the corresponding adducts are obtained with moderate diastereoselectivity and high enantioselectivity, whereas for α-aryl α-methyl aldehydes (R^1=phenyl), the reaction affords the adducts in higher diastereoselectivity, but lower enantioselectivity. The only outstanding stereoselectivity in this last case was obtained in the reaction with β-alkyl nitroalkenes in the presence of a chiral primary amine thiourea catalyst, which bears an amino acid in its structure.[175a] On the basis of these results, it is clear that this reaction is challenging regarding catalyst loading, aldehyde stoichiometry, reaction stereoselectivity, scope and time. Furthermore, in spite of the progress in this transformation, works assisted by Brønsted bases/H-bonding catalysts have not been found in the literature.

[175] For stereoselective conjugate additions of aldehydes with non equivalent α-substituents, see: a) Lalonde, M. P.; Chen, Y; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370. b) Mc Cooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599–602. c) Nugent, T. C.; Shoaib, M.; Shoaib, A. *Org. Biomol. Chem.* **2011**, *9*, 52–56. d) Porta, R.; Benaglia, M.; Coccia, F.; Cozzi, F.; Puglisi, A. *Adv. Synth. Catal.* **2015**, *357*, 377–383. e) Guo, X.-T; Sha, F.; Wu, X.-Y.; *Res. Chem. Intermed.* **2016**, *42*, 6373–6380. For examples of non stereoselective conjugate additions of aldehydes with non equivalent α-substituents, see: f) Kotrusz, P.; Toma, S.; Schmalz, H-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577–1583. g) Yoshida, M.; Sato, A.; Hara, S. *Org. Biomol. Chem.* **2010**, *8*, 3031–3036. h) Ting, Y.-F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem. Eur. J.* **2010**, *16*, 7030–7038. i) Chen, J.-R.; Zou, Y.-Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W.-J. *Tetrahedron* **2010**, *66*, 5367–5372. j) Szcześniak, P.; Staszewska-Krajewska, O.; Furman, B.; Młynarsky, J. *ChemistrySelect* **2017**, *2*, 2670–2676.

[176] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III *Org. Lett.* **2004**, *6*, 2527–2530.

Table 11. Reports on the Michael addition of different α,α-disubstituted aldehydes to nitroolefins assisted by aminocatalysis.



Catalyst/author	Conditions	Results (R^1=Alkyl)	Results (R^1=Ph)
 **C17** Jacobsen, **2006**[175a]	**C17** (20 mol %) H_2O (5 equiv.) CH_2Cl_2, 23°C, 24h Aldehyde: nitroalkene 2:1	R^2= Me: 61% *dr*: 77:23 (*syn* A/*anti*) 99/99 % *ee* (*syn* A/*anti*) R^2= Aryl/heteroaryl: 63–98% *dr*: 68:32 – 87:13 (*syn* A /*anti*) 98-99 /92-99 % *ee* (*syn* A /*anti*)	R^2= Alkyl: 34-91% *dr*: 96:4 – >98:2 (*syn* A /*anti*) 97-99 % *ee* (*syn* A) R^2= Ph:[177] 100% *dr*: 54:46 (*syn* A /*anti*) 67/3 % *ee* (*syn* A /anti)
 **C18** Connon, **2007**[175b]	**C18** (10-15 mol %) PhCOOH (10-15 mol %) rt, neat, 2.3 - 4.1 h Aldehyde: nitroalkene 5:1	R^2=Ph: 95 %, *dr*: 67:33 (*syn* A/*anti*), 92 % *ee* (*syn* A)	R^2=Ph: 93 %, *dr*: >95:5 (*syn* A/*anti*), 66 % *ee* (*syn* A)
 Nugent, **2011**[175c]	**O^{t}Bu-L-threonine** (5 mol %) **Sulfamide** (5 mol %) DMAP (15 mol %) toluene, 25°C, 12 -36 h Aldehyde: nitroalkene 2:1	R^2= Aryl/heteroaryl: 70–84 % *dr*: 70/30 – 78/22 (*syn* B/*anti*) 91-99 % *ee* (*syn* B)	
 **C19** Benaglia and Puglisi, **2015**[175d]	**C19** (load 0.7 mmol/g, 30 mol %) PhCOOH (30 mol %) Toluene, rt, 48h Aldehyde: nitroalkene 5:1	R^1=Et; R^2= Ph: 78 %, *dr*: 70:30 (*syn* B/*anti*), 94 % *ee* (*syn* B)	R^2= Ph: 77 %, *dr*: >95:5 (*syn* B/*anti*), 82 % *ee* (*syn* B)
 **C20** Wu, **2016**[175e]	**C20** (20 mol %) CH_2Cl_2, 25°C, 48 -72 h Aldehyde: nitroalkene 4:1	R^2=4-$NO_2C_6H_4$: 81–85 %, *dr*: 66:34–83:17[178] 94-99 (93-97)% *ee*	R^2=4-$NO_2C_6H_4$: 80 %, *dr*: 80:20[178] 34 (50) % *ee*

[a] Structure of *anti* isomers was not determined.

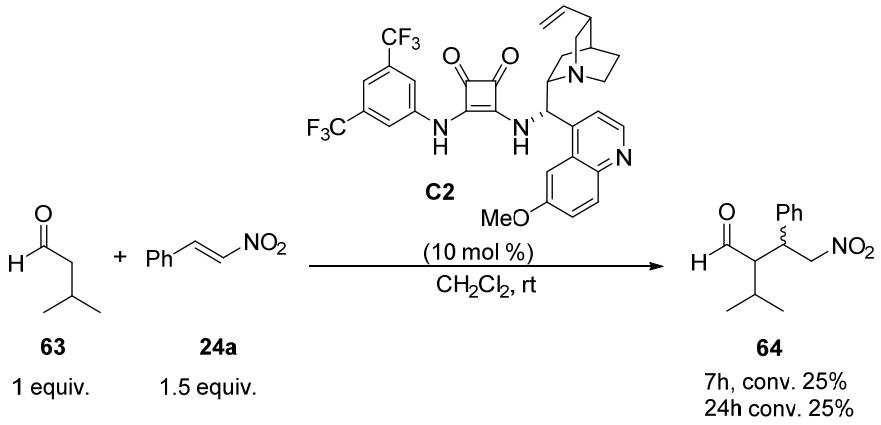
[177] In the Jacobsen's report, for the addition of 2-phenylpropionaldehyde to *trans*-β-nitrostyrene, the best results was obtained in the presence of diphenylethylene diamine derived catalyst: 84 %, 92:8 *dr* (*syn*/*anti*), 97/32 % *ee* (*syn*/*anti*).

[178] Adduct configuration was not determined. The data in parenthesis refer to the minor diastereomer.

4.2 Objective

Inspired by these previous works and in view of the limitations still present for the creation of quaternary stereocenters through the conjugate addition of different α-branched aldehydes to nitroolefins, we envisioned that Brønsted bases incorporating a hydrogen bond donor could address the formation of a particular enolate and provide adducts in high stereoselectivity.

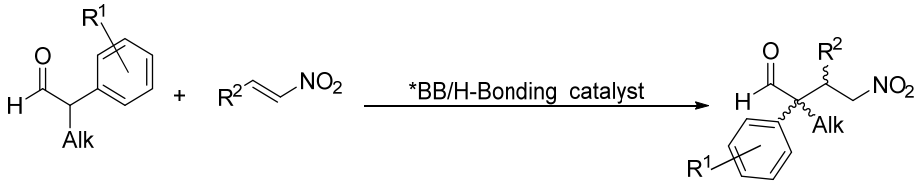
A preliminary study on the conjugate addition of 3-methylbutanal **63** to nitrostyrene **24a** promoted by squaramide-based Brønsted base/H-bonding catalyst **C2** (Scheme 37) was performed to check the reactivity of aliphatic aldehydes with this type of catalysts.



Scheme 37. Preliminary study on the Michael addition of 3-methylbutanal to nitrostyrene assisted by a Brønsted base/H-bonding catalyst.

This reaction did not progress more than 25 %, thus, it confirmed the needed to increase the acidity of the α-carbon in the aldehyde in order to enhance the reactivity of these substrates via Brønsted base/H-bonding catalysis. We envisioned that an aryl substituent could stabilize the formed enolate intermediate due to charge delocalization and therefore, facilitate the development of the reaction towards the desired product.

Therefore, we decided to explore the Michael reaction of α-alkyl α-aryl acetaldehydes with nitroolefins (Scheme 11). Furthermore, these substrates are challenging, since, as previously mentioned, their reactions under aminocatalysis have shown certain difficulty in controlling the diastereo- or/and enantioselectivity.



Scheme 38. Proposed stereoselective Michael additions of α-alkyl α-aryl acetaldehydes to nitroolefins assisted by Brønsted base/H-bonding catalysts.

4.3 Results and discussion

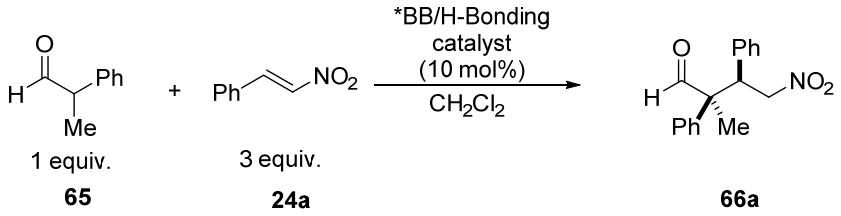
4.3.1 Catalyst screening

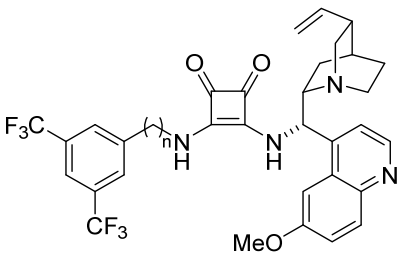
The Michael reaction of the readily available 2-phenylpropanal (**65**) with nitrostyrene (**25a**) was selected to evaluate different Brønsted base/H-bonding catalysts in order to check the validity of our hypothesis. The corresponding results are shown in Table 12. The reaction was first explored with the classical squaramide-cinchona derived catalysts **C2** and **C11** at room temperature and 0 °C. Initially, the Michael addition was performed with 1 equivalent of 2-phenylpropanal (**65**) and 1.5 equivalent of nitrostyrene **24a** in the presence of **C2** at room temperature, but the reaction did not progress more than 77 % conversion, although good diastereoselectivity (89:11 *dr*) and high enantioselectivity (92 % *ee* for the major diastereoisomer and 76 % *ee* for the minor one) were obtained. Then, the ratio of the substrates was changed to 1:3 (2-phenylpropanal:nitrostyrene) in order to bring the transformation to completion. When the reaction was performed at 0 °C in the presence of **C2** similar values of diastereo- and enantioselectivity were observed (89:11 *dr*, 94/82 % *ee*). Therefore, next experiments were all conducted at room temperature and with a 1/3/0.1 molar ratio of phenylpropanal/nitrostyrene/catalyst. Squaramide based catalysts **C11** and **C14**,[179] this latter developed previously in our group and which contains a bulkier group, led to product **66a** with similar stereocontrol outcome. At this point, ureidopeptide like catalysts **C21**–**C24**,[180] previously designed in our group, were also checked, but in all cases, lower enantio- and diastereoselectivity were observed.

[179] Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 12758–12762.

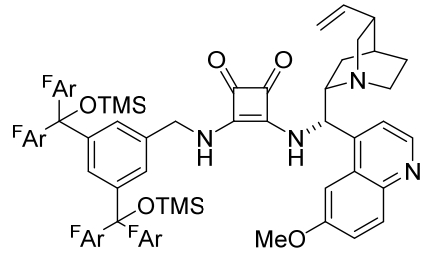
[180] For Michael reaction, see: a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851. For Mannich reaction, see: b) Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526–6531. c) Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 13332–13336. For aldol reaction, see: d) Lapuerta, I.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2016**, *22*, 7229–7237. e) Etxabe, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364–3368.

Table 12. Catalyst screening for the Michael addition of 2-phenylpropanal **65** to nitroalkene **24a**.[a]

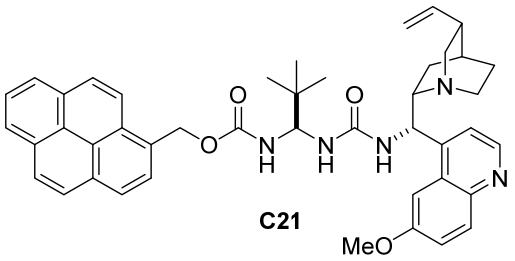




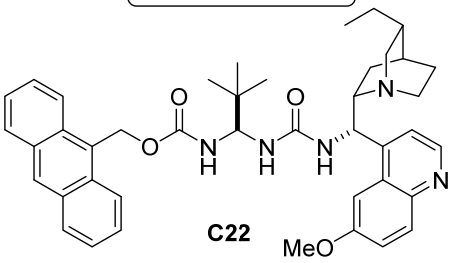
C2 (n=0); rt, 20h, 70 % (77 % conv.), 89:11 *dr*, 92% *ee* (76 % *ee*)[b]
0 ºC, 24h, 78 %, 89:11 *dr*, 94% *ee* (82 % *ee*)
C11 (n=1); rt, 4h, 85 %, 89:11 *dr*, 94% *ee* (94 % *ee*)



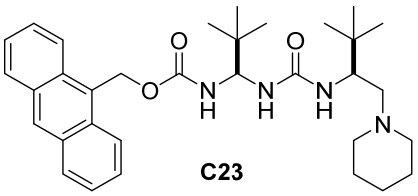
C14
rt, 2.5h, 86%, 88:12 *dr*, 94% *ee* (96% *ee*)
^{F}Ar: 3,5-$(CF_3)_2C_6H_3$



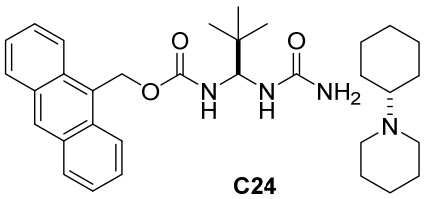
C21
rt, 37h, 80%, 85:15 *dr*, –18% *ee* (54% *ee*)



C22
rt, 14h, 83%, 86:14 *dr*, –2% *ee* (48% *ee*)



C23
rt, 13h, 70%, 81:19 *dr*, 54% *ee* (80% *ee*)

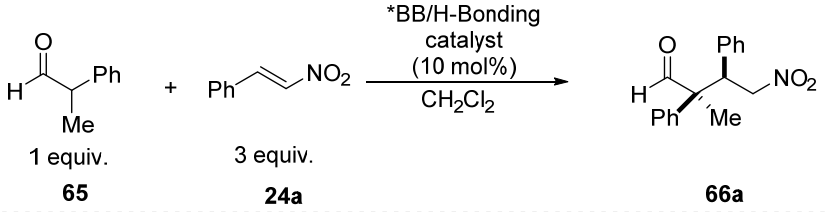


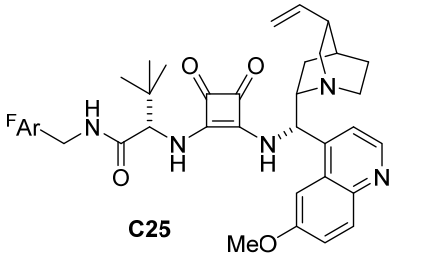
C24
rt, 24h, 45% conv., 72:28 *dr*, 62% *ee* (78% *ee*)

[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; 1:3:0.1 molar ratio of **65**/**24a**/catalyst at room temperature, unless otherwise stated. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis and *ee* in parenthesis refers to the minor diastereomer. [b] Reaction conducted on 1:1.5:0.1 molar ratio of **65**/**24a**/**C2**.

With the aim of improving these results, we decided to synthesize and evaluate a new family of amino acid containing Brønsted base/squaramide catalysts maintaining the same Brønsted base, the cinchona, and bearing the same terminal function (3,5-$(CF_3)_2C_6H_3$–) (Table 13).

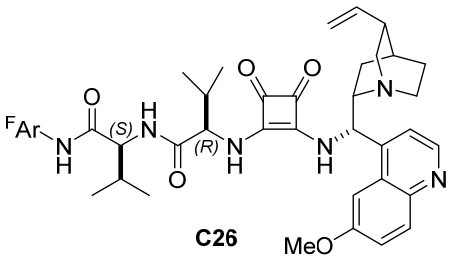
Table 13. Catalyst screening for the Michael addition of 2-phenylpropanal **65** to nitroalkene **24a** promoted by amino acids containin catalysts **C25–C31**.[a]





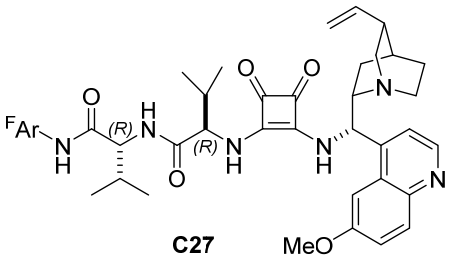
C25

rt, 18h, 88%, 91:9 *dr*, 90% *ee* (90% *ee*)



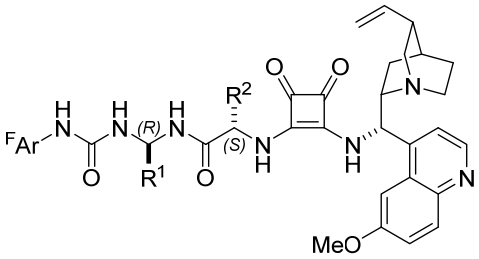
C26

rt, 40h, 79% conv.,
84:16 *dr*, n.d. % *ee* (n.d % *ee*)

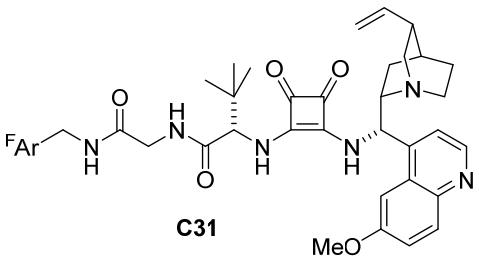


C27

rt, 18h, 18% conv.,
86:14 *dr*, n.d. % *ee* (n.d. % *ee*)



C28, R^1= ^{i}Pr; R^2= ^{i}Pr
rt, 18h, 79%, 90:10 *dr*, 90% *ee* (86% *ee*)
C29, R^1= ^{i}Pr; R^2= ^{t}Bu
rt, 40h, 54% conv., 93:7 *dr*, n.d. % *ee*[b]
C30, R^1= ^{t}Bu; R^2= ^{t}Bu
rt, 15h, 35% conv., nd *dr*, n.d. % *ee*[b]



C31

rt, 40h, 82% conv.,
81:19 *dr*, 88 % *ee* (68 % *ee*)

^{F}Ar: 3,5-$(CF_3)_2$-C_6H_3–

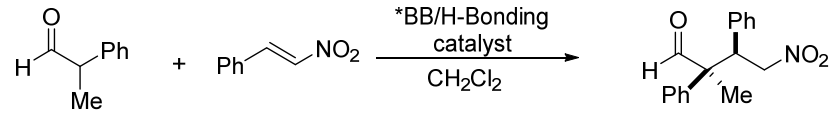
[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; 1:3:0.1 molar ratio of **65**/**24a**/catalyst at room temperature. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis and *ee* in parenthesis refers to the minor diastereomer. [b] The catalyst presented solubility problems.

Catalyst **C25** was first explored under the previously optimized conditions, and led to adduct **66a** with a slight increase in the diastereoselectivity and similar enantioselectivity (91:9 *dr*; 90/90% *ee*) when compared with **C2** and **C11**. At this point, we considered the synthesis of catalysts incorporating an additional amino acid in their structure, then, **C26**, **C27** and **C28** were synthesized and screened with the aim of finding

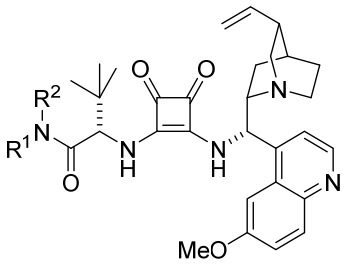
out the matched combination between the amino acids and the Brønsted base. In this context, catalysts **C26** and **C27** provided moderate diastereoselectivity although low reaction conversion was showed. On the contrary, catalyst **C28** afforded similar results to **C25** (90:10 *dr*; 90/86 % *ee*) revealing to be the matched combination. Then, we decided to modify the amino acids as a way to evaluate the influence of a bulky group in these cases. Changing L-valine by L-*tert*-leucine, **C29** and **C30** were synthesized. Unfortunately, both catalyst showed solubility issues and therefore, low reactivity was observed. A less hindered chain incorporating glycine as second amino acid was considered and catalyst **C31** was prepared. Nevertheless, the adduct was obtained in 81:19 *dr* and 88 % *ee* for the major isomer and 68 % *ee* for the minor one without improving the previous results.

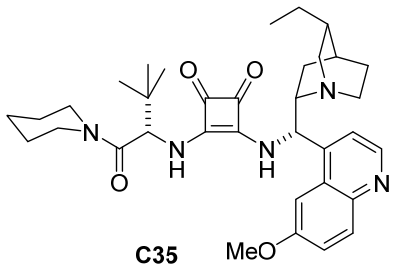
Considering these results, the simplest catalyst **C25**, which contains only one amino acid, demonstrated to be the most effective one. Hence, we tried to improve the stereoselectivity of the reaction through modification of the terminal group at the *tert*-leucine residue in this catalyst. In this line, catalysts **C32**, **C33** and **C34** were prepared and screened in the reaction**.** All three afforded increased enantio- and diastereoselectivity at room temperature (Table 14, entries 1, 3 and 5) and at 0 °C (Table 14, entries 2, 4 and 6). To our delight, **C34** provided practically a single adduct in 91 % yield, 96:4 *dr* and 94 % *ee* for the major isomer. The reduction of the double bond in the cinchona unit (catalyst **C35**) did not enhance the values afforded by its analogue **C34** (Table 14, entry 5 vs. 7). Significantly no products from the self-aldo reactions were detected in none of the catalytic reactions with substrate **65**.

Table 14. Catalyst screening for the Michael addition of 2-phenylpropanal **65** to nitroalkene **24a**.[a]



65 **24a** **66a**





C35

C32 R^1: ^{t}Bu; R^2: H
C33 R^1= R^2: Bn
C34 R^1, R^2: -$(CH_2)_5$-

Entry	Catalyst	T (°C)	t (h)	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**C32**	rt	14	90	95:5	92 (99)
2		0	61	81	95:5	94 (92)
3	**C33**	rt	14	91	93:7	93 (90)
4		0	40	92	94:6	96 (90)
5	**C34**	rt	18	91	96:4	94 (93)
6		0	24	86	92:8	96 (80)
7	**C35**	rt	12	93	92:8	92 (74)

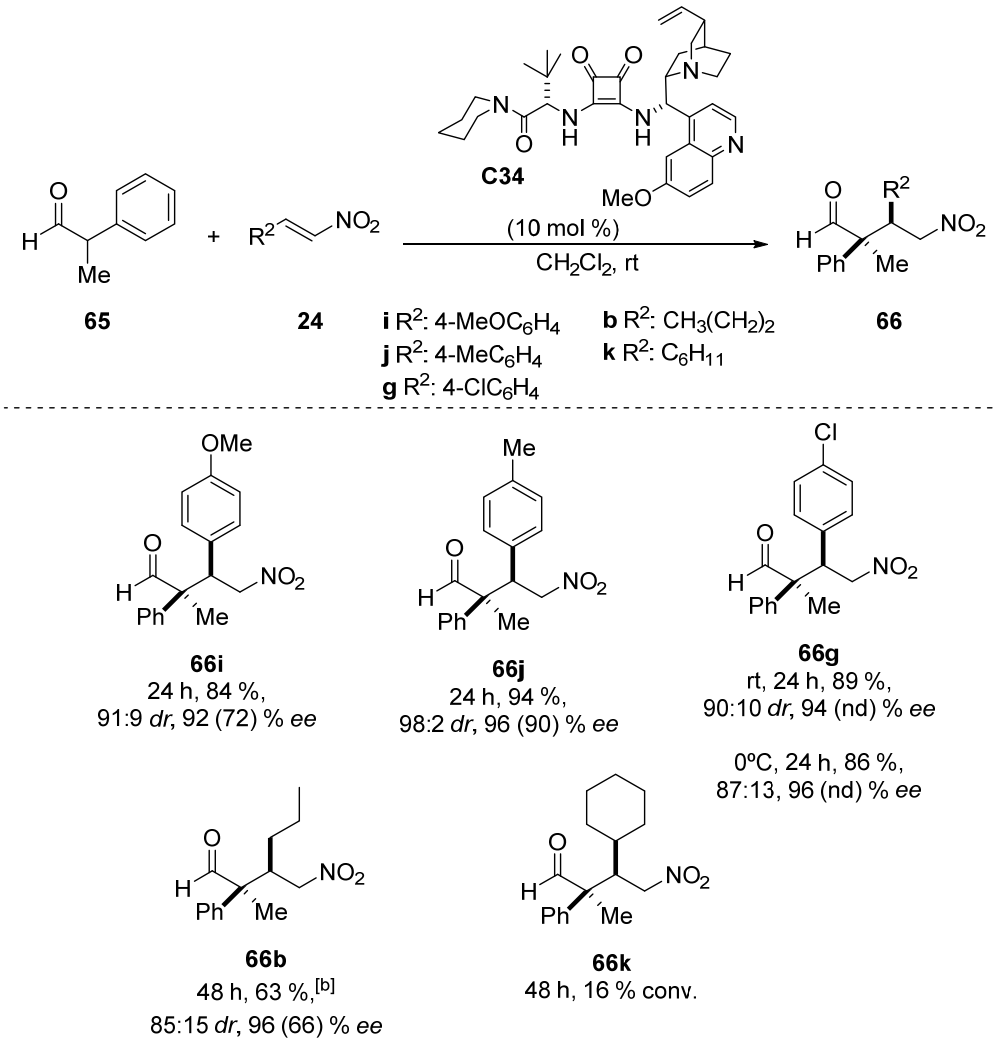
[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; 1:3:0.1 molar ratio of **65**/**24a**/catalyst at room temperature, unless otherwise stated. [b] Yields of products isolated after chromatography. [c] Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. [d] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis, and *ee* in parenthesis refers to the minor diastereomer.

4.3.2 Reaction scope

Taking into account the results of catalyst screening, catalyst **C34** was selected to study the scope of the reaction between 2-phenylpropanal (**65**) and different nitroolefins (**25**) at room temperature in dichloromethane (Table 15). The reaction with nitrostyrenes carrying an electron-donating substituent at the aromatic ring (**24g** and **24i–j**) afforded the corresponding adducts **66** with high enantio- and diastereoselectivity. The reaction also tolerates electron-withdrawing substituents at the aromatic ring of the nitroolefin (**24g**), although a slight fall in the diastereoselectivity was observed in adduct **66g**. Additionally, the troublesome alkyl substituted nitroolefins were used as electrophiles such as the lineal alkyl substituted nitroalkene **24b**, whose reaction afforded adduct **66b** in 63 % yield, due to no total conversion (75 % conversion in 48h), 85:15 *dr* and 96 % *ee*

for the major isomer, while the minor isomer was obtained in 66 % *ee*. In contrast, the conjugate addition of aldehyde **65** to the cyclic alkyl substituted nitroolefin **2k**, regrettably, just attained a 16 % conversion in 48 h.

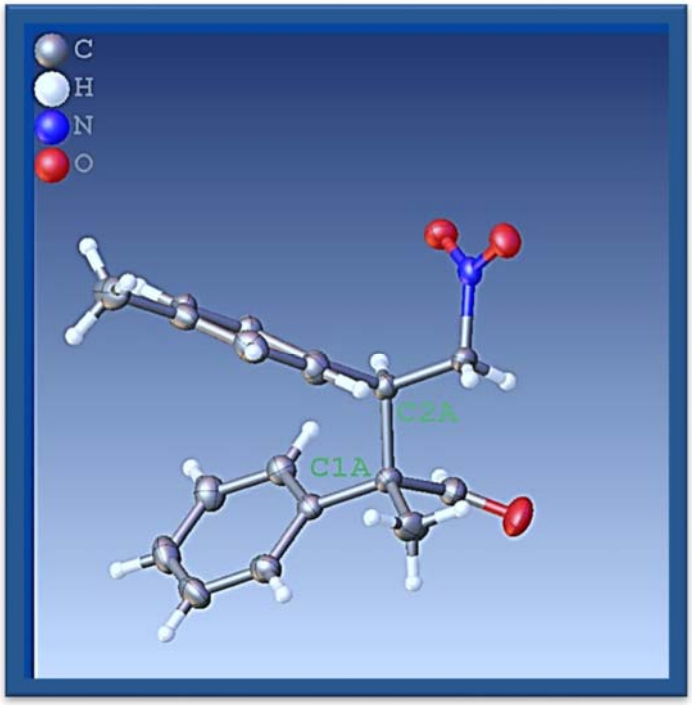
Table 15. Scope of the reaction of α-branched aldehyde **65** with nitroolefin **24** in the presence of catalyst **C34**.[a]

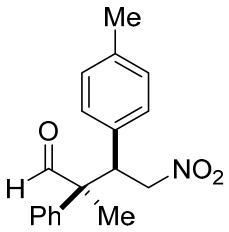


[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; 1:3:0.1 molar ratio of **65**/**24**/**C34** at room temperature. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. Yields of products isolated after chromatography. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis and *ee* in parenthesis refers to the minor diastereomer. [b] Conversion 75 %.

The absolute configuration of the adduct **66i**[181] was established by a single crystal X-ray structure analysis (Figure 30) and that of that other reaction products was assumed by analogy on the basis of a uniform reaction mechanism.

[181] The crystal of **66j** was obtained by PhD student Ane García.





66j

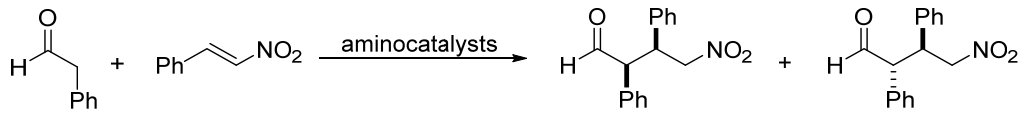
Figure 30. X-Ray crystal structure of the γ-nitroaldehyde **66j**.

4.4 Preliminary studies with phenylacetaldehyde

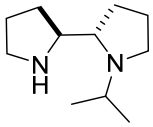
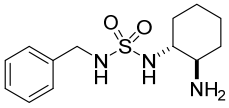
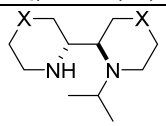
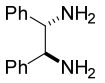
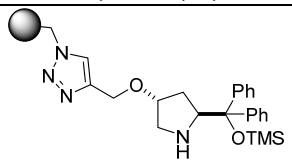
As outlined in the introduction of this chapter 4, there is an extensive number of studies on α-unsubstituted aldehydes as Michael donors for the conjugate addition to nitroolefins assisted by organocatalysis. Nevertheless, a detailed view of these examples discloses that α-unsubstituted phenylacetaldehyde **34** are seldom used as nucleophiles in this transformation (Table 16).[165c,182] The reported results show low enantio- and diastereoselectivity in comparison to the aliphatic counterparts and the best stereocontrol outcome has been described by Yan's group.[182c] Furthermore, the *anti* isomer is obtained only in the Yan[182c] and Comin's[182e] reports, however, in the latter an achiral catalyst was employed and the reaction led to the racemic adduct.

[182] a) Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772–3775. b) Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051–3056. c) Zhang, X.-J.; Liu, S.-P.; Li, X.-M.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833–835. d) Rogozinska-Szymczak, M.; Mlynarski, J. *Eur. J. Org. Chem.* **2015**, 6047–6051. e) Donadío, L. G.; Galetti, M. A.; Giorgi, G.; Rasparini, M.; Comin, M. J. *J. Org. Chem.* **2016**, *81*, 7952–7957.

Table 16. Summary of the reported results on the Michael reaction of α-unsubstituted benzylic aldehydes **34** with nitrostyrene **24a**.



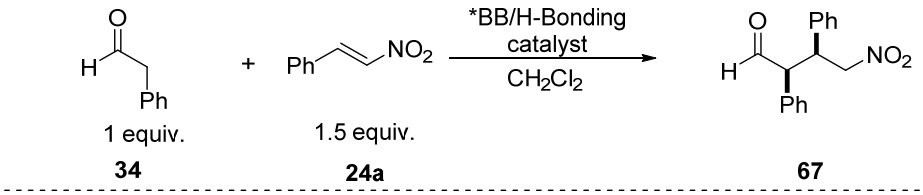
34 **24a** **67** **67'**

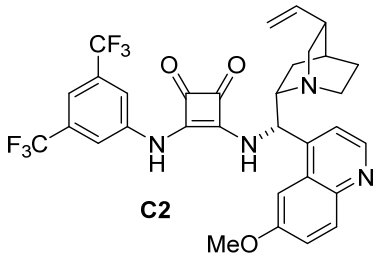
Author	Conditions	Result	Author	Conditions	Result
Alexakis **2004**[165c]	 15 mol % $CHCl_3$, –25 °C, rt, 2d	19 % *dr*: 72:28 (*syn*/*anti*) 26 % *ee syn*	Yan **2009**[182c]	 10 mol % CH_2Cl_2, rt, 21h	90 % *dr*: 20:80 (*syn*/*anti*) 80/82% *ee* (*syn*/*anti*)
Kanger **2009**[182a]	 X: O, $-CH_2-$ 15 mol % $CHCl_3$, –25 °C, rt, 3h	76 % *dr*: 62:38 (*syn*/*anti*) –37 % *ee* (*syn*)	Mlynarski **2015**[182d]	 20 mol % $PhCO_2H$ 40 mol % EtOH/H_2O 1:1, 3d	70 % *dr*: 67:33 (*syn*/*anti*) -50 % *ee* (*syn*)
Pericàs **2009**[182b]	 10 mol % CH_2Cl_2, rt, 2d	<5 % conv.	Comin **2016**[182e]	 20 mol % toluene, 2d	>99 % conv. *dr*: 4:96 (*syn*/*anti*)

Therefore, with the intention of exploring the activation induced by Brønsted base/H-bonding catalysts in this specific reaction some catalysts were tested in the reaction of phenylacetaldehyde **34** and nitrostyrene **24a** (Table 17).[183] The classical squaramide-cinchona catalyst **C2** provided adduct **67** with moderate diastereoselectivity (88:12 *dr*) and high enantioselectivity (99 % *ee* for the major isomer and 91 % *ee* for the minor isomer). Catalysts **C23** and **C36**, of the ureidopeptide type family developed by the group, did not improve the results. Likewise, the most effective catalyst for the reaction of 2-phenylpropanal (**C34**) neither improved the stereoselectivity of this transformation. In addition, it is noteworthy to mention that **C23** led mainly to the *anti*-adduct of the reaction while the other catalysts tested address the *syn*-product as major isomer.

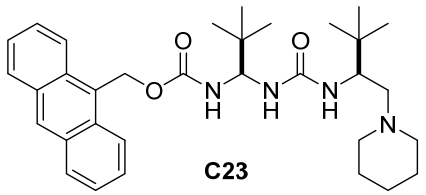
[183] In Chapter 2 it was showed that, in our previous control experiments, the reaction of benzaldehyde **34** and *trans*-4-bromo-β-nitrostyrene **24f** in the presence of Brønsted base/thiourea catalyst **C5** was not stereoselective (95 %, 59:41 *dr*, 60/40 % *ee*), page 64.

Table 17. Catalyst screening for the Michael addition of 2-phenylacetaldehyde **67** to nitrostyrene **24a**.[a]

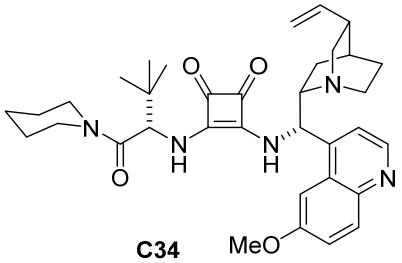




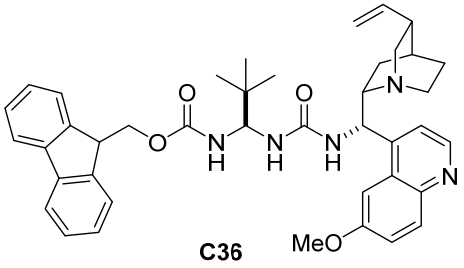
rt, 1h, 87%, 88:12 *dr*, 99% *ee* (91% *ee*)



rt, 1h, 90%, 40:60 *dr*,[b] 74% *ee* (72% *ee*)



rt, 1.5h, 86%, 62:38 *dr*, 94% *ee* (88% *ee*)



rt, 1h, 88%, 60:40 dr, 18% ee (18% ee)

[a] Reactions conducted on a 0.2 mmol scale in CH_2Cl_2 (0.6 mL; 1:1.5:0.1 molar ratio of **34**/**24a**/catalyst at room temperature. Yields of products isolated after chromatography. Diastereomeric ratio (*dr*) was determined by ^{1}H-NMR spectroscopy (300 MHz) analysis of the crude sample. The enantiomeric excess (*ee*) was determined by chiral HPLC analysis and *ee* in parenthesis refers to the minor diastereomer. [b] Opposite isomer.

As conclusion, we have shown that Brønsted base/H-bonding catalysts can promote highly enantioselective Michael reactions of α-substituted arylacetaldehydes to nitroolefins. After an exhaustive catalyst screening, a new family of amino acid derived squaramide-based bifunctional catalysts has been developed. Among all the explored catalysts in the conjugate addition of 2-phenylpropanal to nitroolefins, the best results have been provided by catalyst **C34**. Thus, the resulting γ-nitroaldheydes containing a quaternary stereocenter and derived from nitrostyrenes bearing electro-donating as well as electro-withdrawing substituents at the aromatic ring, have been obtained in good yields (63–94%) and with excellent enantioselectivities (92–96% *ee*) and high *syn* diastereoselectivities (90:10–98:2 *dr*). Therefore, comparable diastereocontrol and higher enantiocontrol has been achieved by these squaric-amino acid catalysts when compared with the previous protocols described *via* enamine activation for this transformation. In

addition, the reaction also tolerates alkyl nitroolefins, but in these cases, the diastereoselectivity is slightly lower than for the aromatic derivatives. Furthermore, a preliminary evaluation of Brønsted base/H-bonding catalysts in the Michael reaction with the problematic α-unsubstituted arylacetaldehydes showed that the adducts can be obtained in very good enantioselectivity, but moderate diastereoselectivity (88:12 *dr*, 98/90 % *ee* and 62:38 *dr*, 94/88 % *ee* for **C2** and **C34** respectively). Notwithstanding, these results enhance the up to now obtained ones, therefore, further work on this project is underway in our lab.

From these data, further new applications of this catalyst family can be predicted. In fact, during the preparation of this manuscript catalyst **C25** and **C34**–**C35** derivatives have also been published for enantioselective cycloaddition reactions with enolizable anhydrides[184] and three-component reactions between γ-aryl-substituted α,β-unsaturated aldehydes and nitroalkenes.[185]

[184] Farid, U.; Aiello, M. L.; Connon, S. J. *Chem. Eur. J.* **2019**, *25*, 10074–10079.
[185] Majee, D.; Jakkampudi, S.; Arman, H. D.; Zhao, J. C.-G. *Org. Lett*. **2019**, *21*, 9166–9170.

CHAPTER 5.

Synthesis of 1-substituted 5-aminotetrazoles

Synthesis of 1-substituted-5-aminotetrazoles

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5. Synthesis of 1-substituted-5-aminotetrazoles

This part of the work was carried out in the group of Prof. Robert Batey in the Lash Miller Chemical Labs at the University of Toronto (UofT) (Toronto, Canada) during a four months internship. In this project, the synthesis of 1-substituted 5-amino tetrazoles by electrocyclization of a guanyl azide intermediate was explored.

5.1 Introduction

Heterocycles are valuable compounds in organic chemistry and synthetic biology. The ability to synthesize them in a high-throughput manner offers many advantages; consequently, new synthetic methods are being developed to find ways of responding to the demands of creating highly diverse compound libraries. Tetrazoles are synthetic compounds with the highest nitrogen content among the stable heterocycles. They are unknown in nature; however, it is possible that tetrazoles alongside the other abnormal polynitrogen heterocycles may form under conditions of the other planets of Solar System or their satellites containing in the composition of the atmosphere or on the surface hydrocarbons and nitrogen.[186] Since their discovery in 1885,[187] tetrazoles have been extensively studied and a variety of applications in organic chemistry, such as important intermediates in the synthesis of other more complex heterocycles through various rearrangements;[188] coordination chemistry;[189] and in applications in the photographic industry,[190] agriculture[191] or as components of special explosives[192] have been reported. However, the most important use of tetrazoles is found in biological and medicinal chemistry.[193]

[186] Butler, R. N. *Comprehensive Heterocyclic Chem. II*, Katrinsky, A. R.; Rees, C. W.; Scriven, E. F. V. Pergamon Press: New York, **1996**, *4*, 621–628.
[187] Bladin, J. A. *Ber. Dtsch. Chem. Ges.* **1885,** *18,* 1544–1551.
[188] a) Moderhack, D. *J. Prakt. Chem.* **1998**, *340*, 687–709. b) Nikulin, V. V.; Artamonova, T. V.; Koldoboskii, G. I. *Russ. J. Org. Chem.* **2003**, *39*, 1525–1529. c) Novakova, V.; Roh, J.; Gela, P.; Kunes, J.; Zimcik, P. *Chem. Commun.* **2012**, *48*, 4326–4328.
[189] a) Gaponik, P. N.; Voitekhovich, S. V.; Ivashkevich, O. A. *Russ. Chem. Rev*. **2006**, *75*, 507–539. b) Popova, E. A.; Trifonov, R. E.; Ostrovskii, V. A. *ARKIVOC* **2011**, 552–572.
[190] a) Ebihara, K.; Hidaka, S. *Jpn. Kokai Tokkyo Koho* **1999**, JP 11084568 A 19990326. b) Burns, P. A.; Friedrich, L. E.; Singer, S. P. *Eur. Pat. Appl.* **2001**, EP 1072950 A1 20010131.
[191] Backor, M.; Fashelt, D. *Environ. Exper. Botany*, **2005**, *53*, 125–133.
[192] a) Miyata, Y.; Date, S.; Hasue, K. *Propellants, Explos., Pyrotech*. **2004**, *29*, 247–252. b) Klapötke, T. M.; Mayer, P.; Schulz, A.; Weigand, J. J. *J. Am. Chem. Soc*. **2005**, *127*, 2032–2033. c) Hasue, K.; Yoshitake, K.; Matsukawa, M. *Cent. Eur. J. Chem*. **2016**, *13*, 247–260.
[193] a) Mohite, P. B.; Bhaskar, V. H. *Int. J. PharmaTech Res.*, **2011**, *3*, 1557–1566. b) Maruthamuthu, Rajam, S.; Ruby, P. C.; Dileepan, A. G. B.; Ranjith, R. *J. Chem. Pharm. Res*., **2016**, *8*, 505–526. c) Arulmozhi, R.;

The wide application of tetrazoles in academic research and industry has become possible due to the development of new synthetic protocols and the considerable improvement of known methods for the preparation of functionally substituted tetrazoles. Based on the number of the substituents, tetrazole rings are divided into four categories: (i) parent tetrazole (the simplest tetrazole), (ii) monosubstituted tetrazoles (1-, 2-, or 5-substituted), (iii) disubstituted tetrazoles (1,5-, or 2,5-disubstituted) and (iv) trisubstituted tetrazolium salts (Figure 31).

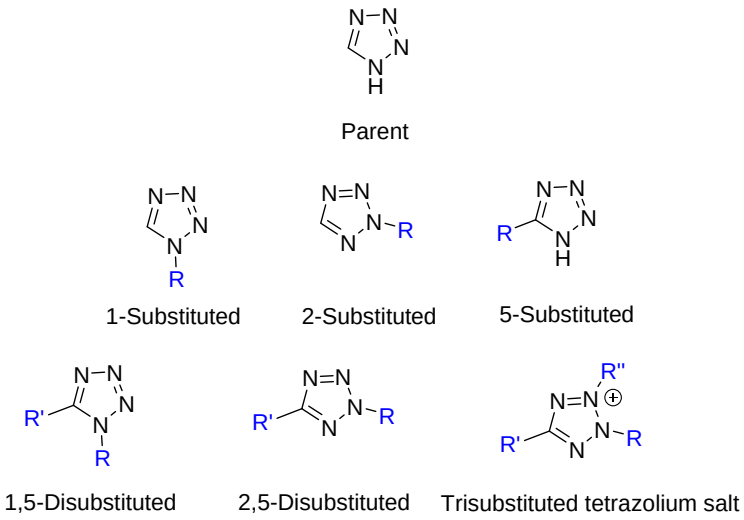


Figure 31. Tetrazole classification.

5-Substituted tetrazoles (5-STs) (Figure 32, **68**) are the non-classical bioisosteres of carboxylic acids[194] and 1,5-disusbstituted tetrazoles (1,5-DTs) (Figure 32, **69**) are bioisosteres of the *cis*-amide bond of peptides.[195] Bioisosterism refers to the concept in which functional groups that have similar physicochemical properties may be interchangeable, resulting in similar biological properties and represents one approach used by medicinal chemists for the rational modification of lead compounds into safer and more clinically effective agents. In the specific case of 5-STs, their free N-H bond makes them acidic molecules, since the negative charge is stabilized by electron delocalization, affording pK_a values similar to corresponding carboxylic acids (4.5–4.9 vs 4.2–4.4, respectively), known as tetrazolic acids. In polypeptides and proteins, the CO–NH group when *N* is substituted adopts a *cis* conformation that requires higher energy than *trans* conformation. 1,5-DTs can be effective *cis* conformational mimics for this corresponding

Abirami, N.; Kavitha, P. H. *Int. J. Pharma. Sci. Rev. Res*. **2017**, *46*, 110–114. d) Popova, E. A.; Protas, A. V.; Trifonov, R. E. *Anticancer Agents Med. Chem*. **2017**, *17*, 1856–1868.

[194] Herr, R. J. *Bioorg. Med. Chem*., **2002**, *10*, 3379–3393.

[195] Zabrocki, J.; Smith, G. D.; Dunbar, J. B.; Iijima, J. H.; Marshall, G. R. *J. Am. Chem. Soc.*, **1988**, *110*, 5875–5880.

peptides. In this way, these kind of tetrazoles (5-STs and 1,5-DTs) have shown comparable acidity, metabolic stability and biopermeability, and equal or greater drug potency, than their non-tetrazole-containing analogs.[196] Therefore, these compounds have become the most interesting ones among all the tetrazole types.

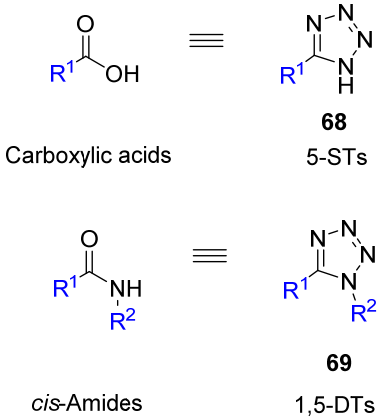


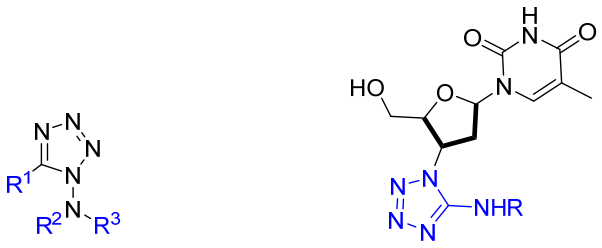
Figure 32. 5-Substituted (5-STs) and 1,5-disubsituted (1,5-DTs) tetrazoles as carboxylic acid and *cis*-amide surrogates.

5.2 1-Substituted-5 aminotetrazoles

Among 1,5-DTs **69**, 5-aminotetrazole derivatives **70** (Figure 33) have been of great interest due to a wide range of applications as high energy density materials (HEDM),[197] useful ligands in coordination chemistry,[198] precursors of compounds with biological activity[199] and as pharmaceuticals with anti-allergic[200] or antiviral and anti-inflammatory[201] properties. For example, 3'-(5-amino-1,2,3,4-tetrazol-1-yl)-3'-

[196] a) Pantani, G. A.; LaVoie, E. J. *Chem Rev*., **1996**, *96*, 3147–3176. b) Fujita, T. *Biosci. Biotech. Biochem*., **1996**, *60*, 557–566.
[197] a) Steinhauser, G.; Klapötke, T.M. *Angew. Chem., Int. Ed*., **2008**, *47*, 3330–3347. b) Singh, R. P.; Verma, R. D.; Meshri, D. T.; Shreeve, J. M. *Angew. Chem., Int. Ed*., **2006**, *45*, 3584–3601.
[198] a) Tappan, B. C.; Huynh, M. H.; Hiskey, M. A.; Chavez, D. E; Luther, E. P.; Mang, J. T.; Son, S. F. *J. Am. Chem. Soc.*, **2006**, *128*, 6589–6594. b) Friedrich, M.; Galvez-Ruiz, J. C.; Klapöte, T. M.; Mayer, P.; Weber, B. J. Weigand, *Inorg. Chem.*, **2005**, *44*, 8044–8052.
[199] a) Vieira, E.; Huwyler, J.; Jolidon, S.; Knoflach, F.; Mutelb, V.; Wichmann, J. *Bioorg. Med. Chem. Lett*., **2005**, *15*, 4628–4631. b) Yamazaki, K.; Hasegawa, H.; Umekawa, K.; Ueki, Y.; Ohashi, N.; Kanaoka, M. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 1275–1278. c) Purchase, C. F.;White, A. D.; Anderson, M. K.; Bocan, T. M. A.; Bousley, R. F.; Hamelehle, K. L.; Homan, R.; Krause, B. R.; Lee, P.; Muller, S. B.; Speyer, C.; Stanfield, R. L.; Reindel, J. F. *Bioorg. Med. Chem. Lett*., **1996**, *6*, 1753–1758.
[200] a) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem*., **1986**, *29*, 538–549. b) Peet, N. P.; Baugh, L. E.; Sundler, S.; Lewis, J. E.; Matthews, E. H; Olberding, E. L.; Shah, D. N. *J. Med. Chem.*, **1986**, *29*, 2403–2409.
[201] Castro, J. L.; Ball, R. G.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Baker, R.; Chapman, K. L.; Fletcher, A. E.; Smith, S. J.; Marshall, G. R.; Ryecroft, W.; Matassa, V. G. *J. Med. Chem*., **1996**, *39*, 842–849.

deoxythimidines and its derivatives were developed as anti-HIV drugs by Bayer (Figure 33, **72**).[202]



70
5-Aminotetrazoles

71
Anti-HIV drug

Figure 33. Structure of 5-aminotetrazoles and related compounds.

In the year 2000, reported syntheses for substituted 5-aminotetrazole derivatives fell into four main types (Scheme 39): (1) amino group or ring functionalization of 5-aminotetrazole, although, the competitive formation of 1- and 2-alkylated-5-aminotetrazoles is almost impossible, since the selective alkylation of aminotetrazoles usually results in mixtures of isomers;[203] (2) the substitution of a leaving group (LG) in the tetrazole 5-position with amines;[204] (3) reactions of aminoguanidine derivatives through the diazotization method;[205] and (4) azide mediated ring construction.

In this last category (4) two strategies had been reported:[206,207] (4.1) addition of azide anion to carbodiimides[202a,208] or cyanamides[209] and (4.2) nucleophilic substitution

[202] a) Habrich, D. *Synthesis*, **1992**, *4*, 358–360. b) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd*., **2007**, *43*, 1–7.

[203] a) Percival, D. F.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 925–933. b) Finnengan, W. G; Henry, R. A. *J. Org. Chem.* **1959**, *24*, 1565–1567. c) Peet, N. P. *J. Heterocycl. Chem.* **1987**, *24*, 223. d) White A. D.; Creswell M. W.; Chucholowski A. W.; Blankley C. J.; Wilson M. W.; Bousley R. F.; Essenburg A. D.; Hamelehle K. L.; Krause B. R.; Stanfield R. L.; Kominick M. A.; Neub M. *J. Med. Chem*. **1996**, *39*, 4382–4395.

[204] a) Barlin, G. B. *J. Chem. Soc. B* **1967**, 641–647. c) Klich, M.; Teutsch, G. *Tetrahedron* **1986**, *42*, 2677–2684.

[205] a) Kurzer, F.; Godfrey, L. E. A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 459–476. b) Jensen, K. A.; Holm, A.; Rachlin, S. *Acta Chem. Scand.* **1966**, *20*, 2795. c) Atherton, F. R.; Lambert, R. W. *Tetrahedron* **1983**, *39*, 2599–2608. d) Karaghiosoff, K.; Klapötke, T. M.; Mayer, P.; Piotrowski, H.; Polborn, K.; Willer, R. L.; Weigand, J. J. *J. Org. Chem.* **2006**, *71*, 1295–1305.

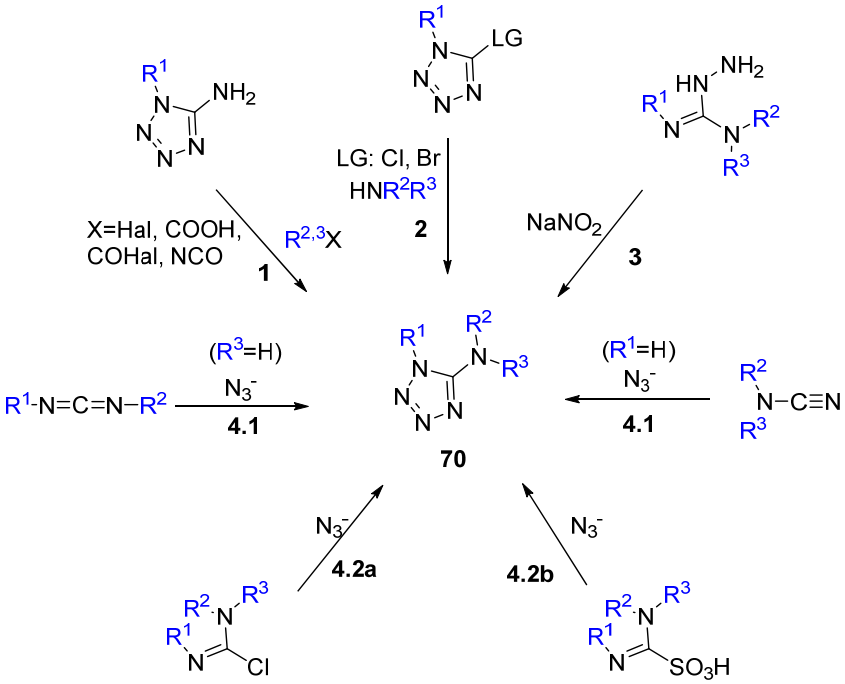
[206] For a more recent methodology from a primary amine and cyanogen bromide, which forms cyanogen azide, see: a) Joo, Y-H.; Twamley, B.; Garg, S.; Shreeve, J. M. *Angew. Chem. Int. Ed*. **2008**, *47*, 6236–6239. b) Joo, Y-H.; Shreeve, J. M. *Org. Lett*. **2008**, *10*, 4665–4667. c) Nag, S.; Bhowmik, S.; Gauniyal, H. M; Batra, S. *Eur. J. Org. Chem.* **2010**, 4705–4712.

[207] For a more recent protocol using selenoureas in the presence of diacetoxybenzene (DIB), see: Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *J. Org. Chem.* **2012**, *77*, 3716–3723.

[208] a) Yamamoto, I. *J. Chem. Soc. Perkin Trans. 1*, **1977**, 1241–1243. b) Tsuge. O; Urano, S; Oe, K. *J. Org. Chem.* **1980**, *45*, 5130–5136. c) Zbiral, E.; Schorkhuber, W. *Liebigs Ann. Chem.* **1982**, 1970. d) Ding, Y.-X.; Weber, W. P. *Synthesis* **1987**, 823–824.

[209] a) Herbst, R. M.; Roberts, C. W.; Harvill, E. *J. Org. Chem.* **1951**, *16*, 139–149. b) Satzinger, G. *Liebigs Ann. Chem.* **1960**, *638*, 159–173. c) Vorobiov, A. N.; Gaponik, P. N.; Petrova, P. T.; Ivashkevich, O. A. *Synthesis*, **2006**, 1307–1312. d) Modarresi Alam, A. R.; Nasrollahzadeh, M. *Turk. J. Chem*. **2009**, *33*, 267–280. e)

by N_3^- of (a) chlorine in α-chlorofomamidines[210] or (b) sulfite anion in aminoiminomethanesulfonic acids.[211,212]



Scheme 39. Strategies for the synthesis of 5-aminotetrazole rings in 2000.

However, at that time, all these approaches showed in general narrow scope and some limitations. For instance, as it will be outlined later, there were almost no protocols for the direct synthesis of trisubstituted derivatives (Scheme 39, **70**; R^1, R^2, $R^3 \neq H$); the only option being the functionalization of the disubstituted ones, which, as previously mentioned, presented some competitive reactions. In addition, most of the azide-mediated procedures required hydrazoic acid or a Brønsted acid (with the concomitant production of hydrazoic acid), which is toxic and extremely explosive in inorganic solution.

5.3 Group precedents and objectives

In this context, in 2000 the group of Prof. Robert Batey initiated a new project focused on the construction of 1-substituted 5-aminotetrazoles starting from thioureas. This project was a part of an interest in "diversity amplifying" (DA) reactions and

Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. *Tetrahedron* **2009**, *65*, 10715. f) Habibi, D.; Nasrollahzadeh, M.; Faragi, A. R.; Bayat, Y. *Tetrahedron*, **2010**, *66*, 3866.

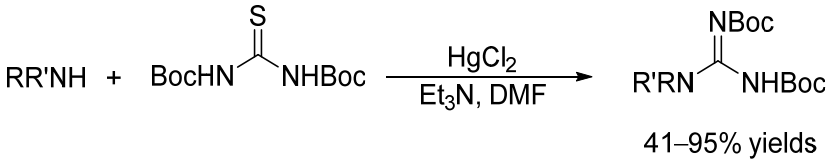
[210] Ried, W.; Erle, H. E. *Liebigs Ann. Chem*. **1982**, 201.

[211] Miller, A. E.; Feenay, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *Synth. Commun*. **1990**, *20*, 217–226.

[212] For a later protocol working through the nucleophilic substitution by N_3^- on benzotriazolyl in carboximidamides, see: Katritzky, A. R.; Rogovoy, B. V.; Kovalenko, K. V. *J. Org. Chem*. **2003**, *68*, 4941–4943.

combinatorial chemistry for the incorporation of 5-aminotetrazoles (Figure 33, **70**) into peptidomimetics. For this goal, the use of thioureas[213,214] as starting materials was appealing because diversity could be easily generated from the coupling of different amines with isothiocyanates, to produce different 5-aminotetrazoles depending on the substitution of the starting thiourea (mono-, di- and tribustituted thiourea).

Some years before, Kim and coworkers had described the mercury(II)-promoted guanylation of di-Boc-protected thioureas with primary or secondary amines (Scheme 40),[215] whose scope and limitations were explored later by Ko's group.[216]



Scheme 40. Reaction between bis-Boc-protected thiourea and amines promoted by $HgCl_2$.

Inspired by this reaction, Batey's group developed the mercury(II)-promoted synthesis of 1-substituted 5-aminotetrazoles **70** from mono-, di- and trisubstituted thioureas in the presence of azide (Scheme 41).[217] The reaction is proposed to occur by sodium azide transformation of the mercury(II)-activated thiourea **74** to generate intermediate guanylazide **75**, which upon electrocyclization would lead to 5-aminotetrazole **70**. In fact, the formation of intermediate **75** had already been observed by the groups of Kim[215] and Ko.[216] One important aspect of this reaction is the control of the regioselectivity during the electrocyclization, which depends on the substituents of the thiourea.[218] As the results in Scheme 41 show in almost all the cases one regioisomer was obtained.

[213] For one example employing di-*p*-tolylthiourea, PbO and sodium azide for the synthesis of the corresponding 5-aminotetrazole, see: Benson, F. R. *Chem. Rev*. **1947**, *41*, 1–61.

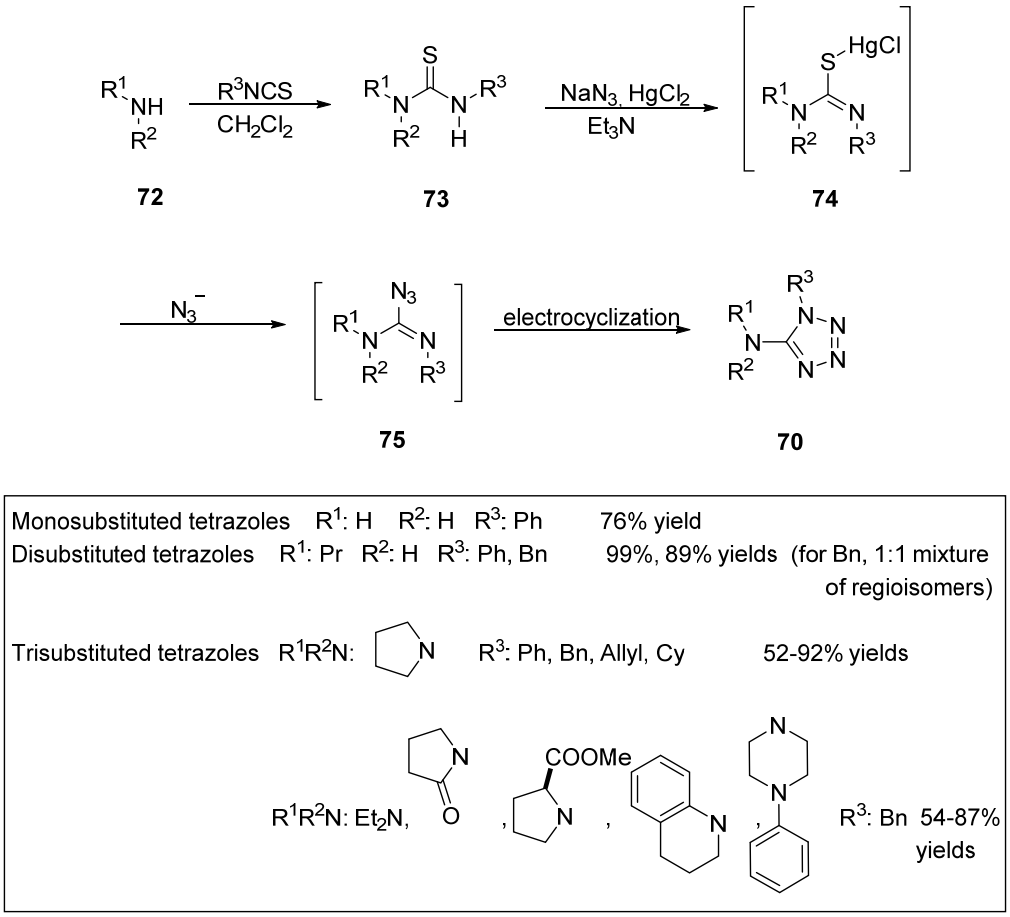
[214] For later new methodologies of synthesis of 5-aminotetrazoles using thioureas, see: a) Yella, R.; Khatun, N.; Rout, S. k.; Patel, B. K. *Org. Biomol. Chem.* **2011**, *9*, 3235–3245. b) Guin, S.; Rourt, S.K.; Gogoi, A.; Nandi, S.; Ghara, K. K.; Patel, B.K. *Adv. Synth. Catal*. **2012**, *354*, 2757–2770. c) Jadhav, N. C.; Jagadhane, P. B.; Patel, K. N.; Telvekar, V. N. *Tetrahedron Lett.* **2013**, *54*, 101–105. For only one example from 4-[2-(acetoxy)-ethyl]-2-methylthiosemicarbazide, see: d) Banert, K.; Klapötke, T. M.; Sproll, S. M. *Eur. J. Org. Chem*. **2009**, 275–281. For a similar version on solid phase using non peptidic thioureas and $HgCl_2$, see: e) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett*. **2004**, *45*, 7787–7789.

[215] Kim, K. S.; Qian, L. *Tetrahedron Lett*. **1993**, *34*, 7677–7680.

[216] Levallet, C.; Lerpiniere, J.; Ko, Y. S. *Tetrahedron* **1997**, *53*, 5291–5304.

[217] Batey, R. A.; Powell, D. A. *Org. Lett*. **2000**, *2*, 3237–3240.

[218] Svetlik, J.; Hrusovsky, I.; Martvon, A. *Collection Czechoslov. Chem. Commun.* **1979**, *44*, 2982–2986.

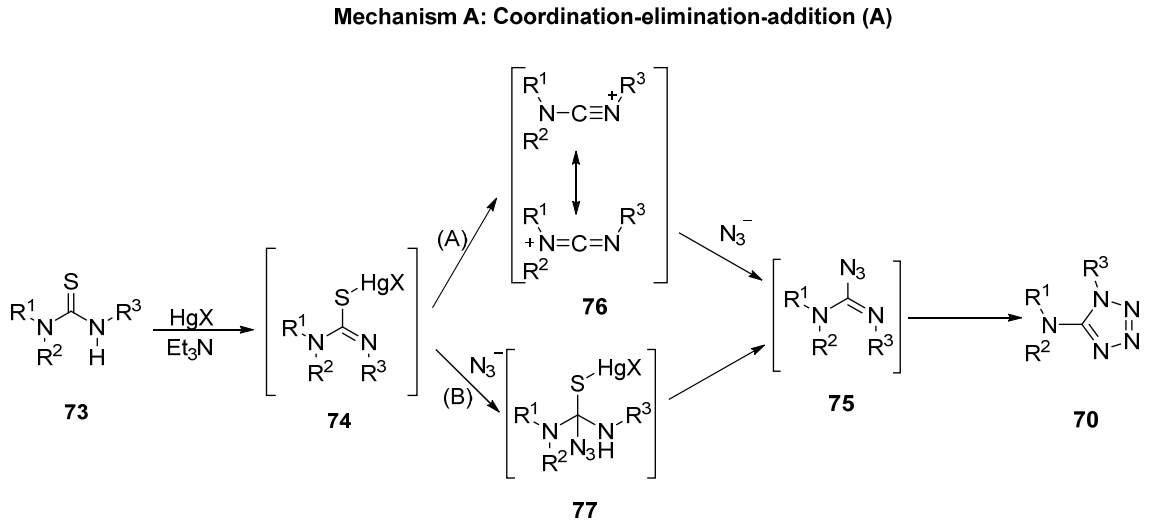


Scheme 41. Reaction leading to 5-aminotetrazoles via mercury(II)-activated thioureas. **Batey, 2000**.

For the transformation of **74** into **75** two mechanisms are proposed depending on the substitution on the starting thiourea. For *N*,*N*'-disubstituted thioureas, a coordination-elimination-addition mechanism has been assumed, in which the formation of the carbodiimide intermediate **76** after an elimination step in mercury(II)-activated thiourea **74** is proposed taking into account that the mercury-promoted dehydration of thioureas leading to carbodiimides is well-known.[219] Subsequently, carbodiimide intermediate **76** would be attacked by sodium azide to generate intermediate guanyl azide **75**, which upon electrocyclization would lead to 5-aminotetrazole **70** (Scheme 42, mechanism A). Nevertheless, the mechanism of 5-aminotetrazole formation from trisubstituted thioureas is not clear. Working on the assumption that carbodiimidium intermediate is formed, as a strong electrophile, it should react with weak nucleophiles too.[220] However, experiments carried out with trisubstituted thioureas by Ko[216] and Batey's group[221] replacing sodium azide by amines did not provide the expected final compounds. Hence,

[219] Williams, A.; Ibrahim, I. T. *Chem. Rev*. **1981**, *81*, 589–636.
[220] Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233–284.
[221] Batey et al. tried the reaction between thiourea **73** (R^1=R^2=H, R^3=Ph) and benzylamine in the presence of $HgCl_2$, which did not give the expected product, even after heating at 60 °C for 24 h.

with these results, the formation of carbodiimide ion intermediate **76** when trisubstituted thioureas are employed can be precluded. In this case, the reaction could occur via a coordination-addition-elimination pathway (Scheme 42, mechanism B), where after Hg(II) coordination to generate **74**, the azide anion would attack to give intermediate **77**, and subsequent elimination and electrocyclic rearrangement.[222]



Scheme 42. Proposed mechanisms leading to 5-aminotetrazoles.

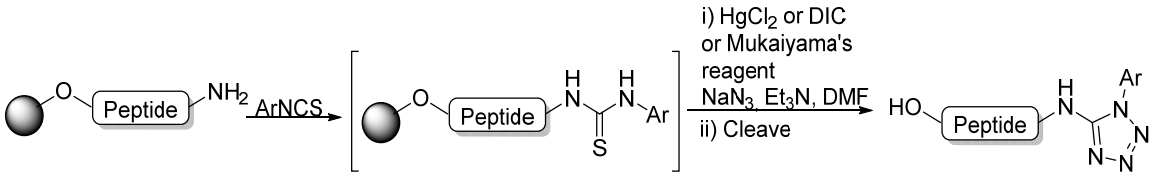
This approach for the synthesis of tetrazoles is interesting because on the one hand, and as mentioned before, to date only one protocol for the direct construction of trisubstituted 5-aminotetrazoles has been reported,[205c] which requires a three-steps procedure involving diazotization under relatively harsh conditions. On the other hand, Batey's method avoids the use of hydrazoic acid, and it answers the need of reactions under mild/soft conditions. In addition, it provides scaffolds for combinatorial chemistry thanks to the commercially availability of the starting materials, instead of, for example, the use of nitriles as starting substrates, which can only react as the dipolarophilic partners with organic azides when they bear strong electron-withdrawing groups.

Additionally, in 2007, Batey's group extended this methodology to solid-phase and reported the synthesis of disubstituted *N*-terminal-5-aminotetrazole peptide hybrid molecules (Scheme 43)[223, 224]

[222] For a similar mechanism proposed for thioamides and mercury carboxylates, see: Avalos, M.; Babiano, R.; Cintas, P.; Duran, C. J.; Higes, F. J.; Jimenez, J. L.; Lopez, I.; Palacios, J. C. *Tetrahedron* **1997**, *53*, 14463–14480.

[223] Gavrilyuk, J. I.; Evindar, G.; Chen, J. Y.; Batey, R. A. *J. Comb. Chem.* **2007**, *9*, 644–651.

[224] For a similar version on solid phase but using non peptidic thioureas in the presence of $HgCl_2$, see: ref. 214e, page 120.



Scheme 43. Formation of peptidic *N*-terminal 5-aminotetrazoles. **Batey, 2007**.

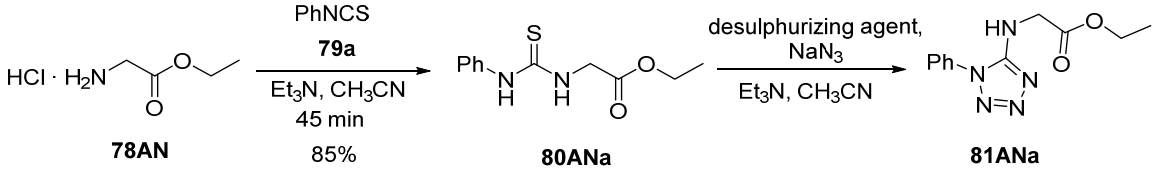
In this context, the research work of this internship was focused on the search of dehydrothiolation agents to avoid the use of toxic mercury salts; as well as on extending the reaction scope to other thioureas to obtain 5-aminotetrazoles with different substitution patterns. The corresponding results are summarized below.

5.4 Results and discussion

5.4.1 Screening of oxidizing agents

Previous results by Batey's group have shown that under the same conditions other mercury(II) salts, for instance, $HgBr_2$, HgI_2 and $Hg(OAc_2)_2$ also promote the reaction with trisubstituted thioureas. Nevertheless, in the presence of red HgO, Zn(II), Cu(I),[225] Cu(II) salts or in the absence of Hg(II) salts the reaction did not provide the expected aminotetrazole compound. In light of these results, a limitation of this synthetic method is the use of toxic mercury salts. Therefore, as a first goal the screening of other oxidants was considered.

Regarding the interest generated by the use of tetrazoles in the synthesis of peptidomimetics, where they replace a native peptide bond, the preparation of glycine derived tetrazole **81ANa** was considered as a test reaction. The starting thiourea **80ANa** was prepared in 85% yield from the reaction of amino acid glycine ethyl ester hydrochloride **78AN** and phenyl isothiocyanate **79a** in acetonitrile and in the presence of excess trimethylamine. With **80ANa** in hand, different desulfurization conditions were checked (Scheme 44).



Scheme 44. Procedure for the synthesis of ethyl (1-phenyl-1*H*-tetrazol-5-yl)glycinate **81ANa**.

[225] For a later related protocol for the synthesis of 5-aminotetrazoles from thioureas with Cs_2CO_3 and catalytic CuI, see: ref. 214b, page 120.

As mentioned before the mechanism of the reaction for *N*,*N*'-disubstituted thioureas with $HgCl_2$ is likely through carbodiimide intermediacy. For this reason, we envisaged that other desulfurizing agents could generate a carbodiimide intermediate and replace the mercury salts used in the previous research.

Initially, the reaction from ethyl (phenylcarbamothioyl) glycinate **78ANa** was studied using the conditions previously reported by the group which furnished exclusively tetrazole **81ANa** in 84% yield (Table 18, entry 1). However, when the reaction was performed with $Cu(OAc)_2$ a mixture of unidentified byproducts was detected together with complete disappearance of the starting material (Table 18, entry 2). Next, another thiophilic metal (silver) was investigated. In this case, Ag_2CO_3[226] was used and the desired product was obtained in a 47% yield together with the corresponding urea (26%), presumably formed by the decomposition of the thiourea or the carbodiimide intermediate (Table 18, entry 3).

Other oxidizing agents from the peracid family such as oxone[227] and *m*-CPBA were also tested (Table 18, entries 4 and 5). In both cases, after 16 hours side products were detected. While in the presence of oxone the starting thiourea was not observed, with *m*-CPBA, the presence of unreacted thiourea was verified.

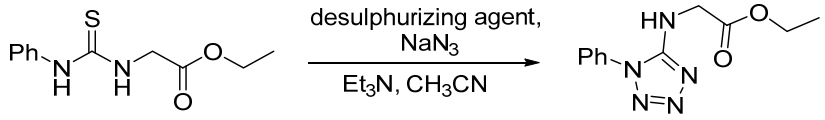
An interesting alternative to highly toxic heavy metal oxidants are hypervalent iodine or iodane reagents. The interest is due to the strong electrophilic character that the central iodine atom shows and the leaving ability of the phenyliodino group. Particularly, desulfurizations of thioureas with hypervalent organoiodine reagents have been reported recently.[228] Accordingly, the reaction with Dess-Martin periodinane (DMP) was tested (Table 18, entry 6), but unfortunately, no final tetrazole was obtained.

[226] For a recent protocol for the synthesis of indolo [2,3-*b*]quinolones from 2-(phenylethynyl)anilines and aryl isothiocynates via carbodiimide using Ag_2CO_3, see: Ali, W., Dahiya, A.; Pandey, R.; Alam, T.; Patel, B. K. *J. Org. Chem.* **2017**, *82*, 2089–2096.

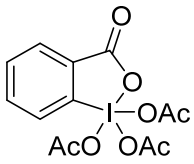
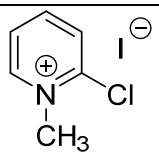
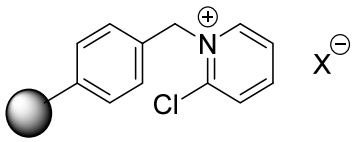
[227] For the reaction of thioureas with iodobenzene/oxone to give 5-aminotetrazoles, see: ref. 214c, page 120.

[228] For a desulfurization protocol of 1,3-disubstituted thioureas in the presence of an hypervalent organoiodine reagent to provide carbodiimides, see: a) Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. *J. Org. Chem.* **2008**, *73*, 2924–2927. b) Chaudhari, P. S.; Dangate, P. S.; Akamanchi, K. G. *Synlett*. **2010**, *20*, 3065–3067.

Table 18. Desulphurizing agent screening for the reaction from thiourea **82ANa.**[a]

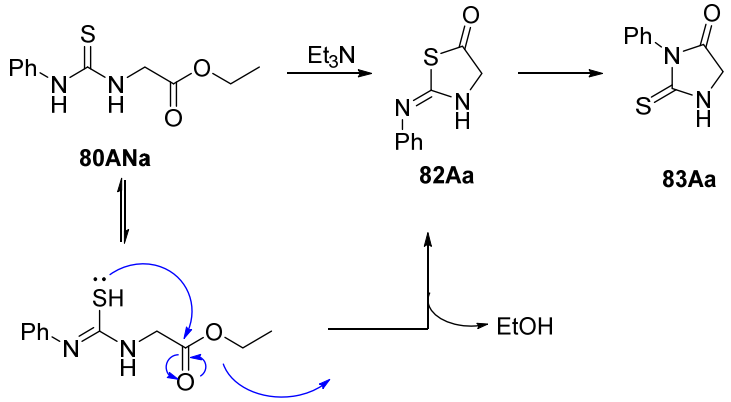


80ANa **81ANa**

Entry	Agent	Eq.	T [h]	Yield [%][b]
1	$HgCl_2$	1.1	2.5	84[c]
2	$Cu(OAc)_2$	2.0	2.5	n.o.
3	Ag_2CO_3	2.0	2.5	47
4	Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)	3.0	16	n.o.
5	m-CPBA	1.2	16	n.o.
6	 Dess-Martin periodinane (DMP)	1.1	1	n.o.
7	I_2	1.1	16	21
8	I_2/PPh_3	1.1/1.1	1.5	40
9	MeI	1.1	16	n.o
10	 Mukaiyama reagent	1.1	2	81
11	 Merrifield's resin supported Mukaiyama reagent	1.1 (0.5 mmol/g)	16	<35[d]
12		2.0 (0.3 mmol/g)	42	55[e]
13		3.0 (0.3 mmol/g)	24	64[e]
14		4.0 (0.3 mmol/g)	3	80

[a] Reactions conducted on a 0.5 mmol scale in 1.4 mL of CH_3CN (**80ANa**/NaN_3/Et_3N molar ratio=1:3:3). [b] Determined after column chromatography except for entries 1 and 14, in which the conversion of the reaction was quantitative and the product was isolated after filtration and NH_4Cl work-up. [c] Previously Batey's group synthetized this compound in a two-step reaction, one-pot procedure, (**78**/**70**/Et_3N/$HgCl_2$/NaN_3 molar ratio=1:1:3:1.1:3) with 88 % yield. [d] Mixture of **81ANa** and Edman degradation product **83Aa**. [e] 80% conversion. n.o.: not observed.

Molecular iodine has also been reported to give similar results to hypervalent iodine reagents for the formation of carbodiimide intermediates.[229,230] Thus, the reaction with iodine as desulfurizing agent was also checked, which provided tetrazole **81ANa** in low yield (21 %) together with other unidentified byproducts (Table 18, entry 7). Subsequently, we explored the possibility of adding PPh_3 (Table 18, entry 8), and a slight improvement in the yield of the desired tetrazole (40 %) was observed. When the reaction was performed with MeI[231] (Table 18, entry 9), another compound was obtained which was isolated and identified as thiohydantoin **83Aa** (Scheme 45) in 61 % yield. It represents the final product of the Edman degradation process, a method used for the analysis of polypeptide components/sequences.[232] In this case, thiourea **80ANa** undergoes an intramolecular cyclization via nucleophilic addition of the thio group to the amide carbonyl to generate thiazolone **82Aa**, which upon rearrangement is converted to the Edman phenylthiohydantoin **83Aa**.



Scheme 45. Formation of thiohydantoin **84Aa**.

Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) (CMPI)[233] is another well-known dehydrothiolation agent compatible with amines and used in the conversion of thioureas to carbodiimides,[234] in particular for the synthesis of guanidines at room

[229] For the synthesis of 2-iminohydantoins by cyclodeselenization of seleneourea-tethered amides/peptides in the presence of I_2, see: a) Prabhu, G.; Santhosh, L.; Nagendra, G.; Panduranga, V.; Sureshbabu, V. V. *ChemistrySelect* **2017**, *2*, 1202–1206. For a desulfurization protocol of 1,3-disubstituted thioureas in the presence of I_2 to provide carbodiimides, see: b) Ali, A. R.; Ghosh, H.; Patel, B. K. *Tetrahedron Lett*. **2010**, *51*, 1019–1021.

[230] For one example of synthesis of 5-aminotetrazoles from thioureas using I_2, see ref. 214a, page 120.

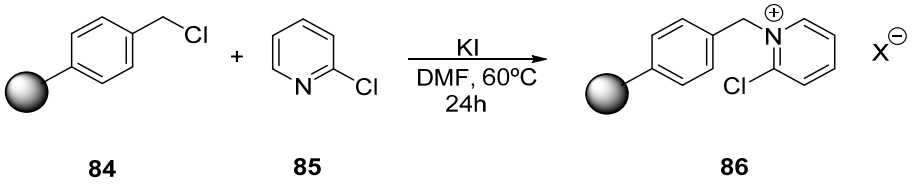
[231] For only one example from 4-[2-(acetoxy)-ethyl]-2-methylthiosemicarbazide using methyl iodide, see: ref. 214d, page 120.

[232] a) Edman, P. *Acta Chem. Scand*. **1950**, *4*, 283–293. B) Edman, P.; Begg, G. *Eur. J. Biochem.* **1967**, *1*, 80–91.

[233] a) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575. b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721.

[234] Drewry, D. H.; Ghiron, C. *Tetrahedron Lett.* **2000**, *41*, 6989–6992.

temperature.[235] Hence, we checked it in this reaction which provided tetrazole **81ANa** in 80 % yield (Table 18, entry 10), similar to the result with $HgCl_2$.[236] However, the product from Mukaiyama reagent required purification by silica gel column chromatography, whereas in the case of $HgCl_2$ it was isolated with excellent purity by a simple filtration through celite and NH_4Cl work-up. In order to simplify the work up and the isolation of the products we considered the use of the solid-supported reagents, which had been reported as an efficient alternative in parallel synthesis and combinatorial chemistry.[237] Therefore, we tried the synthesis of a polymer-bound variant of the Mukaiyama reagent by reacting Merrifield's resin **84** and 2-chloropyridine **85** in the presence of potassium iodide following the procedure described by Tye *et al*.[238] (Scheme 46).



84 **85** **86**

Scheme 46. Preparation of a Merrifield's resin-supported Mukaiyama reagent. **Tye, 2004**.

A difficult point was the determination of the resin loading for **86**, for which, we initially assumed the loadings obtained by Tye's group as reproducible results. In their work, they carried out the determination of the loading of the final resin **86** by the dehydration reaction of 1,3-di-(*p*-tolyl)thiourea with Et_3N previously reported by Mukaiyama using his reagent in solution.[233b] Tye and coworkers used the polymer-supported Mukaiyama reagent in its place and 3-acetylacetanilide as internal standard in DMF at room temperature. The ratio of the residual thiourea to 3-acetylacetanilide was measured by LC-MS analysis and their studies revealed a loading of 1.33 mmol/g for **86** starting from Merrifield's resin **84** with a loading of 3.00 mmol/g. In our experiment, we used the Merrifield's resin **84** at 1.00 mmol/g and, initially, we considered that under these conditions **86** was produced with a loading of 0.50 mmol/g. However, the test of

[235] a) Yong, Y. F.; Kowalsky, J. A., Lipton, M. A. *J. Org. Chem*. **1997**, *62*, 1540–1542. b) Josey, J. A.; Tarlton, C. A.; Payne, C. E. *Tetrahedron Lett.* **1998**, *39*, 5899–5902. c) Chen, J.; Pattarawarapan, M.; Zhang, A. J.; Burgess, K. *J. Comb. Chem*. **2000**, *2*, 276–281.

[236] Batey's group reported the use of Mukaiyama reagent in the solid-phase synthesis of peptide-thiourea hybrid molecules with similar results to $HgCl_2$, see: ref. 223, page 123.

[237] For reviews on solid supported reagents see: a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J.Chem. Soc., Perkin Trans*. **2000**, *1*, 3815–4195. b) Ley, S. V.; Baxendale, I. R.; Brusotti, G.; Caldarelli, M; Massi, A.; Nesi, M. *Farmaco* **2002**, *57*, 321–330. c) Solinas, A.; Taddei, M. *Synthesis* **2007**, *16*, 2409–2453. d) Baskar, B.; Kumar, K. *Solid-Phase Organic Synthesis* **2012**, 207–229. e) Bradley, M.; Galaffu, N. *Encyclopedia of Polymer Science and Technology*, **2014**, *11*, 17–47.

[238] Convers, E.; Tye, H.; Whittaker, M. *Tetrahedron Lett*. **2004**, *45*, 3401–3404.

this resin in the reaction to produce tetrazole **81ANa** provided after 16 hours less than 35% of a mixture of the desired tetrazole and a small quantity of the Edman degradation product **83Aa**. In addition, a 43 % yield of the starting material was also recovered (Table 18, entry 11). Looking again over Tye's work, we realized that they had observed that the loading of the final resin **86** and the starting resin **84** did not follow a linear ratio. In fact, for a starting loading of 1.50 mmol/g they determined a final resin **86** at 0.38 mmol/g. Then, based on that, we assumed that the loading for our polymer-supported (PS) Mukaiyama reagent was 0.3 mmol/g. In the evaluation of PS-Mukaiyama reagent by Tye and coworkers, the assay reaction of dehydration of 1,3-di-(*p*-tolyl)thiourea was not complete with the same number of equivalents that for the Mukaiyama's reaction in solution.[233b] Consequently, we tried to optimize the reaction conditions for thiourea **80ANa** (Table 18, entries 12-14). The best results were observed with 4 equivalents of PS-Mukaiyama reagent which provided ethyl (1-phenyl-1-H-tetrazol-5-yl)glycinate **81ANa** in 80% yield. Even though more experimental studies would be needed for the optimal determination of the loading of resin **86**, these results show that the reaction with the polymer supported Mukaiyama's reagent is possible and allows a straightforward final product purification.

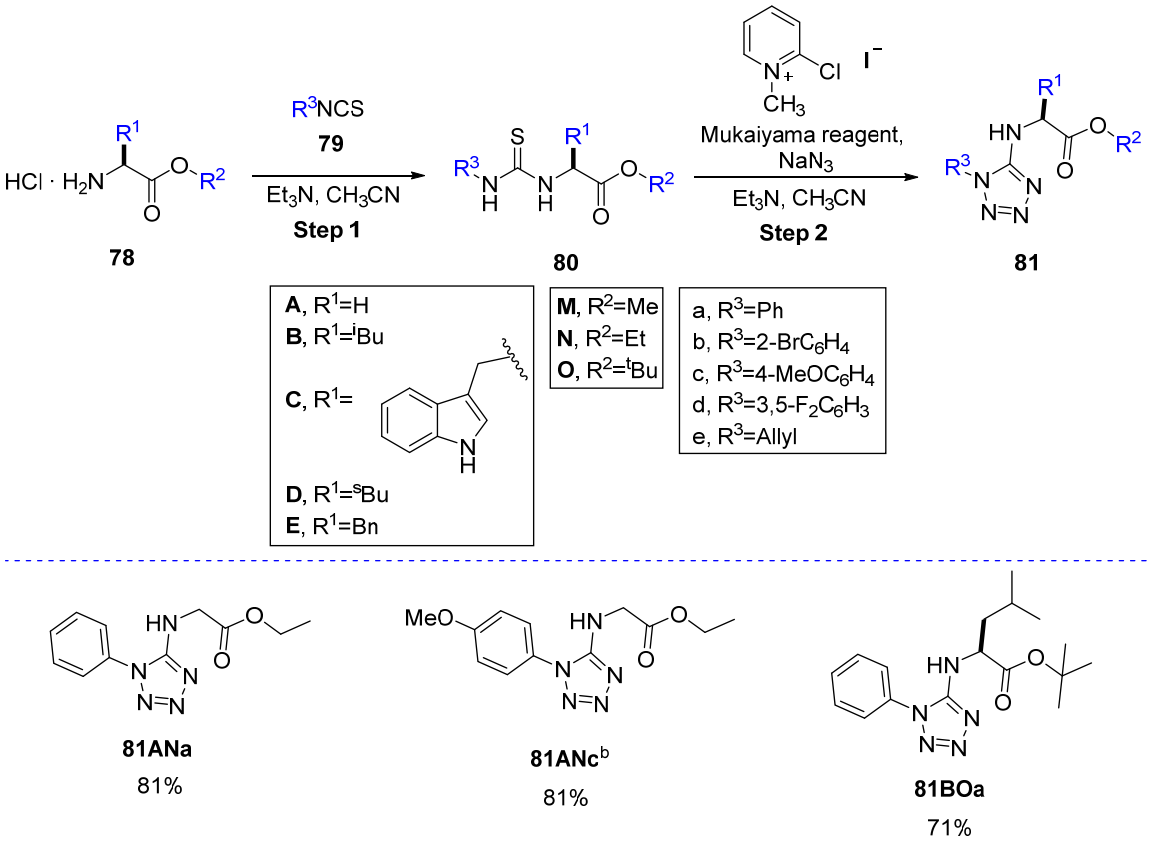
5.4.2 Reaction scope

After optimizing the conditions for the PS-Mukaiyama reagent, we next focused on the reaction scope. For that purpose, the use of Mukaiyama reagent in solution was considered and the synthesis of tetrazoles with different substitution patterns was explored.

5.4.2.1 Amino acid derived tetrazoles

In the first instance, this work focused on the synthesis of tetrazoles **81** shown in Table 19 using Mukaiyama's reagent in solution. Our approach involved two steps. Firstly, 1.0 equivalent of the isothiocyanate and 1.2 equivalent of Et_3N were added to a suspension of the starting amino acid hydrochloride **78** in CH_3CN (0.7M). The reaction mixture was stirred at room temperature for approximately 1 hour. After work-up and evaporation of the solvents, the resulting thiourea **80** was isolated for use in the next step after purification by column chromatography. The purified thiourea was dissolved in CH_3CN (0.3M), and 1.1 equivalents of Mukaiyama reagent, Et_3N (3.0 equivalents) and NaN_3 (3.0 equivalents) were added. The reaction mixture was stirred at room temperature for 2 hours and the final product **81** was purified by column chromatography.

Table 19. Synthesis of amino acid derived 5-aminotetrazoles.[a]



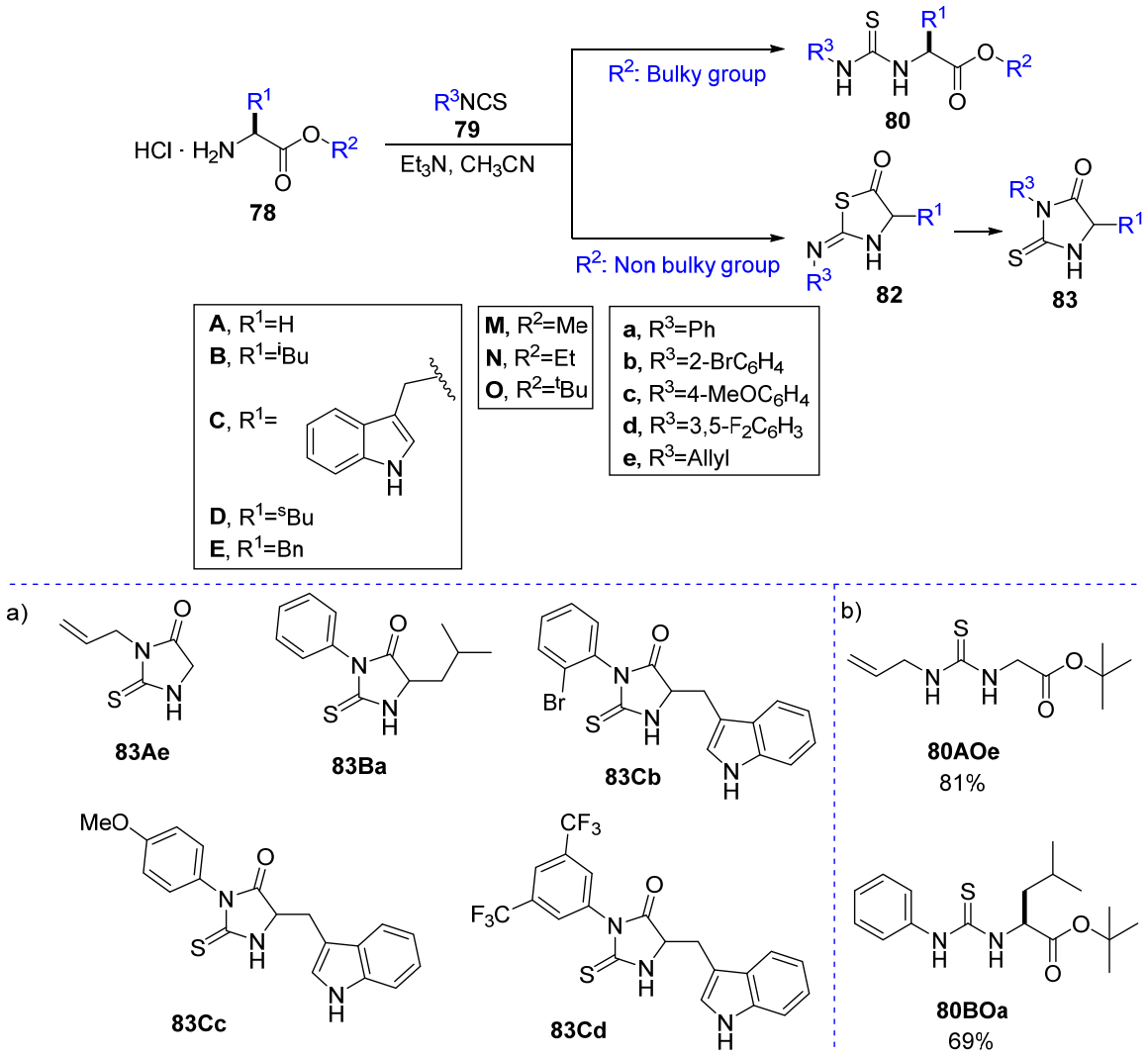
[a] Step 1: Reactions conducted on a 3.0 mmol scale in 3 mL of CH_3CN (**78**/**79**/Et_3N molar ratio=1:1:1.2). Step 2: Reactions conducted on a 1.0 mmol scale in 3 mL of CH_3CN (**80**/Mukaiyama reagent/NaN_3/Et_3N molar ratio=1:1.1:3:3). For **81ANa** and **81ABOa** yield determined after column chromatography. For **81ANc,** which was performed using PS-Mukaiyama reagent, yield determined after filtration. [b] Reaction conditions: **80**/PS-Mukaiyama reagent/NaN_3/Et_3N molar ratio=1:4:3:3.

Initially, we considered the possibility of varying isothiocyanates **79** for studying the reaction scope. As Table 19 shows, when phenyl isothiocyanate bears an electron-rich substituent at the aromatic ring (methoxy group), the reaction provides the corresponding thiourea **80AN** and the tetrazole **81ANc** in good yields. However, when the aryl group from the isothiocyanate was replaced by an alkyl group (R^3=alkyl), the expected thiourea **80ANe** was not obtained and the reaction afforded the Edman degradation product **83Ae** (Table 20a). In the case of $R^1 \neq H$ (R^1=^{i}Bu or tryptophan) and R^2=Me, the same tendency of thiohydantoin formation was showed to produce compounds **83Ba**, **83Cb**, **83Cc** and **83Cd** (Table 20a). Particularly, in the reaction with tryptophan methyl ester **78CM**, no influence of different electron-poor and electron rich substituents at the aromatic ring (R^3) in isothiocyanates **79b-d** was observed.[239] At this point, we envisioned

[239] In a preliminary study by Batey's group, the reaction of tryptophan methyl ester **78CM** with phenyl isothiocyanate **79a** was performed in two steps, one-pot procedure, (**78**/**79**/Et_3N/$HgCl_2$/NaN_3 molar ratio=1:1:3:1.1:3) to afford the corresponding tetrazole **81CMa** in 74 % yield.

that the use of the amino acid *tert*-butyl ester could prevent thiazolone **82** formation through steric destabilization of the transition state in the addition of the sulfur nucleophile to the ester carbonyl. Fortunately, this was the case and the reaction of **78AO** with **79e** led to *tert*-butyl(allylcarbamothioyl)glicinate **80AOe** in 81% yield and leucine *tert*-butyl ester **78BO** gave thiourea **80BOa** in 69% yield (Table 20b). In both cases, the subsequent reaction to obtain tetrazole was performed and, while **80AOe** did not react and was recovered in 77%, **80BOa** led to tetrazole **81BOa** in 71 % yield (Table 19).

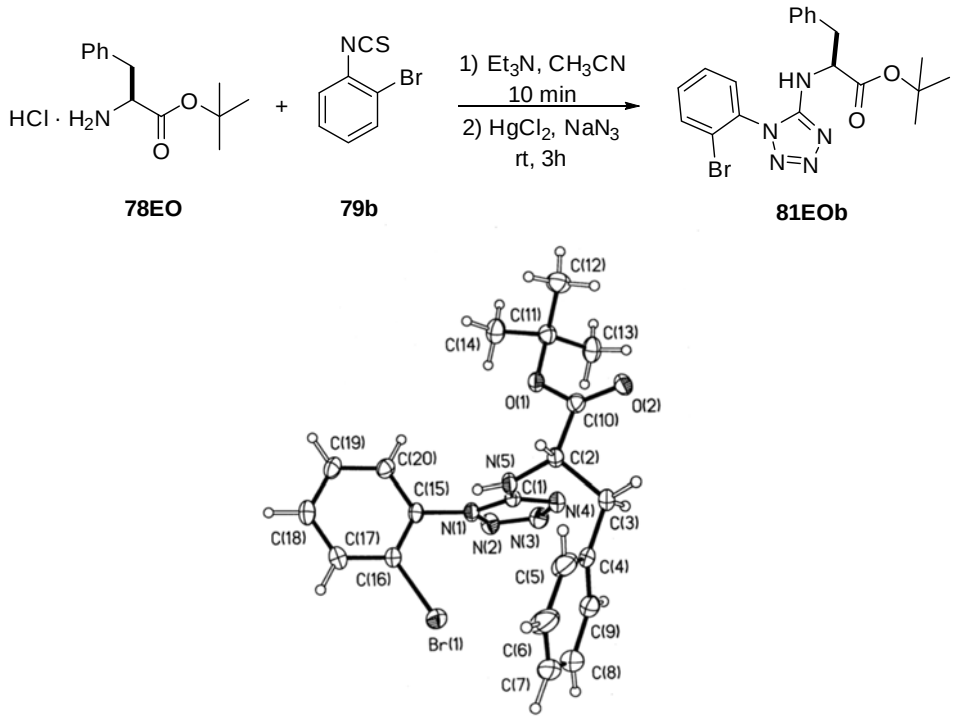
Table 20. Synthesis of thioureas **80**.[a]



[a] Reactions conducted on a 3.0 mmol scale in 3 mL of CH_3CN (**78**/**79**/Et_3N molar ratio=1:1:1.2). Yield determined after column chromatography.

As previously mentioned, the structure of the tetrazole in these reactions is dependent on the regioselectivity during the electrocyclization step. In order to corroborate the predicted structure by literature,[218] Batey's group previously established the structure of **81EOb** by single crystal X-ray structure analysis and that of compounds

81ANa, **81ANc** and **81Boa**, synthesized in this work, was assumed by considering a uniform reaction mechanism for their formation (Scheme 47). Notwithstanding, compound **81EOb** was obtained by reacting phenylalanine *tert*-butyl ester **78EO** with 2-bromophenyl isothioyanate **79b** in the presence of $HgCl_2$ (1.1 equiv.), NaN_3 (3.0 equiv.) and Et_3N (3.0 equiv.) (Scheme 47) while **81ANa**, **81ANc** and **81BOa** were synthesized in the presence of Mukaiyama's reagent.

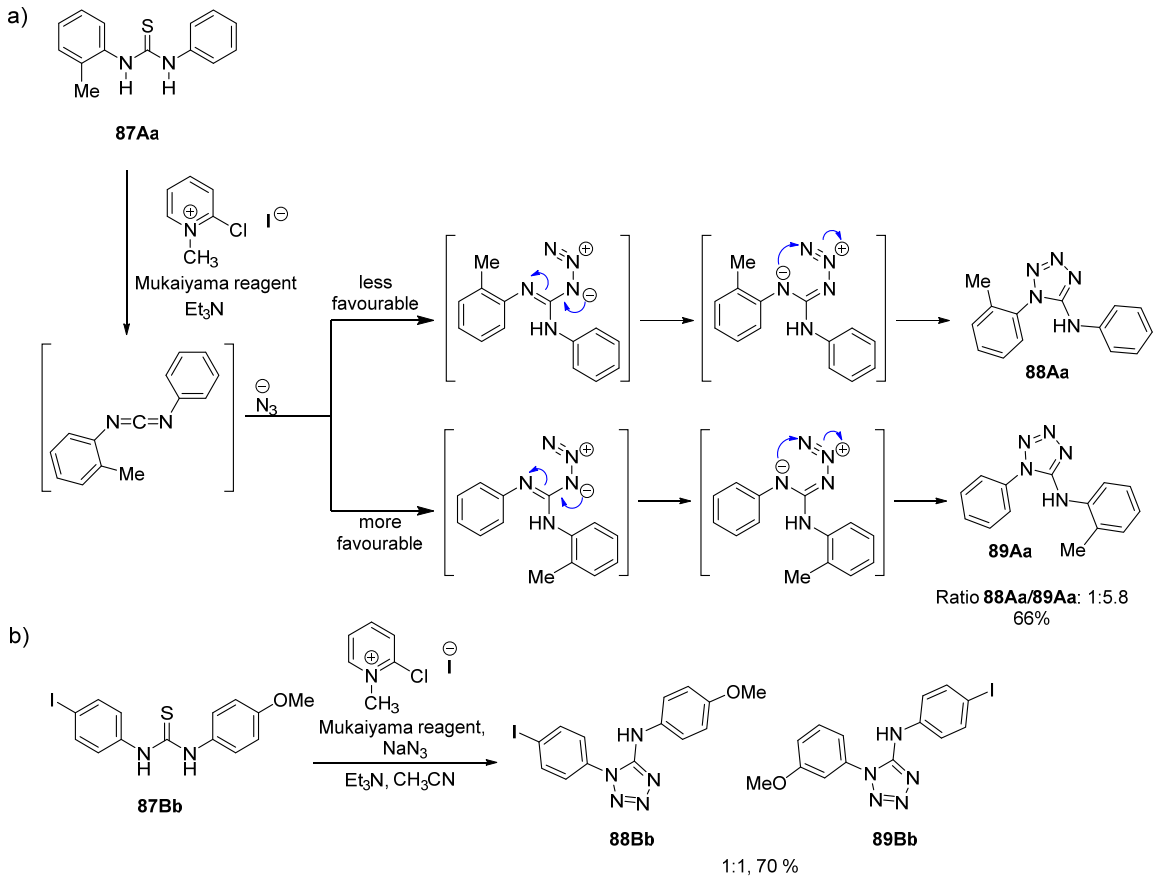


Scheme 47. X-Ray crystal structure of the amino acid-derived tetrazole **81EOb** and reaction carried out for its synthesis.

5.4.2.2 1-Aryl-5-arylaminotetrazoles

Considering the difficulty of synthesizing the amino acid derived thioureas and their lack of reactivity to obtain tetrazoles, which hampers the extension of the reaction scope, we next decided to evaluate the synthesis of 1-aryl-5-arylaminotetrazoles. The electrocyclization reactions were performed from thioureas **87Aa** and **87Bb**, previously synthesized in good yields; however, mixtures of tetrazole isomers were detected. 1-Phenyl-3(*o*-tolyl)thiourea **87Aa** led to a mixture of **88Aa/89Aa** in a 1:5.8 ratio (Scheme 48a). According to Patel's work on the synthesis of tetrazoles from thioureas using iodine,[214a] in which they observed that the reaction of the azide ion with an unsymmetrical carbodiimide leds to the flow of electron (protonation) towards the amine having more basic nature (higher pK_a) in the unsymmetrical cumulene, we may assume that the major tetrazole was **89Aa**. Nevertheless, for thiourea **87Bb** bearing acceptor and donor

substituents the reaction was not selective, providing a 1:1 ratio of the mixture of tetrazoles **88Bb/89Bb** (Scheme 48b). Patel's group obtained similar ratio for the synthesis of the corresponding tetrazole from α-4-methoxyaniline α'-4-bromoaniline thiourea and they proposed that this result could be due to the possible interconversion of the two intermediates, meaning an anomaly to the proposed regioselective mechanism, since a better regioselectivity was expected.[214c]



Scheme 48. Synthesis of 1-aryl-5-arylaminotetrazoles. Reactions conducted on a 1.0 mmol scale in 3 mL of CH_3CN (**87**/Mukaiyama reagent/NaN_3/Et_3N molar ratio=1:2:3:3). Combined yield of **88**/**89** determined after column chromatography.

5.4.2.3 1-Alkyl-5-alkylaminotetrazoles

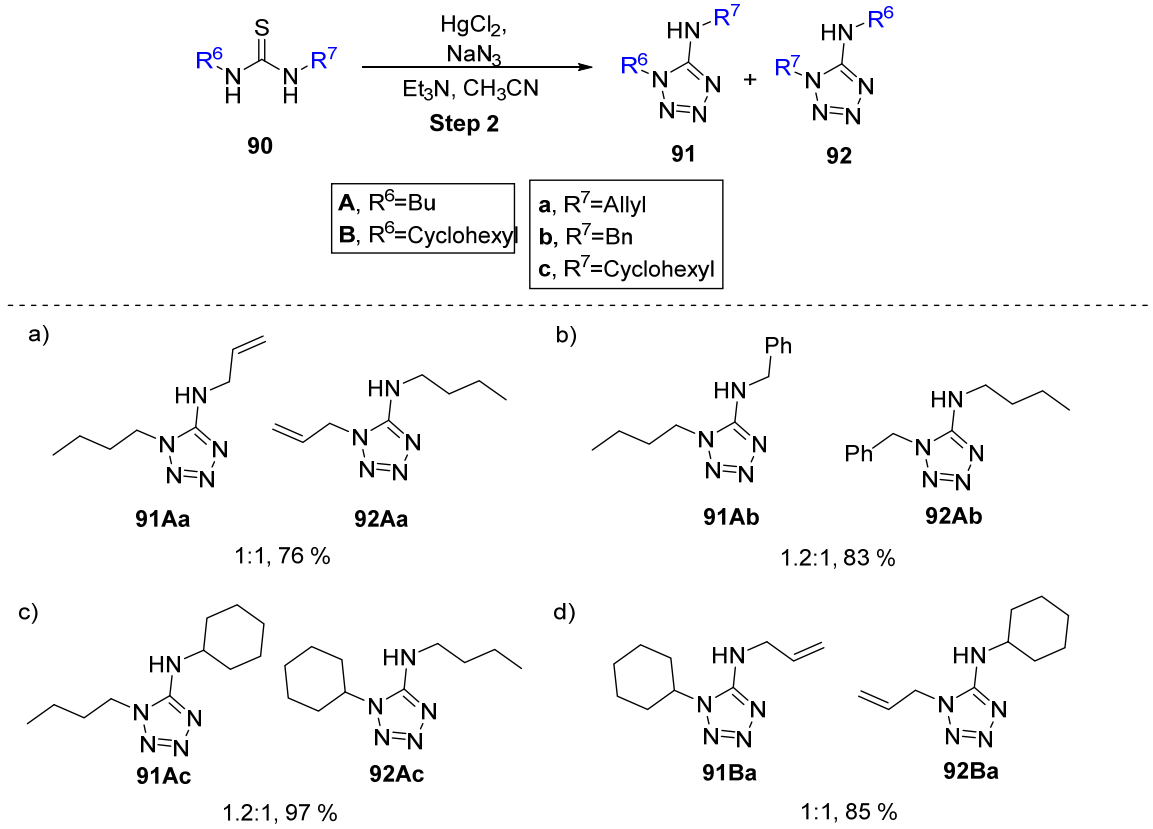
Next, we focused on the reaction leading to 1-alkyl-5-alkylaminotetrazoles. In our first attempt, Mukaiyama's reagent was employed for treating thioureas **90**, synthesized by the standard procedure. However, the corresponding tetrazoles were not detected in any case, and after 24 hours, the starting thioureas were recovered. On the contrary, when the reaction was performed with $HgCl_2$, tetrazoles **91** and **92** were obtained in good yields but in an almost equal ratio. 1-Allyl-3-butylthiourea **90Aa** furnished tetrazoles **91Aa/92Aa** in 76% combined yield (Table 21a)**.** Similarly, thioureas **90Ab**, **90Ac**, and **90Ba**

led to tetrazoles **91/92** in combined yields ranging from 83 to 97 % (Table 21b-c). The isomers were identified by ^{1}H-NMR analysis. For tetrazoles **91Aa/92Aa** and **91Ba/92Ba**, the integration of the signal associated to the methylene group of the allyl substituent showed a ratio of 1:1 in both cases. For tetrazoles **91Ab** and **92Ab**, the signal of the benzylic hydrogens (R^3) showed a different coupling pattern. Likewise, in **92Ab** they consisted of a singlet, while in **91Ab** a doublet was observed due to spin-spin interaction with the vicinal NH group. The integration of these signals provided a 1.2:1 ratio between the isomers **91Ab**/**92Ab** (Table 21b). Lastly, the ratio of tetrazoles **91Ac** and **92Ac** was determined according to the signal shown by the methylene linked to the nitrogen.

Taking into consideration that the reaction with *N,N'*-bis-alkyl-substituted thioureas **90** using Mukaiyama's reagent did not provide the desired tetrazoles **91**/**92** in spite of the fact that NaN_3 is a strong nucleophile,[240] the formation of the carbodiimide intermediate could be excluded. In addition Ko's reaction of *N,N'*-bis-alkyl-substituted thioureas **90** with amines in the presence of $HgCl_2$/Et_3N to yield guanidines revealed that these thioureas do not react.[216] Accordingly bis-alkyl disubstituted thioureas can be considered an exception in relation with other disubstituted thioureas, as their mechanism should occur through a coordination-addition-elimination path as proposed for trisubstituted thioureas.[217]

[240] Batey's group checked the Mukaiyama's reagent in the synthesis of 5-aminotetrazoles from trisubstituted thioureas (R^1R^2N = $-CH_2CH_2CH_2CH_2N-$; R^3 =Bn) and NaN_3, for which the starting thiourea was recovered almost entirely.

Table 21. Synthesis of 1-alkyl-5-alkylaminotetrazoles.[a]



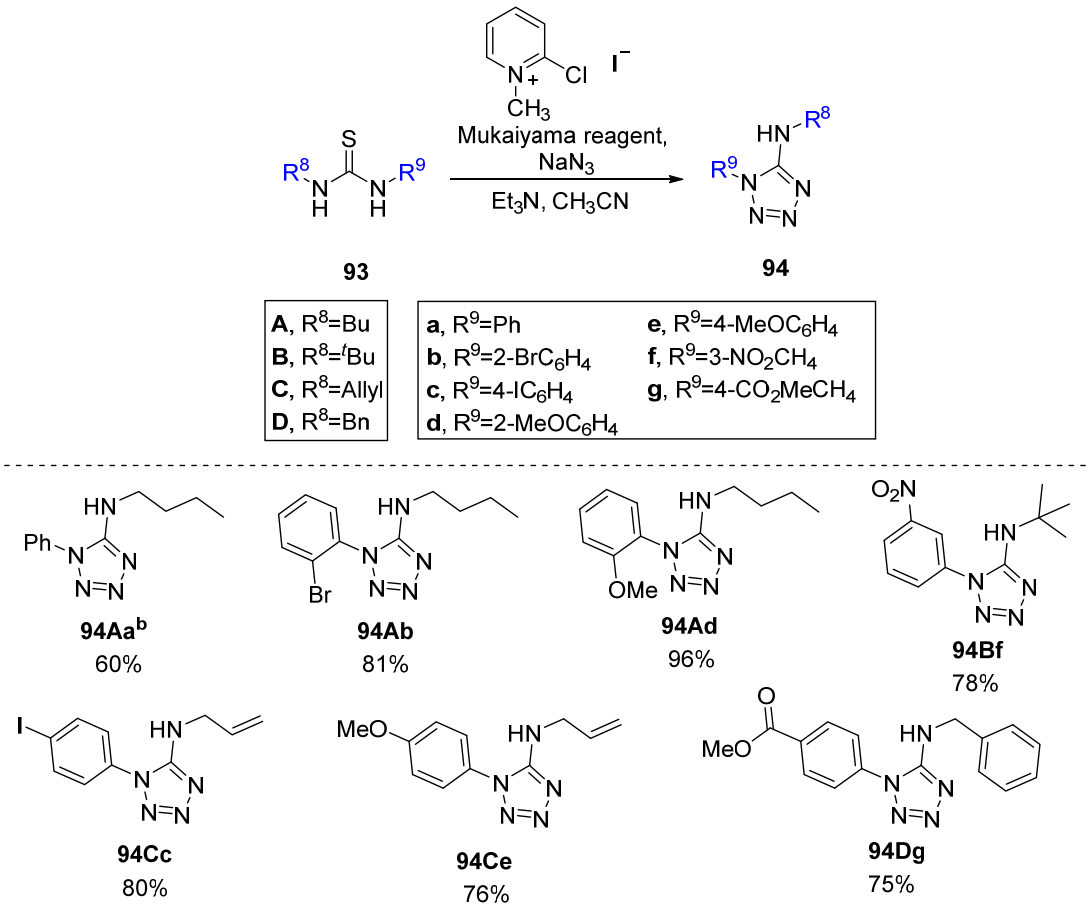
[a] Reactions conducted on a 1.0 mmol scale in 3 mL of CH_3CN (**90**/$HgCl_2$/NaN_3/Et_3N molar ratio=1.0:1.1:3.0:3.0). Combined yield of **91**/**92** determined after filtration.

5.4.2.4 1-Aryl-5-alkylaminotetrazoles

In light of these results, we next decided to explore the reaction with aliphatic-aromatic thioureas **93** to obtain 1-aryl-5alkylamino tetrazoles (Table 22), on account of the fact that the ratio of the adducts depends on the dipolarophilic activity of both double bonds in the carbodiimide. Thus, in this case as thioureas led to carbodiimides with wider dipolarophilic difference between C=N bonds, improvement in the selectivity towards an isomer was expected. In the first instance, thiourea **93Aa** was synthesized, which afforded tetrazole **94Aa** in 60% yield with 90% conversion after 24 hours using 1.1 equivalents of Mukaiyama's reagent. In this case, selectivity was not only increased, but a single isomer was also detected, which is consistent with the literature data, where the more stable tetrazole is produced when an alkyl substituent is linked to the tetrazole NH group.[218] In the case of **93Ab** and **93Ad** with R^8=Bu and electron rich and electron poor substituents at the aromatic group, increasing Mukaiyama's reagent to 2 equivalents, resulted in reaction completion after 2 hours with good yields and the production of only one isomer. The reaction of a thiourea incorporating a bulkier alkyl group, *tert*-butyl, and an electron deficient aryl group, such as 3-nitrophenyl was also evaluated, providing tetrazole **94Bf**

with good yield and excellent selectivity. Similar results were obtained for tetrazoles **94Cc** and **94Ce** for which, the thiourea's substituents are allyl and *p*-iodophenyl groups (**93Cc**) or allyl and *p*-methoxyphenyl groups (**93Ce**). Lastly, methyl-4-(3-benzylthioureido) benzoate **93Dg** was tested which provided tetrazole **94Dg** in 75 % yield.

Table 22. Synthesis of alkyl aryl substituted thioureas and 5-aminotetrazoles.[a]



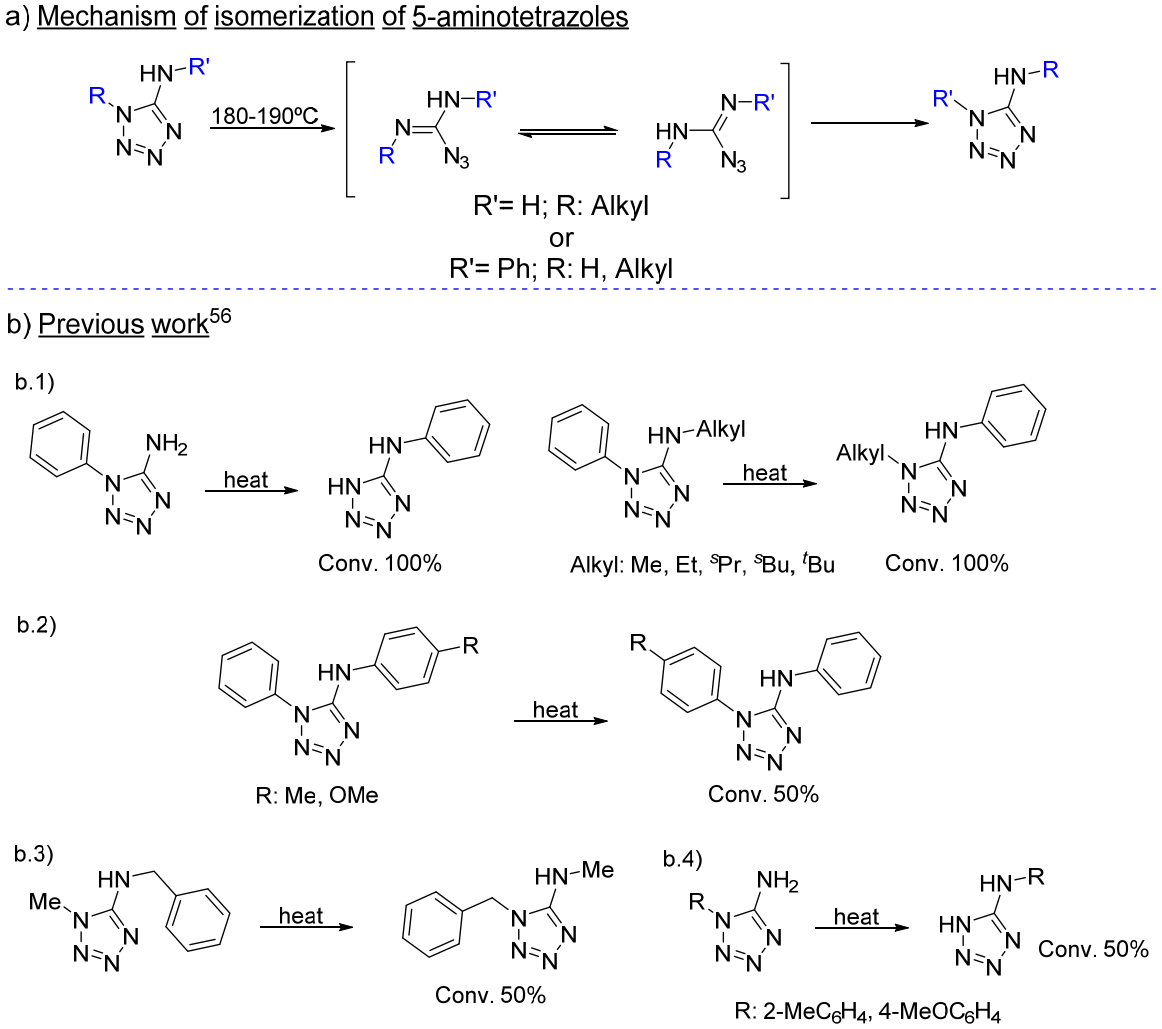
[a] Reactions conducted on a 1.0 mmol scale in 3 mL of CH_3CN (**93**/Mukaiyama's reagent/NaN_3/Et_3N molar ratio=1.0:2.0:3.0:3.0) unless otherwise stated. Yield determined after column chromatography. [b] Reaction conducted on a 1.0 mmol scale in 3 mL of CH_3CN (**93**/Mukaiyama's reagent/NaN_3/Et_3N molar ratio=1.0:1.1:3.0:3.0. Conversion 90% in 24 hours.

5.4.3 5-Aminotetrazole isomerization

As it has already been pointed out, the guanylazide is an intermediate in the formation of tetrazoles, so ring closure in asymmetric substituted carbodiimides should theoretically occur in two different directions. Since the ratio of those adducts depends on the nature of the substituent groups, some researches have evaluated the possibility

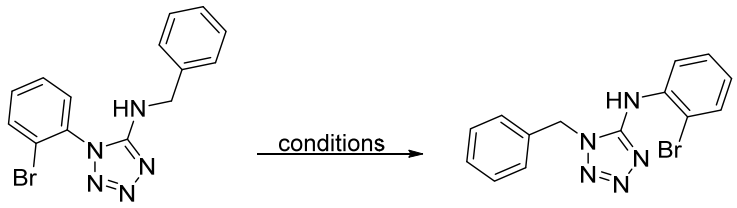
of isomerizing tetrazoles, through rearrangement on heating.[218,241] Lieber and coworkers observed that 5-aminotetrazoles could be isomerized very rapidly and smoothly under thermal conditions and postulated that the isomerization is likely due to a ring opening to the substituted guanylazide followed by a recyclization to the thermodynamically more stable tetrazole, or to an equilibrium in which the most stable tetrazole predominates (Scheme 49, a). For instance, 1-phenyl-5-aminotetrazole and 1-phenyl-5-alkylaminotetrazole (alkyl: Me, Et, ^{s}Pr, ^{s}Bu, ^{t}Bu and cyclohexyl) isomerized completely (Scheme 49, b.1); however if R and R' both were aryl (Ph and *p*-MeC_6H_4 or Ph and *p*-$MeOC_6H_4$) (Scheme 49, b.2) or alkyl groups (Me and Bn) (Scheme 49, b.3), a mixture of isomers was obtained from a single isomer. In addition, the tendency of 1-aryl-5-aminotetrazoles to rearrange to the 5-arylaminotetrazoles decreases as the electronegative character of the aromatic ring is decreased by the introduction of methyl or methoxy substituents in the aryl group leading to a mixture of isomers (Scheme 49, b.4). Furthermore, a catalytic amount of base (NaOH) has been observed to accelerate the isomerization rate.[218]

[241] a) Finnegan, W. G., Henry, R. A.; Lieber, *J. Org. Chem*. **1953**, *18*, 779–791. b) Garbrecht, W. L.; Herbst, R. M. *J. Org. Chem*. **1953**, *18*, 1269–1282. c) Henry, R. A., Finnegan, W. G. Lieber, E. *J. Am. Chem. Soc*. **1954**, *76*, 88–93. d) Herbst, R. M.; Klingbeil, J. E. *J. Org. Chem.* **1958**, *23*, 1912–1916.



Scheme 49. a) Mechanism of isomerization of 5-aminotetrazoles. b) Previous works on isomerization of 5-aminotetrazoles.

Based on these precedents, the group of Prof. R. Batey made a preliminary study in which *N*-benzyl-1-(2-bromophenyl)-1*H*-tetrazol-5-amine **94Db** was heated in toluene at 100 °C for 6 hours leading to the 1-benzyl-*N*-phenyl-1*H*-tetrazol-5-amine isomer **95Db** in 68 % yield. In the presence of Cs_2CO_3 (10 mol %) an almost quantitative yield was obtained. Furthermore, when the same reaction was carried out in refluxing MeCN over a period of 48 hours, either in the absence of base or in the presence of K_2CO_3 (10 mol %) or in the presence of Cs_2CO_3 (10 mol %) the conversions were 16 %, 73 % and 85 % respectively (Scheme 50).



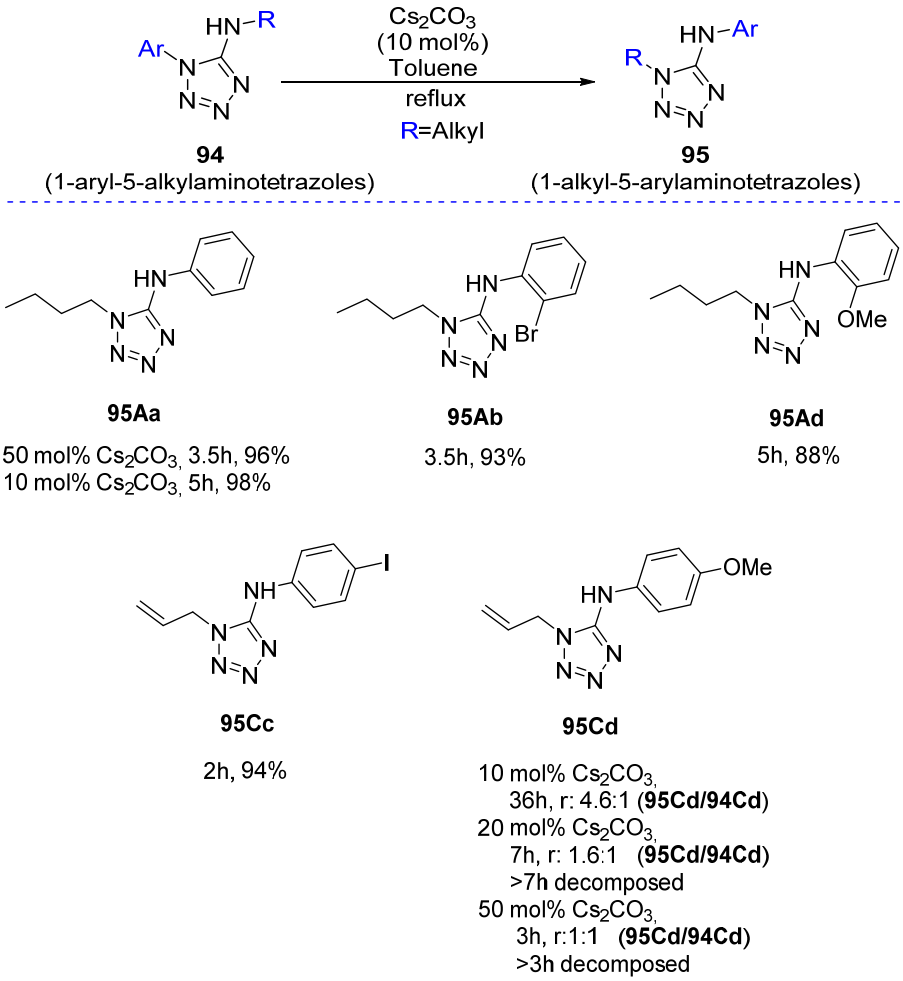
94Db **95Db**

Entry	Conditions	Reaction time	Yield [%]
1	100° C, toluene	6h	68
2	Cs_2CO_3 (10 mol %), 100° C, toluene	12h	99
3	Refluxing MeCN	48h	16
4	K_2CO_3 (10 mol %), refluxing MeCN	48h	73
5	Cs_2CO_3 (10 mol %), refluxing MeCN	48h	85

Scheme 50. Experiments of 5-aminotetrazole **95Db** isomerization by Batey`s group.

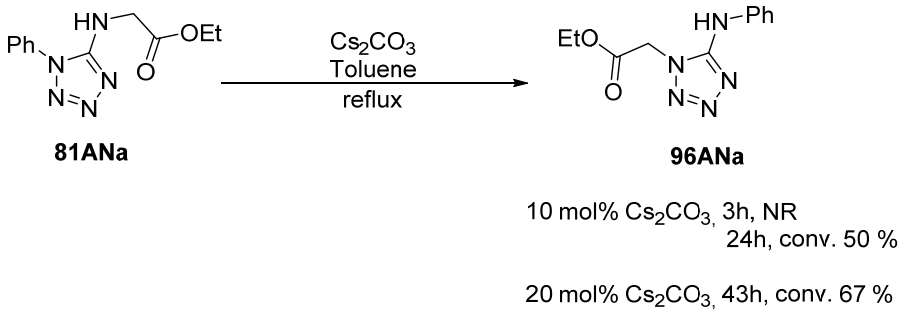
Likewise, we explored the isomerization of our compounds (Table 23) following a standard procedure: substituted 5-aminotetrazoles **94** were dissolved in toluene (0.1M) and 10 mol % of Cs_2CO_3 was added. Then, the reaction mixture was heated to reflux until total conversion or no observation of reaction progress (monitoring by ^{1}H-NMR analysis). 1-Aryl-5-butylaminotetrazoles provided excellent yields for 1-phenyl as well as for *ortho*-bromo phenyl or methoxy phenyl substituted tetrazoles (Table 23, **95Aa**, **95Ab**, **95Ad**). However, when the benzyl group was replaced by an allyl group (**94Cc** and **94Cd**), the influence of the electronegativity of the aryl substituents was observed in reaction conversion. While the reaction of 1-*para*-iodo phenyl derivative (**94Cc**) led to a single isomer **95Cc** in 94 % yield, for 1-*para*-methoxy phenyl-5 allylamino tetrazole **94Cd**, a mixture of isomers was obtained, being the best result 4.6:1 ratio **94Cd**/**95Cd**. The increment of the amount of base (20 or 50 mol % Cs_2CO_3) in this reaction did not address to whole isomerization and loss of the starting material by pyrolytic decomposition was observed.

Table 23. Isomerization of 5-aminotetrazoles.[a]



[a] Reactions conducted on a 0.2 mmol scale in 5 mL of toluene (**94**/Cs_2CO_3 molar ratio: 1:0.1).

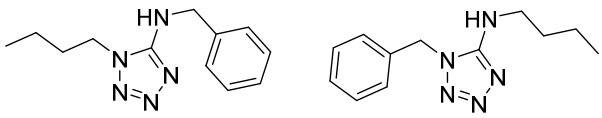
Unfortunately, the isomerization of amino acid derived tetrazole **81ANa** did not provide full reaction conversion either in the presence of 10 mol % or 20 mol % of Cs_2CO_3 (Scheme 51).



Scheme 51. Isomerization of amino acid derived tetrazole **82ANa**.

Finally, a mixture of tetrazoles bearing two alkyl groups as substituents (**91Ab**/**92Ab**) with a 1:1.2 ratio (Scheme 52) was also examined under standard

isomerization conditions, without witnessing any change in the proportion of isomers after 16 hours.



Scheme 52. Mixture of tetrazoles **91Ab**/**92Ab**, under isomerization conditions resulting in no modification of the isomeric ratio.

Additionally, experiments to investigate the influence of the base in the reaction were carried out. The isomerization reaction of tetrazole **94Aa** was performed in the presence of 10 mol % of Cs_2CO_3 and in the absence of base. Both reactions were monitored by ^{1}H-NMR every hour. The isomerization reaction with base was completed in 5 hours and the yield was 98%. On the contrary, the reaction without base did not reach the 80 % of conversion after 24 hours (ratio **94Aa**/**95Aa** 1:3.2) (Figure 34). These results demonstrate the advantages of using base for isomerizations.

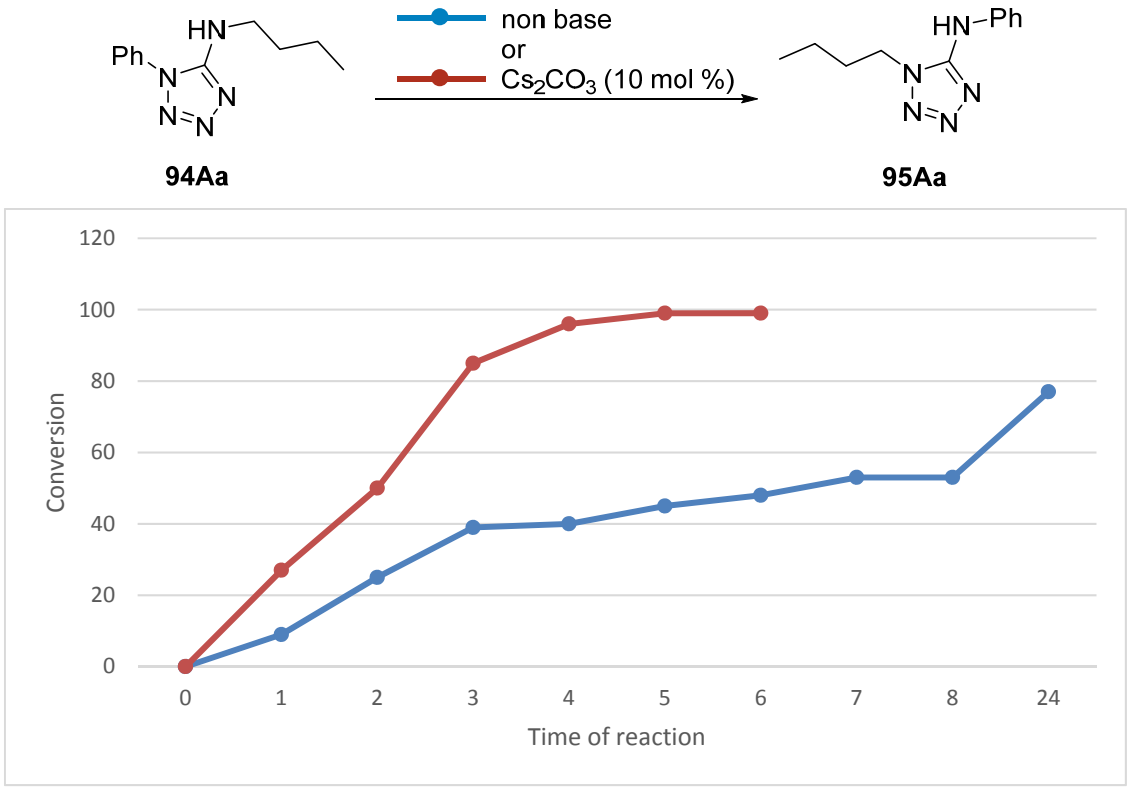


Figure 34. Comparative reactivity of the isomerization reaction of tetrazole **94Aa** in the absence/presence of base.

In summary, these results show that the formation of di-substituted 5-aminotetrazoles from a less toxic oxidant such as Mukaiyama's reagent can be efficiently carried out in both, solution and using the solid-phase supported reagent. Additionally, it should be noted that is possible to incorporate a tetrazole moiety at the *N*-terminal position of commercially available amino acids depending on the type of ester protection, and avoiding the toxicity of the mercury salts. Nevertheless, a limitation of this protocol is the synthesis of 1-alkyl-5-alkylaminotetrazoles, which do not react in the presence of the Mukaiyama's reagent. This maybe due to a different mechanism of reaction, although they can be synthesized in the presence of $HgCl_2$. In this way, a coordination-addition-elimination pathway is proposed for *N,N'*-bisalkylthioureas, based on the similarity to other experiments in the literature. However, when both substituents at the starting thioureas are alkyl or aryl, regioisomeric mixtures of tetrazoles were obtained. For mixed substituted thioureas, high selectivity is achieved and a single isomer is obtained. Moreover, a base catalyzed protocol to shift the equilibrium to the thermodynamically more stable isomer has been described with quantitative yields for most of the compounds and the usefulness of the base has been demonstrated too, although it is pending of a more thorough analysis. In any case, the ease of synthesizing diverse thioureas from commercially available amines and isothiocyanates under mild conditions enables the creation of libraries of di- substituted 5-aminotetrazoles by this methodology.

CHAPTER 6.

Conclusions

6. Conclusions

It has been demonstrated that Brønsted base/H-bonding catalysts can promote enantioselective direct α-functionalization of aldehydes and ketones with some structural characteristics. Specifically, Michael reaction of aldehydes or ketones to nitroolefins provided the corresponding α-addition adducts with very good stereocontrol.

α-Hydroxy ketones have been employed efficiently as Michael donors in the conjugate addition to nitroalkenes assisted by bifunctional tertiary amine based catalysts. The reactivity and stereoselectivity profile of these substrates could be easily modulated by varying the size of the *gem*-substituents at the α-carbon, thus, α-hydroxy α,α-dibenzyl ketones provided the best enantiocontrol with the selected conditions and catalysts. One limitation of this method was the unsuitability of α-hydroxy ketones with decreasing α'-carbon acidity, however, the use of β',γ'-unsaturated α-hydroxy ketones in the conjugate addition and the subsequent reduction of the corresponding adducts affords the α',α'-dialkyl ketones with high regio- (α vs γ) and stereoselectivity. Moreover, the oxidative ketol scission of the resulting Michael products led to enantiopure carboxylic acid and aldehyde products and dibenzylacetone byproduct could be separted and reused. Therefore, α-hydroxy α,α-disubstituted ketones have been described as effective ester and aldehyde donor equivalents in asymmetric catalysis.

Benzylic alkynyl ketones have also shown to be suitable pronucleophiles for their direct α-functionalization with nitroalkenes in the presence of tertiary amine/squaramide bifunctional catalysts, in which adducts with two contiguous stereogenic centers (α and β carbon) and with high diastereo- and enantioselectivity are generated. In addition, elaborations of the α-branched ynone adducts provide access to enantioenrich α-functionalized acyclic dialkyl ketones and allow the synthesis of stereochemically complex structures as spirocyclic dienones and tricyclic carbon skeletons.

A new family of tertiary amine/squaramide based catalysts containing amino acids have been desgined and synthetized. Their high catalityc activity has been shown in which is the first enantioselective Michael reaction of naked aldehydes with nitroolefins assisted by Brønsted base catalysts. This conjugate addition provides γ-nitroaldehydes containing one quaternary stereocenter with high stereoselectivity.

Finally, as a part of an international stay at the University of Toronto (UofT) under the supervision of Prof. Rober Batey, previous methodology described for the preparation

of disubstituted *N*-terminal-5-amino tetrazole peptide hybrid molecules has been validated for the synthesis of 1-substituted 5-substituted aminotetrazoles from thioureas. The reaction from *N*-alkyl *N*'-aryl thioureas provided tetrazoles with high regioselectivity, but a limitiation is found in the reaction from *N*,*N*'-bisalkyl- and *N*,*N*'-bisarylthioureas which led to regioisomeric mixtures of tetrazoles. Besides, a base catalyzed protocol for isomerization of these tetrazoles has been described with quantitative yields.

CHAPTER 7.

Experimental section

Experimental section

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7. Experimental section

7.1. Materials and general techniques

7.1.1. Reagents, solvents and products

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

Triethylamine, DBU 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.[242] Dichloromethane and acetonitrile were distilled over CaH_2, diethyl ether and tetrahydrofuran were dried by filtration through drying columns (Pure Solv It) and toluene was dried over sodium metal/benzophenone ketyl under argon.

Catalysts **C22**[243], **C23**,[244] **C24**[244] and **C36**[243] were available in the laboratory and were synthesized previously by the group. Nitroalkenes **24b–24e**, **24g, 24h** and **24k** were prepared according to the literature[245] and **24a**, **24f**, **24i** and **24j** were purchased from different commercial suppliers. 1,1-bis(phenylsulfonyl)ethylene (**44**)[246] and 1-phenylprop-2-en-1-one (**46**)[247] were synthesized following the procedures described in the literature. Phenyl acetaldehyde (**34**) and 2-phenylpropanal (**65**) were purchased from commercial supplier (Aldrich).

7.1.2. General experimental

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

---

[242] Armarego, W. L. F.; Perrin, D. D. *Purification of laboratory Chemicals* 3rd Edition Butterworth-Heinemann, Oxford **1988**.
[243] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mieglo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.
[244] Sandra Rodríguez del Pozo, PhD. Dissertation, EHU/UPV, 2019.
https://www.ehu.eus/es/web/gicas/tesiak
[245] Aromatic nitroalkenes: a) Bourguignon, J.; Le Naard, G.; Queguiner, G. *Can. J. Chem.* **1985**, *63*, 2354–2361. Aliphatic nitroalkenes: b) Trost, B. M.; Muller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438–2439.
[246] Quintard, A.; Alexakis, A. *Chem. Commun.* **2011**, *47*, 7212–7214.
[247] Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715–1717.

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

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

Solvent evaporation was carried out 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 the products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (~0.5 mmHg) was employed.

7.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under ultraviolet light, Fisher Bioblock lamp VL-4LC, λ=254 and 265 nm. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1g) in 100 mL of water (limited lifetime) and then, they were visualized by heating.

Chromatographic purification was carried out employing Merck ROCC 60 silica gel 40–63 μm as stationary phase and a suitable mixture of solvents (typically hexane/ethyl acetate or dichloromethane/methanol) as eluent. In some particular cases non acid silica gel was used, which was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 hours. After filtration, the residual water was evaporated in an oven at 80 °C during 72 hours.

7.1.4. Optical rotations

Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotations (SR) ($[\alpha]_D$) are reported in 10^{-1} deg·cm^2·g^{-1}, concentrations (*c*) are quoted in g/100 mL, *D* refers to D-line of sodium (589 nm) and temperature (*T*) is given in degree Celsius (°C).

7.1.5. Melting points

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

7.1.6. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C), Bruker 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), Bruker AV-500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C), 300 MHz Varian MercuryPlus (300 MHz for ^{1}H, 75 MHz for ^{13}C), 400 MHz Varian MercuryPlus (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak, usually $CDCl_3$, ^{1}H (δ=7.26) and ^{13}C (δ=77.0). The multiplicity of each signal was designed using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet; br s, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

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

7.1.7. Mass spectra

MS spectra were recorded on an ESI-ion trap Mass spectrometer Agilent 1100 series LC/MSD, SL model, on an UPLC-DAD-QTOF, Ultra High Performance Liquid Chromatography-Mass spectrometer, Waters UPLC ACQUITY, Waters PDA detector, Waters Sunapt G2 or on an Agilent Thermoquest LCT spectrometer. Mass spectrometry analyses were performed in the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU).

Furthermore, at the University of Toronto (UofT), high-resolution mass spectra (HRMS) were recorded on a ABI/SCIEX QStar mass spectrometer (ESI) or a JEOL AccuTOF model JMST1000LC mass spectrometer equipped with an IONICS Direct Analysis in Real Time (DART) ion source. Mass spectrometry analyses were performed by the University of Toronto Advanced Instrumentation for Molecular Structure (AIMS) mass spectrometry facility.

7.1.8. Infrared spectra

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

7.1.9. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on Waters 600E, equipped with 2996 and 1998 photodiode array UV detector, using Dicel Chiralpak AD-H, OD-H, AS-H, IA, IB and IC columns. Flow and solvent conditions are given for each compound.

7.1.10. X-ray diffraction analysis

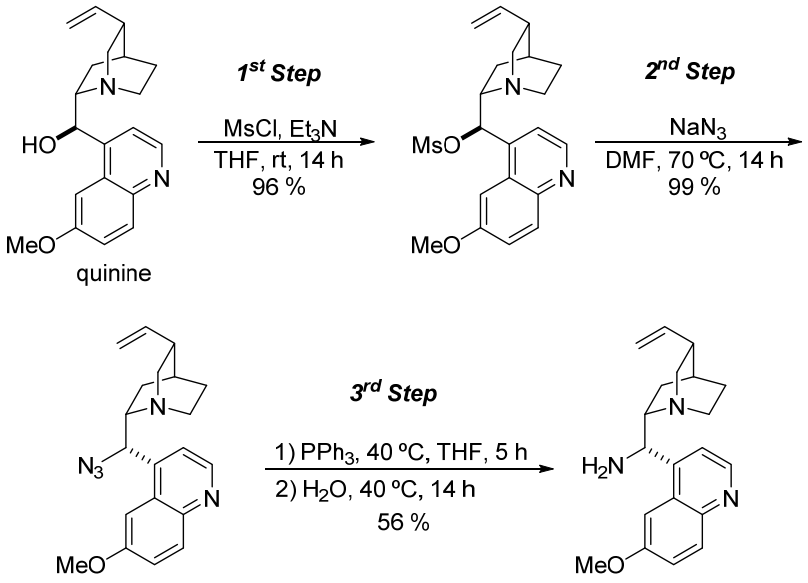
The X-ray diffraction analysis experiments were conducted in the X-ray unit at the General Research Service (SGIker) of the University of the Basque Country (UPV/EHU) using diffractometers for monocrystals.

7.2. General procedure for the synthesis of catalysts

7.2.1. Preparation of chiral Brønsted bases

7.2.1.1. Preparation of 9-epi cinchona-based amines

7.2.1.1.1. Preparation of 9-amino-(9-deoxy)epiquinine[248]



1st Step:[249] A mixture of quinine (16.2 g, 50 mmol, 1 equiv.) and trimethylamine (25.1 mL, 180 mmol, 3.6 equiv.) in dry THF (250 mL) was cooled to 0 °C and then

[248] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.
[249] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

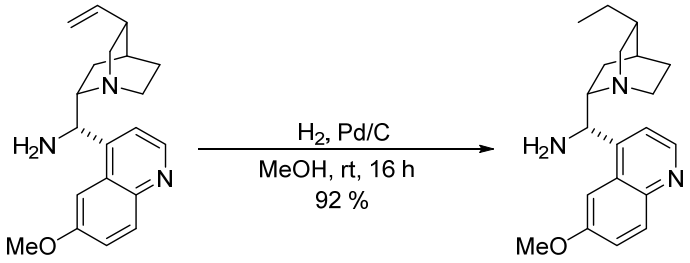
methanesulfonyl chloride (7.0 mL, 90 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentered under vacuum to afford the crude product in 96 % yield, which was used in the next step without further purification.

2nd Step:[250] The crude mesylated product (19.3 g, 48 mmol, 1 equiv.) was dissolved in DMF (150 mL). The solution was cooled to 0 °C and NaN_3 (6.2 g, 96 mmol, 2 equiv.) was added portionwise. The mixture was stirred at 70 °C for 16 h and after this time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield, which was used in the next step without further purification.

3rd Step:[250] The crude product was dissolved in THF (250 mL) and PPh_3 (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated to 40 °C and stirred until the gas evolution ceased (~5 h). 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 dichloromethane (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then, the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40 %. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.75 (d, *J* = 4.6 Hz, 1H), 7.36 – 8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02 – 3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26 – 1.63 (m, 4H), 0.80 (m, 1H).

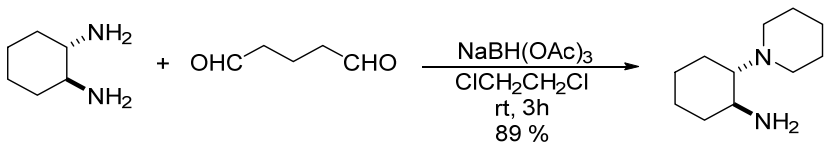
[250] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

7.2.1.1.2. Preparation of 9-amino-(9-deoxy)epihydroquinine[251]



10% Palladium on carbon (10 % w/w, 0.32 g) was added to a solution of 9-amino-(9-deoxy)*epi*quinine (3.2 g, 10 mmol, 1 equiv.) in methanol (10 mL). The reaction mixture was stirred overnight under H_2 atmosphere, and then was filtered over celite and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*hydroquinine as a yellow viscous oil. Yield: 3.0 g, 9.2 mmol, 92 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.69 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.69 (brs, 1H), 7.61 (d, *J* = 4.7 Hz, 1H), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.36 – 3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H), 3.16 (q, *J* = 10.7 Hz, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 1.62 – 1.58 (m, 1H), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.58 – 1.47 (m, 4H), 1.37 – 1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

Preparation of (1S,2S)-2-(piperidin-1-yl)cyclohexan-1-amine[252]



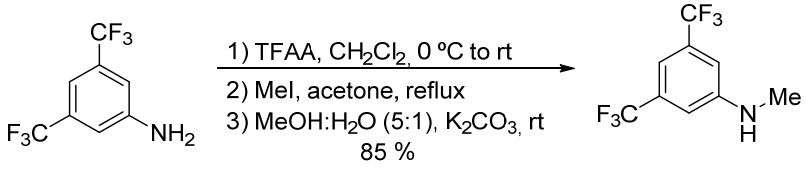
Glutaraldehyde (50 wt % in H_2O, 1.90 mL, 10.4 mmol, 1.04 equiv.) was added dropwise into a mixture of diamine (1.14 g, 10 mmol, 1 equiv.), and $NaBH(OAc)_3$ (8.5 g, 40 mmol, 4 equiv.), in $ClCH_2CH_2Cl$ (60 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 hours, and quenched with NaOH aq. solution (6M, 30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were concentrated. The residue was dissolved in 50 mL CH_2Cl_2, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give the product as a yellow liquid. Yield: 1.61 g, 8.9 mmol, 89 %. All spectroscopy data were identical to those reported in the literature. ^{1}H NMR (300, $CDCl_3$) δ 2.87 – 2.68 (m,

[251] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.
[252] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

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).

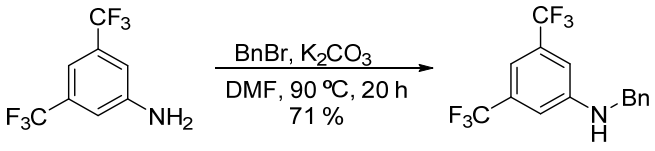
7.2.2. Preparation of *N*-alkyl amines

_N_-Methyl-3,5-bis(trifluoromethyl)aniline[253]



To a solution of 3,5-bis(trifluoromethyl)aniline (1.0 mL, 6.4 mmol, 1 equiv.) in CH_2Cl_2 (14 mL) was added trifluoroacetic anhydride (2.7 mL, 19 mmol, 3 equiv.) at 0 °C. The reaction mixture was stirred at that temperature for 20 min, then the solvent was removed under vacuum. The residue was dissolved in acetone (15 mL). To the solution, anhydrous K_2CO_3 (1.77 g, 12.8 mmol, 2 equiv.) and iodomethane (1.2 mL, 19 mmol, 3 equiv.) were added. The reaction mixture was heated to mild reflux for 2 h and then was filtered. The filtrate was concentrated under vacuum, and the resulting residue was dissolved in methanol (50 mL) and H_2O (10 mL). To the solution, K_2CO_3 (0.880 g, 6.4 mmol, 1 equiv.) was added. The reaction mixture was stirred at room temperature for 1 h. The solvents were partly evaporated, and the residue partitioned between H_2O (25 mL) and CH_2Cl_2 (30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to give the product as a yellowish oil. Yield: 1.03 g, 4.3 mmol, 85 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.77 (s, 1H), 3.89 (s, 2H), 2.48 (s, 3H), 1.47 (S, 1H).

_N_-Benzyl-3,5-bis(trifluoromethyl)aniline[253]

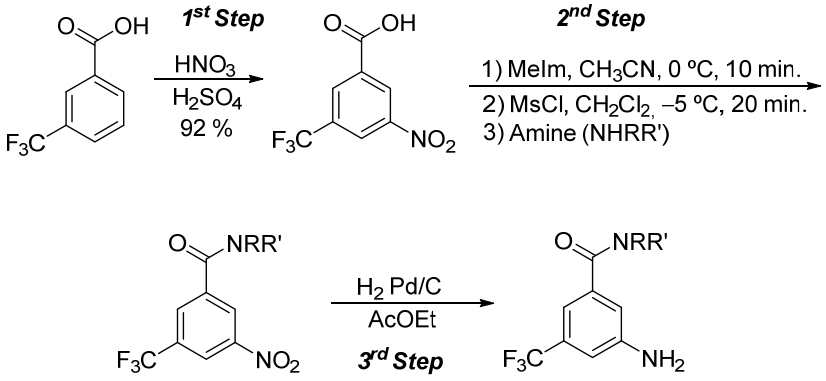


A solution of 3,5-bis(trifluoromethyl)aniline (2.4 g, 10 mmol, 1 equiv.), benzyl bromide (1.18 mL, 10 mmol, 1 equiv.) and K_2CO_3 (1.38 g, 10 mmol, 1 equiv.) in DMF (10 mL) was stirred at 90 °C. After 20 h, the mixture was cooled at room temperature and diluted with EtOAc. The organic phase was washed with brine (6 x 40 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude

[253] Koskinene, A. M. P.; Kataja, O. A. *ARKIVOK*, **2010**, *ii*, 205–223.

was purified by flash column chromatography on silica gel (hexane/EtOAc, 99:1→95:5) to afford the desired product as a yellow pale oil. Yield: 1.13 g, 7.1 mmol, 71 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 6.98 (s, 2H), 4.45 (d, *J*= 4.3 Hz, 1H), 4.38 (d, *J*= 5.3 Hz, 2H).

7.2.3. Preparation of benzamides



1st Step*: *Preparation of 3-nitro-5-(trifluoromethyl)benzoic acid[254]

To a solution of 3-trifluoromethylbenzoic acid (2.0 g, 10 mmol) in concentrated sulphuric acid (10 mL) was added nitric acid (2 mL) at 0 °C over 15 min. The mixture was stirred at 35 °C for 3 h, and slowly poured onto ice. The precipitate was filtered and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water (100 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure to give 3-nitro-5-(trifluoromethyl) benzoic acid as a white powder. Yield: 2.16 g, 9.2 mmol, 92 %. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.74 (s, 1H), 9.1 (s, 1H).

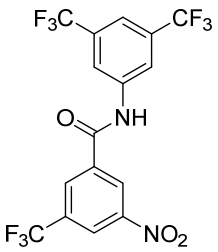
2nd Step*: *General procedure for the coupling of acids with anilines to provide benzamides[255]

1-Methylimidazole (1.2 mL, 22.5 mmol, 2.5 equiv.) was added to a slurry of the aminobenzoic acid (2.12 g, 9 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.0 mL, 13.5 mmol, 1.5 equiv.) in CH_2Cl_2 (1 mL) was added at the same temperature. After the mixture was stirred for 20 min, the corresponding amine (9 mmol, 1 equiv.) was added and the mixture was stirred at room temperature for 2 h.

[254] Shirai, J.; Morimoto, S.; Sugiyama, H.; Sakauchi, N.; Yoshikawa T. *PCT Int. Appl.*, 2008133344, 06 Nov **2008**.
[255] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

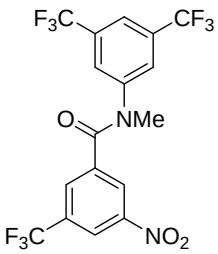
H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved in ethyl acetate (100 mL). The organic layer was washed with brine (3 × 50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether.

_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide



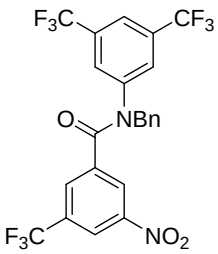
The title compound was prepared from 3,5-bis(trifluoromethyl)aniline (1.4 mL, 9 mmol) according to the General Procedure. The product was obtained as a white solid: 3.89 g, 8.73 mmol, 97 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ 9.17 (s, 1H), 8.79 (s, 1H), 8.77 (s, 1H), 8.49 (s, 2H), 7.81 (s, 1H), 7.79 (s, 1H).

_N_-(3,5-Bis(trifluoromethyl)phenyl)-_N_-methyl-3-nitro-5-(trifluoromethyl)benzamide



The title compound was prepared from *N*-methyl-3,5-bis(trifluoromethyl)aniline (2.2 g, 9 mmol) according to the General Procedure. The product was obtained as a white solid: 3.47 g, 7.56 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.40 (s, 1H), 7.89 (s, 1H), 7.80 (s, 1H), 7.62 (s, 2H), 3.64 (s, 3H).

_N_-Benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide



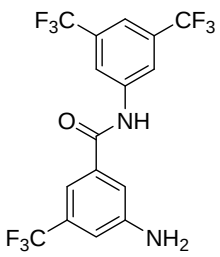
The title compound was prepared from *N*-benzyl-3,5-bis(trifluoromethyl)aniline (2.9 g, 9 mmol) according to the General Procedure. The product was obtained as a white solid: 3.09 g, 5.76 mmol, 64 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.38 (s, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.44 – 7.34 (m, 5H), 7.29 – 7.26 (m, 2H), 5.21 (s, 2H).

3rd Step*: *General procedure for the reduction of benzamides

To a solution of the corresponding aniline in EtOAc (0.4 M) under inert atmosphere, Pd/C was added (Pd 10 % in activated carbon, 10 % in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20 h. After

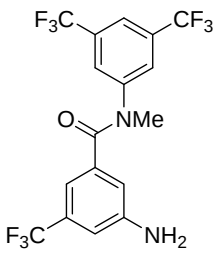
that, the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product.

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



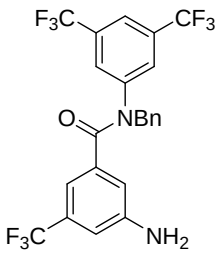
The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide (2.23 g, 5 mmol) according to the General Procedure. The product was obtained as a white solid: 1.81 g, 4.35 mmol, 87 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.44 (s, 2H), 7.81 (s, 1H), 7.72 (s, 1H), 7.71 (s, 1H), 7.48 (s, 1H), 7.44 (s, 1H), 7.15 (s, 1H).

3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-methyl-5-(trifluoromethyl)benzamide



The title compound was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-methyl-3-nitro-5-(trifluoromethyl) benzamide (2.30 g, 5 mmol) according to the General Procedure. The product was obtained as a white solid: 2.06 g, 4.8 mmol, 96 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.57 (s, 2H), 6.91 (s, 1H), 6.86 (s, 1H), 6.73 (s, 1H), 3.57 (s, 3H).

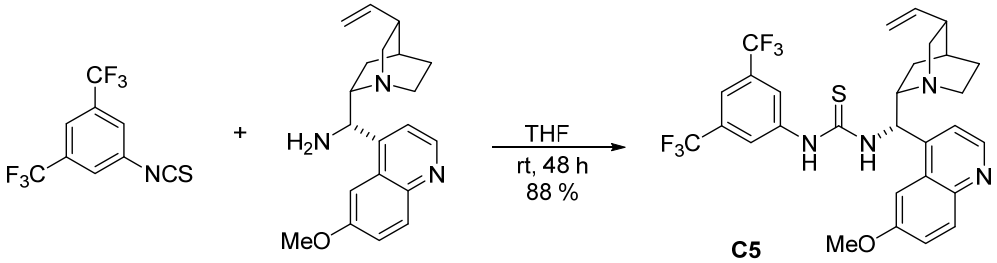
3-Amino-*N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl)benzamide



The title compound was prepared from *N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-nitro-5-(trifluoromethyl)benzamide (2.68 g, 5 mmol) according to the General Procedure. The product was obtained as a white solid: 1.77 g, 3.5 mmol, 70 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.67 (s, 1H), 7.38 – 7.33 (m, 3H), 7.29 – 7.22 (m, 2H), 6.89 (s, 1H), 6.82 (s, 1H), 6.71 (s, 1H), 5.17 (s, 2H), 3.92 (s, 2H).

7.2.4. Preparation of thiourea based catalysts C5, C8–C10

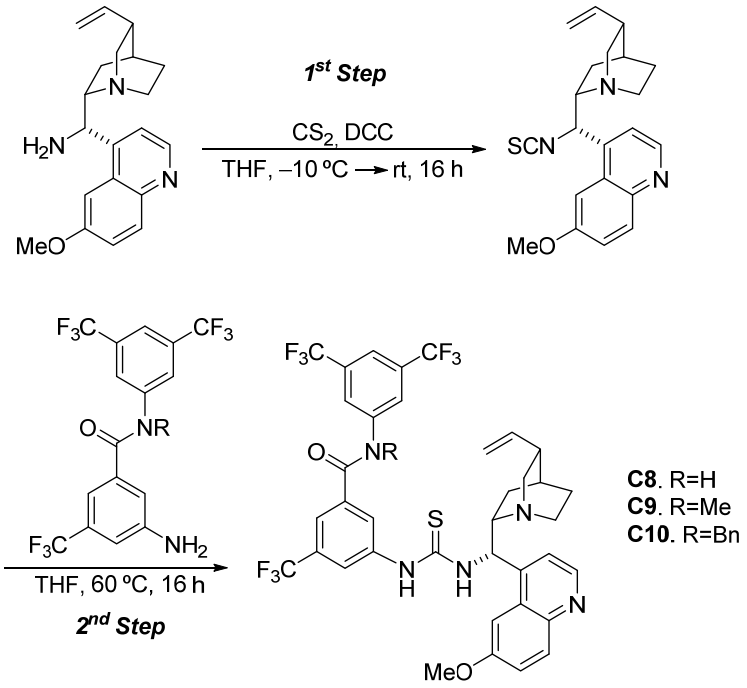
*Preparation of catalyst **C5***[256]



To a solution of 9-amino-(9-deoxy)*epi*quinine (1.6 g, 5 mmol, 1 equiv.) in dry THF (7.5 mL) at 0 °C, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.5 g, 5.5 mmol, 1.1 equiv.) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ EtOAc 80:20 → ethyl acetate). White solid, yield: 2.6 g, 4.4 mmol, 88 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (br s, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H),7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5,1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56 – 3.53 (m, 1H), 3.39 – 3.37 (m, 1H), 3.29 (dd, *J* = 13.6,9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3Hz, 1H), 2.38 – 2.35 (m, 1H), 1.71 – 1.68 (m, 2H), 1.64 – 1.61 (m,1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

[256] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

Preparation of catalysts ***C8–C10***

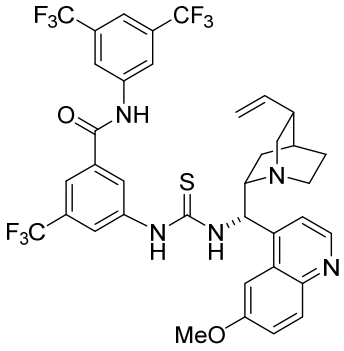


1st Step:[257] To a solution of 9-amino-(9-deoxy)*epi*quinine (0.646 g, 2 mmol, 1 equiv.) in THF (2 mL) at –10 °C, carbon disulfide (0.72 mL, 12 mmol, 6 equiv.) and *N*,*N*'-dicyclohexylcarbodiimide (0.412 g, 2 mmol, 1 equiv.) were added. The reaction mixture was stirred at the same temperature for 15 min and at room temperature for 16 h. Then, the solvent was removed under vacuum and the residue was purified by flash column chromatography on non acid silica gel (eluting with CH_2Cl_2/MeOH 99:1→95:5). The product was obtained as a yellow solid: 0.577 g, 1.58 mmol, 79 %. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.5 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 (d, *J* = 2.5 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1H), 5.36 (d, *J* = 10.1 Hz, 1H), 5.33 (s, 1H), 5.14 (dt, *J* = 8.9, 1.0 Hz, 1H), 5.11 – 5.08 (m, 1H), 4.00 (s, 3H), 3.72 (dd, *J* = 13.7, 10.2 Hz, 1H), 3.54 – 3.27 (m, 3H), 3.14 (dt, *J* = 13.7, 2.9 Hz, 1H), 2.68 – 2.59 (s, 1H), 2.08 (s, 1H), 1.95 – 1.82 (m, 3H), 1.47 (dd, *J* = 13.5, 9.2 Hz, 1H).

***2nd* Step**: The resulting isothiocyanate from the previous step (1 mmol, 1 equiv.) was added to a solution of the corresponding primary amine (1 mmol, 1 equiv.) in dry THF (2.5 mL). The reaction mixture was refluxed for 48 hours and after cooling to room temperature, it was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 98:2).

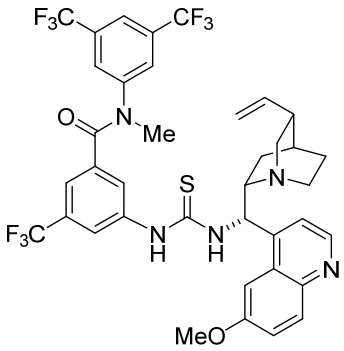
[257] Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340–1351.

_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)thioureido)-5-(trifluoromethyl)benzamide (C8)



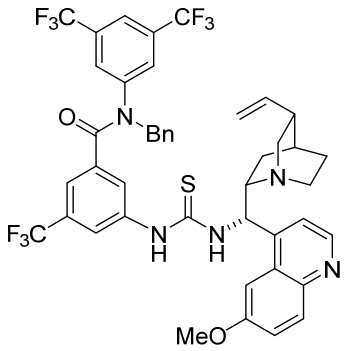
The title compound **C8** was prepared according to the General Procedure described above from 3-amino-_N_-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl) benzamide (0.416 g, 1.0 mmol). The product was obtained as a white solid: 0.476 g, 0.61 mmol, 61 %. Decomp. temp.: 139–141 °C. $[\alpha]_D^{24}$= –63.65° (_c_=0.59, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.48 (s, 1H), 8.24 (s, 2H), 8.08 (s, 1H), 7.95 (s, 2H), 7.66 (s, 1H), 7.40 (d, _J_ = 8.7 Hz, 1H), 7.22 (s, 1H), 6.35 (s, 1H), 5.72 (ddd, _J_ = 17.0, 10.2, 6.9 Hz, 1H), 5.01 (dd, _J_ = 21.1, 13.8 Hz, 2H), 4.04 (s, 3H), 3.75 (s, 1H), 3.53 (s, 1H), 3.10 (s, 1H), 2.72 (s, 2H), 2.35 (s, 1H), 1.90 – 1.48 (m, 5H), 0.90 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.3, 163.7, 159.2, 147.8, 145.4, 140.9, 139.8, 136.0, 133.6, 133.2, 132.7, 132.5, 132.1, 129.0, 126.9, 125.5, 123.5, 121.9, 121.0, 118.7, 116.0, 102.9, 61.1, 56.6, 55.6, 50.1, 43.0, 39.3, 34.4, 27.9, 27.5, 26.9, 26.1, 25.5. UPLC-DAD-QTOF: $C_{37}H_{33}N_5O_2SF_9$ $[M+H]^+$ calcd.: 782.2211, found: 782.2227.

_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)thioureido)-_N_-methyl-5-(trifluoromethyl)benzamide (C9)



The title compound **C9** was prepared according to the General Procedure described above from 3-amino-_N_-(3,5-bis(trifluoromethyl)phenyl)-_N_-methyl-5-(trifluoro methyl)benzamide (0.430 g, 1.0 mmol). The product was obtained as a white solid: 0.446 g, 0.56 mmol, 56 %. Decomp. temp.: 119–121 °C. $[\alpha]_D^{24}$= –32.03° (_c_=0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.73 (d, _J_ = 4.6 Hz, 1H), 8.00 (s, 2H), 7.95 (d, _J_ = 9.2 Hz, 1H), 7.89 (d, _J_ = 12.1 Hz, 2H), 7.81 (d, _J_ = 7.3 Hz, 2H), 7.58 (d, _J_ = 4.6 Hz, 1H), 7.43 (dd, _J_ = 9.2, 2.6 Hz, 1H), 7.34 (s, 1H), 6.03 (s, 1H), 5.81 (ddd, _J_ = 17.5, 10.3, 7.5 Hz, 1H), 5.11 – 4.85 (m, 2H), 3.96 (s, 3H), 3.43 (s, 3H), 3.37 – 3.13 (m, 4H), 2.70 (dd, _J_ = 13.7, 4.6 Hz, 2H), 2.28 (s, 1H), 1.59 (s, 3H), 1.23 (q, _J_ = 12.2, 11.7 Hz, 1H), 0.83 (d, _J_ = 9.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 179.7, 168.0, 157.1, 147.6, 145.4, 144.1, 141.7, 140.6, 136.7, 131.5, 131.2, 131.0, 130.6, 130.2, 129.1, 128.7, 128.2, 127.9, 124.7, 121.3, 119.8, 119.3, 118.7, 114.3, 102.9, 59.3, 55.5, 55.0, 27.2, 26.9, 25.3. UPLC-DAD-QTOF: $C_{38}H_{35}N_5O_2SF_9$ $[M+H]^+$ calcd.: 796.2368, found: 796.2377.

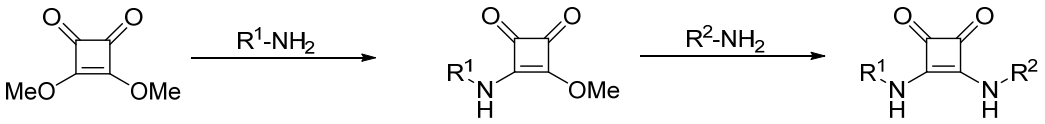
_N_-Benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-3-(3-((_S_)-(6-methoxyquinolin-4-yl) ((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)thioureido)-5-(trifluoromethyl) benzamide (C10)



The title compound **C10** was prepared according to the General Procedure described above from 3-amino-_N_-benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoro methyl)benzamide (0.506 g, 1.0 mmol). The product was obtained as white solid: 0.331 g, 0.38 mmol, 38 %. Decomp. temp.: 125–127 °C. $[\alpha]_D^{22}$= –47.50° (_c_=0.63, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.71 (dd, _J_ = 4.5, 2.0 Hz, 1H), 8.60 – 7.57 (m, 7H), 7.47 – 7.35 (m, 2H), 7.34 – 7.19 (m, 1H), 5.90 – 5.76 (m, 1H), 5.33 (s, 1H), 5.12 – 5.00 (m, 1H), 4.96 (ddt, _J_ = 10.3, 4.3, 1.5 Hz, 1H), 4.05 (s, 3H), 3.84 (s, 1H), 3.67 (s, 1H), 3.56 – 3.16 (m, 2H), 3.04 – 2.69 (m, 2H), 2.61 – 2.25 (m, 1H), 1.96 – 1.35 (m, 5H), 1.04 (ddd, _J_ = 54.7, 12.3, 6.8 Hz, 2H). ^{13}C NMR (75 MHz, Acetone) δ 182.2, 170.0, 166.1, 159.4, 149.1, 149.1, 146.4, 145.9, 143.4, 142.2, 141.9, 138.4, 138.1, 133.1, 130.1, 129.9, 129.1, 127.1, 126.8, 121.5, 116.1, 115.9, 115.2, 104.4, 104.3, 61.9, 56.8, 56.5, 54.4, 43.2, 42.9, 41.1, 40.4, 40.2, 29.7, 29.2, 28.9, 28.2, 27.1, 26.5. UPLC-DAD-QTOF: $C_{44}H_{39}N_5O_2SF_9$ $[M+H]^+$ calcd.: 872.2681, found: 872.2689.

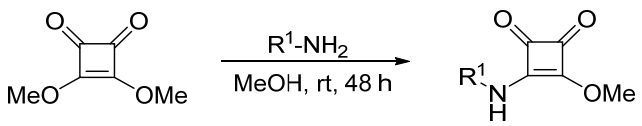
7.2.5. Preparation of squaramide based catalysts C2, C4, C6,C7, C11–C15

Squaramide-based catalysts were prepared according to the following synthetic sequence:



*7.2.5.1. Preparation of catalysts **C2**, **C4**, **C6**, **C7**, **C11** and **C12***

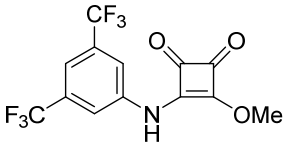
7.2.5.1.1. Preparation of squaric ester monoamides[258]



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

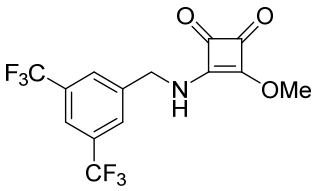
To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (280 mg, 2.0 mmol, 1 equiv.) in MeOH (20 mL) was added the corresponding amine (2.0 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vaccum to give the squaric ester monoamide.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobutane-1,2-dione[259]



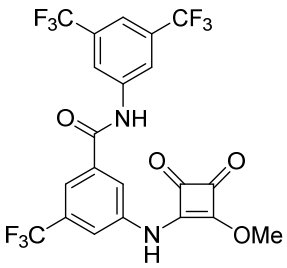
The title compound was prepared from 3,5-bis(trifuluoromethyl)aniline (0.310 g, 2.0 mmol) according to the General Procedure described above. The product was obtained as a white solid, yield: 0.461 mg, 1.36 mmol, 68 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H). All spectroscopic data were consistent with those previously reported.

3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobutane-1,2-dione[258]



The title compound was prepared from 3,5-bis(trifuluoromethyl)benzylaniline (0.486 g, 2.0 mmol) according to the General Procedure described above. The product was obtained as a white solid, yield: 0.551 mg, 1.56 mmol, 78 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 (br s, 1H), 8.09 (s, 2H), 7.94 (s, 1H), 4.78 (br s, 2H), 4.26 (s, 3H). All spectroscopic data were consistent with those previously reported.

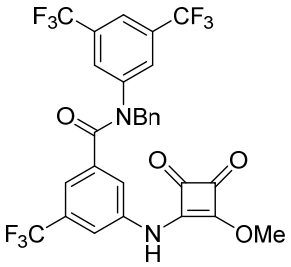
***N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobutyl)amino)-5-(trifluoromethyl)benzamide**



The title compound was prepared from 3-amino-*N*-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl) benzamide (0.832 g, 2.0 mmol) according to the General Procedure described above. The product was obtained as a white solid, yield: 0.926 mg, 1.76 mmol, 88 %. ^{1}H NMR (300 MHz, Acetone-d_6) δ 10.71 (s, 1H), 10.52 (s, 1H), 8.03 (s, 2H), 7.73 (s, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.39 (s, 1H), 3.96 (s, 3H).

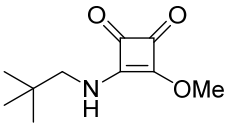
[259] Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450–5453.

