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New Approaches to Optically Active 2-*tert*-Alkyl Azaaryl Compounds and 5,5-Disubstituted Hydantoins

DOCTORAL THESIS

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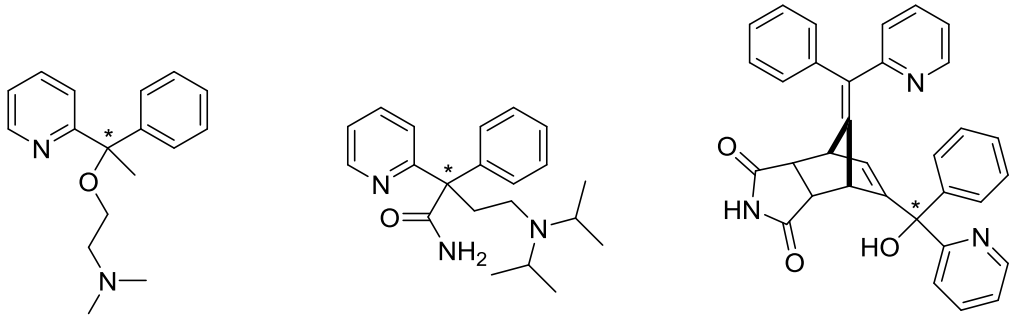
SUMMARY

INTRODUCTION

The field of asymmetric catalysis is a lively, fascinating and highly competitive research field in organic chemistry. The continuous need for novel asymmetric reactions as well as the demands for cheaper and more environmentally friendly catalytic processes is a challenge for all chemists in this field.

The search for new pronucleophiles to obtain tetrasubstituted asymmetric centers using chiral organocatalysts has been the subject of intense study in recent years.[1] This task has gained a great concern due to the fact that optical purity is now a strict requirement for the commercialization of new pharmaceutical products.[2]

On the one hand, 2-substituted pyridines, and more generally azaarenes, have attracted great part of attention since these structures are frequent in chiral compounds, as in pharmaceuticals or chiral ligands (Figure 1).



Doxylamine
antihistamine

Disopyramide
antiarrhythmic

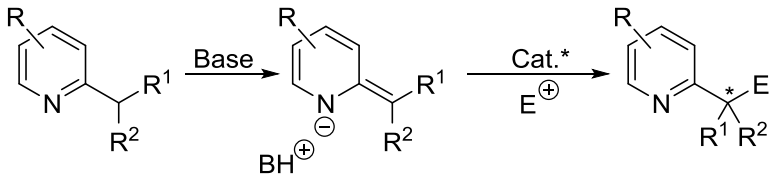
Norbormide
rodenticide

Figure 1.

One of the routes to obtain α-functionalized chiral 2-alkylpyridines by catalytic methods is by using 2-alkylpyridines as pronucleophiles (Scheme 1).

[1] a) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191. b) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751. For an all-carbon quaternary centers in natural products and medicinal chemistry, see: c) Ling, T.; Rivas, F. *Tetrahedron* **2016**, 43, 6729–6777.

[2] a) Kasprzyk-Hordern, B. *Chem. Soc. Rev.* **2010**, *39*, 4466–4503. b) *Chiral Drugs: Chemistry and Biological Action* (Lin, G.-Q. & You, Q.-D. & Chen, J.-F. ed., John Wiley & Sons, Inc.) 2011. c) Molecular, Clinical and Environmental Toxicology, Vol. 3 (Luch, A. ed., Springer Heidelberg Dondrecht London New York) 2012. Pages 413–436.



Scheme 1.

Despite the fact that the asymmetric addition of 2-alkylazaarenes to different electrophiles has been carried out with more or less success,[3] the methods displayed present some limitations:

1. If the alkyl azaarene is not activated, more than stoichiometric amounts of a strong base are needed.
2. The use of preactivated substrates: EWG in either the azaarene ring or the Cα or both positions is needed.
3. None of these methods address the generation of a quaternary Cα-stereocenter, an issue of general importance in organic synthesis, and of particular significance to the present context given the interest of quaternary compounds as potential pharmacophores.

On the other hand, hydantoins constitute a family of nitrogen heterocycles that are present in naturally occurring substances and medicinal compounds (Figure 2).[4] However, only few examples to access to optically active quaternary hydantoins involving new-carbon bond forming reaction have been reported.[5]

[3] a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093. b) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196. c) Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214–11218. d) Vera, S.; Liu, Y.; Marigo, M.; Escudero-Adán, E.; Melchiorre, P. *Synlett* **2011**, *2011*, 489–494.

[4] For reviews of hydantoin chemistry, see: a) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177–228. b) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int*. **2004**, *36*, 391–443. c) Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Rev.* **2017**, *117*, 13757–13809.

[5] a) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 8961–8965. b) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757−10768. Also, see: c) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294–13297.

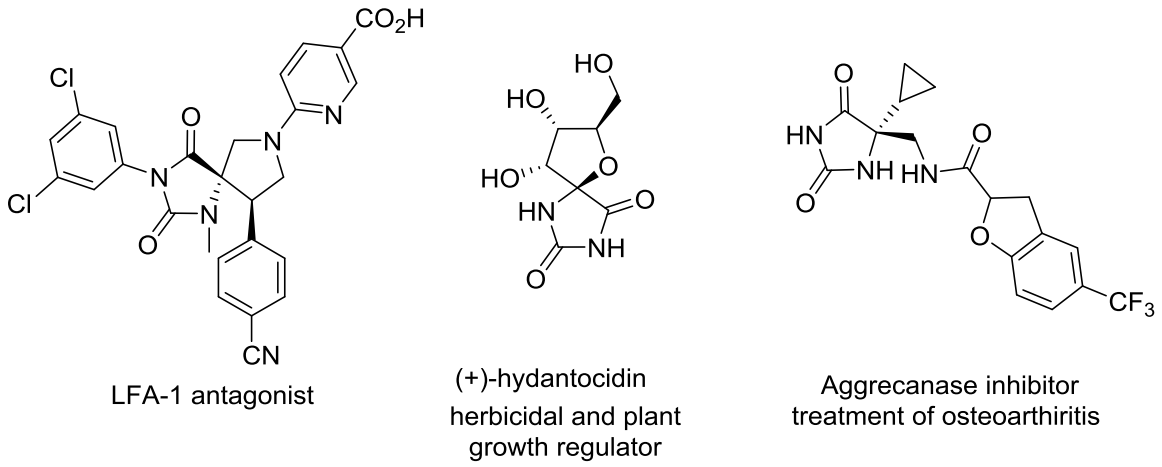
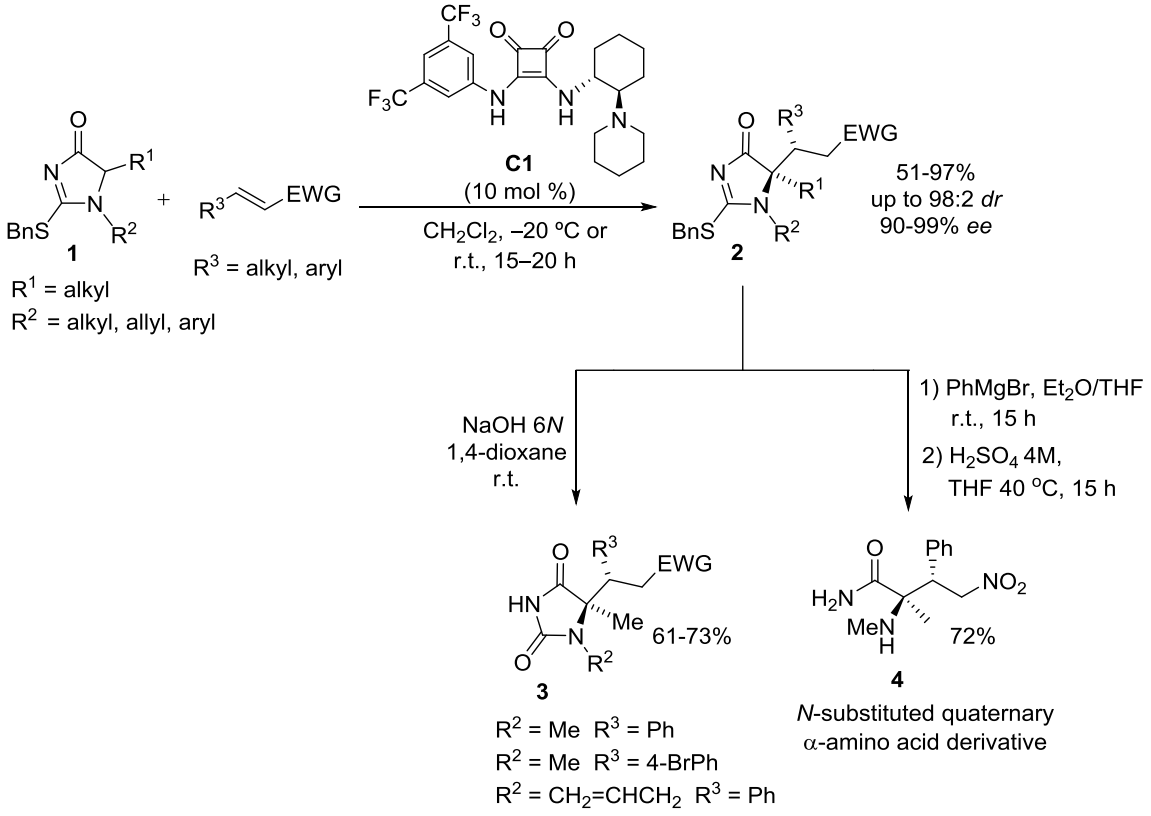


Figure 2.

Recently, our group introduced 1*H*-imidazol-4(5*H*)-ones **1** as novel nuchleophile in asymmetric synthesis.[6] These compounds allowed a highly efficient construction of a tetrasubstituted stereogenic center and a direct access to 5,5-disubstituted hydantoins (**3**) and *N*-substituted (alkyl, allyl, aryl) α-amino acid derivatives (**4**) (Scheme 2).

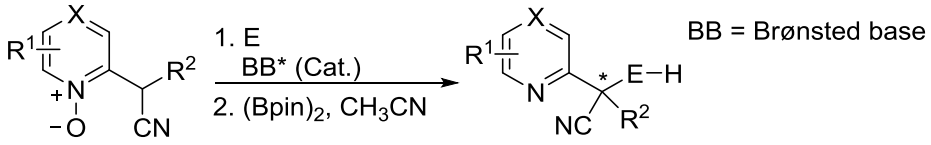


Scheme 2.

[6] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6887.

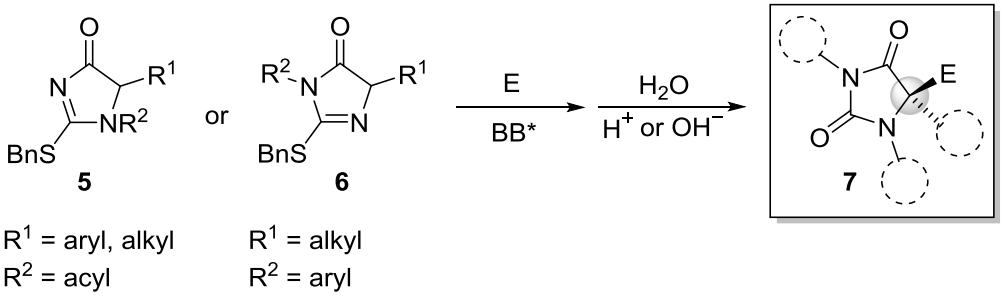
OBJECTIVES

The first objective would be to synthesize highly activated 2-(cyanomethyl)azaarene *N*-oxides and test them for the first time as effective pronucleophiles for the addition to Michael acceptors utilizing a Brønsted base catalyst. This reaction would lead to otherwise elusive optically active α-quaternary alkylazaarenes, compounds that have not been described previously (Scheme 3).



Scheme 3.

The second objective of this work would be, following our previous work concerning the synthesis of 5,5-disubstituted hydantoins **3** from 1*H*-imidazol-4(5*H*)-ones **1** (Scheme 2), the enantioselective synthesis of 5,5-disubstituted hydantoins **7** via Brønsted Base/H-bond donors catalyzed Michael reactions utilizing new 1*H*-imidazol-4(5*H*)ones **5** and 1*H*-imidazol-5(4*H*)ones **6** as pronucleophile templates (Scheme 4). If successful, a broad-scope approach for the enantioselective synthesis of diversely 1,3,5-substituted hydantoins would be at hand.



Scheme 4.

RESULTS AND DISCUSION

CHAPTER 2

We envisioned that the 2-cyanoalkylpyridine could be good candidate to be deprotonated under Brønsted base catalysis, due to the incorporation of two EWG groups (nitrile and phenyl groups) in the Cα position of the azaarene, and be added to different electrophiles (Figure 3).

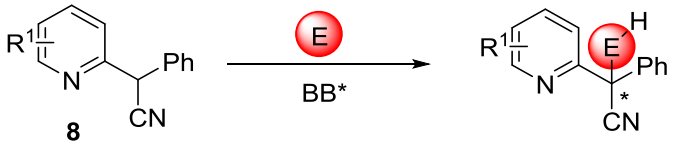


Figure 3. Proposed reaction for the investigation.

Firstly, we evaluated several known bifunctional catalysts containing a Brønsted base and a H bond donor functionalities for the addition of 2-phenyl-2-(2-pyridyl)acetonitrile **8** to α'-hydroxy enone **10**[7] with poor conversion and selectivities.

To increase the low reactivity of the nucleophile we decided to activate it by using the azaarene *N*-oxide **9** (Figure 4). On the one side, it is well known that the oxidation of the pyridine increases the acidity of the Cα[8] and on the other side, the N→O group could work as another strong coordinating site for catalyst binding.[9]

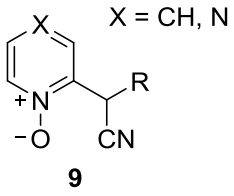


Figure 4.

We show that the *N*-oxide group in compound **9** plays a strategic role as a removable activating and stereodirecting element in conjunction with newly designed multifunctional squaramide-Brønsted base catalysts bearing a bulky silyl group (Figure 5).

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[7] α'-Hydroxy enones: Michael aceptors recently introduced by our group and others as α,β-unsaturated carboxylic acid surrogates through simple oxidative cleavage of the ketol unit, Badiola, E.; Fiser, B.; Gomez-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.

[8] 2-Alkylpyridine *N*-oxides are more acidic than the parent 2-alkylpyridines in about 3–4 pKa units in DMSO: a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. b) http://www.chem.wisc.edu/areas/reich/pkatable/. c) Evans pKa table: *http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf/.*

[9] The oxygen atom in the *N*-oxide has stronger dipole than the oxygen atoms of other common oxo donor such as alcohols, ethers, and amides. a) Karayannis, N. M. *Coord. Chem. Rev.* **1973**, *11*, 93−159. b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedon: Asymmetry* **2004**, *15*, 1373−1389. c) Malkov, A. V.; Kočoskçý, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29−36. d) Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574−587. e) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2014**, *114*, 6081−6129.

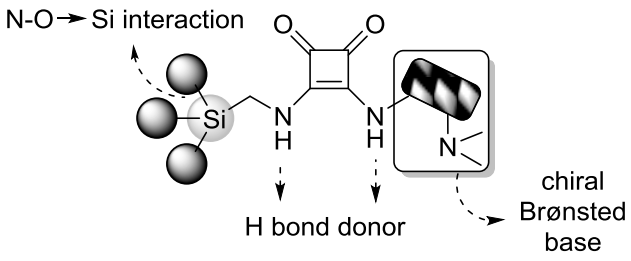
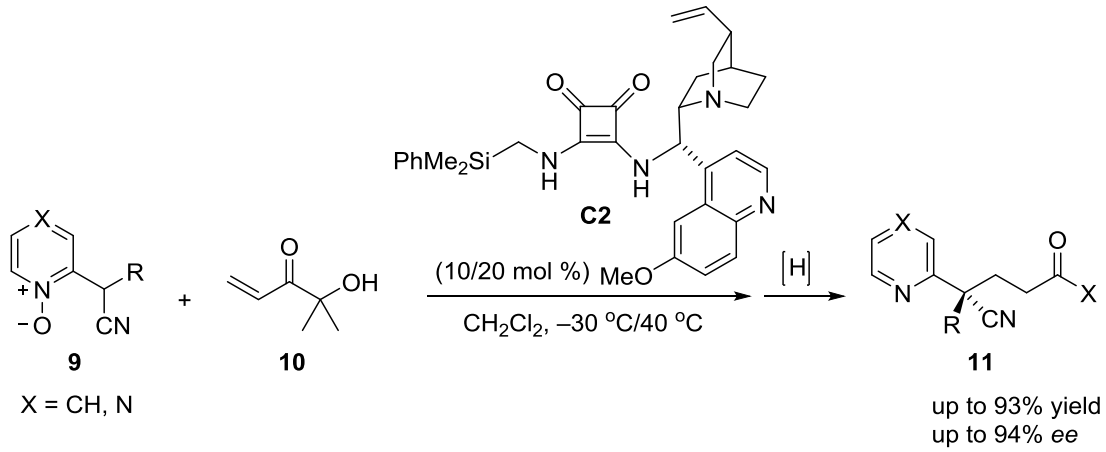


Figure 5.

The reactions carried out with this new type of multifunctional organocatalyst yielded the desired products with very good performance and excellent enantioselectivity (Scheme 5).

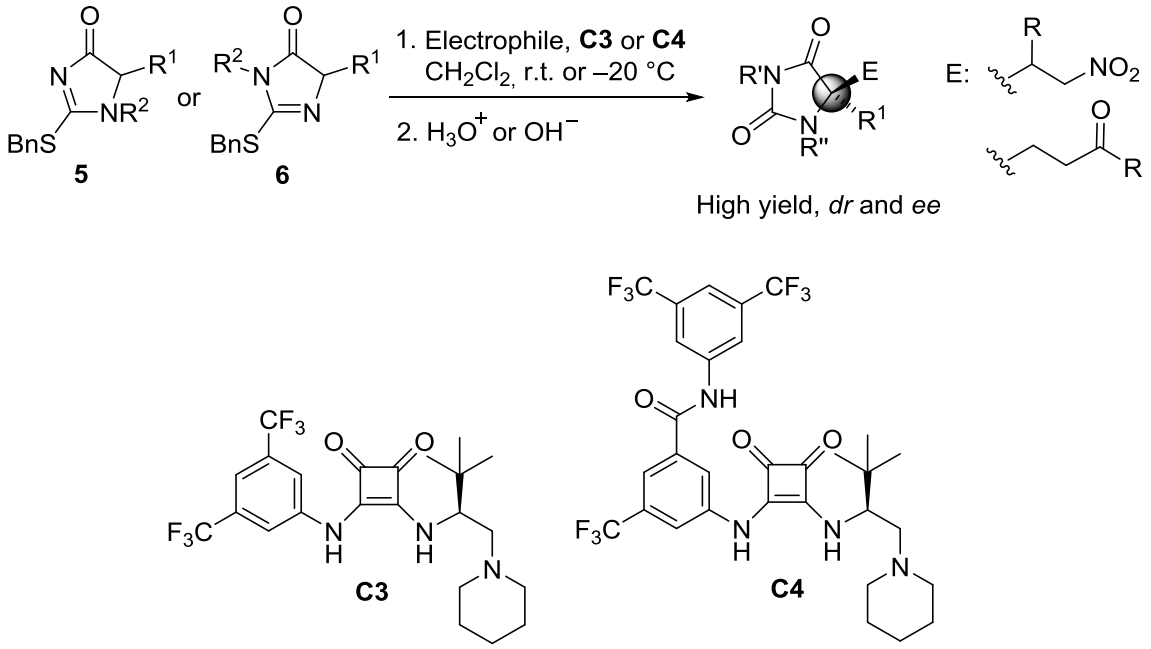


Scheme 5.

The detailed mechanism of these catalytic transformation as well as the precise role played by each element involved remains unclear. However, the N-oxide group and its *ortho*- relationship to the cyanoalkyl substituent are key for the optimal reaction outcome.

CHAPTER 3

In the third part of this thesis we show a continuation of our previous work (see Scheme 6). The efficiency of 1*H*-imidazol-4(5*H*)ones **5** and 1*H*-imidazol-5(4*H*)ones **6** as new pronucleophiles in the enantio- and diastereoselective organocatalytic conjugate additions catalyzed by bifunctional Brønsted bases/H-bond donors (**C3** or **C4**) with different electrophiles is shown. It should be mention that **5** and **6** show similar reactivity than 1*H*-imidazol-4(5*H*)-ones (**1**) and the corresponding final adducts were in general obtained in very good yields and excellent stereoselectivities (up to >98:2 *dr*; up to >99% *ee*) (Scheme 6).



Scheme 6.

NMR studies were carried out to try to understand the interactions between the squaramide type catalyst and the reaction substrates and two plausible transition states (TS) were proposed (A or A') (Figure 6).

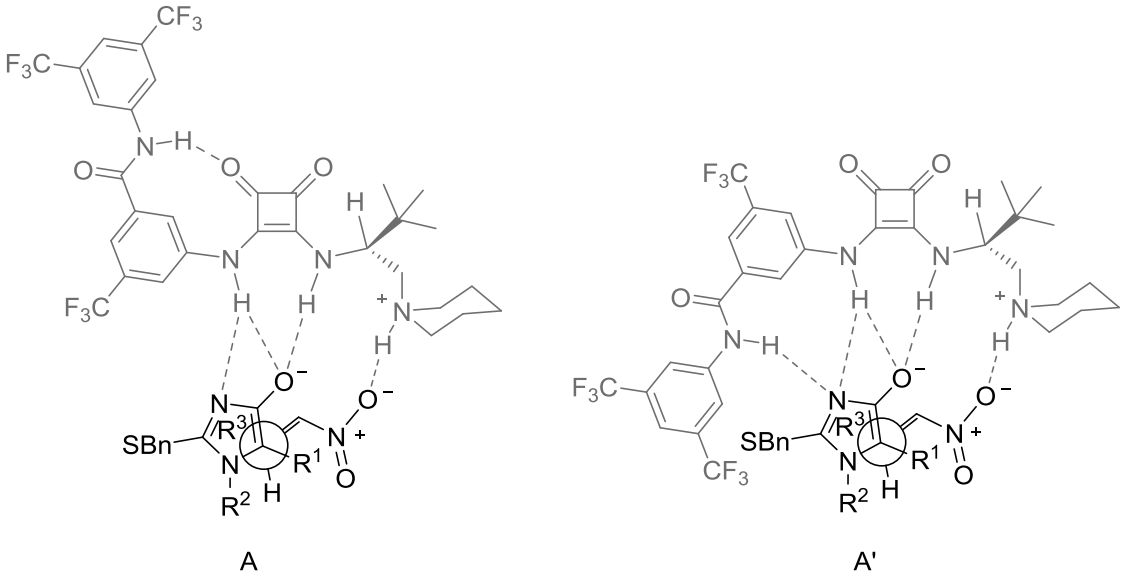


Figure 6.

CONCLUSIONS

In summary, three new pronucleophiles and two new multifunctional organocatalysts have been described for the organocatalytic asymmetric formation of quaternary stereocentres.

First, 2-cyanomethylazaarene *N*-oxides and catalyst **C2** have demonstrated their utility as efficient reagents for the asymmetric synthesis of α-quaternary *o*-substituted alkylazaarenes via mild enolization conditions.

Second, 1*H*-imidazol-4(5*H*)-ones **5** and 1*H*-imidazol-5(4*H*)-ones **6** have proved to be excellent substrates for the synthesis of enantiomerically enriched 5,5-disubstituted hydantoins.

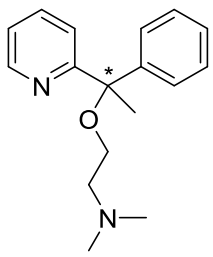
RESUMEN

INTRODUCCIÓN

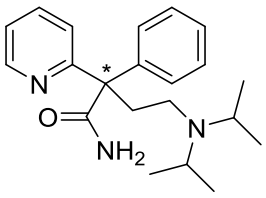
El hecho de que la pureza óptica sea ahora un requisito indispensable para la comercialización de nuevos productos farmacéuticos, hace que la búsqueda de nuevas condiciones de reacción para obtener centros asimétricos de manera eficaz esté siendo objeto de un intenso estudio.[1]

El campo de la organocatálisis asimétrica, es decir el empleo de catalizadores quirales puramente orgánicos, ha experimentado un auge extraordinario en los últimos 15 años debido a las potenciales ventajas de dichos sistemas. Las razones esgrimidas para este inusitado interés son en primer lugar la facilidad de manejo, la no necesidad de secado de los disolventes y el no requerimiento de atmósfera inerte, y en segundo lugar la accesibilidad de los catalizadores en ambas formas enantioméricas.[2]

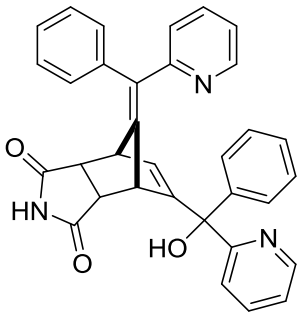
Por un lado, las piridinas *o*-sustituidas con centro estereogénicos cuaternarios, y más generalmente los azaarenos, han atraído parte de la atención de los químicos sintéticos ya que estas estructuras son frecuentes en productos farmacéuticos o ligandos quirales (Figura 1).



Doxilamina
antihistamínico



Disopiramida
antiarrítmico



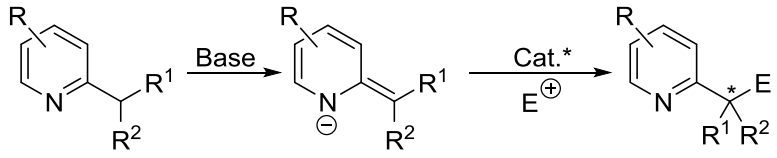
Norbormida
rodenticida

Figura 1.

[1] a) Kasprzyk-Hordern, B. *Chem. Soc. Rev.* **2010**, *39*, 4466–4503. b) *Chiral Drugs: Chemistry and Biological Action* (Lin, G.-Q. & You, Q.-D. & Chen, J.-F. ed., John Wiley & Sons, Inc.) 2011. c) Molecular, Clinical and Environmental Toxicology, Vol. 3 (Luch, A. ed., Springer Heidelberg Dondrecht London New York) 2012. Páginas 413–436.

[2] Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

El uso de 2-alquilpiridinas como pronucleófilos es una de las rutas principales para obtener 2-alquilpiridinas quirales α-funcionalizadas por métodos catalíticos (Esquema 1).



Esquema 1.

A pesar de que la adición de 2-alquilazaarenos a diferentes electrófilos se ha llevado a cabo con más o menos éxito,[3] los métodos descritos hasta la fecha presentan serias limitaciones:

1. En el caso de que el 2-alquil azaareno no esté activado, la utilización de una base fuerte es necesaria para llevar a cabo la reacción.
2. Necesidad de utilizar sustratos preactivados: grupo electronatractor en el anillo del azaareno, en la posición Cα o en ambas posiciones al mismo tiempo.
3. Ninguno de los métodos descritos aborda la generación de un estereocentro cuaternario en la posición Cα del azaareno, un hecho de gran importancia dado el interés de los compuestos cuaternarios como potenciales farmacóforos.

Por otro lado, las hidantoínas constituyen una familia de heterociclos nitrogenados que están presentes en sustancias que poseen una gran importancia farmacológica (Figura 2).[4] A pesar de su importancia, solo se han descrito algunos ejemplos aislados de acceso a hidantoínas cuaternarias ópticamente activas mediante la reacción de formación de nuevos enlaces C-C.[5]

[3] a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093. b) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196. c) Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214–11218. d) Vera, S.; Liu, Y.; Marigo, M.; Escudero-Adán, E.; Melchiorre, P. *Synlett* **2011**, *2011*, 489–494.

[4] Para revisiones de la química de hidantoína, ver: a) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177–228. b) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int*. **2004**, *36*, 391–443. c) Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Rev.* **2017**, *117*, 13757–13809.

[5] a) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 8961–8965. b) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757−10768. Also, see: c) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294–13297.

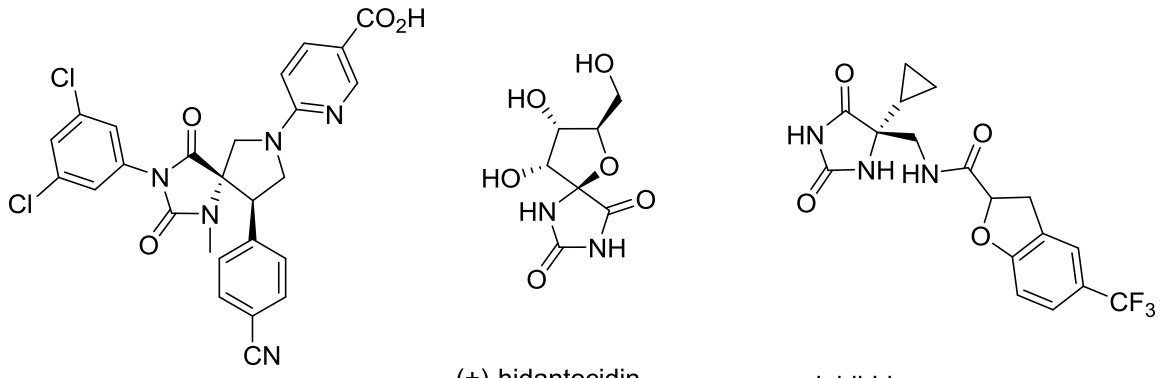
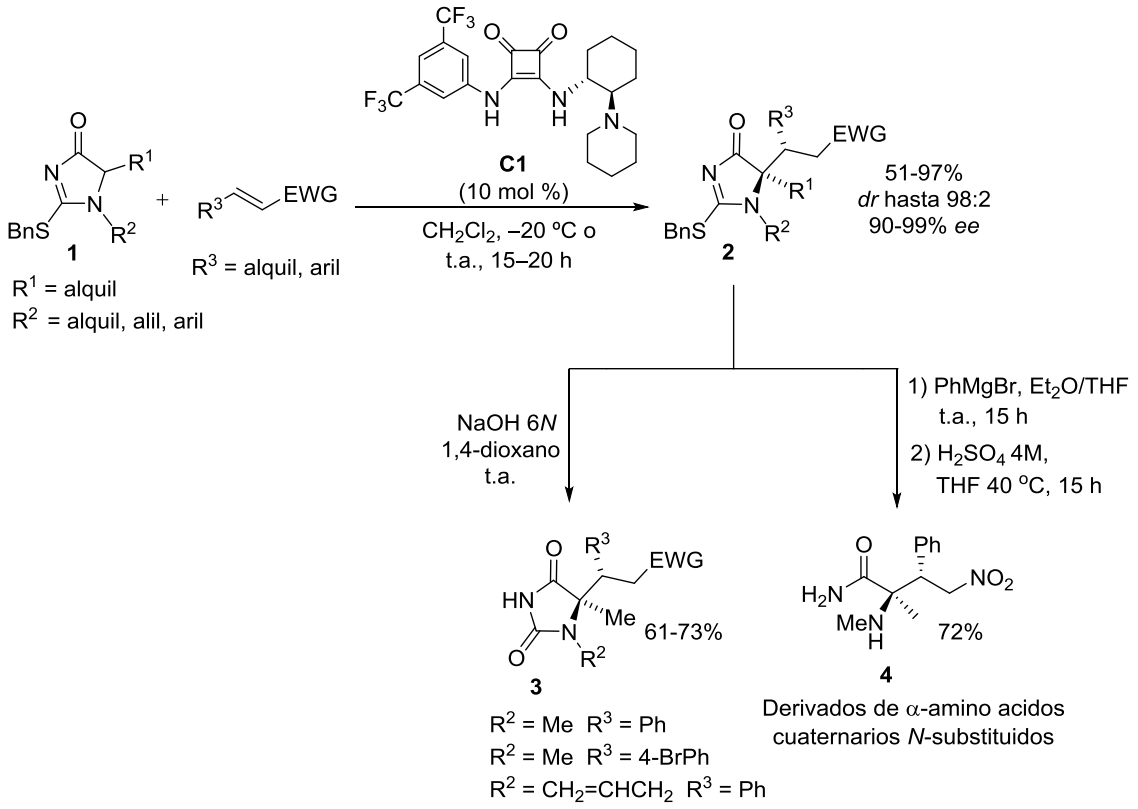


Figura 2.

Recientemente, nuestro grupo ha introducido las 1*H*-Imidazol-4(5*H*)-onas (**1**) como nuevos nucleófilos en síntesis asimétrica.[6] Estos compuestos han permitido de manera eficaz la síntesis de un centro estereogénico cuaternario en la posición Cα al grupo carbonilo y un acceso directo a hidantoínas 5,5-disustituidas (**3**) y derivados de α-aminoácidos *N*-sustituidos (**4**) (Esquema 2).

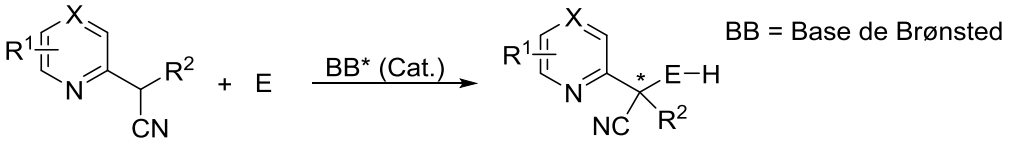


Esquema 2.

[6] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6887.

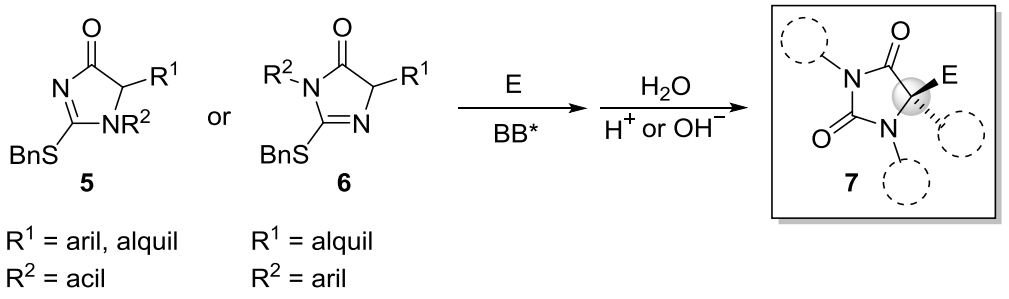
OBJETIVOS

De acuerdo con las líneas expuestas anteriormente, nos propusimos como primer objetivo general la síntesis de α-alquil azaarenos cuaternarios ópticamente activos. Para ello, nos propusimos adicionar bajo condiciones suaves de enolización 2-(cianometil) azaarenos a distintos electrófilos (Esquema 3).



Esquema 3.

En el segundo apartado nos propusimos implementar el trabajo previo en la síntesis de hidantoinas 5,5-disustituidas (**3**) a partir de 1*H*-imidazolonas-4(5*H*)-onas (**1**), utilizando 1*H*-imidazol-4(5*H*)-onas (**5**) y 1*H*-imidazol-5(4*H*)-onas (**6**) como plantillas pronucleófilas equivalentes y sistemas catalíticos del tipo base de Brønsted/enlace de H (Esquema 4). Las etapas clave deberían ser la preparación de las imidazolonas **5** y **6** y la etapa de adición asimétrica a los distintos electrófilos.



Esquema 4.

RESULTADOS Y DISCUSIÓN

CAPÍTULO 2:

En primer lugar, supusimos que la 2-cianoalquilpiridina comercialmente accesible podría ser un buen candidato para ser desprotonada bajo condiciones suaves de enolización, debido a la incorporación de dos grupos electroatractores (grupos nitrilo y fenilo) en la posición Cα de la piridina, y ser adicionada a diferentes electrófilos (Figura 3).

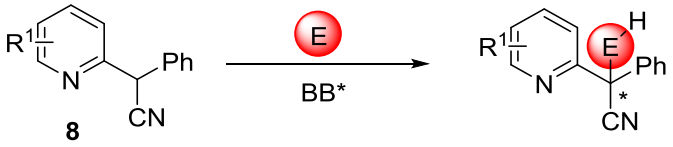
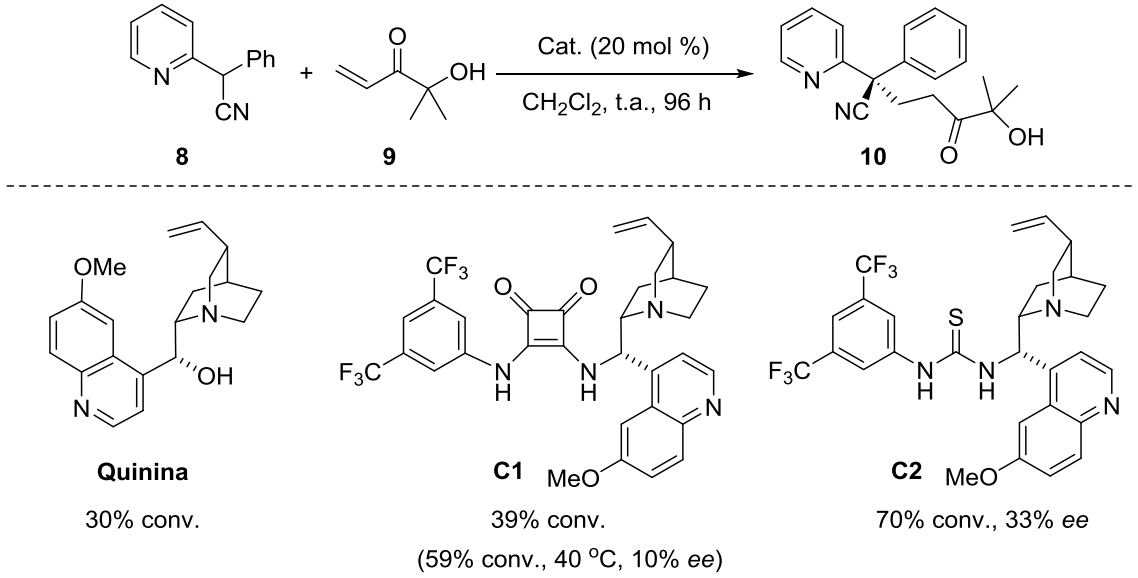


Figura 3.

Evaluamos varios catalizadores bifuncionales conocidos portadores de una base de Brønsted y una funcionalidad donante de enlace H para la adición de 2-fenil-2-(2-piridil)acetonitrilo **8** a la α-hidroxi enona **9**.[7] Desafortunadamente los resultados no fueron los deseados y el producto de adición se obtuvo con conversiones y enantioselectividades muy pobres.



Esquema 5.

Para aumentar la baja reactividad del nucleófilo decidimos activarlo usando el correspondiente *N*-óxido **11** (Figura 4). Por un lado, es bien sabido que la oxidación de la piridina aumenta la acidez del carbono en la posición α[8] y, por otro lado, el grupo

[7] α'-Hidroxi enonas: Aceptores de Michael recientemente introducidos por nuestro grupo y otros como substitutos del ácido carboxílico α, β-insaturado a través de la escisión oxidativa simple de la unidad de cetol, Badiola, E.; Fiser, B.; Gomez-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.

[8] 2-Alkylpyridine *N*-oxides are more acidic than the parent 2-alkylpyridines in about 3–4 pKa units in DMSO: a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. b) http://www.chem.wisc.edu/areas/reich/pkatable/. c) Evans pKa table: *http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf/.*

N→O podría funcionar como otro punto de anclaje para la unión al catalizador y dar mayor rigidez al estado de transición.[9]

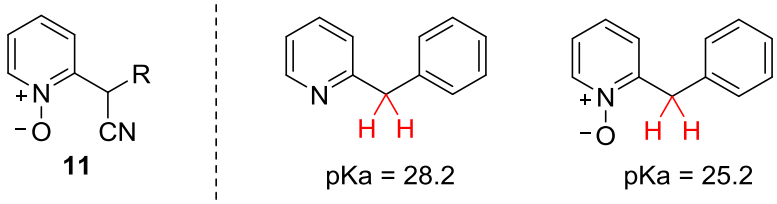
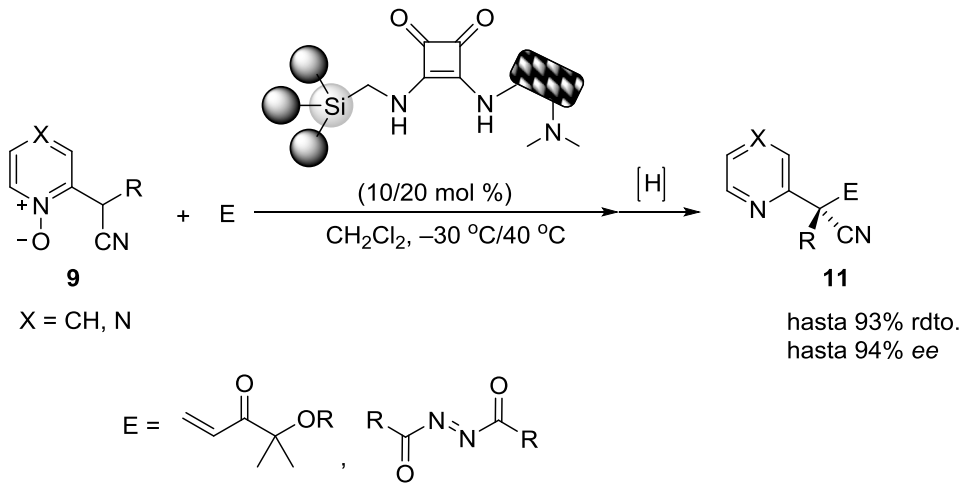


Figura 4.

Con objeto de implementar la interacción entre **11** y el catalizador, se sintetizó una nueva familia de catalizadores multifuncionales del tipo base de Brønsted/escuaramida con un grupo sililo en su estructura. Afortunadamente las reacciones llevadas a cabo con este nuevo tipo de nucleófilo y catalizador condujeron a los productos deseados con muy buenos rendimientos y excelentes enantioselectividades (Esquema 6).



Esquema 6.

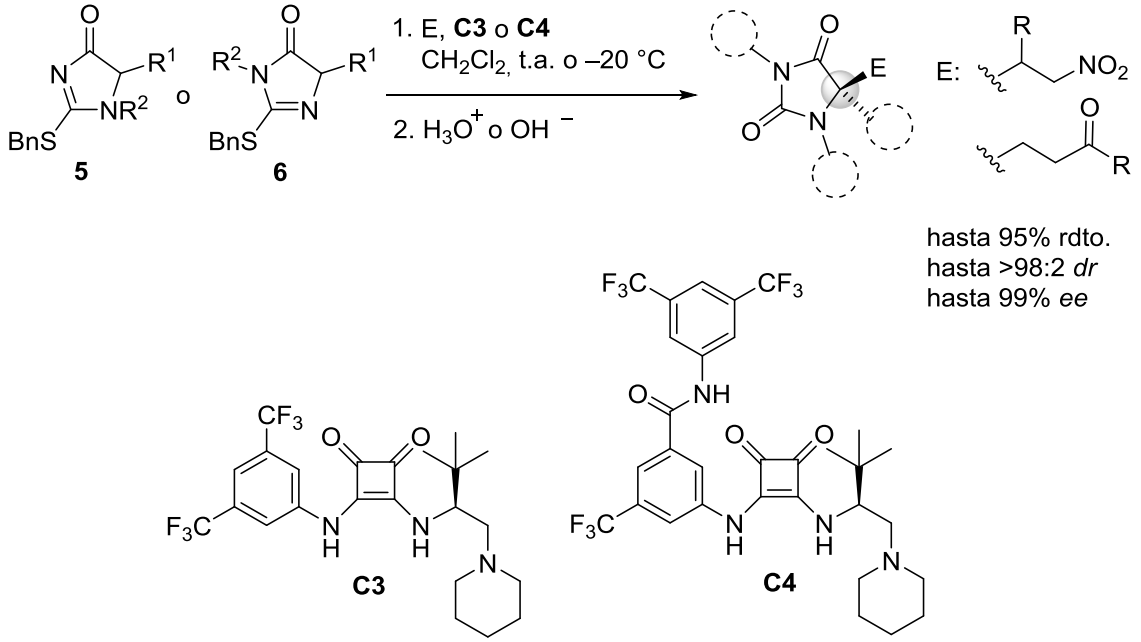
El mecanismo detallado de esta transformación catalítica así como el papel preciso desempeñado por cada elemento involucrado sigue sin estar claro. Se puede afirmar que el grupo *N*-óxido y su relación *orto*- con el sustituyente cianoalquilo y el catalizador multifuncional portador de un grupo sililo han resultado ser claves para el desarrollo eficiente de la reacción.

[9] The oxygen atom in the *N*-oxide has stronger dipole than the oxygen atoms of other common oxo donor such as alcohols, ethers, and amides. a) Karayannis, N. M. *Coord. Chem. Rev.* **1973**, *11*, 93−159. b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedon: Asymmetry* **2004**, *15*, 1373−1389. c) Malkov, A. V.; Kočoskçý, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29−36. d) Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574−587. e) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2014**, *114*, 6081−6129.

CAPÍTULO 3:

En la tercera parte de esta tesis mostramos una continuación de nuestro trabajo previo basado en la adición de 1*H*-imidazol-4(5*H*)-onas (**1**) a nitroalquenos utilizando catalizadores bifuncionales quirales del tipo bases de Brønsted/enlaces de hidrógeno (ver Esquema 2). Aunque la metodología previamente descrita proporciona buenos rendimientos químicos y excelentes selectividades, está limitada al empleo de imidazolonas *N*-alquil derivadas.

En este capítulo se muestra la eficacia de las imidazolonas **5** y **6** como nuevos pronucleófilos en adiciones conjugadas a nitroalquenos y α-hidroxi enonas (**9**) catalizadas por **C3** y **C4** (Esquema 7). Los aductos finales correspondientes se obtuvieron en general con muy buenos rendimientos y excelentes estereoselectividades (>98:2 *dr*; >99% *ee*). Nuestra propuesta ha dado como hecho más rotundo el acceso a la síntesis de hidantoinas sustituidas con funcionalidades adicionales en comparación al precedente expuesto.



Esquema 7.

Se llevaron a cabo estudios de RMN para tratar de comprender las interacciones entre el catalizador bifuncional **C4** y los sustratos de partida y se propusieron dos estados de transición posibles. El primero de ellos, involucra al protón amídico en la activación intramolecular del propio catalizador (activación asistida) (Figura 5, Modelo A). En el segundo estado de transición propuesto, el protón amídico estaría

involucrado en la activación de las correspondientes imidazolonas **5** o **6** (Figura 5, Modelo B).

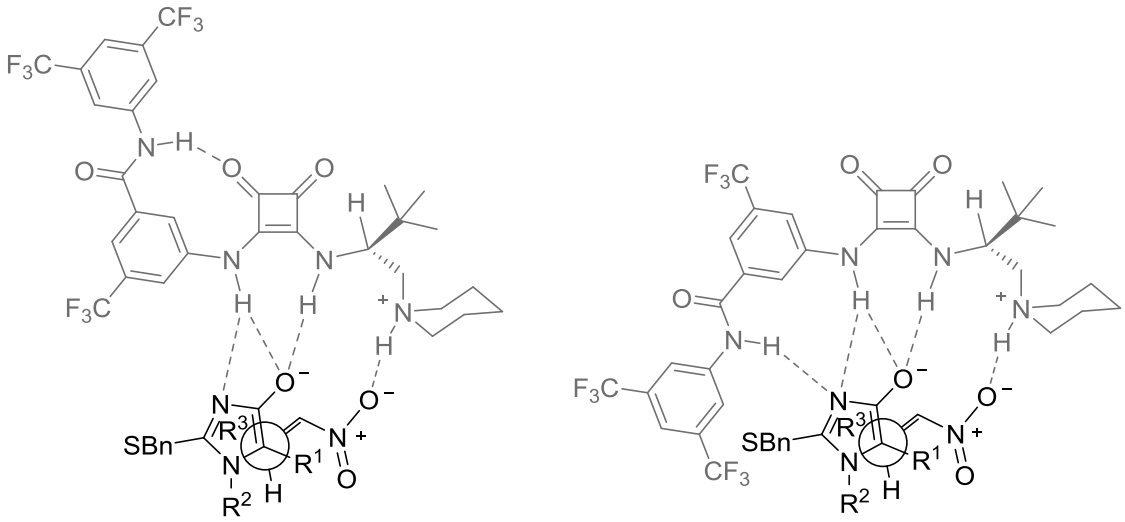


Figura 5.

CONCLUSIONES

En resumen, se han descrito tres nuevos pronucleófilos y dos nuevos organocatalizadores multifuncionales para la formación asimétrica organocatalítica de estereocentros cuaternarios.

Por un lado, se ha descrito por primera vez un nuevo procedimiento altamente estereoselectivo para la obtención de 2-alquil azaarenos con un centro estereogénico cuaternario en la posición α. Como puntos novedosos se han utilizado por primera vez *N*-óxidos de 2-cianometil azaarenos como pronucleófilos carbonados y un nuevo catalizador multifuncional base de Brønsted/escuaramida portador de un grupo sililo.

Por otro lado, las 1*H*-imidazol-4(5*H*)-onas **5** y 1*H*-imidazol-5(4*H*)-onas **6** han demostrado ser excelentes nucleófilos en la reacción asimétrica de Michael a nitroalquenos y α-hidroxi enonas. Los aductos obtenidos han demostrado su valor como intermedios sintéticos de hidantoinas 5,5-disustituidas enantiomericamente enriquecidas. Esta metodología ha sido empleada para obtener inhibidores de la enzima ADAMTS-5 responsable de la degradación del tejido cartilaginoso.

Abbreviations and acronyms

ω	Electrophilicity index
Ac	Acetyl (group)
$Al(Oi\text{-}Pr)_3$	Aluminum isopropoxide
Ar	Aryl (group)
Å	Årmstrong
BB	Brønsted base
BINAM	1,1'-Bi(2-naphthylamine)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl (group)
Boc	*tert*-Butyloxycarbonyl (group)
BOX	Bis(oxazoline)
$(Bpin)_2$	Bis(pinacolato)diboron
*i*Bu	Isobutyl (group)
*t*Bu	*tert*-Butyl (group)
Bz	Benzoyl (group)
Cat.	Catalyst
Conv.	Conversion
Cbz	Benzyloxycarbonyl (group)
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl (group)
DA	Diels-Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIOP	*O*-Isopropyldiene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	Ethane-1,2-diylbis[(2methoxyphenyl)phenylphosphane]
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	Dimethyl formamide
DMPA	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DOPA	3,4-Dihydroxyphenylalanine
DPEN	Diphenylethylenediamine
dr	Diastereomeric ratio
E	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Et	Ethyl (group)
Et_2O	Diethyl ether
EtOH	Ethanol
EWG	Electron withdrawing group
Hex	Hexane
HMPA	Hexamethylphosphoramide

HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LIHMDS	Lithium bis(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
m-	*meta*-
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl (group)
MeOH	Methanol
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MVK	Methyl vinyl ketone
NHC	*N*-heterocyclic carbene
NMO	*N*-Methyl morpholine N-oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o-	*ortho*-
p-	*para*-
PG	Protecting group
Ph	Phenyl (group)
PHOX	Phosphinooxazoline
Piv	Pivaloil
pK_a	Acid dissociation constant (logarithmic scale)
pK_b	Base dissociation constant (logarithmic scale)
PMP	*para*-Methoxyphenyl (4-MeO-C_6H_4-)
*n*Pr	*n*-Propyl (group)
*i*Pr	Isopropyl (group)
PTC	Phase-transfer catalysis
Py	Pyridine
quant.	Quantitative
Ref.	Reference
r.t.	Room temperature
S_N	Nucleophilic substitution
SOMO	Singly occupied molecular orbital
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDPS	*tert*-Butyldiphenylsilyl
TBS	Tributyl silyl (group)
Tf	Triflate (CF_3-SO_3-)
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TMS	Trimethyl silyl (group)
TMSCl	Trimethylsilyl chloride
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl (4-Me-C_6H_4-SO_2-)
TS	Transition state
*p*TSA	*para*-Toluenesulfonic acid
*	Chiral

CHAPTER 1

INTRODUCTION

1. Introduction

1.1. Asymmetric catalysis

1.1.1. General considerations

The only life we know is three-dimensional in which molecular chirality plays a key role. A vast range of physical and biological functions are generated through precise molecular recognition that requires matching of chirality.[1] Life itself depends on chiral recognition, because living systems interact with stereoisomers (spatial isomers)[2] in decisively different manners. Then, it is not a surprise that two enantiomers of a drug could interact differently with the receptor, generating different effects.[3]

An interesting example is L-DOPA, used in the treatment of Parkinson´s disease. The achiral compound dopamine is the active drug, generated after in vivo decarboxylation of L-DOPA. Dopamine cannot cross the blood-brain barrier to reach the required site of action, so the ''prodrug'' L-DOPA is dispensed. L-DOPA is synthesized via asymmetric catalytic hydrogenation on an industrial scale by Monsanto (Scheme 1, Step 1).[4] Enzyme-catalized in vivo decarboxylation releases the drug in its active form. However, this enzyme (L-DOPA decarboxylase, Scheme 1, Step 2) only decarboxylates the L-enantiomer, so it is necessary to administer DOPA in its pure L-form. The accumulation of D-DOPA may be dangerous, because enzymes cannot metabolize it. It is obvious then, that the synthesis of chiral compounds as a single enantiomer, also called asymmetric synthesis, has become an essential subject for research.

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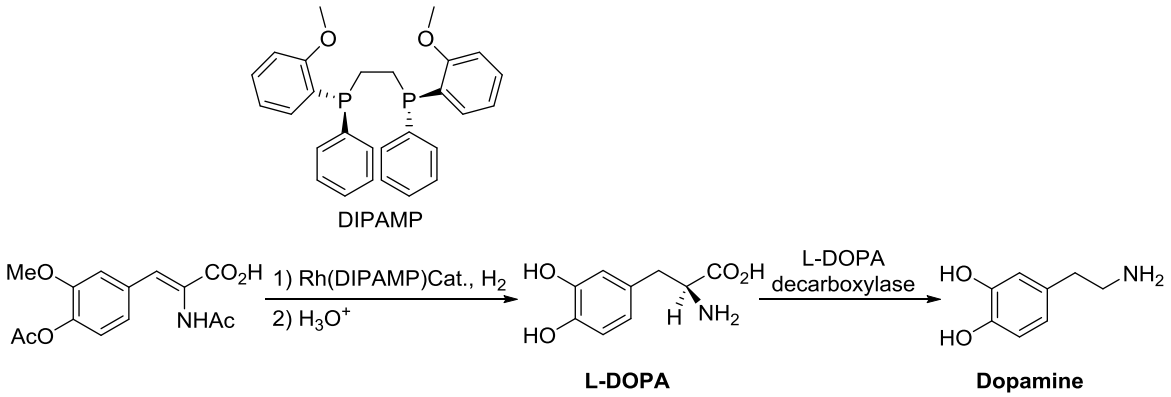
[1] Its basics were first discussed as "Key-lock principle" by Emil Fisher. a) Fisher, E. *Chem. Ber.* **1894**, *27*, 2985–2993. For a short review about the key-lock theory and the induced fit theory, see: b) Koshland, D. E. *Angew. Chem. Int. Ed.* **1994**, *33*, 2375–2378.

[2] Stereoisomers are compounds that share identical molecular formulas, atom-to-atom linkages, and bonding distances, but differ in their three-dimensional arrangement. Diastereomers are stereoisomers which are nonsuperimposable, non-mirror images. Enantiomers are stereoisomers which are nonsuperimposable, mirror images.

[3] a) McConathy, J.; Owens, M. J. *Prim. Care Companion J. Clin. Psychiatry* **2003**, *5*, 70–73. b) Hutt, A. J.; Valentova, J. *Universitas Comeniana. Acta Facultatis Pharmaceuticae* **2003**, *50*, 7–23. c) Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discov. Today* **2004**, *9*, 105–110. d) Smith, S. W. *Toxicol. Sci.* **2009**, *110*, 4–30. e) Kasprzyk-Hordern, B. *Chem. Soc. Rev.* **2010**, *39*, 4466–4503. f) *Chiral Drugs: Chemistry and Biological Action* (Lin, G.-Q. & You, Q.-D. & Chen, J.-F. ed., John Wiley & Sons, Inc.) 2011. g) Molecular, Clinical and Environmental Toxicology, Vol. 3 (Luch, A. ed., Springer Heidelberg Dondrecht London New York) 2012. Pages 413–436.

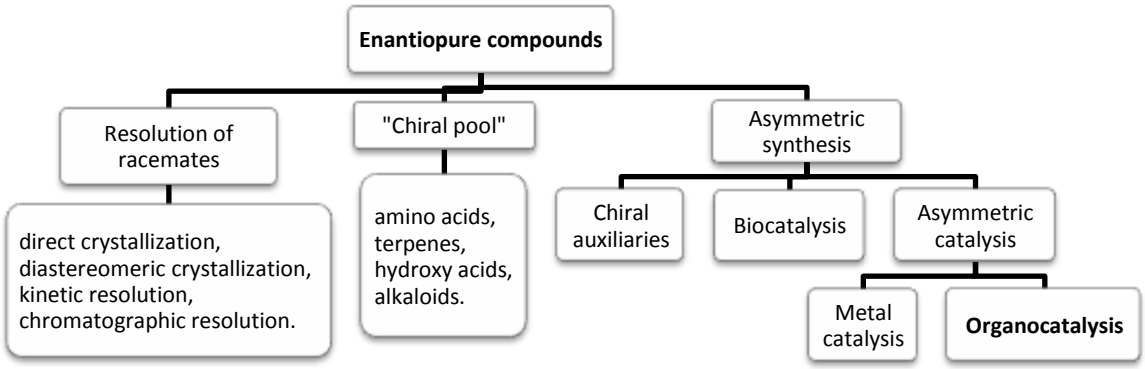
[4] a) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002,** *41***,** 1998–2007. For a review on the history of L-Dopa in the treatment of Parkinson's disease, see: b) García, P. J.; Meseguer, E. *Neurología* **2002**, *17*, 214–217. c) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Blaser, H.-U. & Federsel, H.-J. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2010. Pages 22–38.



Scheme 1. Synthesis of dopamine.

Nevertheless, optically pure pharmaceuticals may undergo racemization *in vivo*, canceling single enantiomer benefits or inducing unexpected effects, as it happened with thalidomide.[5]

Three basic strategies can be considered for obtaining enantiomerically pure compounds: a) the resolution of racemates, b) the use of optically active molecules (chiral building blocks), c) asymmetric synthesis. The proposed methods would enable the synthesis of chiral compounds for testing of biological activity and for studies on structure-activity relationships (SAR).[6]



Scheme 2. Methods to obtain enantiomerically pure compounds.

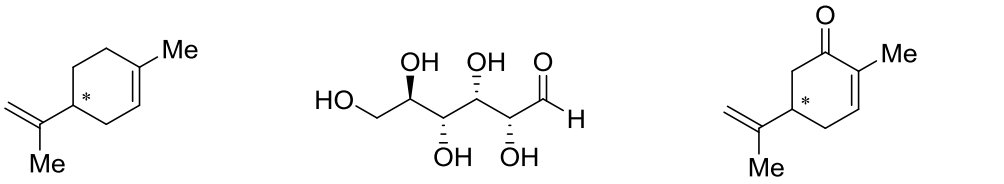
The resolution of racemates is the most classic method and the most attractive at an industrial level due to its operational simplicity. The main methods are crystallization,

[5] For more information about thalidomide, see: a) Kim, J. H.; Scialli, A. R. *Toxicol. Sci.* **2011**, *122*, 1–6. b) González, B.; Hernández, L. *Medicina Clínica* **2007**, *128*, 133–137. c) Maruotti, N.; Cantatore, F. P.; Ribatti, D. *Reumatismo* **2006**, *58*, 187–190.

[6] *Pharmaceutical Process Development: Current Chemical and Engineering Challenges* (Blacker, A. J. & M. T., ed., Royal Society of Chemistry: Cambridge) 2011.

chromatographic resolution, kinetic resolution and dynamic kinetic resolution.[7] The maximum yield is 50% in the first three methods, however, with the dynamic kinetic resolution,[8] which combines the kinetic resolution with an *in situ* racemization process, a single enantiomer can be obtained in quantitative yield.

The "chiral pool" strategy is based on the use of optically pure chiral natural compounds (amino acids, sugars, terpenes…), as starting substrates for the synthesis of the desired compound while maintaining the configuration of the initial stereogenic units (Figure 1).[9] This strategy is especially helpful if the desired molecule bears a great resemblance to cheap enantiopure natural products. On the contrary, this method may involve a long, tortuous synthesis with many steps and consequent losses in yield. At times, it may be difficult to find a suitable enantiopure starting material.



Limonene (both enantiomers available) | D-glucose | Carvone (both enantiomers available)

Figure 1. Selected examples of chiral natural compounds used in "chiral pool" strategy.

The third strategy for obtaining enantiomerically pure compounds is asymmetric synthesis.[10] This method consists in the stereoselective synthesis of chiral compounds from non-chiral compounds. The configuration of the new sterogenic centers generated

[7] For a review on resolution methods, see: a) N. G. Anderson, *Org. Proc. Res. Dev.* **2005**, *9*, 800–813. b) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 3974–4001. c) *Separation of Enantiomers: Synthetic Methods* (Todd, M. H. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2014.

[8] For a review of the subject, see: a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.,* **2001**, *30*, 321–331. b) *Asymmetric Organic Synthesis with Enzymes* (Gotor, V. & Alfonso, I. & García-Urdiales, E. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2009. Pages 87–113. c) *Chirality from Dynamic Kinetic Resolution* (Pellissier, H. ed., Royal Society of Chemistry) 2011.

[9] a) *Total Synthesis of Natural Products: The 'Chiron' Approach* (Hanessian, S. ed., J. E. Pergamon, Oxford, UK) 1983. a) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935–952. b) S. Hanessian, *Pure Appl. Chem.* **1993**, *65,* 1189–1204. c) Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5368–5373. d) Nugent, W. A.; Rajanbabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479–483. For a review on chiral pool in total synthesis of terpenes, see: e) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. *Chem. Rev.* **2017**, *117*, 11753–11795 and references therein.

[10] a) *Asymmetric Synthesis* (Aitken, R. A. & Kilényi, S. N. ed., Chapman & Hall. Cambridge) 1992 b) *Comprehensive Asymmetric Catalysis I-III* (Jacobsen, E. N. & Pfaltz, A. & Yamamoto, H. ed., Springer-Verlag Berlin Heidelberg New York) 2000. c) *Fundamentals of Asymmetric Catalysis* (Walsh, P. J. & Kozlowski, M. C., ed., University Science Books) 2009. d) *Asymmetric Synthesis Vol. I-II* (Christmann, M. & Bräse, S. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2012.

can be controlled by chiral auxiliaries, biocatalytic methods, or by non-enzymatic chiral catalysts (asymmetric catalysis).

Chiral auxiliaries are enantiomerically pure compounds that are linked to a substrate and influence the stereochemical course of a reaction (Figure 2).[11] The auxiliary is introduced prior to the stereoselective reaction and removed afterwards. These additional synthetic steps and the cost of stoichiometric amounts of auxiliary seem to render this approach rather unattractive.

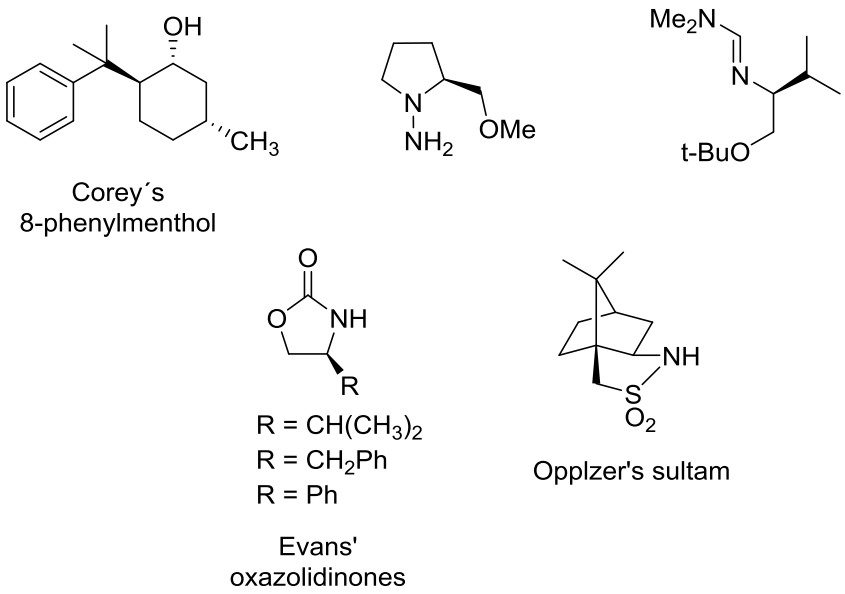


Figure 2. Selected examples of chiral auxiliaries.

Although powerful biocatalytic methods exist, their biomolecular homochirality often poses a problem when the “nonnatural” enantiomer of the product is desired.[12]

In the latter case, asymmetric catalysis, the stereochemistry of the reaction is controlled by a catalyst that induces chirality in a manner similar to enzymes: the "chiral

[11] For a leading review, see: a) Gnas, Y.; Glorius, F. *Synthesis* **2006**, *12*, 1899–1930. For a recent book, see: b) *Key Chiral Auxiliary Applications* (Roos, G. ed., Academic Press) 2014.

[12] For reviews on enzymatic desymmetrizations, see: a) García, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354. b) *Catalytic Asymmetric Synthesis* (Ojima, I. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2010. Pages: 269–342. For reviews on biocatalysis, see: c) Bornscheuer, U. T.; Huisman, G. W.; Kazlauskas, R. J.; Lutz, S.; Moore, J. C.; Robins, K. *Nature* **2012**, *485*, 185–194. d) Diaz, A.; Lavandera, I., Gotor, V. *Curr. Green Chem.* **2015**, *2*, 192–211. e) Albarrán, J.; González, D.; Gotor, V. *Biocatal. Biotransform.* **2018**, *36*, 102–130. For enzymatic asymmetric synthesis of chiral amino acids, see: f) Xue, Y.-P.; Cao, C.-H.; Zheng, Y.-G. *Chem. Soc. Rev*. **2018**, *47*, 1516–1561.

pocket" formed in the transition state favors the formation of one enantiomer against another. [13]

The two fundamental areas within asymmetric catalysis are organometallic catalysis, in which chirality is induced by a chiral organic ligand metal complex, and organocatalysis, in which chiral organic molecules are used as catalysts.

1.1.2. Milestones in catalytic asymmetric reactions

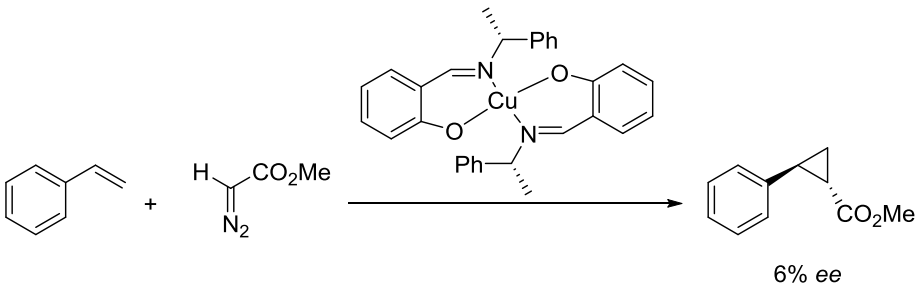
The first catalytic asymmetric reaction was carried out on a racemic mixture (kinetic resolution) in an enzymatic reaction performed by Louis Pasteur in 1858. The organism Penicillium glauca consumed (D)-ammonium tartrate faster from a solution of a racemic (DL)-ammonium tartrate.[14] In the coming years, many researches tried to prepare optically active compounds, but these attempts to generate enantiomercally enriched products were still performed by fermentation in presence of a microorganism. In 1908, Rosenthaler reported the synthesis of optically active mandelonitrile by addition of HCN to benzaldehyde and catalized by emulsin, an enzyme extracted from bitter almonds.[15]

From 1960s to the end of the XX century, organometallic catalysts[16] became the most actively studied homogeneous catalysts, culminating in the award of Nobel Prizes to Noyori, Sharpless and Knowles in 2001.[17] By taking advantage of d orbitals of the transition metals used (Fe, Cu, Pd...), these catalysts can activate substrates and accelerate reactions through coordination, insertion, ligand exchange etc., and lead to the formation of C–H and C–C bonds. In this manner, the revelation that substoichiometric amounts of transition metals in combination with same amount of chiral ligand promoted stereoselective reactions entailed a revolution in organic synthesis.

In the 1960s, significant achievements were carried out in the field of asymmetric organometallic catalysis. In 1966 Nozaky and Noyori reported the cyclopropanation of alkenes using a salen-copper complex as a chiral catalyst. The enantiomeric excess of the

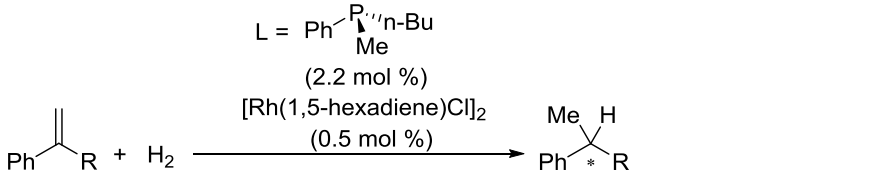
[13] a) *Asymmetric Catalysis in Organic Synthesis* (R. Noyori ed., John Wiley & Sons) **1993**. For catalysis: concepts and green applications, see: b) *Catalysis* (Rothenberg, G. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2008. Asymmetric catalysis in complex target synthesis: c) Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5368–5373. d) *Catalytic Asymmetric Synthesis* (Ojima, I. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2010. e) *Principles of Asymmetric Synthesis (*Gawley, R. E. & Aubé, J. ed., Elsevier Ltd.) 2012.
[14] Pasteur, L. *Compt. Rend. Acad. Sci*. **1858**, *46*, 15.
[15] Rosenthaler, L. *Biochem Z*. **1908**, *14*, 238–253.
[16] *Fundamentals of Organometallic Catalysis* (Steinborn, D. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2011.
[17] Ault, A. *J. Chem. Educ.* **2002**, *79*, 572–577.

resulting adducts did not surpass 6% *ee*. Despite these low values, further research started in this area (Scheme 3).[18]



Scheme 3. Cyclopropanation of alkenes using a salen-copper chiral catalyst.

Thanks to the milestone paper of Wilkinson´s group in 1966,[19] which established the feasibility of homogeneous hydrogenation of alkenes with $RhCl(PPh_3)_3$ as the catalyst precursor, huge developments were achieved in the field of asymmetric hydrogenation.[20] Researchers focused on introducing chiral ligands around rhodium and in 1968, Horner[21] and Knowles[22] independently reported the use of optically active (–) methylpropylphenylphosphine as the chiral ligand in the asymmetric reduction of α-ethylstyrene and α-phenylacrylic acid respectively (Scheme 4). Although the outcome of these reactions were rather poor (<15% *ee*), these works established the possibility of transforming the Wilkinson catalyst into a chiral rhodium catalyst.



Scheme 4. Asymmetric reduction α-ethylstyrene and α-phenylacrylic acid.

[18] a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *43*, 5239–5244. Later, Aratani was able to rich high level of enantioselectivities tuning the structure of the copper catalyst: b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, *21*, 1707–1710. For a leading review on stereoselective cyclopropanation reactions, see: c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.*, **2003**, *103*, 977–1050. For a review on metal-salen complexes, see: d) Cozzi, P. G. *Chem. Soc. Rev.,* **2004**, *33*, 410–421. For more examples on asymmetric cyclopropanations, see: *Asymmetric Synthesis of Three-Membered Rings* (Dalpozzo, R. & Lattanzi, A. & Pellissier, H. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2017.

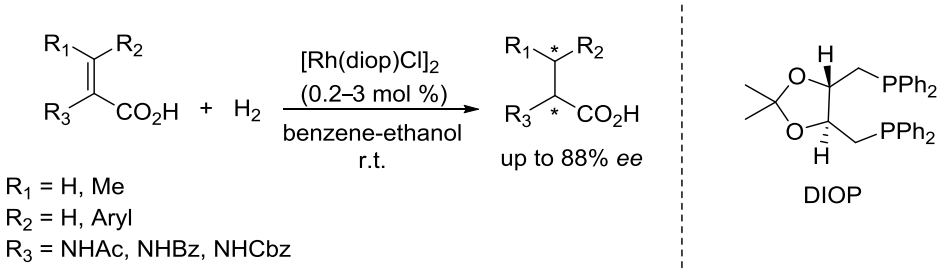
[19] a) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A: Inorg. Phys. Theor.* **1966**, 1711–1732. b) *Inorganic Syntheses, Vol. 28* (Angelici, R. J. ed., John Wiley & Sons) 1990. Pages 77–79.

[20] a) *Science of Synthesis: Stereoselective Synthesis, Vol. 2* (Molander, G. A. ed., Georg Thieme Verlag KG) 2011. Pages 9–57. b) *Comprehensive Chirality, Vol. 5* (Carreira, E. M. & Yamamoto, H. & Maruoka, K. ed., Elsevier) 2012. Pages 246–317.

[21] Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem. Int. Ed.* **1968**, *7*, 942.

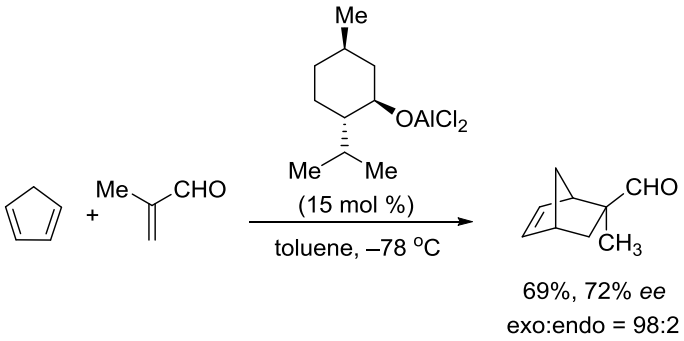
[22] a) Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445–1446. For a review, see: b) Knowles W. S.; Noyori, R. *Acc. Chem. Res.* **2007**, *40*, 1238–1239.

In the early 1970s, Kagan[23] introduced for the first time C2-symmetric a chelating chiral diphosphine named DIOP generating an excellent rhodium dimer catalyst, which was able to give very good enantioselectivities (up to 88% *ee*) in an asymmetric catalytic hydrogenation. The chiral conformation of the chelate ring induced a preferential chiral array of the phenyl rings on phosphorus, enhancing the asymmetric induction (Scheme 5).



Scheme 5. Asymmetric catalytic hydrogenation.

In 1979, Koga reported a pioneering work in the chiral Lewis-acid promoted Diels-Alder (DA) reaction,[24] in which the first catalytic asymmetric reaction proceeding in moderate enantio- and excellent *exo* selectivity was described. The chiral catalyst (–) menthoxyaluminium dichloride, prepared form $EtAlCl_2$ and menthol, promoted the DA reaction of methacrolein and cyclopentadiene obtaining an enantiomeric excess of 72%. Though several chiral ligands containing the cyclohexyl moiety were studied, higher enantioselectivities were not achieved (Scheme 6).



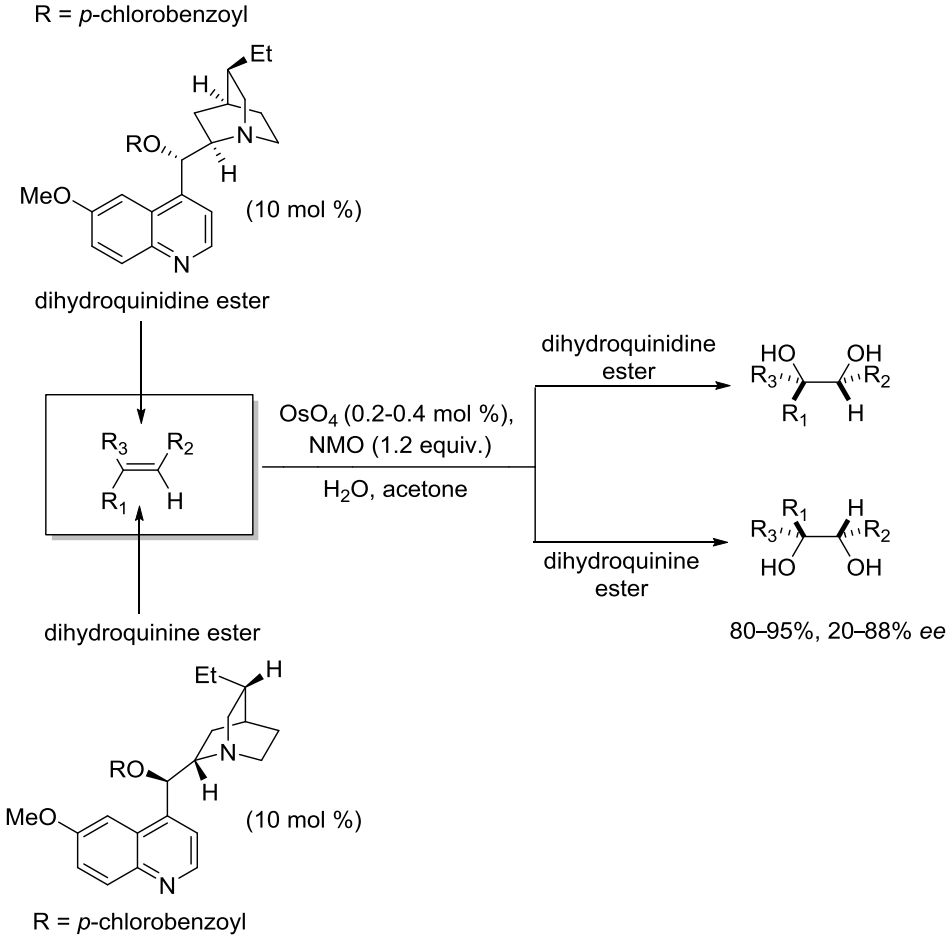
Scheme 6. Chiral Lewis-acid promoted DA reaction.

The 1980s meant an impressive progress in the area of the asymmetric organometallic catalysis. In 1988, Sharpless achieved an asymmetric dihydroxylation of alkenes using

[23] a) Dang, T. P.; Kagan, H. B. *Chem. Commun.* **1971**, 481. b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433. c) *Modern Rhodium-Catalyzed Organic Reactions* (Evans, P. A. ed., Wiley-VHC Verlag GmbH & Co. KGaA) 2005. Pages 1–31. d) *Hydrogenation* (Karamé, I. ed., InTech) 2012.

[24] a) Hashimoto, S.-I.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437–438. For leading books about cycloaddition reactions in organic synthesis, see: b) *Cycloaddition Reactions in Organic Synthesis* (Kobayashi, S. & Jørgensen, K. A. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2001. c) *Handbook of Cyclization Reactions Vol. 1* (Ma, S. ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim) 2010.

substoichiometric amounts of OsO_4 and a catalytic amount of chiral cinchona alkaloid derived ligand, stoichimetric amounts of *N*-methyl morpholine *N*-oxide (NMO) being the secondary and less toxic oxidant to regenerate the OsO_4 catalyst (Scheme 7).[25]



Scheme 7. Asymmetric dihydroxylation of alkenes.

In the late 1980s through the early 1990s started the study of bisoxazoline ligands.[26] These privileged chiral ligands, containing two oxazoline rings, are the most useful ligand classes for asymmetric catalysis due to their capability to coordinate efficiently with a broad amount of transition metals (Cu, Fe, Mg, Zn…). The resulting chiral ligands possess

[25] a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. For a review on catalytic asymmetric dihydroxilation, see: b) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. c) *Transition Metals for Organic Synthesis* (Beller, M. & Bolm, C. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2004. Pages 275–307. d) *Stereoselective Synthesis 1, Stereoselective Reactions of Carbon-Carbon Double bonds* (de Vries, J. G. ed., Thieme) 2011. Pages 5–67.

[26] For the first synthesis of chiral bisoxazoline ligands, see: a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005–6008. b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373–7376. For reviews on chiral bisoxazolines, see: c) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590. d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325–335. e) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, 104, 4151–4202. f) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651. g) Rasappan, R.; Laventine, D.; Reiser, O. *Coord. Chem. Rev.* **2008**, *252*, 702–714. h) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2011**, *111*, PR284–PR437.

C_2 symmetry, a characteristic that has proven most beneficial in designing asymmetric processes because of the reduction of possible reaction pathways caused by the equivalency of structures upon rotation by 180° (Figure 3).[27]

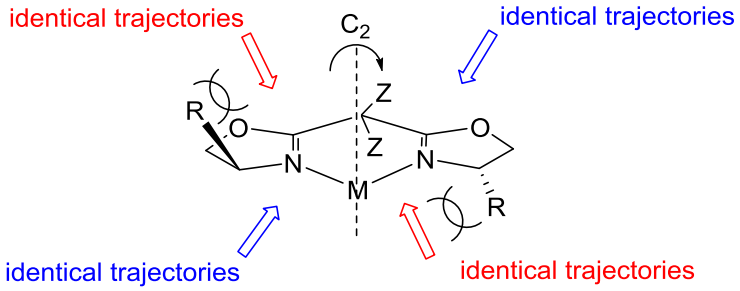
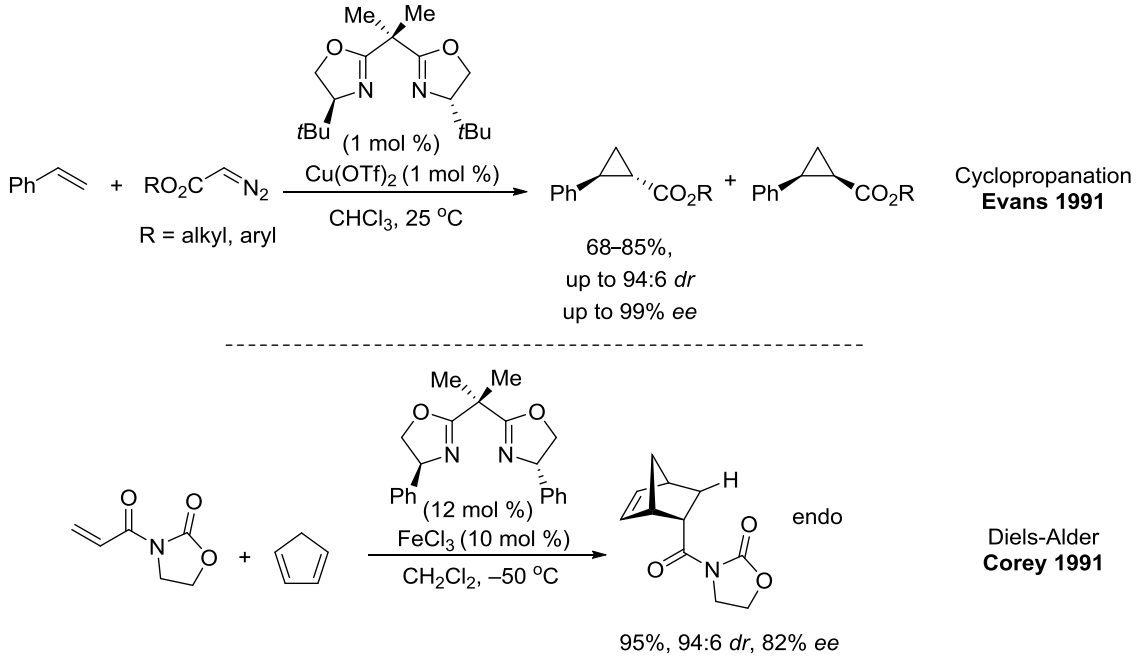


Figure 3. C_2-symmetrical metal-bis(oxazoline) complexes. Blue→Allowed trajectories.

The groups of Evans[28] and Corey[29] in back-to-back communications reported the synthesis and utility of bisoxazoline ligands bearing a fully substituted spacer unit (Scheme 8). Since then, these types of scaffolds have become heavily studied in the literature on the application of bisoxazoline ligands in asymmetric catalysis.



Scheme 8.

Traditionally, the most prominent chiral ligands in enantioselective transition-metal catalysis are shown in Figure 4.

[27] a) Pfaltz, A.; Drury, W. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5723–5726. b) *Privileged Chiral Ligands and* Catalysts (Zhou, Q.-L. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2011. Pages 171–220.
[28] Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726–727.
[29] Corey E. J.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729.

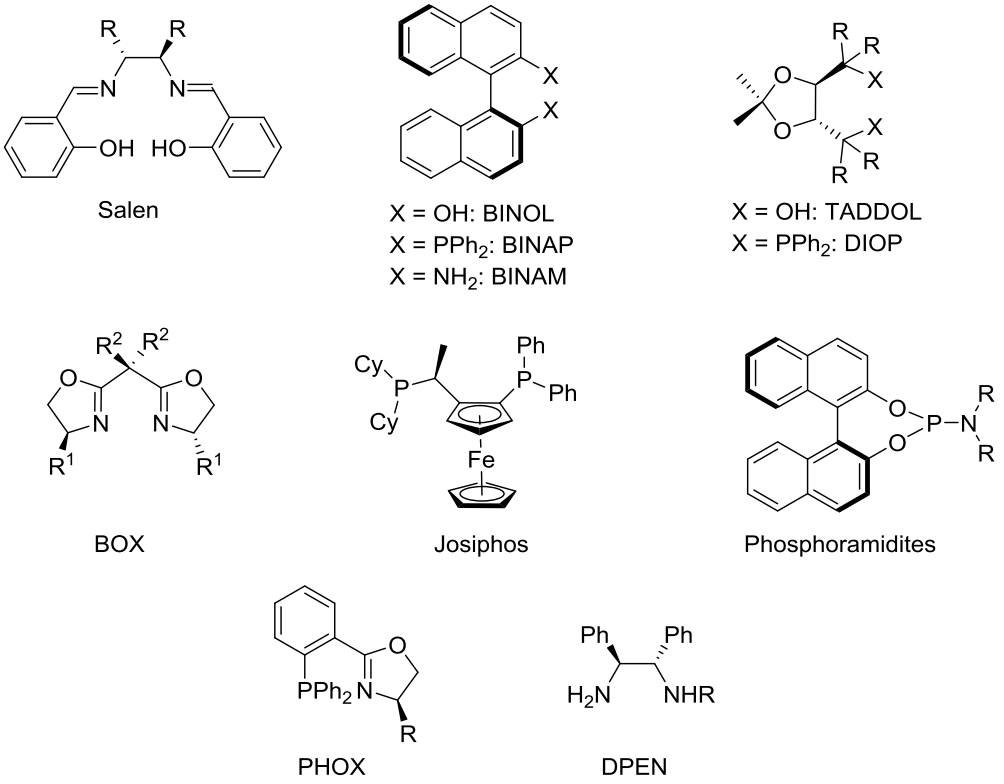


Figure 4. Selected examples of chiral ligands.

For many decades organocatalysis has been eclipsed by the successful transition-metal catalysis. The urge to reduce energy consumption, protect the environment and conserve natural resources boosted the research of chiral metal-free catalysts in the late 1990s. Organocatalytic methods seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination, e. g. pharmaceutical products.[30] This fact has changed the map of catalysis and many organic reactions are now carried out with organocatalysts.

1.1.3. Organocatalysis

Organocatalysis can be defined as the acceleration of chemical reactions with a substoichiometric amount of an organic compound, which does not contain any metallic atom. This activation path has become a very active field in organic synthesis showing several significant advantages over conventional organometallic catalysis. The reasons for this interest are firstly the ease of handing, dry conditions and inert atmosphere

[30] For reviews on toxicity of metal compounds, see: a) Egorova, K. S.; Ananikov, V. P. *Angew. Chem. Int. Ed.* **2016**, 55, 12150–12162. b) Egorova, K. S.; Ananikov, V. P. *Organometallics* **2017**, *36*, 4071–4090. For advances on steroelective organocatalytic reactions. Organocatalytic synthesis of natural products and drugs, see: c) *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications* (Gruttadauria, M. & Giacalone, F. ed., John Wiley & Sons, Inc.) 2011. d) For a review on toxicity of metal-free catalysts, see: e) Nachtergael, A.; Coulembier, O.; Dubois, P.; Helvenstein, M.; Duez, P.; Blankert, B.; Mespouille, L. *Biomolecules* **2015**, *16*, 507–514.

usually not being required, and secondly the availability of cheap catalysts normally in both enantiomeric forms.[31]

In general, organocatalysts provide a chiral environment in the activation of the nucleophile or the electrophile or both at the same time through interactions that can be weak, as in the case of noncovalent activation (hydrogen bonding and ionic pair catalysis),[32] or strong as in covalent bond mediated activation,[33] e. g. in the case of iminium ion[34] and enamine activation.[35]

In 1912, Bredig reported the first nonenzymatic enantioselective catalytic reaction using pseudoenantiomeric bifunctional cinchona alkaloids, quinine and quinidine, in the preparation of mandelonitrile from benzaldehyde and hydrogen cyanide (Scheme 9). The enantioselectivities of the resulting adducts were less than 10%, however the importance of this reaction is conceptually revolutionary.[36]

[31] These reasons are not sufficient to claim the superiority of this approach since metal catalyzed and organocatalyzed reactions are often complementary providing in many cases different optically active compounds.

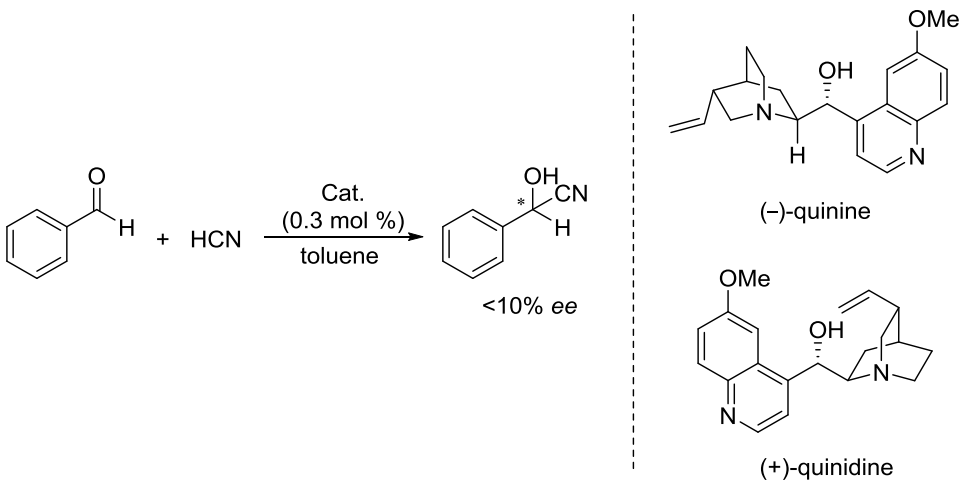
[32] For a general review on the asymmetric catalysis mediated by hydrogen bonds, see: a) Yu, X.; Wang, W. *Chem.-An Asian J.* **2008**, *3*, 516–532. b) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20678–20685.

[33] For a review on asymmetric covalent catalysis, see: Abbasov, M.; Romo, D. *Nat. Prod. Rep.* **2014**, *31*, 1318–1327.

[34] For general reviews on iminium ion catalysis, see: a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79–87. b) Pihko, P. M.; Majander, I.; Erkkila, A. *Chem. Rev.* **2007**, *107*, 5416–5470. c) Bartoli, G.; Melchiorre, P. *Synlett*, **2008**, *12*, 1759–1772. d) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281–347. e) *Lewis base catalysis in Organic Chemistry* (Vedejs, E. & Denmark, S. E. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2016. Pages 805–856.

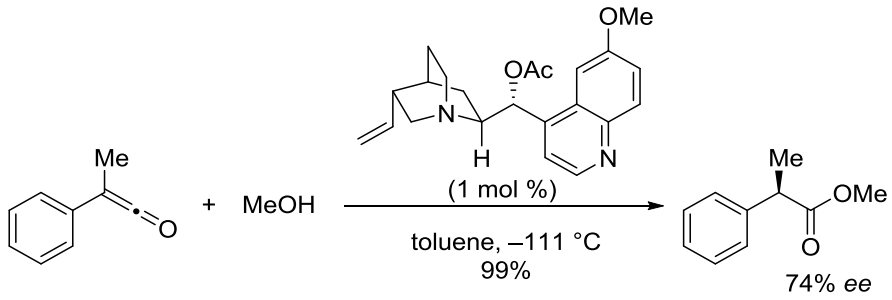
[35] For general reviews on enamine catalysis, see: a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. b) Pihko, P. M.; I. Majander, I.; Erkkila, A. *Top. Curr. Chem.* **2010**, *291*, 29–75. c) Lewis base catalysis in Organic Chemistry (Vedejs, E. & Denmark, S. E. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2016. Pages 857–902.

[36] Bredig, G.; Fiske, P. S. *Biochem. Z*. **1912**, *46*, 7–23.



Scheme 9. First nonenzymatic enantioselective catalysis.

Almost 50 years later, Pracejus developed the first organocatalytic reaction with an acceptable enantioselectivity (74% *ee*).[37] He reported the methanolysis of phenyl methyl ketene to afford (⁻)-α-phenyl methylpropionate by using *O*-acetyl quinine as catalyst (Scheme 10). It should be noted that low temperature was needed to carry out the reaction more or less efficiently.



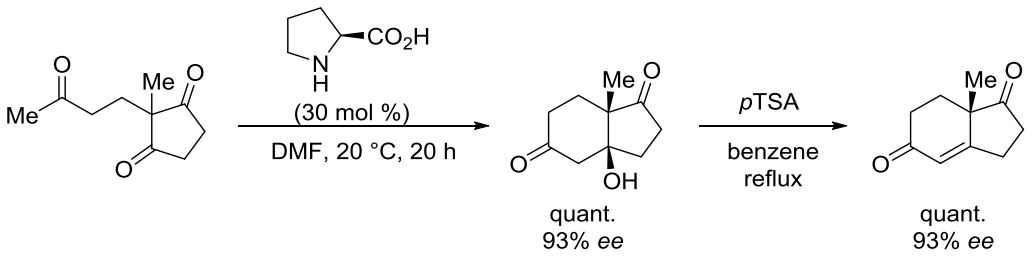
Scheme 10. Methanolysis of phenyl methyl ketene using *O*-acetyl quinine as catalyst.

An important milestone in this area of organocatalysis was the intramolecular aldol reaction catalized by L-proline reported in the early 1970s by the groups of Hajos and Parrish, and Ender, Sauer and Wiechert independently (Scheme 11).[38] This reaction allowed a useful and enantioselective route to the Wieland-Miescher ketone.[39] Moreover, intermediates that are key in the synthesis of some natural products can be obtained.

[37] Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.

[38] a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. For the first moderate asymmetric Robinson-annulation based on the proline-derived enamines, see: c) Yamada, S.; Otani, G. *Tetrahedron Lett.* **1969**, *10*, 4237–4240.

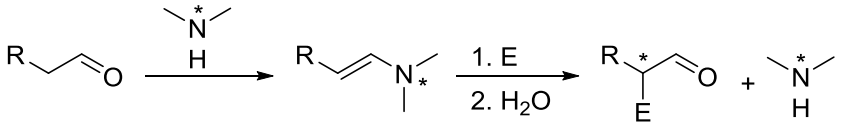
[39] a) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215–2228. For a review concerning the utility of this ketone, see: b) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *23*, 337–356.



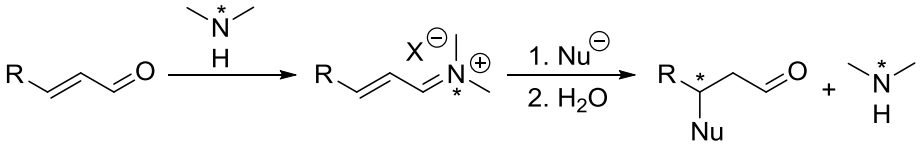
Scheme 11. Intramolecular aldol reaction catalized by L-proline.

The beginning of the twenty first century brought great contributions in the area of organocatalysis with the works of List, Lerner and Barbas III concerning the direct aldol reaction via enamine activation[40] and the work of MacMillan on Diels-Alder reactions via iminium activation[41] opening the way (Scheme 12).

Enamine activation



Iminium ion activation



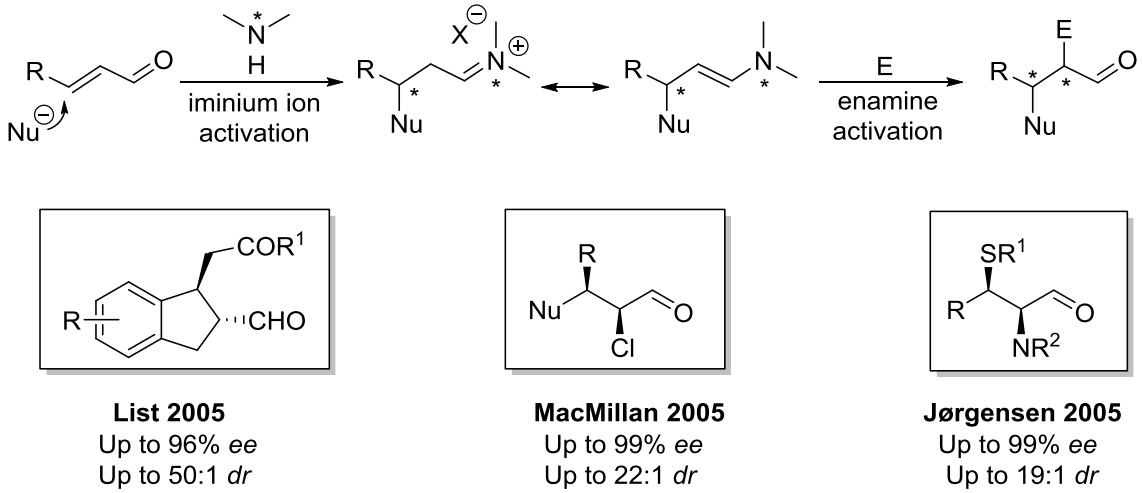
Scheme 12. Iminium ion and enamine activation.

Apart from the pioneering results depicted above, outstandig examples via iminium ion activation include: the Friedel-Crafts reaction to enals by MacMillan in 2001,[42] the selective reduction of enals by List[43] and MacMillan[44] in 2005, and the conjugated amination of enals by MacMillan in 2006.[45] Enamine activation also accomplished further examples: the α-oxidation of enolizable aldehydes using oxygen singlet by Córdova in 2004,[46] the α-chlorination and sulfenilation of aldehydes by Jørgensen in

[40] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[41] a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244. For the first example on iminium ion-activation, see: b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed.* **1993**, *32*, 1176–1178. c) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805–8808.
[42] Paras, N. a; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
[43] Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110.
[44] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.
[45] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.
[46] Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915.

2004 and 2005 respectively, [47] and the first Michael addition of aldehydes to nitroolefins by Hayashi in 2005.[48]

Furthermore, both activation modes have also been combined for the consecutive formation of multiple stereocenters, as in the case of the first iminium ion/enamine tandem reactions by List,[49] MacMillan[50] and Jørgensen[51] reported almost at the same time in 2005 (Scheme 13); and the multicomponent organocatalyzed Michael/Michael/aldol condensation by Enders in 2006.[52] Through this methodology highly functionalized complex structures were synthesized in a one-pot reaction in excellent diastereo- and enantioselectivities.



Scheme 13. Domino iminium ion-enamine catalyzed reaction.

Other covalent activation modes have been developed and explored with success, including: asymmetric phospine catalysis,[53] acylammonium catalysis,[54] acylammonium

[47] For the α-chlorination of aldehydes with NCS, see: a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791. For the α-sulfenilation of aldehydes with 1-(benzylsulfanyl)-1,2,4-triazole b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.

[48] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

[49] Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.

[50] Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

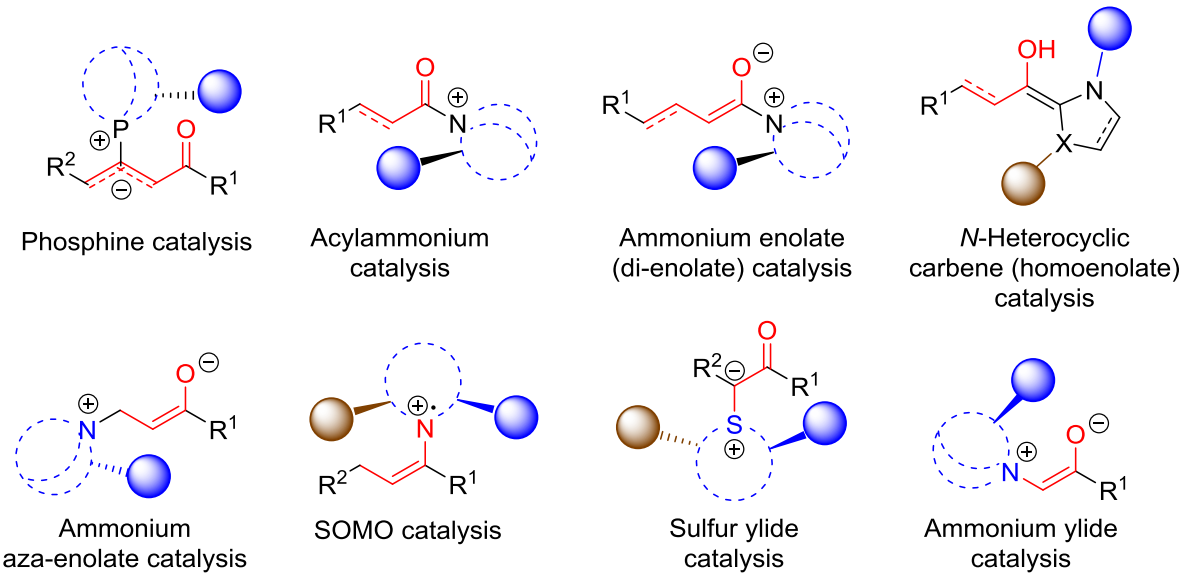
[51] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.

[52] a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. For a review concerning multicomponent and sequential organocatalytic reactions, see: b) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712–7722. For a review on enantioselective organocatalyzed domino synthesis of six-membered carbocycles, see: c) Goudedranche, S.; Raimondi, W.; Bugaut, X.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Synthesis* **2013**, *45*, 1909–1930.

[53] a) Wei, Y.; Shi, M. *Acc. Chem. Res*. **2010**, *43*, 1005–1018. b) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014,** *10,* 2089–2121.

[54] Müller, C. E.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042.

enolate (di-enolate) catalysis,[55] *N*-heterocyclic carbene catalysis (NHC),[56] ammonium aza-enolate catalysis,[57] SOMO catalysis,[58] sulphur ylide catalysis[59] and ammonium ylide catalysis[60] (Scheme 14).



Scheme 14. Activation modes in covalent asymmetric catalysis.

On the other hand, in noncovalent catalysis the interaction between the chiral catalyst and the substrate is established through weak interactions, such as: phase-transfer catalysis (PTC),[61] chiral anion catalysis[62] and hydrogen-bonding catalysis[63] (Figure 5).

[55] a) Morril, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214–6226. b) Vellalath, S.; Romo, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 13934–13943.

[56] a) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485–496. b) Janssen–Müller, D.; Schlepphorst, C.; Glorius, F. *Chem. Soc. Rev.* **2017**, *46*, 4845–4854. c) Zhang, C.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583–2596. d) Murauski, K. J. R.; Jaworski, A. A.; Scheidt, K. A. *Chem. Soc. Rev.* **2018**, *47*, 1773–1782.

[57] a) *The Chemistry of the Morita-Baylis-Hillman Reaction* (Shi, M. & Wang, F. & Zhao, M.-X. & Wei, Y. ed., RSC Publishing) 2011. b) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659–6690.

[58] a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585. For a recent review, see: b) Mečiarová, M.; Tisovský, P.; Šebesta, R. *New. J. Chem.* **2016**, *40*, 4855–4864. For a recent enantioselective catalytic β-alkylation of enals by UV excitation of iminium ions, see: c) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzeti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868–873.

[59] a) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611–620. b) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Dalko, P. I. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2013. Pages 548–565.

[60] Jiang, K.; Chen, Y.-C. *Tetrahedron Lett.* **2014**, *55*, 2049–2055.

[61] a) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393. For information on asymmetric phase transfer catalysis, see: b) *Asymmetric Phase Transfer Catalysis* (Maruoka, K. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2008. c) Schörgenhumer, J.; Tiffner, M.; Waser, M. *Beilstein J. Org. Chem.* **2017**, *13*, 1753–1769.

[62] a) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4195. b) Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518–533. c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603–614.

[63] For a dual hydrogen bonding, see: a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. b) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59*, 216–223.

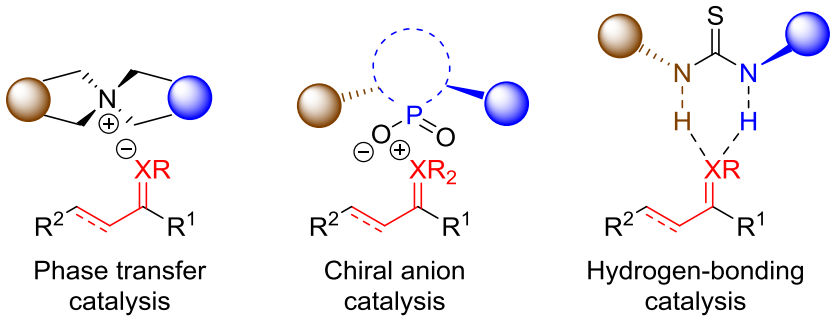


Figure 5. Activation modes in non-covalent asymmetric catalysis.

In recent years, many efforts have been directed towards the development of more efficient organocatalytic asymmetric reactions through the use of several strategies. Two of them have been the development of more active organocatalysts and the development of new efficient pronucleophiles to be deprotonated under mild enolization conditions.

1.1.3.1. Search of more active organocatalysts

The desire of developing efficient synthetic methods encourage chemists to design novel catalysts with high activity and atom economy under environmentally benign conditions. Much effort has been done in the search of new multifunctional organocatalysts,[64] molecules possessing two, or more, distinct functional groups ofLewis base,[65] Lewis acid,[66] Brønsted base,[67] and Brønsted acid[68] character to activate the substrates simultaneously in a controlled chiral environment. Multifunctional catalysis was first described by Shibasaki and coworkers,[69] as an approximate strategy adopted from biomolecular catalysts in nature. This strategy has been applied mainly to polar addition reactions involving of nucleophile and an electrophile reagent (polar reactivity).

[64] a) *Asymmetric Multifunctional Catalysis* (Yu, J.-S. & Zhou, J. ed., John Wiley & Sons) 2014. b) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655–663. c) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051–7071. d) *Multicatalyst System in Asymmetric Catalysis* (Zhou, J. ed., John Wiley & Sons, Inc.) 2015.

[65] *Lewis Base Catalysis in Organic Synthesis* (Vedejs, E. & Denmark, S. E. ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany) 2016. Pages 1215–1258.

[66] *Lewis Acids in Organic Synthesis, Vol. 1-2* (Yamamoto, H. ed., Wiley-VCH Verlag GmbH) 2000.

[67] For a review about chiral Brønsted bases in asymmetric organocatalysis, see: a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. b) *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis and Additional Topics* (Maruoka, K. ed., Thieme, Stuttgart), 2012. c) *Asymmetric Organocatalysis: Vol. 291* (List, B. ed., Springer) 2012.

[68] a) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277–9306. b) Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142–1158. c) Carlone, A.; Bernardi, L. *Org. Chem. Front.* **2017**, *4*, 1651–1654.

[69] Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2210.

Based on the way that multiple functional groups interplay, multifunctional catalysis can be split into four categories (Figure 6): (1) cooperative activation, namely the simultaneous activation of both nucleophile and electrophile by two functional groups of the catalyst; (2) double activation, that is, the concerted activation of a substrate by both functional groups; (3) assisted activation, namely one functional group was assisted by the other to enhance its capacity to activate the substrate; (4) synergistic activation,[70] where at least two different catalysts act on two different substrates simultaneously to allow reaction between the two activated molecules. In cases 1 and 4, the simultaneous LUMO lowering of the electrophile and the HOMO raising of the nucleophile maximize the energetic efficiency of these systems.

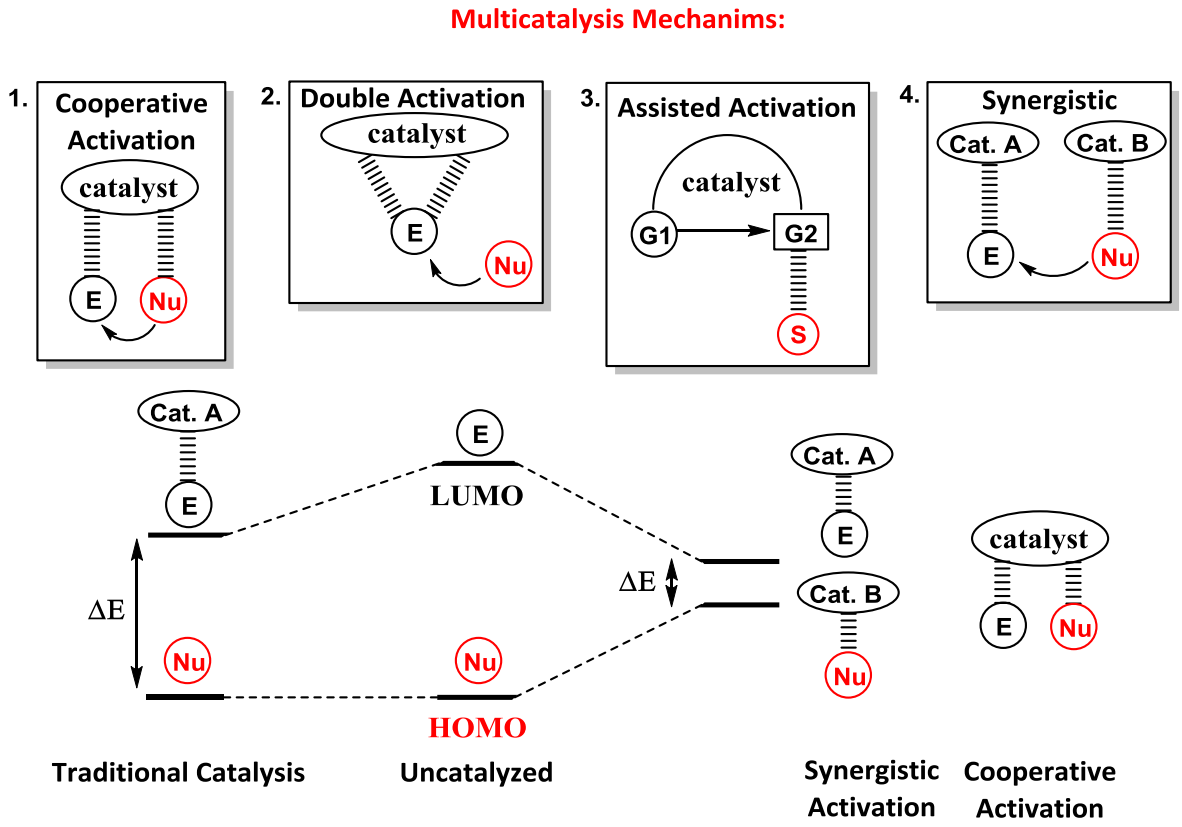


Figure 6. A clasification of multifunctional catalysis with the underlying activation model.

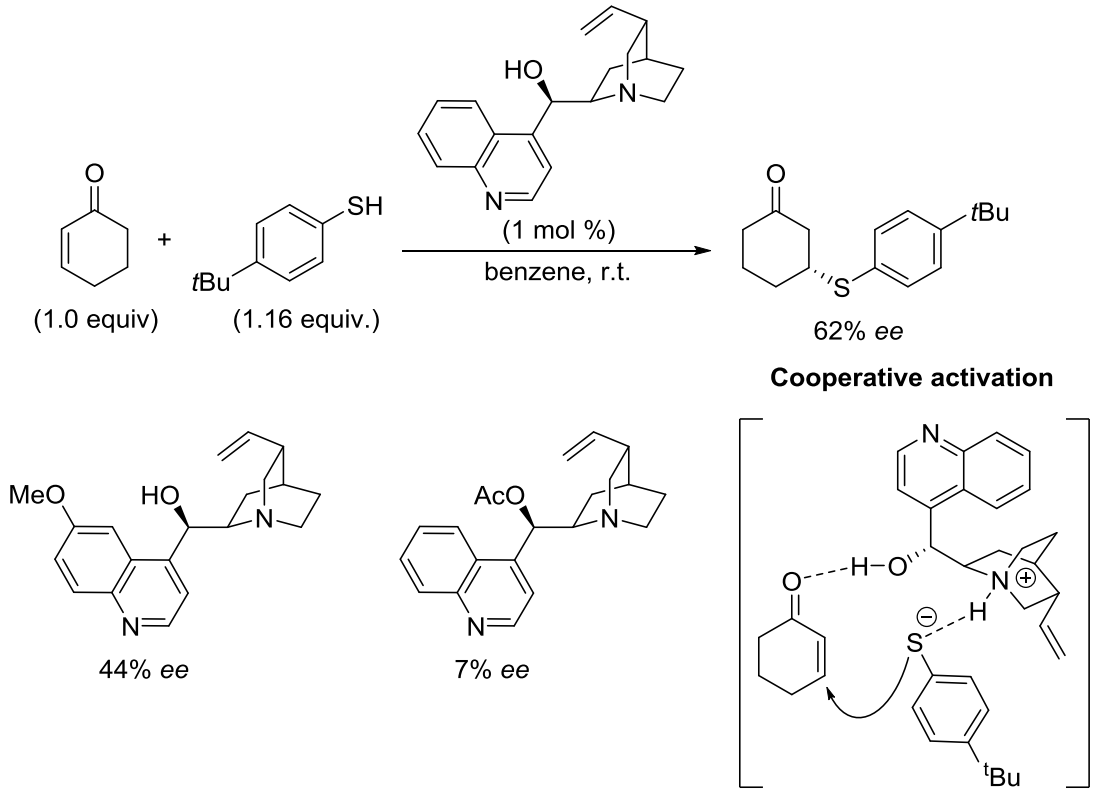
The cooperation model is the most common activation pattern for multifunctional catalysis.[71] An early example, with control experiments to show the role of catalyst functionality, was reported in 1981 by Wynberg[72] who described the cinchonidine

[70] a) Allen, A. E.; MacMillan D. W. C. *Chem. Sci.* **2012**, *3*, 633–658. b) Delaney, J. P.; Brozinski, H. L.; Henderson, L. C. *Org. Biomol. Chem.* **2013**, 11, 2951–2960. c) Afewerki, S.; Córdova, A. *Chem. Rev.* **2016**, *116*, 13512–13570.

[71] a) L.-Q. Lu; X.-L. An; J.-R. Chen; W.-J. Xiao. *Synlett* **2012**, 490–508. b) *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis* (Peters, R. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2015.

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

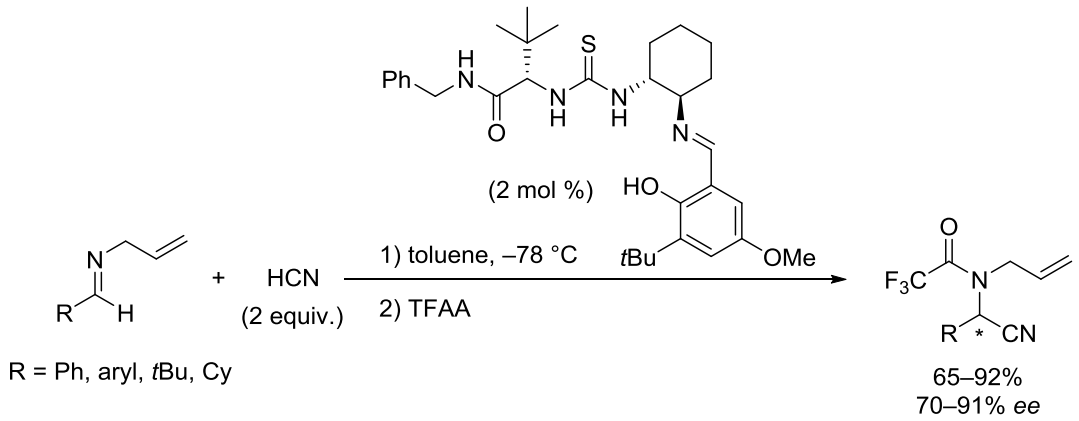
catalyzed asymmetric Michael addition of benzenethiols to cyclic enones to afford the desired product in 62% ee. The hydroxyl group of the catalyst had great influence on the stereocontrol, as quinine afforded the Michael adduct in higher *ee* value than the corresponding *O*-acylated quinine (Scheme 15).



Scheme 15.

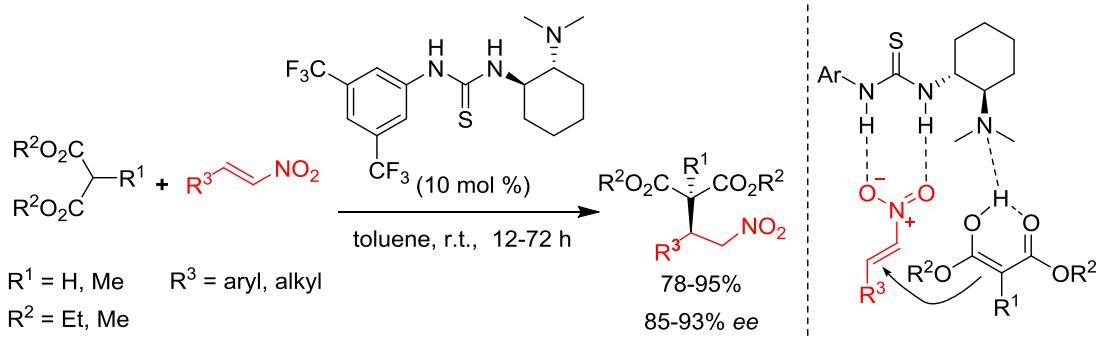
In 1998, Jacobsen utilized chiral thioureas as hydrogen bond donor organocatalysts for the first time in the hidrocyanation of aldimines (from both aromatic and aliphatic aldehydes) (Scheme 16).[73] It should be noted that the two hydrogens of the urea and the phenol hydrogen are essential for optimal catalyst activity.

[73] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902. For a mechanistic analysis, see: b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.



Scheme 16. Strecker reaction catalyzed by a chiral Brønsted acid.

More recently, Takemoto´s group[74] described the first bifunctional Brønsted base/thiourea (H-bond) type organocatalyst and applied it in a highly enantioselective Michael addition of dimethyl malonates to nitroolefins (Scheme 17). The reaction mechanism proposed by the authors involves the cooperative formation of a trimolecular transition state complex where the nitroalkene interacts with the thiourea group by means of two hydrogen bonds and the dimethylamino group promotes the activation of the nucleophile by deprotonation.



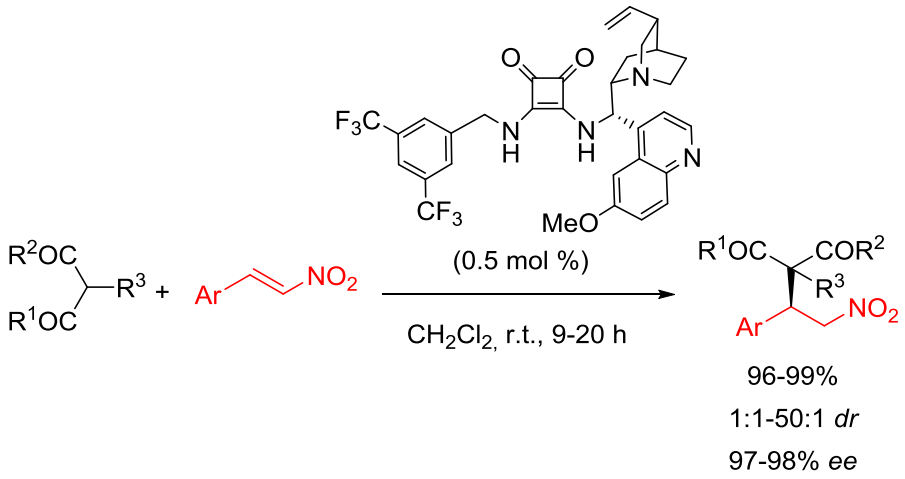
Scheme 17. Enantioselective Michael addition catalyzed by Brønsted base/thiourea type bifunctional organocatalyst.

As a result of the demonstrated compatibility of tertiary amine-(thio)urea bifunctional catalyst shown by Takemoto, the combination of new Brønsted base/Hydrogen bond donor chiral catalysts such as thiourea/cinchona alkaloids has expanded rapidly and applied effectively in a vast number of asymmetric reactions.[75]

[74] a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673. Chen's group determined the effectiveness of bifunctional catalysis using Takemoto's thiourea in the enantioselective Michael reaction between aromatic thiols and carbonylic α,β-unsaturated compounds: b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, *4*, 603–606.

[75] a) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510. For a recent review on Brønsted base/thiourea bifunctional catalysts, see: b) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197. c) Singh, G.; Yeboah, E. *Rep. Org. Chem.* **2016**, *6*, 47–75.

A significant milestone in this kind of bifunctional asymmetric cooperative catalysis (Brønsted base/hydrogen bond) took place in 2008 when Rawal first introduced the squaramide derivatives as excellent hydrogen bond donors in the reaction between active methylenes and nitroalkenes (Scheme 18). The corresponding Michael adducts were obtained with excellent yields and enantiomeric excesses and diastereoselectivities ranging from poor to excellent.[76]



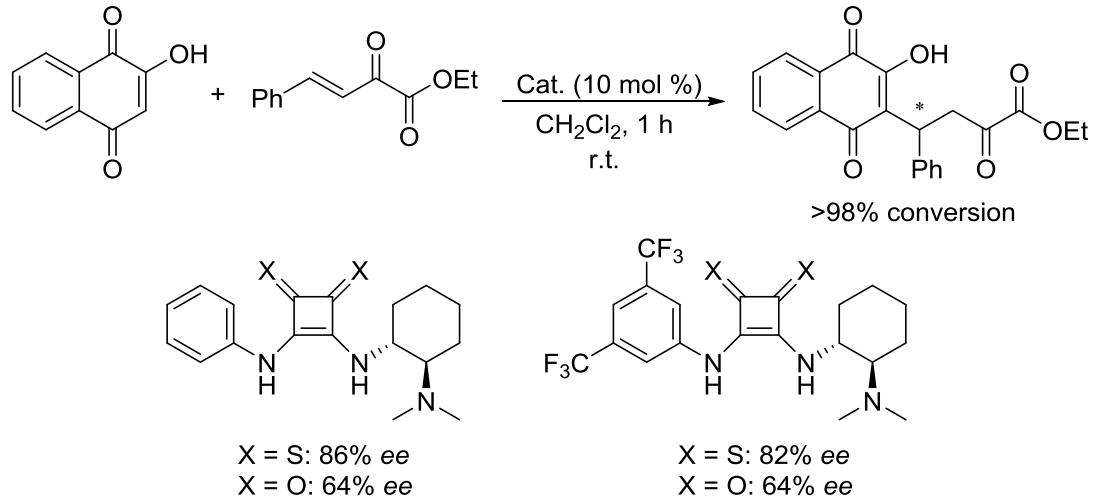
Scheme 18. Enantioselective Michael addition catalyzed by squaramide bifunctional organocatalyst.

Further advance in this area has been the development of highly active bifunctional thiosquaramides which appear to be more reactive than the parent squaramides.[77] For instance, with these new catalysts, same reactivity, but better enantioselectivities than their corresponding oxosquaramide has been achieved in the conjugated addition reaction of lawsone to a β,γ-unsaturated α-keto ester (Scheme 19). [78]

[76] a) Malerich, J. P.; Hagihara, K.; Rawal, V. R. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. b) Zhu, Y.; Malerich, J. P.; Rawal, V. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156. For reviews on squaramide catalysis, see: c) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346. d) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899. e) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253–281.

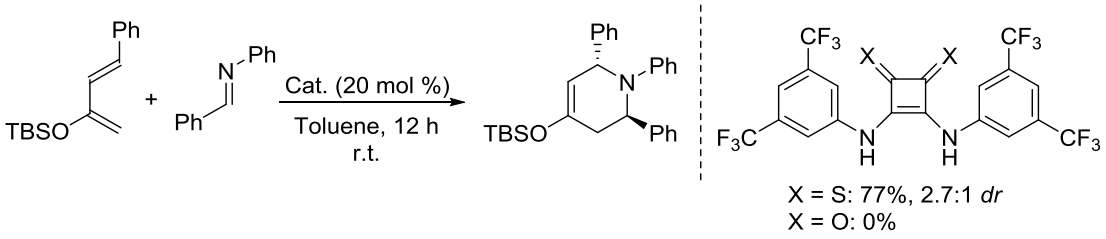
[77] a) Rombola, M.; Sumaria, C. S.; Montgomery, D.; Rawal, V. H. *J. Am. Chem. Soc.* **2017**, *139*, 5297–5300. For the superior performance of (thio)squaramides over (thio)ureas in organocatalysis, see: b) Lu, T.; Wheeler, S. E. *Chem. Eur. J.* **2013**, *19*, 15141–15147.

[78] Rombola, M.; Rawal, V. H. *Org. Lett.* **2018**, 20, 514–517.



Scheme 19.

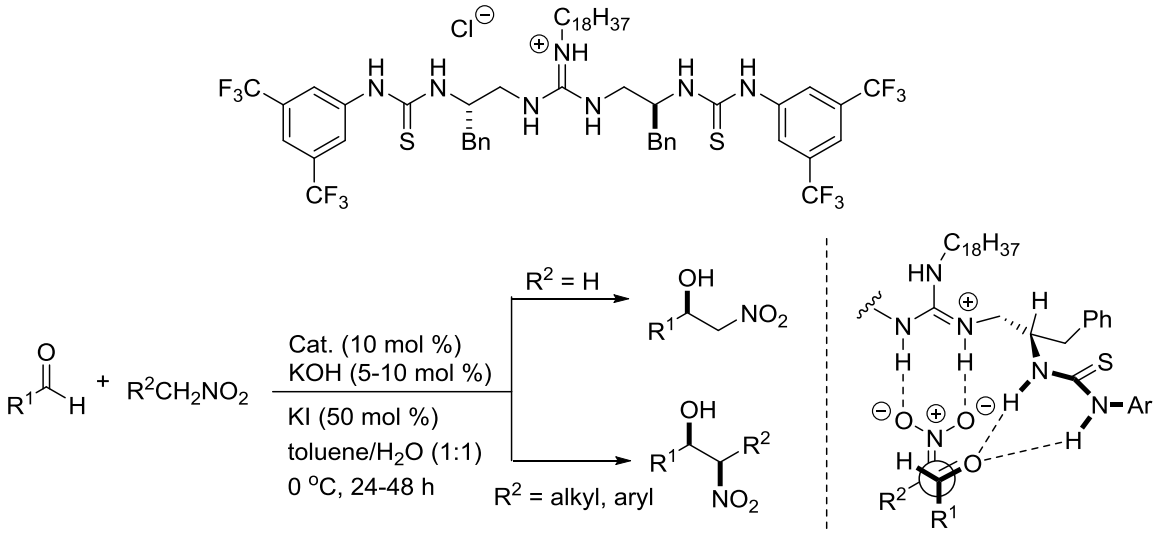
In the same communication, the higher activity of these catalysts is demonstrated in the racemic aza-DA reaction between 2-silyloxydienes and *N*-benzylideneaniline. The reaction catalyzed by the thiosquaramide afforded DA-adduct in 77% yield with a diastereoselectivity of 2.7:1, while utilizing the oxosquaramide catalyst no reaction was observed (Scheme 20).



Scheme 20.

Three years after Takemoto´s work, Nagasawa and coworkers found that molecules comprised with conformationally flexible guanidinium salt/thiourea double functionality catalyze efficiently the diastereoselective Henry reaction with synthetically useful levels of selectivities.[79] The reaction works under PTC with the assistance of KOH, and KI as an additive was required to overcome the retro-nitroaldol reaction. A bifunctional cooperative activation of the substrates predicting the formation of the *syn* adduct was proposed, in which, the *Si*-face of the nitronate would be set up to approach the *Si*-face of the aldehyde without significant sterical hindrance (Scheme 21). No reaction was observed when aromatic aldehydes were used.

[79] a) Shotome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894–2897. For the first highly diastereo- and enantioselective catalytic Henry reactions of nitroalkanes and prochiral aldehydes using La-Li-6,6´-disubstituted BINOL complexes, see: b) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389.



Scheme 21. Diastereoselective and enantioselective Henry (nitroaldol) reaction utilizing a guanidine-thiourea bifunctional organocatalyst.

The organocatalyst assisted activation model is relatively less explored, but its potential is being gradually recognized by synthetic chemists (Figure 7).[80]

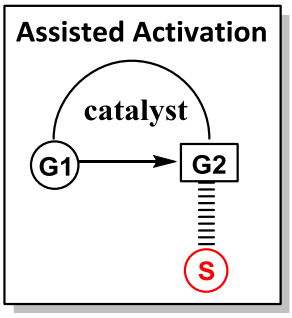


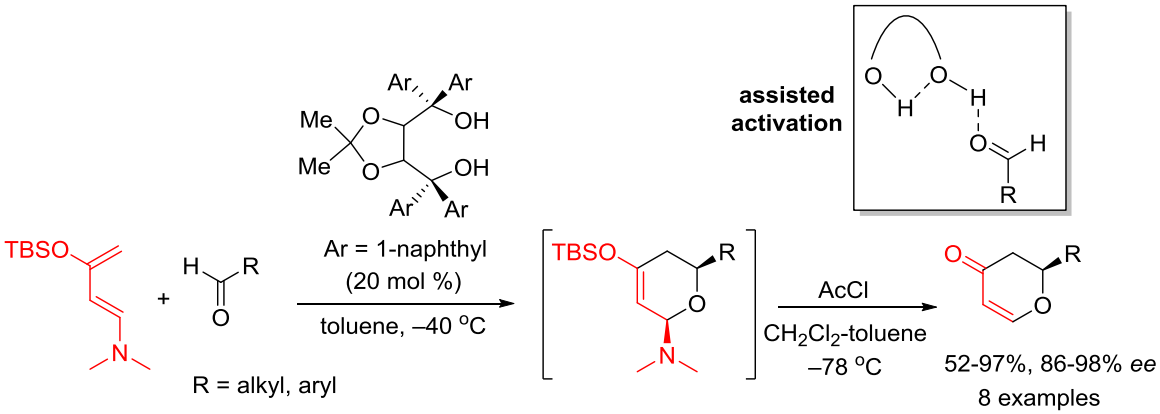
Figure 7.

In 2003, Rawal[81] reported the first organocatalytic asymmetric hetero-DA reaction between aldehydes and Rawal's diene catalyzed by a chiral diol (TADDOL), obtaining in general good yields and excellent enantioselectivities (Scheme 22). The internal H-bond might enhance the acidity of the second hydroxyl group and then get a more effective

[80] For a leading review, see: a) Auvil, T. J.; Schafer, A. G.; Mattson, A. E. *Eur. J. Org. Chem.* **2014**, 2633–2646. For the pioneering Lewis acid assisted Lewis acid metal catalysts by intramolecular activation, see: b) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem. Int. Ed.* **1998**, *37*, 3186–3188. c) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762–766. For an intermolecular activation version, see: d) Oishi, M.; Aratake, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120,* 8271–8272. For the pioneering intramolecular activation of Lewis acids by Brønsted acids using chiral boron catalyst, see: e) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, 116, 1561–1562. For an intermolecular activation version, see: f) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.

[81] a) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. For evidence of the assisted activation of axially chiral biaryl diol catalyst, see: b) Unni, A. K.; Takenaka, N. Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336–1337.

activation of the electrophilic aldehyde through a single-point H-bond (upper right side of Scheme 22).

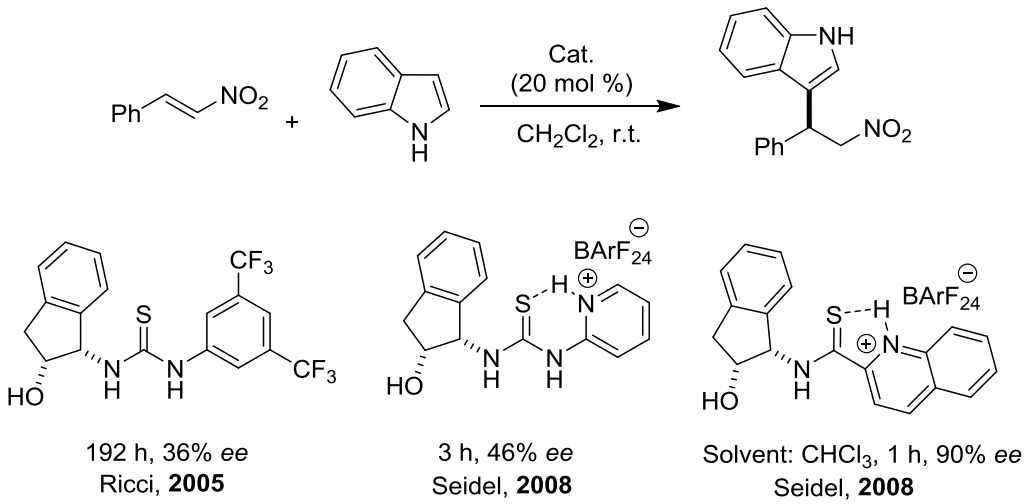


Scheme 22. First organocatalytic asymmetric hetero-DA reaction by Brønsted acid catalysis.

Assisted activation of (thio)ureas has proven to enhance (thio)urea acidity on more than one occasion.

In 2008, Seidel and coworkers[82] designed a more acidic thiourea catalyst through protonated 2-pyridyl substituent (Scheme 23). The authors proposed that the pyridinium subunit was engaged in an intramolecular N–H--S hydrogen bond interaction, resulting in a more active catalyst and similar selectivity compared to Ricci´s 3,5-bis(trifluoromethyl)phenyl substituted thiourea organocatalyst[83] in the enantioselective addition of indoles to nitroalkenes. Finally, the authors found that the removal of one of the thiourea nitrogen atoms greatly enhanced the LUMO lowering properties of the quinolinium thioamide catalyst, leading to full conversion after 1 h and increasing the enantioselectivity to 90%.[84]

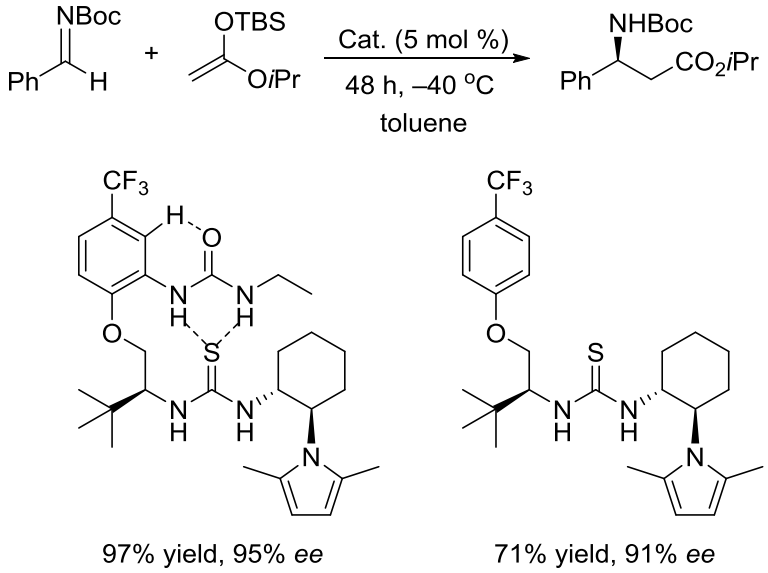
[82] a) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464–16465. For pyridyl thioureas as switchable anion receptors, see: b) Rashdan, S.; Light, M. E.; Kilburn, J. D. *Chem. Commun.* **2006**, 4578–4580.
[83] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576–6579.
[84] The increased catalyst acidity can result not only in rate acceleration but also in increased enantioselectivity, see also: Jensen, K. H.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 4748–4750.



Scheme 23.

1.1.3.2. Development of new activated pronucleophiles

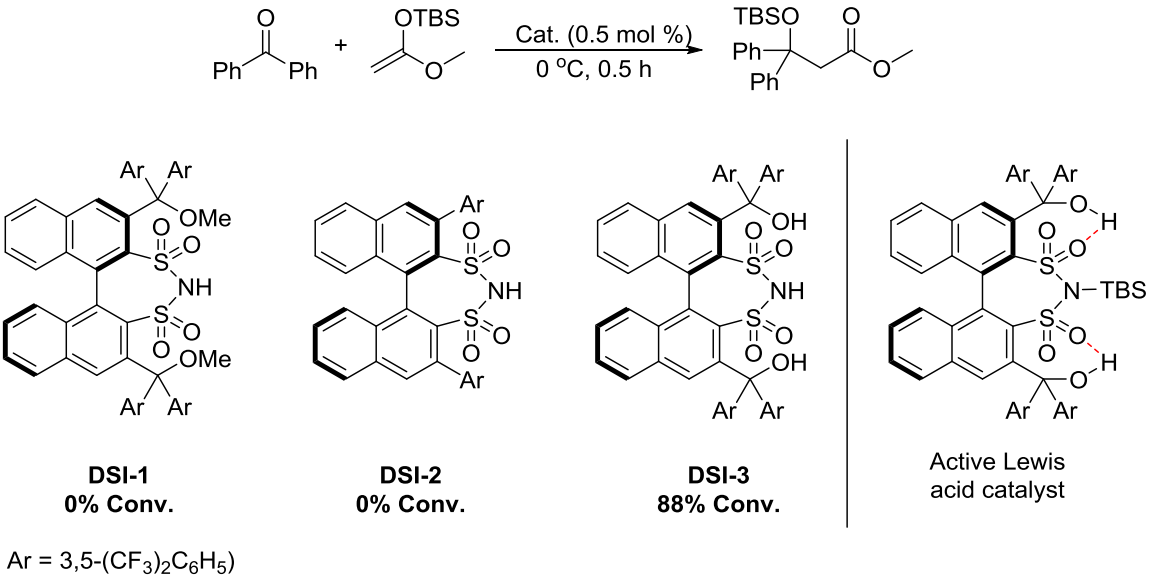
In 2009, Smith and coworkers[85] described conformationally well-defined but flexible thiourea catalysts that benefit from cooperative ligand binding. The noncovalent interactions within β-turn catalyst structure lead to a significant improvement in the yield and slightly higher levels of catalytic efficiency in a Mukaiyama-Mannich reaction (Scheme 24).



Scheme 24.

[85] a) Jones, C. R.; Pantoş, G. P.; Morrison, A. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, 48, 7391–7394. For a similar assisted catalytic activation in Mannich reaction, see: b) Probst, N.; Madarász, Á.; Valkonen, A.; Pápai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8495–8499. For a boronate/urea assited hydrogen bond donor catalysis, see: c) Hong, B.; Dange, N. S.; Hsu, C.; Liao, J.; Lee, G. *Org. Lett.* **2011**, *13*, 2009–2012.

Five years later, List and coworkers[86] reported the design of particularly active chiral disulfonimide (DSI) catalysts based on an assisted activation by hydroxyl groups. They envisioned that the bis-3,5-bis(trifluoromethyl)phenylmethanol group can increase the Lewis acidity (or the Brønsted acidity of **DSI-3**) of the disulfonimide group just by internal hydrogen-bond activation. With catalysts **DSI-1** and **DSI-2** no conversion was observed, while with the catalyst with free alcohols (**DSI-3**) conversion of 88% in just 30 minutes was obtained. A major disadvantage is the somewhat lengthy synthesis of the catalyst (Scheme 25).



Scheme 25.

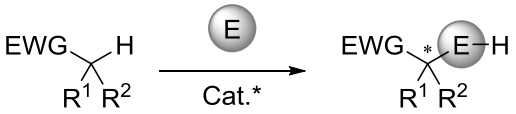
The search of new pronucleophiles plays a central role mainly in pharmaceutical design and in molecular biology, and might play in a host of other fields in the chemical sciences as a supramolecular chemistry, materials, crystal engineering, etc. As a result of this broad importance, efforts are heading toward the search of new active methylenes that can be easily deprotonated. In these cases, a relatively weak amine is generally used to reversibly deprotonate a relatively acidic substrate. To date, the carbonyl components for these reactions are mostly restricted to 1,3 diones, β-ketoesters, α-cyanoacetates, malonates, geminal bis(sulfones).[87]

The reason for this is that pronucleophilic species bearing electron withdrawing groups (EWG) attached to the α *C*(sp^3)-*H* functionality, present a lower pka at the

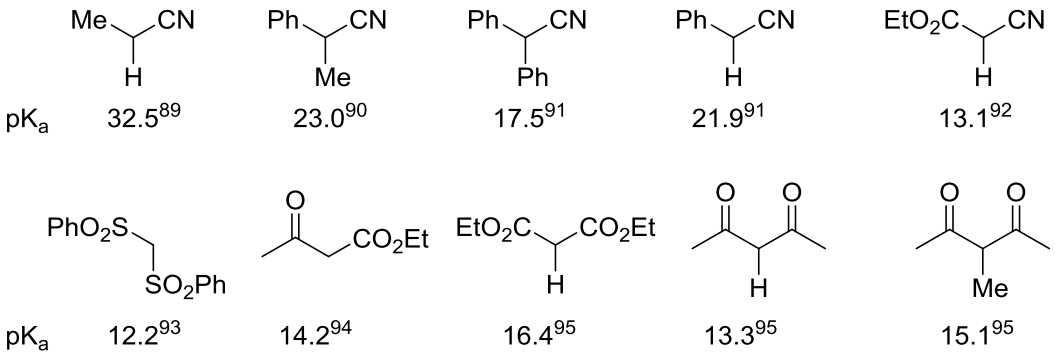
[86] a) Ratjen, L.; van Gemmeren, M.; Pesciaioli, F.; List, B. *Angew. Chem. Int. Ed.* **2014**, *53*, 8765–8769. For a review of disulfonimides in enantioselective organocatalisis, see: b) James, T.; van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388–9409.

[87] a) de Figueiredo, R. M.; Mazziotta, A.; Pereira de Sant' Ana, D.; Palumbo, C.; Gasperi, T. *Curr. Org. Chem.* **2012**, *16*, 2231–2289. b) Mielgo, A.; Palomo, C. *Beilstein J. Org. Chem.* **2016**, *12,* 918–936.

desired deprotonation site increasing the reactivity. This is because the carbanion formed by the removal of a proton from the methylene group is stabilized by the adjacent EWG. Obviously, extra resonance stabilization of the enolate anion makes such C(sp^3) more acidic than that adjacent to a single EWG.



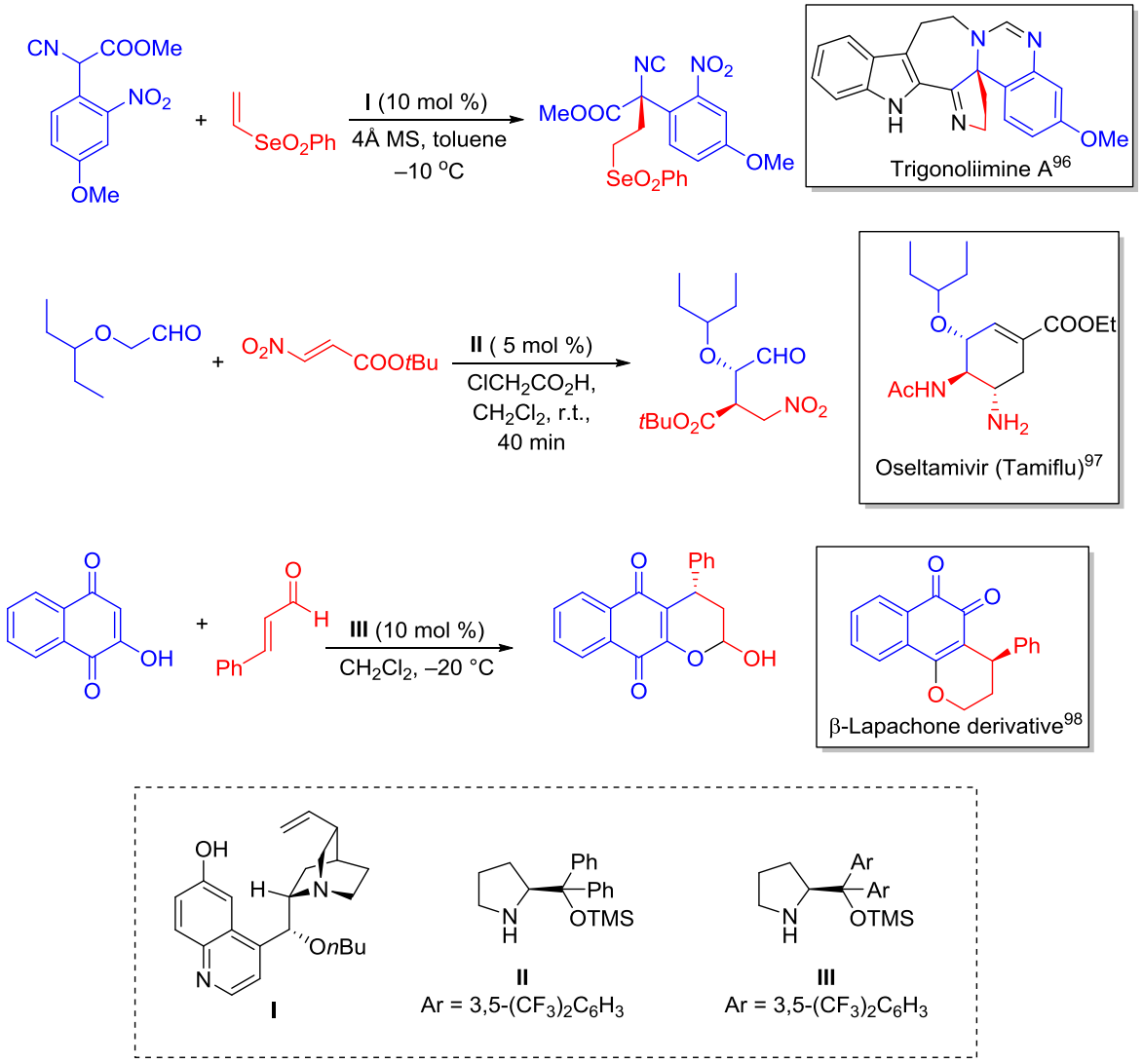
EWG = Electron Withdrawing Group



Scheme 26. pK_a values of selected CH pronucleophiles.

This strategy has often been used in organocatalysis, where the enantioselective transformation is accompanied by a thoughtful design of the nucleophile.[88] The careful and efficient pronucleophile design can help us to elaborate more easily complex adducts that are present in biologically active compounds or in interesting synthetic structures (Scheme 27).

[88] Sun, B.-F. *Tetrahedron Letters* **2015**, *56*, 2133–2140.
[89] Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885–1886.
[90] Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209–223.
[91] Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325.
[92] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.
[93] Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883–1885.
[94] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
[95] Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.



Scheme 27. Selected examples of activated carbonyl compounds as nucleophiles.

To date, in the case of less acidic carbons, we are required to use superbases to abstract the proton to yield the desired carbanion species (Figure 8).[99]

[96] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.
[97] Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem. Int.* Ed. **2009**, *48*, 1304–1307.
[98] Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049.
[99] For selected examples, see: a) Bandar J. S.; Lambert, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 5552–5555. b) Avila, A.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1625–1627. c) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351. d) Takeda, T.; Kondoh, A.; Terada, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 4734–4737. For reviews, see: e) *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts* (Ishikawa, T. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2009. f) Selig, P; *Synthesis* **2013**, *45*, 703–718. g) Krawczyk, H.; Dzięgielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, Ł. *Chem. Eur. J.* **2015**, *21*, 10268–10277.

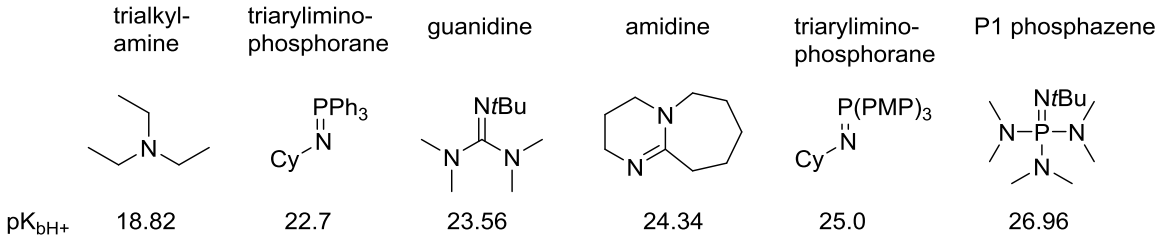
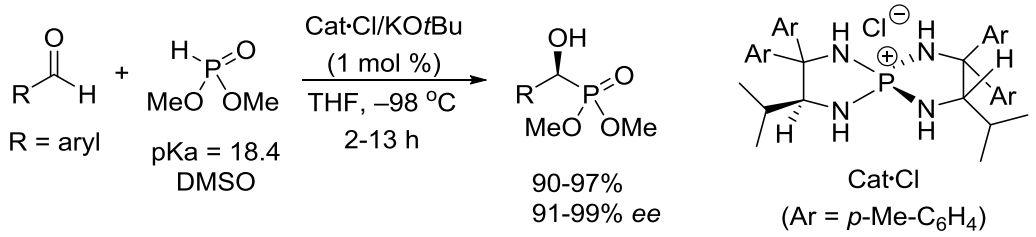


Figure 8. pK$_{bH+}$ (MeCN) of tertiary amine and some common superbases.[99c]

However, despite the fact that chiral organosuperbases are promising catalysts in organic chemistry, they are difficult to modify or recycle, and their possible toxicity and instability means that their synthesis has not been developed properly. For this reasons, only a few groups have been able to obtain satisfactory results in terms of yields and selectivities.

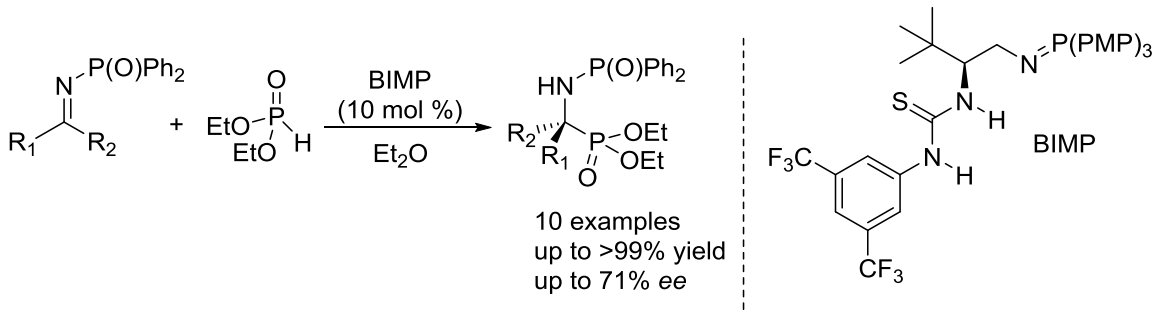
For example, Ooi et al.[100] described in 2009 a highly efficient and enantioselective hydrophosphonylation of aldehydes catalyzed by a chiral tetraaminophosphonium salt. (Scheme 28).



Scheme 28.

More recently, Dixon and co-workers reported an efficient enantioselective ketimine phospha-Mannich reaction of diethyl phosphite to N-diphenylphosphine (DPP) ketimines catalized by a bifunctional iminophosphorane (BIMP) superbase organocatalyst.[101] The reaction is applicable to ketimines bearing electron-rich and electron-poor aryl substituents and occurs with excellent yields and moderate enantioselectivities under mild reaction conditions (Scheme 29).

[100] Uraguchi, D.; Ito, T.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 3836–3837.
[101] Robertson, G. P.; Farley, A. J. M.; Dixon, D. J. *Synlett* **2016**, *27*, 21–24. Also, see ref 99c.



Scheme 29. Bifunctional iminophosphorane catalyzed enantioselective ketimine phospha-Mannich reaction.

1.1.4. Formation of quaternary stereocenters

For a long time, achiral aromatic and heteroaromatic molecules have been potential drug candidates due to their relative easy synthesis, principally since the rise of cross-coupling reactions and parallel synthesis.[102] Although many of these molecules have been developed into successful drugs, their absence of stereochemistry presents several disadvantages. Firstly, from a structural diversity perspective, a huge amount of possibilities have not been investigated. Secondly, interactions between target proteins, which have a three-dimensional structure, and two-dimensional aromatic molecules, will be restricted. As a result, high selectivity for binding to the desired molecule over undesired ones is hard to obtain. A promising solution to solve this issue has been the incorporation of sp^3-hybridized carbon stereocenters into the molecule, especially quaternary stereocenters.[103] Molecules with quaternary or tetrasubstituted carbon stereogenic centers are ubiquitous motifs in organic molecules with biological activity.[104]

[102] *Metal-Catalyzed Cross-Coupling Reactions Vol. 1 and 2* (de Meijere, A. & Diederich, F. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2004.

[103] a) Escape from flatland: Increasing saturation as an approach to improving clinical success: Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756. b) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. *Chem. Rev.* **2018**, *118*, 3887–3964.

[104] Carbon atoms to which four different carbon substituents are bonded, are defined as quaternary carbons, whereas structures bearing heteroatom substitutions (e.g. tertiary alcohols or thiols) are referred to tetrasubstituted carbons. 12% of the top 200 prescription drugs sold in the US in 2011 contained a quaternary stereocenter: Bartholow, M. Top 200 drugs of 2011. Pharm. Times 48–51.

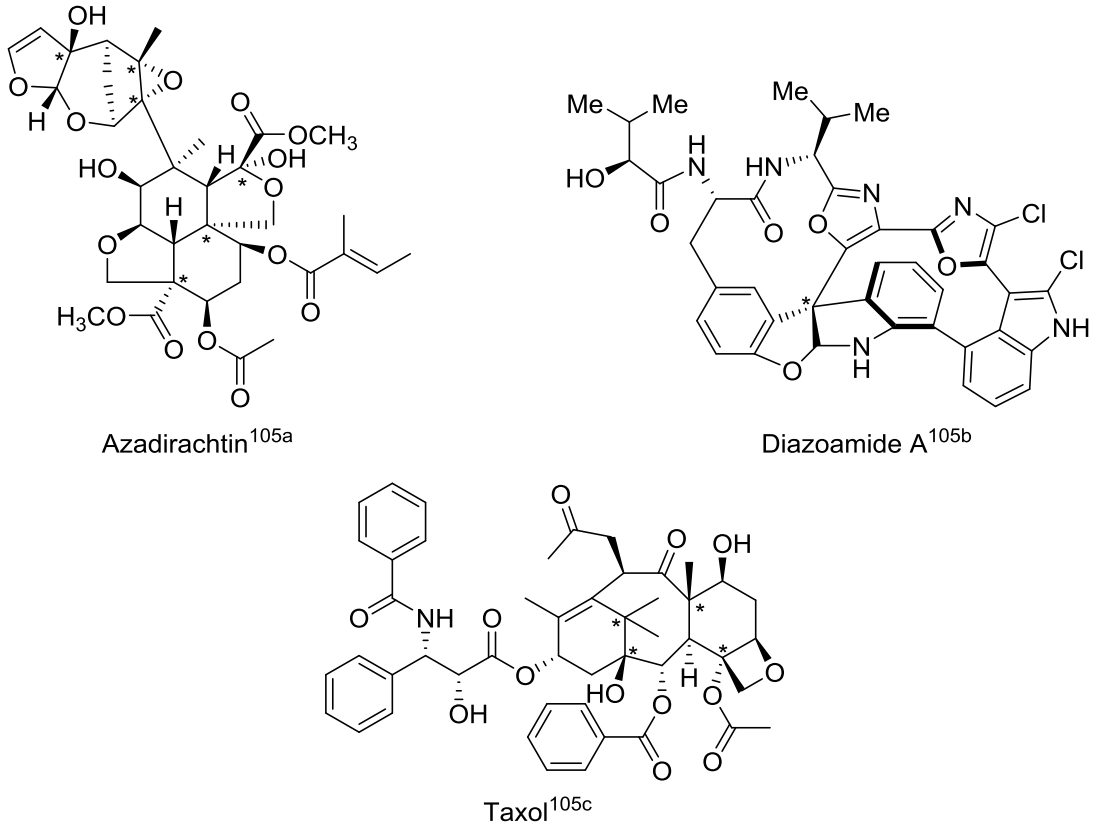


Figure 9. Drug molecules containing quaternary stereocenters.

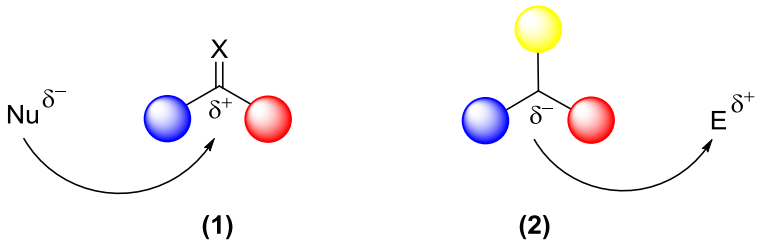
Although the development of synthetic methodologies in the last decades has been really impressive, the stereoselective synthesis of quaternary carbon stereocentres remains an important challenge in the synthesis of biologically active compounds (Figure 9).[105] This task has gained a great concern due to the fact that optical purity is now a strict requirement for the commercialization of new pharmaceutical products. Thus, the more stereoselective procedures are feasible, the more efficiency could be obtained in the synthesis of such compounds.[106] The formation of quaternary stereocenters in a

[105] Selected examples: Azadirachtin: a) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7633–7635. Diazonamide A: b) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D. W. C. *Chem. Sci.* **2011**, *2*, 308–311 and references therein. Taxol: c) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634.

[106] For some selected reviews on the asymmetric formation of quaternary stereocenters, see: a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401. b) Ramon, D.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. c) Peterson, E. A.; Overman, L. E. **2004**, *101*, 11943–11948. d) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Christoffers, J. & Baro, A. ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2005. e) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, 1473–1482. f) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994. h) Bella, M.; Gasperi, T. *Synthesis* **2009**, *10*, 1583–1614. i) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623. j) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191. k) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751. For an all-carbon quaternary centers in natural products and medicinal chemistry, see: l) Ling, T.; Rivas, F. *Tetrahedron* **2016**, 43, 6729–6777. For an asymmetric catalytic formation of quaternary carbons by iminium ion trapping radicals, see: m) Murphy, J. J.; Bastida,

complex molecule has its own limitations. Owing to steric hindrance,[107] relatively harsh conditions (high concentration and temperatures and exceptionally long reaction times) are necessary and only limited combinations of nucleophile and electrophile can be suitable. This is why in most of the cases enantioselectivity can be strongly affected. Moreover, subtle changes either in the electrophile or in the nucleophile could lead to a complete loss of stereocontrol.[108] For instance, in an S_N2 reaction, it is unlikely for a nucleophile to attack a highly substituted carbon; on the other hand, a crowded tertiary anion could not react with electrophiles.

To date, we can consider that two of the most common approaches to obtain quaternary or tetrasubstituted carbons are the polar addition of nucleophile species to trisubstituted unsaturated carbonyl substrates (Scheme 30, 1) and the addition of tertiary anions to electrophiles (Scheme 30, 2).[109]



Scheme 30. Graphical depiction of attenuated reactivity of trisubstituted carbon nucleophile and electrophile.

D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218–222. For a review concerning to catalytic enantioselective desymmetrization reactions to get all-carbon quaternary stereocenters, see: n) Zeng, X.-P.; Cao, Z.-Y.; Wang, Y.-H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330–7396.

[107] For the synthesis of adjacent quaternary stereocenters, see: Rauful, A.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc.* **2015**, *137*, 11262−11265.

[108] For an example, see: Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc*. **2007**, *129*, 1038–1039.

[109] For different approaches in the construction of asymmetric quaternary carbon centers, see: Shimizu, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 5998–6000 and references therein.

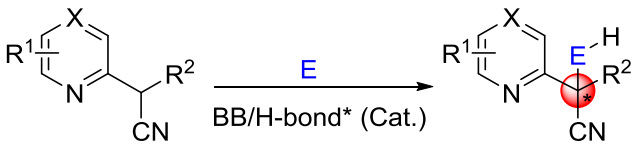
1.2. Working hypothesis and objectives

The present work has been carried out in the line with the research field of the group and it is focused on the development of new asymmetric reactions employing organocatalysis as the main tool.

Precedents mentioned in previous section make clear the importance of the development of new strategies for the stereoselective creation of carbon atoms bonded to four different substituents (quaternary stereocenters), since they are common structural motifs in complex molecules found in nature. Thus, the finding of new pronucleophiles for organocatalytic reactions that allow simpler synthetic pathways to compounds with quaternary α-C(sp^3) moieties has been the aim of several research groups throughout decades.

The objectives of this Ph. D. work will be design a new methodologies for the organocatalytic synthesis of optically active compounds, with possible biological activity, possessing quaternary stereocenters.

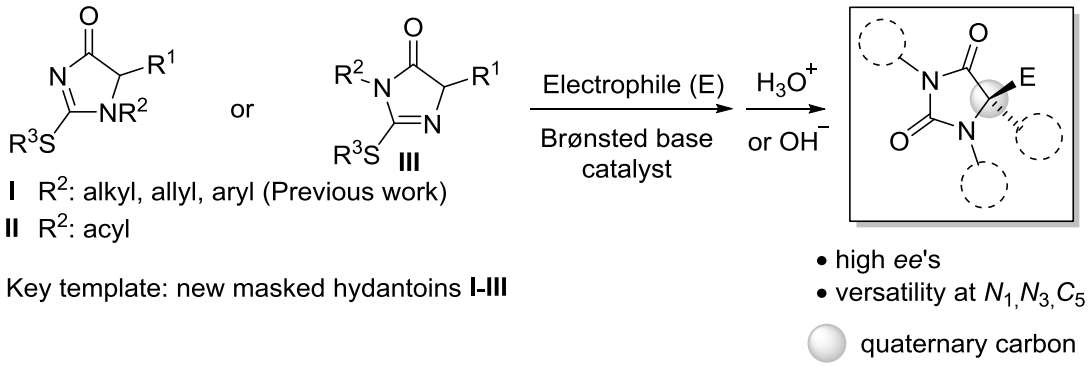
O-Substituted pyridines, and more generally azaarenes, have attracted great part of attention since these structures are frequently found in pharmaceuticals or chiral ligands. Thus, the first objective of this work was to test activated 2-(cyanomethyl)azaarenes for the first time as effective pronucleophiles. This reaction would lead to otherwise elusive optically active α-quaternary alkylazaarenes, compounds that have not been described previously (Scheme 31).



Scheme 31.

Based on previous observations from our laboratory, where we show that heterocycles of type **I** reacts smoothly with some Michael acceptors to yield 5,5-disubstituted 2-alkylthio 1*H*-imidazol-4(5*H*)-ones, thus serving, after hydrolysis, as 5,5-disubstituted hydantoins surrogates. Our next goal would be the evaluation of related heterocycles **II** and **III** to be engaged with selected Michael acceptors under catalytic mild enolization conditions. If the reaction proceeds in a satisfactory way the obtained Michael adducts could be transformed easily into the corresponding optically active 5,5-disubstituted hydantoins through a water mediated nucleophilic displacement of

the thioether group. So, a broad-scope new method for the synthesis of diversely 5,5-disubstituted hydantoins could be obtained.



Scheme 32.

CHAPTER 2

α-FUNCTIONALIZATION OF 2-(CYANOMETHYL)AZAARENE *N*-OXIDES

2. α-FUNCTIONALIZATION OF 2-(CYANOMETHYL)AZAARENE *N*-OXIDES

2.1. Introduction

Nitrogen-containing heterocycles are among the most significant structural components of pharmaceuticals.[110] In 2012, 1086 drugs were approved by U. S. Food and Drugs administration (FDA) and 59% of them include an *N*-heterocycle. Moreover, from the 10 most prescribed drugs in the U. S. in 2016, 7 of them also incorporated this structure (Figure 10).[111]

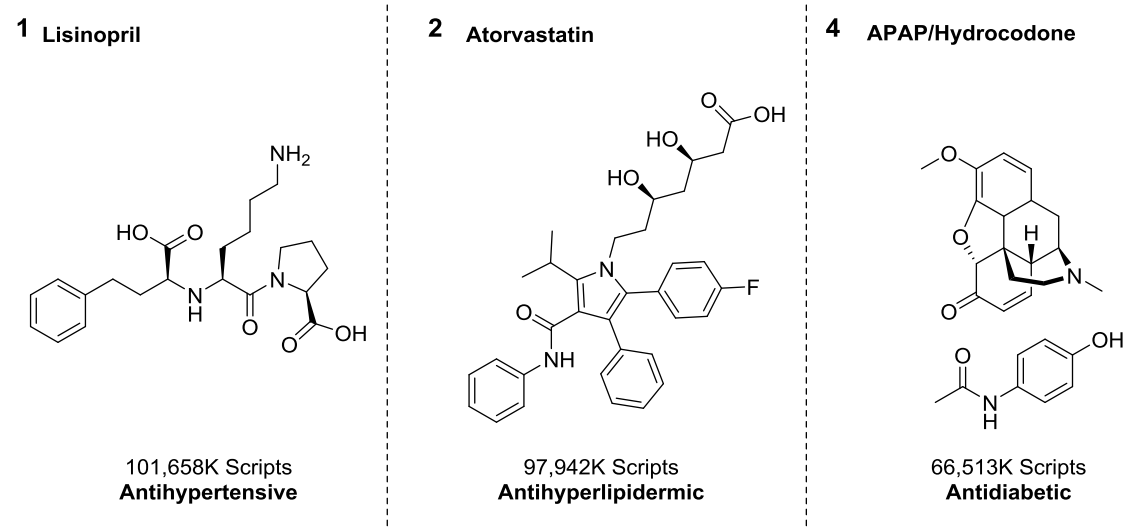


Figure 10. Top pharmaceutical products by prescriptions in 2016.

From all these *N*-heterocycles, pyridine containing basic heteroarene structure core were the second most commonly used (Figure 11a), being the C2-position the preferred position for substitution with a frequency of 66% (Figure 11b).[112]

[110] For a survey of the heterocyclic drugs approved by the U.S. from 2000 to 2012, see: a) Wu, Y.-J. *Prog. Heterocycl. Chem.* **2012**, *24*, 1–53. For a structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities, see: b) *The Chemistry of Heterocycles* (Eicher, T. & Hauptmann, S. ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim) 2003. c) *Asymmetric Synthesis of Nitrogen Heterocycles* (Royer, J. ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim) 2009. d) *Heterocycles in Natural Product Synthesis* (Majumdar, K. C. & Chattopadhyay, S. K. ed.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany) 2011. Pages 63–95. e) Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Shahar Yar, M. *Eur. J. Med.* **2017**, *125*, 143–149.

[111] http://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster

[112] a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257–10274. For a leading review on the synthesis of substituted pyridines, see: b) Yoshiaki, N. *Synlett* **2011**, *20*, 3209–3219. c) Bull, J. A.; Mousseau, J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642–2713. d) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043–6061. For a review concerning to the pioneering work in pyridine chemistry, see: e) Lewis, D. E. *Angew. Chem. Int. Ed.* **2017**, *56*, 9660–9668.

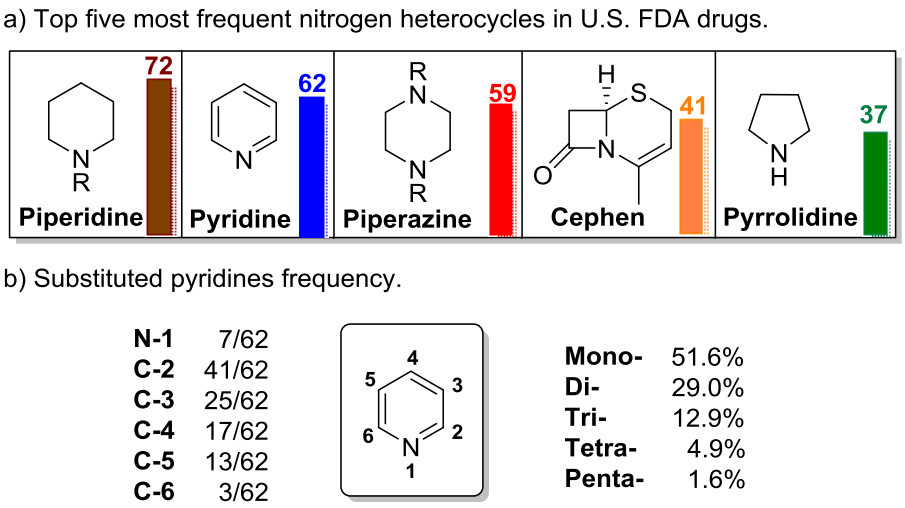


Figure 11. Most frequent *N*-heterocycles and substituted pyridines in U. S. FDA approved drugs (2012).

To emphasize the importance of C-2 substituted (*o*-substituted) aromatic *N*-heterocycles or azaarenes, these are frequent structures in chiral compounds, as in pharmaceuticals,[113] natural products,[114] supramolecular chemistry,[115] and as chiral ligands for asymmetric catalysis[116] (Figure 12). Therefore, the synthesis of 2-substituted chiral azaarene-containing building blocks has gained much attention.[117]

[113] For information about doxylamine, see: a) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M. *J. Am. Chem. Soc.* **1949**, *71*, 887–890. b) Nuangchamnong, N.; Niebyl, J. *Int. J. Women's Health* **2014**, 6, 401–409. For information about disopyramide, see: c) Hinderling, P. H.; Garrett, E. R. *J. Pharmacokinet. Biopharm.* **1976**, *4*, 199–230. d) Nelson, W. L.; Sneed, C. K. *J. Med. Chem.* **1981**, *24*, 614–617. e) Karim, A.; Nissen, C.; Azarnoff, D. L. *J. Pharmacokinet. Biopharm.* **1982**, *10*, 465–493. f) Kuroda, Y.; Matsumoto, S.; Shibukawa, A.; Nakagawa, T. *Analyst* **2003**, *128*, 1023−1027. For a review about norbormide, see: g) Bova, S.; Cima, L.; Golovina, V.; Luciani, S.; Cargnelli, G. *Cardiovasc. Drug Rev.* **2001**, *19*, 226–233.

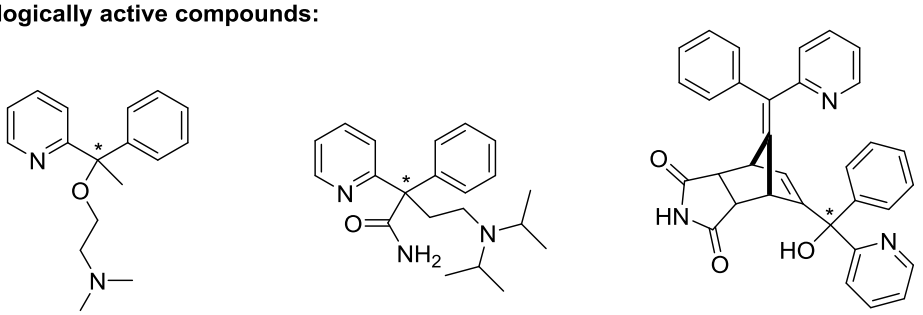
[114] Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361.

[115] a) *Supramolecular Chemistry – Concepts and Perspectives* (Lehn, J. M. ed.; VCH, Weinheim) 1995. b) *Supramolecular Chemistry: From molecules to Nanomaterials* (Steed, J. W. & Gale, P. A. ed.; John Wiley & Sons) 2012. c) Liu, M.; Zhang, L.; Wang, T. *Chem. Rev.* **2015**, *115*, 7304–7397.

[116] For reviews on azaarenes as a chiral ligands, see: a) Kwong, H.-L.; Yeung, H.-L.; Yeung, C.-T.; Lee, W.-S.; Lee, C.-S.; Wong, W.-L. *Coord. Chem. Rev.* **2007**, *251*, 2188–2222. b) Chelucci, G. Coord. *Chem. Rev.* **2013**, *257*, 1887–1932. c) Li, W.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 1657–1677.

[117] For reviews, see: a) Chelucci, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2353–2383. b) Best, D.; Lam, H. W. *J. Org. Chem.* **2014**, *79*, 831–845.

-Biologically active compounds:



Doxylamine
antihistamine

Disopyramide
antiarrhythmic

Norbormide
rodenticide

-Chiral ligands:

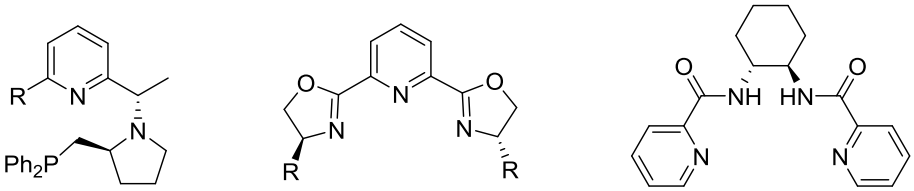
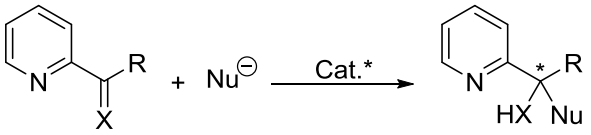


Figure 12. C-2 substituted biologically active compounds and chiral ligands.

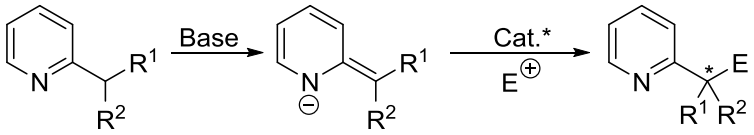
There are three main routes to obtain α-functionalized chiral 2-alkylpyridines by catalytic methods; i) by nucleophilic addition to 2-acylpyridines or their imines (Scheme 33a), ii) using 2-alkylpyridines as pronucleophiles (Scheme 33b) or iii) by asymmetric transfer hydrogenation of 2-acylpyridines or 2-pyridyl imines[118] (Scheme 33c).

a)

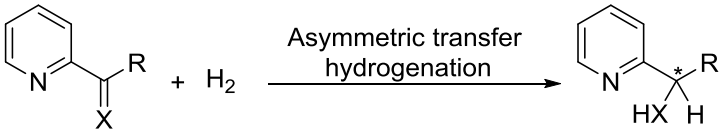


R = H, alkyl, aryl
X = O, NR

b)



c)



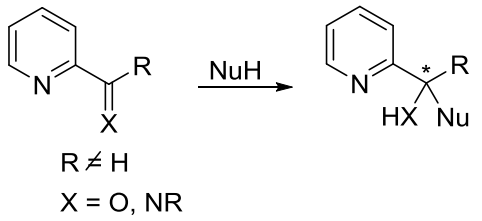
R = H, alkyl, aryl
X = O, NR

Scheme 33.

[118] Using this protocol, only tertiary alcohols and tertiary amines can be obtained.

2.1.1. Nucleophilic addition to 2-acyl pyridines or imines derived thereof

In recent years, a considerable advance in the development of asymmetric procedures for the addition of nucleophiles to 2-pyridine carboxaldehyde and to 2-pyridylimines leading to products with tertiary stereocenters has been achieved.[119] In contrast, the asymmetric addition of nucleophiles to 2-acylpyridines and 2-pyridyl ketimines which will result in formation of a quaternary stereogenic center has experienced little progress, despite the significance of the resulting compounds (Scheme 34).

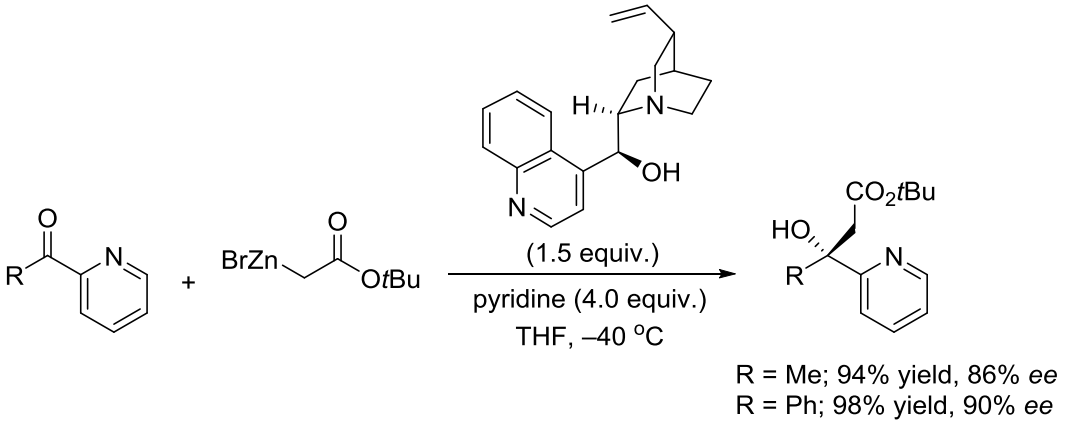


Scheme 34.

Among all processes described, the asymmetric addition of nucleophiles to 2-pyridyl ketones is the most widely used method for the synthesis of C-2 substituted pyridine derivatives with quaternary stereocenters. Next, the existing works to date will be explained.

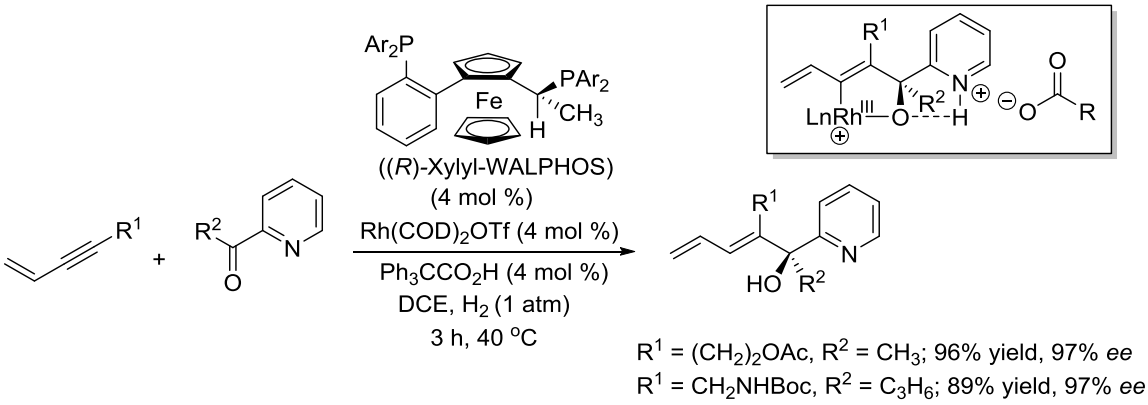
In 2002, Yamano and coworkers performed a highly enantioselective Reformatsky reaction of 2-pyridyl ketones forming a quaternary Cα-stereocenter with high yields and enantioselectivities.[120] Nevertheless, 4 equivalents of pyridine as a basic coordinating additive and 1.5 equivalents of quinine are necessary to enhance the enantioselectivity and reactivity (Scheme 35).

[119] For selected examples, see: a) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284–3289. b) Landa, A.; Minkkilä, A; Blay, G.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 3472–3483. c) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567–3570. d) Qu, Y.; Jing, L.; Wu, Z.; Wu, D.; Zhou, X. *Tetrahedron: Asymmetry* **2010**, *21*, 187–190. e) Pascual-Escudero, A.; González-Esguevillas, M.; Padilla, S.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2014**, *16*, 2228–2231. f) Beckendorf, S.; García-Mancheño, O. *Synthesis* **2012**, *44*, 2162–2172. g) Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 5003–5006.
[120] Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051–3054.



Scheme 35. Asymmetric synthesis of tertiary alcohols via Reformatsky reaction.

As already shown in the introductory part (chapter 1), the interplay of multiple catalyst can increase overall reactivity substantially. For instance, the group of Krische described an enantioselective reductive coupling of 1,3-enynes to 2-acetylpyridine and cyclopropyl 2-pyridyl ketone catalyzed by a chiral rhodium complex and an achiral Brønsted acid (Scheme 36). The reaction was carried out in dichloroethane at 40 °C, rendering the reductive coupling products in excellent yields and enantioselectivities.[121] The proposed mechanism for the reductive coupling involves the activation of the 1,3-enyne by the rhodium complex and the activation of the 2-pyridinecarboxaldehyde (LUMO lowering) by the Brønsted acid cocatalyst (upper right Scheme 36).[122]

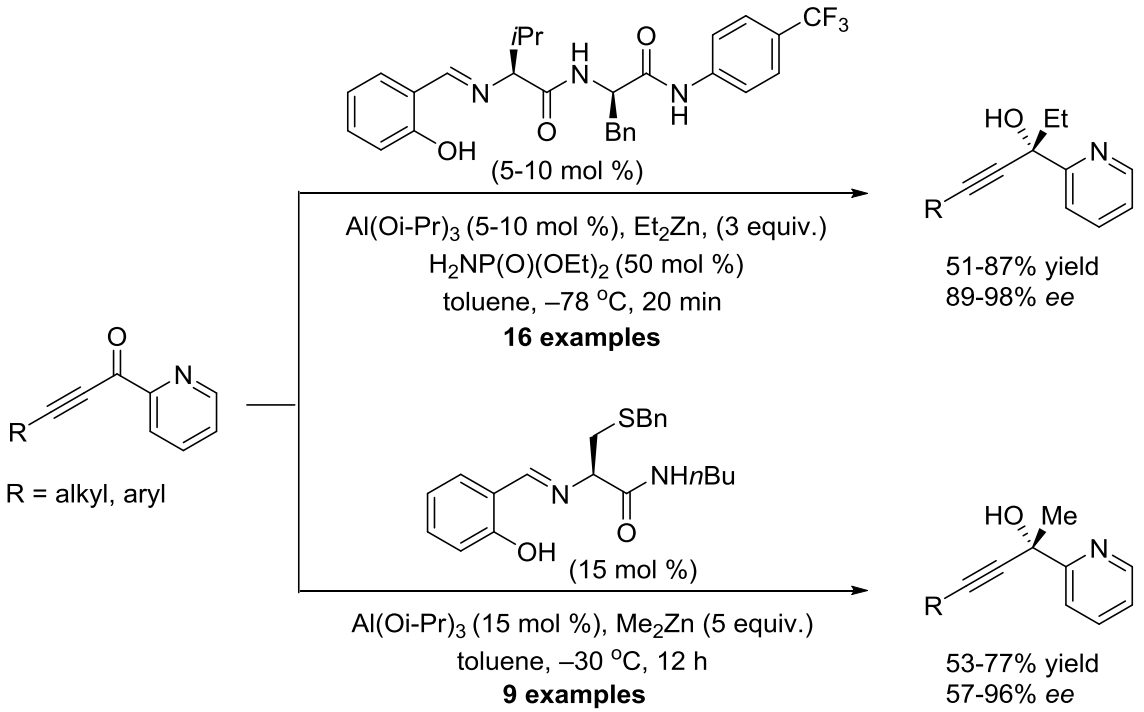


Scheme 36. Asymmetric reductive coupling and plausible intermediate reaction.

Shortly after the achievement of Kirsche, Hoveyda's research group[123] reported an aluminium-catalyzed asymmetric alkylation of pyridyl-substituted alkynyl ketones with dialkylzinc reagents (Et_2Zn or Me_2Zn). In the case of the addition of Et_2Zn, the presence of a Brønsted acid (50 mol % of diethyl phosphoramidate) was necessary in order to get

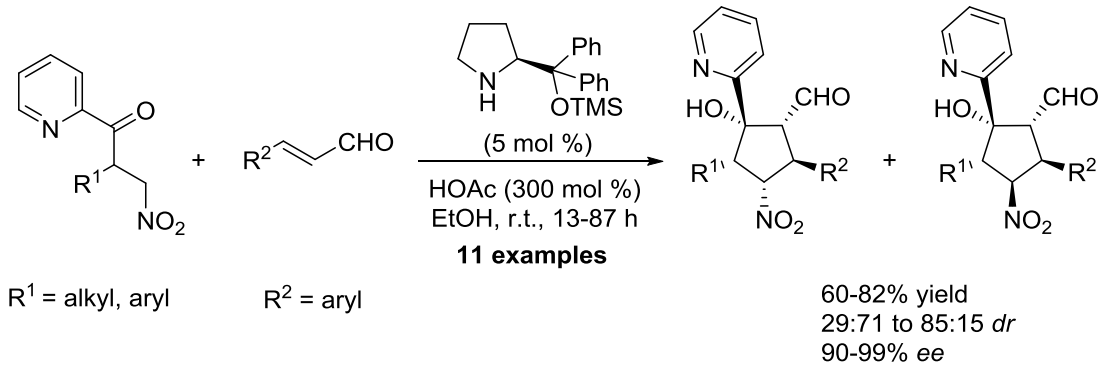
[121] Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448–16449.
[122] The reaction using an achiral rhodium catalyst in the presence of 4 mol% of the Akiyama-Terada type chiral phosphoric acid catalyst derived from BINOL, gave moderate yield (56%) and *ee* (82%).
[123] Friel, D. K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2008**, *130*, 9942–9951.

good yields and enantioselectivities. Products that contain a quaternary carbon stereogenic center bearing three highly versatile substituents (an alcohol, a pyridine, and an alkyne) were generated in very good yields and excellent enantioselectivities (Scheme 37).



Scheme 37. Al catalyzed asymmetric alkylations of pyridyl ynones.

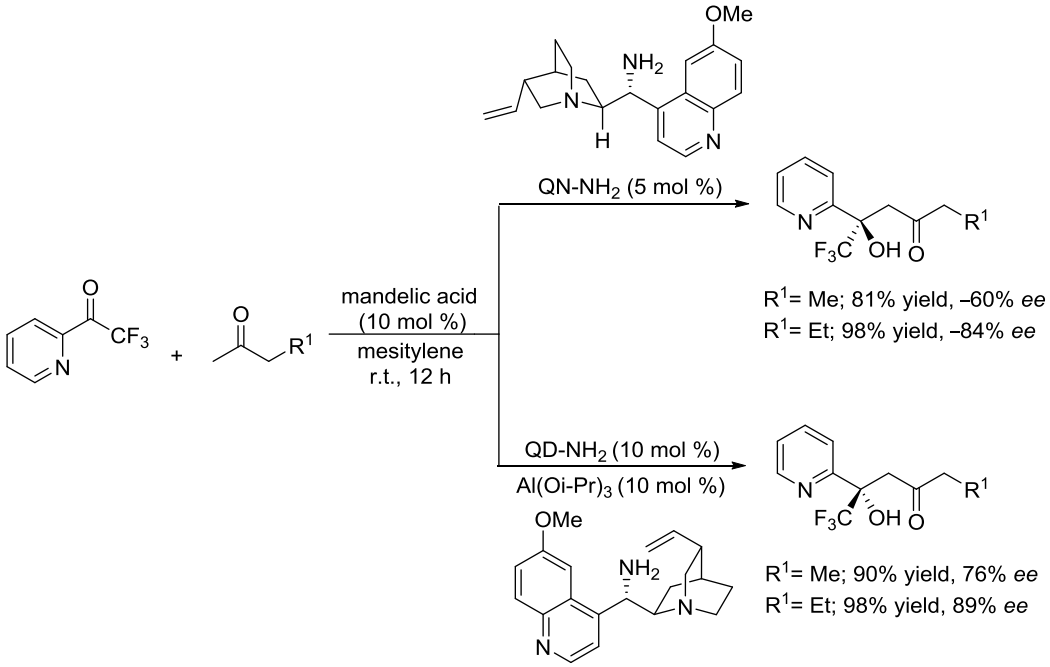
In 2011, Hong et al. reported a stereoselective organocatalytic domino Michael–Aldol reaction, affording highly functionalized cyclopentanecarbaldehyde with five new stereogenic centers in high yield and stereoselectivities from moderate to high.[124] The best reaction conditions were obtained with 5 mol % of Jørgensen-Hayashi catalyst[125] (iminium-ion activation), needing in general long reaction times (Scheme 38).



Scheme 38.

[124] Hong, B.-C.; Dange, N. S.; Hsu, C.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2011**, 13, 1338–1341.
[125] For reviews, see: a) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922–948. b) Jensen, K. I. M. L.; Dickmeiss, G.; Jiang, H. A. O.; Albrecht, Ł. U.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

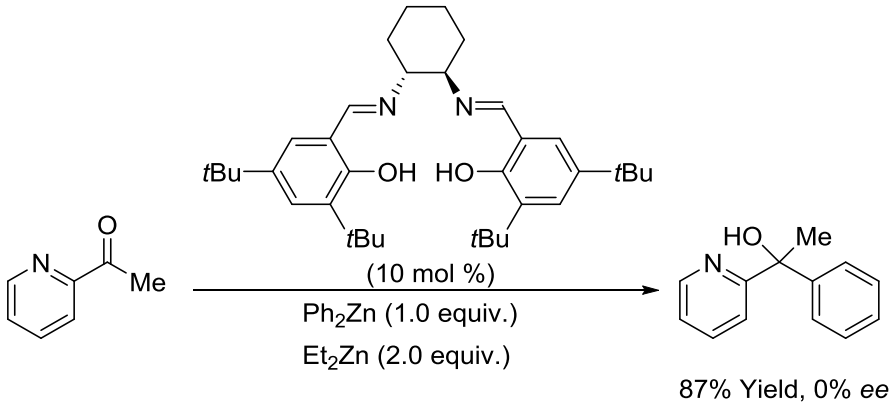
Another application in the synthesis of α-functionalized chiral 2-alkylpyridines using enamine activation was reported by the group of Xu in 2011. They described the formation of trifluoromethylated tertiary alcohols through asymmetric primary amine catalyzed aldol reaction between aliphatic ketones and activated 2,2,2-trifluoro-1-(pyridin-2-yl)ethan-1-one with excellent yields and moderate to very good enantioselectivities.[126] Interestingly, both possible enantiomers of the final adduct were obtained using the proper cinchona catalyst. In the case of QN-NH_2/Al(Oi-Pr)$_3$ catalytic system, the role of Al(Oi-Pr)$_3$ is attributed to the activation of the trifluoromethyl ketone and to the stabilization of the enamine transition state (TS) (Scheme 39).



Scheme 39.

[126] Yang, W.; Cui, Y.-M.; Zhou, W.; Li, L.; Yang, K.-F.; Zheng, Z.-J.; Lu, Y.; Xu, L.-W. *Synlett* **2014**, *25*, 1461–1465.

Shortly after the achievements of Xu, and following the seminal works of Bolm and Fu using arylzinc reagents as nucleophiles,[127] the group of Ito reported an efficient Zn(salen)-catalyzed enantioselective phenyl transfer to aldehydes and ketones with organozinc reagents. They performed just one example of the Zn(salen)-catalyzed enantioselective phenyl transfer to 2-acetylpyridine, unfortunately a racemic mixture of the tertiary carbinol was obtained (Scheme 40).[128]



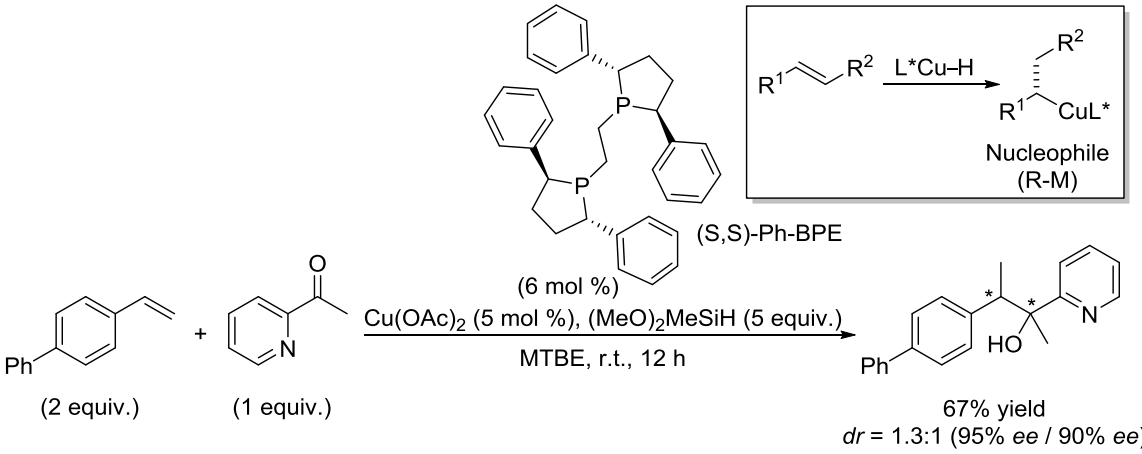
Scheme 40.

Recently, in an original contribution, Buchwald's group[129] has reported one example of a copper-catalyzed asymmetric addition of 4-phenylstyrene to 2-acetyl pyridine with moderate yield and poor diastereoselectivity, but excellent enantioselectivity for both diastereomers (Scheme 41). It was proposed that the activation of C=C double bond of an olefin by chiral copper hydride catalyst (L^*Cu-H) would provide the enantioenriched alkylcopper carbanion equivalent (upper right Scheme 41) that after interception of the ketone and ligand exchange with metyltert-butyl ether (MTBE) would furnish the asymmetric addition product. The absolute and relative configuration of the obtained adduct was not determined.

[127] a) Dosa, P. I.; Ruble, C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445. b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem. Int. Ed.* **2000**, *39,* 3465–3467. For a leading review concerning to the catalytic asymmetric synthesis of diarylmethanols and diarylmethylamines by aryl transfer reaction, see: c) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, 35, 454–470.

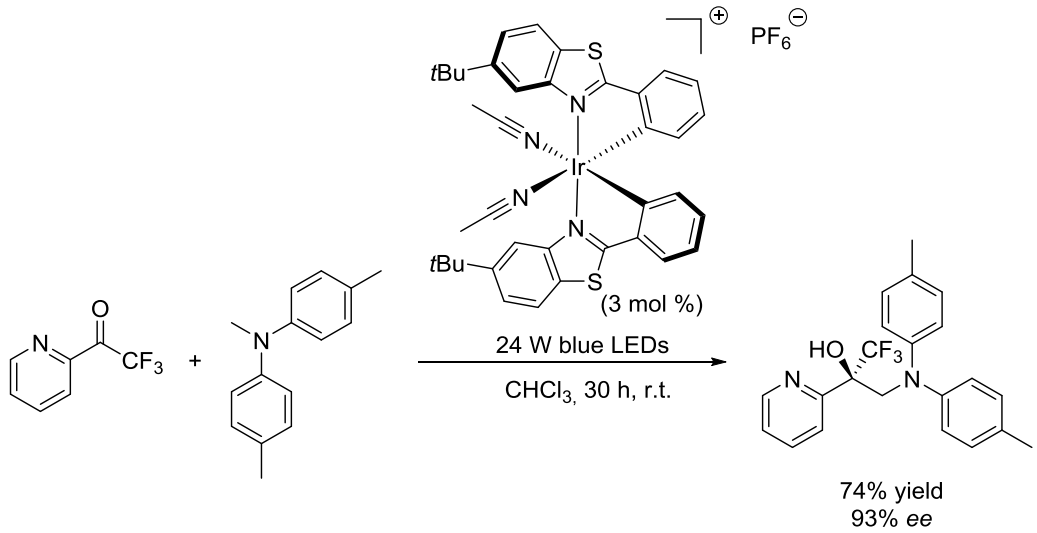
[128] Shimizu, K.; Uetsu, H.; Gotanda, T.; Ito, K. *Synlett* **2015**, *26*, 1238–1242.

[129] Yang, Y.; Perry, I. B.; Lu, G.; Liu, P.; Buchwald, S. L. *Science* **2016**, *353*, 144−149.



Scheme 41.

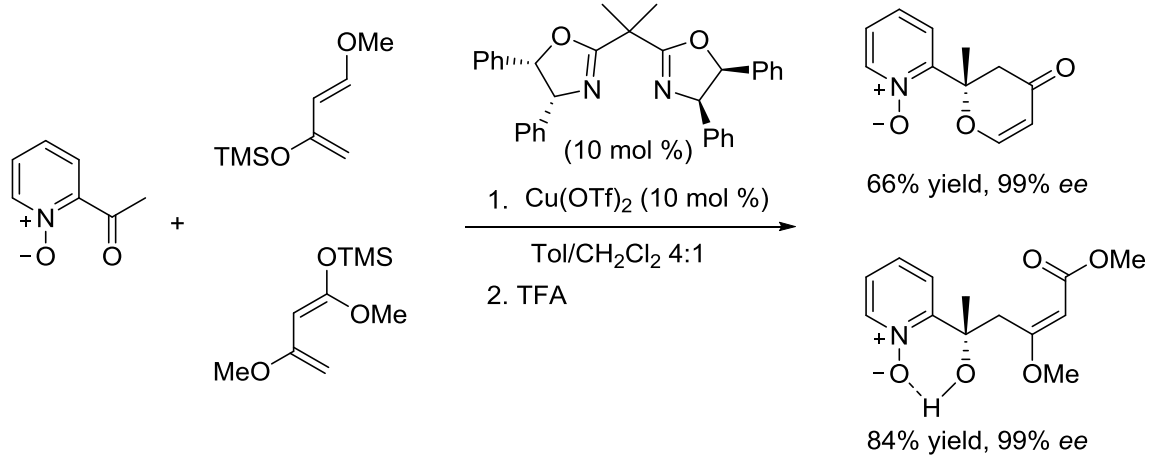
The same year, Meggers and coworkers developed an asymmetric radical-radical cross-coupling reaction through visible-light activated iridium catalysis.[130] With a chiral iridium complex as a dual Lewis acid/photoredox catalyst, optically active 1,2-amino alcohols were synthesized from trifluoromethyl ketones and tertiary amines. Just in one example a 2-pyridyl ketone was employed resulting in very good yield and excellent enantioselectivity (Scheme 42).



Scheme 42.

[130] a) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2016**, *55,* 685–688. For a Brønsted acid catalyzed Michael addition of α-amino radicals to alkenylpyridines, see: b) Hepburn, H. B.; Melchiorre, P. *Chem. Commun.* **2016**, *52*, 3520–3523. For a recent article concerning to the direct addition of α-amino alkyl radicals to the 2-position of heteroarenes yielding tertiary stereocenters, see: c) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* 10.1126/science.aar6376. For a recent article concerning to the conjugate addition-enantioselective protonation of *N*-aryl glycines to α-branched 2-vinylazaarenes via cooperative photoredox and asymmetric catalysis, see: d) Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc.* 10.1021/jacs.8b01575.

Jørgensen and cowoworkers were the first to employ 2-acetylpyridine N-oxides in a *oxo*-HDA reaction catalyzed by a chiral copper(II)-BOX complex forming optically pure adducts with a quaternary Cα-stereocenter satisfactorily (Scheme 43).[131] When using Danishefsky's diene the unsaturated six membered ring was obtained, while with Brassard`s diene, non silylated vinylogous Mukaiyama-aldol adduct was formed. An explanation for the isolation of the Mukaiyama-aldol adduct could be the stability of the formed open-chain methyl ester, due to hydrogen-bond stabilization between the N-oxide and the hydroxyl group. These observations indicated that the *oxo*-HDA reaction might proceed by a stepwise Mukaiyama-aldol mechanism.



Scheme 43. Cu-Lewis acid catalyzed *O*-HDA by Jørgensen et al.

Besides 2-pyridyl ketones, 2-pyridyl ketimines have also been used as electrophiles, although in less extent. Just a few examples can be found in the literature and in most of the cases a chiral auxiliary was employed.

For instance, Spero[132] and Palmieri[133] have described the asymmetric synthesis of α,α-disubstituted alkylamines via Grignard additions to ketimines bearing chiral auxiliaries derived from (S)-phenylglycinol and (R)-1-phenyl ethylamine (Figure 13a). Ellmans´ sulphinamide auxiliary[134] has been used more frequently in the nucleophilic addition of

[131] a) Landa. A.; Richter, B.; Johansen, R. L.; Minkkilä A.; Jørgensen K. A. *J. Org. Chem.* **2007**, *72*, 240−245. For a recent example using 2-acylpyridine *N*-oxides generating a quaternary Cα-stereocenter in a Henry reaction, see: b) Holmquist, M.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Org. Lett.* **2014**, *16*, 1204–1207. For the L-phenylalanine potassium catalyzed asymmetric formal [3+3] annulations of 2-enoyl pyridine *N*-oxides with acetone, see: c) Xu, Y.; Zhang, S.; Li, L.; Wang, Y.; Zha, Z.; Wang, Z. *Org. Chem. Front.* **2018**, *5*, 376–379.

[132] Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537–5541.

[133] Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2011–2018.

[134] Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, 119, 9913–9914.

diethyl thiophosphonate,[135] acylsilanes,[136] organolithium reagents,[137] acetonitrile anion,[138] and fluoro(phenylsulfonyl)methyl anion[139] (Figure 13b).

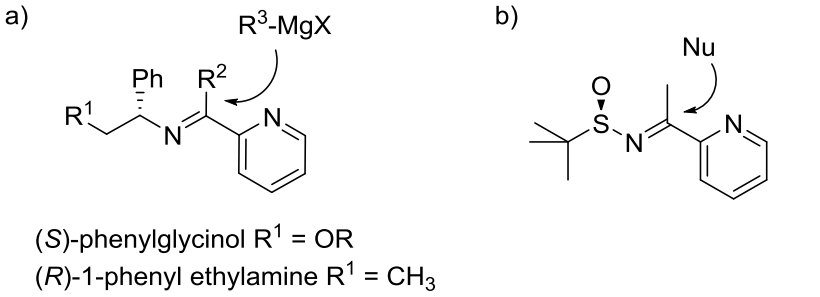
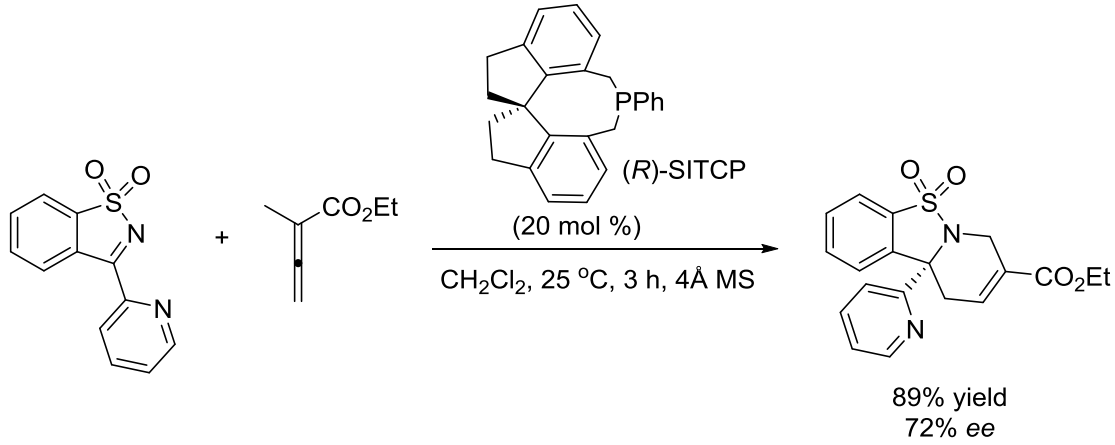


Figure 13. Ketimines bearing chiral auxiliaries.

As far as we know, only two examples of asymmetric catalysis using 2-pyridyl ketimines as electrophiles have been described so far.

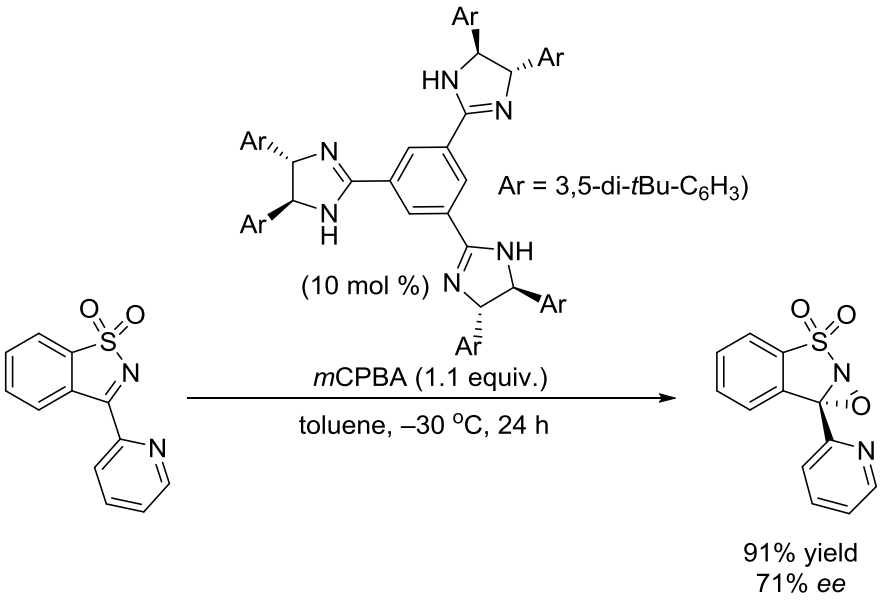
In 2014, the group of Sasai and Takizawa reported an enantioselective formal [4+2] cycloaddition of *N*-sulfonyl ketimines with allenoates catalyzed by 20 mol % of a spiro-type monoaryl phosphine catalyst.[140] This transformation proceeds under mild reaction conditions to afford a tetrahydropyridine framework with a tetrasubstituted stereogenic carbon center in good yield and moderate enantioselectivity (Scheme 44).



Scheme 44. Enantioenriched tetrahydropyridines via organocatalytic cycloaddition.

[135] Chen, Z.; Li, J.; Yuan, C. *Synthesis*, **2009**, *23*, 3930–3940.
[136] Liu, B.; Lu, C.-D. *J. Org. Chem.* **2011**, *76*, 4205–4209.
[137] Kamau, M. G.; Harikrishnan, L. S.; Finlay, H. J.; Qiao, J. X.; Jiang, J.; Poss, M. A.; Salvati, M. E.; Wexler, R. R.; Lawrence, R. M. *Tetrahedron* **2012**, *68*, 2696–2703.
[138] Harikrishnan, L. S.; Finlay, H. J.; Qiao, J. X.; Kamau, M. G.; Jiang, J.; Wang, T. C.; Li, J.; Cooper, C. B.; Poss, M. A.; Adam, L. P.; Taylor, D. S.; Chen, A. Y. A.; Yin, X.; Sleph, P. G.; Yang, R. Z.; Sitko, D. F.; Galella, M. A.; Nirschl, D. S.; Van Kirk, K.; Miller, A. V.; Huang, C. S.; Chang, M.; Chen, X.-Q.; Salvati, M. E.; Wexler, R. R.; Lawrence, R. M. *J. Med. Chem.* **2012**, *55*, 6162–6175.
[139] a) Liu, J.; Zhang, L.; Hu, J. *Org. Lett.* **2008**, *10*, 5377–5380. b) Liu, J.; Hu, J. *Chem. Eur. J.* **2010**, *16*, 11443–11454.
[140] Takizawa, S.; Arteaga, F.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Asian J. Org. Chem.* **2014**, *3*, 412–415.

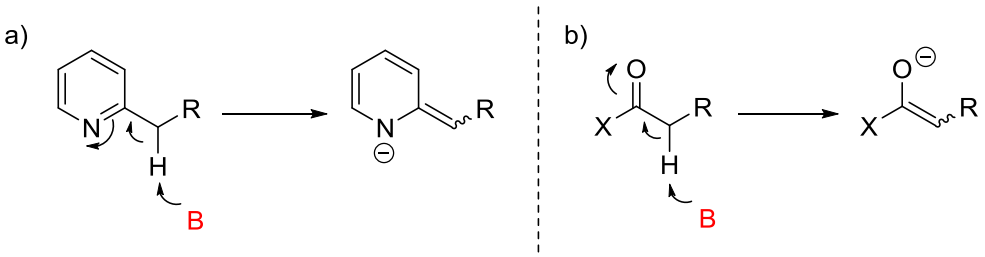
More recently, the same group reported the organocatalytic nucleophilic oxaziridination of *N*-sulfonyl ketimines with *m*CPBA promoted by 10 mol % of a basic C_3-symmetric chiral trisimidazoline (Scheme 45).[141] Just in one example a 2-pyridyl substituent was employed resulting in very good yield and moderate enantioselectivity.



Scheme 45.

2.1.2. 2-Alkylazaarenes as pronucleophiles

The α-deprotonation of 2-alkylazaarenes has a remarkable parallelism with the enolization of carbonyl compounds (Scheme 46). Though the second process has been used in many direct catalytic enantioselective C-C bond forming reactions (aldol, Mannich or Michael) (Scheme 46b), the use of 2-alkylazaarenes in analogous processes was vaguely explored (Scheme 46a). The principal obstacle in the development of such reactions is the lower acidity of 2-alkylazaarenes compared with the parent carbonyl compounds.



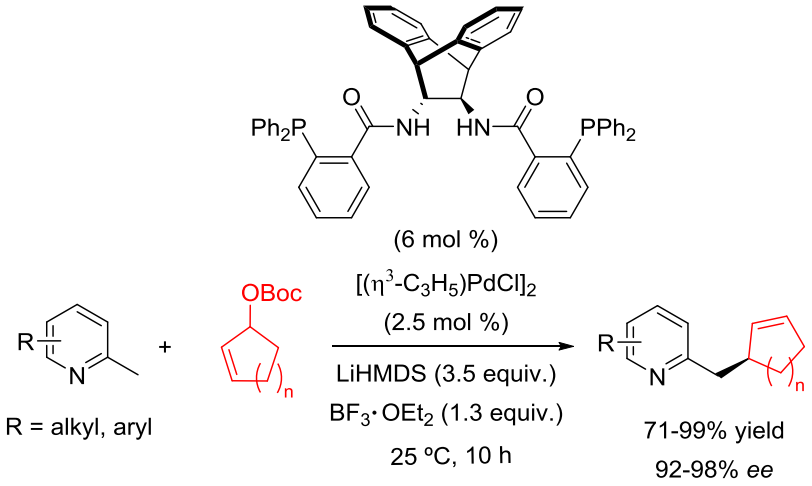
Scheme 46. α-deprotonation of 2-alkylazaarenes and enolization of carbonyl compounds.

[141] Takizawa, S.; Kishi, K.; Abozeid, M. A.; Murai, K.; Fujioka, H.; Sasai, H. *Org. Biomol. Chem.* **2016**, *14*, 761–767.

Despite these difficulties, several non asymmetric methods have been reported for the C(sp^3)-H functionalization of 2-alkylazaarenes employing transition-metal catalysts.[142] However, harsh reaction conditions were necessary, such as the use of more than stoichiometric amounts of strong bases (K_2CO_3, NaO*t*Bu, and Cs_2CO_3), high reaction temperatures or microwave irradiation.

The problems described above have compromised the development of the asymmetric version of these reactions and only a few precedents can be found in the literature concerning the catalytic enantioselective reactions of 2-alkylazaarenes as pronucleophiles.

In 2008, Trost et al. have applied palladium chiral complexes for the asymmetric allylic alkylation of 2-methyl pyridines. Despite the excellents yields an enantioselectivities, over stoichiometric amounts of a strong base (LiHMDS, 3.5 equiv.) and a Lewis acid ($BF_3{\cdot}OEt_2$, 1.3 equiv.) were required for the reaction to proceed to full conversion, thus compromising practicality (Scheme 47).[143]

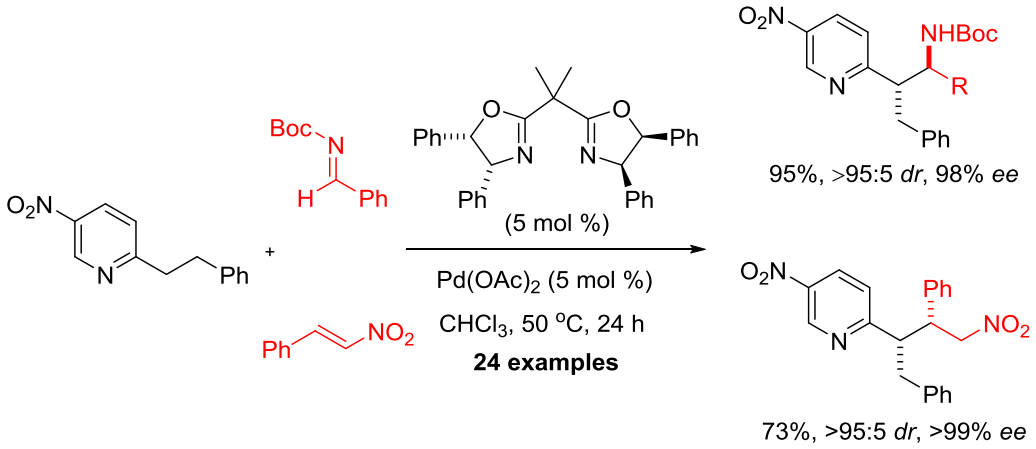


Scheme 47. Palladium-catalyzed asymmetric allylic alkylation.

[142] For the palladium-catalyzed direct arylation reaction, see: a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. For the palladium-catalyzed addition to *N*-sulfonylaldimines, see: b) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650–3651. For the palladium-catalyzed benzylic arylation reaction, see: c) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359–5361. For the scandium-catalyzed addition to *N*-sulfonylaldimines, see: d) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195–3200. For the copper-catalyzed direct Mannich reaction, see: e) Rueping, M.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095–1097. For the scandium-catalyzed addition to enones, see: f) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706–1709. For the palladium-catalyzed diarylation, see: g) Song, G.; Su, Y.; Gong, X.; Han, K.; Li, X. *Org. Lett.* **2011**, *13*, 1968–1971. For the catalyst-free benzylic C–H bond olefination, see: h) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849–6855. For the ytterbium-catalyzed conjugate addition to methylenemalononitriles, see: i) Qian, B.; Shi, D.; Yang, L.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2146–2150.

[143] a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092–14093. b) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056–12057. c) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439–12441. Also, see: d) Hamana, H.; Sugasawa, T. *Chem. Lett.* **1984**, *13*, 1591–1594.

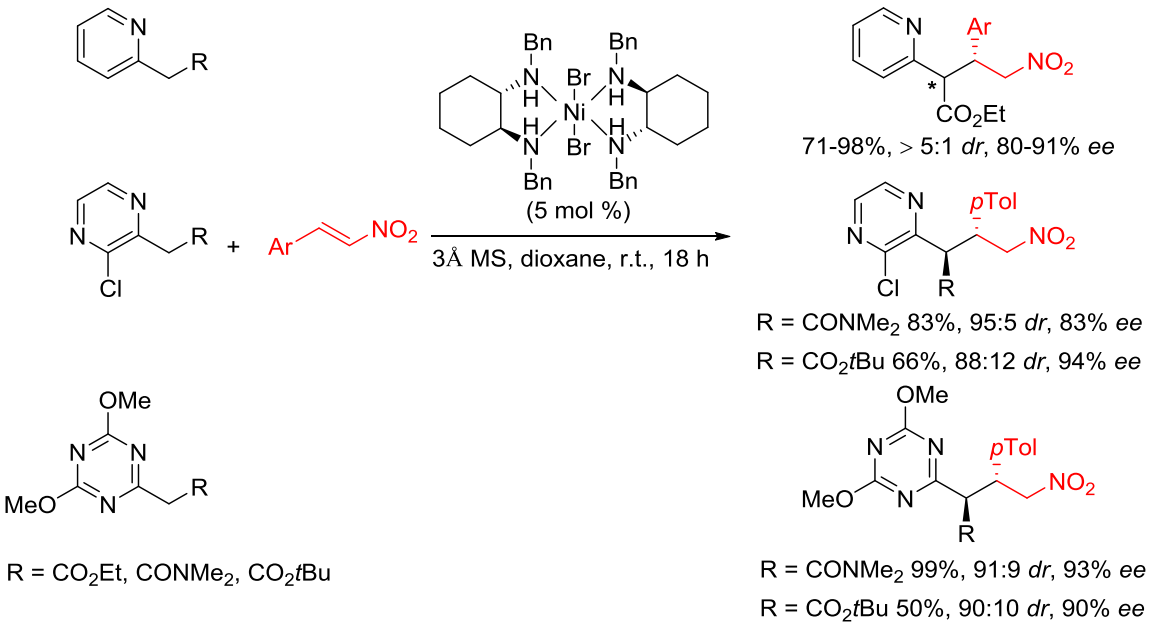
Milder conditions have been developed for the α-functionalization of preactivated substrates. In 2012, Lam and coworkers described the diastereo- and enantioselective Pd(II)-catalyzed additions of 2-alkylazaarenes to *N*-Boc imines and nitroalkenes (Scheme 48).[144] The incorporation of an EWG in the azaarene ring would further acidify the α-carbon of the pendant alkyl substituent by stabilization of the conjugate base. The reactions are promoted by a chiral Pd(II)-BOX complex where an acetate ligand deprotonates the alkylazaarene. High temperature (50 ^{o}C) and long reaction times are required to perform the reactions in good yields, without compromising the estereoselectivity.



Scheme 48.

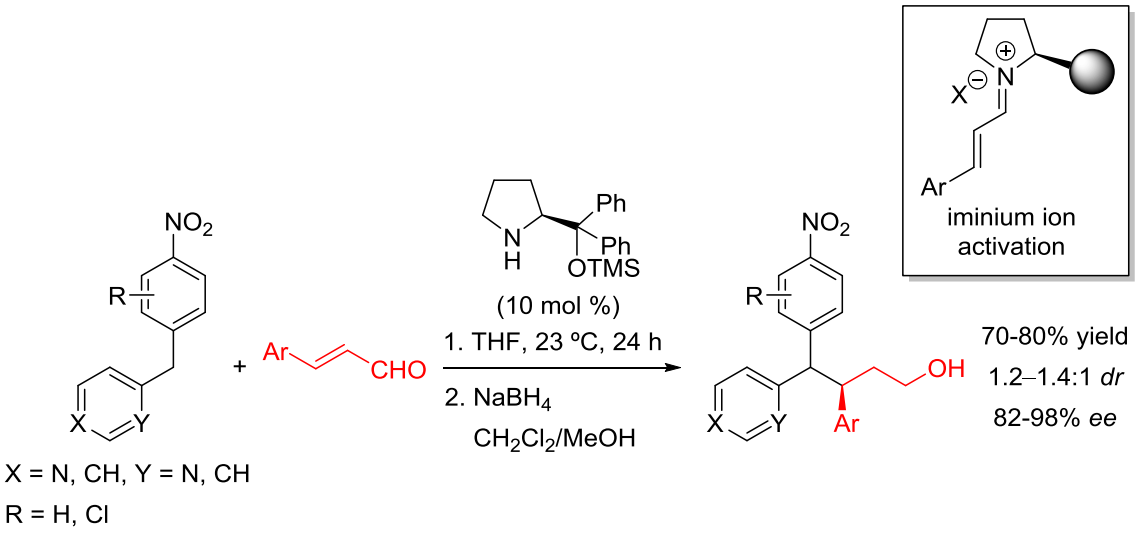
In the same year this group developed a similar strategy consisting of the Nickel (II) catalyzed Michael addition of activated alkyl azaarenes to nitroolefins.[145] In this case, the activation of the pronucleophile was made incorporating and EWG in the Cα position of the azaarene ring (Scheme 49). It was proposed that the catalyst releases one diamine ligand that deprotonates the azaarene substrate to form the reactive enolate. When using azaarylacetates excellent enantioselectivities were achieved. However, after purification in column chromatography epimerization of the newly generated Cα stereocenter (R = CO_2R) was observed. On the other hand, azaaryl acetamide products were configurationally stable and in these cases very good to excellent estereoselectivities were obtained after column chromatography. The presence of 3Å molecular sieves was necessary to get excellent *ee* values.

[144] Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196.
[145] Fallan, C.; Lam, H. W. *Chem. Eur. J.* **2012**, *18*, 11214–11218.



Scheme 49. Asymmetric Michael additions of azaarylacetates and acetamides to nitroalkenes.

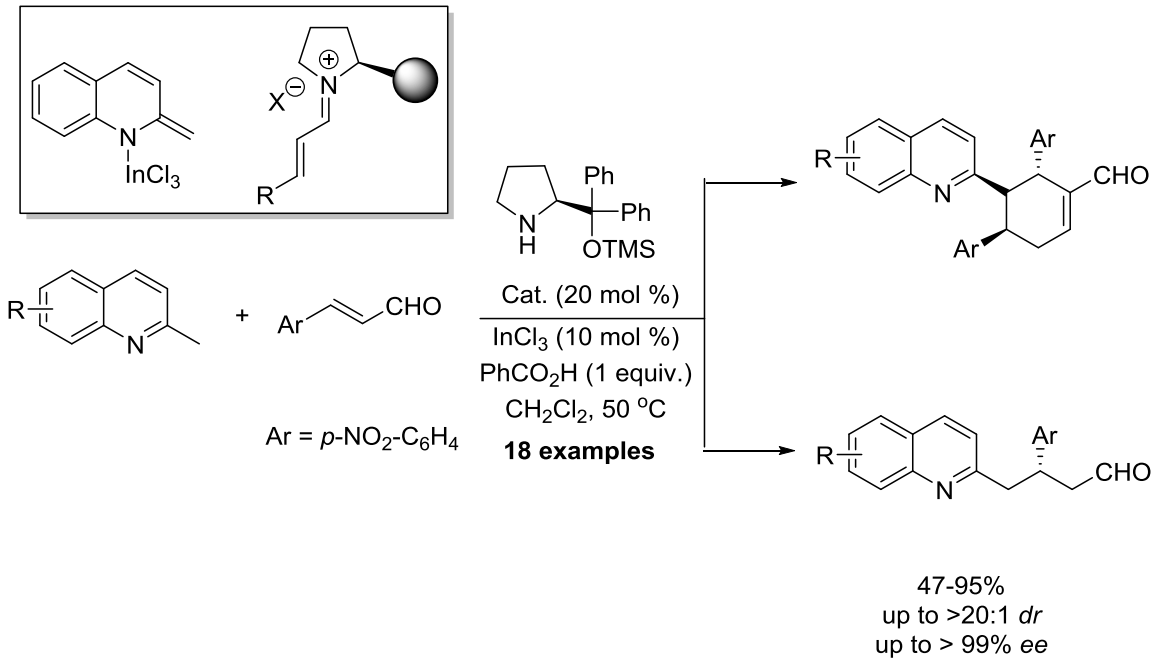
Within the field of aminocatalysis, Melchiorre and coworkers[146] reported in 2011 the asymmetric Michael addition of nitrobenzyl pyridines to enals via iminium ion activation. The reaction proceeded generally in poor diastereoselectivities and very good to excellent enantioselectivities for both diastereomers (Scheme 50).



Scheme 50. Asymmetric Michael addition of nitrobenzyl pyridines to enals.

[146] a) Vera, S.; Liu, Y.; Marigo, M.; Escudero-Adán, E.; Melchiorre, P. *Synlett* **2011**, *2011*, 489–494. For more examples on aminocatalysis, see: b) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem. Eur. J.* **2013**, *19*, 9147–9150. c) Meazza, M.; Ceban, V.; Pitak, M. B.; Coles, S. J.; Ríos, R. *Chem. Eur, J.* **2014**, *20*, 16853−16857. d) Meazza, M.; Potter, M.; Pitak, M. B.; Coles, S. J.; Mazzanti, A.; Ríos, R. *Eur. J. Chem.* **2017**, 719−725. For related reactions involving 2-alkylarenes, see: e) Cid, M. B.; Duce, S.; Morales, S.; Rodrigo, E.; García-Ruano, J. L. *Org. Lett.* **2010**, *12*, 3586–3589. f) Duce, S.; Jorge, M.; Alonso, I.; García-Ruano, J. L.; Cid, M. B. *Eur. J. Org. Chem.* **2013**, 7067−7075. g) Dell'Amico, L.; Companyó, X.; Naicher, T.; Bräuer, T. M.; Jørgensen, K. A. *Eur. J. Org. Chem.* **2013**, 5262−5265.

Last year and after our work on this subject, Jørgensen´s research group[147] described a synergistic estereoselective functionalization of unactivated alkyl quinolines with α,β-unsaturated aldehydes combining a synergistic metal catalysis with organocatalytic activation. The reaction required neither pre-activated alkyl quinoline substrates with electron-withdrawing substituents nor highly activated electrophiles (Scheme 51).



Scheme 51. Estereoselective functionalization of unactivated alkyl quinolines.

As far as we know, at that time, there were no more examples on the use of 2-alkyl azaarenes as nucleophiles for the asymmetric formation of C-C bonds.

Despite the fact that the addition of 2-alkylazaarenes to different electrophiles has been carried out with more or less success, the methods displayed above present some limitations:

1. If the alkyl azaarene is not activated, more than stoichiometric amounts of a strong base are needed.

[147] a) Meazza, M.; Tur, F.; Hammer, N.; Jørgensen K. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 1634–1638. For a highly enantioselective metallation-substitution α to a chiral nitrile, see: b) Sadhukan, A.; Hobbs, M. C.; Meijer, A. J. H. M.; Coldham, I. *Chem. Sci.* **2017**, *8*, 1436−1441. For a S_N1-type alkylation of *N*-heteroaromatics with alcohols, see: c) Xiao, M.; Ren, D.; Xu, L.; Li, S.-S.; Yu, L.; Xiao, J. *Org. Lett.* **2017**, *19*, 5724–5727. For catalytic direct-type 1,4-addition reactions of alkylazaarenes, see: d) Suzuki, H.; Igarashi, R.; Yamashita, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 4520–4524. e) Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc*. **2017**, *139*, 5003–5006. For the yttrium-catalyzed C(sp^3)-H asymmetric addition of 2-methyl azaarenes to cyclopropenes getting Cβ sereocenter, see: f) Luo, Y.; Teng, H.-L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.*, **2017**, *56*, 9207–9210. For the racemic addition of alkylpyridines to styrenes using potassium bis(trimethylsilyl)amide as a strong base, see: g) Zhai, D.; Zhang, X.; Liu, Y.; Zheng, L.; Guan, B. *Angew. Chem. Int. Ed.*, **2018**, *57*, 1650–1653.

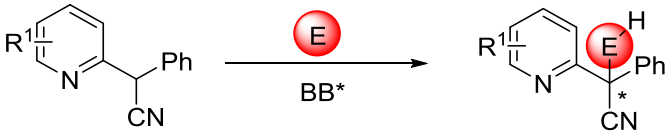
2. The use of preactivated substrates: EWG in either the azaarene ring or the Cα or both positions is needed.
3. None of these methods address the generation of a quaternary Cα-stereocenter, an issue of general importance in organic synthesis, and of particular significance to the present context given the interest of quaternary compounds as potential pharmacophores.

2.2. Michael addition of 2-(cyanomethyl)azaarenes to α'-hydroxy enones

2.2.1. Working hypothesis and synthetic plan

As mentioned above, due to the lack of methods in the literature to generate a quaternary α-stereocenter using 2-alkylazaarenes as nucleophiles, this work was focused on the study of the enantioselective α-functionalization of *o*-substituted azaarenes via mild enolization conditions.

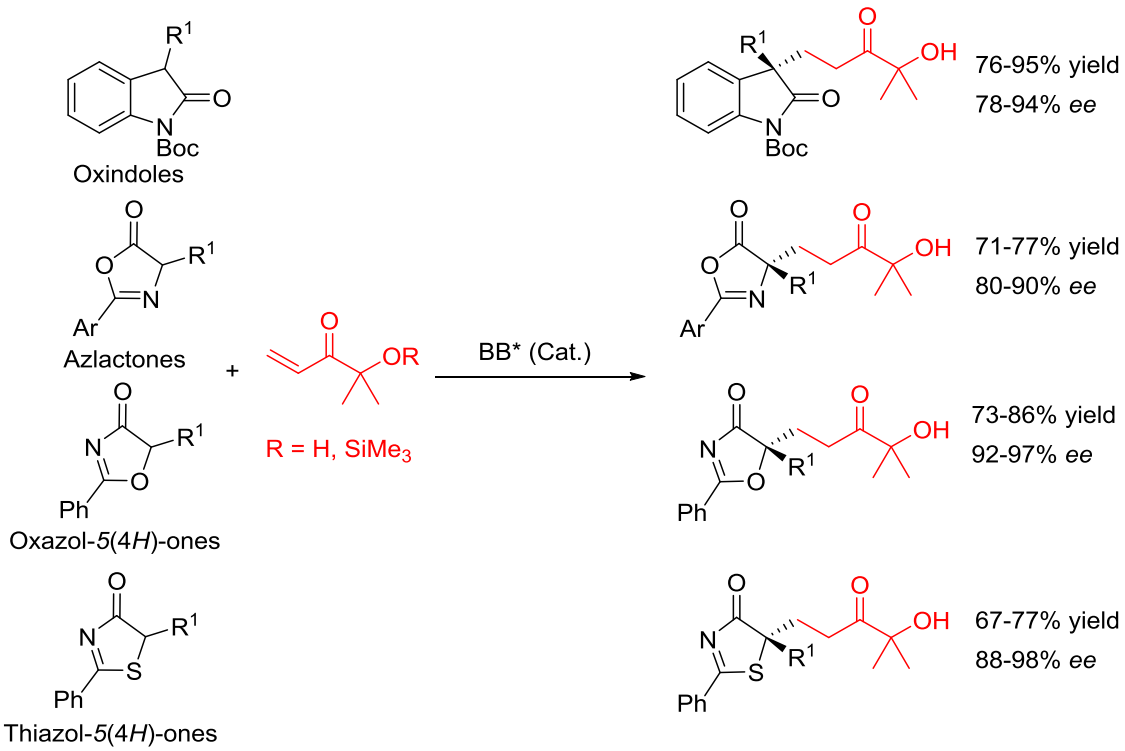
We envisioned that the 2-cyanoalkylpyridine could be good candidate to be deprotonated under Brønsted base catalysis, due to the incorporation of two EWG groups (nitrile and phenyl) in the Cα position of the azaarene, and be added to different electrophiles (Scheme 52).



Scheme 52. Proposed reaction for the investigation.

In 2014, our group[148] reported the first organocatalytic Brønsted based Michael addition of a range of enolizable heterocycles (α-subtituted 2-oxindoles, cyanoesters, oxazolones, thiazolones and azlactones) to α'-oxyenones as enabling Michael acceptors with ambivalent H-bond acceptor/donor character, creating a tetrasubstituted carbon stereocenter with excellent yields and selectivities (Scheme 53).

[148] a) Badiola, E.; Fiser, B.; Gomez-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. For a review on the use of α'-hydroxy enones in asymmetric synthesis, see: b) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev*. **2012**, *41*, 4150–4164.



Scheme 53.

These electrophiles exhibit higher reactivity than most acrylate surrogates (e.g. methyl vinyl ketone (MVK)) favored by a lower HOMO-LUMO energy gap, due to the intramolecular interactions between the carbonyl and the hydroxyl (**1a**) or silyloxy group (**1b**) (Figure 14).

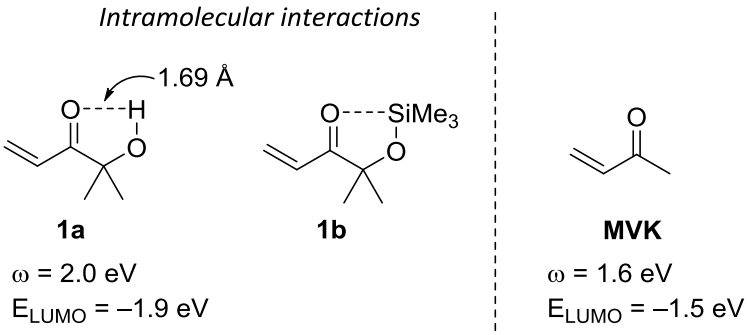
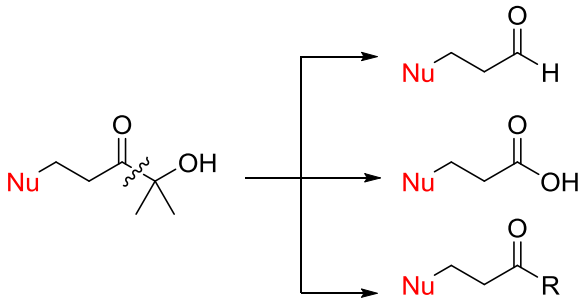


Figure 14. Intramolecular interactions between the carbonyl and the hydroxyl or silyloxy group.

Moreover, the interest in this family of Michael acceptors comes from the synthetic potential of their adducts, since several functional groups , such as aldehydes, carboxylic acids and ketones can be accessed by simple elaboration processes (Scheme 54).



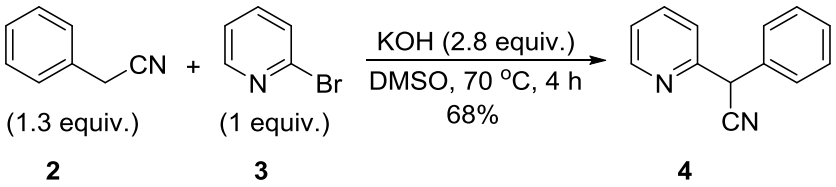
Scheme 54. Readily accessible functional groups via ketol scission.

On these basis, the reaction of 2-phenyl-2-(2-pyridyl)acetonitrile **4**, and α´-hydroxyenones **1a**-**b** was elected for evaluation under the presence of several BB catalysts (Scheme 55).

Scheme 55.

2.2.2. Results and discussion

Compound **4** was prepared in good yield through a S_NAr reaction between 2-phenyl-ethanenitrile **2** and 2-bromo pyridine **3** in the presence of KOH in DMSO keeping the reaction temperature at 70 °C for 4 h (Scheme 56).[149]

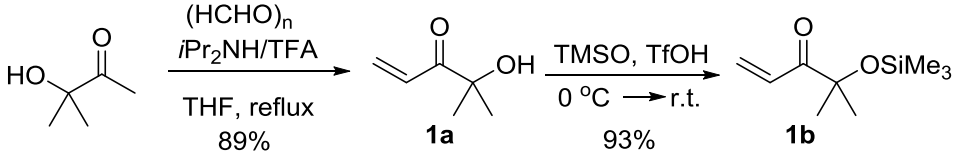


Scheme 56. Synthesis of **4**.

α´-Hydroxy enone **1a** was prepared in high yield from commercially available 3-hydroxy-3-methyl-2-butanone via aldol addition/elimination reaction sequence (Scheme 57).[150] Enone **1a** was silylated, via TMSOTf, mixing with 3-(trimethylsilyl)-2-oxazolidinone (TMSO) and catalytic amounts of trifluoroacetic acid at room temperature

[149] Kawano, T.; Kurimoto, M.; Hatanaka, M.; Ueda, I. *Chem. Pharm. Bull.* **1992**, *40*, 3067–3071.
[150] Adapted from: Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, 46, 1715–1717.

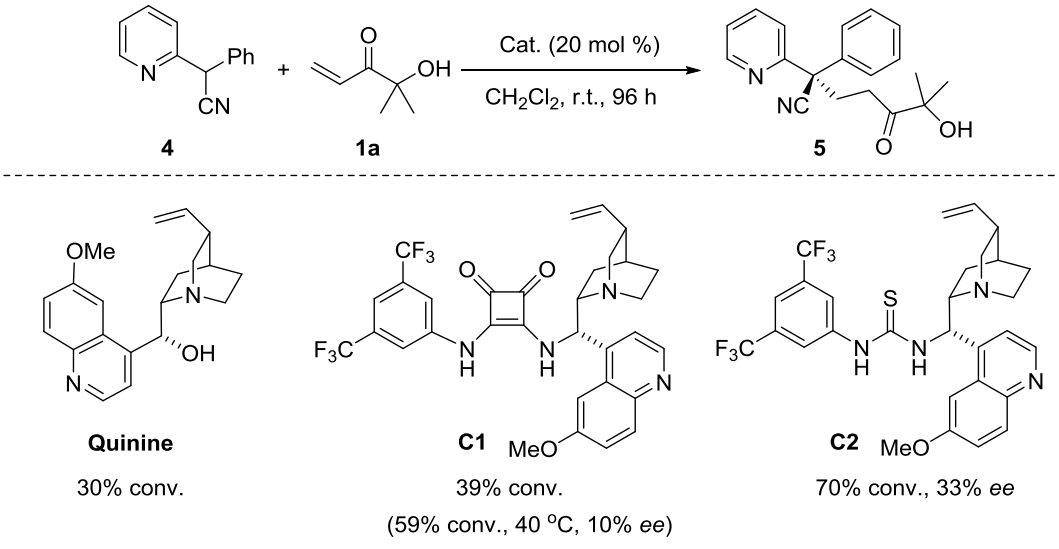
under neat conditions.[151] The desired α'-silyloxy enone **1b** was obtained in excellent yield after column chromatography.



Scheme 57. Synthesis of α´-hydroxy enone **1a** and α'-silyloxy enone **1b**.

After having the starting materials in hand, our study began with the evaluation of several bifunctional catalysts (Brønsted base/H bond donor) for the addition of 2-phenyl-2-(2-pyridyl)acetonitrile **4** to α'-hydroxy enone **1a** (Table 1). First, quinine was tested for the reaction in dichloromethane at 0 °C with a 20 mol % catalyst loading, rendering poor conversion after 96 h. Similar conversion was obtained with bifunctional squaramide **C1**, improving it slightly at 40 °C but with poor enantioselectivity (10% *ee*). Thiourea-based catalyst **C2** rendered better conversion, but still with poor enantioselectivity (33% *ee*).

Table 1. Catalyst screening for the Michael addition of **4** to **1a**.[a]

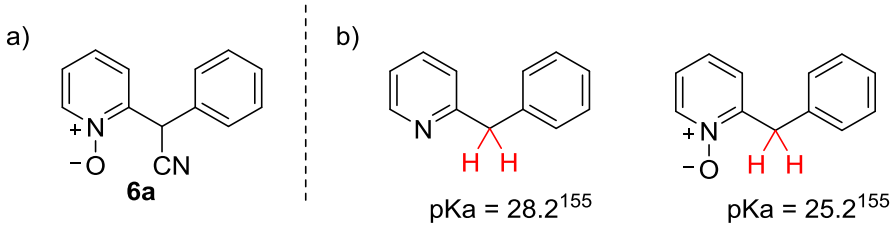


[a] Reaction conditions: **4** (1 equiv., 0.2 mmol), **1a** (3 equiv., 0.6 mmol), catalyst (20 mol %) were stirred at room temperature for 96 h in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. *ee*'s determined by HPLC: chiralpak IC column, eluent Hex/*i*Pr 90:10 f = 0.5 mL/min.

At this point, to increase the low reactivity of the nucleophile we decided to activate it by using the pyridine oxide **6a** (Scheme 57a). On the one side, it is well known that the

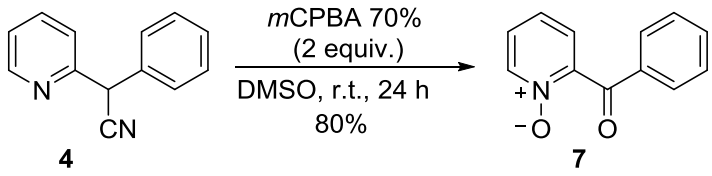
[151] Adapted from: Aizpurua, J. M.; Palomo, C., Palomo, A. L. *Can. J. Chem.* **1984**, *62*, 336−340.

oxidation of the pyridine increases the acidity of the Cα (Scheme 57b)[152] and in the other side, the N→O group could work as another strong coordinating site for catalyst binding.[153] As far as we know azaarene *N*-oxides have not been investigated within the context of asymmetric C(sp^3)–H functionalizations.[154]



Scheme 58.

A reasonable approach to obtain the desired product was the direct oxidation of 2-cyanomethylpyridine **4** in the presence of *meta*-chloroperoxybenzoic acid (*m*CPBA) oxidant. Unfortunately, the desired compound was not observed, obtaining only the benzoylpyridine *N*-oxide as a white solid in very good yield (Scheme 59).[156]



Scheme 59. Direct oxidation of 2-cyanomethylpyridine **2** with *m*CPBA.

Taking this result into account, the problem was solved performing the reaction of 2-phenyl-ethanenitrile **2** and 2-bromo pyridine *N*-oxide **8** in the presence of potassium

[152] 2-Alkylpyridine *N*-oxides are more acidic than the parent 2-alkylpyridines in about 3–4 pKa units in DMSO: a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463. b) http://www.chem.wisc.edu/areas/reich/pkatable/. c) Evans pKa table: http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf/.

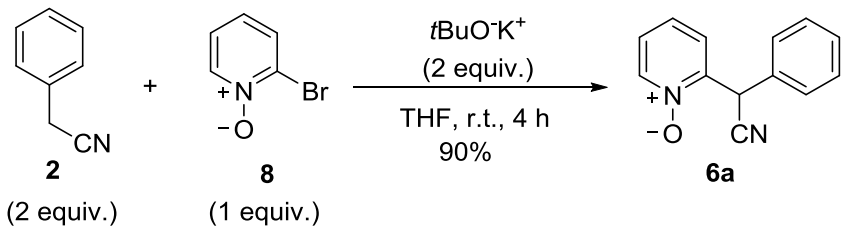
[153] The oxygen atom in the *N*-oxide has stronger dipole than the oxygen atoms of other common oxo donor such as alcohols, ethers, and amides. a) Karayannis, N. M. *Coord. Chem. Rev.* **1973**, *11*, 93–159. b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedon: Asymmetry* **2004**, *15*, 1373–1389. c) Malkov, A. V.; Kočoskçý, P. *Eur. J. Org. Chem.* **2007**, *2007*, 29–36. d) Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574–587. e) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2014**, *114*, 6081–6129.

[154] Use of pyridine *N*-oxides has been mainly applied to the activation of the pyridine core, see: a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charrette, A. B. *Chem. Rev.* **2012**, *112*, 2642–2713. b) Yan, G.; Borah, A. J.; Yang, M. *Adv. Synth. Catal.* **2014**, *356*, 2375–2394. c) Wang, Y.; Zhang, L. *Synthesis* **2015**, *47*, 289–305. For an *N*-oxide-assisted α-C(sp^3)-trifluoromethylation of (mainly) *o*-methyl pyridines, see: d) Kuninobu, Y.; Nagase, M.; Kanai, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 10263–10266. For palladium-catalyzed Cα-arylation of 2-methyl azine *N*-oxides, see: e) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267. f) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155–3164.

[155] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

[156] For a plausible mechanism for this transformation, see: a) Brünjes, M; Ford, M. J.; Dietrich H.; Wlison, K. *Synlett* **2015**, *26*, 1365–1370. For a recent synthesis of benzoylpyridine *N*-oxide, see: b) Sterckx, H.; Sambiagio, C.; Médran-Navarrete, V. *Adv. Synth. Catal.* **2017**, *359*, 3226–3236.

tert-butoxide at room temperature for 4 h. The desired product **6a** was obtained in 90% yield (Scheme 60).[149]

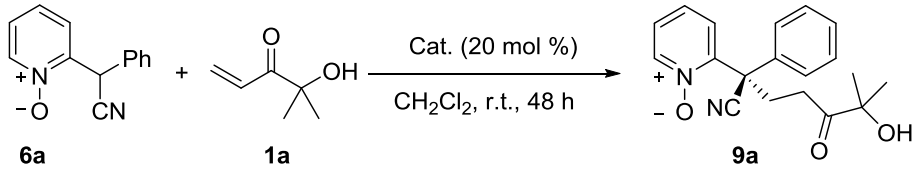


Scheme 60. Synthesis of **6a**.

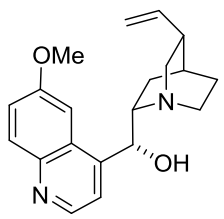
In order to check the reactivity of the new pronucleophile, the same catalysts employed before were evaluated (Table 2). As expected, *N*-oxide **6a** showed greater reactivity than **4**. Using quinine as catalyst a 72% conversion and 22% *ee* were reached after 2 days at ambient temperature. With catalyst **C1** same conversion was obtained at room temperature, but the enantioselectivity increased significantly to 88% *ee*. Reaction conversion was improved to 92% increasing the temperature to 40 ^{o}C, however enantioselectivity dropped to 75%. Finally, changing the squaramide moiety for the thiourea moiety **C2** did not perform well and lower conversion (60%) and enantioselectivity (17% *ee*) were obtained.[157]

[157] When using monofunctional Brønsted bases such as $(DHQD)_2PYR$ and $(DHQD)_2PHAL$, no reaction was observed.

Table 2. Catalyst screening for the Michael addition of 2-(cyano(phenyl)methyl)pyridine 1-oxide **6a** to α'-hydroxyenone **1a**.[a]

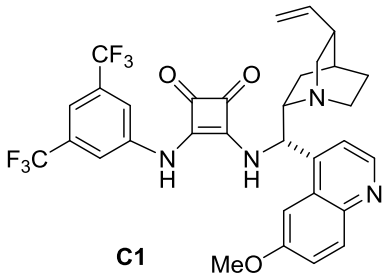


6a **1a** **9a**



Quinine

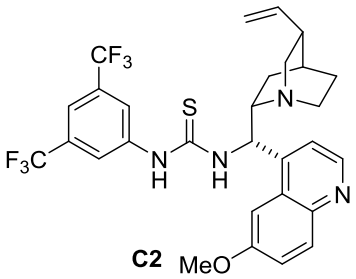
72% conv, 22% *ee*



C1

72% conv., 88% *ee*

(92% conv., 75% *ee* at 40 °C)



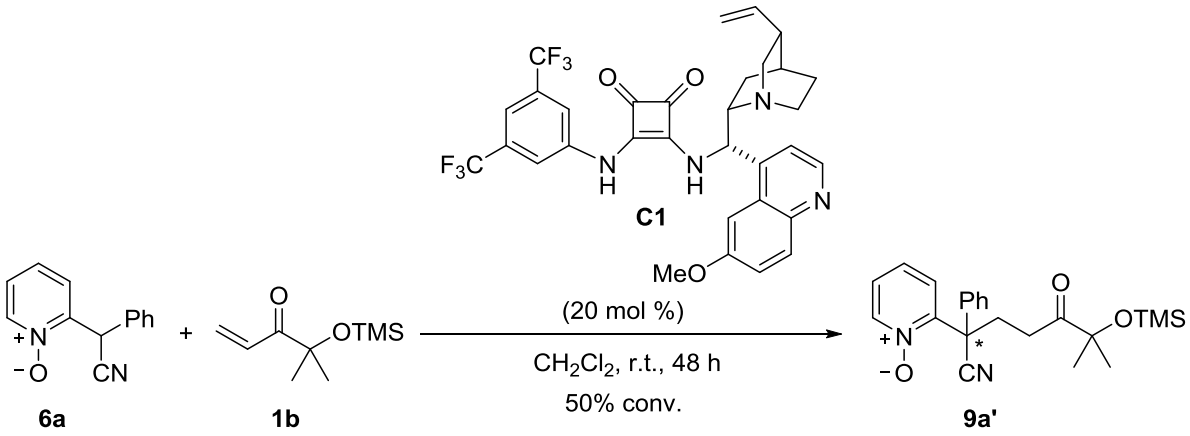
C2

60% conv., 17% *ee*

[a] Reaction conditions: **6a** (1 equiv., 0.2 mmol), **1a** (3 equiv., 0.6 mmol), catalyst (20 mol %) were stirred at room temperature for 48 h in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. *ee*'s determined by HPLC: chiralpak AD-H column, eluent Hex/EtOH 50:50 f = 0.5 mL/min.