_N_-Benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide



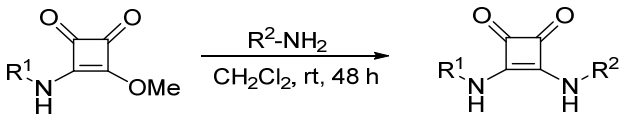
The title compound was prepared from 3-amino-_N_-benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-5-(trifluoromethyl) benzamide (1.012 g, 2.0 mmol) according to the General Procedure described above. The product was obtained as a yellow pale solid, yield: 1.023 g, 1.66 mmol, 83 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.69 (s, 1H), 7.64 (s, 1H), 7.50 (s, 1H), 7.40 – 7.19 (m, 8H), 7.16 (s, 1H), 5.17 (s, 2H), 4.48 (s, 3H).

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



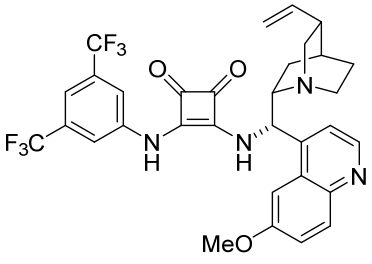
The title compound was prepared from neopentylamine (0.23 mL, 2.0 mmol) according to the General Procedure described above. The product was obtained as a white solid, yield: 0.355 mg, 1.80 mmol, 90 %. ^{1}H NMR (300 MHz, Chloroform-_d_) δ 5.94 (br s, 1H), 4.44 (s, 3H), 3.20 (d, _J_ = 6.9 Hz, 2H), 0.97 (s, 9H).

7.2.5.1.2. Coupling with squaric ester monoamide



To a suspension of the corresponding squaric ester monoamide prepared above (1.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL), the corresponding chiral Brønsted base (1.0 mmol, 1 equiv.) was added and the reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the oil residue was purified by silica flash column chromatography (eluting with CH_2Cl_2/MeOH 95:5) to afford the pure catalyst.

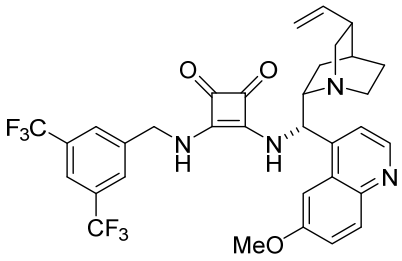
3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((_S_)-(6-methoxyquinolin-4-yl) ((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C2)[259]



The title compound **C2** was prepared from 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxy cyclobut-3-ene-1,2-dione (0.339 g, 1.0 mmol) and 9-amino-(9-deoxy)_epi_quinine (0.323 g, 1.0 mmol) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.441 g, 0.70 mmol, 70 %.

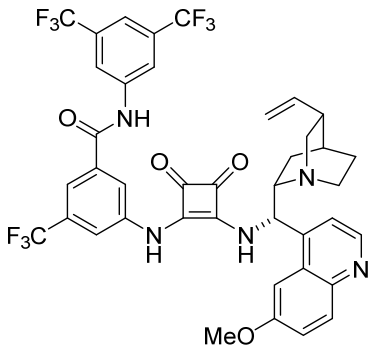
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52 – 3.42 (m, 1H), 3.30 – 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H). All spectroscopic data were consistent with those previously reported.

3-((3,5-Bis(trifluoromethyl)benzyl)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 (C11)[258]



The title compound **C11** was prepared from 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxy cyclobut-3-ene-1,2-dione (0. 353 g, 1.0 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*quinine (0.323 g, 1.0 mmol) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.413 g, 0.64 mmol, 64 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (br s, 1H), 8.04 – 7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19 – 5.73 (m, 2H), 5.13 – 4.92 (m, 2H), 3.95 (s, 3H), 3.52 – 3.42 (m, 1H), 3.30 – 3.25 (m, 1H) 2.77 – 2.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.60 – 1.47 (m, 4H), 0.66 (m, 1H). All spectroscopic data were consistent with those previously reported.

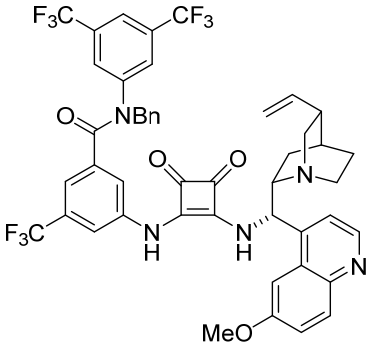
***N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,*4S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoro methyl)benzamide (C6)**



The title compound **C6** was prepared from *N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl) benzamide (0.416 g, 1.0 mmol) and 9-amino-(9-deoxy)*epi*quinine (0.323 g, 1.0 mmol) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.556 g, 0.68 mmol, 68 %. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.16 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 2H), 8.27 (s, 1H), 8.17 (s, 1H), 7.97 (t, *J* = 4.5 Hz, 3H), 7.84 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 4.6 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.22 – 5.82 (m, 2H), 5.30 – 4.81 (m, 2H), 3.96 (s, 3H), 3.56 – 3.06 (m, 3H), 2.85 – 2.55 (m, 2H), 2.28 (q, *J* = 8.0, 7.2 Hz, 1H),

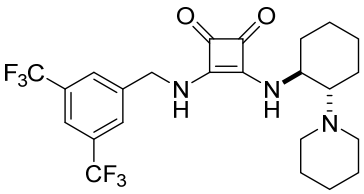
1.84 – 1.34 (m, 4H), 0.68 (s, 1H). All spectroscopic data were consistent with those previously reported.[260]

_N_-Benzyl-_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-(((_S_)-(6-methoxyquinolin-4-yl) ((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl) amino)-5-(trifluoromethyl)benzamide (C7)



The title compound **C7** was prepared from *N*-benzyl-*N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy -3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl) benzamide (0.506 g, 1.0 mmol) and 9-amino-(9-deoxy)*epi*quinine (0.323 g, 1.0 mmol) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.708 g, 0.78 mmol, 78 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.02 – 7.66 (m, 3H), 7.57 (s, 1H), 7.43 – 7.02 (m, 10H), 6.85 (s, 1H), 6.17 (s, 1H), 5.81 – 5.62 (m, 1H), 5.05 – 4.91 (m, 4H), 3.93 (s, 3H), 3.63 – 3.30 (m, 2H), 3.13 (s, 1H), 2.78 (s, 1H), 2.66 (s, 1H), 2.30 (s, 1H), 1.63 (br s, 4H), 0.84 (m, 1H). All spectroscopic data were consistent with those previously reported.[261]

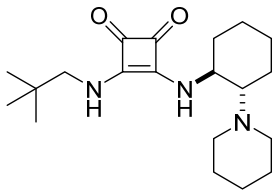
3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(((1_S_,2_S_)-2-(piperidin-1-yl)cyclohexyl) amino)cyclobut-3-ene-1,2-dione (C4)[262]



The title compound **C4** was prepared from 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxy cyclobut-3-ene-1,2-dione (0.353 g, 1.0 mmol, 1 equiv.) and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (0.273 g, 1.5 mmol, 1.5 equiv.) according to the General Procedure described above. The product was obtained as a white solid, yield: 0.363 g, 0.72 mmol, 72 %. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 3H), 7.50 (s, 1H), 4.92 (d, *J*= 8.7 Hz, 2H), 3.82 (s, 1H), 2.56 (d, *J*= 9.6 Hz, 2H), 2.22 (dd, *J*= 10.7, 5.0 Hz, 3H), 2.07 – 1.91 (m, 1H), 1.84 – 1.58 (m, 4H), 1.19 (d, *J*= 22.1 Hz, 10H). All spectroscopic data were consistent with those previously reported.

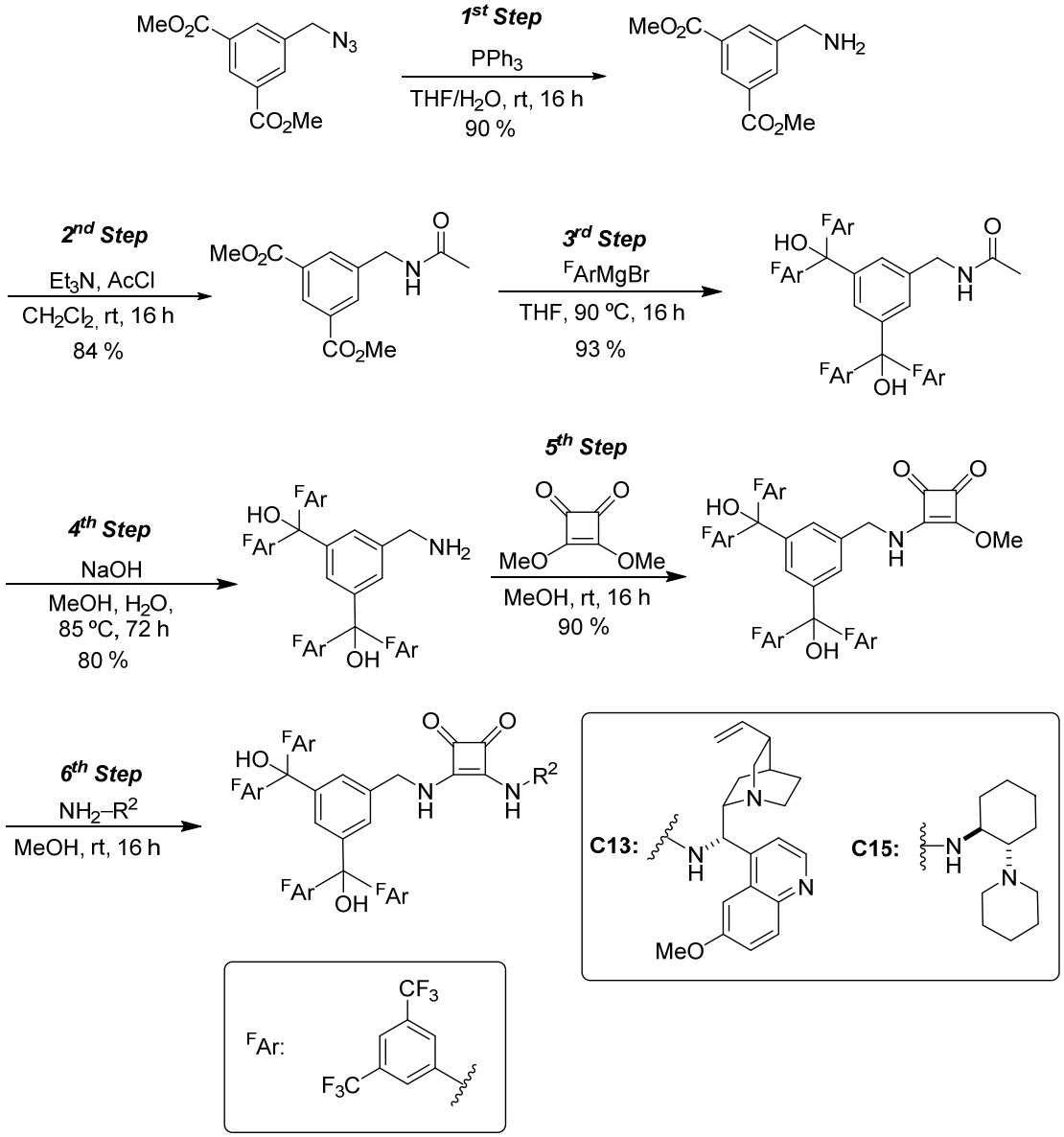
[260] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.
[261] Haizea Echave de Domingo, Ph D. Dissertation, EHU/UPV, 2017.
https://www.ehu.eus/es/web/gicas/tesiak
[262] Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed*. **2017**, *56*, 8860–8864.

3-(Neopentylamino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (C12)



The title compound **C12** was prepared from 3-methoxy-4-(neopentylamino)cyclobut-3-ene-1,2-dione (0.197 g, 1.0 mmol, 1 equiv.) and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (0.273 g, 1.5 mmol, 1.5 equiv.) according to the General Procedure describe above. The product was obtained as a white solid, yield: 0.226 g, 0.65 mmol, 65 %. Decomp. temp.: 169–171 °C. $[\alpha]_D^{22}$ = +59.1° (*c*=0.5, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (br s, 1H), 7.39 (br s, 1H), 3.81 (s, 1H), 3.70 – 3.09 (m, 8H), 2.68 – 2.56 (m, 1H), 2.32 – 2.16 (m, 2H), 2.08 – 1.77 (m, 2H), 1.75 – 1.62 (m, 2H), 1.44 – 1.12 (m, 6H), 0.88 (s, 9H). ^{13}C NMR (75 MHz, DMSO) δ 182.3, 181.8, 168.1, 68.4, 54.5, 54.4, 53.7, 49.3, 34.3, 32.4, 32.3, 26.5, 26.3, 24.8, 24.6, 24.5, 23.7. UPLC-DAD-QTOF: $C_{20}H_{34}N_3O_2$ $[M+H]^+$ calcd.: 348.2651, found: 348.2653.

*7.2.5.2. Preparation of catalysts **C13** and **C15***



1st Step:[250] To a solution of dimethyl 5-(azidomethyl) isophthalate[263] (4.16 g, 16.8 mmol, 1.0 equiv.) in THF (80.0 mL) was added water (16.0 mL) and triphenylphosphine (4.88 g, 18.4 mmol, 1.1 equiv.), and the resulting mixture was stirred at room temperature for 16 h. The solvent was removed and the crude material was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 90:10) to give the desired product as a white solid, yield: 3.37 g, 15.1 mmol, 90 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (t, *J* = 1.6 Hz, 1H), 8.20 (dd, *J* = 1.6, 0.7 Hz, 2H), 3.99 (d, *J* = 0.7 Hz, 2H), 3.95 (s, 6H).

[263] For the synthesis, see: Dimick, S. M.; Powell, S. C.; McMahon, S. A.; Moothoo, D. N.; Naismith, J. H.; Toone, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 10286–10296.

2nd Step:[264] To a solution of the previous amine (2.49 g, 11.1 mmol, 1.0 equiv.) and Et_3N (1.56 mL, 11.1 mmol, 1.0 equiv.) in CH_2Cl_2 (60.0 mL), acetyl chloride (0.81 mL, 11.7 mmol, 1.05 equiv.) was added dropwise at 0 °C. After stirring for 16 h at room temperature, the reaction mixture was washed with water (60.0 mL) and brine (60.0 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The desired product was obtained as a white solid, yield: 2.47 g, 9.3 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.18 (dd, *J* = 1.5, 0.7 Hz, 2H), 5.87 (s, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 3.99 (s, 6H), 2.11 (s, 3H).

3rd Step:[264] To a solution of the crude material of the previous reaction (2.64 g, 10.0 mmol, 1.0 equiv.) in THF (20.0 mL), a solution of 3,5-bis(trifluoromethyl)-phenyl magnesium bromide (0.5M in THF, 160.0 mL, 80.0 mmol, 8.0 equiv.) was added dropwise at 0 °C. The mixture was stirred at reflux overnight. The reaction was quenched with NH_4Cl saturated solution (20.0 mL), the solvent was evaporated under reduced pressure and diluted with water (40.0 mL). The mixture was extracted with CH_2Cl_2 (3 × 20.0 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 50:50) to give the product as a brown solid, yield: 9.8 g, 9.3 mmol, 93 %. 1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 4H), 7.67 (d, *J*= 1.6 Hz, 8H), 7.27 (d, *J*= 1.8 Hz, 2H), 6.70 (t, *J*= 1.8 Hz, 1H), 4.26 (d, *J*= 6.0 Hz, 2H), 1.88 (s, 3H).

4th Step:[264] NaOH (6.18 g, 154.4 mmol, 20.0 equiv.) was added to a solution of the amide product obtained above (8.02 g, 7.6 mmol, 1.0 equiv.) in MeOH (60.0 mL) and water (7.6 mL). The reaction mixture was heated at 85 °C and stirred for 72 h. Afterwards, it was neutralized by adding dropwise HCl 1.0 M until pH 7 and then, extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel flash column chromatography (eluting with CH_2Cl_2/MeOH 95:5) to afford the product as a brown solid, yield: 6.18 g, 7.1 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (br s, 2H), 7.83 (s, 4H), 7.60 (d, *J*= 1.8 Hz, 8H), 6.49 (s, 1H), 4.61 (br s, 2H), 4.06 (s, 2H).

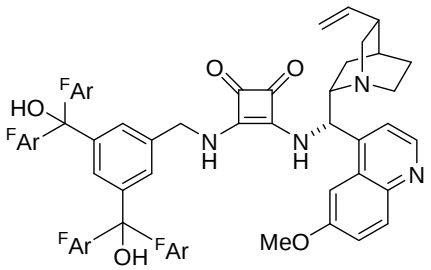
5th Step:[265] To a solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.130 g, 0.9 mmol, 0.9 equiv.) in MeOH (4.0 mL) was added the free amine product obtained above (1.01 g, 1.0 mmol, 1.0 equiv.) and the mixture was stirred at room temperature for 16h. Then, the solvent was evaporated under reduced pressure and the oily residue was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 70:30) to

[264] Adapted from: Odriozola, A.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 12758–12762.
[265] Adapted from: Ref. 258, page: 167.

afford the desired compound as a white solid, yield: 0.894 g, 0.8 mmol, 90 %. ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.92 (s, 4H), 7.77 – 7.55 (m, 8H), 7.47 (d, *J*= 8.5 Hz, 2H), 6.71 (d, *J*= 30.8 Hz, 1H), 4.66 (d, *J*= 48.8 Hz, 2H), 4.25 (d, *J*= 44.5 Hz, 3H).

6th Step:[265] To a suspension of the hemisquaramide obtained above (0.563 g, 0.5 mmol, 1.0 equiv.) in MeOH (2.0 mL), the corresponding chiral Brønsted base (0.55 mmol, 1.1 equiv.) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the oily residue was purified by silica gel flash column chromatography (eluting with CH_2Cl_2/MeOH 97:3) to give the corresponding pure catalysts **C13** or **C15**.

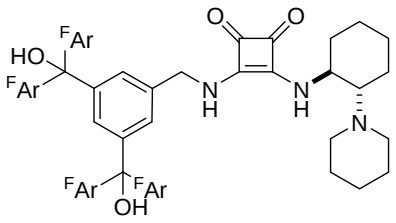
3-((3,5-Bis(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)benzyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino) cyclobut-3-ene-1,2-dione (C13)



^{F}Ar: 3,5-$(CF_3)_2C_6H_3$

The title compound **C13** was prepared from 9-amino-(9-deoxy)*epi*quinine (0.179 g, 0.55 mmol, 1.1 equiv.) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.639 g, 0.45 mmol, 90 %. Decomp. temp. 165–167 °C. $[\alpha]_D^{22}$= –10.32° (*c*=1.0, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.77 (d, *J* = 4.5 Hz, 1H), 8.01 (s, 4H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.79 (s, 1H), 7.60 (s, 8H), 7.57 (d, *J* = 18.4 Hz, 1H), 7.54 (s, 1H), 7.44 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.35 (br s, 2H), 6.04 – 5.82 (m, 1H), 5.16 – 4.87 (m, 2H), 4.72 (s, 2H), 3.93 (s, 3H), 3.54 – 3.23 (m, 4H), 3.12 (d, *J* = 24.9 Hz, 1H), 2.77 – 2.55 (m, 1H), 2.29 (s, 1H), 1.54 (d, *J* = 20.9 Hz, 3H), 0.58 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ 182.4, 181.7, 167.1, 166.4, 157.8, 148.5, 147.6, 144.8, 144.2, 142.0, 140.2, 131.4, 130.9, 130.4, 130.0, 129.5, 128.3, 127.6, 126.4, 125.9, 124.7, 121.9, 121.7, 121.0, 117.4, 114.3, 109.5, 101.5, 79.7, 58.8, 55.6, 46.5, 27.2, 26.0. UPLC-DAD-QTOF: $C_{65}H_{45}N_4O_5F_{24}[M\text{-}H]^+$ calcd.: 1417.2977, found: 1417.2979.

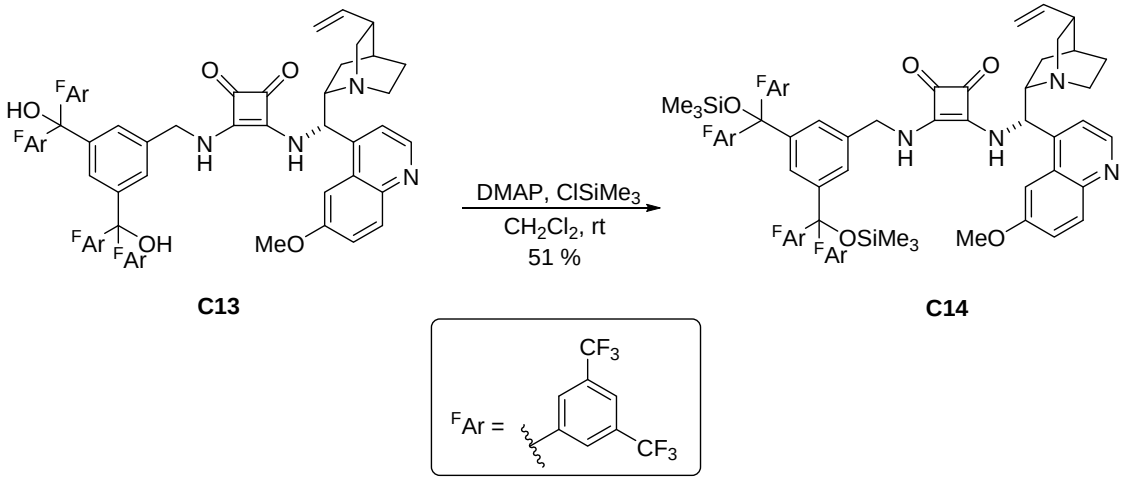
3-((3,5-Bis(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)benzyl)amino)-4-(((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (C15)



FAr: 3,5-$(CF_3)_2C_6H_3$

The title compound **C15** was prepared from (1S,2S)-2-(piperidin-1-yl)cyclohexan-1-amine (0.100 g, 0.55 mmol, 1.1 equiv.) according to the General Procedure described above. The product was obtained as a yellow solid, yield: 0.408 g, 0.32 mmol, 64 %. Decomp. temp. 149–150 °C. $[\alpha]_D^{22}$ = – 9.35° (*c*= 1.0, MeOH). ^{1}H NMR (300 MHz, Methanol-*d*$_4$) δ 7.90 (s, 4H), 7.75 – 7.65 (m, 8H), 7.63 (d, *J* = 1.6 Hz, 2H), 6.55 (t, *J* = 1.5 Hz, 1H), 4.85 (s, 2H), 4.02 (s, 1H), 2.95 (s, 2H), 2.63 (s, 2H), 2.13 – 1.26 (m, 15H). ^{13}C NMR (75 MHz, MeOD) δ 183.6, 183.5, 169.4, 169.2, 150.2, 146.9, 142.1, 132.8 (q, *J* = 33.6 Hz), 129.9, 128.9, 128.0, 127.8, 126.3, 122.8, 122.7, 119.0, 81.4, 70.0, 55.1, 50.9, 48.6, 35.7, 26.5, 26.0, 25.6, 24.7. UPLC-DAD-QTOF: $C_{56}H_{42}N_3O_4F_{24}$ $[M-H]^+$ calcd.: 1276.2792, found: 1276.2778.

*Preparation of catalyst **C14***

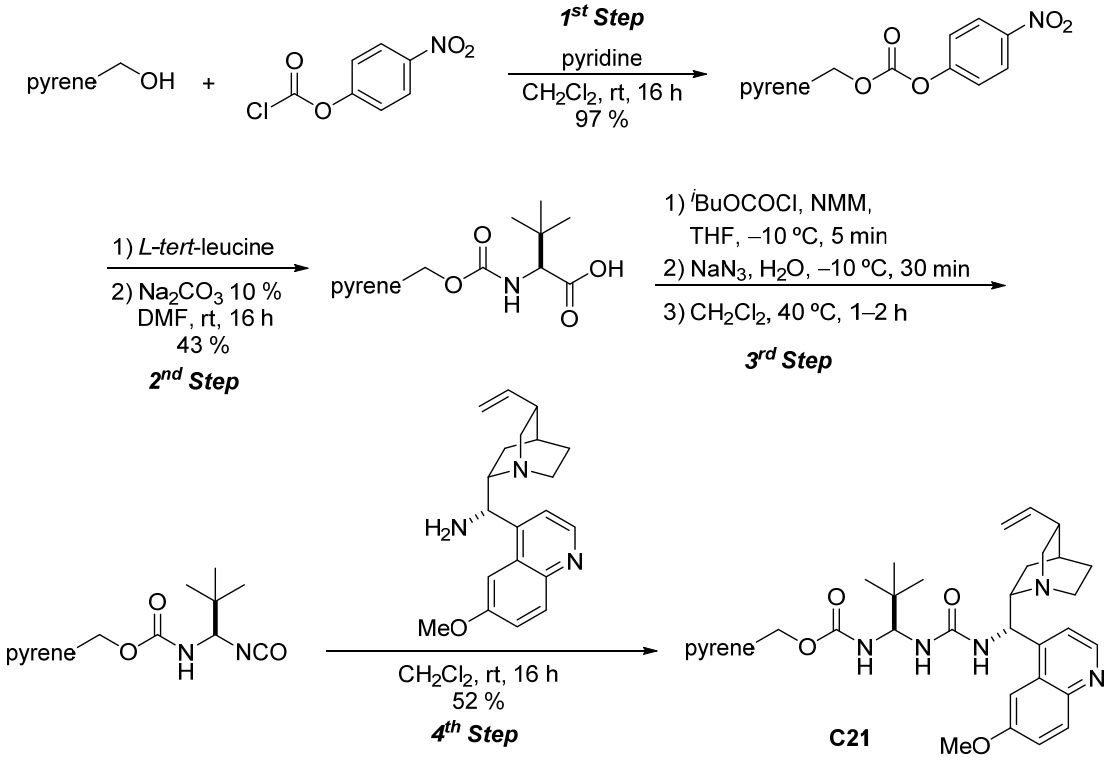


C13 **C14**

To a suspension of the previously prepared catalyst **C13** (0.160 g, 0.2 mmol, 1 equiv.) and DMAP (80.0 mg, 0.6 mmol, 3 equiv.) in CH_2Cl_2 (0.8 mL) was added dropwise chlorotrimethylsilane (80 μL, 0.6 mmol, 3 equiv.) and the reaction mixture was stirred at room temperature for 14 h. Then, additional CH2Cl2 (4 mL) was added and the mixture was washed with water (2 x 4 mL) and HCl 1M (2 x 4 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting residue was subjected to purification by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 98:2) to afford the pure catalyst **C14** as a white solid, yield: 0.159 g, 0.10 mmol, 51 %. Decomp. temp.: 128–130 °C. $[\alpha]_D^{26}$= –3.7° (*c*=0.25, CH_2Cl_2). ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.54 (d, *J* = 3.7 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.83 (s, 4H), 7.74 (s, 8H), 7.39 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.26 (s, 1H), 7.24 (s, 2H), 6.00 (br s, 2H), 5.77 (dt, *J* = 17.2, 9.9 Hz, 1H), 5.16 – 4.91 (m, 2H), 4.66 – 4.38 (m, 2H), 3.94 (s, 3H), 3.52 – 3.11 (m, 3H), 2.78 – 2.64 (m, 2H), 2.36 (s, 1H), 1.78 – 1.58 (m, 3H), 1.51 (t, *J* = 11.2 Hz, 1H), 1.38 – 1.20 (m, 1H), 0.99 – 0.70 (m, 1H), -0.31 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 183.3, 167.9, 167.3, 159.5, 148.3, 147.7, 146.0, 141.47, 140.3, 132.6 (q, *J* = 33.6 Hz), 129.0, 128.5, 128.3, 127.6, 125.4, 122.7, 121.7, 118.1, 115.6, 84.0, 56.6, 48.3, 41.3, 39.8, 30.4, 28.1, 27.9, 26.7, 1.7. UPLC-DAD-QTOF: $C_{71}H_{61}N_4O_5F_{24}Si_2$ $[M-H]^+$ calcd.: 1561.3797, found: 1561.3818.

7.2.6. Preparation of ureidopeptide-based catalyst C21[266]



1st Step: To a stirred solution of *p*-nitrophenylchloroformate (2.2 g, 11 mmol, 1.1 equiv.) in dichloromethane (13.6 mL) was added pyridine (0.9 mL, 11 mmol, 1.1 equiv.). The formed white slurry was cooled to 0 °C, and 1-pyrenemethanol (2.3 g, 10 mmol, 1 equiv.) 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 overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and subsequently washed with 1 N HCl (20 mL), water (20 mL) and brine (20 mL), dried with $MgSO_4$ and concentred under reduced pressure. The residue was obtained in 97 % yield and used in the next step

[266] Adapted from: Ref. 243, page 149.

without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 – 7.91 (m, 9H), 7.43 (dd, *J* = 38.6, 9.3 Hz, 3H), 6.05 (s, 2H).

2nd Step: To a stirred solution of the *L-tert*-leucina (0.655 g, 5 mmol, 1 equiv.) in 10 % aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0°C a solution of the crude 4-nitrophenyl carbonate derivative (1.98 g, 5 mmol, 1 equiv.) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 hour and then, allowed to warm to room temperature and subsequently stirred at the same temperature overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 80:20) to afford the *N*-protected α-amino acid as a white solid: 0.835 g, 2.14 mmol, 43 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 – 7.93 (m, 9H), 5.95 –5.76 (m, 2H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.27 (d, *J* = 9.4 Hz, 1H), 1.02 (s, 9H).

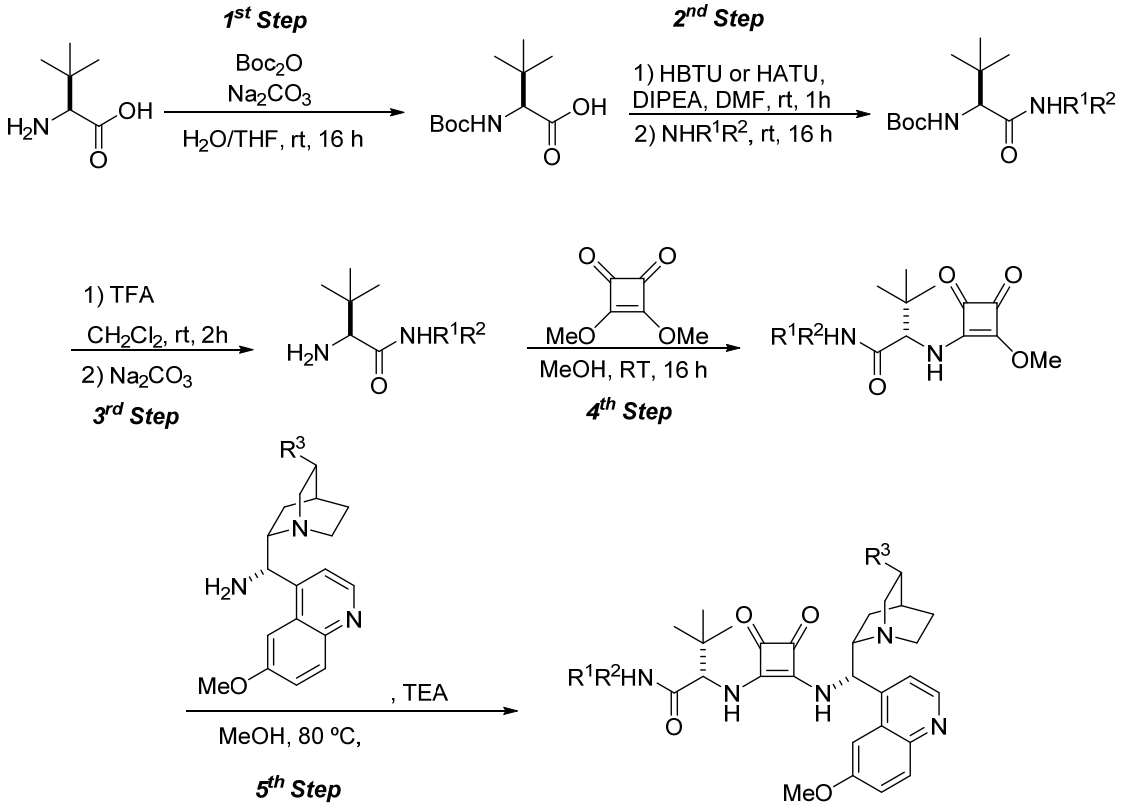
3rd Step: To a cooled solution of the *N*-protected α-amino acid (0.780 g, 2 mmol, 1 equiv.) in dry THF (20 mL), isobutyl chloroformate (0.26 mL, 2 mmol, 1 equiv.) and *N*-methylmorpholine (0.24 mL, 2 mmol, 1 equiv.) were added and the mixture was stirred at –10 °C for 5 min. Then, a suspension of NaN_3 (0.192 g, 3 mmol, 1.5 equiv.) in H_2O (1.5 mL) was added and the reaction mixture was stirred at the same temperature. After 30 min, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated under vaccum 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 for 1–2 hours. The reaction was monitored by IR analysis until disappearance of the isocyanate band (~2250 cm^{-1}).

4th Step: After completion of the reaction described in 3rd step, the 9-amino-(9-deoxy)*epi*quinine (0.492 g, 1.4 mmol, 0.7 equiv.) was added to the reaction mixture, which was then stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluting with CH_2Cl_2/MeOH 98:2) to afford the pure catalyst **C21** as a white solid, yield: 0.740 g, 1.04 mmol, 52 %. Decomp. temp.: 160–162 °C. $[\alpha]_D^{25}$= +0.294° (*c*=1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.9 Hz, 1H), 8.29 (d, *J* = 8.9 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 2H), 8.15 (dd, *J* = 7.9, 3.7 Hz, 2H), 8.09 (d, *J* = 6.1 Hz, 2H), 8.06 – 7.99 (m, 2H), 7.76 (s, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.23 (d, *J* = 4.4 Hz, 1H), 5.82 (s, 3H), 5.14 – 4.94 (m, 4H), 4.79 (s, 1H), 3.99 (s, 3H), 3.37 – 2.94 (m, 2H), 2.91 – 2.74 (m, 1H), 2.73 – 2.51 (m, 1H), 2.36 – 2.16 (m,

1H), 1.73 – 1.33 (m, 5H), 1.28 (s, 1H), 0.91 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 158.4, 157.0, 148.0, 145.3, 132.2, 131.7, 131.2, 130.1, 129.0, 128.7, 128.4, 127.9, 126.7, 126.1, 126.0, 125.2, 125.1, 123.8, 122.5, 119.2, 115.9, 102.7, 67.5, 65.6, 60.5, 56.4, 55.9, 41.3, 36.0, 30.3, 27.4, 26.1. UPLC-DAD-QTOF: $C_{43}H_{45}N_5O_4$ $[M+H]^+$ calcd.: 710.3707, found: 713.3706.

7.2.7. Preparation of amino acid-squaramide based catalysts C25–C35

*7.2.7.1. Preparation of catalysts **C25, C32–C35** (only one amino acid in their structure).*



C25, R^1= 3,5-$(CF_3)_2C_6H_3CH_2$–; R^2 = H; R^3 = CH_2CH–
C32, R^1= ^{t}Bu; R^2 = H; R^3 = CH_2CH–
C33, R^1= R^2 = Bn; R^3 = CH_2CH–
C34, R^1, R^2 = –$(CH_2)_5$–; R^3 = CH_2CH–
C35, R^1, R^2 = –$(CH_2)_5$–; R^3 = CH_3CH_2–

1st Step:[267] Na_2CO_3 (4.24 g, 40 mmol, 2 equiv.) and Boc_2O (6.55 g, 30 mmol, 1.5 equiv.) were added to a suspension of *L-tert*-leucine (2.62 g, 20 mmol, 1 equiv.) in H_2O (40 mL) and THF (10 mL) at 0 °C. After the reaction mixture had been stirred at room

[267] Adapted from: Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16*, 13068–13071.

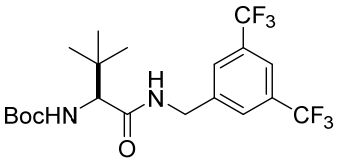
temperature for 16 h, it was carefully neutralized with HCl (10 %) until pH 2 had been reached. The mixture was then extracted with EtOAc (50 mL x 3), washed with brine, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude Boc-protected amino acid intermediate as a white solid, which was used in the next step without further purification. Yield: 4.59 g, 19.8 mmol, 99 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 8.9 Hz, 1H), 4.16 (d, J = 8.5 Hz, 1H), 1.47 (s, 9H), 1.05 (s, 9H).

2nd Step:[267]

General Method A: The crude intermediate obtained in the previous step (1.39 g, 6 mmol, 1 equiv.) was dissolved in dry DMF (12 mL). To this solution was added diisopropylethylamine (2.1 mL, 12 mmol, 2 equiv.) and HBTU (3.4 g, 9 mmol, 1.5 equiv.). After stirring at room temperature for 1 h, the corresponding amine (6.6 mmol, 1.1 equiv.) was added, and the reaction was allowed to stir for 16 h. After that, the reaction was quenched by the addition of 1 N HCl and extracted with EtOAc (3 x 20 mL). The organic phase was washed with 1 N HCl, brine and dried over $MgSO_4$. The solution was concentrated and the resulting residue was purified by silica gel flash chromatography to yield the corresponding *N*-Boc-aminoamide.

General Method B: The crude intermediate obtained in the previous step (1.39 g, 6 mmol, 1.2 equiv.) was dissolved in dry DMF (7 mL). To this solution was added diisopropylethylamine (6.2 mL, 36 mmol, 7.2 equiv.) and HATU (2.0 g, 5.5 mmol, 1.1 equiv.). After stirring at room temperature for 1 h, the corresponding amine (5 mmol, 1 equiv.) was added, and the reaction mixture was allowed to stir for 16 h. Then, the reaction was quenched by the addition of H_2O/EtOAc 50:50 and extracted with EtOAc (3 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the corresponding *N*-Boc-aminoamide.

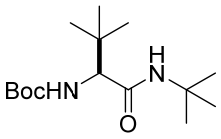
tert-Butyl (_S_)-(1-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-oxopentan-3-yl) carbamate



The title compound was prepared using 3,5-bis(trifluoromethyl)benzylamine (1.39 g, 6.6 mmol, 1.1 equiv.) following the General Method A described above. The product was obtained as a white solid, yield: 2.32 g, 5.1 mmol, 85 %. . ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.75 (s, 2H), 6.31 (t, 1H), 5.17 (d, J

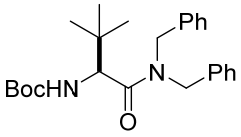
= 5.6 Hz, 1H), 4.57 (d, J = 6.1 Hz, 1H), 3.84 (d, J = 8.9 Hz, 2H), 1.42 (s, 9H), 1.02 (s, 9H). All spectroscopic data were consistent with those previously reported.[268]

tert-Butyl (_S_)-(1-(_tert_-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



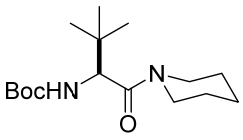
The title compound was preparated using *tert*-butylamine (0.52 mL, 5 mmol, 1 equiv.) following the General Method B described above. The product was obtained as a white solid, yield: 1.35 g, 4.7 mmol, 95 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (br s, 1H), 3.65 (d, *J* = 9.4 Hz, 1H), 1.45 (s, 9H), 1.36 (s, 9H), 0.99 (s, 9H).

tert-Butyl (_S_)-(1-(dibenzylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



The title compound was preparated using dibenzylamine (0.96 mL, 5 mmol, 1 equiv.) following the General Method B described above. The product was obtained as a red oil, yield: 1.02 g, 2.5 mmol, 50 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 5H), 7.39 – 7.31 (m, 3H), 7.26 – 7.15 (m, 2H), 5.17 (d, *J* = 14.7 Hz, 1H), 4.88 (d, *J* = 16.2 Hz, 1H), 4.31 (d, *J* = 15.7 Hz, 1H), 3.97 (d, *J* = 14.7 Hz, 1H), 1.45 (s, 9H), 1.01 (s, 9H).

tert-Butyl (_S_)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate

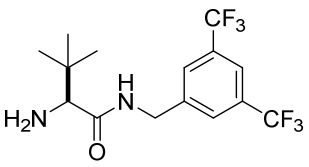


The title compound was preparated using piperidine (0.65 mL, 6.6 mmol, 1.1 equiv.) following the General Method A described above. The product was obtained as a white solid, yield: 1.54 g, 5.2 mmol, 86 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (d, *J* = 9.3 Hz, 1H), 4.56 (d, *J* = 9.7 Hz, 1H), 3.71 – 3.59 (m, 2H), 3.58 – 3.47 (m, 2H), 1.70 – 1.56 (m, 6H), 1.45 (s, 9H), 1.00 (s, 9H). All spectroscopic data were consistent with those previously reported.[267]

3^rd^ Step (General Procedure): To a stirred solution of the corresponding *N*-Boc-aminoamide (1 equiv.) in CH_2Cl_2 (1mL / mmol) at 0 °C, TFA (2 mL/mmol) was added dropwise. The mixture was warmed up to room temperature and stirred 2 h. Then, the solvents were removed and the resulting residue was cooled down to 0 °C and basified with a saturated Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with saturated $NaHCO_3$ solution (x2) and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the corresponding free amine, which was used in the next step without further purification.

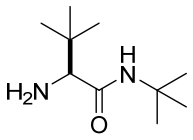
[268] Manna, M. S.; Mukherjee, S. *Chem. Sci*. **2014,** *5*, 1627–1633.

(*S*)-2-Amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3,3-dimethylbutanamide



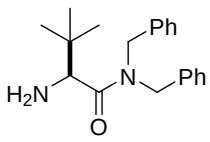
The title compound was prepared following to the General Procedure described above starting from *tert*-butyl (*S*)-(1-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-oxo penta -3-yl)carbamate (2.3 g, 5 mmol, 1 equiv.). The reaction was followed by TLC and it was finished in 2 h. The product was obtained as a white solid, yield: 1.69 g, 4.75 mmol, 95 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 (s, 2H), 7.56 (br s, 1H), 4.59 (dd, *J* = 15.4, 6.3 Hz, 1H), 4.49 (dd, *J* = 15.4, 6.3 Hz, 1H), 3.22 (s, 1H), 1.02 (s, 9H). All spectroscopic data were consistent with those previously reported.[268]

(*S*)-2-Amino-*N*-(*tert*-butyl)-3,3-dimethylbutanamide



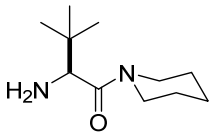
The title compound was prepared following to the General Procedure described above starting from *tert*-butyl (*S*)-(1-(*tert*-butylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (1.35 g, 4.7 mmol, 1 equiv.). The reaction was followed by TLC and it was finished in 3 h. The product was obtained as a white solid, yield: 0.54 g, 2.9 mmol, 61 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 – 3.63 (m, 1H), 1.35 (s, 9H), 0.97 (s, 9H).

(*S*)-2-Amino-*N*,*N*-dibenzyl-3,3-dimethylbutanamide



The title compound was prepared following to the General Procedure described above starting from *tert*-butyl (*S*)-(1-(dibenzylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (1.02 g, 2.5 mmol, 1 equiv.). The product was obtained as an orange oil, yield: 0.46 g, 1.5 mmol, 61 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 8H), 7.23 – 7.18 (m, 2H), 3.85 (s, 2H), 3.51 (s, 1H), 2.97 (s, 2H), 1.03 (s, 9H).

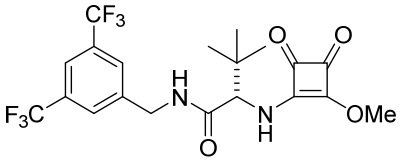
(*S*)-2-Amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one



The title compound was prepared following to the General Procedure described above starting from *tert*-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate (0.89 g, 3 mmol, 1 equiv.). The reaction was followed by TLC and it was finished in 3 h. The product was obtained as a white solid, yield: 0.429 g, 2.16 mmol, 72 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 – 3.40 (m, 5H), 1.76 – 1.51 (m, 6H), 1.00 (s, 9H). All spectroscopic data were consistent with those previously reported.[267]

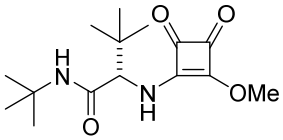
4th Step (General Procedure): To a stirred solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (0.9 equiv.) in MeOH (2 mL/mmol) the corresponding amine (1 equiv.) was added. The reaction mixture was stirred at room temperature for 48 h. The mixture was then filtered in the cases when a precipitate was formed. Otherwise, the solvent was evaporated under reduced pressure and the crude was purified by silica gel flash column chromatography.

(*S*)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl) amino)-3,3-dimethylbutanamide



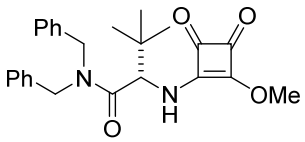
The title compound was prepared following the General Procedure described before starting from (*S*)-2-amino-*N*-(3,5-bis(trifluoromethyl)benzyl)-3,3-dimethylbutanamide (1.610 g, 4.52 mmol, 1 equiv.). The crude was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 80:20) to afford the product as a white foam, yield: 1.36 g, 2.91 mmol, 64 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 2H), 7.77 (s, 1H), 6.26 (d, J = 30.2 Hz, 1H), 4.82 – 4.60 (m, 2H), 4.52 (d, J = 5.9 Hz, 1H), 4.40 (s, 3H), 1.57 (s, 1H), 1.02 (s, 9H).

(*S*)-*N*-(*tert*-Butyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl butanamide



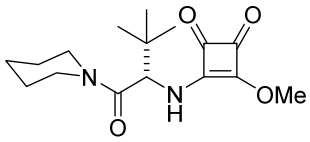
The title compound was prepared following the General Procedure described before starting from (*S*)-2-amino-*N*-(*tert*-butyl)-3,3-dimethylbutanamide (0.54 g, 2.9 mmol, 1 equiv.). The crude was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 80:20) to afford the product as a yellow oil, yield: 0.454 g, 1.5 mmol, 59 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 3H), 4.31 (d, *J* = 9.6 Hz, 1H), 1.39 (s, 9H), 1.03 (s, 9H).

(*S*)-*N*,*N*-Dibenzyl-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl butanamide



The title compound was prepared following the General Procedure described before starting from (*S*)-2-amino-*N*,*N*-dibenzyl-3,3-dimethylbutanamide (0.465 g, 1.5 mmol, 1 equiv.). The crude was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 80:20) to afford the product as a yellow oil, yield: 0.345 g, 1.1 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 7H), 7.27 – 7.15 (m, 3H), 4.30 (s, 3H), 3.10 (s, 4H), 1.04 (s, 9H).

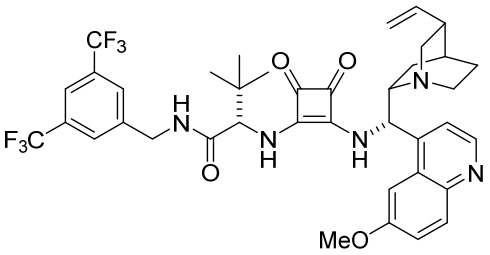
(*S*)-3-((3,3-Dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione



The title compound was prepared following the General Procedure described before starting from (*S*)-2-amino-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one (0.297 g, 1.5 mmol, 1 equiv.). The product was isolated by filtration as a white solid, yield: 0.453 g, 1.47 mmol, 98 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 1H), 4.41 (s, 3H), 3.73 – 3.54 (m, 4H), 1.75 – 1.70 (m, 6H), 1.03 (s, 9H).

5th Step (General Procedure): To a suspension of the hemisquaramide obtained above (1 equiv.) in MeOH (2.0 mL/mmol), the corresponding chiral Brønsted base (1 equiv.) and Et_3N (1 equiv.) were added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the oily residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH 98:2) to give the corresponding pure catalysts **C25** and **C32**–**C35**.

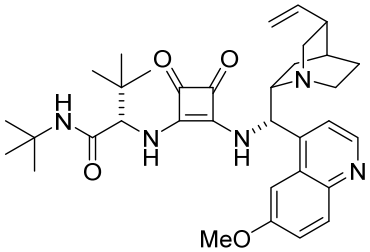
(S)-*N*-(3,5-Bis(trifluoromethyl)benzyl)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4S,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (C25)



The title compound **C25** was obtained following the General Procedure described above starting from the previously prepared compound (S)-*N*-(3,5-bis(trifluoro methyl)benzyl)-2-((2-methoxy-3,4-dioxocyclo but-1-en-1-yl)amino)-3,3-dimethylbutanamide (1.4 g, 3 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*quinine (1.1 g, 3 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 1.5 g, 2.04 mmol, 68 %. Decomp. temp.: 169–171 °C. $[\alpha]_D^{24}$ = −104.3° (*c*=1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.65 (d, *J* = 4.2 Hz, 1H), 8.01 – 7.87 (m, 4H), 7.84 (s, 1H), 7.58 (d, *J* = 4.4 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.30 – 6.15 (m, 1H), 6.02 – 5.85 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.78 – 4.57 (m, 2H), 4.38 (d, *J* = 15.3 Hz, 1H), 3.98 (s, 3H), 3.69 – 3.38 (m, 2H), 3.31 – 3.11 (m, 1H), 2.87 – 2.55 (m, 2H), 2.31 (s, 1H), 1.70 – 1.45 (m, 5H), 0.96 (s, 9H), 0.86 – 0.69 (m, 2H). ^{13}C NMR (75 MHz, , Acetone) δ 183.9, 183.5, 171.2, 168.6, 167.9, 159.5, 148.6, 146.0, 144.9, 143.6, 143.2, 132.7, 132.0 (q, *J* = 33.1 Hz), 129.4, 128.9, 124.4 (q, *J* = 272.1 Hz), 123.0, 121.6, 120.4, 114.6, 102.5, 65.0, 60.7, 57.1, 56.4,

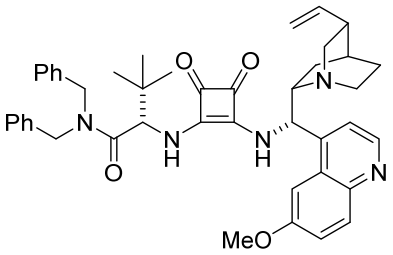
54.8, 42.8, 41.5, 41.0, 36.1, 29.0, 28.7, 27.3, 26.6. UPLC-DAD-QTOF: $C_{39}H_{42}N_5O_4F_6$ $[M+H]^+$ calcd.: 758.3141, found: 758.3138.

(*S*)-*N*-(*tert*-Butyl)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinyl quinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethyl butanamide (C32)



The title compound **C32** was obtained following the General Procedure described above starting from the previously prepared compound (*S*)-*N*-(*tert*-butyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl) amino)-3,3-dimethylbutanamide (0.454 g, 1.5 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*quinine (0.484 g, 1.5 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 0.485 g, 0.82 mmol, 55 %. Decomp. temp.: 150–152 °C. $[\alpha]_D^{24} = -78.12°$ (*c*=1, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.72 (d, *J* = 4.3 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 4.5 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.33 (s, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 5.98 (dd, *J* = 17.2, 9.4 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 4.40 (s, 1H), 4.03 (s, 3H), 3.75 – 3.44 (m, 2H), 3.25 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.88 – 2.64 (m, 2H), 2.40 – 2.26 (m, 1H), 1.68 – 1.49 (m, 5H), 1.24 (s, 9H), 0.99 (s, 9H), 0.83 – 0.66 (m, 2H). ^{13}C NMR (75 MHz, Acetone) δ 184.8, 183.7, 170.5, 168.9, 160.0, 149.2, 146.5, 145.4, 143.8, 133.3, 129.5, 123.5, 121.0, 115.2, 103.1, 65.7, 61.3, 57.7, 57.1, 52.5, 42.0, 41.6, 36.6, 29.5, 29.4, 29.2, 28.0. UPLC-DAD-QTOF: $C_{34}H_{46}N_5O_4$ $[M+H]^+$ calcd.: 588.3550, found: 588.3548.

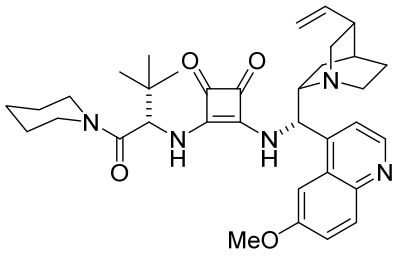
(*S*)-*N*,*N*-Dibenzyl-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5R)-5-vinylquinuclidin -2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (C33)



The title compound **C33** was obtained following the General Procedure described above starting from the previously prepared compound (*S*)-*N*,*N*-dibenzyl-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (0.170 g, 0.4 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*quinine (0.129 g, 0.4 mmol, 1 equiv.). The product was obtained as a brown foam, yield: 0.18 g, 0.25 mmol, 63 %. $[\alpha]_D^{24} = -12.16°$ (*c*=0.41, CH_2Cl_2). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.80 (d, *J* = 3.9 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.89 (d, *J* = 2.1 Hz, 1H), 7.62 (d, *J* = 4.2 Hz, 1H), 7.58 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.26 – 7.05 (m, 6H), 7.00 – 6.90 (m, 2H), 6.89 – 6.77 (m, 3H), 6.24 (d, *J* = 9.1 Hz, 1H), 6.01 (ddd, *J* = 17.5, 10.2, 7.6 Hz, 1H), 5.20 – 5.03 (m, 4H), 4.92 (d, *J* = 17.3 Hz, 2H), 4.38 (d, *J* = 17.3 Hz, 1H), 4.02 (s,

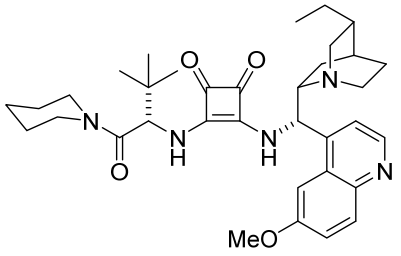
3H), 3.91 (d, *J* = 19.0 Hz, 1H), 3.75 – 3.51 (m, 2H), 3.04 – 2.75 (m, 3H), 2.55 – 2.44 (m, 1H), 1.83 – 1.61 (m, 5H), 1.44 – 1.17 (m, 1H), 1.05 (s, 9H), 0.82 –0.71 (m, 1H). ^{13}C NMR (75 MHz, Acetone) δ 184.8, 184.5, 169.5, 167.9, 160.0, 149.1, 146.5, 145.0, 143.0, 137.8, 133.5, 133.4, 133.2, 130.2, 130.0, 129.9, 12.9, 129.5, 129.4, 128.8, 128.6, 123.6, 121.4, 115.6, 103.3, 61.1, 57.1, 54.9, 53.2, 42.2, 40.9, 39.4, 29.2, 28.6, 27.4, 27.3. UPLC-DAD-QTOF: $C_{44}H_{50}N_5O_4$ $[M+H]^+$ calcd.: 712.3863, found: 712.3875.

3-(((*S*)-3,3-Dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-4-(((*S*)-(6-methoxy quinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C34)



The title compound **C34** was obtained following the general procedure describe above starting from the previously prepared compound (*S*)-3-((3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl) amino)-4-methoxycyclobut-3-ene-1,2-dione (0.419 g, 1.36 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*quinine (0.439 g, 1.36 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 0.530 g, 0.88 mmol, 65 %. Decomp. temp.: 157–159 °C. $[\alpha]_D^{24}$ = –87.72° (*c*=0.41, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.70 (d, *J* = 4.5 Hz, 1H), 7.98 (s, 1H), 7.96 (d, *J* = 5.6 Hz, 1H), 7.77 (br s, 1H), 7.58 (d, *J* = 4.6 Hz, 1H), 7.40 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.24 (br s, 1H), 5.95 (ddd, *J* = 17.7, 10.2, 7.9 Hz, 1H), 5.39 – 5.24 (m, 1H), 5.04 (dt, *J* = 17.1, 1.5 Hz, 1H), 4.96 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.03 (s, 3H), 3.54 (dtq, *J* = 20.9, 10.9, 5.5, 4.5 Hz, 5H), 3.40 – 3.22 (m, 2H), 2.87 – 2.77 (m, 1H), 2.73 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.35 (t, *J* = 10.4 Hz, 1H), 1.81 – 1.25 (m, 11H), 0.94 (s, 9H), 0.84 – 0.72 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 182.6, 169.7, 168.4, 167.1, 159.6, 148.4, 145.5, 145.0, 141.8, 132.6, 128.2, 123.6, 120.0, 115.4, 101.0, 61.7, 58.9, 56.7, 56.5, 53.9, 48.5, 43.7, 41.5, 40.0, 36.4, 28.3, 28.1, 26.8, 26.5, 26.2, 24.9. UPLC-DAD-QTOF: $C_{35}H_{46}N_5O_4$ $[M+H]^+$ calcd.: 600.3550, found: 600.3545.

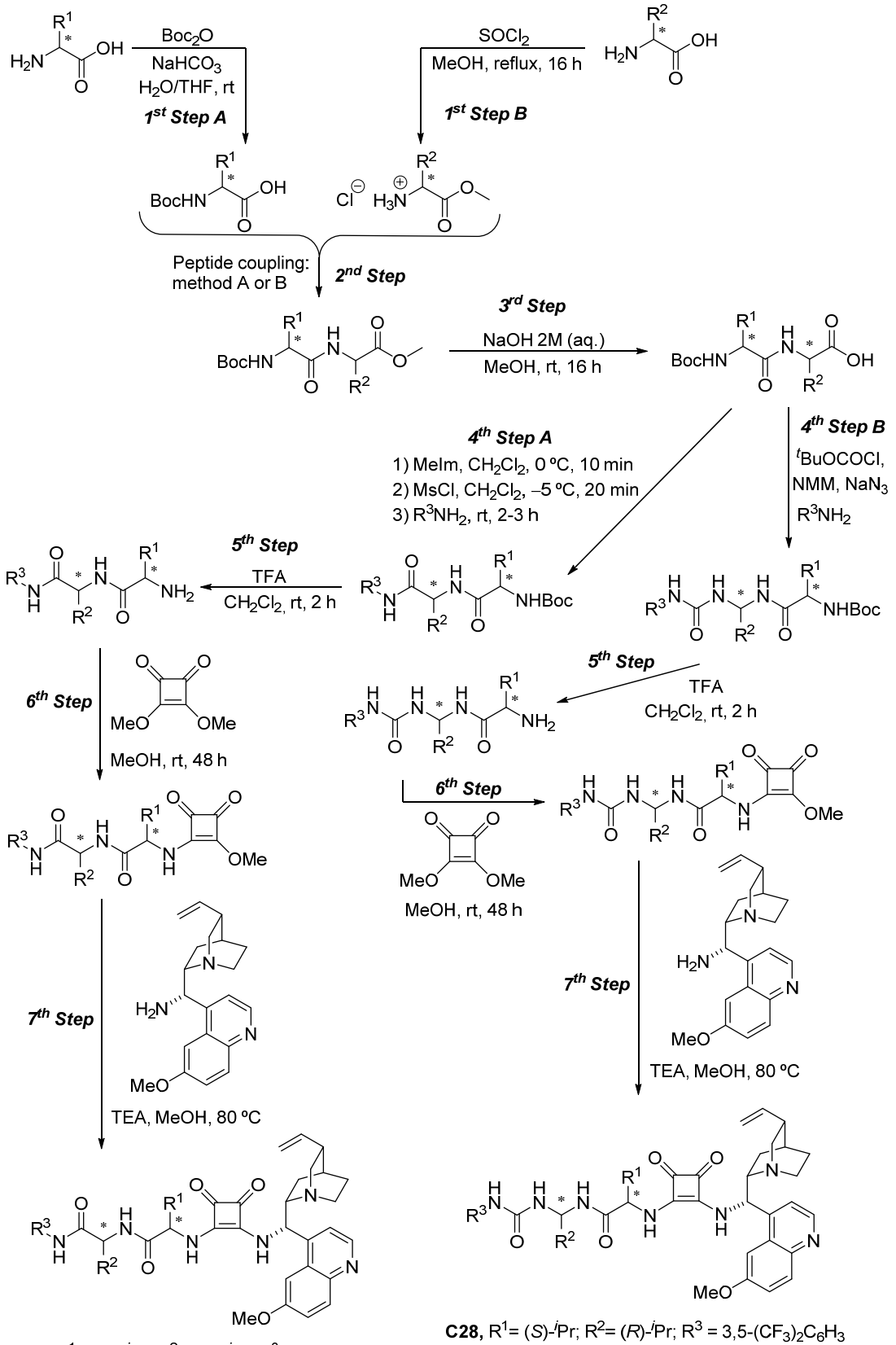
3-(((*S*)-3,3-Dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)amino)-4-(((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C35)



The title compound **C35** was obtained following the General Procedure described above starting from the previously prepared compound (*S*)-3-((3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl) amino)-4-methoxycyclobut-3-ene-1,2-dione (0.242 g,

0.78 mmol, 1 equiv.) and 9-amino-(9-deoxy)*epi*hydroquinine (0.253 g, 0.78 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 0.272 g, 0.45 mmol, 58 %. Decomp. temp.: 140–142 °C. $[\alpha]_D^{24}$ = −88.33° (*c*=0.71, CH_2Cl_2). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.76 (d, *J* = 4.7 Hz, 1H), 7.99 (d, *J* = 9.3 Hz, 1H), 7.86 (d, *J* = 2.6 Hz, 1H), 7.59 (d, *J* = 4.7 Hz, 1H), 7.48 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.26 (d, *J* = 11.0 Hz, 1H), 5.22 (s, 1H), 4.01 (s, 3H), 3.77 – 3.40 (m, 6H), 3.39 – 3.36 (m, 1H), 2.90 – 2.76 (m, 1H), 2.68 – 2.58 (m, 1H), 1.74 – 1.54 (m, 9H), 1.53 – 1.39 (m, 5H), 1.36 – 1.24 (m, 1H), 1.05 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.77 – 0-75 (m, 1H). ^{13}C NMR (75 MHz, Acetone) δ 184.8, 184.0, 170.0, 168.9, 168.5, 160.0, 149.1, 146.6, 145.7, 133.3, 129.4, 123.6, 121.0, 111.5, 103.0, 61.2, 59.3, 57.0, 55.0, 48.8, 43.8, 42.2, 38.9, 37.1, 28.7, 27.8, 27.2, 27.1, 26.9, 25.6, 13.0. UPLC-DAD-QTOF: $C_{35}H_{48}N_5O_4$ $[M+H]^+$ calcd.: 602.3706, found: 602.3693.

7.2.7.2. *Preparation of catalysts* ***C26–C30*** *(two amino acids in their structure)*



C26, R^1 = (*R*)-^{i}Pr; R^2 = (*S*)-^{i}Pr; R^3 = 3,5-$(CF_3)_2C_6H_3$
C27, R^1 = (*R*)-^{i}Pr; R^2 = (*R*)-^{i}Pr; R^3 = 3,5-$(CF_3)_2C_6H_3$

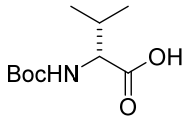
C28, R^1= (*S*)-^{i}Pr; R^2= (*R*)-^{i}Pr; R^3 = 3,5-$(CF_3)_2C_6H_3$
C29, R^1= (*S*)-^{i}Pr; R^2= (*R*)-^{t}Bu; R^3 = 3,5-$(CF_3)_2C_6H_3$
C30, R^1= (*S*)-^{t}Bu; R^2= (*R*)-^{t}Bu; R^3 = 3,5-$(CF_3)_2C_6H_3$

***1st Step A*: Synthesis of Boc-protected amino acids**[267]

General procedure:

Na_2CO_3 (2 equiv.) and Boc_2O (1.5 equiv.) were added to a solution of the corresponding amino acid (1 equiv.) in H_2O (2 mL/ mmol) and THF (0.5 mL/mmol) at 0 °C. After the reaction mixture had been stirred at room temperature for 16 h, it was carefully neutralized with HCl (10 %) until pH 2 had been reached. The mixture was then extracted with EtOAc (x3), washed with brine (x4), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to afford the crude Boc-protected amino acid intermediate that was used in the next step without further purification.

(*tert*-Butoxycarbonyl)-*D*-valine



The title compound was obtained following the General Procedure described above starting from *D*-valina (4.7 g, 40 mmol, 1 equiv.). The product was obtained as a white solid, yield: 7.73 g, 35.6 mmol, 89 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (d, *J* = 8.9 Hz, 1H), 4.23 (s, 1H), 2.20 (q, *J* = 6.4 Hz, 1H), 1.45 (s, 9H), 0.97 (dd, *J* = 19.2, 6.9 Hz, 6H). All spectroscopic data were coincident with those previously reported.[269]

(*tert*-Butoxycarbonyl)-*L*-valine was commercially available and the synthesis of (*tert*-butoxycarbonyl)-*L*-*tert*-leucine is described in Section 7.2.7.1, page 178.

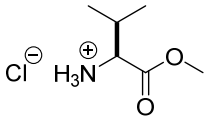
1st Step B: Carboxylic acid protection[270]

General procedure:

To a stirred solution of the corresponding amino acid (1 equiv.) in MeOH (1 mL / mmol) at 0 °C, $SOCl_2$ (2 equiv.) was added dropwise. The reaction mixture was stirred at reflux for 16 h. Afterwards, the solvent was evaporated under reduced pressure and the crude was used in the next step without further purification.

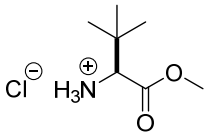
[269] King, A. M.; Salomé, C.; Dinsmore, J.; Salomé-Grosjean, E.; de Ryck, M.; Kaminski, R.; Valade, A.; Kohn H. *J. Med. Chem.* **2011**, 54, *13*, 4815–4830.
[270] Imramovsky, A.; Jorda, R.; Paul, K.; Řezníčková, E.; Dušek, J.; Hanusek, J.; Kryštof, V. *Eur. J. Med. Chem.* **2013**, *68*, 253–259.

(*S*)-1-Methoxy-3-methyl-1-oxobutan-2-aminium chloride



The title compound was obtained following the General Procedure described above starting from *L*-valine (4.7 g, 40 mmol, 1 equiv.). The product was obtained as a white solid, yield: 5.56 g, 33.2 mmol, 83 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 2H), 3.97 (t, *J* = 5.1 Hz, 1H), 3.82 (s, 3H), 2.52 – 2.51 (m, 1H), 1.22 –1.02 (m, 6H). All spectroscopic data were consistent with those previously reported. [271]

(*S*)-1-Methoxy-3,3-dimethyl-1-oxobutan-2-aminium chloride



The title compound was obtained following the General Procedure described above starting from *L*-*tert*-leucine (1.3 g, 10 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.8 g, 10 mmol, 99 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (s, 3H), 3.87 (s, 3H), 2.77 (br s, 1H) 1.22 (s, 9H). All spectroscopic data were consistent with those previously reported.[271]

2nd Step: Peptidic coupling

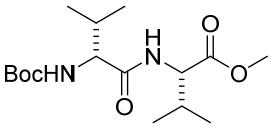
General Method A:[272] To a solution of the Boc-protected amino acid (1 equiv.) and the carboxylic acid protected amino acid (1.1 equiv.) in DMF (3 mL / mmol), HOAt (1.5 equiv.) was added. The resulting mxture was stirred at room temperature for 20 min and then, cooled down to 0 °C. *N*,*N*'-Diisopropylcarbodiimide (1.5 equiv.) and 2,4,6-collidine (2 equiv.) were added and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and the organic phase washed with 1N HCl (x3), $NaHCO_3$ saturated (x3) and brine (x3). The solvents were evaporated under reduced pressure and the crude was purified by silica flash column chromatography (eluting with hexane/EtOAc 80:20).

General Method B: To a solution of the Boc-protected amino acid (1 equiv.) in dry DMF (1.4 mL / mmol), diisopropylethylamine (6 equiv.), HATU (1.1 equiv.) and the corresponding carboxylic acid protected amino acid (1.2 equiv.) were added and the reaction mixture was stirred at room temperature for 16 h. Then, the reaction was quenched by the addition of H_2O/EtOAc 50:50 and extracted with EtOAc. The organic

[271] Anantharaj, S.; Jayakannan, M. *Biomacromolecules* **2012**, *13*, 2446–2455.
[272] Adapted from: Babine, Robert Edwards, et al. *PTC Int. Appl.* 2002018369, **2002**.

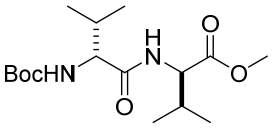
phase was dried by $MgSO_4$ and the solvent was evaporated. The corresponding dimer was purified by silica flash column chromatography (eluting with hexane/EtOAc 80:20).

Methyl (*tert*-butoxycarbonyl)-*D*-valyl-*L*-valinate



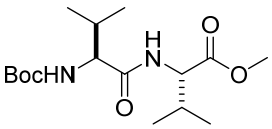
The title compound was obtained following the General Method A described above and starting from Boc-*D*-valine (4.3 g, 20 mmol, 1 equiv.) and (*S*)-1-methoxy-3-methyl-1-oxobutan-2-aminium chloride (3.35 g, 20 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.3 g, 10 mmol, 50 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 1H), 4.55 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.98 (dd, *J* = 8.1, 5.6 Hz, 1H), 3.73 (s, 3H), 2.33 – 2.05 (m, 2H), 1.45 (s, 9H), 1.03 – 0.84 (m, 12H).

Methyl (*tert*-butoxycarbonyl)-*D*-valyl-*D*-valinate



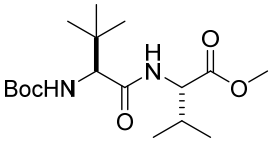
The title compound was obtained following the General Method A described above and starting from Boc-*D*-valine (4.3 g, 20 mmol, 1 equiv.) and (*R*)-1-methoxy-3-methyl-1-oxobutan-2-aminium chloride (3.35 g, 20 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.6 g, 11 mmol, 54 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, *J* = 8.6 Hz, 1H), 5.01 (s, 1H), 4.55 (dd, *J* = 8.8, 4.9 Hz, 1H), 3.90 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.74 (s, 3H), 2.26 – 2.10 (m, 2H), 1.45 (s, 9H), 1.00 – 0.88 (m, 12H).

Methyl (*tert*-butoxycarbonyl)-*L*-valyl-*L*-valinate



The title compound was obtained following the General Method A described above and starting from Boc-*L*-valine (4.3 g, 20 mmol, 1 equiv.) and (*S*)-1-methoxy-3-methyl-1-oxobutan-2-aminium chloride (3.35 g, 20 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.6 g, 11 mmol, 55 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, *J* = 8.6 Hz, 1H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.54 (dd, *J* = 8.7, 4.8 Hz, 1H), 3.90 (dd, *J* = 8.7, 6.3 Hz, 1H), 3.73 (s, 3H), 2.26 – 2.10 (m, 2H), 1.45 (s, 9H), 1.03 – 0.86 (m, 12H). All spectroscopic data were coincident with those previously reported.[273]

Methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-*L*-valinate

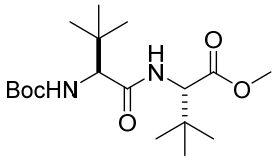


The title compound was obtained following the General Method B described above and starting from Boc-*L*-*tert*-leucine (0.964 g, 4.2 mmol, 1 equiv.) and (*S*)-1-methoxy-3-methyl-

[273] Chen, H.; Xu, X.; Liu, L.; Tang, G.; Zhao, Y. *RSC Advances*, **2013**, *3*, 16247–16250.

1-oxobutan-2-aminium chloride (0.913 g, 5 mmol, 1.2 equiv.). The product was obtained as a white solid, yield: 1.15 g, 3.4 mmol, 81 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (d, *J* = 8.1 Hz, 1H), 5.23 (d, *J* = 8.6 Hz, 1H), 4.57 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.87 (d, *J* = 9.4 Hz, 1H), 3.76 (s, 3H), 2.25 – 2.15 (m, 1H), 1.46 (s, 9H), 1.04 (s, 9H), 0.95 (dd, *J* = 8.0, 6.9 Hz, 6H).

Methyl (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanamido)-3,3-dimethylbutanoate



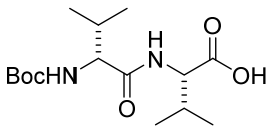
The title compound was obtained following the General Method B described above and starting from Boc-*L*-*tert*-leucine (1.16 g, 5.0 mmol, 1 equiv.) and (*S*)-1-methoxy-3,3-dimethyl-1-oxobutan-2-aminium (01.09 g, 6 mmol, 1.2 equiv.). The product was obtained as a white solid, yield: 1.44 g, 4.0 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, *J* = 8.8 Hz, 1H), 5.21 (d, *J* = 8.7 Hz, 1H), 4.45 (d, *J* = 9.1 Hz, 1H), 3.86 (d, *J* = 9.3 Hz, 1H), 3.74 (s, 3H), 1.45 (s, 9H), 1.02 (s, 9H), 1.00 (s, 9H).

3rd Step*: *Methyl ester deprotection[274]

General Procedure:

To a stirred suspension of the starting protected methyl ester (1 equiv.) in MeOH (5 mL / mmol), NaOH 2M (3.2 equiv.) was added and the resulting suspension was stirred at room temperature for 16 h. Then, MeOH was evaporated under reduced pressure and the mixture was cooled down to 0 °C, acidified with HCl 3M to pH=2 and extracted with EtOAc (x3). The organic layers were combined, dried over $MgSO_4$ and evaporated under vaccum. The crude product was used in the next step without further purification.

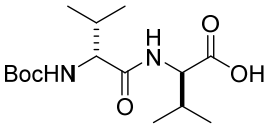
(*tert*-Butoxycarbonyl)-*D*-valyl-*L*-valine



The title compound was obtained following the General Procedure described above and starting from methyl (*tert*-butoxycarbonyl)-*D*-valyl-*L*-valinate (3.3 g, 10 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.16 g, 8.45 mmol, 85 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 7.8 Hz, 1H), 5.36 (d, *J* = 9.3 Hz, 1H), 4.67 – 4.49 (m, 1H), 4.40 (t, *J* = 7.9 Hz, 1H), 2.33 – 2.23 (m, 2H), 1.45 (s, 9H), 1.01 – 0.97 (m, 12H).

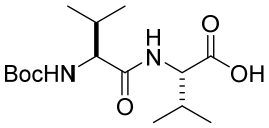
[274] Adapted from: Hata, R.; Nonaka, H.; Takakusagi, Y.; Ichikawa, K.; Sando, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 1765–1768.

(*tert*-Butoxycarbonyl)-*D*-valyl-*D*-valine



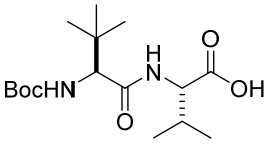
The title compound was obtained following the General Procedure described above and starting from methyl (*tert*-butoxycarbonyl)-*D*-valyl-*D*-valinate (3.6 g, 11 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.48 g, 8.17 mmol, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, *J* = 8.5 Hz, 1H), 5.13 (br s, 1H), 4.56 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.94 (dd, *J* = 8.7, 6.6 Hz, 1H), 2.32 – 2.21 (m, 2H), 1.44 (s, 9H), 0.99 – 0.93 (m, 12H).

(*tert*-Butoxycarbonyl)-*L*-valyl-*L*-valine



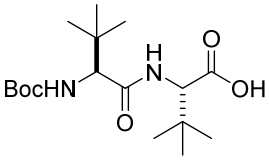
The title compound was obtained following the General Procedure described above and starting from methyl (*tert*-butoxycarbonyl)-*L*-valyl-*L*-valinate (3.6 g, 11 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.4 g, 10.5 mmol, 96 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 8.2 Hz, 1H), 4.57 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.94 (dd, *J* = 8.7, 6.6 Hz, 1H), 2.32 – 2.21 (m, 2H), 1.44 (s, 9H), 0.99 – 0.93 (m, 12H). All spectroscopic data were consistent with those previously reported.[275]

((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-L-valine



The title compound was obtained following the General Procedure described above and starting from methyl ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-L-valinate (1.15 g, 3.3 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.1 g, 3.2 mmol, 97 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (br s, 1H), 5.38 (br s, 1H), 4.60 (dd, *J* = 8.4, 4.7 Hz, 1H), 4.02 (dq, *J* = 9.3, 5.4, 4.4 Hz, 1H), 1.45 (s, 9H), 1.02 (s, 9H), 0.98 (t, *J* = 7.0 Hz, 6H).

(*S*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanamido)-3,3-dimethylbutanoic acid



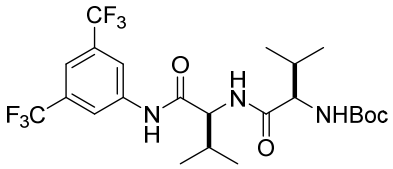
The title compound was obtained following the General Procedure described above and starting from methyl (*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutan amido)-3,3-dimethylbutanoate (1.44 g, 4.0 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.3 g, 3.8 mmol, 95 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ

[275] Thaqi, A.; McCluskey, A.; Scott, J. L. *Tetrahedron Lett.* **2008**, *49*, 6962–6964.

6.59 (br s, 1H), 5.46 (br s, 1H), 4.47 (d, *J* = 9.0 Hz, 1H), 4.05 (d, *J* = 7.7 Hz, 1H), 1.45 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H).

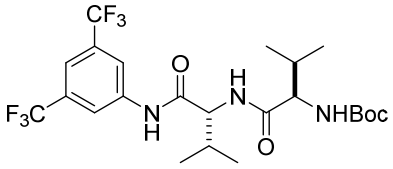
***4th Step A (General Procedure)*:**[276] 1-Methylimidazole (2.5 equiv.) was added to a slurry of the corresponding Boc-protected dipeptide obtained above (1 equiv.) in CH_2Cl_2 (2.5 mL / mmol) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.5 equiv.) in CH_2Cl_2 (1 mL) was added to the mixture under –5 °C. After stirring the mixture at this temperature for 20 min, 3,5-bis(trifluoromethyl)aniline (1 equiv.) was added. Stirring was then continued at room temperature for 2 h. Afterwards, H_2O (10 mL / mmol) and EtOAc (10 mL / mmol) were added. The organic layer was washed with brine (x3) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified flash column chromatography on silica gel (eluting with hexane/EtOAc 80:20).

***tert*-Butyl ((*R*)-1-(((*S*)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate**



The title compound was obtained following the General Procedure described above and starting from (*tert*-butoxycarbonyl)-*D*-valyl-*L*-valine (2.7 g, 8.5 mmol, 1 equiv.). The product was obtained as a white solid, yield: 3.43 g, 6.5 mmol, 76 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.74 (s, 2H), 6.57 (d, *J* = 9.2 Hz, 1H), 5.17 (d, *J* = 5.8 Hz, 1H), 4.61 – 4.49 (m, 1H), 3.80 –3.76 (m, 1H), 2.64 – 2.48 (m, 1H), 2.38 – 2.27 (m, 1H), 1.40 (s, 9H), 1.07 – 0.98 (m, 12H).

***tert*-Butyl ((*R*)-1-(((*R*)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate**

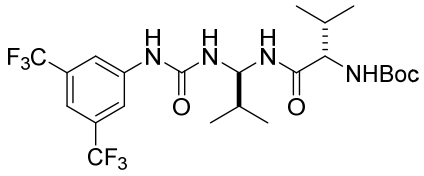


The title compound was obtained following the General Procedure described above and starting from (*tert*-butoxycarbonyl)-*D*-valyl-*D*-valine (2.9 g, 5.4 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.1 g, 2.5 mmol, 46 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.69 (s, 2H), 6.51 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.50 (dd, *J* = 8.0, 4.3 Hz, 1H), 3.99 (t, *J* = 4.0 Hz, 1H), 2.70 – 2.55 (m, 1H), 2.45 – 2.29 (m, 1H), 1.48 (s, 9H), 1.12 – 0.94 (m, 12H).

[276] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

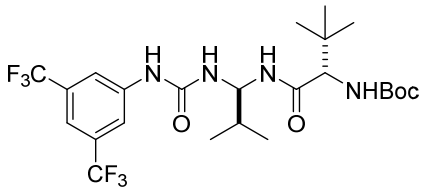
4th Step B (General Procedure): To a stirred solution of the corresponding *N*-protected dipeptide (1 equiv.) in dry THF at –20 °C, isobutyl chloroformate (1 equiv.) and *N*-methylmorpholine (1 equiv.) were added and the resulting suspension was stirred at the same temperature for 20 min. Then, a previously prepared solution of NaN_3 (1.5 equiv.) in H_2O (0.7 mL / mmol) was added *in situ* and the mixture was stirred at –20 °C for 30 min. The organic layer was separated, concentrated under reduced pressure and the resulting residue redissolved in CH_2Cl_2 (5 mL / mmol). The solution was washed with H_2O (x3), dried over $MgSO_4$ and evaporated. The resulting slurry was redissolved again in dry CH_2Cl_2 (3 mL / mmol) and stirred at 40 °C until the disappearance of the azide band in the IR spectrum (~2140 cm^{-1}). After completion, the reaction mixture was cooled to room temperature, 3,5-bis(trifluoromethyl)aniline (0.8 equiv.) was added and the mixture was stirred at room temperature 16 h. The solvent was evaporated under vaccum and the oily residue was crashed with CH_2Cl_2 to afford the desired product.

tert-Butyl ((*S*)-1-(((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl) amino)-3-methyl-1-oxobutan-2-yl)carbamate



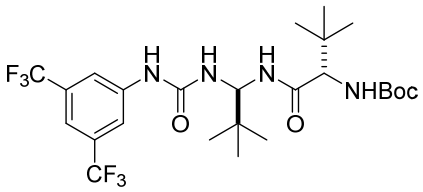
The title compound was obtained following the General Procedure described above and starting from (*tert*-butoxycarbonyl)-*L*-valyl-*L*-valine (3.2 g, 10 mmol, 1 equiv.). The oily residue was purified by silica flash column chromatography (eluting with hexane/EtOAc 50:50) to afford the desired product as a white solid, yield: 1.8 g, 3.3 mmol, 33 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.49 (s, 1H), 6.97 (br s, 1H), 5.08 (br s, 1H), 4.94 (br s), 3.84 (d, *J* = 8.0 Hz, 1H), 3.39 (br s), 3.26 – 3.13 (m, 1H), 2.36 – 2.14 (m, 2H), 1.44 (s, 9H), 1.06 (dd, *J* = 8.4, 6.7 Hz, 6H), 0.95 (d, *J* = 6.7 Hz, 6H).

tert-Butyl ((*S*)-1-(((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl) amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



The title compound was obtained following the General Procedure described above and starting from ((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-*L*-valine (0.661 g, 2 mmol, 1 equiv.). The product was obtained as a white solid, yield: 0.391 g, 0.7 mmol, 44 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.51 (s, 1H), 6.64 (br s, 1H), 5.24 – 5.00 (m, 2H), 3.84 (d, *J* = 8.5 Hz, 1H), 1.46 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 6H), 1.02 (s, 9H).

tert-Butyl ((_S_)-1-(((_R_)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2,2-dimethyl propyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate



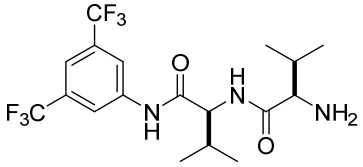
The title compound was obtained following the General Procedure described above and starting from (_S_)-2-((_S_)-2-((_tert_-butoxycarbonyl)amino)-3,3-dimethylbutanamido)-3,3-dimethylbutanoic acid (1.38 g, 4.0 mmol, 1 equiv.) The product was obtained as a white solid, yield: 0.659 g, 1.16 mmol, 36 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (br s, 1H), 8.06 (s, 2H), 7.52 (s, 1H), 6.56 (br s, 1H), 5.26 – 5.04 (m, 3H), 3.84 (d, *J* = 8.9 Hz, 1H), 1.46 (s, 9H), 1.09 (s, 9H), 1.03 (s, 9H).

5th Step*: *Boc deprotection

General Procedure

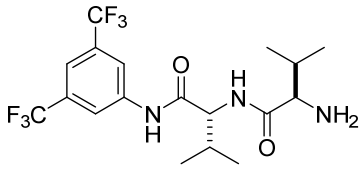
To a stirred solution of the corresponding *N*-Boc-aminoamide (1 equiv.) in CH_2Cl_2 (1mL / mmol) at 0 °C, TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach to room temperature and then stirred for 2 h. Afterwards, the solvents were removed under reduced pressure and the resulting residue was cooled down to 0 °C and basified with a saturated Na_2CO_3 solution. The formed solid was extracted with EtOAc (x3) and the organic layer was washed with saturated $NaHCO_3$ solution (x3) and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the corresponding free amine, which was used as such in the next step.

(_R_)-2-Amino-_N_-((_S_)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)-3-methylbutanamide



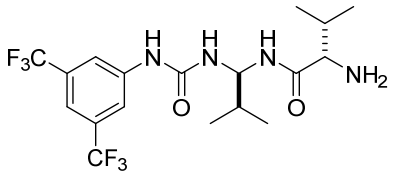
The title compound was obtained following the General Procedure described above and starting from (_tert_-butyl ((_R_)-1-(((_S_)-1-((3,5-bis(trifluoromethyl)phenyl) amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (4.5 g, 6.5 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.1 g, 2.5 mmol, 38 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (br s, 1H), 8.20 (br, s), 8.16 (d, *J* = 4.3 Hz, 1H), 8.02 (s, 2H), 7.52 (s, 1H), 4.34 (t, *J* = 7.7 Hz, 1H), 3.39 (d, *J* = 3.6 Hz, 1H), 2.48 – 2.26 (m, 2H), 1.08 (dd, *J* = 6.8, 2.6 Hz, 6H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).

(*R*)-2-Amino-*N*-((*R*)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)-3-methylbutanamide



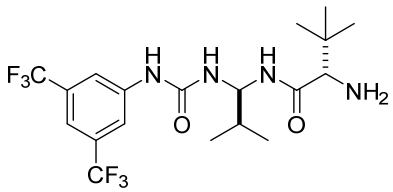
The title compound was obtained following the General Procedure described above and starting from *tert*-butyl ((*R*)-1-(((*R*)-1-((3,5-bis(trifluoromethyl)phenyl) amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (3.5 g, 8.2 mmol, 1 equiv.). The product was obtained as a white solid, yield: 2.9 g, 5.4 mmol, 67 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (br s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.10 (s, 2H), 8.08 (br s, 1H), 7.57 (s, 1H), 4.46 – 4.38 (m, 1H), 3.41 (d, *J* = 3.5 Hz, 2H), 2.50 – 2.26 (m, 2H), 1.11 – 1.04 (m, 9H), 0.89 (d, *J* = 6.9 Hz, 3H).

(*S*)-2-Amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-3-methylbutanamide



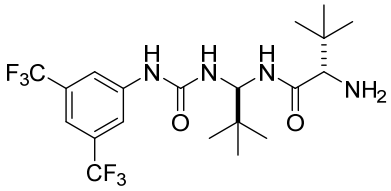
The title compound was obtained following the General Procedure described above and starting from *tert*-butyl ((*S*)-1-(((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl)ureido)-2-methylpropyl)amino)-3-methyl -1-oxobutan-2-yl)carbamate (1.8 g, 3.32 mmol, 1 equiv.). The product was obtained as white solid, yield: 0.97, 2.2 mmol, 66 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (br s, 1H), 8.37 (br s, 1H), 7.89 (s, 2H), 7.50 (br s, 1H), 6.48 (d, J = 10.9 Hz, 1H), 4.93 (s, 2H), 3.84 (t, *J* = 7.3 Hz, 2H), 3.32 (d, J = 3.6, Hz, 1H), 2.42 – 2.30 (m, 2H), 1.01 (d, *J* = 7.0 Hz, 6H), 0.83 (d, *J* = 6.9 Hz, 6H).

(*S*)-2-Amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-3,3-dimethylbutanamide



The title compound was obtained following the General Procedure described above and starting from *tert*-butyl ((*S*)-1-(((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl)ureido)-2-methylpropyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (0.305 g, 0.55 mmol, 1 equiv.). The product was obtained as a white solid, yield: 0.188, 0.41 mmol, 75 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.90 (s, 2H), 7.62 (s, 1H), 7.50 (br s, 1H), 5.08 (br s, 1H), 5.05 (s, 2H), 3.24 (s, 1H), 2.12 – 2.02 (m, 1H), 1.07 (s, 9H), 1.05 (s, 3H), 0.98 (d, *J* = 4.9 Hz, 3H).

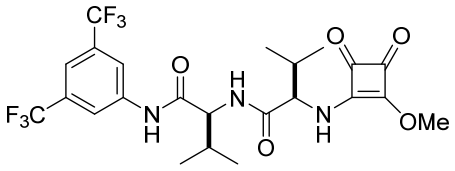
(*S*)-2-Amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2,2-dimethylpropyl)-3,3-dimethylbutanamide



The title compound was obtained following the General Procedure described above and starting from t*ert*-butyl ((*S*)-1-(((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl)ureido)-2,2-dimethylpropyl)amino)-3,3 -dimethyl-1-oxobutan-2-yl)carbamate (0.431 g, 0.75 mmol, 1 equiv.) The product was obtained as a white solid, yield: 0.183 g, 0.39 mmol, 52 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (br s, 1H), 8.20 (d, *J* = 11.5 Hz, 1H), 8.07 (s, 2H), 7.50 (s, 1H), 5.12 (br s, 1H), 5.10 (s, 1H), 3.25 (s, 1H), 1.10 (s, 9H), 1.09 (s, 9H).

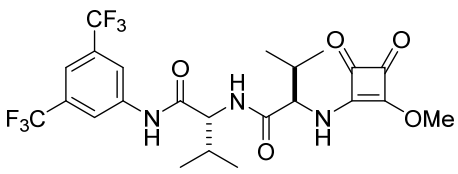
6th Step (General Procedure): To a stirred solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (0.9 equiv.) in MeOH (2 mL/mmol) the corresponding amine (1 equiv.) was added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the crude was purified by silica flash column chromatography (eluting with hexane/EtOAc 80:20).

(*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methylbutanamide



The title compound was obtained following the General Procedure described above and starting from (*R*)-2-amino-*N*-((*S*)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)-3-methylbutanamide (1.1 g, 2.5 mmol, 1 equiv.). The product was obtained as a white solid, yield: 1.0 g, 1.9 mmol, 77 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 2H), 7.68 (s, 1H), 4.38 (s, 3H), 4.32 (d, *J* = 7.3 Hz, 1H), 2.30 – 2.10 (m, 3H), 1.05 (dd, *J* = 6.8, 3.6 Hz, 12H).

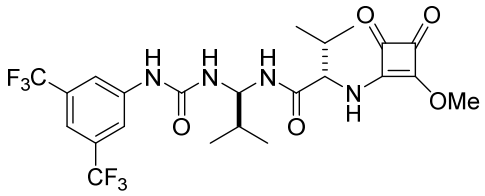
(*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methylbutanamide



The title compound was obtained following the General Procedure described above and starting from (*R*)-2-amino-*N*-((*R*)-1-((3,5-bis(trifluoromethyl)phenyl)amino)-3-methyl-1-oxobutan-2-yl)-3-methylbutanamide (0.78 g, 1.83 mmol, 1 equiv.). The product was

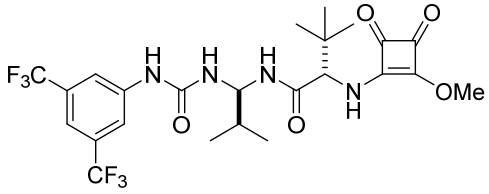
obtained as a white solid, yield: 0.661 g, 1.23 mmol, 67 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 8.80 (br s), 8.09 (s, 2H), 7.88 (br s, 1H), 7.57 (s, 1H), 4.36 (s, 3H), 4.30 (s, 1H), 2.46 – 2.10 (m, 2H), 1.16 – 0.78 (m, 12H).

(*S*)-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamide



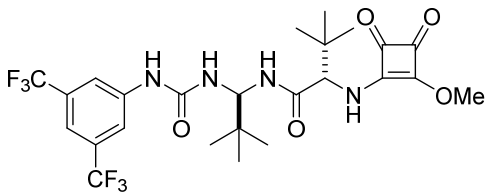
The title compound was obtained following the General Procedure described above and starting from (*S*)-2-amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methyl propyl)-3-methylbutanamide (0.96 g, 2.2 mmol, 1 equiv.). The product was obtained as white solid, yield: 0.47, 0.85 mmol, 39 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 2H), 7.50 (s, 1H), 6.46 (d, J = 10.3 Hz, 1H), 5.18 (br s, 1H), 4.40 (s, 3H), 3.99 (s, 1H), 2.16 (d, J = 9.0 Hz, 1H), 1.78 – 1.57 (m, 6H), 1.01 (dd, *J* = 6.8, 5.1 Hz, 6H).

(*S*)-*N*-((*R*)-1-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide



The title compound was obtained following the General Procedure described above and starting from (*S*)-2-amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-3,3-dimethylbutanamide (0.188 g, 0.41 mmol, 1.1 equiv.). The product was obtained as a white solid, yield: 85.1 mg, 0.15 mmol, 41 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.21 (br s, 1H), 7.85 (s, 2H), 7.43 (s, 1H), 6.75 (d, *J* = 18.6 Hz, 1H), 5.73 (br s, 1H), 4.85 (d, *J* = 10.2 Hz, 1H), 4.52 (s, 3H), 2.61 (s, 1H), 2.37 – 2.28 (m, 1H), 1.03 (s, 9H), 0.99 – 0.88 (m, 6H).

(*S*)-*N*-((*R*)-1-(3-(3,5-bis(Trifluoromethyl)phenyl)ureido)-2,2-dimethylpropyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide

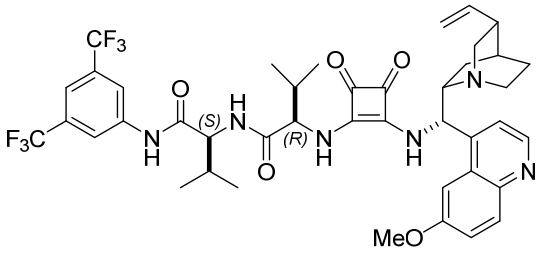


The title compound was obtained following the General Procedure described above and starting from (*S*)-2-amino-*N*-((*R*)-1-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-2,2-dimethylpropyl)-3,3-dimethylbutanamide (0.183 g, 0.40 mmol, 1.1 equiv.) The product was obtained as a white solid, yield: 0.182 g, 0.31

mmol, 87 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.92 (s, 2H), 7.45 (s, 1H), 6.48 (br s, 1H), 5.65 (t, *J* = 8.9 Hz, 1H), 4.85 (d, *J* = 9.0 Hz, 1H), 4.39 (s, 3H), 1.02 (s, 9H), 0.92 (s, 9H).

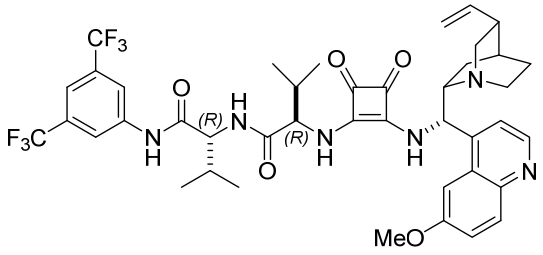
7th Step (General Procedure): To a suspension of the hemisquaramide obtained above (1 equiv.) in MeOH (2.0 mL/mmol), the corresponding 9-amino-(9-deoxy)*epi*quinine (1 equiv.) and Et_3N (1 equiv.) were added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the oily residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH 98:2) to give the corresponding pure catalysts **C26**–**C29**.

(*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methylbutanamide (C26)



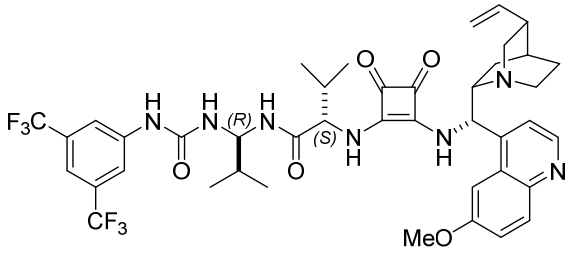
The title compound **C26** was obtained following the General Procedure described above and starting from (*S*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methyl butanamide (1.1 g, 1.9 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 0.92 g, 1.12 mmol, 59 %. Decomp. temp.: 190–193 °C. $[\alpha]_D^{25}$= –19.66° (*c*=1.0, MeOH). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.24 (s, 2H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 7.71 – 7.54 (m, 2H), 7.41 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.27 (d, *J* = 10.4 Hz, 1H), 5.93 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H), 5.16 – 4.97 (m, 2H), 4.90 (s, 3H), 4.66 (d, *J* = 5.8 Hz, 1H), 4.36 (d, *J* = 7.7 Hz, 1H), 3.95 (s, 3H), 3.78 (s, 1H), 3.54 (s, 1H), 3.37 – 3.21 (m, 1H), 3.02 – 2.68 (m, 2H), 2.44 (s, 1H), 2.34 – 2.16 (m, 1H), 2.16 – 1.98 (m, 1H), 1.69 (s, 4H), 1.08 – 0.99 (m, 6H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, MeOD) δ 183.7, 172.9, 169.0, 168.4, 160.4, 148.4, 145.4, 141.8, 141.5, 133.4, 133.0, 131.7, 129.3, 126.4, 124.2, 122.8, 120.6, 117.9, 115.6, 102.3, 63.6, 61.4, 61.0, 56.7, 54.8, 41.7, 40.1, 33.6, 31.6, 28.7, 27.8, 26.9, 19.8, 19.4, 19.1, 17.7. UPLC-QTOF: $C_{42}H_{46}N_6O_5F_6$ $[M+H]^+$ calc. 829.3512, found: 829.3510.

(*R*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methylbutanamide (C27)



The title compound **C27** was obtained following the General Procedure described above and starting from (*R*)-*N*-(3,5-bis(trifluoromethyl)phenyl)-2-((*R*)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamido)-3-methylbutanamide (0.66 g, 1.23 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 0.48 g, 0.58 mmol, 47 %. Decomp. temp.: 174–176 °C. $[\alpha]_D^{25}$= –18.66° (*c*=1.0, MeOH). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.70 (d, *J* = 4.7 Hz, 1H), 8.19 (s, 2H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.88 (s, 1H), 7.68 (d, *J* = 4.8 Hz, 1H), 7.64 (s, 1H), 7.43 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.28 (d, *J* = 10.0 Hz, 1H), 5.95 (ddd, *J* = 17.5, 10.3, 7.6 Hz, 1H), 5.19 – 4.98 (m, 2H), 4.89 (s, 3H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.38 (d, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 3.81 (s, 1H), 3.57 (s, 1H), 3.44 – 3.27 (m, 2H), 2.99 – 2.71 (m, 2H), 2.45 (s, 1H), 2.26 – 2.12 (m, 1H), 2.10 – 1.94 (m, 1H), 1.69 (s, 4H), 1.04 (d, *J* = 6.3 Hz, 6H), 0.82 (dd, *J* = 16.7, 6.7 Hz, 6H). ^{13}C NMR (75 MHz, MeOD) δ 183.6, 172.9, 168.7, 160.4, 148.4, 145.4, 142.1, 141.3, 134.0, 133.5, 133.1, 132.6, 131.7, 129.3, 126.3, 124.2, 122.7, 120.4, 118.0, 115.5, 102.3, 63.2, 61.4, 61.0, 56.7, 54.8, 41.8, 40.4, 33.7, 31.8, 28.8, 28.1, 27.0, 19.6, 19.3, 19.1, 17.7. UPLC-QTOF: $C_{42}H_{46}N_6O_5F_6$ $[M+H]^+$ calc. 829.3512, found: 829.3515.

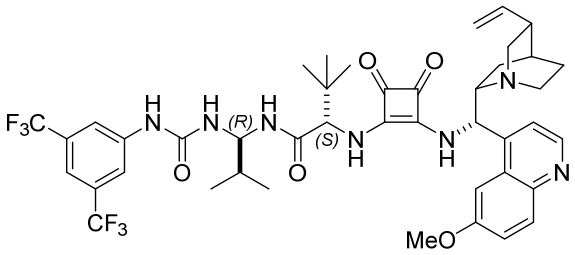
(*S*)-*N*-((*R*)-1-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamide (C28)



The title compound **C28** was obtained following the General Procedure described above and starting from (*S*)-*N*-((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl) ureido)-2-methylpropyl)-2-((2-methoxy-3,4 -dioxocyclobut-1-en-1-yl)amino)-3-methylbutanamide (0.27 g, 0.85 mmol, 1 equiv.). The product was obtained as an orange solid, yield: 0.37 g, 0.46 mmol, 54 %. Decomp. temp.: 135–137 °C. $[\alpha]_D^{25}$= –123.52° (*c*=1.02, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.46 (d, *J* = 9.7 Hz, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.59 (d, *J* = 4.5 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 6.05 – 5.89 (m, 2H), 5.17 – 4.85 (m, 2H), 4.69 (dd, *J* = 9.4, 5.4 Hz,

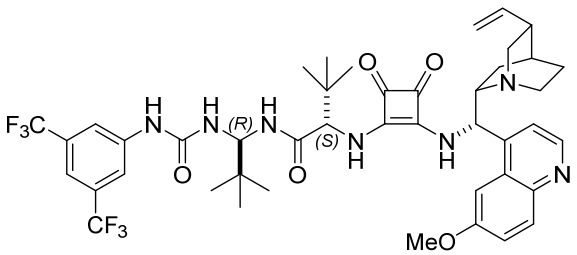
1H), 3.92 (s, 3H), 3.38 (s, 5H), 3.27 – 3.11 (m, 1H), 2.79 – 2.60 (m, 2H), 2.29 (s, 1H), 2.01 (dt, *J* = 12.6, 7.1 Hz, 1H), 1.60 (s, 7H), 1.53 (s, 2H), 0.86 (dd, *J* = 16.7, 6.6 Hz, 6H), 0.61 (s, 1H).[13]C NMR (75 MHz, $CDCl_3$) δ 183.6, 182.1, 169.8, 169.3, 166.8, 159.3, 157.9, 148.4, 145.3, 145.0, 142.5, 142.3, 132.3, 128.5, 123.0, 120.7, 120.1, 119.1, 117.0, 115.3, 102.2, 63.3, 59.4, 56.5, 53.9, 41.4, 40.3, 33.3, 30.4, 28.5, 26.8, 23.0, 19.4, 17.6. UPLC-QTOF: $C_{42}H_{47}N_7O_5F_6$ $[M+H]^+$ calc. 843.3543, found: 843.3539.

(*S*)-*N*-((*R*)-1-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-2-methylpropyl)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (C29)



The title compound **C29** was obtained following the General Procedure described above and starting from (*S*)-*N*-((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl)ureido)-2-methylpropyl)-2-((2-methoxy-3,4-dioxo cyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (85.0 mg, 0.15 mmol, 1 equiv.). The product was obtained as a yellow solid, yield: 77.1 mg, 0.09 mmol, 60 %. Decomp. temp.: 190–192 °C. $[\alpha]_D^{24}$= –146.90° (*c*=0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.61 (s, 1H), 8.06 (s, 2H), 8.00 (s, 1H), 7.97 (s, 1H), 7.62 (d, *J* = 4.4 Hz, 1H), 7.53 (s, 1H), 6.26 (s, 1H), 6.02 (dd, *J* = 17.8, 9.6 Hz, 1H), 5.40 (d, *J* = 7.2 Hz, 1H), 5.04 (dd, *J* = 23.4, 13.7 Hz, 2H), 4.65 (s, 1H), 3.95 (s, 3H), 3.72 (s, 1H), 3.57 (s, 1H), 3.37 – 3.19 (m, 1H), 2.98 – 2.63 (m, 3H), 2.36 (s, 1H), 1.67 (s, 4H), 1.01 (s, 9H), 0.79 (d, *J* = 6.5 Hz, 6H), 0.64 (s, 1H). ^{13}C NMR (75 MHz, Acetone) δ 184.5, 183.7, 160.0, 155.7, 149.1, 146.6, 145.0, 143.7, 133.4, 129.4, 126.8, 123.2, 116.0, 115.3, 111.6, 103.3, 66.0, 57.6, 57.0, 42.1, 41.6, 36.4, 33.9, 18.8. UPLC-QTOF: $C_{42}H_{47}N_7O_5F_6$ $[M+H]^+$ calc. 843.3543, found: 843.3539. UPLC-QTOF: $C_{43}H_{50}N_7O_5F_6$ $[M+H]^+$ calc. 858.3778, found: 858.3792.

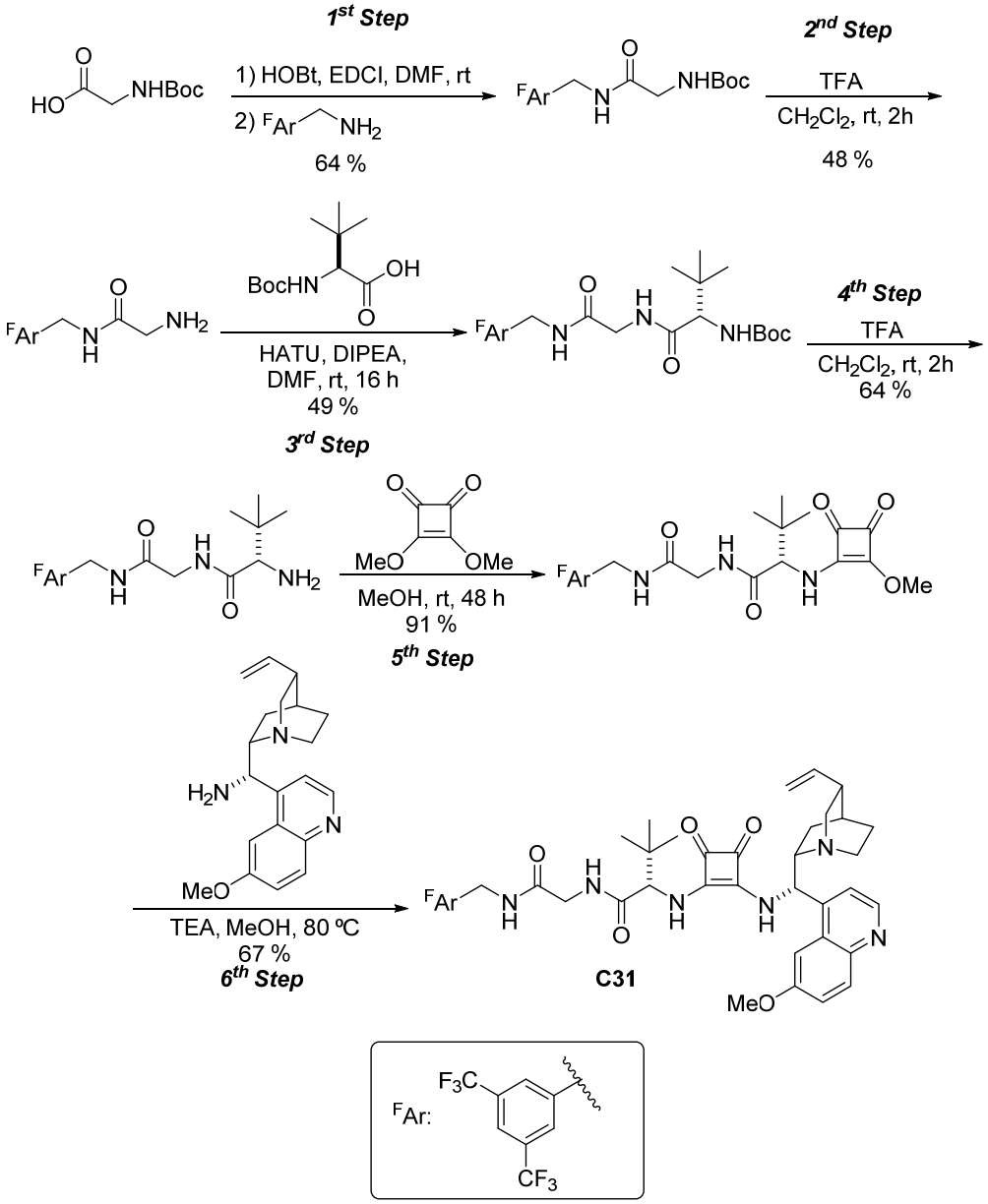
(*S*)-*N*-((*R*)-1-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-2,2-dimethylpropyl)-2-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (C29)



The title compound **C29** was obtained following the General Procedure described above and starting from (*S*)-*N*-((*R*)-1-(3-(3,5-bis(trifluoro methyl)phenyl) ureido)-2,2-dimethyl propyl)-2-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanamide (0.203 g, 0.35

mmol, 1.1 equiv.). The product was obtained as a yellow solid, yield: 0.147 g, 0.17 mmol, 48 %. Decomp. temp.: 180–183 °C. $[\alpha]_D^{24}$= –19.65° (*c*=0.84, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.44 (s, 1H), 8.18 (s, 2H), 8.00 (s, 1H), 7.87 (s, 2H), 7.69 (s, 1H), 7.55 (s, 1H), 7.35 (d, *J* = 11.3 Hz, 1H), 6.23 (s, 1H), 6.01 (s, 1H), 5.38 – 4.60 (m, 3H), 3.95 (s, 4H), 3.24 (d, *J* = 40.6 Hz, 1H), 2.91 (s, 1H), 2.41 (s, 1H), 1.68 (s, 4H), 1.08 (s, 9H), 0.65 (s, 9H). ^{13}C NMR (75 MHz, Acetone) δ 206.9, 184.4, 183.0, 170.5, 169.2, 168.5, 160.5, 160.1, 159.9, 155.8, 149.4, 149.2, 149.0, 146.5, 146.3, 143.9, 143.2, 138.2, 133.7, 133.4, 133.3, 132.8, 132.4, 130.5, 129.6, 129.1, 128.5, 126.9, 124.0, 123.3, 123.1, 119.7, 119.2, 118.4, 115.7, 103.4, 102.7, 67.0, 64.2, 61.3, 57.3, 57.2, 56.9, 56.8, 54.5, 54.0, 42.2, 41.3, 39.3, 37.1, 36.5, 31.3, 31.0, 30.7, 30.5, 30.2, 30.0, 29.7, 29.5, 29.2, 28.8, 27.5, 26.5, 26.3, 20.1, 20.0. UPLC-QTOF: $C_{41}H_{52}N_7O_5F_6$ $[M+H]^+$ calc. 872.3934, found: 872.3948.

*7.2.7.3. Preparation of catalyst **C31***



1st Step: To a solution of Boc-glycine (3.5 g, 20 mmol, 1 equiv.) in dry DMF (2 mL / mmol), HOBt (4.6 g, 34.5 mmol, 1.5 equiv.), EDCI (4.4 g, 23 mmol, 1.15 equiv.) and 3,5-bis(trifluoromethyl)benzylamine (4.9 g, 20 mmol, 1 equiv.) were added and the mixture reaction was stirred at room temperature for 16 h. Then, the reaction was quenched with HCl 1M (50 mL) and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (5 x 30 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by silica column flash chromatography (eluting with hexane/EtOAc 90:10 → 50:50) to afford the desired compound as a white solid. Yield: 5.1 g, 12.8 mmol, 64 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.76 (s, 2H),

7.08 (br s, 1H), 4.59 (d, *J* = 6.2 Hz, 2H), 3.94 (d, *J* = 5.3 Hz, 1H), 3.87 (d, *J* = 6.0 Hz, 2H), 1.43 (s, 9H).

2nd Step: To a stirred solution of the compound obtained above (5.1 g, 12.8 mmol, 1 equiv.) in CH_2Cl_2 (1mL / mmol) at 0 °C, TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach room temperature and then stirred for 2 h. Afterwards, the solvents were removed under reduced pressure and the resulting residue was cooled down to 0 °C and basified with saturated Na_2CO_3 solution. The formed solid was extracted with EtOAc (3 x 40 mL) and the organic layer was washed with $NaHCO_3$ saturated (3 x 40 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the corresponding free amine as yellow oil. Yield: 1.82 g, 6.1 mmol, 48 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.80 (s, 1H), 7.76 (s, 2H), 4.61 (d, *J* = 6.3 Hz, 2H), 3.47 (s, 2H).

3rd Step: To a solution of Boc-*L-tert*-leucine (1.7 g, 7.32 mmol, 1.2 equiv.) in dry DMF (1.4 mL / mmol), diisopropylethylamine (6.32 mL, 36.6 mmol, 6 equiv.), HATU (2.5 g, 6.7 mmol, 1.1 equiv.) and the compound obtained in the previous step (1.8 g, 6.1 mmol, 1 equiv.) were added and the mixture reaction was stirred at room temperature for 16 h. Then, the reaction was quenched by the addition of H_2O/EtOAc 50:50 and extracted with EtOAc (3 x 30 mL). The organic phase was dried by $MgSO_4$ and the solvent was evaporated. The corresponding dimer was purified by silica flash column chromatography (eluting with hexane/EtOAc 80:20) to give a yellow oil, yield: 1.5 g, 3 mmol, 49 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.77 (s, 2H), 7.69 (br s, 1H), 6.63 (br s, 1H), 5.12 (br s, 1H), 4.70 – 4.42 (m, 2H), 4.26 – 4.14 (m, 2H), 3.91 (dd, *J* = 16.9, 5.3 Hz, 1H), 3.70 (d, *J* = 6.6 Hz, 1H), 1.34 (s, 9H), 1.03 (s, 9H).

4th Step: To a stirred solution of the compound obtained above (1.5 g, 3 mmol, 1 equiv.) in CH_2Cl_2 (1mL / mmol) at 0 °C, TFA (2 mL/mmol) was added dropwise. The mixture was allowed to reach room temperature and stirred 2 h. Afterwards, the solvents were removed under reduced pressure and the resulting residue was cooled down to 0 °C and basified with saturated Na_2CO_3 solution. The formed solid was extracted with EtOAc (3 x 20 mL) and the organic layer was washed with $NaHCO_3$ saturated (3 x 20 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure to afford the corresponding free amine as yellow oil. Yield: 0.799 g, 1.92 mmol, 64 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.74 (s, 2H), 7.70 (br s, 1H), 7.57 (br s, 1H), 4.55 (d, *J* = 6.1 Hz, 2H), 4.01 (d, *J* = 5.7 Hz, 2H), 3.15 (s, 1H), 0.96 (s, 9H).

5th Step: To a stirred solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (0.250 g, 1.77 mmol, 1 equiv.) in MeOH (2 mL/mmol) the corresponding amine obtained in the 4th

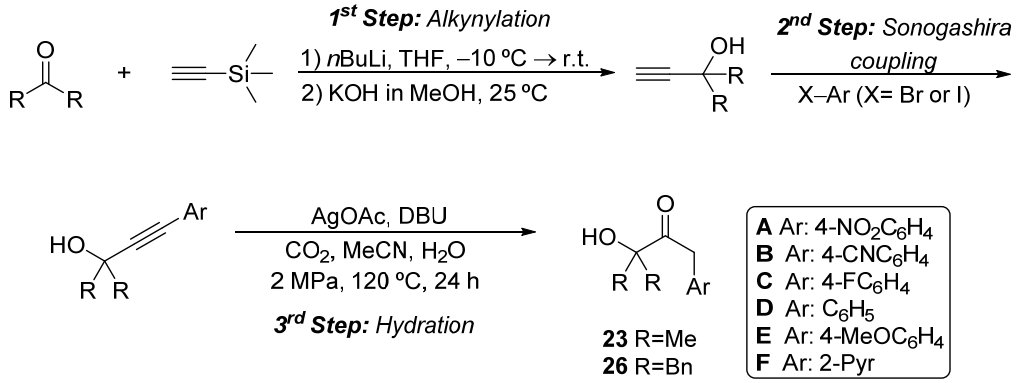
step (0.799 g, 1.92 mmol, 1.1 equiv.) was added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the crude product was purified by silica flash column chromatography (eluting with hexane/EtOAc 80:20). The squaric compound was obtained as yellow solid, yield: 0.844 g, 1.6 mmol, 91 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.78 (s, 1H), 7.75 (s, 2H), 7.39 (br s, 1H), 6.63 (br s, 1H), 4.58 (d, *J* = 6.1 Hz, 2H), 4.65 –4.59 (m, 1H), 4.39 (s, 3H), 4.18 – 4.04 (m, 2H), 1.00 (s, 9H).

6th Step: To a suspension of the hemisquaramide obtained above (0.844, 1.6 mmol, 1 equiv.) in MeOH (4.0 mL / mmol), the corresponding 9-amino-(9-deoxy)*epi*quinine (0.521 g, 1.6 mmol, 1 equiv.) and Et_3N (0.23 mL, 1.6 mmol, 1 equiv.) were added. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the oily residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH 98:2) to give the corresponding pure catalysts **C31**, yield: 0.878 g, 1.1 mmol, 67 %. Decomp. temp.: 118–120 °C. $[\alpha]_D^{24}$= –78.80° (*c*=0.63, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.81 (d, *J* = 4.5 Hz, 1H), 8.54 (dt, *J* = 30.0, 5.8 Hz, 2H), 8.25 (d, *J* = 9.1 Hz, 1H), 7.96 (s, 1H), 7.90 (s, 2H), 7.82 – 7.73 (m, 1H), 7.60 (d, *J* = 4.6 Hz, 1H), 7.43 (dd, *J* = 9.2, 2.6 Hz, 1H), 5.96 (dd, *J* = 24.9, 10.1 Hz, 2H), 5.12 – 4.88 (m, 2H), 4.57 – 4.35 (m, 3H), 3.91 (s, 3H), 3.74 (qd, *J* = 16.4, 5.9 Hz, 3H), 3.56 – 3.40 (m, 3H), 3.32 – 3.08 (m, 2H), 2.79 – 2.59 (m, 2H), 2.37 – 2.34 (m, 1H), 1.64 – 1.42 (m, 3H), 0.94 (s, 9H), 0.59 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ 188.5, 182.6, 181.5, 169.6, 169.0, 167.3, 166.6, 157.9, 147.8, 144.3, 143.0, 131.5, 130.12 (q, *J* = 32.7 Hz), 127.9, 121.9, 120.4, 114.4, 101.4, 63.7, 58.8, 55.6, 41.9, 41.3, 38.2, 35.0, 27.3, 26.3, 26.1. UPLC-DAD-QTOF: $C_{41}H_{45}N_6O_5F_6$ $[M+H]^+$ calcd.: 815.3356, found: 815.3374.

7.3. Experimental section for Chapter 2

7.3.1. Preparation of α-hydroxy α'-phenyl ketones

α-Hydroxy α'-phenyl ketones **23** and **26** were prepared by the three-step sequence shown in the scheme:

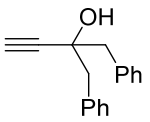


***1st Step*: *Alkynylation of ketones*[277]**

General Procedure

*n*BuLi (2.5M in hexane, 4.0 mL, 10 mmol, 2 equiv.) was added dropwise under N_2 to a solution of ethynyltrimethylsilane (1.4 mL, 10 mmol, 2 equiv.) in THF (16.7 mL) at –10 °C. After stirring for 30 min at –10 °C, benzophenone or dibenzyl ketone (5 mmol, 1 equiv.) was added. The mixture was stirred at room temperature for 4 h. Then, a solution of potassium hydroxide (1.4 g, 25 mmol, 5 equiv.) in MeOH (2 mL) was added to the mixture at 0 °C. Desilylation was complete within 30 min as monitored by TLC. The mixture was poured into a satured solution of NH_4Cl (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with Hexane/EtOAc 95:5 → 90:10) to afford the desired product.

2-Benzyl-1-phenylbut-3-yn-2-ol



The title compound was prepared from 1,3-diphenylpropan-2-one (1.1 g, 5 mmol) according to the General Procedure. Colorless oil, yield: 1.23

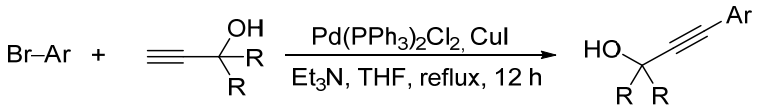
[277] Gawel, P.; Dengiz, C.; Finke, A. D.; Trapp, N.; Boudon, C.; Gisselbrecht, J. P.; Diederich, F. *Angew. Chem. Int. Ed*. **2014**, *53*, 4341–4345.

g, 4.3 mmol, 86 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.42 – 7.25 (m, 10H), 3.02 (s, 4H), 2.48 (s, 1H).

Propargylic alcohol bearing *gem*-dimethyl substituents is commercially available.

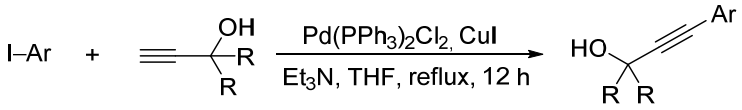
2nd Step*: *Sonogashira coupling

General Method A[278] *(For Ar= 4-$NO_2C_6H_3$, 4-CNC_6H_3):*



To a solution of *p*-bromo-nitrobenzene, *p*-bromobenzonitrile or 2-bromopyridine (1 equiv.) and the corresponding alkyne (R= Me or Bn) (1.3 equiv.) in THF (3 mL/mmol) were added $Pd(PPh_3)_2Cl_2$ (2 mol %) and CuI (4 mol %), and the reaction mixture was degassed with N_2. To this solution was added Et_3N (2 equiv.), and the reaction mixture was stirred under refluxing for 12 h. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 90:10 → 80:20) to afford the desired coupling product.

General Method B[279] *(For Ar= 4-$F_2C_6H_3$, Ph):*

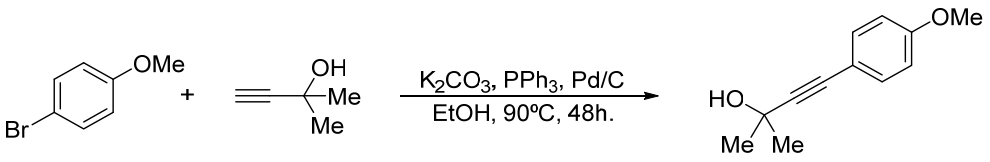


To a solution of Et_3N (3.75 mL), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (1 mol %), and iodobenzene or *p*-fluoroiodobenzene (1 equiv.) was added the corresponding propargylic alcohol (R= Me or Bn) (1.2 equiv.) under inert N_2 atmosphere. The mixture was allowed to stir at room temperature for 4 h. After completion, the reaction was quenched with saturated NH_4Cl (20 mL) solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EOAct 95:5 → 90:10) to afford the desired product.

[278]Li, Y.; Zou, H.; Gong, J.; Xiang, J.; Luo, T.; Quan, J.; Wang, G.; Yang, Z. *Org. Lett*. **2007**, *9*, 4057–4060.

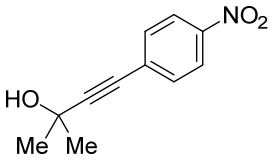
[279] Hussain, M. K.; Ansari, M. I.; Kant, R.; Hajela, K. *Org.Lett*. **2014**, *16*, 560–563.

General Method C[280] *(For Ar= 4-MeOC$_6$H$_3$):*



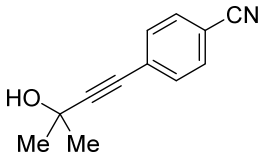
A mixture of K_2CO_3 (2.8 g, 20 mmol, 4 equiv.), PPh_3 (26.5 mg, 0.1 mmol, 2 mol %) and 10% palladium on charcoal (53.6 mg, 0.05 mmol, 1 mol %) in EtOH (50 mL) was stirred gently for 30 min, then 1-bromo-4-methoxybenzene (0.63 mL, 5 mmol, 1 equiv.) and propargylic alcohol (0.58 mL, 6 mmol, 1.2 equiv.) were added. The mixture was stirred at reflux for 48 h. The resulting precipitate was filtered through a pad of silica gel and the EtOH was evaporated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 95:5 → 90:10) to afford the desired product.

2-Methyl-4-(4-nitrophenyl)but-3-yn-2-ol



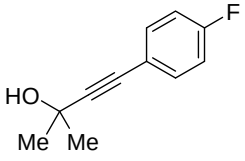
The title compound was prepared from 2-methyl-3-butyn-2-ol (0.6 mL, 6 mmol) and 1-bromo-4-nitrobenzene (1.0 g, 5 mmol) according to the General Method A. Orange oil, yield: 1.02 g, 5 mmol, 99 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.18 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 8.9 Hz, 2H), 2.01 (s, 1H), 1.64 (s, 6H).

4-(3-Hydroxy-3-methylbut-1-yn-1-yl)benzonitrile



The title compound was prepared from 2-methyl-3-butyn-2-ol (0.6 mL, 6 mmol) and 4-bromobenzonitrile (0.9 g, 5 mmol) according to the General Method A. Orange oil, yield: 0.95 g, 4.9 mmol, 97 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.63 (d, *J* = 8.6Hz, 2H), 7.53 (d, *J* = 8.6Hz, 2H), 2.05 (s,1H), 1.66 (s, 6H).

4-(4-Fluoropheny)-2-methylbut-3-yn-2-ol

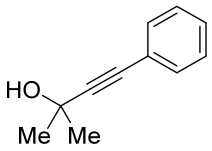


The title compound was prepared from 2-methyl-3-butyn-2-ol (0.6 mL, 6 mmol) and 1-fluoro-4-iodobenzene (0.6 mL, 5.0 mmol) according to the General Method B. Orange oil, yield: 0.87 g, 4.9

[280] Arsenyan P.; Rubina, K.; Vasiljeva, J.; Belyakov, S. *Tetrahedron Letters* **2013**, *54*, *6524-6528*.

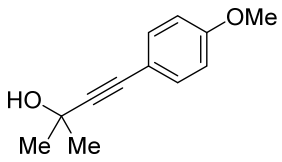
mmol, 97 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48 – 7.35 (m, 2H), 7.07 – 6.96 (m, 2H), 2.34 (s, 1H), 1.64 (s, 6H).

2-Methyl-4-phenylbut-3-yn-2-ol



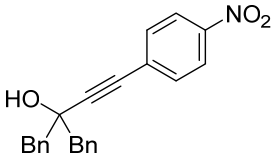
The title compound was prepared from 2-methyl-3-butyn-2-ol (0.5 mL, 5 mmol) and iodobenzene (0.5 mL, 4.1 mmol) according to the General Method B. Orange oil, yield: 0.62 g, 4.1 mmol, 99 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.47 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 2.00 (s, 1H), 1.62 (s, 6H).

4-(4-Methoxyphenyl)-2-methylbut-3-yn-ol



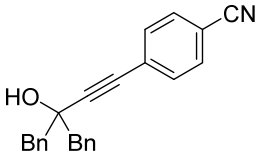
The title compound was prepared from 1-bromo-4-methoxybenzene (0.6 mL, 5 mmol) and propargylic alcohol (0.6 mL, 6 mmol) according to the General Method C. Orange oil, yield: 0.76 g, 4 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39 (d, *J* = 8.9Hz, 2H), 6.87 (d, *J* = 8.9Hz, 2H), 3.84 (s,3H), 2.02 (s, 1H), 1.65 (s, 6H).

2-Benzyl-4-(4-nitrophenyl)-1-phenylbut-3-yn-2-ol



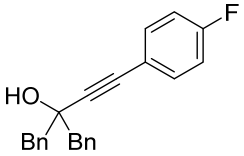
The title compound was prepared from 2-benzyl-1-phenylbut-3-yn-2-ol (1.2 g. 4.3 mmol) and 1-bromo-4-nitrobenzene (0.7 g, 3.3 mmol) according to the General Method A. Orange oil, yield: 1.14 g, 3.2 mmol, 97 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.19 (d, *J* = 9.0 Hz, 2H), 7.55 – 7.20 (m, 12H), 3.16 (s, 4H), 2.22 (s, 1H).

4-(3-Benzyl-3-hydroxy-4-phenylbut-1-yn-1-yl)benzonitrile



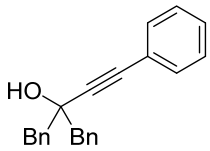
The title compound was prepared from 2-benzyl-1-phenylbut-3-yn-2-ol (1.0 g, 4.2 mmol) and 4-bromobenzonitrile (0.6 g, 3.3 mmol) according to the General Method A. Orange solid, yield: 1.03 g, 3.0 mmol, 92 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.60 (d, *J* = 8.6Hz, 2H), 7.47 – 7.31 (m, 12H), 3.15 (s, 4H).

2-Benzyl-4-(4-fluorophenyl)-1-phenylbut-3-yn-2-ol



The title compound was prepared from 2-benzyl-1-phenylbut-3-yn-2-ol (0.9 g, 3.8 mmol) and 1-fluoro-4-iodobenzene (0.4 mL, 3.2 mmol) according to the General Method B. Orange oil, yield: 1.04 g, 3.2 mmol, 99 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.54 – 7.23 (m, 12H), 7.09 – 6.94 (m, 2H), 3.14 (s, 4H), 2.16 (s, 1H).

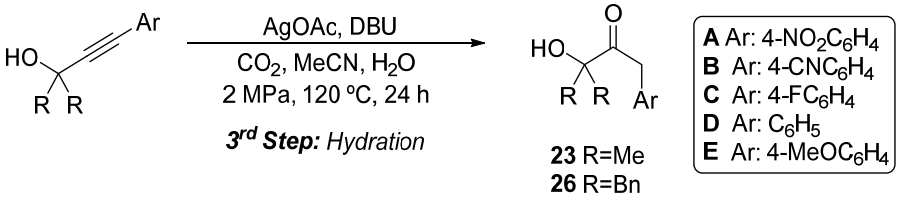
2-Benzyl-1,4-diphenylbut-3-yn-2-ol



The title compound was prepared from 2-benzyl-1-phenylbut-3-yn-2-ol (1.2 g, 5 mmol) and iodobenzene (0.5 mL, 4.1 mmol) according to the General Method B. Orange oil, yield: 1.21 g, 3.8 mmol, 96 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.81 – 7.04 (m, 15H), 3.15 (s, 4H), 2.16 (s, 1H).

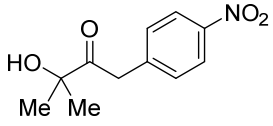
3rd Step*: *Alkyne hydration[281]

General Procedure



To a pressure reactor, the corresponding propargylic alcohol (1equiv.), AgOAc (10 mol %), DBU (0.5 equiv.), H_2O (0.6 mL/mmol) and MeCN (2 mL/mmol) were succesively added. The reactor was filled up with dry ice (CO_2), closed and the mixture was stirred for 24 h at 120 °C and 30-40 bar. Then the reaction mixture was cooled and the pressure was released slowly to atmospheric pressure. The residual material was diluted with diethyl ether and MeCN, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 90:10 → 80:20) to afford the desired products **23** or **26**.

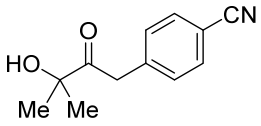
3-Hydroxy-3-methyl-1-(4-nitrophenyl)butan-2-one (23A)



The title compound **23A** was prepared from 2-methyl-4-(4-nitrophenyl)but-3-yn-2-ol (0.9 g, 4.5 mmol) according to the General Procedure. Orange solid, yield: 0.77 g, 3.5 mmol, 77 %. m.p. 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.20 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 4.02 (s, 2H), 3.20 (s, 1H), 1.47 (s, 6H). All the spectroscopic data were consistent with those previously reported.[281]

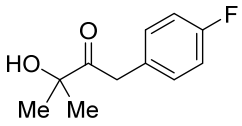
[281] He, H.; Qi, C.; Hu, X.; Guan, Y.; Jiang, H. *Green Chem*. **2014**, *16*, 3729–3733.

4-(3-Hydroxy-3methyl-2-oxobutyl)benzonitrile (23B)



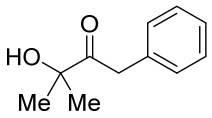
The title compound **23B** was prepared from 4-(3-hydroxy-3-methylbut-1-yn-1-yl)benzonitrile (0.9 g, 5 mmol) according to the General Procedure. Yellow oil, yield: 0.91 g, 4.5 mmol, 90 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.65 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.00 (s, 2H), 1.48 (s, 6H). All the spectroscopic data were consistent with those previously reported.[281]

1-(4-Fluorophenyl)-3-hydroxy-3-methylbutan-2-one (23C)



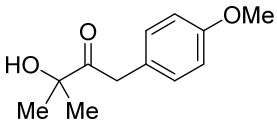
The title compound **23C** was prepared from 4-(4-fluoropheny)-2-methylbut-3-yn-2-ol (0.9 g, 5 mmol) according to the General Procedure. Yellow oil, yield: 0.43 g, 2.2 mmol, 44 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.20 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.06 (t, *J* = 8.7 Hz (s, 2H), 3.89 (s, 2H), 1.48 (s, 6H). All the spectroscopic data were consistent with those previously reported.[281]

3-Hydroxy-3-methyl-1-phenylbutan-2-one (23D)



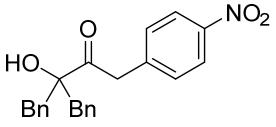
The title compound **23D** was prepared from 2-methyl-4-(4-phenyl)but-3-yn-2-ol (0.6 g, 4 mmol) according to the General Procedure. Colorless oil, yield: 0.23 g, 1.3 mmol, 43 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 – 7.12 (m, 5H), 3.88 (s, 2H), 1.45 (s, 6H). All the spectroscopic data were consistent with those previously reported.[281]

3-Hydroxy-1-(4-methoxyphenyl)-3-methylbutan-2-one (23E)



The title compound **23E** was prepared from 4-(4-methoxyphenyl)-2-methylbut-3-yn-ol) (0.65 g, 3.4 mmol) according to the General Procedure. Orange oil, yield: 0.37 g, 1.8 mmol, 52 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.16 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 2H), 3.83 (s, 3H), 1.47 (s, 6H). All the spectroscopic data were consistent with those previously reported.[281]

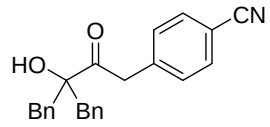
3-Benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (26A)



The title compound **26A** was prepared from 2-benzyl-4-(4-nitrophenyl)-1-phenylbut-3-yn-2-ol (1.1 g, 3 mmol) according to the General Procedure. Orange solid, yield: 0.94 g, 2.5 mmol, 83 %. m.p. 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.04 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.04 (m, 10H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.41 (s, 2H), 3.29 (d, *J* = 13.5 Hz, 2H), 2.97 (d, *J* = 13.6 Hz, 2H), 2.66 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.3, 146.7, 141.2, 135.1, 130.5, 130.3, 128.6,

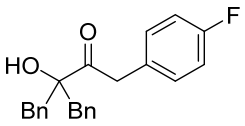
127.2, 123.2, 83.4, 46.2, 45.5. UPLC-DAD-QTOF: $C_{23}H_{20}NO_4$ $[M–H]^-$ calcd.: 374.1392, found: 374.1382.

4-(3-Benzyl-3-hydroxy-2-oxo-4-phenylbutyl)benzonitrile (26B)



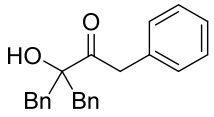
The title compound **26B** was prepared from 4-(3-benzyl-3-hydroxy-4-phenylbut-1-yn-1-yl)benzonitrile (0.6 g, 1.8 mmol) according to the General Procedure. White solid, yield: 0.36 g, 1.0 mmol, 56 %. m.p. 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.49 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.29 (m, 6H), 7.23 – 7.20 (m, 4H), 6.80 (d, *J* = 8.2 Hz, 2H), 3.38 (s, 2H), 3.29 (d, *J* = 13.6 Hz, 2H), 2.97 (d, *J* = 13.6 Hz, 2H), 2.64 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.9, 139.4, 135.6, 132.3, 130.9, 130.7, 129.0, 127.7, 119.2, 111.0, 83.8, 46.8, 45.9. UPLC-DAD-QTOF: $C_{24}H_{21}NO_2Na$ $[M+Na]^+$ calcd.: 378.1470, found: 378.1477.

3-Benzyl-1-(4-fluorophenyl)-3-hydroxy-4-phenylbutan-2-one (26C)



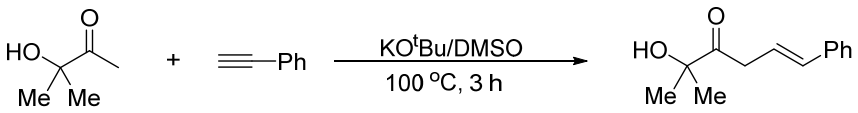
The title compound **26C** was prepared from 2-methyl-4-phenylbut-3-yn-2-ol (1.0 g, 3.1 mmol) according to the General Procedure. White solid, yield: 0.66 g, 1.9 mmol, 60 %. m.p. 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 – 7.21 (m, 11H), 7.01 – 6.90 (m, 2H), 6.82 – 6.72 (m, 2H), 3.44 (s, 2H), 3.32 (d, *J* = 13.6 Hz, 2H), 3.03 (d, *J* = 13.6 Hz, 2H), 2.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.4,163.7, 135.7, 131.5, 131.4, 130.7, 128.9, 127.5, 115.6, 115.3, 83.6, 45.7, 45.5. UPLC-DAD-QTOF: $C_{23}H_{22}O_2F$ $[M+H]^+$ calcd.: 349.1604, found: 349.1605.

3-Benzyl-3-hydroxy-1,4-diphenylbutan-2-one (26D)



The title compound **26D** was prepared from 2-benzyl-1,4-diphenylbut-3-yn-2-ol (1.1 g, 3.5 mmol) according to the General Procedure. White solid, yield: 0.74 g, 2.1 mmol, 60 %. m.p. 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 – 7.10 (m, 13H), 6.83 (dd, *J* = 6.8, 2.7 Hz, 2H), 3.49 (s, 2H), 3.29 (d, *J* = 13.6 Hz, 2H), 3.02 (d, *J* = 13.6 Hz, 2H), 2.89 (s,1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.3, 135.8, 130.7, 130.1, 128.9, 128.7, 127.5, 127.2, 83.5, 46.2, 45.6. UPLC-DAD-QTOF: $C_{23}H_{23}O_2$ $[M+H]^+$ calcd.: 331.1698, found: 331.1703.

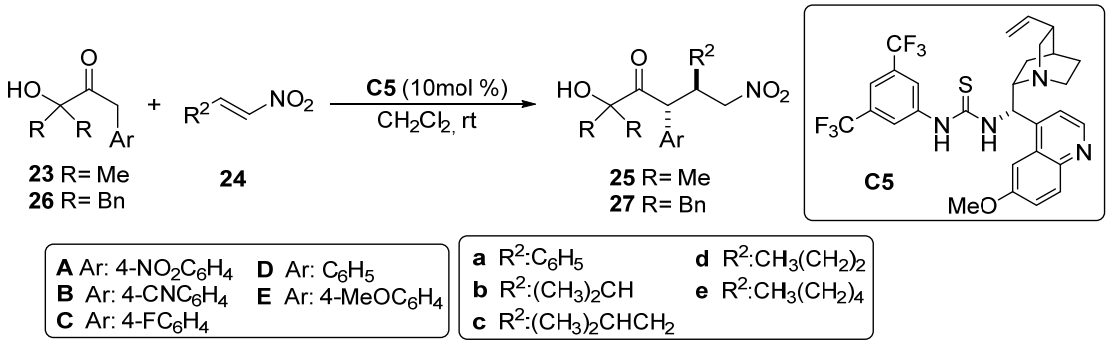
7.3.2. Preparation of alkenyl hydroxy ketone 38[282]



38

A mixture of commercial 3-hydroxy-3-methyl-2-butanone (1.6 mL , 15 mmol, 3 equiv.), phenylacetylene (0.6 mL, 5 mmol, 1 equiv.) and KO^{t}Bu (0.78 g, 7 mmol, 1.4 equiv.) in DMSO (12.5 mL) was heated (100 °C) and stirred for 3 hours. The reaction mixture, after cooling, was diluted with H_2O, neutralized with NH_4Cl, and extracted with Et_2O. The organic extract was washed with H_2O, dried over $MgSO_4$, and filtered. The solvent was then evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 95:5). Yellow oil, yield: 0.41 g, 2 mmol, 40 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.45 – 7.23 (m, 5H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.55 (d, *J* = 7.9 Hz, 2H), 1.47 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.6, 137.1, 134.1, 128.9, 128.0, 126.6, 121.9, 76.8, 40.1, 26.9. UPLC-DAD-QTOF: $C_{13}H_{17}O_2$ $[M+H]^+$ calcd.: 205.1229, found: 205.1230.

7.3.3. General procedure for the 1,4-conjugate addition of α-hydroxy α'-phenyl ketones 23 to nitroolefins 24



23 R= Me
26 R= Bn

24

25 R= Me
27 R= Bn

A Ar: 4-$NO_2C_6H_4$ **D** Ar: C_6H_5
B Ar: 4-CNC_6H_4 **E** Ar: 4-$MeOC_6H_4$
C Ar: 4-FC_6H_4

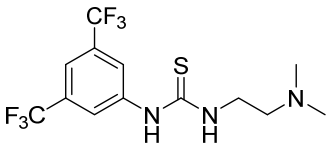
a R^2:C_6H_5 **d** R^2:$CH_3(CH_2)_2$
b R^2:$(CH_3)_2CH$ **e** R^2:$CH_3(CH_2)_4$
c R^2:$(CH_3)_2CHCH_2$

To a mixture of the corresponding α-hydroxy α'-phenyl ketone **23** or **26** (0.1 mmol, 1 equiv.) and the nitroalkene **24** (0.3 mmol, 3.0 equiv.) in dichloromethane (0.3 mL) at room temperature, catalyst **C5** (10 mol % for ketone **23**; 20 mol % for ketone **26**) was added, unless otherwise stated. The resulting suspension was stirred at the same temperature, until consumption of the α-hydroxyketone or no observation of reaction progress monitoring by ^{1}H NMR. The reaction was quenched with HCl 2M (1 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over $MgSO_4$,

[282] Adapted from: Trofimov, B. A.; Schmidt, E. Y.; Zorina, N. V.; Ivanova, E. V.; Ushakov, I. A. *J. Org. Chem*. **2012**, *77*, 6880–6886.

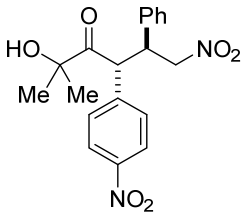
filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5 → 90:10) to afford the desired product.

The corresponding racemic compounds were prepared following the above procedure at room temperature, but using as catalyst either TEA, DBU or the achiral thiourea showed below (10 mol%), which was prepared following literature protocols.[283]



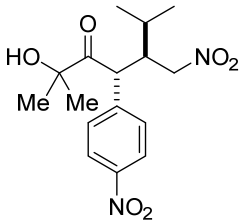
Achiral thiourea used for the synthesis of racemic compounds.

2-Hydroxy-2-methyl-6-nitro-4-(4-nitrophenyl)-5-phenylhexan-3-one (25Aa)



The title compound **25Aa** was prepared from 3-hydroxy-3-methyl-1-(4-nitrophenyl)butan-2-one (**23A**) (22.3 mg, 0.1 mmol) and nitrostyrene **24a** (29.8 mg, 0.2 mmol) according to the General Procedure at –20 °C, affording a white solid as a single diastereomer. Yield: 36.8 mg, 0.098 mmol, 98 %. m.p. 170–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.25 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.44 – 7.16 (m, 5H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.53 (dd, *J* = 12.5, 10.1 Hz, 1H), 4.43–4.28 (m, 1H)4.19 (dd, *J* = 12.5, 4.3 Hz, 1H), 0.89 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.5, 147.9, 142.3, 136.9, 129.8, 129.0, 128.5, 128.3, 124.5, 77.8, 77.8, 55.0, 47.1, 26.6, 25.9. UPLC-DAD-QTOF: $C_{19}H_{19}N_2O_6$ $[M–H]^-$ calcd.: 371.1243, found: 371.1239. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 24.6 min (minor) and 30.1 min (major)). The product was obtained with 80 % *ee*.

2-Hydroxy-2,6-dimethyl-5-(nitromethyl)-4-(4-nitrophenyl)heptan-3-one (25Ab)

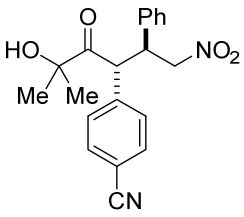


The title compound **25Ab** was prepared from 3-hydroxy-3-methyl-1-(4-nitrophenyl)butan-2-one (**23A**) (22.3 mg, 0.1 mmol) and 3-methyl-1-nitrobut-1-ene (**24b**) (34.5 mg, 0.3 mmol) according to the General Procedure, affording a yellow solid as a single diastereomer. Yield: 20.3 mg, 0.060 mmol, 60 %. ^{1}H NMR (300 MHz,

[283] Synthesis adapted from: R. C. Pratt, B. G. Lohmeijer, D. A. Long, P. N. Lundberg, A. P. Dove, H. B. Li, C. G. Wade, R. M. Waymouth, J. L. Hedrick, *Macromolecules*, **2006**, *39*, 7863–7871.

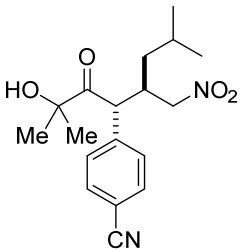
$CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 4.76 (d, *J* = 11.3 Hz, 1H), 4.23 – 4.00 (m, 2H), 3.30 (dtd, *J* = 11.1, 5.4, 3.1 Hz, 1H), 2.51 (s, 1H), 1.86 – 1.74 (m, 1H), 1.25 (d, *J* = 3.1 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 148.3, 143.2, 131.1, 124.9, 78.8, 74.3, 53.6, 46.0, 30.0, 28.5, 27.8, 21.8, 17.1.UPLC-DAD-QTOF: $C_{16}H_{22}N_2O_6Na$ $[M+Na]^+$ calcd.: 361.1376, found: 361.1381. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak ODH, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: 21.1 min (major) and 25.1 min (minor)). The product was obtained with 62% *ee*.

4-(5-Hydroxy-5-methyl-1-nitro-4-oxo-2-phenylhexan-3-yl)benzonitrile (25Ba)



The title compound **25Ba** was prepared from 4-(3-hydroxy-3-methyl-2-oxobutyl)benzonitrile (**23B**) (20.3 mg, 0.1 mmol) and nitrostyrene **24a** (17.9 mg, 1.2 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 31.7 mg, 0.089 mmol, 89 %. $[\alpha]_D^{25}$= –70.0 (*c* = 0.19, 82 % *ee*, CH_2Cl_2). m.p. 181–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.74 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.25 (m, 5H), 4.90 (d, *J* = 11.5 Hz, 1H), 4.55 (dd, *J* = 12.5, 10.2 Hz, 1H), 4.40 – 4.29 (m, 1H), 4.21 (dd, *J* = 12.5, 4.3 Hz, 1H), 0.92 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.6, 140.3, 136.9, 133.1, 129.7, 129.0, 128.5, 128.3, 118.0, 112.6, 77.9, 47.0, 26.6, 25.9. UPLC-DAD-QTOF: $C_{20}H_{20}N_2O_4Na$ $[M+Na]^+$ calcd.: 375.1321, found: 375.1327. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 21.5 min (major) and 26.5 min (minor)).

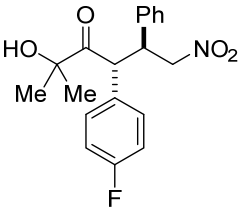
4-(2-Hydroxy-2,7-dimethyl-5-(nitromethyl)-3-oxooctan-4-yl)benzonitrile (25Bc)



The title compound **25Bc** was prepared from 4-(3-hydroxy-3-methyl-2-oxobutyl)benzonitrile (**23B**) (20.3 mg, 0.1 mmol) and 4-methyl-1-nitropent-1-ene (**24c**) (38.7 mg, 0.3 mmol) according to the General Procedure, affording a yellow oil as a single diastereomer. Yield: 21.3 mg, 0.064 mmol, 64 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.68 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 4.69 (d, *J* = 10.6 Hz, 1H), 4.44 (dd, *J* = 13.2, 4.6 Hz, 1H), 3.91 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.92 – 2.86 (m, 1H), 1.80 – 1.70 (m, 1H), 1.45 – 1.37 (m, 1H), 1.35 (s, 3H), 1.21 (s,3H), 1.12–1.03 (m, 1H), 0.95 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 213.0, 141.4, 133.2, 130.5, 118.5, 112.7, 78.2, 75.3, 54.4, 39.8, 39.6, 27.5, 27.1, 25.7, 24.1, 21.3. UPLC-DAD-QTOF: $C_{18}H_{24}N_2O_4Na$ $[M+Na]^+$ calcd.: 355.1634, found: 355.1639. The enantiomeric purity of the major

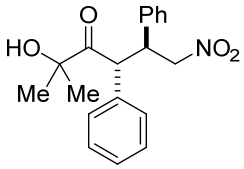
diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: 26.5 min (minor) and 33.1 min (major)). The product was obtained with 63 % *ee*.

4-(4-Fluorophenyl)-2-hydroxy-2-methyl-6-nitro-5-phenylhexan-3-one (25Ca)



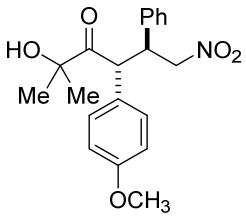
The title compound **25Ca** was prepared from 1-(4-fluorophenyl)-3-hydroxy-3-methylbutan-2-one (**23C**) (19.6 mg, 0.1 mmol) and nitrostyrene **24a** (44.7 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 24.2 mg, 0.070 mmol, 70 %. m.p. 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.50 – 7.42 (m, 2H), 7.33 (qd, *J* = 6.9, 2.3 Hz, 5H), 7.13 (t, *J* = 8.6 Hz, 2H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.56 (dd, *J* = 12.3, 10.3 Hz, 1H), 4.34 (td, *J* = 10.8, 10.4, 4.3 Hz, 1H), 4.24 (dd, *J* = 12.3, 4.3 Hz, 1H), 0.88 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.2, 164.3, 161.0, 137.4, 130.5, 130.4, 128.9, 128.3, 116.7, 116.5, 78.1, 77.5, 54.8, 47.1, 26.4, 25.9. UPLC-DAD-QTOF: $C_{19}H_{20}FNO_4Na$ $[M+Na]^+$ calcd.: 368.1274, found: 368.1271. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 11.8 min (major) and 13.5 min (minor)). The produc was obtained with 66 % *ee*.

2-Hydroxy-2-methyl-6-nitro-4,5-diphenylhexan-3-one (25Da)



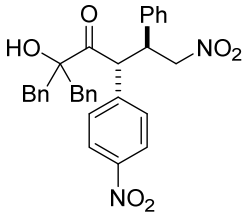
The title compound **25Da** was prepared from 3-hydroxy-3-methyl-1-phenylbutan-2-one (**23D**) (17.8 mg, 0.1 mmol) and nitrostyrene **24a** (29.8 mg, 0.2 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 12.1 mg, 0. 037 mmol, 37 %. m.p. 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.58 – 7.10 (m, 10H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.57–4.50 (m, 1H), 4.42 – 4.28 (m, 1H), 4.18 (dd, *J* = 12.5, 4.2 Hz, 1H), 2.63 (s, 1H), 0.87 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.1, 137.7, 134.7, 129.6, 128.9, 128.7, 128.7, 128.3, 128.1, 78.3, 75.9, 55.9, 47.0, 26.4, 25.9. UPLC-DAD-QTOF: $C_{19}H_{20}NO_4$ $[M–H]^–$ calcd.: 326.1392, found: 326.1380. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 10.4 min (major) and 13.0 min (minor)). The product was obtained with 60 % *ee*.

2-Hydroxy-4-(4-methoxyphenyl)-2-methyl-6-nitro-5-phenylhexan-3-one (25Ea)



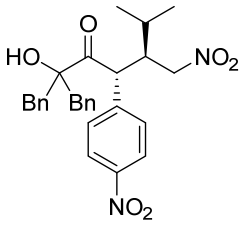
The title compound **25Ea** was prepared from 3-hydroxy-1-(4-methoxyphenyl)-3-methylbutan-2-one (**23E**) (20.83 mg, 0.1 mmol) and nitrostyrene **24a** (44.7 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 16.1 mg, 0.045 mmol, 45 %. m.p. 142–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 – 7.25 (m, 7H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.64 – 4.49 (m, 2H), 4.42 – 4.20 (m, 2H), 3.85 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.8, 159.3, 137.4, 129.4, 128.4, 127.8, 127.8, 127.6, 125.9, 114.6, 77.9, 54.9, 54.6, 46.6, 26.0, 25.6. UPLC-DAD-QTOF: $C_{20}H_{23}NO_5Na$ $[M+Na]^+$ calcd.: 380.1474, found: 380.1470. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 16.5 min (major) and 21.6 min (minor)). The product was obtained with 77 % *ee*.

2-Benzyl-2-hydroxy-6-nitro-4-(4-nitrophenyl)-1,5-diphenylhexan-3-one (27Aa)



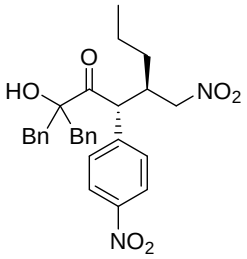
The title compound **27Aa** was prepared from 3-benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (**26A**) (37.5 mg, 0.1 mmol) and nitrostyrene **24a** (29.8 mg, 0.2 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 51.9 mg, 0. 099 mmol, 99 %. m.p. 187–188 °C. $[\alpha]_D^{25}$= –97.0° (*c* = 0.54, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.86 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.24 (m, 8H), 7.16 (d, *J* = 9.3 Hz, 2H), 7.00 – 6.88 (m, 3H), 6.86 – 6.75 (m, 2H), 6.58 (d, *J* = 7.1 Hz, 2H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.43 (dd, *J* = 12.0, 10.3 Hz, 1H), 4.28 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.17 (dd, *J* = 12.1, 4.0 Hz, 1H), 3.01 (d, *J* = 13.5 Hz, 1H), 2.27 (dd, *J* = 28.1, 13.6 Hz, 2H), 1.95 (d, *J* = 13.7 Hz, 1H), 1.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 208.9, 147.2, 139.9, 137.4, 134.6, 134.2, 130.8, 130.1, 129.8, 129.1, 128.8, 128.5, 128.5, 128.1, 127.3, 126.5, 124.0, 83.4, 78.1, 55.5, 46.2, 42.8, 42.4. UPLC-DAD-QTOF: $C_{31}H_{27}N_2O_6$ $[M–H]^–$ calcd.: 523.1869, found: 523.1880. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 16.7 min (major) and 22.7 min (minor)).

2-Benzyl-2-hydroxy-6-methyl-5-(nitromethyl)-4-(4-nitrophenyl)-1-phenylheptan-3-one (27Ab)



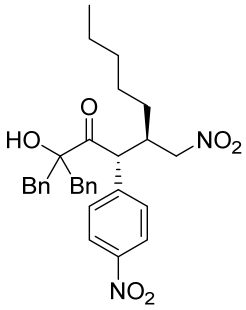
The title compound **27Ab** was prepared from 3-benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (**26A**) (37.5 mg, 0.1 mmol) and 3-methyl-1-nitrobut-1-ene (**24b**) (34.5 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 22.1 mg, 0. 045 mmol, 45 %. m.p. 159–160 °C. $[\alpha]_D^{25}$= –24.2° (*c* = 0.80, 97 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.92 (d, *J* = 8.8 Hz, 2H), 7.46 – 7.25 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.15 – 6.97 (m, 3H), 6.77 (d, *J* = 6.9 Hz, 2H), 4.70 (d, *J* = 10.9 Hz, 1H), 4.13 – 3.92 (m, 2H), 3.23 – 3.18 (m, 1H), 3.15 (d, *J* = 13.6, 1H), 2.92 (d, *J* = 13.5 Hz, 1H), 2.79 (d, *J* = 13.5 Hz, 1H), 2.54 (d, *J* = 13.5 Hz, 1H), 1.95 (s, 1H), 1.56 – 1.45 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.3, 147.5, 141.3, 135.0, 134.8, 131.3, 130.9, 130.6, 129.0, 128.9, 127.8, 127.4, 124.2, 84.1, 74.1, 54.0, 44.8, 44.6, 44.3, 29.4, 21.6, 16.3. UPLC-DAD-QTOF: $C_{28}H_{30}N_2O_6Na$ $[M+Na]^+$ calcd.: 513.2002, found: 513.2001. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 99:1, flow rate = 1.0 mL/min, retention times: 84.8 min (major) and 114.7 min (minor)).

2-Benzyl-2-hydroxy-5-(nitromethyl)-4-(4-nitrophenyl)-1-phenyloctan-3-one (27Ad)



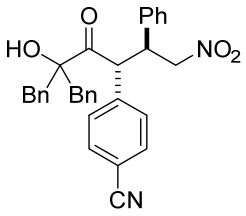
The title compound **27Ad** was prepared from 3-benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (**26A**) (37.5 mg, 0.1 mmol) and 1-nitropent-1-ene (**24d**) (34.5 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 37.2 mg, 0. 076 mmol, 76 %. m.p. 128–129 °C. $[\alpha]_D^{25}$= –41.0° (*c* = 1.0, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.91 (d, *J* = 8.8 Hz, 2H), 7.44 – 7.31 (m, 5H), 7.19 – 6.96 (m, 5H), 6.79 (d, *J* = 7.0 Hz, 2H), 4.63 (d, *J* = 10.0 Hz, 1H), 4.35 (dd, *J* = 13.0, 4.3 Hz, 1H), 3.81 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.14 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 13.5 Hz, 1H), 2.83 (d, *J* = 13.6 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.57 (d, *J* = 13.5 Hz, 1H), 1.94 (s, 1H), 1.43 – 1.23 (m, 2H), 1.13 – 1.05 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.5, 147.4, 141.5, 135.0, 131.3, 130.7, 129.0, 128.8, 127.8, 127.3, 124.1, 84.2, 75.7, 54.9, 45.1, 44.0, 39.8, 32.4, 20.1, 14.3. UPLC-DAD-QTOF: $C_{28}H_{30}N_2O_6Na$ $[M+Na]^+$ calcd.: 513.2002, found: 513.2000. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD–H, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 14.2 min (major) and 26.9 min (minor)).

2-Benzyl-2-hydroxy-5-(nitromethyl)-4-(4-nitrophenyl)-1-phenyldecan-3-one (27Ae)



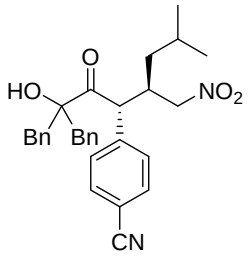
The title compound **27Ae** was prepared from 3-benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (**26A**) (37.5 mg, 0.1 mmol) and 1-nitrohept-1-ene (**24e**) (42.9 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 38.9 mg, 0. 075 mmol, 75 %. m.p.122–123 °C. $[\alpha]_D^{25}$= –47.3° (*c* = 0.73, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.90 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.30 (m, 5H), 7.16 – 6.98 (m, 5H), 6.79 (d, *J* = 6.9 Hz, 2H), 4.62 (d, *J* = 10.0 Hz, 1H), 4.37 (dd, *J* = 12.9, 4.3 Hz, 1H), 3.81 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.10 (dd, *J* = 18.9, 13.5 Hz, 1H), 2.83 (d, *J* = 13.5 Hz, 1H), 2.79 –2.69 (m,1H), 2.57 (d, *J* = 13.5 Hz, 1H), 1.95 (s, 1H), 1.41 – 1.17 (m, 8H), 0.93 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.5, 147.3, 141.4, 135.0, 131.2, 130.6, 129.0, 128.8, 127,8, 127.3, 124.1, 84.2, 75.8, 69.0, 54.8, 45.1, 44.0, 40.0, 31.9, 30.2, 26.6, 22.8, 14.4. UPLC-DAD-QTOF: $C_{30}H_{34}N_2O_6Na$ $[M+Na]^+$ calcd.: 541.2315, found: 541.2325. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 9.4 min (minor) and 10.9 min (major)).

4-(5-Benzyl-5-hydroxy-1-nitro-4-oxo-2,6-diphenylhexan-3-yl)benzonitrile (27Ba)



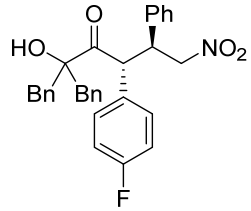
The title compound **27Ba** was prepared from 4-(3-benzyl-3-hydroxy-2-oxo-4-phenylbutyl)benzonitrile (**26B**) (35.5 mg, 0.1 mmol) and nitrostyrene **24a** (17.9 mg, 1.2 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 35.3 mg, 0. 070 mmol, 70 %. m.p. 220–221 °C. $[\alpha]_D^{25}$= –66.1° (*c* = 1.0, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 – 7.24 (m, 10H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.97 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 2H), 4.96 (t, *J* = 11.0 Hz, 1H), 4.46 (dd, *J* = 11.9, 10.3 Hz, 1H), 4.29 (dd, *J* = 10.9, 3.9 Hz, 1H), 4.24 – 4.18 (m, 1H), 3.04 (d, *J* = 13.5 Hz, 1H), 2.35 (d, *J* = 13.5 Hz, 1H), 2.24 (d, *J* = 13.7 Hz, 1H), 2.00 (d, *J* = 13.7 Hz, 1H, 1.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 209.0, 138.0, 137.4, 134.5, 134.2, 132.6, 130.8, 130.0, 129.6, 129.0, 128.5, 128.4, 128.1, 127.2, 126.6, 118.2, 111.5, 83.4, 78.1, 55.6, 46.1, 42.7, 42.3. UPLC-DAD-QTOF: $C_{32}H_{28}N_2O_4Na$ $[M+Na]^+$ calcd.: 527.1947, found: 527.1942. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 15.1 min (major) and 18.6 min (minor)).

4-(2-Benzyl-2-hydroxy-7-methyl-5-(nitromethyl)-3-oxo-1-phenyloctan-4-yl) benzonitrile (27Bc)



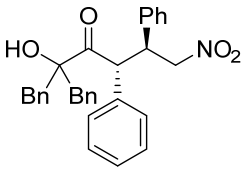
The title compound **27Bc** was prepared from 4-(3-benzyl-3-hydroxy-2-oxo-4-phenylbutyl)benzonitrile (**26B**) (35.5 mg, 0.1 mmol) and 4-methyl-1-nitropent-1-ene (**24c**) (38.7 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 17.4 mg, 0. 036 mmol, 36 %. m.p. 121–122 °C. $[\alpha]_D^{25}$= –61.9 (*c* = 0.21, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.43 –7.31 (m, 6H), 7.20 – 7.06 (m, 5H), 6.82 (d, *J* = 7.1 Hz, 2H), 4.58 (d, *J* = 9.9 Hz, 1H), 4.38 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.77 (dd, *J* = 13.0, 4.5 Hz, 1H), 3.14 (d, *J* = 13.6 Hz, 1H), 3.02 (d, *J* = 13.5 Hz, 1H), 2.86 – 2.70 (m, 2H), 2.57 (d, *J* = 13.5 Hz, 1H), 1.93 (s, 1H), 1.30 (s, 1H), 1.06 – 0.96 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.6, 139.7, 135.1, 135.0, 132.7, 131.3, 130.7, 129.0, 128.9, 127.8, 127.4, 118.8, 111.7, 84.1, 75.7, 55.5, 44.9, 44.1, 39.4, 37.8, 25.5, 24.0, 21.5. UPLC-DAD-QTOF: $C_{30}H_{32}N_2O_4Na$ $[M+Na]^+$ calcd.: 507.2260, found: 507.2263. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 98:2, flow rate = 1.0 mL/min, retention times: 29.4 min (min.) and 32.0 min (major.)).

2-Benzyl-4-(4-fluorophenyl)-2-hydroxy-6-nitro-1,5-diphenylhexan-3-one (27Ca)



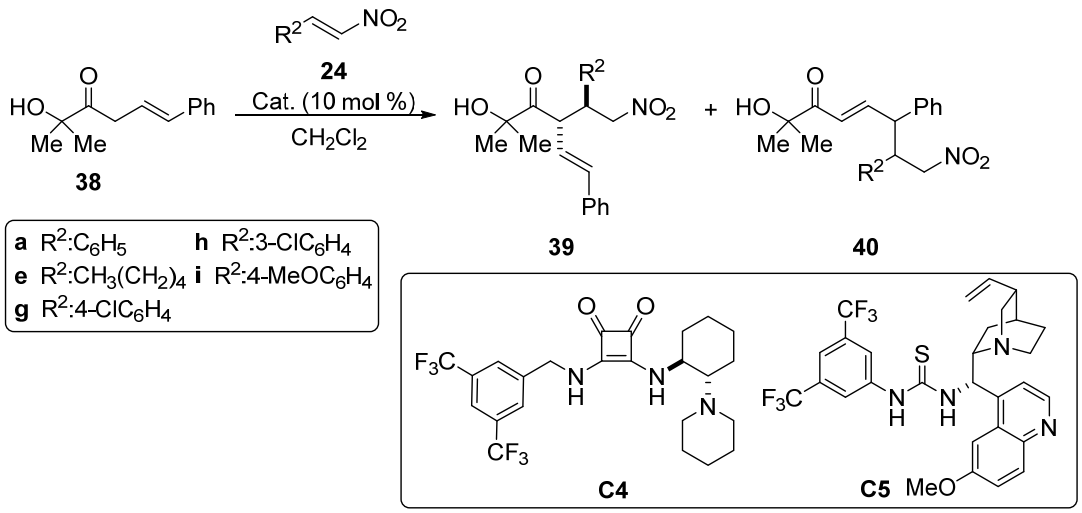
The title compound **27Ca** was prepared from 3-benzyl-1-(4-fluorophenyl)3-hydroxy-4-phenylbutan-2-one (**26C**) (34.8 mg, 0.1 mmol) and nitrostyrene **24a** (44.7 mg, 0.3 mmol) to the General Procedure, affording a white solid as a single diastereomer. Yield: 24.4 mg, 0. 049 mmol, 49 %. m.p. 198-199 °C. $[\alpha]_D^{25}$= –65.7° (*c* = 1.0, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.45 – 7.18 (m, 8H) 7.10 – 6.90 (m, 6H), 6.79 (t, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 7.1 Hz, 2H), 4.83 (d, *J* = 10.7 Hz, 2H), 4.57 – 4.37 (m, 1H), 4.34 – 4.13 (m, 2H), 3.05 (d, *J* = 13.4 Hz, 1H), 2.37 (d, *J* = 13.4 Hz, 1H), 2.29 – 2.08 (m, 2H), 1.77 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.1, 164.2, 138.4, 135.0, 131.2, 131.0, 130.8, 130.5, 123.3, 128.9, 128.6, 127.4, 127.0, 116.7, 116.4, 83.8, 78.9, 55.4, 46.6, 43.0, 42.5. UPLC-DAD-QTOF: $C_{31}H_{28}FNO_4Na$ $[M+Na]^+$ calcd.: 520.1900, found: 520.1895. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 98:2, flow rate = 1.0 mL/min, retention times: 14.1 min (minor) and 15.9 min (major)).

2-Benzyl-2-hydroxy-6-nitro-1,4,5-triphenylhexan-3-one (27Da)



The title compound **27Da** was prepared from 3-benzyl-3-hydroxy-1,4-diphenylbutan-2-one (**26D**) (33.0 mg, 0.1 mmol) and nitrostyrene **24a** (44.7 mg, 0.3 mmol) according to the General Procedure, affording a white solid as a single diastereomer. Yield: 22.1 mg, 0. 046 mmol, 46 %. m.p. 194–195 °C. $[\alpha]_D^{25}$= –98.60° (*c* = 0.23, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41 – 6.87 (m, 18H), 6.68 (d, *J* = 6.9 Hz, 2H), 4.80 (d, *J* = 10.7 Hz, 1H), 4.54 – 4.39 (m, 1H), 4.37 – 4.15 (m, 2H), 3.03 (d, *J* = 13.4 Hz, 1H), 2.38 (d, *J* = 13.4 Hz, 1H) 2.34 – 2.17 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.2, 138.6, 135.2, 135.0, 133.1, 131.2, 130.5, 129.7, 129.3, 128.9, 128.6, 128.6, 128.5, 128.3, 127.3, 127.0, 83.8, 79.1, 56.5, 46.6, 42.9, 42.5. UPLC-DAD-QTOF: $C_{31}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 502.1994, found: 502.1993. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 98:2, flow rate = 1.0 mL/min, retention times: 18.1 min (major) and 21.6 min (minor)).

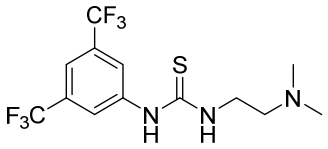
7.3.4. General procedure for the 1,4-conjugate addition of alkenyl α-hydroxy ketones 38 to nitroolefins 24



To a solution of the alkenyl α-hydroxy ketone **38** (0.2 mmol, 1 equiv.) and *trans*-β-nitrostyrene **24** (0.22 mmol, 1.1 equiv.) in dichloromethane (0.4 mL), catalyst **C4** (5.0 mg, 0.01 mmol, 5 mol %) was added at room temperature. The resulting mixture was stirred to completion of the reaction (2.5–14 h, monitoring by TLC). Then the reaction mixture was submitted to flash column chromatography (eluent hexane/EtOAc 90:10).

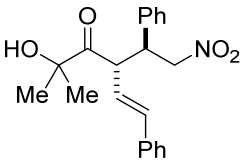
The same procedure was employed for the reactions involving catalyst **C5**, but with a molar ratio of ketone/**5**/catalyst of 1.5:1:0.1 at room temperature or at temperature below zero.

The corresponding racemic compounds were prepared following the above procedure at room temperature, but using the achiral thiourea showed below (10 mol %), which was prepared following literature protocols.[283]



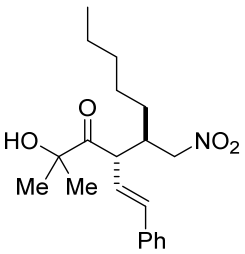
Achiral thiourea used for the synthesis of racemics compounds.

2-Hydroxy-2-methyl-4-(2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (39a)



The title compound **39a** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24a** (32.8 mg, 0.22 mmol) according to the General Procedure for **C4**, affording a white solid as a single diastereomer. Yield: 60.1 mg, 0.17 mmol, 85 %. m.p. 143–145 °C. $[\alpha]_D^{25}$= –123.0° (*c* = 0.6, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52 – 7.16 (m, 10H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.95 – 4.61 (m, 2H), 4.35 – 4.13 (m, 2H), 2.73 (s, 1H), 1.08 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.6, 137.4, 136.4, 135.5, 128.9, 128.8, 128.6, 128.3, 126.5, 124.32, 78.0, 77.3, 54.5, 45.7, 26.1, 25.9. UPLC-DAD-QTOF: $C_{21}H_{24}NO_4$ $[M+H]^+$ calcd.: 354.1705, found: 354.1703. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 15.8 min (minor) and 22.1 min (major)).

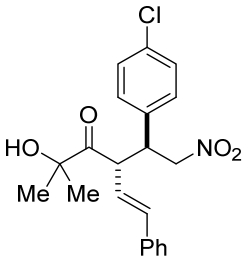
2-Hydroxy-2-methyl-5-(nitromethyl)-4-styryldecan-3-one (39e)



The title compound **39e** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24e** (31.5 mg, 0.22 mmol) according to the General Procedure for **C4**, affording a yellow oil as a single diastereomer. Yield: 65.3 mg, 0.19 mmol, 94 %. $[\alpha]_D^{25}$= –64.4° (*c*= 1.0, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40 – 7.26 (m, 5H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.00 (dd, *J* = 15.9, 9.8 Hz, 1H), 4.67 (dd, *J* = 13.0, 4.6 Hz, 1H), 4.46 (dd, *J* = 13.0, 5.6 Hz, 1H), 4.10 (t, *J* = 9.3 Hz, 1H), 3.36 (s, 1H), 2.72 (s, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.37 – 1.24 (m, 8H),

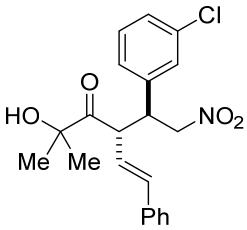
0.91 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 215.6, 138.2, 137.7, 130.7, 130.4, 128.4, 126.2, 79.4, 77.7, 53.4, 41.7, 33.5, 32.1, 28.9, 28.8, 28.3, 24.3, 15.9. UPLC-DAD-QTOF: $C_{20}H_{29}NO_4Na$ $[M+Na]^+$ calcd.: 370.1994, found: 370.1994. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: 9.0 min (minor) and 10.5 min (major)).

4-(1-(4-Chlorophenyl)-2-nitroethyl)-2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (39g)



The title compound **39g** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24a** (40.4 mg, 0.22 mmol) according to the General Procedure for **C4**, affording a white solid as a single diastereomer. Yield: 63.5 mg, 0.16 mmol, 82 %. m.p. 166–168 °C. $[\alpha]_D^{25}$= –146.6° (*c* = 0.87, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 – 7.28 (m, 7H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.07 (dd, *J* = 15.9, 9.5 Hz, 1H), 4.83 (dd, *J* = 13.1, 4.8 Hz, 1H), 4.69 (dd, *J* = 13.1, 10.1Hz, 1H), 4.34 – 4.12 (m, 2H), 2.73 (s, 1H), 1.09 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.7, 137.2, 136.4, 135.8, 134.6, 130.1, 129.5, 129.3, 129.2, 127.0, 124.2, 78.4, 54.6, 45.4, 26.9, 26.7 UPLC-DAD-QTOF: $C_{21}H_{22}NO_4ClNa$ $[M+Na]^+$ calcd.: 410.1135, found: 410.1126. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 17.1 min (minor) and 22.4 min (major)).

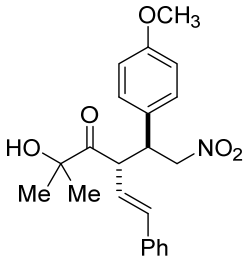
4-(1-(3-Chlorophenyl)-2-nitroethyl)-2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (39h)



The title compound **39h** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one **38** (40.8 mg, 0.2 mmol) and nitrostyrene **24h** (40.4 mg, 0.22 mmol) according to the General Procedure for **C4**, affording a white solid as a single diastereomer. Yield: 70.6 mg, 0.18 mmol, 91 %. m.p. 158–160 °C. $[\alpha]_D^{25}$= –117.94° (*c* = 0.5, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 – 7.24 (m, 8H), 7.20 – 7.12 (m, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.05 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.81 (dd, *J* = 13.2, 4.9 Hz, 1H), 4.68 (dd, *J* = 13.2, 10.0 Hz, 1H), 4.35 – 4.24 (m, 1H), 4.16 (td, *J* = 10.4, 4.9 Hz, 1H), 2.74 (s, 1H), 1.09 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 211.1, 139.5, 136.7, 135.2, 134.6, 130.0, 128.7, 128.6, 128.3, 128.2, 126.5, 126.4, 123.6, 77.7, 54.0, 45.0, 26.2, 26.1. UPLC-DAD-QTOF: $C_{21}H_{22}NO_4ClNa$ $[M+Na]^+$ calcd.: 410.1135, found: 410.1125. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel

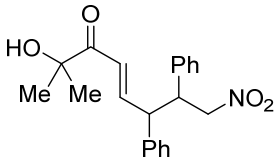
Chiralpak IB, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 19.5 min (minor) and 25.3 min (major)).

2-Hydroxy-4-(1-(4-methoxyphenyl)-2-nitroethyl)-2-methyl-6-phenylhex-5-en-3-one (39i)



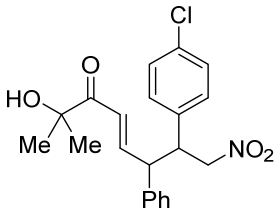
The title compound **39i** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24i** (39.4 mg, 0.22 mmol) according to the General Procedure for **C4**, affording a white solid as a single diastereomer. Yield: 57.5 mg, 0.15 mmol, 75 %. m.p. 154–156 °C. $[\alpha]_D^{25}$= –124.5° (*c* = 0.94, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.46 – 7.31 (m, 5H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9, 9.6 Hz, 1H), 4.89 – 4.61 (m, 2H), 4.31 – 4.07 (m, 2H), 3.80 (s, 1H), 2.80 (s, 1H), 1.10 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 210.4, 158.1, 134.9, 134.2, 128.1, 127.9, 127.5, 127.3, 125.2, 123.2, 77.0, 53.9, 53.3, 43.8, 24.9, 24.7. UPLC-DAD-QTOF: $C_{22}H_{25}NO_5Na$ $[M+Na]^+$ calcd.: 406.1630, found: 406.1633. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 22.3 min (minor) and 33.1 min (major)).

2-Hydroxy-2-methyl-8-nitro-6,7-diphenyloct-4-en-3-one (40a)



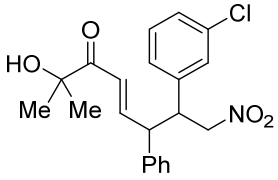
The title compound **40** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24a** (19.4 mg, 0.13 mmol) according to the General Procedure for **C5**, affording a white solid as a single diastereomer. Yield: 7.78 mg, 0.022 mmol, 11 %. m.p. 138–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.39–7.15 (m, 7H), 7.07 – 6.96 (m, 4H), 6.59 (d, *J* = 15.2 Hz, 1H), 4.78 – 4.63 (m, 2H), 4.00 (td, *J* = 8.8, 6.5 Hz, 1H), 3.82 (t, *J* = 9.6 Hz, 1H), 3.70 (s, 1H), 1.41 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 202.9, 149.0, 139.3, 137.4, 129,9, 129.7, 129.0, 128.6, 125.1, 79.4, 76.6, 54.0, 49.8, 27.3. UPLC-DAD-QTOF: $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ calcd.: 376.1525, found: 376.1526. The enantiomeric excess was not determined.

7-(4-Chloropheynyl)-2-hydroxy-2-methyl-8-nitro-6-phenyloct-4-en-3-one (40g)



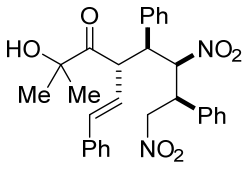
The title compound **40g** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24g** (23.9 mg, 0.13 mmol) according to the General Procedure for **C5**, affording an orange solid as a single diastereomer. Yield: 14.6 mg, 0.04 mmol, 29 %. m.p. 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37 – 7.17 (m, 7H), 7.04 (dd, *J* = 7.8, 1.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 15.7 Hz, 1H), 4.80 – 4.60 (m, 2H), 3.99 (td, *J* = 9.3, 5.8 Hz, 1H), 3.79 (t, *J* = 9.7 Hz, 1H), 3.66 (s, 1H), 1.43 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 202.9, 148.6, 139.0, 136.0, 134.9, 130.6, 130.1, 130.0, 129.1, 128.8, 125.3, 79.4, 76.6, 53.9, 49.3, 27.3, 27.3 UPLC-DAD-QTOF: $C_{21}H_{22}NO_4ClNa$ $[M+Na]^+$ calcd.: 410.1135, found: 410.1133. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 17.7 min (minor) and 19.8 min (major)). The product was obtained with 66 % *ee*.

7-(3-Chloropheynyl)-2-hydroxy-2-methyl-8-nitro-6-phenyloct-4-en-3-one (40h)



The title compound **40h** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol) and nitrostyrene **24h** (23.9 mg, 0.13 mmol) according to the General Procedure for **C5**, affording a yellow oil as a single diastereomer. yield: 18.2 mg, 0.05 mmol, 36 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36 – 7.09 (m, 5H), 7.07 – 6.99 (m, 2H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 4.80 – 4.60 (m, 2H), 3.97 (td, *J* = 9.2, 6.0 Hz, 1H), 3.79 (t, *J* = 9.7 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 201.5, 146.9, 138.3, 137.6, 134.2, 129.6, 128.6, 127.8, 127.7, 127.4, 126.2, 77.7, 75.2, 52.4, 48.1, 25.8. UPLC-DAD-QTOF: $C_{21}H_{22}ClNO_4Na$ $[M+Na]^+$ calcd.: 410.1135, found: 410.1138. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 19.2 min (minor) and 24.9 min (major)). The product was obtained with 71 % *ee*.

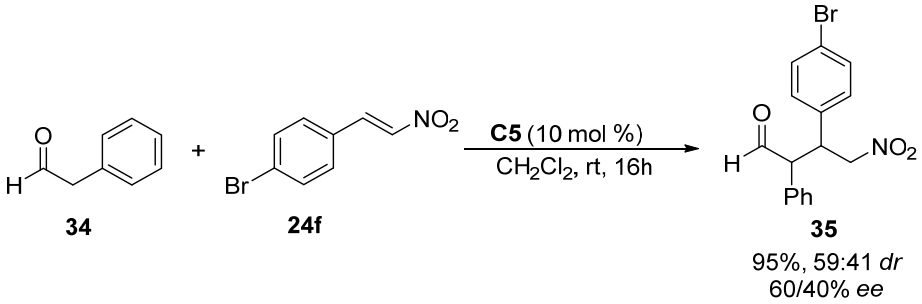
2-Hydroxy-2-methyl-6,8-dinitro-5,7-diphenyl-4-(styryl)octan-3-one (41)



The title compound **41** was prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one (**38**) (40.8 mg, 0.2 mmol, 1 equiv.) and nitrostyrene **24a** (89.46 mg, 0.6 mmol, 3 equiv.) according to the General Procedure for **C5** (for 96 h), affording a white solid as a single diastereomer. Yield: 75.4 mg, 0.15 mmol, 78 %. Decomp. temp.: 185–187 °C. $[\alpha]_D^{24}$= +22.7° (*c* = 0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.48 (t, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.3

Hz, 1H), 7.36 – 7.29 (m, 7H), 7.27 – 7.24 (m, 3H), 7.03 – 6.95 (m, 2H), 6.65 (d, *J* = 15.8 Hz, 1H), 5.80 (dd, *J* = 15.8, 9.9 Hz, 1H), 5.10 (dd, *J* = 10.6, 4.0 Hz, 1H) 5.00 – 4.83 (m, 2H), 4.52 (t, *J* = 10.2 Hz, 1H), 4.14 (t, *J* = 10.5 Hz, 1H), 3.77 (dt, *J* = 11.0, 3.6 Hz, 1H), 2.46 (s, 1H), 0.94 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 211.2, 136.8, 136.6, 135.6, 134.6, 129.8, 129.3, 129.0, 128.7, 128.8, 128.5, 128.3, 127.1, 126.5, 122.6, 93.7, 77.6, 73.4, 56.6, 47.9, 44.0, 26.8, 26.3. UPLC-DAD-QTOF: $C_{29}H_{30}N_2O_6Na$ $[M+Na]^+$ calcd.: 525.2002, found: 525.2007.

7.3.5. Conjugate addition of 2-phenylacetaldehyde (34) to 4-bromo nitrostyrene (24f)

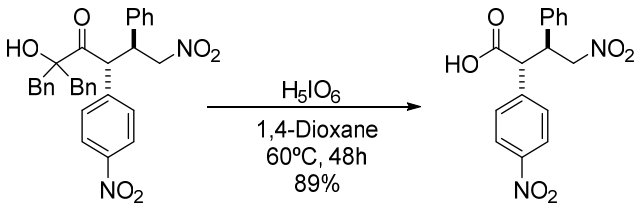


To a mixture of 2-phenylacetaldehyde (**34**) (12 mg, 0.1 mmol, 1 equiv.) and 4-bromonitrostyrene (**24f**) (45.6 mg, 0.2 mmol, 2 equiv.) in dichloromethane (0.3 mL) at room temperature, catalyst **C5** (5.9 mg, 0.01 mmol, 10 mol %) was added. The resulting solution was stirred at room temperature, until consumption of 2-phenylacetaldehyde as monitored by ^{1}H NMR. The reaction was quenched with HCl 2M (1 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with Hexane/ EtOAc 90:10) to afford 3-(4-bromophenyl)-4-nitro-2-phenylbutanal (**35**) as a diastereomeric mixture *dr* 59:41, major diastereomer 60 % *ee*, minor diastereomer 40 % *ee*. White solid. Yield: 33.0 mg, 0.095 mmol, 95 %. m.p. 152–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.72 (d, *J* = 1.0 Hz, 1H), 9.55 (d, *J* = 1.7 Hz, 1H), 7.52 – 7.38 (m, 3H), 7.34 – 7.21 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.99 – 6.92 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.91 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.73 (dd, *J* = 12.7, 8.9 Hz, 1H), 4.54 – 4.38 (m, 2H), 4.33 (dd, *J* = 18.6, 4.8 Hz, 1H), 4.27 – 4.21 (m, 1H), 4.05 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.98 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 197.9, 196.4, 136.2, 135.3, 132.2, 131.7, 130.0, 130.0, 129.8, 129.8, 129.4, 129.2, 129.1, 129.1, 128.4, 128.4, 122.2, 121.8, 78.0, 77.8, 61.5, 60.8, 43.7, 43.6. UPLC-DAD-QTOF: $C_{16}H_{13}BrNO_3$ $[M–H]^–$ calcd.: 346.0079, found: 346.0078. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention

times: major diastereomer: 19.5 min (minor) and 21.6 min (major)); minor diastereomer: 12.1 min (major) and 17.8 min (minor)).

7.3.6. Chemical elaboration of adducts 27

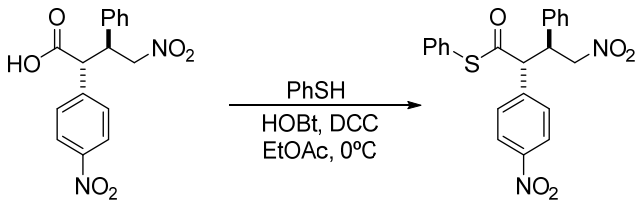
*7.3.6.1. Ketol cleavage in adduct **27Aa** to yield carboxylic acid **28***



27Aa **28**

To a suspension of **27Aa** (52 mg, 0.1 mmol, 1 equiv.) in dioxane (3 mL), periodic acid (228 mg, 1 mmol, 10 equiv.) was added. The resulting mixture was stirred at 60 °C for 24 h and afterwards the reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was suspended in dioxane (3 mL) and periodic acid (228 mg, 1 mmol, 10 equiv.) was added. The resulting mixture was stirred at 60 °C for 24 h and afterwards the reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 50:50) to give the carboxylic acid **28** as a white solid. Yield: 29.4 mg, 0.089 mmol, 89 %. m.p. 174–176 °C. $[\alpha]_D^{25}$= –22.0° (*c*= 1.47, 99 % *ee*, MeOH). ^{1}H NMR (300 MHz, CD_3OD), δ: 8.29 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.53 – 7.17 (m, 5H), 4.65 (dd, *J* = 12.8, 9.8 Hz, 1H), 4.44 – 4.07 (m, 3H). ^{13}C NMR (75 MHz, CD3OD), δ: 173.5, 149.2, 144.9, 139.0, 131.0, 129.7, 129.5, 129.0, 125.1, 79.3, 56.0, 48.4. UPLC-DAD-QTOF: $C_{16}H_{14}N_2O_6Na$ $[M+Na]^+$ calcd.: 355.0750, found: 353.0739.

*7.3.6.2. Conversion of carboxylic acid **28** into thioester **30***[284]



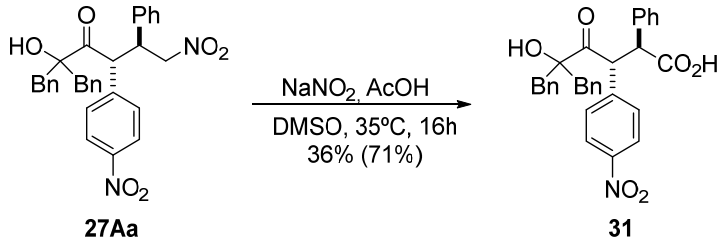
28 **30**

86 % yield,
dr: 99:1,
97/ 99% *ee*

To a solution of carboxylic acid **28** (33 mg, 0.1 mmol, 1 equiv.) and 1-hydroxybenzotriazole hydrate (13.5 mg, 0.1 mmol, 1 equiv.) in ethyl acetate (1 mL) under argon at 0 °C, thiophenol (20 µL, 0.2 mmol, 2 equiv.) was added. After 5 min, dicyclohexylcarbodiimide (23 mg, 0.11 mmol, 1.1 equiv.) was added. After stirring overnight, a 50 % solution of acetic acid in ethyl acetate (0.3 mL) was added. The reaction mixture was filtered through a pad of celite and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 80:20) to give the title compound **30** as a white solid. Yield: 36.3 mg, 0.086 mmol, 86 %. m.p. 152–153 °C. $[\alpha]_D^{25}$= –38.8° (*c*= 0.5, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.30 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.30 (m, 3H), 7.03 – 6.93 (m, 2H), 4.58 – 4.41 (m, 2H), 4.37 – 4.24 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.0, 148.2, 141.5, 135.7, 134.1, 129.9, 129.6, 129.3, 129.1, 128.6, 128.2, 126.1, 124.5, 77.8, 62.0, 47.3. UPLC-DAD-QTOF: $C_{22}H_{17}N_2O_5S$ $[M–H]^-$ calcd.: 421.0858, found: 421.0858. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80:20, flow rate = 1.0 mL/min, retention times: major diastereomer: 13.6 min (minor) and 17.4 min (major)); minor diastereomer: 15.6 min (major) and 24.6 min (minor)).

[284] Garnier-Amblard, E. C.; Mays, S. G.; Arrendale, R. F.; Baillie, M. T.; Bushnev, A. S.; Culver, D. G.; Evers, T.J.; Holt, J. J.; Howard, R. B.; Liebeskind, L. S.; Menaldino, D. S.; Natchus, M. G.; Petros, J. A.; Ramaraju, H.; Reddy, G. P.; Liotta, D. C. *Med. Chem. Lett*. **2011**, *2*, 438–443.

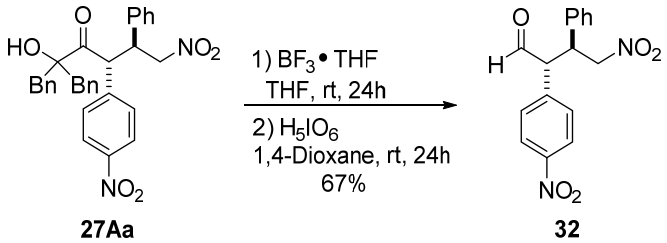
*7.3.6.3. Nef reaction in adduct **27Aa** to yield carboxylic acid **31***[285]



27Aa **31**

A solution of 2-benzyl-2-hydroxy-6-nitro-4-(4-nitrophenyl)-1,5-diphenylhexan-3-one (**27Aa**) (104.9 mg, 0.2 mmol, 1 equiv.), $NaNO_2$ (82.8 mg, 1.2 mmol, 6 equiv.) and AcOH (120.1 mg, 2 mmol, 10 equiv.) in DMSO (2 mL) was stirred overnight at 35 °C. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed successively with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting with hexane/EtOAc 90:10 → 70:30). Yield 36.7 mg, 0.072 mmol, 36 %. m.p. 169–170 °C. $[\alpha]_D^{25}$= –30.3° (*c*= 0.40, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD), δ: 7.77 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.53 – 7.28 (m, 4H), 7.27 – 7.15 (m, 5H), 6.85 – 6.62 (m,7H), 5.51 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.36 (d, *J* = 13.5 Hz, 1H), 2.27 (d, *J* = 13.5 Hz, 1H), 2.08 (d, *J* = 13.5 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD), δ: 211.0, 175.1, 147.9, 143.4, 138.8, 137.3, 136.4, 134.0, 132.0, 131.7, 131.4, 130.7, 130.5, 129.8, 129.4, 129.1, 128.9, 128.3, 127.6, 126.6, 123.9, 84.7, 56.6, 56.1, 45.7, 43.7. UPLC-DAD-QTOF: $C_{31}H_{27}NO_6Na$ $[M+Na]^+$ calcd.: 532.1736, found: 532.1732.

*7.3.6.4. Conversion of adduct **27Aa** into aldehyde **32** and alcohol **33***

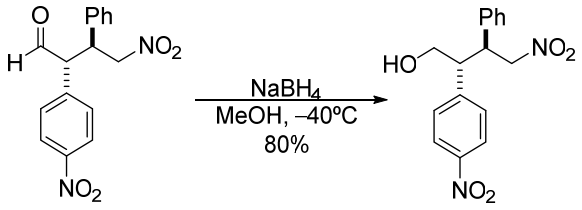


27Aa **32**

To a suspension of **27Aa** (105 mg, 0.2 mmol, 1 equiv.) in tetrahydrofuran (2 mL), borane tetrahydrofuran solution complex 1.0 M (0.8 mL, 0.8 mmol, 4 equiv.) was added. The resulting mixture was stirred at room temperature for 24 h and afterwards methanol (1 mL) was added at 0 °C and the solvent was evaporated. The resulting crude material

[285] Adapted from: Huang, J.-Z.; Wu, X.; Gong, L., *Adv. Synth. Catal*. **2013**, *355*, 2531-2537.

was suspended in dioxane (4 mL), periodic acid (0.456 g, 2 mmol, 10 equiv.) was added and the mixture was stirred at room temperature for 24 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was crushed with diethyl ether to give the corresponding aldehyde **32** as a white solid. Yield 42.2 mg, 0.13 mmol, 67 %. m.p. 140–142 °C. $[\alpha]_D^{25}$= –9.9° (*c*= 0.40, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.30 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.42 – 7.31 (m, 3H), 7.30 – 7.21 (m, 2H), 4.63 – 4.40 (m, 2H), 4.34 – 4.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.2, 148.1, 140.0, 135.8, 130.4, 129.4, 128.7, 128.1, 124.6, 77.8, 60.1, 45.0. UPLC-DAD-QTOF: $C_{16}H_{13}N_2O_5$ $[M–H]^-$ calcd.: 313.0824, found: 313.0821.

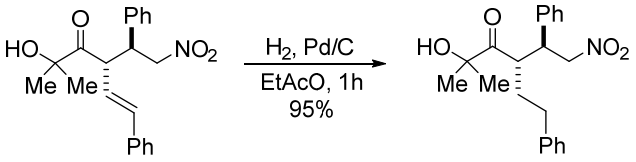


32 **33**

A mixture of aldehyde, 4-nitro-2-(4-nitrophenyl)-3-phenylbutanal (**32**) (62.9 mg, 0.2 mmol, 1 equiv.) and $NaBH_4$ (15.1 mg, 0.4 mmol, 2 equiv.) in MeOH (0.4mL) was stirred at –40 °C for 2 h. Then the reaction was quenched with NH_4Cl and extracted with DCM (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (eluting with hexane/EtOAc 90:10). Orange solid, yield 50.6 mg, 0.16 mmol, 80 %. m.p. 128–129 °C. $[\alpha]_D^{25}$= +3.21° (*c*= 0.51, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, ($CDCl_3$), δ: 8.31 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.48 – 7.31 (m, 5H), 4.58 (dd, *J* = 12.6, 10.5 Hz, 1H), 4.43 – 4.31 (m, 1H), 4.00 (td, *J* = 10.6, 4.5 Hz, 1H), 3.68 (d, *J* = 5.6 Hz, 2H), 3.26 (dt, *J* = 10.6, 5.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD), δ: 147.9, 137.3, 129.7, 128.9, 128.3, 124.7, 79.6, 64.5, 51.1, 46.5. UPLC-DAD-QTOF: $C_{16}H_{15}N_2O_5$ $[M–H]^-$ calcd.: 315.0981, found: 315.0976.

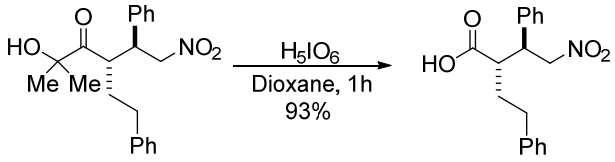
7.3.7. Chemical elaboration of adduct 39a

Hydrogenation of adduct **39a** to **42** and subsequent ketol cleavage to yield carboxylic acid **43**.



39a **42**

To a solution of 2-hydroxy-2-methyl-4-(2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one (**39a**) (206.6 mg, 0.58 mmol) in dry EtOAc (20 mL), Pd/C (Pd 10% in activated carbon) was added. The air was evacuated by vacuum and H_2 was introduced (this process was carried out three times). The reaction mixture was stirred under H_2 atmosphere at room temperature for 1 h. Then, the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product **42** as a yellow solid. Yield: 196 mg, 0.55 mmol, 95 %. m.p. 94–96 °C. $[\alpha]_D^{25}$= +5.5° (c= 0.32, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, ($CDCl_3$), δ: 7.41 – 7.19 (m, 8H), 7.14 – 7.06 (m, 2H), 4.90 – 4.76 (m, 2H), 4.09 – 4.01 (m, 1H), 3.70 – 3.64 (m, 1H), 2.64 – 2.39 (m, 2H), 2.12 – 1.97 (m, 1H), 1.96 – 1.81 (m, 1H), 1.30 (s, 1H), 1.25 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD), δ: 215.3, 140.6, 138.0, 129.0, 128.6, 128.1, 128.0, 128.0, 126.3, 75.9, 48.7, 44.2, 33.2, 29.8, 26.6. UPLC-DAD-QTOF: $C_{21}H_{25}NO_4Na$ $[M+Na]^+$ calcd.: 378.1681, found: 378.1686.

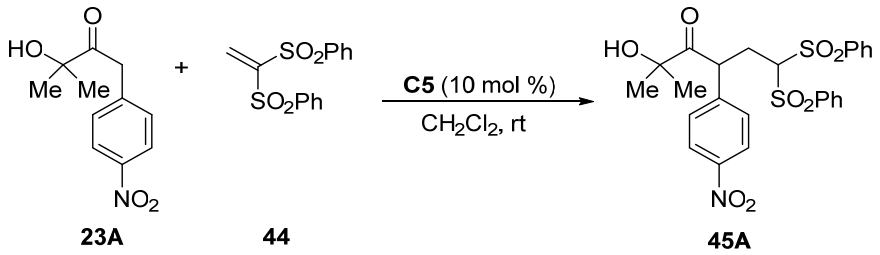


42 **43**

To a suspension of **42** (49 mg, 0.12 mmol, 1 equiv.) in dioxane (3 mL), periodic acid (274 mg, 1.2 mmol, 10 equiv.) was added. The resulting mixture was stirred at room temperature for 1 h and afterwards the reaction was quenched with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated to give the corresponding carboxylic acid **43** as an orange oil. Yield: 34.9 mg, 0.11 mmol, 93 %. $[\alpha]_D^{24}$= –45.77° (c= 0.6, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD), δ: 7.38 – 7.14 (m, 10H), 4.91 – 4.69 (m, 2H), 3.90 – 3.82 (m, 1H), 2.92 – 2.52 (m, 3H), 2.11 – 1.98 (m, 1H), 1.93 – 1.82 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD), δ: 177.9, 139.9, 135.8, 128.2, 127.9, 127.7, 127.6, 127.3, 125.7, 77.0, 47.4,

44.9, 32.8, 30.6. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1215.

7.3.8. Conjugate addition of α-hydroxy ketones 23A and 26A to vinyl 1,1-bissulfone (44)



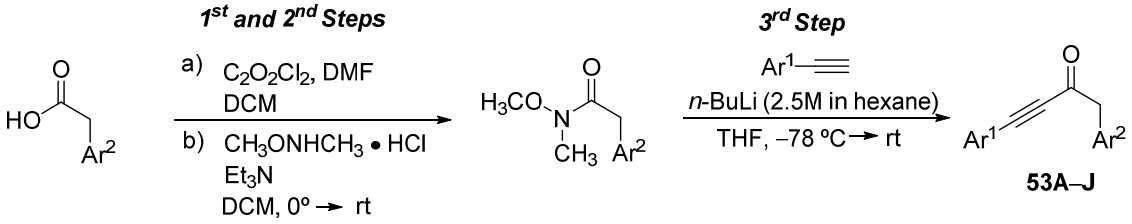
23A **44** **45A**

To a mixture of α-hydroxy ketone **23A** (22.3 mg, 0.1 mmol, 1 equiv.) and 1,1-bis(phenylsulfonyl)ethylene (**44**) (92.5 mg, 0.3 mmol, 3 equiv.) in dichloromethane (0.3 mL) at room temperature, catalyst **C5** (5.9 mg, 0.01 mmol, 10 mol %) was added. The resulting suspension was stirred at room temperature, until consumption of the α-hydroxy ketone as monitored by 1H NMR (40 h). The reaction was quenched with HCl 2M (1 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 90:10 → 70:30) to afford the product **45A** (2-hydroxy-2-methyl-4-(4-nitrophenyl)-6,6-bis(phenylsulfonyl)hexan-3-one). The product was obtained as a single diastereomer whose absolute configuration was not determined. White foam, yield: 47.8 mg, 0.090 mmol, 90 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.08 (d, *J* = 8.8 Hz, 2H), 7.95 – 7.87 (m, 2H), 7.78 – 7.68 (m, 4H), 7.63 – 7.49 (m, 4H), 7.31 (d, *J* = 8.7 Hz, 2H), 5.18 (t, *J* = 7.7 Hz, 1H), 4.13 – 4.02 (m, 1H), 2.73 (s, 1H), 2.70 – 2.59 (m, 2H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 212.2, 147.5, 143.2, 140.4, 137.6, 137.0, 135.0, 134.9, 129.5, 129.3, 129.3, 128.5, 124.2, 80.2, 77.9, 48.4, 29.8, 27.2, 26.6. UPLC-DAD-QTOF: $C_{25}H_{29}N_2O_8S_2$ $[M+NH_4]^+$ calcd.: 549.1365, found: 549.1368. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 50:50, flow rate= 1.0 mL/min, retention times: 8.4 min (major) and 10.5 min (minor)). The product was obtained with 38 % *ee*.

7.4. Experimental section for Chapter 3

7.4.1. Preparation of benzylic alkynyl ketones 53

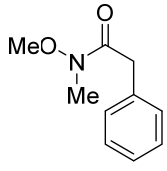
Ynones **53** were prepared by the three-step sequence shown in the scheme.



A Ar^1: C_6H_5 **E** Ar^2: C_6H_5 **I** Ar^2: 4-ClC_6H_4
B Ar^1: 4-MeC_6H_4 **F** Ar^2: 4-MeC_6H_4 **J** Ar^2: 3-ClC_6H_4
C Ar^1: 4-ClC_6H_4 **G** Ar^2: 3-MeC_6H_4
D Ar^1: 4-$MeOC_6H_4$ **H** Ar^2: 4-$MeOC_6H_4$

***1st* and *2nd* Steps**: A solution of the corresponding acetic acid (10 mmol, 1 equiv.), oxalyl chloride (1.72 mL, 20 mmol, 2 equiv.) and DMF (catalytic quantity) in dry DCM (25 mL) was stirred at room temperature for 2–3 h. The solvent was evaporated under reduced pressure to afford an oil product, which was dissolved in CH_2Cl_2 (2 mL) and dropwise moved to a stirred suspension of *N*-methoxymethylamine hydrochloride salt (1.95 g, 20 mmol, 2 equiv.) in CH_2Cl_2 (22 mL) at 0°C. Triethylamine was then slowly added (4.2 mL, 30 mmol, 3 equiv.). The mixture was then allowed to warm to room temperature and stirred. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL). The two layers were separated and the organic phase was washed with 1M HCl (5 mL) and brine (5 mL) and dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5→ 80:20) to afford the desired product.

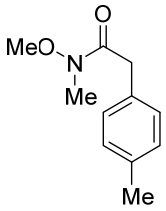
_N_-Methoxy-_N_-methyl-2-phenylacetamide



The title compound was prepared from 2-phenylacetyl chloride (1.32 mL, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.6 g, 87 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.42 – 7.24 (m, 5H), 3.81 (s, 2H), 3.64 (s, 3H), 3.23 (s, 3H). All the spectroscopic data were consistent with those previously reported.[286]

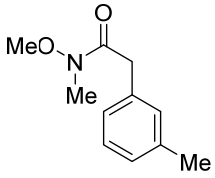
[286] Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100.

_N_-Methoxy-_N_-methyl-2-(_p_-tolyl)acetamide



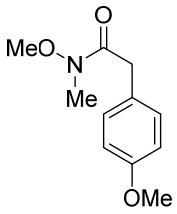
The title compound was prepared from 2-(_p_-tolyl)acetic acid (1.5 g, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.3 g, 70 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.25 – 7.10 (m, 4H), 3.77 (s, 2H), 3.64 (s, 3H), 3.22 (s, 3H), 2.36 (s, 3H). All the spectroscopic data were consistent with those previously reported.[287]

_N_-Methoxy-_N_-methyl-2-(_m_-tolyl)acetamide



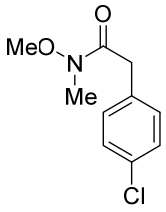
The title compound was prepared from 2-(_m_-tolyl)acetic acid (1.5 g, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.6 g, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.26 – 7.04 (m, 4H), 3.76 (s, 2H), 3.63 (s, 3H), 3.22 (s, 3H), 2.36 (s, 3H). All the spectroscopic data were consistent with those previously reported.[286]

_N_-Methoxy-_N_-methyl-2-(4-methoxyphenyl)acetamide



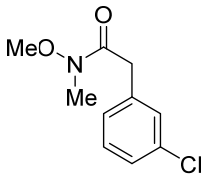
The title compound was prepared from 2-(4-methoxyphenyl)acetic acid (1.7 g, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.7 g, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.23 (d, _J_ = 8.7 Hz, 2H), 6.87 (d, _J_ = 8.7 Hz, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.64 (s, 3H), 3.21 (s, 3H). All the spectroscopic data were consistent with those previously reported.[286]

_N_-Methoxy-_N_-methyl-2-(4-chlorophenyl)acetamide



The title compound was prepared from 2-(4-chlorophenyl)acetic acid (1.7 g, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.8 g, 85 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.27 (d, _J_ = 9.1 Hz, 2H), 6.92 (d, _J_ = 9.0 Hz, 2H), 4.83 (s, 2H), 3.79 (s, 3H), 3.27 (s, 3H). All the spectroscopic data were consistent with those previously reported.[286]

_N_-Methoxy-_N_-methyl-2-(3-chlorophenyl)acetamide

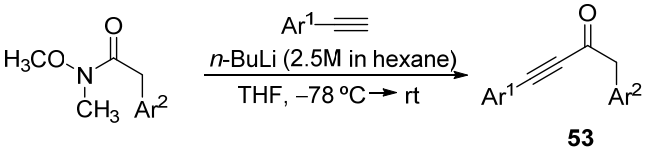


The title compound was prepared from 2-(3-chlorophenyl)acetic acid (1.7 g, 10 mmol) according to the General Procedure. Yellow oil, yield: 1.8 g, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ:

[287] Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 13045.

7.36 – 7.16 (m, 4H), 3.76 (s, 2H), 3.66 (s, 3H), 3.22 (s, 3H). All the spectroscopic data were consistent with those previously reported.[288]

***3rd Step* (General procedure):**

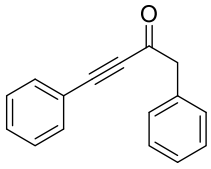


53

A Ar^1: C_6H_5	**E** Ar^2: C_6H_5	**I** Ar^2: 4-ClC_6H_4
B Ar^1: 4-MeC_6H_4	**F** Ar^2: 4-MeC_6H_4	**J** Ar^2: 3-ClC_6H_4
C Ar^1: 4-ClC_6H_4	**G** Ar^2: 3-MeC_6H_4	
D Ar^1: 4-$MeOC_6H_4$	**H** Ar^2: 4-$MeOC_6H_4$	

To a solution of the corresponding acetylene (3 equiv.) in anhydrous THF (4mL/mmol) was added *n*-BuLi (2.5M in hexane, 3 equiv.) at –78 °C. After stirring at –78 °C for 3 h, the corresponding Weinreb amide (1equiv.) in THF (1mL/mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, then allowed to warm up to room temperature overnight and afterwards, quenched with a mixture of NH_4Cl and aqueous HCl 2M. The resulting mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5→ 90:10).[289]

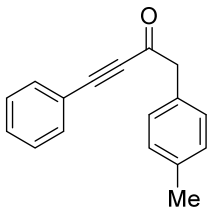
1,4-Diphenylbut-3-yn-2-one (53AE)



The title compound was prepared from *N*-methoxy-*N*-methyl-2-phenylacetamide (1.4 g, 8 mmol) according to the General Procedure. Yellow oil, yield: 1.1 g, 60 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 – 7.29 (m, 10H), 3.96 (s, 2H). All the spectroscopic data were consistent with those previously reported.[290]

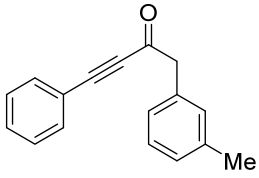
[288] Mocci, R.; Luca, L. D.; Delogu, F.; Porcheddu A. *Adv. Synth. Catal.* **2016**, *358*, 3135.
[289] Procedure adapted from: Silva, F.; Sawcki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417–5419.
[290] Sachdev, A.; Matai, I.; Kumar, S. U.; Bhushan, B.; Dubey, P.; Gopinath, P. *RSC Advances*, **2013**, *3*, 18985–18991.

4-Phenyl-1-(*p*-tolyl)but-3-yn-2-one (53AF)



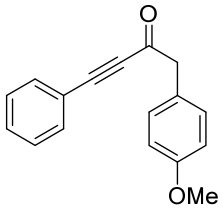
The title compound was prepared from *N*-methoxy-*N*-methyl-2-(*p*-tolyl)acetamide (0.9 g, 4.8 mmol) according to the General Procedure. Yellow oil, yield: 0.6 g, 53 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.57 – 7.15 (m, 9H), 3.92 (s, 2H), 2.38 (s, 3H). All the spectroscopic data were consistent with those previously reported.[290]

4-Phenyl-1-(*m*-tolyl)but-3-yn-2-one (53AG)



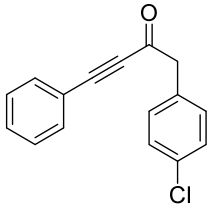
The title compound was prepared from *N*-methoxy-*N*-methyl-2-(*m*-tolyl)acetamide (1.6 g, 8.3 mmol) according to the General Procedure. Yellow oil, yield: 0.5 g, 25 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.71 – 7.00 (m, 9H), 3.94 (s, 2H), 2.40 (s, 3H). All the spectroscopic data were consistent with those previously reported.[291]

1-(4-Methoxyphenyl)-4-phenylbut-3-yn-2-one (53AH)



The title compound was prepared from 2-(4-methoxyphenyl)acetamide (2.5 g, 11.7 mmol) according to the General Procedure. Yellow solid, yield: 1.7 g, 58 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.55 – 7.33 (m, 5H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.90 (s, 2H), 3.83 (s, 3H). All the spectroscopic data were consistent with those previously reported.[290]

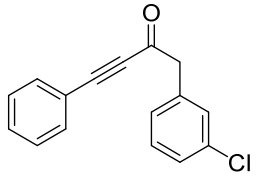
1-(4-Chlorophenyl)-4-phenylbut-3-yn-2-one (53AI)



The title compound was prepared from *N*-methoxy-*N*-methyl-2-(4-chlorophenyl)acetamide (1.8 g, 8.5 mmol) according to the General Procedure. Yellow oil, yield: 1.8 g, 45 %. ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.60 – 7.37 (m, 5H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 157.0, 134.0, 132.0, 130.2, 129.4, 127.5, 119.9, 116.8, 96.0, 86.2, 74.2. UPLC-DAD-QTOF: $C_{16}H_{10}OCl$ $[M-H]^-$ calcd.: 253.0420, found: 253.0422.

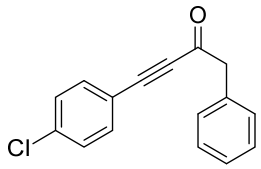
1-(3-Chlorophenyl)-4-phenylbut-3-yn-2-one (53AJ)

[291] Wu, X.; Neumann, H.; Beller, M. *Organic & Biomolecular Chemistry*, **2011**, *9*, 8003-8005.



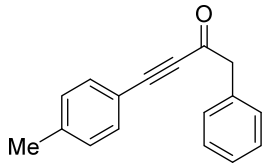
The title compound was prepared from *N*-methoxy-*N*-methyl-2-(3-chlorophenyl)acetamide (1.8 g, 8.4 mmol) according to the General Procedure. Yellow solid, yield: 0.8 g, 39%. m.p. 47–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.67 – 7.14 (m, 9H), 3.93 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 136.2, 135.5, 134.2, 132.1, 131.1, 131.0, 129.7, 129.1, 128.7, 120.7, 94.5, 88.6, 52.7. UPLC-DAD-QTOF: $C_{16}H_{10}OCl$ $[M-H]^-$ calcd.: 253.0420, found:253.0422.

4-(4-Chlorophenyl)-1phenylbut-3-yn-2-one (53BE)



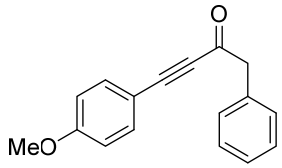
The title compound was prepared from *N*-methoxy-*N*-methyl-2-phenylacetamide (1.2 g, 6.7 mmol) according to the General Procedure. Orange solid, yield: 0.8 g, 50 %. m.p. 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 – 7.22 (m, 9H), 3.95 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.0, 138.3, 135.3, 134.2, 130.9, 130.1, 129.8, 128.5, 119.3, 92.5, 89.4, 53.2. UPLC-DAD-QTOF: $C_{16}H_{12}OCl$ $[M+H]^+$ calcd.: 255.0577, found: 255.0576.

1-Phenyl-4-(*p*-tolyl)but-3-yn-2-one (53CE)



The title compound was prepared from *N*-methoxy-*N*-methyl-2-phenylacetamide (0.7 g, 4 mmol) according to the General Procedure. Yellow oil, yield: 0.4 g, 43 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.32 (m, 6H), 7.20 – 7.12 (m, 3H), 3.95 (s, 2H), 2.40 (s, 3H). All the spectroscopic data were consistent with those previously reported.[292]

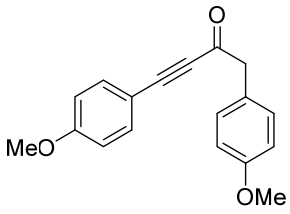
4-(4-Methoxyphenyl)-1-phenylbut-3-yn-2-one (53DE)



The title compound was prepared from *N*-methoxy-*N*-methyl-2-phenylacetamide (0.6 g, 3 mmol) according to the General Procedure. Yellow oil, yield: 0.29 g, 39 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 – 7.28 (m, 7H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.93 (s, 2H), 3.83 (s, 3H). All the spectroscopic data were consistent with those previously reported.[293]

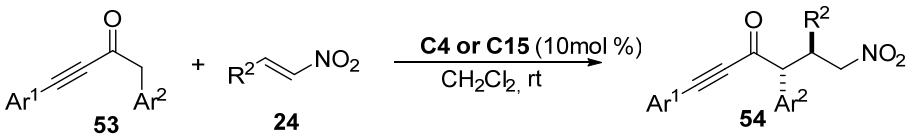
1,4-Bis(4-methoxyphenyl)but-3-yn-2-one (53DH)

[292] Sans, V.; Trzeciak, A. M.; Luis, S.; Ziolkowski, J. J. *Catal. Lett.* **2006**, *109*, 37–41.
[293] Perrone, S.; Bona, F.; Troisi, L. *Tetrahedron* **2011**, *67*, 7386–7391.

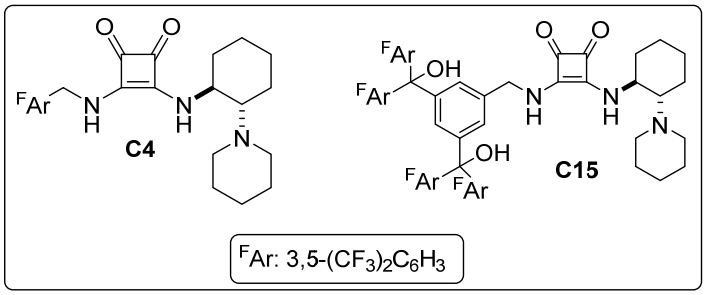


The title compound was prepared from 2-(4-methoxyphenyl)acetamide (1.3 g, 6.2 mmol) according to the General Procedure. White solid, yield: 1.3 g, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H). All the spectroscopic data were consistent with those previously reported.[294]

7.4.2. General procedure for the 1,4-conjugate addition of benzylic alkynyl ketone 53 to nitroolefins 24



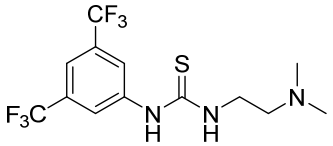
A Ar^1: C_6H_5 **E** Ar^2: C_6H_5 **I** Ar^2: 4-ClC_6H_4 **i** R^2: 4-$MeOC_6H_4$ **f** R^2: 4-BrC_6H_4
B Ar^1: 4-MeC_6H_4 **F** Ar^2: 4-MeC_6H_4 **J** Ar^2: 3-ClC_6H_4 **a** R^2: C_6H_5 **c** R^2: $(CH_3)_2CHCH_2$
C Ar^1: 4-ClC_6H_4 **G** Ar^2: 3-MeC_6H_4 **g** R^2: 4-ClC_6H_4 **e** R^2: $CH_3(CH_2)_4$
D Ar^1: 4-$MeOC_6H_4$ **H** Ar^2: 4-$MeOC_6H_4$ **j** R^2: 4-MeC_6H_4



To a mixture of the corresponding benzylic ynone **53** (0.1 mmol, 1 equiv.) and nitroalkene **24** (0.12 mmol, 1 equiv.), in dichloromethane (0.3 mL) at room temperature, the catalyst (**C4** or **C15** 10 mol %) was added. The resulting suspension was stirred at the same temperature until consumption of the starting ynone as monitored by ^{1}H NMR. The mixture was directly submitted to a flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5 → 90:10) to afford the desired product.

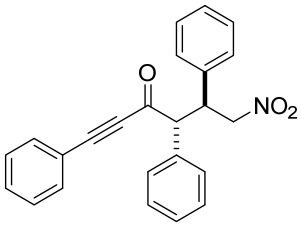
The corresponding racemic reaction was ran following the above procedure at room temperature, but using as catalyst the achiral amine/thiourea showed below (10 mol %), which was prepared following literature protocols.[283]

[294] Koswatta, P. B.; Das, J.; Yousufuddin, M.; Lovely, C. J. *Eur. J. Org. Chem.* **2015**, 2603–2613.



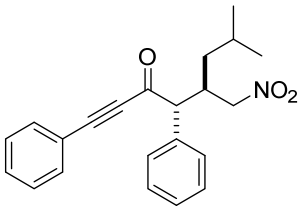
Achiral thiourea used for the synthesis of racemic compounds.

6-Nitro-1,4,5-triphenylhex-1-yn-3-one (54AEa)



The title compound **54AEa** was prepared from 1,4-diphenylbut-3-yn-2-one (**53AE**) (22.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 83:17) determined by ^{1}H NMR after column chromatography. Yield: 31.7 mg, 86 %. Crystallization from Et_2O gives the title compound. m.p. 174–176 °C. $[\alpha]_D^{25}$= –54.8° (*c* = 0.3, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 – 7.05 (m, 15H), 4.56 – 4.37 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.5, 137.9, 134.7, 133.7, 131.7, 130.3, 129.7, 129.7, 129.6, 129.3, 128.8, 120.2, 94.0, 88.1, 79.5, 64.3, 46.1. UPLC-DAD-QTOF: $C_{24}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 392.1263, found: 392.1263. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 11.2 min (major) and 15.2 min (minor) and for minor diastereomer. 21.9 min (major) and 25.7 min (minor).

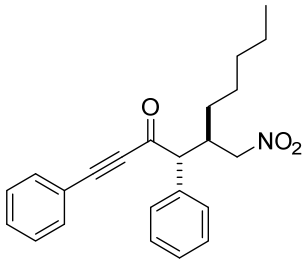
7-Methyl-5-(nitromethyl)-1,4-diphenyloct-1-yn-3-one (54AEc)



The title compound **54AEc** was prepared from 1,4-diphenylbut-3-yn-2-one (**53AE**) (22.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a yellow oil as a mixture of diastereomers (*dr*: 60:40) determined by ^{1}H NMR after column chromatography. . Yield: 24.8 mg, 71 %. *anti*: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 – 7.30 (m, 10H), 4.47 (dd, *J* = 13.1, 4.5 Hz, 1H), 4.18 (d, *J* = 10.0 Hz, 1H), 4.08 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.23 – 3.09 (m, 1H), 1.46 – 1.39 (m, 2H), 1.02 – 0.85 (m, 7H). *syn*: 7.56 – 7.30 (m, 10H), 4.72 (dd, *J* = 12.3, 4.8 Hz, 1H), 4.54 (dd, *J* = 12.4, 4.9 Hz, 1H), 4.15 (d, *J* = 7.2 Hz, 1H), 4.08 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.03 – 2.97 (m, 1H), 1.20 – 1.08 (m, 2H), 0.85 (dd, *J* = 6.7, 6.7 Hz, 6H). *anti*: ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.4, 134.4, 133.8, 131.7, 130.1, 130.0, 129.6, 129.3, 129.1, 76.8, 63.8, 40.3, 37.6, 26.1, 24.1, 22.2. UPLC-DAD-QTOF: $C_{22}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 372.1576, found: 372.1576.. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ASH, hexane/isopropanol 98:2, flow rate = 1.0 mL/min, retention times for the major

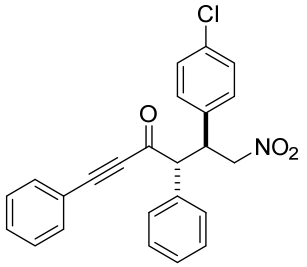
diastereomer: 15.1 min (major) and 23.3 min (min) and for minor diastereomer. 12.1 min (major) and 13.7 min (min). The product was obtained with 94/98 % *ee*.

5-(Nitromethyl)-1,4-diphenyldec-1-yn-3-one (54AEe)



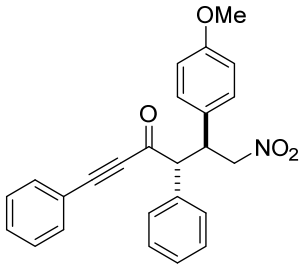
The title compound **54AEe** was prepared from 1,4-diphenylbut-3-yn-2-one (**53AE**) (22.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a yellow oil as a mixture of diastereomers (*dr*: 55:45) determined by ^{1}H NMR after column chromatography. Yield: 24.6 mg, 68 %. *anti+syn:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 – 7.29 (m, 20H, *anti+syn*, Ar), 4.73 – 4.48 (m, 2H, *syn*), 4.39 (dd, *J* = 12.9, 4.3 Hz, 1H, *anti*), 4.17 – 4.06 (m, 3H, *anti+syn*), 3.21 – 3.07 (m, 1H, *anti*), 3.00 (m, 1H, *syn*), 1.67 – 1.09 (m, 16H, *anti+syn*), 0.91 (t, *J* = 6.9 Hz, 3H, *anti*), 0.84 (t, *J* = 6.1 Hz, 3H, *syn*). *anti:* ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 136.3, 134.7, 132.6, 131.0, 130.9, 130.2, 130.1, 121.2, 94.8, 89.4, 77.7, 64.2, 40.6, 31.7, 27.6, 24.0, 15.5. UPLC-DAD-QTOF: $C_{23}H_{25}NO_3Na$ $[M+Na]^+$ calcd.: 386.1732, found: 386.1733. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times for the major diastereomer: 6.7 min (major) and 9.0 min (minor) and for minor diastereomer. 9.8 min (major) and 11.2 min (minor). The product was obtained with 94/88 % *ee*.

5-(4-Chlorophenyl)-6-nitro-1,4-diphenylhex-1-yn-3-one (54AEg)



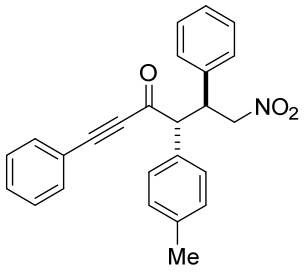
The title compound **54AEg** was prepared from 1,4-diphenylbut-3-yn-2-one (**53AE**) (22.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 81:19) determined by determined by ^{1}H NMR after column chromatography. Yield: 37.6 mg, 93 %. Crystallization from Et_2O gives the title compound. m.p. 149–151 °C. $[\alpha]_D^{25}$= –58.5° (*c* = 0.49, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CDCl3), δ: 7.71 – 7.26 (m, 14H), 4.61 – 4.22 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.1, 136.5, 134.7, 134.4, 133.7, 131.8, 130.4, 130.2, 129.9, 129.7, 129.6, 129.3, 120.0, 94.3, 88.1, 79.2, 64.2, 45.5. UPLC-DAD-QTOF: $C_{24}H_{18}NO_3ClNa$ $[M+Na]^+$ calcd.: 426.0873, found: 426.0860. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 9.5 min (major) and 12.9 min (minor) and for minor diastereomer: 18.2 min (major) and 22.6 min (minor).

5-(4-Methoxyphenyl)-6-nitro-1,4-diphenylhex-1-yn-3-one (54AEi)



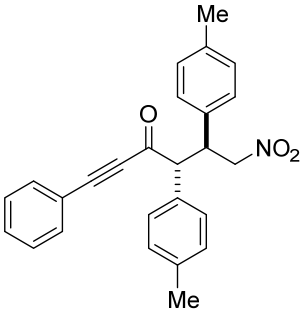
The title compound **54AEi** was prepared from 1,4-diphenylbut-3-yn-2-one (**53AE**) (22.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 83:17) determined by ^{1}H NMR after column chromatography. Yield: 38.6 mg, 97 %. Crystallization from Et_2O gives the title compound. m.p. 156–158 °C. $[\alpha]_D^{25}$= –62.9° (*c* = 0.53, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.59–7.29 (m, 12H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.56–4.28 (m, 4H), 3.79 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 160.0, 134.8, 133.7, 131.6, 130.3, 129.9, 129.6, 129.5, 129.3, 120.2, 115.1, 110.7, 94.0, 88.1, 79.6, 64.5, 55.9, 45.5. UPLC-DAD-QTOF: $C_{25}H_{22}NO_4$ $[M+H]^+$ calcd.: 400.1549, found: 400.1550. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 18.2 min (major) and 22.6 min (minor) and for minor diastereomer. 30.7 min (major) and 35.2 min (minor).

6-Nitro-1,5-diphenyl-4-(*p*-tolyl)hex-1-yn-3-one (54AFa)



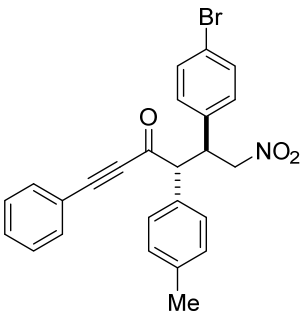
The title compound **54AFa** was prepared from 4-phenyl-1-(*p*-tolyl)but-3-yn-2-one (**53AF**) (23.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 86:14) determined by ^{1}H NMR after column chromatography. Yield: 34.5 mg, 90 %. Crystallization from Et_2O gives the title compound. m.p. 150–152 °C. $[\alpha]_D^{25}$= –34.57° (*c* = 0.3, 84 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 – 7.21 (m, 14H), 4.55 – 4.25 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 139.5, 138.0, 133.7, 131.6, 131.0, 129.7, 129.5, 129.3, 128.8, 128.8, 120.3, 93.8, 88.2, 79.6, 63.9, 46.1, 21.8. UPLC-DAD-QTOF: $C_{23}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 406.1419, found: 406.1414. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 11.1 min (major) and 13.6 min (minor) and for minor diastereomer: 20.7 min (major) and 27.2 min (minor).

6-Nitro-1-phenyl-4,5-di-*p*-tolylhex-1-yn-3-one (54AFj)



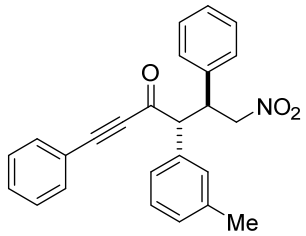
The title compound **54AFj** was prepared from 4-phenyl-1-(*p*-tolyl)but-3-yn-2-one (**53AF**) (23.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 80:20) determined by ^{1}H NMR after column chromatography. Yield: 35.7 mg, 90 %. Crystallization from Et_2O gives the title compound. m.p. 160–162 °C. $[\alpha]_D^{25}$= –39.2° (*c* = 0.51, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.60 – 6.95 (m, 13H), 4.54 – 4.29 (m, 4H), 2.39 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.7, 139.4, 138.5, 134.8, 133.7, 131.6, 131.0, 130.4, 129.5, 129.3, 128.7, 120.3, 93.7, 88.2, 79.7, 64.0, 45.8, 21.8. UPLC-DAD-QTOF: $C_{26}H_{23}NO_3Na$ $[M+Na]^+$ calcd.: 420.1576, found: 420.1573. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times for the major diastereomer: 11.4 min (major) and 12.6 min (minor) and for minor diastereomer. 19.3 min (major) and 24.2 min (minor).

5-(4-Bromophenyl)-6-nitro-1-phenyl-4-(*p*-tolyl)hex-1-yn-3-one (54AFf)



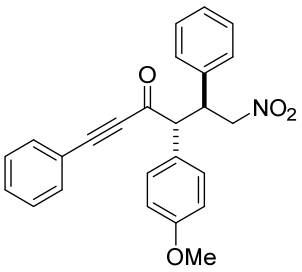
The title compound **54AFf** was prepared from 4-phenyl-1-(p-tolyl)but-3-yn-2-one (**53AF**) (23.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 92:8) determined by ^{1}H NMR after column chromatography. Yield: 42.9 mg, 93 %. Crystallization from Et_2O gives the title compound. m.p. 149–151 °C. $[\alpha]_D^{25}$= –54.88° (*c* = 0.72, 96 % ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.58 – 7.21 (m, 13H), 4.54 – 4.27 (m, 4H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.2, 139.7, 137.2, 133.7, 132.8, 131.7, 131.1, 130.6, 129.4, 129.3, 122.8, 120.1, 94.1, 88.1, 79.2, 63.8, 45.5, 21.8. UPLC-DAD-QTOF: $C_{25}H_{20}NO_3BrNa$ $[M+Na]^+$ calcd.: 484.0524, found: 484.0526. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 10.3 min (major) and 13.1 min (minor) and for minor diastereomer: 19.2 min (major) and 26.6 min (minor).

6-Nitro-1,5-diphenyl-4(*m*-tolyl)hex-1-yn-3-one (54AGa)



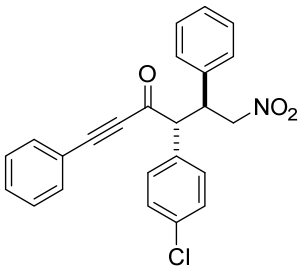
The title compound **54AGa** was prepared from 4-phenyl-1-(*m*-tolyl)but-3-yn-2-one (**53AG**) (23.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 87:13) determined by ^{1}H NMR after column chromatography. Yield: 36.0 mg, 96 %. Crystallization from Et_2O gives the title compound. m.p. 89–91 °C. $[\alpha]_D^{25}$= –45.86° (*c* = 1.1, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 – 7.29 (m, 14H), 4.53 – 4.31 (m, 4H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.6, 138.3, 136.1, 132.7, 131.8, 129.7, 128.5, 128.3, 127.8, 127.4, 127.0, 126.9, 124.9, 118.4, 92.0, 86.3, 78.0, 62.3, 44.2, 20.3. UPLC-DAD-QTOF: $C_{25}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 406.1419, found: 406.424. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 8.9 min (major) and 11.2 min (minor) and for minor diastereomer: 17.5 min (major) and 19.3 min (minor).

4-(4-Methoxyphenyl)-6-nitro-1,5-diphenylhex-1-yn-3-one (54AHa)



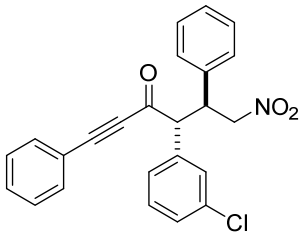
The title compound **54AHa** was prepared from 1-(4-methoxyphenyl)-4-phenylbut-3-yn-2-one (**53AH**) (25.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 82:18) determined by ^{1}H NMR after column chromatography. Yield: 38.34 mg, 96 %. Crystallization from Et_2O gives the title compound. m.p. 134–136 °C. $[\alpha]_D^{25}$= –55.5° (*c* = 0.3, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52 – 7.26 (m, 14H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.53 – 4.32 (m, 4H), 3.85 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$ δ: 182.7, 158.8, 136.1, 131.8, 129.7, 128.9, 127.8, 127.4, 127.0, 126.9, 124.6, 118.4, 113.9, 92.0, 86.3, 78.0, 61.5, 54.1, 44.3. UPLC-DAD-QTOF: $C_{25}H_{22}NO_4$ $[M+H]^+$ calcd.: 400.1549, found: 400.1551. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times for the major diastereomer: 29.3 min (major) and 54.9 min (minor) and for minor diastereomer: 51.3 min (major) and 71.0 min (minor).

4-(4-Chlorophenyl)-6-nitro-1,5-diphenylhex-1-yn-3-one (54AIa)



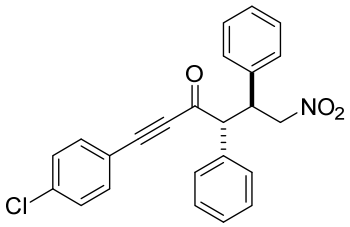
The title compound **54AIa** was prepared from 1-(4-Chlorophenyl)-4-phenylbut-3-yn-2-one (**53AI**) (27.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a yellow oil as a single diastereomer determined by ^{1}H NMR after column chromatography. Yellow oil, yield: 12.1 mg, 30 %. $[\alpha]_D^{25}$= –9.37° (*c* = 0.4, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.56 – 7.29 (m, 10H), 7.26 (d, *J* = 9.1 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 5.14 – 4.76 (m, 3H), 4.39 (dt, *J* = 8.6, 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.3, 156.8, 136.0, 134.6, 132.8, 130.8, 130.4, 129.9, 129.4, 117.9, 111.1, 98.4, 87.1, 86.0, 84.0, 77.0, 47.1, 30.8, 30.0. UPLC-DAD-QTOF: $C_{24}H_{17}NO_3Cl$ $[M-H]^-$ calcd.: 402.0897, found: 402.0882. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 12.9 min (major) and 25.9 min (minor) and for minor diastereomer. 14.8 min (major) and 21.2 min (minor).

4-(3-Chlorophenyl)-6-nitro-1,5-diphenylhex-1-yn-3-one (54AJa)



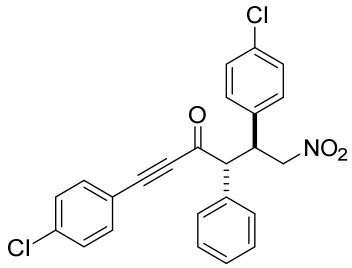
The title compound **54AJa** was prepared from 1-(3-Chlorophenyl)-4-phenylbut-3-yn-2-one (**53AJ**) (25.4 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a yellow oil as a mixture of diastereomers (*dr*: 86:14) determined by ^{1}H NMR after column chromatography. Yield: 35.5 mg, 88 %. $[\alpha]_D^{25}$= –21.87° (*c* = 1.6, 90 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.62 – 7.03 (m, 14H), 4.60 – 4.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.3, 135.9, 135.2, 132.2, 130.3, 130.0, 129.1, 128.6, 128.2, 127.8, 127.5, 127.3, 127.1, 126.6, 126.2, 118.4, 92.1, 86.5, 77.7, 62.1, 61.7, 44.7. UPLC-DAD-QTOF: $C_{24}H_{18}NO_3ClNa$ $[M+Na]^+$ calcd.: 426.0873, found: 426.0864. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 9.7 min (major) and 13.4 min (minor) and for minor diastereomer. 16.8 min (major) and 20.3 min (minor).

1-(4-Chlorophenyl)-6-nitro-4,5-diphenylhex-1-yn-3-one (54BEa)



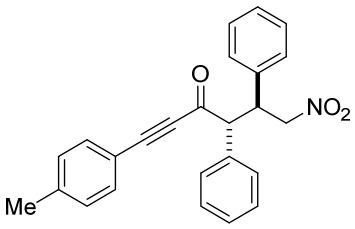
The title compound **54BEa** was prepared from 4-(4-chlorophenyl)-1phenylbut-3-yn-2-one (**54BE**) (25.5 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 75:25) determined by ^{1}H NMR after column chromatography. Yield: 35.1 mg, 87 %. Crystallization from Et_2O gives the title compound. m.p. 148–150 °C. $[\alpha]_D^{25}$= –28.8° (*c* = 0.5, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.54 – 7.29 (m, 14H), 4.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.7, 138.2, 135.3, 135.0, 130.8, 130.2, 130.1, 130.1, 129.3, 129.2, 119.1, 111.1, 93.0, 89.2, 79.8, 64.6, 46.5. UPLC-DAD-QTOF: $C_{24}H_{18}NO3ClNa$ $[M+Na]^+$ calcd.: 426.0873, found: 426.0862. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 11.8 min (major) and 16.1 min (minor) and for minor diastereomer. 23.3 min (major) and 25.5 min (minor).

1,5-Bis(4-chlorophenyl)-6-nitro-4-phenylhex-1-yn-3-one (54BEg)



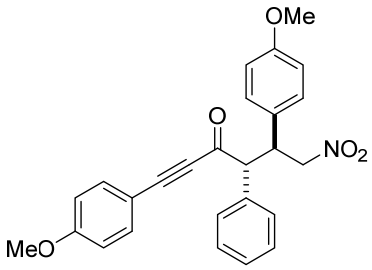
The title compound **54BEg** was prepared from 4-(4-chlorophenyl)-1phenylbut-3-yn-2-one (**53BE**) (25.5 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 82:18) determined by ^{1}H NMR after column chromatography. Yield: 39.4 mg, 90 %. Crystallization from Et_2O gives the title compound. m.p. 142–144 °C. $[\alpha]_D^{25}$= –63.1° (*c* = 0.3, 9 2% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.53 – 7.29 (m, 13H), 4.47 – 4.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.9, 138.3, 136.4, 135.0, 134.2, 130.4, 130.2, 129.9, 129.8, 129.6, 118.5, 110.7, 92.7, 88.8, 79.1, 64.1, 45.5. UPLC-DAD-QTOF: $C_{24}H_{17}NO_3Cl_2Na$ $[M+Na]^+$ calcd.: 460.0483, found: 460.0486.The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 10.1 min (major) and 14.0 min (minor) and for minor diastereomer. 19.2 min (major) and 23.0 min (minor).

6-Nitro-4,5-diphenylhex-1-(*p*-tolyl)hex-1-yn-3-one (54CEa)



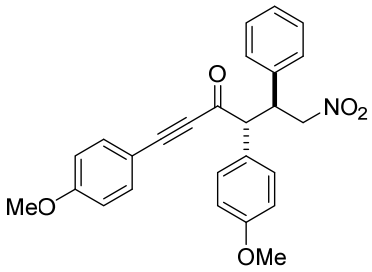
The title compound **54CEa** was prepared from 1-phenyl-4-(*p*-tolyl)but-3-yn-2-one (**54CE**) (23.43 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of isomers (*dr*: 98:2) determined by HPLC analysis using a chiral stationary phase after column chromatography.. Yield: 33.3 mg, 87 %. Crystallization from Et_2O gives the title compound. m.p. 151–153 °C. $[\alpha]_D^{25}$= –56.7° (*c* = 0.2, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.58 – 7.30 (m, 12H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.58 – 4.33 (m, 4H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.5, 142.5, 137.9, 134.8, 133.8, 130.3, 130.1, 129.7, 129.5, 128.9, 117.1, 110.7, 94.8, 88.1, 79.5, 64.2, 46.2, 22.4. UPLC-DAD-QTOF: $C_{25}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 406.1419, found: 406.1420. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times for the major diastereomer: 18.1 min (major) and 26.6 min (minor).

1,5-Bis(4-methoxyphenyl)-6-nitro-4-phenylhex-1-yn-3-one (54DEi)



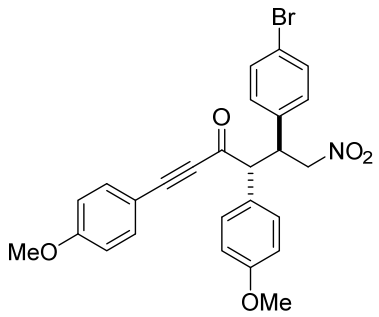
The title compound **54DEi** was prepared from 4-(4-methoxyphenyl)-1-phenylbut-3-yn-2-one (**53DE**) (75.1 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 82:18) determined by HPLC analysis using a chiral stationary phase after column chromatography. Yield: 36.9 mg, 86 %. Crystallization from Et_2O gives the title compound. m.p. 98–101 °C. $[\alpha]_D^{25}$= –56.5° (*c* = 0.6, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52 – 7.37 (m, 7H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 3.2 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 2H), 4.51 – 4.29 (m, 4H), 3.85 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 162.5, 159.9, 135.8, 135.1, 130.2, 129.9, 129.6, 129.4, 115.1, 112.0, 95.3, 88.3, 79.7, 64.4, 56.1, 55.9, 45.6. UPLC-DAD-QTOF: $C_{25}H_{21}NO_3Na$ $[M+Na]^+$ calcd.: 452.1474, found: 452.1467. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 31.5 min (major) and 38.1 min (minor) and for minor diastereomer: 63.3 min (major) and 81.6 min (minor).

1,4-Bis(4-methoxyphenyl)-6-nitro-5-phenylhex-1-yn-3-one (54DHa)



The title compound **54DHa** was prepared from 1,4-bis(4-methoxyphenyl)but-3-yn-2-one (**53DH**) (28.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 89:11) determined by HPLC analysis using a chiral stationary phase after column chromatography. White solid, yield: 41.2 mg, 96 %. Crystallization from Et_2O gives the title compound. m.p. 142–144 °C. $[\alpha]_D^{25}$= –1.4° (*c* = 0.2, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.29 (m, 5H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.51 – 4.30 (m, 4H), 3.85 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 160.6, 138.1, 135.8, 131.7, 130.7, 129.6, 128.8, 128.7, 128.2, 126.7, 115.7, 115.0, 110.7, 95.0, 88.3, 79.6, 63.3, 56.0, 46.3. UPLC-DAD-QTOF: $C_{26}H_{23}NO_5Na$ $[M+Na]^+$ calcd.: 452.1474, found: 452.1470. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 34.1 min (major) and 49.9 min (minor) and for minor diastereomer: 25.9 min (major) and 27.8 min (minor).

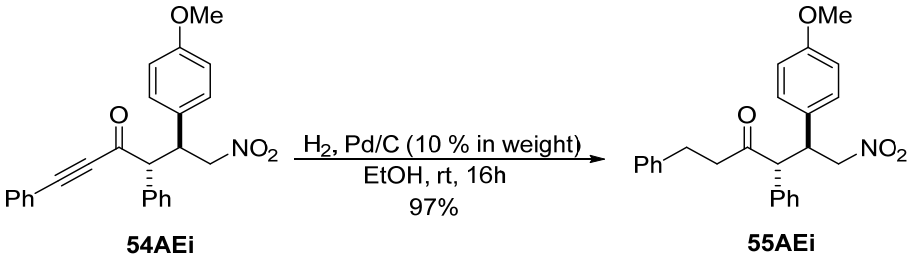
5-(4-Bromophenyl)-1,4-bis(4-methoxyphenyl)-6-nitrohex-1-yn-3-one (54DHf)



The title compound **54DHf** was prepared from 1,4-bis(4-methoxyphenyl)but-3-yn-2-one (**54DH**) (28.0 mg, 0.1 mmol) and catalyst **C15** according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 96:3) determined by HPLC analysis using a chiral stationary phase after column chromatography. Yield: 41.6 mg, 82 %. Crystallization from Et_2O gives the title compound. m.p. 135–137 °C. $[\alpha]_D^{25}$= –35.7° (*c* = 0.4, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.48 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.53 – 4.23 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.2, 162.6, 160.7, 137.2, 135.8, 132.8, 130.7, 130.5, 126.3, 122.8, 115.7, 115.1, 111.8, 95.4, 88.3, 79.2, 63.1, 56.1, 45.7. UPLC-DAD-QTOF: $C_{26}H_{22}NO_5BrNa$ $[M+Na]^+$ calcd.: 530.0579, found: 530.0580. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times for the major diastereomer: 13.1 min (minor) and 17.8 min (major) and for minor diastereomer: 20.8 min (minor) and 30.6 min (major).

7.4.3. Chemical elaboration of adducts 54

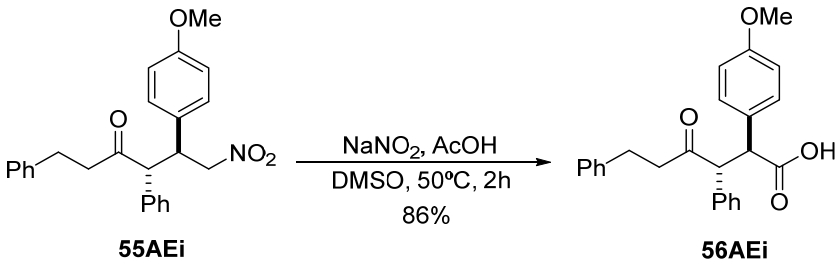
*7.4.3.1. Reduction of adduct **54AEi***



54AEi **55AEi**

To a solution of the adduct **54AEi** (0.1 g, 0.3 mmol, 1 equiv.) in EtOAc (3 mL/mmol) under H_2 atmosphere, Pd/C was added (12 mg, 10% in weight), and the mixture was stirred at room temperature for 16 h. Then, the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford product **55AEi**, which was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 90:10 → 80:20). Yield: 117 mg, 97 %. $[\alpha]_D^{25}$= –32.5° (*c* = 0.7, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52 – 6.76 (m, 14H), 4.51 – 4.19 (m, 3H), 4.13 (d, *J* = 10.8 Hz, 1H), 3.82 (s, 3H), 2.78 – 2.28 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.0, 157.9, 139.2, 133.4, 128.5, 127.8, 127.4, 127.3, 127.1, 126.8, 124.7, 113.1, 77.7, 60.6, 54.0, 44.0, 43.2, 27.9. UPLC-DAD-QTOF: $C_{25}H_{26}NO_4$ $[M+H]^+$ calcd.: 404.1862, found: 404.1859.

*7.4.3.2. Nef oxidation of adduct **55AEi** into carboxylic acid **56AEi**[285]*

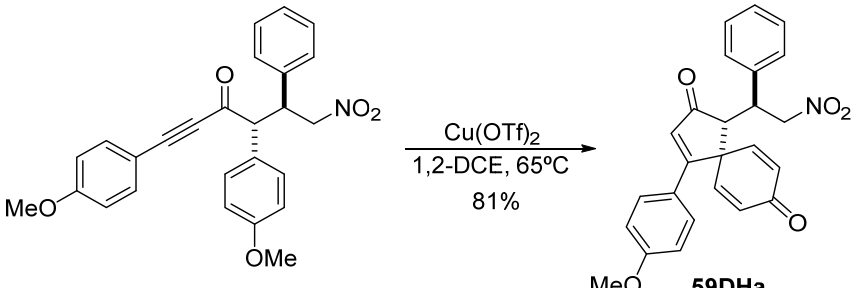


55AEi **56AEi**

A solution of adduct **55AEi** (64.5 mg, 0.16 mmol, 1 equiv.), $NaNO_2$ (66.2 mg, 0.96 mmol, 6 equiv.) and AcOH (0.09 mL, 1.6 mmol, 10 equiv.) in DMSO (2 mL) was stirred at 50 °C for 2 h. Then, the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluting hexane/EtOAc 90:10 → 70:30). White solid, yield 53.8 mg, 86 %. m.p. 144-146 °C. $[\alpha]_D^{25}$= –129.6° (*c* = 0.1, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40 – 6.80 (m, 14H), 4.53 – 4.33 (m, 2H), 3.82 (s, 3H), 2.77 – 2.32 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$), δ: 207.6, 177.6, 160.3, 141.6, 136.5, 133.4, 130.7, 130.0, 129.8, 129.4, 129.1, 129.0, 127,0, 115.3, 62.3, 56.3, 54.1, 45.4, 30.1. UPLC-DAD-QTOF: $C_{25}H_{24}O_4Na$ $[M+Na]^+$ calcd.: 411.1572, found: 411.1570.

7.4.3.3. Electrophilic cyclization of adduct ***54DHa***[295]

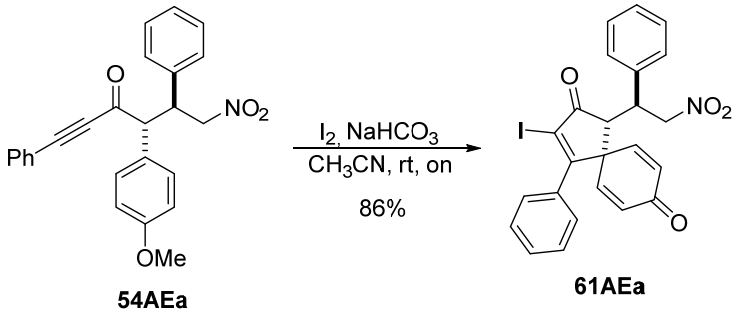


54DHa **59DHa**

To a solution of ynone **54DHa** (55.3 mg, 0.1 mmol, 1 equiv.) in 1,2-DCE (1mL) was added $Cu(OTf)_2$ (46.6 mg, 0.1 mmol, 1 equiv.). The reaction mixture was stirred at 65°C for 3 h. Then mixture was filtered, rinsed with CH_2Cl_2 and concentrated under vacuum to afford the spirocyclic product **59DHa** as brown foam. Yield: 43.6 mg, 81 %. $[\alpha]_D^{25}$= –9.5° (*c* = 1.5, 98 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 8.7 Hz, 3H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 6.56 (d, *J* = 10.1 Hz, 1H), 6.34 – 6.12 (m, 2H), 5.24 (dd, *J* = 13.2, 7.5 Hz, 1H), 5.02 – 4.84 (m, 1H), 3.81 (s, 3H), 3.65 (td, *J* = 7.2, 3.5 Hz, 1H), 3.32 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.2, 185.4, 173.1, 163.3, 151.4, 151.1, 137.4, 131.0, 130.1, 129.6, 128.9, 127.7, 125.6, 115.1, 94.1, 79.4, 73.8, 56.3, 56.1, 43.1, 30.3. UPLC-DAD-QTOF: $C_{25}H_{21}NO_5Na$ $[M+Na]^+$ calcd.: 438.1317, found: 438.1314.

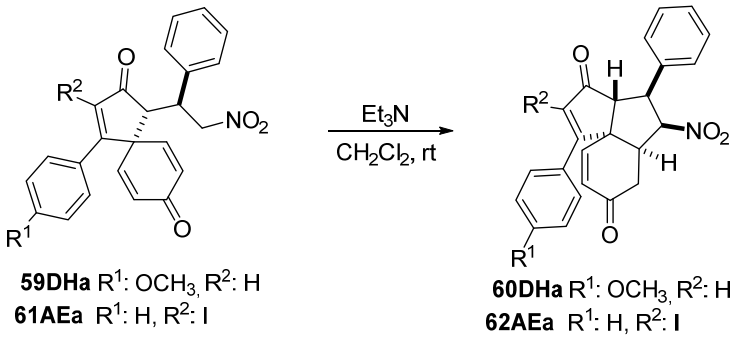
[295] Adapted from: Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.*, **2006**, *71*, 236–243.

*7.4.3.4. Spirocyclization of adduct **54AEa**[296]*



To a solution of adduct **54AEa** (39.9 mg, 0.1 mmol, 1 equiv.) in CH_3CN (0.3 mL) at room temperature was added I_2 (76.1 mg, 0.3 mmol, 3 equiv.) and $NaHCO_3$ (16.8 mg, 0.2 mmol, 2 equiv.). The reaction mixture was stirred at room temperature overnight, and then was diluted with ether and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting residue was crashed with hexane to afford the spyrocycled product **61AEa** as brown foam. Yield: 43.97 mg, 86 %. $[\alpha]_D^{25}$= –11.8 ° (*c* = 1.0, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.21 (m, 9H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.79 (dd, *J* = 10.0, 2.6 Hz, 1H), 6.39 (dd, *J* = 10.0, 1.4 Hz, 1H), 6.27 – 6.16 (m, 2H), 5.22 (dd, *J* = 13.4, 7.5 Hz, 1H), 4.89 (dd, *J* = 13.4, 7.6 Hz, 1H), 3.90 – 3.64 (m, 2H), 3.54 (d, *J* = 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.1, 184.9, 175.8, 148.5, 147.7, 136.9, 134.4, 132.6, 132.5, 131.2, 130.6, 129.8, 129.3, 129.2, 127.5, 106.1, 78.8, 59.4, 57.31, 43.5, 30.5. UPLC-DAD-QTOF: $C_{24}H_{18}NO_4INa$ $[M+Na]^+$ calcd.: 534.0178, found: 534.0184.

*7.4.3.5. Cyclization of spirocompounds **59DHa** and **61AEa***

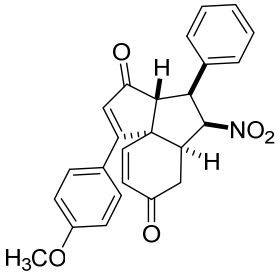


To a solution of spirocyclic compound **59DHa** or **61AEa** (0.1 mmol, 1 equiv.) in DCM (0.6 mL) was added Et_3N (2 mmol, 20 equiv.), and mixture was stirred at room

[296] Adapted from: Clarke, A. K.; Liddon, J. T. R.; Cuthbertson, J. D.; Taylor, R. J. K.; Unsworth, W. P. *Org. Biomol. Chem.* **2017**, 15, 233–245.

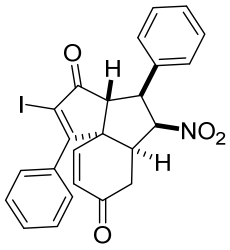
temperature for 2 h. Then the mixture was directly submitted to a non-acidic silica gel flash column chromatography (eluting with hexane/EtOAc 95:5→ 90:10) affording essentially pure tricyclic compounds **60DHa** and **62AEa**.

1-(4-Methoxyphenyl)-5-nitro-4-phenyl-4,5,5a,6-tetrahydro-3*H*-cyclopenta[*c*]indene-3,7(3a*H*)-dione (60DHa)



The title compound **60DHa** was prepared from spirocompound **59DHa** (41.5 mg, 0.1 mmol) according to the General Procedure. Brown solid, yield: 28.7 mg, 69 %. Decomp. temp.: 130 °C. $[\alpha]_D^{25}$= –9.0° (*c* = 0.4, 98 % *ee*, CH_2Cl_2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.9 Hz, 2H), 7.46 – 7.24 (m, 5H), 7.05 – 6.90 (m, 3H), 6.45 (d, *J* = 10.2 Hz, 1H), 6.34 (s, 1H), 4.99 (t, *J* = 11.1 Hz, 1H), 3.89 (s, 3H), 3.84 (d, *J* = 10.9 Hz, 1H), 3.21 – 3.12 (m, 1H), 3.10 (d, *J* = 9.5 Hz, 1H), 2.61 – 2.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 195.0, 174.9, 163.0, 150.7, 137.0, 130.3, 129.1, 128.2, 128.1, 126.7, 115.4, 96.0, 63.9, 56.2, 51.2, 46.7, 36.8. UPLC-DAD-QTOF: $C_{25}H_{22}NO_5$ $[M+H]^+$ calcd.: 416.1498, found: 416.1500.

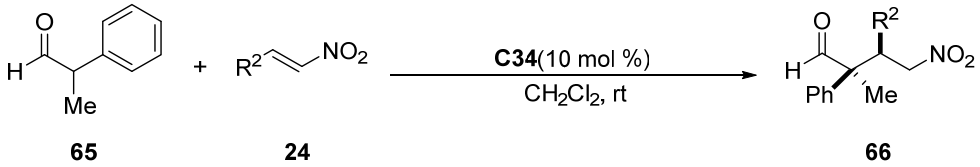
2-Iodo-5-nitro-1,4-diphenyl-4,5,5a,6-tetrahydro-3*H*-cyclopenta[*c*]indene-3,7(3aH)-dione (62AEa)



The title compound **62AEa** was prepared from spirocompound **61AEa** (51.1 mg, 0.1 mmol) according to the General Procedure. Brown solid, yield: 36.8 mg, 72 %. Decomp. temp.: 135 °C. $[\alpha]_D^{25}$= –35.1° (*c* = 0.3, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.23 (m, 10H), 6.81 (dd, *J* = 10.2, 1.6 Hz, 1H), 6.36 (dd, *J* = 10.2, 0.7 Hz, 1H), 5.00 (t, *J* = 11.2 Hz, 1H), 3.96 – 3.84 (m, 1H), 3.24 (d, *J* = 9.1 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.37 (d, *J* = 17.7 Hz, 1H), 1.94 (dd, *J* = 17.8, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 194.2, 176.7, 147.7, 136.8, 134.8, 131.3, 131.2, 130.1, 129.8, 129.2, 128.0, 127.6, 105.5, 94.7, 60.3, 50.7, 47.3, 35.7. UPLC-DAD-QTOF: $C_{24}H_{18}NO_4INa$ $[M+Na]^+$ calcd.: 534.0175, found: 534.0184.

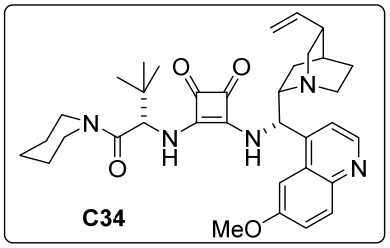
7.5. Experimental section for Chapter 4

7.5.1. General procedure for the 1,4-conjugate addition of 2-phenylpropanal (65) to nitroolefins 24



65 **24** **66**

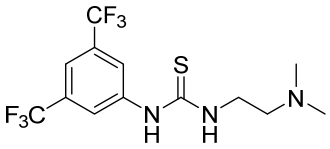
i R^2: 4-$MeOC_6H_4$ **j** R^2: 4-MeC_6H_4 **b** R^2: $CH_3(CH_2)_2$
k R^2: 3-$MeOC_6H_4$ **g** R^2: 4-ClC_6H_4 **l** R^2: C_6H_{11}



C34

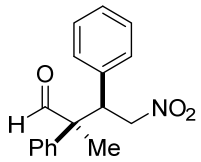
To a mixture of the commercially available 2-phenylpropanal **65** (0.2 mmol, 1 equiv.) and the nitroalkene **24** (0.6 mmol, 3.0 equiv.) in dichloromethane (0.6 mL) at room temperature, catalyst **C34** (12.0 mg, 10 mol %) was added. The resulting suspension was stirred at the same temperature, until consumption of the α-hydroxyketone as monitored by ^{1}H NMR. The mixture was directly submitted to a flash column chromatography on silica gel (eluting with hexane/EtOAc 95:5 → 90:10) to afford the desired product.

The corresponding racemic compounds were prepared following the above procedure at room temperature, but using as catalyst the achiral thiourea showed below (10 mol%), which was prepared following literature protocols.[283]



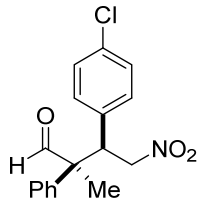
Achiral thiourea used for the synthesis of racemic compounds.

2-Methyl-4-nitro-2,3-diphenylbutanal (66a)



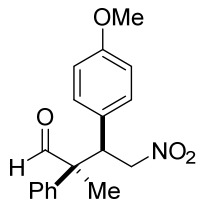
The title compound **66a** was prepared from 2-phenylpropanal (**65**) (26.8 mg, 0.2 mmol) and nitrostyrene **24a** (89.49 mg, 0.6 mmol) in the presence of **C34**, according to the General Procedure, affording a white solid as a mixture of diastereomers (*dr*: 93:7) determined by ^{1}H NMR after column chromatography. Yield: 49.0 mg, 0.18 mmol, 91 %. For the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.40 – 7.26 (m, 4H), 7.21 – 6.92 (m, 6H), 5.17 – 4.81 (m, 2H), 4.22 (dd, *J* = 11.5, 3.8 Hz, 1H), 1.55 (s, 3H). All the spectroscopic data were consistent with those previously reported.[297] The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: for the major diastereomer 21.2 min (minor) and 31.2 min (major); for the minor diastereomer: 19.6 min (major) and 26.2 min (minor)).

3-(4-Chlorophenyl)-2-methyl-4-nitro-2-phenylbutanal (66g)



The title compound **66g** was prepared from 2-phenylpropanal (**65**) (26.8 mg, 0.2 mmol) and nitrostyrene **24g** (110.1 mg, 0.6 mmol) according to the General Procedure, affording a white sticky solid as a mixture of diastereomers (*dr*: 87:13) determined by ^{1}H NMR after column chromatography. Yield: 54.0 mg, 0.17 mmol, 86 %. For the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.49 – 7.11 (m, 5H), 7.07 (dd, *J* = 7.7, 2.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.05 – 4.83 (m, 2H), 4.21 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 138.6, 135.7, 132.3, 130.9, 130.1, 130.0, 129.0, 78.0, 50.7, 18.1. UPLC-DAD-QTOF: $C_{17}H_{16}ClNO_3Na$ $[M+Na]^+$ calcd.: 340.0716, found: 340.0731. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: 20.9 min (minor) and 22.7 min (major)). The product was obtained with 94 % *ee* for the major diastereomer.

3-(4-Methoxyphenyl)-2-methyl-4-nitro-2-phenylbutanal (66i)

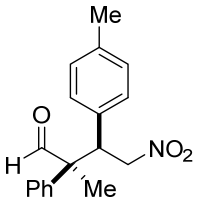


The title compound **66i** was prepared from 2-phenylpropanal (**65**) (26.8 mg, 0.2 mmol) and nitrostyrene **24i** (107.5 mg, 0.6 mmol) according to the General Procedure, affording a yellow oil as a mixture of diastereomers (*dr*: 93:7) determined by ^{1}H NMR after column

[297] Felluga, F.; Nitti, P.; Pitacco, G; Valentin, E. *J. Chem. Soc. Perkin Trans. 1, 1992*, 2331–2335.

chromatography. Yield: 52.6 mg, 0.17 mmol, 84 %. For the major diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.37 – 7.29 (m, 3H), 7.10 (dd, *J* = 8.0, 1.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.07 – 4.78 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.73 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 160.2, 138.7, 131.6, 130.3, 129.7, 129.3, 128.6, 127.3, 114.9, 77.7, 58.0, 56.4, 50.3, 18.2. UPLC-DAD-QTOF: $C_{18}H_{19}NO_4Na$ $[M+Na]^+$ calcd.: 336.1212, found: 336.1213. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 95:5, flow rate = 1.0 mL/min, retention times: for the major diastereomer 28.5 min (minor) and 44.7 min (major); for the minor diastereomer 26.6 min (major) and 33.0 (minor)).

2-Methyl-4-nitro-2-phenyl-3-(*p*-tolyl)butanal (66j)

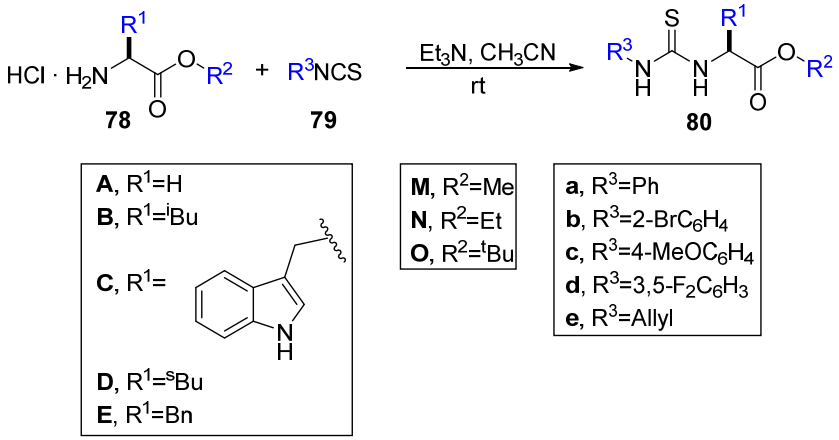


The title compound **66j** was prepared from 2-phenylpropanal (**65**) (26.8 mg, 0.2 mmol) and nitrostyrene **24j** (97.9 mg, 0.6 mmol) according to the General Procedure, affording a white sticky solid as a mixture of diastereomers (*dr*: 89:11) determined by ^{1}H NMR after column chromatography. Yield: 54.5 mg, 0.19 mmol, 94 %. For the major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.42 – 7.24 (m, 3H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.15 – 4.75 (m, 2H), 4.18 (dd, *J* = 11.5, 3.8 Hz, 1H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 138.7, 133.5, 130.9, 130.5, 130.4, 130.3, 129.4, 128.7, 77.7, 58.0, 50.8, 22.3, 18.4. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1266. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 90:10, flow rate = 1.0 mL/min, retention times: 12.9 min (minor) and 16.7 min (major)).

7.6. Experimental section for Chapter 5

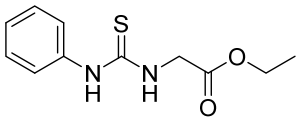
7.6.1. Preparation of thioureas

7.6.1.1. Preparation of amino acid derived thioureas:



To a suspension of the starting amino acid hydrochloride **78** (3 mmol, 1 equiv.) in CH_3CN (1.4 mL/mmol), the corresponding isothiocyanate **79** (3 mmol, 1 equiv.) and Et_3N (3.6 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature for 1–3 h as monitored by TLC and then diluted with EtOAc (25 mL) and washed with 10 % NH_4Cl (2 x 25 mL) and saturated NaCl (1 x 15 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduce pressure. The crude product was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 90:10 → 70:30) to afford the corresponding amino acid derived thiourea **80**.

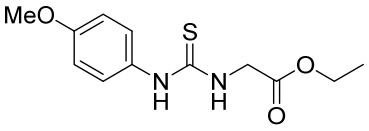
Ethyl (phenylcarbamothioyl)glycinate (80ANa)



The title compound **80ANa** was prepared from ethyl glycinate hydrochloride (**78AN**) (0.419 g, 3.0 mmol) and phenyl isothiocyanate (**79a**) (0.36 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.529 g, 2.22 mmol, 74 %. m.p. 86–88 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 7.40–7.36 (m, 2H), 7.27–7.22 (m, 3H), 6.74 (br s, 1H), 4.38 (d, *J* = 4.8 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 169.8, 136.2, 130.0, 127.0, 124.8, 61.7, 46.7, 14.1.

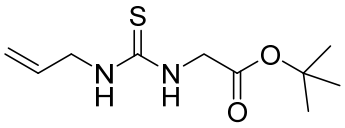
HRMS (EIS): $C_{11}H_{15}N_2O_2S$ $[M+H]^+$ calcd.: 239.08515, found: 239.08542. All the spectroscopy data were consistent with those previously reported.[298]

Ethyl ((4-methoxyphenyl)carbamothioyl)glycinate (80ANc)



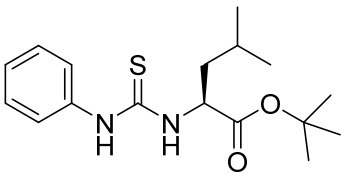
The title compound **80ANc** was prepared from ethyl glycinate hydrochloride (**78AN**) (0.419 g, 3.0 mmol) and 1-methoxy-4-thiocyanatobenzene (**79c**) (0.41 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.587 g, 2.19 mmol, 73 %. m.p. 138–140 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.19 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.45 (br s, 1H), 4.39 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 169.7, 158.9, 128.3, 127.4, 115.3, 61.6, 55.5, 46.8, 14.1. HRMS (EIS): $C_{12}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 269.09599, found: 269.09660.

***tert*-Butyl (allylcarbamothioyl)glycinate (80AOe)**



The title compound **80AOe** was prepared from *tert*-butyl glycinate hydrochloride (**78AO**) (0.503 g, 3.0 mmol) and allyl isothiocyanate (**79e**) (0.29 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.559 g, 2.43 mmol, 81 %. m.p. 47–49 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 6.86 (br s, 1H), 6.69 (br s, 1H), 5.82 (ddt, *J* = 15.9, 10.8, 5.5 Hz, 1H), 5.20 (dd, *J* = 36.1, 13.6 Hz, 2H), 4.24 (d, *J* = 4.9 Hz, 2H), 4.01 (br s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 169.8, 133.1, 117.5, 82.7, 47.2, 46.6, 28.0. HRMS (EIS): $C_{10}H_{19}N_2O_2S$ $[M+H]^+$ calcd.: 231.11672, found: 231.11668.

***tert*-Butyl (phenylcarbamothioyl)-L-leucinate (80BOa)**

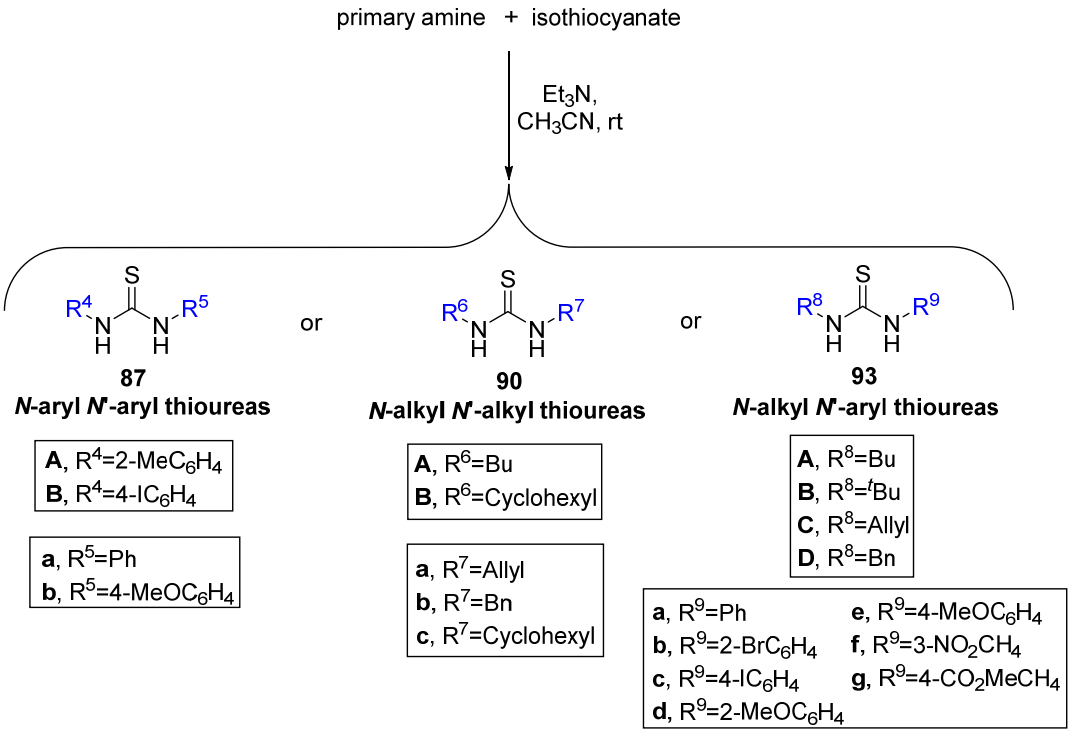


The title compound **80BOa** was prepared from *tert*-butyl *L*-leucinate hydrochloride (**78BO**) (0.671 g, 3.0 mmol) and phenyl isothiocyanate (**79a**) (0.36 mL, 3.0 mmol) according to the General Procedure. The product was obtained as white solid: 0.667 g, 2.07 mmol, 69 %. m.p. 98–100 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.42–7.38 (m, 2H), 7.28–7.23 (m, 3H), 6.61 (br s, 1H), 5.08 – 5.00 (m, 1H), 1.69–1.62 (m, 2H), 1.62 – 1.53 (m, 1H), 1.43 (s, 9H), 0.93–0.91 (m, 6H). ^{13}C NMR

[298] Kuznetsova, O. Y.; Antipin, R. L.; Udina, A. V.; Krasnovskaya, O. O.; Beloglazkina, E. K.; Terenin, V. I.; Koteliansky, V. E.; Zyk, N. V.; Majouga, A. G. *Journal of Heterocyclic Chemistry*, **2016**, *53*, 1570–1577.

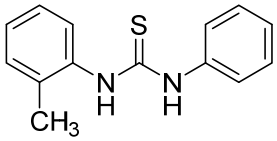
(100 MHz, $CDCl_3$) δ 180.2, 172.1, 136.3, 130.0, 126.9, 124.8, 82.2, 57.0, 41.5, 28.0, 25.0, 22.6. HRMS (EIS): $C_{11}H_{15}N_2O_2S$ $[M+H]^+$ calcd.: 323.17932, found: 323.17875.

*7.6.1.2. Preparation of N-aryl N'-aryl thioureas **87**, N-alkyl N'-alkyl thioureas **90** and N-alkyl N'-aryl thioureas **93**.*



To a suspension of the starting amine (3 mmol, 1 equiv.) in CH_3CN (1.4 mL/mmol), the corresponding isothiocyanate (3 mmol, 1 equiv.) and Et_3N (3.6 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature for 1–3 hours as monitored by TLC and then diluted with EtOAc (25 mL) and washed with 10 % NH_4Cl (2 x 25 mL) and saturated NaCl (1 x 15 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduce pressure. The crude product was purified by silica gel column chromatography (loaded in CH_2Cl_2, eluting with hexane/EtOAc 90:10 → 70:30) to afford the corresponding *N*-aryl *N*'-aryl thiourea **87**, *N*-alkyl *N*'-alkyl thiourea **90,** *N*-alkyl *N*'-aryl thiourea **93**.

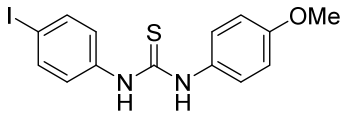
1-Phenyl-3-(*o*-tolyl)thiourea (87Aa)



The title compound **87Aa** was prepared from *o*-toluidine (0.32 mL, 3.0 mmol) and phenyl isothiocyanate (0.36 mL, 3.0 mmol) according to the General Procedure. The product was obtained as white solid: 0.611 g, 2.52 mmol, 84 %. m.p. 136–138 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.44 – 7.31 (m, 5H), 7.28 – 7.21 (m, 4H), 2.31 (s, 3H). ^{13}C NMR (100

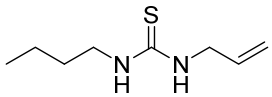
MHz, $CDCl_3$) δ 180.3, 137.5, 135.5, 135.4, 131.3, 129.3, 128.2, 127.8, 127.1, 126.8, 125.3, 18.0. HRMS (EIS): $C_{14}H_{15}N_2S$ $[M+H]^+$ calcd.: 243.09559, found: 243.09543. All the spectroscopy data were consistent with those previously reported.[299]

1-(4-Iodophenyl)-3-(4-methoxyphenyl)thiourea (87Bb)



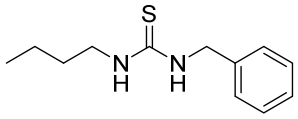
The title compound **87Bb** was prepared from *o*-toluidine (0.657 g, 3.0 mmol) and 1-isothiocyanato-4-methoxybenzene (0.42 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.981 g, 2.55 mmol, 85 %. ^{1}H NMR (399 MHz, DMSO-d_6) δ 9.65 (br s, 2H), 9.64 (br s, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8, 2H), 7.29 (d, *J* = 8.9, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.2, 157.1, 140.0, 137.4, 132.4, 126.5, 126.2, 114.2, 88.8, 55.7. HRMS (EIS): $C_{14}H_{14}IN_2OS$ $[M+H]^+$ calcd.: 384.98715, found: 384.98765.

1-Allyl-3-butylthiourea (90Aa)



The title compound **90Aa** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and allyl isothiocyanate (0.29 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a yellow oil: 0.475 g, 2.76 mmol, 92 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 14.3, 9.6, 4.7 Hz, 1H), 5.84 (br s, 2H), 5.37 – 5.20 (m, 2H), 4.10 (br s, 2H), 3.43 (br s, 2H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.40 (sex, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). All the spectroscopy data were consistent with those previously reported.[300]

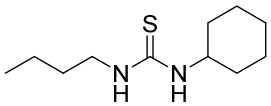
1-Benzyl-3-butylthiourea (90Ab)



The title compound **90Ab** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and benzyl isothiocyanate (0.40 mL, 3.0 mmol) according to the General Procedure. The product was obtained as an orange solid: 0.550 g, 2.47 mmol, 82 %. m.p. 49–51 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.28 (m, 5H), 6.43 (br s, 1H), 6.09 (br s, 1H), 4.60 (s, 2H), 3.33 (s, 2H), 1.47 (br s, 2H), 1.26 (br s, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 137.2, 128.8, 127.8, 127.5, 48.4, 44.2, 30.9, 19.9, 13.7. HRMS (EIS): $C_{12}H_{19}IN_2S$ $[M+H]^+$ calcd.: 223.12689, found: 223.12711.

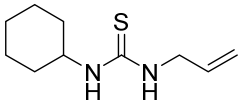
[299] Singh, K.; Sharma, S. *Tetrahedron Lett.* **2017**, *58*, 197–201.
[300] Young, M. C.; Liew, E.; Hooley, R. J. *Chem. Commun.* **2014**, *50*, 5043–5045.

1-Butyl-3-cyclohexylthiourea (90Ac)



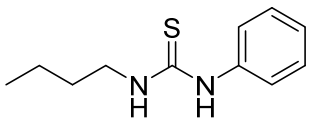
The title compound **90Ac** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and isothiocyanatocyclohexane (0.44 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.457 g, 2.13 mmol, 71 %. m.p. 79–81 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 6.22 (s, 1H), 6.05 (s, 1H), 3.88 (s, 1H), 3.34 (s, 2H), 2.02 – 1.00 (m, 14H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 53.0, 44.0, 32.9, 31.1, 25.4, 24.7, 20.1, 13.7. HRMS (EIS): $C_{11}H_{23}IN_2S$ $[M+H]^+$ calcd.: 215.15819, found: 215.15850. All the spectroscopy data were consistent with those previously reported.[301]

1-Butyl-3-cyclohexylthiourea (90Ba)



The title compound **90Ba** was prepared from cyclohexanamine (0.34 mL, 3.0 mmol) and allyl isothiocyanate (0.29 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.457 g, 2.30 mmol, 77 %. m.p. 69–71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 – 5.81 (m, 1H), 5.87 (br s, 1H), 5.74 (br s, 1H), 5.38 – 5.16 (m, 2H), 4.08 (br s, 2H), 3.93 (br s, 1H), 2.11 – 2.00 (m, 2H), 1.69 (ddt, *J* = 28.8, 12.1, 3.8 Hz, 3H), 1.48 – 1.11 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 133.4, 117.3, 53.1, 46.7, 32.8, 25.4, 24.6. HRMS (EIS): $C_{10}H_{18}N_2S$ $[M+H]^+$ calcd.: 199.12689, found: 199.12648. All the spectroscopy data were consistent with those previously reported.[302]

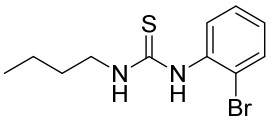
1-Butyl-3-phenylthiourea (93Aa)



The title compound **93Aa** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and phenyl isothiocyanate (0.36 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.560 g, 2.69 mmol, 90 %. m.p. 58–60 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.48 – 7.33 (m, 2H), 7.32 – 7.10 (m, 3H), 6.06 (br s, 1H), 3.59 (td, *J* = 7.3, 5.4 Hz, 2H), 1.56 – 1.48 (m, 2H), 1.34 – 1.22 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 136.3, 130.1, 127.1, 125.1, 45.2, 31.0, 20.0, 13.7. HRMS (EIS): $C_{11}H_{17}IN_2S$ $[M+H]^+$ calcd.: 209.11124, found: 209.11139. All the spectroscopy data were consistent with those previously reported.[303]

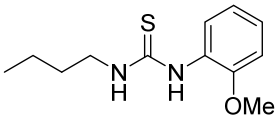
[301] Gan, S.-F.; Wan, J.-P.; Pan Y.-J.; Sun, C.-R. *Mol Divers* **2011**, *15*, 809–815.
[302] Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Synthesis*, **2014**, *46*, 3172–3179.
[303] Liu, J.; Deng, Y.; Lin, C.; Lei, A. *Chem. Sci.* **2012**, *3*, 1211–1214.

1-(2-Bromophenyl)-3-butylthiourea (93Ab)



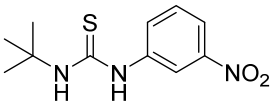
The title compound **93Ab** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and 1-bromo-2-isothiocyanatobenzene (0.40 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.589 g, 2.05 mmol, 68 %. m.p. 81–83 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.42 (br s, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 5.94 (br s, 1H), 3.58 (s, 2H), 1.59 – 1.51 (m, 2H), 1.36 – 1.27 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 135.1, 133.9, 128.6, 127.4, 45.3, 30.9, 20.1, 13.7. HRMS (EIS): $C_{11}H_{16}BrN_2S$ $[M+H]^+$ calcd.: 287.02176, found: 287.02173.

1-Butyl-3-(2-methoxyphenyl)thiourea (93Ad)



The title compound **93Ad** was prepared from butan-1-amine (0.30 mL, 3.0 mmol) and 1-isothiocyanato-3-methoxybenzene (0.42 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.443 g, 1.86 mmol, 63 %. m.p. 71–73 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.26 (t, *J* = 8.1 Hz, 1H), 6.82 – 6.68 (m, 3H), 6.16 (s, 1H), 3.75 (s, 3H), 3.57 (s, 2H), 1.51 (p, *J* = 7.6 Hz, 2H), 1.29 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 160.8, 137.5, 130.8, 116.8, 112.6, 110.5, 55.4, 45.2, 31.00, 20.0, 13.7. HRMS (EIS): $C_{12}H_{19}N_2OS$ $[M+H]^+$ calcd.: 239.1218, found: 239.1221.

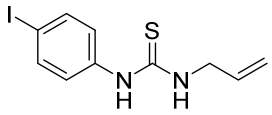
1-(*tert*-Butyl)-3-(3-nitrophenyl)thiourea (93Bf)



The title compound **93Bf** was prepared from *tert*-butyl amine (0.31 mL, 3.0 mmol) and 3-nitrophenyl isothiocyanate (0.540 g, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.676 g, 2.67 mmol, 89 %. m.p. 144–146 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.96 (br s, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 8.1 Hz, 1H), 6.23 (br s, 1H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 148.8, 138.8, 130.4, 130.0, 120.6, 118.7, 54.5, 29.0. HRMS (EIS): $C_{11}H_{16}N_3O_2S$ $[M+H]^+$ calcd.: 254.09632, found: 254.09558. All the spectroscopy data were consistent with those previously reported.[304]

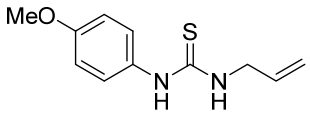
[304] Yoshizumi, K.; Ikeda, S; Goto, K.; Morita, T.; Nishimura, N.; Sukamoto, T.; Yoshino, K. *Chem. Pharm. Bull.* **1996**, *44*, 2042–2050.

1-Allyl-3-(4-iodophenyl)thiourea (93Cc)



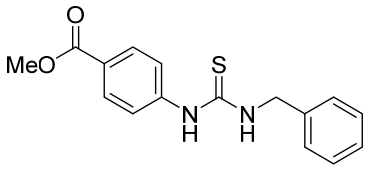
The title compound **93Cc** was prepared from 4-iodoaniline (0.647 g, 3.0 mmol) and allyl isothiocyanate (0.29 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.664 g, 2.09 mmol, 70 %. m.p. 97–99 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.04 (br s, 1H), 5.87 (ddt, *J* = 16.1, 10.3, 5.7 Hz, 1H), 5.28 – 5.06 (m, 2H), 4.26 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 139.3, 132.9, 127.0, 117.5, 103.1, 91.9, 47.9. HRMS (EIS): $C_{10}H_{11}IN_2S$ $[M+H]^+$ calcd.: 318.97659, found: 318.97691.

1-Allyl-3-(4-methoxyphenyl)thiourea (93Ce)



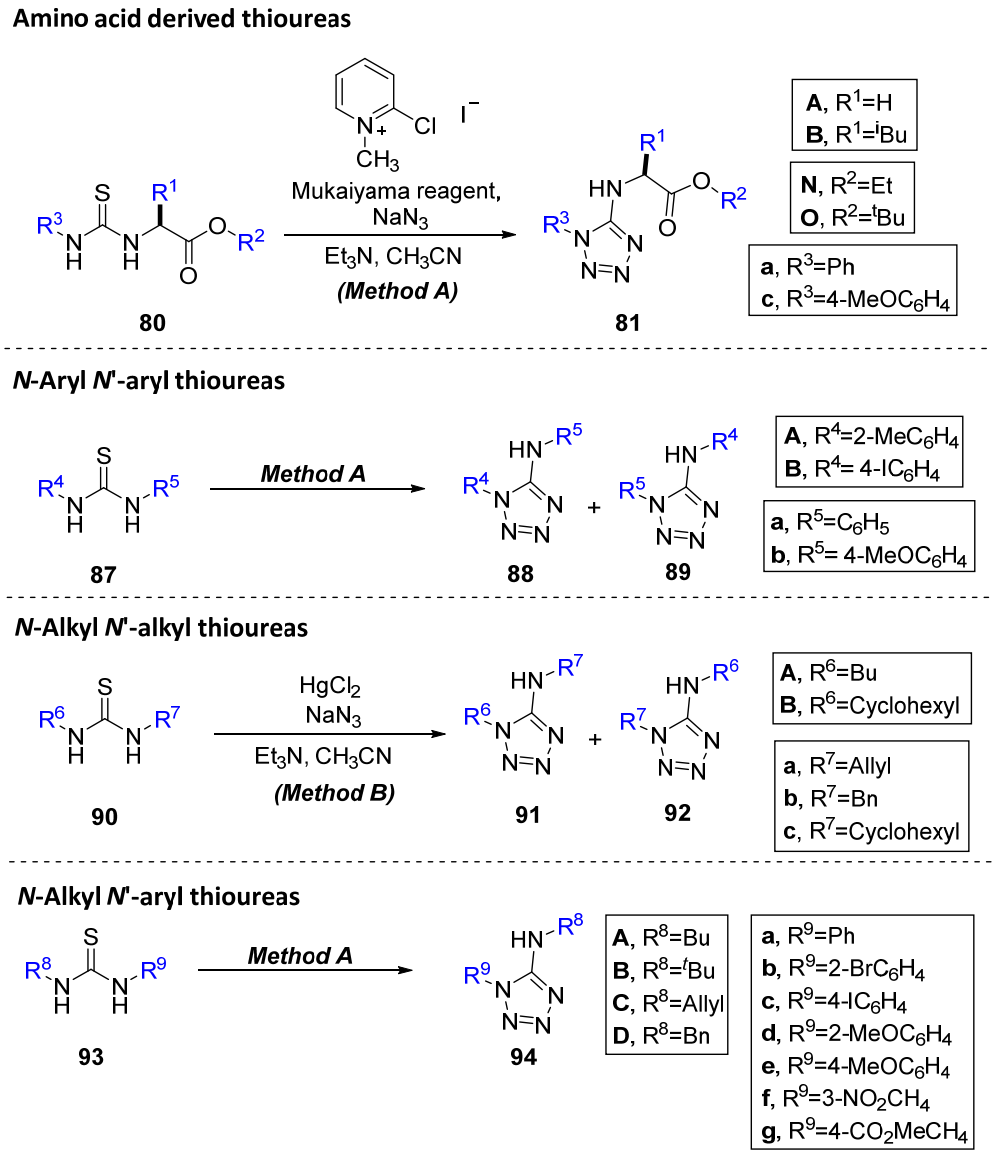
The title compound **93Ce** was prepared from 4-methoxyaniline (0.369 g, 3.0 mmol) and allyl isothiocyanate (0.29 mL, 3.0 mmol) according to the General Procedure. The product was obtained as a white solid: 0.517 g, 2.33 mmol, 78 %. m.p. 71–73 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.94 – 5.77 (m, 2H), 5.17 – 5.04 (m, 2H), 4.24 – 4.21 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 158.9, 133.4, 128.4, 127.7, 116.8, 115.3, 55.5, 47.6. HRMS (EIS): $C_{11}H_{14}N_2OS$ $[M+H]^+$ calcd.: 223.09051, found: 223.09064. All the spectroscopy data were consistent with those previously reported.[301]

Methyl 4-(3-benzylthioureido)benzoate (93Dg)



The title compound **93Dg** was prepared from methyl 4-aminobenzoate (0.453 g, 3.0 mmol) and benzyl isothiocyanate (0.40 mL, 3.0 mmol) according to the general procedure. The product was obtained as white solid: 0.232 g, 0.77 mmol, 26 % (67% regarding starting material recovered). m.p. 152–154 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.40 – 7.28 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.46 (br s, 1H), 4.87 (d, *J* = 4.6 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 180.46, 165.97, 145.17, 136.07, 131.65, 128.92, 128.01, 127.92, 127.81, 123.14, 52.26, 49.71. HRMS (EIS): $C_{16}H_{17}N_2O_2S$ $[M+H]^+$ calcd.: 301.10107, found: 301.10188.

7.6.2. Preparation of tetrazoles



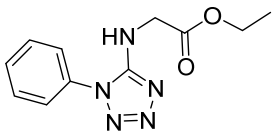
General Method A:

To a suspension of thiourea **80, 87** or **93** (1 mmol, 1.0 equiv.), triethylamine (0.42 mL, 3 mmol, 3 equiv.) and Mukaiyama reagent (0.281g, 1.1 mmol, 1.1 equiv.) in dry CH_3CN (3 mL/mmol) was added sodium azide (0.195 g, 3 mmol, 3.0 equiv.). The resulting suspension was stirred at room temperature until TCL or NMR monitoring indicated complete consumption of the starting material. Then reaction mixture was diluted with EtOAc and washed with 10 % NH_4Cl and saturated NaCl. It was then dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (eluting with hexane/EtOAc 90:10) to afford the corresponding pure regioisomers **81** and **94** or the corresponding regioisomers **88**/**89** as an inseparable mixture.

General Method B:

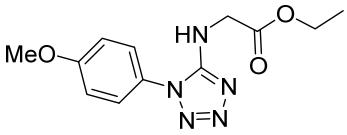
To a suspension of thiourea **90** (1 mmol, 1.0 equiv.), triethylamine (0.42 mL, 3 mmol, 3 equiv.) and mercuric chloride (0.299 g, 1.1 mmol, 1.1 equiv.) in dry CH_3CN (3 mL/mmol) was added sodium azide (0.195 g, 3 mmol, 3.0 equiv.). The resulting suspension was stirred at room temperature until TCL or NMR monitoring indicated complete consumption of starting material. Then reaction mixture was filtered through a layer of Celite using EtOAc. The organic layer was diluted with EtOAc and washed with 10 % NH_4Cl and saturated NaCl. It was then dried over $MgSO_4$ and the solvent was removed under reduce pressure to afford the corresponding pure regioisomers **91**/**92** as an inseparable mixture.

Ethyl (1-phenyl-1*H*-tetrazol-5-yl)glycinate (81ANa)



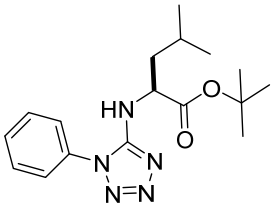
The title compound **81ANa** was prepared from ethyl (phenylcarbamothioyl)glycinate (**80ANa**) (0.238 g, 1.0 mmol) according to the General Method A. The product was obtained as a white solid: 0.200 g, 0.81 mmol, 81 %. m.p. 73–74 °C. IR (film) ν 3345, 2984, 1745, 1605, 1510, 1458, 1375, 1209, 1098, 1020, 763 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.64 – 7.43 (m, 5H), 5.04 (br t, *J* = 5.4 Hz 1H), 4.24 (d, *J* = 5.4 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 154.2, 133.0, 130.3, 129.9, 123.9, 61.9, 45.5, 14.1. HRMS (EIS): $C_{11}H_{14}N_2O_5$ $[M+H]^+$ calcd.: 248.11475, found: 248.11472.

Ethyl (1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)glycinate (81ANc)



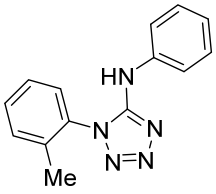
The title compound **81ANc** was prepared from ethyl ((4-methoxyphenyl)carbamothioyl)glycinate (**80ANc**) (0.268 g, 1.0 mmol) according to the General Method B using PS-Mukaiyama reagent (13.333 g, 4.0 mmol, 4 equiv.) instead of mercury chloride. The product was obtained as a white solid: 0.213 g, 0.81 mmol, 81 %. m.p. 98–99 °C. IR (film) ν 3333, 2981, 1742, 1602, 1518, 1253, 1207, 1097, 1023, 837 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.85 (br t, 1H), 4.30 – 4.14 (m, 4H), 3.87 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 166.0, 145.2, 136.1, 131.6, 128.9, 128.0, 127.9, 127.8, 123.1, 52.3, 49.7. HRMS (EIS): $C_{12}H_{16}N_5O_3$ $[M+H]^+$ calcd.: 278.12531, found: 278.12502.

tert-Butyl (1-phenyl-1*H*-tetrazol-5-yl)-*L*-leucinate (81BOa)

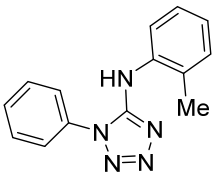


The title compound **81BOa** was prepared from *tert*-butyl (phenylcarbamothioyl)-*L*-leucinate (**80BOa**) (0.322 g, 1.0 mmol) according to the general procedure A. The product was obtained as a white solid: 0.235 g, 0.71 mmol, 71 %. m.p. 103–105 °C. IR (film) ν 3306, 2957, 1722, 1576, 1507, 1457, 1367, 1146, 842, 760, 687 cm^{-1}. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.64 – 7.49 (m, 5H), 4.78 (d, *J* = 8.9 Hz, 1H), 4.57 (td, *J* = 8.8, 5.1 Hz, 1H), 1.85 – 1.67 (m, 2H), 1.64 – 1.56 (m, 1H), 1.45 (s, 9H), 0.97 (t, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 154.4, 133.2, 130.3, 129.8, 123.9, 82.6, 56.2, 41.8, 28.0, 25.0, 22.8, 22.1. HRMS (EIS): $C_{17}H_{26}N_5O_2$ $[M+H]^+$ calcd.: 332.2087, found: 332.2083.

_N_-Phenyl-1-(*o*-tolyl)-1*H*-tetrazol-5-amine (88Aa) and 1-phenyl-*N*-(*o*-tolyl)-1*H*-tetrazol-5-amine (89Aa)



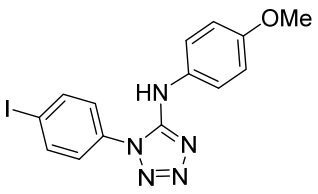
88Aa



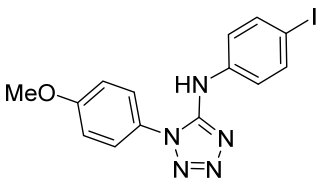
89Aa

The title compounds **88Aa** and **89Aa** were prepared from 1-phenyl-3-(*o*-tolyl)thiourea (**87Aa**) (0.242 g, 1.0 mmol) following the General Method A to afford a white solid as mixture of regioisomers (**88Aa/89Aa** 1:4.2) determined by ^{1}H NMR after silica gel flash column chromatography. Yield: 0.165 g, 0.66 mmol, 66 %. ^{1}H NMR (399 MHz, DMSO-d_6), for the major regioisomer **89Aa**: δ 7.57 – 7.52 (m, 3H), 7.38 – 7.33 (m, 3H), 7.12 – 7.06 (m, 1H), 6.04 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), for the major regioisomer **89Aa**: δ 153.3, 140.1, 136.1, 131.8, 131.4, 129.2, 128.4, 127.8, 122.6, 118.6, 18.2, 17.3. HRMS (EIS): $C_{14}H_{14}N_5$ $[M+H]^+$ calcd.: 252.12492, found: 252.12554. All the spectroscopy data were consistent with those previously reported.[305]

1-(4-Iodophenyl)-*N*-(4-methoxyphenyl)-1*H*-tetrazol-5-amine (88Bb) and *N*-(4-iodo phenyl)-1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine (89Bb)



88Bb



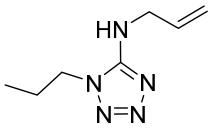
89Bb

The title compounds **88Bb** and **89Bb** were prepared from 1-(4-iodophenyl)-3-(4-methoxy phenyl)thiourea (**87Bb**) (0.384 g, 1.0 mmol) following the General Method A to afford as a white solid a mixture of regioisomers (**88Bb/89Bb** 1:1) determined by 1H NMR after silica gel flash column chromatography. Yield : 0.275 g, 0.70

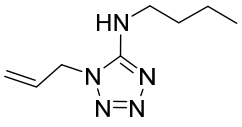
[305] Chandrasekhar, A.; Ramkumar, V.; Sankararaman, S. *Org. Biomol. Chem*. **2018**, *16*, 8629–8638.

mmol, 70 %. For major isomer: ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.39 (br s, 1H), 3.89 (s, 3H). For minor isomer: ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.37 (br s, 1H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (89Bb + 90Bb): δ 151.5, 140.7, 139.6, 138.1, 136.1, 133.9, 126.8, 126.2, 120.8, 119.9, 115.7, 114.6, 113.3, 88.2, 86.0, 55.8, 55.5. HRMS (EIS): $C_{14}H_{13}IN_5O$ $[M+H]^+$ calcd.: 394.01648, found: 394.01722.

_N_-Allyl-1-butyl-1_H_-tetrazol-5-amine (91Aa) and 1-allyl-_N_-butyl-1_H_-tetrazol-5-amine (92Aa)



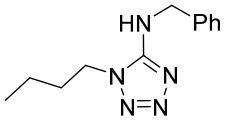
91Aa



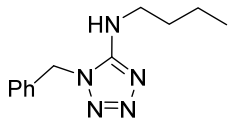
92Aa

The title compounds **91Aa** and **92Aa** were prepared from 1-allyl-3-butylthiourea **90Aa** (0.172 g, 1.0 mmol) following the General Method B to afford as a yellow oil a mixture of regioisomers (**91Aa**/**92Aa**, 1.4:1) determined by ^{1}H NMR after filtration. Yield: 0.123 g, 0.68 mmol, 68 %. ^{1}H NMR (300 MHz, $CDCl_3$), for **91Aa**: δ 6.02 – 5.89 (m, 1H), 5.28 – 5.22 (m, 1H), 5.16 – 5.09 (m, 1H), 4.98 (br s, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.42 (q, *J* = 7.1 Hz, 2H), 1.62 (p, *J* = 7.6 Hz, 2H), 1.44 – 1.26 (m, 2H), 0.92 (t, *J* = 6.6 Hz, 3H); for **92Aa**: δ 6.02 – 5.89 (m, 1H), 5.51 (br s, 1H), 5.33 (d, *J* = 10.3 Hz, 1H), 5.19 (d, *J* = 7.4 Hz, 1H), 4.80 (d, *J* = 5.5 Hz, 2H), 4.06 (t, *J* = 5.7 Hz, 2H), 1.81 (p, *J* = 7.5 Hz, 2H), 1.44 – 1.26 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (**91Aa** + **92Aa**), δ 156.3, 156.0, 134.7, 130.6, 120.2, 117.4, 48.4, 47.2, 45.9, 44.8, 32.1, 31.1, 20.5, 20.2, 14.3, 14.1. UPLC-DAD-QTOF: $C_8H_{15}N_5Na$ $[M+Na]^+$ calcd.: 204.1221, found: 204.1228.

_N_-Benzyl-1-butyl-1_H_-tetrazol-5-amine (91Ab) and 1-benzyl-_N_-butyl-1_H_-tetrazol-5-amine (92Ab)



91Ab

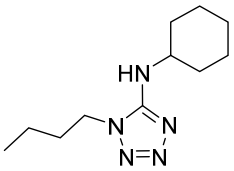


92Ab

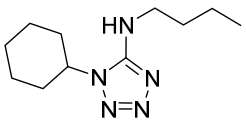
The title compounds **91Ab** and **92Ab** were prepared from 1-benzyl-3-butylthiourea (**90Ab**) (0.222 g, 1.0 mmol) following the General Method B to afford a white solid as mixture of regioisomers (**91Aa**/**92Aa**, 1.2:1) determined by ^{1}H NMR after filtration. Yield: 0.180 g, 0.83 mmol, 83 %. ^{1}H NMR (399 MHz, $CDCl_3$), for **91Ab**, δ 7.57 – 7.26 (m, 5H), 4.58 (d, *J* = 5.7 Hz, 2H), 4.03 (t, *J* = 7.2 Hz, 2H), 1.77 (p, *J* = 7.4 Hz, 2H), 1.18 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); for **92Ab**, δ 7.52 – 7.26 (m, 4H), 7.22 – 7.14 (m, 1H), 5.29 (s, 2H), 3.30 (q, *J* = 7.0 Hz, 2H), 1.46 (p, *J* = 7.4 Hz, 2H), 1.30 (dt, *J* = 14.7, 7.4 Hz, 2H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), (**91Ab** + **92Ab**), δ 155.5, 155.3, 129.3, 128.9, 128.7, 128.6, 127.8, 127.7, 127.6, 127.4, 49.2, 48.3,

45.2, 44.1, 31.4, 30.5, 19.6, 13.6, 13.4. HRMS (EIS): $C_{12}H_{18}N_5$ $[M+H]^+$ calcd.: 232.15622, found: 232.15649.

1-Butyl-*N*-(cyclohexylmethyl)-1H-tetrazol-5-amine (91Ac) and *N*-butyl-1-(cyclohexyl methyl)-1H-tetrazol-5-amine (92Ac)



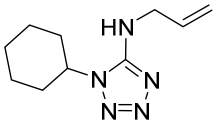
91Ac



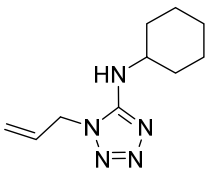
92Ac

The title compound **91Ac** and **92Ac** was prepared from 1-butyl-3-cyclohexylthiourea **90Ac** (0.214 g, 1.0 mmol) according to the general procedure B, affording as white solid a mixture of regioisomers (**91Ac**/**92Ac**, 1.2:1) determined by 1H NMR after filtration. Yield: 0.216 g, 0.97 mmol, 97 %. ^{1}H NMR (399 MHz, $CDCl_3$), for (**91Ab + 92Ac**), δ 4.80 (br s, 1H), 4.40 (br s, 1H), 4.05 (t, *J* = 7.2 Hz, 2H), 3.95 (ddt, *J* = 10.7, 7.4, 3.7 Hz, 1H), 3.69 (dtt, *J* = 14.3, 7.4, 4.0 Hz, 1H), 3.55 – 3.38 (m, 2H), 2.26 – 1.55 (m, 21H), 1.51 – 1.10 (m, 15H), 0.94 (td, *J* = 7.3, 3.3 Hz, 6H) .^{13}C NMR (100 MHz, $CDCl_3$), (**91Ac** + **92Ac**), δ 155.4, 155.3, 56.3, 54.2, 45.7, 44.9, 34.0, 32.7, 32.5, 32.3, 31.2, 26.1, 25.8, 25.5, 20.6, 20.3, 14.4, 14.1. UPLC-DAD-QTOF: $C_{11}H_{21}N_5Na$ $[M+Na]^+$ calcd.: 246.1695, found: 246.1695.

***N*-allyl-1-cyclohexyl-1*H*-tetrazol-5-amine (91Ba) and 1-allyl-*N*-cyclohexyl-1*H*-tetrazol-5-amine (92Ba)**



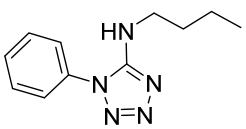
91Ba



92Ba

The title compound **91Ba** and **92Ba** was prepared from 1-butyl-3-cyclohexylthiourea (**90Ba**) (0.199 g, 1.0 mmol) following the General Method B to afford a white solid as mixture of regioisomers (**91Ba**/**92Ba**, 1.2:1) determined by 1H NMR after filtration. Yield: 0.184 g, 0.89 mmol, 89 %. ^{1}H NMR (399 MHz, DMSO-d_6), for (**91Ba + 92Ba**), δ 7.09 (t, *J* = 5.7 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.03 – 5.83 (m, 2H), 5.28 – 4.93 (m, 4H), 4.80 (d, *J* = 5.3 Hz, 2H), 4.20 (tt, *J* = 11.5, 3.9 Hz, 1H), 3.91 (tt, *J* = 5.6, 1.6 Hz, 3H), 2.04 – 1.53 (m, 17H), 1.46 – 1.33 (m, 3H). ^{13}C NMR (75 MHz, DMSO) δ 154.7, 154.6, 135.2, 131.8, 117.5, 115.7, 54.1, 52.8, 45.4, 32.4, 31.6, 24.7, 24.6, 8.5. UPLC-DAD-QTOF: $C_{10}H_{17}N_5Na$ $[M+Na]^+$ calcd.: 230.1382, found: 230.1383.

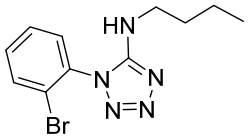
***N*-butyl-1-phenyl-1H-tetrazol-5-amine (94Aa)**



The title compound **94Aa** was prepared from 1-butyl-3-phenylthiourea (**93Aa**) (0.208 g, 1.0 mmol) according to the General Method A. The product was obtained as a white solid: 0.130 g, 0.60

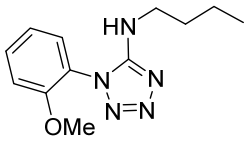
mmol, 60 %. m.p. 100–102 °C. IR (film) ν 3230, 2957, 1610, 1496, 1147, 1084, 765, 695 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.61 – 7.44 (m, 5H), 4.37 (br s, 1H), 3.52 – 3.40 (m, 2H), 1.63 (p, *J* = 7.4 Hz, 2H), 1.37 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 133.3, 130.3, 129.8, 124.0, 44.4, 31.6, 19.9, 13.7. HRMS (EIS): $C_{11}H_{16}N_5$ $[M+H]^+$ calcd.: 218.14057, found: 218.14038.

1-(2-Bromophenyl)-*N*-butyl-1H-tetrazol-5-amine (94Ab)



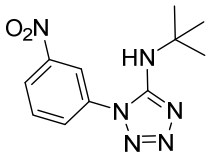
The title compound **94Ab** was prepared from 1-(2-bromophenyl)-3-butylthiourea **93Ab** (0.287 g, 1.0 mmol) according to the General Method A. The product was obtained as a white solid: 0.229 g, 0.81 mmol, 81 %. m. p. 120–122 °C. IR (film) ν 3199, 2955, 1610, 1482, 1083, 761, 623 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.57 – 7.35 (m, 3H), 4.09 (br s, 1H), 3.46 (q, *J* = 6.7 Hz, 2H), 1.60 (p, *J* = 7.4 Hz, 2H), 1.35 (dq, *J* = 14.5, 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 134.3, 132.4, 132.1, 129.7, 129.1, 121.4, 44.3, 31.6, 19.8, 13.7. HRMS (EIS): $C_{11}H_{15}BrN_5$ $[M+H]^+$ calcd.: 296.05108, found: 296.05049.

***N*-Butyl-1-(2-methoxyphenyl)-1H-tetrazol-5-amine (94Ad)**



The title compound **94Ad** was prepared from 1-butyl-3-(2-methoxyphenyl)thiourea (**93Ad**) (0.238 g, 1.0 mmol) according to the General Method A. The product was obtained as white solid: 0.237 g, 0.96 mmol, 96 %. m. p. 116–119 °C. IR (film) ν 3225, 2957, 1609, 1471, 1231, 1086, 866, 797 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.45 (t, *J* = 8.0 Hz, 1H), 7.02 (dt, *J* = 11.0, 2.2 Hz, 3H), 4.38 (s, 1H), 3.85 (s, 3H), 3.48 (q, *J* = 7.2, 6.6 Hz, 2H), 1.63 (p, *J* = 7.5 Hz, 2H), 1.37 (dt, *J* = 14.7, 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 160.92, 154.65, 131.00, 115.54, 115.44, 113.27, 109.74, 55.65, 44.35, 31.63, 19.89, 13.69. HRMS (EIS): $C_{12}H_{18}N_5O$ $[M+H]^+$ calcd.: 248.15190, found: 248.15113.

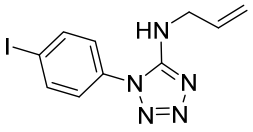
***N*-(*tert*-Butyl)-1-(3-nitrophenyl)-1H-tetrazol-5-amine (94Bf)**



The title compound **94Bf** was prepared from 1-(tert-butyl)-3-(3-nitrophenyl)thiourea (**93Bf**) (0.253 g, 1.0 mmol) according to the General Method A. The product was obtained as white solid: 0.205 g, 0.78 mmol, 78 %. IR (film) ν 3322, 2972, 1572, 1534, 1351, 1218, 738 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 8.37 – 7.85 (m, 3H), 7.80 (td, *J* = 8.0, 0.7 Hz, 1H), 4.46 (br s, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 149.0, 134.5, 131.5, 129.8,

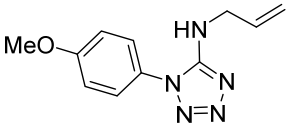
124.2, 119.1, 53.7, 28.7. HRMS (EIS): $C_{11}H_{14}N_6O_2$ $[M+H]^+$ calcd.: 263.12612, found: 263.12565.

_N_-Allyl-1-(4-iodophenyl)-1H-tetrazol-5-amine (94Cc)



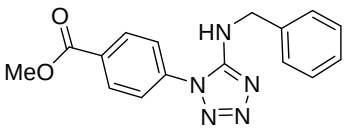
The title compound **94Cc** was prepared from 1-allyl-3-(4-iodophenyl)thiourea (**93Cc**) (0.318 g, 1.0 mmol) according to the General Method A. The product was obtained as awhite solid: 0.262 g, 0.80 mmol, 80 %. IR (film) ν 3284, 3078, 1602, 1490, 1084, 1006, 824 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.06 – 5.75 (m, 1H), 5.28 – 5.06 (m, 2H), 4.98 (br s, 1H), 4.04 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.3, 133.4, 132.8, 125.5, 117.5, 95.1, 46.9. HRMS (EIS): $C_{10}H_{11}IN_5$ $[M+H]^+$ calcd.: 328.00591, found: 328.00576.

_N_-Allyl-1-(4-methoxyphenyl)-1H-tetrazol-5-amine (95Ce)



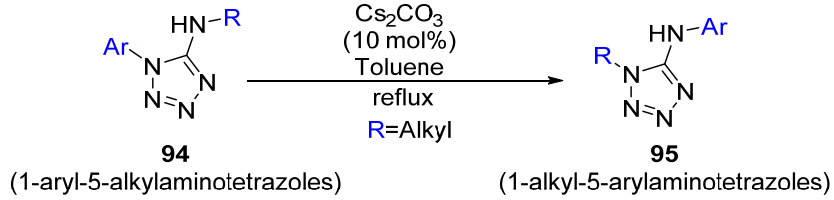
The title compound **95Ce** was prepared from 1-allyl-3-(4-methoxyphenyl)thiourea (**94Ce**) (0.222 g, 1.0 mmol) according to the General Method A. The product was obtained as a white solid: 0.176 g, 0.76 mmol, 76 %. m. p. 120–121 °C. IR (film) ν 3247, 2997, 1616, 1521, 1258, 1085, 1026, 836 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.9 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 2H), 5.93 (ddt, *J* = 16.1, 10.4, 5.7 Hz, 1H), 5.29 – 5.10 (m, 2H), 4.43 (br s, 1H), 4.07 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 154.8, 133.6, 126.0, 125.5, 117.3, 115.3, 55.7, 46.8. HRMS (EIS): $C_{11}H_{14}N_5O$ $[M+H]^+$ calcd.: 232.11983, found: 232.12003.

Methyl 4-(5-(benzylamino)-1H-tetrazol-1-yl)benzoate (94Dg)



The title compound **94Dg** was prepared from methyl 4-(3-benzylthioureido)benzoate **93Ce** (0.300 g, 1.0 mmol) according to the General Method A. The product was obtained as a white solid: 0.232 g, 0.75 mmol, 75 %. IR (film) ν 3334, 3027, 1721, 1600, 1435, 1280, 1112, 769, 698 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.26 (m, 5H), 4.95 (br s, 1H), 4.66 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 154.5, 137.2, 136.8, 131.6, 131.0, 128.8, 128.1, 128.0, 123.2, 52.5, 48.7.HRMS (EIS): $C_{16}H_{16}N_5O_2$ $[M+H]^+$ calcd.: 310.13040, found: 310.13018.

7.6.3. General Procedure for isomerization of tetrazoles

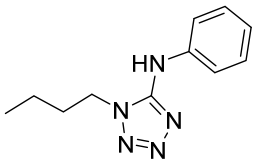


94
(1-aryl-5-alkylaminotetrazoles)

95
(1-alkyl-5-arylaminotetrazoles)

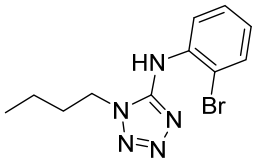
To a solution of the corresponding 5-amino tetrazole **94** (0.2 mmol, 1 equiv.) in toluene (5 mL) at room temperature was added Cs_2CO_3 (0.02 mmol, 10 mol%). The reaction mixture was refluxed to completion of the reaction as monitored by ^{1}H NMR. Then, the mixture was diluted with EtOAc (25 mL) and washed with H_2O (2 X 25 mL) and saturated NaCl (1 X 50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under vaccum to obtain the corresponding 1-alkyl-5-arylaminotetrazole **95**.

1-Butyl-*N*-phenyl-1H-tetrazol-5-amine (95Aa)



The title compound **95Aa** was prepared from *N*-butyl-1-phenyl-1*H*-tetrazol-5-amine (**94Aa**) (43.4 mg, 0.2 mmol) according to the General Procedure. The product was obtained as white solid: 42.6 mg, 0.196 mmol, 98 %. m. p. 122–123 °C. IR (film) ν 3275, 2959, 1622, 1575, 1536, 1501, 746, 691 cm^{-1}. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.26 (t, *J* = 7.3 Hz, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.39 – 1.28 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 139.2, 129.5, 129.1, 123.0, 118.5, 45.9, 30.7, 19.6, 13.4. HRMS (EIS): $C_{11}H_{16}N_5$ $[M+H]^+$ calcd.: 218.14057, found: 218.14077.

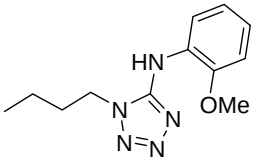
***N*-(2-Bromophenyl)-1-butyl-1*H*-tetrazol-5-amine (95Ab)**



The title compound **95Ab** was prepared from 1-(2-bromophenyl)-*N*-butyl-1*H*-tetrazol-5-amine (**94Aa**) (59.2 mg, 0.2 mmol) according to the General Procedure. The product was obtained as a white solid: 55.1 mg, 0.186 mmol, 93 %. m. p. 101–103 °C. IR (film) ν 3382, 2958, 1596, 1564, 1474, 1111, 1025, 749 cm^{-1}. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.33 (td, *J* = 8.5, 8.1, 1.4 Hz, 1H), 6.92 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 6.82 (br s, 1H), 4.23 (t, *J* = 7.2 Hz, 2H), 1.92 (p, *J* = 7.4 Hz, 2H), 1.41 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100

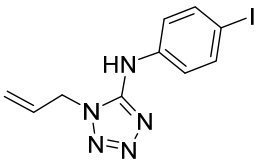
MHz,$CDCl_3$) δ 151.4, 136.2, 132.3, 128.9, 123.9, 118.7, 112.0, 45.9, 30.6, 19.7, 13.4. HRMS (EIS): $C_{11}H_{15}BrN_5$ $[M+H]^+$ calcd.: 296.05108, found: 296.05080.

1-Butyl-*N*-(2-methoxyphenyl)-1*H*-tetrazol-5-amine (95Ad)



The title compound **95Ad** was prepared from N-butyl-1-(2-methoxyphenyl)-1H-tetrazol-5-amine (**94Ad**) (49.5 mg, 0.2 mmol) according to the general procedure. The product was obtained as white solid: 43.5 mg, 0.176 mmol, 88 %. m. p. 57–59 °C. IR (film) ν 3281, 2957, 1616, 1575, 1533, 1470, 1111, 755 cm^{-1}. ^1H NMR (399 MHz, $CDCl_3$) δ 7.23 (t, *J* = 2.2 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.62 (td, *J* = 6.8, 1.5 Hz, 1H), 4.27 (t, *J* = 7.3 Hz, 2H), 3.73 (s, 3H), 1.84 (p, *J* = 7.4 Hz, 2H), 1.33 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 155.9, 152.4, 140.9, 135.9, 134.2, 113.5, 110.6, 55.3, 45.9, 30.7, 19.6, 13.4. HRMS (EIS): $C_{12}H_{18}N_5O$ $[M+H]^+$ calcd.: 248.1511, found: 248.1513.

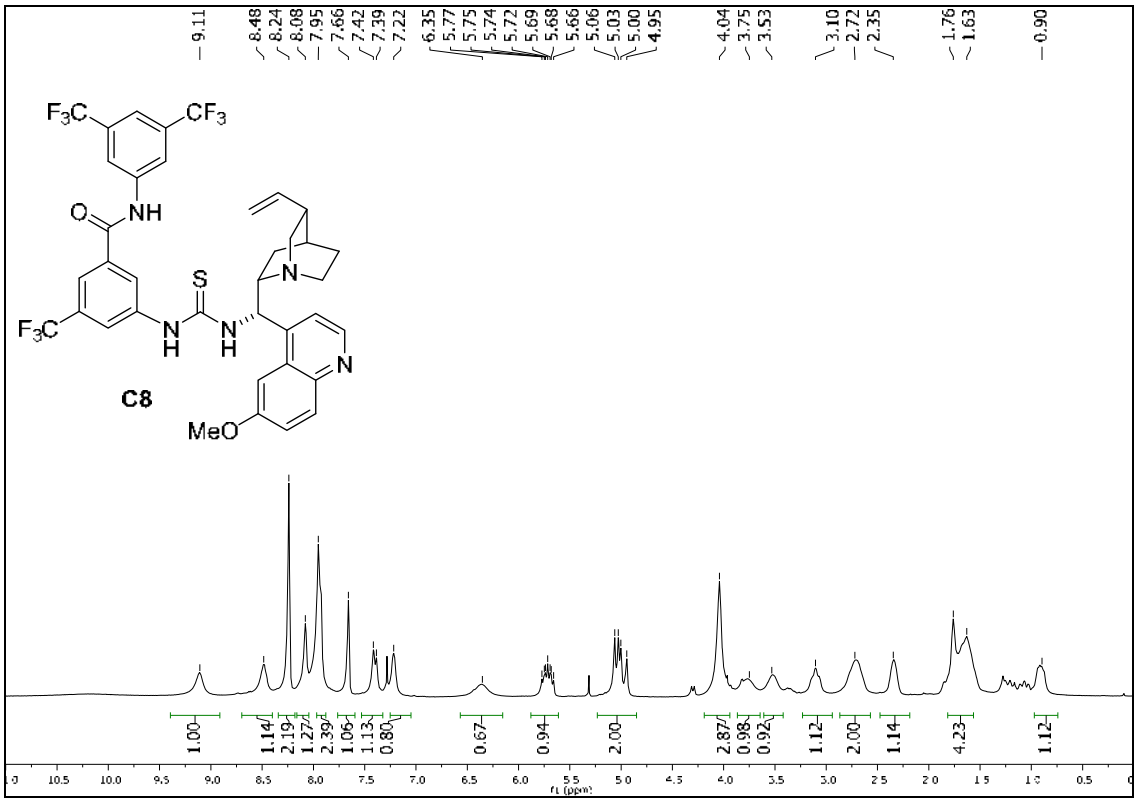
1-Allyl-*N*-(4-iodophenyl)-1*H*-tetrazol-5-amine (95Cc)

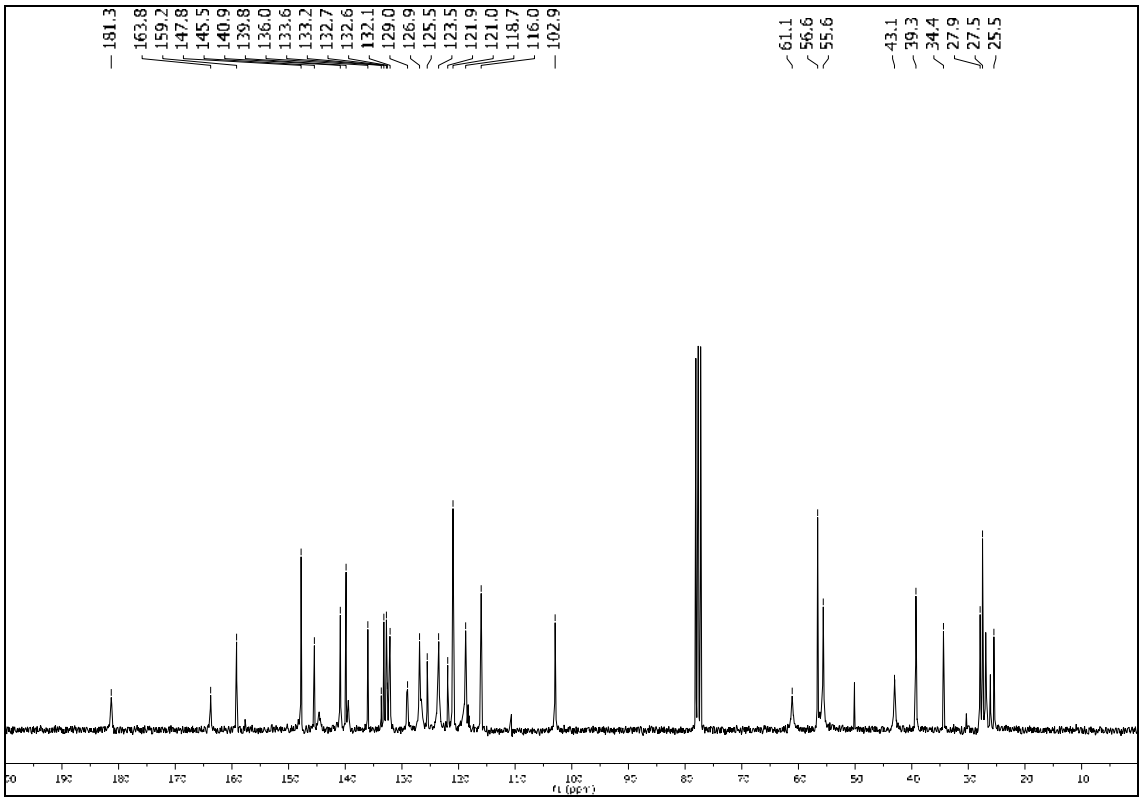


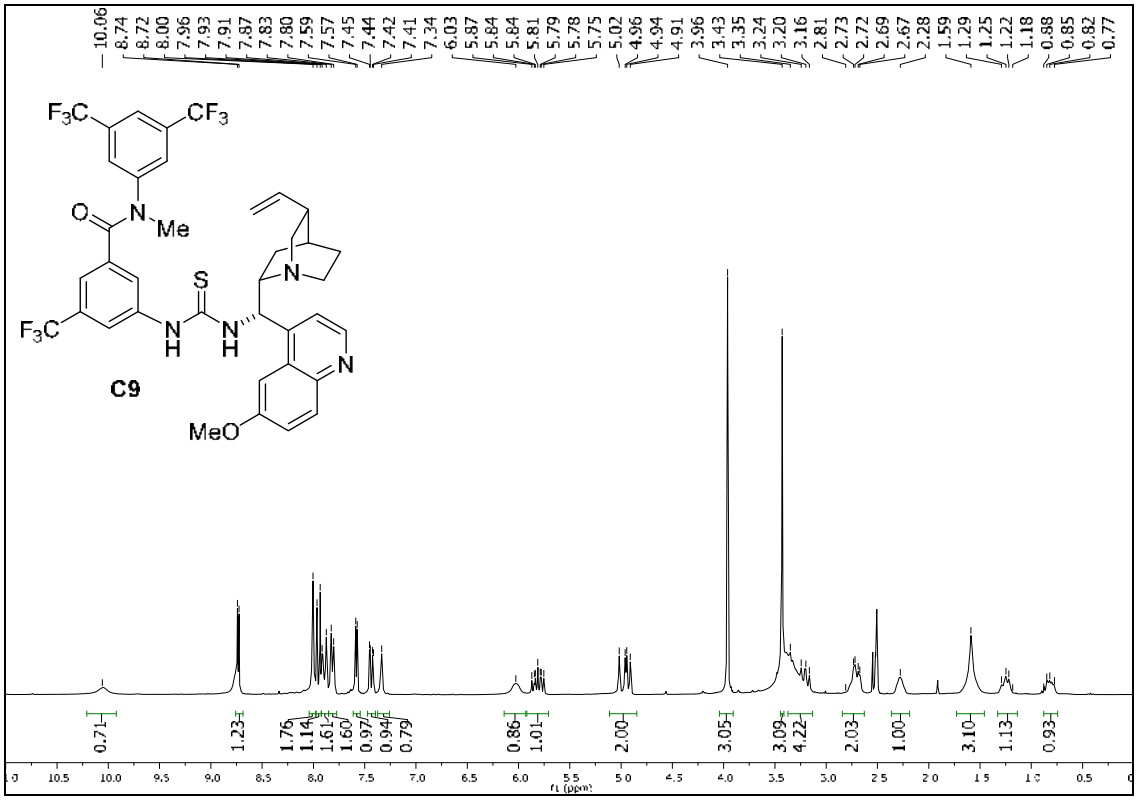
The title compound **95Cc** was prepared from *N*-allyl-1-(4-iodophenyl)-1*H*-tetrazol-5-amine (**94Cc**) (65.4 mg, 0.2 mmol) according to the General Procedure. The product was obtained as a white solid: 61.5 mg, 0.188 mmol, 94 %. ^1H NMR (399 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 5.98 (ddt, *J* = 17.3, 12.6, 6.3 Hz, 1H), 5.37 (dd, *J* = 46.2, 13.7 Hz, 2H), 5.05 – 4.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 138.5, 138.1, 129.7, 129.0, 120.5, 120.1, 85.9, 48.5. HRMS (EIS): $C_{10}H_{11}IN_5$ $[M+H]^+$ calcd.: 328.00591, found: 328.00624.