In its turn, when α'-trimethylsilyloxy enone **1b** was employed under best reaction condition for **1a** (cat. **C1** 20 mol %, r.t., 48 h) low conversion (50%) of the substrate was achieved even after prolonged reaction time (196 h, r.t., 60% conversion). Enantiomeric excess was not calculated due to the low conversion of the reaction (Table 3).

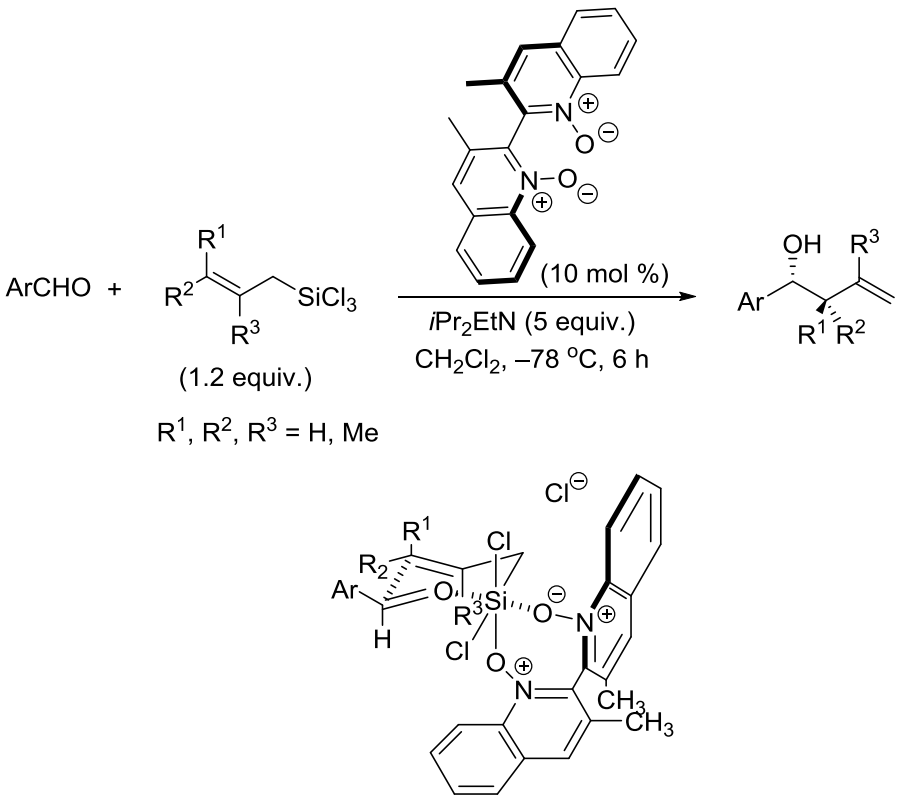
Table 3. Catalyst screening for the Michael addition of **6a** to **1b**.



After these rather disappointing results, we decided to focus in a way to improve both the conversion and the enantiocontrol of the reaction and the design of new catalyst with additional sites for substrate interactions was pursued.

To this end, we were inspired by work by Hashimoto on the enantioselective allylation of aldehydes with allyltrichlorosilanes involving chiral azaarene *N*-oxide catalyst.[158] They suggested that the allylations of aromatic and unsaturated aldehydes mediated by (S)-3,3´-dimethyl-2,2´-biquinoline *N*,*N*´-dioxide proceed via cyclic chairlike transition structures, involving hypervalent silicates where one of a pair of *N*-oxide moieties occupies an axial position (Scheme 61).

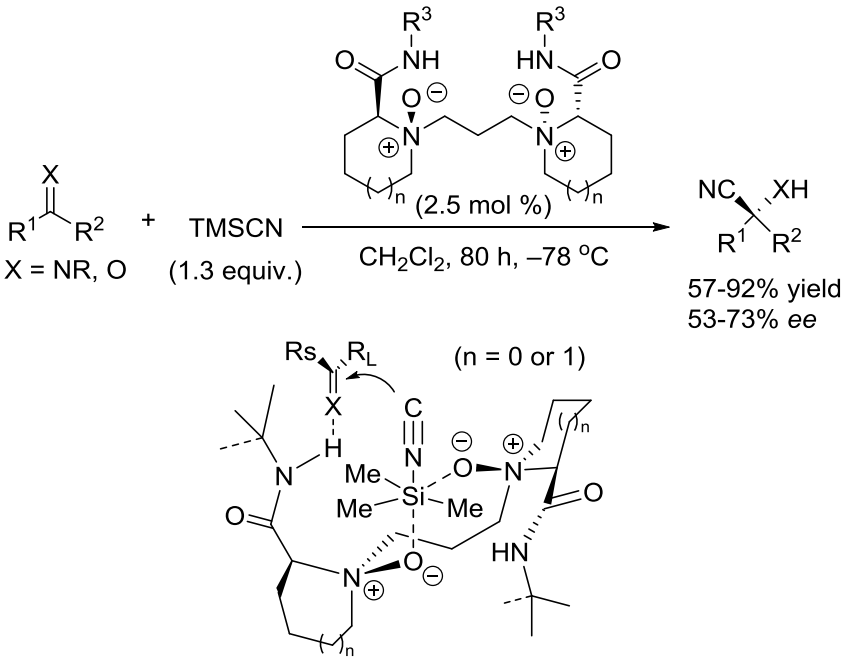
[158] a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420. For a similar activation pathways, see: b) Tao, B.; Lo, M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353–354. c) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235.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



Scheme 61.

Feng´s group developed an enantioselective cyanation of carbonyl compounds and imines utilizing trimethylsilylcyanide (TMSCN) as a nucleophile.[159] The reactions were catalyzed by L-proline or L-piperidinamide based *N*,*N*´-dioxides activating cooperatively both TMSCN and the electrophile. The possible mechanism consists in generation of a hypervalent silicon intermediate from the bidentate *N*,*N*´-dioxide which enhances both the nucleophilicity of the cyano group and the rigidity of the reaction environment. Then, the electrophile, which is activated by the hydrogen bond of a nearby amide, is attacked by the cyano group (Scheme 62).

[159] a) Wen, Y.; Huang, X.; Huang, J.; Xiong, Y.; Qin, B.; Feng, X. *Synlett* **2005**, 16, 2445–2448. b) Huang, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X.; V, S. U. *J. Org. Chem.* **2007**, *72*, 204–208. c) Qin, B.; Liu, X.; Shi, J.; Zheng, K.; Zhao, H.; Feng, X. *J. Org. Chem.* **2007**, *72*, 2374–2378. d) For a review on chiral *N*,*N*'-dioxides: new ligands and organocatalysts for catalytic asymmetric reactions, see: Liu, X.; Lin, L.; Feng, X. *Acc. Chem. Res.* **2011**, *44*, 574–587. For the proline-based *N*-oxides as chiral catalysts in the enantioselective reactions with aldehydes, see: e) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151–3154.



Scheme 62.

Taking these works into account and given the high chemical affinity of silicon for oxygen, we envisioned a multifunctional catalyst based on *N*-oxide/silicon interactions as a suitable candidate to carry out satisfactorily the reaction (Figure 15).

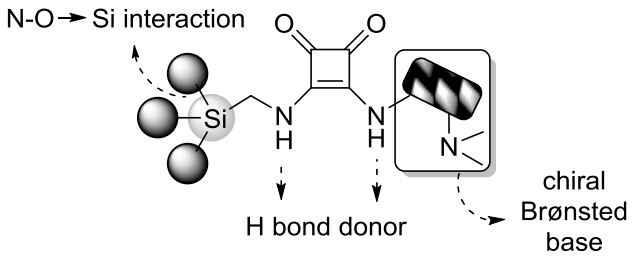
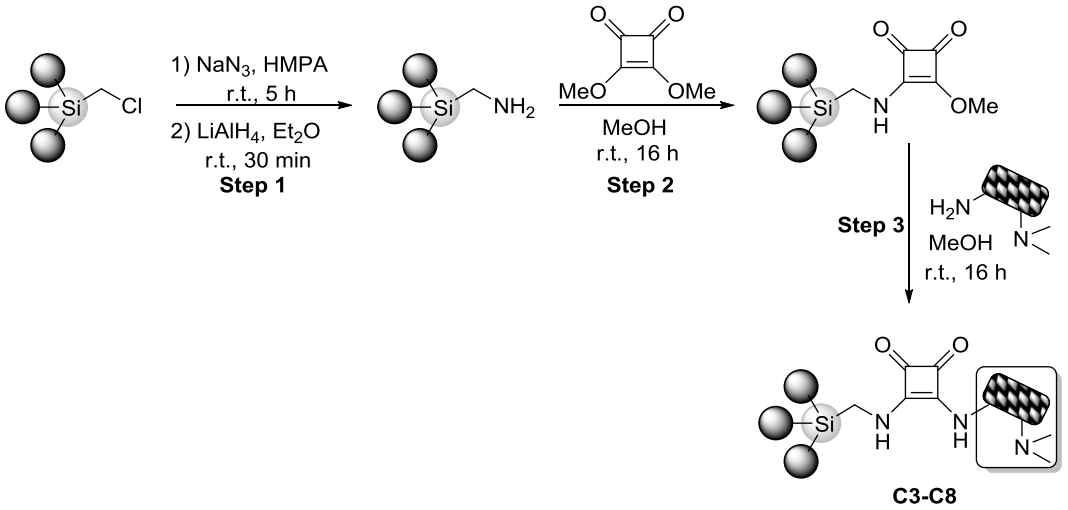


Figure 15. New design for the multifunctional squaramide-based Brønsted base catalyst.

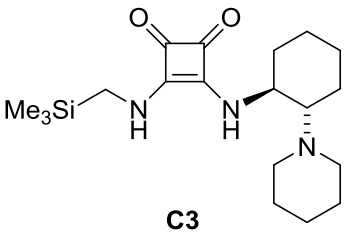
The proposed general synthetic sequence for these catalysts is outlined in Scheme 63. The sequence involves the amination of the corresponding (chloromethyl)silyl derivative in a two steps sequence; first the synthesis of the azide by treatment of the alkyl chloride with 1.1 equivalents of NaN_3 in HMPA at room temperature[160] and second, the addition of the azide to a suspension of $LiAlH_4$ (1 equivalent) in dry Et_2O at 0 ^oC to obtain the amine.[161] The coupling between the 3,4-dimethoxy-3-cyclobutene-1,2-diene and the amine was performed in MeOH at room temperature and, finally, the coupling of the second amino group containing the corresponding Brønsted base was performed also in MeOH at room temperature for 16 h. Using these reaction sequence, changing substituent at the silicon moiety and the Brønsted base, a series of new multifunctional catalysts were synthetized. Yield of different steps are summarized in Table 4.



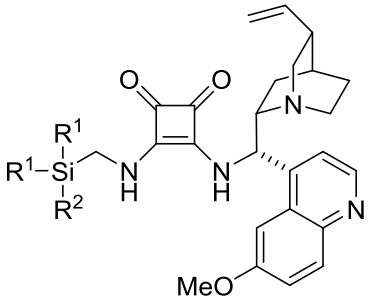
Scheme 63. Squaramide-based Brønsted base catalyst preparation.

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

Table 4. Yield by stages in the preparation of catalysts.



C3



C4 R^1, R^2 = Me
C5 R^1 = Me, R^2 = Ph
C6 R^1 = Me, R^2 = 2-Naphthyl
C7 R^1 = Ph, R^2 = Me
C8 R^1, R^2 = Me

Entry		Step 1 (%)[a]	Step 2 (%)	Step 3 (%)
1	**C3**	--[b]	83	45
2	**C4**	--[b]	83	68
3	**C5**	90	70	70
4	**C6**	80	70	75
5	**C7**	81	90	60
6	**C8**	84	85	67

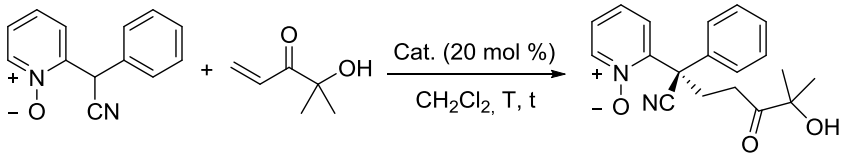
[a] Yield of the product after the S_N2 and the reductive steps. [b] This intermediate is commercially available and was purchased.

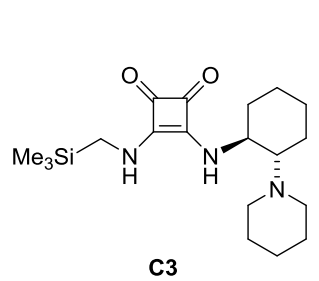
2.2.2.1. Catalysts screening

Gratifyingly, we observed that catalyst **C4** led to a full conversion in just 20 h at 40 ^oC and with high selectivity (90% *ee*). However, the conversion and selectivity dropped significantly after replacing the aminoquinine group in **C4** with the 1,2-diaminocyclohexane scaffold (**C3**, 83% conv., 58% *ee*). Then, we explored the effect of the bulkiness of the silyl group on the selectivity. For example, increasing the Lewis acidity and the bulkiness of the silyl group changing the methyl group of the silyl moiety for the phenyl group (**C5**), excellent enantioselectivity was achieved (92% *ee*) with full conversion after 64 h at room temperature.[162] Nevertheless, a further increase of the size of the silyl site did not improve the enantioselectivity but it made it worse **C6**-**C8**. The use of more coordinating solvent as THF provided poorer results than the one obtained with DCM, just 14% *ee* was obtained after 48 h. In this case, solvent might interact with the catalyst, hindering coordination with the nucleophile.

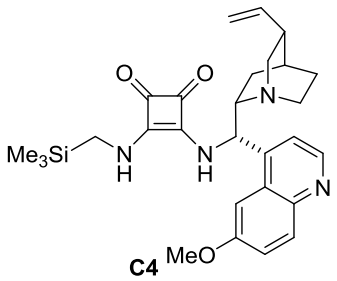
[162] No reaction was observed using silylated enone **1b** and **C5** as catalyst at 40 ^oC for 24 h.

Table 5. Catalyst screening for the Michael addition of **6a** to **1a**.[a]

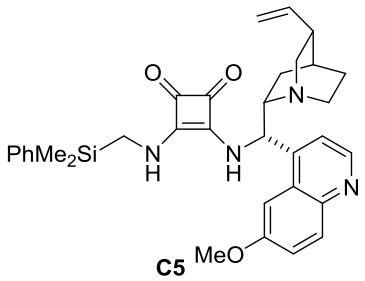




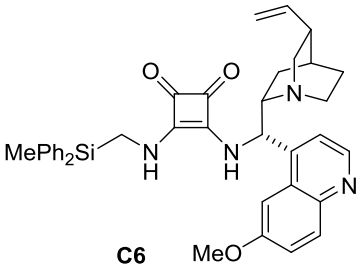
40 °C, 96 h, 83% conv., 58% *ee*



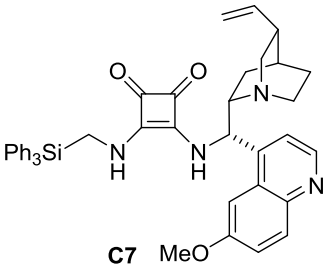
40 °C, 20 h, 100% conv., 90% *ee*



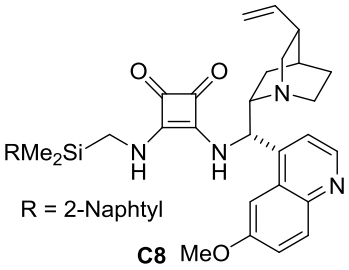
20 °C, 64 h, 100% conv., 92% *ee*
THF; 0 °C, 48 h, 85% conv., 14% *ee*[b]



40 °C, 24 h, 100% conv., 85% *ee*



20 °C, 64 h, 100% conv., 81% *ee*



40 °C, 24 h, 100% conv., 84% *ee*

[a] Reaction conditions: **6a** (1 equiv., 0.2 mmol), **1a** (3 equiv., 0.6 mmol), catalyst (20 mol %) were stirred in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. *ee*'s determined by HPLC: chiralpak AD-H column, eluent Hex/EtOH 50:50 f = 0.5 mL/min. [b] Using THF as a solvent had not positive effect on enantiomeric excess.

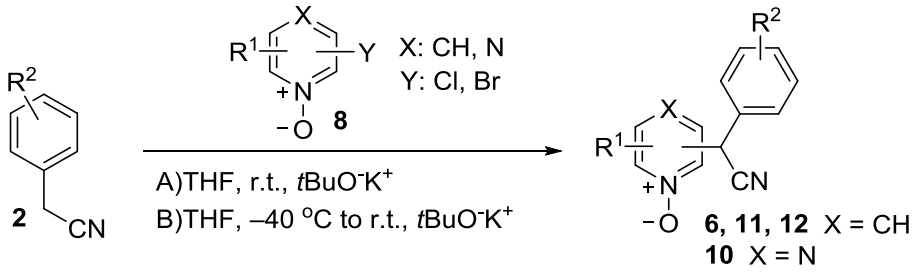
Thus, the optimal reaction conditions for the addition of 2-(cyano(phenyl)methyl)pyridine 1-oxide **6a** to the α'-hydroxyenone **1a** (3 equiv.) included the presence of catalyst **C5** at room temperature using dichloromethane as a solvent.

2.2.2.2. Synthesis of α-substituted 2-(cyanomethyl)azaarene *N*-oxides

With the best conditions found for the catalytic enantioselective Michael addition reaction, we continued with the preparation of the substrates for the study of the reaction scope.

The same procedure used in the synthesis of the substrate **6a** was followed for the preparation of adducts **6**, **10**, **11** and **12** in general obtaining very good yields. In the case of benzyl cyanides bearing strong EWGs, reaction was carried out at –40 °C to avoid decomposition of the substrate.

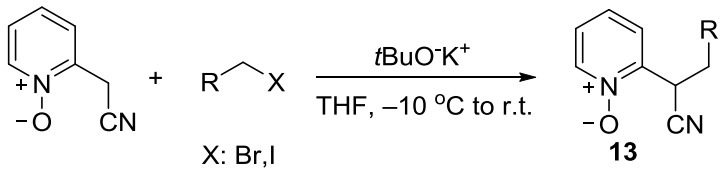
Table 6. Synthesis of adducts **6**, **10**, **11** and **12**.



Entry		R^1	R^2	X	Y	T(°C)	Yield (%)
1	**6a**	H	H	CH	2-Br	r.t.	90
2	**6b**	6-Br	H	CH	2-Br	r.t.	71
3	**6c**	5-Me	H	CH	2-Br	r.t.	70
4	**6d**	5-Cl	H	CH	2-Br	r.t.	68
5	**6e**	H	4-Me	CH	2-Br	r.t.	84
6	**6f**	H	4-Br	CH	2-Br	r.t.	88
7	**6g**	H	3-thiophene	CH	2-Br	–40	60
8	**6h**	H	4-OMe	CH	2-Br	r.t.	71
9	**6i**	H	4-CF_3	CH	2-Br	–40	56
10	**6j**	H	4-CO_2Me	CH	2-Br	–40	80
11	**6k**	5-Cl	4-Me	CH	2-Br	r.t.	83
12	**6l**	6-Br	4-CF_3	CH	2-Br	–40	84
13	**10a**	H	H	N	2-Cl	r.t.	87
14	**10b**	6-Cl	H	N	2-Cl	r.t.	50
15	**10c**	H	4-Br	N	2-Cl	r.t.	81
16	**11**	H	H	CH	3-Br	r.t.	70
17	**12**	H	H	CH	4-Cl	r.t.	65

The 2-(α-cyanoalkyl)pyridine *N*-oxides **13a**-**d** were prepared from 2-(cyanomethyl)pyridine 1-oxide and the corresponding alkyl halide in the presence of potassium *tert*-butoxide using THF as a solvent. The desired products were isolated in good yields; adduct **13a** (35% yield) being an exception (Table 7).

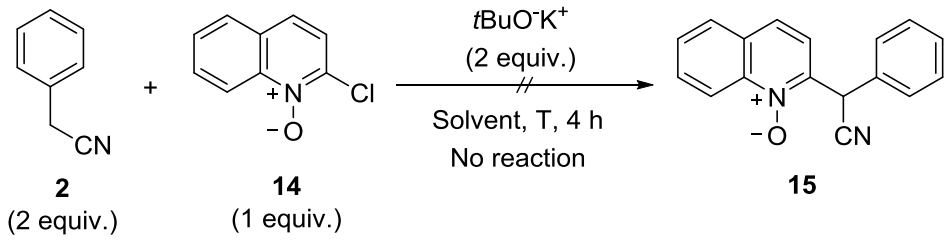
Table 7. Synthesis of adducts **13a**-**d**.



Entry		R	X	Yield (%)[a]
1	**13a**	Me	I	35
2	**13b**	Ph	Br	70
3	**13c**	4-$CF_3C_6H_4$	Br	74
4	**13d**	4-ClC_6H_4	Br	71

[a] Yield of isolated product.

Several attempts were made for the synthesis of 2-(cyano(phenyl)methyl)quinoline 1-oxide **15** without any success. Under conditions employed for the synthesis of **6**, **10**, **11** and **12**, decomposition of the starting product **14** was observed. It was also observed that lower temperatures and different solvents, lead to the appearance of several by-products in the reaction mixture of which only benzyl cyanide **2** could be identified.

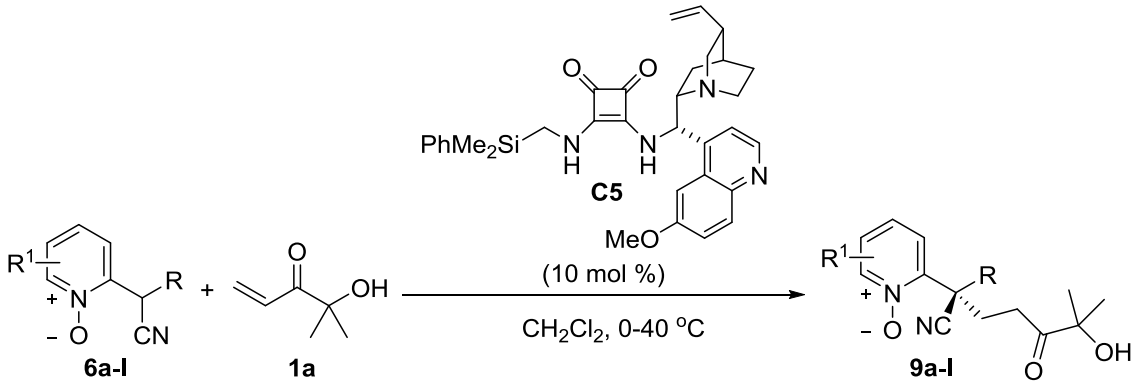


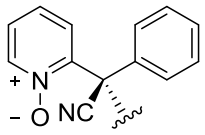
Scheme 64.

2.2.2.3. Reaction scope

Once the starting products were prepared, the scope and limitation of the system were investigated. As results in Table 8 show, it was found that the reaction tolerated well pyridine *N*-oxides with both electron-releasing and withdrawing groups attached at different positions of the pyridine ring (**9b**-**d**). Similarly, substrates bearing both electron-rich and -poor aryl substituents at Cα (**9e**-**j**) were equally effective in providing the corresponding addition adducts in generally very good yield and high enantioselectivity. Pyridine *N*-oxides with substituents in both pyridine ring and Cα also worked well, without compromising the yield or the stereocontrol of the reaction. It was found that 2-(cyanomethyl)pyridine *N*-oxides bearing electron-withdrawing groups (**6b**, **6d**, **6f**, **6g**, **6i**, **6j** and **6l**) were more reactive than those with electron-releasing groups (**6c**, **6e**, **6k**) and in these cases full conversions were reached with lower temperatures.

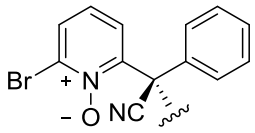
Table 8. Scope of the reaction of α-substituted 2-(cyanomethyl)pyridine *N*-oxides **6a**-**l** with **1a** catalyzed by **C5**[a]





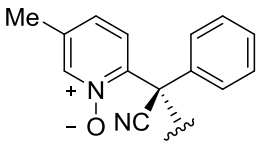
9a

r.t., 90 h, 80% (92% *ee*)
r.t., 64 h, 82% (92% *ee*)[b]



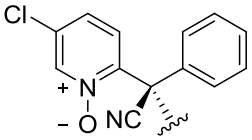
9b

0 °C, 40 h, 83% (94% *ee*)



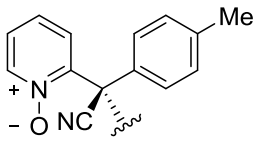
9c

40 °C, 48 h, 66% (90% *ee*)



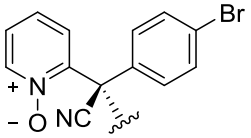
9d

0 °C , 72 h, 72% (90% *ee*)



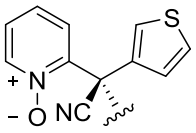
9e

40 °C, 48 h, 79% (90% *ee*)



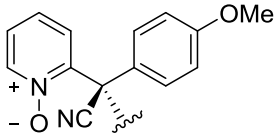
9f

0 °C, 40 h, 90% (90% *ee*)



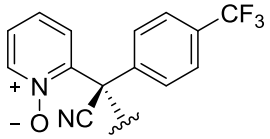
9g

0 °C, 48 h, 70% (94% *ee*)[b]



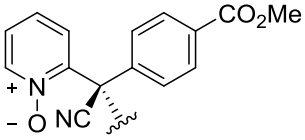
9h

r.t., 72 h, 71% (89% *ee*)



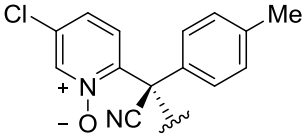
9i

0 °C, 40 h, 77% (90% *ee*)
0 °C, 24 h, 75% (92% *ee*)[b]



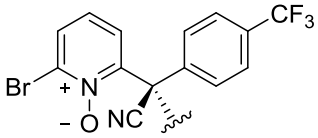
9j

0 °C, 40 h, 82% (94% *ee*)



9k

r.t., 48 h, 87% (87% *ee*)



9l

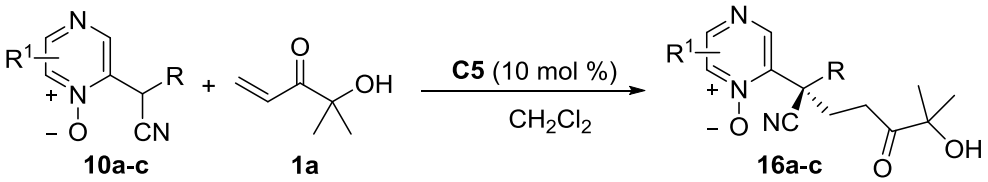
0 °C, 14 h, 85% (94% *ee*)

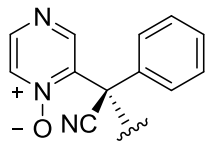
[a] Reactions conducted on a 0.2 mmol scale in 1 mL CH_2Cl_2 (molar ratio of **6**/**1a**/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase. [b] 20 mol % of **C5** was used.

The 2-cyanomethylpyrazines **10a**-**c** showed to be compatively more reactive, so lower reaction temperatures could be applied (–10 °C or –30 °C) in order to improve the

results. The quaternary α,α-diaryl acetonitriles **16a**-**c** were obtained in good yields, but somewhat lower enantioselectivities.

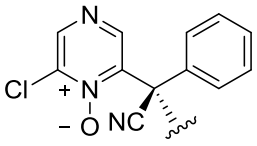
Table 9. Scope of the reaction of α-substituted 2-(cyanomethyl)pyrazine *N*-oxides **10a**-**c** with **1a** catalyzed by **C5**.[a]





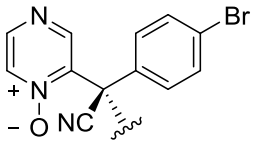
16a

–10 °C, 72 h, 82% (85% *ee*)
20 °C, 24 h, 85% (68% *ee*)



16b

–10 °C, 24 h, 78% (84% *ee*)



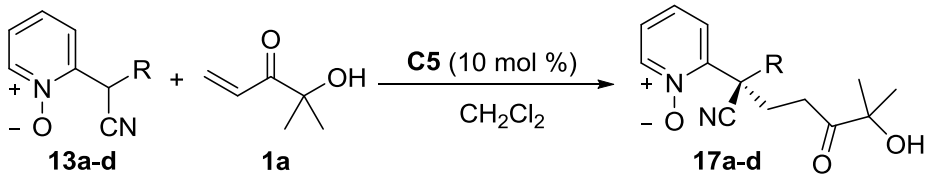
16c

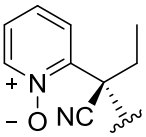
–30 °C, 24 h, 54% (86% *ee*)

[a] Reactions conducted on a 0.2 mmol scale in 1 mL CH_2Cl_2 (molar ratio of **10**/**1a**/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase.

As we expected, the method was less efficient with the corresponding α-alkyl substituted 2-(cyanomethyl)azaarene *N*-oxides **13a**-**d** (Table 10). For instance, **17a**, with an ethyl substituent, led to only 33% conversion at 40 °C after 72 h. On the other side, better conversions were achieved when the substituent is benzyl. For instance, conversion of 70% and 80% *ee* was obtained for adduct **17b**. Electron-withdrawing subtituent in the benzyl group did not improve conversions or enantioselectivities (**17c** and **17d**).

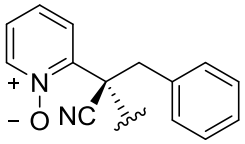
Table 10. Scope of the reaction of α-substituted 2-(cyanomethyl)azaarene *N*-oxides with **1a** catalyzed by **C5**.[a]





17a

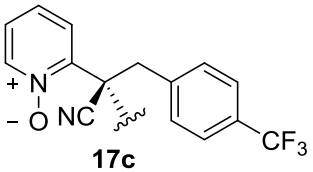
40 °C, 72 h, 33% conv.



17b

35 °C, 72 h, 70% conv.

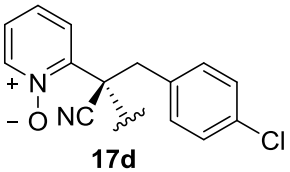
(80% *ee*)



17c

r.t., 96 h, 70% conv.

(82% *ee*)



17d

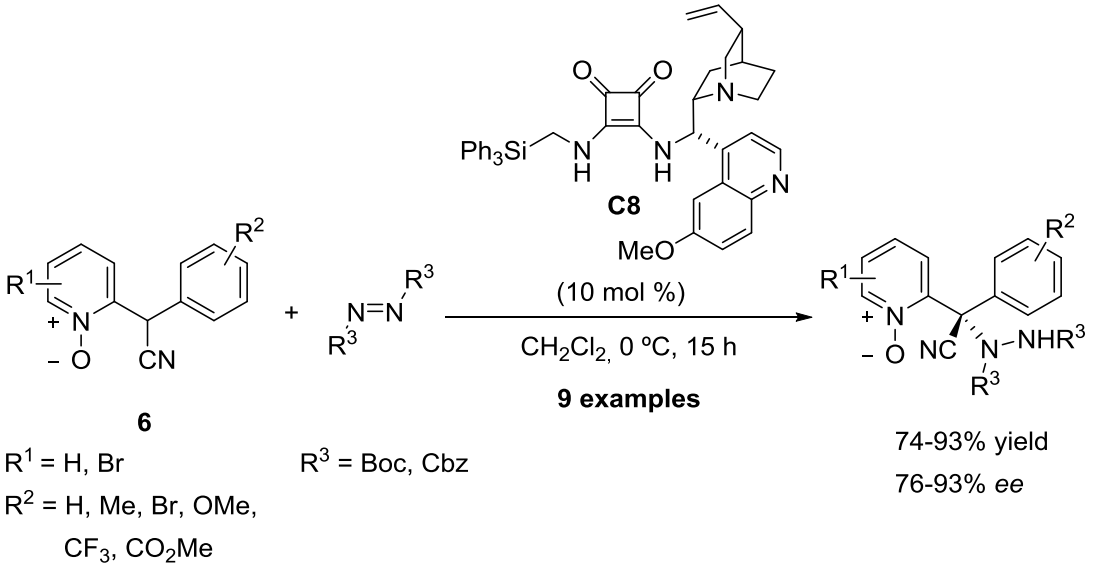
r.t., 96 h, 60% conv.

(72% *ee*)

[a] Reactions conducted on a 0.2 mmol scale in 1 mL CH_2Cl_2 (molar ratio of **13**/**1a**/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase.

Apart from their suitability in C-C bond forming reaction, it was subsequently proven by Iñaki Bastida that these 2-cyanomethylpyridine *N*-oxides may also work as enabling substrates for stereoselective α-heterofunctionalization reactions under conditions similar to those mentioned above.[163] For example, pyridine *N*-oxides **6** reacted with both di(tert-butyl) and dibenzyl azodicarboxylate in the presence of 10 mol % of the bulkiest catalyst **C8** to afford the corresponding α-aminated adducts in yields and enantioselectivities from very good to excellent (Scheme 65).

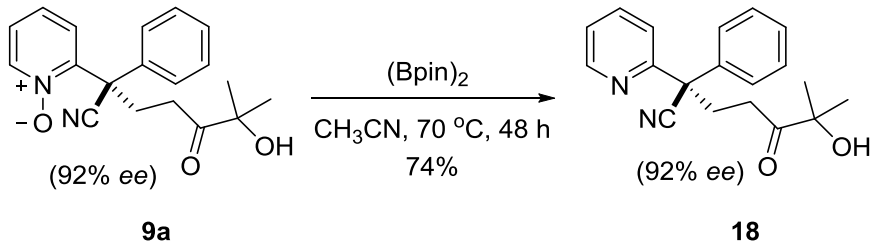
[163] For more information, see: Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282–3285.



Scheme 65. Extension of the catalytic system to the α-amination reaction.

2.2.2.4. Elaboration of adducts

The next aspect that we explored was the modification of the reaction products. For instance, reduction of the *N*-oxide group on adduct **9a** by treatment with $(Bpin)_2$[164] afforded pyridine **18** in 74% isolated yield and unaltered enantioselectivity (92% *ee*, Scheme 66).

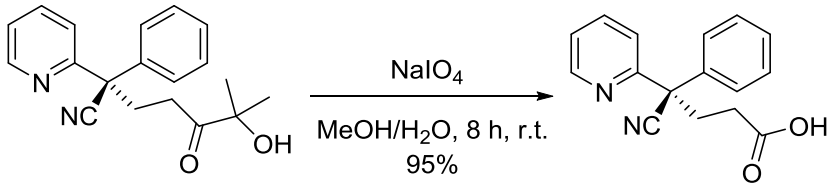


Scheme 66. Reduction of the *N*-oxide group on adduct **9a**.

As we mentioned in the introductory part, the high versatility of the oxyenone moiety allows the access to several functional groups.

For instance, oxidative cleavage of the ketol moiety in adduct **18** employing $NaIO_4$ in a mixture of $MeOH/H_2O$ at room temperature afforded carboxylic acid **19** in excellent yield (Scheme 67).

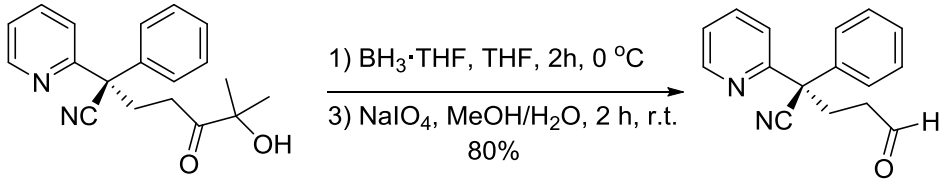
[164] Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842−7848.



18 **19**

Scheme 67.

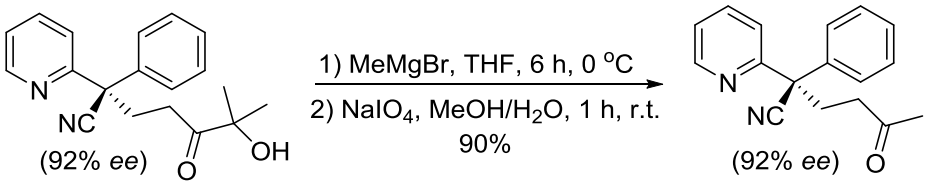
Aldehyde derivative **20** was obtained straightly from **18** through reduction of the carbonyl moiety with BH_3·THF in THF at 0 °C and subsequent oxidation of the resulting diol using sodium periodate in very good overall yield (Scheme 68).



18 **20**

Scheme 68.

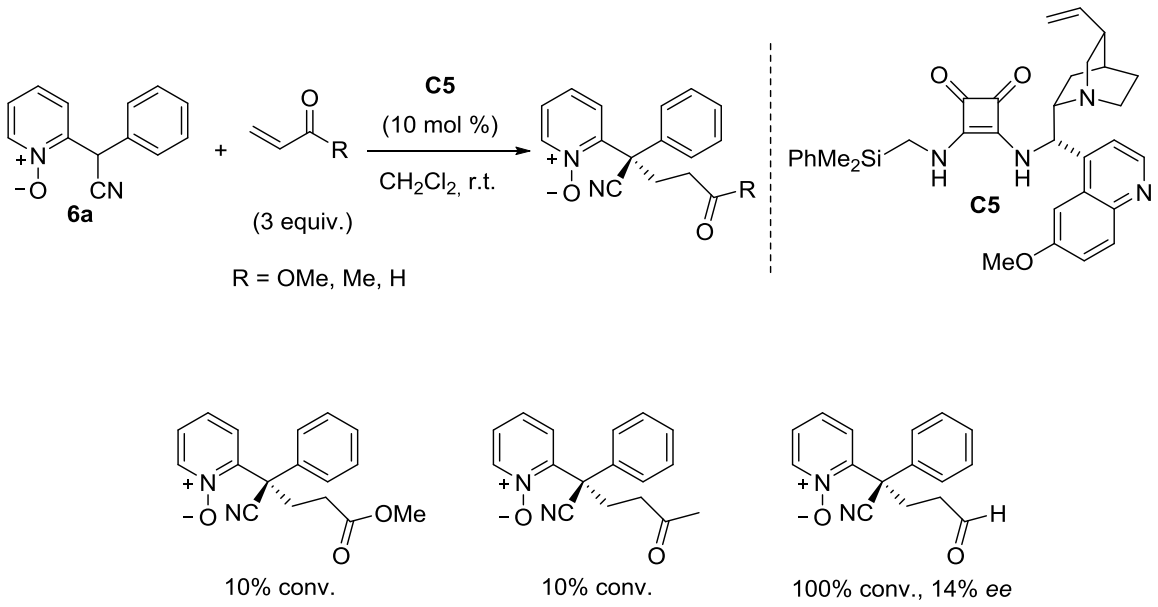
Finally, access to ketone **21** required first nucleophilic methylation of **18** using MeMgBr in THF at 0 °C and then the oxidative cleavage employing sodium periodate. Under these conditions, the desired ketone was afforded in high yield (90%, after 2 steps) without the loss of enantiopurity (Scheme 69).



18 **21**

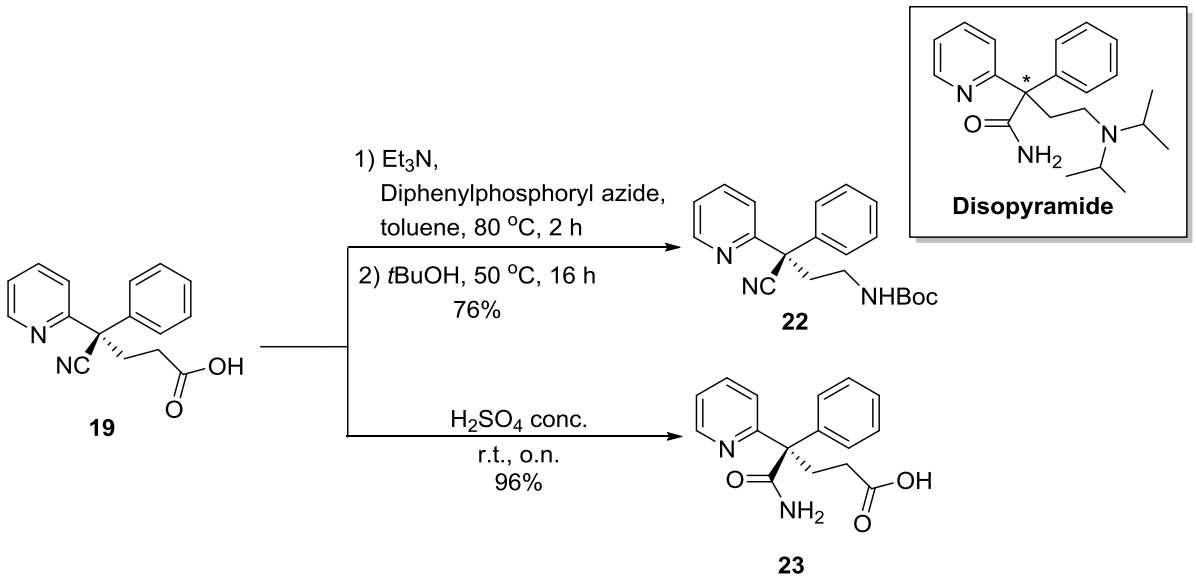
Scheme 69.

The feasibility of the ketol moiety for several manifold elaboration pathways is of particular interest in that the direct conjugate addition of azaarene *N*-oxide **6a** to simple enones, i.e. methyl vinyl ketone, or unsaturated esters, i.e. methyl acrylate, did not work under the present catalytic conditions. In addition, the reaction of **6a** with acrolein afforded the corresponding 1,4-addition adduct, but with only 14% *ee* (Scheme 70).



Scheme 70.

Another illustration of the synthetic versatility of adducts is shown by transformation of the nitrile carboxylic acid **19** into the protected amine **22** in two steps (Scheme 71); firstly the isocyanate is formed throughout Curtius rearrangement and secondly the isocyanate undergoes attack of the alcohol. On the other side, amide **23** was obtained in excellent yield from **19** in the presence of concentrated H_2SO_4 at room temperature. These molecules have a structural resemblance with disopyramide, an antiarrhythic medication used in the treatment of ventricular tachycardia.



Scheme 71.

Crystallization of adduct **9a** allowed the determination of its absolute configuration by a single-crystal X-ray analysis (Figure 16). Configuration of the rest of adducts was established by assuming the uniformity of the reaction mechanism.

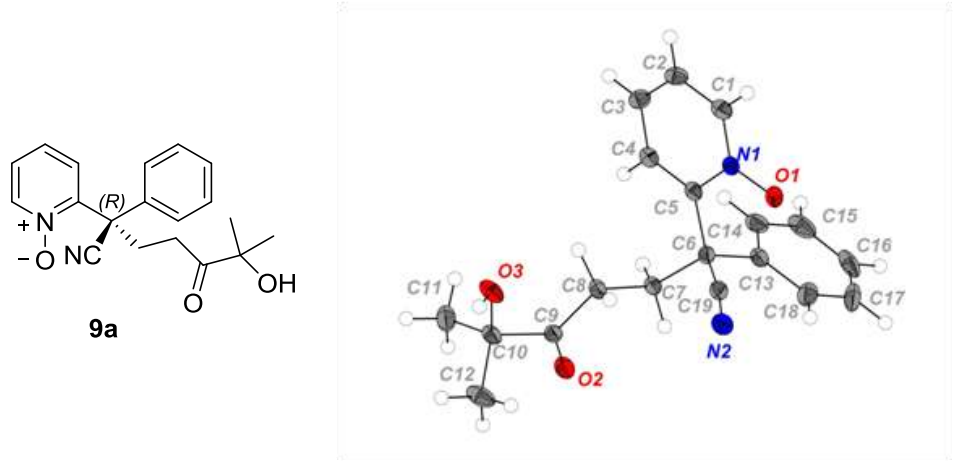
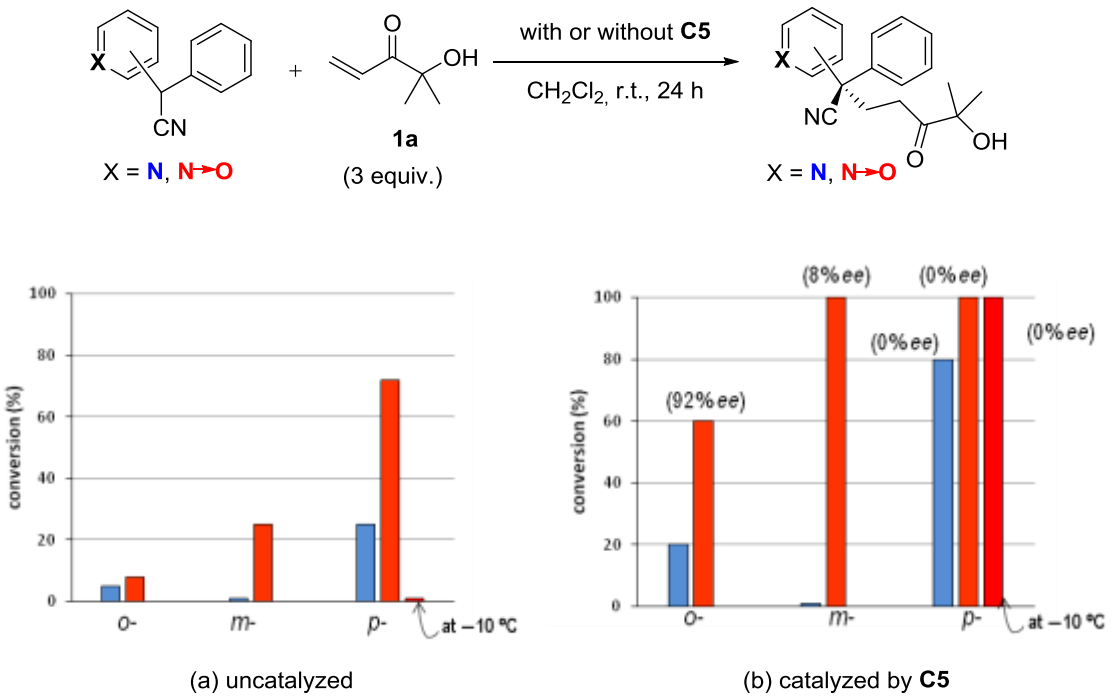


Figure 16. ORTEP diagram of compound **9a**.

The detailed mechanism of these catalytic transformations as well as the precise role played by each element involved remains unsolved yet. However, data in Figure 17 indicate that the *N*-oxide group and its *ortho*-relationship to the cyanoalkyl substituent are key for optimal reaction outcome. As a general trend, for the three positional isomers *ortho*, *meta* and *para*, the corresponding pyridine *N*-oxide was more reactive than the parent pyridine in both the catalyzed and uncatalyzed reactions. In fact, among the six experiments involving cyanoalkylpyridines, only that using *p*-cyanoalkylpyridine in the presence of **C5** provided practical conversion after 24 h, leading to racemic product. Equally important is the position of the *N*-oxide group relative to the cyanoalkyl substituent on the ring. Among the three cyanoalkylpyridine *N*-oxides, the *meta* and *para* isomers proved to be inherently more reactive than the *ortho* isomer, also in the presence of catatalyst **C5**, although both led to essentially racemic product. In contrast, the *ortho* isomer led to 92% *ee*.



(a) uncatalyzed (b) catalyzed by **C5**

Figure 17. Conversion after 24 h for the reactions of **1a** with *o*-, *m*-, and *p*- substituted cyanoalkylpyidine *N*-oxides.

In order to establish the possible interactions between the catalyst and the substrates ^{1}H NMR spectra were recorded for compounds **4**, **6a** and **12** in the presence/absence of 1 mmol equiv. of **C5**, respectively (Figure 18). As the insets in Figure 18 show (starred peaks), the singlet corresponding to the benzylic proton of pyridine *N*-oxide **6a** at 6.12 ppm (inset B) split into two peaks upon addition of **C5** (inset C), while an upfield shielding of 0.14 ppm is observed. This large effect suggests that because of the strong interaction between catalyst **C5** and *N*-oxide **6a**, the two possible diastereomers created are distinguishable. On the contrary, the singlet at 5.30 ppm, corresponding to the benzylic proton of **4** (inset D), remained essentially unchanged after admixing with **C5** (inset E). Similarly, the spectrum of the *p*-substituted pyridine *N*-oxide **12** experienced no appreciable variation upon admixing with **C5** (insets F and G).

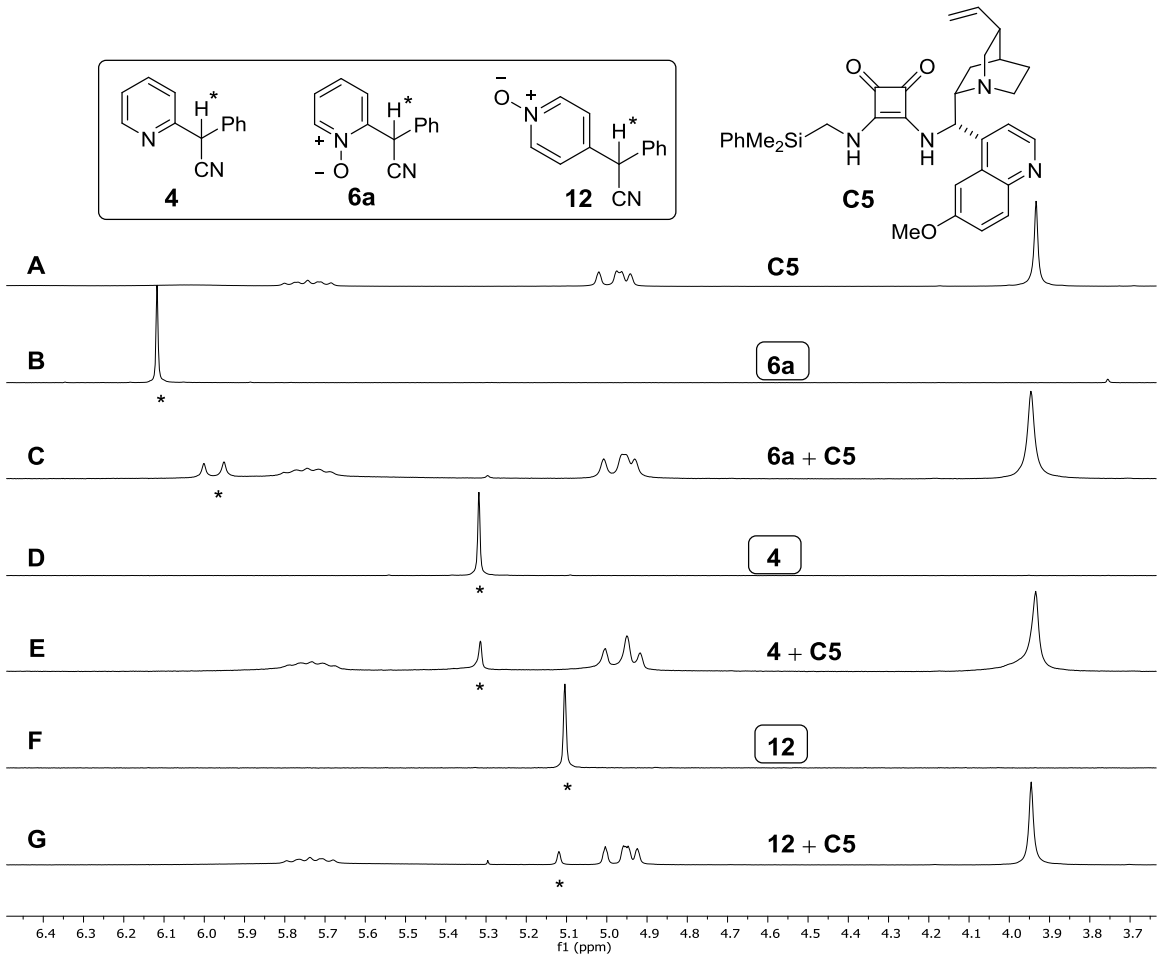


Figure 18. Insets (3.8–6.4 ppm) of ^{1}H NMR spectra taken in $CDCl_3$ (0.1 M, 300 MHz) at r.t.

On the other hand, to study the influence of the silicon group ^{1}H NMR spectra were recorded for compound **6a** in the presence/absence of 1 mmol equiv. of **C5** and **C9** respectively (Figure 19). The singlet corresponding to the benzylic proton of pyridine *N*-oxide **6a** at 6.12 ppm remained almost unchanged in the presence of catalyst **C9** (inset I), suggesting a weaker interaction between **6a** and **C9** compared to a catalyst containing a Si group (**C5**). Furthermore, lower enantioselectivity was obtained with catalyst **C9** (84% *ee*), meaning that the incorporation of silicon to the catalyst is necessary in order to obtain enantioselectivities higher than 90%.

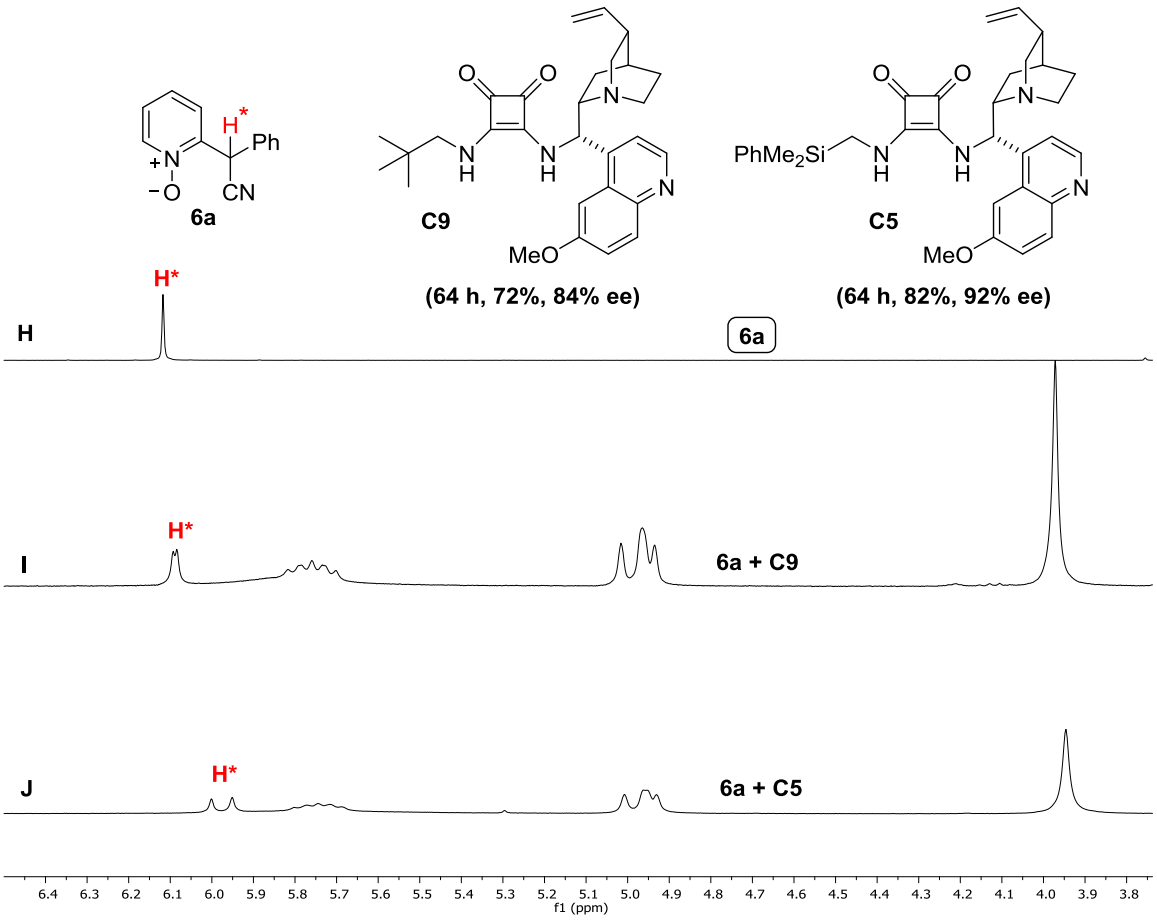
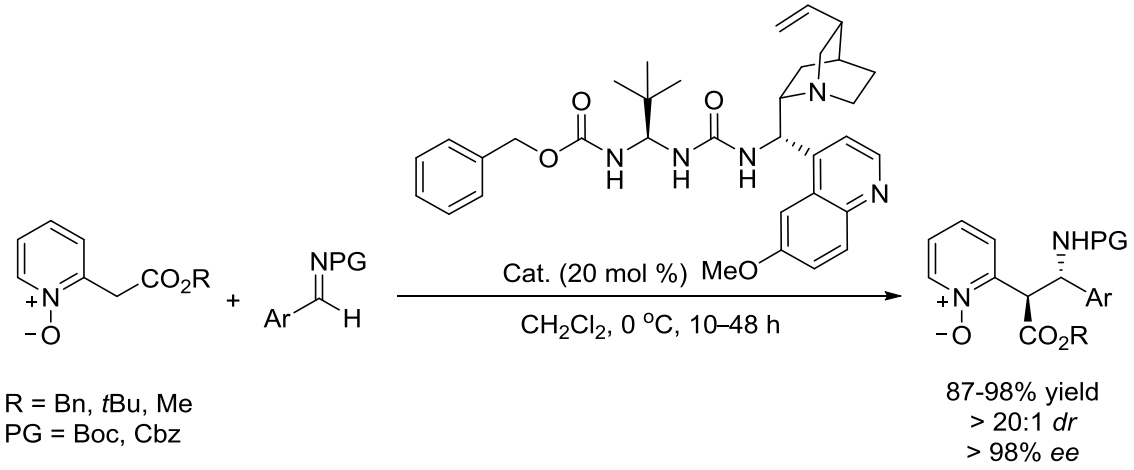


Figure 19. Insets (3.8–6.4 ppm) of ^{1}H NMR spectra taken in $CDCl_3$ (0.1 M, 300 MHz) at r.t.

After this work, our group reported the ureidopeptide derived Brønsted base[165] catalyzed stereoselective α-functionalization of 2-azaaryl acetates *N*-oxide with *N*-Boc Imines (Scheme 73).[166] The presence of *N*-oxide functionality was necessary to obtain reactivity and excellent selectivity and unlike Lam's work,[145] no epimerization at the Cα position was observed after column chromatography.

[165] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.
[166] Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 13332–13336.



Scheme 73. Stereoselective α-functionalization of 2-azaaryl acetates with *N*-Boc imines.

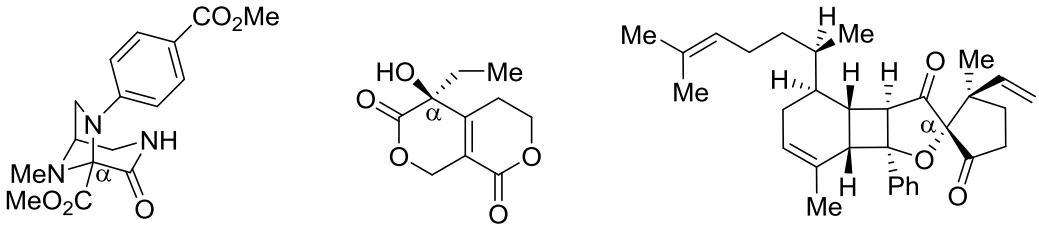
CHAPTER 3

TEMPLATE BASED ENANTIOSELECTIVE SYNTHESIS OF α-QUATERNARY HYDANTOINS

3. Template based enantioselective synthesis of α-quaternary hydantoins

3.1. Introduction

Chiral heterocyclic structural skeletons are prevalent in natural products or bioactive substances.[167] In many cases, a heteroatom is attached to the quaternary α *C*(sp^3) position of a carbonyl moiety (Figure 20). Not unexpectedly, the type and extend of activity of these chiral compounds depend, among other things, on the configuration of this stereocenter.



(-)-Apaminal[168a] (+)-Gentiollactone[168b] Biyouyanagin A[168c]

Figure 20.

The development of new synthetic methodologies to access these targets in a stereochemically controlled manner is undoubtedly appealing in organic and medicinal chemistry. As mentioned in the general introduction, many efforts have been devoted to the search of new active methylenes with a defined structure that can be easily deprotonated and be used in the synthesis of biologically active compounds. One of the strategies for the generation of five member heterocycles with tetrasubstituted carbon stereocenters is the use of α-enolizable lactam or (thio)lactone-based heterocycles as pronucleophiles (Figure 21).

[167] *Heterocycles in Natural Product Synthesis* (Majumdar, K. C. & Chattopadhyay, S. K. ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany) 2011.

[168] For the first total synthesis of (-)-apaminal, see: a) Smith III, A. B.; Liu, Z. *Org. Lett.* **2008**, *10*, 4363–4365. For the aminocatalyzed synthesis of biyouyanagin A, see: b) For the total synthesis of (+)-gentiollactone, see: Kakuda, R.; Machida, K.; Yaoita, Y.; Kikuchi, M.; Kikuchi, M. *Chem. Pharm. Bull.* **2003**, *51*, 885–887. c) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4708–4711.

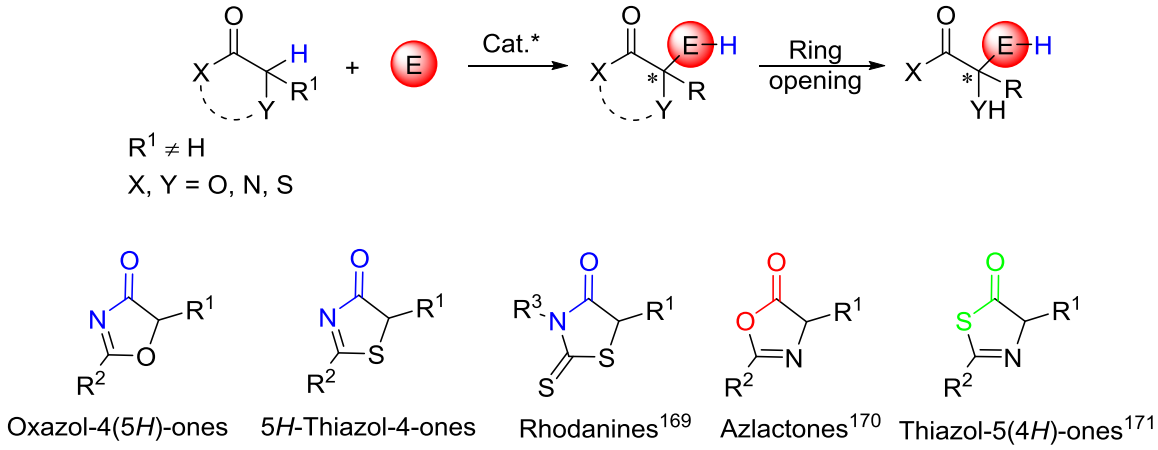


Figure 21. Selection of heterocyclic pronucleophiles employed in organocatalysis.

These heterocycles exhibit very interesting features; i) easy deprotonation under mild enolization conditions due to formation of an aromatic enolate (except for rhodanines); ii) the geometry of the resulting starting enolate or equivalent is fixed due to their cyclic nature, thus facilitating the control of the stereoselectivity; iii) they are substituted at the α-position of the carbonyl ($R^1 \neq H$) and therefore, after reaction with an electrophile, a tetrasubstituted stereocenter is created, iv) they have the potential to convert racemic starting materials to a single highly enantioenriched final products (enantioconvergent catalysis)[172] and v) all of them can be opened under appropriate conditions to afford α-mercapto, α-hydroxy and α-amino acid derivatives with a tetrasubstituted stereocenter.

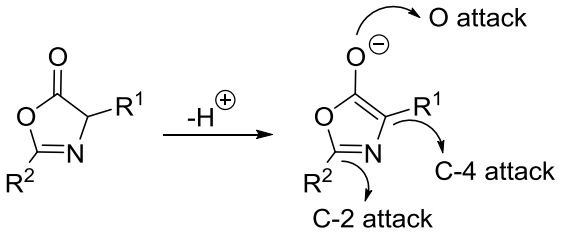
In the last years, these pronucleophiles have been employed with success in catalytic enantioselective addition to a large number of electrophiles and therefore only selected contributions will be presented here.

3.1.1. Azlactones (Oxazol-5(4*H*)-ones)

The azlactone scaffolds have been utilized in a diversity of transformations due to its dual behavior, meaning that can be used as both nucleophiles and electrophiles. This

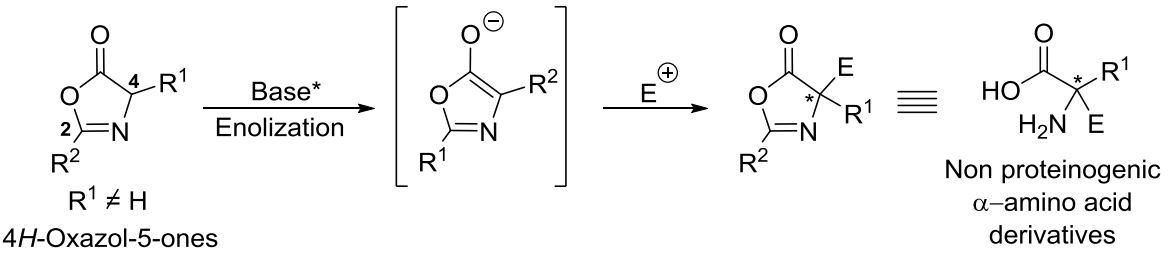
[169] For reviews, see: a) Lesyk, R.; Zimenkovsky, B. *Curr. Org. Chem.* **2004**, *8*, 1547–1577. b) Tomasic, T.; Masic, L. *Curr. Med. Chem.* **2009**, *16*, 1596–1629. For the first organocatalyzed Michael addition of rhodanines to β-substituted enones, see: c) Yu, F.; Hu, H.; Gu, X.; Ye, J. *Org. Lett.* **2012**, *14*, 2038–2041.
[170] For reviews on azlactones, see: a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432–1440. b) Alba. A.-N. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720–734. c) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. *Chem. Eur. J.* **2016**, *22*, 10294–10318.
[171] For the first organocatalytic asymmetric reaction of thiazol-5(4*H*)-ones to *N*-Boc imines catalyzed by C_1-symmetic chiral ammonium betaine, see: Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun.* **2010**, *46*, 300–302.
[172] Mohr, J. T.; Moore, J. T.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2016**, *12*, 2038–2045.

multiple reactivity can be directed depending on the counterpart that is added to the reaction (Scheme 74).



Scheme 74.

The acidity of the 4-substituted azlactones (pKa ≈ 9)[173] allows its facile deprotonation with mild Brønsted bases to obtain an aromatic enolate, which in the presence of an electrophile would form a quaternary stereocenter contiguous to the carbonyl (Scheme 75). These compounds are the most common heterocycles employed in the stereoselective synthesis of quaternary stereocenters, probably, due to its easy conversion into optically active structurally complex quaternary α-amino acids.[174]



Scheme 75.

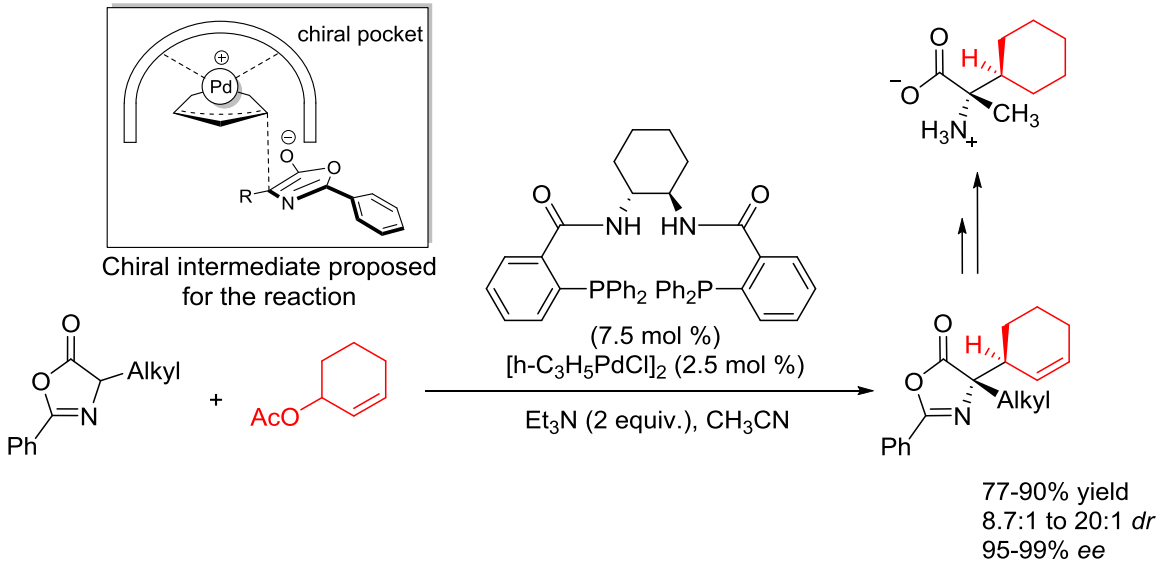
In 1997, Trost and Ariza reported the first nucleophilic addition of azlactones in an asymmetric Tsuji-Trost α-allylation reaction catalyzed by chiral Salen-Pd complex (Scheme 76).[175] The corresponding C-4 adducts were obtained in very good yields and enantioselectivities, presumably because a tightly embedded chiral pocket formed between the catalyst and the allyl moiety. The absolute configuration of the newly formed quaternary stereogenic center could be predicted by the enolate approach to

[173] Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918–2922.

[174] a) *Amino Acids, Peptides and Proteins in Organic Chemistry, Vols. 1&2* (Hughes, A. B. ed., Wiley-VCH, Weinheim) 2009. b) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260 and references therein. c) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260. d) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7.

[175] a) Trost, B. M.; Ariza, X. *Angew. Chem. Int. Ed.* **1997**, *36*, 2635–2637. For later examples of Pd catalyzed alkylation of azlactones, see: b) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, *134*, 5778–5781 and references therein. c) Zhou, H.; Yang, H.; Liu, M.; Xia, C.; Jiang, G. *Org. Lett.* **2014**, *16*, 5350–5353. For a rearrangement of *O*-acylated azlactones catalyzed by a planar-chiral derivative of 4-(pyrrolidino)pyridine, see: Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, 120, 11532–11533.

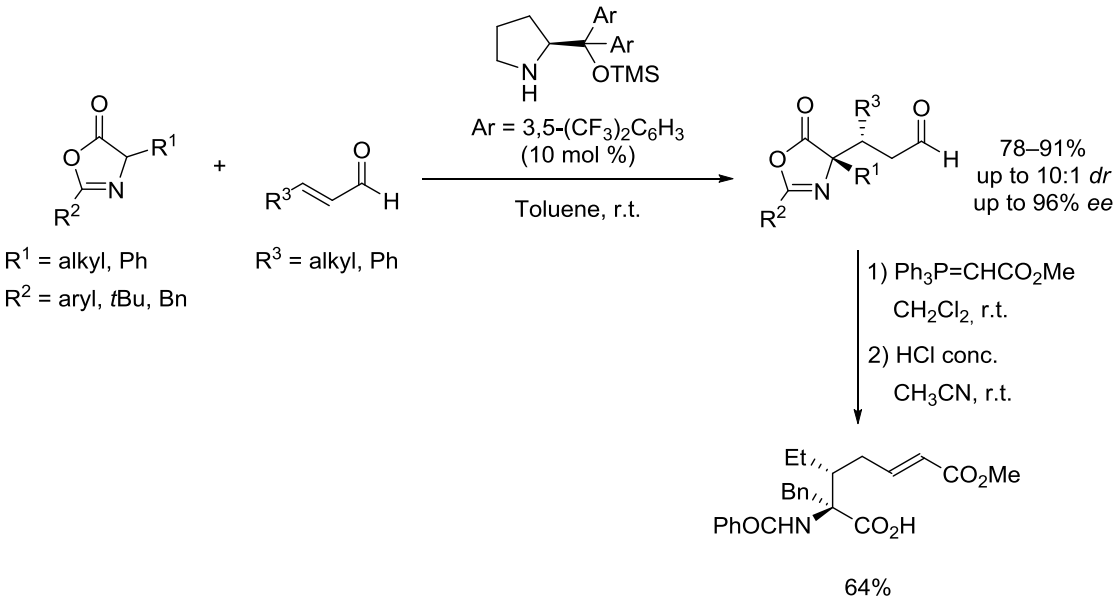
the π-allyl palladium chiral complex by its *Si* face (upper left side of Scheme 76). Interestingly, an alkylated azlactone (alkyl = CH_3) was converted smoothly, upon acidic hydrolysis with TMSCl in MeOH, into the quaternary α-amino acid.



Scheme 76.

It was not until 2008 when Jørgensen et al.[176] reported the first organocatalytic example; the nucleophilic addition of azlactones to α,β-saturated aldehydes catalyzed by 10 mol % of Jørgensen-Hayashi catalyst proceeded at the C-4 position in moderate to high yields and diastereoselectivities and with high enantioselectivities. Wittig reaction followed by hydrolysis of one of the azlactones using HCl (conc.) in CH_3CN provided an α,α-disubstituted amino acid derivative in moderate yield (Scheme 77).

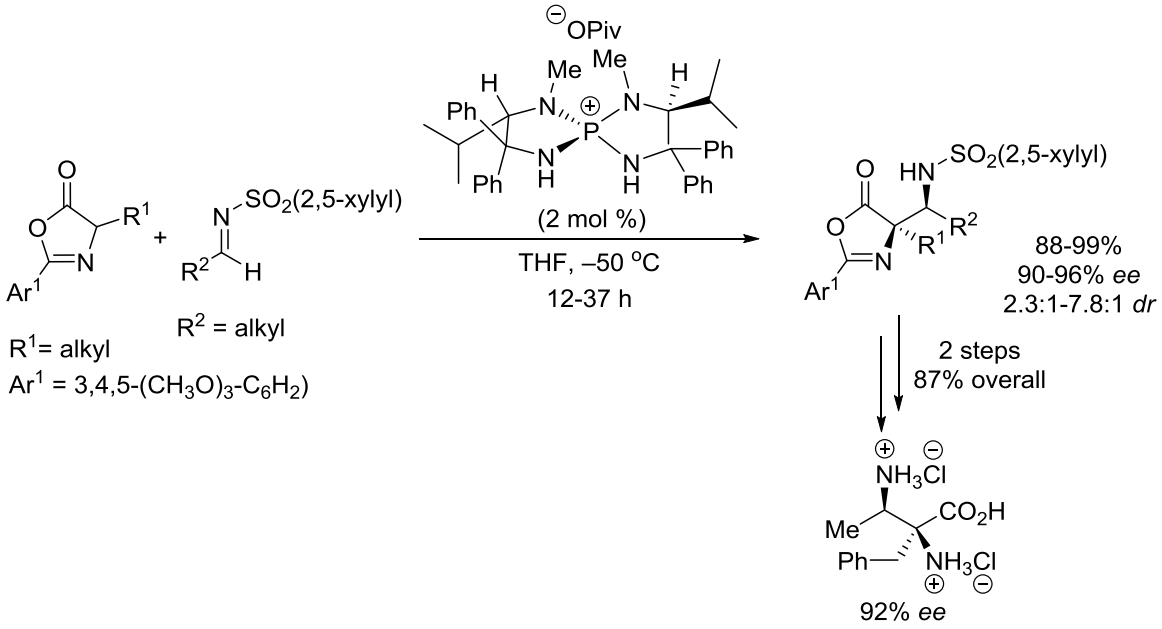
[176] a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037. After this work several organocatalytic examples have been reported; for a highly enantioselective alkylation of azlactones with alkyl bromides, see: b) Uraguchi, D.; Asai, Y.; Seto, Y.; Ooi, T. *Synlett* **2009**, 4, 658–660. c) Tarí, S.; Avila, A.; Chinchilla, R.; Najera, C. *Tetrahedron: Asymmetry* **2012**, 23, 176–180. For an asymmetric aldol reaction of azlactones and aliphatic aldehydes, see: d) Zheng, Y.; Deng, L. *Chem. Sci.* **2015**, *6*, 6510–6514.



Scheme 77.

The same year, Ooi´s group developed a highly enantioselective direct Mannich-type reaction between azlactones and *N*-sulfonyl imines catalyzed by a chiral tetraaminophosphonium salt.[177] It was thought that the basic carboxylate anion ($^{-}$OPiv) present in the catalyst abstracts the acidic proton of the azlactone providing the chiral phosphonium enolate. One of the Mannich adduct was easily converted into the corresponding α,β-diamino acid dihydrochloride after two steps without loss of enantiopurity (Scheme 78).

[177] a) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088–14089. For a selected examples of asymmetric Mannich type reaction between imines and azlactones, see: b) Zhang, H.; Yang, Z.; Zhao, B. N.; Li, G. *J. Org. Chem.* **2018**, *83*, 644–655 and references therein.



Scheme 78.

As we comented above, since azlactone anions are ambifunctional nucleophiles, depending on the substituents and reaction conditions, they can react with activated electrophilic compounds through their C-2 or at C-4 positions (Figure 22).

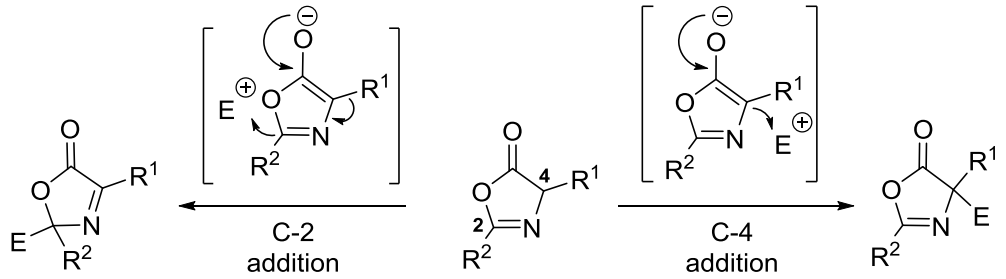
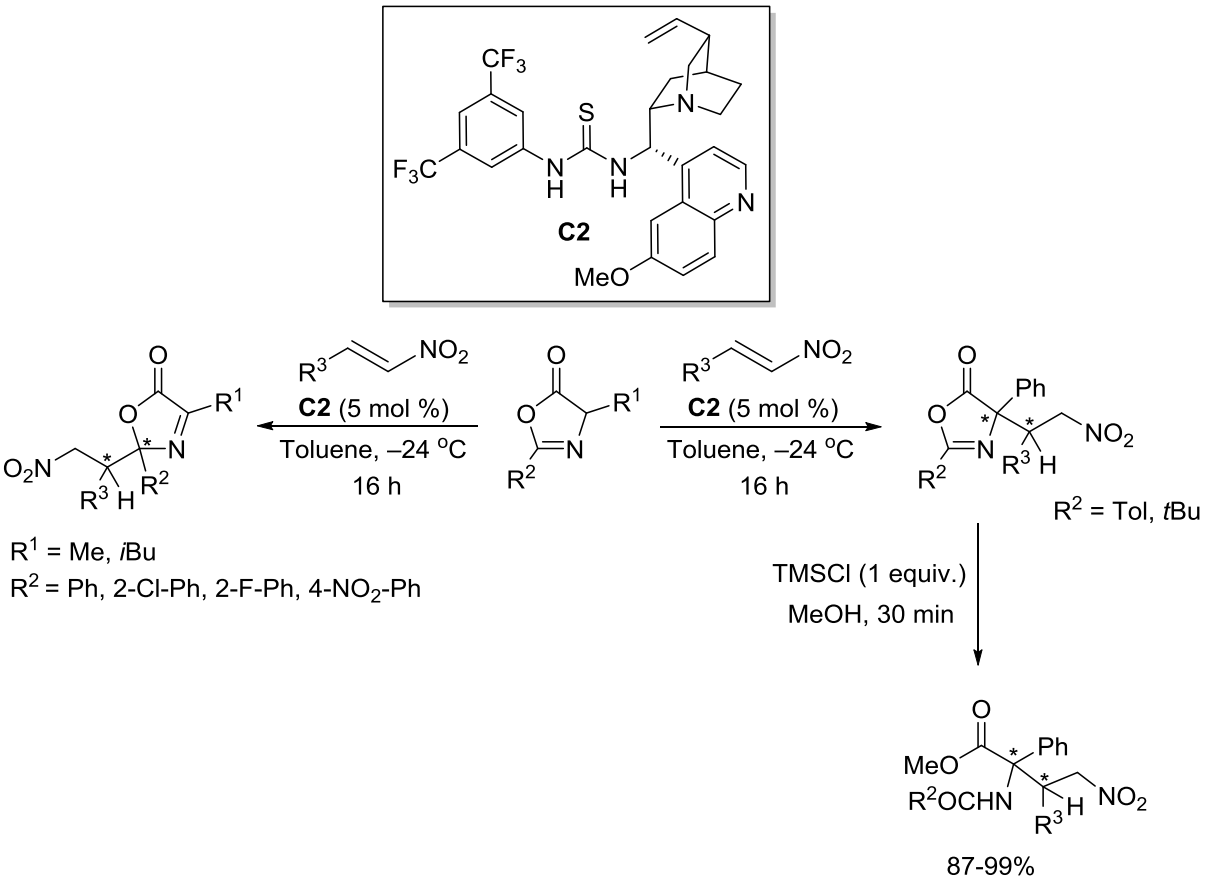


Figure 22. Regioselectivity of the addition of azlactones to electrophiles.

Jørgensen et al. extended their previous work with enals describing the addition of azlactones to nitroalkenes (Scheme 79). The reaction was catalyzed by 5 mol % of a bifunctional cinchona alkaloid/thiourea derivative yielding the corresponding adducts with good yields, excellent diastereoselectivities, and enantioselectivities from moderate to good.[178] The reaction was founded to be extremely catalyst and substituent

[178] a) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958–10966. After this work some examples reporting C-2 Michael addition reaction have been reported. For a diastereoselective addition to nitrostyrenes catalyzed by Et_3N, see: b) Balaguer, A.-N.; Companyó, X.; Calvet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, 199–203. For an asymmetric organocatalytic addition to maleimides catalyzed by bifuctional thiourea-amine catalyst, see: c) Alba, A.-N. R.; Valero, G.; Calbet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2010**, *16*, 9884–9889. For an asymmetric addition of a 2-unsubstituted azlactone to α,β-unsaturated acylbenzotriazoles, see: d)

dependent, addition to the electrophile took place selectively at C-4 position of the azlactone when R^2 = tolyl, *t*-butyl and R^1 = Ph. However, vinylogous C-2 addition was observed with some azlactones with R^1 = alkyl and R^2 = electron poor aromatic group. Again, the ring opening of 4-substituted azlactones, in the presence of TMSCl in MeOH, gave the α-amino acid esters in very high yields and without loss of enantioselectivity.



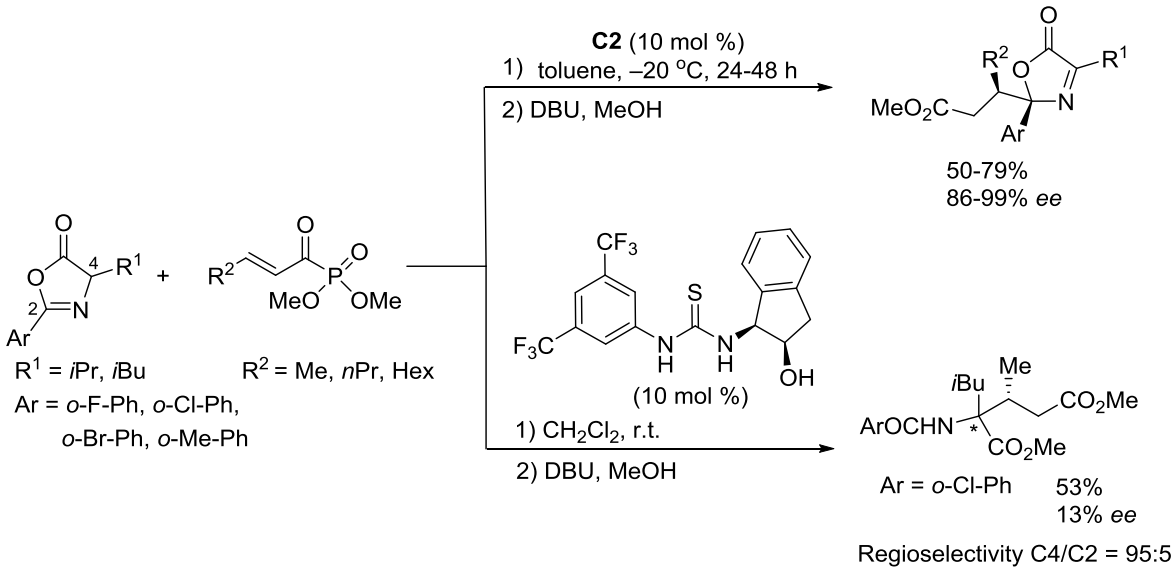
Scheme 79.

However, it should be noted that the nature of the electrophile and the catalyst also plays an important role in the regiochemisty of the addition.[179]

Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120–123. For C-4 1,6-addition of azlactones to δ-aryl dienyl carbonyl compounds, see: e) Uraguchi, D.; Yoshioka, K.; Ooi, T. *Nat. Commun.* **2017**, *8*, 14793.

[179] α,β-unsaturated aldehydes appear to give C-4-substituted azlactones only independently of the nature of substitutent at the azlactone ring, see: Ref 176.

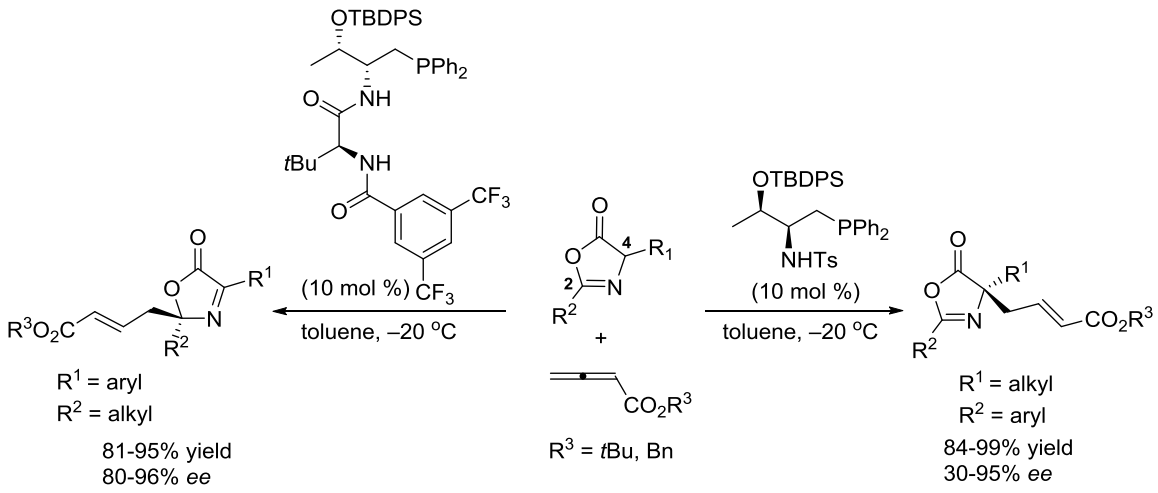
In 2010, Jørgensen and coworkers reported the asymmetric addition of azlactones to acyl phophonates (Scheme 80).[180] They showed that employing the bifunctional cinchona alkaloid/thiourea catalyst **C2**, the nucleophilic addition of the azlactone took place exclusively at the C-2 position giving the N,O-aminals in moderate to good yields and excellent enantioselectivities. On the other hand, removing the basic site of the cinchona-derived catalyst and adding an additional hydroxy-directing group switched the regioselectivity completely from C-2 to C-4, although in this case moderate yield (53%) and bad enantioselectivity (13% *ee*) was achieved. As a limitation of the reaction, the Michael reaction was only shown to be efficient with aliphatic 2-enoylphosphonates (R^2 = alkyl).



Scheme 80.

Recently, Lu`s group reported a phosphine-catalyzed C-2 and C-4 selective γ-addition of azlactones to 2,3-butadienoates in a highly enantioselective manner (Scheme 81).[181] Unlike other cases, when 2-aryl-4-alkyloxazol-5-(4*H*)-ones were employed C-4 selective γ-addition of oxazolones occurred, while C-2 selective γ-addition took place with 2-alkyl-4-aryloxazol-5-(4*H*)-ones.

[180] Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783.
[181] Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265–271.



Scheme 81.

3.1.2. Oxazolones (Oxazol-4(5*H*)-ones)

Oxazol-4(5*H*)-ones differ from azlactones in the relative position of oxygen and nitrogen atoms and have been employed as highly reactive equivalents of α-alkyl α-hydroxy acids (Figure 23). The facility to deprotonate oxazol-4(5*H*)-ones compared to other acyclic equivalents of α-alkyl α-hydroxy acids,[182] as it happens with azlactones, is attributed to the aromatization resulting from enolization of 5*H*-oxazol-4-ones.

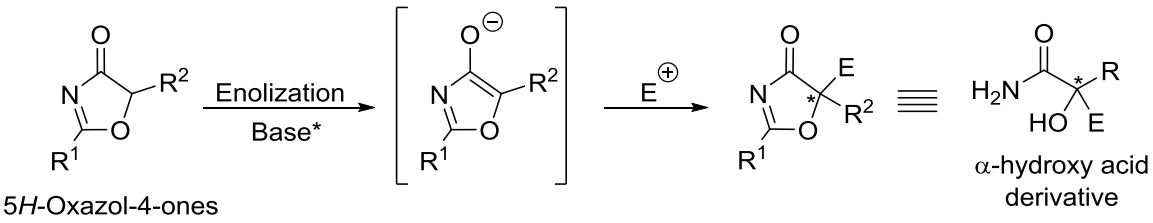
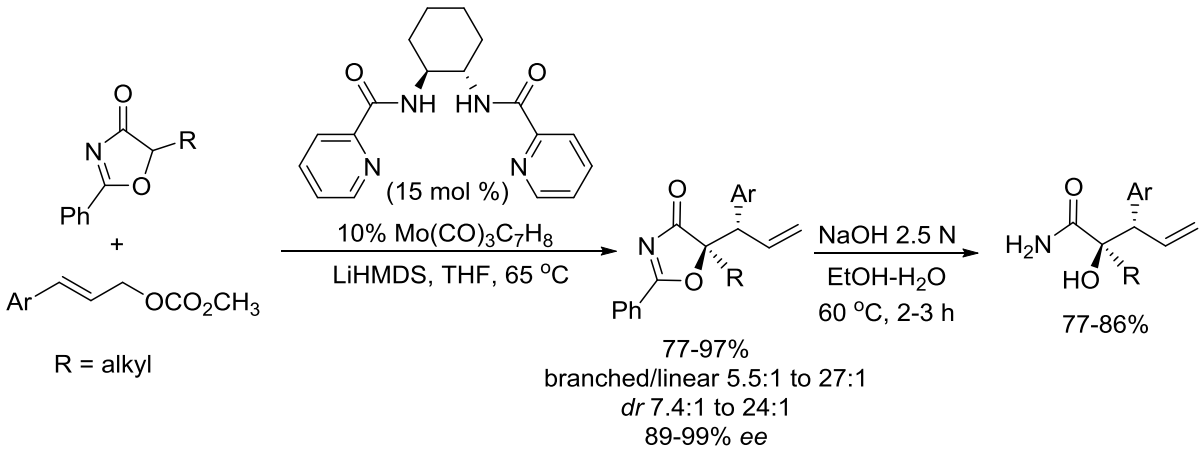


Figure 23.

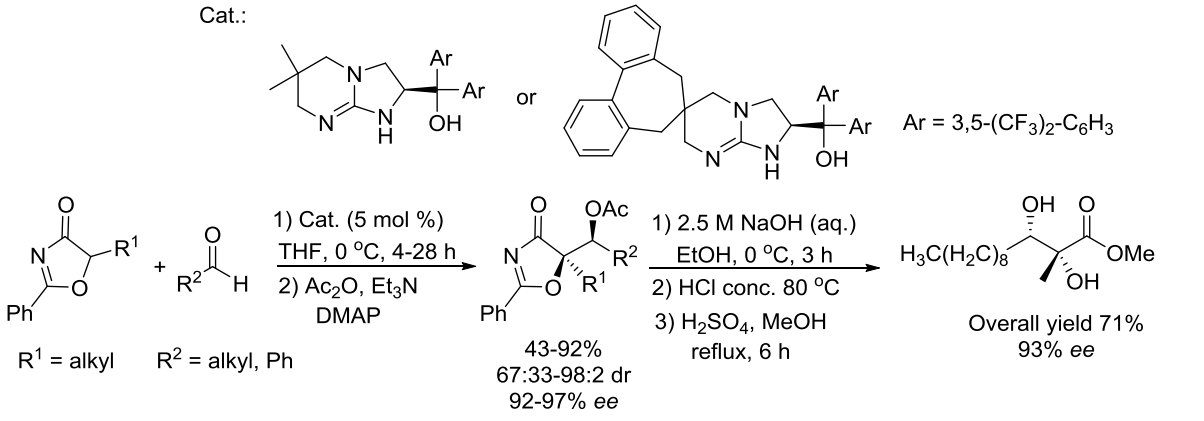
In 2004, Trost et al.[183] introduced oxazolones in an asymmetric allylic alkylation reaction catalyzed by a chiral molybdenum *C2*-symmetric complexes. The presence of the strong and hindered base lithium hexamethyldisilamide (LiHMDS) was found to be necessary for optimal asymmetric induction. Subsequent NaOH mediated saponification of obtained adducts provided the corresponding quaternary α-hydroxy amides in good yields (Scheme 82).

[182] For oxazolidindiones as α-hydroxy acid surrogates, see: Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 3839–3842.
[183] Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945.



Scheme 82.

Sugimura and coworkers have also applied oxazolones as pronucleophiles in an organocatalytic syn-aldol reaction, wherein 5 mol % of chiral guanidines bearing a free hydroxyl group afforded the corresponding adducts without observing retro-aldol reaction. In this reaction, syn-aldol adducts with contiguous quaternary-tertiary stereocenters were obtained in variable yields and diastereoselectivities and with excellent enantiomeric excesses.[184] One of the aldol adduct was easily converted into a α,β-dihydroxycarboxylic ester after saponification, acid hydrolysis and sterification (71% overall yield after 3 steps) without loss of enantiopurity.



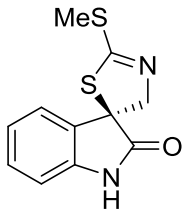
Scheme 83.

[184] a) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287. For asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds, see: b) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, *133*, 5695–5697. c) Misaki, T.; Jin, N.; Kawano, K.; Sugimura, T. *Chem. Lett.* **2012**, *41*, 1675–1677.

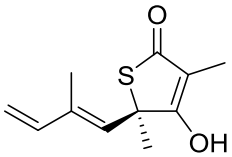
Reactive intermediates derived from oxazolones have recently been employed as nucleophiles in a number of transformations including Mannich,[185] Michael,[186] phase-transfer,[187] α-sulfenylation[188] and [4+2] cycloaddition[189] reactions.

3.1.3. 5*H*-thiazol-4-ones

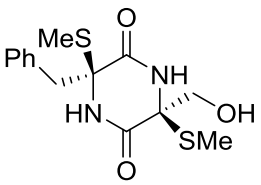
Sulfur-functionalized quaternary carbon stereocenters are present in natural or non-natural products with interesting biological activities and as mentioned before, a catalytic asymmetric strategy to access these entities would involve the nucleophilic addition of *S*-containing prochiral carbon centers (Figure 24).



Spirobrassinin[189a]
antifungal and antitumor activity



Thiolactomycin[189b]
antibiotic



Bis-*N*-norgliovictin[189c]
anti-inflammatory

Figure 24.

In 2013, our group[191] employed for the first time 5*H*-thiazol-4-ones, as α-mercapto carboxylate surrogates, in the catalytic Michael reaction to nitroolefins providing α,α-

[185] a) Han. Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2013**, *355*, 1505–1511. For the highly diastereo- and enantioselective zinc-catalyzed Mannich reaction, see: b) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527.

[186] a) Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. *Chem. Commun.* **2012**, *48*, 461–463. For the first organocatalytic addition of 5*H*-oxazol-4-ones to nitroolefins catalyzed by a thiourea-based bifunctional Brønsted base, see: b) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358–2361. For the first addition to nitroolefins catalyzed by Zn, see: c) Trost, B. M.; Hirano, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 6480–6483. For our group contribution to this field, see: d) Ref 157. For a chiral guanidine catalyzed 1,4- and 1,6-addition to enones and dienones, see: e) Morita, A.; Misaki, T.; Sugimura, T. *Tetrahedron Lett.* **2015**, *56*, 264–267. For a tertiary amine-catalized asymmetric addition to maleimides, see: f) Li, J.; Qiu, S.; Ye, X.; Zhu, B.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2016**, *81*, 11916–11923.

[187] Duan, S.; Li, S.; Ye, X.; Du, N.-N.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 7770–7778.

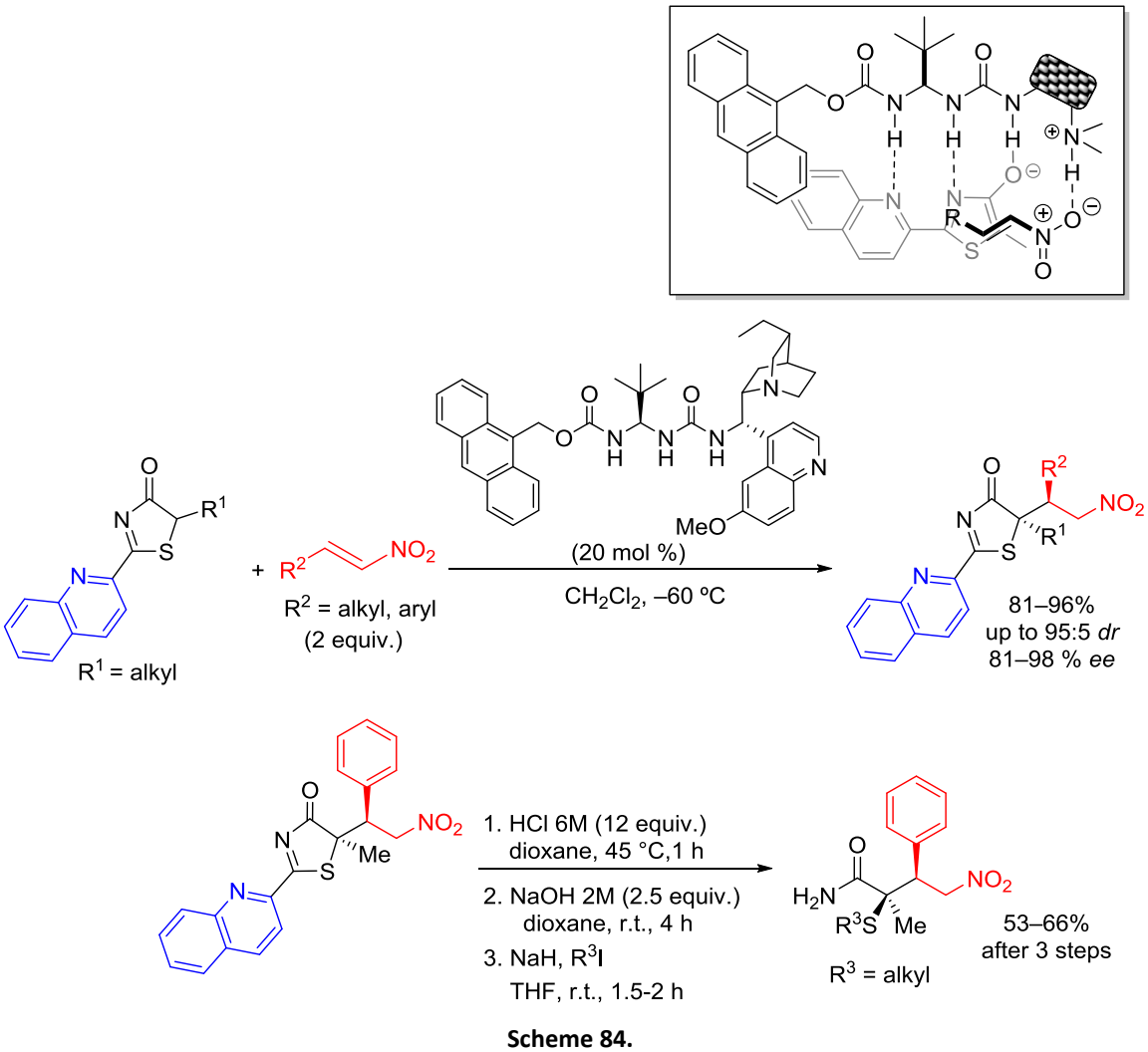
[188] Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696–8702.

[189] Zhu, B.; Lee, R.; Li, J.; Ye, X.; Hong, S.-N.; Qiu, S.; Coote, M. L.; Jiang, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 1299–1303.

[190] a) Liu, L.; Zhang, S.-L.; Xue, F.; Lou, G.-S.; Zhang, H.-Y.; Ma, S.-C.; Duan, W.; Wang, W. *Chem. Eur. J.* **2011**, *17*, 7791–7795. b) Salyden, R. A.; Lee, R. E.; Armour, J. W.; Cooper, A. M.; Orme, I. M.; Brennan, P. J.; Besra, G. S. *Antimicrob. Agents. Chemother.* **1996**, 2813–2819. c) Song, Y.; Dou, H.; Gong, W.; Liu, X.; Yu, Z.; Li, E.; Tan, R.; Hou, Y. *Eur. J. Pharmacol*. **2013**, *705*, 49–60.

[191] 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 an asymmetric iridium-catalyzed allylation, see: b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377–382. For an asymmetric phosphine-catalyzed γ-addition to allenoates, see: c) Wang, T.; Yu, Z.; Hoon, D. L.; Huang, K.-W.; Lan, Y.; Lu, Y. *Chem. Sci.* **2015**, *6*, 4912–4922. For a dipeptide-based chiral tertiary amine-catalyzed asymmetric conjugated addition to maleimides, see: d) Li, J.; Qiu, S.; Ye, X.; Zhu, B.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2016**, *81*, 11916–11923.

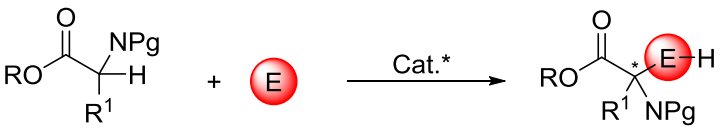
disubstituted α-mercapto carboxylic acid derivatives with good yields and high diastereo- and enantioselectivities (Scheme 84). The reaction was conducted using 20 mol % of a novel bifunctional ureopeptide-based Brønsted base catalyst and it should be noted that quinoline N atom of the thiazolone template plays a significant role in reaction stereocontrol. It was proposed that the coordination between the quinolinyl group of the nucleophile with the aminal moiety in the catalyst would enhance the fixation of the transition state, thus providing better stereocontrol during the reaction (upper right side of Scheme 84). Adducts were transformed into the α,α-disubstituted α-mercapto carboxylic acid derivatives, by simple ring opening under acidic conditions and subsequent saponification of the resulting thioester intermediate. Finally, the corresponding *S*-alkylated adduct were obtained in the presence of a series of alkyl iodides and sodium hydride as a base.



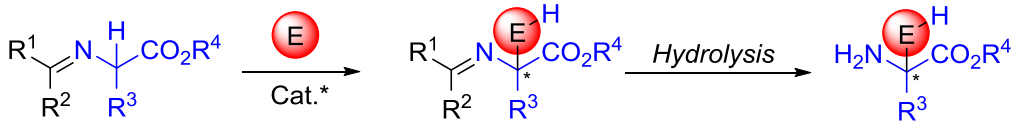
Scheme 84.

3.1.4. 1*H*-Imidazol-4(5*H*)-ones

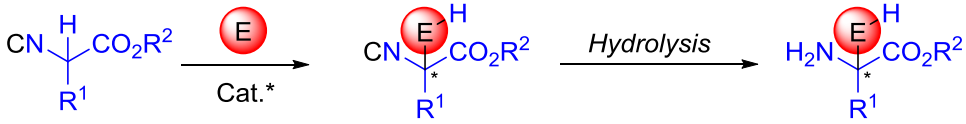
The stereoselective preparation of α,α-disubstituted quaternary α-amino acids have gained much attention in the last years.[192] They have proved to be useful as pharmaceuticals (e.g. methyldopa) or as building blocks for the construction of peptidomimetics.[193] As previously mentioned, a principal enantioselective approach to quaternary NH α-amino acids consists in the α-functionalization of nucleophilic templates. However, the majority of these methods are unable to afford the *N*-substituted analogues directly, and an additional *N*-alkylation process is required.[194] Some of these procedures are illustrated in Scheme 85.



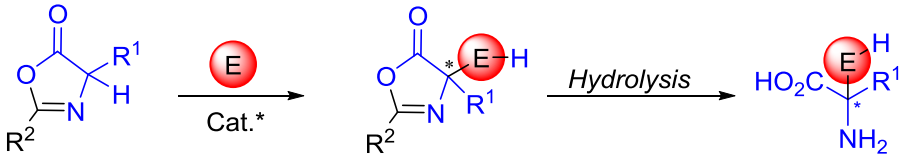
α–Substituted Schiff bases:



α–Isocyanoacetates:



Azlactones:



Scheme 85. Pronucleophiles for synthesis of quaternary amino acids.

[192] See Ref 174.

[193] Although peptides and proteins have several conformations in solution due to their flexible nature, only a few conformers are responsible for their diverse biological properties. Cα-tetrasubstituted amino acids are useful tools to reduce the conformational space available in the peptide-protein or protein-protein interactions and these peptidomimetics are often more resistant to chemical and enzymatic degradation. a) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Peptide Science* **2001**, *60*, 396–419. b) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, *2006*, 1295–1310.

[194] Synthetic preparation of *N*-methyl α-amino acids: Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev*. **2004**, *104*, 5823–5846.

On the other side, hydantoins or 2,4-imidazolidinediones, constitute a family of nitrogen heterocycles that are present in naturally occurring substances, such as marine organisms and bacteria.[195] The finding of biological activities of hydantoins has made big progress during the last decades, and in particular, it has been demonstrated that optically 5-substituted and 5,5-disubstituted hydantoins are important medicinal compounds (Figure 25).

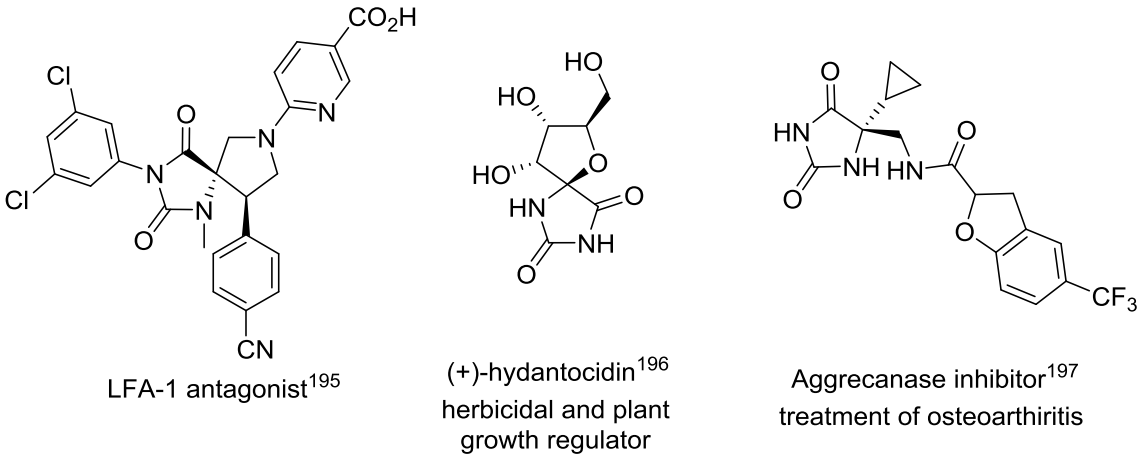


Figure 25. Biologically active 5,5-disubstituted hydantoins.

Hydantoins are also interesting from a purely chemical point of view. 5-Substituted hydantoins have been employed in the context of molecular recognition,[199] chiral auxiliaries in organic synthesis,[200] or constituents of optically active polymers[201] and metal complexes.[202] Structurally, they can be viewed as masked α-amino acids and, as such, 5-substituted hydantoins also serve as precursors to unnatural α-amino acid derivatives.[203]

[195] For reviews of hydantoin chemistry, see: a) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177–228. b) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int*. **2004**, *36*, 391–443. c) Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Rev.* **2017**, *117*, 13757–13809.

[196] Zhang, H.; Watterson, S. H.; Xiao, Z.; Dhar, T. G. M.; Balasubramanian, B.; Barrish, J. C.; Chen, B. *Org. Process Res. Dev.* **2010**, *14*, 936–938.

[197] Shiozaki, M. *Carbohydr. Res.* **2001**, *335*, 147–150.

[198] Wiley, M. R.; Durham, T. B.; Adams, L. A.; Chambers, M. G.; Lin, C.; Liu, C.; Marimuthu, J.; Mitchell, P. G.; Mudra, D. R.; Swearingen, C. A.; Toth, J. L.; Weller, J. M.; Thirunavukkarasu, K. *J. Med. Chem.* **2016**, 59, 5810–5822.

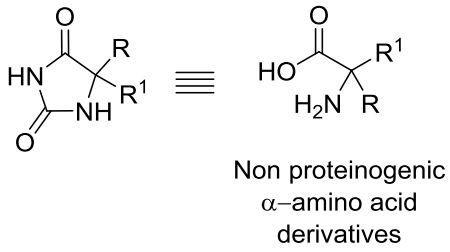
[199] Famulok, M.; Jeong, K.-S.; Deslongchamps, G.; Rebek Jr., J. *Angew. Chem. Int. Ed.* **1991**, *30*, 858−860.

[200] Feng, C.; Cuifen, L.; Junqi, N.; Zuxing, C.; Guichun, Y. *Chem. Res. Chin. Univ*. **2016**, *32*, 219–225.

[201] a) Faghihi, K.; Zamani, K.; Mirsamie, A.; Reza Sangi, M. *Eur. Polym. J*. **2003**, *39*, 247–254. b) Faghihi, K.; Naghavi, H., *J. Appl. Polym. Sci*. **2005**, *96*, 1776–1782.

[202] Ambroladze, L. N.; Turkadze, T. D.; Moseshvili, I. Z. *Russ. J. Inorg. Chem*. **2008**, *53*, 714–717.

[203] Férnandez-Nieto, F.; Mas Roselló, J.; Lenoir, S.; Hardy, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 3838–3841.

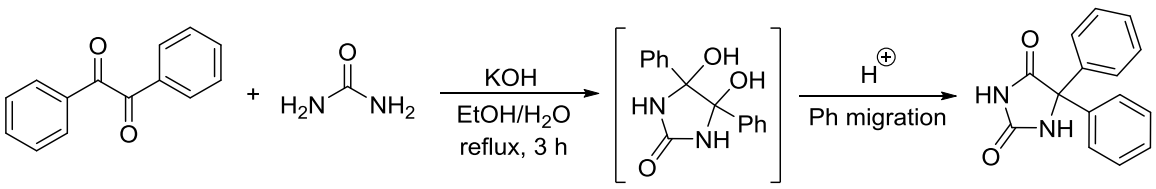


Scheme 86.

The first efforts to prepare hydantoins were devoted to the synthesis of 5- and 5,5-disubstituted hydantoins. Principally, three different methods are known:

1. The Biltz reaction and the historical process for the synthesis of phenytoin.
2. The Bucherer-Bergs reaction: involving a carbonyl compound, potassium cyanide or sodium cyanide and ammonium carbonate.
3. The Read synthesis: consists on the reaction between amino acid derivatives and isocyanates or equivalents.

Carried out by Heinrich Biltz in 1908,[204] the reaction consists on the double condensation of urea with benzyl in strong basic conditions to yield the cyclic antiepileptic drug phenytoin (dilantin) (Scheme 87).

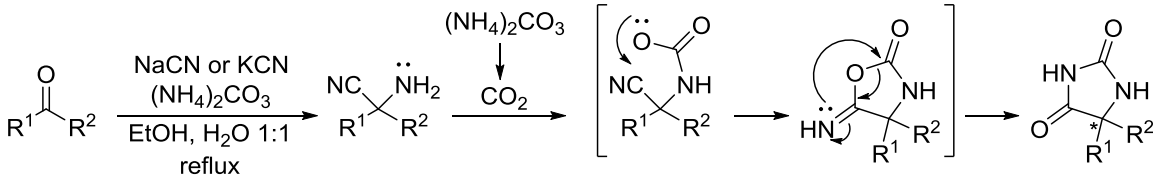


Scheme 87. Biltz synthesis.

In the last decade, new conditions have been described for this reaction, for instance using heterogeneous catalysts,[205] microwave irradiation[206] and ultrasonication.[207] These alternative methods that afford phenytoin derivatives in excellent yield make the reaction faster than the original methodology.

[204] Biltz, H. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1379–1393.
[205] a) Sachdev, D.; Dubey, A. *Catal. Commun.* **2010**, *11*, 1063–1067. b) Tang, Y.; Cheng, Q.; Wang, S.; Zhang, J. *Monatsh. Chem.* **2014**, *145*, 1501–1506.
[206] a) Safari, J.; Naeimi, H.; Ghanbari, M. M.; Sabzi Fini, O. *Russ. J. Org. Chem*. **2009**, *45*, 477–479. b) Gbaguidi, F. A.; Kpoviessi, S. S. D.; Kapanda, C. N.; Muccioli, G. G.; Lambert, D. M.; Accrombessi, G. C.; Moudachirou, M.; Poupaert, J. H. *Afr. J. Pure Appl. Chem*. **2011**, *5*, 168–175.
[207] a) Arani, N. M.; Safari, J. *Ultrason. Sonochem.* **2011**, *18*, 640−643. b) Safari, J.; Moshtael Arani, N.; Ramezan Isfahani, A. *Chin. J. Chem.* **2010**, *28*, 255−258. c) Du, T.; Li, J.; Min, L. *Adv. Mater. Res.* **2012**, 518−523, 3917−3920.

The classic Bucherer-Bergs reaction[208] is carried out between carbonyl compounds (aldehyde or ketone), ammonia and a cyanide anion forming an α-amino nitrile. Subsequent carbamoylation with carbon dioxide, issued from $(NH_4)_2CO_3$, and cyclization followed by rearrangement of the five-membered ring affords the desire hydantoin (Scheme 88). An important limitation of the Bucherer-Bergs reactions is that it only has one point of diversity. Only changes in the structure of the starting ketone or aldehyde will lead to variations in the final hydantoin. Moreover, heating an aqueous solution of highly toxic KCN poses several hazards, formation of hydrogen cyanide due to hydrolysis, especially on large scale.



Scheme 88. Bucherer-Bergs reaction.

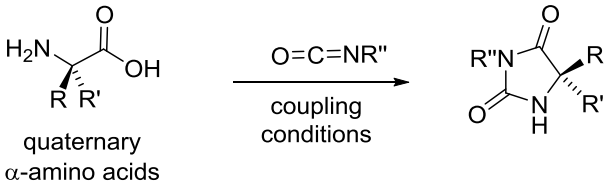
The Read reaction[209] is the main synthetic route to obtain 5-substituted hydantoins, starting from the corresponding α-amino acid derivative. The reaction involves the condensation with an isocyanate or equivalent promoted by some highly reactive coupling reagents (Scheme 89).[210] While this route is in principle simple and straightforward, lacks generality as depends on the availability of the corresponding α-amino acid precursor in enantiomerically pure form. This is a serious problem, especially when 5,5-disubstituted (quaternary) hydantoins are targeted.[211]

[208] a) Bucherer, H. T.; Libe, V. A. *J. Prakt. Chem.* **1934**, *141*, 5–43. b) Bucherer, H. T.; Steiner, W. *J. Prakt. Chem.* **1934**, *140*, 291–316. For recent examples using this methodology to access 5,5-disubstituted hydantoins, see: c) Faghihi, K.; Zamani, K.; Mirsamie, A.; Reza Sangi, M. *Eur. Polym. J.* **2003**, *39*, 247–254. d) Safari, J.; Gandomi-Ravandi, S.; Javadian, L. *Synth. Commun.* **2013**, *43*, 3115−3120. c) Kumar, V.; Rana, H.; Sankolli, R.; Kaushik, M. P. *Tetrahedron Lett.* **2011**, *52*, 6148–6151. e) Safari, J.; Javadian, L. *C. R. Chim.* **2013**, *16*, 1165–1171.

[209] a) Read, W. T. *J. Am. Chem. Soc.* **1922**, *44*, 1746–1755. b) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909–6913.

[210] For recent examples, see: a) Johnson, A.; Saunders, M. J.; Back, T. G. *Org. Biomol. Chem*., **2015**, *13*, 1463–1469. b) Konnert, L.; Gonnet, L.; Halasz, I.; Suppo, J.-S.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2016**, *81*, 9802–9809. For a semi-continuous flow synthesis of hydantoins using a photooxidative cyanation step, see: c) Vukelić, S.; Koksch, B.; Seeberger, P. H.; Gilmore, K. *Chem. Eur. J.* **2016**, *22*, 13451–13454. For a synthesis of hydantoins from carbamates, see: d) Tanwar, D. K.; Ratan, A.; Gill, M. S. *Synlett* **2017**, *28*, 2285–2290.

[211] For the synthesis of racemic quaternary hydantoins through rearrangement of aminobarbituric acid, see: a) Meusel, M.; Ambrożak, A.; Hecker, T. K.; Gütschow, M. *J. Org. Chem.* **2003**, *68*, 4684–4692; through a domino process: b) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M.; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 4026−4029; through Cα-functionalylation of hydantoins (C-prenylation) c) Schmitt, D. C.; Lee, J.; Dechert-Schmitt, A.-M. R.; Yamaguchi, E.; Krische, M. J. *Chem. Commun.* **2013**, *49*,

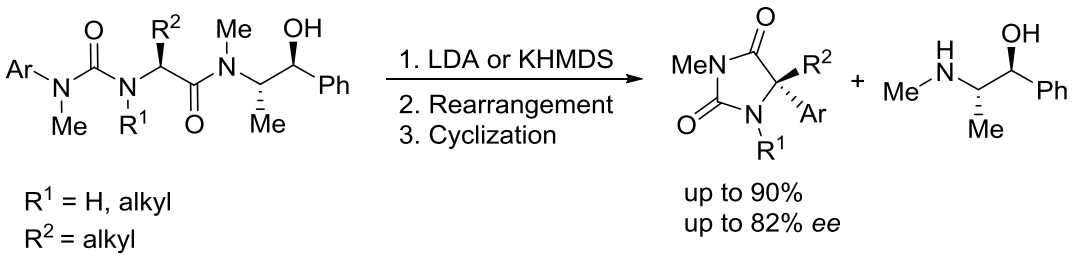


Scheme 89. Conventional synthesis of optically active 5,5-disubstituted hydantoins from the *chiral pool*.

To the best of our knowledge, at the time of the work presented herein started, no examples to access optically active quaternary hydantoins involving new-carbon bond forming reaction had been reported.

Only very recently practical syntheses of enantiomerically enriched quaternary hydantoins have appeared.[212]

In 2015, Clayden and co-workers[213] developed a protocol to access quaternary hydantoins and compounds derived thereof in good enantioselectivity. This method is based on an asymmetric arylation at the α position of available α-amino acids, ligated to pseudoephedrine as a chiral auxiliary, followed by a cyclization. The arylation avoids the use of heavy-metal additives, and is successful with a range of amino acids and with aryl rings of varying electronic character. This represents truly remarkable results, but unfortunately only migration of *N*-aryl groups to the α position of the amino acid can be done (Scheme 90).



Scheme 90.

A year later, Terada[214] reported a chiral phosphoric acid-catalyzed Friedel-Crafts-type addition of 2-methoxyfuran to in situ generated aliphatic ketimines. The enantiopure

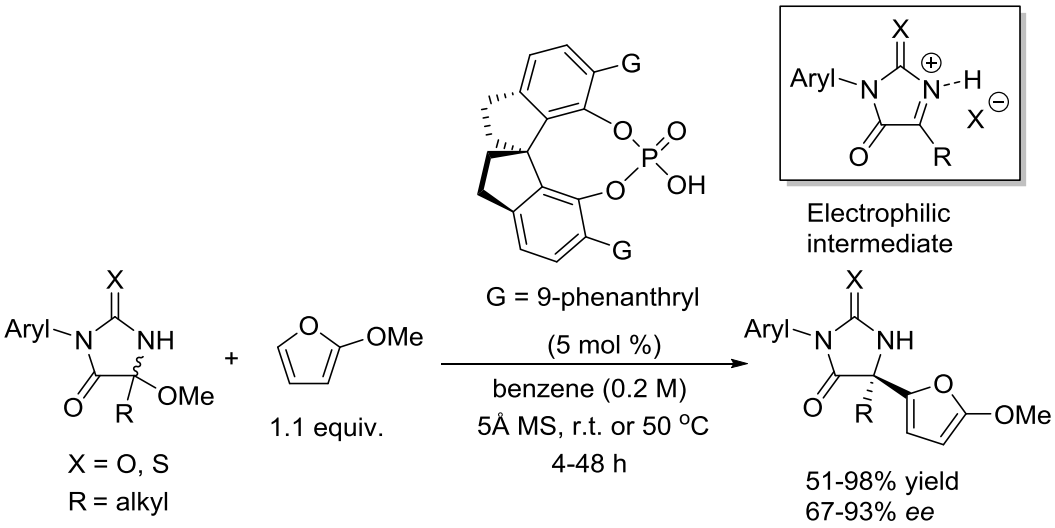
6096–6098. (Arylation) d) Fernández-Nieto, F.; Mas Roselló, J.; Lenoir, S.; Hardy, S.; Clayden, J. *Org. Lett.* **2015**, *17*, 3838–3841.

[212] For the asymmetric synthesis of 5-substituted hydantoins throughout α-amination of esters with diaziridinone, see: Song, J.; Zhang, Z.-J.; Chen, S.-S.; Fan, T.; Gong, L.-Z. *J. Am. Chem. Soc.* **2018,** *140*, 3177–3180.

[213] a) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem. Int. Ed*. **2015**, *54*, 8961–8965. b) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757−10768. Also, see: c) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294–13297.

[214] Kondoh, A.; Ota, Y.; Komuro, T.; Egawa, F.; Kanomata, K.; Terada, M. *Chem. Sci*. **2016**, *7*, 1057−1062.

chiral Brønsted acid catalyst serves both to form the ketimine and induce asymmetry. Adducts possessing a quaternary stereogenic center were obtained in moderated to excellent yields with good to excellent enantioselectivities. The excellent results are limited to just 2-methoxyfuran as a nucleophile (Scheme 91).

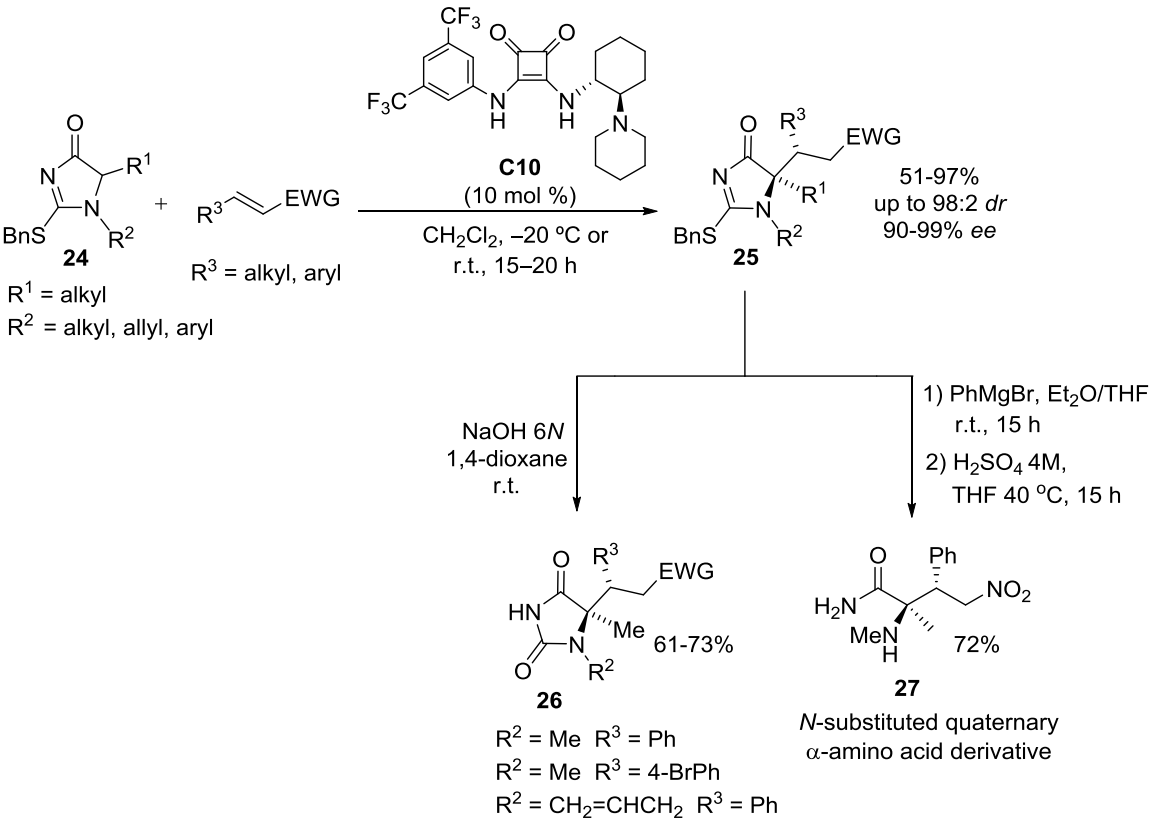


Scheme 91. Chiral Brønsted acid-catalyzed Friedel-Crafts reaction of in situ-generated ketimines.

Despite these significant advances, the scope of optically active quaternary hydantoins available continues to be rather narrow (essentially restricted to some 5-aryl hydantoins).

Recently, we introduced 1*H*-imidazol-4(5*H*)-ones **24** as novel nucleophile in asymmetric synthesis.[215] These compounds allowed a highly efficient construction of a tetrasubstituted stereogenic center and a direct access to N-substituted (alkyl, allyl, aryl) α-amino acid derivatives and 5, 5-disubstituted hydantoins (Scheme 92). Unlike azlactones, these heterocycles do not present the C-2/C-4 selectivity problem. One drawback of the reaction is the limited thermal stability of template **24**, which partially decomposes upon storage at room temperature for several hours, or during standard silica gel chromatographic purification, making storage in the freezer at –40 °C necessary.

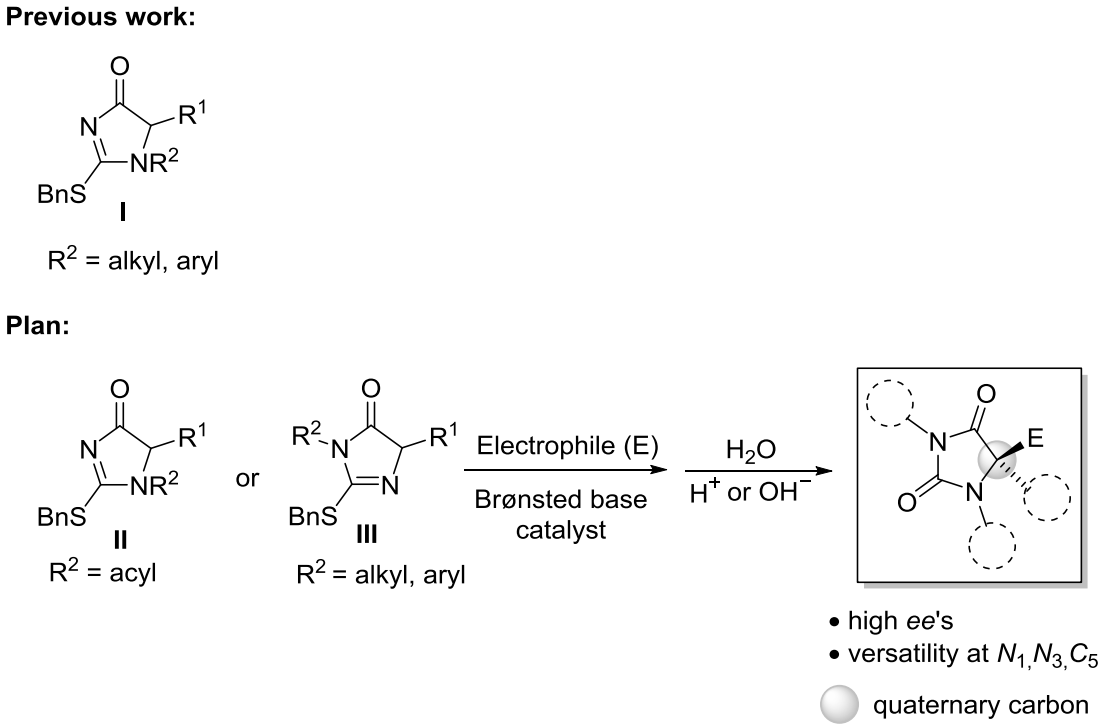
[215] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6887.



Scheme 92. Our preliminary finding.

3.2. Working hypothesis and synthetic plan

Due to the lack of procedures in the literature to generate optically active quaternary hydantoins, our preliminary plan was to develop a catalyst-controlled, enantioselective method for the synthesis of diversely functionalized 5,5-disubstituted hydantoins. Taking into account our previous work and given the simplicity and the high selectivity of the method, we sought to investigate the behavior of the related heterocyclic systems **II** and **III** (Scheme 93). If successful, a broad-scope approach for the enantioselective synthesis of diversely 1,3,5-substituted hydantoins would be at hand.



Scheme 93. Template-based catalytic enantioselective synthesis of diversely substituted quaternary hydantoins.

The effectiveness of template **I** to react under the above mild enolization conditions may be ascribed to the aromatic character of the transiently formed enolate **I'**. From a similar reasoning, it was envisaged that the related heterocyclic systems **II** and **III**, with an N_1-acyl and an N_3-aryl substituents, respectively, would lead, in the presence of a base promoter, the corresponding aromatic enolates **II'** and **III'**. Moreover, in view of the structural similarities of the three enolates, their interaction with the protonated amine/squaramide catalyst might be equally productive in order to afford the addition adducts (Figure 26).

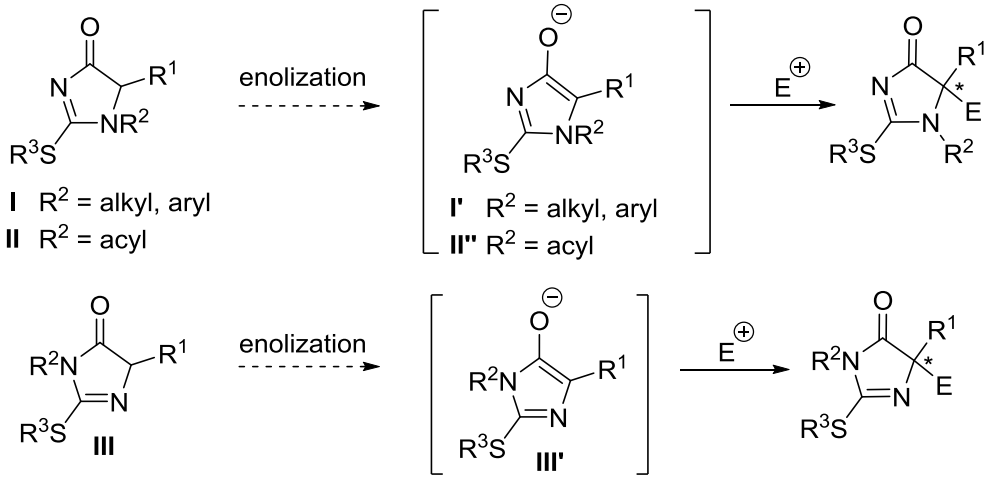
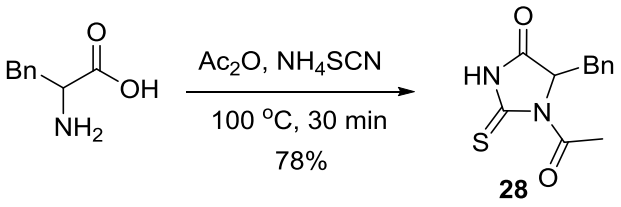


Figure 26. Imidazolone templates with various substitution patterns and their enolization.

3.3. Results and discussion

3.3.1. Preparation and evaluation as pronucleophiles of N_1-acyl templates (II)

First, the preparation of *N*-acyl thiohydantoin **28** was carried out accordingly to the procedure of Burgess.[216] Thus, racemic phenylalanine and NH_4SCN were mixed in Ac_2O for 30 min at 100 ^oC affording the racemic thiohydantoin **28** in 78% yield (Scheme 94).

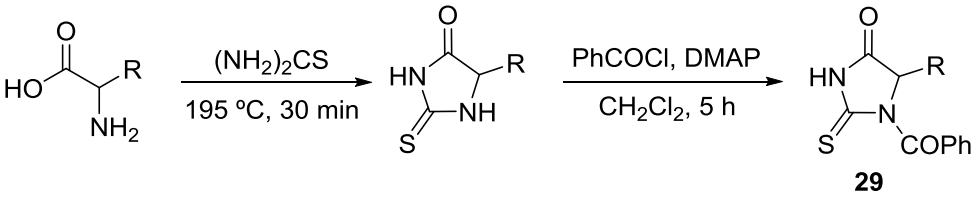


Scheme 94.

Alternative methods were employed for the preparation of the remaining thiohydantoins. Thus, condensation reaction between thiourea and the corresponding aliphatic amino acid[217] followed by an acylation with benzoyl chloride afforded *N*-benzoyl thiohydantoins **29** in yields from moderate to good after two steps (Table 11).

[216] Reyes, S.; Burgess, K. *J. Org. Chem.* **2006**, *71*, 2507−2509.
[217] Han, J.; Wang, J.; Dong, H.; Lei, J.; Wang, M.; Fang, J. *Molecules* **2011**, *16*, 2833−2845.

Table 11. Synthesis of thiohydantoins **29**.

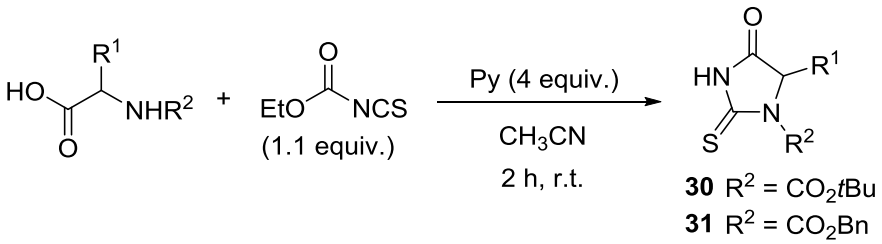


Entry		R	Yield (%)[a] 2 steps
1	**29A**	Me	58
2	**29B**	Et	53
3	**29C**	Bn	69
4	**29D**	*i*Bu	56
5	**29E**	*n*Hex	50
6	**29F**	$CH_3S(CH_2)_2$	48

[a] Overall yield after column chromatography.

Finally, the synthesis of *N*-Boc and *N*-Cbz thiohydantoins **30** and **31** was achieved by condensation of the corresponding *N*-Boc or *N*-Cbz protected α-amino acid and ethoxycarbonyl isothiocyanate in the presence of 4 equivalents of pyridine, which generally proceeded in very good yields (Table 12).[218]

Table 12. Synthesis of thiohydantoins **30** and **31**.



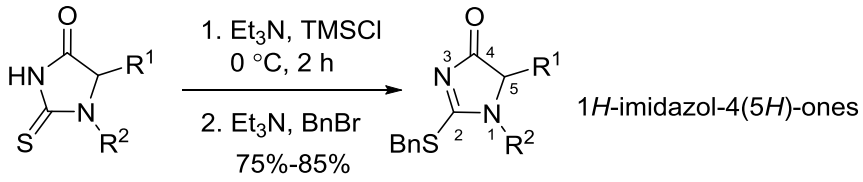
Entry		R^1	R^2	Yield (%)[a]
1	**30A**	Me	Boc	88
2	**30B**	Et	Boc	86
3	**30C**	Bn	Boc	90
4	**30D**	*i*Bu	Boc	83
5	**30E**	*n*Hex	Boc	75
6	**30G**	$BnOCH_2$	Boc	90
7	**30H**	Ph	Boc	72
8	**31C**	Bn	Cbz	81
9	**31G**	$BnOCH_2$	Cbz	82

[a] Overall yield after column chromatography.

[218] Boyd, V. L.; Bozzini, M.; Guga, P. J.; Zon, G., *U.S. Patent* 5185266, Feb 9, 1993.

After *O*-silylation of **28**-**31** with trimethylchlorosilane and triethylamine,[219] the crude reaction was treated again with Et_3N and with benzyl bromide giving, after the hydrolysis of the *O*-sylilated enolate, the desired N_1-acyl imidazolones **32**-**35** in good overall yields (Table 13).

Table 13. Synthesis of 1*H*-imidazol-4(5*H*)-ones **32**, **33**, **34** and **35**.



28 R^2 = COMe
29 R^2 = COPh
30 R^2 = CO_2tBu
31 R^2 = CO_2Bn

32 R^2 = COMe
33 R^2 = COPh
34 R^2 = CO_2tBu
35 R^2 = CO_2Bn

Entry		R^1	R^2	Yield (%)[a]
1	**32C**	Bn	Ac	75
2	**33A**	Me	Bz	76
3	**33B**	Et	Bz	72
4	**33C**	Bn	Bz	81
5	**33D**	*i*Bu	Bz	70
6	**33E**	*n*Hex	Bz	70
7	**33F**	$CH_3S(CH_2)_2$	Bz	64
8	**34A**	Me	Boc	84
9	**34B**	Et	Boc	76
10	**34C**	Bn	Boc	80
11	**34D**	*i*Bu	Boc	80
12	**34E**	*n*Hex	Boc	72
13	**34G**	$BnOCH_2$	Boc	82
14	**34H**	Ph	Boc	82
15	**35A**	Me	Cbz	76
16	**35C**	Bn	Cbz	70
17	**35G**	$BnOCH_2$	Cbz	78

[a] Overall yield after column chromatography.

Thus, this synthetic strategy allowed us a rapid access to a variety of 1*H*-imidazol-4(5*H*)-ones and an important point is that these *N*-acyl dihydroimidazolones (**32**-**35**) were observed to be stable solids for months at room temperature under air atmosphere.

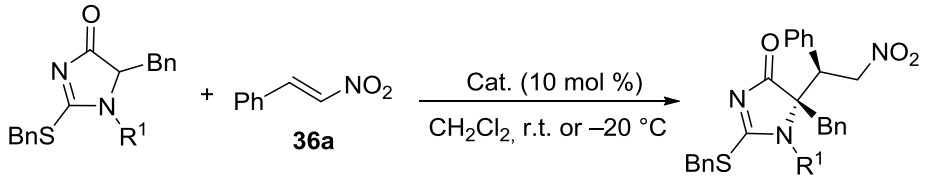
[219] This step was necessary to avoid a mixture of *O*-benzyl and *O*,*S*-dibenzyl products due to the greater reactivity of enolate respect to the thiocarbonyl moiety.

3.3.2. Catalyst screening. Reaction between *N*-acyl-templates and nitroolefins

To assess the viability of these substrates, we started evaluating the behavior of **32C** and **33C** against nitroolefin **36a**. Gratifyingly, as the brief screening in Table 14 shows, the reaction of *N*-acetyl **32C** with nitrostyrene **36a** to afford adduct **37Ca** proceeded at room temperature in the presence of various bifunctional Brønsted base catalysts with remarkable selectivity, whilst reactivity was more catalyst-dependent. For instance, both catalysts **C10** and **C11**[220] were able to afford adduct **37Ca** as a 97:3 mixture of diastereomers in very high (but opposite) enantioselectivity, although no full conversion could be reached in either case after 24 h (entries 1, 5). As expected, catalyst **ent-C10** (entry 2) afforded the same enantiomer as **C11** with reproducible reactivity and selectivity compared to **C10**. The newly developed catalyst **C12**[221] was more active, leading to essentially full conversion after 24 h (90% conversion after 16 h) with nearly the same degree of diastereo- and enantiocontrol (entry 8). Regardless the catalyst employed, the *N*-benzoyl analog **33C** proved to be more reactive than the *N*-acetyl derivative **32C** and upon reaction with nitrostyrene afforded the corresponding adduct **38Ca**, again, in essentially perfect diastereo- and enantioselectivity (entries 3, 6 and 9). This same order of catalyst activity, namely **ent-C10** < **C11** < **C12**, was observed at subzero temperatures. Thus, whilst **ent-C10** was completely unactive at –20 °C, **C11** (entry 7) and specially the catalyst **C12** (entry 10), did promote the reaction between **33C** and nitrostyrene at that temperature, affording compound **38Ca** in very high yield and selectivity. With the N-Me derivative **C13** longer reaction times are needed and gives same diastereoselectivity but worst enantioselectivity (90% *ee*). It should be noted that catalyst **ent-C10** and **C13** were completely soluble at the conditions employed, but **C11** and **C12** were only partially soluble. It was also observed that cinchona-based squaramide catalyst **C1** was equally active, albeit less selective (*dr* 90:10, entry 12), whilst the corresponding thiourea analog **C2** was both less active and selective (entry 13). In their turn, quinine and $(DHQD)_2PYR$ were completely ineffective catalyst for this reaction.

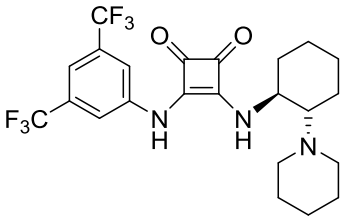
[220] Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953−957.
[221] Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185−8195.

Table 14. Catalyst screening for the reaction of **32C**/**33C** with nitrostyrene **36a**.[a]

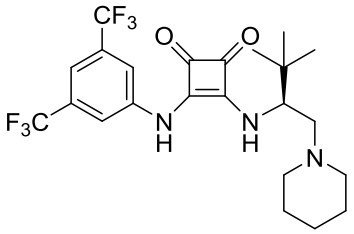


32C R^1 = COMe
33C R^1 = COPh

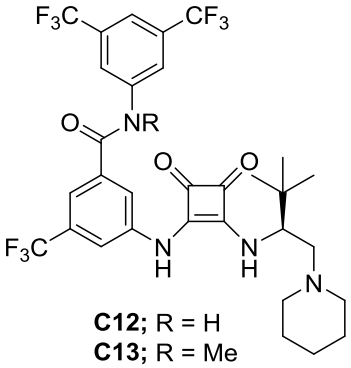
37Ca R^1 = COMe
38Ca R^1 = COPh



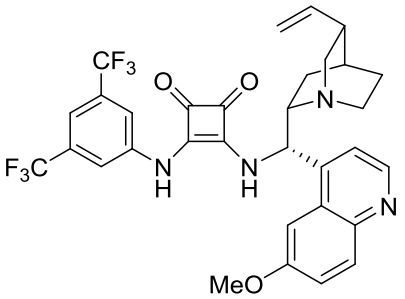
ent-C10



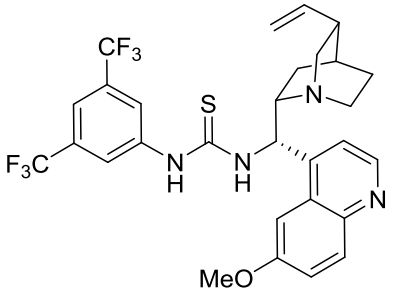
C11



C12; R = H
C13; R = Me



C1



C2

Entry	Cat.	R^1	T(°C)	T(h)	Conv. (%)[b]	*dr*[c]	*ee* (%)[d]
1	**C10**	COMe	r.t.	24	80	97:3	−98
2	**ent-C10**	COMe	r.t.	24	80	97:3	98
3		COPh	r.t.	16	>98	>98:2	98
4			−20	96	NR	--	--
5	**C11**	COMe	r.t.	24	50	97:3	98
6		COPh	r.t.	16	>98	>98:2	97
7			−20	96	65	>98:2	98
8	**C12**	COMe	r.t.	16	90	98:2	99
9		COPh	r.t.	2	>98	98:2	99
10			−20	48	>98	>98:2	98
11	**C13**	COPh	r.t.	2	77	>98:2	90
12	**C1**	COMe	r.t.	16	95	90:10	99
13	**C2**	COMe	r.t.	16	60	80:20	90

[a] The reactions were performed using 0.3 mmol of **32C**/**33C**, 0.6 mmol of nitrostyrene **36a** and 10 mol % of the catalyst in 0.6 mL CH_2Cl_2. [b] The conversion was estimated from the crude by ^{1}H-NMR. [c] Diastereomeric ratio determined by ^{1}H-NMR and by chiral HPLC. [d] *Ee* of major diastereomer was determined by HPLC.

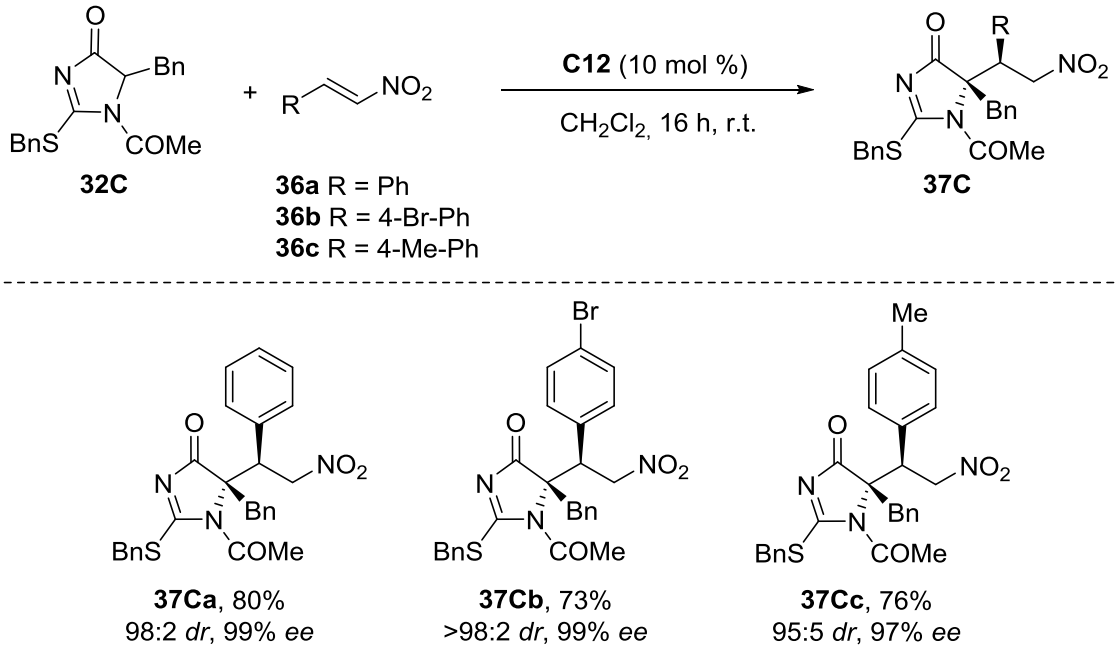
Thus, the optimal conditions for the addition of **32C** or **33C** with the nitroolefin **36a** (2 equiv.) included the presence of 10 mol % catalyst **C12** at room temperature and in dichloromethane as a solvent.

3.3.3. Scope and limitations

With the optimized conditions for the catalytic diastereo- and enantioselective Michael addition reaction at hand, the scope and the limitation of the system were investigated.

The reactions of *N*-acyl imidazolone **32C** with nitroolefins **36a**-**c** proceeded with very good yields and excellent stereocontrol, regardless of the electron neutral, rich or poor character of the β-aryl substituent in the nitroalkene (Table 15).

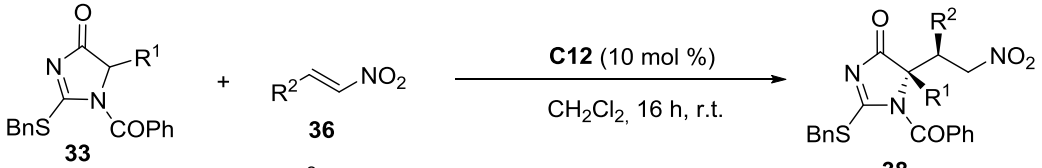
Table 15. Conjugate addition of imidazolone **32C** to nitroolefins **36a**-**c** promoted by catalyst **C12**.[a]



[a] Reaction conditions: dihydroimidazolone **32C** (1 equiv., 0.2 mmol), nitroolefins **36a**-**c** (2 equiv., 0.4 mmol), and **C12** (10 mol %) were stirred at r.t. in 1.0 mL of CH_2Cl_2 for 16 h. Diastereomeric ratios and *ee* were determined by ^{1}H-NMR and by chiral HPLC.

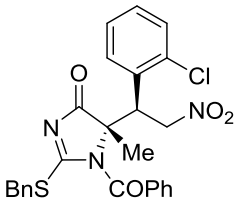
The reaction between *N*-benzoyl imidazolones **33** bearing different C_5-substituents (e.g. methyl, ethyl, benzyl, isobutyl, *n*-hexyl and methyl tioethyl) and nitroolefins **36a**-**g** also rendered in high yields and enantioselectivities (92-98% *ee*), and diastereoselectivities generally higher than 96:4, adducts **38Cg** (*dr* = 85:15) and **38Ce** (*dr* = 74:26) being exceptions (Table 16).

Table 16. Conjugate addition of imidazolones **33A**-**F** to nitroolefins **36a**-**g** promoted by catalyst **C12**.[a]

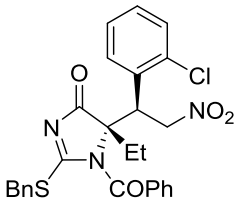


A R^1 = Me
B R^1 = Et
C R^1 = Bn
D R^1 = *i*Bu
E R^1 = *n*Hex
F R^1 = $CH_3S(CH_2)_2$

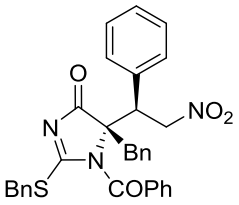
a R^2 = Ph
b R^2 = 4-Br-Ph
c R^2 = 4-Me-Ph
d R^2 = 2-Cl-Ph
e R^2 = 3-Cl-Ph
f R^2 = 2-MeO-Ph
g R^2 = 3-furyl



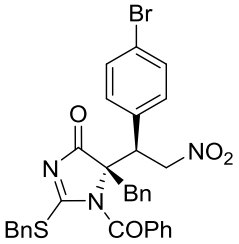
38Ad, 72%[b]
97:3 *dr*, 96% *ee*



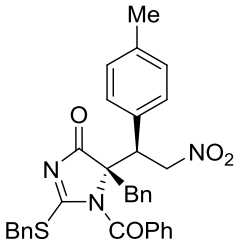
38Bd, 70%[b]
97:3 *dr*, 98% *ee*



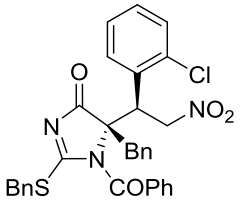
38Ca, 76%
>98:2 *dr*, 98% *ee*



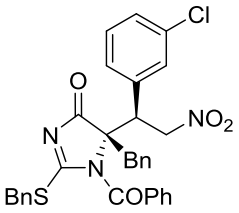
38Cb, 78%
>98:2 *dr*, 98% *ee*



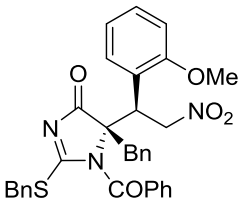
38Cc, 73%
>98:2 *dr*, 94% *ee*



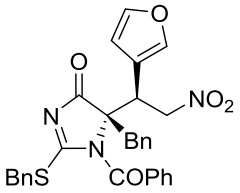
38Cd, 89%
96:4 *dr*, 98% *ee*



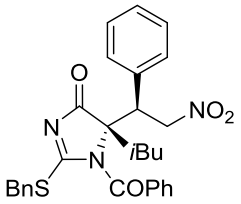
38Ce, 80%
74:26 *dr*, 98% *ee*



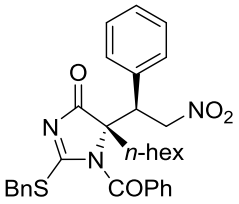
38Cf, 87%
>98:2 *dr*, 98% *ee*



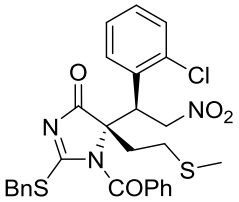
38Cg, 74%
85:15 *dr*, 98% *ee*



38Da, 88%
98:2 *dr*, 92% *ee*



38Ea, 73%
>98:2 *dr*, 97% *ee*



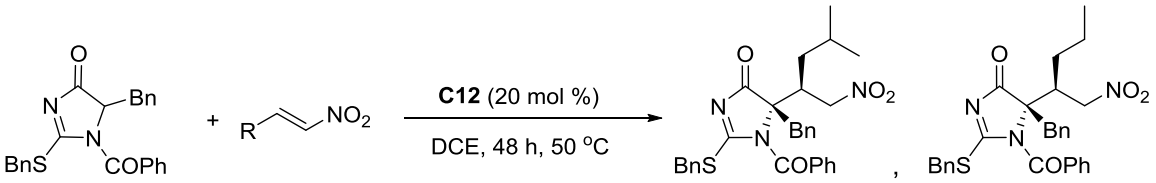
38Fd, 73%
>98:2 *dr*, 98% *ee*

[a] Reaction conditions: dihydroimidazolone **33** (1 equiv., 0.2 mmol), nitroolefins **36a**-**g** (2 equiv., 0.4 mmol), and **C12** (10 mol %) were stirred at 20 °C in 1.0 mL of CH_2Cl_2 for 16 h. Diastereomeric ratios and *ee* were determined by ^{1}H-NMR and by chiral HPLC. [b] Reaction run for 48 h.

The reactions involving the more problematic aliphatic nitroolefins did also proceed with very good diastereo- and enantioselectivity (adducts **38Ch** and **38Ci**). However, these latter substrates resulted comparatively less reactive than the aromatic congeners

and required 5 equiv. of nitroalkene and 20 mol % catalyst in DCE at 50 °C for practical reaction conversions (Table 17).

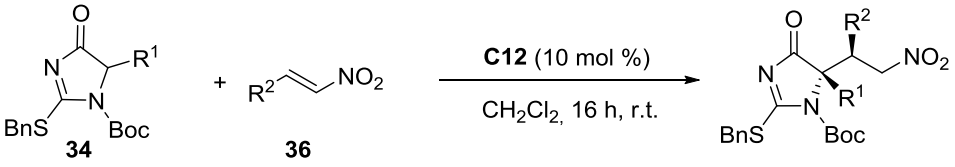
Table 17. Conjugate addition of imidazolone **33C** to nitroolefins **36h**-**i** promoted by catalyst **C12**.[a]

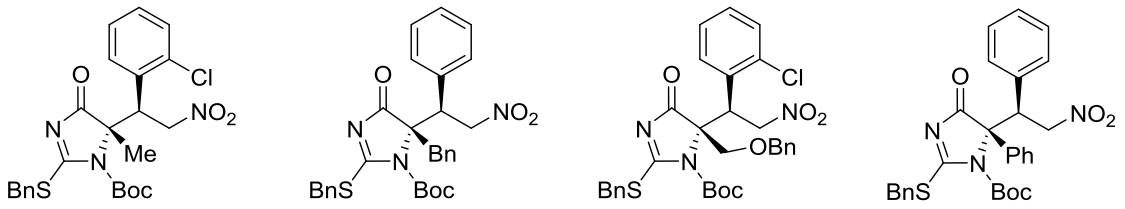


[a] Reaction conditions: dihydroimidazolone **33C** (1 equiv., 0.2 mmol), nitroolefins **36h**-**i** (5 equiv., 1.0 mmol), and **C12** (20 mol %) were stirred at 50 °C in 1.0 mL of DCE for 48 h. Diastereomeric ratios and *ee* were determined by ^{1}H-NMR and by chiral HPLC.

N-Boc dihydroimidazolone templates **34** were also competent substrates for this reaction, affording adducts **39** with essentially perfect stereoselectivity and good yields. As formation of product **39Ha** in 69% yield and high selectivity proves, the method is also suitable for templates with an aryl group at the C5 position (Table 18).

Table 18. Conjugate addition of dihydroimidazolones **34A**,**C**,**G**,**H** to nitroolefins **36a**,**d** promoted by catalyst **C12**.[a]



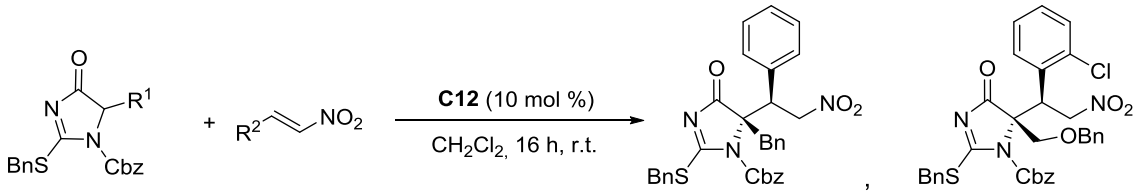


[a] Reaction conditions: dihydroimidazolones **34** (1 equiv., 0.2 mmol), nitroolefins **36a**,**d** (2 equiv., 0.4 mmol), and **C12** (10 mol %) were stirred at 20 °C in 1.0 mL of CH_2Cl_2 for 16 h. Diastereomeric ratios and *ee* were determined by ^{1}H-NMR and by chiral HPLC. [b] Reaction run for 72 h.

Finally, *N*-Cbz imidazolones **35** were also tested. Thus, moderate yield (60 %) and excellent selectivity (>98:2 *dr*, 99% *ee*) was obtained in the reaction between **35C** and

nitroestirene **36a**, while excellent yield (91%) and selectivity (95:5 *dr*, 98% *ee*) was observed for the reaction between **35G** and **36d** (Table 19).

Table 19. Conjugate addition of dihydroimidazolones **35C**-**G** to nitroolefins **35a**,**d** promoted by catalyst **C12**.[a]

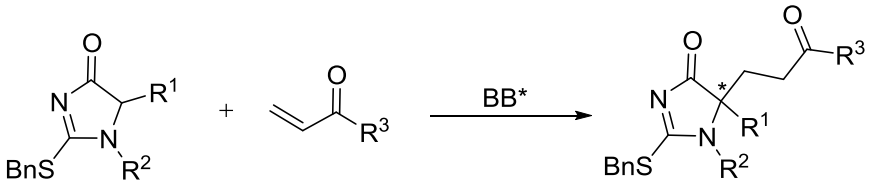


35C R^1 = Bn; **35G** R^1 = $BnOCH_2$ | **36a** R^2 = Ph; **36d** R^2 = 2-Cl-Ph | **40Ca**, 60%[b] >98:2 *dr*, 99% *ee* | **40Gd**, 91% 95:5 *dr*, 98% *ee*

[a] Reaction conditions: dihydroimidazolones **35C**-**G** (1 equiv., 0.2 mmol), nitroolefins **36a**,**d** (2 equiv., 0.4 mmol), and **C12** (10 mol %) were stirred at 20 °C in 1.0 mL of CH_2Cl_2 for 16 h. Diastereomeric ratios and *ee* were determined by ^{1}H-NMR and by chiral HPLC. [b] Reaction run for 48 h.

3.3.4. Addition of *N*-acyl-templates (II) to other Michael acceptors

Given the excellent results regarding both the reactivity and stereocontrol afforded in the Michael addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins using a bifunctional squaramide/Brønsted base catalyst, and seeing the synthetic possibilities that these heterocycles bear, we decided to test our proucleophiles with a different electrophile, in this case, Michael acceptors, especially simple vinyl ketones (Scheme 95).

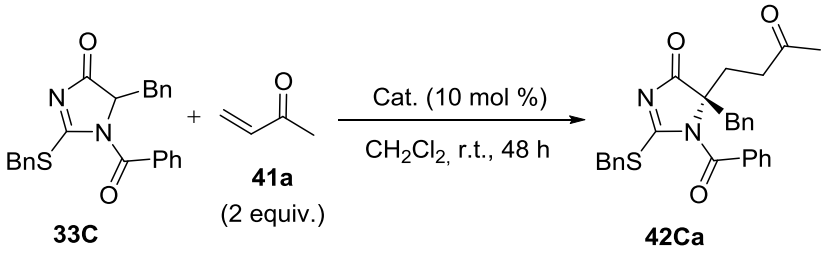


Scheme 95. Proposed reaction.

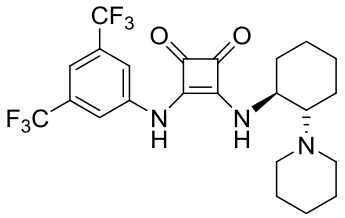
Our study began with the evaluation of several Brønsted bases for the addition of the imidazolone **33C** to methyl vinyl ketone **41a** at room temperature in dichloromethane. Catalysts showed a trend in activity and selectivity similar to that observed with nitroalkenes. Thus, **ent-C10** could promote the addition of **33C** to **41a**, although the reaction progressed slowly, 50% conversion after 48 h, and with suboptimal enantioselectivity (72% *ee*). In contrast, catalyst **C12** and, especially, **C11** resulted comparatively more active (reaction conversion after 48 h at room temperature, 70% and 85%, respectively) and led to *ee*'s of 95% and 96%. With **C1** the reactivity improved to almost full conversion, however only 80% of enantioselectivity was obtained. Thus,

the optimal reaction conditions included the presence of catalyst **C11** at room temperature in dichloromethane.

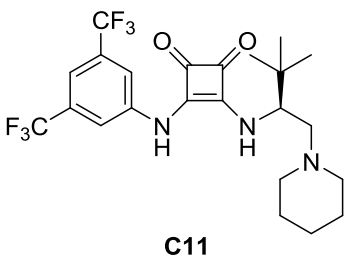
Table 20. Catalyst screening for the Michael addition of dihydroimidazolone **33C** to methyl vinyl ketone.[a]



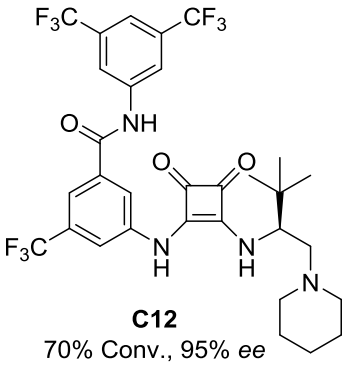
33C **42Ca**



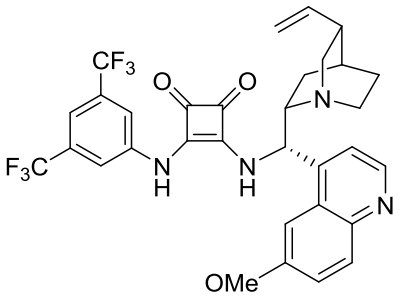
ent-C10
50% Conv., 72% *ee*



C11
85% Conv., 96% *ee*



C12
70% Conv., 95% *ee*



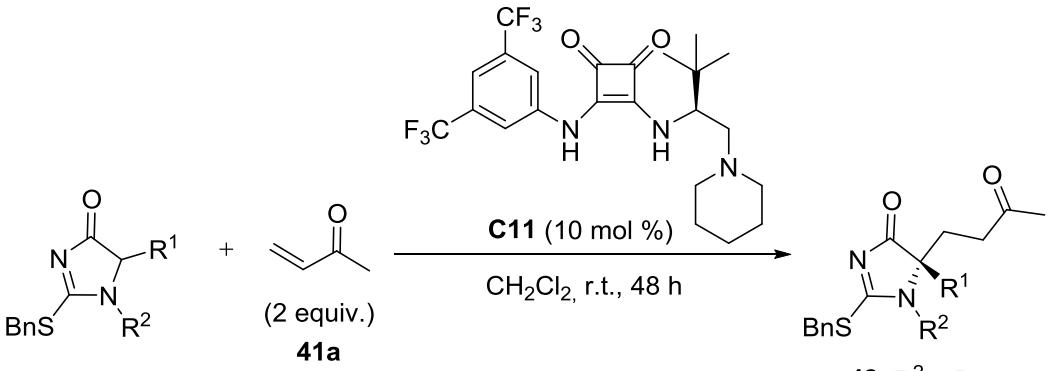
C1
95% Conv., 80% *ee*

[a] Reaction conditions: dihydroimidazolone **33C** (1 equiv., 0.3 mmol), methyl vinyl ketone **41a** (2 equiv., 0.6 mmol), and catalyst (10 mol %) were stirred at r.t. in 0.6 mL of CH_2Cl_2 for 48 h. *Ee* was determined by chiral HPLC.

Once with the optimal conditions in hand, we then started to check the generality of the method, testing different vinyl ketones and dihydroimidazolones.

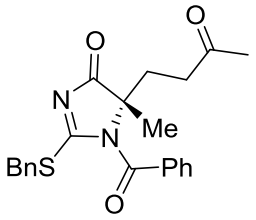
Firstly, the reactions of dihydroimidazolones **33**, **34** and **35** with methyl vinyl ketone **41a** were explored. As data in Table 21 shows, independently of the substitution pattern, each imidazolone was equally competent reaction partner giving rise to the respective Michael adducts **42**, **43** and **44** in generally moderate yields and excellent enantioselectivities.

Table 21. Conjugate addition of dihydroimidazolones **33**-**35** to methyl vinyl ketone promoted by catalyst **C11**. [a]

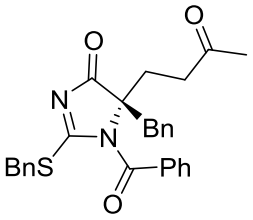


33 R^2 = Bz
34 R^2 = Boc
35 R^2 = Cbz

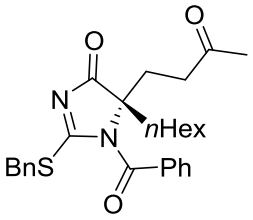
42 R^2 = Bz
43 R^2 = Boc
44 R^2 = Cbz



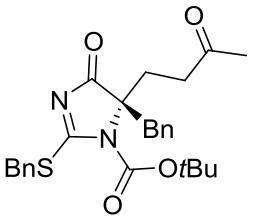
42Aa
48%, 94% *ee*



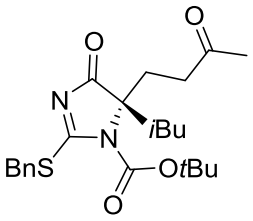
42Ca
67%, 96% *ee*



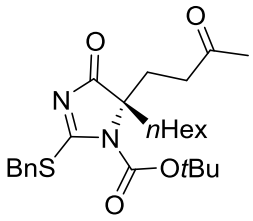
42Ea
52%, 96% *ee*



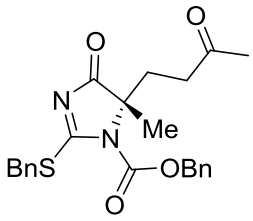
43Ca
62%, 89% *ee*



43Da
81%, 97% *ee*



43Ea
62%, 97% *ee*

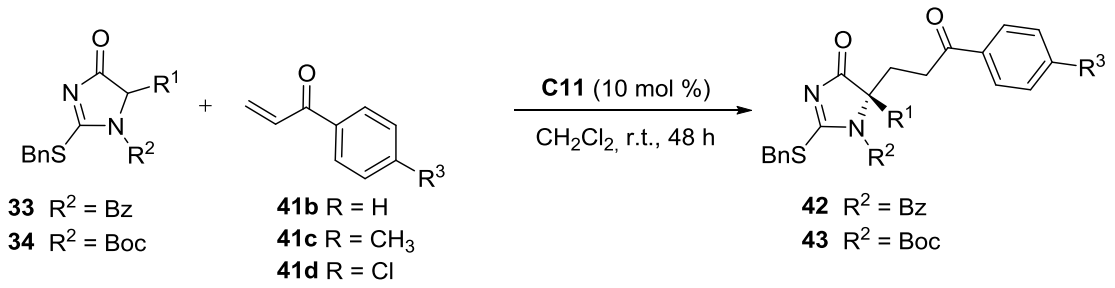


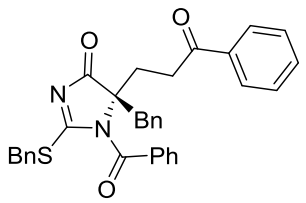
44Aa
61%, 97% *ee*

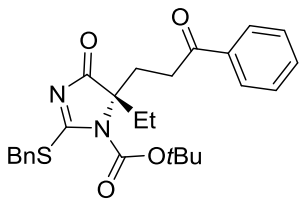
[a] Reaction conditions: **33**-**35** (1 equiv., 0.3 mmol), methyl vinyl ketone **41a** (2 equiv., 0.6 mmol), and **C11** (10 mol %) were stirred at r.t. in 0.6 mL of CH_2Cl_2 for 48 h. *Ee* was determined by chiral HPLC.

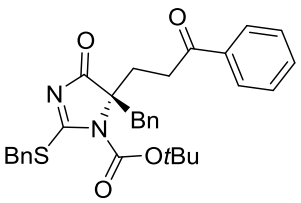
Michael addition of the *N*-benzoyl and *N*-Boc substrates **33** and **34** to aryl vinyl ketones **41b**-**d** was also tested, resulting again in excellent enantioselectivities in all cases. As expected, aryl vinyl ketones **41b**-**d** showed more reactivity than methyl vinyl ketone **41a** and led to better conversions and yields (Table 22).

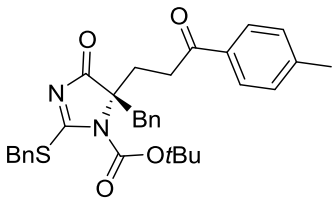
Table 22. Conjugate addition of dihydroimidazolones **33** and **34** to aryl vinyl ketones **41b**-**d** promoted by catalyst **C11**.[a]

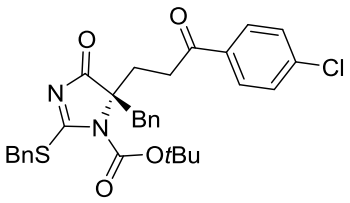


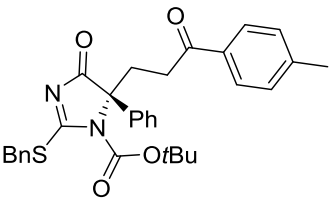

42Cb, 81%, 94% *ee*


43Bb, 70%, 97% *ee*


43Cb, 83%, 96% *ee*

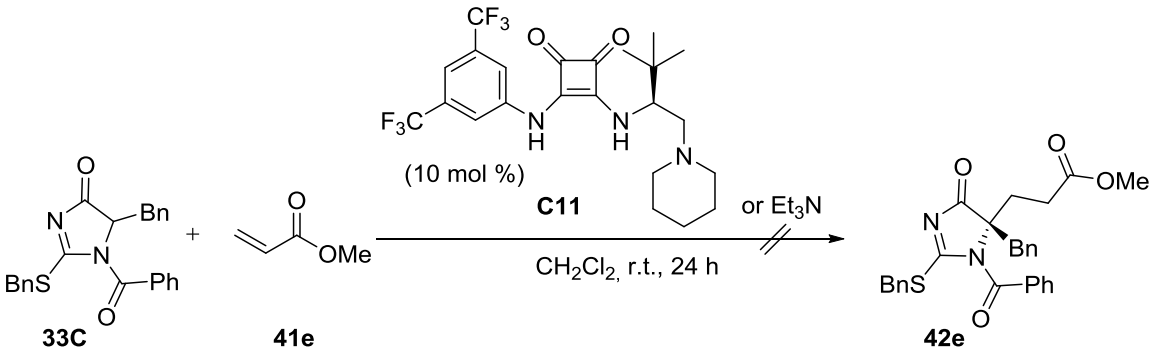

43Cc, 84%, 96% *ee*


43Cd, 85%, 96% *ee*


43Hc, 84%, 99% *ee*

[a] Reaction conditions: **33**-**34** (1 equiv., 0.3 mmol), **41b**-**d** (2 equiv., 0.6 mmol), and **C11** (10 mol %) were stirred at r.t. in 0.6 mL of CH_2Cl_2 for 48 h. *Ee* was determined by HPLC.

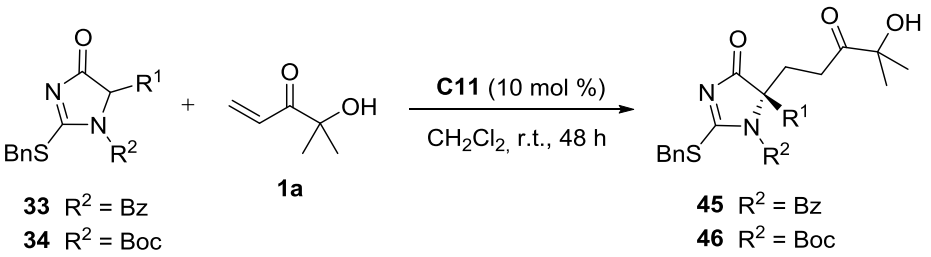
Unlike nitroolefins and vinyl ketones which had led to successful reaction, α,β-unsaturated esters appeared to be unsuitable reaction partners likely due to their attenuated reactivity/electrophilicity as compared to the later. Thus, when Michael addition of imidazolone **33C** to methyl acrylate was tested, no conversion was obtained neither with achiral nor with chiral catalysts (Scheme 96).



Scheme 96. Addition of imidazolone **33C** to methyl acrylate.

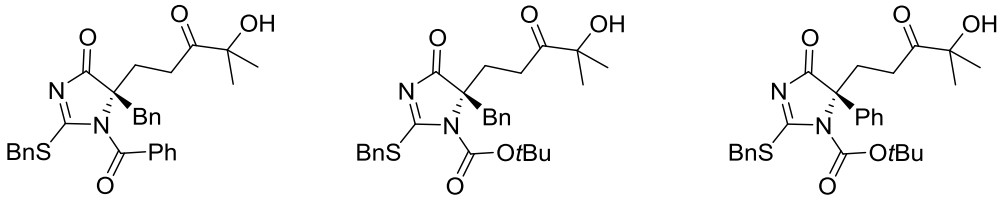
On the other hand, the reaction of dihydroimidazolones **33** and **34** to highly electrophilic α´-hydroxy enone **1a** (see chapter 2, page 56) provided adducts **45** and **46** in excellent yields and enantioselectivities (Table 23).

Table 23. Conjugate addition of imidazolones **33**-**34** to α´-hydroxy enone **1a** promoted by catalyst **C11**. [a]



33 R^2 = Bz
34 R^2 = Boc

45 R^2 = Bz
46 R^2 = Boc



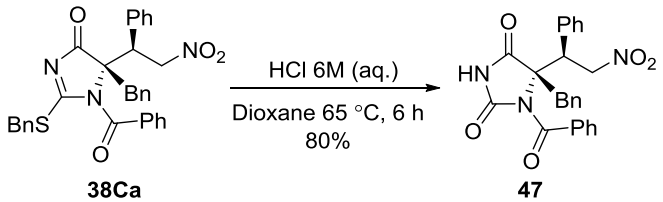
45C, 80%, 94% *ee* **46C,** 81%, 90% *ee* **46H,** 82%, 91% *ee*

[a] Reaction conditions: **33**-**34** (1 equiv., 0.3 mmol), **1a** (2 equiv., 0.6 mmol), and **C11** (10 mol %) were stirred at r.t. in 0.6 mL of CH_2Cl_2 for 48 h. *Ee* was determined by chiral HPLC.

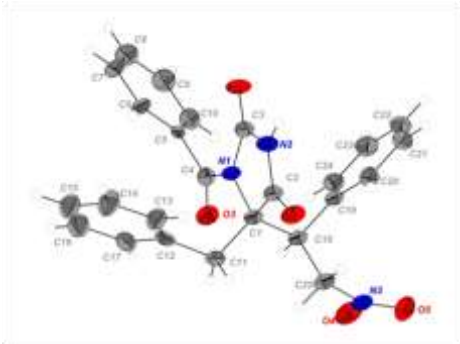
3.3.5. Elaboration of adducts

Next, the chemical elaboration of adducts was investigated. On the one side, as shown in Scheme 97, treatment of N_1 benzoyl adduct **38Ca** with HCl 6M in dioxane at 65 ^{o}C for 6 hours gave rise, after water mediated nucleophilic displacement of the thioether group, to *N*-acyl hydantoin **47** in 80% yield. Under these conditions no hydrolysis of the benzoyl imide function occurred. Crystallization of adduct **47** allowed the determination

of its absolute and relative configuration by a single-crystal X-ray analysis, which was extrapolated to the remaining adducts by assuming a uniform reaction mechanism.

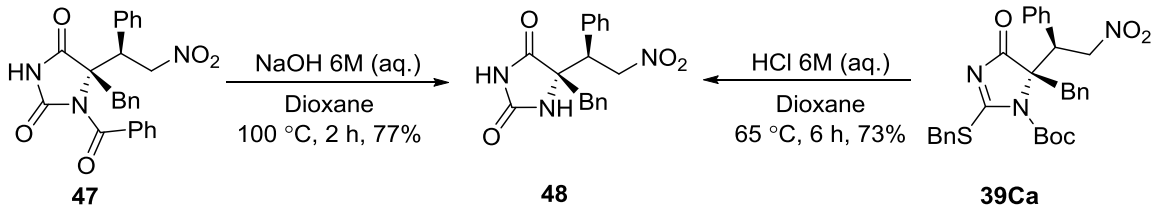


38Ca **47**



Scheme 97.

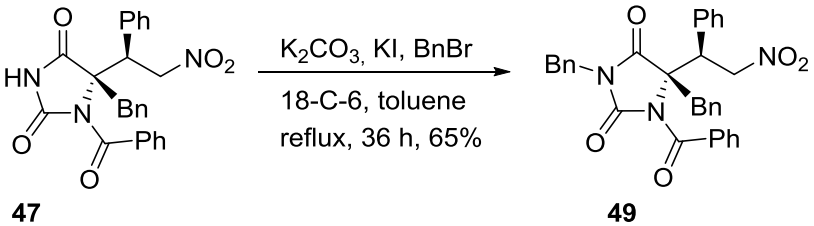
On the other hand, hydantoin **48** was obtained from compounds **47** and **39Ca** following a basic hydrolysis or alternatively from **39Ca** through acid hydrolisis. Thus, saponification of **47** with NaOH 6M at 100 ^{o}C for 2 hours gave the free hydantoin **48** in 77% yield (Scheme 98). On the other hand, the concomitant acidic hydrolysis of the Boc group and the displacement of the thioether group afforded also the free hydantoin **48** in 73% overall yield.



47 **48** **39Ca**

Scheme 98.

Finally, alkylation of imide nitrogen in adduct **47** under standard Williamson conditions at reflux of toluene for 36 hours, allowed access to the corresponding N-benzylated adduct **49** in moderate yield (Scheme 99).



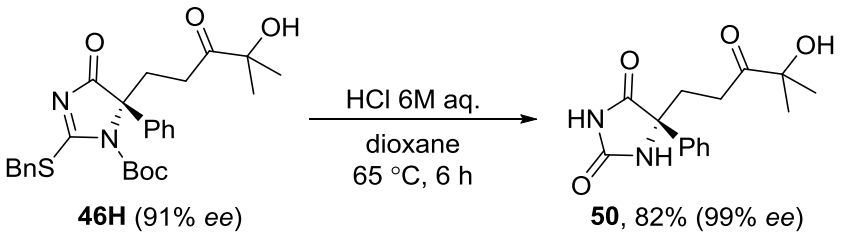
47 **49**

Scheme 99.

3.3.6. Synthesis of ADAMTS-5 inhibitors 52 and 53

Starting from adduct **46H**, we designed a three-step sequence for the synthesis of cartilage degrading enzyme ADAMTS-5 inhibitors **52** and **53** used for the treatment of osteoarthritis degenerative joint diseases.[222]

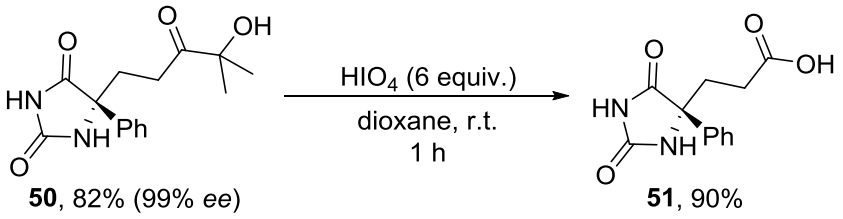
First, an acid hydrolysis of the *S*-benzylisothiourea moiety in **46H** afforded in good yield **50** after washing the solid crude once with warm Et_2O optically pure hydantoin (Scheme 100).



46H (91% *ee*) **50**, 82% (99% *ee*)

Scheme 100.

Afterwards, cleavage of the ketol moiety in adduct **50** employing periodic acid, afforded carboxylic acid **51** in very good yield (Scheme 101), with acetone being the only mayor organic side product formed.

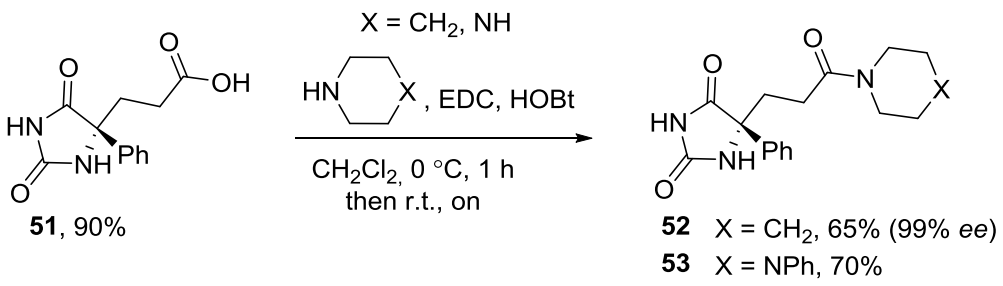


50, 82% (99% *ee*) **51**, 90%

Scheme 101.

Finally, coupling of acid **51** with piperidine and *N*-phenyl piperazine using EDC/HOBt coupling reagents led to amides **52** and **53** in 65% and 70% yield respectively. Preservation of the configurational integrity of adduct **52** was assesed (Scheme 102).

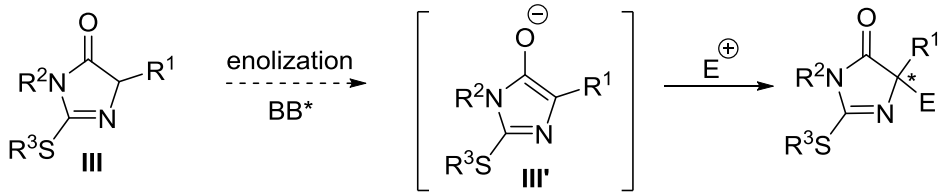
[222] Brebion, F. L; Alvey, L. J.; Amantini, D.; Deprez, P. M. M. J.; Gosmini, R. L. M.; Jary, H. M.; Peixoto, C.; Varin, M. L. C.; De Ceuninck, F. A.; Pop-Botez, I. E. PCT Int. Appl. (2016), WO 2016102347 A1.



Scheme 102.

3.3.7. Preparation and evaluation as pronucleophiles of N_1-acyl templates (III)

Our next goal was to check the behavior of related heterocyclic systems **III** (Scheme 103). While it was expected that these compounds would also provide an extended aromatic enolate species **III'** upon enolization in the presence of a bifunctional Brønsted base catalyst, whether or not these latter would react as efficiently as **I'/II'** was unanswered yet.

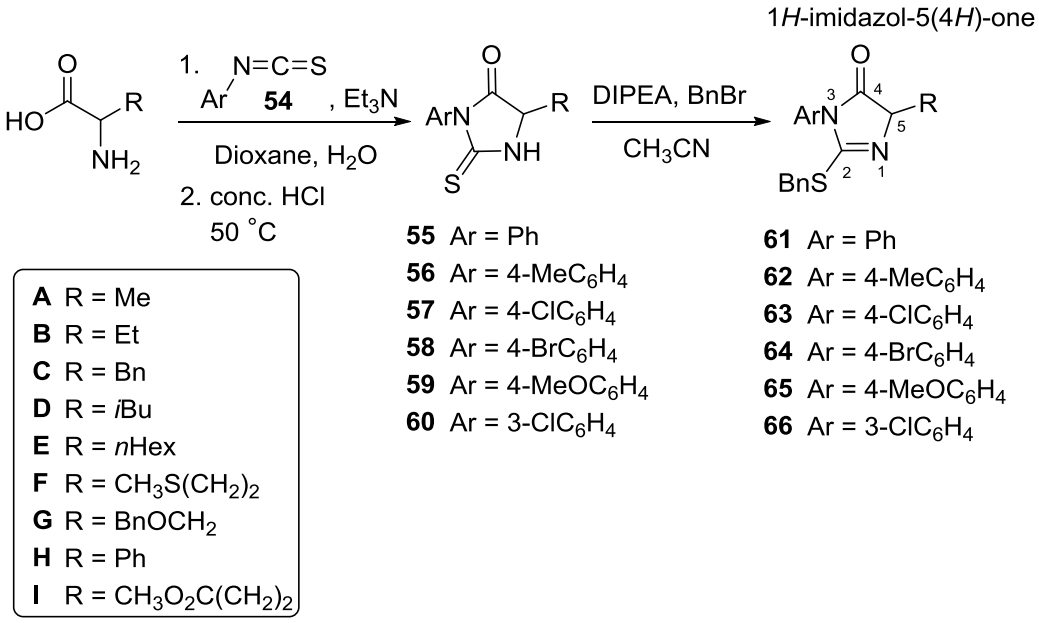


Scheme 103.

3.3.8. Preparation of N_3-aryl templates

The preparation of the N_3-aryl templates **61**–**66** (Scheme 104) started according to a established procedure,[223] from the condensation of the respective amino acid with phenyl(aryl) isothiocyanate **54** and triethylamine to yield the corresponding thiohydantoins **55**–**60**. Each one was *S*-benzylated by treatment with benzyl bromide and diisopropyl ethyl amine to yield the corresponding adducts **61**–**66**. It is important to note at this point that these compounds also turned out to be comparatively more stable than the corresponding *N*–alkylated compounds **I** (see Figure 26).

[223] Zhu, L.; Lu, C.; Chen, Z.; Yang, G.; Li, Y.; Nie, J. *Tetrahedron: Asymmetry* **2015**, *26*, 6−15.

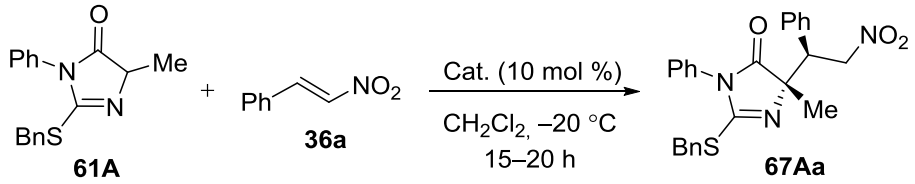


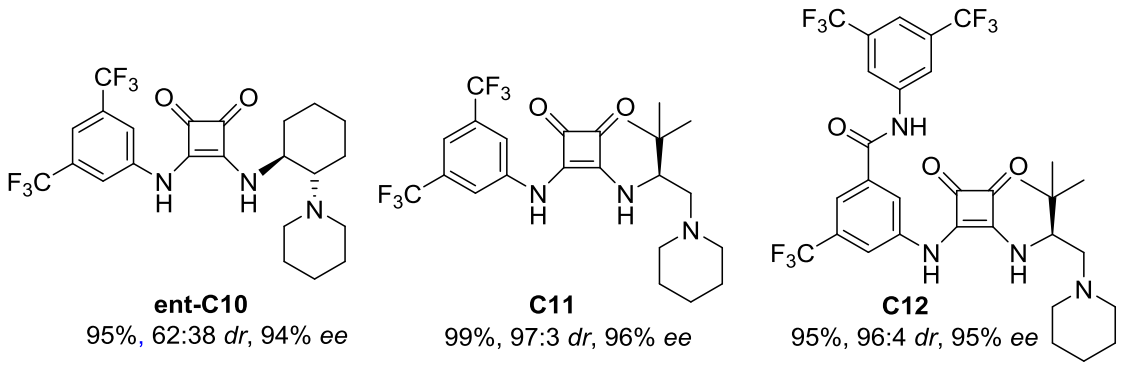
Scheme 104.

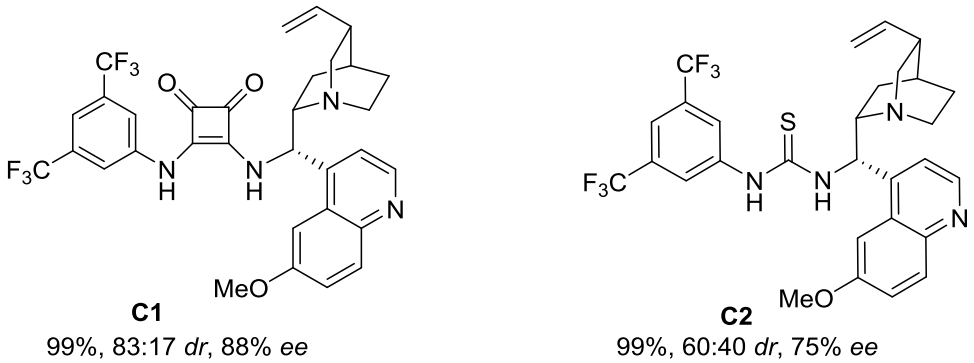
3.3.9. Screening of conditions for the addition reaction to nitroolefins

To begin the study, the reaction of **61A** with β-nitrostyrene **36a** was carried out in the presence of different base catalysts. As the results in Table 24 show, catalyst **ent-C10** was able to promote the formation of the contiguous quaternary and tertiary carbon stereoceters of **67Aa** with good isolated yield, moderate diastereoselectivity (62:38) and very high enantioselectivity for the major isomer. Under such smooth reaction conditions, with both catalyst **C11** and **C12** better results were achieved, affording product **67Aa** in nearly quantitative yield, diastereoselectivities higher than 95:5 and excellent enantioselectivity (96% and 95% *ee*, respectively). On the other side, squaramide **C1** did not perform so well (88% *ee* and diastereoselectivity of 83:17) and with thiourea **C2** enantioselectivity dropped to 75% and diasteroselectivity to 60:40.

Table 24. Catalyst screening for the reaction of **61A** with nitrostyrene **36a**. [a]







[a] The reactions were performed using 0.3 mmol of **61A**, 0.6 mmol of nitrostyrene **36a** and 10 mol % catalyst in 0.6 mL CH_2Cl_2. Ee of major diastereomer was determined by ^{1}H-NMR and by chiral HPLC.

Thus, the optimal reaction conditions for the addition of **61A** with the nitroolefin **36a** (2 equiv.) involved the use of catalyst **C11** (10 mol %) at –20 ^{o}C in dichloromethane as a solvent.

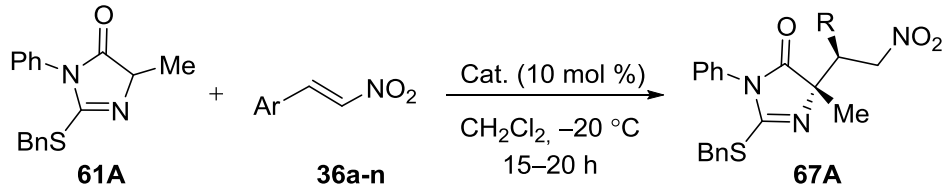
3.3.10. Reaction scope

Once with the optimal conditions in hand, we then checked the generality of the method for dihydroimidazolones **61**-**66**.

During his PhD Thesis, Julen Etxabe from our research group performed the Michael addition of imidazolone **61A** to aryl-substituted nitroolefins **36a**-**n** (Table 25). Aryl-substituted nitroolefins with either electron-rich, neutral or poor character were equally competent reaction partners affording the corresponding adduct **67** in very good yields and with nearly perfect diastereo- and enantioselectivity in most cases. During these

substrate screening, catalyst **C12** revealed to be less efficient than **C13**, as the inferior diastereoselectivity attained for products **67Ac** and **67Al** indicates (compare entries 2/3 and 8/9).

Table 25. Scope of the catalytic reaction of 1*H*-imidazol-5(4*H*)-one **61A** with nitroolefins **36a**-**n**.[a]

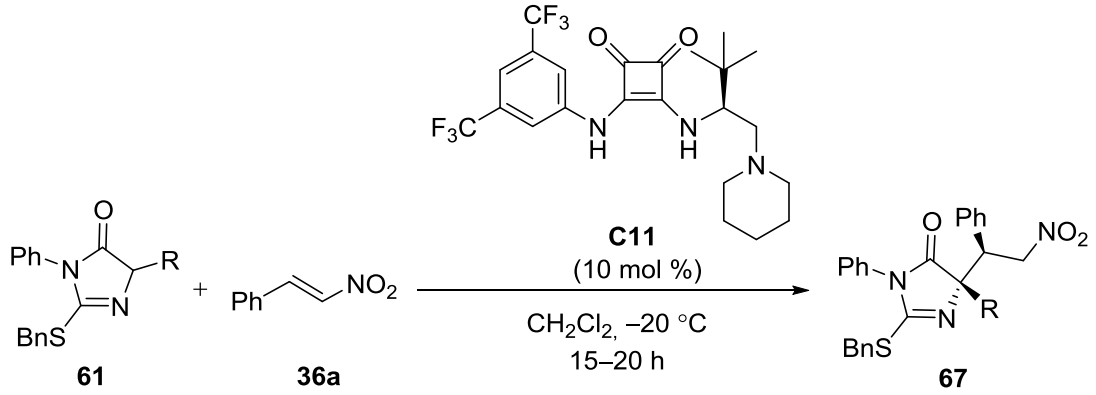


Entry	Ar	product	Cat.	yield (%)	*dr*	*ee* (%)
1	4-Br-C_6H_4	**67Ab**	**C11**	95	>98:2	99
2	4-Me-C_6H_4	**67Ac**	**C11**	87	>98:2	90
3			**C12**	83	84:16	90
4	2-Cl-C_6H_4	**67Ad**	**C11**	90	>98:2	99
5	3-Cl-C_6H_4	**67Ae**	**C11**	86	>98:2	99
6	4-Cl-C_6H_4	**67Aj**	**C11**	94	>98:2	99
7	4-CN-C_6H_4	**67Ak**	**C11**	88	>98:2	96
8	4-MeO-C_6H_4	**67Al**	**C11**	85	95:5	98
9			**C12**	86	70:30	99
10	3-MeO-C_6H_4	**67Am**	**C11**	94	>98:2	98
11	4-Me_2N-C_6H_4	**67An**	**C11**	92	>98:2	99

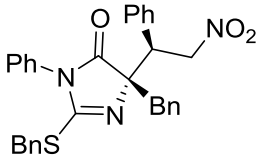
[a] Reaction conditions: **61A** (1 equiv., 0.3 mmol), **36a**-**n** (2 equiv., 0.6 mmol), catalyst (10 mol %) were stirred at –20 °C for 15–20 h in 0.6 mL of CH_2Cl_2. Diastereomeric ratio and *ee* for the major diastereomer were determined by ^{1}H-NMR and by chiral HPLC.

To complete Dr. Etxabe´s work, I studied the variation of the R substituent of the imidazolidinone substrate, without observing appreciable impact on the reaction outcome (Table 26). Thus, not only methyl, but also benzyl, *i*-butyl and functionalized aliphatic chains were tolerated at the substrate C_4 position without affecting the reaction efficiency and selectivity.

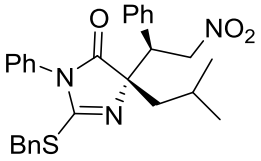
Table 26. Scope of the catalytic reaction of 1*H*-imidazol-5(4*H*)-ones **61C**-**I** with β-nitroestirene **36a**. [a]



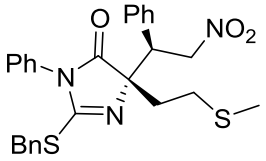
C R = Bn
D R = *i*Bu
F R = $CH_3S(CH_2)_2$
I R = $CH_3O_2C(CH_2)_2$



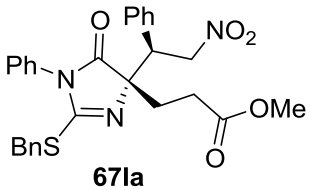
67Ca
90%, 93:7 *dr*, 98% *ee*



67Da
90%, >98:2 *dr*, 99% *ee*



67Fa
85%, >98:2 *dr*, 86% *ee*

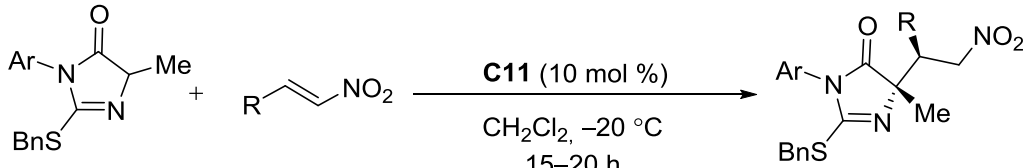


67Ia
90%, >98:2 *dr*, 99% *ee*

[a] Reaction conditions: **61C**-**I** (1 equiv., 0.3 mmol), **36a**-**n** (2 equiv., 0.6 mmol), **C11** (10 mol %) were stirred at –20 °C for 15–20 h in 0.6 mL of CH_2Cl_2. Diastereomeric ratio and *ee* for the major diastereomer were determined by ^{1}H-NMR and by chiral HPLC.

Finally, Eider Duñabeitia from our research group, during her Master work, carried out the Michael reaction with *N*-aryl substrates **62**-**66** (Table 27). Aromatic groups substituted with electron withdrawing and electron donating substituents at the *para* position show comparable results to the unsubstituted imidazolone **61A** (see Table 24). Whereas the imidazolone possessing an electron withdrawing substituent at the meta position (Ar = 3-ClC_6H_4) shows same diastereoselectivity and lower enantioselectivity (87% *ee*).

Table 27. Scope of the catalytic reaction of 1*H*-imidazol-5(4*H*)-ones **62**-**66** with nitroalkenes **36a**-**l**.[a]



62 Ar = 4-MeC_6H_4
63 Ar = 4-ClC_6H_4
64 Ar = 4-BrC_6H_4
65 Ar = 4-$MeOC_6H_4$
66 Ar = 3-ClC_6H_4

36a-l

68-72

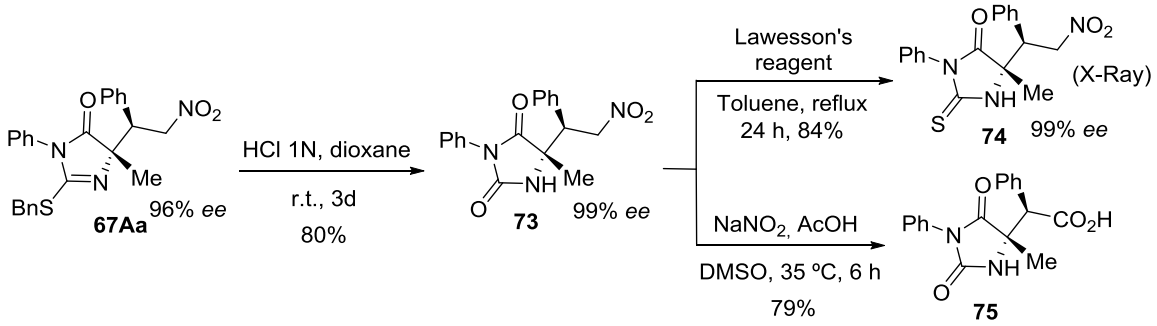
Entry	Ar	R	product	yield (%)	*dr*	*ee* (%)
1	4-MeC_6H_4	Ph	**68Aa**	89	93:7	97
2	4-ClC_6H_4	Ph	**69Aa**	90	>98:2	94
3	4-BrC_6H_4	Ph	**70Aa**	86	>98:2	99
4	4-$MeOC_6H_4$	2-ClC_6H_4	**71Ad**	91	>98:2	94
5	3-ClC_6H_4	4-$MeOC_6H_4$	**72Al**	90	>98:2	87

[a] Reaction conditions: **62**-**66** (1 equiv., 0.3 mmol), **36a**-**l** (2 equiv., 0.6 mmol), **C11** (10 mol %) were stirred at –20 °C for 15–20 h in 0.6 mL of CH_2Cl_2. Diastereomeric ratio and *ee* for the major diastereomer were determined by ^{1}H-NMR and by chiral HPLC.

3.3.11. Elaboration of adducts

Duñabeitia also worked in the elaboration of adducts (Scheme 105). Hydrolysis of *N*-phenylthio-4,5-dihydroimidazol-4-one **67Aa** to the respective hydantoin **73** could be carried out by treatment with HCl 1M at room temperature. Temperature control for this reaction is important for clean hydrolysis. The same reaction carried out at more forcing conditions (65 °C) led to a 1:1 mixture of compounds **73** and the thio-analog **74**. In any event, the resulting adduct **73** could be fully converted into its thiohydantoin analog **74** applying Lawesson's reagent, which served to establish the compound identity and configuration by X-ray analysis. On the other hand, Nef type oxidation of the nitro group in **73** under Mioskowski conditions[224] proceeded smoothly to furnish the carboxylic acid **74** in 79% isolated yield. Configurational integrity of adducts was not affected during all these transformations and the final products were obtained as essentially single enantiomer (≥99% *ee*).

[224] Hatt, C.; Wagner, C.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234–235.

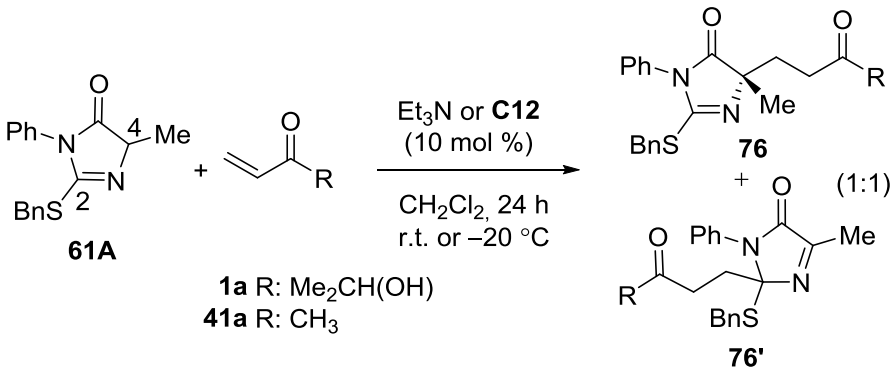


Scheme 105.

3.3.12. Michael addition of 1*H*-imidazol-5(4*H*)-ones to vinyl ketones

Given the excellent results obtained in the Michael addition of 1*H*-imidazol-4(5*H*)-ones **32**-**35** to vinyl ketones **1a** and **41a**, we decided to test 1*H*-imidazol-5(4*H*)-one **61A** for the analog reaction.

Gratifingly, vinyl ketones **1a** and **41a** were competent electrophilic partners in the reactions of dihydroimidazolone **61A**. However, in contrast to what was observed with the nitroalkenes, the reactions involving vinyl ketones followed two divergent pathways, one producing the 4-addition products **76** and that producing the 2-addition aminal **76'** (Scheme 106). Attempts to favour either reaction pathway were unsuccessful, regardless the catalyst and reaction temperature, an essentially equimolar ratio of either product was formed for the studied cases. As mentioned above, similar observations were previously reported in Brønsted base catalyzed addition reactions involving azlactones as the nucleophile.[225]



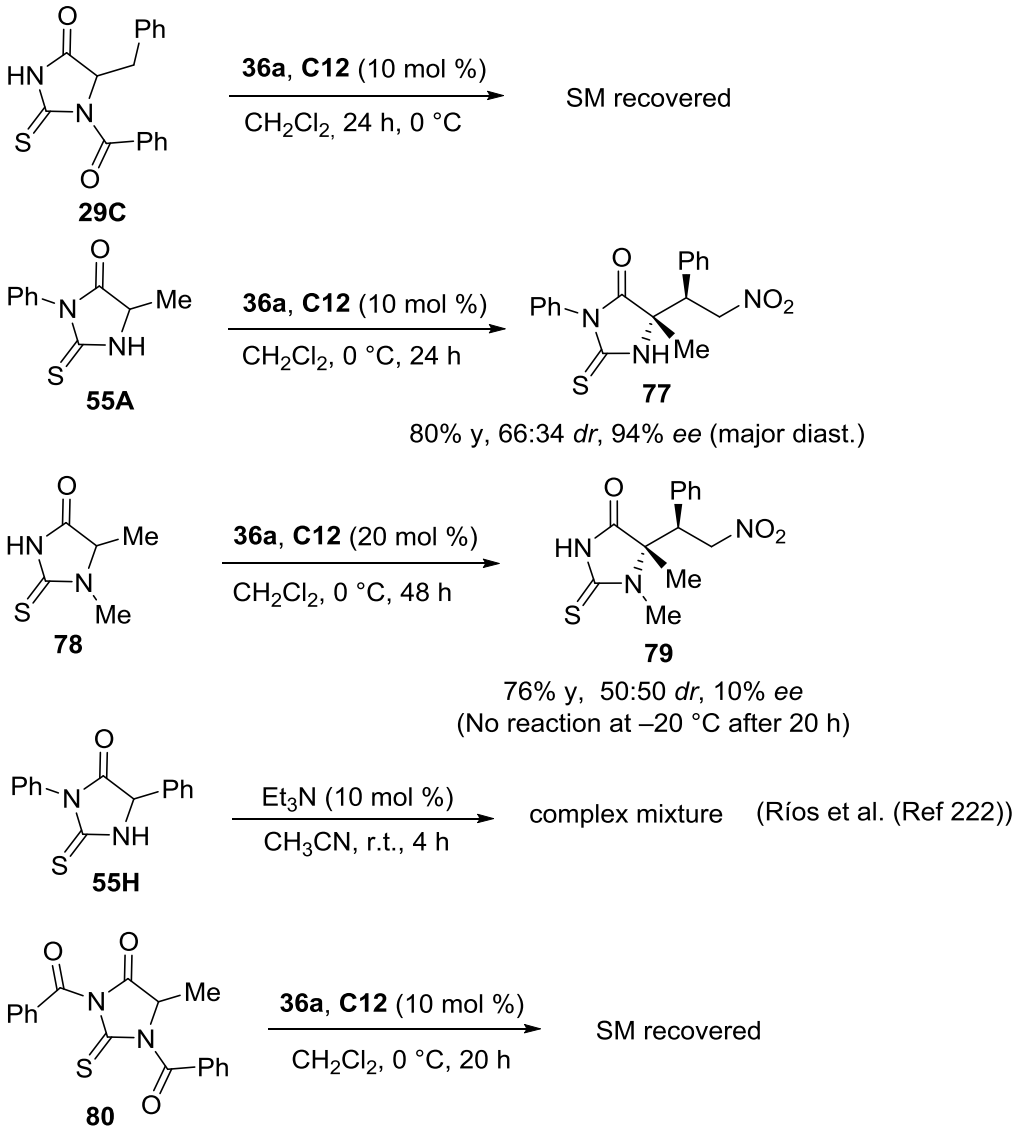
Scheme 106. Splitting reaction pathway between imidazolone **61A** and vinyl ketones.

[225] See Ref 178a and 178b.

3.3.13. Control experiments using the related thiohydantoins

To put in context the reactivity and, particularly, selectivity profiles of templates **I–III** under the present mild enolization conditions, the behavior of **29C**, **55A**, **78** and **80**, four parent thiohydantoins with comparable substitution patterns at N_1 and N_3, was explored (Scheme 107). Initial control experiments showed that, in contrast to templates **I–III**, none of these four thiohydantoins reacted at all with nitrostyrene **36a** in the presence of catalyst **C12** at low temperature (experiments carried out at –20 °C). This lack of reactivity was most evident in the case of thiohydantoin **29C** which remained unchanged even after stirring the mixture for 24 h at 0 °C. Again, we ascribe the comparatively higher reactivity of templates **I–III** to their tendency towards enolization owing to the aromatic character of the resulting enol/enolate intermediate species. At higher temperatures (0 °C) N_3-phenyl thiohydantoin **55A** reacted with nitrostyrene **36a** in the presence of catalyst **C12**, but product **77** was obtained as a 66:34 mixture of diastereomers. Similarly, N_1-methyl thiohydantoin **78** also reacted with nitrostyrene **36a** at 0 °C, but, led to a roughly equimolecular mixture of diastereomers with marginal enantioselection. In its turn, it has been reported by Rios[226] that **55H** upon treatment with nitrostyrene at room temperature gave a complex mixture. Finally, the *N*,*N*-dibenzoyl derivative **80** showed to be completely unreactive under these conditions.

[226] Ceban, V.; Hands, K.; Meazza, M.; Light, M. E.; Rios, R. *Tetrahedron Lett.* **2013**, *54*, 7183−7187.



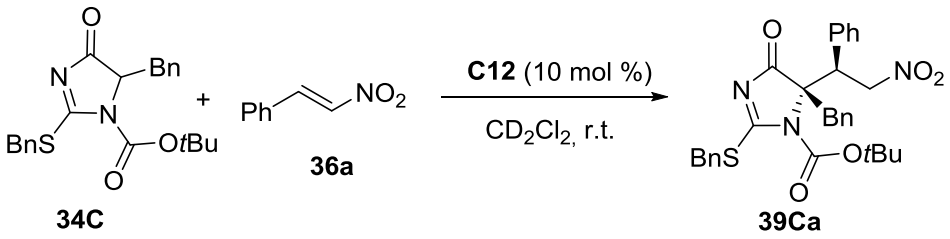
Scheme 107. Reactivity profile of the related thiohydantoins **29C**, **55A**, **55H**, **78**, **80**.

3.3.14. Mechanistic proposal

The description of a reaction model which would accurately explain the outcome of the reaction was our next concern. For that purpose several experiments were carried out in order to get insights on the reaction mechanism.

In a first set of experiments (Figure 27), the conversion for the reaction between **34C** and **36a** was measured as a function of time, maintaining the concentration of **36a** pseudoconstant (15 equiv.) and in the presence of 10 mol % of catalyst **C12**. The plotting in of $-\ln([\mathbf{34C}]/[\mathbf{34C}]_o)$ versus time gave a straight line ($R^2 = 0.996$) which indicates first-order dependence in the nucleophile. The reaction order in the electrophilic component was determined similarly by measuring the reaction conversion as a function of time under pseudoconstant concentration of nucleophile **34C** (15 mol equiv.) and in the

presence of 10 mol % of catalyst **C12**. In this instance, plotting ln([**36a**]/[**36a**]$_o$) versus time afforded again a straight line (R^2 = 0.9815) indicating first-order reaction with respect to the acceptor component too. Unfortunately, the reaction order in the catalyst could not be determined by this means due to the limited solubility of the catalyst.



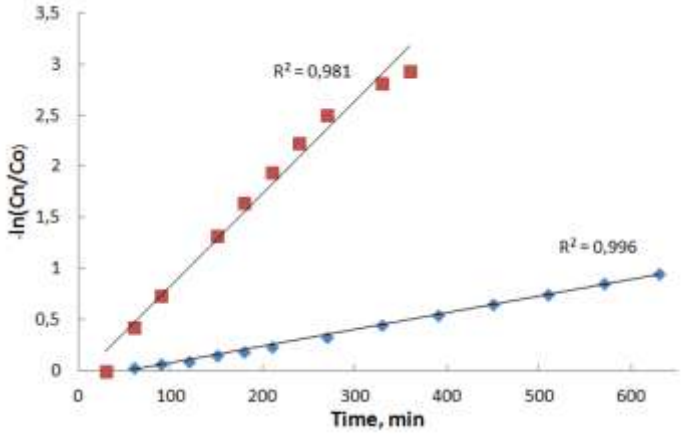
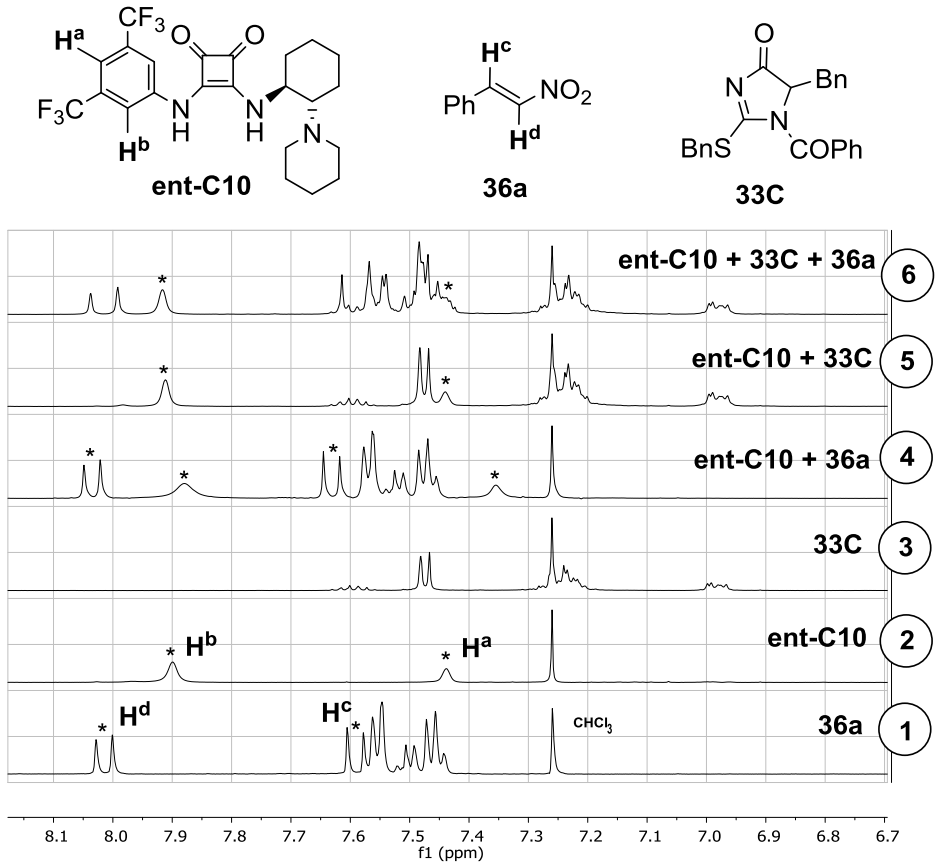


Figure 27. Ploting of reaction conversion vs. time for the **C12**-catalyzed reaction between **34C** and **36a** under pseudoconstant concentration of **36a** (♦) and **34C** (■).

On the other hand, the collective experimental data shown above reveal the unique reactivity profile of templates **I–III**, as opposite to the variable results attained with the parent thiohydantoins (see Scheme 107). An interesting aspect of this high reactivity is that it appears quite general regardless the catalyst employed, and therefore it should be ascribed to an inherent feature of the template design. As shown in Figure 26, the pseudoaromatic character of the enolic forms **I'–III'** would facilitate the enolization process, but this effect alone would not necessarily justify the subsequent reactivity against the electrophilic acceptor. In order to get additional insights in this respect, and more specifically with regard to the affinity of the templates for these type of bifunctional catalysts, we performed competitive ^{1}H NMR experiments involving template **33C**, nitrostyrene **36a** and catalyst **ent-C10** (Scheme 108). Catalyst **ent-C10** was chosen because its complete solubility in halogenated solvents as noted above. As the comparison of spectra 1, 2 and 4 shows, admixing **36a** and **ent-C10** caused a slight downfield shift of the olefinic protons **H^c**/**H^d** of **36a** along with an upfield shift of **H^a** and

H^b of **ent-C10**, quite significant ($\Delta\delta \approx 0.1$ ppm) in the former case, clearly indicating some degree of molecular recognition between nitrostyrene **36a** and the catalyst. In its turn, variation of the chemical shifts when admixing the template **33C** and the catalyst (compare spectra 2, 3 and 5) seemed to be less pronounced, with only a slight downfield shift of **H^b**. However, spectrum 6, in which both substrates **36a** and **33C** must compete for best catalyst binding, reveals that the molecular affinity between **33C** and **ent-C10** is relatively high. Indeed, the chemical shift pattern of **ent-C10** in 6, in particular the chemical shifts of both **H^a** and **H^b**, remained essentially that of spectrum 5 and distinct from spectrum 4.



Scheme 108. Insets of ^{1}H NMR spectra corresponding to individual samples of **33C**, **36a**, **ent-C10**, and three 1:1 combinations of them taken in $CDCl_3$ at r.t. (concentration ~0.1 M).

These observations reinforce the idea that the new hydantoin template upon enolization would remain tightly bound to the catalyst during the key C–C bond-forming event, allowing an efficient transfer of chiral information.

In order to get more insights on the structural/functional requirements of these catalysts for optimal activity and selectivity, the performances of catalyst **C12**, featuring a free NH amide, and its *N*-Me derivative were compared. As the conversion profiles in

Figure 28 show for the reaction between **33C** and **36a**, catalyst **C12** resulted significantly more active than its *N*-methylated form. For instance, with **C12** the reaction conversion was over 70% after 30 min at r.t. (over 90% after 1 h), whilst with **C13** barely reached 27% after 30 min (45% after 1 h). While erosion of the stereoselectivity was less important (**C12**, *dr* = 98:2, 99% *ee*, Table 14, entry 9; **C13**, *dr*>98:2, 90% *ee*), the difference in catalyst activity is significant, especially considering that, unlike **C12**, **C13** is completely soluble, and may be attributable to the ability of the free amide in **C12** for additional H-bonding.

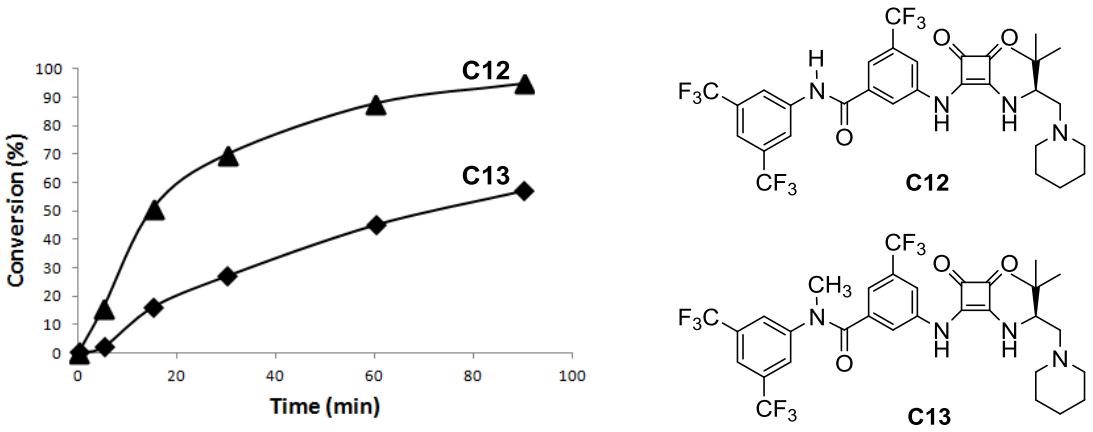


Figure 28. Conversions for the reaction between **33C** and **36a** catalyzed by **C12** (▲) and its *N*-Me derivative **C13** (♦), respectively, under standard conditions.

Although the number of individual H-bond interactions within the substrate-catalyst complex in the transition state, and their precise orientation, are unknown yet, and based on previous studies in the literature for related catalytic systems,[227] a simultaneous activation of both reactants as in stereomodel **A**/**A'** (Figure 29) may be proposed tentatively for the reactions catalyzed by **C12**. The free amide NH would be H-bonded internally as in **A** (assited activation), to assist catalyst preorganization or intermolecularly as in **A'** to better fix one of the approaching reactants. Similar models are conceivable for the remaining templates and catalysts in which the approaching trajectory of both reactants correctly explains the observed configuration, both relative and absolute, of adducts.

[227] Kótai, B.; Kardos, G.; Hamza A.; Farkas V.; Pápai, I.; Soós, T. *Chem. Eur. J.* **2014**¸ *20*, 5631–5639.

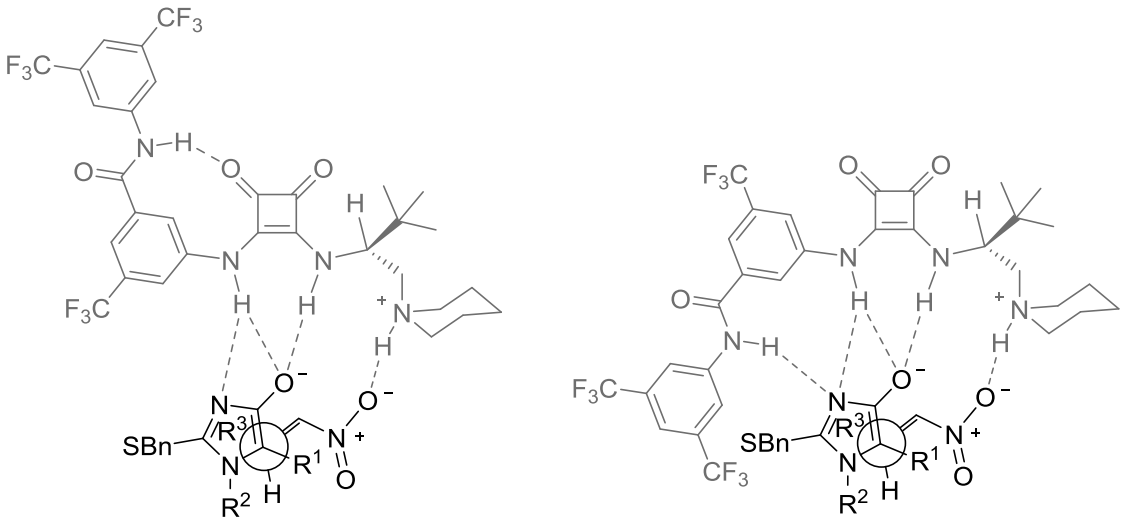


Figure 29. Plausible TS stereomodels for the **C12**-catalyzed reaction between templates **II** and nitroolefins.

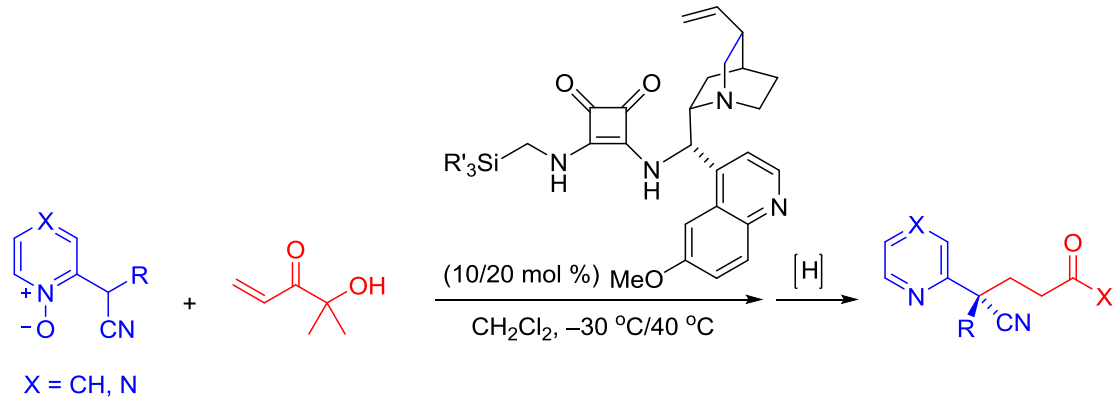
CHAPTER 4

CONCLUSIONS

4. CONCLUSIONS

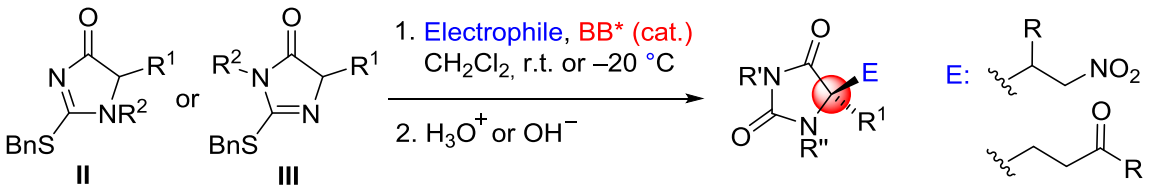
In summary, three new pronucleophiles have been described for the organocatalytic asymmetric formation of quaternary stereocentres.

2-Cyanomethylazaarene *N*-oxides have demonstrated their utility as efficient reagents for the asymmetric synthesis of α-quaternary *o*-substituted alkylazaarenes via soft enolization conditions. The *N*-oxide group plays a strategic role as a removable activating and stereodirecting element in conjunction with newly designed multifunctional squaramide-Brønsted base catalysts bearing a bulky silyl group. Taking advantage of the high modulability of the adducts, several useful transformations have been carried out.



Scheme 109.

1*H*-Imidazol-4(5*H*)-ones **II** and 1*H*-Imidazol-5(4*H*)-ones **III** have proved to be excellent substrates for the organocatalytic Michael reaction of enantiomerically enriched 5,5-disubstituted hydantoins. Among the catalysts examined, **C11** and the newly prepared squaramide-tertiary amine catalyst **C12** provided the highest selectivity in the reactions with either nitroolefins or vinyl ketones as acceptors. Various modifications of the adducts have been carried out, including the synthesis of ADAMTS-5 inhibitors.



Scheme 110.

CHAPTER 5

EXPERIMENTAL SECTION

5. EXPERIMENTAL SECTION

5.1. Materials and general techniques

5.1.1. General experimental

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

5.1.2. Solvents and reagents

All reagents bought from commercial sources were used as sold. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. Anhydrous dichloromethane was dried over CaH_2, and diethyl ether and tetrahydrofuran were dried by filtration through activated alumina (powder ≈ 150 mesh, pore size 58 Å, basic, Sigma Aldrich) columns. $(DHQD)_2PYR$ was purchased from Sigma Aldrich, quinine was purchased from Alfa Aesar.

5.1.3. Chromatography

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in EtOH (limited lifetime), followed by heating. Chromatographic purification was performed on ROCC 60 silica gel 40–63 μm.

5.1.4. Melting points

Melting points were obtained on a Stuart SHP3 melting point apparatus and microscope and are uncorrected.

5.1.5. Mass spectra

MS spectra were recorded on an ESI–ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model)

5.1.6. Infrared spectra

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

5.1.7. NMR spectra

NMR spectra were recorded using a Bruker Avance 300 MHz or 500 MHz spectrometer, chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak. In case of diastereomeric mixture, data of the major diastereomer were provided. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz).

5.1.8. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on a Waters 600 (Photodiode Array Detector Waters 2996) (column and solvent conditions are given with the compound).

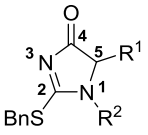
5.1.9. Optical rotations

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

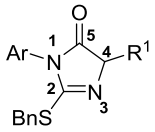
5.1.10. Chemical names of the heterocyclic compounds involved (Chapter 3)

The numbering of atoms within the three main heterocyclic systems involved in this work according to the IUPAC rules is represented in the top structures below. We have applied such a numbering to both structure families, **I/II** and (thio)hydantoins across the main Manuscript and the Supporting Information. However, for the sake of clarity and in order to keep a consistent numbering for the three heterocyclic systems (templates **I/II**, templates **III** and the final (thio)hydantoins), we have adopted a modified numbering for heterocycles **III** and their derivatives (bottom structure) across the Manuscript. As per the Supporting Information, both chemical nomenclatures, namely the one following IUPAC rules and the alternate, are given for compounds **III**

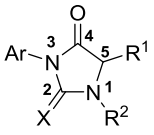
and their derivatives. An example is provided in the scheme. There exist precedents in the literature applying either nomenclature to heterocycles related to **III**.[228]



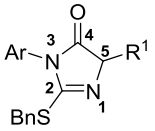
I/II



III (IUPAC numbering)

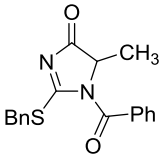


X: O, S
(Thio)hydantoins

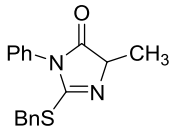


III (this work numbering)

Examples:

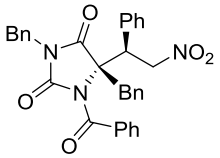


1-Benzoyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**33A**)



2-(Benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (**61A**)

[2-(Benzylthio)-5-methyl-3-phenyl-3*H*-imidazol-4(5*H*)-one (**61A**)]



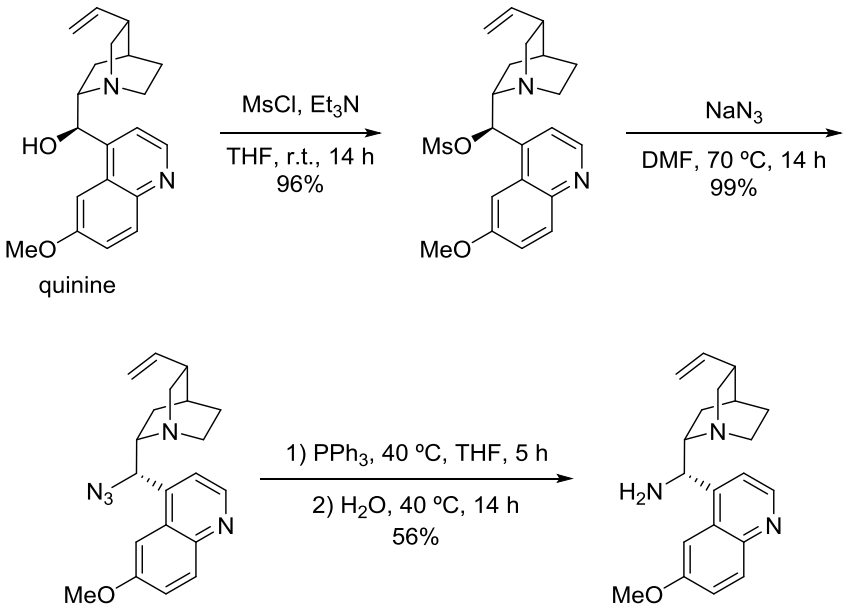
(*S*)-1-Benzoyl-3,5-dibenzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione

[228] Example of using IUPAC nomenclature for heterocyckes **III**: a) A. S. Salman, A. Abdel-Aziem, M. J. Alkubbat, *Am. J. Org. Chem* **2015**, 5, 57–72. Example of using the same modified nomenclature employed by us: b) S. Gosling, C. El Amri, A. Tatibouët, *Synthesis* **2014**, 46, 1079–1084.

5.2. General procedure for the synthesis of catalysts

$(DHQ)_2PYR$ is commercially available and was purchased from commercial suppliers.

5.2.1. Preparation of 9-amino-(9-deoxy)epiquinine[229]



1st step:[230] A mixture of quinine (1 equiv., 16.2 g, 50 mmol) and triethylamine (3.6 equiv., 25.1 mL, 180 mmol) in dry THF (250 mL) was cooled to 0 ^{o}C and then methanesulfonyl chloride (1.8 equiv., 7.0 mL, 90 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford crude mesylated product with 96% yield, which was used in the next step without further purification.

2nd step:[231] The crude mesylated product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 ^{o}C and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 ^{o}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

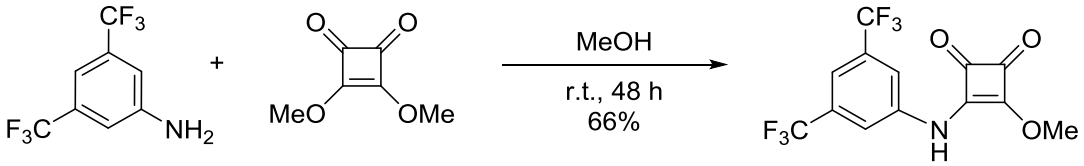
[229] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.
[230] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.
[231] Adapted from: Sudermeier, U.; Döbler, C.; Mehltretter, G. M.; Baumann, W.; Beller, M. *Chirality*, **2003**, *15*, 127–134.

crude azide derived product in quantitative yield which was used in the next step without further purification.

3rd step:[231] The azide derived crude product was dissolved in THF (250 mL) and PPh_3 (1 equiv., 12.6 g, 48 mmol) was added. The reaction mixture was heated to 40 °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).

5.2.2. Preparation of squaramide-based catalysts C1

5.2.2.1. Preparation of squaric ester monoamine[234]

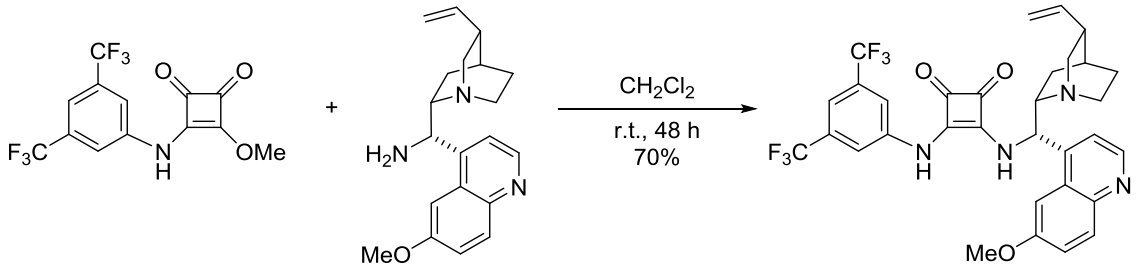


To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 1.42 g, 10 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1 equiv., 1.56 mL, 10 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vacuum to give title compound as a white solid. Yield: 2.25 g, 6.6 mmol, 66%. m.p. = 179–181 °C. All data were consistent with those previously reported. ^{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).

5.2.2.1.1. Preparation of catalyst C1

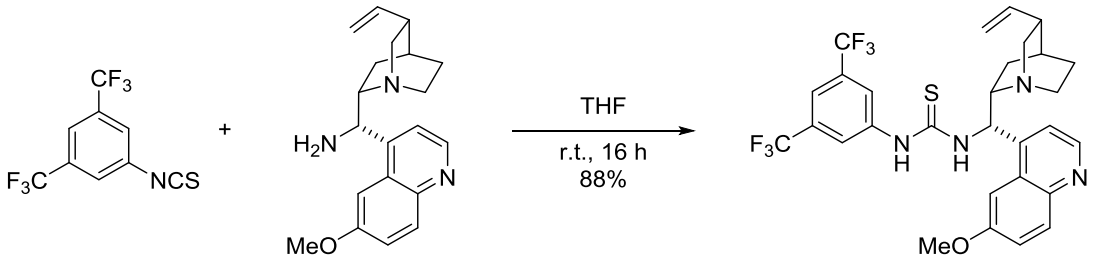
3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione

(C1)¡Error! Marcador no definido.



To a solution of squaric ester monoamide prepared as above (1 equiv., 2.25 g, 6.6 mmol) in dichloromethane (33 mL), 9-amino-(9-deoxy)*epi*quinine (1 equiv., 2.13 g, 6.6 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ethyl acetate 80/20 → ethyl acetate) to afford **C1** as white solid. Yield: 2.91 g, 4.6 mmol, 70%. m. p. = 224–225 °C. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.88 (brs, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (brs, 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).

5.2.3. Preparation of thiourea containing Brønsted base catalyst C2[232]

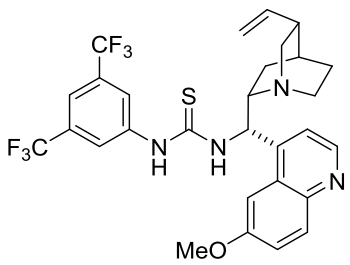


To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 1.6 g, 5 mmol) in dry THF (7.5 mL) at 0 °C, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.1 equiv., 1.5 g, 5.5 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred

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

overnight at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the title compound.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea (C2)

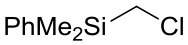


White solid, yield: 2.6 g, 4.4 mmol, 88%. m.p. = 123–125 ^{o}C. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (brs, 2H), 8.07 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.59 (br s, 1H), 7.55 (d, *J* = 4.7 Hz, 1H), 7.44 (dd, *J* = 9.3, 2.6 Hz, 1H), 6.32 (d, *J* = 11.0 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.5, 6.2 Hz, 1H), 5.02 (dt, *J* = 10.5, 1.5 Hz, 1H,), 4.98 (dt, *J* = 17.2, 1.5 Hz, 1H), 4.03 (s, 3H), 3.56 – 3.53 (m, 1H), 3.39 – 3.37 (m, 1H), 3.29 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.82 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H), 2.38 – 2.35 (m, 1H), 1.71 – 1.68 (m, 2H), 1.64 – 1.61 (m, 1H), 1.45 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H), 0.89 (dd, *J* = 13.3, 10.4 Hz, 1H).

5.2.4. Synthesis of catalysts C3-C8

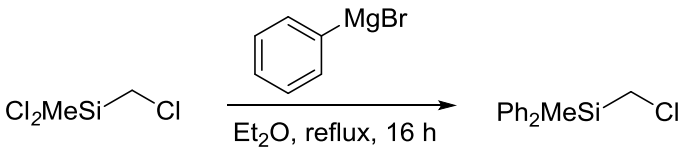
5.2.4.1. Preparation of (chloromethyl)silyl derivatives

(Chloromethyl)dimethyl(phenyl)silane



The title compound was purchased from Sigma Aldrich.

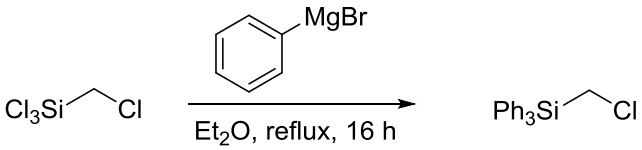
(Chloromethyl)(methyl)diphenylsilane[4a]



To a solution of dichloro(chloromethyl)methylsilane (1 equiv., 60 mmol, 7.62 mL) in anhydrous diethyl ether (30 mL) Grignard reagent (3.0 M in ether) (2 equiv., 120 mmol, 40 mL) was added dropwise at room temperature and the reaction mixture was refluxed for 16 h. Then, the mixture was cooled to 0 ^{o}C, saturated solution of NH_4Cl (20

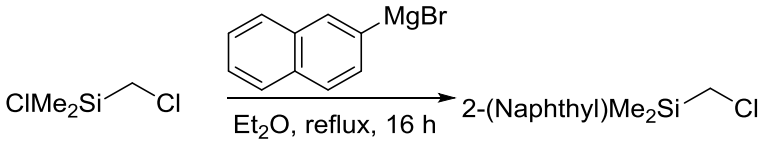
mL) was added and it was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over $MgSO_4$ and concentred under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford the title compound as a colourless liquid; yield: 33.0 mmol, 8.22 g, 55%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 – 7.52 (m, 4H), 7.49 – 7.32 (m, 6H), 3.26 (s, 2H), 0.72 (s, 3H).

(Chloromethyl)triphenylsilane[4b]



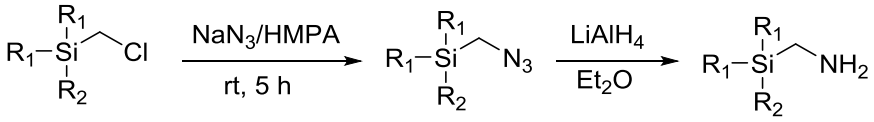
The title compound was prepared according to the procedure shown above from trichloro(chloromethyl)silane (1 equiv., 10 mmol, 1.25 mL) and phenylmagnesium bromide (3.0 M in ether) (3 equiv., 30 mmol, 10 mL). The crude material was purified by crystallization on methanol. The crystals were washed with petroleum ether to afford the title compound as a white solid; yield: 4.5 mmol, 1.40 g, 45%. m. p. 110-113 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 – 7.52 (m, 6H), 7.53 – 7.29 (m, 9H), 3.53 (s, 2H).

(chloromethyl)dimethyl(naphthalen-2-yl)silane[4c]



To a solution of chloro(chloromethyl)dimethylsilane (1 equiv., 20 mmol, 2.63 mL) in anhydrous diethyl ether (15 mL,) Grignard reagent (0.5 M in THF) (1.4 equiv., 28 mmol, 56 mL) was added dropwise at room temperature and the reaction mixture was refluxed for 16 h. Then, the mixture was cooled to 0 ^{o}C, saturated solution of NH_4Cl (20 mL) was added and it was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over $MgSO_4$ and concentred under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane) to afford the title compound as a colourless liquid; yield: 10.0 mmol, 2.34 g, 50%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.86 – 7.45 (m, 6H), 3.02 (s, 2H), 0.50 (s, 6H).

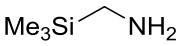
5.2.4.2. General procedure for the preparation of aminomethyl silanes[233]



Step 1: To a solution of the corresponding chloromethyl sylane (20.0 mmol) in HMPA (10 mL) was added sodium azide (1.43 g, 22 mmol) and the reaction mixture was stirred for 5 h at room temperature. Then, the mixture was poured into H_2O (30 mL) and extracted with hexane (3 x 30 mL). The combined extracts were washed with saturated solution of NH_4Cl, dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

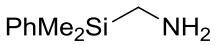
Step 2: To a suspension of $LiAlH_4$ (1 equiv., 10.0 mmol) in dry Et_2O (10 mL) was slowly added at 0 ^oC a solution of the corresponding azide (10.0 mmol) in dry diethyl ether (5 ml). The mixture was stirred in an ice bath for 10 min and then stirred at room temperature until liberation of nitrogen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

(Trimethylsilyl)methylamine



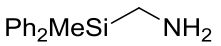
The title compound was purchased from Fluka.

(dimethyl(phenyl)silyl)methanamine



The title compound was prepared according to the general procedure. Colourless liquid; yield: 18.0 mmol, 2.97 g, 90%. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.57 – 7.53 (m, 2H), 7.38 – 7.36 (m, 3H), 2.40 (s, 2H), 0.33 (s, 6H).

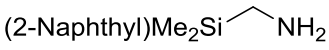
(methyldiphenylsilyl)methanamine



The title compound was prepared according to the general procedure. Colourless liquid; yield: 16.2 mmol, 3.68 g, 81 %. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.60 – 7.55 (m, 4H), 7.41 – 7.34 (m, 6H), 2.72 (s, 2H), 0.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.4, 134.5, 133.9, 129.4, 129.2, 127.8, 127.6, 29.1, –5.7. UPLC-DAD-QTOF: $C_{14}H_{18}NSi$ $[M+H]^+$ calcd.: 228.1209, found: 228.1197.

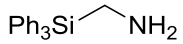
[233] Lettelier, M.; McPhee, D. J.; Griller, D. *Synthetic Commun*. **1988**, 18, 1975–1978.

(Dimethyl(2-naphthyl)silyl)mathanamine



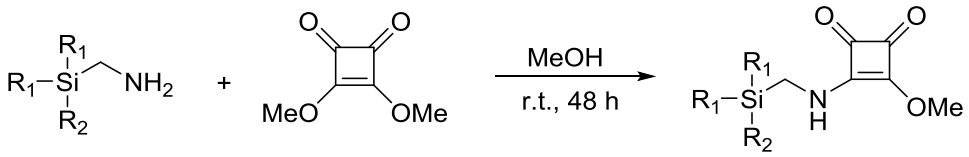
The title compound was prepared according to the general procedure. Colourless liquid; yield: 3.68 g, 16.2 mmol, 80%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.04 (s, 1H), 7.87 – 7.81 (m, 3H), 7.63 – 7.60 (m, 1H), 7.51 – 7.48 (m, 2H), 2.49 (s, 2H), 0.42 (s, 6H).

(Methyldiphenylsilyl)methanamine



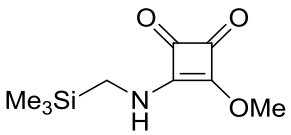
The title compound was prepared according to the general procedure. Colourless liquid; yield: 16.8 mmol, 4.85 g, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.54 (m, 6H), 7.54 – 7.31 (m, 9H), 3.04 (s, 2H).

5.2.4.3. Preparation of squaric ester monoamine[234]



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

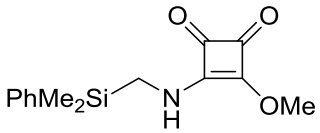
3-methoxy-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione



The title compound was prepared according to the general procedure. White solid; yield: 4.15 mmol, 884.0 mg, 83%. m. p. 119–122 ^{o}C. IR (ν/cm^{-1}): 3205, 3014, 2969, 2948, 2357, 1790, 1692, 1576, 1493, 1366, 1228, 862, 584. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.68 (s, 1H, NH), 4.40 (s, 3H), 2.99 (m, 2H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.4, 182.1, 176.9, 172.1, 60.1, 35.8, –3.42. UPLC-DAD-QTOF: $C_9H_{16}NO_3Si$ $[M+H]^+$ calcd.: 214.0899, found: 214.0892.

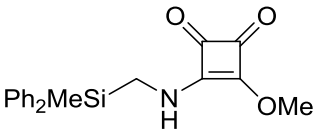
3-((dimethyl(phenyl)silyl)methylamino)-4-methoxycyclobut-3-ene-1,2-dione

[234] Adapted from Yang, W.; Du, D. *Org. Lett.* **2010**, 12, 5450–5453.



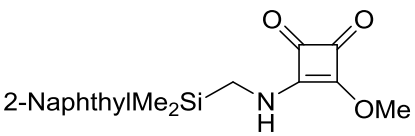
The title compound was prepared according to the general procedure. White solid; yield: 3.50 mmol, 962.8 mg, 70%. m. p. 117–120 °C. IR (ν/cm^{-1}): 3247, 3135, 3046, 2968, 2359, 1799, 1691, 1586, 1357, 1229, 1112, 1051, 980, 934, 807, 697, 587, 467. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 – 7.48 (m, 2H), 7.42 – 7.35 (m, 3H), 6.20 (s, 1H, NH), 4.32 (s, 3H), 3.18 (m, 2H), 0.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.5, 182.6, 177.4, 172.5, 134.9, 133.9, 130.2, 128.4, 60.5, 35.6, –4.6. UPLC-DAD-QTOF: $C_{14}H_{18}NO_3Si$ $[M+H]^+$ calcd.: 276.1056, found: 276.1058.