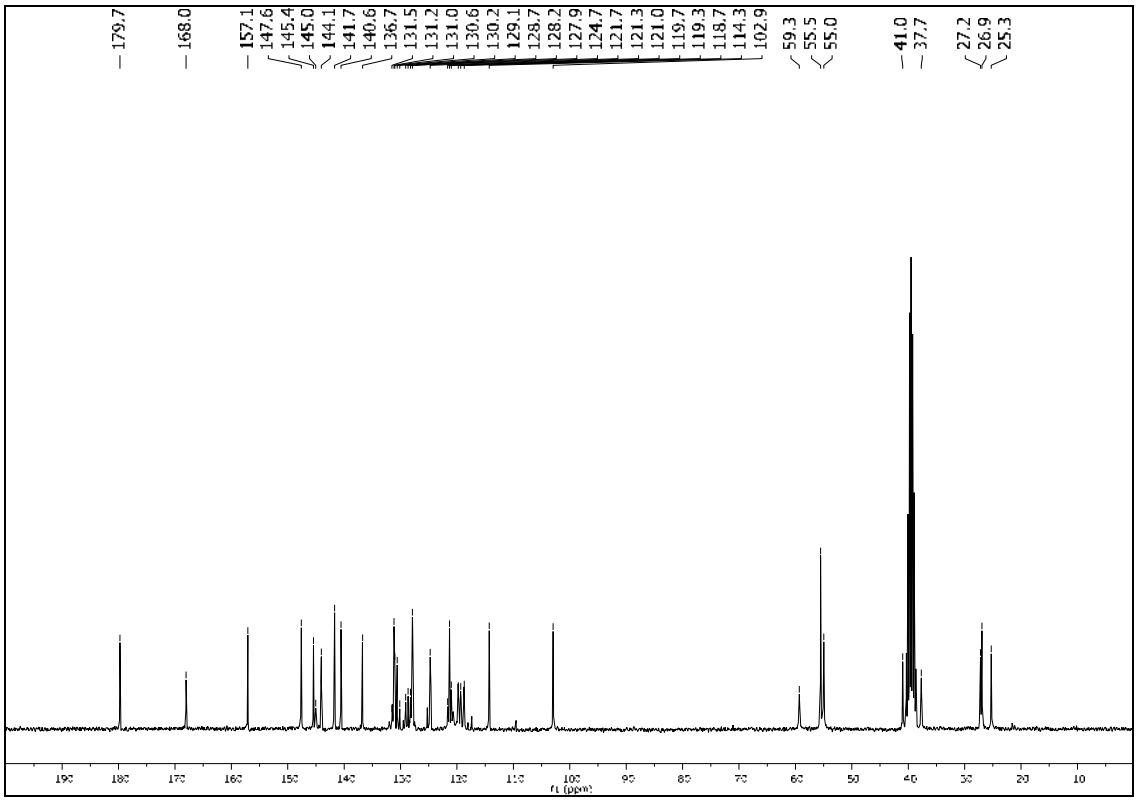
7.7. NMR spectra of representative compounds

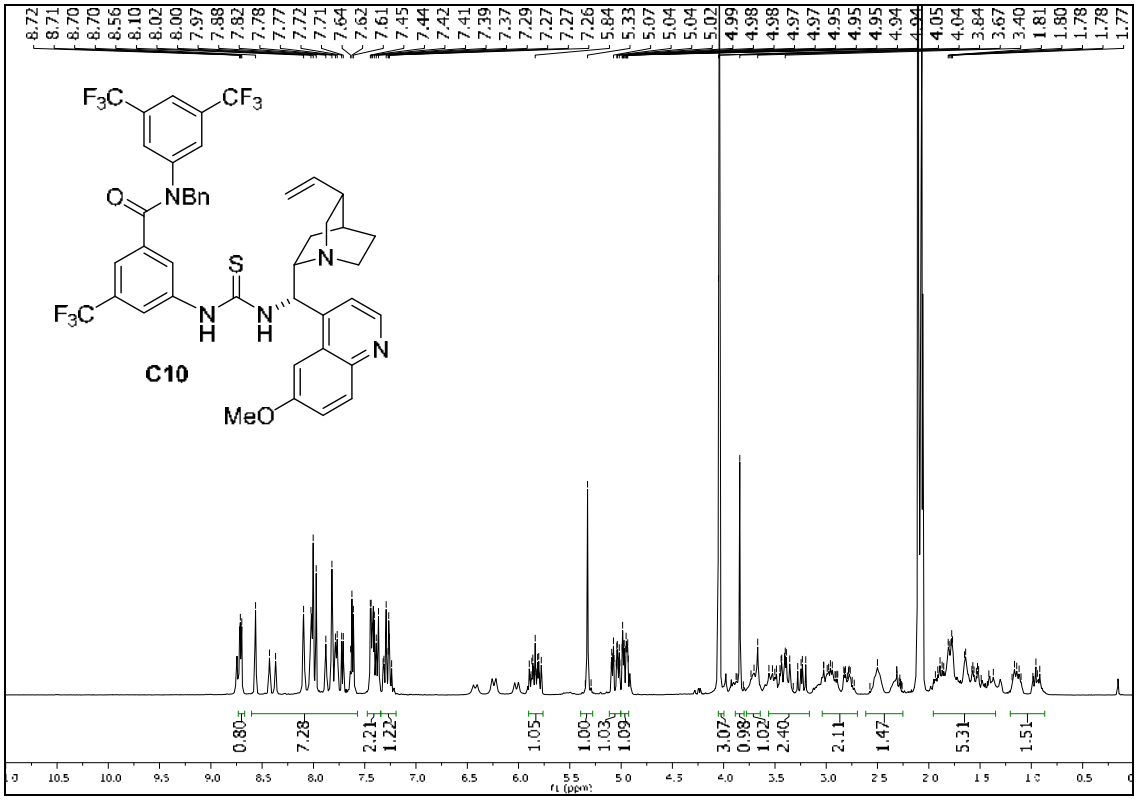
7.7.1. NMR spectra of catalysts

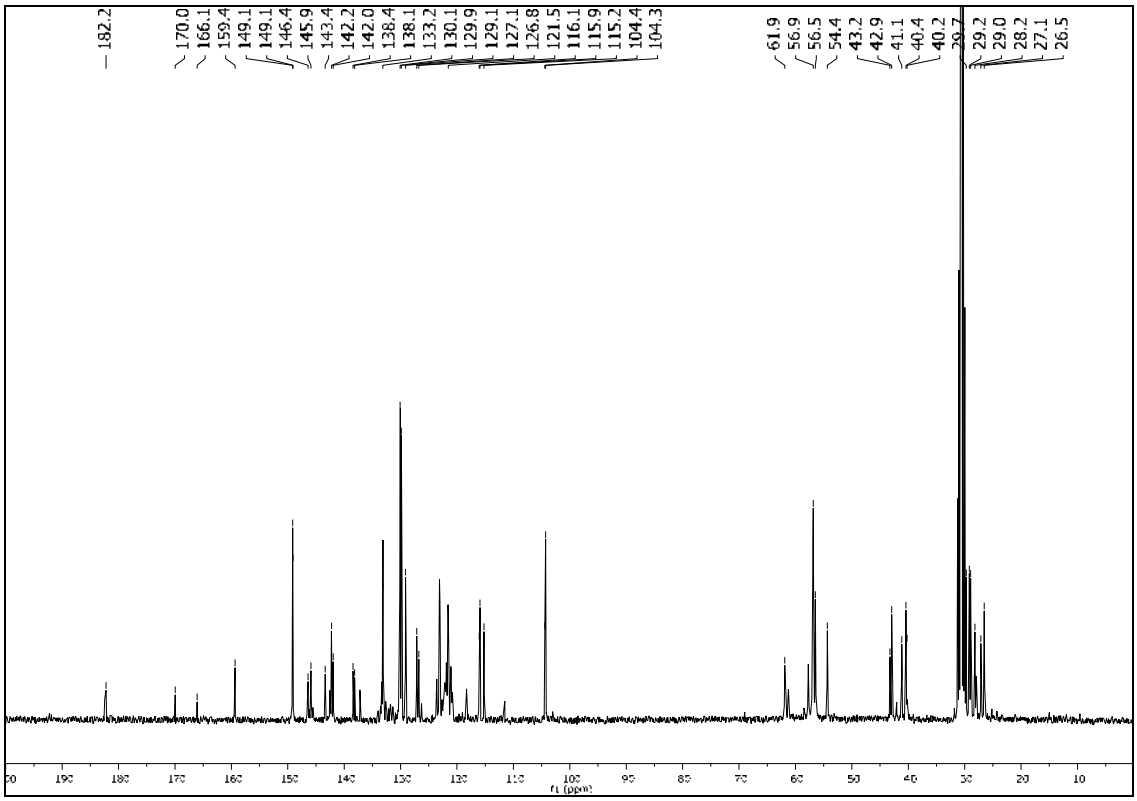


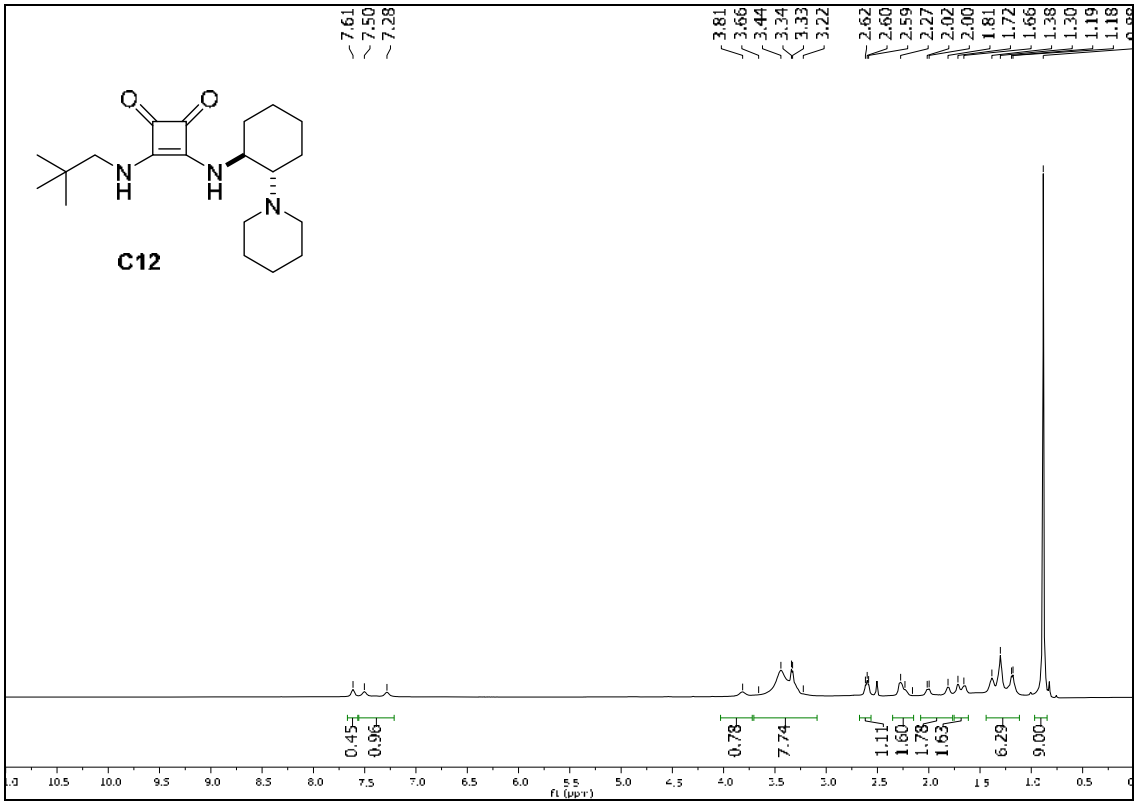


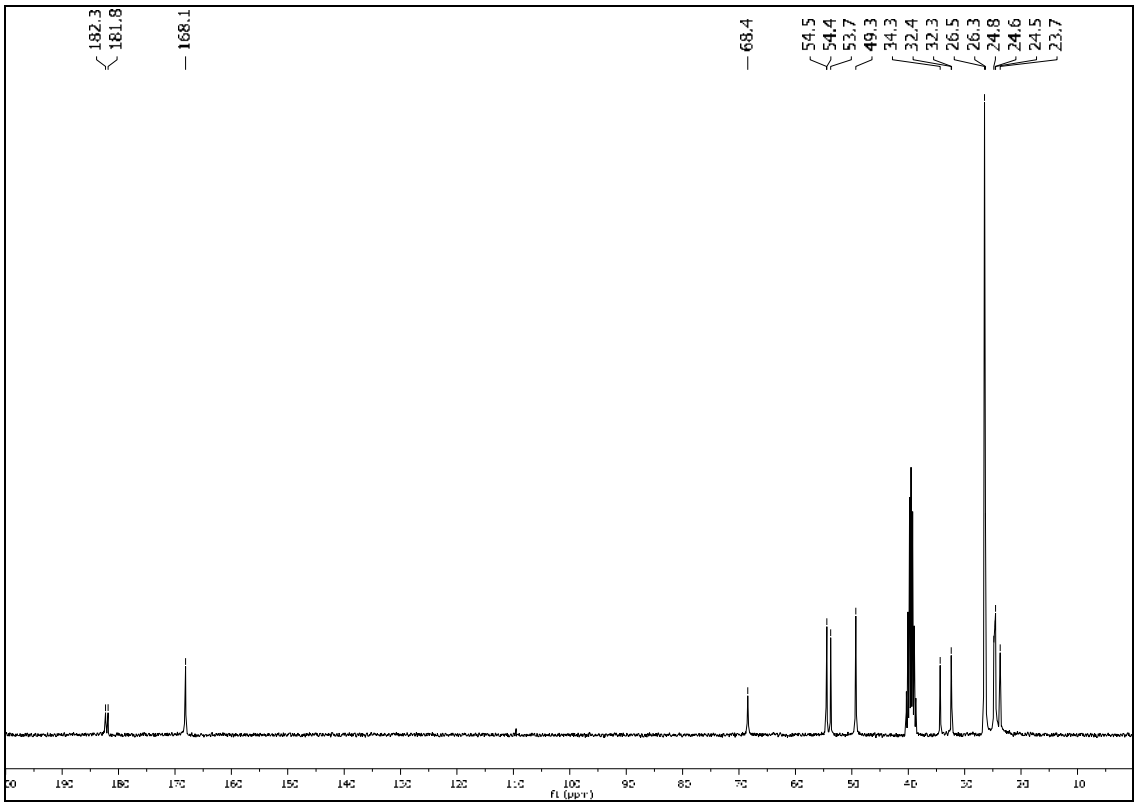

C9
MeO

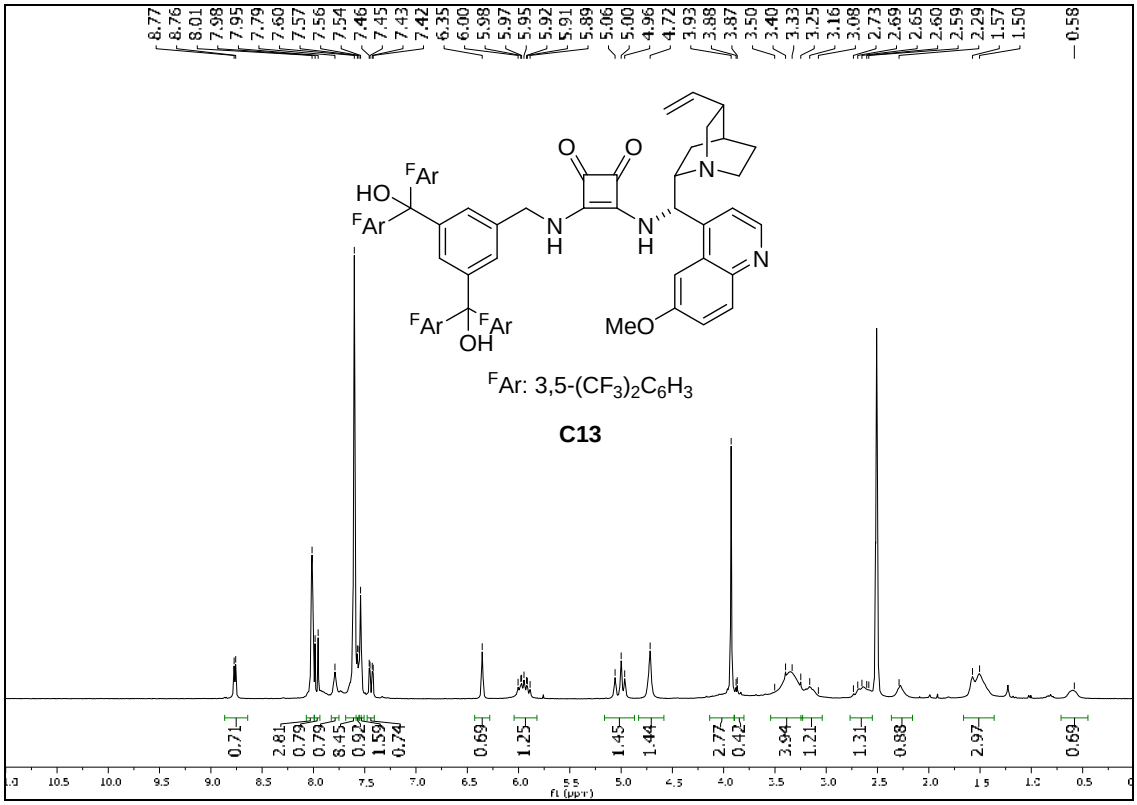



C10



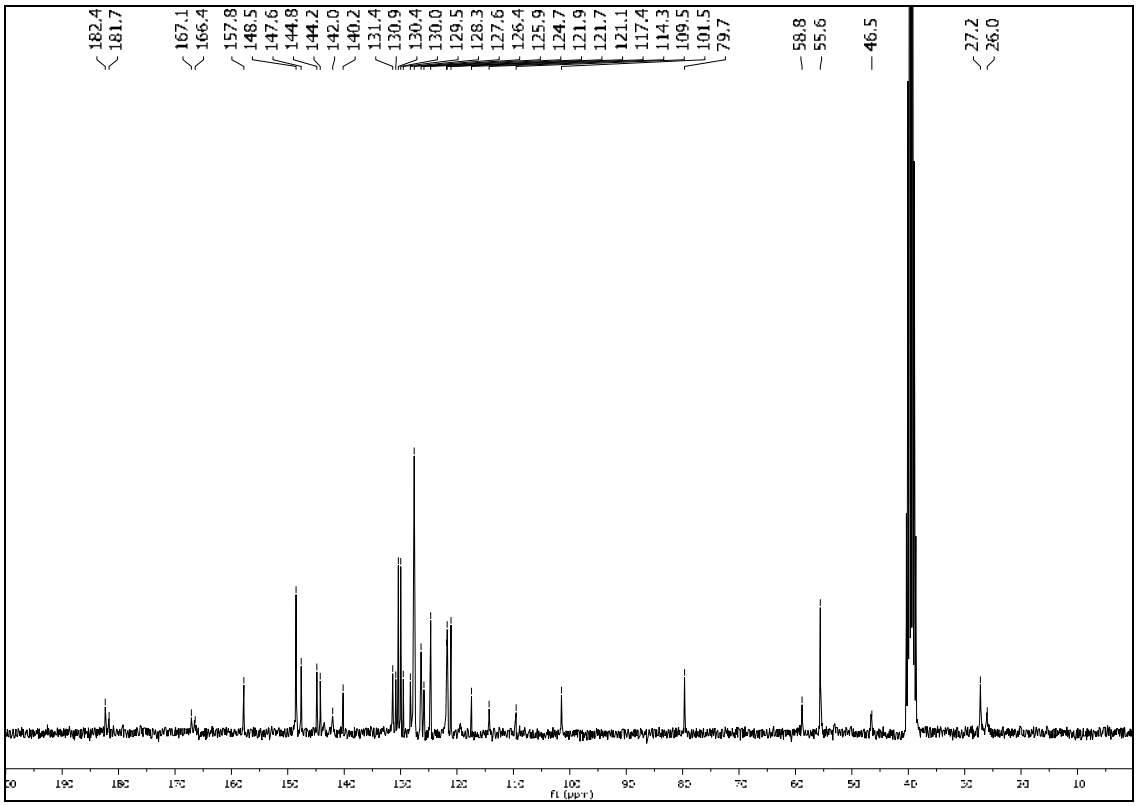

7.61
7.50
7.28
3.81
3.66
3.44
3.34
3.33
3.22
2.62
2.60
2.59
2.27
2.02
2.00
1.81
1.72
1.66
1.38
1.30
1.19
1.18
O
O
N
H
N
H
N
C12
0.45
0.96
0.78
7.74
1.11
1.60
1.78
1.63
6.29
9.00
f1 (ppm)

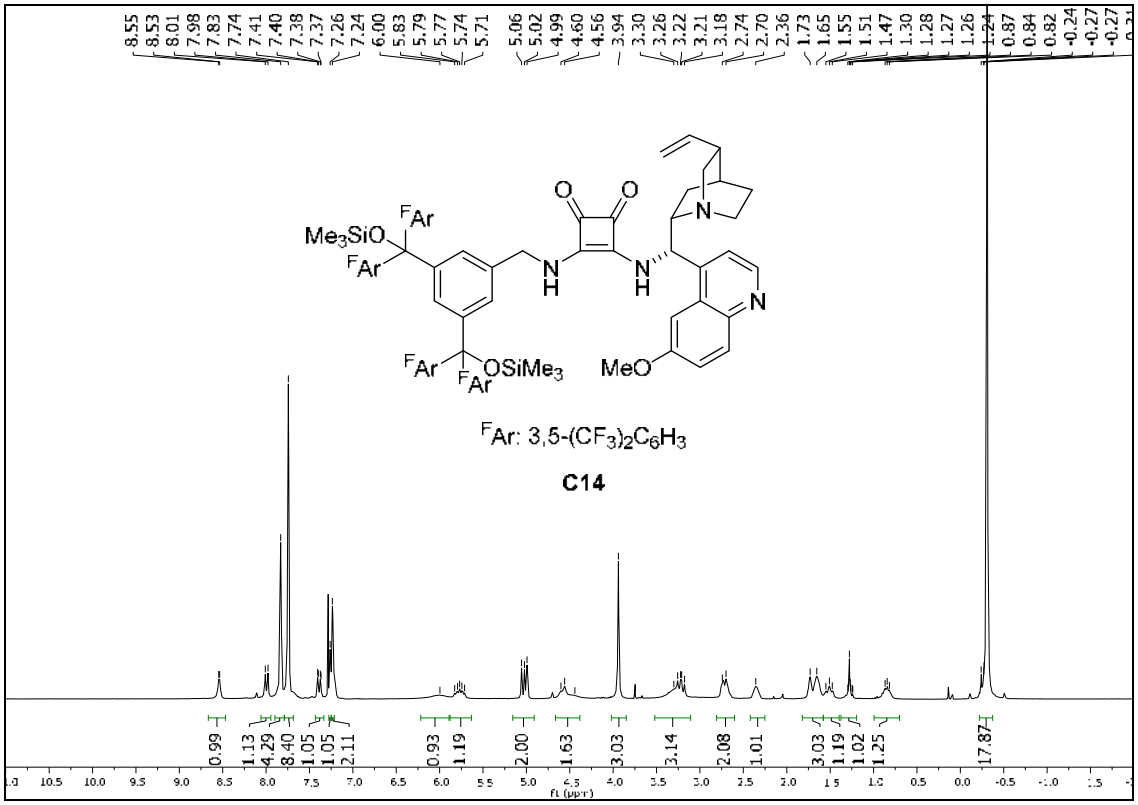

182.3
181.8
168.1
68.4
54.5
54.4
53.7
49.3
34.3
32.4
32.3
26.5
26.3
24.8
24.6
24.5
23.7
f1 (ppm)

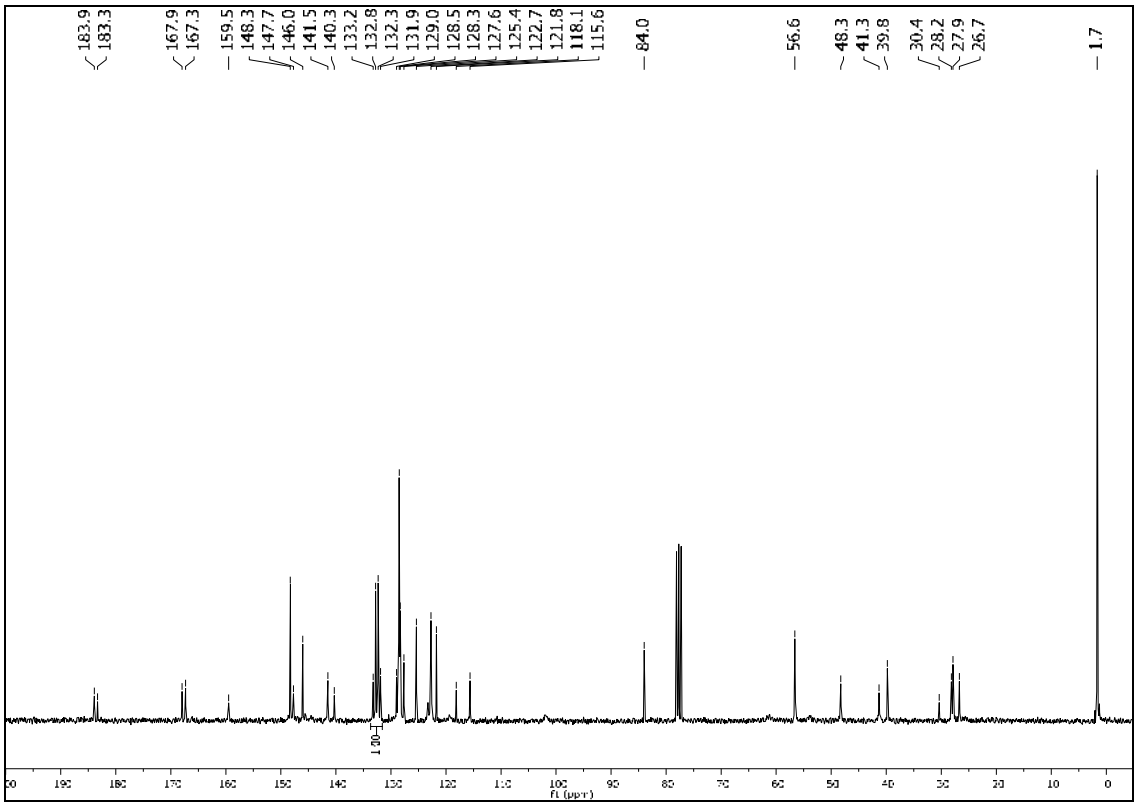


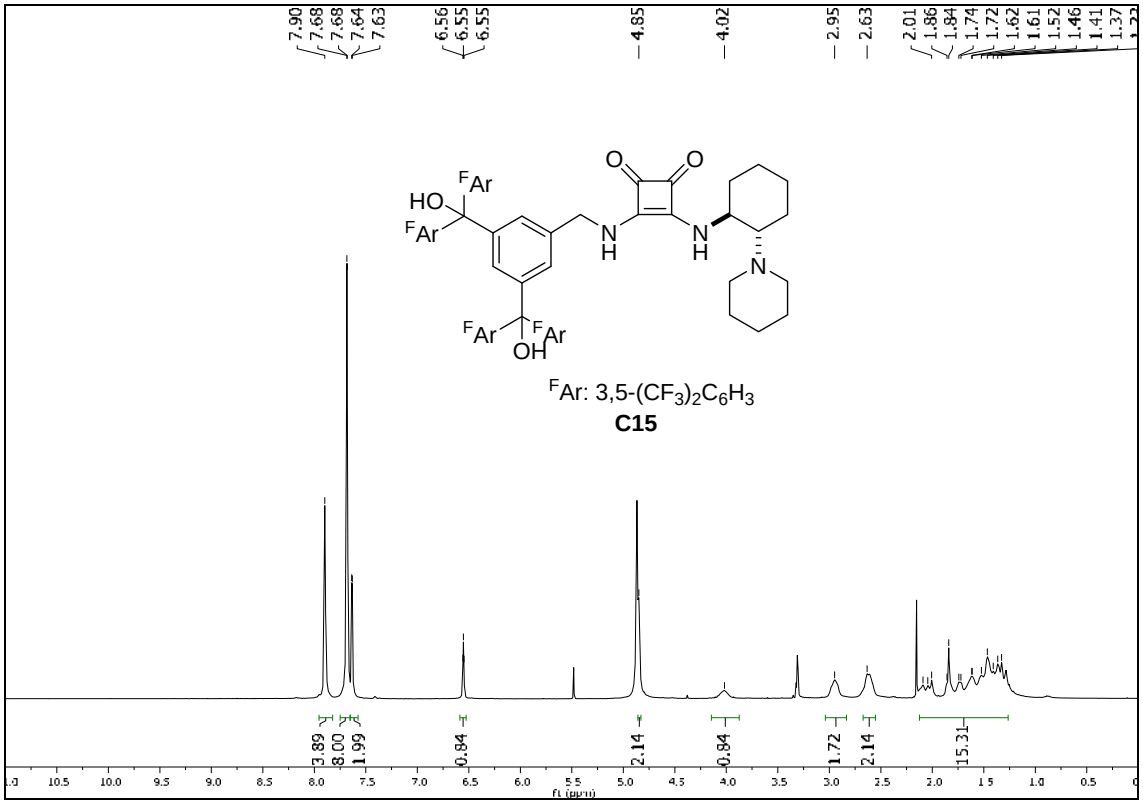
^{F}Ar: 3,5-$(CF_3)_2C_6H_3$

C13



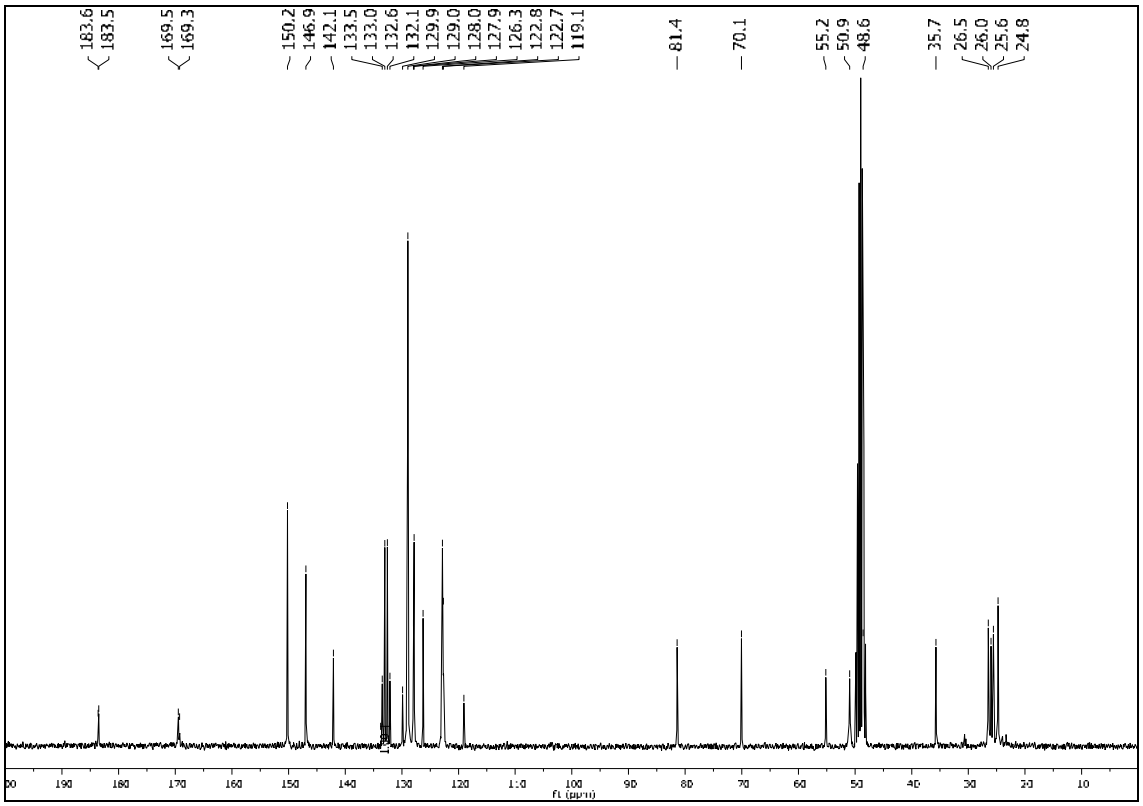

8.55
8.53
8.01
7.98
7.83
7.74
7.41
7.40
7.38
7.37
7.26
7.24
6.00
5.83
5.79
5.77
5.74
5.71
5.06
5.02
4.99
4.60
4.56
3.94
3.30
3.26
3.22
3.21
3.18
2.74
2.70
2.36
1.73
1.65
1.55
1.51
1.47
1.30
1.28
1.27
1.26
1.24
0.87
0.84
0.82
-0.24
-0.27
-0.27
Me3SiO
FAr
FAr
FAr
FAr
OSiMe3
O
O
N
H
N
H
N
N
MeO
FAr: 3,5-(CF3)2C6H3
C14
0.99
1.13
4.29
8.40
1.05
1.05
2.11
0.93
1.19
2.00
1.63
3.03
3.14
2.08
1.01
3.03
1.19
1.02
1.25
17.87
f1 (ppm)

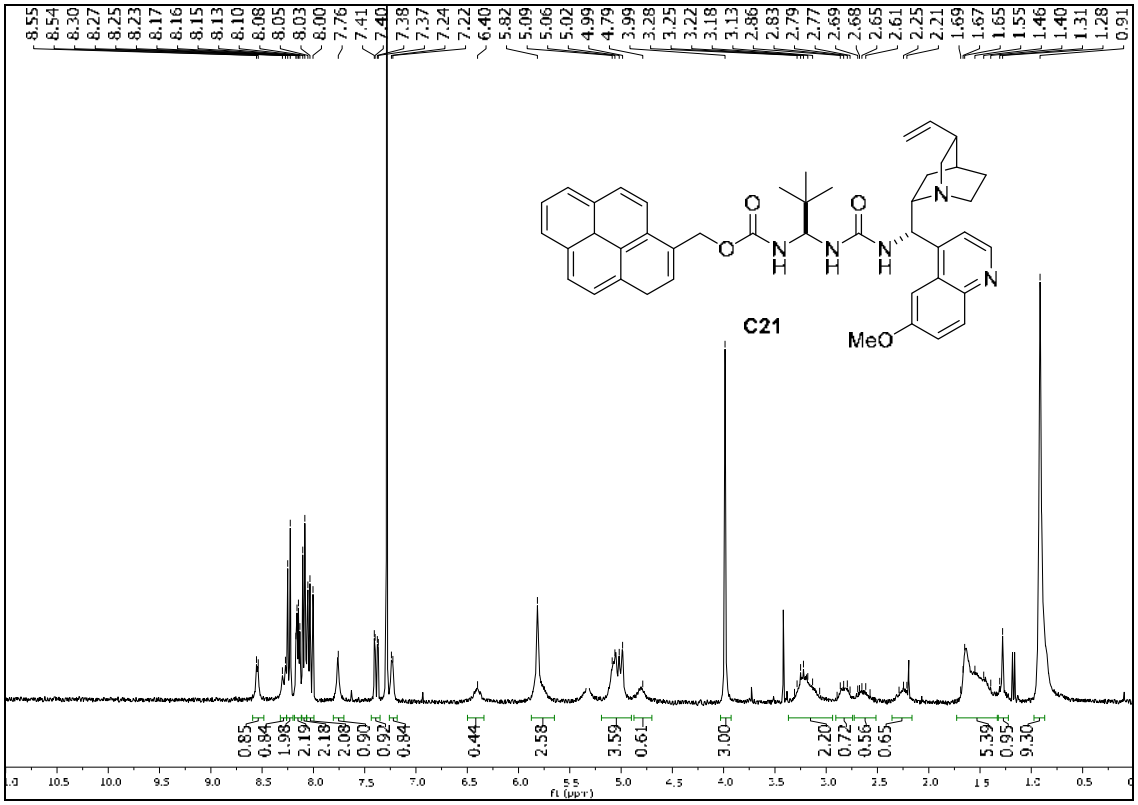

183.9
183.3
167.9
167.3
159.5
148.3
147.7
146.0
141.5
140.3
133.2
132.8
132.3
131.9
129.0
128.5
128.3
127.6
125.4
122.7
121.8
118.1
115.6
84.0
56.6
48.3
41.3
39.8
30.4
28.2
27.9
26.7
1.7
100.1
f1 (ppm)

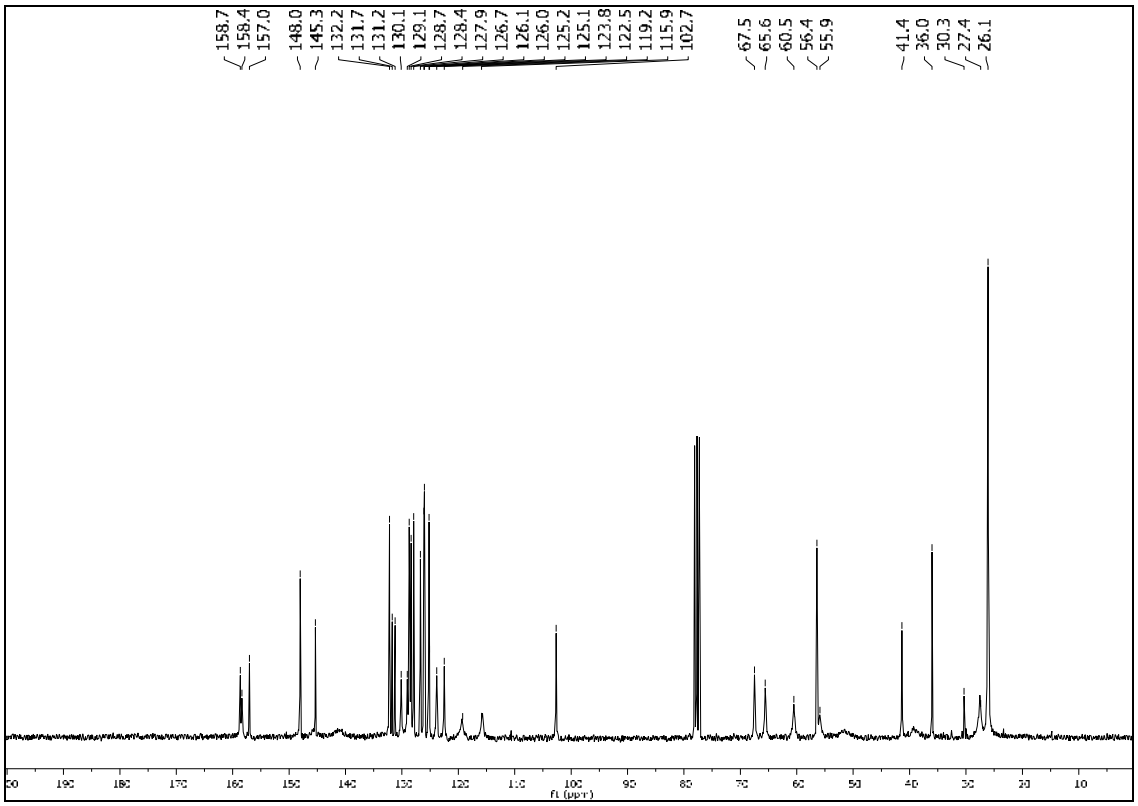


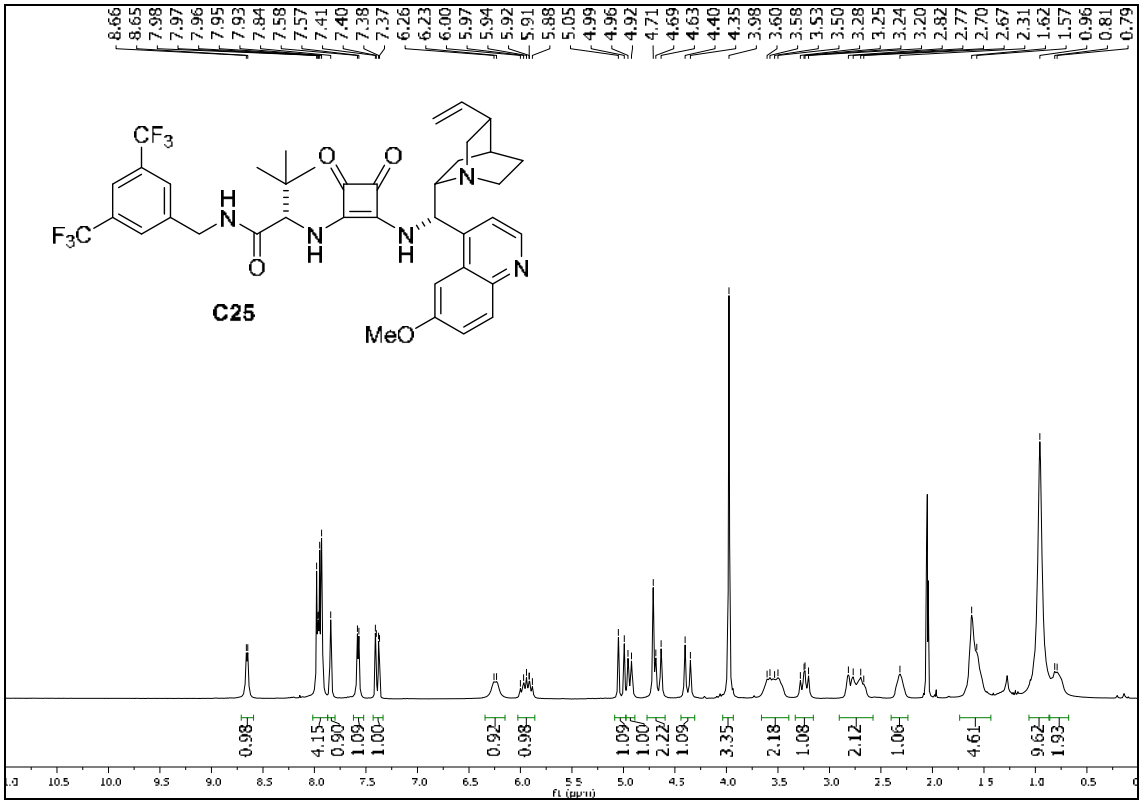
^{F}Ar: 3,5-$(CF_3)_2C_6H_3$

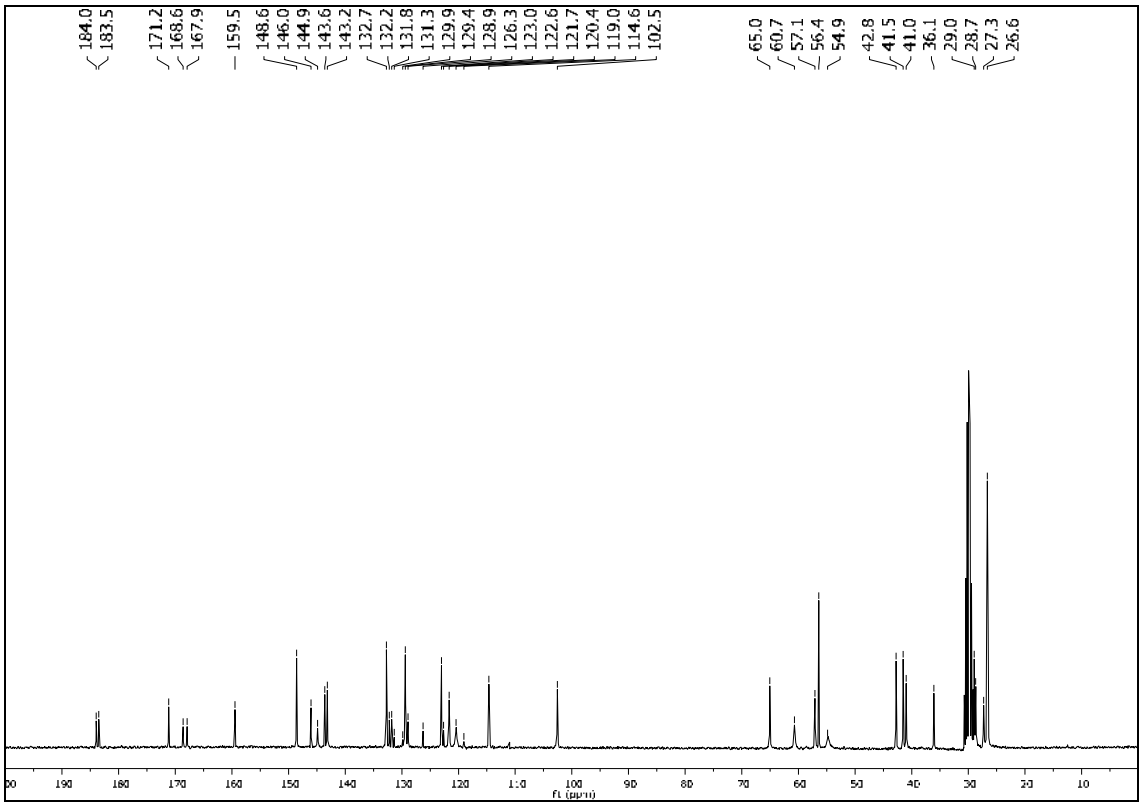
C15

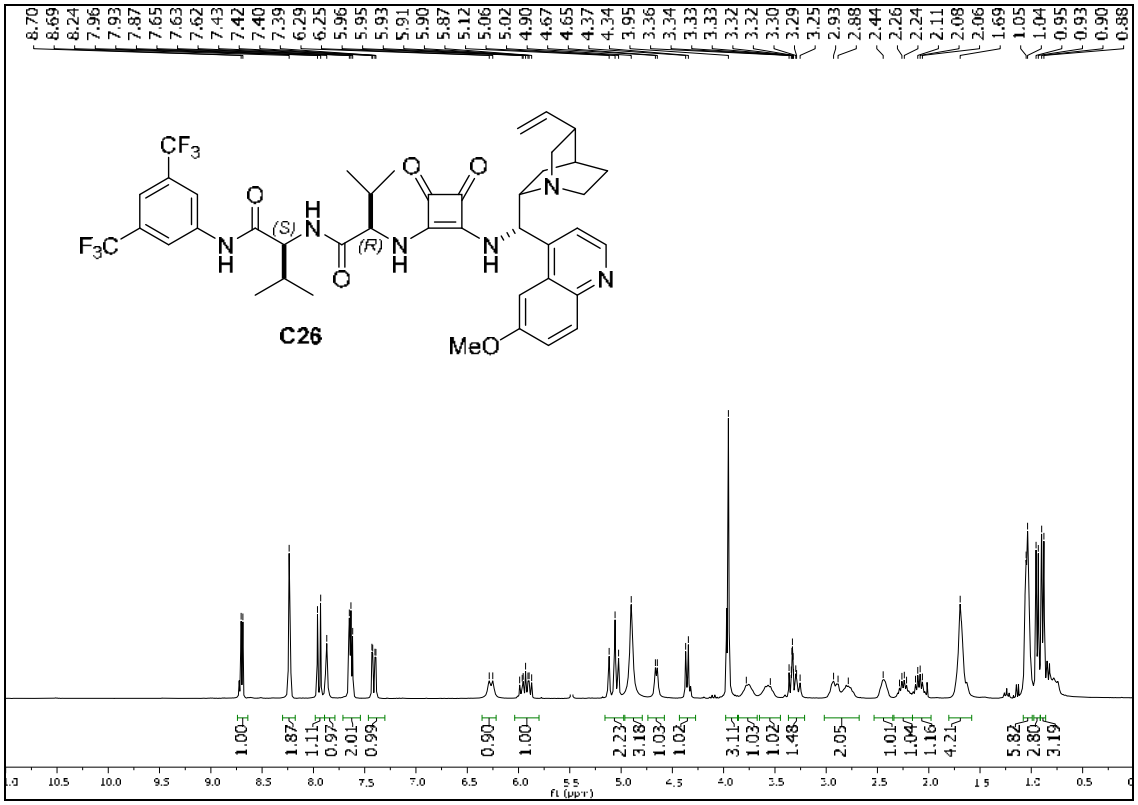


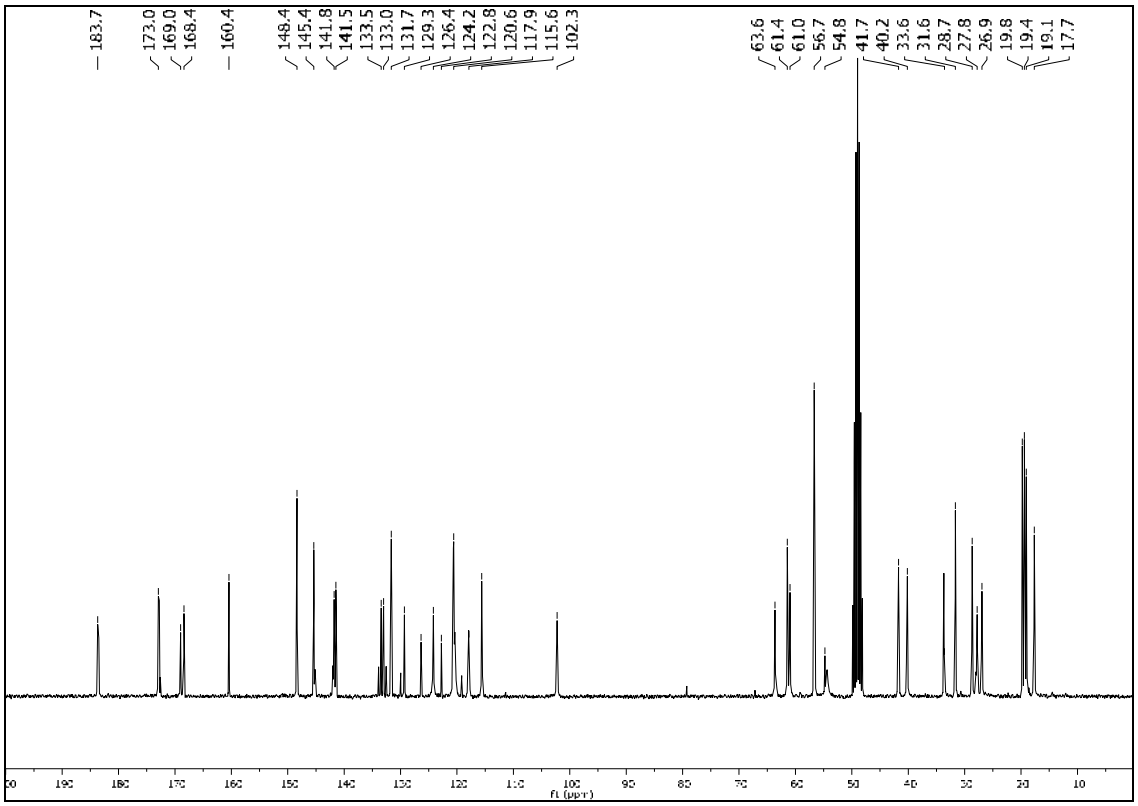

C21
MeO

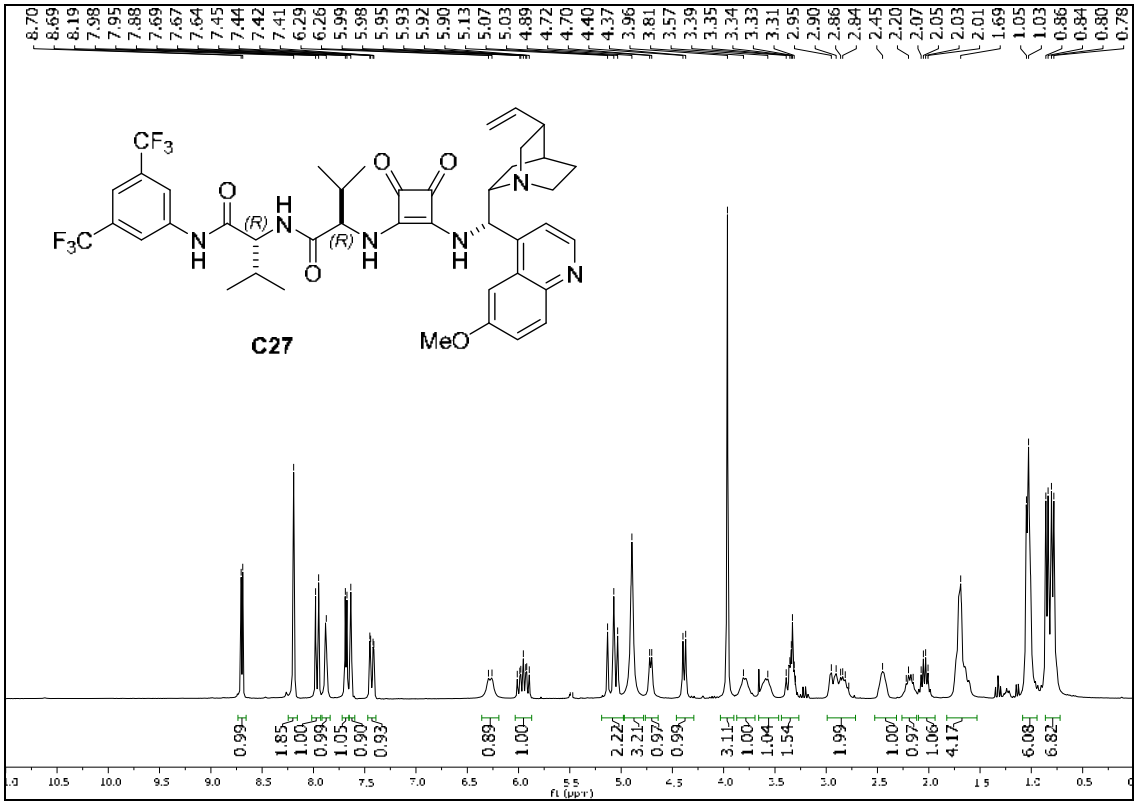


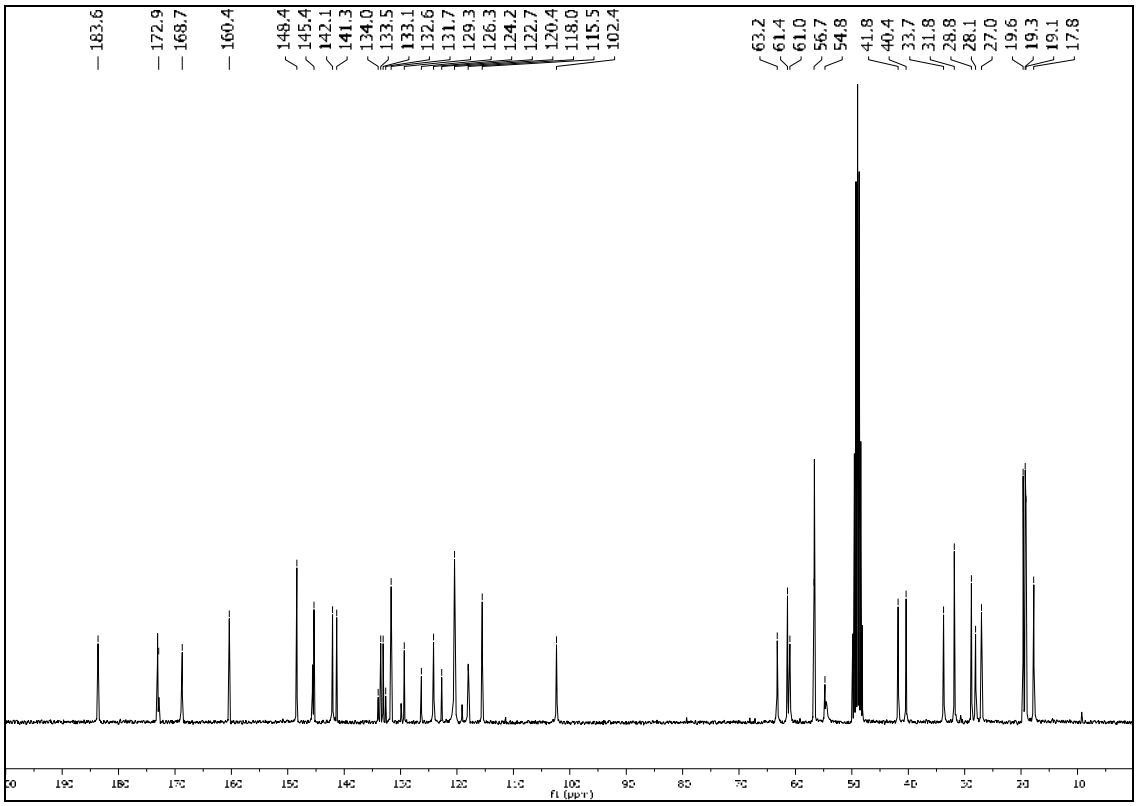

C25
MeO
F3C
CF3

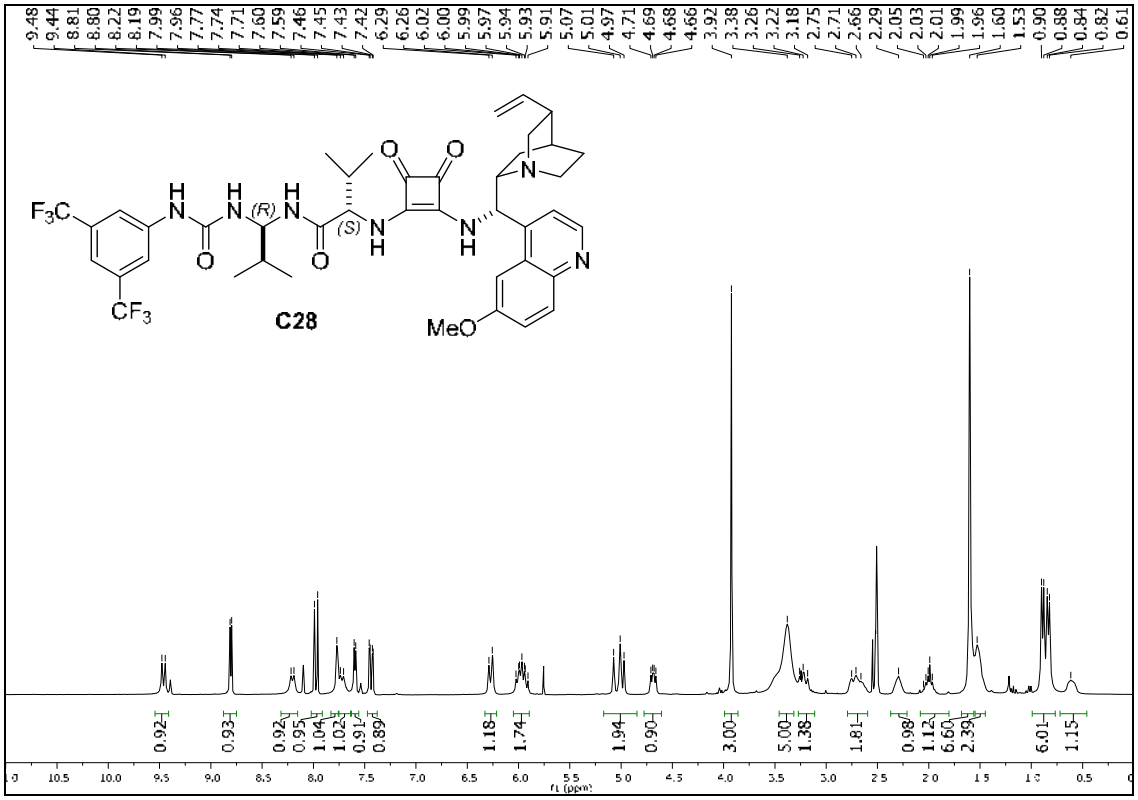


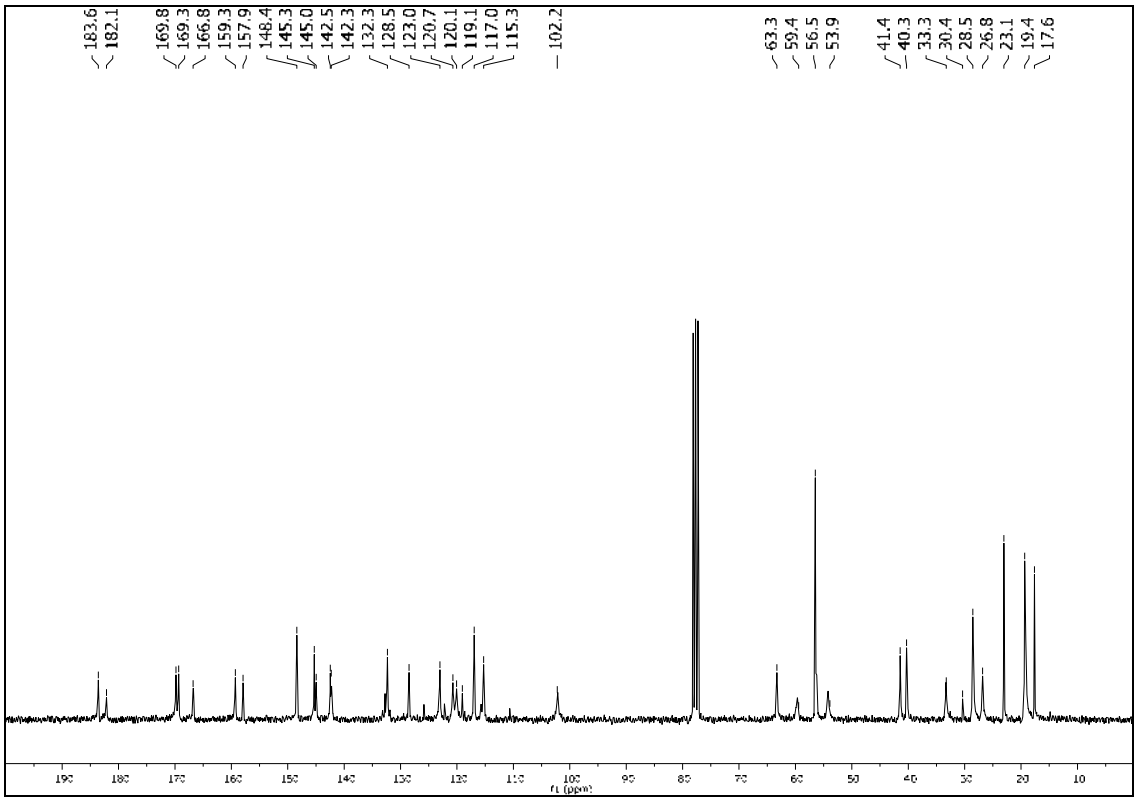

CF3
F3C
O
N
H
(S)
(R)
C26
MeO
fl (ppm)

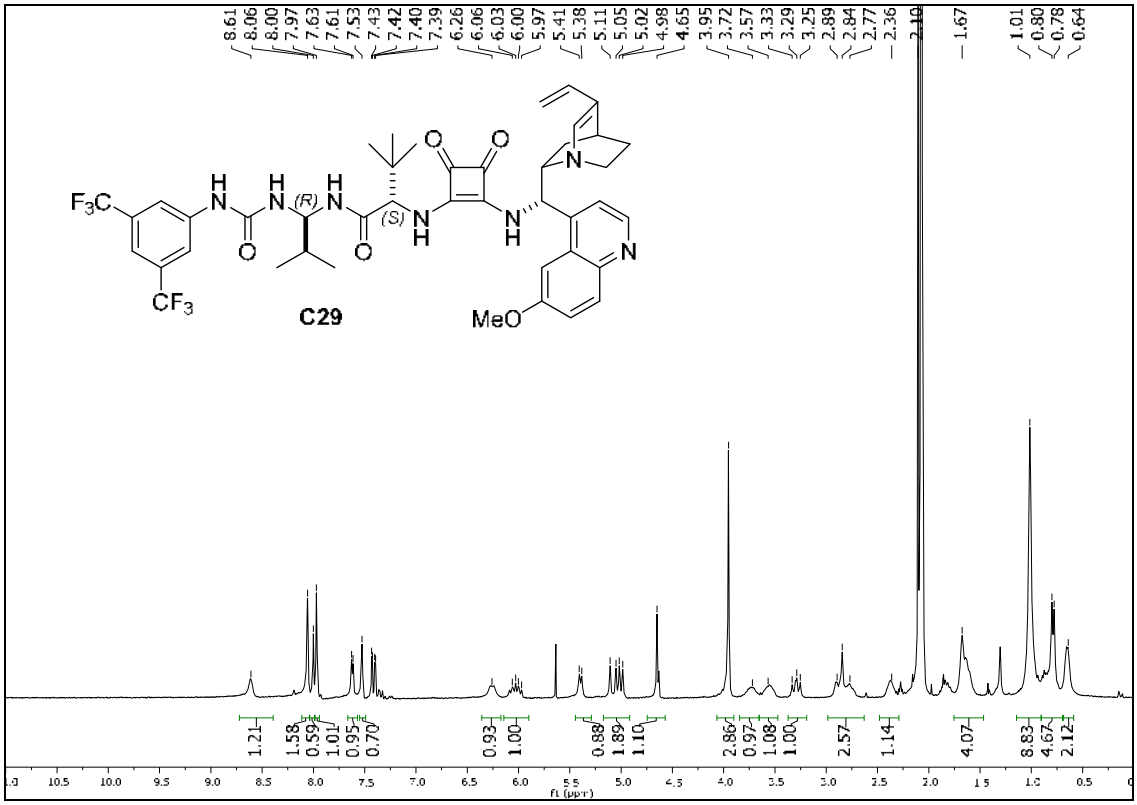

183.7
173.0
169.0
168.4
160.4
148.4
145.4
141.8
141.5
133.5
133.0
131.7
129.3
126.4
124.2
122.8
120.6
117.9
115.6
102.3
63.6
61.4
61.0
56.7
54.8
41.7
40.2
33.6
31.6
28.7
27.8
26.9
19.8
19.4
19.1
17.7
fl (ppm)

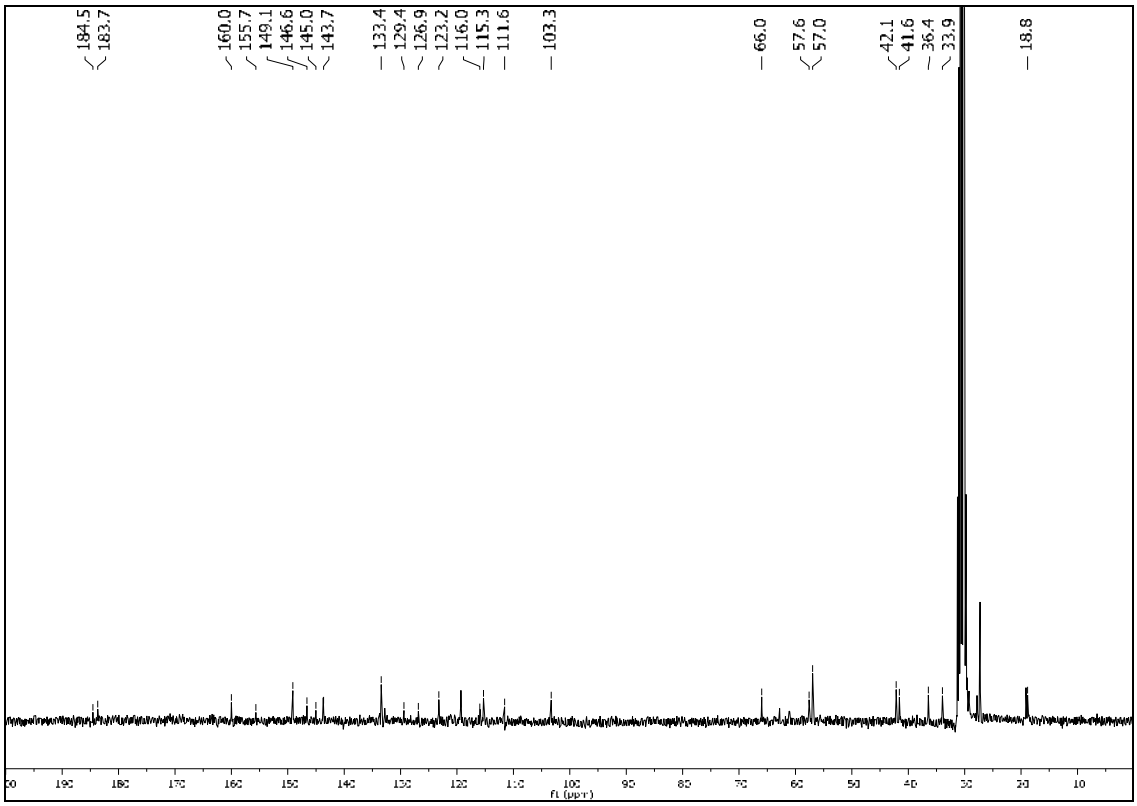

C27
MeO

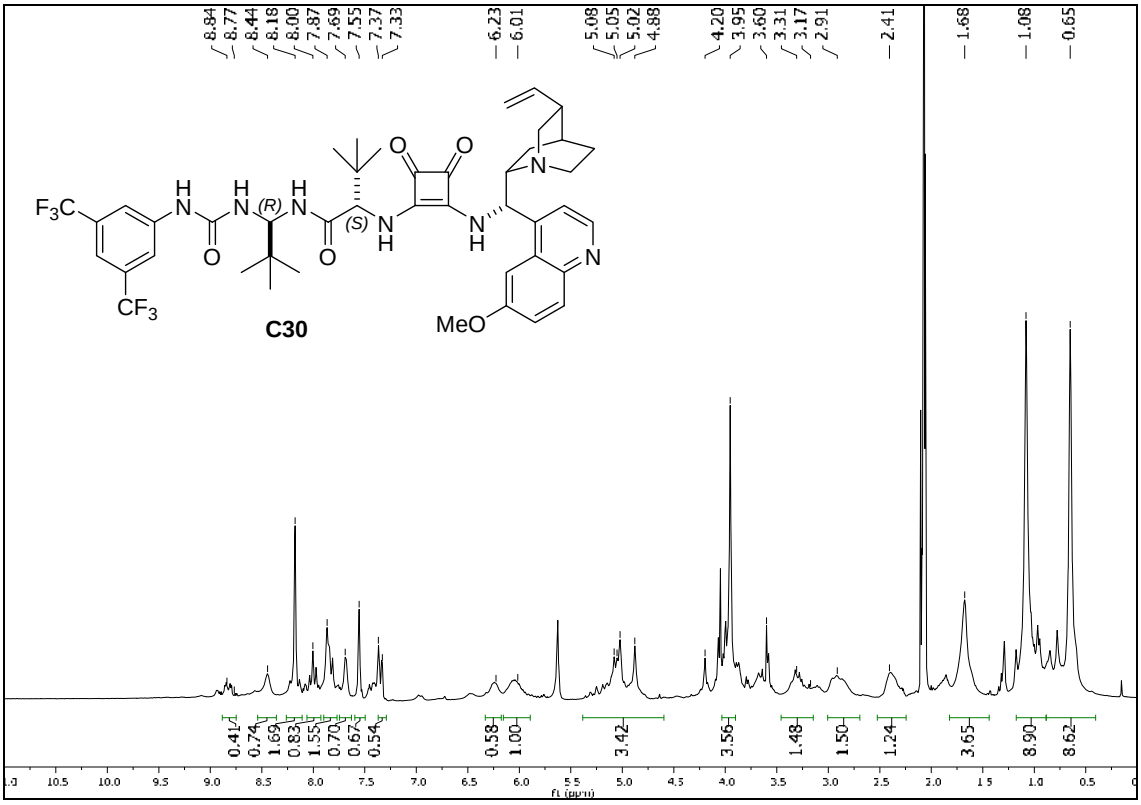



C28
F3C
CF3
MeO
(R)
(S)




C29
MeO
F3C
CF3

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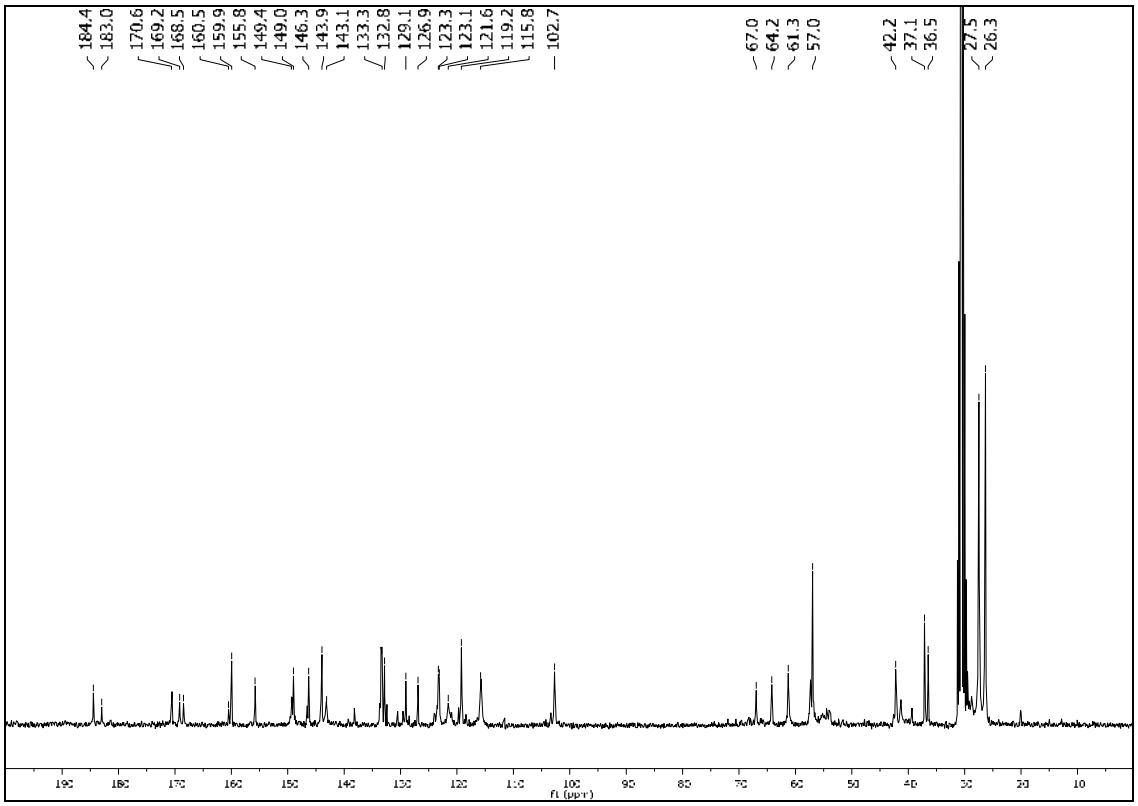
8.77
8.44
8.18
8.00
7.87
7.69
7.55
7.37
7.33
6.23
6.01
5.08
5.05
5.02
4.88
4.20
3.95
3.60
3.31
3.17
2.91
2.41
1.68
1.08
0.65
F3C
CF3
H
N
O
(R)
(S)
MeO
C30
0.41
0.74
1.69
0.83
1.55
0.70
0.67
0.54
0.58
1.00
3.42
3.56
1.48
1.50
1.24
3.65
8.90
8.62
f1 (ppm)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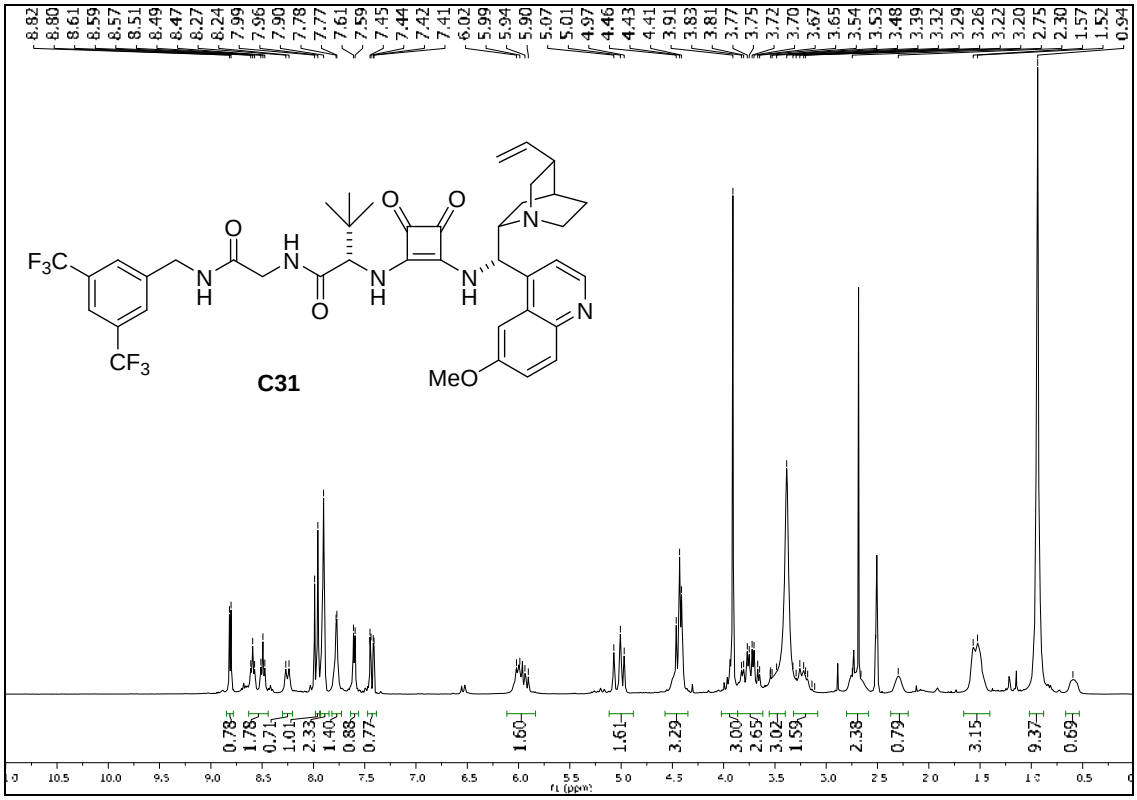
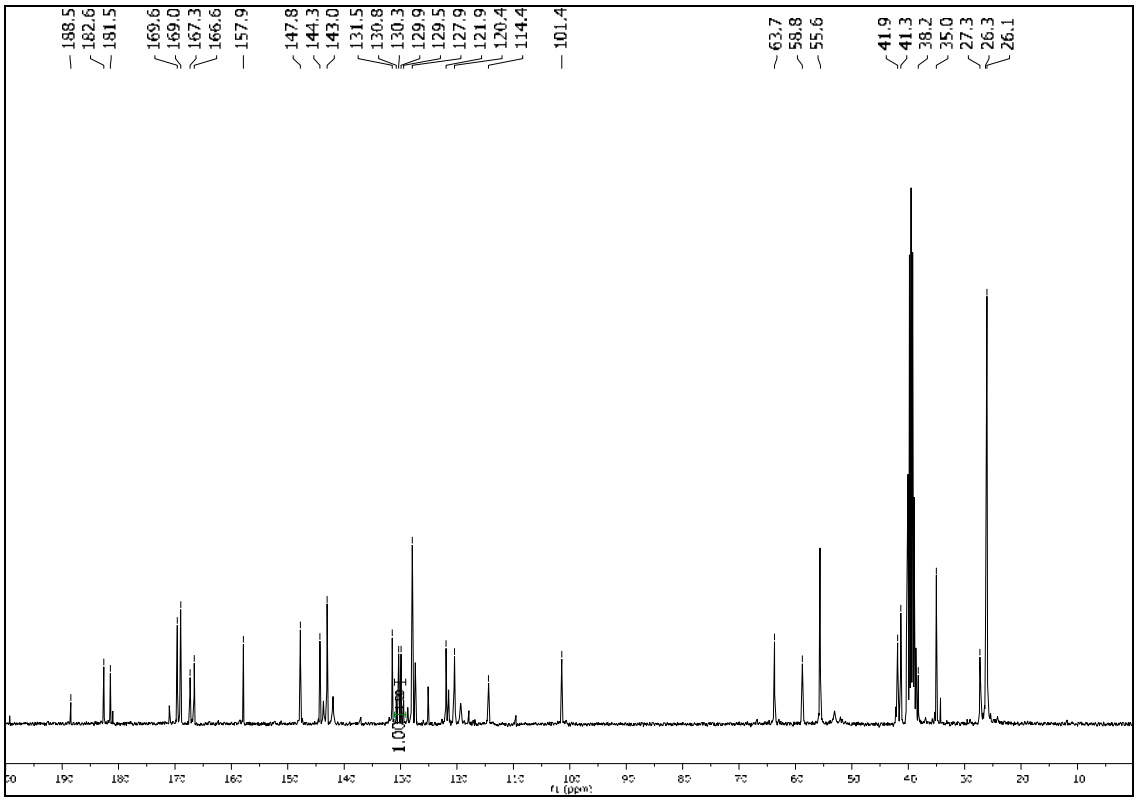
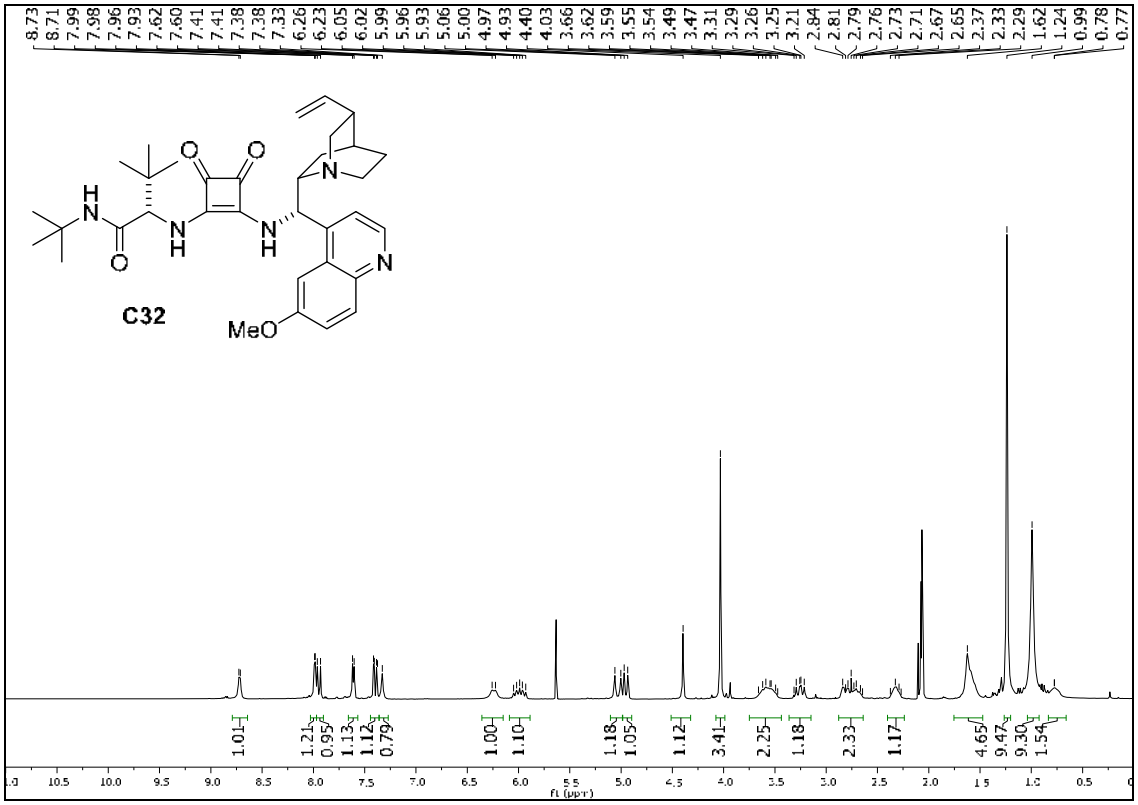
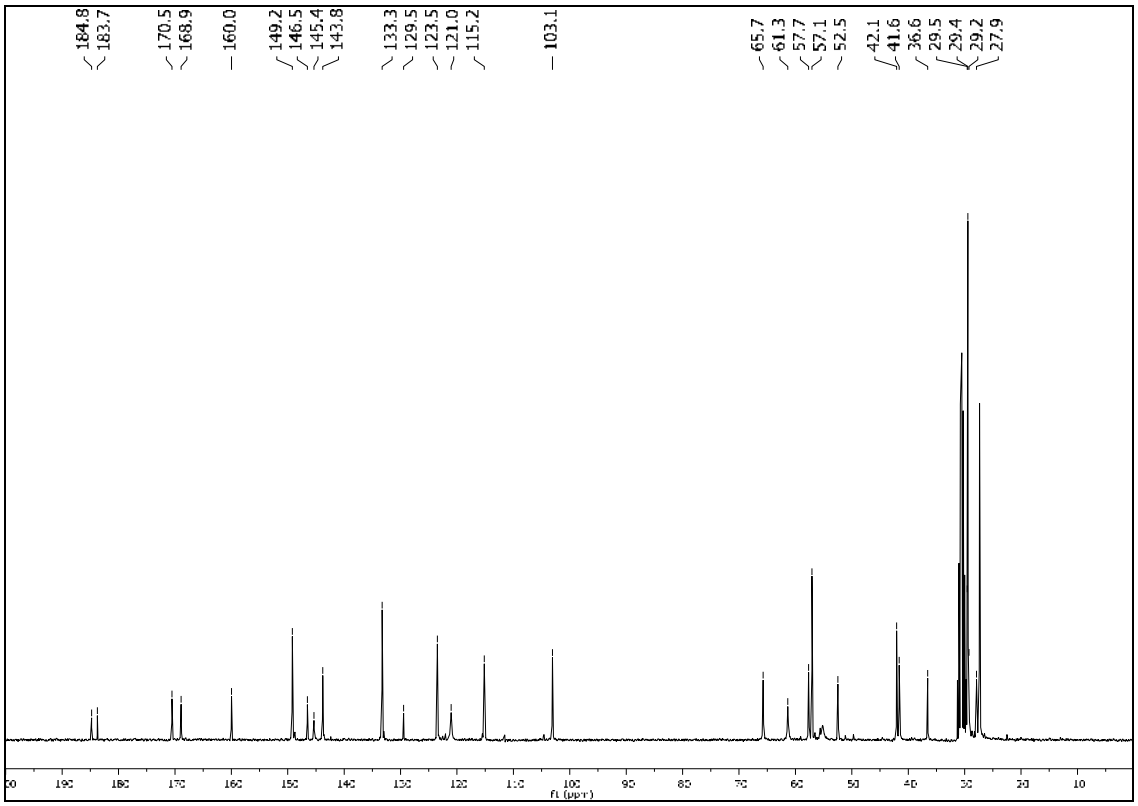
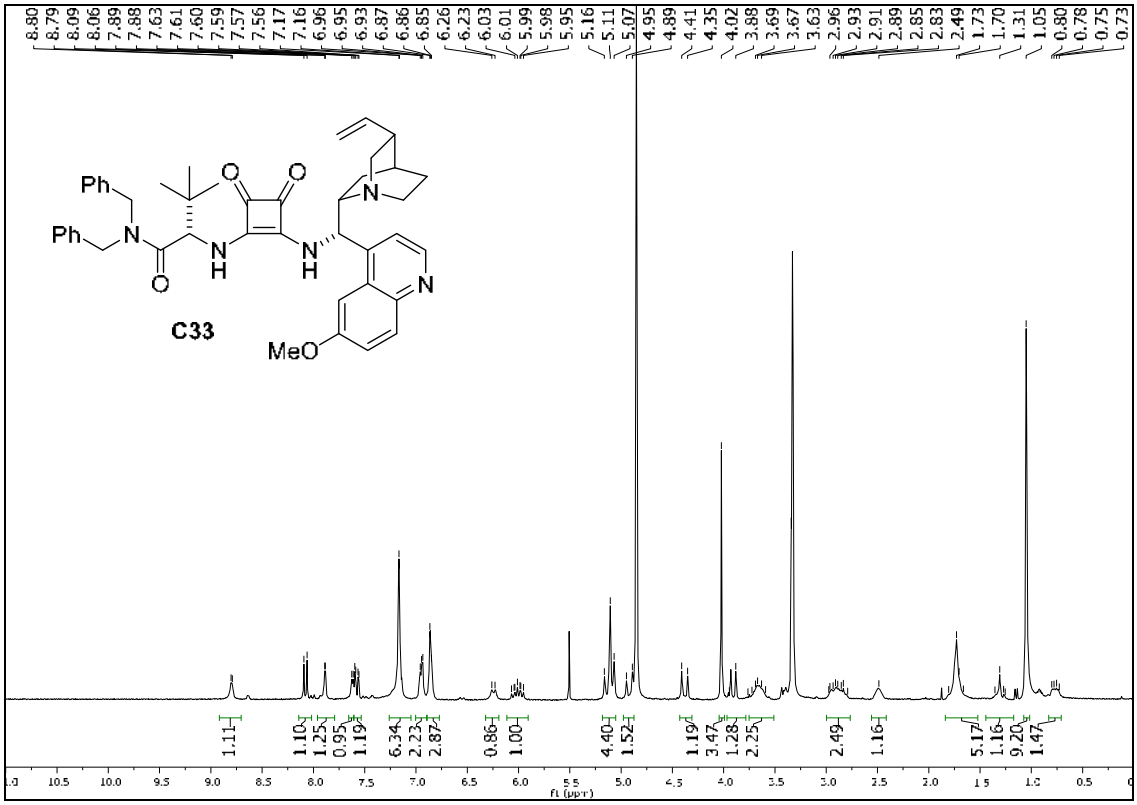
170.6
169.2
168.5
160.5
159.9
155.8
149.4
149.0
146.3
143.9
143.1
133.3
132.8
129.1
126.9
123.3
123.1
121.6
119.2
115.8
102.7
67.0
64.2
61.3
57.0
42.2
37.1
36.5
27.5
26.3
f1 (ppm)

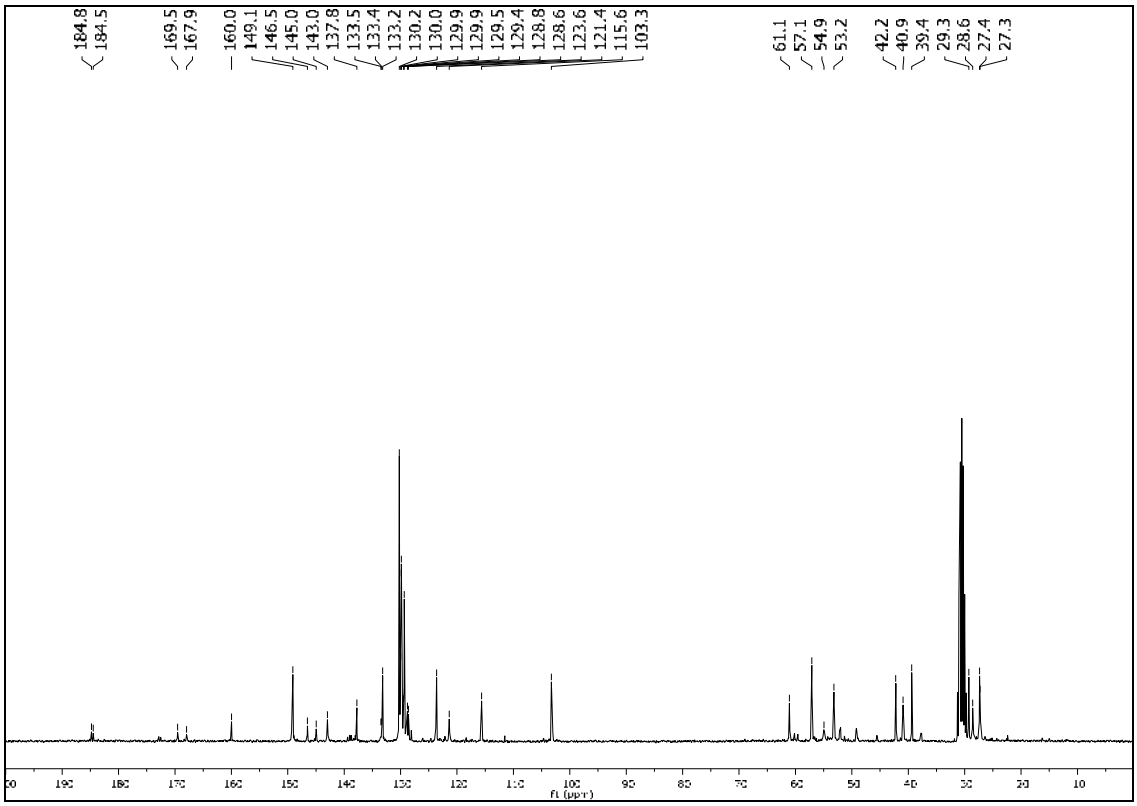

C31
F3C
CF3
MeO
N
H
O

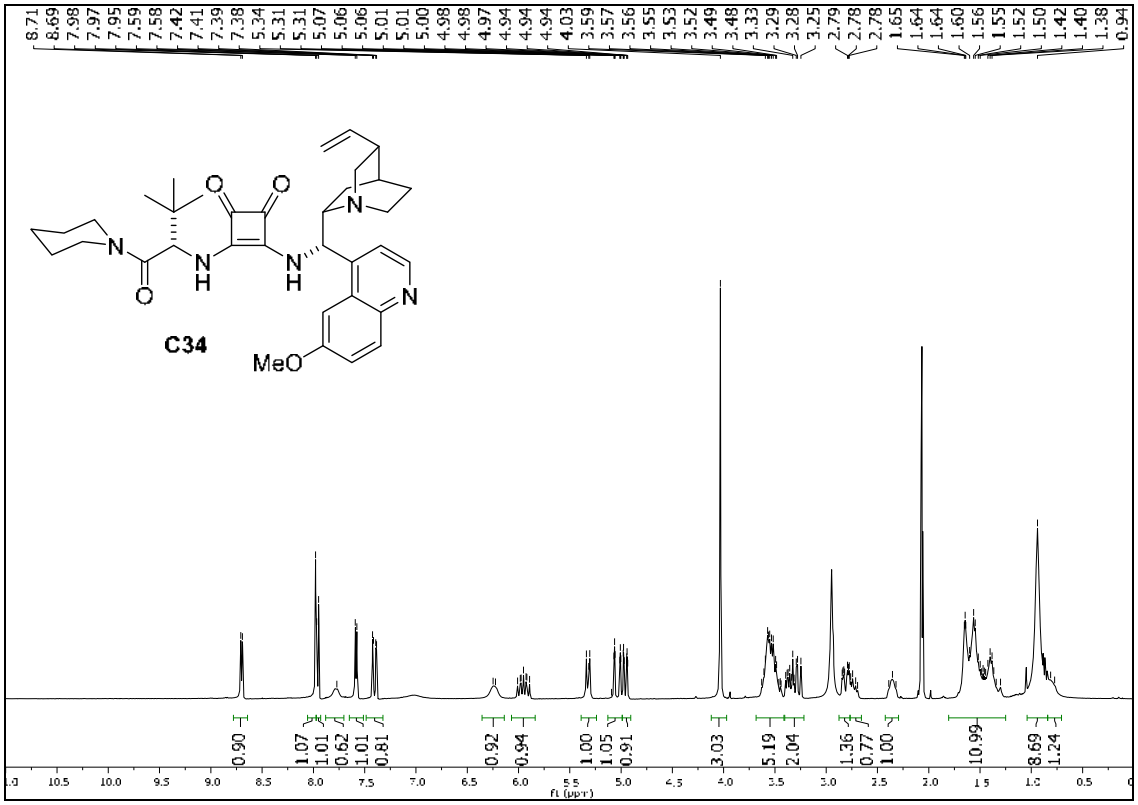


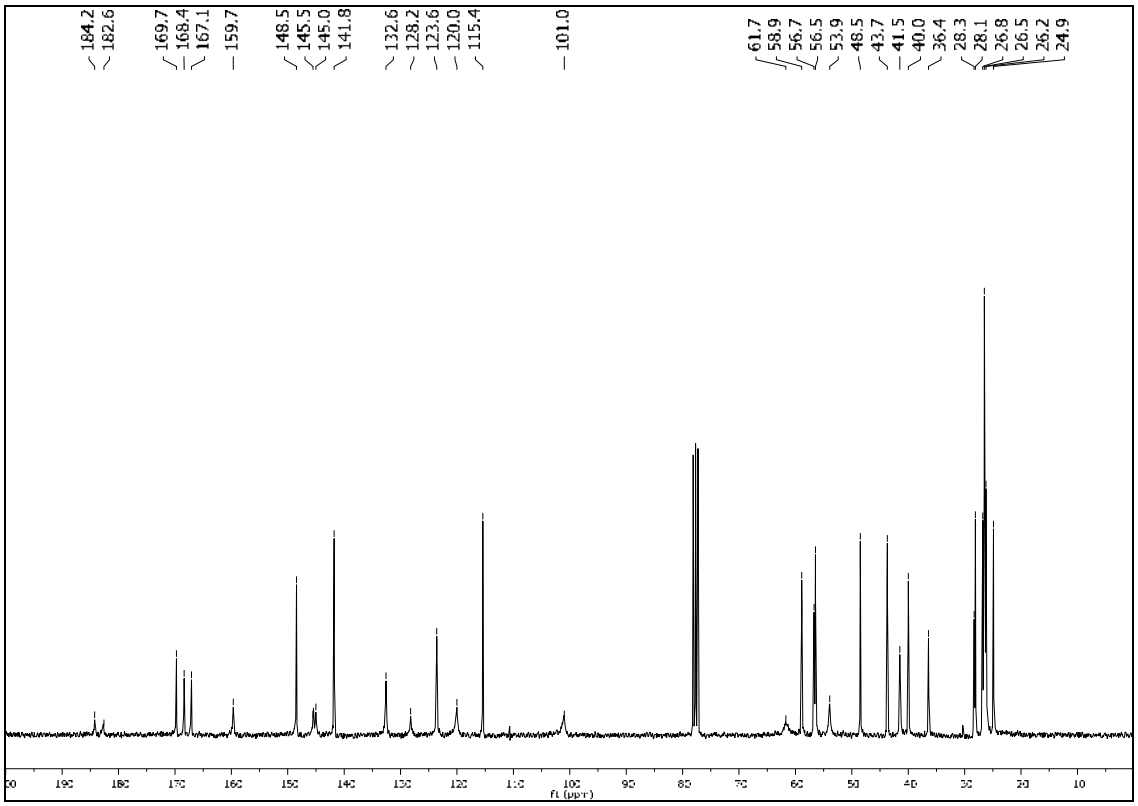

C32
MeO

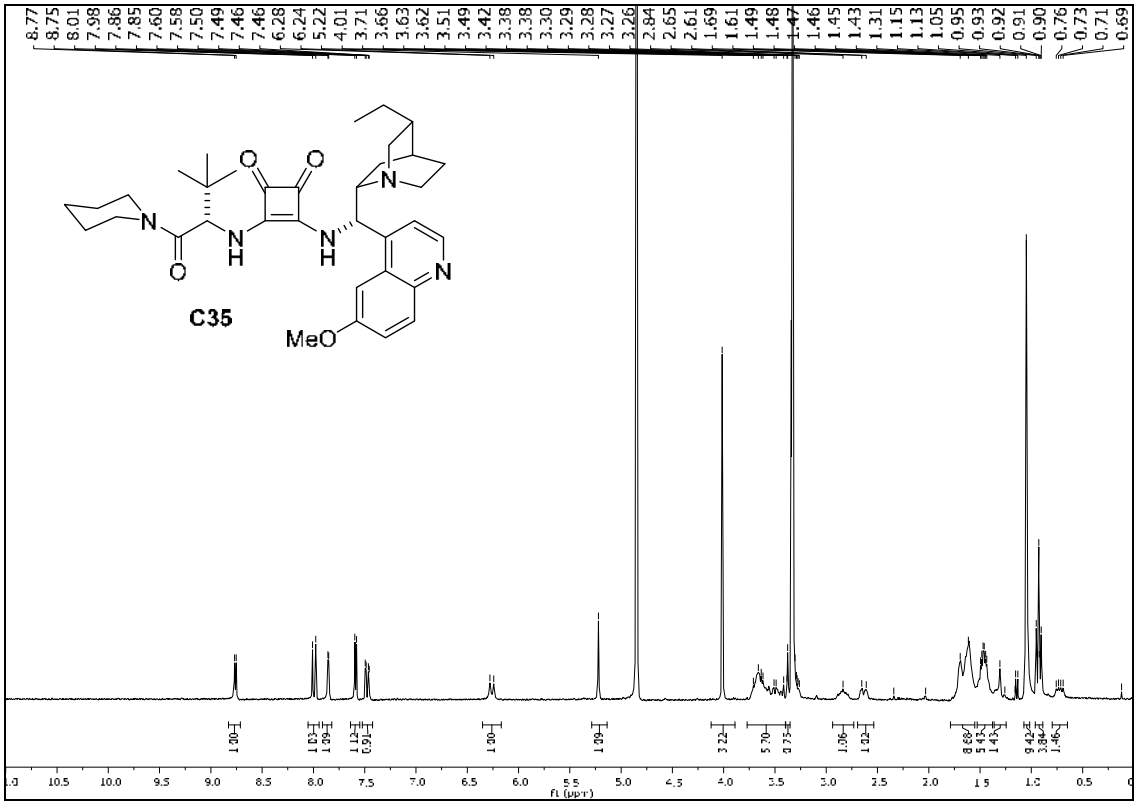


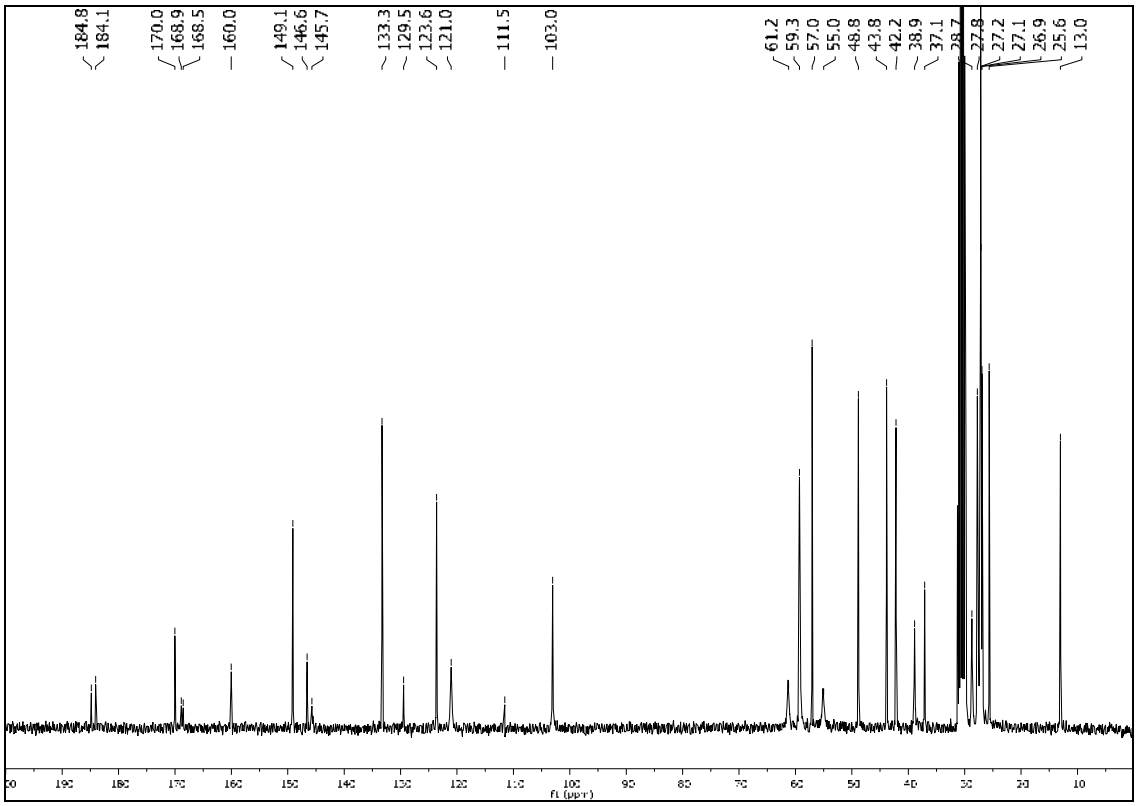

C33
Ph
Ph
N
O
O
O
N
H
N
H
N
MeO



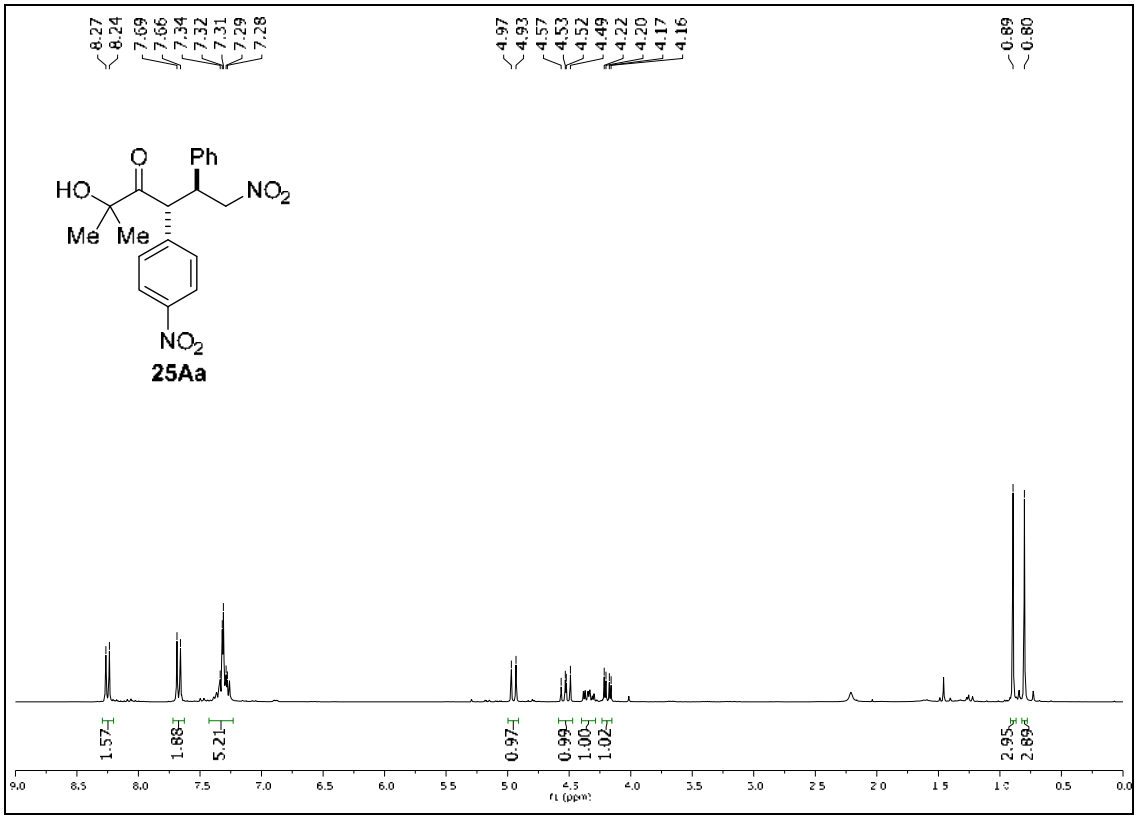

C34
MeO

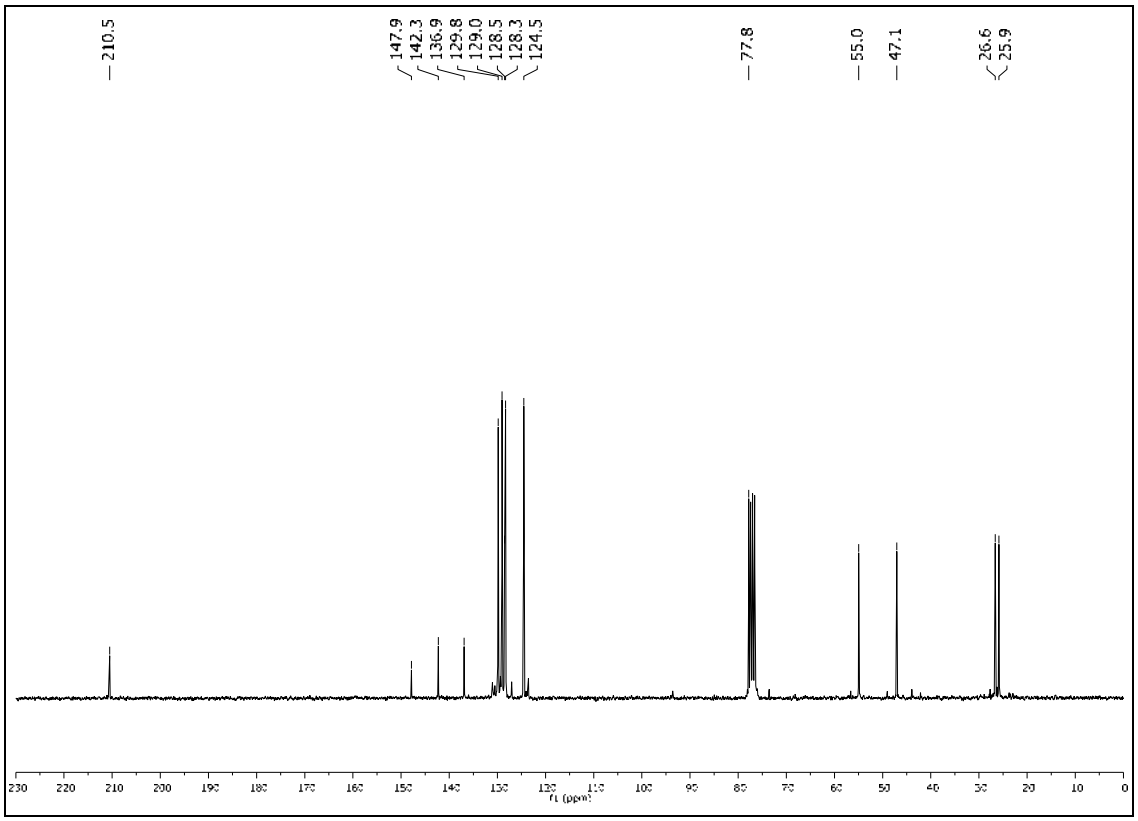


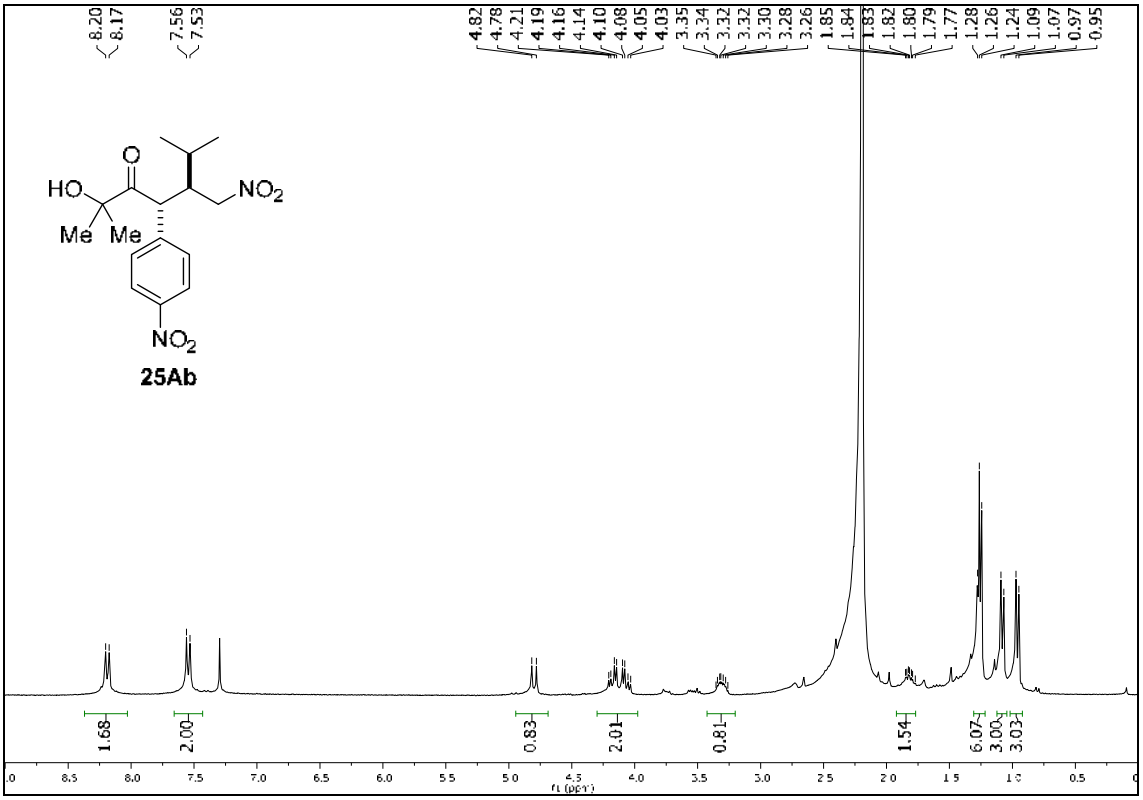

C35
MeO



7.7.2. NMR spectra for Chapter 2



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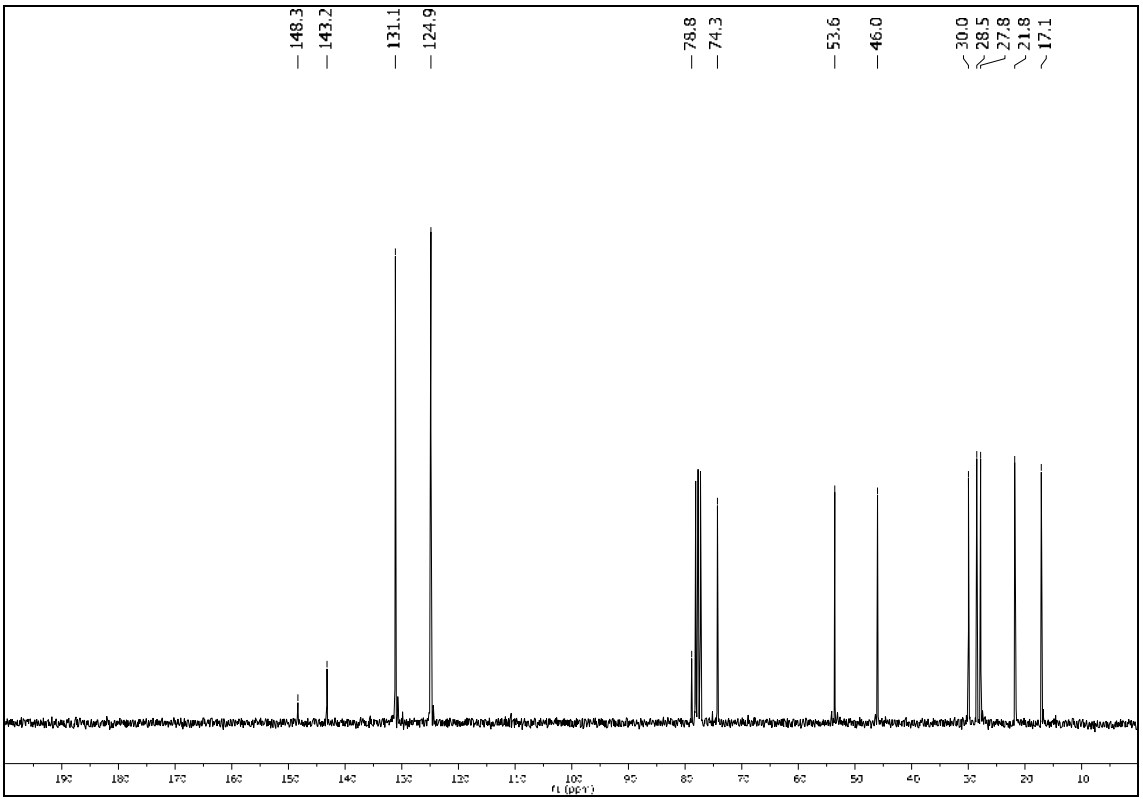
8.17
7.56
7.53
4.82
4.78
4.21
4.19
4.16
4.14
4.10
4.08
4.05
4.03
3.35
3.34
3.32
3.32
3.30
3.28
3.26
1.85
1.84
1.83
1.82
1.80
1.79
1.77
1.28
1.26
1.24
1.09
1.07
0.97
0.95
HO
O
NO2
Me
Me
NO2
25Ab
1.68
2.00
0.83
2.01
0.81
1.54
6.07
3.00
3.03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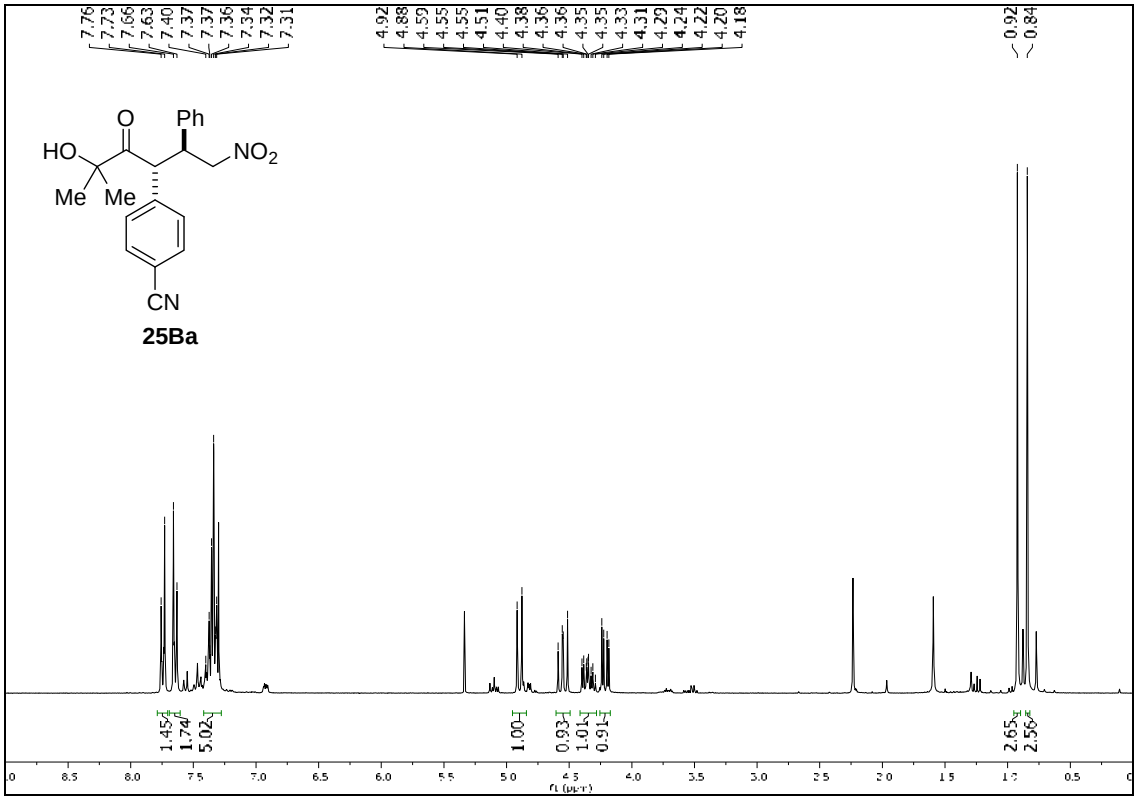
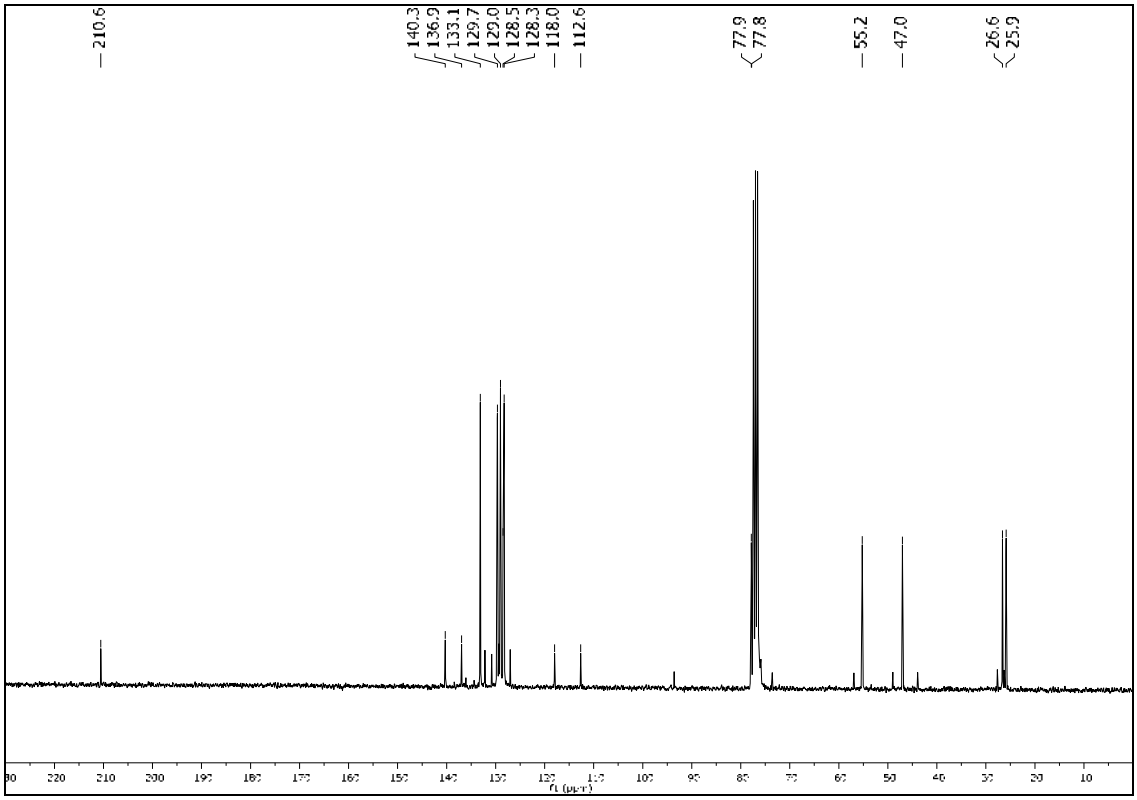
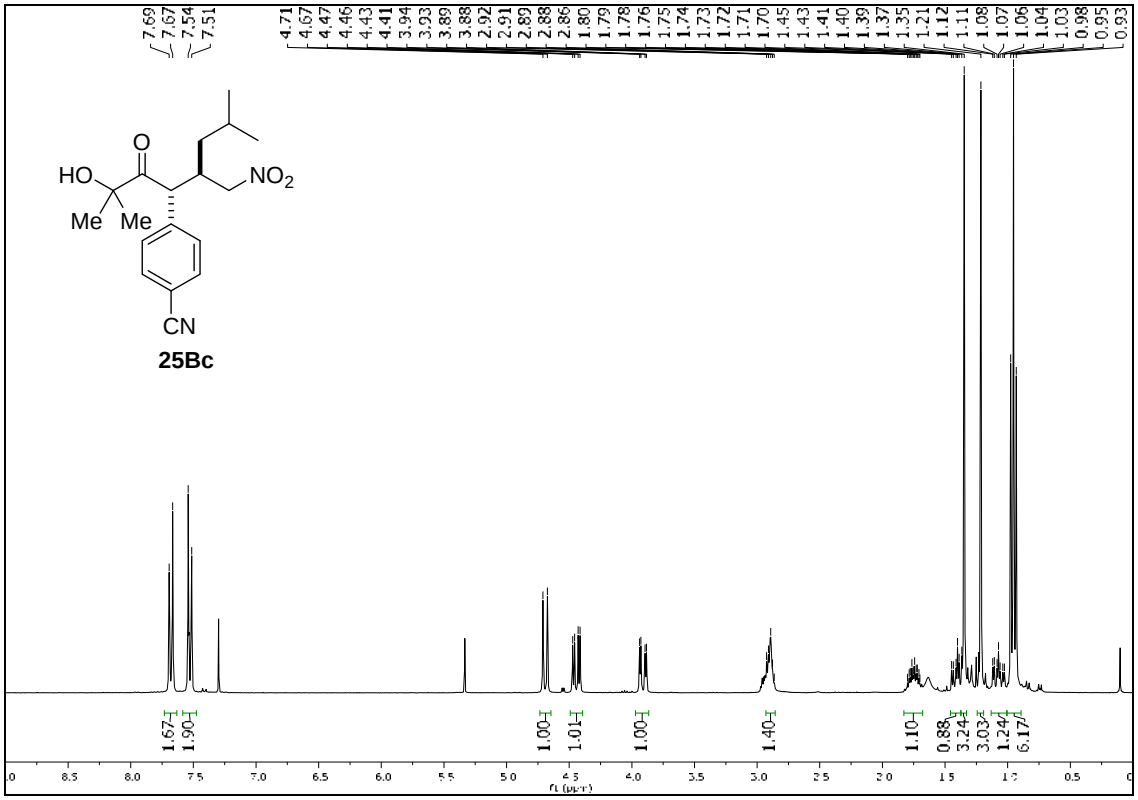
143.2
131.1
124.9
78.8
74.3
53.6
46.0
30.0
28.5
27.8
21.8
17.1


7.76
7.73
7.66
7.63
7.40
7.37
7.37
7.36
7.34
7.32
7.31
4.92
4.88
4.59
4.55
4.55
4.51
4.40
4.38
4.36
4.36
4.35
4.35
4.33
4.31
4.29
4.24
4.22
4.20
4.18
0.92
0.84
O
Ph
HO
NO2
Me
Me
CN
25Ba
1.45
1.74
5.02
1.00
0.93
1.01
0.91
2.65
2.56


210.6
140.3
136.9
133.1
129.7
129.0
128.5
128.3
118.0
112.6
77.9
77.8
55.2
47.0
26.6
25.9


7.69
7.67
7.54
7.51
4.71
4.67
4.47
4.46
4.43
4.41
3.94
3.93
3.89
3.88
2.92
2.91
2.89
2.88
2.86
1.80
1.79
1.78
1.76
1.75
1.74
1.73
1.72
1.71
1.70
1.45
1.43
1.41
1.40
1.39
1.37
1.35
1.21
1.12
1.11
1.08
1.07
1.06
1.04
1.03
0.98
0.95
0.93
O
HO
NO2
Me
Me
CN
25Bc
1.67
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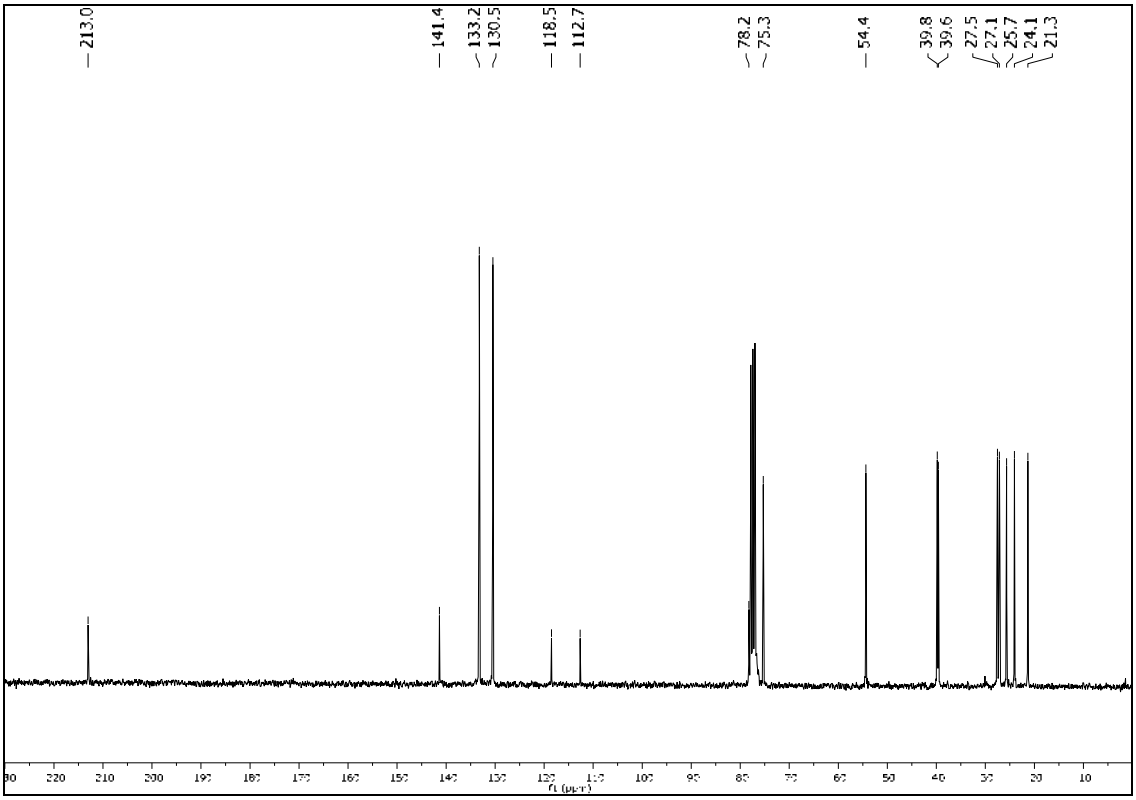
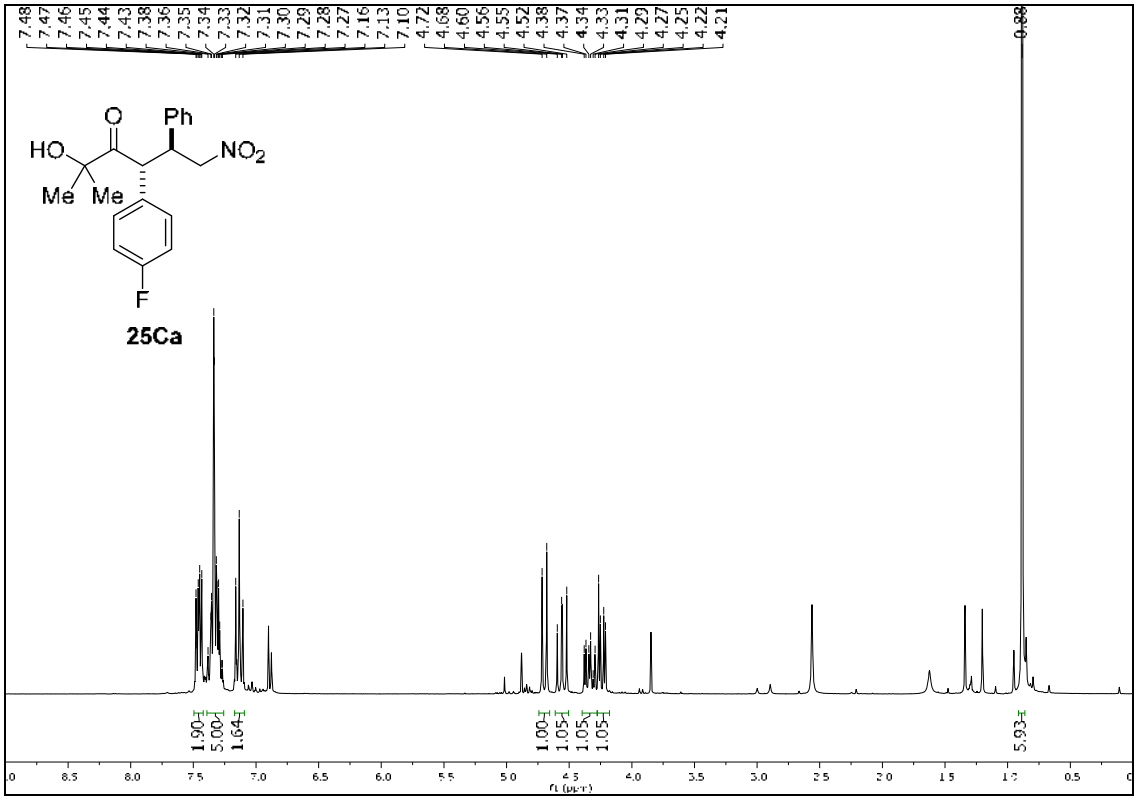
1.01
1.00
1.40
1.10
0.88
3.24
3.03
1.24
6.17


213.0
141.4
133.2
130.5
118.5
112.7
78.2
75.3
54.4
39.8
39.6
27.5
27.1
25.7
24.1
21.3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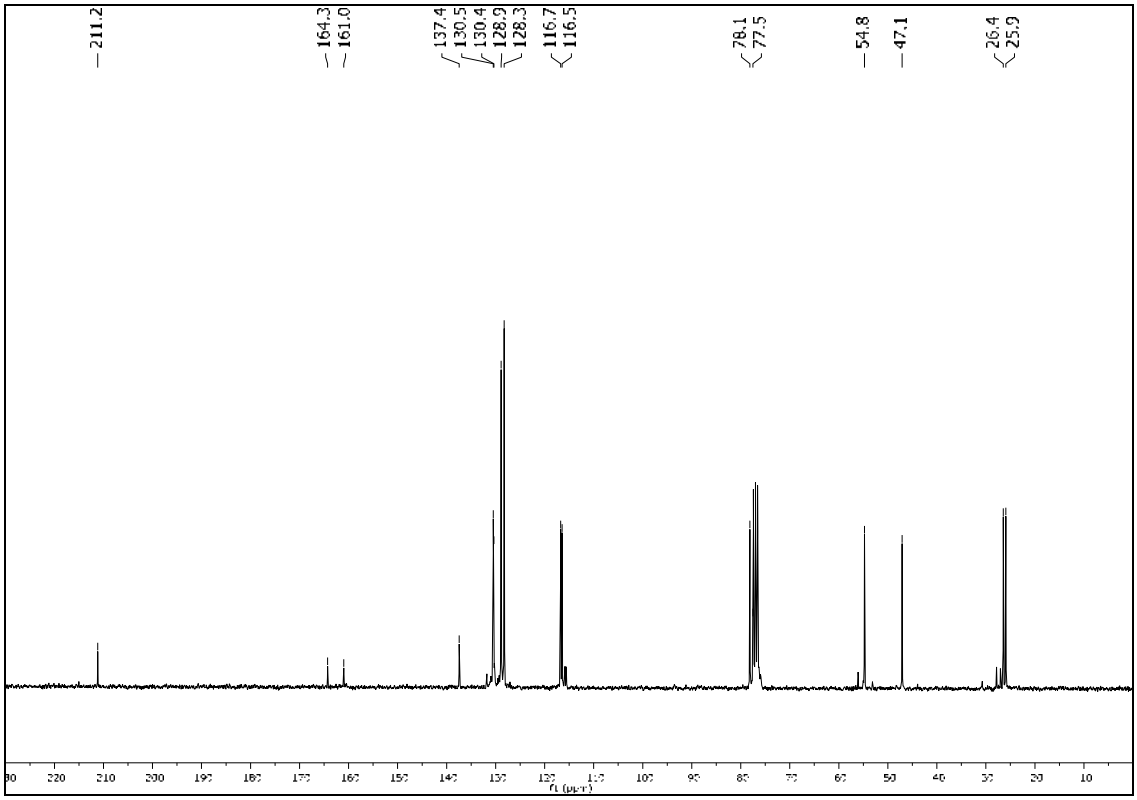
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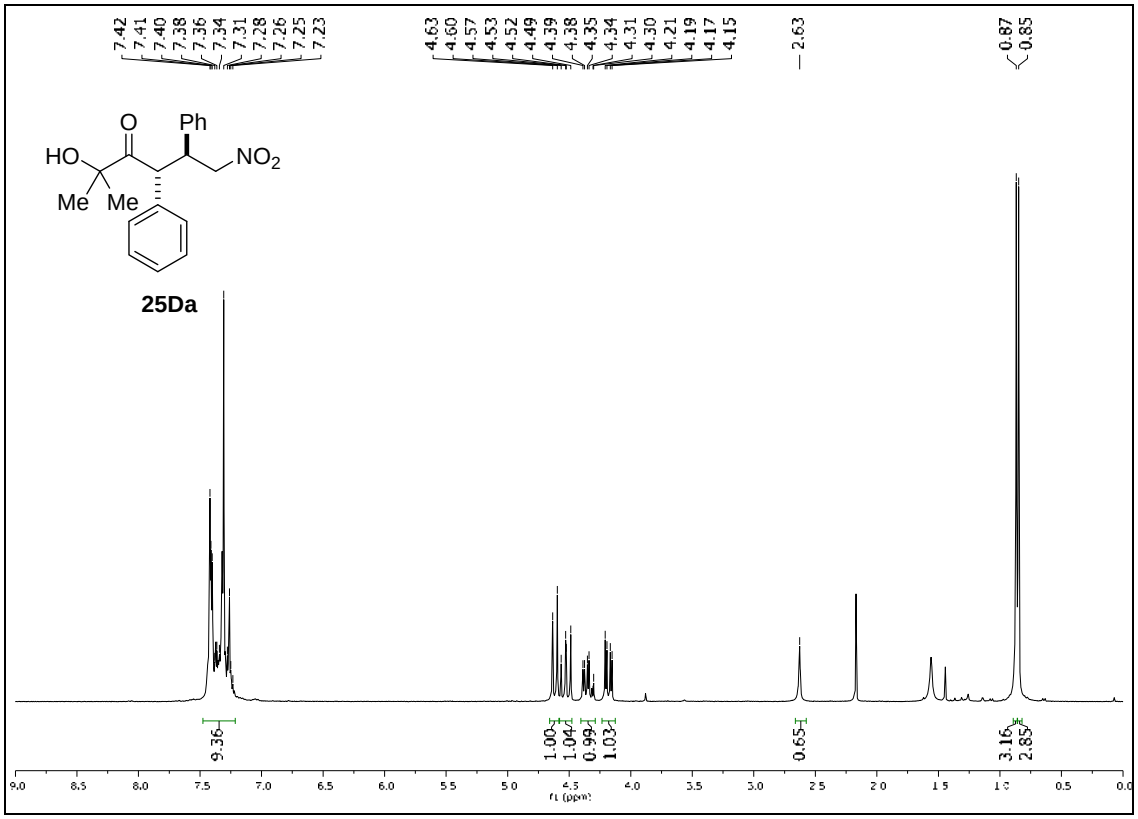
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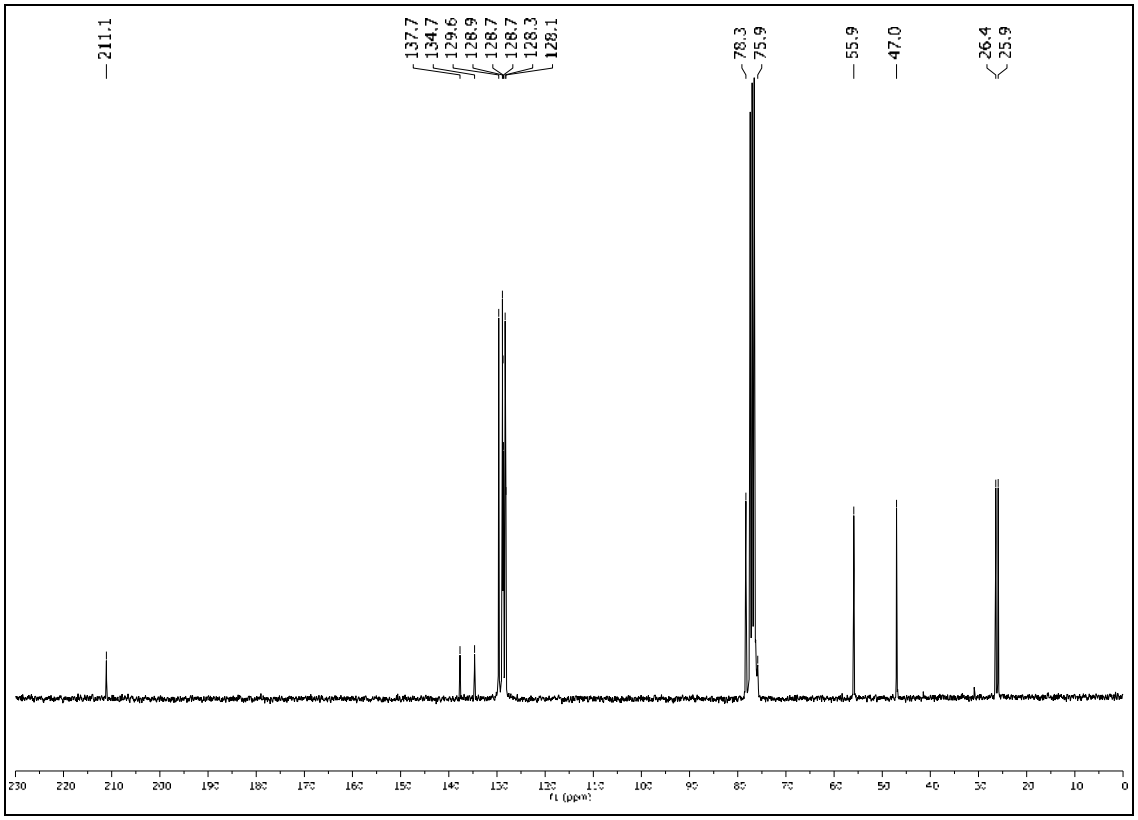
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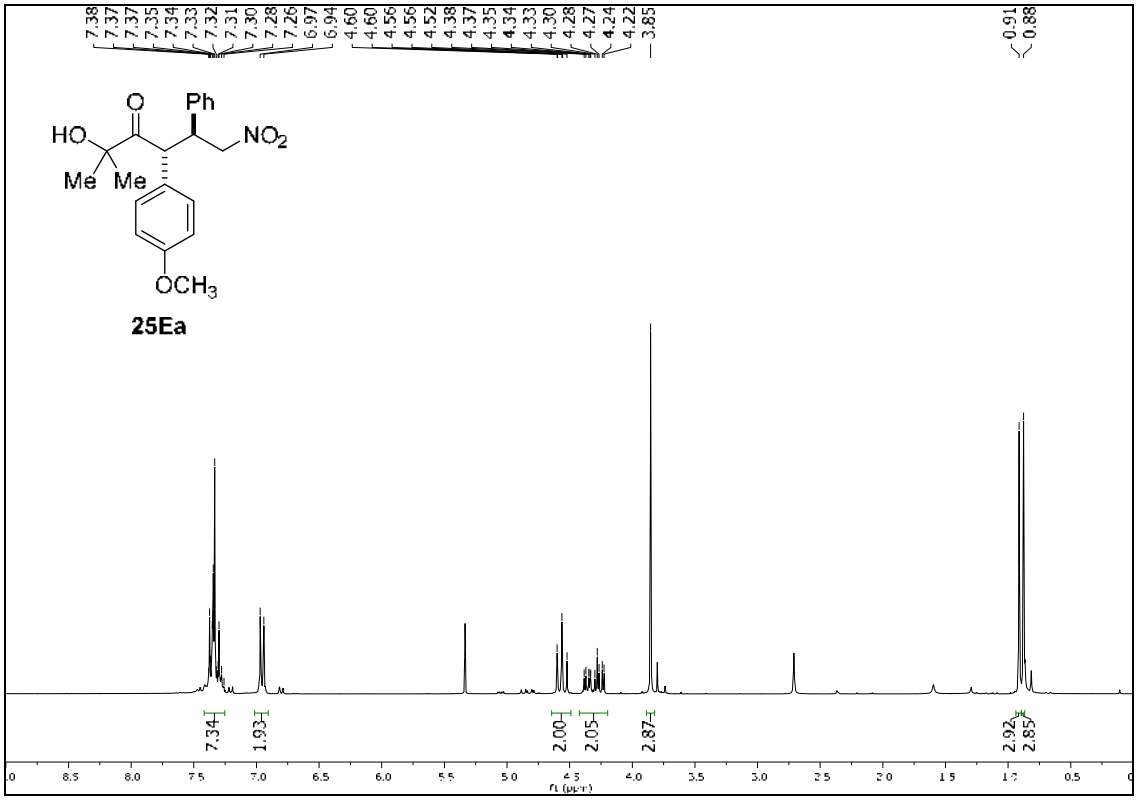
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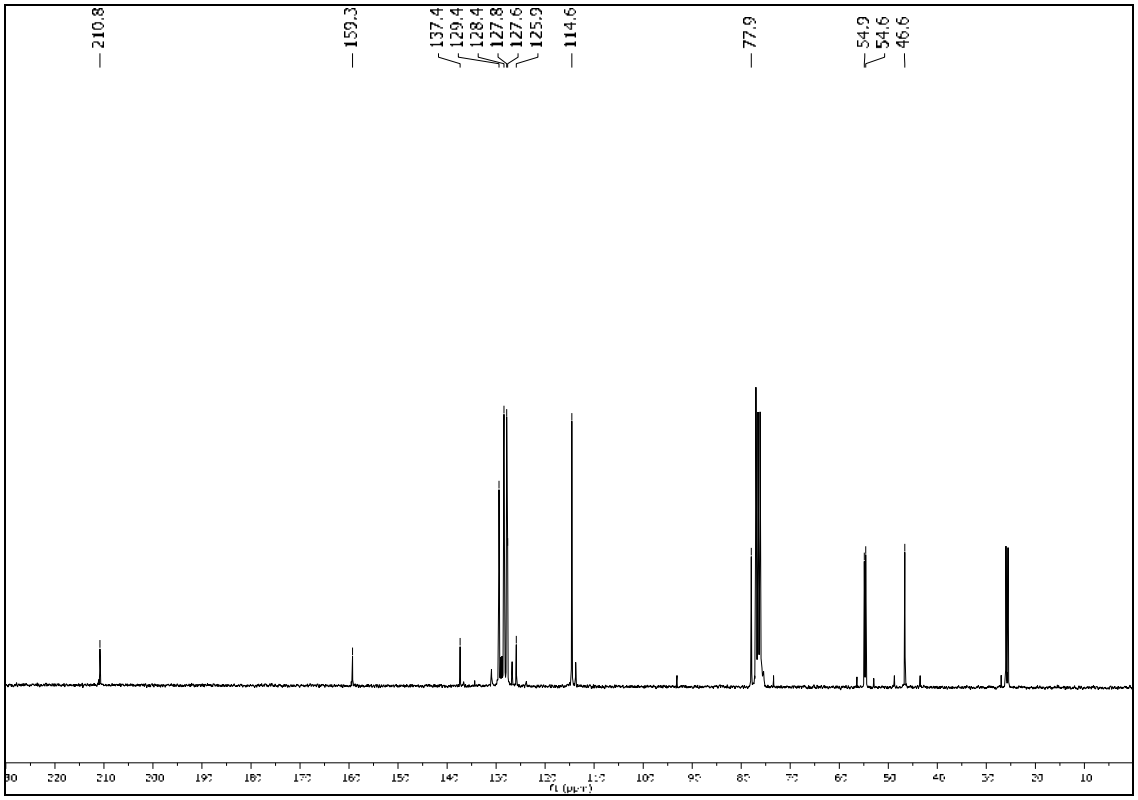
f1 (ppm)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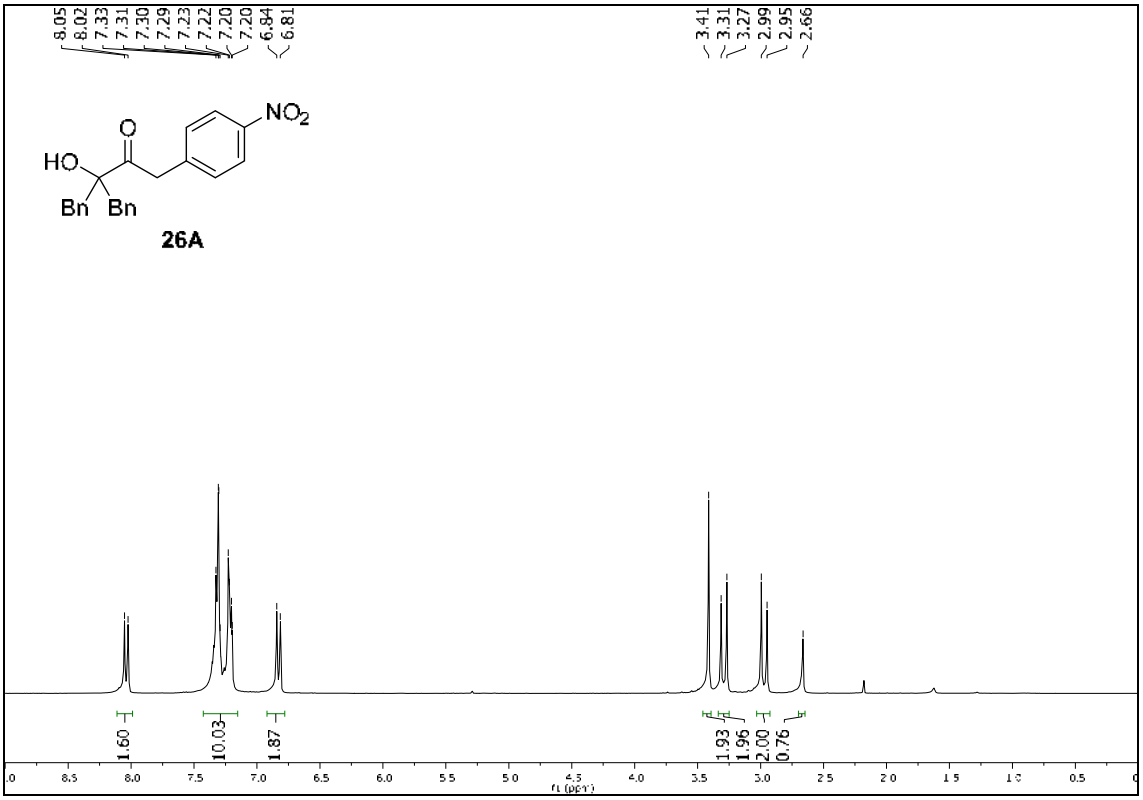
f1 (ppm)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3.27
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2.95
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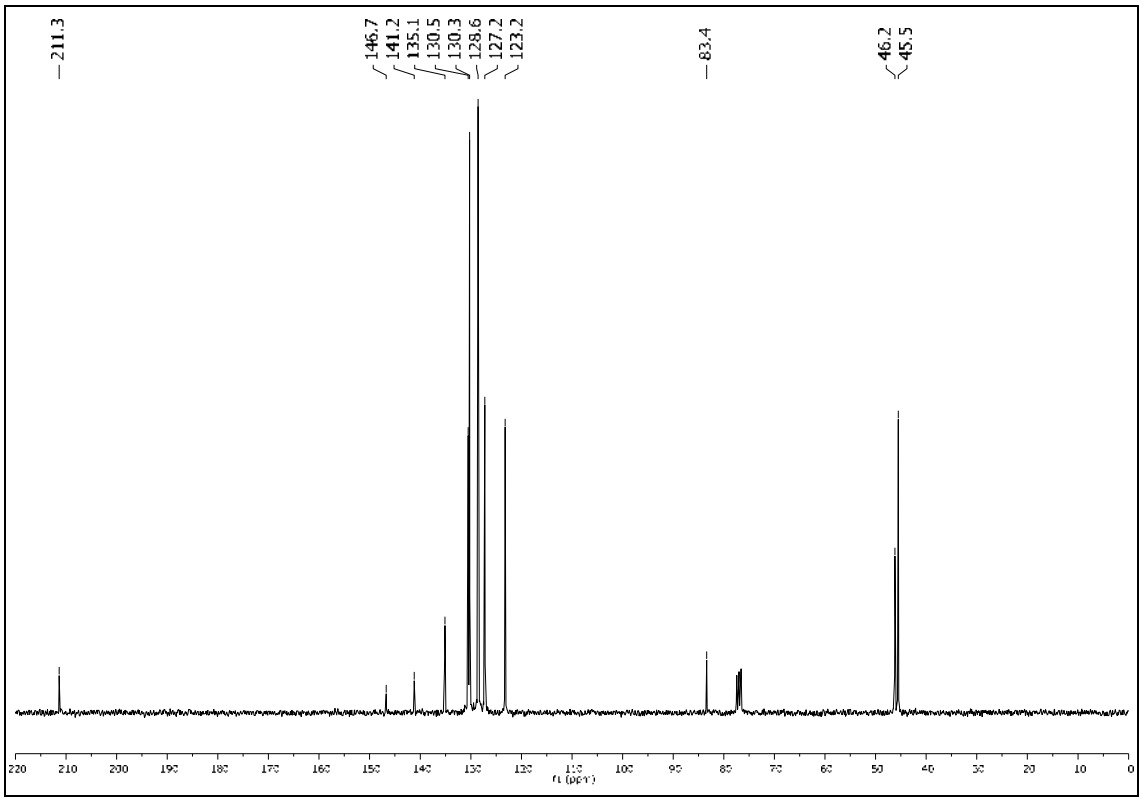
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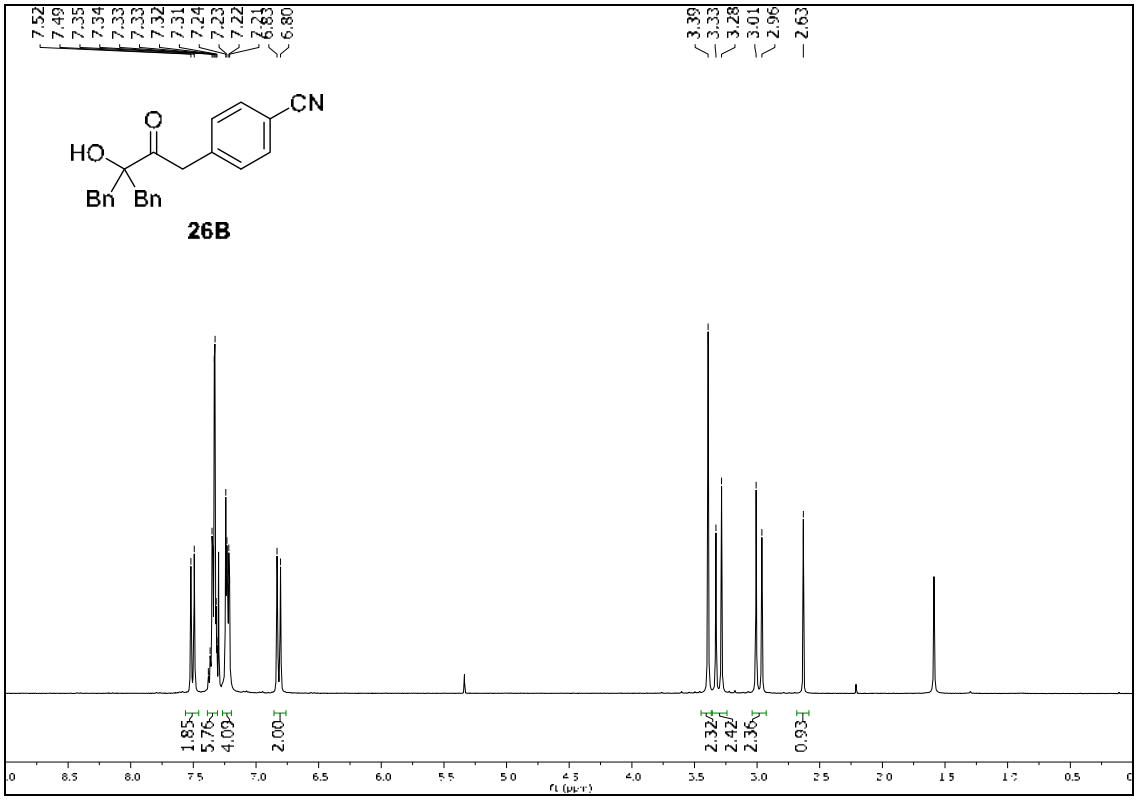
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3.33
3.28
3.01
2.96
2.63
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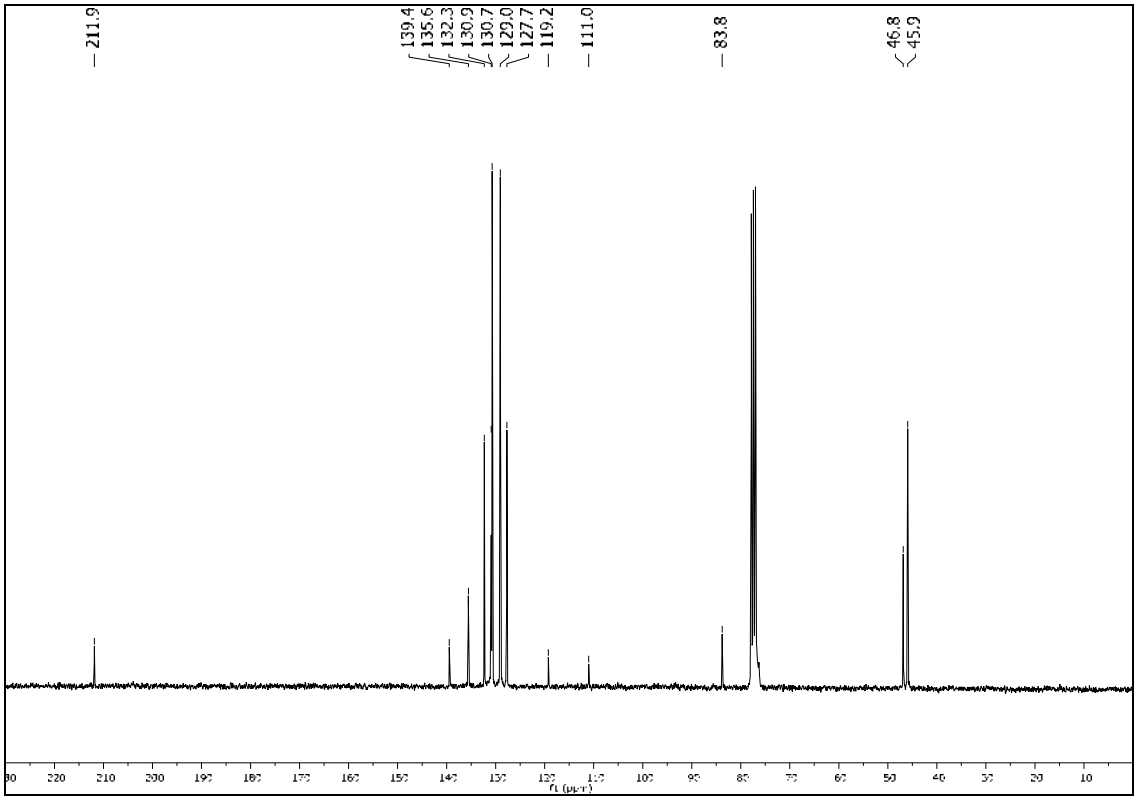
0.93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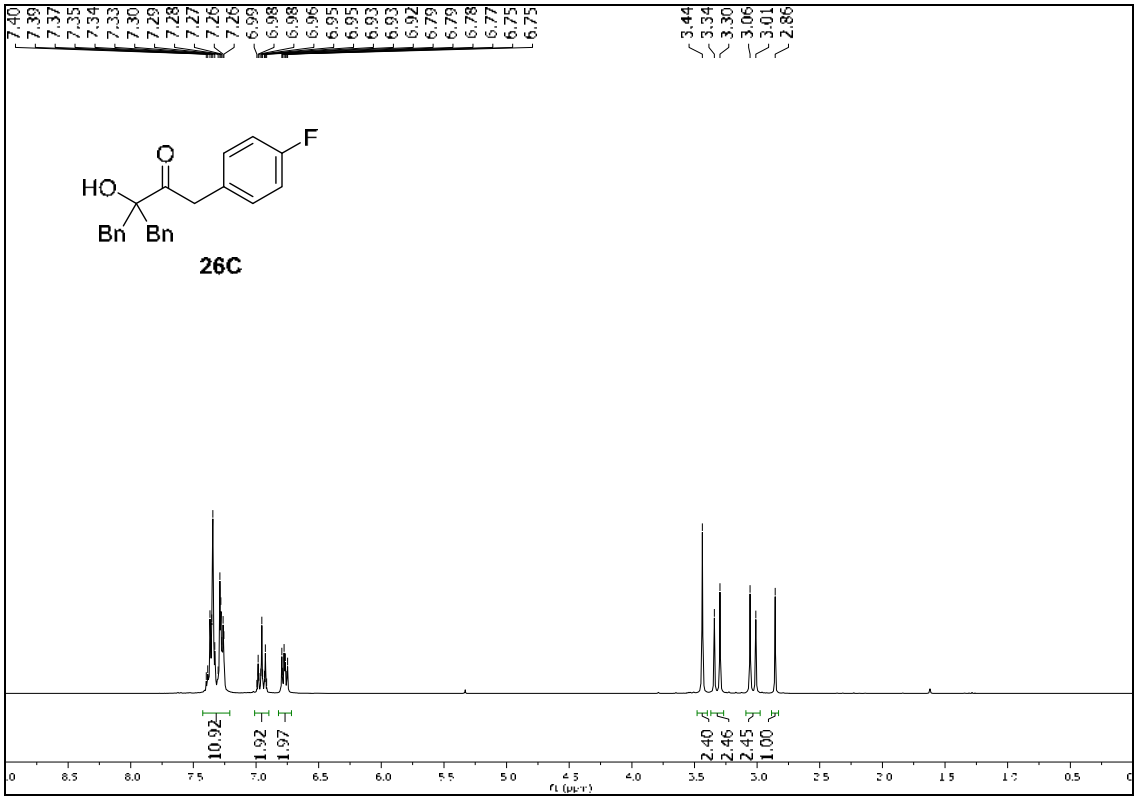
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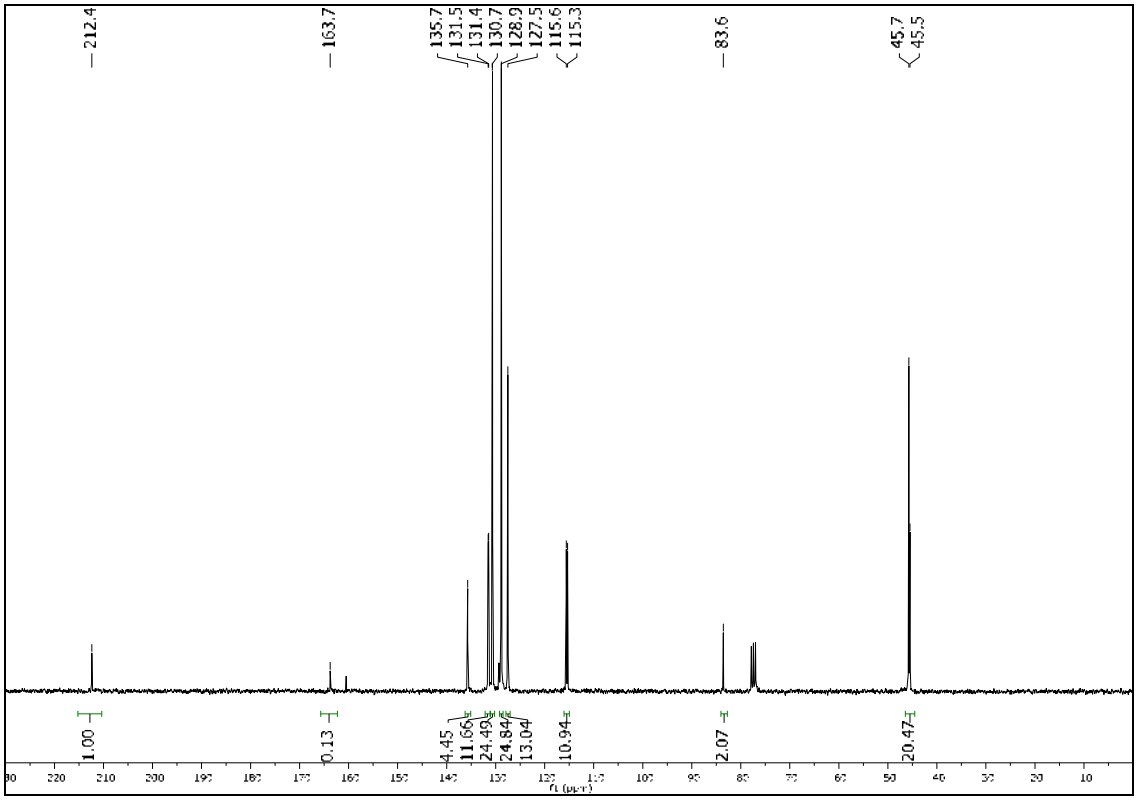
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2.07
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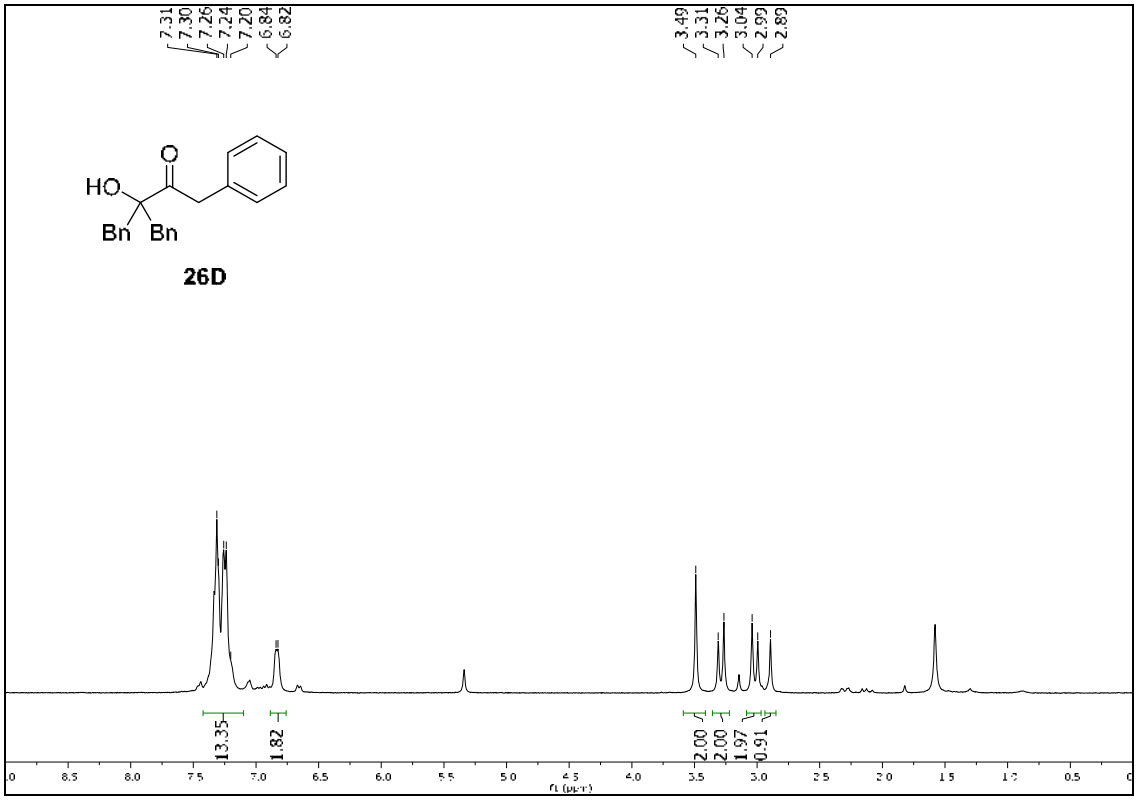
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2.00
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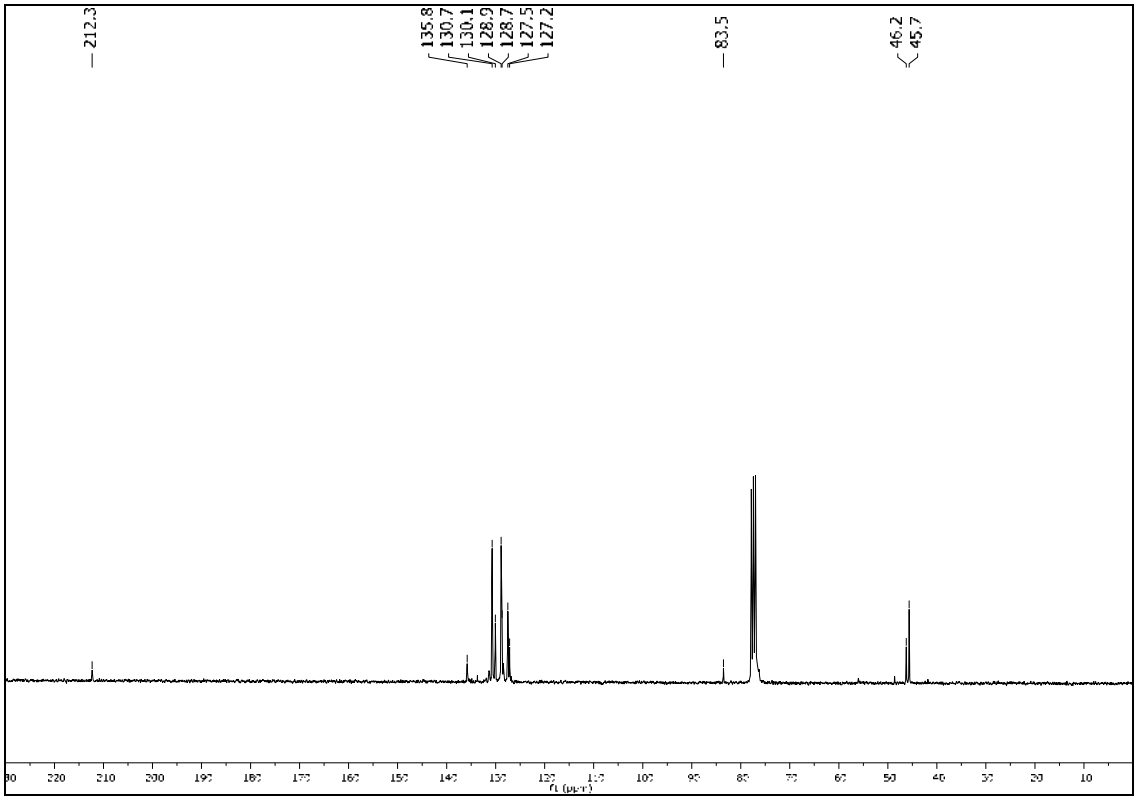
0.91

26D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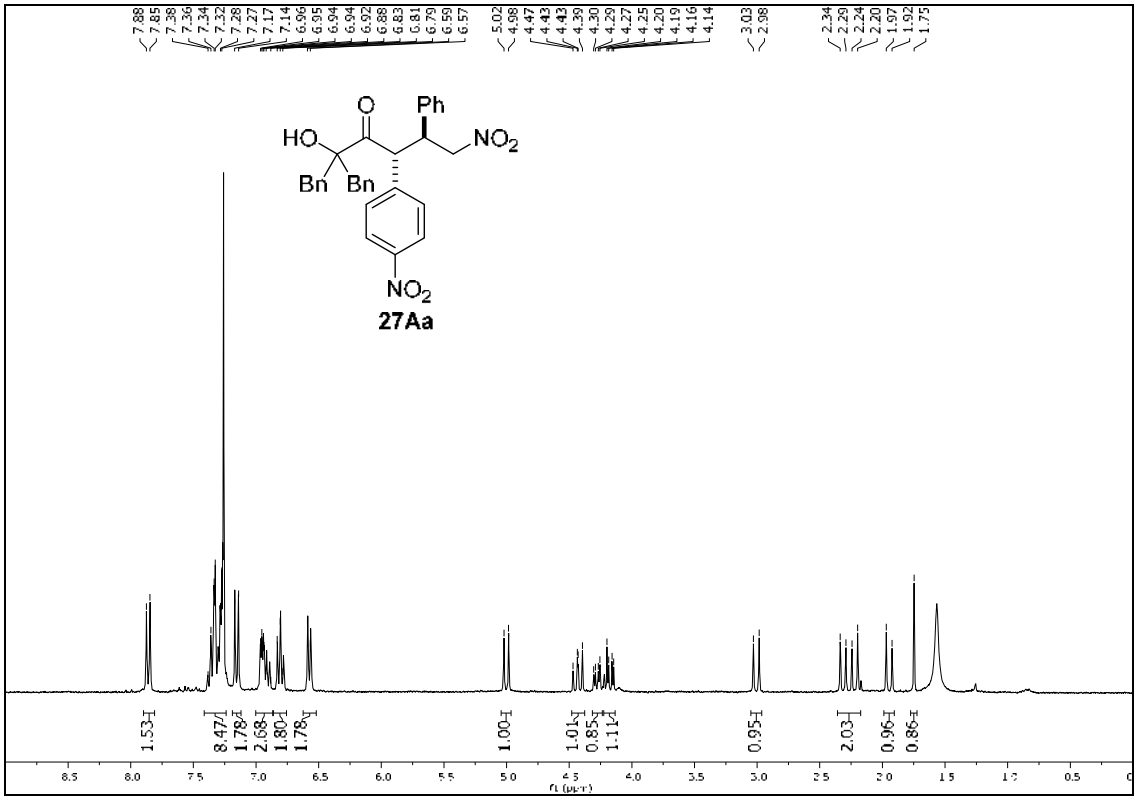
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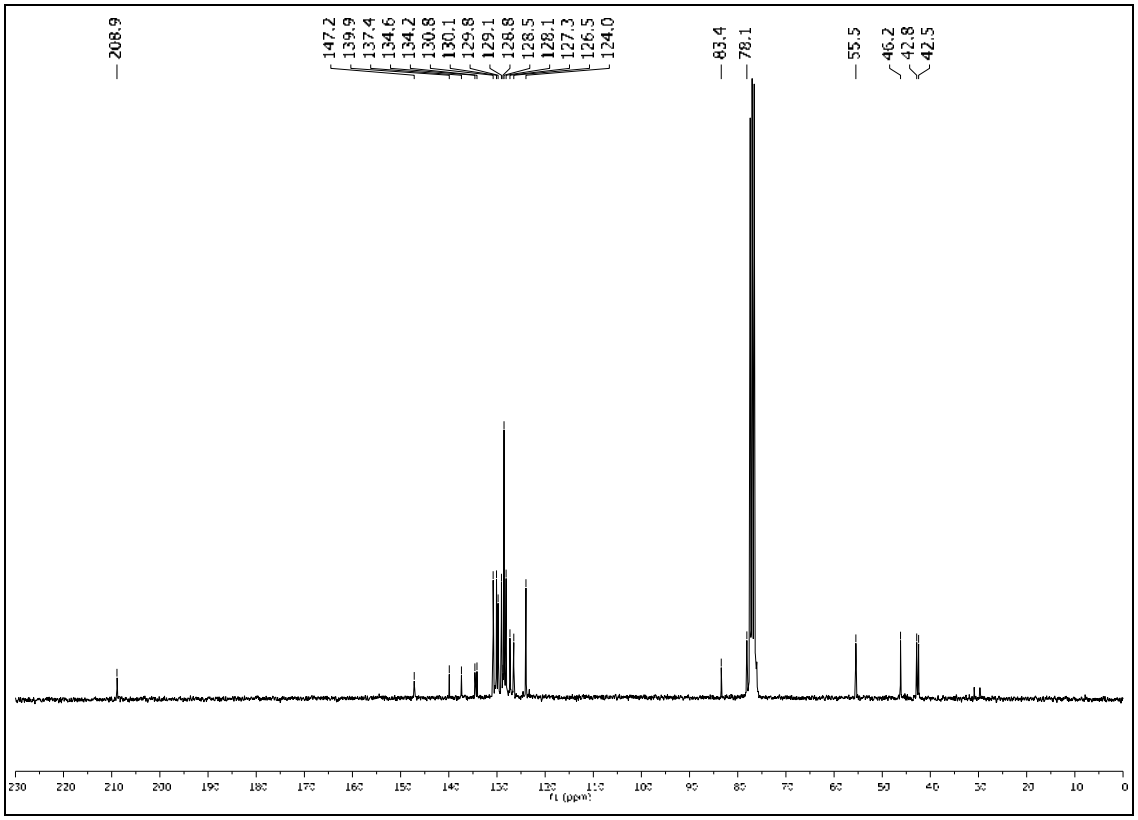
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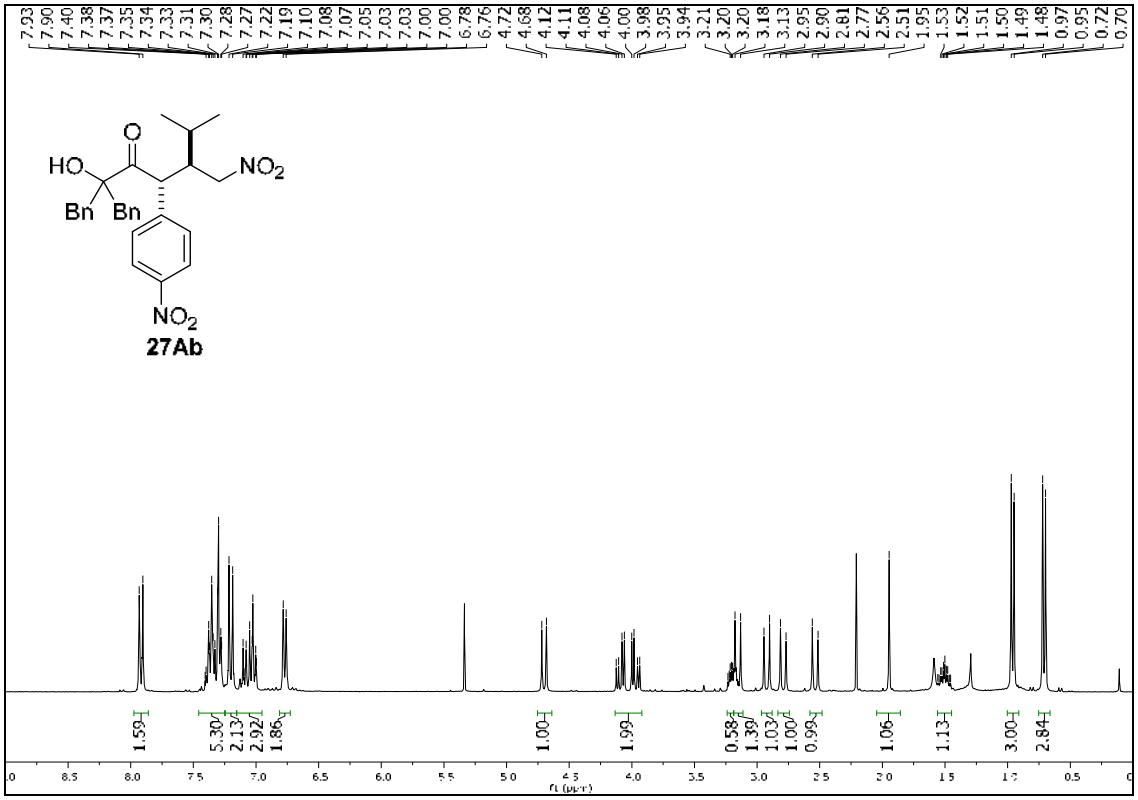
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Bn
Bn
NO2
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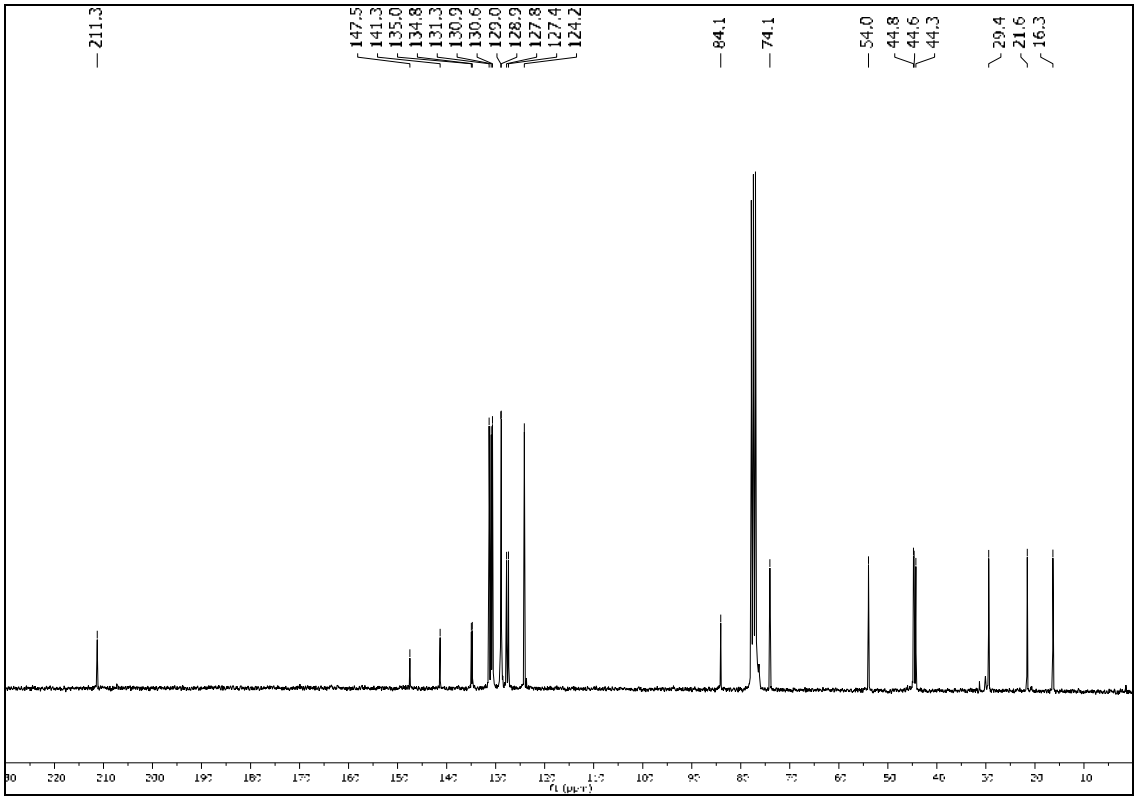

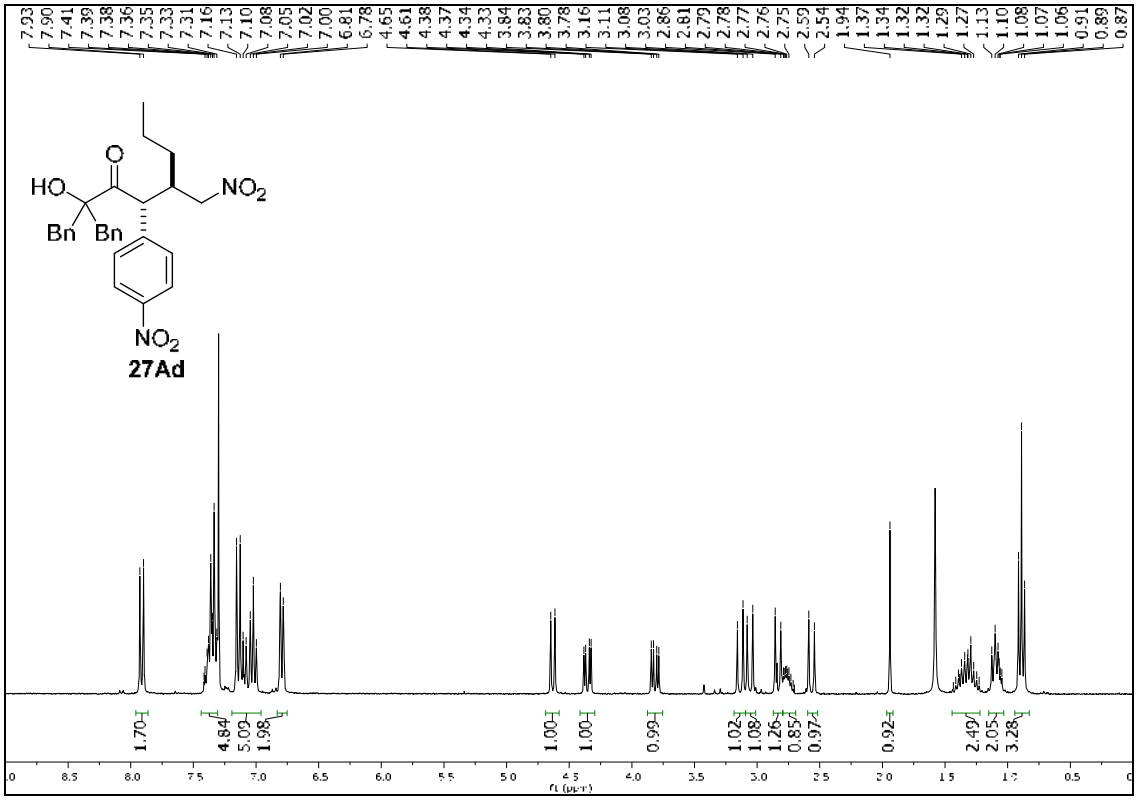
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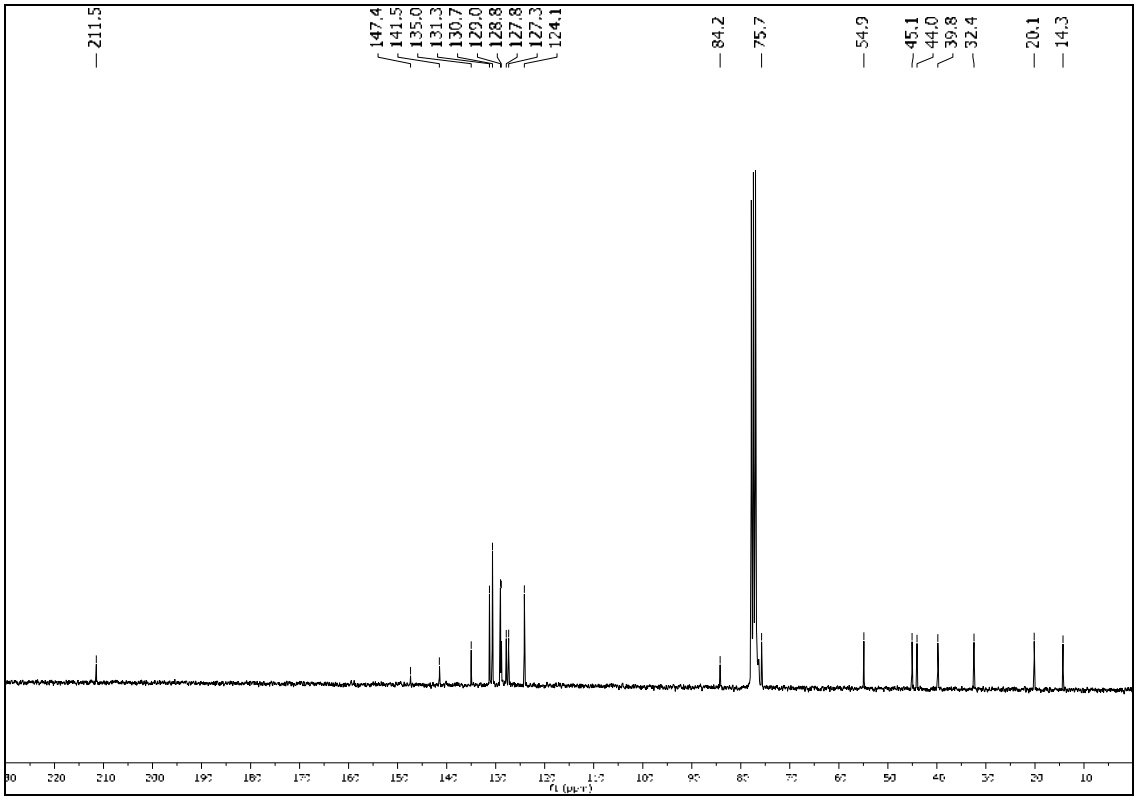

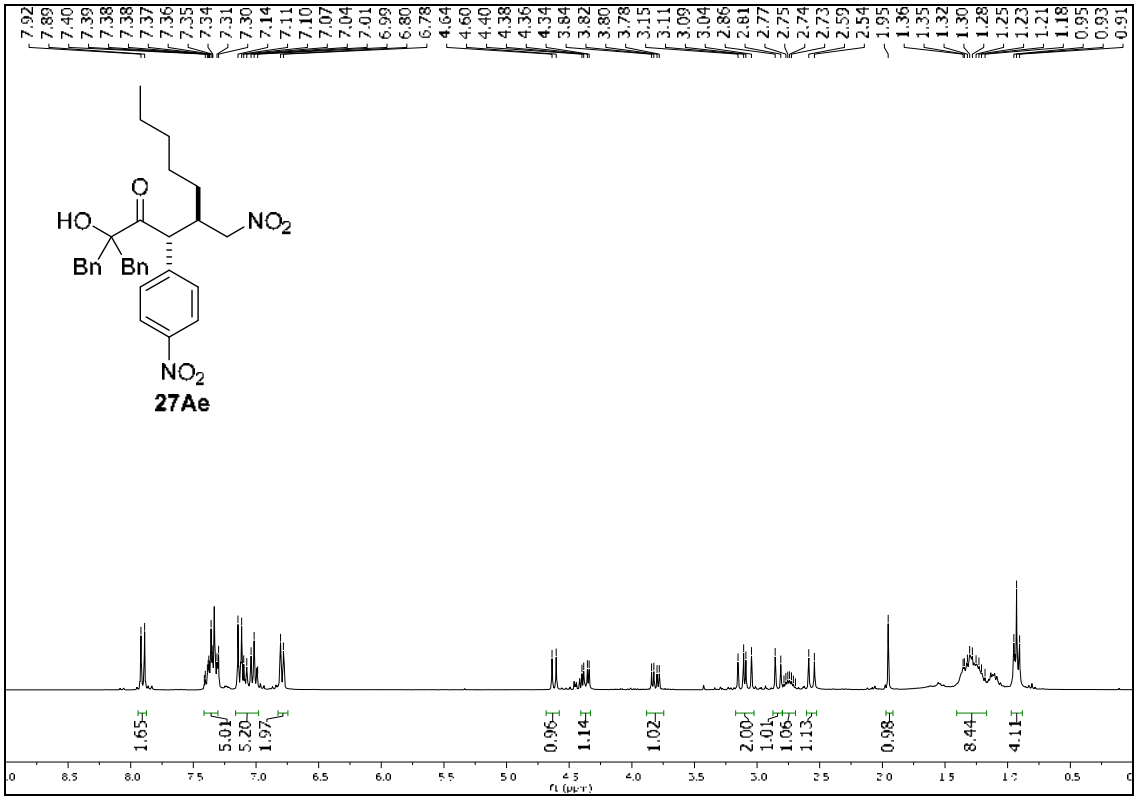
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Bn
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NO2
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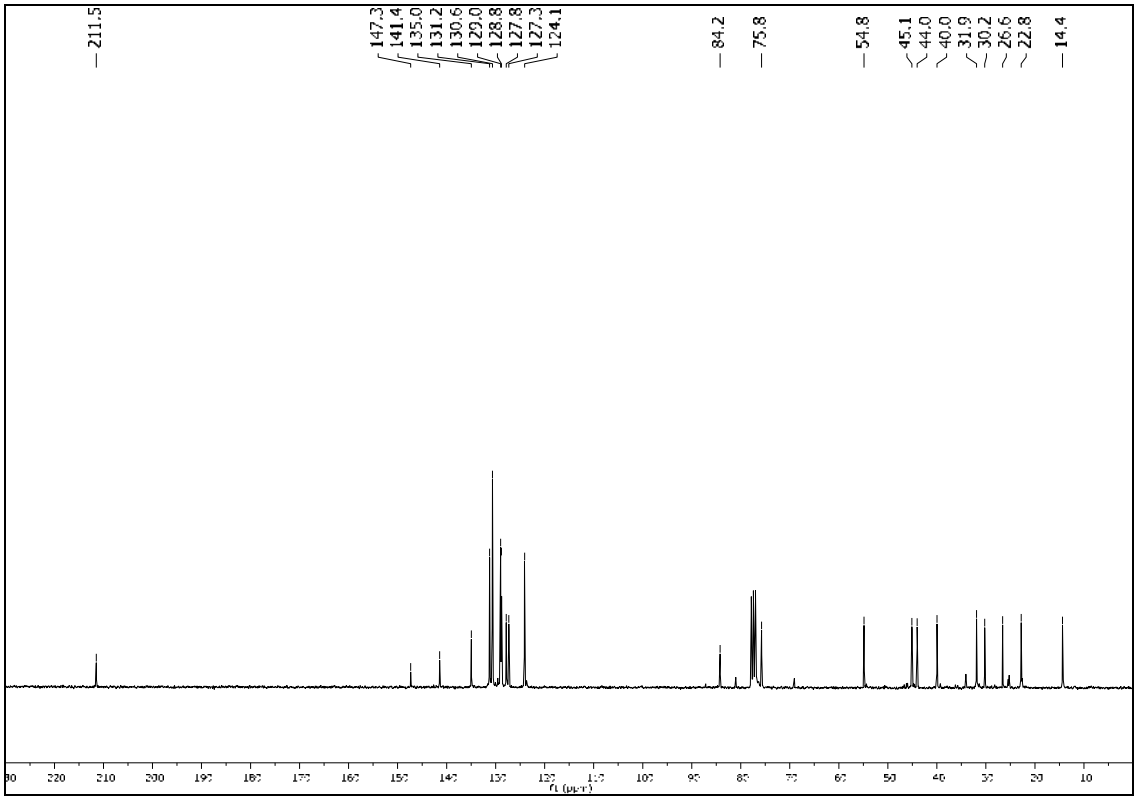

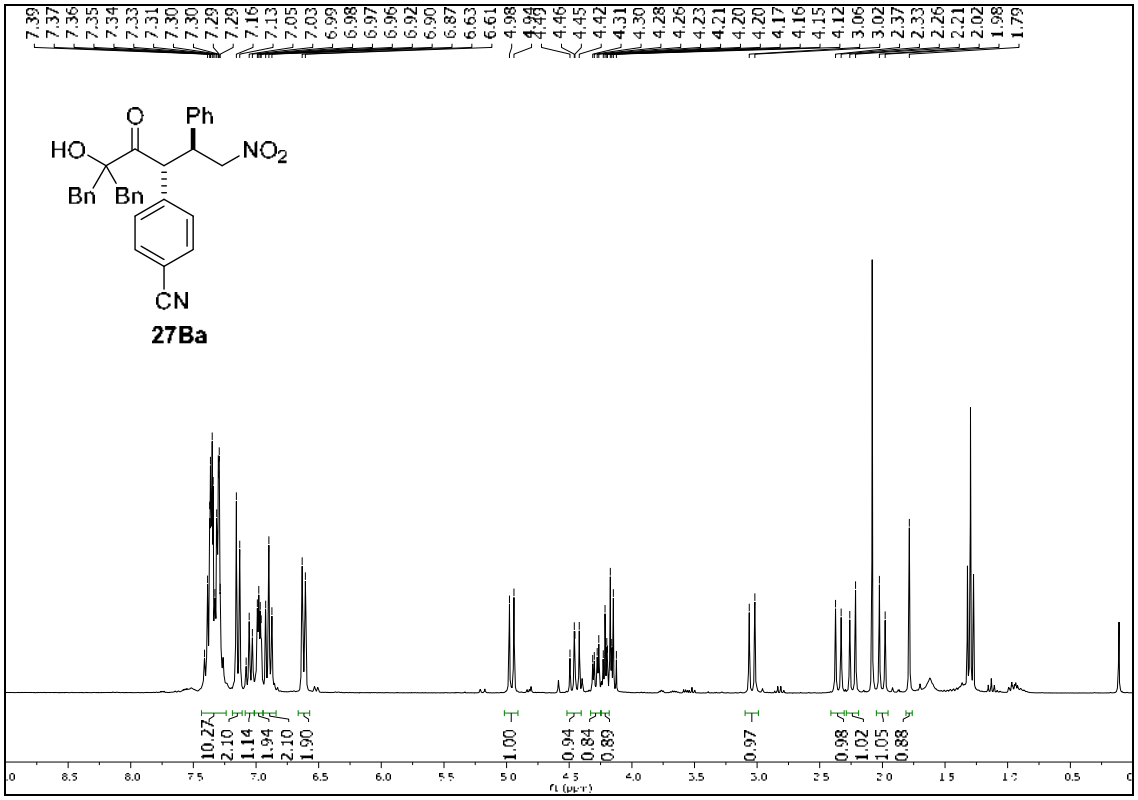
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O
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Bn
Bn
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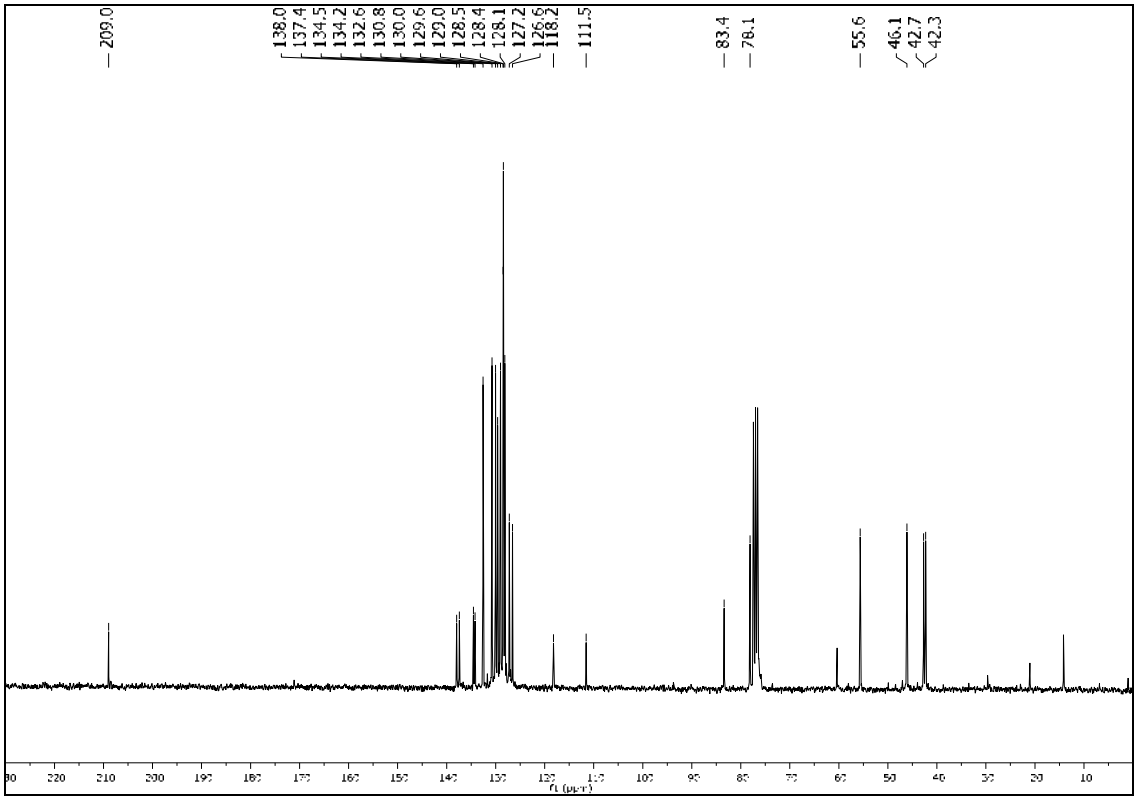

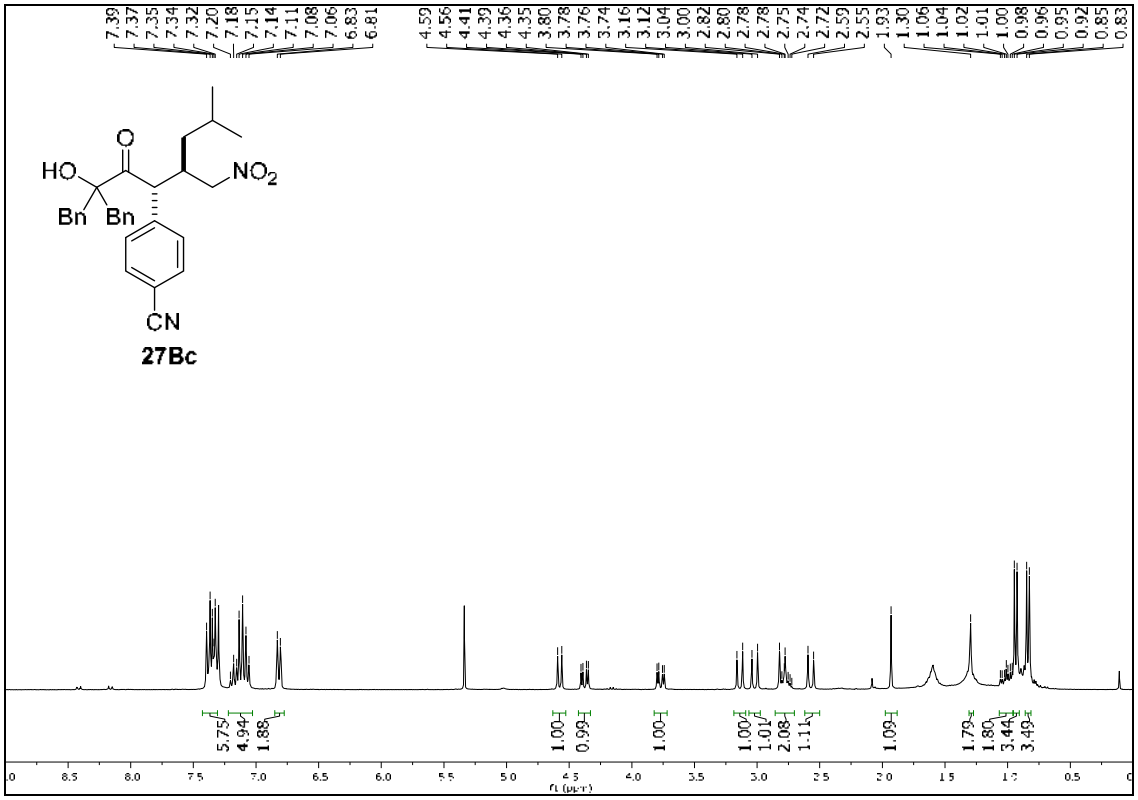
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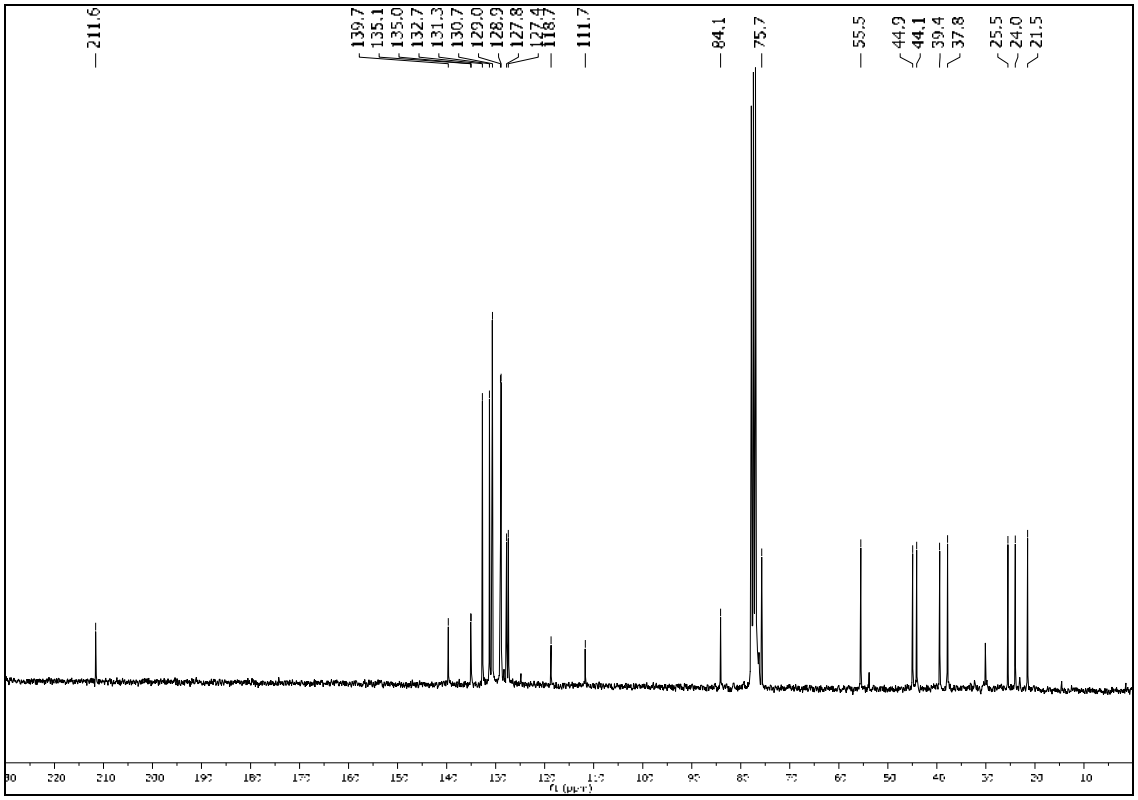

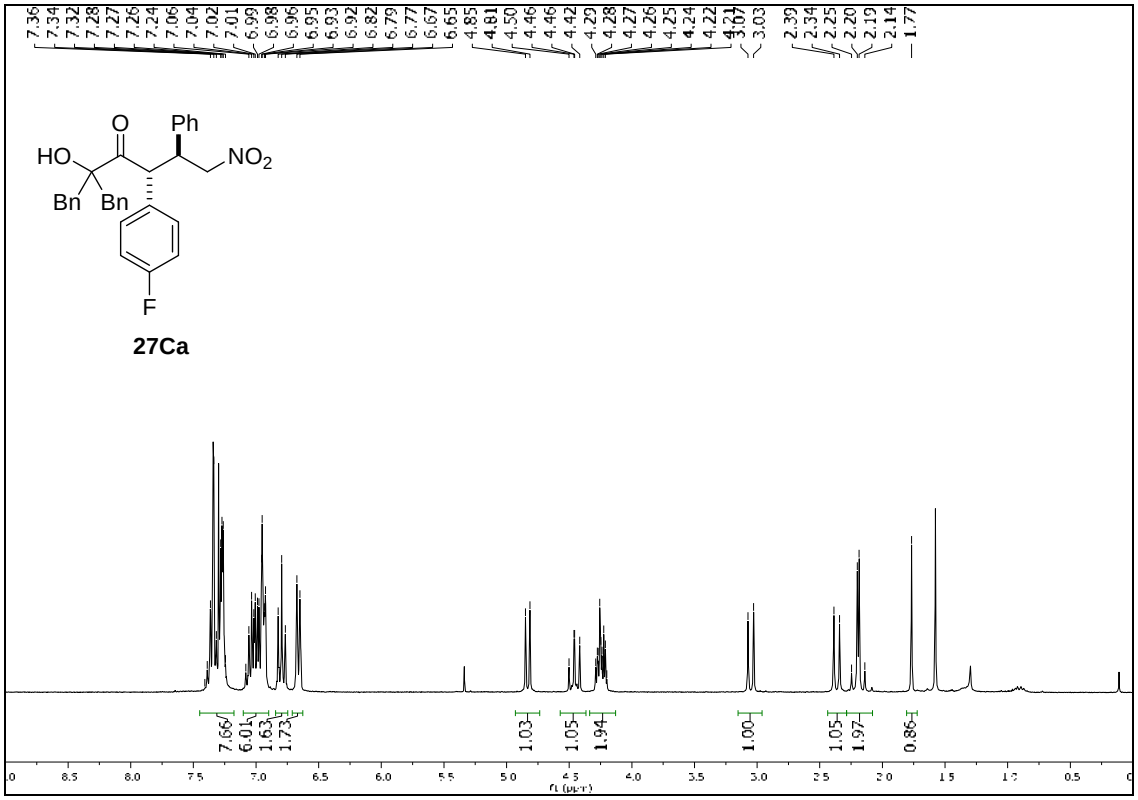
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HO
NO2
Bn
Bn
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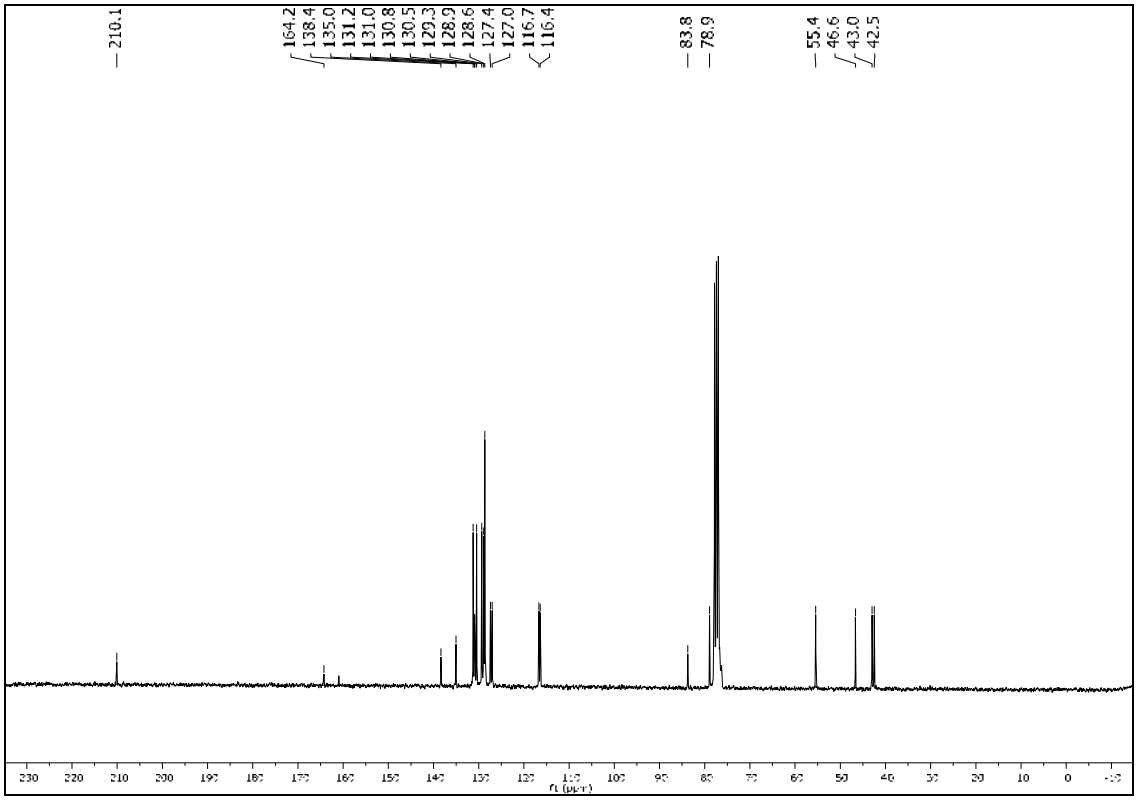
27Ca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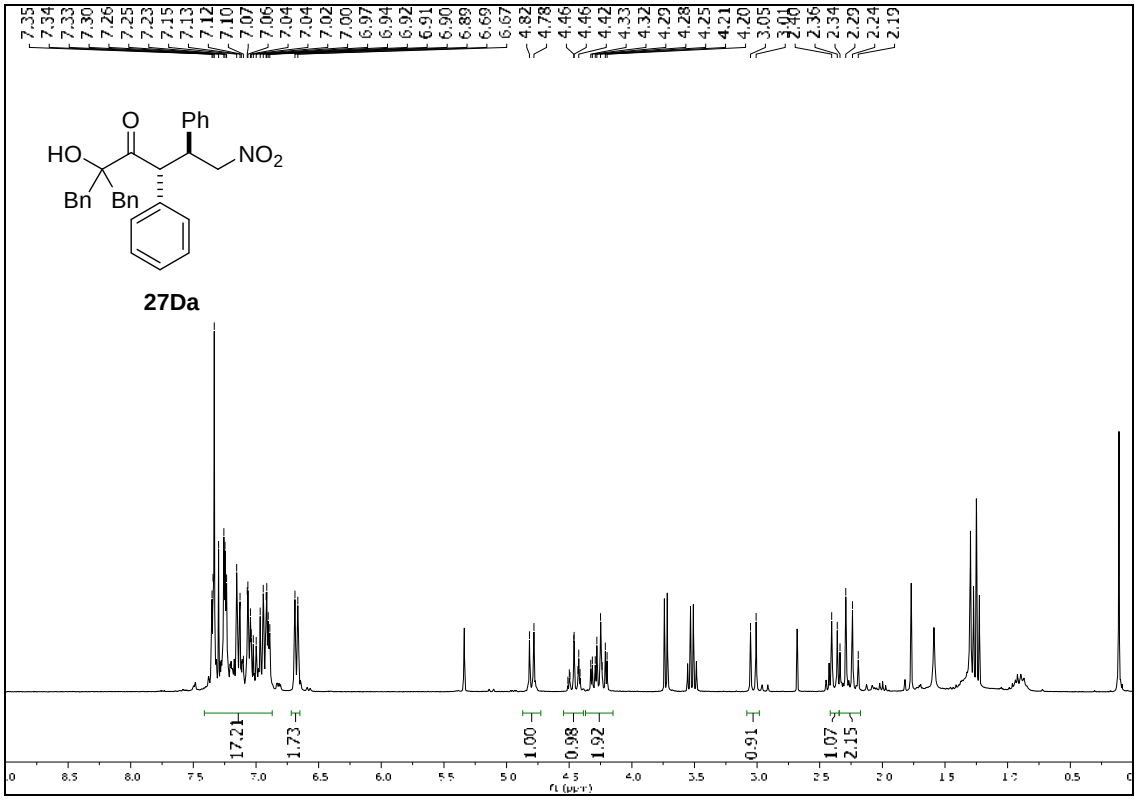
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3.01
2.40
2.36
2.34
2.29
2.24
2.19
O
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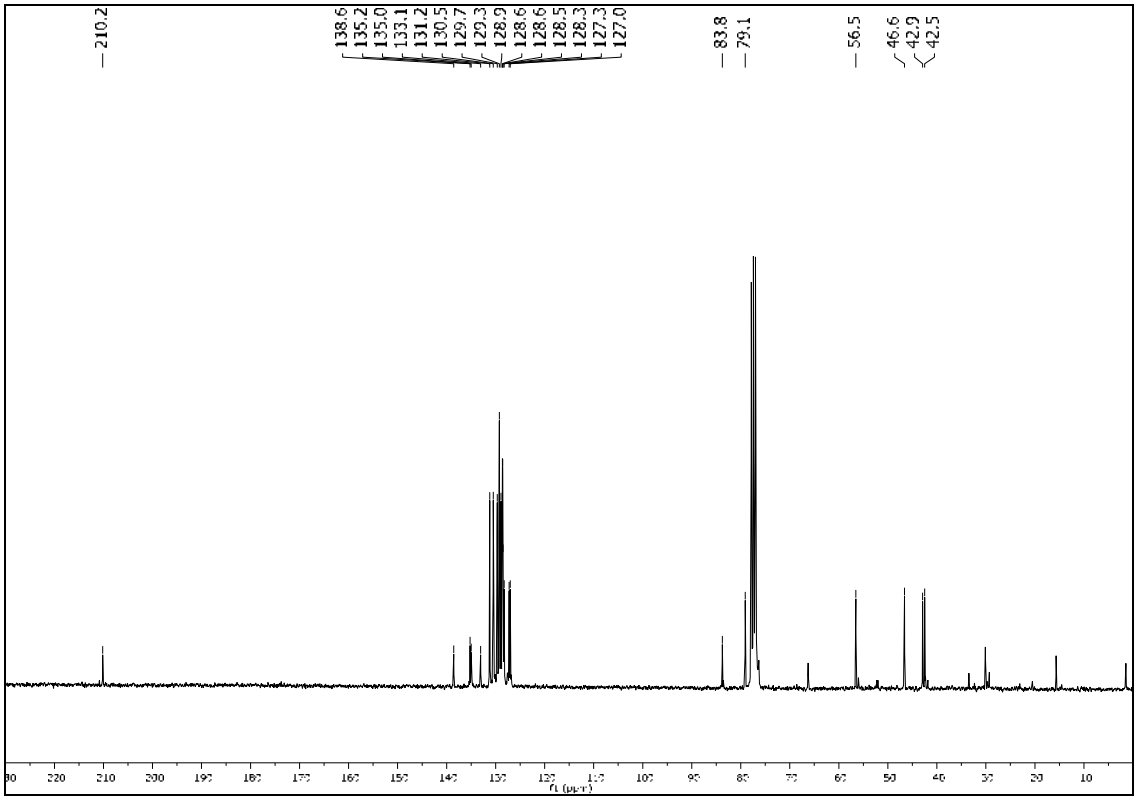
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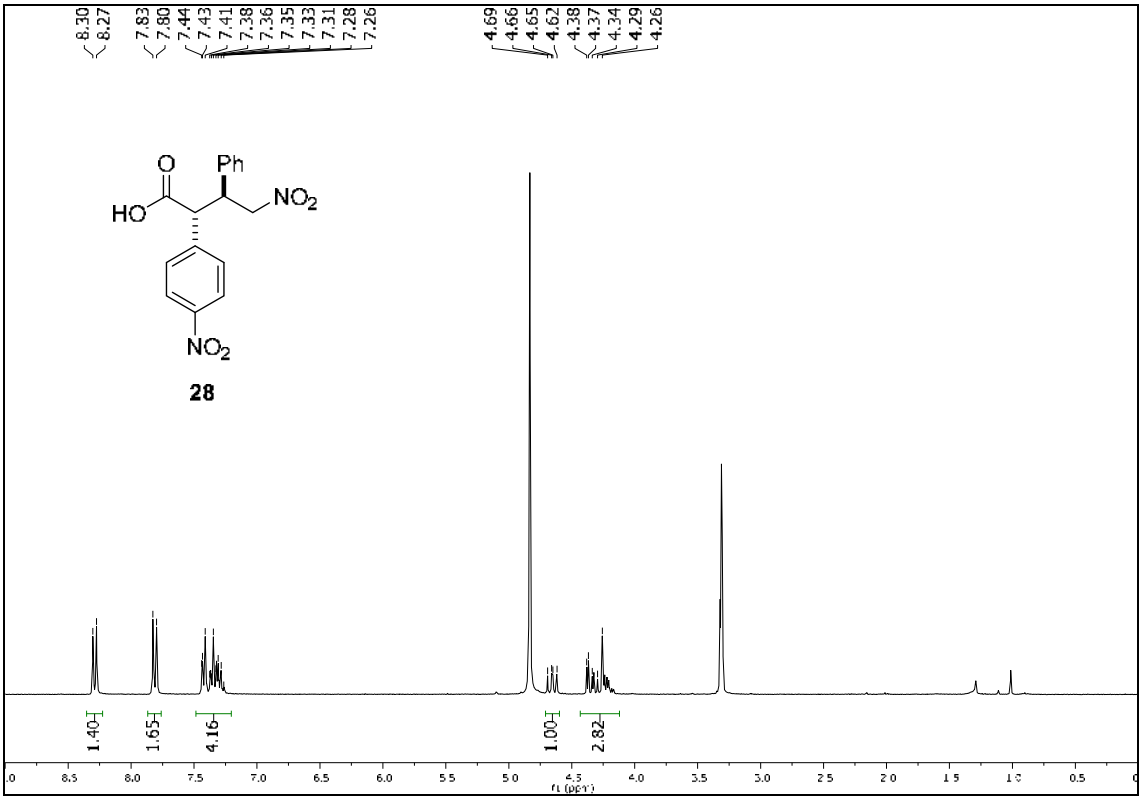
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NO2
NO2
28
1.40
1.65
4.16
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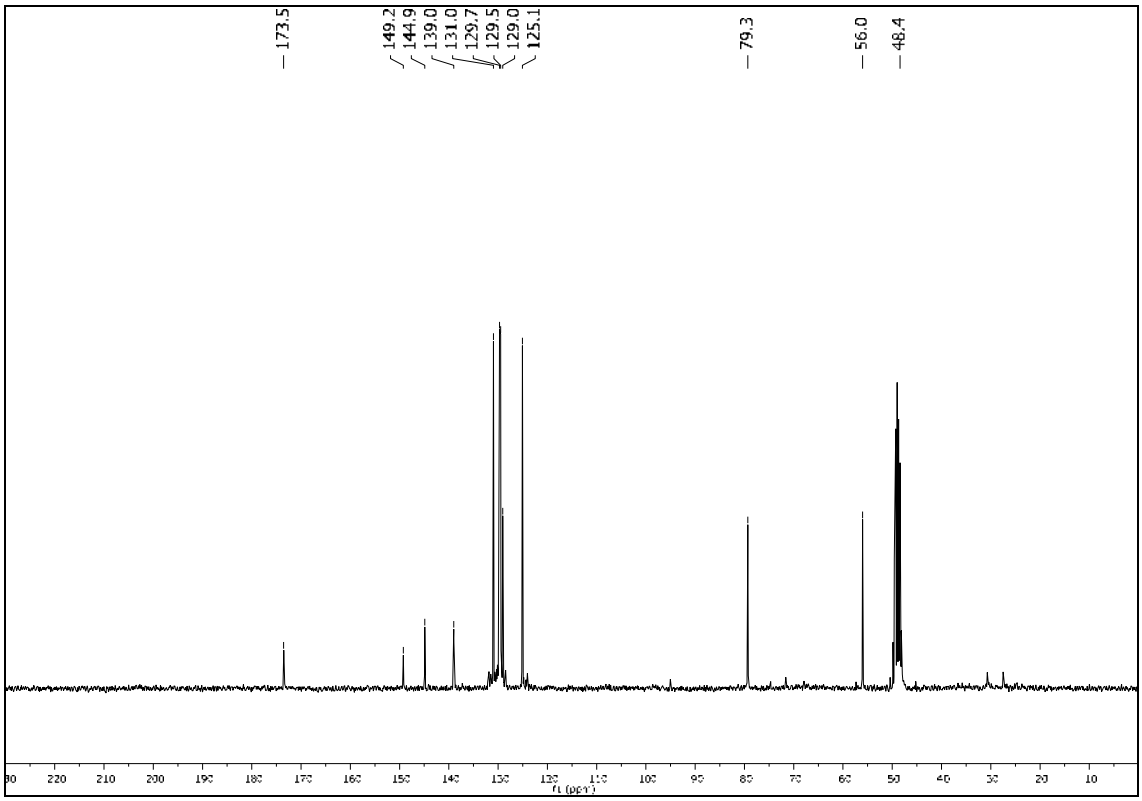
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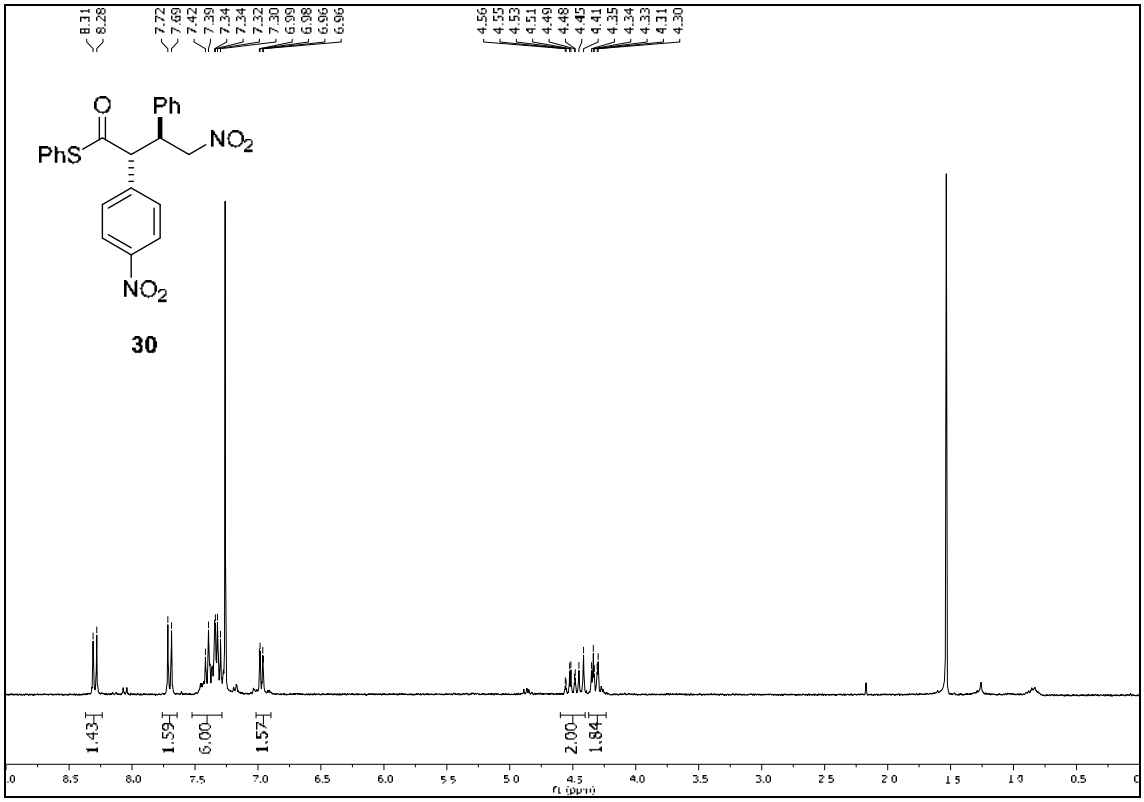
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4.35
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4.33
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PhS
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NO2
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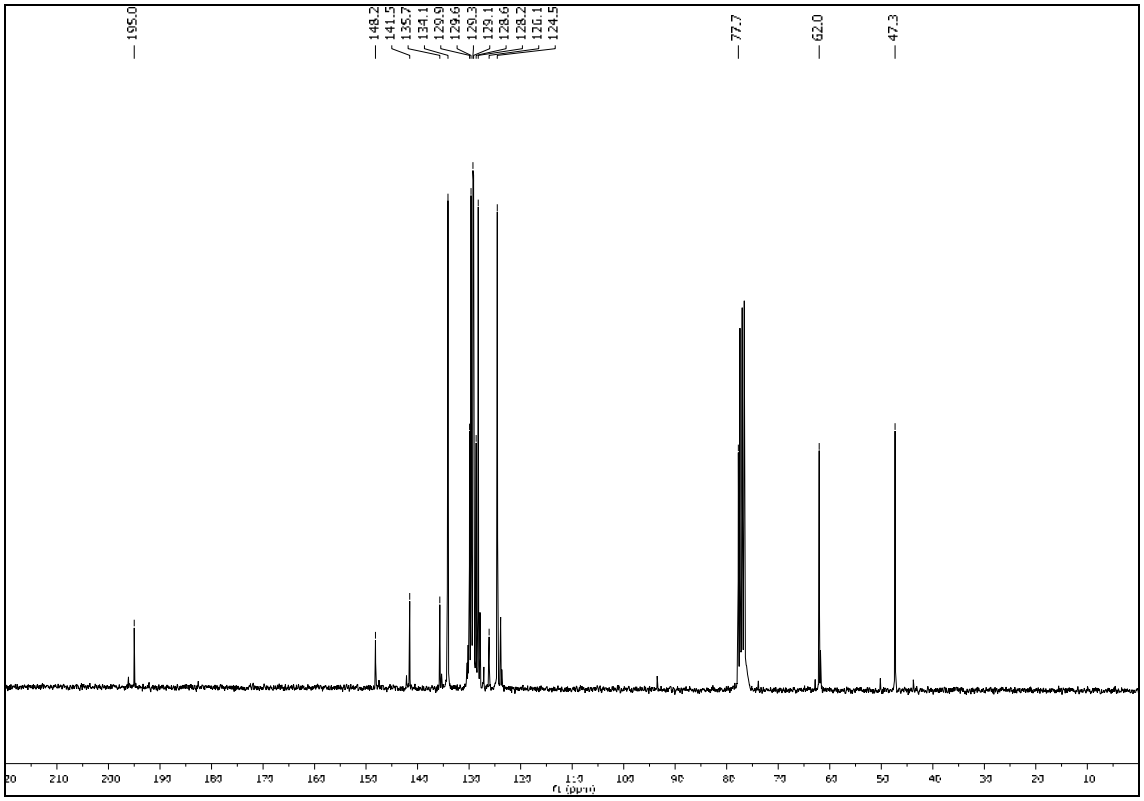
1.84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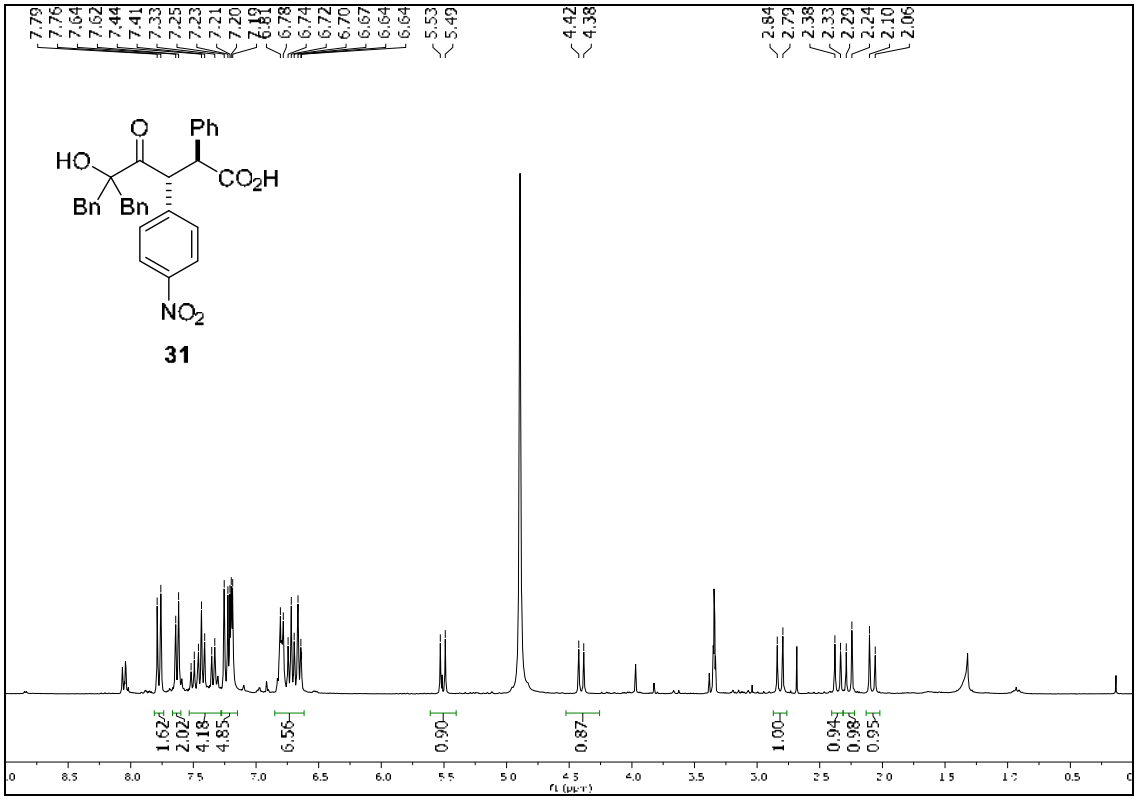
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Ph
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CO2H
Bn
Bn
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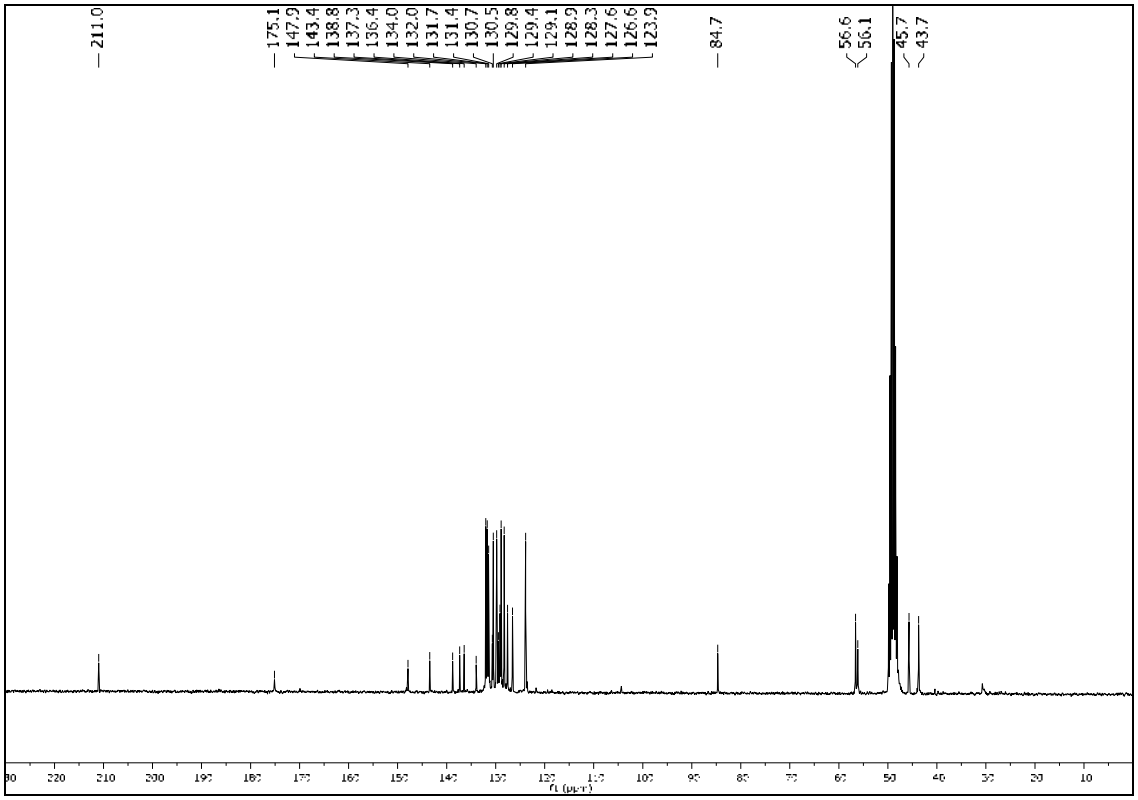
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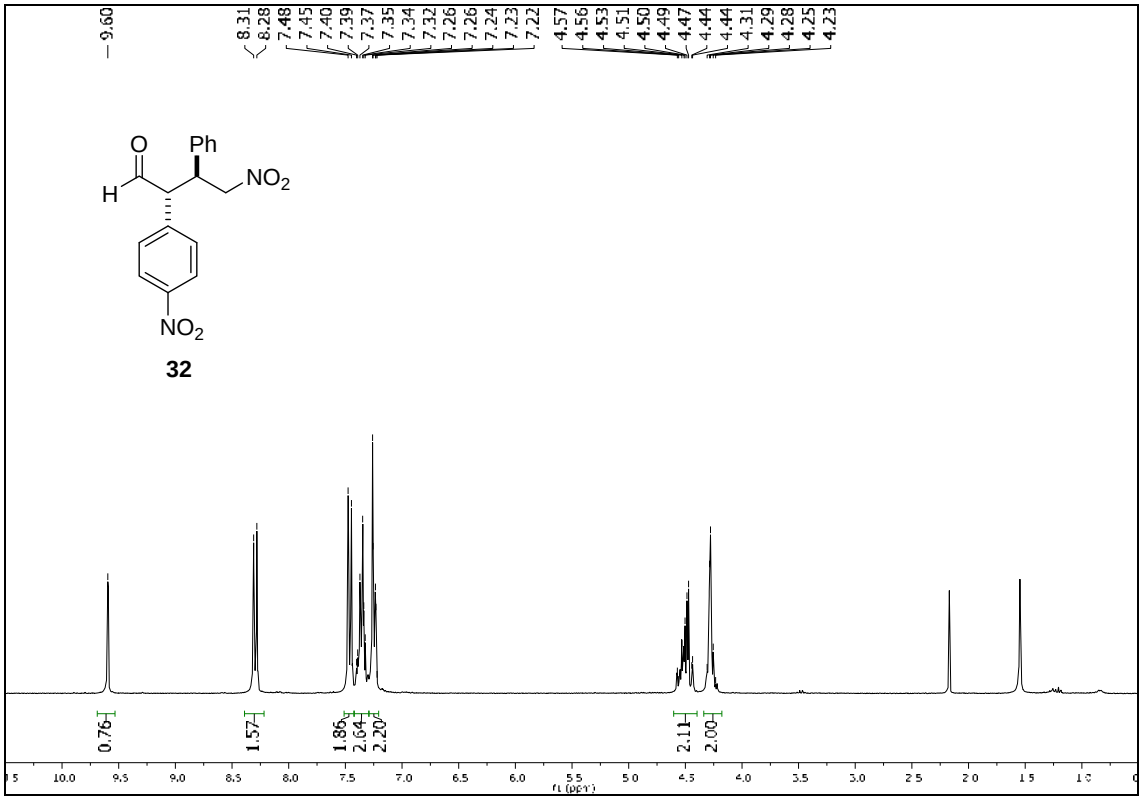
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4.47
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4.28
4.25
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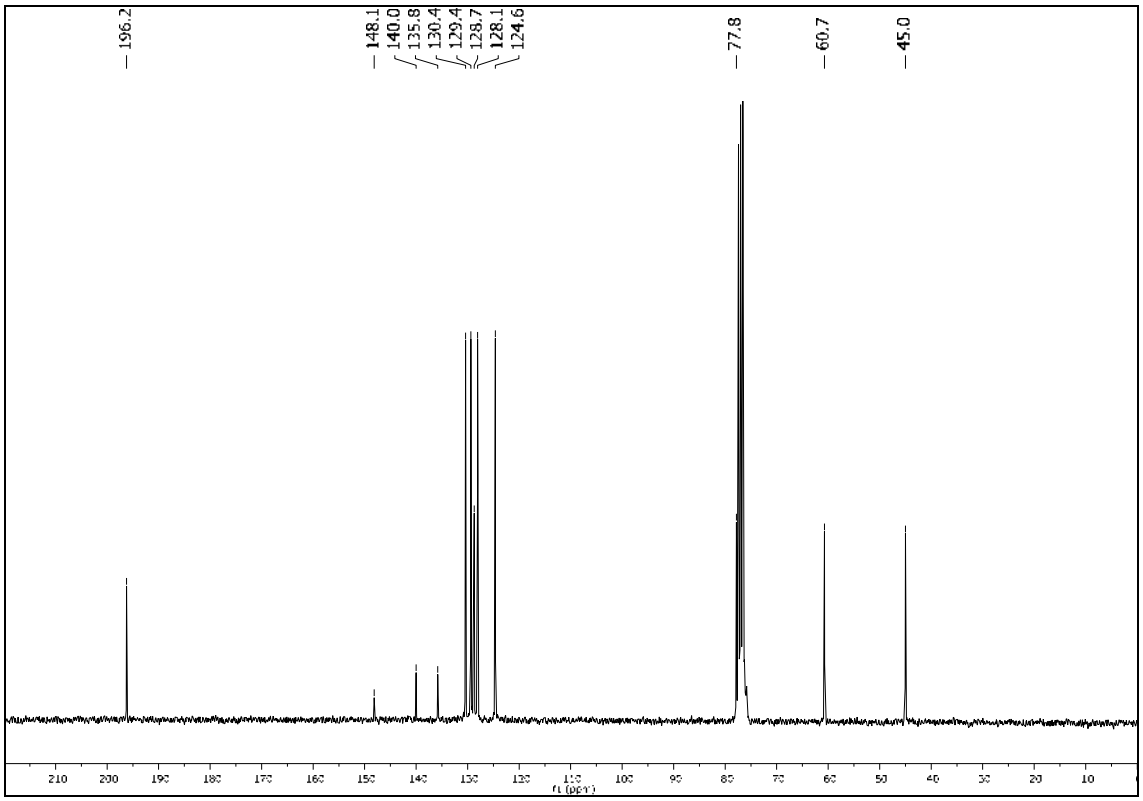
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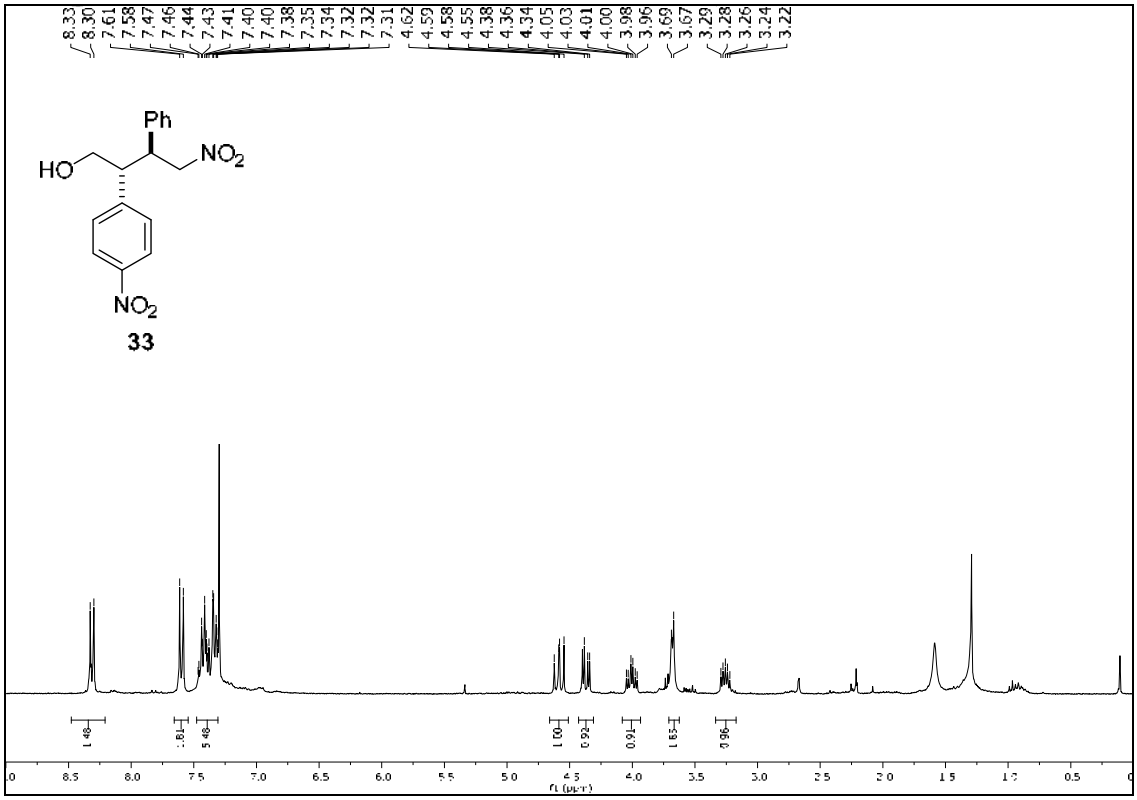
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4.00
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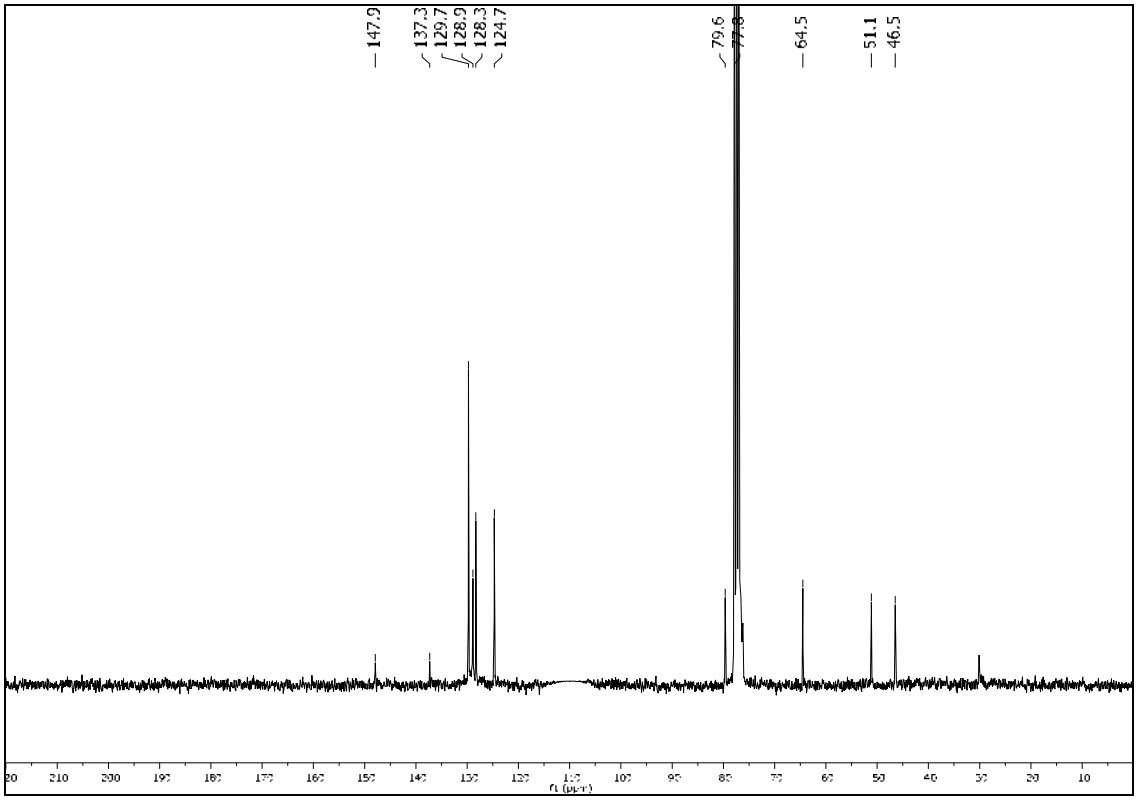
3.24
3.22
Ph
HO
NO2
NO2
33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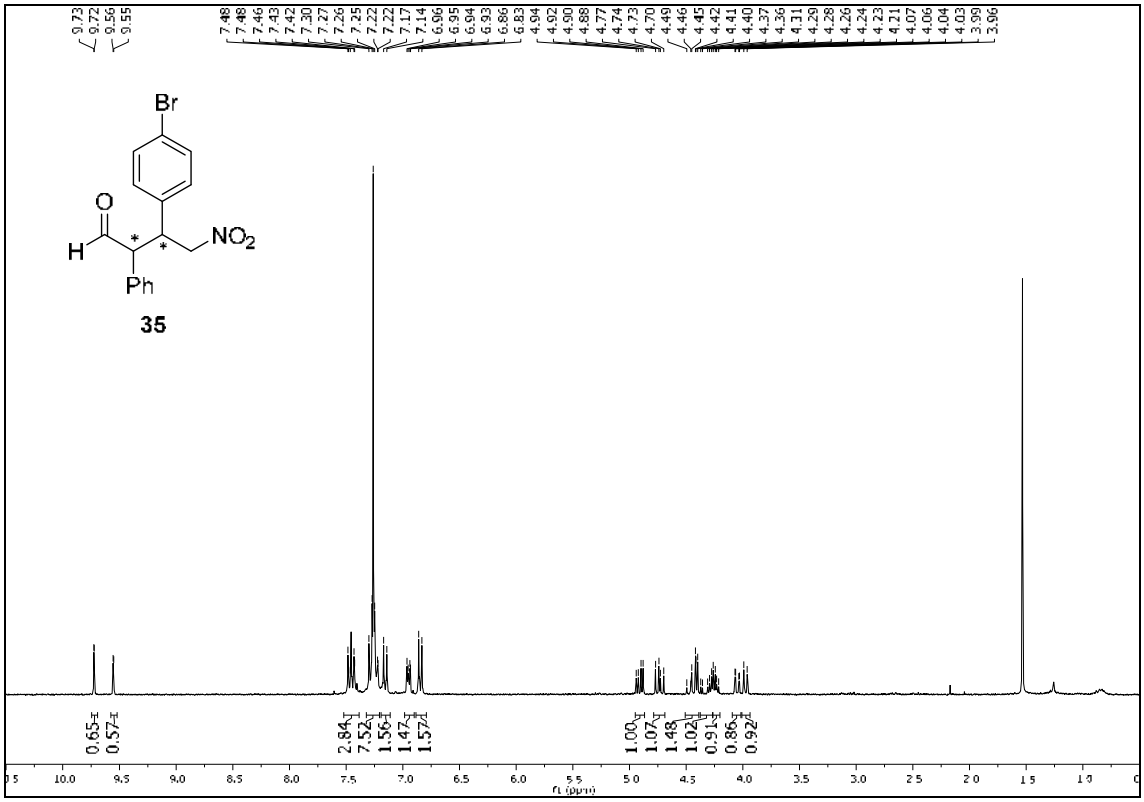
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H
*
*
NO2
Ph
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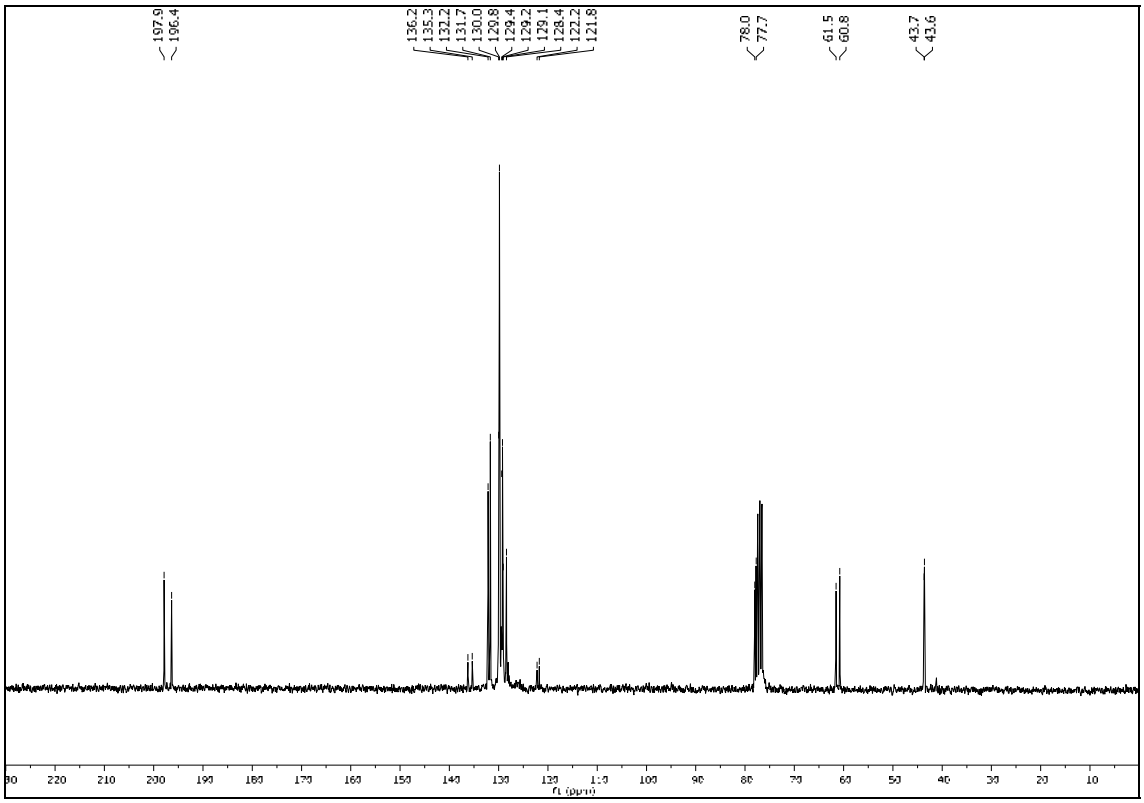

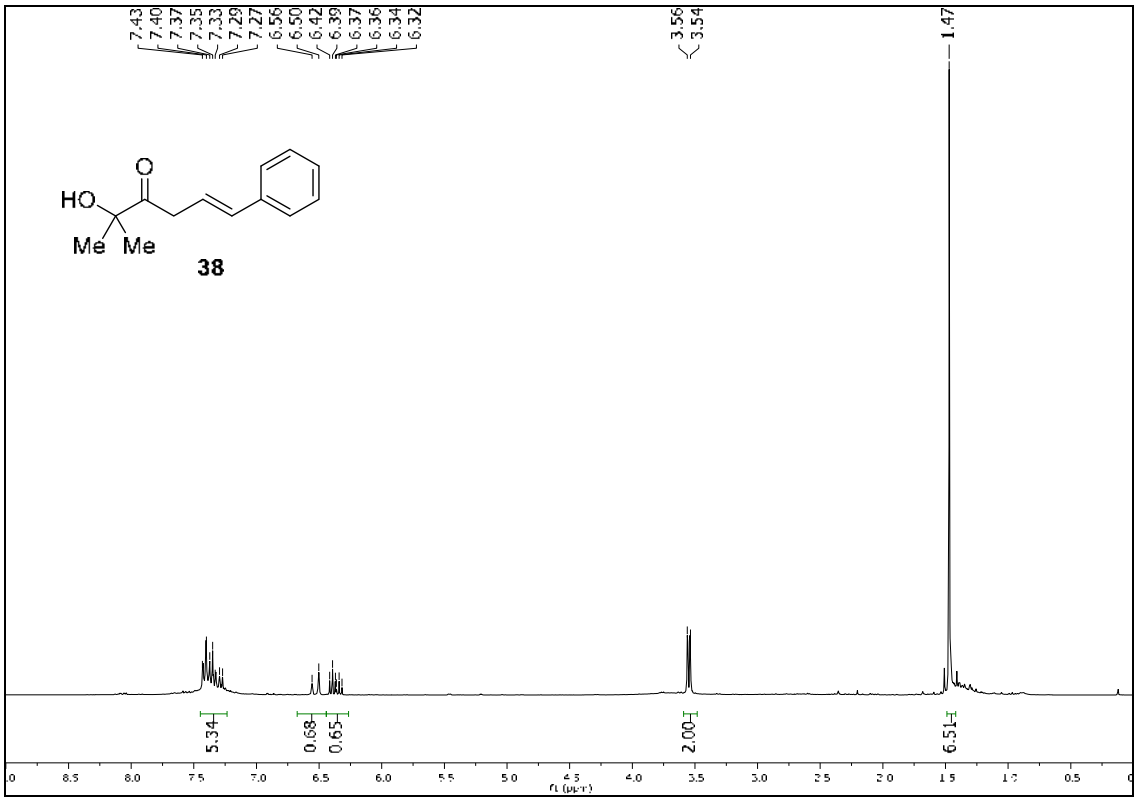
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HO
Me Me
O
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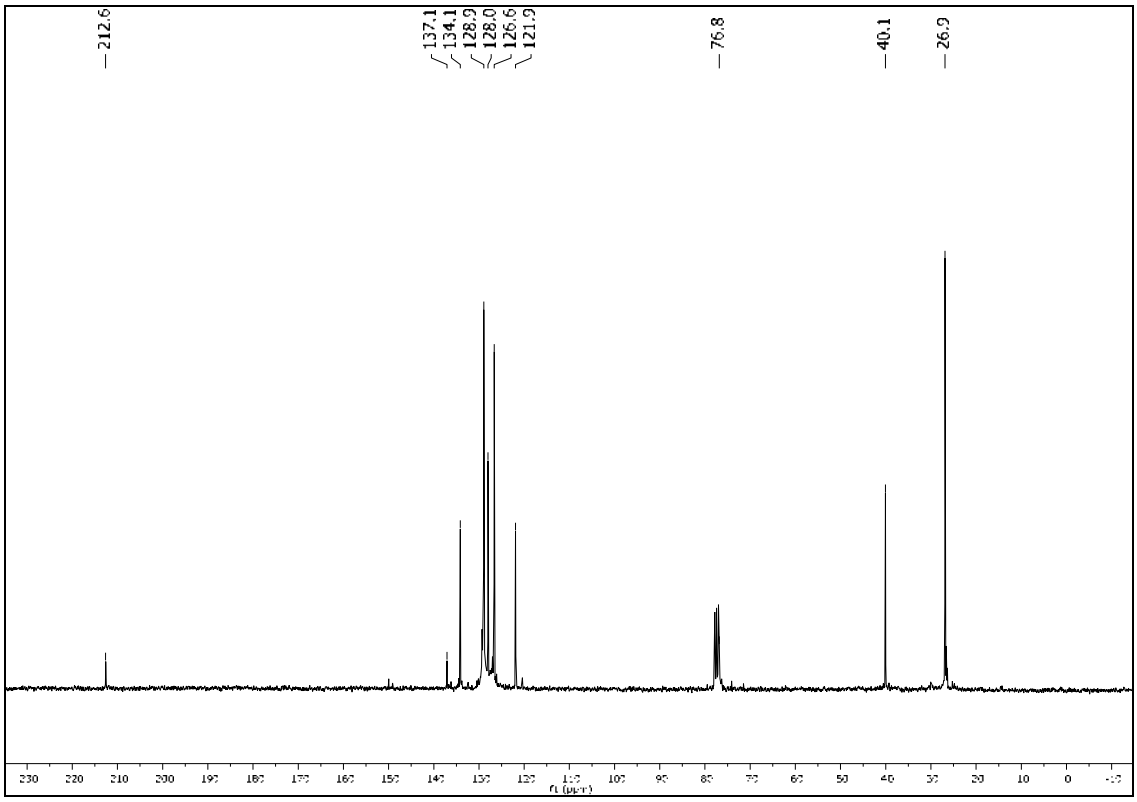
0.65
2.00
6.51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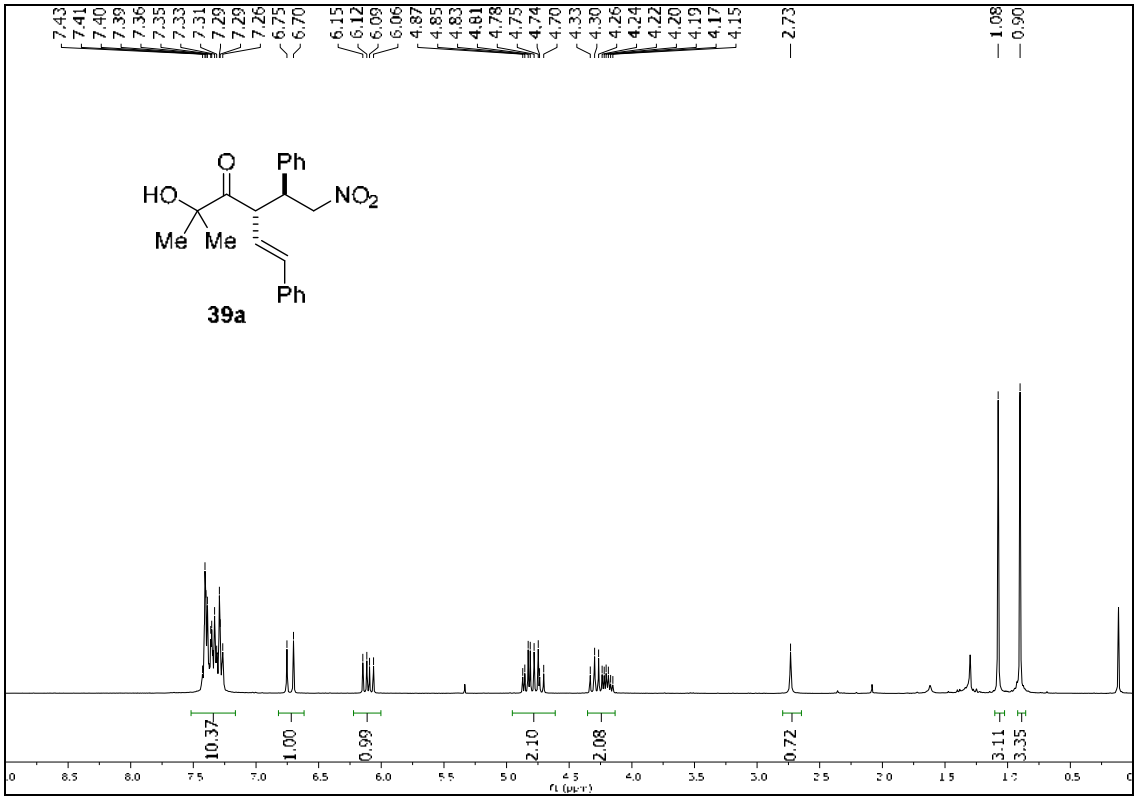
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4.24
4.22
4.20
4.19
4.17
4.15
2.73
1.08
0.90
O
Ph
HO
NO2
Me
Me
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0.72
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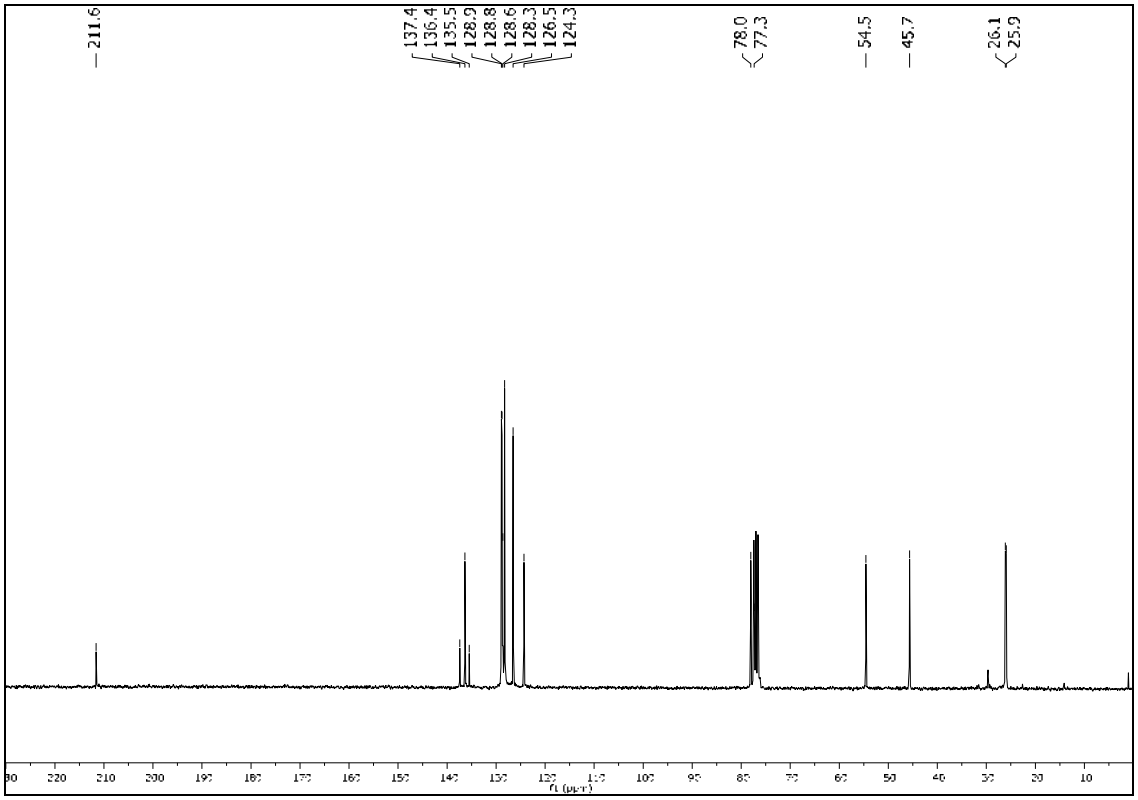
3.35
f1 (ppm)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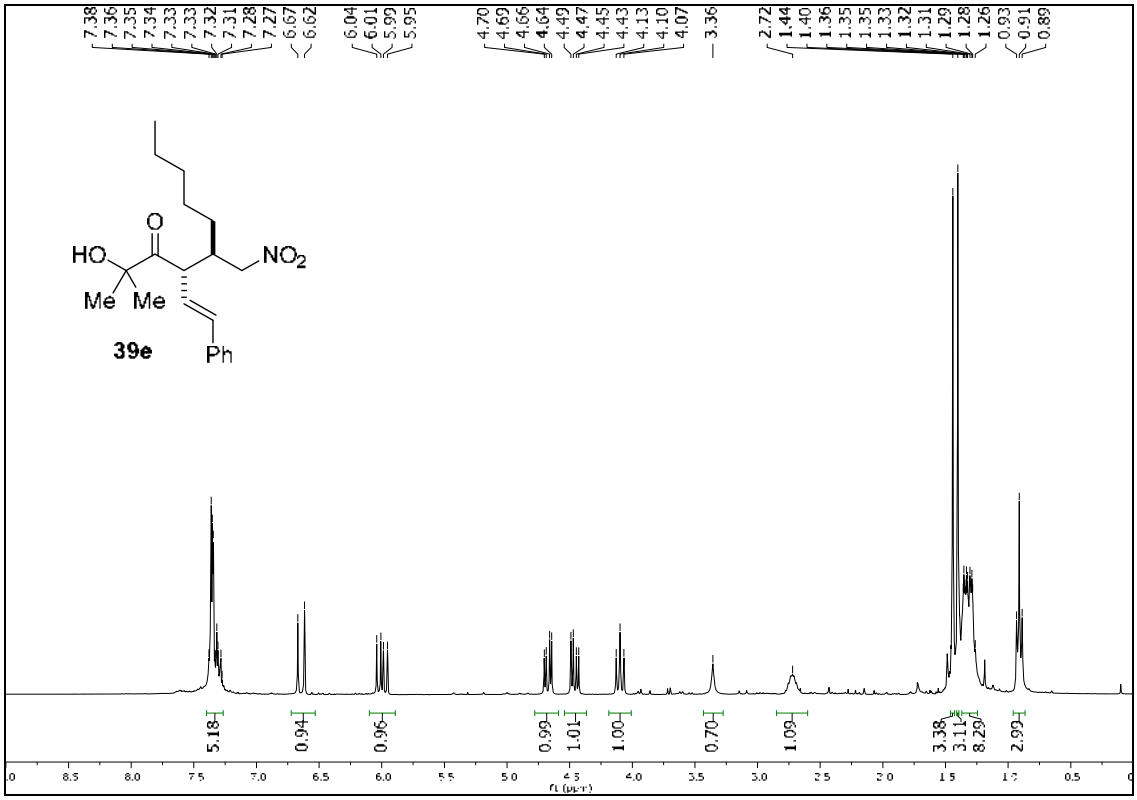
25.9
f1 (ppm)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1.28
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0.91
0.89
O
HO
NO2
Me Me
39e
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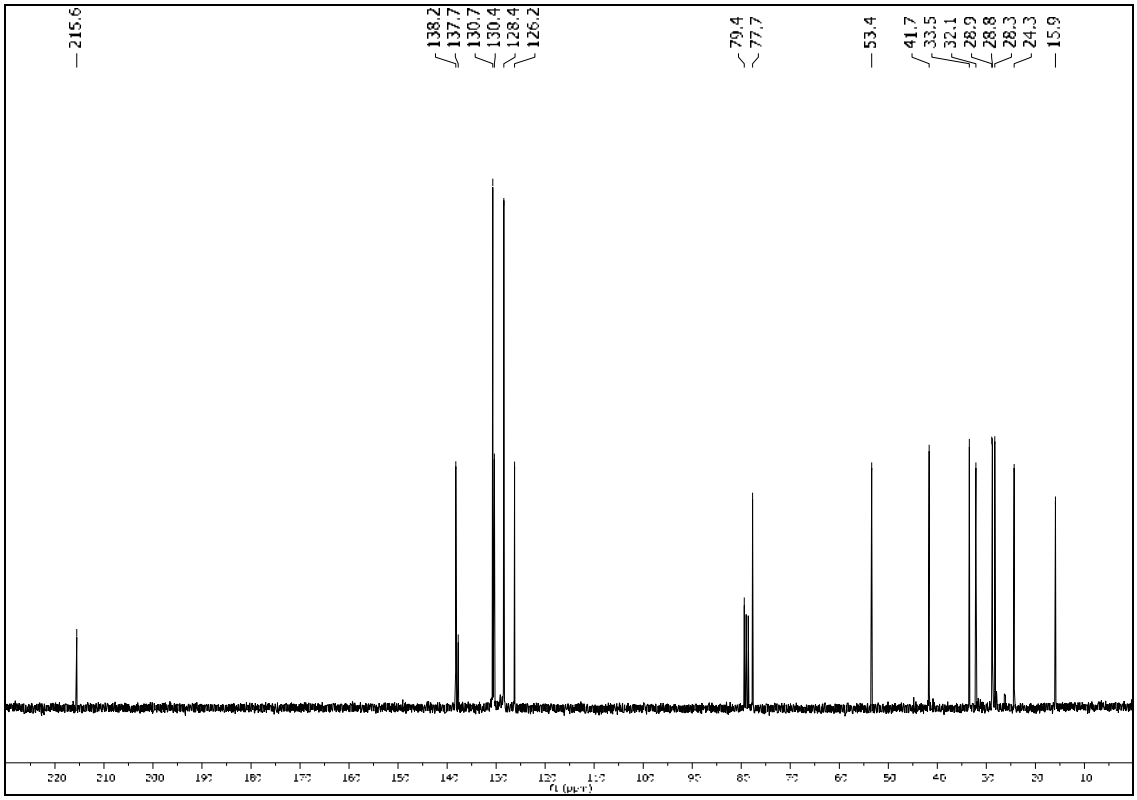
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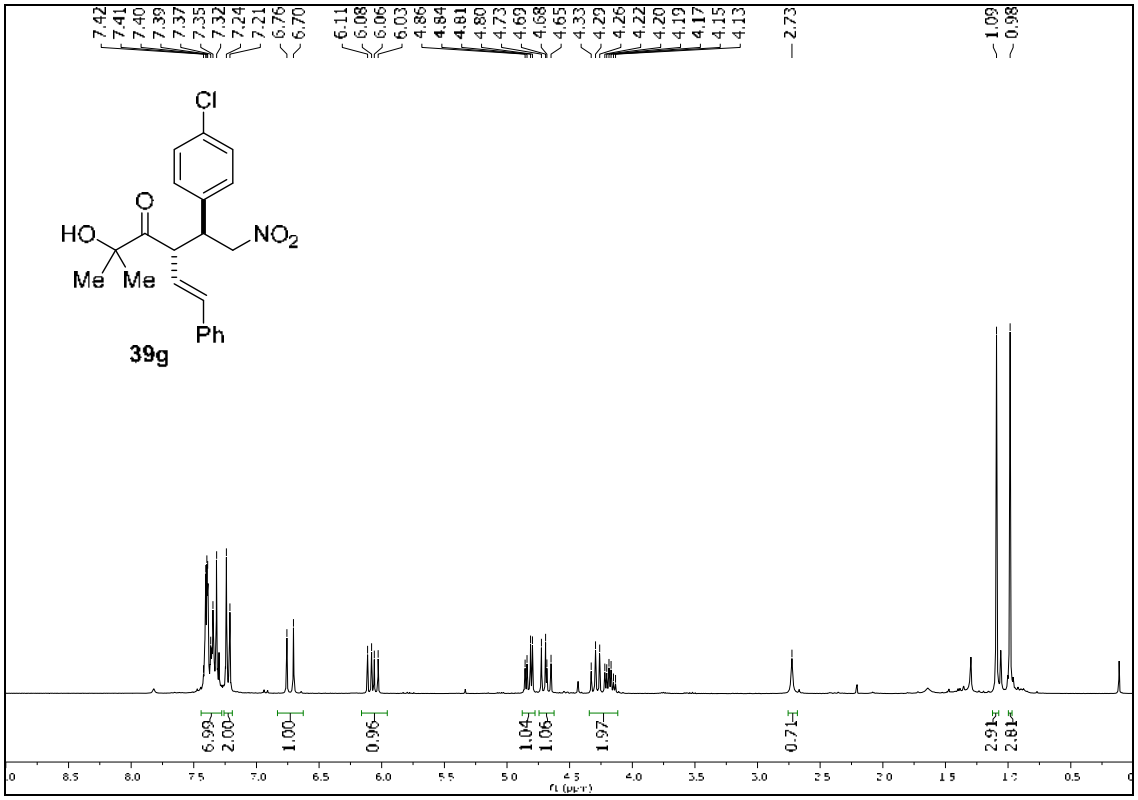
15.9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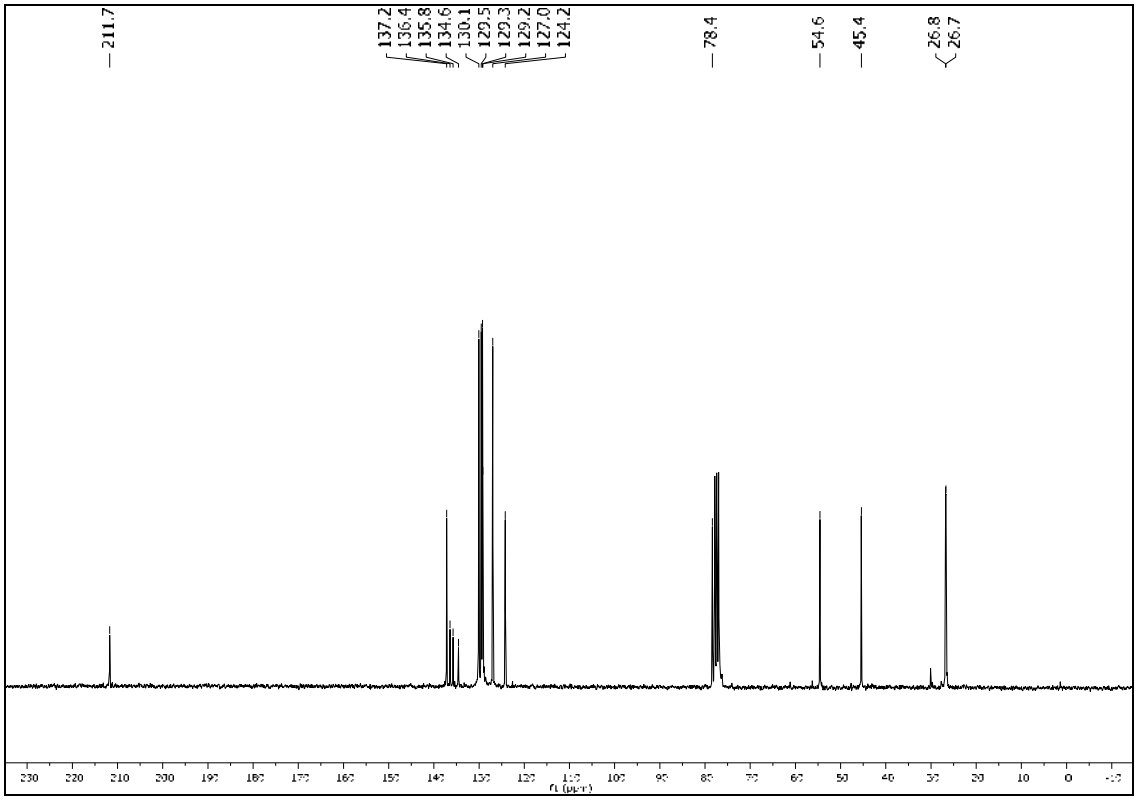
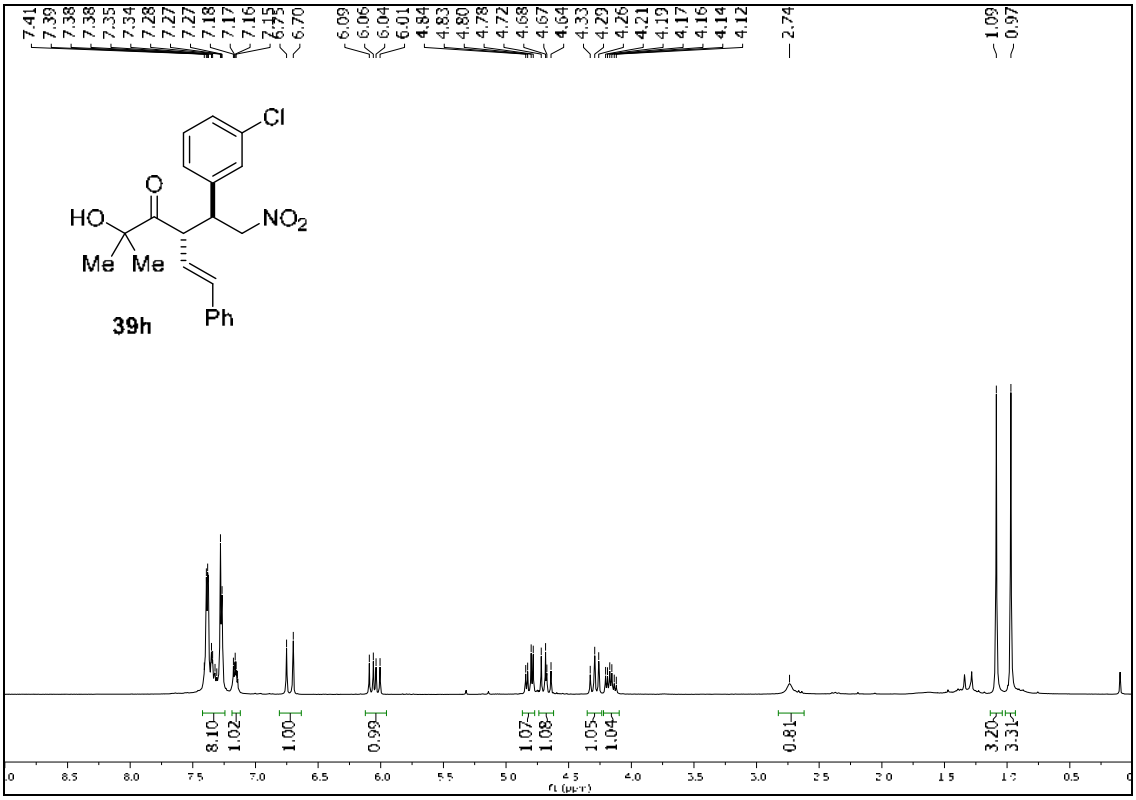
O
HO
NO2
Me Me
Ph
39g

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HO
NO2
Me
Me
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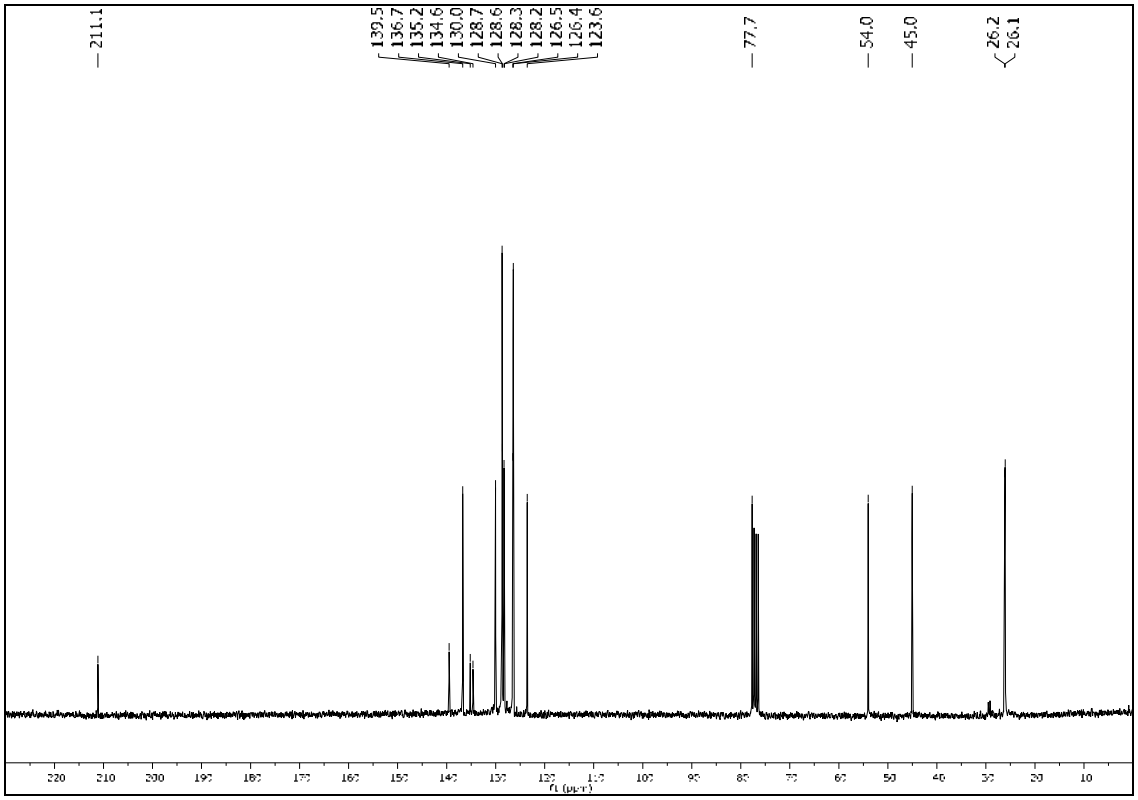
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77.7
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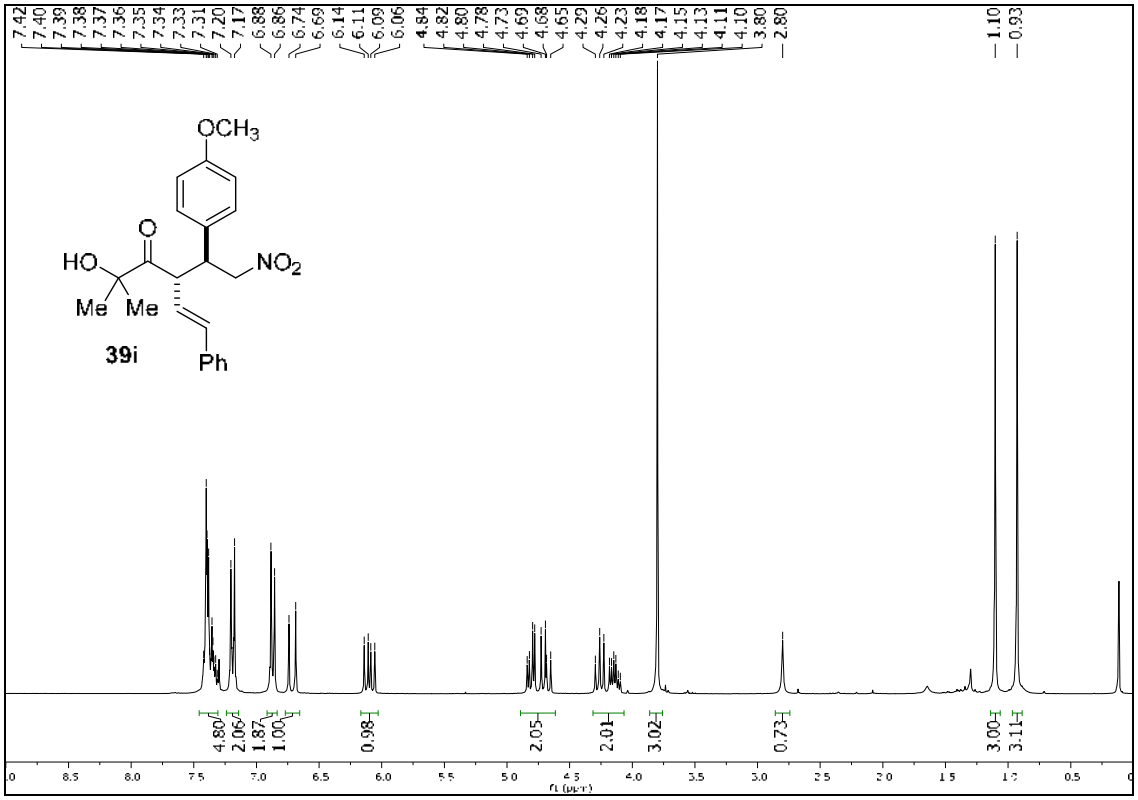
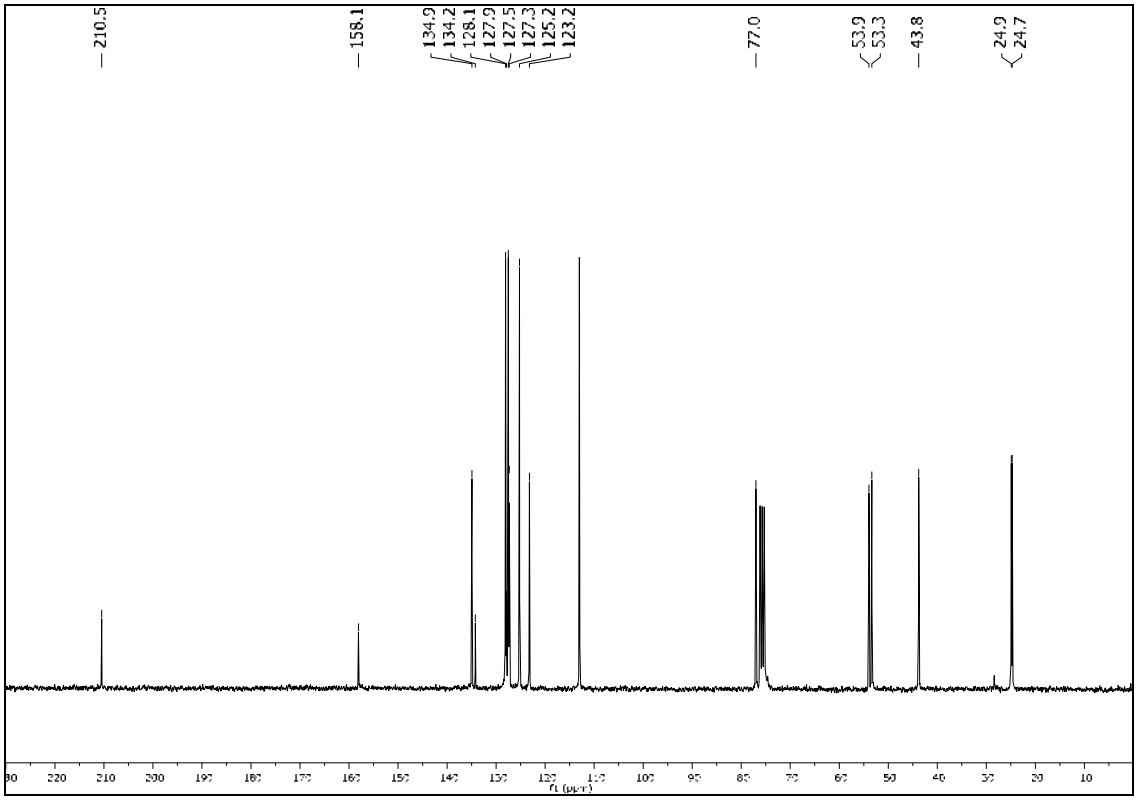
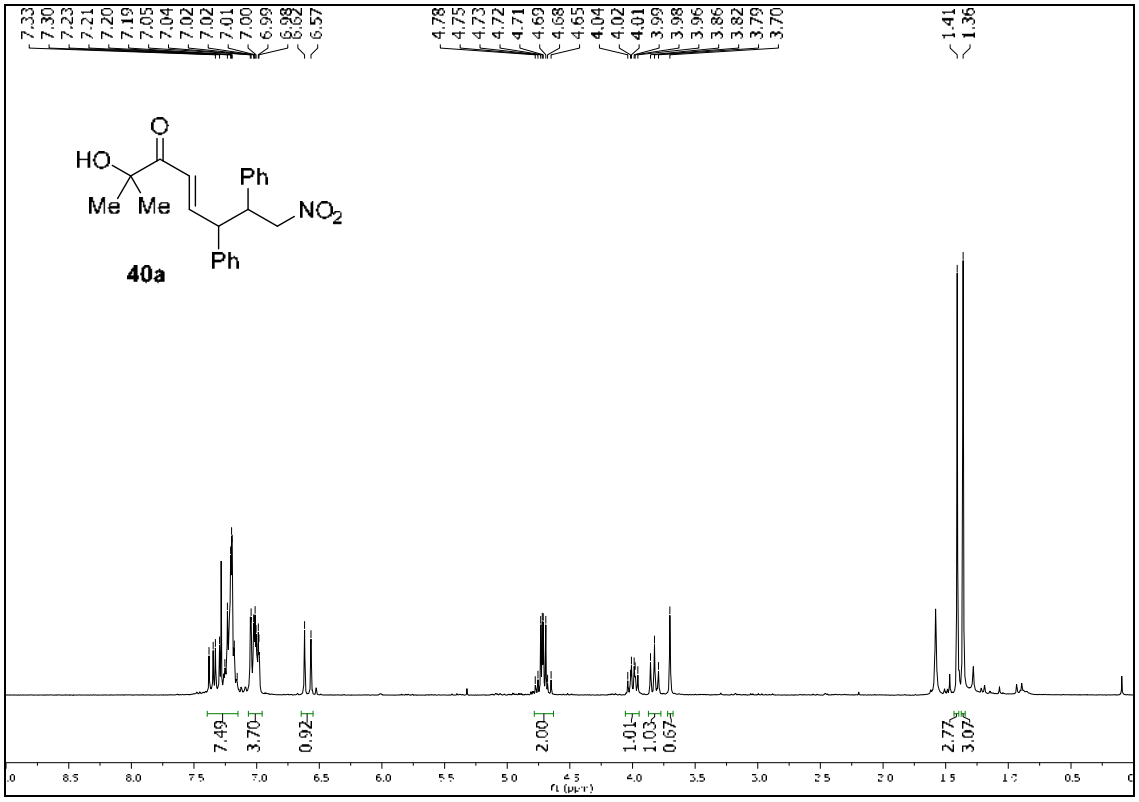
26.1


OCH3
O
HO
NO2
Me Me
Ph
39i

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1.41
1.36
HO
O
Me
Me
Ph
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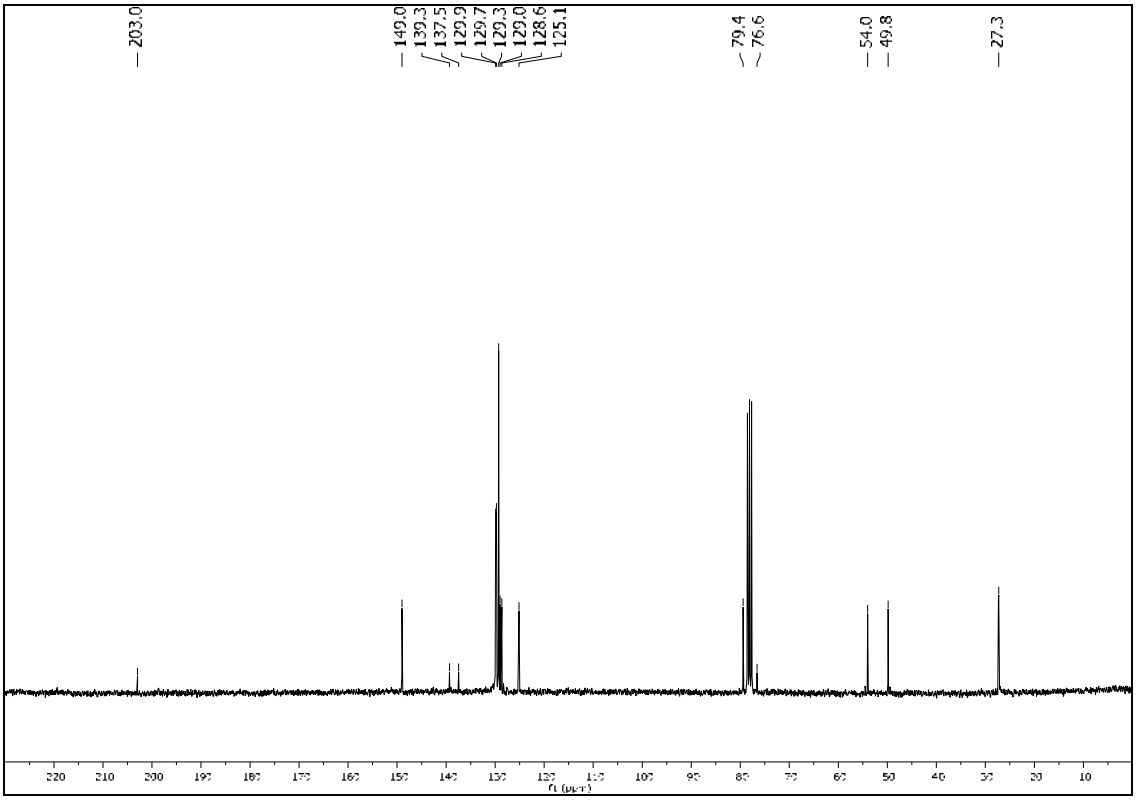
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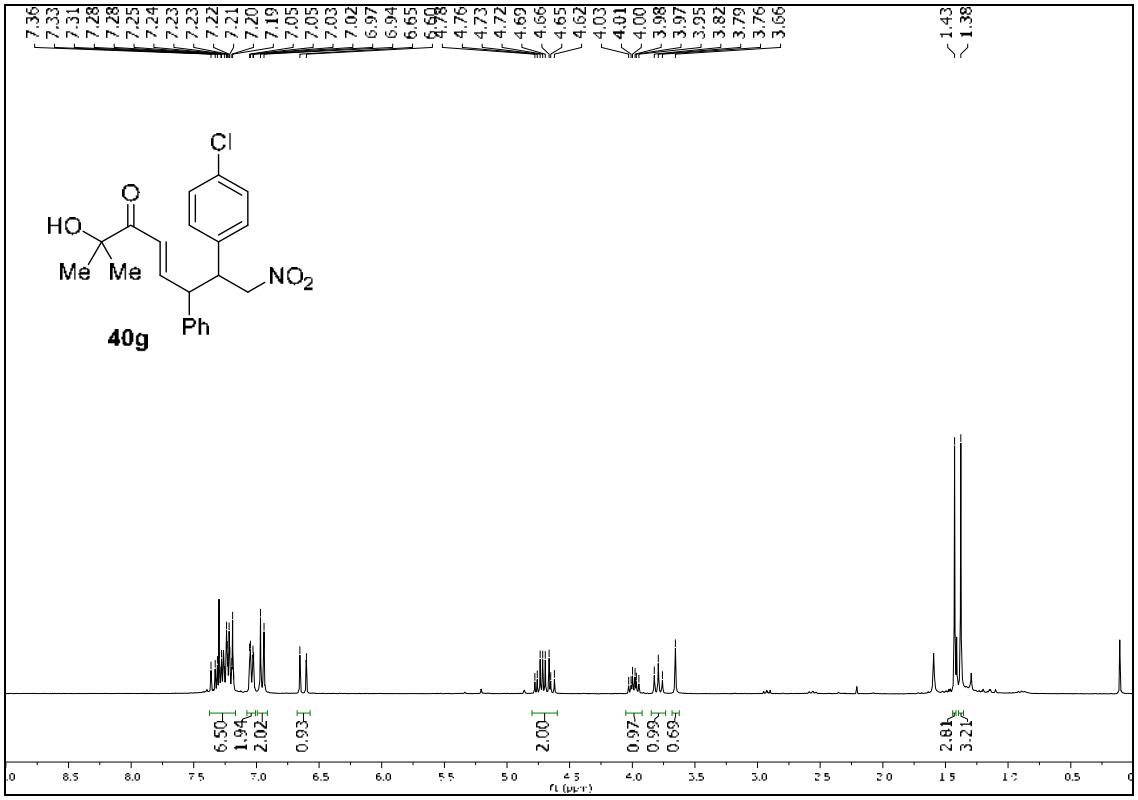
27.3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7.05
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7.02
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4.76
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4.72
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4.00
3.98
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3.79
3.76
3.66
1.43
1.38
Cl
O
HO
Me
Me
NO2
Ph
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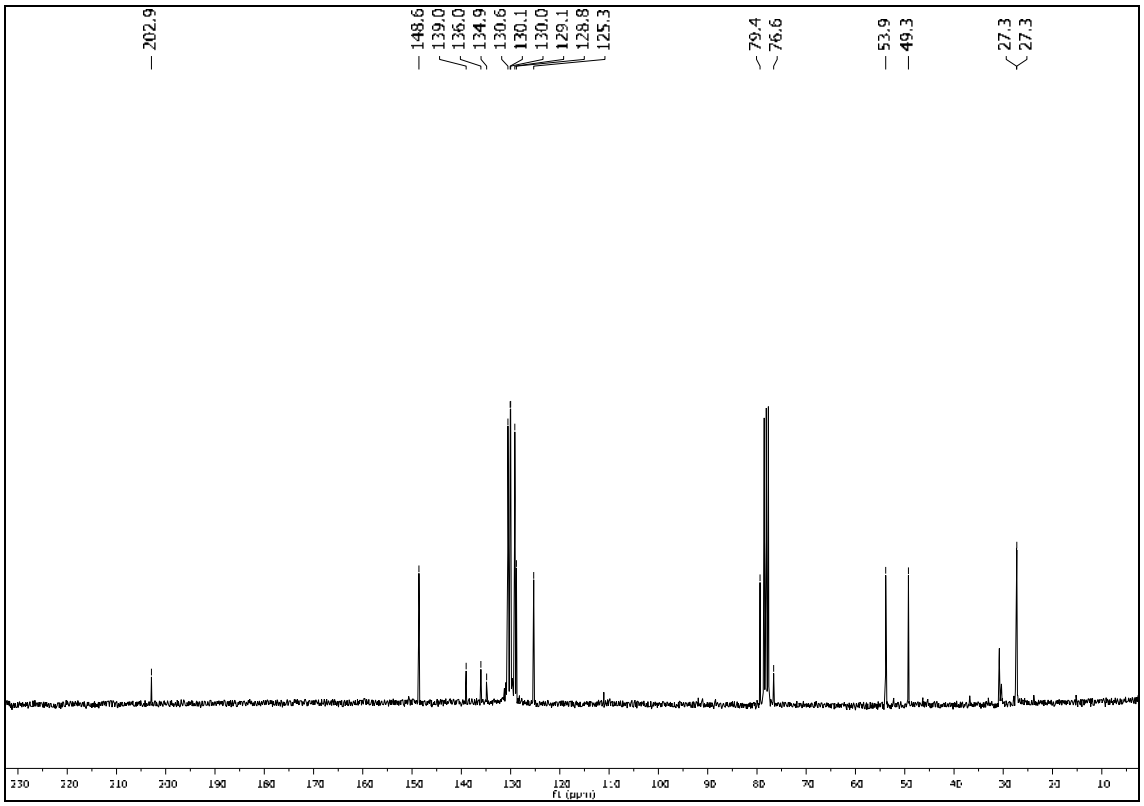
f1 (ppm)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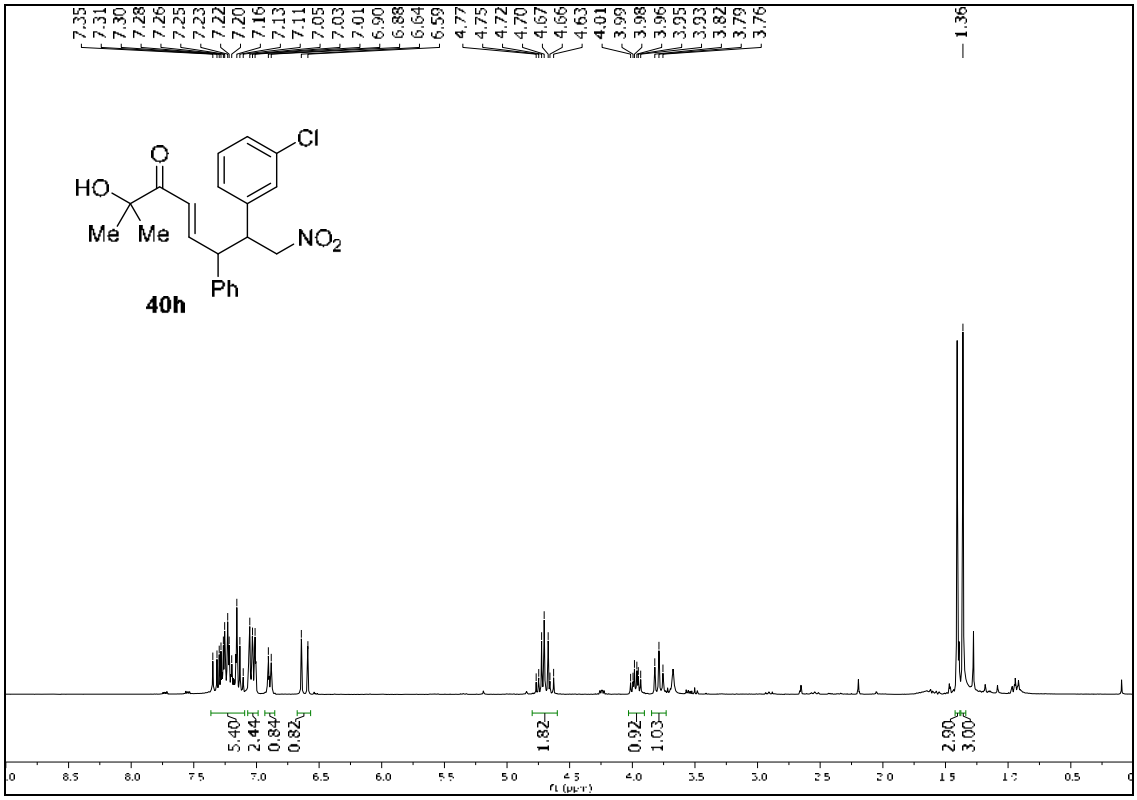
76.6
53.9
49.3
27.3
27.3
f1 (ppm)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3.82
3.79
3.76
1.36
Cl
O
HO
Me
Me
NO2
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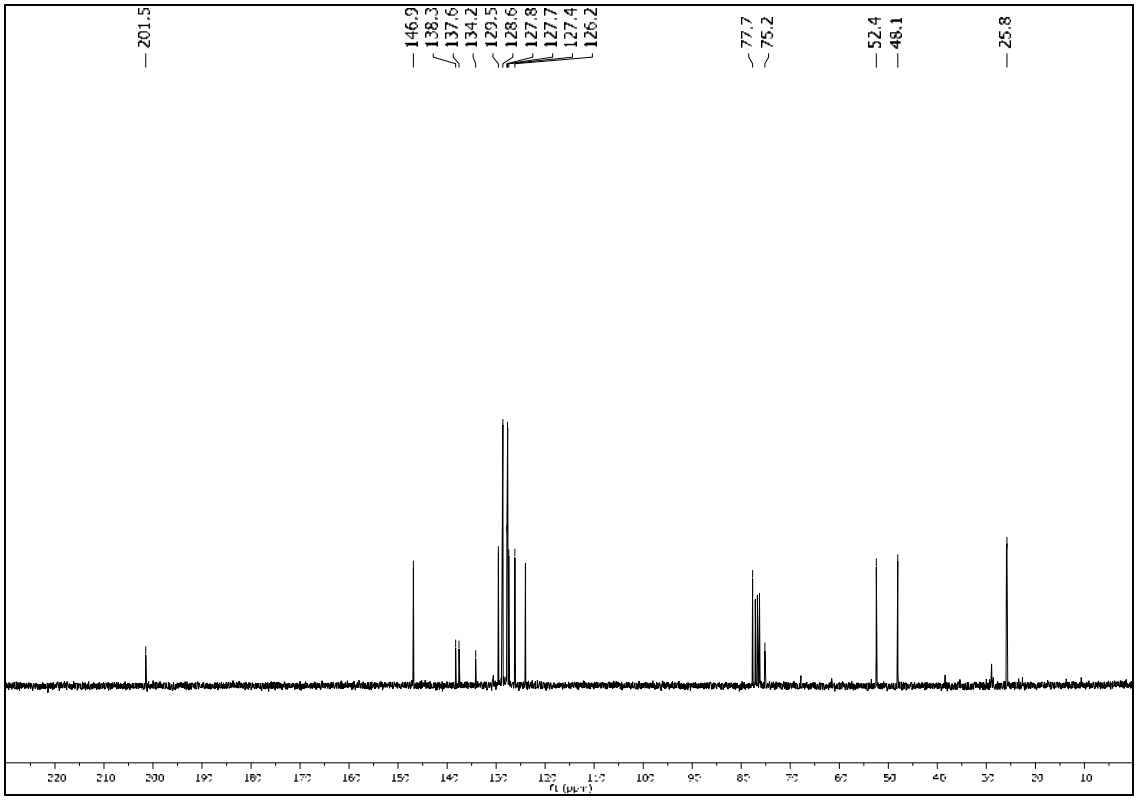
3.00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77.7
75.2
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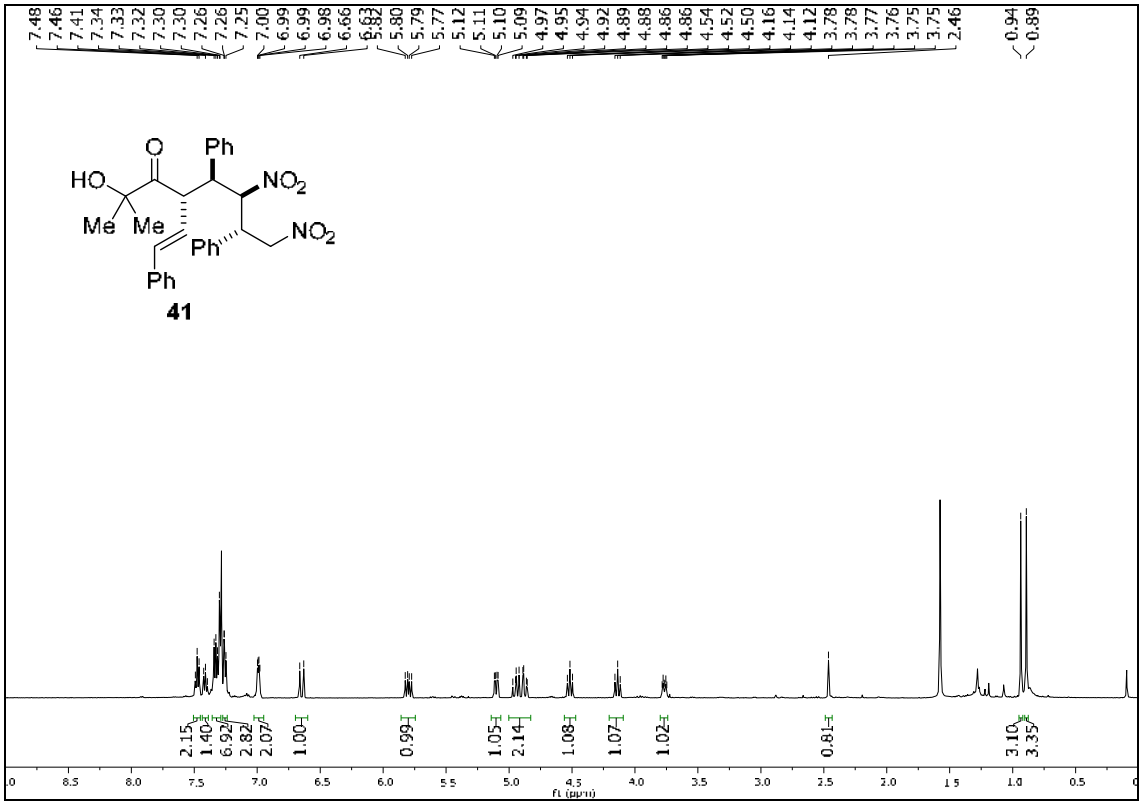
48.1
25.8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4.86
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3.78
3.77
3.76
3.75
3.75
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0.94
0.89
O
Ph
HO
NO2
Me
Me
Ph
NO2
Ph
41
2.15
1.40
6.92
2.82
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1.02
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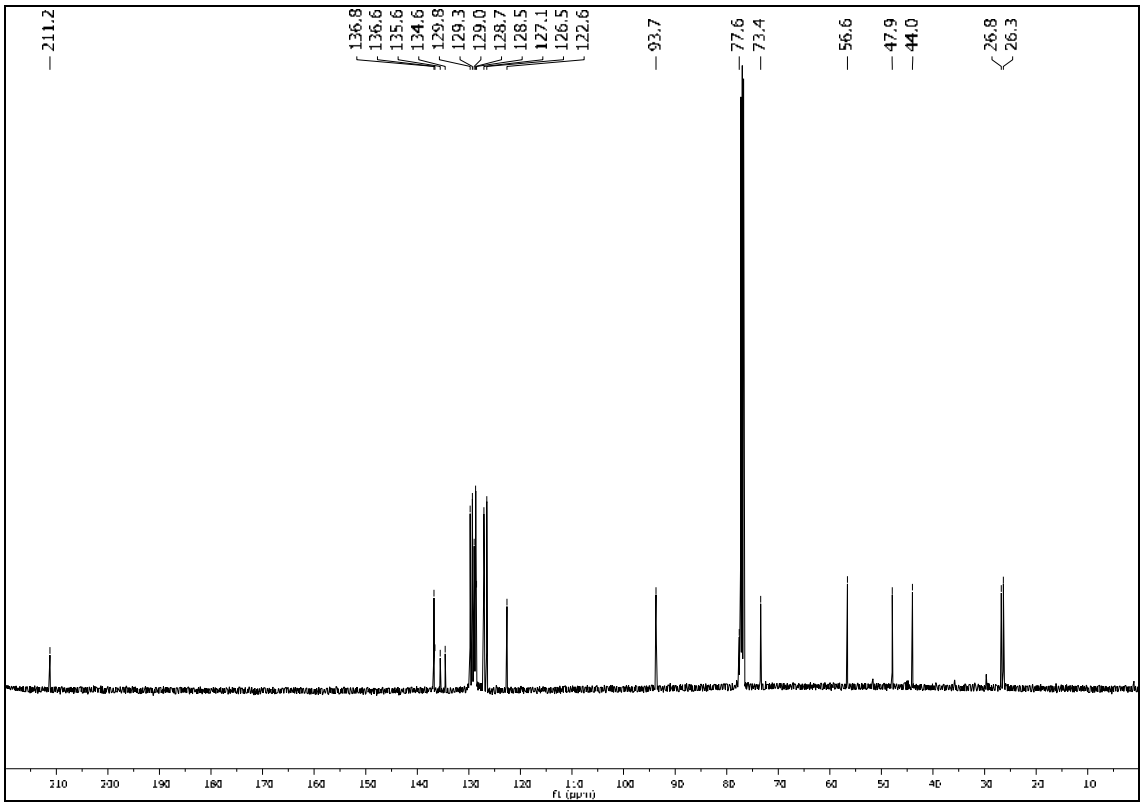
f1 (ppm)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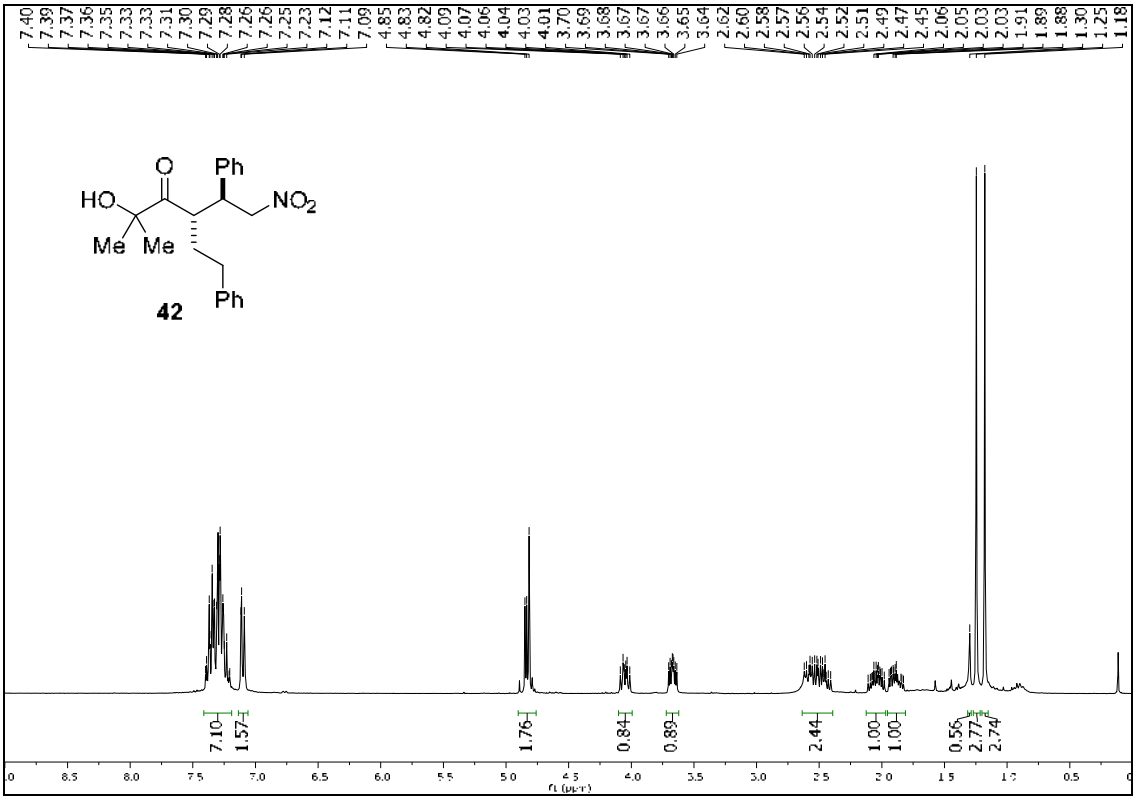
f1 (ppm)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2.56
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2.51
2.49
2.47
2.45
2.06
2.05
2.03
2.03
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1.30
1.25
1.18
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Ph
HO
NO2
Me
Me
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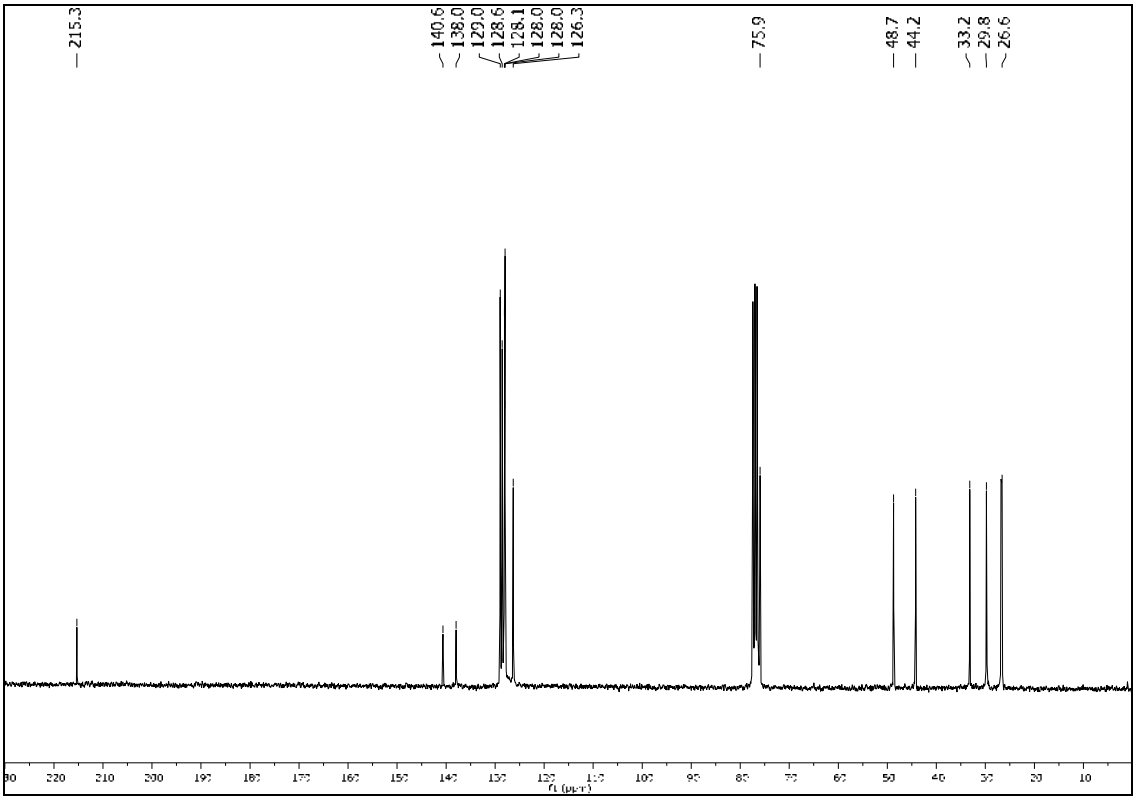
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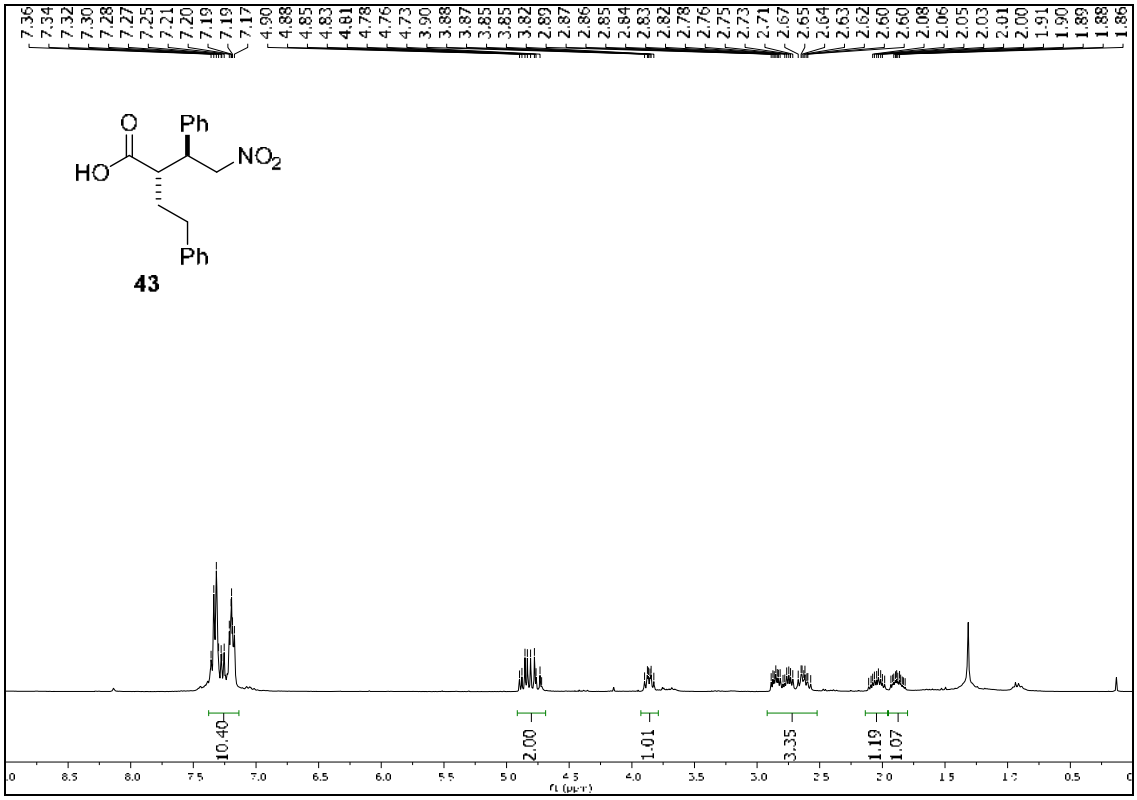
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2.05
2.03
2.01
2.00
1.91
1.90
1.89
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HO
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Ph
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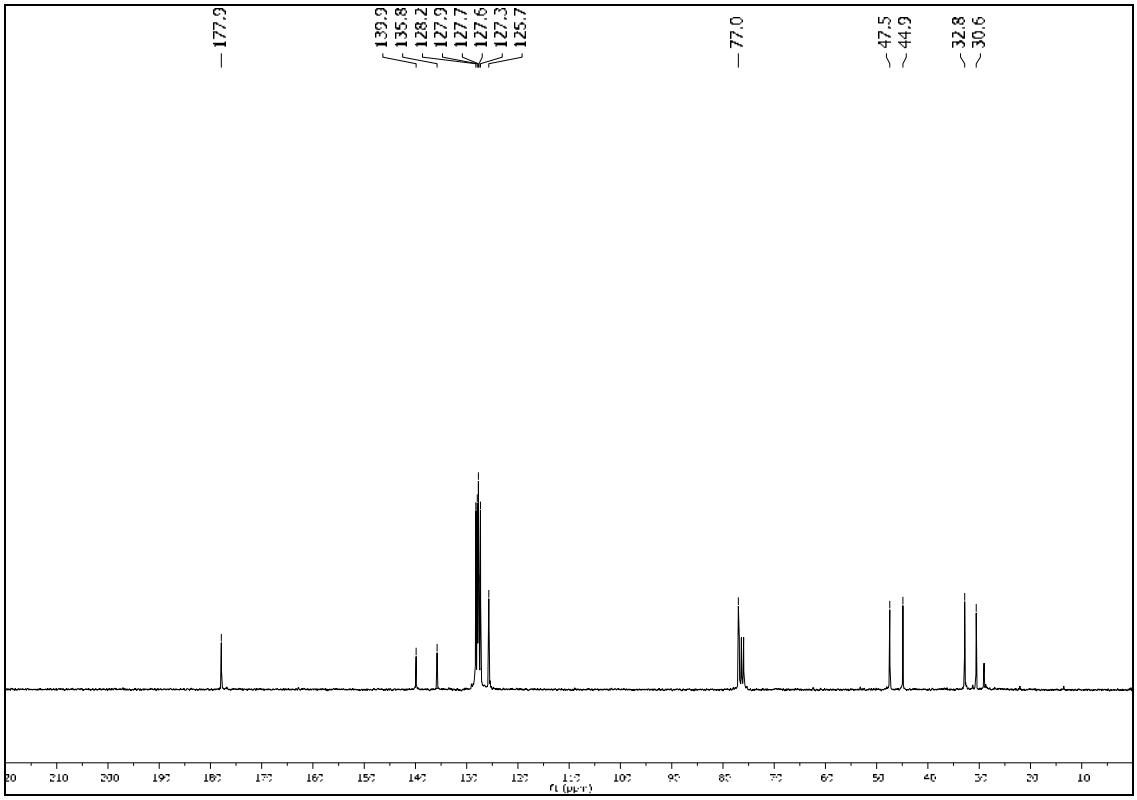
1.07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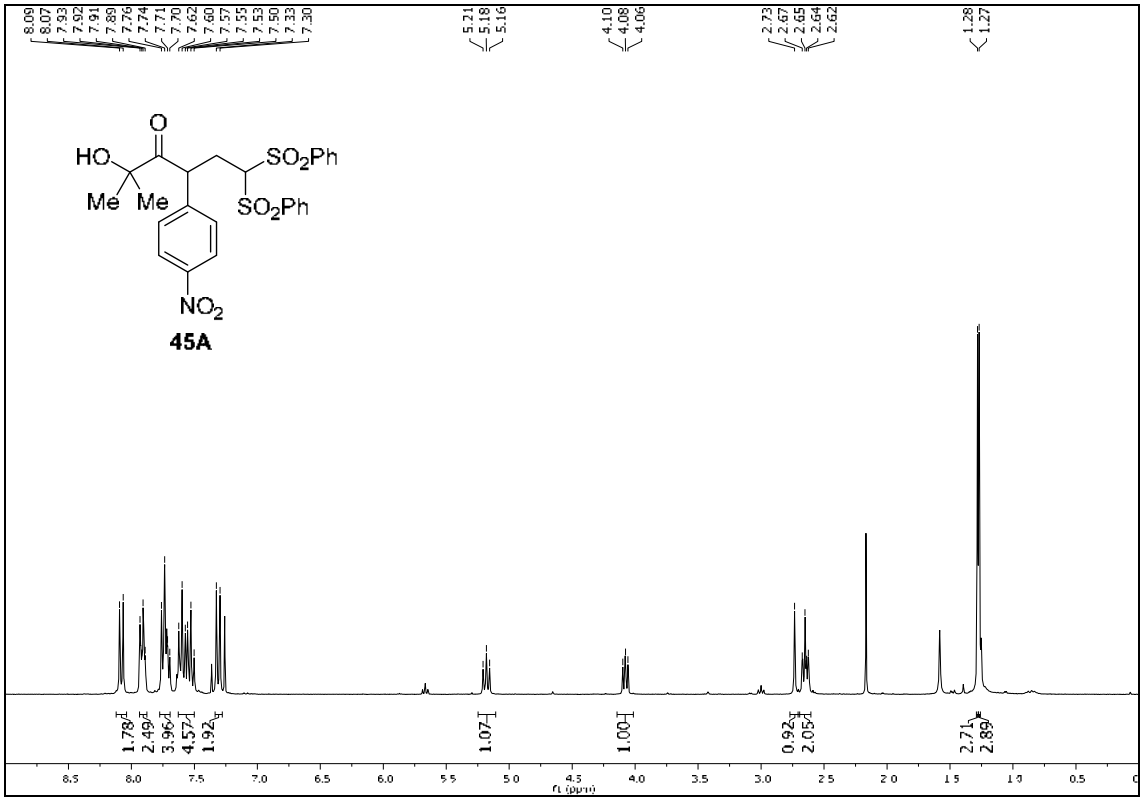
30.6



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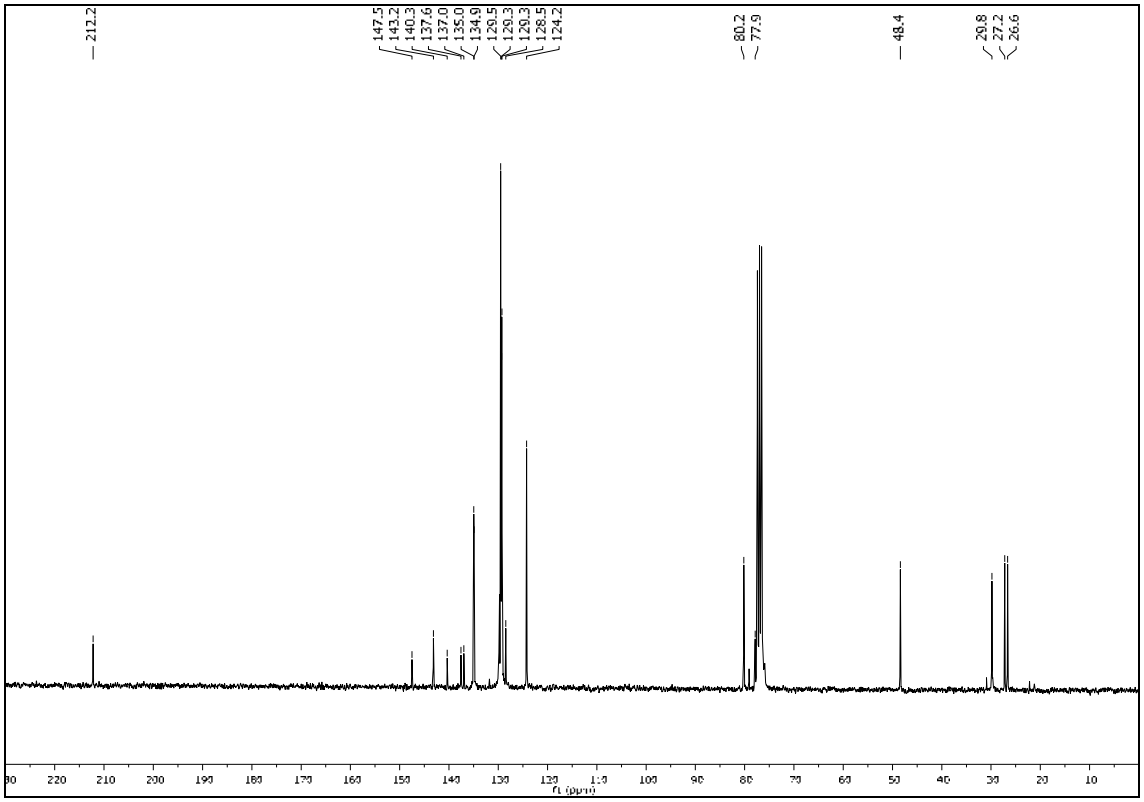
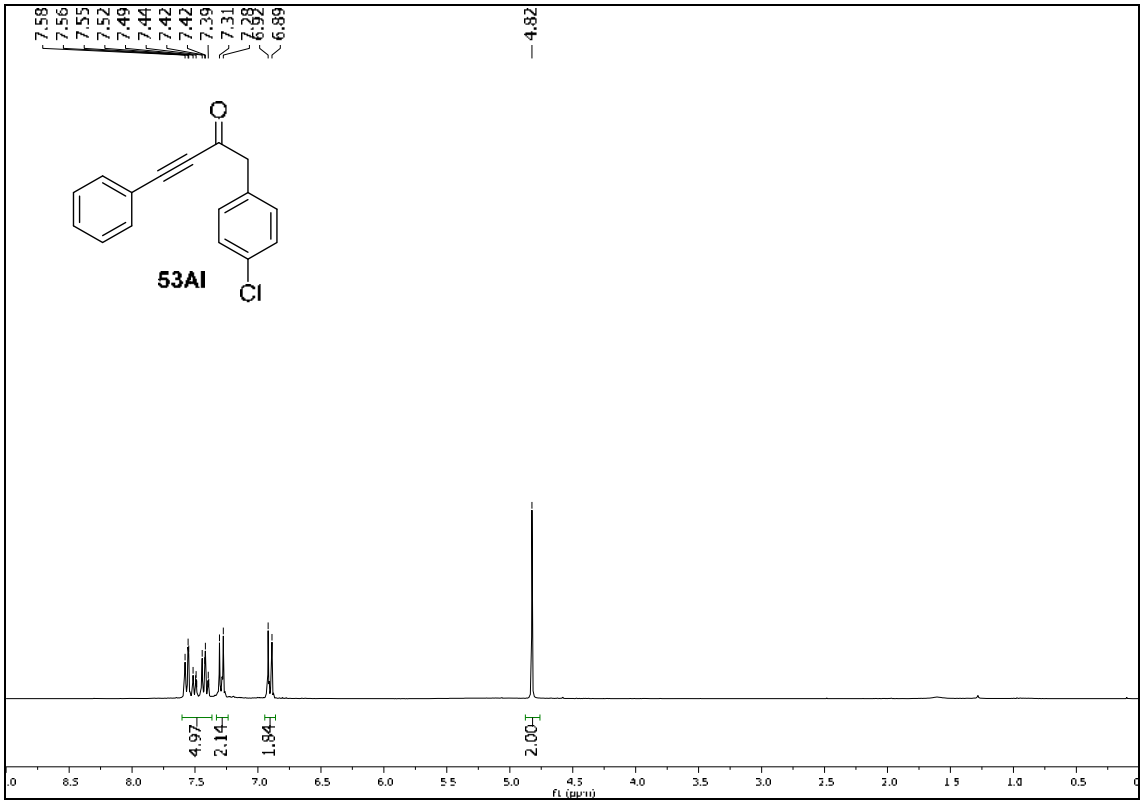
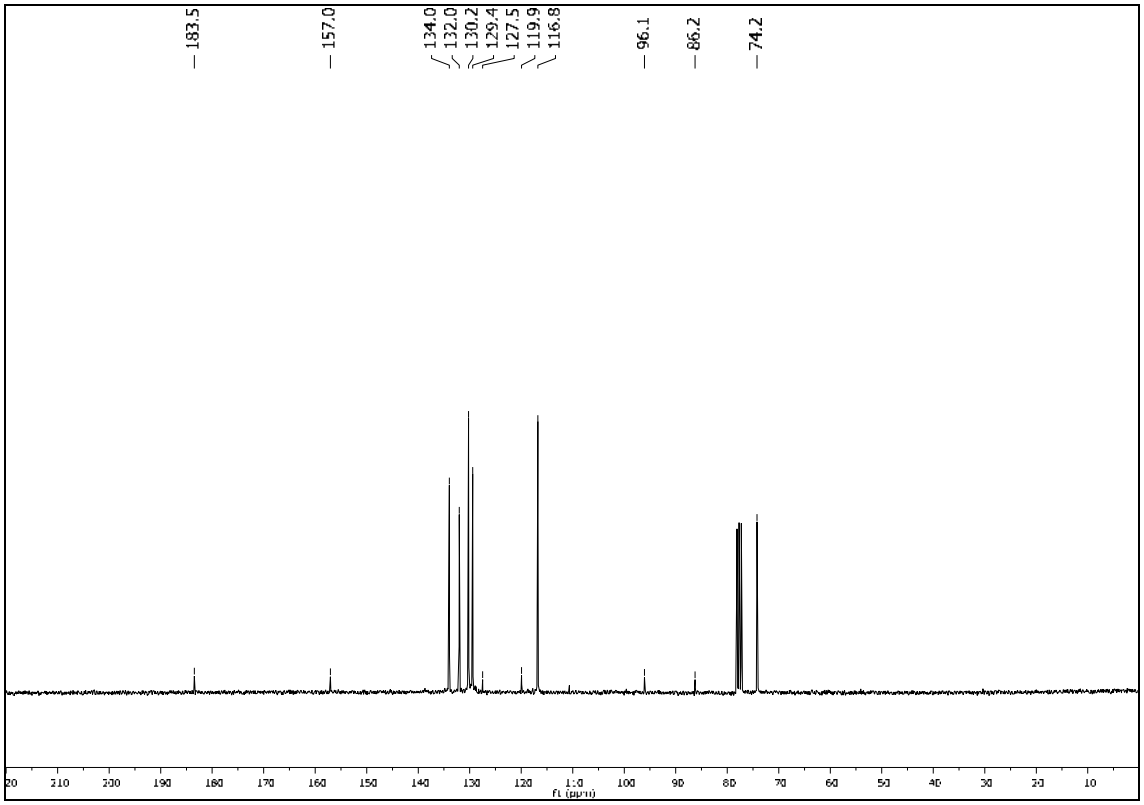
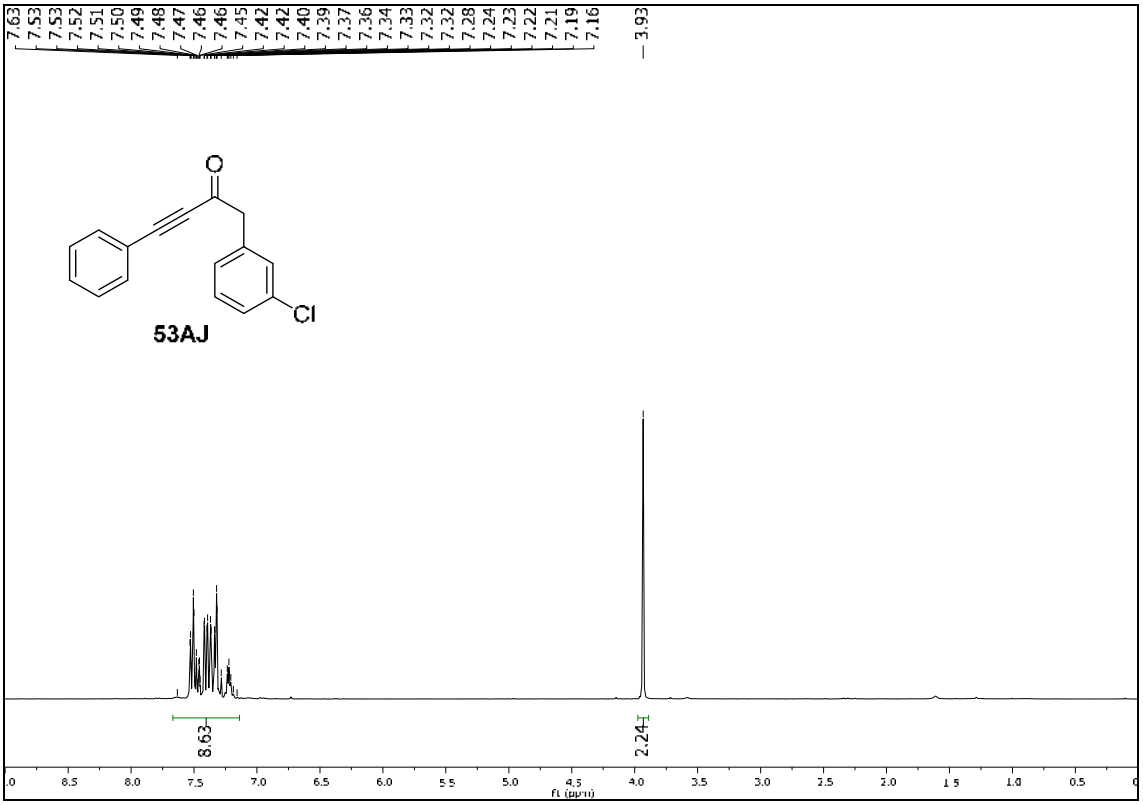