3-methoxy-4-((methyldiphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione



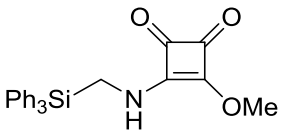
The title compound was prepared according to the general procedure. White solid; yield: 4.50 mmol, 1633.5 mg, 90%. m. p. 148–152 °C. IR (ν/cm^{-1}): 3247, 3051, 2968, 2898, 2359, 1810, 1691, 1643, 1536, 1463, 1354, 1062, 933, 854, 816, 745, 648, 483. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 – 7.37 (m, 10H), 5.86 (s, 1H, NH), 4.30 (s, 3H), 3.49 – 3.46 (m, 2H), 0.67 (s, 3H). UPLC-DAD-QTOF: $C_{19}H_{20}NO_3Si$ $[M+H]^+$ calcd.: 338.1212, found: 338.1218.

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



The title compound was prepared according to the general procedure. White solid; yield: 3.50 mmol, 1137.9 mg, 70%. m. p. 140–144 °C. IR (ν/cm^{-1}): 3277, 3065, 3001, 2939, 2904, 1803, 1696, 1622, 1495, 1396, 1275, 1109, 918, 848, 779, 725, 580, 459. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.86 – 7.81 (m, 3H), 7.55 – 7.49 (m, 3H), 6.63 (s, 1H, NH), 4.23 (s, 3H), 3.21 (d, *J* = 6Hz, 1H), 0.48 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.7, 182.3, 177.3, 172.2, 135.0, 134.1, 132.9, 129.5, 128.2, 127.9, 127.6, 127.0, 126.4, 60.4, 35.6, –4.5. UPLC-DAD-QTOF: $C_{18}H_{20}NO_3Si$ $[M+H]^+$ calcd.: 326.1212, found: 326.1212.

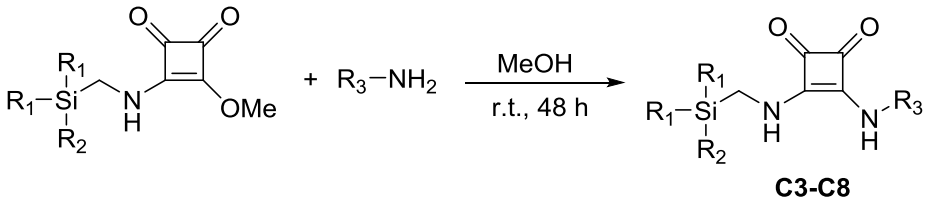
3-methoxy-4-(triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione



The title compound was prepared according to the general procedure. White solid; yield: 1702.0 mg, 4.25 mmol, 85%. m. p. 167–171 °C. IR (ν/cm^{-1}): 3254, 3046, 1801, 1702, 1601, 1426, 1360, 1111, 698, 505. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.35 (m, 15H), 5.32 (s, 1H), 4.28 (s, 3H), 3.76 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 182.9, 177.6, 172.9, 136.0,

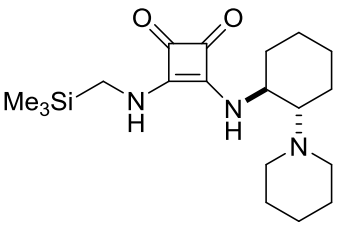
135.7, 130.8, 128.7, 60.5, 27.8. UPLC-DAD-QTOF: $C_{24}H_{21}NO_3Si$ $[M+H]^+$ calcd.: 400.1363, found: 400.1360.

5.2.4.4. Formation of catalysts C3-C8



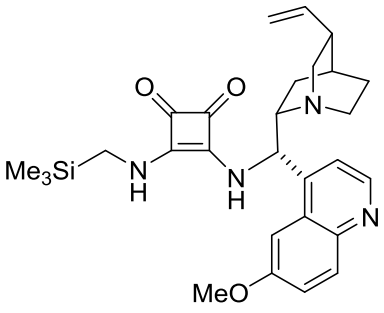
To a solution of monosubstituted squarate (1.5 mmol) in 6 mL MeOH was added the corresponding cinchona-base chiral amine (3.0 mmol) and the reaction mixture was stirred for 48 h at room temperature. The reaction product was obtained after flash column chromatography on basic silica gel (eluting with ethyl acetate) to afford the desired catalysts **C3-C8**.

3-(((1S,2S)-2-(piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C3)



The title compound **C3** was prepared according to the general procedure. White solid; yield: 0.68 mmol, 247.0 mg, 45%. m. p. 239–242 °C. $[\alpha]_D^{25}$= +42.1 (*c* = 0.25, DMSO-d_6). IR (ν/cm^{-1}): 3160, 3014, 2929, 2851, 1791, 1633, 1551, 1462, 1365, 1216, 846, 762. ^{1}H NMR (300 MHz, DMSO) δ: 7.10 (s, 1H), 3.82 (s, 1H), 3.21 – 3.08 (m, 2H), 2.63 – 2.47 (m, 2H), 2.30 – 2.20 (m, 2H), 2.04 – 1.99 (m, 1H), 1.83 – 1.63 (m, 2H), 1.41 – 1.14 (m, 8H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.3, 181.6, 168.1, 167.6, 68.4, 53.8, 49.3, 34.4, 26.4, 24.9, 24.6, 24.6, 23.8, –3.1. UPLC-DAD-QTOF: $C_{19}H_{34}N_3O_2Si$ $[M+H]^+$ calcd.: 364.2420, found: 276.2409.

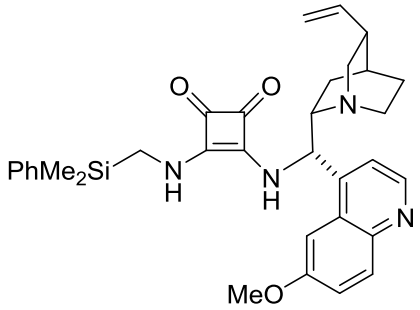
3-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C4)



The title compound **C4** was prepared according to the general procedure. White solid; yield: 1.02 mmol, 514.3 mg, 68%. m. p. 209–213 °C. $[\alpha]_D^{25}$= –102.6 (*c* = 0.25, CH_2Cl_2). IR (ν/cm^{-1}): 3203, 3014, 2936, 2871, 1788, 1636, 1545, 1455, 1366, 1232, 1037, 842. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.66 (d, *J* = 4.5 Hz, 1H), 8.06 – 8.02 (d, *J* =

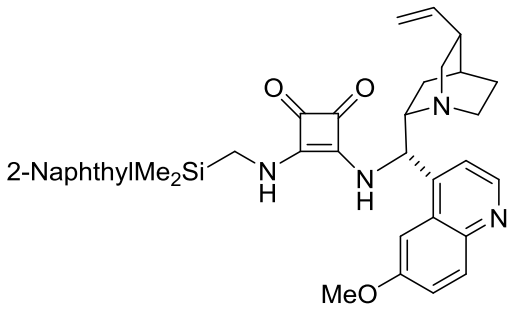
9.2 Hz, 1H), 7.84 (s, 1H), 7.56 (d, *J* = 3 Hz, 1H), 7.40 (dd, *J* = 3,3 Hz, 1H), 5.85 – 5.73 (m, 1H), 5.01 – 4.91 (m, 2H), 3.92 (s, 3H), 3.51 – 3.06 (m, 6H), 2.78-2.68 (m, 2H), 2.24 (s, broad signal, 1H), 1.62 – 1.42 (m, 4H), 0.78 – 0.72 (m, 1H), 0.02 (s, 3H), –0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.5, 181.8, 181.7, 168.0, 167.7, 158.7, 147.9, 144.9, 141.5, 132.0, 128.0, 122.3, 114.8, 101.9, 56.1, 41.0, 39.7, 36.0, 35.9, 29.8, 28.0, 27.7, 26.2, –2.9. UPLC-DAD-QTOF: $C_{28}H_{37}N_4O_3Si$ $[M+H]^+$ calcd.: 505.2635, found: 505.2597.

3-((dimethyl(phenyl)silyl)methylamino)-4-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C5)



The title compound **C5** was prepared according to the general procedure. White solid; yield: 1.05 mmol, 594.6 mg, 70%. m. p. 221–224 °C. $[\alpha]_D^{25}$= –106.0 (*c* = 0.25, CH_2Cl_2). IR (ν/cm^{-1}): 3183, 3047, 2919, 2862, 1788, 1631, 1542, 1455, 1399, 1232, 1032, 838, 711, 469. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 (d, *J* = 3.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.42 – 7.38 (m, 2H), 7.35 – 7.32 (m, 2H), 7.22 – 7.19 (m, 3H), 5.80 – 5.68 (m, 1H), 5.02 – 4.94 (m, 2H), 3.93 (s, 3H), 3.45-7.39 (m, 2H), 3.29-3.12 (m, 3H), 2.77 – 2.67 (m, 2H), 2.29 (s, 1H), 1.68 – 1.61 (m, 3H), 1.50 – 1.42 (m, 1H), 0.83 – 0.77 (m, 1H), 0.19 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 183.4, 181.0, 168.3, 167.2, 158.8, 147.7, 145.0, 140.9, 135.5, 133.8, 132.0, 129.9, 128.1, 122.6, 115.2, 101.8, 56.2, 41.0, 39.4, 35.1, 27.5, 26.1, –4.5. UPLC-DAD-QTOF: $C_{33}H_{39}N_4O_3Si$ $[M+H]^+$ calcd.: 567.2791, found: 567.2800.

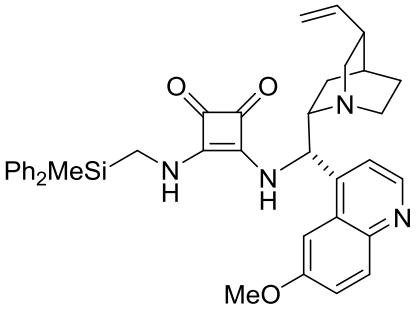
3-(((dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C6)



The title compound was **C6** prepared according to the general procedure. White solid; yield: 1.12 mmol, 693 mg, 75%. m. p. 229–232 °C. $[\alpha]_D^{25}$= –109.5 (*c* = 0.5, CH_2Cl_2). IR (ν/cm^{-1}): 3227, 2937, 2862, 1790, 1637, 1567, 1544, 1264, 1086, 1038, 817. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.84 (s, 1H), 7.75 – 7.70 (m, 4H), 7.43 – 7.35 (m, 5H), 5.78 – 5.65 (m, 1H), 4.98 – 4.89 (m, 2H), 3.89 (s, 3H), 3.31 – 3.06 (m, 5H), 2.71 – 2.61 (m, 2H), 2.22 (m, 1H), 1.62 – 1.52 (m, 3H), 1.41 – 1.32 (m, 1H), 0.77-0.70 (m, 1H), 0.20 – 0.18 (m, 6H). ^{13}C

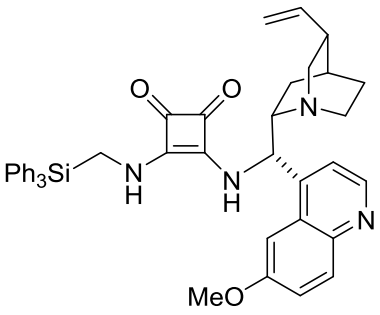
NMR (75 MHz, $CDCl_3$) δ: 184.0, 182.8, 167.7, 159.2, 148.1, 145.5, 141.9, 135.3, 134.5, 133.3, 132.5, 130.0, 128.5, 128.3, 128.0, 127.4, 126.8, 122.9, 115.2, 102.2, 56.5, 41.3, 40.1, 35.2, 28.4, 28.0, 26.7, –4.0. UPLC-DAD-QTOF: $C_{37}H_{41}N_4O_3Si$ $[M+H]^+$ calcd.: 617.2948, found: 617.2961.

3-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((methyldiphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C7)



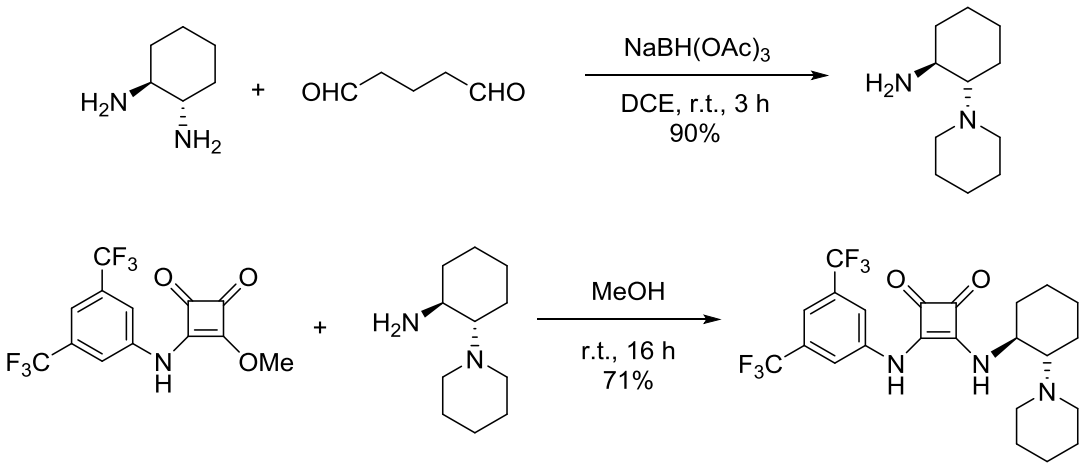
The title compound **C7** was prepared according to the general procedure. White solid; yield: 0.9 mmol, 565.5 mg, 60%. m. p. 152–156 °C. $[\alpha]_D^{23}$= –105.3 (*c* = 1.0, CH_2Cl_2). IR (ν/cm^{-1}): 3193, 2929, 2859, 1788, 1628, 1547, 1456, 1230, 1114, 803, 760, 730, 700, 489. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.79 (s, 1H), 7.48 – 6.97 (m, 12H), 5.75 (ddd, *J* = 17.6, 10.9, 7.6 Hz, 1H), 5.08 – 4.80 (m, 2H), 3.89 (s, 3H), 3.43 (ddd, *J* = 32.6, 16.8, 9.5 Hz, 4H), 3.15 (dd, *J* = 13.8, 10.0 Hz, 1H), 2.68 (dq, *J* = 14.9, 7.5, 6.1 Hz, 2H), 2.15 (s, 2H), 1.73 – 1.18 (m, 4H), 0.86 – 0.65 (m, 1H), 0.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.6, 181.9, 167.8, 158.7, 147.6, 144.9, 141.6, 134.6, 133.6, 133.5, 131.9, 130.1, 128.2, 128.2, 122.5, 114.7, 101.9, 56.1, 40.9, 39.7, 33.7, 28.0, 27.7, 26.3, -5.7. UPLC-DAD-QTOF: $C_{38}H_{41}N_4O_3Si$ $[M+H]^+$ calcd.: 629.2948, found: 629.2956.

3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methylamino)-4-((triphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C8)



The title compound **C8** was prepared according to the general procedure. White solid; yield: 687.5 mg, 1.0 mmol, 67%. m. p. 252–256 °C. $[\alpha]_D^{23}$= –58.9 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (s, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.61 – 7.08 (m, 19H), 5.71 (dt, *J* = 17.4, 9.3 Hz, 1H), 5.03 – 4.83 (m, 2H), 3.90 (s, 3H), 3.72 (td, *J* = 20.5, 20.0, 10.0 Hz, 3H), 3.36 – 3.01 (m, 3H), 2.63 (dt, *J* = 14.6, 7.5 Hz, 2H), 2.23 (dt, *J* = 10.8, 6.3 Hz, 1H), 1.72 – 1.28 (m, 4H), 0.72 (q, *J* = 7.6, 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.6, 182.0, 167.9, 167.8, 158.7, 147.4, 144.9, 141.5, 135.9, 135.7, 135.4, 131.8, 130.3, 128.4, 128.3, 128.2, 128.0, 122.7, 114.7, 101.9, 56.2, 40.8, 39.6, 32.6, 28.0, 27.8, 27.7, 26.4. UPLC-DAD-QTOF: $C_{43}H_{43}N_4O_3Si$ $[M+H]^+$ calcd.: 691,3104, found: 691.3129.

5.2.5. Preparation of catalyst C10[235]



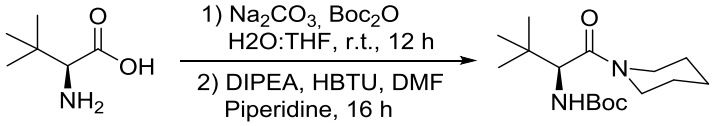
Aqueous glutaraldehyde (50%, 1.0 mL) was added dropwise into a mixture of $NaBH(OAc)_3$ (4.24g, 20.0 mmol) and (1*S*,2*S*)-1,2-diaminocyclohexane (570 mg, 5.0 mmol) in dichloroetane (30 mL) at room temperature. The resulting mixture was stirred at room temperature for 3h, and then quenched with aqueous NaOH (10%, 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude product as a yellow liquid (820 mg, 90% yield).

To a solution of the crude amine (273 mg, 1.5 mmol) in 5 mL CH_2Cl_2 was added squaric ester monoamine (271 mg, 1.0 mmol). The reaction was stirred at room temperature for 24 h. Then the mixture was concentrated and purified by basic silica gel column chromatography (using CH_2Cl_2 as eluant) to afford the desired product VII as a pale yellow solid (347 mg, 71% yield). m.p. 134−136 °C, $[\alpha]_D^{25}$ = +150.3 (c = 0.62, CH_2Cl_2). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (s, 2H), 7.42 (s, 1H), 4.00 (s, 1H), 2.62 (br s, 2H), 2.35 − 2.27 (m, 3H), 2.18 − 2.16 (m, 1H), 1.89 − 1.87 (m, 1H), 1.78 (d, *J* = 10.5 Hz, 1H), 1.70 (d, *J* = 11.0 Hz, 1H), 1.40 − 1.12 (m, 10H).

[235] Yang, W.; Du, D-M *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

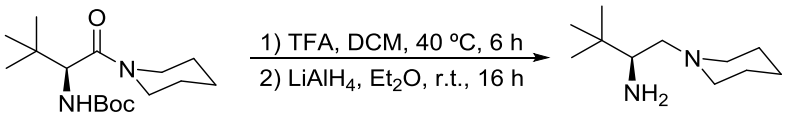
5.2.6. Preparation of catalyst C11

Step 1) Protection of the amine and amide formation[236]



Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3g, 15 mmol, 1.5 equiv.) were added to a solution of t-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) and THF (5 mL) at 0 °C. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aqueous phases were united and washed with brine (50 mL) and dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was then redissolved in dry DMF dissolution (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 gm 15 mmol, 1.5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were united and washed with a HCl 1 M and brine (20 mL) and dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 85/15) to afford tert-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 2.5 g, 8.3 mmol, 83%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62 (m, 6H), 3.46 – 3.69 (m, 4 H), 4.54 (d, *J* = 9.7 Hz, 1H), 5.38 (d, *J* = 9.6 Hz, 1H).

Step 2) Deprotection and reduction

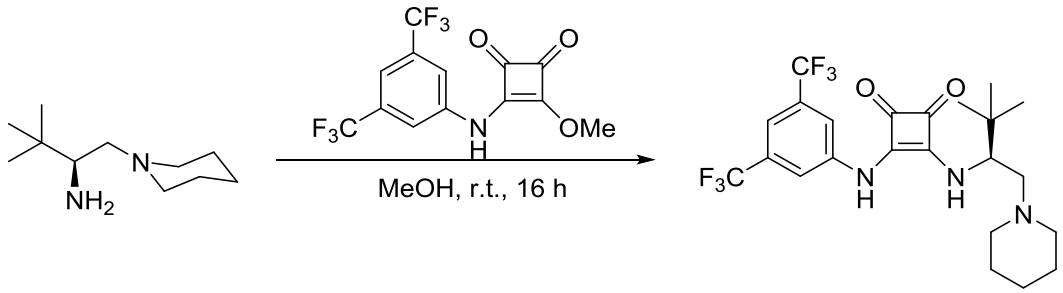


Previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane/EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40%), dried over $MgSO_4$ and the solvent was

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

removed under reduced pressure obtaining the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwaise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 ^{o}C under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched adding water (1.2 mL), NaOH 15% (1.2 mL) and water (3.6 mL) at 0 ^{o}C. The result was filtered and the liquid was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over MgSO4 and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/EtOAc 1/1) to afford (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 1.16 g, 6.8 mmol, 92%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.66 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.52 (d, *J* = 12.3 Hz, 4H), 2.28 (dd, *J* = 12.3, 2.8 Hz, 3H), 2.13 (dd, *J* = 12.1, 11.2 Hz, 1H), 1.61 – 1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

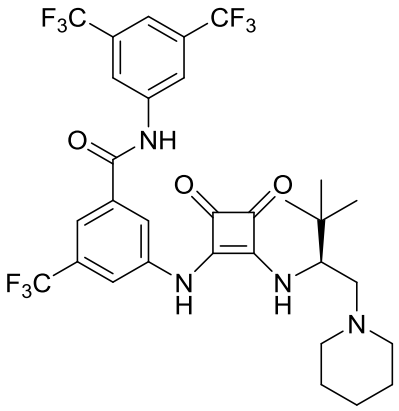
Step 3) Amine coupling[237]



To a solution of the diamine (780 mg, 4,6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4,6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure **C11** as a white solid. m.p. 246–248 °C. Yield: 1.29 g, 2.6 mmol, 59%. All spectroscopic data were identical to those reported in the literature.

[237] Hu, K.; Lu, A.; Wang, Y.; Zhou, Z.; Tang, C. *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.

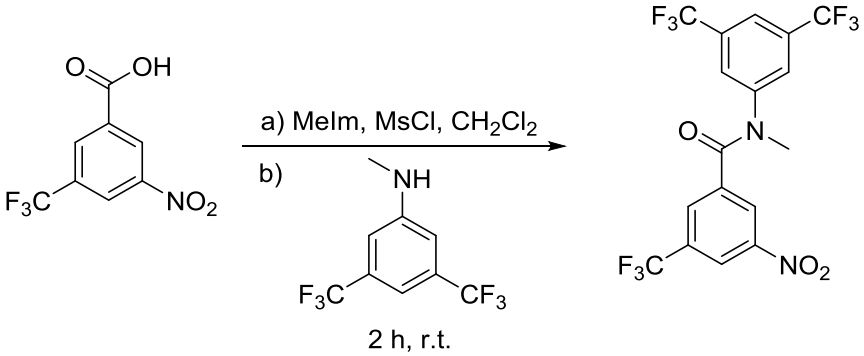
5.2.7. Preparation of catalyst C12[238]



Catalyst **C12** was prepared according to the literature procedure. All data were consistent with those previously reported.

5.2.8. Preparation of catalyst C13

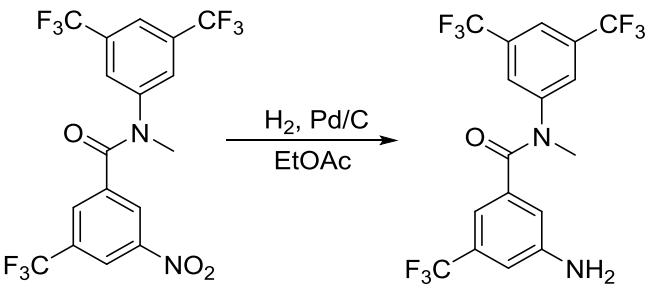
Step 1) Peptide coupling[239]



1-Methylimidazole (2.5 equiv., 15.5 mmol, 1.2 mL) was added to a slurry of 3-nitro-5-(trifluoromethyl)benzoic acid (1 equiv., 6.2 mmol, 1.5 g) in DCM (2.5 mL/mmol) at 0 ^{o}C, and the mixture was stirred for 10 min. MsCl (1.5 equiv., 9.3 mmol, 0.7 mL) in DCM (0.1 mL/mmol) was added to the mixture under –5 ^{o}C. After the mixture was stirred under that temperature for 20 minutes, *N*-methyl-3,5-bis(trifluoromethyl)aniline (1 equiv., 6.2 mmol, 1.0 mL) was added. The mixture was stirred at room temperature for 2 hours. H_2O (10 mL/mmol) was added to the mixture and a solid precipitated, which was dissolved in EtOAc (10 mL/mmol). The organic layer was washed with brine (3 x 10 mL/mmol), dried over $MgSO_4$ and evaporated under reduced pressure. The crude was crushed with diethyl ether to afford the pure compound as a white solid. Yield: 4.8 mmol, 2.2 g, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (s, 1H), 8.36 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.59 (s, 2H), 3.60 (s, 3H).

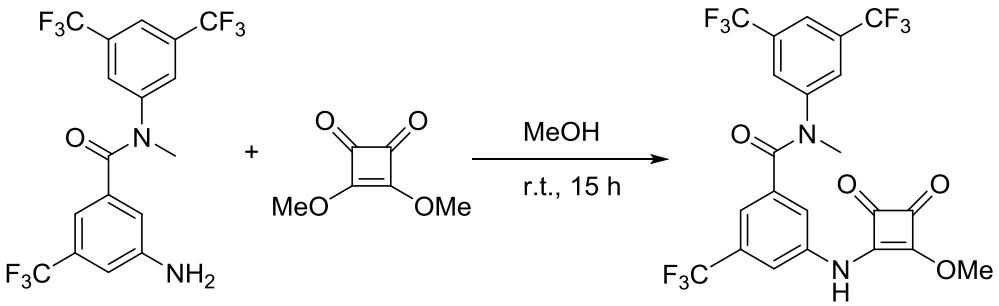
[238] Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 8185–8195.
[239] Adapted from: Mao, L.; Wang, Z.; Li, Y.; Han, X.; Zhou, W. *Synlett* **2011**, *1*, 129–133.

Step 2) Hydrogenation



To a solution of *N*-(3,5-Bis(trifluoromethyl)phenyl)-*N*-methyl-3-nitro-5-(trifluoromethyl)benzamide (4.8 mmol, 2.2 g) in EtOAc (10 mL) 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 hours. After that the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford the pure hydrogenated product. White solid. Yield: 1.9 g, 4.7 mmol, 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (s, 1H), 7.53 (s, 2H), 6.87 (s, 1H), 6.83 (s, 1H), 6.69 (s, 1H), 3.92 (s, 2H), 3.53 (s, 3H).

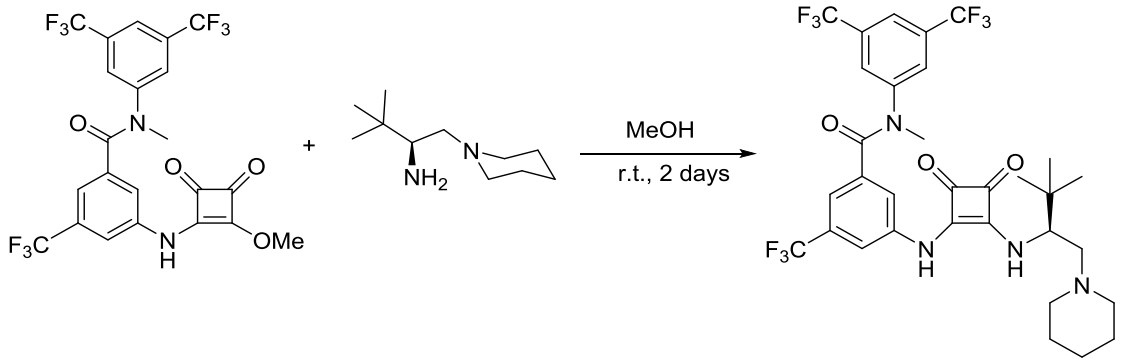
Step 3) Benzamide coupling with methyl squarate[240]



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 4.3 mmol, 613 mg) in MeOH (2 mL/mmol) *N*-(3,5-Bis(trifluoromethyl)phenyl)-3-amino-5-(trifluoromethyl)-*N*-methyl benzamide (1.1 equiv., 4.7 mmol, 2.0 g) was added at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated and washed with MeOH. White solid. Yield: 4.08 mmol, 2.2 g, >95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (d, J = 5.0 Hz, 2H), 7.57 (s, 2H), 7.51 (s, 1H), 7.18 (s, 1H), 4.52 (s, 3H), 3.58 (s, 3H).

[240] Adapted from: Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, *46*, 3004–3006.

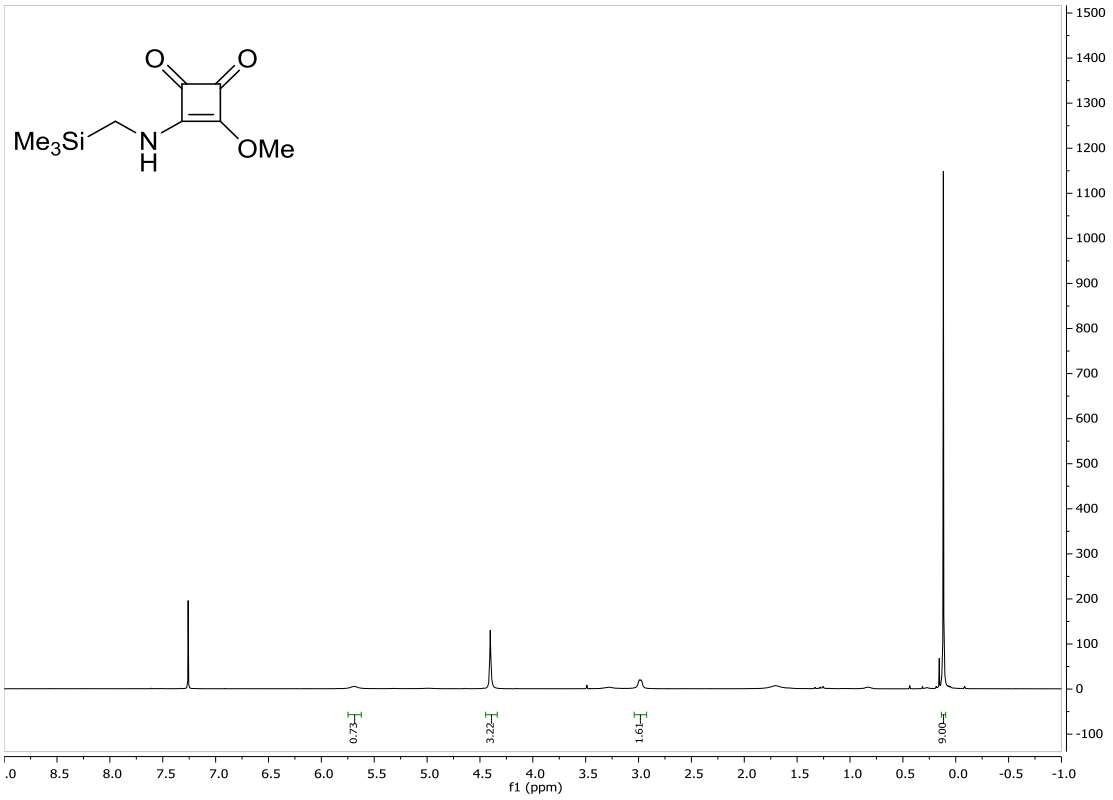
Step 4) Amine coupling

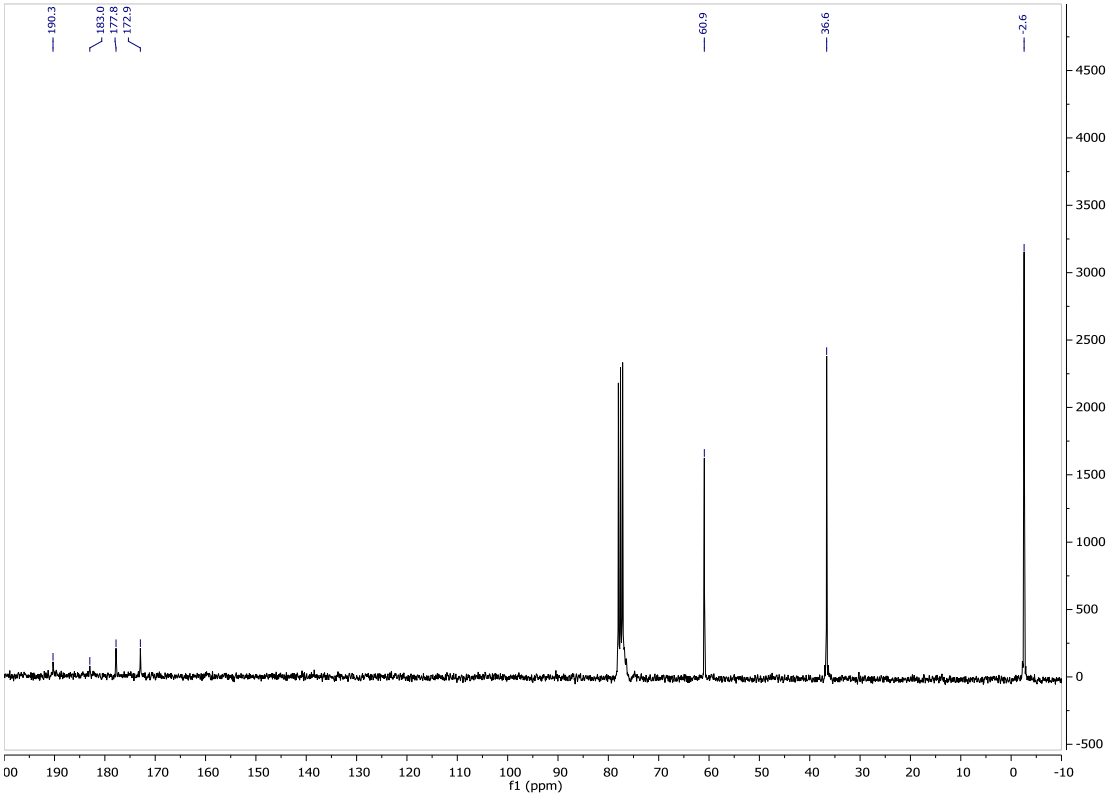


To a suspension of 3-(2-Methoxy-3,4-dioxocyclobut-1-enylamino)-*N*-(3,5-bis(trifluoromethyl)phenyl)-*N*-ethylbenzamide (1 equiv., 2.0 mmol, 653 mg) in MeOH (10 mL) (S)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine was added (1 equiv., 2.0 mmol, 368 mg) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was evaporated and purified by column chromatography (eluting with 50:50 Hex:EtOAc; 0:100 Hex:EtOAc to 90:10 CH_2Cl_2:MeOH). Yellow solid. Yield: 969 mg, 1.4 mmol, 70%. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.04 (s, 2H), 7.92 (s, 1H), 7.80 (s, 1H), 7.78 – 7.74 (m, 1H), 7.20 (s, 1H), 4.14 – 3.91 (m, 1H), 3.47 (s, 3H), 2.39 – 2.13 (m, 2H), 1.39 (m, 6H), 0.94 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 185.6, 181.5, 172.0, 169.3, 163.3, 147.0, 141.7, 139.1, 132.8 (q, *J* = 32.7 *Hz*, $2CF_3$), 132.0 (q, *J* = 30.0 *Hz*, $1CF_3$), 128.7, 121.8, 120.7, 118.9, 116.2, 61.5, 59.9, 55.4, 38.4, 35.00, 26.7, 26.4, 24.6. UPLC-DAD-QTOF: $C_{32}H_{34}F_9N_4O_3$ $[M+H]^+$ calcd.: 692.2409, found: 692.2413.

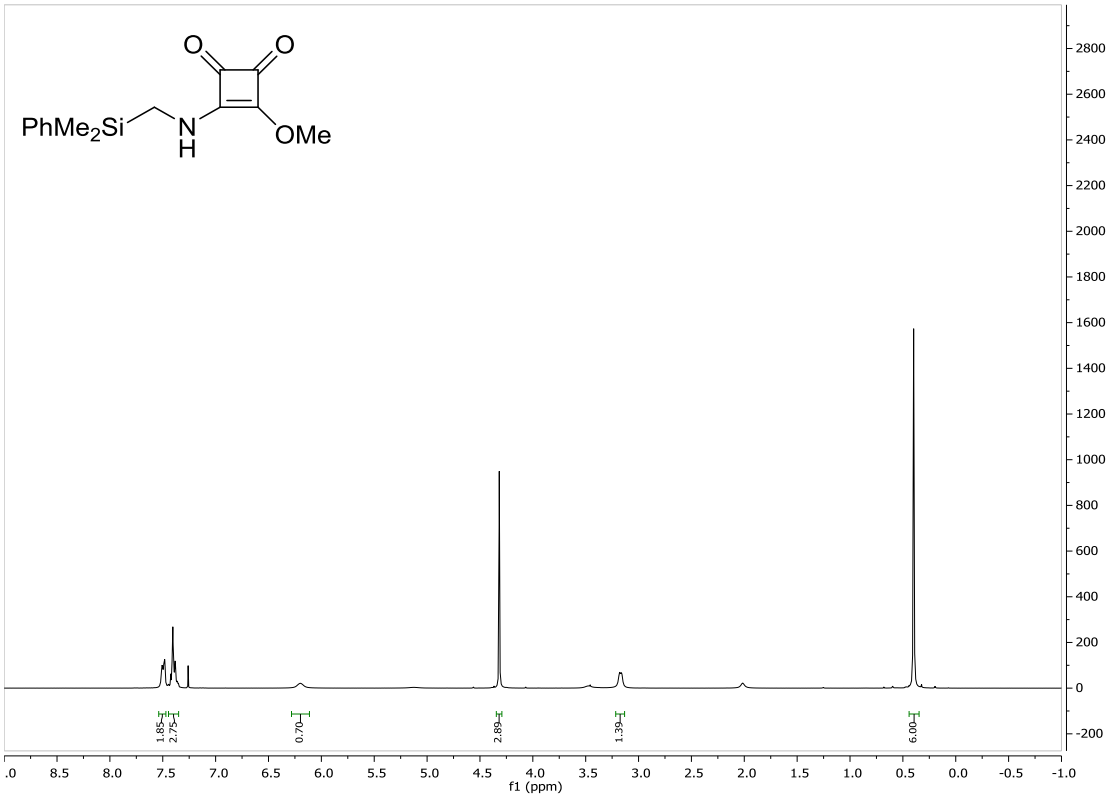
5.2.9. Representative NMR spectra

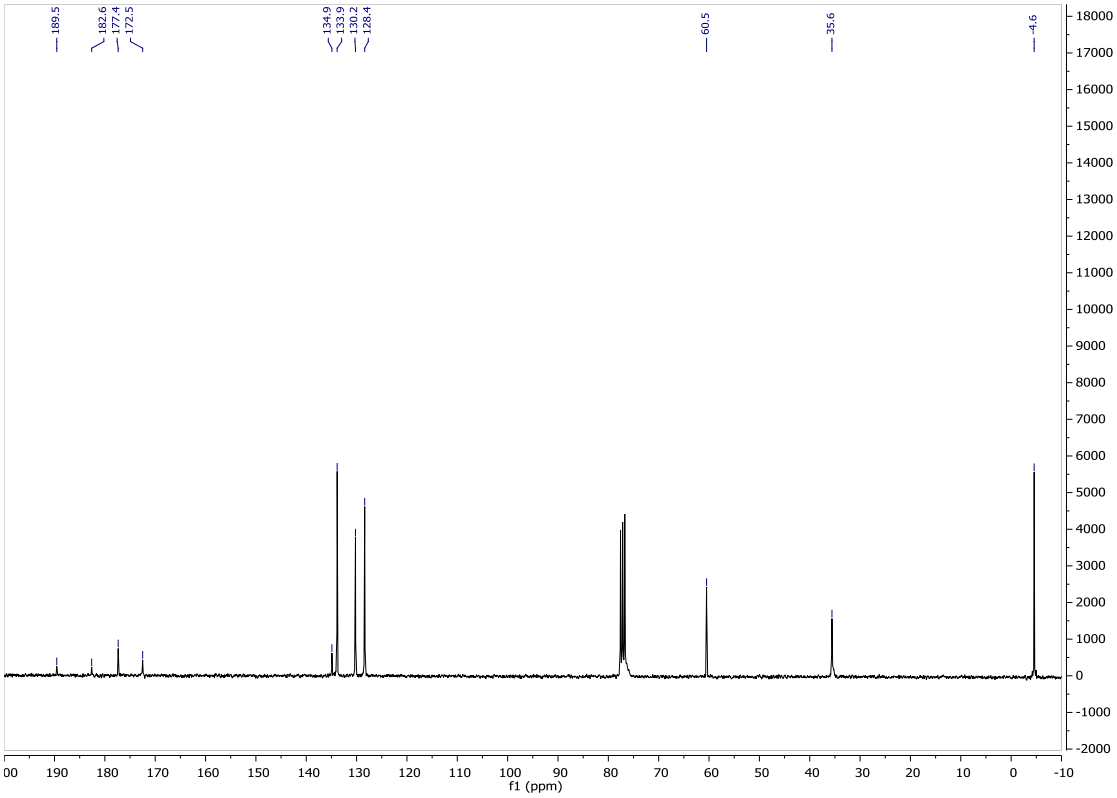
3-methoxy-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione



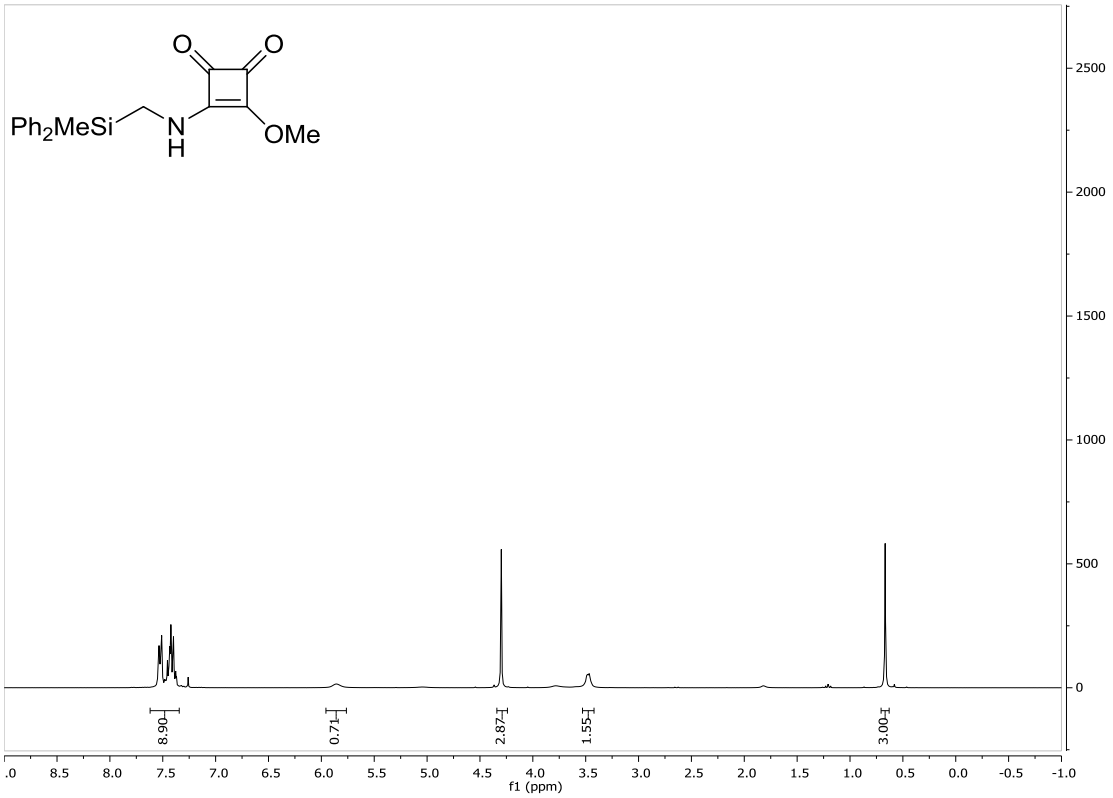


3-((dimethyl(phenyl)silyl)methylamino)-4-methoxycyclobut-3-ene-1,2-dione

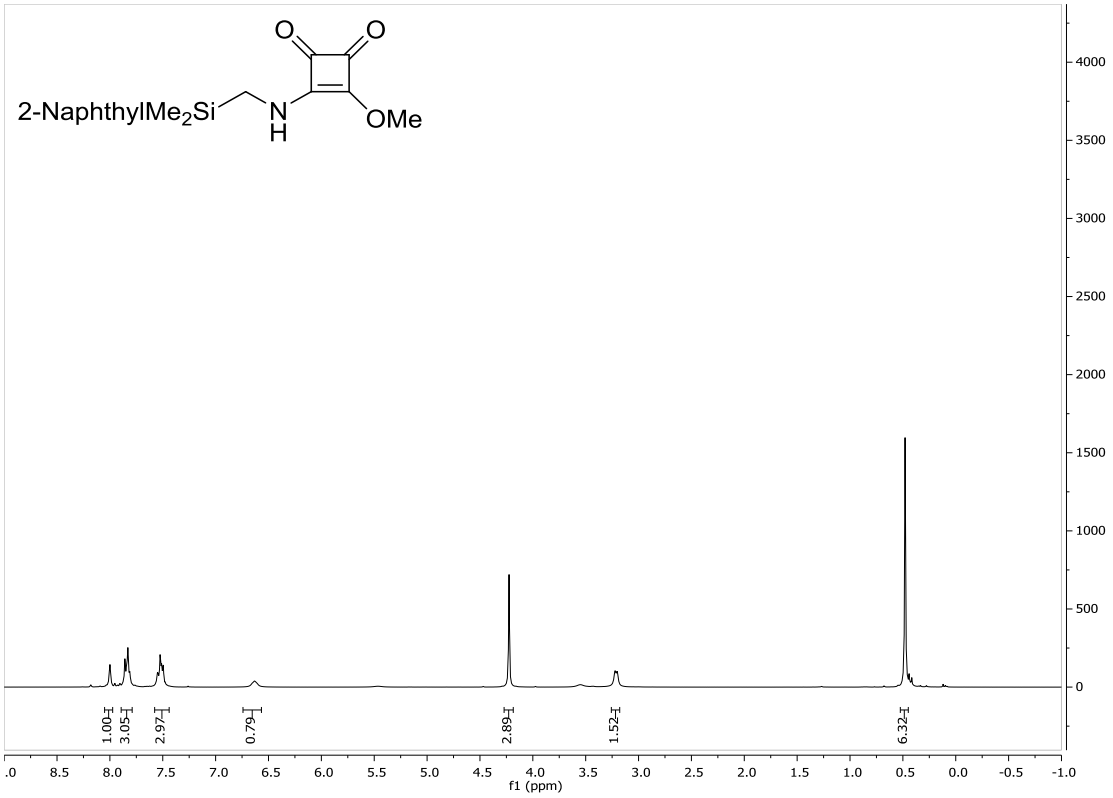


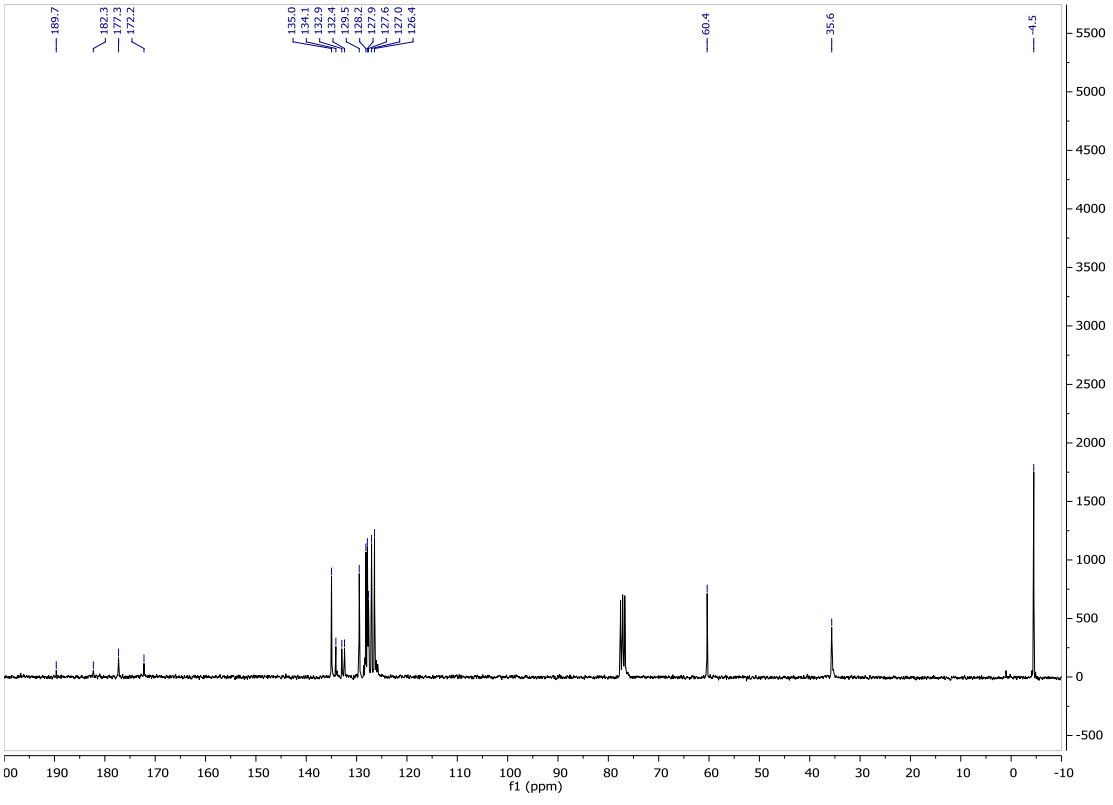


3-methoxy-4-((methyldiphenylsilyl)methylamino)cyclobut-3-ene-1,2-dione

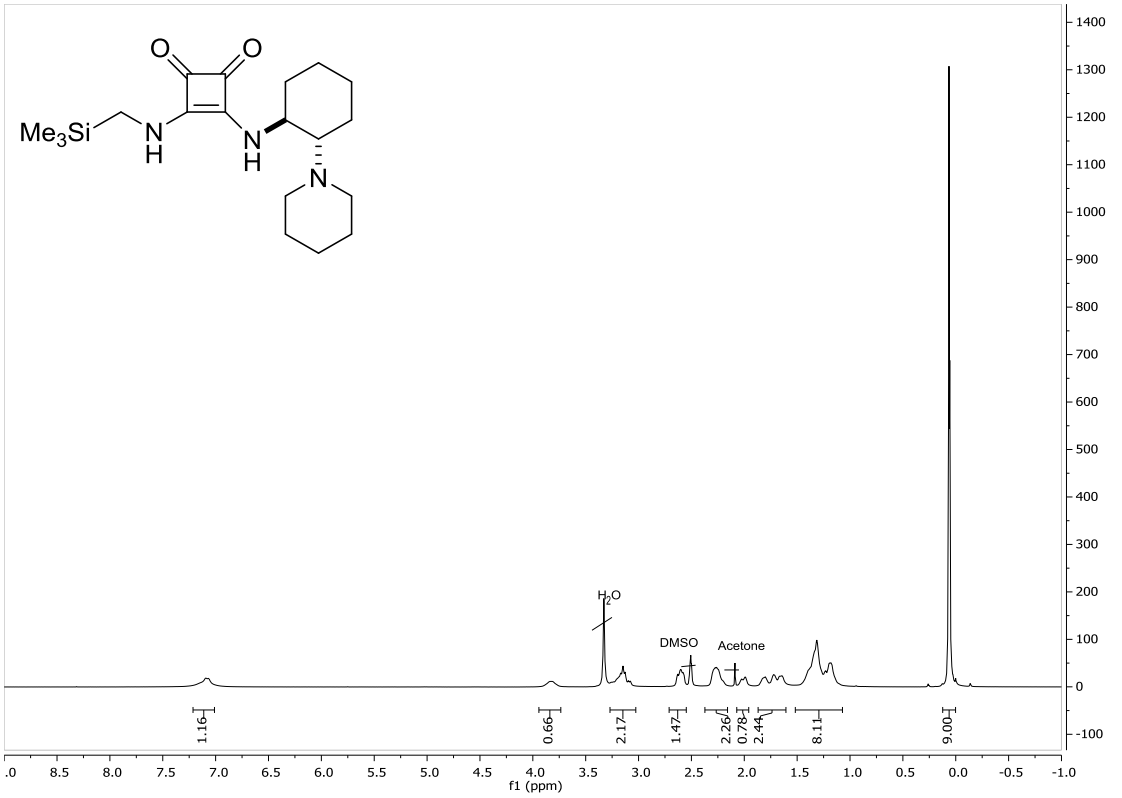


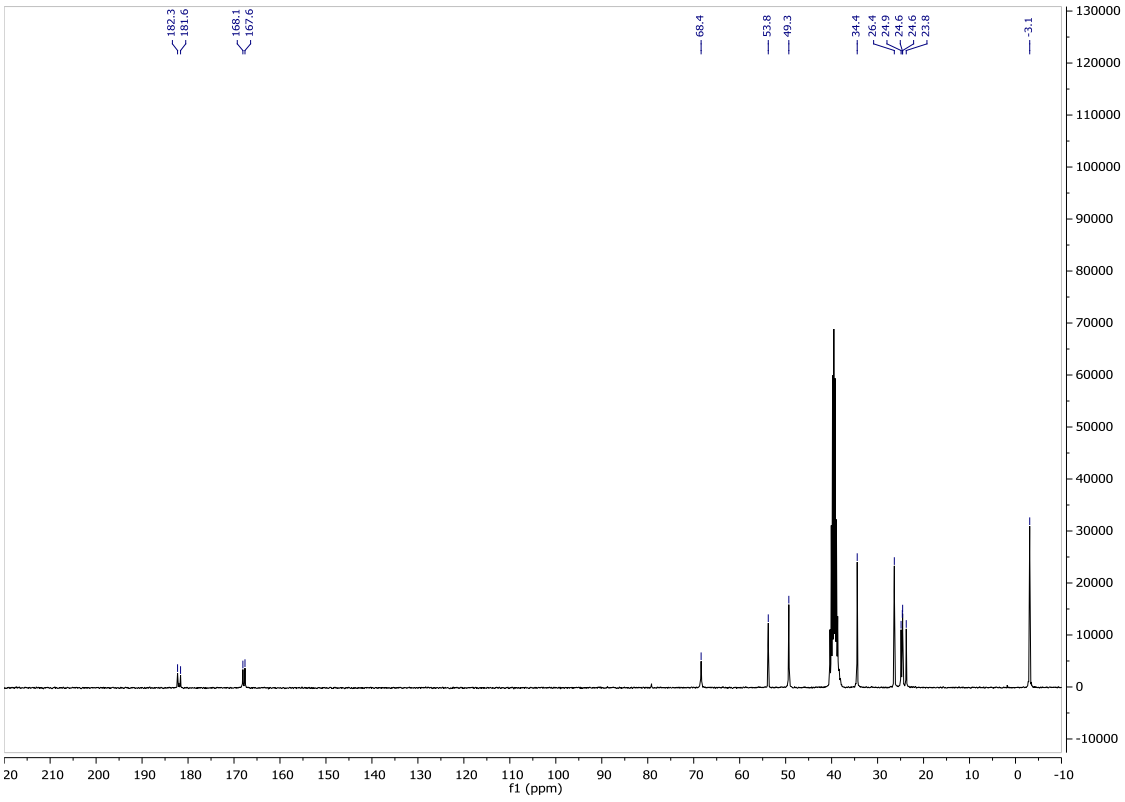
3-(((dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-methoxycyclobut-3-ene-1,2-dione



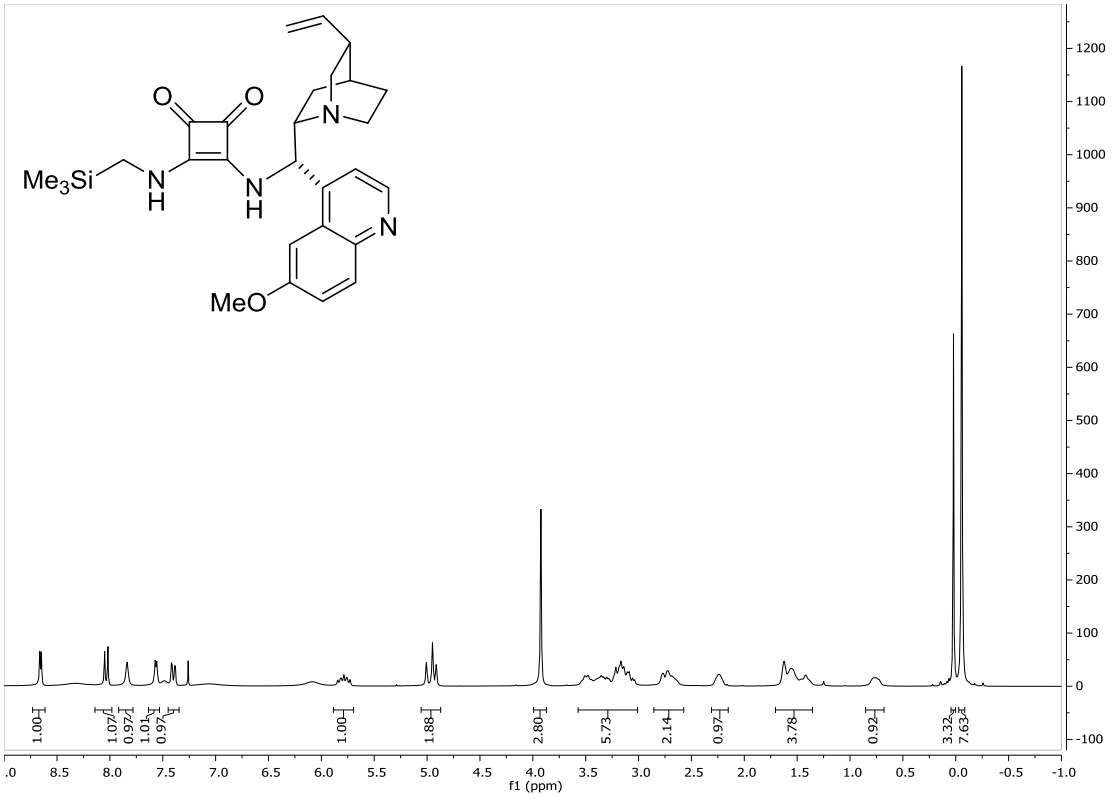


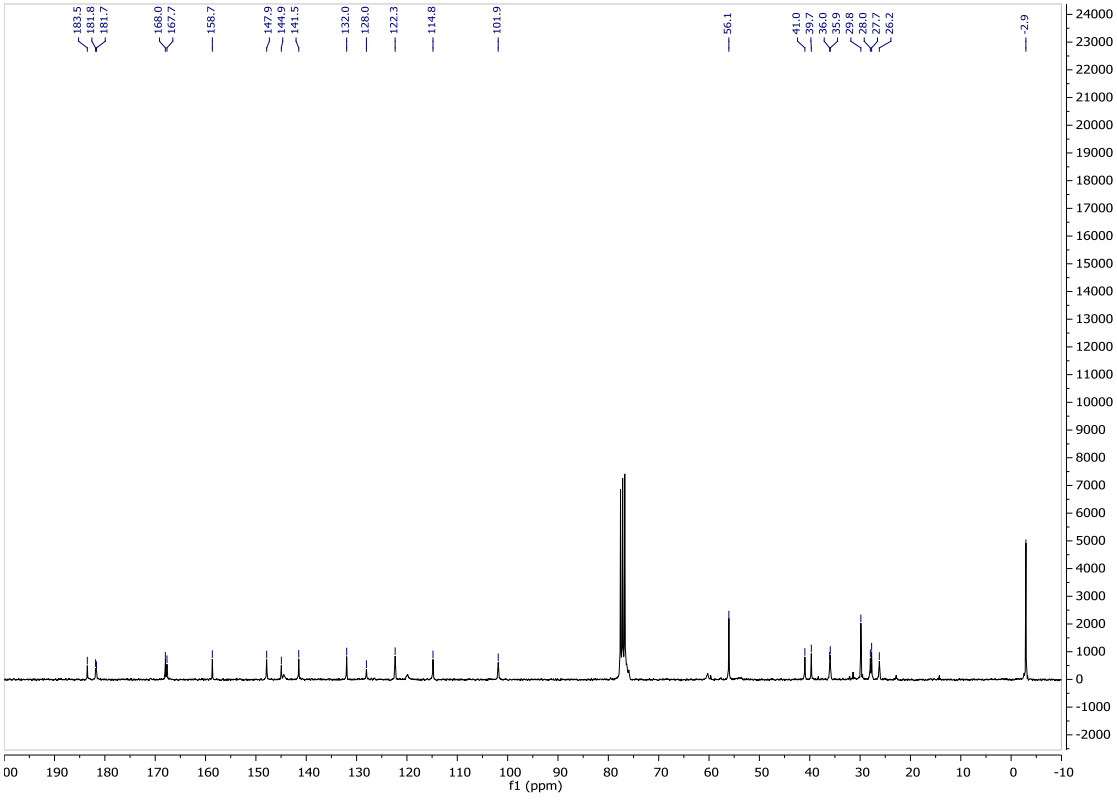
3-(((1S,2S)-2-(piperidin-1-yl)cyclohexyl)amino)-4-(((trimethylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C3)



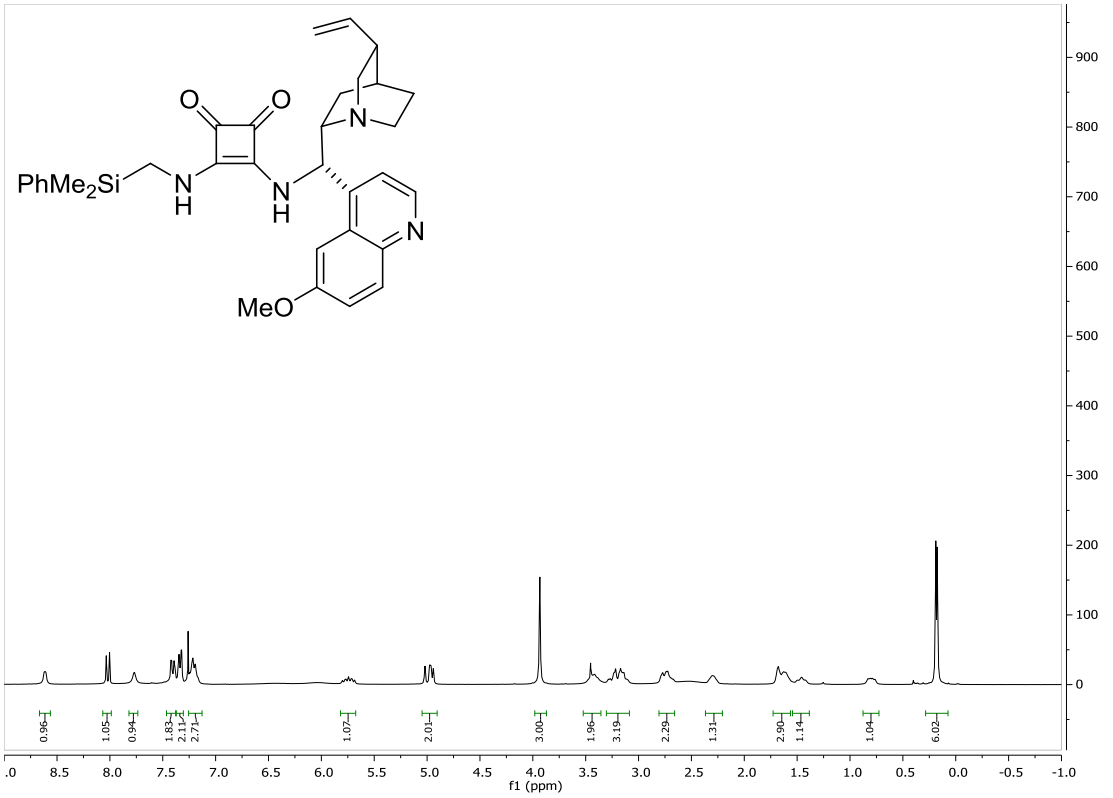


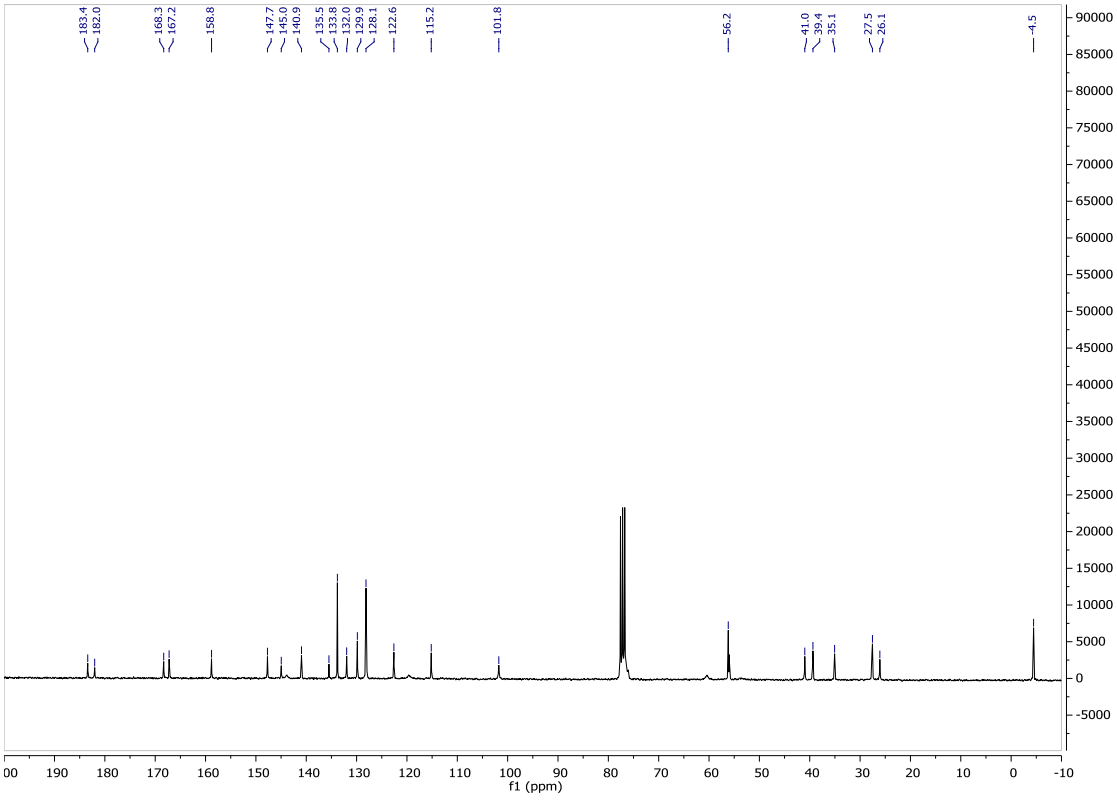
3-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)-4-((trimethylsilyl)methylamino)cyclobut-3-ene-1,2-dione (C4)



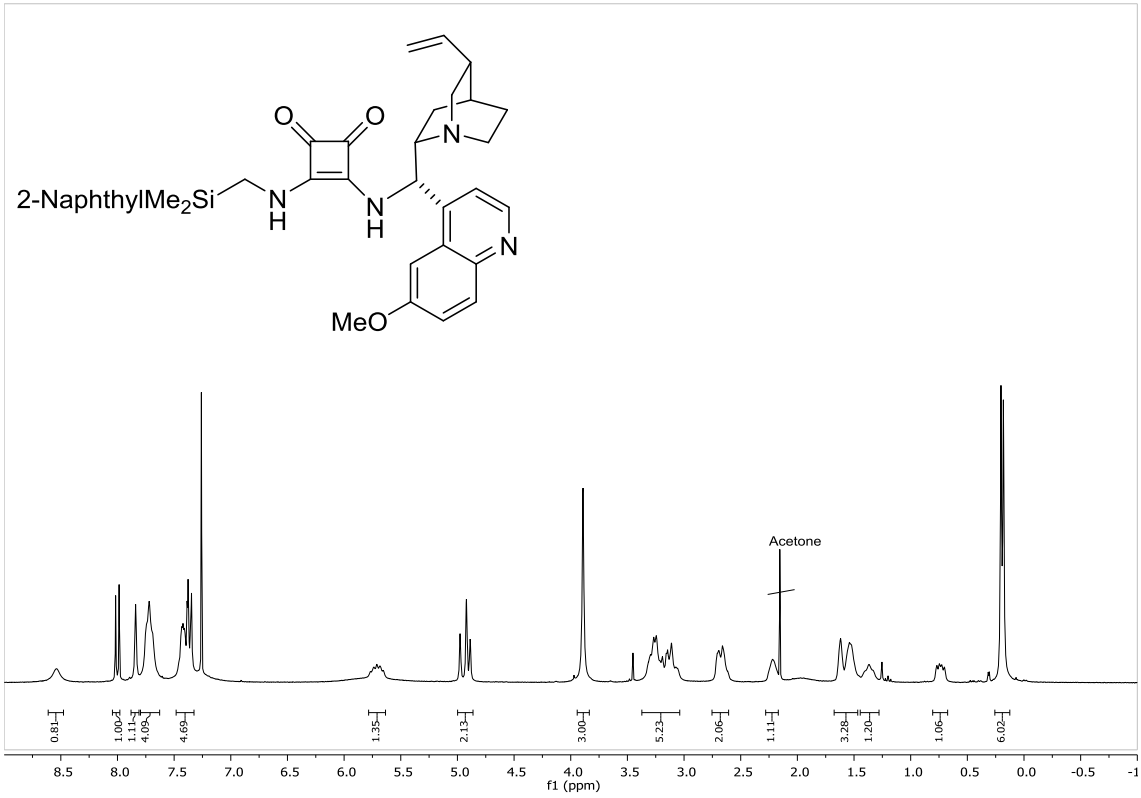


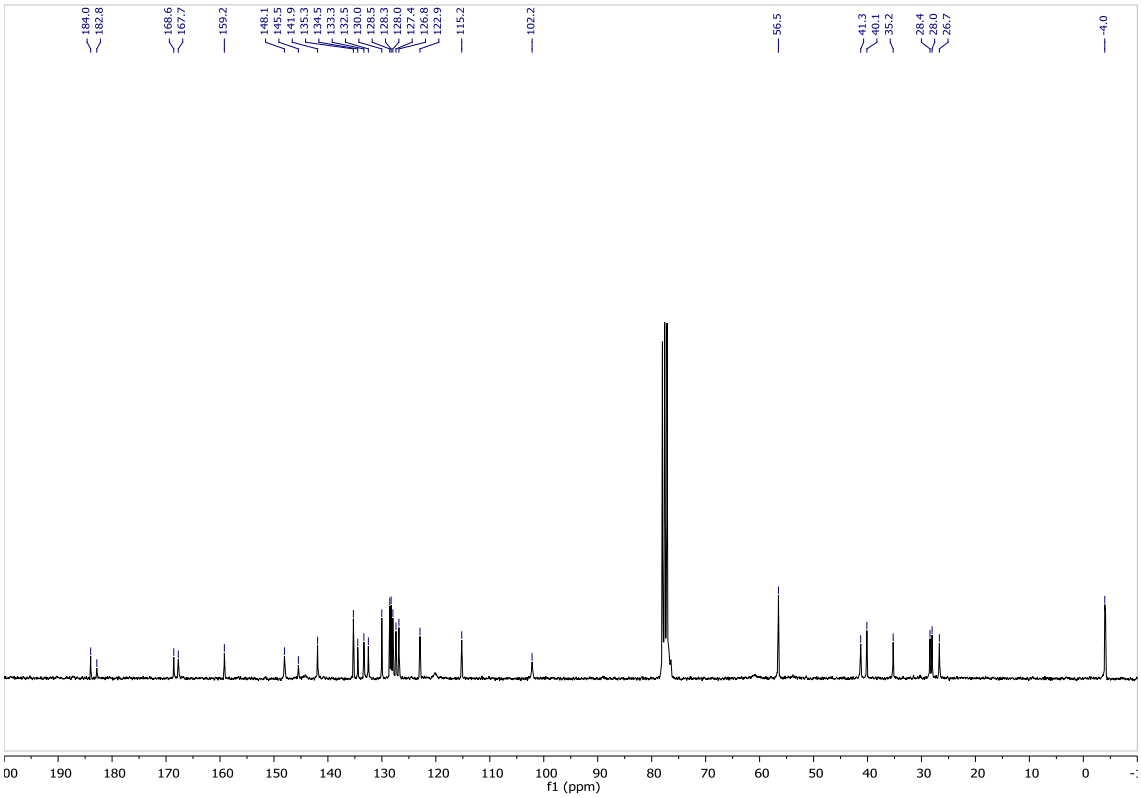
3-((dimethyl(phenyl)silyl)methylamino)-4-((S)-(6-methoxyquinolin-4-yl)((2S,4S,8R)-8-vinylquinuclidin-2-yl)methylamino)cyclobut-3-ene-1,2-dione (C5)



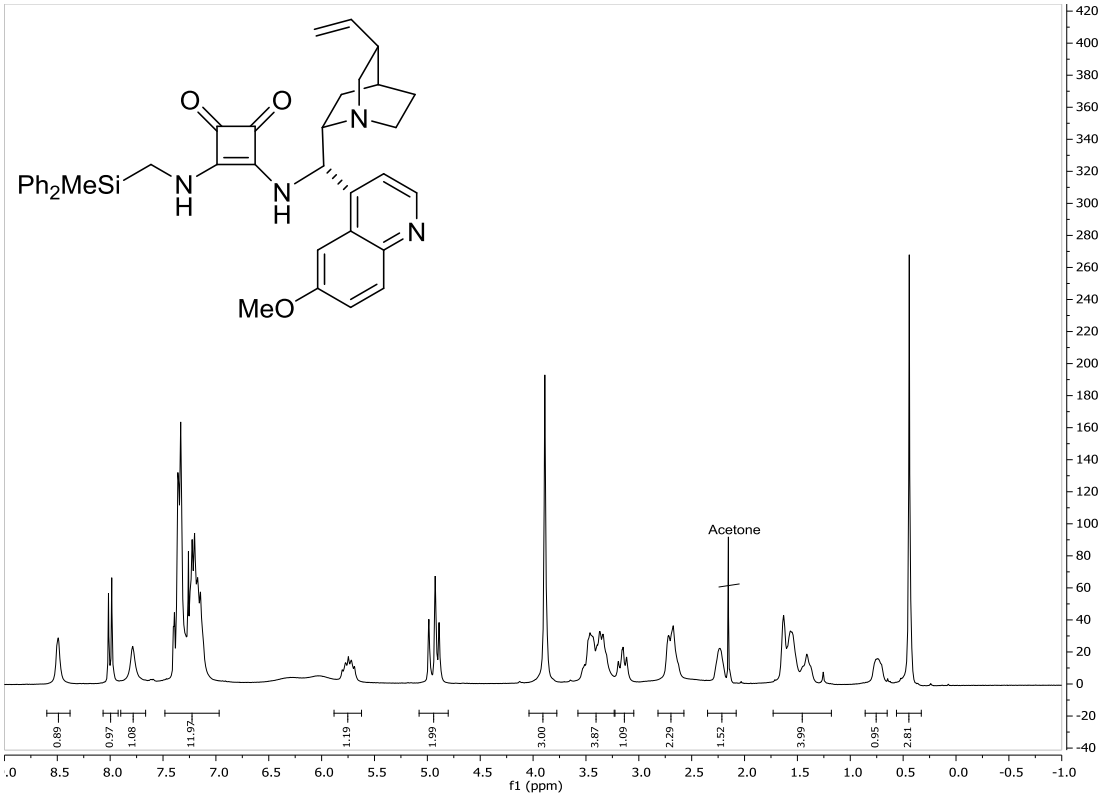


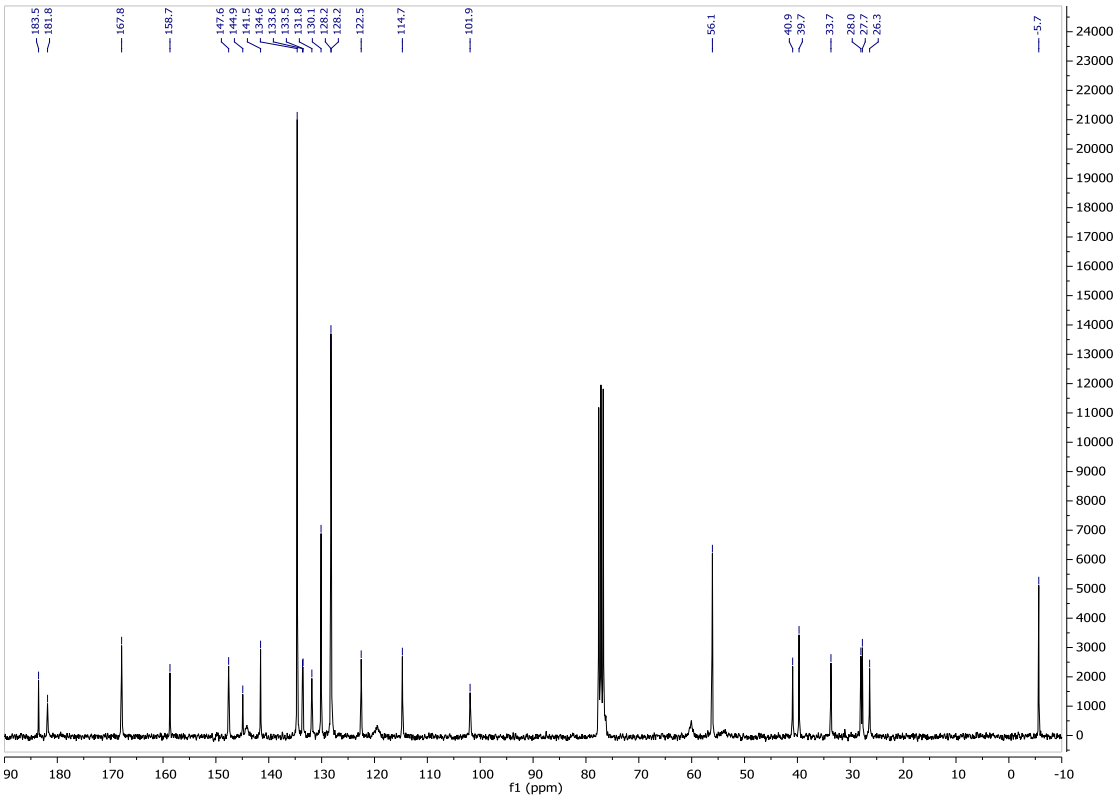
3-(((dimethyl(naphthalen-2-yl)silyl)methyl)amino)-4-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C6)



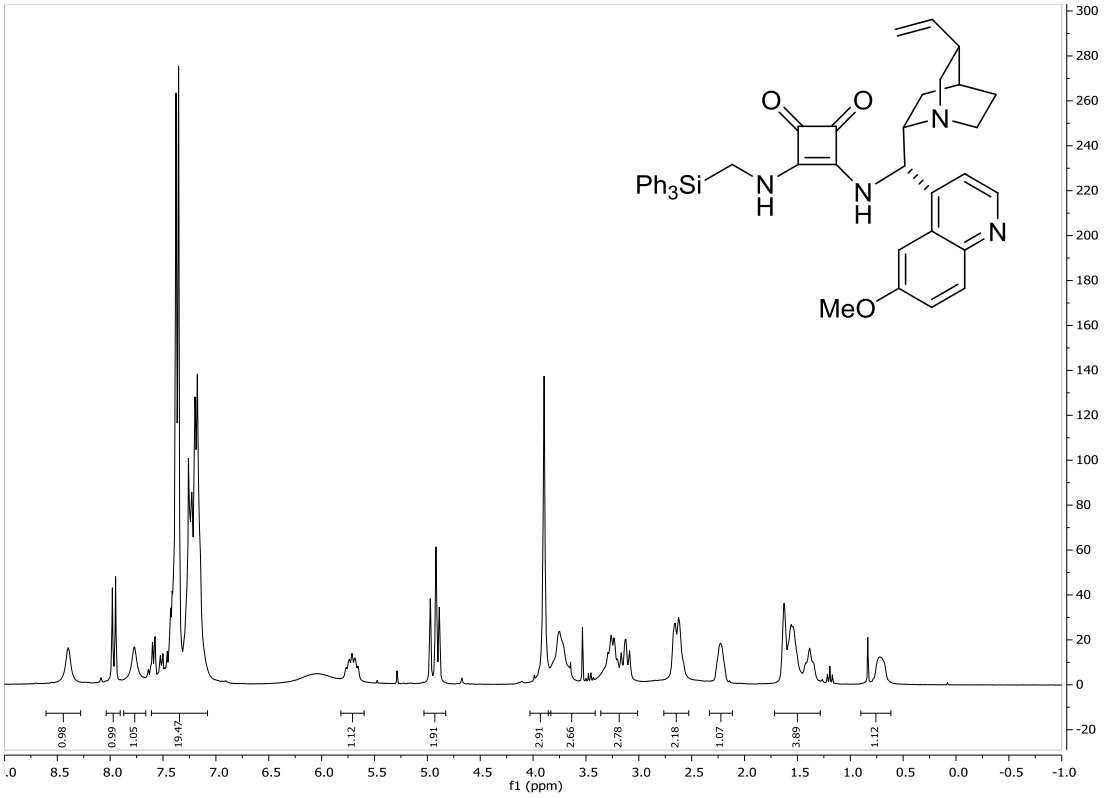


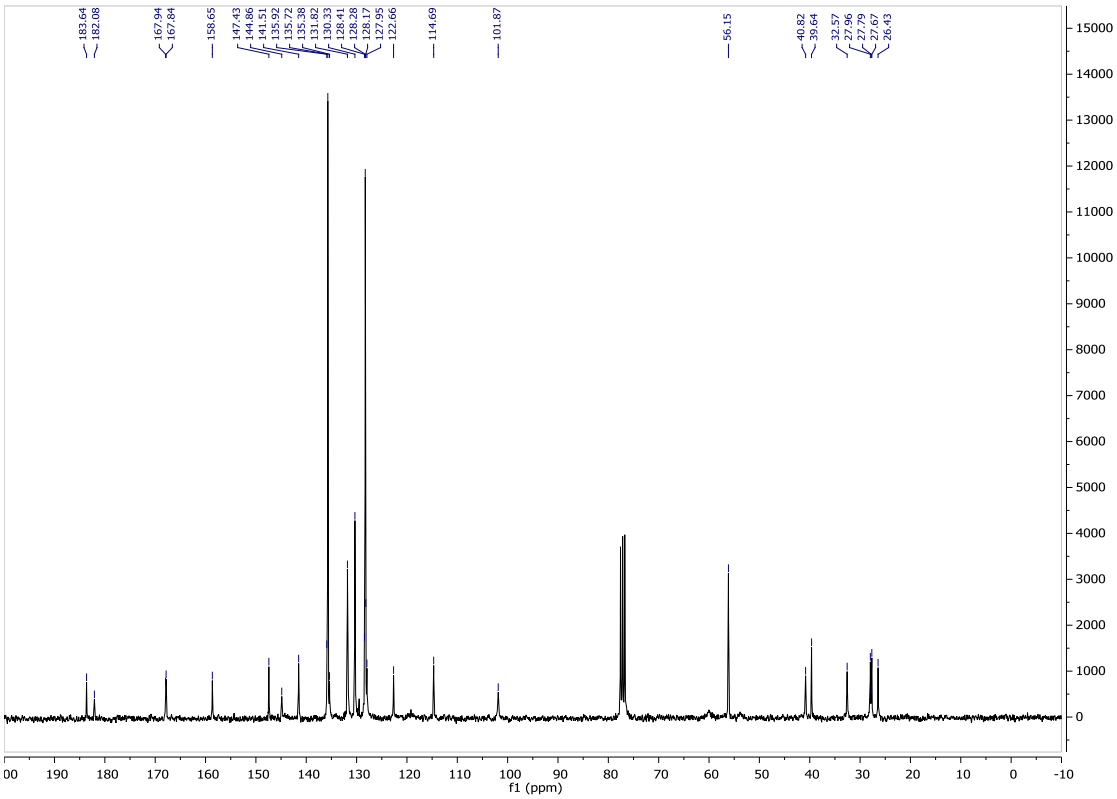
3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((methyldiphenylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C7)



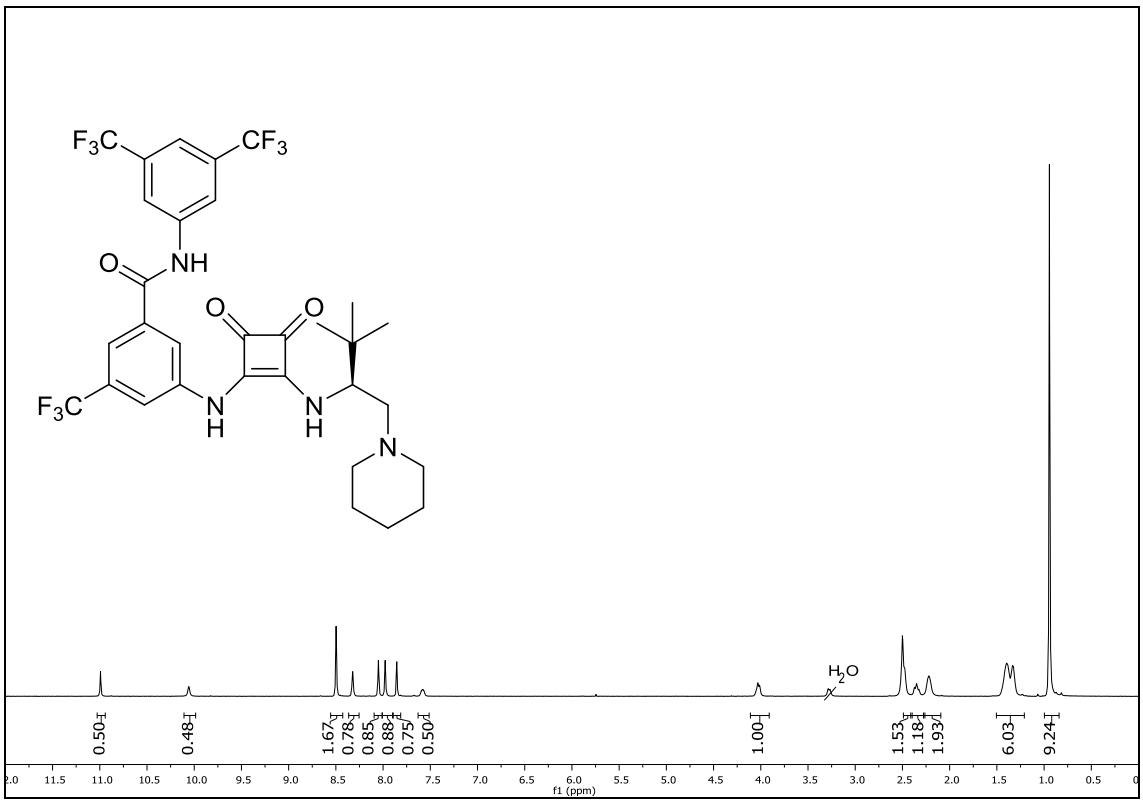


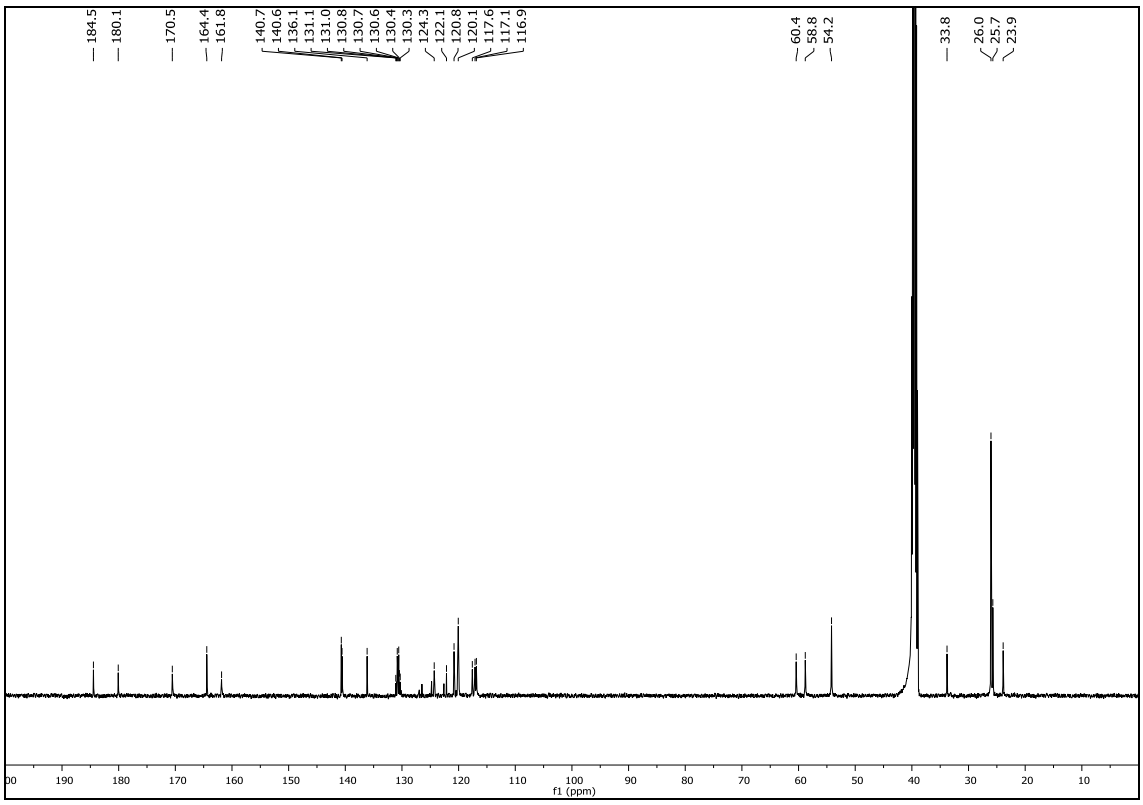
3-(((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((triphenylsilyl)methyl)amino)cyclobut-3-ene-1,2-dione (C8)



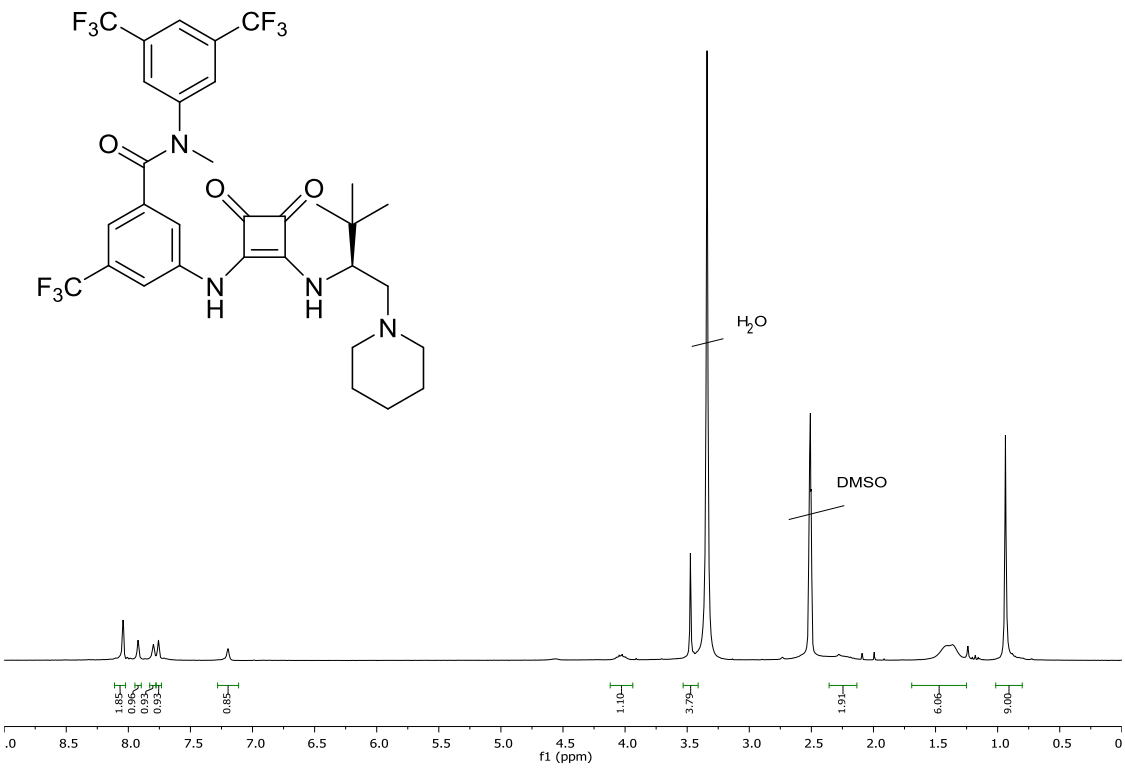


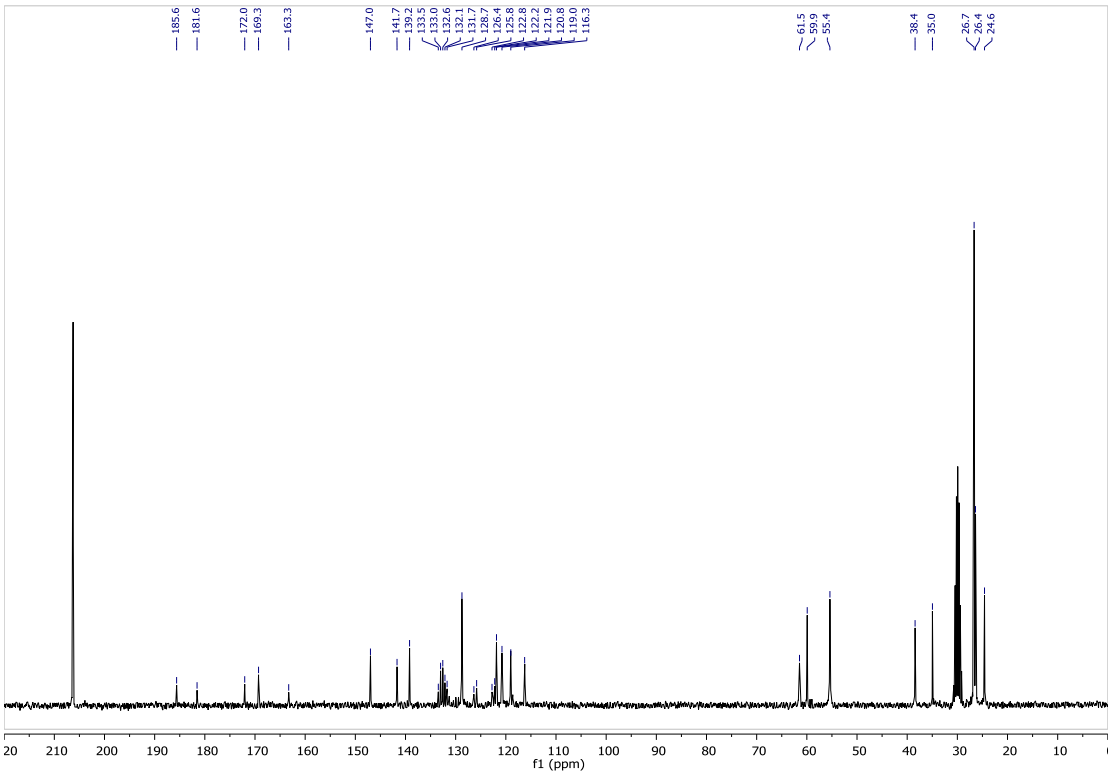
(S)-N-(3,5-bis(trifluoromethyl)phenyl)-3-((2-((3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-5-(trifluoromethyl)benzamide (C12)





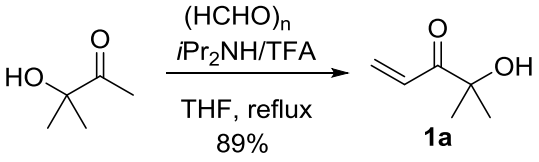
(*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-((3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-N-methyl-5-(trifluoromethyl)benzamide (C13)





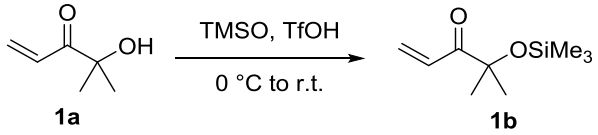
5.3. Experimental section of chapter 2

5.3.1. General procedure for the synthesis of α'-hydroxy enone 1a[241]



Commercially available 3-hydroxy-3-methyl-2-butanone (1 equiv., 5.3 mL, 50 mmol) and paraformaldehyde (2 equiv., 3 g, 100 mmol) were added to a solution of iPr$_2$NH (2 equiv., 14.0 mL, 100 mmol) and TFA (2.5 equiv., 9.6 mL, 125 mmol) in THF (250 mL). The mixture was refluxed and paraformaldehyde (2 equiv., 3 g, 100 mmol) was added every 2 h three times. The mixture was stirred at reflux overnight and then was cooled to room temperature. CH_2Cl_2 (100 mL) was added and the mixture was washed with 1N HCl (75 mL), 1N NaOH (75 mL) and brine (75 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure (230 mbar/ bath 40 ^oC). The residue was purified by flash column chromatography on silica gel (eluent: diethyl ether) to afford 4-hydroxy-4-methylpent-1-en-3-one (**1a**) as colorless oil. Yield: 5.0 g, 44.5 mmol, 89%. ^1H NMR ($CDCl_3$) δ: 6.73 (dd, J = 9.5 Hz, 16.8 Hz, 1H), 6.50 (dd, J = 2.2 Hz, 16.8 Hz, 1H), 5.82 (dd, J = 2.2 Hz, 10.3 Hz, 1H), 1.38 (s, 6H). ^{13}C NMR ($CDCl_3$) δ: 202.3, 131.1, 128.8, 75.4, 26.1.

5.3.2. General procedure for the synthesis of α'-silyloxienone 1b[242]

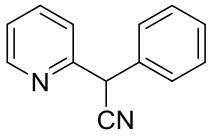


3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (3.4 mL, 22.5 mmol, 1.5 equiv) and 3 drops of trifluoromethanesulfonic acid were added to 4-hydroxy-4-methylpent-1-en-3-one (1.68 g, 15 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h. The resulting brown suspension was diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (eluent pentane/Et_2O, 98:2) to afford the title compound (**1b**) as a colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. ^1H NMR (300 MHz,

[241] Palomo, C.; Oiarbide, M.; García, J.; González, A.; Arceo E. *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.
[242] Adapted from: Aizpurua, J. M.; Palomo, C.; Palomo A. L. *Can. J. Chem.* **1984**, *62*, 336–340.

$CDCl_3$) δ: 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H).

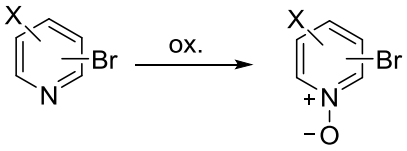
5.3.3. Synthesis of 2-cyanoalkyl pyridine 4[243]



Compound **4** was prepared according the literature provedure. All data were consistent with those previously reported. White solid, yield: 68%.

5.3.4. Synthesis of cyanoalkyl azaarene *N*-oxides

5.3.4.1. Oxidation of 2-bromo and 3-bromo-pyridines



X: H, Me, Cl, Br

General procedure A:[244] To a solution of corresponding bromo-pyridine (30 mmol) in CH_2Cl_2 (2 mL/mmol) was added *m*CPBA (1.4 equiv.) and the resulting mixture was stirred at room temperature for 3-4 days. The organic layer was removed and the crude was purified purified by flash column chromatography on silica gel.

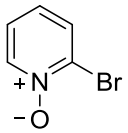
General procedure B:[245] To a solution of corresponding bromo-pyridine (10 mmol) in $CHCl_3$ (2 mL/mmol) was added m-CPBA (1.4 equiv.) and the resulting mixture was stirred overnight at 50 ^oC. The organic layer was removed and the crude was purified by flash column chromatography on silica gel.

General procedure C:[246] To an ice–cold solution of corresponding bromo-pyridine (10 mmol) in trifluoroacetic acid (12 mL) was added dropwise an aqueous solution of H_2O_2 (30%) (3.3 mL). The reaction mixture was heated to 100 ^oC overnight and then cooled to rt, poured into 50 mL of water and the precipitate filtered. The solid obtained was the starting material. The filtrate was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with 0.5 M K_2CO_3 solution (3 x 20 mL). The

[243] Kawano, T.; Kurimoto, M.; Hatanaka, M.; Ueda, I. *Chem. Pharm. Bull.* **1992**, *40*, 3067–3071.
[244] PCT Int. Appl., 2011150156, 01 Dec 2011.
[245] Brasse, M.; Cámpora, J.; Palma, P.; Álvarez, E. *Organometallics* **2008**, *27*, 4711–4723.
[246] PCT Int. Appl., 2012045124, 12 Apr 2012.

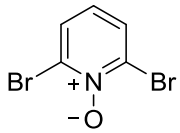
organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure.

2-bromopyridine 1-oxide



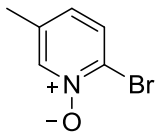
The title compound was prepared from 2-bromopyridine (30 mmol, 4.74 g) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a grey oil; yield: 24.0 mmol, 4.15 g, 80%. IR (ν/cm^{-1}): 3096, 3035, 1697, 1589, 1541, 1411, 1251, 1121, 1065, 1037, 838, 762, 674, 565, 519, 446. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 – 8.38 (m, 1H), 7.68 – 7.64 (m, 1H), 7.28 – 7.22 (m, 1H), 7.14 – 7.08 (m, 1H).

2,6-dibromopyridine 1-oxide



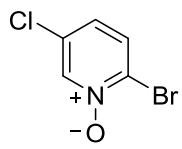
The title compound was prepared from 2,6-dibromopyridine (10 mmol, 2.37 g) according to procedure **C**. White solid; yield: 8.4 mmol, 2.10 g, 84%. m.p. 180–183 °C. IR (ν/cm^{-1}): 3090, 3034, 1696, 1554, 1403, 1268, 1125, 1066, 1032, 808, 743, 660, 567, 528, 444. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 9 Hz, 2H), 6.93 (t, *J* = 6, 9 Hz, 1H).

2-bromo-5-methylpyridine 1-oxide



The title compound was prepared from 2-bromo-5-methylpyridine (10 mmol, 1.71 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with ethyl acetate/methanol, 100:0 to 90:10) to afford the title compound as a white solid; yield: 1.70 g, 9.1 mmol, 91%. m.p. 65–69 °C. IR (ν/cm^{-1}): 3088, 3054, 3021, 1697, 1467, 1367, 1307, 1276, 1208, 1172, 1130, 1066, 1018, 951, 806, 743, 617, 573, 523, 454. ^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.26 (s, 1H), 7.53 (d, *J* = 6 Hz, 1H), 6.95 (d, *J* = 9 Hz, 1H), 2.28 (s, 3H).

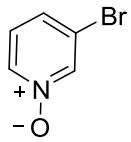
2-bromo-5-chloropyridine 1-oxide



The title compound was prepared from 2–bromo–5–chloropyridine (10 mmol, 1.91 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 80:20 to 50:50) to afford the title compound; yield: 1.45 g,

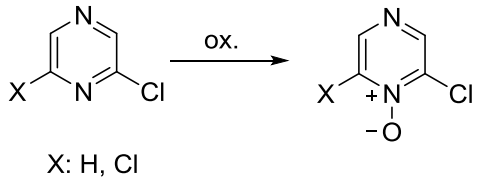
7.0 mmol, 70%. m. p. 103–106 °C. IR (ν/cm^{-1}): 3094, 3067, 3023, 170, 1573, 1475, 1353, 1297, 1251, 1229, 1110, 1067, 919, 847, 823, 746, 708, 651, 590, 568, 447. ^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.42 – 8.41 (m, 1H), 7.59 (d, *J* = 6 Hz, 1H), 7.14 – 7.11 (m, 1H).

3-bromopyridine 1-oxide



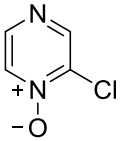
The title compound was prepared from 3-bromopyridine (10 mmol, 1.57 g) according to procedure **A**. Brown oil; yield: 8.6 mmol, 1.49 g, 86%. IR (ν/cm^{-1}): 3087, 3030, 1699, 1589, 1532, 1462, 1417, 1290, 1247, 1155, 1083, 1008, 886, 780, 664, 546, 489. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 – 8.36 (m, 1H), 8.17–8.14 (m, 1H), 7.42 – 7.39 (m, 1H), 7.18 – 7.13 (m, 1H).

5.3.4.2. Oxidation of 2-chloro-pyrazines[247]



To a stirred solution of corresponding 2-choro-pyrazine (10 mmol) in 7.5 mL of H_2SO_4 at 0 °C is gradually added $K_2S_2O_8$ (1.1 equiv.). The reaction mixture is stirred for 24 h at room temperature and carefully poured into ice water. The aqueous solution is extracted with CH_2Cl_2 and the extract is washed with saturated $NaHCO_3$ solution and brine and dried over magnesium sulfate. Evaporation of the solvent affords the desired compound which was used without further purification.

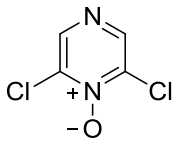
2-chloropyrazine 1-oxide



The title compound was prepared from 2-chloropyrazine (10 mmol, 1.30 g) according to the general procedure. White solid; yield: 0.62 g, 4.8 mmol, 48 %. m. p. 131–134 °C. IR (ν/cm^{-1}): 3085, 3040, 1689, 1556, 1501, 1454, 1289, 1247, 1105, 1097, 1004, 887, 780, 651, 552. ^{1}H NMR (300 MHz, $CDCl_3$) δ**:** 8.64 (m, 1H), 8.36 – 8.35 (m, 1H), 8.23 – 8.21 (m, 1H).

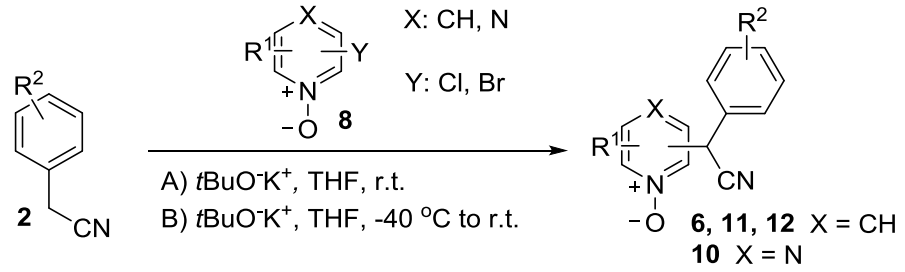
2,6-dichloropyrazine 1-oxide

[247] Mixan, C. E.; Pews, R. G. *J. Org. Chem*. **1977**, 42, 1869–1871.



The title compound was prepared from 2,6-dichloropyrazine (10 mmol, 1.48 g) according to the general procedure. White solid; yield: 4.6 mmol, 0.68 g, 46%. m. p. 120–123 °C. IR (ν/cm^{-1}): 3067, 3001, 1709, 1576, 1465, 1424, 1304, 1247, 1155, 1083, 1008, 923, 648, 567. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.55 (s, 2H).

5.3.4.3. Synthesis of adducts 6, 10, 11 and 12

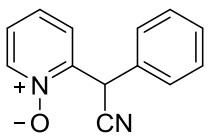


General procedure A: To a solution of potassium tert-butoxide (2 equiv., 6 mmol, 673 mg) in dry THF (10 mL) at room temperature was added 2-phenylacetonitrile (1.5 equiv., 4.5 mmol) and the resulting mixture was stirred for 45 min at the same temperature. Afterwards the corresponding pyridine *N*-oxide (1 equiv., 3 mmol) was added as a solution in dry THF (5 mL) and the mixture was stirred for an additional 3 h at the same temperature. The reaction mixture was quenched with H_2O and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford the crude product which was purified by flash column chromatography on silica gel.

General procedure B: To a solution of potassium tert-butoxide (2 equiv., 6 mmol, 673 mg) in dry THF (10 mL) at –40 °C was added 2–phenylacetonitrile (1.5 equiv.) and the resulting mixture was stirred for 45 min at the same temperature. A solution of the corresponding pyridine *N*-oxide (1 equiv., 3 mmol) in dry THF (5 mL) was added as a solution in dry THF and the mixture was stirred for an additional 3 h at –40 °C and then warmed to room temperature over 30 min. The reaction mixture was quenched with H_2O and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford the crude product which was purified by flash column chromatography on silica gel.

(**Note:** Pyridine *N*-Oxides **6**, **10, 11 and 12** decompose over time and should be stored in a refrigerator (at –30 °C they are stable for several months)).

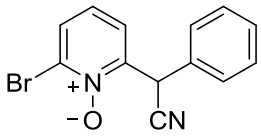
2-(cyano(phenyl)methyl)pyridine 1-oxide (6a)



The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50) to afford the title compound as a yellow solid; yield: 2.70 mmol, 567.0

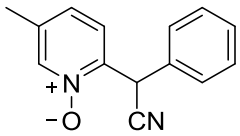
mg, 90%. m. p. 112–115 °C. IR (ν/cm^{-1}): 3110, 3052, 2894, 2246, 1489, 1438, 1246, 884, 794, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 – 8.27 (m, 1H), 7.52 – 7.28 (m, 8H), 6.11 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.2, 139.6, 132.0, 129.3, 12.9, 128.1, 125.8, 125.7, 125.4, 117.5, 36.8. UPLC–DAD–QTOF: $C_{13}H_{11}N_2O_3$ $[M+H]^+$ calcd.: 211.0871, found: 211.0863.

2–bromo-6-(cyano(phenyl)methyl)pyridine 1-oxide (6b)



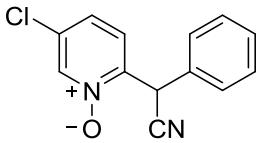
The title compound was prepared from 2,6–dibromopyridine 1–oxide (3 mmol, 0.75 g) and 2–phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50) to afford the title compound as a yellow solid; yield: 2.13 mmol, 613.4 mg, 71%. m. p. 100–104 °C. IR (ν/cm^{-1}): 3067, 3029, 2969, 2881, 2241, 1450, 1403, 1366, 1254, 1204, 783, 695, 666. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 – 7.66 (m, 1H), 7.51 – 7.36 (m, 6H), 7.12 (t, *J* = 8 Hz, 1H), 6.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.3, 134.2, 132.2, 131.0, 129.9, 129.6, 128.8, 125.7, 124.6, 117.9, 38.6. UPLC–DAD–QTOF: $C_{13}H_{10}BrN_2O$ $[M+H]^+$ calcd.: 288.9976, found: 288.9983.

2-(cyano(phenyl)methyl)-5-methylpyridine 1-oxide (6c)



The title compound was prepared from 2–bromo–5–methylpyridine 1–oxide (3 mmol, 0.56 g) and 2–phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with ethyl acetate) to afford the title compound as a white solid; yield: 470.4 mg, 2.10 mmol, 70%. m. p. 98–102 °C. IR (ν/cm^{-1}): 3126, 3050, 2902, 2245, 1611, 1491, 1451, 1401, 1278, 1199, 1177, 965, 829, 756, 730, 692, 642, 573, 525, 446. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.46 – 7.29 (m, 6H), 7.08 – 7.05 (m, 1H), 6.05 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.3, 139.3, 136.6, 132.3, 129.2, 128.8, 128.0, 127.2, 124.7, 117.7, 36.5, 18.1. UPLC–DAD–QTOF: $C_{14}H_{13}N_2O$ $[M+H]^+$ calcd.: 276.1028, found: 225.1027.

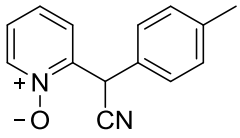
5–chloro–2–(cyano(phenyl)methyl)pyridine 1–oxide (6d)



The title compound was prepared from 2–bromo–5–chloropyridine 1–oxide (3 mmol, 0.62 g) and 2–phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure **A**. The crude material was purified by flash column

chromatography on silica gel (eluting with Hex/EtOAc, 50:50) to afford the title compound as a red oil; yield: 2.04 mmol, 497.8 mg, 68%. IR (ν/cm^{-1}): 3103, 3052, 2246, 1690, 1599, 1481, 1453, 1374, 1242, 1090, 925, 825, 730, 695, 633, 562, 524, 437. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (s, 1H), 7.50 – 7.27 (m, 7H), 6.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.0, 138.8, 133.1, 131.6, 129.4, 129.1, 128.1, 126.0, 125.2, 117.2, 36.5. UPLC–DAD–QTOF: $C_{13}H_{10}ClN_2O$ $[M+H]^+$ calcd.: 245.0482, found: 245.0478.

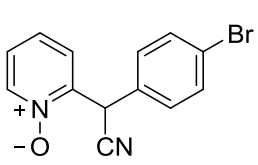
2–(cyano(p–tolyl)methyl)pyridine 1–oxide (6e)



6e

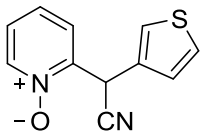
The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-(p-tolyl)acetonitrile (4.5 mmol, 0.60 mL) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50 to 0:100) to afford the title compound as a yellow solid; yield: 2.52 mmol, 564.5 mg, 84%. m. p. 96–99 ^{o}C. IR (ν/cm^{-1}): 3082, 3042, 3013, 2909, 2247, 1687, 1513, 1488, 1429, 1279, 1242, 837, 798, 765, 705. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 – 8.23 (m, 1H), 7.43 – 7.33 (m, 3H), 7.27 – 7.24 (m, 2H), 7.20 – 7.17 (m, 2H), 6.03 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.5, 139.6, 138.9, 130.0, 129.0, 128.1, 125.8, 125.6, 125.4, 117.7, 36.5, 21.1. UPLC–DAD–QTOF: $C_{14}H_{13}N_2O$ $[M+H]^+$ calcd.: 225.1028, found: 225.1046.

2-((4-bromophenyl)(cyano)methyl)pyridine 1-oxide (6f)



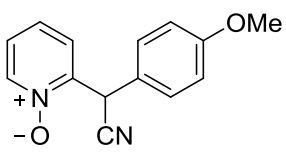
The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-(4-bromophenyl)acetonitrile (4.5 mmol, 0.87 g) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a red oil; yield: 2.64 mmol, 760.3 mg, 88%. IR (ν/cm^{-1}): 3112, 3078, 3050, 3023, 2896, 2247, 1692, 1587, 1484, 1428, 1404, 1237, 1047, 1010, 824, 782, 729, 625. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 – 8.24 (m, 1H), 7.53 – 7.50 (m, 3H), 7.39 – 7.39 (m, 2H), 7.32 – 7.29 (m, 2H), 6.05 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.9, 139.8, 132.6, 131.2, 129.9, 125.3, 123.3, 117.3, 36.6. UPLC-DAD-QTOF: $C_{13}H_{10}N_2OBr$ $[M+H]^+$ calcd.: 288.9977, found: 288.9973.

2-(cyano(thiophen-3-yl)methyl)pyridine 1-oxide (6g)



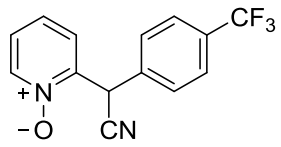
The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-(thiophen-3-yl)acetonitrile (4.5 mmol, 0.56 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a red oil; yield: 1.80 mmol, 383 mg, 60%. IR (ν/ cm^{-1}): 3114, 3083, 2890, 2240, 1711, 1604, 1483, 1427, 1272, 1237, 1142, 943, 837, 762, 621. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 – 8.28 (m, 1H), 7.51 – 7.50 (m, 1H), 7.45 – 7.42 (m, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.26 (m, 2H), 7.15 – 7.13 (m, 1H), 6.18 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.8, 139.6, 131.5, 127.6, 126.7, 126.0, 125.8, 125.2, 124.6, 117.3, 32.5. UPLC-DAD-QTOF: $C_{11}H_9N_2OS$ $[M+H]^+$ calcd.: 217.0436, found: 217.0428.

2-(cyano(4-methoxyphenyl)methyl)pyridine 1-oxide (6h)



The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-(4-methoxyphenyl)acetonitrile (4.5 mmol, 0.66 g) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a red oil; yield: 2.13 mmol, 511 mg, 71%. IR (ν/cm^{-1}): 3110, 3071, 3013, 2934, 2837, 2245, 1607, 1583, 1509, 1429, 1365, 1178, 1027, 830, 762. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 – 8.19 (m, 1H), 7.38 – 7.33 (m, 3H), 7.23 – 7.20 (m, 2H), 6.87 – 6.84 (m, 2H), 5.95 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 146.3, 139.5, 129.3, 125.8, 125.5, 125.1, 123.7, 117.7, 114.6, 55.3, 36.1. UPLC-DAD-QTOF: $C_{14}H_{13}N_2O_2$ $[M+H]^+$ calcd.: 241.0977, found: 241.0974.

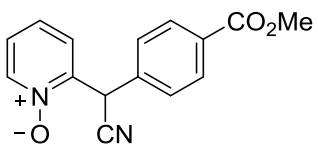
2-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide (6i)



The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-(4-(trifluoromethyl)phenyl)acetonitrile (4.5 mmol, 0.83 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a red oil; yield: 1.68 mmol, 459 mg, 56%. IR (ν/cm^{-1}): 3115, 3075, 3019, 2924, 2248, 1727, 1617, 1487, 1431, 1322, 1240, 1164, 1110, 1066, 1018, 847, 832, 763. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.26 – 8.23 (m, 1H), 7.62 (s, 4H), 7.55 – 7.52 (m, 1H), 7.32 – 7.29 (m, 2H), 6.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.3,

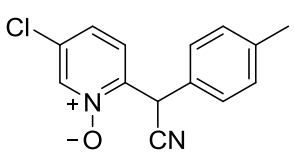
139.7, 136.0, 128.7, 126.3, 126.2, 126.2, 126.0, 125.4, 117.0, 36.8. UPLC-DAD-QTOF: $C_{14}H_{10}N_2OF_3$ $[M+H]^+$ calcd.: 279.0745, found: 279.0736.

2-(cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine 1-oxide (6j)



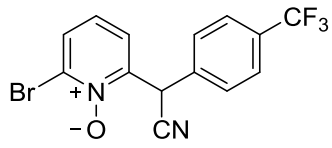
The title compound was prepared from 2-bromopyridine 1-oxide (3 mmol, 0.52 g) and methyl 4-(cyanomethyl)benzoate (4.5 mmol, 0.79 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a red oil; yield: 2.40 mmol, 643 mg, 80%. IR (ν/cm^{-1}): 3111, 3080, 3013, 2926, 2245, 1710, 1620, 1590, 1469, 1240, 1113, 1054, 840, 631. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.28 – 8.25 (m, 1H), 8.06 – 8.02 (m, 2H), 7.58 – 7.49 (m, 3H), 7.32 – 7.29 (m, 2H), 6.16 (s, 1H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3, 145.7, 139.8, 136.9, 130.9, 130.6, 128.3, 126.1, 126.0, 125.5, 117.2, 52.4, 36.9. UPLC-DAD-QTOF: $C_{15}H_{13}N_2O_3$ $[M+H]^+$ calcd.: 269.0926, found: 269.0923.

5-chloro-2-(cyano(p-tolyl)methyl)pyridine 1-oxide (6k)



The title compound was prepared from 2-bromo-5-chloropyridine 1-oxide (3 mmol, 0.62 g) and 2-(p-tolyl)acetonitrile (4.5 mmol 0.59 g) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 80:20 to 50:50) to afford the title compound as a red oil; yield: 2.49 mmol, 642.4 mg, 83%. IR (ν/cm^{-1}): 3103, 3039, 2919, 2246, 1687, 1599, 1511, 1459, 1374, 1243, 1112, 1090, 925, 836, 810, 728. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 – 8.29 (m, 1H), 7.38 – 7.19 (m, 6H), 5.94 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.0, 139.0, 138.7, 132.9, 129.9, 128.4, 127.9, 125.9, 125.1, 117.2, 36.2, 21.1. UPLC-DAD-QTOF: $C_{14}H_{12}N_2OCl$ $[M+H]^+$ calcd.: 259.0638, found: 259.0635.

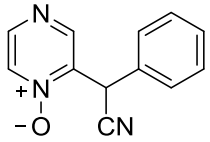
2-bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide (6l)



The title compound was prepared from 2,6–dibromopyridine 1-oxide (3 mmol, 0.75 g) and 2-(4-(trifluoromethyl)phenyl)acetonitrile (4.5 mmol, 0.83 g) according to procedure **B**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 70:30 to 0:100) to afford the title compound as a red solid; yield: 2.52 mmol, 897 mg, 84%. m. p. 92–96

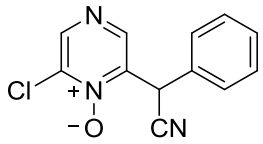
°C. IR (ν/cm^{-1}): 3086, 3043, 2984, 2893, 2248, 1691, 1618, 1576, 1556, 1462, 1378, 1322, 1240, 1163, 1113, 1066, 857, 844, 783. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 – 7.55 (m, 6H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.12 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.9, 135.7, 133.9, 133.0, 128.9, 126.4, 126.4, 125.5, 124.1, 117.0, 38.0. UPLC-DAD-QTOF: $C_{14}H_9N_2OF_3Br$ $[M+H]^+$ calcd.: 356.9850, found: 356.9843.

2-(cyano(phenyl)methyl)pyrazine 1-oxide (10a)



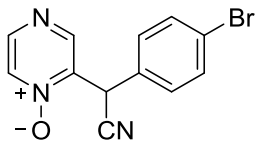
The title compound was prepared from 2-chloropyrazine 1-oxide (3 mmol, 0.52 g) and 2-phenylacetonitrile (4.5 mmol, 0.52 ml) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 80:20 to 0:100) to afford the title compound as a white solid; yield: 2.61 mmol, 551 mg, 87%. m. p. 123–127 °C. IR (ν/cm^{-1}): 3082, 3064, 2893, 2249, 1586, 1451, 1421, 1308, 1214, 899, 847, 742, 696, 508. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 8.44 (d, *J* = 4.1 Hz, 1H), 8.13 (d, *J* = 4.0 Hz, 1H), 7.49 – 7.38 (m, 6H), 5.84 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.3, 147.0, 141.8, 133.6, 130.7, 129.6, 129.4, 128.2, 116.4, 35.0. UPLC-DAD-QTOF: $C_{12}H_{10}N_3O$ $[M+H]^+$ calcd.: 212.0824, found: 212.0836.

2-chloro-6-(cyano(phenyl)methyl)pyrazine 1-oxide (10b)



The title compound was prepared from 2,6-dichloropyrazine 1-oxide (3 mmol, 0.49 g) and 2-phenylacetonitrile (4.5 mmol, 0.52 ml) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 90:10 to 70:30) to afford the title compound as a red oil; yield: 367 mg, 1.50 mmol, 50%. IR (ν/cm^{-1}): 3060, 3029, 2969, 2250, 1718, 1581, 1495, 1405, 1321, 1217, 1144, 866, 731, 697, 546. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.63 (s, 1H), 8.49 (s, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.38 (m, 3H), 5.83 (s, 1H). UPLC-DAD-QTOF: $C_{12}H_9N_3OCl$ $[M+H]^+$ calcd.: 246.0434, found: 246.0447.

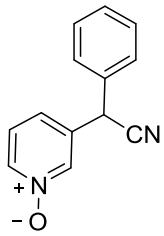
2-((4-bromophenyl)(cyano)methyl)pyrazine 1-oxide (10c)



The title compound was prepared from 2-chloropyrazine 1-oxide (3 mmol, 0.52 g) and 2-(4-bromophenyl)acetonitrile (4.5 mmol, 0.88 g) according to procedure **A**. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 70:30 to 0:100) to afford the title compound as a white solid; yield: 2.43 mmol, 702 mg, 81%. m. p. 106–109 °C. IR (ν/cm^{-1}): 3084, 3065, 2887, 2250, 1582,

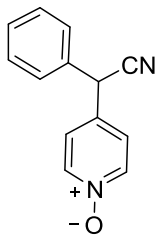
1487, 1455, 1426, 1309, 1210, 1073, 1011, 981, 899, 776, 508. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.65 (s, 1H), 8.48 (d, *J* = 4.1 Hz, 1H), 8.12 (d, *J* = 4.1 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 5.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 147.6, 146.8, 141.3, 133.7, 132.8, 129.9, 129.8, 123.8, 116.0, 34.7. UPLC-DAD-QTOF: $C_{12}H_9N_3OBr$ $[M+H]^+$ calcd.: 289.9929, found: 289.9937.

3-(cyano(phenyl)methyl)pyridine 1-oxide (11)



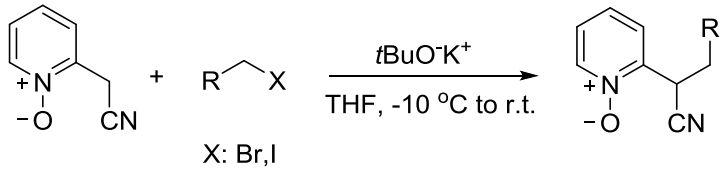
The title compound was prepared from 3-bromopyridine 1-oxide (3 mmol, 0.52 g) and 2-phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure A. The crude material was purified by flash column chromatography on silica gel (eluting with EtOAc to MeOH: CH_2Cl_2 10:90) to afford the title compound as a brown oil; yield: 2.10 mmol, 441 mg, 70%. IR (ν/ cm^{-1}): 3071, 3029, 3004, 2910, 2243, 1665, 1596, 1481, 1448, 1265, 1155, 1004, 783, 697, 679, 551, 495. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 – 8.07 (m, 2H), 7.40 – 7.20 (m, 7H), 5.08 (s, 1H). UPLC-DAD-QTOF: $C_{13}H_{11}N_2O_3$ $[M+H]^+$ calcd.: 211.0871, found: 211.0870.

4-(cyano(phenyl)methyl)pyridine 1-oxide (12)



The title compound was prepared from 4-chloropyridine 1-oxide (3 mmol, 0.39 g) and 2-phenylacetonitrile (4.5 mmol, 0.52 mL) according to procedure A. The crude material was purified by flash column chromatography on silica gel (eluting with EtOAc to MeOH: CH_2Cl_2 10:90) to afford the title compound as a brown oil; yield: 1.95 mmol, 409 mg, 65%. IR (ν/ cm^{-1}): 3105, 3061, 3033, 2241, 1656, 1606, 1475, 1446, 1246, 1170, 1002, 912, 829, 728, 695, 599. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.41 (m, 2H), 7.34 – 7.31 (m, 2H), 7.25 – 7.23 (m, 2H), 5.10 (s, 1H). UPLC–DAD–QTOF: $C_{13}H_{11}N_2O_3$ $[M+H]^+$ calcd.: 211.0871, found: 211.0877.

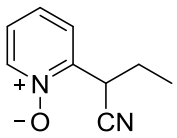
5.3.4.4. Preparation of 2-(α-cyanoalkyl)pyridine *N*-oxides 13



To a solution of potassium tert-butoxide (1.03 equiv., 3.1 mmol, 336 mg) in dry THF (10 mL) at –10 °C was added 2-(cyanomethyl)pyridine 1-oxide (1.0 equiv., 3 mmol, 402 mg) as a solution in dry THF (5 mL) and the resulting mixture was stirred for 2 h at the

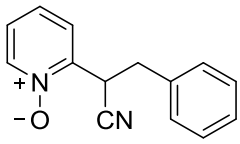
same temperature. Afterwards the corresponding alkyl halide (1.03 equiv., 3.1 mmol) was added dropwise and the mixture was stirred for an additional 16 h at room temperature. The reaction mixture was quenched with H_2O and extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford the crude product which was purified by flash column chromatography on silica gel.

2-(1-cyanopropyl)pyridine 1-oxide (13a)



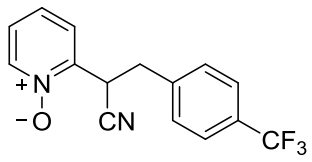
The title compound was prepared from 2-(cyanomethyl)pyridine 1-oxide (3 mmol, 0.39 g) and iodoethane (3.1 mmol, 249 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to $MeOH/CH_2Cl_2$, 10:90) to afford the title compound as a pink oil; yield: 1.05 mmol, 170 mg, 35%. IR (ν/cm^{-1}): 3117, 3080, 2972, 2935, 2878, 2242, 1646, 1489, 1431, 1228, 840, 768. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.28 – 8.26 (m, 1H), 7.62 – 7.59 (m, 1H), 7.36 – 7.28 (m, 2H), 4.77 (dd, *J* = 8.4, 4.7 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.01 – 1.87 (m, 1H), 1.16 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.9, 139.7, 125.9, 125.6, 125.4, 125.0, 118.6, 33.6, 23.8, 11.3. UPLC-DAD-QTOF: $C_9H_{11}N_2O$ $[M+H]^+$ calcd.: 163.0871, found: 163.0875.

2-(1-cyano-2-phenylethyl)pyridine 1-oxide (13b)



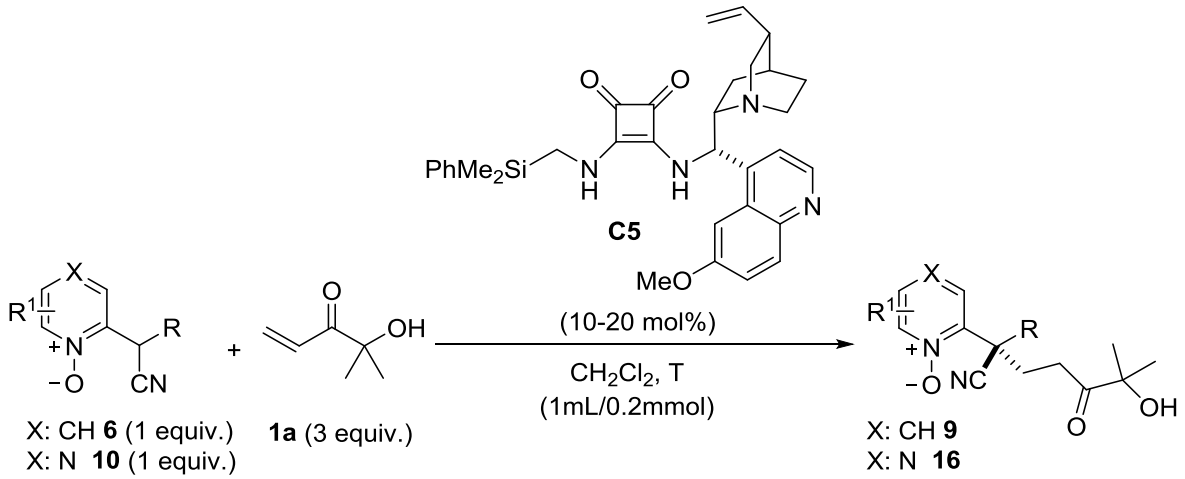
The title compound was prepared from from 2-(cyanomethyl)pyridine 1-oxide (3 mmol, 0.39 g) and benzyl bromide (3.1 mmol, 369 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a white solid; yield: 2.10 mmol, 470 mg, 70%. m. p. 100–103 °C. IR (ν/cm^{-1}): 3107, 3085, 2997, 2931, 2912, 2245, 1485, 1428, 1270, 1231, 1151, 842, 771, 751, 706, 580, 557, 540, 486, 410. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.33 – 8.30 (m, 1H), 7.39 – 7.21 (m, 8H), 5.02 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.46 – 3.40 (m, 2H), 3.21 – 3.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.2, 139.6, 135.7, 129.3, 128.6, 127.6, 125.6, 125.5, 118.4, 35.6, 34.9. UPLC-DAD-QTOF: $C_{14}H_{13}N_2O$ $[M+H]^+$ calcd.: 225.1028, found: 225.1031.

2-(1-cyano-2-(4-(trifluoromethyl)phenyl)ethyl)pyridine 1-oxide (13c)



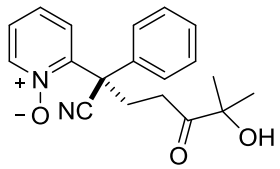
The title compound was prepared from 2-(cyanomethyl)pyridine 1-oxide (3 mmol, 0.39 g) and 4-(trifluoromethyl)benzyl bromide (3.1 mmol, 369 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc, 50:50 to 0:100) to afford the title compound as a yellow solid; yield: 2.22 mmol, 648 mg, 74%. m. p. 139–141 °C. IR (ν/ cm^{-1}): 3110, 3071, 3057, 3027, 2927, 2243, 1617, 1488, 1442, 1328, 1254, 1159, 1107, 1067, 840, 767, 597. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 – 8.35 (m, 1H), 7.63 – 7.60 (m, 2H), 7.47 – 7.28 (m, 5H), 5.04 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.56 – 3.50 (m, 2H), 3.30–3.23 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.7, 139.9, 139.7, 129.7, 125.8, 125.8, 125.6, 125.6, 125.3, 122.2, 118.0, 35.3, 34.7. UPLC-DAD-QTOF: $C_{15}H_{12}N_2OF_3$ $[M+H]^+$ calcd.: 293.0902, found: 293.0907.

5.3.5. General procedure for the BB-catalized addition of 6 and 10 to enone 1a



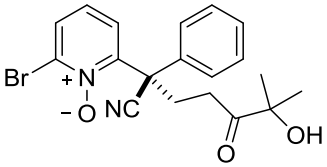
To a solution of the 2-cyanoalkyl pyridine *N*-oxide **6** or 2-cyanoalkyl pirazine *N*-oxide **10** (1 equiv., 0.2 mmol) in dichlorometane (1 mL) the enone **1a** (3.0 equiv., 0.6 mmol) and the catalyst were added at the corresponding temperature (see below). The resulting mixture was stirred until consumption of the pyridine *N*-oxide (monitored by ^{1}H-NMR). Afterwards, the reaction mixture was washed with 0.1 M aqueous solution of HCl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residues were purified by flash column chromatography on silica gel to afford the expected adducts.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9a)



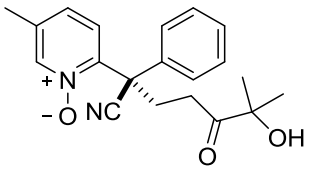
The title compound **9a** was prepared from 2-(cyano(phenyl)methyl)pyridine 1-oxide **6a** (0.2 mmol, 42.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) according to the general procedure at r.t. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white solid; yield: 0.16 mmol, 53.1 mg, 82%. m. p. 188–191 ^{o}C. $[\alpha]_D^{25}$= +102.9 (*c* = 1.00, 92% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3333, 3119, 3059, 2973, 2926, 2236, 1711, 1599, 1428, 1261, 1191, 760, 733, 698, 569. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 1.6 Hz, 1H), 7.56 (dd, *J* = 2.3 Hz, 1H), 7.39 – 7.27 (m, 6H), 3.60 (s, 1H), 3.03 – 2.82 (m, 2H), 2.65 – 2.47 (m, 2H), 1.29 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.1, 147.6, 140.7, 135.1, 129.0, 128.5, 126.6, 126.0, 125.3, 124.3, 118.1, 48.4, 31.7, 31.6, 26.6, 26.5. UPLC-DAD-QTOF: $C_{19}H_{21}N_2O_3$ $[M+H]^+$ calcd.: 325.1552, found: 325.1538.

(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9b)



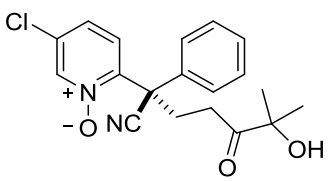
The title compound **9b** was prepared from 2-bromo-6-(cyano(phenyl)methyl)pyridine 1-oxide **6b** (0.2 mmol, 57.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) according to the general procedure at 0 ^{o}C. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam; yield: 0.17 mmol, 66.7 mg, 83%. $[\alpha]_D^{25}$= +61.1 (*c* = 1.00, 94% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3444, 3026, 2969, 2935, 2238, 1716, 1463, 1376, 1216, 1033, 911, 759, 728, 697. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (dd, *J* = 1.8 Hz, 1H), 7.53 (dd, J = 1.9 Hz, 1H), 7.55 – 7.29 (m, 5H), 7.19 (t, *J* = 8.1 Hz, 1H), 3.38 (s, 1H), 3.04 – 2.81 (m, 2H), 2.66 – 2.44 (m, 2H), 1.32 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.0, 149.1, 134.7, 130.9, 129.1, 128.6, 126.7, 124.5, 123.1, 117.9, 49.3, 32.0, 31.6, 26.7, 26.5. UPLC-DAD-QTOF: $C_{19}H_{20}N_2O_3Br$ $[M+H]^+$ calcd.: 403.0657, found: 403.0651.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)-5-methylpyridine 1-oxide (9c)



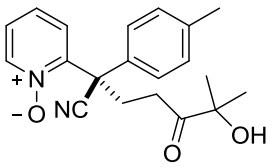
The title compound **9c** was prepared from 2-(cyano(phenyl)methyl)-5-methylpyridine 1-oxide **6c** (0.2 mmol, 45 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) according to the general procedure at 40 ^{o}C. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam. Yield: 45.6 mg, 0.13 mmol, 66%. $[\alpha]_D^{25}$= +65.2 (*c* = 1.00, 90% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3327, 3061, 3027, 2969, 2929, 2236, 1714, 1448, 1374, 1274, 1197, 1019, 962, 730, 697, 575. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.45 – 7.15 (m, 7H), 3.57 (s, 1H), 3.02 – 3.82 (m, 2H), 2.64 – 2.46 (m, 2H), 2.30 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.2, 144.7, 140.5, 136.9, 135.5, 129.0, 128.4, 126.7, 126.5, 123.6, 118.3, 48.2, 31.8, 31.6, 26.7, 26.5, 18.1. UPLC-DAD-QTOF: $C_{20}H_{23}N_2O_3$ $[M+H]^+$ calcd.: 339.1709, found: 339.1712.

(R)-5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9d)



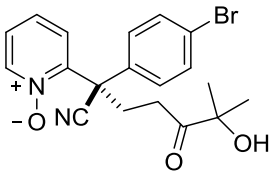
The title compound **9d** was prepared from 5-chloro-2-(cyano(phenyl)methyl)pyridine 1-oxide **6d** (0.2 mmol, 49 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 ^{o}C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70:30 to 0:100) to give the title compound as a white foam. Yield: 0.14 mmol, 51.5 mg, 72%. $[\alpha]_D^{25}$= +66.8 (*c* = 1.00, 89% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3398, 3110, 3056, 2970, 2238, 1710, 1484, 1449, 1375, 1260, 1187, 1095, 1018, 947, 805, 756, 697, 579, 523. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 (m, 1H), 7.52 – 7.49 (m, 1H), 7.37 – 7.28 (m, 6H), 3.45 (s, 1H), 3.02 – 2.79 (m, 2H), 2.63 – 2.45 (m, 2H), 1.31 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.0, 146.5, 139.9, 134.7, 133.6, 129.1, 128.7, 126.5, 125.5, 124.2, 117.7, 48.1, 31.7, 31.5, 26.7, 26.5. UPLC-DAD-QTOF: $C_{19}H_{20}N_2O_3Cl$ $[M+H]^+$ calcd.: 359.1162, found: 359.1165.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9e)



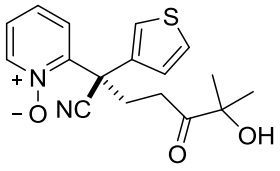
The title compound **9e** was prepared from 2-(cyano(p-tolyl)methyl)pyridine 1-oxide **6e** (0.2 mmol, 45 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 40 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam. . Yield: 0.16 mmol, 53.4 mg, 79%. $[\alpha]_D^{25}$= +52.6 (*c* = 1.00, 90% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3333, 3119, 2974, 2929, 2870, 2237, 1709, 1427, 1359, 1248, 1190, 956, 765, 730, 520. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18-8.16 (m, 1H), 7.54 – 7.51 (m, 1H), 7.37 – 7.24 (m, 4H), 7.16 – 7.13 (m, 2H), 3.51 (s, 1H), 3.04 – 2.85 (m, 2H), 2.66 – 2.47 (m, 2H), 2.31 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.1, 147.9, 140.8, 138.4, 132.0, 129.8, 126.6, 125.9, 125.2, 124.3, 118.3, 48.2, 31.7, 31.5 26.7, 26.5, 21.1. UPLC-DAD-QTOF: $C_{20}H_{23}N_2O_3$ $[M+H]^+$ calcd.: 339.1709, found: 339.1712.

(R)-2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyridine 1-oxide (9f)



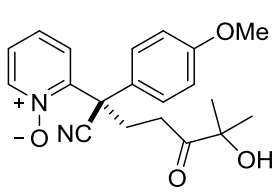
The title compound **9f** was prepared from 2-((4-bromophenyl)(cyano)methyl)pyridine 1-oxide **6f** (0.2 mmol, 57.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a yellow oil. Yield: 0.18 mmol, 72.4 mg, 90%. $[\alpha]_D^{25}$= +58.4 (*c* = 1.00, 90% *ee*, CH_2Cl_2). IR (ν/ cm^{-1}): 3343, 3118, 3058, 2974, 2930, 2237, 1712, 1586, 1487, 1428, 1262, 1192, 1076, 1009, 836, 766, 735, 518. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 – 8.18 (m, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.34 (m, 2H), 7.30 – 7.25 (m, 2H), 3.43 (s, 1H), 3.06 – 2.84 (m, 2H), 2.67 – 2.50 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.9, 147.2, 140.8, 134.4, 132.2, 128.3, 126.3, 125.4, 124.1, 122.7, 117.8, 31.8, 31.5, 26.7, 26.6. UPLC-DAD-QTOF: $C_{19}H_{20}BrN_2O_3$ $[M+H]^+$ calcd.: 403.0657, found: 403.0659.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(thiophen-3-yl)hexyl)pyridine 1-oxide (9g)



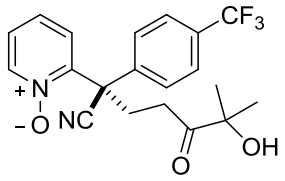
The title compound **9g** was prepared from 2-(cyano(thiophen-3-yl)methyl)pyridine 1-oxide **6g** (0.2 mmol, 43.2 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 ^{o}C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam. Yield: 0.14 mmol, 46.2 mg, 70%. $[\alpha]_D^{25}$= +13.4 (*c* = 1.00, 94% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3382, 3102, 3040, 2235, 1710, 1570, 1421, 1348, 1271, 1187, 1023, 854, 775, 532. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.24 – 8.22 (m, 1H), 7.48 – 7.46 (m, 1H), 7.41 – 7.38 (m, 1H), 7.33 – 7.19 (m, 3H), 7.06 (dd, *J* = 1.5, 1.5 Hz, 1H), 3.48 (s, 1H), 3.21 – 2.97 (m, 2H), 2.65 – 2.53 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.0, 147.4, 140.8, 135.5, 127.6, 126.3, 125.9, 125.5, 124.7, 124.6, 118.4, 45.7, 32.0, 29.9, 26.8, 26.6. UPLC-DAD-QTOF: $C_{17}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 331.1116, found: 331.1119.

(R)-2-(1-cyano-5-hydroxy-1-(4-methoxyphenyl)-5-methyl-4-oxohexyl)pyridine 1-oxide (9h)



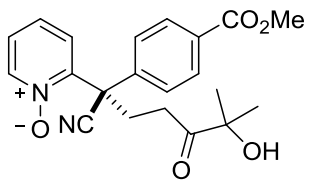
The title compound **9h** was prepared from 2-(cyano(4-methoxyphenyl)methyl)pyridine 1-oxide **6h** (0.2 mmol, 48 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at room temperature according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam. Yield: 0.14 mmol, 49.6 mg, 71%. $[\alpha]_D^{25}$= +69.1 (*c* = 1.00, 89% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3331, 3118, 3058, 2961, 2928, 2236, 1711, 1607, 1509, 1427, 1250, 1182, 1029, 829, 764, 732, 535. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 – 8.17 (m, 1H), 7.52 – 7.48 (m, 1H), 7.36 – 7.27 (m, 4H), 6.89 – 6.86 (m, 2H), 3.78 (s, 3H), 3.46 (s, 1H), 3.04 – 2.88 (m, 2H), 2.67 – 2.48 (m, 2H), 1.34 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.1, 159.6, 148.0, 140.8, 128.1, 126.7, 125.9, 125.3, 124.2, 118.4, 114.5, 55.4, 47.9, 31.7, 31.3, 26.7, 26.6. UPLC-DAD-QTOF: $C_{20}H_{23}N_2O_4$ $[M+H]^+$ calcd.: 355.1658, found: 355.1666.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4-(trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9i)



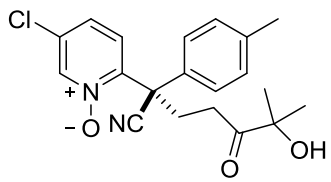
The title compound **9i** was prepared from 2-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide **6i** (0.2 mmol, 55.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white foam. Yield: 0.15 mmol, 58.8 mg, 75%. $[\alpha]_D^{25}$= +107.6 (*c* = 1.00, 92% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3292, 2976, 2930, 2233, 1701, 1618, 1430, 1324, 1167, 1117, 1068, 1016, 917, 838, 773, 721, 570. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 – 8.16 (m, 1H), 7.73 – 7.34 (m, 7H), 3.34 (s, 1H), 3.04 – 2.84 (m, 2H), 2.68 – 2.47 (m, 2H), 1.32 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 146.9, 140.8, 139.5, 127.0, 126.5, 126.1 126.0, 125.5, 124.2, 117.6, 48.4, 32.0, 31.5 26.7 26.6. UPLC-DAD-QTOF: $C_{20}H_{20}N_2O_3F_3$ $[M+H]^+$ calcd.: 393.1426, found: 393.1425.

(R)-2-(1-cyano-5-hydroxy-1-(4-(methoxycarbonyl)phenyl)-5-methyl-4-oxohexyl)pyridine 1-oxide (9j)



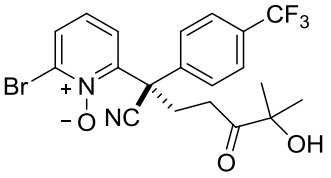
The title compound **9j** was prepared from 2-(cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine 1-oxide **6j** (0.2 mmol, 53.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a yellow foam. Yield: 0.16 mmol, 62.7 mg, 82%. $[\alpha]_D^{25}$= +111.2 (*c* = 1.00, 94% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3469, 3124, 3073, 2923, 2250, 1715, 1684, 1569, 1425, 1334, 1179, 1112, 1054, 990, 771, 569. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (dd, *J* = 1.6, 1.5 Hz, 1H), 8.02 – 7.97 (m, 2H), 7.67 (dd, *J* = 2.2, 2.1 Hz, 1H), 7.45 – 7.33 (m, 4H), 3.88 (s, 3H), 3.43 (s, 1H), 3.04 – 2.82 (m, 2H), 2.66 – 2.44 (m, 2H), 1.30 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.8, 166.3, 147.1, 140.7, 140.4, 130.2, 126.6, 126.3, 125.5, 124.2, 117.6, 32.0, 31.5, 26.7, 26.6. UPLC-DAD-QTOF: $C_{21}H_{23}N_2O_5$ $[M+H]^+$ calcd.: 383.1607, found: 383.1616.

(R)-5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9k)



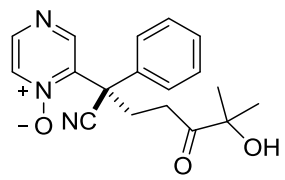
The title compound **9k** was prepared from 5-chloro-2-(cyano(p-tolyl)methyl)pyridine 1-oxide **6k** (0.2 mmol, 51.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at room temperature according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80:20 to 0:100) to give the title compound as a yellow foam. Yield: 64.7 mg, 0.17 mmol, 87%. $[\alpha]_D^{25}$= +78.2 (*c* = 1.00, 87% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3378, 3108, 3050, 2971, 2924, 2235, 1710, 1595, 1483, 1374, 1259, 1188, 1095, 937, 810, 575, 524. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 1.9 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.34 – 7.31 (m, 1H), 7.26 – 7.23 (m, 2H), 7.19 – 7.15 (m, 2H), 3.39 (s, 1H), 3.03 – 2.82 (m, 2H), 2.63 – 2.46 (m, 2H), 2.32 (s,3H), 1.33 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.0, 146.7, 140.0, 138.7, 133.6, 131.5, 129.9, 126.6, 125.4, 124.2, 117.9, 48.0, 31.6, 31.4, 26.7, 26.6, 21.6. UPLC-DAD-QTOF: $C_{20}H_{22}N_2O_3Cl$ $[M+H]^+$ calcd.: 373.1319, found: 373.1323.

(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4-(trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9l)



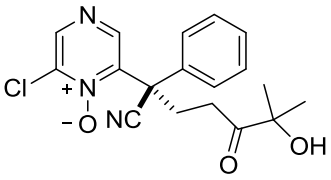
The title compound **9l** was prepared from 2-bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide **6l** (0.2 mmol, 71.2 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at 0 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70:30 to 0:100) to give the title compound as a brown foam. Yield: 79.9 mg, 0.17 mmol, 85%. $[\alpha]_D^{25}$= +69.6 (*c* = 0.5, 94% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3444, 3105, 2978, 2235, 1714, 1618, 1596, 1466, 1380, 1326, 1167, 1120, 1070, 1016, 960, 843, 773, 699. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 – 7.48 (m, 6H), 7.29 – 7.24 (m, 1H), 3.27 (s, 1H), 3.04 – 2.79 (m, 2H), 2.67 – 2.44 (m, 2H), 1.31 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 148.3, 139.1, 134.8, 131.3, 126.9, 126.1, 124.8, 123.0, 117.4, 49.2, 32.4, 31.5, 26.7, 26.6. UPLC-DAD-QTOF: $C_{20}H_{19}N_2O_3BrF_3$ $[M+H]^+$ calcd.: 471.0531, found: 471.0526.

(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16a)



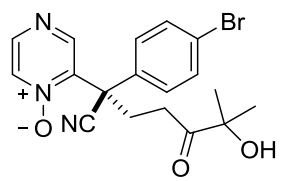
The title compound **16a** was prepared from 2-(cyano(phenyl)methyl)pyrazine 1-oxide **10a** (0.2 mmol, 53.6 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at –10 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70:30 to 0:100) to give the title compound as a white solid. m. p. 154-157 °C. Yield: 53.3 mg, 0.16 mmol, 82%. $[\alpha]_D^{25}$= +65.2 (*c* = 0.5, 85% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3409, 3102, 3059, 2977, 2239, 1713, 1587, 1449, 1407, 1325, 1186, 945, 836, 734, 698, 538. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.73 (s, 1H), 8.48 (d, *J* = 4.1 Hz, 1H), 8.06 (d, *J* = 4.0 Hz, 1H), 7.40 – 7.33 (m, 5H), 3.40 (s, 1H), 3.04 – 2.88 (m, 2H), 2.74 – 2.48 (m, 2H), 1.32 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.6, 147.5, 145.7, 143.5, 134.6, 133.7, 129.3, 129.0, 126.6, 117.2, 47.1, 31.5, 30.8, 26.7, 26.6. UPLC-DAD-QTOF: $C_{18}H_{20}N_3O_3$ $[M+H]^+$ calcd.: 326.1505, found: 326.1500.

(R)-2-chloro-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16b)



The title compound **16b** was prepared from 2-chloro-6-(cyano(phenyl)methyl)pyrazine 1-oxide **10b** (0.2 mmol, 49.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at –10 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70:30 to 0:100) to give the title compound as a yellow solid. m. p. 188–191 °C. Yield: 0.16 mmol, 56.0 mg, 78%. $[\alpha]_D^{25}$= +72.1 (*c* = 0.5, 84% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3357, 3055, 2980, 2951, 2241, 1717, 1585, 1403, 1189, 1164, 974, 909, 867, 738, 695, 576, 503. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 8.63 (s, 1H), 7.43 – 7.34 (m, 5H), 3.27 (s, 1H), 3.05 – 2.88 (m, 2H), 2.76 – 2.67 (m, 1H), 2.58 – 2.47 (m, 1H), 1.34 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.5, 147.2, 144.6, 142.8, 140.5, 133.3, 129.5, 129.2, 126.7, 116.9, 47.6, 31.5, 31.1, 26.8, 26.6. UPLC-DAD-QTOF: $C_{18}H_{19}N_3O_3Cl$ $[M+H]^+$ calcd.: 360.1115, found: 360.1109.

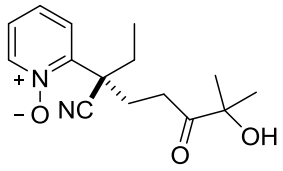
(R)-2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyrazine 1-oxide (16c)



The title compound **16c** was prepared from 2-((4-bromophenyl)(cyano)methyl)pyrazine 1-oxide **10c** (0.2 mmol, 58.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6

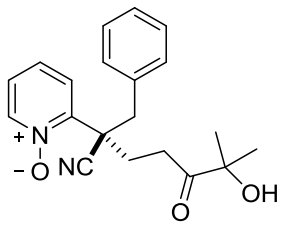
mmol, 68.4 mg) at –30 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to 0/100) to give the title compound as a white solid. Yield: 0.11 mmol, 43.6 mg, 54%. m. p. 152–155 °C. $[\alpha]_D^{25}$= +90.6 (*c* = 0.3, 86% ee, CH_2Cl_2). IR (ν/cm^{-1}): 3361, 3097, 2974, 2952, 2907, 2242, 1715, 1583, 1463, 1405, 1325, 1186, 1074, 1005, 840, 540, 523. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 8.52 (d, *J* = 4.0 Hz, 1H), 8.07 (d, *J* = 4.0 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.30-7.27 (m, 2H), 3.34 (s, 1H), 3.05 – 2.87 (m, 2H), 2.74 – 2.49 (m, 2H), 1.34 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.4, 147.7, 145.6, 143.0, 134.6, 133.0, 132.4, 128.3, 123.2, 116.8, 46.7, 31.5, 30.9, 26.7, 26.7. UPLC-DAD-QTOF: $C_{18}H_{19}N_3O_3Br$ $[M+H]^+$ calcd.: 404.0610, found: 404.0609.

(S)-2-(3-cyano-7-hydroxy-7-methyl-6-oxooctan-3-yl)pyridine 1-oxide (17a)



The title compound **17a** was prepared from 2-(1-cyanopropyl)pyridine 1-oxide **13a** (0.2 mmol, 32.4 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.8 mmol, 91.2 mg) at 40 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to MeOH/CH_2Cl_2 10/90) to give the title compound as a pink oil. An inseparable mixture of 5m and 4m was obtained after column chromatography. The NMR spectra, ^{1}H and ^{13}C, were recorded from the racemic reaction. IR (ν/cm^{-1}): 3406, 3077, 2972, 2934, 2878, 2241, 1719, 1608, 1489, 1431, 1171, 1092, 1049, 941, 906, 841, 768, 724, 643, 570, 549. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 – 8.20 (m, 1H), 7.68 – 7.64 (m, 1H), 7.35 – 7.30 (m, 2H), 3.52 (s, 1H), 3.15 – 3.05 (m, 2H), 2.87 – 2.69 (m, 2H), 2.57 – 2.33 (m, 2H), 2.19 – 2.07 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 145.4, 141.6, 126.8, 125.8, 125.7, 120.8, 49.1, 32.2, 28.6, 27.9, 26.8, 26.7, 10.2. UPLC-DAD-QTOF: $C_{15}H_{21}N_2O_3$ $[M+H]^+$ calcd.: 277.1552, found: 277.1557.

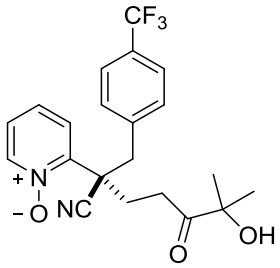
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-phenylheptan-2-yl)pyridine 1-oxide (17b)



The title compound **17b** was prepared from 2-(1-cyano-2-phenylethyl)pyridine 1-oxide **13b** (0.2 mmol, 44.8 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.8 mmol, 91.2 mg) at 35 °C according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to 0/100) to give the title compound as a white foam. An inseparable mixture of **17b** and **13b** was obtained after column chromatography.

The NMR spectra, ^{1}H and ^{13}C, were recorded from the racemic reaction. IR (ν/cm^{-1}): 3318, 2971, 2925, 2853, 2236, 1711, 1487, 1425, 1362, 1243, 1170, 962, 763, 733, 703, 569, 545, 494. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29 – 8.23 (m, 1H),7.31 – 7.23 (m, 2H), 7.18 – 7.08 (m, 6H), 4.19 (d, *J* = 13.3 Hz, 1H), 3.61 (s, 1H), 3.35 – 3.31 (m, 2H), 2.86 – 2.74 (m, 1H), 2.57 – 2.42 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.6, 144.8, 141.4, 135.0, 129.7, 128.4, 127.6, 127.2, 125.8, 125.6, 120.6, 50.3, 39.6, 32.2, 29.8, 28.8, 26.8, 26.7. UPLC-DAD-QTOF: $C_{20}H_{23}N_2O_3$ $[M+H]^+$ calcd.: 339.1709, found: 339.1713.

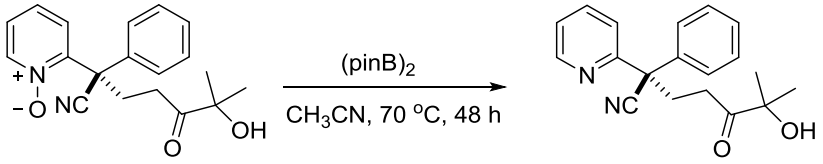
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-(4-(trifluoromethyl)phenyl)heptan-2-yl)pyridine 1-oxide (17c)



The title compound **17c** was prepared from 2-(1-cyano-2-(4-(trifluoromethyl)phenyl)ethyl)pyridine 1-oxide **13c** (0.2 mmol, 58.4 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.8 mmol, 91.2 mg) at rt according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to 0/100) to give the title compound as a white solid. An inseparable mixture of **17c** and **13c** was obtained after column chromatography. The NMR spectra, ^{1}H and ^{13}C, were recorded from the racemic reaction. m. p. 162–164 ^{o}C. IR (ν/cm^{-1}): 3246, 2979, 2933, 2233, 1707, 1617, 1492, 1430, 1321, 1240, 1170, 1107, 1065, 1019, 965, 848, 772, 687, 661, 570, 487. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 6.3 Hz, 1H), 7.44 – 7.41 (m, 2H), 7.35 – 7.24 (m, 2H), 7.18 – 7.12 (m, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 3.58 (s, 1H), 3.36 – 3.32 (m, 2H), 2.86 – 2.74 (m, 1H), 2.56 – 2.43 (m, 2H), 1.33 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.5, 144.2, 141.5, 139.2, 130.0, 129.7, 127.3, 126.1, 125.8, 125.4, 125.3, 122.2, 120.3, 50.2, 39.3, 32.2, 28.6, 26.7. UPLC-DAD-QTOF: $C_{21}H_{22}F_3N_2O_3$ $[M+H]^+$ calcd.: 407.1583, found: 407.1571.

5.3.6. Elaboration of adduct 9a

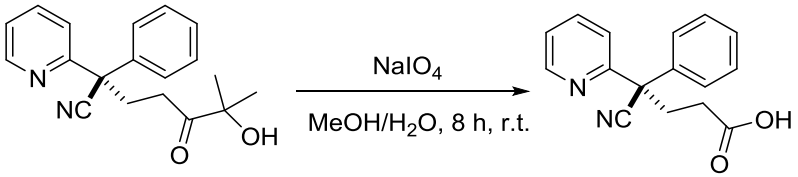
5.3.6.1. Reduction of 9a to the parent pyridine 18[248]



9a **18**

A solution of adduct **9a** (1 equiv., 1 mmol, 324 mg) in acetonitrile (10 mL) was stirred in an oven-dried reaction vial, bis(pinacolato)diboron ($(pinB)_2$) (3 equiv., 3 mmol, 761.82 mg) was added and the mixture was stirred at 70 °C for 24 h. Afterwards 3 equiv. more of $(pinB)_2$ were added and the reaction stirred at 70 °C for additional 24 h. Then, ethylendiamine (120 equiv, 120 mmol, 8 mL) was added to the mixture, and the stirring was continued for 1 h at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80/20 to 50/50) to give the desired compound as a colourless oil. Yield: 228 mg, 0.74 mmol, 74%. $[\alpha]_D^{25}$= +21.0 (*c* = 1.00, 92% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3408, 3001, 2969, 2945, 2236, 1709, 1588, 1430, 1365, 1216, 1139, 1012, 971, 789, 749, 694, 622, 542. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.62 – 8.59 (m, 1H), 7.69 – 7.63 (m, 1H), 7.49 – 7.42 (m, 3H), 7.37 – 7.21 (m, 4H), 3.61 (s, 1H), 3.01 – 2.96 (m, 1H), 2.84 – 2.58 (m, 3H), 1.31 (S, 3H), 1.28 (S, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.1, 157.5, 149.1, 138.6, 137.5, 129.1, 128.3, 126.5, 123.1, 122.4, 121.6, 53.5, 33.2, 32.3, 26.5, 26.5. UPLC-DAD-QTOF: $C_{19}H_{21}N_2O_2$ $[M+H]^+$ calcd.: 309.1606, found: 309.1606.

5.3.6.2. Synthesis of carboxylic acid 19

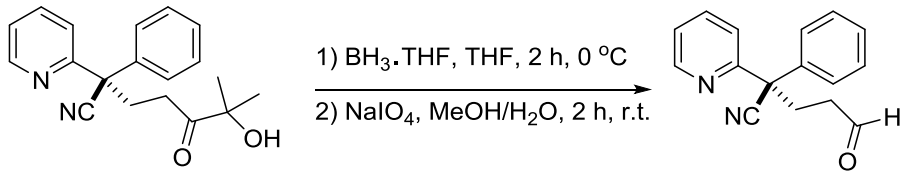


18 **19**

[248] Adapted from Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K.; *J. Org. Chem.* **2011**, 76, 7842–7848.

To a solution of **18** (1 equiv., 0.75 mmol, 231 mg) in MeOH (3 mL) a water (1.5 mL) solution of $NaIO_4$ (5 equiv., 3.75 mmol, 800 mg) was added at 0 °C. After stirring the reaction mixture at room temperature for 8 h, MeOH was evaporated under reduce pressure. Water (10 mL) was added to the crude product and the resulting mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, affording essentially pure product **19**. White solid; Yield: 0.72 mmol, 191 mg, 95%. m. p. 100–104 °C. IR (ν/cm^{-1}): 3445, 3034, 2969, 2237, 1713, 1588, 1535, 1446, 1345, 1216, 1143, 1054, 966, 860, 789, 749, 701, 634. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.20 (s, 1h, broad signal), 8.67 – 8.65 (m, 1H), 7.52 – 7.49 (m, 3H), 7.40 – 7.24 (m, 4H), 3.13 – 3.03 (m, 1H), 2.87 – 2.77 (m, 1H), 2.65 – 2.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.0, 157.3, 149.4, 138.4, 137.6, 129.1, 128.4, 126.5, 123.2, 122.6, 121.3, 55.3, 33.8, 30.7. UPLC-DAD-QTOF: $C_{16}H_{15}N_2O_2$ $[M+H]^+$ calcd.: 267.1134, found: 267.1131.

5.3.6.3. Synthesis of aldehyde 20

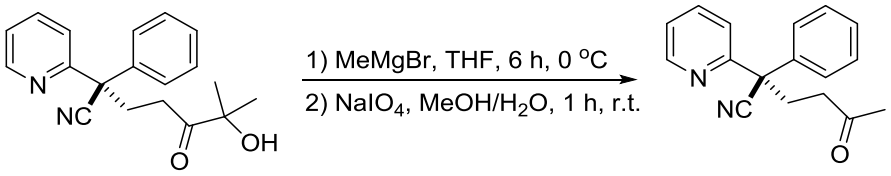


18 **20**

To a solution of **18** (1 equiv., 0.3 mmol, 92.4 mg) in dry THF (2 mL) at 0 °C BH_3·THF complex (1 M in THF, 2 equiv., 0.6 mmol, 0.6 mL) was added. The resulting solution was stirred at the same temperature for 2 h (the reaction was monitored by TLC (Hex/EtOAc, 50:50)) and after completion, MeOH (1 mL) was added and the resulting mixture stirred at room temperature for 30 min. The solvents were evaporated under reduced pressure and the residue thus obtained was disolved in MeOH (2 mL) and a suspension of $NaIO_4$ (320 mg, 1.5 mmol, 5 equiv) in water (1 mL) was added at room temperature. The reaction mixture was stirred at the same temperature for 2 h and solvents were evaporated under reduced pressure. Water (6 mL) was added to the crude product and the resulting mixture was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (Hex/EtOAc, 80:20) affording title product **20** as a colorless oil. Yield: 0.24 mmol, 60 mg, 80%. $[\alpha]_D^{25}$= +62.8 (*c* = 1.00, 92% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3059, 2969, 2831, 2726, 2238, 1718, 1586, 1493, 1448, 1430, 1363, 1216, 1031, 993, 963,

912, 746, 697, 538. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.74 (s, 1H), 7.70 – 7.64 (m, 1H), 7.51 – 7.21 (m, 7H), 3.10 – 2.97 (m, 1H), 2.85 – 2.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.1, 157.4, 149.5, 138.6, 137.5, 129.1, 128.4, 126.5, 123.1, 122.6, 121.5, 53.4, 40.6, 31.5. UPLC-DAD-QTOF: $C_{16}H_{15}N_2O$ $[M+H]^+$ calcd.: 251.1184, found: 251.1182.

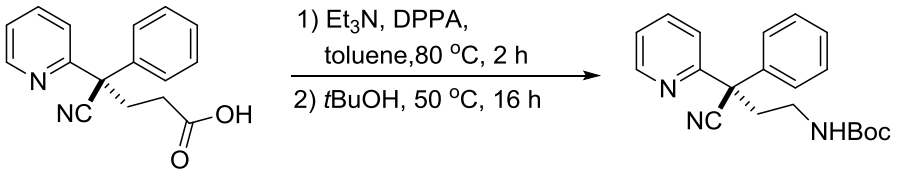
5.3.6.4. Synthesis of ketone 21



18 **21**

MeMgBr (3 M in Et_2O, 5 equiv., 0.5 mmol) was added to a solution of α-hydroxy ketone **18** (1 equiv., 0.3 mmol, 92.4 mg) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at the same temperature until the reaction was finished (monitored by TLC). Then a saturated aqueous solution of NH_4Cl (9 mL) was added at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). The solvents were evaporated under reduced pressure and the residue thus obtained was disolved in MeOH (1.8 mL). A suspension of $NaIO_4$ (5 equiv., 1.5 mmol, 321 mg) in water (0.9 mL) was added to the solution at room temperature and the resulting mixture was stirred at the same temperature for 1 h. Then solvents were evaporated under reduced pressure, water (9 mL) was added to the residue and the resulting mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, affording essentially pure product **21** as a colorless oil. Yield: 0.27 mmol, 71.3 mg, 90%. $[\alpha]_D^{25}$= +30.7 (*c* = 0.5, 92% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3080, 3004, 2918, 2849, 2236, 1715, 1573, 1466, 1433, 1369, 1165, 993, 765, 749, 697, 541. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.63 – 8.60 (m, 1H), 7.69 – 7.63 (m, 1H), 7.50 – 7.42 (m, 3H), 7.38 – 7.19 (m, 4H), 3.01 – 2.89 (m, 1H), 2.78 – 2.69 (m, 1H), 2.66 – 2.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.8, 157.2, 149.5, 138.8, 137.4, 129.1, 128.3, 126.6, 123.0, 122.3, 121.7, 53.5, 40.0, 32.9, 30.1. UPLC-DAD-QTOF: $C_{17}H_{17}N_2O$ $[M+H]^+$ calcd.: 265.1341, found: 265.1342.

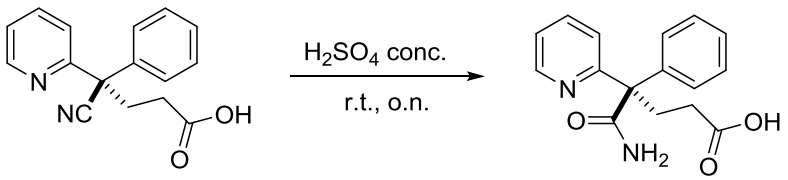
5.3.6.5. Synthesis of Boc-amine 22



19 **22**

To a solution of acid **19** (0.4 mmol, 106.5 mg) in toluene (1 mL) were added Et_3N (0.40 mmol, 55 µL) and diphenylphosphoryl azide (DPPA) (0.4 mmol, 86 µL), and the reaction mixture was heated at 80 °C for 2 h. After cooling to 50 °C, *tert*-butanol (4 mmol, 0.38 mL) was added and the resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was allowed to cool to room temperature and the solvents were removed by rotary evaporation. The resulting oil was diluted with 10 mL of Et_2O, 5 mL of water, and 2.5 mL of saturated solution of Na_2CO_3. The aqueous layer was separated and extracted with DCM (3 x 15 mL), and the combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash column chromatography on silica gel (eluting wit Hex/EtOAc 90:10 to 70:30) to give the desired compound as a colorless oil. Yield: 0.30 mmol, 102.5 mg, 76%. $[\alpha]_D^{25}$= +36.5 (*c* = 0.26, 89% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3412, 3066, 297, 2929, 2240, 1687, 1585, 1494, 1470, 1432, 1366, 1272, 1248, 1161, 1053, 977, 921, 859, 782, 732, 694, 651, 542. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.63 – 8.60 (m, 1H), 7.69 – 7.63 (m, 1H), 7.51 – 7.44 (m, 3H), 7.38 – 7.19 (m, 4H), 4.66 (s, 1H, NH), 3.30 – 3.23 (m, 2H), 2.94 – 2.84 (m, 1H), 2.73 – 2.63 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 155.8, 149.5, 138.8, 137.5, 129.2, 128.3, 126.6, 123.0, 122.4, 121.6, 79.4, 38.9, 37.8, 28.5. UPLC-DAD-QTOF: $C_{20}H_{24}N_3O_2$ $[M+H]^+$ calcd.: 338.1869, found: 338.1872.

5.3.6.6. Synthesis of amide 23

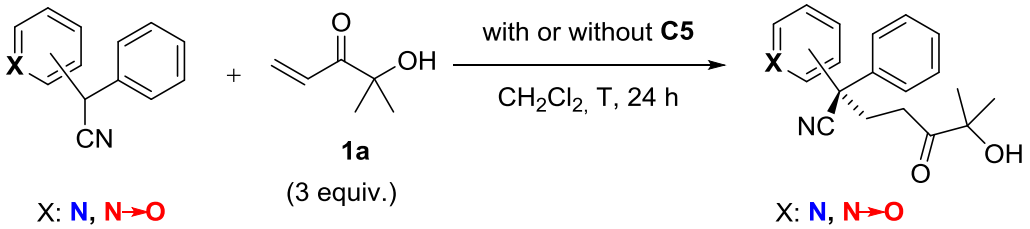


19 **23**

To a round-bottom flask with (R)-4-cyano-4-phenyl-4-(pyridin-2-yl)butanoic acid **19** (0.6 mmol, 159.7 mg) at 0 °C was added slowly concentrated H_2SO_4 (1.2 mL). The reaction mixture was stirred at room temperature overnight. Afterwards, an aqueous solution of NaOH 6 M was added to the reaction until white precipitate appeared (pH =

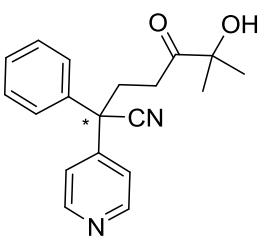
4–5). The solution was then extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$ and concentrated under vacuum to give the title compound as a white solid. Yield: 0.58 mmol, 163.8 mg, 96%. m.p. 185–188 °C. $[\alpha]_D^{25}$= +43.1 (*c* = 1.00, 90% *ee*, CH_2Cl_2). IR (ν/cm^{-1}): 3180, 3087, 2855, 1726, 1687, 1587, 1428, 1332, 1273, 1210, 1183, 955, 861, 776, 743, 688, 617, 543, 499, 409. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.63 (s, 1H), 7.60 (m, 1H), 7.42 – 7.34 (m, 3H), 7.28 – 7.20 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 1H), 3.35 – 3.24 (m, 1H), 2.71 – 2.61 (m, 2H), 2.54 – 2.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 172.9, 160.2, 148.7, 139.7, 136.6, 128.9, 127.9, 124.8, 122.6, 59.0, 30.2, 29.6. UPLC-DAD-QTOF: $C_{16}H_{17}N_2O_3$ $[M+H]^+$ calcd.: 285.1239, found: 285.1225.

5.3.7. Conversion for the reaction of *o*-, *m*- and *p*-substituted cyanoalkylpyridines and pyridine *N*-oxides with enone 1a



To a solution of the corresponding cyanoalkylpyridine or pyridine *N*-oxides (1 equiv., 0.2 mmol) in dichlorometane (1 mL) the α'-hydroxy enone **1a** (3.0 equiv., 0.6 mmol) and the catalyst (0.2 equiv., 0.04 mmol) were added at the corresponding temperature (see below). The resulting mixture was stirred for 24 h (reaction conversion was calculated by ^{1}H-NMR). Afterwards, the reaction mixture was washed with 0.1 M aqueous solution of HCl and purified by flash column chromatography on silica gel to afford the expected adducts.

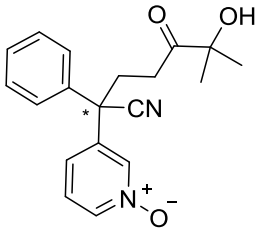
6-hydroxy-6-methyl-5-oxo-2-phenyl-2-(pyridin-4-yl)heptanenitrile



The title compound was prepared from 2-phenyl-2-(pyridin-4-yl)acetonitrile (0.2 mmol, 38.8 mg) and 4-hydroxy-4-methylpent-1-en-3-one (0.6 mmol, 68.4 mg) at rt according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80/20 to 50/50) to give the title compound as a white foam. Yield: 0.16 mmol, 49.3 mg, 80%. IR (ν/cm^{-1}): 3391, 3237, 3060, 2974, 2929, 2238, 1713, 1593, 1493, 1448, 1410, 1363, 1193, 1085, 966, 816, 759, 699, 650, 554. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 – 8.62 (s, 2H), 7.42 – 7.32 (m, 6H), 3.36 (s, 1H), 2.80 – 2.67 (m, 4H), 1.31

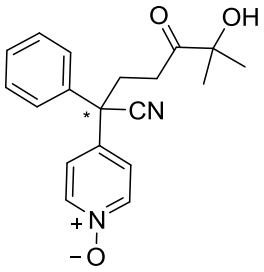
(s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 150.8, 148.6, 137.5, 129.6, 129.0, 126.8, 121.6, 120.6, 77.6, 50.9, 32.8, 32.2, 26.7, 26.7. UPLC-DAD-QTOF: $C_{19}H_{21}N_2O_2$ $[M+H]^+$ calcd.: 309.1606, found: 309.1603.

(R)-3-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide



The title compound was prepared from 3-(cyano(phenyl)methyl)pyridine 1-oxide **11** (0.2 mmol, 58.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at r.t. according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to 0/100) to give the title compound as a yellow oil. Yield: 0.16 mmol, 51.8 mg, 79%. IR (ν/cm^{-1}): 3398, 3098, 2956, 2913, 2235, 1711, 1610, 1407, 1267, 1145, 771, 730, 678, 559. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 – 8.21 (s, 1H), 8.13 – 8.10 (s, 1H), 7.44 – 7.25 (m, 7H), 4.00 (s, 1H), 2.85 – 2.63 (m, 4H), 1.32 (s, 3H), 1.29 (s, 3H). UPLC-DAD-QTOF: $C_{19}H_{21}N_2O_3$ $[M+H]^+$ calcd.: 325.1552, found: 325.1555.

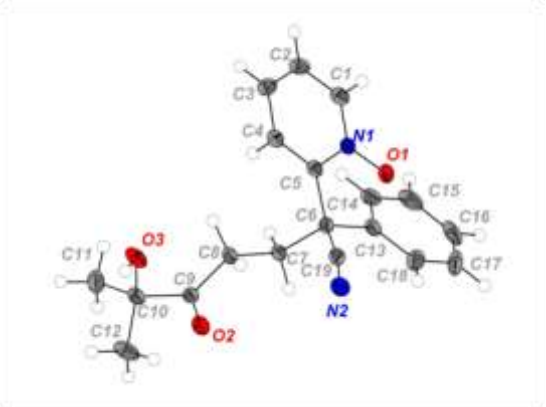
4-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide

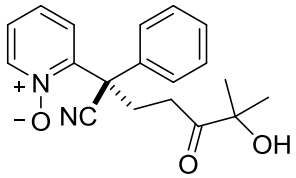


The title compound was prepared from 4-(cyano(phenyl)methyl)pyridine 1-oxide **12** (0.2 mmol, 58.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.6 mmol, 68.4 mg) at r.t. according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 70/30 to 0/100) to give the title compound as a white foam. Yield: 0.16 mmol, 50.5 mg, 78%. IR (ν/cm^{-1}): 3420, 3115, 3068, 2965, 2236, 1710, 1587, 1413, 1261, 1167, 764, 732, 701, 556. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 (d, *J* = 7.4 Hz, 1H), 7.43 – 7.39 (m, 5H), 7.28 (d, *J* = 7.4 Hz, 1H), 3.29 (s, 1H), 2.79 – 2.64 (m, 4H), 1.33 (s, 3H), 1.30 (s, 3H). UPLC-DAD-QTOF: $C_{19}H_{21}N_2O_3$ $[M+H]^+$ calcd.: 325.1552, found: 325.1548.

5.3.8. X-Ray Analysis: ORTEP diagram of compound 9a

CCDC 1437384 contains the supplementary crystallographic data for the structural analysis of **9a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deposit/.

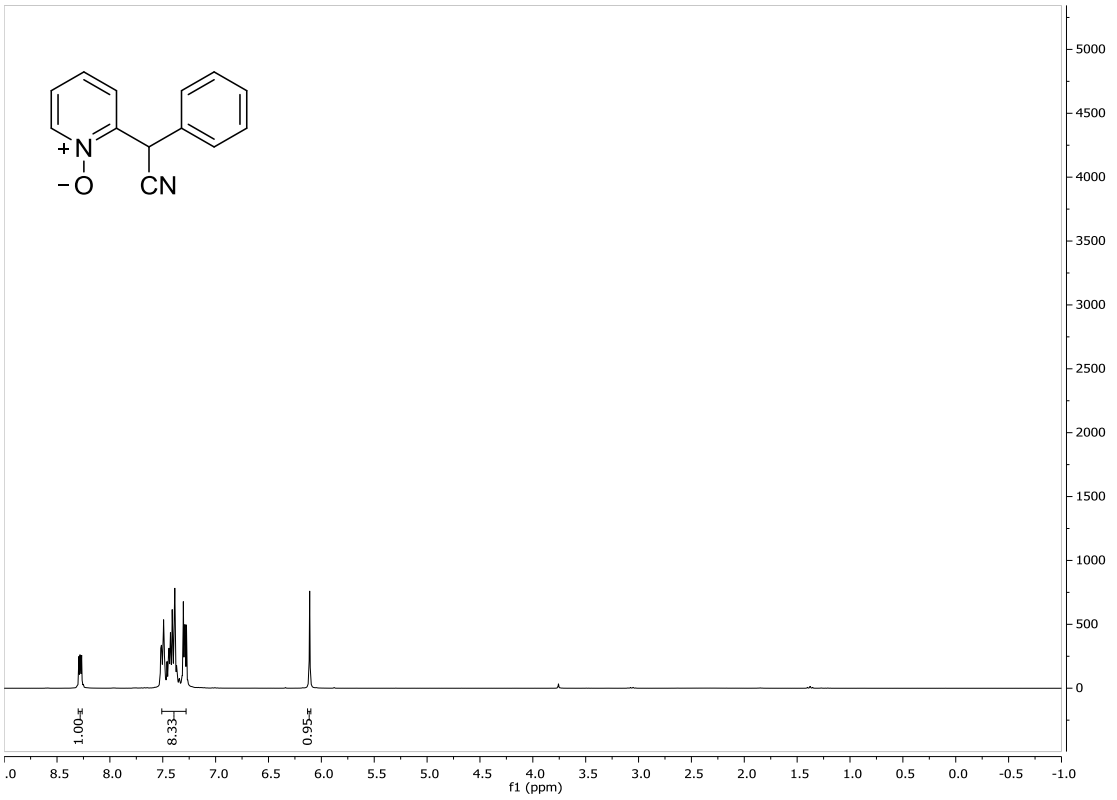


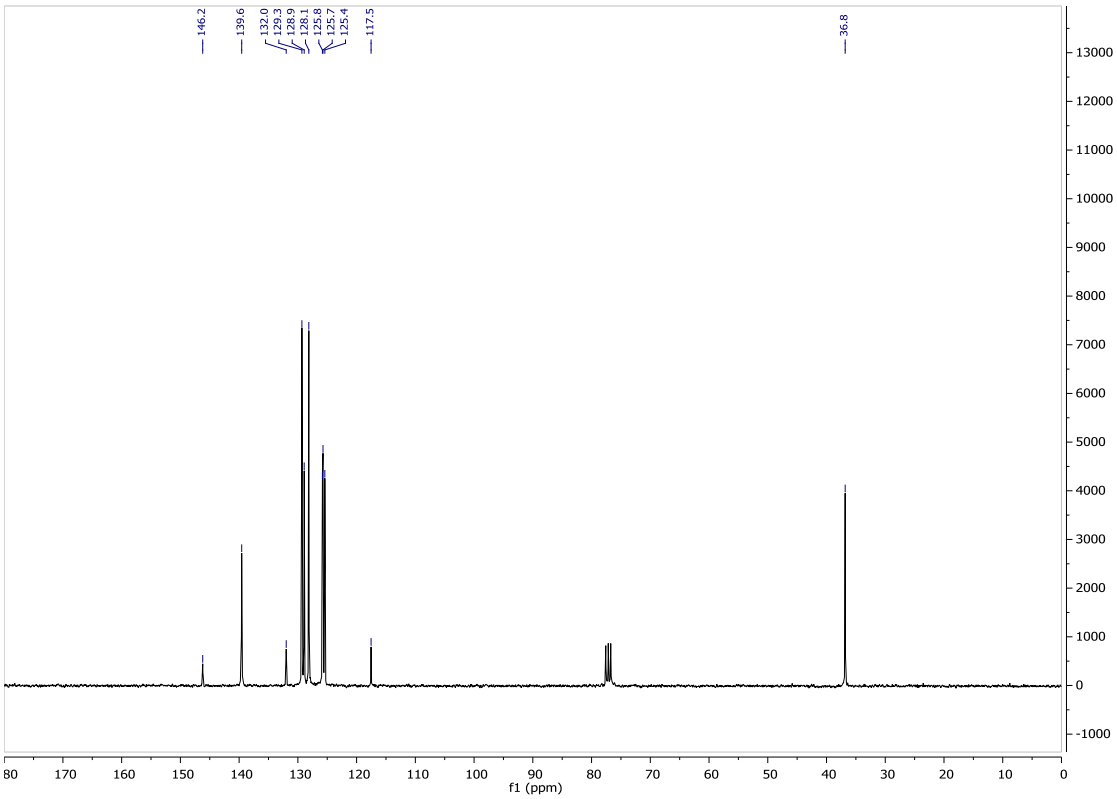


9a

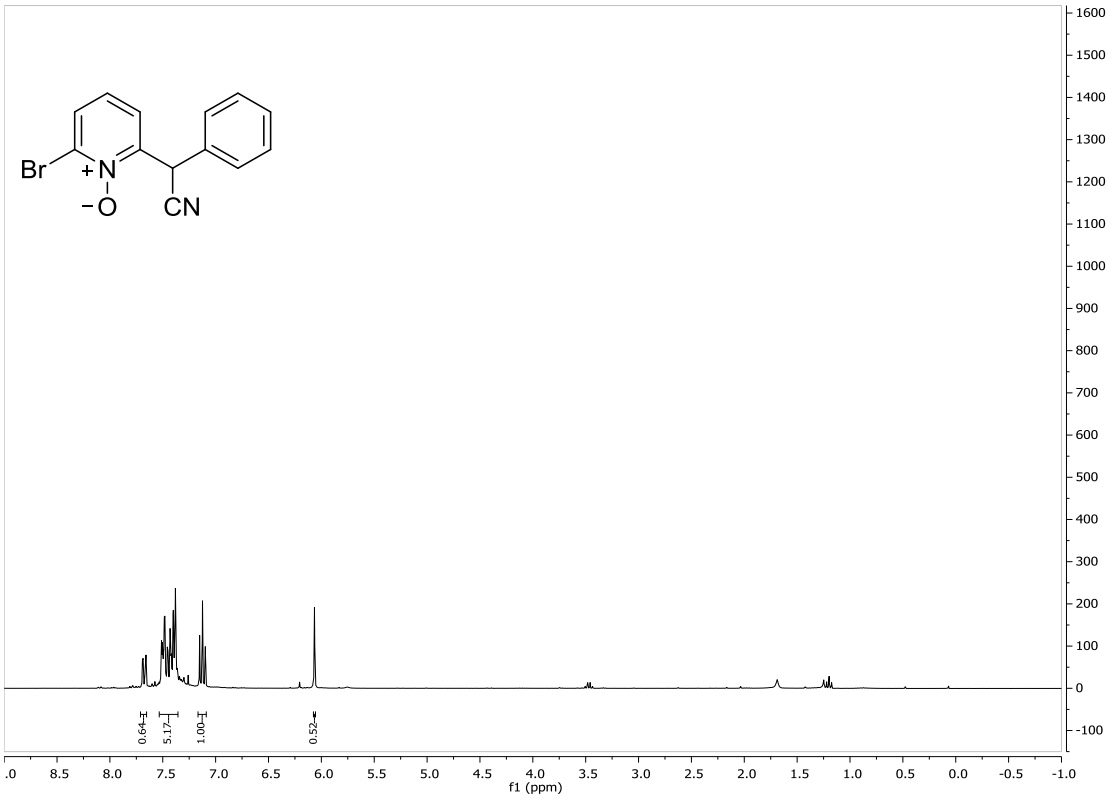
5.3.9. ^{1}H and ^{13}C NMR Spectra

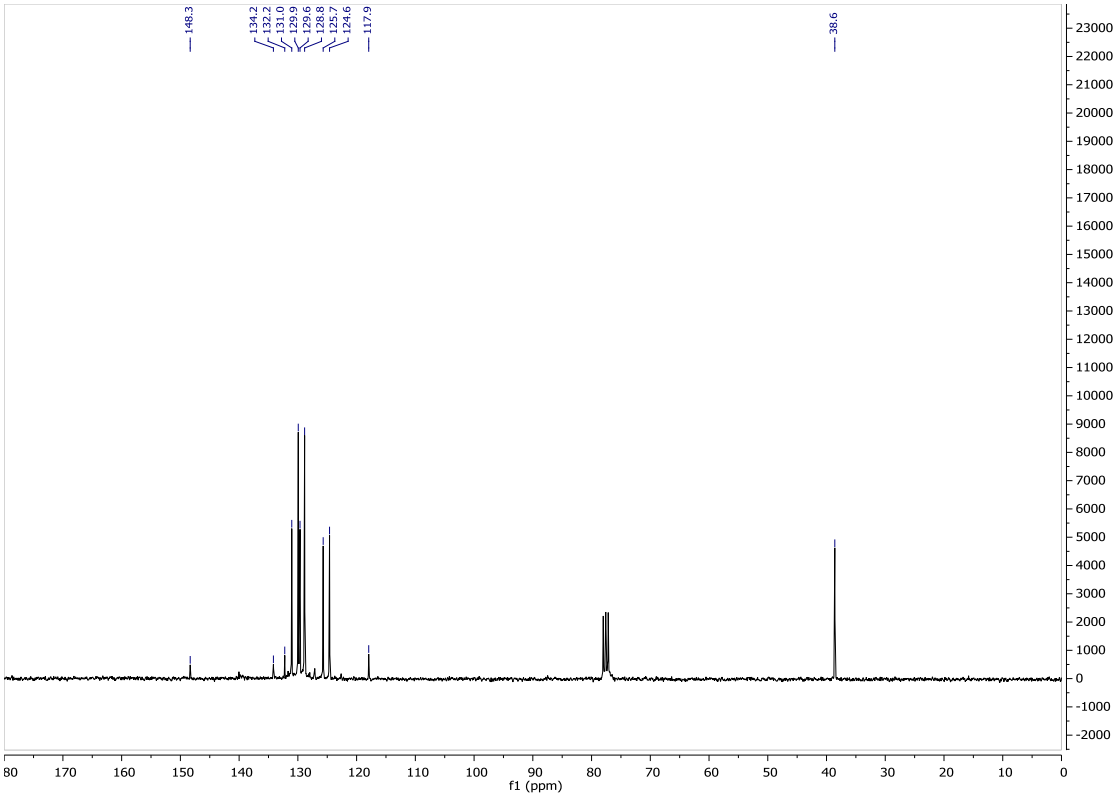
2-(cyano(phenyl)methyl)pyridine 1-oxide (6a)



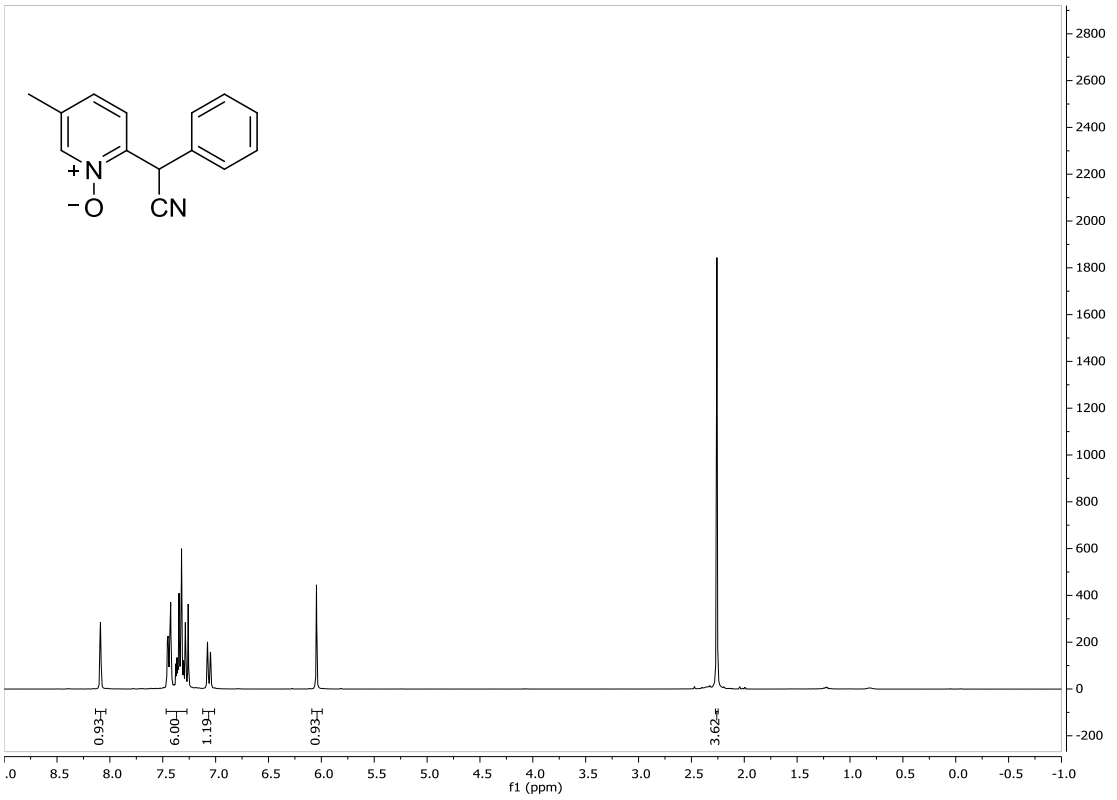


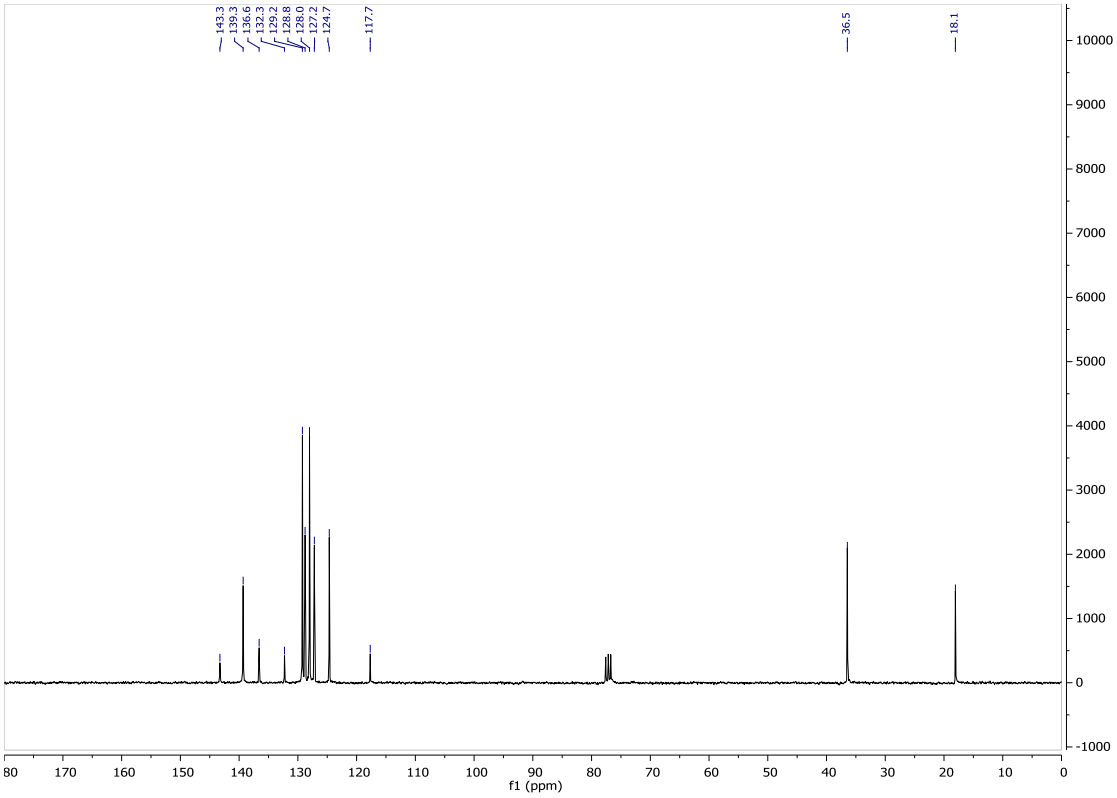
2-bromo-6-(cyano(phenyl)methyl)pyridine 1-oxide (6b)



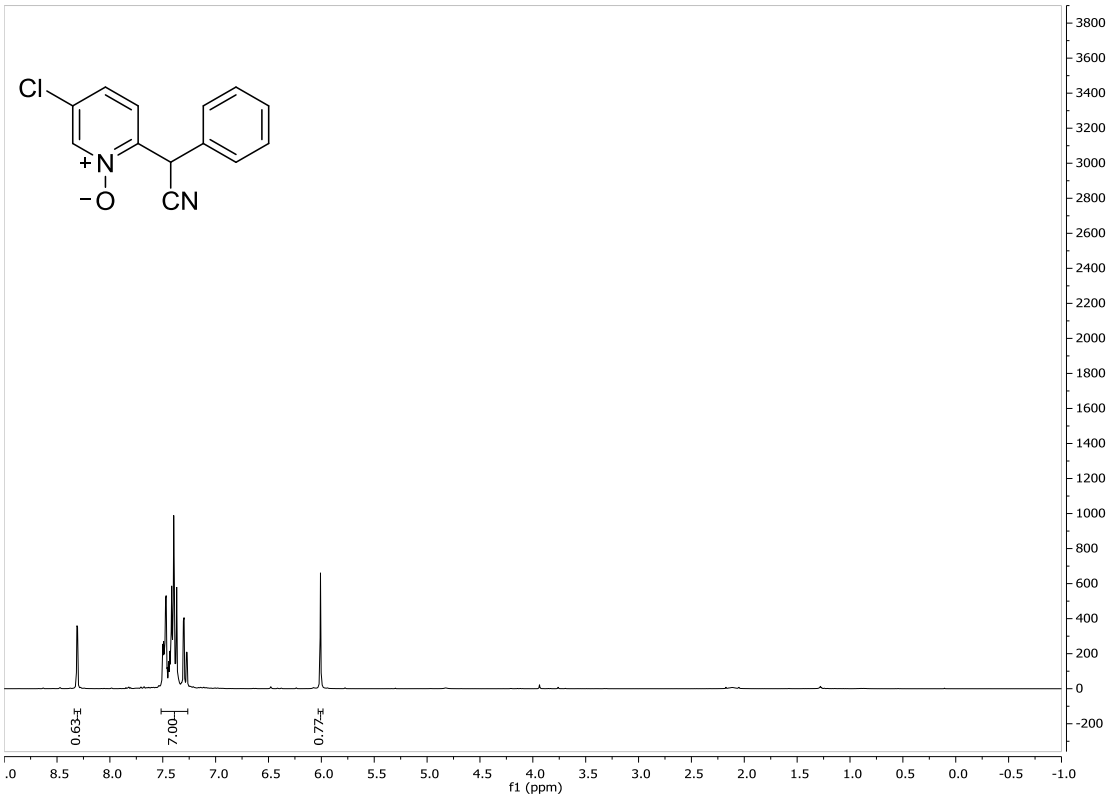


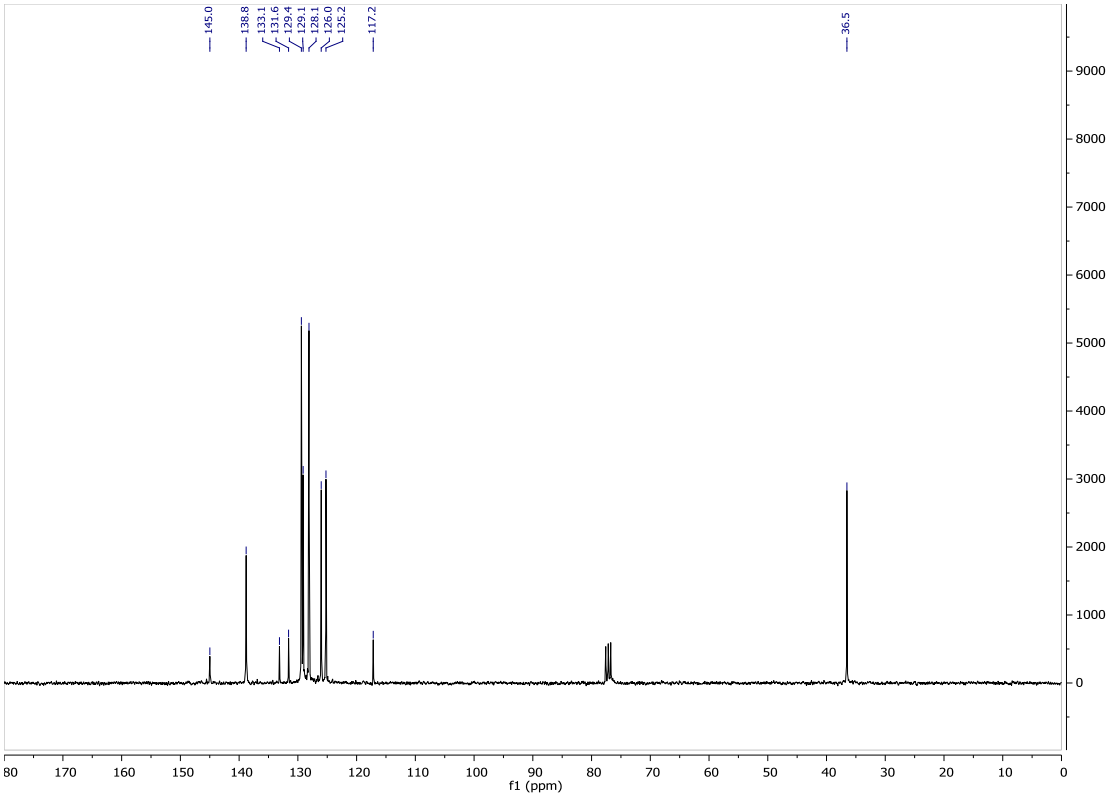
2-(cyano(phenyl)methyl)-5-methylpyridine 1-oxide (6c)



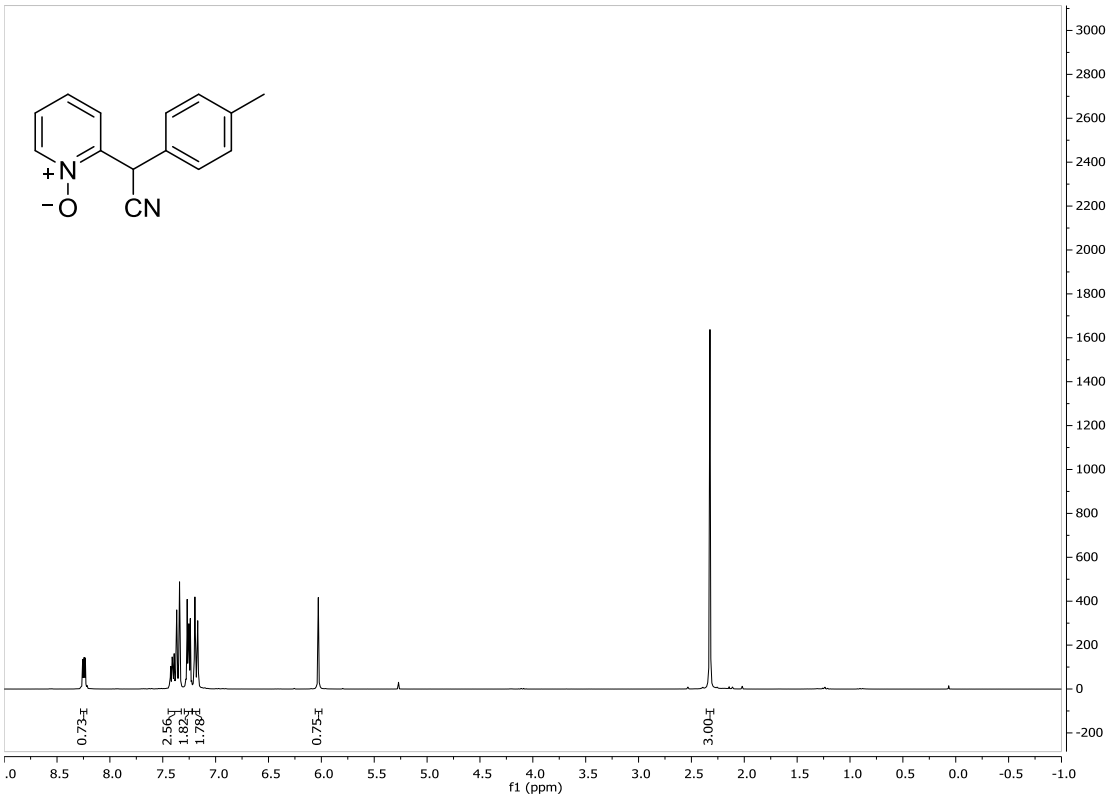


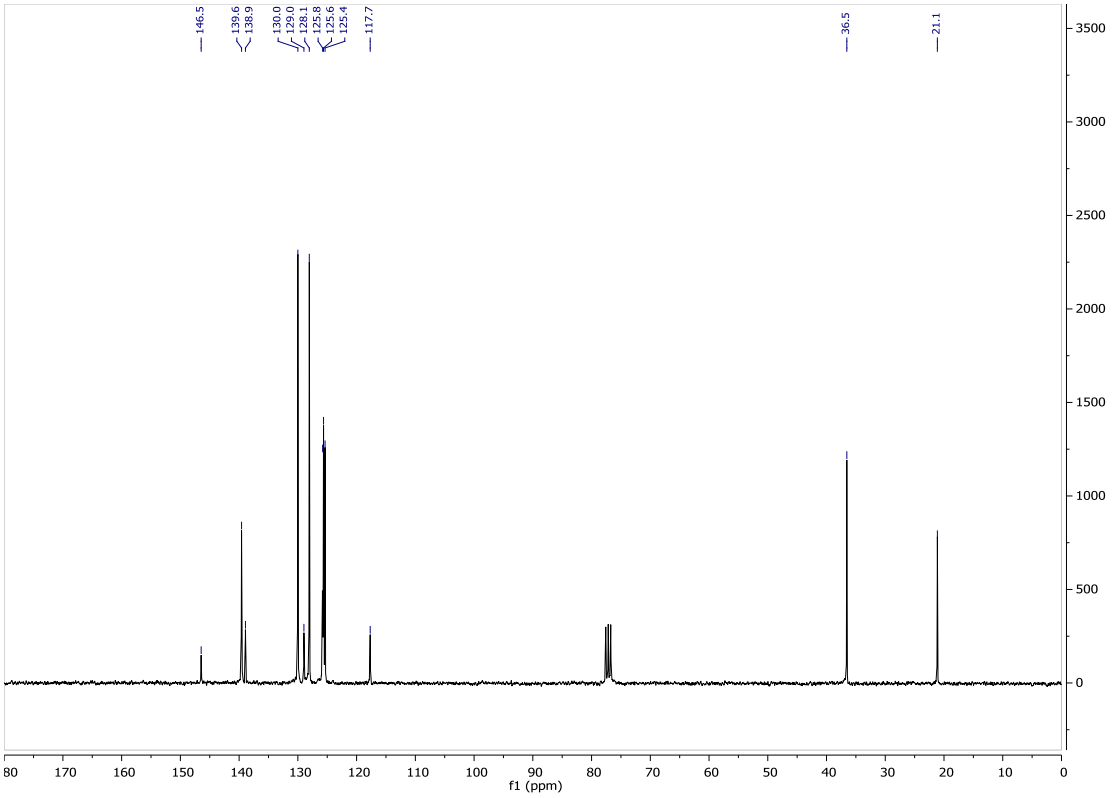
5-chloro-2-(cyano(phenyl)methyl)pyridine 1-oxide (6d)



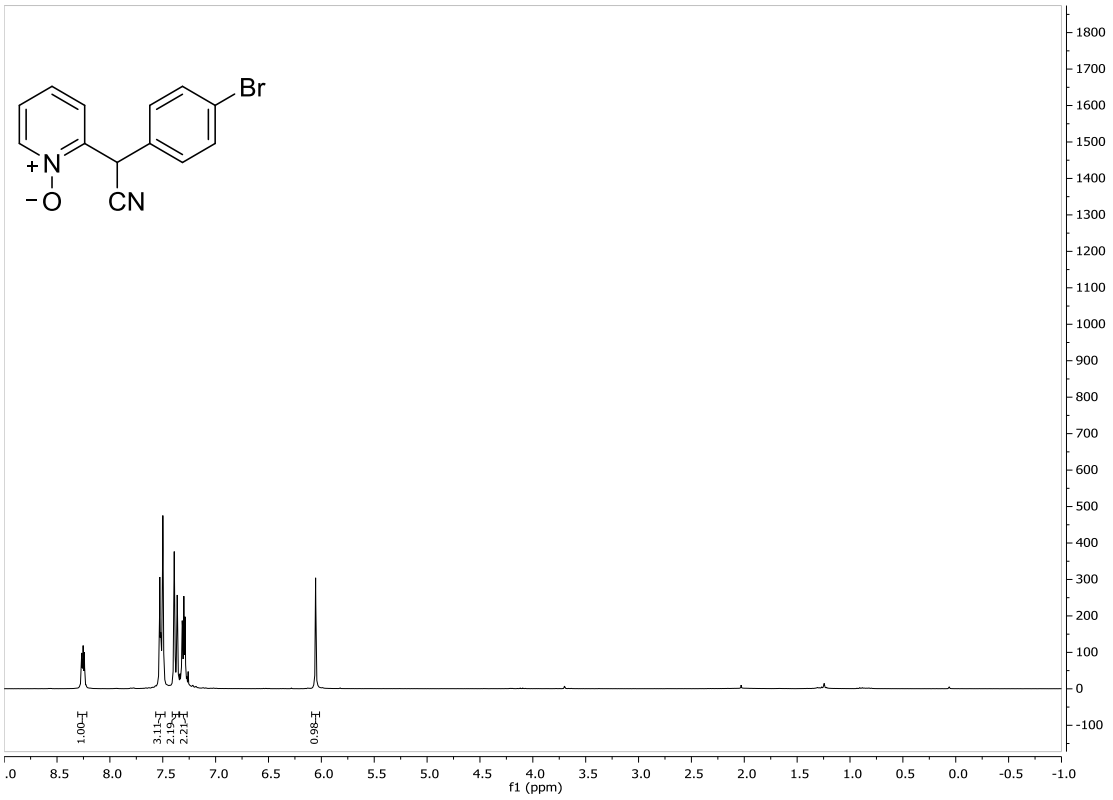


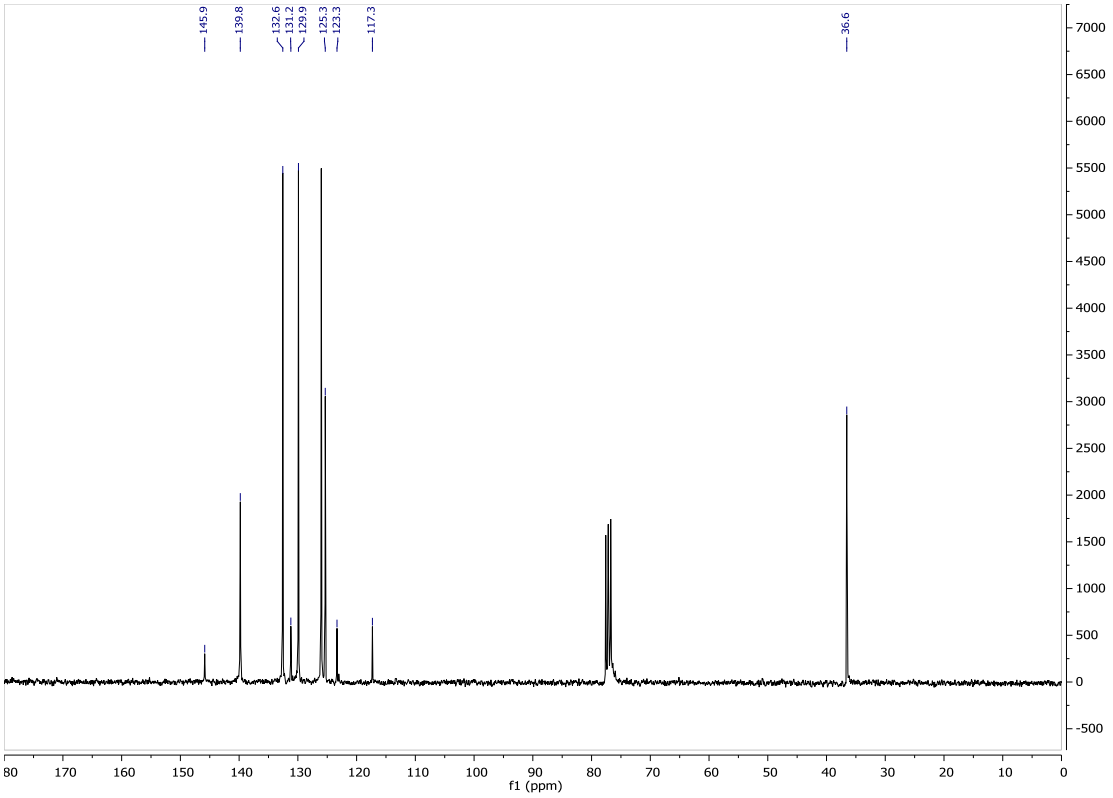
2-(cyano(phenyl)methyl)-3-methoxypyridine 1-oxide (6e)



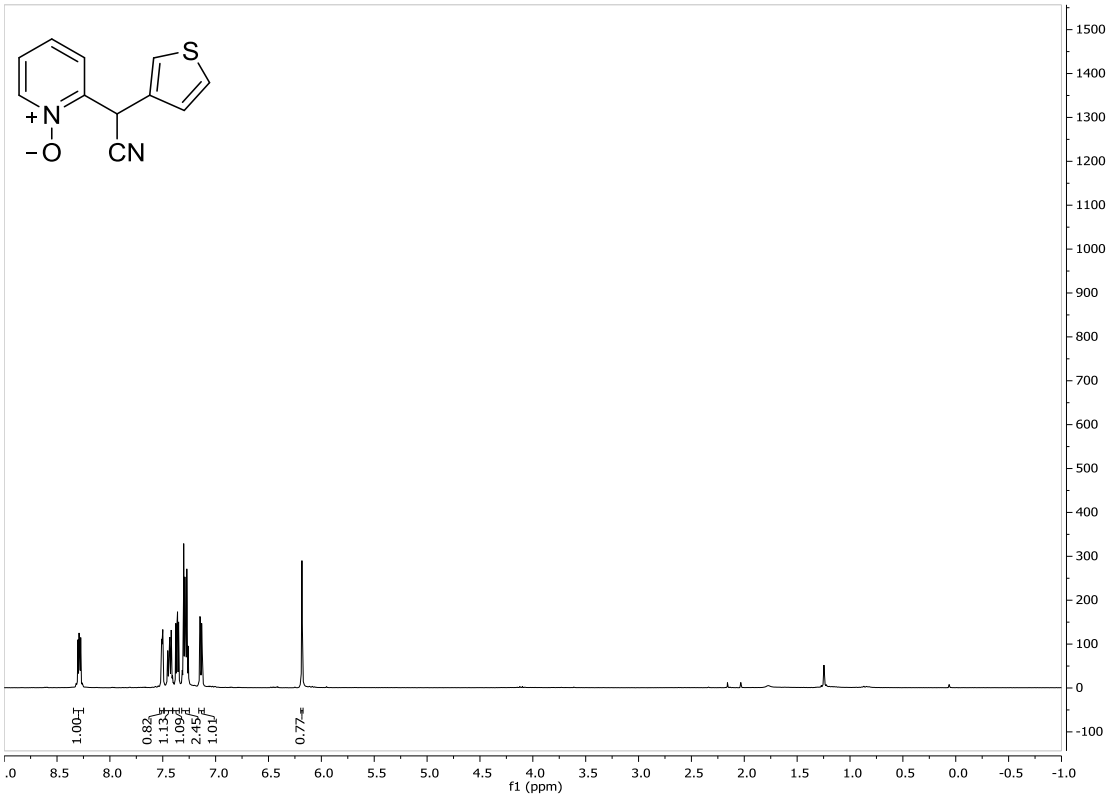


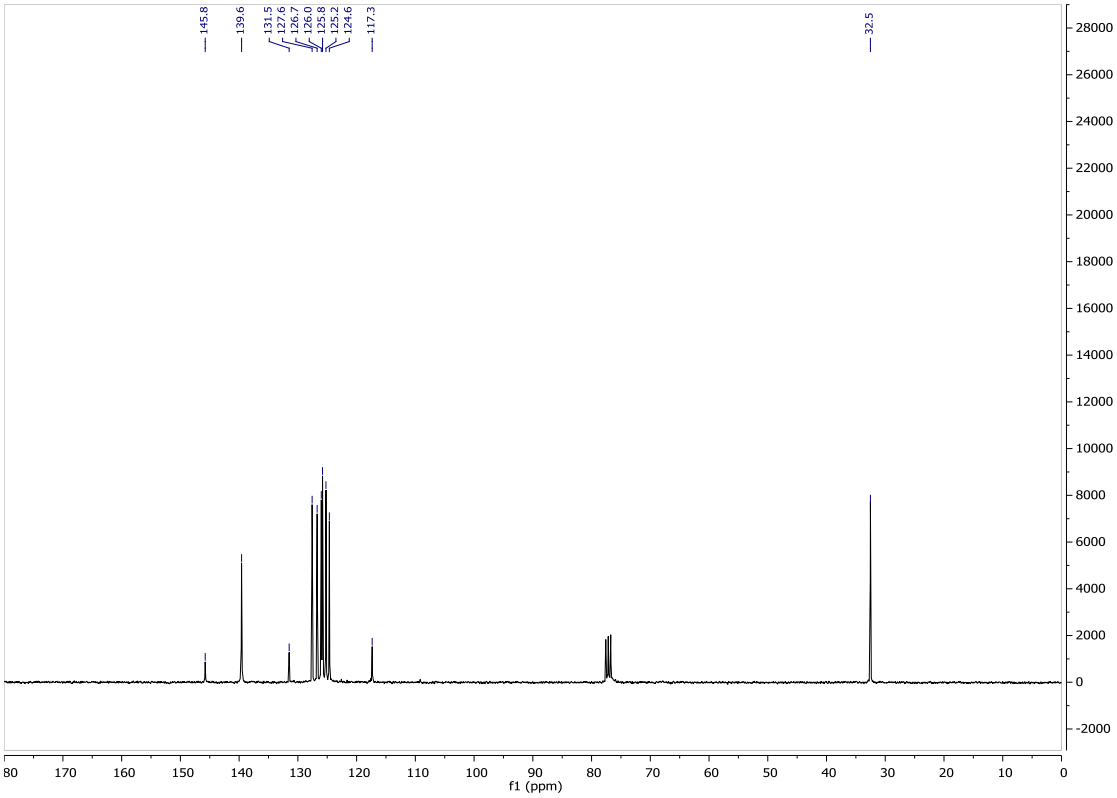
2-((4-bromophenyl)(cyano)methyl)pyridine 1-oxide (6f)



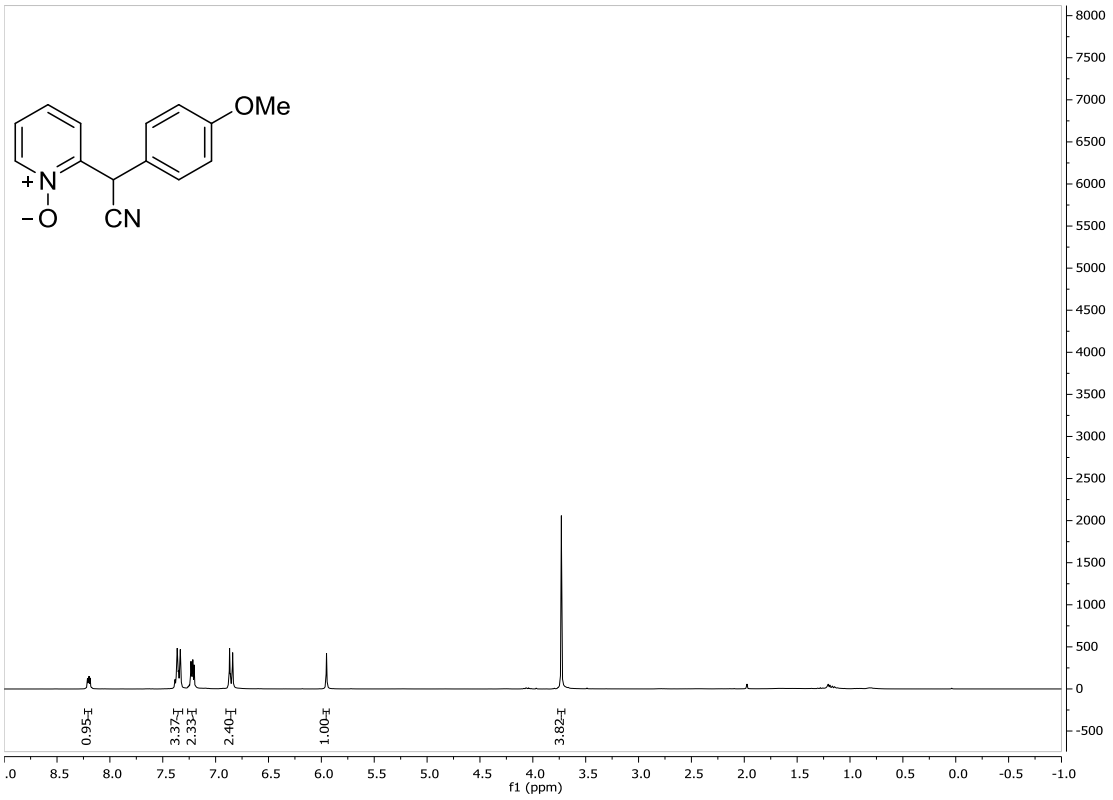


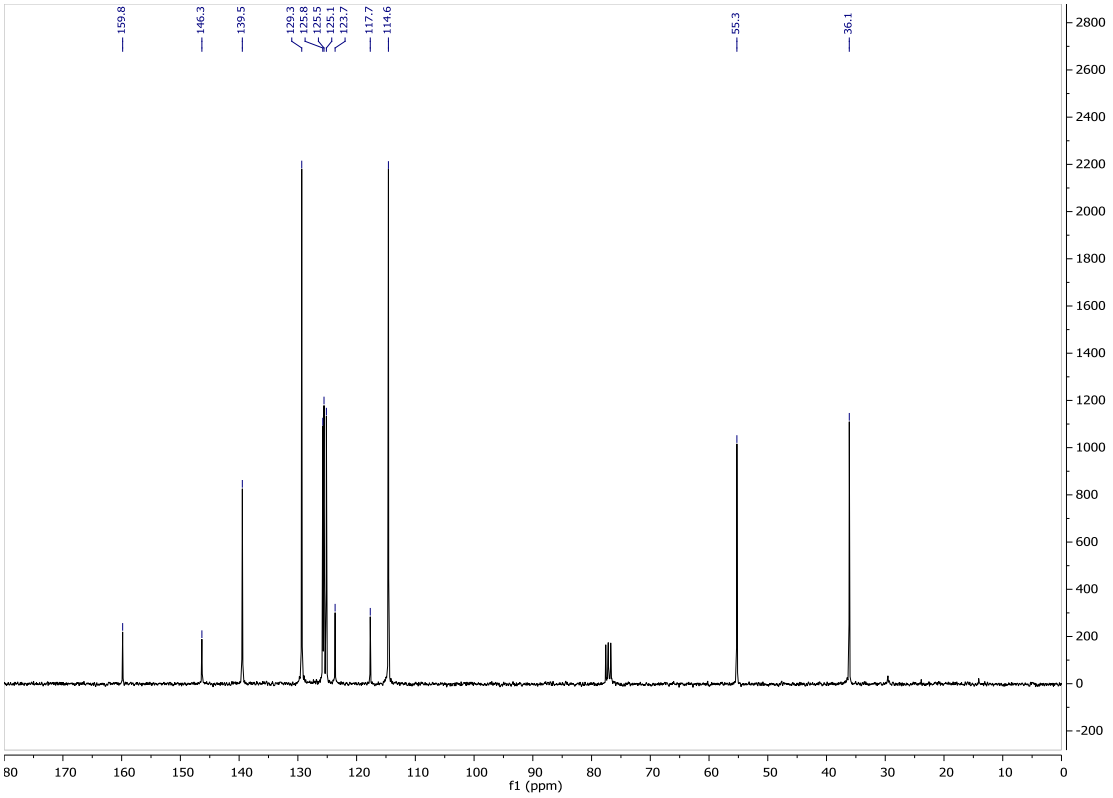
2-(cyano(thiophen-3-yl)methyl)pyridine 1-oxide (6g)



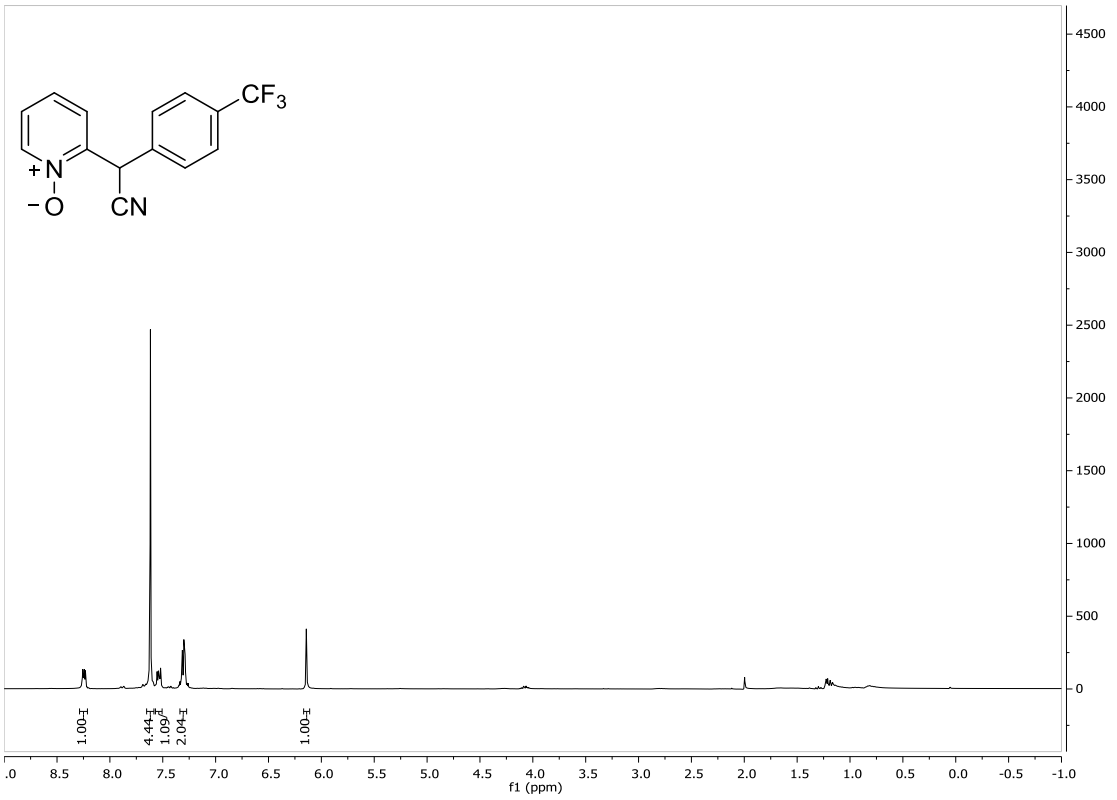


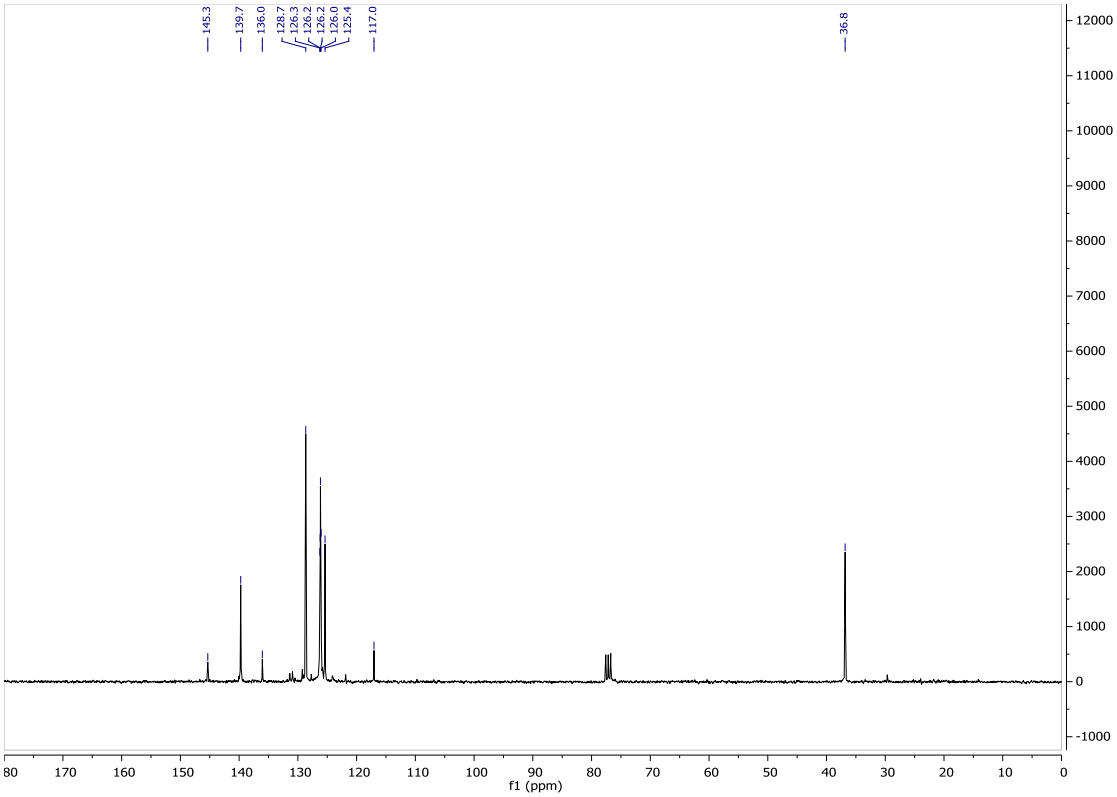
2-(cyano(4-methoxyphenyl)methyl)pyridine 1-oxide (6h)



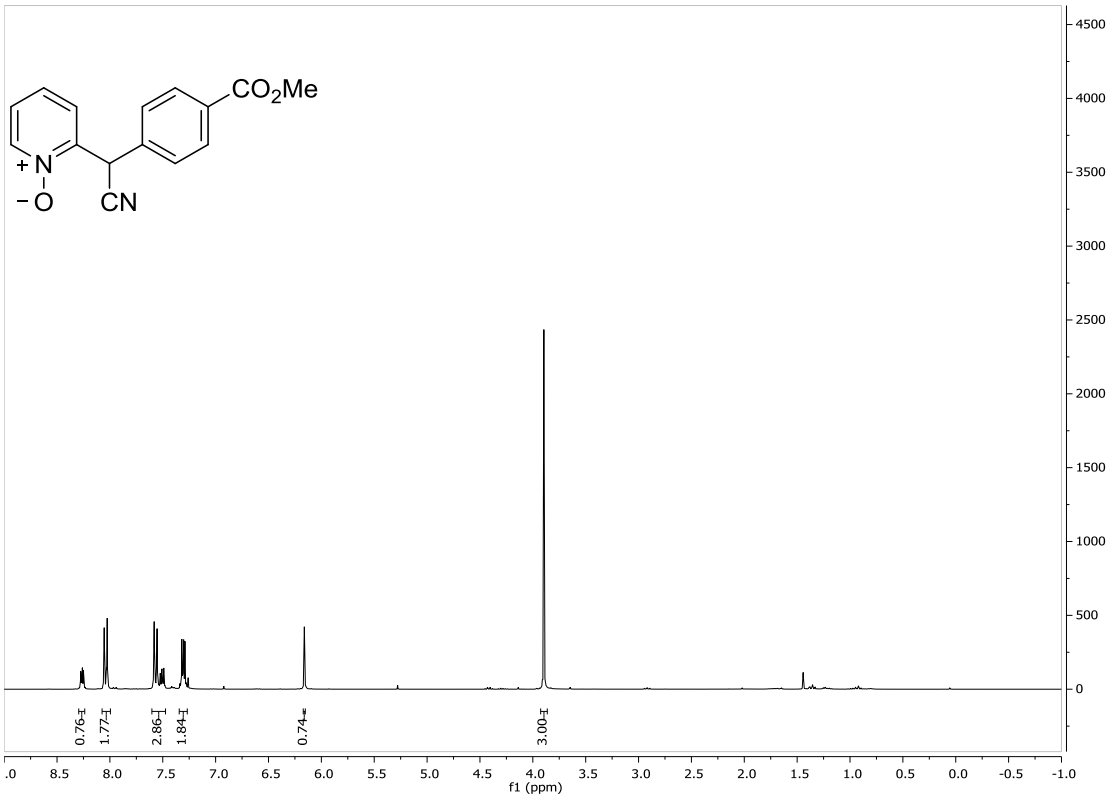


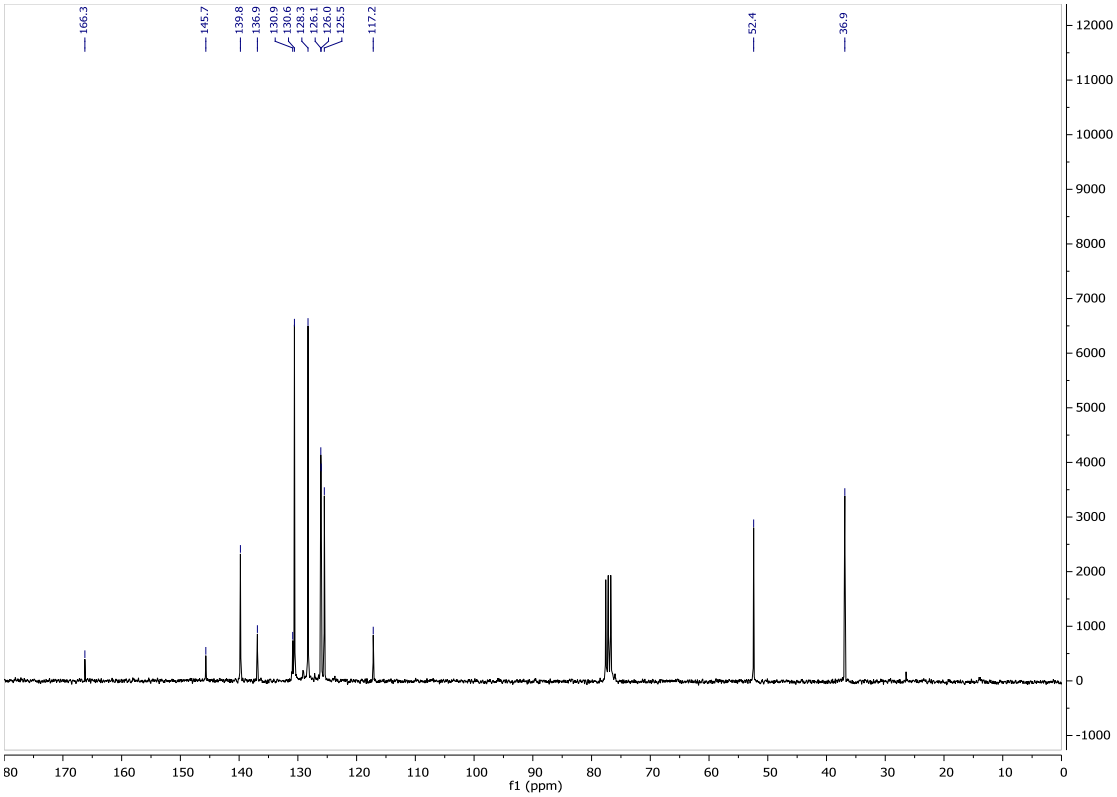
2-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide (6i)



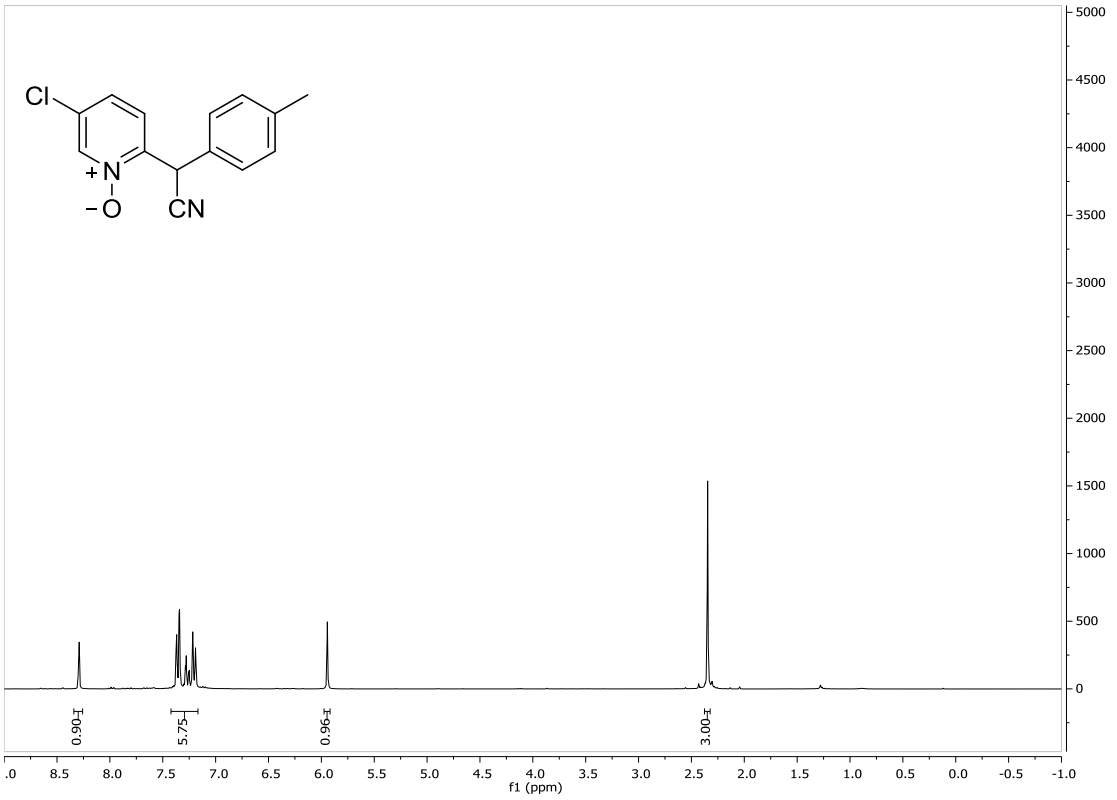


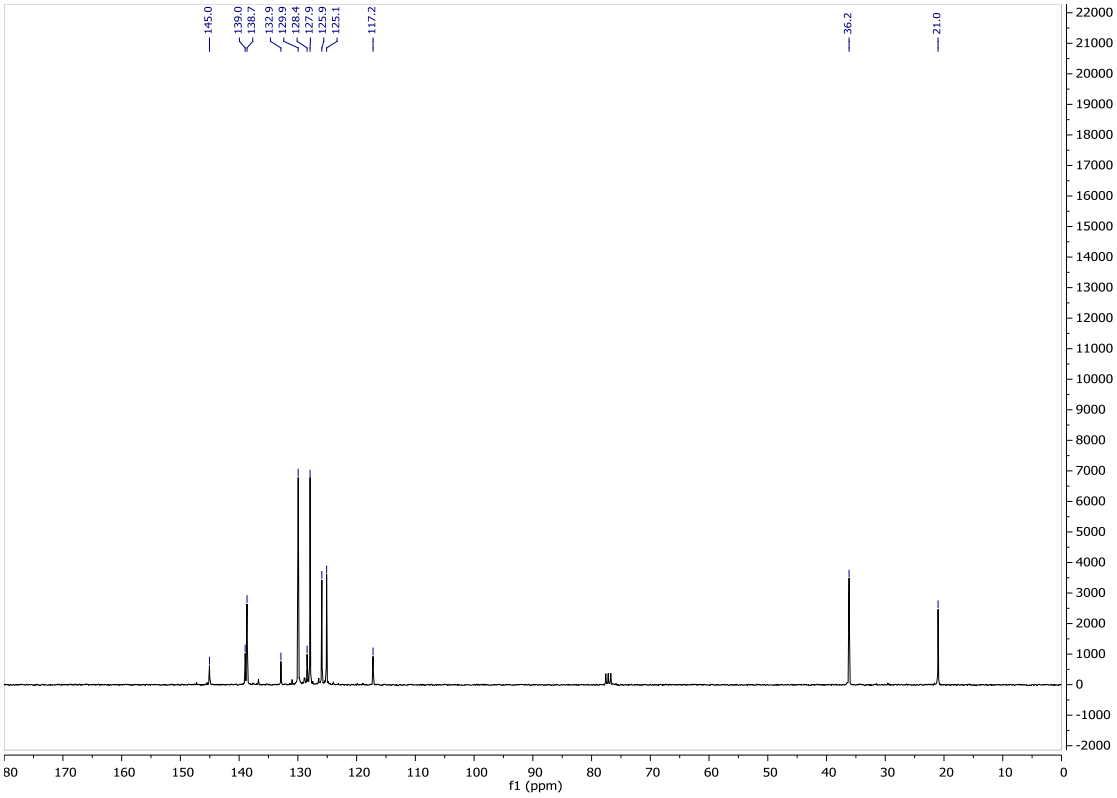
2-(cyano(4-(methoxycarbonyl)phenyl)methyl)pyridine 1-oxide (6j)



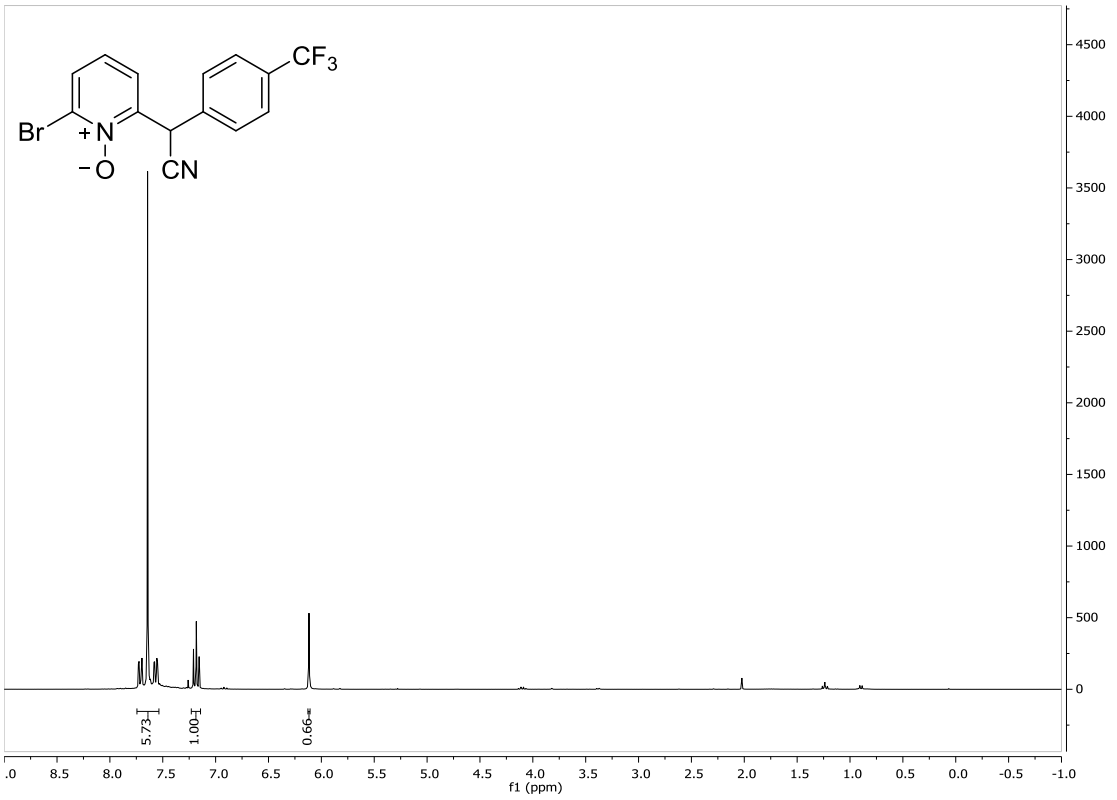


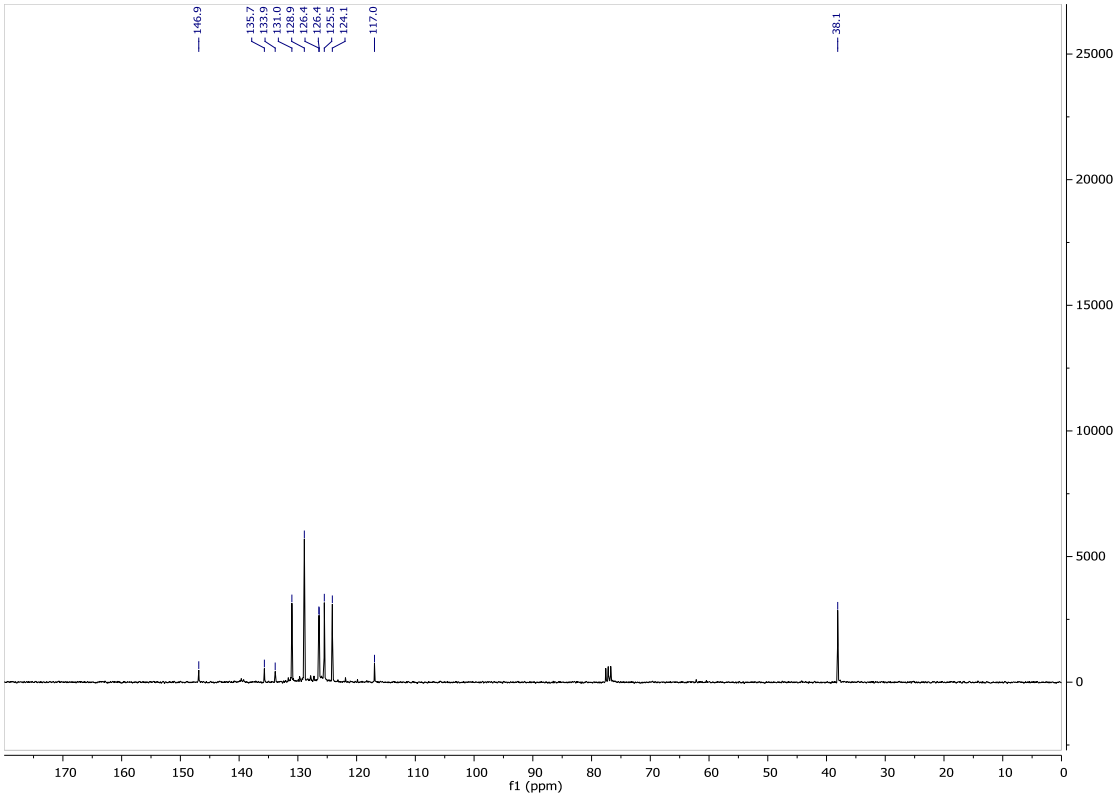
5-chloro-2-(cyano(p-tolyl)methyl)pyridine 1-oxide (6k)