7.7.3. NMR spectra for Chapter 3

7.7.3.1. ^{1}H and ^{13}C NMR



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7.36
7.34
7.33
7.32
7.32
7.28
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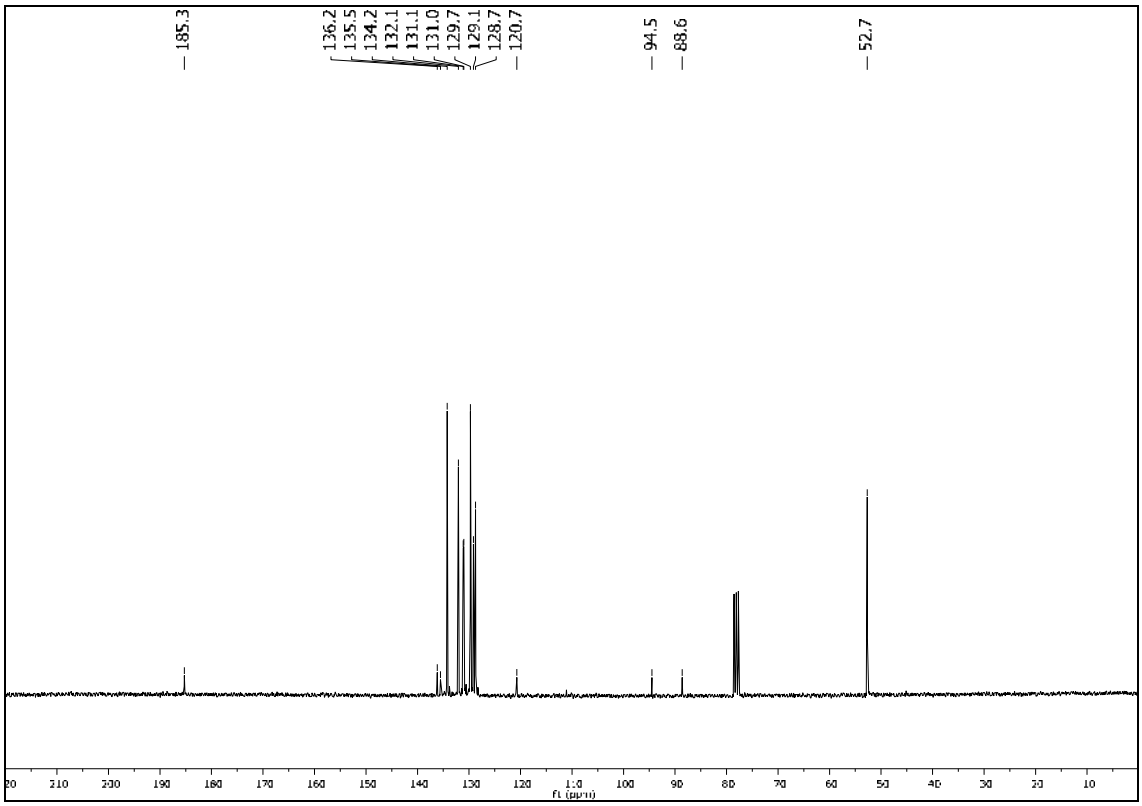
7.19
7.16
3.93
O
Cl
53AJ
8.63
2.24
f1 (ppm)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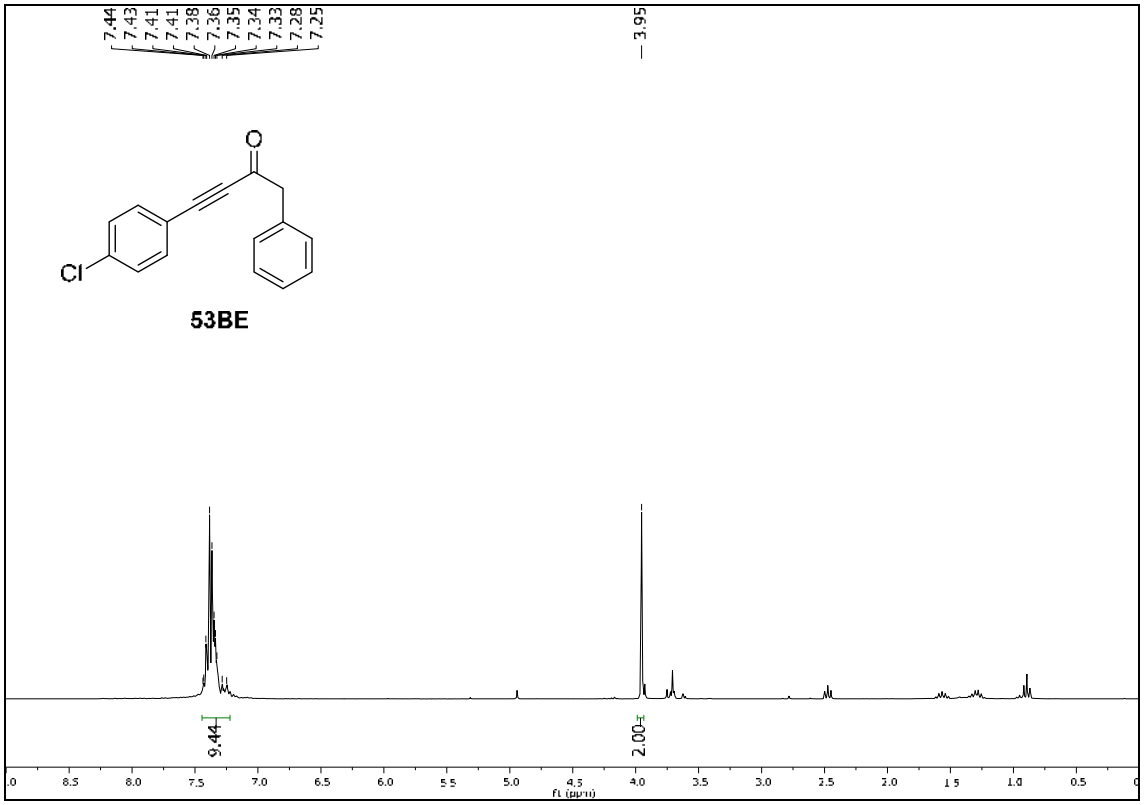
52.7
f1 (ppm)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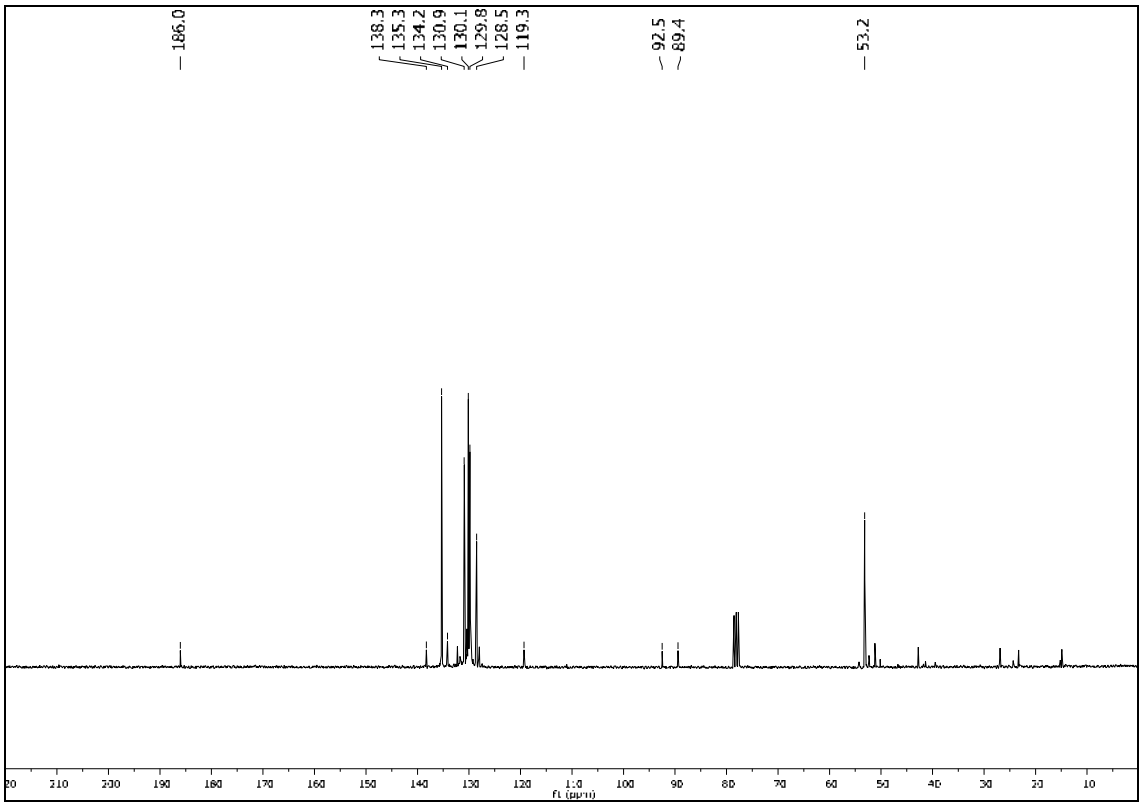
O
Cl
53BE
9.44
2.00
f1 (ppm)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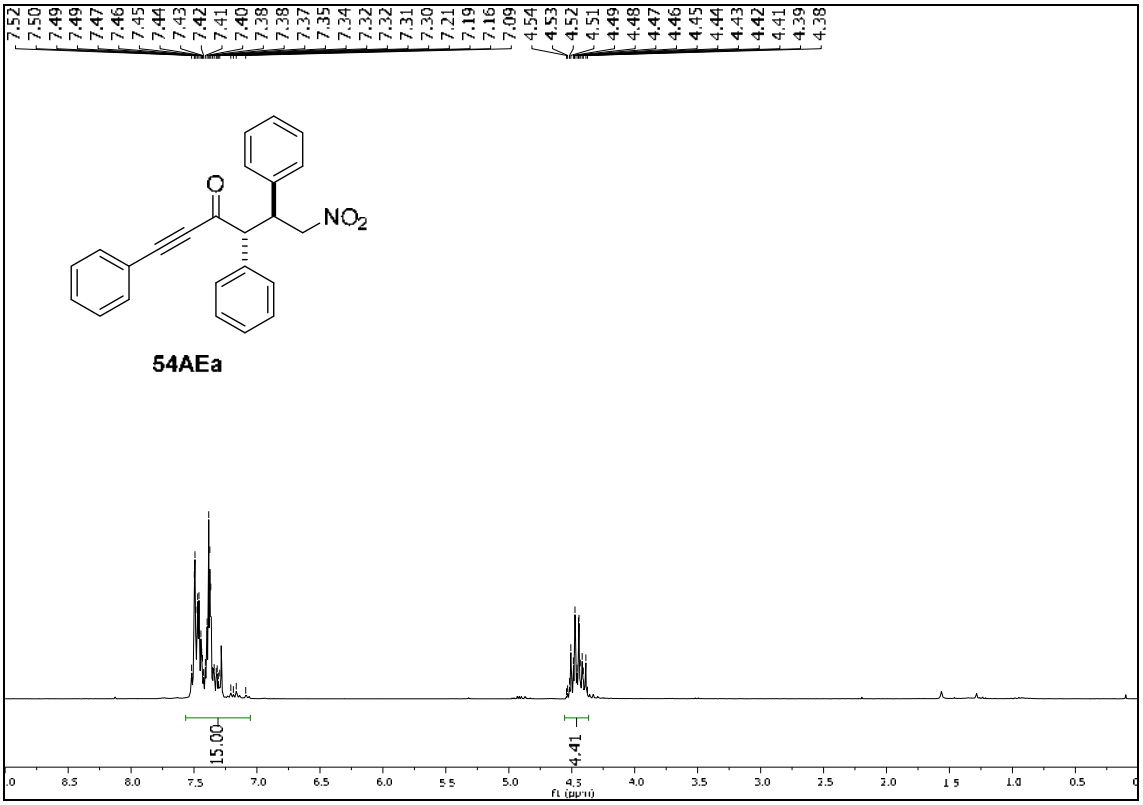
f1 (ppm)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7.31
7.30
7.21
7.19
7.16
7.09
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4.52
4.51
4.49
4.48
4.47
4.46
4.45
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NO2
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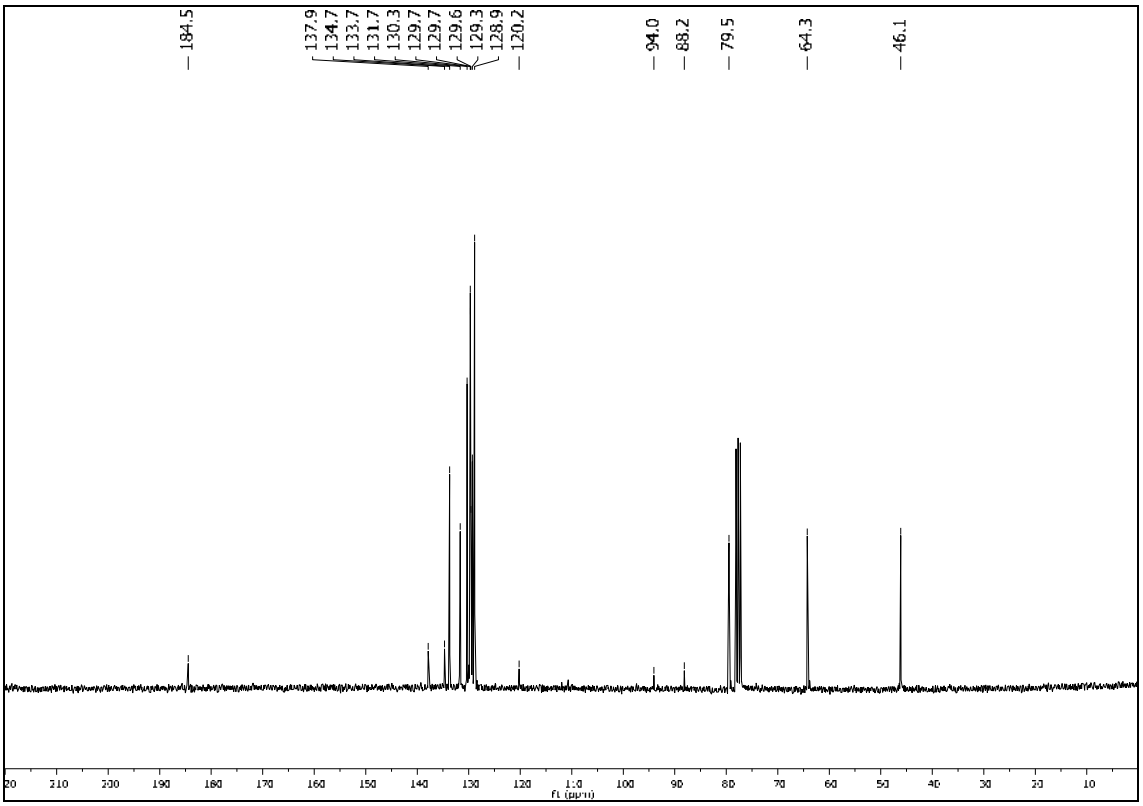
4.41
f1 (ppm)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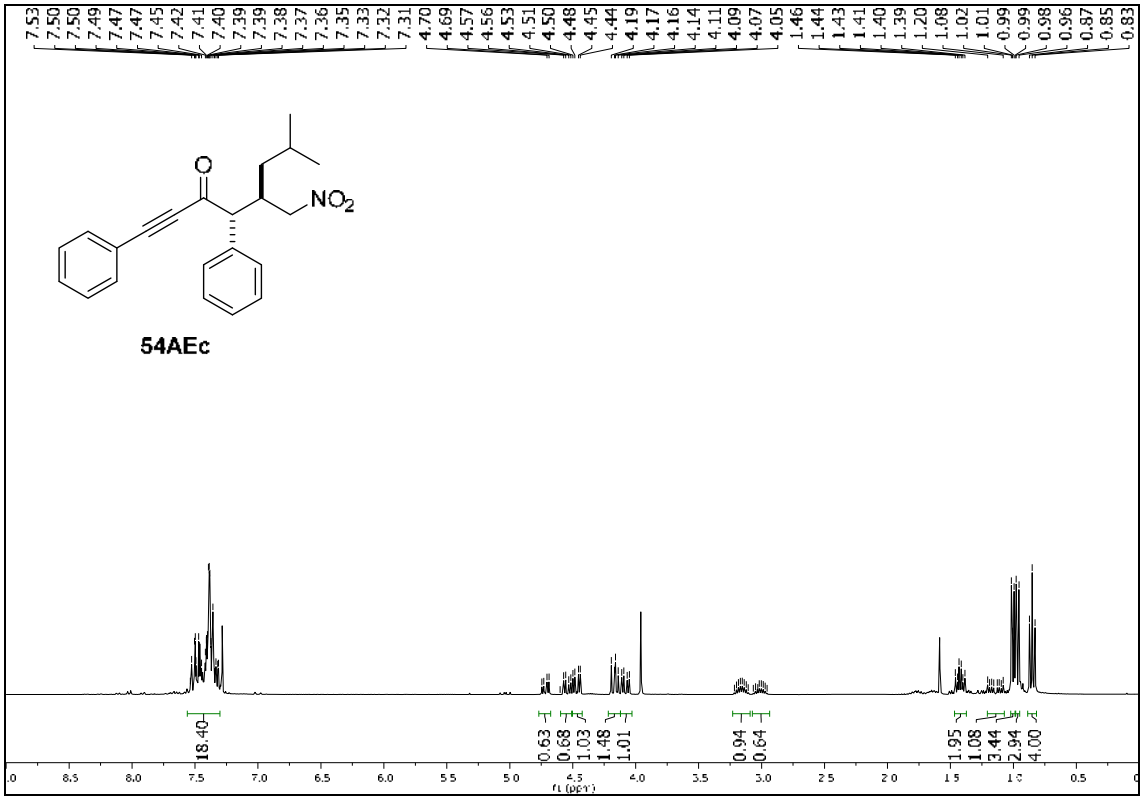
f1 (ppm)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1.46 1.44 1.43 1.41 1.40 1.39 1.20 1.08 1.02 1.01 0.99 0.99 0.98 0.96 0.87 0.85 0.83
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NO2
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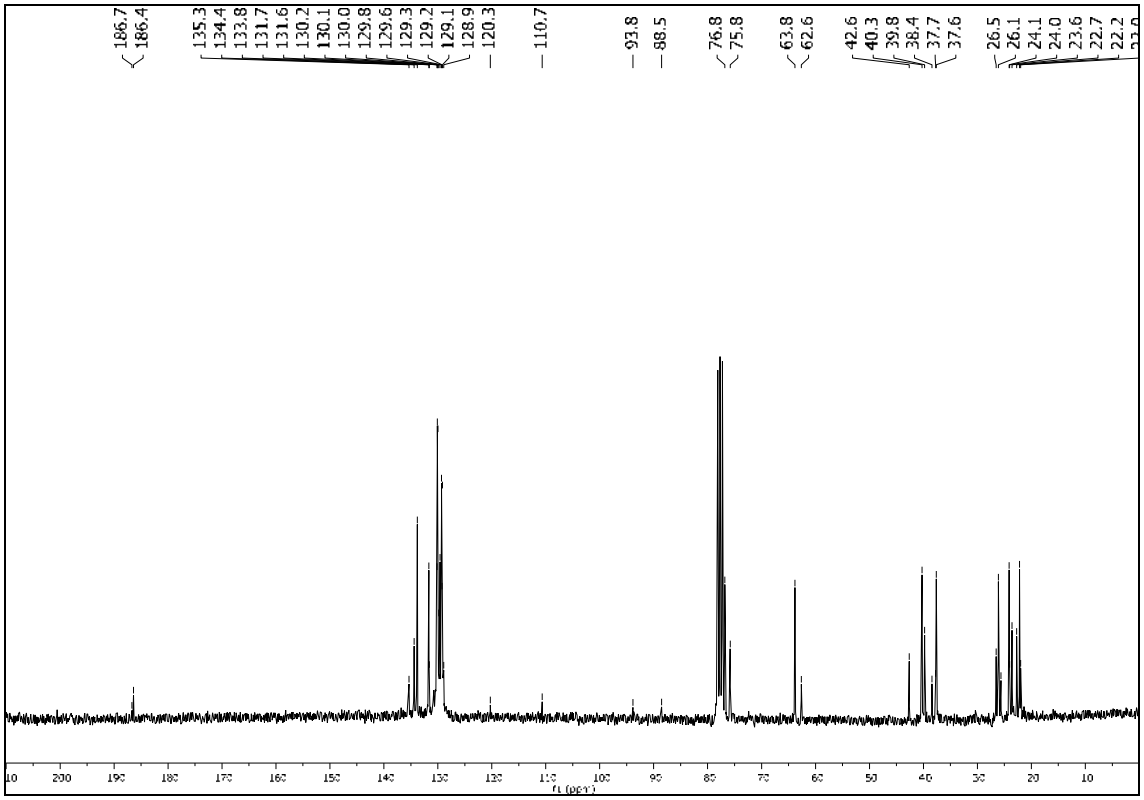
18.40
0.63 0.68 1.03 1.48 1.01
0.94 0.64
1.95 1.08 3.44 2.94 4.00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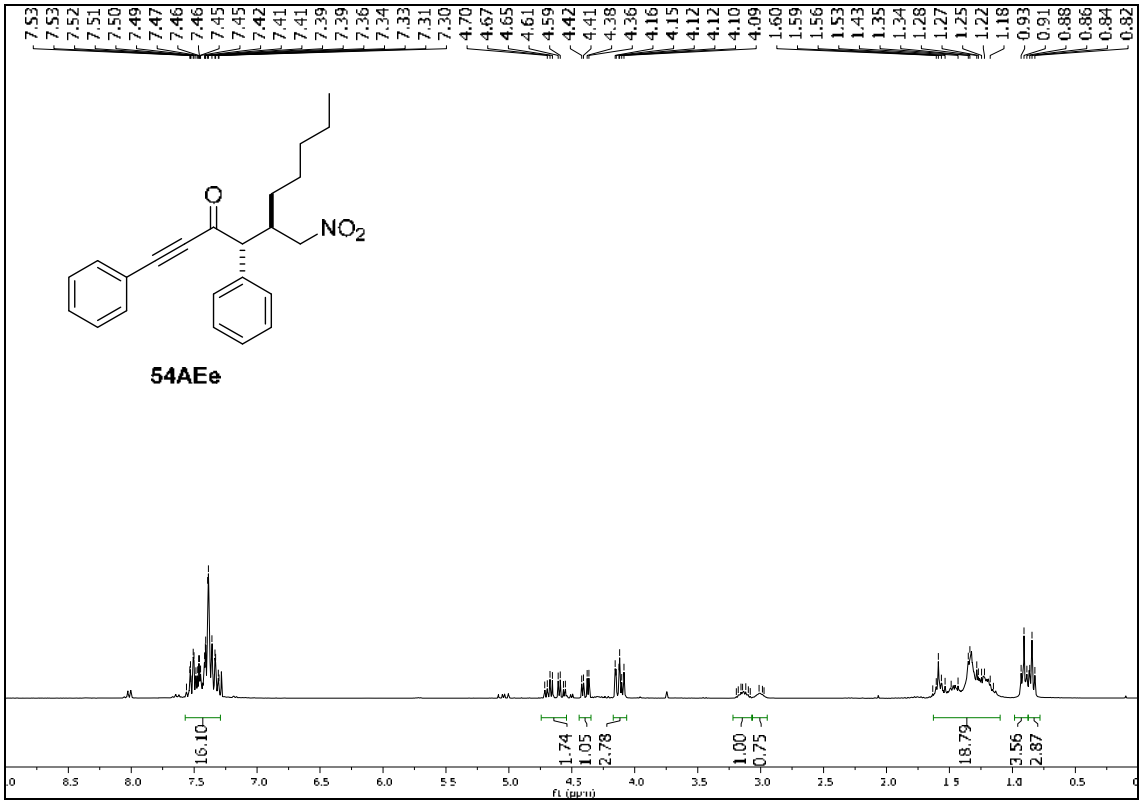
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7.39
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7.33
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7.30
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4.41
4.38
4.36
4.16
4.15
4.12
4.12
4.10
4.09
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1.59
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1.35
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1.27
1.25
1.22
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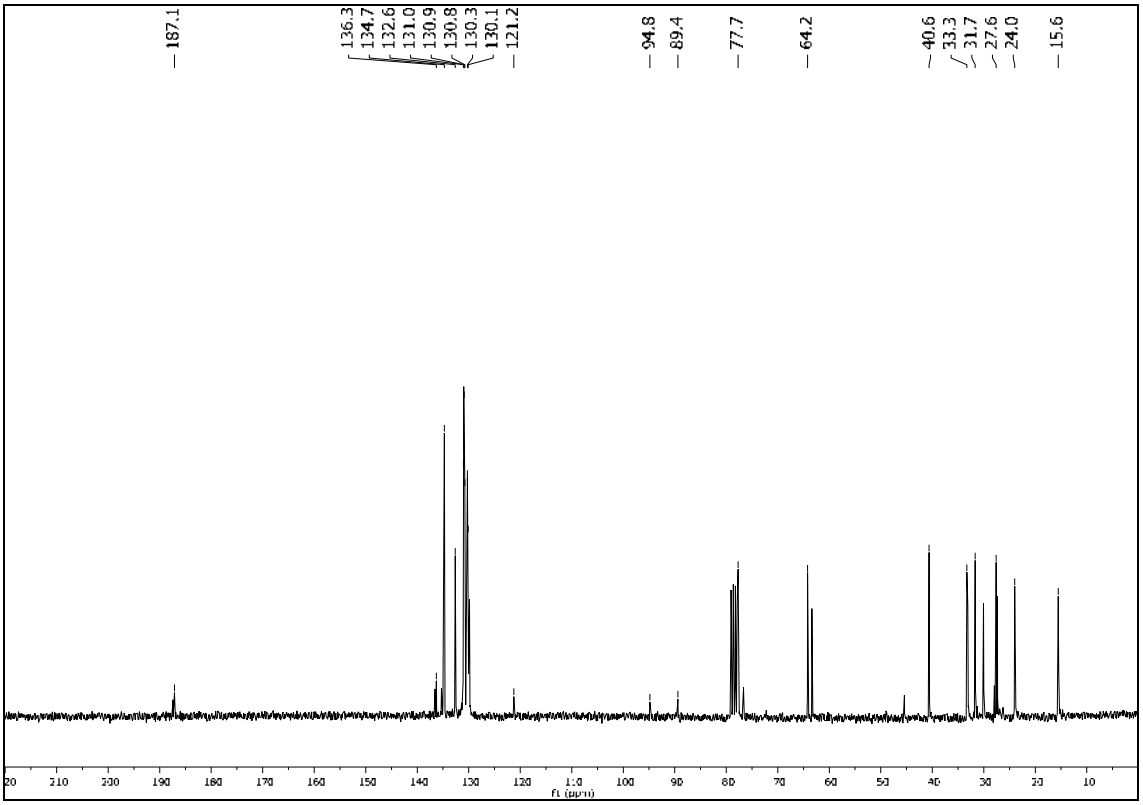
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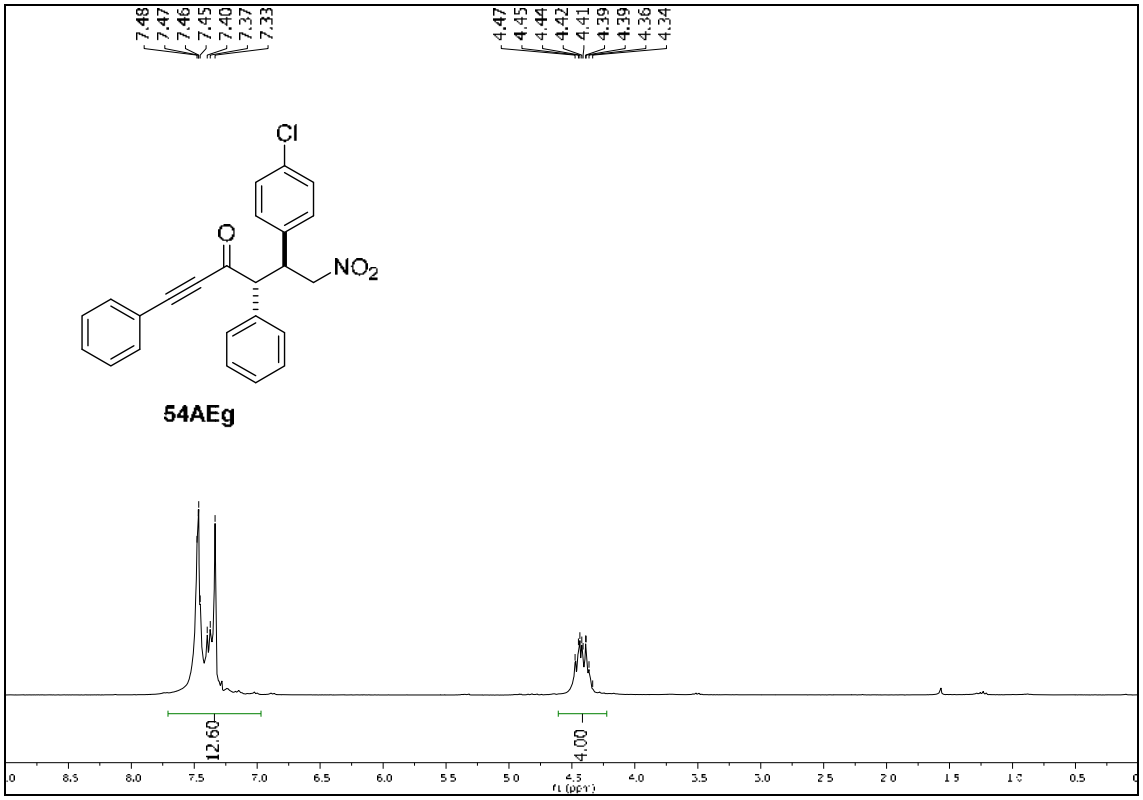
f1 (ppm)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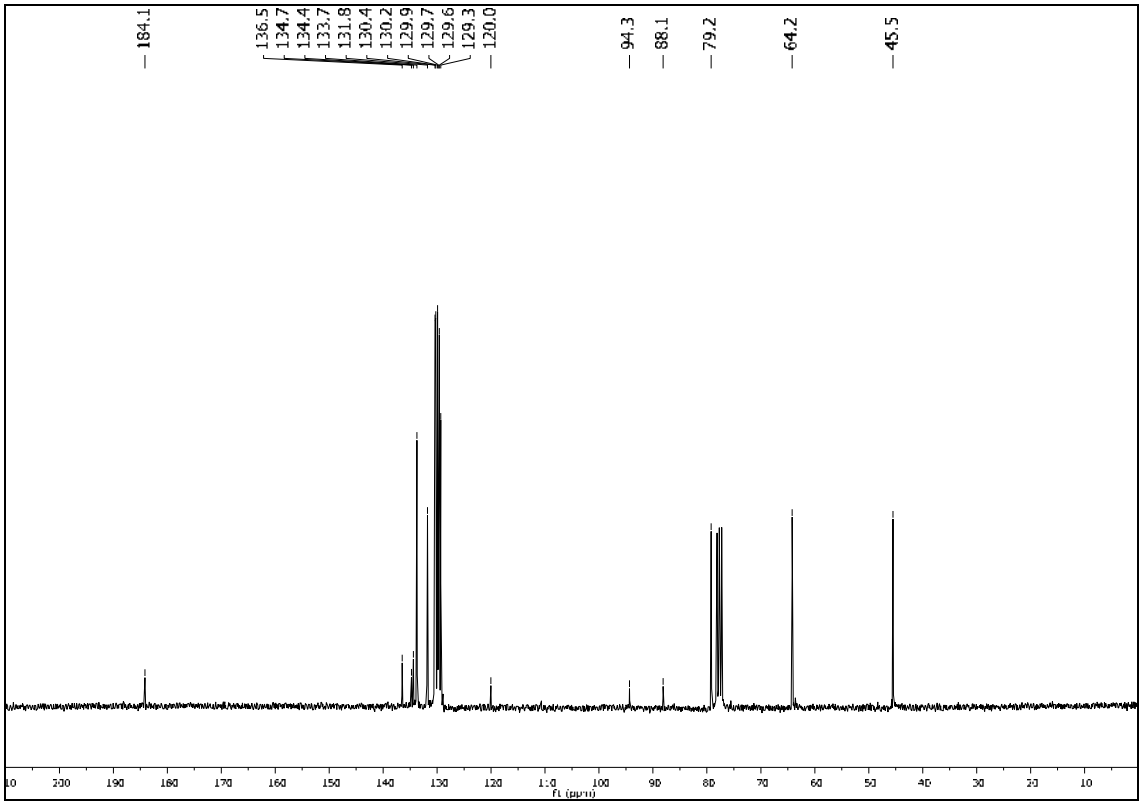
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79.2
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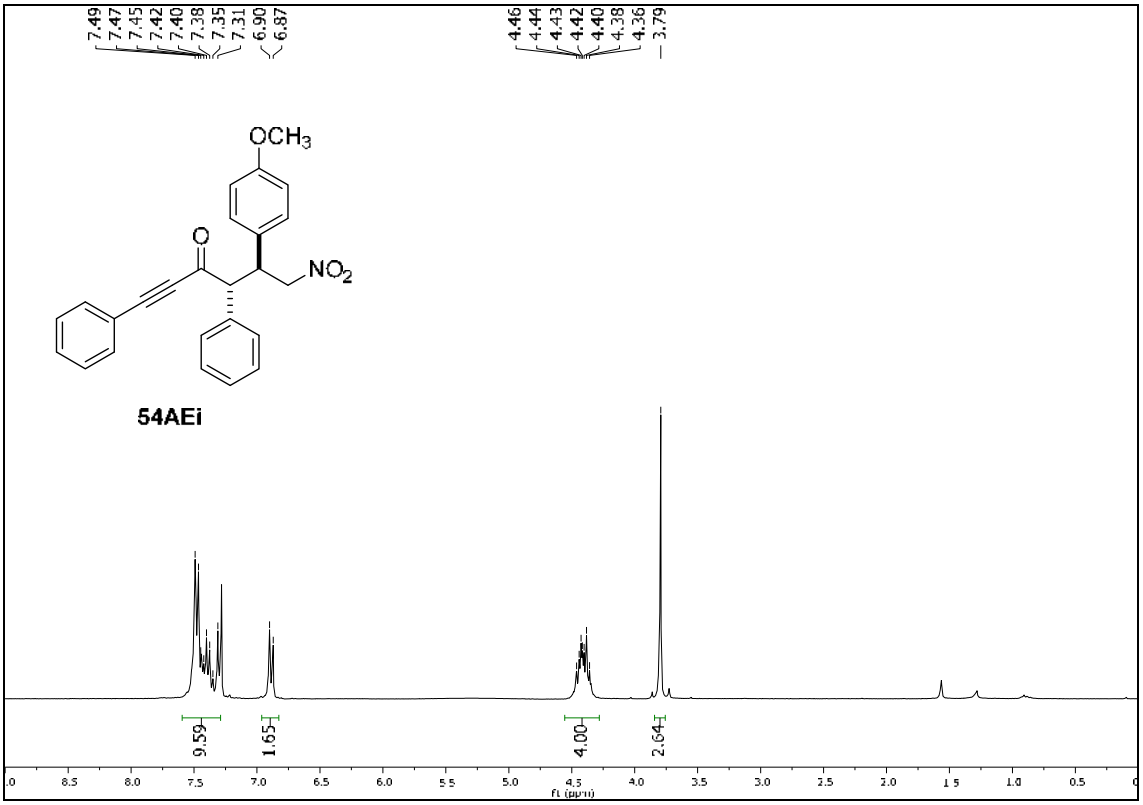
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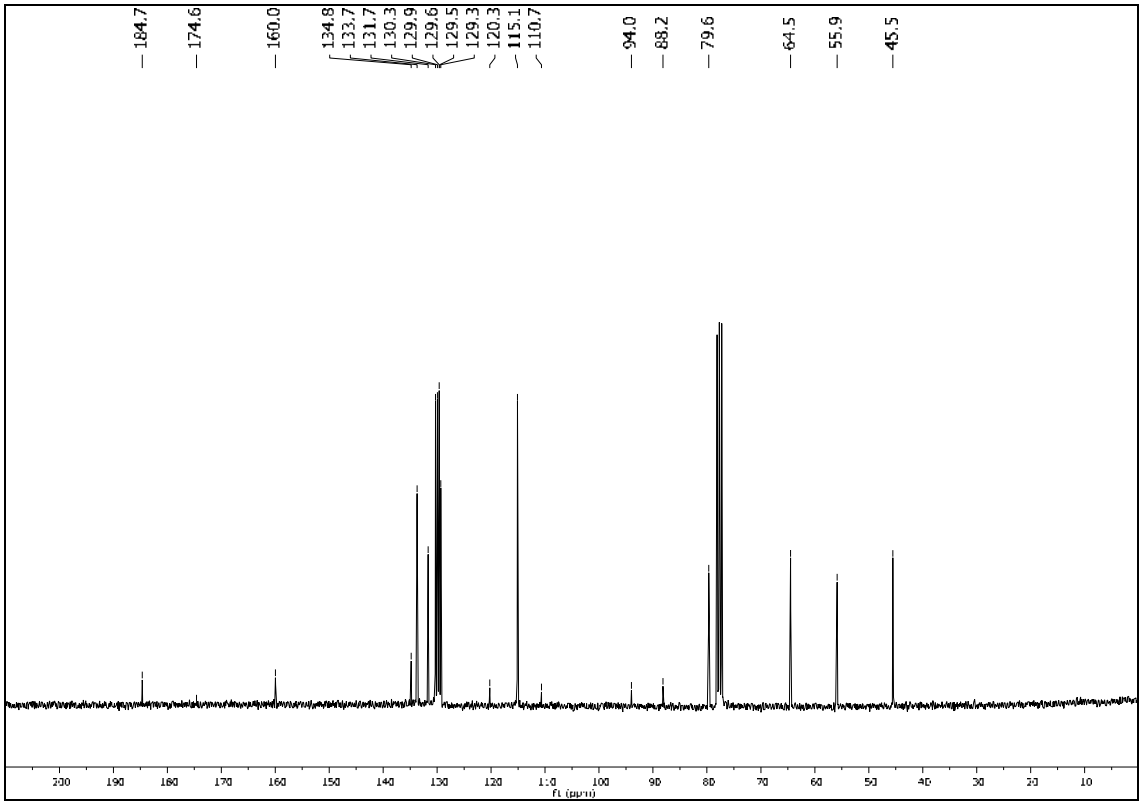
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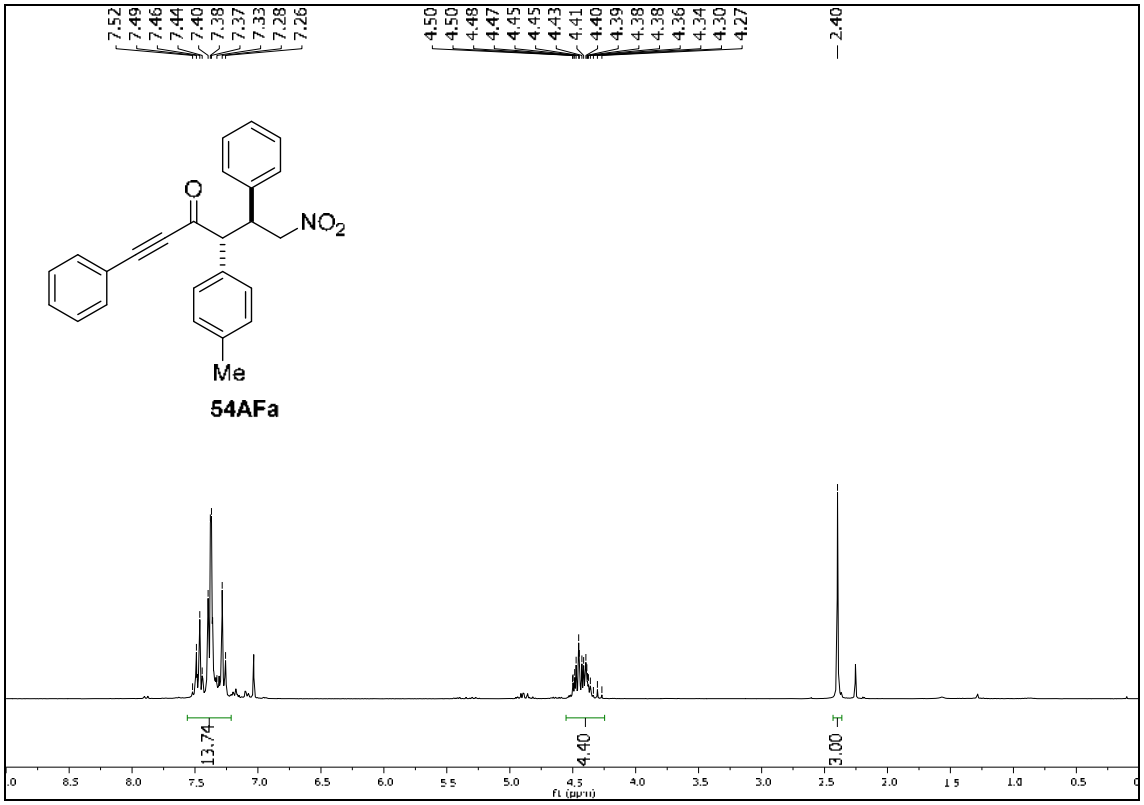
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4.43
4.41
4.40
4.39
4.38
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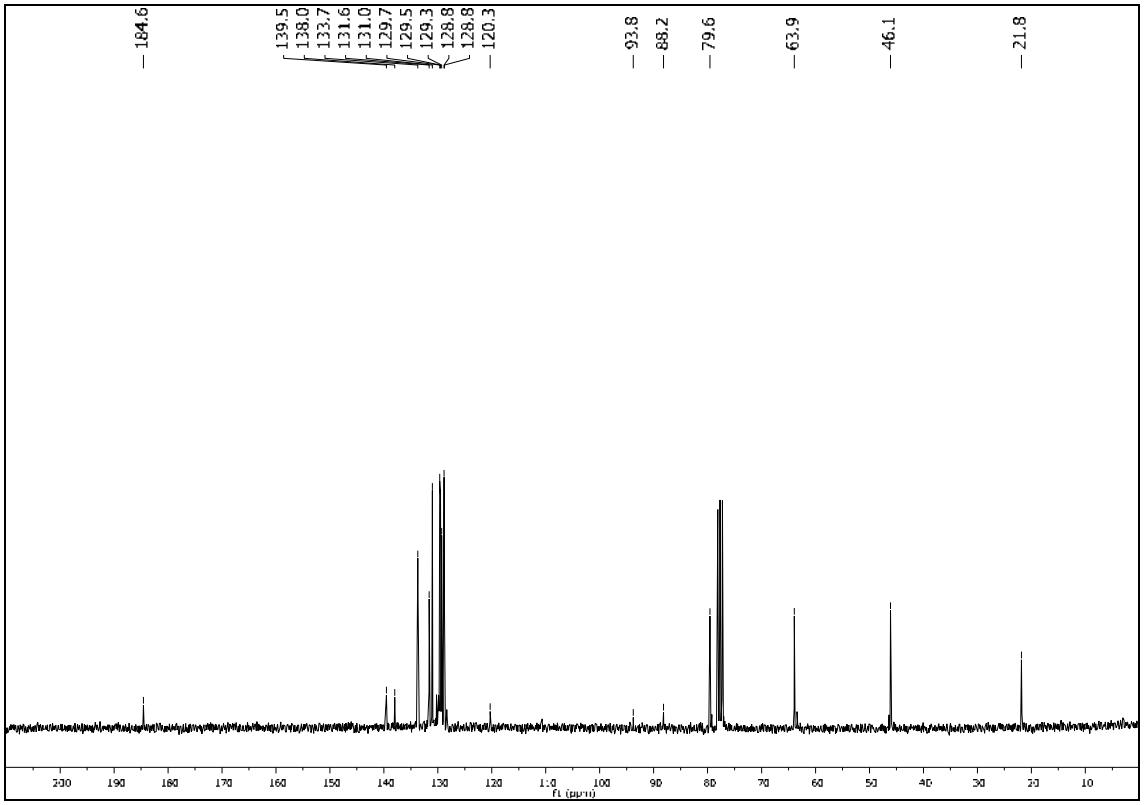
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88.2
79.6
63.9
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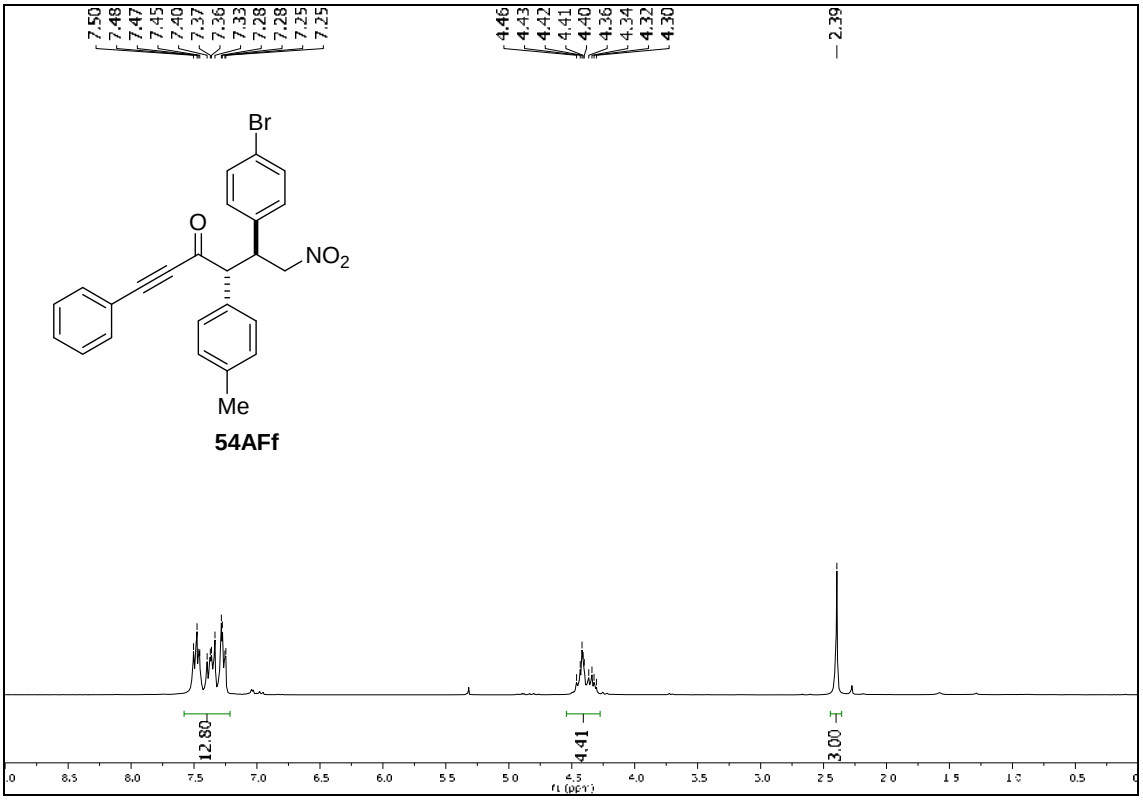
21.8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4.42
4.41
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Me
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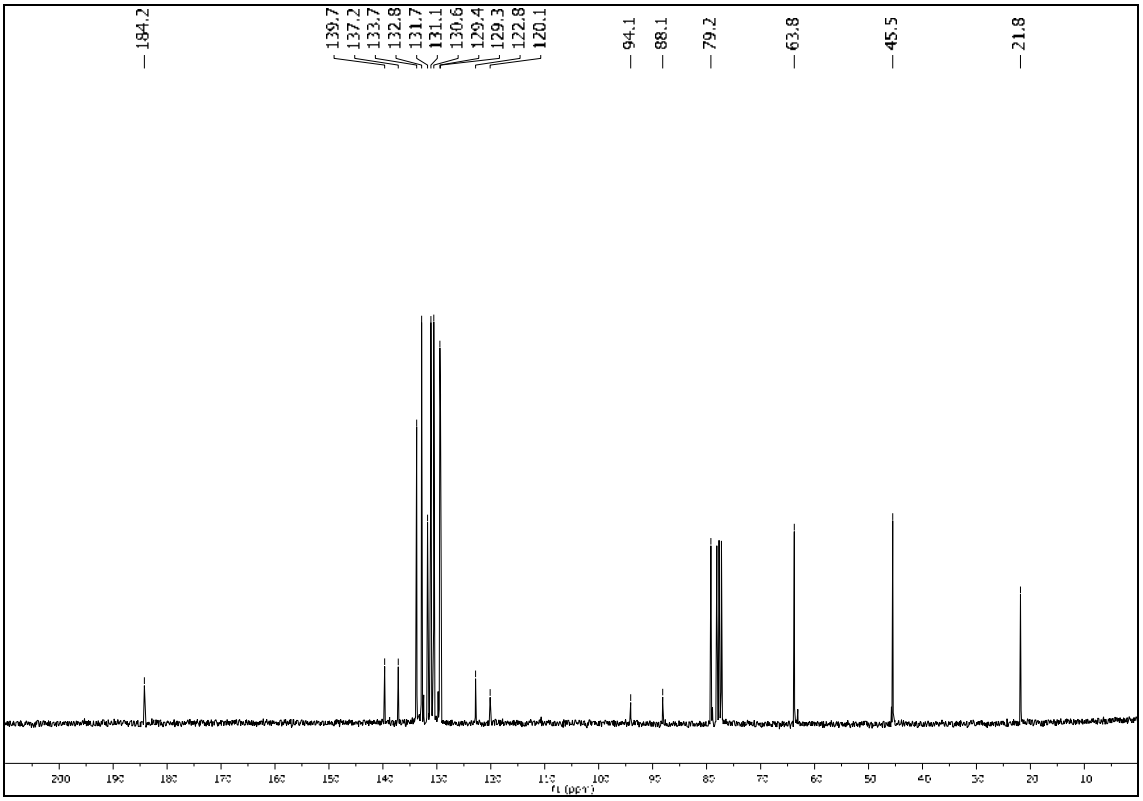
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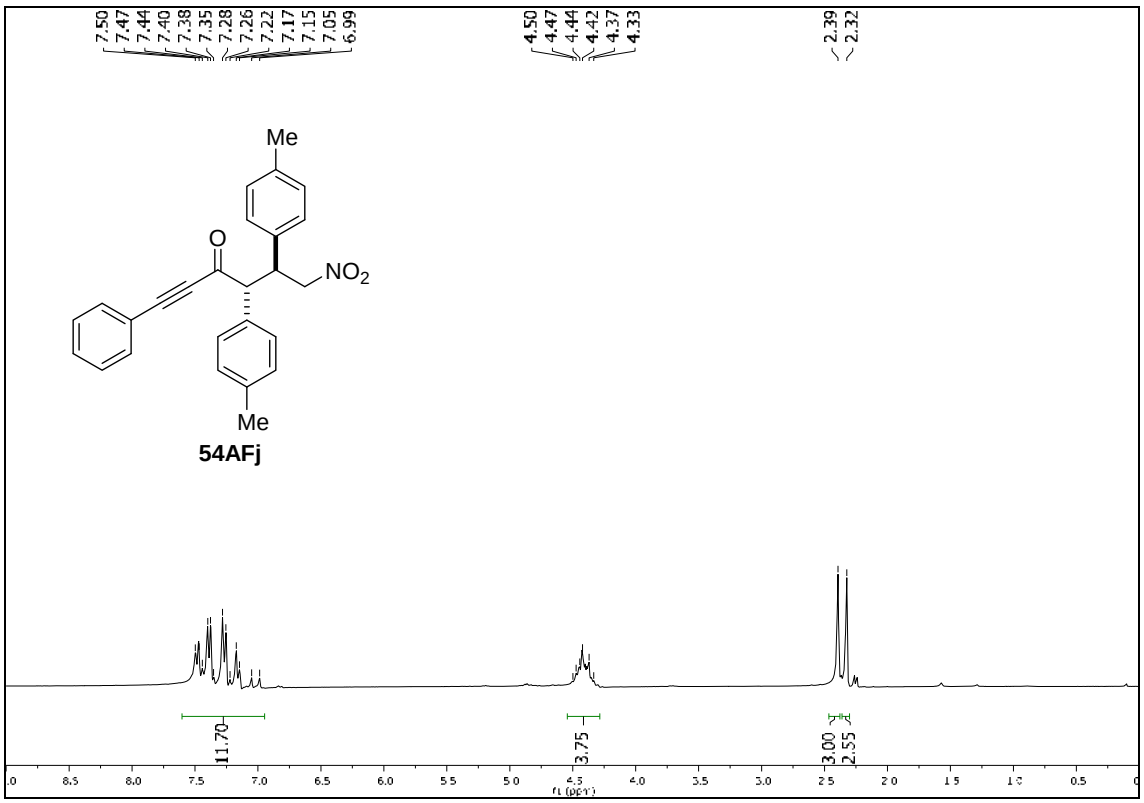
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2.32
Me
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Me
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3.75
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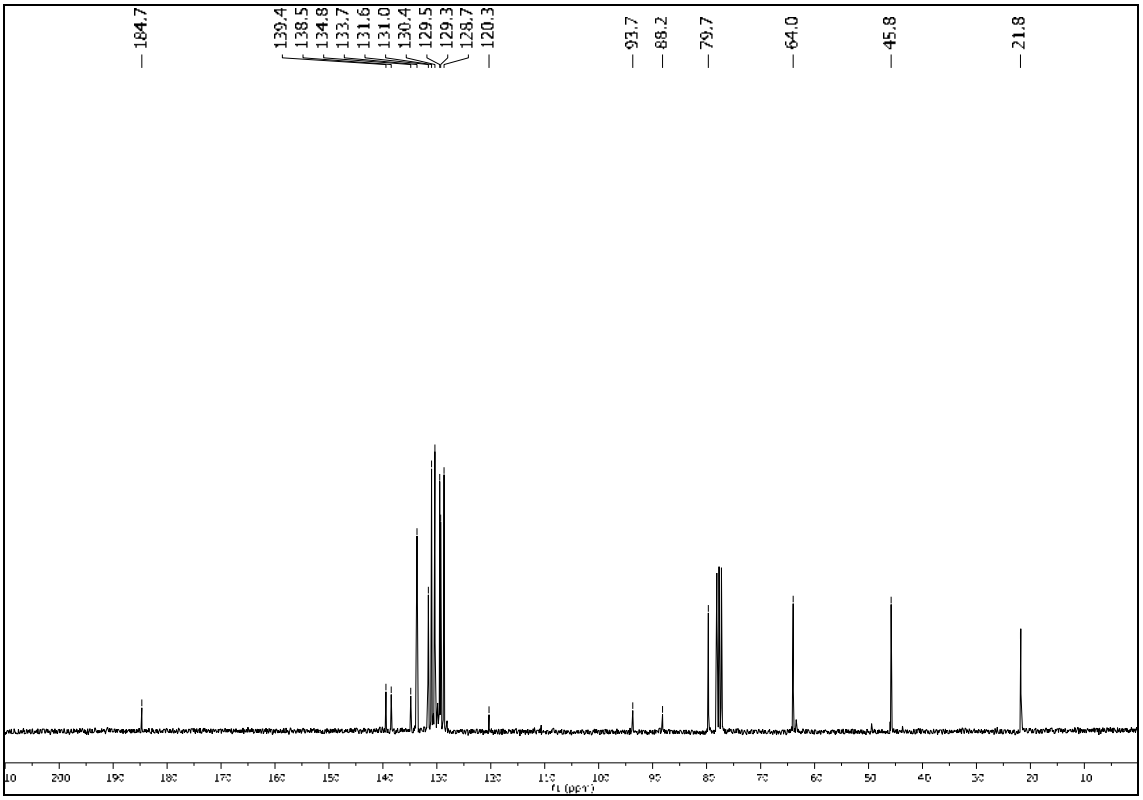
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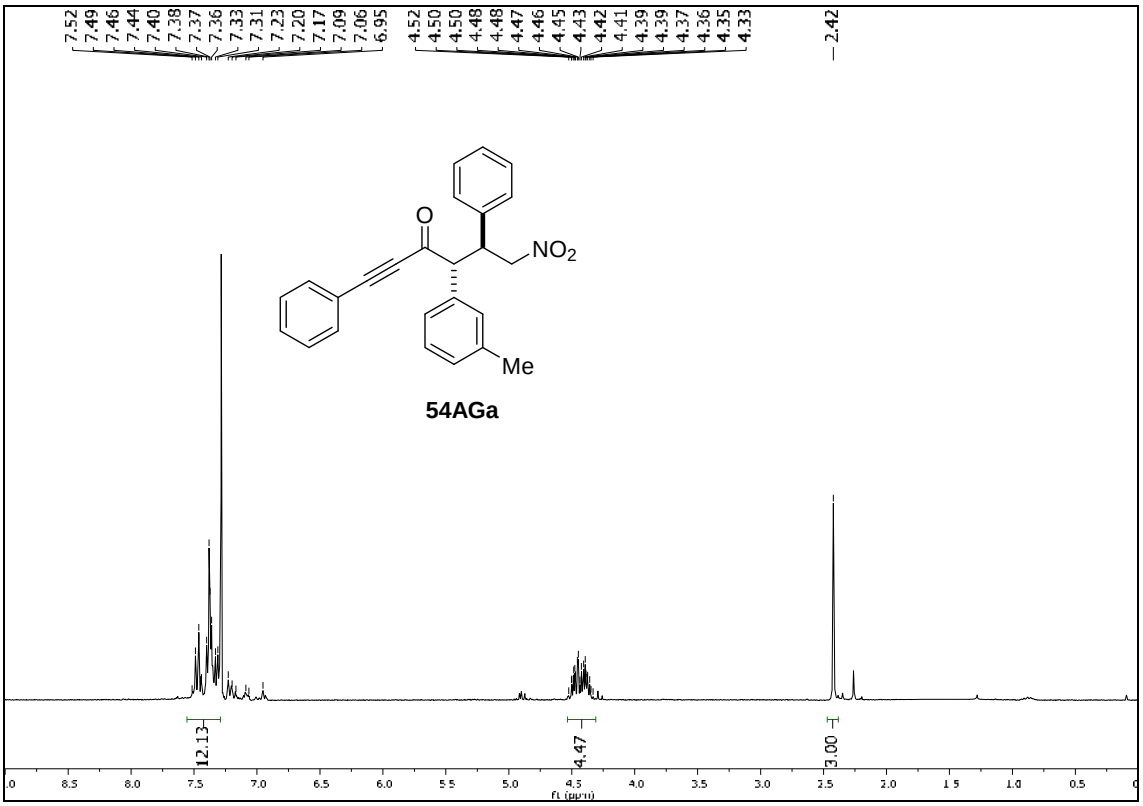
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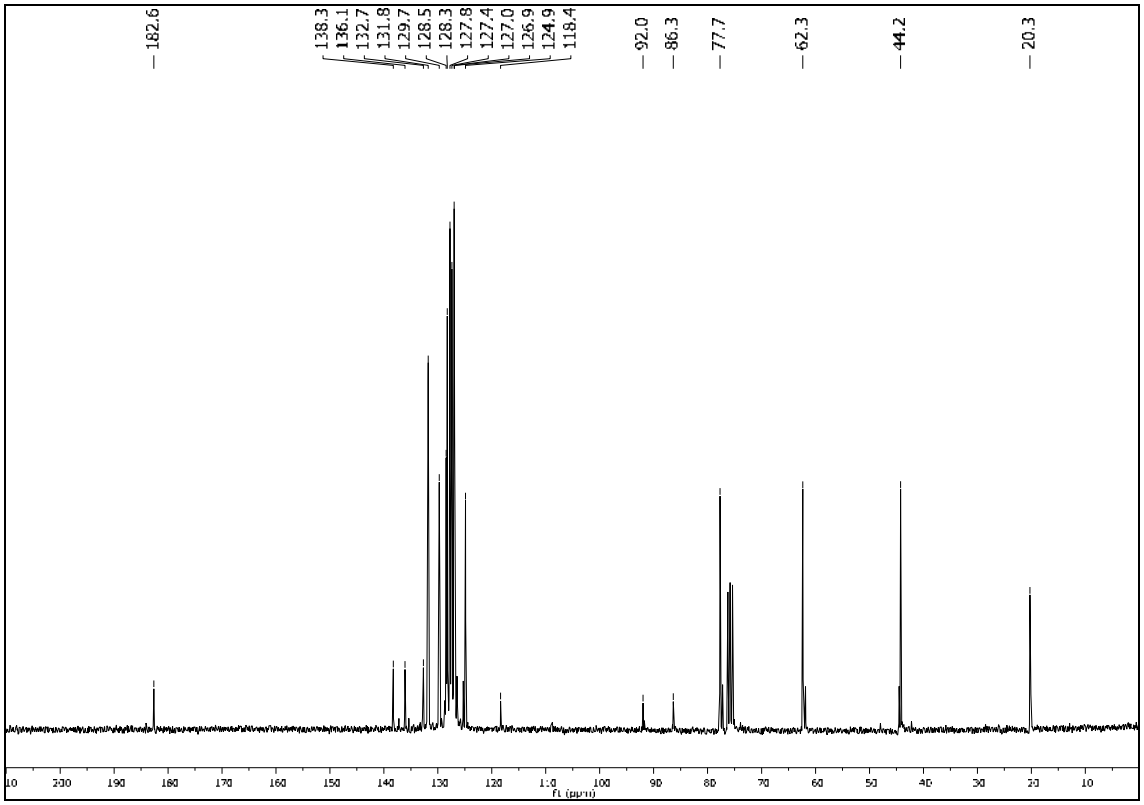
54AGa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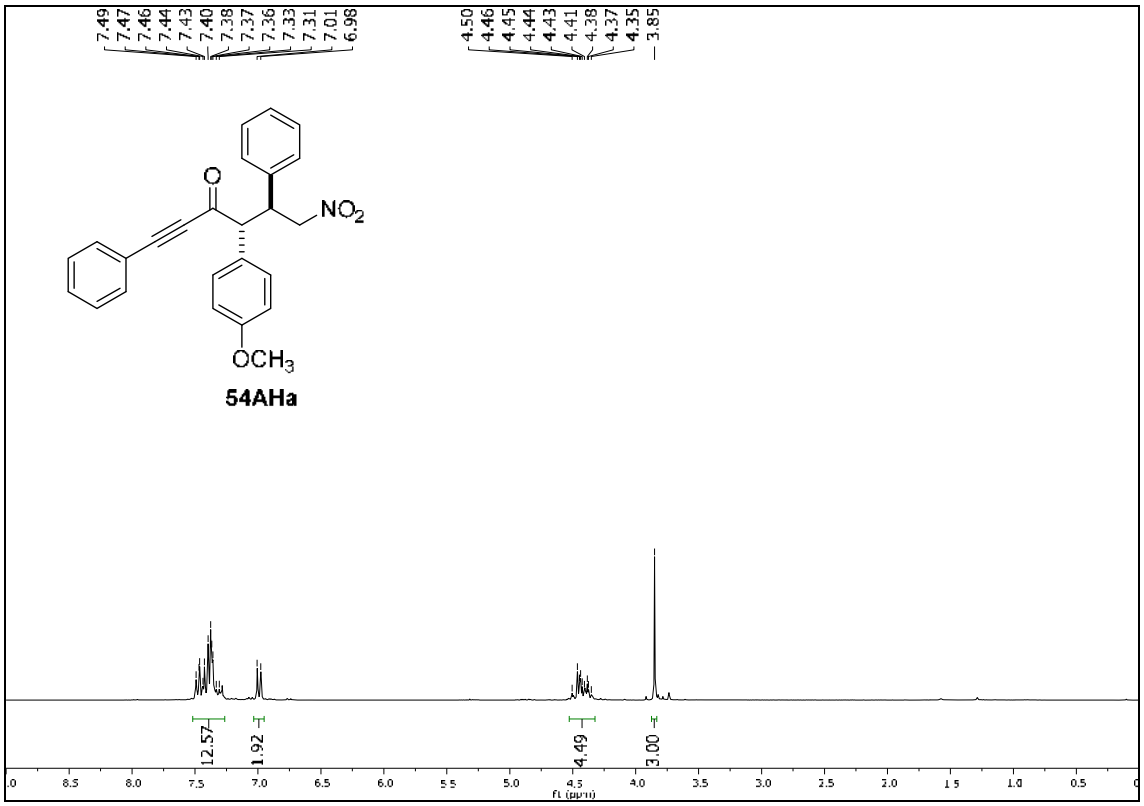
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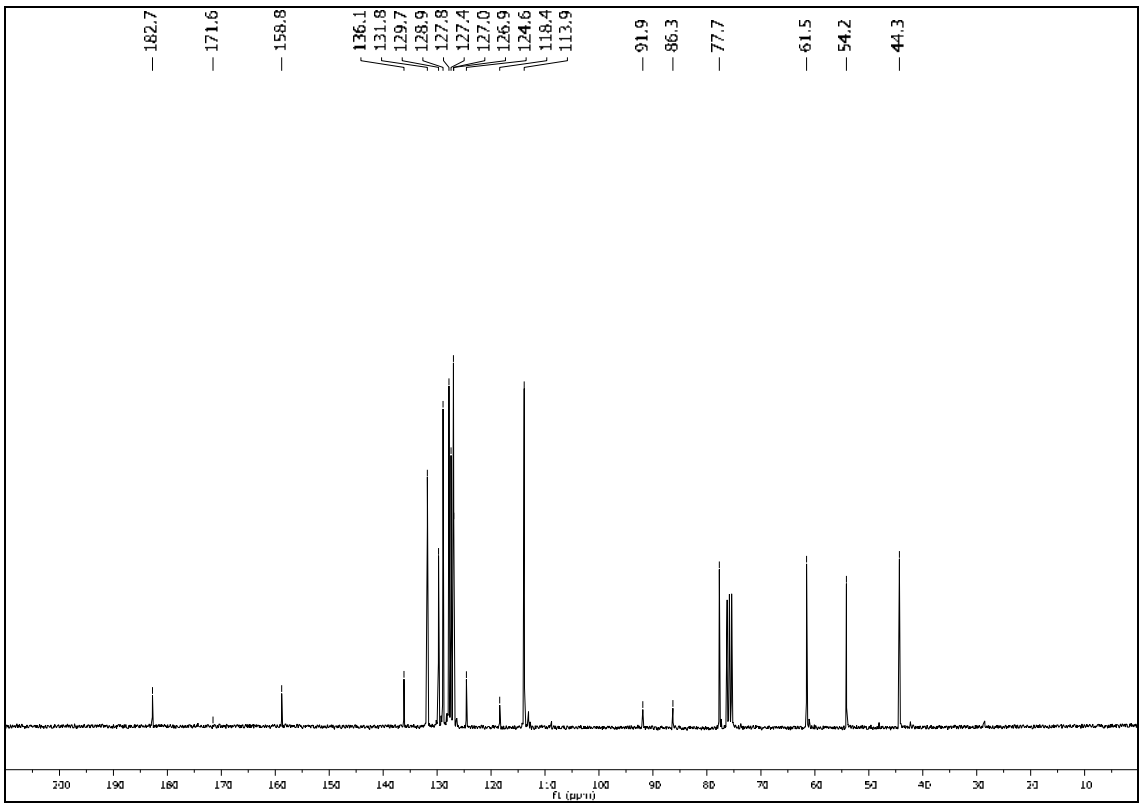
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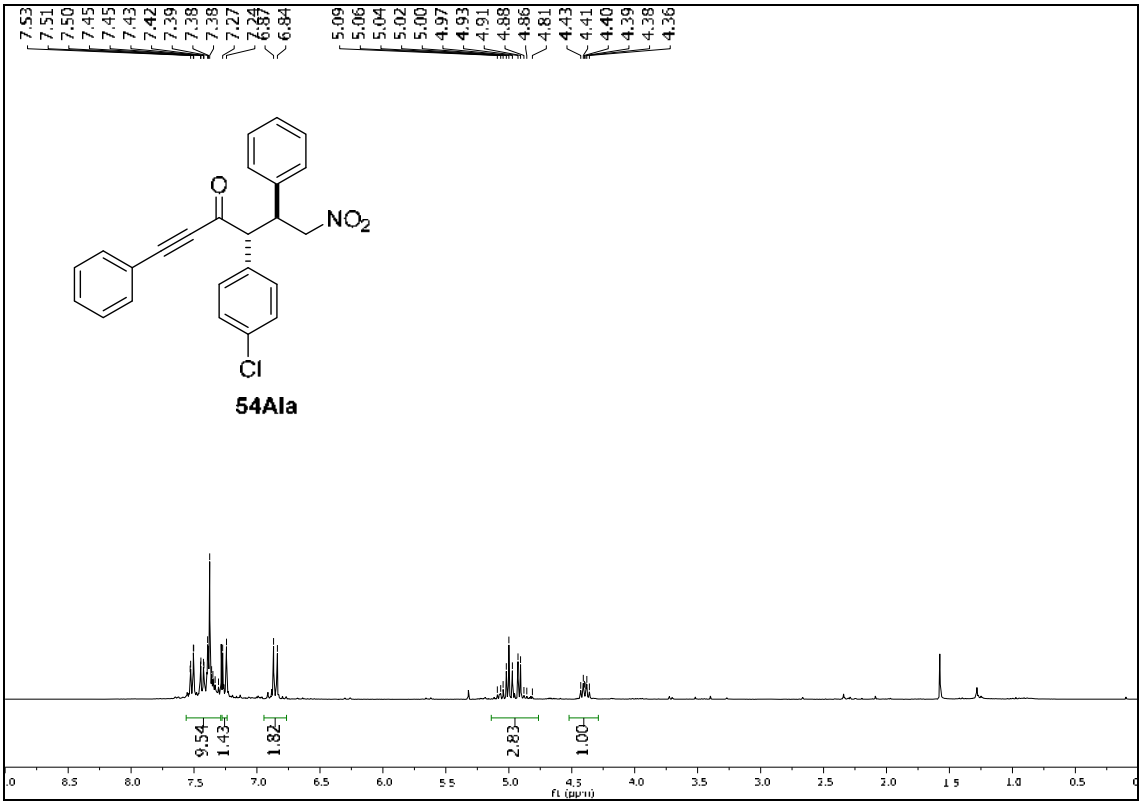
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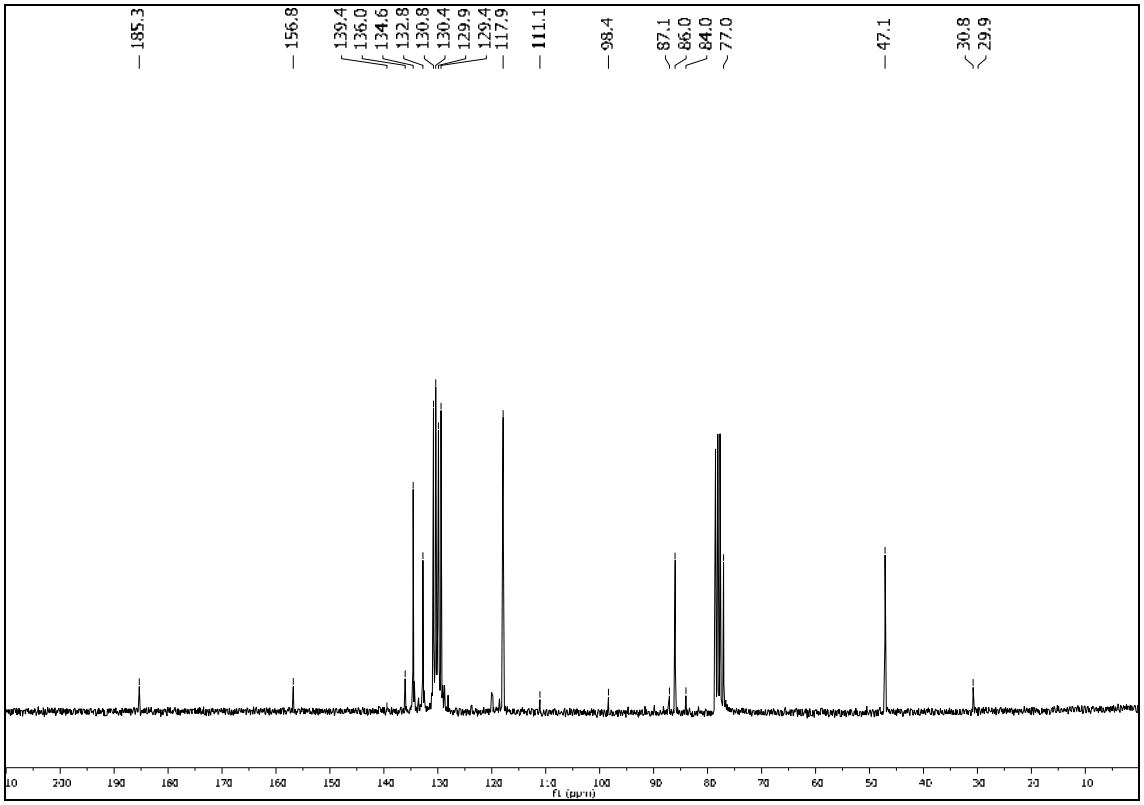
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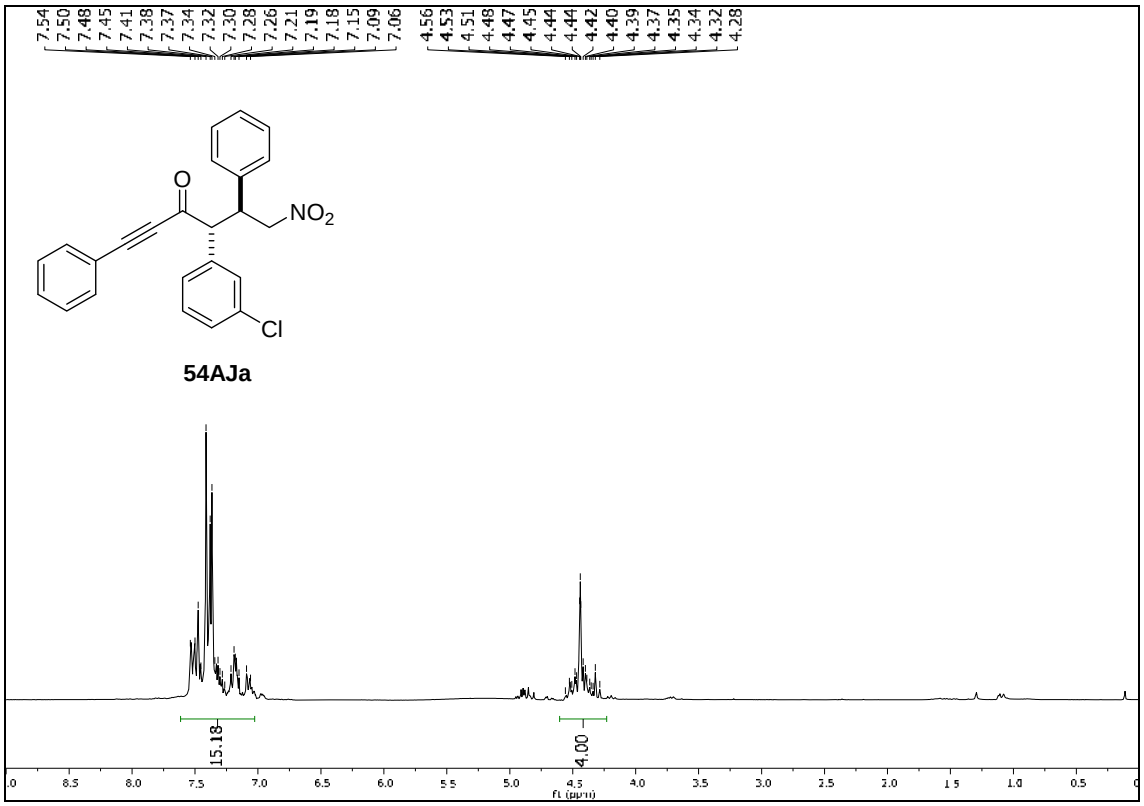
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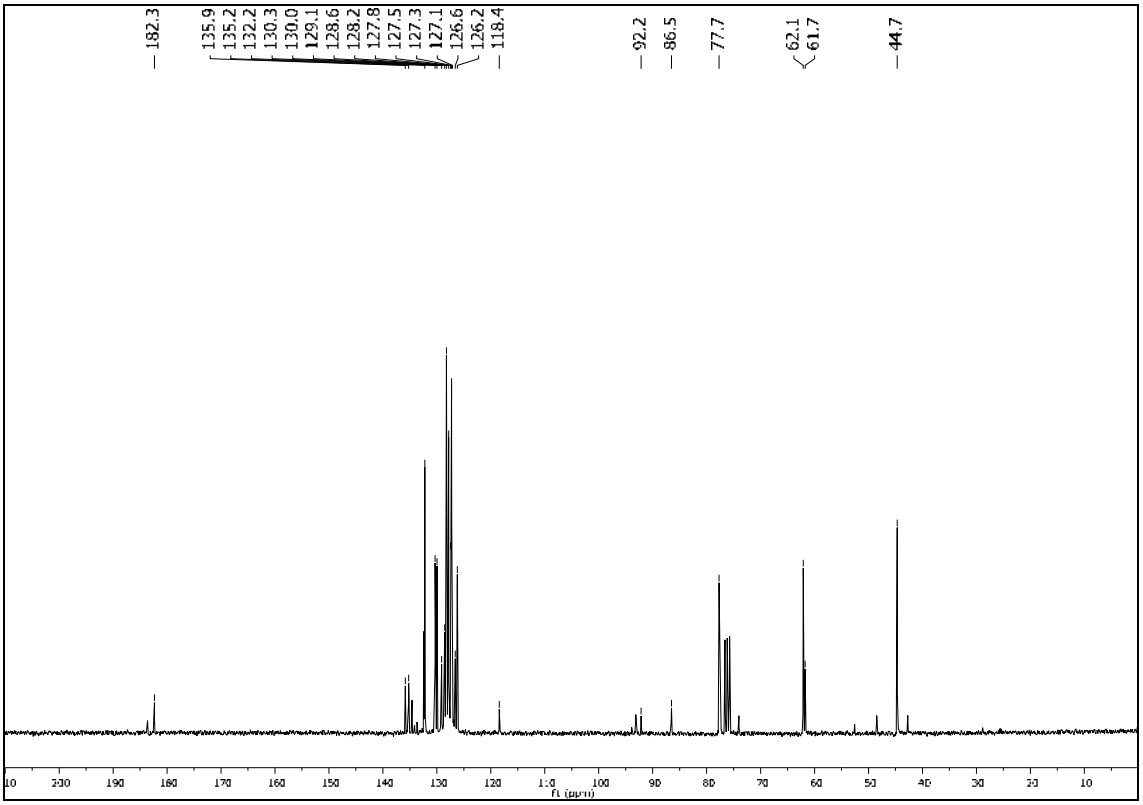
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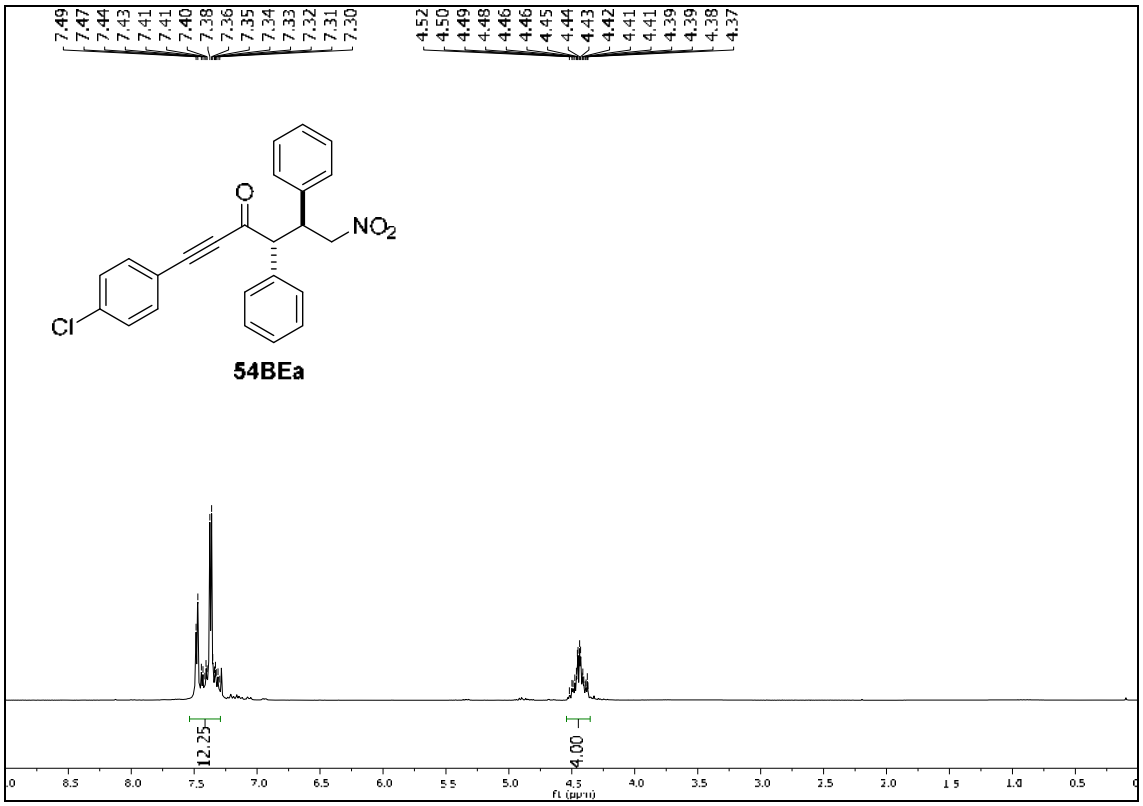
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Cl
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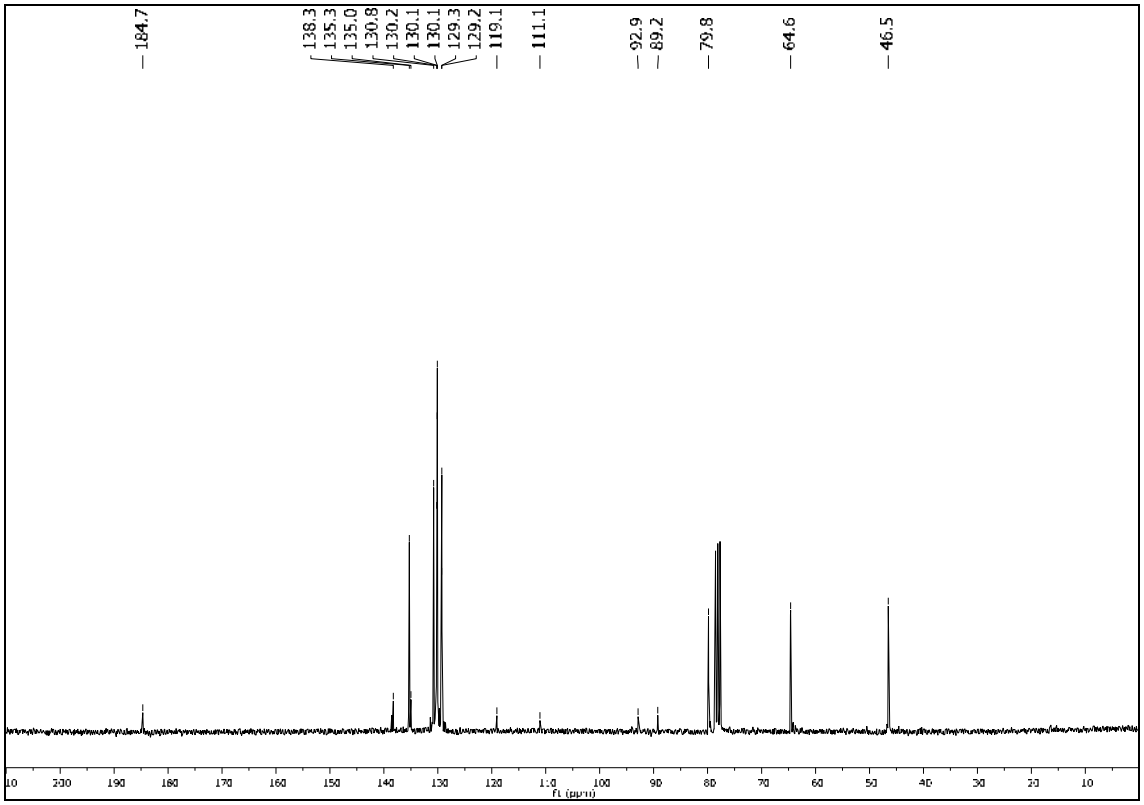
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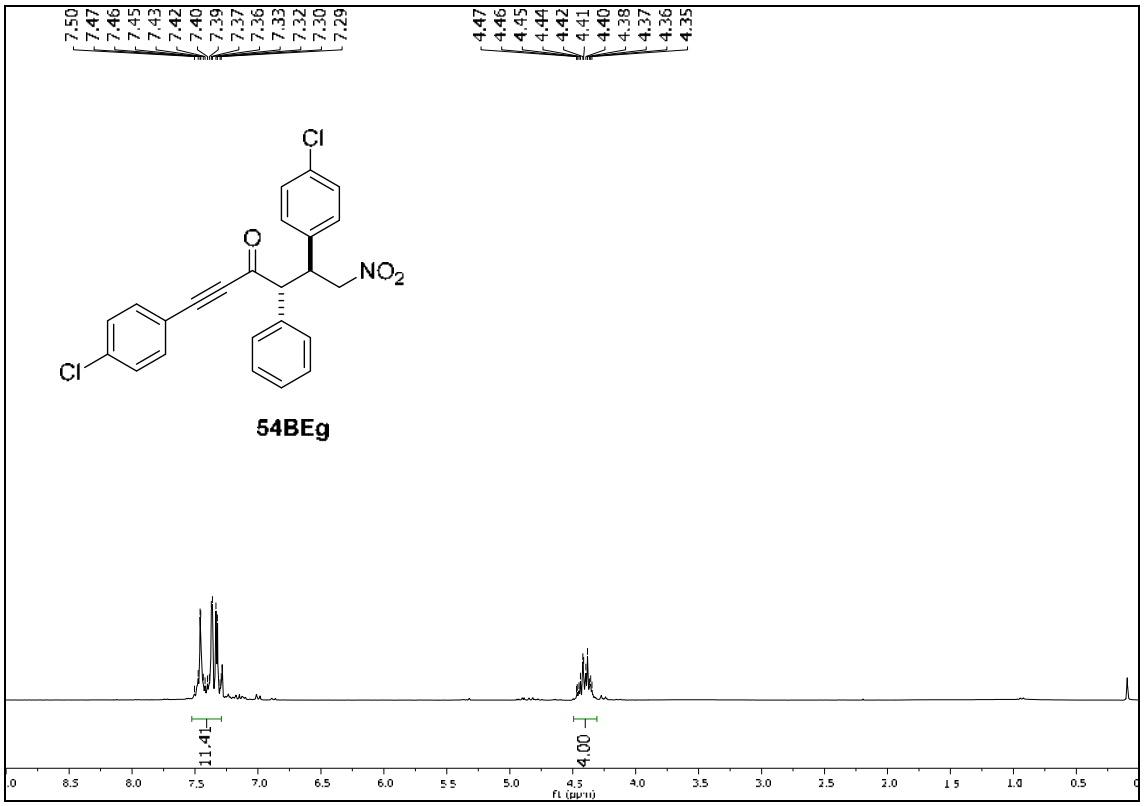
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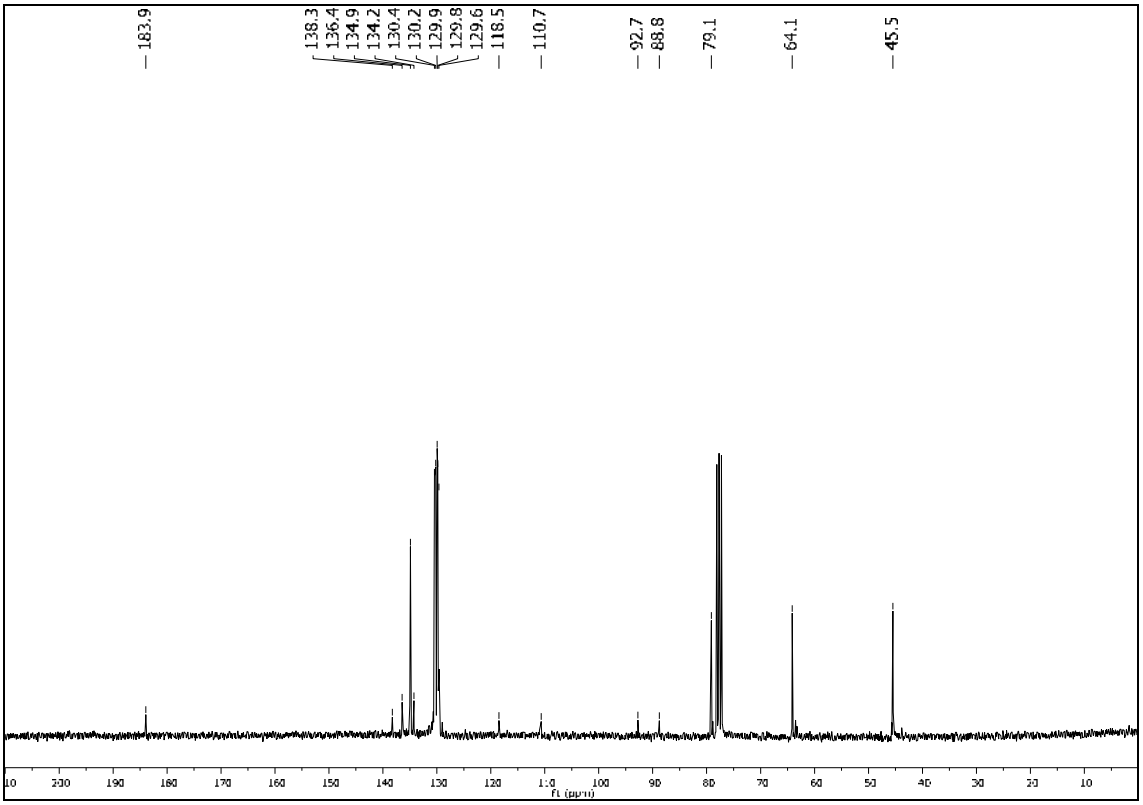
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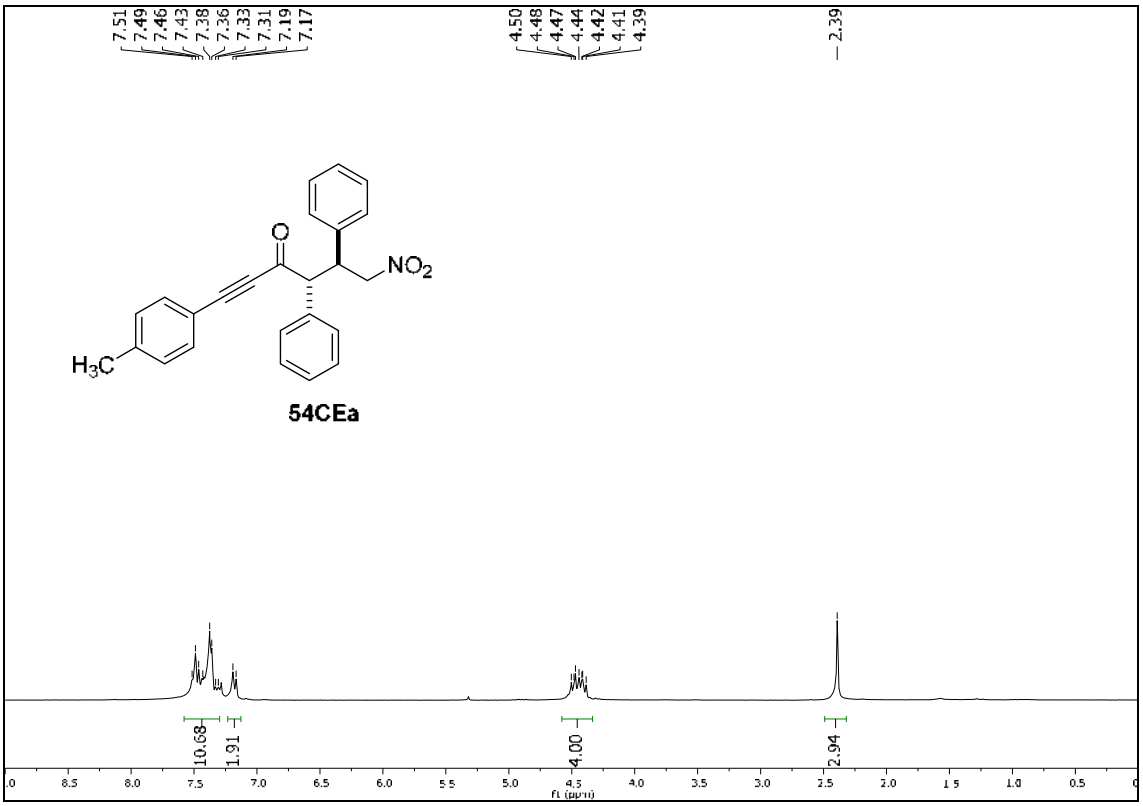
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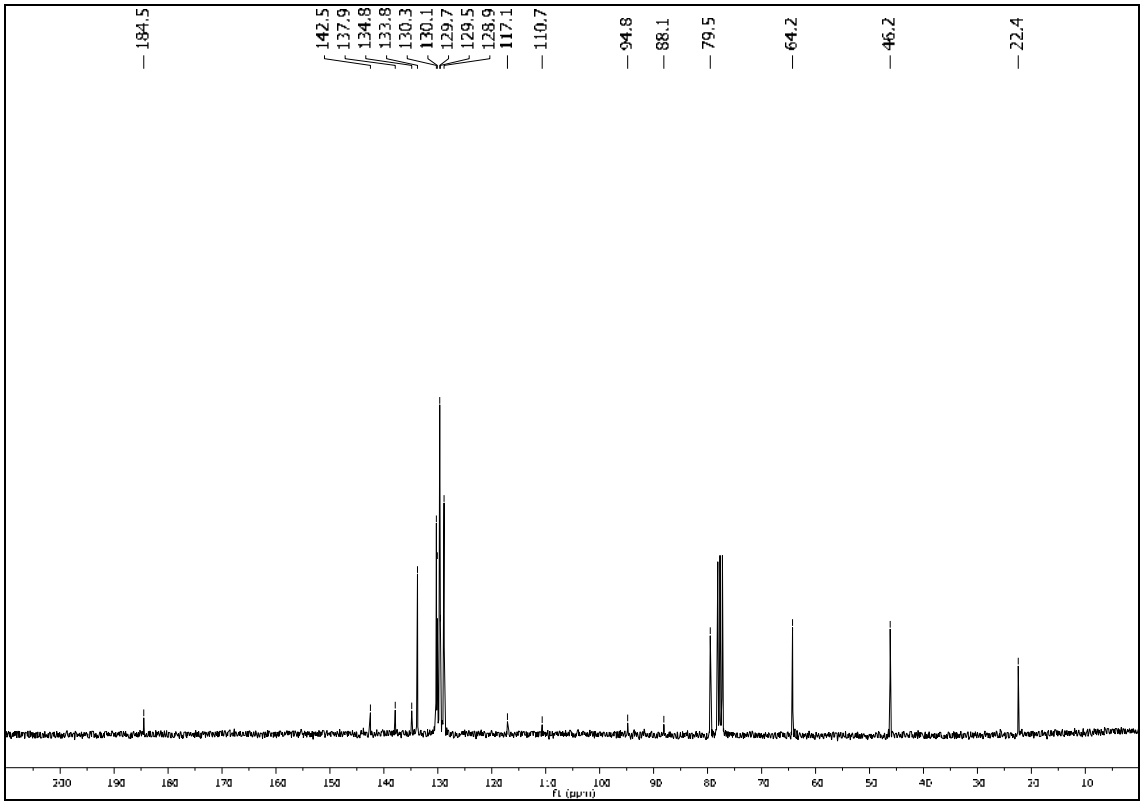
54CEa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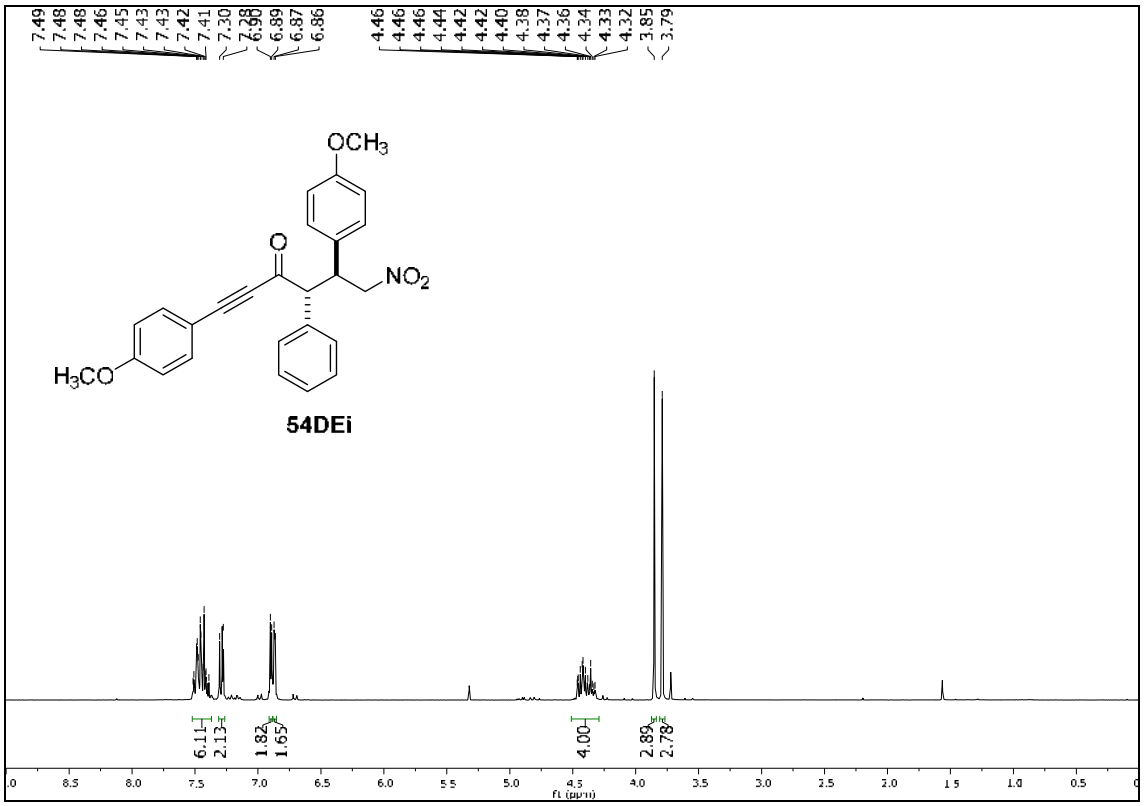
f1 (ppm)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4.32
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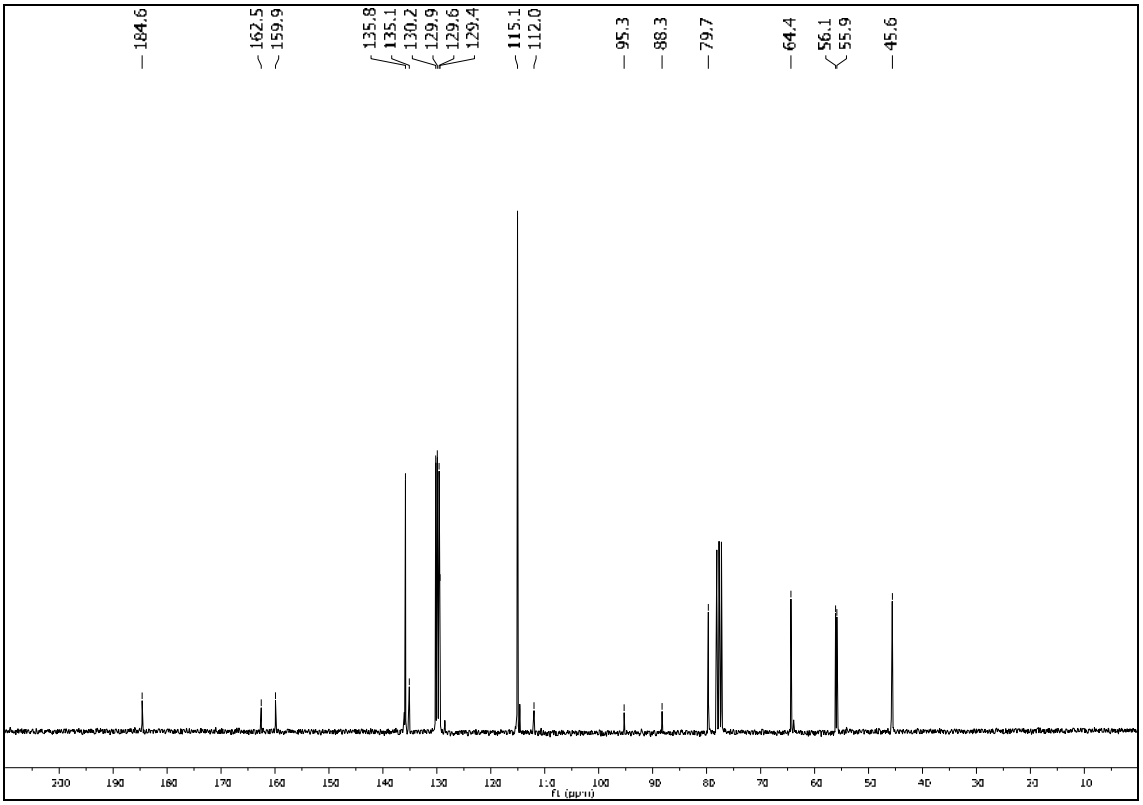
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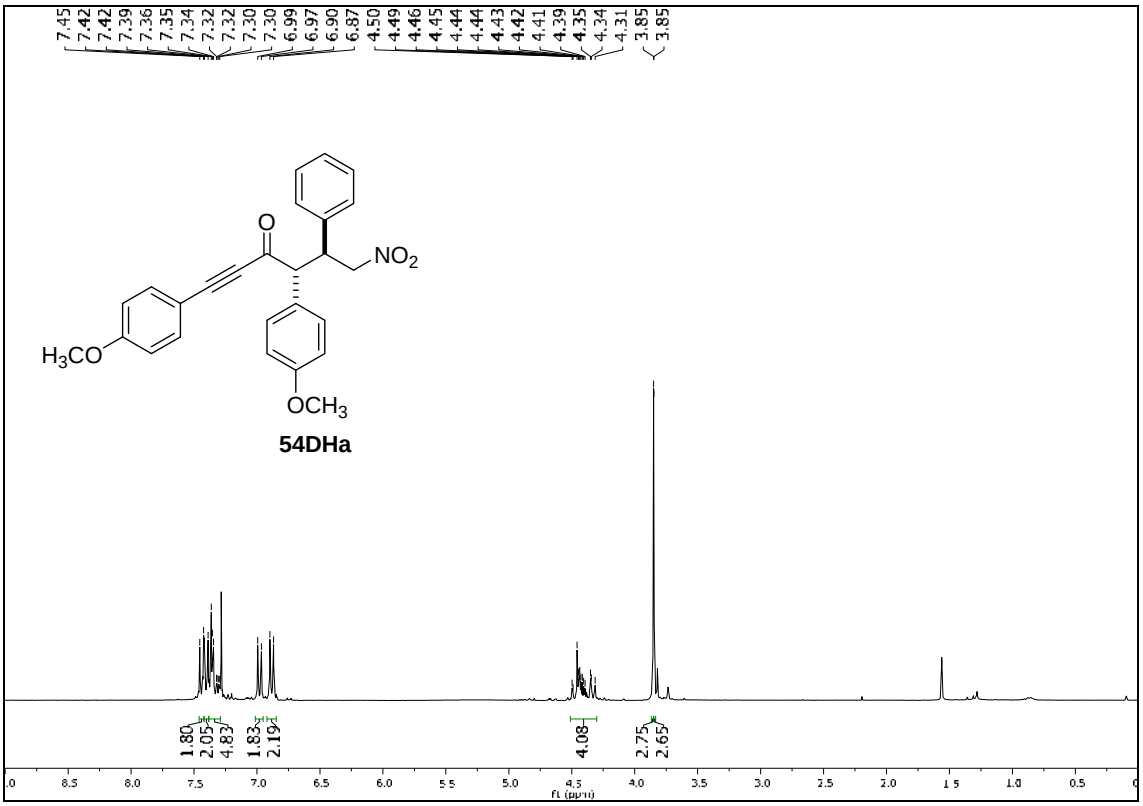
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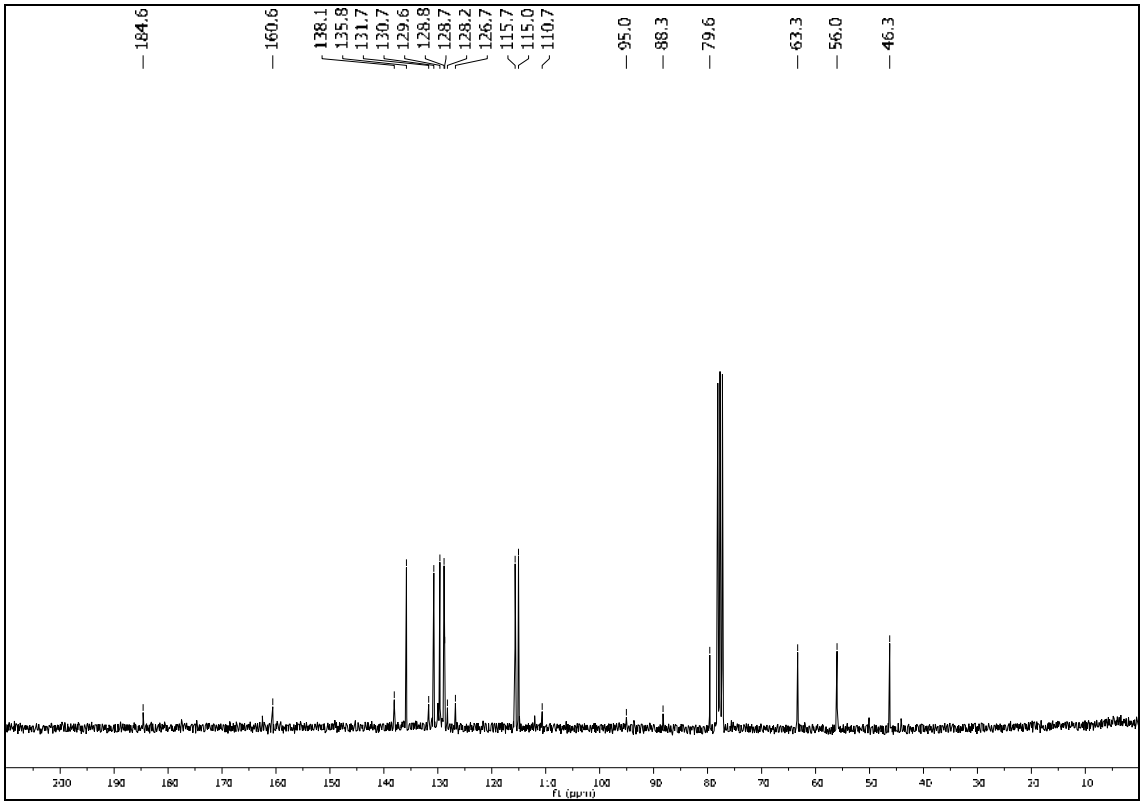
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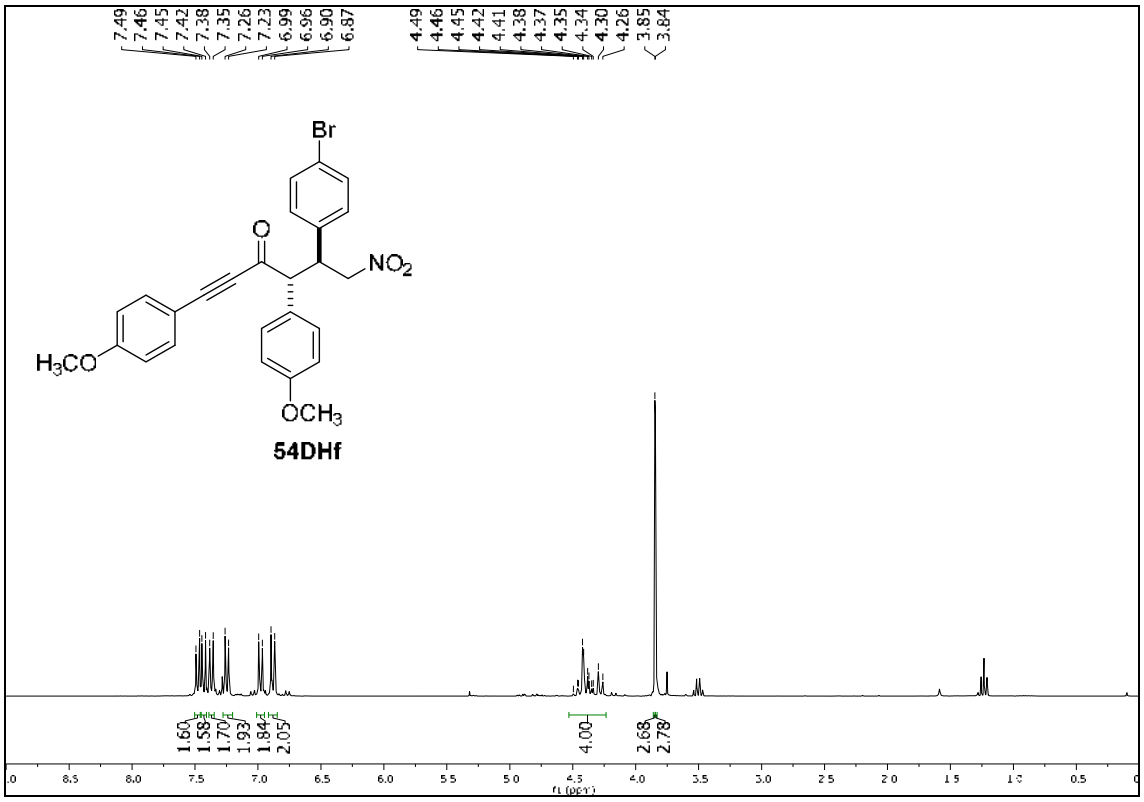
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3.84
Br
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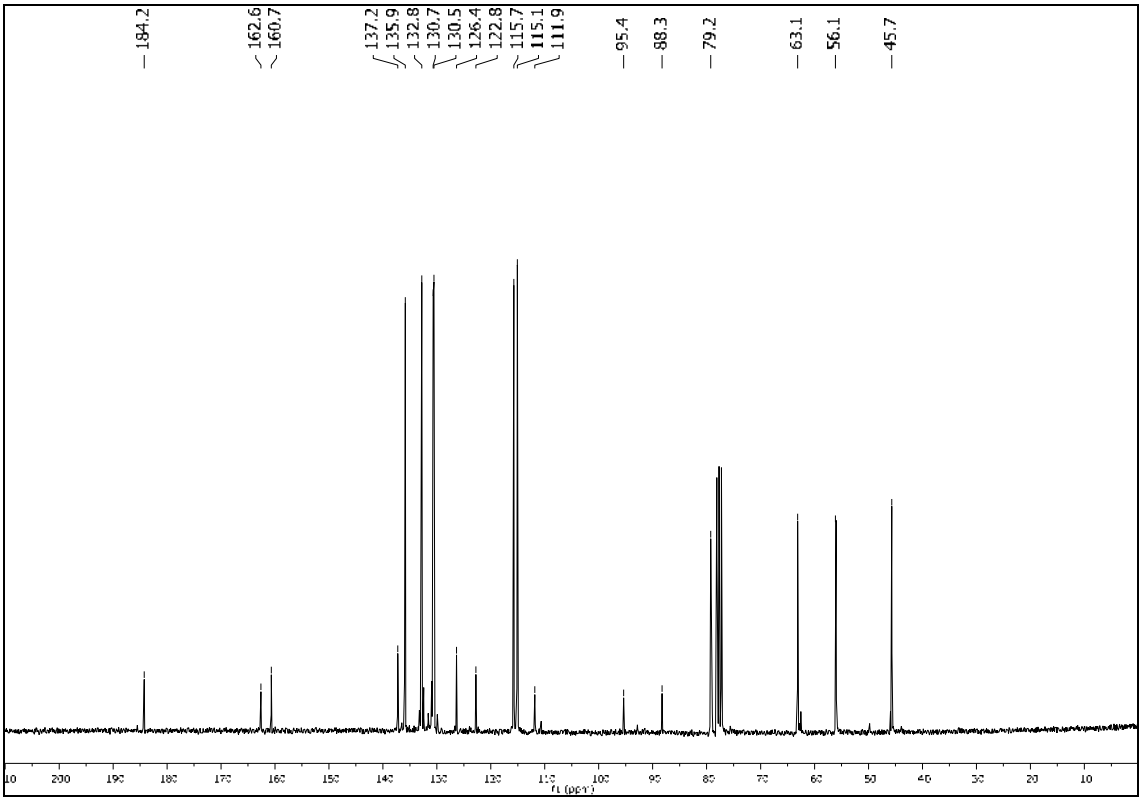
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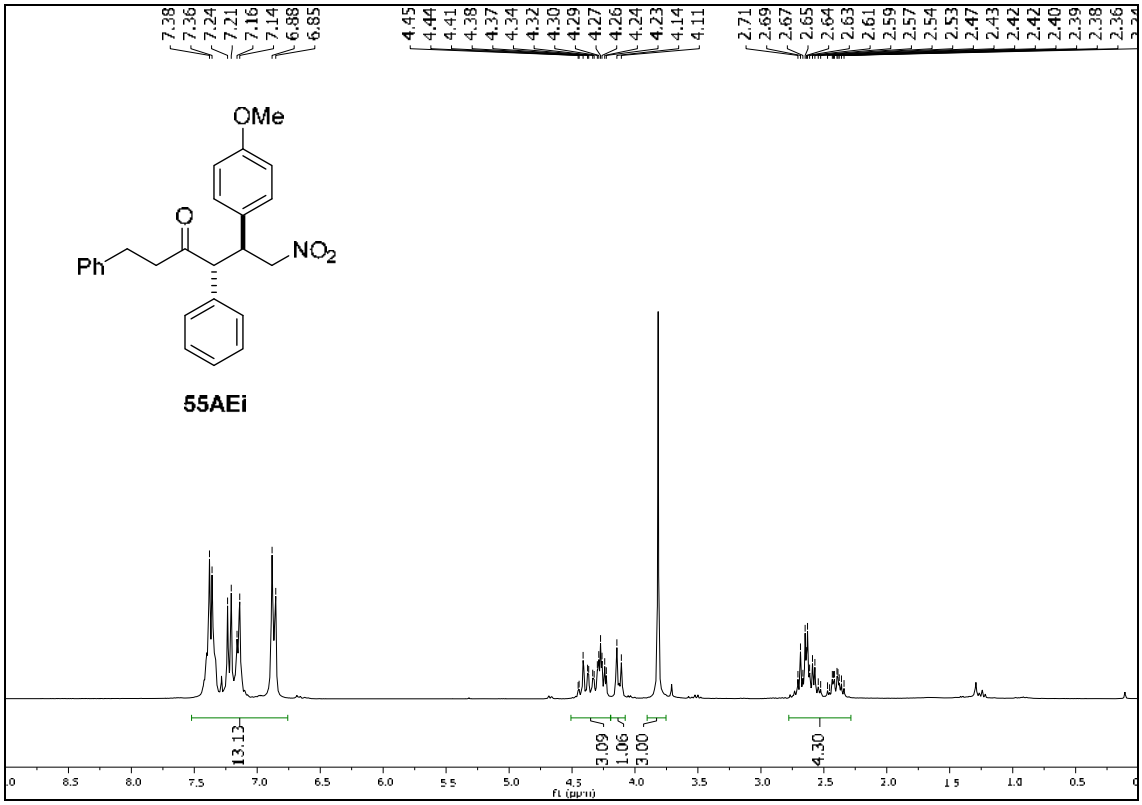
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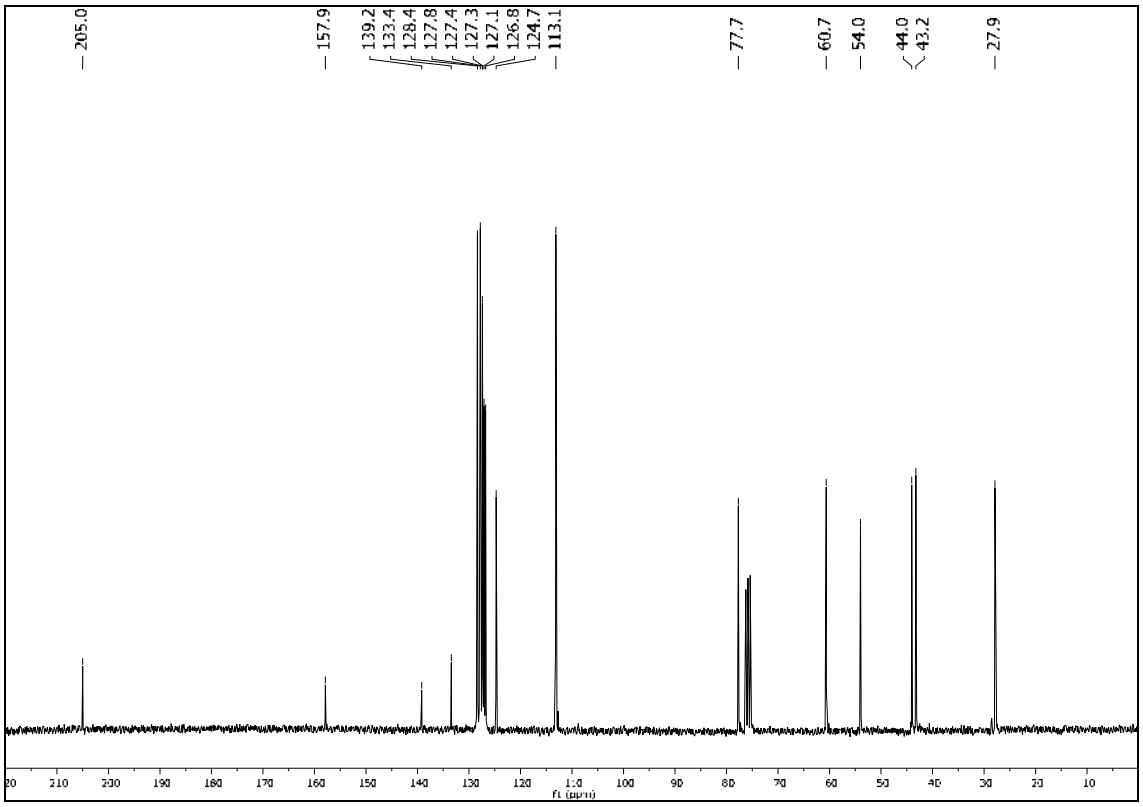
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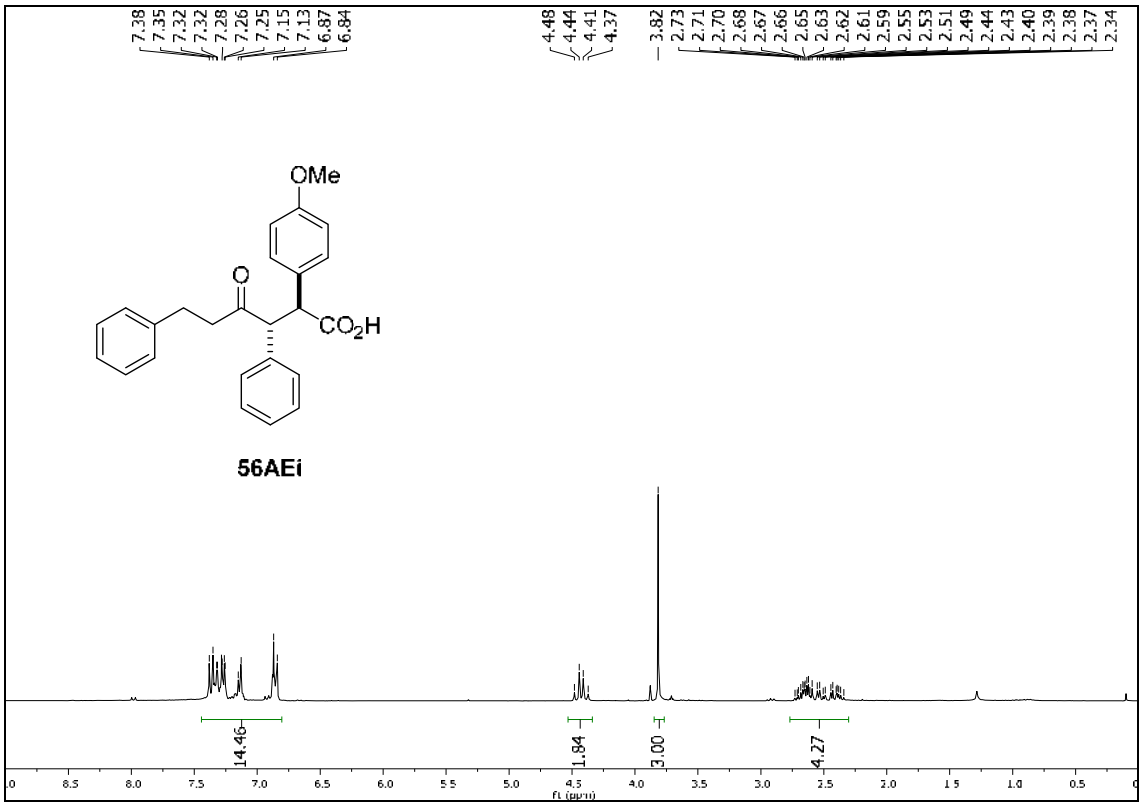
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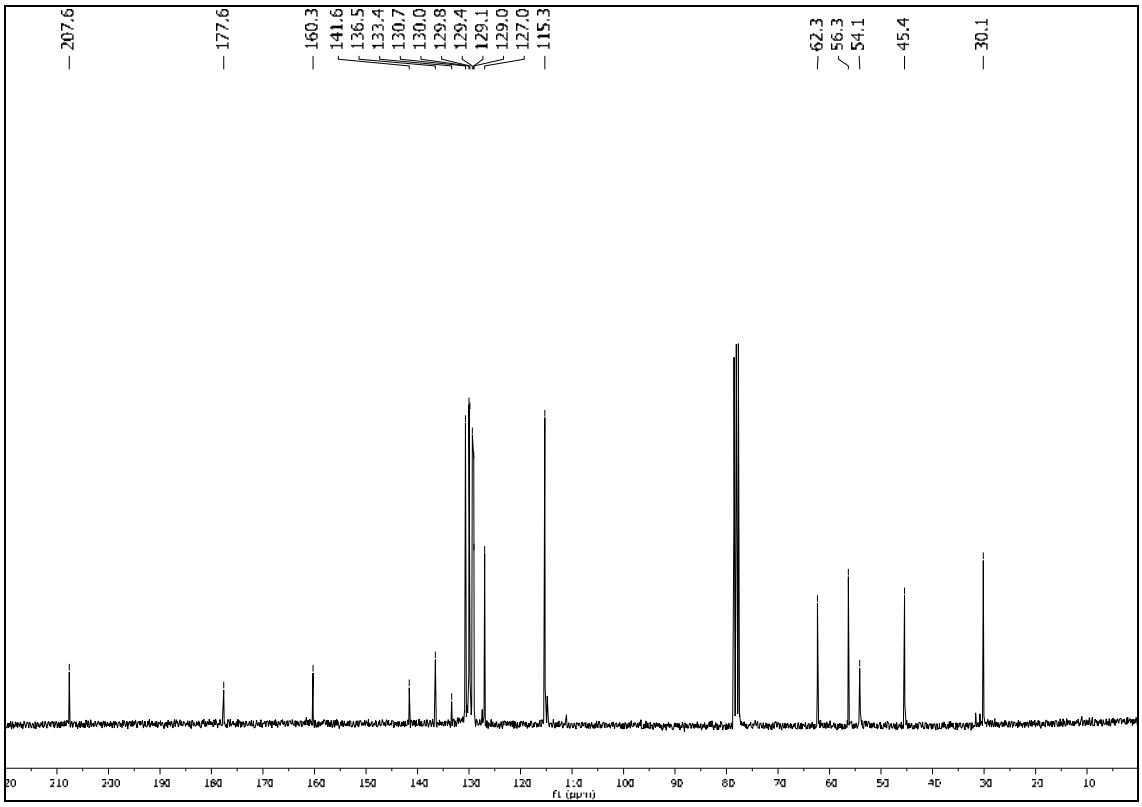
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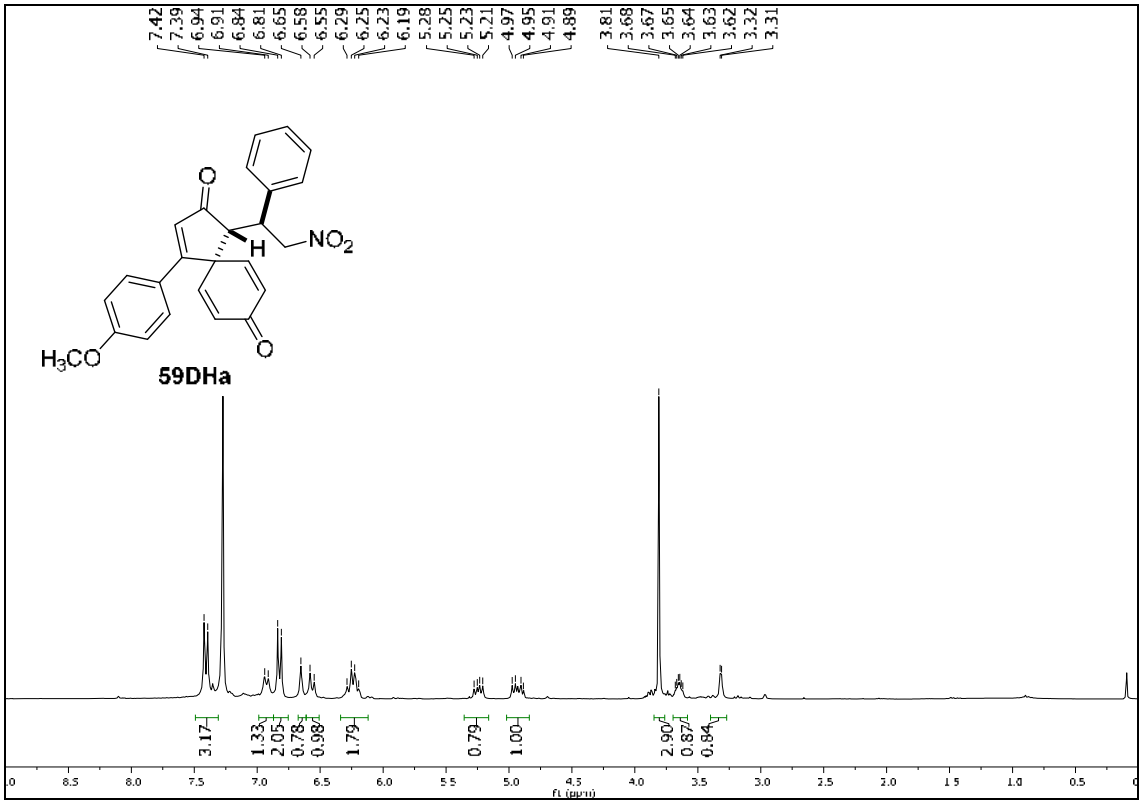
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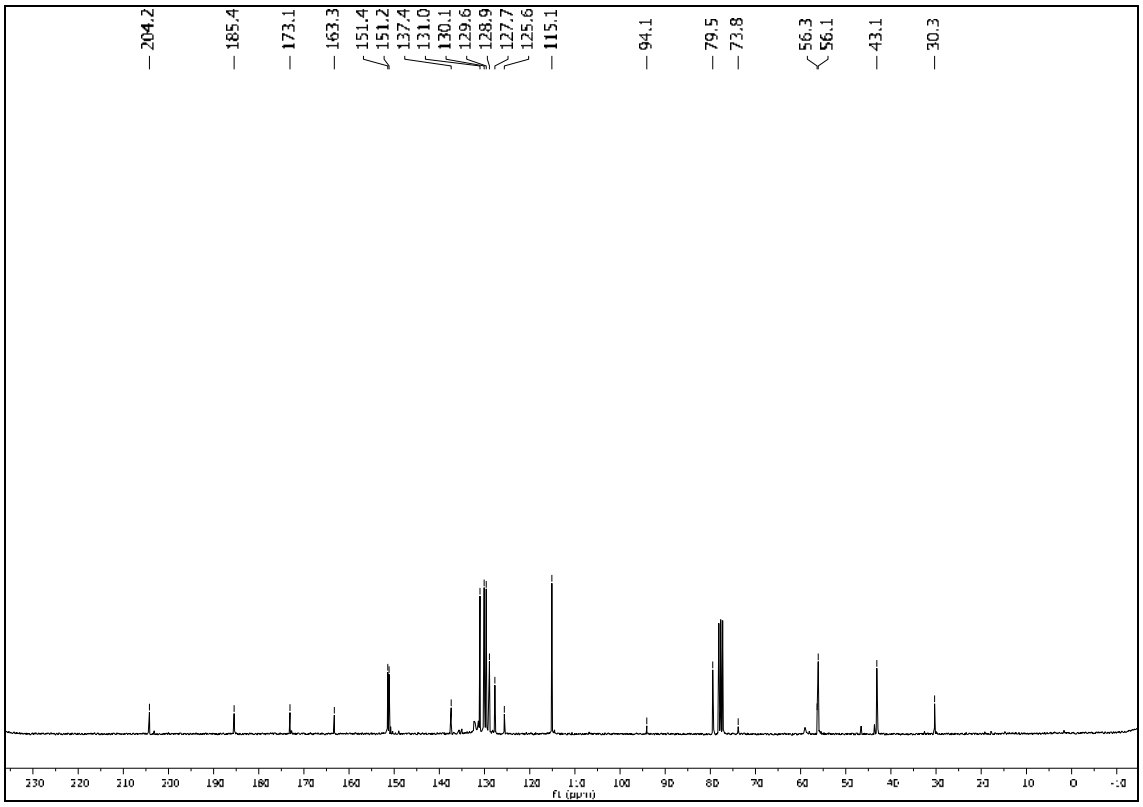
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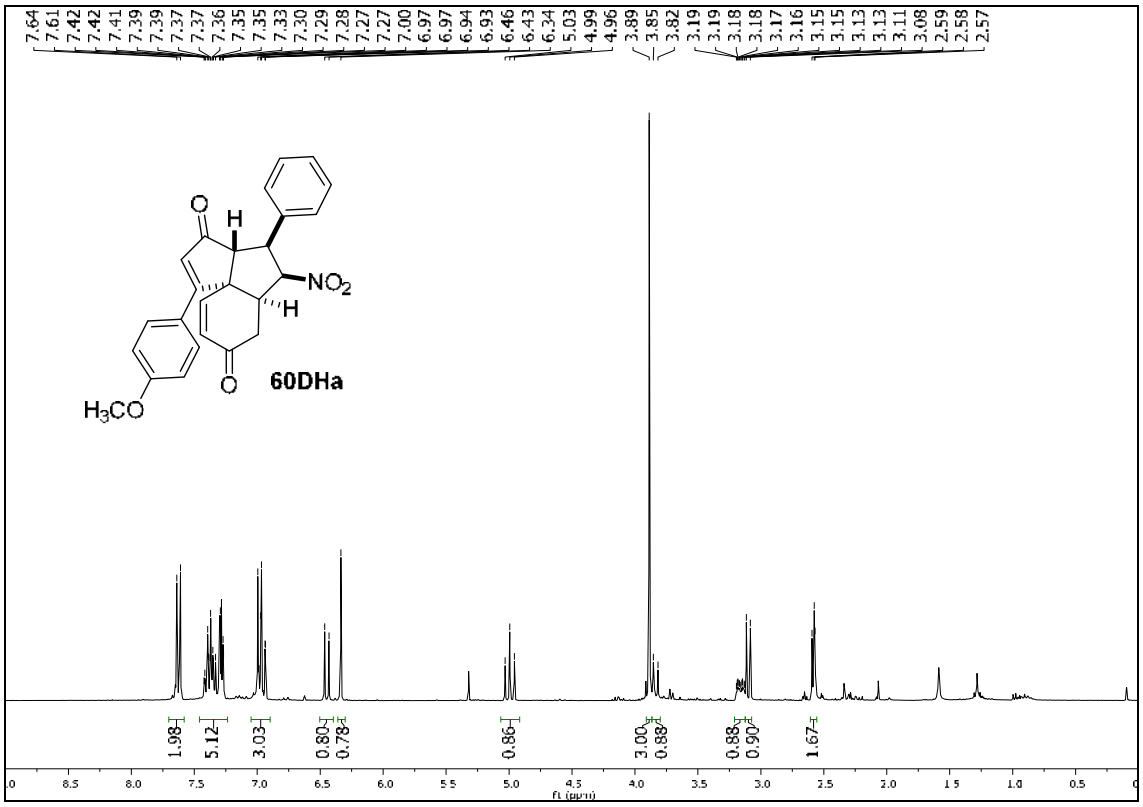
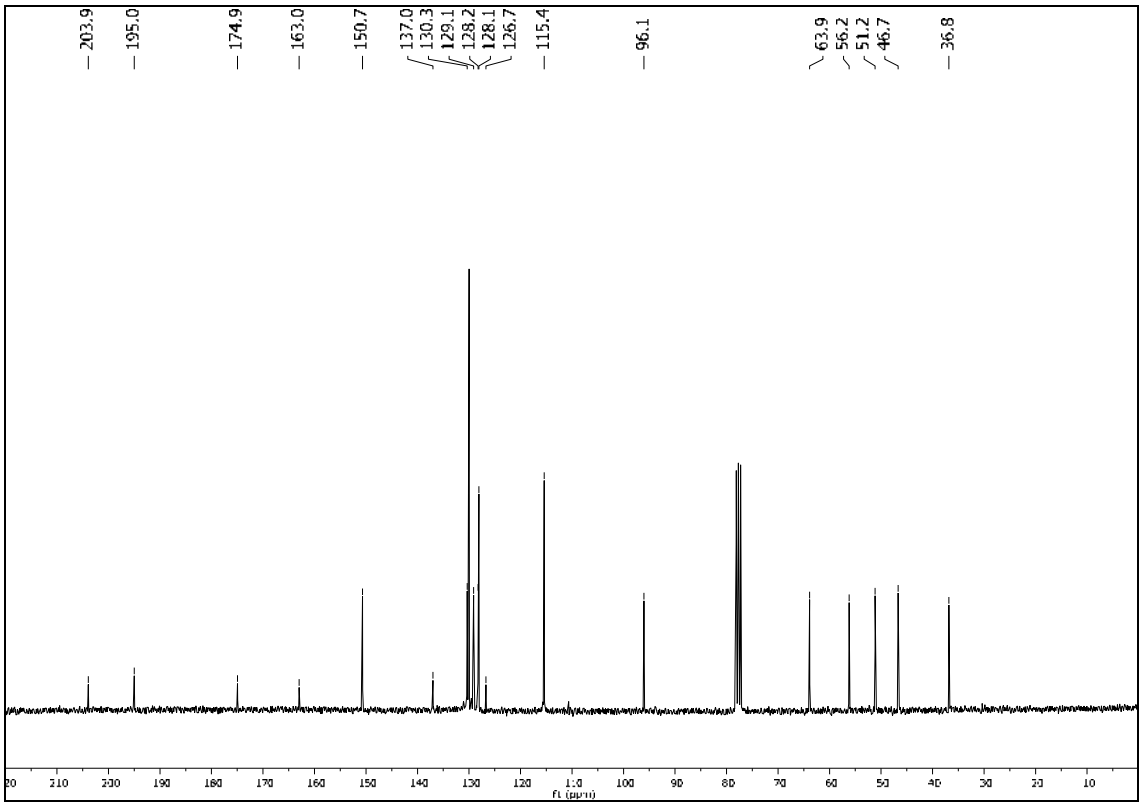
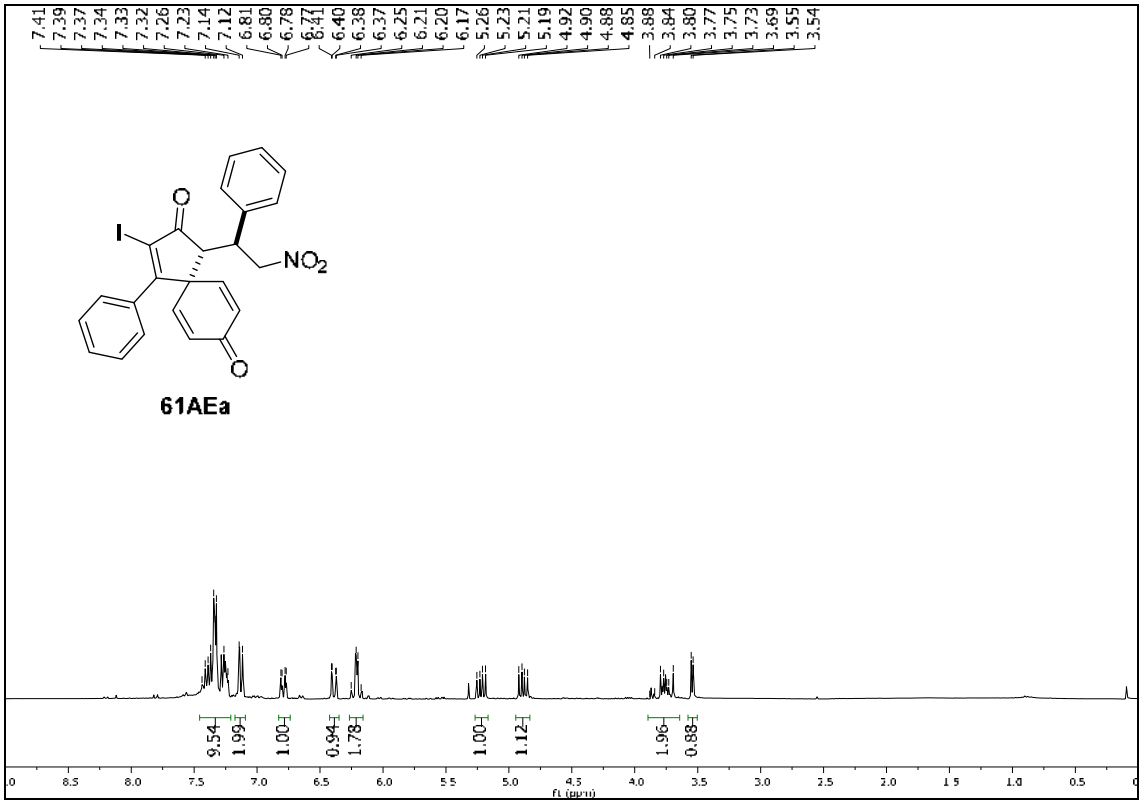
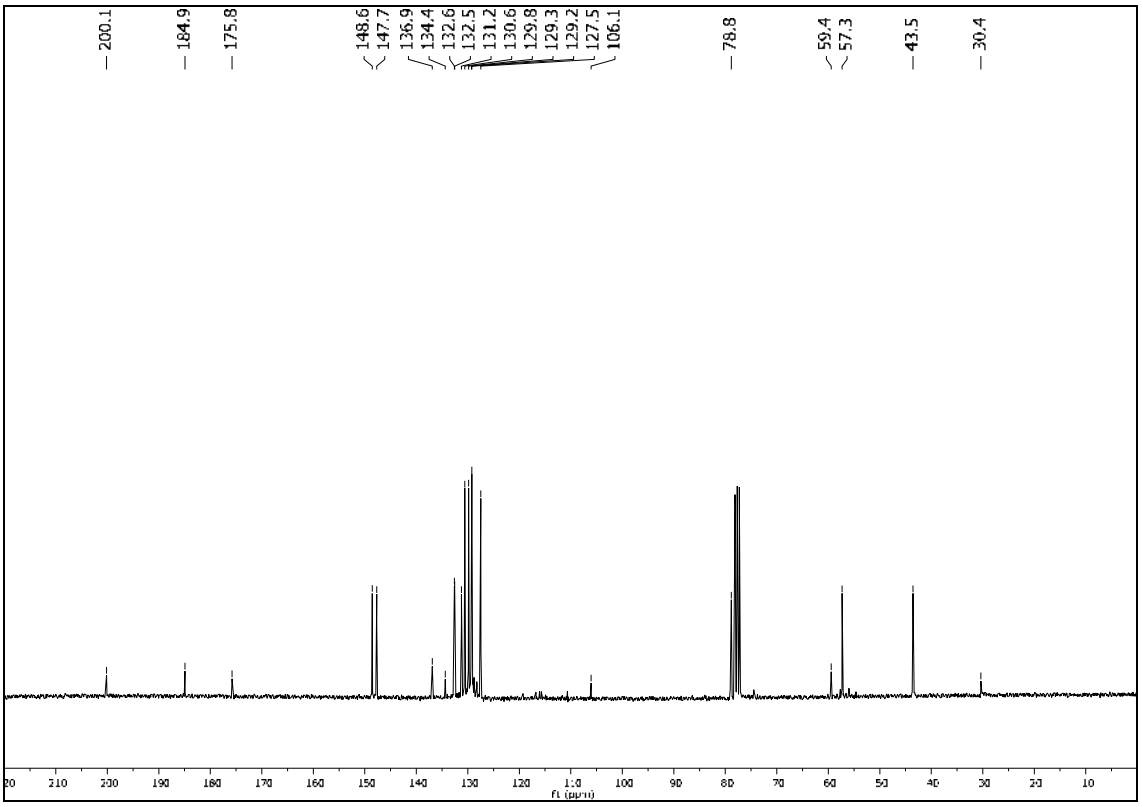
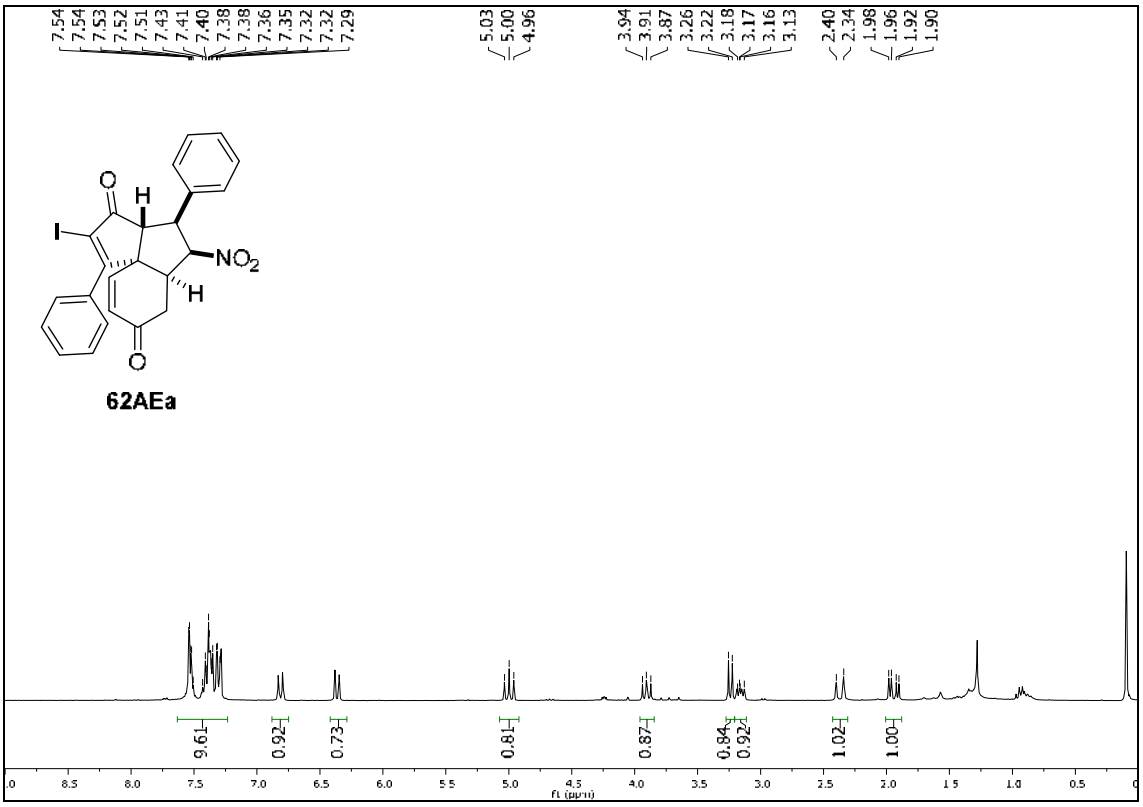

7.64
7.61
7.42
7.42
7.41
7.39
7.39
7.37
7.37
7.36
7.35
7.35
7.33
7.30
7.29
7.28
7.27
7.27
7.00
6.97
6.97
6.94
6.93
6.46
6.43
6.34
5.03
4.99
4.96
3.89
3.85
3.82
3.19
3.19
3.18
3.18
3.17
3.16
3.15
3.15
3.13
3.13
3.11
3.08
2.59
2.58
2.57
O
H
NO2
H
O
H3CO
60DHa
1.98
5.12
3.03
0.80
0.78
0.86
3.00
0.88
0.88
0.90
1.67


203.9
195.0
174.9
163.0
150.7
137.0
130.3
129.1
128.2
128.1
126.7
115.4
96.1
63.9
56.2
51.2
46.7
36.8

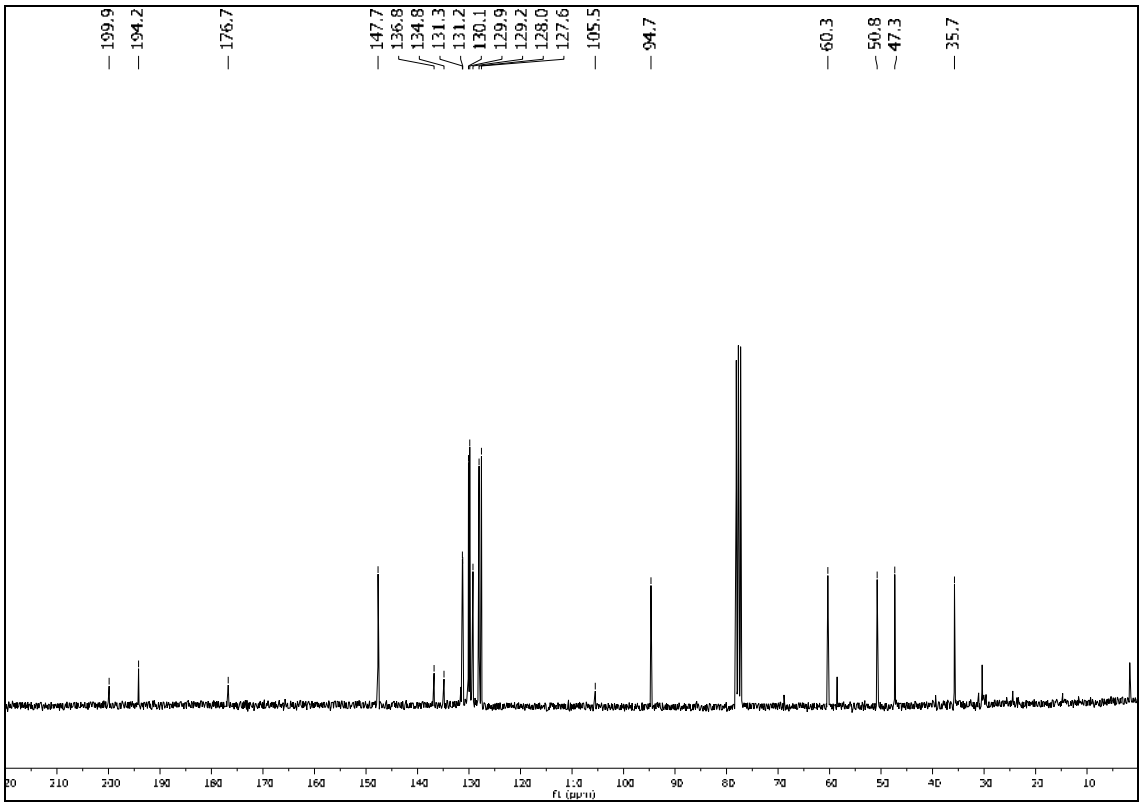

7.41
7.39
7.37
7.34
7.33
7.32
7.26
7.23
7.14
7.12
6.81
6.80
6.78
6.77
6.41
6.40
6.38
6.37
6.25
6.21
6.20
6.17
5.26
5.23
5.21
5.19
4.92
4.90
4.88
4.85
3.88
3.84
3.80
3.77
3.75
3.73
3.69
3.55
3.54
O
I
NO2
O
61AEa
9.54
1.99
1.00
0.94
1.78
1.00
1.12
1.96
0.88


200.1
184.9
175.8
148.6
147.7
136.9
134.4
132.6
132.5
131.2
130.6
129.8
129.3
129.2
127.5
106.1
78.8
59.4
57.3
43.5
30.4

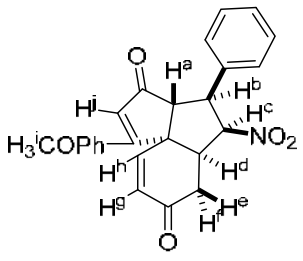

7.54
7.54
7.53
7.52
7.51
7.43
7.41
7.40
7.38
7.38
7.36
7.35
7.32
7.32
7.29
5.03
5.00
4.96
3.94
3.91
3.87
3.26
3.22
3.18
3.17
3.16
3.13
2.40
2.34
1.98
1.96
1.92
1.90
9.61
0.92
0.73
0.81
0.87
0.84
0.92
1.02
1.00

O
H
I
NO2
H
O

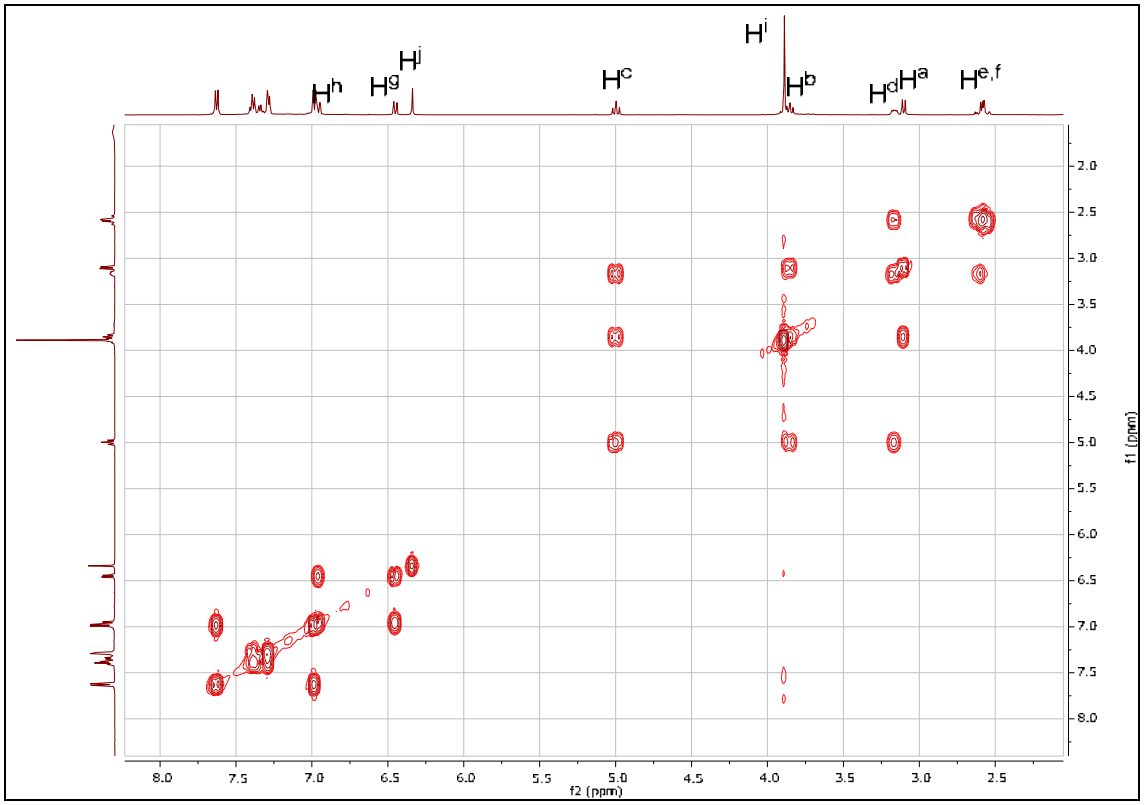
62AEa

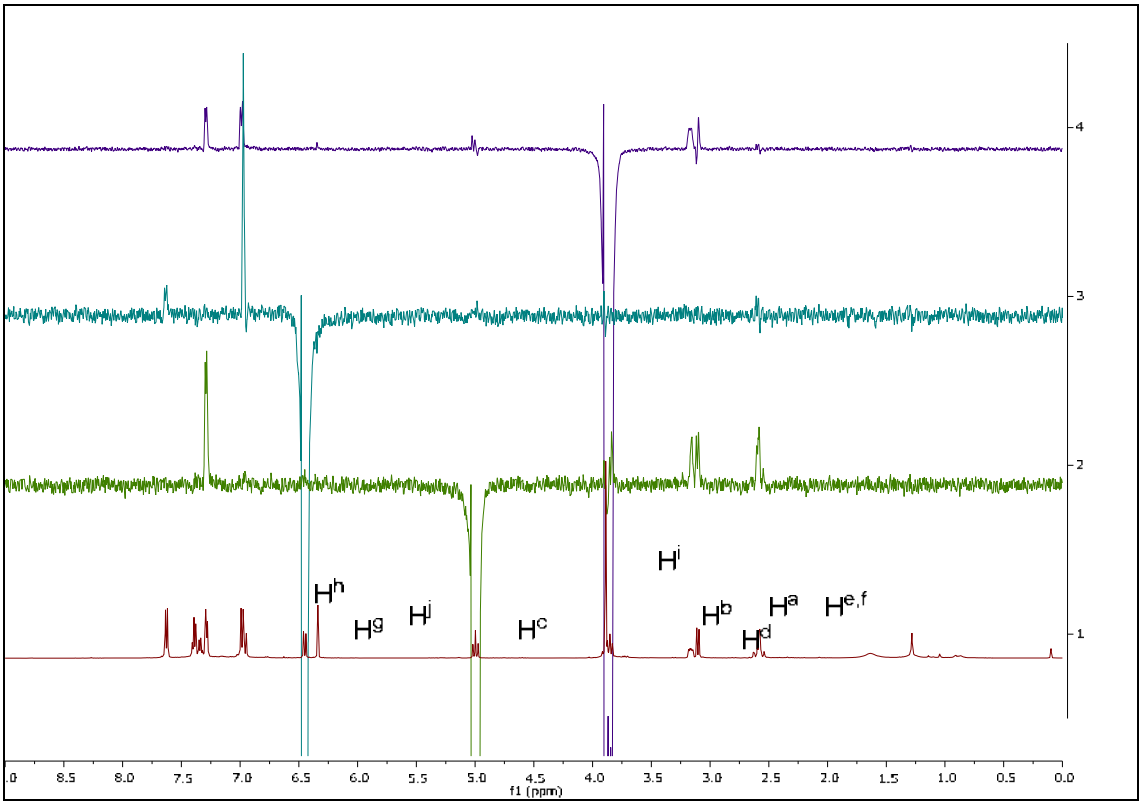


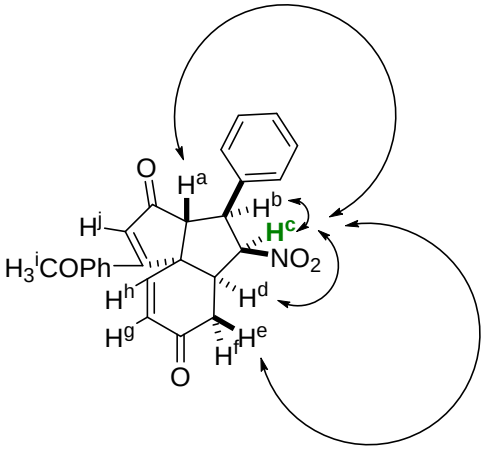
*7.7.3.2. NOE and NOESY spectra for the compounds **60DHa** and **62AEa***

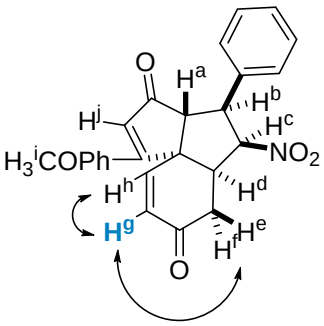


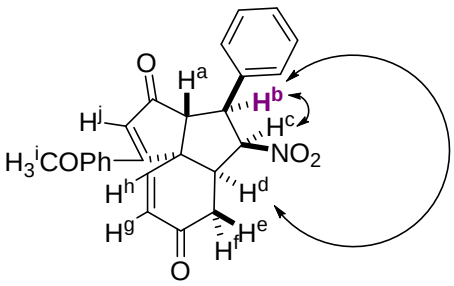
60DHa

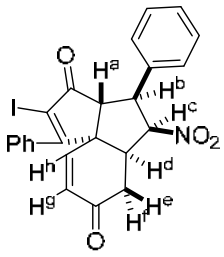

H^i
H^h
H^g
H^j
H^c
H^b
H^d
H^a
H^e,f
f2 (ppm)
f1 (ppm)


H^h
H^g
H^j
H^c
H^i
H^b
H^a
H^e,f
H^d
f1 (ppm)

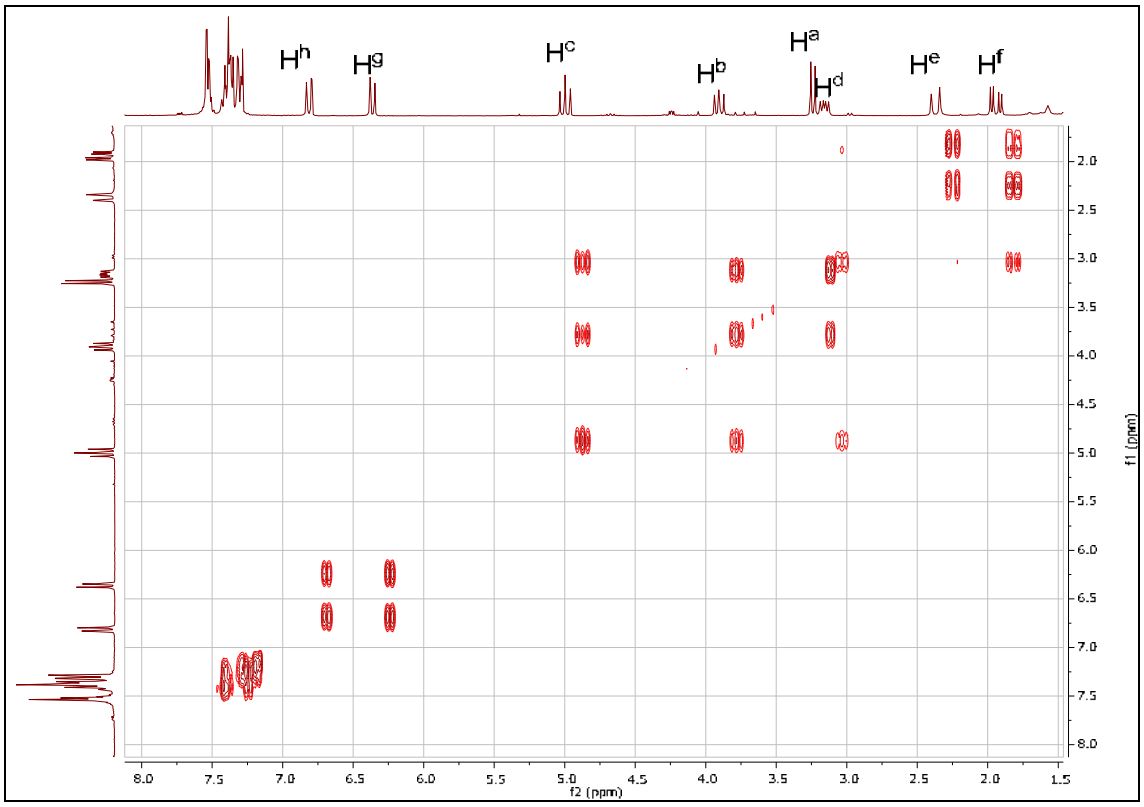

O
H^a
H^b
H^c
H^j
H3^iCOPh
NO2
H^h
H^d
H^g
H^f
H^e
O

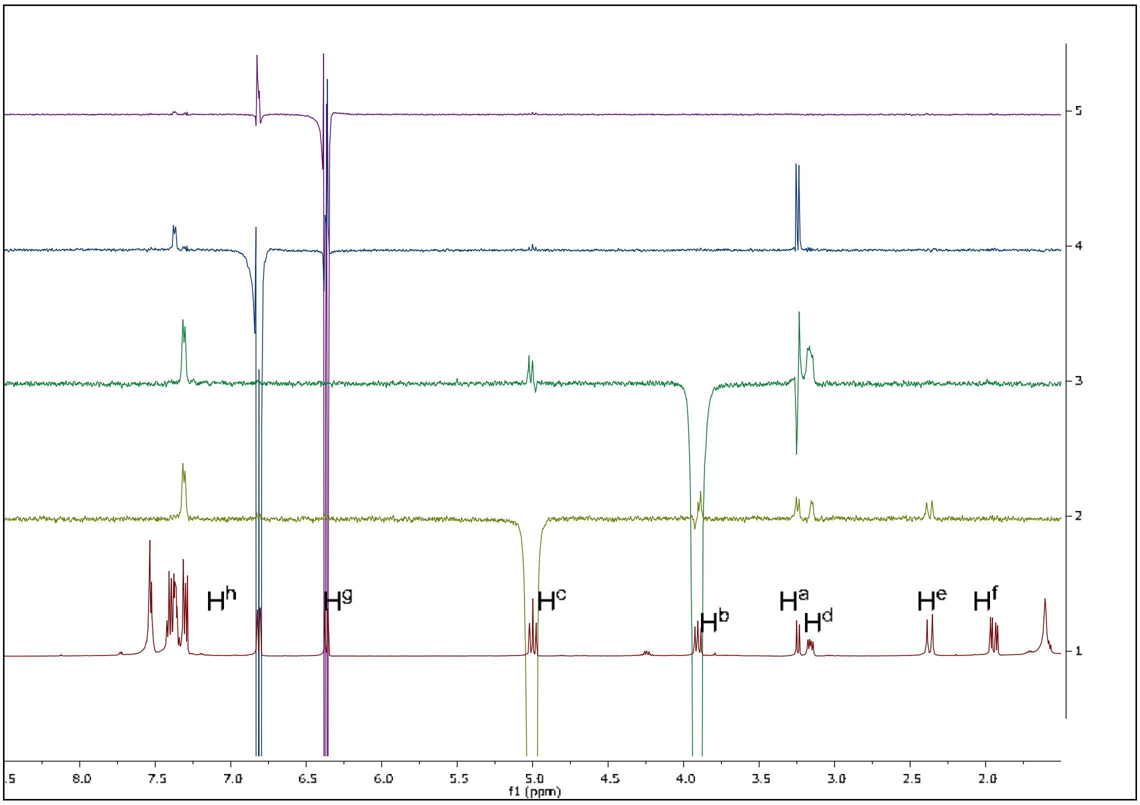

O
H^a
H^b
H^c
H^j
H3^iCOPh
NO2
H^h
H^d
H^g
H^f
H^e
O

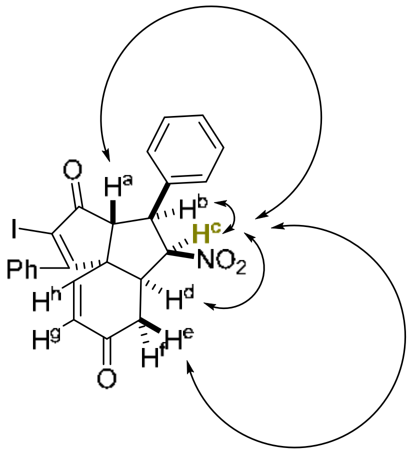

O
H^a
H^b
H^c
H^j
H3^iCOPh
NO2
H^h
H^d
H^g
H^f
H^e
O

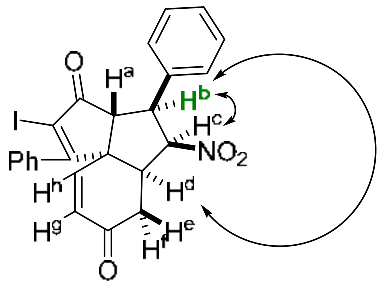

O
Ha
Hb
Hc
I
NO2
Ph
Hh
Hd
Hg
He
Hf
O

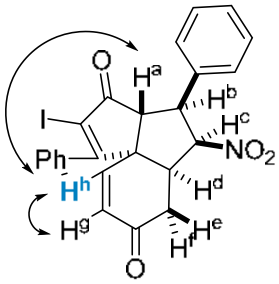
62AEa

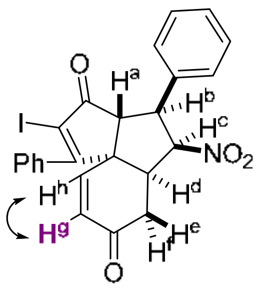

Hh
Hg
Hc
Hb
Ha
Hd
He
Hf
f2 (ppm)
f1 (ppm)


Hh
Hg
Hc
Hb
Ha
Hd
He
Hf
5
4
3
2
1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

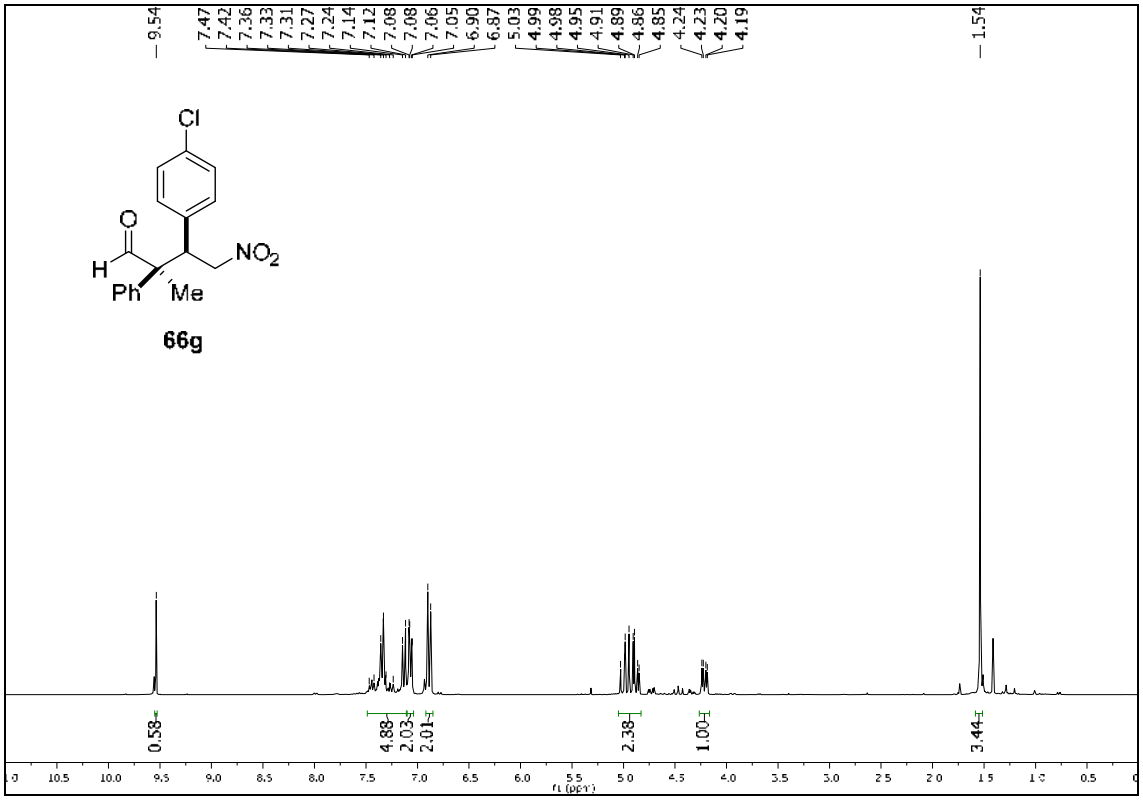

O
Ha
I
Hb
Hc
NO2
Ph
Hh
Hd
Hg
He
Hf
O

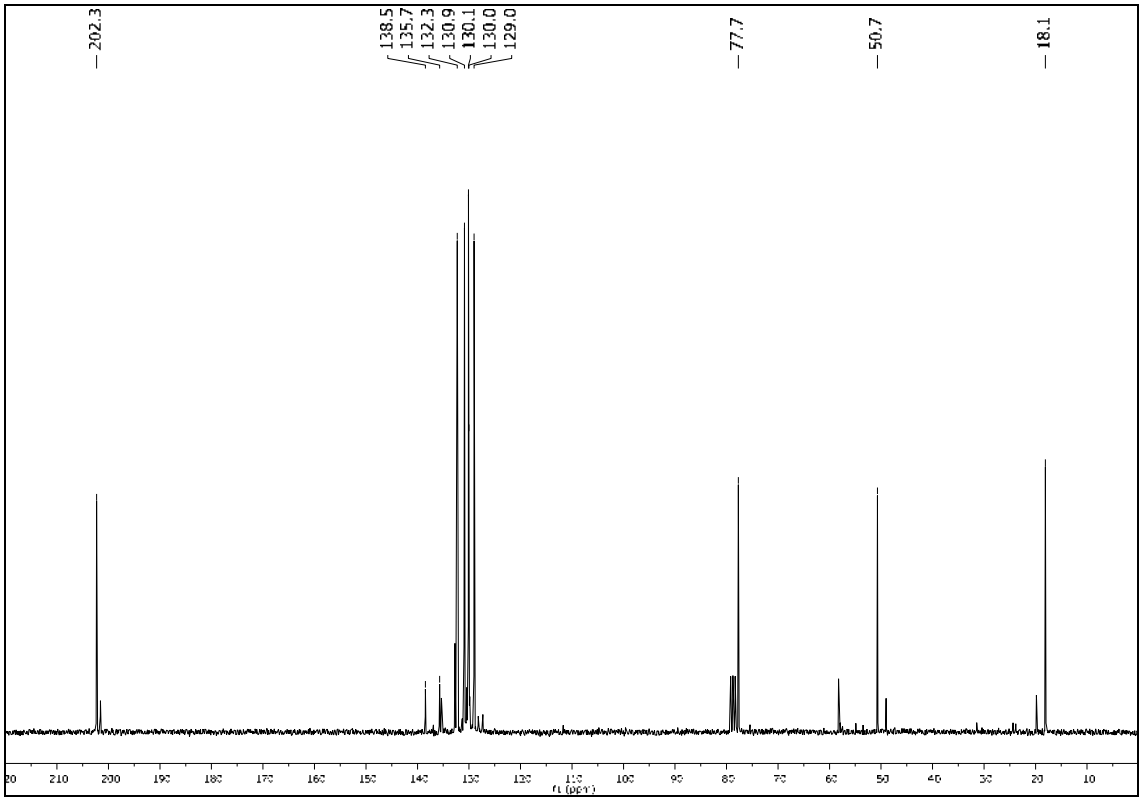

O
Ha
Hb
I
Hc
NO2
Ph
Hh
Hd
Hg
He
Hf
O

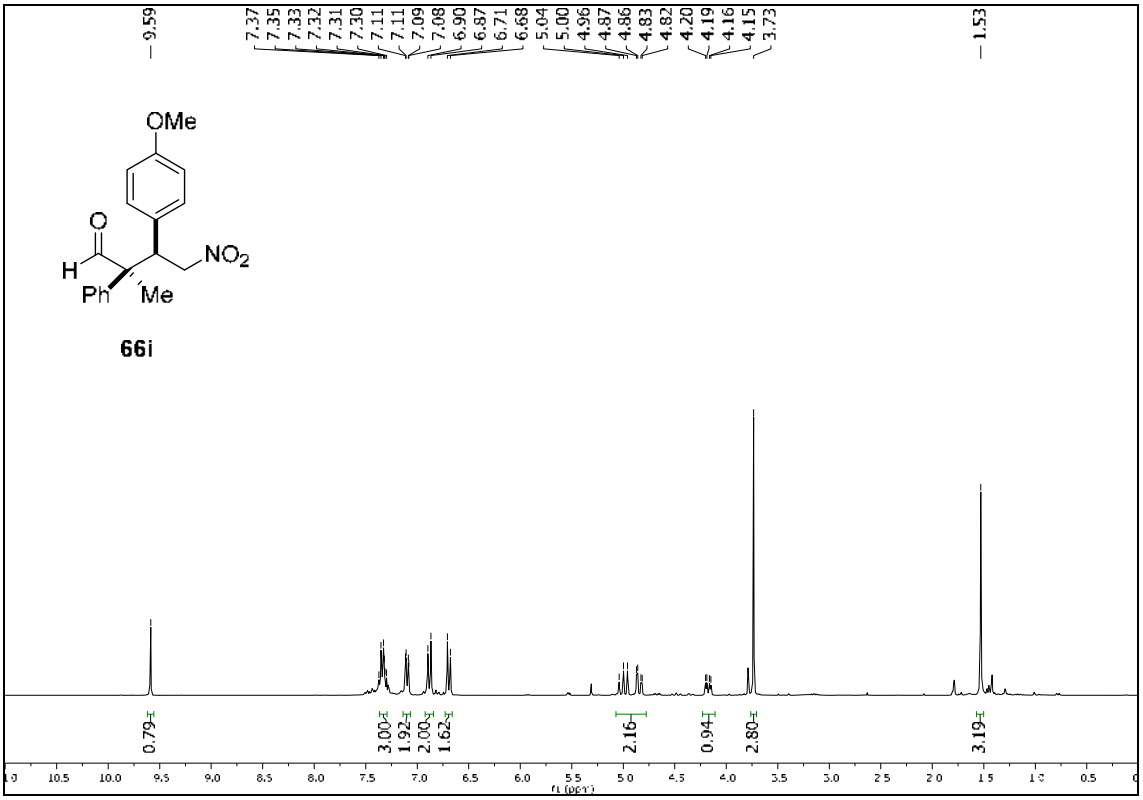

O
Ha
Hb
I
Hc
NO2
Ph
Hh
Hd
Hg
He
Hf
O

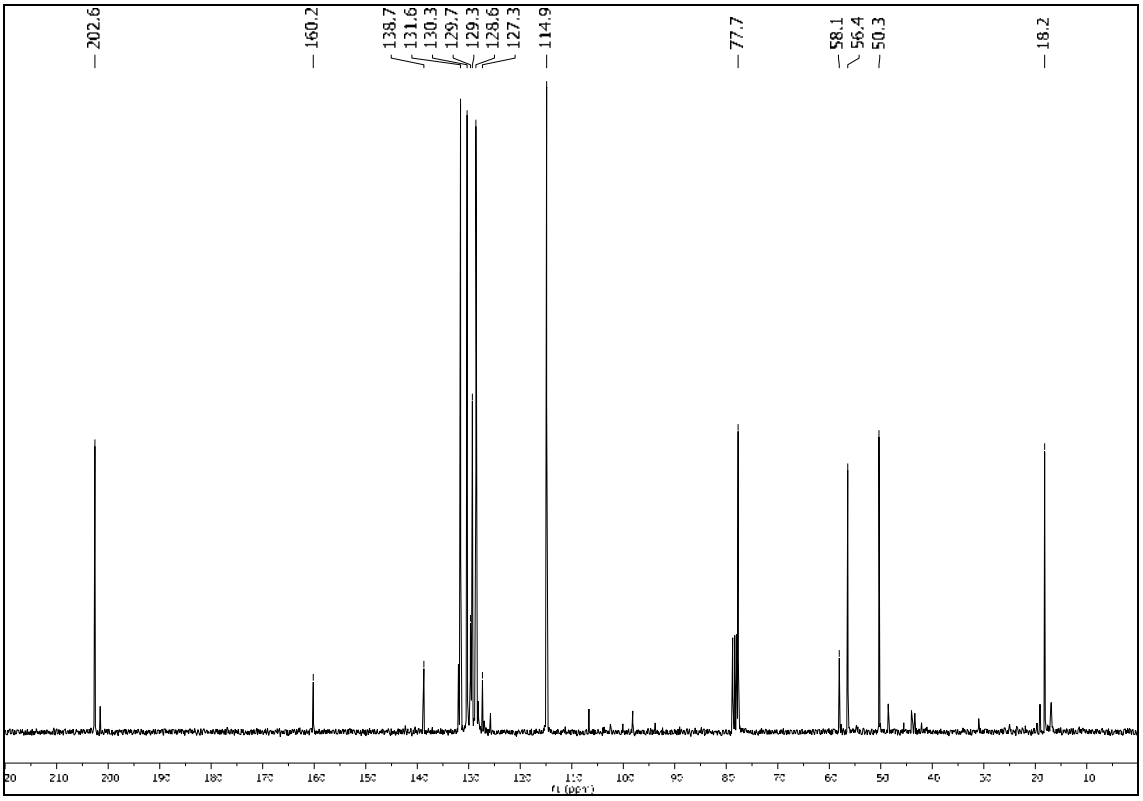

O
Ha
Hb
I
Hc
NO2
Ph
Hh
Hd
Hg
He
Hf
O

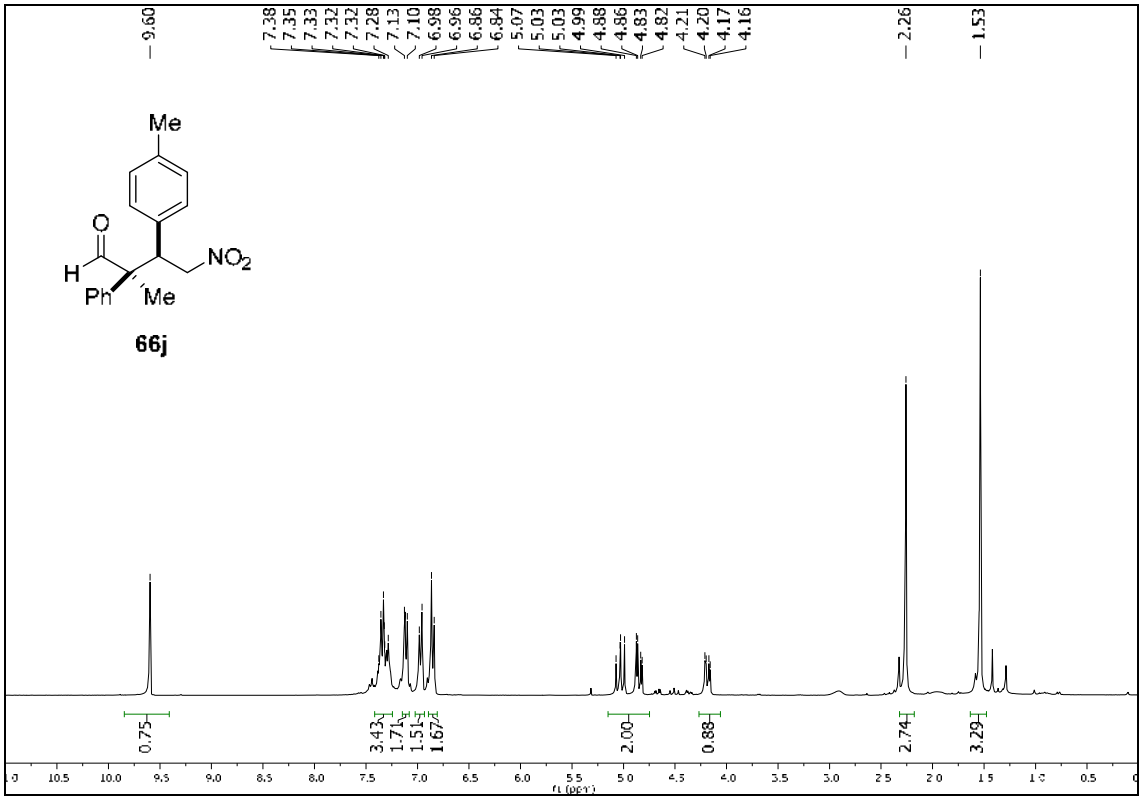
7.7.4. NMR spectra for Chapter 4

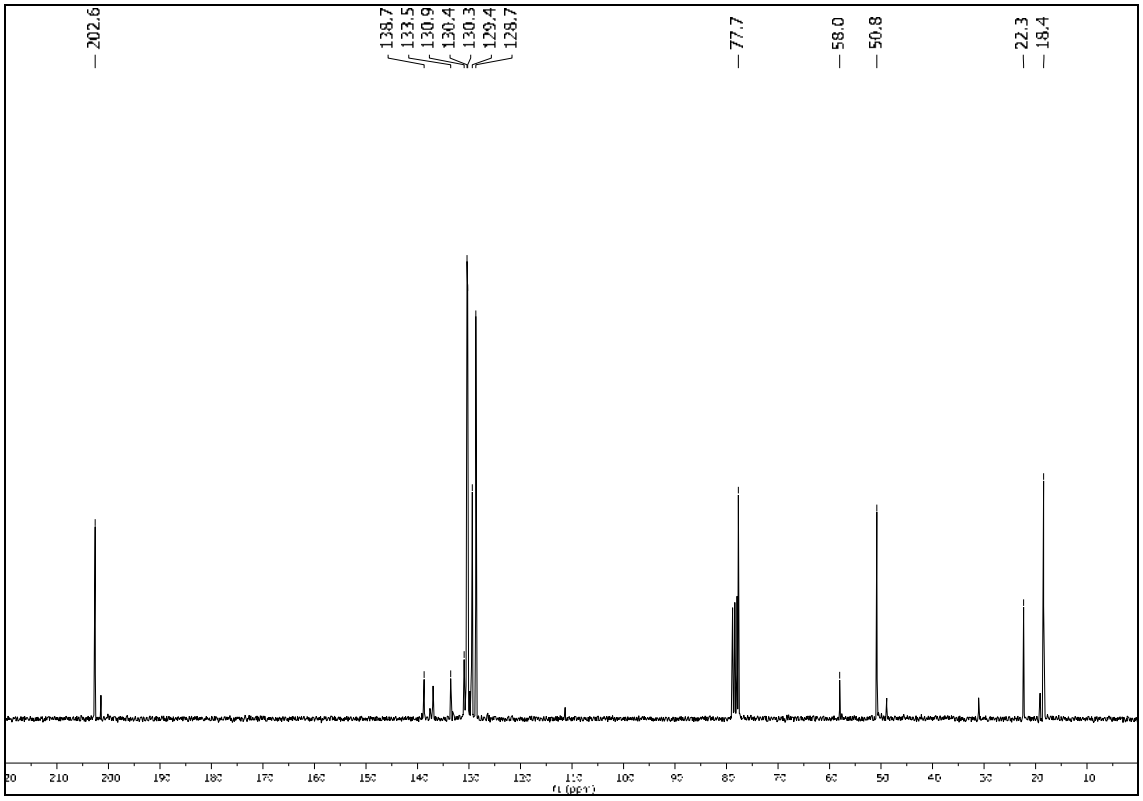




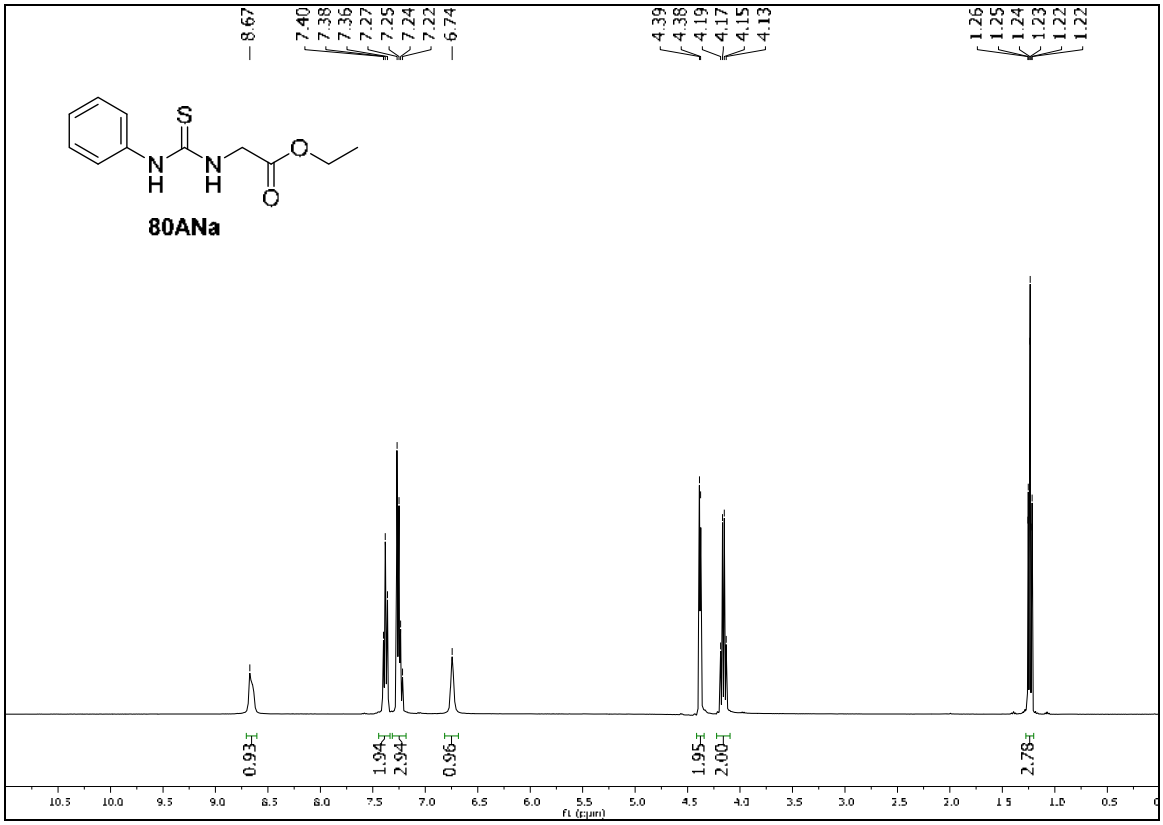

9.59
7.37
7.35
7.33
7.32
7.31
7.30
7.11
7.11
7.09
7.08
6.90
6.87
6.71
6.68
5.04
5.00
4.96
4.87
4.86
4.83
4.82
4.20
4.19
4.16
4.15
3.73
1.53
OMe
O
H
NO2
Ph
Me
66i
0.79
3.00
1.92
2.00
1.62
2.16
0.94
2.80
3.19

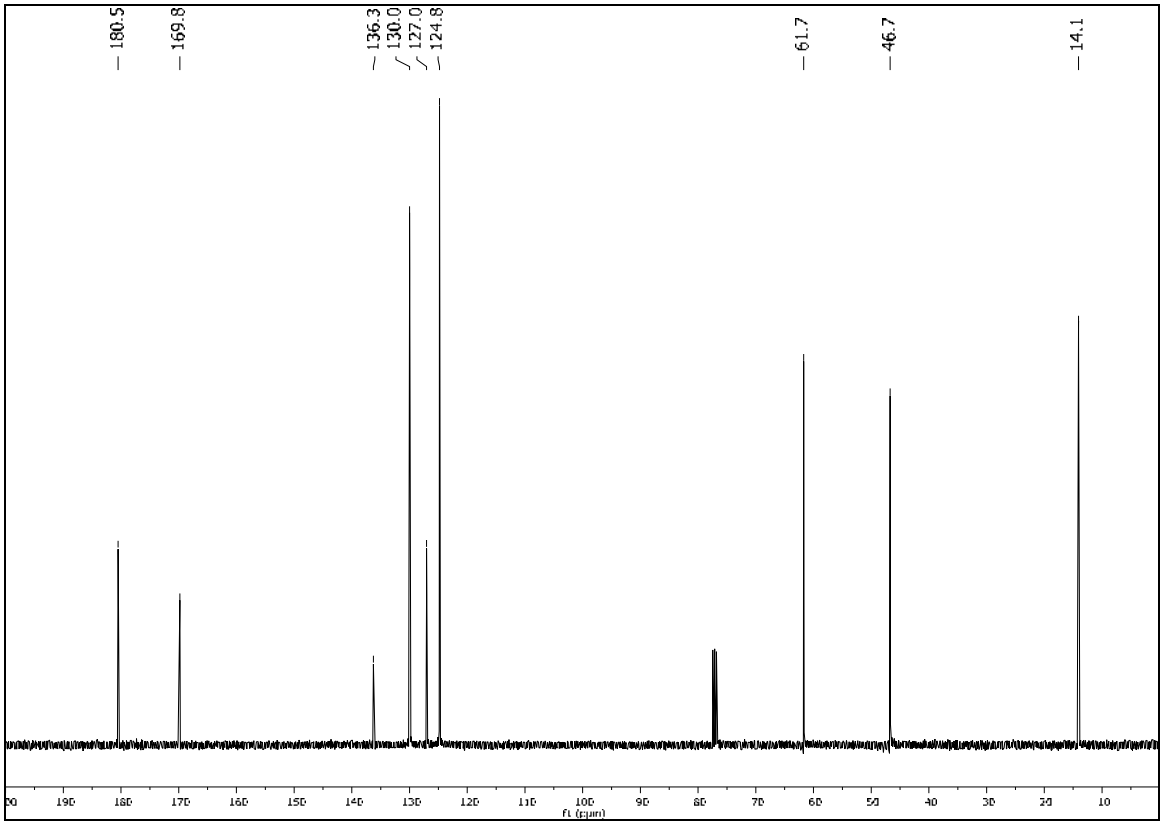

202.6
160.2
138.7
131.6
130.3
129.7
129.3
128.6
127.3
114.9
77.7
58.1
56.4
50.3
18.2

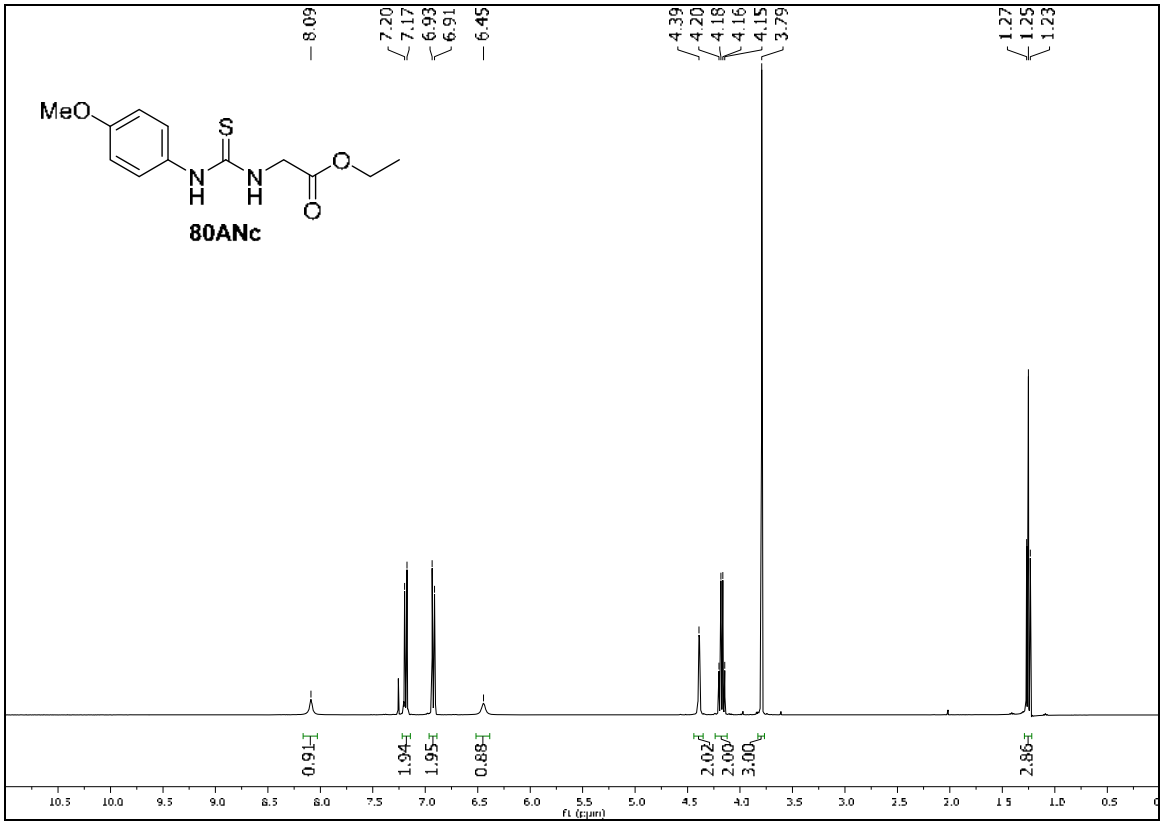

9.60
7.38
7.35
7.33
7.32
7.32
7.28
7.13
7.10
6.98
6.96
6.86
6.84
5.07
5.03
5.03
4.99
4.88
4.86
4.83
4.82
4.21
4.20
4.17
4.16
2.26
1.53
Me
O
H
NO2
Ph
Me
66j
0.75
3.43
1.71
1.51
1.67
2.00
0.88
2.74
3.29

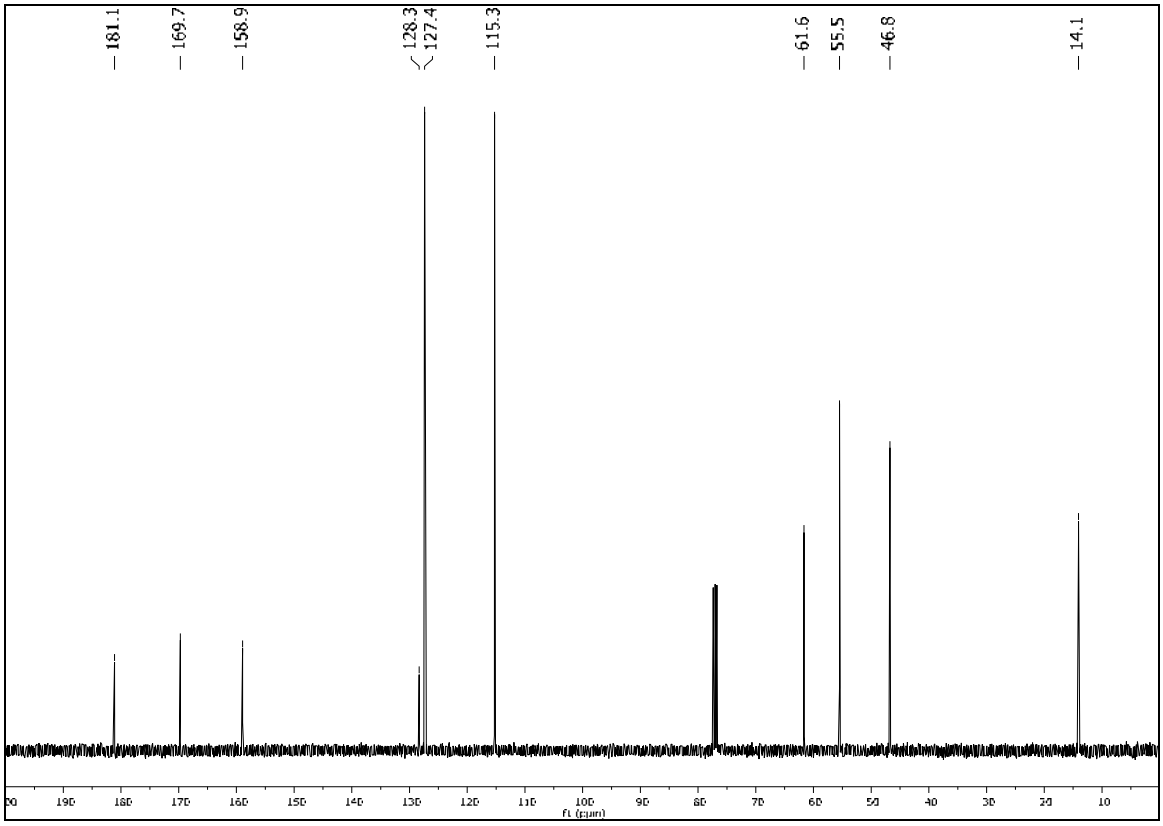

202.6
138.7
133.5
130.9
130.4
130.3
129.4
128.7
77.7
58.0
50.8
22.3
18.4

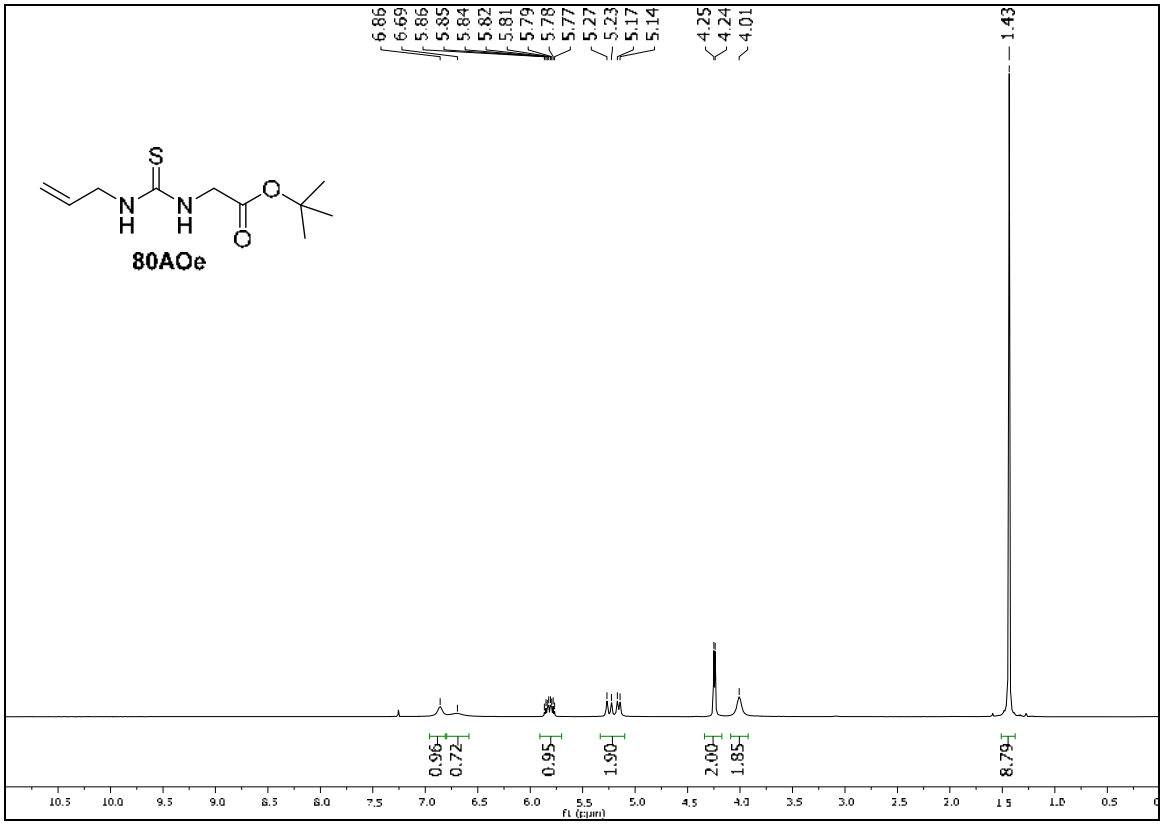
7.7.5. NMR spectra for Chapter 5

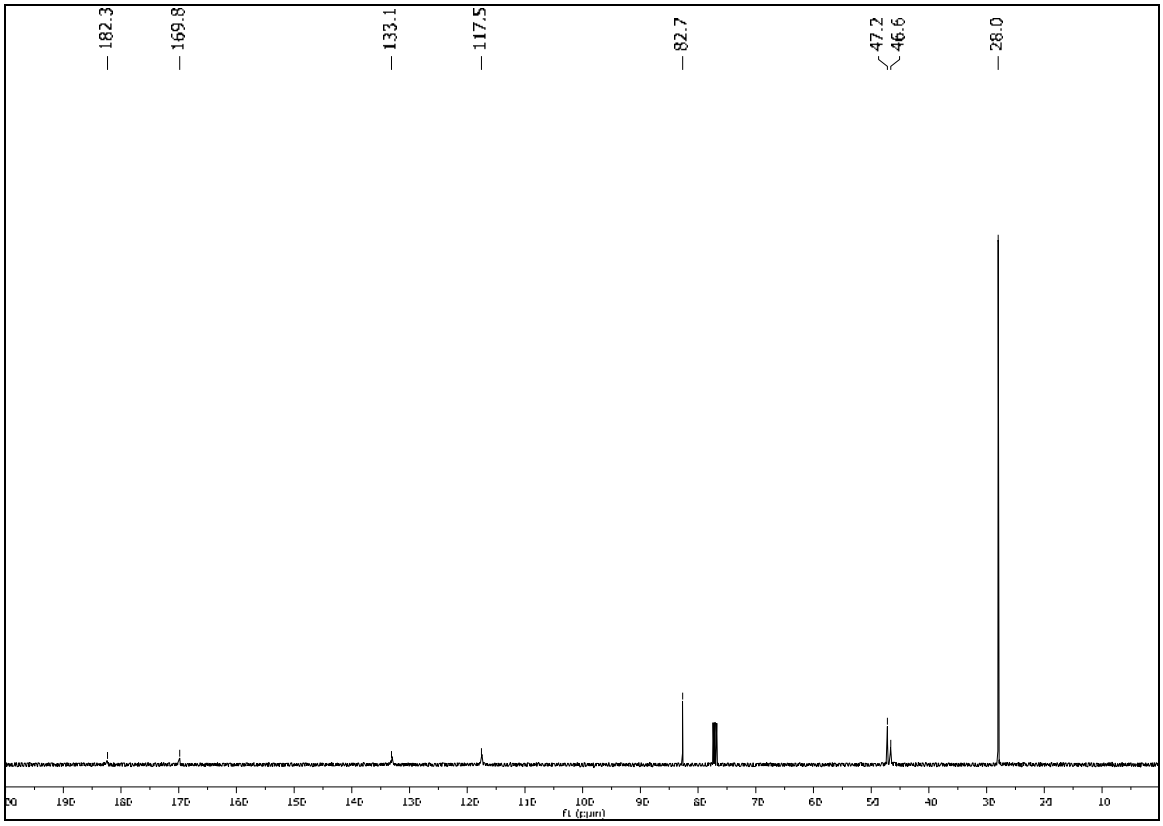


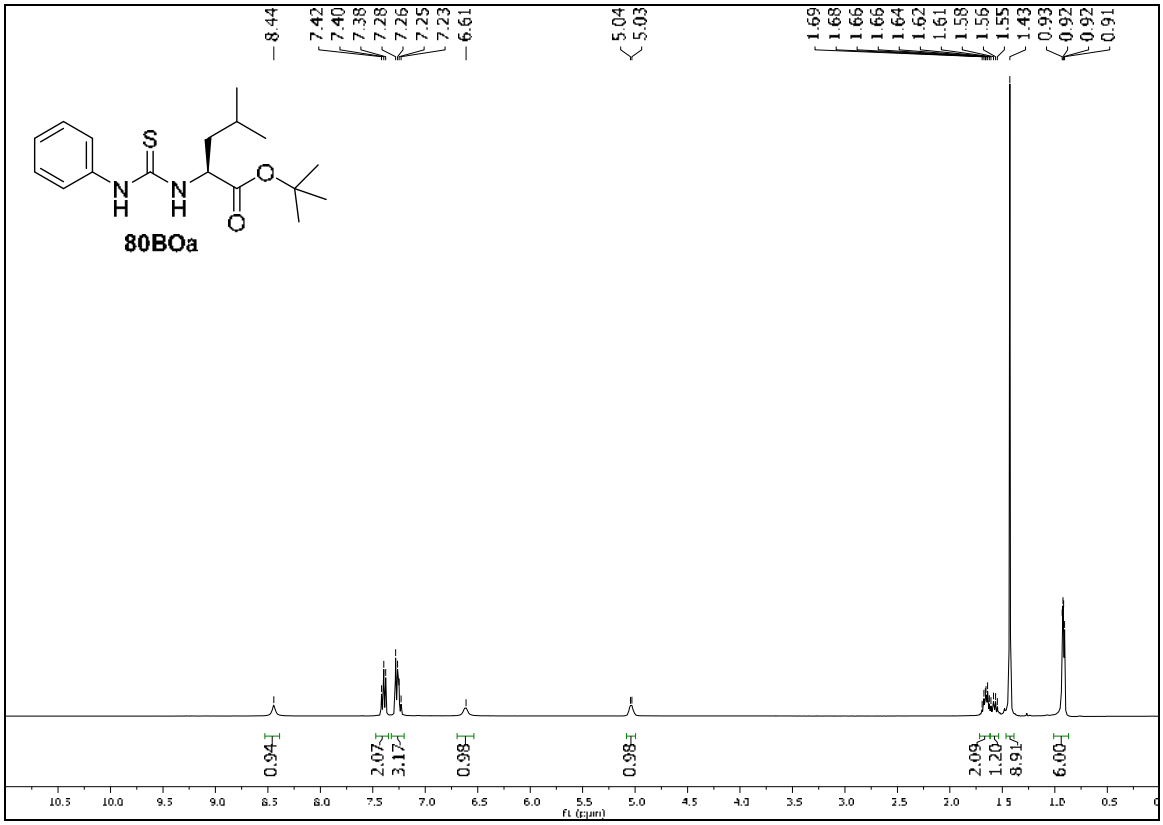


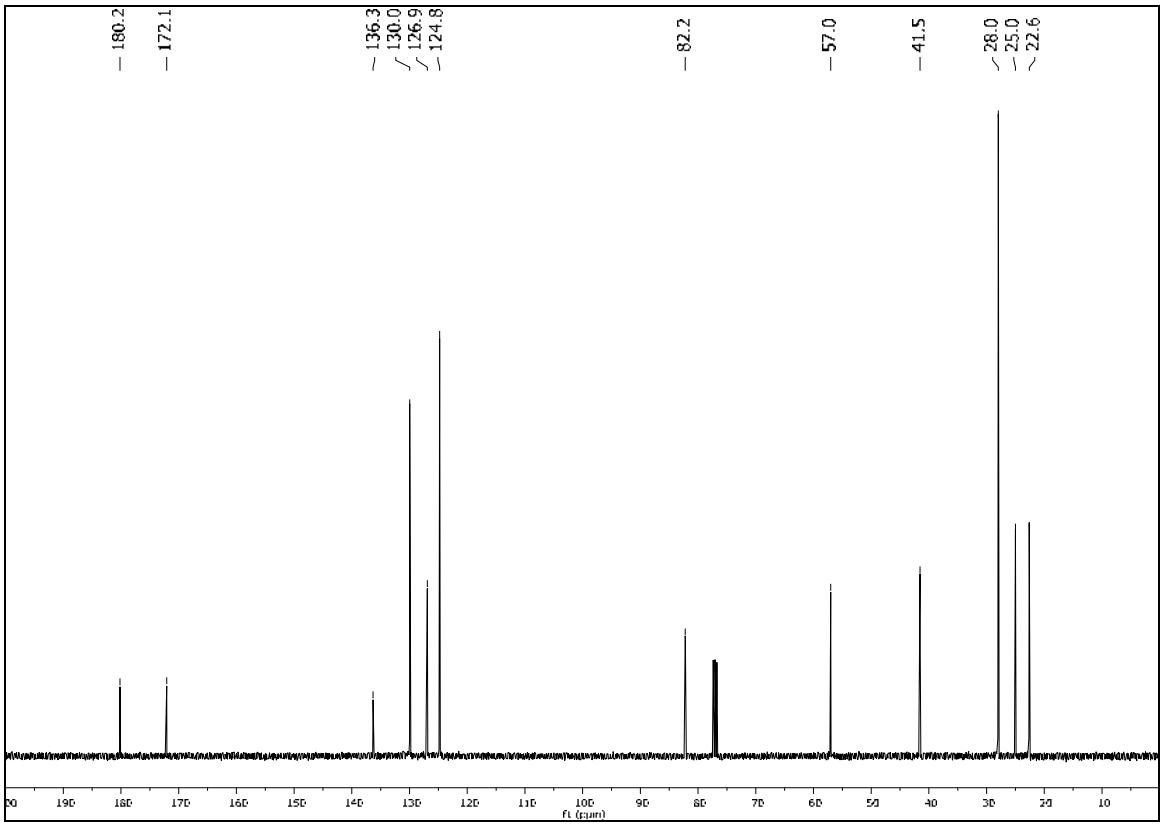

8.09
7.20
7.17
6.93
6.91
6.45
4.39
4.20
4.18
4.16
4.15
3.79
1.27
1.25
1.23
MeO
S
N
H
N
H
O
O
80ANc
0.91
1.94
1.95
0.88
2.02
2.00
3.00
2.86
f1 (ppm)

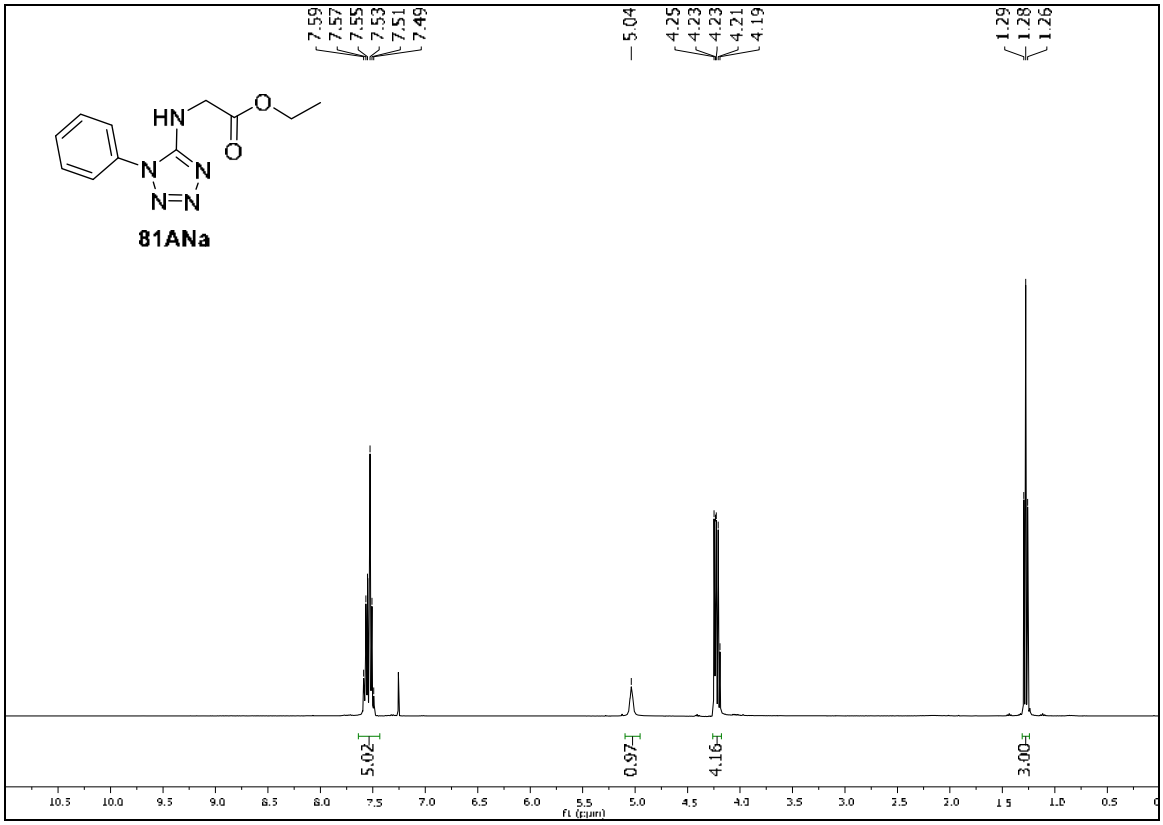

181.1
169.7
158.9
128.3
127.4
115.3
61.6
55.5
46.8
14.1
f1 (ppm)

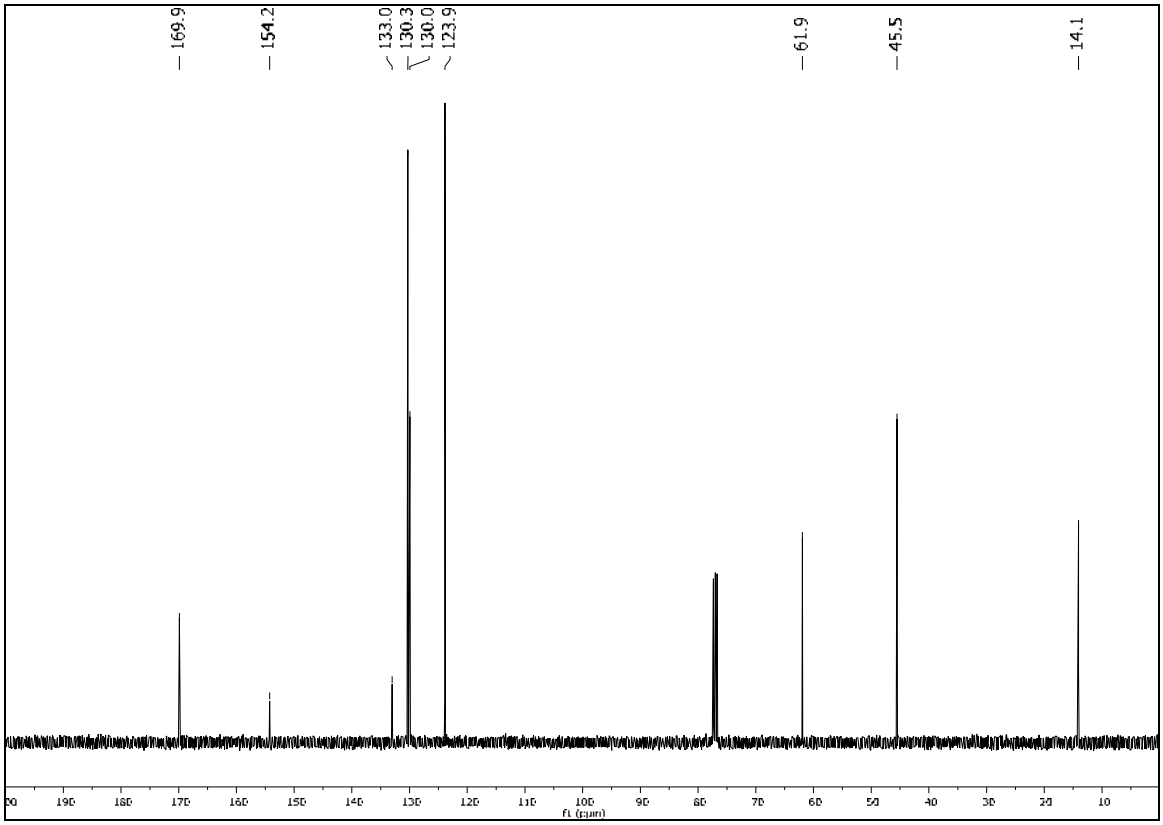

6.86
6.69
5.86
5.85
5.84
5.82
5.81
5.79
5.78
5.77
5.27
5.23
5.17
5.14
4.25
4.24
4.01
1.43
S
N
H
N
H
O
O
80AOe
0.96
0.72
0.95
1.90
2.00
1.85
8.79
f1 (ppm)


182.3
169.8
133.1
117.5
82.7
47.2
46.6
28.0
f1 (ppm)


8.44
7.42
7.40
7.38
7.28
7.26
7.25
7.23
6.61
5.04
5.03
1.69
1.68
1.66
1.66
1.64
1.62
1.61
1.58
1.56
1.55
1.43
0.93
0.92
0.92
0.91
S
N
H
N
H
O
O
80BOa
0.94
2.07
3.17
0.98
0.98
2.09
1.20
8.91
6.00
f1 (ppm)


180.2
172.1
136.3
130.0
126.9
124.8
82.2
57.0
41.5
28.0
25.0
22.6
f1 (ppm)


7.59
7.57
7.55
7.53
7.51
7.49
5.04
4.25
4.23
4.23
4.21
4.19
1.29
1.28
1.26
HN
O
O
N
N
N=N
81ANa
5.02
0.97
4.16
3.00
f1 (ppm)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130.3
130.0
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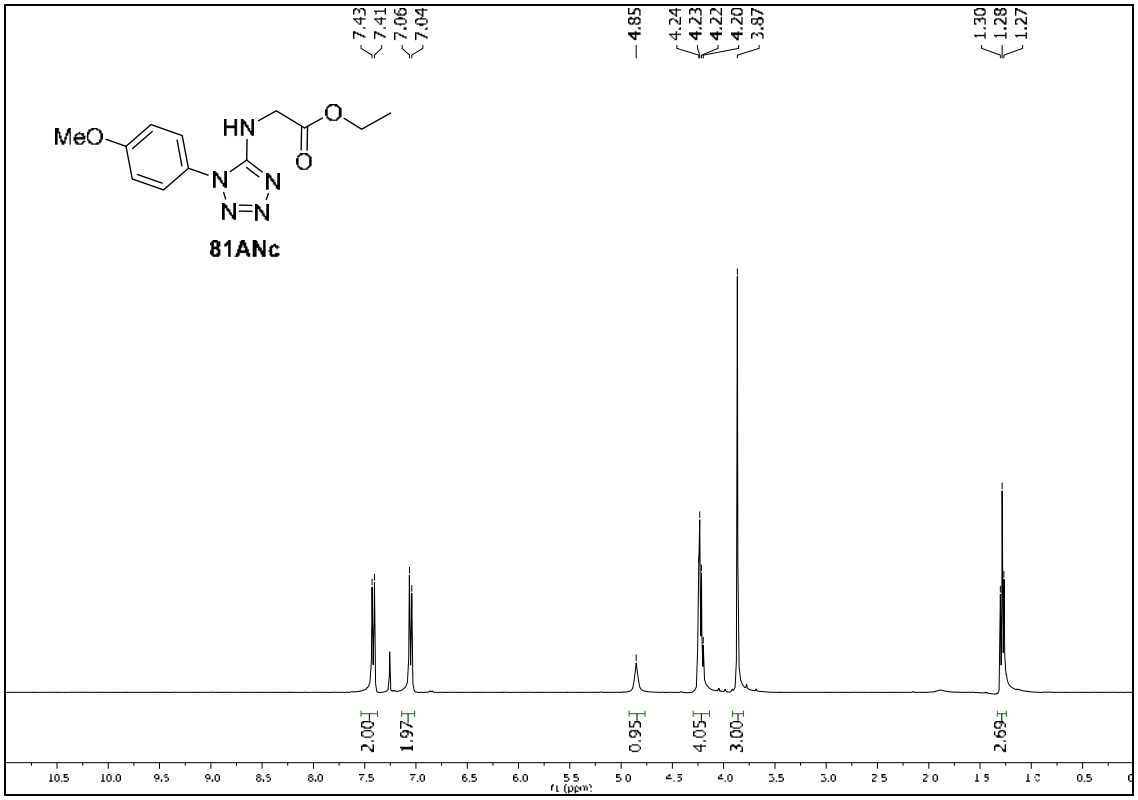
61.9
45.5
14.1
f1 (ppm)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4.22
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1.28
1.27
MeO
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N
N=N
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1.97
0.95
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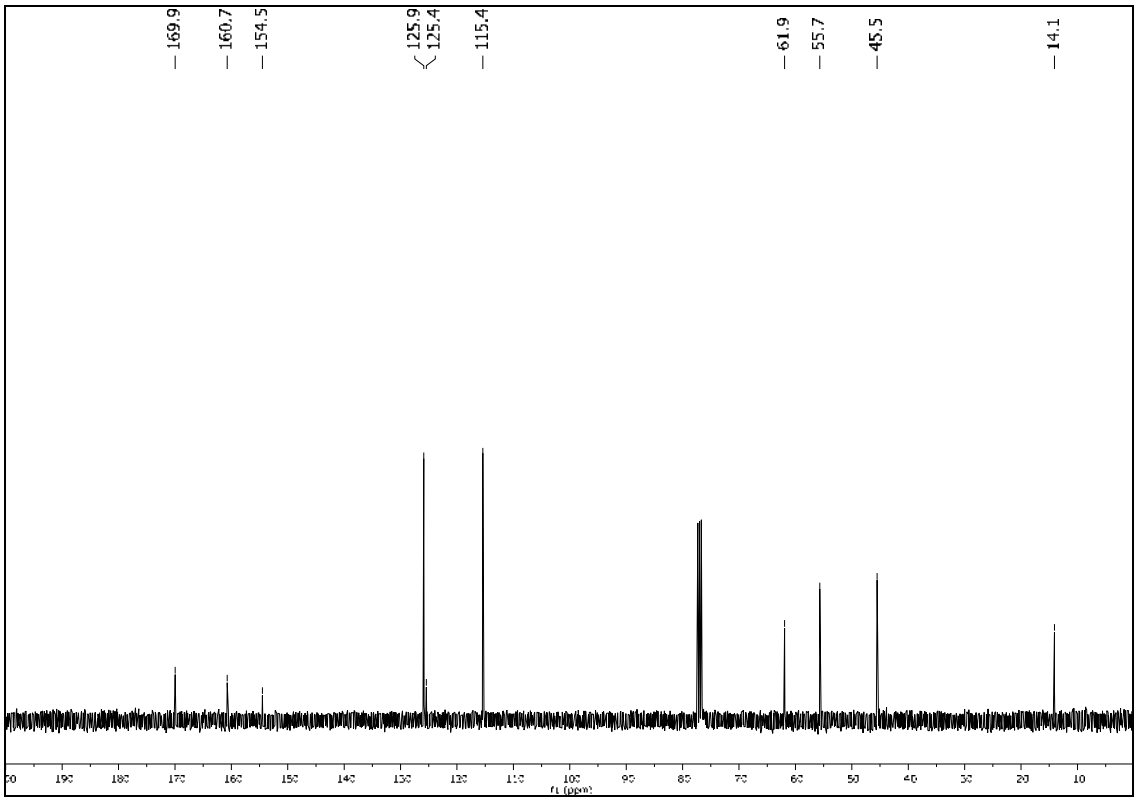
f1 (ppm)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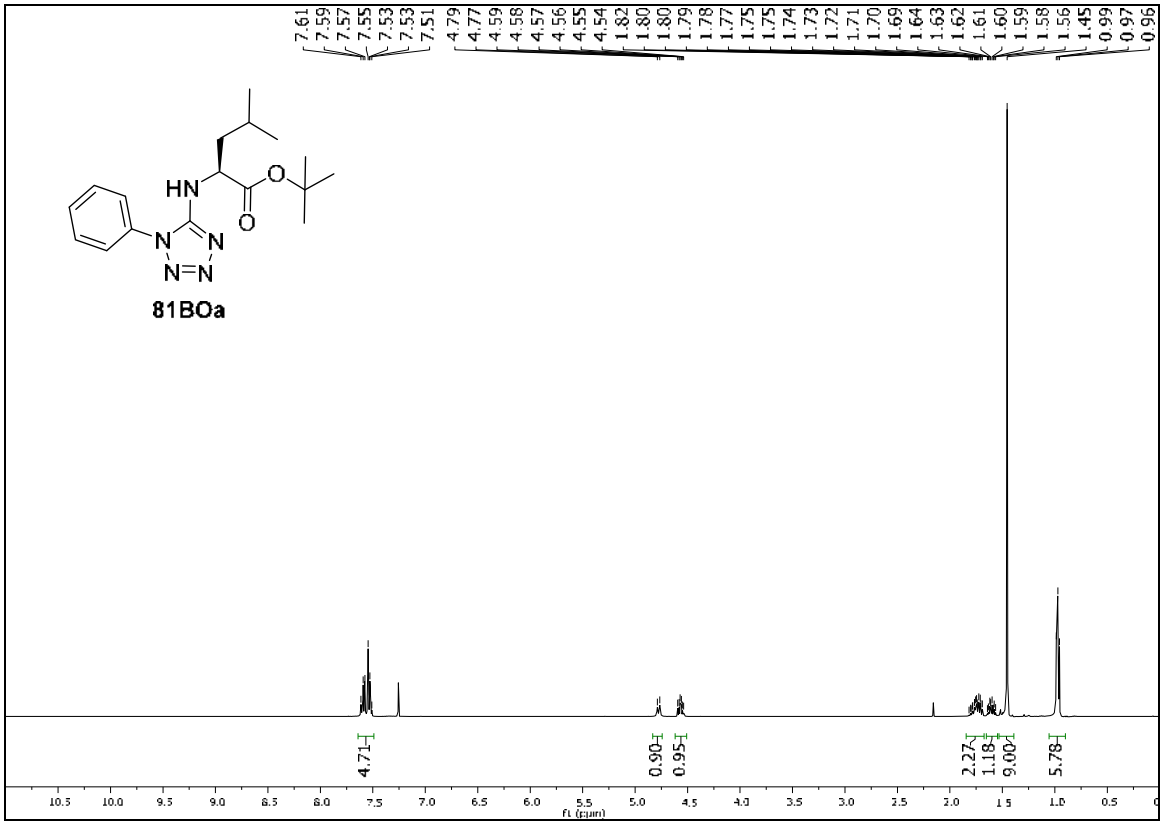
f1 (ppm)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4.54
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1.80
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1.79
1.78
1.77
1.75
1.75
1.74
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1.72
1.71
1.70
1.69
1.64
1.63
1.62
1.61
1.60
1.59
1.58
1.56
1.45
0.99
0.97
0.96
HN
O
O
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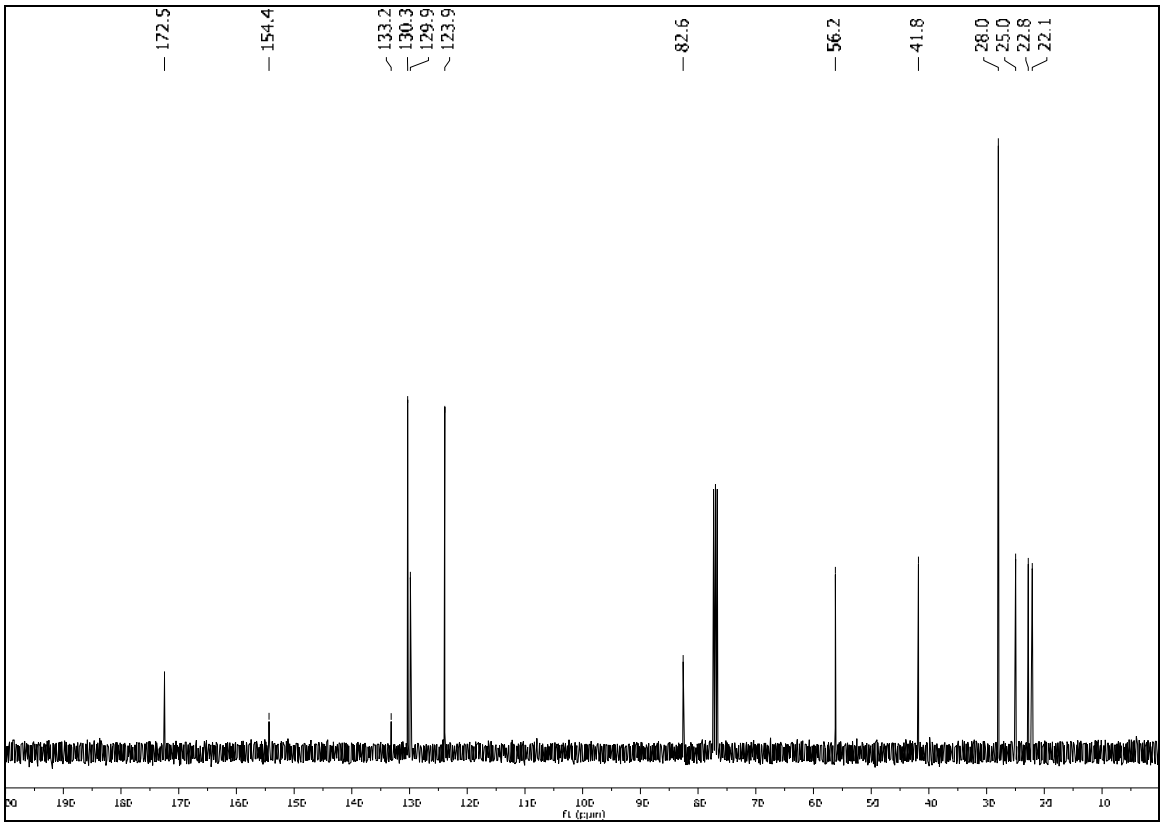
f1 (ppm)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56.2
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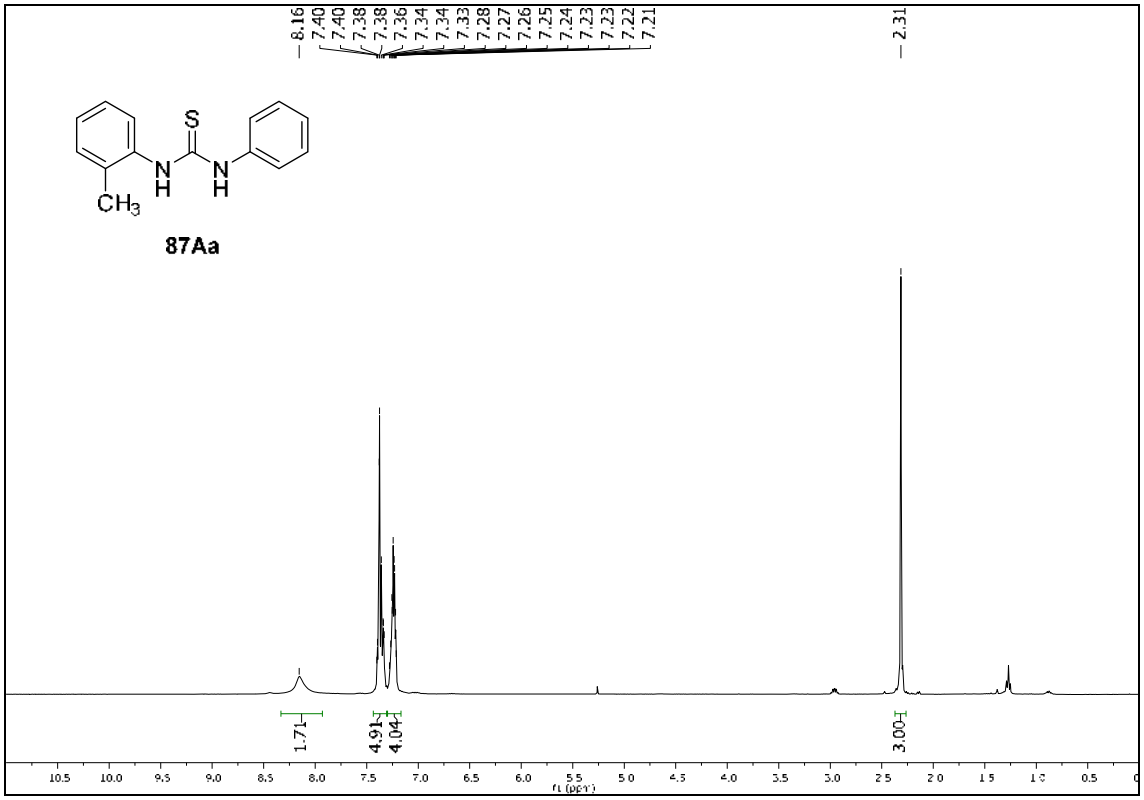
25.0
22.8
22.1
f1 (ppm)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7.25
7.24
7.23
7.23
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7.21
2.31
S
N
H
N
H
CH3
87Aa
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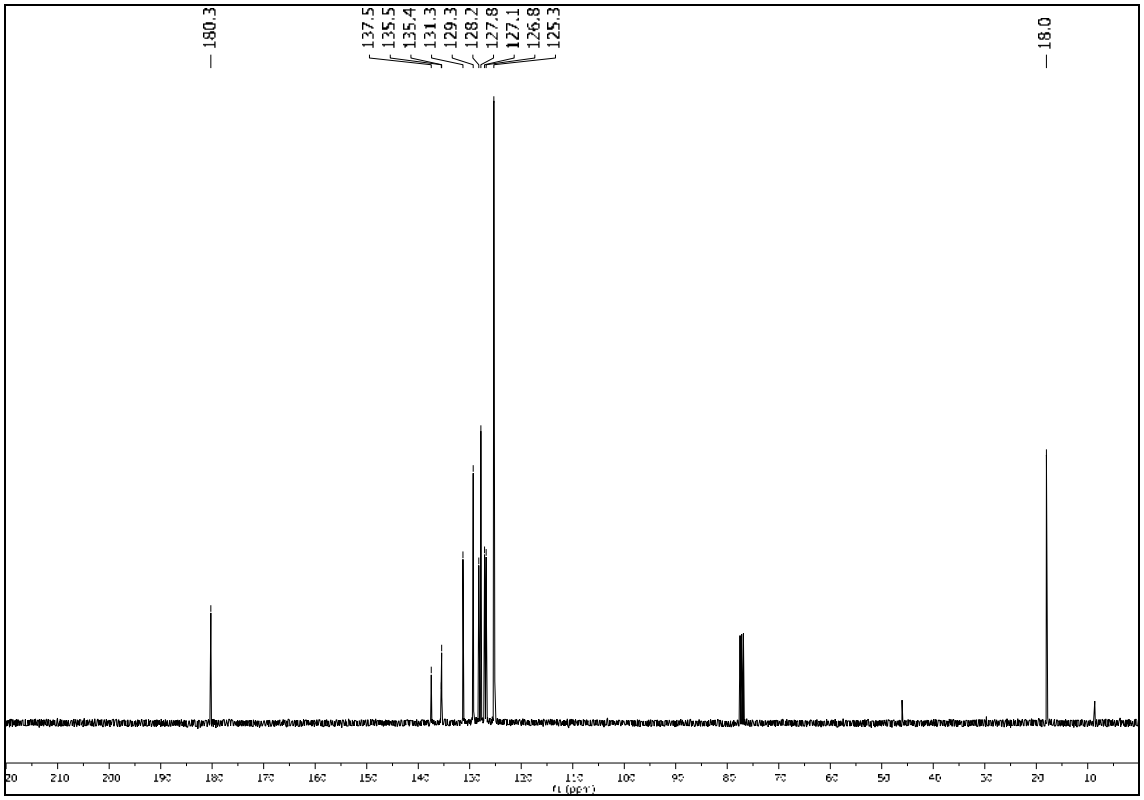
4.91
4.04
3.00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135.5
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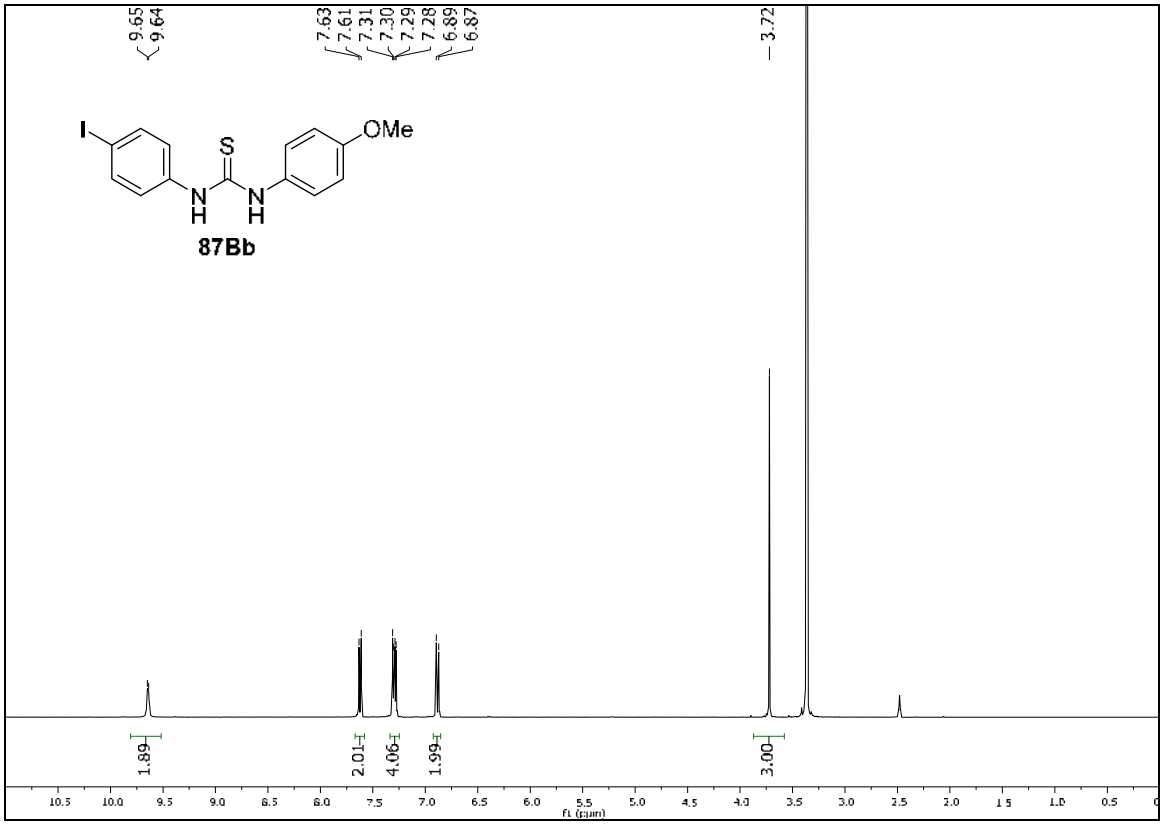
131.3
129.3
128.2
127.8
127.1
126.8
125.3
18.0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7.63
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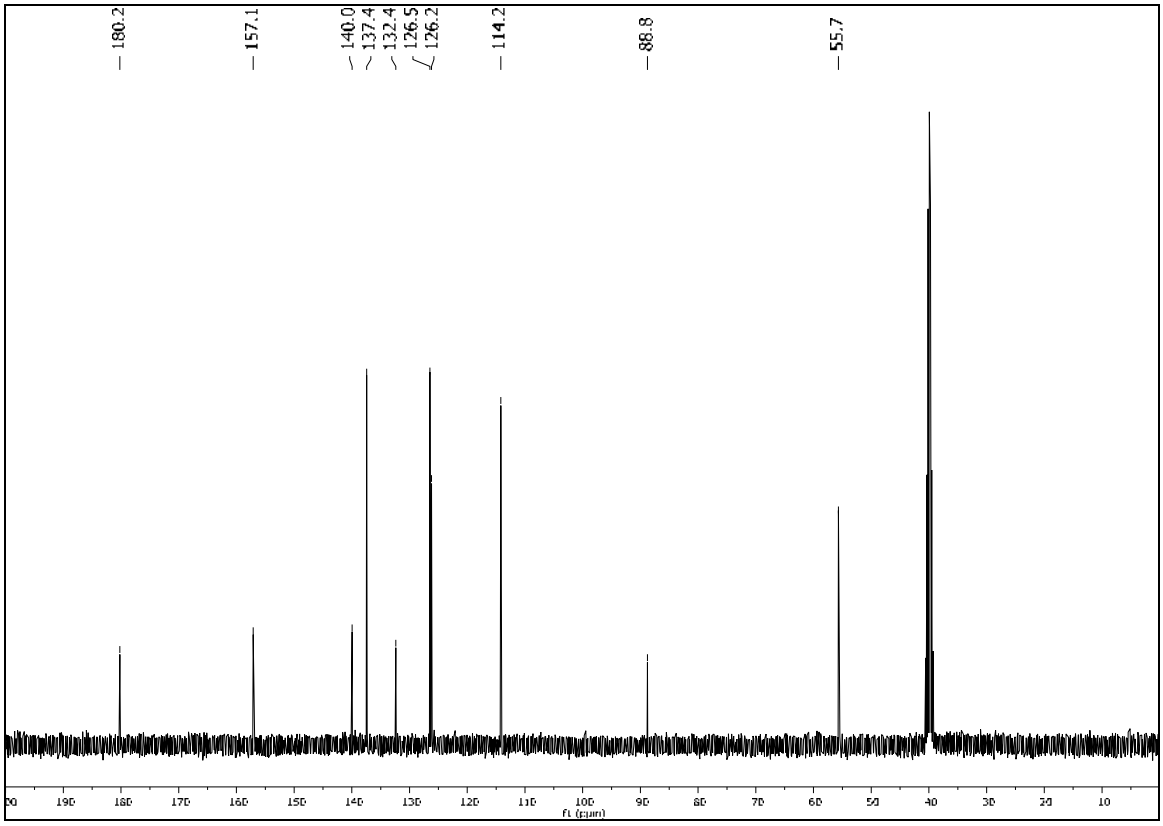
7.30
7.29
7.28
6.89
6.87
3.72
I
S
OMe
N
H
N
H
87Bb
1.89
2.01
4.06
1.99
3.00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132.4
126.5
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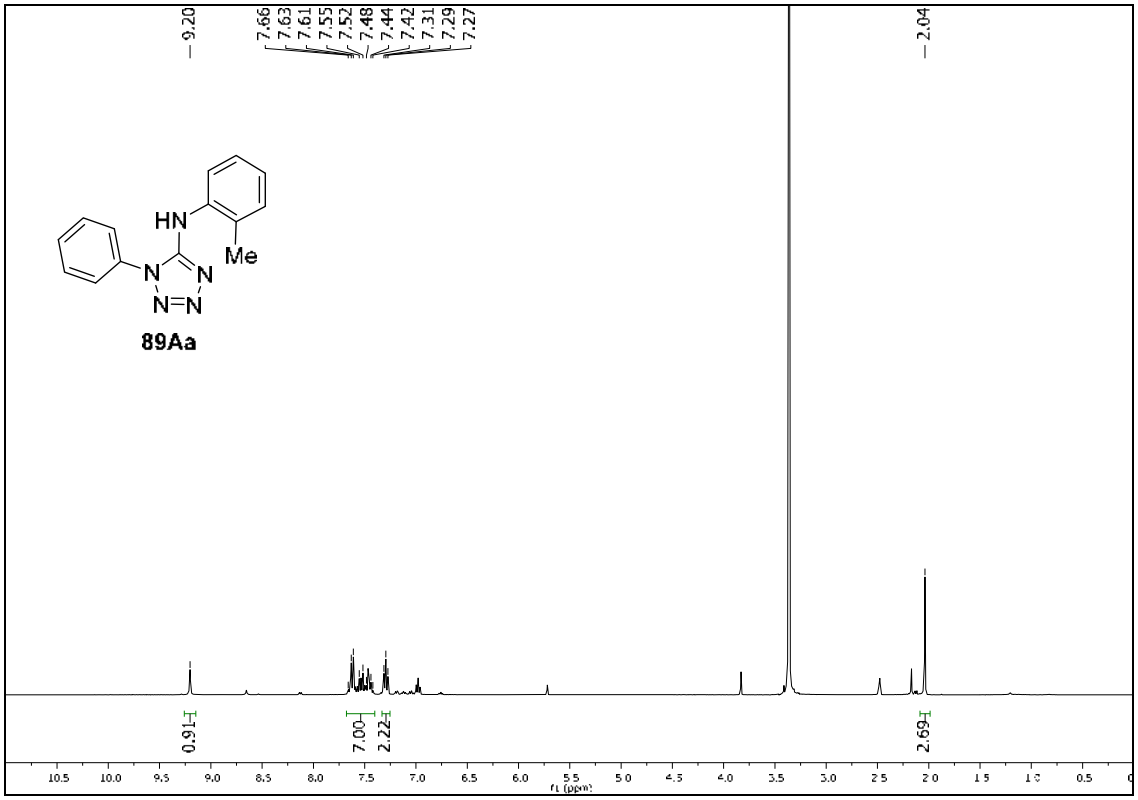
114.2
88.8
55.7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7.52
7.48
7.44
7.42
7.31
7.29
7.27
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Me
N
N
N=N
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0.91
7.00
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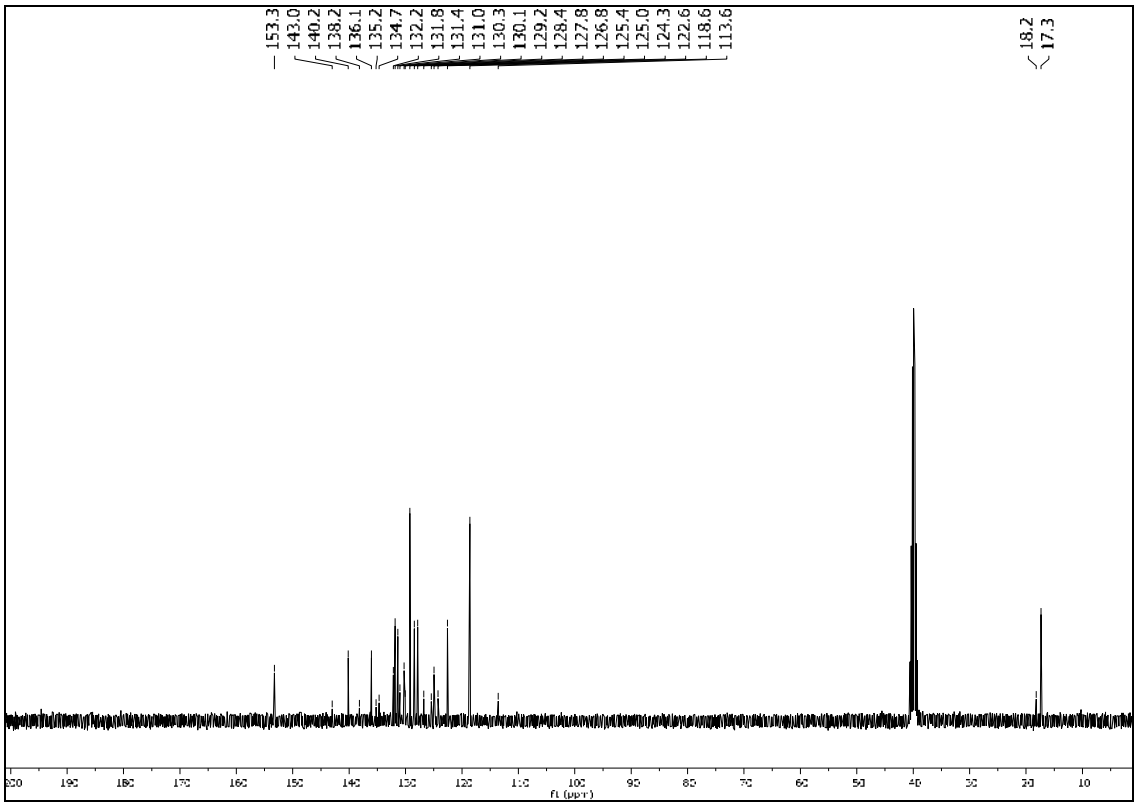
2.69
f1 (ppm)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132.2
131.8
131.4
131.0
130.3
130.1
129.2
128.4
127.8
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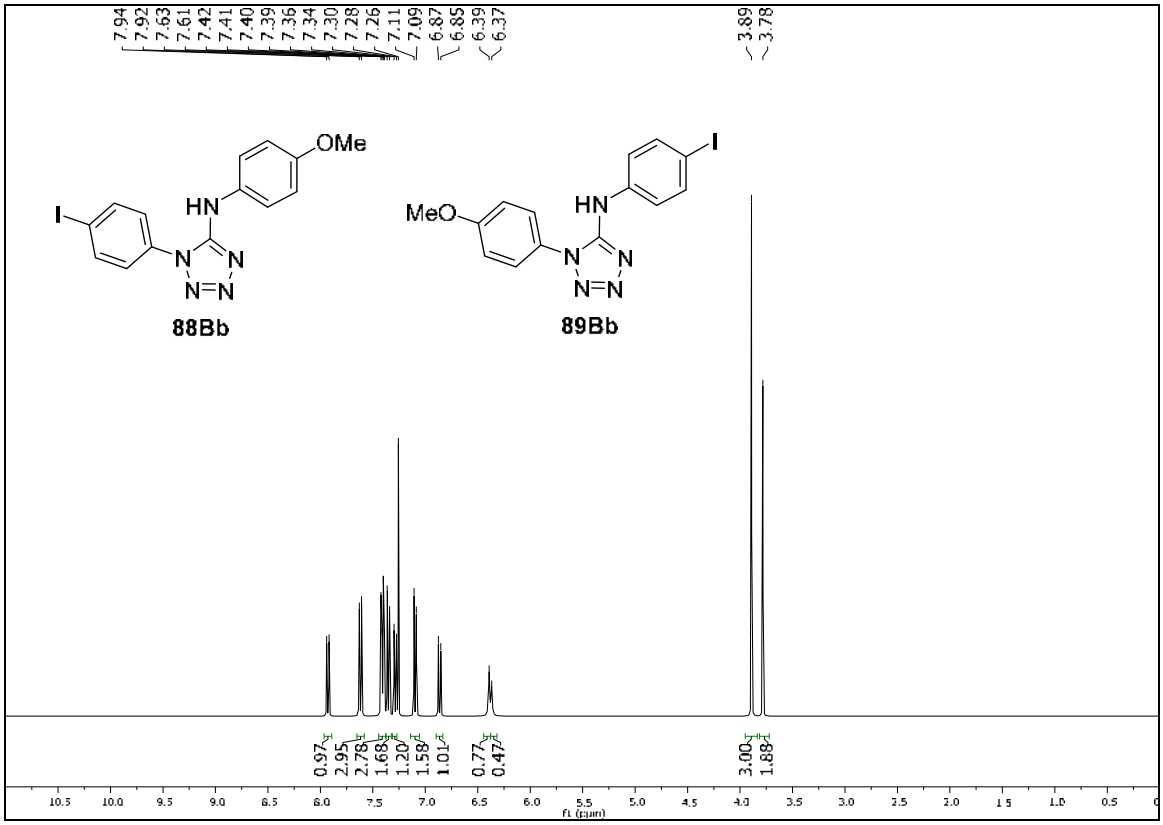
125.4
125.0
124.3
122.6
118.6
113.6
18.2
17.3
f1 (ppm)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7.42
7.41
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7.36
7.34
7.30
7.28
7.26
7.11
7.09
6.87
6.85
6.39
6.37
3.89
3.78
OMe
HN
I
N
N
N=N
88Bb
MeO
HN
I
N
N
N=N
89Bb
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2.95
2.78
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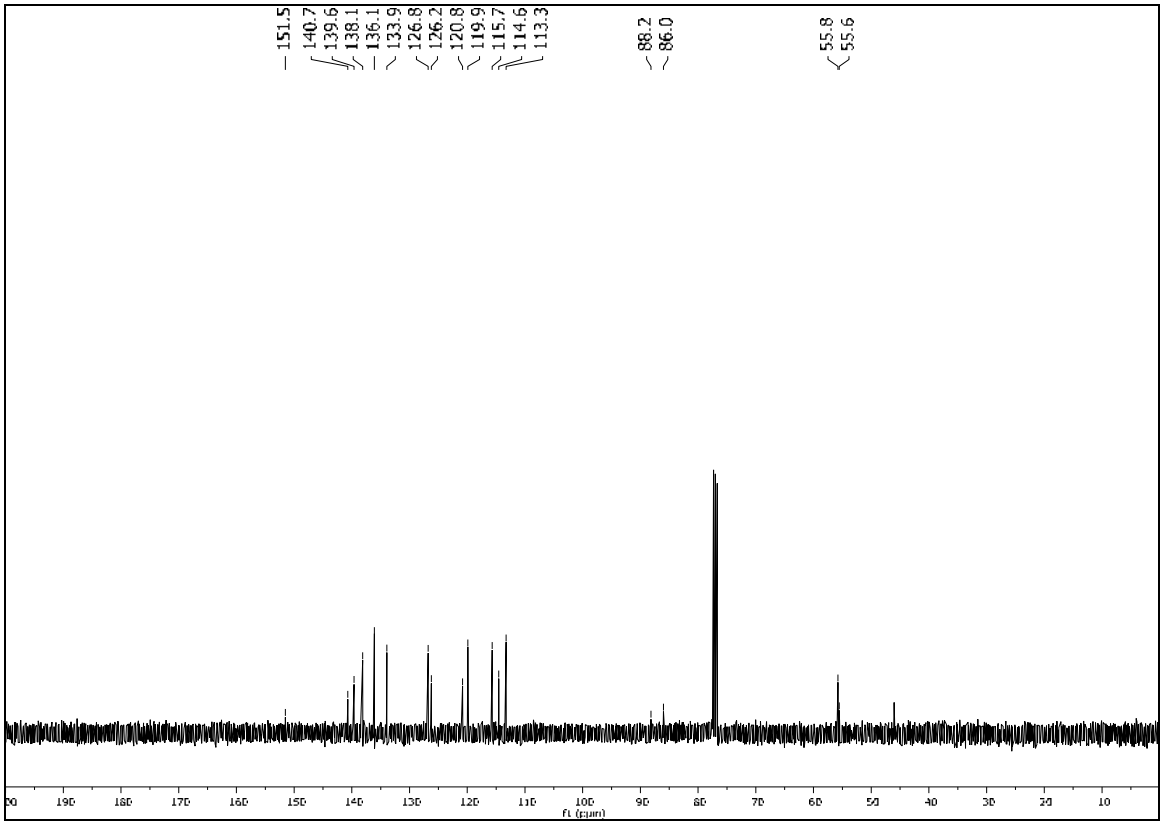
1.20
1.58
1.01
0.77
0.47
3.00
1.89
f1 (ppm)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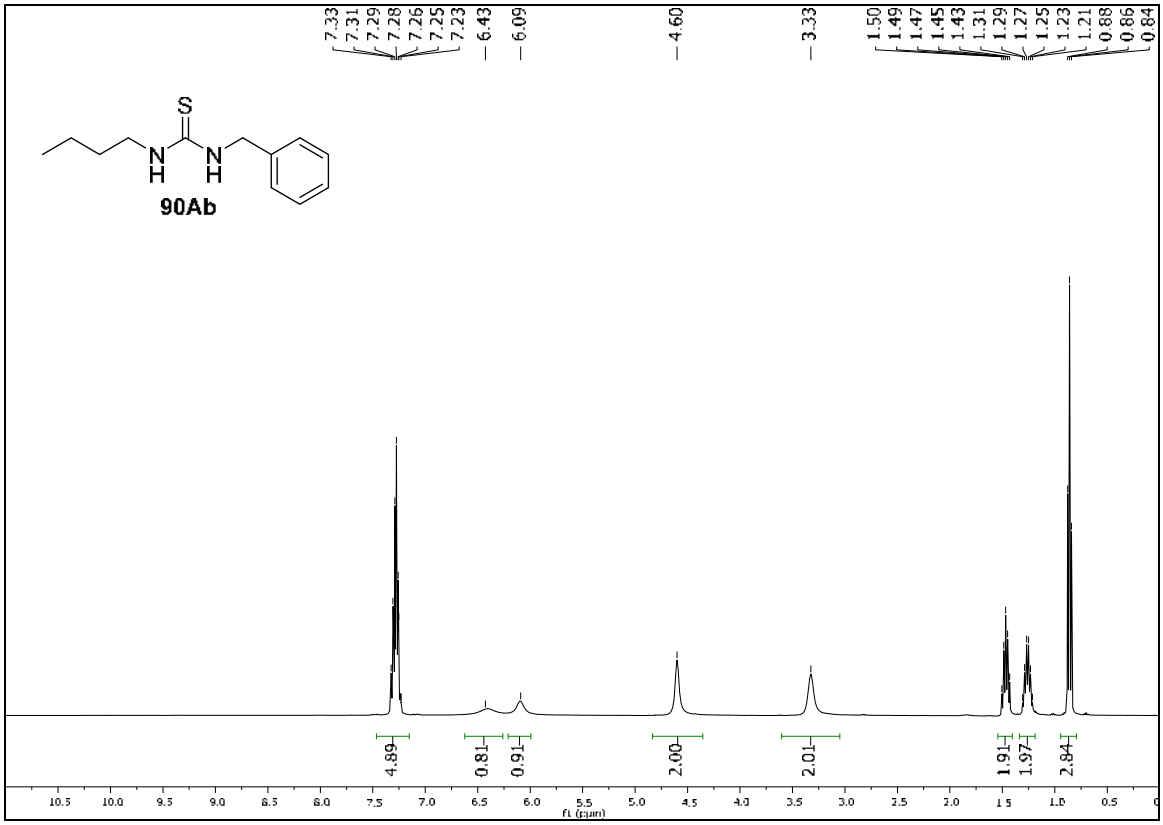
140.7
139.6
138.1
136.1
133.9
126.8
126.2
120.8
119.9
115.7
114.6
113.3
88.2
86.0
55.8
55.6
f1 (ppm)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7.28
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6.09
4.60
3.33
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1.49
1.47
1.45
1.43
1.31
1.29
1.27
1.25
1.23
1.21
0.88
0.86
0.84
S
N
H
N
H
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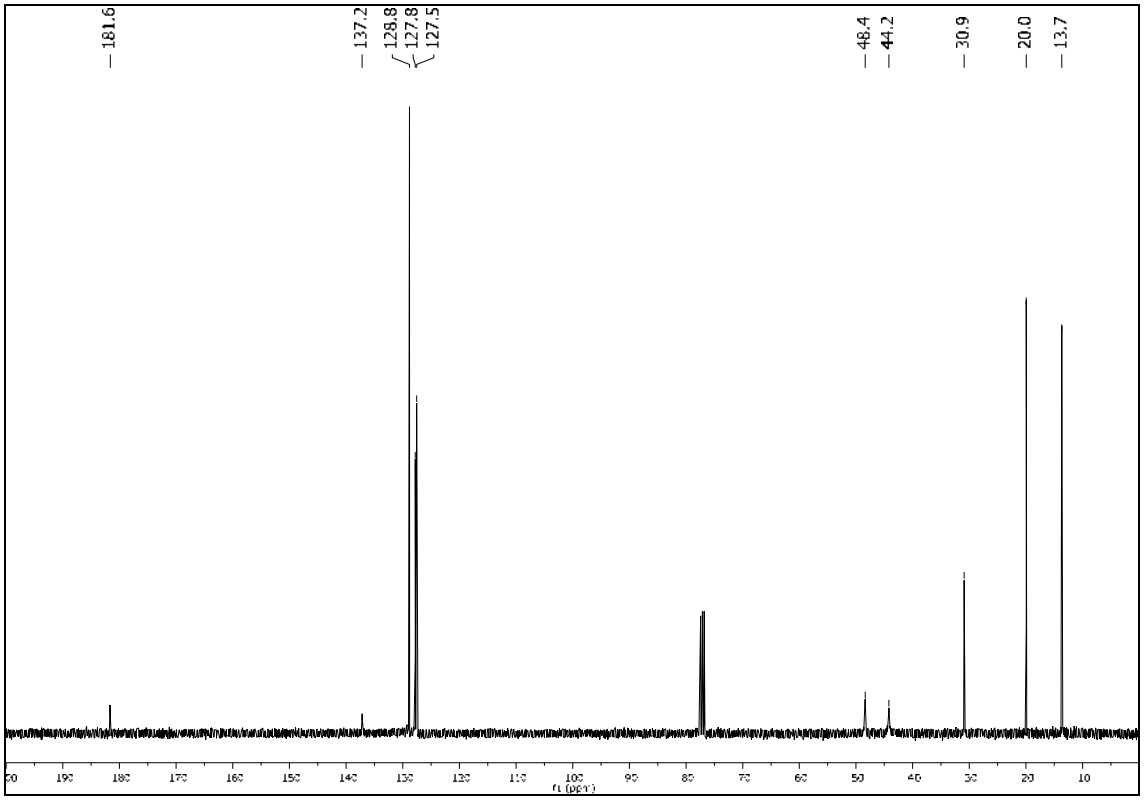
4.89
0.81
0.91
2.00
2.01
1.91
1.97
2.84
f1 (ppm)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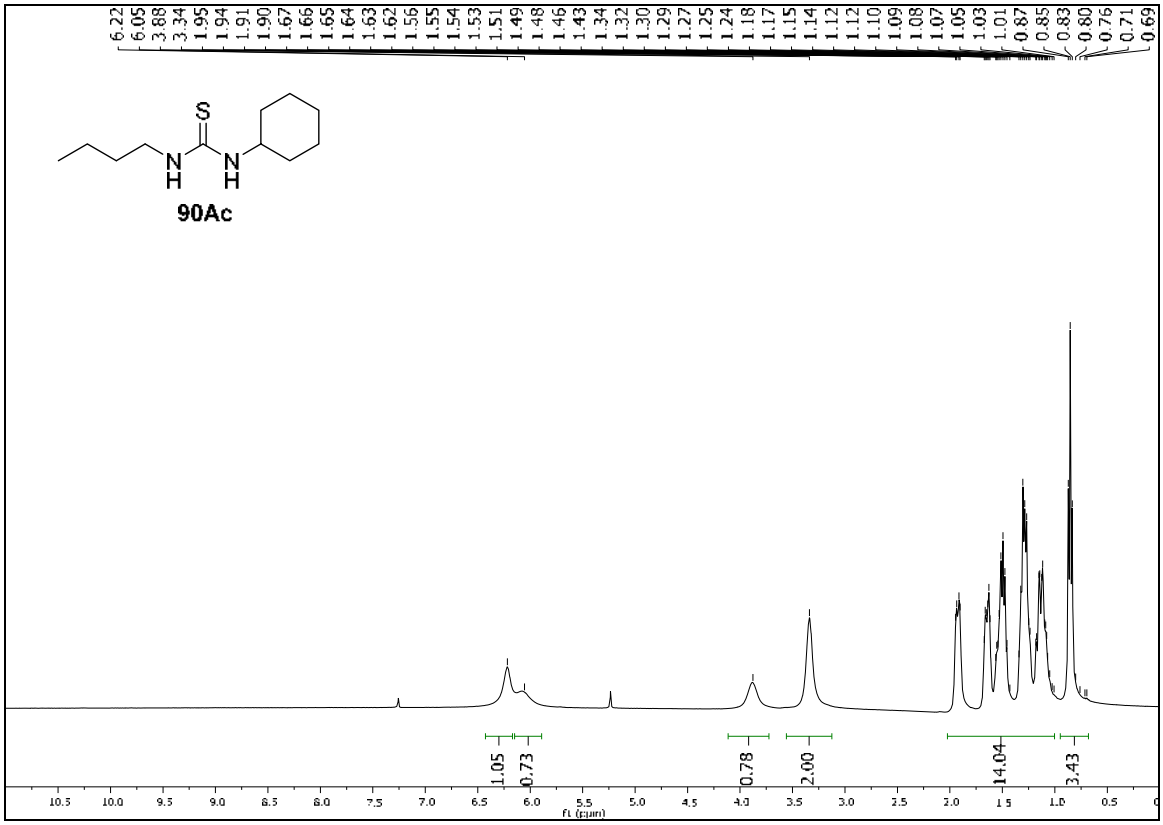
13.7
f1 (ppm)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1.63
1.62
1.56
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1.53
1.51
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1.34
1.32
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1.27
1.25
1.24
1.18
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1.15
1.14
1.12
1.12
1.10
1.09
1.08
1.07
1.05
1.03
1.01
0.87
0.85
0.83
0.80
0.76
0.71
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H
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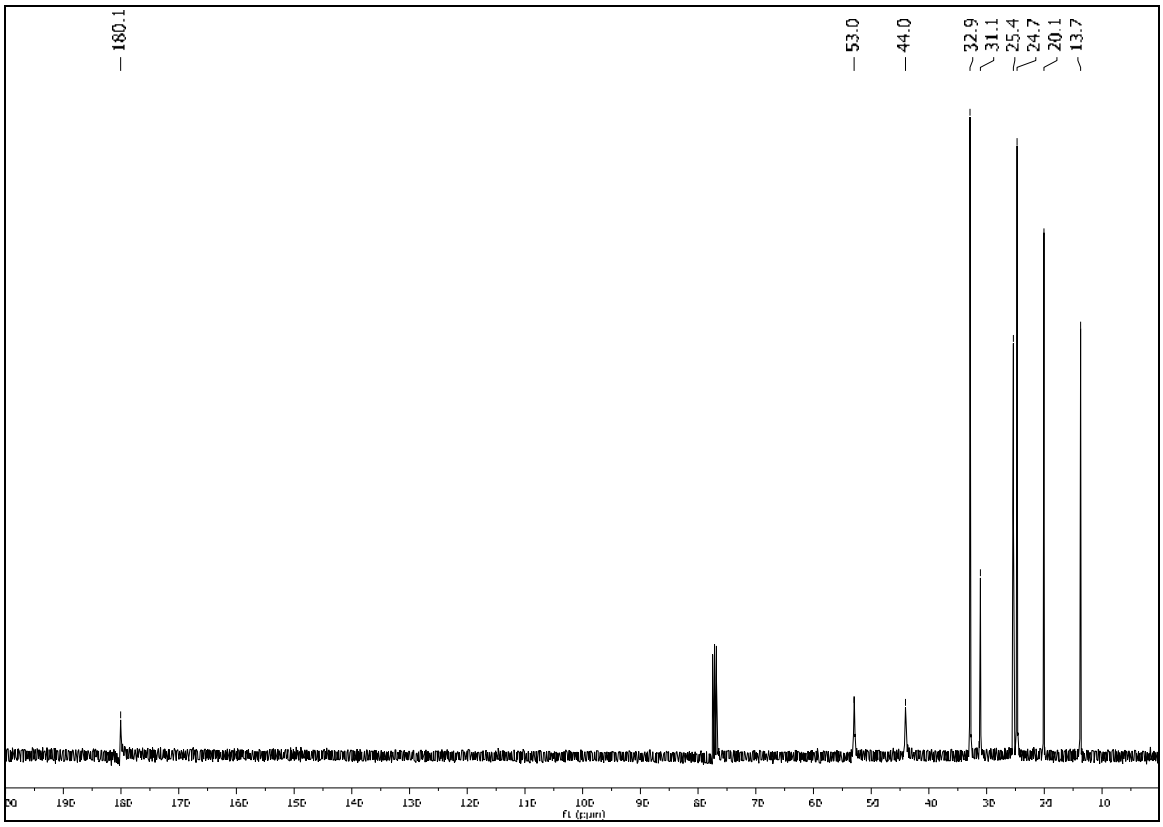
f1 (ppm)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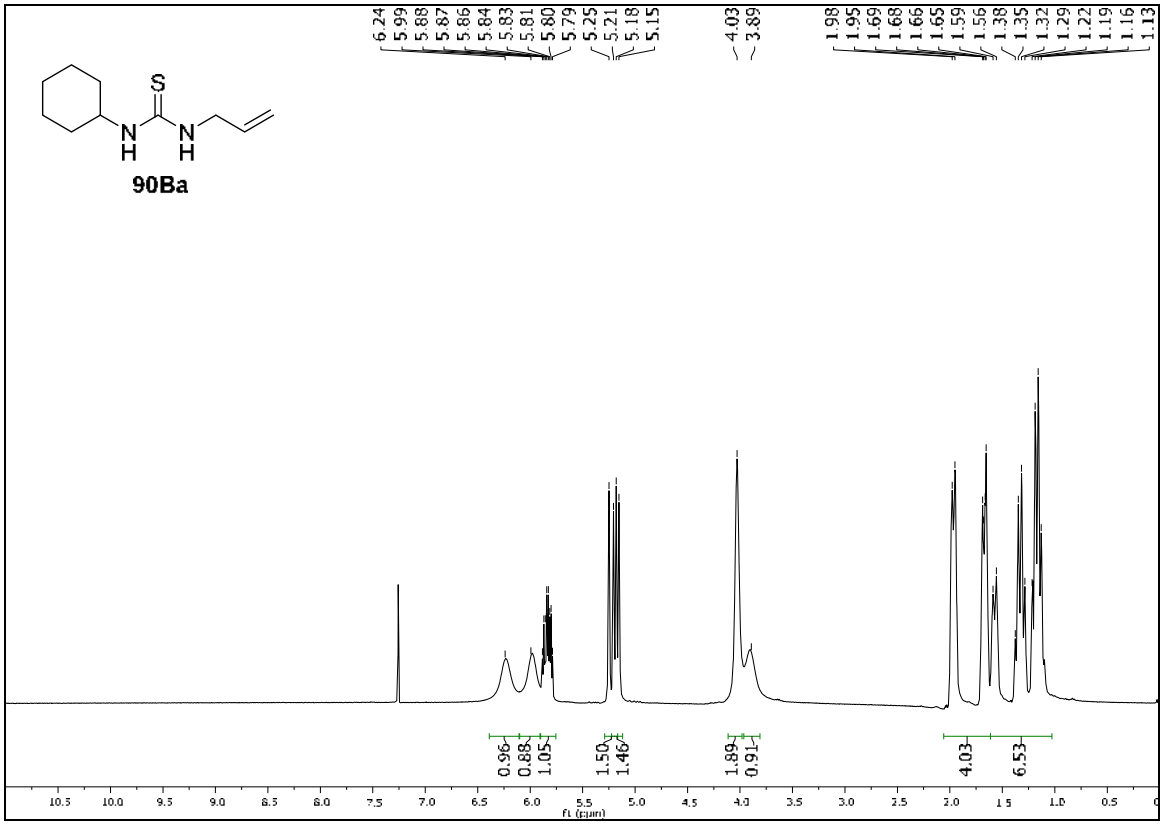
25.4
24.7
20.1
13.7
f1 (ppm)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N
H
N
H
90Ba
6.24
5.99
5.88
5.87
5.86
5.84
5.83
5.81
5.80
5.79
5.25
5.21
5.18
5.15
4.03
3.89
1.98
1.95
1.69
1.68
1.66
1.65
1.59
1.56
1.38
1.35
1.32
1.29
1.22
1.19
1.16
1.13
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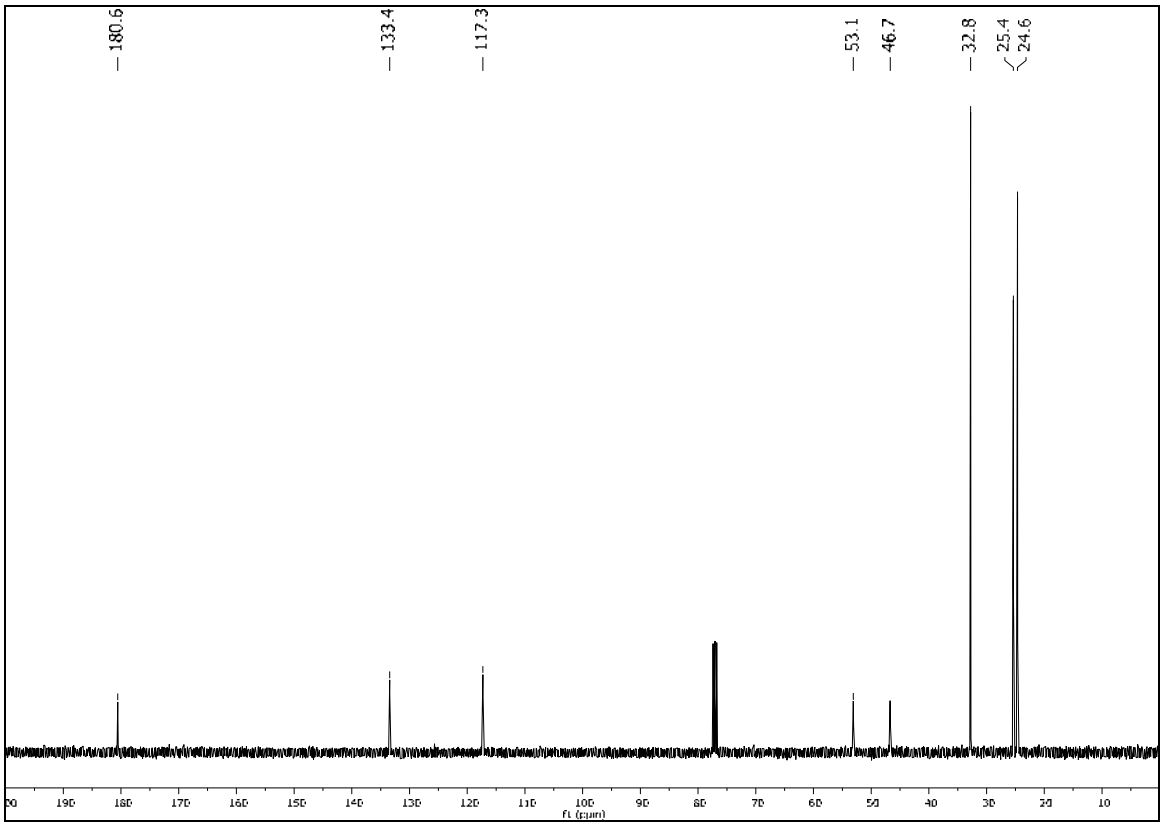
0.88
1.05
1.50
1.46
1.89
0.91
4.03
6.53
f1 (ppm)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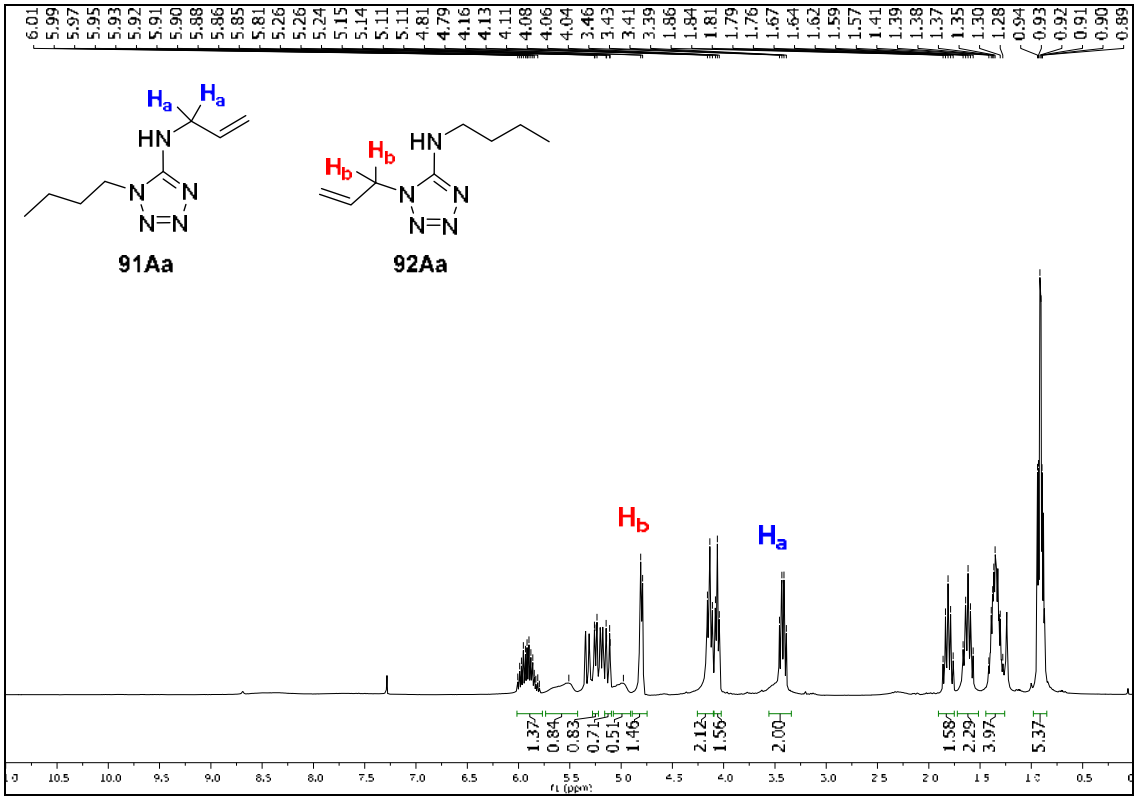
32.8
25.4
24.6
f1 (ppm)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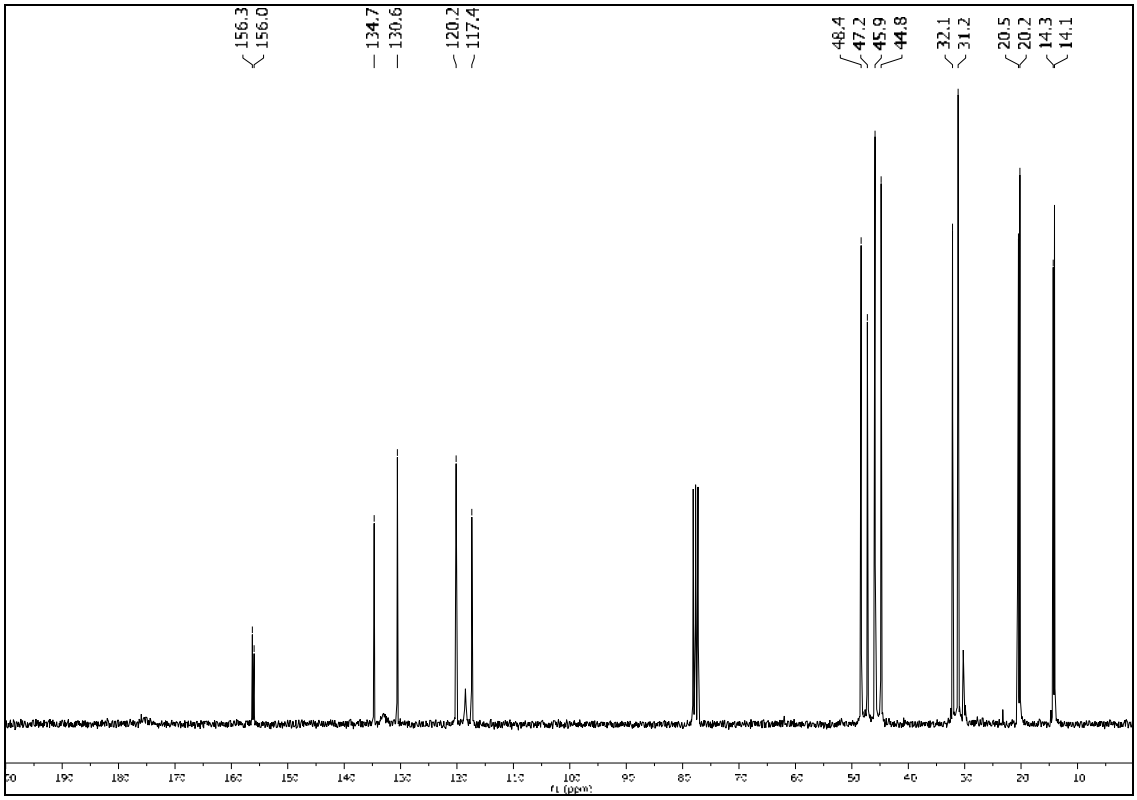
Ha Ha
HN
N N
N=N
91Aa
Hb
Hb HN
N N
N=N
92Aa
Hb
Ha
1.37 0.84 0.83 0.71 0.51 1.46 2.12 1.56 2.00 1.58 2.29 3.97 5.37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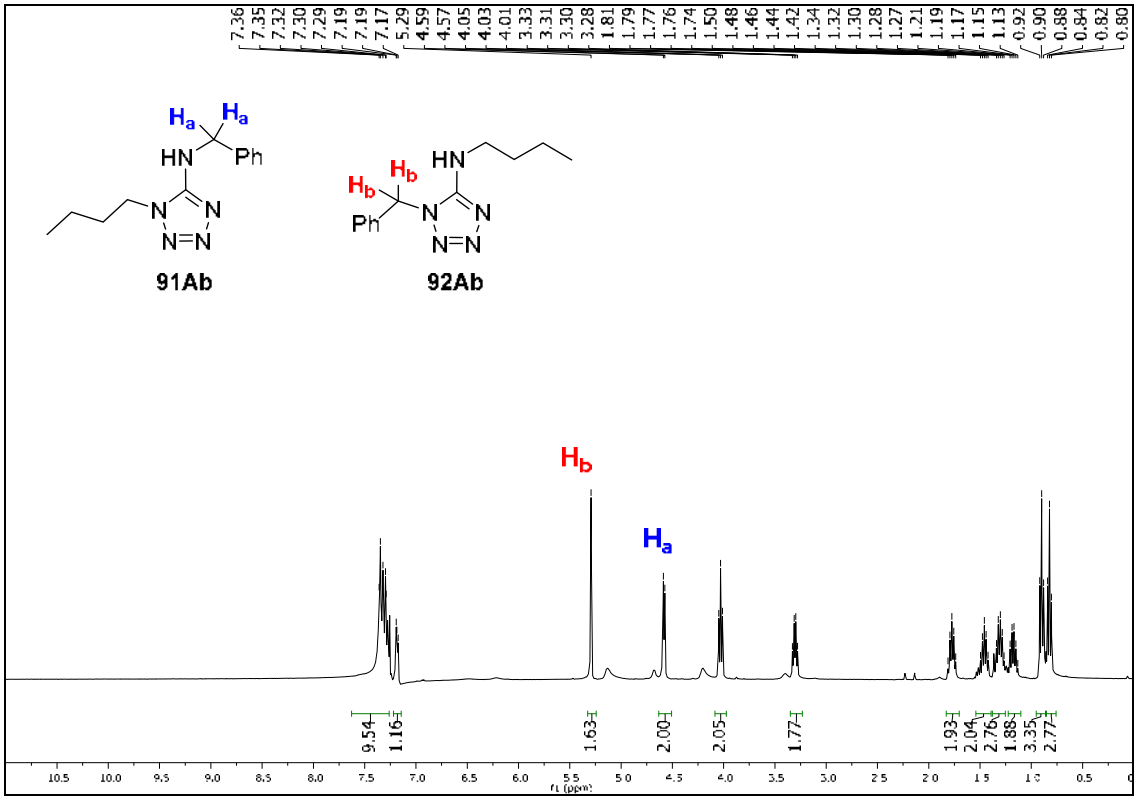
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4.57
4.05
4.03
4.01
3.33
3.31
3.30
3.28
1.81
1.79
1.77
1.76
1.74
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1.44
1.42
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1.32
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1.27
1.21
1.19
1.17
1.15
1.13
0.92
0.90
0.88
0.84
0.82
0.80
Ha
Ha
HN
Ph
N
N
N=N
91Ab
Hb
Hb
HN
Ph
N
N
N=N
92Ab
Hb
Ha
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1.77
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2.04
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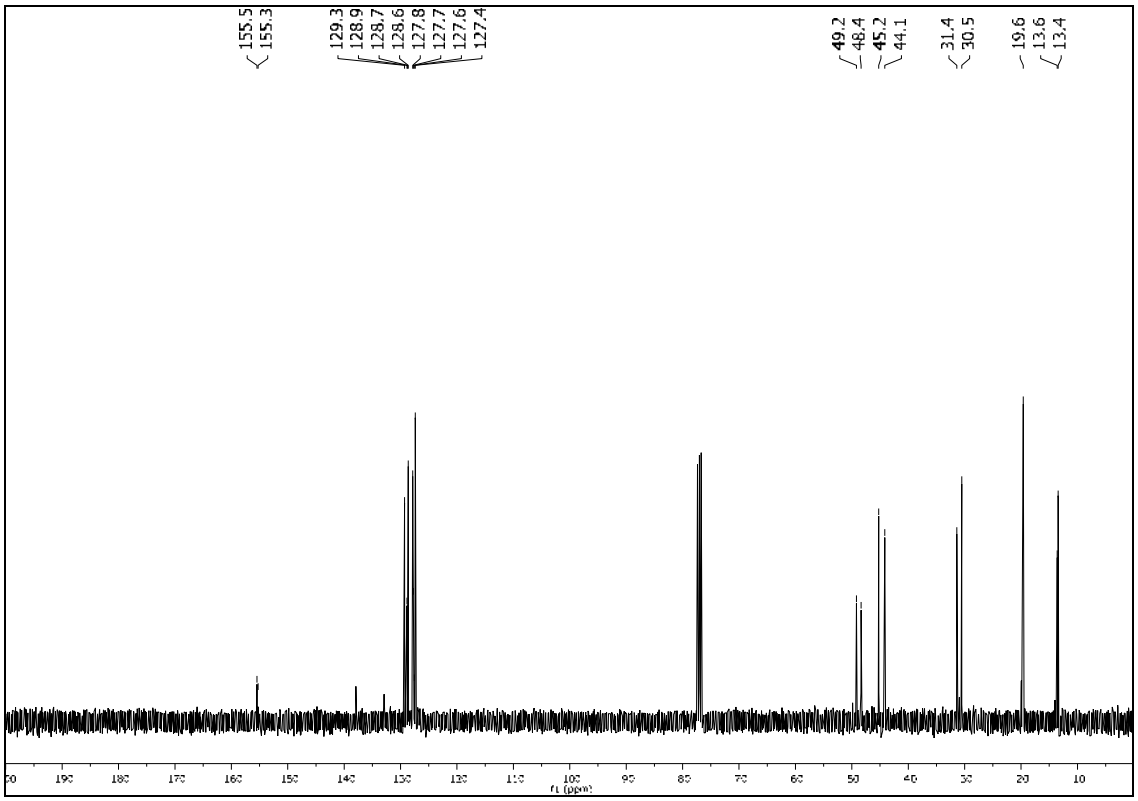
3.35
2.72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155.3
129.3
128.9
128.7
128.6
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127.6
127.4
49.2
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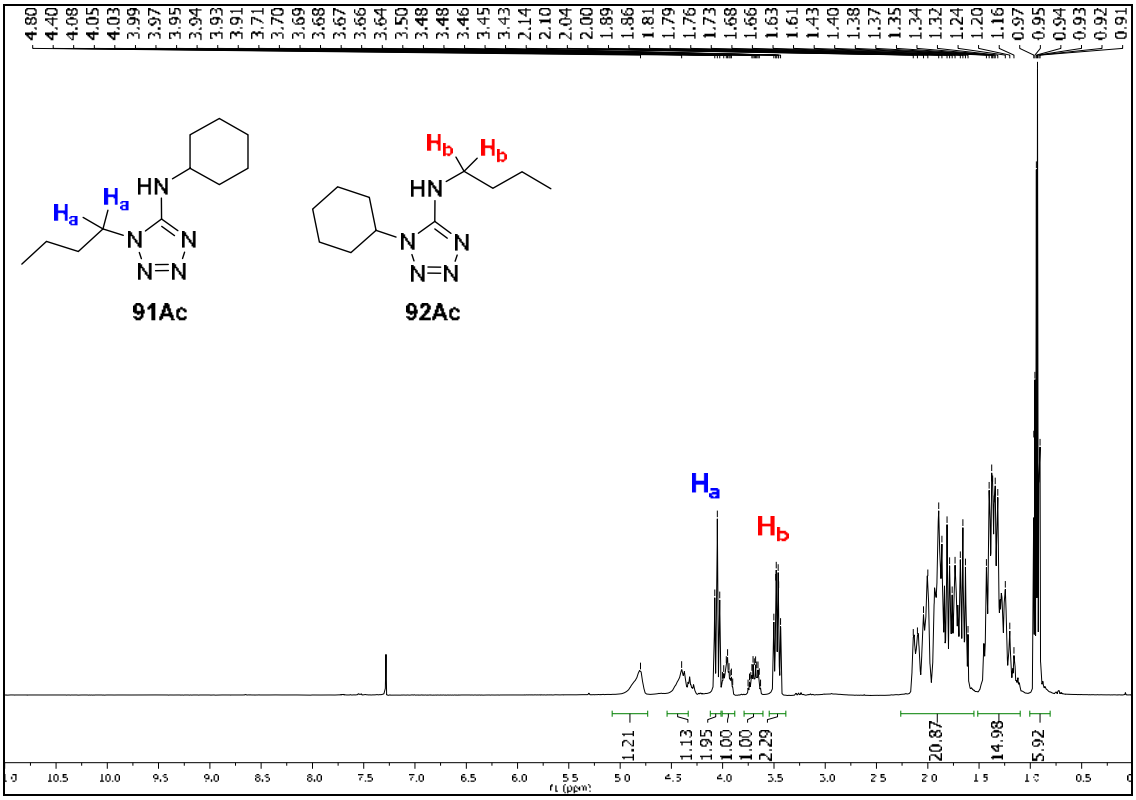
44.1
31.4
30.5
19.6
13.6
13.4


4.80 4.40 4.08 4.05 4.03 3.99 3.97 3.95 3.94 3.93 3.91 3.71 3.70 3.69 3.68 3.67 3.66 3.64 3.50 3.48 3.48 3.46 3.45 3.43 2.14 2.10 2.04 2.00 1.89 1.86 1.81 1.79 1.76 1.73 1.68 1.66 1.63 1.61 1.43 1.40 1.38 1.37 1.35 1.34 1.32 1.24 1.20 1.16 0.97 0.95 0.94 0.93 0.92 0.91
HN
Ha
Ha
N
N
N=N
91Ac
HN
Hb
Hb
N
N
N=N
92Ac
Ha
Hb
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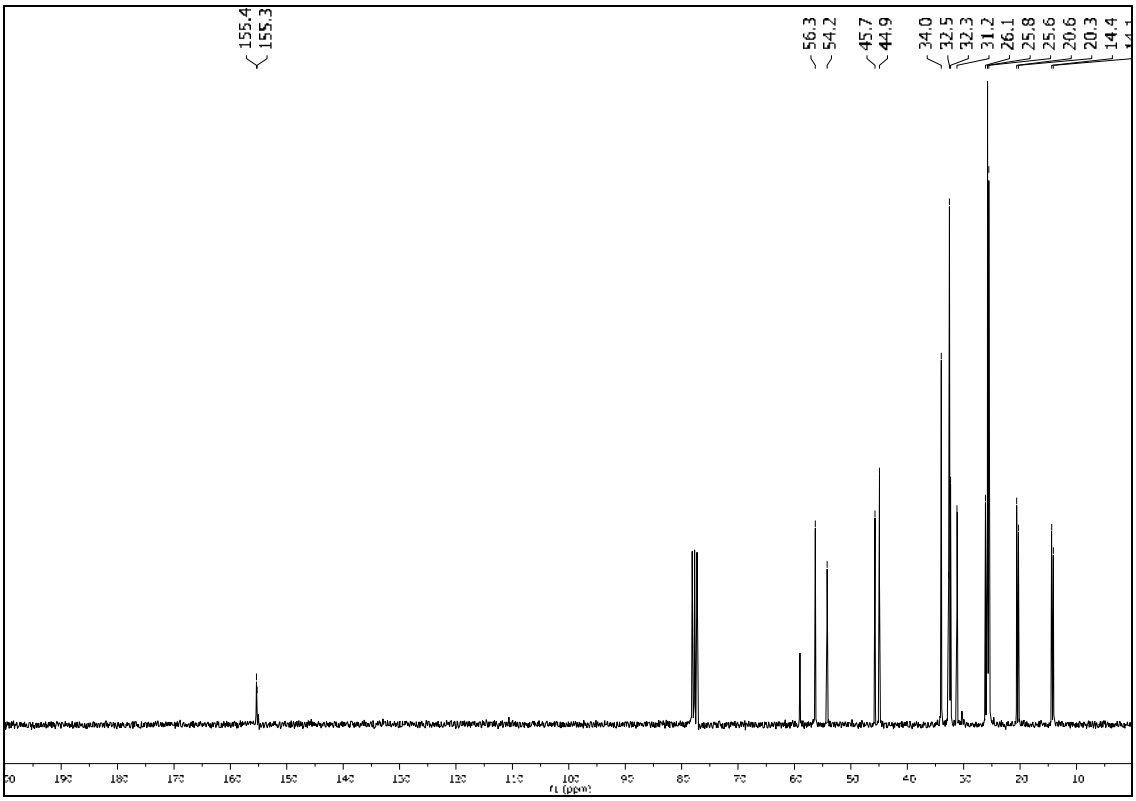
1.13
1.95
1.00
1.00
2.29
20.87
14.98
5.92
f1 (ppm)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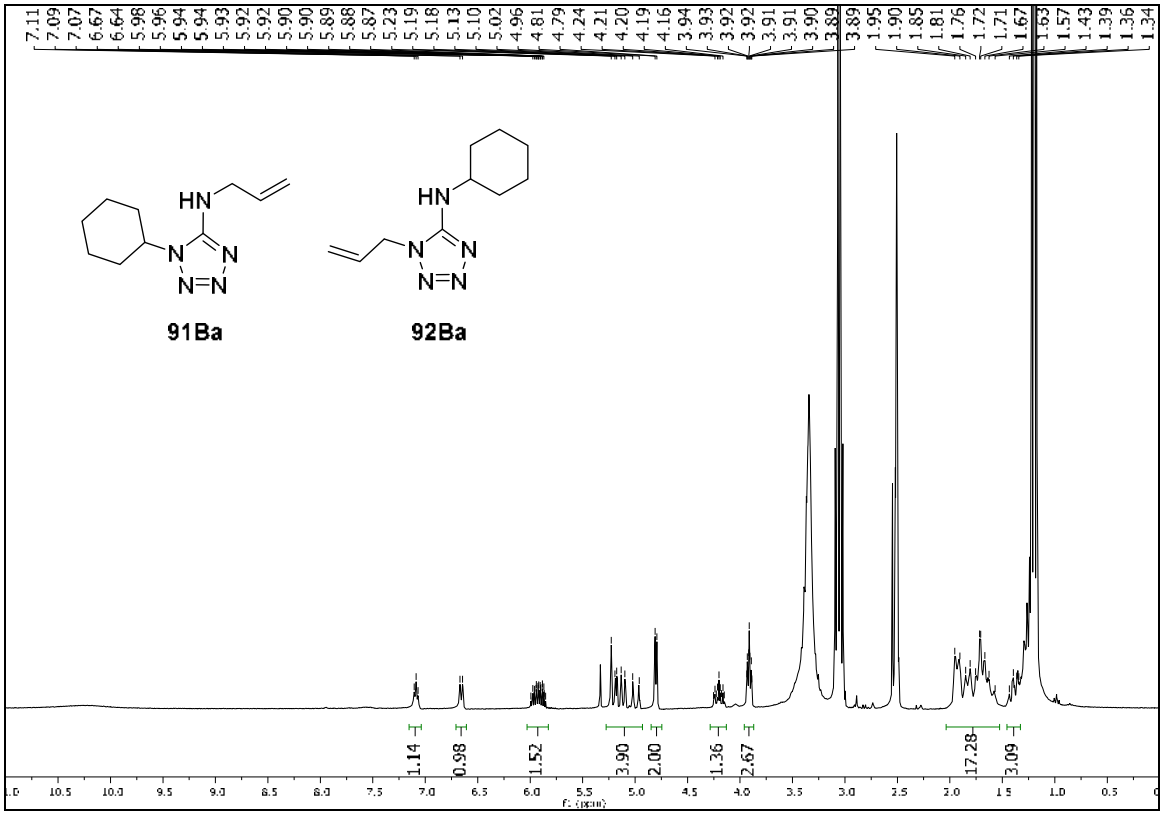
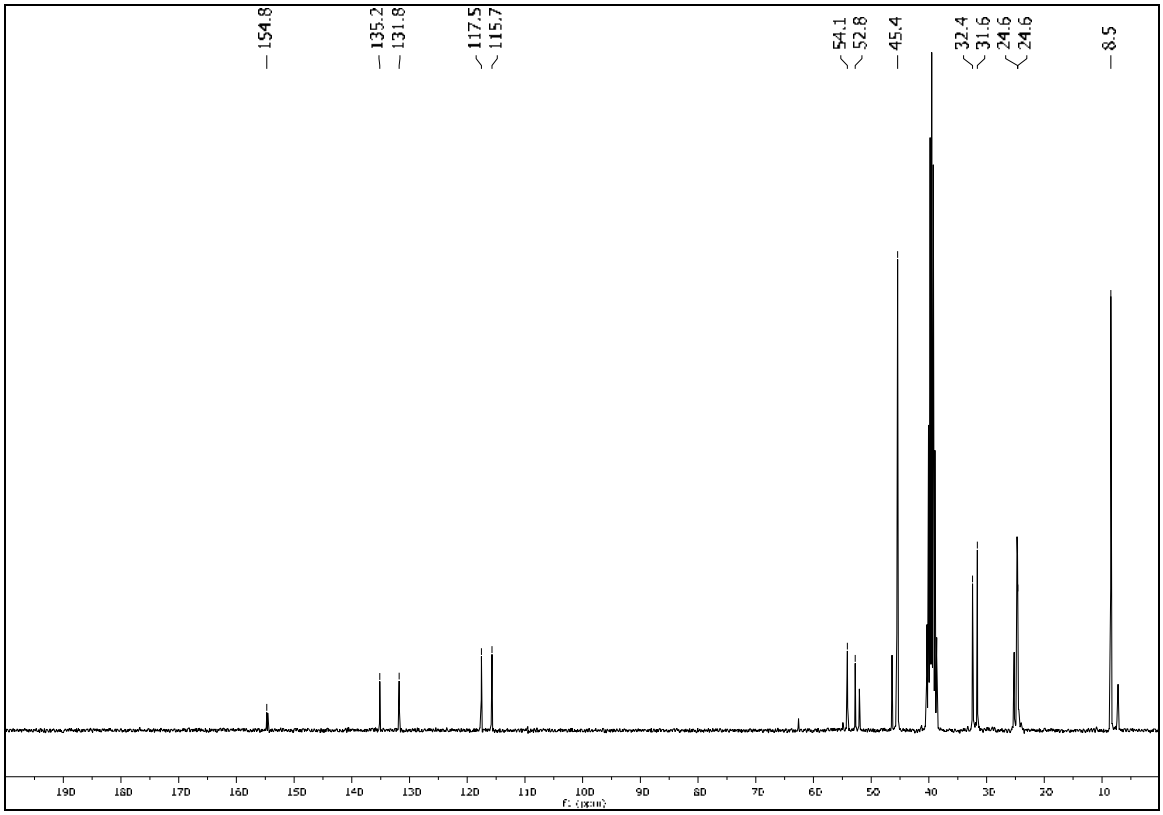
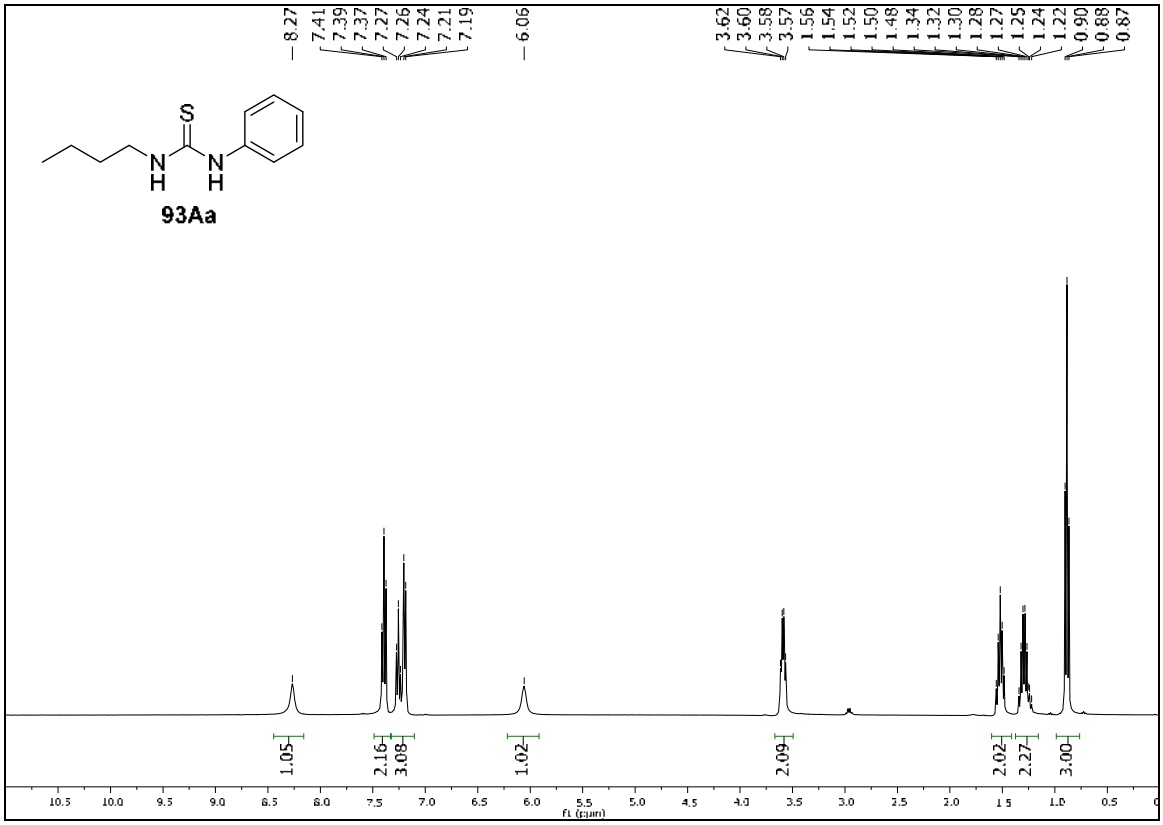
155.3
56.3
54.2
45.7
44.9
34.0
32.5
32.3
31.2
26.1
25.8
25.6
20.6
20.3
14.4
f1 (ppm)


91Ba
92Ba

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6.06
3.62
3.60
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1.52
1.50
1.48
1.34
1.32
1.30
1.28
1.27
1.25
1.24
1.22
0.90
0.88
0.87
S
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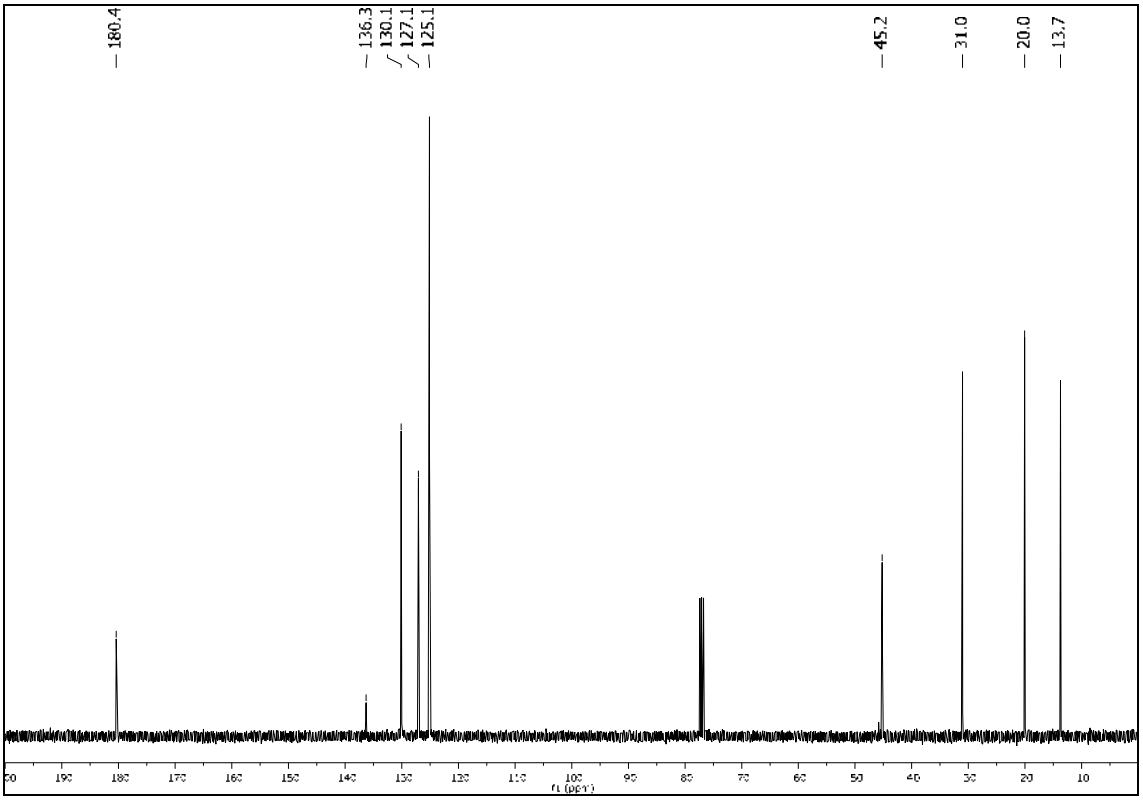
H
N
H
93Aa
1.05
2.16
3.08
1.02
2.09
2.02
2.27
3.00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130.1
127.1
125.1
45.2
31.0
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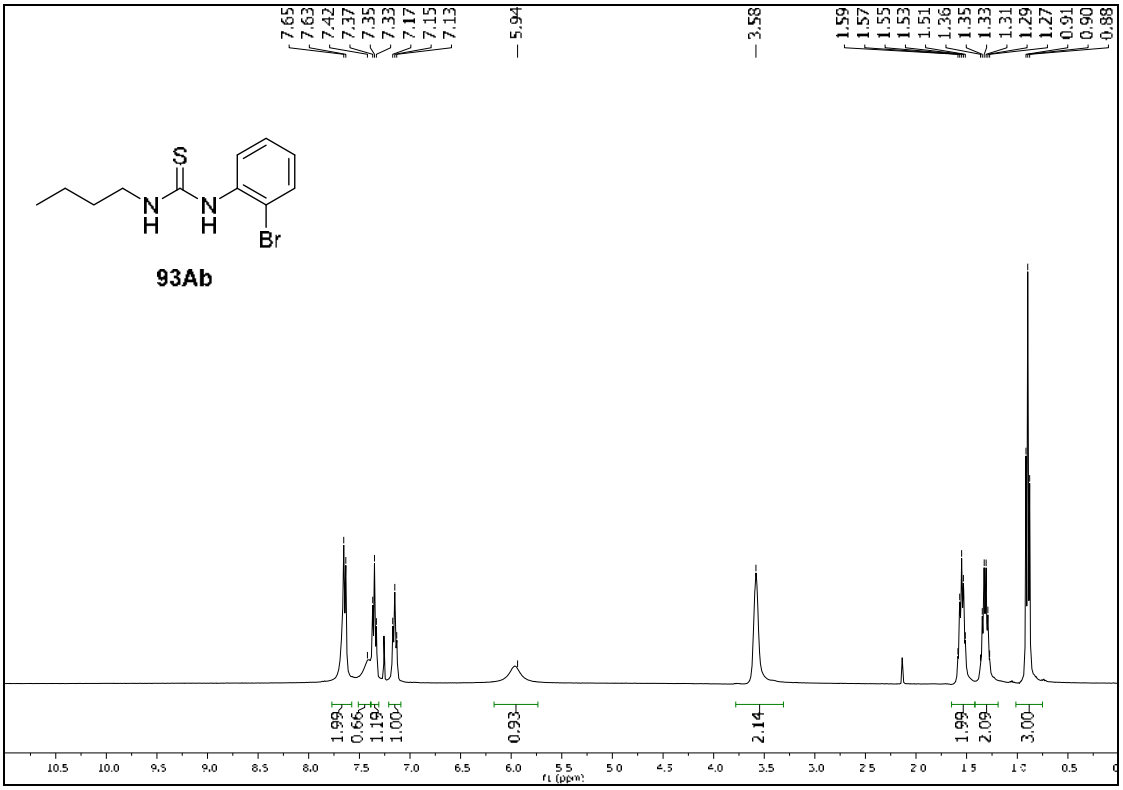
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1.57
1.55
1.53
1.51
1.36
1.35
1.33
1.31
1.29
1.27
0.91
0.90
0.88
S
N
H
N
H
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0.66
1.19
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0.93
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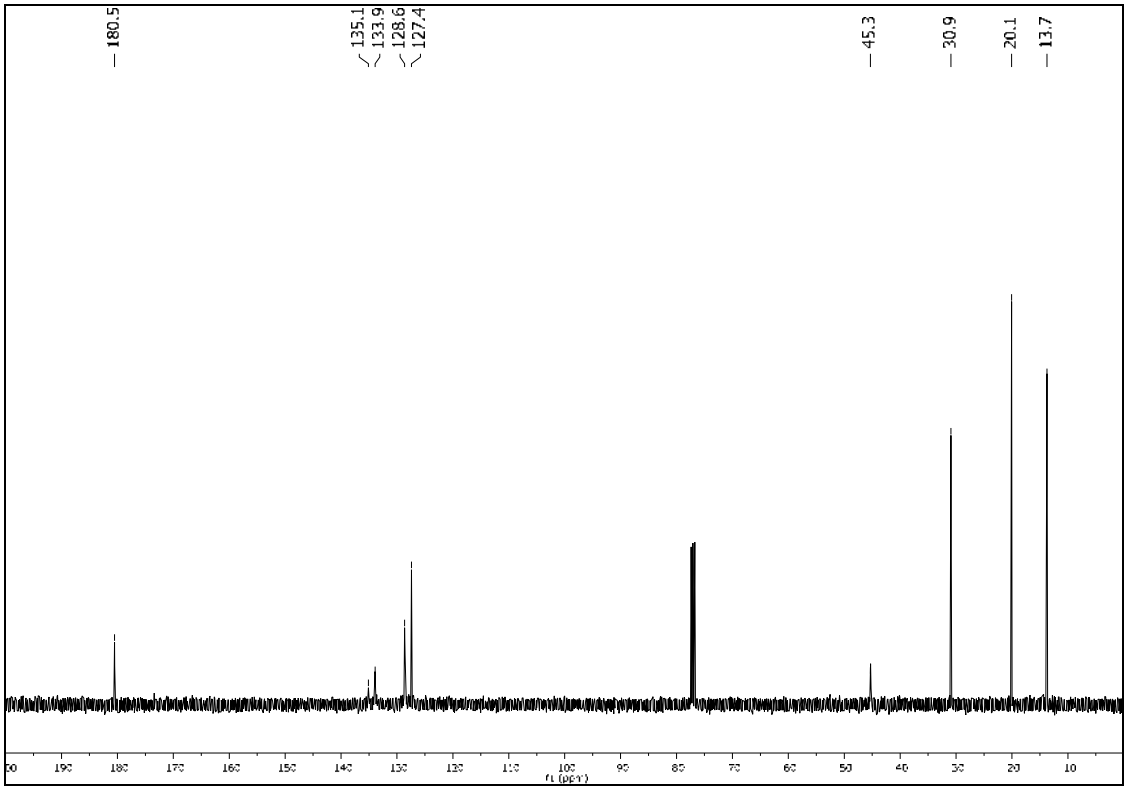
1.99
2.09
3.00
f1 (ppm)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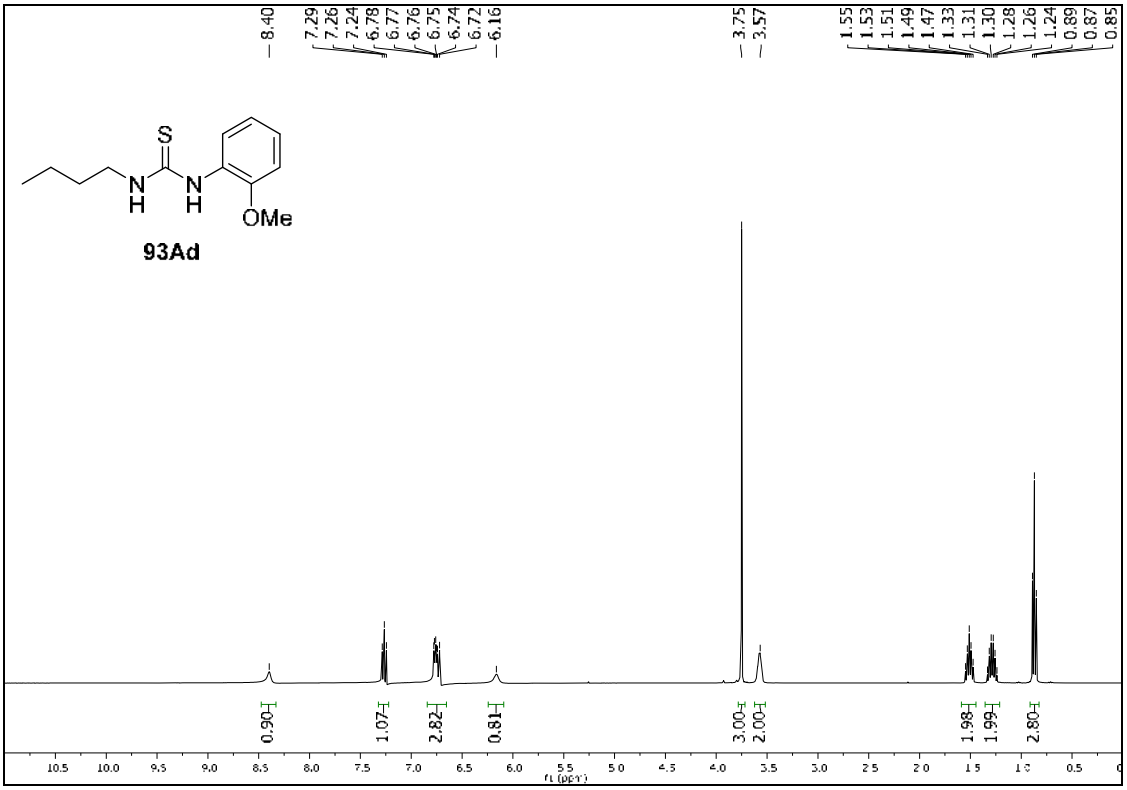
f1 (ppm)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1.55
1.53
1.51
1.49
1.47
1.33
1.31
1.30
1.28
1.26
1.24
0.89
0.87
0.85
S
N
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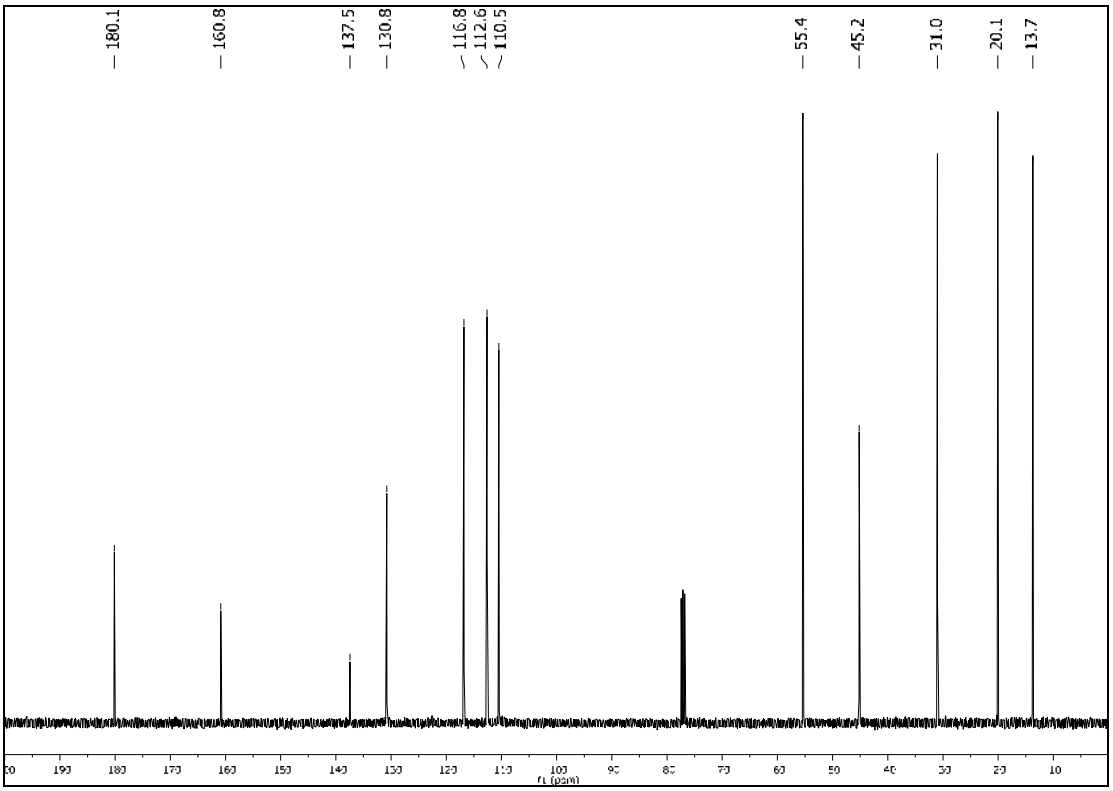
2.80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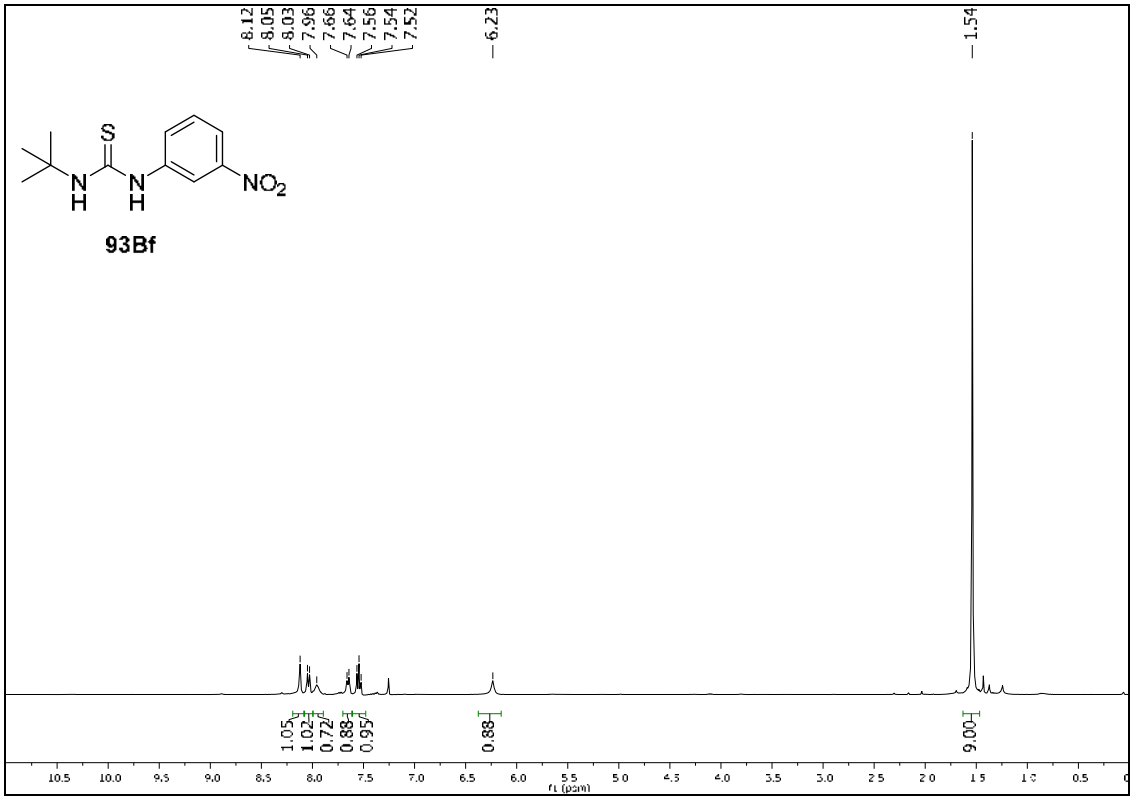
13.7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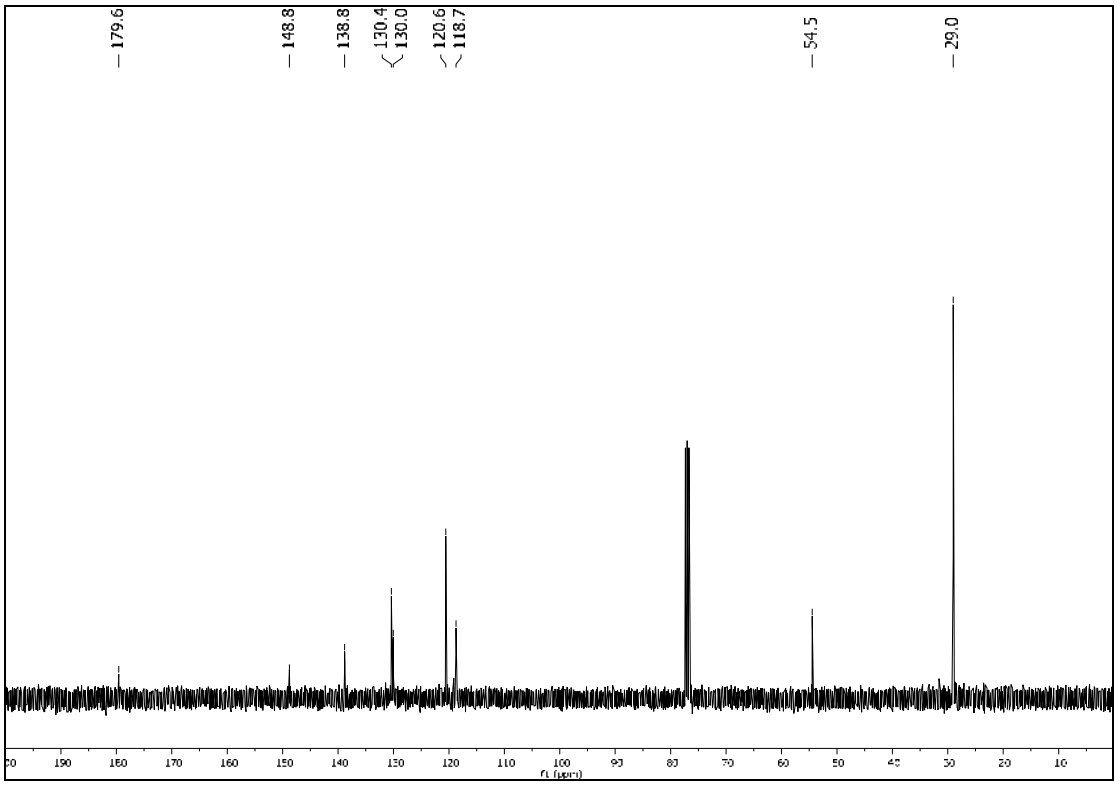
f1 (ppm)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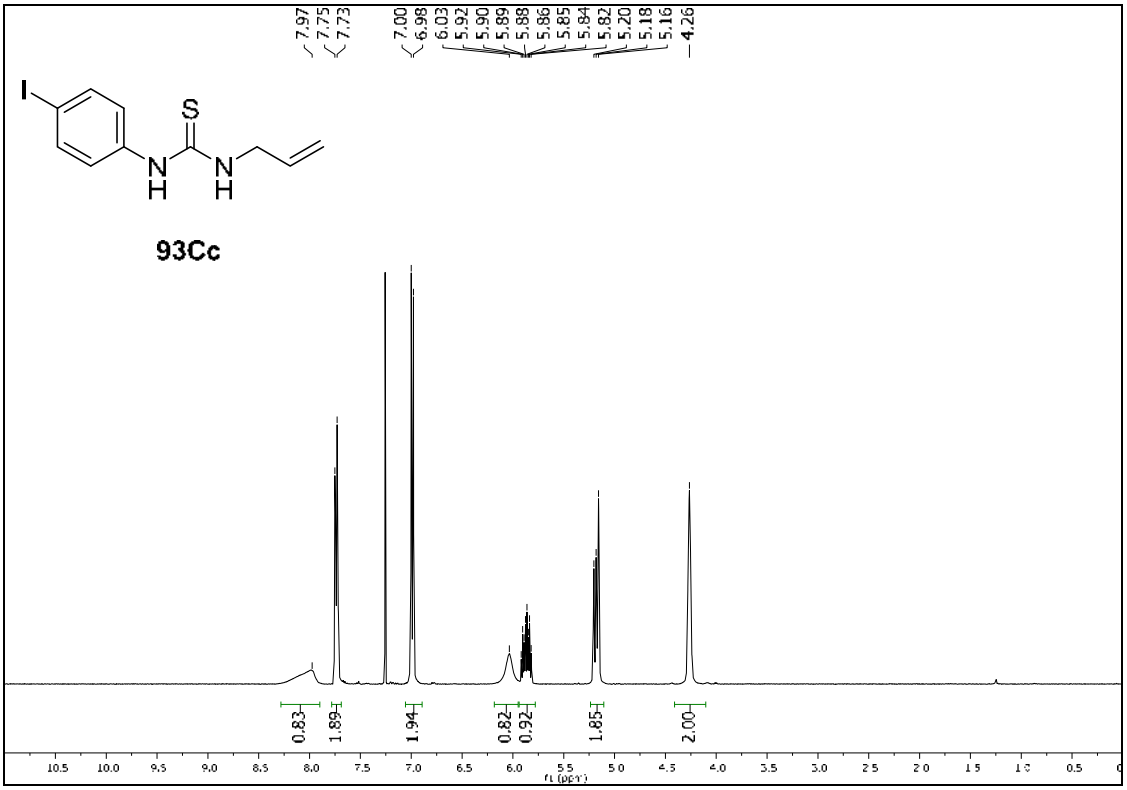
29.0
f1 (ppm)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5.16
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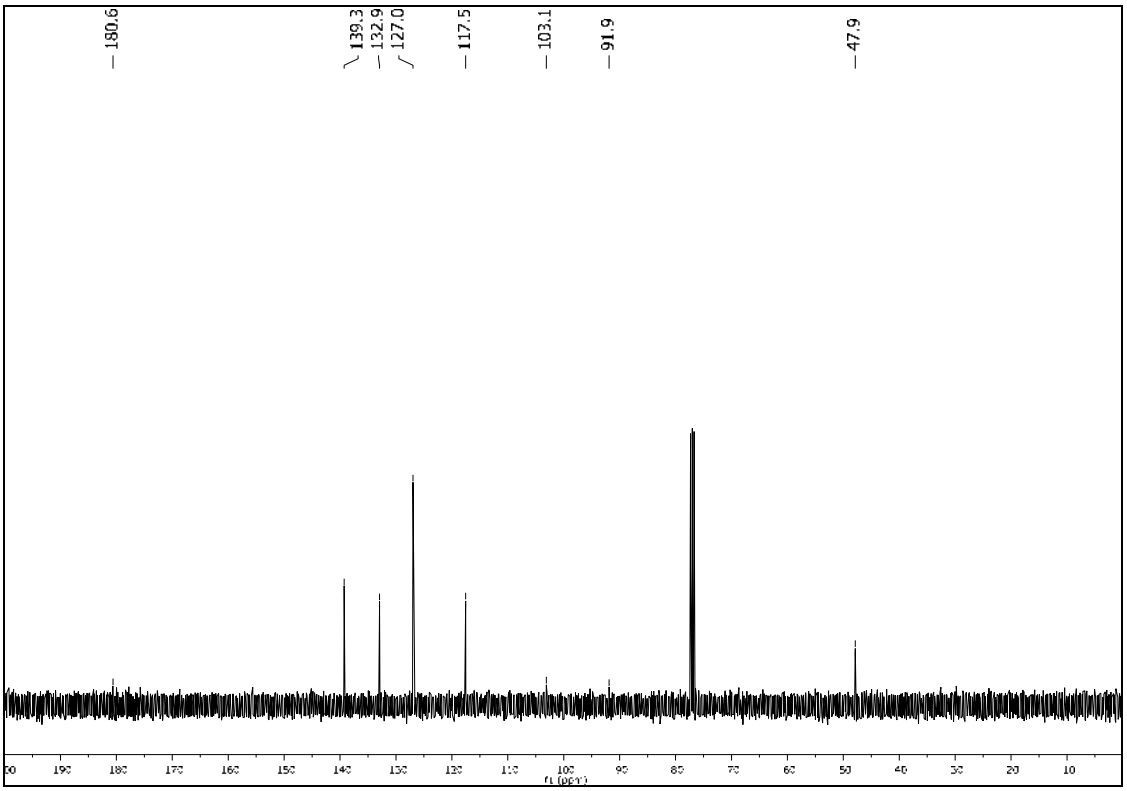
2.00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103.1
91.9
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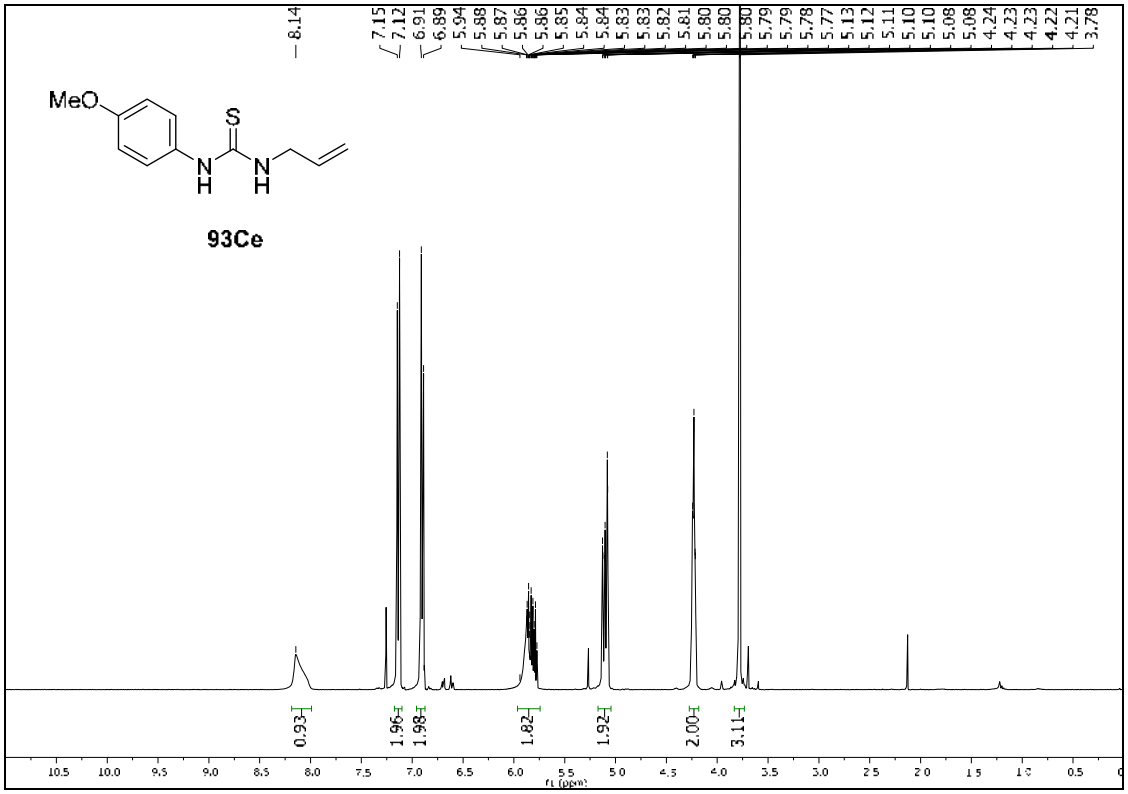
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N
H
N
H
93Ce
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7.12
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5.94
5.88
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5.86
5.86
5.85
5.84
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5.12
5.11
5.10
5.10
5.08
5.08
4.24
4.23
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1.92
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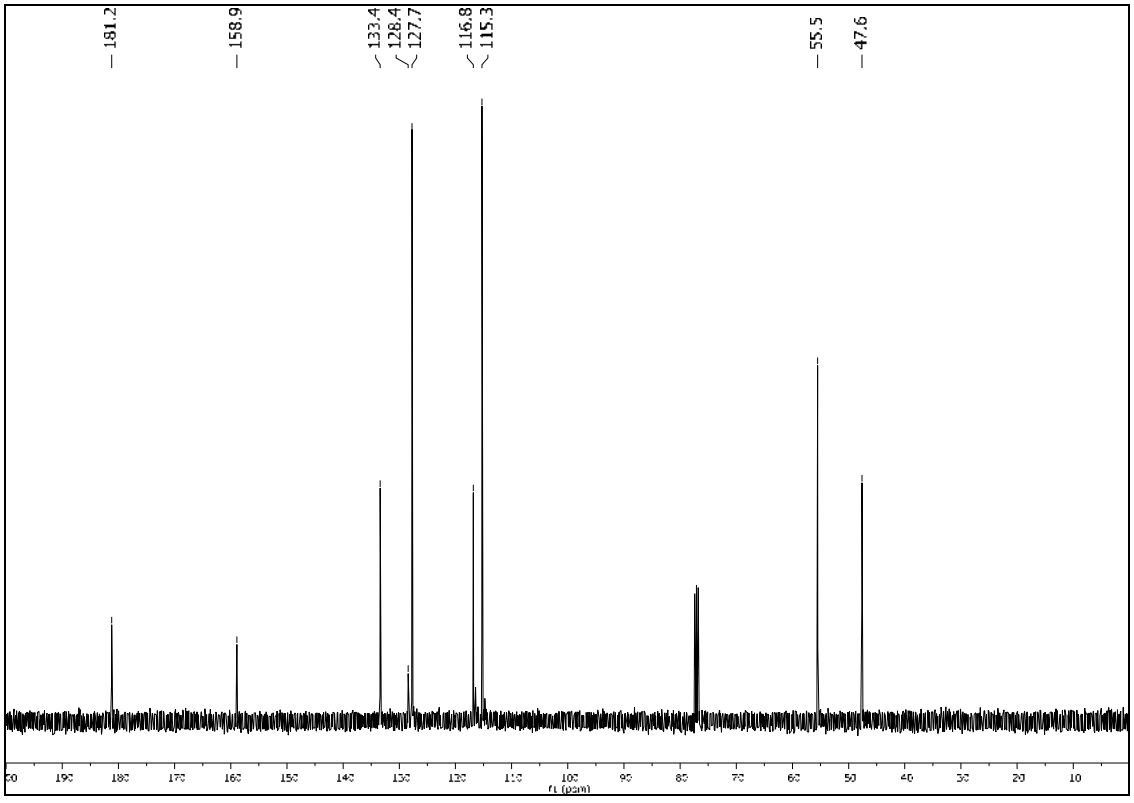
3.11
f1 (ppm)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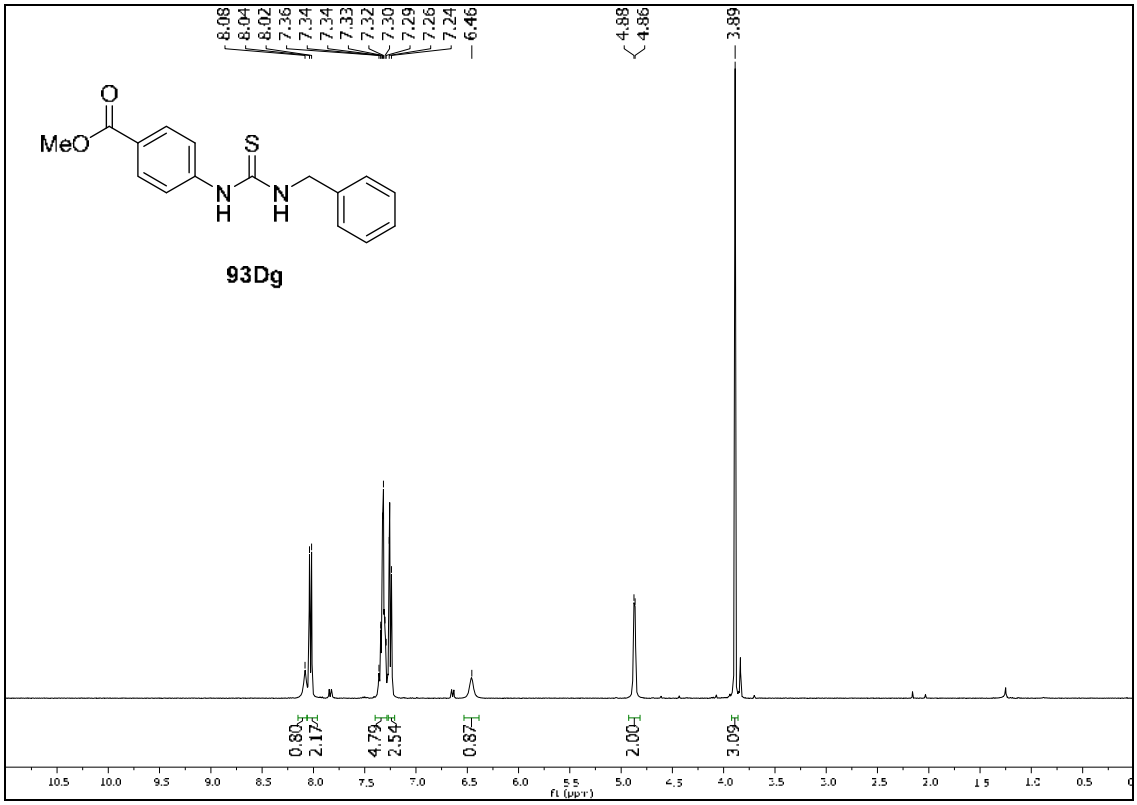
115.3
55.5
47.6
f1 (ppm)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7.32
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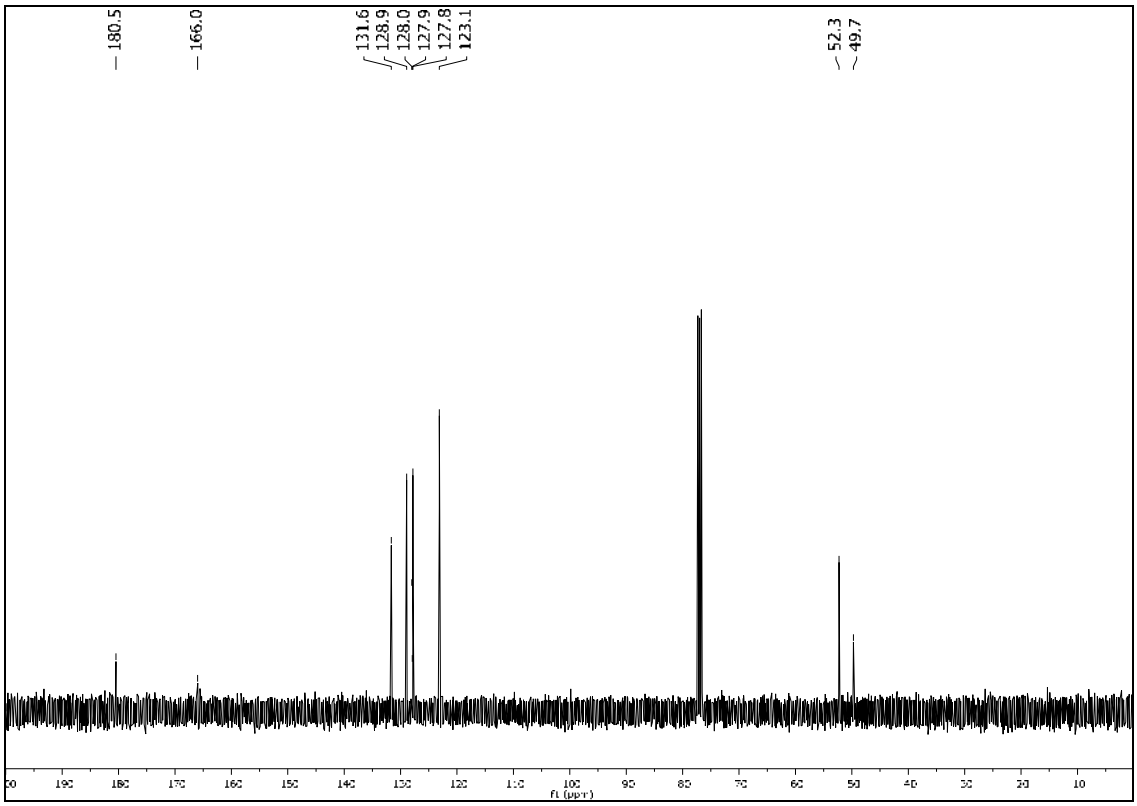
7.29
7.26
7.24
6.46
4.88
4.86
3.89
MeO
O
S
N
H
N
H
93Dg
0.80
2.17
4.79
2.54
0.87
2.00
3.09
f1 (ppm)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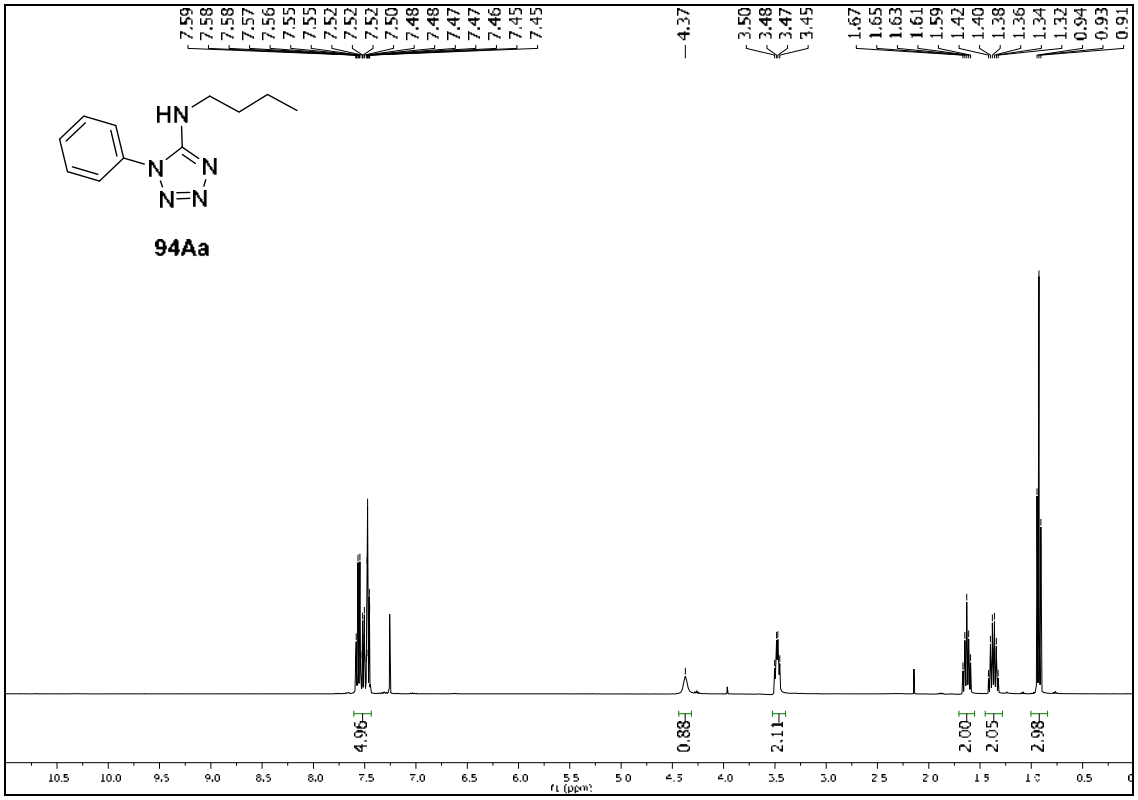
128.0
127.9
127.8
123.1
52.3
49.7
f1 (ppm)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7.47
7.47
7.46
7.45
7.45
4.37
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3.45
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1.65
1.63
1.61
1.59
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1.40
1.38
1.36
1.34
1.32
0.94
0.93
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0.88
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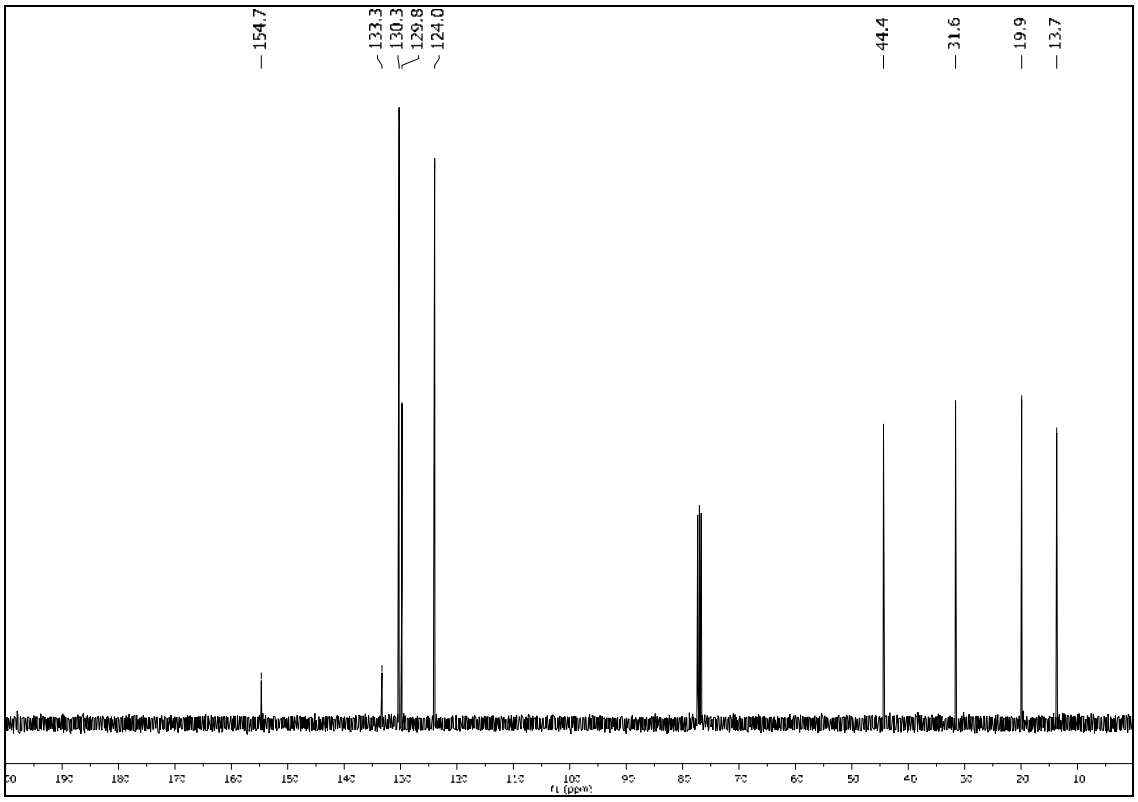
2.98
f1 (ppm)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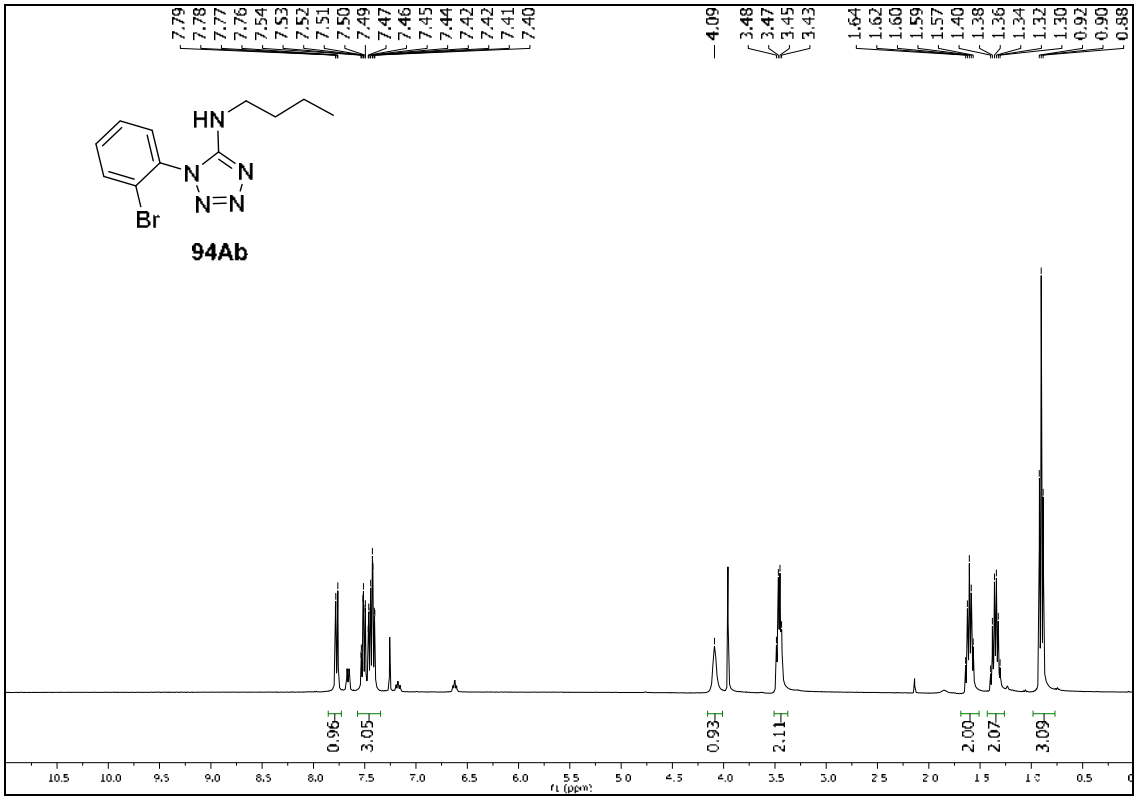
129.8
124.0
44.4
31.6
19.9
13.7
f1 (ppm)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7.42
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3.45
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1.62
1.60
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1.57
1.40
1.38
1.36
1.34
1.32
1.30
0.92
0.90
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N
N=N
Br
94Ab
0.96
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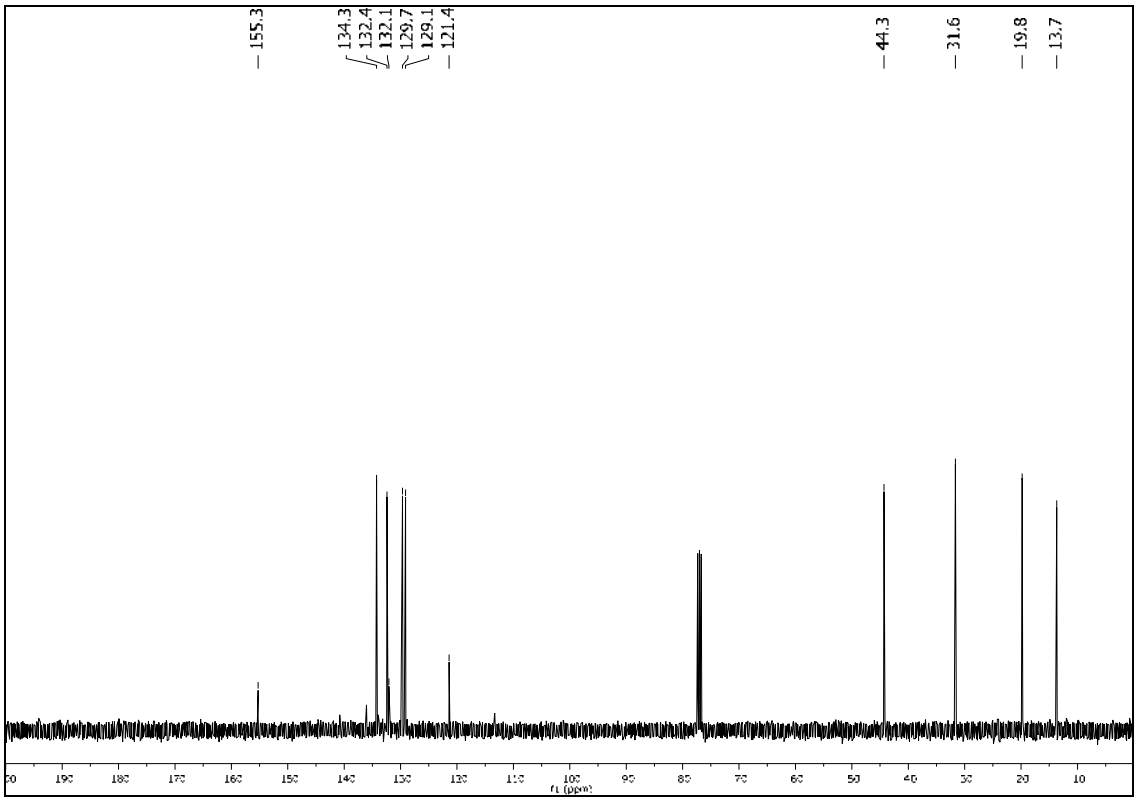
0.93
2.11
2.00
2.07
3.09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31.6
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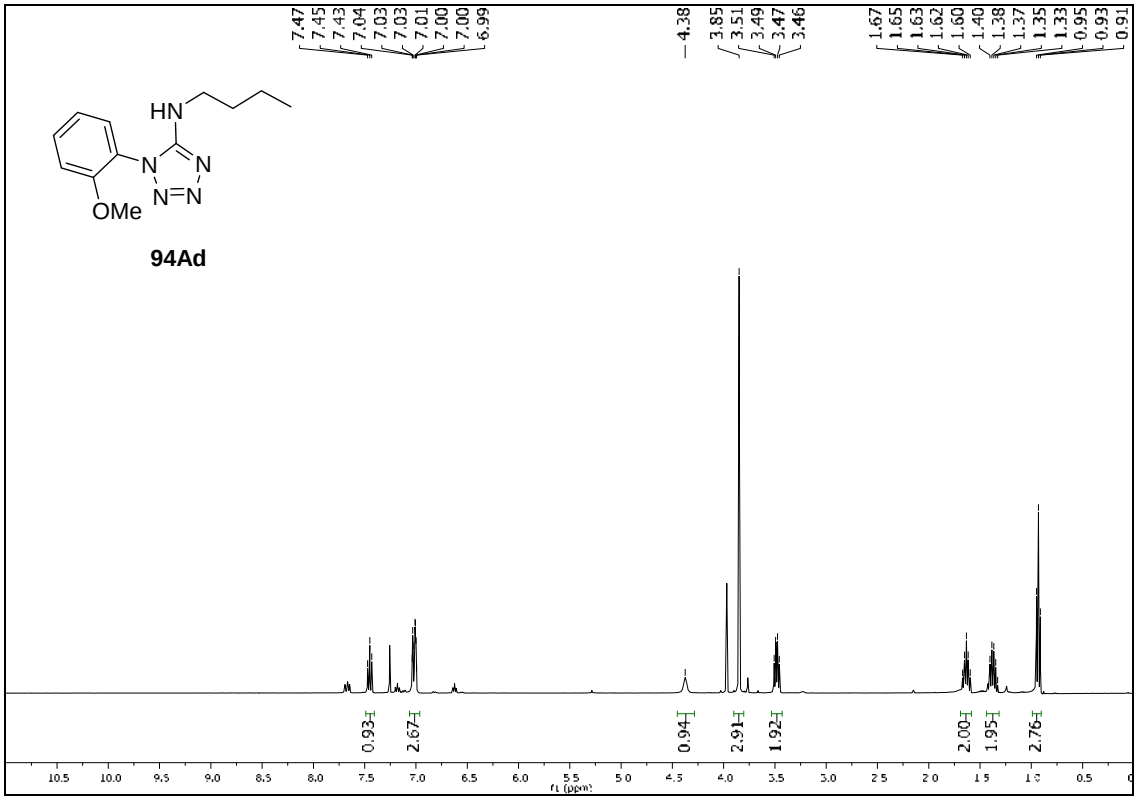
13.7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7.00
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3.51
3.49
3.47
3.46
1.67
1.65
1.63
1.62
1.60
1.40
1.38
1.37
1.35
1.33
0.95
0.93
0.91
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0.94
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1.92
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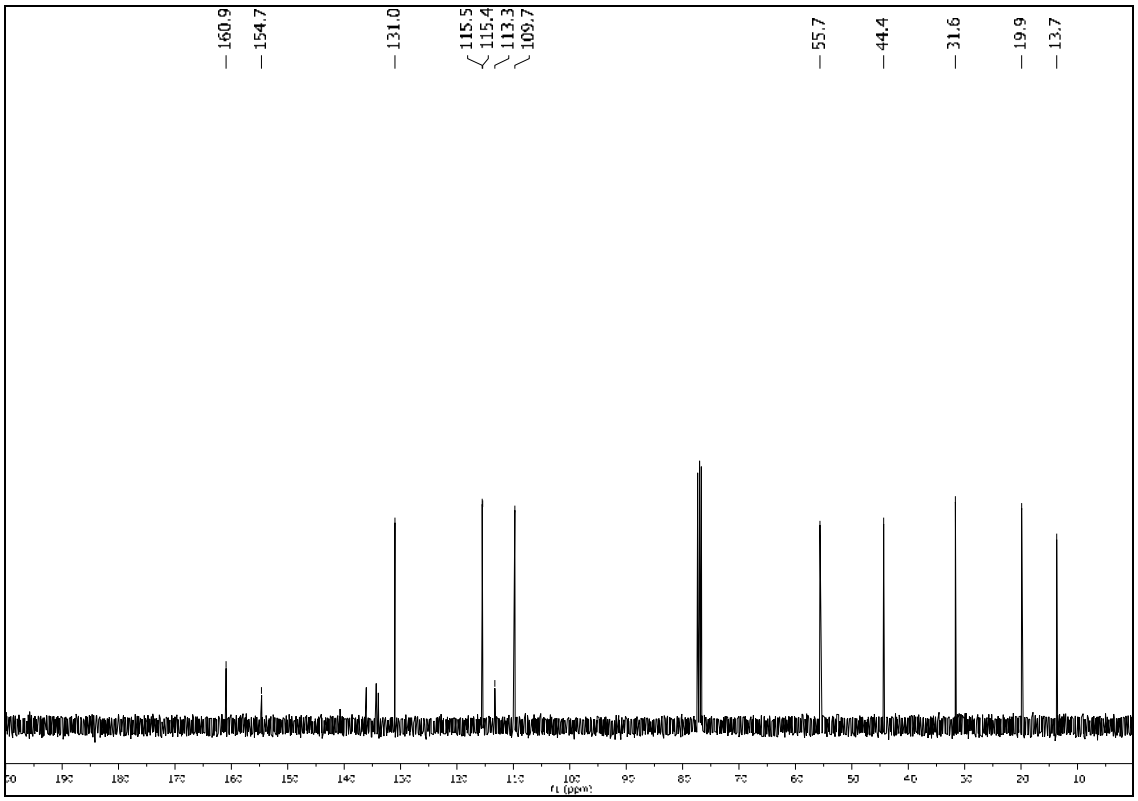
1.95
2.76

94Ad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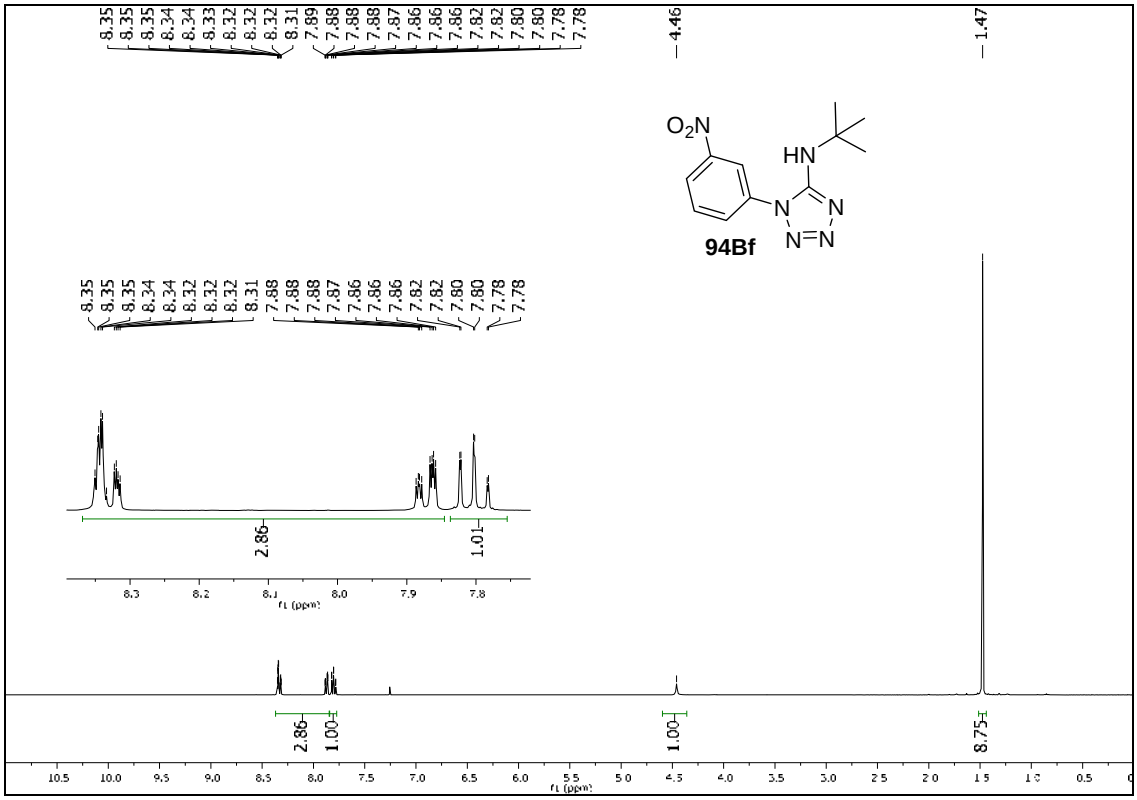
13.7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7.86
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7.82
7.80
7.78
7.78
4.46
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1.01
2.86
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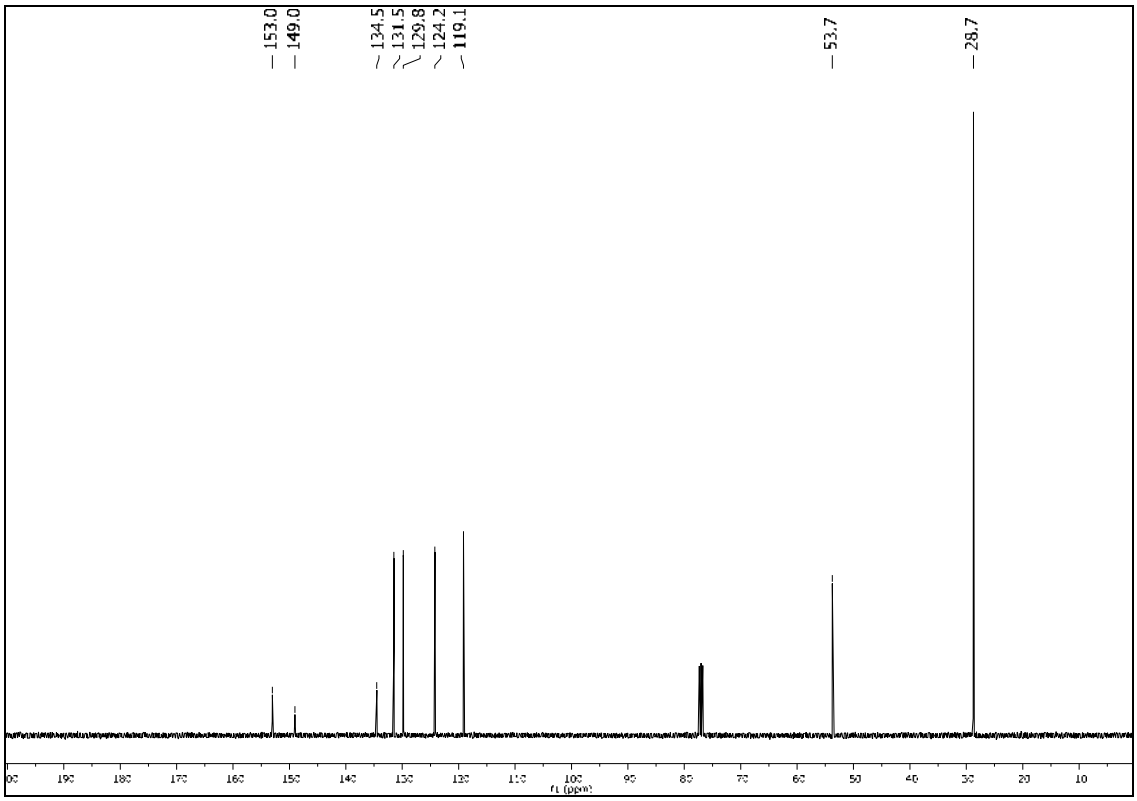
1.00
8.75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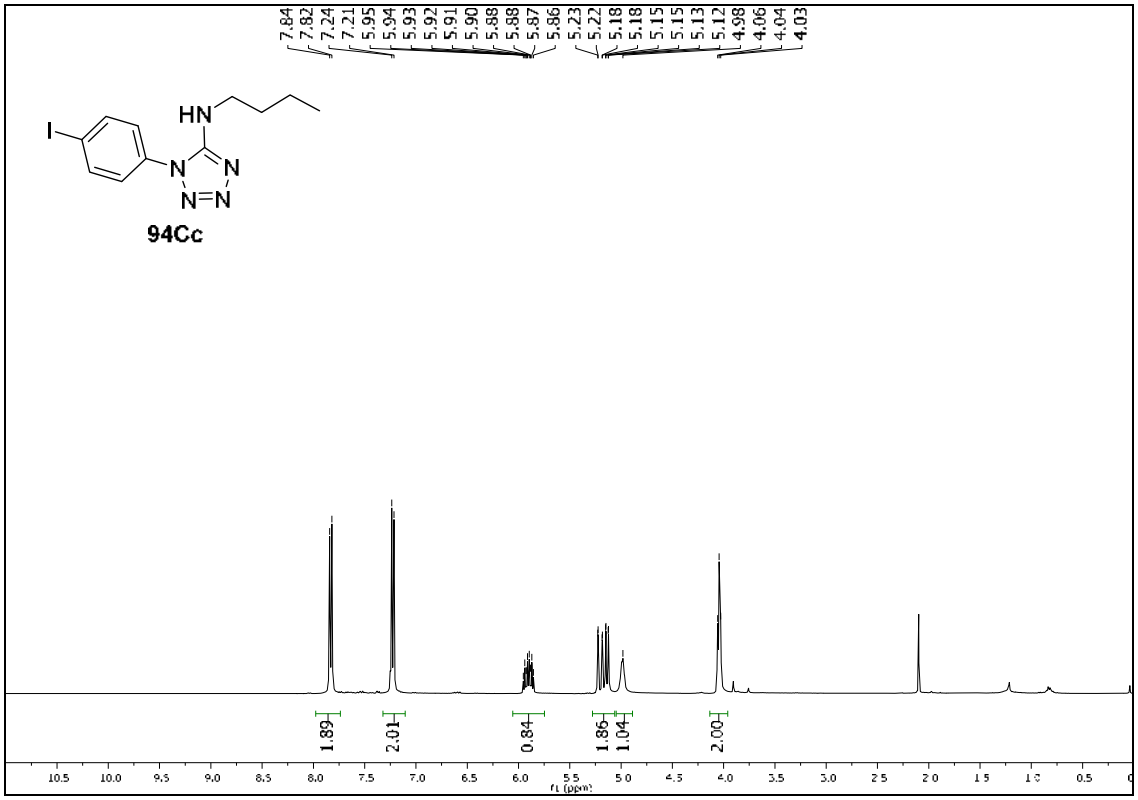
28.7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5.86
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5.18
5.18
5.15
5.15
5.13
5.12
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4.06
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N
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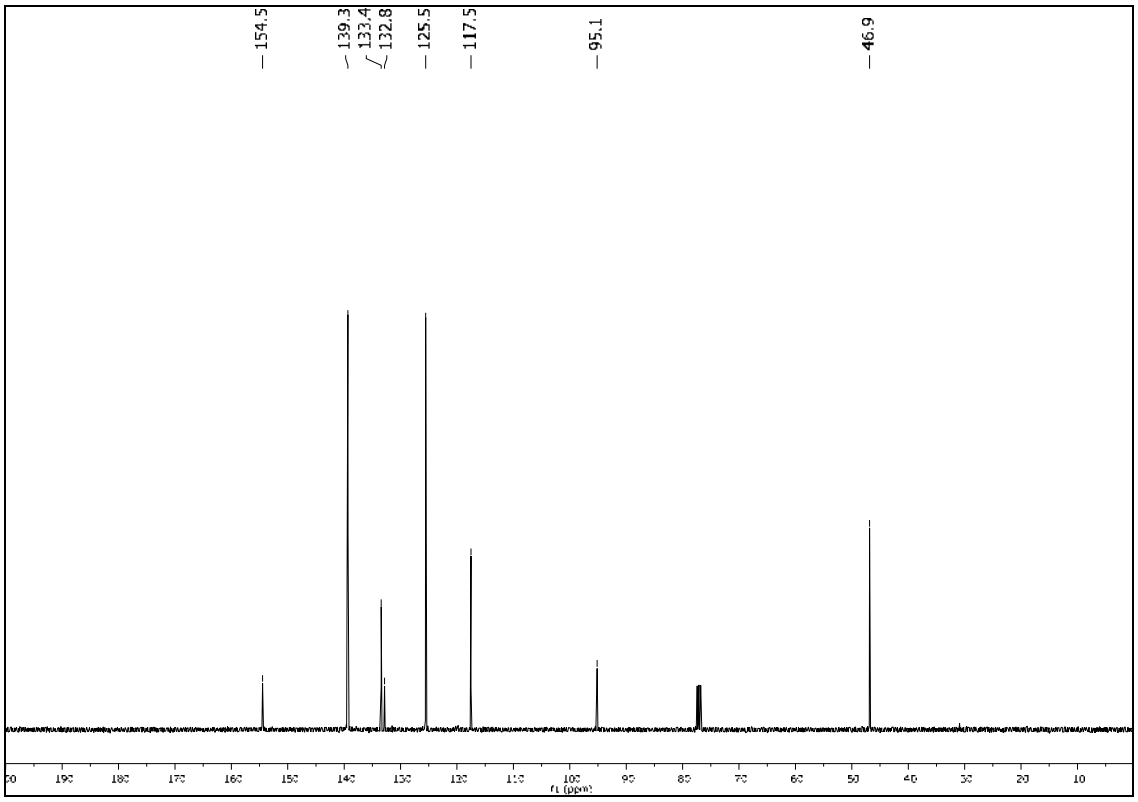
2.00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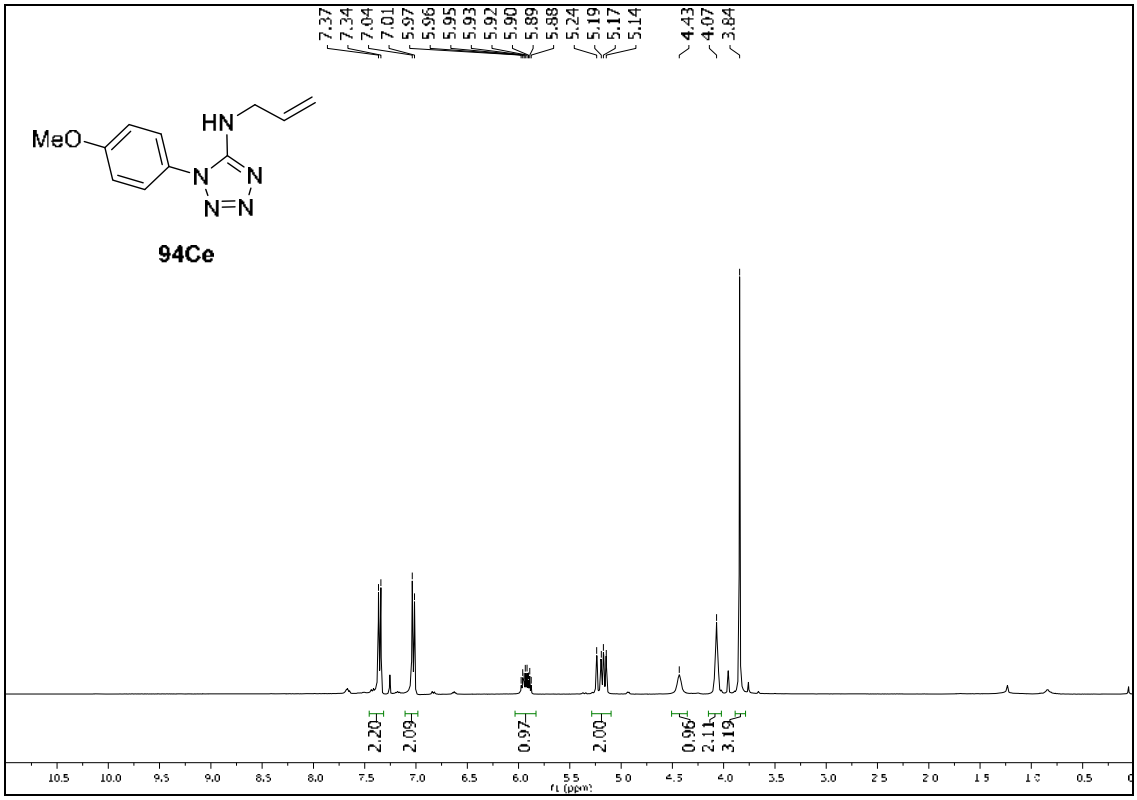
46.9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5.19
5.17
5.14
4.43
4.07
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N=N
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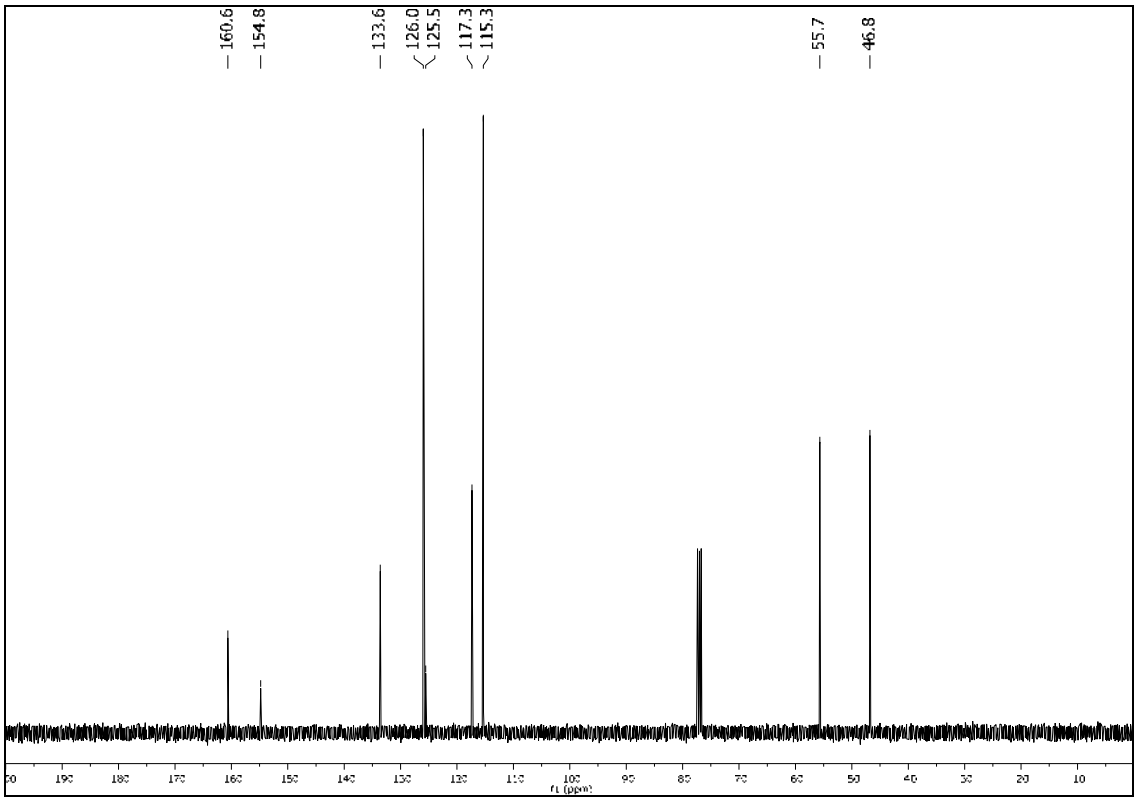
2.11
3.19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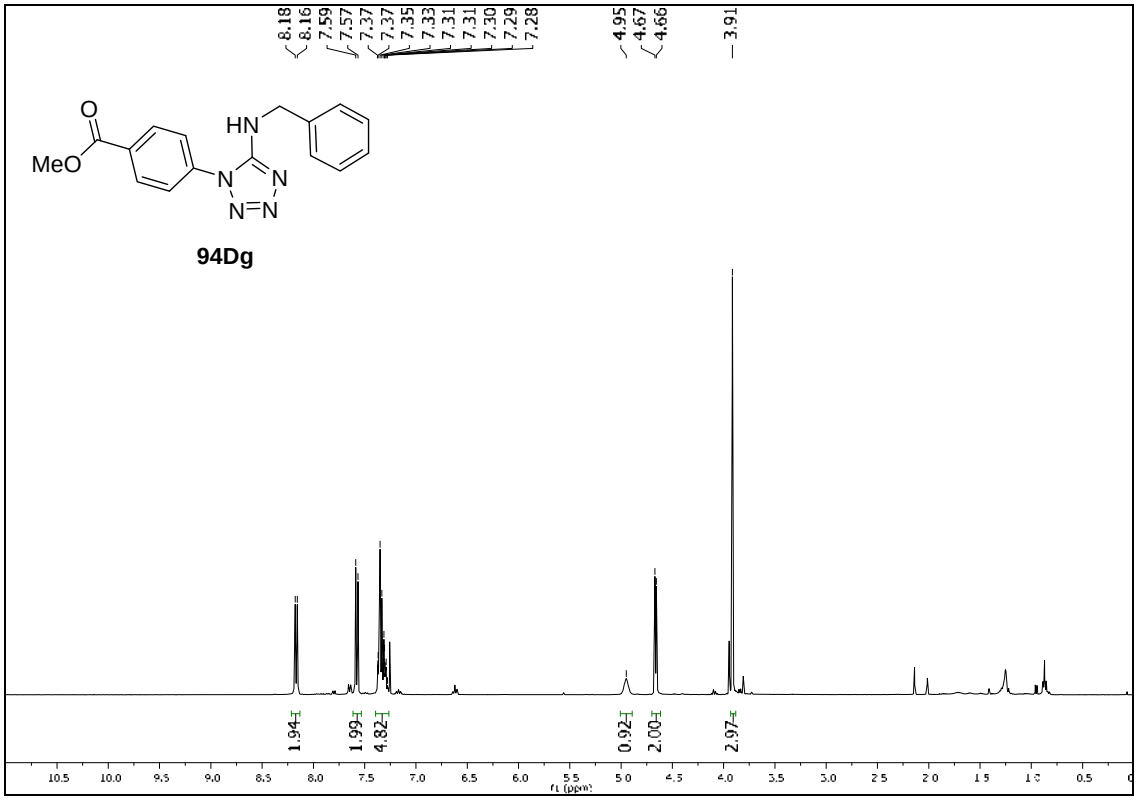
46.8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7.30
7.29
7.28
4.95
4.67
4.66
3.91
O
MeO
HN
N
N
N=N
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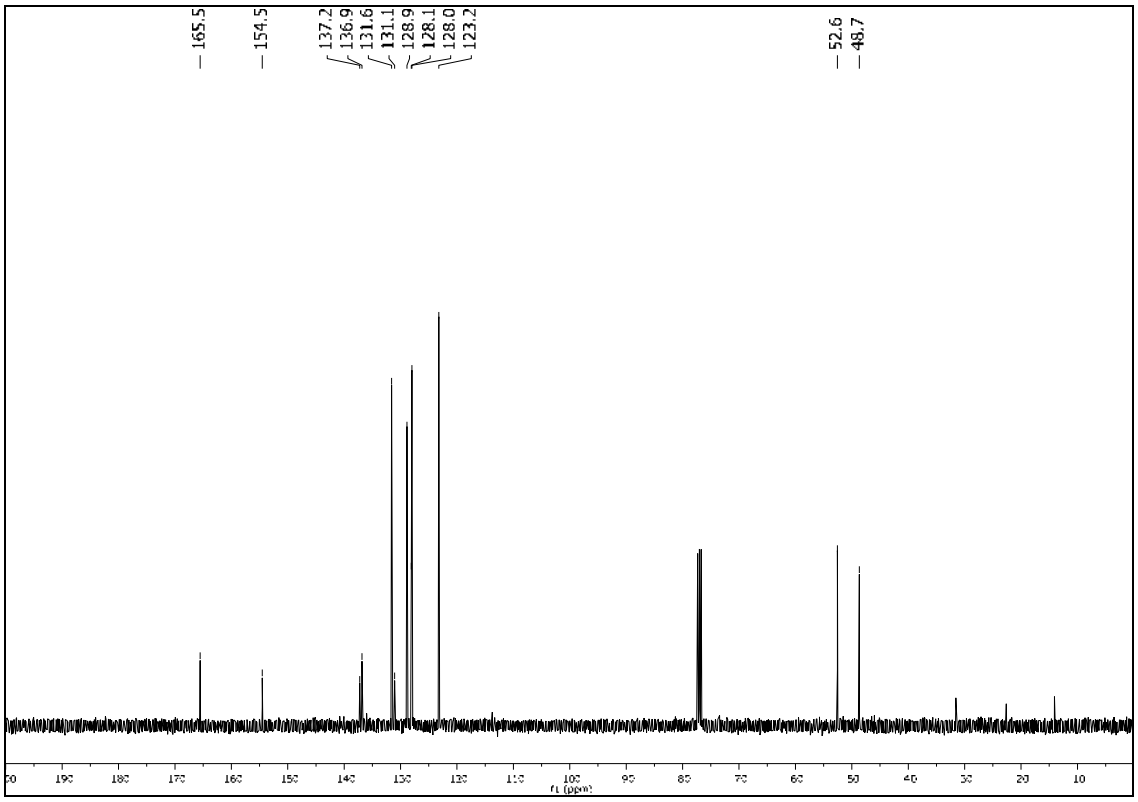
1.99
4.82
0.92
2.00
2.97
f1 (ppm)