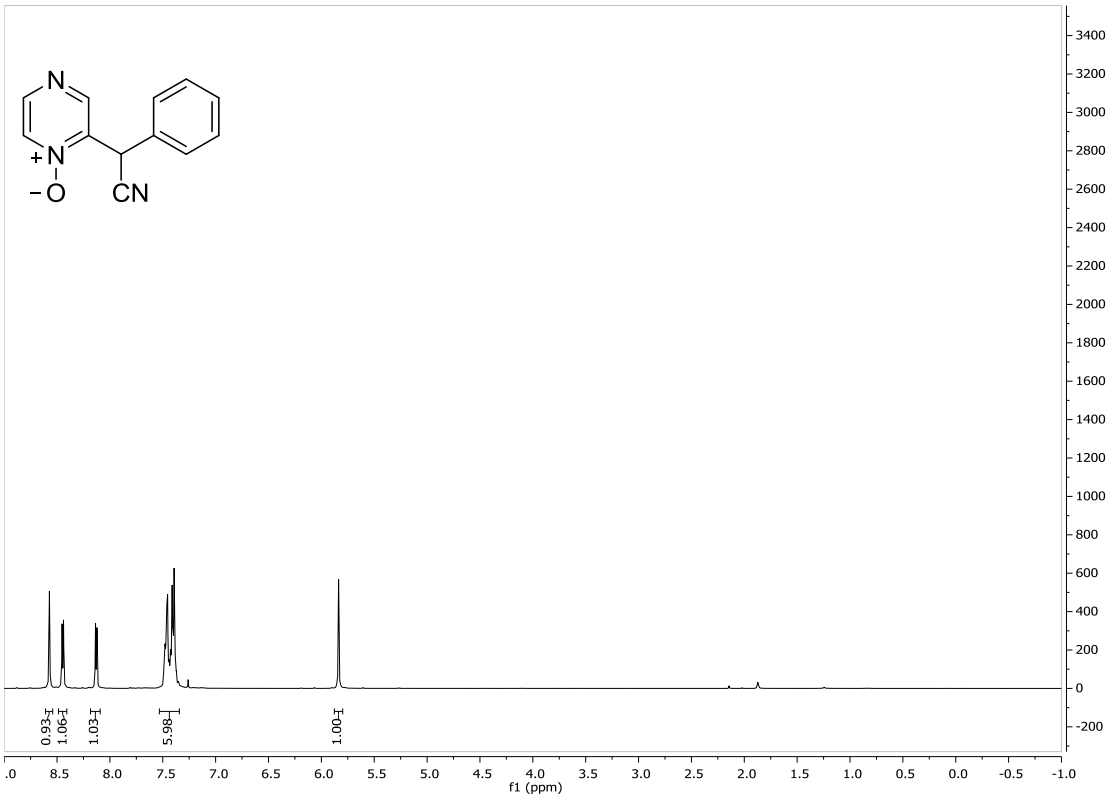


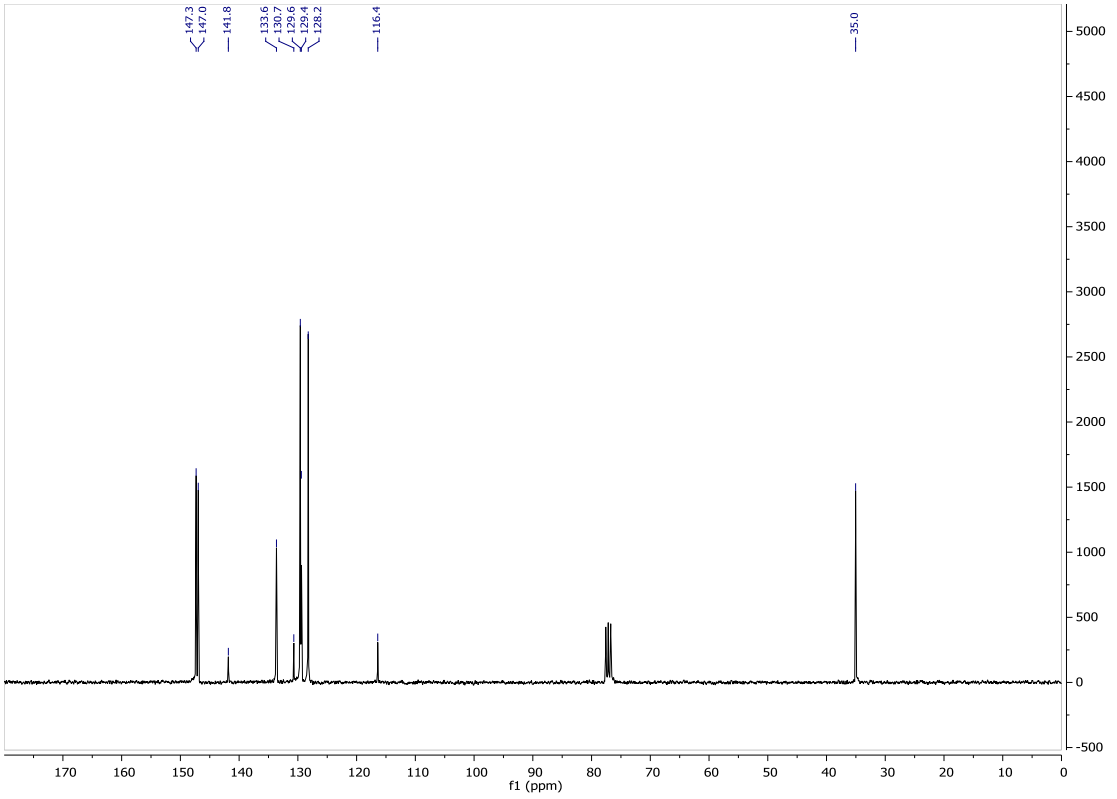
2-bromo-6-(cyano(4-(trifluoromethyl)phenyl)methyl)pyridine 1-oxide (6l)



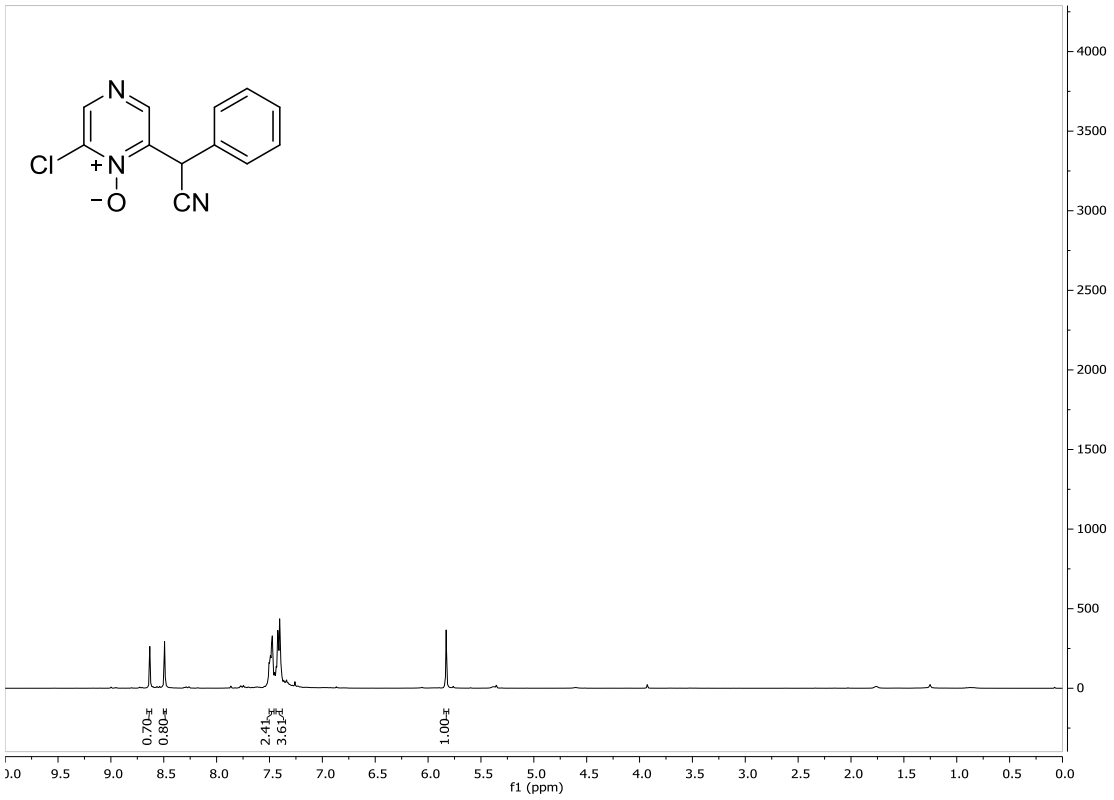


2-(cyano(phenyl)methyl)pyrazine 1-oxide (10a)

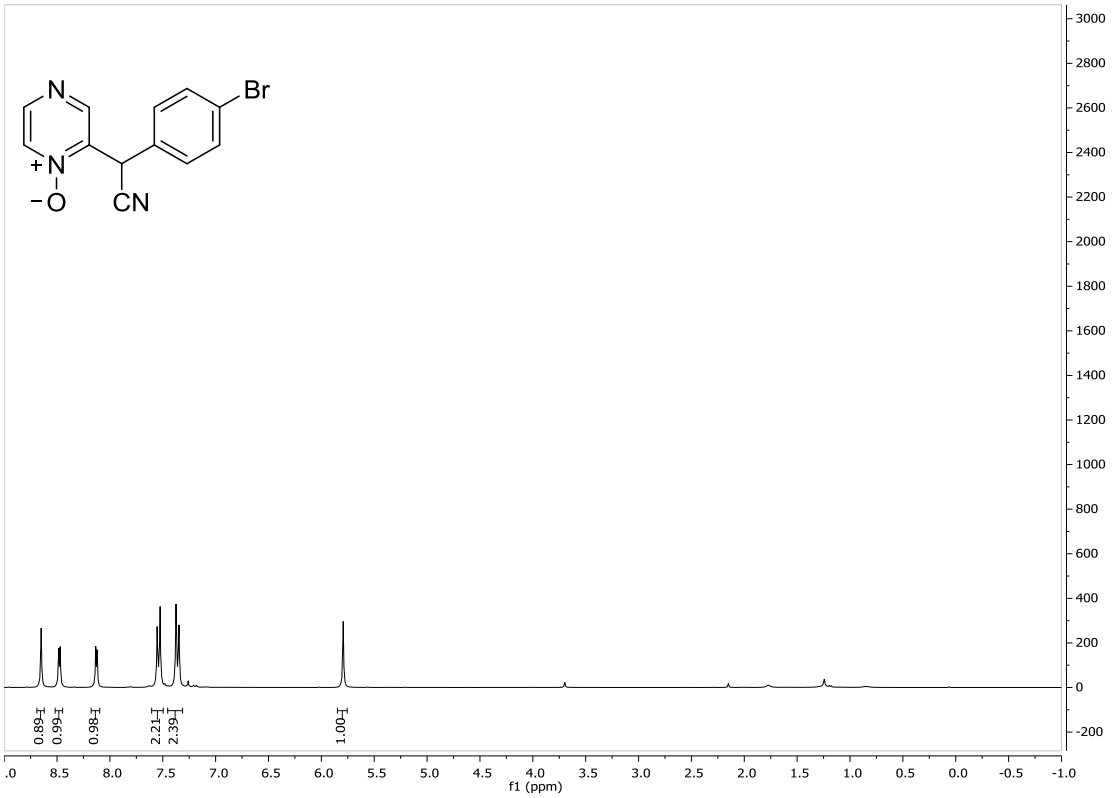


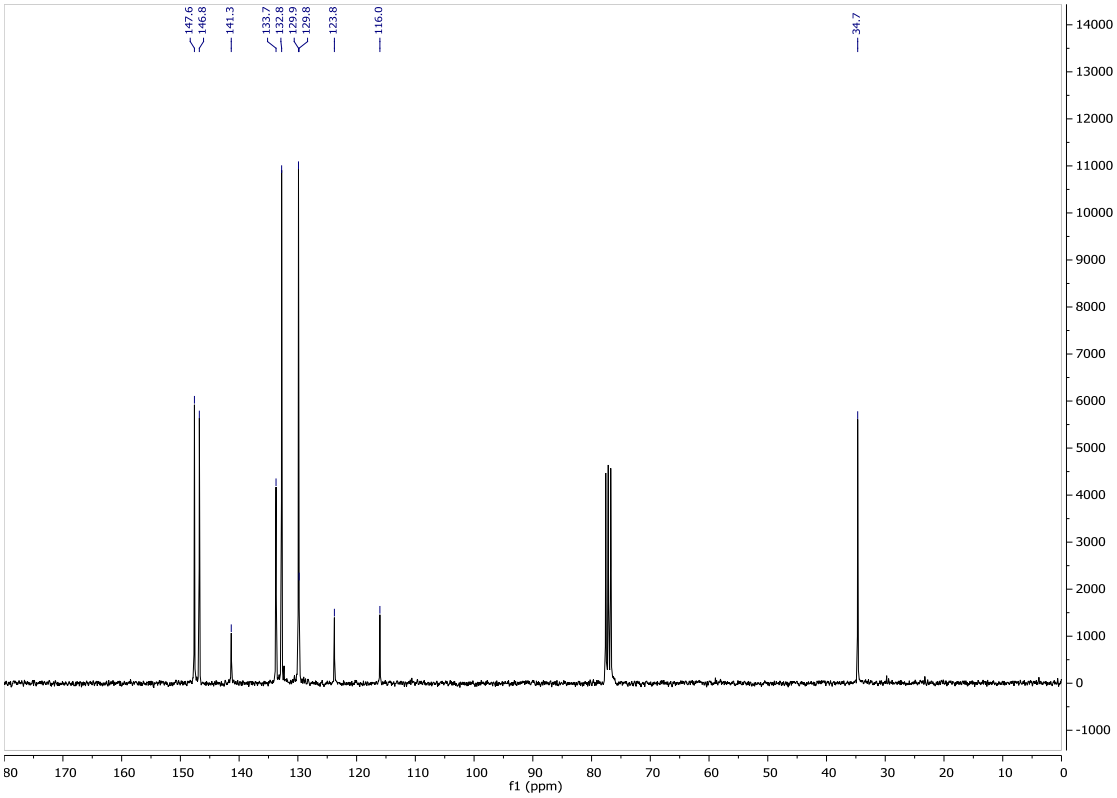


2-chloro-6-(cyano(phenyl)methyl)pyrazine 1-oxide (10b)

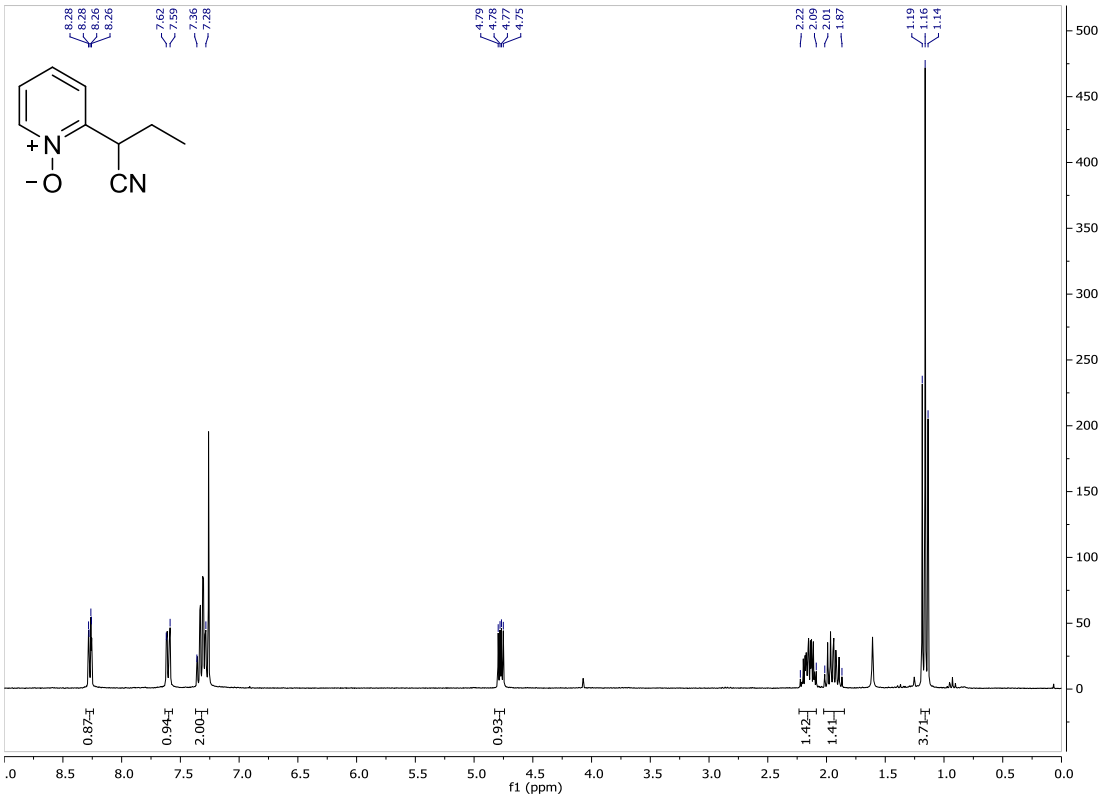


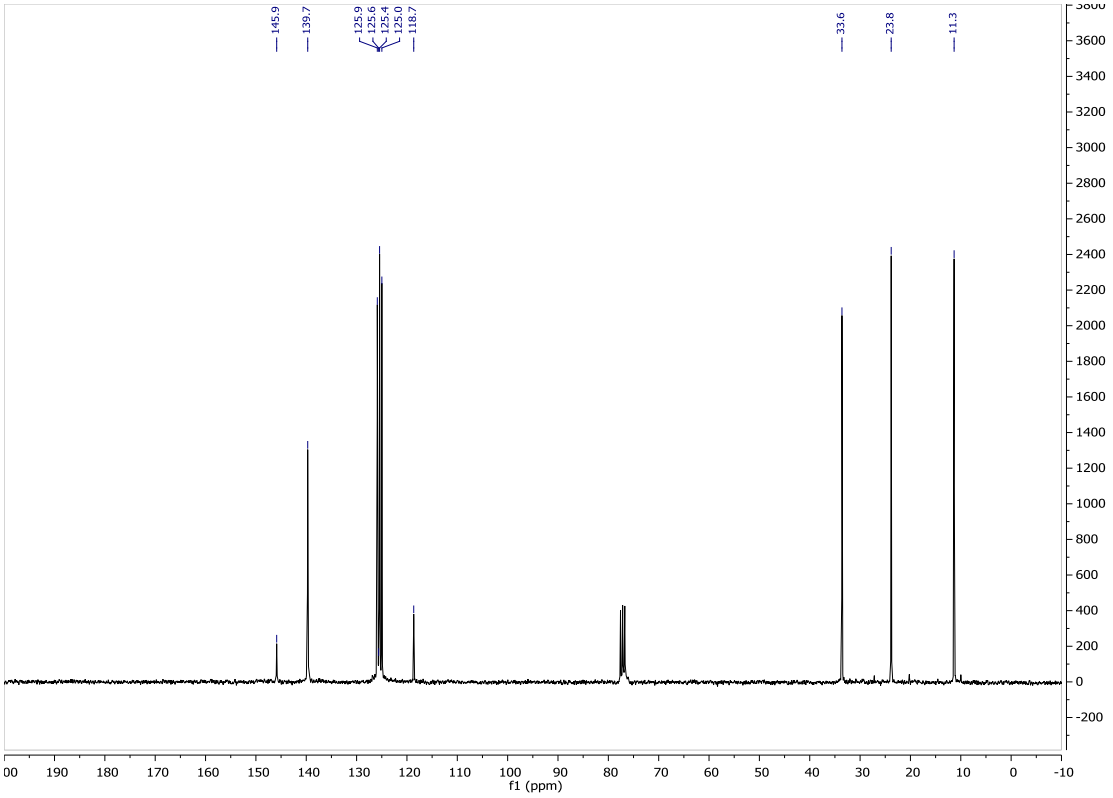
2-((4-bromophenyl)(cyano)methyl)pyrazine 1-oxide (10c)



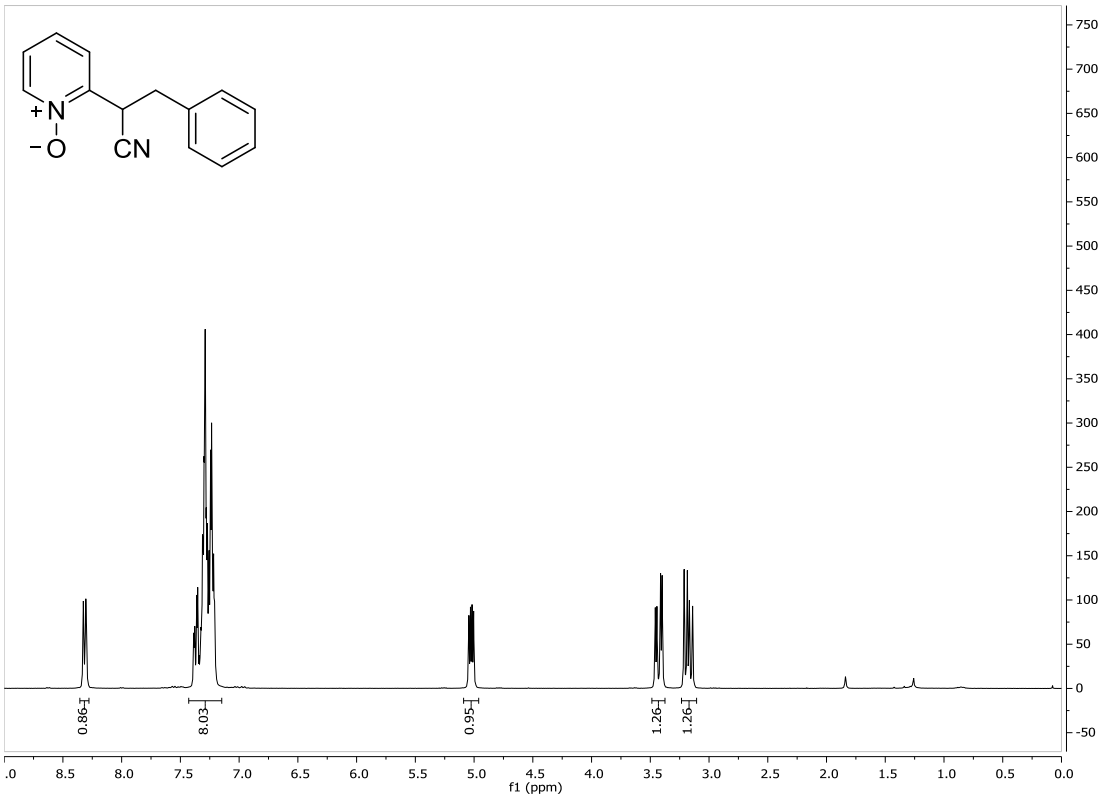


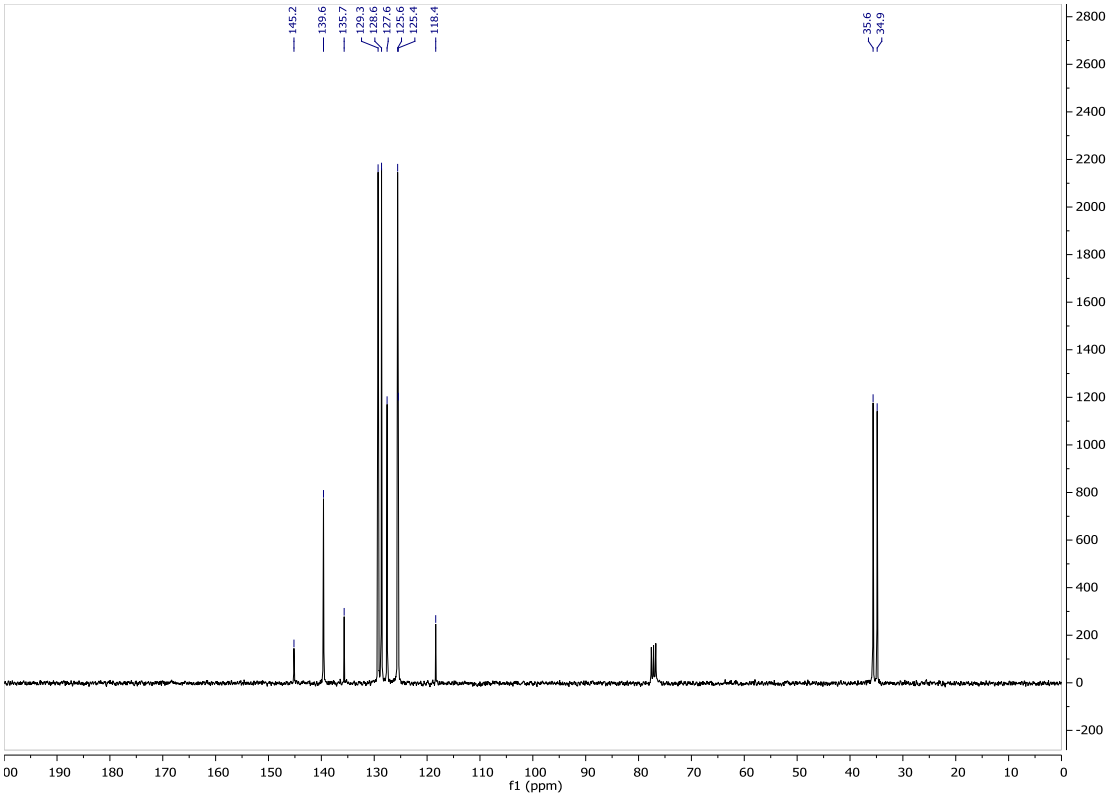
2-(1-cyanopropyl)pyridine 1-oxide (13a)



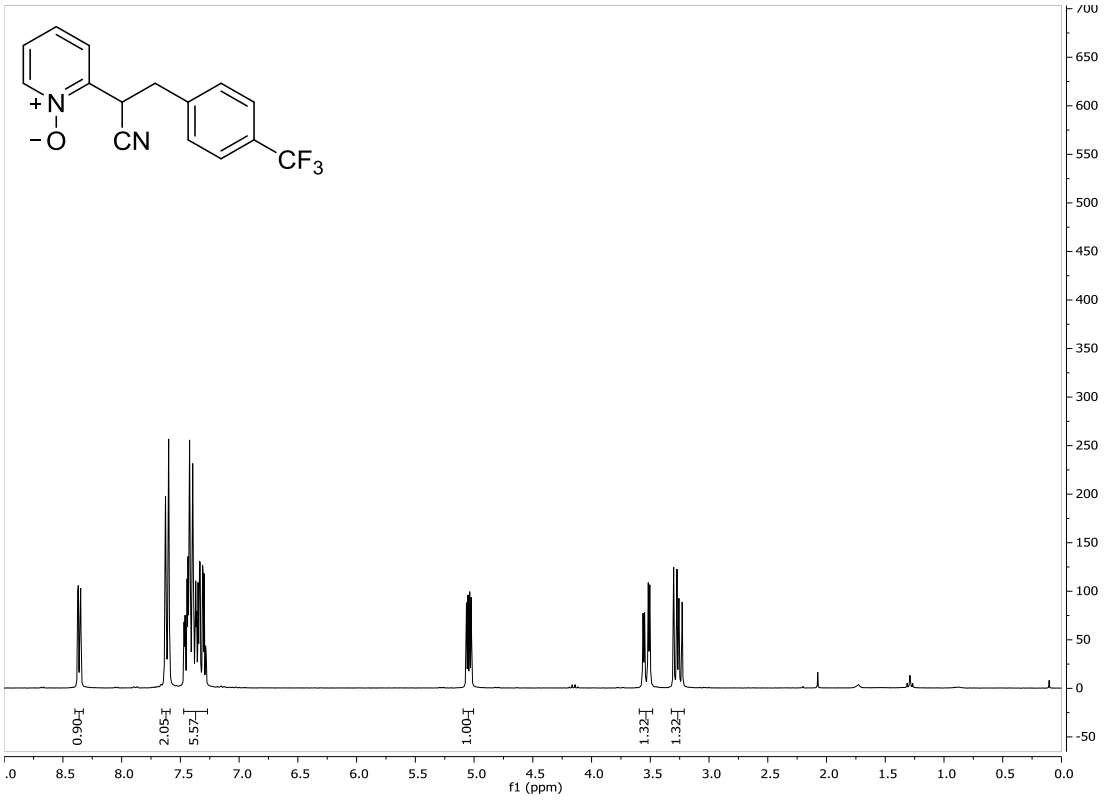


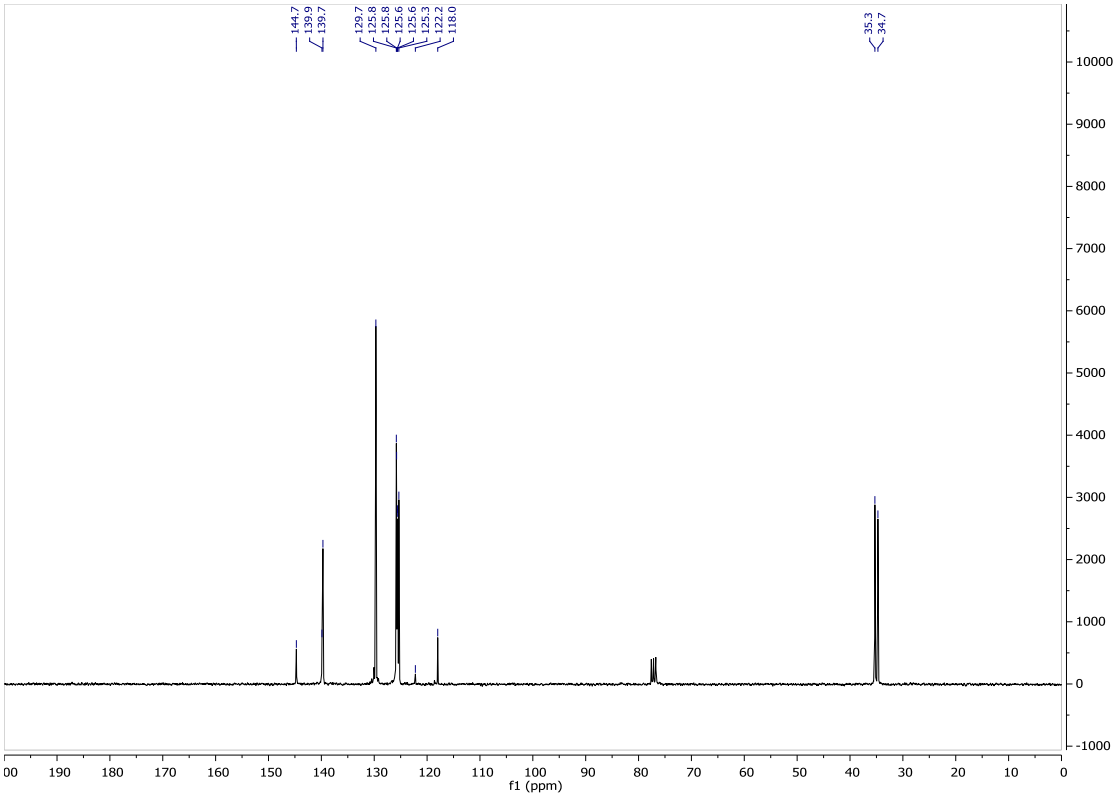
2-(1-cyano-2-phenylethyl)pyridine 1-oxide (13b)



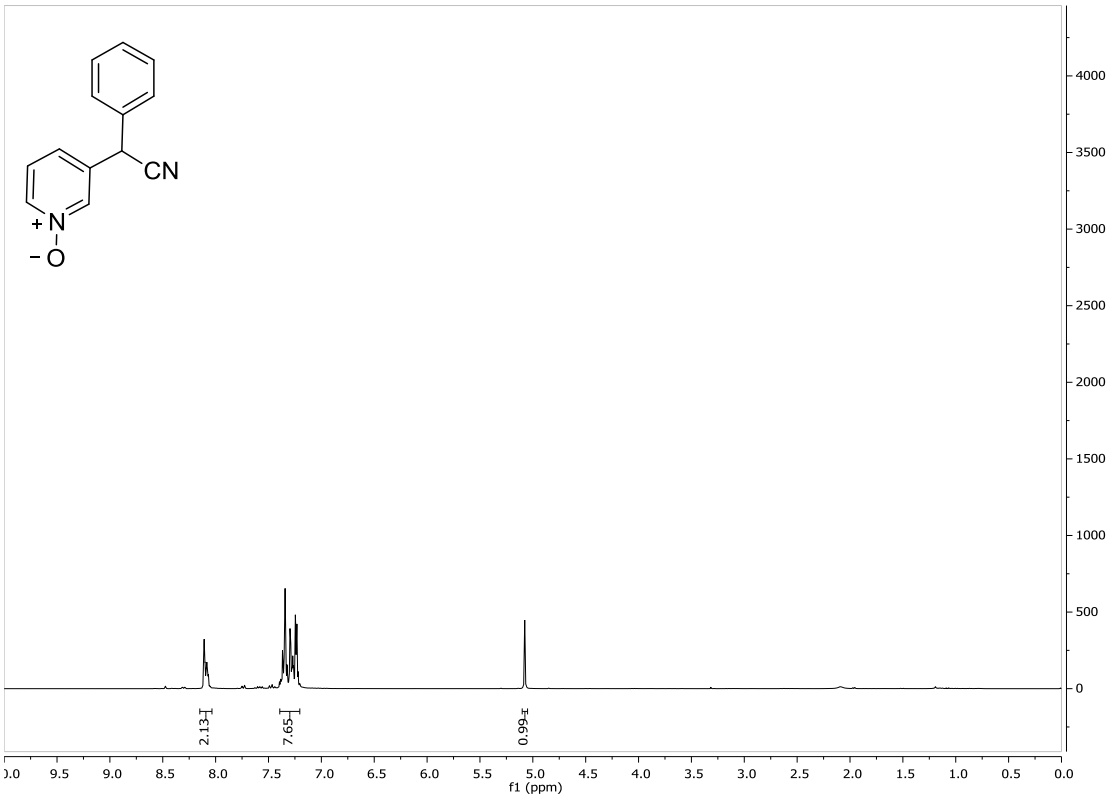


2-(1-cyano-2-(4-(trifluoromethyl)phenyl)ethyl)pyridine 1-oxide (13c)

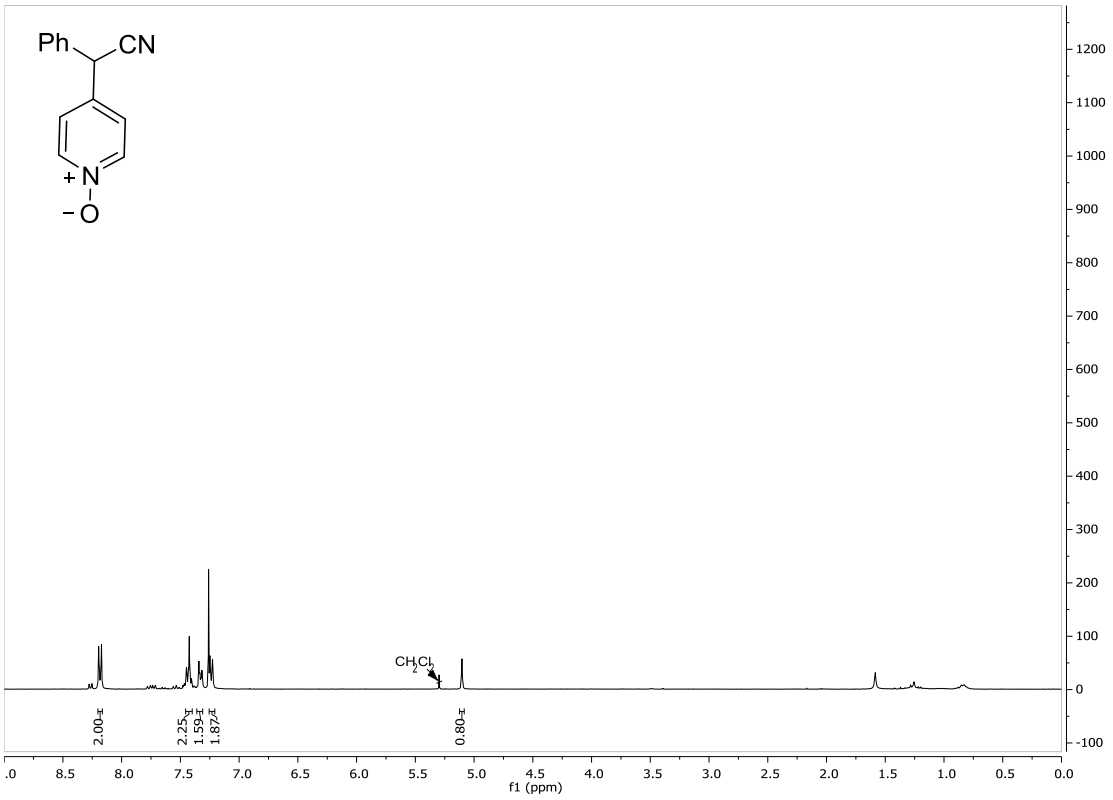




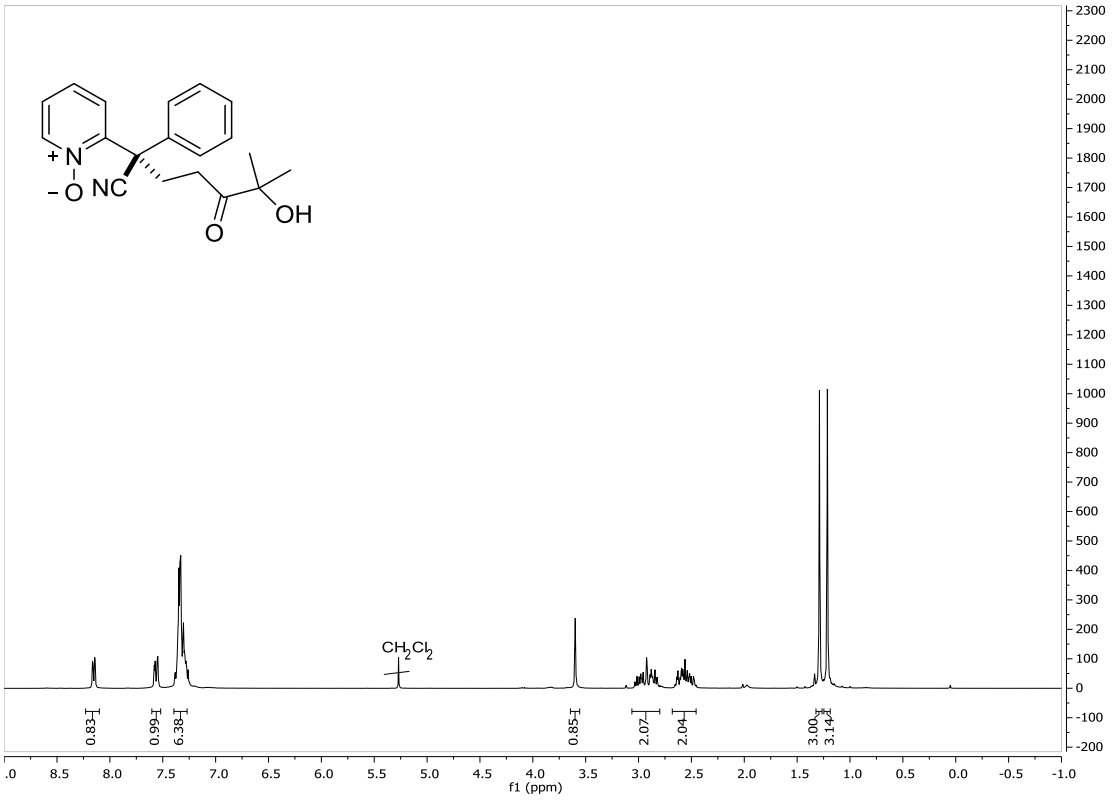
3-(cyano(phenyl)methyl)pyridine 1-oxide (11)

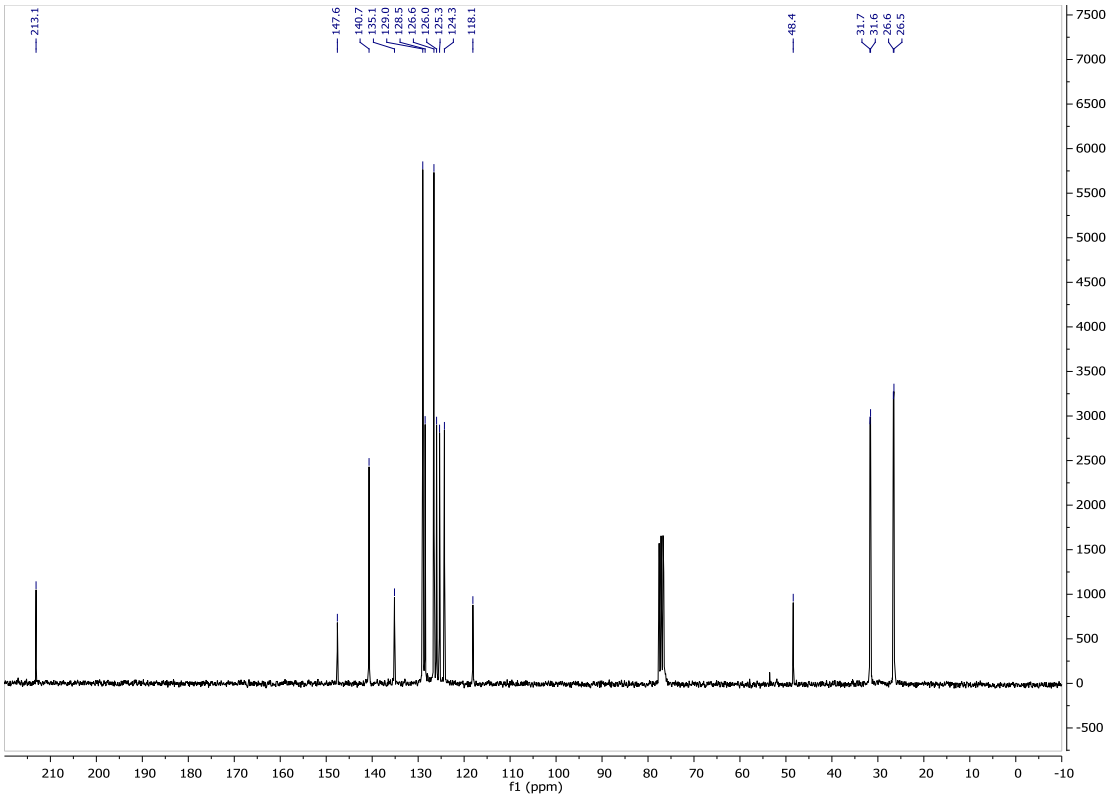


4-(cyano(phenyl)methyl)pyridine 1-oxide (12)

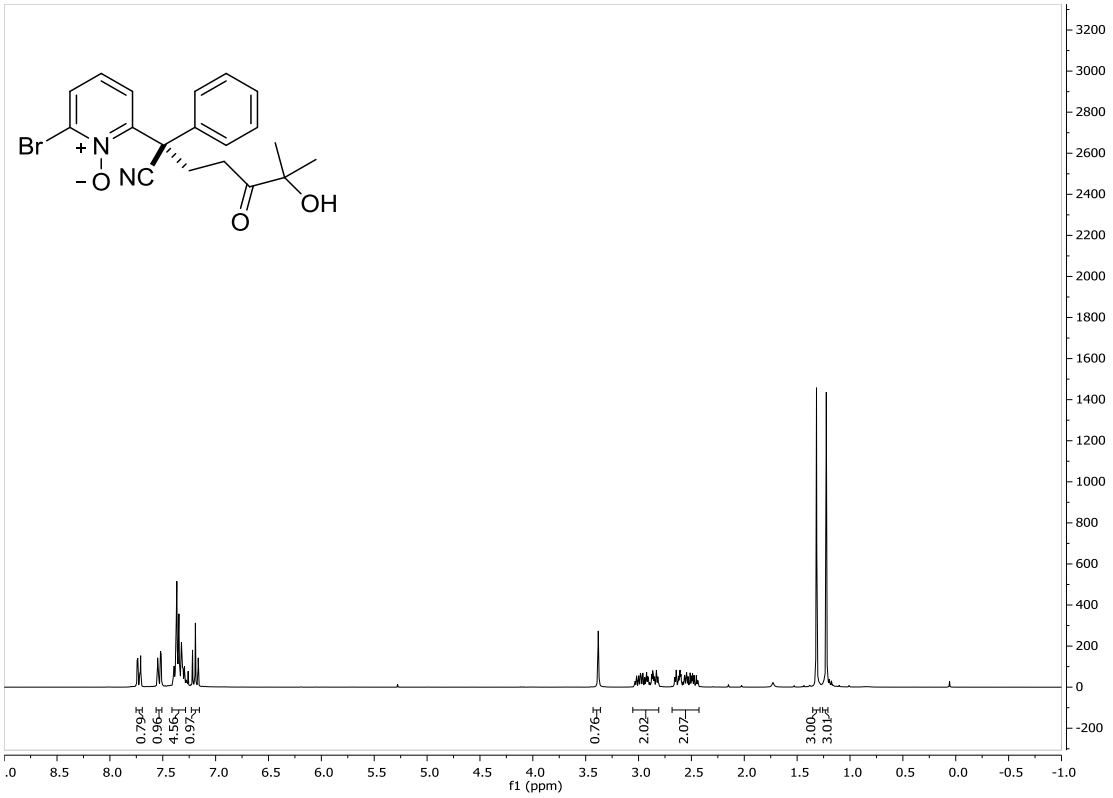


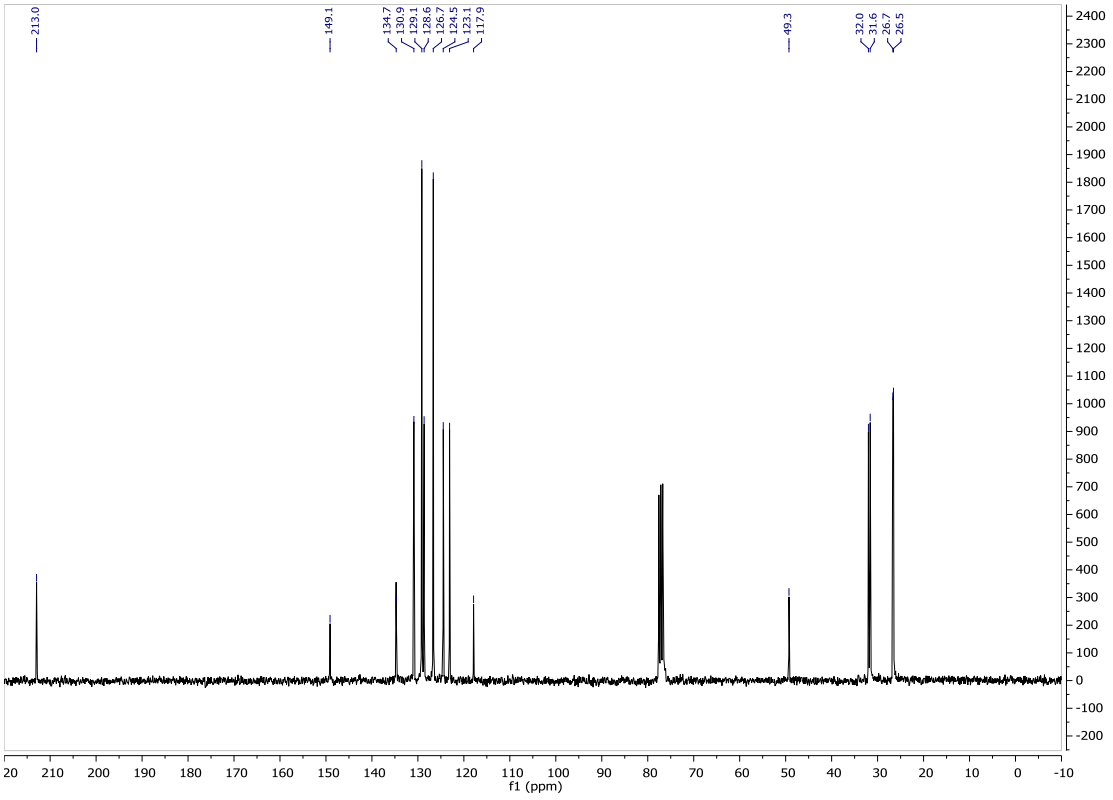
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9a)



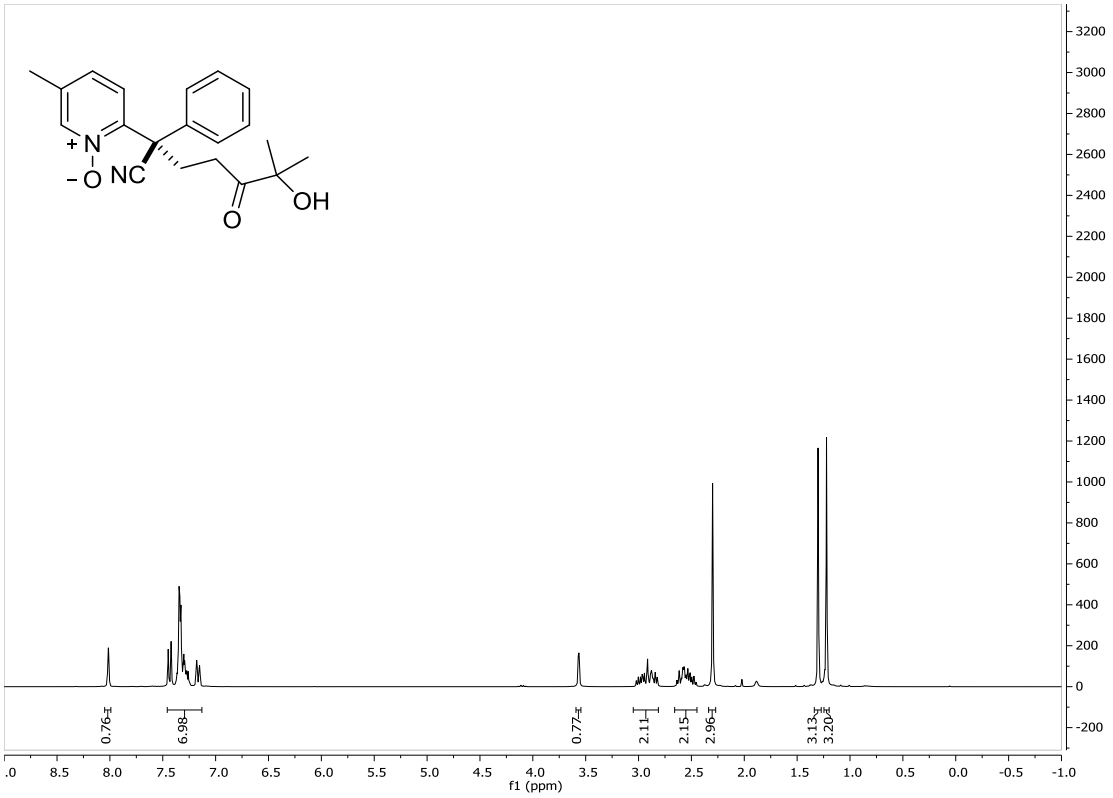


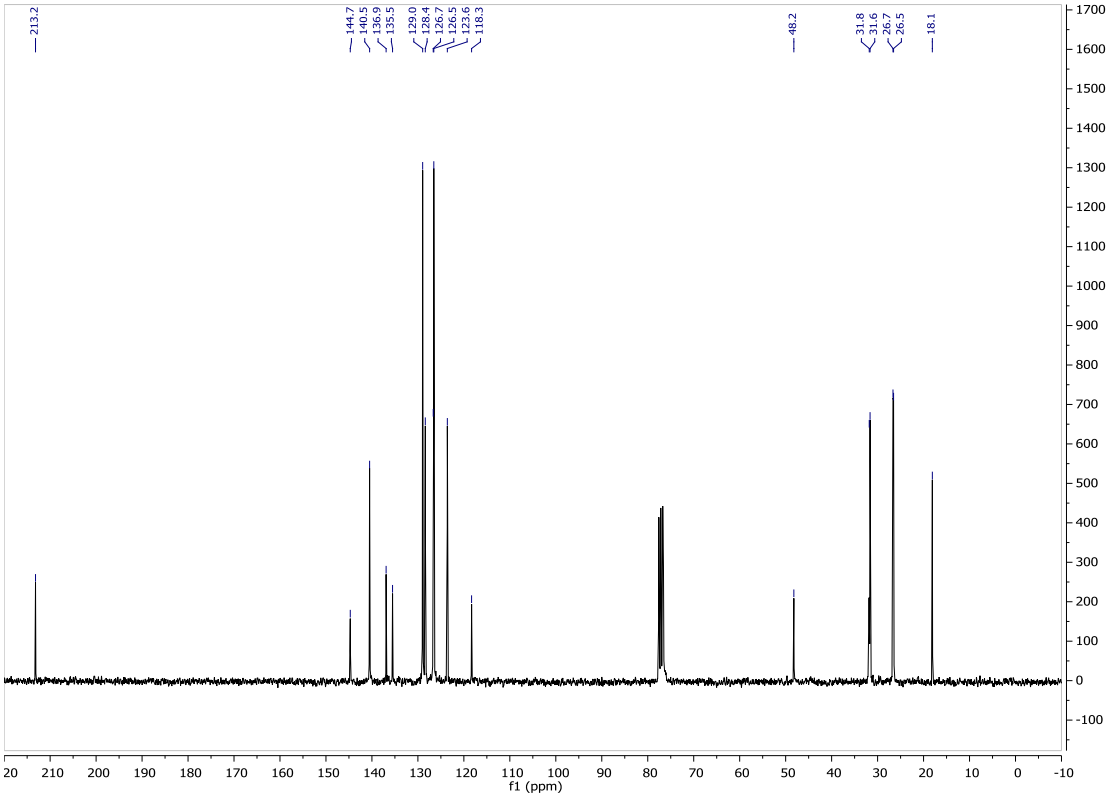
(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9b)



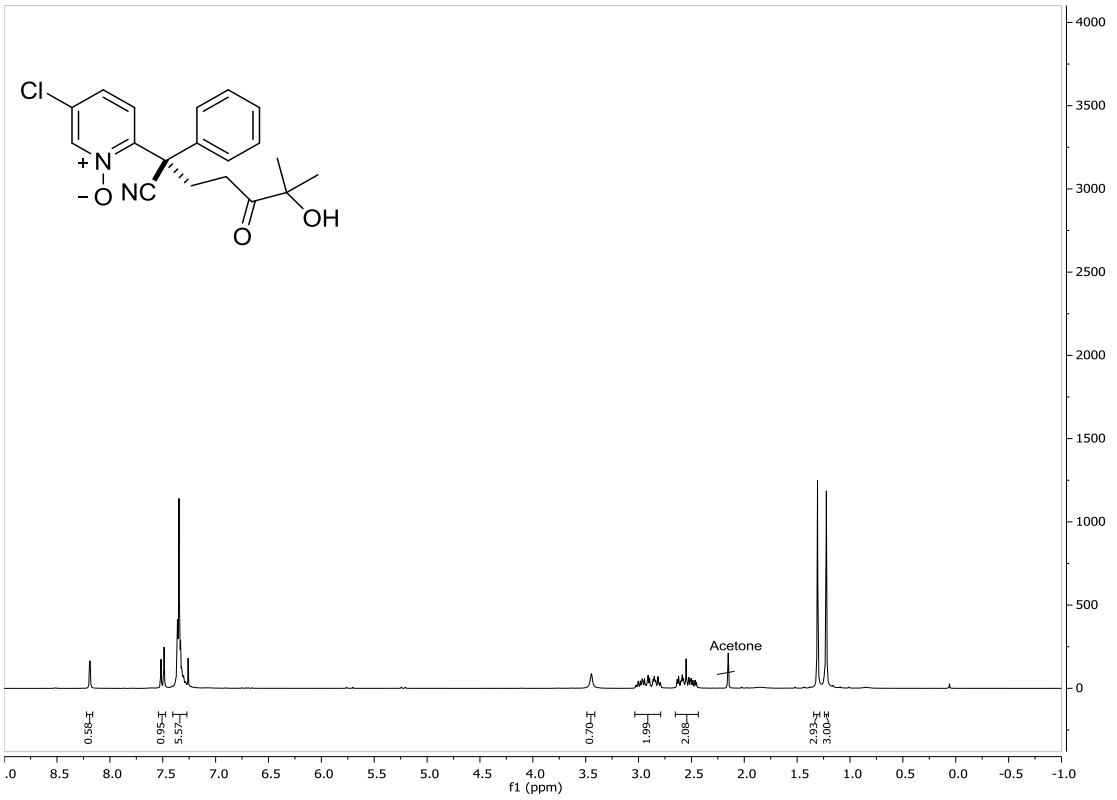


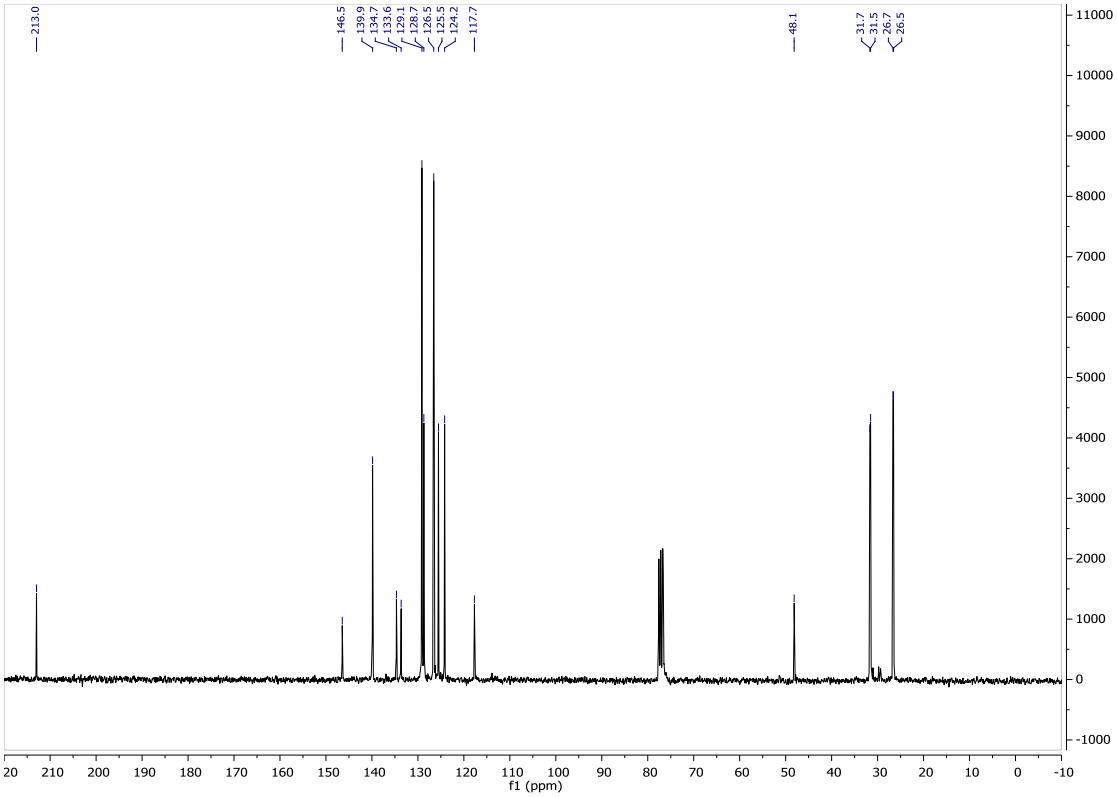
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)-5-methylpyridine 1-oxide (9c)



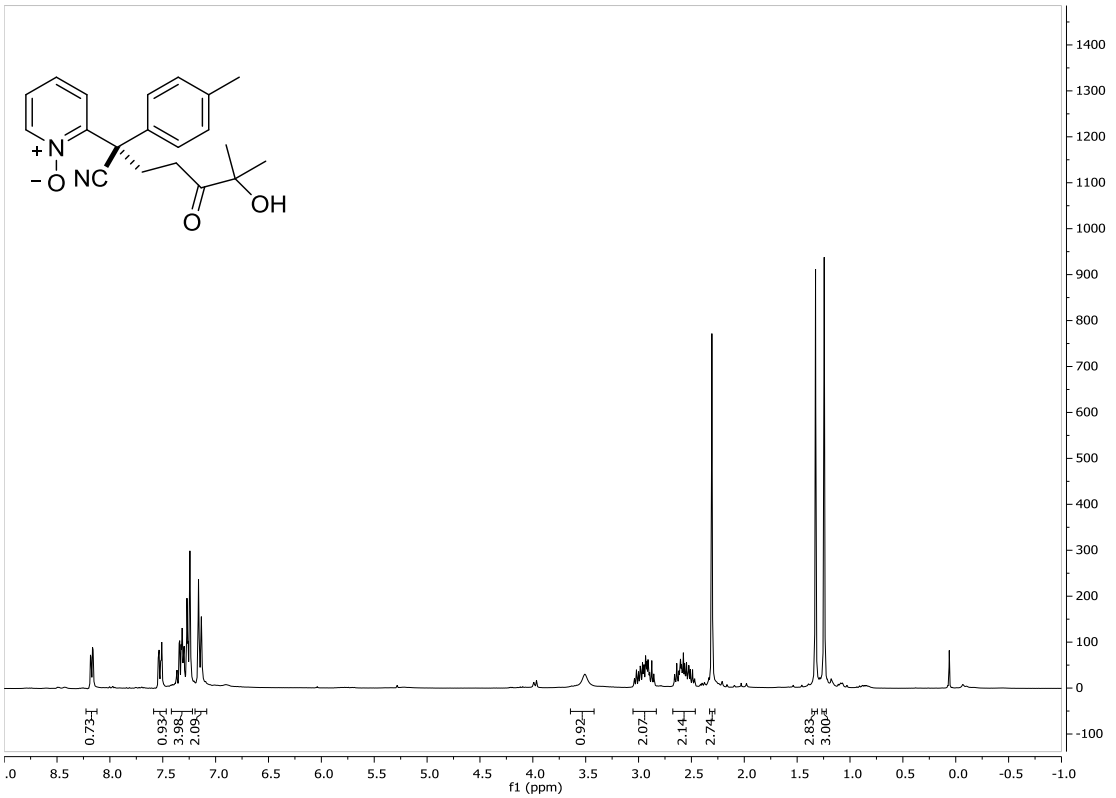


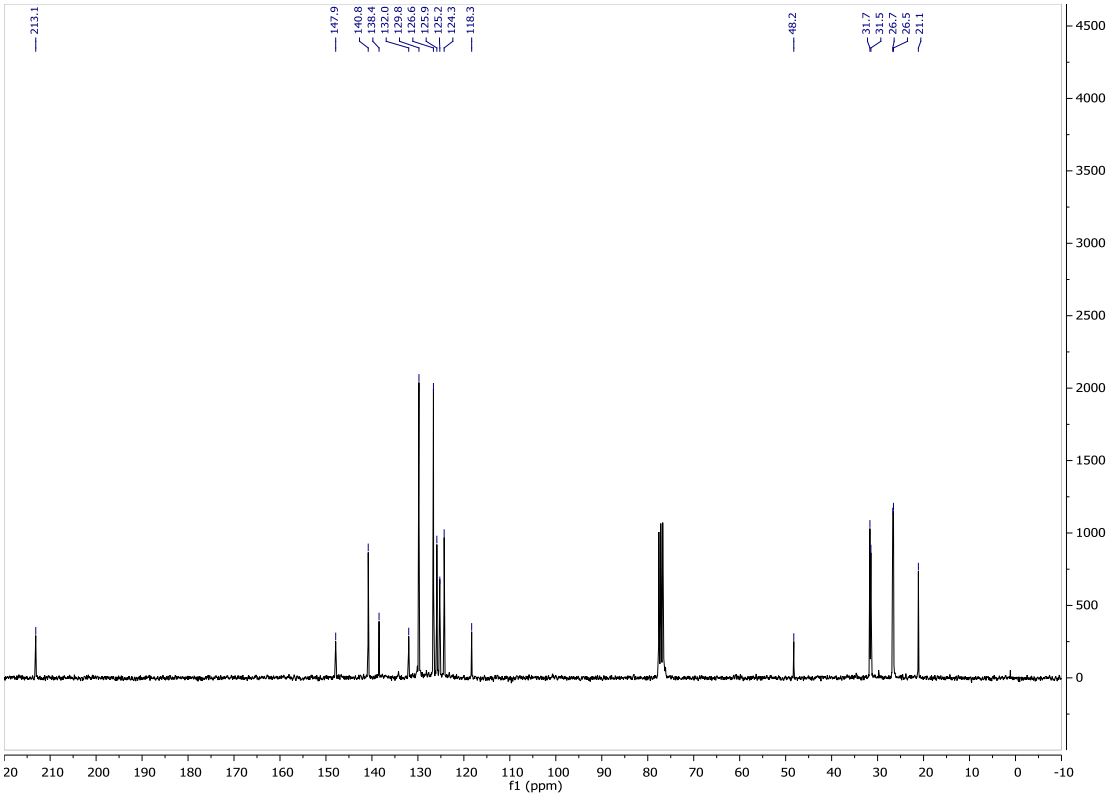
5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9d)



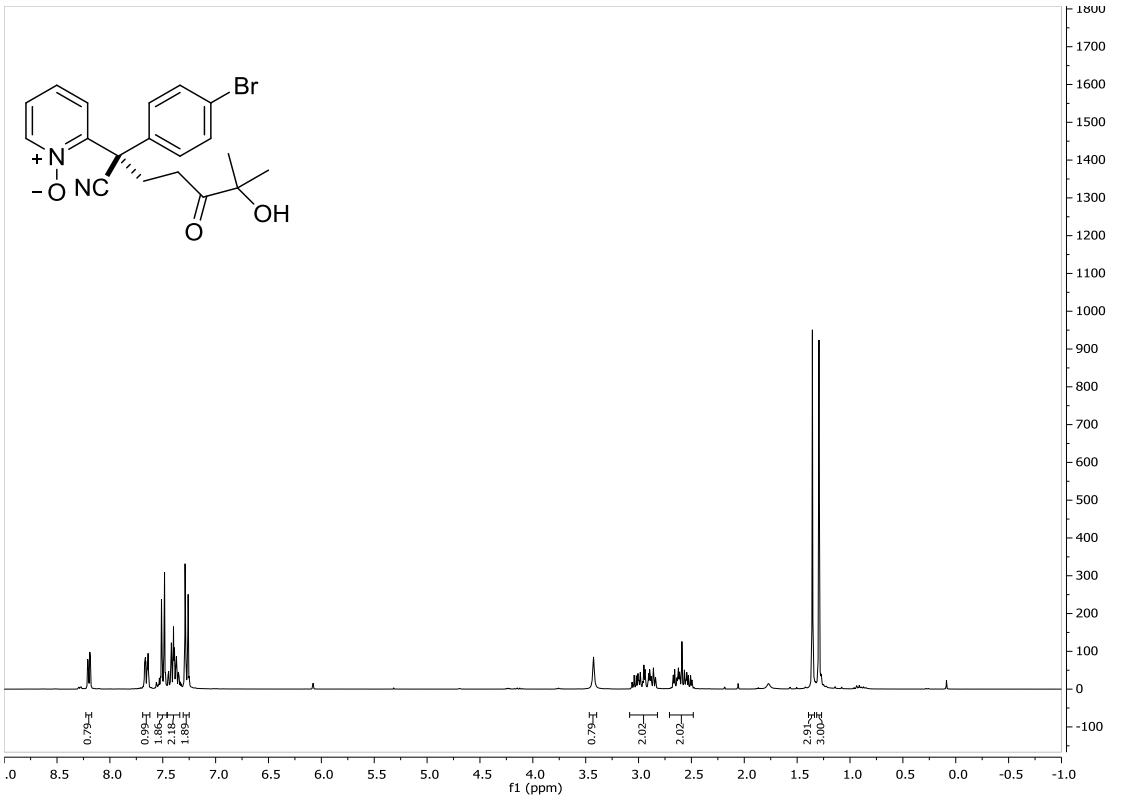


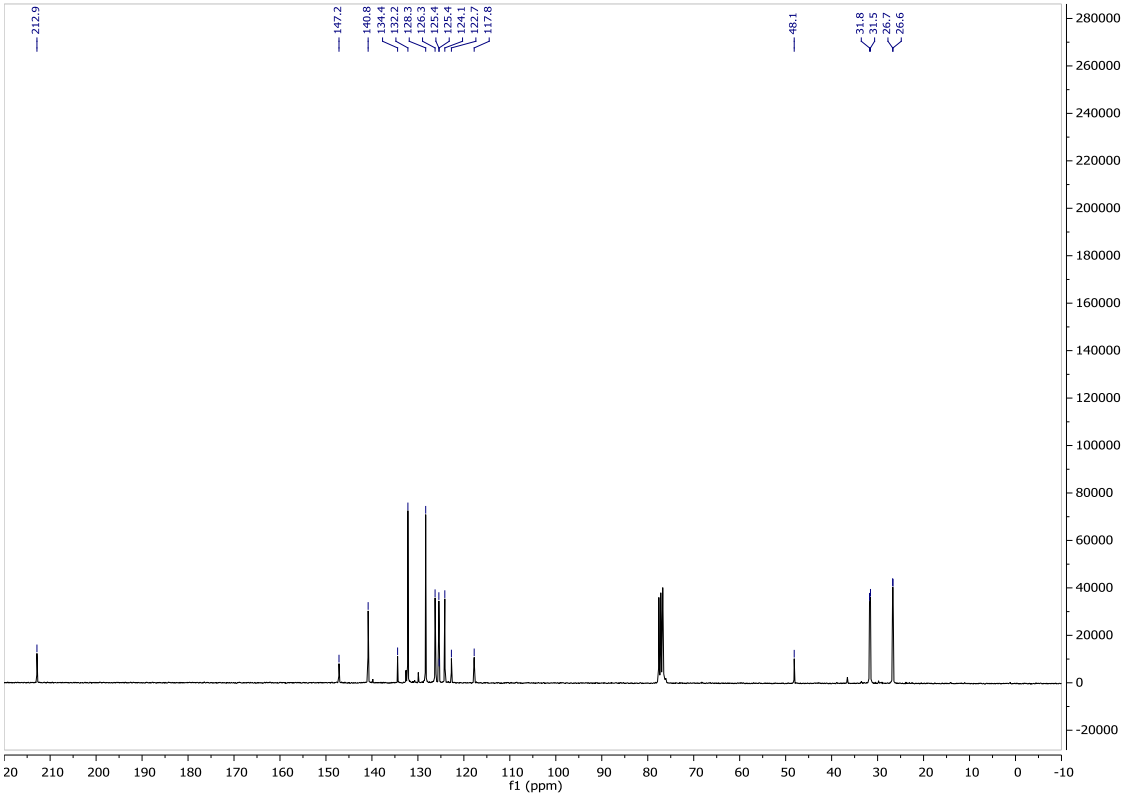
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9e)



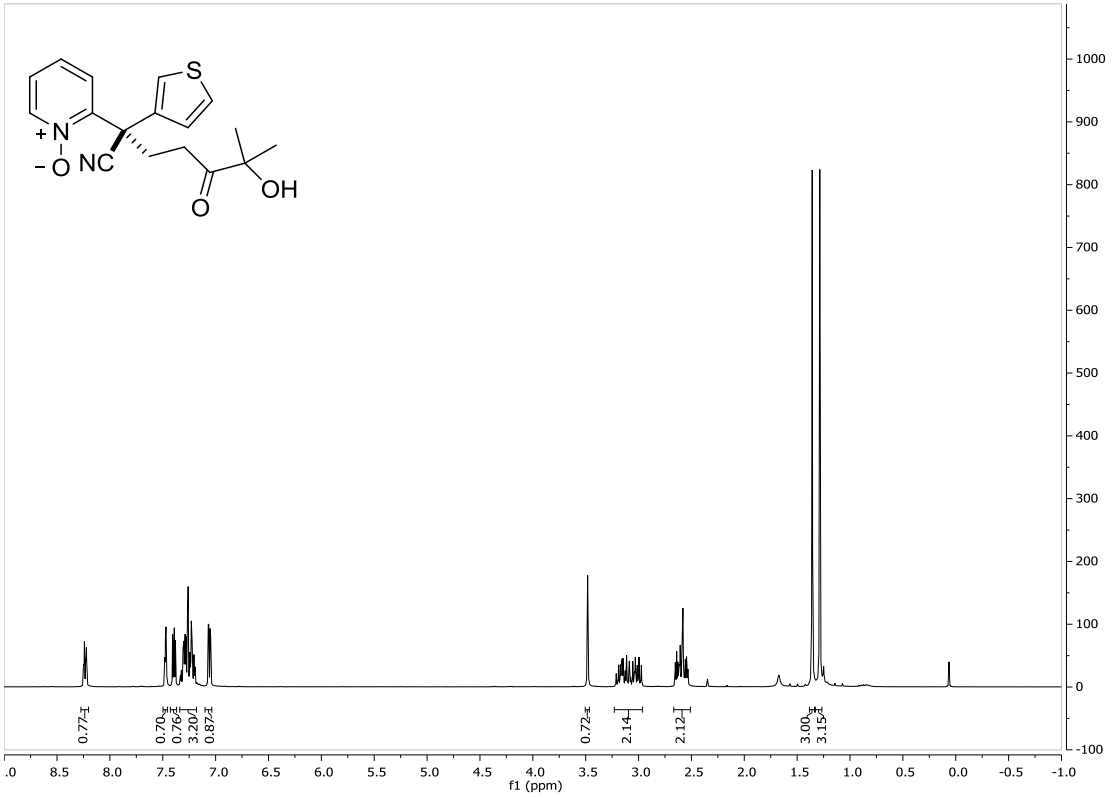


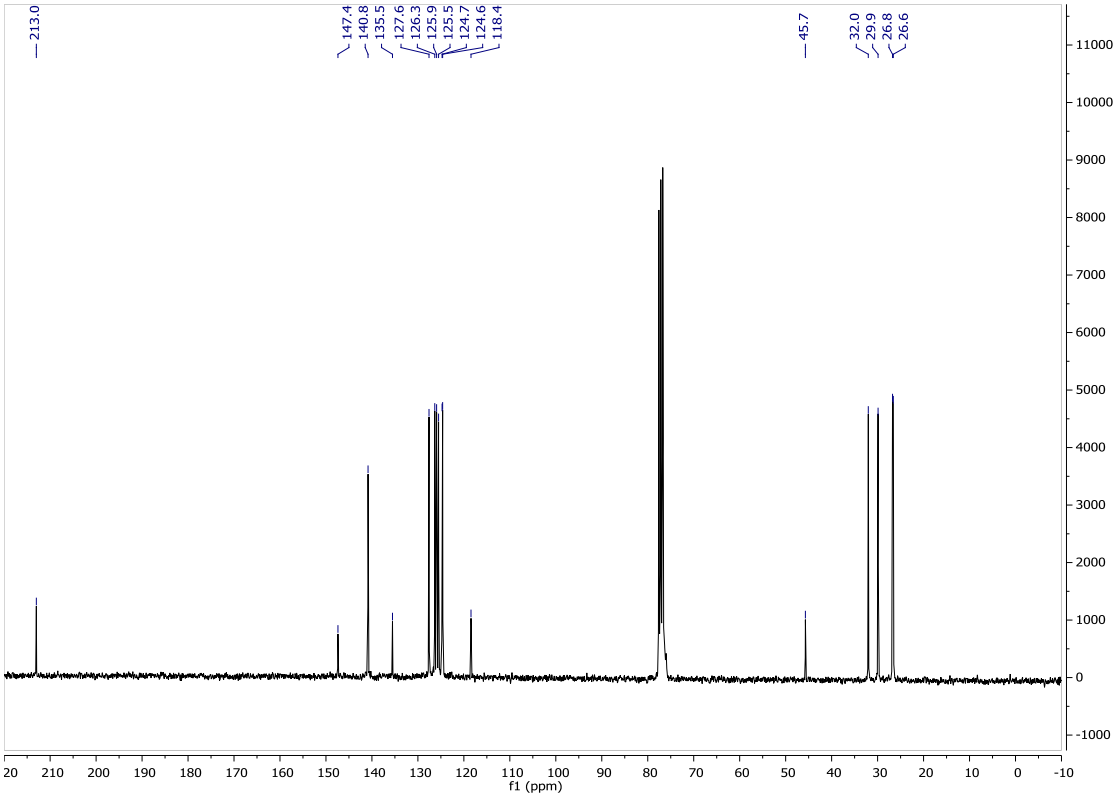
(R)-2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyridine 1-oxide (9f)



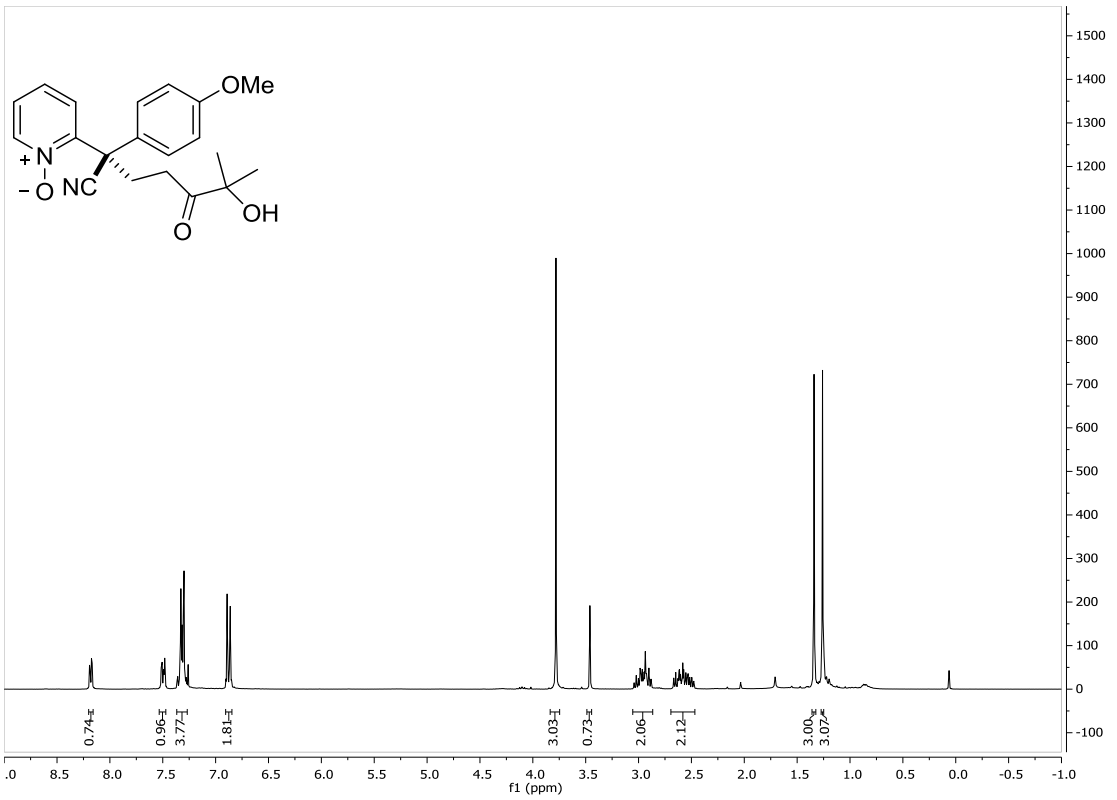


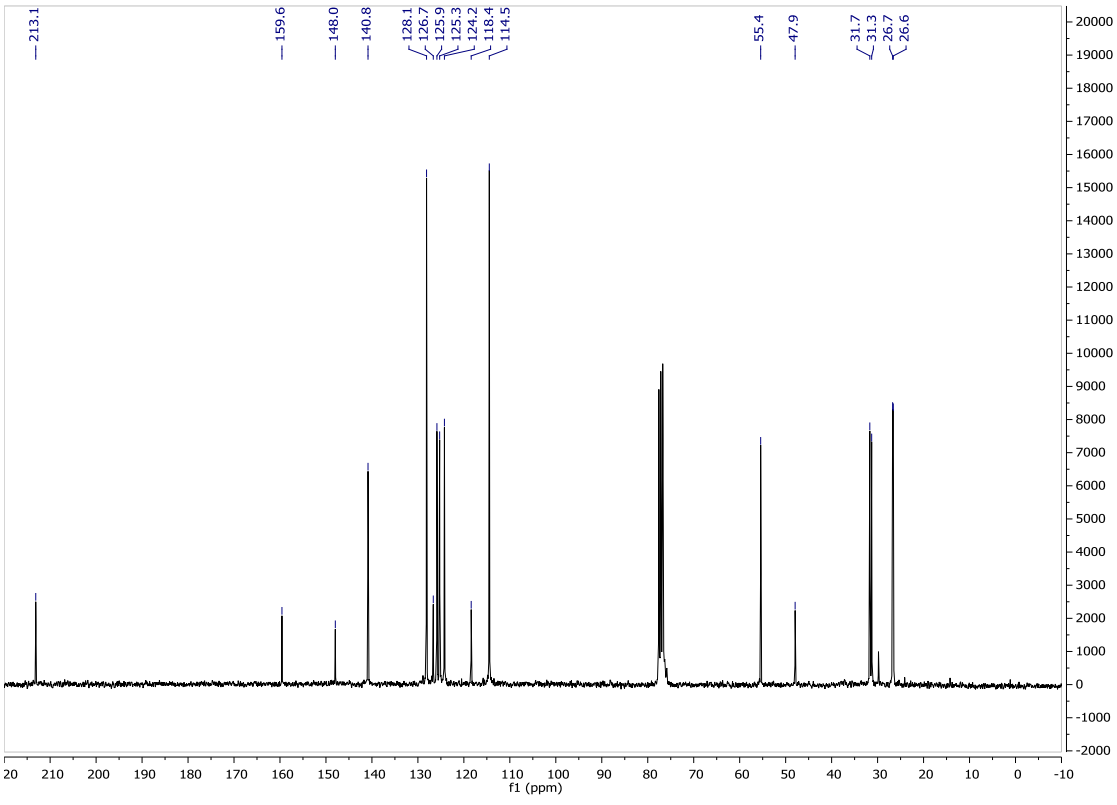
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(thiophen-3-yl)hexyl)pyridine 1-oxide (9g)



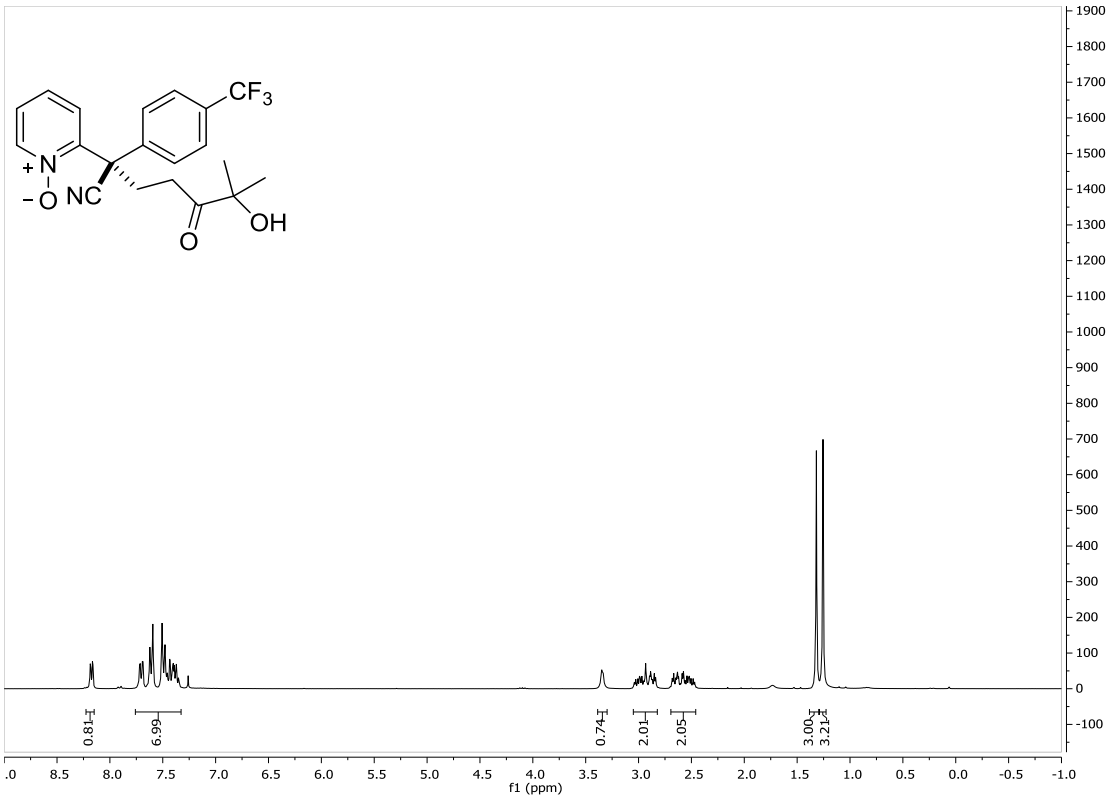


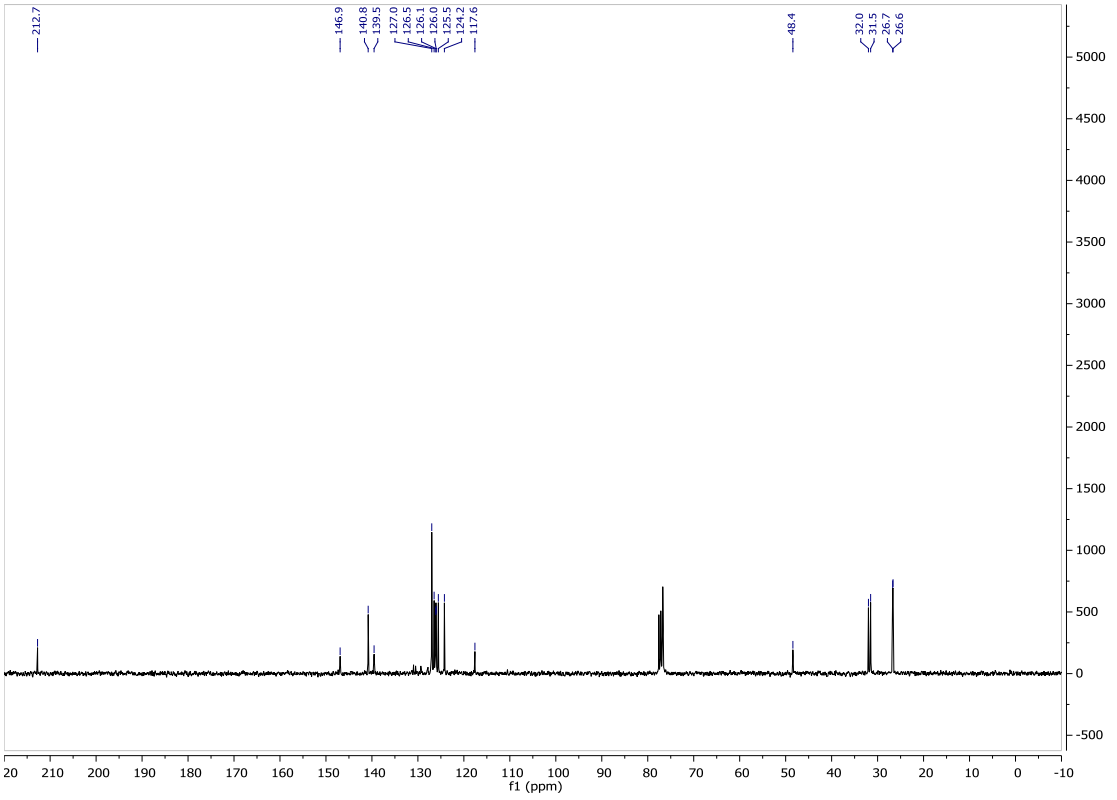
(R)-2-(1-cyano-5-hydroxy-1-(4-methoxyphenyl)-5-methyl-4-oxohexyl)pyridine 1-oxide (9h)



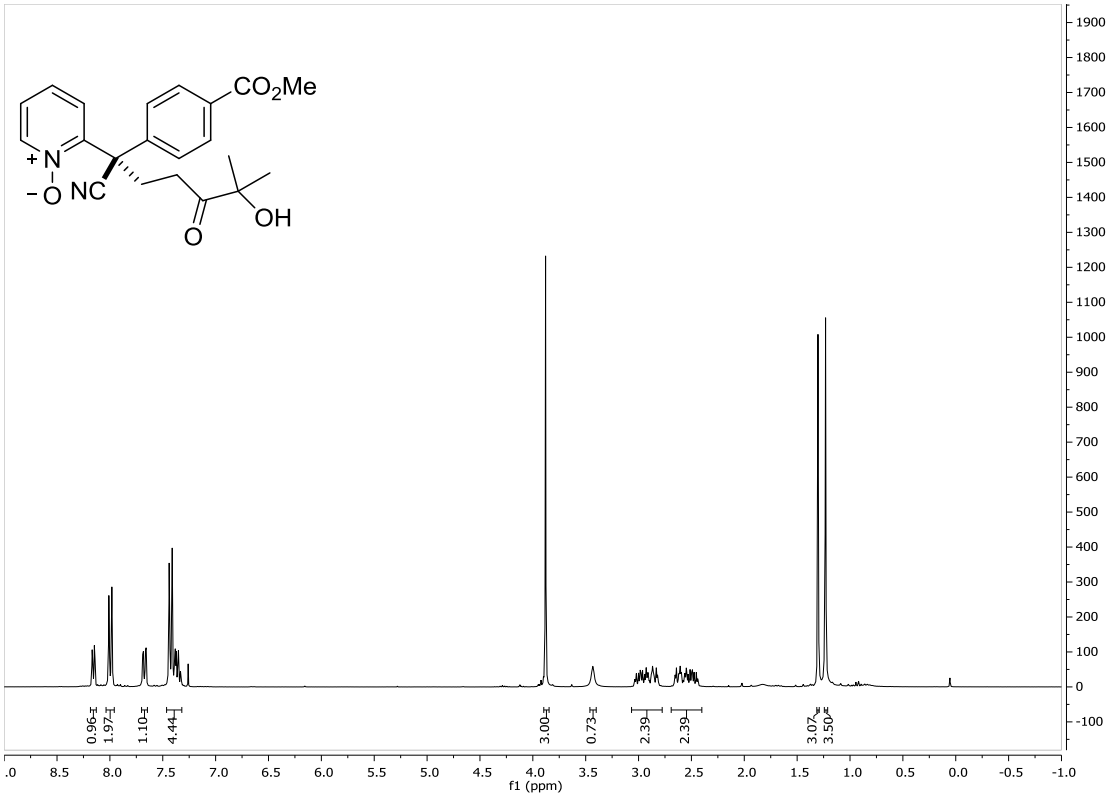


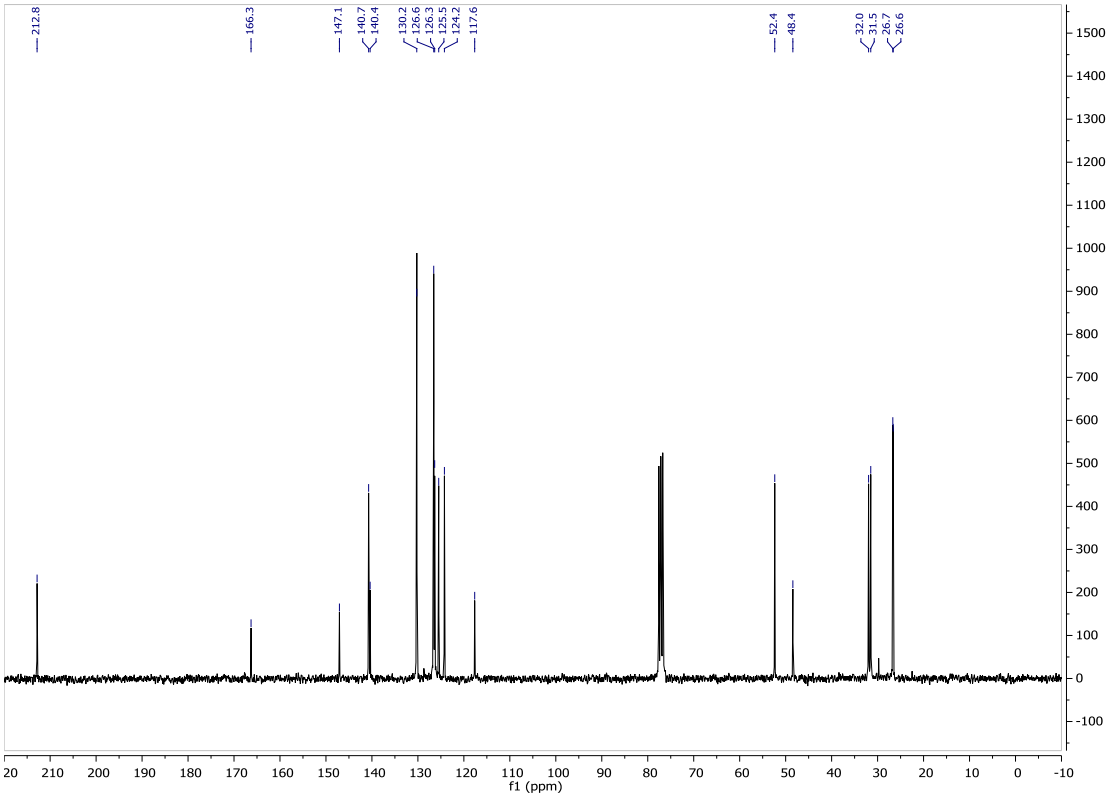
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4(trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9i)



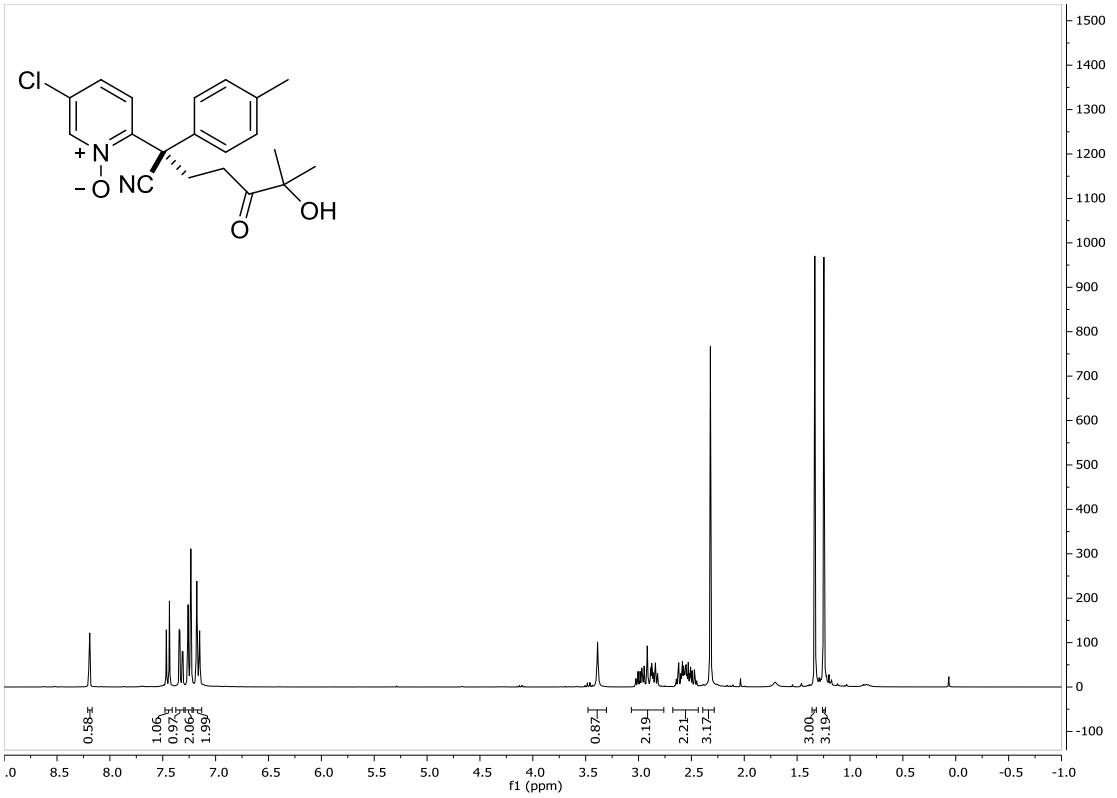


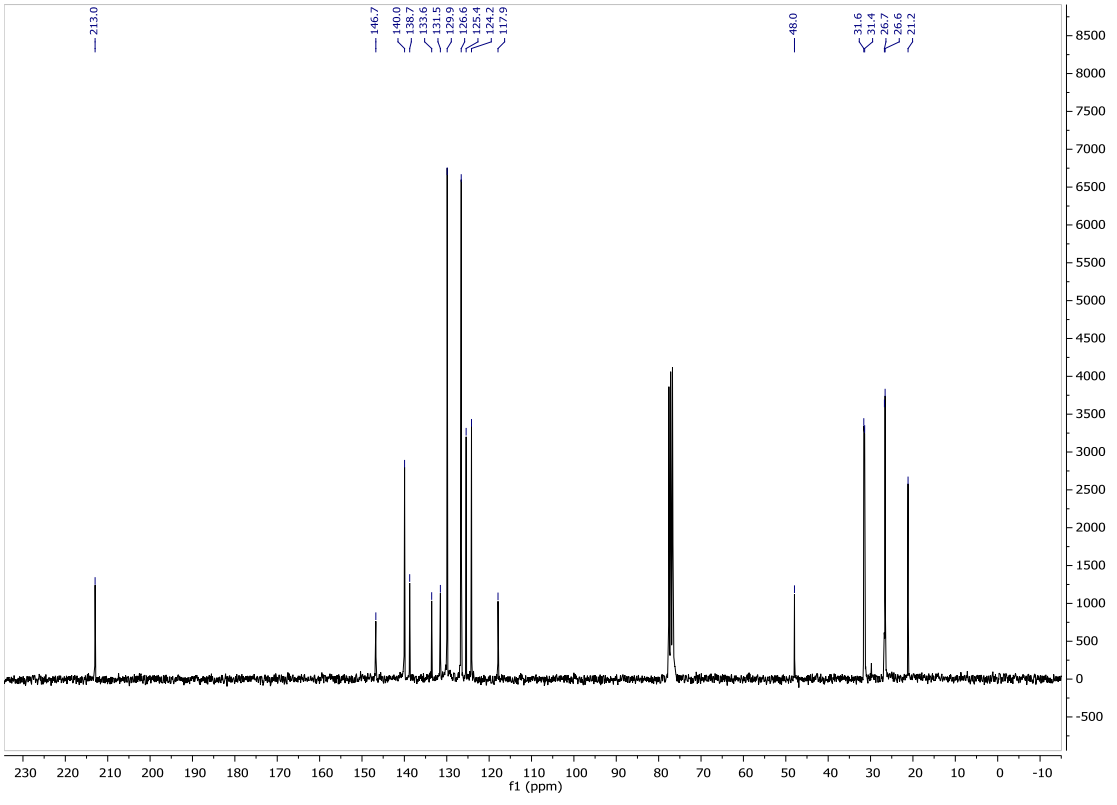
(R)-2-(1-cyano-5-hydroxy-1-(4-(methoxycarbonyl)phenyl)-5-methyl-4 oxohexyl)pyridine 1-oxide (9j)



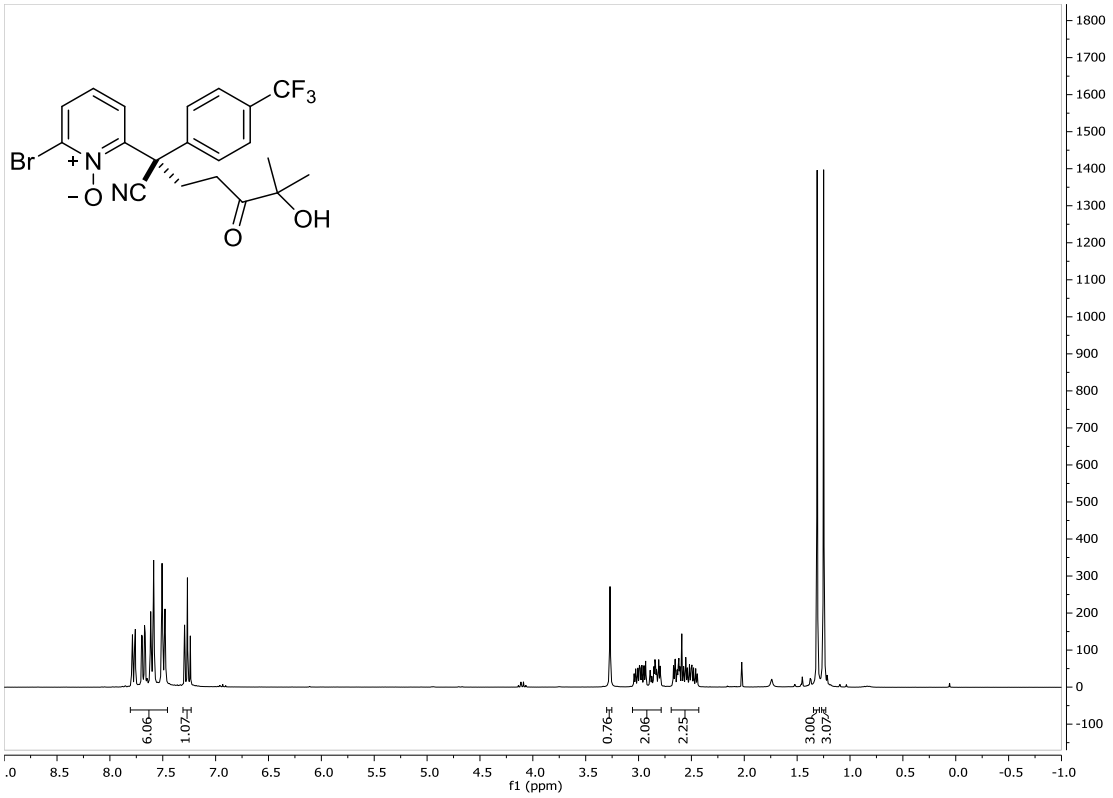


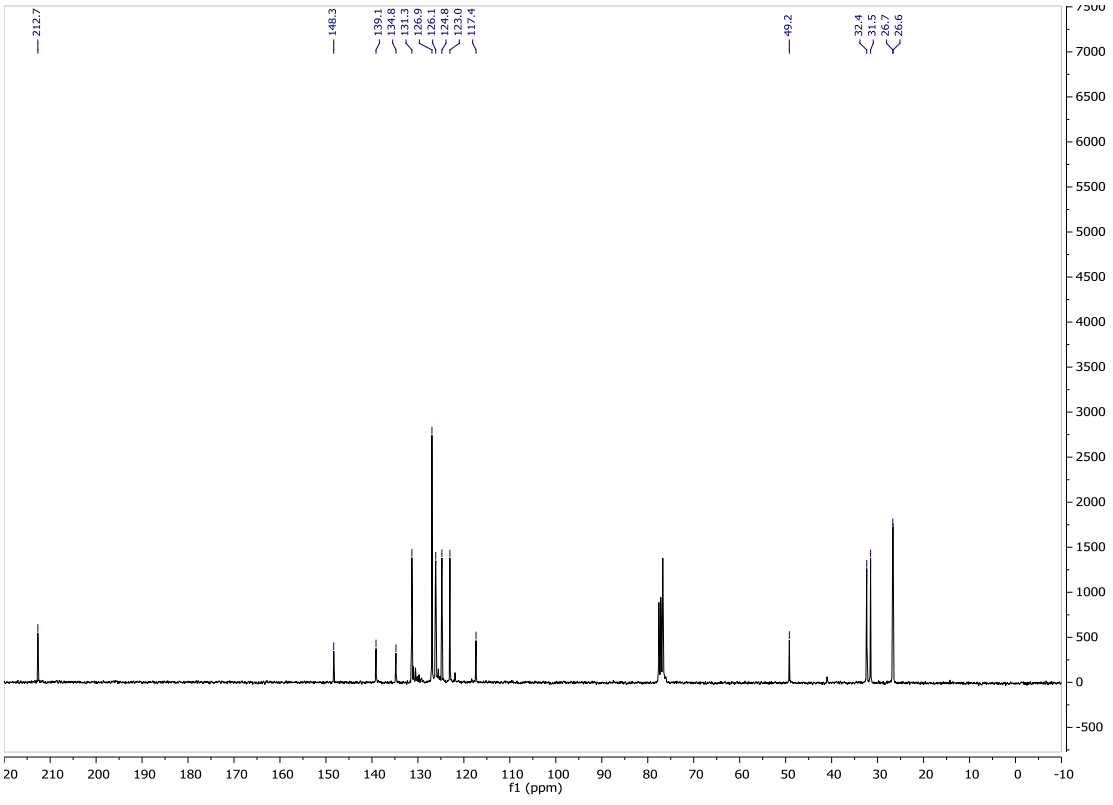
(R)-5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9k)



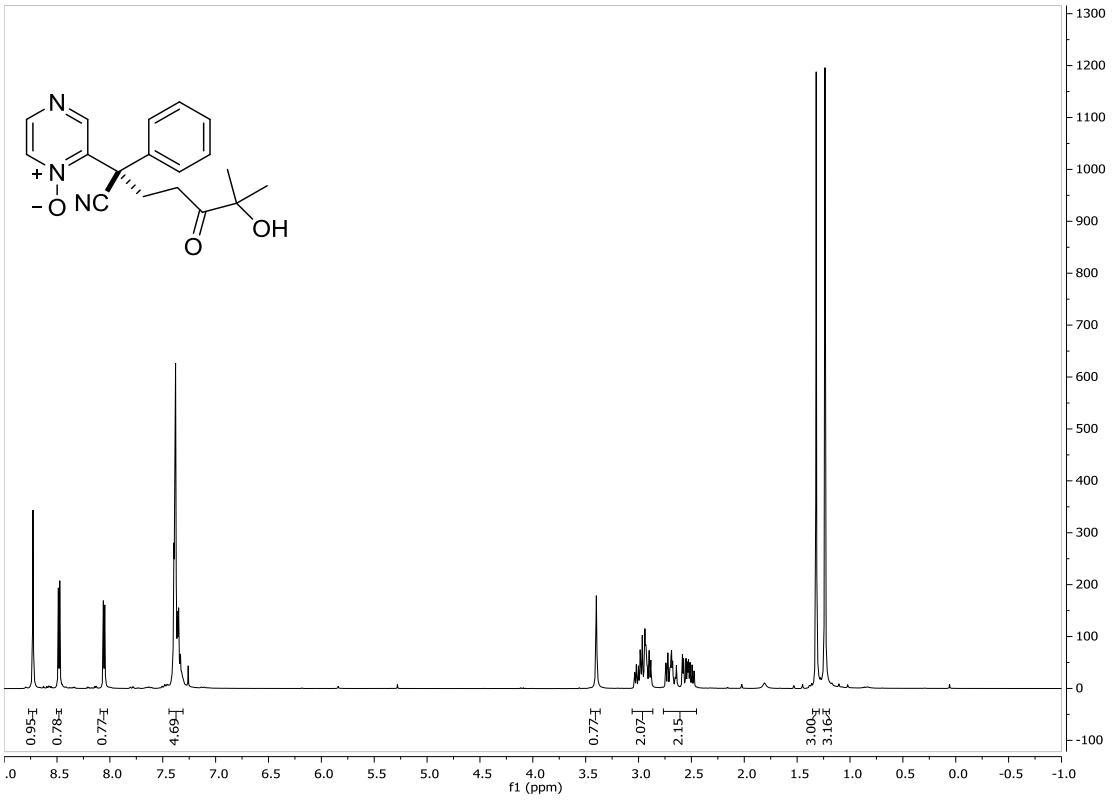


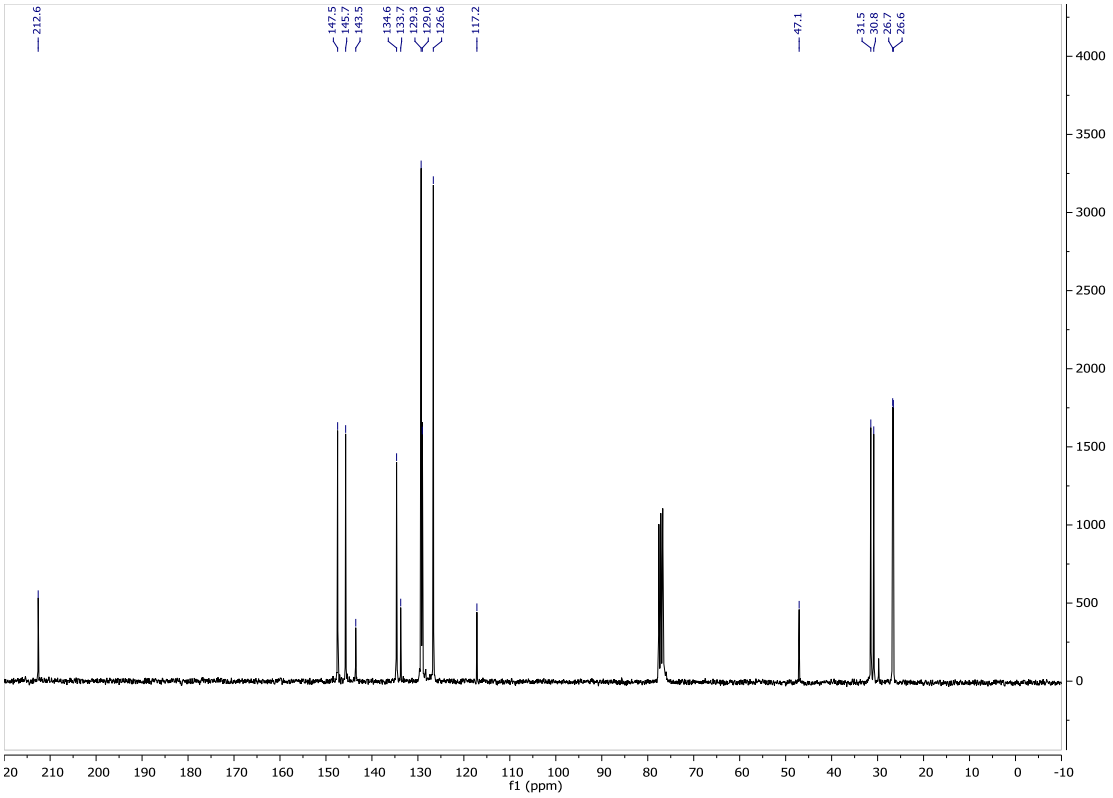
(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4 (trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9l)



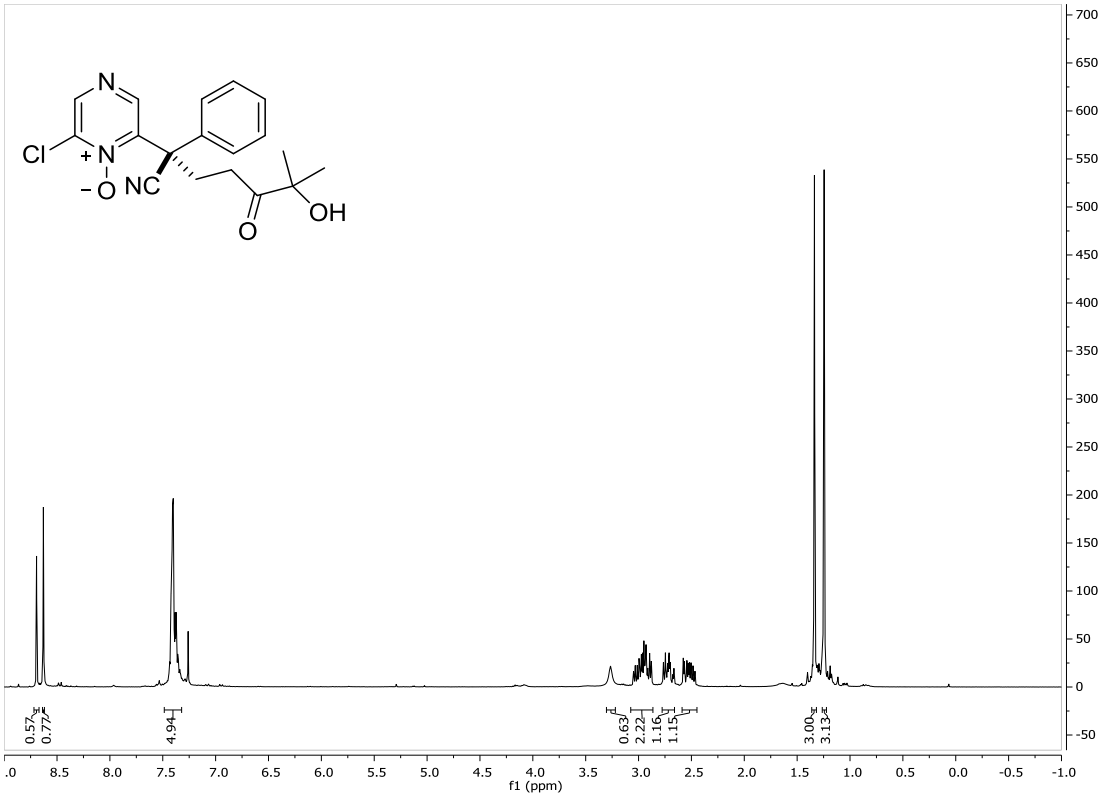


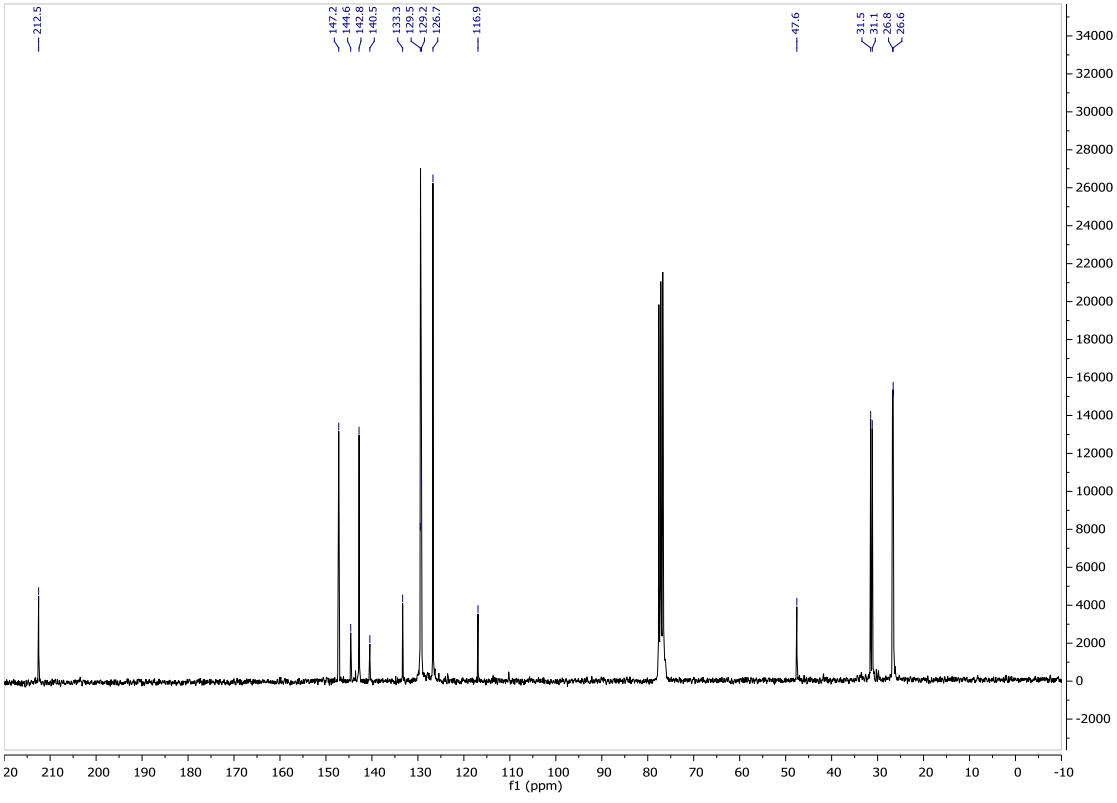
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16a)



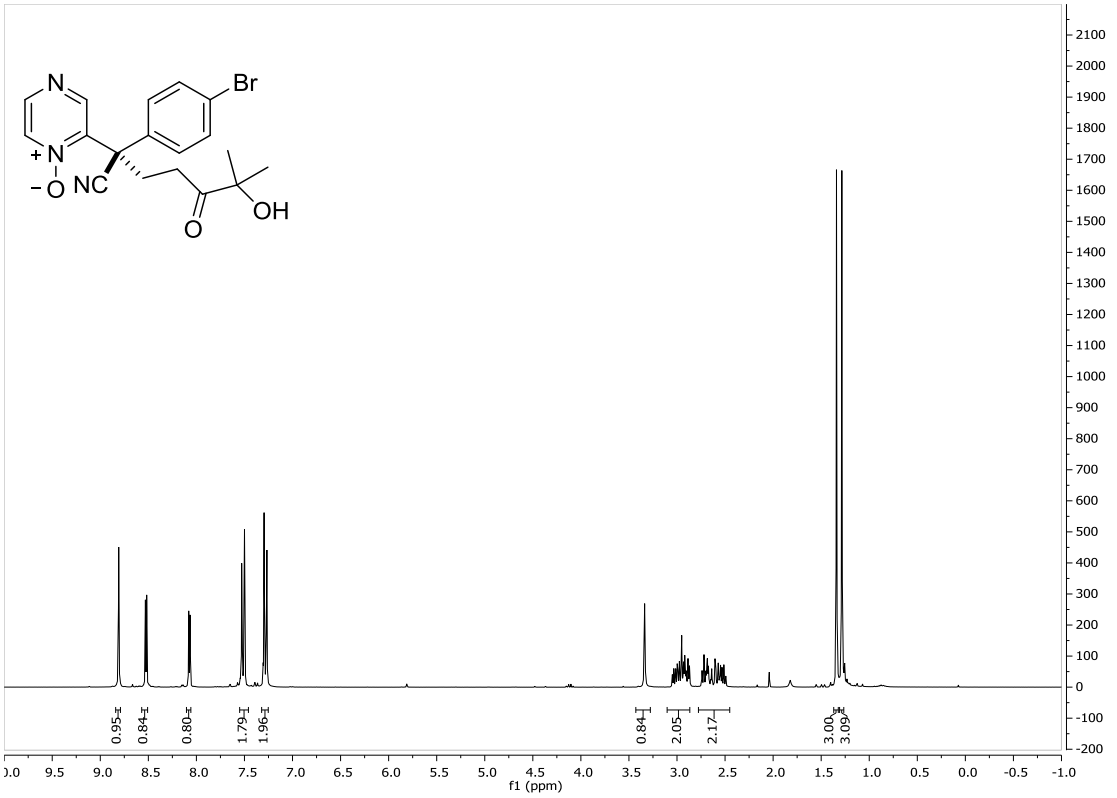


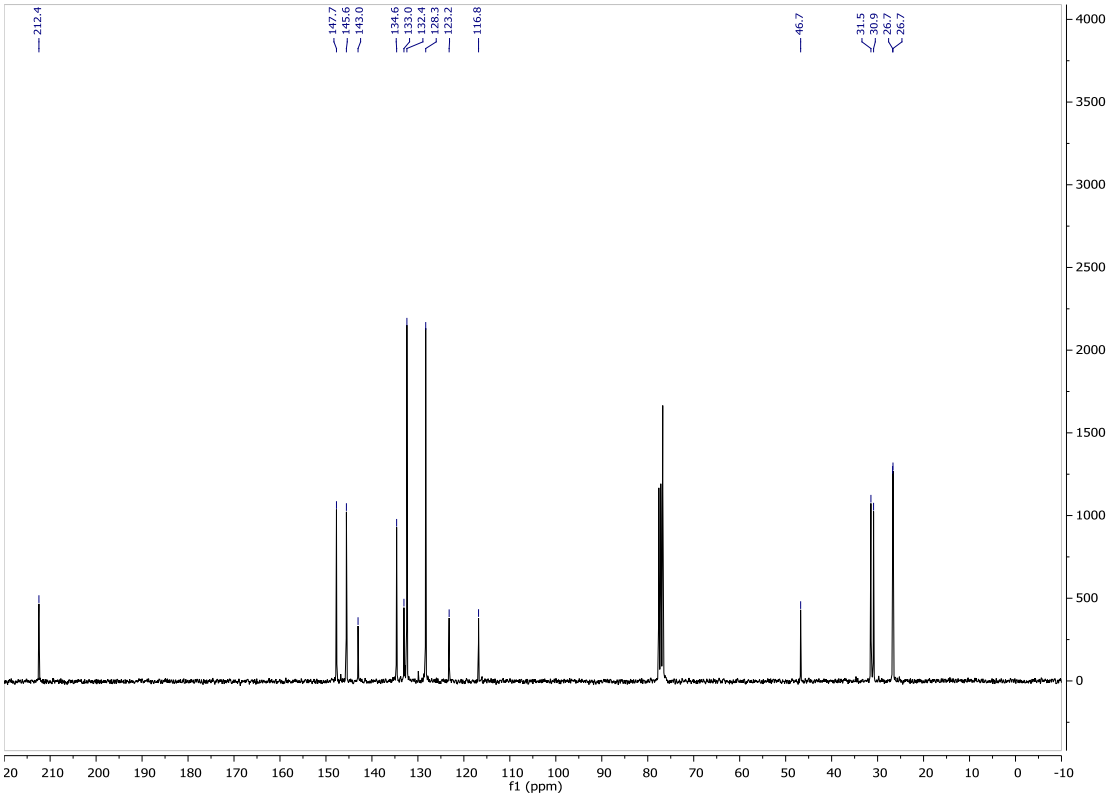
(R)-2-chloro-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16b)



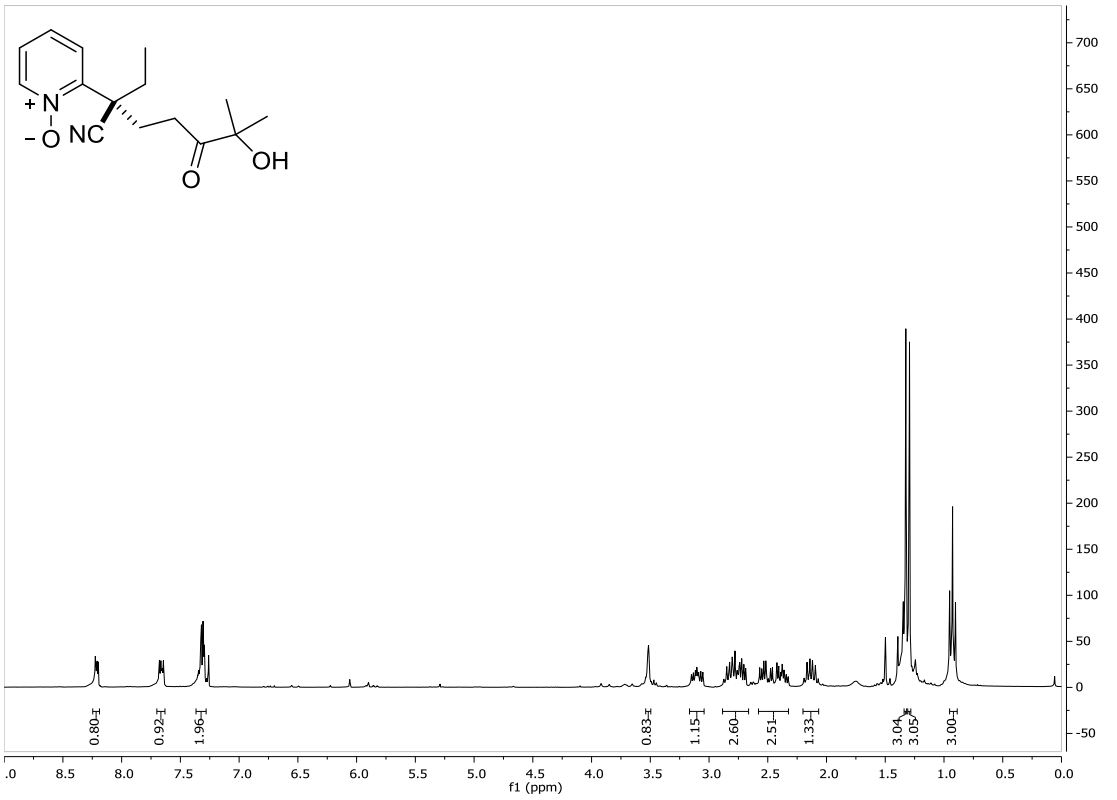


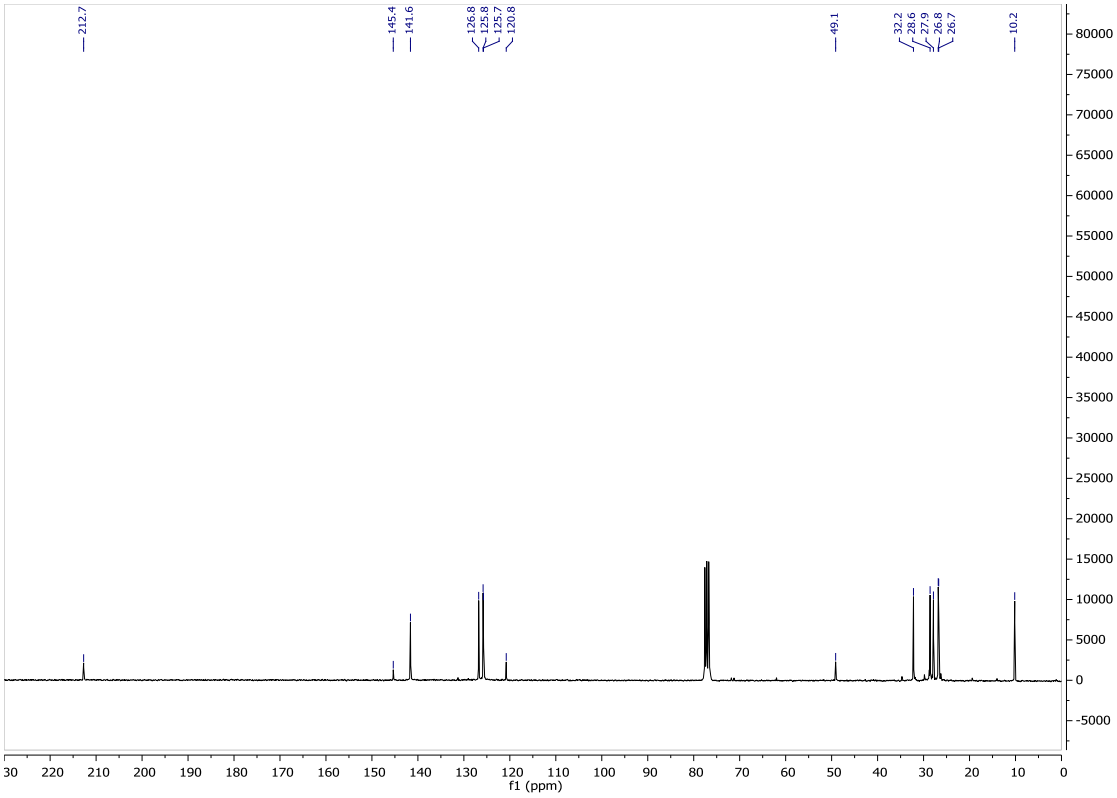
(R)- 2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyrazine 1-oxide (16c)



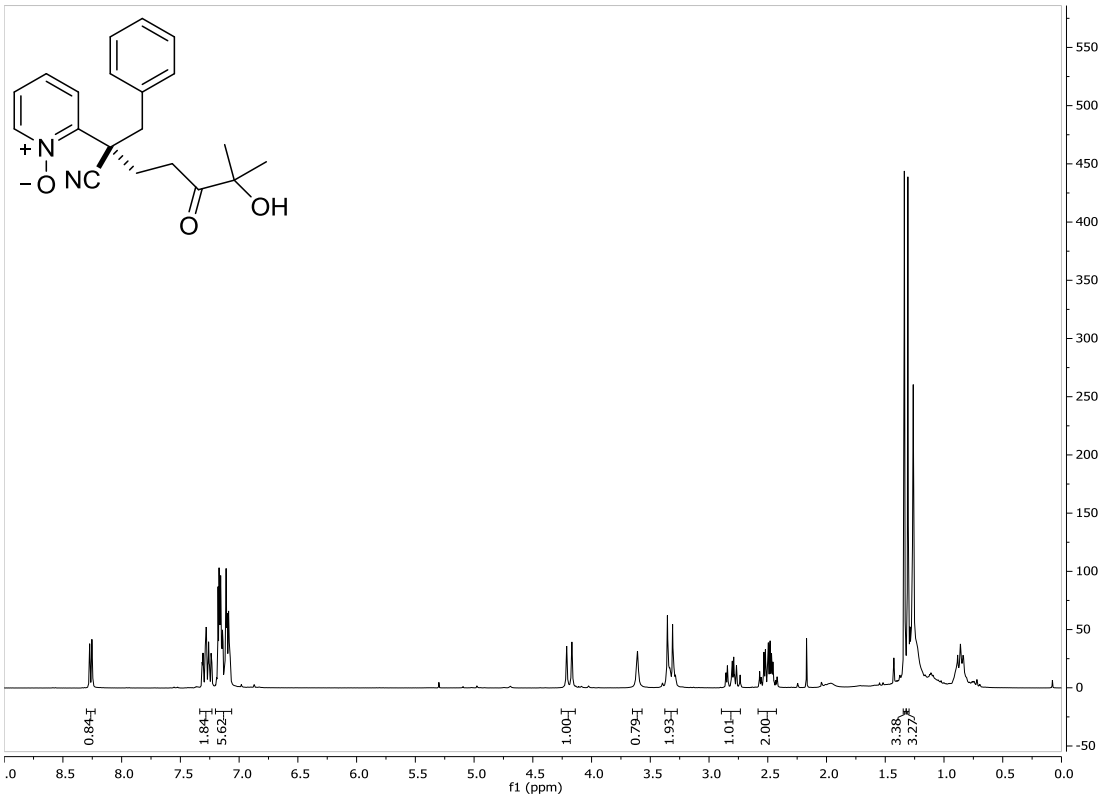


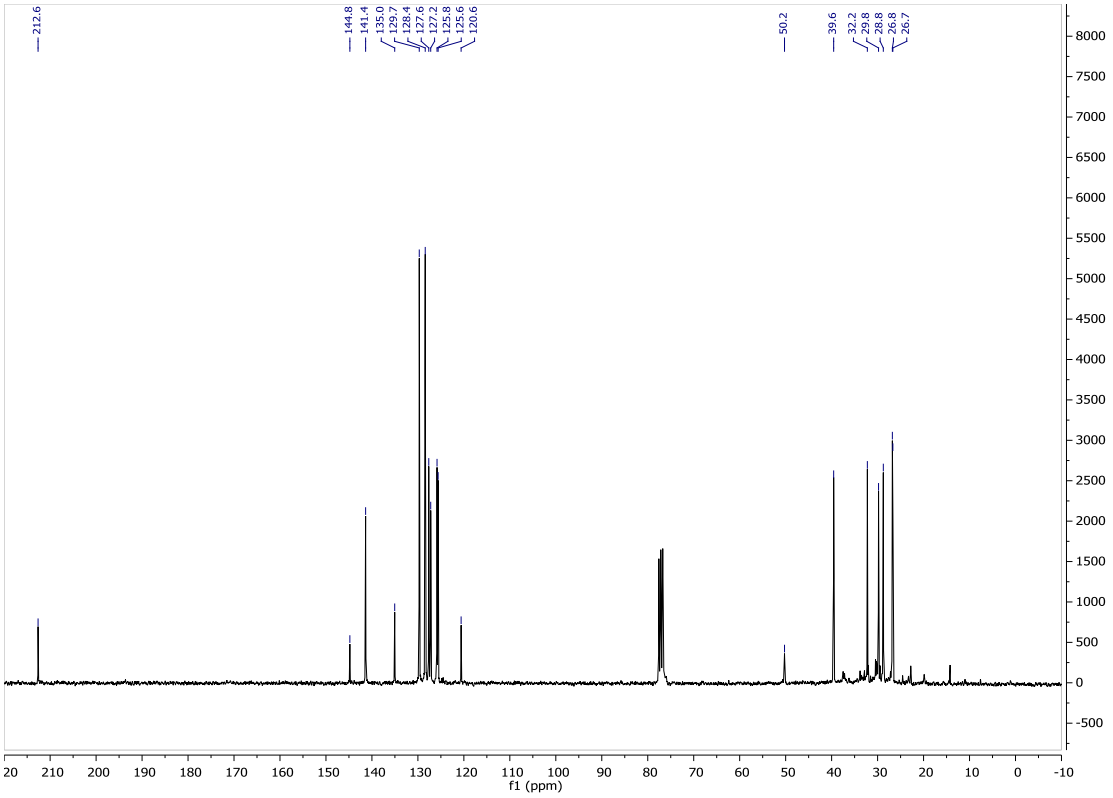
(S)-2-(3-cyano-7-hydroxy-7-methyl-6-oxooctan-3-yl)pyridine 1-oxide (17a)



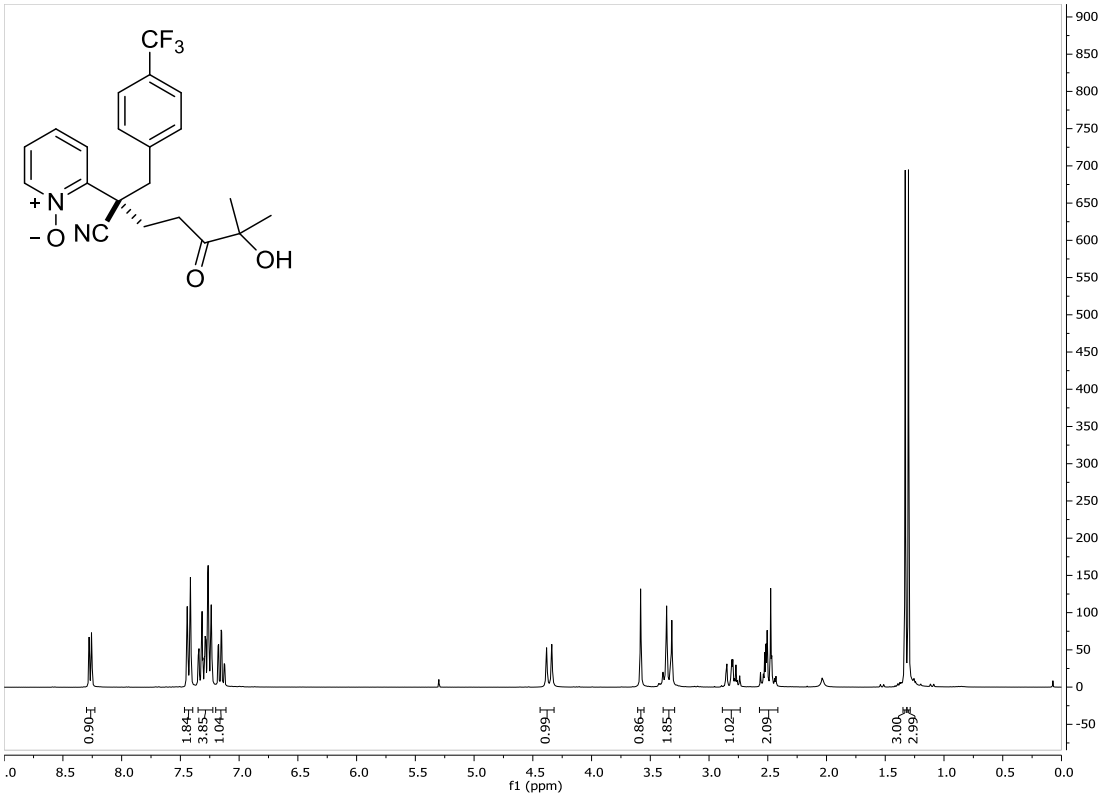


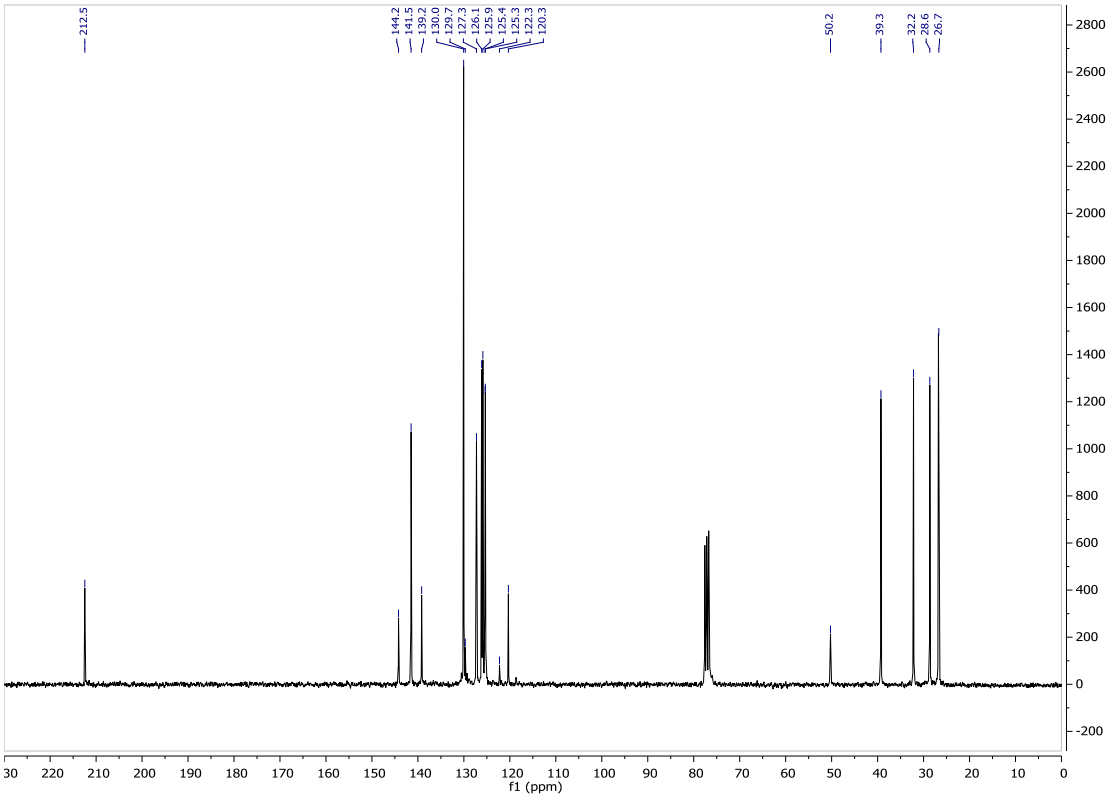
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-phenylheptan-2-yl)pyridine 1-oxide (17b)



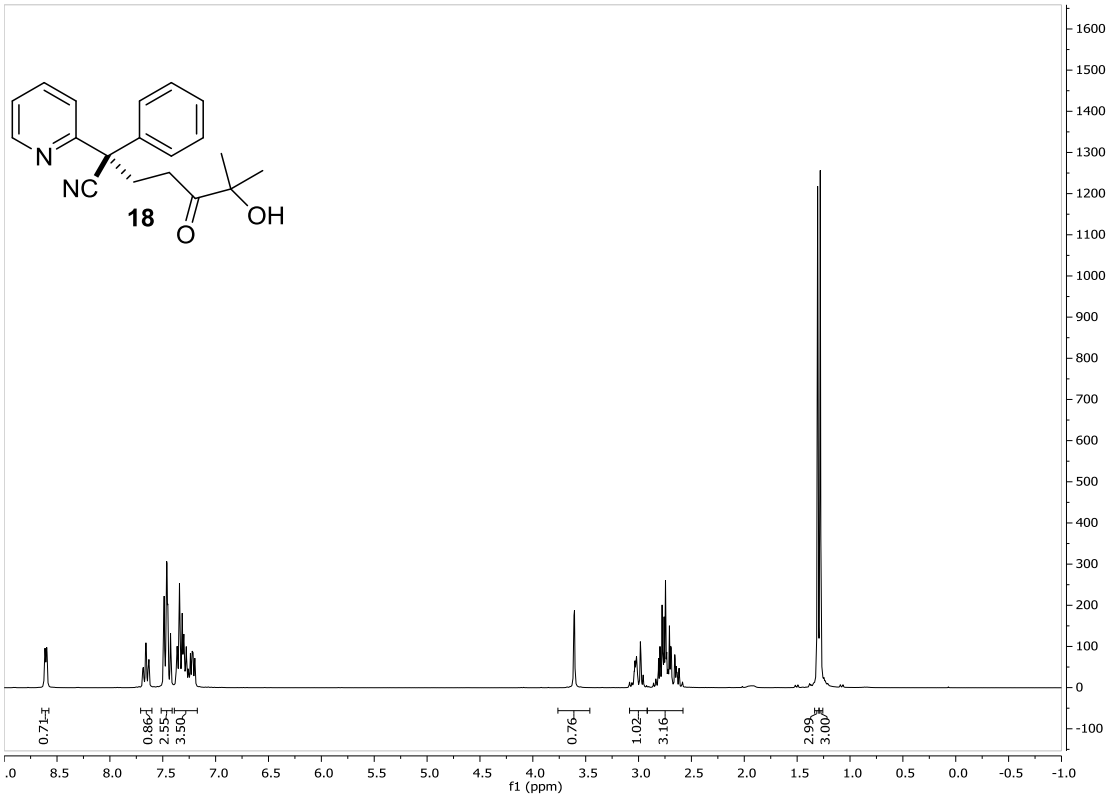


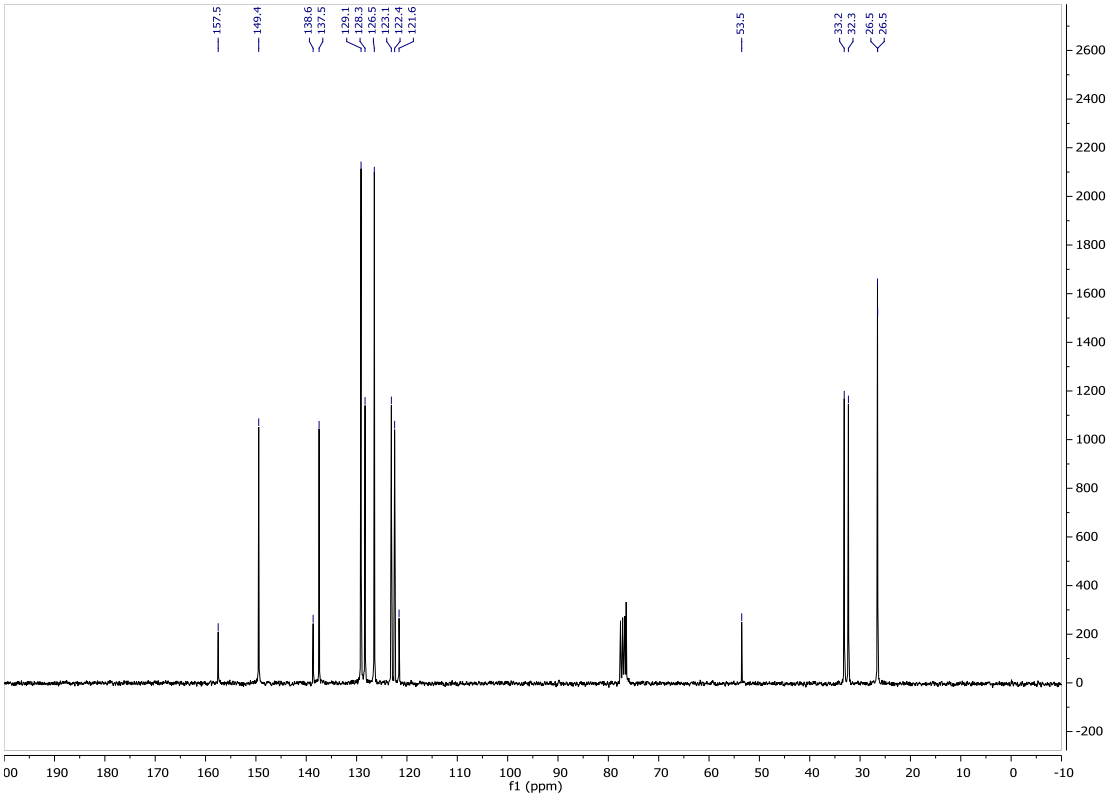
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-(4-(trifluoromethyl)phenyl)heptan-2-yl)pyridine 1-oxide (17c)



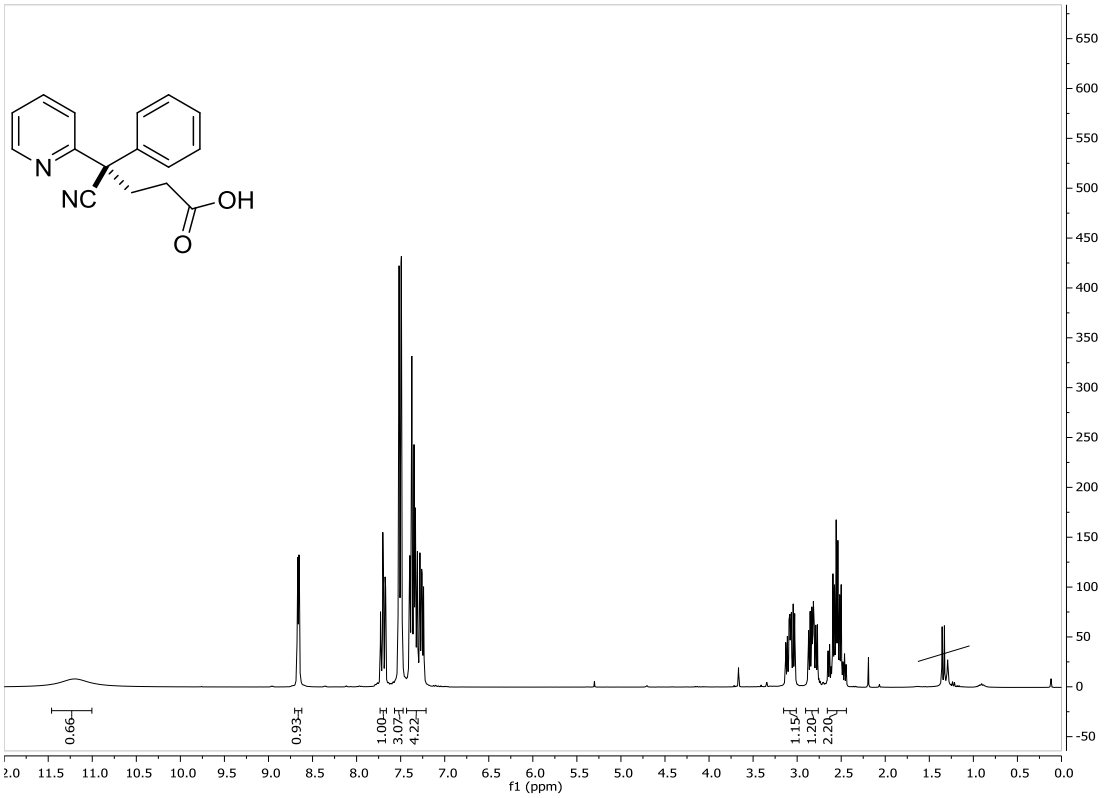


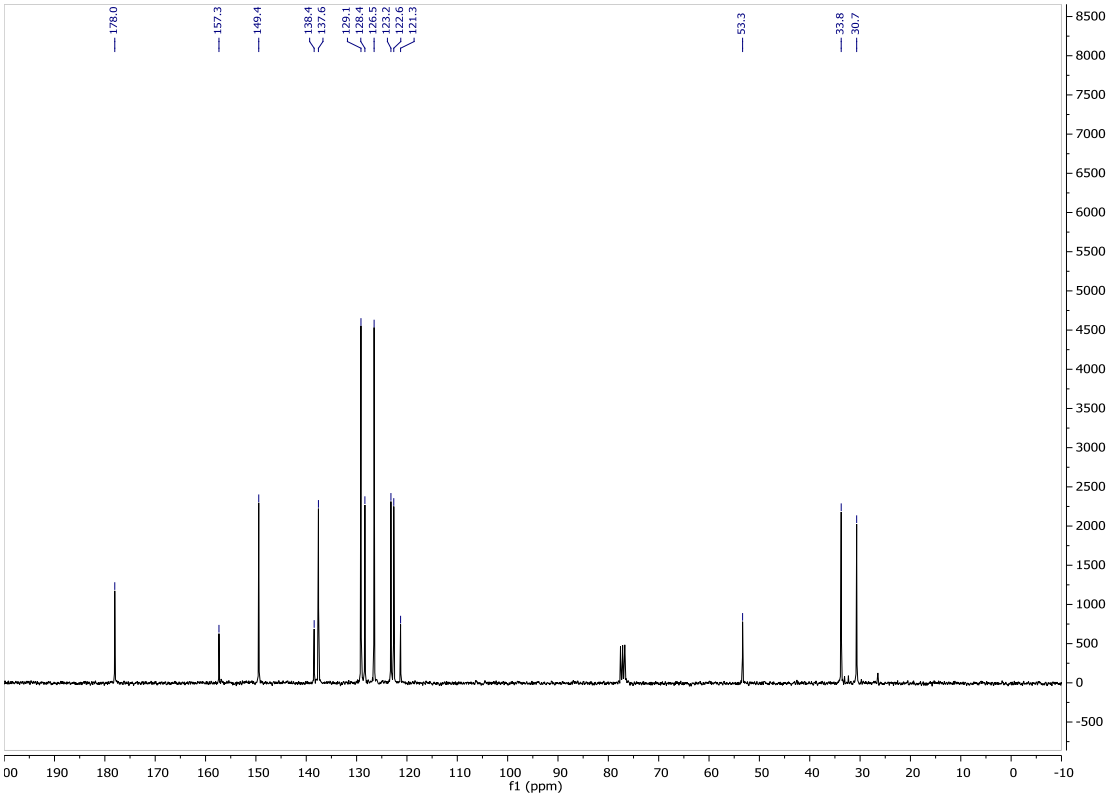
(R)-6-hydroxy-6-methyl-5-oxo-2-phenyl-2-(pyridin-2-yl)heptanenitrile (18)



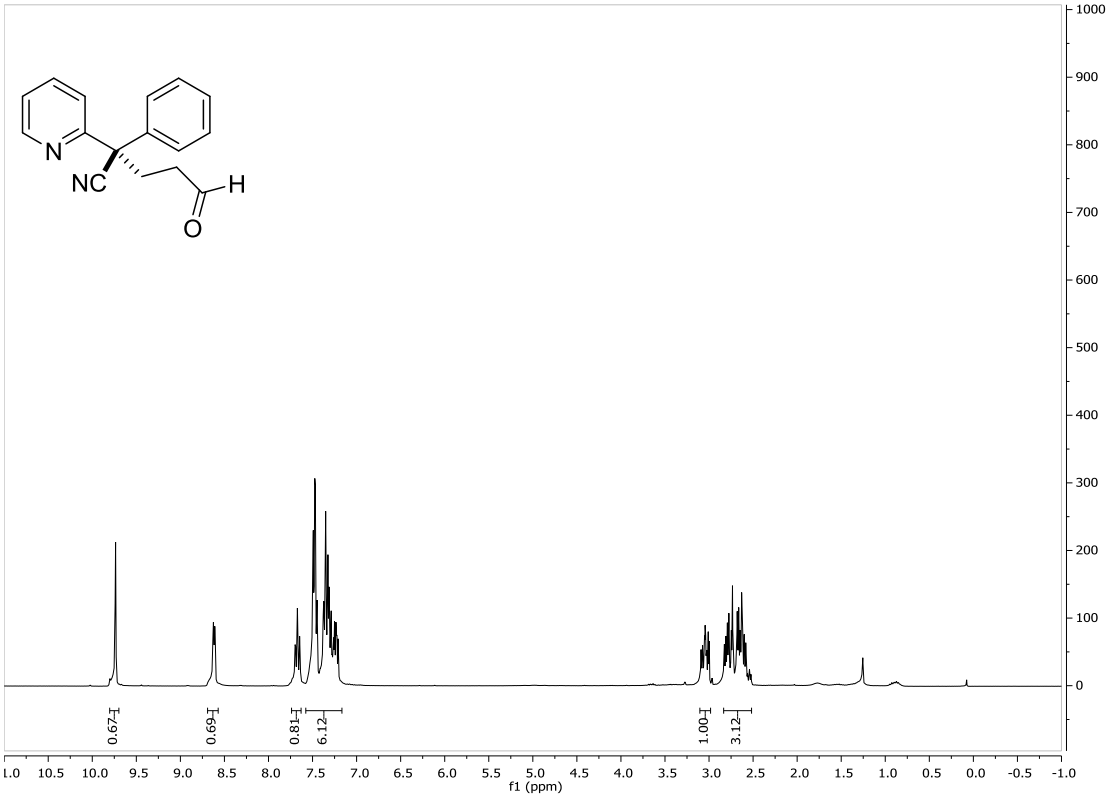


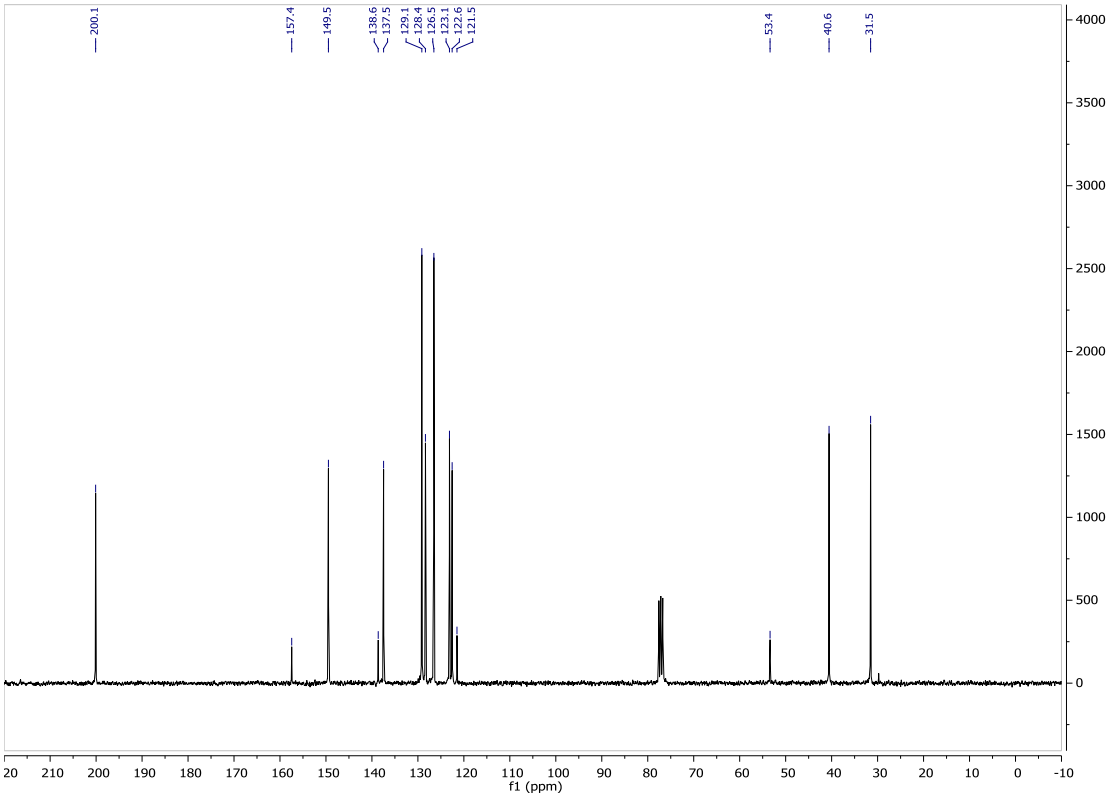
(R)-4-cyano-4-phenyl-4-(pyridin-2-yl)butanoic acid (19)



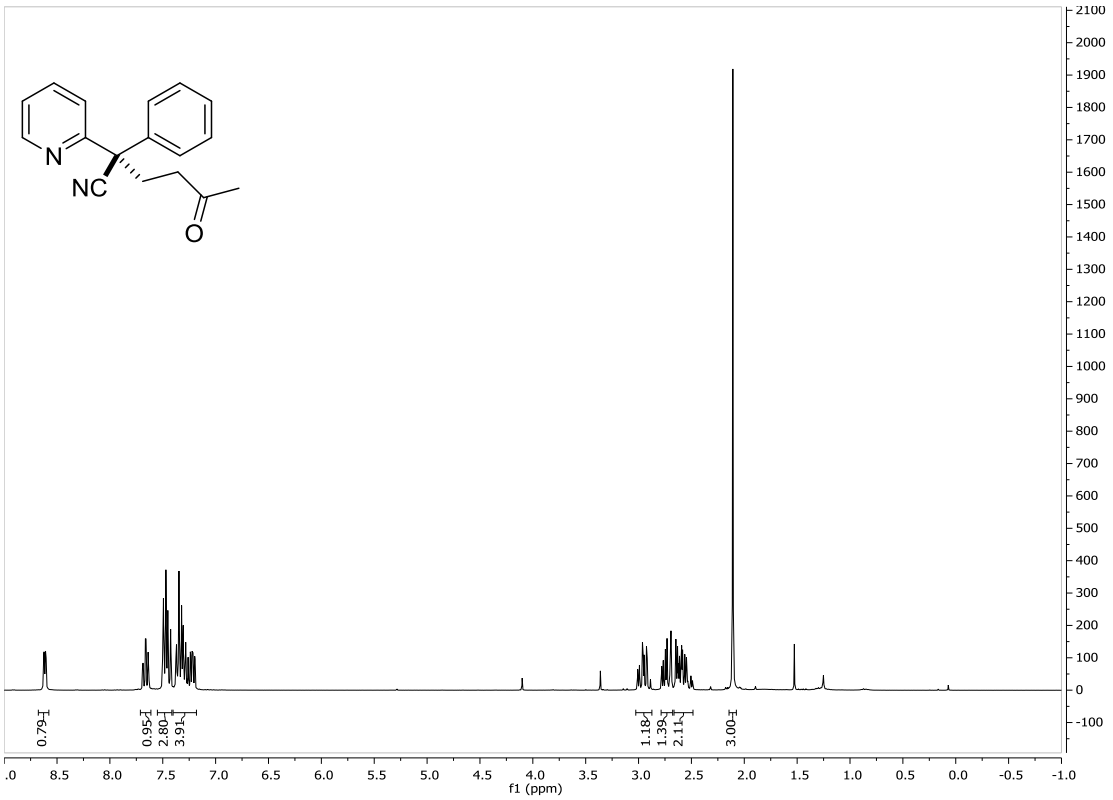


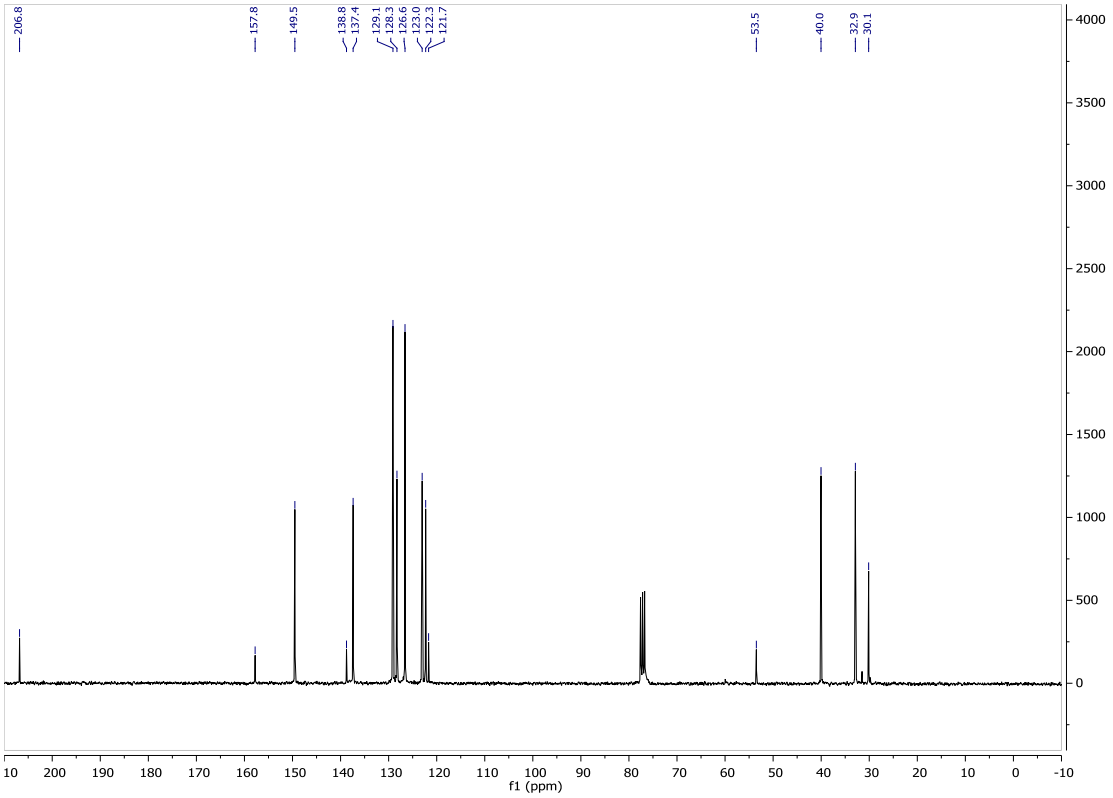
(R)-5-oxo-2-phenyl-2-(pyridin-2-yl)pentanenitrile (20)



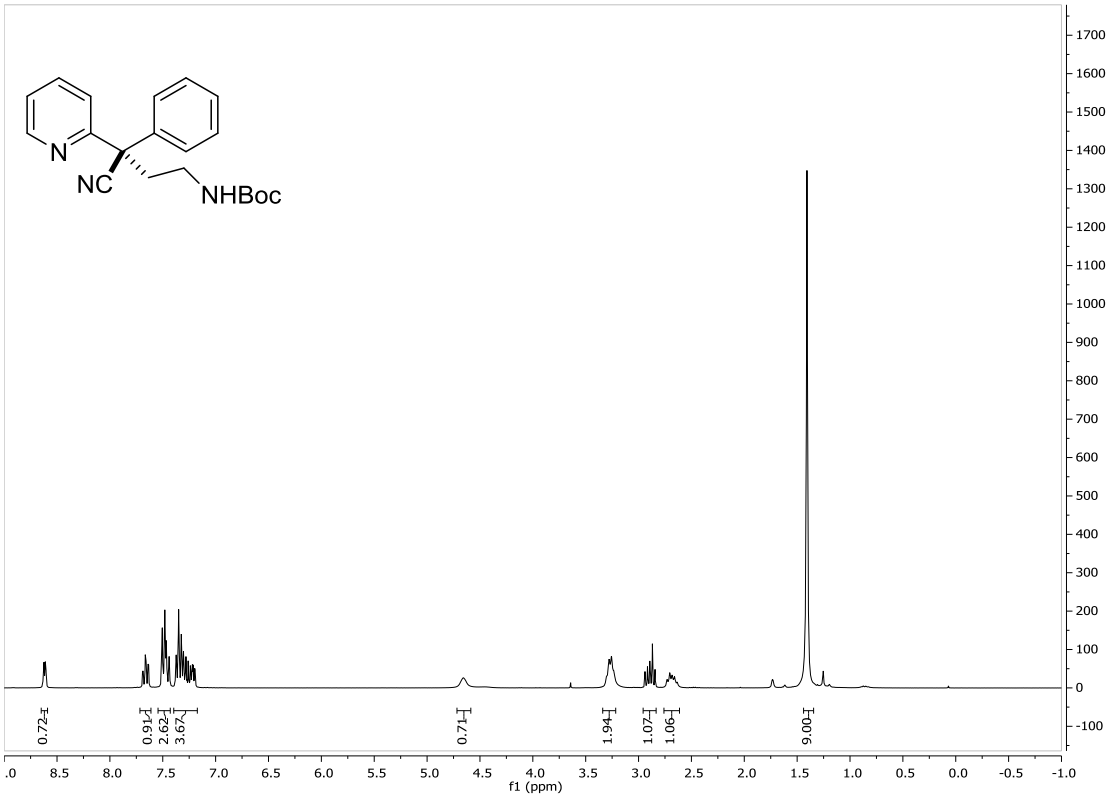


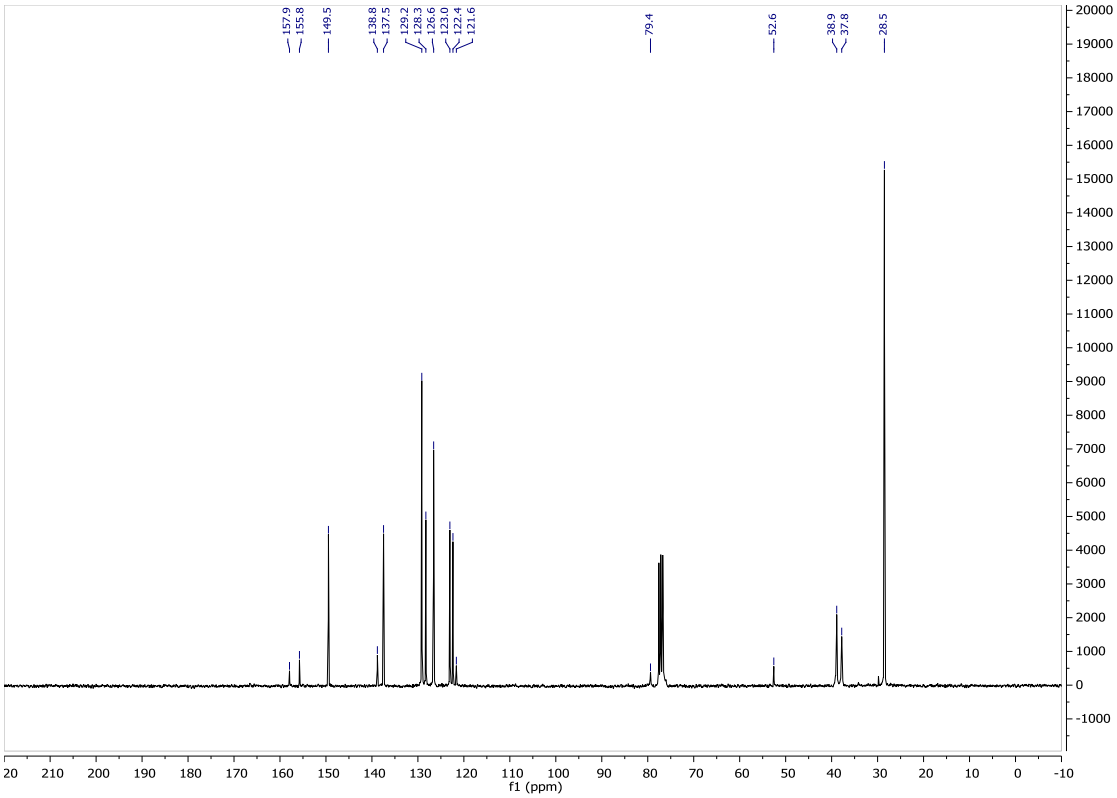
(R)-5-oxo-2-phenyl-2-(pyridin-2-yl)hexanenitrile (21)



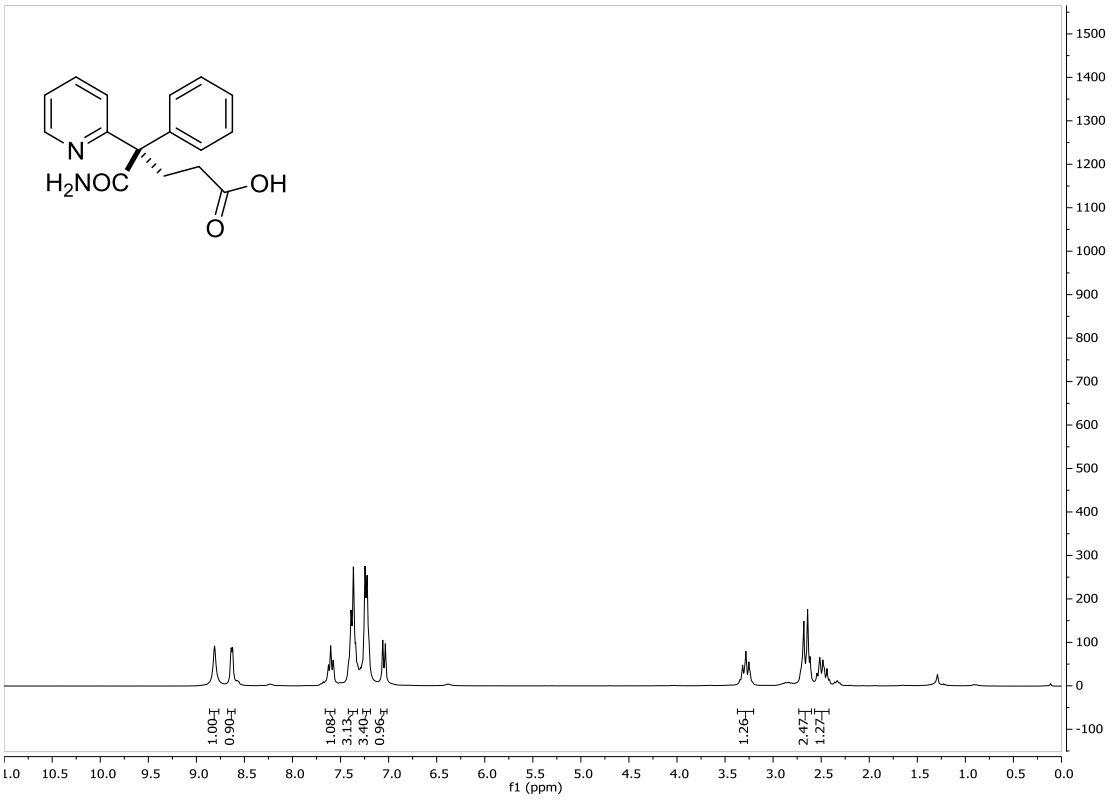


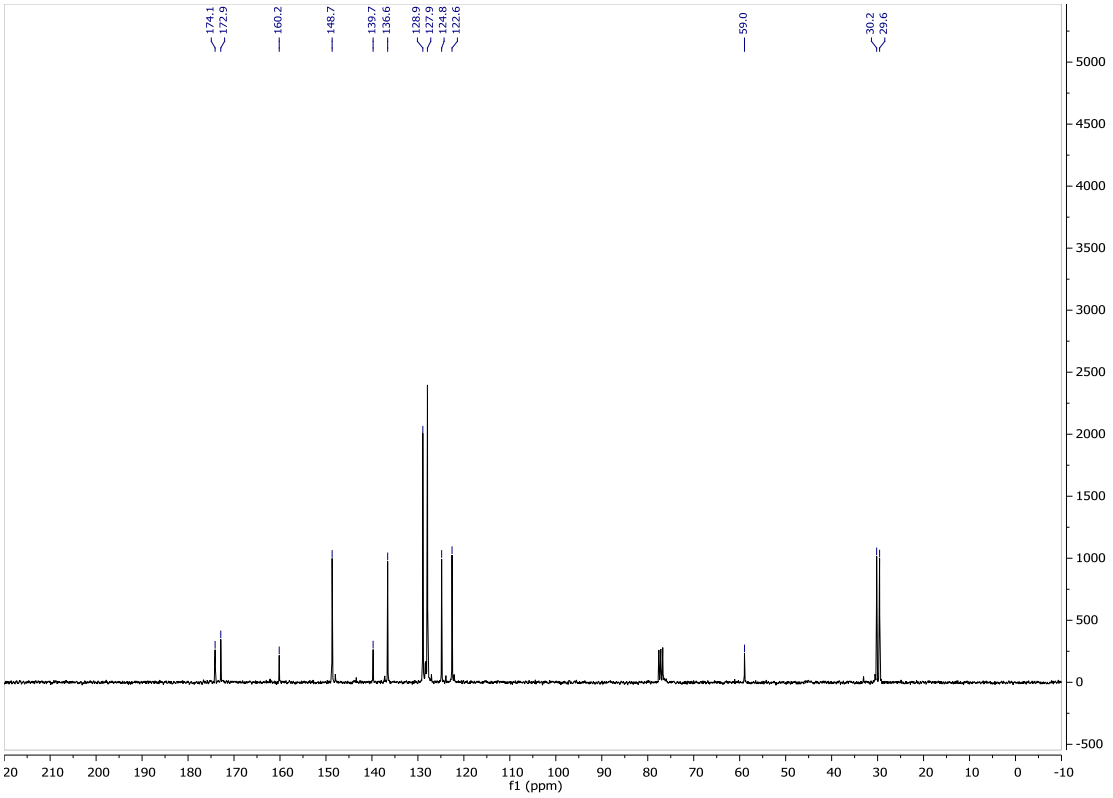
tert-butyl (R)-(3-cyano-3-phenyl-3-(pyridin-2-yl)propyl)carbamate (22)



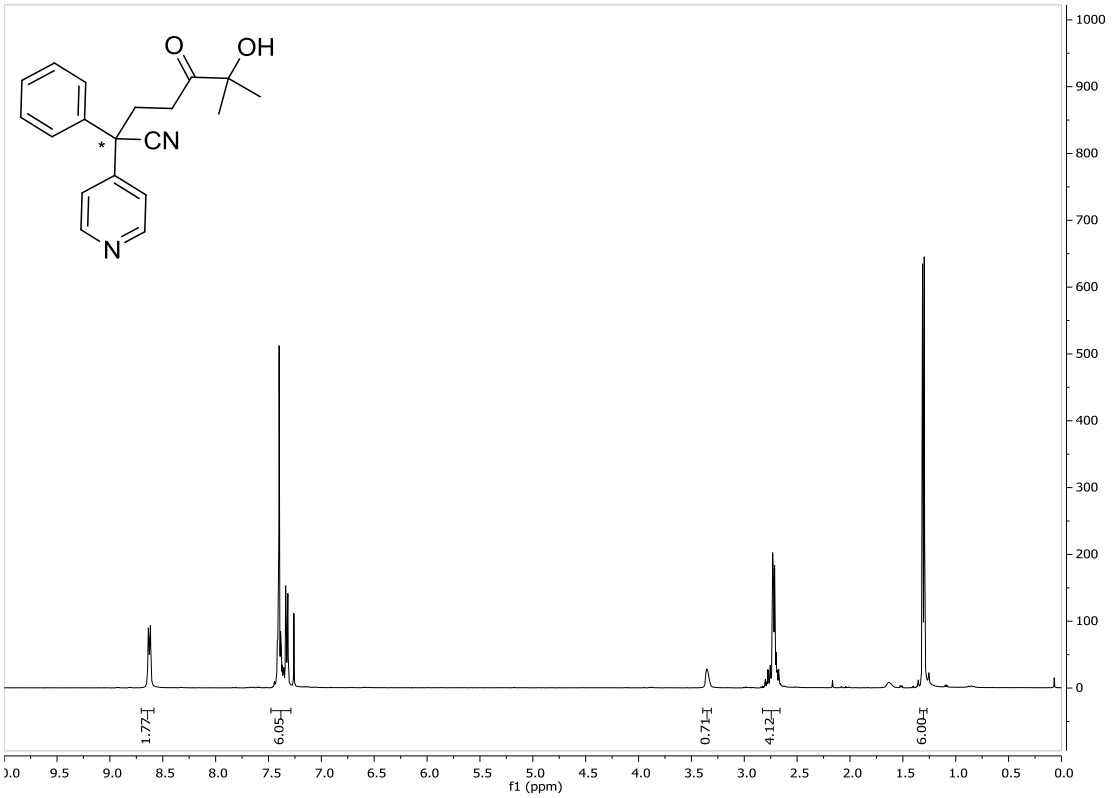


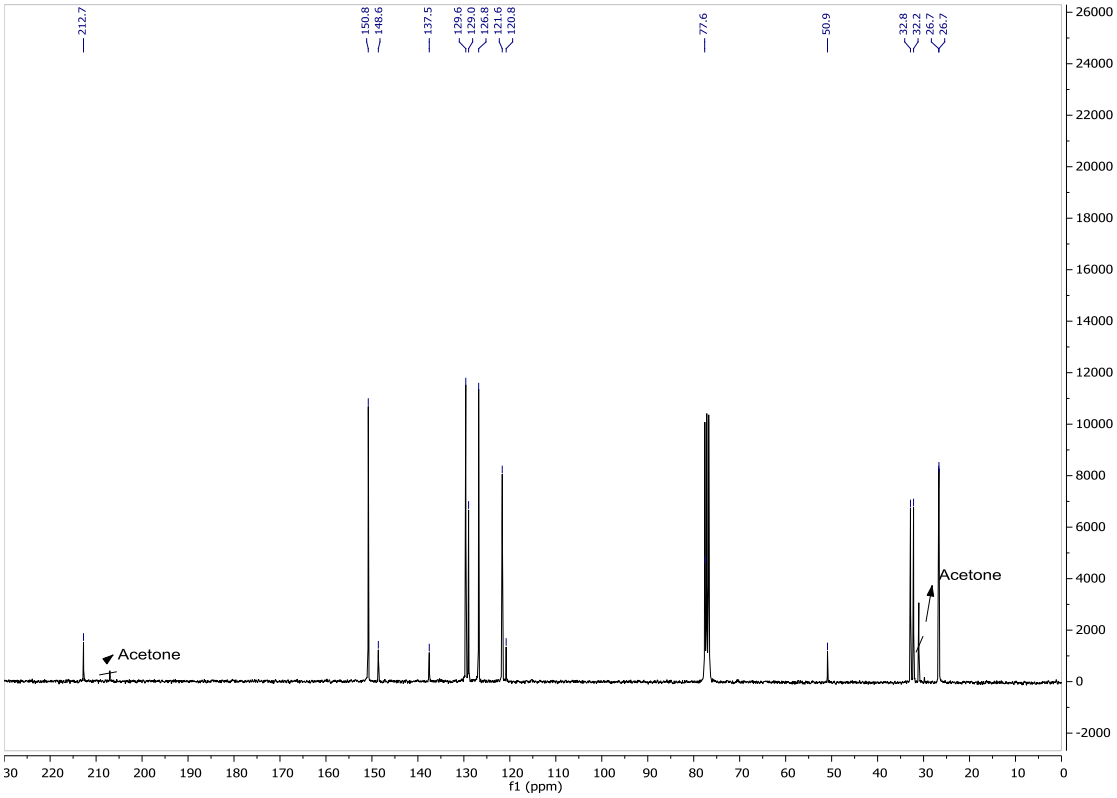
(R)-5-amino-5-oxo-4-phenyl-4-(pyridin-2-yl)pentanoic acid (23)





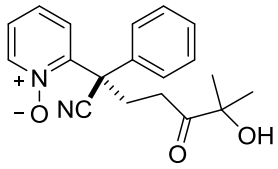
6-hydroxy-6-methyl-5-oxo-2-phenyl-2-(pyridin-4-yl)heptanenitrile



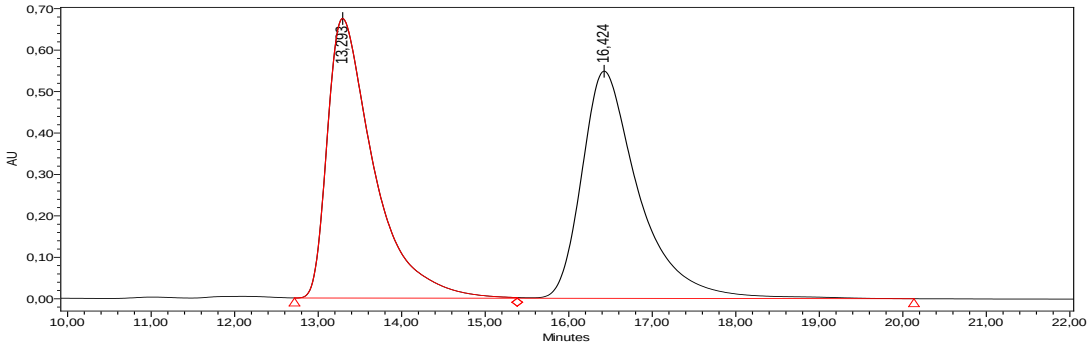


5.3.10. HPLC chromatograms

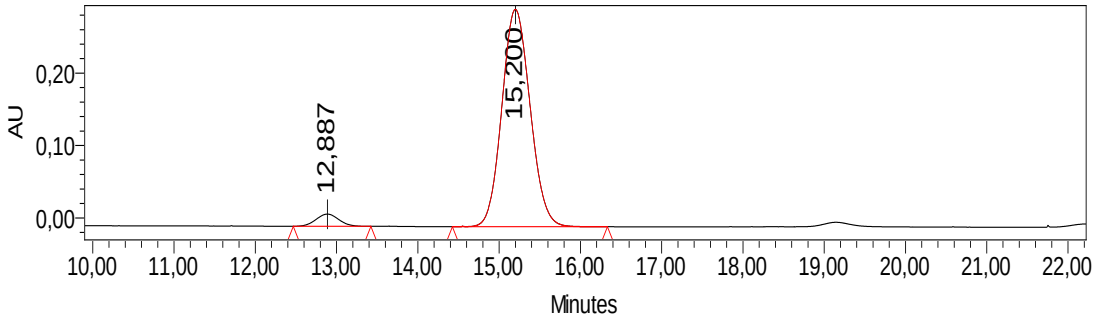
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 12.9 min (min.) and 15.2 min (major.). Processed Channel Descr.: PDA 210.0 nm).

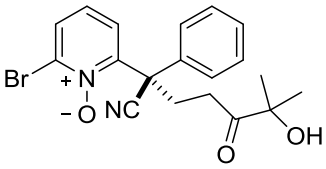


	Retention Time	% Area
1	13.293	50.08
2	16.424	49.92

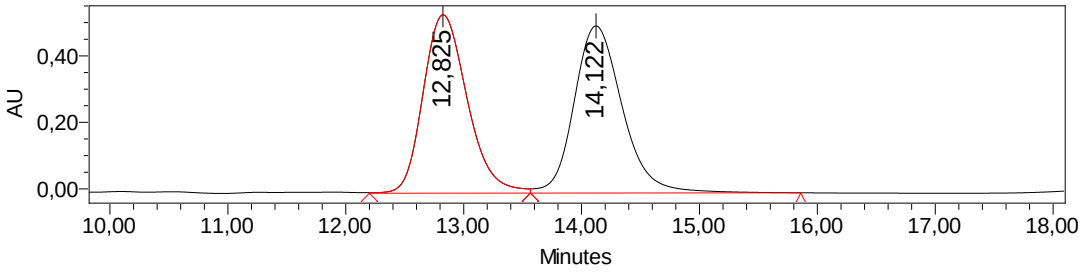


	Retention Time	% Area
1	12.887	4.29
2	15.200	95.71

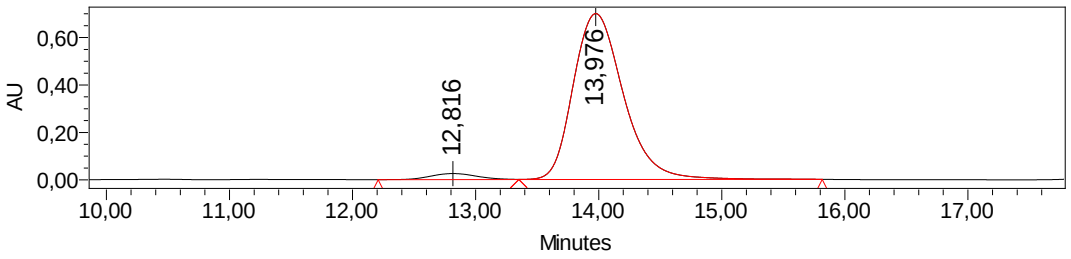
(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9b)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 60/40, flow rate = 0.5 mL/min, retention times: 12.8 min (min.) and 14.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

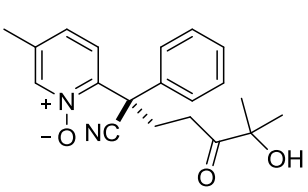


	Retention Time	% Area
1	12.825	49.42
2	14.122	50.58

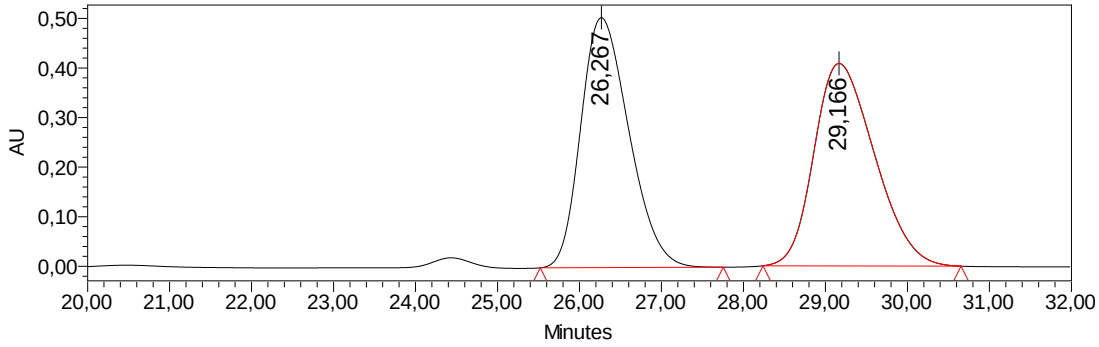


	Retention Time	% Area
1	12.816	3.29
2	13.976	96.71

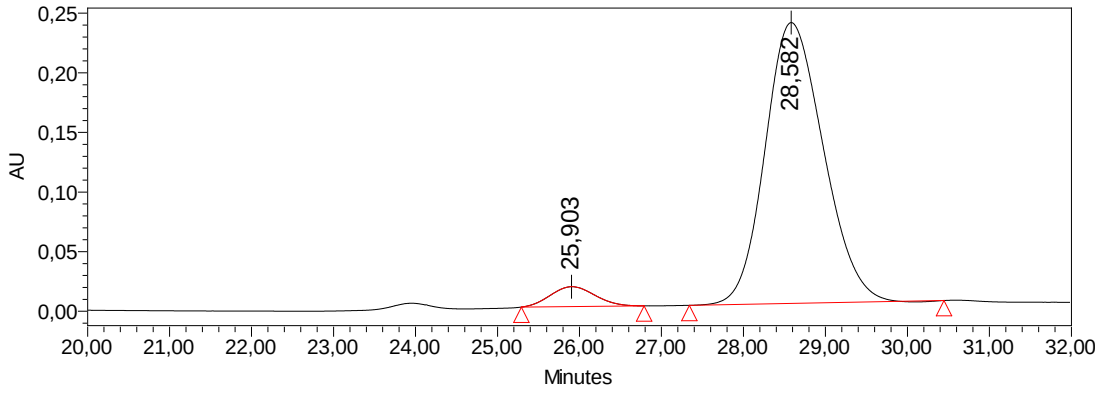
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)-5-methylpyridine 1-oxide (9c)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 70/30, flow rate = 0.5 mL/min, retention times: 25.9 min (min.) and 28.6 min (major.). Processed Channel Descr.: PDA 210.0 nm).

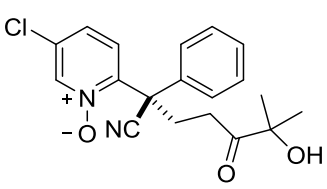


	Retention Time	% Area
1	26.267	49.20
2	29.166	50.80

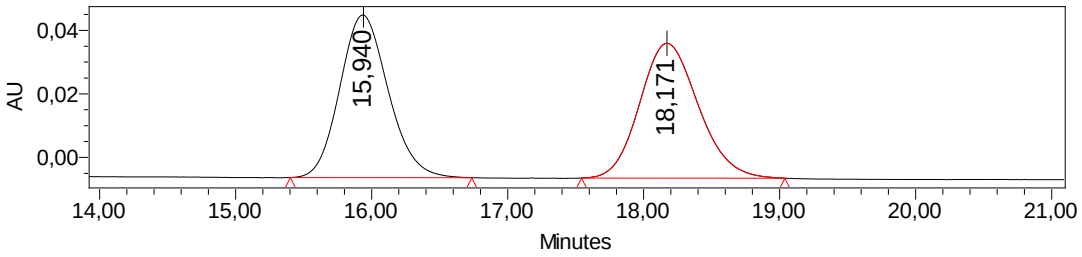


	Retention Time	% Area
1	25.903	5.08
2	28.582	94.92

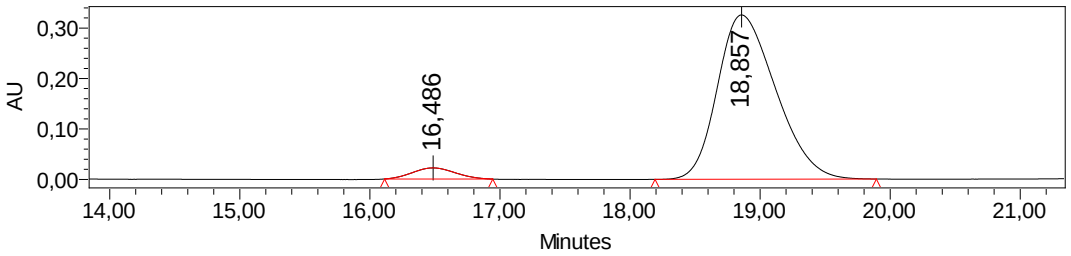
(R)-5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide (9d)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 16.5 min (min.) and 18.9 min (major.). Processed Channel Descr.: PDA 210.0 nm).

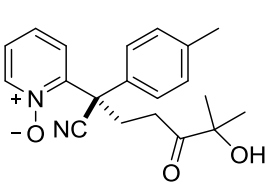


	Retention Time	% Area
1	15.940	49.91
2	18.171	50.09

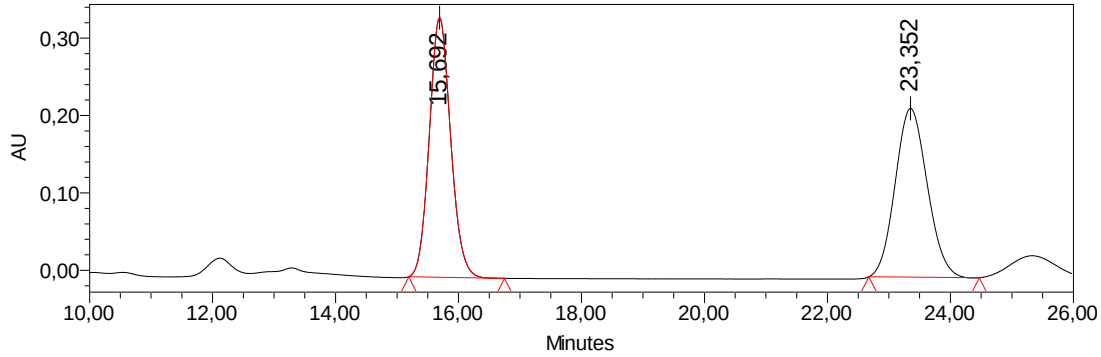


	Retention Time	% Area
1	16.486	4.71
2	18.857	95.29

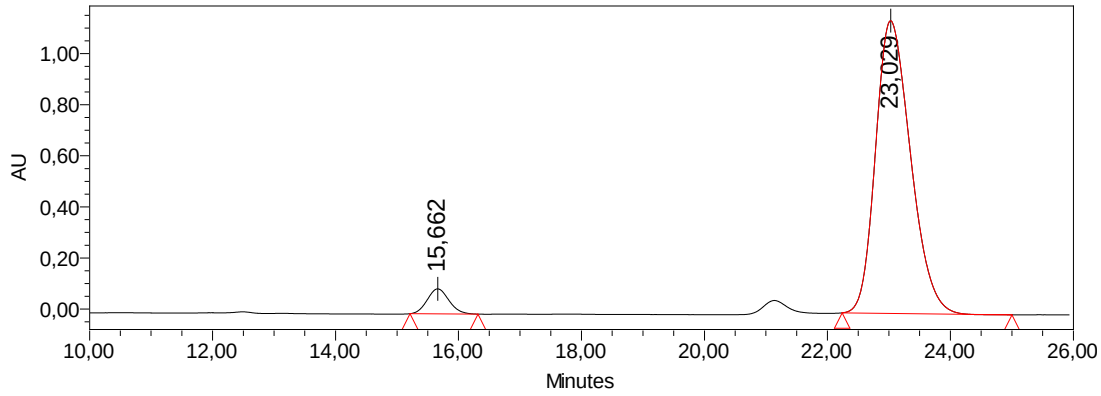
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9e)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 15.7 min (min.) and 23.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

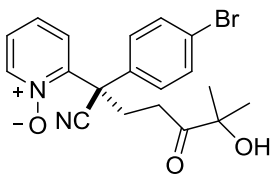


	Retention Time	% Area
1	15.692	49.97
2	23.352	50.03

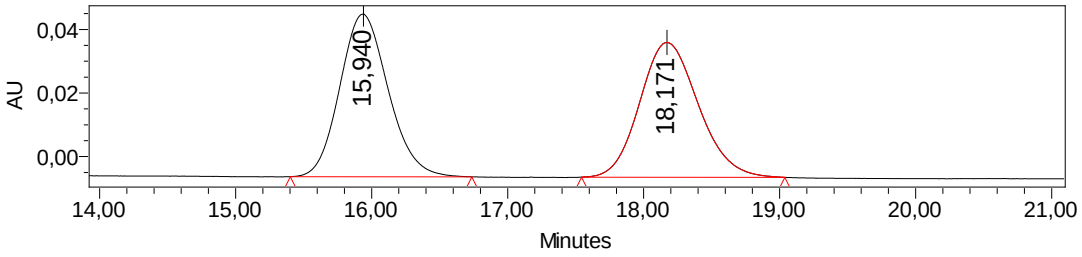


	Retention Time	% Area
1	15.662	5.14
2	23.029	94.86

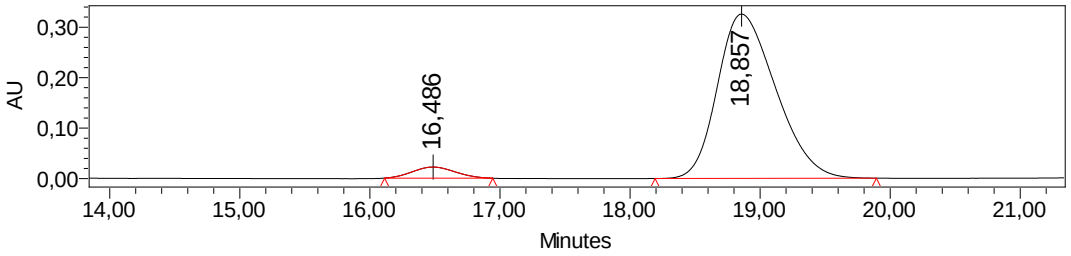
(R)-2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyridine 1-oxide (9f)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 16.5 min (min.) and 18.9 min (major.). Processed Channel Descr.: PDA 210.0 nm).

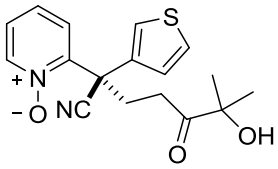


	Retention Time	% Area
1	15.940	49.91
2	18.171	50.09

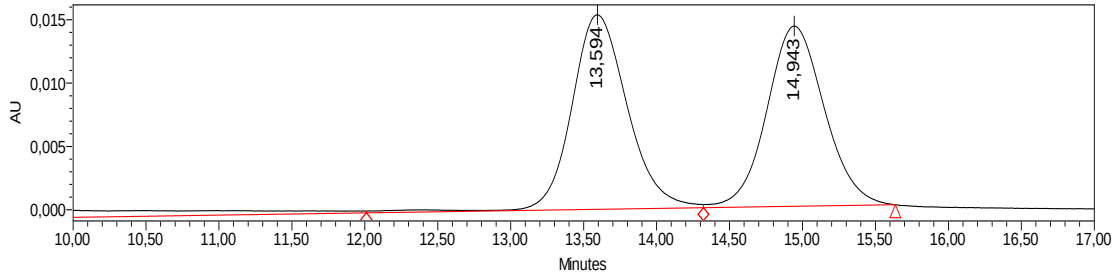


	Retention Time	% Area
1	16.486	4.71
2	18.857	95.29

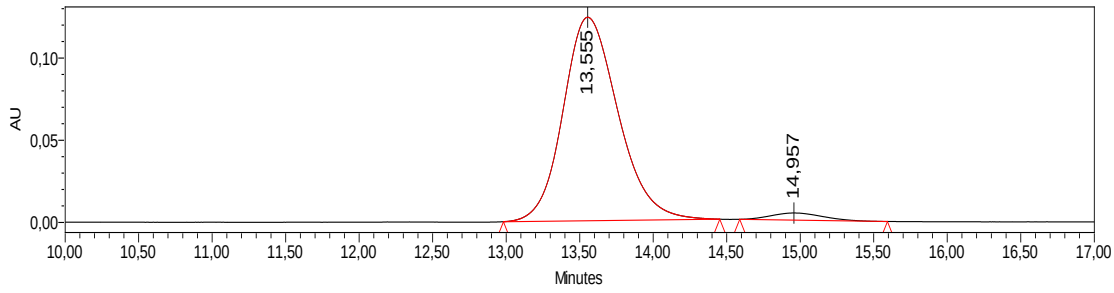
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(thiophen-3-yl)hexyl)pyridine 1-oxide (9g)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 13.3 min (major.) and 14.8 min (min.). Processed Channel Descr.: PDA 210.0 nm).

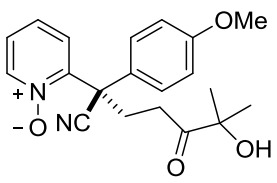


	Retention Time	% Area
1	13.594	47.82
2	14.439	52.18

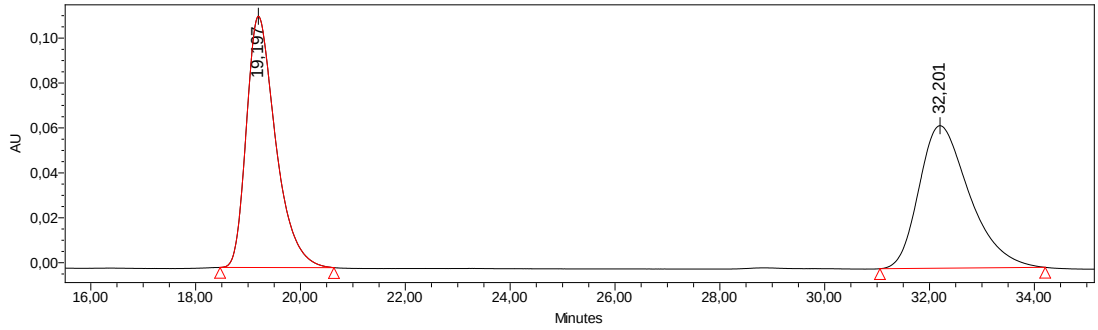


	Retention Time	% Area
1	13.555	96.66
2	14.957	3.34

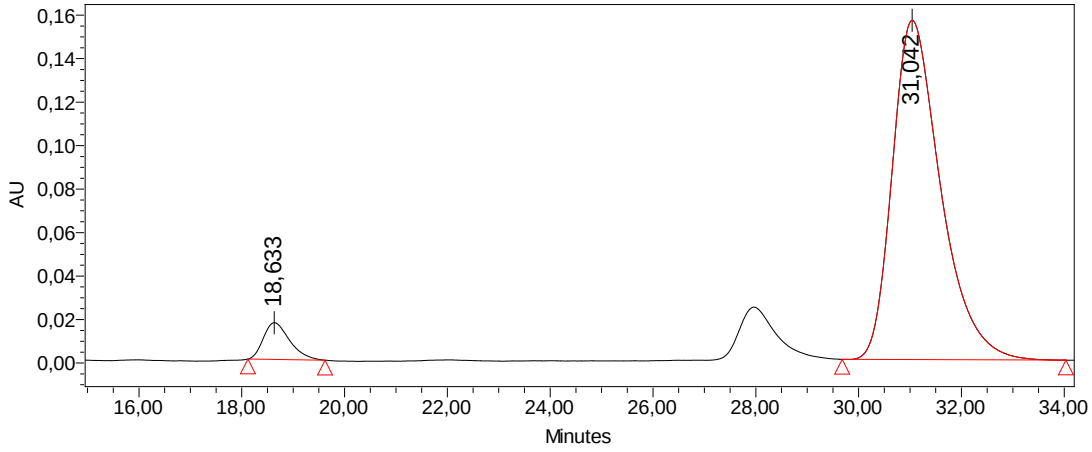
(R)-2-(1-cyano-5-hydroxy-1-(4-methoxyphenyl)-5-methyl-4-oxohexyl)pyridine 1-oxide (9h)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 18.6 min (min.) and 31.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

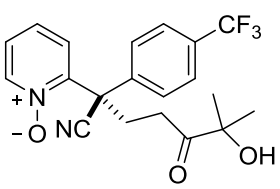


	Retention Time	% Area
1	19.197	50.51
2	32.201	49.49

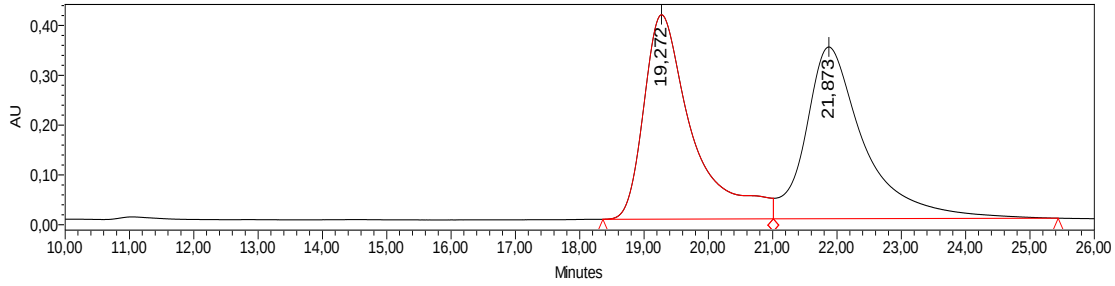


	Retention Time	% Area
1	18.633	5.56
2	31.042	94.44

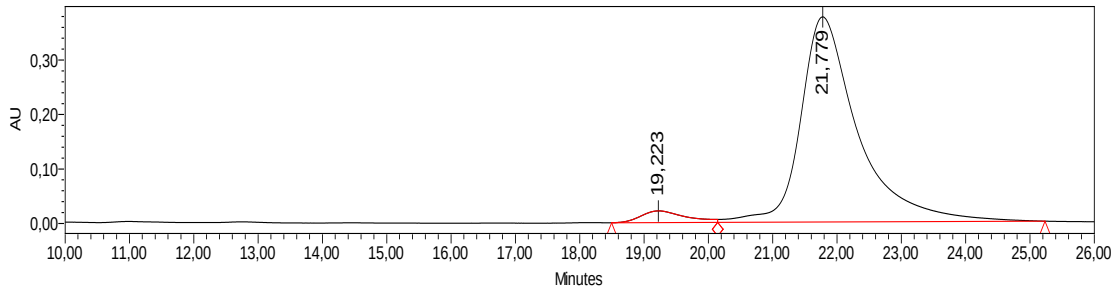
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4(trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9i)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 70/30, flow rate = 0.5 mL/min, retention times: 19.2 min (min.) and 21.8 min (major.). Processed Channel Descr.: PDA 210.0 nm).

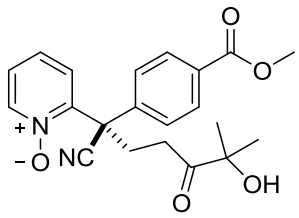


	Retention Time	% Area
1	19.272	49.72
2	21.873	50.28

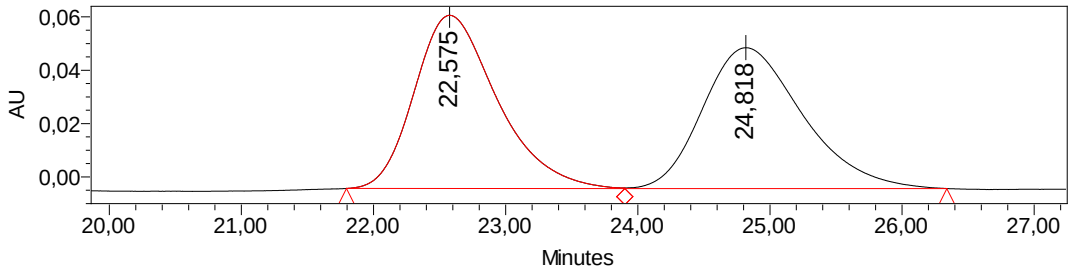


	Retention Time	% Area
1	19.223	4.10
2	21.779	95.90

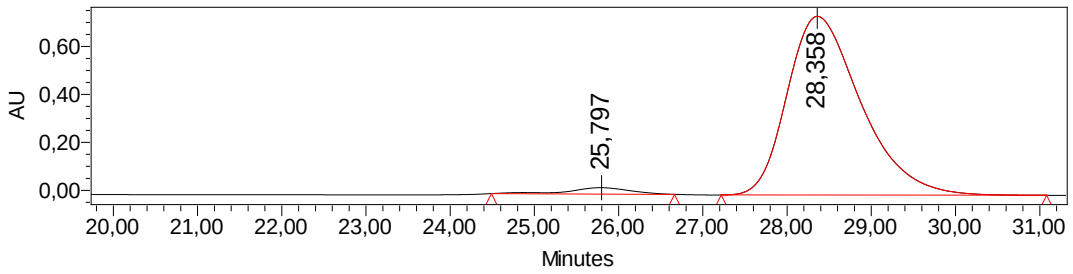
(R)-2-(1-cyano-5-hydroxy-1-(4-(methoxycarbonyl)phenyl)-5-methyl-4-oxohexyl)pyridine 1-oxide (9j)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 25.8 min (min.) and 28.4 min (major.). Processed Channel Descr.: PDA 210.0 nm).

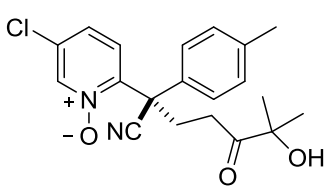


	Retention Time	% Area
1	22.575	50.51
2	24.818	49.49

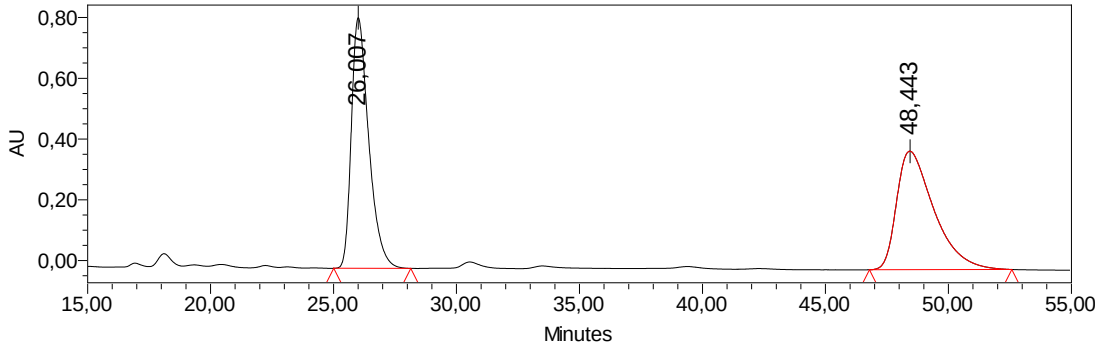


	Retention Time	% Area
1	25.797	2.87
2	28.358	97.13

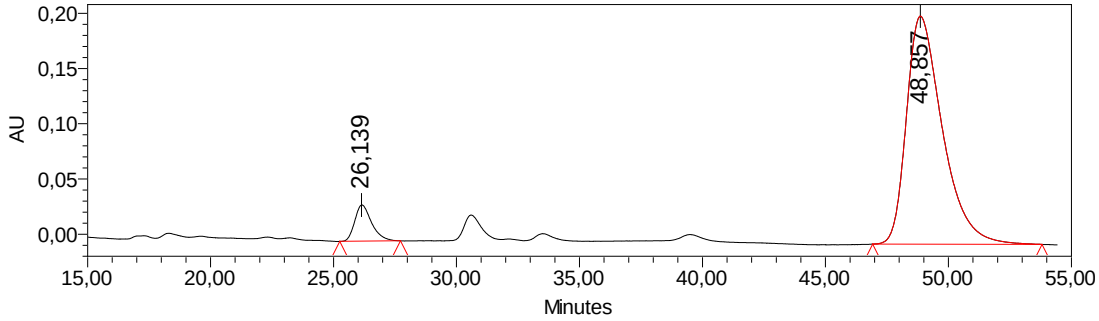
(R)-5-chloro-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(p-tolyl)hexyl)pyridine 1-oxide (9k)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 24.4 min (min.) and 45.4 min (major.). Processed Channel Descr.: PDA 210.0 nm).

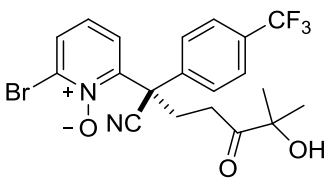


	Retention Time	% Area
1	26.007	49.39
2	48.443	50.61

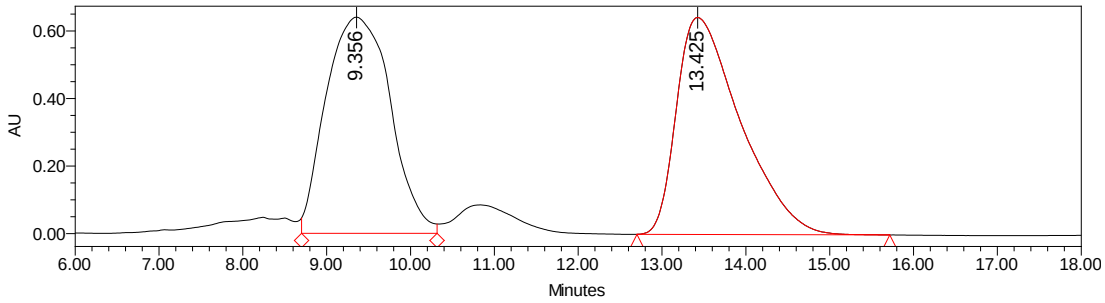


	Retention Time	% Area
1	26.139	6.63
2	48.857	93.37

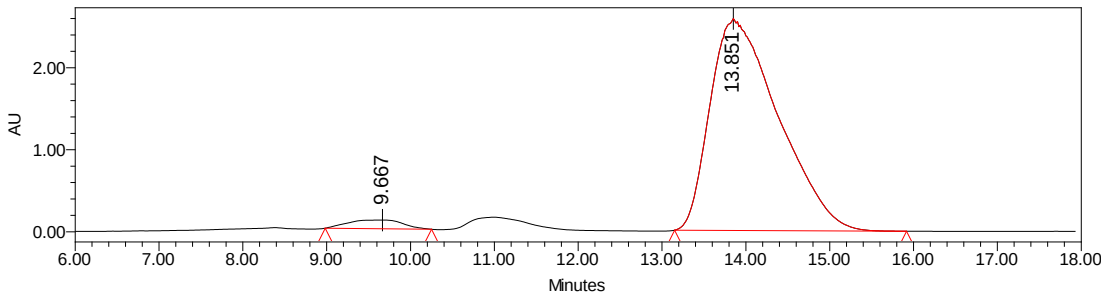
(R)-2-bromo-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-(4 (trifluoromethyl)phenyl)hexyl)pyridine 1-oxide (9l)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 35/65, flow rate = 0.5 mL/min, retention times: 9.7 min (min.) and 13.8 min (major.). Processed Channel Descr.: PDA 264.0 nm).

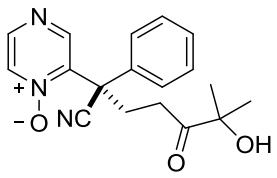


	Retention Time	% Area
1	9.353	50.74
2	13.423	49.26

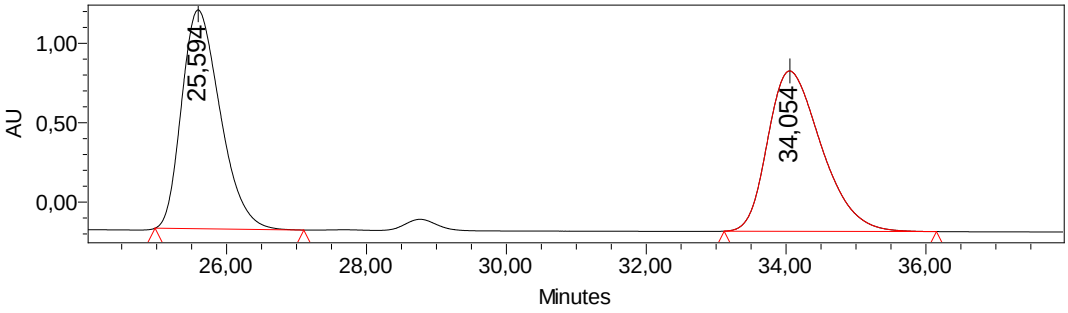


	Retention Time	% Area
1	9.700	3.02
2	13.847	96.98

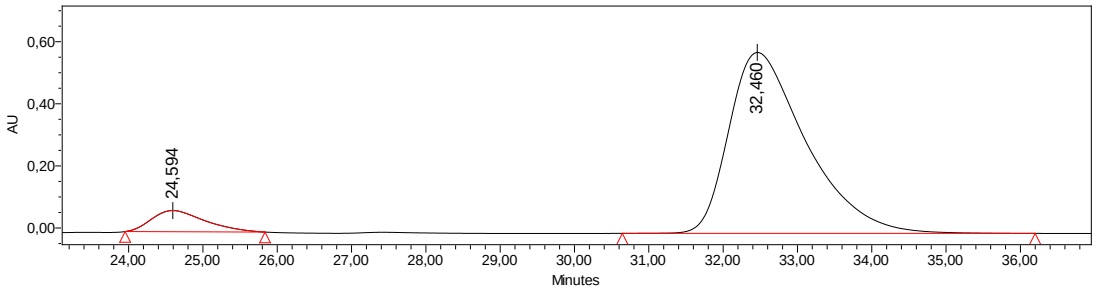
(R)-2-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/ethanol 60/40, flow rate = 0.5 mL/min, retention times: 24.6 min (min.) and 32.5 min (major.). Processed Channel Descr.: PDA 210.0 nm).

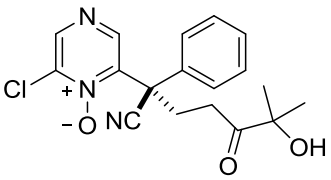


	Retention Time	% Area
1	25.594	49.55
2	34.054	50.45

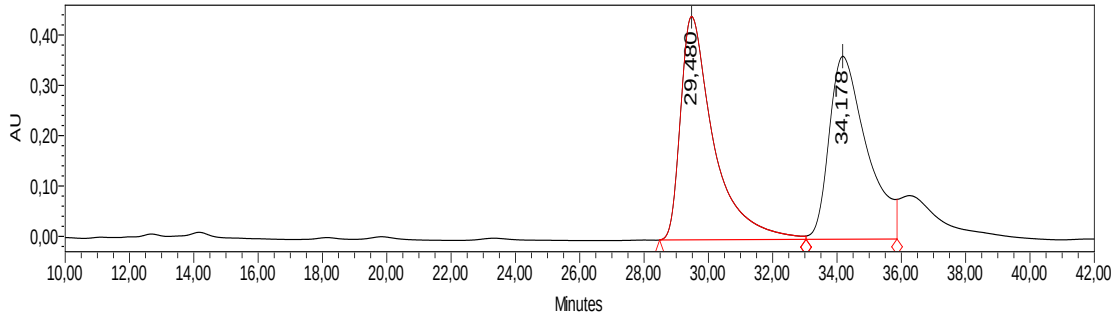


	Retention Time	% Area
1	24.594	7.46
2	32.480	92.54

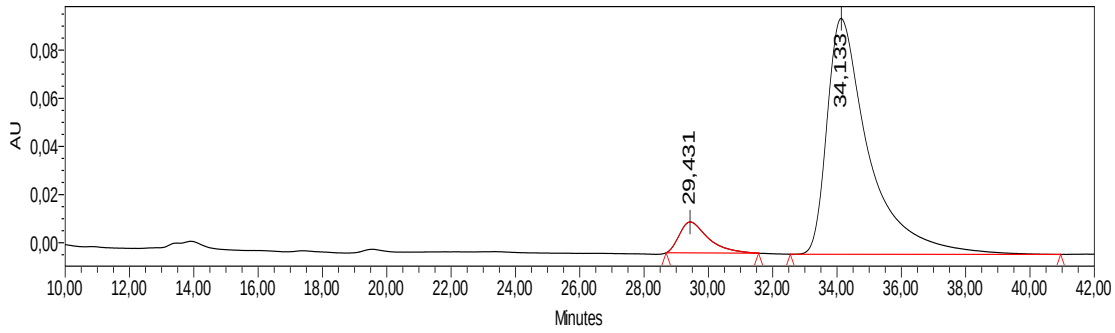
(R)-2-chloro-6-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyrazine 1-oxide (16b)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 70/30, flow rate = 0.5 mL/min, retention times: 29.2 min (min.) and 33.8 min (major.). Processed Channel Descr.: PDA 210.0 nm).

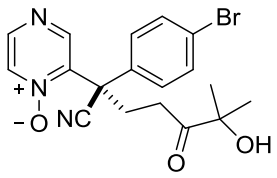


	Retention Time	% Area
1	29.480	51.61
2	34.178	48.39

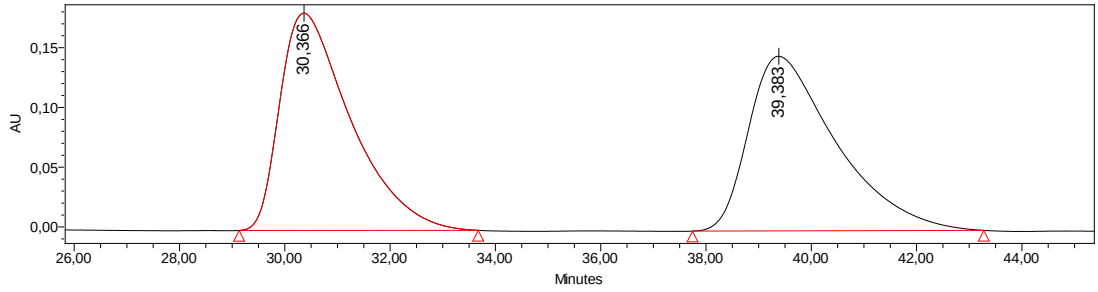


	Retention Time	% Area
1	29.431	8.14
2	34.133	91.86

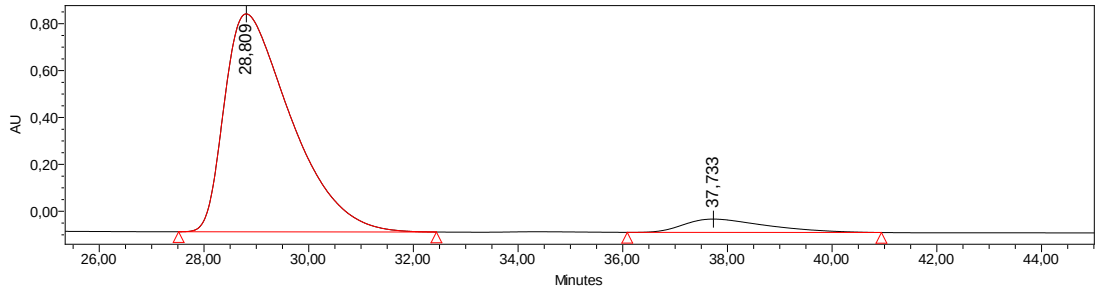
(R)-2-(1-(4-bromophenyl)-1-cyano-5-hydroxy-5-methyl-4-oxohexyl)pyrazine 1-oxide (16c)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 28.8 min (major.) and 37.7 min (min.). Processed Channel Descr.: PDA 210.0 nm).

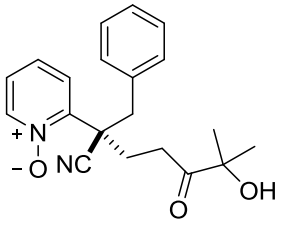


	Retention Time	% Area
1	30.366	50.17
2	39.383	49.83

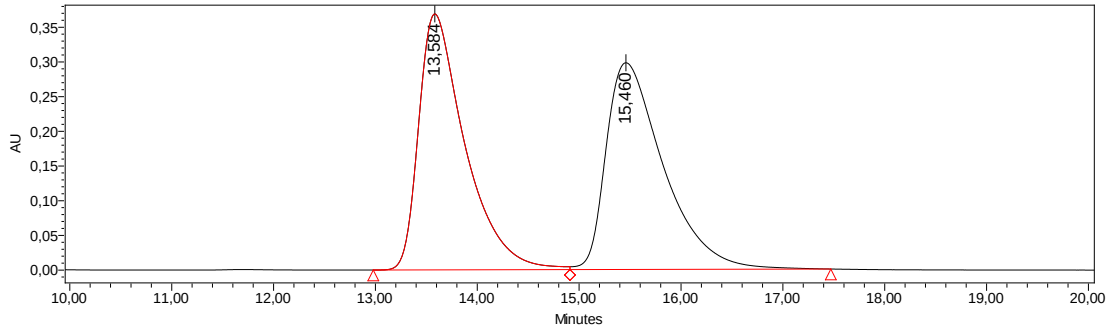


	Retention Time	% Area
1	28.809	92.91
2	37.733	7.09

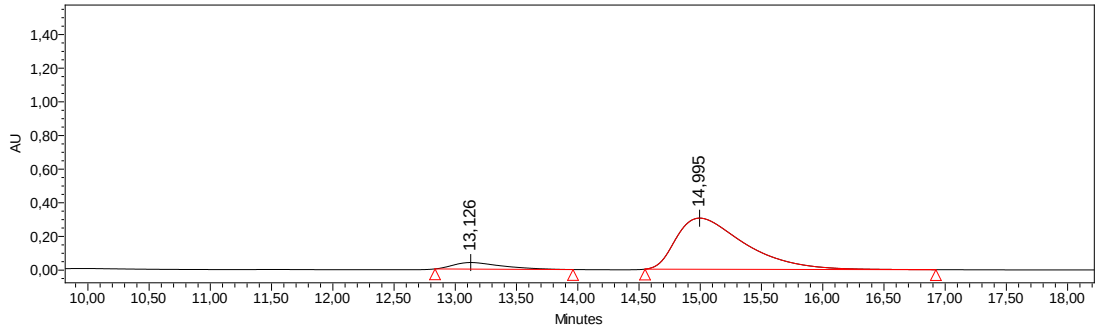
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-phenylheptan-2-yl)pyridine 1-oxide (17b)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 13.1 min (min.) and 14.9 min (major.). Processed Channel Descr.: PDA 210.0 nm).

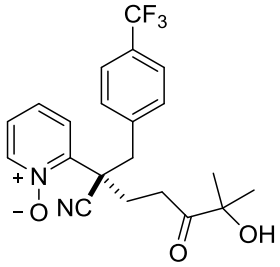


	Retention Time	% Area
1	13.584	49.98
2	15.460	50.02

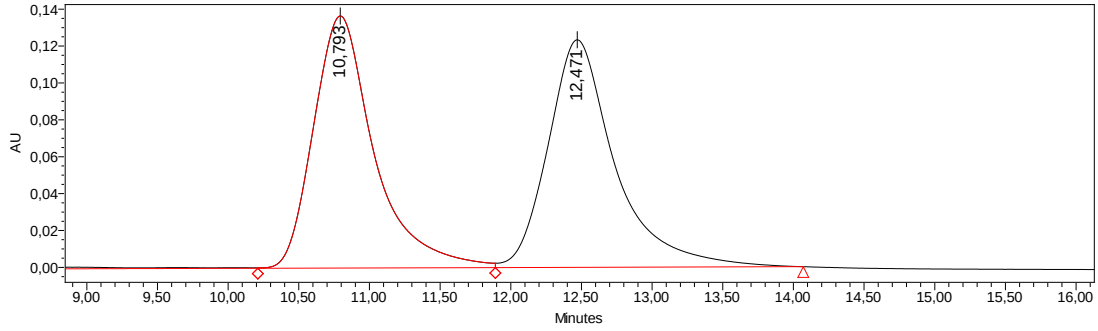


	Retention Time	% Area
1	13.126	8.26
2	14.995	91.74

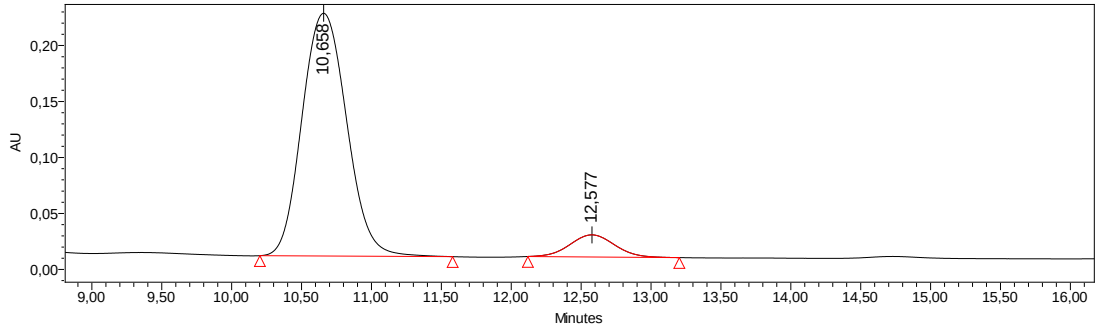
(R)-2-(2-cyano-6-hydroxy-6-methyl-5-oxo-1-(4-(trifluoromethyl)phenyl)heptan-2-yl)pyridine 1-oxide (17c)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 10.7 min (major.) and 12.6 min (min.). Processed Channel Descr.: PDA 210.0 nm).

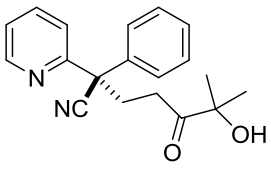


	Retention Time	% Area
1	10.793	50.05
2	12.471	49.95

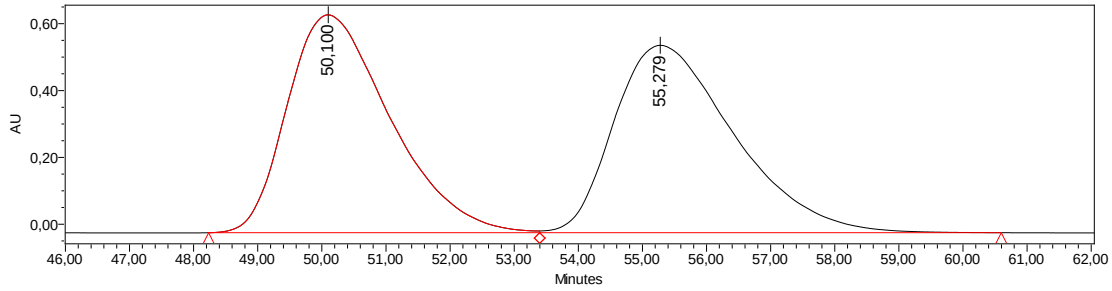


	Retention Time	% Area
1	10.658	91.61
2	12.577	8.39

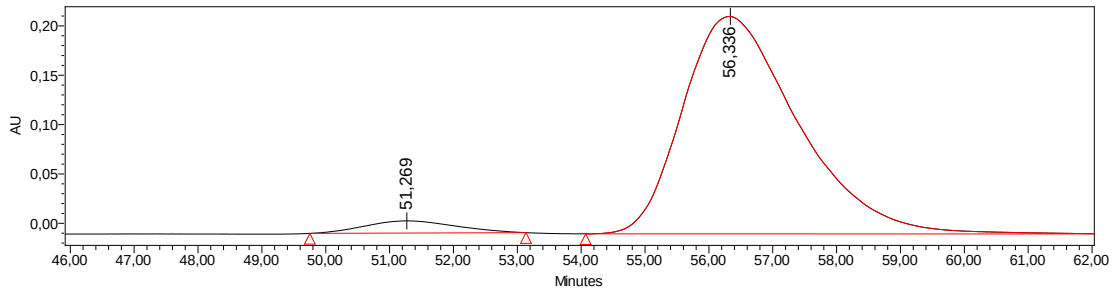
(R)-6-hydroxy-6-methyl-5-oxo-2-phenyl-2-(pyridin-2-yl)heptanenitrile (18)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 51.3 min (min.) and 56.3 min (major.). Processed Channel Descr.: PDA 210.0 nm).

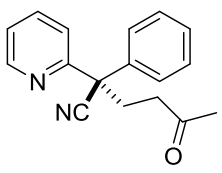


	Retention Time	% Area
1	50.100	49.93
2	55.279	50.07

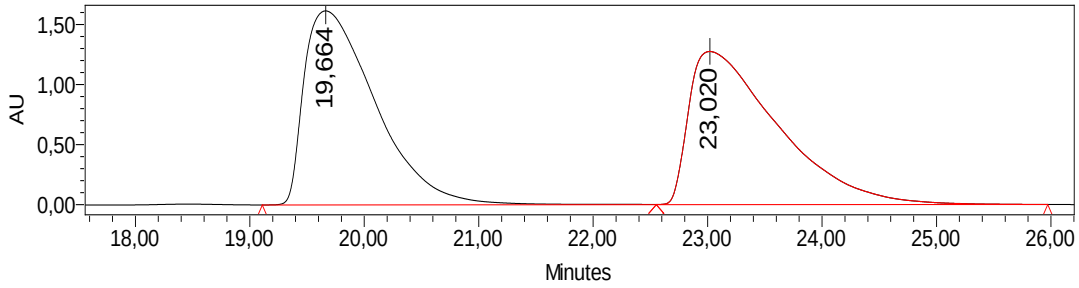


	Retention Time	% Area
1	51.269	4.23
2	56.336	95.77

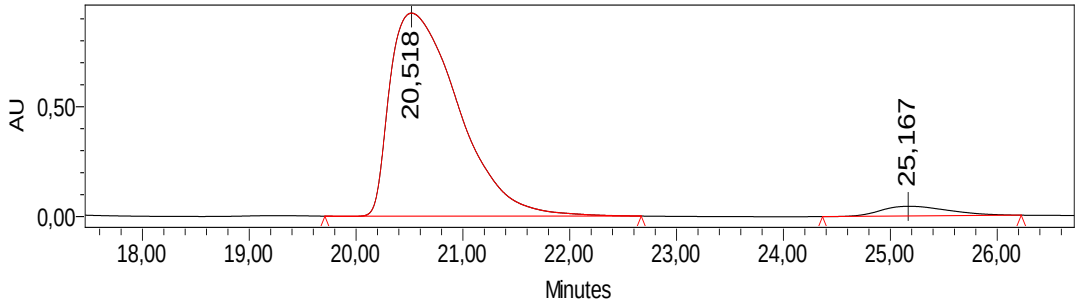
(R)-5-oxo-2-phenyl-2-(pyridin-2-yl)hexanenitrile (21)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 20.5 min (major.) and 25.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

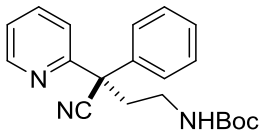


	Retention Time	% Area
1	19.664	50.32
2	23.020	49.68

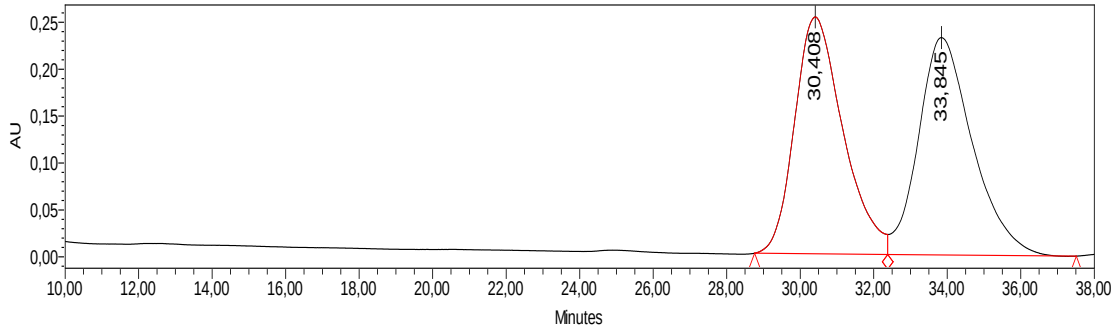


	Retention Time	% Area
1	20.518	95.50
2	25.167	4.50

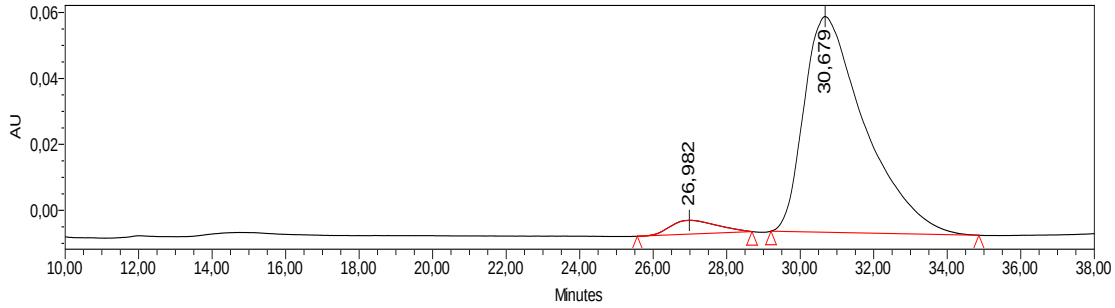
tert-butyl (R)-(3-cyano-3-phenyl-3-(pyridin-2-yl)propyl)carbamate (22)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 90/5/5, flow rate = 0.5 mL/min, retention times: 27.0 min (min.) and 30.7 min (major.). Processed Channel Descr.: PDA 210.0 nm).

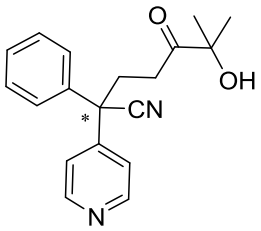


	Retention Time	% Area
1	30.408	49.44
2	33.845	50.56

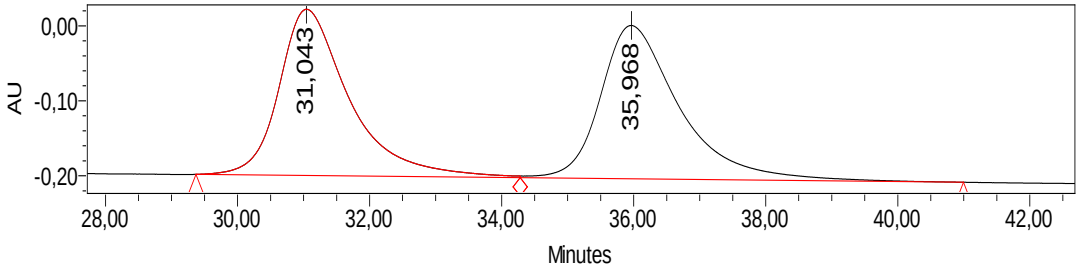


	Retention Time	% Area
1	26.982	5.56
2	30.679	94.44

6-hydroxy-6-methyl-5-oxo-2-phenyl-2-(pyridin-4-yl)heptanenitrile

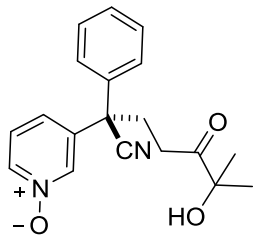


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 31.0 min and 36.0 min. Processed Channel Descr.: PDA 210.0 nm).

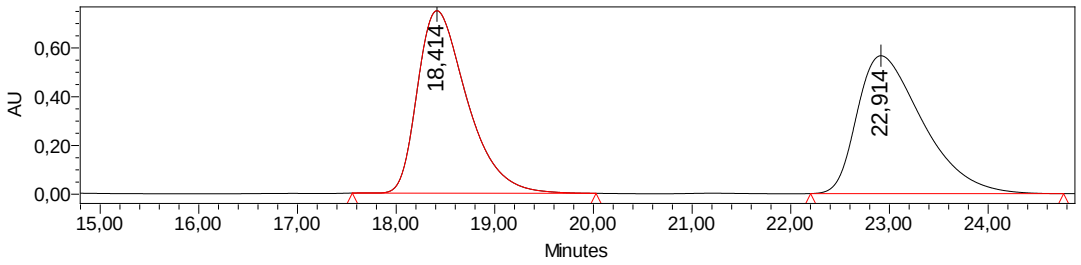


	Retention Time	% Area
1	31.043	49.08
2	35.968	50.92

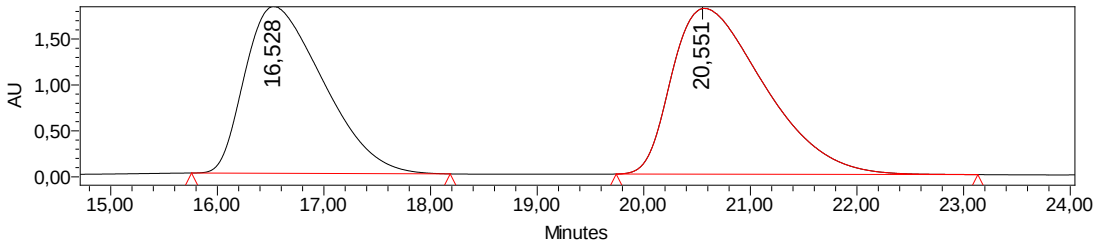
(R)-3-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide



The enantiomeric ratio was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 16.5 min (major.) and 20.6 min (min.). Processed Channel Descr.: PDA 210.0 nm).

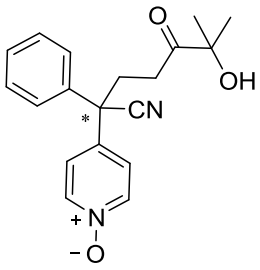


	Retention Time	% Area
1	18.414	49.93
2	22.914	50.07

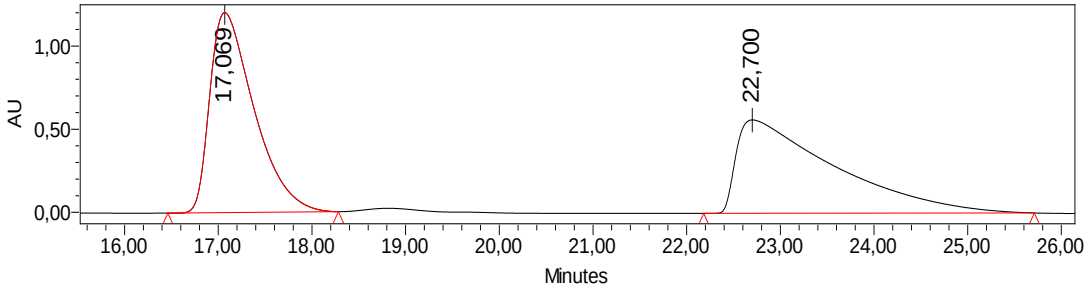


	Retention Time	% Area
1	16.528	54.01
2	20.551	45.99

4-(1-cyano-5-hydroxy-5-methyl-4-oxo-1-phenylhexyl)pyridine 1-oxide



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 50/50, flow rate = 0.5 mL/min, retention times: 17.1 min and 22.7 min. Processed Channel Descr.: PDA 210.0 nm).



	Retention Time	% Area
1	17.069	50.89
2	22.700	49.11

5.4. Experimental section of chapter 3

5.4.1. General procedure for the synthesis of nitroalkenes 36a–c, 36e and 36l

36a–c, 36e and **36l** are commercially available and were purchased from commercial suppliers. Nitroalkenes **36d**, **36f–g**, **36j–k**, **36m–n** were prepared according to the general procedure A. Aliphatic nitroalkenes **36h–i** were prepared according to the general procedure B.

5.4.1.1. General procedure A[249]

The corresponding aldehyde (2 mmol), ammonium acetate (0.1 g, 2.6 mmol) and nitromethane (3 mL) were placed in a 10 mL round bottomed flask equipped with a condenser. The mixture was refluxed and stirred for 2 hours and then evaporated to give a residue that was dissolved in CH_2Cl_2 (5 mL), washed successively with saturated brine and water, and the organic layer was evaporated to give the target compounds that were used without further purification (yields: 70–95%).

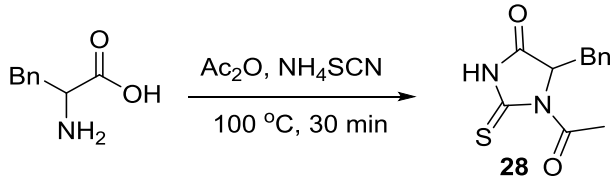
5.4.1.2. General procedure B[250]

Nitromethane (1 equiv., 1.1 mL, 20 mmol) was added to a stirred solution of the corresponding aldehyde (1 equiv., 20 mmol) in ethanol (35 mL) at 0 ^{o}C, followed by dropwise addition of 10N NaOH solution (1.05 equiv., 201 mL, 21 mmol). The resulting mixture was stirred at 0 ^{o}C for 1 hour and then a mixture of 1:1 HCl 37%: H_2O (12 mL:12 mL) was added. The reaction mixture was stirred at 0 ^{o}C for 1 hour, then extracted with dichloromethane (3 x 50 mL), dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (yields: 70–95%).

[249] Cheng, P.; Chen, J.-J.; Huang, N.; Wang, R.-R.; Zheng, Y.-T.; Liang, Y.-Z. *Molecules* **2009**, *14*, 3176–3186.
[250] Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem*. **1985**, *63*, 2354–2361.

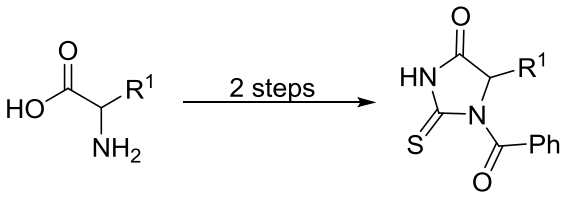
5.4.2. Preparation of *N*[1]-Acyl templates 32-35

5.4.2.1. Synthesis of 1-acetyl-5-benzyl-2-thioxoimidazolidin-4-one 28[251]

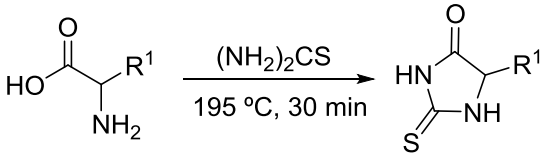


Phenylalanine (1 equiv., 4 mmol, 661 mg) and NH_4SCN (1 equiv., 4 mmol, 334 mg) were mixed in Ac_2O (6 equiv., 24 mmol, 2.26 mL). The resulting mixture was heated at 100 °C for 30 min in an oil bath, by which time all solids dissolved. The reaction was then quenched with ice and H_2O (30 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the crude product purified by column chromatography on silica gel. Yield: 3.1 mmol, 774 mg, 78%. m. p. 163–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.09 (s, 1H), 7.30 – 7.25 (m, 3H), 7.08 – 7.02 (m, 2H), 5.03 (dd, *J* = 5.9, 2.6 Hz, 1H), 3.59 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.30 (dd, *J* = 14.0, 2.6 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.9, 171.4, 170.7, 133.3, 129.5, 128.9, 127.9, 64.3, 35.2, 27.6.UPLC-DAD-QTOF: $C_{12}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 249.0698, found: 249.0699. UPLC-DAD-QTOF: $C_{12}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 249.0698, found: 249.0704.

5.4.2.2. Synthesis of *N*-benzoyl 2-thiohydantoins 29.



5.4.2.2.1. Synthesis of 2-thiohydantoins[252]

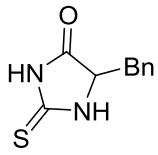


A mixture of the corresponding racemic amino acid (1 equiv., 40 mmol) and thiourea (3 equiv., 120 mmol) was placed in a flask and heated under stirring. When the

[251] Gosling, S.; Rollin, P.; Tatiboët, A. *Synthesis* **2011**, 22, 3649–3660.
[252] Wang, Z. D.; Sheikh, S. O.; Zhang, Y. *Molecules* **2006**, *11*, 739–750.

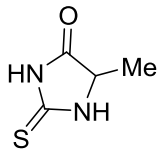
reaction temperature reached 180 °C, the mixture started to melt (m. p. of thiourea 175–178 °C) and about 5 minutes later (when the temperature reached 190 °C) the homogenous liquid started to fume and reflux and the solution turned an amber color. After 10 minutes, the fuming ceased and the reaction mixture was kept at this temperature for an additional 30 min. The flask was allowed to cool down and water (20 mL) was added while the flask was still warm. The solution was reheated to dissolve all the solids and allowed to cool to room temperature, then extracted with ethyl acetate (3 x 30 mL). The organic solvent was evaporated under reduced pressure and afterwards to this residue 100 mL of H_2O was added. This mixture was warm up to 50 °C and stirred for 30 min (to remove the excess of thiourea). The water phase was discarded. This process was repeated 3 times. To the organic residue was added 100 mL of Et_2O. The orange solid was filtered off to yield the title compound.

5-Benzyl-2-thioxoimidazolidin-4-one



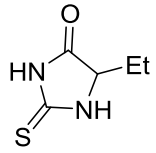
The title compound was prepared from DL-phenylalanine (6.60 g, 40 mmol) according to the general procedure. Orange solid. Yield: 7.25 g, 35.2 mmol, 88%. ^{1}H NMR (300 MHz, MeOD) δ: 7.45 – 6.92 (m, 5H), 4.51 (dd, *J* = 5.6, 4.7 Hz, 1H), 3.25 – 2.99 (m, 3H).

5-Methyl-2-thioxoimidazolidin-4-one



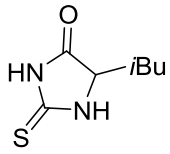
The title compound was prepared from DL-alanine (3.56 g, 40 mmol) according to the general procedure. Orange solid. Yield: 4.68 g, 36.0 mmol, 90%. ^{1}H NMR (300 MHz, MeOD) δ: 4.29 – 4.19 (m, 1H), 1.42 (d, *J* = 7.1 Hz, 5H).

5-Ethyl-2-thioxoimidazolidin-4-one



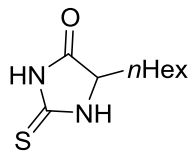
The title compound was prepared from DL-2-aminobutyric acid (4.12 g, 40 mmol) according to the general procedure. Orange solid. Yield: 5.24 g, 36.4 mmol, 91%. ^{1}H NMR (300 MHz, MeOD) δ: 4.19 (dd, *J* = 6.1, 5.0 Hz, 1H), 2.00 – 1.67 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

5-Isobutyl-2-thioxoimidazolidin-4-one



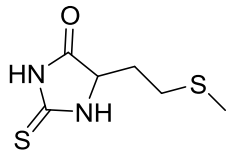
The title compound was prepared from DL-leucine (5.24 g, 40 mmol) according to the general procedure. Orange solid. Yield: 6.26 g, 36.4 mmol, 91%. ^{1}H NMR (300 MHz, MeOD) δ: 1.95 – 1.80 (m, 1H), 4.25 (dd, *J* = 8.4, 5.0 Hz, 1H), 1.75 – 1.54 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 9H).