94Dg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131.1
128.9
128.1
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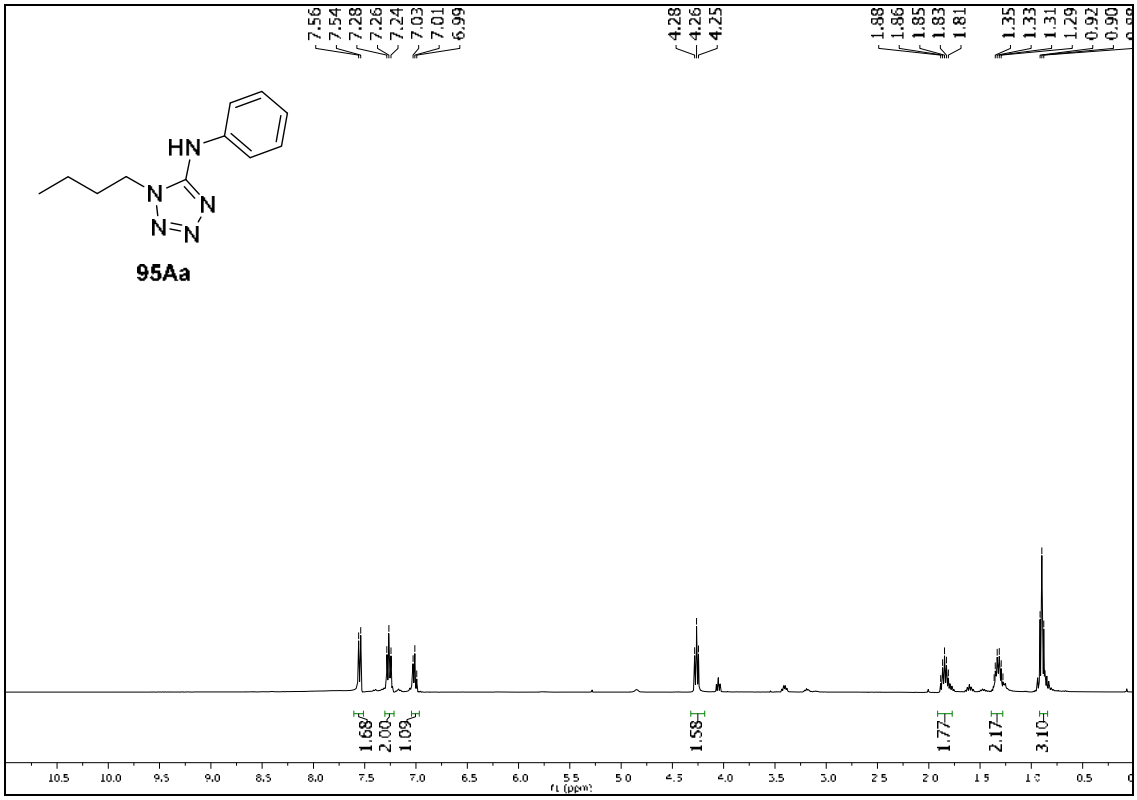
48.7
f1 (ppm)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1.86
1.85
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1.81
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1.33
1.31
1.29
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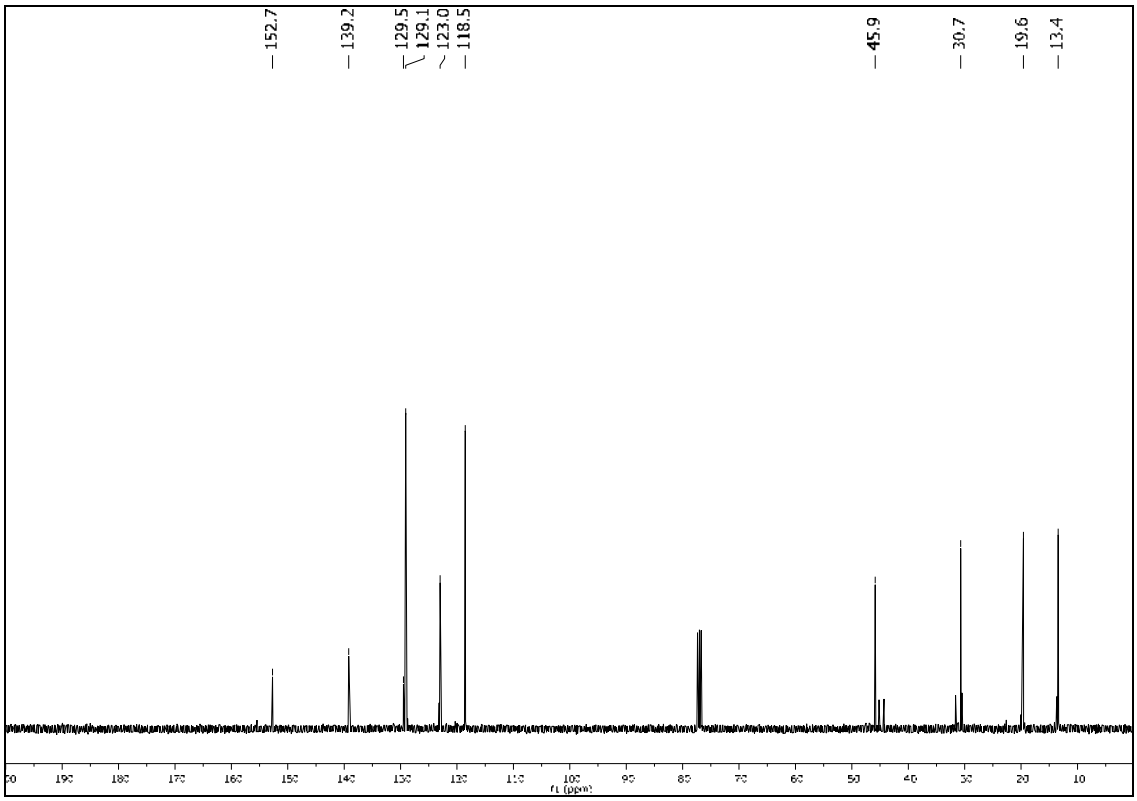
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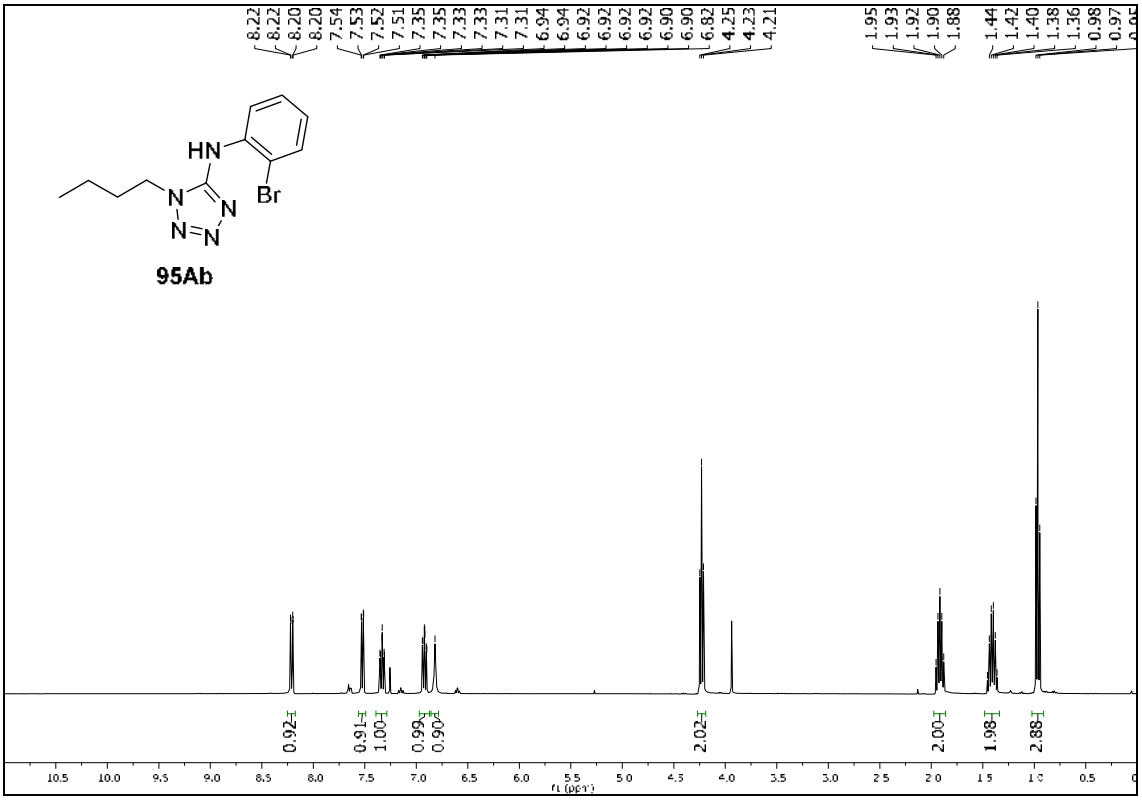
13.4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7.31
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6.92
6.92
6.92
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4.21
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1.92
1.90
1.88
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1.42
1.40
1.38
1.36
0.98
0.97
HN
N
N
N
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Br
95Ab
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0.91
1.00
0.99
0.90
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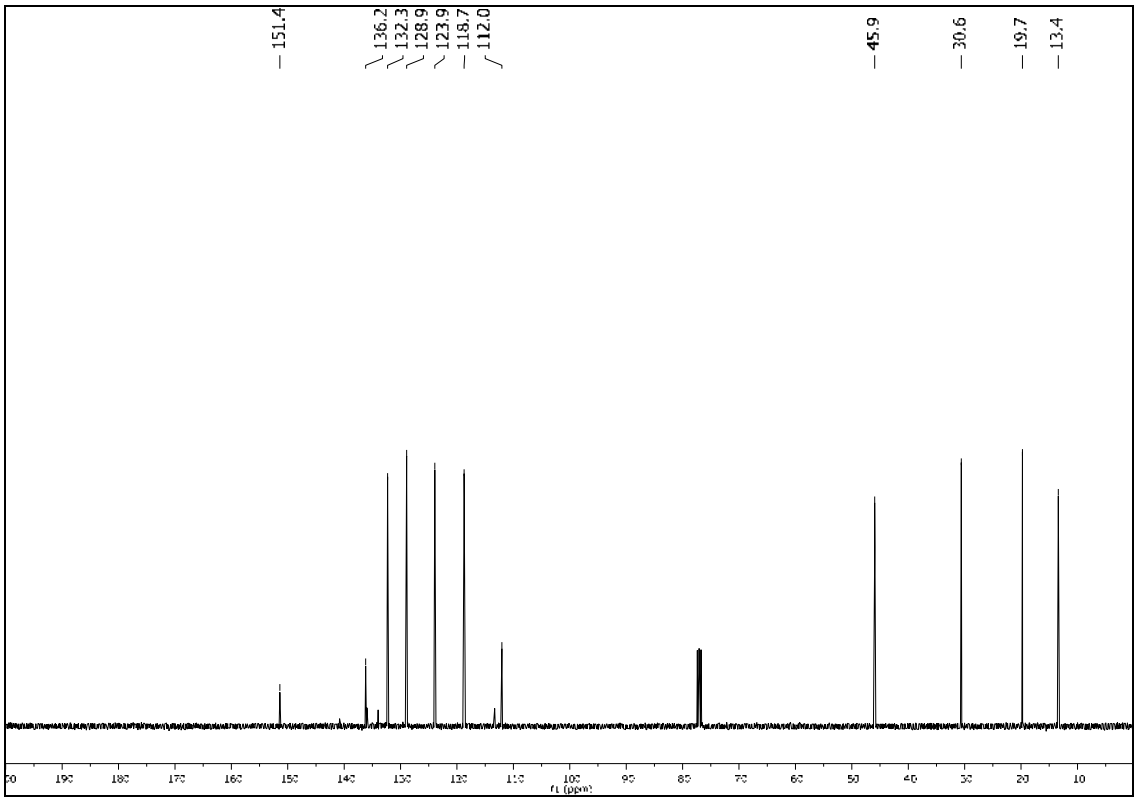
2.00
1.98
2.88
f1 (ppm)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128.9
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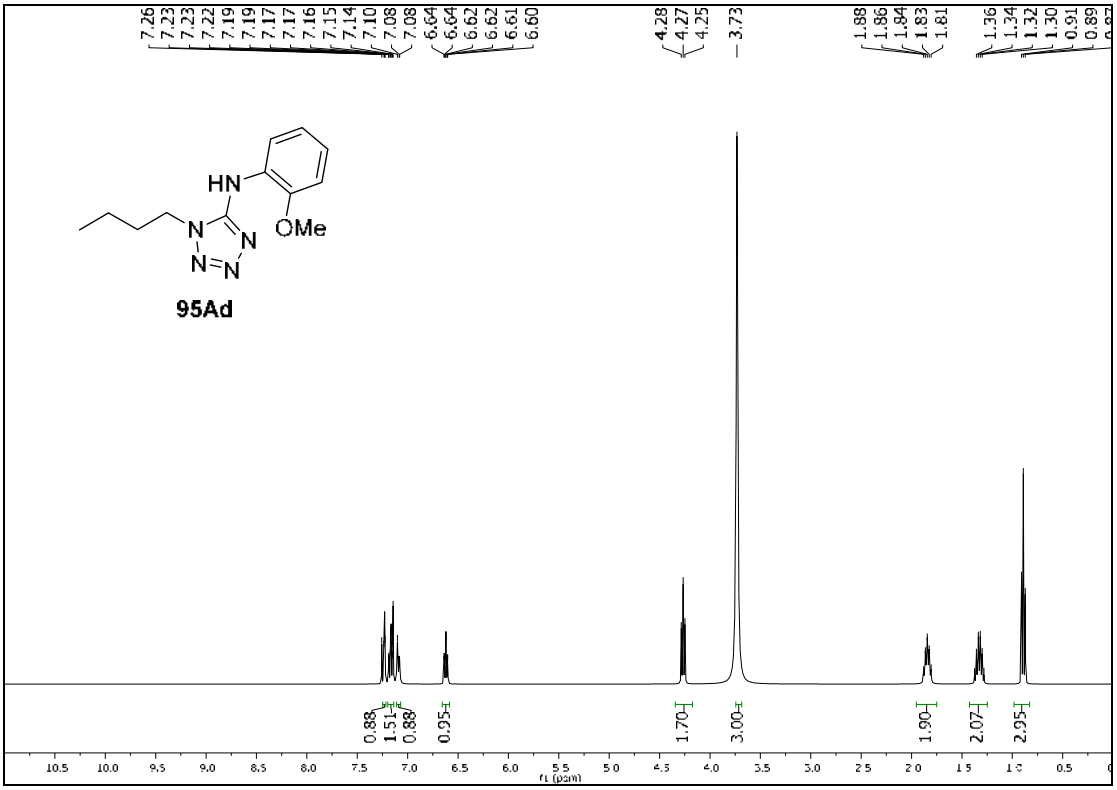
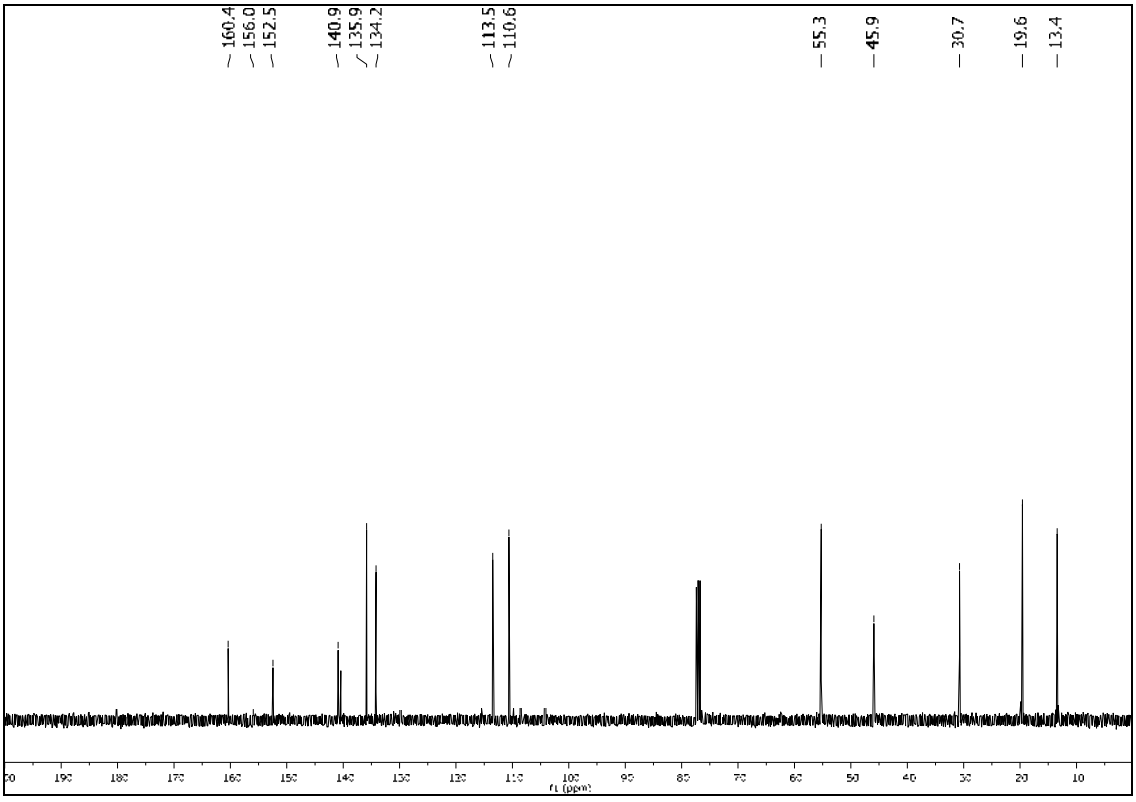
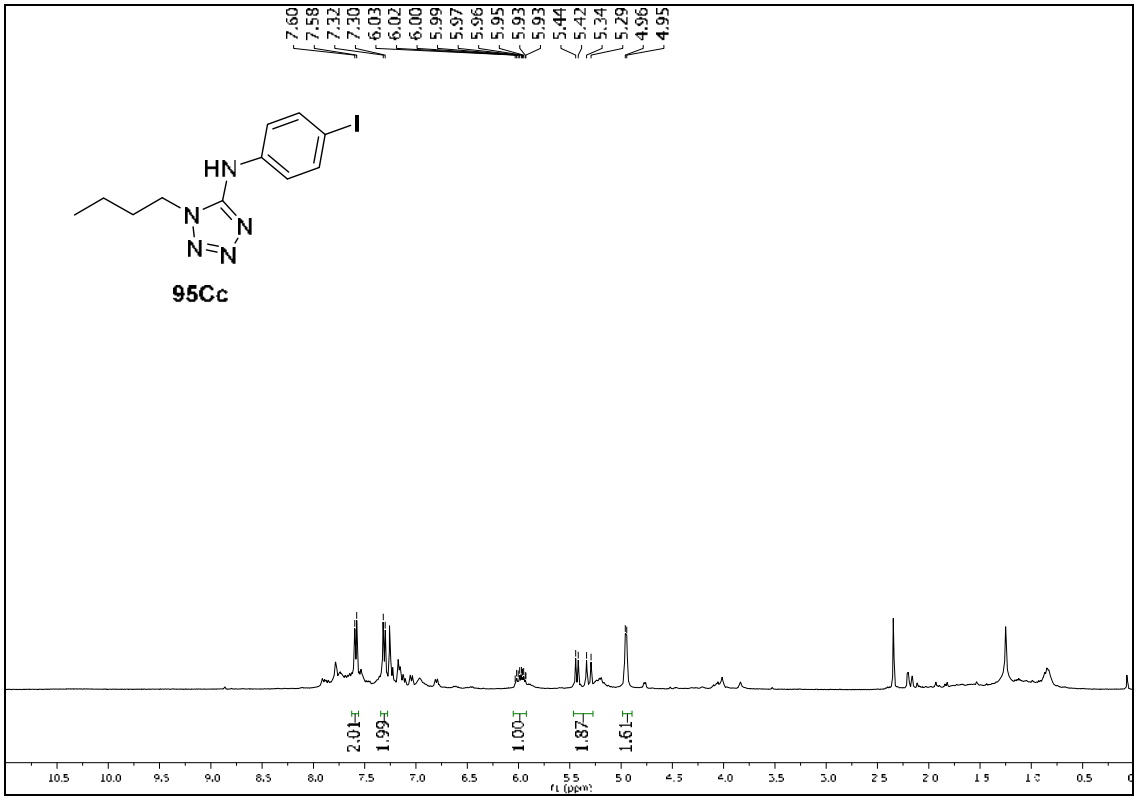
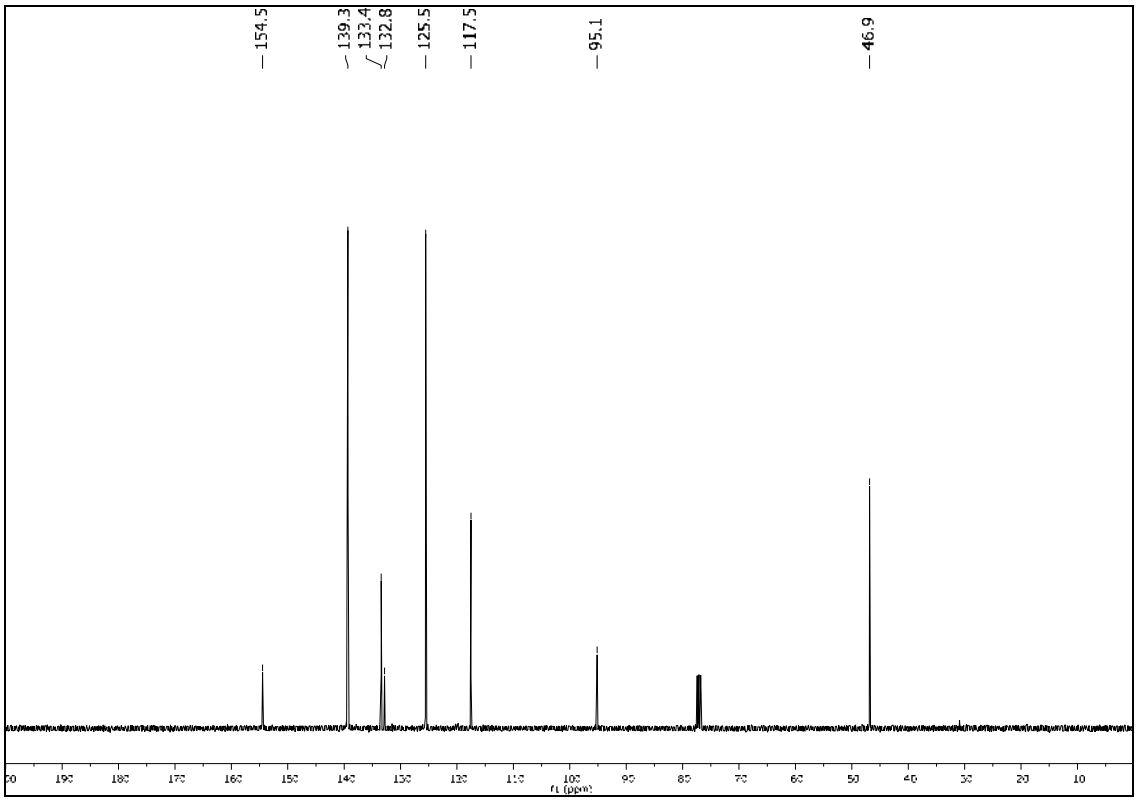
30.6
19.7
13.4
f1 (ppm)


HN
OMe
N
N
N
N
95Ad

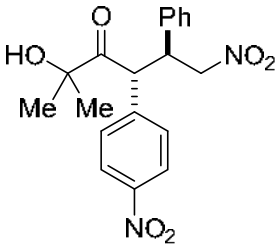



7.60
7.58
7.32
7.30
6.03
6.02
6.00
5.99
5.97
5.96
5.95
5.93
5.93
5.44
5.42
5.34
5.29
4.96
4.95
HN
I
N
N
N
N
95Cc
2.01
1.99
1.00
1.87
1.61
f1 (ppm)


154.5
139.3
133.4
132.8
125.5
117.5
95.1
46.9
f1 (ppm)

7.8. HPLC chromatograms

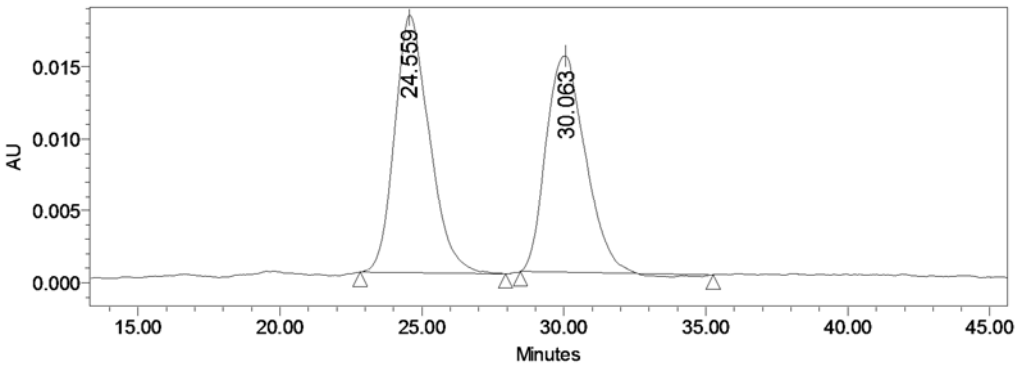
7.8.1. HPLC chromatograms for Chapter 2



25Aa

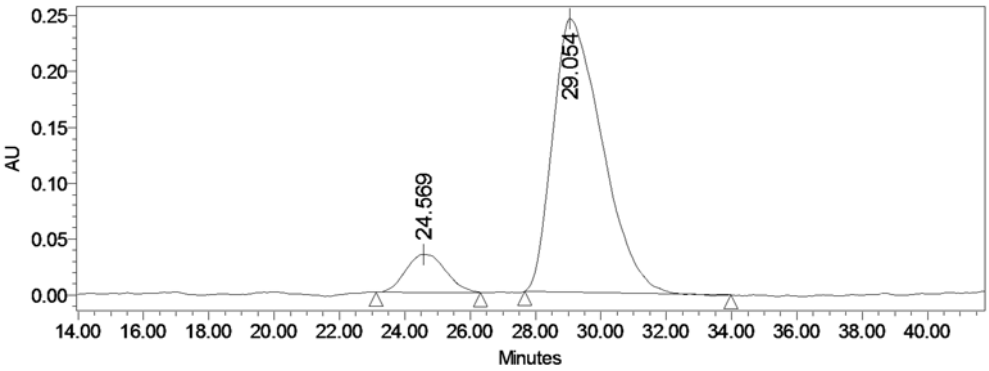
Daicel Chiralpak OD-H, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Aa**



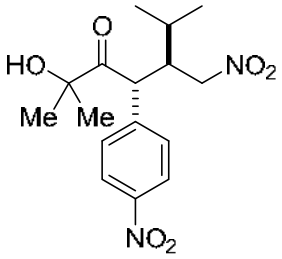
	Retention Time	% Area
1	24.559	50.77
2	30.063	49.23

25Aa



	Retention Time	% Area
1	24.569	9.96
2	29.054	90.04

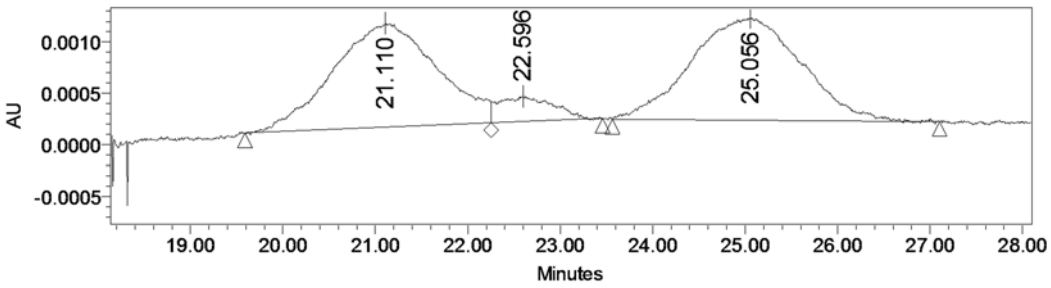
dr* >95:5, 80 % *ee



25Ab

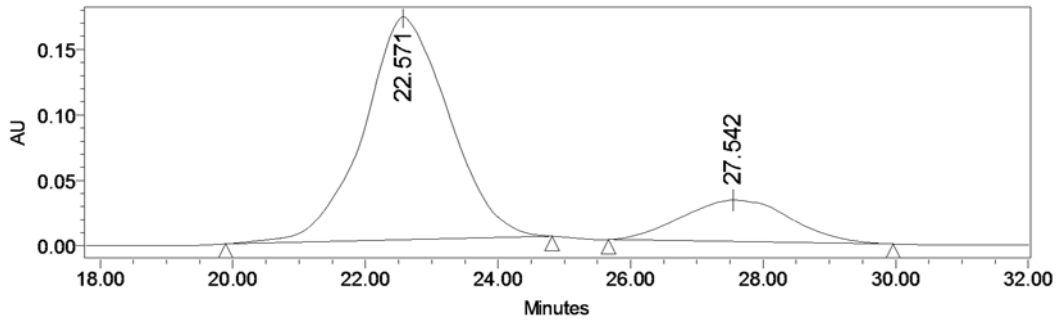
Daicel Chiralpak OD-H, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Ab**



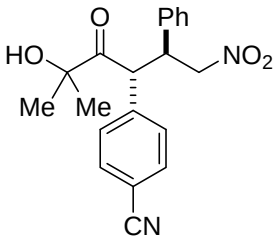
	Retention Time	% Area
1	21.110	46.00
2	22.596	5.79
3	25.056	48.20

25Ab



	Retention Time	% Area
1	22.571	80.80
2	27.542	19.20

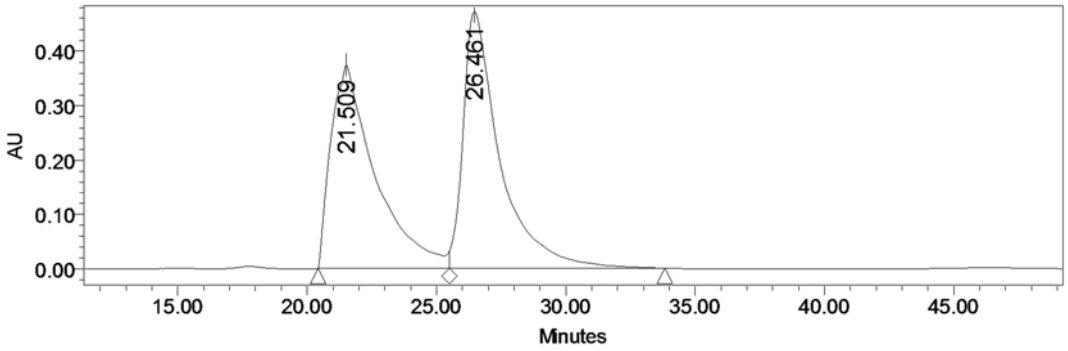
dr* >95:5, 62 % *ee



25Ba

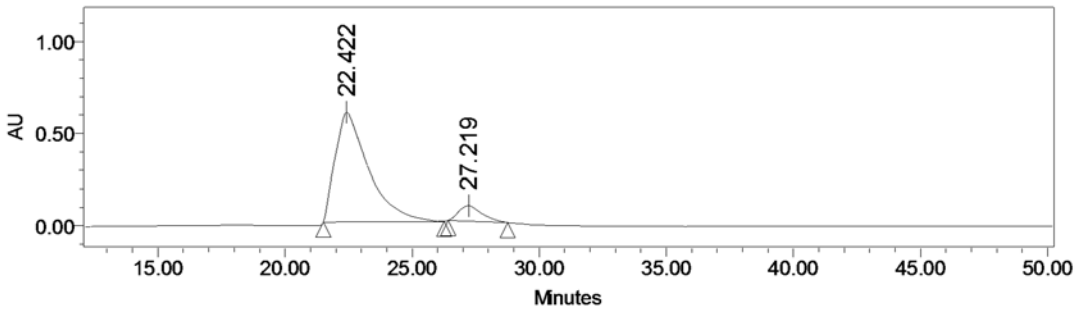
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Ba**



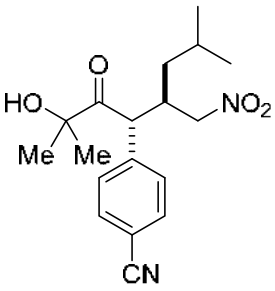
	Retention Time	% Area
1	21.509	48.85
2	26.461	51.15

25Ba



	Retention Time	% Area
1	22.422	91.11
2	27.219	8.89

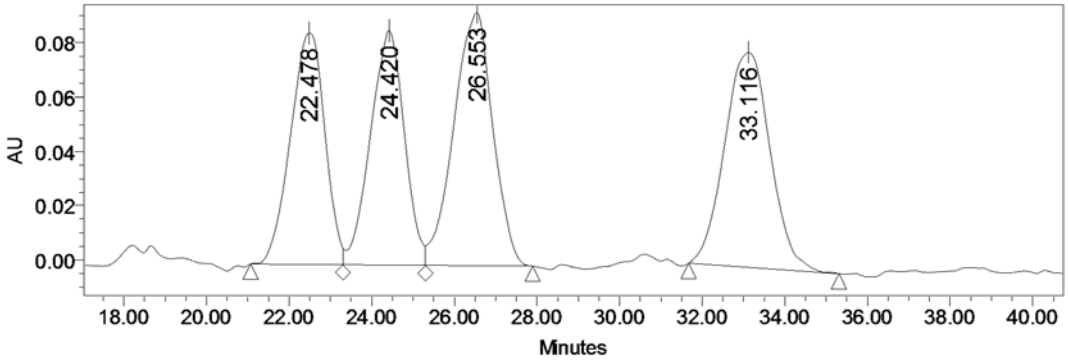
dr* >95:5, 82 % *ee



25Bc

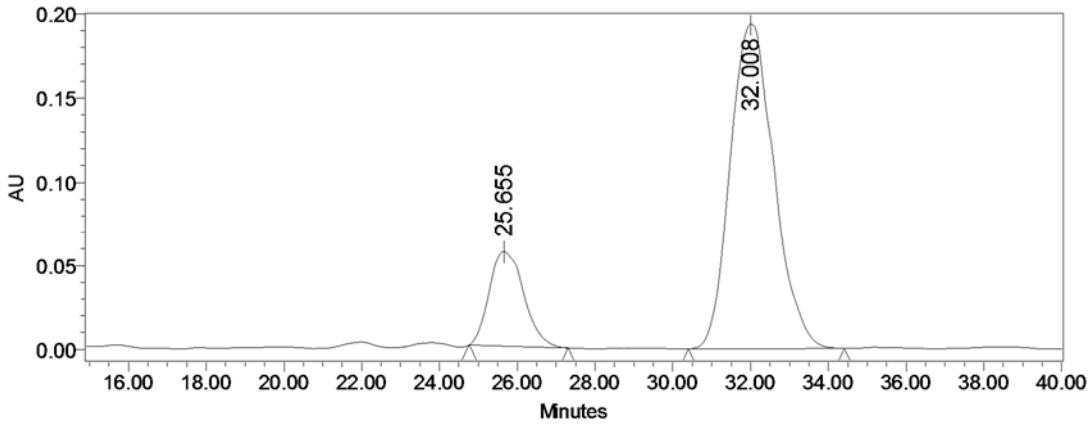
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Bc**



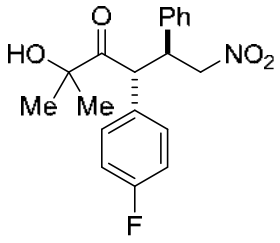
	Retention Time	% Area
1	22.478	22.35
2	24.420	22.34
3	26.553	27.74
4	33.116	27.57

25Bc



	Retention Time	% Area
1	25.655	18.60
2	32.008	81.40

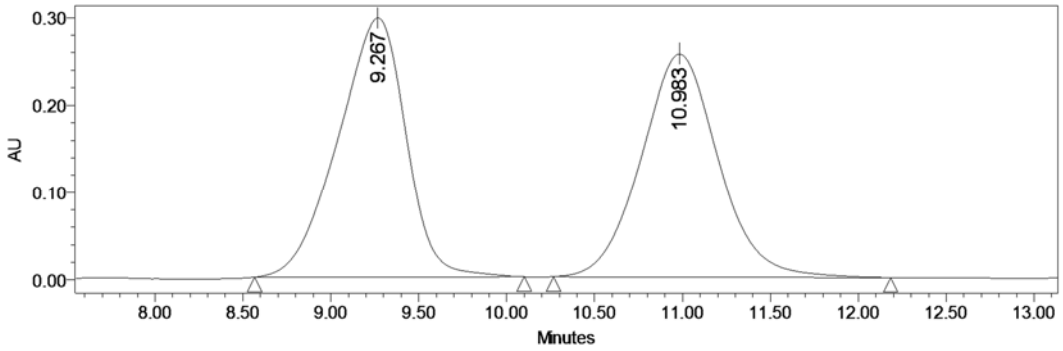
dr* >95:5, 63 % *ee



25Ca

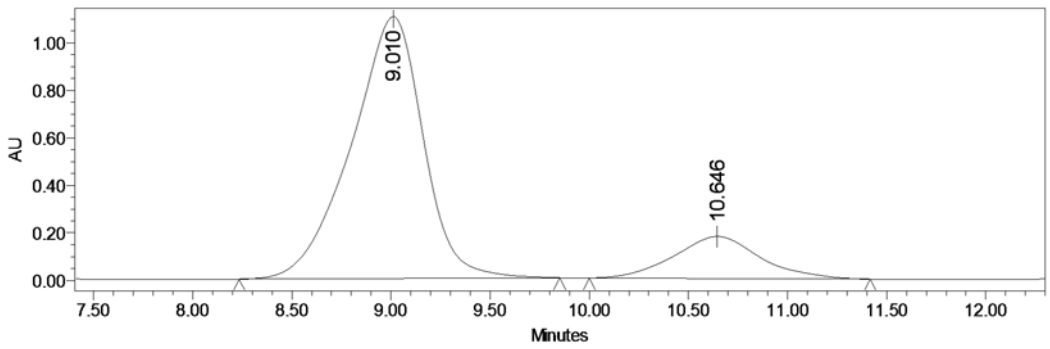
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210 nm.

Rac-**25Ca**



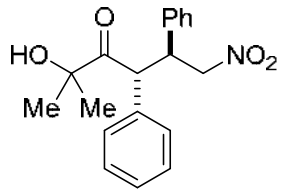
	Retention Time	% Area
1	9.267	50.50
2	10.983	49.50

25Ca



	Retention Time	% Area
1	9.010	83.25
2	10.646	16.75

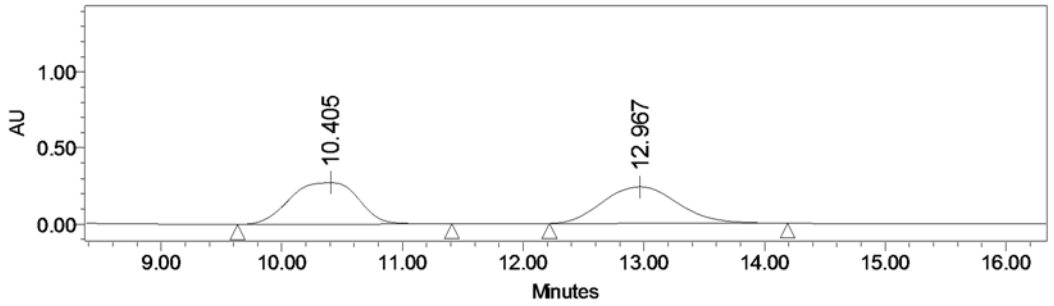
dr* >95:5, 66 % *ee



25Da

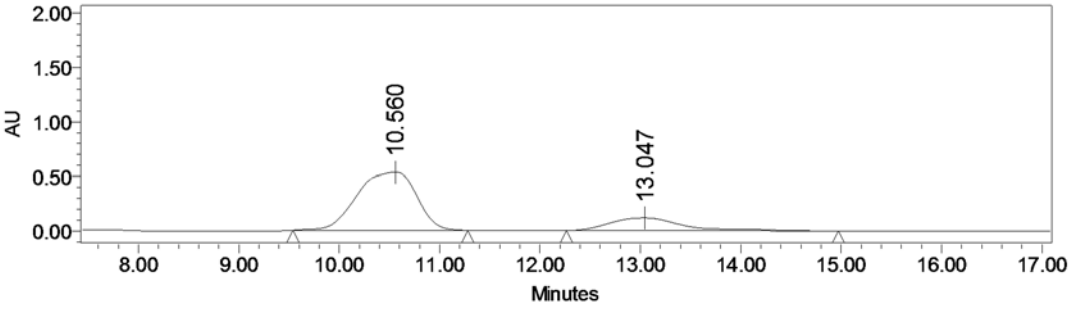
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Da**



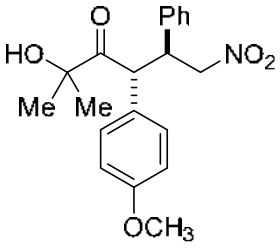
	Retention Time	% Area
1	10.405	50.79
2	12.967	49.21

25Da



	Retention Time	% Area
1	10.560	79.83
2	13.047	20.17

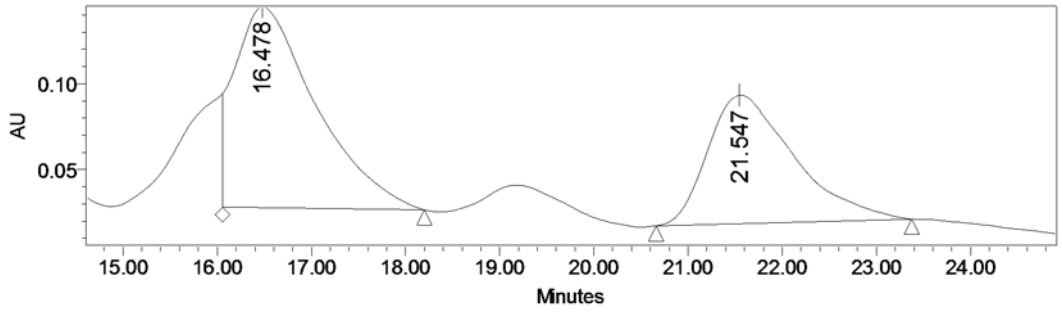
dr* >95:5, 60 % *ee



25Ea

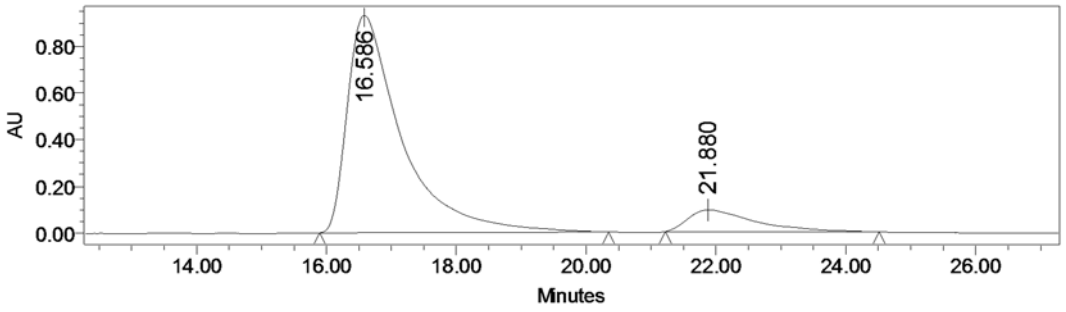
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**25Ea**



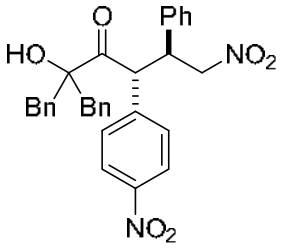
	Retention Time	% Area
1	16.478	59.67
2	21.547	40.33

25Ea



	Retention Time	% Area
1	16.586	88.92
2	21.880	11.08

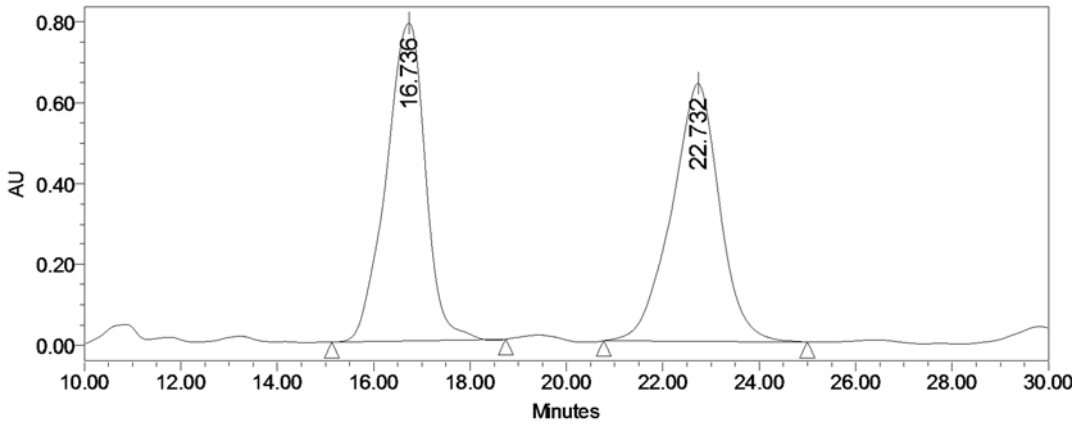
dr* >95:5, 77 % *ee



27Aa

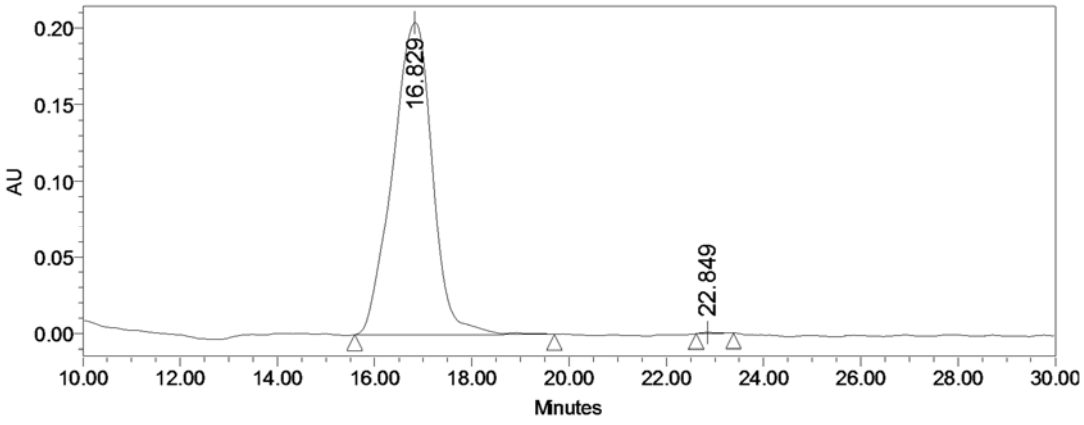
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**27Aa**



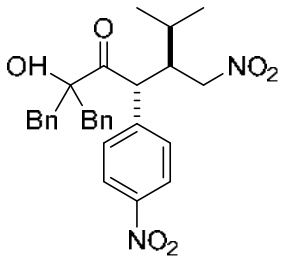
	Retention Time	% Area
1	16.736	50.24
2	22.732	49.76

27Aa



	Retention Time	% Area
1	16.829	99.86
2	22.849	0.14

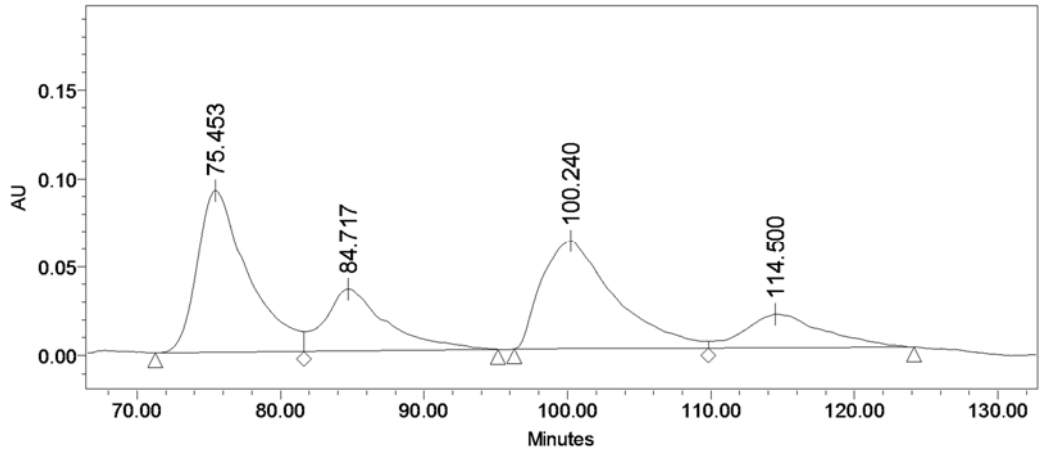
dr* >95:5, 99 % *ee



27Ab

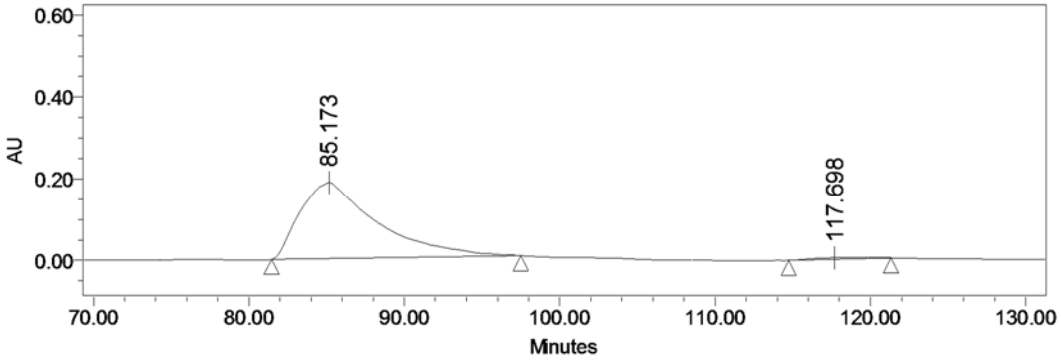
Daicel Chiralpak IA, hexane/isopropanol 99:1 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**27Ab**



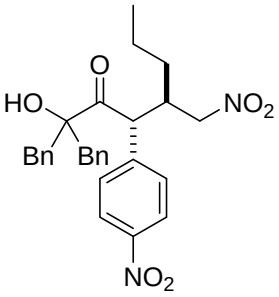
	Retention Time	% Area
1	75.453	36.51
2	84.717	16.91
3	100.240	34.85
4	114.500	11.73

27Ab



	Retention Time	% Area
1	85.173	98.65
2	117.698	1.35

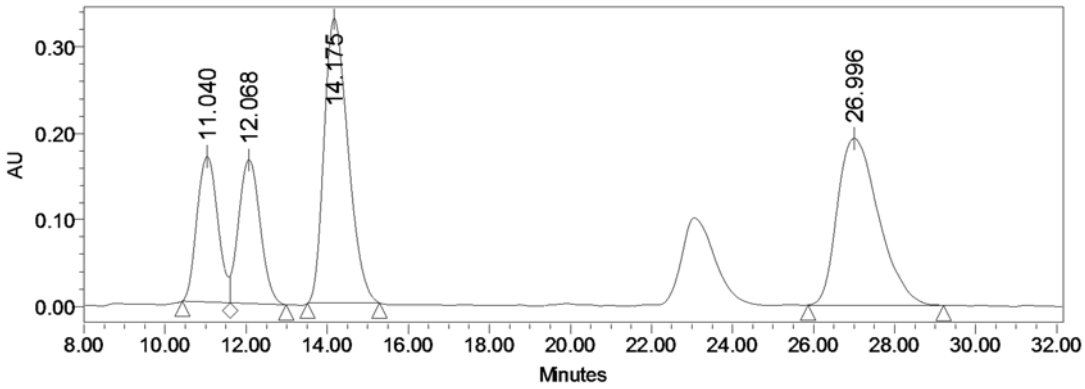
dr* >95:5, 97 % *ee



27Ad

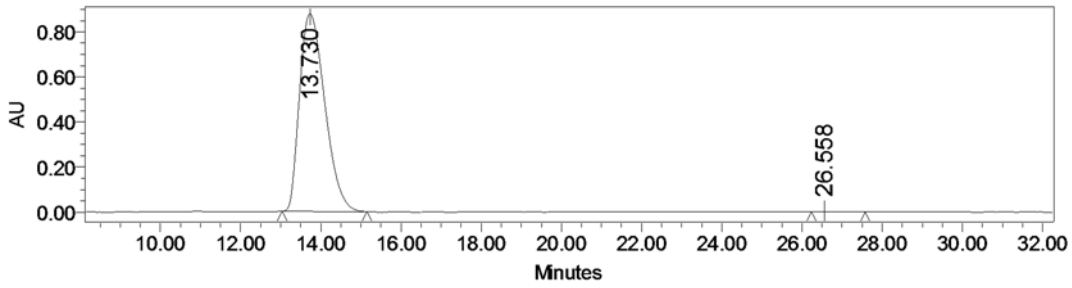
Daicel Chiralpak ADH, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210 nm.

Rac-**27Ad**



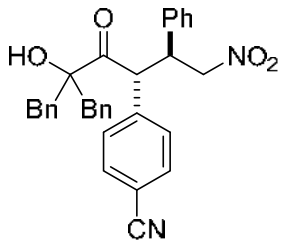
	Retention Time	% Area
1	11.040	15.36
2	12.068	15.55
3	14.175	34.38
4	26.996	34.72

27Ad



	Retention Time	% Area
1	13.730	99.95
2	26.558	0.05

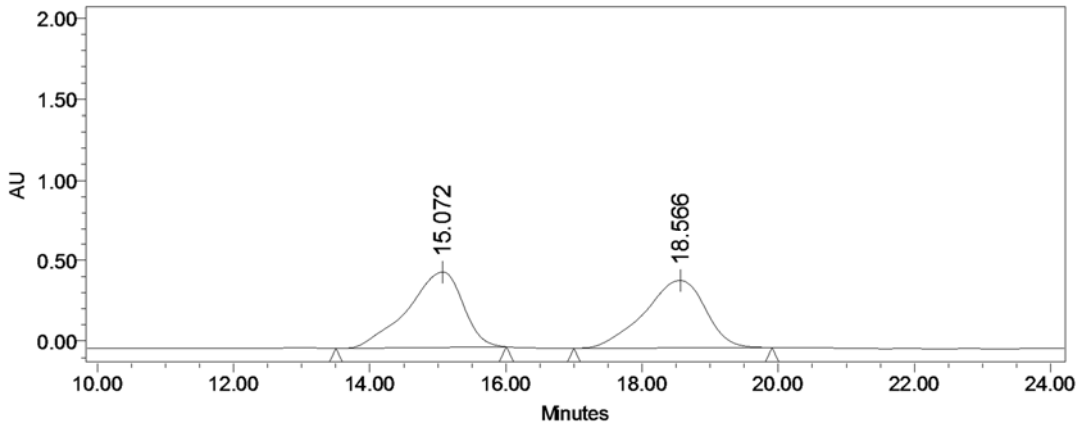
dr* >95:5, 99 % *ee



27Ba

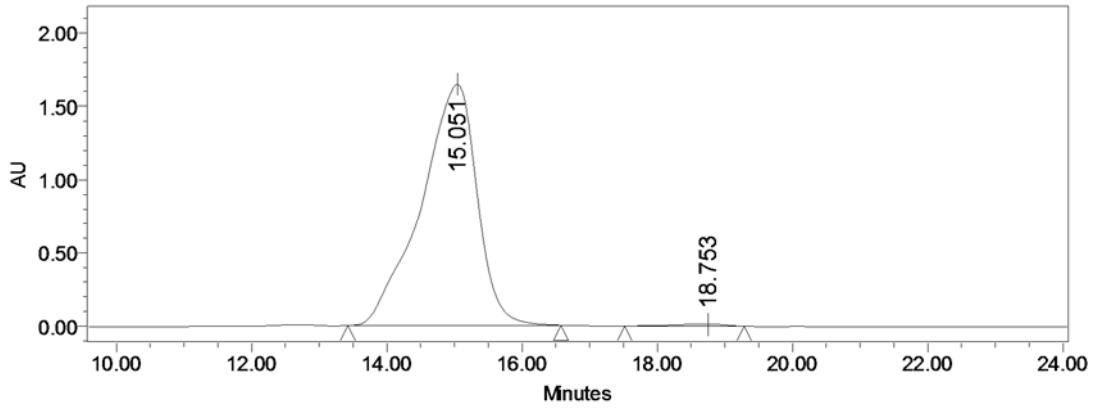
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**27Ba**



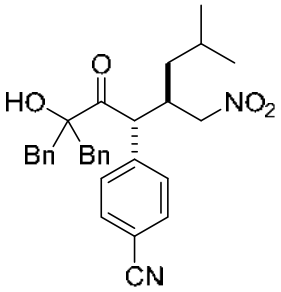
	Retention Time	% Area
1	15.072	50.33
2	18.566	49.67

27Ba



	Retention Time	% Area
1	15.051	99.29
2	18.753	0.71

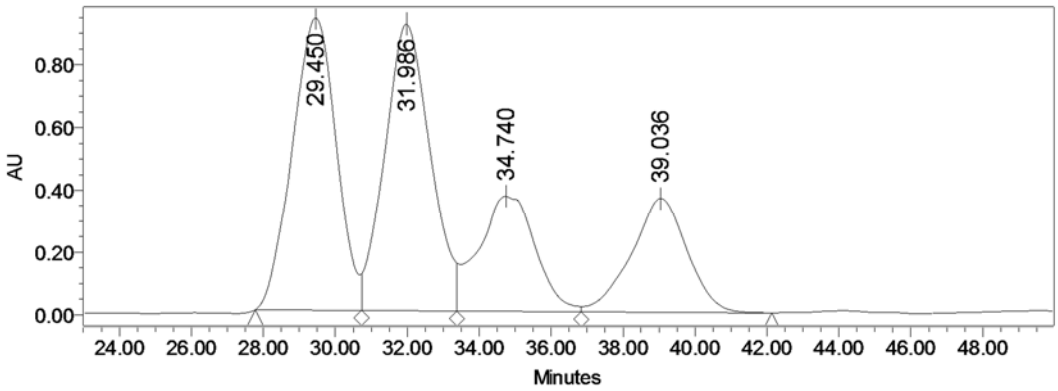
dr* >95:5, 99 % *ee



Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

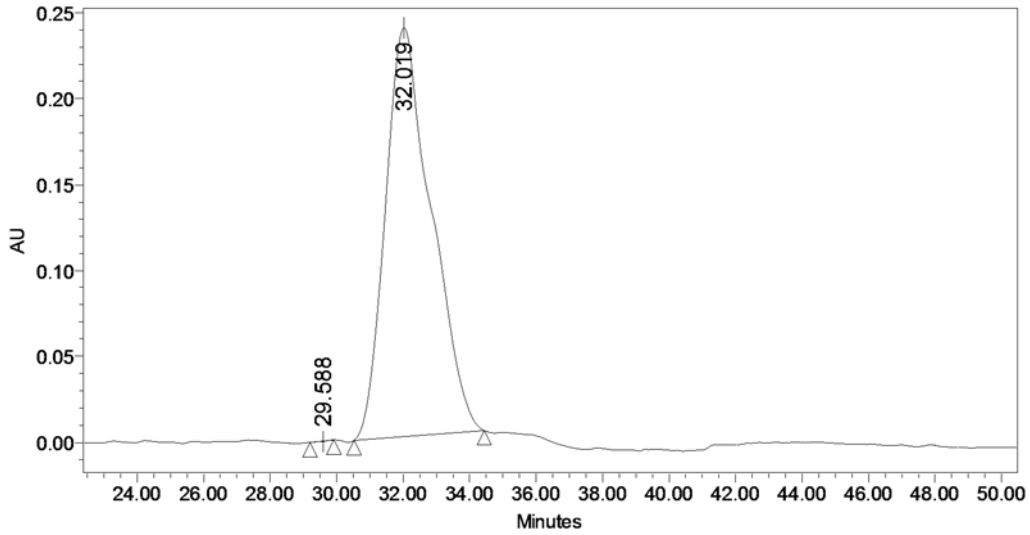
27Bc

Rac-**27Bc**



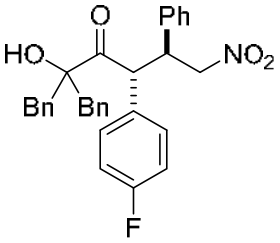
	Retention Time	% Area
1	29.450	34.05
2	31.986	34.56
3	34.740	15.84
4	39.036	15.55

9Bk



	Retention Time	% Area
1	29.588	0.02
2	32.019	99.98

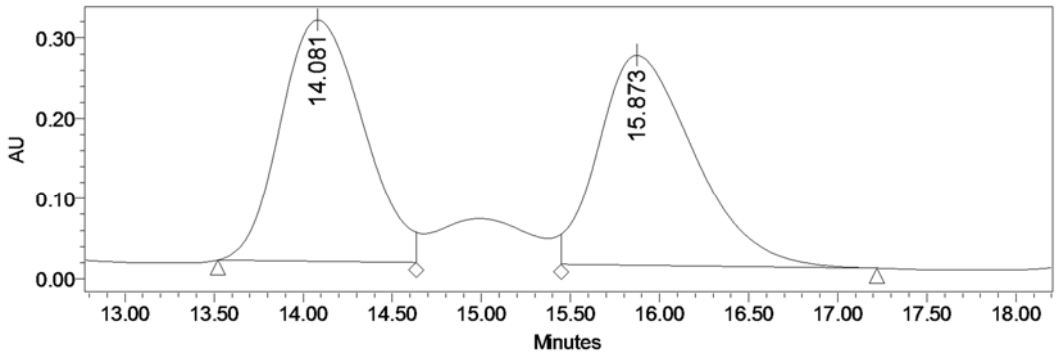
dr* >95:5, 99 % *ee



27Ca

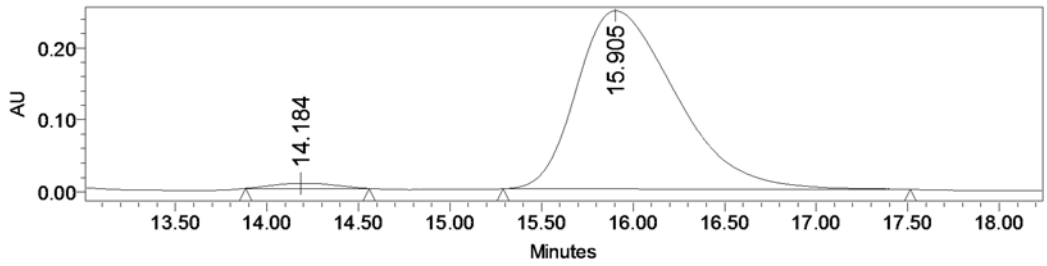
Daicel Chiralpak IB, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**27Ca**



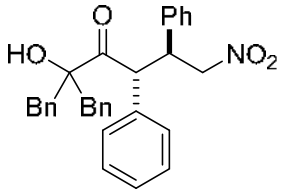
	Retention Time	% Area
1	14.081	49.74
2	15.873	50.26

27Ca



	Retention Time	% Area
1	14.184	1.80
2	15.905	98.20

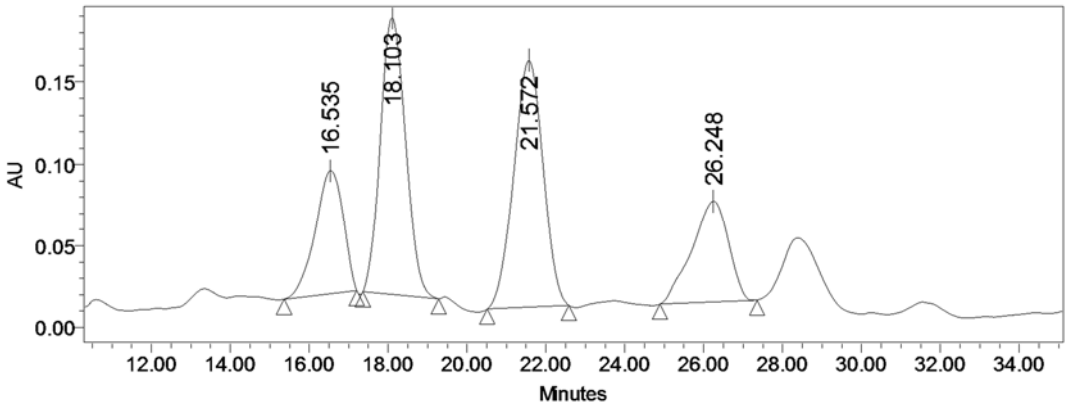
dr* >95:5, 96 % *ee



27Da

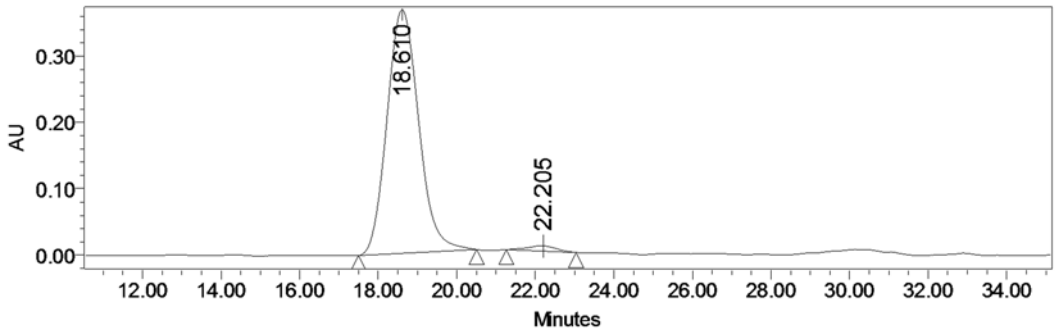
Daicel Chiralpak IC, hexane/isopropanol 98:2 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**27Da**



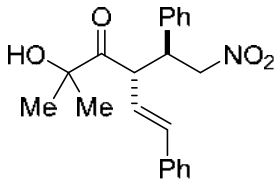
	Retention Time	% Area
1	16.535	16.17
2	18.103	32.59
3	21.572	33.97
4	26.248	17.27

27Da



	Retention Time	% Area
1	18.610	98.07
2	22.205	1.93

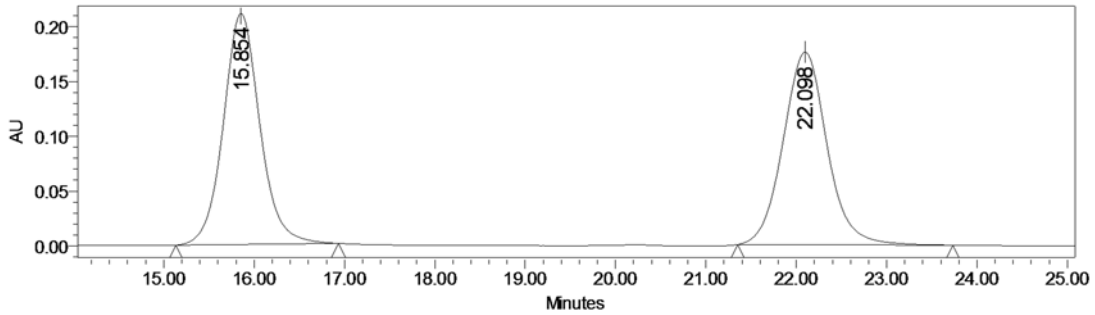
dr* >95:5, 96 % *ee



39a

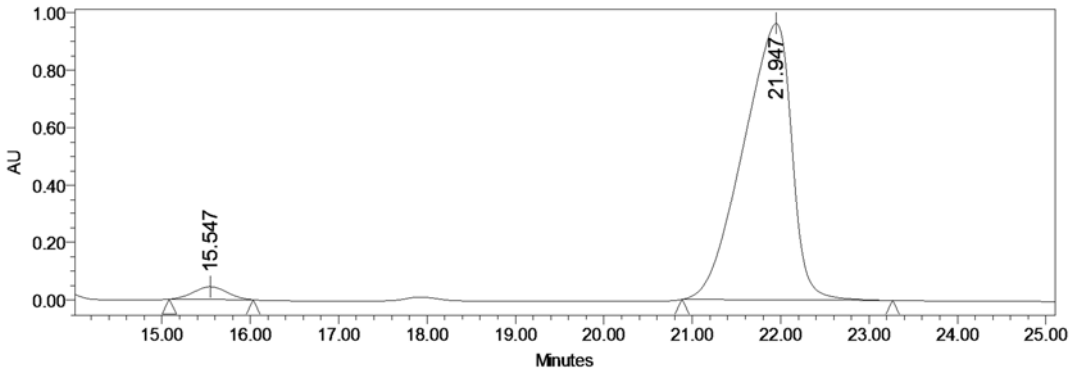
Daicel Chiralpak IB, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 256.0 nm.

Rac-**39a**



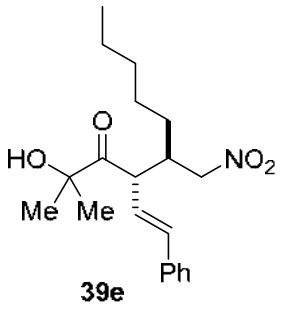
	Retention Time	% Area
1	15.854	49.99
2	22.098	50.01

39a



	Retention Time	% Area
1	15.547	3.04
2	21.947	96.96

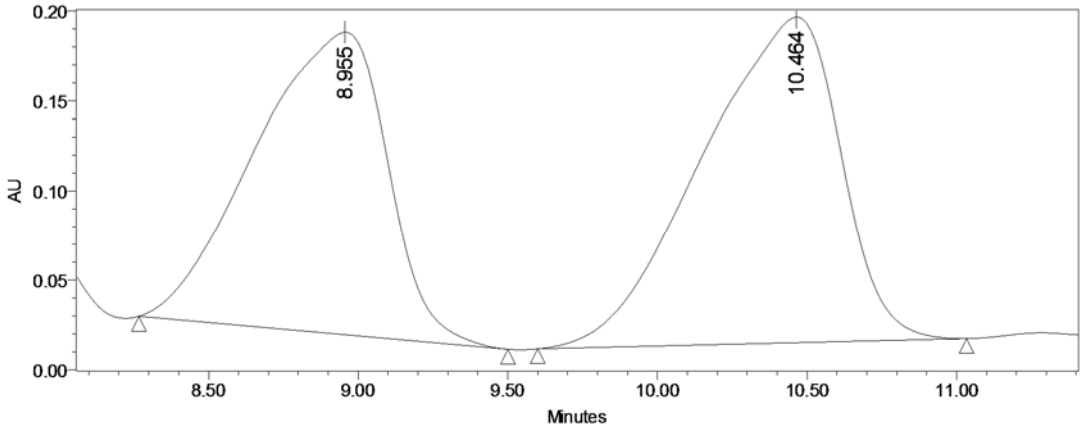
dr* >95:5, 94 % *ee



39e

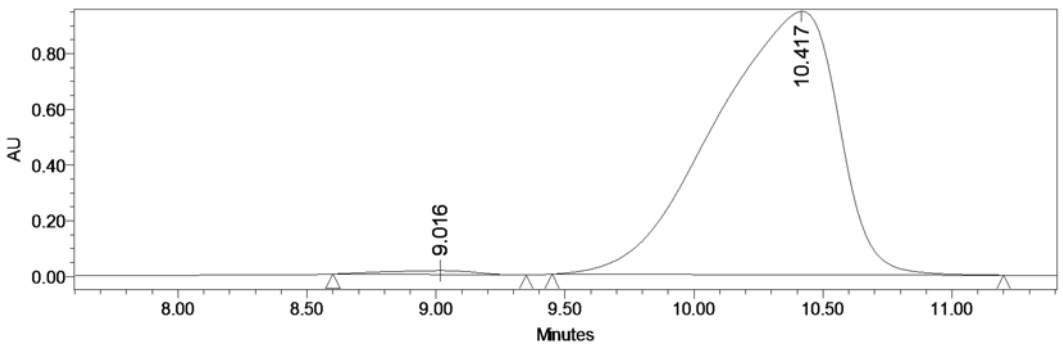
Daicel Chiralpak IB, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, □: 256.0 nm.

Rac-**39e**



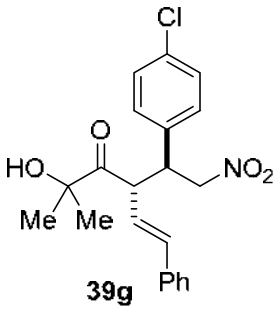
	Retention Time	% Area
1	8.955	46.92
2	10.464	53.08

39e



	Retention Time	% Area
1	9.016	1.06
2	10.417	98.94

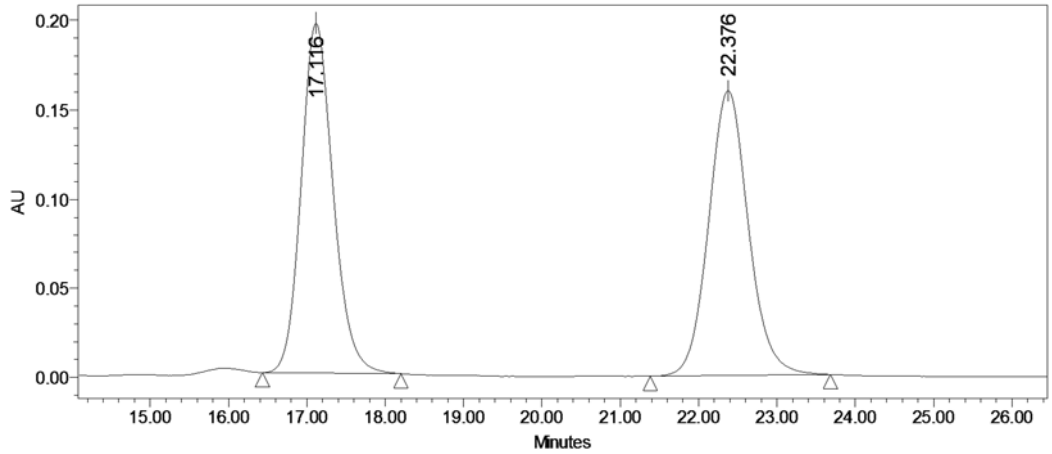
dr* >95:5, 98 % *ee



39g

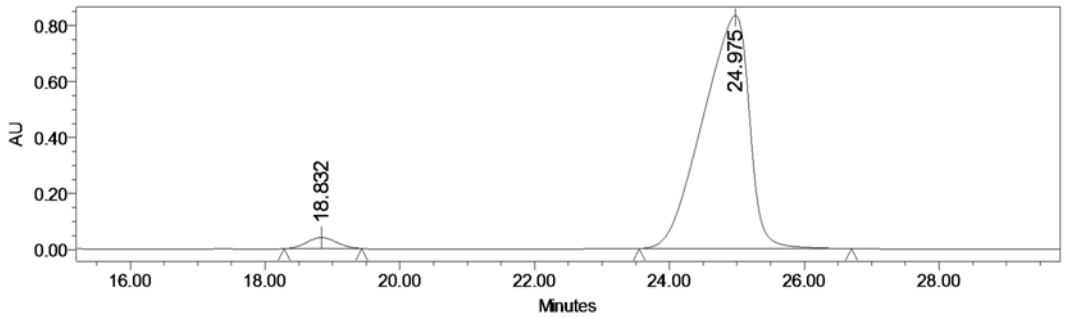
Daicel Chiralpak IB, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 256.0 nm.

Rac-**39g**



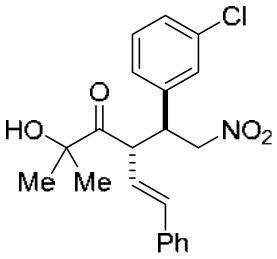
	Retention Time	% Area
1	17.116	49.68
2	22.376	50.32

39g



	Retention Time	% Area
1	18.832	3.00
2	24.975	97.00

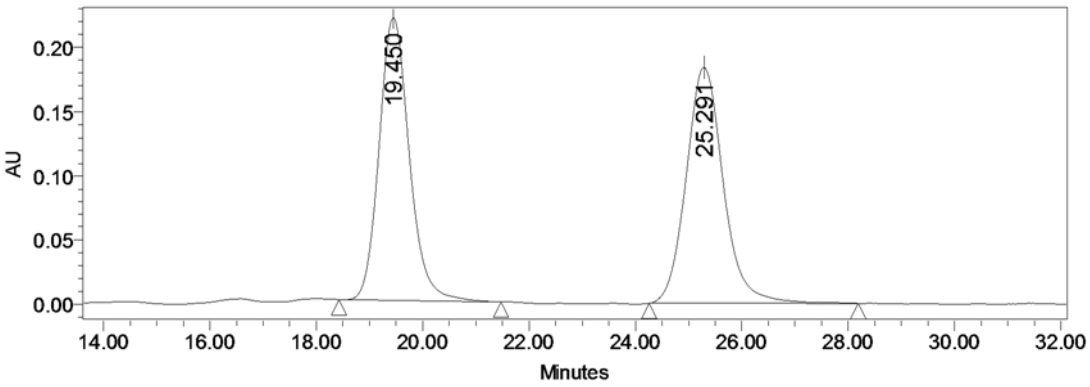
dr* >95:5, 94 % *ee



39h

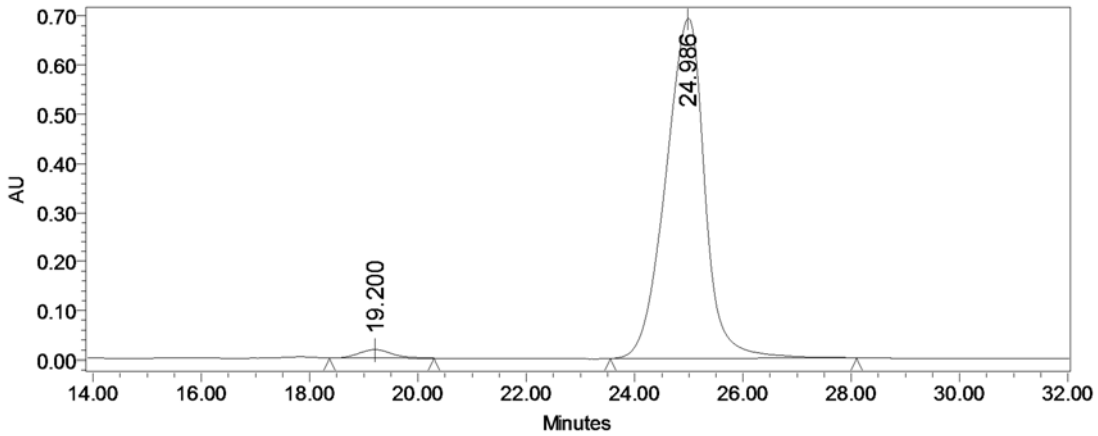
Daicel Chiralpak IB, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**39h**



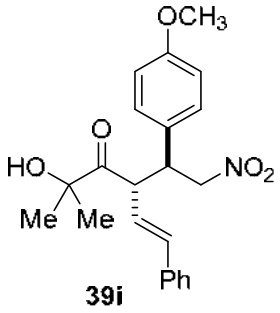
	Retention Time	% Area
1	19.450	49.24
2	25.291	50.76

39h



	Retention Time	% Area
1	19.200	2.03
2	24.986	97.97

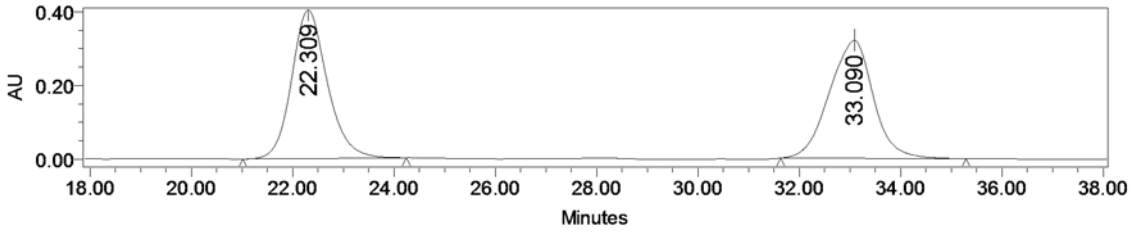
dr* >95:5, 96 % *ee



39i

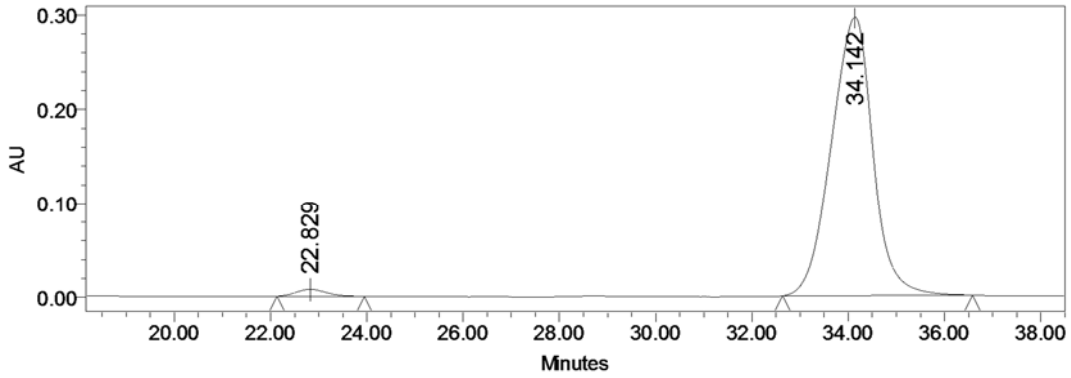
Daicel Chiralpak IB, hexane/isopropanol 90/10 flow rate = 1.0 mL/min, λ: 256.0 nm.

Rac-**39i**



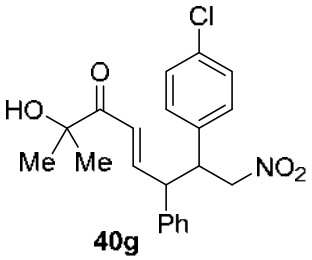
	Retention Time	% Area
1	22.309	50.52
2	33.090	49.48

39i



	Retention Time	% Area
1	22.829	1.80
2	34.142	98.20

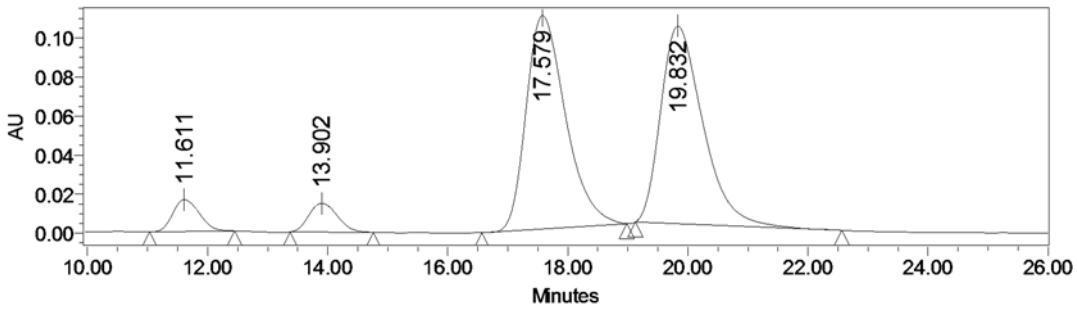
dr* >95:5, 96 % *ee



40g

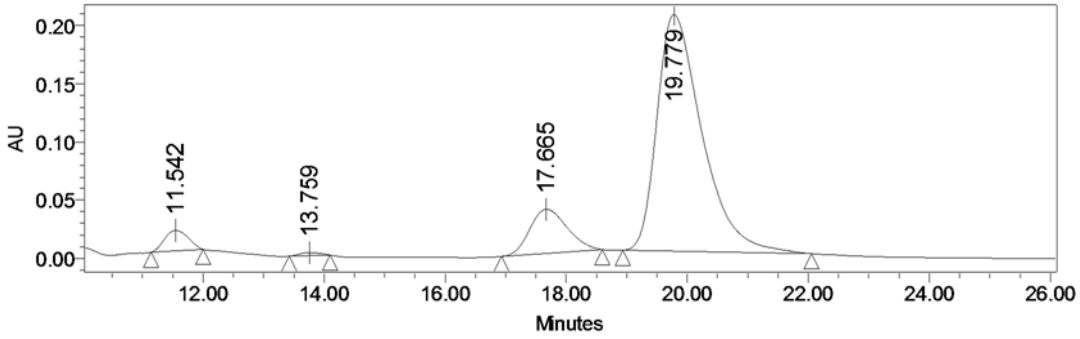
Daicel Chiralpak IB, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 256.0 nm.

Rac-**40g**



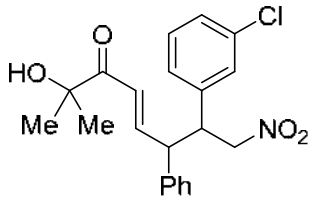
	Retention Time	% Area
1	11.611	4.57
2	13.902	4.45
3	17.579	45.73
4	19.832	45.25

40g



	Retention Time	% Area
1	11.542	3.75
2	13.759	0.50
3	17.665	12.73
4	19.779	83.02

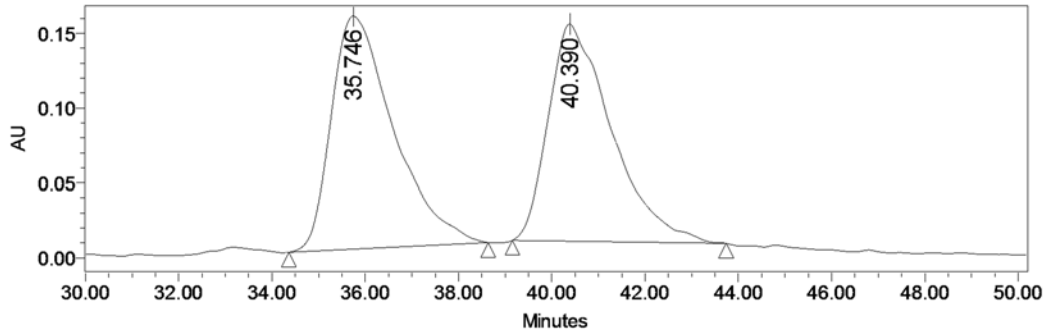
***dr* >93:7, 73/76 %**



40h

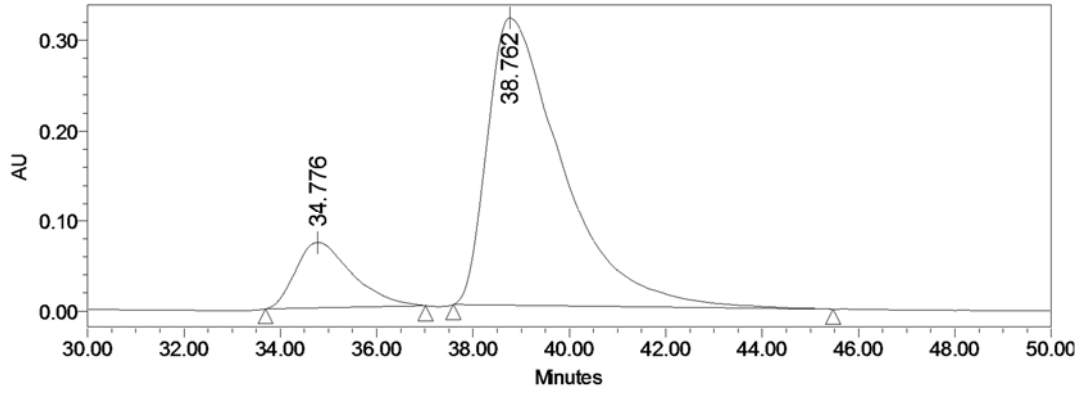
Daicel Chiralpak IB, hexane/isopropanol 95/05 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**40h**



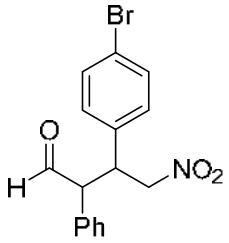
	Retention Time	% Area
1	35.746	51.34
2	40.390	48.66

40h



	Retention Time	% Area
1	34.776	14.48
2	38.762	85.52

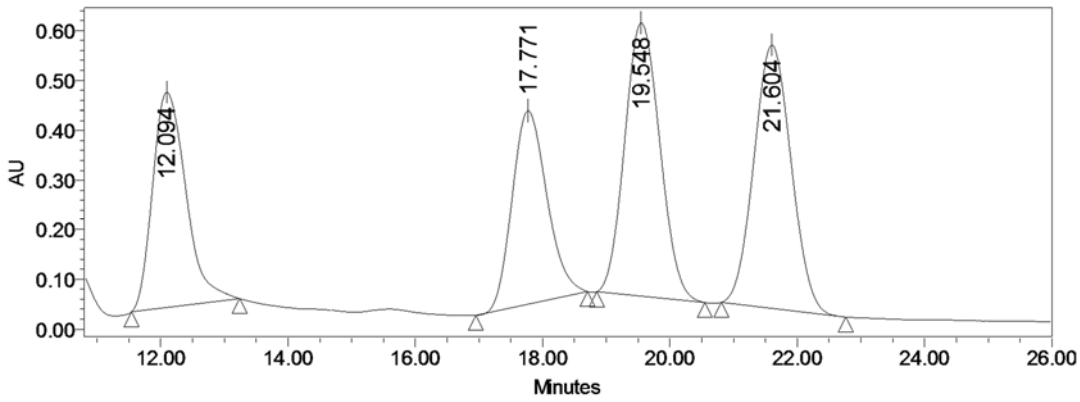
dr* >95:5, 71 % *ee



35

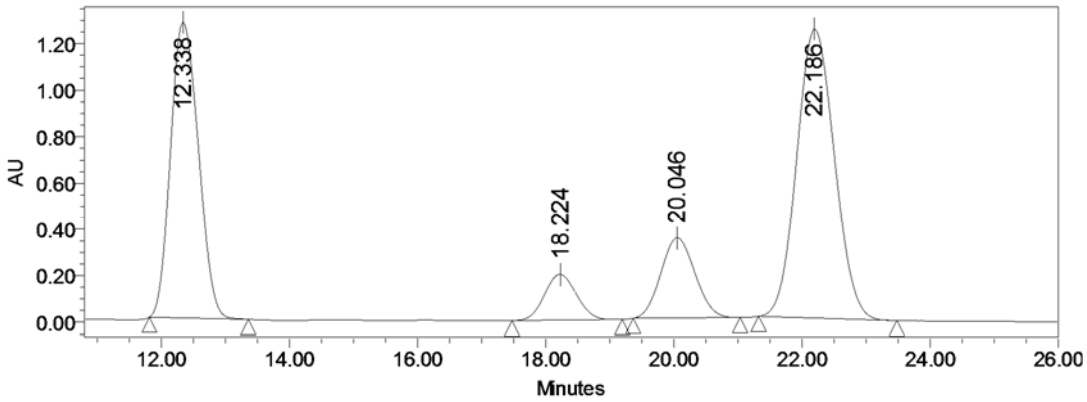
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**35**



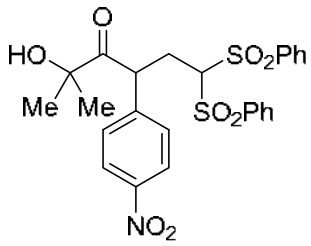
	Retention Time	% Area
1	12.094	21.54
2	17.771	20.21
3	19.548	28.80
4	21.604	29.45

39



	Retention Time	% Area
1	12.338	35.33
2	18.224	6.19
3	20.046	11.68
4	22.186	46.81

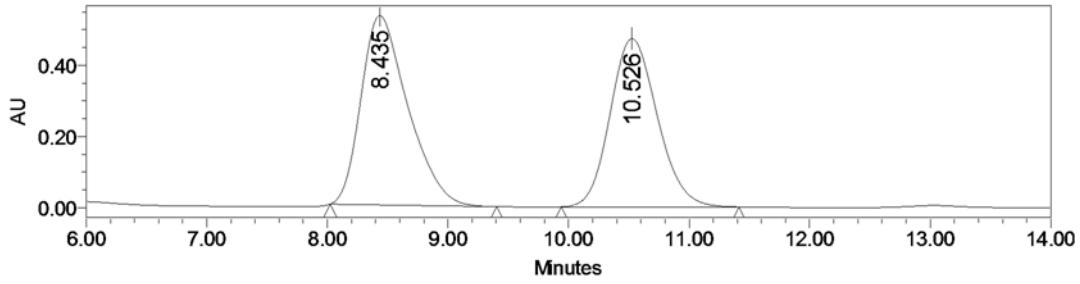
dr* 59:41, 60/40 % *ee



45A

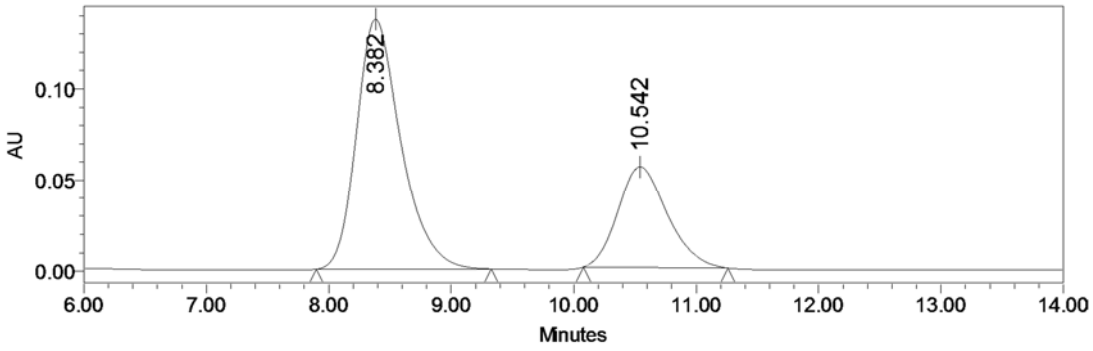
Daicel Chiralpak IA, hexane/isopropanol 50:50 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**45A**



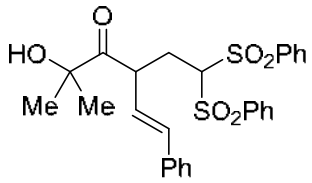
	Retention Time	% Area
1	8.435	52.80
2	10.526	47.20

45A



	Retention Time	% Area
1	8.382	69.09
2	10.542	30.91

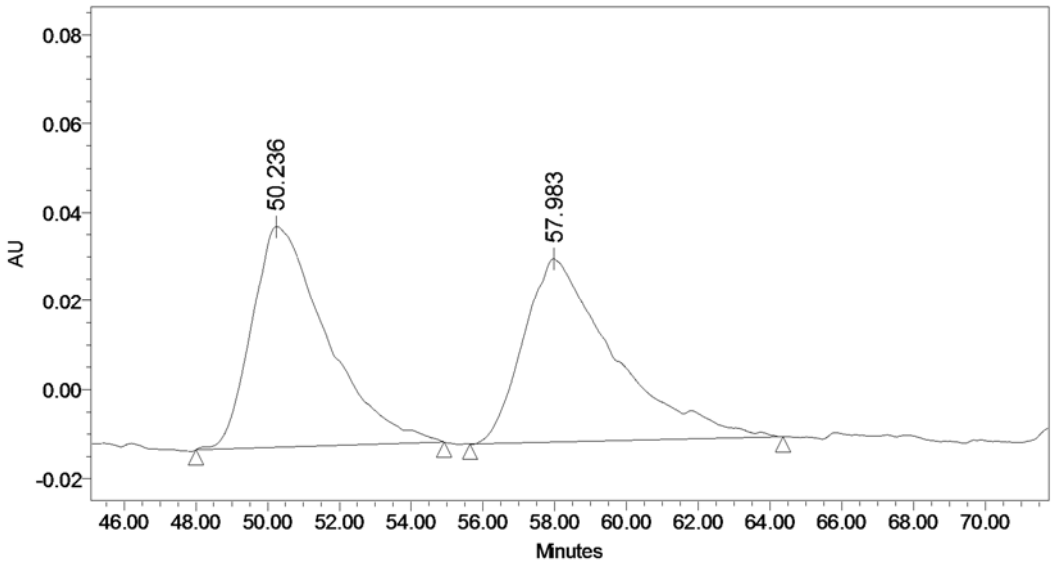
38 % *ee*



47

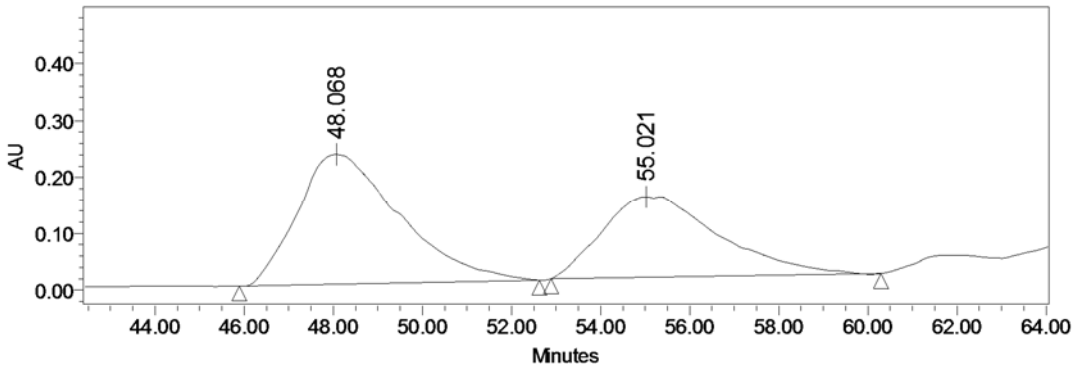
Daicel Chiralpak IB, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**47**



	Retention Time	% Area
1	50.236	49.95
2	57.983	50.05

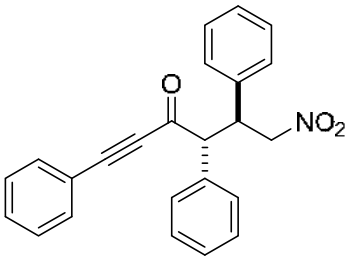
47



	Retention Time	% Area
1	48.068	58.47
2	55.021	41.53

17 % *ee*

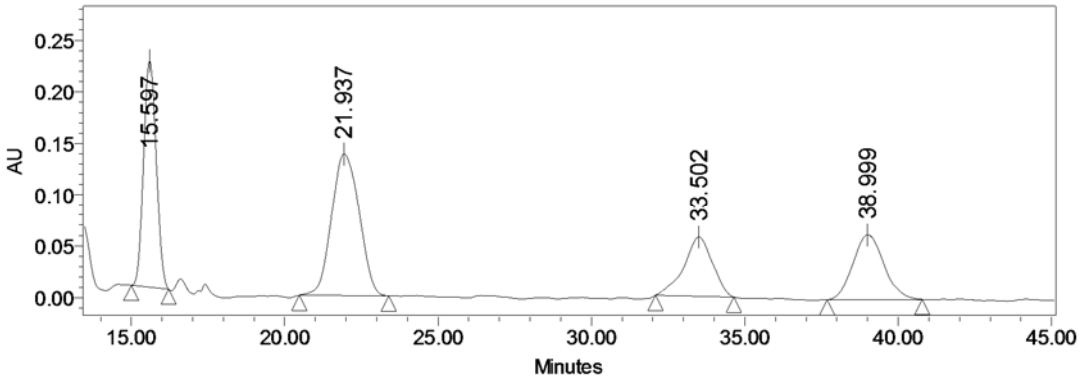
7.8.2. HPLC chromatograms for Chapter 3



Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

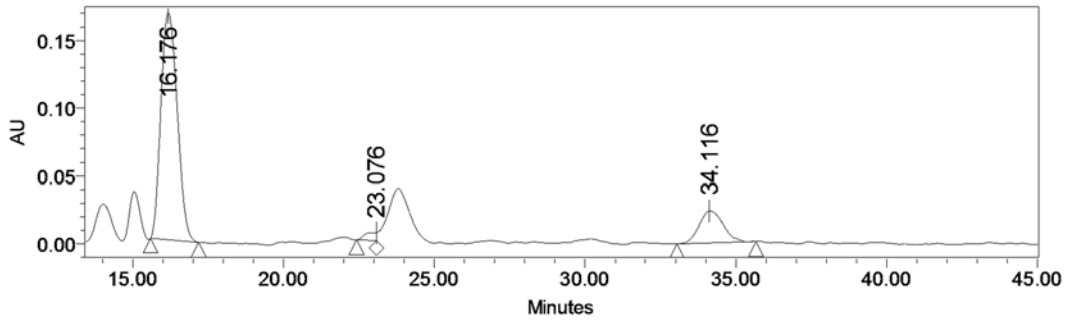
54AEa

Rac-**54AEa**



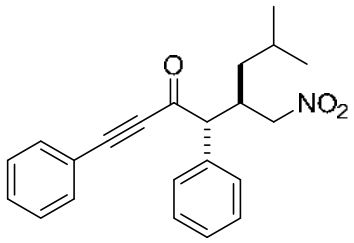
	Retention Time	% Area
1	15.597	27.37
2	21.937	37.43
3	33.502	16.16
4	38.999	19.05

53AEa



	Retention Time	% Area
1	16.176	81.28
2	23.076	1.97
3	34.116	16.74

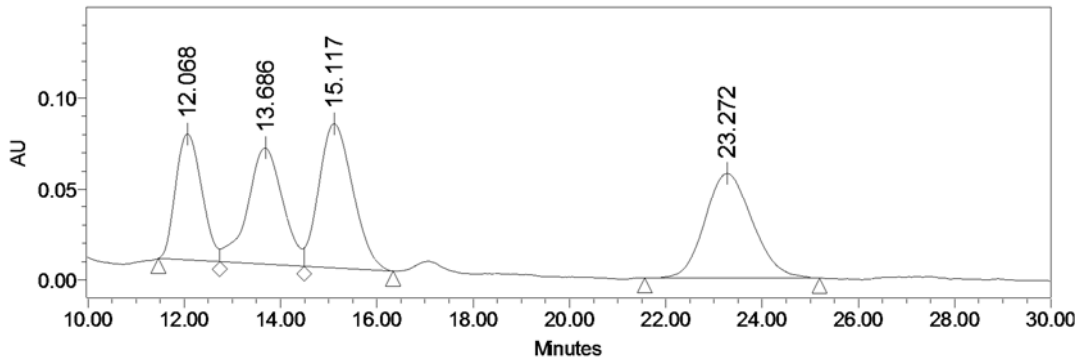
96/99 % *ee*



54AEc

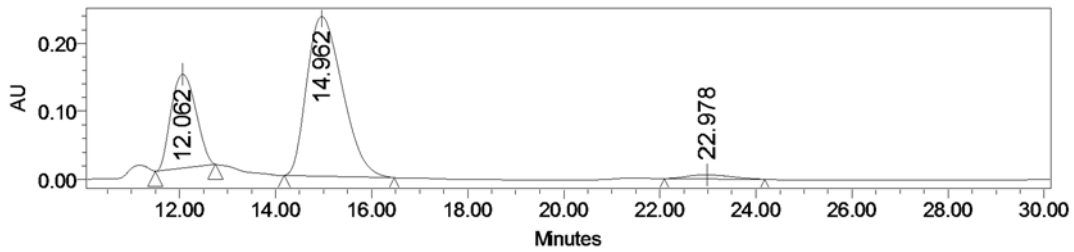
Daicel Chiralpak ASH, hexane/isopropanol 98:2 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AEc**



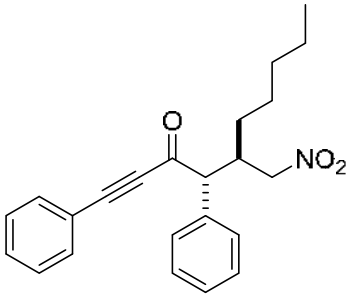
	Retention Time	% Area
1	12.068	19.09
2	13.686	23.80
3	15.117	28.36
4	23.272	28.75

54AEc



	Retention Time	% Area
1	12.062	28.36
2	14.962	69.43
3	22.978	2.21

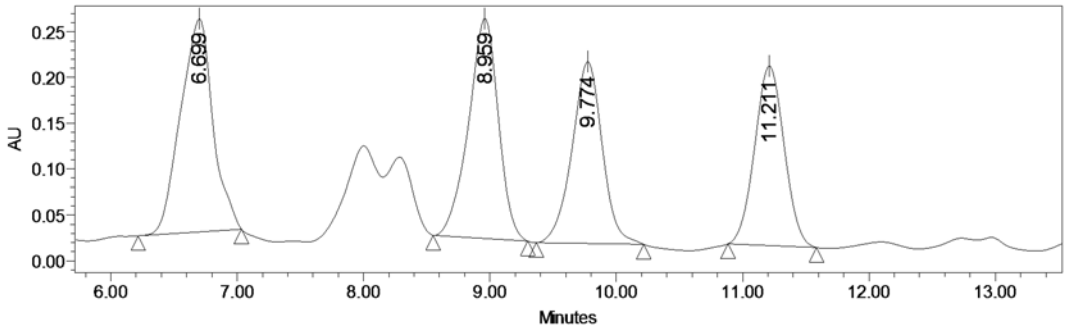
94/98 % *ee*



54AEe

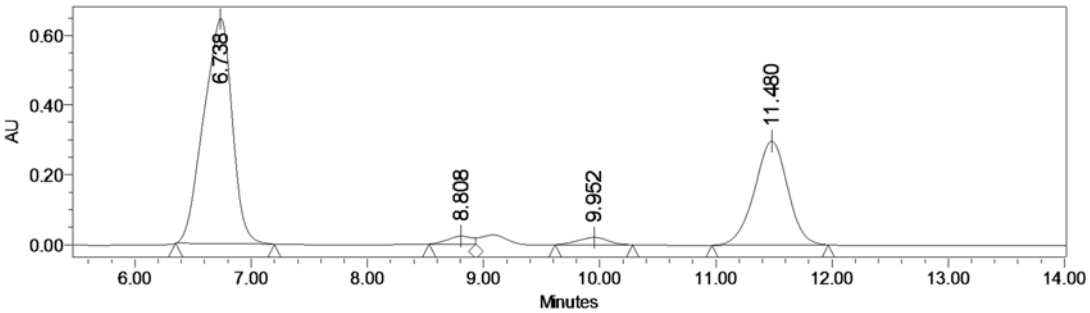
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AEe**



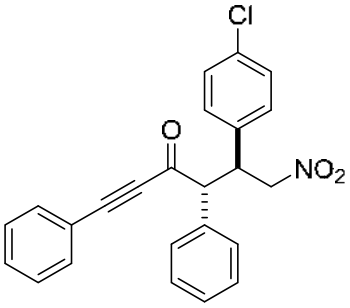
	Retention Time	% Area
1	6.699	28.44
2	8.959	27.08
3	9.774	22.64
4	11.211	21.83

54AEe



	Retention Time	% Area
1	6.738	62.40
2	8.808	1.89
3	9.952	2.15
4	11.480	33.56

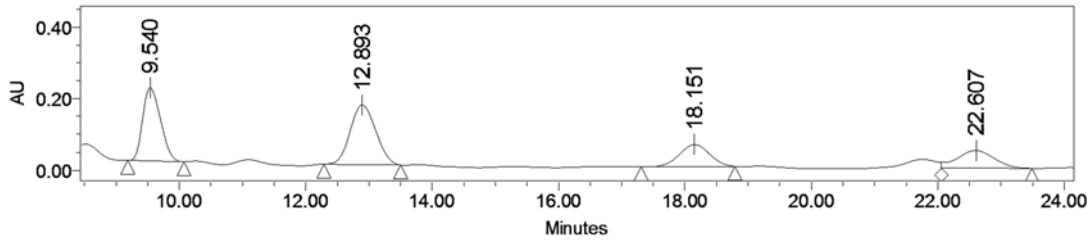
94/88 % *ee*



54AEg

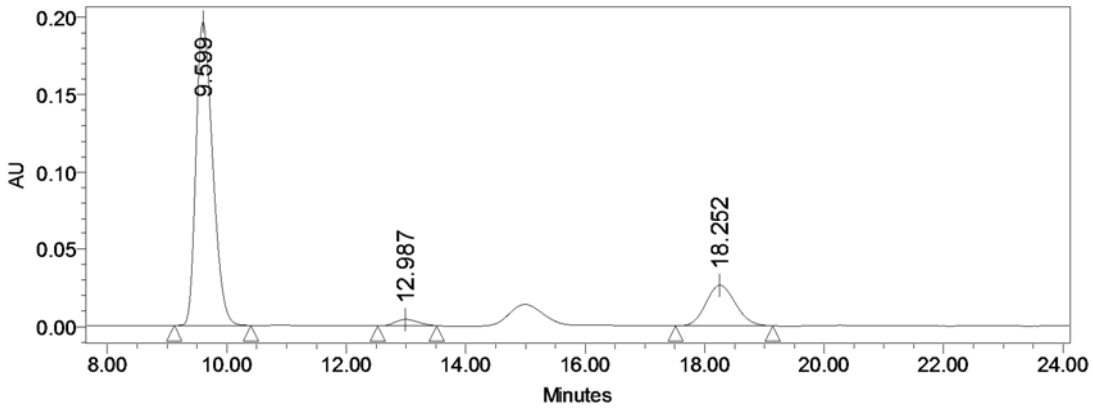
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AEg**



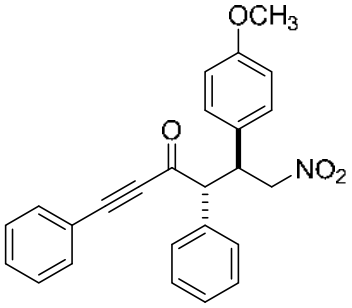
	Retention Time	% Area
1	9.540	31.35
2	12.893	36.63
3	18.151	16.10
4	22.607	15.92

54AEg



	Retention Time	% Area
1	9.599	79.11
2	12.987	2.29
3	18.252	18.60

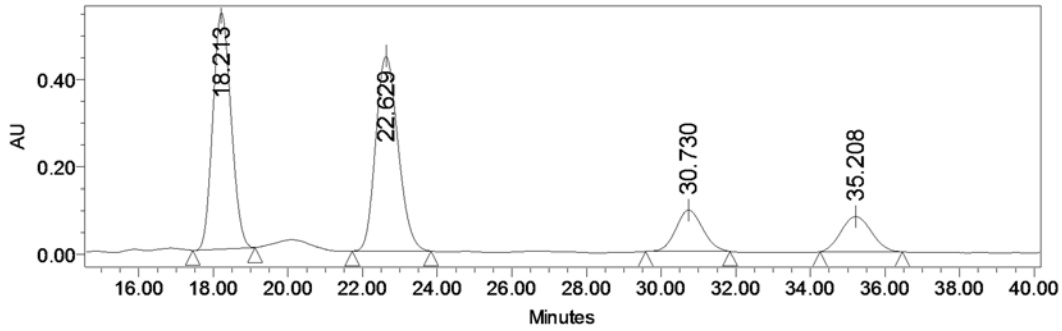
94/99 % *ee*



54AEi

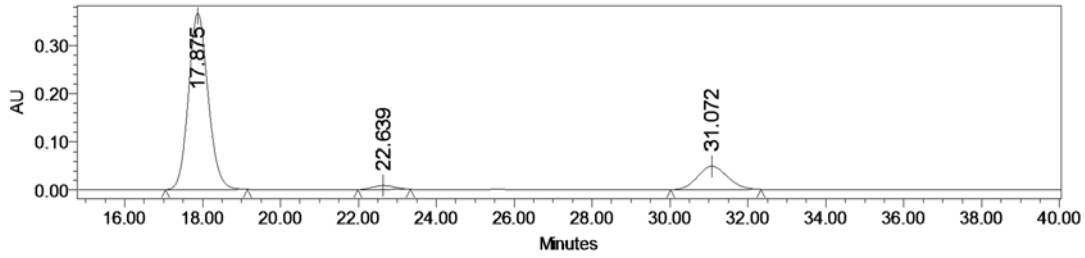
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AEi**



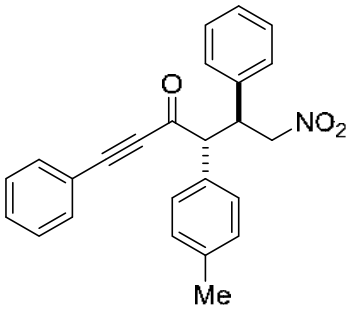
	Retention Time	% Area
1	18.213	39.67
2	22.629	40.21
3	30.730	10.22
4	35.208	9.90

54AEi



	Retention Time	% Area
1	17.875	81.29
2	22.639	2.11
3	31.072	16.61

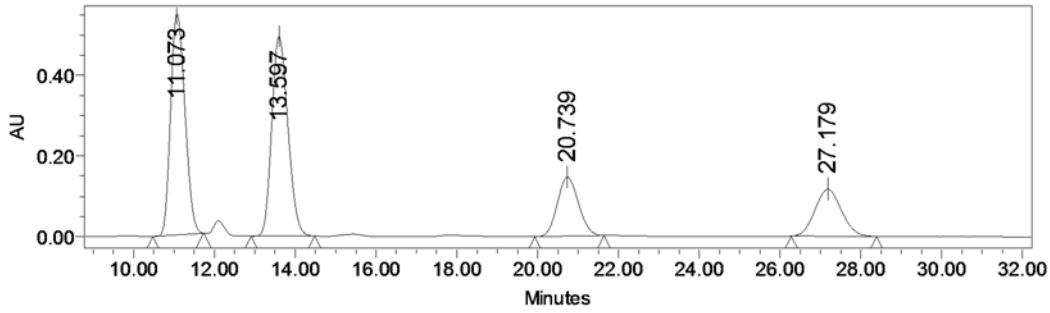
96/99 % *ee*



Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

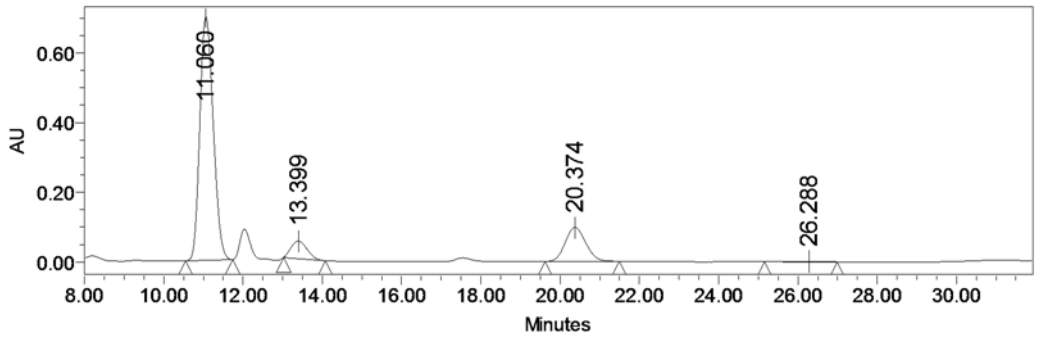
54AFa

Rac-54AFa



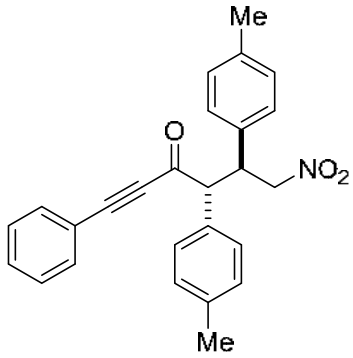
	Retention Time	% Area
1	11.073	35.65
2	13.597	36.21
3	20.739	14.06
4	27.179	14.08

54AFa



	Retention Time	% Area
1	11.060	76.69
2	13.399	6.64
3	20.374	16.41
4	26.288	0.26

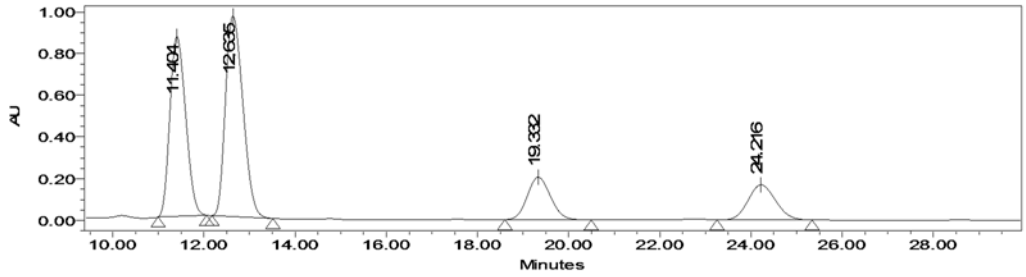
84/99 % *ee*



54AFj

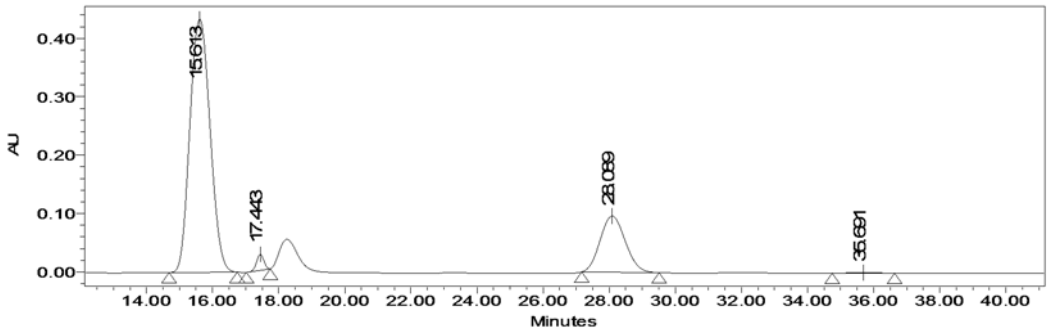
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AFj**



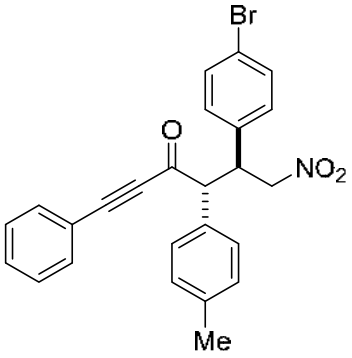
	Retention Time	% Area
1	11.404	34.20
2	12.635	42.23
3	19.332	11.96
4	24.216	11.61

54AFj



	Retention Time	% Area
1	15.613	80.61
2	17.443	1.81
3	28.089	17.40
4	35.691	0.18

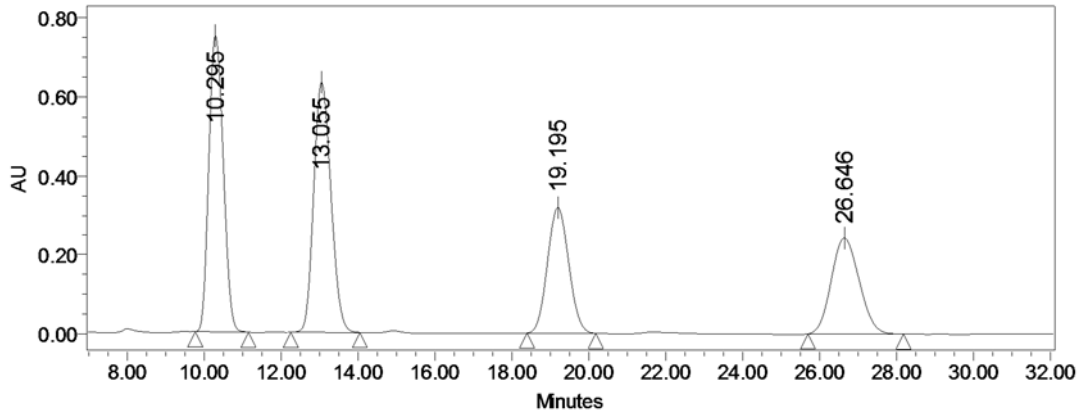
96/98 % *ee*



54AFf

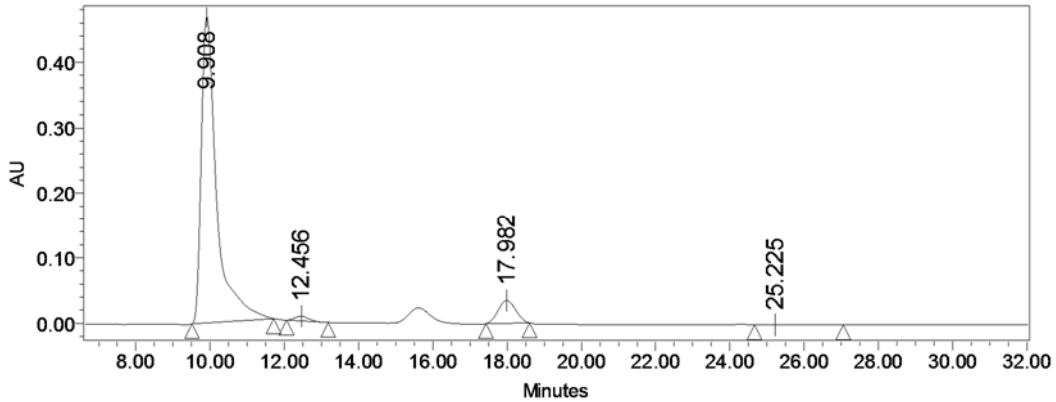
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AFf**



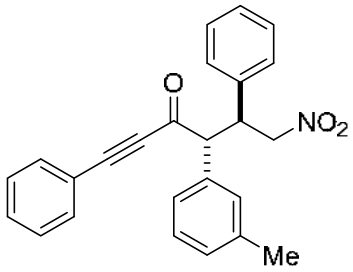
	Retention Time	% Area
1	10.295	30.77
2	13.055	30.96
3	19.195	19.19
4	26.646	19.09

54AFf



	Retention Time	% Area
1	9.908	90.92
2	12.456	1.25
3	17.982	7.67
4	25.225	0.16

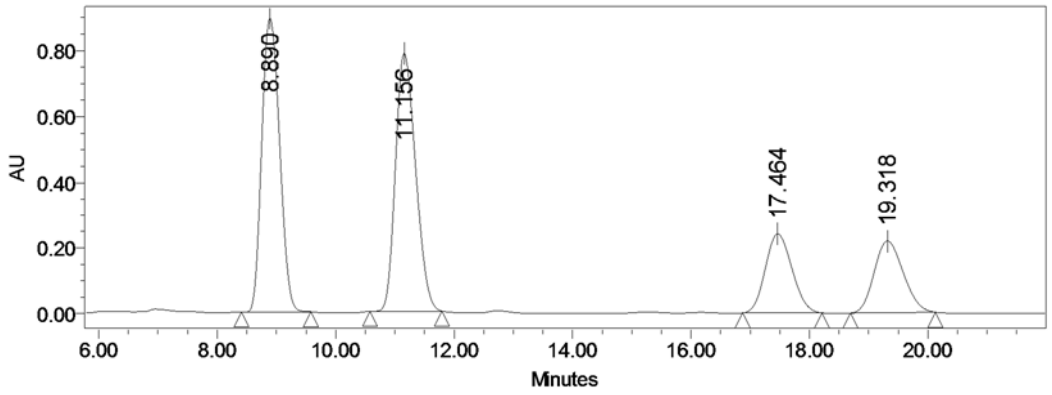
96/99 % *ee*



Daicel Chiralpak IC, hexane/isopropanol 90/10 flow rate = 1.0 mL/min, λ: 210.0 nm.

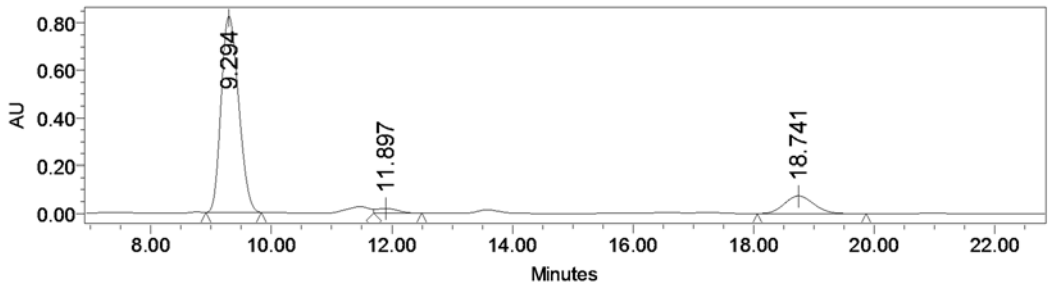
54AGa

Rac-**54AGa**



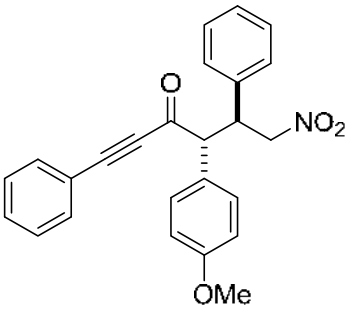
	Retention Time	% Area
1	8.890	35.75
2	11.156	35.60
3	17.464	14.38
4	19.318	14.26

54AGa



	Retention Time	% Area
1	9.294	84.81
2	11.897	2.44
3	18.741	12.75

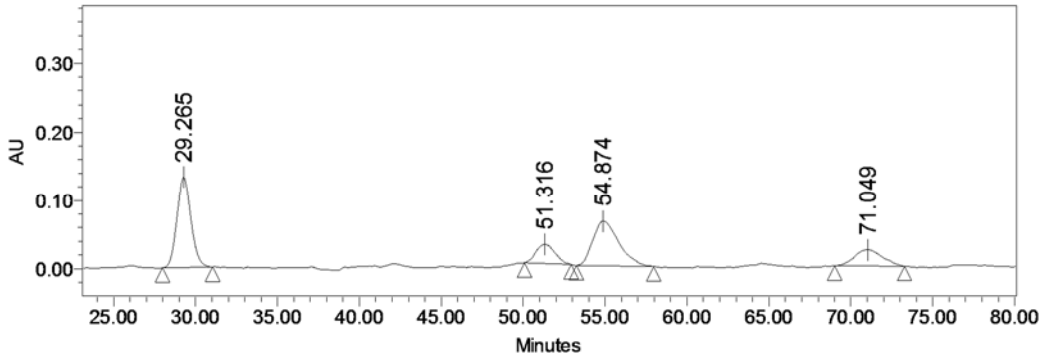
94/99 % *ee*



54AHa

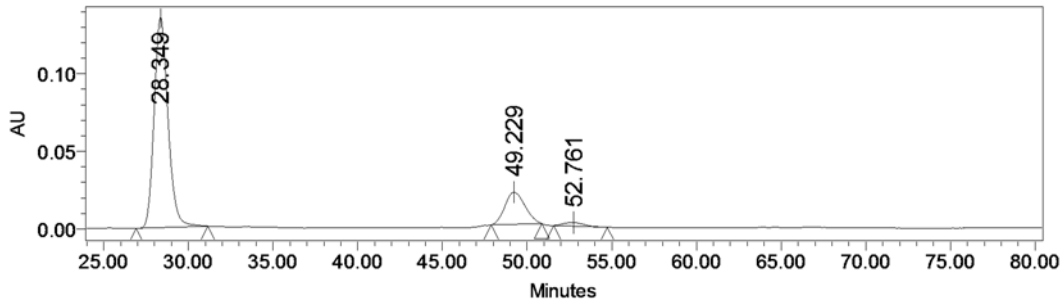
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AHa**



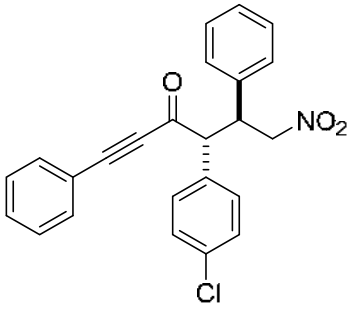
	Retention Time	% Area
1	29.265	39.05
2	51.316	11.24
3	54.874	35.69
4	71.049	14.02

54AHa



	Retention Time	% Area
1	28.349	80.29
2	49.229	17.74
3	52.761	1.97

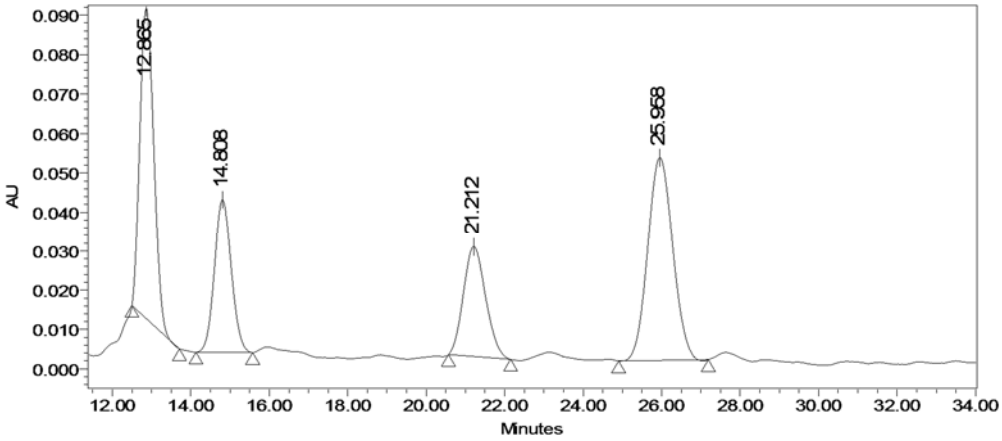
96/99 % *ee*



54AIa

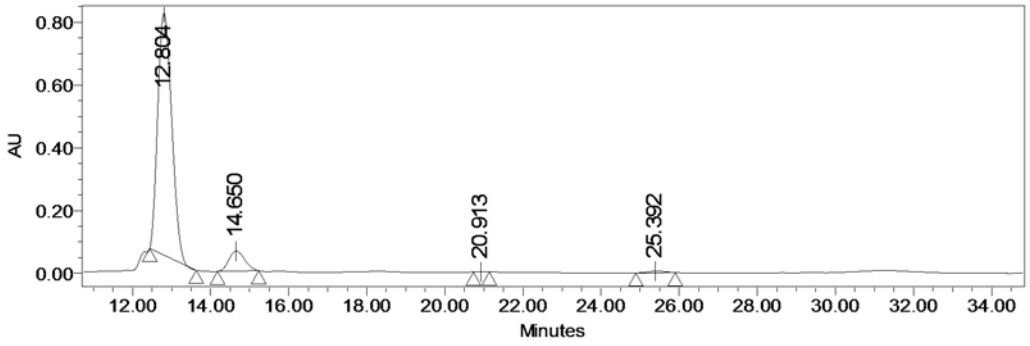
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AIa**



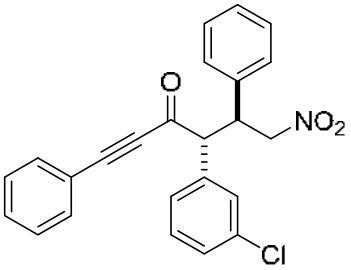
	Retention Time	% Area
1	12.865	29.96
2	14.808	17.92
3	21.212	16.87
4	25.958	35.25

54AIa



	Retention Time	% Area
1	12.804	90.66
2	14.650	8.55
3	20.913	0.05
4	25.392	0.73

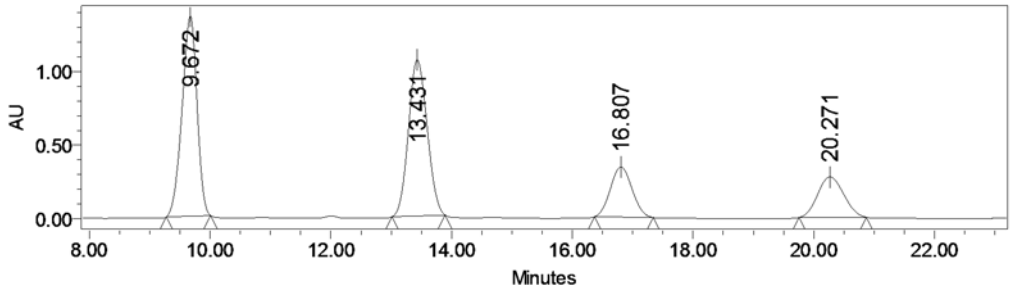
98/99 % *ee*



54AJa

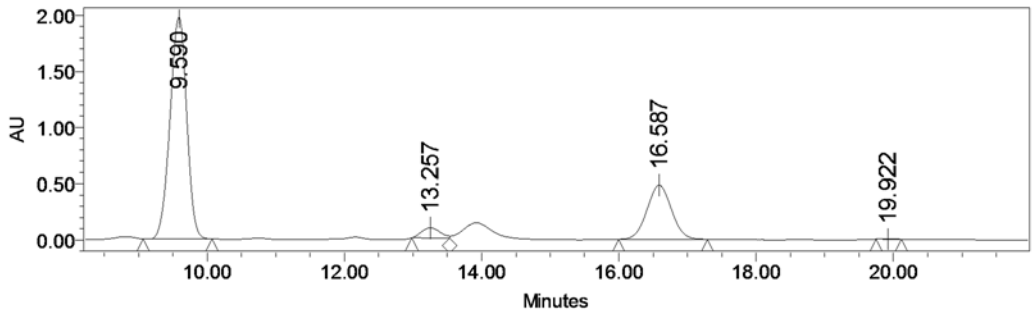
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54AJa**



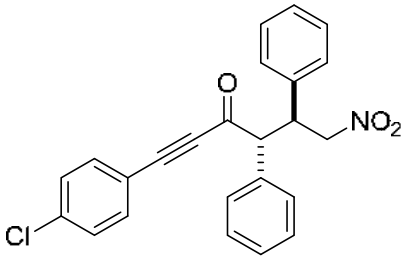
	Retention Time	% Area
1	9.672	37.14
2	13.431	36.29
3	16.807	13.47
4	20.271	13.10

54AJa



	Retention Time	% Area
1	9.590	77.92
2	13.257	2.62
3	16.587	19.37
4	19.922	0.09

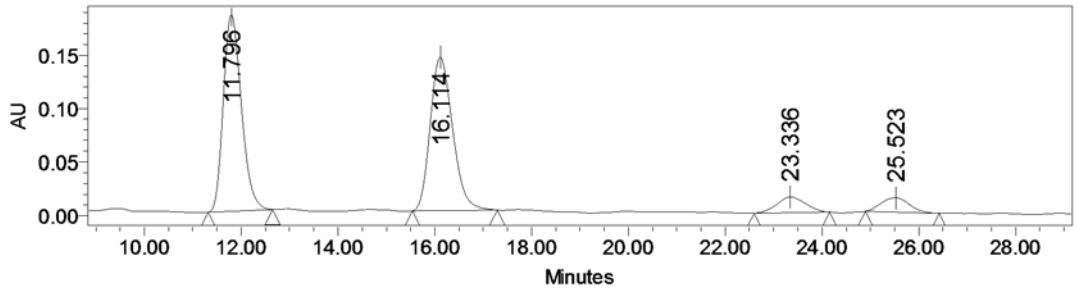
95/99 % *ee*



54BEa

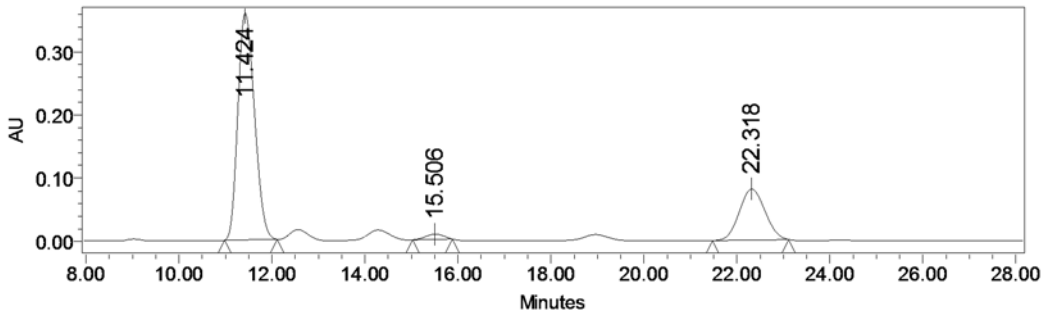
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54BEa**



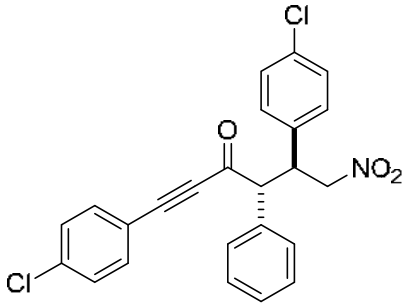
	Retention Time	% Area
1	11.796	45.33
2	16.114	43.74
3	23.336	5.74
4	25.523	5.18

54BEa



	Retention Time	% Area
1	11.424	72.82
2	15.506	1.84
3	22.318	25.34

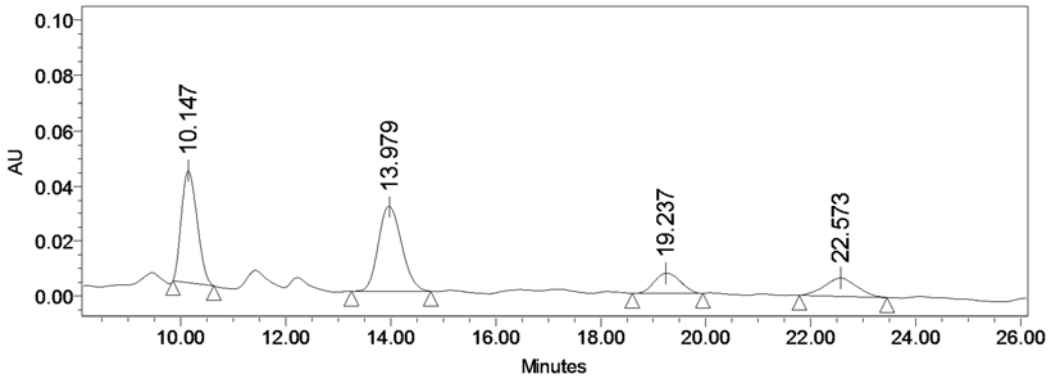
96/99 % *ee*



54BEg

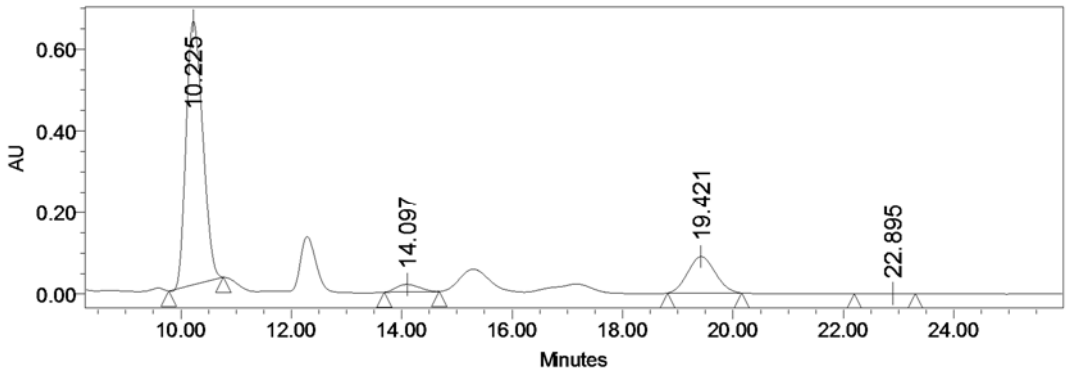
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54BEg**



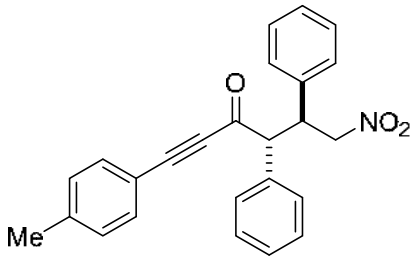
	Retention Time	% Area
1	10.147	36.35
2	13.979	40.77
3	19.237	10.67
4	22.573	12.22

54BEg



	Retention Time	% Area
1	10.225	79.02
2	14.097	3.09
3	19.421	17.82
4	22.895	0.07

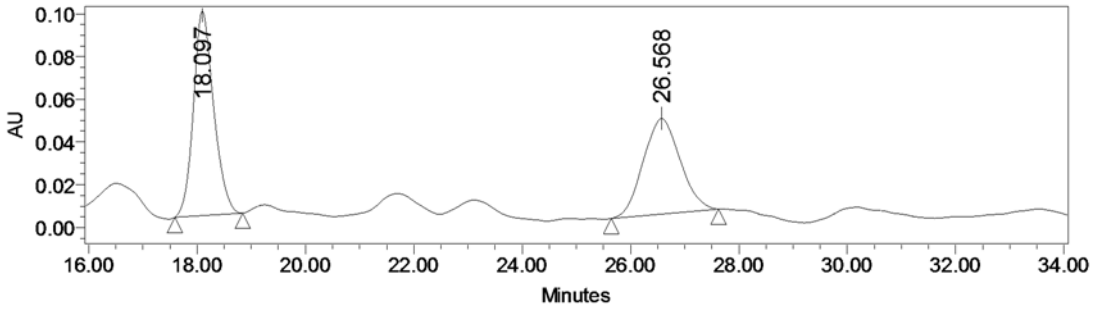
92/99 % *ee*



54CEa

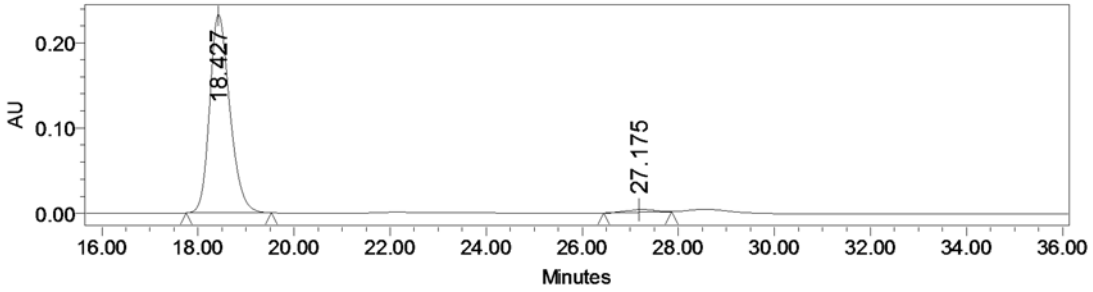
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54CEa**



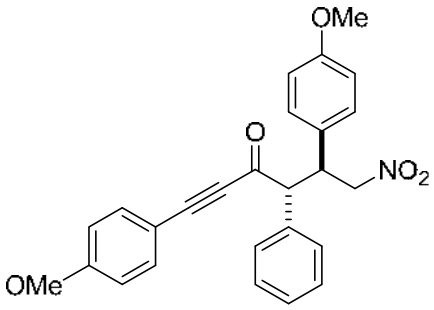
	Retention Time	% Area
1	18.097	54.05
2	26.568	45.95

54CEa



	Retention Time	% Area
1	18.427	98.11
2	27.175	1.89

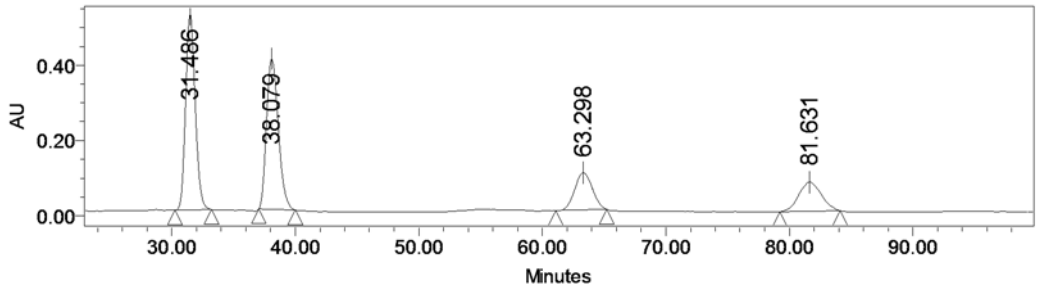
96/n.d. % *ee*



54DEi

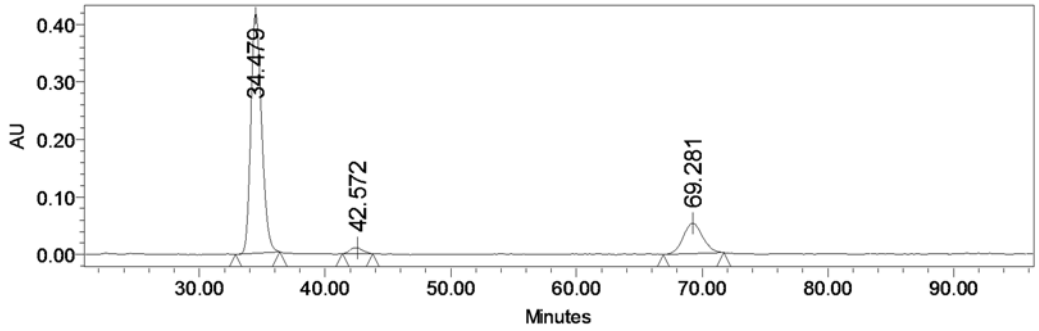
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54DEi**



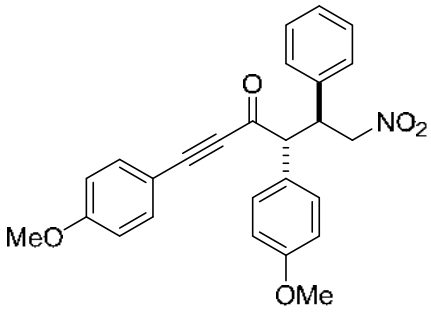
	Retention Time	% Area
1	31.486	37.69
2	38.079	35.84
3	63.298	13.22
4	81.631	13.25

54DEi



	Retention Time	% Area
1	34.479	79.45
2	42.572	2.38
3	69.281	18.17

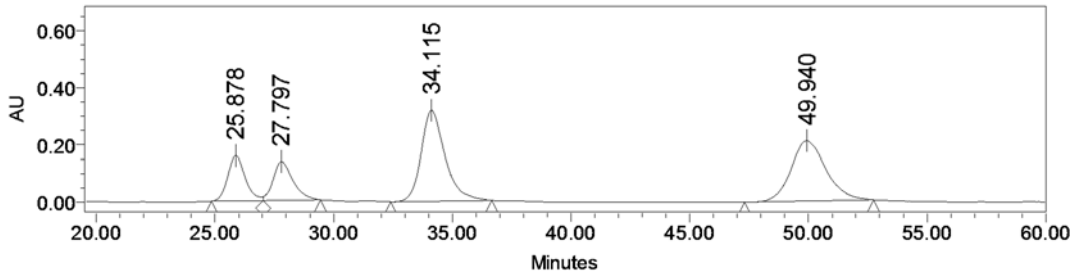
94/99 % *ee*



54DHa

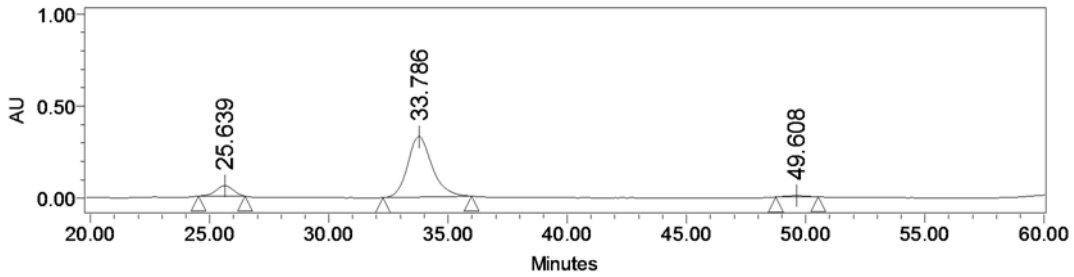
Daicel Chiralpak IA, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54DHa**



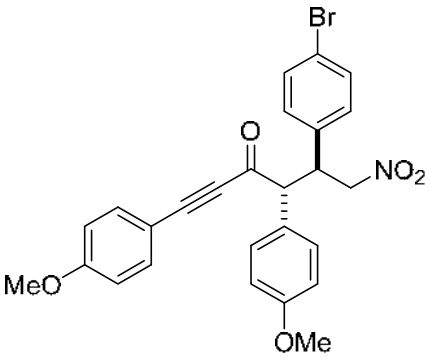
	Retention Time	% Area
1	25.878	13.59
2	27.797	13.13
3	34.115	37.20
4	49.940	36.07

54DHa



	Retention Time	% Area
1	25.639	10.65
2	33.786	87.96
3	49.608	1.40

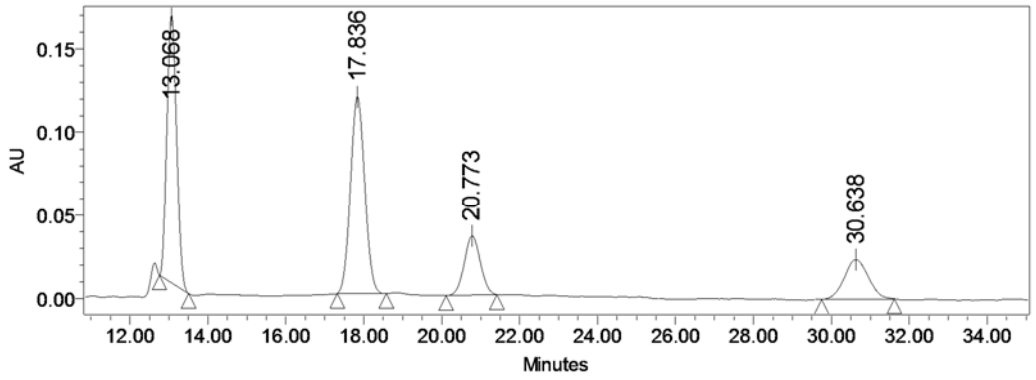
98/99 % *ee*



54DHf

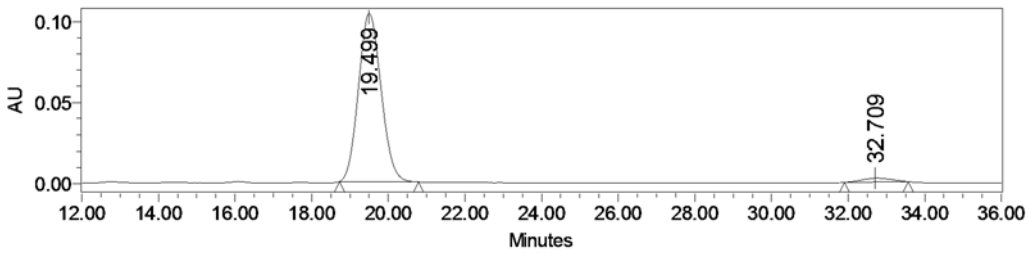
Daicel Chiralpak IC, hexane/isopropanol 90:10 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**54DHf**



	Retention Time	% Area
1	13.068	35.54
2	17.836	38.50
3	20.773	12.98
4	30.638	12.98

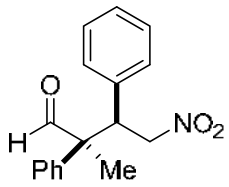
54DHf



	Retention Time	% Area
1	19.502	96.35
2	32.711	3.65

99/99 % *ee*

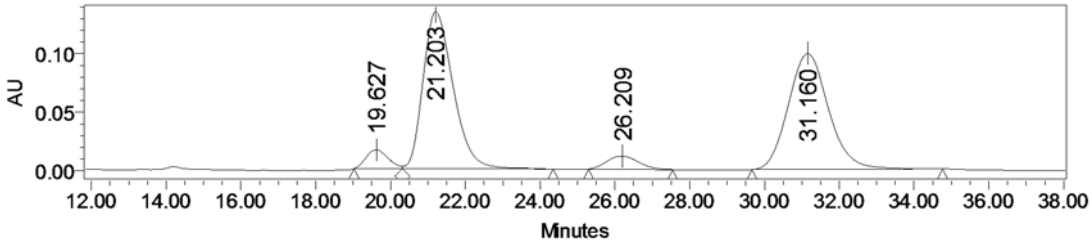
7.8.3. HPLC chromatograms for Chapter 4



66a

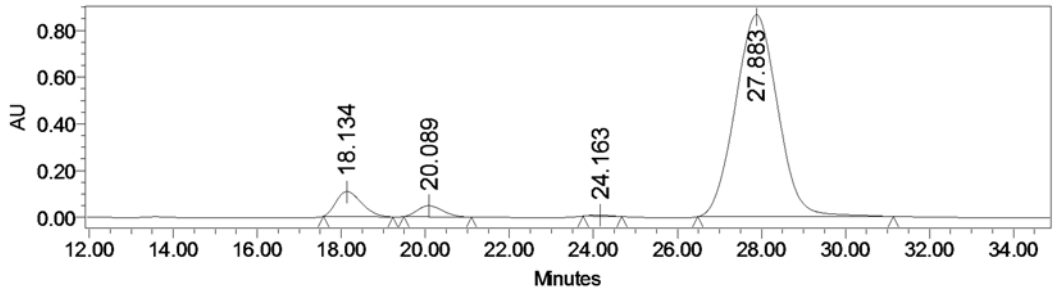
Daicel Chiralpak ODH, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**66a**



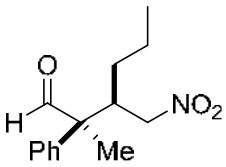
	Retention Time	% Area
1	19.627	4.05
2	21.203	46.23
3	26.209	4.10
4	31.160	45.62

66a



	Retention Time	% Area
1	18.134	6.65
2	20.089	2.97
3	24.163	0.25
4	27.883	90.13

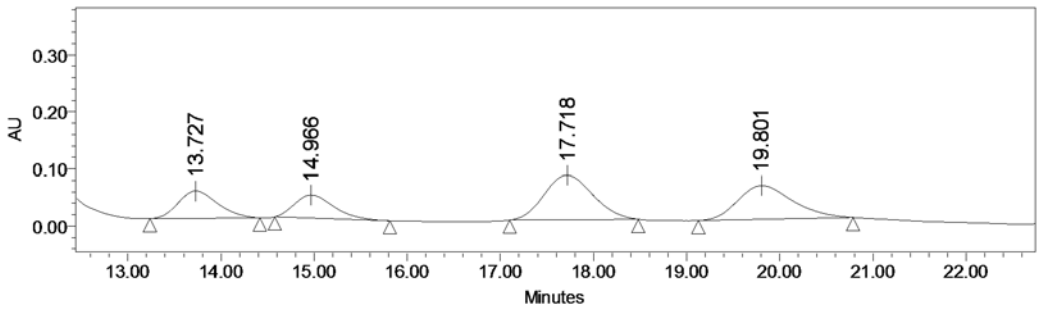
94/93 % *ee*



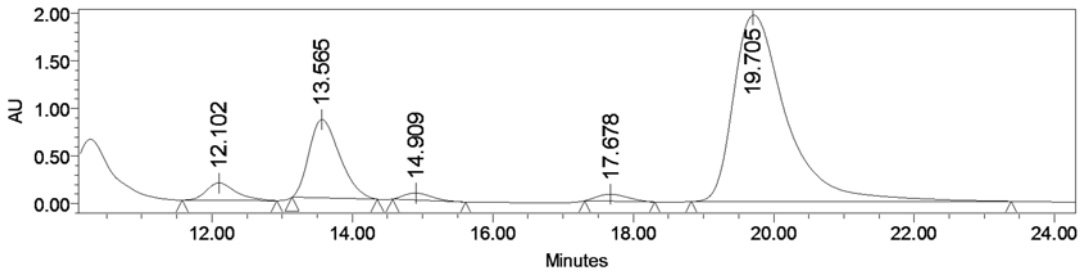
66b

Daicel Chiralpak ODH, hexane/isopropanol 98:2 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**66b**

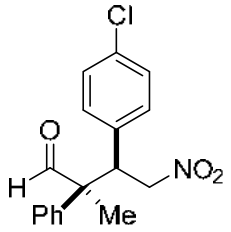


	Retention Time	% Area
1	13.727	18.02
2	14.966	15.17
3	17.718	35.96
4	19.801	30.85



	Retention Time	% Area
1	12.102	3.88
2	13.565	18.27
3	14.909	1.44
4	17.678	1.62
5	19.705	74.79

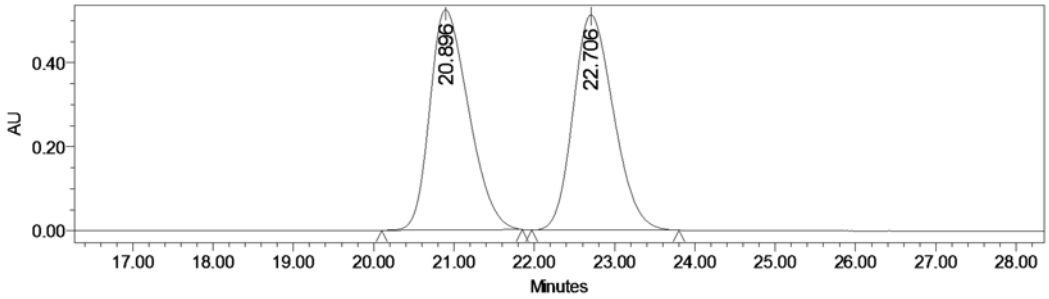
95/66 % *ee*



66g

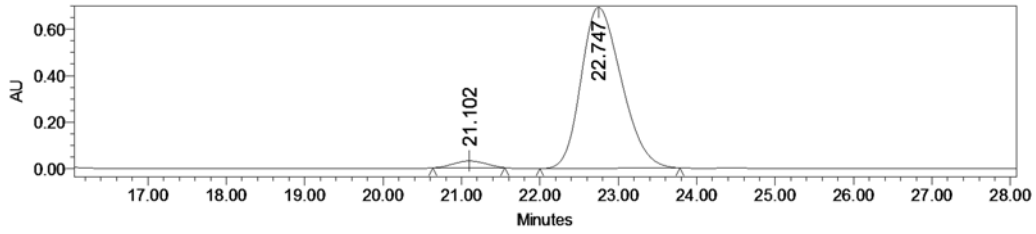
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**66g**



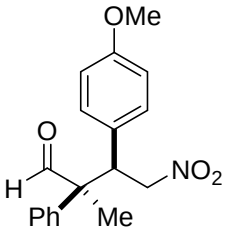
	Retention Time	% Area
1	20.896	49.54
2	22.706	50.46

66g



	Retention Time	% Area
1	21.102	3.25
2	22.747	96.75

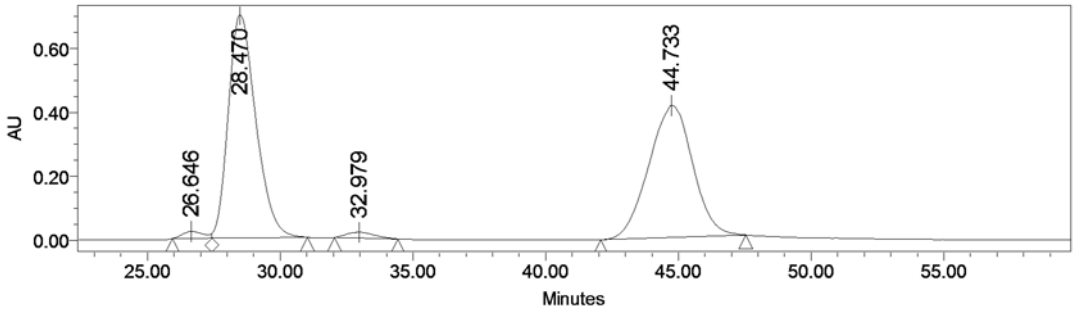
94/n.d. % *ee*



66i

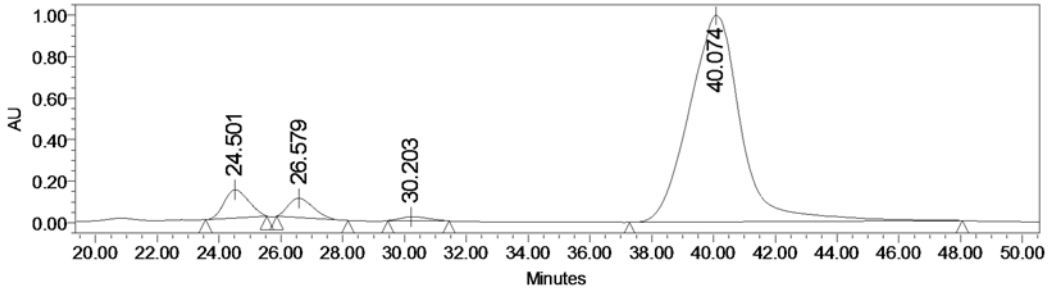
Daicel Chiralpak ODH, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 210.0 nm.

Rac-**66i**



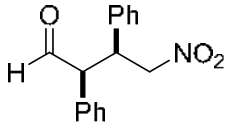
	Retention Time	% Area
1	26.646	1.21
2	28.470	50.15
3	32.979	1.33
4	44.733	47.31

66i



	Retention Time	% Area
1	24.501	5.75
2	26.579	4.04
3	30.203	0.93
4	40.074	89.28

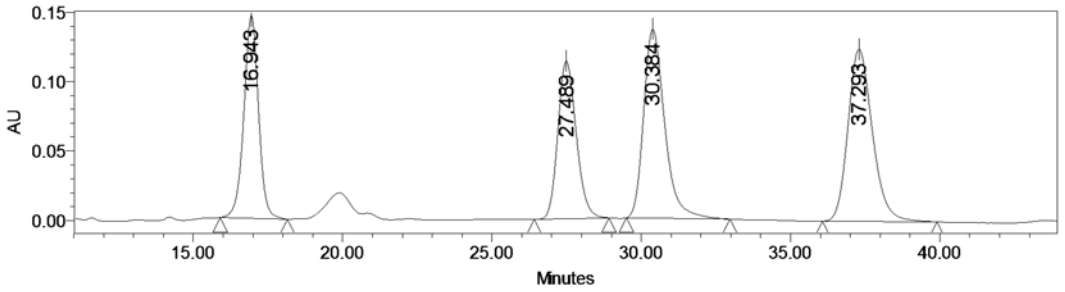
92/72 % *ee*



67

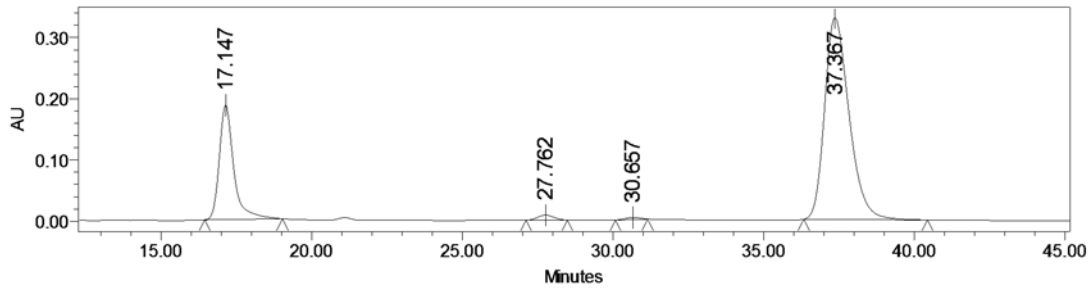
Daicel Chiralpak IC, hexane/isopropanol 95:5 flow rate = 1.0 mL/min, λ: 220.0 nm.

Rac-**67**



	Retention Time	% Area
1	16.943	21.15
2	27.489	20.61
3	30.384	28.25
4	37.293	29.99

67 from Michael reaction promoted by **C2**



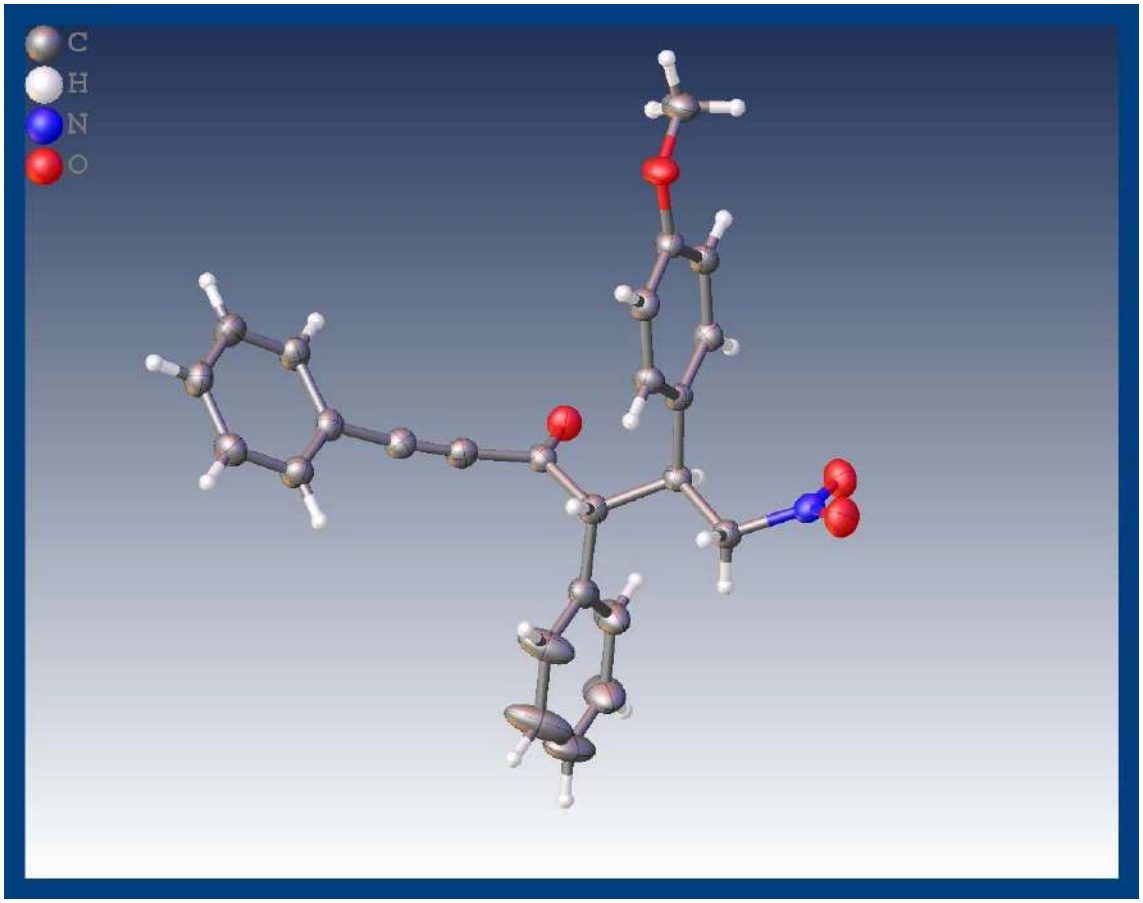
	Retention Time	% Area
1	17.147	24.72
2	27.762	1.21
3	30.657	0.47
4	37.367	73.60

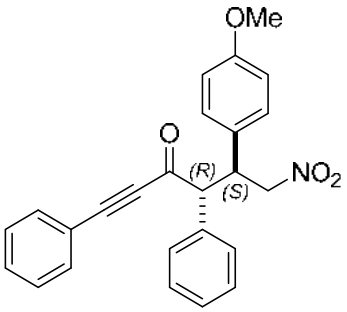
99/91 % *ee*

7.9. X-Ray analysis

7.9.1. ORTEP diagram of compound 54AEi

CCDC-1858603 contains the supplementary crystallographic data for the structural analysis of **54AEi** These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif





54AEi

Publications