5-Hexyl-2-thioxoimidazolidin-4-one



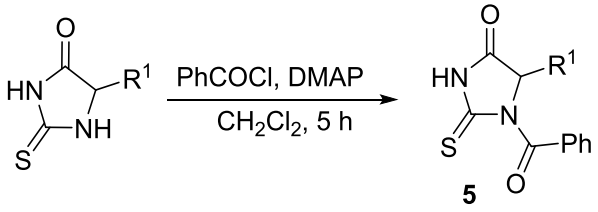
The title compound was prepared from DL-2-aminooctanoic acid (6.37 g, 40 mmol) according to the general procedure. Orange solid. Yield: 6.80 g, 34.0 mmol, 85%.

5-(2-(Methylthio)ethyl)-2-thioxoimidazolidin-4-one



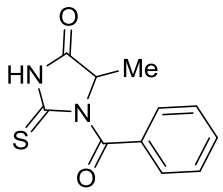
The title compound was prepared from DL-methionine (5.97 g, 40 mmol) according to the general procedure. Orange solid. Yield: 5.32 g, 28.0 mmol, 70%. ^{1}H NMR (300 MHz, MeOD) δ: 4.37 (dd, *J* = 7.1, 5.1 Hz, 1H), 2.75 – 2.58 (m, 3H), 2.23 – 1.92 (m, 5H).

5.4.2.2.2. Synthesis of *N*-benzoyl 2-thiohydantoins 29



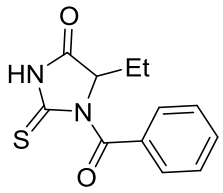
To a solution of the corresponding 2-thiohydantoin (1 equiv., 4 mmol) in dry CH_2Cl_2, DMAP (1.05 equiv., 4.2 mmol, 513 mg) and benzoyl chloride (1.05 equiv., 4.2 mmol, 487.9 µL) was added at 0 ^{o}C. Afterwards, the reaction was stirred at room temperature for 5 h. After concentration under vacuum, the crude product was purified by column chromatography on silica gel to give the desires compound.

1-Benzoyl-5-methyl-2-thioxoimidazolidin-4-one (29A)



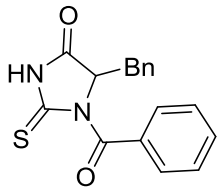
The title compound was prepared from 5-methyl-2-thioxoimidazolidin-4-one (4 mmol, 521 mg) and benzoyl chloride (4.2 mmol, 486 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 80:20) to give the title compound as a yellow solid. Yield: 3.0 mmol, 707 mg, 76%. m. p. 159–161 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (s, 1H), 7.73 – 7.70 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.42 (m, 2H), 5.04 (q, *J* = 6.9 Hz, 1H), 1.66 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.1, 173.0, 169.9, 133.8, 133.3, 129.5, 128.4, 59.5, 15.5. UPLC-DAD-QTOF: $C_{11}H_{11}N_2O_2S$ $[M+H]^+$ calcd.: 235.0541, found: 235.0542.

1-Benzoyl-5-ethyl-2-thioxoimidazolidin-4-one (29B)



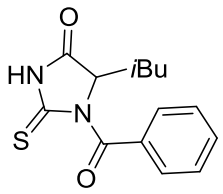
The title compound was prepared from 5-ethyl-2-thioxoimidazolidin-4-one (4 mmol, 577 mg) and and benzoyl chloride (4.2 mmol, 486 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a white solid. Yield: 2.9 mmol, 719 mg, 73%. m. p. 144–147 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 7.76 – 7.73 (m, 2H), 7.63 – 7.57 (m, 1H), 7.48 – 7.42 (m, 2H), 5.08 (dd, *J* = 5.3, 4.0 Hz, 1H), 2.20 – 2.10 (m, 2H), 1.06 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 172.3, 169.9, 133.7, 133.3, 129.8, 128.4, 64.3, 22.5, 8.2. UPLC-DAD-QTOF: $C_{12}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 249.0698, found: 249.0695.

1-Benzoyl-5-benzyl-2-thioxoimidazolidin-4-one (29C)



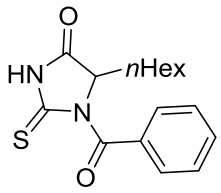
The title compound was prepared from 5-benzyl-2-thioxoimidazolidin-4-one (4 mmol, 824 mg) and benzoyl chloride (4.2 mmol, 486 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow foam. Yield: 3.4 mmol, 1.06 g, 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 7.60 – 7.50 (m, 1H), 7.43 – 7.25 (m, 7H), 7.18 – 7.11 (m, 2H), 5.30 (dd, *J* = 5.7, 3.1 Hz, 1H), 3.61 – 3.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.3, 171.7, 169.8, 133.8, 133.4, 133.0, 130.8, 130.6, 129.9, 129.9, 129.1, 128.0, 128.0, 64.2, 34.0. UPLC-DAD-QTOF: $C_{17}H_{15}N_2O_2S$ $[M+H]^+$ calcd.: 311.0854, found: 311.0858.

1-Benzoyl-5-isobutyl-2-thioxoimidazolidin-4-one (29D)



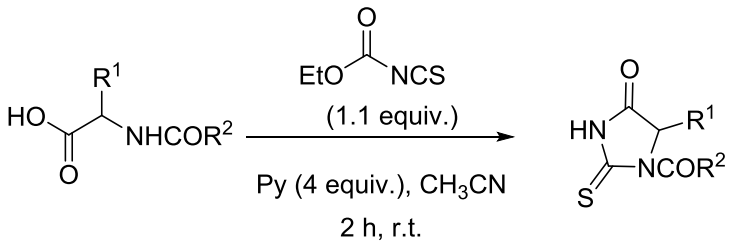
The title compound was prepared from 5-isobutyl-2-thioxoimidazolidin-4-one (4 mmol, 689 mg) and benzoyl chloride (4.2 mmol, 486 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 80:20) to give the title compound as a white solid. Yield: 2.4 mmol, 662 mg, 80%. m. p. 160–162 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 7.79 – 7.68 (m, 2H), 7.64 – 7.54 (m, 1H), 7.52 – 7.36 (m, 2H), 5.06 (dd, *J* = 7.2, 4.5 Hz, 1H), 2.24 – 1.70 (m, 3H), 0.98 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 172.7, 170.0, 133.5, 129.8, 128.5, 61.9, 38.9, 24.6, 23.1, 22.1. UPLC-DAD-QTOF: $C_{14}H_{17}N_2O_2S$ $[M+H]^+$ calcd.: 277.1011, found: 277.1013.

1-Benzoyl-5-hexyl-2-thioxoimidazolidin-4-one (29E)



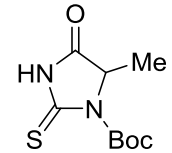
The title compound was prepared from 5-hexyl-2-thioxoimidazolidin-4-one (4 mmol, 800 mg) and benzoyl chloride (4.2 mmol, 486 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 80:20) to give the title compound as a yellow solid. Yield: 2.9 mmol, 875 mg, 72%. m. p. 79–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.93 (s, 1H), 7.80 – 7.72 (m, 2H), 7.64 – 7.56 (m, 1H), 7.51 – 7.42 (m, 2H), 5.10 (dd, *J* = 5.6, 4.0 Hz, 1H), 2.17 – 2.03 (m, 2H), 1.55 – 1.25 (m, 9H), 0.90 – 0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.7, 173.9, 170.8, 134.6, 134.2, 131.2, 130.6, 129.3, 64.4, 32.4, 30.1, 29.8, 24.7, 23.4, 15.0. UPLC-DAD-QTOF: $C_{16}H_{21}N_2O_2S$ $[M+H]^+$ calcd.: 305.1324, found: 305.1324.

5.4.2.3. Synthesis of N^1-Boc and N^1-Cbz 2-thiohydantoins 30 and 31[253]



To a solution of the corresponding *N*-Boc or *N*-Cbz amino acid (1.0 equiv, 4 mmol) in CH_3CN, pyridine (4 equiv., 16 mmol, 1.23 mL) and ethoxycarbonyl isothiocyanate (1.1 equiv., 4.4 mmol, 519 µL) were added at room temperature. The reaction mixture was stirred for 2 h at the same temperature. Afterwards, the solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography to obtain the desired product.

***tert*-Butyl 5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30A)**

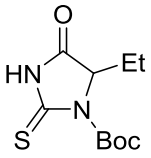


The title compound was prepared from (*tert*-butoxycarbonyl)alanine (4 mmol, 757 mg) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white solid. Yield: 3.5 mmol, 810 mg, 88%. m. p. 138–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 4.54 (q, *J* = 6.9 Hz, 1H), 1.59 (d, *J* = 6.9 Hz, 3H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.7, 173.0,

[253] Boyd, V.; Zon, G. U. S., 5185266 A, 09 Feb 1993

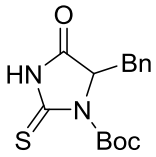
148.4, 85.4, 59.8, 28.0, 16.9. UPLC-DAD-QTOF: $C_9H_{14}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 253.0623, found: 253.0632.

***tert*-Butyl 5-ethyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30B)**



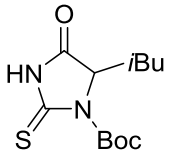
The title compound was prepared from 2-((*tert*-butoxycarbonyl)amino)butanoic acid (4 mmol, 812 mg) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white solid. Yield: 3.4 mmol, 839 mg, 86%. m. p. 70–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.49 (dd, *J* = 6.0, 3.0 Hz, 1H), 2.10 – 1.86 (m, 2H), 1.42 (s, 9H), 0.76 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.2, 172.4, 148.2, 84.8, 64.0, 27.6, 23.4, 6.9. UPLC-DAD-QTOF: $C_{10}H_{16}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 267.0779, found: 267.0788.

***tert*-Butyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30C)**



The title compound was prepared from (*tert*-butoxycarbonyl)phenylalanine (4 mmol, 1.06 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white solid. Yield: 3.6 mmol, 1.10 g, 90%. m. p. 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.05 (s, 1H), 7.11 – 7.06 (m, 3H), 7.11 – 7.06 (m, 2H), 4.82 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.49 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.29 (dd, *J* = 14.1, 2.9 Hz, 1H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.3, 171.5, 148.6, 133.0, 129.6, 128.8, 127.8, 85.5, 64.4, 35.9, 28.1. UPLC-DAD-QTOF: $C_{15}H_{18}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 329.0936, found: 329.0940.

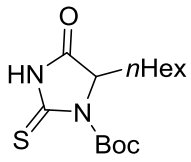
***tert*-Butyl 5-isobutyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30D)**



The title compound was prepared from (*tert*-butoxycarbonyl)leucine (4 mmol, 925 mg) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a yellow oil. Yield: 3.3 mmol, 903 mg, 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.92 (s, 1H), 4.55 – 4.49 (m, 2H), 1.93 – 1.79 (m, 3H), 1.51 (s, 9H), 0.89 – 0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.9, 172.8,

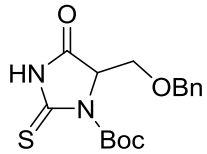
148.2, 85.1, 62.2, 39.2, 27.8, 23.7, 23.3, 22.0. UPLC-DAD-QTOF: $C_{12}H_{20}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 295.1092, found: 295.1096.

***tert*-Butyl 5-hexyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30E)**



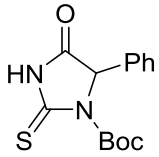
The title compound was prepared from 2-((*tert*-butoxycarbonyl)amino)octanoic acid (4 mmol, 1.04 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure at 50 °C. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a yellow oil. Yield: 3.0 mmol, 900 mg, 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (s, 1H), 4.58 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.13 – 1.98 (m, 2H), 1.57 (s, 9H), 1.36 – 1.23 (m, 8H), 0.89 – 0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.9, 171.9, 148.5, 85.4, 63.8, 31.5, 30.6, 28.9, 28.1, 23.0, 22.6, 14.1. UPLC-DAD-QTOF: $C_{14}H_{24}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 323.1405, found: 323.1409.

***tert*-Butyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (30G)**



The title compound was prepared from *O*-benzyl-*N*-(*tert*-butoxycarbonyl)serine (4 mmol, 1.18 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as an orange oil. Yield: 3.6 mmol, 1.21 g, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.67 (tt, *J* = 4.0, 2.0 Hz, 1H), 7.69 (tt, *J* = 7.7, 1.8 Hz, 1H), 7.33 – 7.20 (m, 4H), 4.58 – 4.39 (m, 2H), 4.04 – 3.89 (m, 1H), 1.46 (d, *J* = 1.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.8, 171.4, 148.9, 148.7, 148.4, 137.1, 136.8, 136.6, 128.4, 127.8, 127.4, 123.9, 123.89, 84.8, 84.8, 73.3, 66.6, 64.2, 27.9. UPLC-DAD-QTOF: $C_{16}H_{20}N_2O_4SNa^*$ $[M+Na]^+$ calcd.: 359.1041, found: 359.1046.

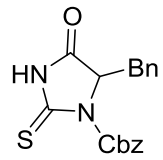
***tert*-Butyl 4-oxo-5-phenyl-2-thioxoimidazolidine-1-carboxylate (30H)**



The title compound was prepared from 2-((*tert*-butoxycarbonyl)amino)-2-phenylacetic acid (4 mmol, 1.00 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 50:50 to 0:100) to give the title compound as a white solid. Yield: 2.9 mmol, 841 mg, 72%. m. p. decomposition at 238 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.64 (s, 1H), 7.46 – 7.39 (m, 3H), 7.25 – 7.23 (m, 2H), 5.63 (s, 1H), 1.18 (s, 9H). ^{13}C NMR (75 MHz, DMSO) δ: 180.9, 171.3, 147.5, 134.9, 129.0, 128.7,

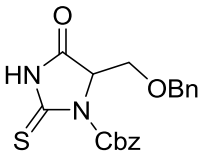
126.4, 83.3, 66.7, 27.2. UPLC-DAD-QTOF: $C_{14}H_{16}N_2O_3SNa^*$ $[M+Na]^+$ calcd.: 315.0779, found: 315.0787.

Benzyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (31C)



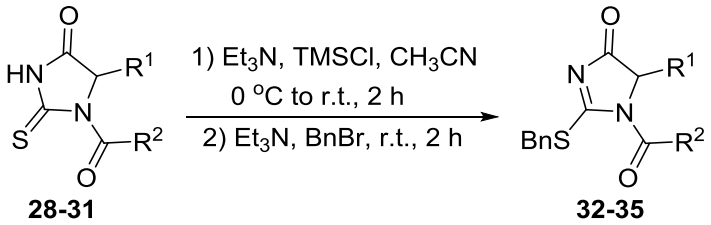
The title compound was prepared from ((benzyloxy)carbonyl)phenylalanine (4 mmol, 1.20 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80:20 to 50:50) to give the title compound as a white solid. Yield: 3.2 mmol, 1.10 g, 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.96 (s, 1H), 7.54 – 7.35 (m, 4H), 7.24 – 7.13 (m, 3H), 6.94 – 6.87 (m, 2H), 5.46 – 5.33 (m, 2H), 4.84 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.42 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.23 (dd, *J* = 14.1, 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 171.2, 150.2, 134.4, 132.8, 129.5, 129.1, 129.0, 128.9, 128.8, 127.8, 69.5, 64.6, 35.8. UPLC-DAD-QTOF: $C_{18}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 341.0960, found: 341.0963.

Benzyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (31G)



The title compound was prepared from *O*-benzyl-*N*-((benzyloxy)carbonyl)serine (4 mmol, 1.32 g) and ethoxycarbonyl isothiocyanate (4.4 mmol, 519 µL) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80:20 to 50:50) to give the title compound as a white solid. Yield: 3.3 mmol, 1.21 g, 82%. m. p. 154–158 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (s, 1H), 7.39 – 7.18 (m, 10H), 5.23 (s, 2H), 4.53 – 4.35 (m, 2H). 3.95 (qd, *J* = 10.2, 2.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.7, 169.9, 150.0, 137.2, 134.4, 129.0, 128.9, 128.7, 128.7, 128.1, 127.7, 73.4, 69.4, 66.3, 64.5. UPLC-DAD-QTOF: $C_{19}H_{18}N_2O_4SNa^*$ $[M+Na]^+$ calcd.: 393.0885, found: 393.0885.

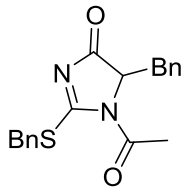
5.4.2.4. *S*-Benzylation of N^1-acyl thiohydantoins 28-31. Products 32-35[27]



28-31 **32-35**

A solution of the corresponding thiohydantoin (1 equiv., 3 mmol) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with freshly distilled triethylamine (0.50 mL, 3.6 mmol, 1.2 equiv.) and, after 5 min at 0 °C, freshly distilled TMSCl (0.45 mL, 3.6 mmol, 1.2 equiv) was added. A white precipitate formed instantaneously. The reaction mixture was warmed up to room temperature and stirred for 2 hours. Afterwards, freshly distilled triethylamine (1.7 mL, 12 mmol, 4 equiv.) and benzyl bromide (0.714 mL, 6 mmol, 2 equiv.) were added at the same temperature. The mixture was monitored by TLC (Hex/EtOAc, 1:2). After reaction completion (2-3 h), the reaction mixture was diluted with CH_2Cl_2 and washed with water. The clear yellow solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography.

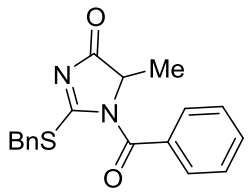
1-Acetyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (32C)



The title compound was prepared 1-acetyl-5-benzyl-2-thioxoimidazolidin-4-one (3 mmol, 744 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a white solid. Yield: 3.0 mmol, 1.01 g, 75%. m. p. 132–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 – 7.02 (m, 10H), 4.63 (t, *J* = 4.4 Hz, 1H), 4.32 – 4.22 (m, 2H), 3.39 (d, *J* = 4.4 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.2, 184.3, 167.3, 135.1, 133.1, 129.4, 129.4, 128.8, 128.7, 127.8, 64.5, 37.9, 37.5, 24.0. UPLC-DAD-QTOF: $C_{19}H_{19}N_2O_2S$ $[M+H]^+$ calcd.: 339.1167, found: 339.1170.

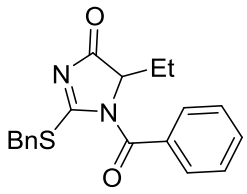
[27] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chemie Int. Ed.* **2015**, *54*, 6883-6886.

1-Benzoyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (33A)



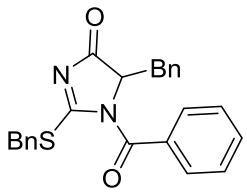
The title compound was prepared from 1-benzoyl-5-methyl-2-thioxoimidazolidin-4-one (3 mmol, 702 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 50:50) to give the title compound as a colourless oil. Yield: 2.3 mmol, 739 mg, 76%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58-7.23 (m, 10H), 4.60 (q, *J* = 7.0 Hz, 1H), 4.47 (s, 2H), 1.14 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.6, 185.1, 167.0, 134.96, 133.2, 132.4, 129.4, 128.9, 128.65, 127.7, 127.2, 60.5, 38.1, 16.8. UPLC-DAD-QTOF: $C_{18}H_{17}N_2O_2S$ $[M+H]^+$ calcd.: 325.1011, found: 325.1011.

1-Benzoyl-2-(benzylthio)-5-ethyl-1*H*-imidazol-4(5*H*)-one (33B)



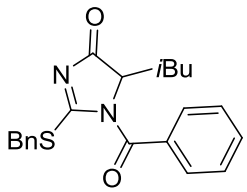
The title compound was prepared from 1-benzoyl-5-ethyl-2-thioxoimidazolidin-4-one (3 mmol, 744 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 80:20) to give the title compound as a white solid. m. p. 116 – 119 ^{o}C. Yield: 2.2 mmol, 730 mg, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.19 (m, 10H), 4.64 (dd, *J* = 6.1, 2.7 Hz, 1H), 4.54 – 4.34 (m, 2H), 1.86 – 1.73 (m, 1H), 1.37 – 1.27 (m, 1H), 0.68 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.7, 185.1, 167.1, 135.0, 133.3, 132.6, 129.4, 129.0, 128.7, 127.8, 127.2, 65.2, 38.2, 23.4, 6.8. UPLC-DAD-QTOF: $C_{19}H_{19}N_2O_2S$ $[M+H]^+$ calcd.: 339.1167, found: 339.1162.

1-Benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (33C)



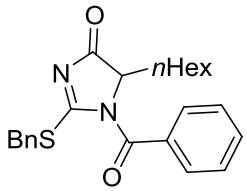
The title compound was prepared from 1-benzoyl-5-benzyl-2-thioxoimidazolidin-4-one (3 mmol, 930 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a yellow solid. m. p. 131 – 135 ^{o}C. Yield: 2.4 mmol, 973 mg, 81%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 – 7.48 (m, 5H), 7.29 – 7.26 (m, 8H), 7.05 – 7.02 (m, 2H), 5.01 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.32 (s, 2H), 3.26 (dd, *J* = 14.3, 2.8 Hz, 1H), 2.88 (dd, *J* = 14.2, 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.4, 184.6, 166.9, 135.0, 133.3, 133.1, 132.8, 129.3, 129.2, 128.9, 128.6, 128.0, 127.7, 127.5, 65.2, 38.0, 35.7. UPLC-DAD-QTOF: $C_{24}H_{21}N_2O_2S$ $[M+H]^+$ calcd.: 401.1324, found: 401.1319. UPLC-DAD-QTOF: $C_{24}H_{21}N_2O_2S$ $[M+H]^+$ calcd.: 401.1323, found: 401.1324.

1-Benzoyl-2-(benzylthio)-5-isobutyl-1*H*-imidazol-4(5*H*)-one (33D)



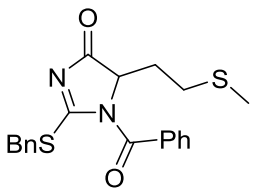
The title compound was prepared from 1-benzoyl-5-isobutyl-2-thioxoimidazolidin-4-one (3 mmol, 828 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a white solid. Yield: 2.1 mmol, 769 mg, 70%. m. p. 133-135 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 – 7.30 (m, 10H), 4.66 – 4.62 (s, 1H), 4.57 – 4.46 (m, 2H), 1.86 – 1.73 (m, 1H), 1.51 – 1.40 (m, 2H), 0.74 (d, *J* = 6.7 Hz, 1H), 0.67 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.5, 185.2, 167.3, 135.2, 133.5, 132.7, 129.6, 129.1, 128.9, 128.0, 127.6, 63.4, 39.6, 38.3, 23.5, 23.3, 21.8. UPLC-DAD-QTOF: $C_{21}H_{23}N_2O_2S$ $[M+H]^+$ calcd.: 367.1480, found: 367.1483.

1-Benzoyl-2-(benzylthio)-5-hexyl-1*H*-imidazol-4(5*H*)-one (33E)



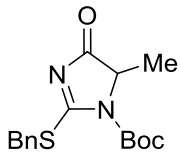
The title compound was prepared from 1-benzoyl-5-hexyl-2-thioxoimidazolidin-4-one (3 mmol, 912 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 50:50) to give the title compound as a white solid. Yield: 2.1 mmol, 827 mg, 70%. m. p. 96–99 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62-7.21 (m, 10H), 4.63 (dd, *J* = 6.4, 2.9 Hz, 1H), 4.57 – 4.39 (m, 2H), 1.88 – 1.55 (m, 1H), 1.41 – 0.94 (m, 9H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.7, 185.3, 167.3, 135.2, 133.5, 132.7, 129.6, 129.2, 128.9, 128.0, 127.4, 64.7, 38.3, 31.3, 30.2, 28.6, 22.5, 22.5, 14.0. UPLC-DAD-QTOF: $C_{23}H_{27}N_2O_2S$ $[M+H]^+$ calcd.: 395.1798, found: 395.1793.

1-Benzoyl-2-(benzylthio)-5-(2-(methylthio)ethyl)-1*H*-imidazol-4(5*H*)-one (33F)



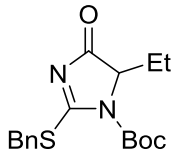
The title compound was prepared from 1-benzoyl-5-(2-(methylthio)ethyl)-2-thioxoimidazolidin-4-one (3 mmol, 882 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 80:20 to 60: 40) to give the title compound as a red oil. Yield: 1.9 mmol, 737 mg, 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 – 7.23 (m, 10H), 4.78 (dd, *J* = 7.5, 3.2 Hz, 1H), 4.54 – 4.39 (m, 2H), 2.55 – 2.22 (m, 2H), 2.04 – 1.92 (m, 1H), 1.81 (s, 3H), 1.77 – 1.61 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.6, 184.7, 167.0, 135.0, 133.1, 132.8, 129.5, 129.1, 128.8, 127.9, 127.6, 63.1, 38.3, 29.5, 27.9, 15.3. UPLC-DAD-QTOF: $C_{20}H_{21}N_2O_2S_2$ $[M+H]^+$ calcd.: 385.1044, found: 385.1046.

2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (34A)



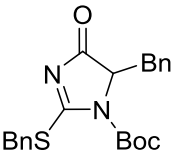
The title compound was prepared from *tert*-butyl 5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 690 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white solid. Yield: 2.5 mmol, 806 mg, 84%. m. p. 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.20 (m, 5H), 4.48 (d, *J* = 2.9 Hz, 2H), 4.29 (q, *J* = 7.0 Hz, 2H), 1.60 (d, *J* = 7.1 Hz, 3H), 1.57 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.0, 184.4, 148.5, 135.2, 129.5, 128.8, 127.9, 85.5, 59.6, 37.9, 28.1, 17.0. UPLC-DAD-QTOF: $C_{16}H_{21}N_2O_3S$ $[M+H]^+$ calcd.: 321.1273, found: 321.1273.

2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one (34B)



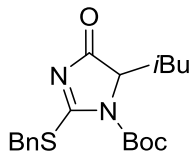
The title compound was prepared from *tert*-butyl 5-ethyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 732 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a white solid. Yield: 2.3 mmol, 762 mg, 76%. m. p. 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.22 (m, 5H), 4.50 – 4.38 (m, 2H), 4.29 (dd, *J* = 5.7, 3.2 Hz, 1H), 2.22 – 1.98 (m, 2H), 1.53 (s, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.4, 185.0, 148.6, 135.2, 129.5, 128.8, 127.9, 85.5, 64.3, 37.9, 28.1, 23.6, 7.2. UPLC-DAD-QTOF: $C_{17}H_{23}N_2O_3S$ $[M+H]^+$ calcd.: 335.1429, found: 335.1431.

5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-4-oxo-1*H*-imidazol-4(5*H*)-one (34C)



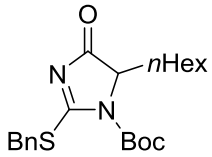
The title compound was prepared from *tert*-butyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 918 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a white solid. Yield: 2.4 mmol, 950 mg, 80%. m. p. 132–135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 6.98 (m, 10H), 4.57 (dd, *J* = 5.8, 2.8 Hz, 2H), 4.37 – 4.18 (m, 2H), 3.54 – 3.31 (m, 2H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.0, 184.8, 148.4, 135.4, 133.8, 129.5, 129.4, 128.7, 128.7, 127.8, 127.5, 85.8, 64.5, 37.6, 36.2, 28.2. UPLC-DAD-QTOF: $C_{22}H_{25}N_2O_3S$ $[M+H]^+$ calcd.: 397.1586, found: 397.1588.

2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-isobutyl-1*H*-imidazol-4(5*H*)-one (34D)



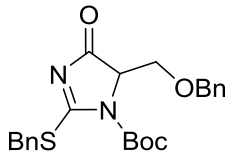
The title compound was prepared from *tert*-butyl 5-isobutyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 816 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a yellow oil. Yield: 2.4 mmol, 869 mg, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.18 (m, 5H), 4.47 (d, *J* = 1.4 Hz, 2H), 4.37 – 4.16 (m, 1H), 2.07 – 1.79 (m, 3H), 1.56 (s, 9H), 0.94 (dd, *J* = 6.2, 3.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.7, 184.4, 148.5, 135.2, 129.5, 128.8, 127.9, 85.5, 62.3, 39.4, 37.9, 28.1, 23.8, 23.6, 22.3. UPLC-DAD-QTOF: $C_{19}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 363.1742, found: 363.1749

2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-1*H*-imidazol-4(5*H*)-one (34E)



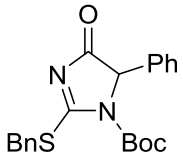
The title compound was prepared from *tert*-butyl 5-hexyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 900 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a yellow oil. Yield: 2.2 mmol, 842 mg, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.24 (m, 4H), 4.51 – 4.41 (m, 2H), 4.34 – 4.28 (m, 1H), 2.11 – 2.02 (m, 2H), 1.54 (s, 9H), 1.34 – 1.15 (m, 8H), 0.91 – 0.83 (m, 3H). UPLC-DAD-QTOF: $C_{21}H_{31}N_2O_3S$ $[M+H]^+$ calcd.: 391.2055, found: 391.2053.

5-((Benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one (34G)



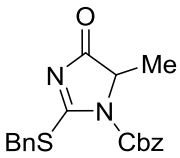
The title compound was prepared from *tert*-butyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 1.08 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a white solid. Yield: 2.5 mmol, 1.05 g, 82%. m. p. 104-108 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.26 (m, 10H), 4.64 – 4.44 (m, 4H), 4.32 – 4.30 (m, 1H), 4.11 – 3.96 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.7, 183.8, 148.4, 137.5, 135.3, 129.5, 128.8, 128.5, 127.9, 127.9, 127.7, 85.5, 73.4, 67.0, 64.0, 38.0, 28.0. UPLC-DAD-QTOF: $C_{23}H_{27}N_2O_4S$ $[M+H]^+$ calcd.: 427.1692, found: 427.1693.

2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-4-oxo-5-phenyl-1*H*-imidazol-4(5*H*)-one (34H)



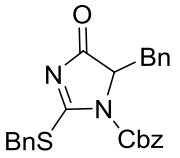
The title compound was prepared from *tert*-butyl 4-oxo-5-phenyl-2-thioxoimidazolidine-1-carboxylate (3 mmol, 876 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a white solid. Yield: 2.5 mmol, 940 mg, 82%. m. p. 153-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.19 (m, 10H), 5.19 (s, 1H), 4.62 – 4.49 (m, 2H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.4, 183.0, 148.3, 135.1, 134.4, 129.5, 129.0, 128.9, 128.7, 128.0, 126.4, 85.4, 67.3, 38.0, 27.6. UPLC-DAD-QTOF: $C_{21}H_{23}N_2O_3S$ $[M+H]^+$ calcd.: 383.1429, found: 383.1433.

1-(Benzyloxycarbonyl)-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (35A)



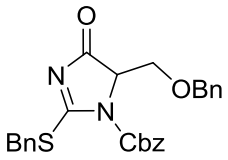
The title compound was prepared from benzyl 5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 792 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a white solid. Yield: 2.3 mmol, 807 mg, 76%. m. p. 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.22 (m, 10H), 5.28 (q, *J* = 12.0 Hz, 2H), 4.57 – 4.40 (m, 2H), 4.32 (q, *J* = 7.0 Hz, 1H), 1.56 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.6, 184.3, 149.7, 135.0, 134.1, 129.4, 129.1, 128.8, 128.8, 128.7, 127.9, 69.4, 59.4, 37.9, 17.0. UPLC-DAD-QTOF: $C_{19}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 355.1116, found: 355.1115.

5-Benzyl-1-(Benzyloxycarbonyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (35C)



The title compound was prepared from benzyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 1,42 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a yellow oil. Yield: 2.1 mmol, 903 mg, 70%. m. p.: 111-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 – 7.43 (m, 15H), 7.37 – 7.03 (m, 8H), 7.03 – 6.57 (m, 2H), 5.61 – 5.22 (m, 1H), 4.59 (dd, *J* = 5.6, 2.8 Hz, 1H), 4.41 – 4.16 (m, 2H), 3.35 (qd, *J* = 13.9, 4.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.0, 184.5, 149.6, 135.2, 134.1, 133.4, 129.4, 129.3, 129.3, 129.0, 128.7, 128.6, 127.8, 127.4, 69.6, 64.2, 37.5, 36.1. UPLC-DAD-QTOF: $C_{25}H_{23}N_2O_3S$ $[M+H]^+$ calcd.: 431.1429, found: 431.1425.

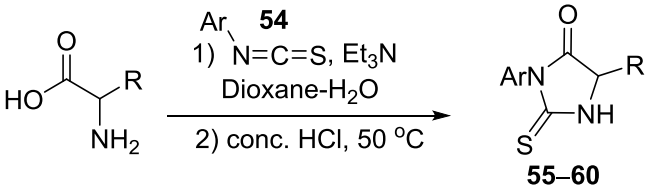
1-(Benzyloxycarbonyl)-5-((benzyloxy)methyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (35G)



The title compound was prepared from benzyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (3 mmol, 1.11 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 70:30) to give the title compound as a colourless oil. Yield: 2.3 mmol, 1.08 g, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 – 7.10 (m, 15H), 5.27 – 5.03 (m, 2H), 4.59 – 4.45 (m, 3H), 4.42 – 4.24 (m, 2H), 3.99 (qd, *J* = 10.0, 2.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.2, 183.1, 149.2, 137.3, 135.0, 133.9, 129.2, 128.8, 128.5, 128.5, 128.2, 127.6, 127.5, 127.3, 72.8, 69.0, 66.5, 63.5, 37.6. UPLC-DAD-QTOF: $C_{26}H_{25}N_2O_4S$ $[M+H]^+$ calcd.: 461.1535, found: 461.1539.

5.4.3. Preparation of N^3-aryl templates 61-66

5.4.3.1. Synthesis of N^3-aryl thiohydantoins 55-60[28]

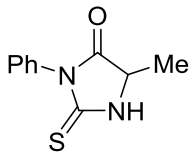


Ar: **55** Ar: Ph
56 Ar: 4-MeC_6H_4
57 Ar: 4-ClC_6H_4
58 Ar: 4-BrC_6H_4
59 Ar: 4-MeOC_6H_4
60 Ar: 3-ClC_6H_4

The corresponding amino acid (50 mmol, 1.0 equiv) was added to a solution of phenyl isothiocyanate (5.92 mL, 50 mmol, 1.0 equiv) in 1,4-dioxane-H_2O (120 mL, 1:1, v/v) and cooled to 0 °C. Then Et_3N (14.0 mL, 100 mmol, 2.0 equiv) was slowly added and the solution was stirred for 1 h, followed by the addition of concentrated HCl (12.50 mL, 150 mmol, 3.0 equiv) at 0 °C until the pH was approximately 2. The reaction mixture was stirred for another 12 h at 50 °C, and the precipitate formed was filtered and dried to afford the desired compound.

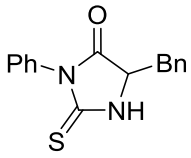
5-Methyl-3-phenyl-2-thioxoimidazolidin-4-one (55A)

[28] Zhu, L.; Lu, C.; Chen, Z.; Yang, G.; Li, Y.; Nie, J. *Tetrahedron: Asymmetry* **2015**, *26*, 6–15.



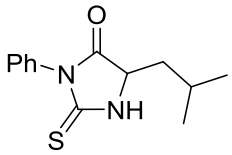
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. White solid. Yield: 6.99 g, 33.86 mmol, 68% (two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 7.54 – 7.31 (m, 5H), 4.35 (q, *J* = 7.0 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 4H).

5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (55C)



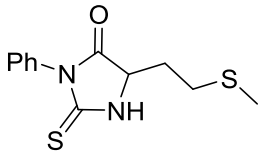
The title compound was prepared from phenylalanine (8.25 g, 50 mmol) according to the general procedure. White solid. Yield: 10.15 g, 36 mmol, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 – 7.25 (m, 8H), 7.10 – 7.07 (m, 2H), 4.53 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.13 – 3.06 (m, 1H).

5-Isobutyl-3-phenyl-2-thioxoimidazolidin-4-one (55D)



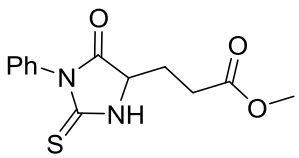
The title compound was prepared from leucine (6.55 g, 50 mmol) according to the general procedure. White solid. Yield: 8.68 g, 35 mmol, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.55 – 7.45 (m, 3H), 7.35 – 7.29 (m, 2H), 4.29 (dd, *J* = 9.2, 4.0 Hz, 1H), 1.97 – 1.69 (m, 3H), 0.99 (t, *J* = 6.2 Hz, 6H).

5-(2-(Methylthio)ethyl)-3-phenyl-2-thioxoimidazolidin-4-one (55F)



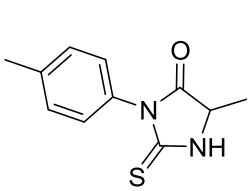
The title compound was prepared from methionine (7.46 g, 50 mmol) according to the general procedure. Orange solid. Yield: 9.32 g, 35 mmol, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.54 – 7.43 (m, 3H), 7.34 – 7.31 (m, 2H), 2.77 – 2.72 (m, 2H), 2.42-2.31 (m, 1H), 2.22 – 2.10 (m, 4H).

Methyl 3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate (55I)



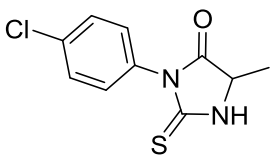
The title compound was prepared from glutamine (7.3 g, 50 mmol) according to the general procedure. White solid Yield: 9.03 g, 32.5 mmol, 65%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.54 – 7.43 (m, 3H), 7.33 – 7.29 (m, 2H), 4.36 (dd, *J* = 6.6, 5.0 Hz, 1H), 3.73 (s, 3H), 2.61 – 2.53 (m, 2H), 2.42 – 2.31 (m, 1H), 2.25– 2.13 (m, 1H).

5-Methyl-2-thioxo-3-(p-tolyl)imidazolidin-4-one (56A)



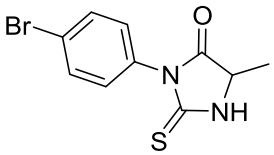
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a yellow solid. Yield: 6.60 g, 30 mmol, 60%. m. p. 184–186 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.65 – 6.94 (m, 4H), 4.31 (q, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.9, 174.4, 139.6, 130.0, 130.0, 128.1, 55.6, 21.4, 17.1. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0753.

3-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (57A)



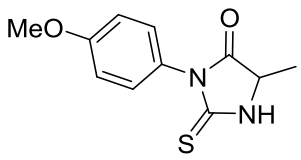
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. Yield: 7.68 g, 32 mmol, 64%. m. p. 202–206 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.58 (s, 1H), 7.59 – 7.53 (m, 2H), 7.38 – 7.32 (m, 2H), 4.45 (q, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ: 181.7, 174.8, 133.2, 132.4, 130.8, 128.8, 55.2, 16.1. UPLC-DAD-QTOF: $C_{10}H_{10}N_2OSCl$ $[M+H]^+$ calcd.: 241.0202, found: 241.0196.

3-(4-Bromophenyl)-5-methyl-2-thioxoimidazolidin-4-one (58A)



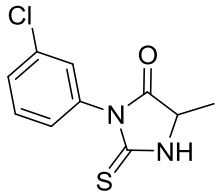
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. Yield: 9.23 g, 32 mmol, 65%. m. p. 211–215 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 – 7.60 (m, 2H), 7.53 (s, 1H), 7.33 – 7.14 (m, 2H), 4.35 (qd, *J* = 7.0, 1.3 Hz, 1H), 1.60 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.2, 173.7, 132.5, 131.7, 130.0, 123.5, 55.6, 17.3. UPLC-DAD-QTOF: $C_{10}H_{10}N_2OSBr$ $[M+H]^+$ calcd.: 284.9697, found: 284.9702.

3-(4-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (59A)



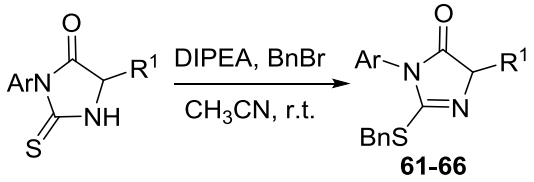
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. Yield: 7.79 g, 33 mmol, 66%. m. p. 182–185 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.47 (s, 1H), 7.22 – 7.15 (m, 2H), 7.04 – 6.97 (m, 2H), 4.46 – 4.36 (m, 1H), 3.78 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ: 182.5, 175.2, 159.1, 130.0, 126.0, 113.9, 55.4, 55.0, 16.3. UPLC-DAD-QTOF: $C_{11}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 237.0698, found: 237.0700.

3-(3-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (60A)



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a yellow solid. Yield: 7.44 g, 31 mmol, 62%. m. p. 169–171 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.56 – 7.22 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 1H), 1.61 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.1, 173.8, 134.8, 133.7, 130.2, 129.7, 128.8, 126.7, 55.6, 17.1. UPLC-DAD-QTOF: $C_{10}H_{10}N_2OSCl$ $[M+H]^+$ calcd.: 241.0202, found: 241.0205.

5.4.3.2. S-Benzylation of N^3-aryl thiohydantoins 55-60. Products 61-66

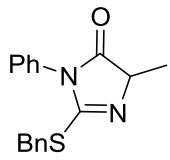


Ar: **61** Ar: Ph
62 Ar: 4-MeC_6H_4
63 Ar: 4-ClC_6H_4
64 Ar: 4-BrC_6H_4
65 Ar: 4-$MeOC_6H_4$
66 Ar: 3-ClC_6H_4

A solution of the corresponding thiohydantoin (5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with freshly distilled DIPEA (20 mmol, 4 equiv.) and benzyl bromide (1.19 mL, 10 mmol, 2 equiv.), unless stated otherwise. The mixture was then warmed up to room temperature and monitored by

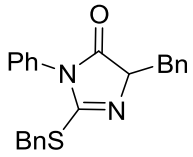
TLC (hexane/ethyl acetate, 50:50). After reaction completion (2–3 h), the reaction mixture was diluted with CH_2Cl_2 and washed with water. The clear yellow solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography (hexane/ethyl acetate) to obtain the desired product.[29]

2-(Benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (61A)



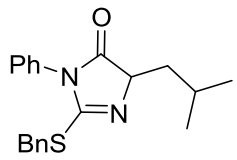
The title compound was prepared from 5-methyl-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.03 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a white solid. Yield: 4.1 mmol, 1.21 g, 82%. m. p. 113–117 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51-7.30 (m, 10H), 4.42 (s, 1H), 4.37 (q, 1.61 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.7, 161.2, 135.8, 132.3, 129.5, 129.3, 129.1, 128.7, 127.8, 127.4, 64.9, 34.9, 17.2. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1062, found: 297.1079.

4-Benzyl-2-(benzylthio)-1-phenyl-1*H*-imidazol-5(4*H*)-one (61C)



The title compound was prepared from 5-benzyl-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.41 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a colourless oil; yield: 3.9 mmol, 1.47 g, 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.18 (m, 13H), 7.09 – 6.75 (m, 2H), 4.74 – 4.57 (m, 1H), 4.52 – 4.33 (m, 2H), 3.46 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.30 (dd, *J* = 13.5, 5.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.2, 161.6, 136.1, 135.6, 132.0, 130.0, 129.3, 129.2, 129.1, 128.6, 128.0, 127.7, 127.3, 126.9, 69.7, 37.5, 34.6. UPLC-DAD-QTOF: $C_{23}H_{20}N_2OS$ $[M+H]^+$ calcd.: 373.1375, found: 373.1388.

2-(Benzylthio)-4-isobutyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (61D)

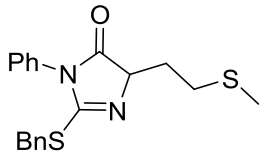


The title compound was prepared from 5-isobutyl-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.24 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl

[29] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.

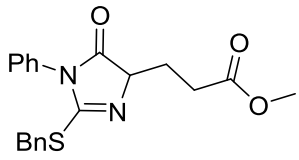
acetate, 80:20) to afford the title compound as a white solid. Yield: 4.0 mmol, 1.35 g, 80%. m. p. 90–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 – 7.29 (m, 10H), 4.47–4.33 (m, 3H), 2.24 – 2.10 (m, 8H), 1.97 – 1.88 (m, 8H), 1.71 – 1.62 (m, 1H), 1.13 – 1.08 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.7, 160.7, 136.3, 132.4, 129.4, 129.3, 129.1, 128.6, 127.7, 68.0, 41.0, 34.8, 25.5, 23.2, 22.3. UPLC-DAD-QTOF: $C_{20}H_{23}N_2OS$ $[M+H]^+$ calcd.: 339.1531, found: 339.1548.

2-(Benzylthio)-4-(2-(methylthio)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (61F)



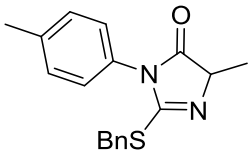
The title compound was prepared from 5-(2-(methylthio)ethyl)-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.33 g) utilizing 8 equiv. of freshly distilled DIPEA and 4 equiv. of benzyl bromide. The reaction was carried out at –20 °C for 6 h. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a red oil; yield: 3.0 mmol, 1.07 g, 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.26 (m, 10H), 4.45 – 4.31 (m, 3H), 2.71 (t, *J* = 7.2 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.14 (s, 3H). UPLC-DAD-QTOF: $C_{19}H_{21}N_2OS_2$ $[M+H]^+$ calcd.: 357.1095, found: 357.1110.

Methyl 3-(2-(benzylthio)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate (61I)



The title compound was prepared from methyl 3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate (5 mmol, 1.39 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a colourless oil; yield: 4.0 mmol, 1.47 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 – 7.20 (m, 10H), 4.60 – 4.36 (m, 2H), 3.74 (s, 3H), 2.63 – 2.58 (m, 2H), 2.49 – 2.37 (m, 1H), 2.26 – 2.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 173.2, 161.9, 136.0, 132.1, 129.5, 129.2, 128.7, 127.7, 127.3, 67.9, 51.7, 34.7, 29.9, 26.9. UPLC-DAD-QTOF: $C_{20}H_{21}N_2O_3S$ $[M+H]^+$ calcd.: 369.1273, found: 369.1286.

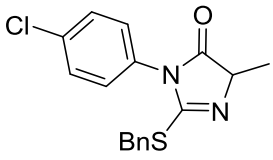
2-(Benzylthio)-4-methyl-1-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (62A)



The title compound was prepared from 5-methyl-2-thioxo-3-(*p*-tolyl)imidazolidin-4-one (5 mmol, 1.10 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl

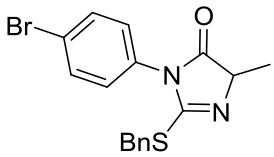
acetate, 80:20) to afford the title compound as a yellow solid. Yield: 4.0 mmol, 1.25 g, 81%. m. p. 78-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.05 (m, 9H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 2.41 (s, 3H), 1.59 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.6, 139.4, 135.9, 130.2, 129.6, 129.3, 128.7, 127.8, 127.2, 65.0, 34.9, 21.3, 17.2. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1236.

2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (63A)



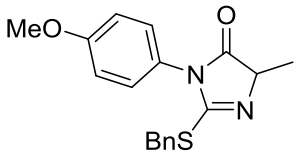
The title compound was prepared from 3-(4-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.20 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a white solid. Yield: 4.1 mmol, 1.37 g, 83%. m. p. 133-135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 – 6.75 (m, 9H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 1.57 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.7, 135.8, 135.2, 130.8, 129.8, 129.3, 128.8, 128.7, 128.0, 65.0, 35.0, 17.2. UPLC-DAD-QTOF: $C_{17}H_{16}N_2OSCl$ $[M+H]^+$ calcd.: 331.0672, found: 331.0675.

2-(Benzylthio)-1-(4-bromophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (64A)



The title compound was prepared from 3-(4-bromophenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.41 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a white solid. m. p. 127-131 °C. Yield: 4.0 mmol, 1.50 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.56 (m, 2H), 7.42 – 7.26 (m, 5H), 7.20 – 7.13 (m, 2H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 1.57 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.5, 160.6, 135.8, 132.8, 131.3, 129.3, 128.9, 128.8, 127.9, 123.2, 65.0, 35.0, 17.2. UPLC-DAD-QTOF: $C_{17}H_{16}N_2OSBr$ $[M+H]^+$ calcd.: 375.0167, found: 375.0168.

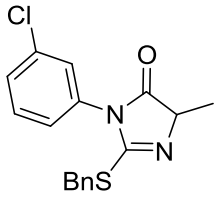
2-(Benzylthio)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (65A)



The title compound was prepared from 3-(4-methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.18 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a yellow solid. Yield: 3.9 mmol, 1.29 g, 79%. m. p. 94–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ:

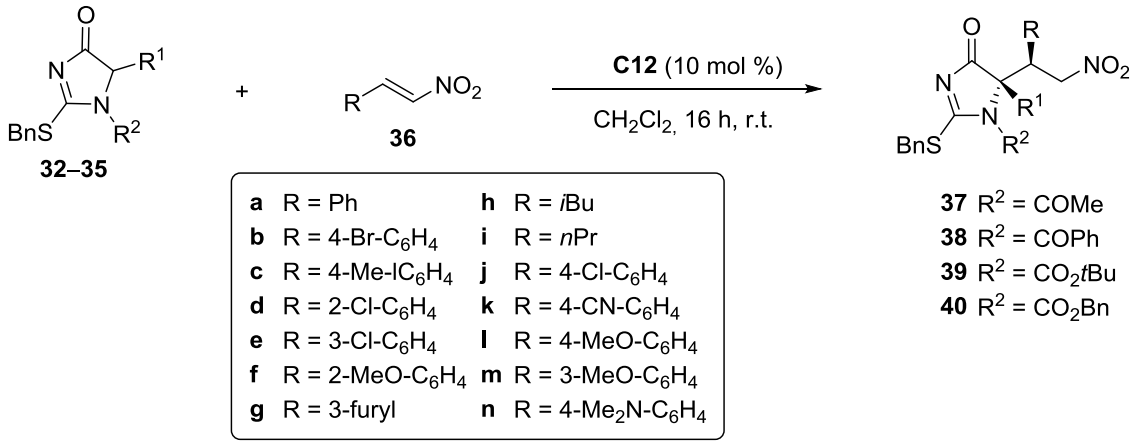
7.50 – 7.15 (m, 2H), 7.06 – 6.81 (m, 2H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 1.59 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.7, 160.0, 135.8, 129.2, 128.7, 128.6, 127.7, 124.6, 114.6, 114.5, 64.8, 55.4, 34.7, 17.1. UPLC-DAD-QTOF: $C_{18}H_{19}N_2O_2S$ $[M+H]^+$ calcd.: 327.1167, found: 327.1178.

2-(Benzylthio)-1-(3-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one(66A)



The title compound was prepared from 3-(3-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.20 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a yellow oil. Yield: 4.0 mmol, 1.32 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.03 (m, 9H), 4.41 (s, 2H), 4.35 (q, *J* = 7.5 Hz, 1H), 1.58 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.4, 160.5, 135.7, 135.0, 133.4, 130.4, 129.4, 129.3, 128.8, 127.9, 127.6, 125.5, 64.9, 35.0, 17.1. UPLC-DAD-QTOF: $C_{17}H_{16}N_2OSCl$ $[M+H]^+$ calcd.: 331.0672, found: 331.0676.

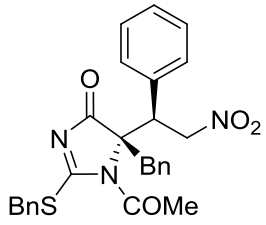
5.4.3.3. Reaction scope.



a	R = Ph	**h**	R = *i*Bu
b	R = 4-Br-C_6H_4	**i**	R = *n*Pr
c	R = 4-Me-IC_6H_4	**j**	R = 4-Cl-C_6H_4
d	R = 2-Cl-C_6H_4	**k**	R = 4-CN-C_6H_4
e	R = 3-Cl-C_6H_4	**l**	R = 4-MeO-C_6H_4
f	R = 2-MeO-C_6H_4	**m**	R = 3-MeO-C_6H_4
g	R = 3-furyl	**n**	R = 4-Me_2N-C_6H_4

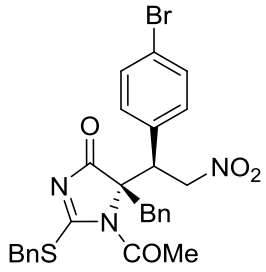
To a solution of the corresponding imidazolone **8**-**11** (1 equiv., 0.2 mmol) and nitroalkene (2.0 equiv., 0.4 mmol) in dichlorometane (0.6 mL) catalyst **C3** (0.02 mmol, 13.6 mg) was added at room temperature. The resulting mixture was stirred until consumption of the imidazolone (monitored by ^{1}H-NMR). Afterwards, he reaction was purified by flash column chromatography on silica gel to afford the expected adducts.

(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (37Ca)



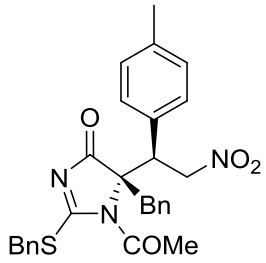
The title compound was prepared from 1-acetyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **32C** (0.2 mmol, 68 mg) and (E)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/DCM 90:10 to 70:30) to give the title compound as a white foam. Yield: 0.16 mmol, 78 mg, 80%. $[\alpha]_D^{25}$= –43.44 (*c* = 0.58, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.31 – 7.02 (m, 15H) 5.38 – 5.22 (m, 2H), 4.84 (dd, *J* = 10.4, 4.7 Hz, 1H), 4.17 (s, 2H), 3.78 (d, *J* = 12.9 Hz, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.1, 167.8, 134.4, 133.5, 129.4, 129.3, 128.9, 128.8, 128.7, 128.3, 127.9, 127.8, 48.1, 40.3, 39.0, 26.5. UPLC-DAD-QTOF: $C_{27}H_{26}N_3O_4S$ $[M+H]^+$ calcd.: 488.1644, found: 488.1644.

(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (37Cb)



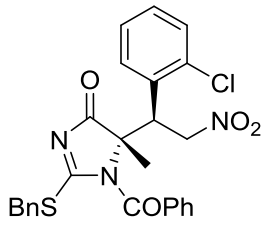
The title compound was prepared from 1-acetyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **32C** (0.2 mmol, 68 mg) and (E)-1-bromo-4-(2-nitrovinyl)benzene **36b** (0.4 mmol, 91 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/DCM 90:10 to 70:30) to give the title compound as a white foam. $[\alpha]_D^{25}$= +2.64 (*c* = 1.30, >98:2 dr, 99% *ee*, CH_2Cl_2). Yield: 0.15 mmol, 82.5 mg, 73%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.37 – 6.92 (m, 14H), 5.35 – 5.10 (m, 2H), 4.81 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.26 – 4.07 (m, 2H), 3.72 (d, *J* = 12.9 Hz, 1H), 3.45 (d, *J* = 12.8 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.9, 167.9, 134.0, 133.5, 133.3, 132.1, 129.6, 129.3, 129.0, 128.7, 128.4, 127.9, 123.0, 75.3, 47.6, 40.2, 39.1, 26.5. UPLC-DAD-QTOF: $C_{27}H_{25}N_3O_4SBr$ $[M+H]^+$ calcd.: 566.0749, found: 566.0756.

(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (37Cc)



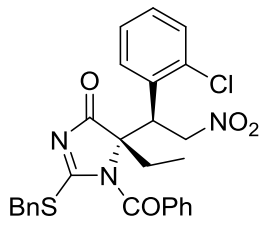
The title compound was prepared from 1-acetyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **32C** (0.2 mmol, 68 mg) and (E)-1-methyl-4-(2-nitrovinyl)benzene **36c** (0.4 mmol, 65 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/DCM 90:10 to 70:30) to give the title compound as a 95:5 mixture of diastereomer (white foam). Yield: 0.15 mmol, 76.2 mg, 76%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.34 – 6.95 (m, 14H), 5.37 – 5.19 (m, 2H), 4.79 (dd, *J* = 10.5, 4.6 Hz, 1H), 4.27 – 4.09 (m, 2H), 3.77 (d, *J* = 12.9 Hz, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 2.28 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.2, 167.8, 138.5, 134.3, 133.6, 131.2, 129.6, 129.4, 129.3, 128.9, 128.6, 128.3, 127.7, 75.7, 47.8, 40.3, 38.9, 26.4, 21.2. UPLC-DAD-QTOF: $C_{28}H_{28}N_3O_4S$ $[M+H]^+$ calcd.: 502.1801, found: 502.1806.

(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (38Ad)



The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one **33A** (0.2 mmol, 67.6 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 97:3 mixture of diastereomer (white foam). Yield: 0.14 mmol, 73.0 g, 72%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.52 – 6.88 (m, 14H), 5.35 – 5.18 (m, 3H), 4.25 – 4.13 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.3, 184.4, 166.9, 136.1, 134.4, 133.6, 133.4, 132.9, 130.8, 129.9, 129.4, 129.2, 129.0, 128.9, 128.6, 128.2, 128.0, 127.6, 76.2, 72.5, 43.5, 39.6, 24.5. UPLC-DAD-QTOF: $C_{26}H_{23}N_3O_4SCl$ $[M+H]^+$ calcd.: 508.1098, found: 508.1104.

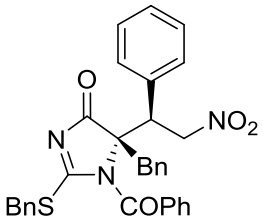
(*S*)-1-Benzoyl-2-(benzylthio)-5-((S)-1-(2-chlorophenyl)-2-nitroethyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one (38Bd)



The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-ethyl-1*H*-imidazol-4(5*H*)-one **33B** (0.2 mmol, 67.6 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was

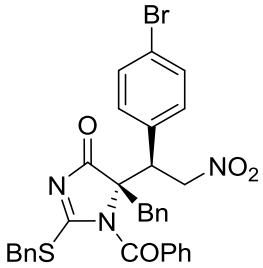
purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 97:3 mixture of diastereomer (white foam). Yield: 0.14 mmol, 104.2 mg, 70%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.57 – 6.77 (m, 13H), 5.32 – 5.11 (m, 2H), 4.25 (d, *J* = 13.4 Hz, 1H), 4.09 (d, *J* = 13.4 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.33 – 2.14 (m, 1H), 0.76 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.9, 185.3, 166.9, 136.1, 134.6, 133.8, 133.5, 132.8, 130.8, 129.9, 129.3, 129.1, 128.8, 128.5, 128.1, 128.0, 127.8, 76.2, 43.5, 39.5, 30.5, 8.0. UPLC-DAD-QTOF: $C_{27}H_{26}N_3O_4SCl$ $[M+H]^+$ calcd.: 522.1254, found: 522.1253.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((S)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ca)



The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/DCM 80:20 to 50:50) to give the title compound as a white foam. Yield: 0.15 mmol, 83.4 mg, 76%. $[\alpha]_D^{25}$= –22.31 (*c* = 0.80, >98:2 dr, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.45 – 7.39 (m, 1H), 7.35 – 7.16 (m, 14H), 6.92 – 6.89 (m, 2H), 6.76 – 6.36 (m, 2H), 5.44 – 5.30 (m, 2H), 4.96 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.94 (d, *J* = 12.9 Hz, 1H), 3.84 (m, 2H), 3.65 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.4, 185.6, 167.8, 134.8, 133.9, 133.7, 133.0, 129.8, 129.3, 128.9, 128.9, 128.7, 128.6, 128.4, 128.1, 127.9, 76.1, 48.9, 41.2, 39.9. UPLC-DAD-QTOF: $C_{32}H_{28}N_3O_4S$ $[M+H]^+$ calcd.: 550.1801, found: 550.1806.

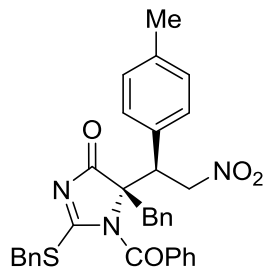
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cb)



The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-1-bromo-4-(2-nitrovinyl)benzene **36b** (0.4 mmol, 91 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/DCM 90:10 to 50:50) to give the title compound as a yellow foam. Yield: 0.16 mmol, 97.8 mg, 78%. $[\alpha]_D^{25}$= –3.90 (*c* = 0.70, >98:2 dr, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.80 – 7.04 (m, 15H), 7.03 – 6.92 (m, 2H), 6.59 – 6.57 (m, 2H), 4.97 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.95 – 3.78 (m, 3H), 3.68 – 3.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.1, 185.8, 167.9, 133.7, 133.6, 133.3, 132.5, 132.3, 129.8,

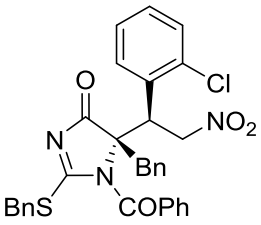
129.4, 129.0, 128.8, 128.7, 128.5, 128.2, 128.0, 123.2, 75.6, 48.5, 40.8, 40.1. UPLC-DAD-QTOF: $C_{32}H_{27}N_3O_4SBr$ $[M+H]^+$ calcd.: 628.0906, found: 628.0909.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(p-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (38Cc)



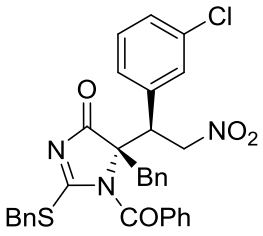
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene **36c** (0.4 mmol, 65.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a white foam. Yield: 0.15 mmol, 84.5 mg, 75%. $[\alpha]_D^{25}$= –31.73 (*c* = 0.9, >98:2 dr, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 6.44 (m, 19H), 5.42 – 5.27 (m, 2H), 4.93 – 4.88 (m, 1H), 3.95 – 3.79 (m, 3H), 3.66 – 3.61 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.5, 185.6, 167.8, 138.7, 134.0, 133.8, 133.0, 132.8, 131.7, 129.8, 129.3, 128.8, 128.7, 128.3, 128.1, 127.8, 76.2, 48.6, 41.2, 40.0, 21.3. UPLC-DAD-QTOF: $C_{33}H_{30}N_3O_4S$ $[M+H]^+$ calcd.: 564.1957, found: 564.1959.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cd)



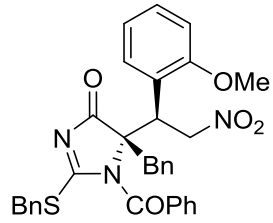
The title compound **33C** was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **36d** (0.2 mmol, 80 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene (0.4 mmol, 73.2 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a 94:6 mixture of diastereomers (orange foam). Yield: 0.18 mmol, 103.8 mg, 89%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.47 – 6.54 (m, 19H), 5.63 – 5.58 (m, 1H), 5.46 – 5.30 (m, 2H), 4.11 (d, *J* = 12.7 Hz, 1H), 3.87 (d, *J* = 13.4 Hz, 2H), 3.62 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.7, 185.7, 167.1, 137.0, 134.0, 133.4, 133.3, 133.0, 132.9, 130.8, 130.0, 129.8, 129.2, 128.7, 128.5, 128.0, 127.9, 127.8, 76.1, 43.6, 41.6, 39.7. UPLC-DAD-QTOF: $C_{32}H_{27}N_3O_4SCl$ $[M+H]^+$ calcd.: 584.1411, found: 584.1422.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Ce)



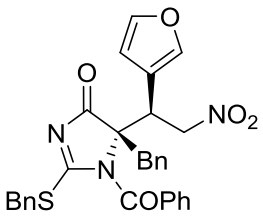
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-1-chloro-3-(2-nitrovinyl)benzene **36e** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a 74:26 mixture of diastereomers (yellow oil). Yield: 0.16 mmol, 93.3 mg, 80%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.53 – 6.88 (m, 17H), 6.62 (s, 2H), 5.38 – 5.29 (m, 2H), 4.98 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.91 – 3.77 (m, 3H), 3.64 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.0, 185.8, 167.9, 136.7, 134.9, 133.6, 133.1, 130.4, 129.8, 129.2, 129.1, 129.0, 128.7, 128.5, 128.1, 128.0, 75.3, 48.4, 40.7, 39.9. UPLC-DAD-QTOF: $C_{32}H_{27}N_3O_4SCl$ $[M+H]^+$ calcd.: 584.1411, found: 584.1418.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(2-methoxyphenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cf)



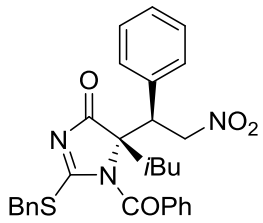
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-1-methoxy-2-(2-nitrovinyl)benzene **36f** (0.4 mmol, 71.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a colourless oil. Yield: 0.17 mmol, 100.7 mg, 87%. $[\alpha]_D^{25}$= –3.90 (*c* = 1.90, >98:2 dr, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.56 – 6.71 (m, 19H), 5.49 – 5.33 (m, 2H), 4.78 (t, *J* = 7.1 Hz, 1H), 4.10 (d, *J* = 12.6 Hz, 0H), 3.94 – 3.73 (m, 2H), 3.64 (s, 3H), 3.58 – 3.47 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.2, 182.8, 167.7, 157.8, 134.2, 133.7, 132.6, 130.2, 130.0, 129.1, 128.6, 128.5, 127.9, 127.7, 121.2, 110.6, 74.8, 54.0, 49.8, 42.9, 39.4. UPLC-DAD-QTOF: $C_{33}H_{30}N_3O_5S$ $[M+H]^+$ calcd.: 580.1906, found: 580.1915.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cg)



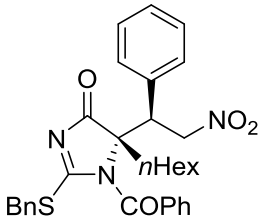
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-3-(2-nitrovinyl)furan **36g** (0.4 mmol, 55.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a 85:15 mixture of diastereomers (orange foam). Yield: 0.15 mmol, 79.8 mg, 74%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.49 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.39 – 7.13 (m, 11H), 7.04 – 6.93 (m, 2H), 6.75 (d, *J* = 7.8 Hz, 2H), 6.34 – 6.24 (m, 1H), 5.21 (m, 2H), 4.98 (dd, *J* = 9.4, 5.6 Hz, 1H), 4.04 (d, *J* = 13.1 Hz, 1H), 3.96 – 3.80 (m, 2H), 3.60 (d, *J* = 12.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.3, 185.7, 167.8, 144.0, 142.0, 134.2, 133.8, 133.2, 132.8, 129.7, 129.3, 128.9, 128.7, 128.5, 128.1, 127.9, 118.9, 108.8, 77.0, 75.8, 40.5, 40.3, 39.7. UPLC-DAD-QTOF: $C_{30}H_{26}N_3O_5S$ $[M+H]^+$ calcd.: 540.1593, found: 540.1594.

(*S*)-1-Benzoyl-2-(benzylthio)-5-isobutyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one(38Da)



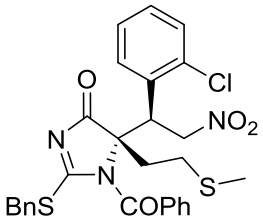
The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-isobutyl-1*H*-imidazol-4(5*H*)-one **33D** (0.2 mmol, 73 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 95:5 to 90:10) to give the title compound as a white foam. Yield: 0.18 mmol, 90.6 mg, 88%. $[\alpha]_D^{25}$= –21.15 (*c* = 0.5, >98:2 dr, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.55 – 6.84 (m, 15H), 5.27 – 5.11 (m, 2H), 4.75 – 4.70 (m, 1H), 4.23 (d, *J* = 13.3 Hz, 1H), 4.00 (d, *J* = 13.3 Hz, 1H), 2.76 – 2.70 (m, 1H), 2.17 – 2.10 (m, 1H), 1.60 – 1.47 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.8, 184.9, 167.4, 134.5, 134.5, 133.2, 132.9, 129.3, 129.1, 128.9, 128.7, 128.6, 128.1, 76.2, 75.9, 49.8, 44.0, 39.7, 25.5, 24.2, 22.8. UPLC-DAD-QTOF: $C_{29}H_{30}N_3O_4S[M+H]^+$ calcd.: 516.1957, found: 516.1964.

(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ea)



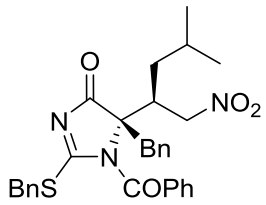
The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-hexyl-1*H*-imidazol-4(5*H*)-one **33E** (0.2 mmol, 78.8 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 50:50) to give the title compound as a yellow foam. Yield: 0.15 mmol, 79.3 g, 73%. $[\alpha]_D^{25}$= –18.67 (*c* = 0.96, >98:2 dr, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.50 – 7.45 (m, 1H), 7.34 – 7.07 (m, 12H), 6.91 – 6.71 (m, 2H), 5.25 – 5.11 (m, 2H), 4.62 (dd, *J* = 10.6, 4.4 Hz, 1H), 4.26 (d, *J* = 13.4 Hz, 1H), 4.03 (d, *J* = 13.4 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.17 – 2.07 (m, 1H), 1.33 – 0.85 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.7, 185.0, 167.2, 135.1, 134.7, 133.2, 132.7, 129.3, 129.3, 129.0, 128.9, 128.7, 128.5, 128.1, 76.5, 48.8, 39.5, 36.2, 31.6, 28.9, 23.8, 22.6, 14.2. UPLC-DAD-QTOF: $C_{31}H_{34}N_3O_4S$ $[M+H]^+$ calcd.: 544.2270, found: 544.2271.

(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-(2-(methylthio)ethyl)-1*H*-imidazol-4(5*H*)-one (38Fd)



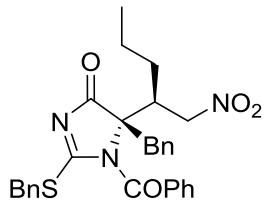
The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-(2-(methylthio)ethyl)-1*H*-imidazol-4(5*H*)-one **33F** (0.2 mmol, 76.8 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as an orange foam. Yield: 0.15 mmol, 82.8 mg, 73%. $[\alpha]_D^{25}$= –9.42 (*c* = 0.85, 99:1 dr, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.57 – 6.91 (m, 14H), 5.35 – 5.16 (m, 3H), 4.28 (d, *J* = 13.4 Hz, 1H), 4.11 (d, *J* = 13.4 Hz, 1H), 3.20 (ddd, *J* = 12.8, 10.7, 5.0 Hz, 1H), 2.48 (ddd, *J* = 12.8, 10.0, 5.4 Hz, 1H), 2.30 (ddd, *J* = 13.0, 10.0, 5.0 Hz, 1H), 2.23 – 1.96 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.2, 185.2, 167.0, 136.2, 134.5, 133.6, 133.2, 132.5, 130.9, 130.0, 129.3, 129.1, 128.8, 128.6, 128.2, 127.9, 127.8, 76.1, 75.8, 43.6, 39.6, 36.5, 28.1, 15.6. UPLC-DAD-QTOF: $C_{28}H_{27}N_3O_4S_2Cl$ $[M+H]^+$ calcd.: 568.1132, found: 568.1144.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-4-methyl-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ch)



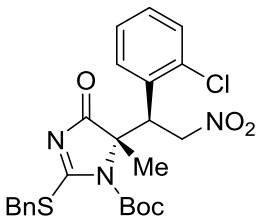
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-4-methyl-1-nitropent-1-ene **36h** (51.6 mg, 0.4 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as an orange oil. Yield: 0.11 mmol, 54.6 mg, 53%. $[\alpha]_D^{25}$= –29.24 (*c* = 0.75, >98:2 dr, 92% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.56 – 7.49 (m, 2H), 7.37 – 7.20 (m, 8H), 7.15 – 7.06 (m, 3H), 7.02 – 6.85 (m, 2H), 5.45 (dd, *J* = 14.4, 5.8 Hz, 1H), 4.42 (dd, *J* = 14.4, 4.8 Hz, 1H), 4.31 (d, *J* = 13.4 Hz, 1H), 3.98 (d, *J* = 13.4 Hz, 1H), 3.68 – 3.49 (m, 2H), 1.63 – 1.52 (m, 1H), 1.22 – 1.12 (m, 1H), 1.01 – 0.96 (m, 1H), 0.91 – 0.89 (m, 1H), 0.85 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.7, 185.4, 167.4, 134.7, 134.2, 133.2, 132.9, 129.7, 129.2, 129.0, 128.9, 128.8, 128.5, 128.1, 127.8, 75.2, 40.7, 39.5, 39.3, 38.3, 29.8, 25.6, 23.9, 21.7. UPLC-DAD-QTOF: $C_{30}H_{32}N_3O_4S$ $[M+H]^+$ calcd.: 530.2114, found: 530.2122.

(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ci)



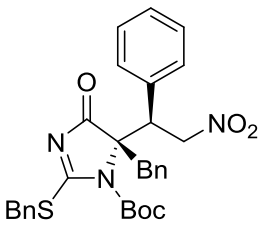
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and (*E*)-1-nitropent-1-ene **36i** (0.4 mmol, 46.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.08 mmol, 41.2 mg, 40%. $[\alpha]_D^{25}$= –6.72 (*c* = 0.72, >98:2 dr, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.62 – 7.41 (m, 2H), 7.35 – 7.19 (m, 8H), 7.14 – 7.08 (m, 3H), 6.94 – 6.89 (m, 2H), 5.34 (dd, *J* = 14.3, 5.1 Hz, 1H), 4.53 (dd, *J* = 14.3, 6.1 Hz, 1H), 4.29 (d, *J* = 13.4 Hz, 1H), 3.99 (d, *J* = 13.4 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.71 – 3.48 (m, 2H), 1.45 – 1.26 (m, 2H), 1.23 – 1.12 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.7, 185.3, 167.5, 134.7, 134.1, 133.3, 133.0, 130.1, 129.8, 129.4, 129.3, 129.0, 129.0, 128.8, 128.6, 128.1, 128.0, 127.8, 75.1, 42.5, 39.7, 39.5, 31.1, 20.0, 14.2. UPLC-DAD-QTOF: $C_{29}H_{30}N_3O_4S$ $[M+H]^+$ calcd.: 516.1957, found: 516.1968.

(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (39Ad)



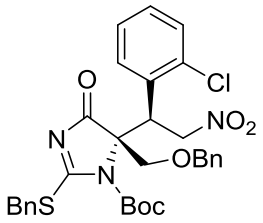
The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-methyl-1*H*-imidazol-4(5*H*)-one **34A** (0.2 mmol, 64 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 91:9 mixture of diastereomers (white foam). Yield: 0.17 mmol, 83.5 mg, 83%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.48 – 7.02 (m, 9H), 5.26 – 5.14 (m, 2H), 5.10 – 4.96 (m, 1H), 4.31 – 4.12 (m, 2H), 1.85 (s, 3H), 1.65 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.9, 185.7, 135.1, 132.3, 130.2, 129.8, 129.4, 128.8, 128.3, 127.9, 127.5, 87.1, 75.1, 70.7, 43.4, 38.5 (minor. dr.), 37.9, 28.2, 25.5 (minor. dr.), 22.0, 20.7 (minor. dr.). UPLC-DAD-QTOF: $C_{24}H_{27}N_3O_5SCl$ $[M+H]^+$ calcd.: 504.1360, found: 504.1364.

(*S*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (39Ca)



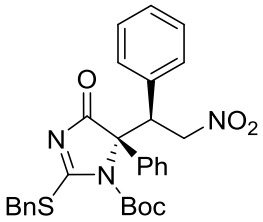
The title compound was prepared from 5-benzyl-1-(*tert*-butyloxycarbonyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and (E)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white foam. Yield: 0.14 mmol, 76.3 mg, 70%. $[\alpha]_D^{25}$= –38.53 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.36 – 6.96 (m, 15H), 5.41 – 5.22 (m, 2H), 4.82 – 4.63 (m, 1H), 4.01 (s, 2H), 3.71 – 3.56 (m, 1H), 3.48 (d, *J* = 12.8 Hz, 1H), 1.81 – 1.50 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.16, 135.25, 134.36, 133.28, 129.47, 129.19, 128.93, 128.88, 128.67, 128.02, 127.81, 127.72, 87.11, 75.67, 48.30, 40.17, 37.67, 28.27. UPLC-DAD-QTOF: $C_{30}H_{32}N_3O_5S$ $[M+H]^+$ calcd.: 546.2063, found: 546.2074.

(*R*)-5-((Benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)- 1*H*-imidazol-4(5*H*)-one (39Gd)



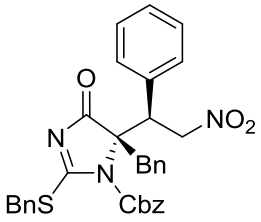
The title compound was prepared from 5-((benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34G** (0.2 mmol, 85.2 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 94:6 mixture of diastereomers (white foam). Yield: 0.17 mmol, 102.3 mg, 84%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.34 – 7.12 (m, 14H), 5.17 – 4.93 (m, 3H), 4.58 – 4.47 (m, 2H), 4.36 – 4.14 (m, 3H), 3.96 (d, *J* = 8.3 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 185.9, 148.2, 136.9, 135.3, 135.1, 131.9, 130.2, 129.9, 129.6, 129.3, 128.9, 128.7, 128.6, 128.5, 128.1, 127.8, 127.6, 86.8, 74.4, 73.8, 73.7, 70.2, 40.9, 37.9, 28.1. UPLC-DAD-QTOF: $C_{31}H_{33}N_3O_6SCl$ $[M+H]^+$ calcd.: 610.1779, found: 610.1798.

(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-2-nitro-1-phenylethyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (39Ha)



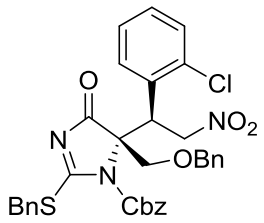
The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one **34H** (0.2 mmol, 76.4 mg) and (*E*)-(2-nitrovinyl)benzene (0.4 mmol, 60 mg) **36a** according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 92:8 mixture of diastereomers (white foam). Yield: 0.14 mmol, 73.2 mg, 69%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.53 – 7.21 (m, 15H), 5.28 – 5.17 (m, 2H), 4.39 (d, *J* = 13.4 Hz, 1H), 4.27 (d, *J* = 13.4 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.7, 186.2, 147.7, 135.1, 133.6, 129.7, 129.5, 129.3, 129.2, 129.0, 128.8, 128.4, 128.0, 127.8, 86.8, 77.6, 77.2, 76.7, 76.6, 74.9, 45.6, 38.1, 27.9. UPLC-DAD-QTOF: $C_{29}H_{30}N_3O_5S$ $[M+H]^+$ calcd.: 531.1828, found: 531.1829.

(*S*)-5-Benzyl-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (40Ca)



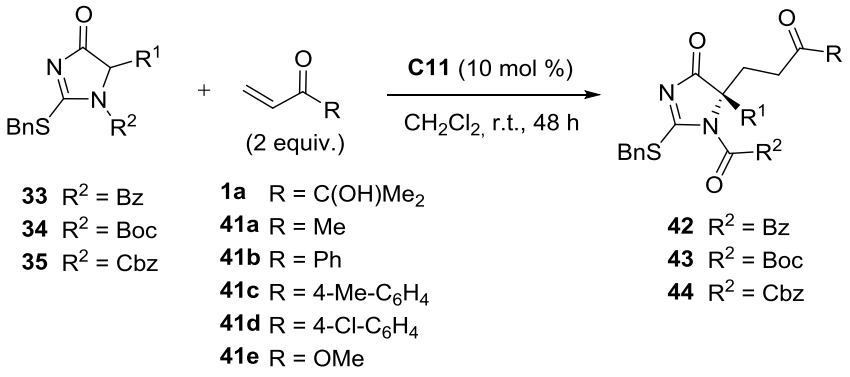
The title compound was prepared from 5-benzyl-1-(benzyloxycarbonyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **35C** (0.2 mmol, 92.0 mg) and (*E*)-(2-nitrovinyl)benzene (0.4 mmol, 60 mg) **36a** according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white foam. Yield: 0.18 mmol, 104.2 mg, 90%. $[\alpha]_D^{25}$= –31.04 (*c* = 0.23, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.66 – 6.79 (m, 20H), 5.51 – 5.36 (m, 2H), 5.27 – 5.24 (m, 2H), 4.03 – 3.93 (m, 2H), 3.45 – 3.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.9, 135.0, 134.0, 132.9, 129.8, 129.5, 129.3, 129.2, 129.0, 128.8, 128.7, 127.8, 127.2, 88.4, 75.5, 70.0, 48.3, 40.2, 37.6, 31.1, 29.8. UPLC-DAD-QTOF: $C_{33}H_{30}N_3O_5S$ $[M+H]^+$ calcd.: 580.1906, found: 580.1909.

(*R*)-5-((Benzyloxy)methyl)-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (40Gd)



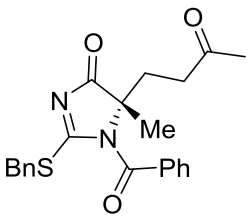
The title compound was prepared from 1-(benzyloxycarbonyl)-5-((benzyloxy)methyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **35G** (0.2 mmol, 92 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 95:5 mixture of diastereomers (white foam). Yield: 0.18 mmol, 117.1 mg, 91%. ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.48 – 6.97 (m, 19H), 5.34 (d, *J* = 11.8 Hz, 1H), 5.19 (d, *J* = 11.8 Hz, 1H), 5.13 – 4.88 (m, 3H), 4.41 – 4.09 (m, 5H), 3.89 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 185.4, 149.6, 137.0, 135.1, 135.0, 133.8, 131.5, 130.4, 130.0, 129.6, 129.4, 129.3, 129.1, 129.0, 128.8, 128.6, 128.3, 128.1, 127.9, 127.6, 127.5, 74.2, 73.8, 73.4, 70.0, 69.9, 40.8, 37.8. UPLC-DAD-QTOF: $C_{34}H_{31}N_3O_6SCl$ $[M+H]^+$ calcd.: 644.1622, found: 644.1617.

5.4.4. Reaction of N^1-acyl 2-benzylthioimidazolones 33-35 with vinyl ketones 41 and 1a.



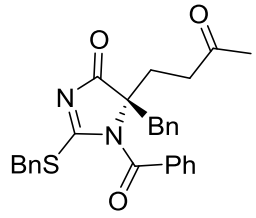
To a solution of the corresponding imidazolone **33-35** (1 equiv., 0.2 mmol) in dichlorometane (0.6 mL) the corresponding vinyl ketone (2.0 equiv., 0.4 mmol) and the catalyst were added at room temperature. The resulting mixture was stirred until consumption of the nucleophile (monitored by ^{1}H-NMR). Afterwards, the reaction was purified by flash column chromatography on silica gel to afford the expected adducts.

(*S*)-1-Benzoyl-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Aa)



The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one **33A** (0.2 mmol, 64.8 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.10 mmol, 37.8 mg, 48%. $[\alpha]_D^{25}$= –13.9 (*c* = 0.51, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 – 7.24 (m, 10H), 4.53 – 4.27 (m, 2H), 2.52 – 2.40 (m, 1H), 2.31 – 2.13 (m, 3H), 2.08 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.3, 187.9, 184.1, 168.0, 135.1, 133.6, 133.1, 129.5, 128.9, 128.7, 128.1, 71.1, 39.1, 37.9, 31.1, 30.0, 23.1. UPLC-DAD-QTOF: $C_{22}H_{23}N_2O_3S$ $[M+H]^+$ calcd.: 395.1429, found: 395.1429.

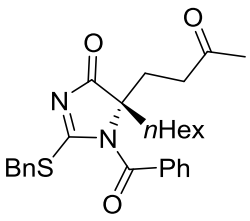
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Ca)



The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc

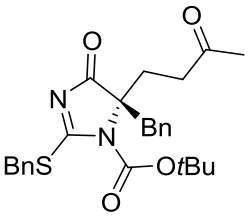
90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.13 mmol, 63.0 mg, 67%. $[\alpha]_D^{25}$= –6.9 (*c* = 1.02, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 – 6.97 (m, 15H), 4.28 (d, *J* = 13.5 Hz, 1H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.60 – 3.42 (m, 2H), 2.89 – 2.75 (m, 1H), 2.49 – 2.37 (m, 1H), 2.32 – 2.21 (m, 2H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.2, 187.4, 184.5, 167.6, 135.0, 134.7, 133.1, 129.7, 129.3, 129.1, 128.8, 128.7, 128.5, 128.0, 127.6, 76.6, 41.3, 39.2, 37.7, 31.1, 30.0. UPLC-DAD-QTOF: $C_{28}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 471.1742, found: 471.1753.

(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Ea)



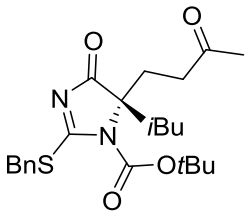
The title compound was prepared from 1-benzoyl-2-(benzylthio)-5-hexyl-1*H*-imidazol-4(5*H*)-one **33E** (0.2 mmol, 78.8 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.10 mmol, 48.2 mg, 52%. $[\alpha]_D^{25}$= –18.5 (*c* = 0.65, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 – 7.17 (m, 10H), 4.60 – 4.22 (m, 1H), 2.52 – 2.43 (m, 1H), 2.34 – 2.12 (m, 3H), 2.09 (s, 3H), 1.96 – 1.86 (m, 1H), 1.40 – 1.01 (m, 9H), 0.92 – 0.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.4, 187.6, 184.7, 167.8, 135.2, 133.5, 133.1, 129.4, 128.9, 128.8, 128.6, 128.1, 75.4, 39.1, 37.6, 35.9, 31.6, 30.9, 30.0, 29.0, 23.8, 22.6, 14.1. UPLC-DAD-QTOF: $C_{27}H_{33}N_2O_3S$ $[M+H]^+$ calcd.: 465.2212, found: 465.2220.

(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ca)



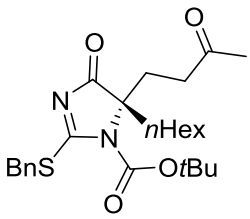
The title compound was prepared from 5-benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90: 10 to 80:20) to give the title compound as a white foam. Yield: 0.12 mmol, 57.8 mg, 62%. $[\alpha]_D^{25}$= –20.76 (*c* = 1.145, 89% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.14 (m, 8H), 7.13 – 7.02 (m, 2H), 4.23 (q, *J* = 13.4 Hz, 2H), 3.40 (d, *J* = 13.5 Hz, 1H), 3.21 (d, *J* = 13.4 Hz, 1H), 2.65 (ddd, *J* = 13.5, 9.7, 4.7 Hz, 1H), 2.50 – 2.14 (m, 3H), 2.13 (s, 3H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.4, 187.1, 185.6, 148.6, 135.3, 133.9, 129.3, 128.7, 128.6, 127.8, 127.6, 86.4, 74.4, 42.1, 37.7, 30.2, 29.6, 28.3. UPLC-DAD-QTOF: $C_{26}H_{31}N_2O_4S$ $[M+H]^+$ calcd.: 467.2005, found: 467.2006.

(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-isobutyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Da)



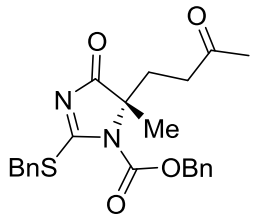
The title compound **x** was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-isobutyl-1*H*-imidazol-4(5*H*)-one **34D** (0.2 mmol, 72.4 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.16 mmol, 70.0 mg, 81%. $[\alpha]_D^{25}$= +4.3 (*c* = 0.465, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.21 (m, 5H), 4.50 (s, 2H), 2.56 – 2.22 (m, 2H), 2.20 – 1.97 (m, 6H), 1.87 (dd, *J* = 14.1, 7.5 Hz, 1H), 1.59 (s, 9H), 1.51 – 1.35 (m, 1H), 0.85 (dd, *J* = 18.0, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.5, 188.1, 185.3, 148.9, 135.4, 129.6, 128.9, 128.0, 86.0, 72.5, 45.0, 38.0, 37.0, 31.1, 30.2, 28.1, 24.9, 24.00, 23.2. UPLC-DAD-QTOF: $C_{23}H_{33}N_2O_4S$ $[M+H]^+$ calcd.: 433.2161, found: 433.2159.

(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ea)



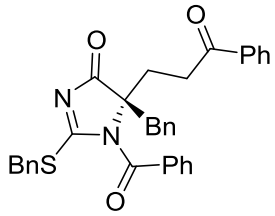
The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-1*H*-imidazol-4(5*H*)-one **34E** (0.2 mmol, 78.0 mg) and methyl vinyl ketone **1a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.12 mmol, 57.0 mg, 62%. $[\alpha]_D^{25}$= +1.4 (*c* = 0.25, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.25 (m, 4H), 4.46 (s, 2H), 2.47 – 2.21 (m, 2H), 2.19 – 2.07 (m, 3H), 2.06 (d, *J* = 1.2 Hz, 3H), 1.87 (ddd, *J* = 13.5, 10.9, 5.5 Hz, 1H), 1.54 (s, 9H), 1.28 – 1.18 (m, 6H), 0.98 (ddd, *J* = 16.5, 11.1, 6.8 Hz, 2H), 0.85 (td, *J* = 6.9, 6.0, 2.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.5, 187.9, 185.5, 148.9, 135.2, 129.59, 128.9, 128.0, 85.9, 73.3, 38.1, 37.4, 36.36, 31.6, 30.2, 30.1, 29.0, 28.1, 23.3, 22.6, 14.1. UPLC-DAD-QTOF: $C_{25}H_{37}N_2O_4S$ $[M+H]^+$ calcd.: 461.2474, found: 461.2474.

(*S*)-1-(Benzyloxycarbonyl)-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (44Aa)



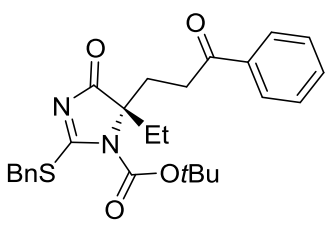
The title compound was prepared from 1-(benzyloxycarbonyl)-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one **35A** (0.2 mmol, 70.8 mg) and methyl vinyl ketone **41a** (0.4 mmol, 28.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.12 mmol, 51.7 mg, 61%. $[\alpha]_D^{25}$= +18.9 (*c* = 1.2, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.28 (m, 10H), 5.31 (s, 2H), 4.48 (s, 2H), 2.54 – 2.38 (m, 1H), 2.30 – 2.05 (m, 3H), 2.02 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.3, 187.7, 184.8, 150.1, 135.0, 134.0, 129.6, 129.3, 129.1, 129.0, 129.0, 128.1, 69.8, 69.4, 38.2, 37.6, 30.0, 23.0. UPLC-DAD-QTOF: $C_{23}H_{25}N_2O_4S$ $[M+H]^+$ calcd.: 425.1535, found: 425.1537.

(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (42Cb)



The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80 mg) and phenyl vinyl ketone **41b** (0.4 mmol, 52.8 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white foam. Yield: 0.16 mmol, 86.1 mg, 81%. $[\alpha]_D^{25}$= –12.8 (*c* = 0.5, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 – 6.32 (m, 20H), 4.29 (d, *J* = 13.3 Hz, 1H), 4.03 (d, *J* = 13.4 Hz, 1H), 3.79 – 3.35 (m, 2H), 3.18 – 2.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.8, 187.5, 184.6, 167.6, 136.5, 135.0, 134.8, 133.3, 133.1, 129.7, 129.2, 129.1, 128.8, 128.7, 128.5, 128.2, 128.0, 127.5, 76.9, 41.5, 39.2, 32.9, 31.7. UPLC-DAD-QTOF: $C_{33}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 533.1899, found: 533.1900.

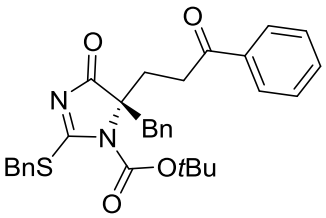
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Bb)



The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one **34B** (0.2 mmol, 66.8 mg) and phenyl vinyl ketone **41b** (0.4 mmol, 52.8 mg) according to the general procedure. The crude material was purified by flash column

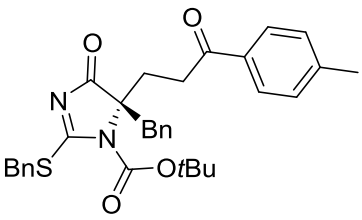
chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.14 mmol, 65.2 mg, 70%. $[\alpha]_D^{25}$= –6.71 (*c* = 0.25, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 – 7.82 (m, 2H), 7.60 – 7.52 (m, 1H), 7.47 – 7.25 (m, 7H), 4.42 (s, 2H), 2.90 – 2.79 (m, 1H), 2.68 – 2.58 (m, 2H), 2.29 – 2.11 (m, 2H), 1.99 (dq, *J* = 14.4, 7.4 Hz, 1H), 1.55 (s, 9H), 0.73 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.2, 187.8, 185.8, 148.8, 136.5, 135.2, 133.4, 129.6, 128.9, 128.8, 128.2, 128.0, 86.0, 74.2, 38.1, 32.4, 30.7, 29.6, 28.1, 7.8. UPLC-DAD-QTOF: $C_{26}H_{30}N_2O_4S$ $[M+H]^+$ calcd.: 467.2005, found: 467.2004.

(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Cb)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and 1-phenylprop-2-en-1-one **41b** (0.4 mmol, 52.8 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white foam. Yield: 0.17 mmol, 87.6 mg, 83%. $[\alpha]_D^{25}$= –8.3 (*c* = 0.99, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 – 7.88 (m, 2H), 7.64 – 7.56 (m, 1H), 7.50 – 7.44 (m, 2H), 7.31 – 7.20 (m, 5H), 7.20 – 7.14 (m, 2H), 7.13 – 7.06 (m, 2H), 4.30 – 4.12 (m, 2H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 13.4 Hz, 1H), 3.03 – 2.79 (m, 2H), 2.70 – 2.56 (m, 1H), 2.51 – 2.42 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.1, 187.2, 185.7, 148.6, 136.4, 135.3, 133.9, 133.5, 129.4, 129.3, 128.8, 128.7, 128.6, 128.3, 127.8, 127.6, 42.2, 37.7, 32.6, 30.4, 28.3. UPLC-DAD-QTOF: $C_{31}H_{33}N_2O_4S$ $[M+H]^+$ calcd.: 529.2161, found: 529.2175.

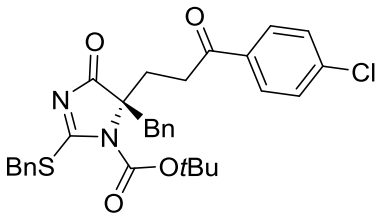
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(*p*-tolyl)propyl)-1*H*-imidazol-4(5*H*)-one (43Cc)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and 1-(*p*-tolyl)prop-2-en-1-one **41c** (0.4 mmol, 58.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.17 mmol, 91.1 mg, 84%. $[\alpha]_D^{25}$= –1.4 (*c* = 1.61, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.2 Hz, 2H), 7.46 – 6.96

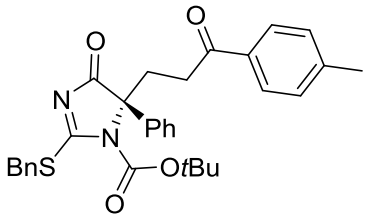
(m, 11H), 4.48 – 4.04 (m, 2H), 3.45 (d, *J* = 13.5 Hz, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 3.04 – 2.78 (m, 2H), 2.70 – 2.49 (m, 2H), 2.44 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.7, 187.2, 185.7, 148.6, 144.3, 135.3, 134.0, 129.4, 129.4, 129.3, 128.7, 128.6, 128.4, 127.7, 127.5, 86.4, 74.7, 42.2, 37.7, 32.4, 30.5, 28.2, 21.8. UPLC-DAD-QTOF: $C_{31}H_{33}N_2O_4S$ $[M+H]^+$ calcd.: 529.2161, found: 529.2168.

(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-(4-chlorophenyl)-3-oxopropyl)-1*H*-imidazol-4(5*H*)-one (43Cd)



The title compound was prepared from 5-benzyl 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and 1-(4-chlorophenyl)propenone **41d** (0.4 mmol, 66.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.17 mmol, 95.5 mg, 85%. $[\alpha]_D^{25}$= +5.7 (*c* = 1.9, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.34 – 6.95 (m, 10H), 4.20 (q, *J* = 13.4 Hz, 2H), 3.45 (d, *J* = 13.4 Hz, 1H), 3.26 (d, *J* = 13.4 Hz, 1H), 3.05 – 2.76 (m, 2H), 2.75 – 2.36 (m, 2H), 1.68 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 196.9, 187.1, 185.7, 148.5, 140.0, 135.3, 134.7, 133.8, 129.7, 129.4, 129.3, 129.1, 128.7, 128.6, 127.8, 127.6, 86.5, 74.6, 42.2, 37.7, 32.6, 30.3, 28.3. UPLC-DAD-QTOF: $C_{31}H_{32}N_2O_4SCl$ $[M+H]^+$ calcd.: 563.1771, found: 563.1763.

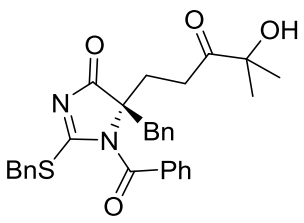
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(p-tolyl)propyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (43Hc)



The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one **34H** (0.2 mmol, 76.4 mg) and 1-(4-methylphenyl)prop-2-en-1-one **41d** (0.4 mmol, 58.4 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a white foam. Yield: 0.17 mmol, 88.7 mg, 84%. $[\alpha]_D^{25}$= –32.5 (*c* = 1.00, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.84 – 7.78 (m, 2H), 7.48 – 7.24 (m, 12H), 4.60 – 4.48 (m, 2H), 3.12 – 2.89 (m, 3H), 2.79 – 2.69 (m, 1H), 2.44 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.6, 186.2, 185.9, 148.6, 144.4, 137.2, 135.2, 134.0, 129.6, 129.5, 129.0, 128.9, 128.5, 128.4, 128.0, 127.7, 125.2, 85.8, 74.0,

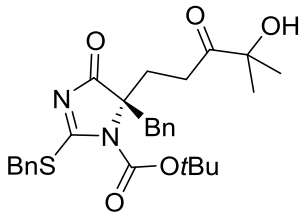
38.2, 32.2, 29.0, 27.6, 21.8. UPLC-DAD-QTOF: $C_{31}H_{33}N_2O_4S$ $[M+H]^+$ calcd.: 529.2161, found: 401.2156.

(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (45C)



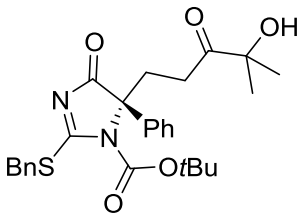
The title compound was prepared from 1-benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one **33C** (0.2 mmol, 80.0 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.4 mmol, 45.6 mg) to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.16 mmol, 82.2 mg, 80%. $[\alpha]_D^{25}$= –1.9 (*c* = 1.33, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 6.71 (m, 15H), 4.25 (d, *J* = 13.4 Hz, 1H), 4.00 (d, *J* = 13.4 Hz, 1H), 3.58 (d, *J* = 13.7 Hz, 1H), 3.44 (d, *J* = 13.0 Hz, 1H), 2.90 – 2.72 (m, 1H), 2.57 – 2.37 (m, 3H), 1.29 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.6, 187.3, 184.6, 167.7, 134.9, 134.6, 133.2, 133.0, 129.7, 129.3, 129.1, 128.9, 128.8, 128.6, 128.1, 127.6, 76.6, 76.5, 41.5, 39.2, 31.0, 29.9, 26.8, 26.7. UPLC-DAD-QTOF: $C_{30}H_{31}N_2O_4S$ $[M+H]^+$ calcd.: 515.2005, found: 515.2013.

(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (46C)



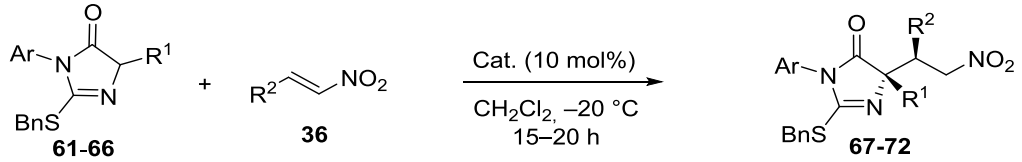
The title compound was prepared from 5-benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one **34C** (0.2 mmol, 79.2 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.4 mmol, 45.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.16 mmol, 82.6 mg, 81%. $[\alpha]_D^{25}$= –12.5 (*c* = 0.25, 90% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 – 7.13 (m, 8H), 7.08 – 7.03 (m, 2H), 4.27 – 4.12 (m, 2H), 3.51 (s, 1H), 3.39 (d, *J* = 13.4 Hz, 1H), 3.20 (d, *J* = 13.4 Hz, 2H), 2.76 – 2.44 (m, 2H), 2.38 – 2.21 (m, 2H), 1.66 (s, 9H), 1.34 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 186.9, 185.7, 148.5, 135.2, 133.7, 129.3, 129.3, 128.7, 128.6, 127.8, 127.6, 86.4, 76.5, 74.4, 42.2, 37.7, 29.97, 29.6, 28.2, 26.6, 26.5. UPLC-DAD-QTOF: $C_{28}H_{35}N_2O_5S$ $[M+H]^+$ calcd.: 511.2267, found: 511.2267.

(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (46H)



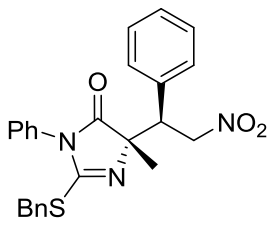
The title compound was prepared from 2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one **34H** (0.2 mmol, 76.4 mg) and 4-hydroxy-4-methylpent-1-en-3-one **1a** (0.4 mmol, 45.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.16 mmol, 81.3 mg, 82%. $[\alpha]_D^{25}$= –44.7 (*c* = 4.2, 91% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 – 7.00 (m, 10H), 4.90 – 4.33 (m, 2H), 3.49 (s, 1H), 2.97 – 2.75 (m, 2H), 2.62 – 2.51 (m, 1H), 2.42 – 2.31 (m, 1H), 1.33 (d, *J* = 9.3 Hz, 6H), 1.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.7, 186.2, 185.5, 148.5, 137.0, 135.1, 129.5, 129.0, 128.9, 128.6, 128.1, 125.0, 85.8, 76.5, 73.7, 38.1, 29.7, 28.0, 27.6, 26.6, 26.5. UPLC-DAD-QTOF: $C_{27}H_{33}N_2O_5S$ $[M+H]^+$ calcd.: 497.2110, found: 497.2106.

5.4.5. Reaction of N^3-aryl 2-benzylthioimidazolones 61-66 and nitroolefins 36.



To a solution of the corresponding imidazolone **61-66** (1 equiv., 0.2 mmol) and nitroalkene **36** (2.0 equiv., 0.4 mmol) in dichlorometane (0.6 mL) the catalyst was added at –20 °C. The resulting mixture was stirred until consumption of the imidazolone (monitored by ^{1}H-NMR). Afterwards, the reaction was directly submitted to flash column chromatography on silica gel to afford the corresponding adducts **67**–**72** essentially pure.

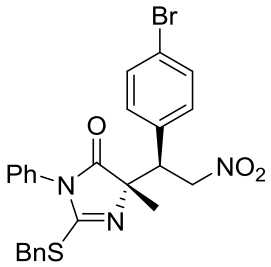
(*S*)-2-(Benzylthio)-4-methyl-4-((S)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aa)



The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 97:3 mixture of diastereomers (colourless oil). Yield: 0.20 mmol, 88.1 mg, 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 –

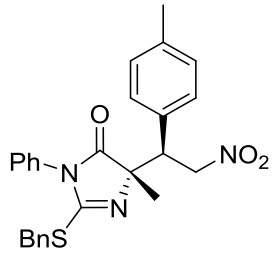
7.02 (m, 15H), 4.89 (dd, *J* = 13.1, 10.1 Hz, 1H), 4.73 (dd, *J* = 13.1, 5.3 Hz, 1H), 4.43 – 4.25 (m, 2H), 4.05 (dd, *J* = 10.1, 5.3 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 161.0, 135.9, 135.2, 131.8, 129.6, 129.5, 129.2, 129.2, 128.8, 128.5, 128.4, 127.9, 127.3, 75.6, 73.1, 50.1, 34.9, 22.7. UPLC-DAD-QTOF: $C_{25}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 446.1538, found: 446.1545.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ab)



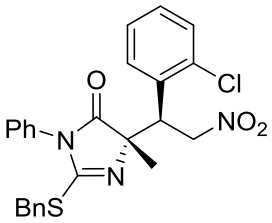
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-bromo-4-(2-nitrovinyl)benzene **36b** (0.4 mmol, 91.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.19 mmol, 99.4 mg, 95%. $[\alpha]_D^{25}$= –133.94 (*c* = 0.65, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 – 7.03 (m, 14H), 4.78 – 4.56 (m, 2H), 4.32 (q, *J* = 13.5 Hz, 2H), 3.95 (dd, *J* = 10.3, 5.1 Hz, 1H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 161.3, 135.9, 134.3, 131.7, 131.0, 129.7, 129.6, 129.0, 128.8, 128.0, 127.2, 122.5, 75.5, 72.9, 49.5, 34.8, 22.8. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SBr$ $[M+H]^+$ calcd.: 524.0644, found: 524.0640.

(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ac)



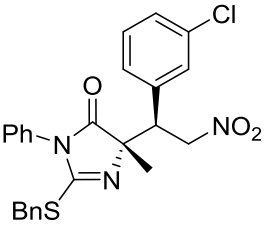
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene **36c** (0.4 mmol, 65.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.17 mmol, 79.9 mg, 87%. $[\alpha]_D^{25}$= –45.14 (*c* = 1.2, >98:2 dr, 97% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 – 7.02 (m, 14H), 4.80 (dd, *J* = 13.0, 10.1 Hz, 1H), 4.65 (dd, *J* = 13.0, 5.2 Hz, 1H), 4.39 – 4.27 (m, 2H), 3.97 (dd, *J* = 10.1, 5.2 Hz, 1H), 2.35 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 160.9, 138.0, 136.0, 132.1, 131.8, 129.6, 129.5, 129.2, 129.1, 129.1, 128.8, 127.9, 127.3, 75.8, 73.2, 49.8, 34.9, 22.8, 21.3. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 460.1695, found: 460.1707.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ad)



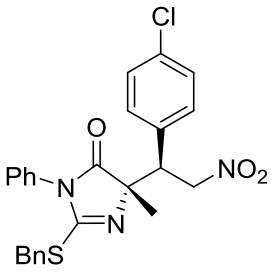
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.18 mmol, 86.2 mg, 90%. $[\alpha]_D^{25}$= –32.86 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 – 6.90 (m, 14H), 4.97 – 4.63 (m, 3H), 4.37 (s, 2H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.5, 161.3, 136.3, 135.8, 133.6, 131.8, 130.1, 129.6, 129.5, 129.4, 129.1, 128.8, 128.6, 127.9, 127.2, 127.0, 75.4, 73.3, 44.8, 34.9, 22.4. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SCl$ $[M+H]^+$ calcd.: 480.1149, found: 480.1152.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ae)



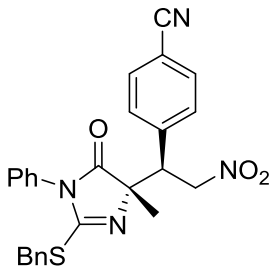
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-chloro-3-(2-nitrovinyl)benzene **36e** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.17 mmol, 82.4 mg, 86%. $[\alpha]_D^{25}$= –25.74 (*c* = 0.90, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.17 (m, 12H), 7.10 – 7.05 (m, 2H), 4.72 (ddd, *J* = 13.4, 10.1, 0.9 Hz, 1H), 4.60 (ddd, *J* = 13.3, 5.2, 1.0 Hz, 1H), 4.40 – 4.27 (m, 2H), 3.98 (dd, *J* = 10.1, 5.1 Hz, 1H), 1.40 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.5, 161.4, 137.4, 135.8, 134.4, 131.7, 129.8, 129.7, 129.6, 129.4, 129.1, 128.9, 128.6, 128.0, 127.5, 127.2, 75.3, 72.8, 49.7, 35.0, 22.8. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SCl$ $[M+H]^+$ calcd.: 480.1149, found: 480.1154.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aj)



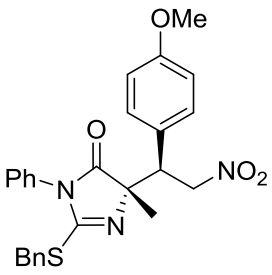
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-chloro-4-(2-nitrovinyl)benzene **36j** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.19 mmol, 90.1 mg, 94%. $[\alpha]_D^{25}$= –11.35 (*c* = 0.85, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 – 7.23 (m, 12H), 7.14 – 7.02 (m, 2H), 4.88 – 4.59 (m, 2H), 4.51 – 4.25 (m, 2H), 4.00 (dd, *J* = 10.3, 5.1 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 161.3, 135.9, 134.3, 133.8, 130.6, 129.7, 129.6, 129.0, 128.8, 128.7, 128.0, 127.2, 75.6, 72.9, 49.4, 34.8, 22.8. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SCl$ $[M+H]^+$ calcd.: 480.1149, found: 480.1149.

4-((*S*)-1-((*S*)-2-(Benzylthio)-4-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)-2-nitroethyl)benzonitrile (67Ak)



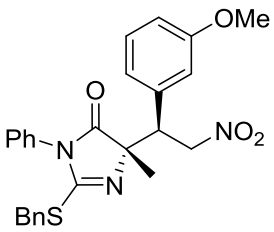
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-4-(2-nitrovinyl)benzonitrile **36k** (0.4 mmol, 69.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 95:5 mixture of diastereomers (orange oil). Yield: 0.18 mmol, 82.7 mg, 88%. $[\alpha]_D^{25}$= –27.32 (*c* = 0.3, 99:1 dr, 96% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 – 6.75 (m, 14H), 4.87 – 4.56 (m, 2H), 4.48 – 4.20 (m, 2H), 4.03 (dd, *J* = 10.5, 4.9 Hz, 1H), 1.37 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.2, 161.7, 140.8, 135.9, 132.2, 131.5, 130.2, 129.8, 129.0, 128.9, 128.1, 127.1, 118.5, 112.4, 75.1, 72.7, 49.8, 34.8, 22.8. UPLC-DAD-QTOF: $C_{26}H_{23}N_4O_3S$ $[M+H]^+$ calcd.: 471.1491, found: 471.1491.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Al)



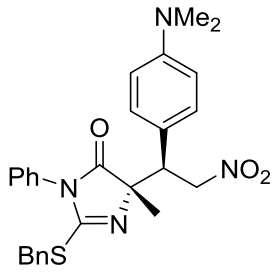
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **36l** (0.4 mmol, 71.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 95:5 mixture of diastereomers (colourless oil). Yield: 0.17 mmol, 80.8 mg, 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.25 (m, 10H), 7.09 – 7.07 (m, 2H), 6.87 – 6.84 (m, 2H), 4.81 (dd, *J* = 12.9, 10.3 Hz, 0H), 4.66 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.41 – 4.34 (m, 2H), 3.97 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.83 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 160.9, 159.5, 136.0, 131.8, 131.0, 130.4, 130.0, 129.6, 129.5, 129.4, 129.2, 128.8, 128.1, 127.9, 127.9, 127.6, 127.4, 127.3, 127.1, 75.9, 73.3, 55.4, 49.4, 34.9, 22.7. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_4S$ $[M+H]^+$ calcd.: 476.1644, found: 476.1645.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Am)



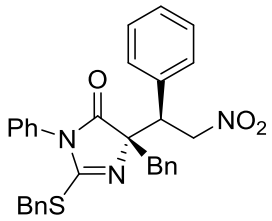
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (E)-1-methoxy-3-(2-nitrovinyl)benzene **36m** (0.4 mmol, 71.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a orange oil. Yield: 0.19 mmol, 89.3 mg, 94%. $[\alpha]_D^{25}$= –20.02 (*c* = 1.00, >98:2 dr, 98% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 – 6.84 (m, 14H), 4.84 (dd, *J* = 13.1, 9.9 Hz, 1H) 4.69 (dd, *J* = 13.1, 5.3 Hz, 1H), 4.36 (s, 2H) 4.02 (dd, *J* = 9.9, 5.3 Hz, 1H), 3.81 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 161.1, 159.6, 136.9, 135.8, 131.8, 129.6, 129.5, 129.2, 128.8, 128.0, 127.3, 121.5, 115.3, 75.8, 73.1, 55.3, 50.1, 35.0, 22.8. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_4S$ $[M+H]^+$ calcd.: 476.1644, found: 476.1649.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-(dimethylamino)phenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67An)



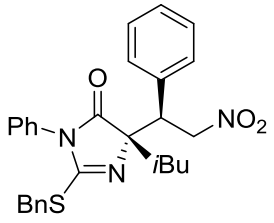
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61A** (0.2 mmol, 59.2 mg) and (*E*)-*N*,*N*-dimethyl-4-(2-nitrovinyl)aniline **36n** (0.4 mmol, 76.8 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.18 mmol, 89.8 mg, 92%. $[\alpha]_D^{25}$= –38.60 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 – 6.87 (m, 14H), 4.87 (dd, *J* = 13.1, 10.3 Hz, 1H), 4.72 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.41 (dd, *J* = 10.3, 5.0 Hz, 1H), 4.31 (d, *J* = 3.0 Hz, 2H), 2.49 (s, 3H), 2.35 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.7, 138.3, 137.5, 135.9, 131.9, 131.6, 131.2, 129.6, 129.4, 129.1, 128.8, 127.9, 127.3, 126.9, 126.5, 76.1, 73.7, 44.4, 34.8, 22.8, 21.2, 20.3. UPLC-DAD-QTOF: $C_{27}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 474.1854, found: 474.1849.

(*S*)-4-Benzyl-2-(benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ca)



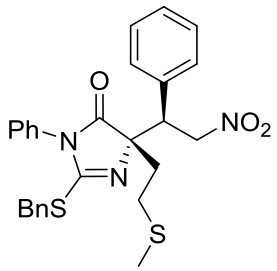
The title compound was prepared from 4-benzyl-2-(benzylthio)-1-phenyl-1*H*-imidazol-5(4*H*)-one **61C** (0.2 mmol, 74.4 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 91:9 mixture of diastereomers (colourless oil). Yield: 0.18 mmol, 93.8 mg, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 – 7.07 (m, 16H), 7.10 – 6.91 (m, 2H), 6.61 – 6.35 (m, 2H), 4.90 – 4.52 (m, 2H), 4.36 (d, *J* = 1.3 Hz, 2H), 4.19 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 2.83 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 161.6, 136.3, 135.6, 134.2, 131.5, 130.6, 130.5, 129.6, 129.5, 129.4, 129.2, 128.8, 128.7, 128.5, 128.0, 127.9, 127.3, 127.2, 76.5, 49.5, 42.5, 34.8. UPLC-DAD-QTOF: $C_{31}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 522.1851, found: 522.1848.

(*S*)-2-(Benzylthio)-4-isobutyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Da)



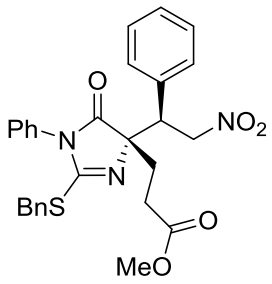
The title compound was prepared from 2-(benzylthio)-4-isobutyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **61D** (0.2 mmol, 67.2 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.18 mmol, 87.7 mg, 90%. $[\alpha]_D^{25}$= –16.85 (*c* = 0.25, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 – 7.21 (m, 14H), 6.98 – 6.86 (m, 1H), 5.06 (dd, *J* = 13.2, 10.9 Hz, 1H), 4.83 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.32 (s, 2H), 4.04 (dd, *J* = 10.9, 4.7 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.75 – 1.60 (m, 1H), 0.92 (dd, *J* = 12.2, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.5, 136.0, 134.8, 131.8, 129.6, 129.4, 129.4, 129.3, 129.2, 128.8, 128.7, 128.3, 127.9, 127.4, 127.1, 76.3, 75.0, 50.9, 44.6, 34.9, 24.9, 24.5, 23.4. UPLC-DAD-QTOF: $C_{28}H_{30}N_3O_3S$ $[M+H]^+$ calcd.: 488.2008, found: 488.2011.

(*S*)-2-(Benzylthio)-4-(2-(methylthio)ethyl)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Fa)



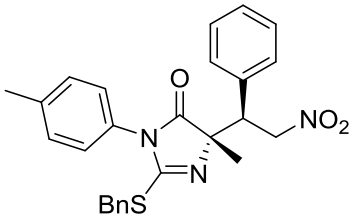
The title compound was prepared from 2-(benzylthio)-4-(2-(methylthio)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one **61F** (0.2 mmol, 71.2 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as colourless oil. Yield: 0.17 mmol, 85.9 mg, 85%. $[\alpha]_D^{25}$= –29.64 (*c* = 0.40, >98:2 dr, 86% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 – 7.28 (m, 13H), 7.07 – 7.02 (m, 2H), 4.92 (dd, *J* = 13.1, 10.4 Hz, 1H), 4.76 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.06 (dd, *J* = 10.4, 5.0 Hz, 1H), 2.41 – 2.09 (m, 4H), 2.05 (s, 3H). UPLC-DAD-QTOF: $C_{27}H_{28}N_3O_3S_2$ $[M+H]^+$ calcd.: 506.1572, found: 506.1569.

Methyl 3-((*S*)-2-(Benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate (67Ia)



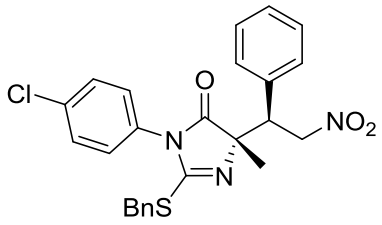
The title compound was prepared from methyl 3-(2(benzylthio)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate **61I** (0.2 mmol, 73.6 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow foam. Yield: 0.18 mmol, 93.1 mg, 90%. $[\alpha]_D^{25}$= –23.48 (*c* = 0.75, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.23 (m, 3H), 7.13 – 6.92 (m, 2H), 4.92 (dd, *J* = 13.1, 10.5 Hz, 1H), 4.46 – 4.25 (m, 1H), 4.46 – 4.25 (m, 2H), 4.05 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.68 (s, 3H), 2.30 – 2.08 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 172.7, 162.1, 135.9, 134.7, 131.6, 130.00, 129.3, 129.2, 128.8, 128.5, 128.0, 127.3, 52.0, 49.7, 34.9, 30.8, 28.7. UPLC-DAD-QTOF: $C_{28}H_{28}N_3O_5S$ $[M+H]^+$ calcd.: 518.1750, found: 518.1760.

(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (68Aa)



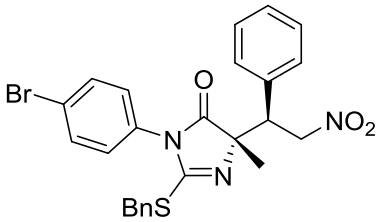
The title compound was prepared from 2-(benzylthio)-4-methyl-1-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one **62A** (0.2 mmol, 62.0 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 93:7 mixture of diastereomers (yellow oil). Yield: 0.18 mmol, 81.7 mg, 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.21 (m, 11H), 6.99 – 6.88 (m, 2H), 4.89 (dd, *J* = 13.1, 10.2 Hz, 1H), 4.73 (dd, *J* = 13.1, 5.2 Hz, 1H), 4.45 – 4.27 (m, 2H), 4.04 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.39 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.2, 139.7, 136.0, 135.2, 130.2, 129.2, 129.1, 129.0, 128.7, 128.4, 128.3, 127.9, 127.1, 50.1, 34.8, 22.7, 21.3. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 460.1695, found: 460.1700.

(*S*)-2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (69Aa)



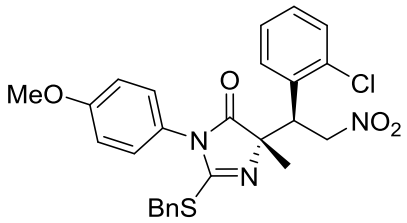
The title compound was prepared from 2-(benzylthio)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **63A** (0.2 mmol, 66.0 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.18 mmol, 86.2 mg, 90%. $[\alpha]_D^{25}$= –12.73 (*c* = 0.97, >98:2 dr, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.22 (m, 12H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.94 – 4.68 (m, 2H), 4.35 (d, *J* = 2.5 Hz, 2H), 4.03 (dd, *J* = 9.8, 5.6 Hz, 1H), 1.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.4, 135.8, 135.5, 135.1, 130.2, 129.8, 129.2, 128.8, 128.5, 128.5, 128.4, 128.0, 75.5, 73.1, 50.0, 34.9, 22.6. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SCl$ $[M+H]^+$ calcd.: 480.1149, found: 480.1156.

(*S*)-2-(Benzylthio)-1-(4-bromophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (70Aa)



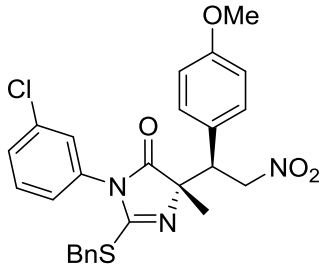
The title compound was prepared from 2-(benzylthio)-1-(4-bromophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **64A** (0.2 mmol, 74.8 mg) and (*E*)-(2-nitrovinyl)benzene **36a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.17 mmol, 90.0 mg, 86%. $[\alpha]_D^{25}$= –15.32 (*c* = 0.60, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.51 (m, 2H), 7.40 – 7.22 (m, 10H), 6.91 – 6.85 (m, 2H), 4.85 (dd, *J* = 13.1, 9.8 Hz, 1H), 4.70 (dd, *J* = 13.1, 5.5 Hz, 1H), 4.37 – 4.27 (m, 2H), 4.01 (dd, *J* = 9.8, 5.6 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.5, 160.4, 135.8, 135.1, 132.8, 129.2, 128.8, 128.8, 128.5, 128.4, 128.0, 123.6, 75.5, 73.2, 50.0, 35.0, 22.6. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SBr$ $[M+H]^+$ calcd.: 524.0644, found: 524.0653.

(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (71Ad)



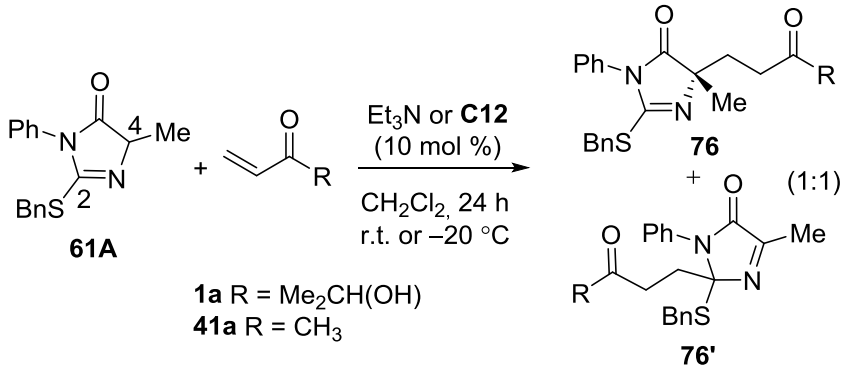
The title compound was prepared from 2-(benzylthio)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **65A** (0.2 mmol, 65.2 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **36d** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.18 mmol, 92.6 mg, 91%. $[\alpha]_D^{25}$= –32.62 (*c* = 0.82, >98:2 dr, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.23 (m, 8H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.90 – 4.62 (m, 1H), 4.36 (s, 2H), 3.84 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 161.9, 160.3, 136.3, 135.9, 133.6, 130.1, 129.3, 129.0, 128.8, 128.6, 127.9, 126.0, 124.2, 114.9, 75.4, 73.2, 55.6, 44.8, 34.8, 22.4. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4SCl$ $[M+H]^+$ calcd.: 510.1254, found: 510.1254.

(*S*)-2-(Benzylthio)-1-(3-chlorophenyl)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (72Al)



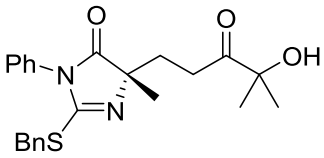
The title compound was prepared from 2-(benzylthio)-1-(3-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **66A** (0.2 mmol, 66.0 mg) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **36l** (0.4 mmol, 71.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.18 mmol, 91.6 mg, 90%. $[\alpha]_D^{25}$= –20.30 (*c* = 0.60, >98:2 dr, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 6.82 (m, 13H), 4.89 – 4.65 (m, 2H), 4.36 (d, *J* = 2.3 Hz, 2H), 3.97 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.83 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.2, 159.6, 135.8, 135.1, 132.9, 130.5, 130.3, 129.7, 129.2, 128.8, 128.0, 127.6, 126.9, 125.5, 75.7, 73.4, 55.4, 49.4, 35.0, 22.6. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4SCl$ $[M+H]^+$ calcd.: 510.1254, found: 510.1264.

5.4.6. Reaction of 61A with vinylketone 1a/41a



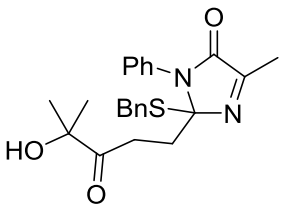
To a solution of imidazolone **61A** (1 equiv., 0.2 mmol) in dichlorometane (0.6 mL) the corresponding vinyl ketone (2.0 equiv., 0.4 mmol) and the catalyst were added at room temperature. The resulting mixture was stirred until consumption of the nucleophile (monitored by ^{1}H-NMR). Afterwards, the reaction was purified by flash column chromatography on silica gel to afford **76** and **76'** in (1:1) proportion.

(*S*)-2-(Benzylthio)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (76)



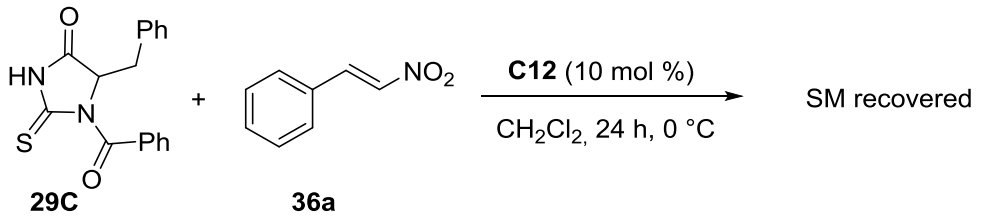
White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.20 (m, 10H), 4.40 – 4.26 (m, 2H), 3.72 (s, 1H), 2.69 – 2.46 (m, 2H), 2.27 – 2.06 (m, 2H), 1.48 (s, 3H), 1.35 (d, *J* = 2.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 182.9, 160.0, 136.0, 132.2, 129.5, 129.3, 128.7, 127.8, 127.3, 76.4, 71.0, 34.8, 31.9, 30.1, 26.7, 26.7, 23.3. UPLC-DAD-QTOF: $C_{23}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 410.1664, found: 410.1666.

2-(Benzylthio)-2-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-phenyl-1H-imidazol-5(2*H*)-one (76')

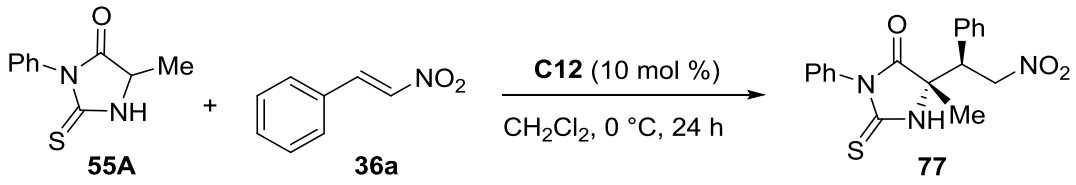


White foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.11 (m, 10H), 5.44 (d, *J* = 1.3 Hz, 1H), 4.53 (dd, *J* = 10.3, 8.9 Hz, 1H), 4.46 – 4.21 (m, 2H), 3.41 – 3.29 (m, 1H), 2.74 (dd, *J* = 16.8, 8.9 Hz, 1H), 1.50 (s, 3H), 1.27 (d, *J* = 1.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 215.6, 174.9, 173.4, 137.0, 136.7, 129.1, 128.9, 128.7, 127.6, 125.3, 120.6, 82.5, 78.0, 47.6, 43.5, 35.6, 27.5, 27.4, 23.2. UPLC-DAD-QTOF: $C_{23}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 410.1664, found: 410.1667.

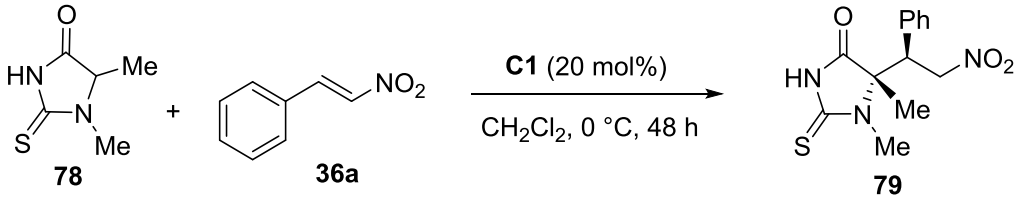
5.4.7. Reaction of thiohydantoins 29C, 55A, 78 and 80 with 36a



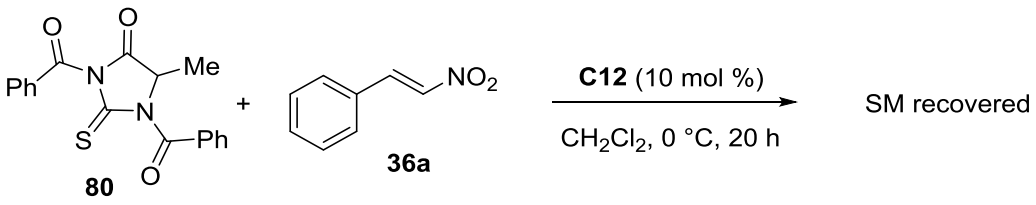
To a solution of thiohidantoin **29C** (1 equiv., 0.2 mmol) in dichlorometane (0.6 mL) nitroalkene **36a** (2.0 equiv., 0.4 mmol) and the catalyst were added at 0 ^{o}C. The resulting mixture was stirred for 24h and no reation was observed (monitored by ^{1}H-NMR).



To a solution of thiohidantoin **55A** (1 equiv., 0.2 mmol) and nitroalkene **36a** (2.0 equiv., 0.4 mmol) in dichlorometane (0.6 mL) the catalyst was added at 0 ^{o}C. The resulting mixture was stirred until consumption of the thiohidantoin (monitored by ^{1}H-NMR). Afterwards, the reaction was directly submitted to flash column chromatography on silica gel to afford the adduct **77** essentially pure. Yield: 56.8 mg, 0.16 mmol, 80%. Dr 1.9:1, 94% *ee*.



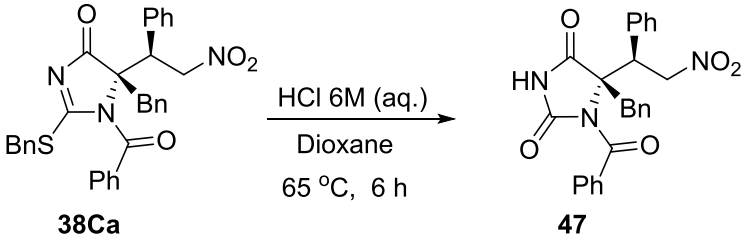
To a solution of thiohidantoin **78** (1 equiv., 0.2 mmol) and nitroalkene **36a** (2.0 equiv., 0.4 mmol) in dichlorometane (0.6 mL) the catalyst was added at 0 ^{o}C. The resulting mixture was stirred until consumption of the thiohidantoin (monitored by ^{1}H-NMR). Afterwards, the reaction was directly submitted to flash column chromatography on silica gel to afford the adduct **79** essentially pure. Yield: 43.9 mg, 0.15 mmol, 76%. Dr 1:1, 10% *ee*.



To a solution of thiohidantoin **80** (1 equiv., 0.2 mmol) in dichlorometane (0.6 mL) nitroalkene **36a** (2.0 equiv., 0.4 mmol) and the catalyst were added at 0 ^{o}C. The resulting mixture was stirred for 24h and no reation was observed (monitored by ^{1}H-NMR).

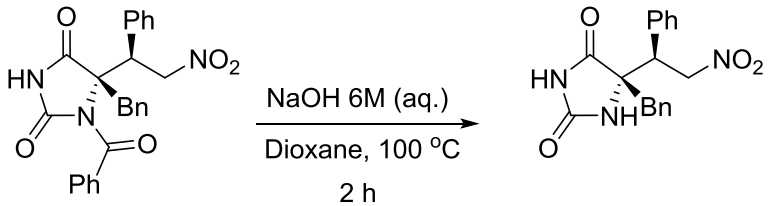
5.4.8. Elaboration of adducts

5.4.8.1. Conversion of adduct 38Ca to 47



Adduct **38Ca** (549 mg, 1.0 mmol, 1 equiv.) was dissolved in 1,4-dioxane (2 mL/mmol). The solution was cooled to 0 °C and an aqueous solution of HCl 6M (1.9 mL, 11 mmol, 11 equiv.) was added. The reaction mixture was stirred at 65 ^{o}C for 3 h. Afterwards 12 equiv. more of HCl 6M were added and the reaction was stirred at 65 ^{o}C for an additional 3 h. Then, the reaction mixture was cooled to 0 °C, and a saturated solution of $NaHCO_3$ was added until basic pH was obtained. The aqueous layer was extracted with CH_2Cl_2 (2x 5mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. m. p.: 239–243^{o}C. Yield: 354 mg, 0.80 mmol, 80%. $[\alpha]_D^{25}$= –25.30 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.52 (s, 1H), 7.50 – 7.13 (m, 13H), 7.06 – 6.50 (m, 2H), 5.53 – 5.26 (m, 2H), 5.08 (dd, *J* = 10.4, 4.8 Hz, 1H), 4.05 (d, *J* = 13.2 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.4, 169.5, 150.9, 134.2, 133.1, 132.0, 129.8, 129.5, 129.4, 129.1, 128.3, 127.8, 127.7, 75.9, 74.3, 47.6, 39.4. UPLC-DAD-QTOF: $C_{25}H_{22}N_3O_5$ $[M+H]^+$ calcd.: 444.1559, found: 444.1556.

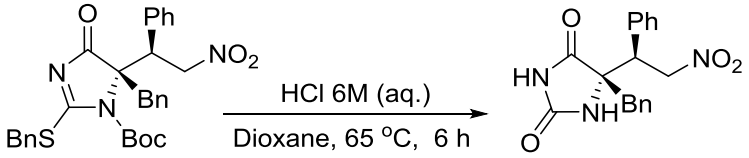
5.4.8.2. Synthesis of 48 by saponification of 47



47 **48**

N-Benzoylimide **47** (221.5 mg, 0.5 mmol, 1 equiv.) was dissolved in dioxane (2.5 mL). The solution was cooled to 0 °C and an aqueous solution of NaOH 6M (890 µL, 5.5 mmol, 11 equiv.) was added. The reaction mixture was stirred at 100 °C for 2 h. After reaction completion, the reaction mixture was cooled to 0 °C, and a saturated solution of NH_4Cl (sat.) was added until slightly acid pH. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 50:50) to obtain the desired product as a white solid. m. p.: 257–261 °C. Yield: 130.5 mg, 0.39 mmol, 77%. $[\alpha]_D^{25}$= –30.40 (*c* = 0.85, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.40 (d, *J* = 4.1 Hz, 4H), 7.30 – 7.15 (m, 5H), 5.29 – 4.99 (m, 2H), 4.02 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.21 (d, *J* = 13.5 Hz, 1H), 2.67 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (75 MHz, MeOD) δ: 177.6, 158.5, 136.0, 135.1, 131.4, 130.2, 129.8, 129.5, 129.23, 128.3, 76.8, 70.5, 51.2, 42.5. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_4$ $[M+H]^+$ calcd.: 340.1297, found: 340.1290.

5.4.8.3. Synthesis of adduct 48 by acid hydrolysis of 39Ca

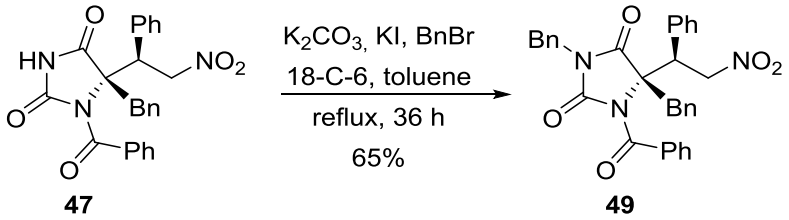


39Ca **48**

The reaction adduct **39Ca** (545 mg, 1.0 mmol, 1 equiv.) was dissolved in dioxane (5 mL). The solution was cooled to 0 °C and an aqueous solution of HCl 6M (1.9 mL, 11 mmol, 11 equiv.) was added. The reaction mixture was stirred at 65 °C for 3 h. Afterwards 12 equiv. more of HCl 6M were added and the reaction stirred at 65 °C for additional 3 h. Then, the reaction mixture was cooled to 0 °C, and a saturated solution of $NaHCO_3$ was added until basic pH was obtained. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The

solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 20:80) to obtain the desired product as a white solid. Yield: 247 mg, 0.73 mmol, 73%.

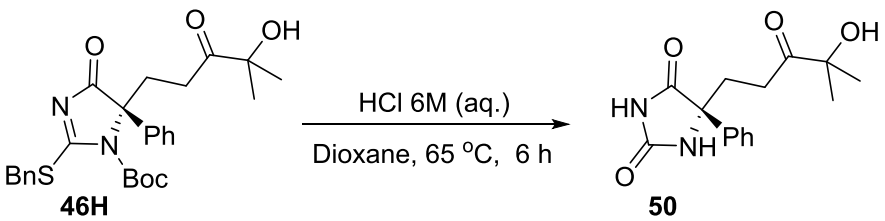
5.4.8.4. Synthesis of adduct 49 by *N*-alkylation of hydantoin 47[30]



To a mixture of **47** (1 equiv., 0.5 mmol, 222 mg) and 18-crown-6 (1% *w/w*) in 5 mL of dry toluene were added K_2CO_3 (0.1 equiv., 0.05 mmol, 7 mg) and KI (0.1 equiv., 0.05 mmol, 8.3 mg). After stirring for 20 min, BnBr (1.1 equiv., 0.55 mmol, 65.4 µL) in 10 mL of dry toluene was added dropwise. The mixture was then refluxed for 36 h and cooled. After filtration over a short column of celite, the organic phase was concentrated under reduced pressure and the crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30)) to obtain the desired product as a white foam. Yield: 173 mg, 0.325 mmol, 65%. $[\alpha]_D^{25}$= –34.76 (*c* = 0.50, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3Cl) δ: 7.48 – 6.97 (m, 20H), 6.80 – 6.76 (m, 2H), 5.36 – 5.28 (m, 2H), 5.04 (dd, *J* = 9.8, 5.4 Hz, 1H), 4.32 (s, 2H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.57 (d, *J* = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 169.9, 152.5, 135.2, 134.7, 134.6, 133.6, 132.2, 130.5, 130.1, 129.9, 129.8, 129.6, 129.5, 129.4, 129.0, 128.8, 128.6, 128.2, 128.1, 76.6, 72.8, 48.2, 43.4, 39.9. UPLC-DAD-QTOF: $C_{32}H_{28}N_3O_5$ $[M+H]^+$ calcd.: 534.2029, found: 534.2036.

5.4.9. Synthesis of ADAMTS inhibitors 53 and 54

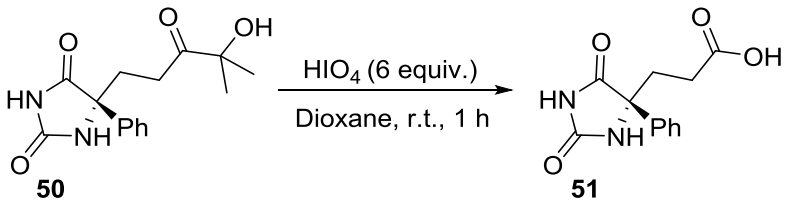
Synthesis of (*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-phenylimidazolidine-2,4-dione (50)



[30] Pesquet, A.; Van Hijfte, L.; Daïch A. *ARKIVOC* **2010**, 27.

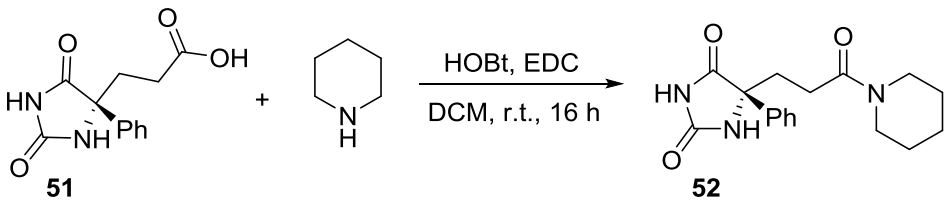
Adduct **46H** (496 mg, 1.0 mmol, 1 equiv.) was dissolved in dioxane (5 mL). The solution was cooled to 0 °C and an aqueous solution of HCl 6M (1.9 mL, 11 mmol, 11 equiv.) was added. The reaction mixture was stirred at 65 ^{o}C (bath temperature) for 3 h. Afterwards 12 equiv. more of HCl 6M were added and the reaction was stirred at 65 ^{o}C for additional 3 h. Then, the reaction mixture was cooled to 0 °C, and a saturated solution of $NaHCO_3$ was added until basic pH was obtained. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 0:100) to obtain the desired product as a white solid. m. p.: 205–209 ^{o}C. Yield: 212 mg, 0.73 mmol, 73%. $[\alpha]_D^{25}$= –17.54 (*c* = 0.40, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, MeOD) δ: 7.63 – 7.53 (m, 2H), 7.51 – 7.30 (m, 3H), 2.80 – 2.66 (m, 2H), 2.45 – 2.29 (m, 2H), 1.27 (d, *J* = 1.6 Hz, 6H). ^{13}C NMR (75 MHz, MeOD) δ: 215.7, 178.1, 159.0, 139.7, 129.8, 129.4, 126.5, 77.9, 69.1, 33.3, 31.8, 26.7. UPLC-DAD-QTOF: $C_{15}H_{19}N_2O_4$ $[M+H]^+$ calcd.: 291.1345, found: 291.1353.

Synthesis of (*R*)-3-(2,5-dioxo-4-phenylimidazolidin-4-yl)propanoic acid (51)



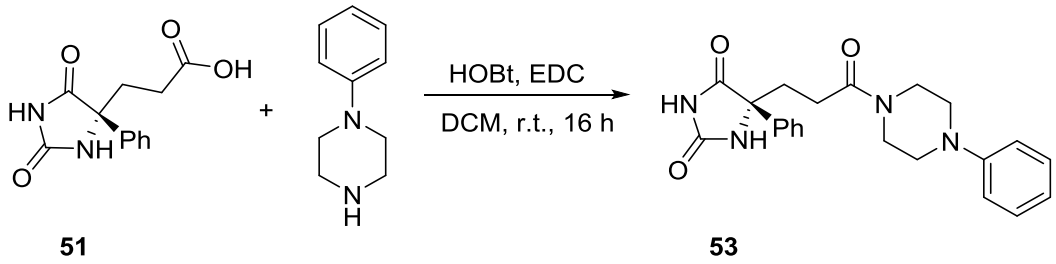
Hydantoin **50** (290 mg, 1 mmol, 1 equiv.) was dissolved in dioxane (10 mL) and HIO_4 (1.36 g, 6 mmol, 6 equiv.) was added. The solution was stirred at room temperature for 1 h. The reaction mixture was then diluted with brine (15 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure obtaining a white solid. m. p.: 198–200 ^{o}C. Yield: 223 mg, 0.9 mmol, 90%. $[\alpha]_D^{25}$= –22.94 (*c* = 0.5, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, MeOD) δ: 7.59 – 7.54 (m, 2H), 7.47 – 7.33 (m, 3H), 2.60 – 2.24 (m, 4H). ^{13}C NMR (75 MHz, MeOD) δ: 177.8, 175.9, 158.9, 139.4, 129.8, 129.4, 126.5, 69.0, 34.6, 29.7. UPLC-DAD-QTOF: $C_{12}H_{13}N_2O_4$ $[M+H]^+$ calcd.: 249.0875, found: 249.0884.

Synthesis of (*R*)-5-(3-oxo-3-(piperidin-1-yl)propyl)-5-phenylimidazolidine-2,4-dione (52)



To a solution of acid **51** (1 equiv., 0.5 mmol, 157 mg) in CH_2Cl_2 (5 mL) were successively added piperidine (1 equiv., 0.5 mmol, 49.4 µL), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) (1.4 equiv, 0.7 mmol, 134 mg) and hydroxybenzotriazole (HOBt) (1 equiv., 0.5 mmol, 77 mg) at 0 ^{o}C and the reaction mixture was stirred for 1 h and then 16 h at room temperature. Afterwards, the reaction was quenched with H_2O (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The crude material was purified by flash column chromatography on silica gel (eluting wit Hex/EtOAc 80:20 to 0:100) to give product **52** as a white solid. m. p.: 201–204 ^{o}C. Yield: 102.4 mg, 0.33 mmol, 65%. $[\alpha]_D^{25}$= –34.17 (*c* = 0.5, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, MeOD) δ: 7.62 – 7.55 (m, 2H), 7.47 – 7.33 (m, 3H), 3.56 – 3.49 (m, 2H), 3.43 – 3.36 (m, 2H), 2.49 – 2.31 (m, 4H), 1.73 – 1.48 (m, 6H). ^{13}C NMR (75 MHz, MeOD) δ: 177.9, 171.9, 158.9, 139.5, 129.8, 129.4, 126.5, 69.1, 44.1, 35.1, 28.8, 27.5, 26.6, 25.4. UPLC-DAD-QTOF: $C_{17}H_{22}N_3O_3$ $[M+H]^+$ calcd.: 316.1661, found: 316.1662.

Synthesis of (*R*)-5-(3-oxo-3-(4-phenylpiperazin-1-yl)propyl)-5-phenylimidazolidine-2,4-dione (53):



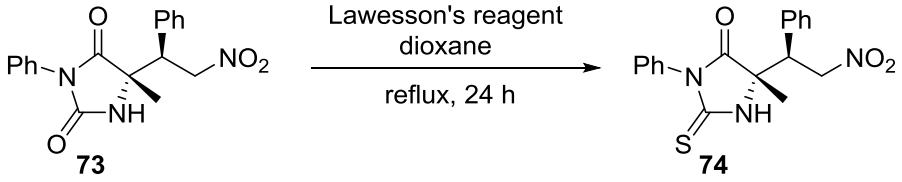
The above procedure was followed using 1-phenylpiperazine (1 equiv., 0.5 mmol, 75.7 µL) as the coupling amine partner. White solid. m. p.: 203-207 ^{o}C. Yield: 137.2 mg, 0.35 mmol, 70%. $[\alpha]_D^{25}$= –40.36 (*c* = 1.0, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.83 (s, 1H), 8.71 (s, 1H), 7.59 – 7.14 (m, 7H), 6.98 – 6.73 (m, 3H), 3.61 – 3.43 (m, 4H), 3.12 – 3.05 (m, 4H), 2.47 – 2.10 (m, 4H). ^{13}C NMR (75 MHz, DMSO) δ: 176.0, 169.3, 156.4, 150.7, 138.5, 129.0, 128.6, 128.0, 125.4, 119.3, 115.8, 66.9, 48.5, 48.2, 44.6,

41.0, 33.6, 27.2. UPLC-DAD-QTOF: $C_{22}H_{25}N_4O_3$ $[M+H]^+$ calcd.: 393.1927, found: 393.1929.

5.4.9.1. Synthesis of adduct 73

Adduct **67Aa** (445 mg, 1.0 mmol, 1 equiv.) was dissolved in 1,4-dioxane (5 mL). The solution was cooled to 0 °C and an aqueous solution of HCl 6M (1.9 mL, 11 mmol, 11 equiv.) was added. The reaction mixture was stirred at room temperature for 3 days. Then, the reaction mixture was cooled to 0 °C, and a saturated solution of $NaHCO_3$ was added until basic pH was obtained. The aqueous layer was extracted with CH_2Cl_2 (2 x 5mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 0:100) to obtain the desired product as a white solid. Yield: 271 mg, 0.80 mmol, 80%. m. p. 169–172 °C. $[\alpha]_D^{25}$= –23.55 (*c* = 0.60, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 – 7.03 (m, 10H), 6.74 (s, 1H), 5.31 – 4.63 (m, 2H), 3.98 (dd, *J* = 10.4, 5.0 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, Acetone) δ: 182.9, 175.9, 135.3, 134.3, 129.9, 129.7, 129.6, 129.6, 129.5, 75.6, 66.8, 51.1, 22.2. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_4$ $[M+H]^+$ calcd.: 340.1297, found: 340.1304.

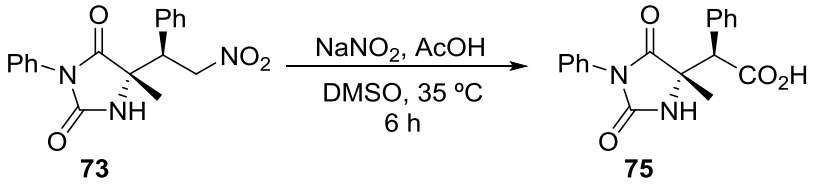
5.4.9.2. Conversion of 73 to thiohydantoin 74 from adduct 67Aa



A suspension of hydantoin **73** (0.5 mmol) and Lawesson's reagent (202.2 mg, 0.5 mmol) in 2.3 mL of dry dioxane was refluxed for 24 h. The mixture was then concentrated, and the residue was submitted to flash chromatography on silica gel, eluent hexane/ethyl acetate (80:20 to 50:50) to afford **74** as a white solid. Yield: 149 mg, 0.42 mmol, 84%. m. p. 235–237 °C. $[\alpha]_D^{25}$= –29.01 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone) δ: 9.51 (s, 1H), 7.46 – 7.36 (m, 8H), 7.07 – 7.00 (m, 2H), 5.38 – 5.24 (m, 2H), 4.12 (dd, *J* = 9.8, 6.2 Hz, 1H), 1.74 (s, 4H). ^{13}C NMR (75

MHz, Acetone) δ: 182.80, 175.81, 135.25, 134.20, 129.76, 129.62, 129.57, 129.48, 129.45, 129.41, 75.47, 66.76, 50.98, 22.15. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 356.1069, found: 356.1069.

5.4.9.3. Conversion of 73 to acid 75

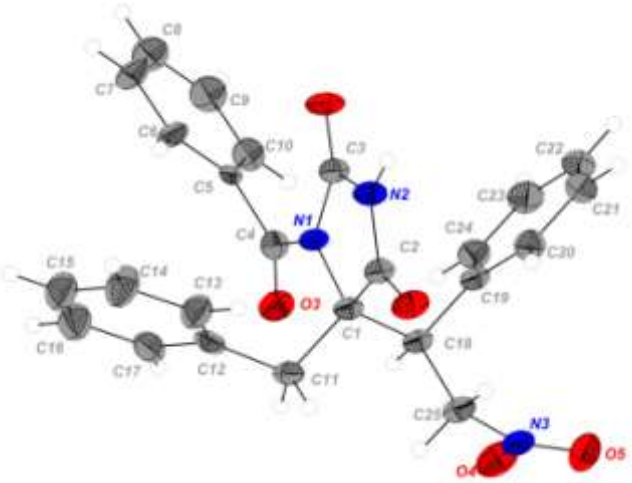


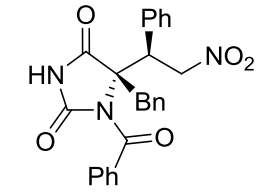
73 **75**

A solution of **73** (0.19 mmol, 64 mg), sodium nitrite (3 equiv., 0.55 mmol, 34 mg) and acetic acid (10 equiv., 1.9 mmol, 120 µL) in DMSO (0.5 mL) was stirred at 35 ^{o}C for 6 h. After this period, the reaction mixture was quenched with HCl 1N (5 mL) and the product was extracted with Et_2O (4 x 5 mL). The combined organic phases were dried with anhyd. $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure and ulterior washing of the solid with Et_2O gave essentially pure **75** as orange foam. Yield: 48.6 mg, 0.15 mmol, 79%. $[\alpha]_D^{25}$= –32.99 (*c* = 1.00, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, Acetone) δ: 7.51 – 7.33 (m, 10H), 7.24 (s, 1H), 4.23 (s, 1H), 2.57 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, Acetone) δ: 206.3, 176.7, 172.5, 156.6, 135.2, 134.0, 131.1, 129.4, 129.4, 128.8, 128.4, 127.6, 62.6, 56.9, 24.0. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 325.1183, found: 325.1190.

5.4.10. X-Ray analysis: ORTEP diagram of compounds 47 and 74

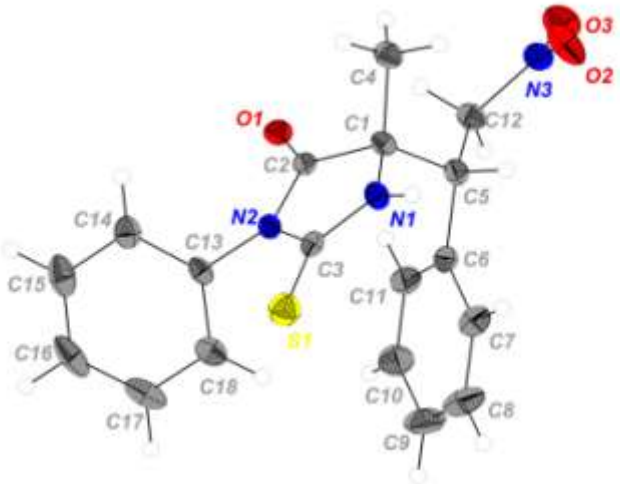
CCDC 1581118 contains the supplementary crystallographic data for the structural analysis of **47**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deposit/.

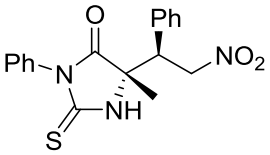




47

CCDC 1581122 contains the supplementary crystallographic data for the structural analysis of **74** derivate. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/deposit/.

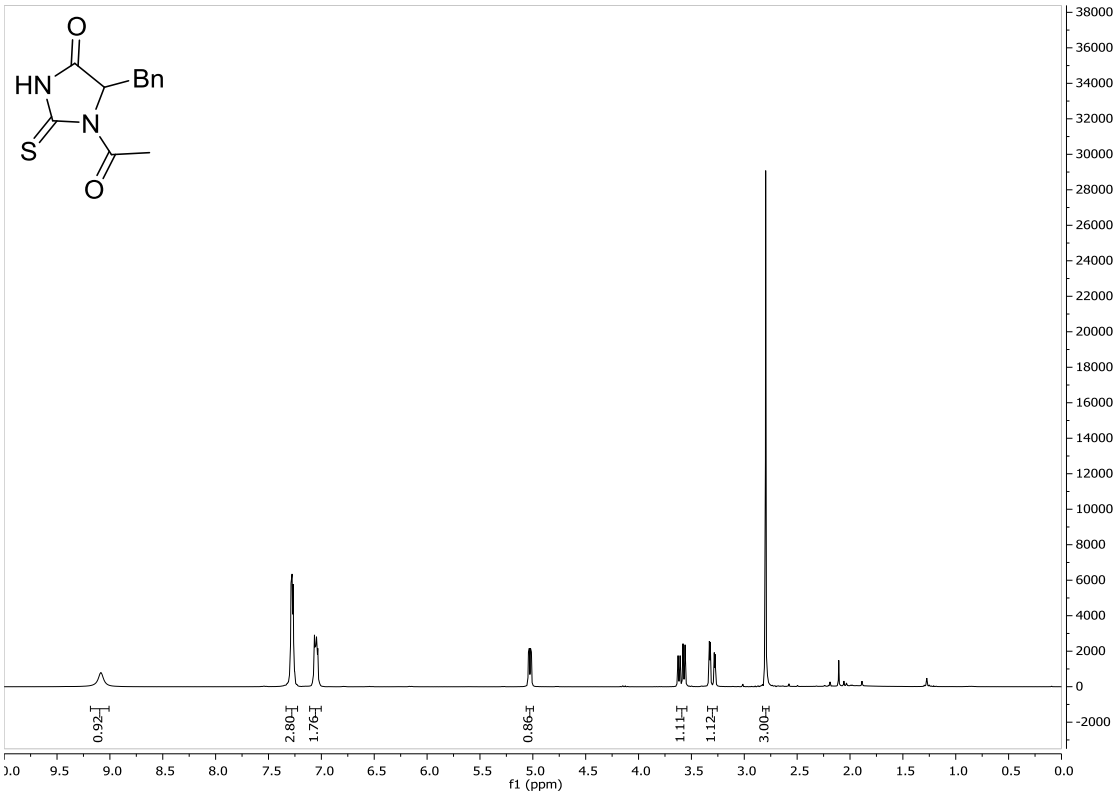


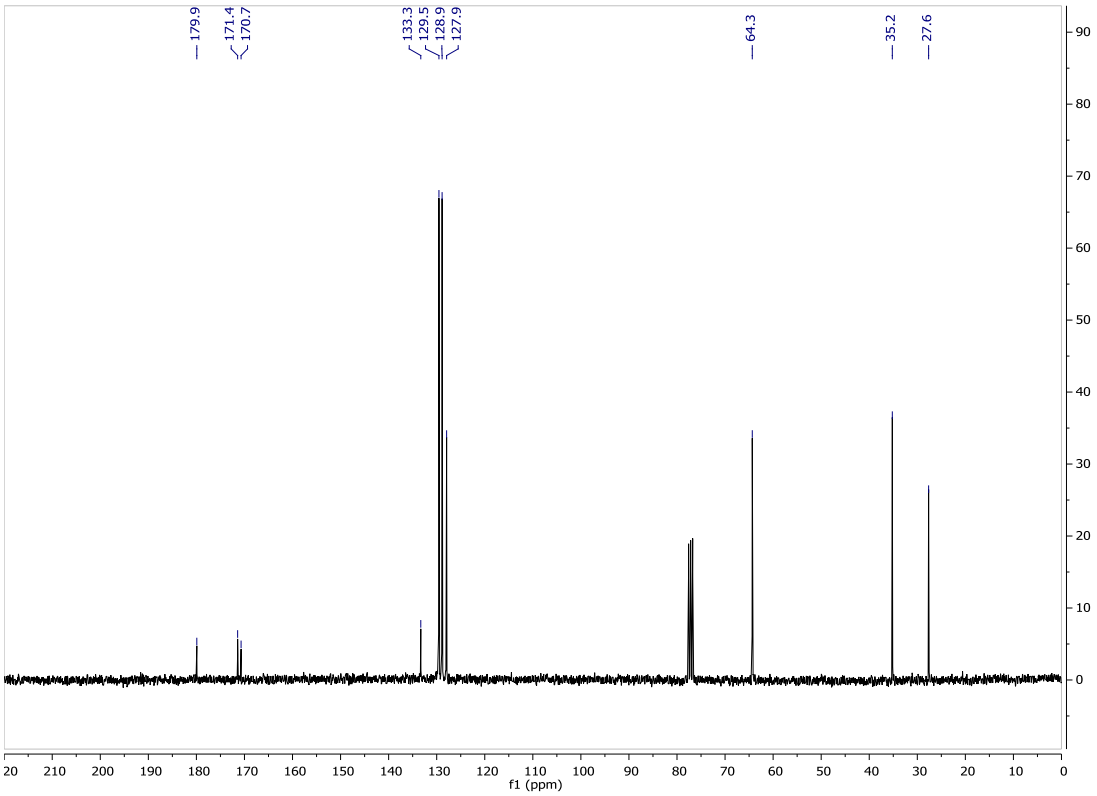


74

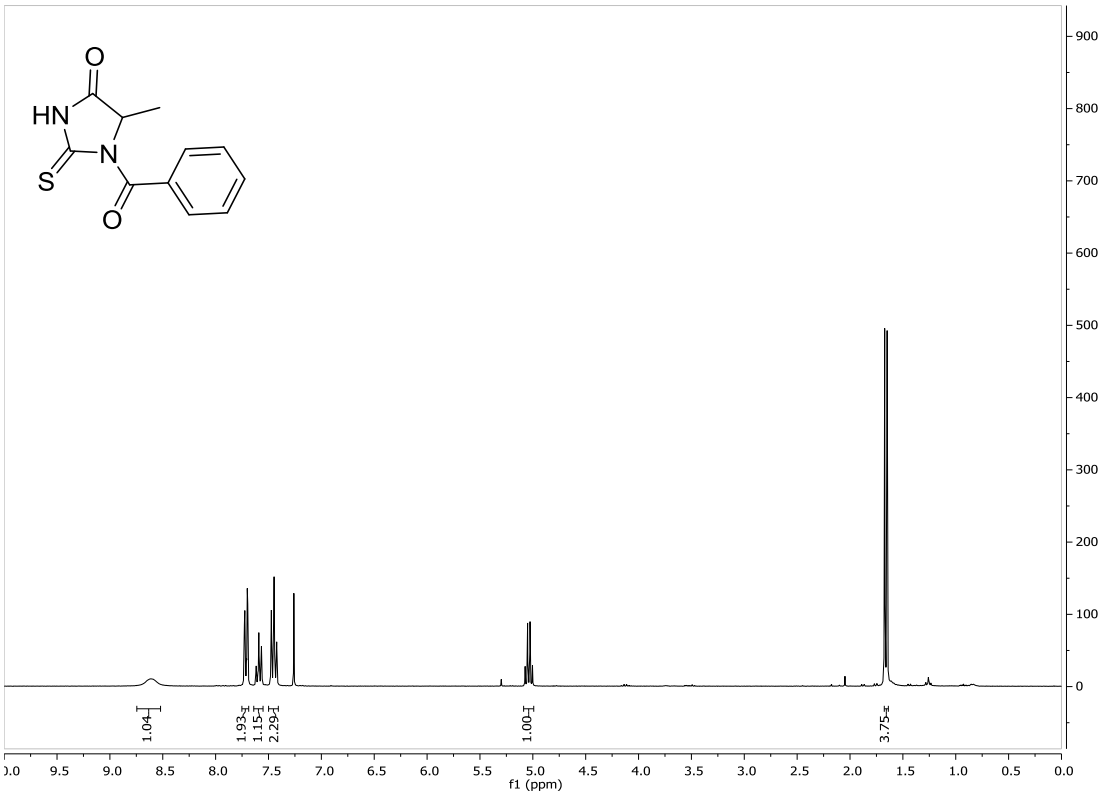
5.4.11. ^{1}H and ^{13}C NMR Spectra

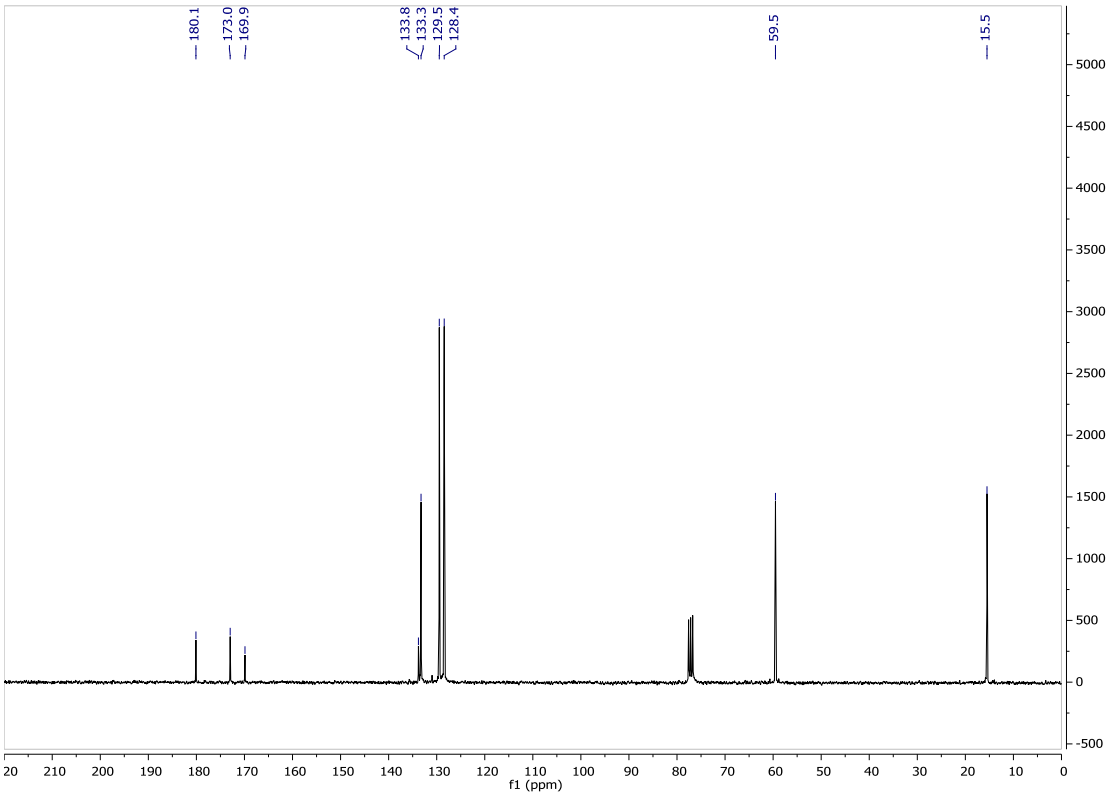
1-Acetyl-5-benzyl-2-thioxoimidazolidin-4-one (28)



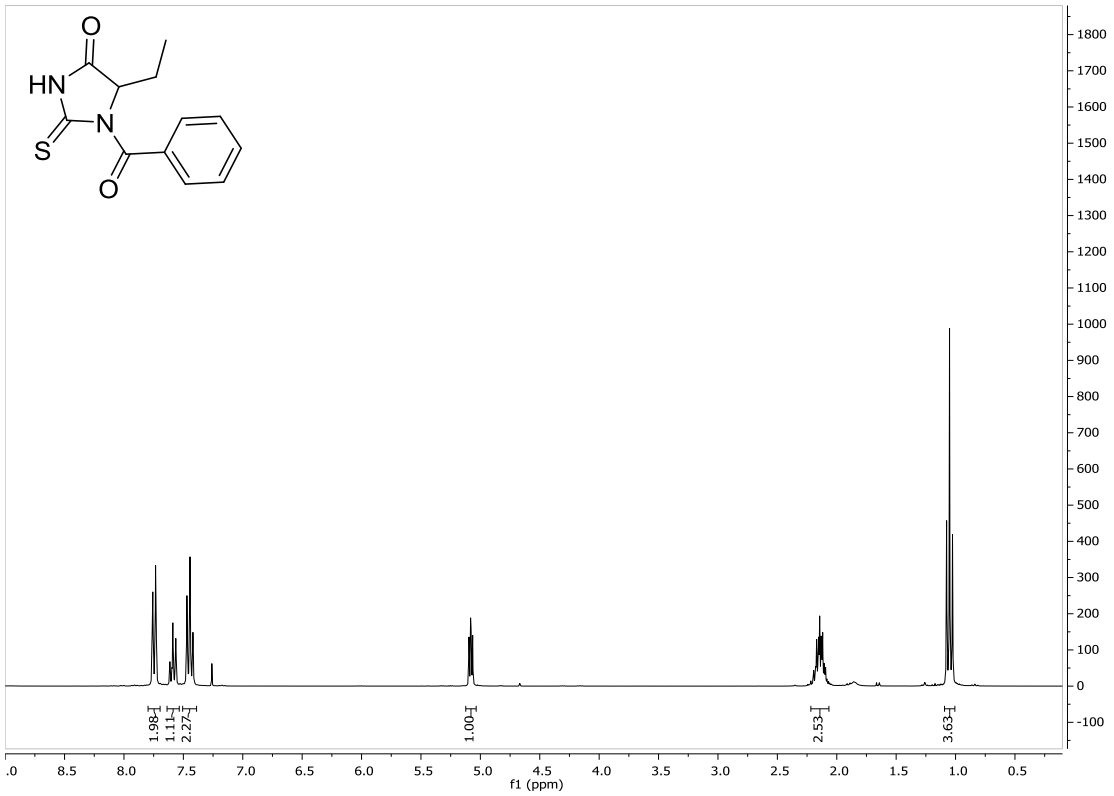


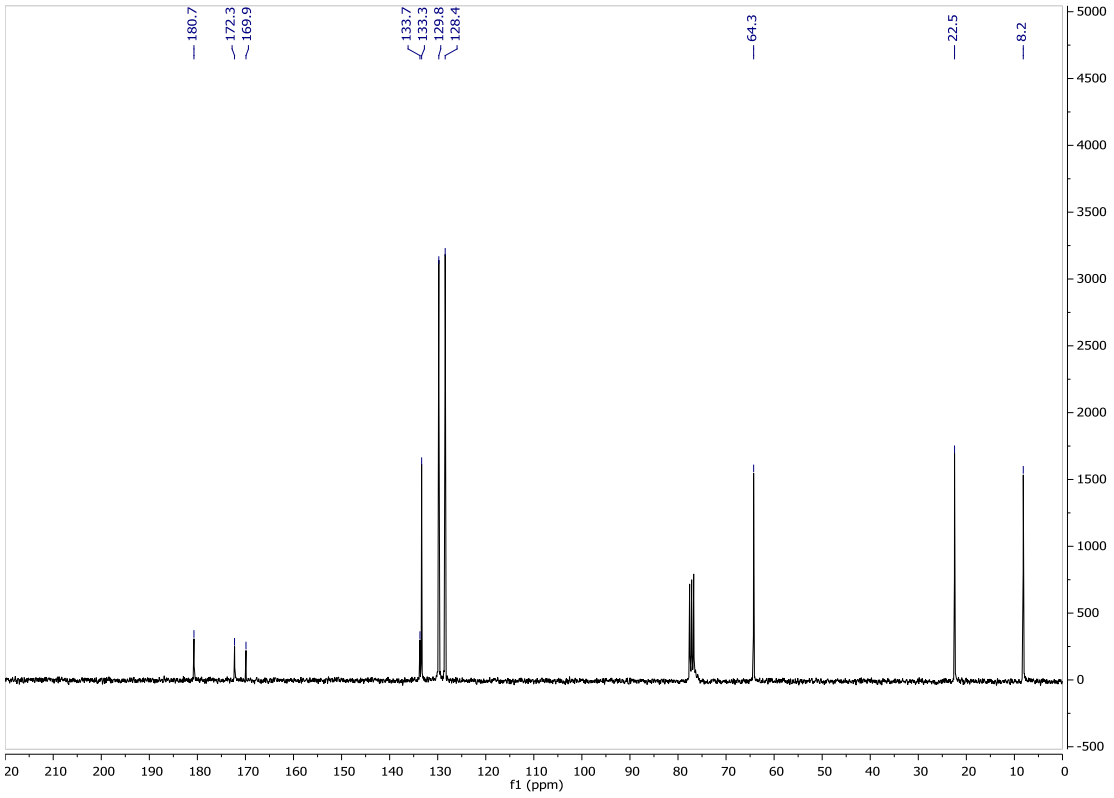
1-Benzoyl-5-methyl-2-thioxoimidazolidin-4-one (29A)



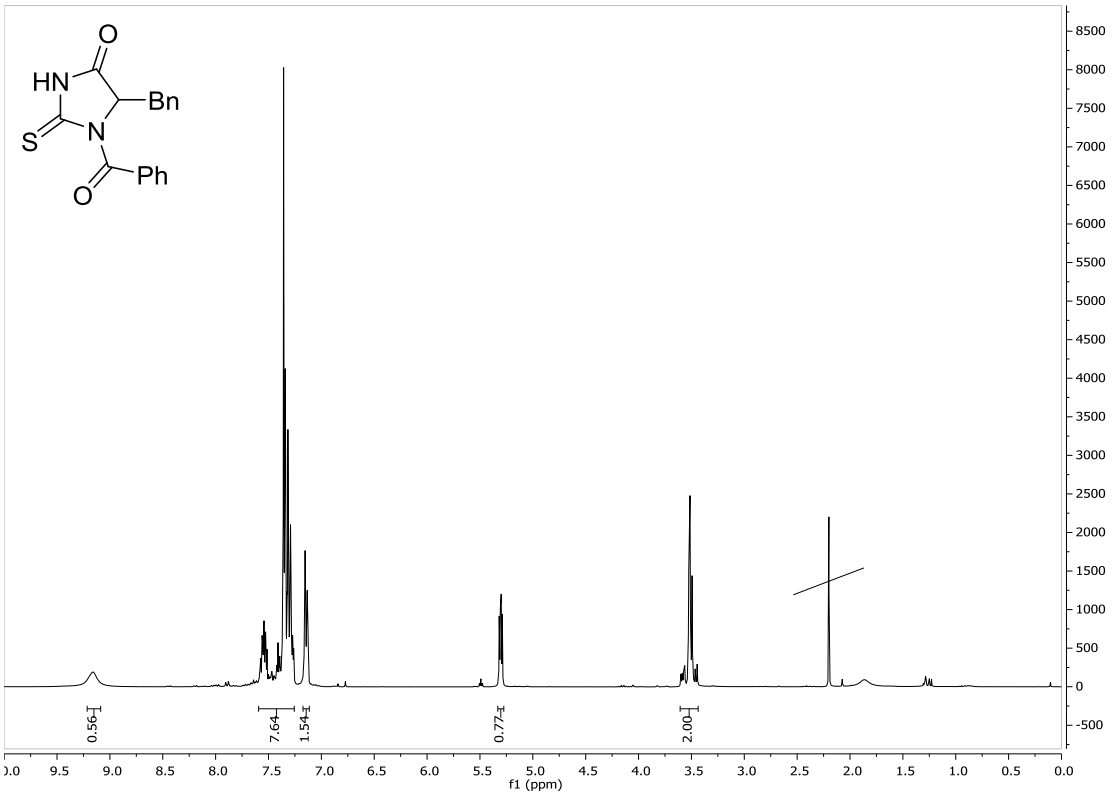


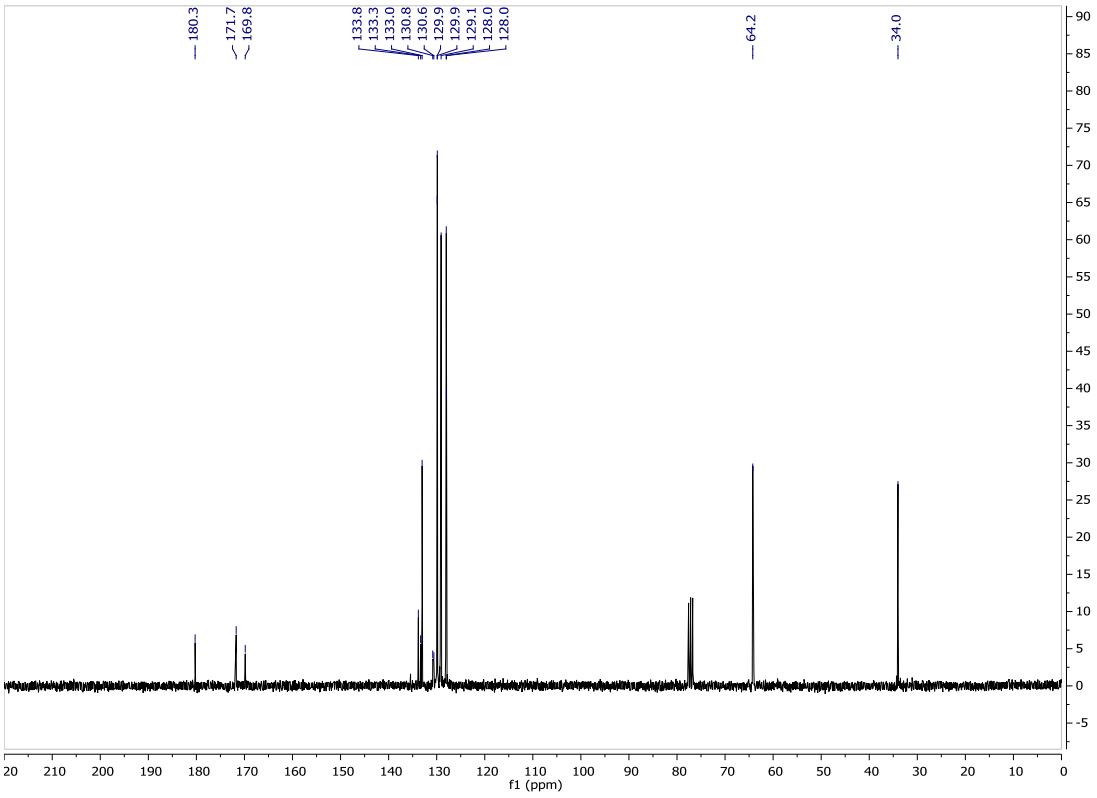
1-Benzoyl-5-ethyl-2-thioxoimidazolidin-4-one (29B)



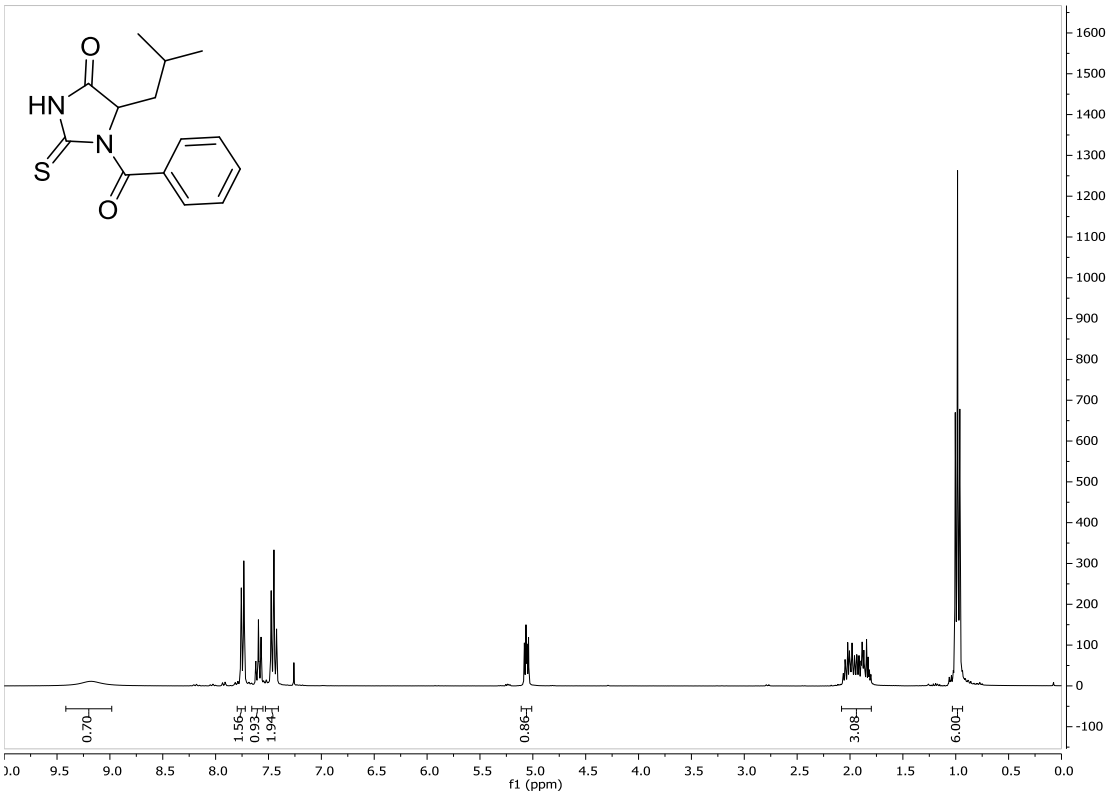


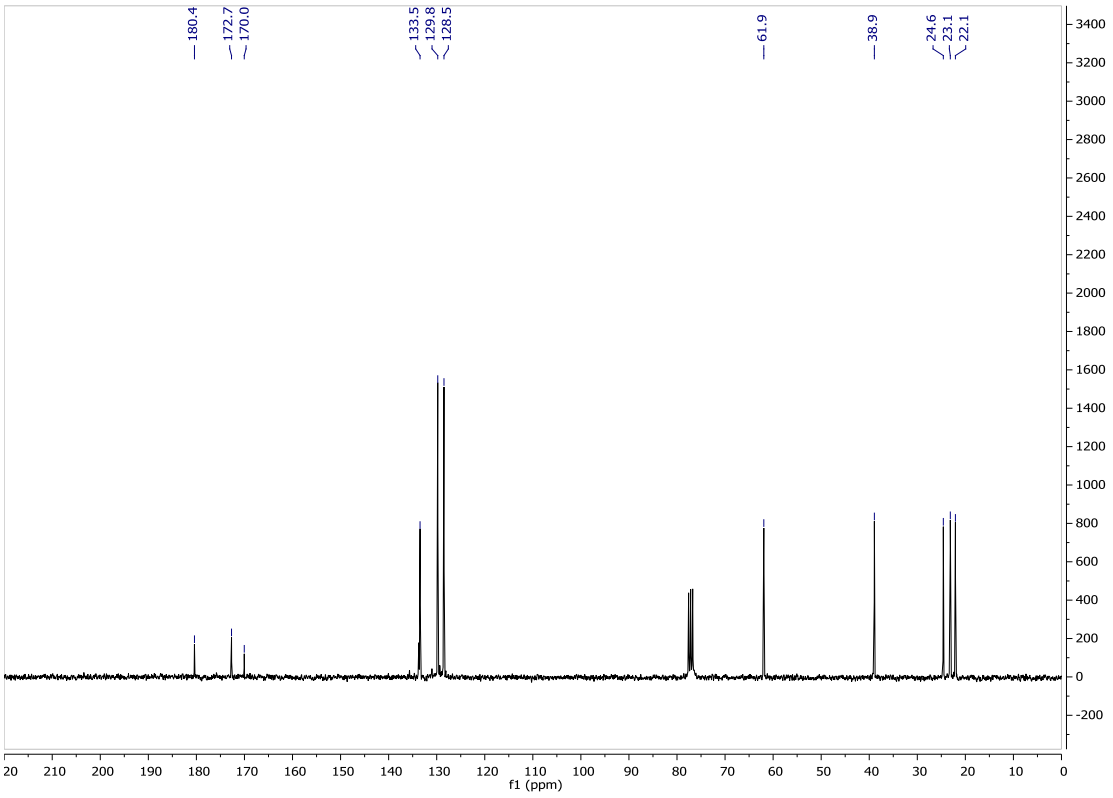
1-Benzoyl-5-benzyl-2-thioxoimidazolidin-4-one (29C)



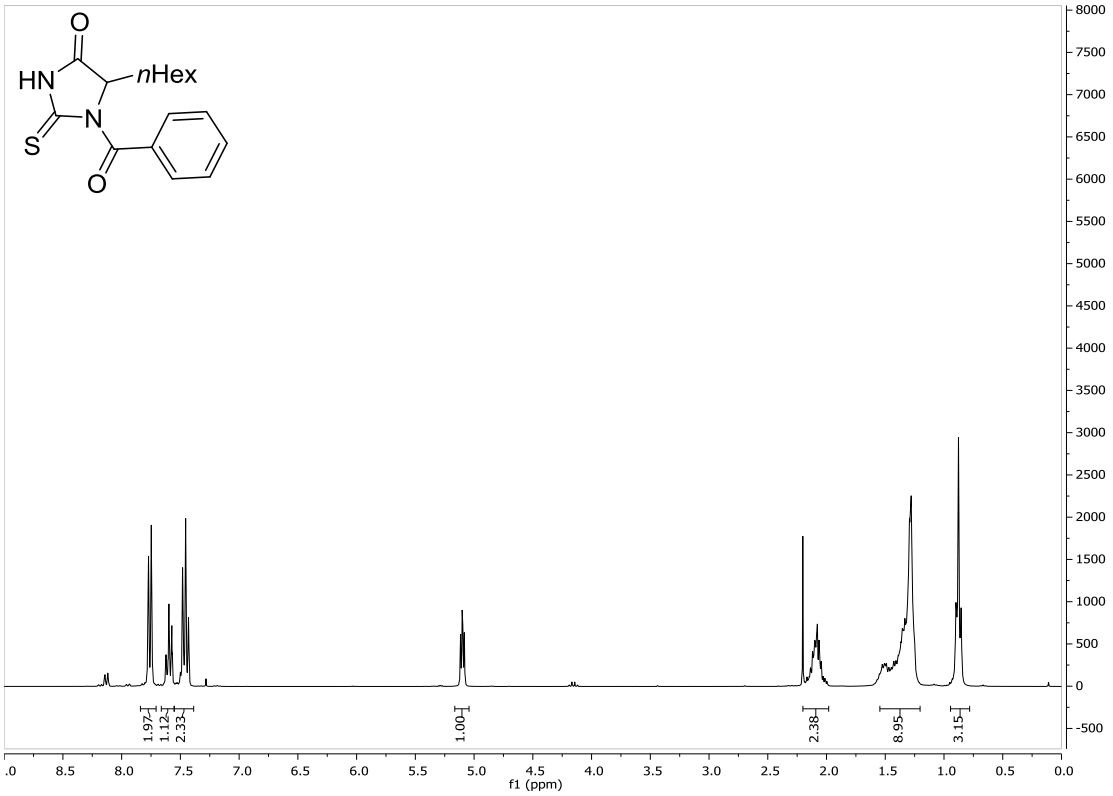


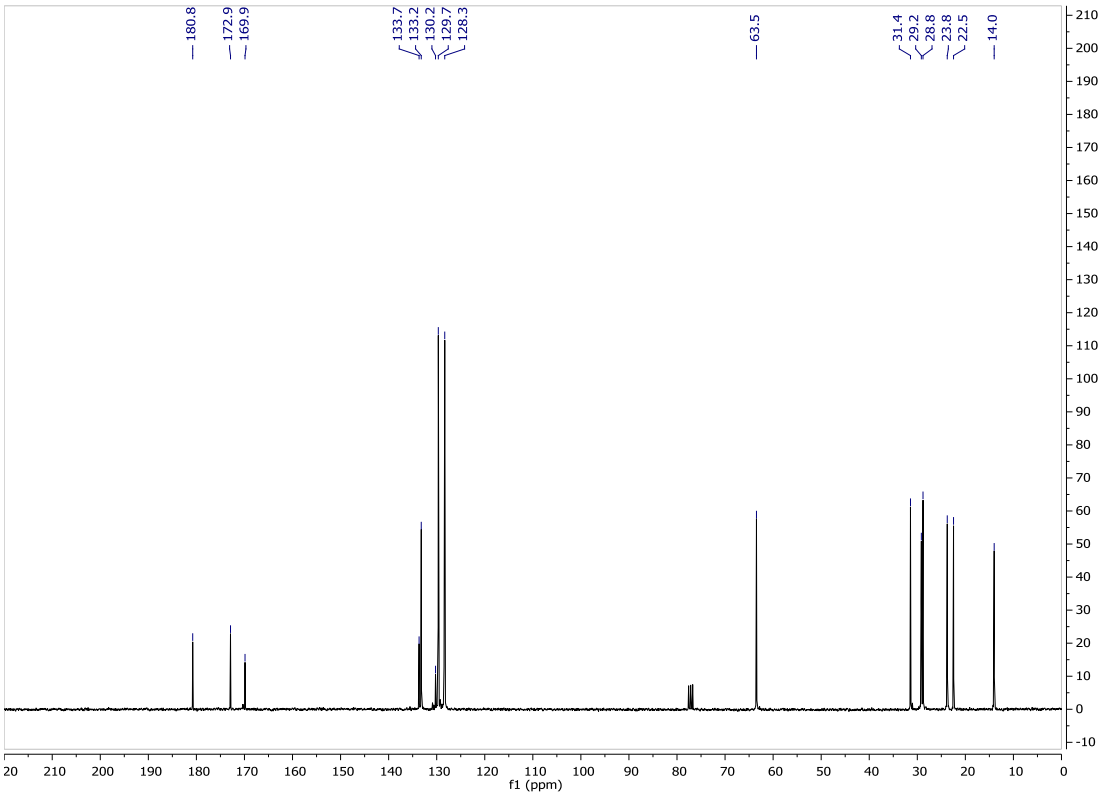
1-Benzoyl-5-isobutyl-2-thioxoimidazolidin-4-one (29D)



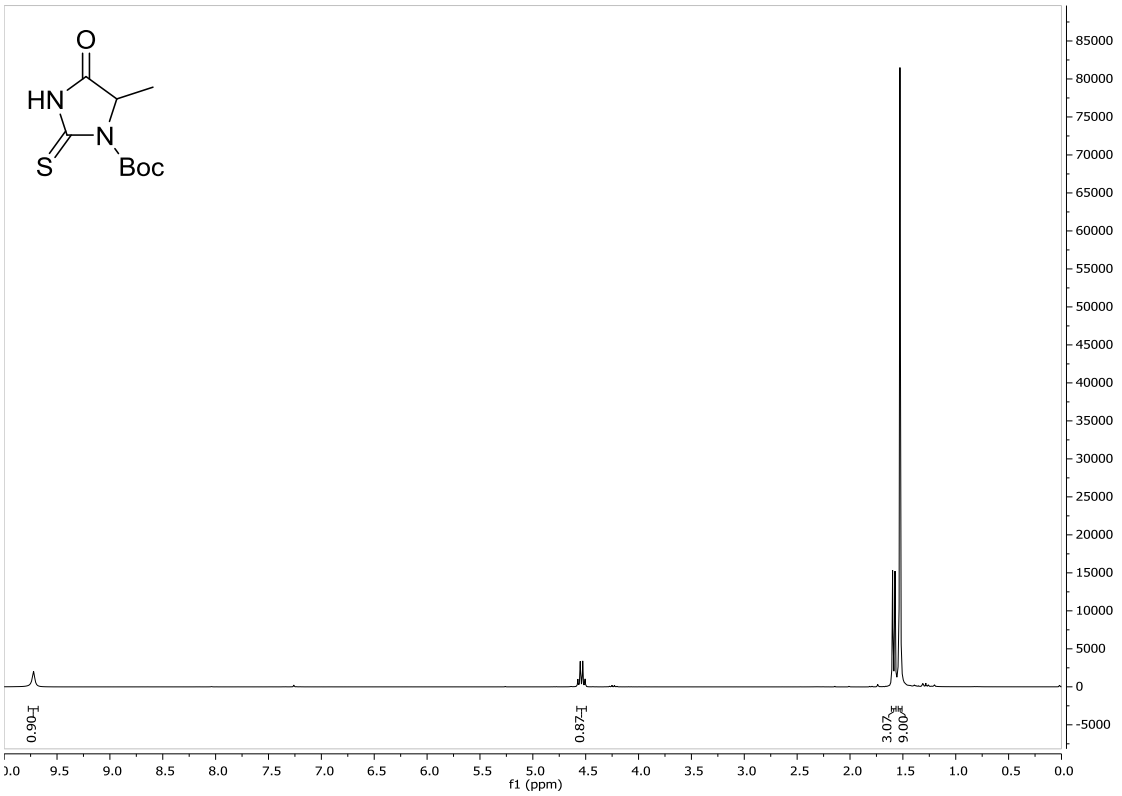


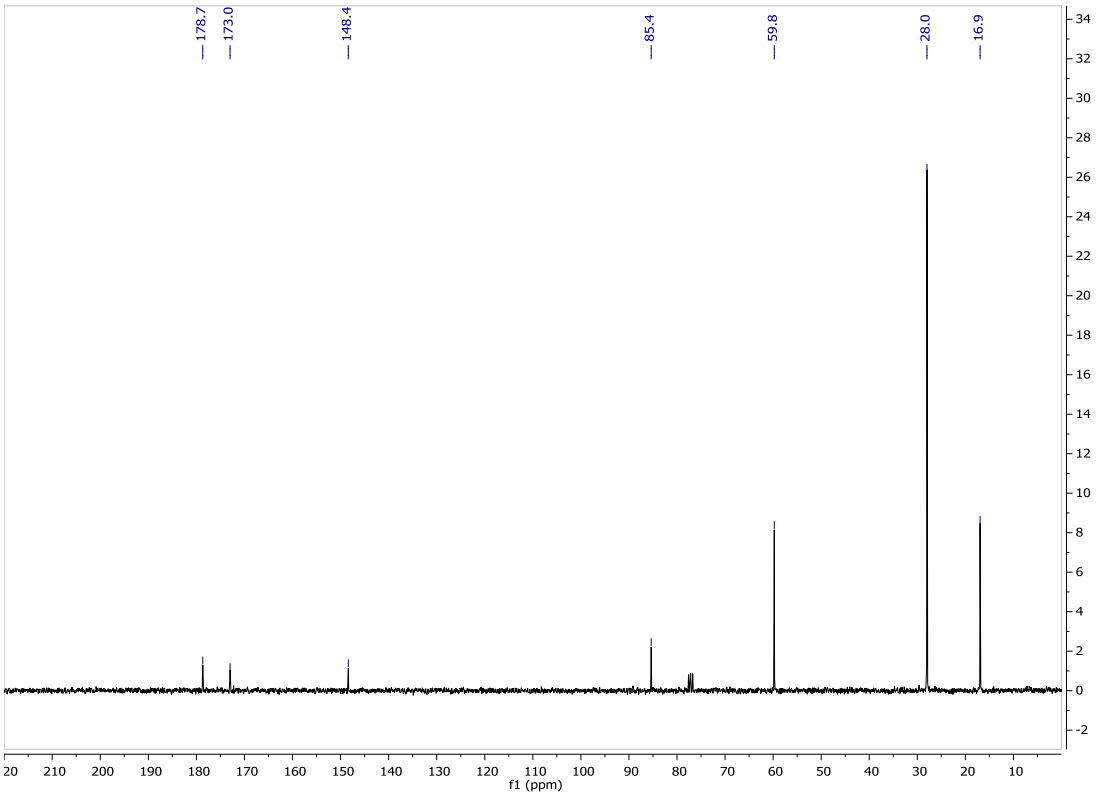
1-Benzoyl-5-hexyl-2-thioxoimidazolidin-4-one (29E)



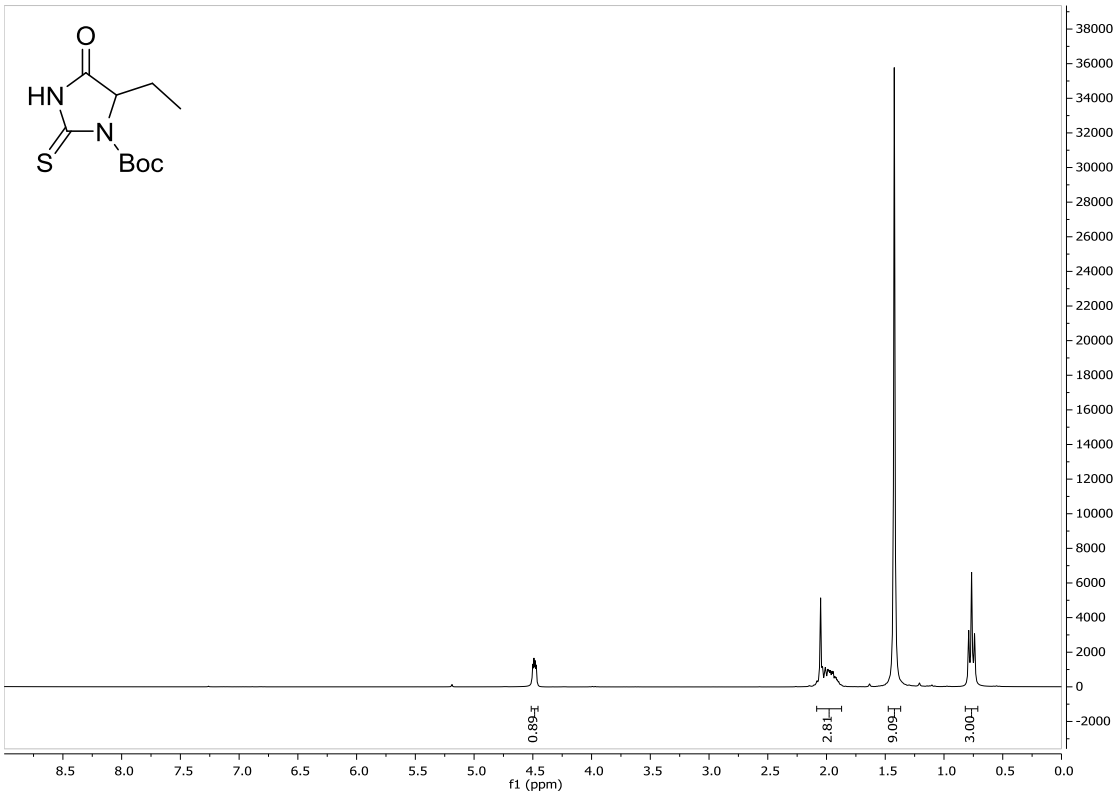


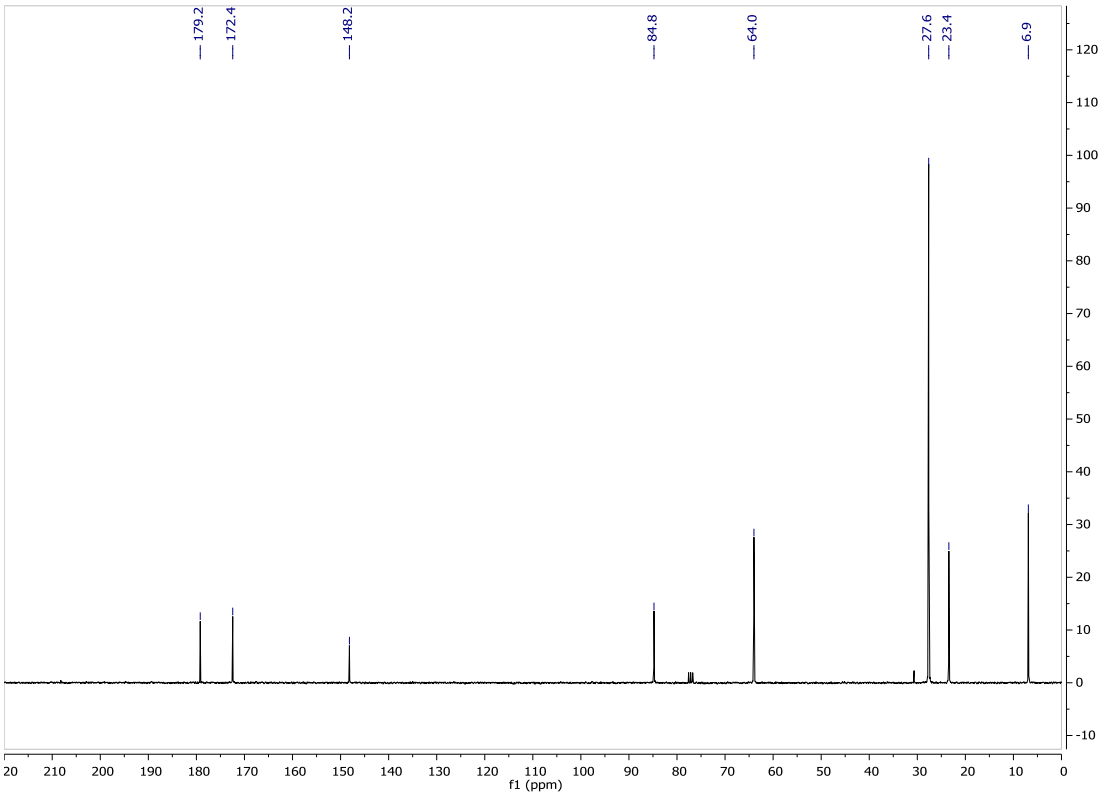
tert-Butyl 5-methyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30A)



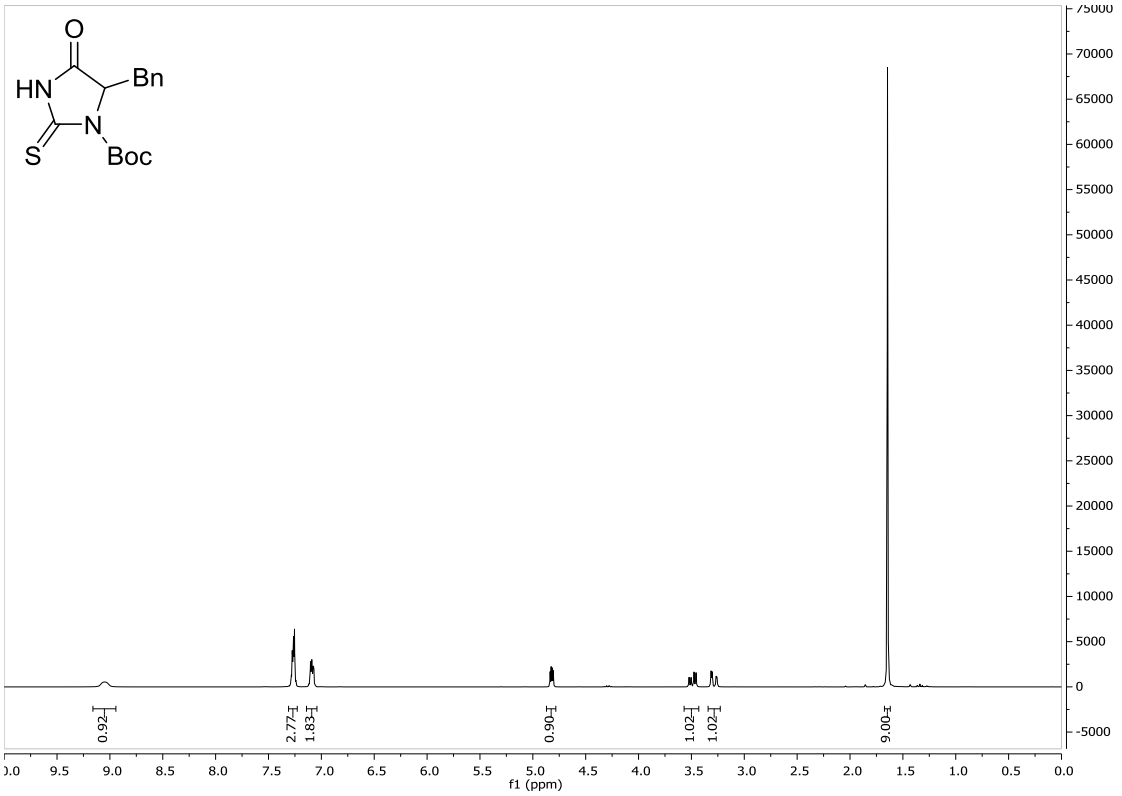


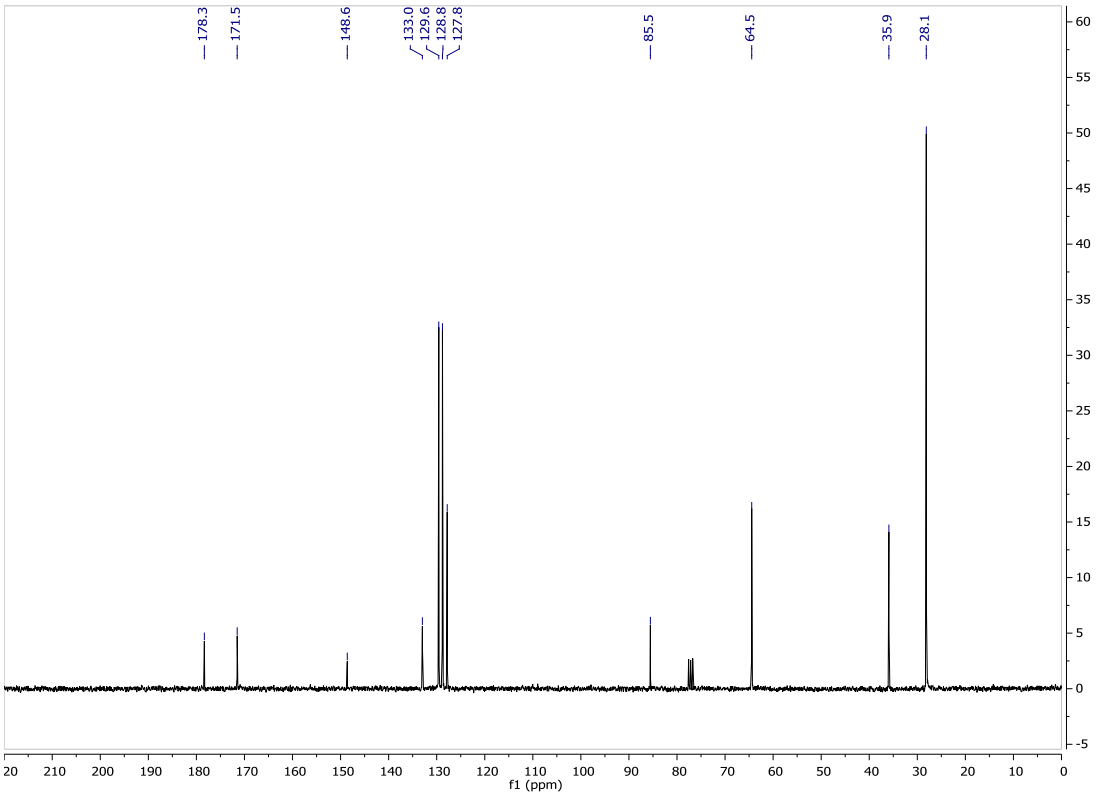
tert-Butyl 5-ethyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30B)



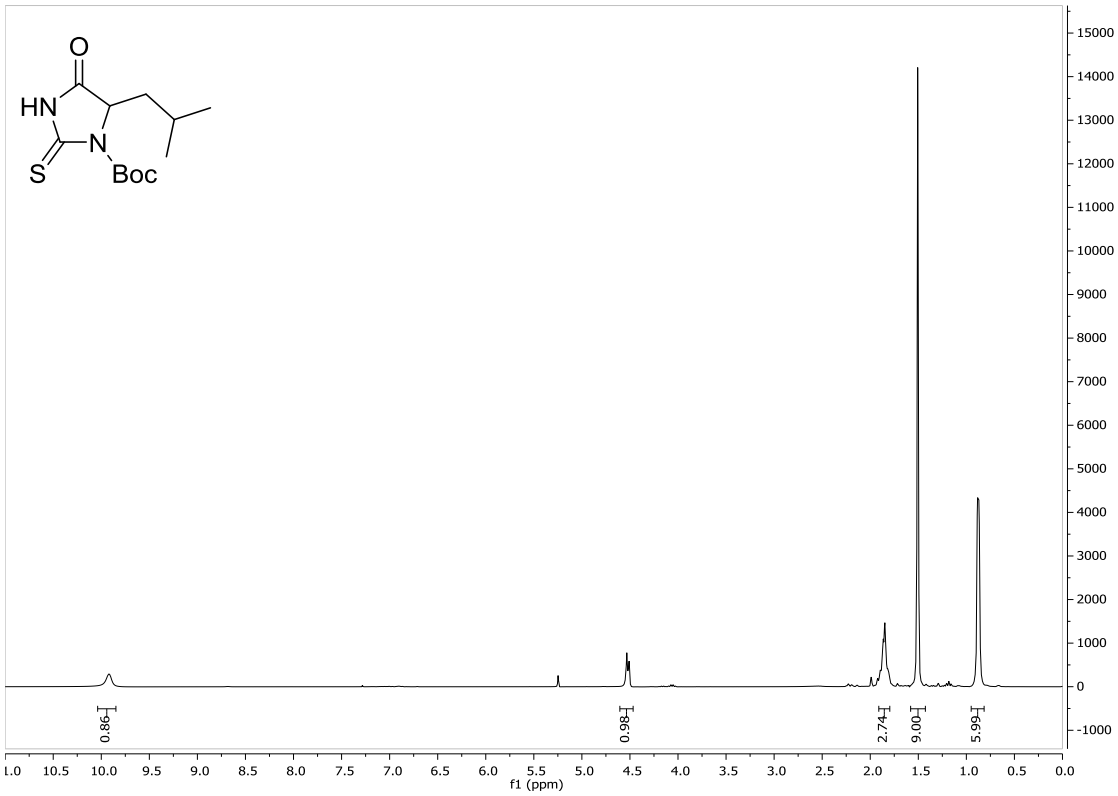


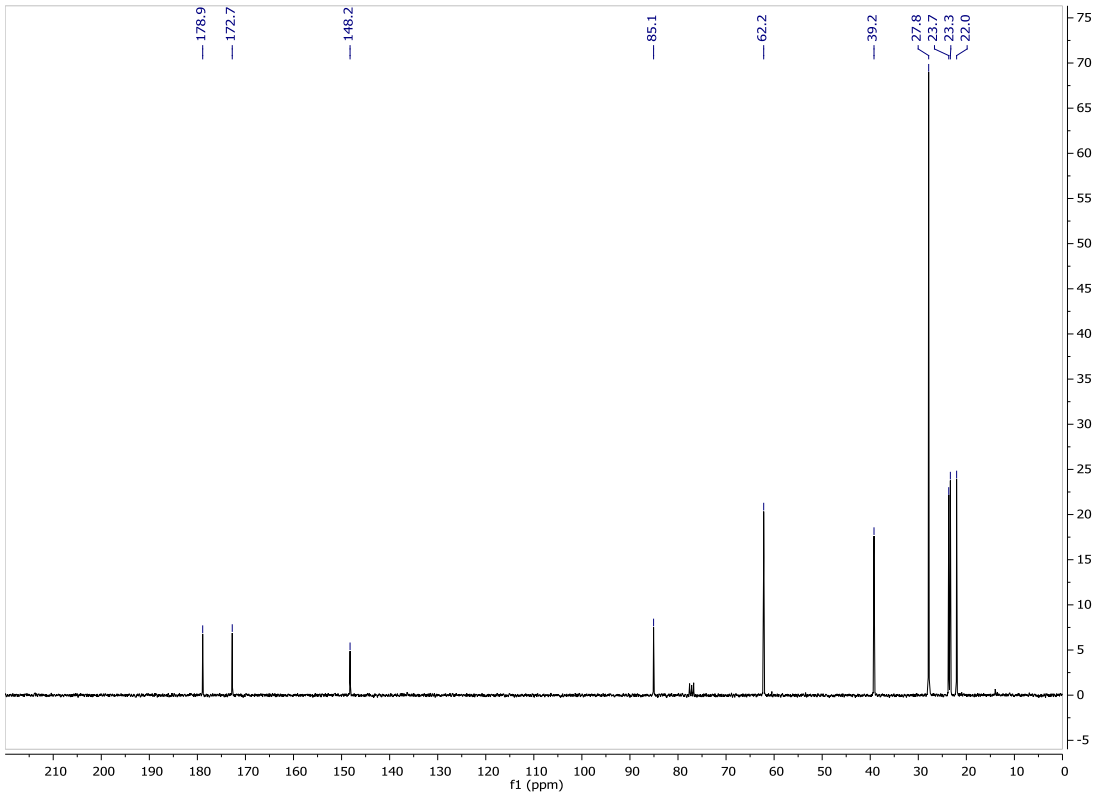
tert-Butyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30C)



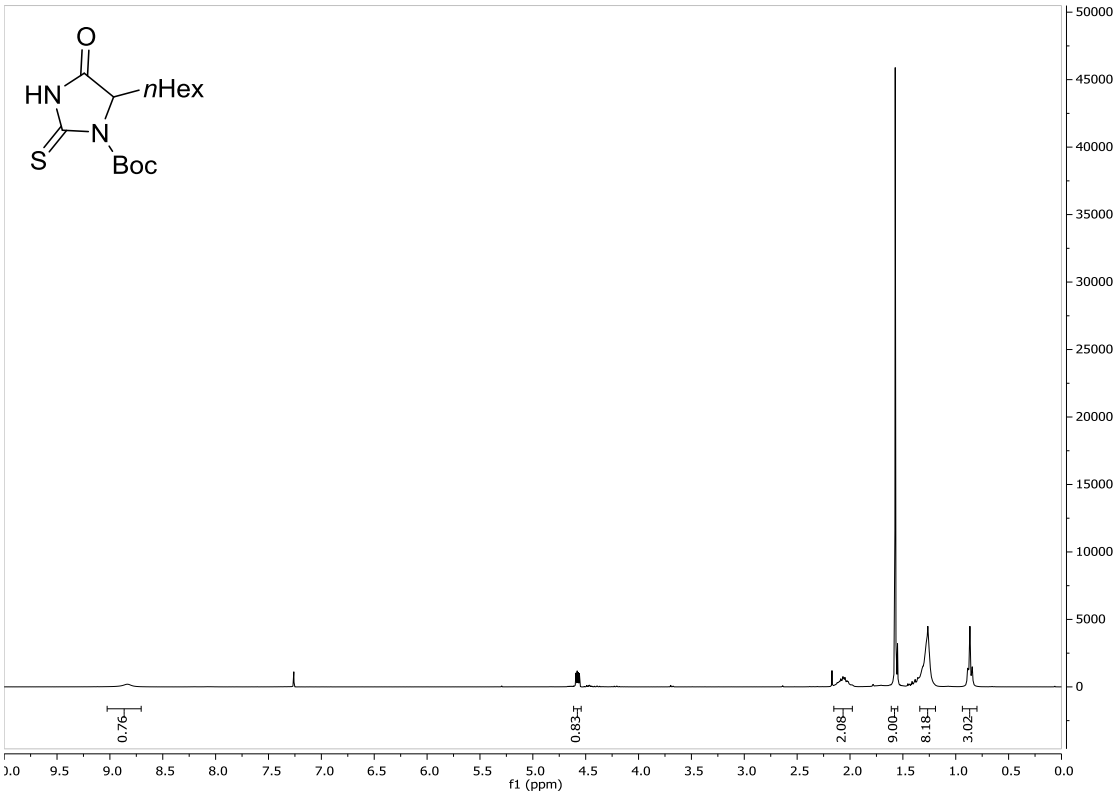


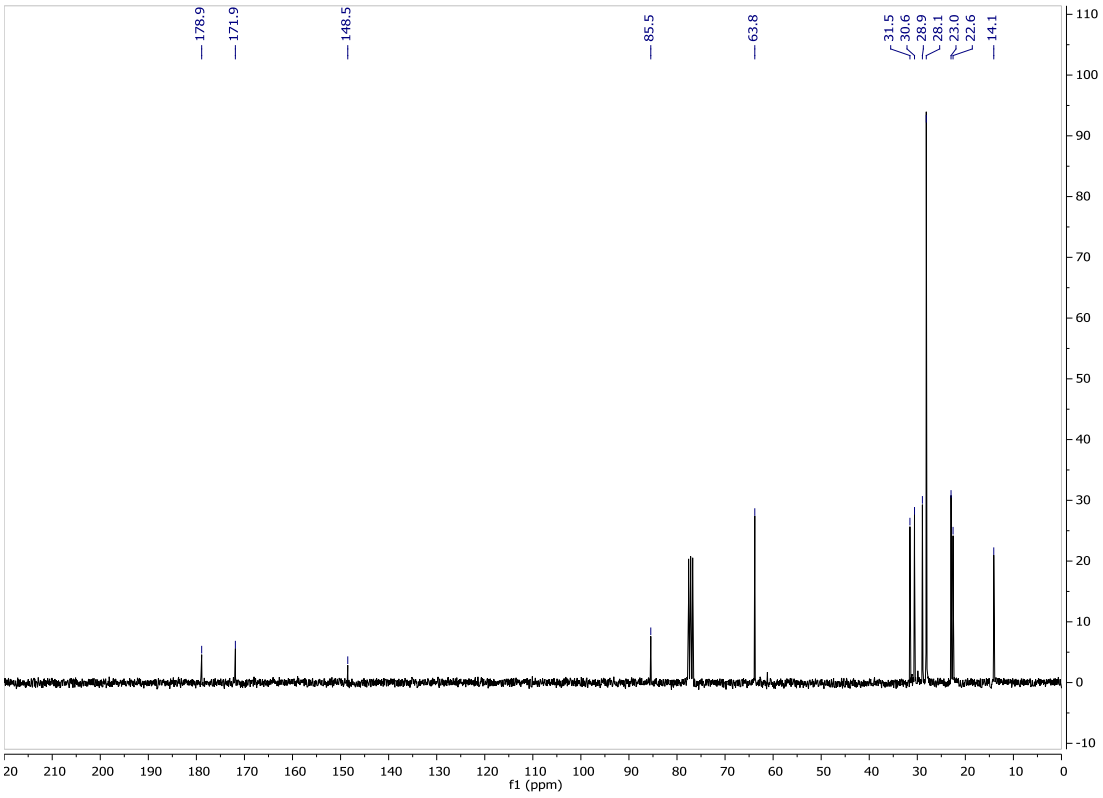
tert-Butyl 5-isobutyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30D)



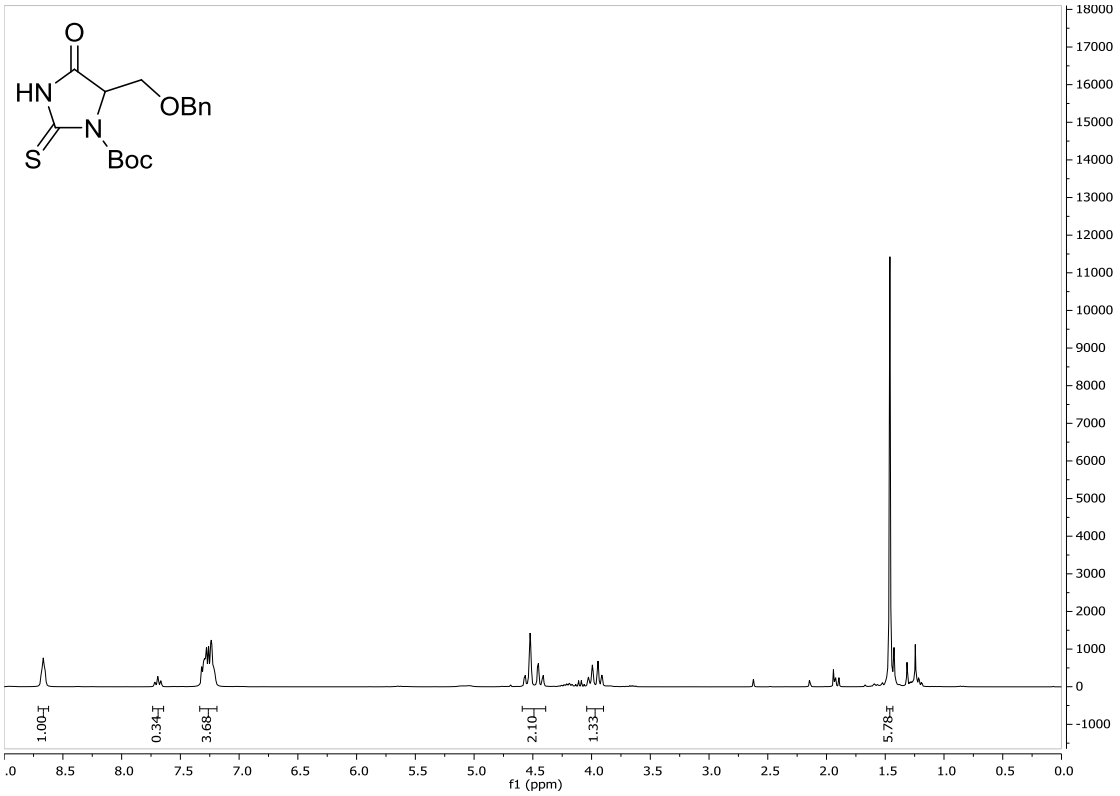


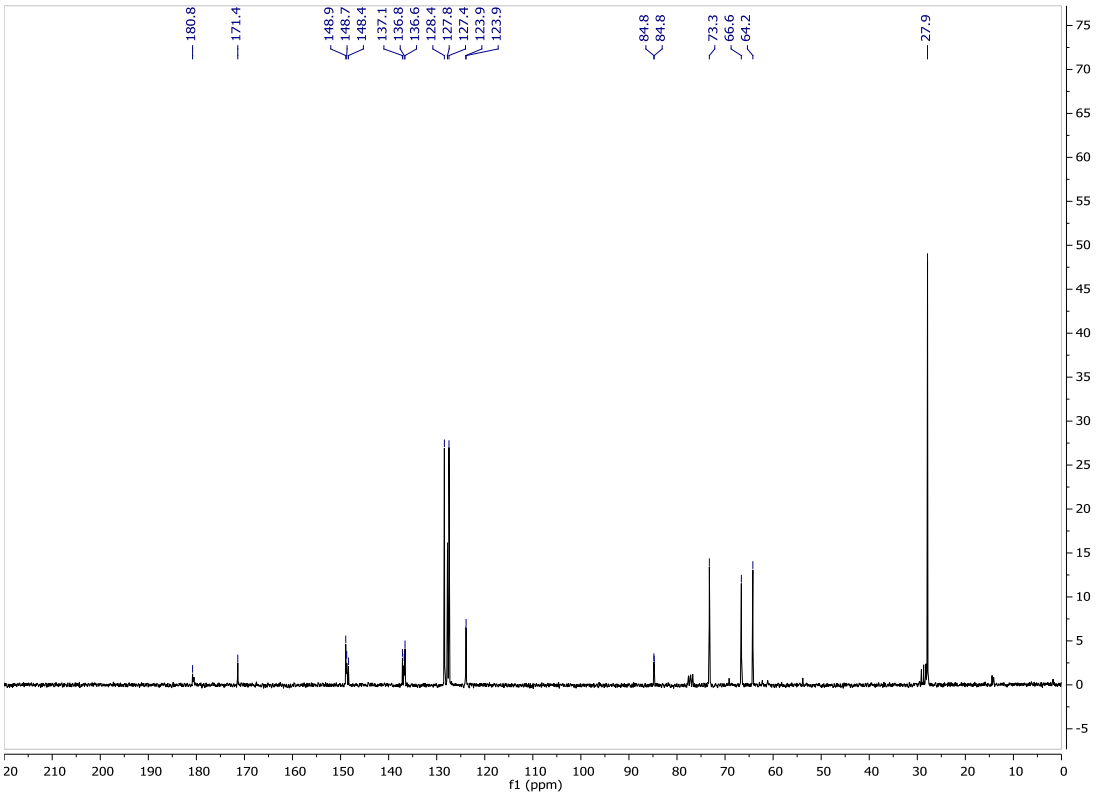
tert-Butyl 5-hexyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (30E)



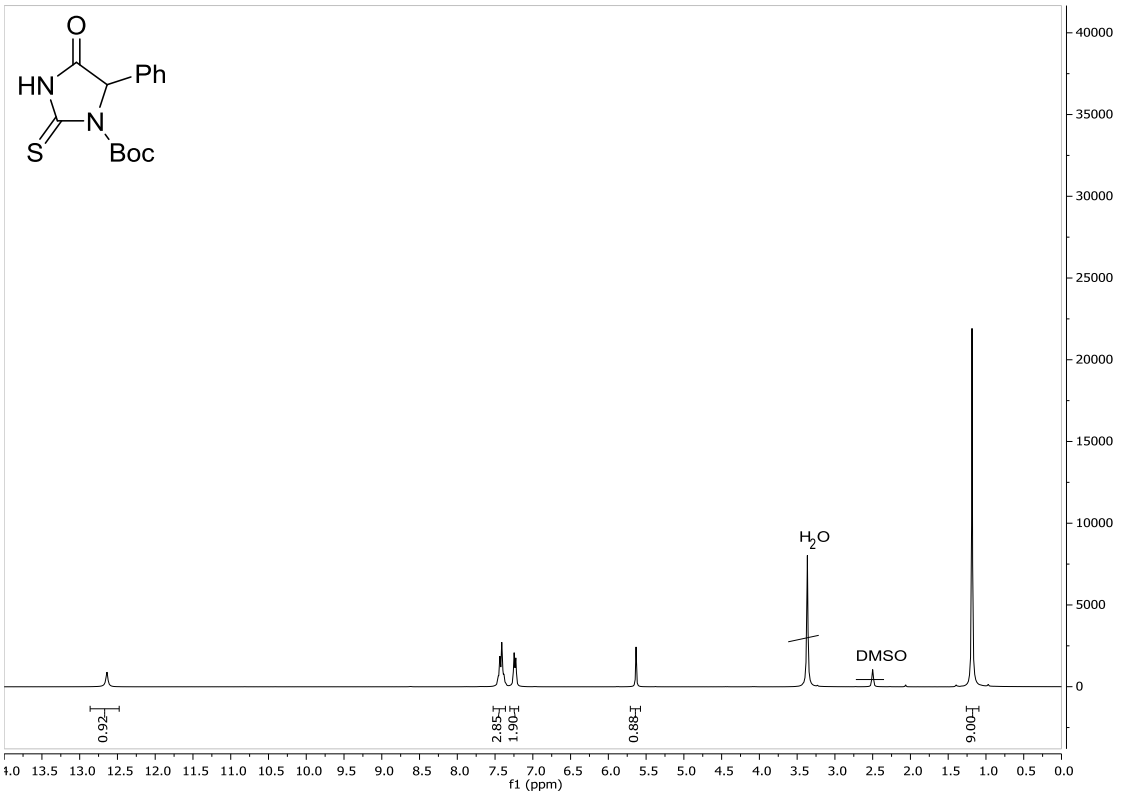


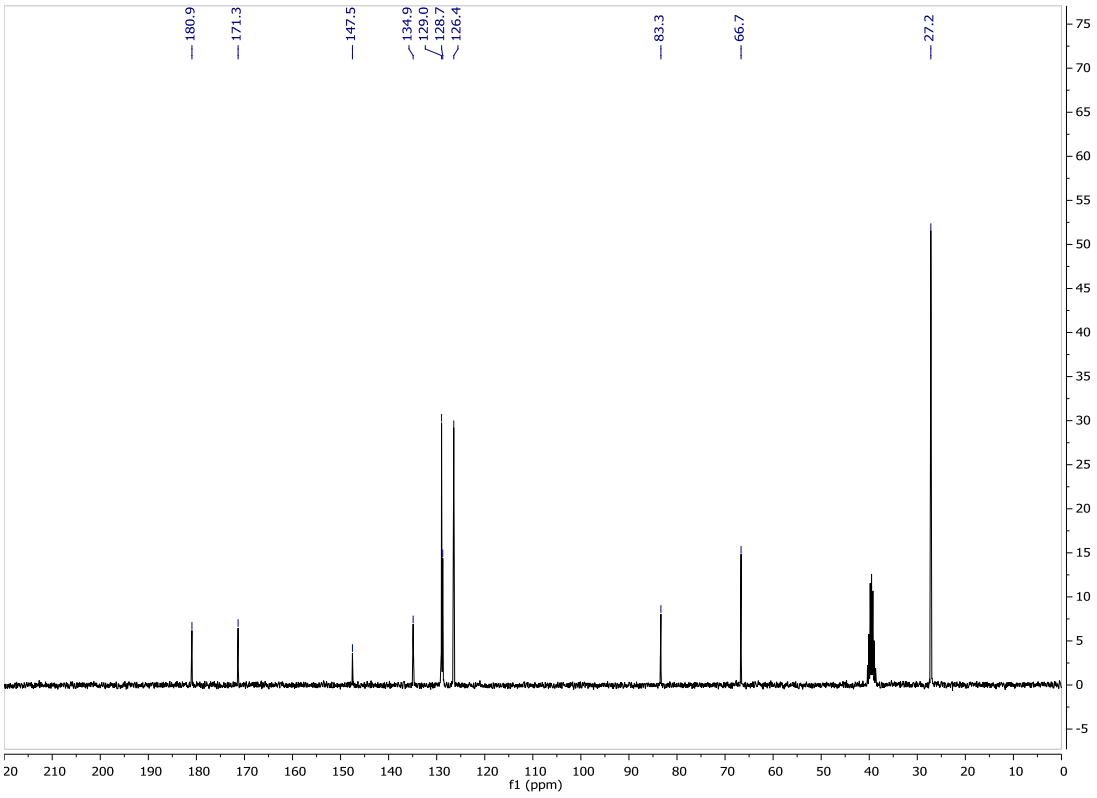
tert-Butyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (30G)



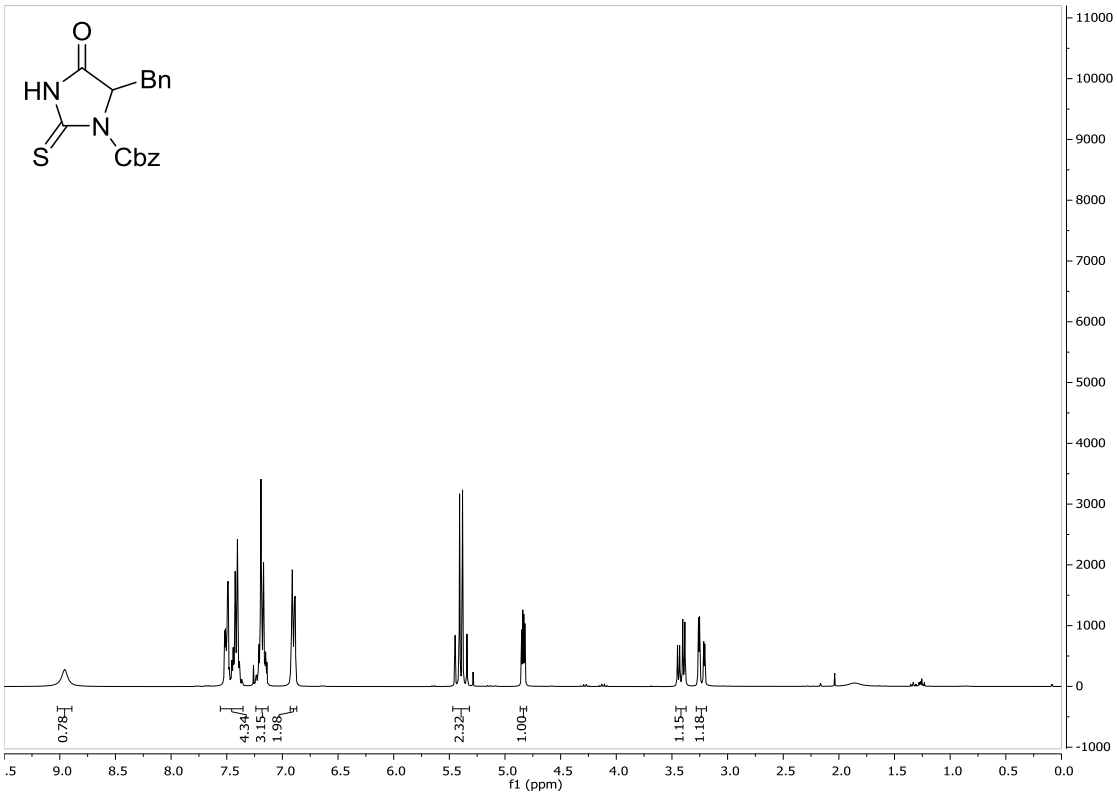


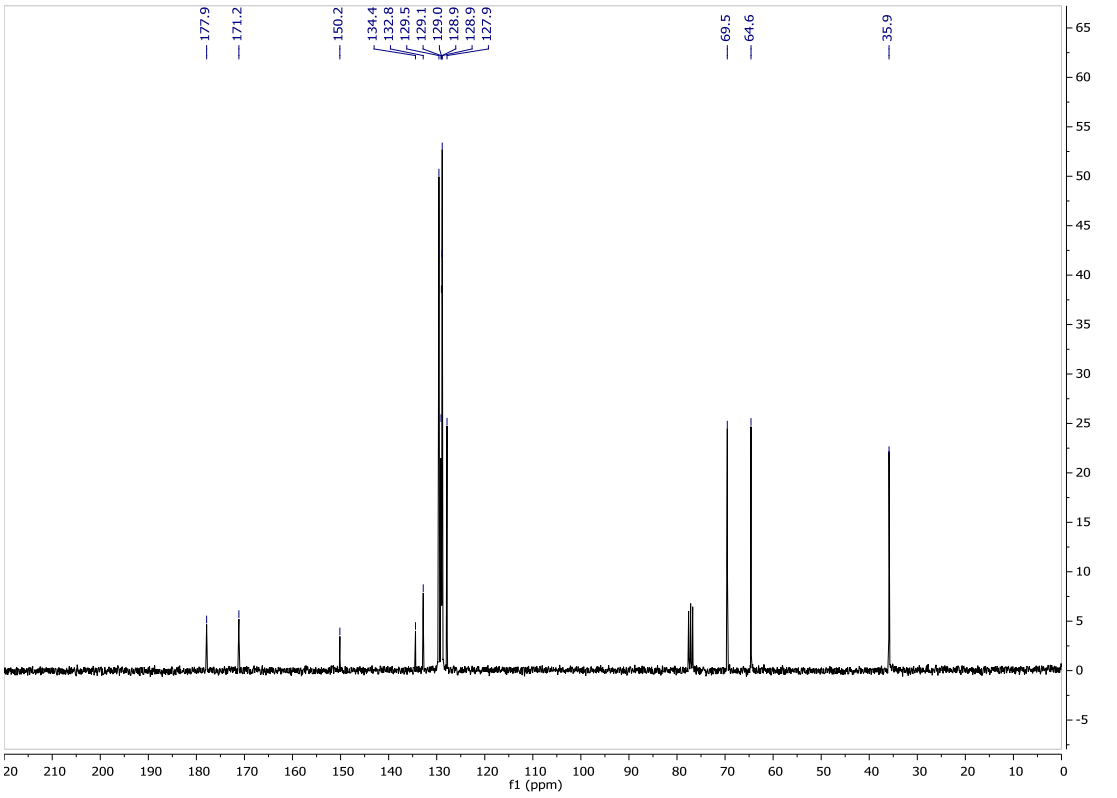
tert-Butyl 4-oxo-5-phenyl-2-thioxoimidazolidine-1-carboxylate (30H)



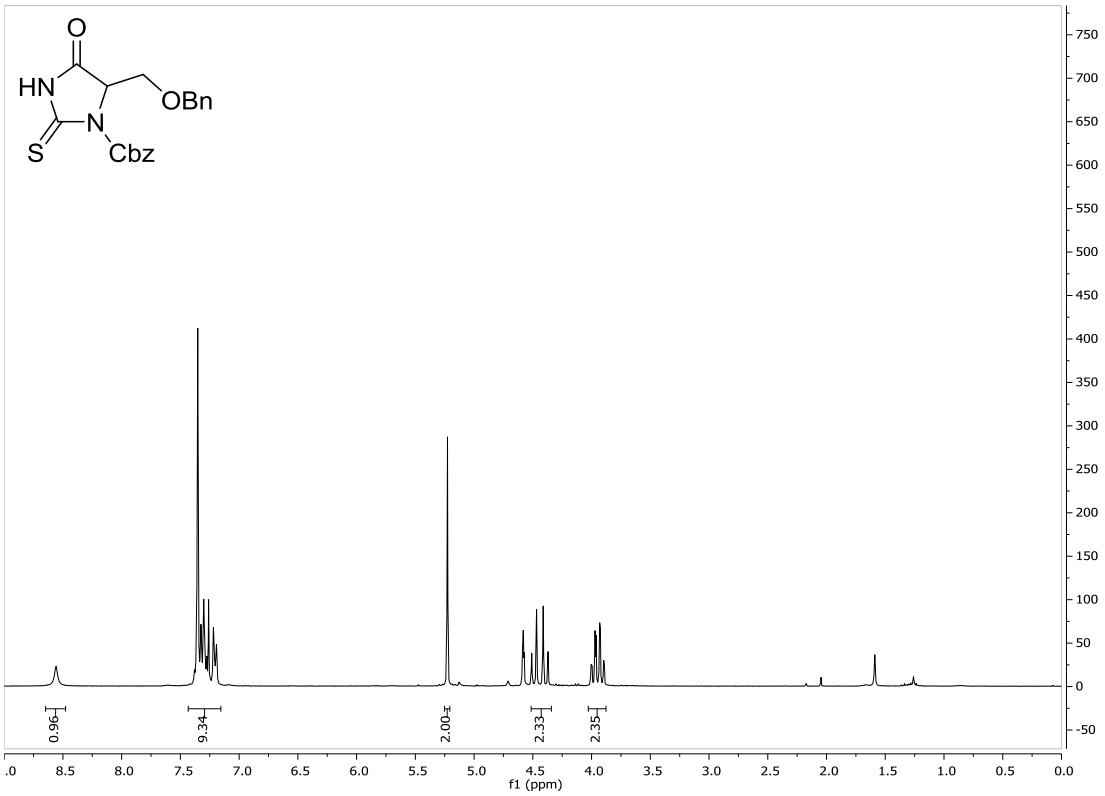


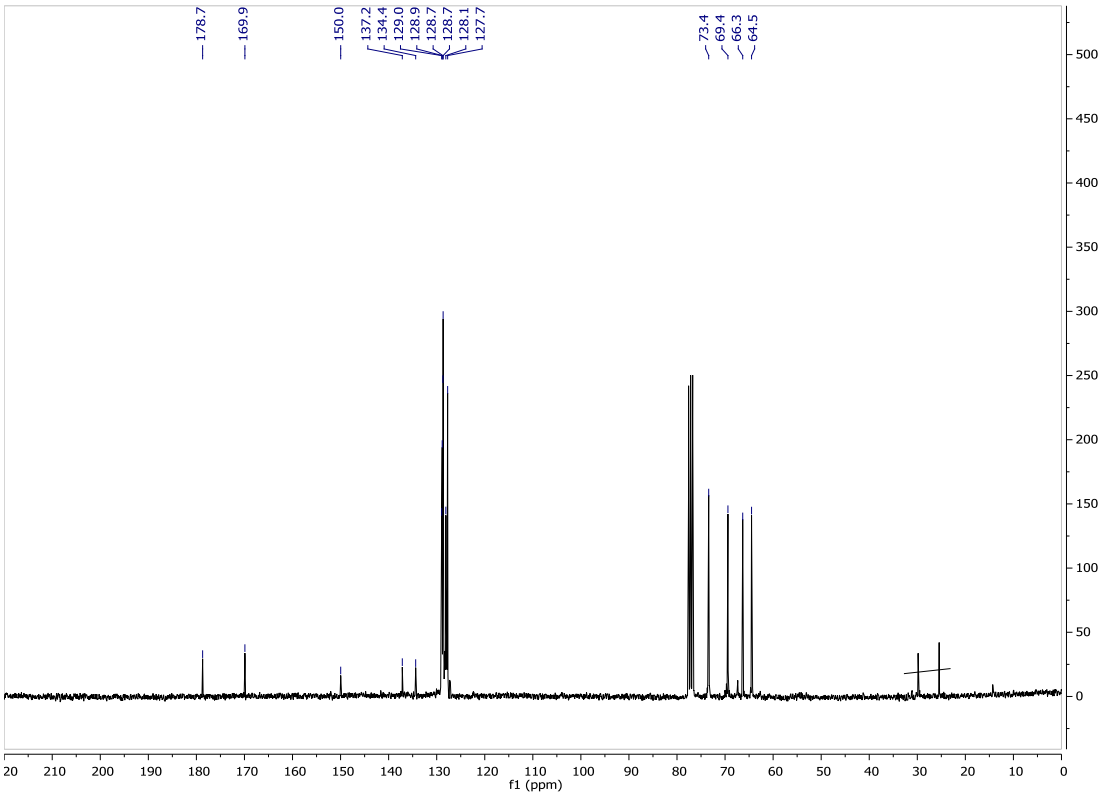
Benzyl 5-benzyl-4-oxo-2-thioxoimidazolidine-1-carboxylate (31C)



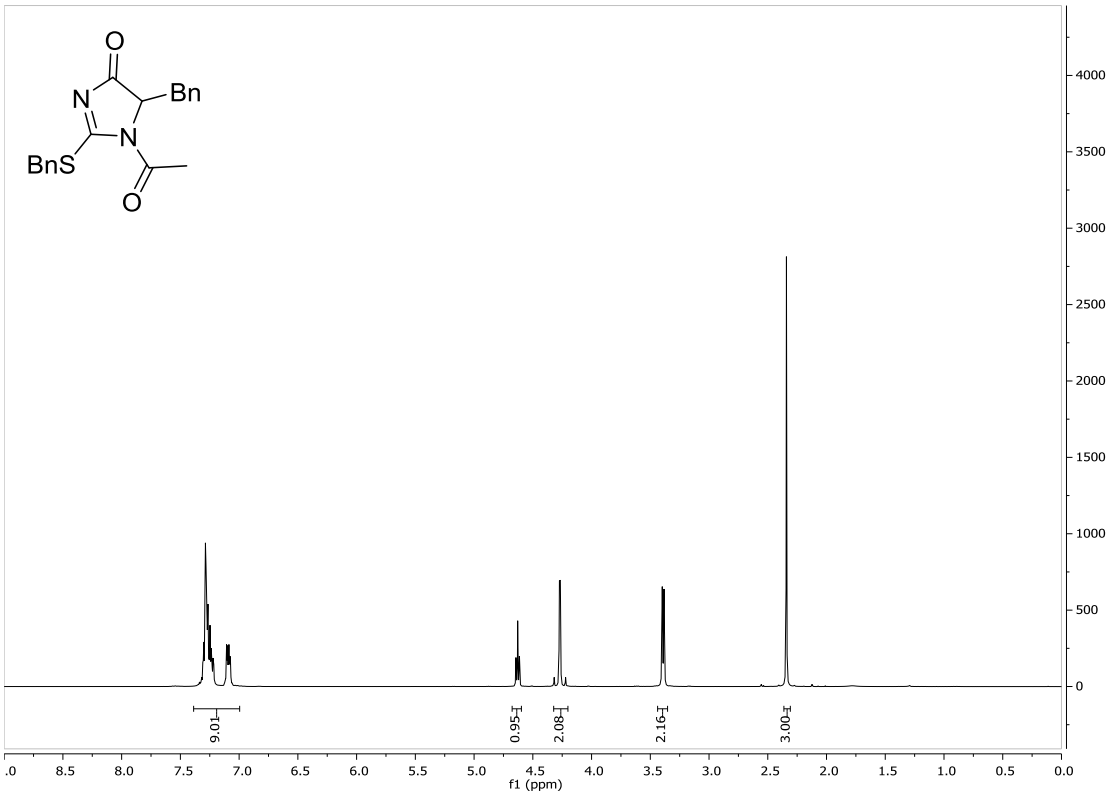


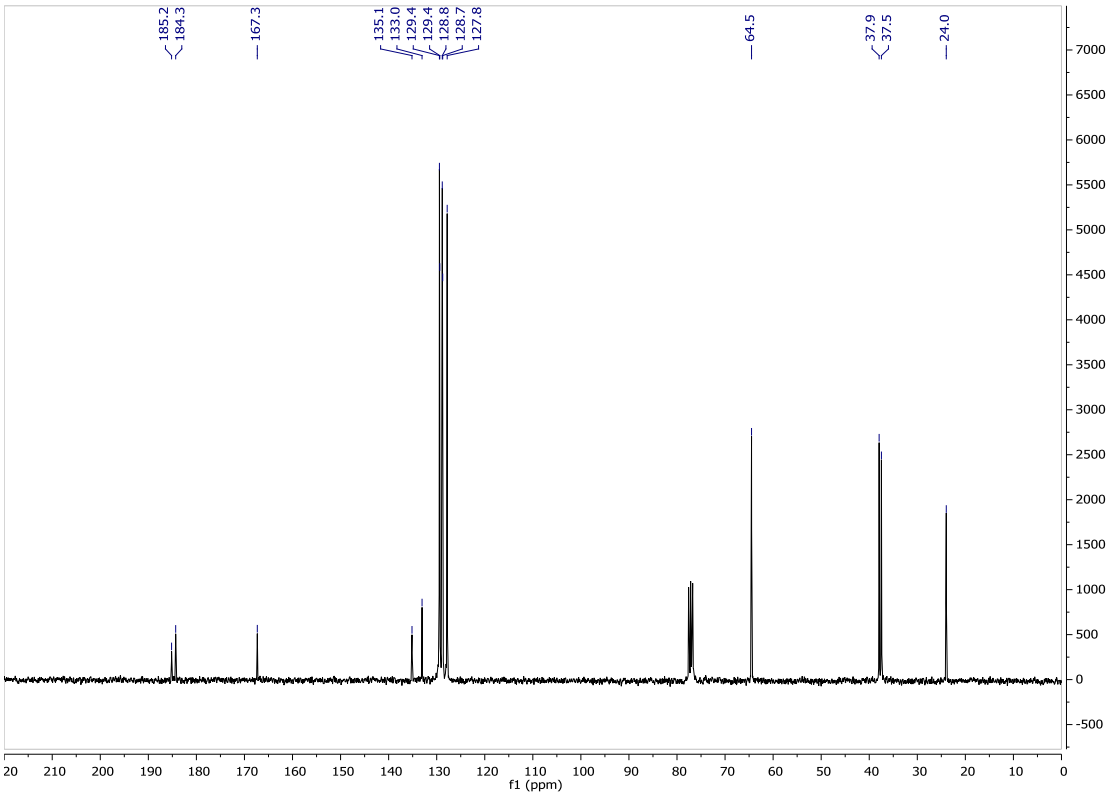
Benzyl 5-((benzyloxy)methyl)-4-oxo-2-thioxoimidazolidine-1-carboxylate (31G)



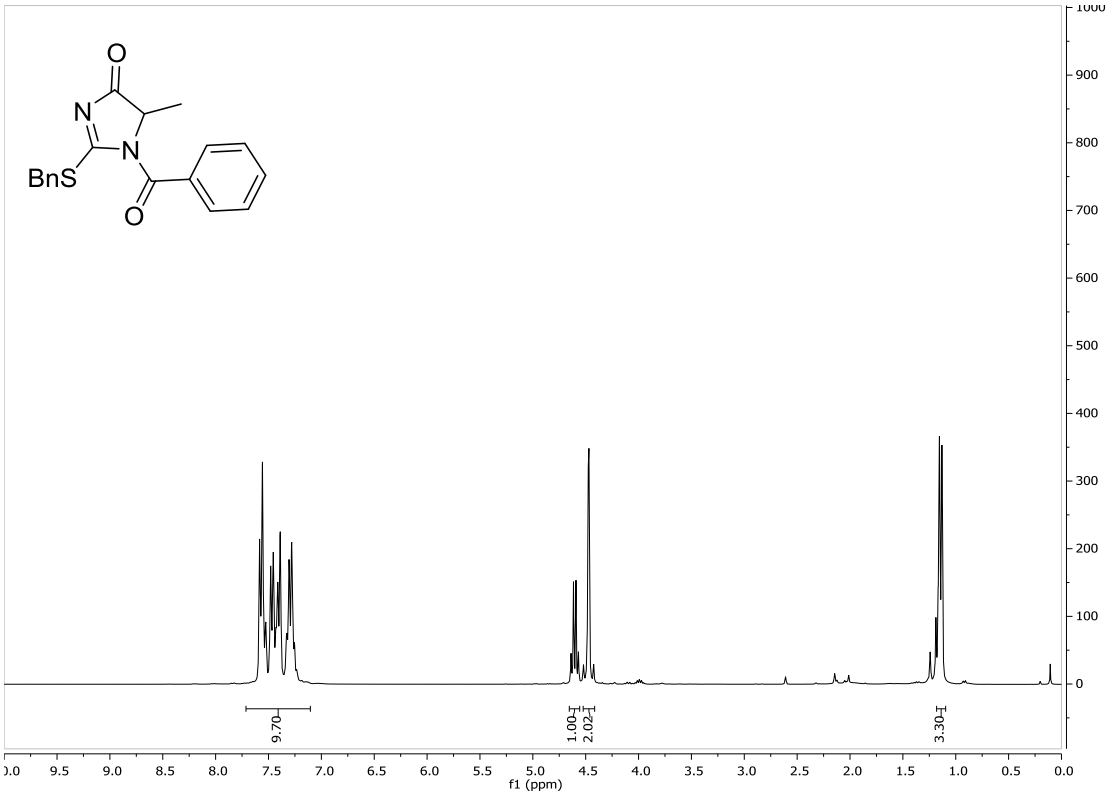


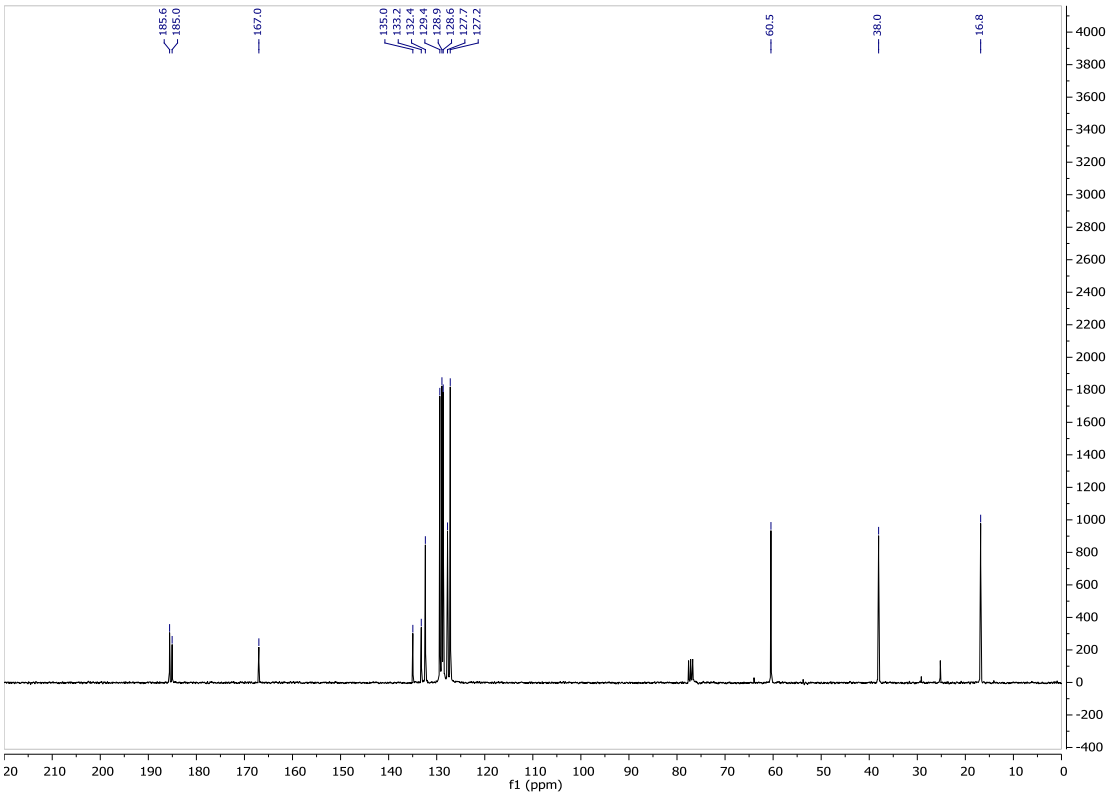
1-Acetyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (32C)



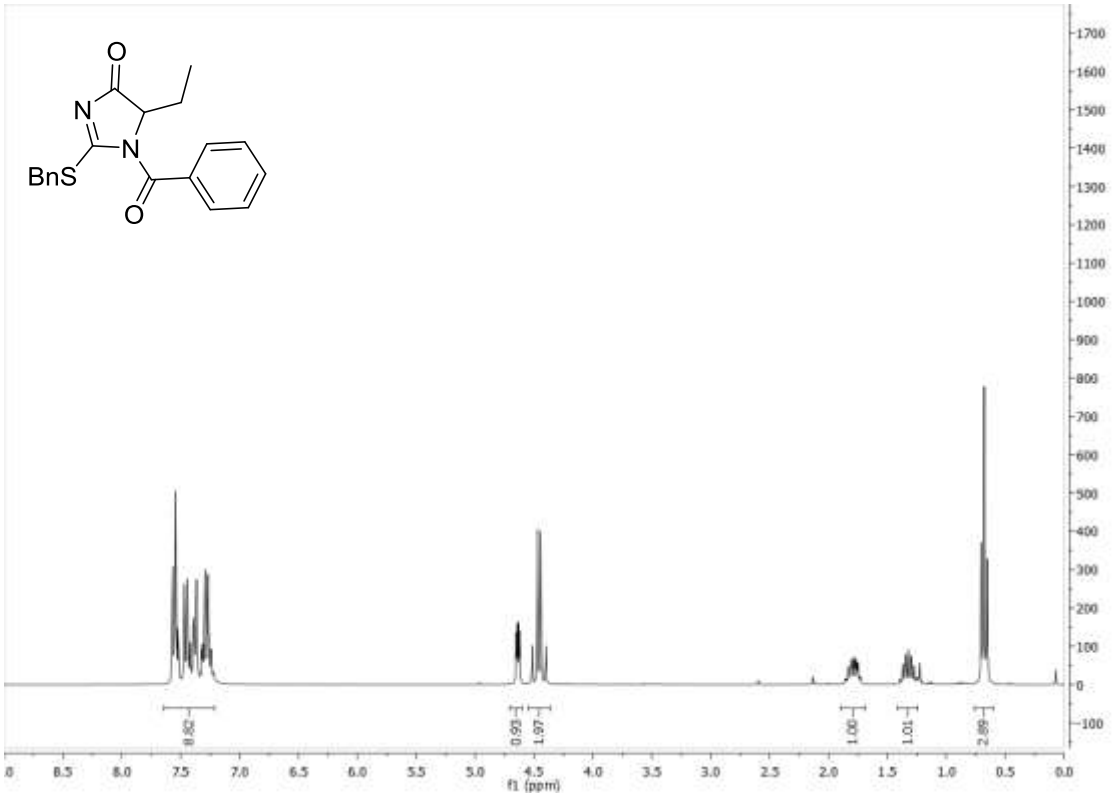


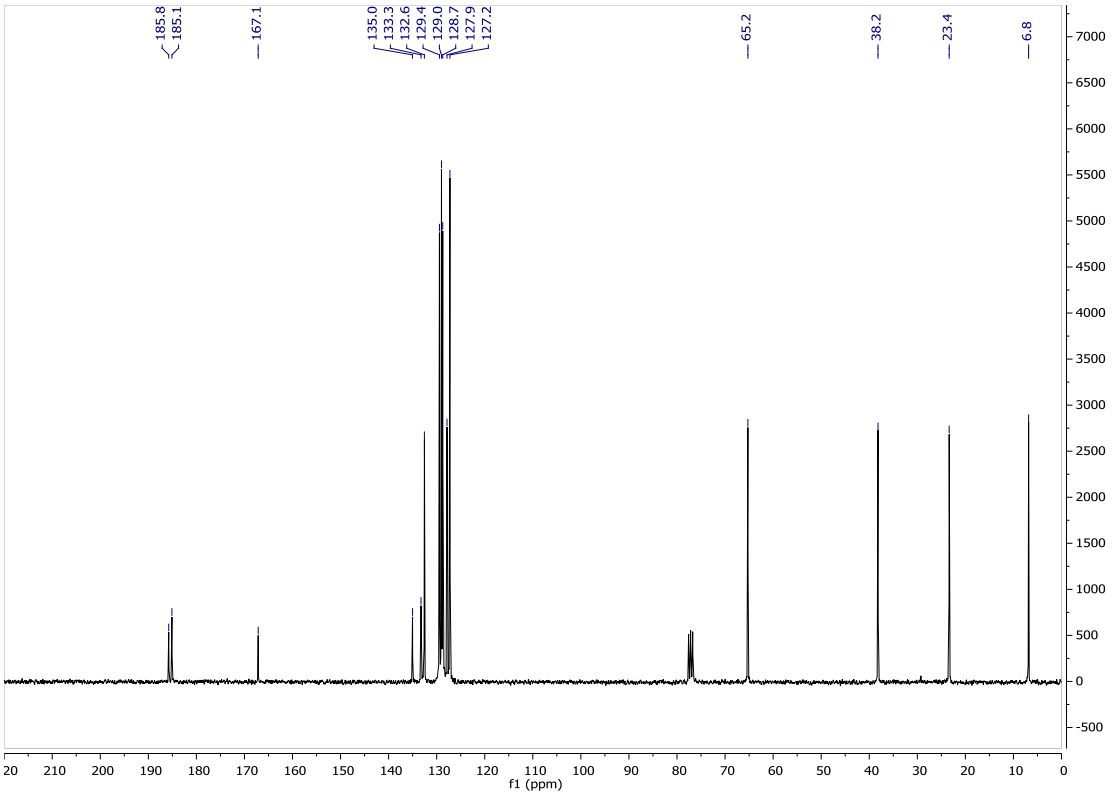
1-Benzoyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (33A)



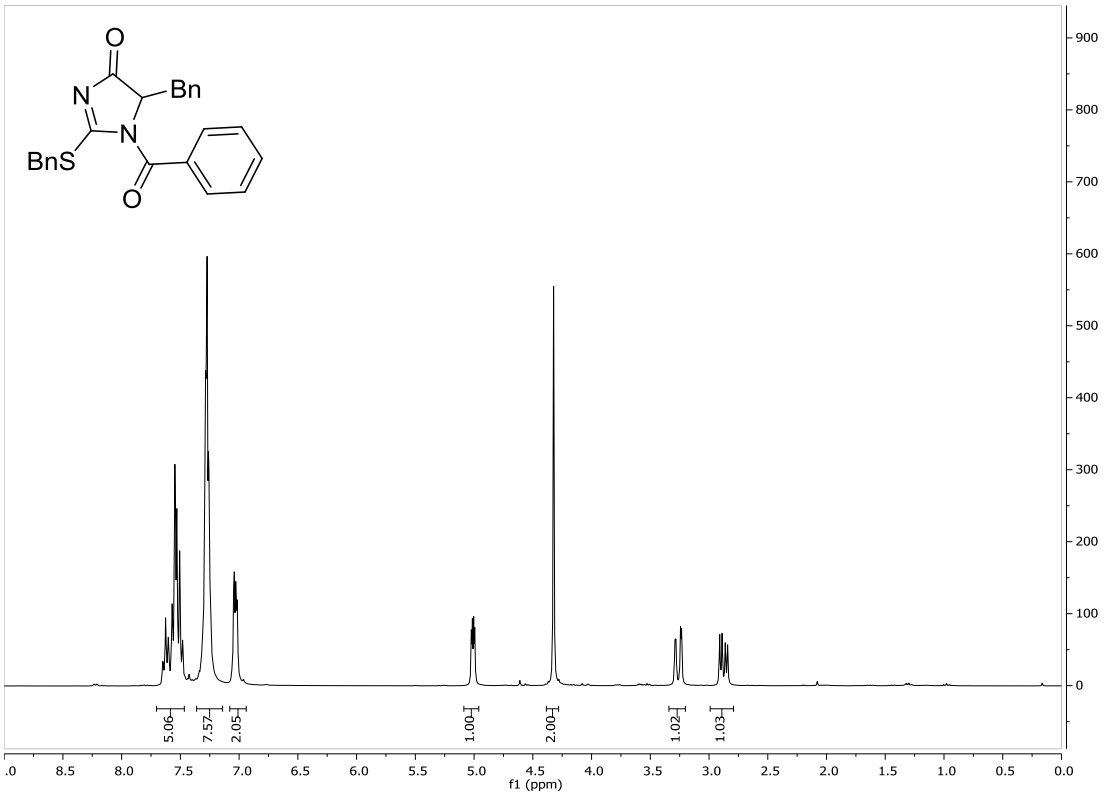


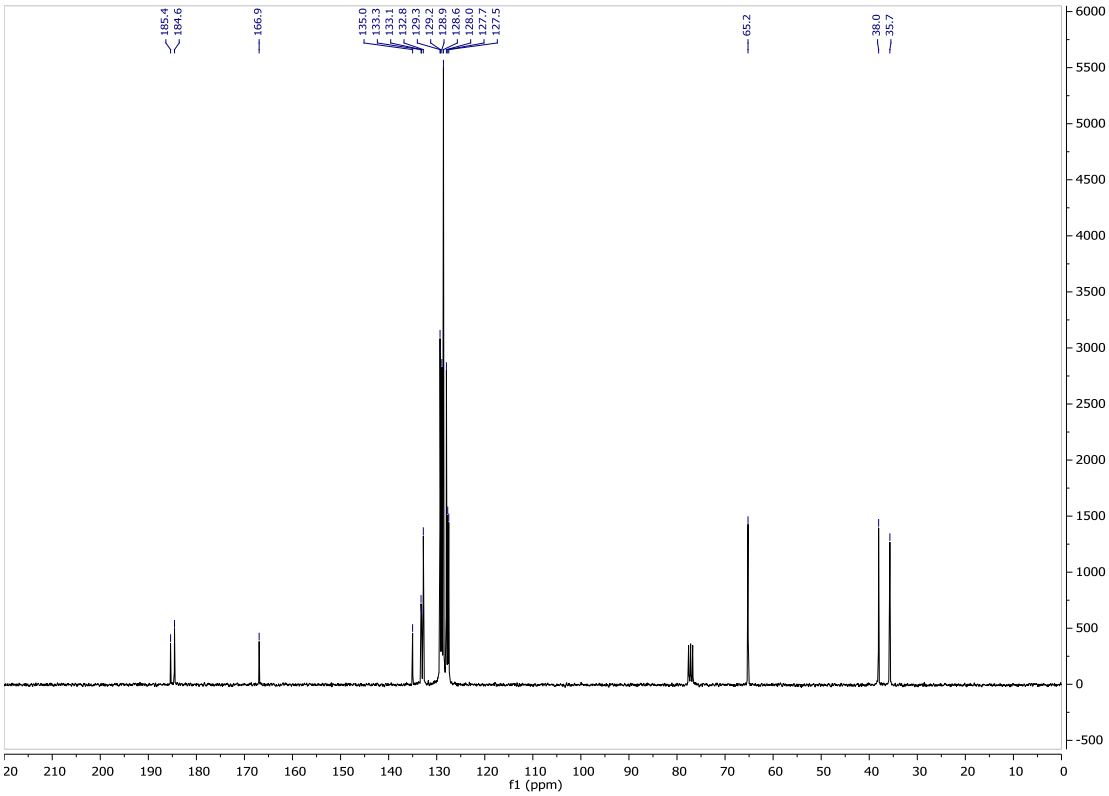
1-Benzoyl-2-(benzylthio)-5-ethyl-1*H*-imidazol-4(5*H*)-one (33B)



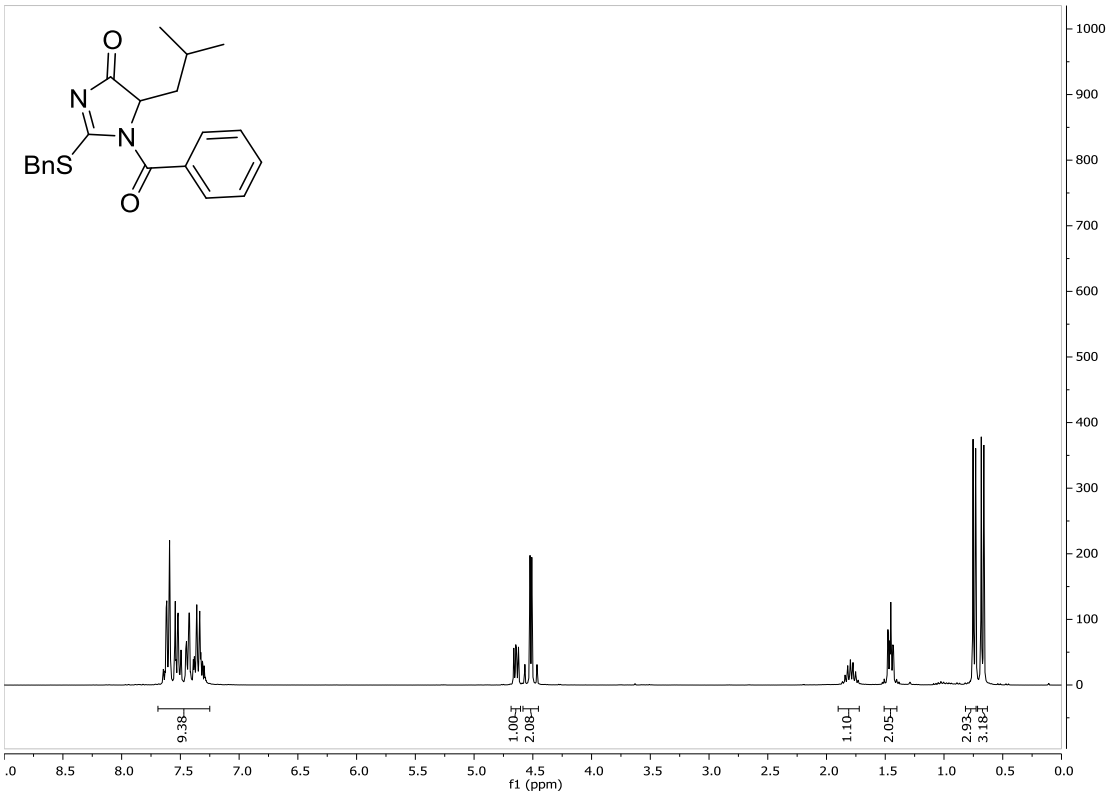


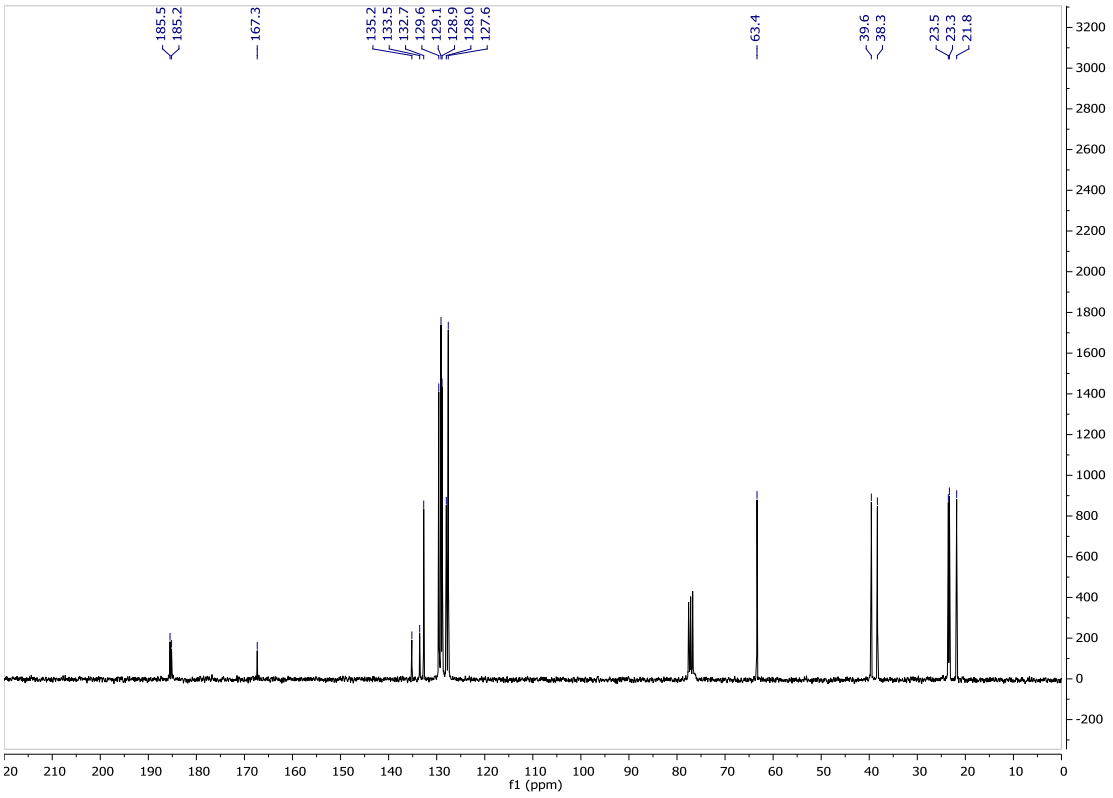
1-Benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (33C)



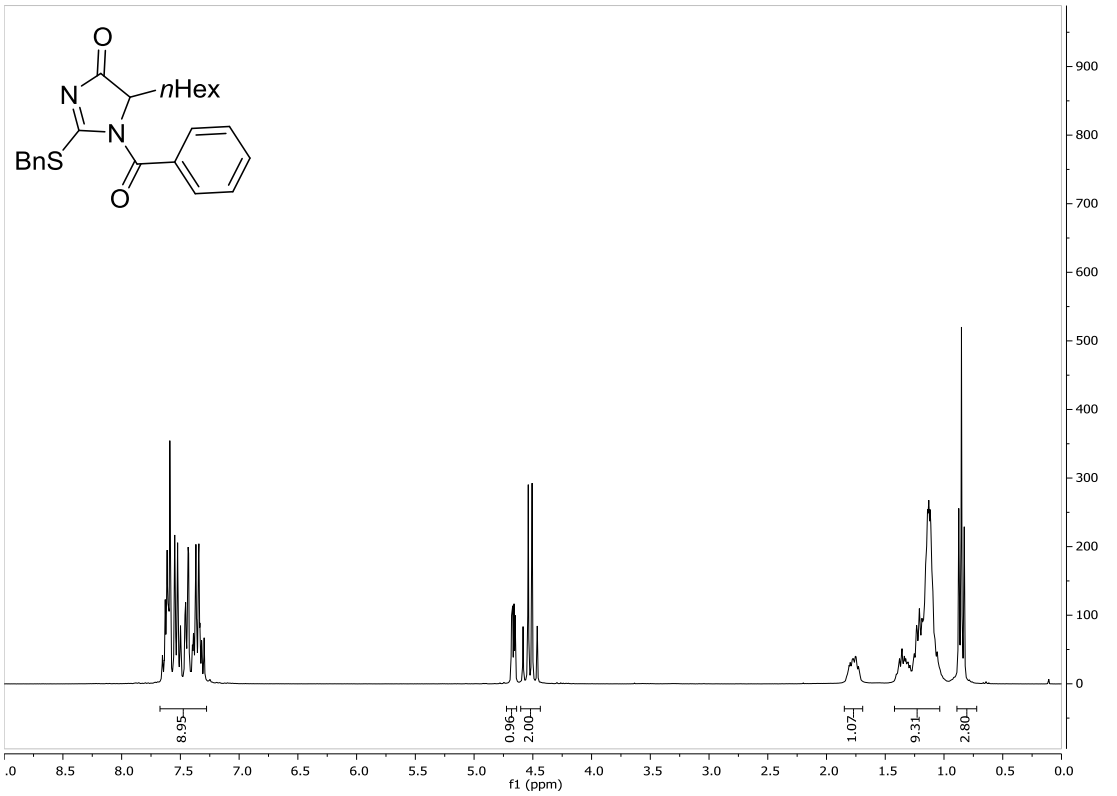


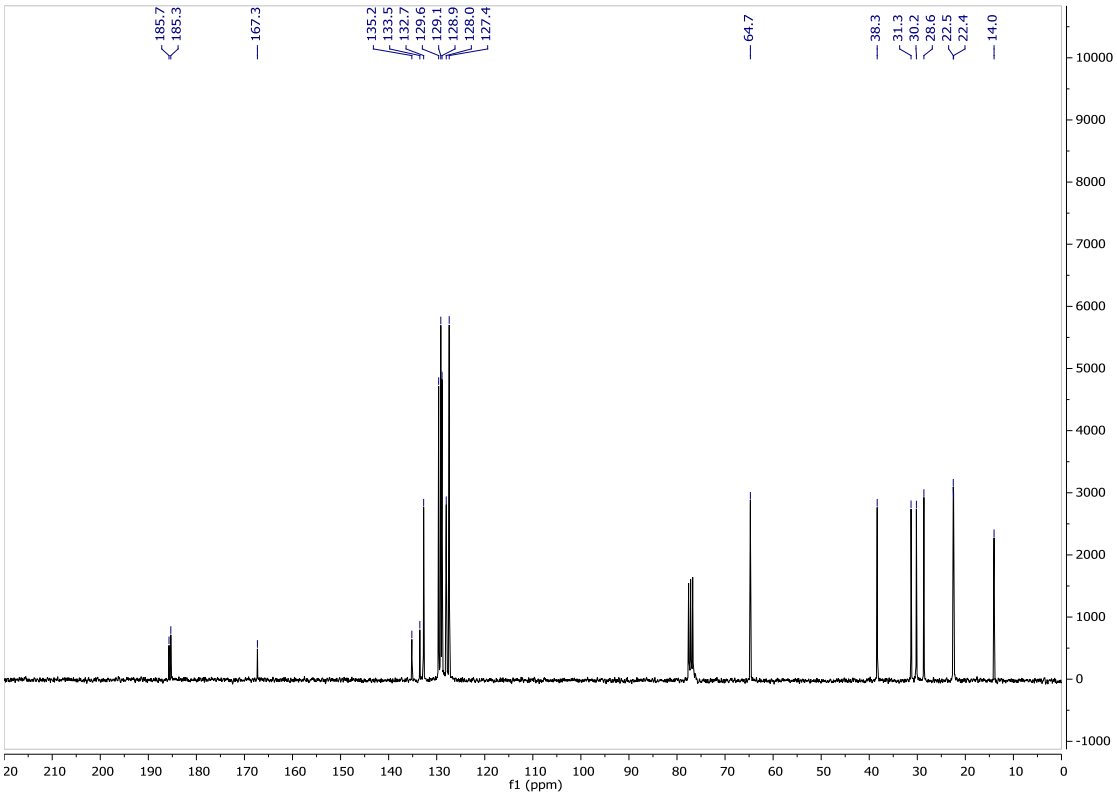
1-Benzoyl-2-(benzylthio)-5-isobutyl-1*H*-imidazol-4(5*H*)-one (33D)



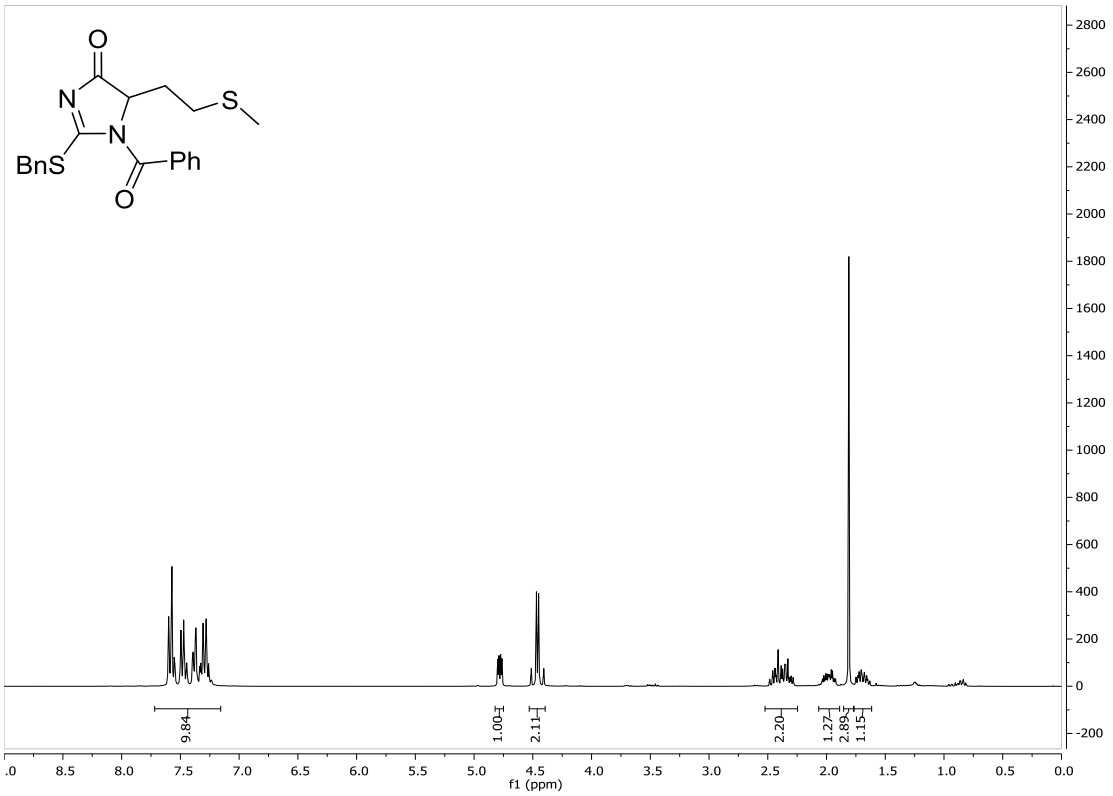


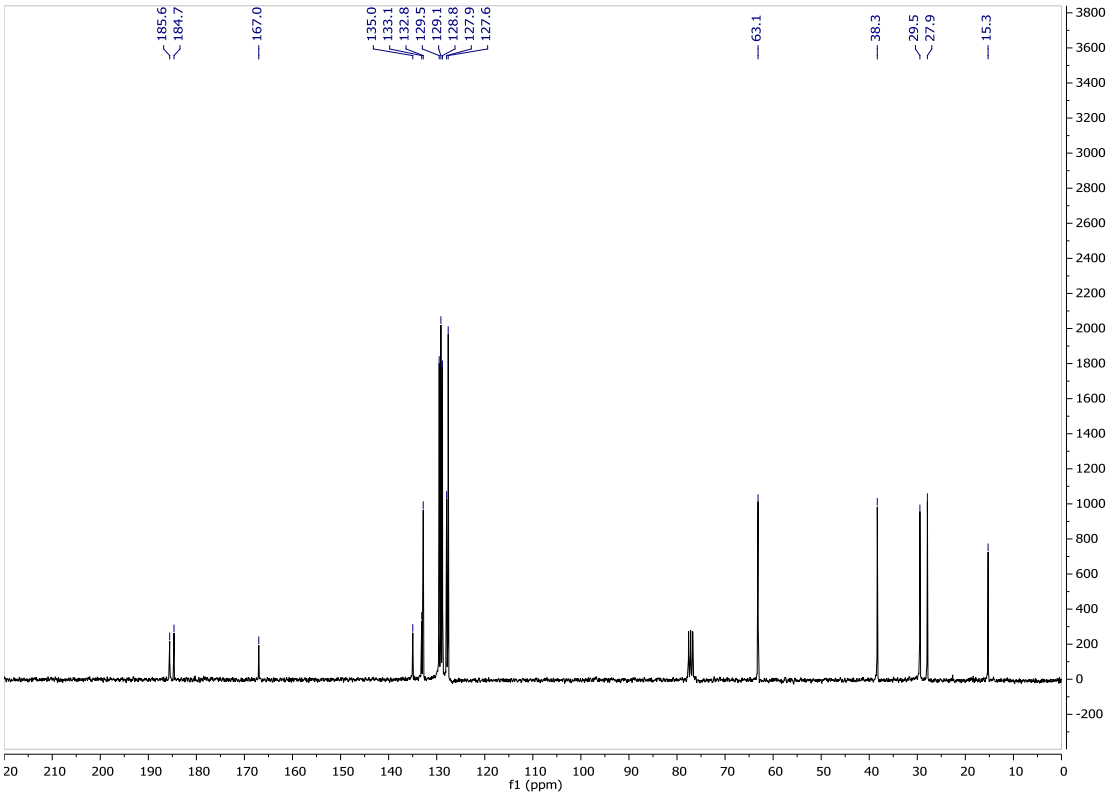
1-Benzoyl-2-(benzylthio)-5-hexyl-1*H*-imidazol-4(5*H*)-one (33E)



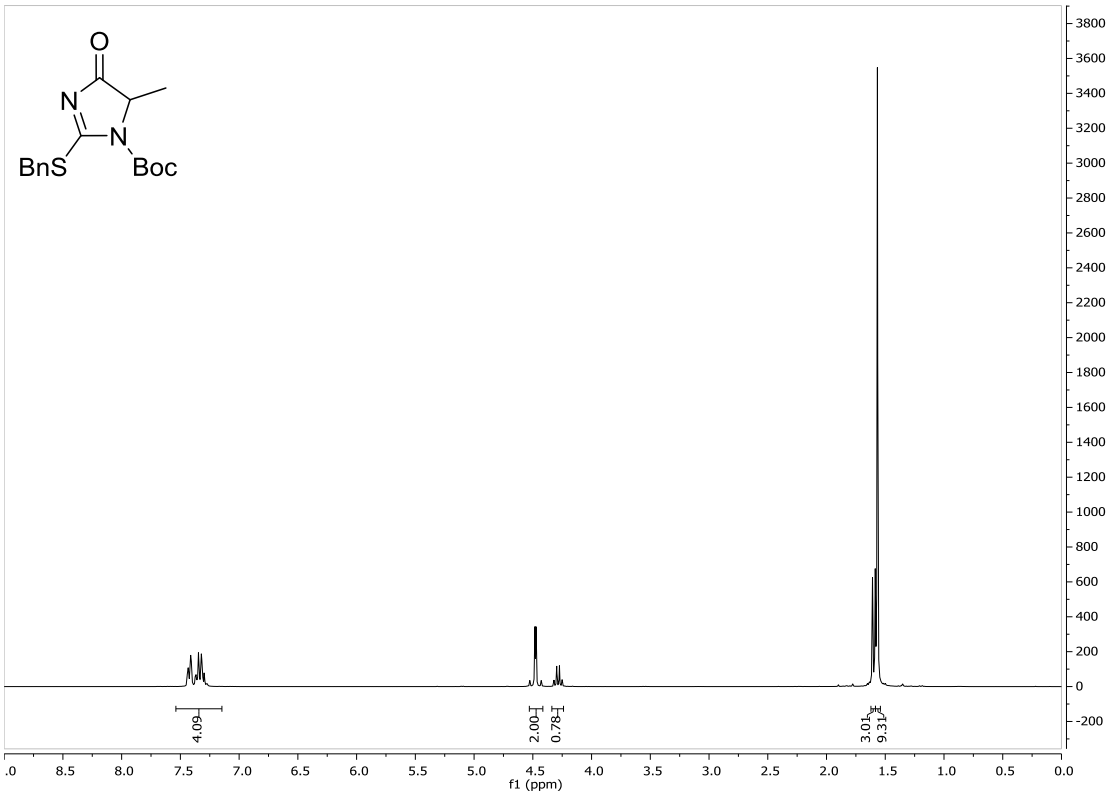


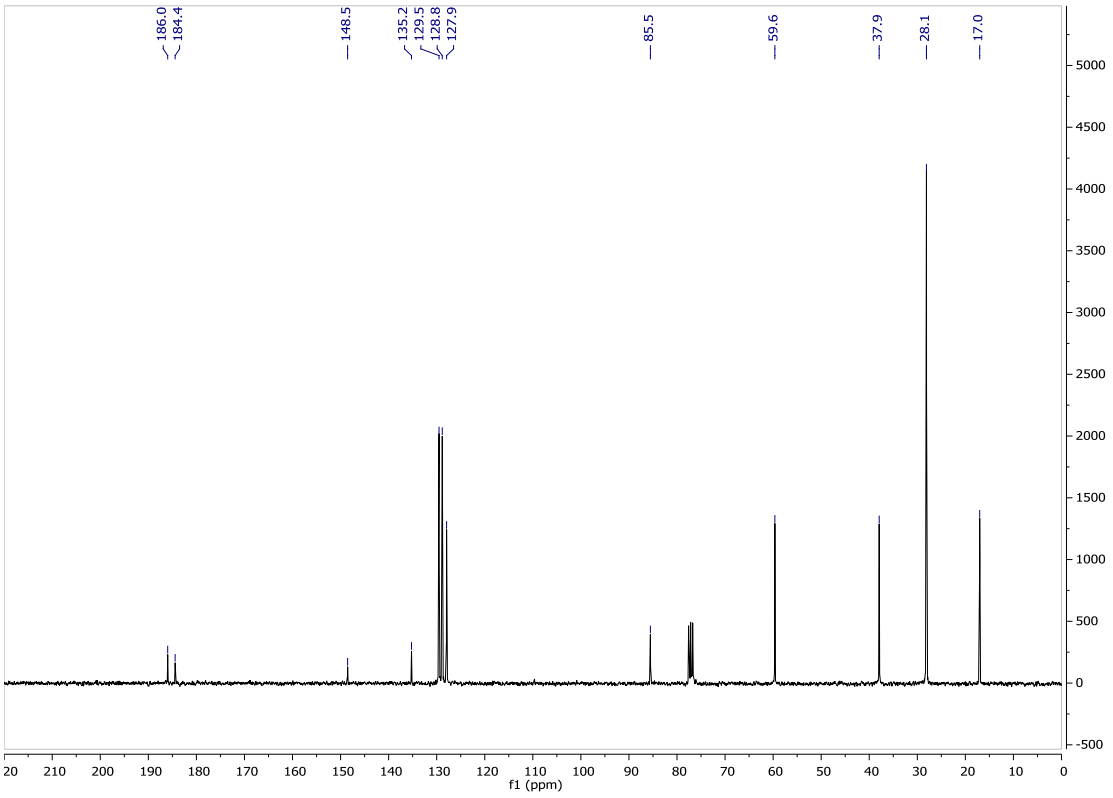
1-Benzoyl-5-benzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (33F)



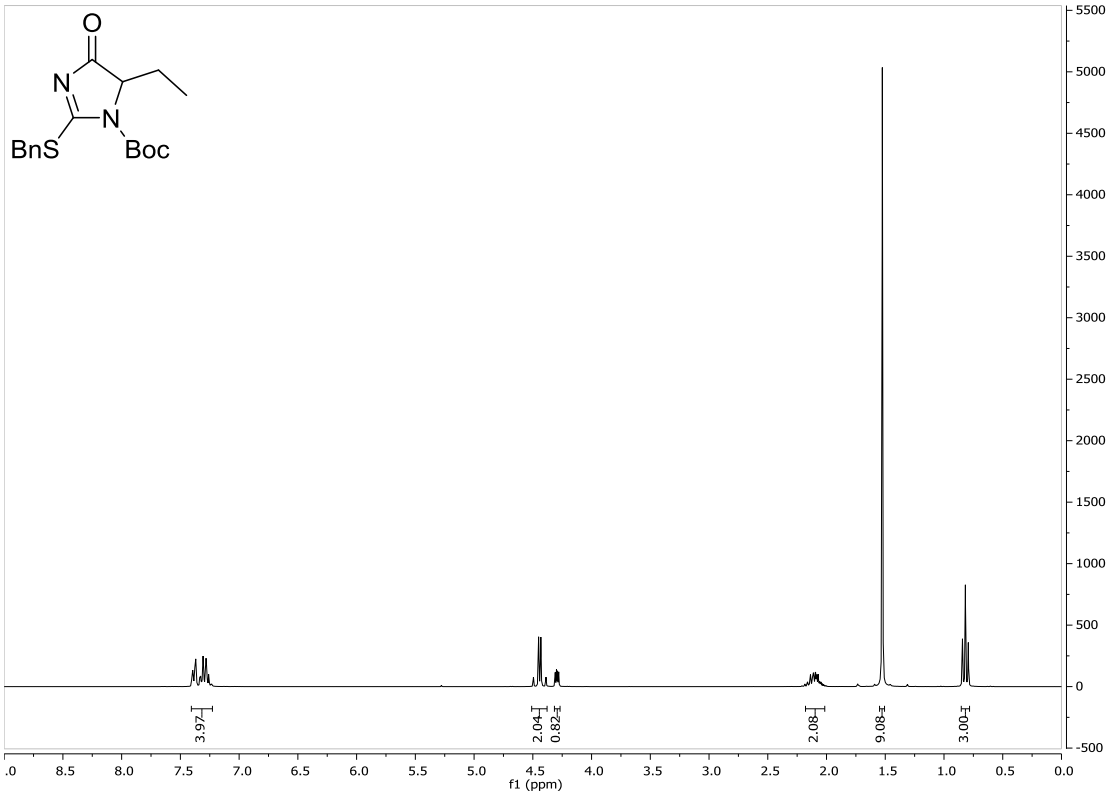


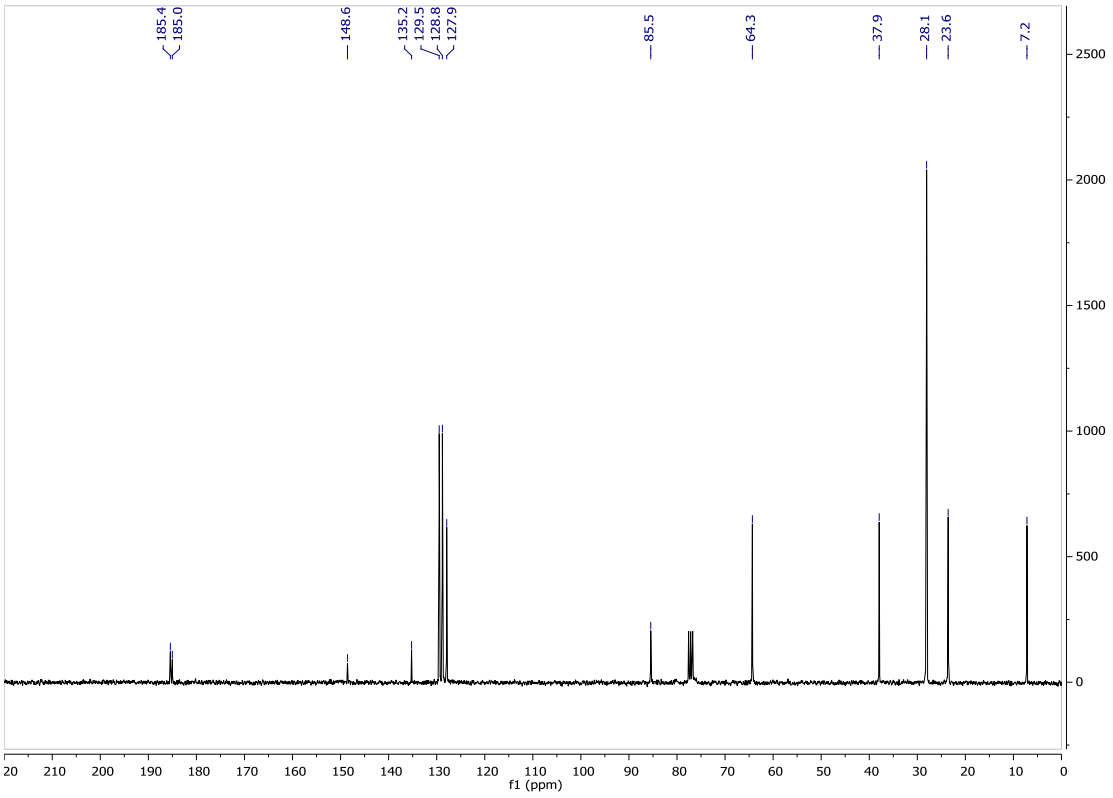
2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (34A)



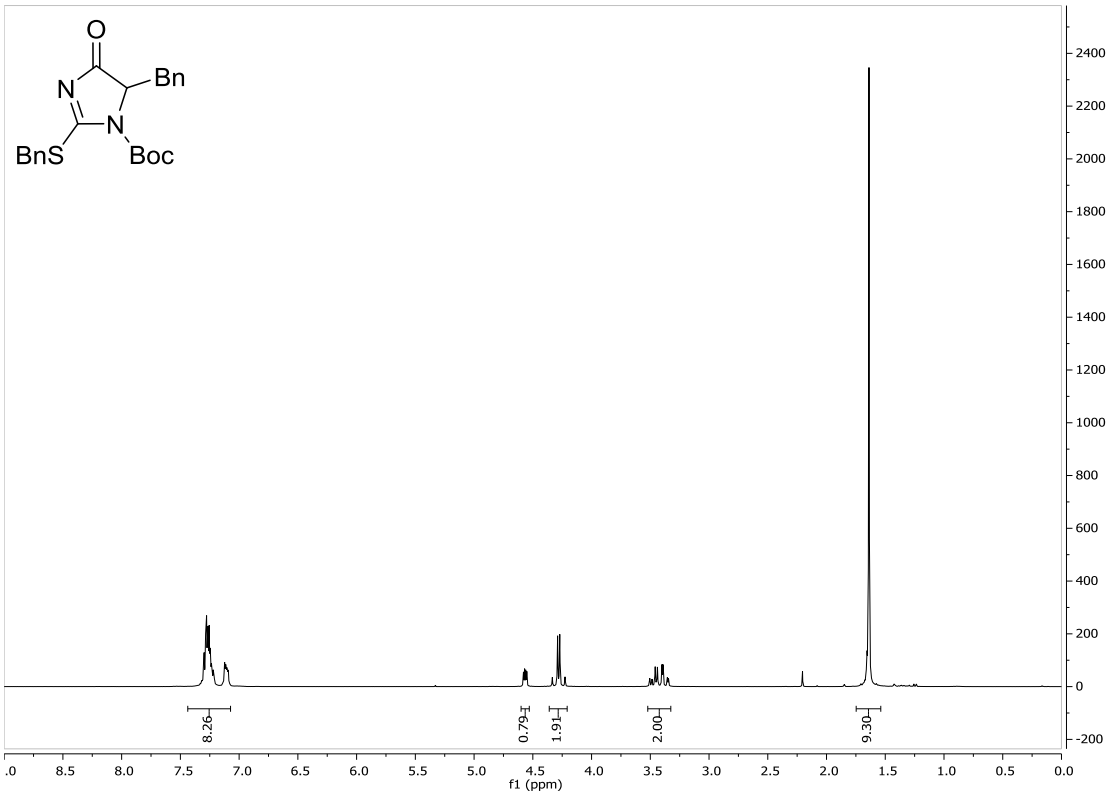


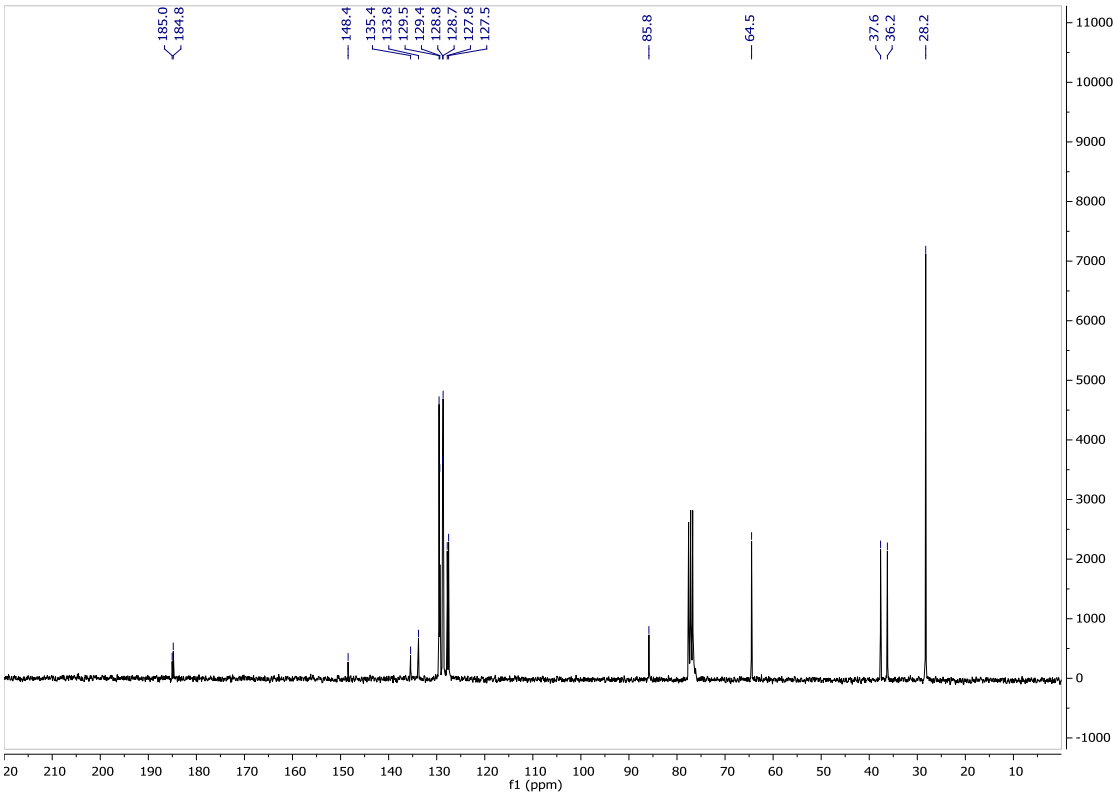
2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one (34B)



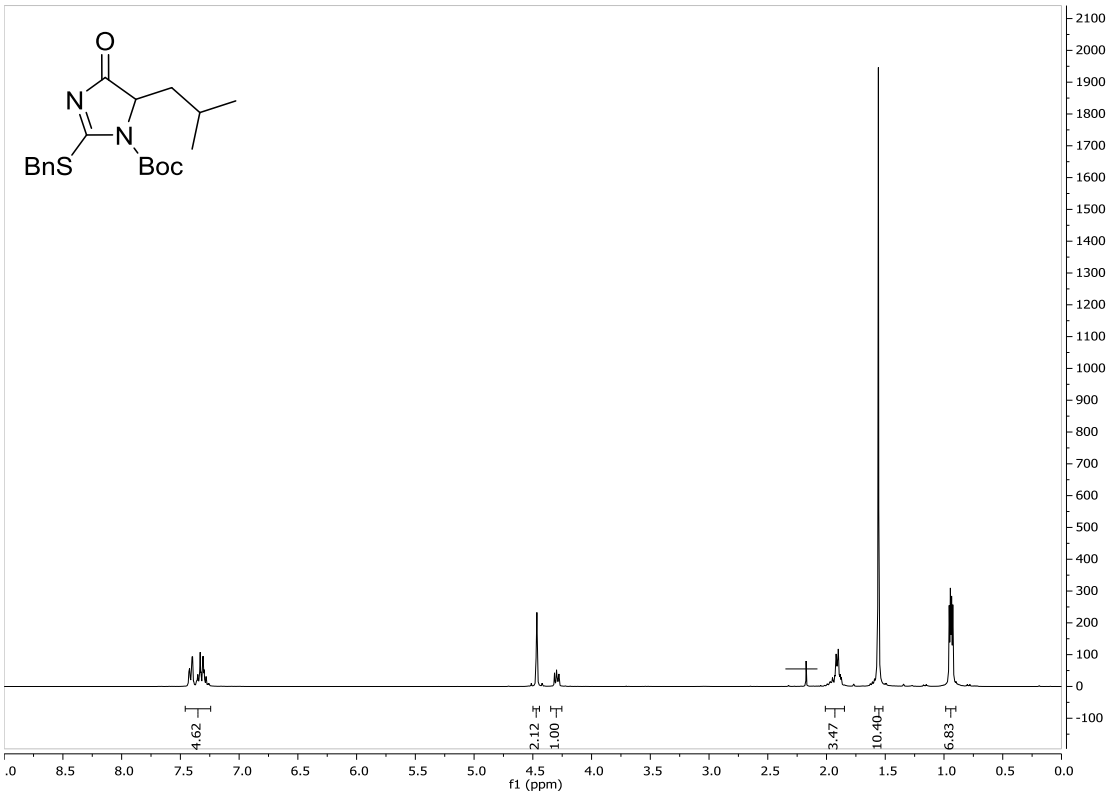


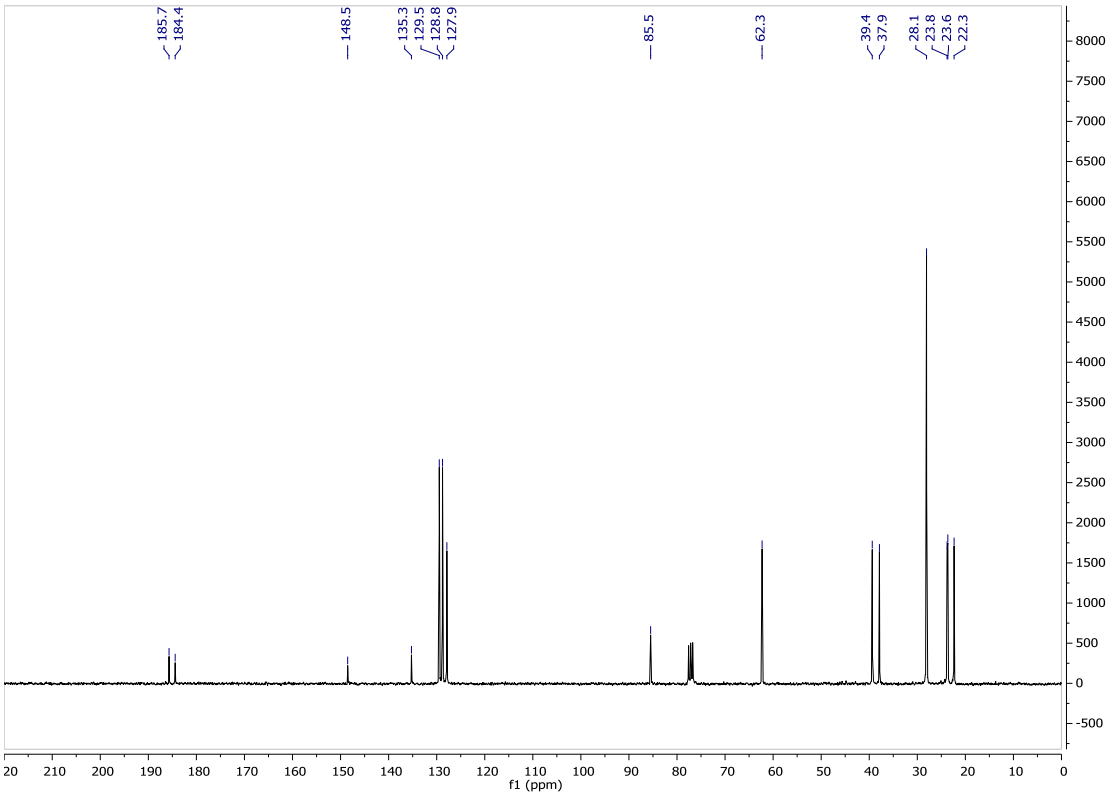
5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one (34C)



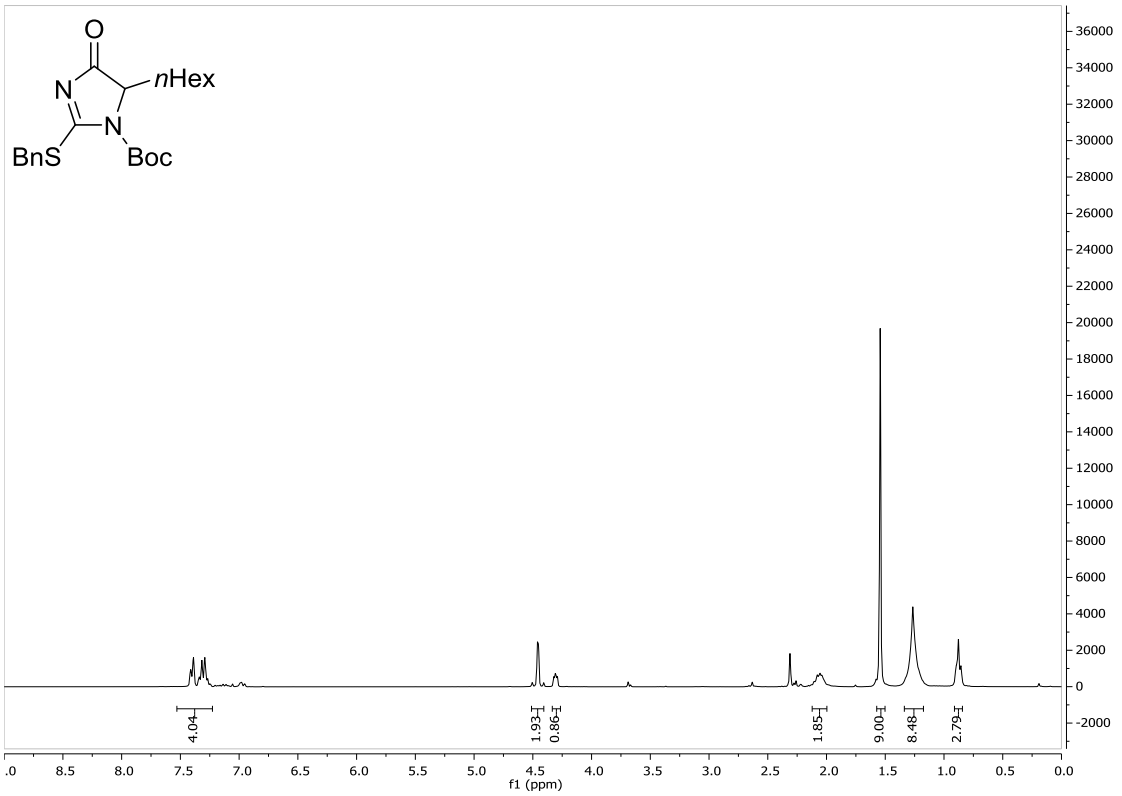


2-(Benzylthio)- 1-(*tert*-butyloxycarbonyl)-5-isobutyl-1*H*-imidazol-4(5*H*)-one (34D)

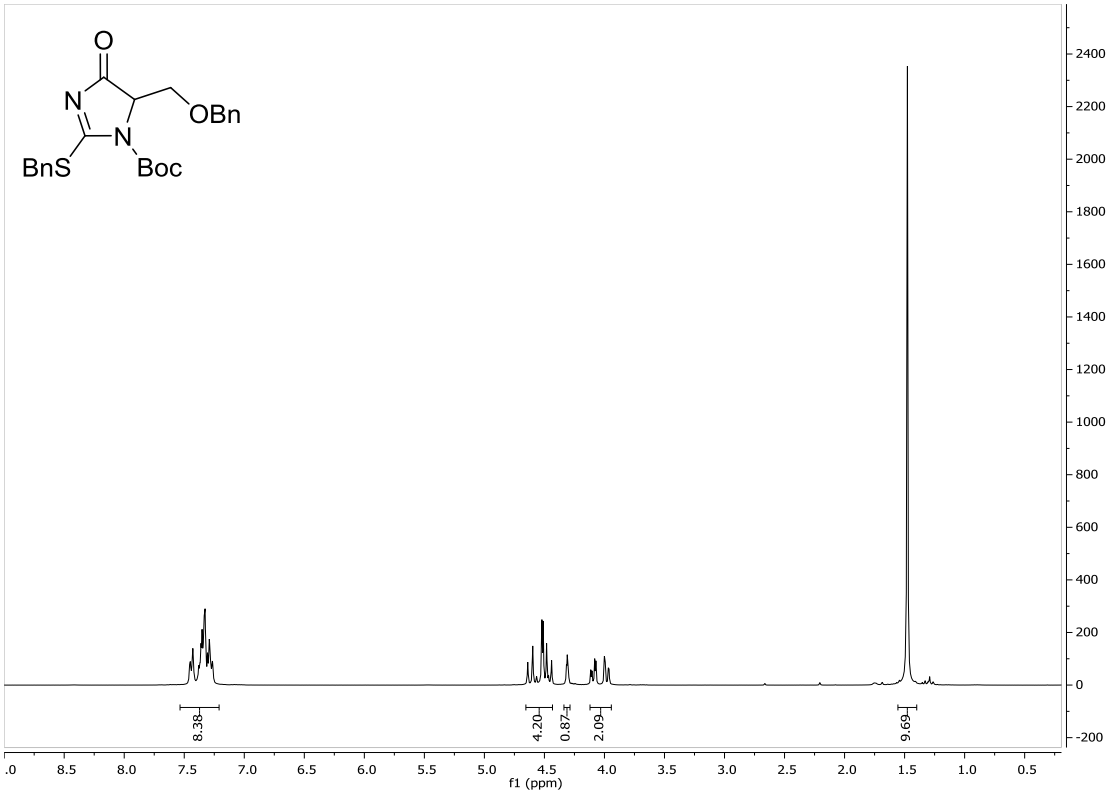


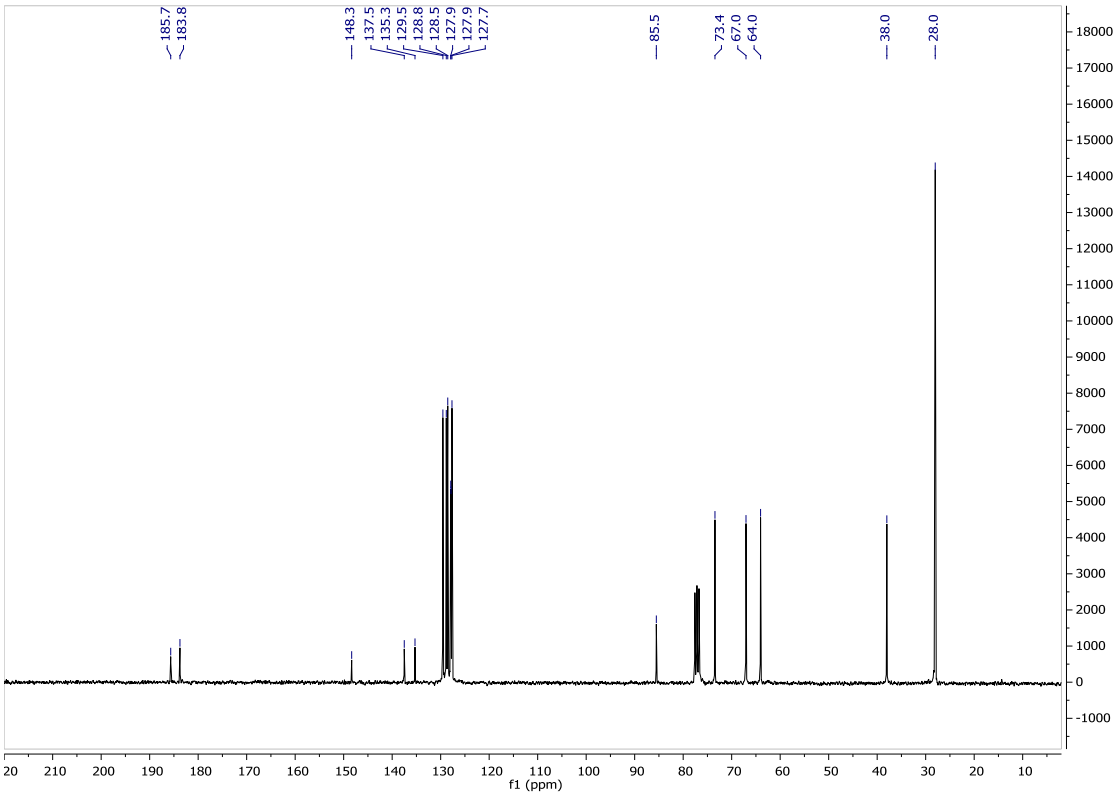


2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-1*H*-imidazol-4(5*H*)-one (34E)

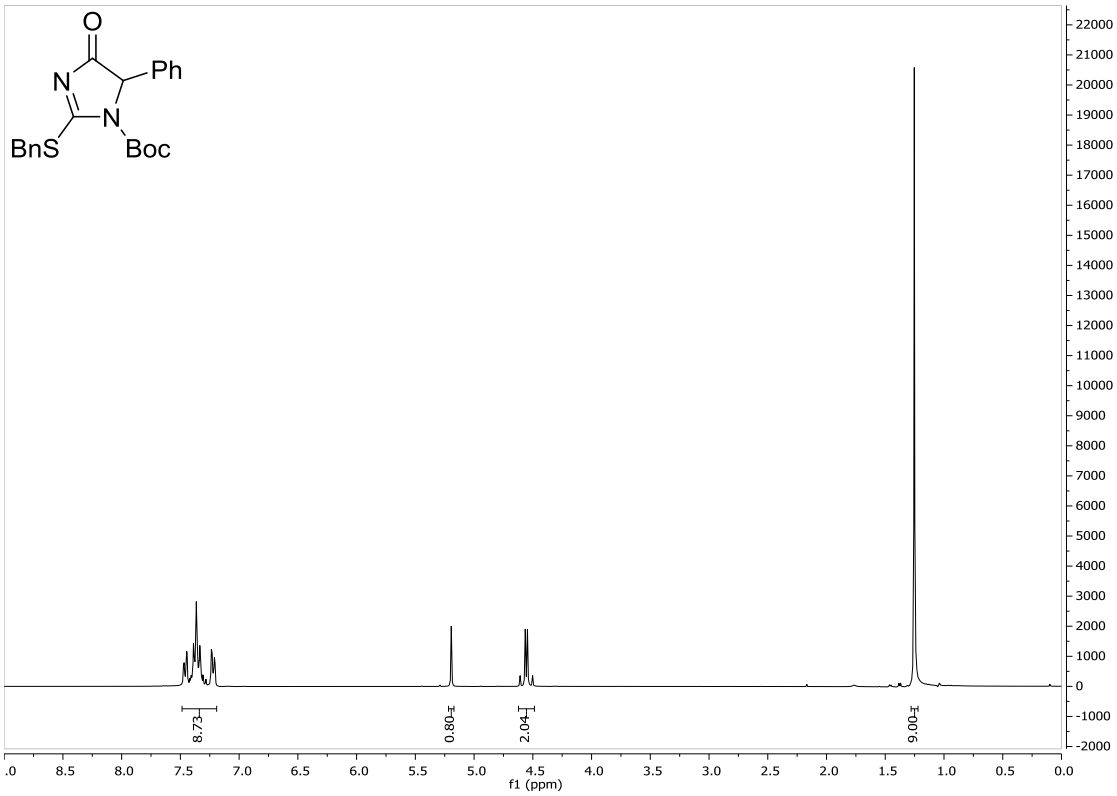


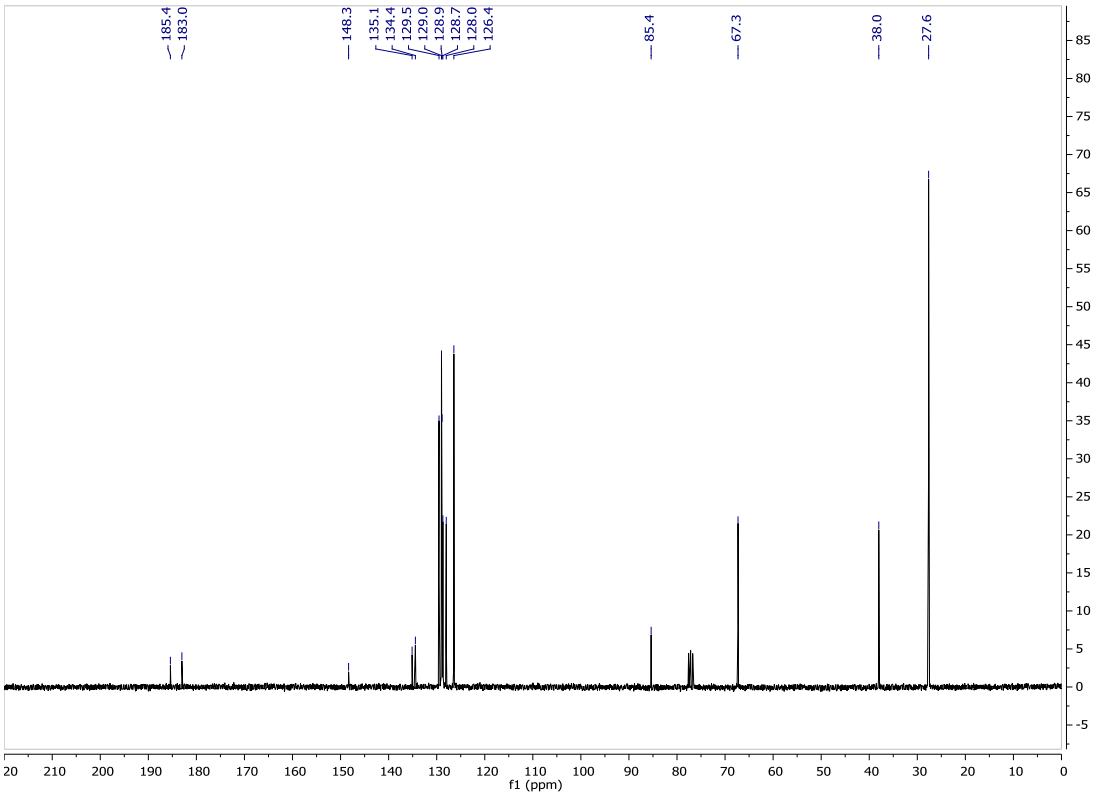
5-((Benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-1*H*-imidazol-4(5*H*)-one (34G)



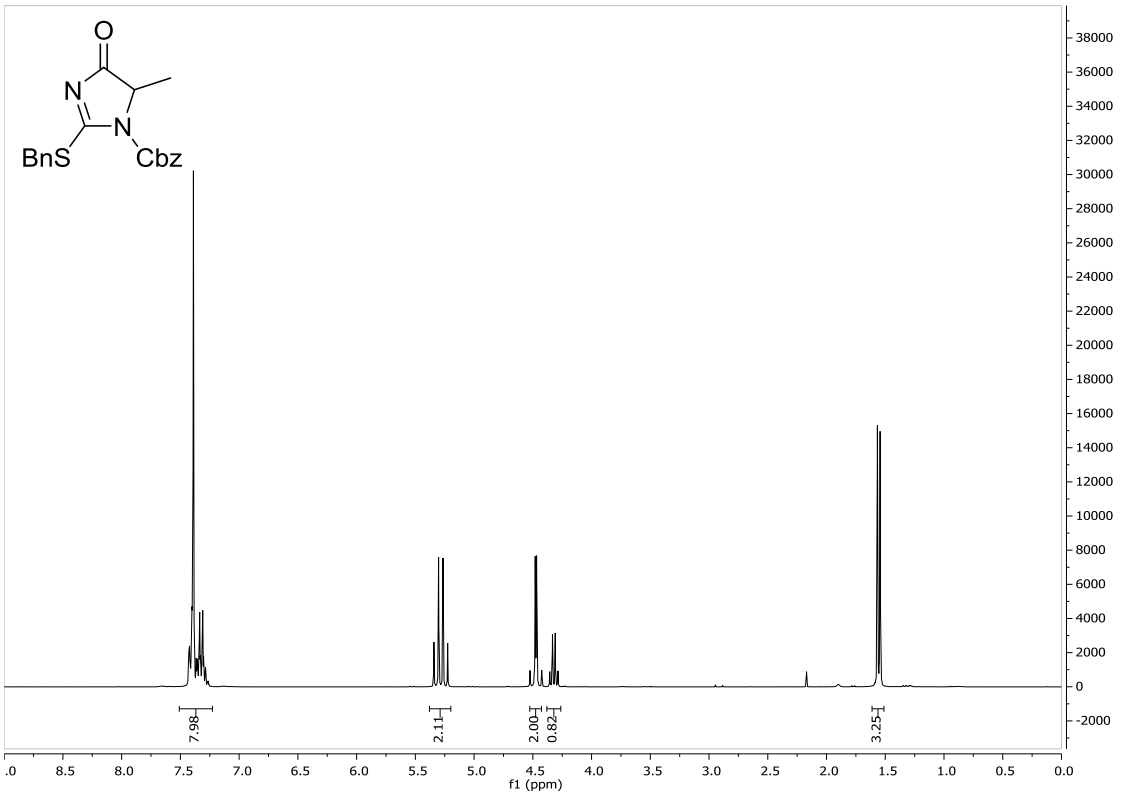


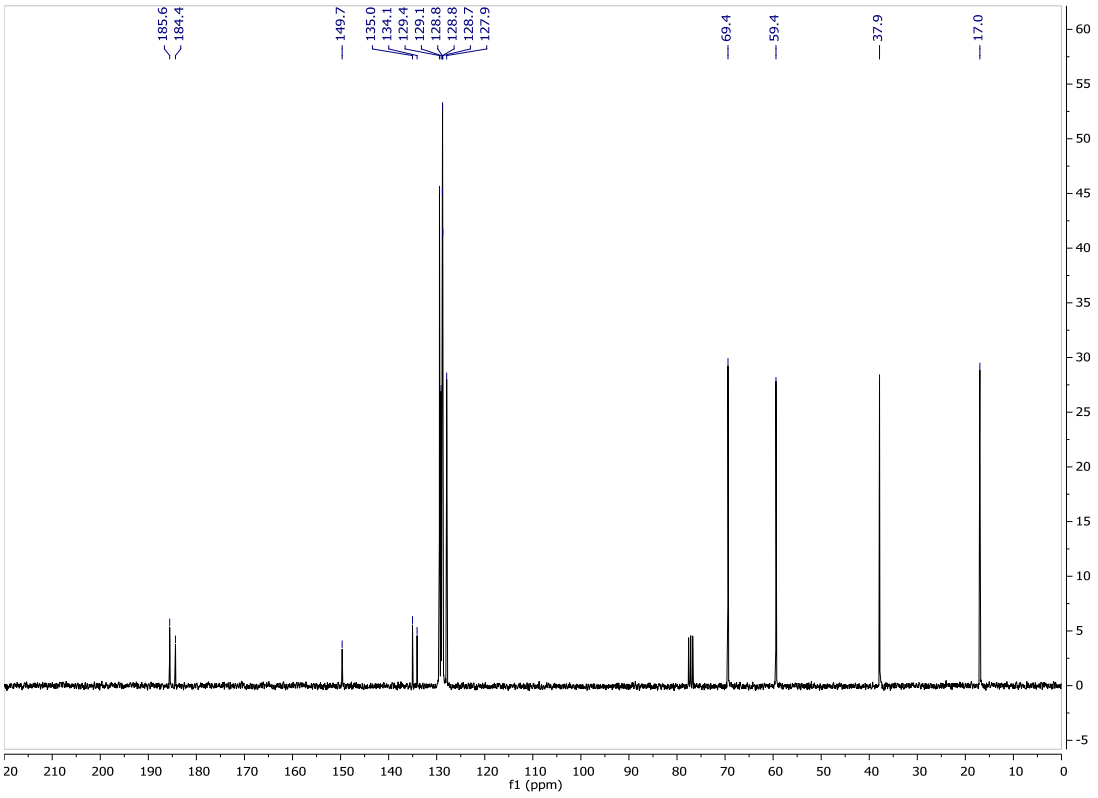
2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (34H)



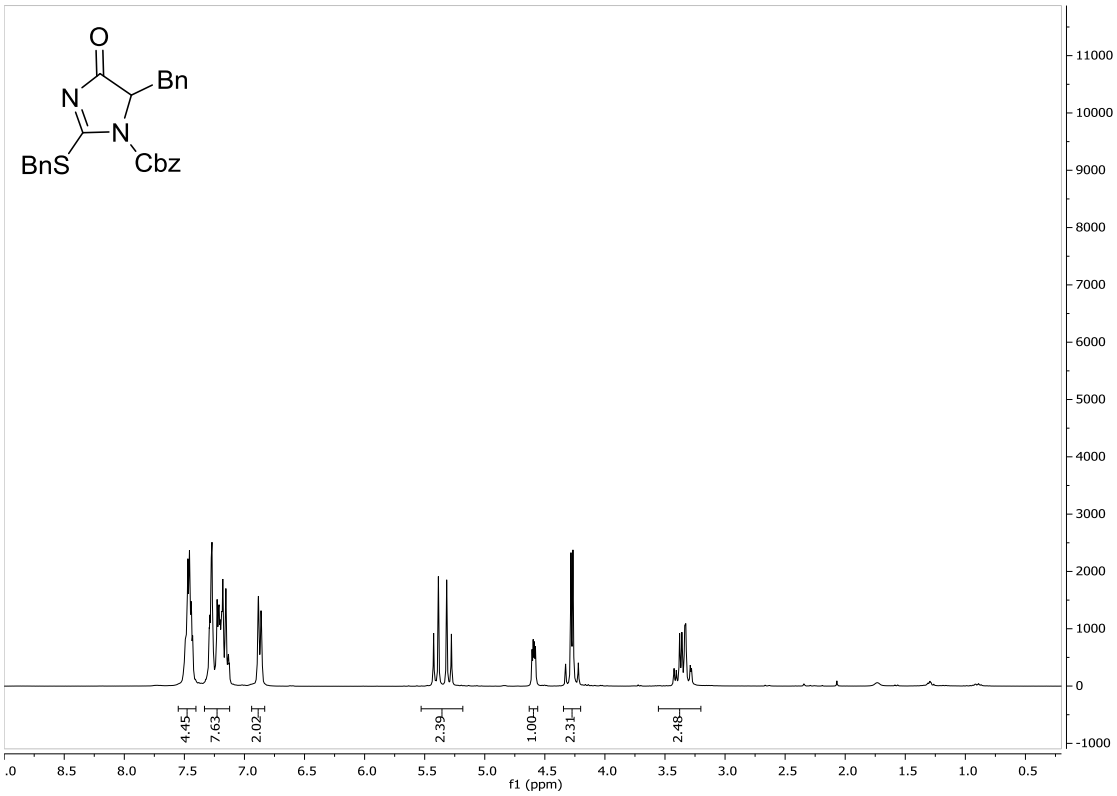


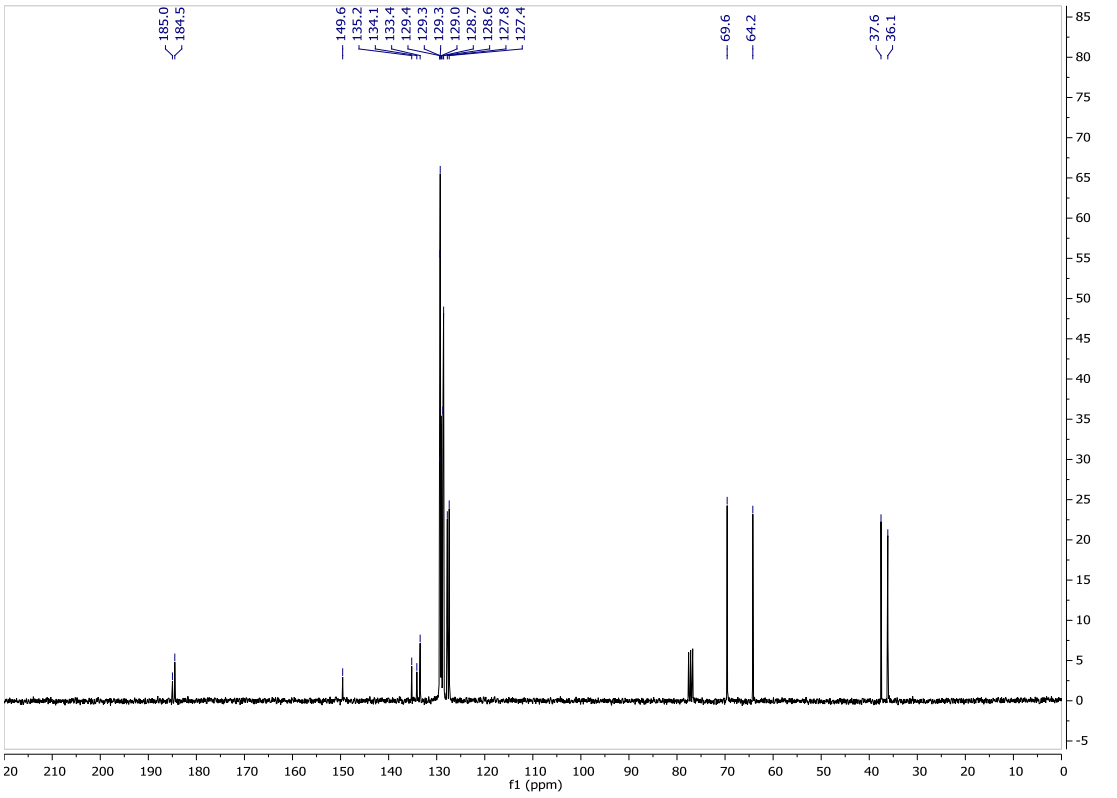
1-(Benzyloxycarbonyl)-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (35A)



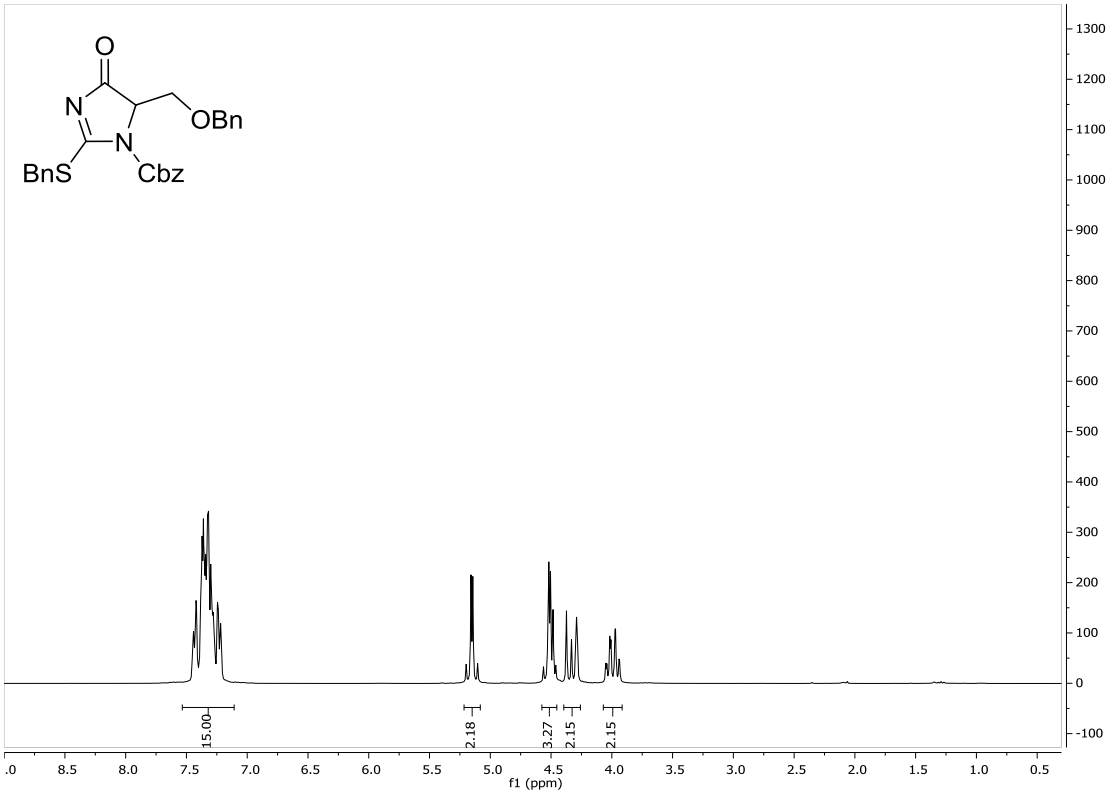


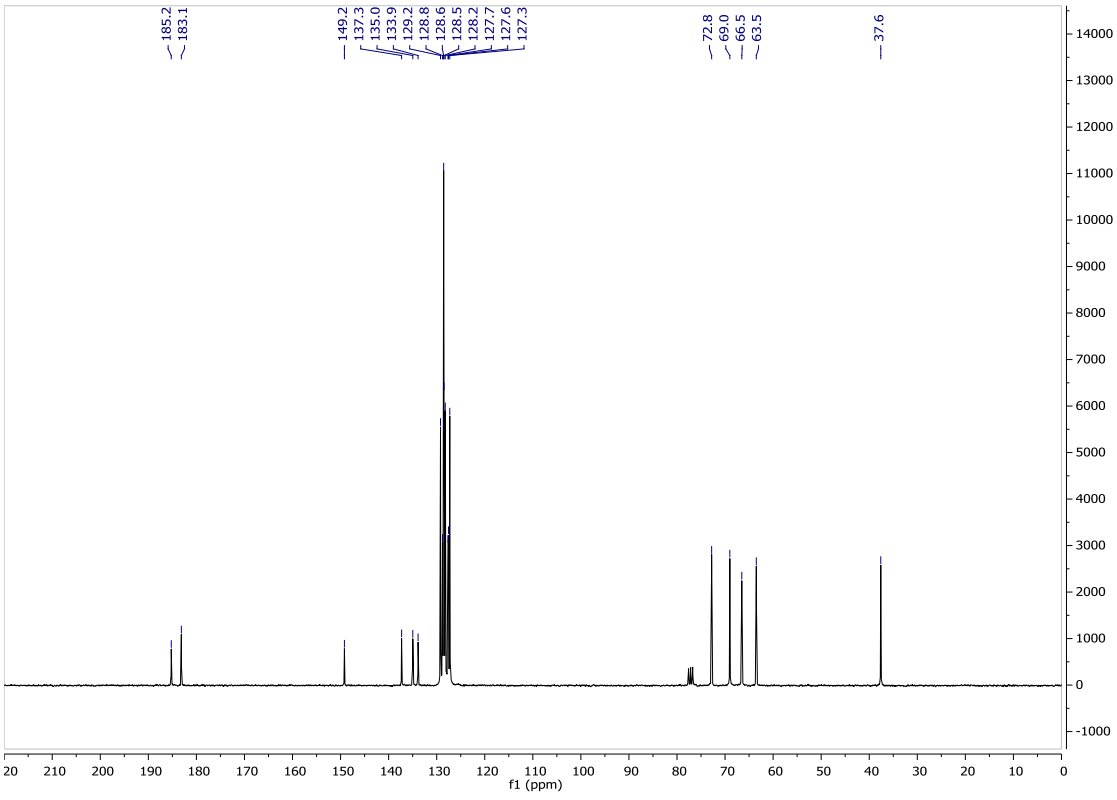
5-Benzyl-1-(benzyloxycarbonyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (35C)



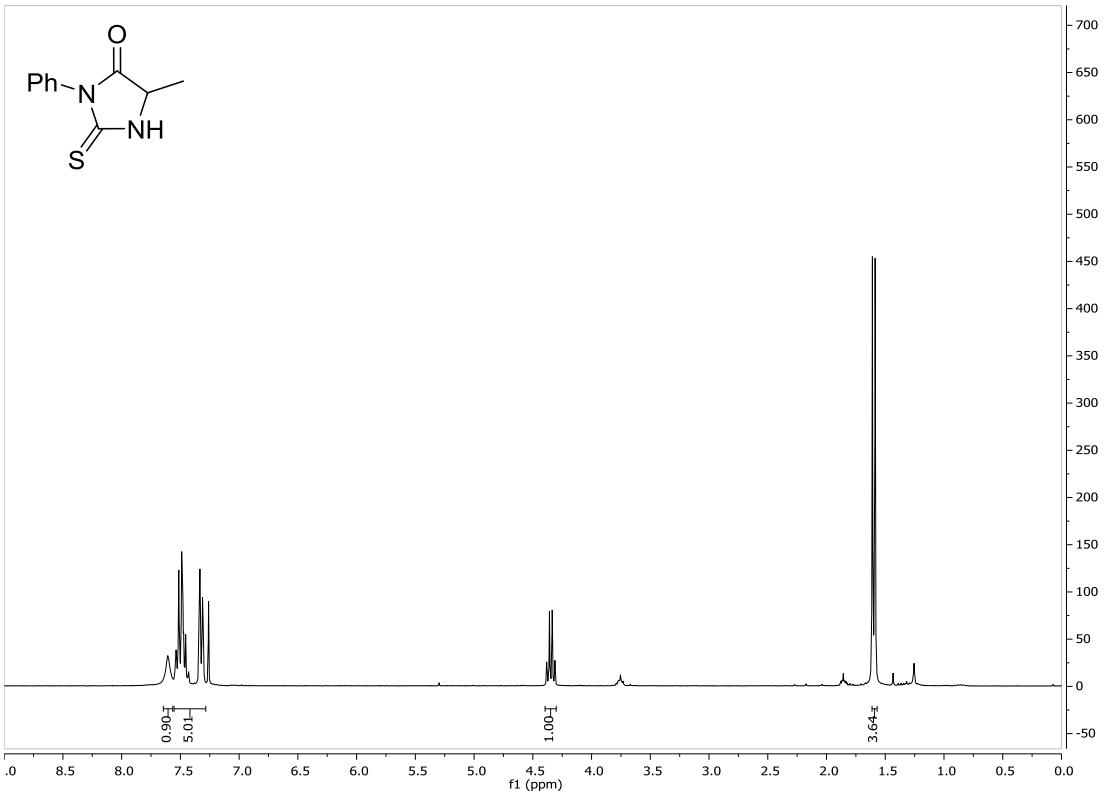


1-(Benzyloxycarbonyl)-5-((benzyloxy)methyl)-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (35G)

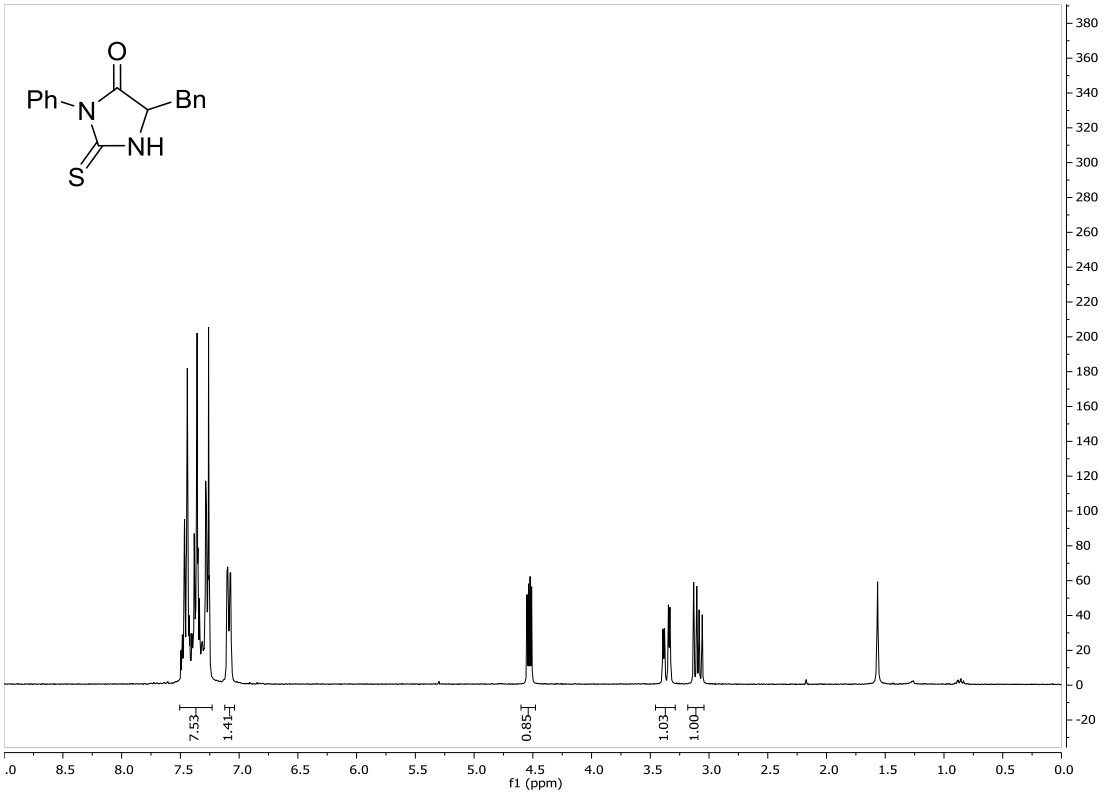




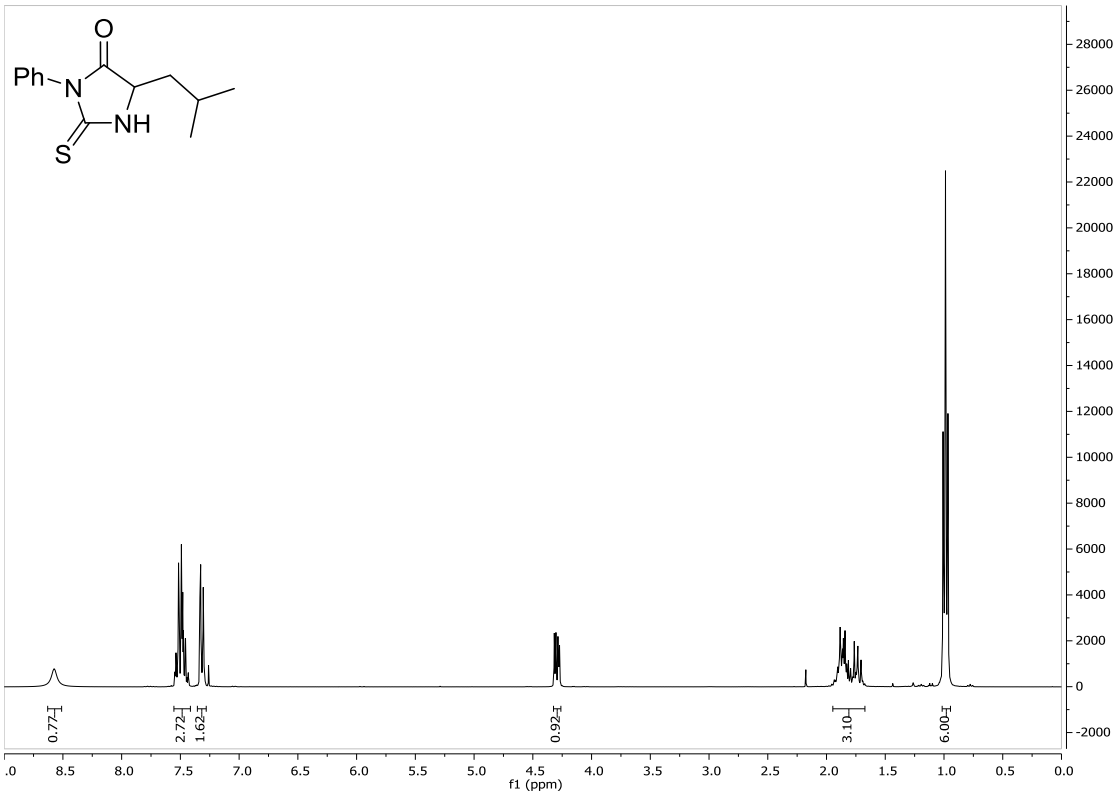
5-Methyl-3-phenyl-2-thioxoimidazolidin-4-one (55A)



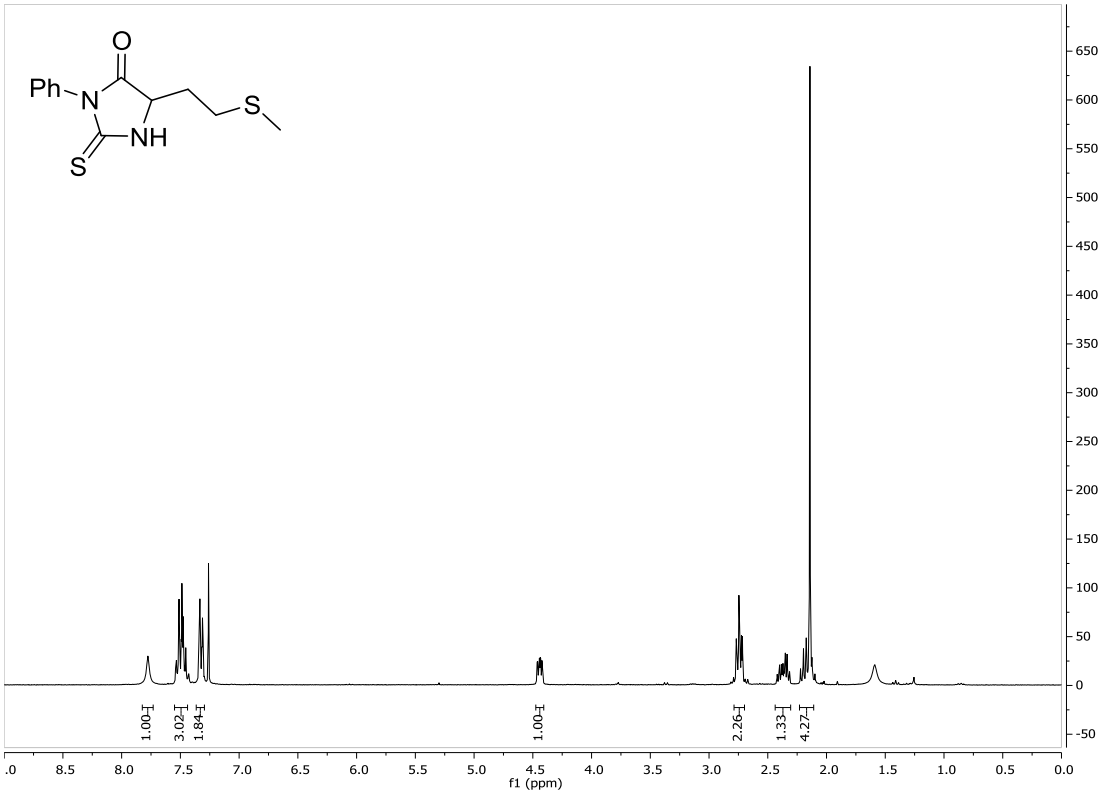
5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (55C)



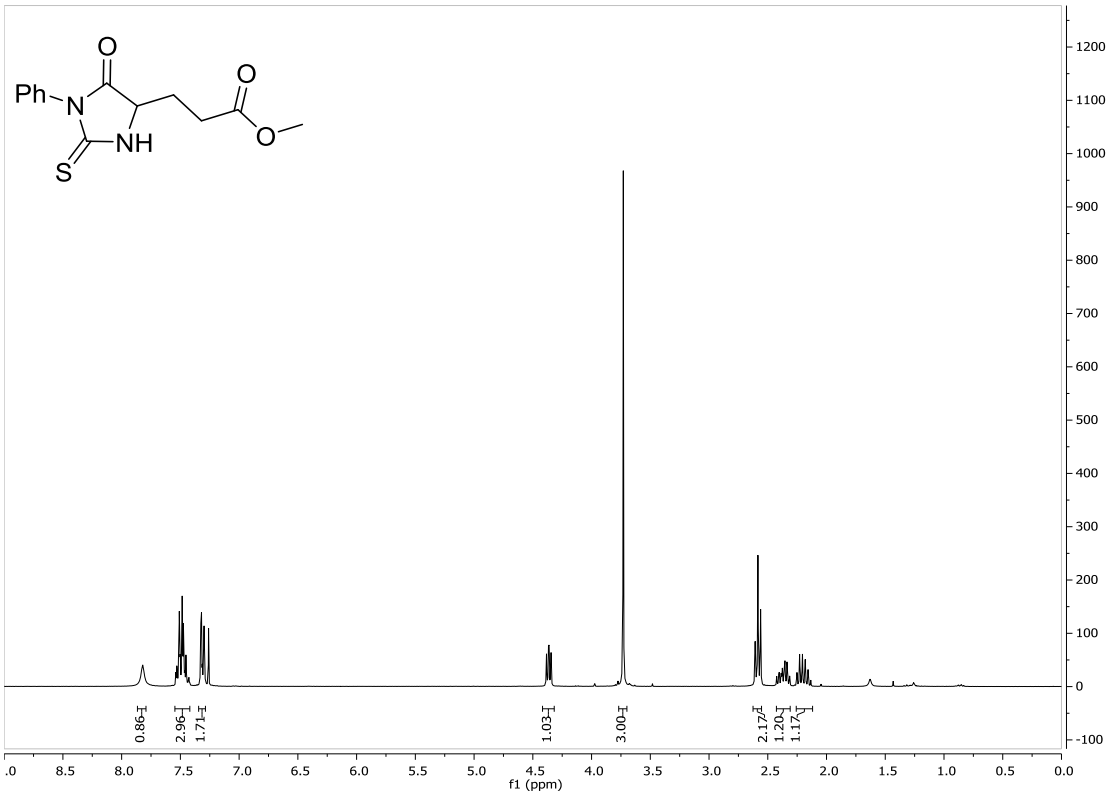
5-Isobutyl-3-phenyl-2-thioxoimidazolidin-4-one (55D)



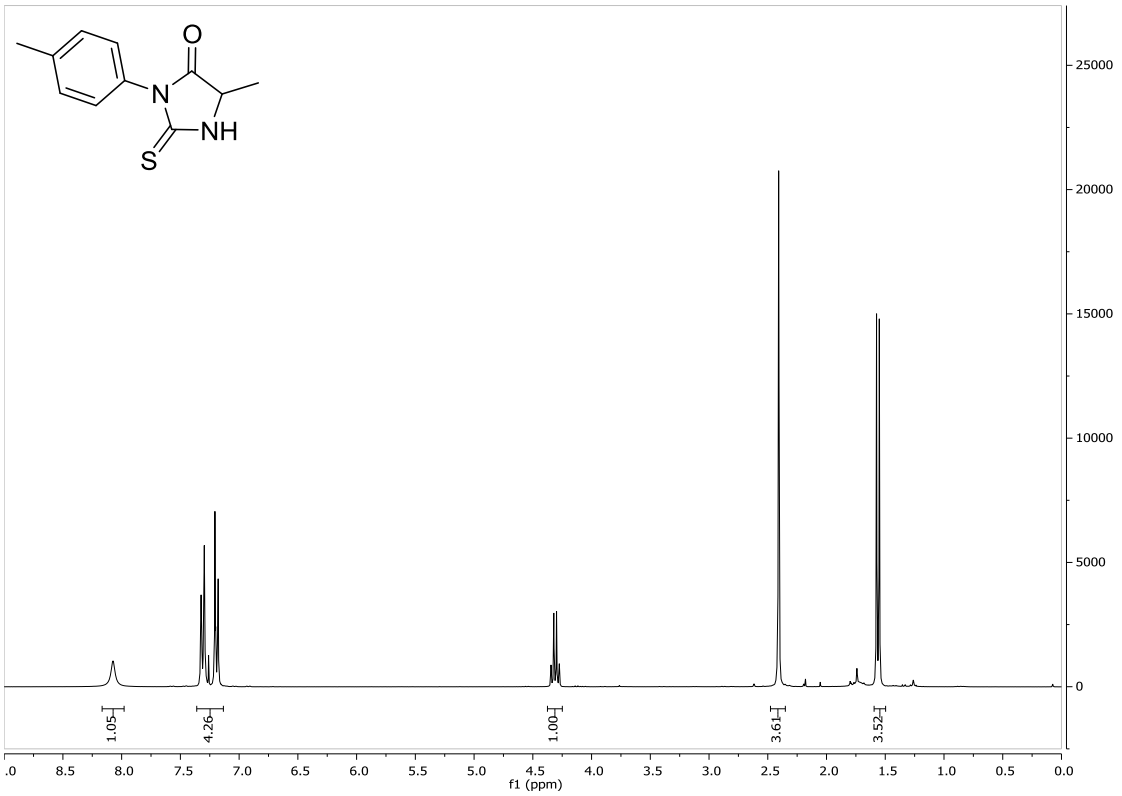
5-(2-(Methylthio)ethyl)-3-phenyl-2-thioxoimidazolidin-4-one (55F)

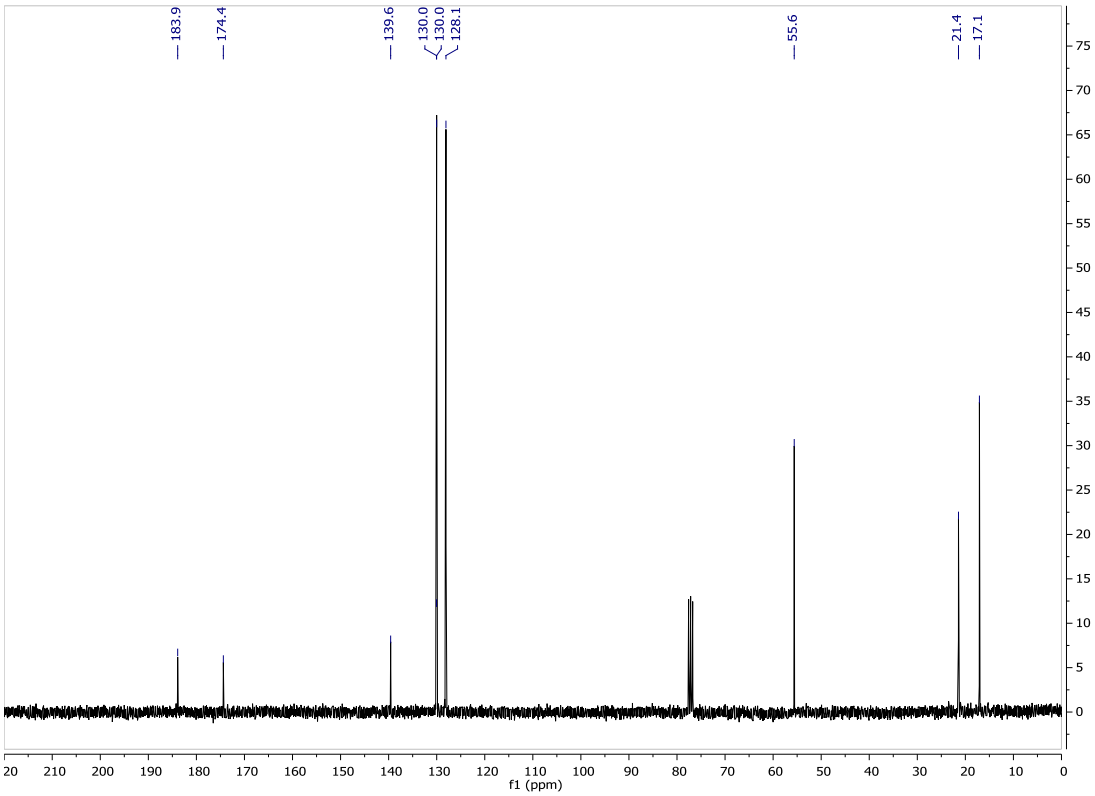


Methyl 3-(5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)propanoate (55I)

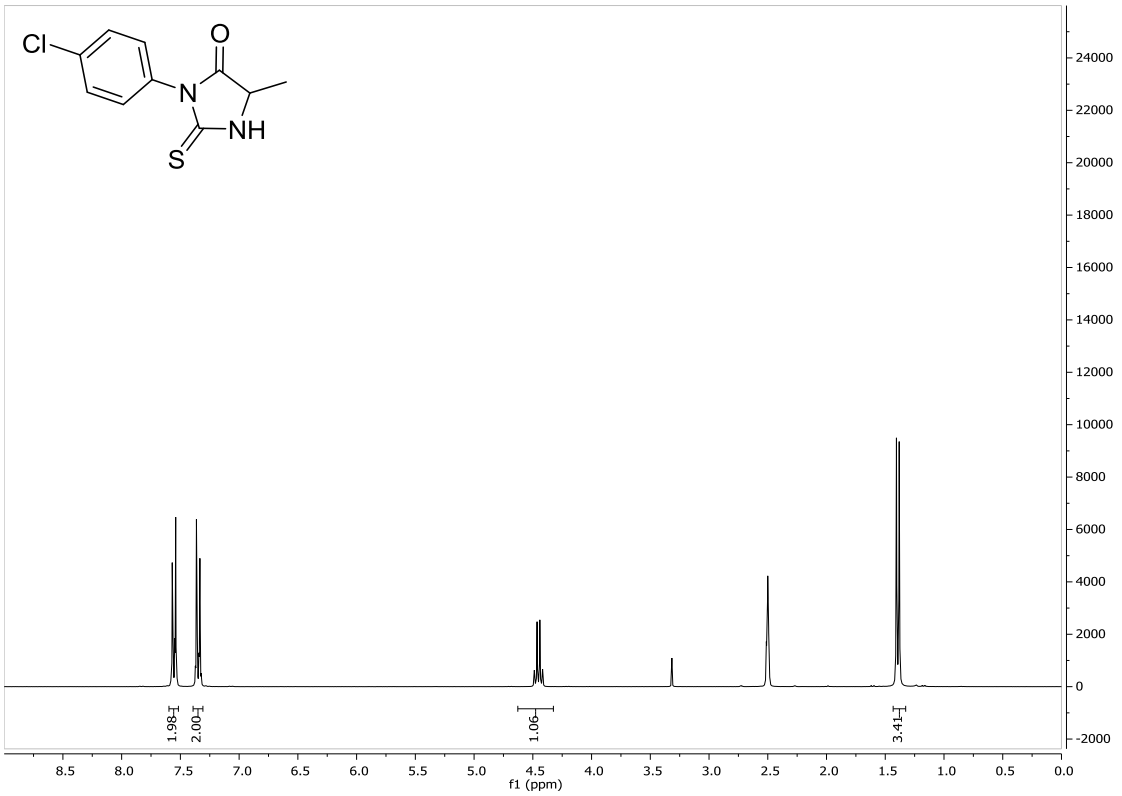


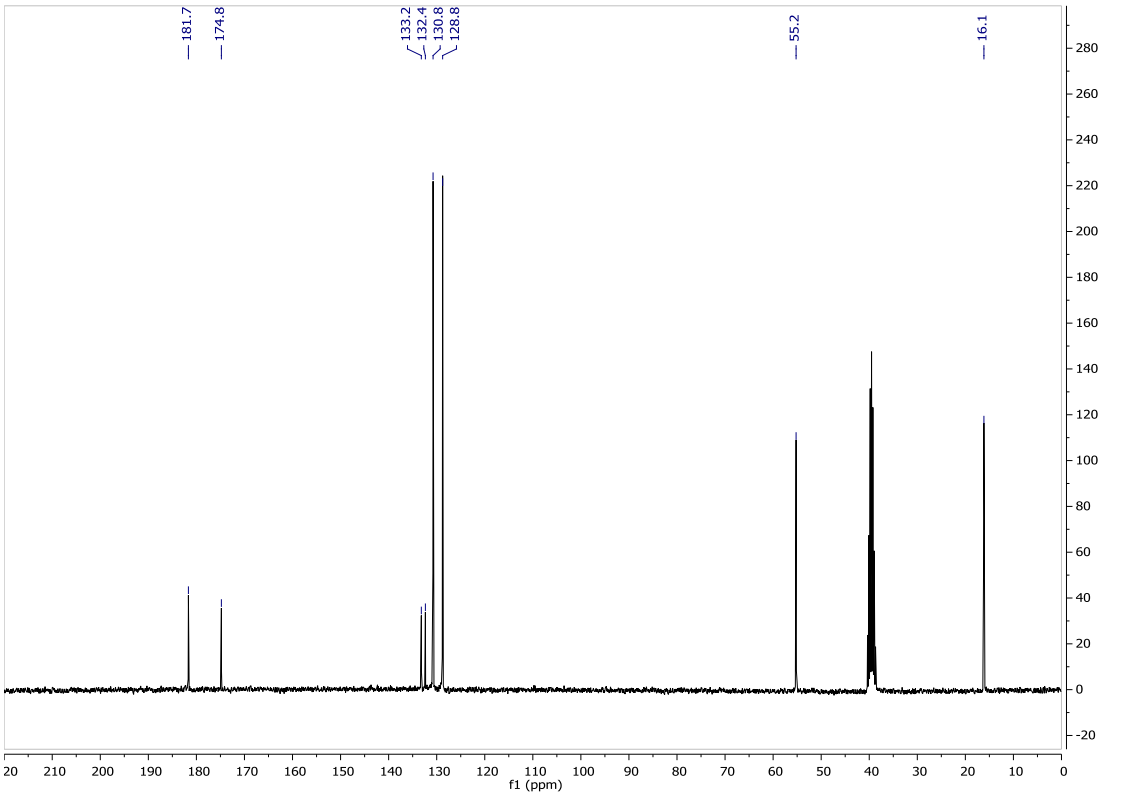
5-Methyl-2-thioxo-3-(p-tolyl)imidazolidin-4-one (56A)



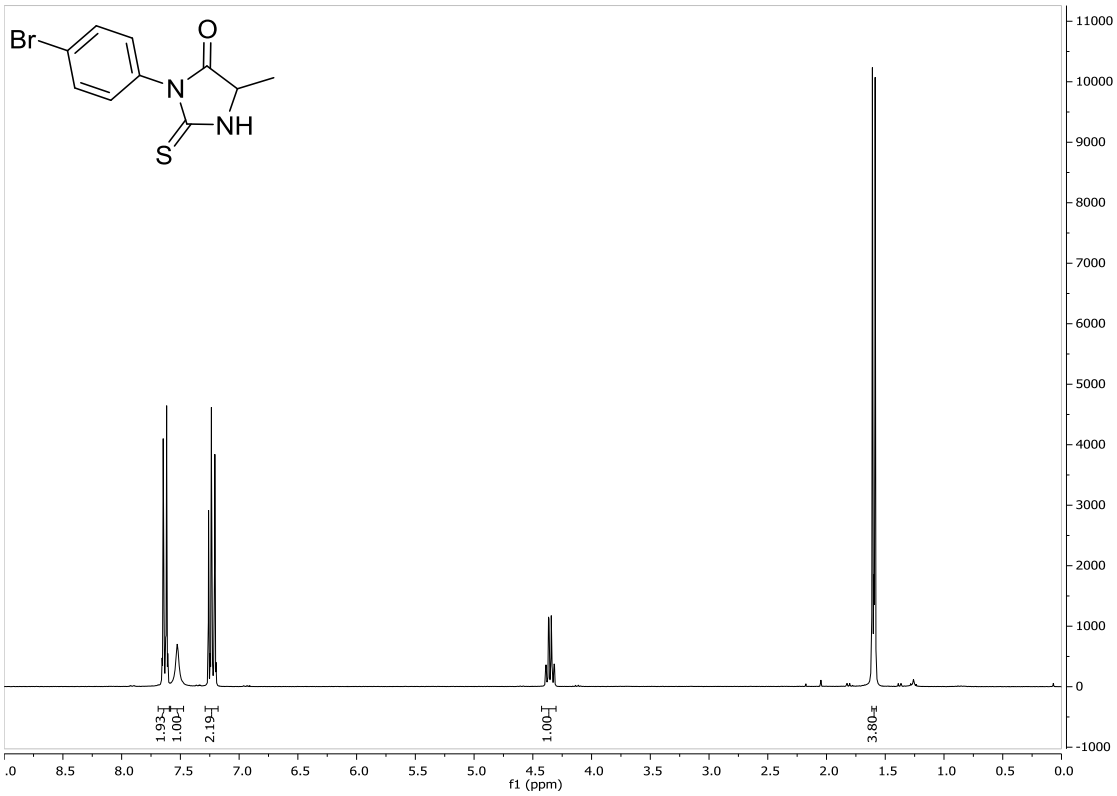


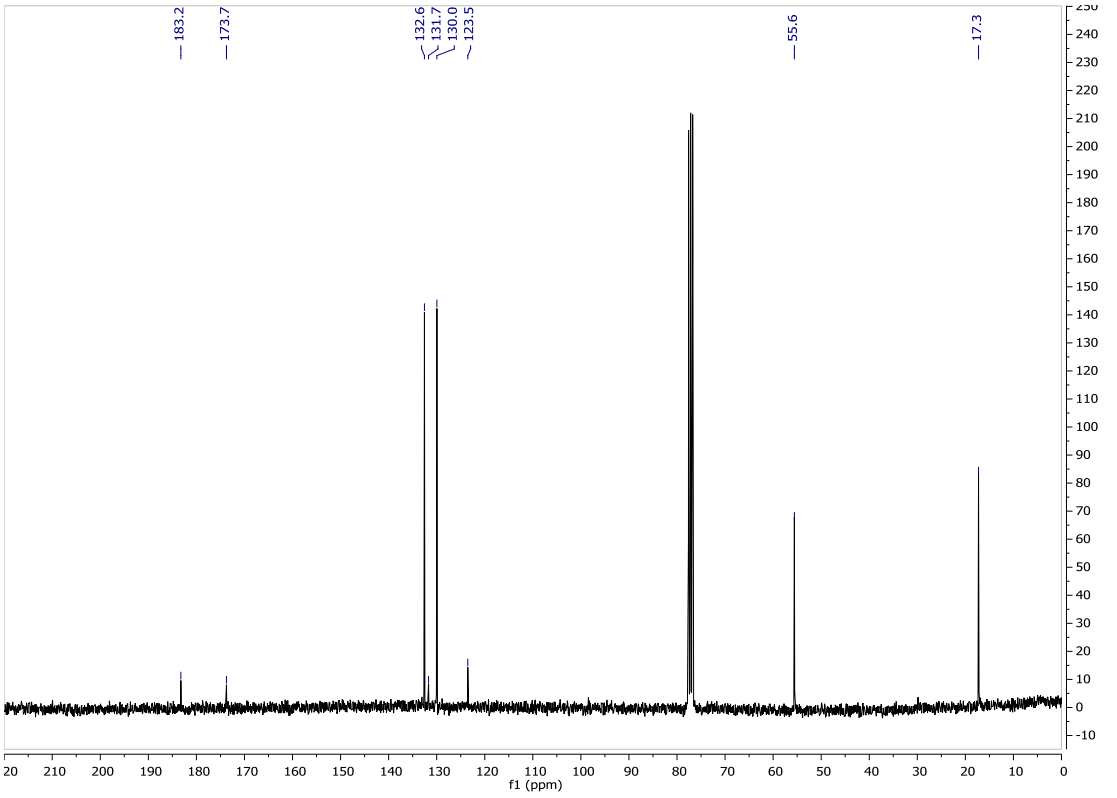
3-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (57A)



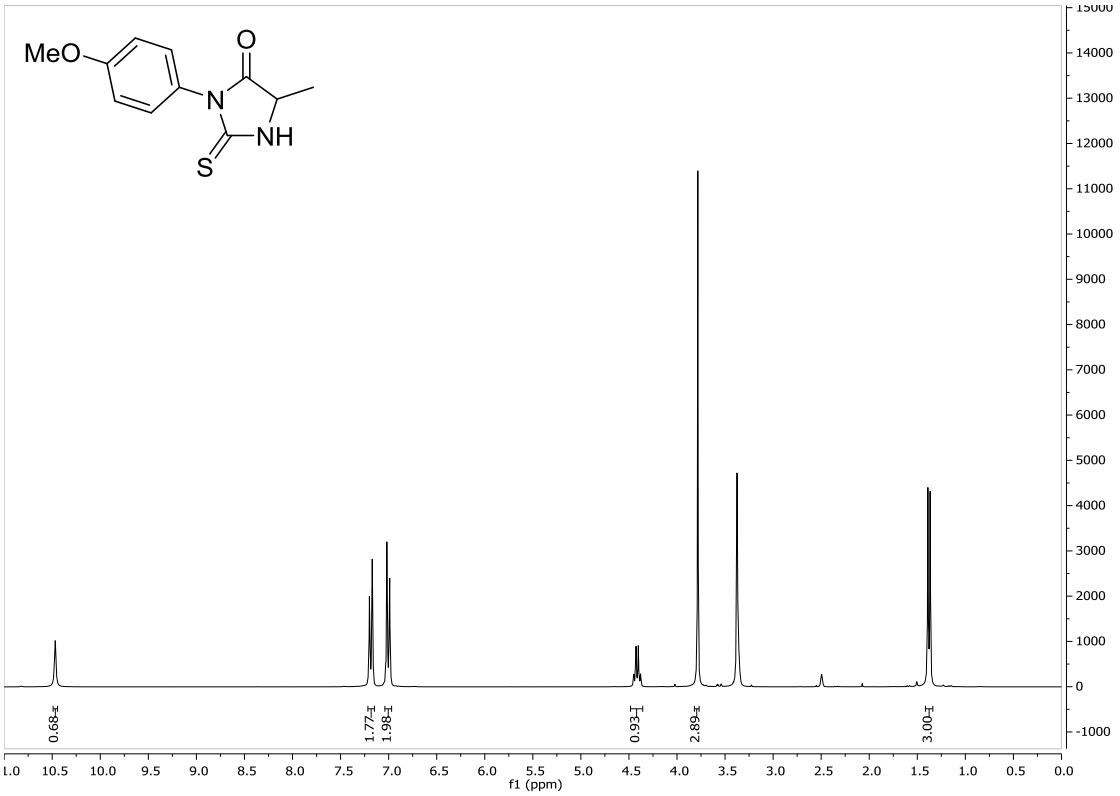


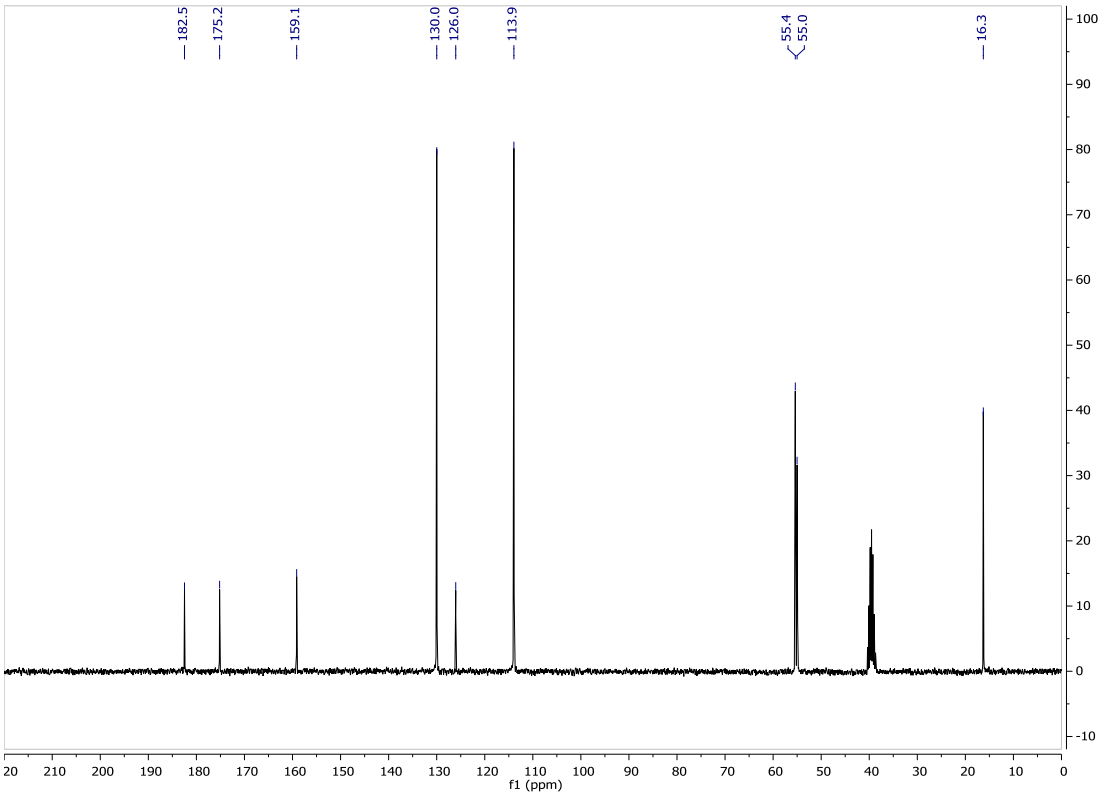
3-(4-Bromophenyl)-5-methyl-2-thioxoimidazolidin-4-one (58A)



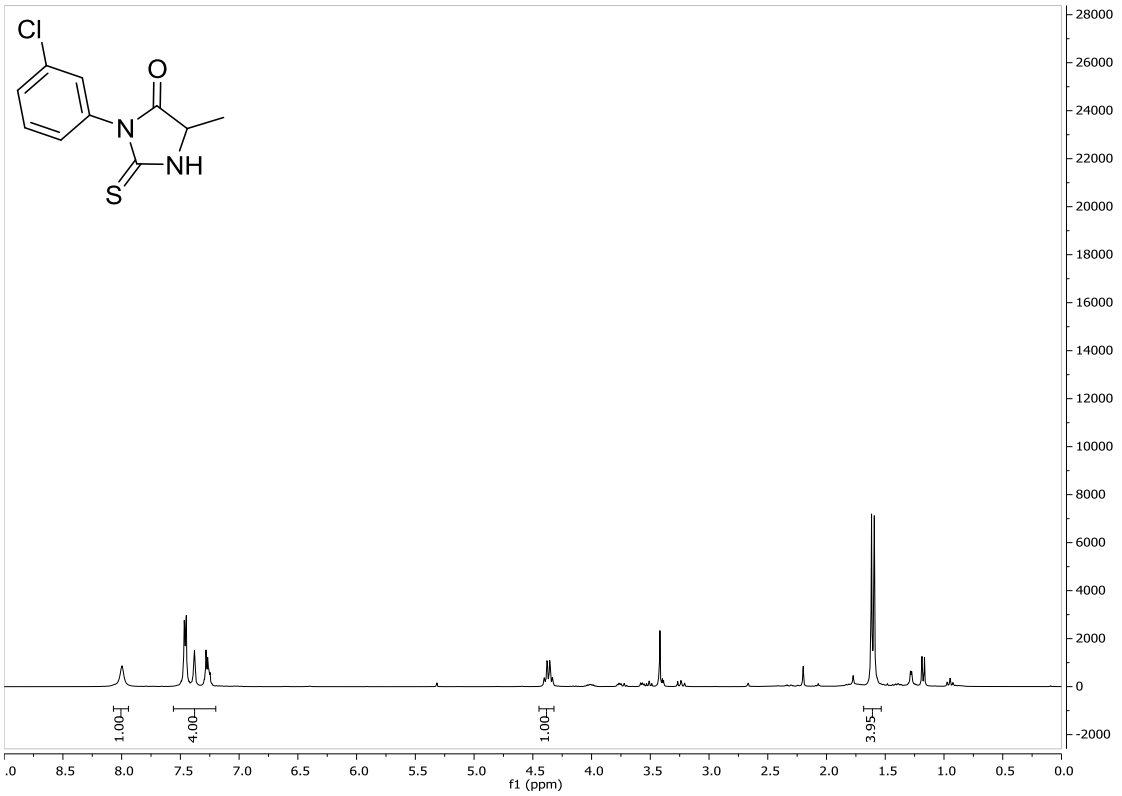


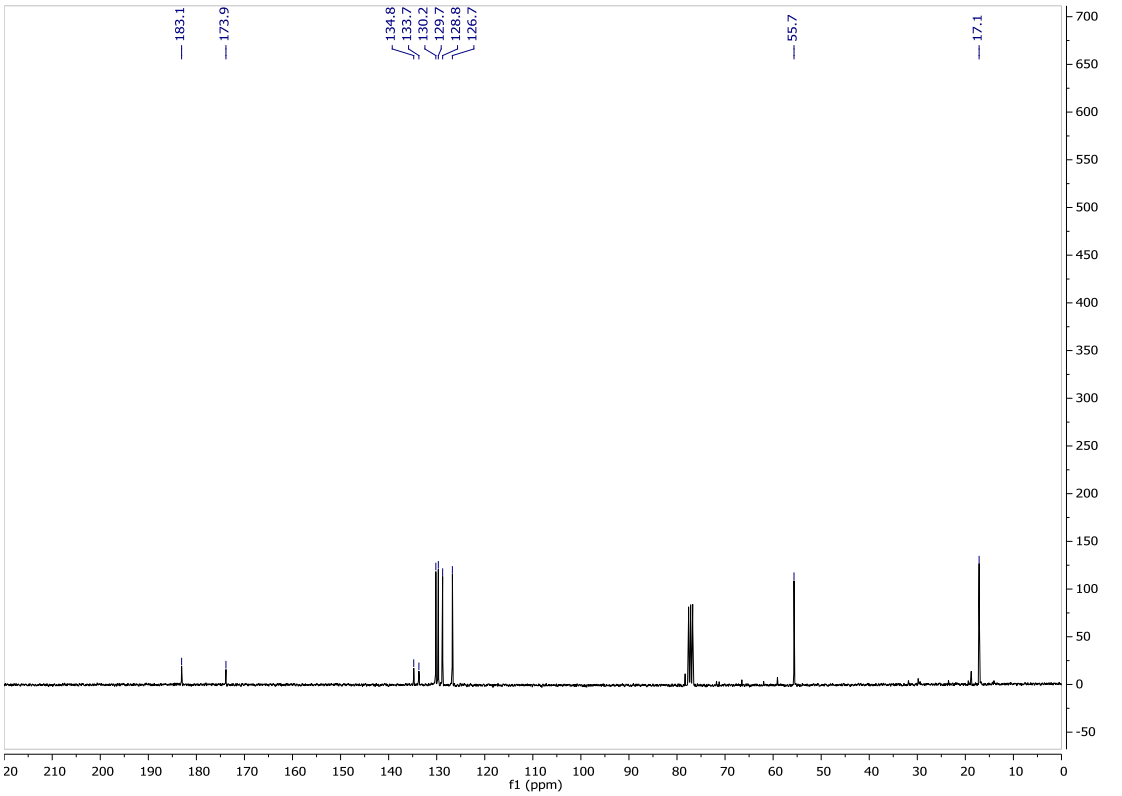
3-(4-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (59A)



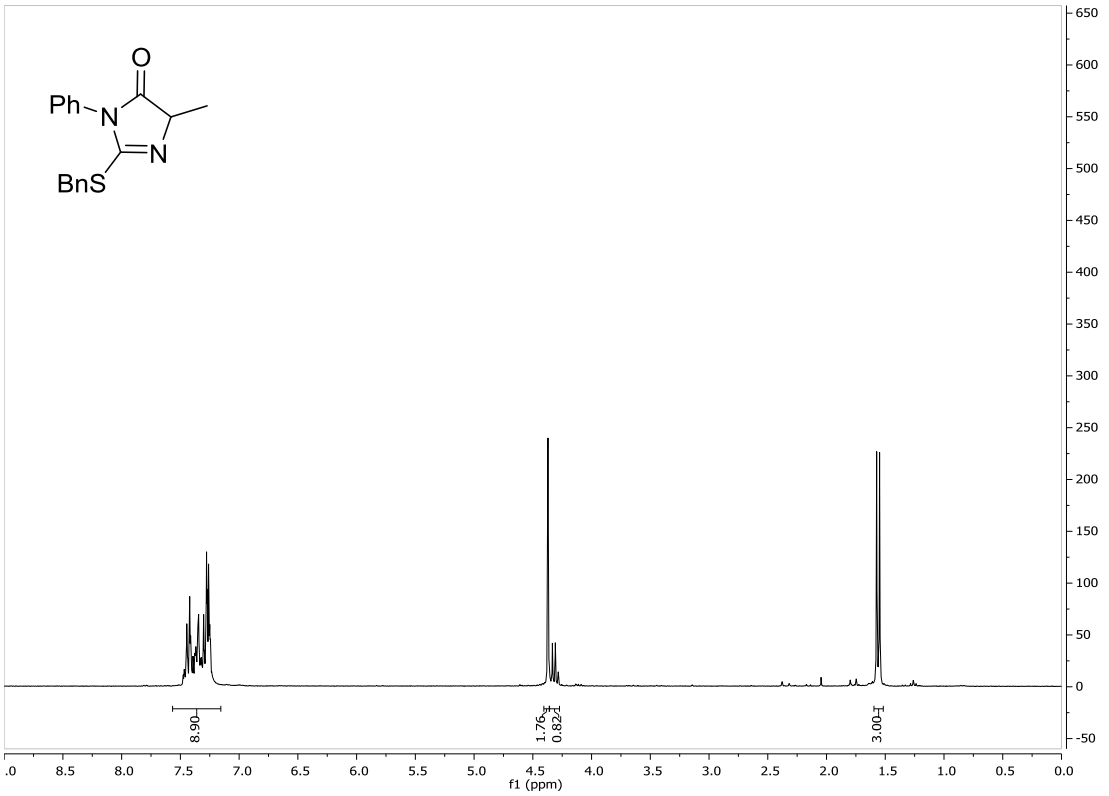


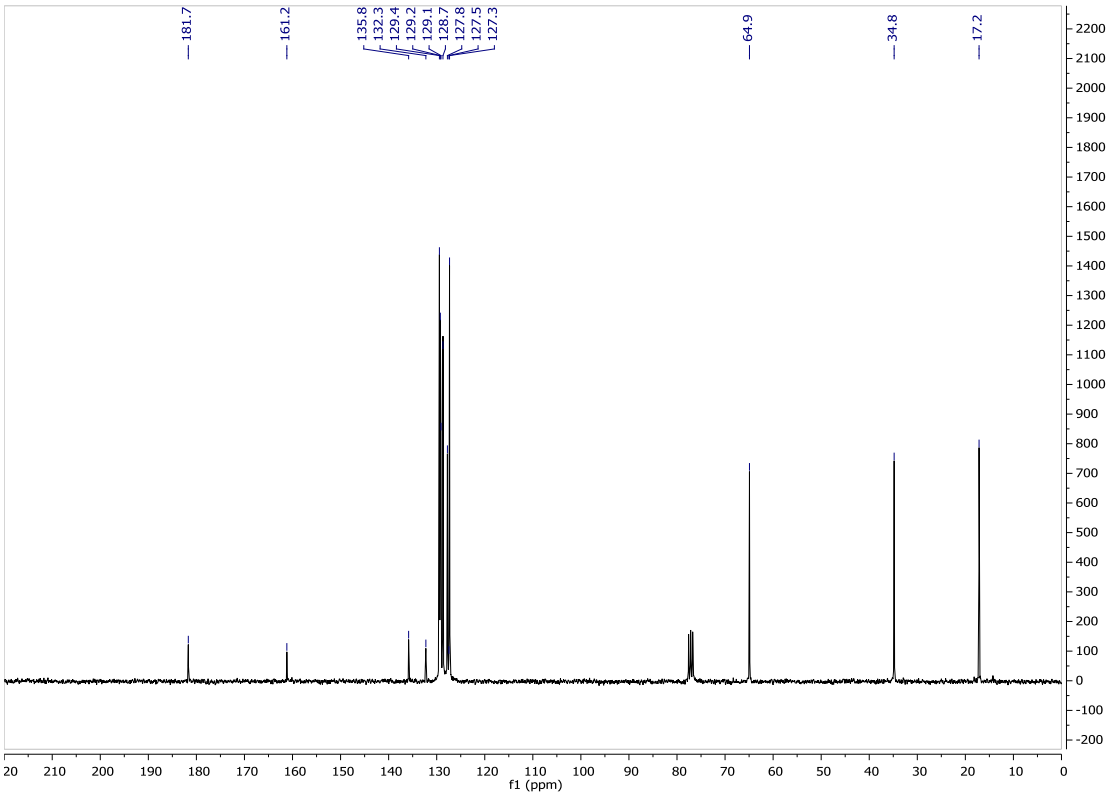
3-(3-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (60A)



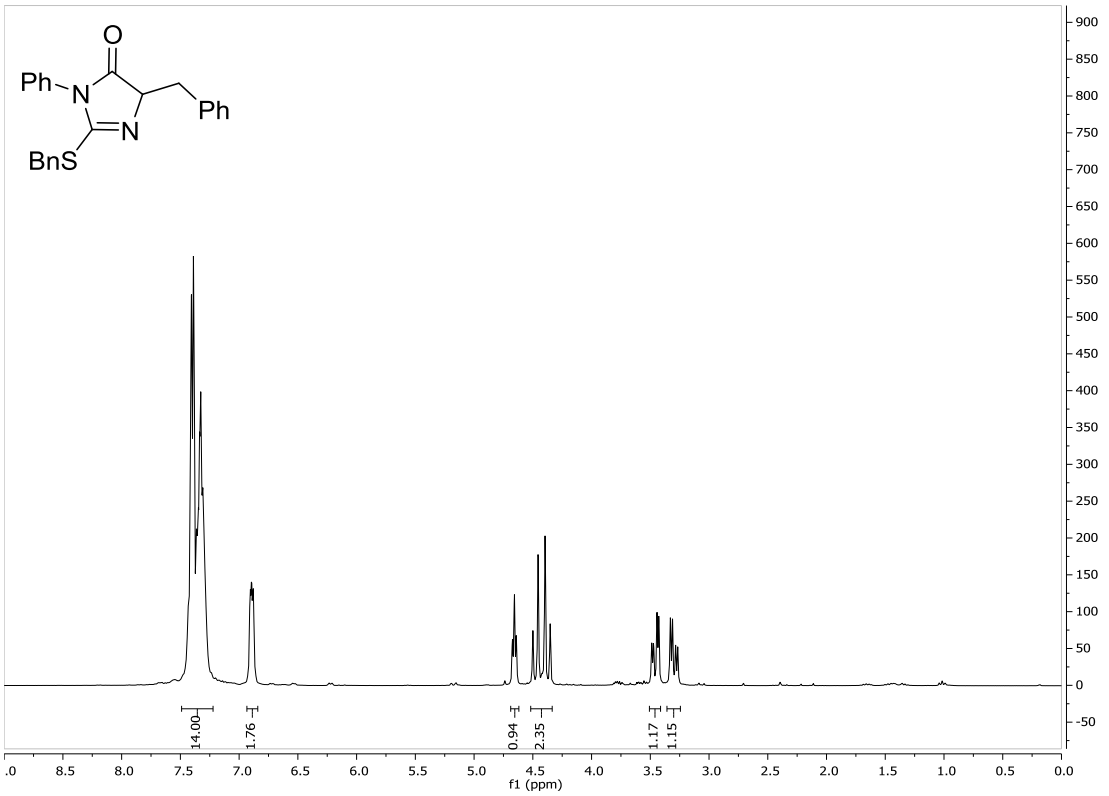


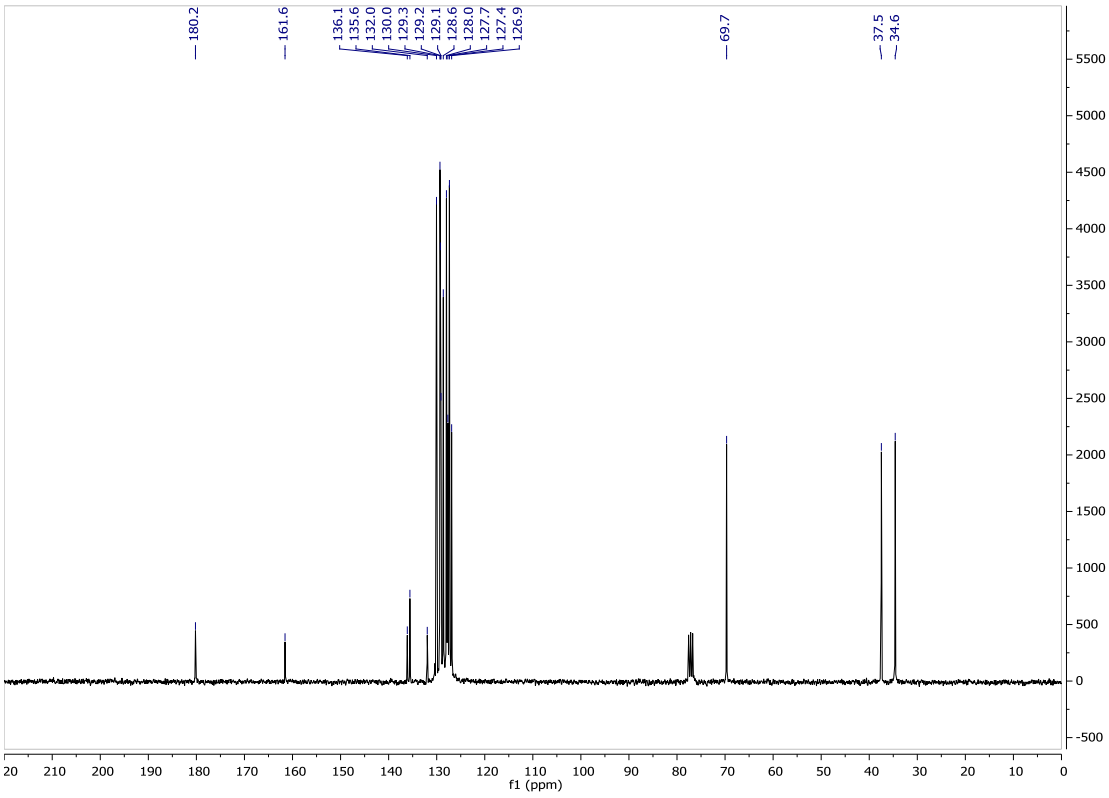
2-(Benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (61A)



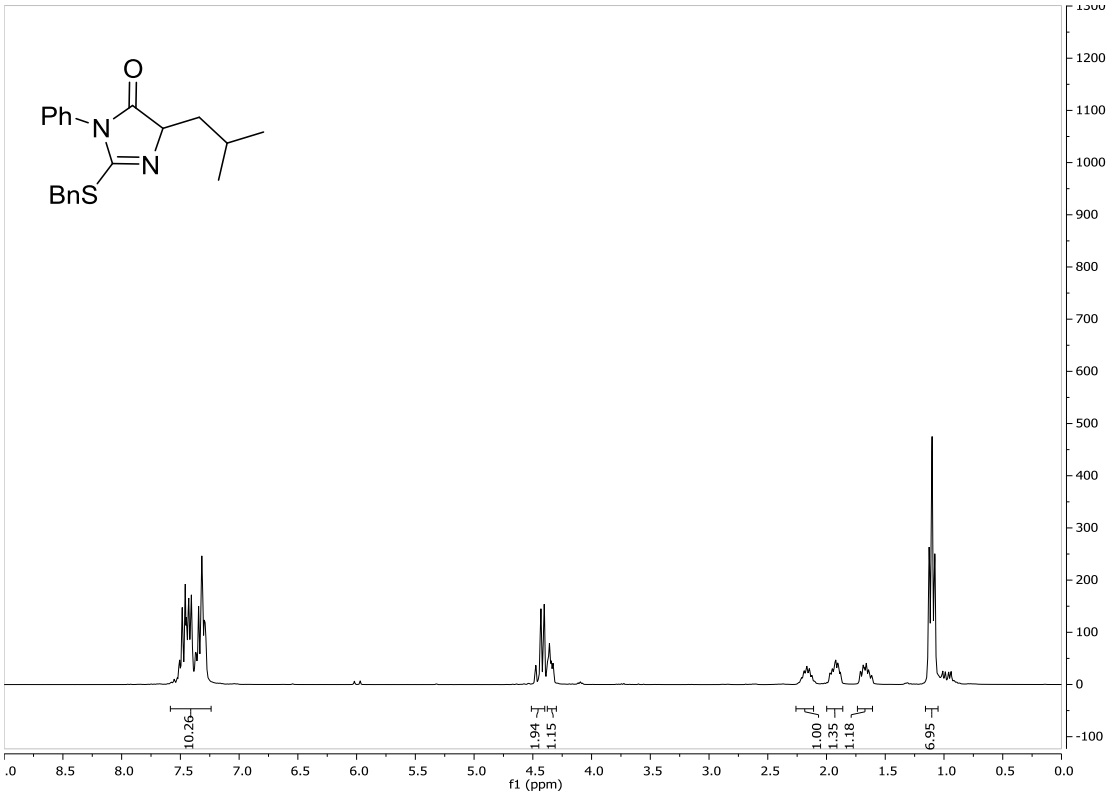


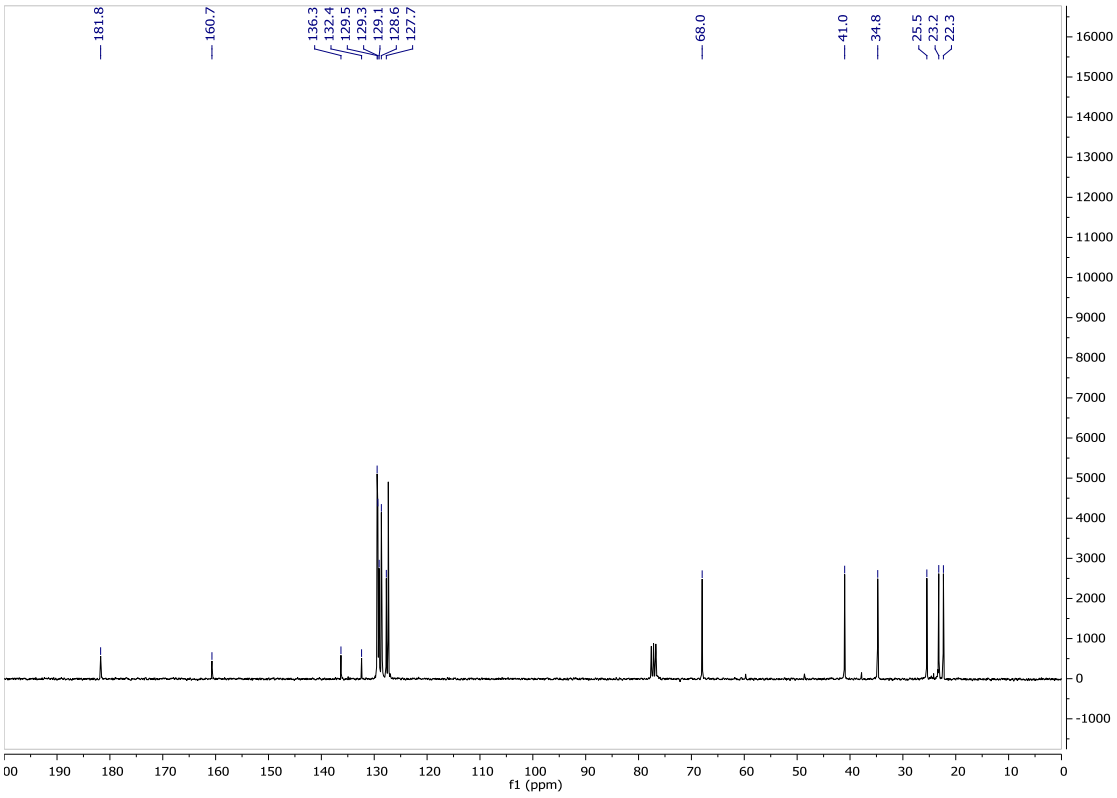
4-Benzyl-2-(benzylthio)-1-phenyl-1*H*-imidazol-5(4*H*)-one (61C)



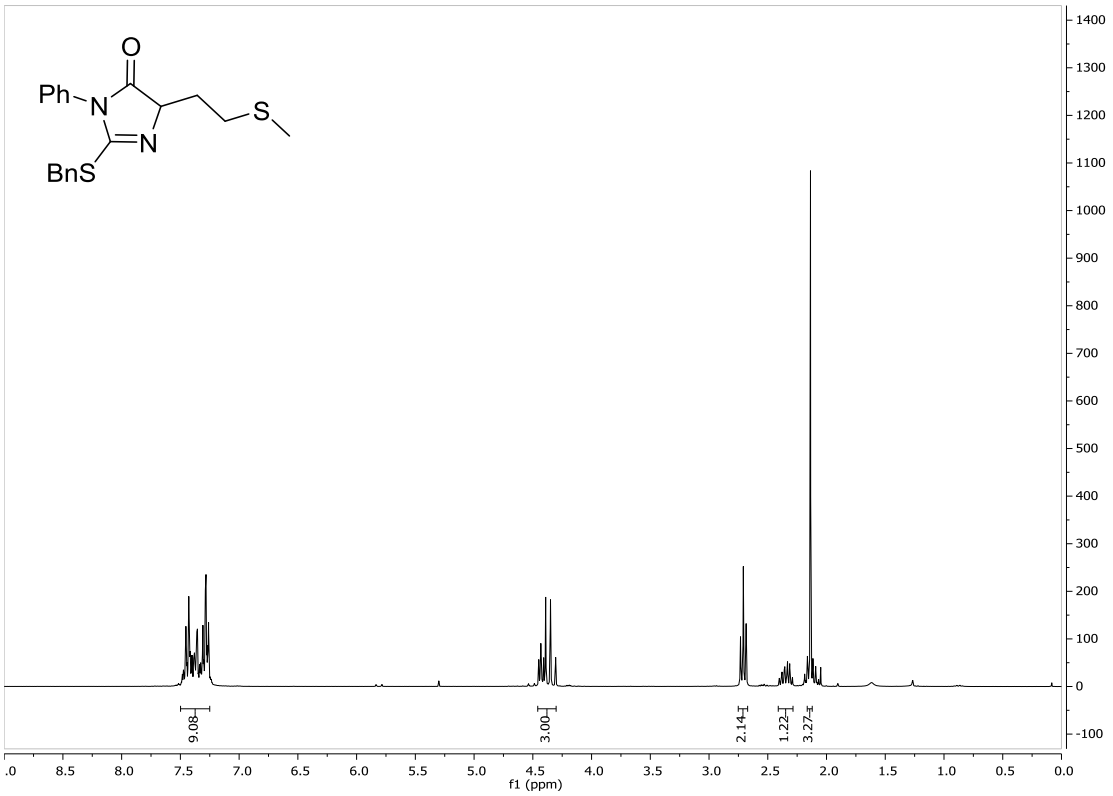


2-(Benzylthio)-4-isobutyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (61D)

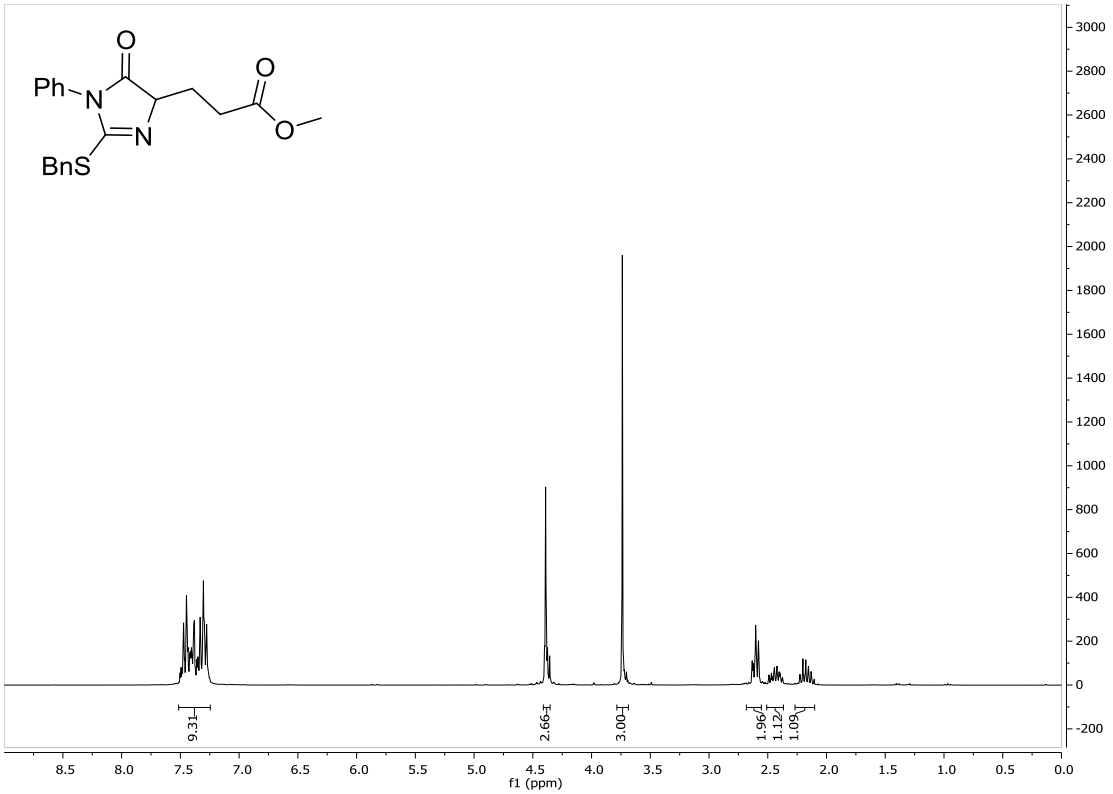


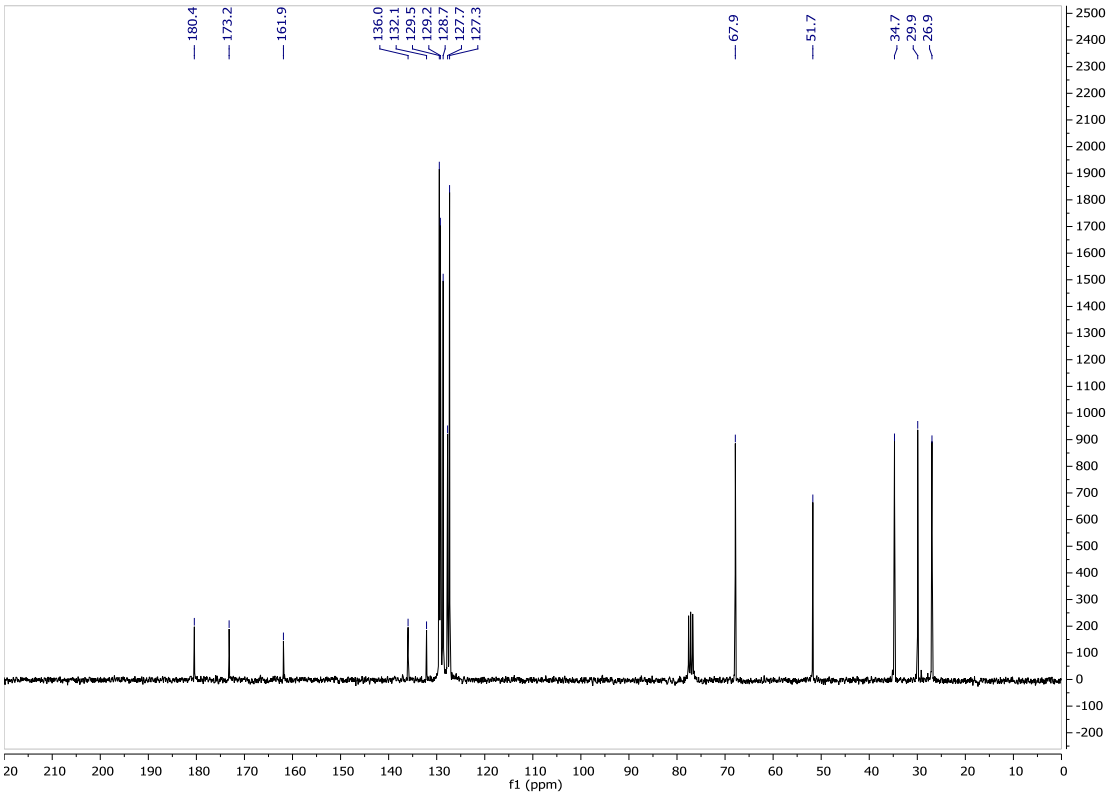


2-(Benzylthio)-4-(2-(methylthio)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (61F)

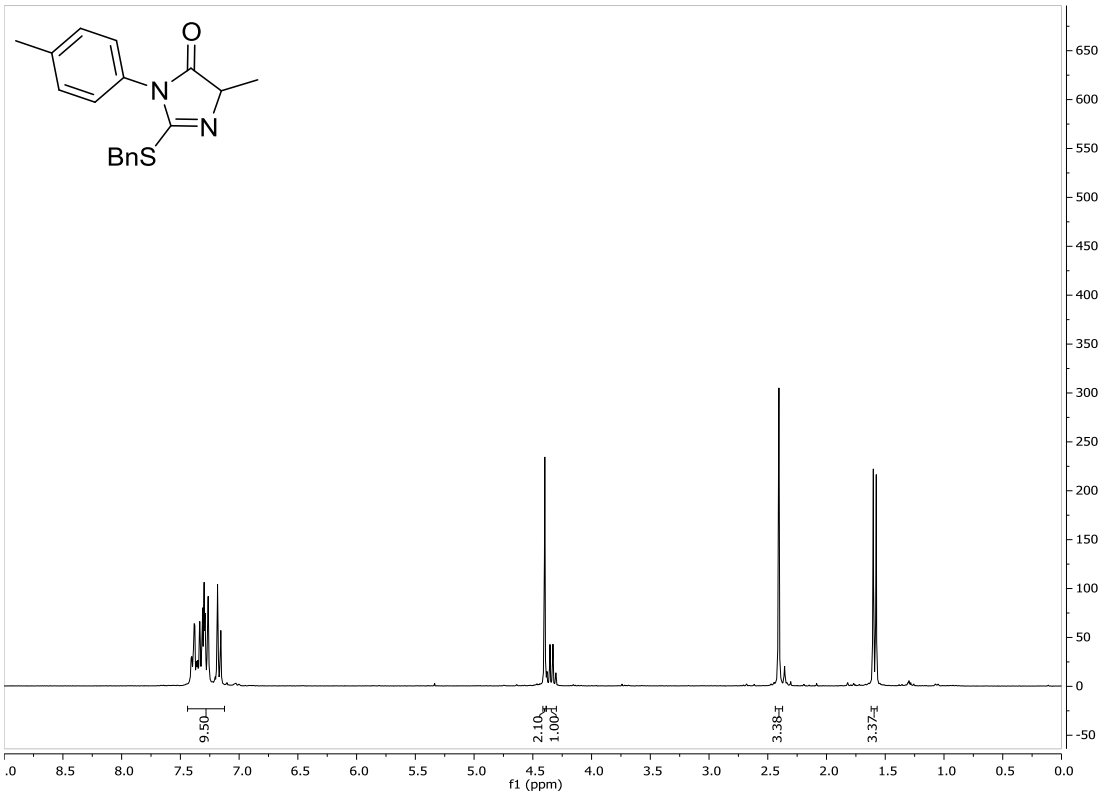


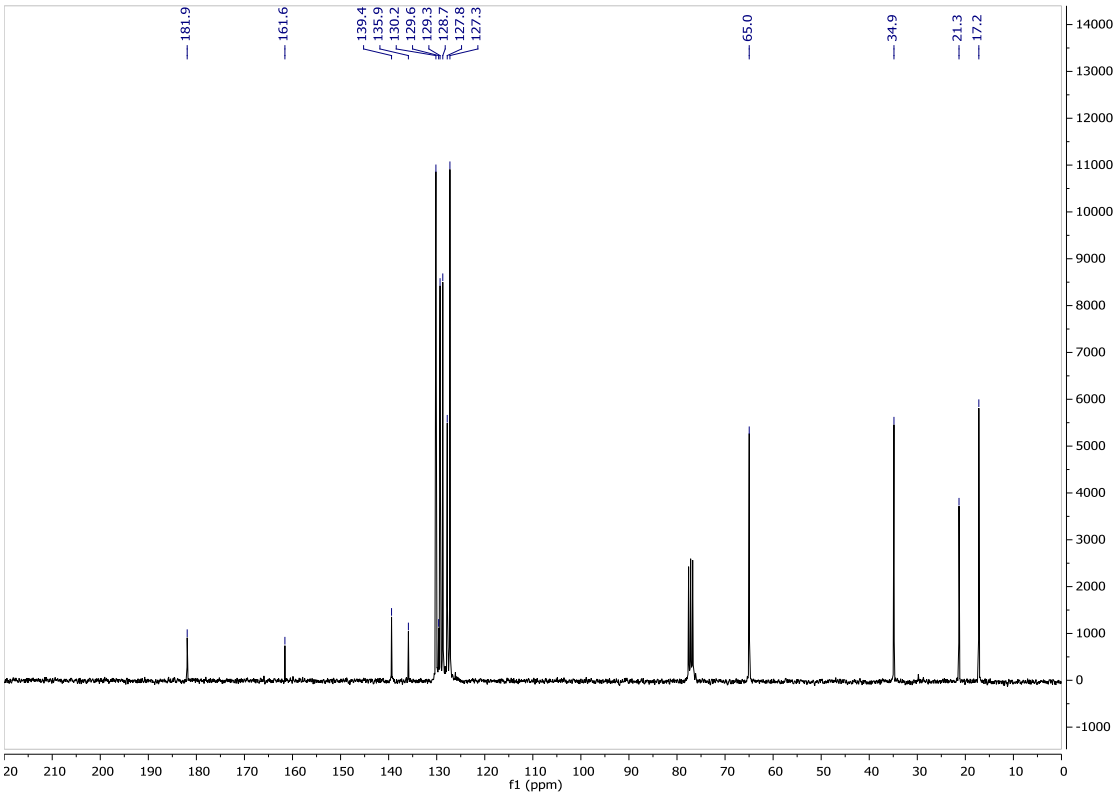
Methyl 3-(2-(benzylthio)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate (61l)



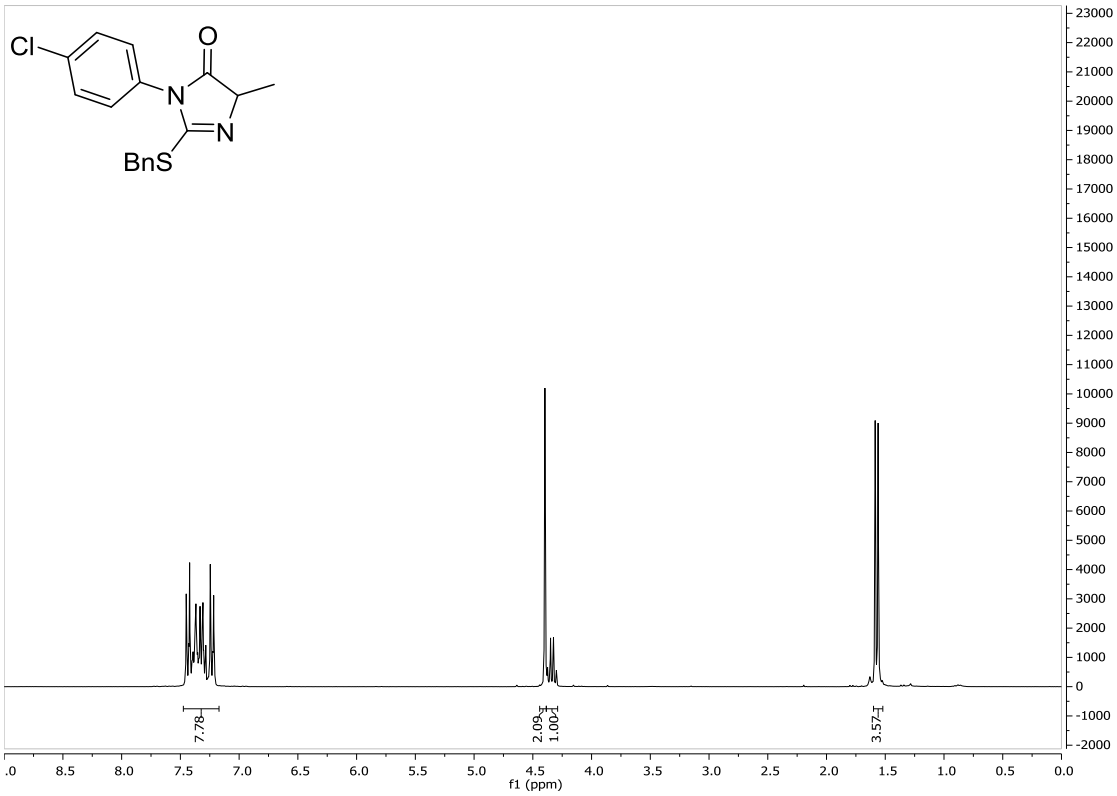


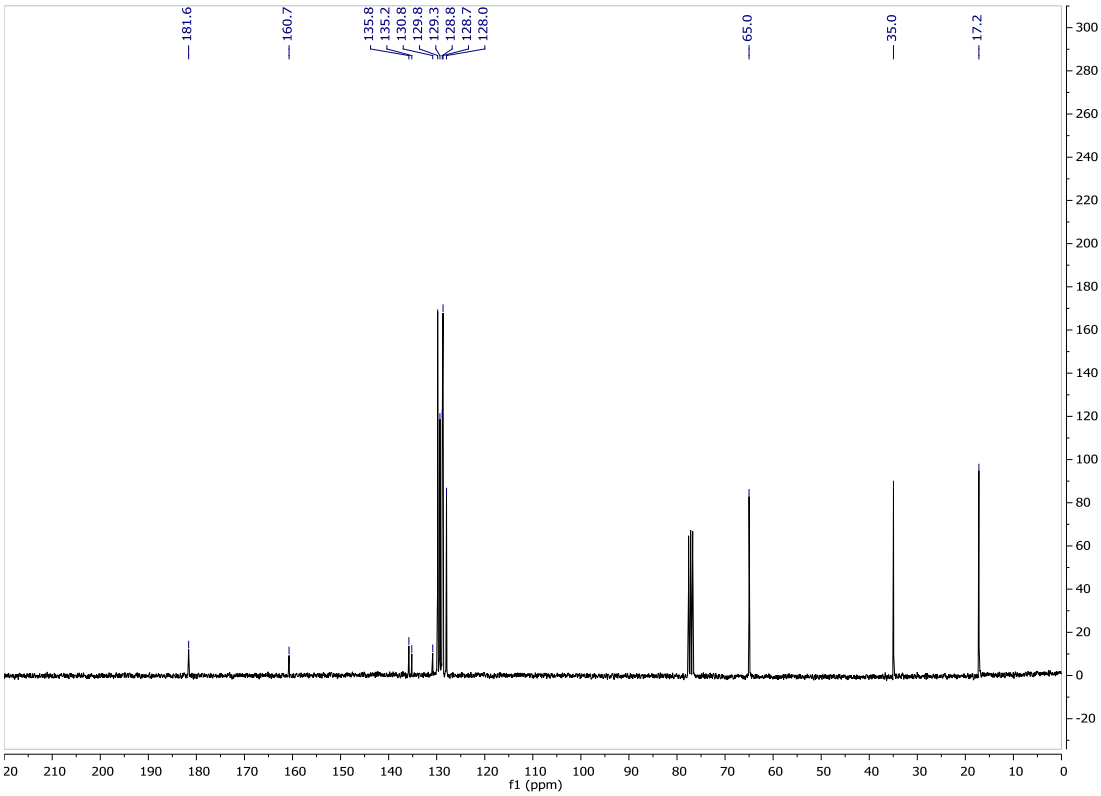
2-(Benzylthio)-4-methyl-1-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (62A)



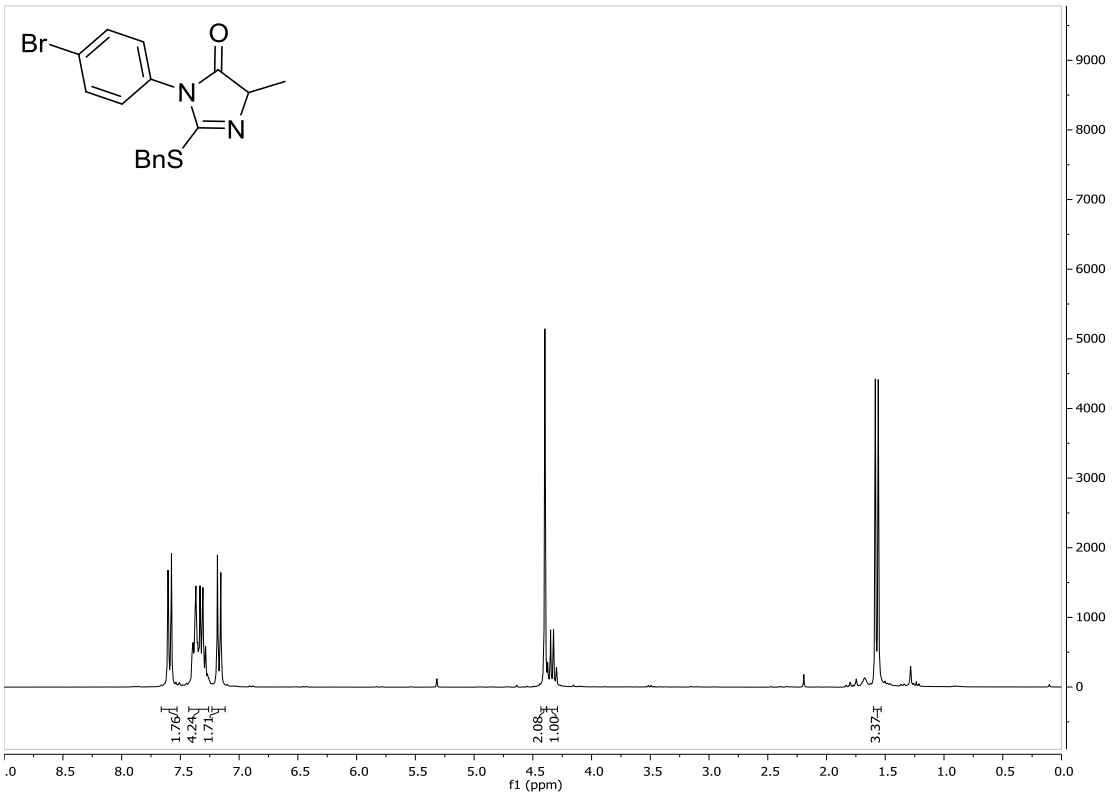


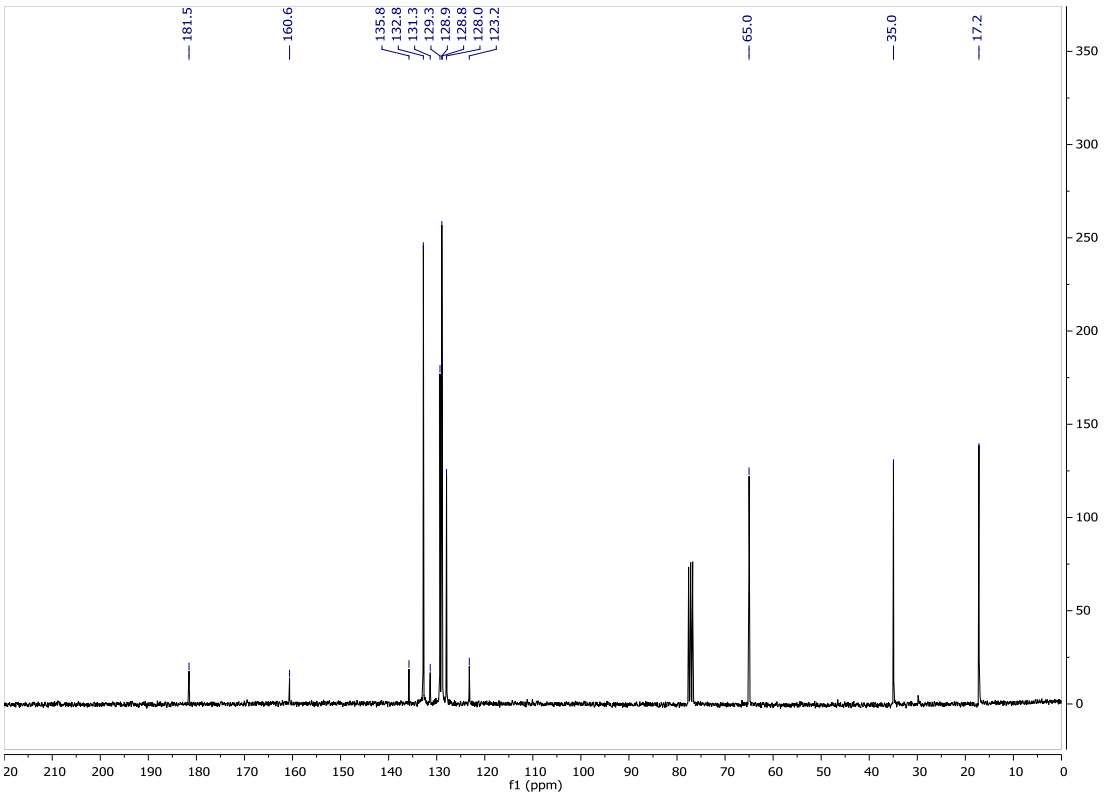
2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (63A)



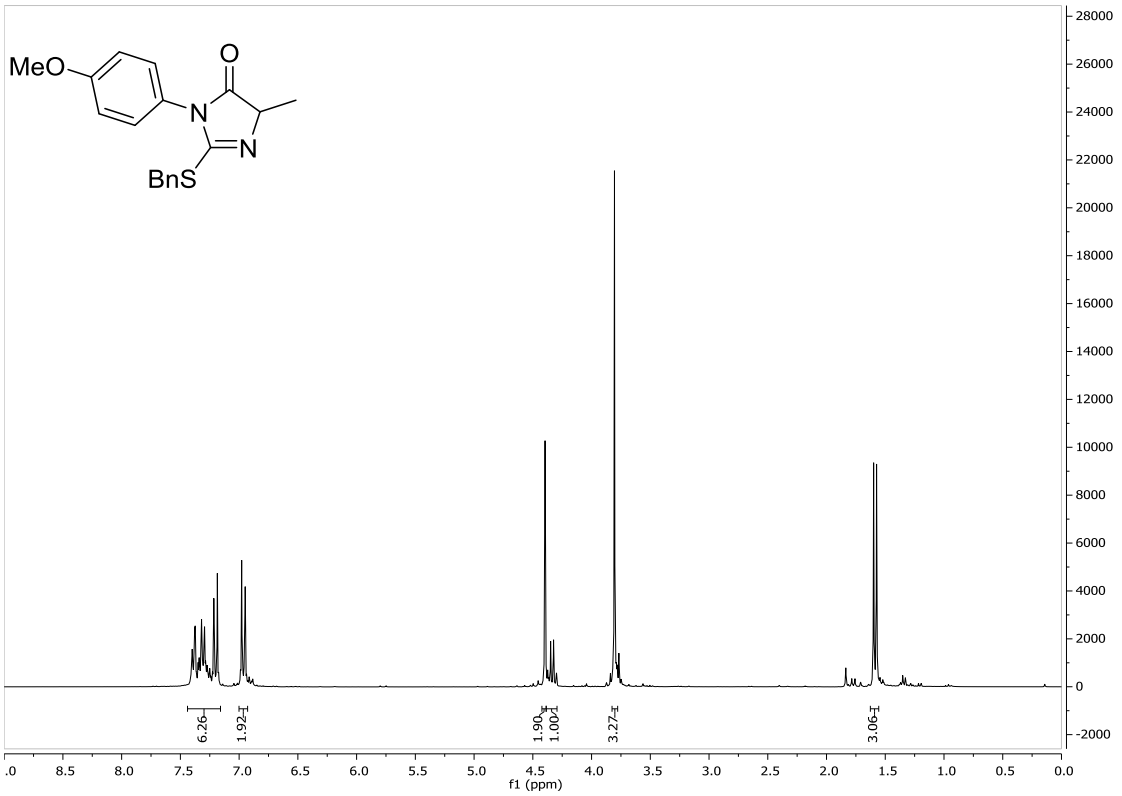


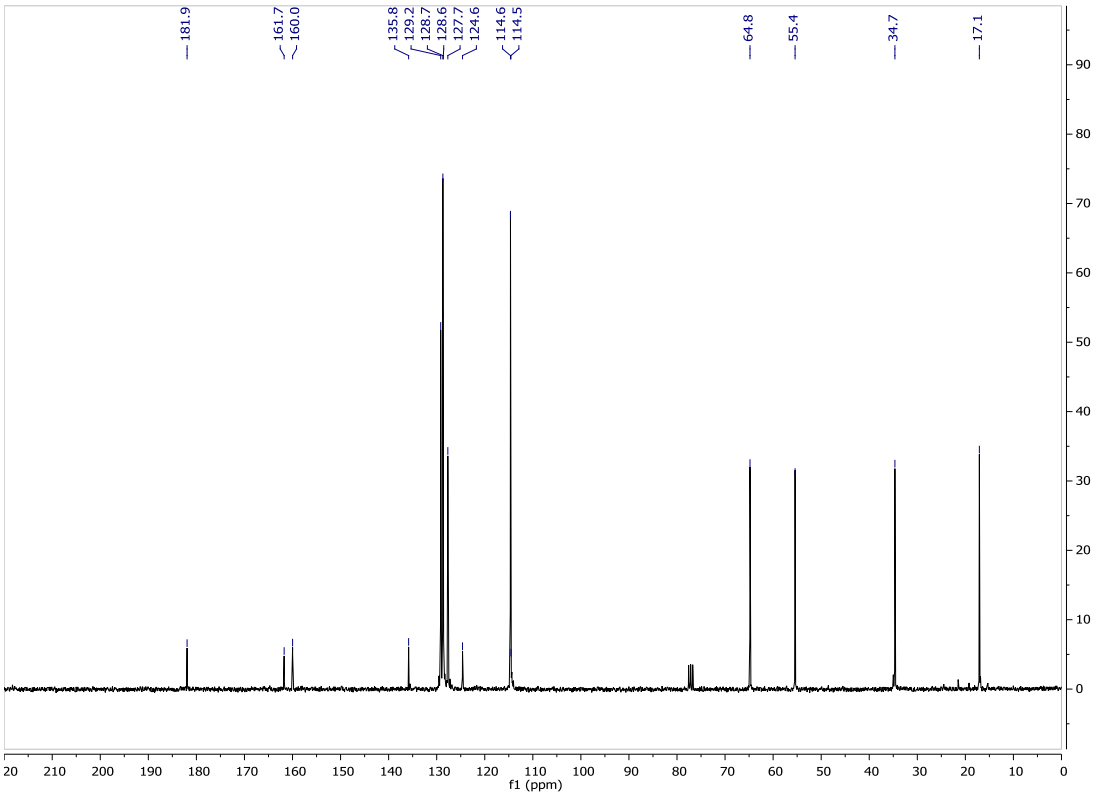
2-(Benzylthio)-1-(4-bromophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (64A)



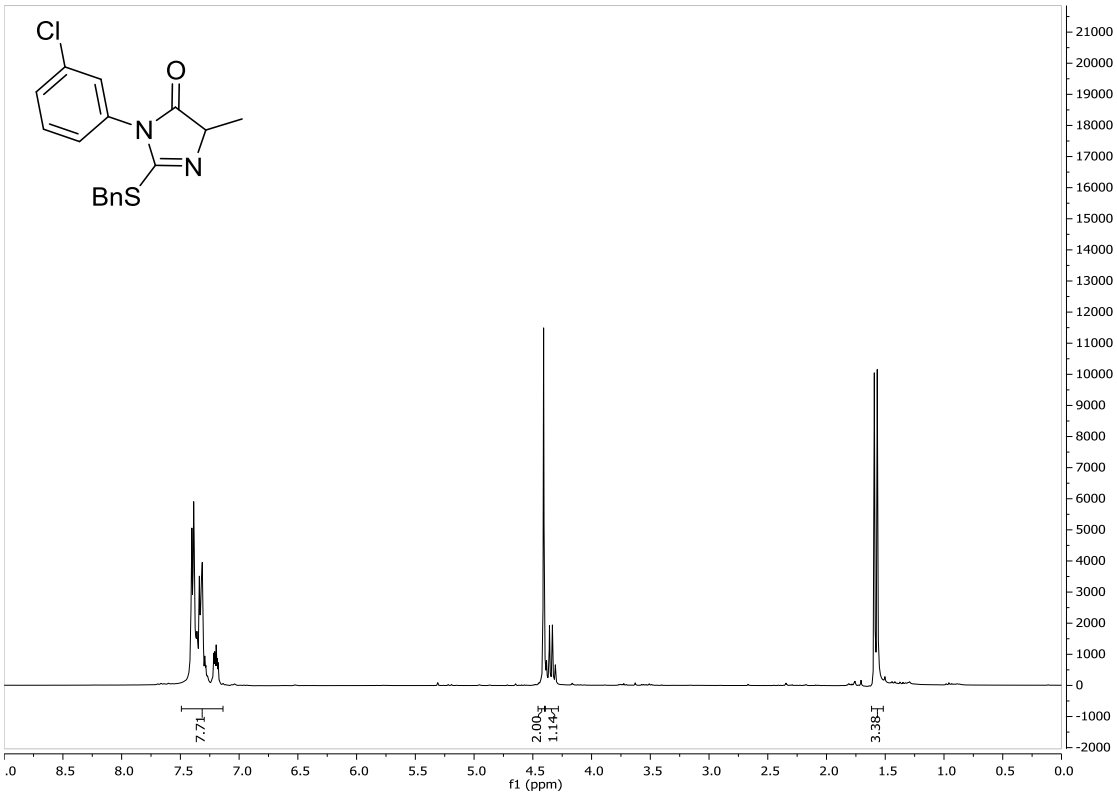


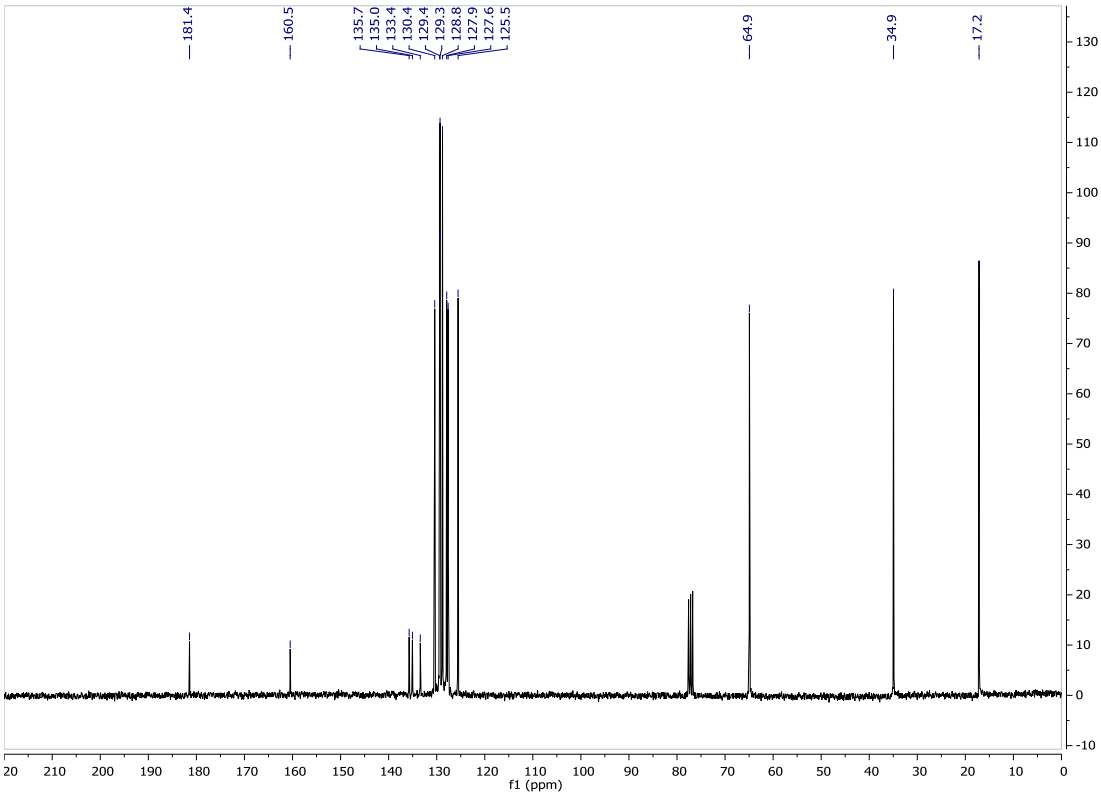
2-(Benzylthio)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (65A)



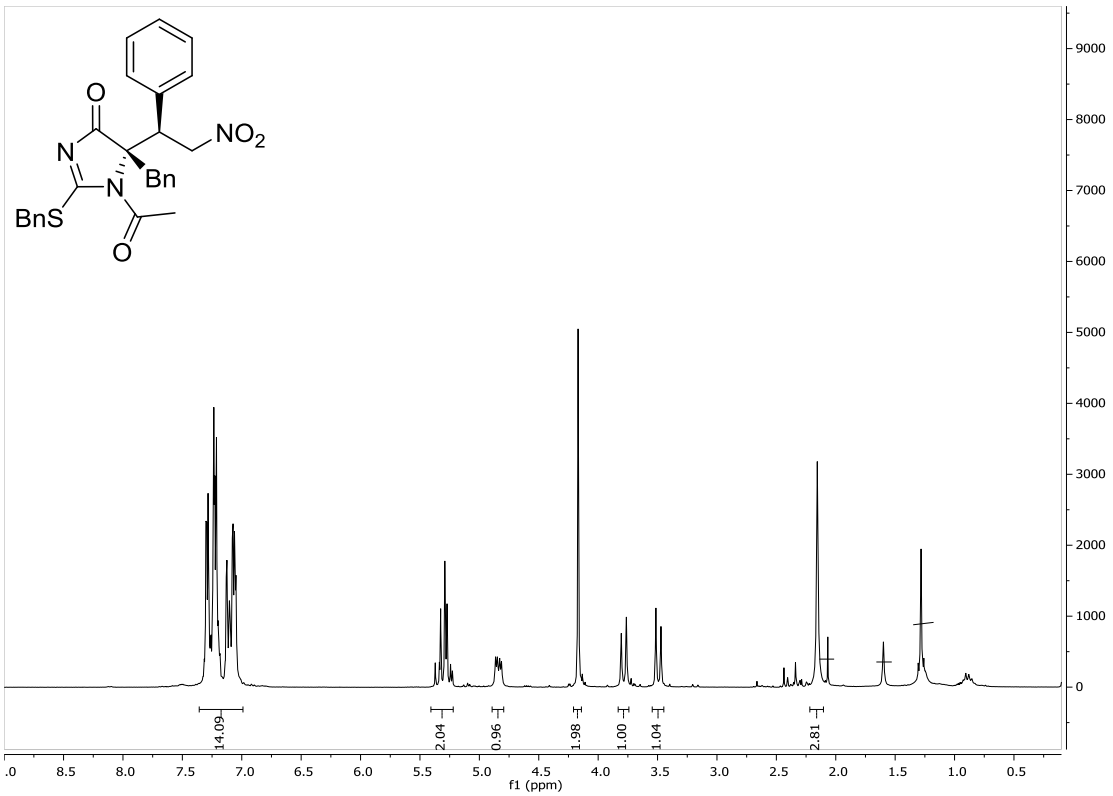


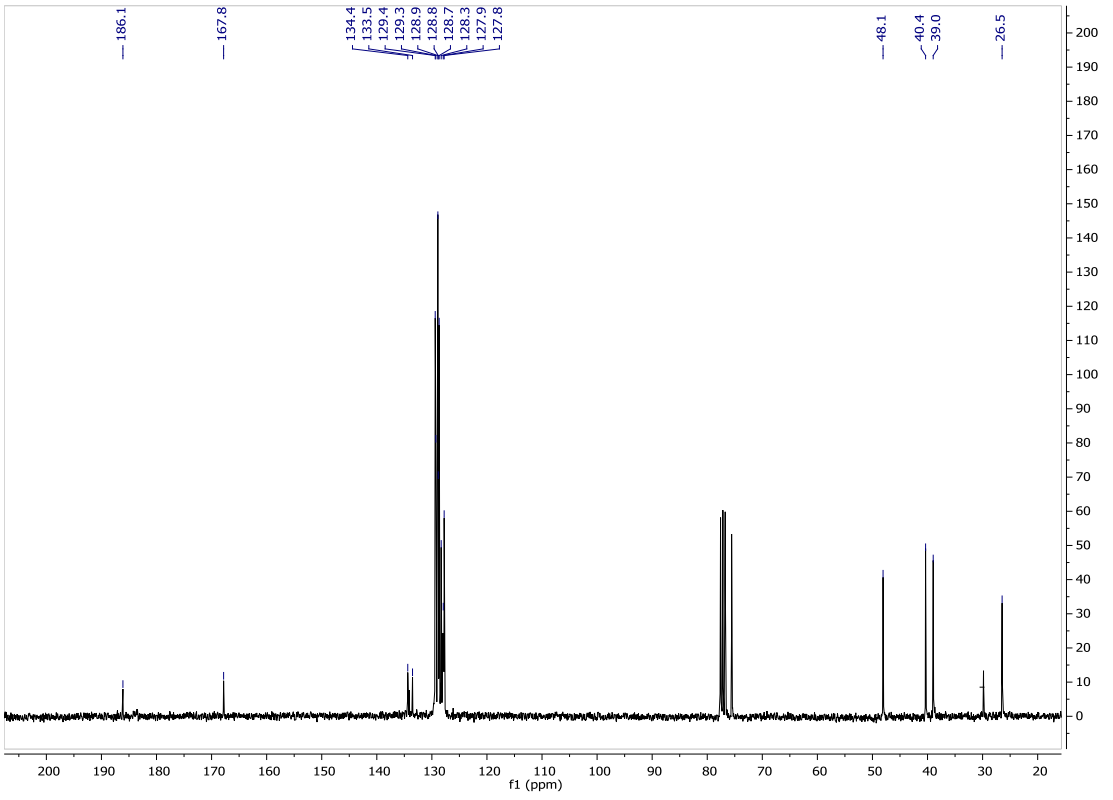
2-(Benzylthio)-1-(3-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (66A)



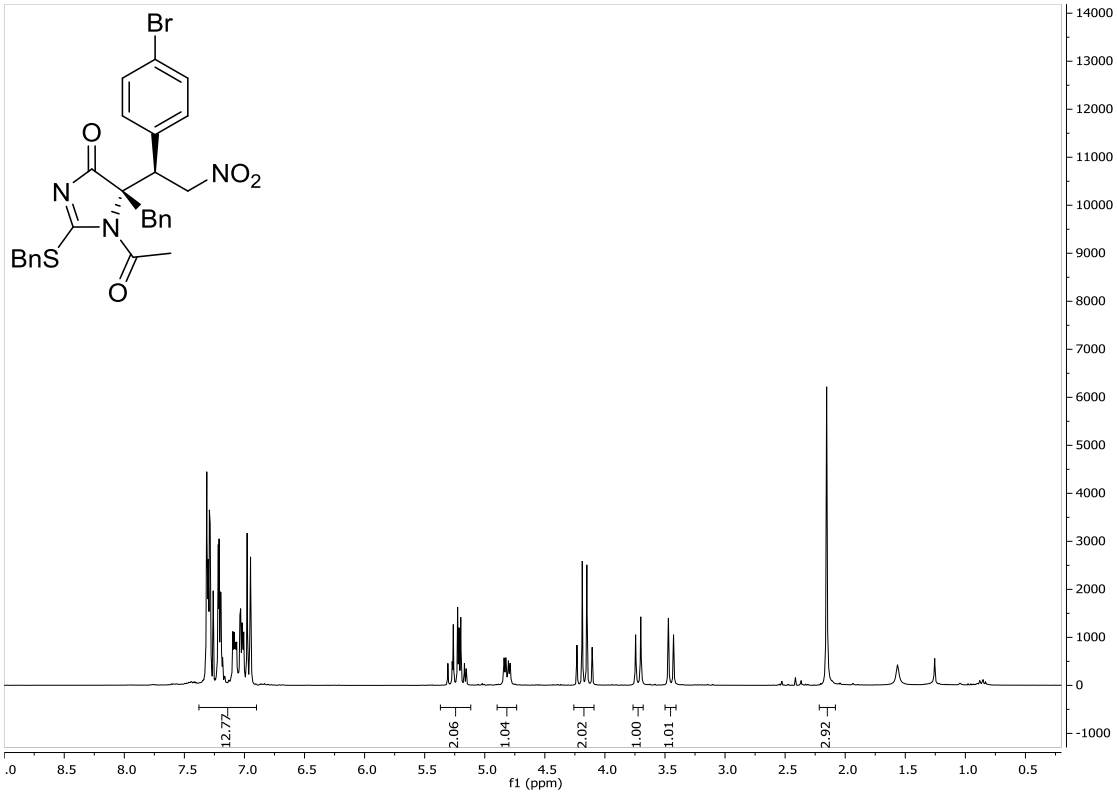


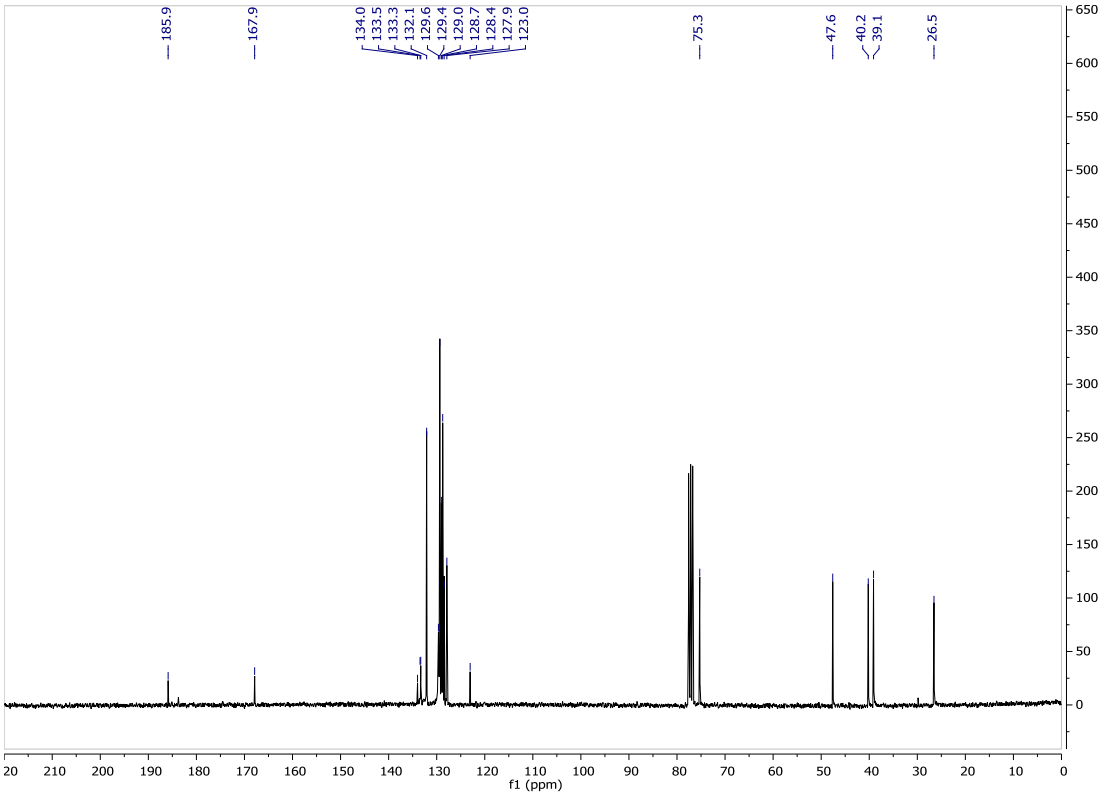
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (37Ca)



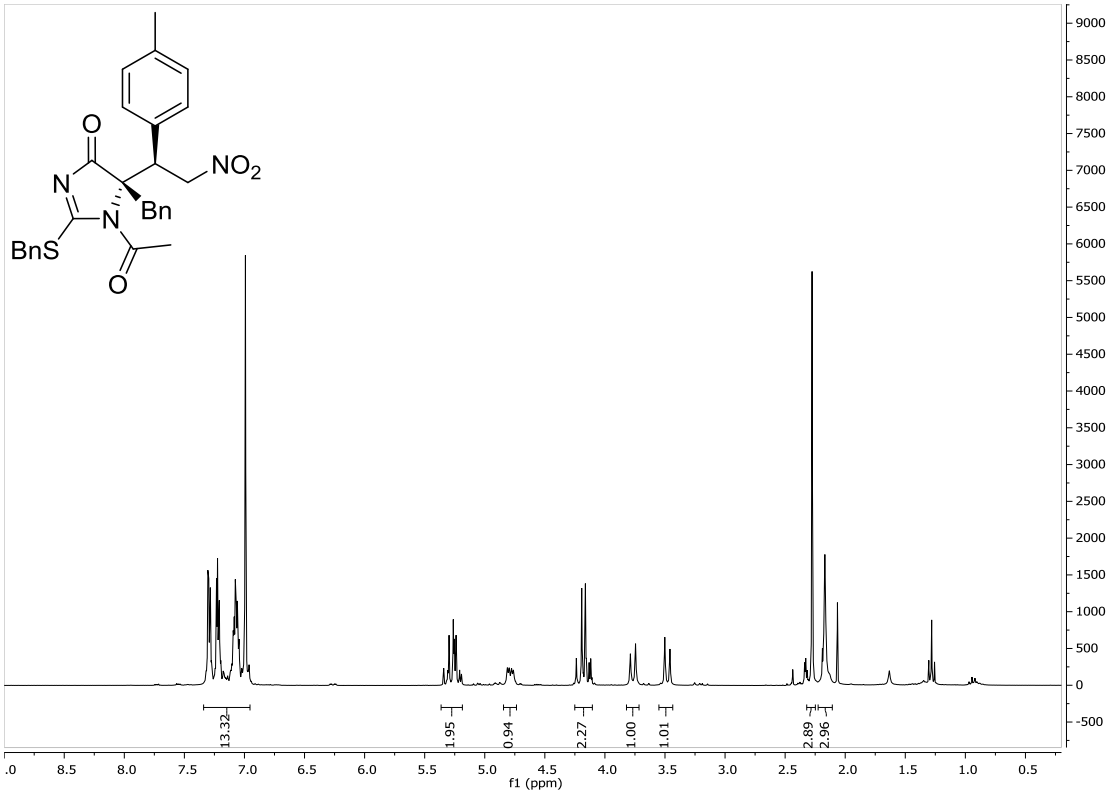


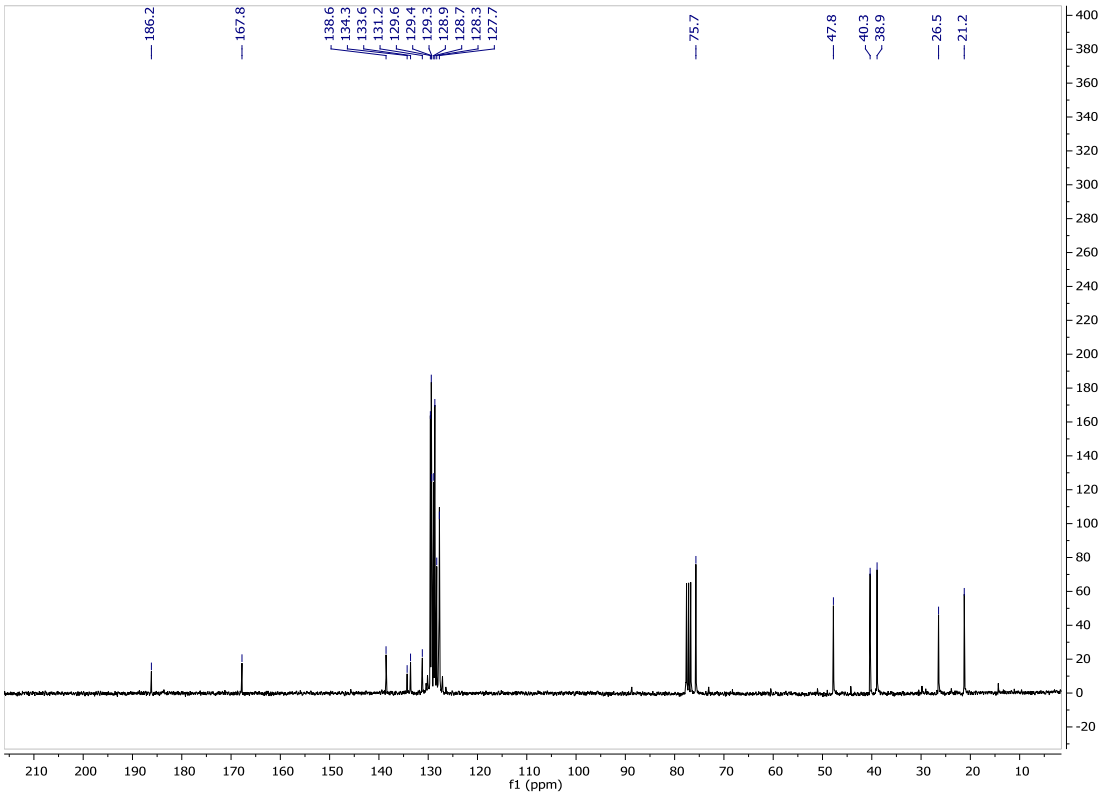
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (37Cb)



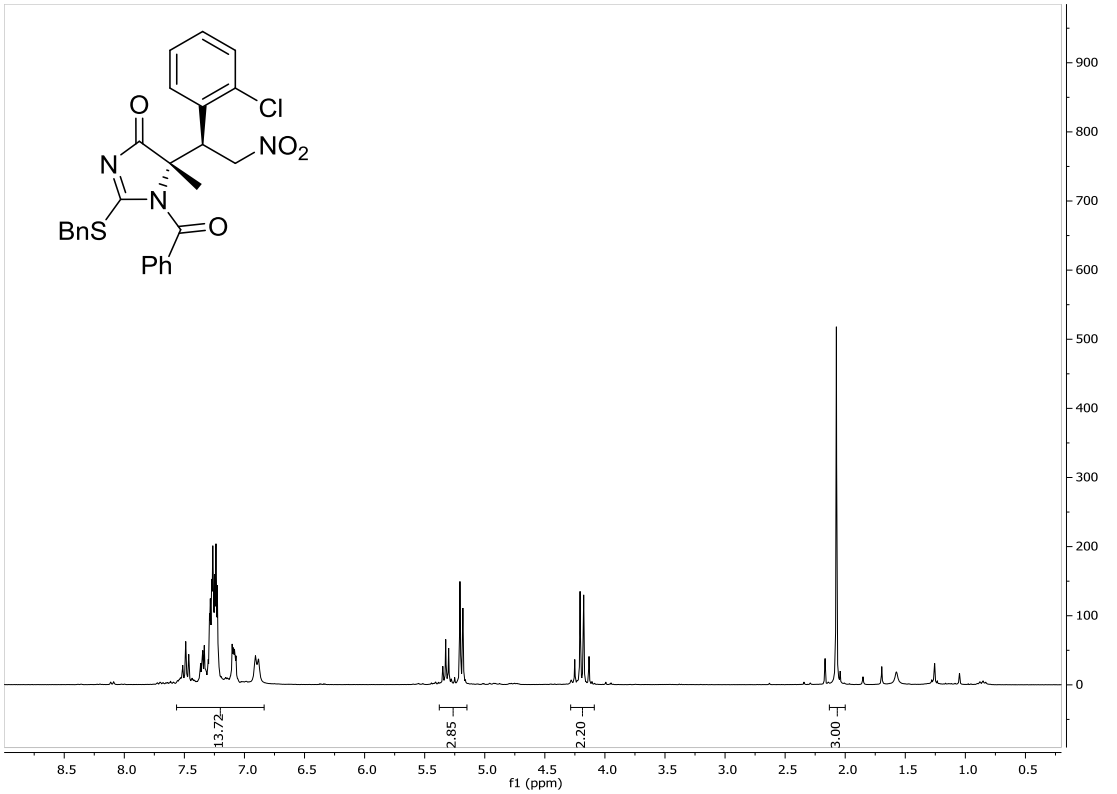


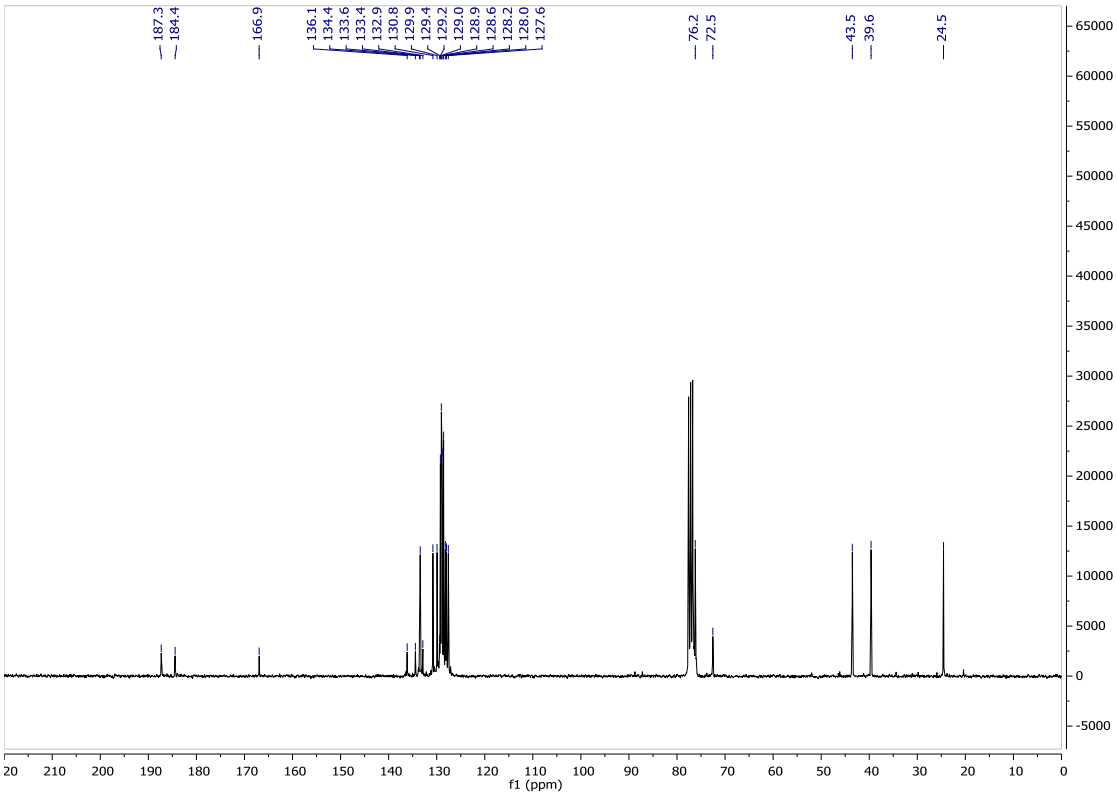
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (37Cc)



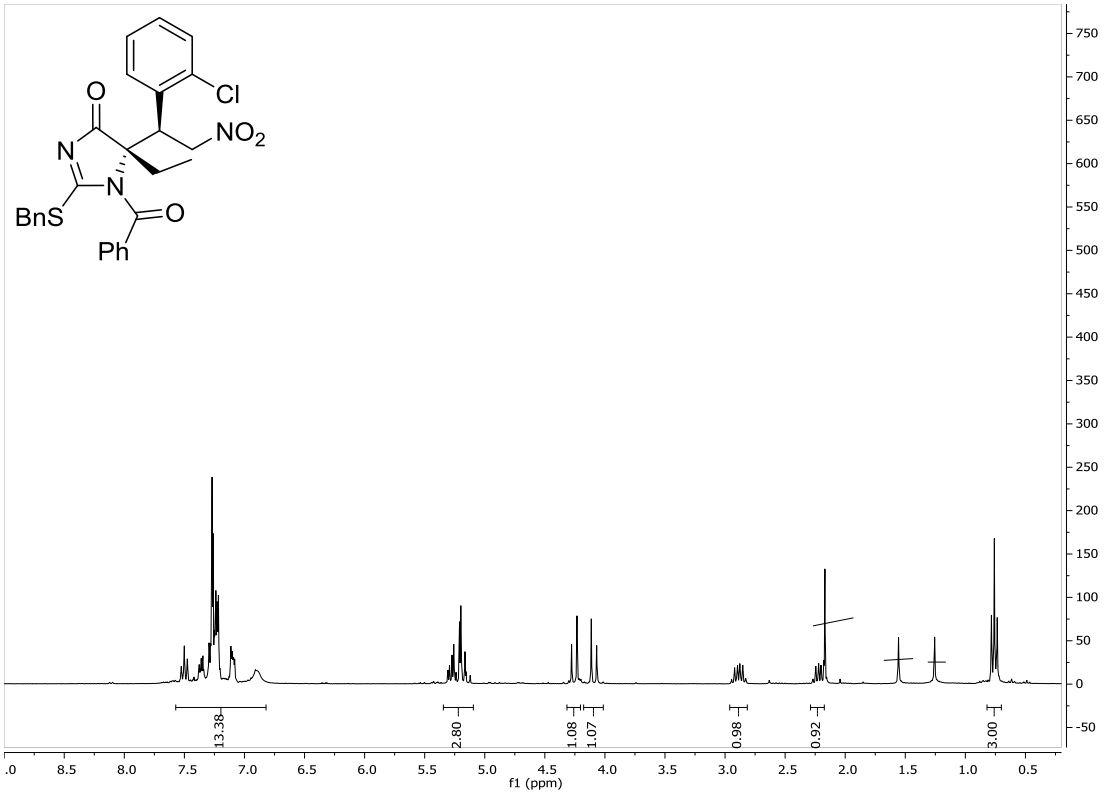


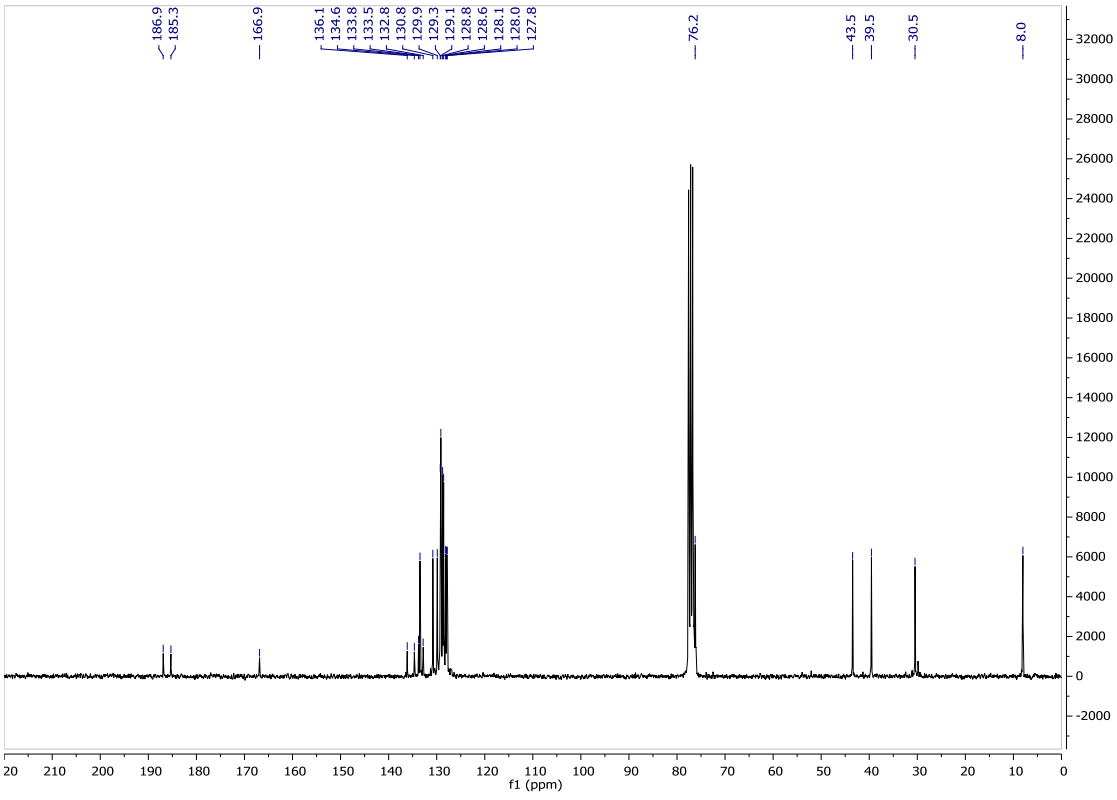
(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (38Ad)



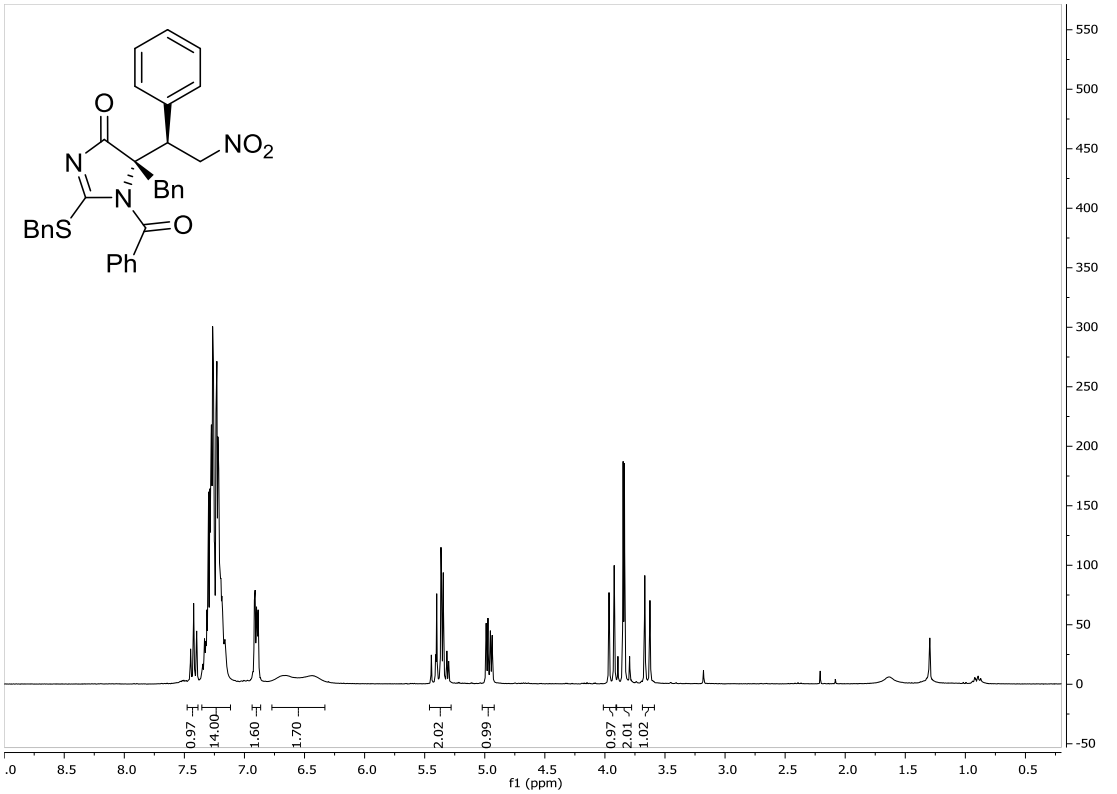


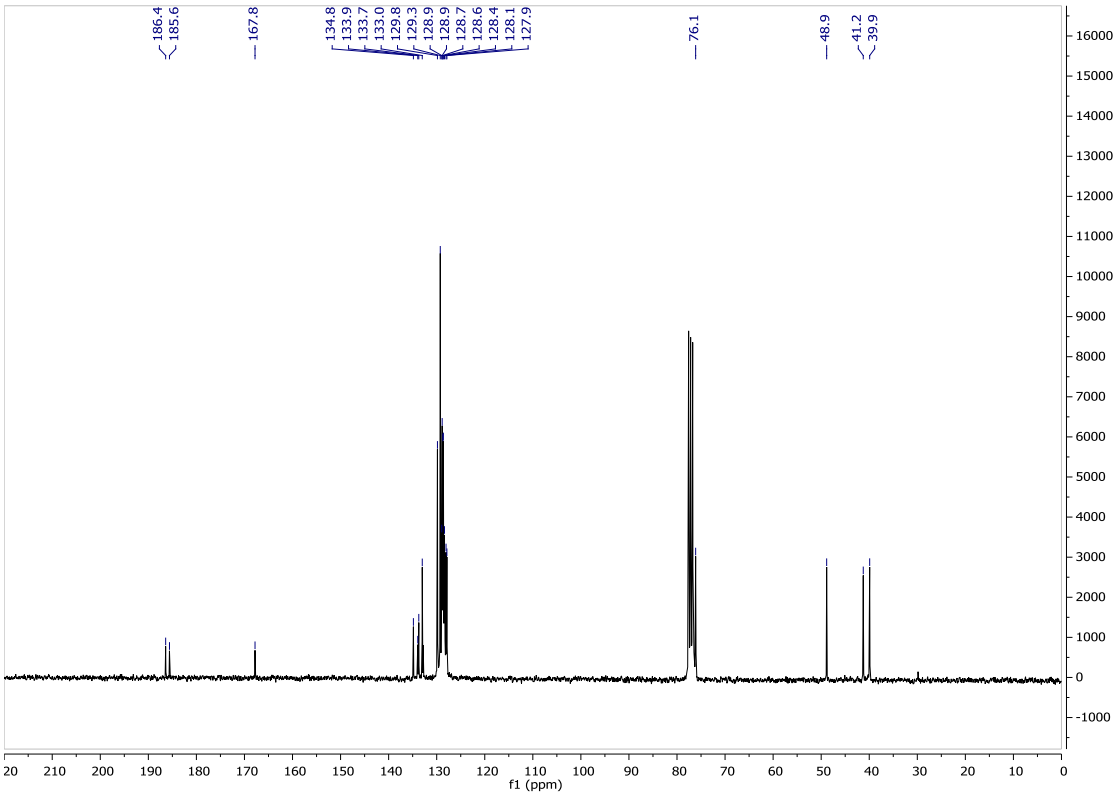
(*S*)-1-Benzoyl-2-(benzylthio)-5-((S)-1-(2-chlorophenyl)-2-nitroethyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one (38Bd)



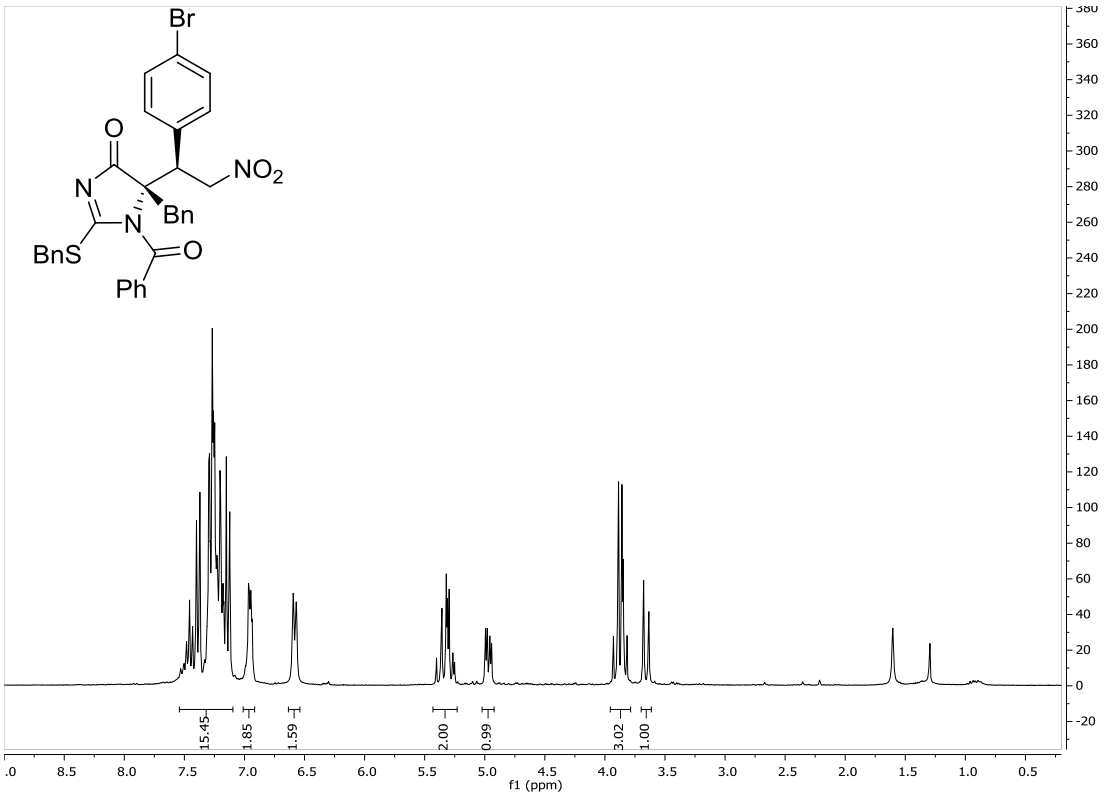


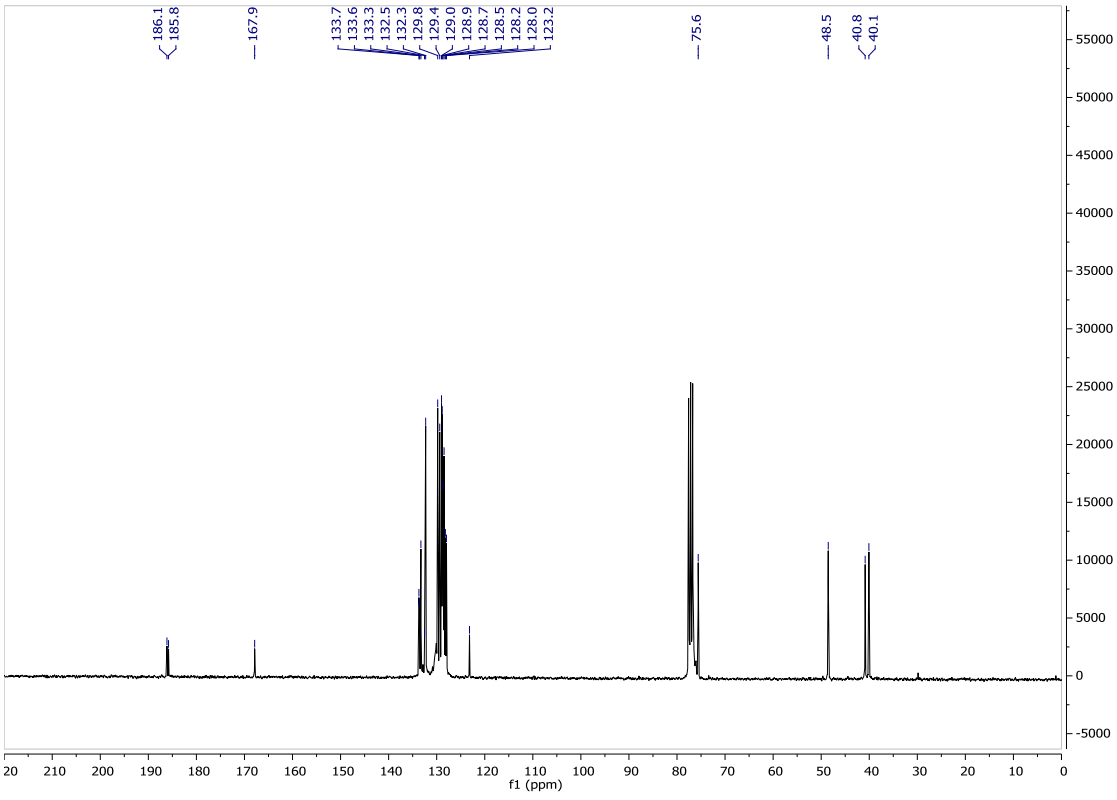
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ca)



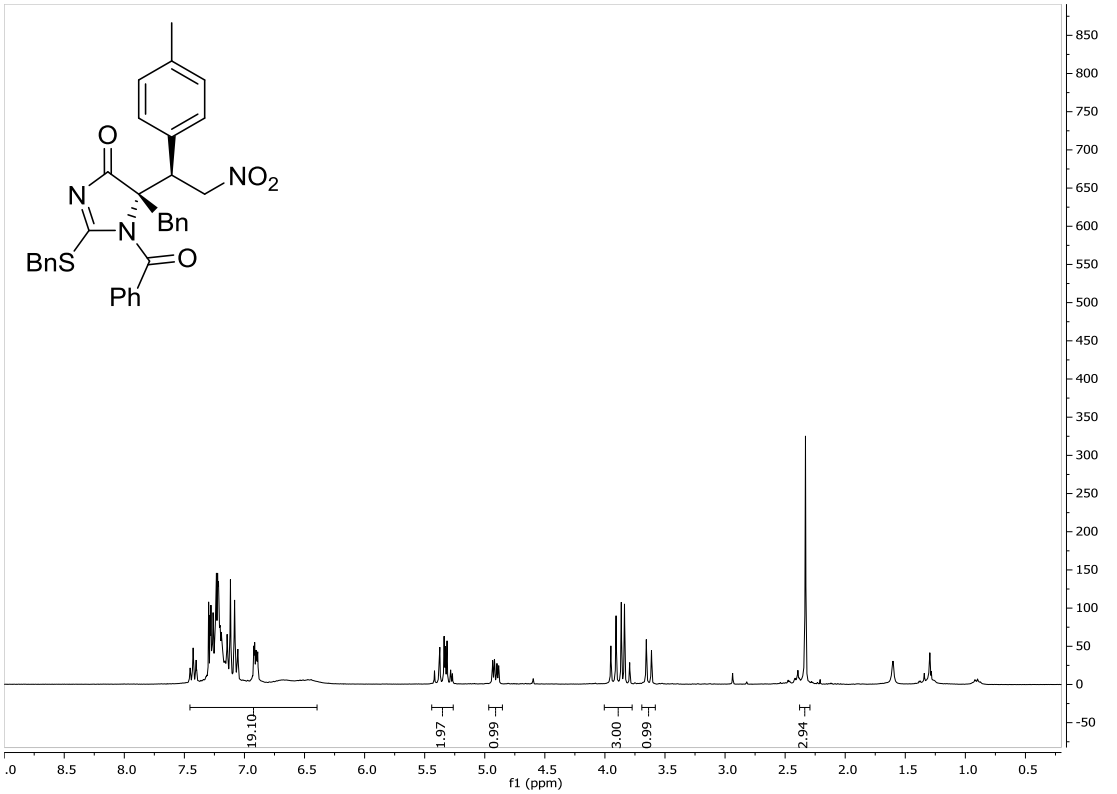


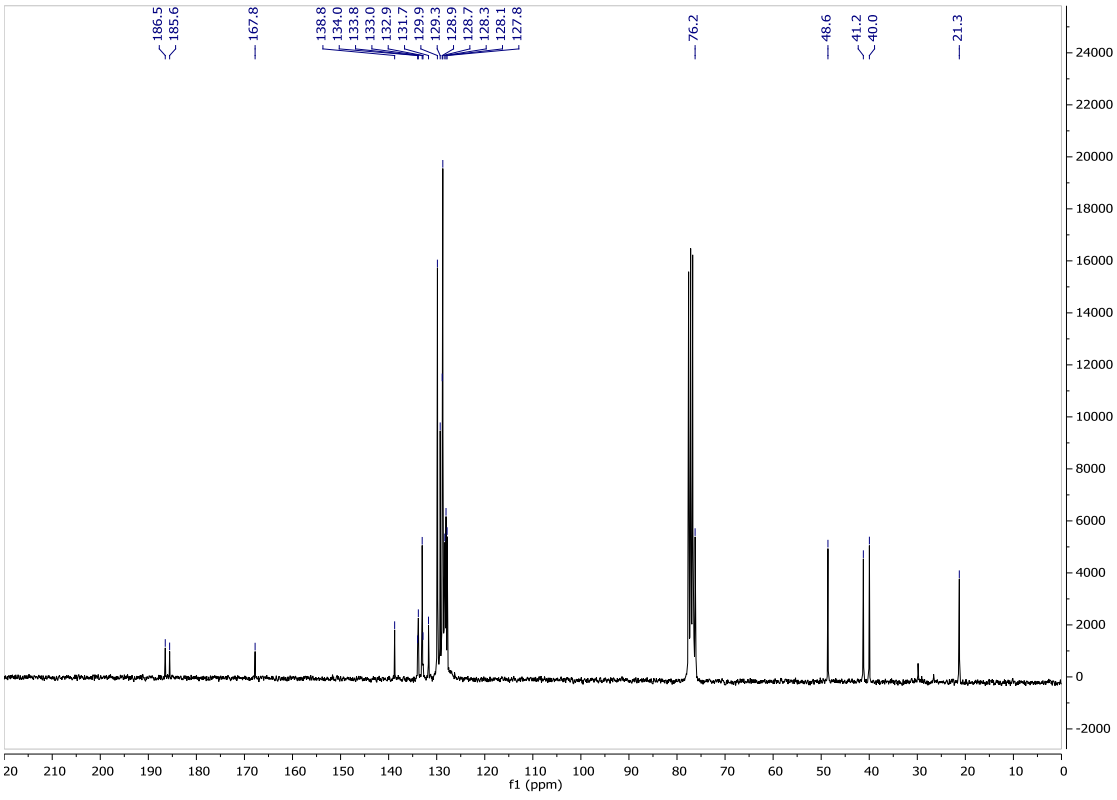
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cb)



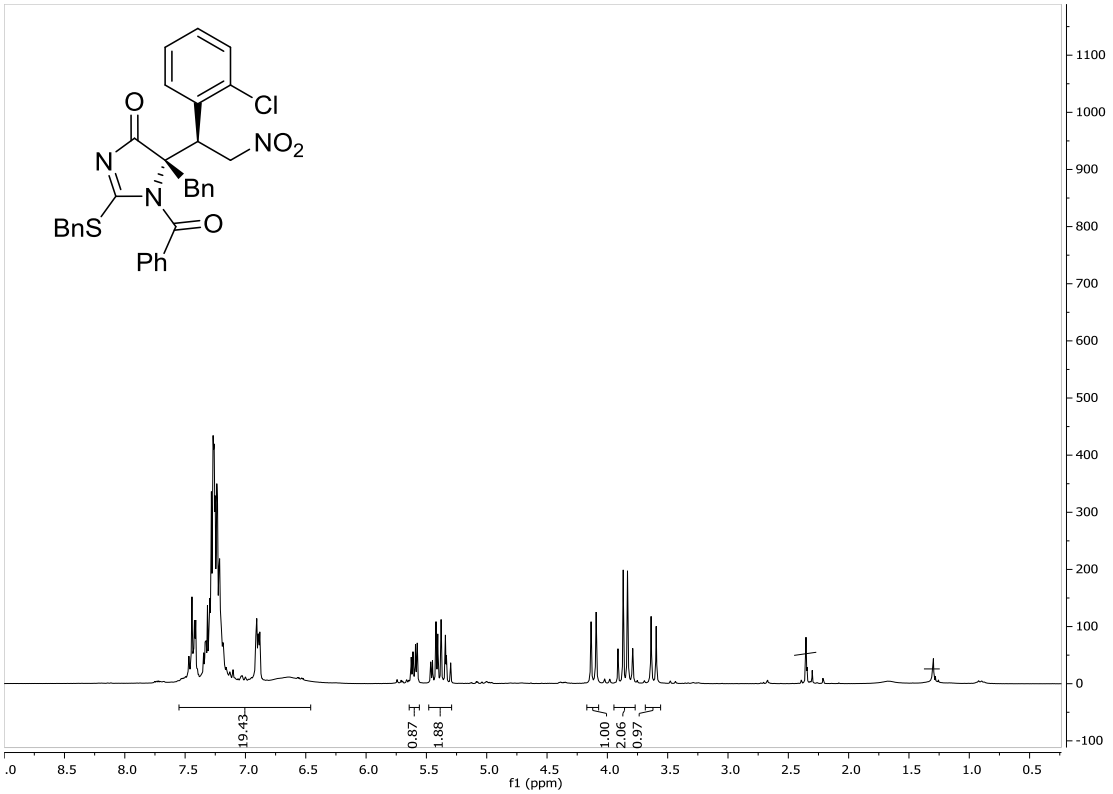


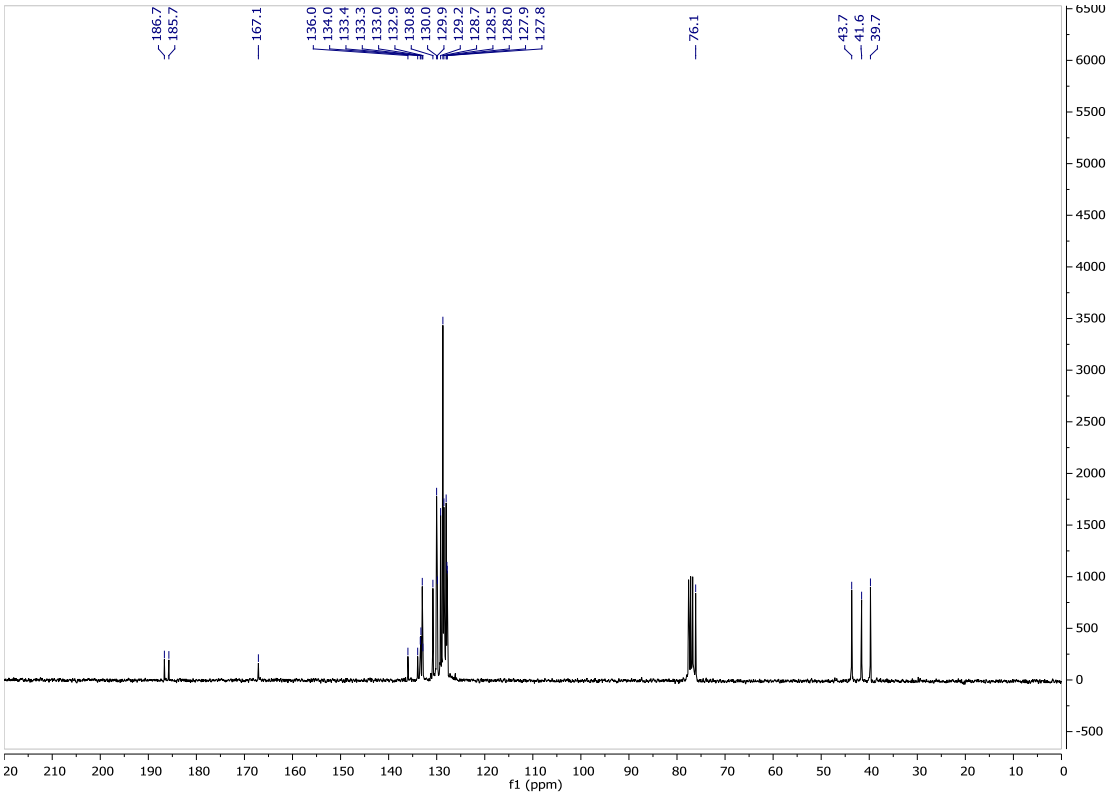
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(p-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (38Cc)



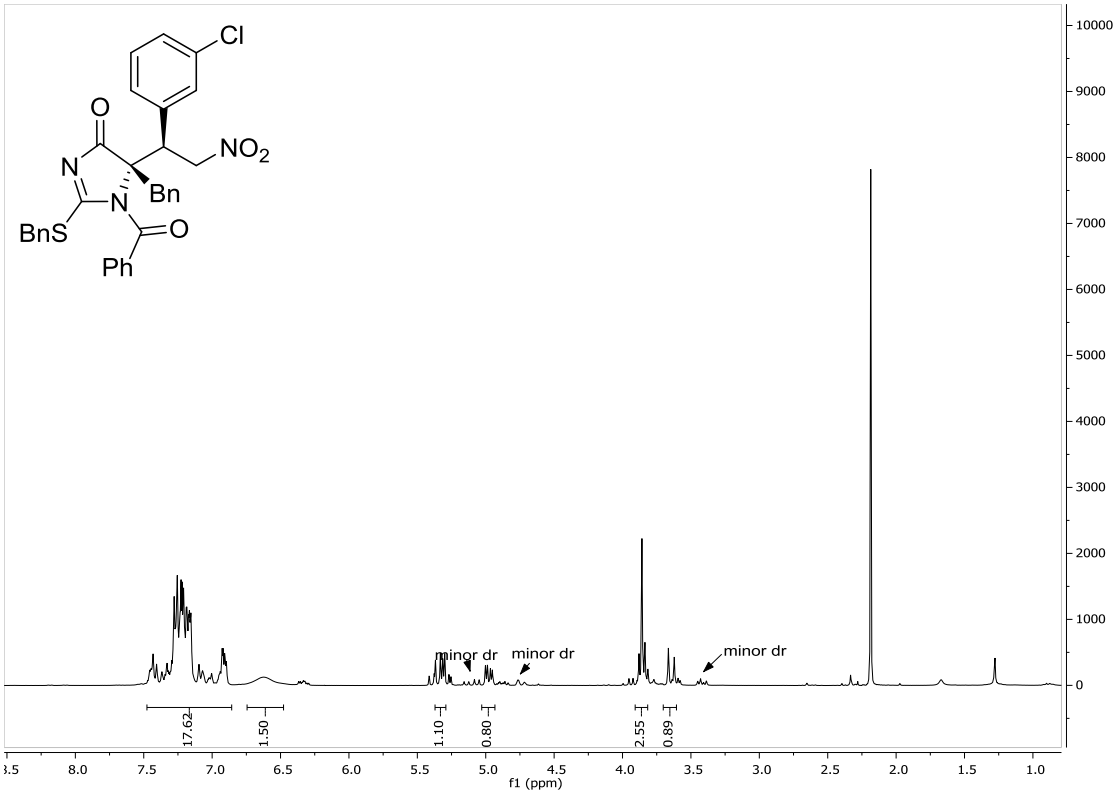


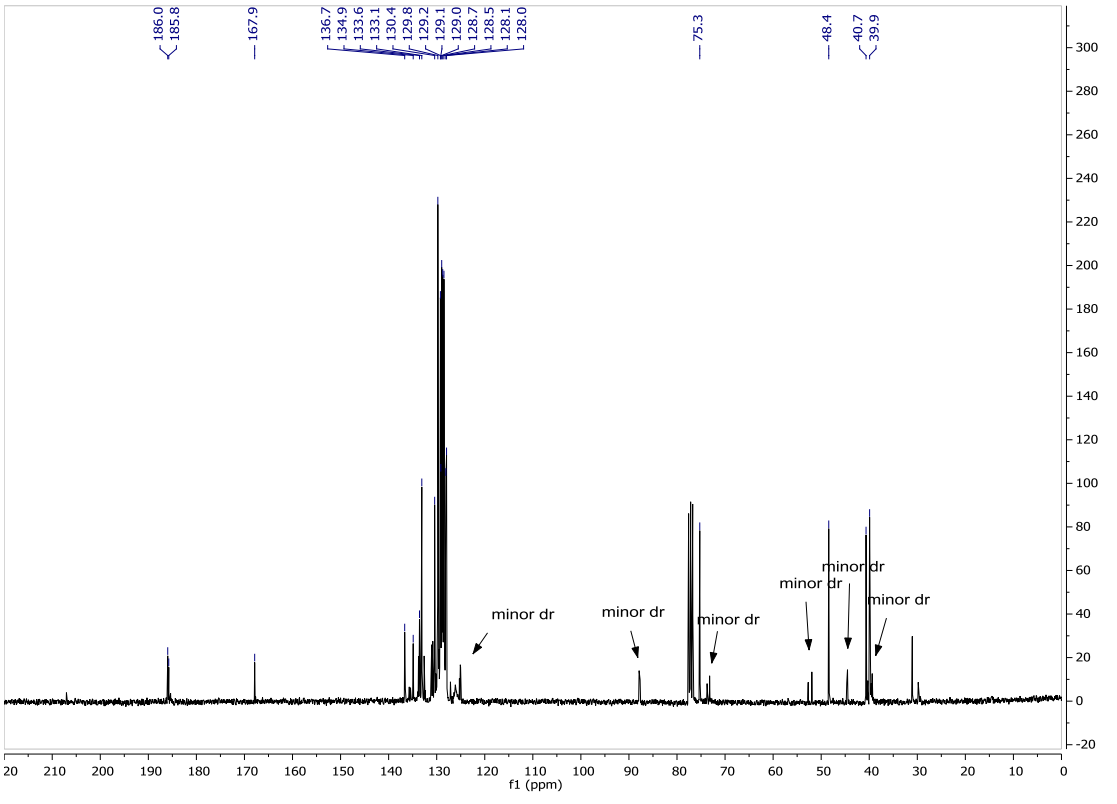
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cd)



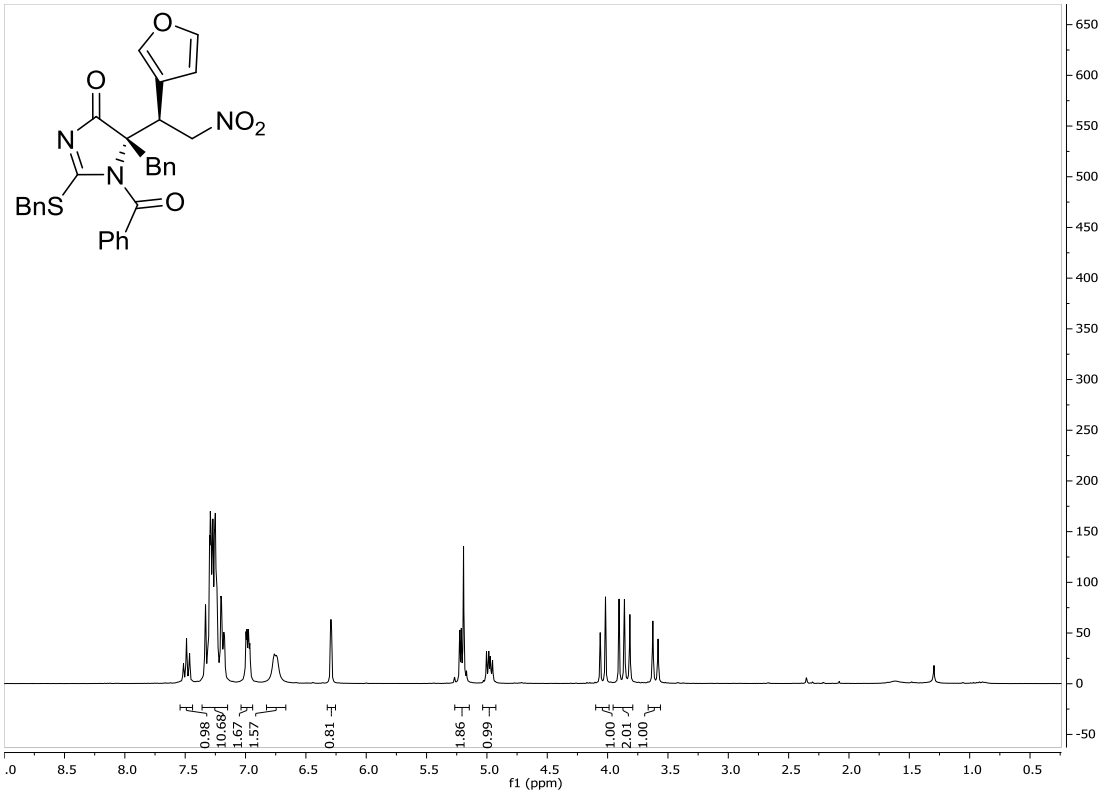


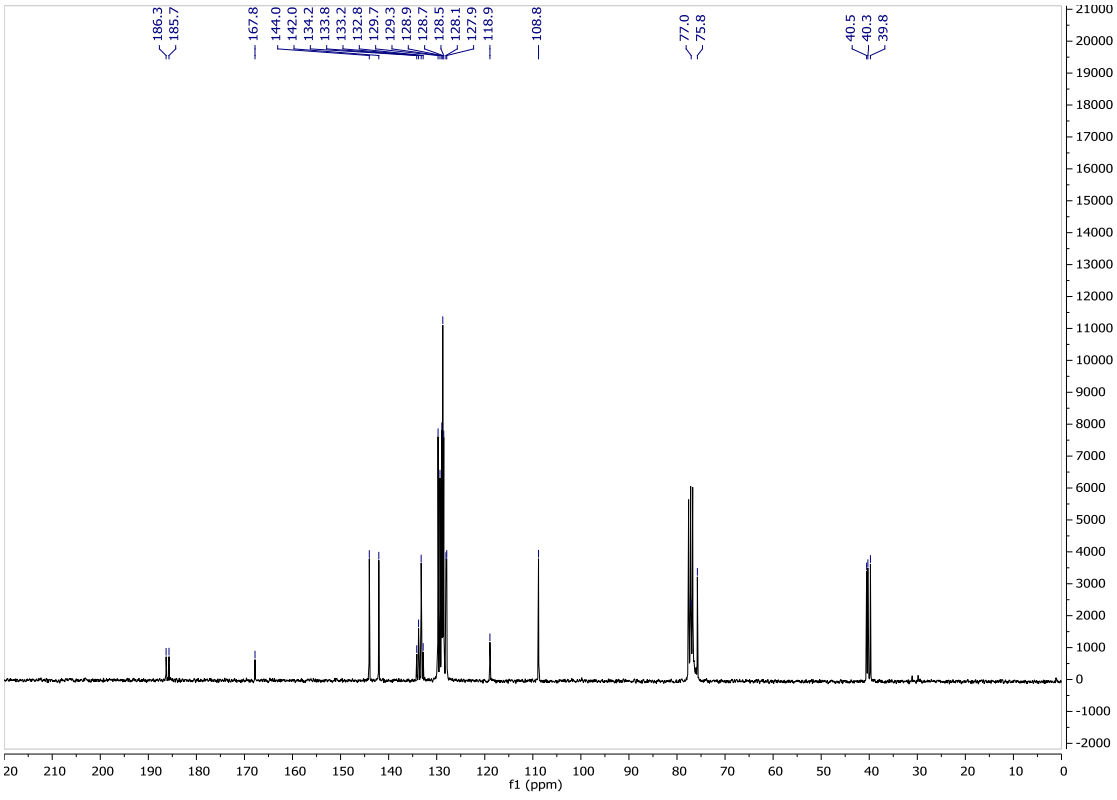
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Ce)



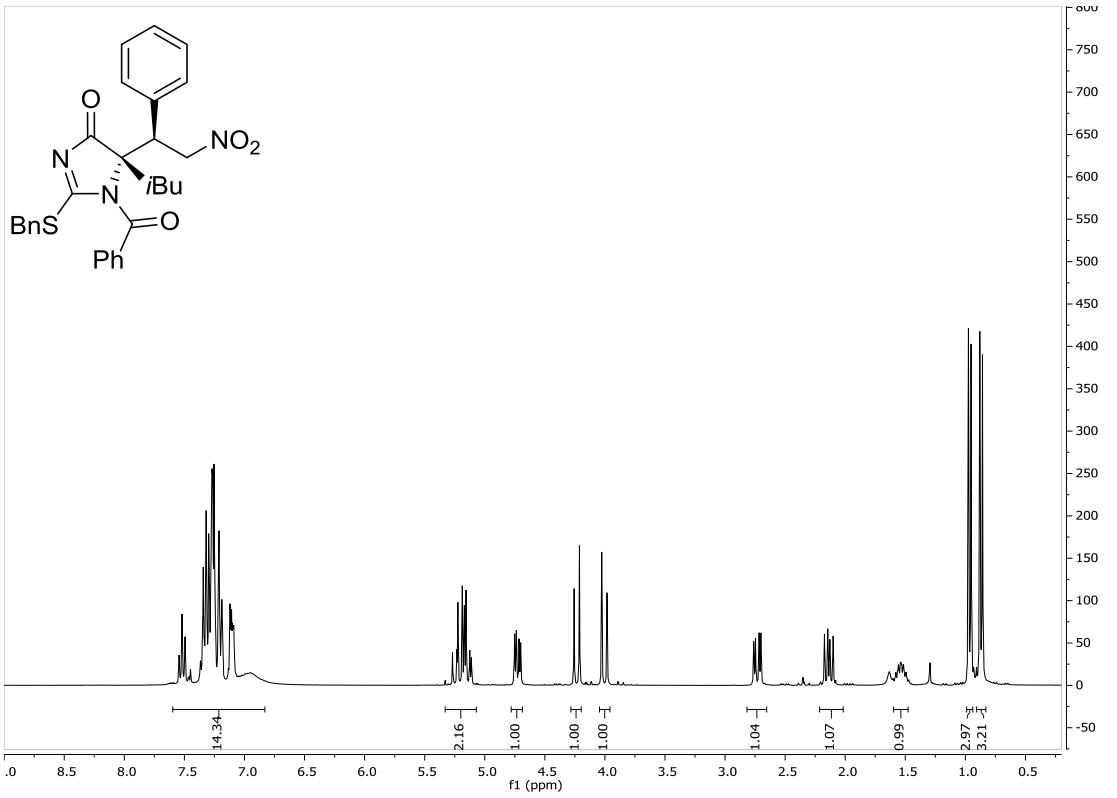


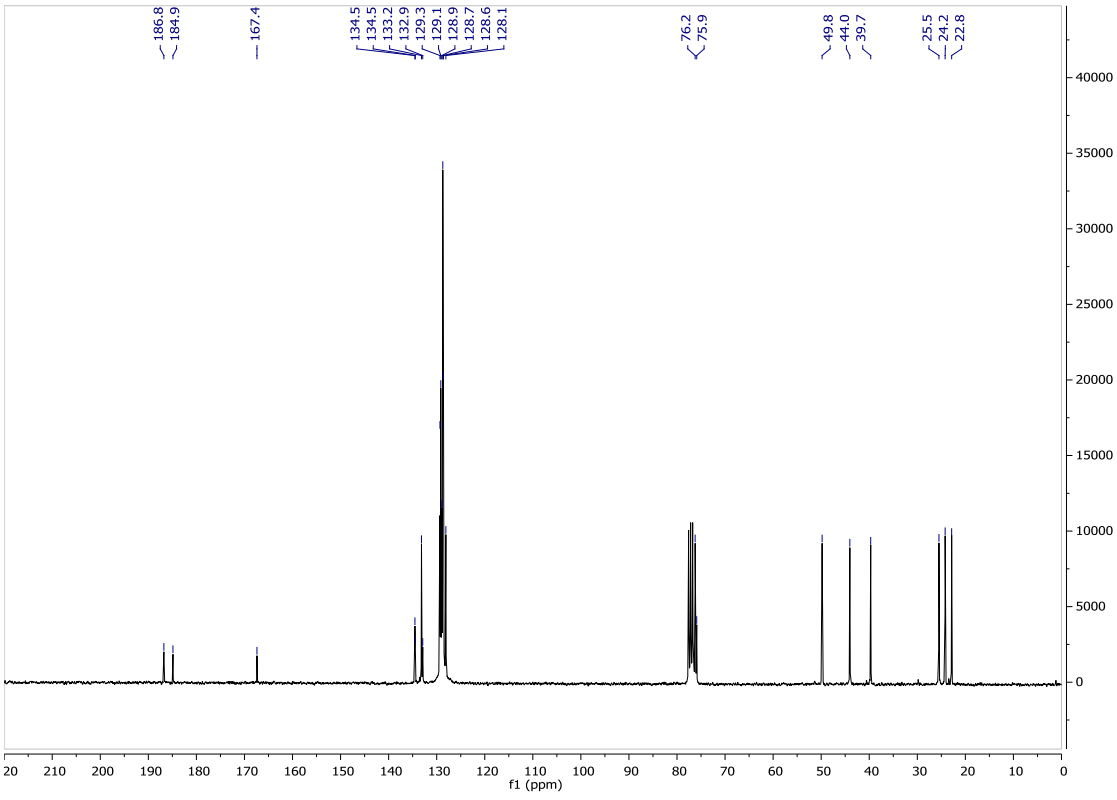
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cg)



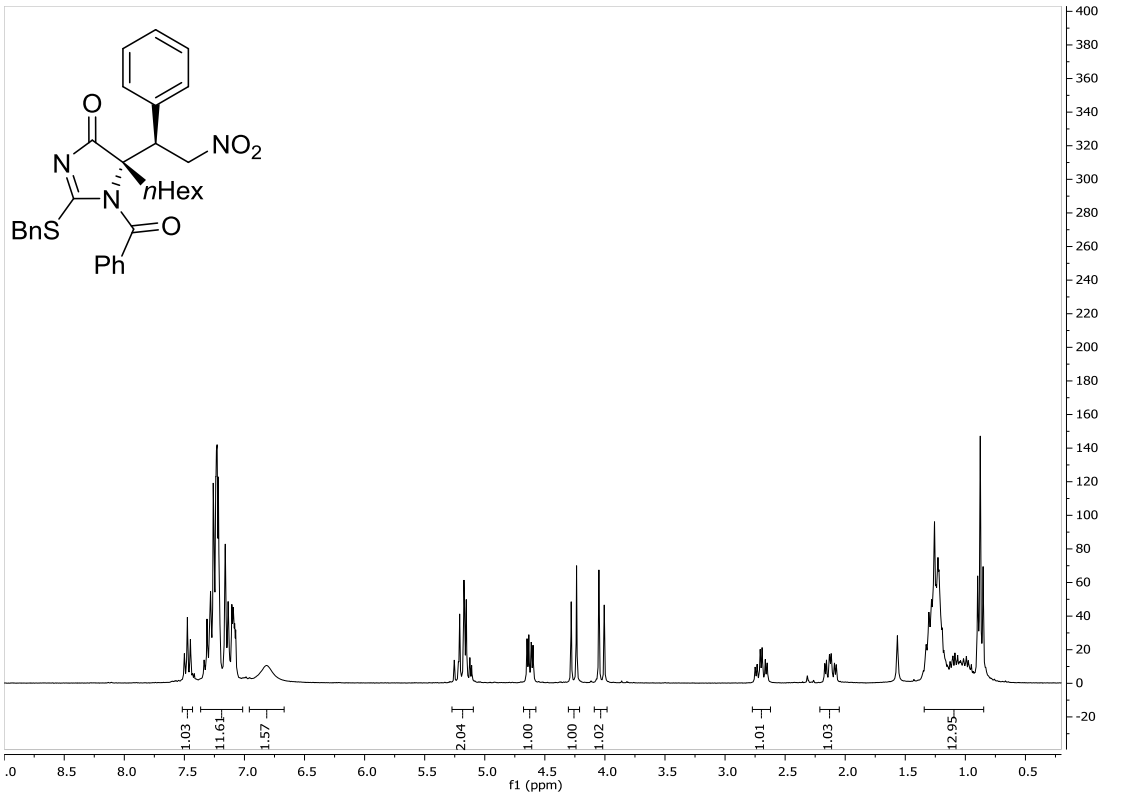


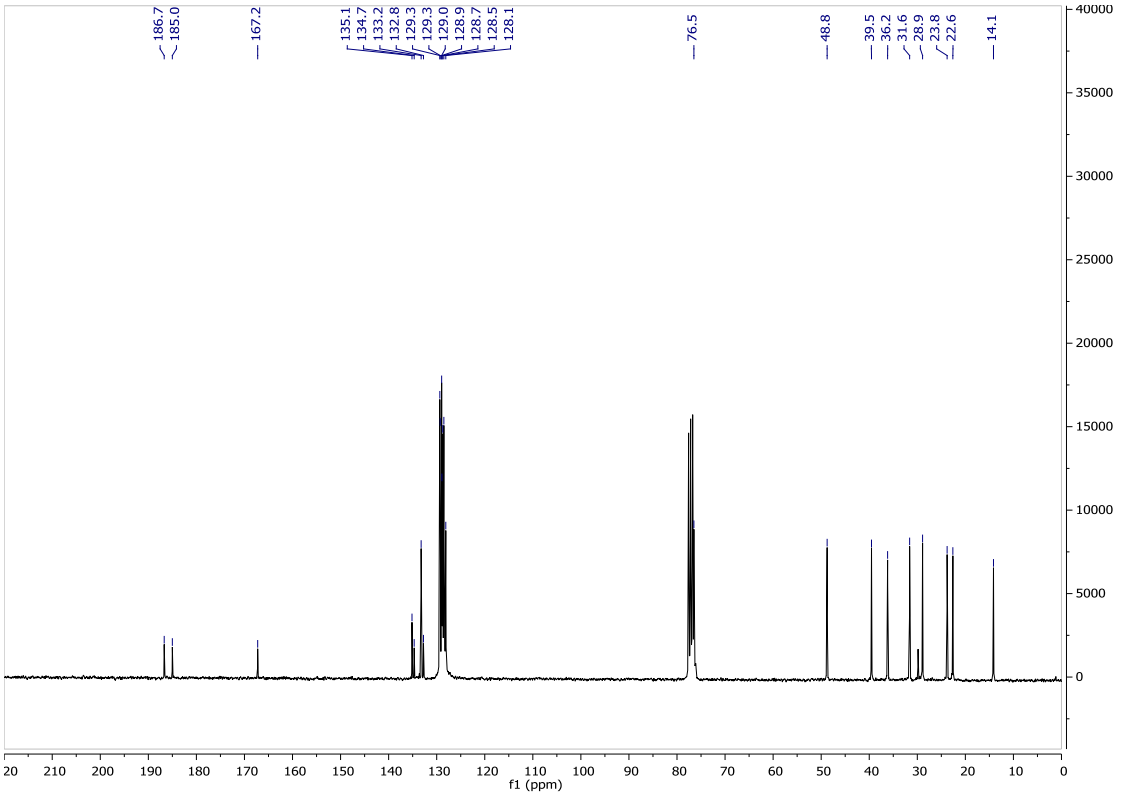
(*S*)-1-Benzoyl-2-(benzylthio)-5-isobutyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one(38Da)



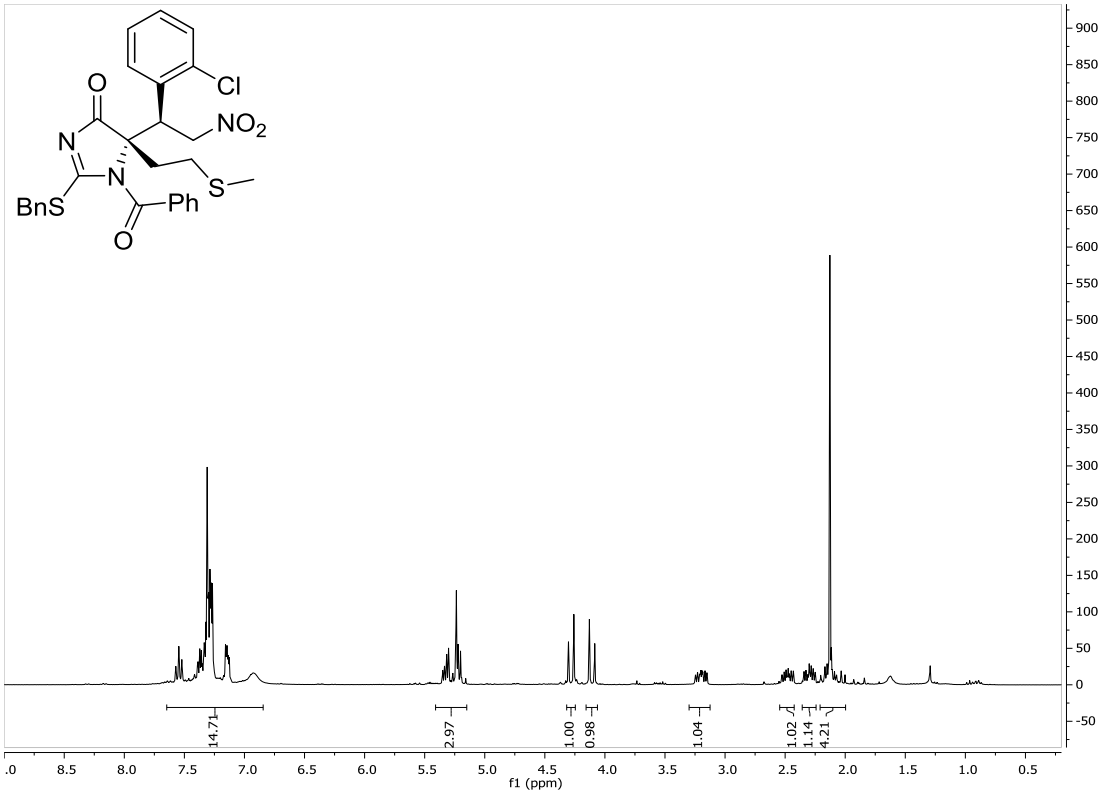


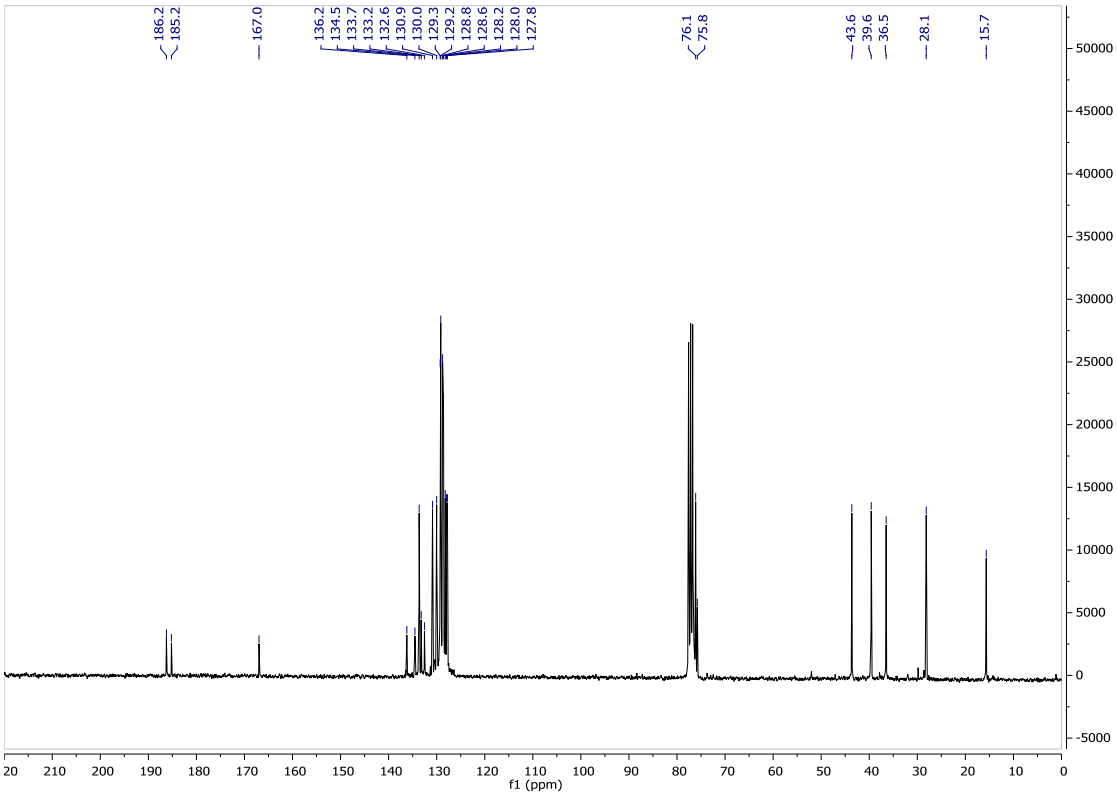
(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ea)



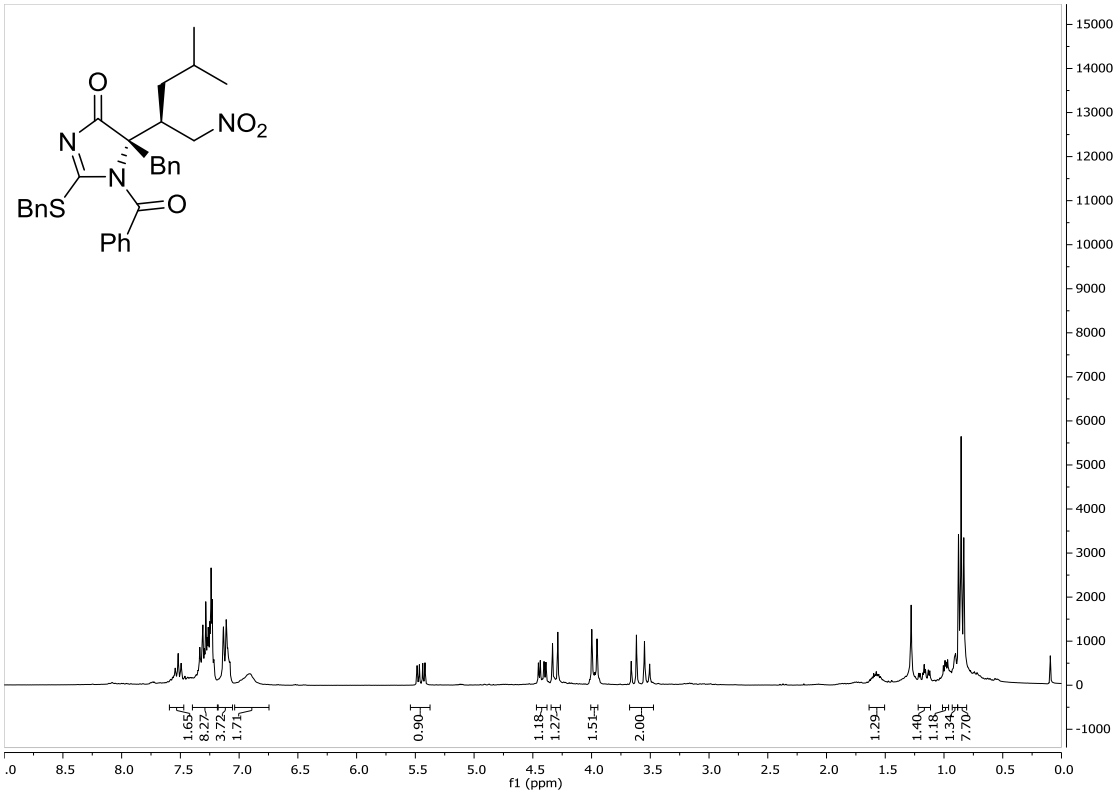


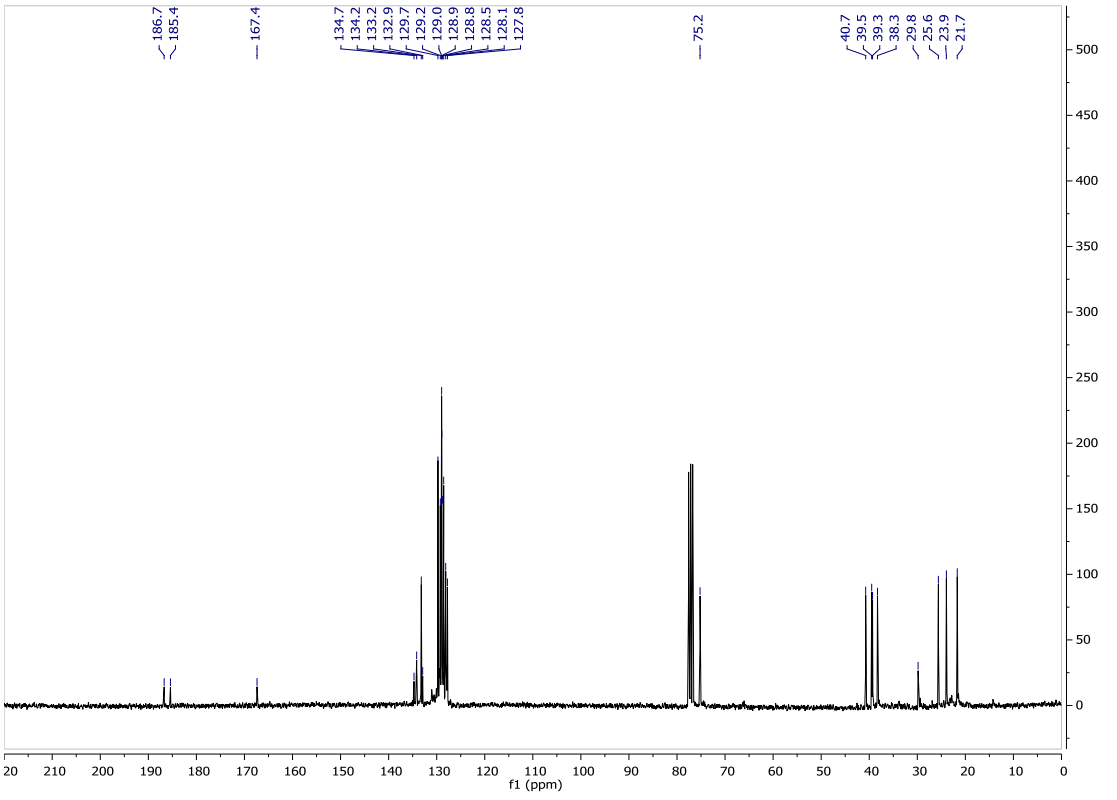
(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-(2-(methylthio)ethyl)-1*H*-imidazol-4(5*H*)-one (38Fd)



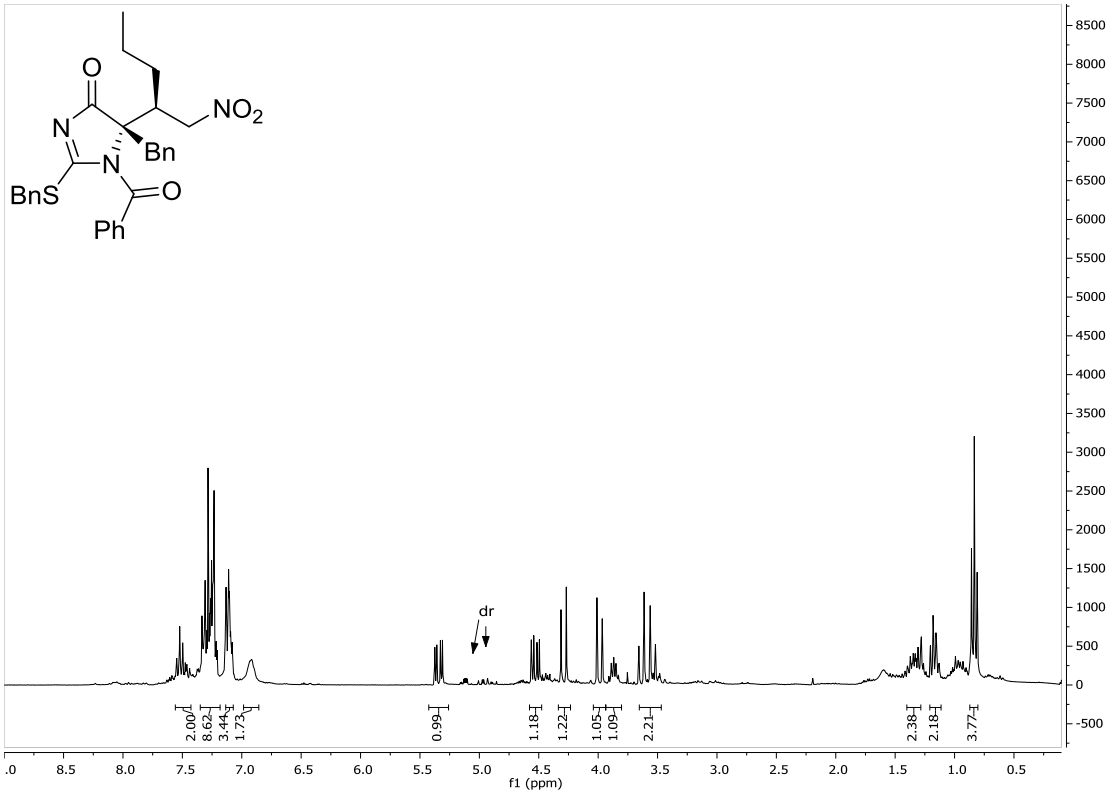


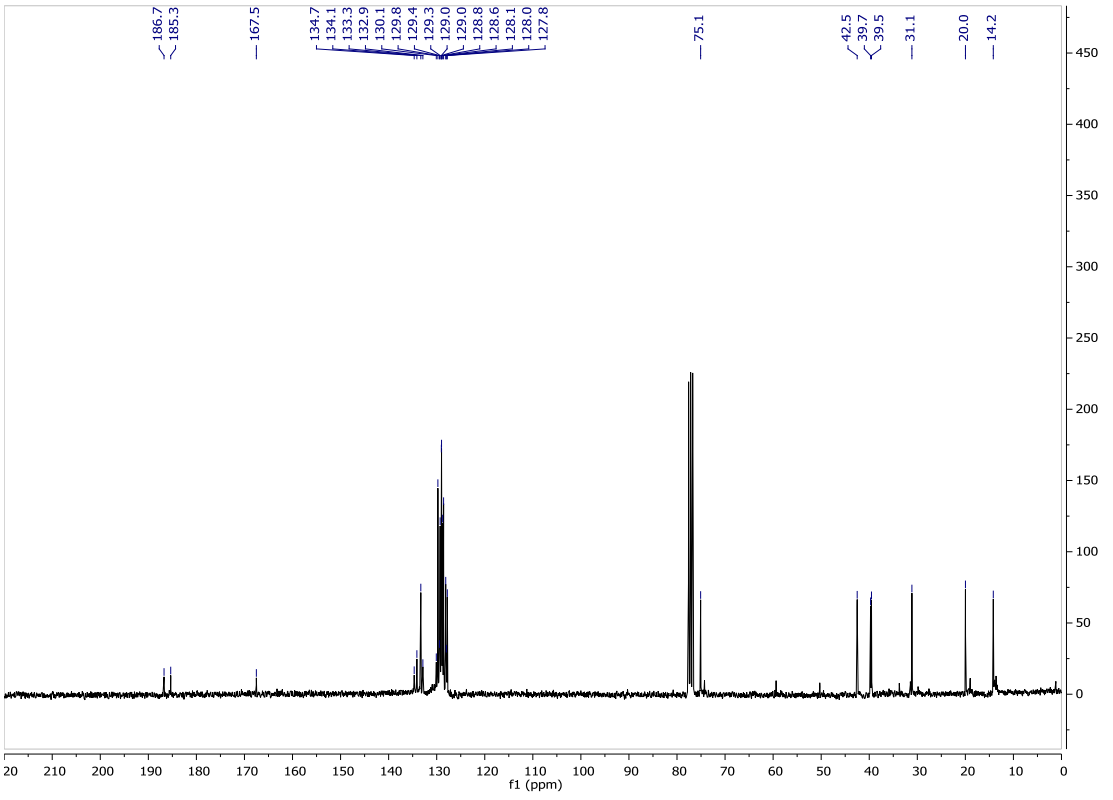
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-4-methyl-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ch)



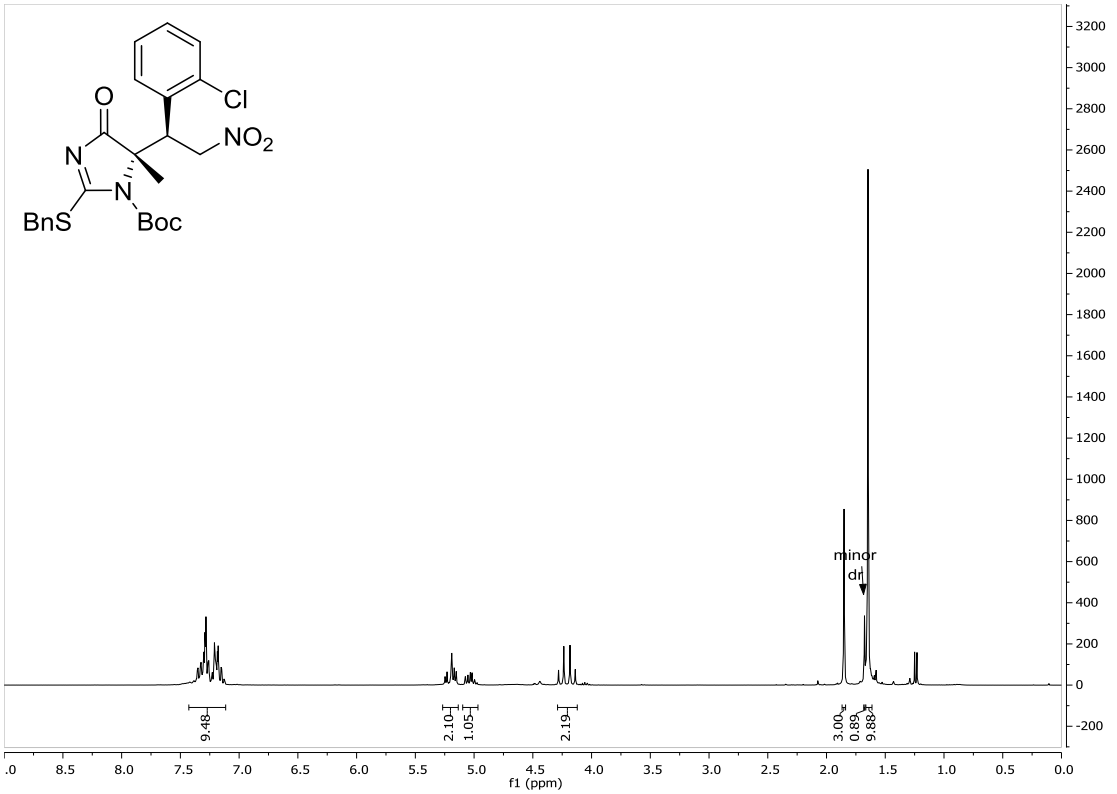


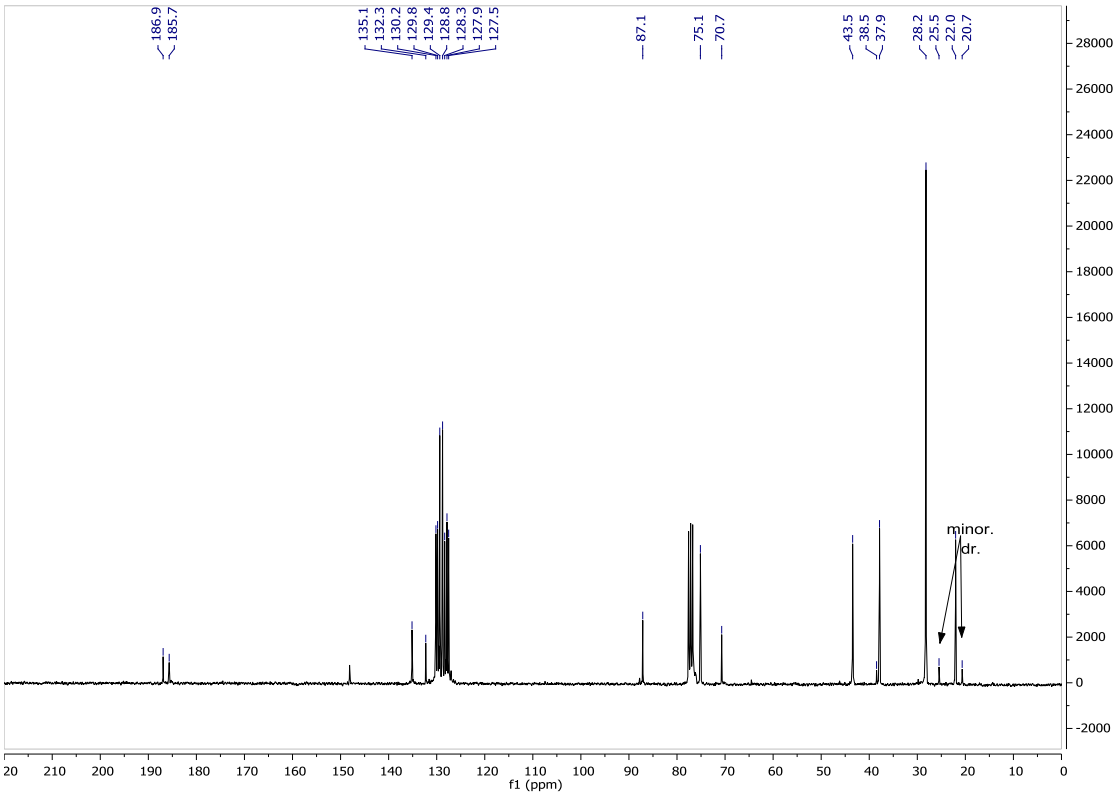
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ci)



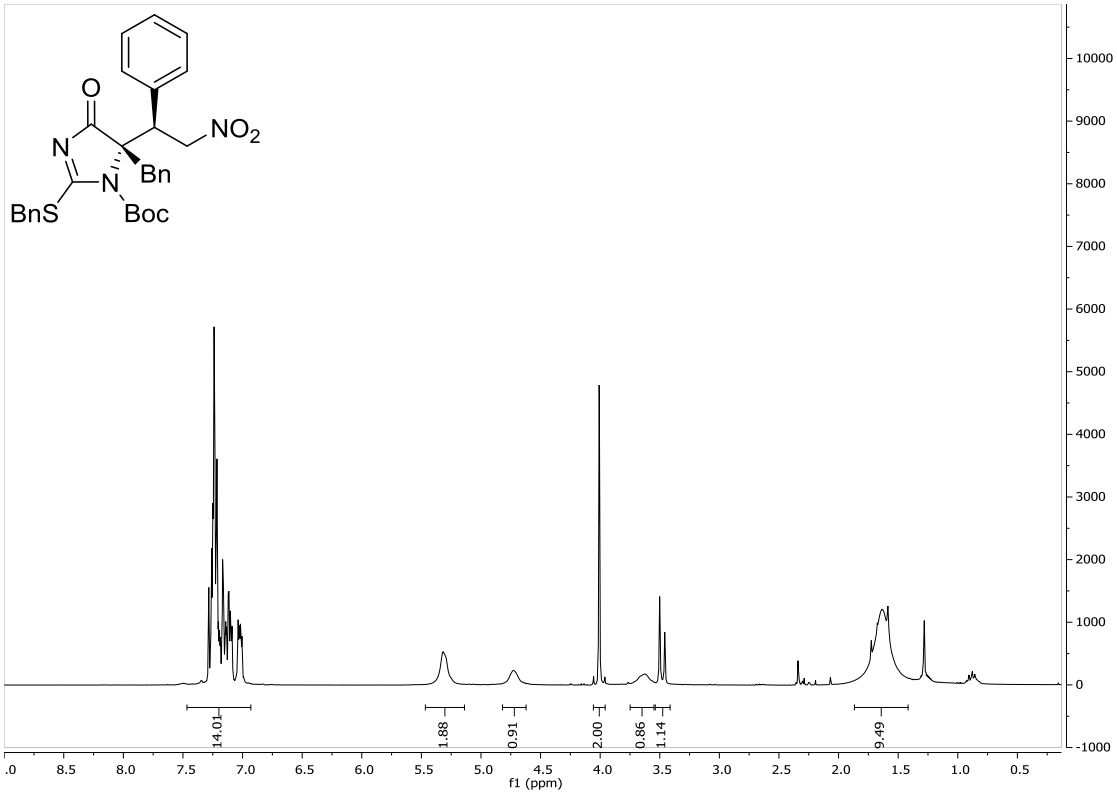


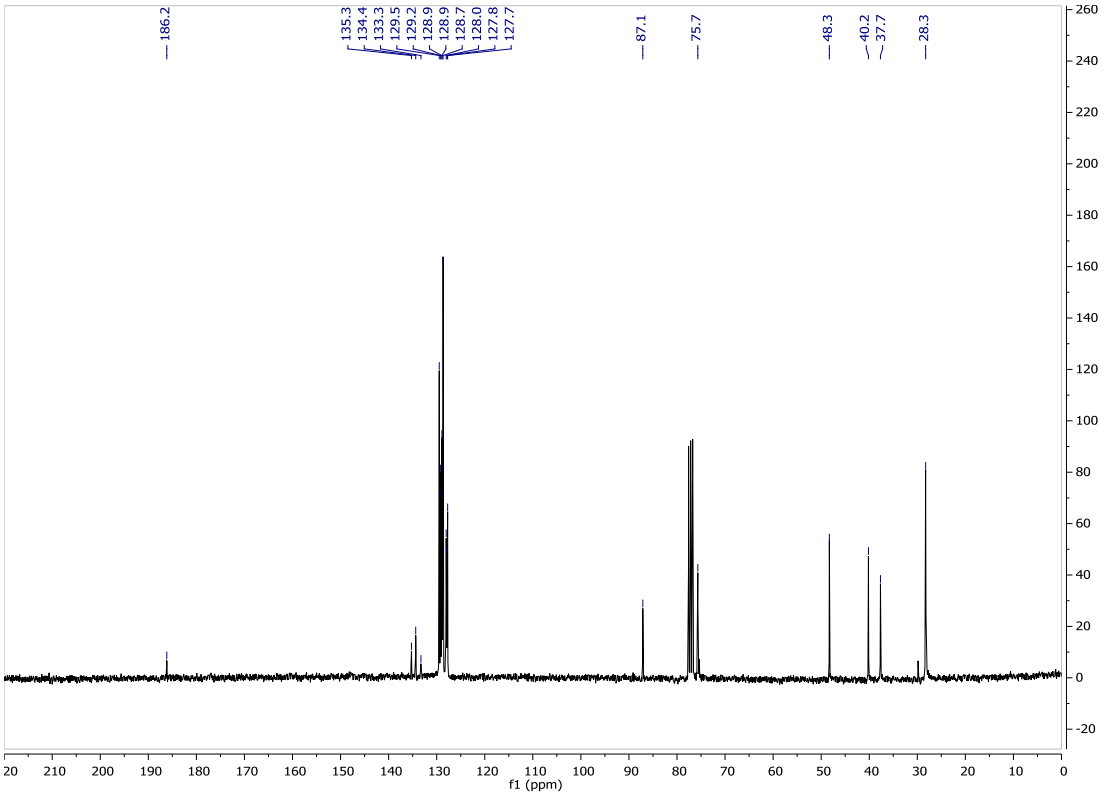
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (39Ad)



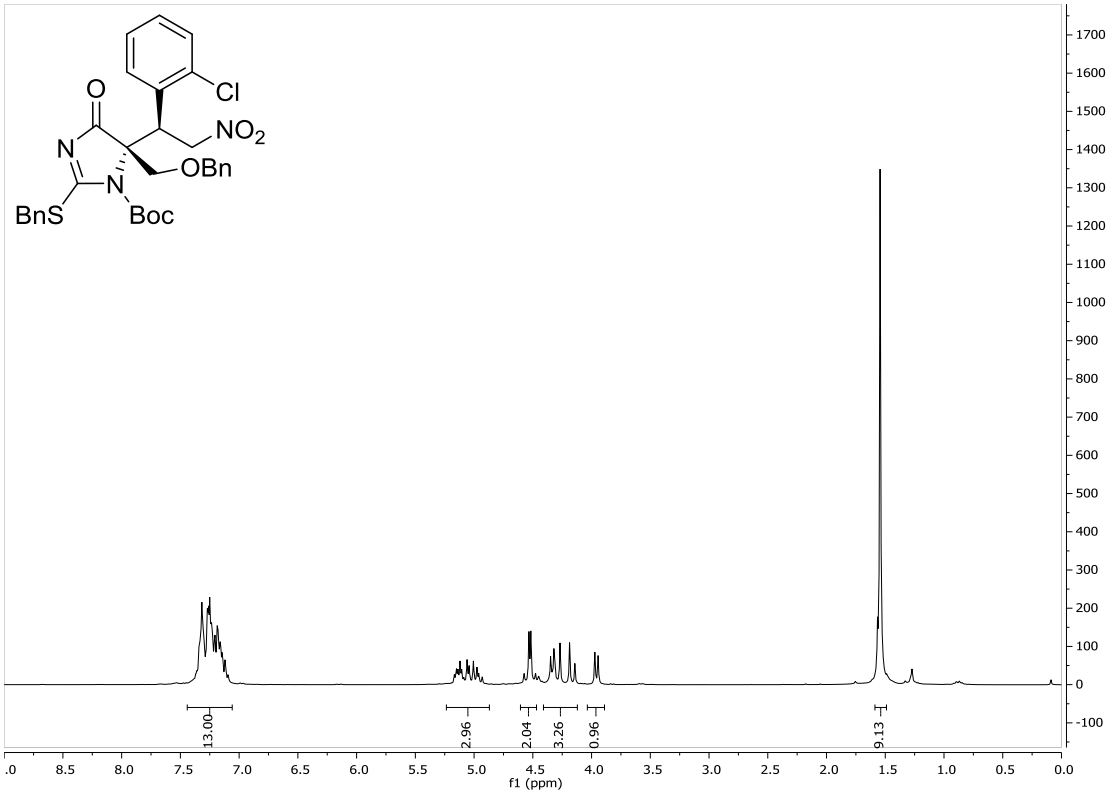


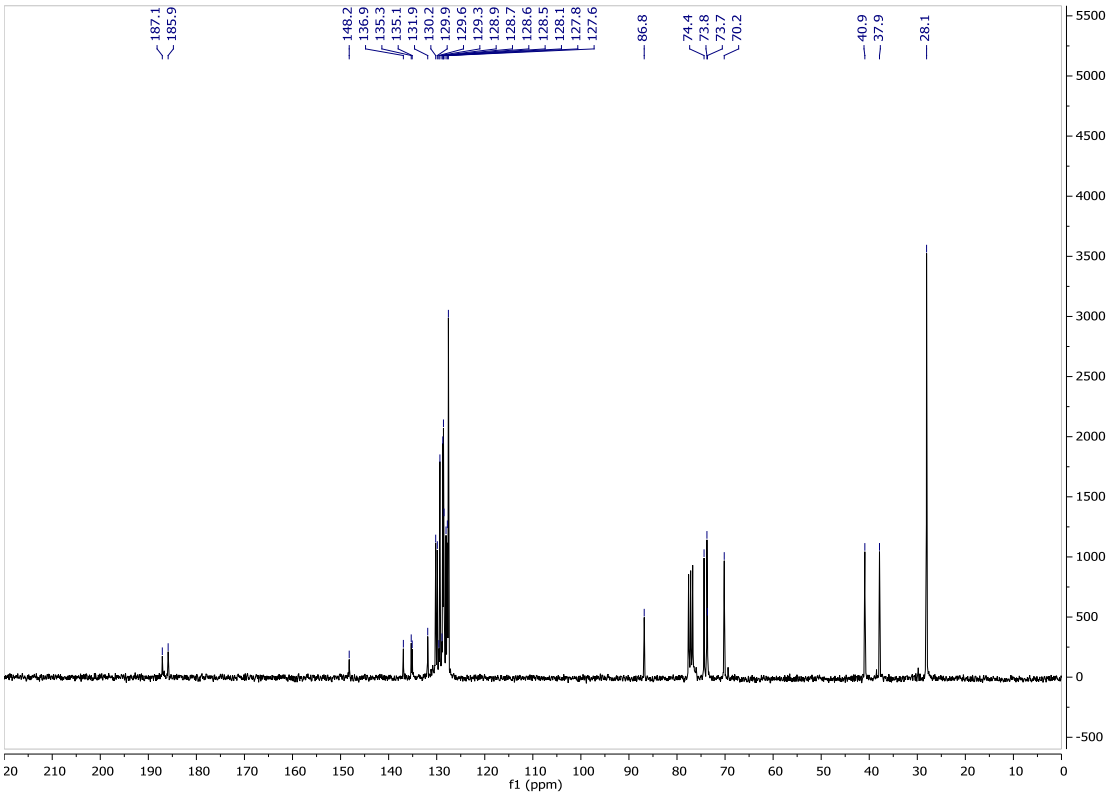
(*S*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (39Ca)



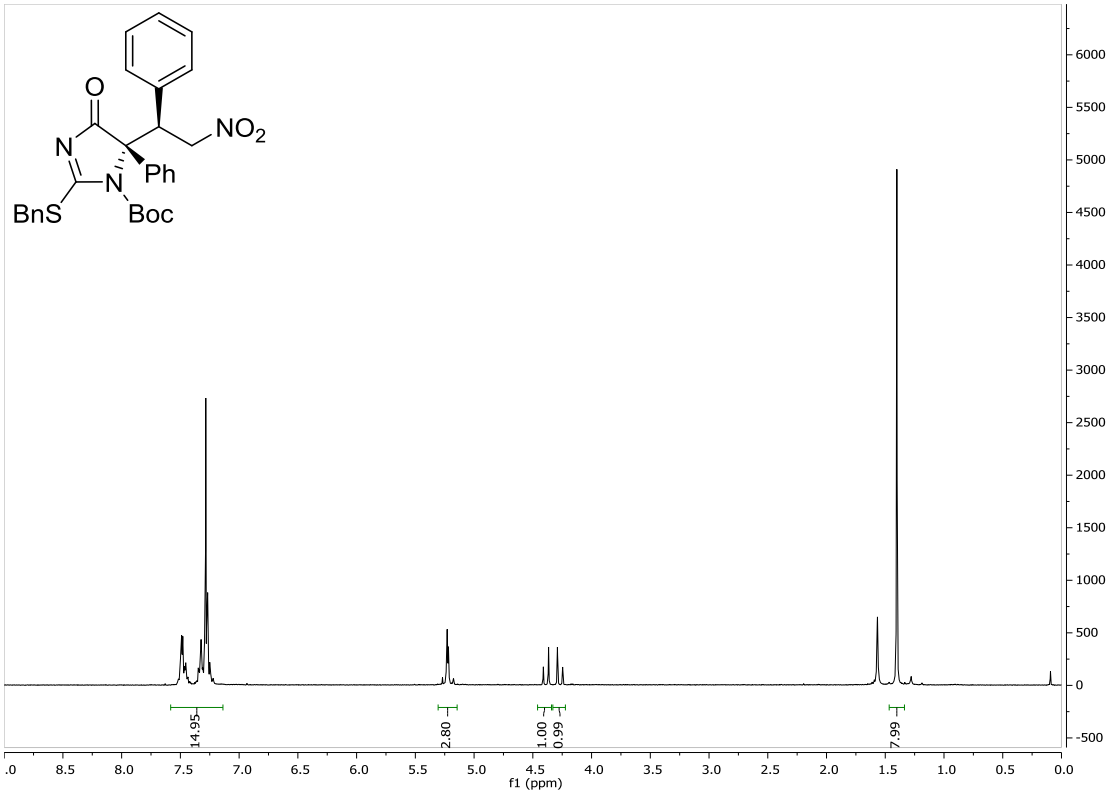


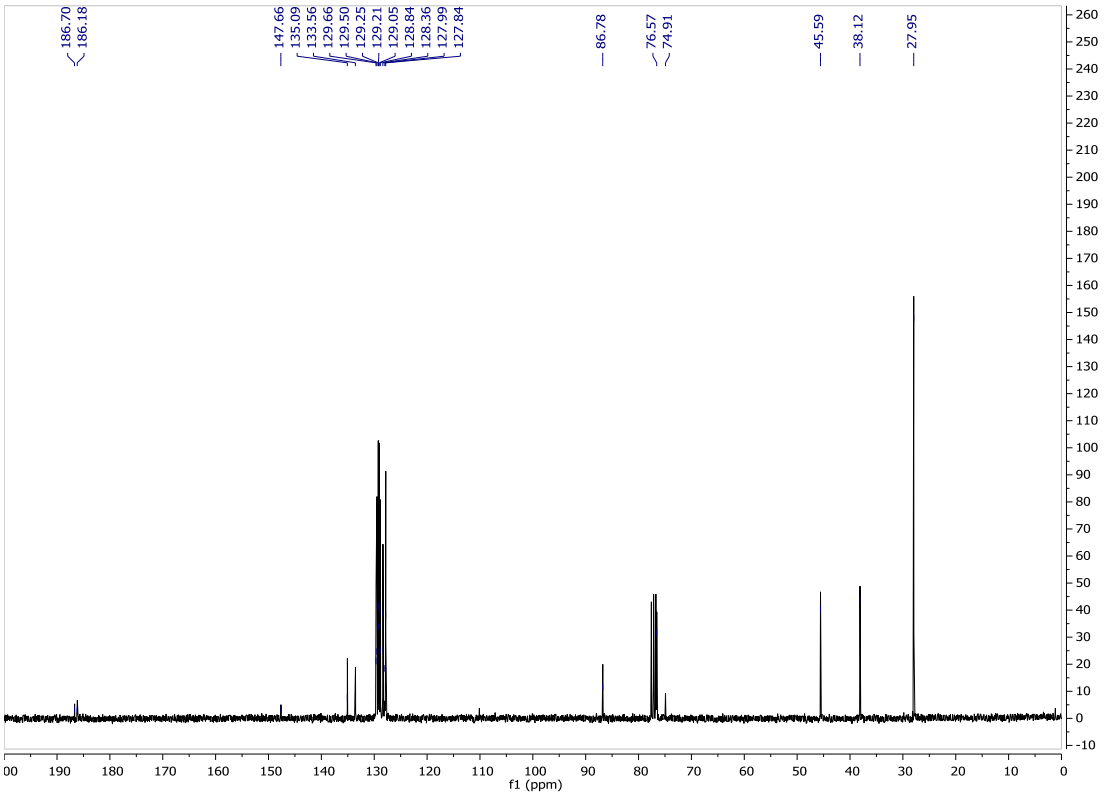
(*R*)-5-((Benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)- 1*H*-imidazol-4(5*H*)-one (39Gd)



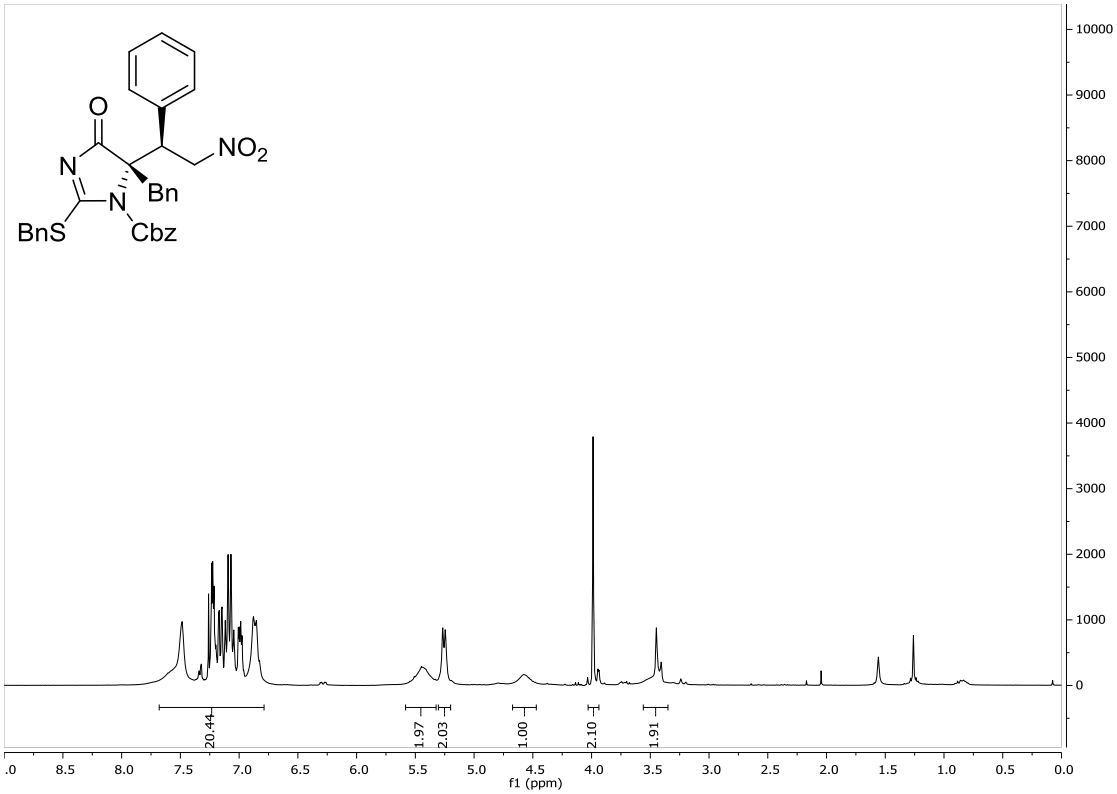


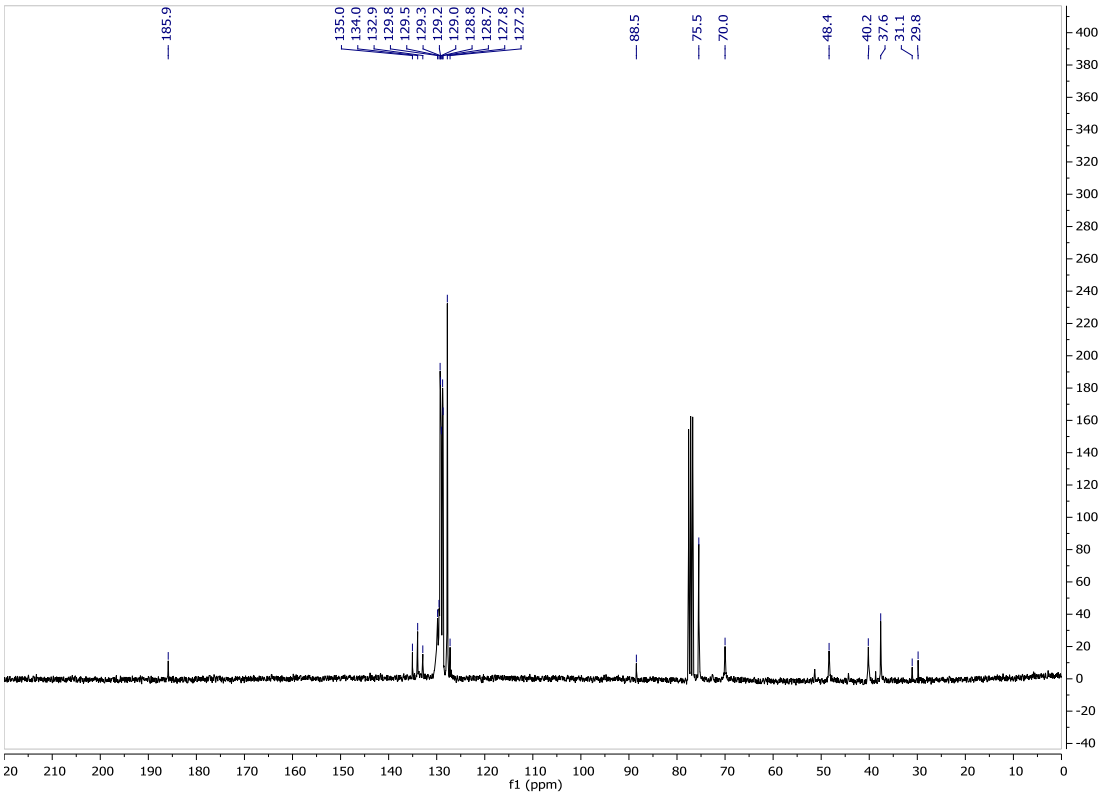
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-2-nitro-1-phenylethyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (39Ha)



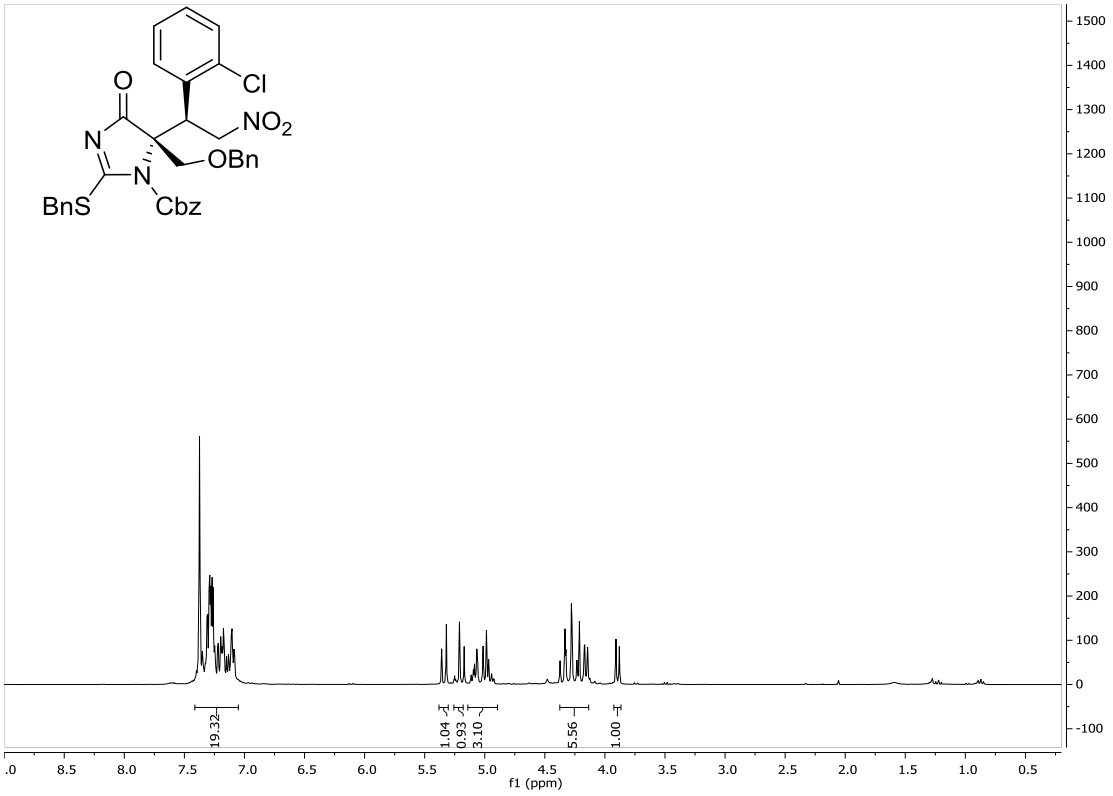


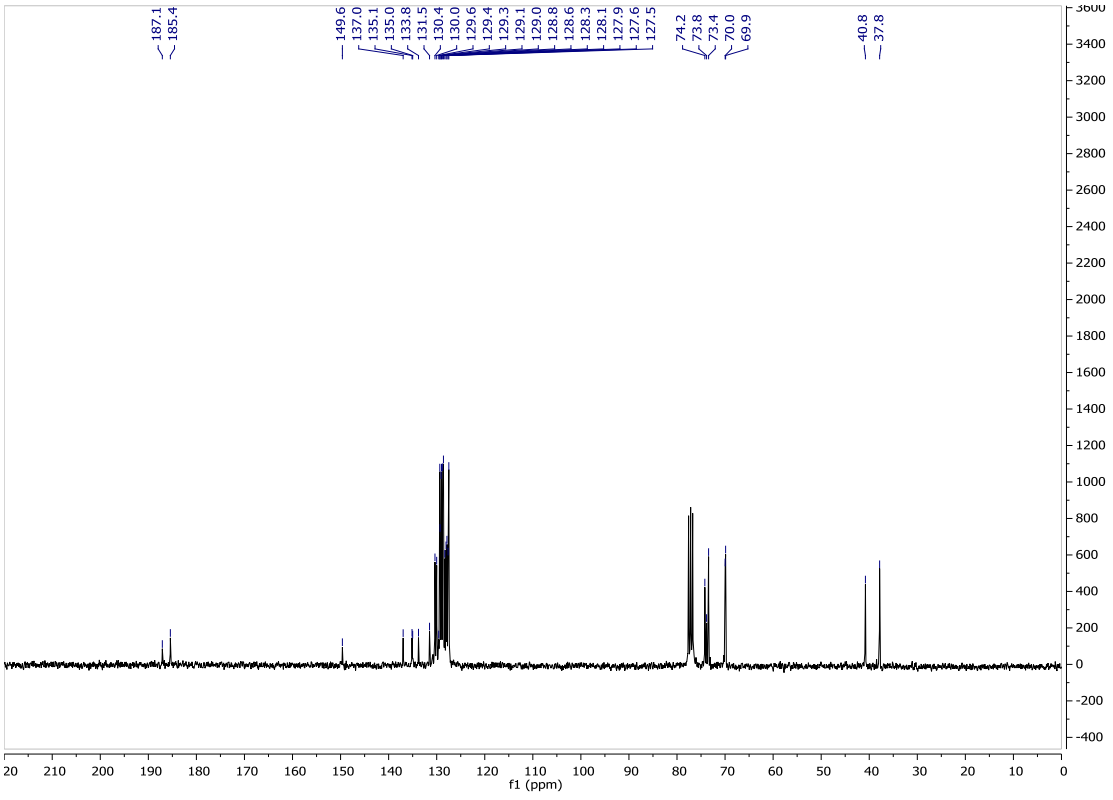
(*S*)-5-Benzyl-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (40Ca)



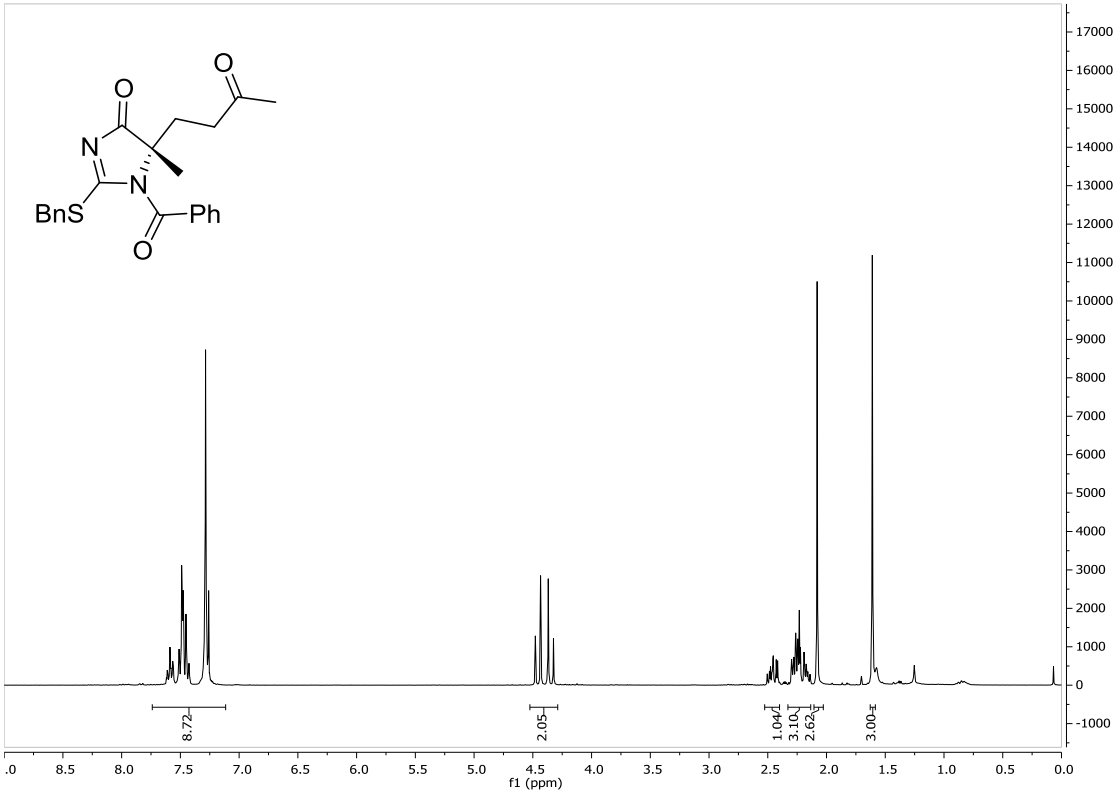


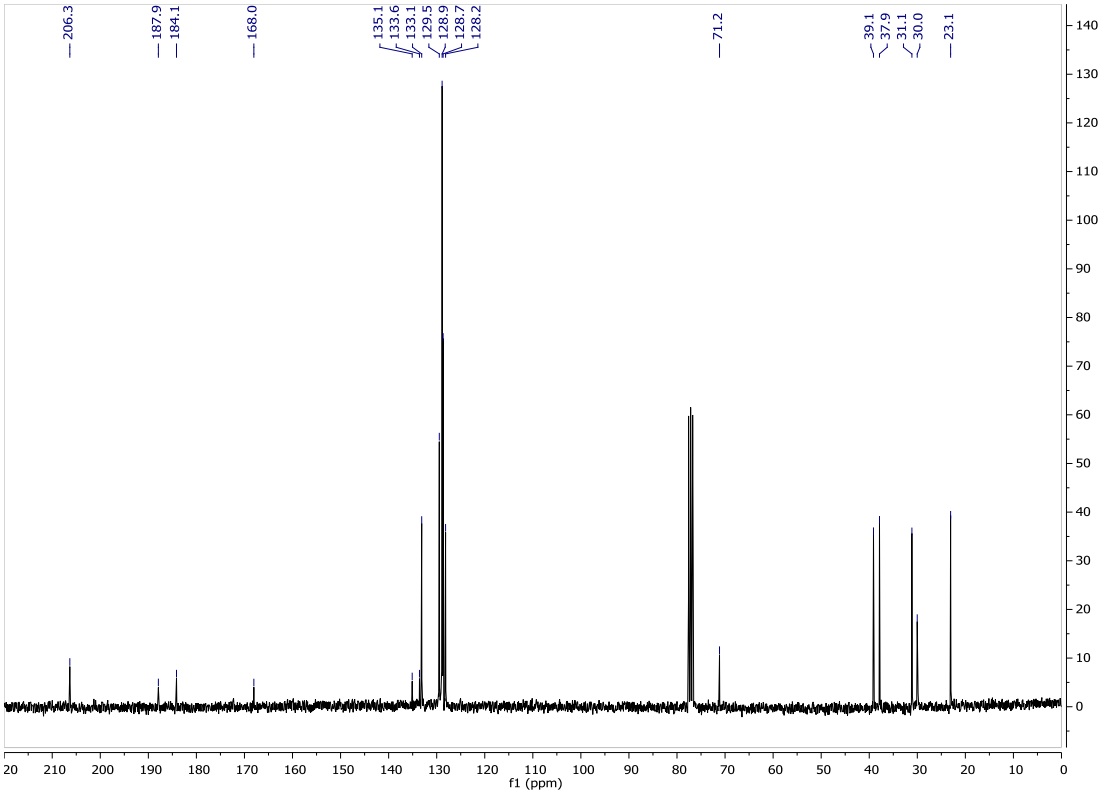
(*R*)-5-((Benzyloxy)methyl)-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (49Gd)



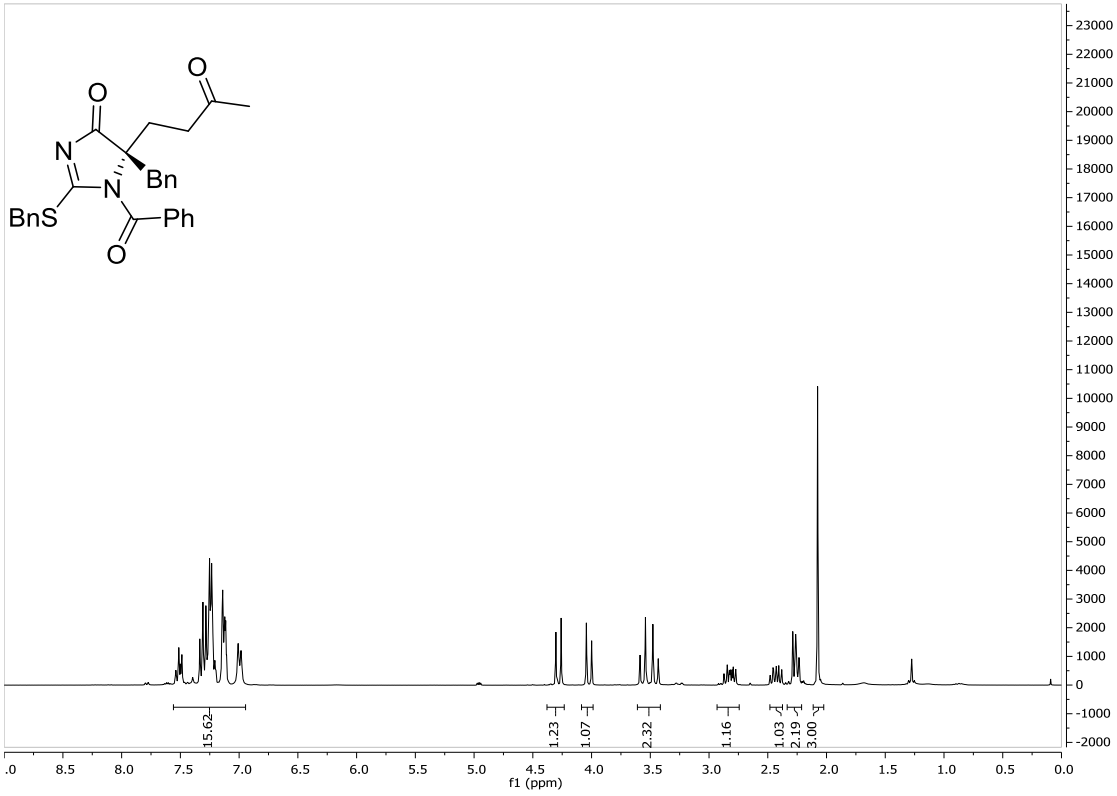


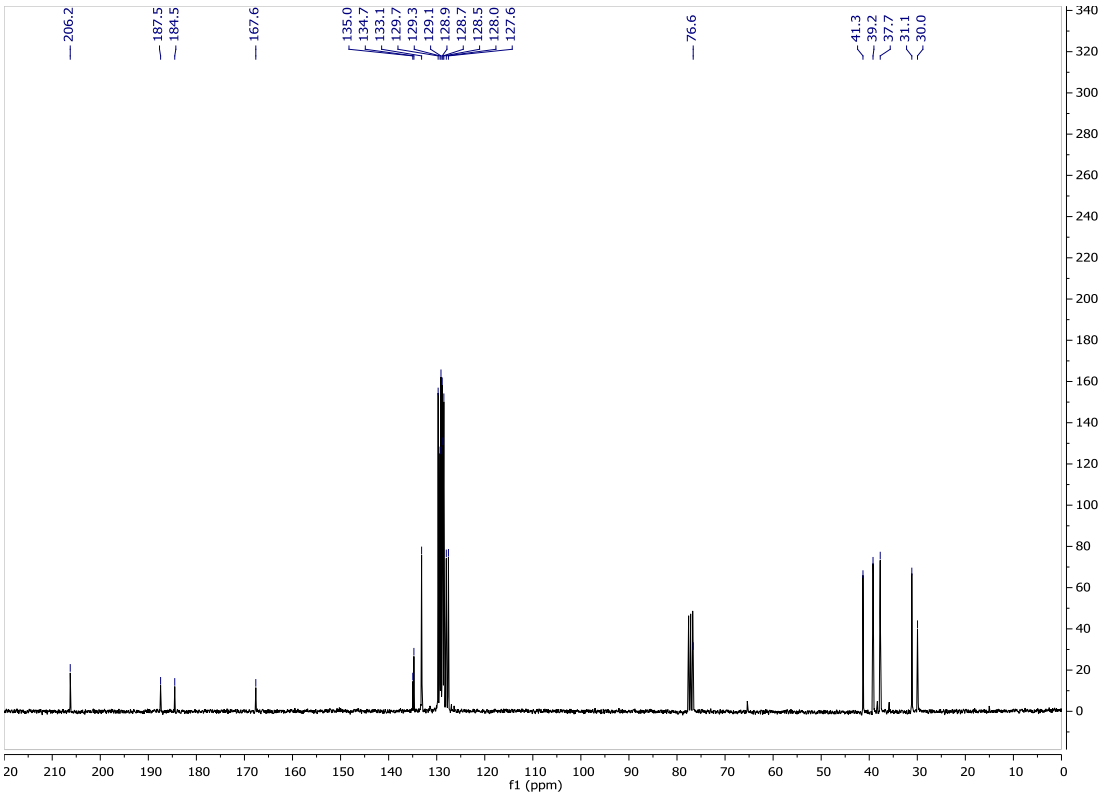
(*S*)-1-Benzoyl-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Aa)



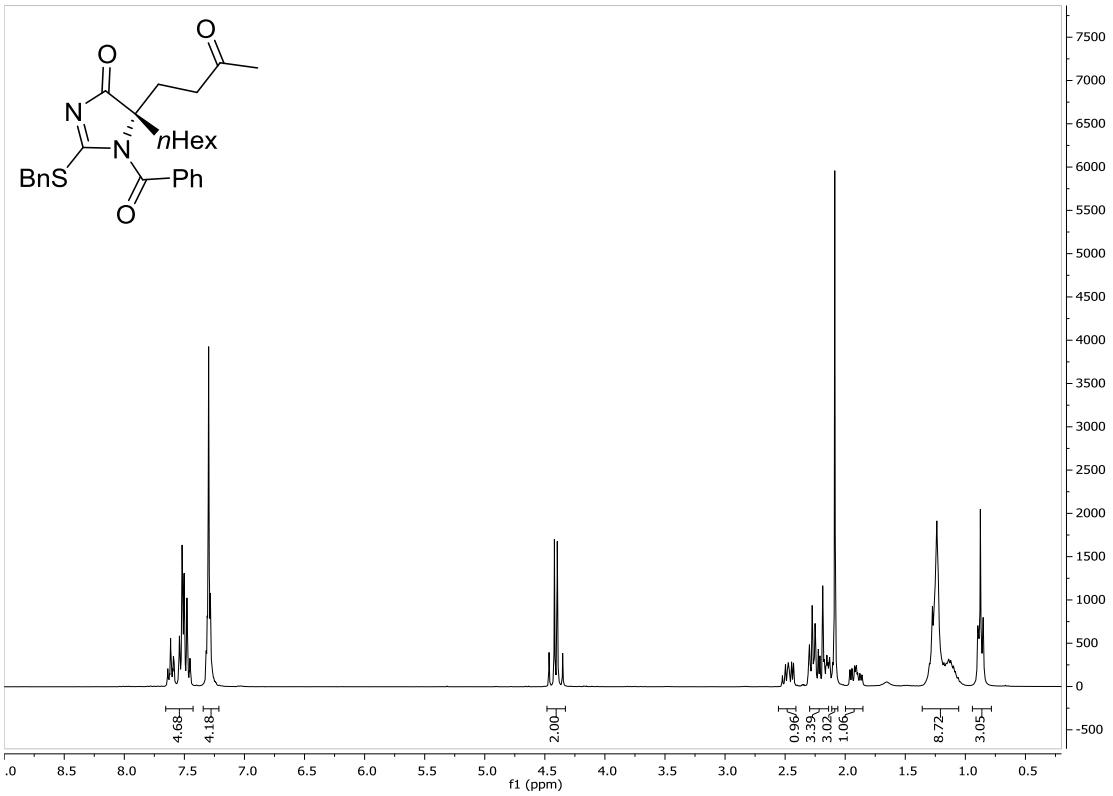


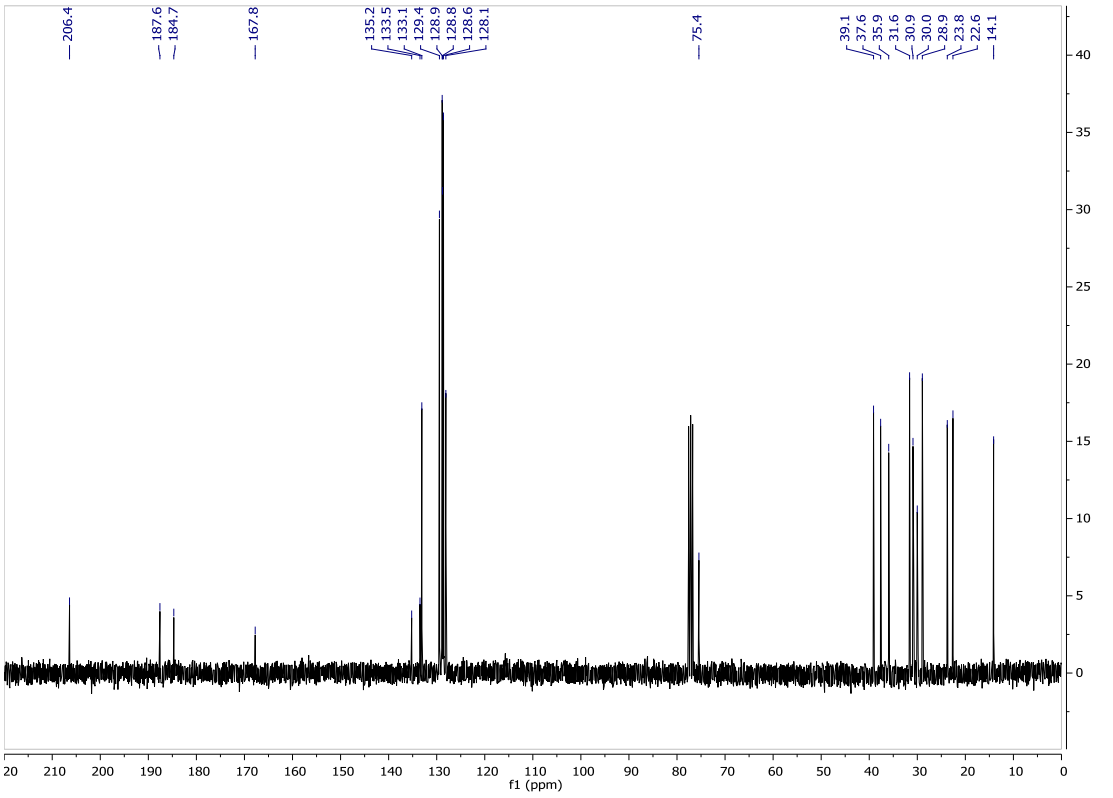
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Ca)



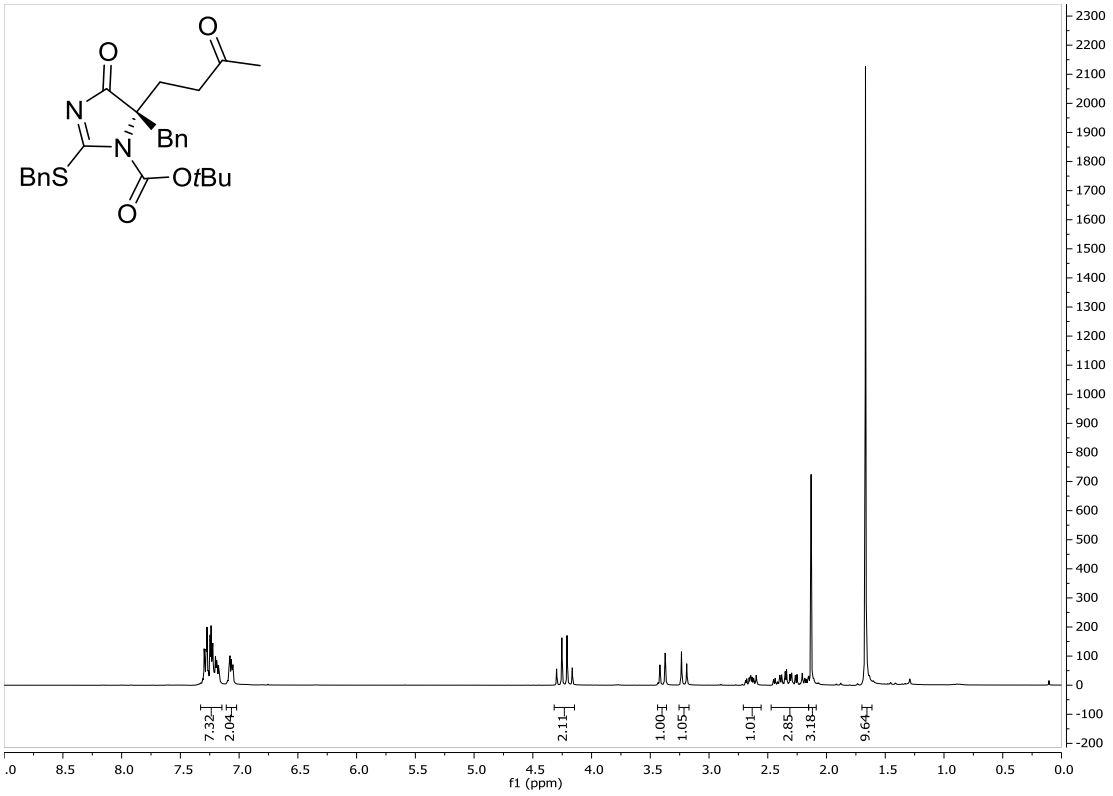


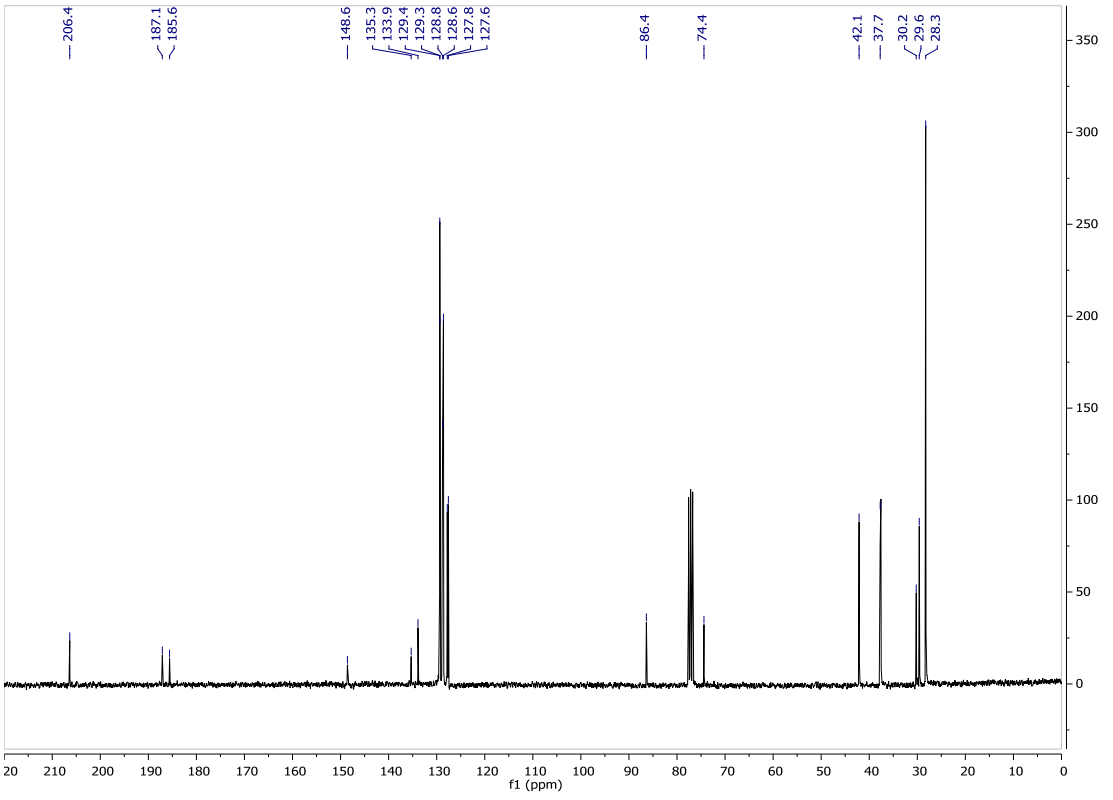
(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-(3-oxobutyl)-1H-imidazol-4(5*H*)-one (42Ea)



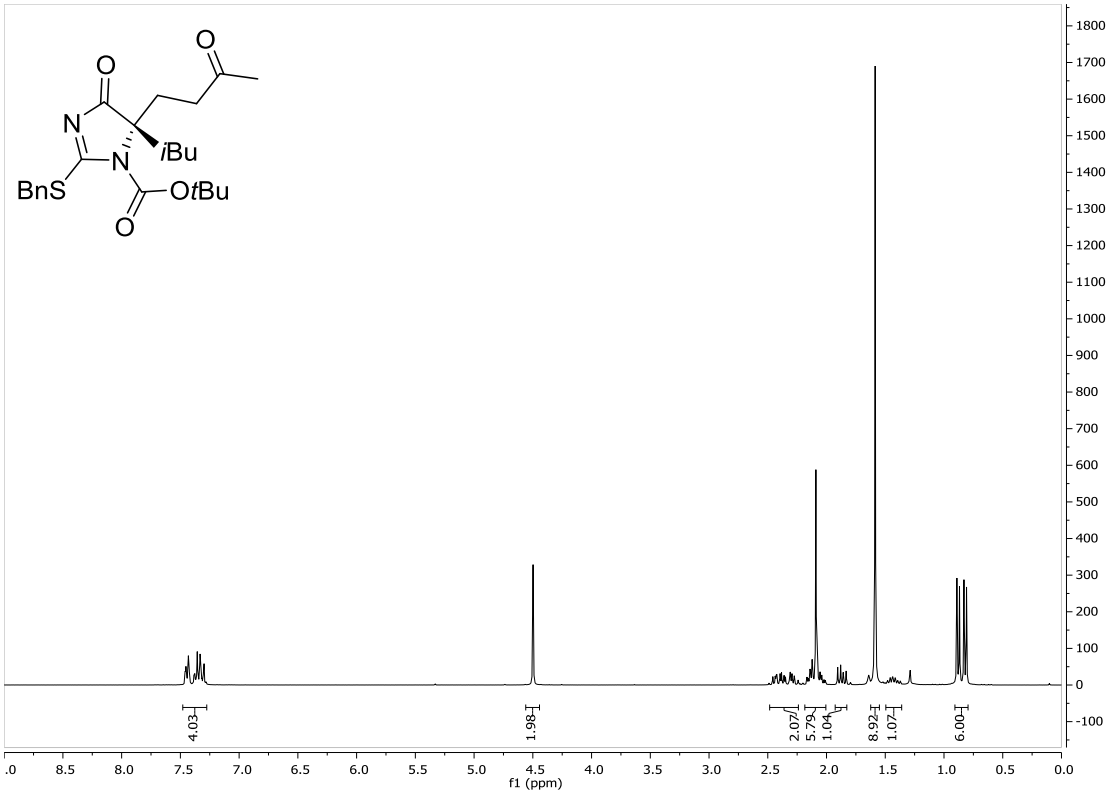


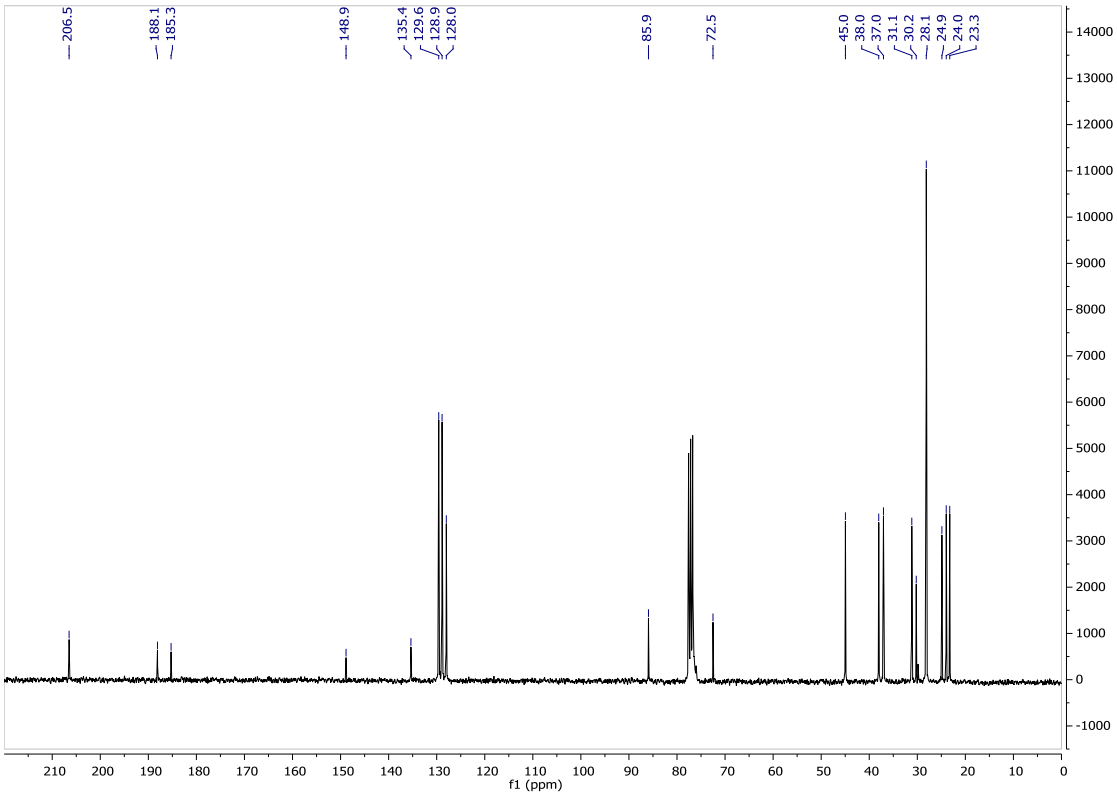
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ca)



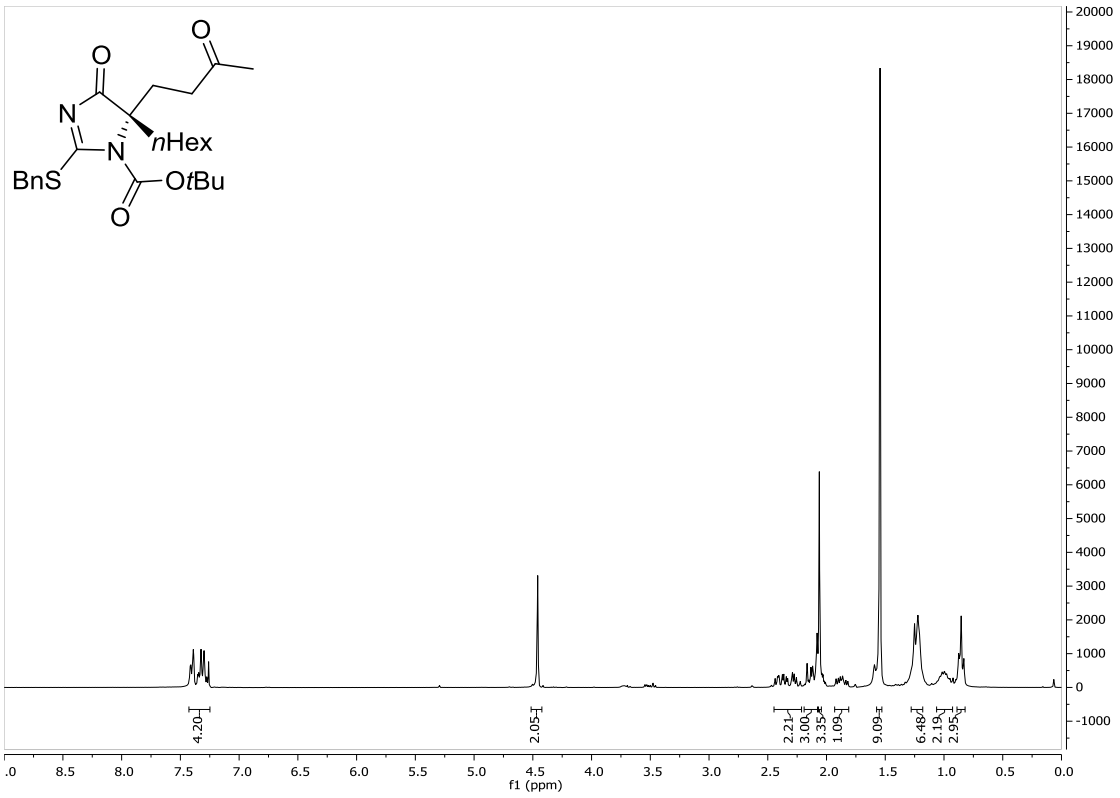


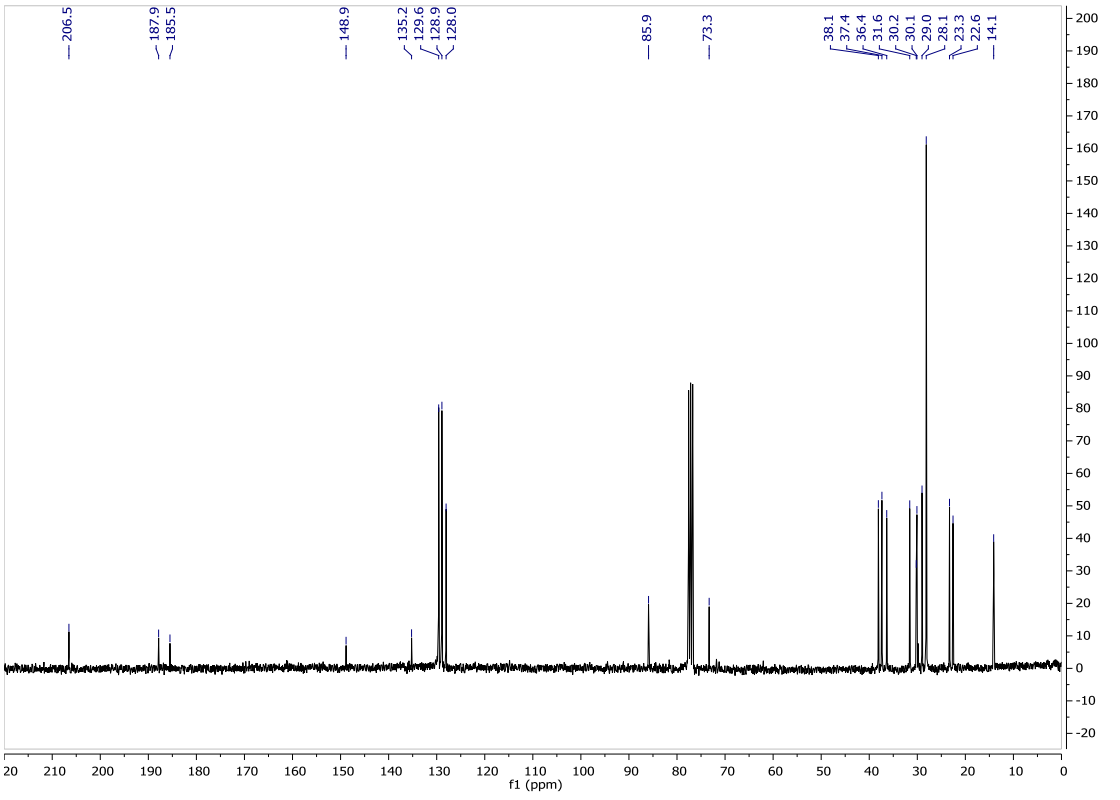
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-isobutyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Da)



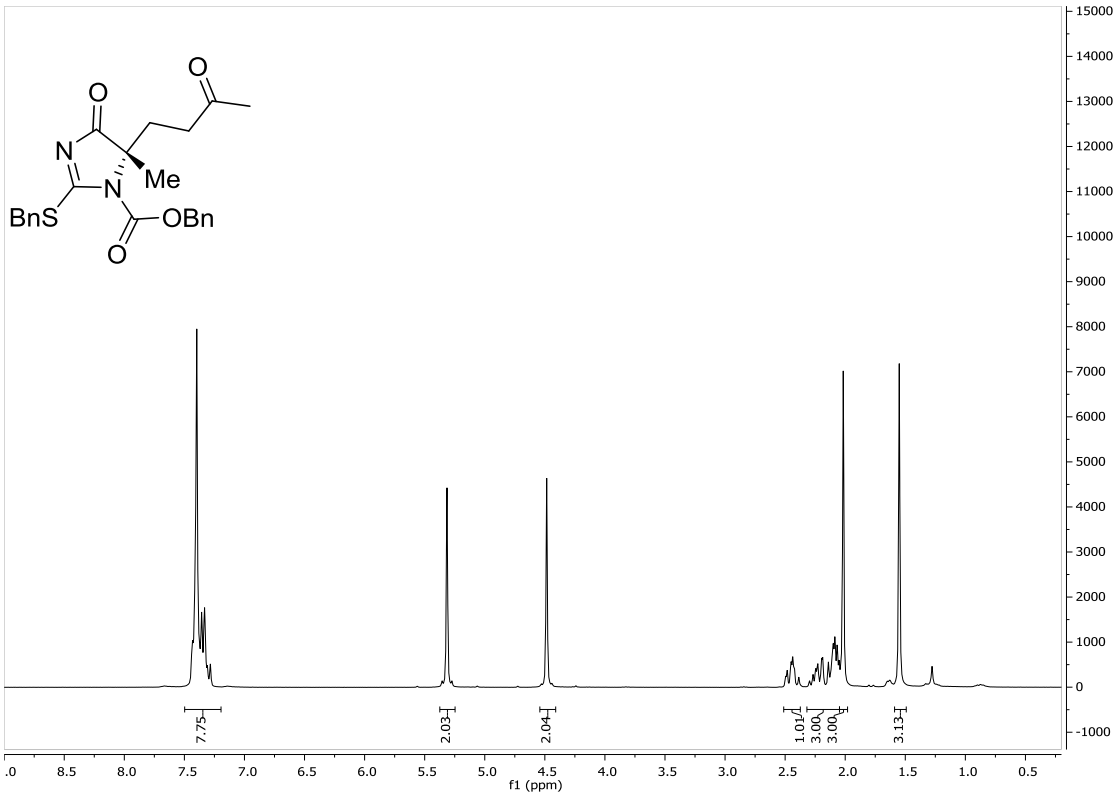


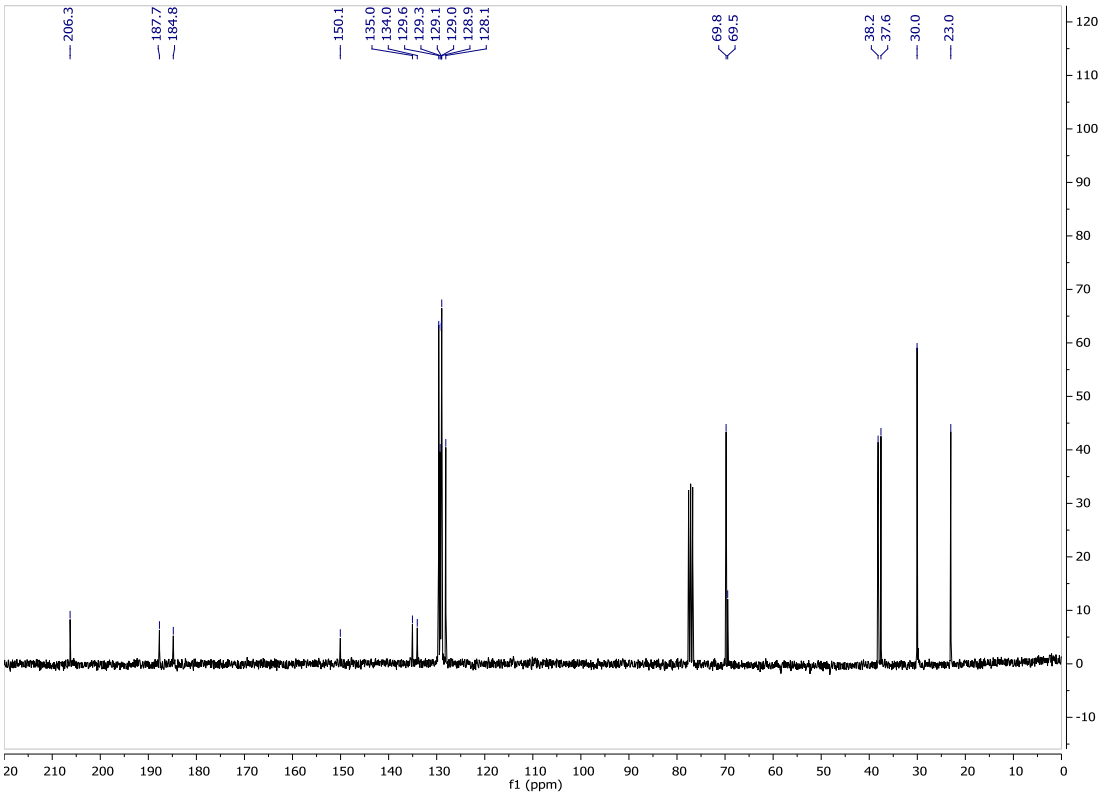
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ea)



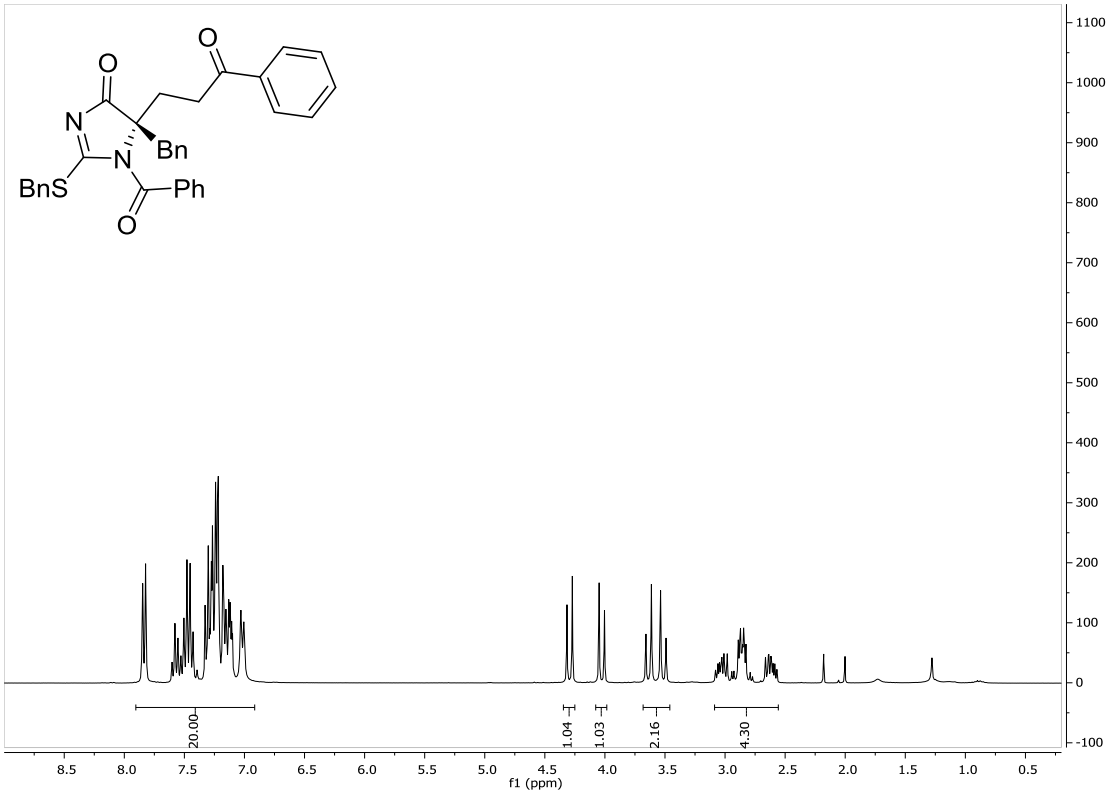


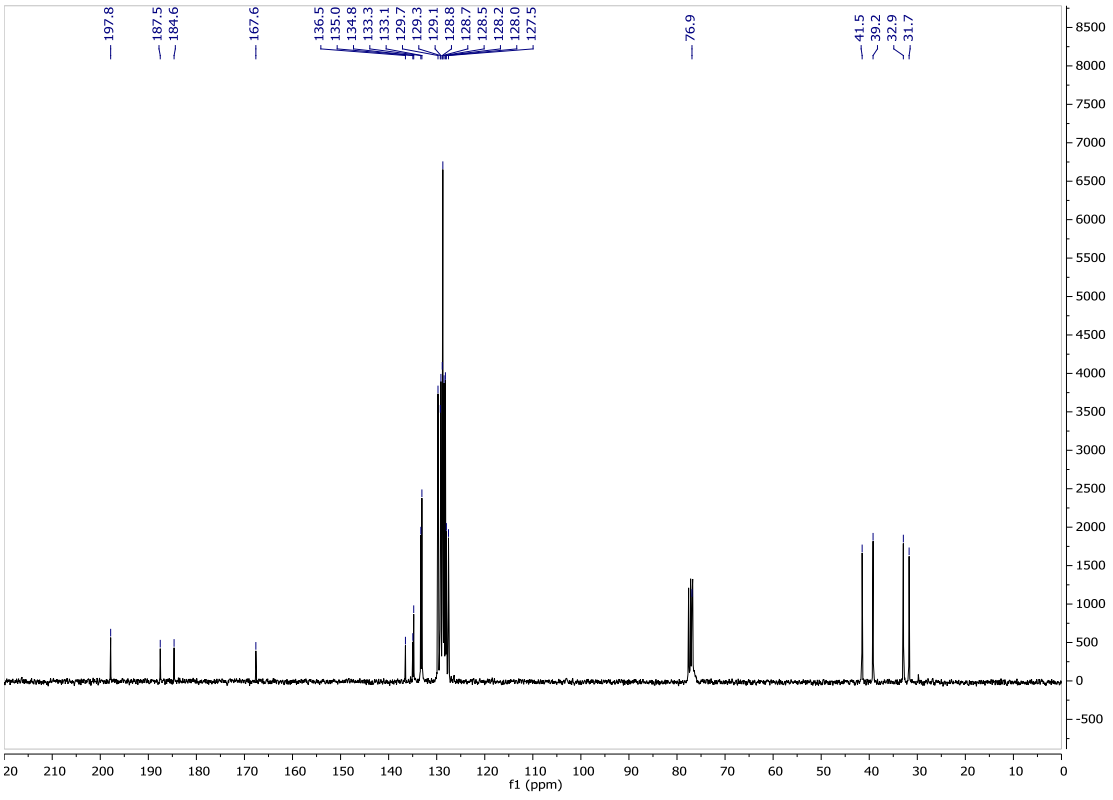
(*S*)-1-(Benzyloxycarbonyl)-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (44Aa)



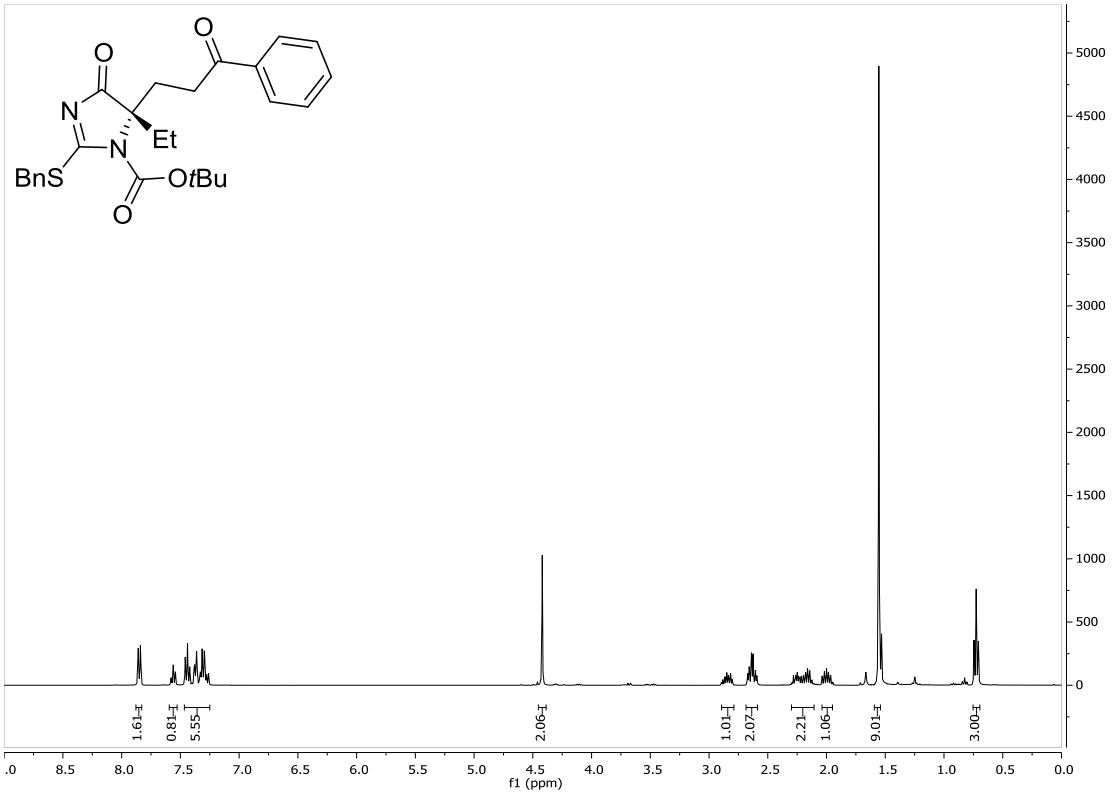


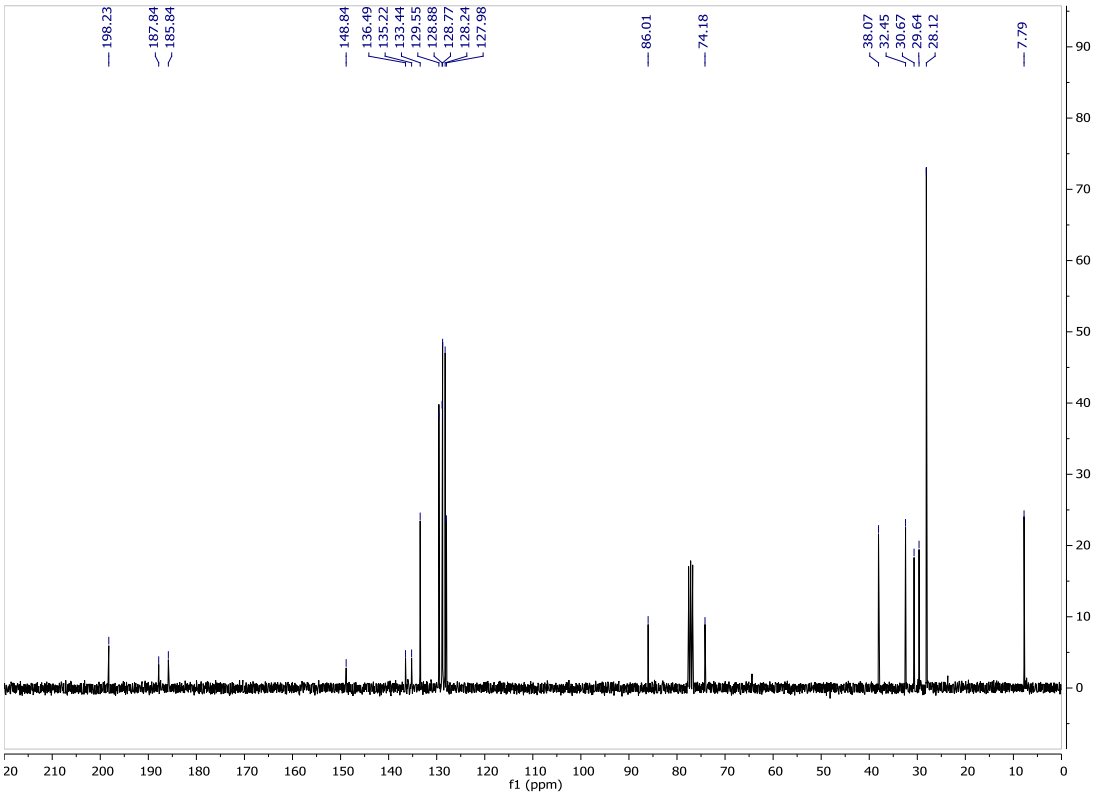
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (42Cb)



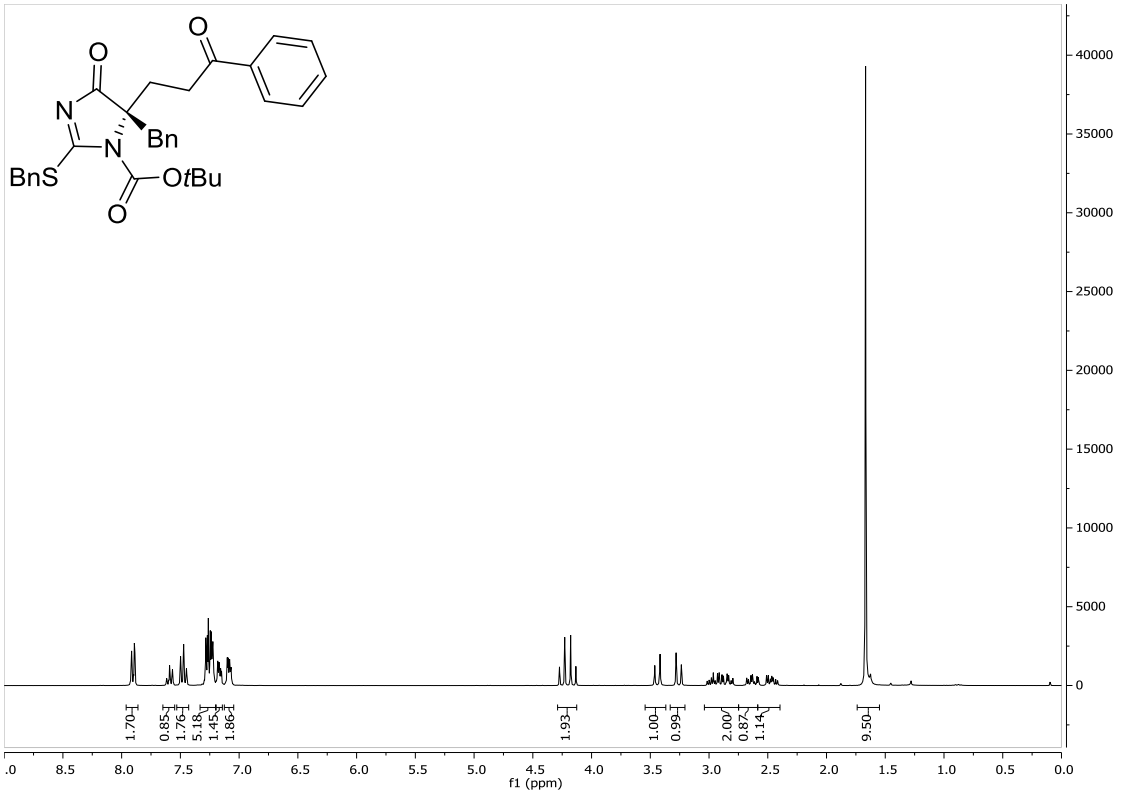


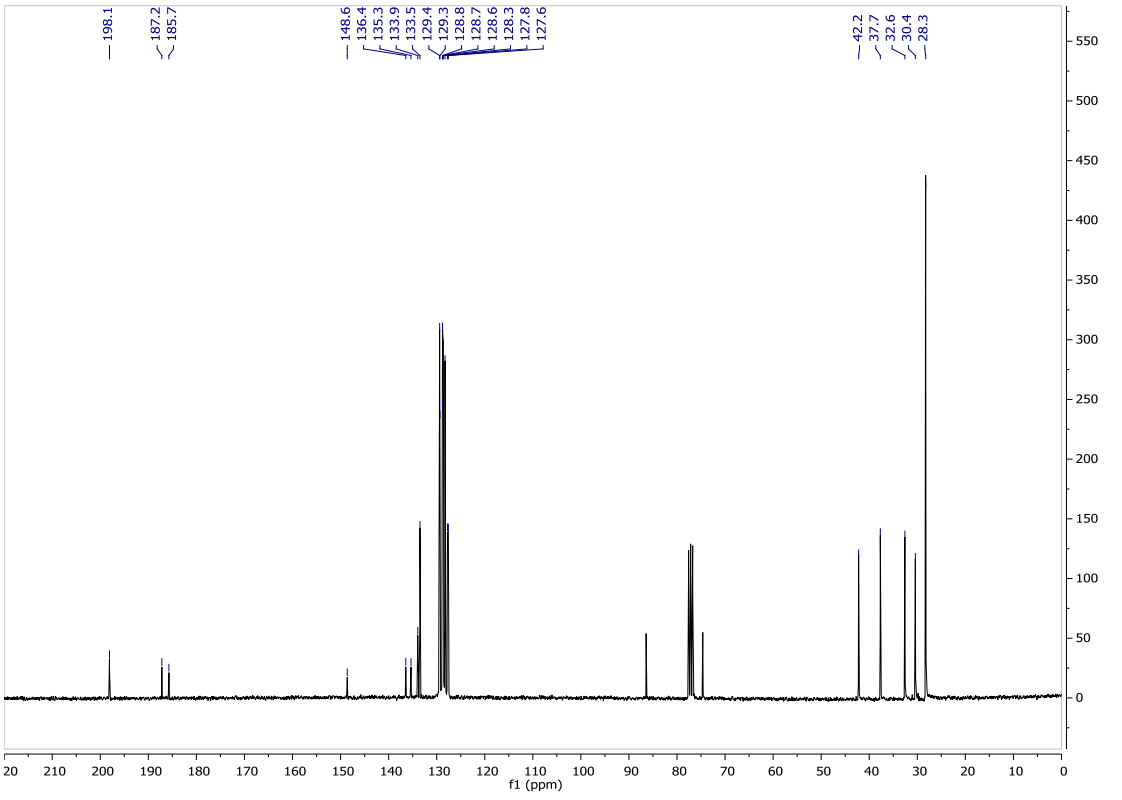
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Bb)



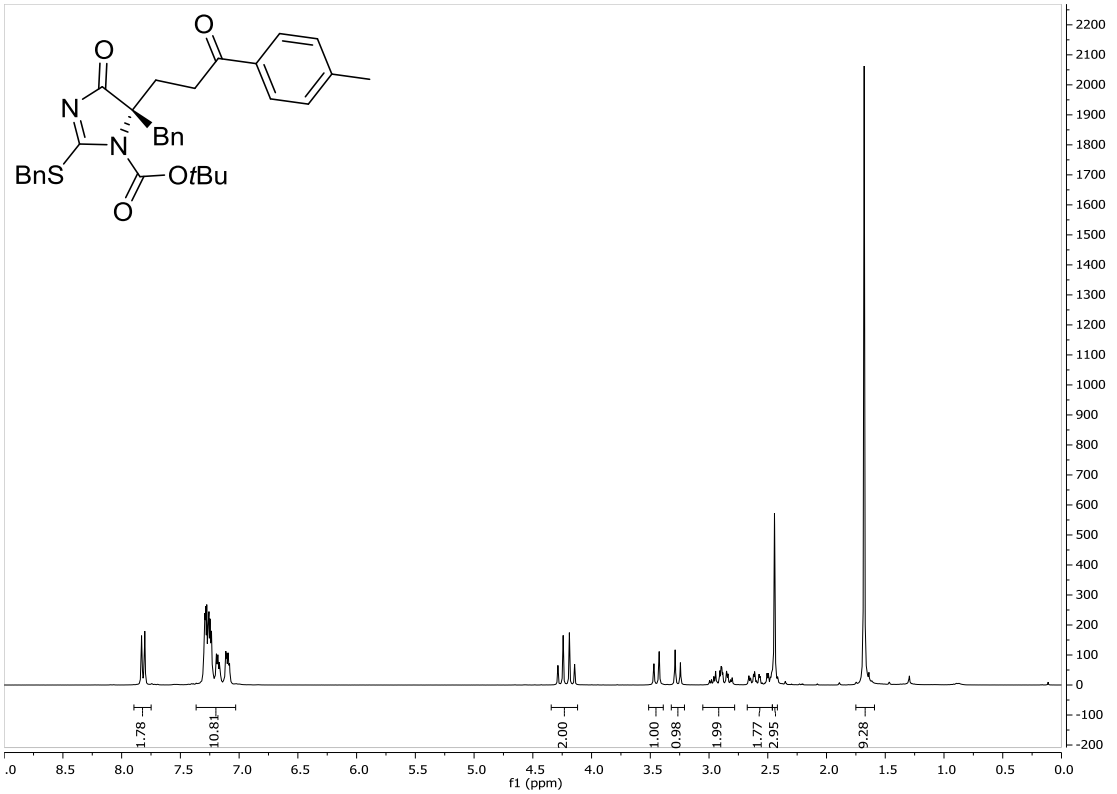


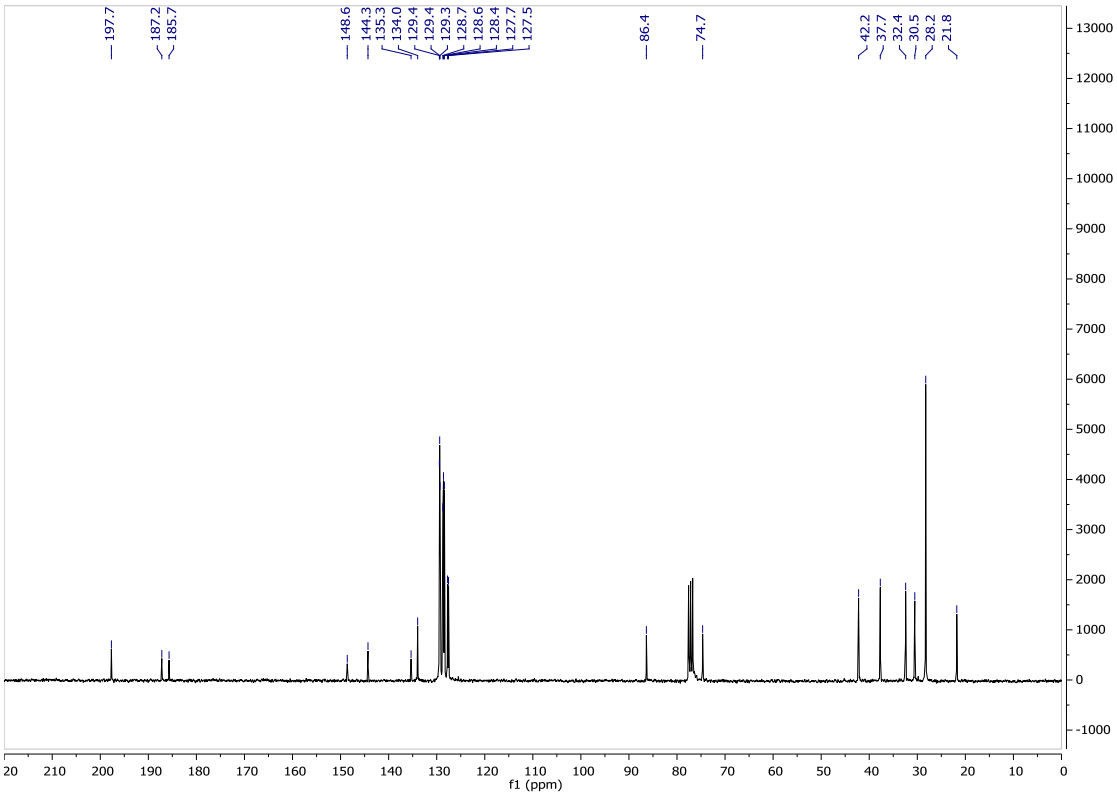
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Cb)



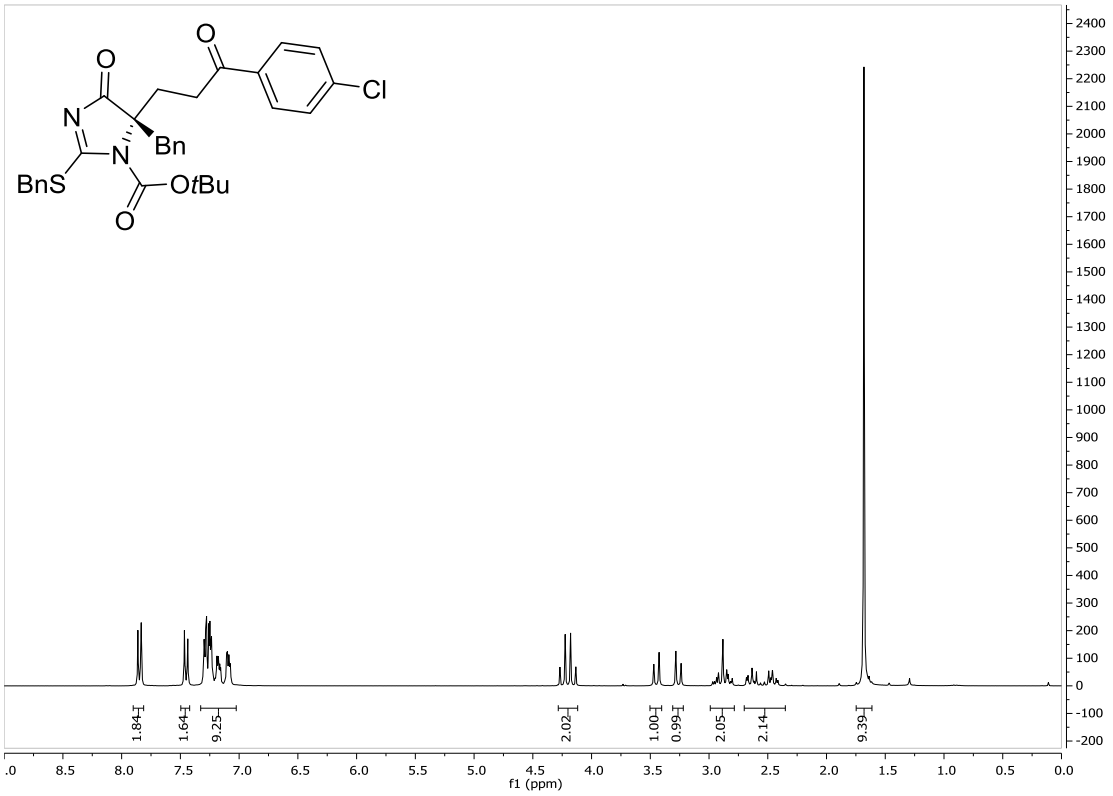


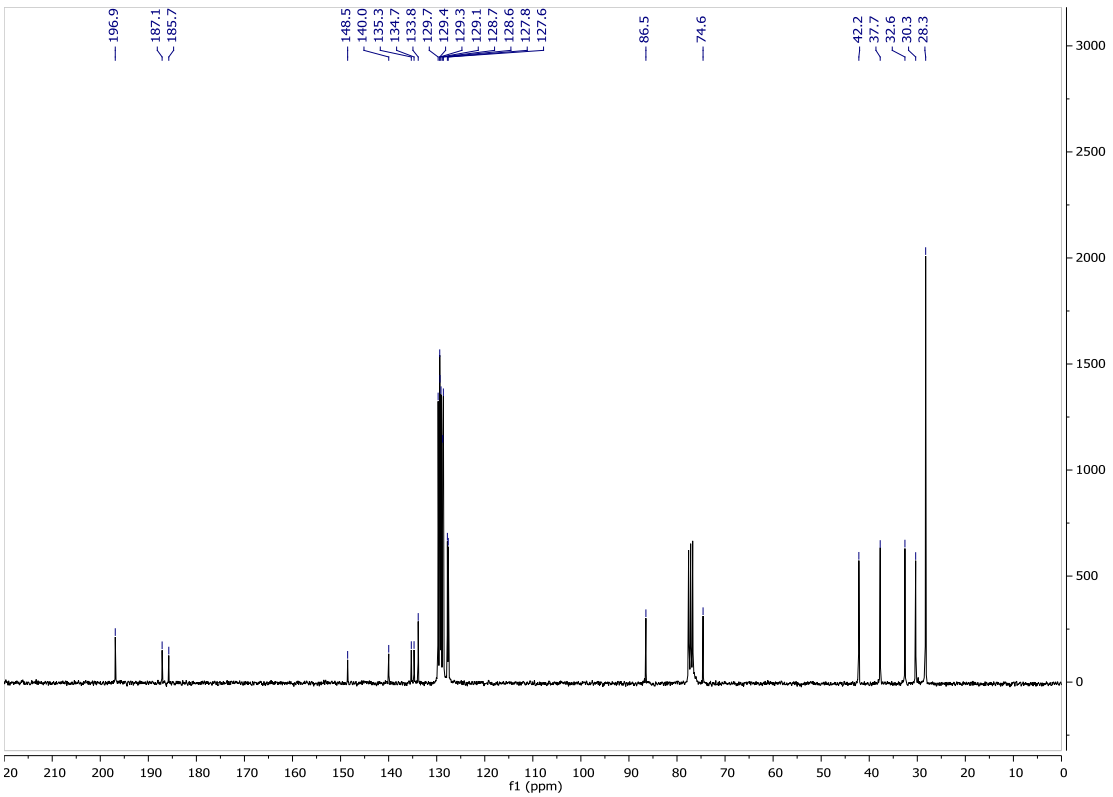
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(*p*-tolyl)propyl)-1*H*-imidazol-4(5*H*)-one (43Cc)



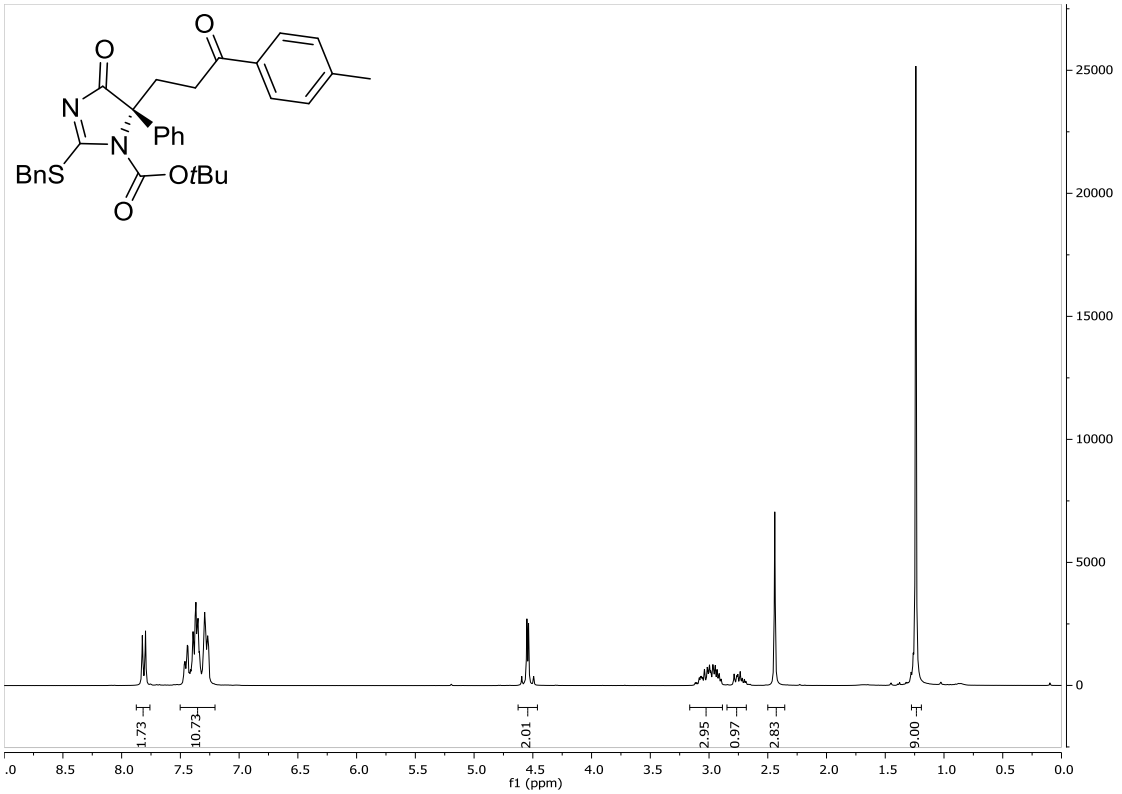


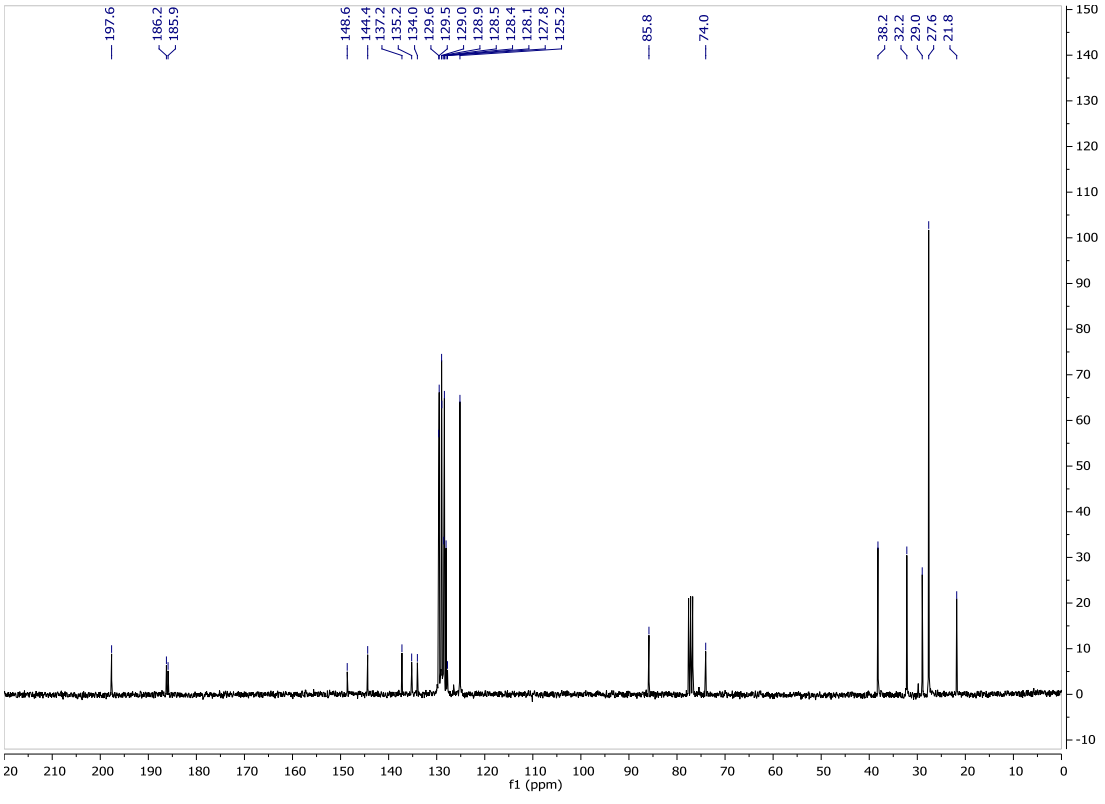
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-(4-chlorophenyl)-3-oxopropyl)-1*H*-imidazol-4(5*H*)-one (43Cd)



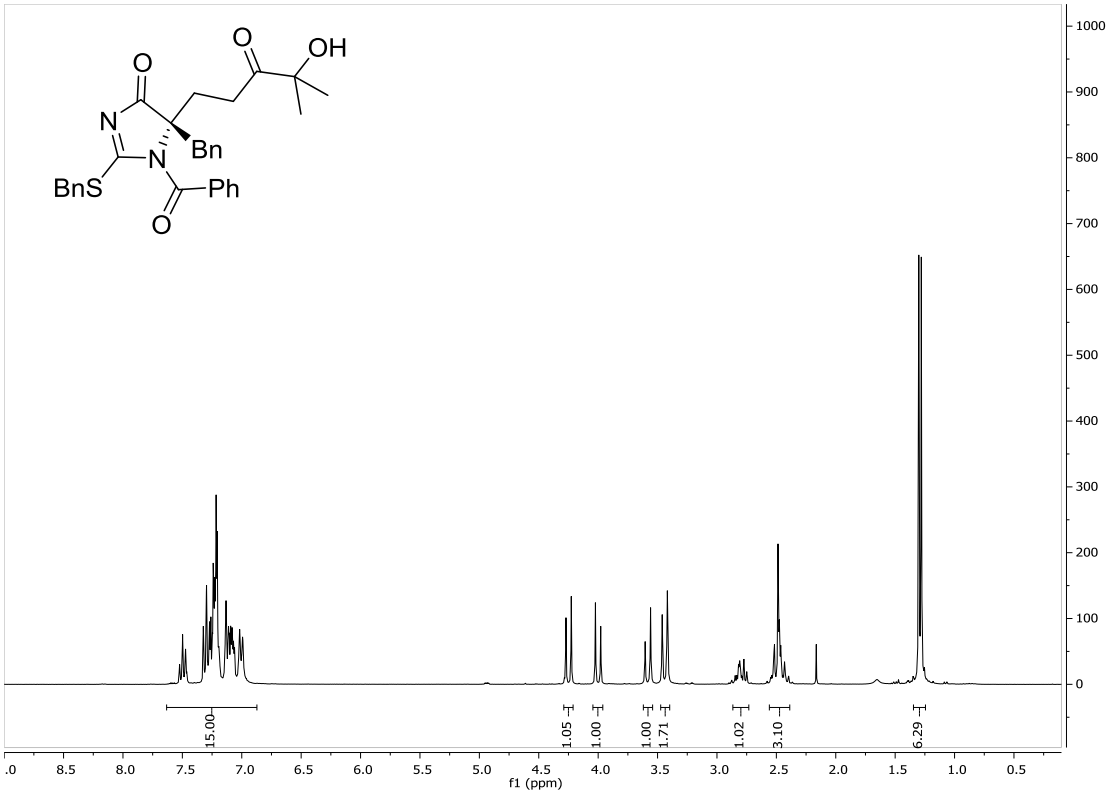


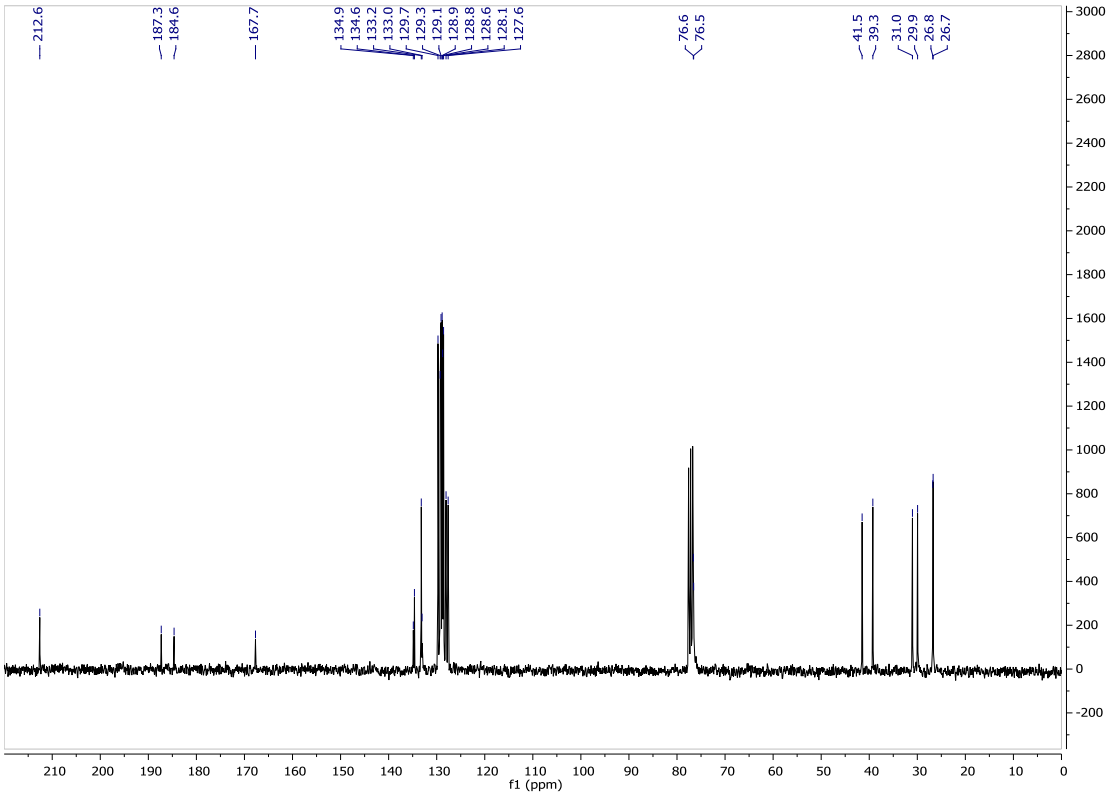
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(p-tolyl)propyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (43Hc)



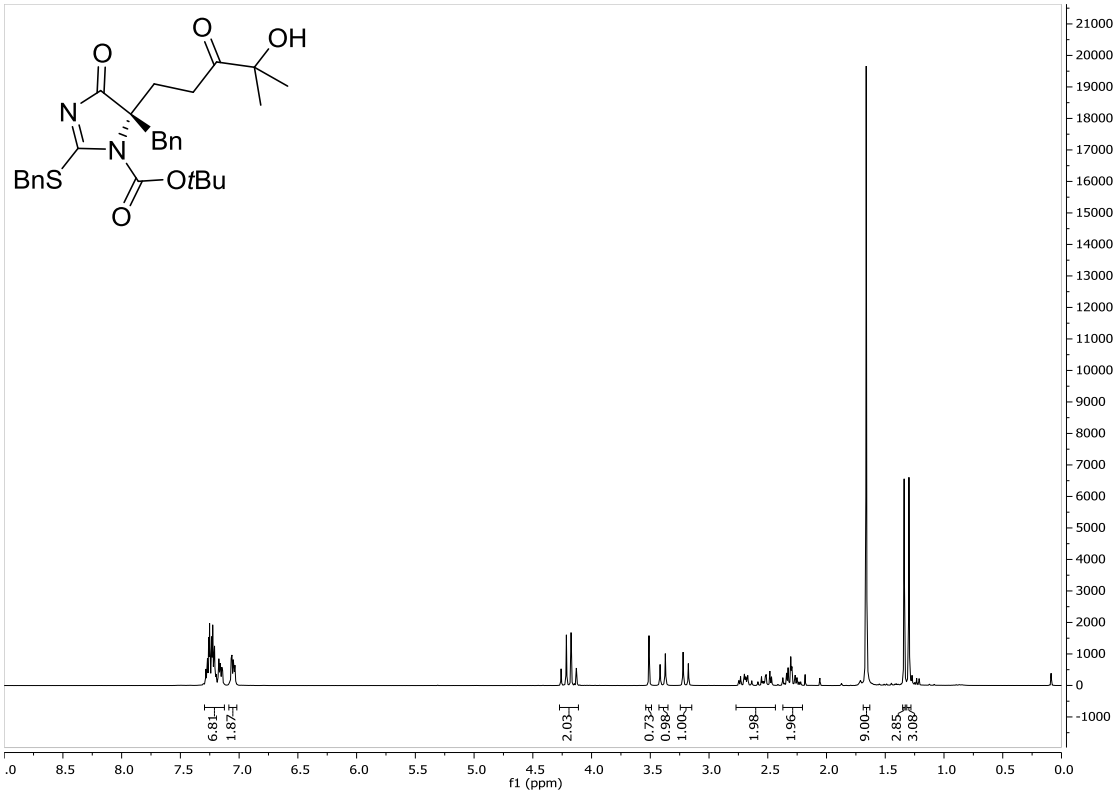


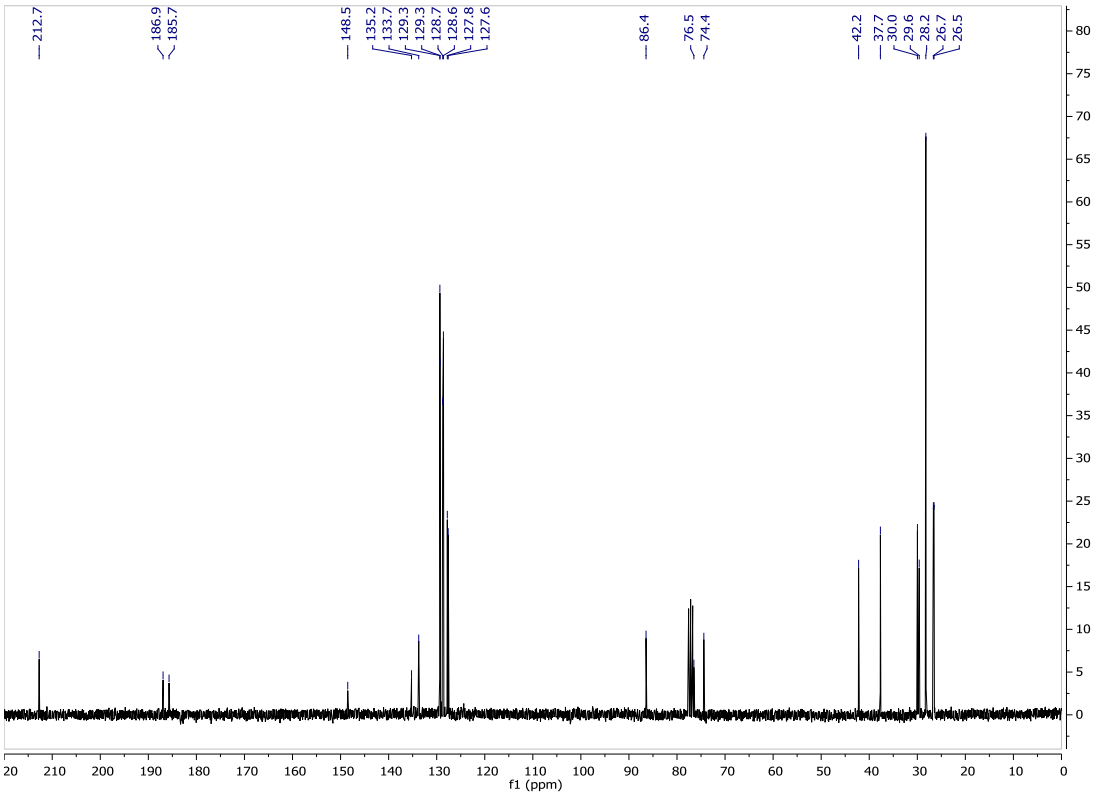
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (45C)



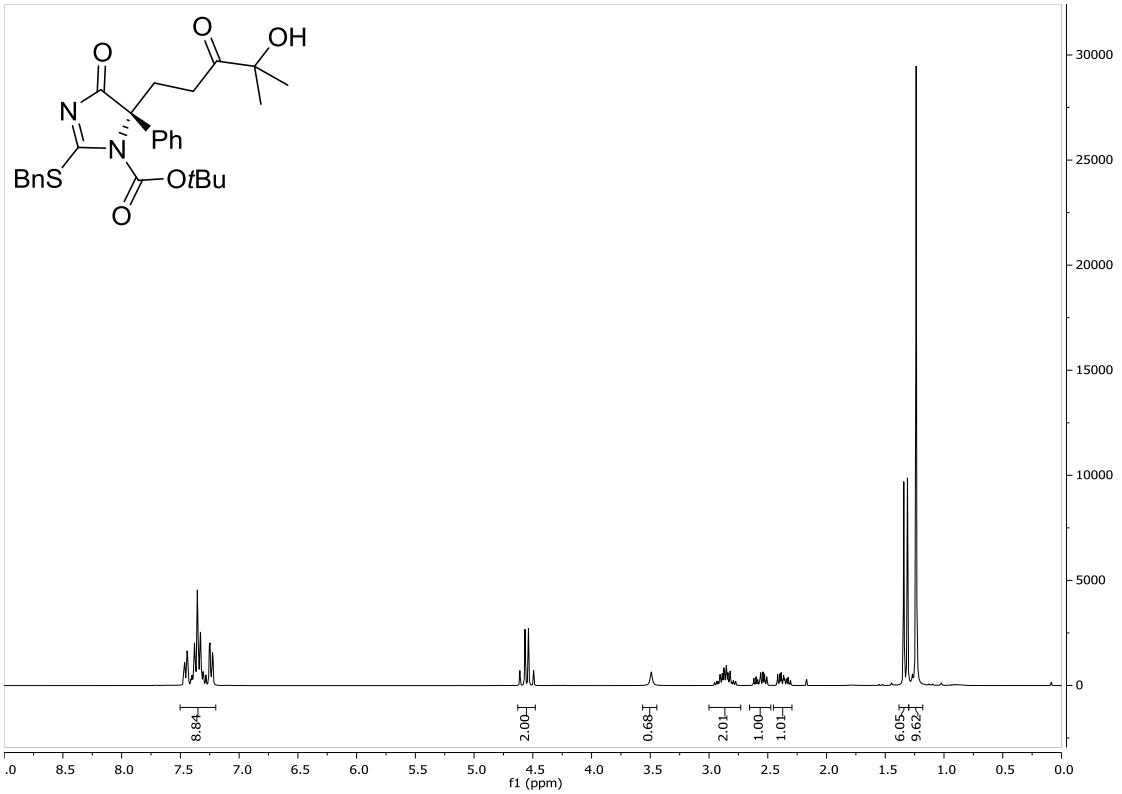


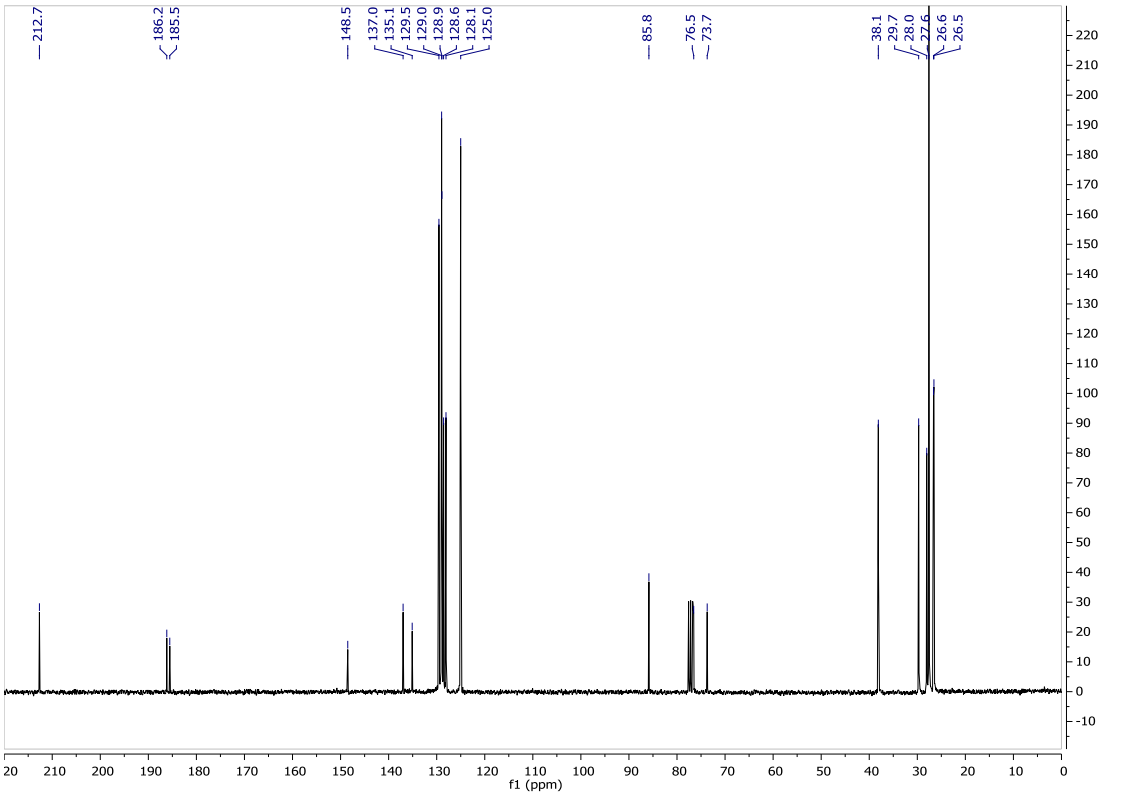
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (46C)



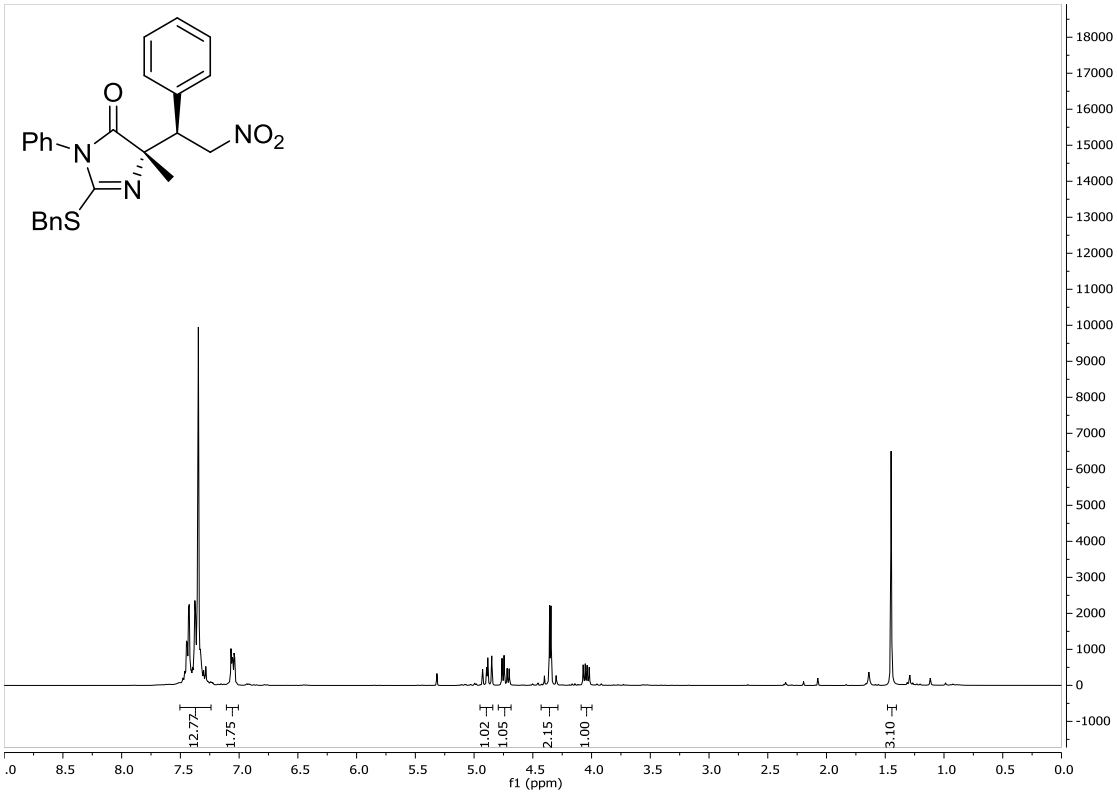


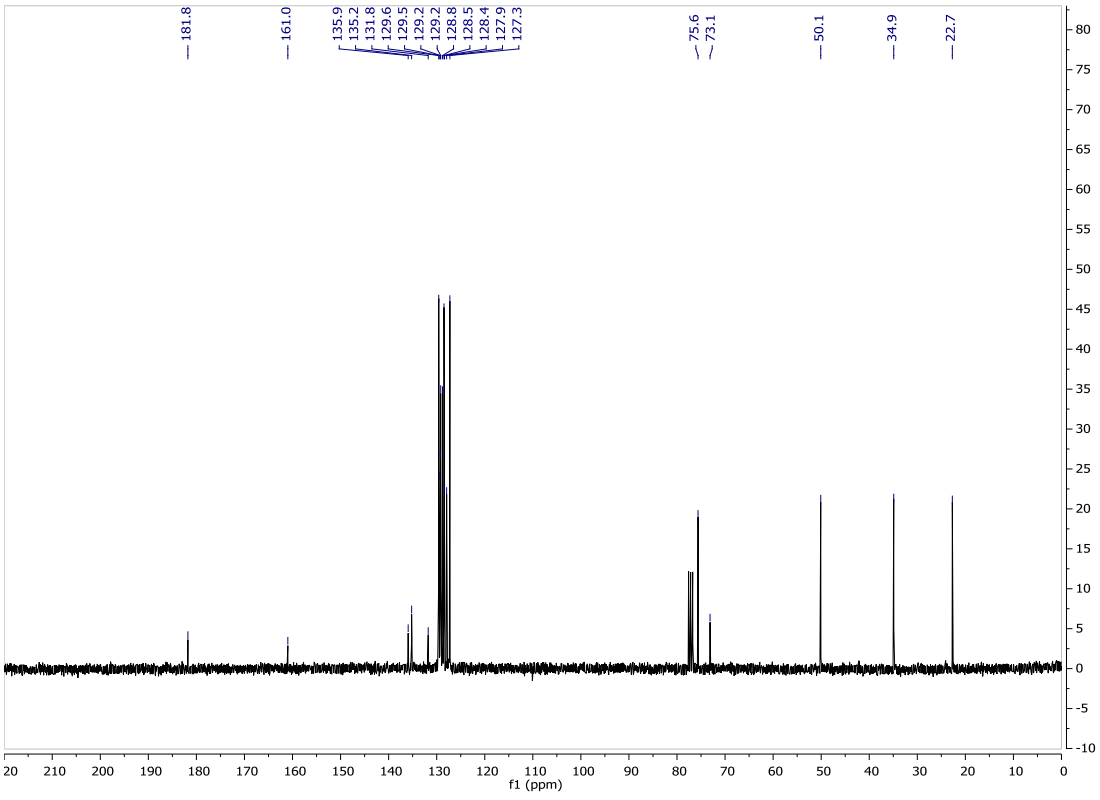
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (46H)



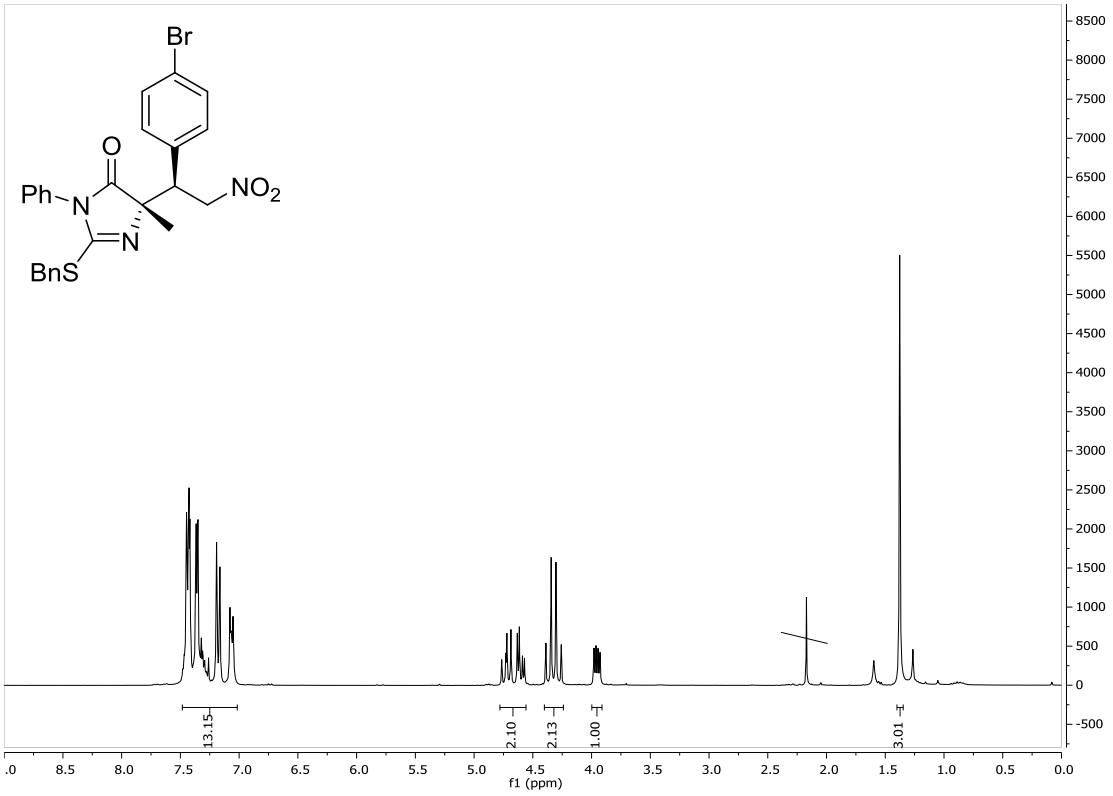


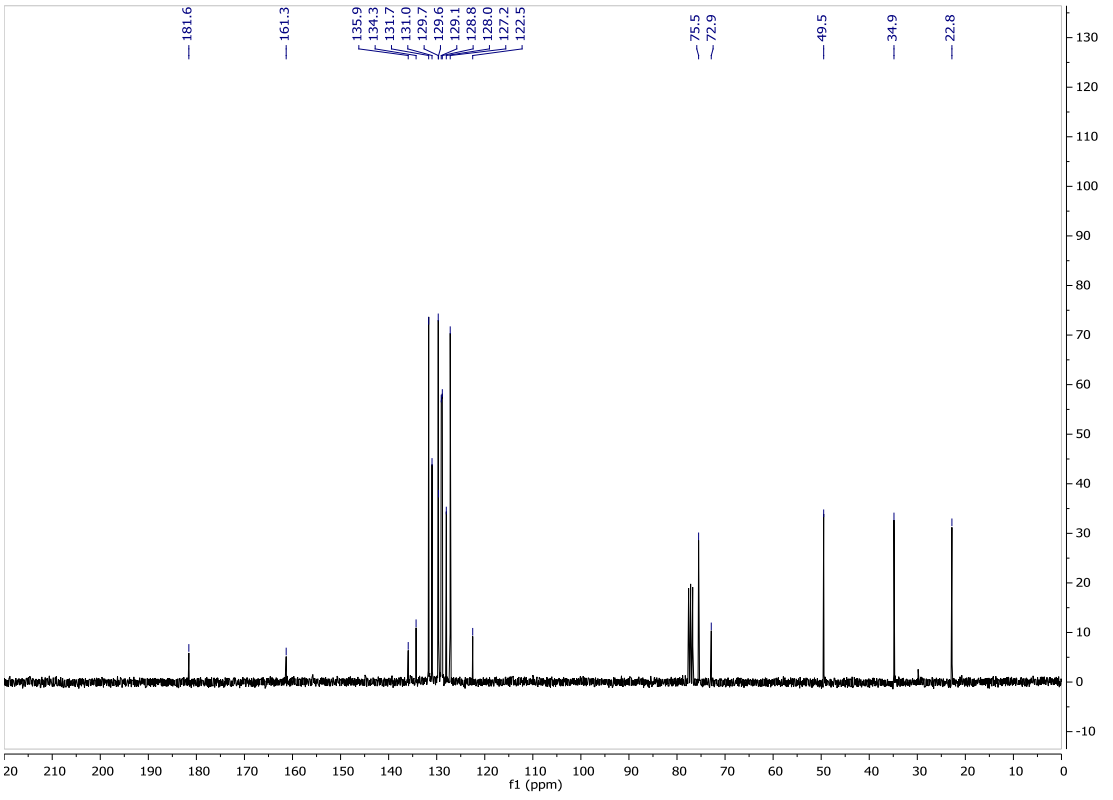
(*S*)-2-(Benzylthio)-4-methyl-4-((S)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aa)



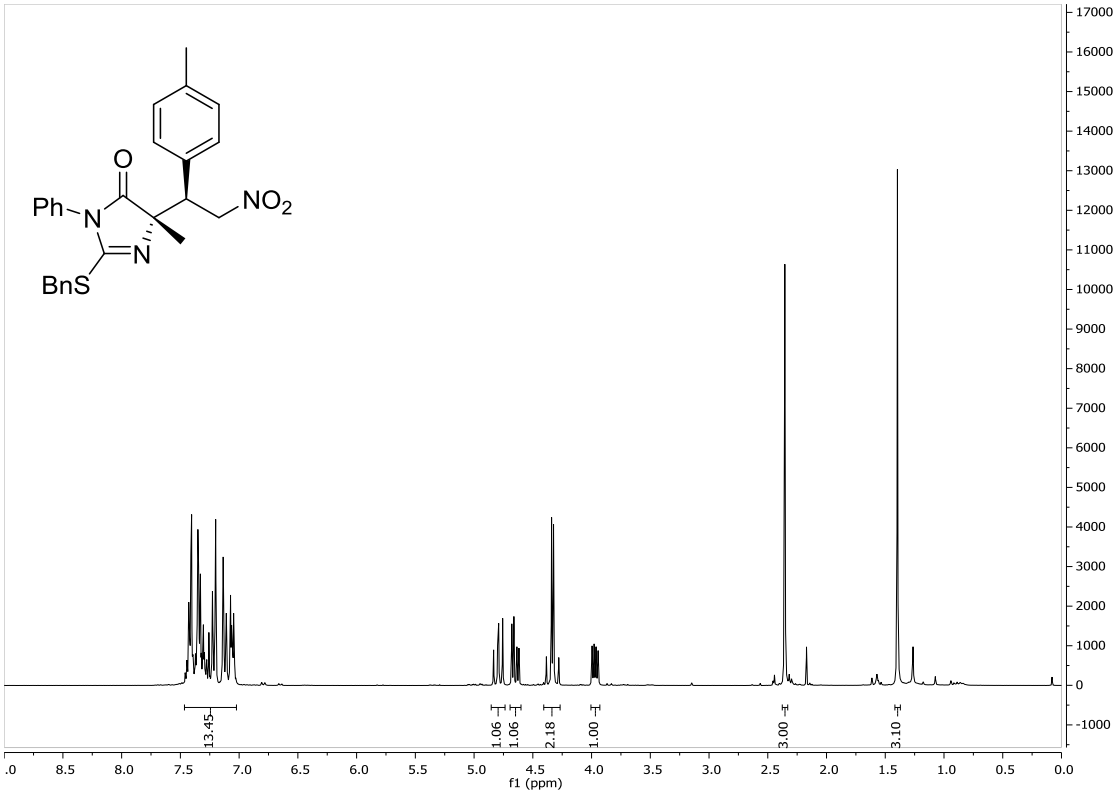


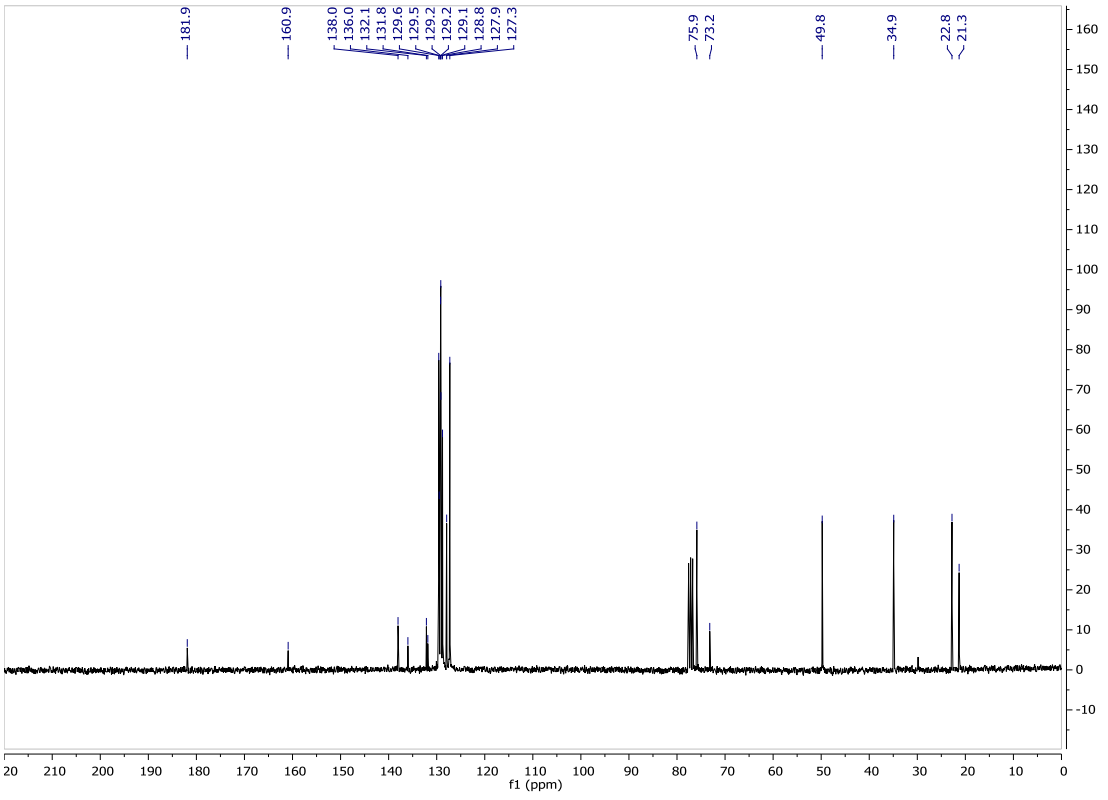
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ab)



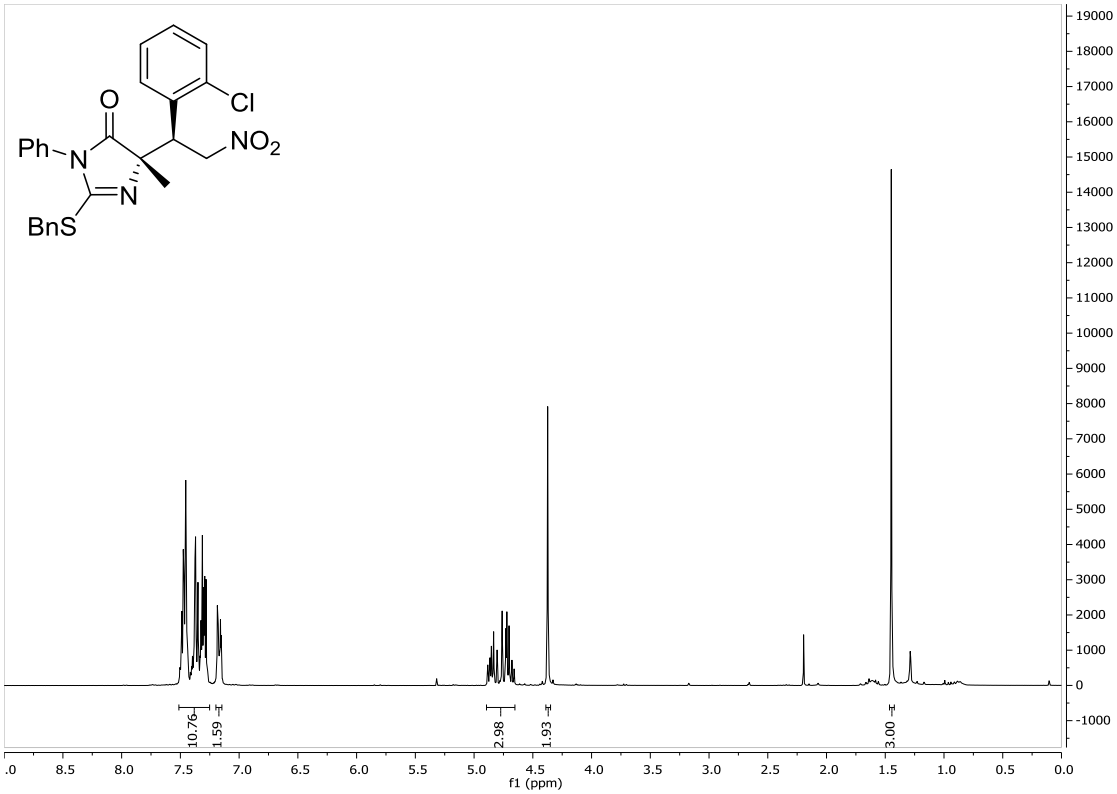


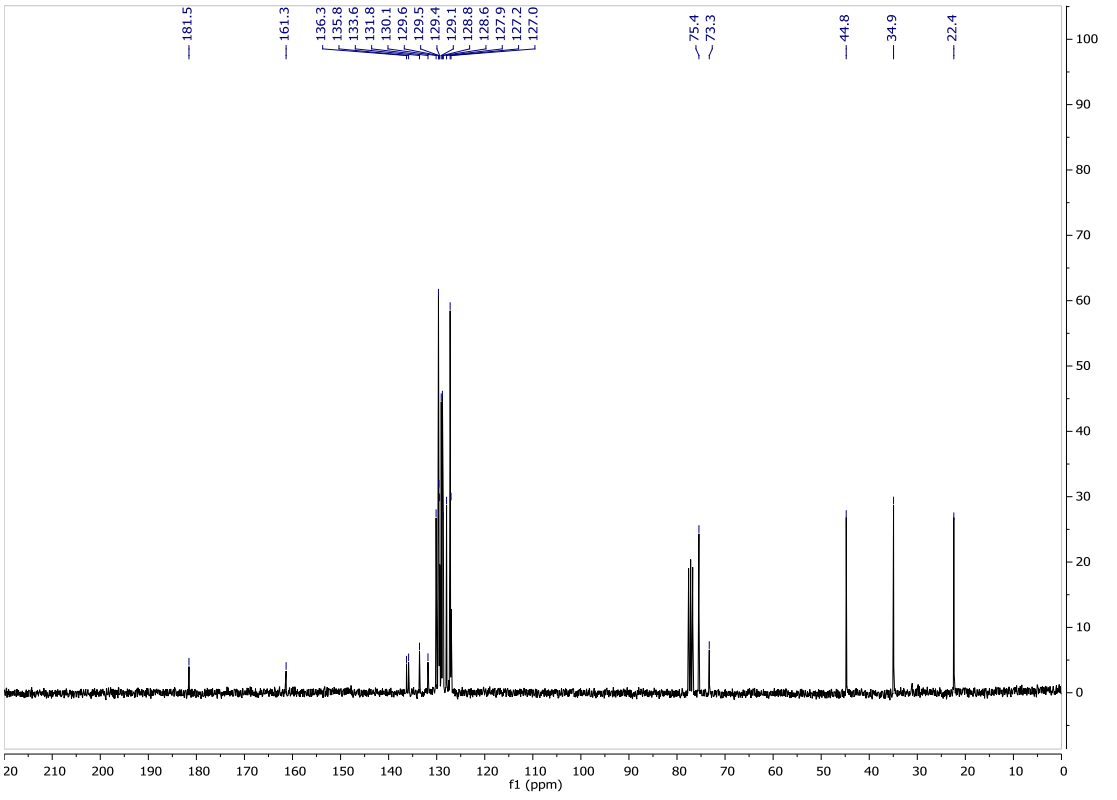
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ac)



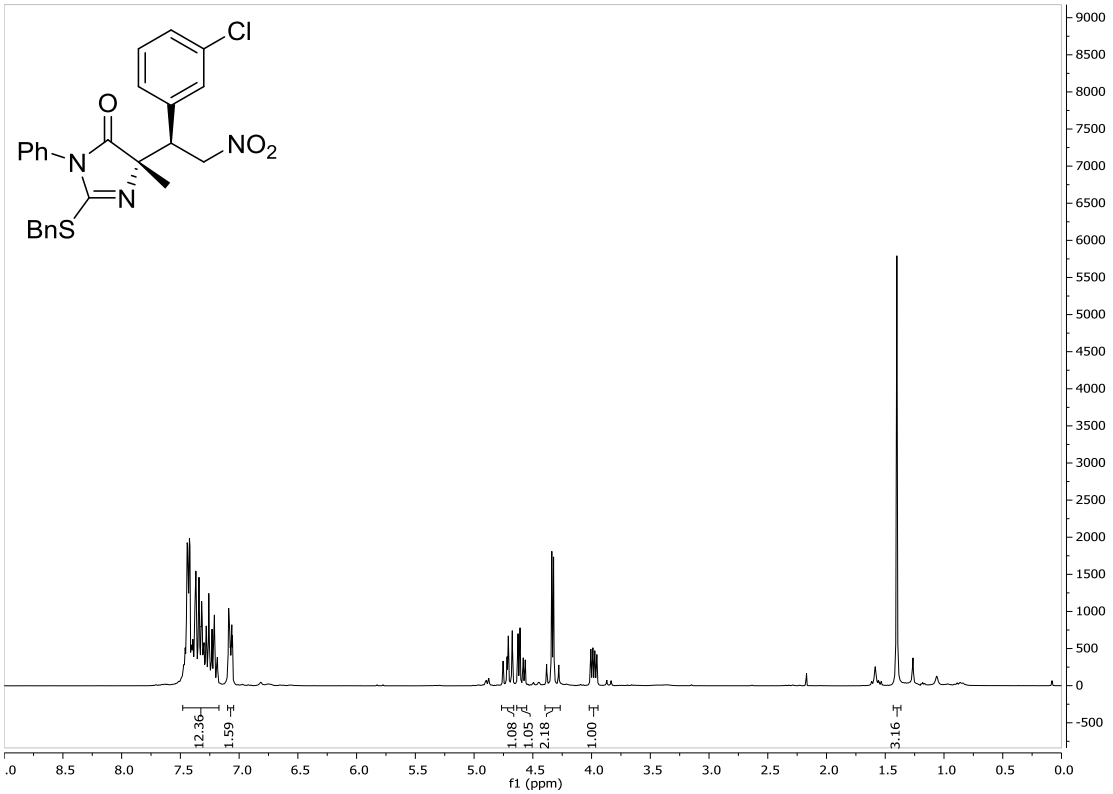


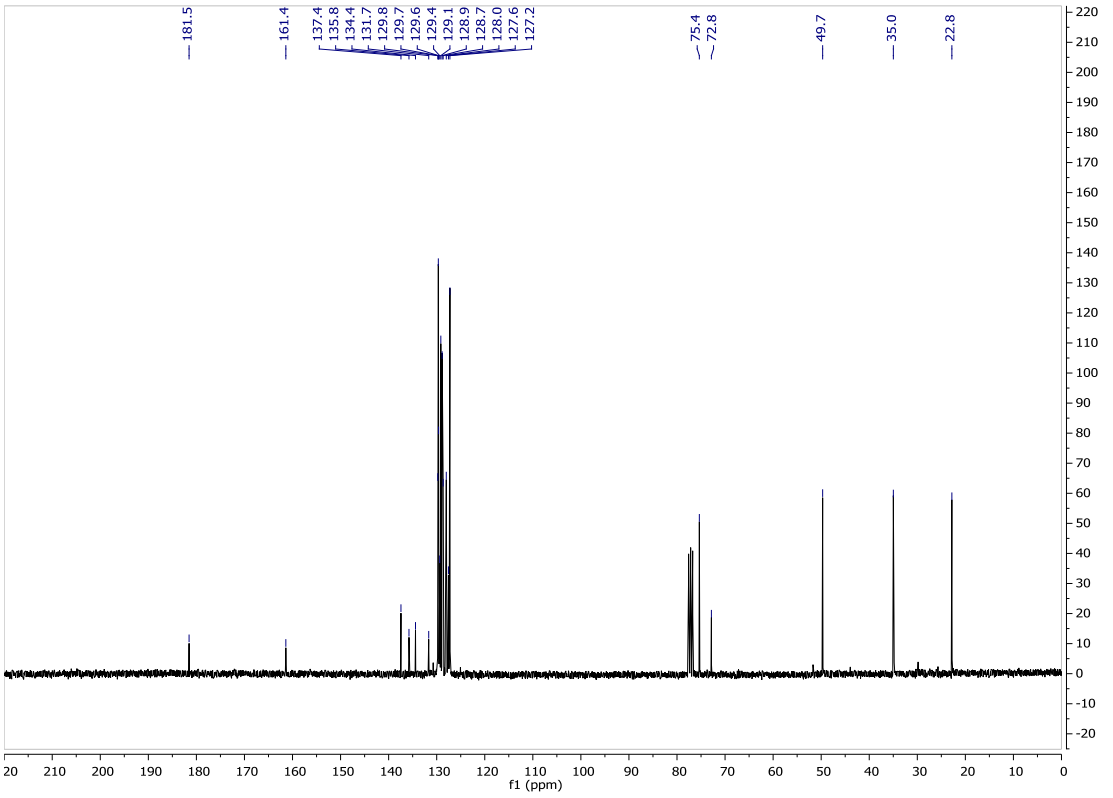
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ad)



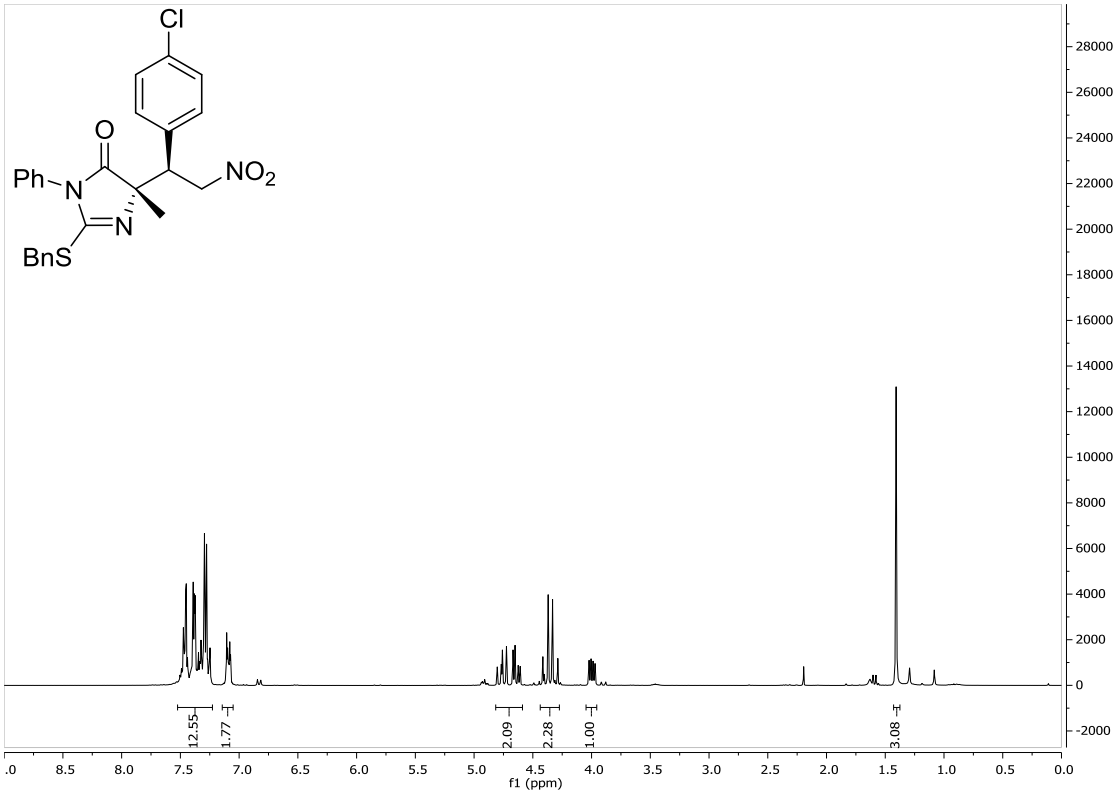


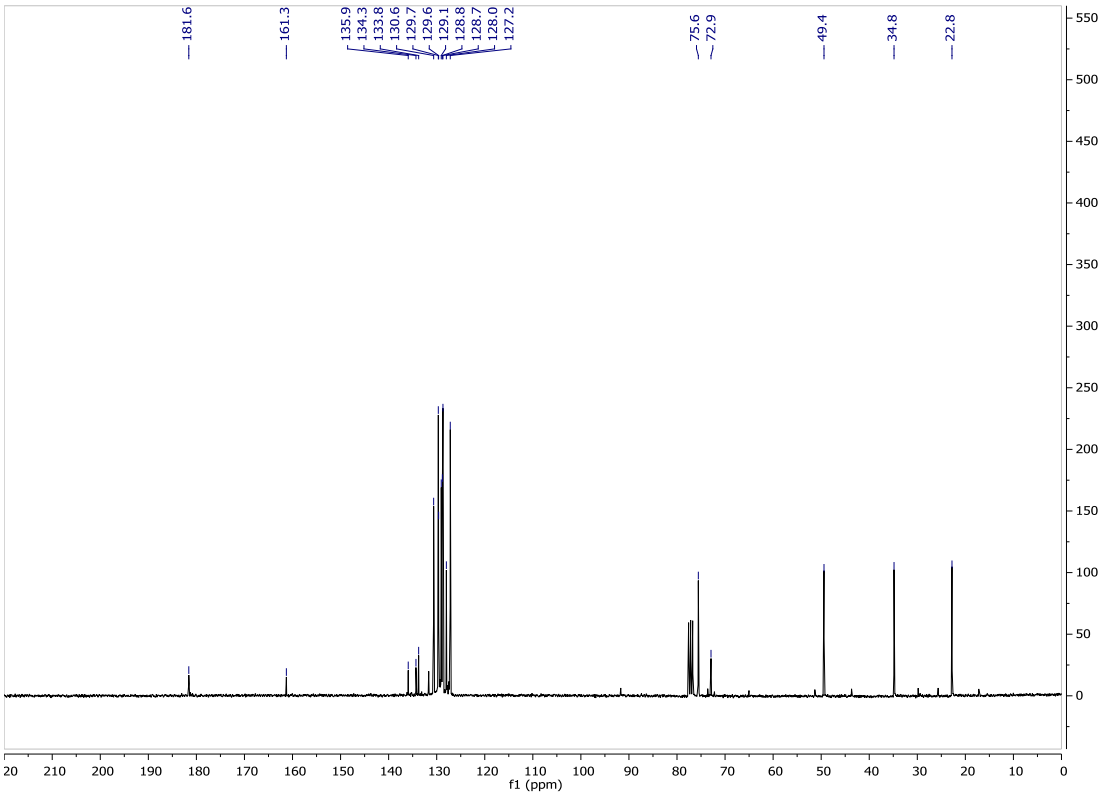
(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ae)



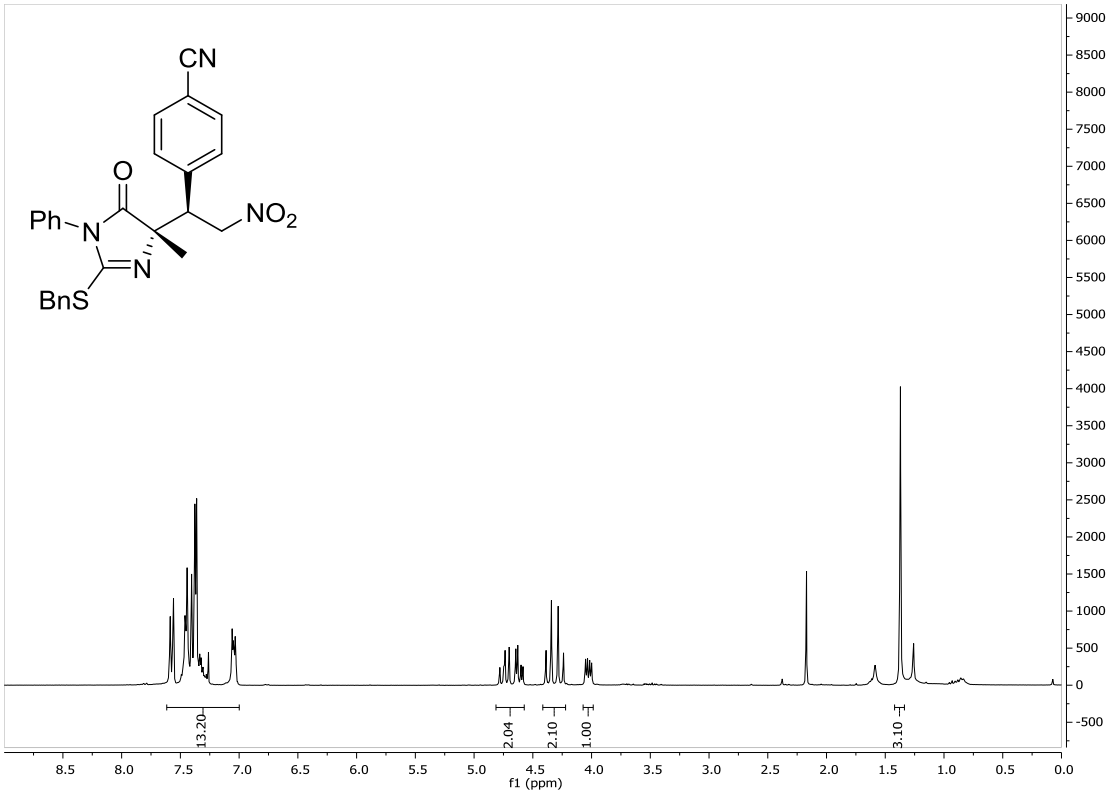


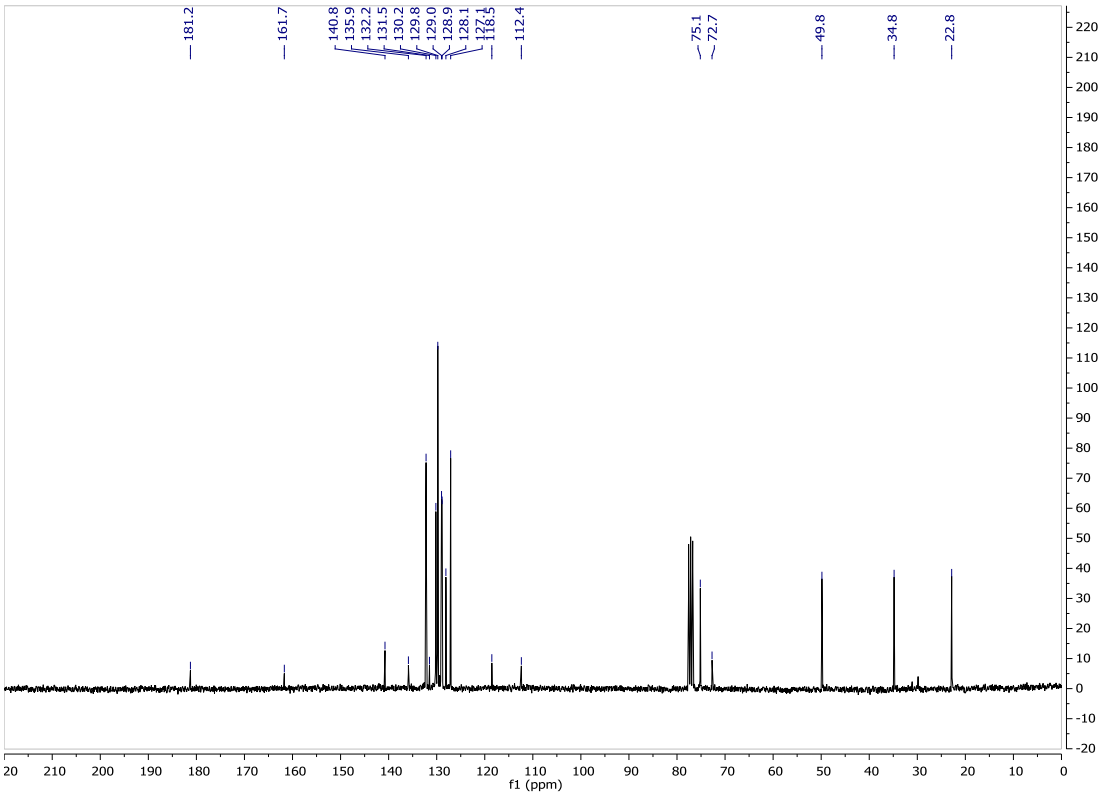
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aj)



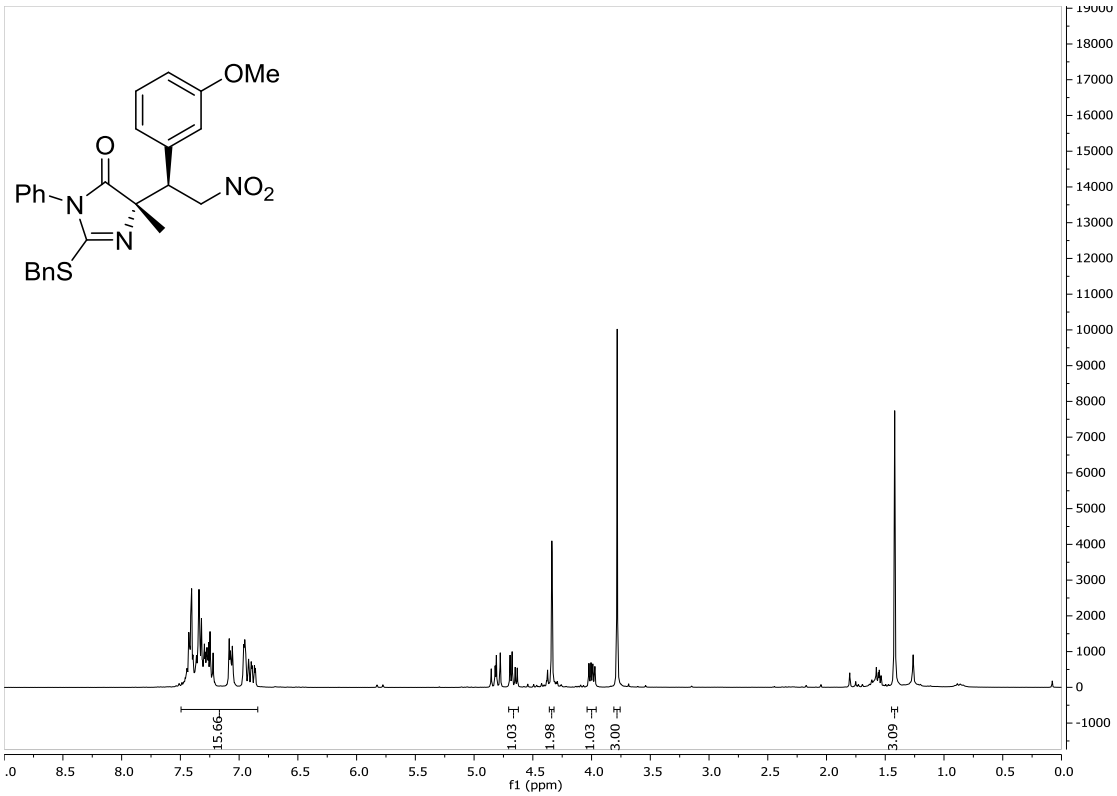


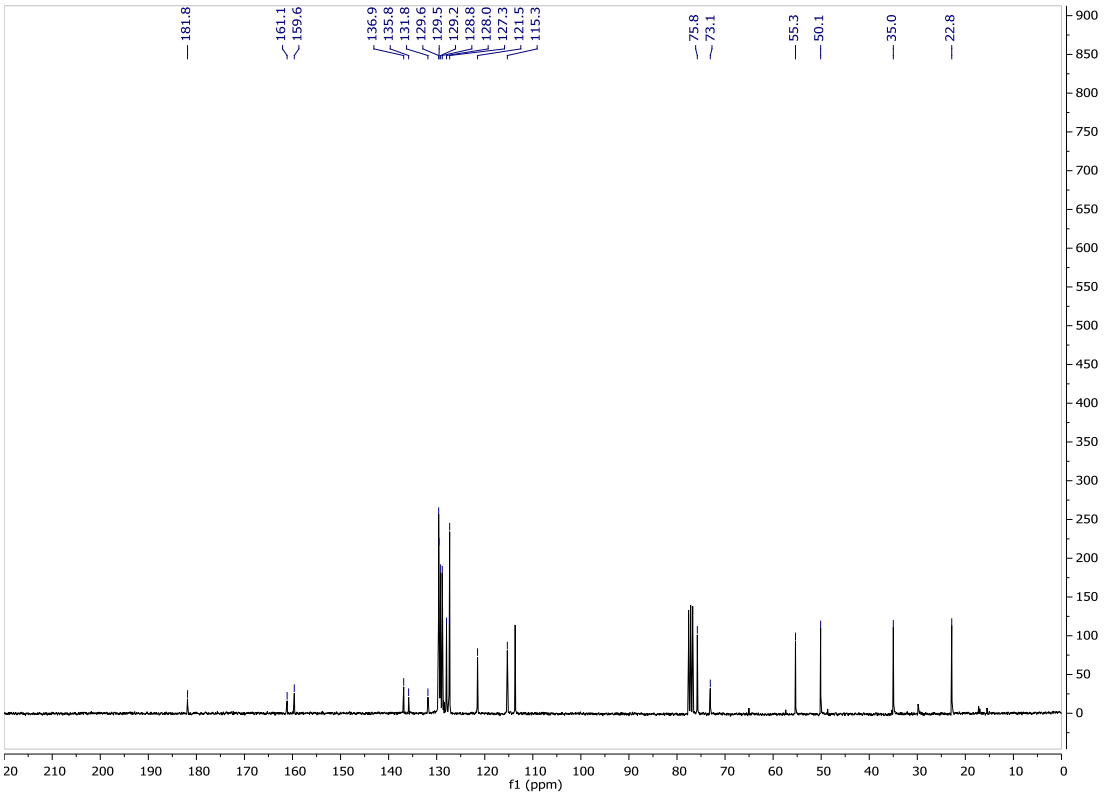
4-((*S*)-1-((*S*)-2-(Benzylthio)-4-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)-2-nitroethyl)benzonitrile (67Ak)



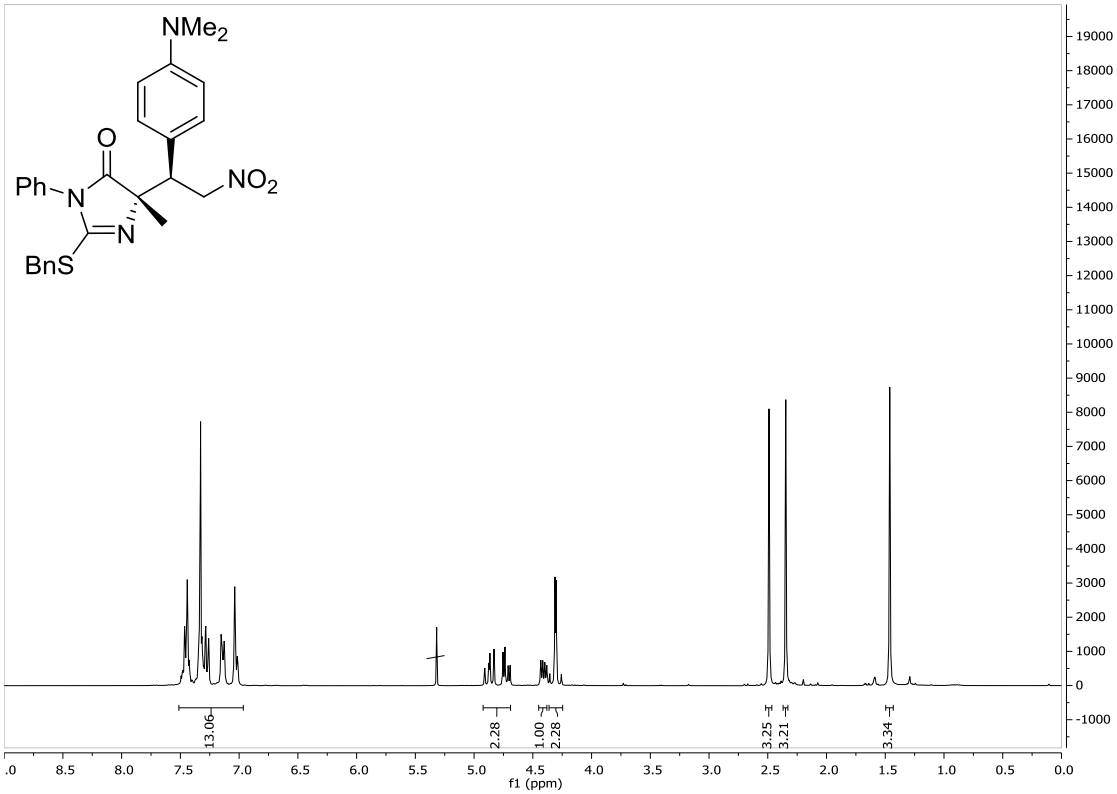


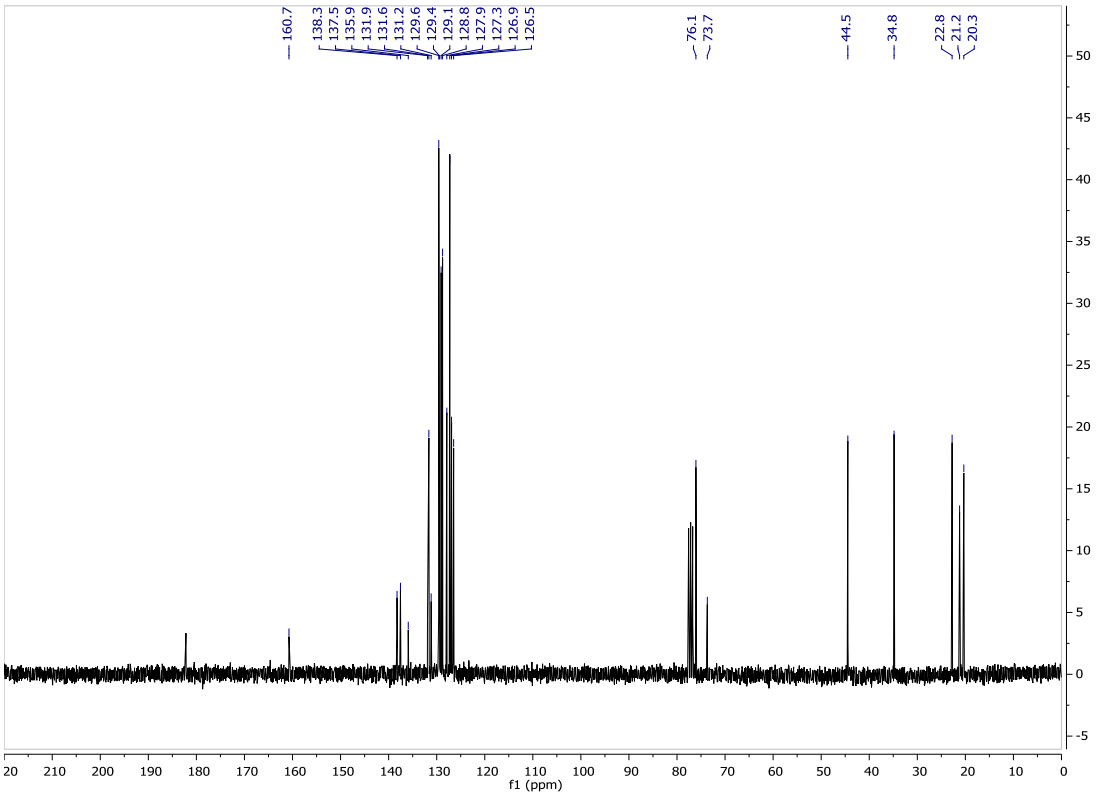
(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Am)



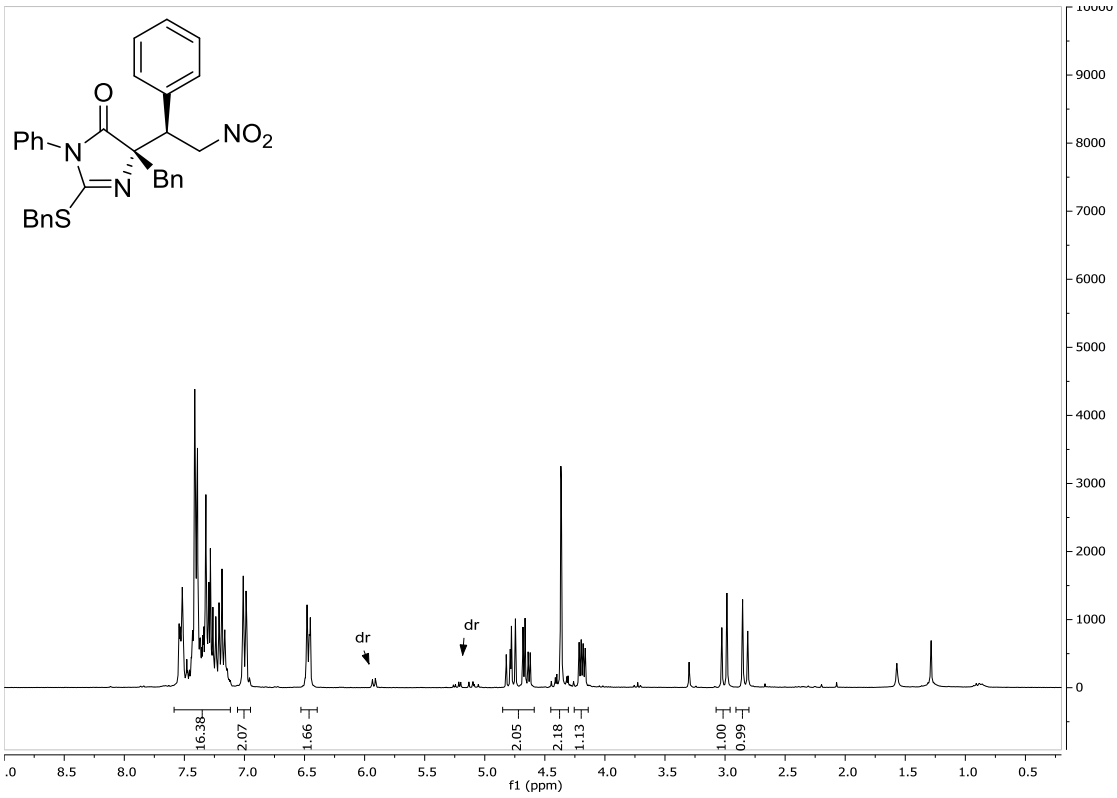


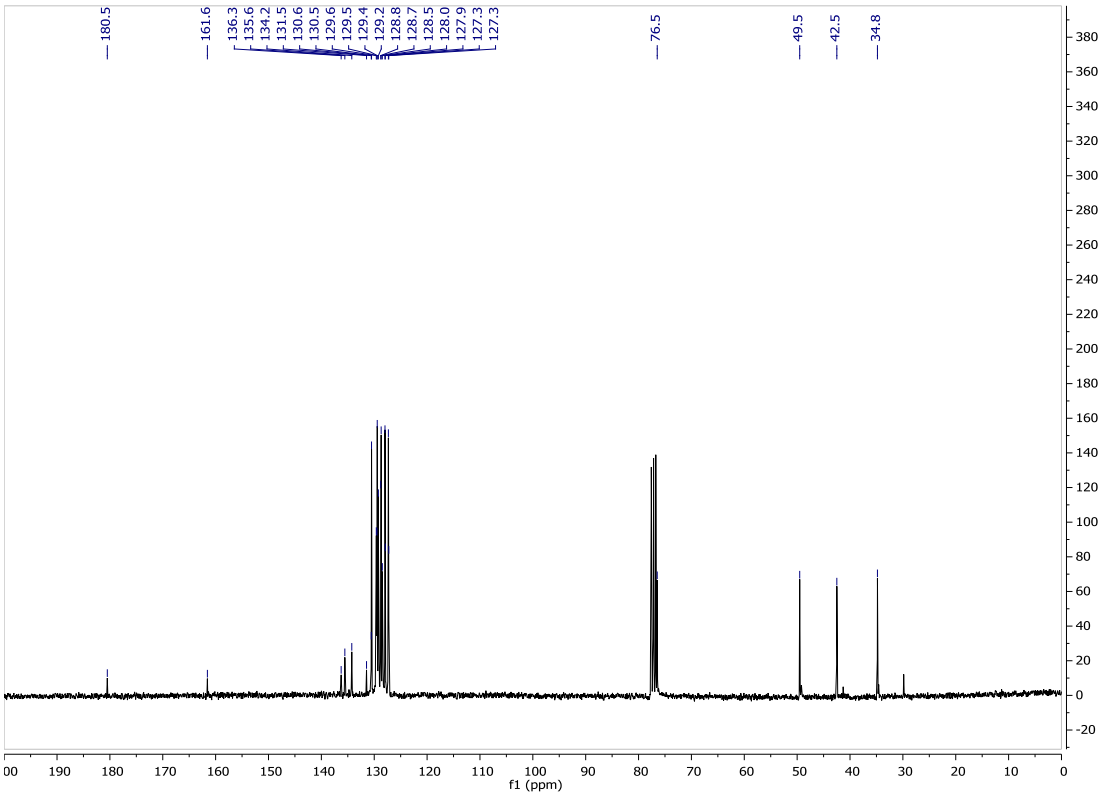
(S)-2-(Benzylthio)-5-((S)-1-(4-(dimethylamino)phenyl)-2-nitroethyl)-5-methyl-3-phenyl-1H-imidazol-5(4H)-one (67An)



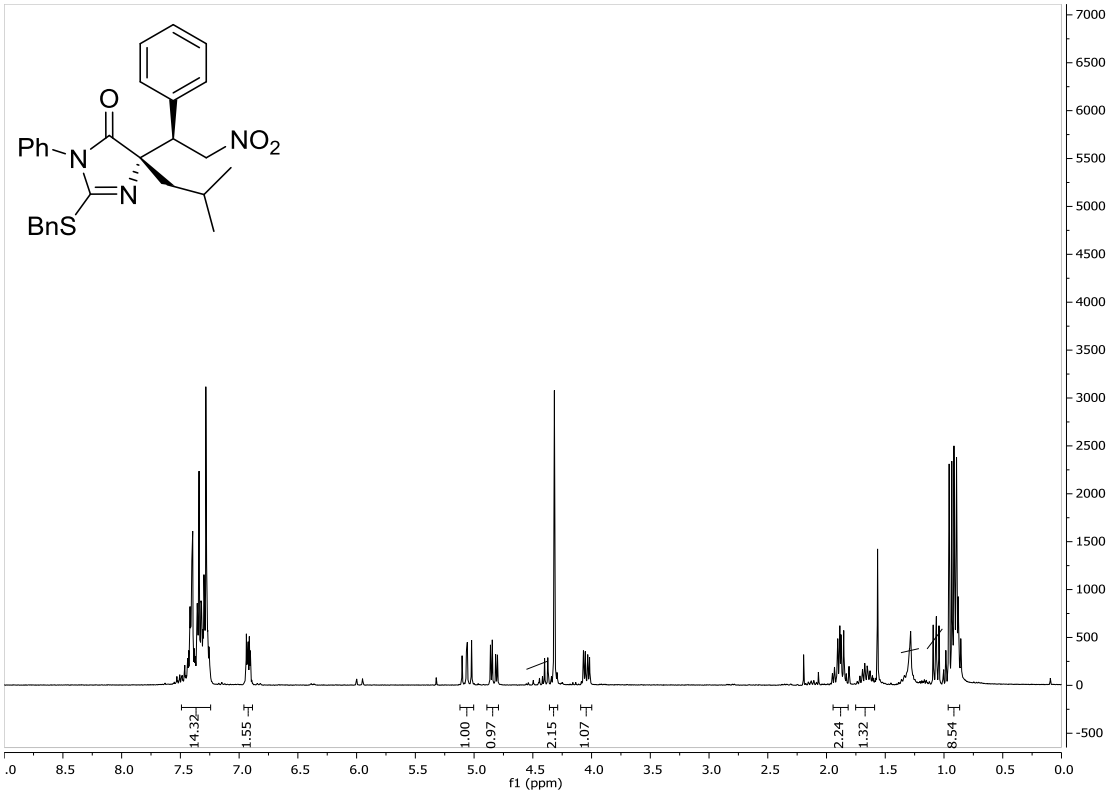


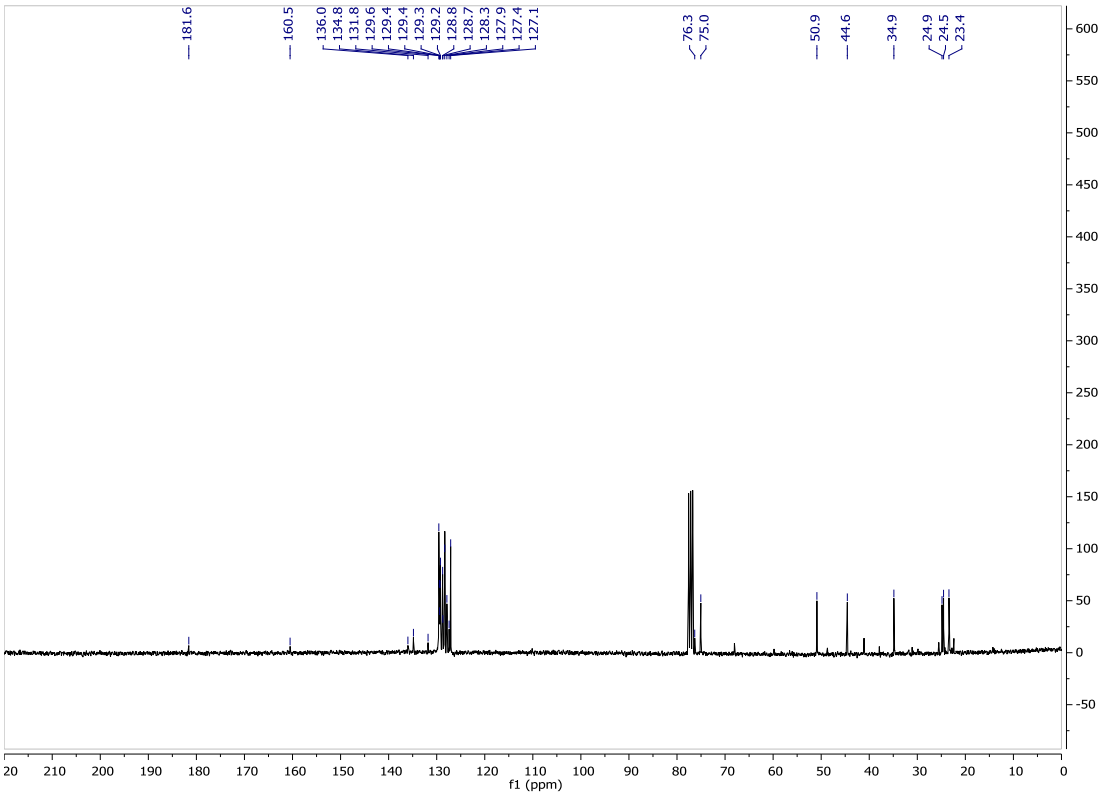
(*S*)-4-Benzyl-2-(benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ca)



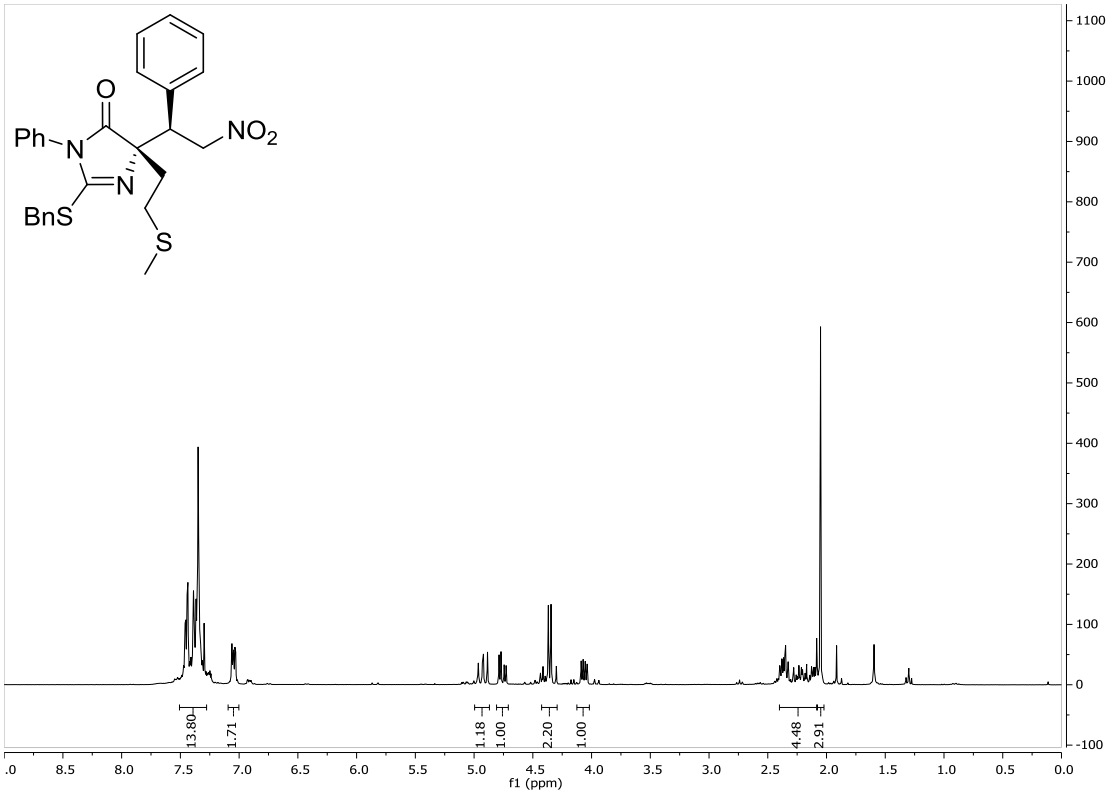


(*S*)-2-(Benzylthio)-4-isobutyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Da)

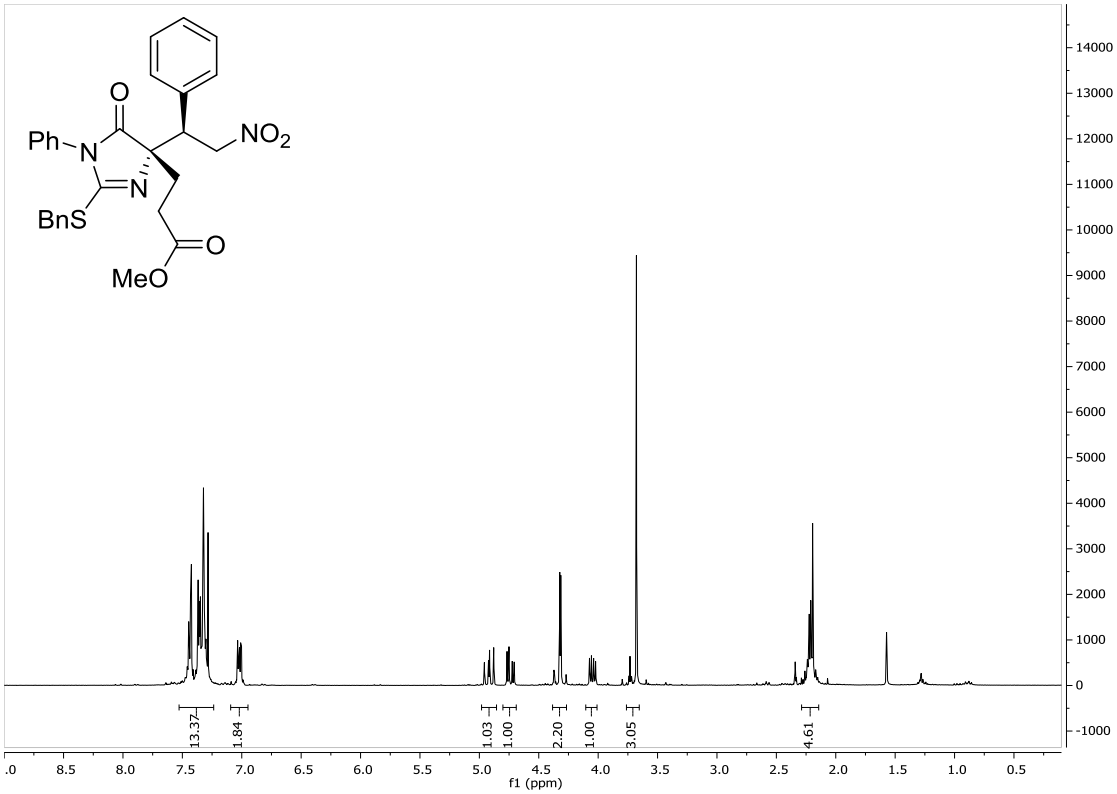


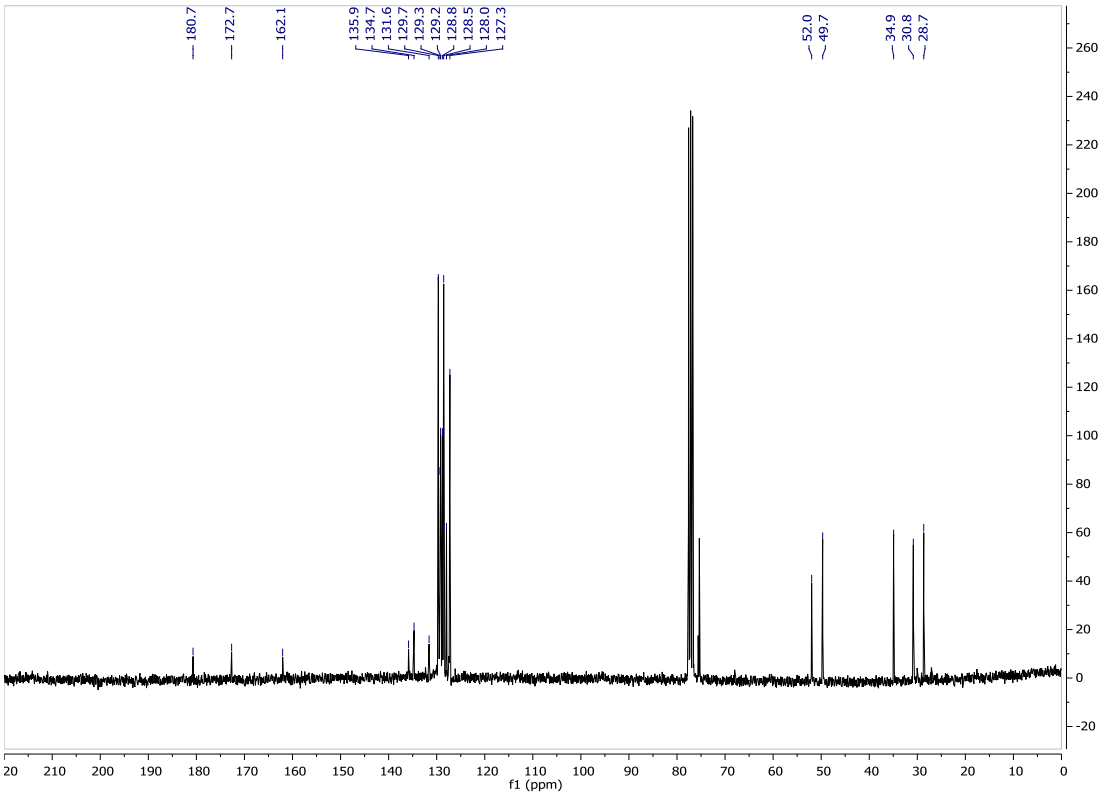


(*S*)-2-(Benzylthio)-4-(2-(methylthio)ethyl)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Fa)

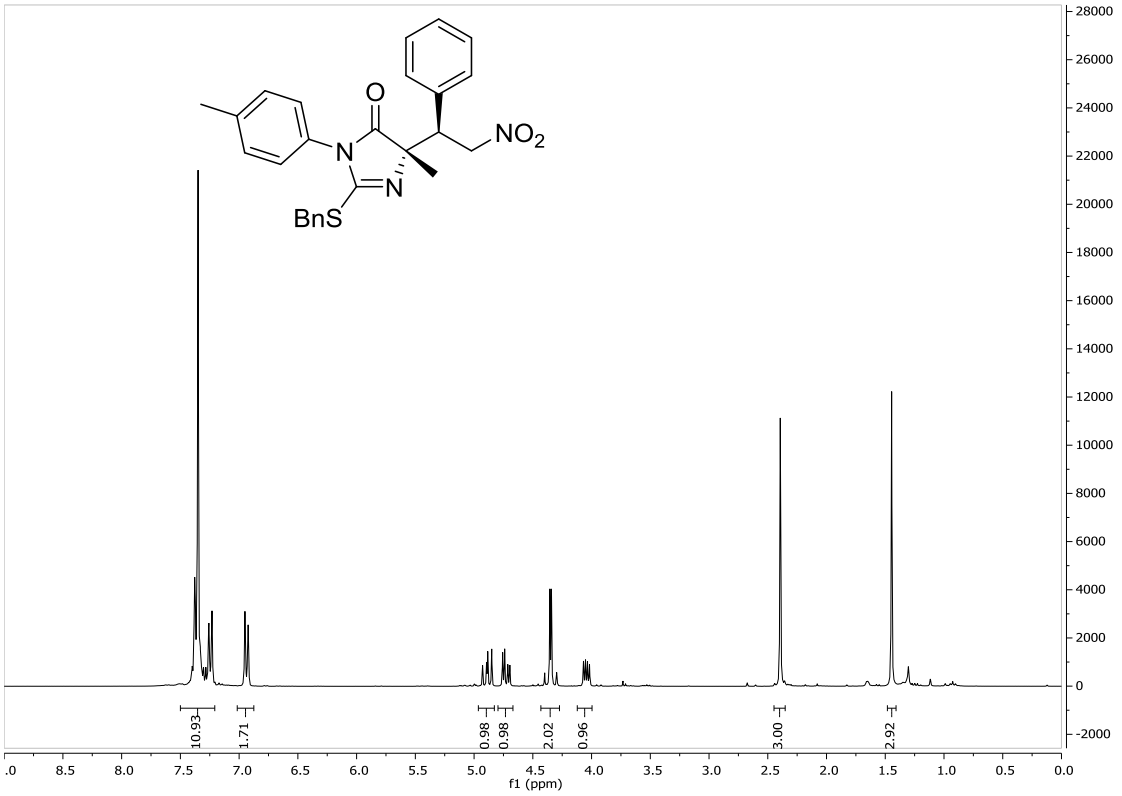


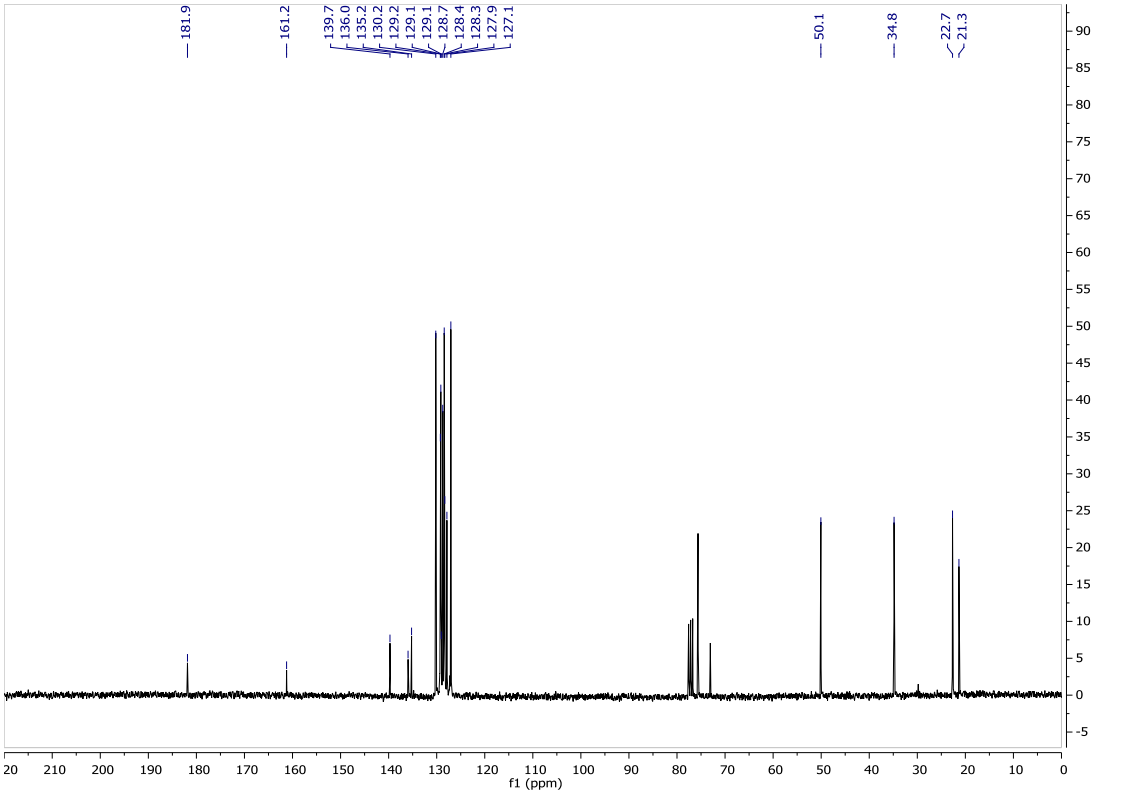
Methyl 3-((*S*)-2-(Benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate (67Ia)



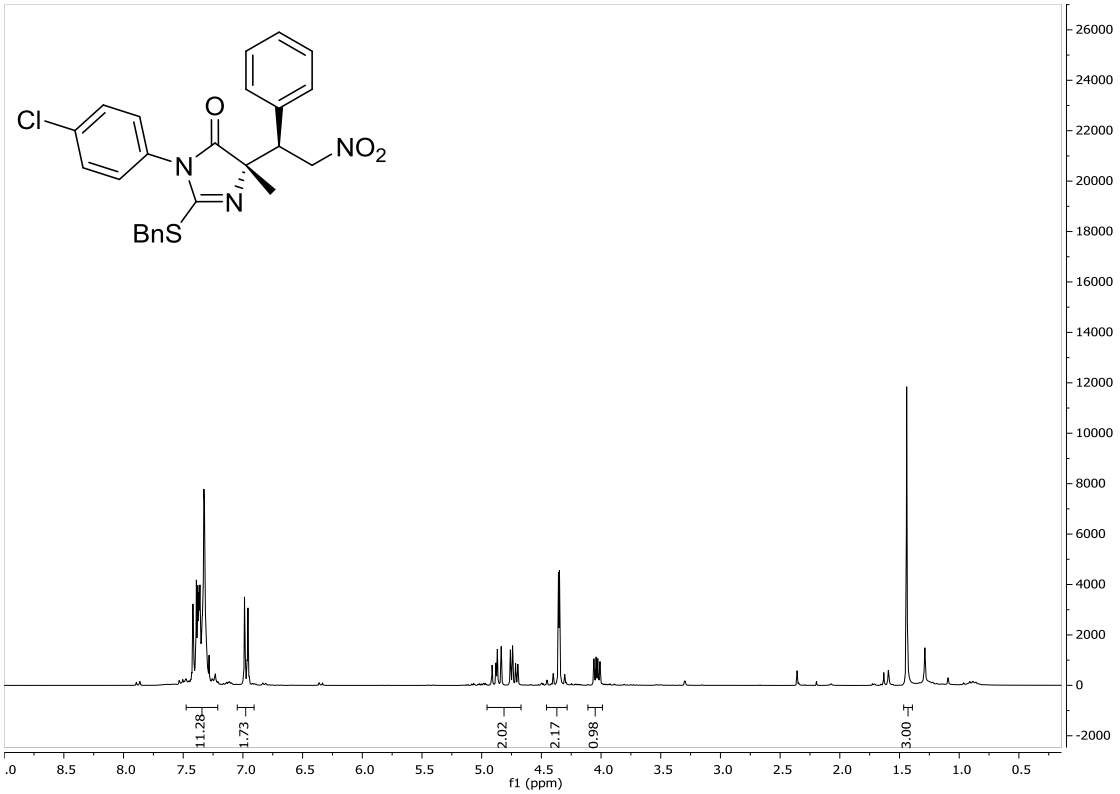


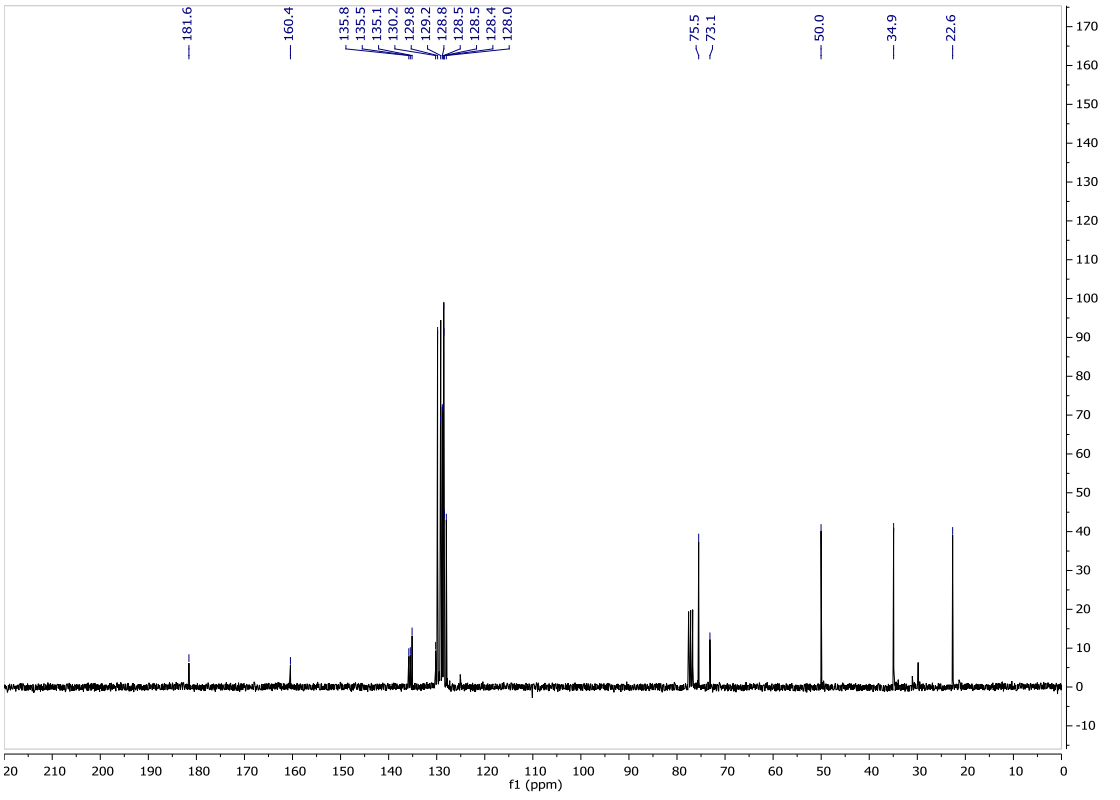
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (68Aa)



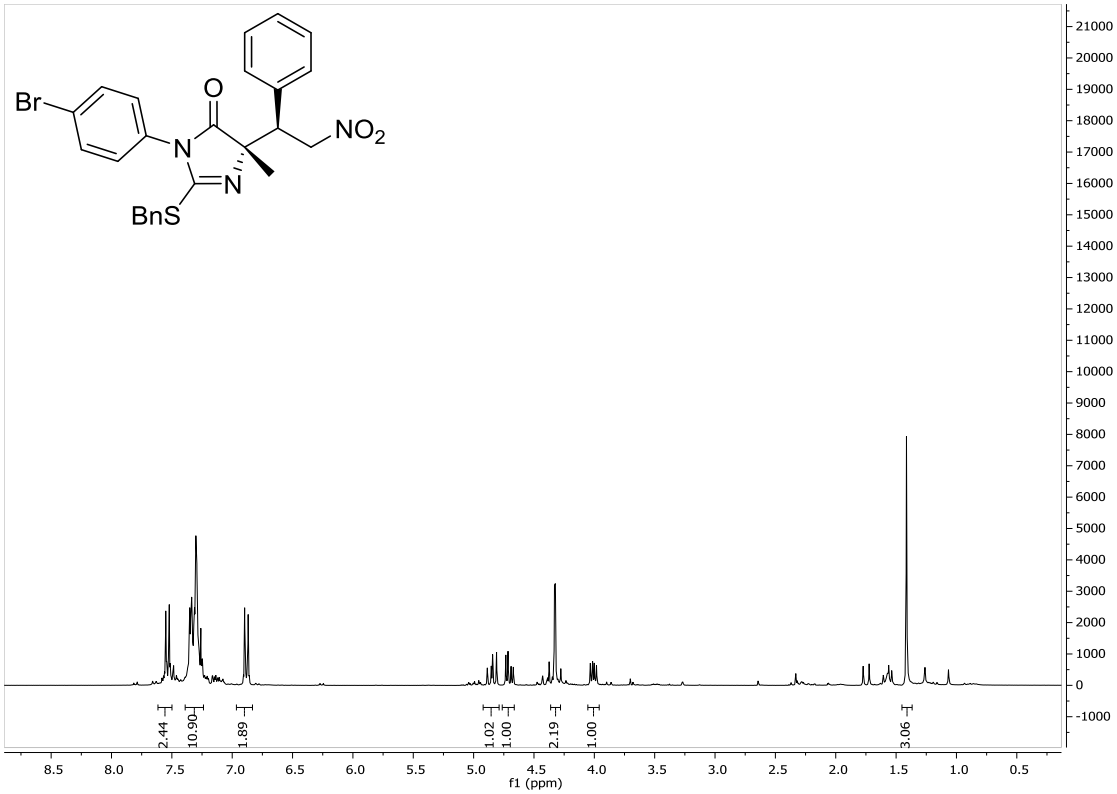


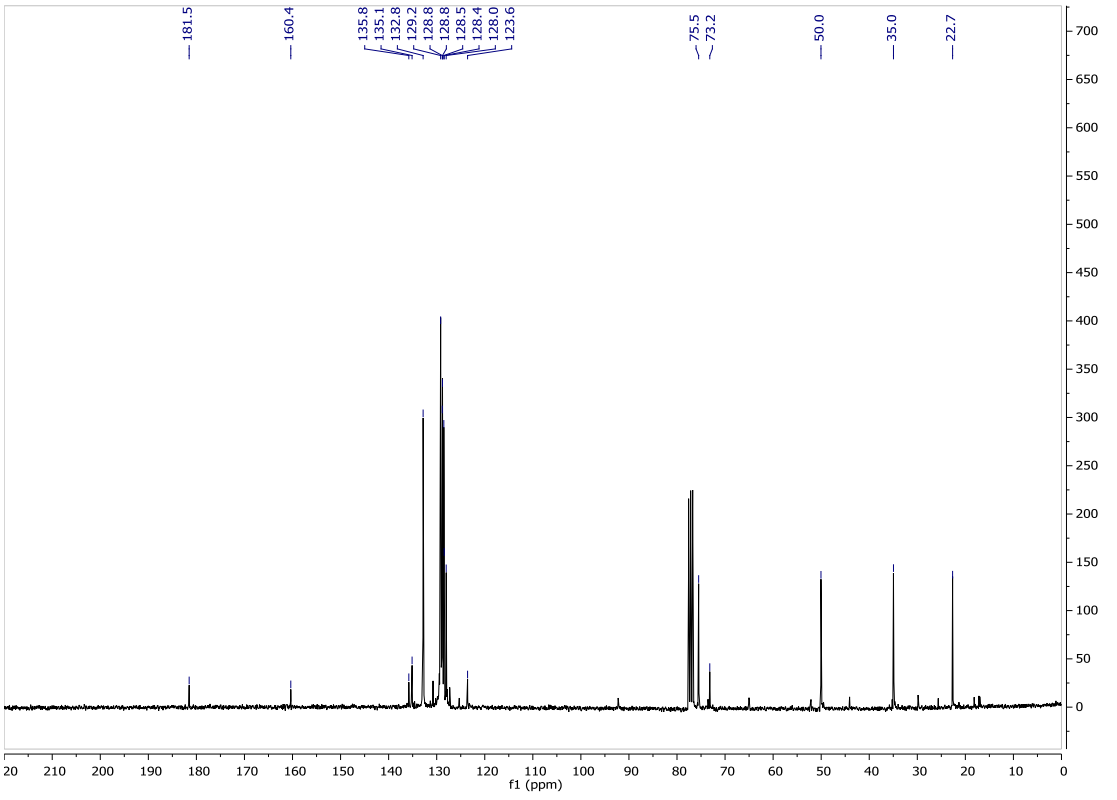
(*S*)-2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (69Aa)



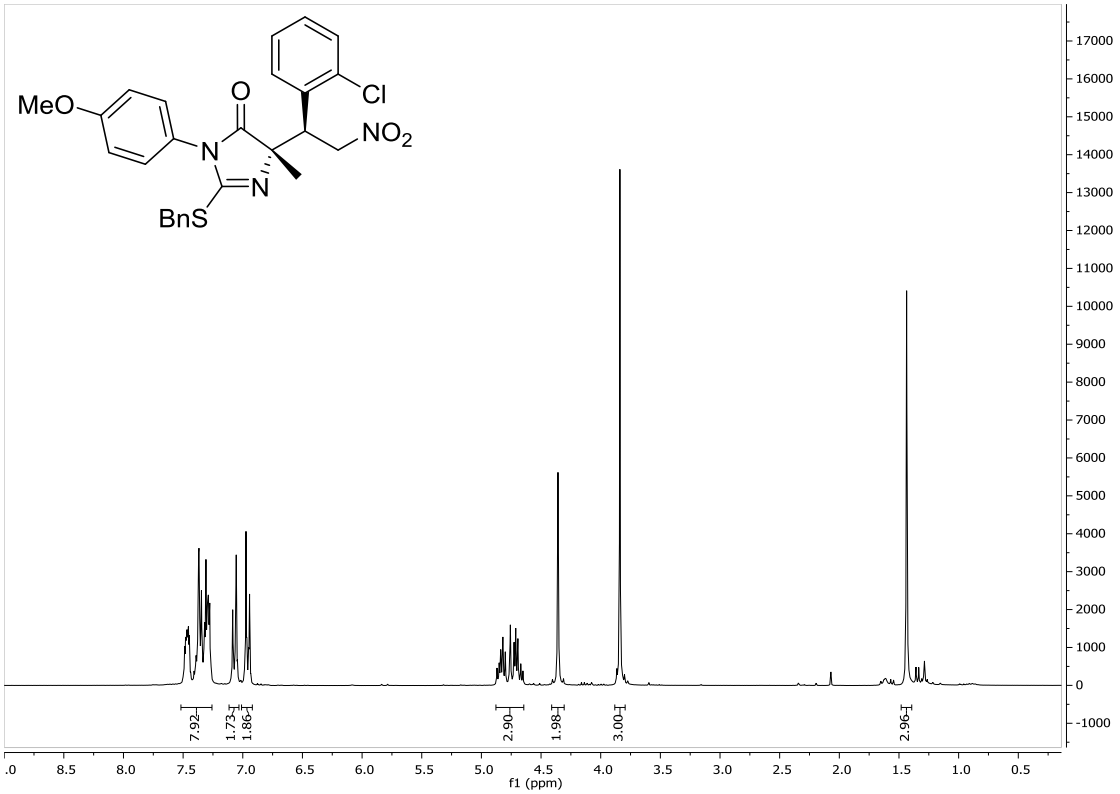


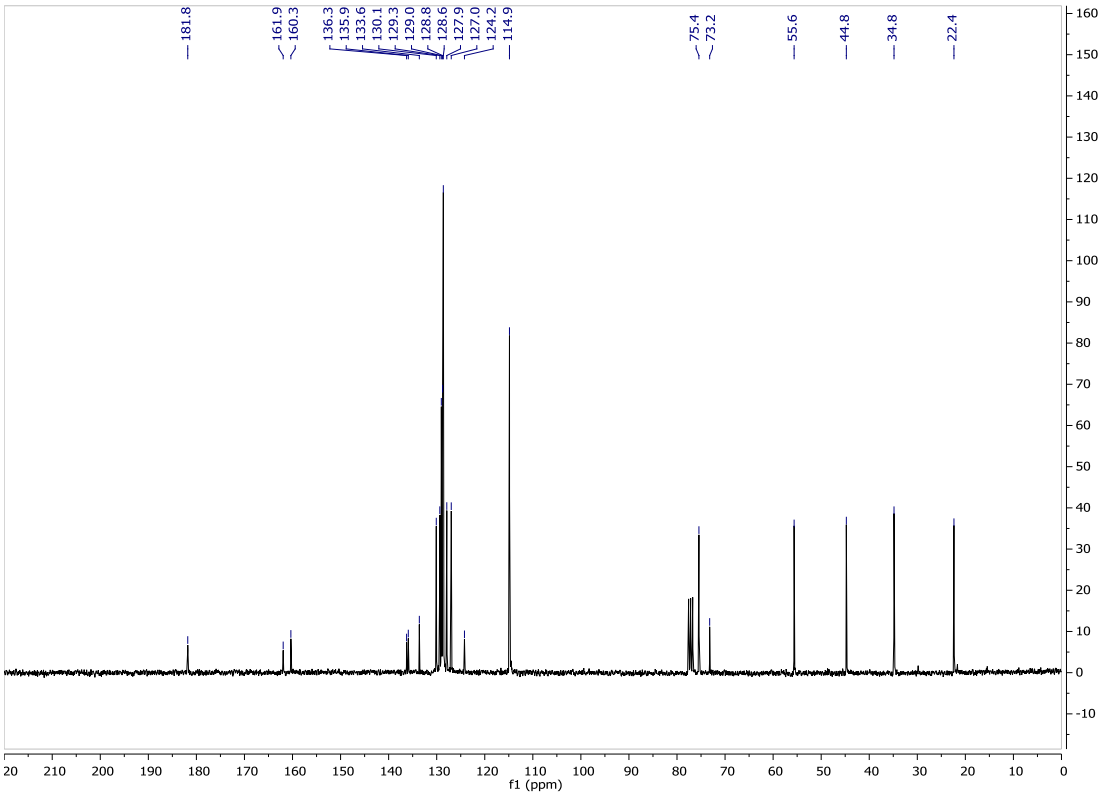
(*S*)-2-(Benzylthio)-1-(4-bromophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (70Aa)



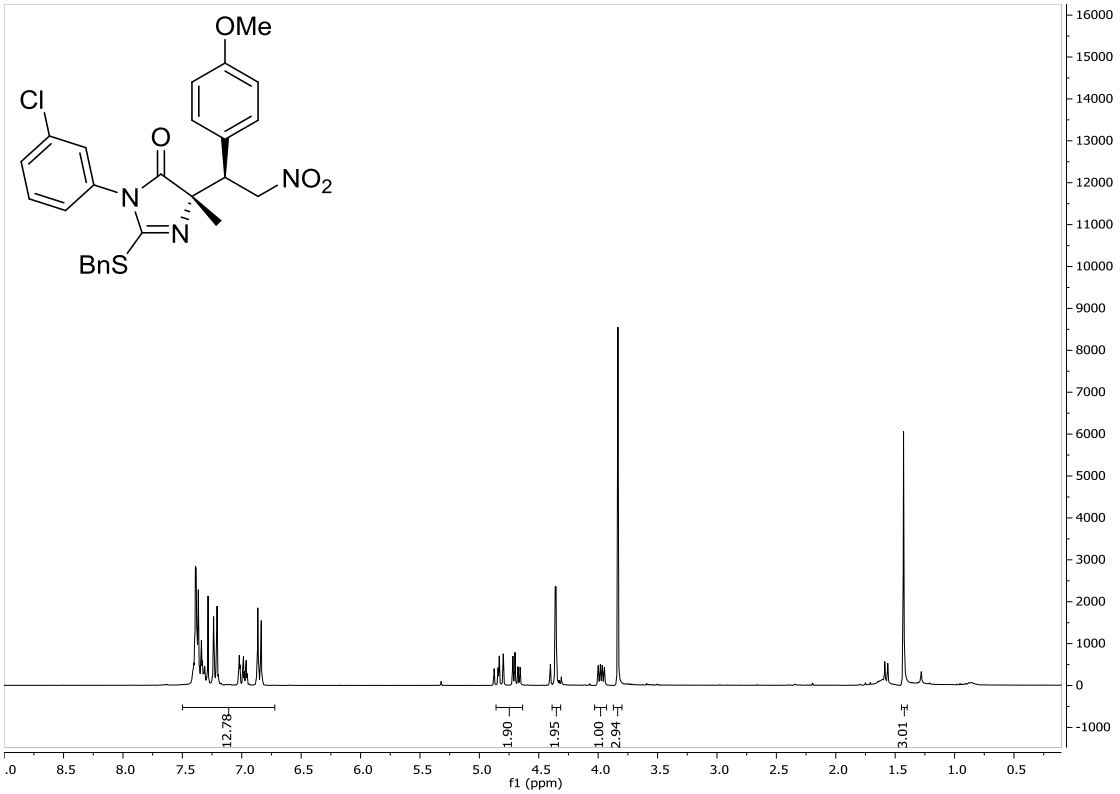


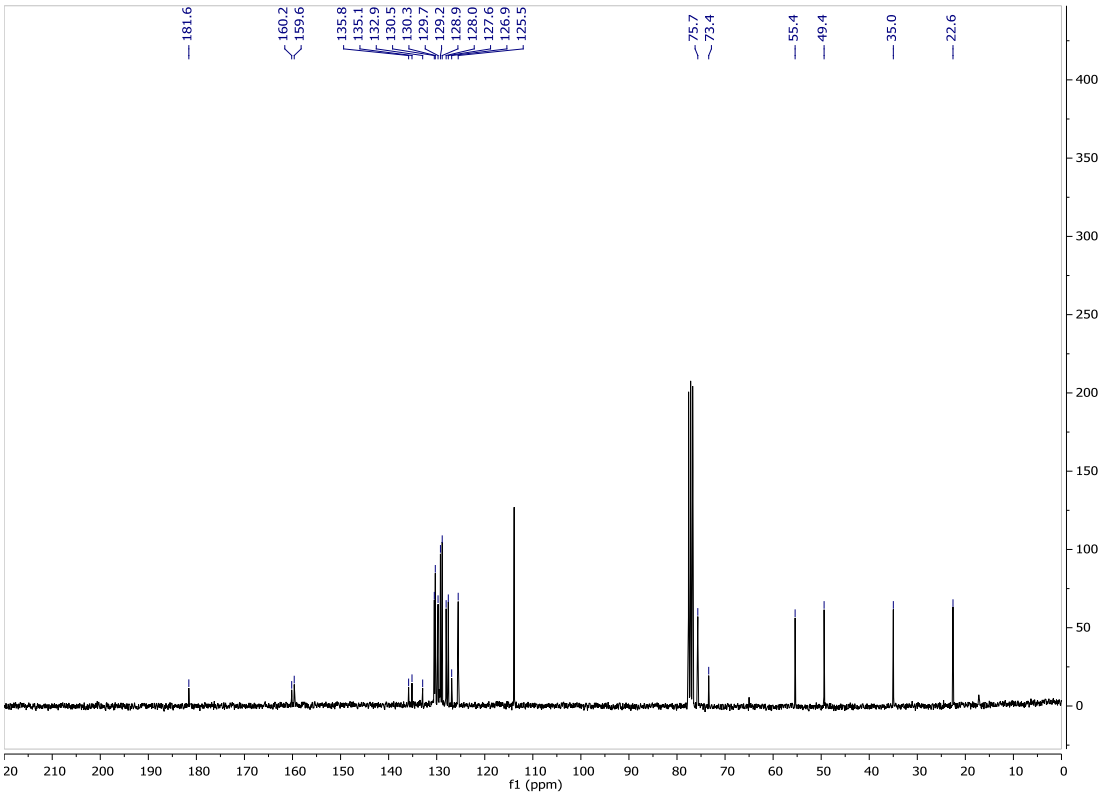
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (71Ad)



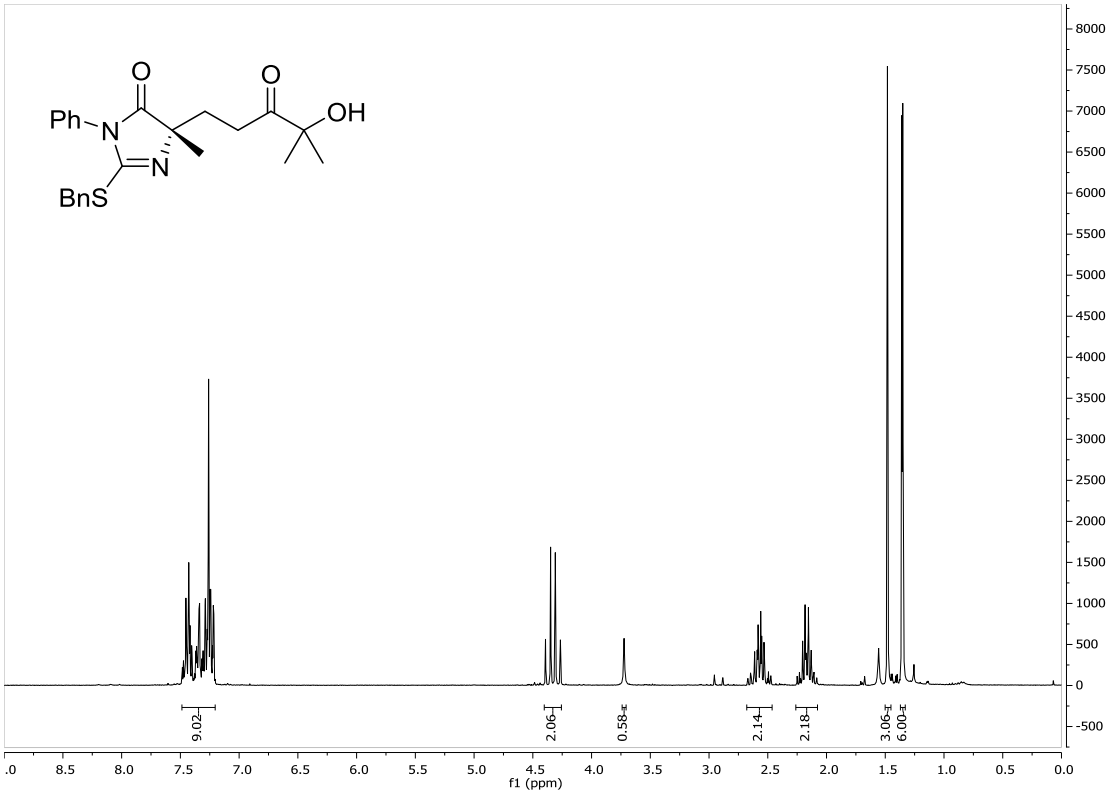


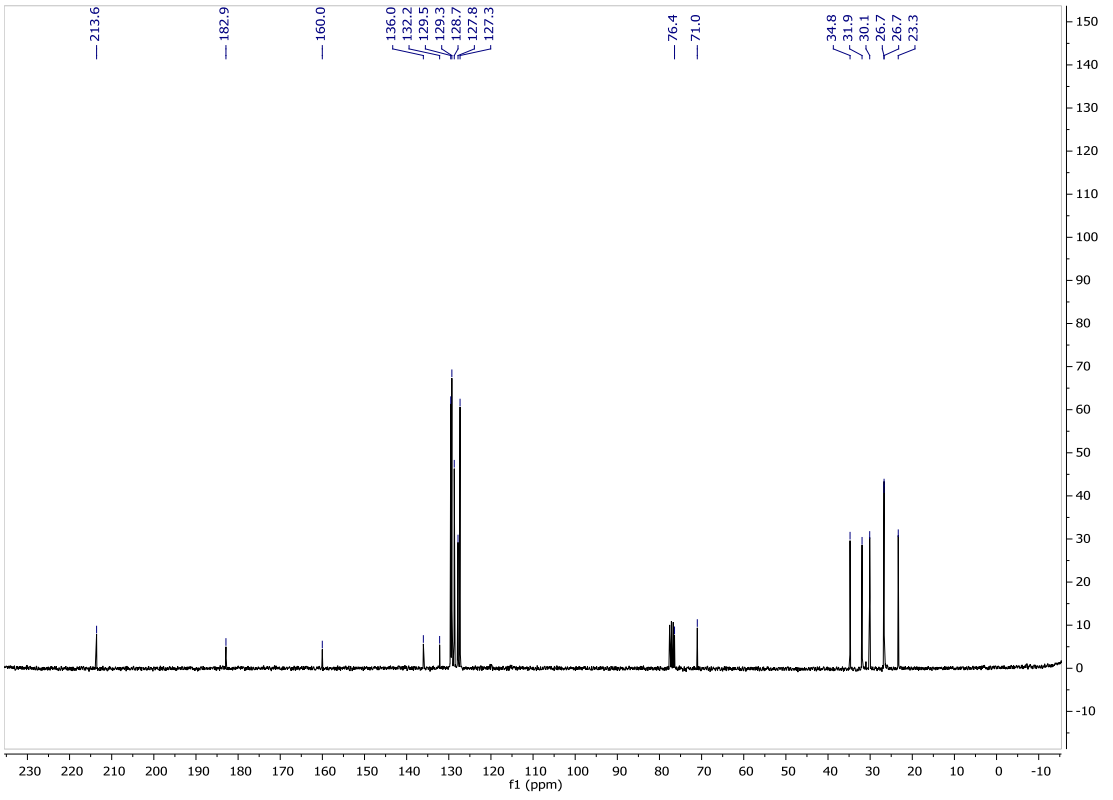
(*S*)-2-(Benzylthio)-1-(3-chlorophenyl)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (72Al)



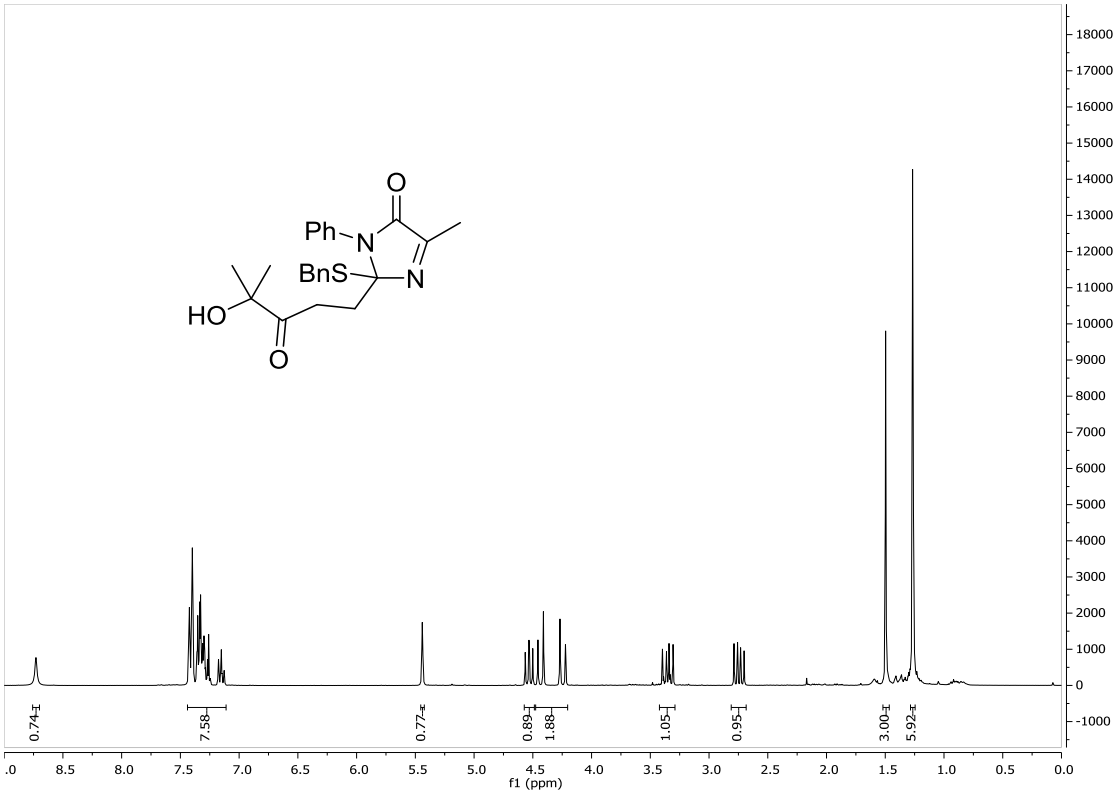


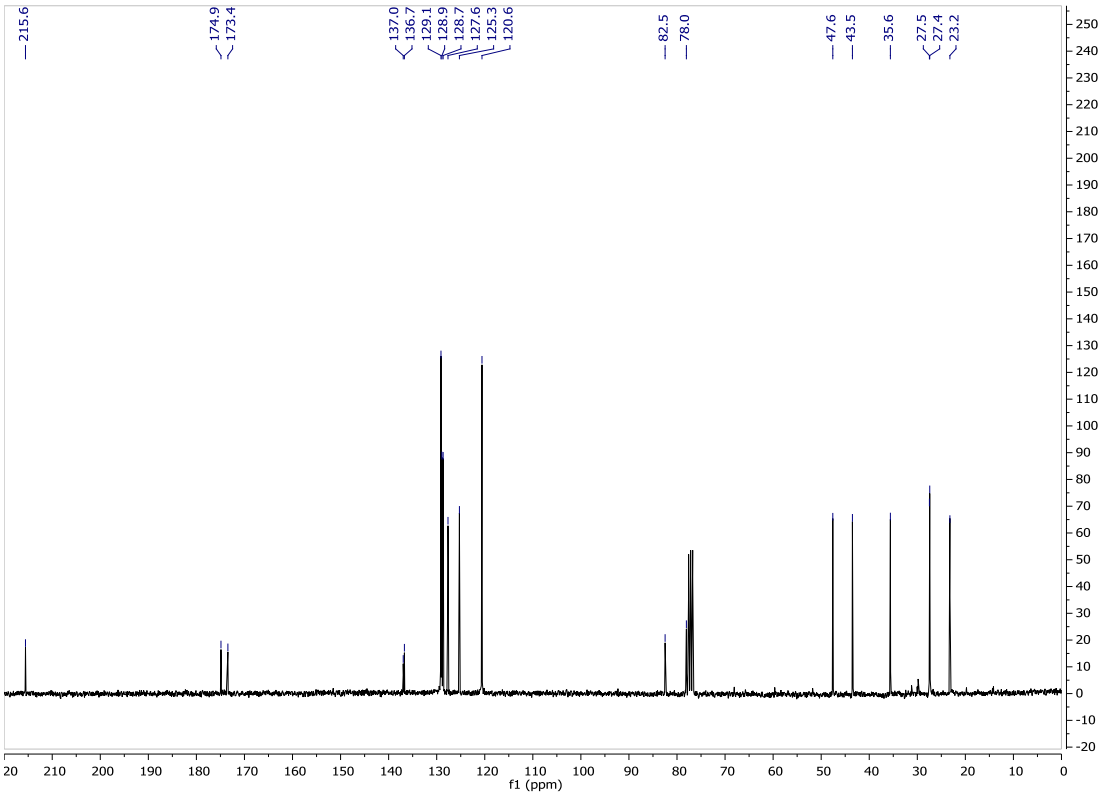
(*S*)-2-(Benzylthio)-4-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (76)



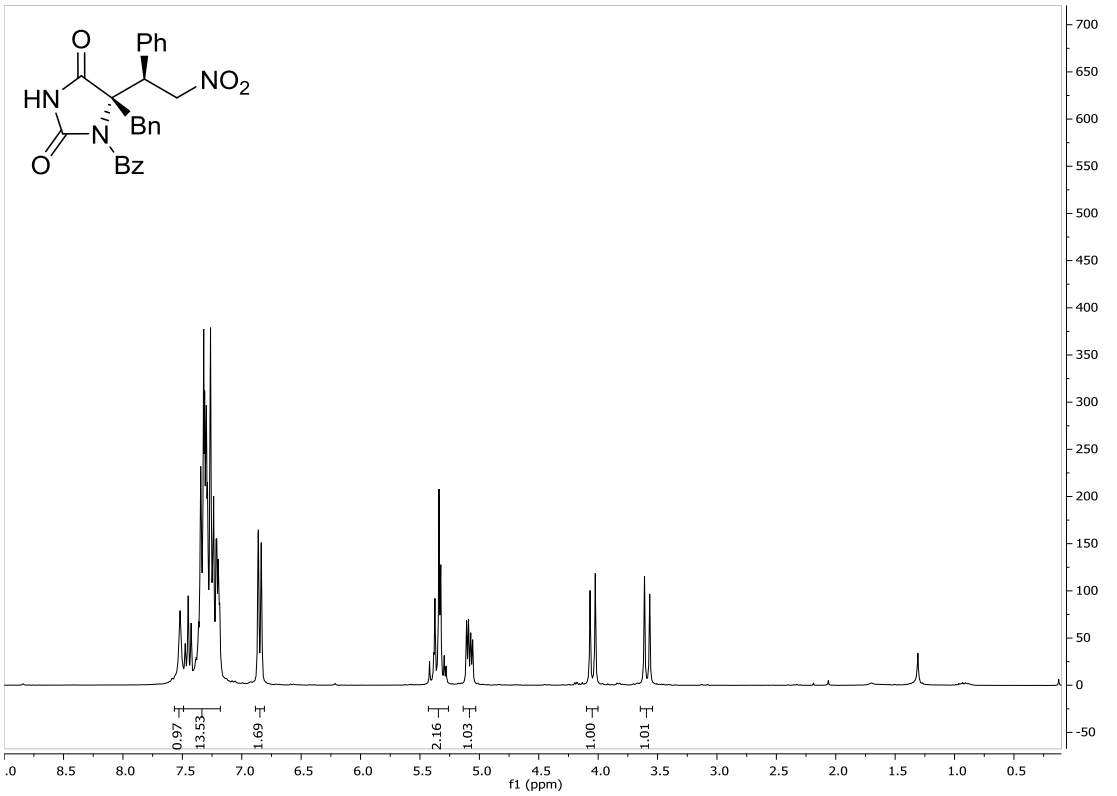


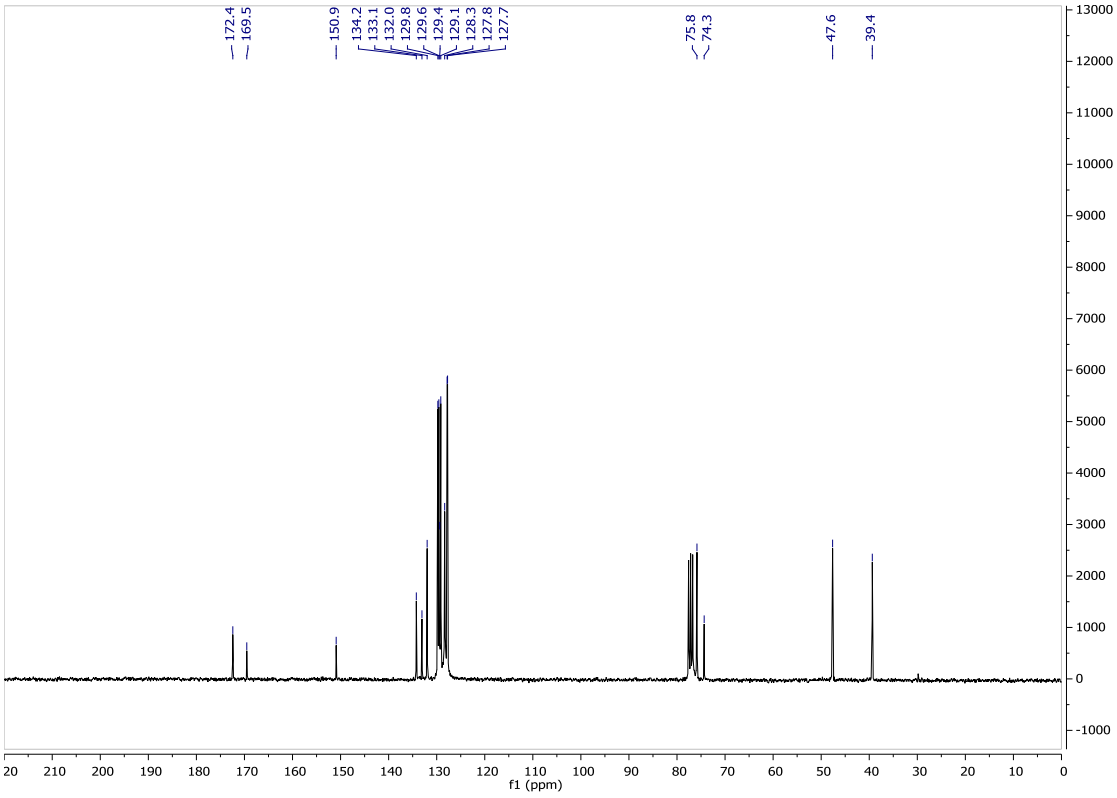
2-(Benzylthio)-2-(4-hydroxy-4-methyl-3-oxopentyl)-4-methyl-1-phenyl-1H-imidazol-5(2*H*)-one (76')



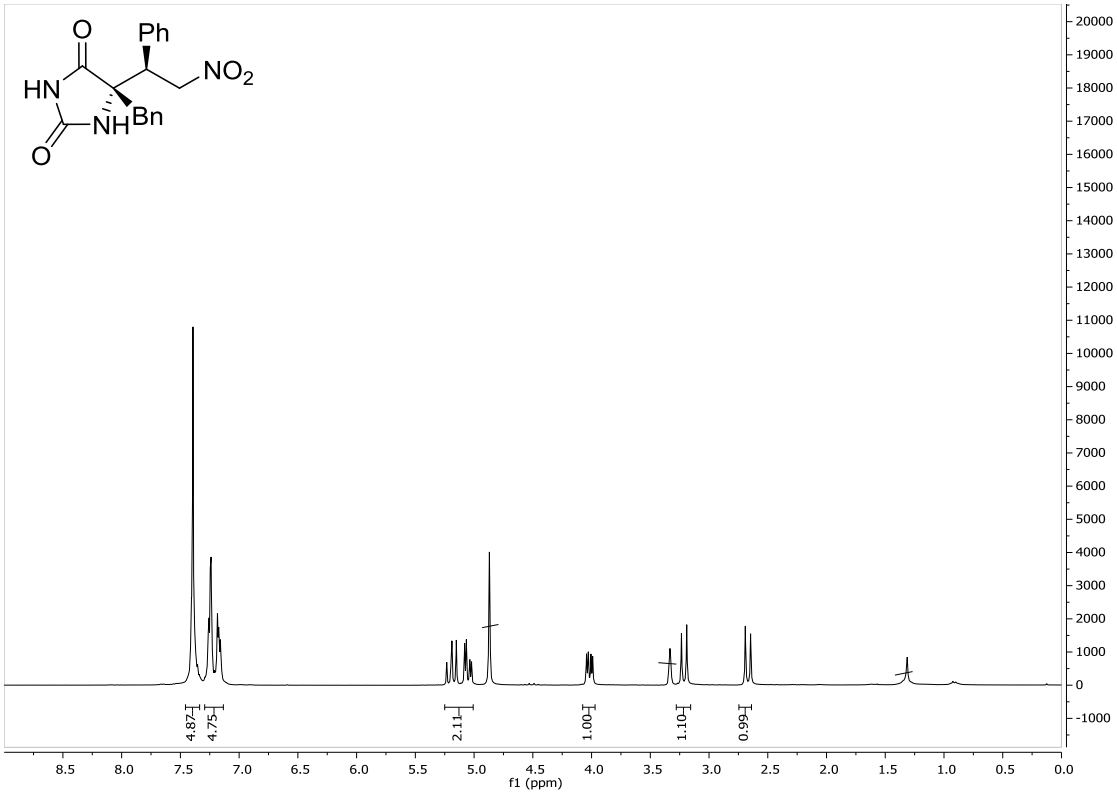


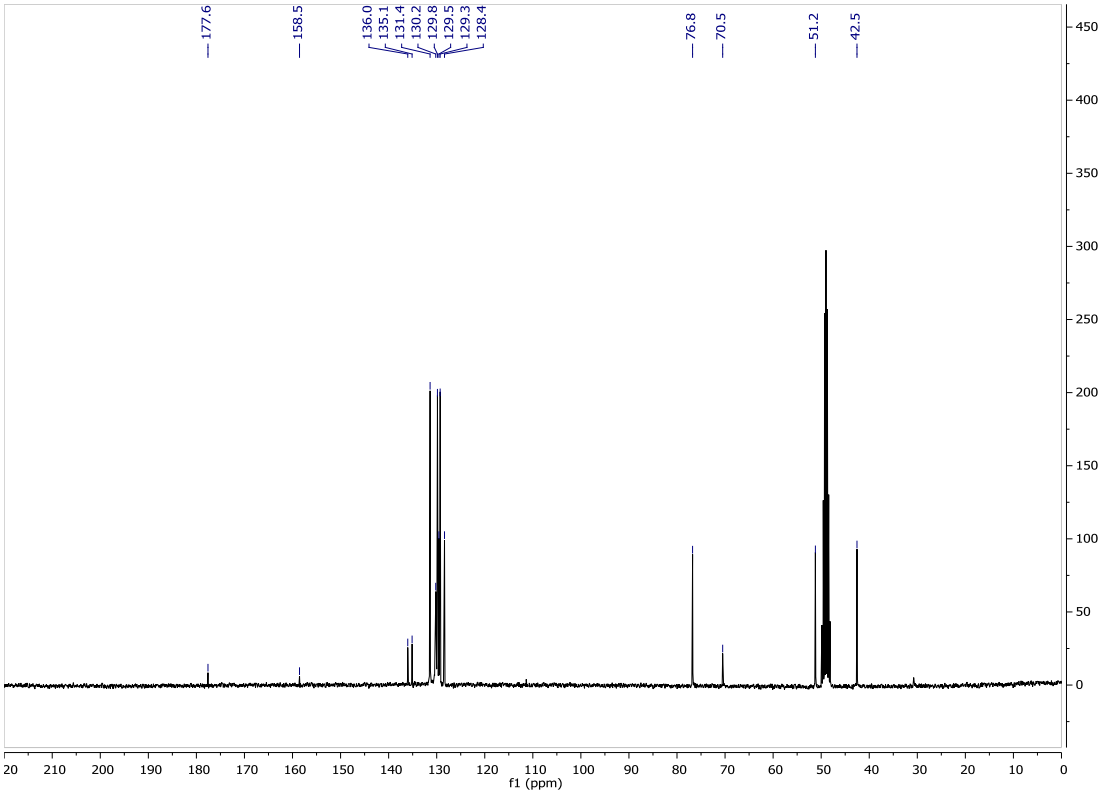
(*S*)-1-Benzoyl-5-benzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (47)



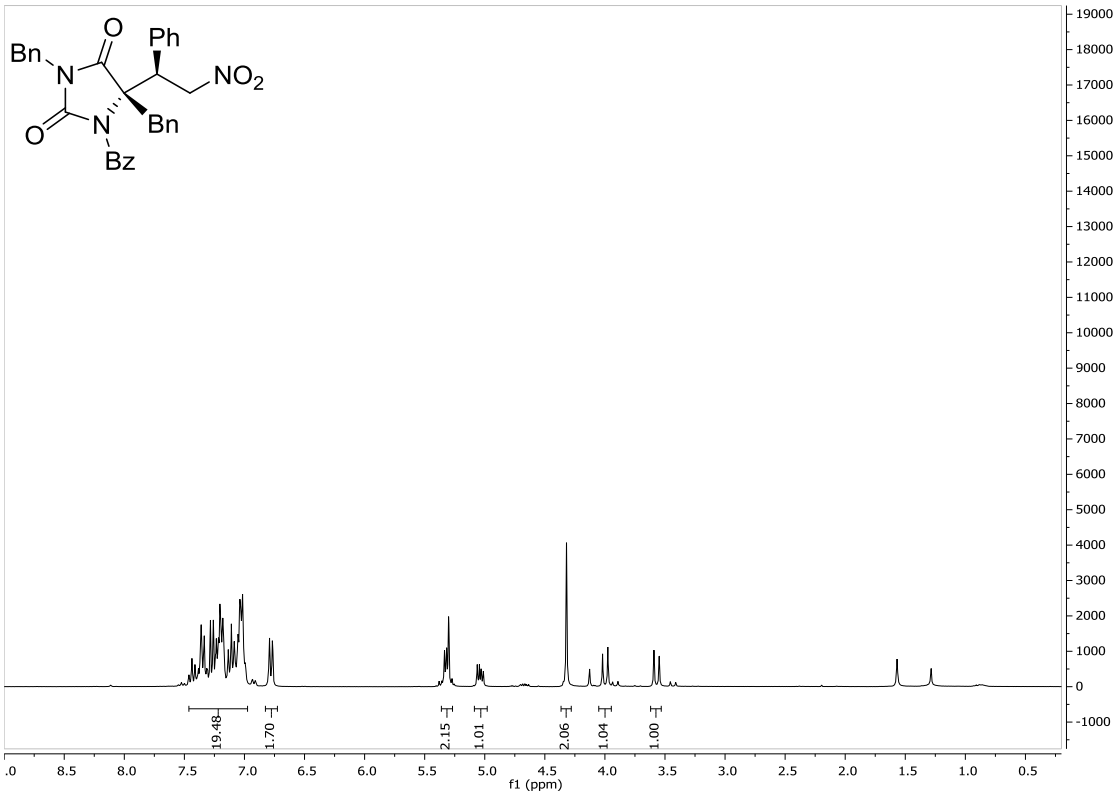


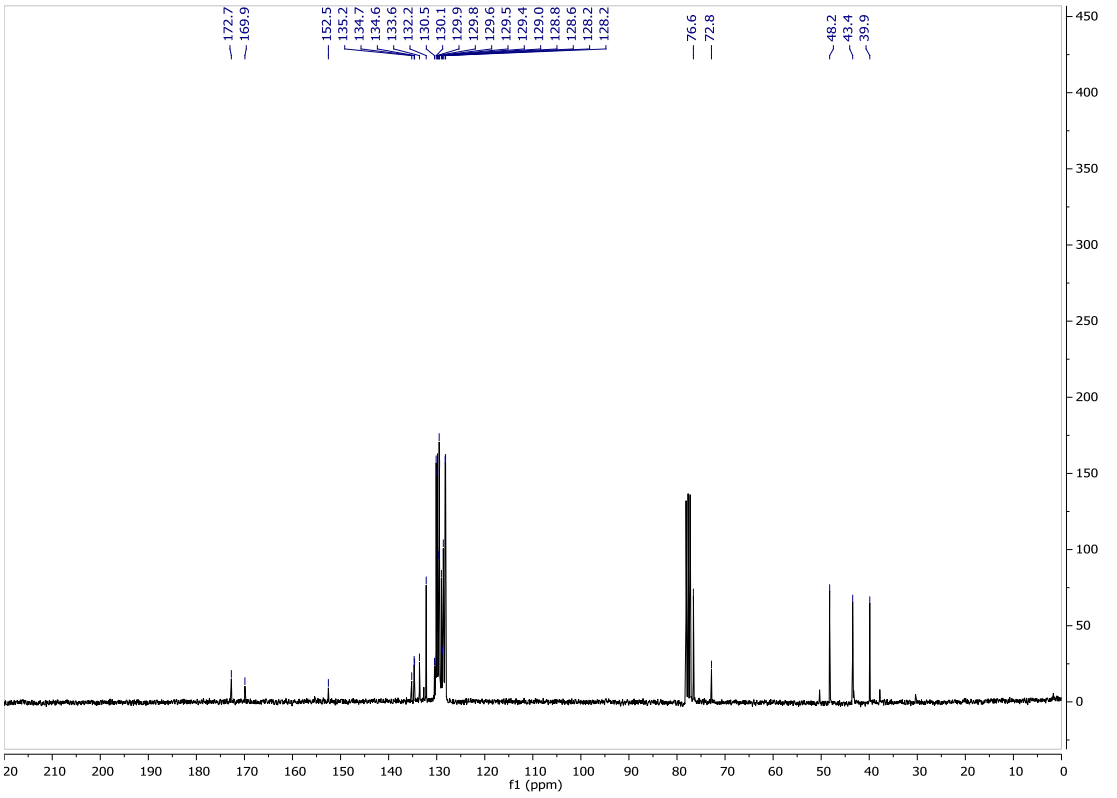
(*S*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (48)



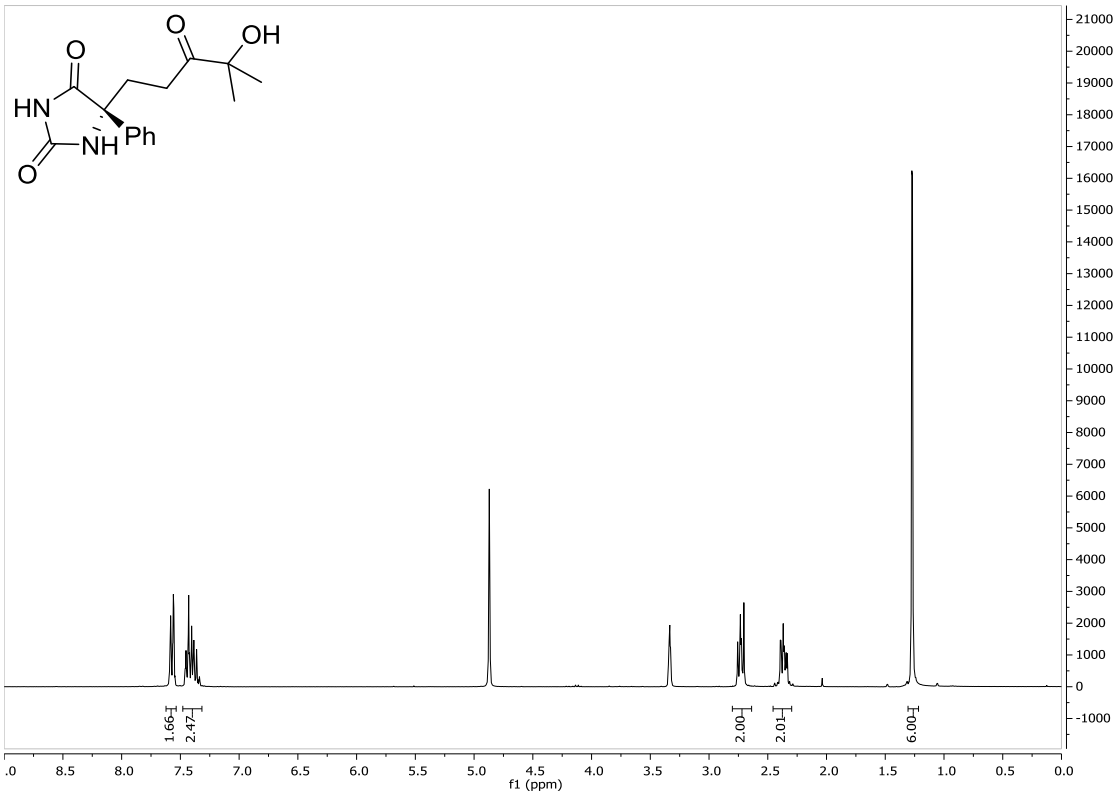


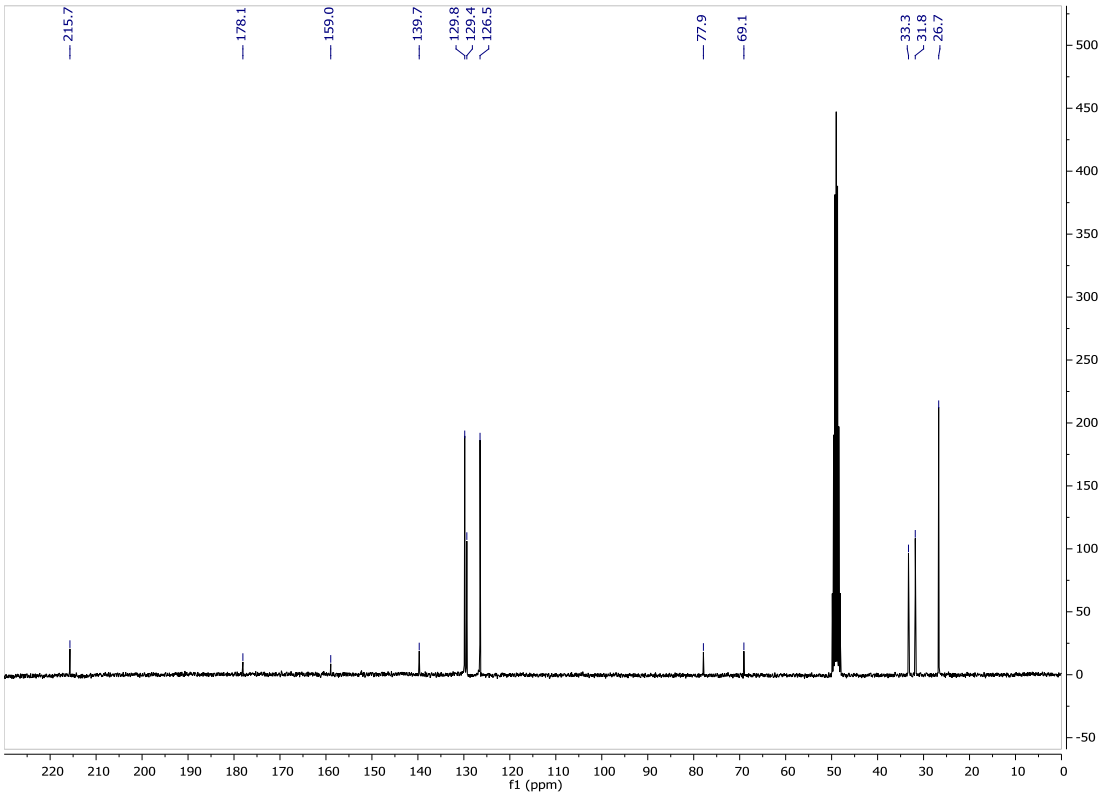
(*S*)-1-Benzoyl-3,5-dibenzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (49)



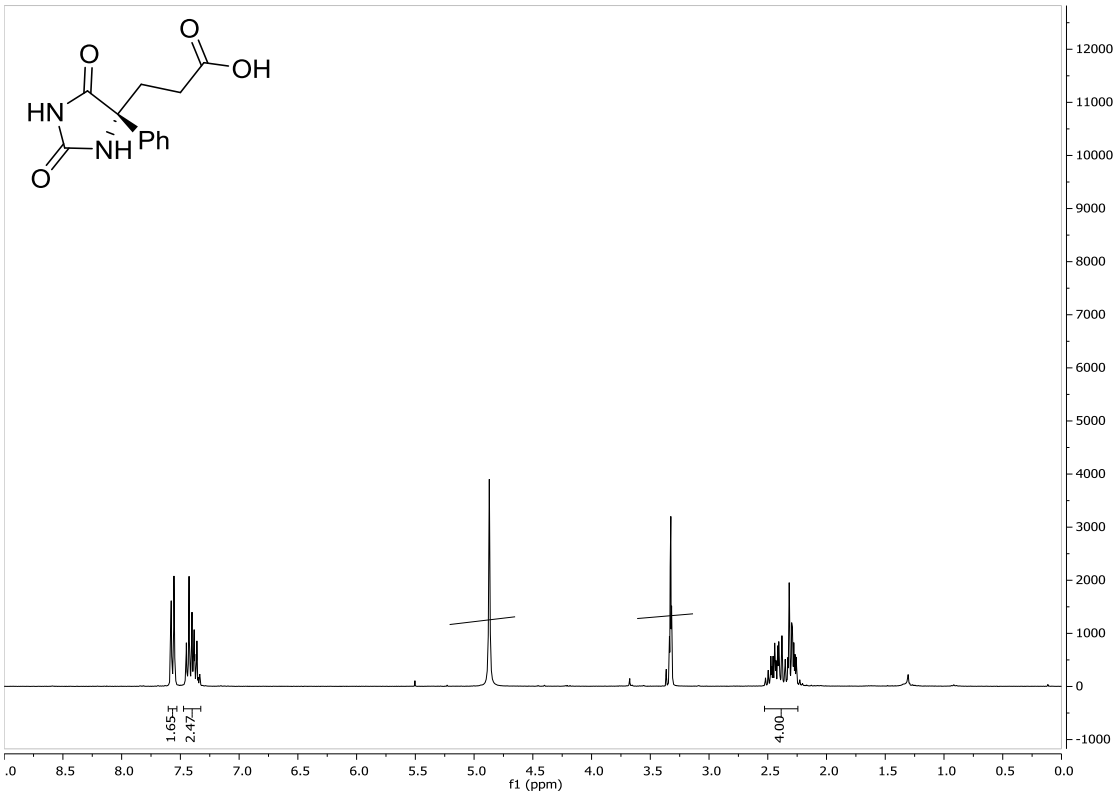


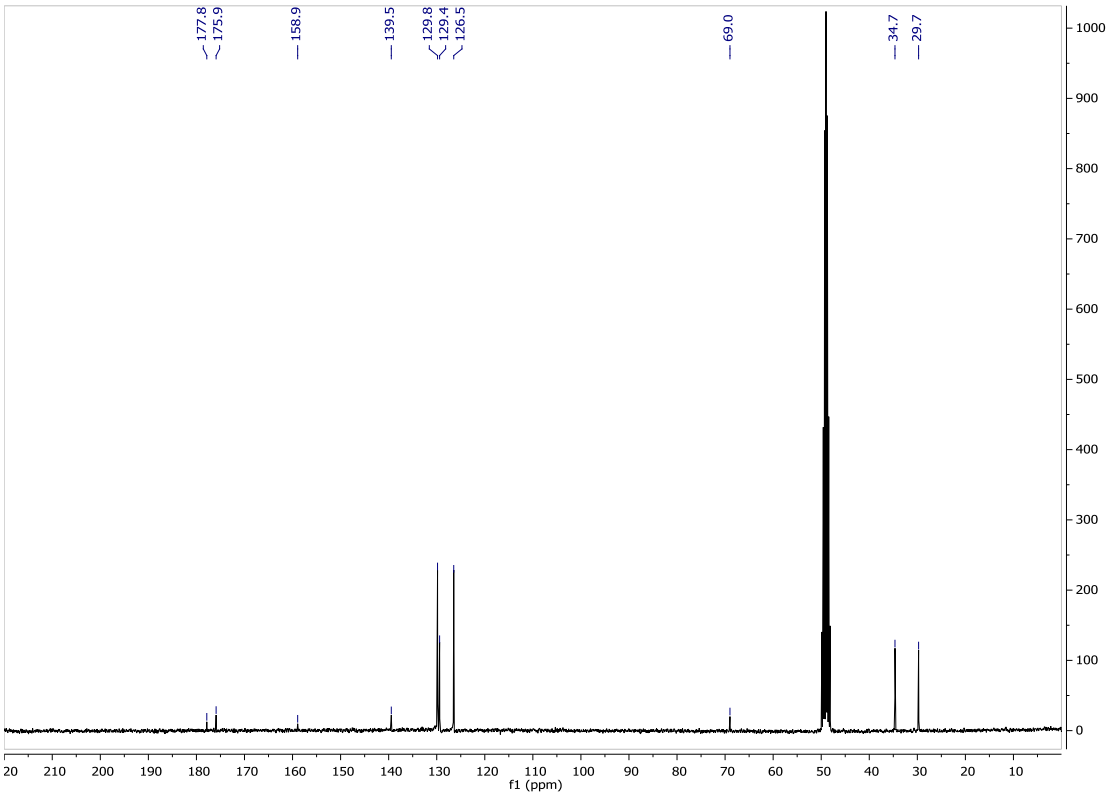
(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-phenylimidazolidine-2,4-dione (50)



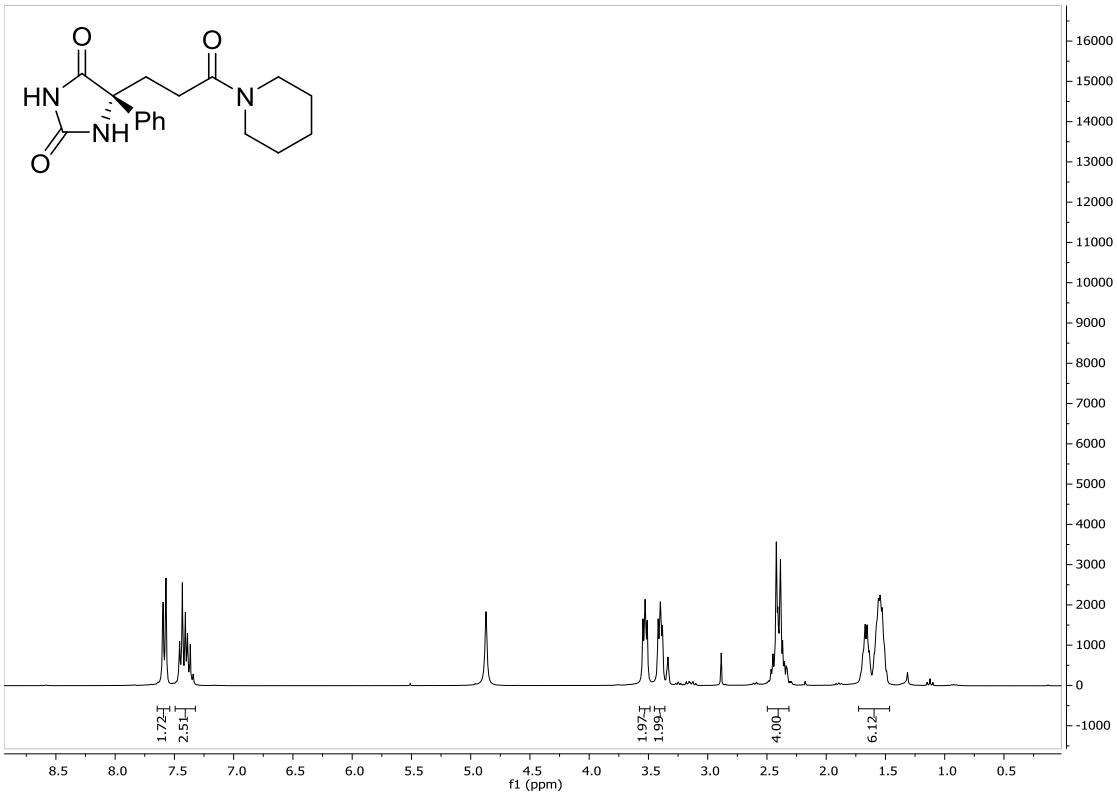


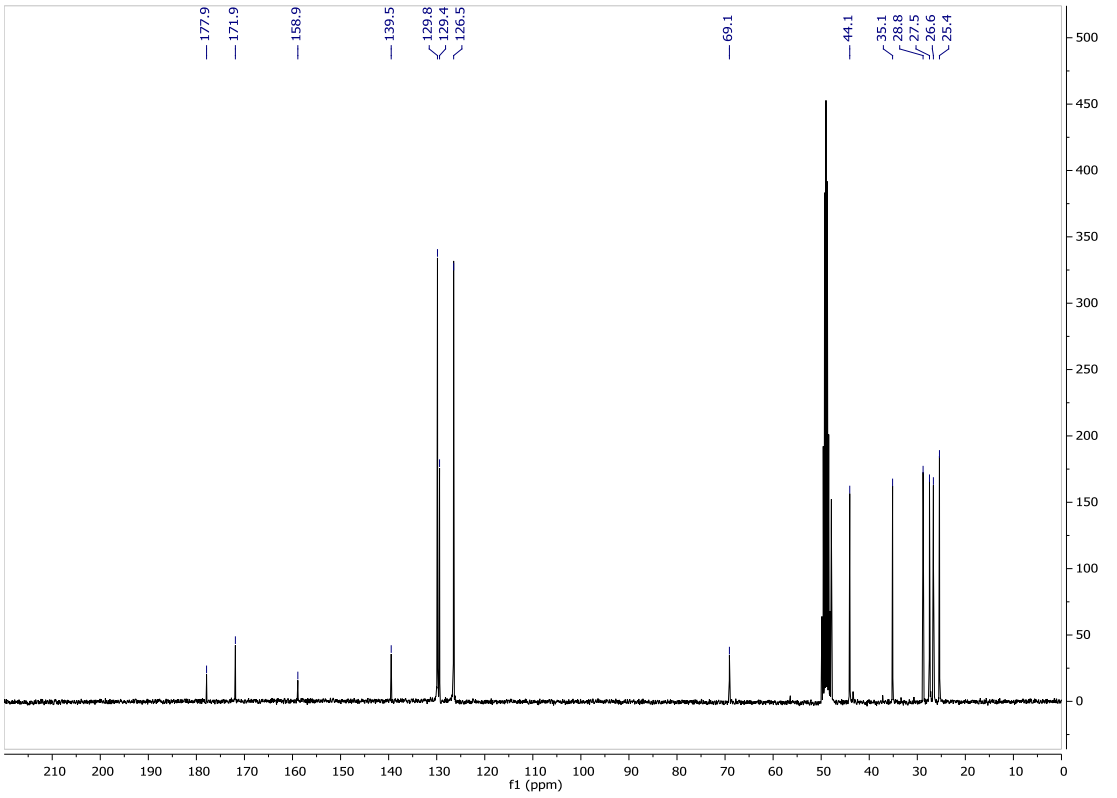
(*R*)-3-(2,5-Dioxo-4-phenylimidazolidin-4-yl)propanoic acid (51)



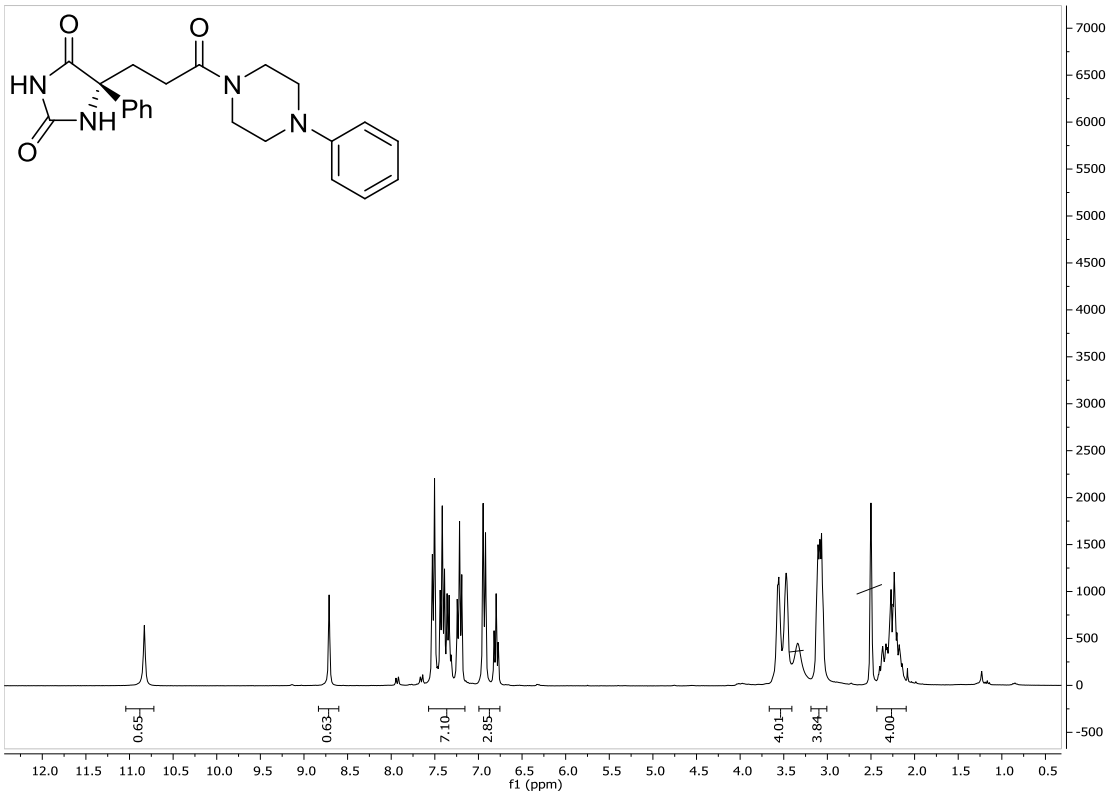


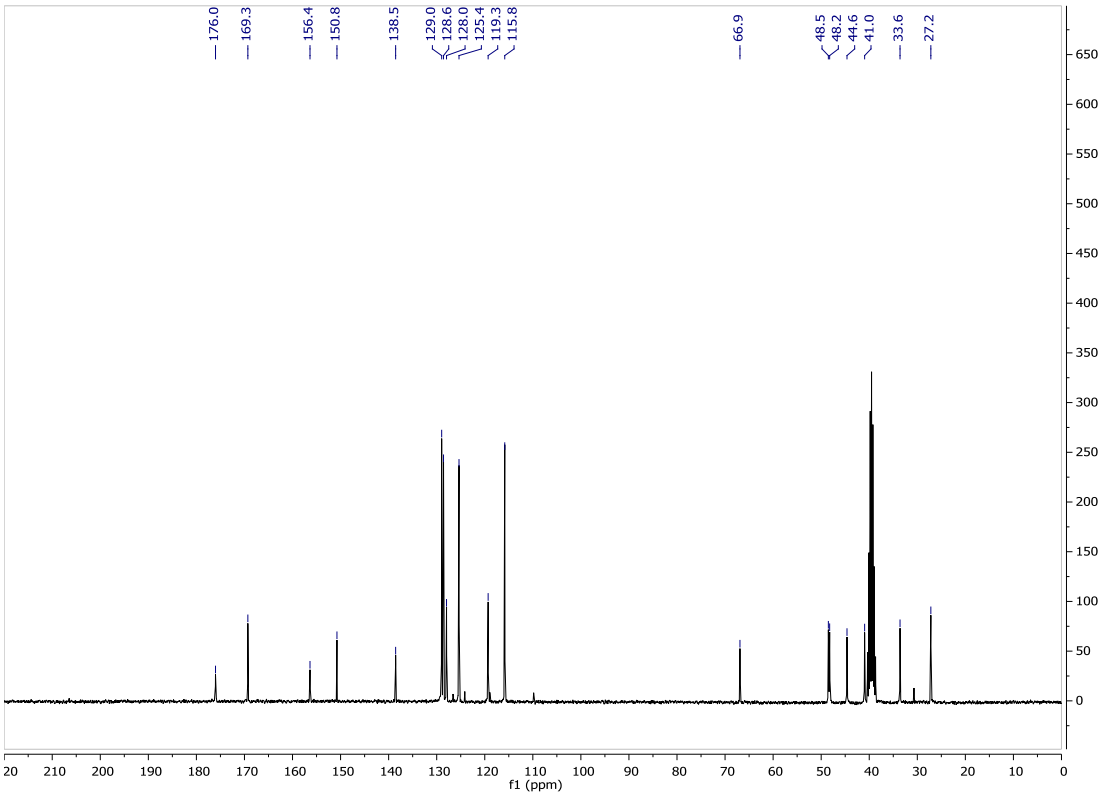
(*R*)-5-(3-Oxo-3-(piperidin-1-yl)propyl)-5-phenylimidazolidine-2,4-dione (52)



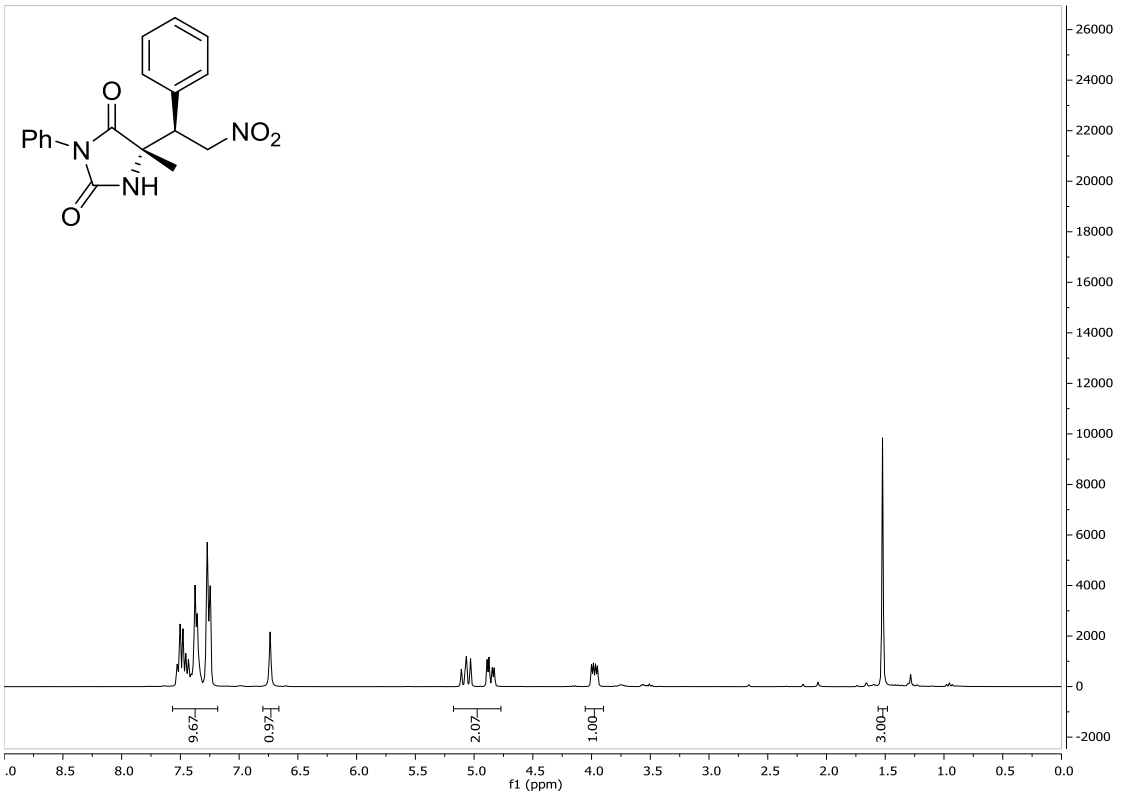


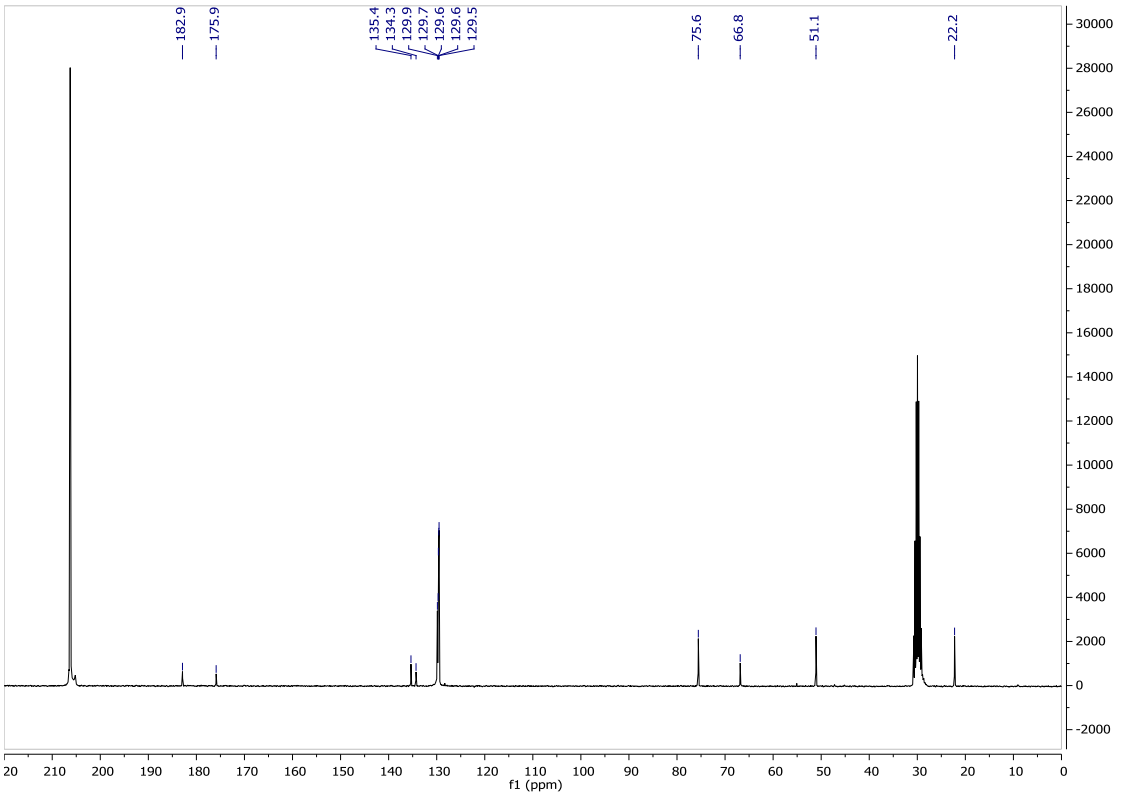
(*R*)-5-(3-Oxo-3-(4-phenylpiperazin-1-yl)propyl)-5-phenylimidazolidine-2,4-dione (53)



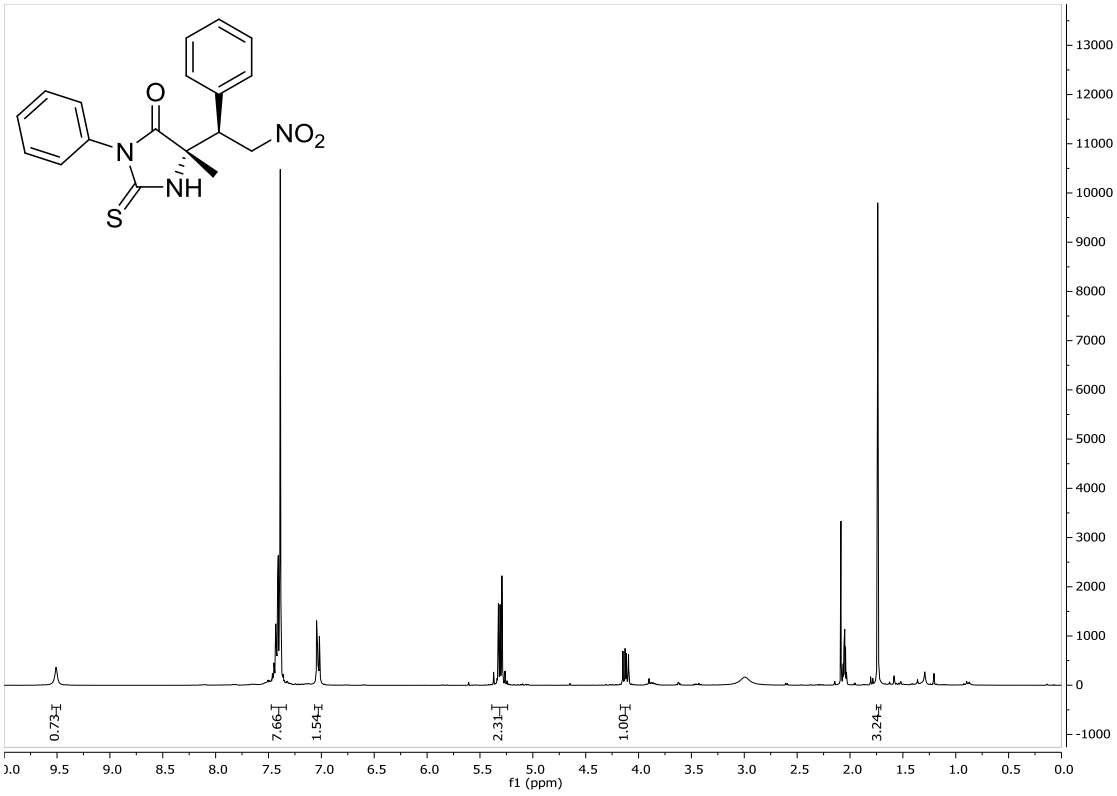


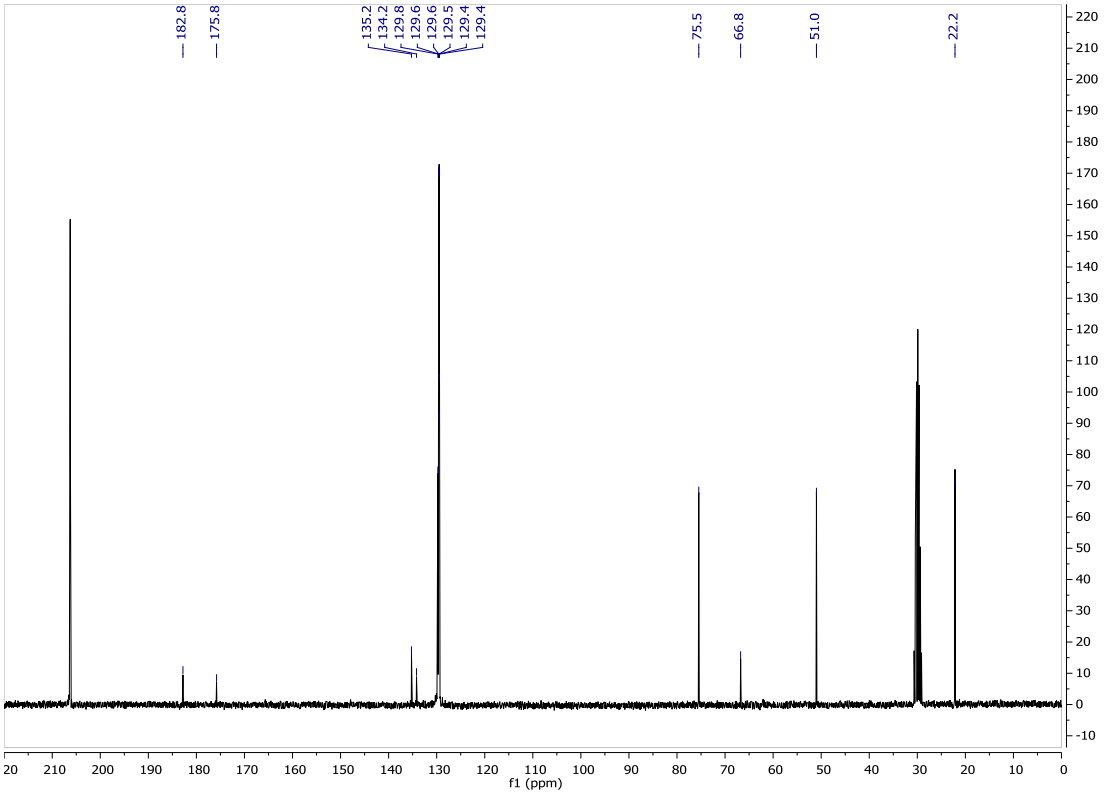
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (73)



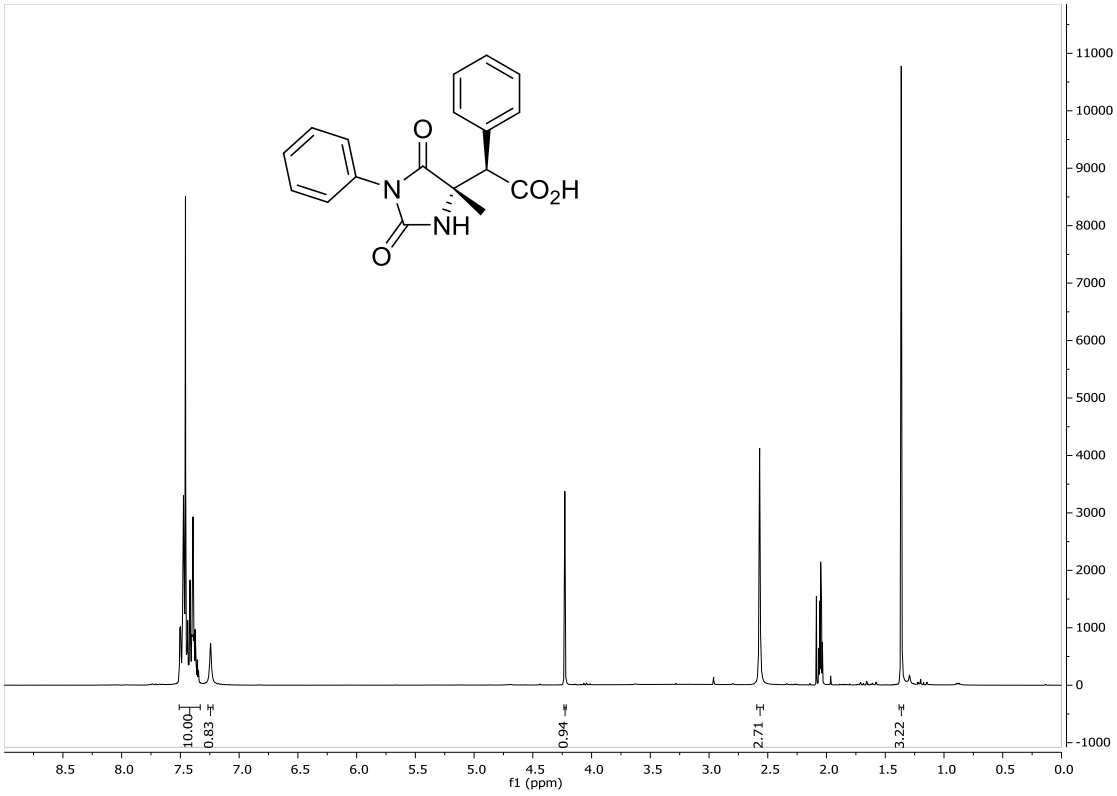


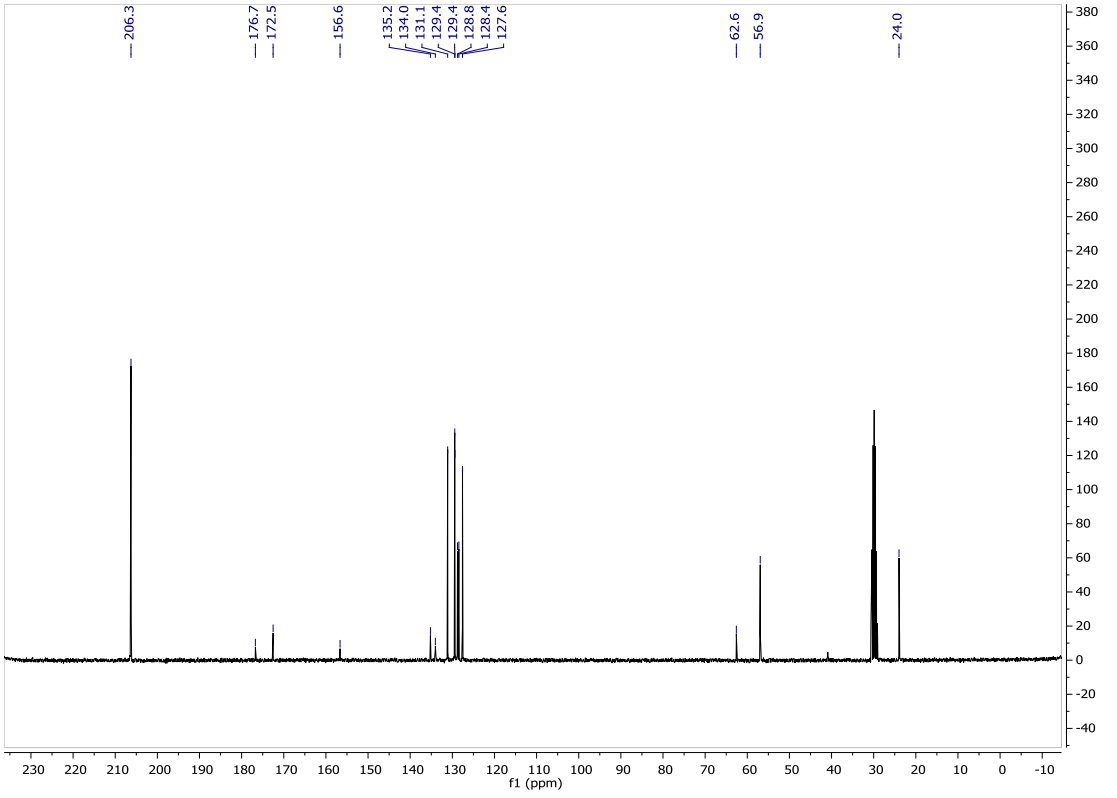
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenyl-2-thioxoimidazolidin-4-one (74)





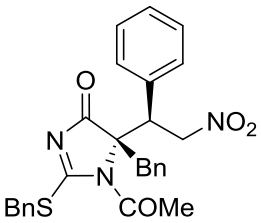
(*R*)-2-((*S*)-4-Methyl-2,5-dioxo-1-phenylimidazolidin-4-yl)-2-phenylacetic acid (75)



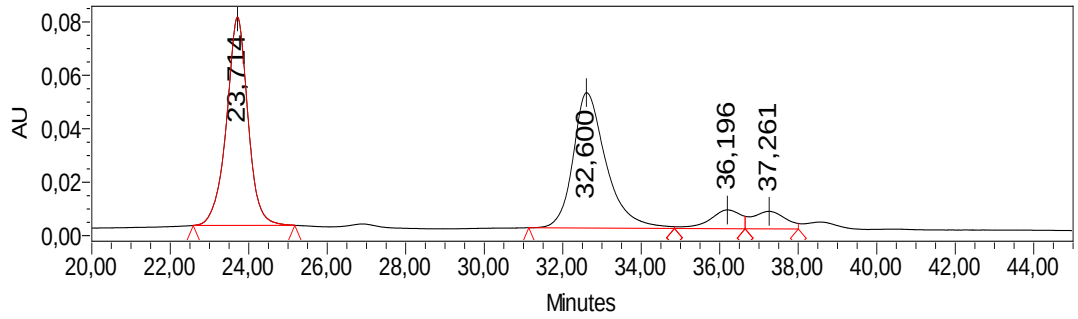


5.4.12. HPLC chromatograms of representative compounds

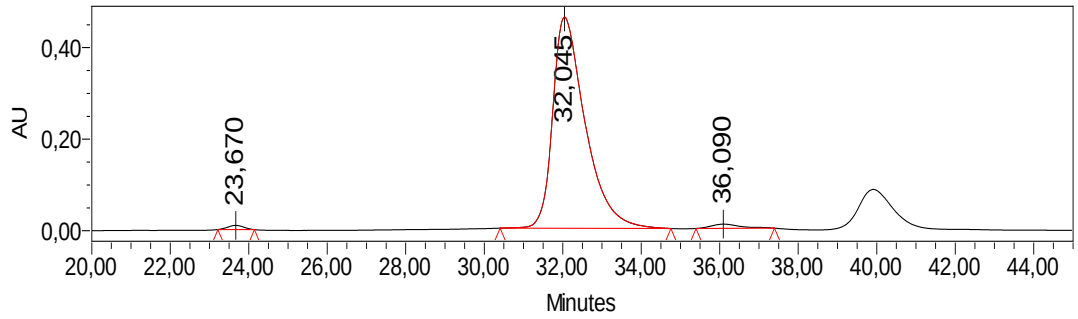
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (37Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 80/20, flow rate = 0.5 mL/min, retention times: 32.0 min (major.) and 23.7 min (min.). Processed Channel Descr.: PDA 210.0 nm).

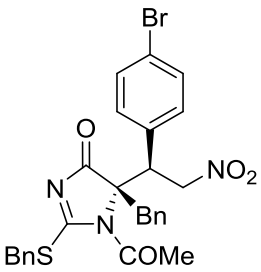


	Retention Time	% Area
1	23.714	44.23
2	32.600	44.20
3	36.196	5.74
4	37.261	5.82

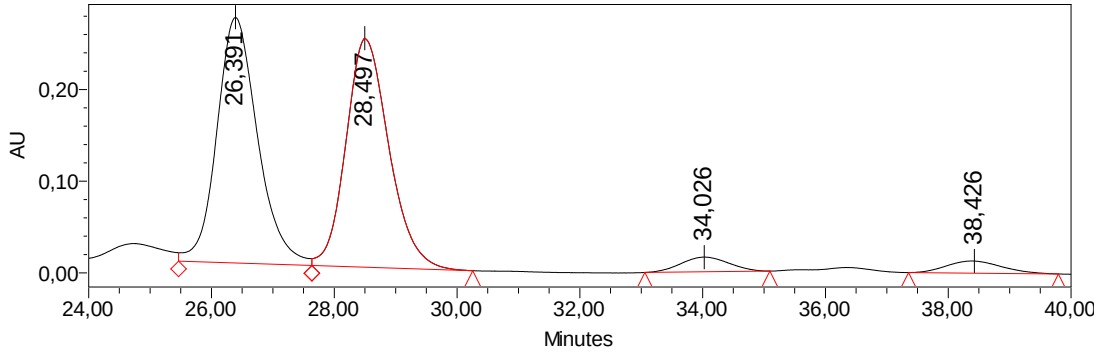


	Retention Time	% Area
1	23.670	0.95
2	32.045	97.33
3	36.090	1.72

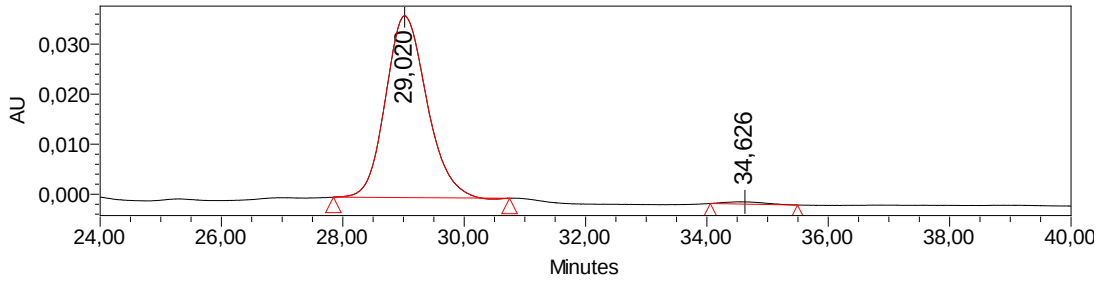
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (37Cb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate = 0.5 mL/min, retention times: 29.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

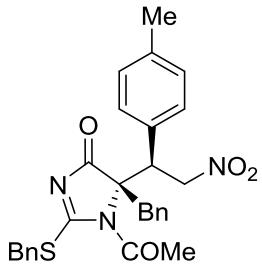


	Retention Time	% Area
1	26.391	47.16
2	28.497	46.36
3	34.026	3.33
4	38.426	3.15

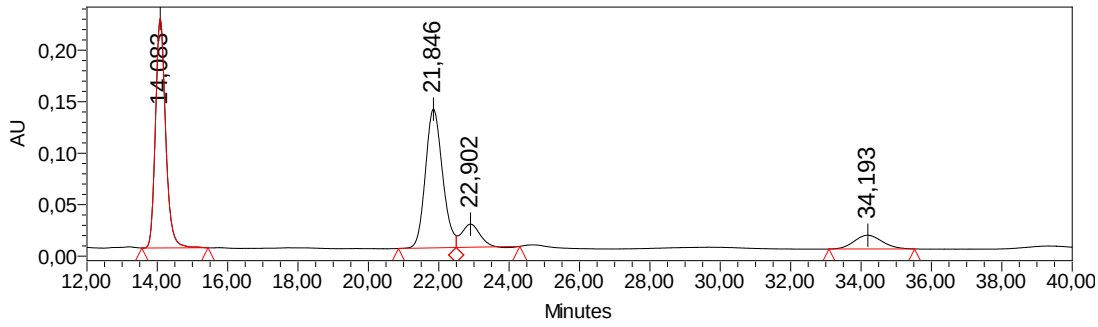


	Retention Time	% Area
1	29.020	98.86
2	34.626	1.14

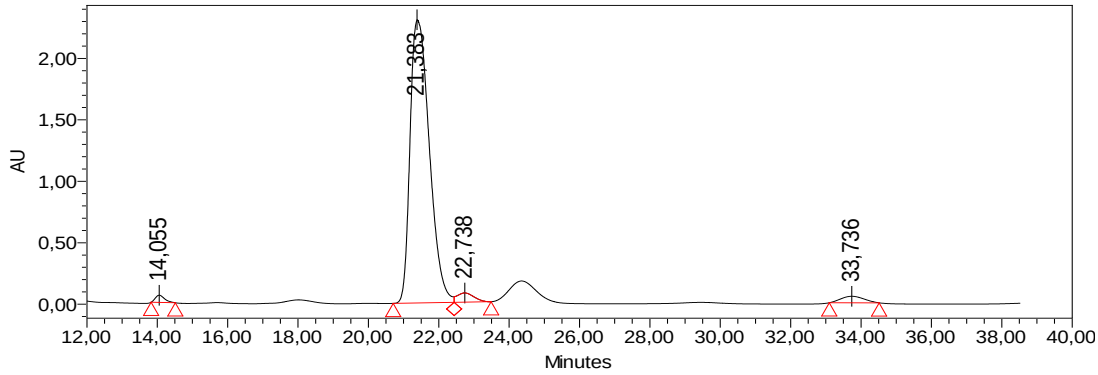
(*S*)-1-Acetyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (37Cc)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 40/60, flow rate = 0.5 mL/min, retention times: 21.4 min (major.) and 14.1 min (min.). Processed Channel Descr.: PDA 210.0 nm).

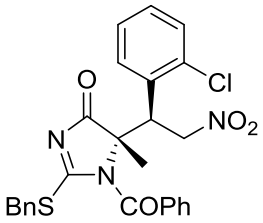


	Retention Time	% Area
1	14.083	42.10
2	21.846	42.89
3	22.902	8.00
4	34.193	7.01

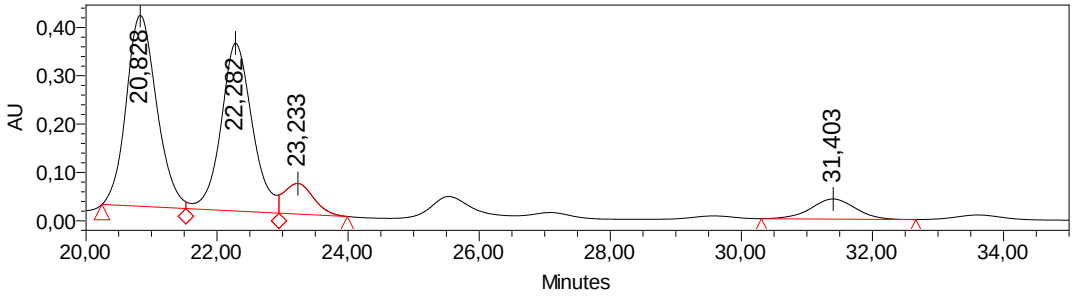


	Retention Time	% Area
1	14.065	1.14
2	21.383	93.63
3	22.738	2.65
4	33.736	2.57

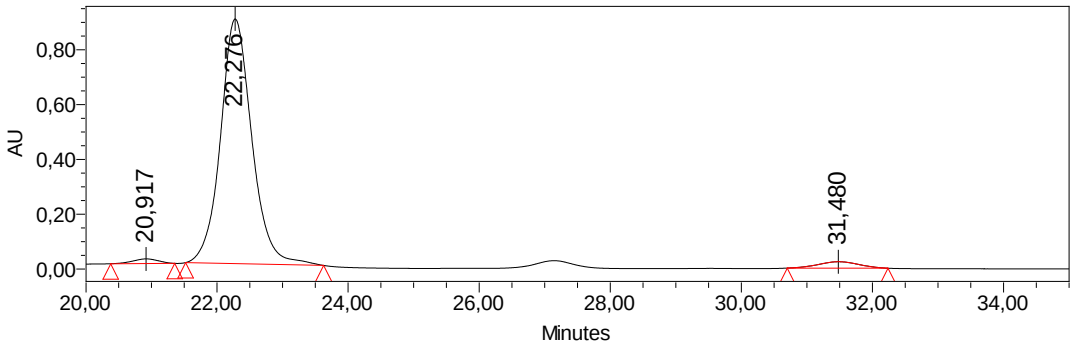
(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (38Ad)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 22.3 min (major.) and 20.9 min (min.). Processed Channel Descr.: PDA 210.0 nm).

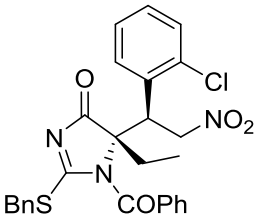


	Retention Time	% Area
1	20.828	45.15
2	22.282	40.90
3	23.233	7.00
4	31.403	6.95

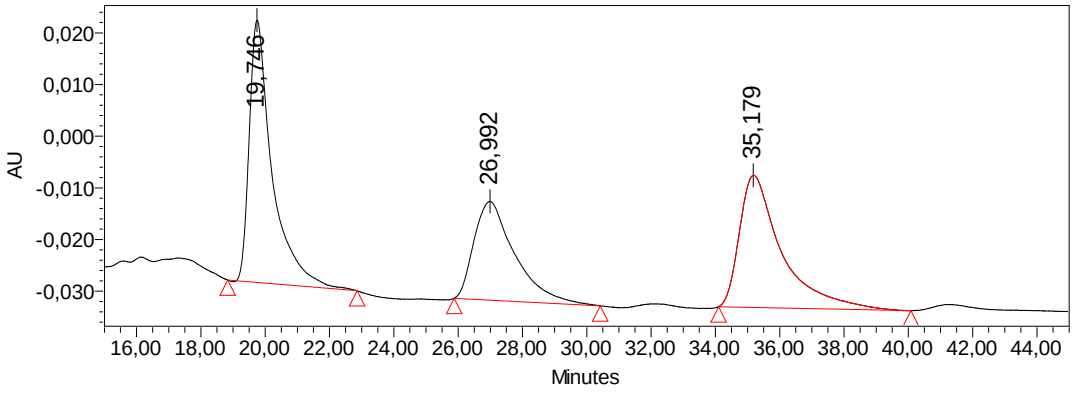


	Retention Time	% Area
1	20.917	1.47
2	22.276	94.71
3	31.480	3.82

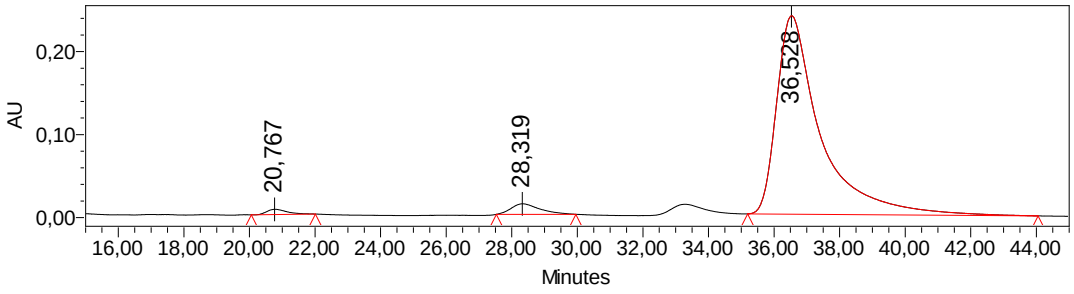
(*S*)-1-Benzoyl-2-(benzylthio)-5-((S)-1-(2-chlorophenyl)-2-nitroethyl)-5-ethyl-1*H*-imidazol-4(5*H*)-one (38Bd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 36.5 min (major.) and 20.8 min (min.). Processed Channel Descr.: PDA 210.0 nm).

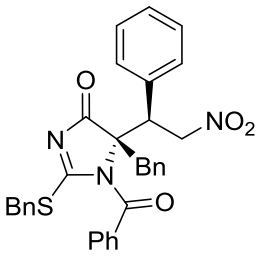


	Retention Time	% Area
1	19.746	38.13
2	26.992	24.64
3	35.179	37.23

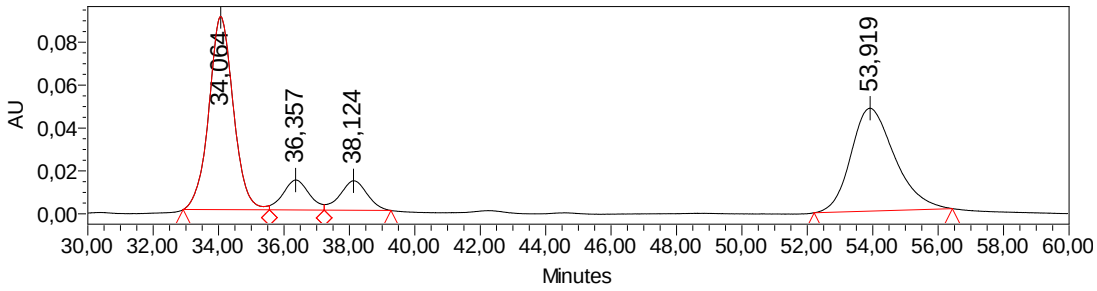


	Retention Time	% Area
1	20.767	1.16
2	28.319	3.31
3	36.528	95.52

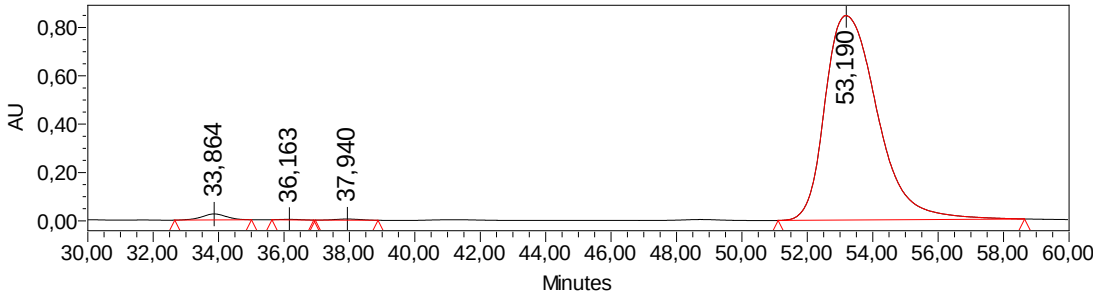
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times for major diastereoisomer: 53.2 min (major.) and 33.9 min (min.), minor diastereoisomer: 36.2 min and 38.0 min. Processed Channel Descr.: PDA 210.0 nm).

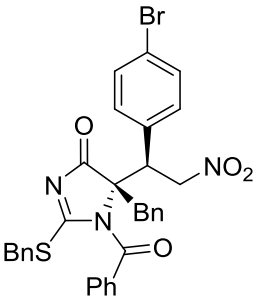


	Retention Time	% Area
1	34.064	43.69
2	36.357	7.22
3	38.124	7.39
4	53.919	41.70

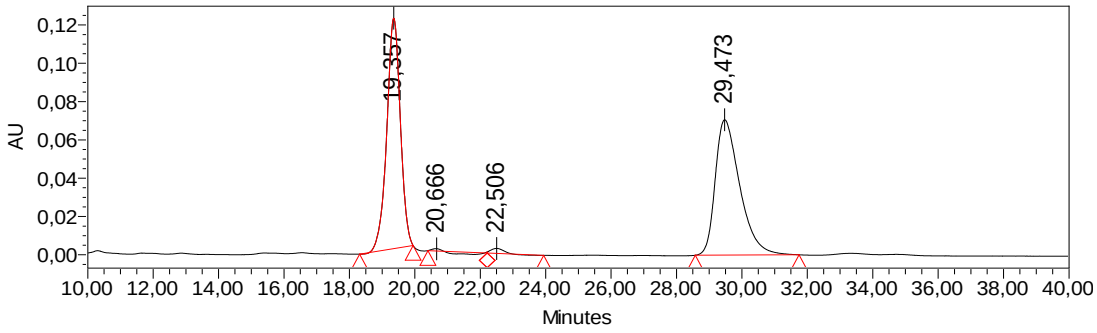


	Retention Time	% Area
1	33.864	1.36
2	36.163	0.10
3	37.940	0.27
4	53.190	98.27

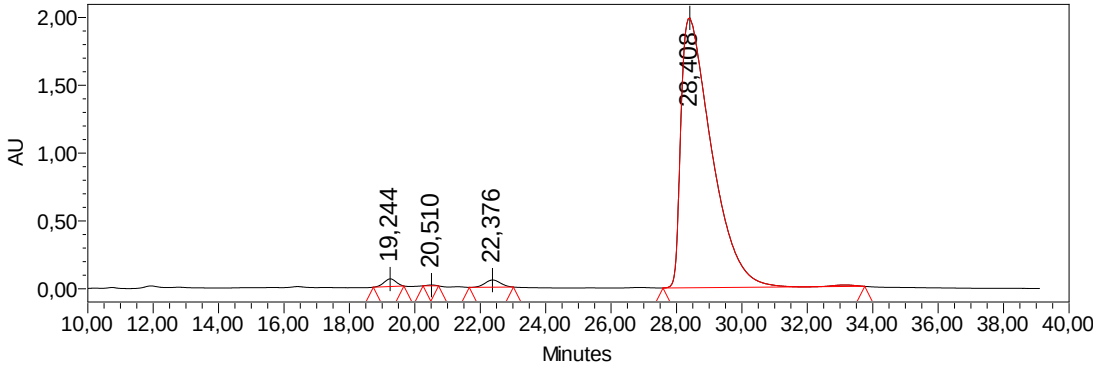
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times for major diastereoisomer: 28.4 min (major.) and 19.2 min (min.), minor diastereoisomer: 20.5 min and 22.4 min. Processed Channel Descr.: PDA 210.0 nm).

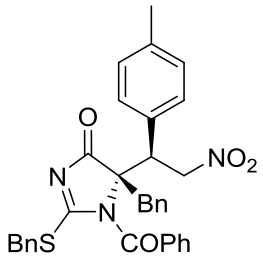


	Retention Time	% Area
1	19.357	47.43
2	20.666	1.19
3	22.506	1.07
4	29.473	50.31

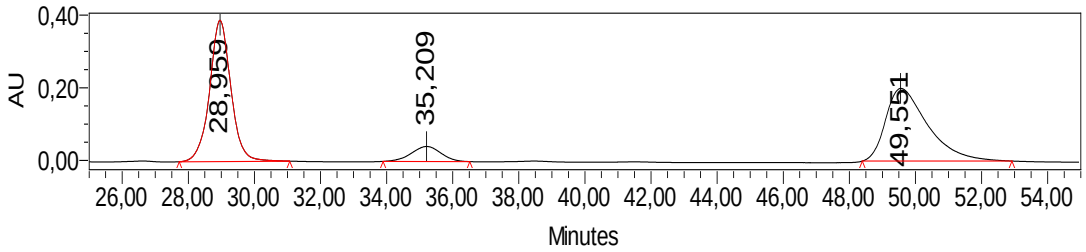


	Retention Time	% Area
1	19.244	1.08
2	20.510	0.08
3	22.376	1.33
4	28.408	97.51

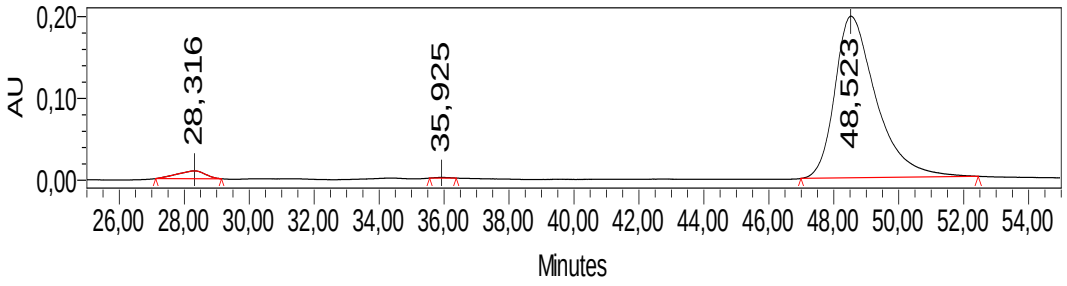
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-2-nitro-1-(p-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (38Cc)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 48.5 min (major.) and 28.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

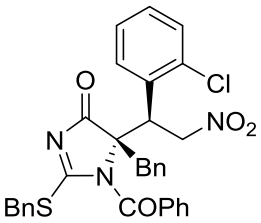


	Retention Time	% Area
1	28.959	46.21
2	35.209	6.84
3	49.554	46.94

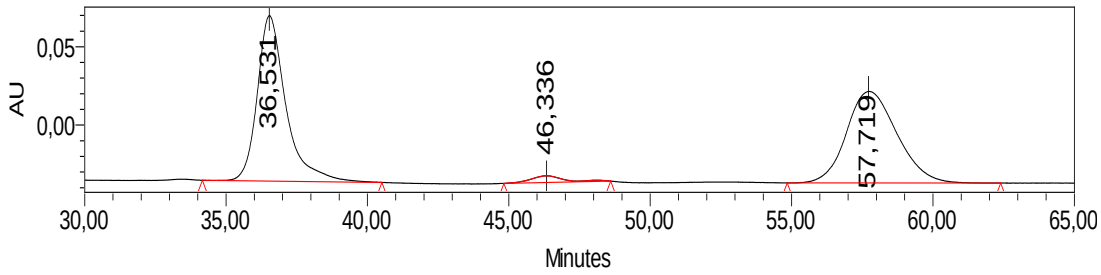


	Retention Time	% Area
1	28.316	3.20
2	35.925	0.13
3	48.523	96.67

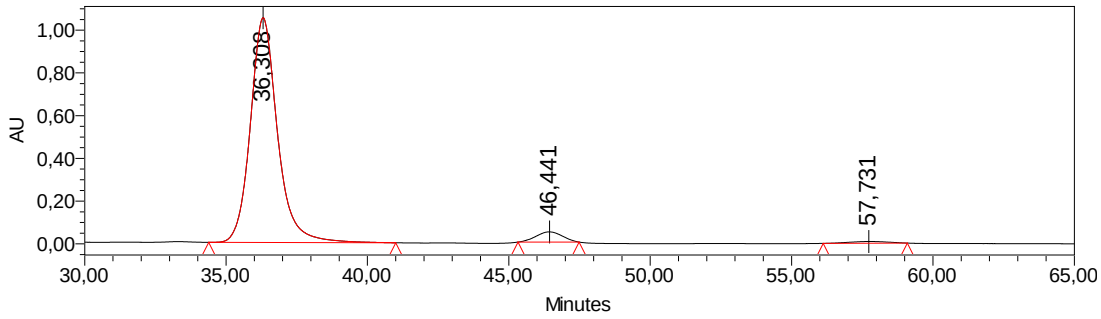
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 36.3 min (major.) and 57.7 min (min.). Processed Channel Descr.: PDA 210.0 nm).

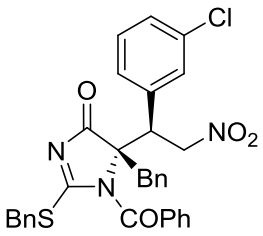


	Retention Time	% Area
1	36.531	49.43
2	46.336	2.28
3	57.719	48.29

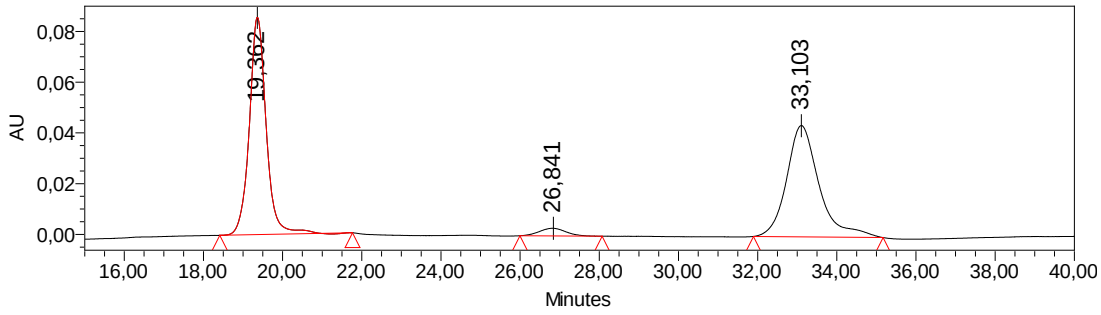


	Retention Time	% Area
1	28.959	94.80
2	35.209	4.16
3	49.554	1.05

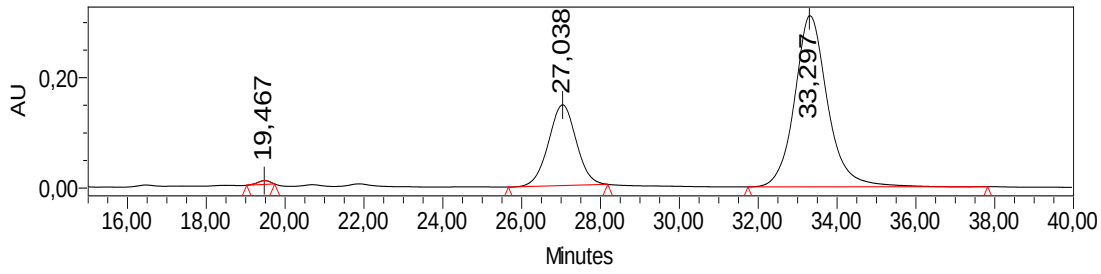
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Ce)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 33.3 min (major.) and 19.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

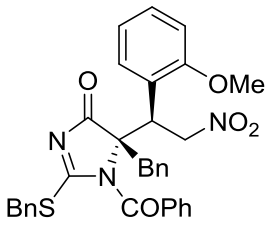


	Retention Time	% Area
1	19.302	49.01
2	26.841	2.71
3	33.103	48.28

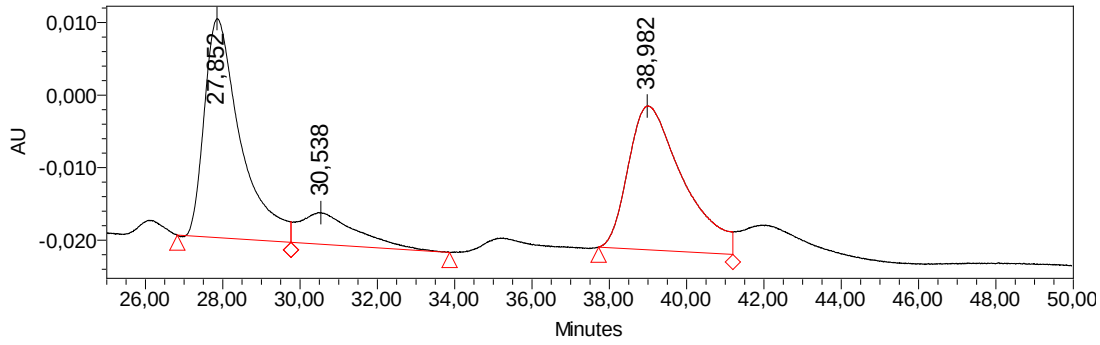


	Retention Time	% Area
1	19.467	0.61
2	27.038	28.29
3	33.297	71.11

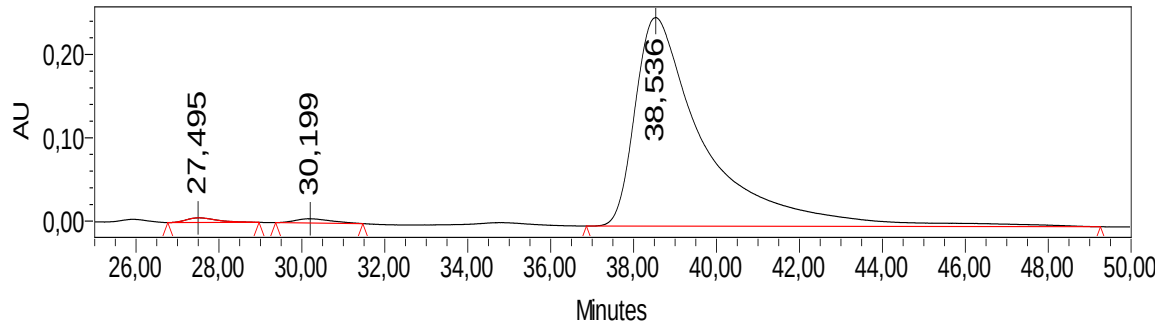
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(2-methoxyphenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cf)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 38.5 min (major.) and 27.5 min (min.).Processed Channel Descr.: PDA 210.0 nm).

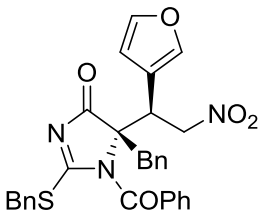


	Retention Time	% Area
1	27.852	44.89
2	30.538	10.28
3	38.982	44.83

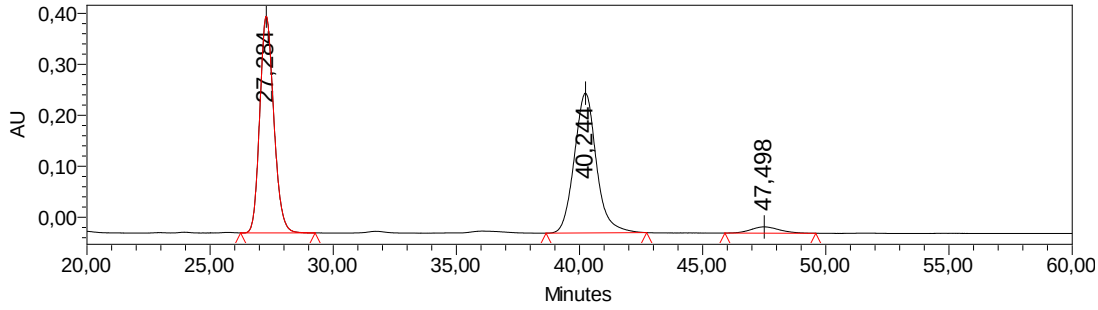


	Retention Time	% Area
1	27.495	0.96
2	30.199	1.03
3	38.536	98.02

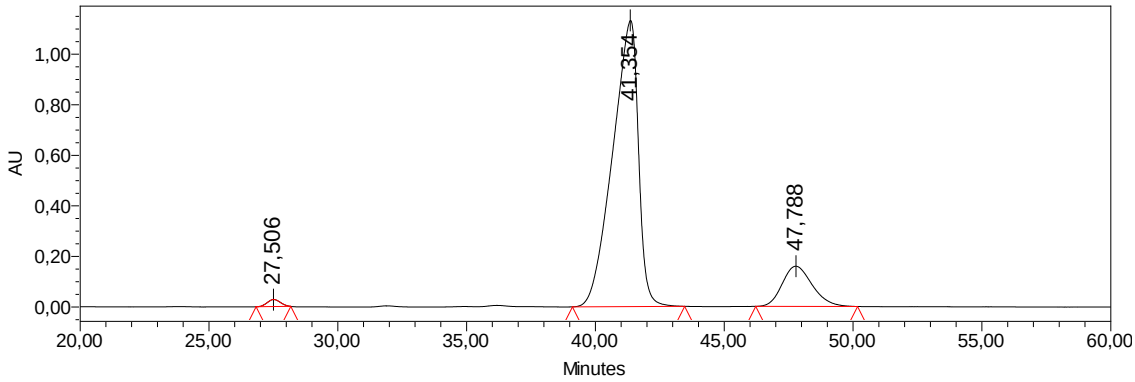
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (38Cg)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 19.3 min (major.) and 15.6 min (min.). Processed Channel Descr.: PDA 210.0 nm).

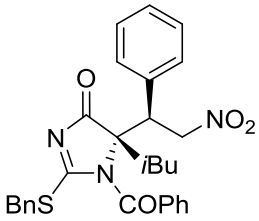


	Retention Time	% Area
1	27.284	48.15
2	40.244	49.02
3	47.498	2.83

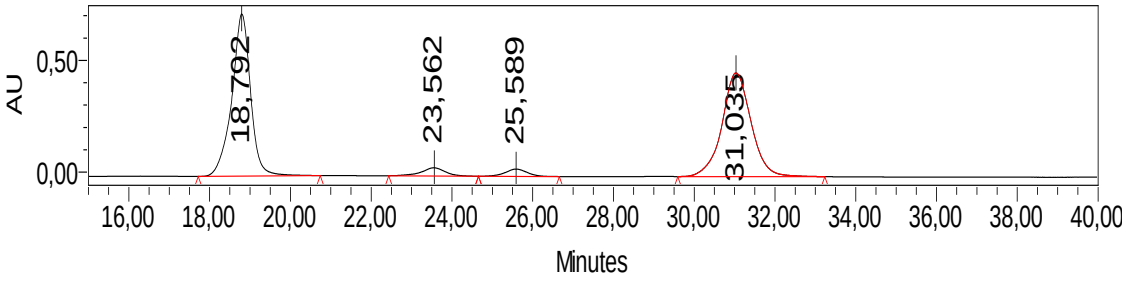


	Retention Time	% Area
1	27.506	1.08
2	41.354	85.01
3	47.788	13.92

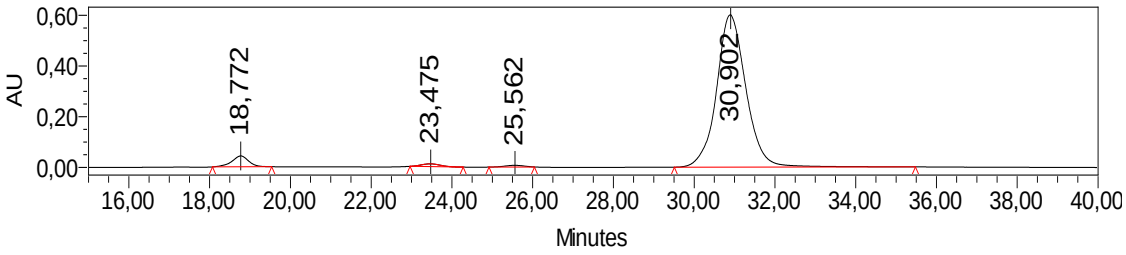
(*S*)-1-Benzoyl-2-(benzylthio)-5-isobutyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one(38Da)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 30.9 min (major.) and 18.8 min (min.). Processed Channel Descr.: PDA 210.0 nm).

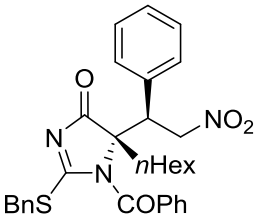


	Retention Time	% Area
1	18.792	46.97
2	23.562	2.53
3	25.589	3.05
4	31.036	47.45

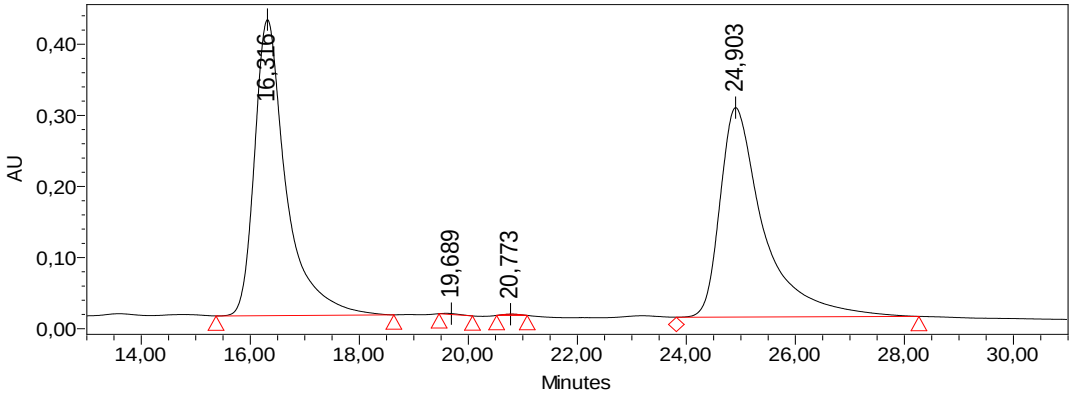


	Retention Time	% Area
1	18.772	3.87
2	23.475	1.12
3	25.562	0.66
4	30.902	94.35

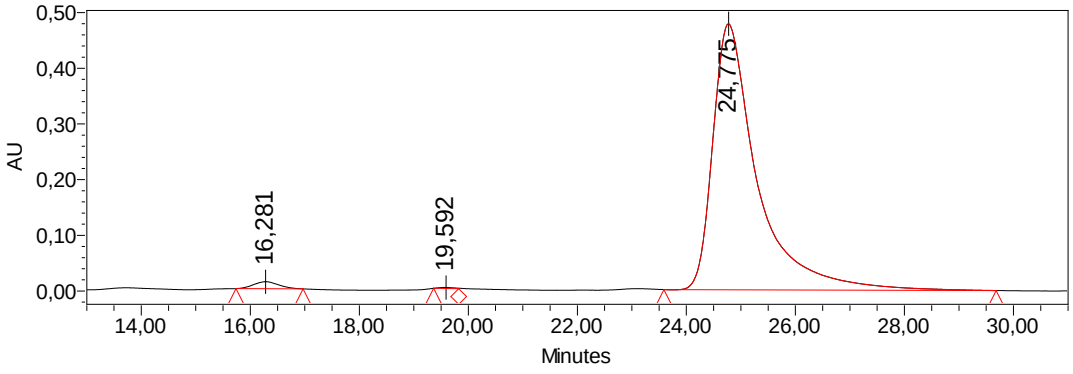
(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (38Ea)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 24.8 min (major.) and 16.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

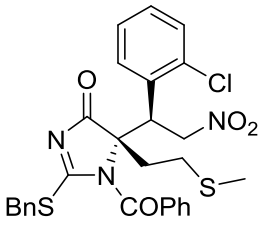


	Retention Time	% Area
1	16.316	50.40
2	19.689	0.08
3	20.773	0.11
4	24.903	49.41

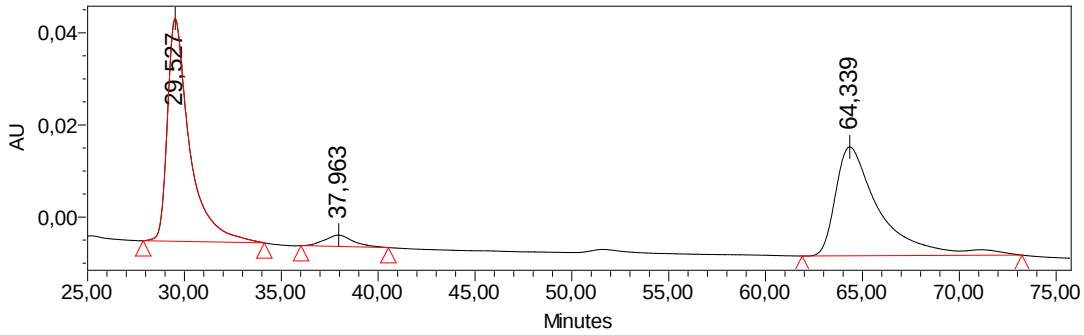


	Retention Time	% Area
1	16.281	1.48
2	19.592	0.13
3	24.775	98.39

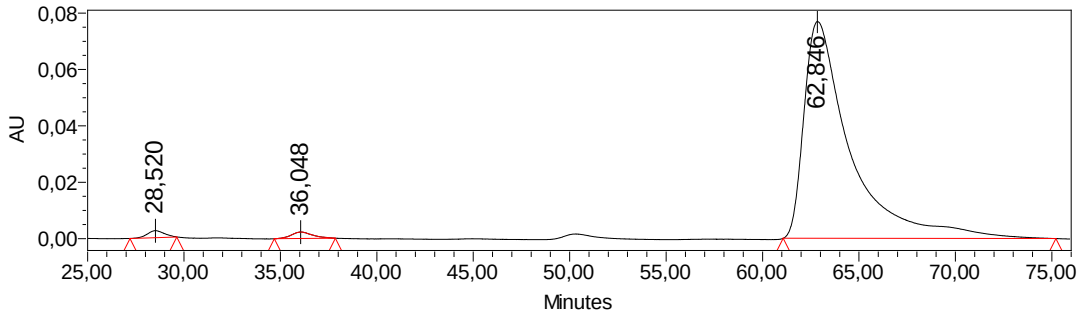
(*S*)-1-Benzoyl-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-(2-(methylthio)ethyl)-1*H*-imidazol-4(5*H*)-one (38Fd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times for major diastereoisomer: 62.8 min (major.) and 28.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

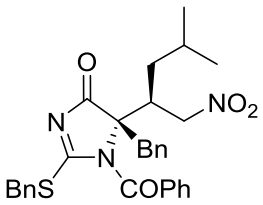


	Retention Time	% Area
1	29.527	48.93
2	37.963	3.25
3	64.339	47.83

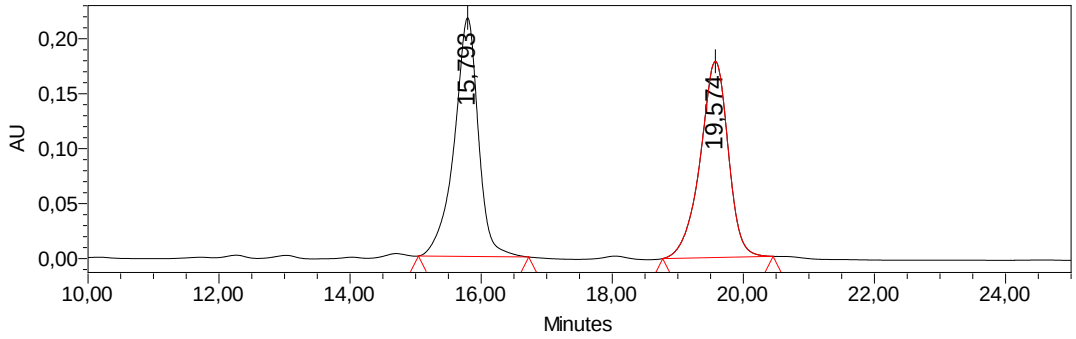


	Retention Time	% Area
1	28.520	1.14
2	36.048	1.33
3	62.846	97.52

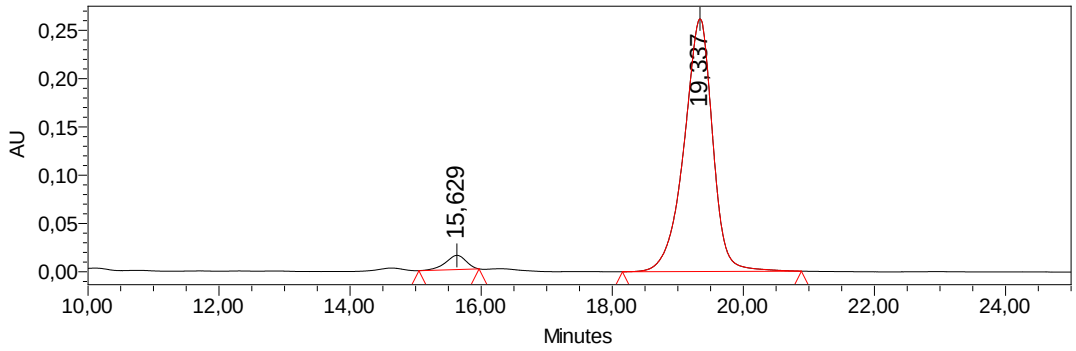
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-4-methyl-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ch)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 19.3 min (major.) and 15.6 min (min.). Processed Channel Descr.: PDA 210.0 nm).

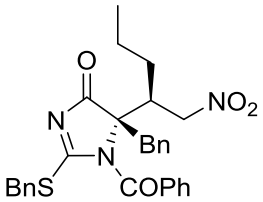


	Retention Time	% Area
1	15.793	49.86
2	19.574	50.14

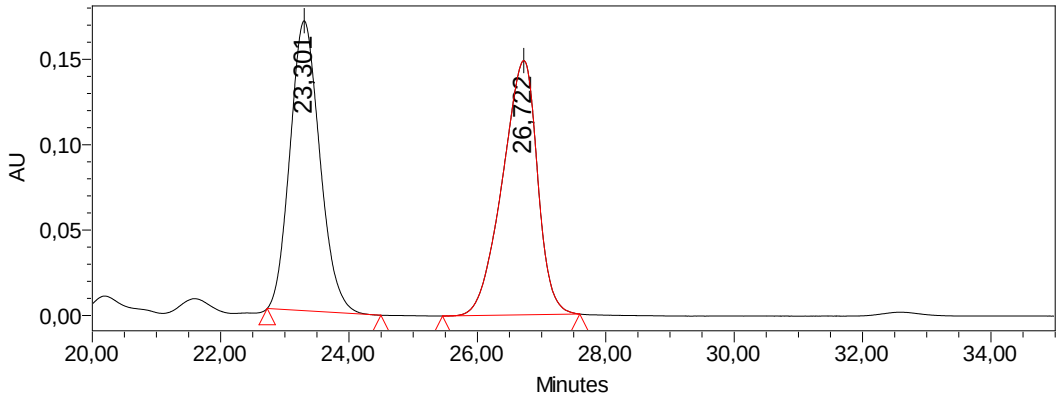


	Retention Time	% Area
1	15.629	3.86
2	19.337	96.14

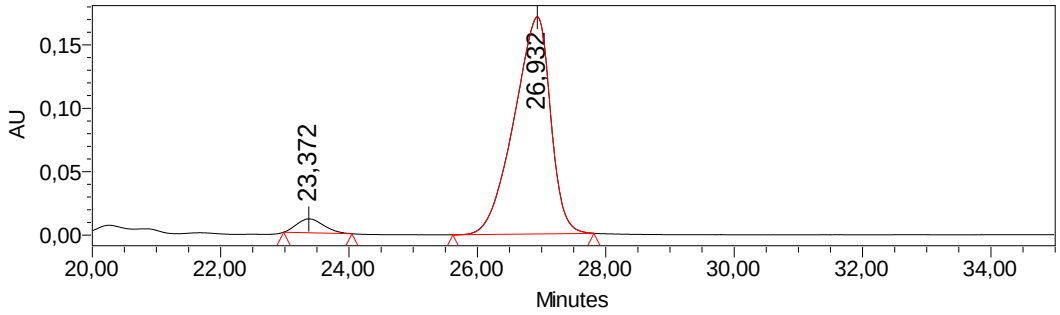
(*S*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-((*S*)-1-nitropentan-2-yl)-1*H*-imidazol-4(5*H*)-one (38Ci)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 26.9 min (major.) and 23.4 min (min.). Processed Channel Descr.: PDA 210.0 nm).

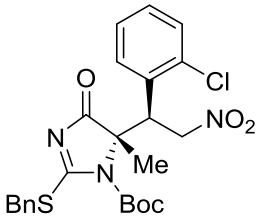


	Retention Time	% Area
1	23.301	49.21
2	26.722	50.79

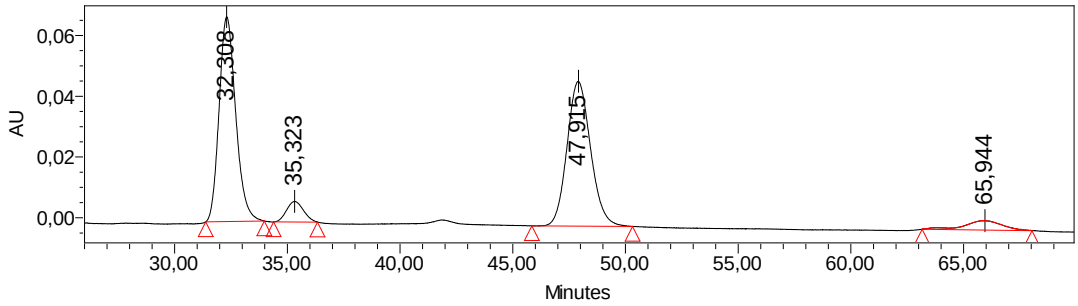


	Retention Time	% Area
1	23.372	4.53
2	26.932	95.47

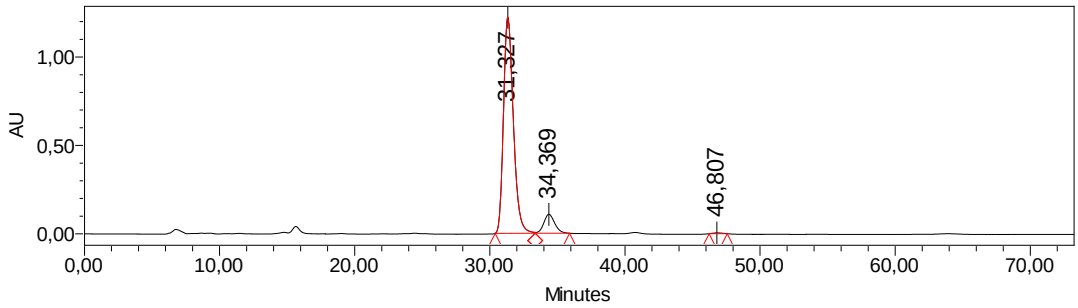
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (39Ad)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate = 0.5 mL/min, retention times: 31.3 min (major.) and 46.8 min (min.). Processed Channel Descr.: PDA 210.0 nm).

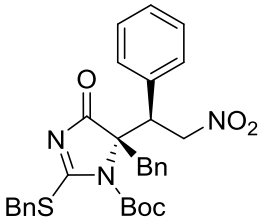


	Retention Time	% Area
1	32.308	45.29
2	35.323	4.64
3	47.915	45.38
4	65.944	4.68

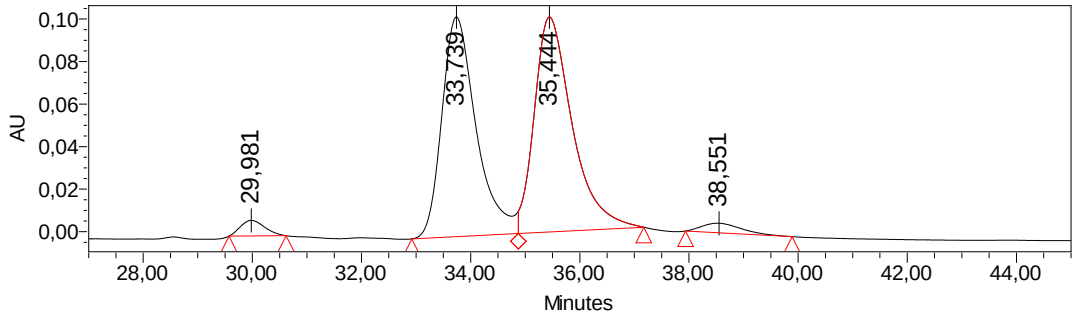


	Retention Time	% Area
1	31.327	90.83
2	34.369	8.85
3	46.807	0.32

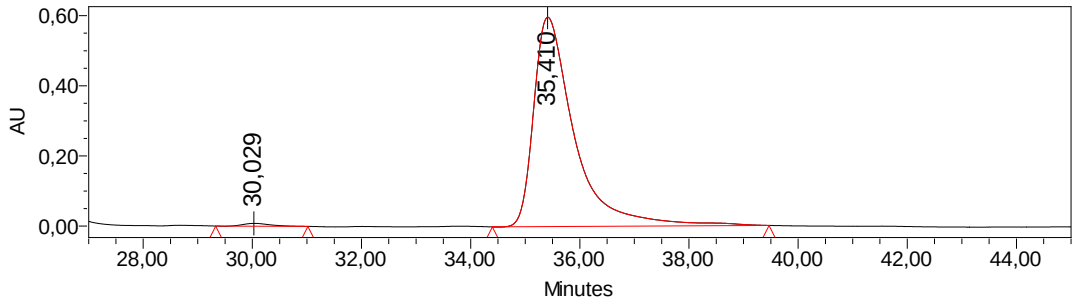
(*S*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (39Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC-IB, hexane/isopropanol 60/40, flow rate = 0.5 mL/min, retention times: 35.4 min (major.). Processed Channel Descr.: PDA 210.0 nm).

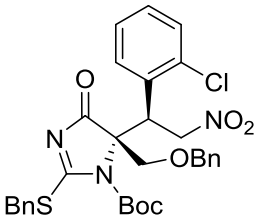


	Retention Time	% Area
1	29.981	2.29
2	33.739	49.60
3	35.444	45.83
4	38.551	2.27

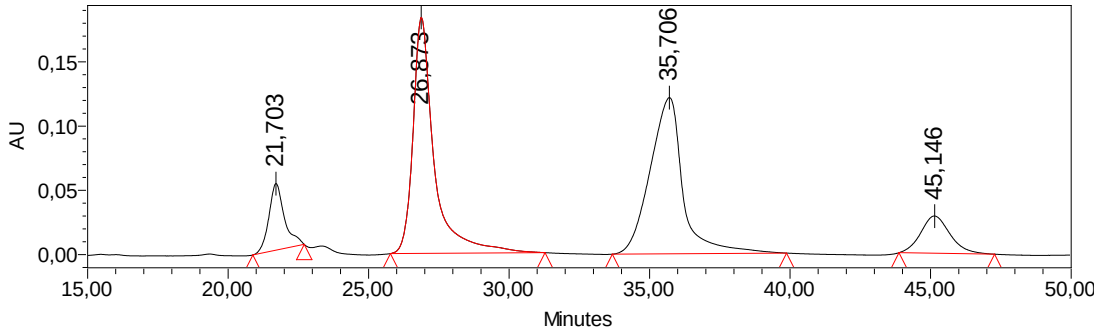


	Retention Time	% Area
1	30.029	0.91
2	35.410	90.09

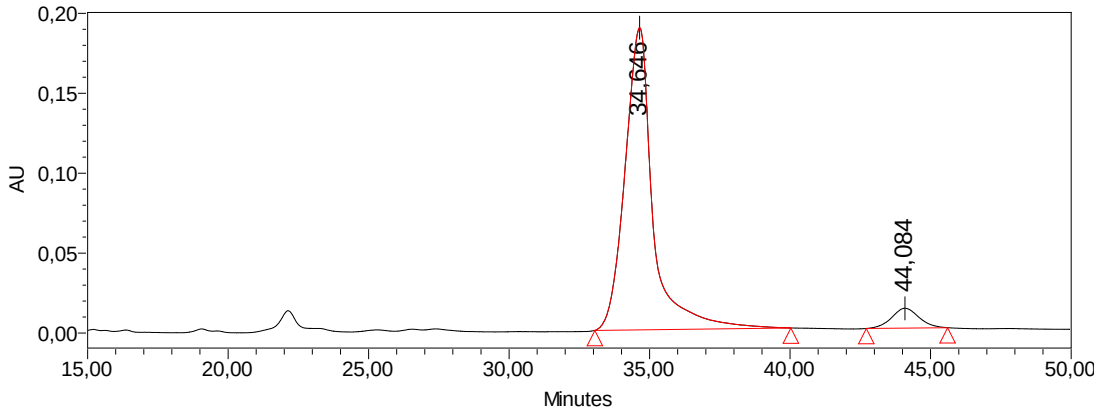
(*R*)-5-((Benzyloxy)methyl)-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)- 1*H*-imidazol-4(5*H*)-one (39Gd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 34.6 min (major.) Processed Channel Descr.: PDA 210.0 nm).

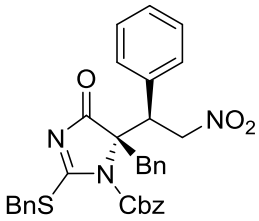


	Retention Time	% Area
1	21.703	8.47
2	26.673	40.80
3	35.706	41.82
4	45.146	8.91

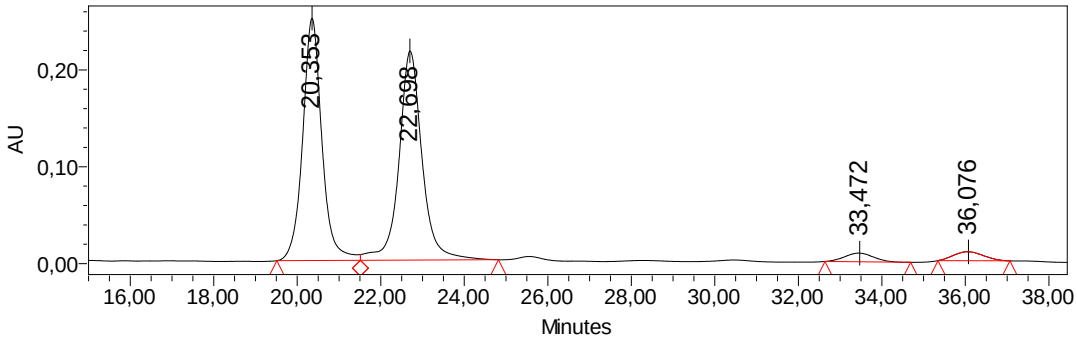


	Retention Time	% Area
1	34.646	93.98
2	44.084	6.02

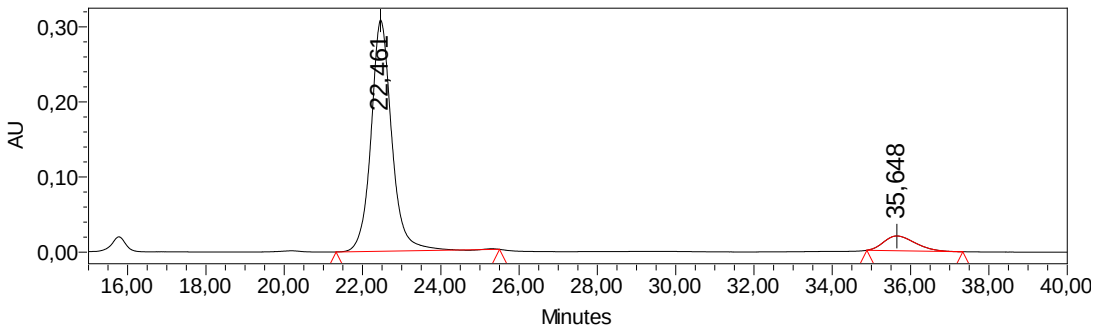
(*S*)-5-Benzyl-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (40Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 65/35, flow rate = 0.5 mL/min, retention times: 22.5 min (major.). Processed Channel Descr.: PDA 210.0 nm).

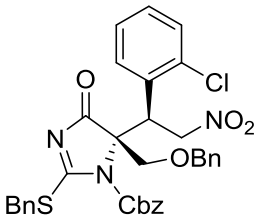


	Retention Time	% Area
1	20.353	46.49
2	22.698	48.33
3	33.472	2.50
4	36.076	2.68

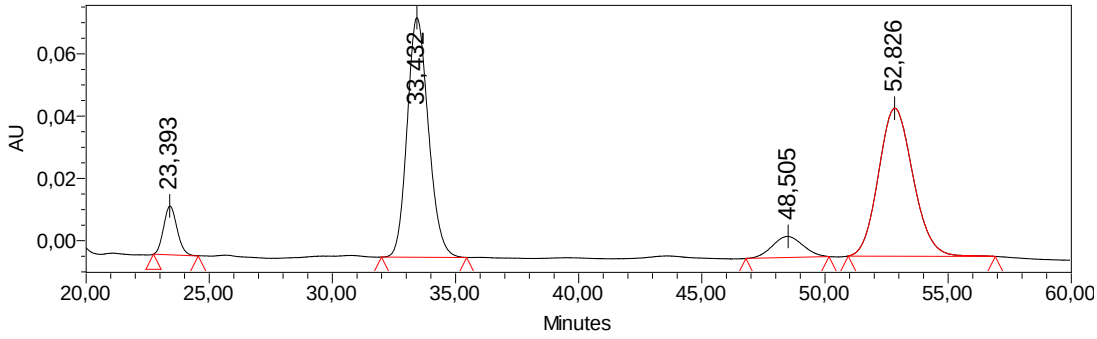


	Retention Time	% Area
1	22.461	91.16
2	35.648	8.84

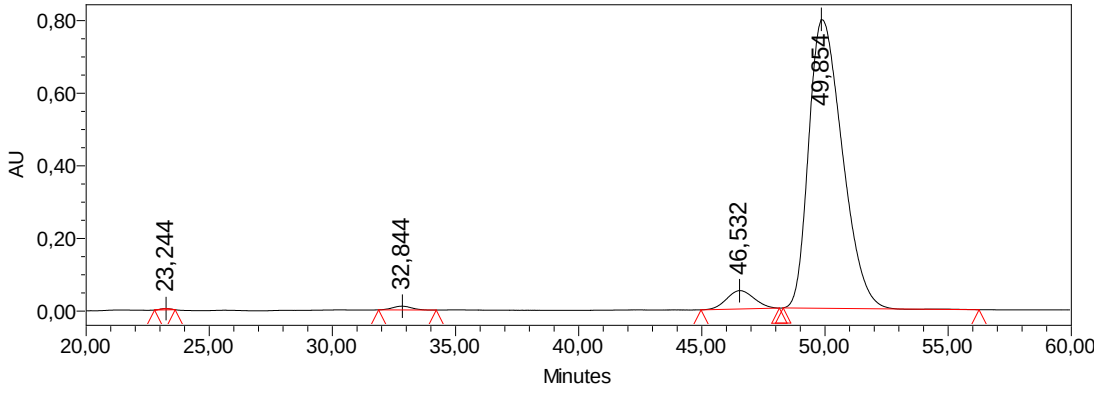
(*R*)-5-((Benzyloxy)methyl)-1-(benzyloxycarbonyl)-2-(benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1*H*-imidazol-4(5*H*)-one (40Gd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 49.8 min (major.) and 32.8 min (min.) Processed Channel Descr.: PDA 210.0 nm).

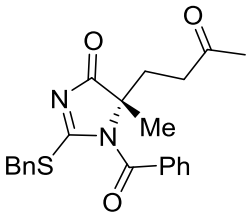


	Retention Time	% Area
1	23.393	5.71
2	33.432	44.24
3	48.505	5.60
4	52.826	44.44

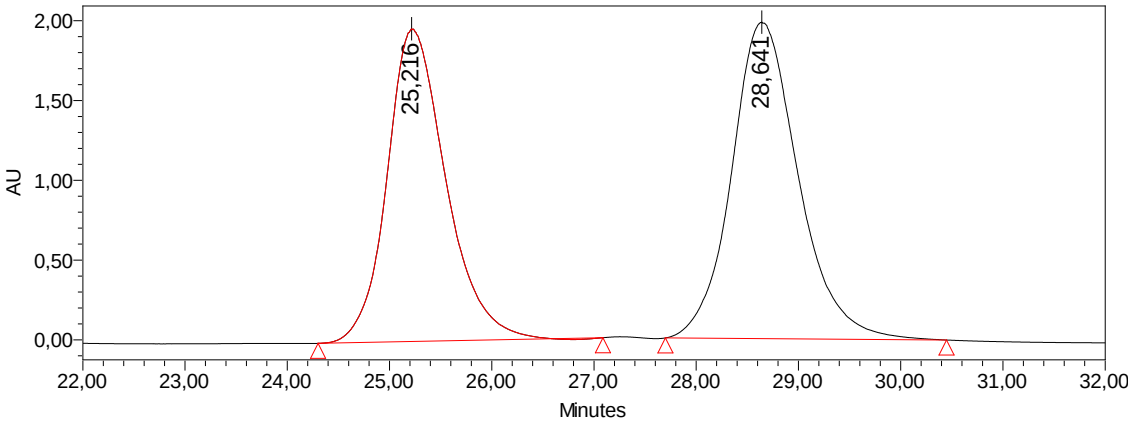


	Retention Time	% Area
1	23.244	0.13
2	32.844	0.71
3	46.532	4.92
4	49.854	94.25

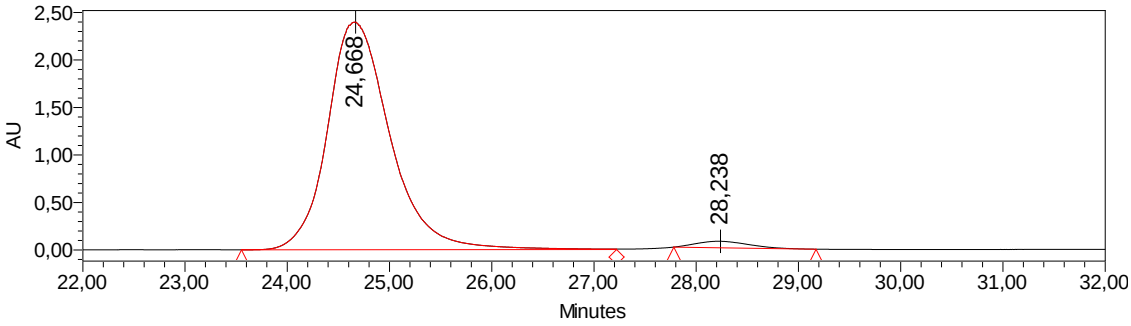
(*S*)-1-Benzoyl-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 24.6 min (major.) and 28.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

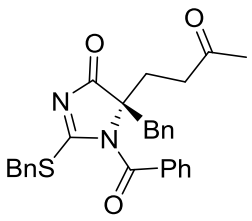


	Retention Time	% Area
1	25.216	46.57
2	28.641	53.43

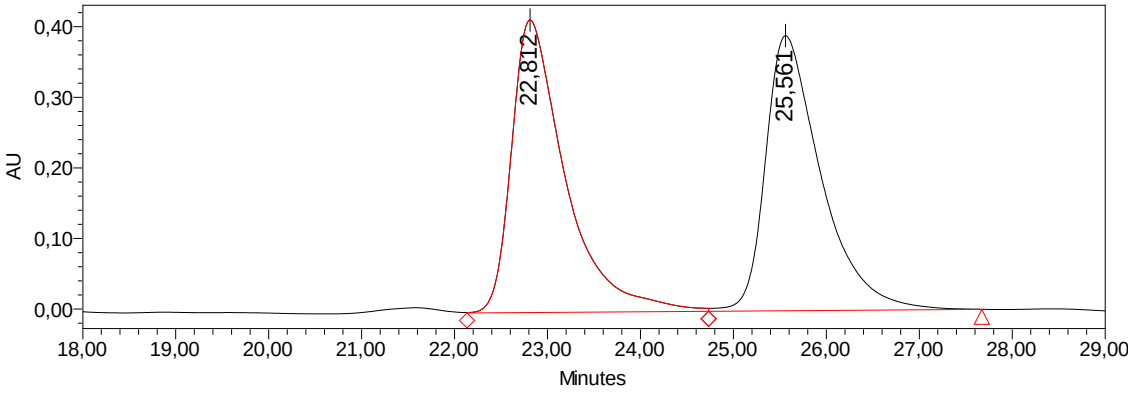


	Retention Time	% Area
1	24.668	97.70
2	28.238	2.30

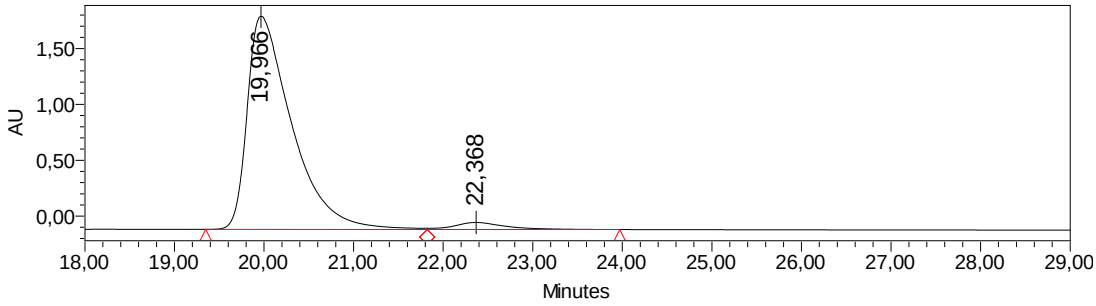
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (42Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 19.9 min (major.) and 22.4 min (min.). Processed Channel Descr.: PDA 210.0 nm).

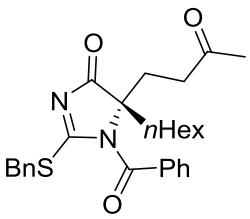


	Retention Time	% Area
1	22.812	50.68
2	25.561	49.32

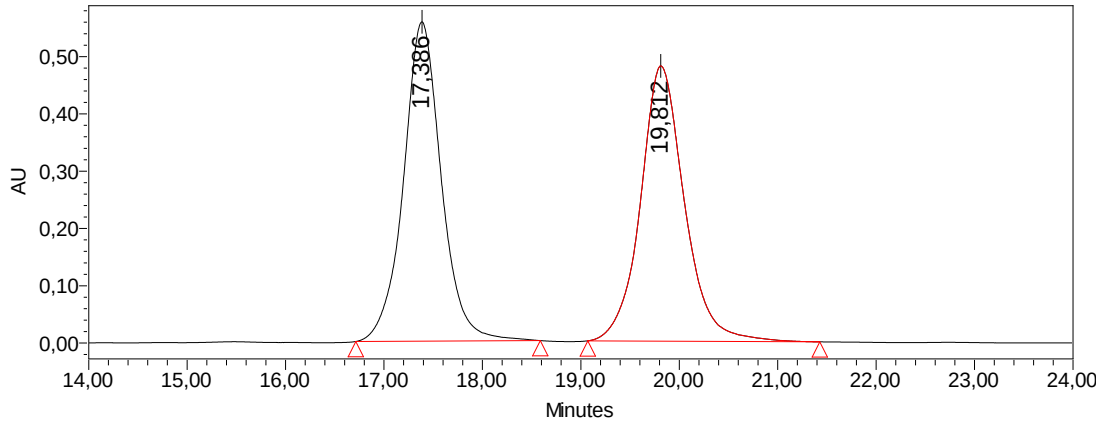


	Retention Time	% Area
1	19.966	97.71
2	22.368	2.29

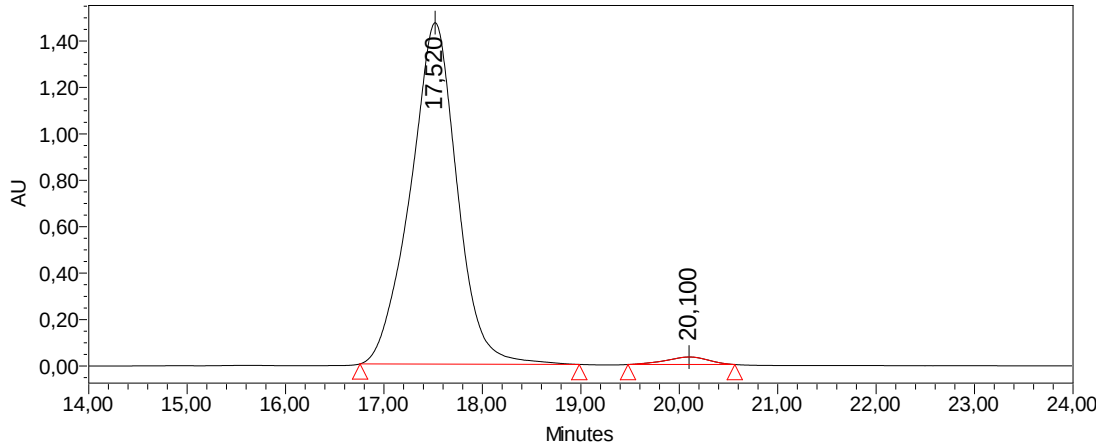
(*S*)-1-Benzoyl-2-(benzylthio)-5-hexyl-5-(3-oxobutyl)-1H-imidazol-4(5*H*)-one (42Ea)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 17.5 min (major.) and 20.1 min (min.). Processed Channel Descr.: PDA 210.0 nm).

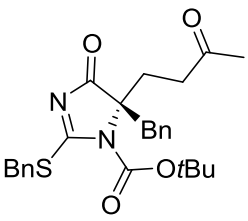


	Retention Time	% Area
1	17.386	49.96
2	19.812	50.04

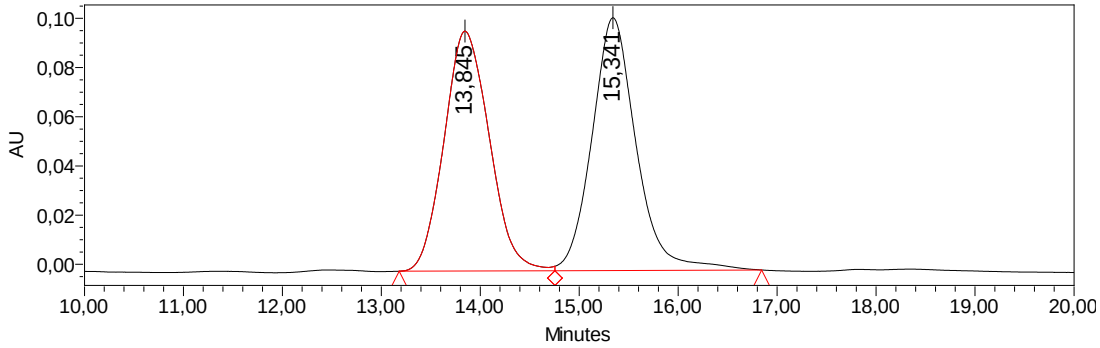


	Retention Time	% Area
1	17.520	98.02
2	20.100	1.98

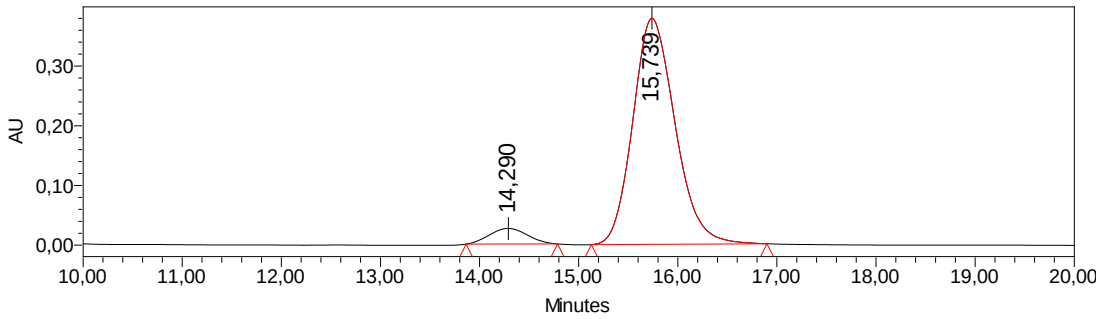
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 15.7 min (major.) and 14.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

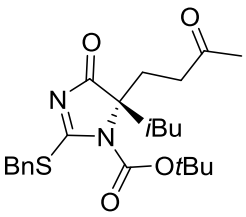


	Retention Time	% Area
1	13.845	49.29
2	15.341	50.71

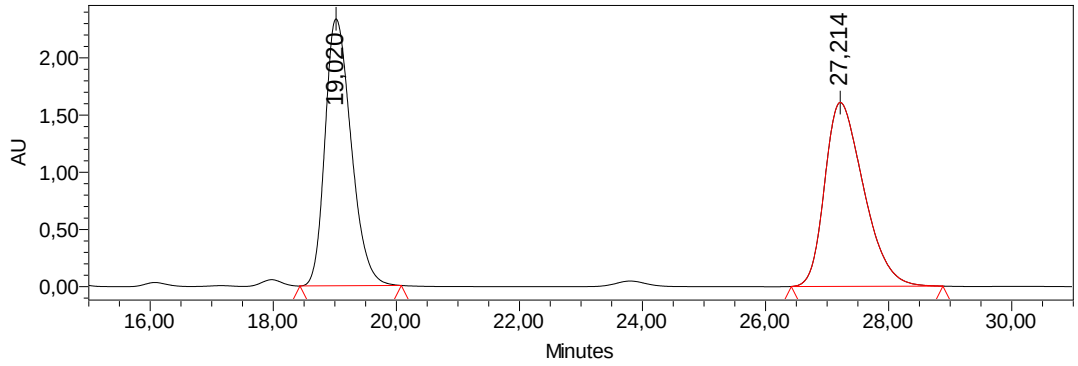


	Retention Time	% Area
1	14.290	5.85
2	15.739	94.15

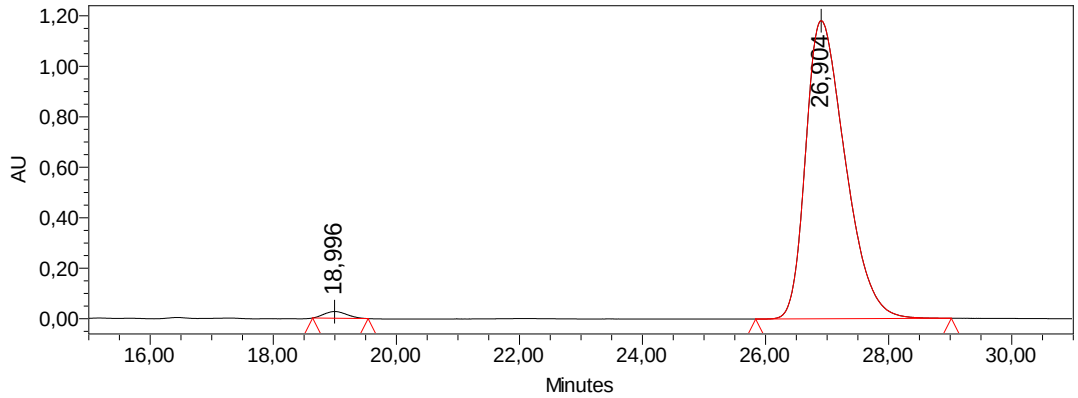
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-isobutyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Da)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate = 0.5 mL/min, retention times: 26.9 min (major.) and 19.0 min (min.). Processed Channel Descr.: PDA 210.0 nm).

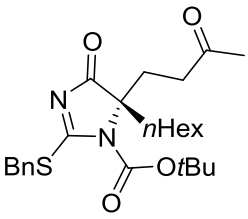


	Retention Time	% Area
1	19.020	49.37
2	27.214	50.63

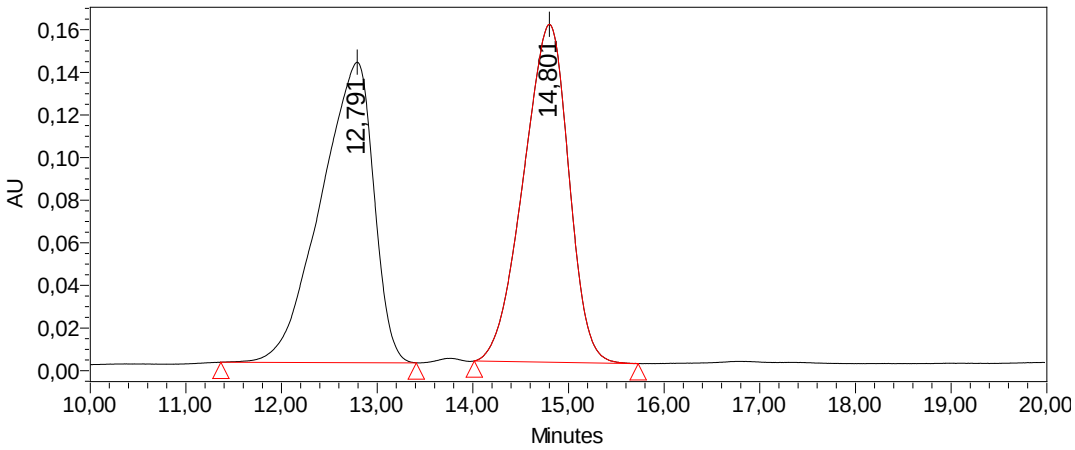


	Retention Time	% Area
1	18.996	1.28
2	26.904	98.72

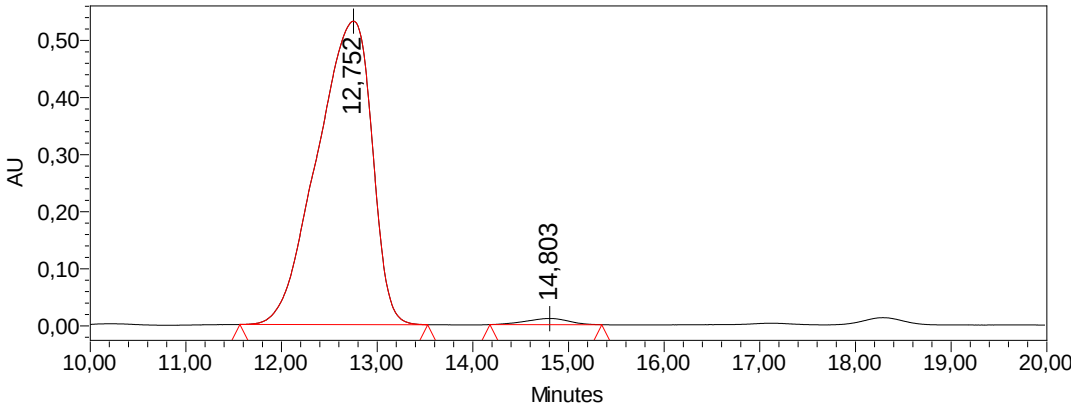
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-hexyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (43Ea)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 12.7 min (major.) and 14.8 min (min.). Processed Channel Descr.: PDA 210.0 nm).

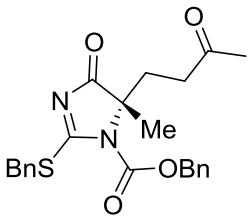


	Retention Time	% Area
1	12.791	49.09
2	14.801	50.91

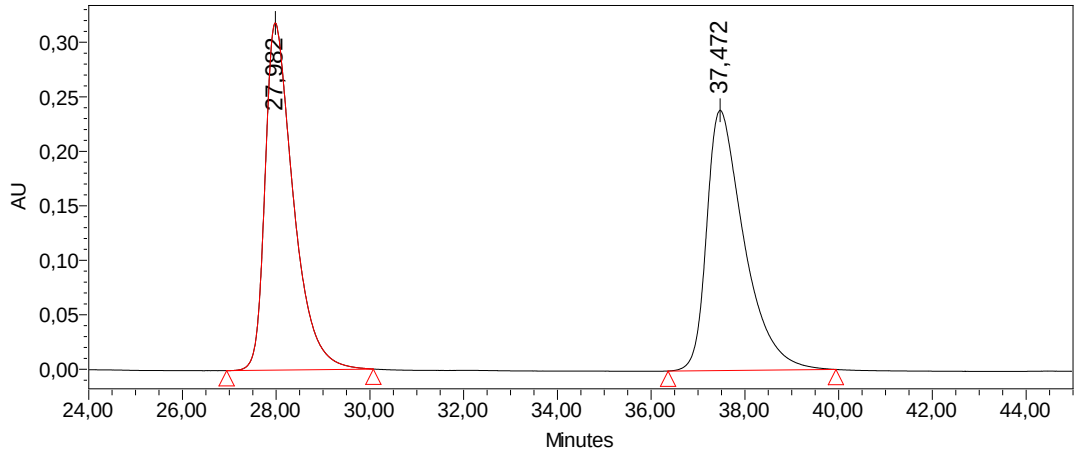


	Retention Time	% Area
1	12.752	98.43
2	14.803	1.57

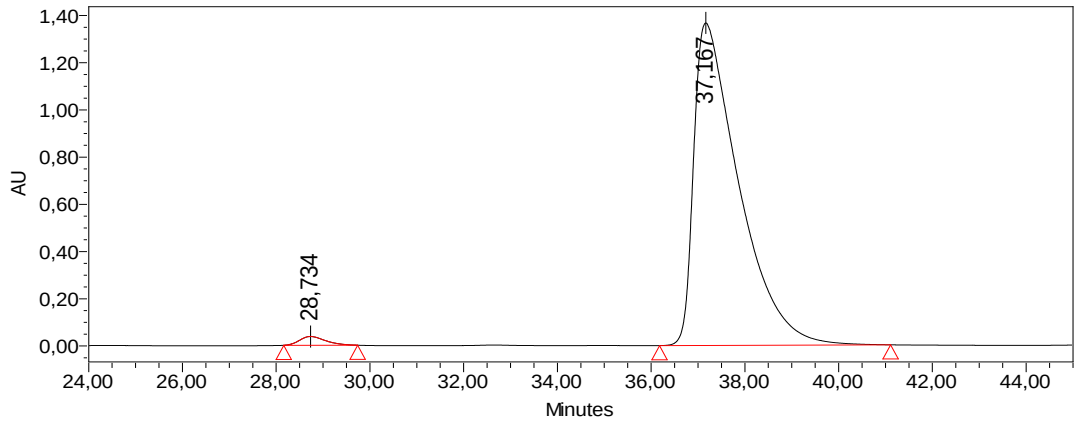
(*S*)-1-(Benzyloxycarbonyl)-2-(benzylthio)-5-methyl-5-(3-oxobutyl)-1*H*-imidazol-4(5*H*)-one (44Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 37.2 min (major.) and 28.0 min (min.). Processed Channel Descr.: PDA 210.0 nm).

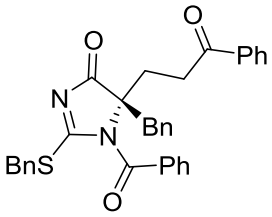


	Retention Time	% Area
1	27.982	50.19
2	37.472	49.81

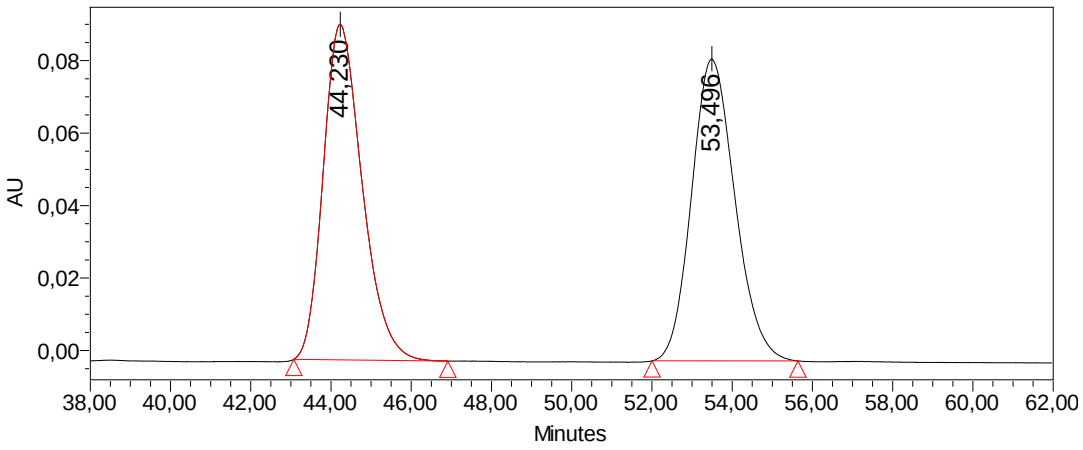


	Retention Time	% Area
1	28.734	1.55
2	37.167	98.45

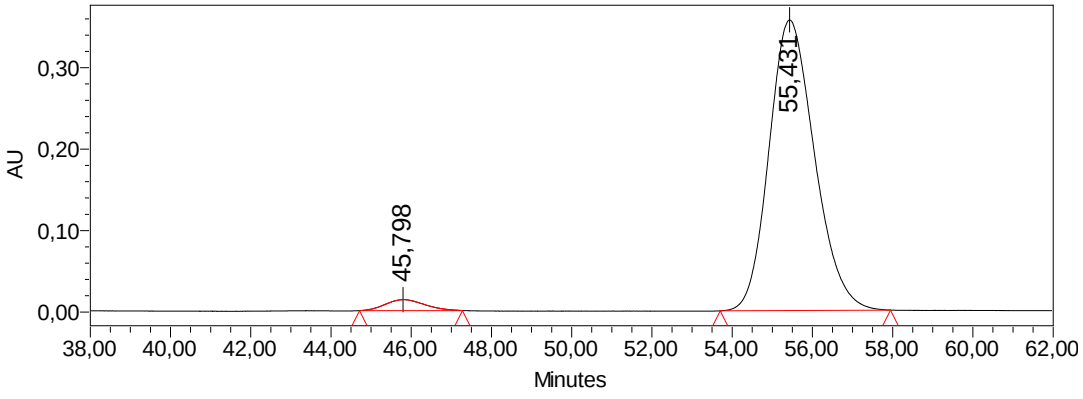
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (42Cb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 55.4 min (major.) and 45.8 min (min.).Processed Channel Descr.: PDA 210.0 nm).

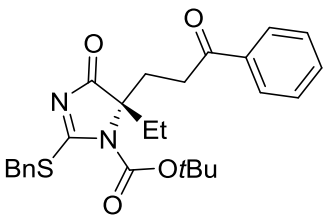


	Retention Time	% Area
1	44.230	49.95
2	53.496	50.05

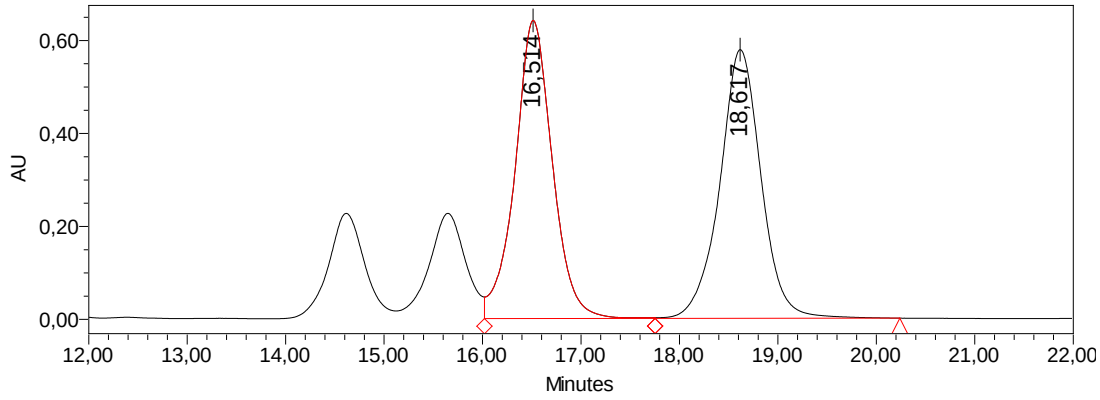


	Retention Time	% Area
1	45.798	3.15
2	55.431	96.85

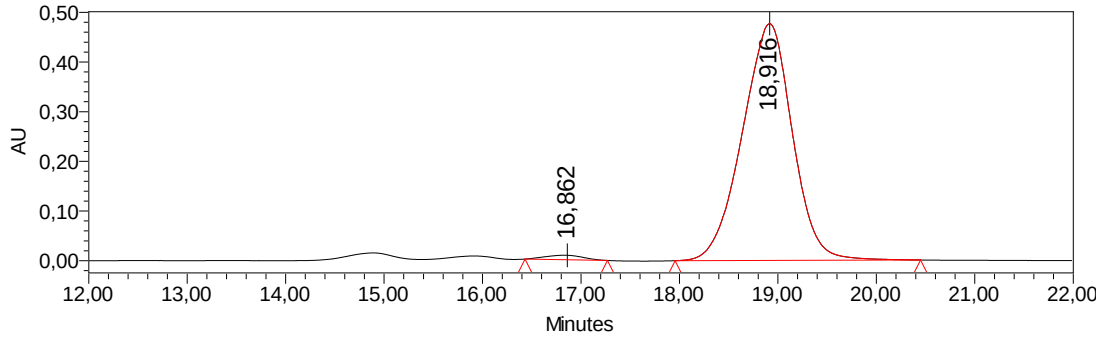
(*S*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-ethyl-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Bb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 18.9 min (major.) and 16.9 min (min.). Processed Channel Descr.: PDA 210.0 nm).

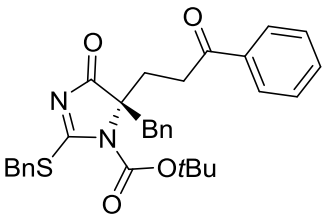


	Retention Time	% Area
1	16.514	50.09
2	18.617	49.91

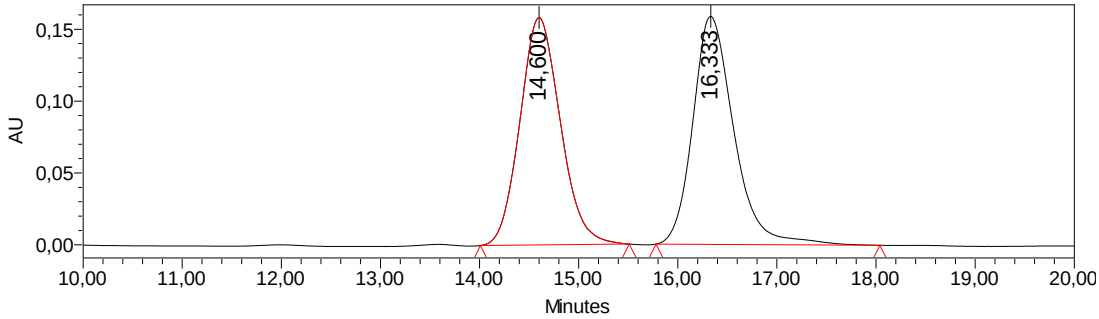


	Retention Time	% Area
1	16.862	1.40
2	18.916	98.60

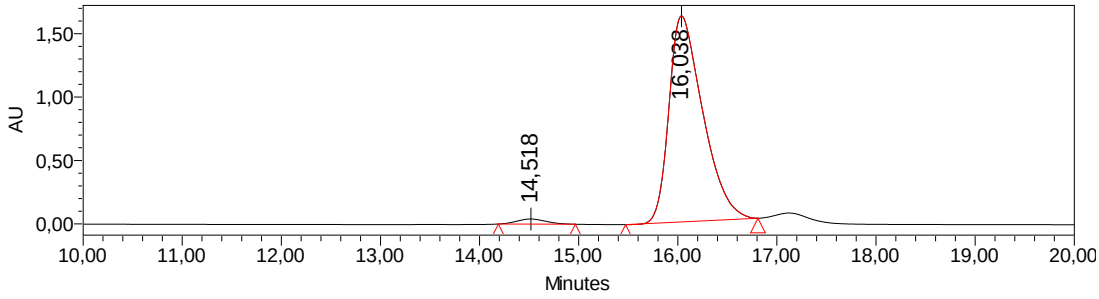
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-phenylpropyl)-1*H*-imidazol-4(5*H*)-one (43Cb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 16.0 min (major.) and 14.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

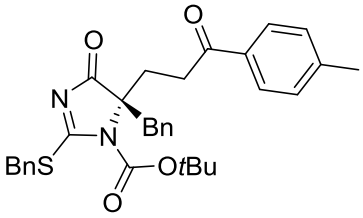


	Retention Time	% Area
1	14.600	50.47
2	16.333	49.53

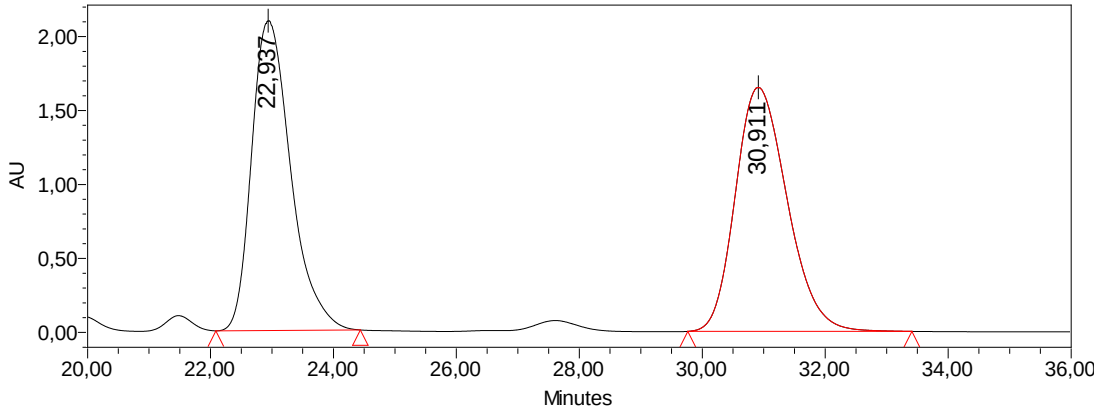


	Retention Time	% Area
1	14.518	2.08
2	16.038	97.92

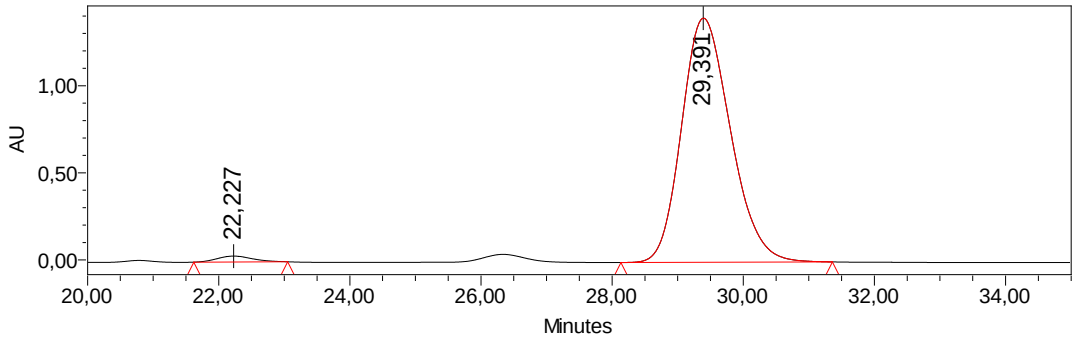
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(*p*-tolyl)propyl)-1*H*-imidazol-4(5*H*)-one (43Cc)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times: 29.4 min (major.) and 22.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

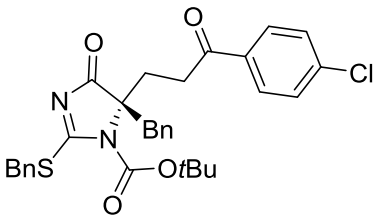


	Retention Time	% Area
1	22.937	48.97
2	30.911	51.03

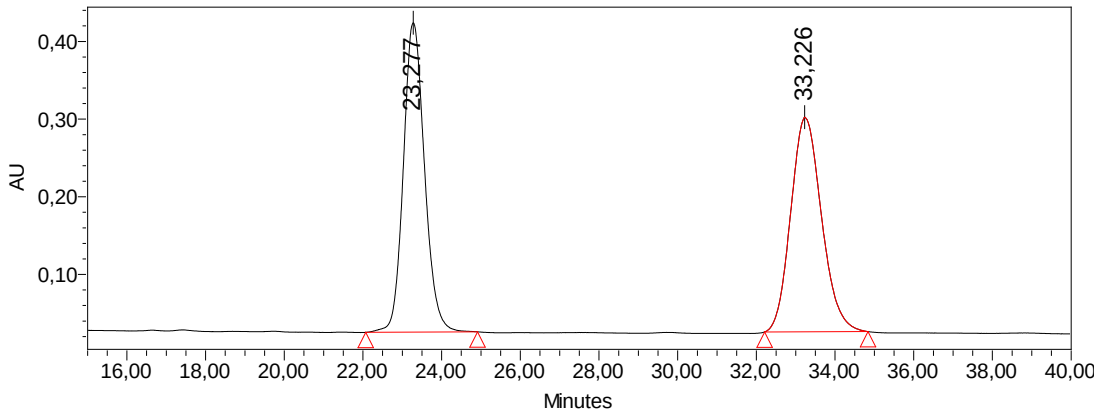


	Retention Time	% Area
1	22.227	1.73
2	29.391	98.27

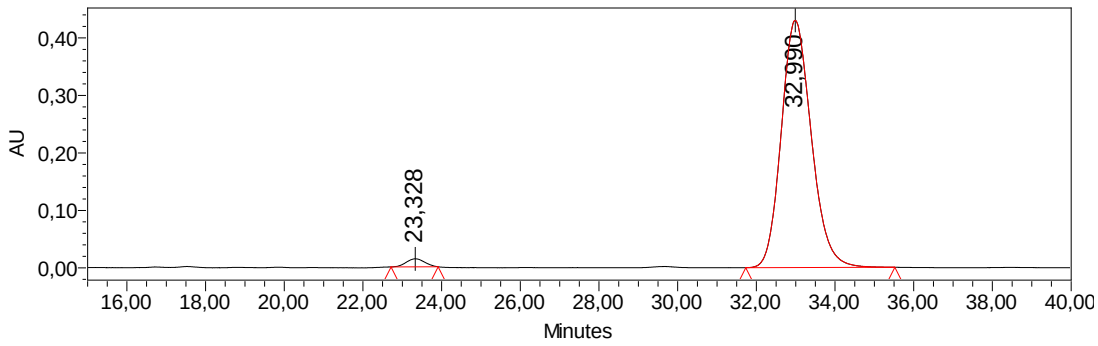
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-(4-chlorophenyl)-3-oxopropyl)-1*H*-imidazol-4(5*H*)-one (43Cd)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 33.0 min (major.) and 23.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

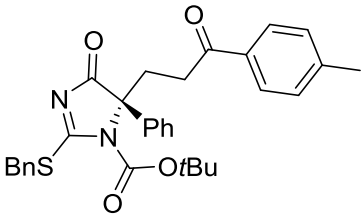


	Retention Time	% Area
1	23.277	49.81
2	33.226	50.19

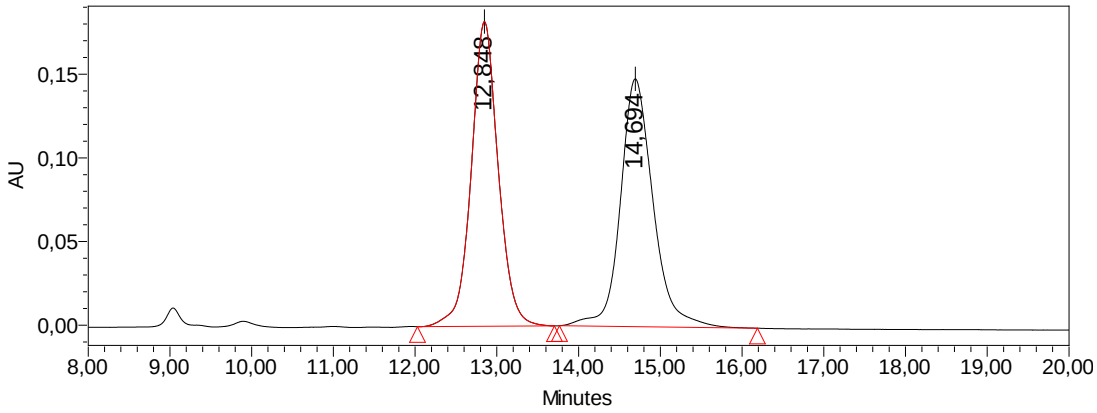


	Retention Time	% Area
1	23.328	1.95
2	32.990	98.05

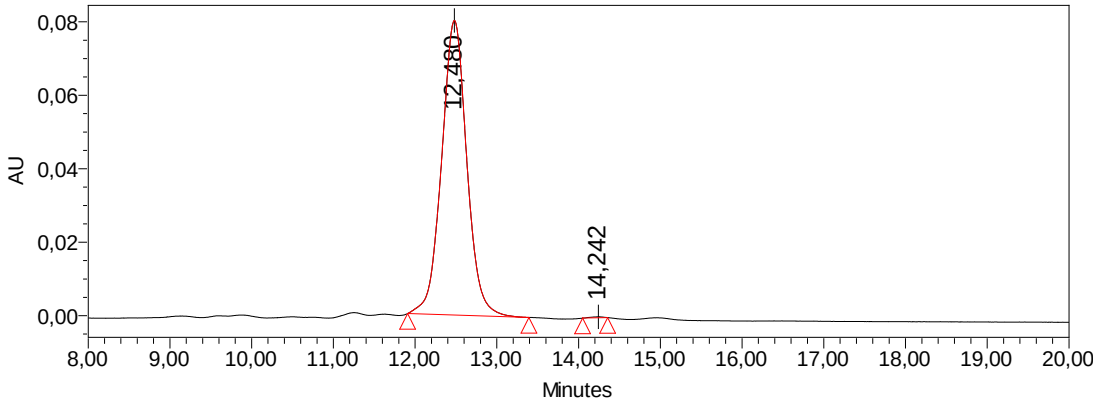
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(3-oxo-3-(p-tolyl)propyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (43Hc)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 12.4 min (major.) and 14.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

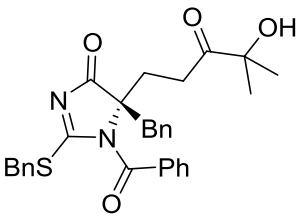


	Retention Time	% Area
1	12.848	50.38
2	14.694	49.62

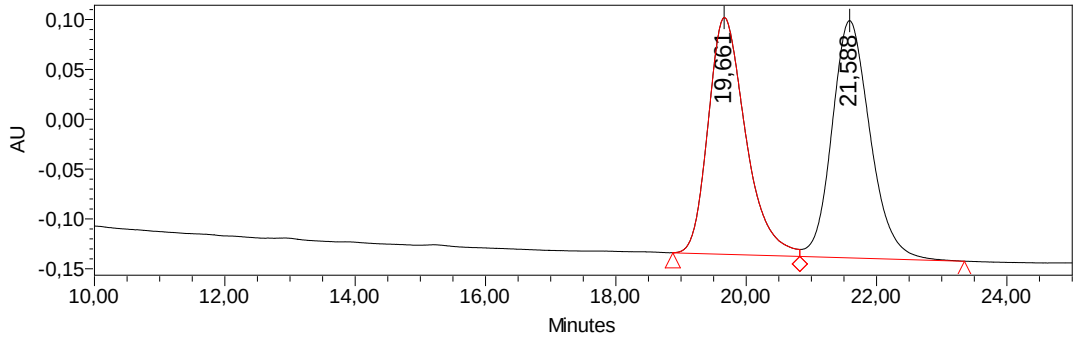


	Retention Time	% Area
1	12.460	99.83
2	14.242	0.17

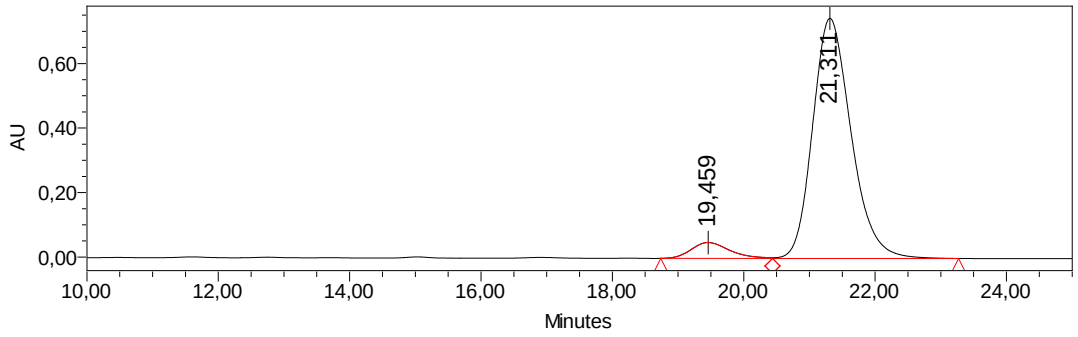
(*R*)-1-Benzoyl-5-benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (45C)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate = 0.5 mL/min, retention times: 21.3 min (major.) and 19.4 min (min.). Processed Channel Descr.: PDA 210.0 nm).

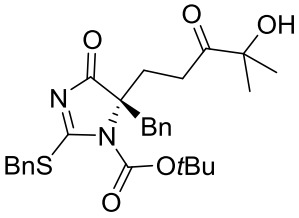


	Retention Time	% Area
1	19.661	49.46
2	21.588	50.54

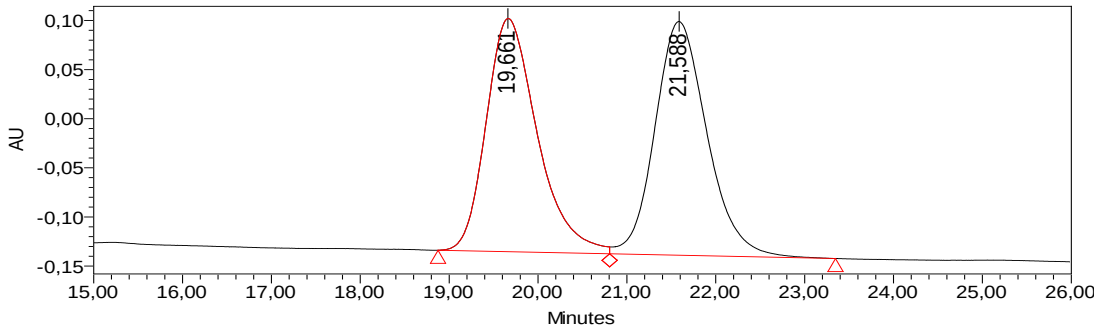


	Retention Time	% Area
1	19.459	6.18
2	21.311	93.82

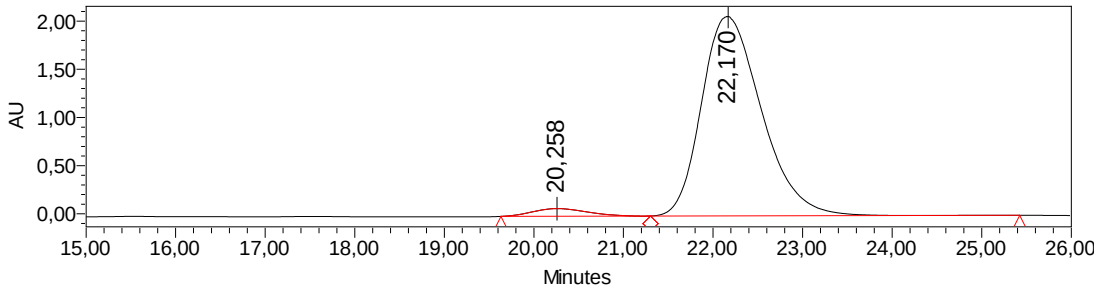
(*R*)-5-Benzyl-2-(benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (46C)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate = 0.5 mL/min, retention times: 22.2 min (major.) and 20.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

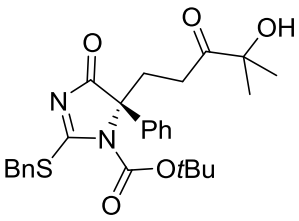


	Retention Time	% Area
1	19.661	49.47
2	21.588	50.53

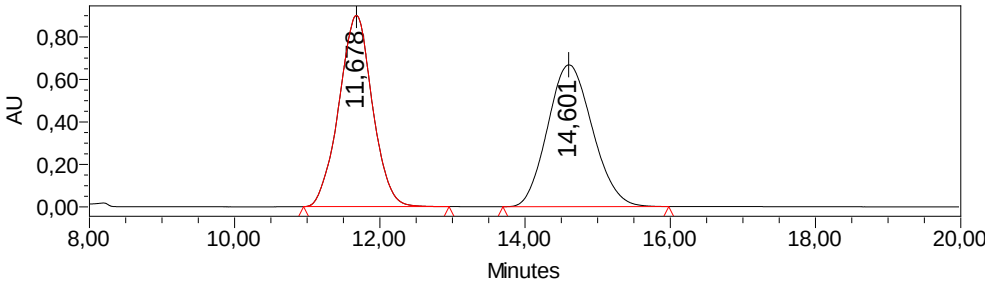


	Retention Time	% Area
1	20.258	3.39
2	22.170	96.61

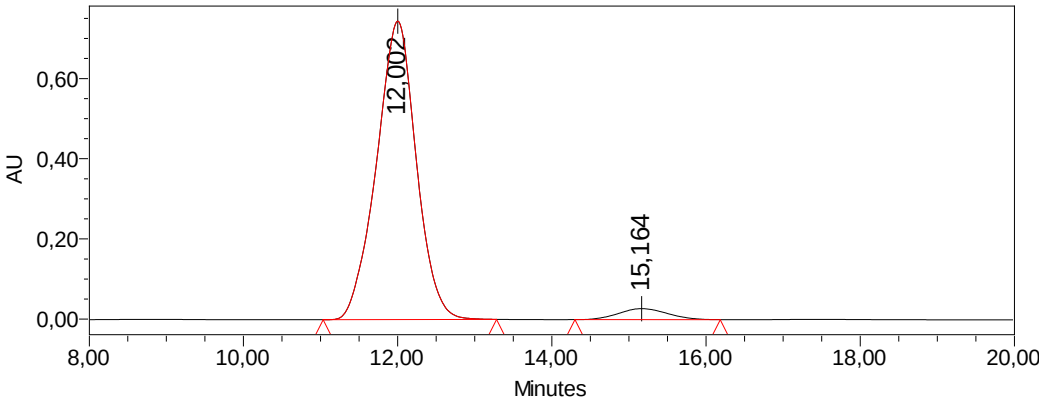
(*R*)-2-(Benzylthio)-1-(*tert*-butyloxycarbonyl)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-phenyl-1*H*-imidazol-4(5*H*)-one (46H)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 12.0 min (major.) and 15.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

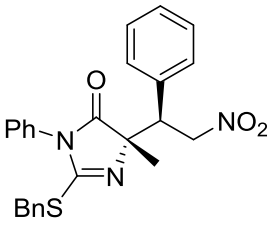


	Retention Time	% Area
1	11.678	50.12
2	14.601	49.88

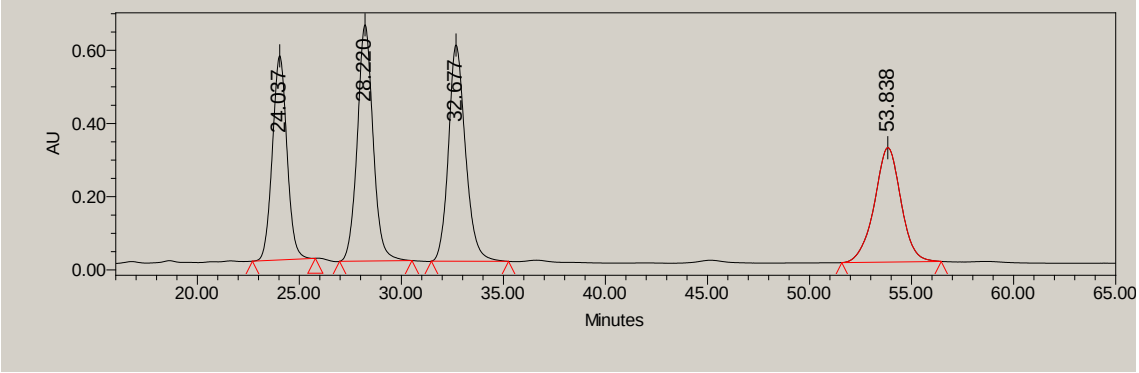


	Retention Time	% Area
1	12.002	95.67
2	15.164	4.33

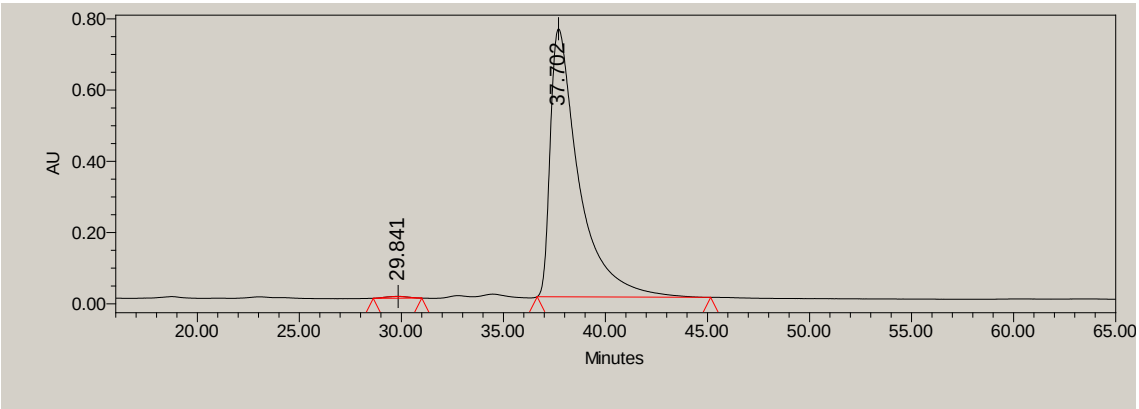
(*S*)-2-(Benzylthio)-4-methyl-4-((S)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 37.3 min (major.). Processed Channel Descr.: PDA 210.0 nm).

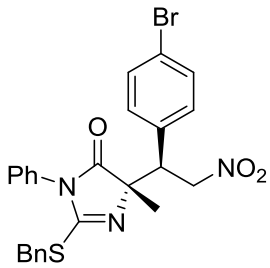


	Retention Time	% Area
1	24.037	22.62
2	28.220	27.42
3	32.677	27.77
4	53.838	20.14

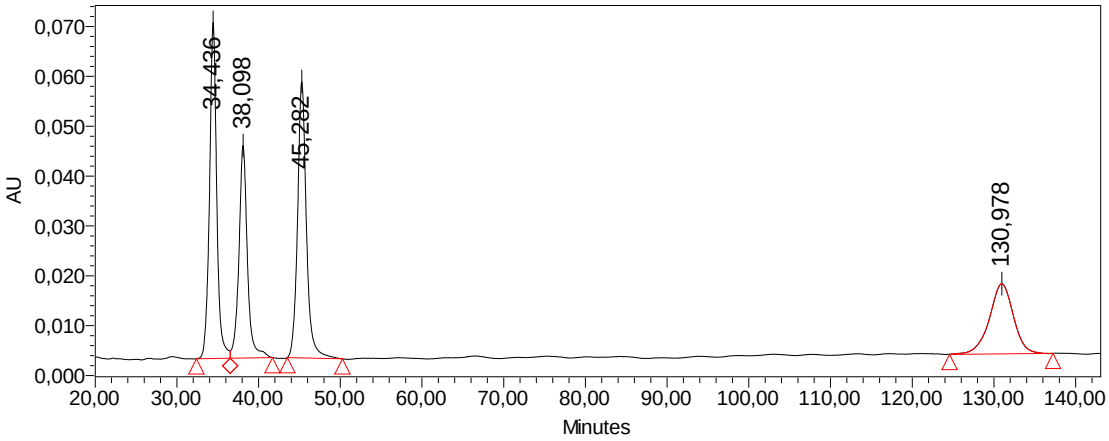


	Retention Time	% Area
1	29.841	0.52
2	37.702	99.48

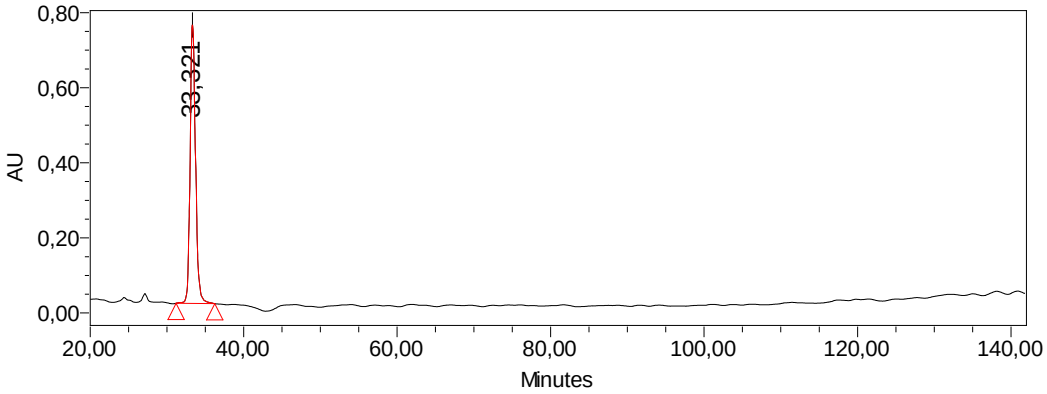
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ab)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 33.3 min (major.). Processed Channel Descr.: PDA 210.0 nm).

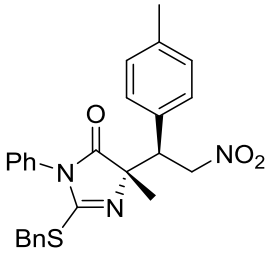


	Retention Time	% Area
1	34.436	29.02
2	38.098	21.61
3	45.282	29.22
4	13.978	20.14

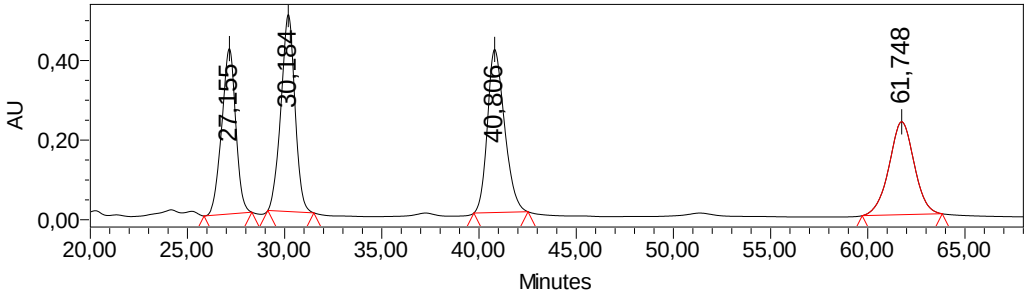


	Retention Time	% Area
1	33.321	100.00

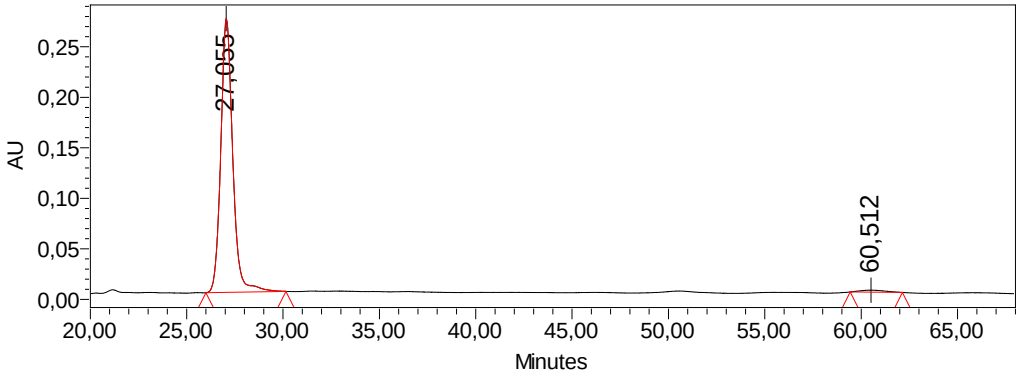
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ac)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 27.1 min (major.) and 60.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

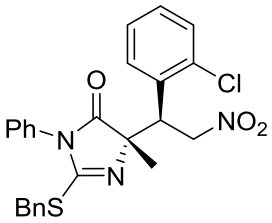


	Retention Time	% Area
1	27.155	22.63
2	30.184	27.11
3	40.806	27.40
4	61.748	22.86

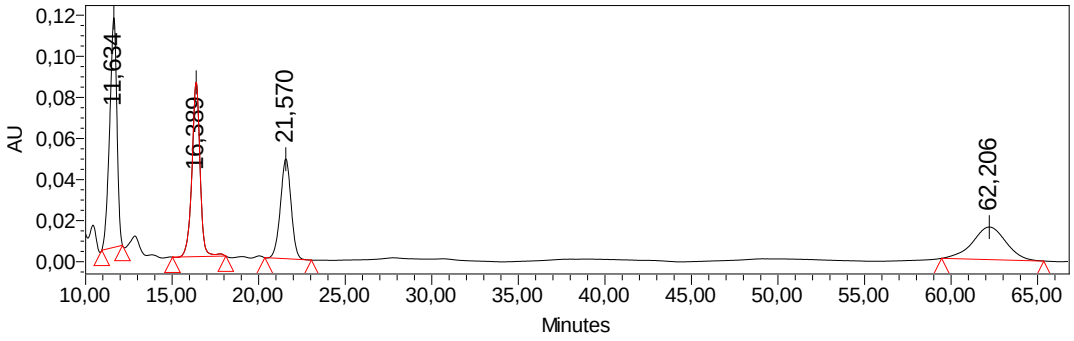


	Retention Time	% Area
1	27.055	98.52
2	60.512	1.48

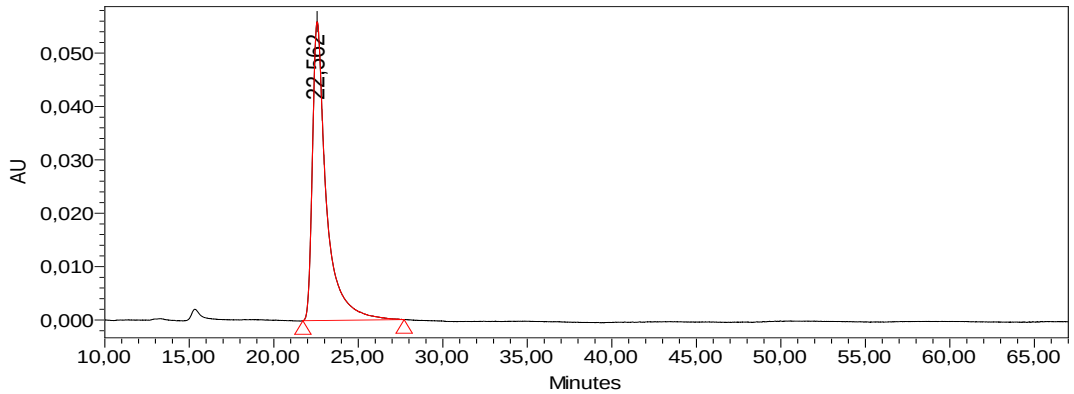
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ad)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 1.0 mL/min, retention times: 22.6 min (major.). Processed Channel Descr.: PDA 210.0 nm).

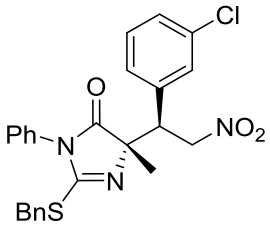


	Retention Time	% Area
1	11.634	31.60
2	16.389	27.14
3	21.570	20.39
4	62.206	20.87

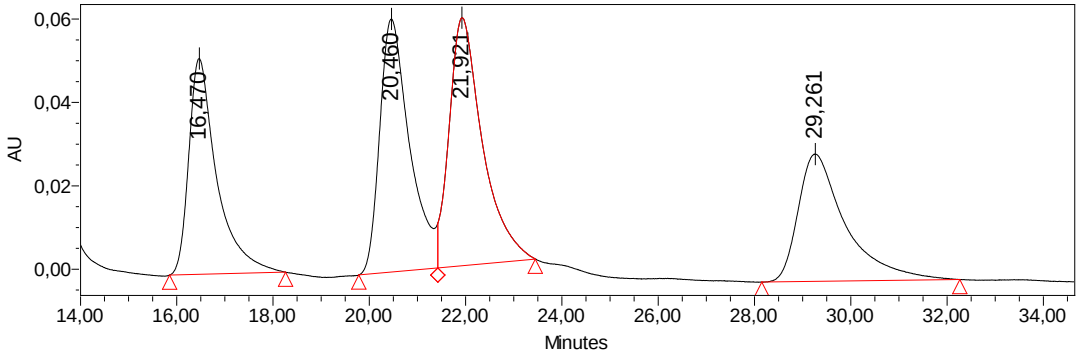


	Retention Time	% Area
1	22.562	100.00

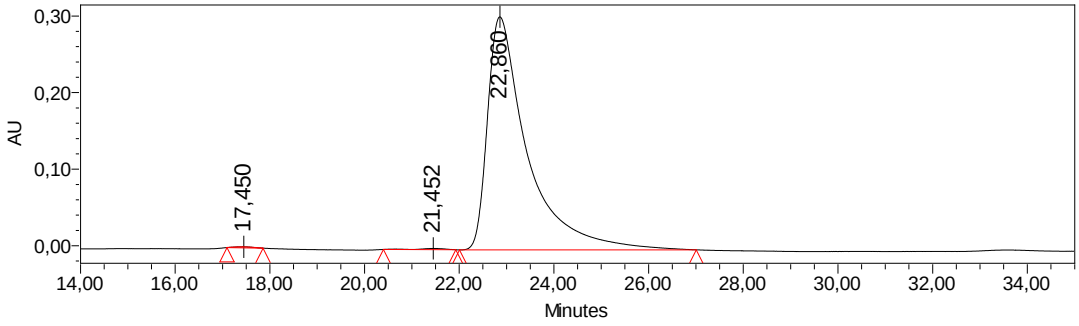
(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ae)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 1.0 mL/min, retention times: 22.9 min (major.) and 21.5 min (min.).Processed Channel Descr.: PDA 210.0 nm).

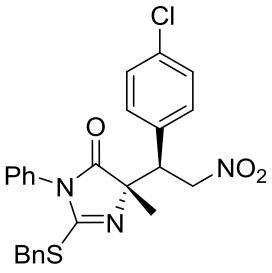


	Retention Time	% Area
1	16.470	21.57
2	20.460	27.23
3	21.921	29.64
4	29.261	21.56

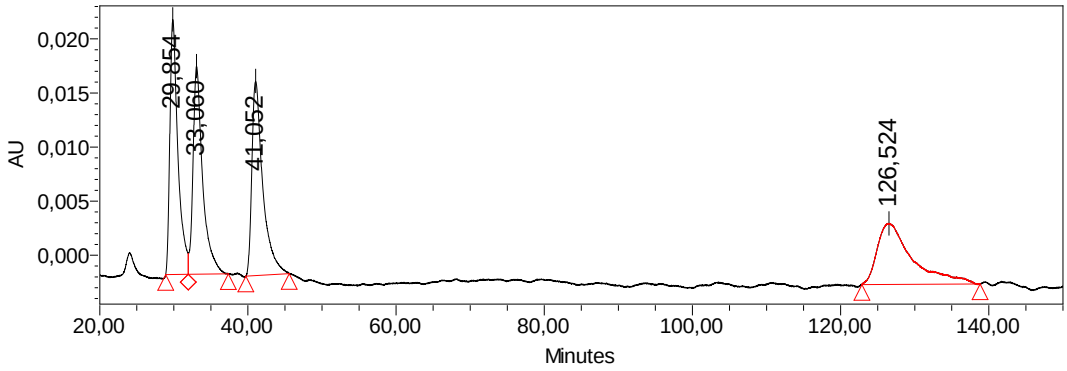


	Retention Time	% Area
1	17.450	0.20
2	21.452	0.33
3	22.860	99.47

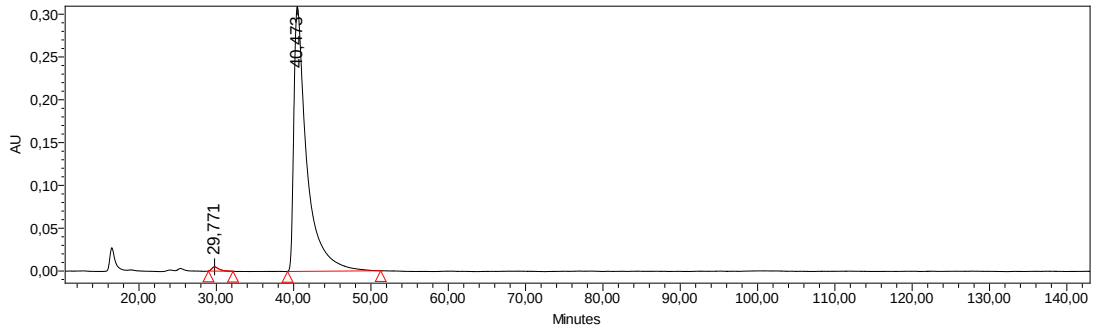
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Aj)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 1.0 mL/min, retention times: 40.5 min (major.). Processed Channel Descr.: PDA 210.0 nm).

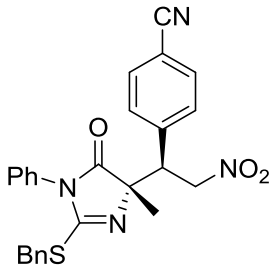


	Retention Time	% Area
1	29.854	24.57
2	30.060	24.10
3	41.052	25.55
4	126.524	25.78

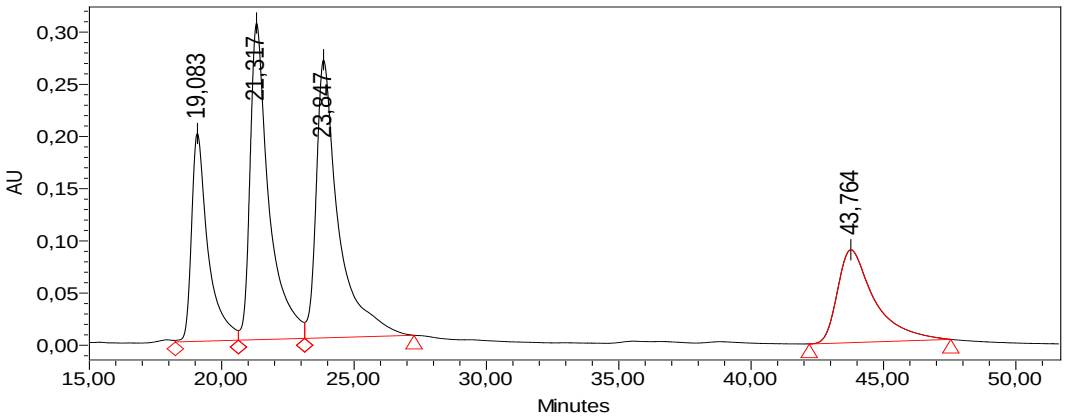


	Retention Time	% Area
1	29.771	0.91
2	40.479	99.09

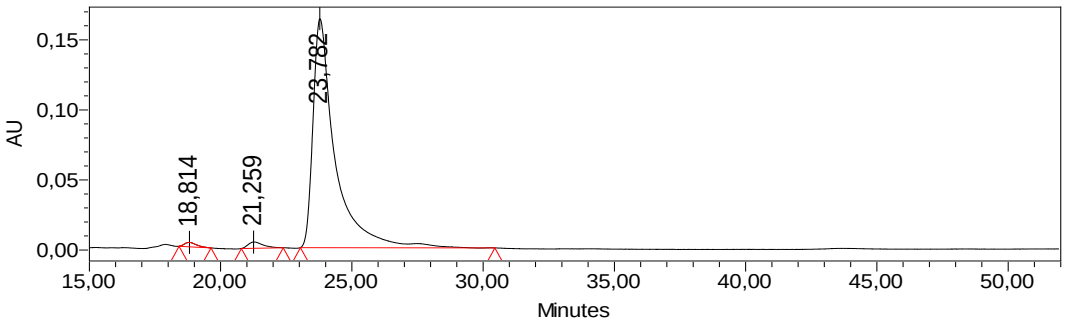
4-((*S*)-1-((*S*)-2-(Benzylthio)-4-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)-2-nitroethyl)benzonitrile (67Ak)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 23.8 min (major.) and 21.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

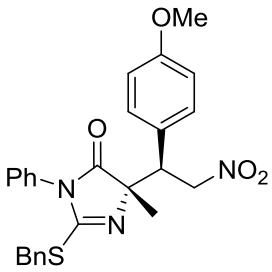


	Retention Time	% Area
1	19.083	18.03
2	21.317	31.43
3	23.847	32.53
4	43.764	18.01

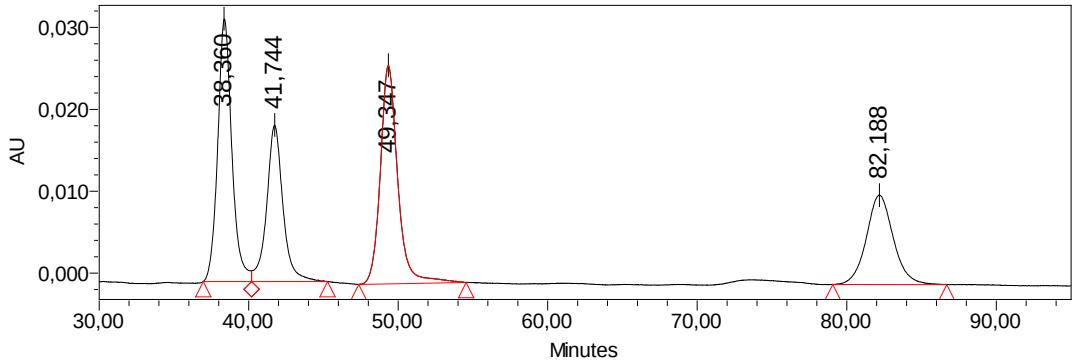


	Retention Time	% Area
1	18.814	0.99
2	21.259	1.80
3	23.782	97.21

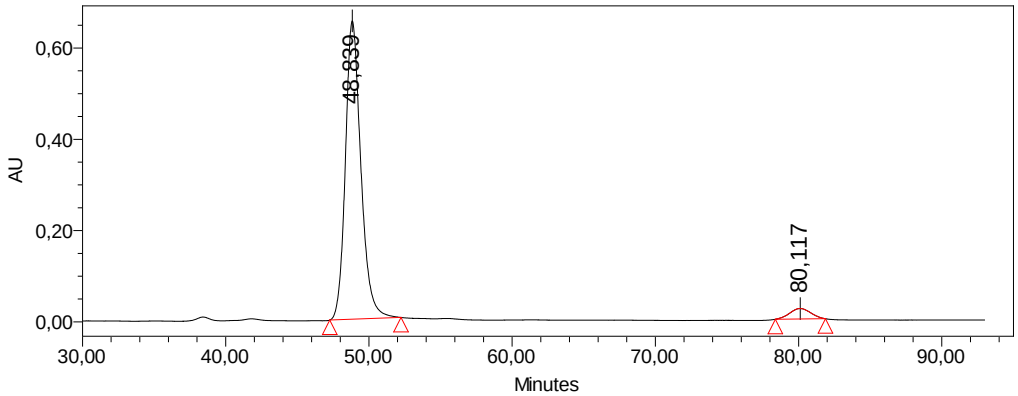
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Al)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 48.9 min (major.). Processed Channel Descr.: PDA 210.0 nm).

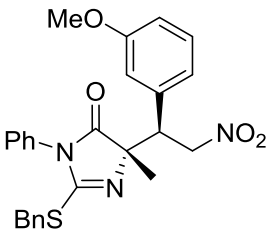


	Retention Time	% Area
1	38.360	29.71
2	41.744	20.44
3	49.347	30.47
4	82.188	19.37

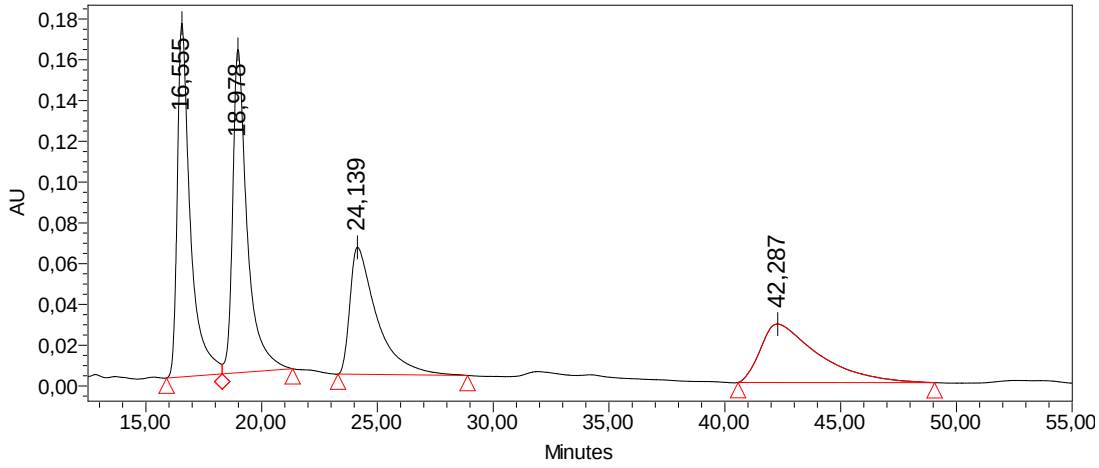


	Retention Time	% Area
1	48.839	95.55
2	80.117	4.45

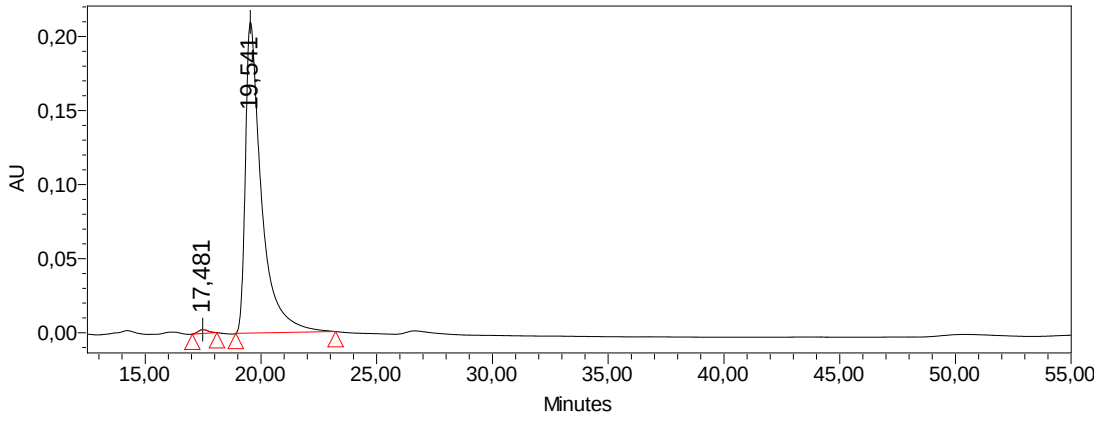
(*S*)-2-(Benzylthio)-4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Am)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate = 1.0 mL/min, retention times: 19.5 min (major.) and 17.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

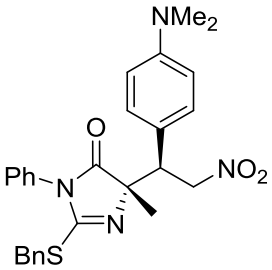


	Retention Time	% Area
1	16.555	28.58
2	18.978	29.16
3	24.139	21.24
4	42.287	21.01

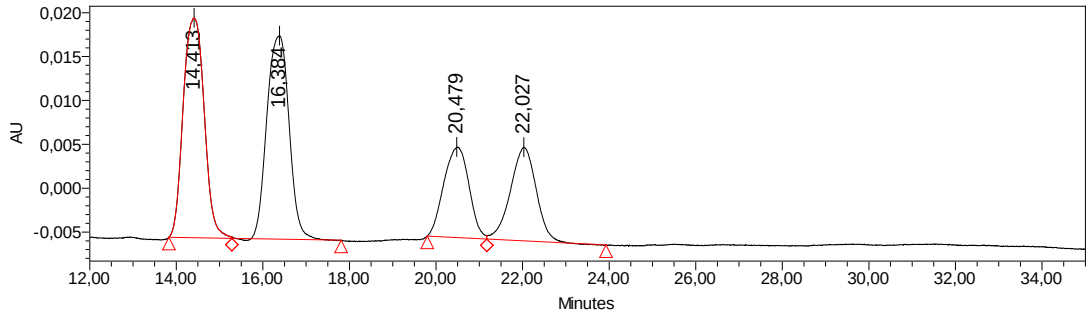


	Retention Time	% Area
1	17.481	0.79
2	19.541	99.21

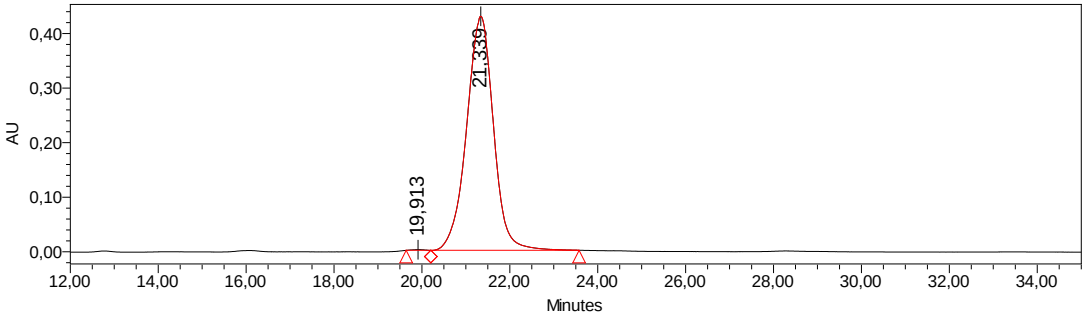
(*S*)-2-(Benzylthio)-4-((*S*)-1-(4-(dimethylamino)phenyl)-2-nitroethyl)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (67An)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times for major diastereoisomer: 21.3 min (major.) and 19.9 min (min.). Processed Channel Descr.: PDA 210.0 nm).

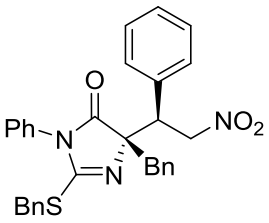


	Retention Time	% Area
1	14.413	33.30
2	16.384	32.78
3	20.479	16.42
4	22.027	17.51

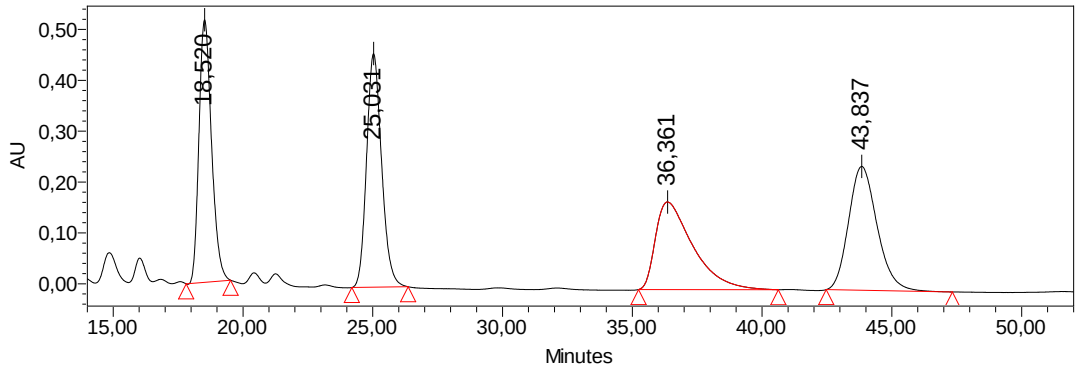


	Retention Time	% Area
1	19.913	0.13
2	21.339	99.87

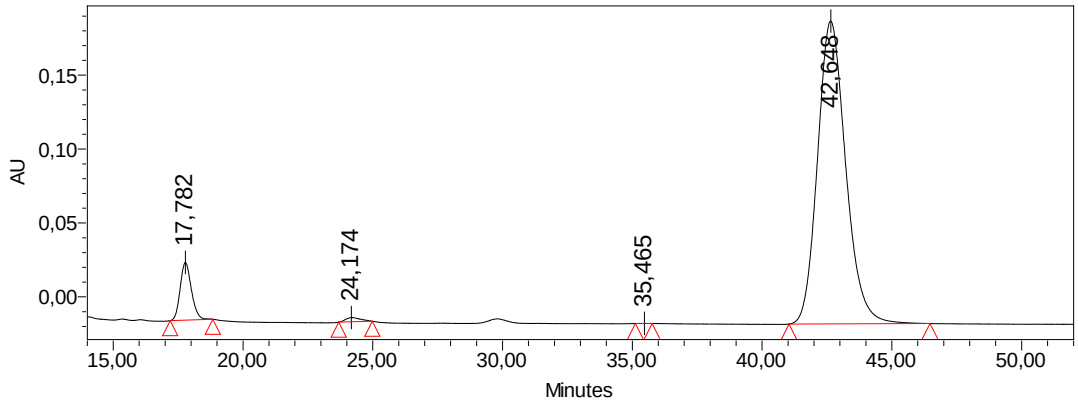
(*S*)-4-Benzyl-2-(benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 42.6 min (major.) and 24.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

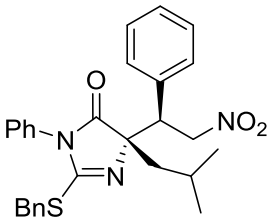


	Retention Time	% Area
1	18.520	25.93
2	25.031	24.03
3	36.361	25.77
4	43.837	24.26

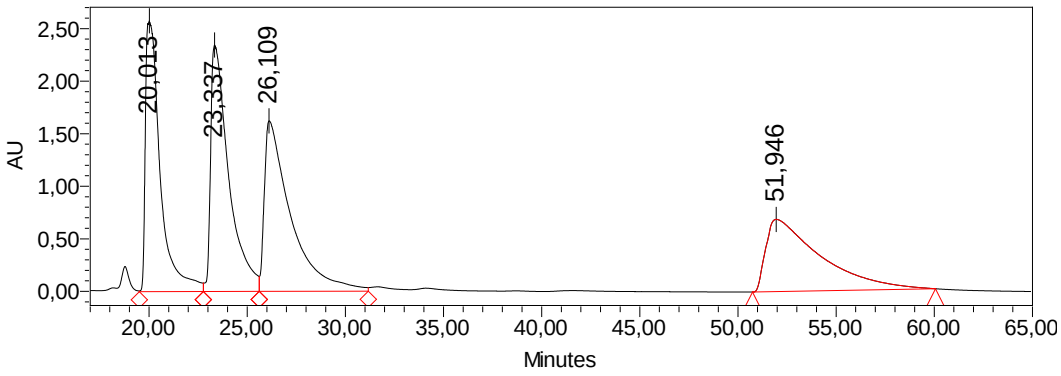


	Retention Time	% Area
1	17.782	6.98
2	24.174	0.68
3	35.465	0.01
4	42.648	92.32

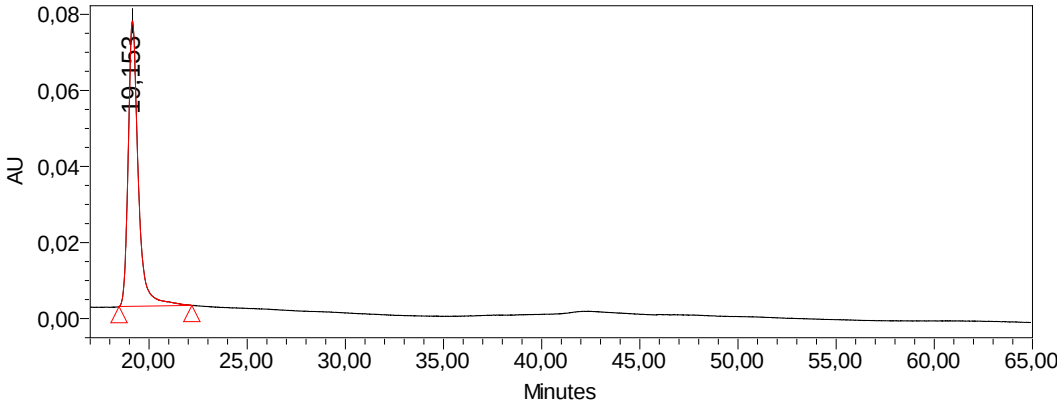
(*S*)-2-(Benzylthio)-4-isobutyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Da)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 19.1 min (major.). Processed Channel Descr.: PDA 210.0 nm).

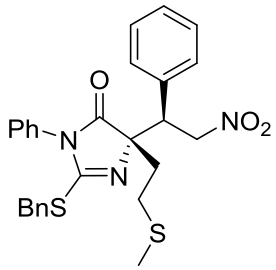


	Retention Time	% Area
1	20.013	23.85
2	23.337	26.36
3	26.109	26.50
4	51.946	23.28

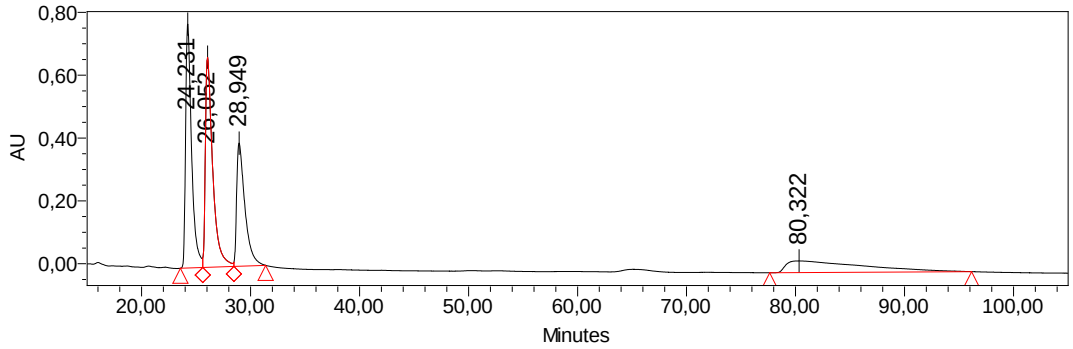


	Retention Time	% Area
1	19.153	100.00

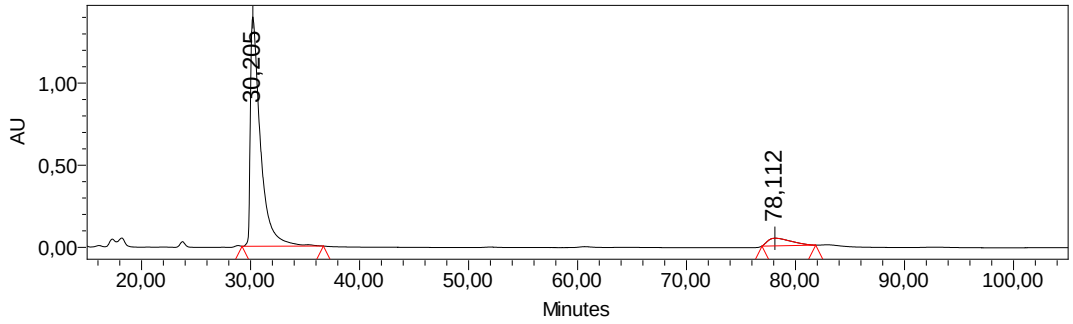
(*S*)-2-(Benzylthio)-4-(2-(methylthio)ethyl)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (67Fa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IB, hexane/ethanol 90/10, flow rate = 0.5 mL/min, retention times: 30.2 min (major.). Processed Channel Descr.: PDA 210.0 nm).

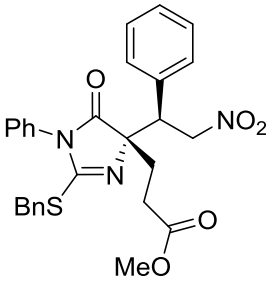


	Retention Time	% Area
1	24.231	29.67
2	26.052	31.37
3	28.949	20.62
4	80.322	18.33

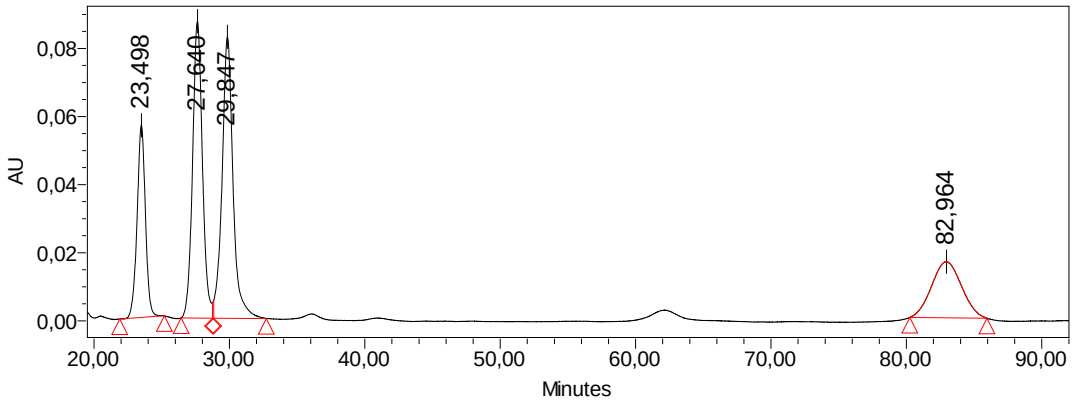


	Retention Time	% Area
1	30.205	92.74
2	78.112	7.26

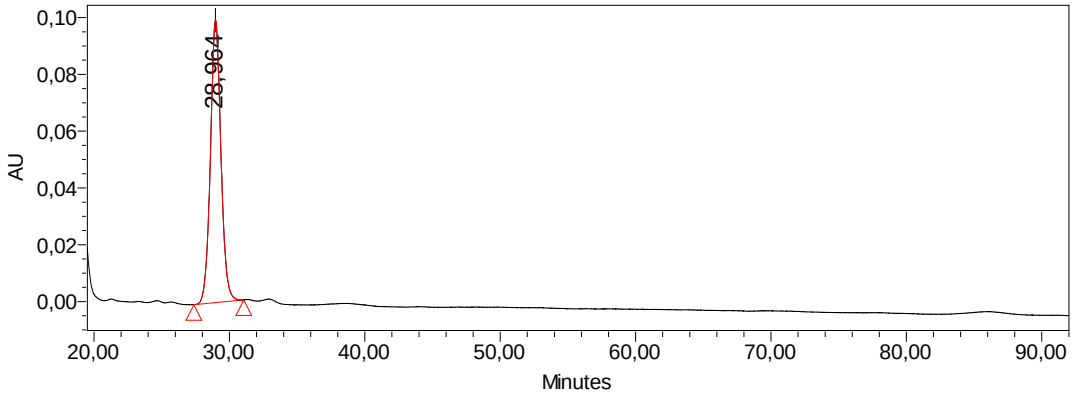
Methyl 3-((*S*)-2-(Benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-5-oxo-1-phenyl-4,5-dihydro-1*H*-imidazol-4-yl)propanoate (67Ia)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 95/5, flow rate = 1.0 mL/min, retention times: 29.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

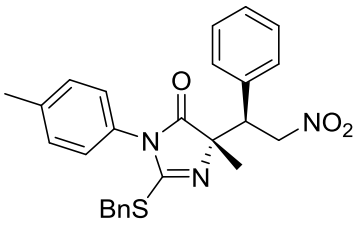


	Retention Time	% Area
1	23.498	18.17
2	27.640	17.28
3	29.847	33.18
4	82.964	31.38

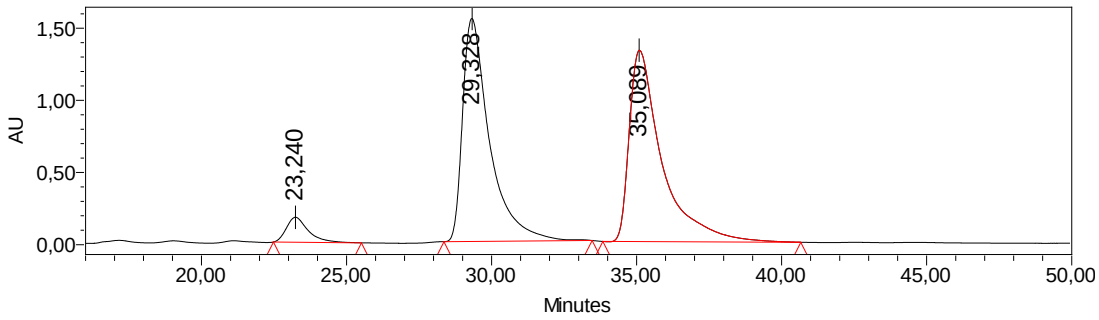


	Retention Time	% Area
1	28.964	100.00

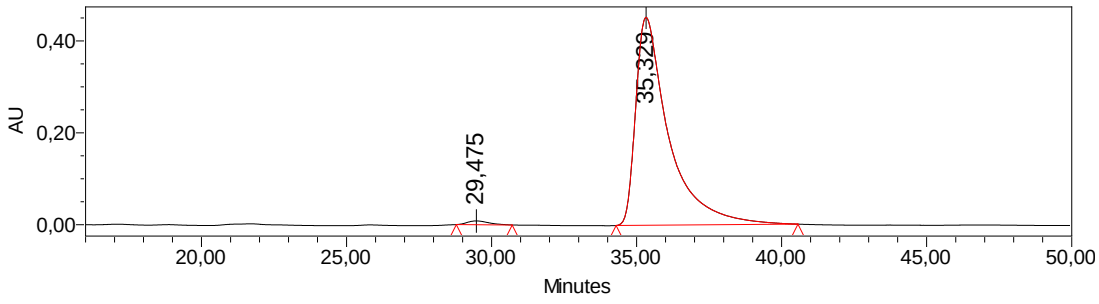
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (68Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 35.3 min (major.) and 29.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

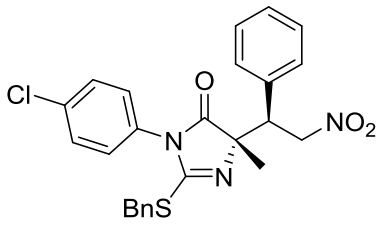


	Retention Time	% Area
1	23.240	4.26
2	29.326	47.03
3	35.089	48.71

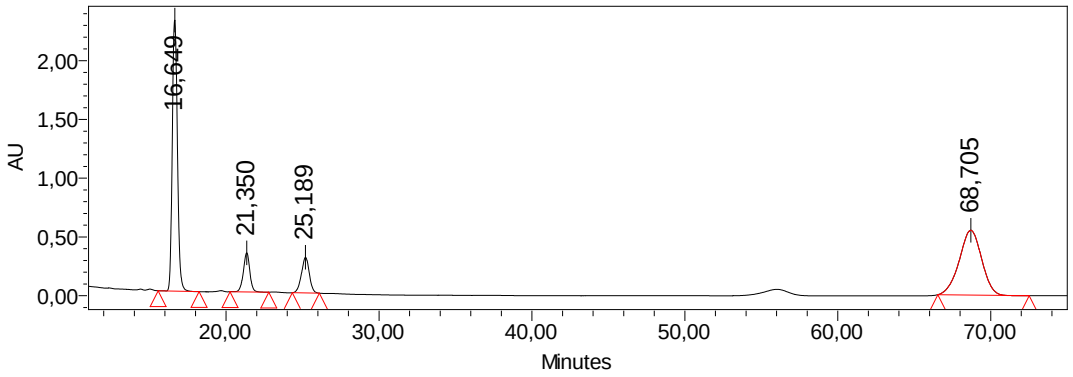


	Retention Time	% Area
1	29.475	1.18
2	35.329	98.82

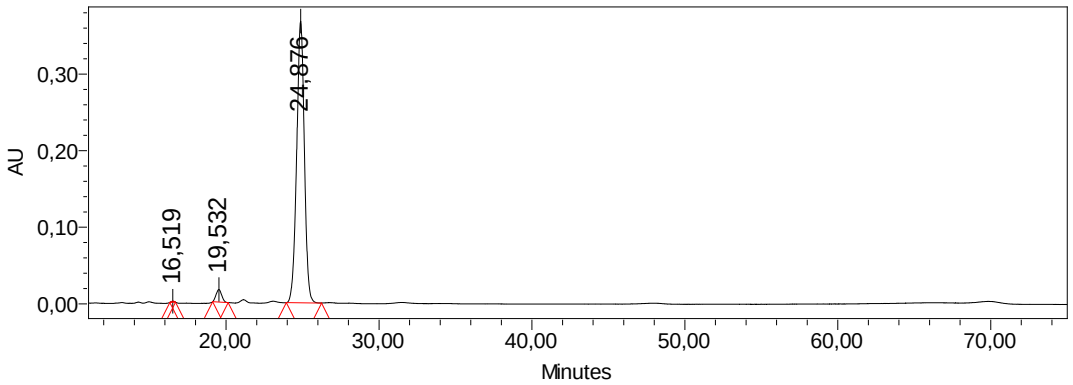
(*S*)-2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (69Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 24.9 min (major.) and 19.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

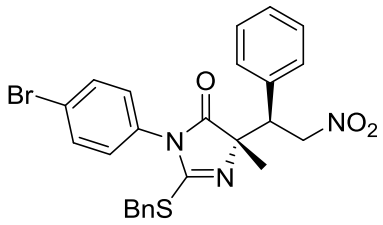


	Retention Time	% Area
1	16.649	41.22
2	21.350	7.48
3	25.189	8.35
4	68.705	42.96

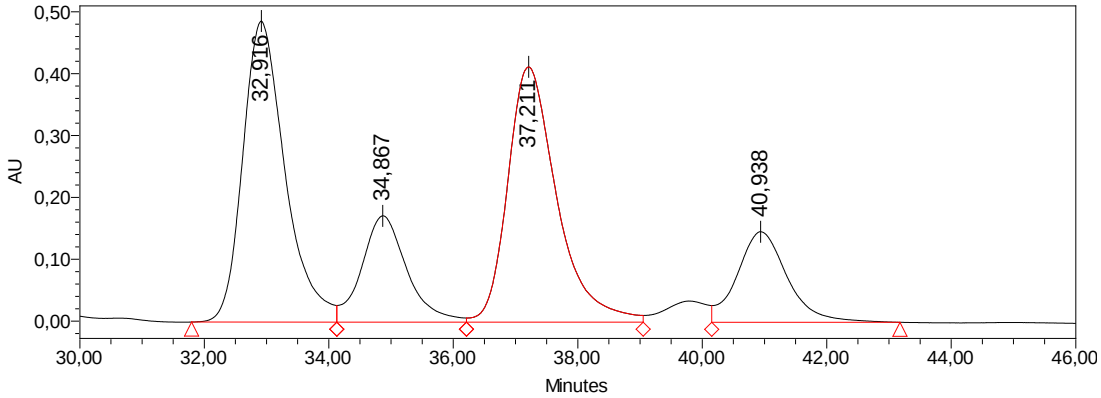


	Retention Time	% Area
1	16.519	0.16
2	19.532	3.14
3	24.876	96.70

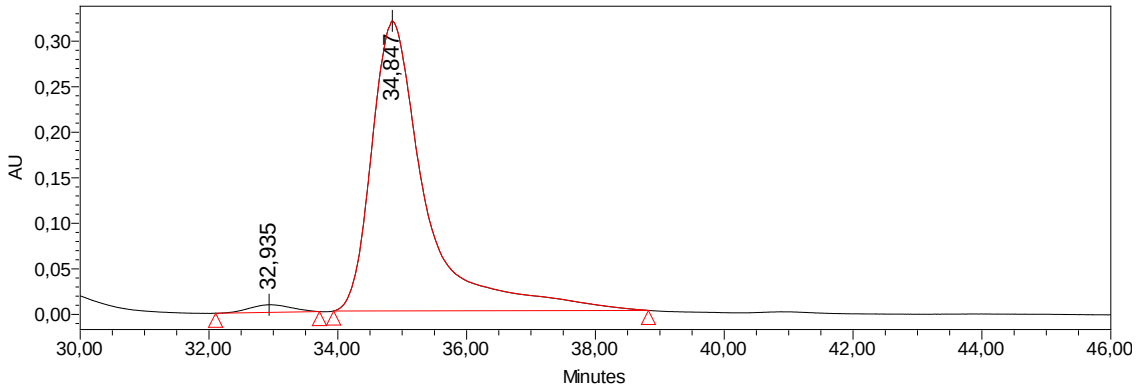
(*S*)-2-(Benzylthio)-1-(4-bromophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (70Aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 34.8 min (major.). Processed Channel Descr.: PDA 210.0 nm).

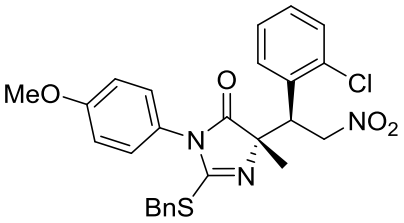


	Retention Time	% Area
1	32.916	36.79
2	34.867	13.84
3	37.211	36.30
4	40.938	13.06

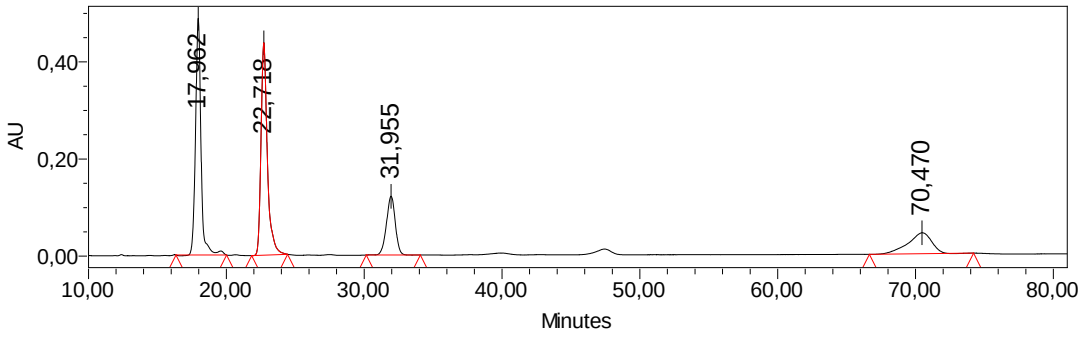


	Retention Time	% Area
1	32.935	1.98
2	34.847	98.02

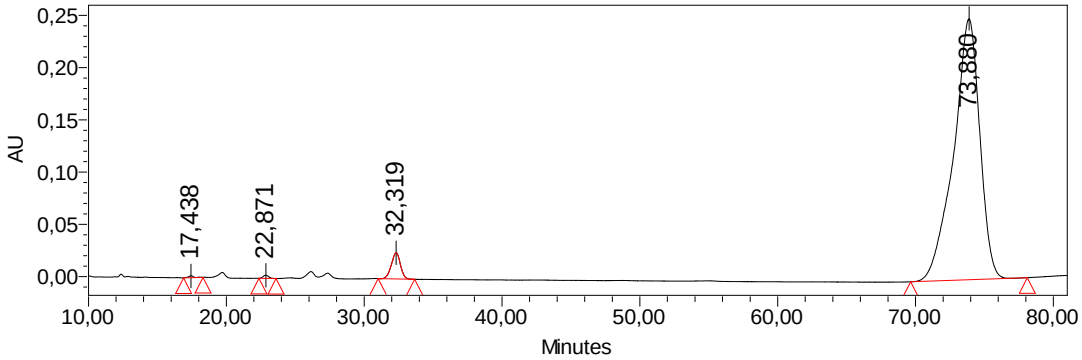
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (71Ad)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 73.9 min (major.) and 32.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

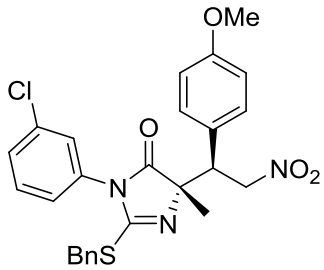


	Retention Time	% Area
1	17.962	35.53
2	22.718	36.56
3	31.955	14.16
4	70.470	13.76

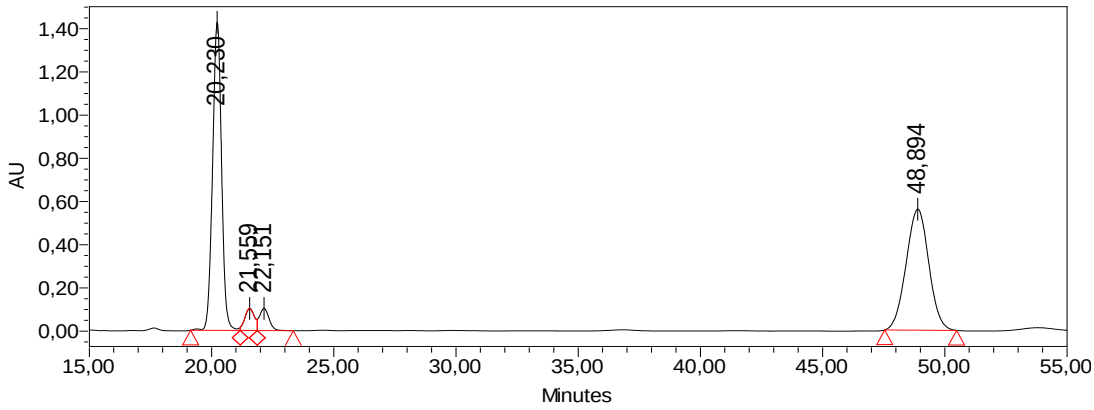


	Retention Time	% Area
1	17.438	0.13
2	22.871	0.24
3	32.319	3.35
4	73.880	96.28

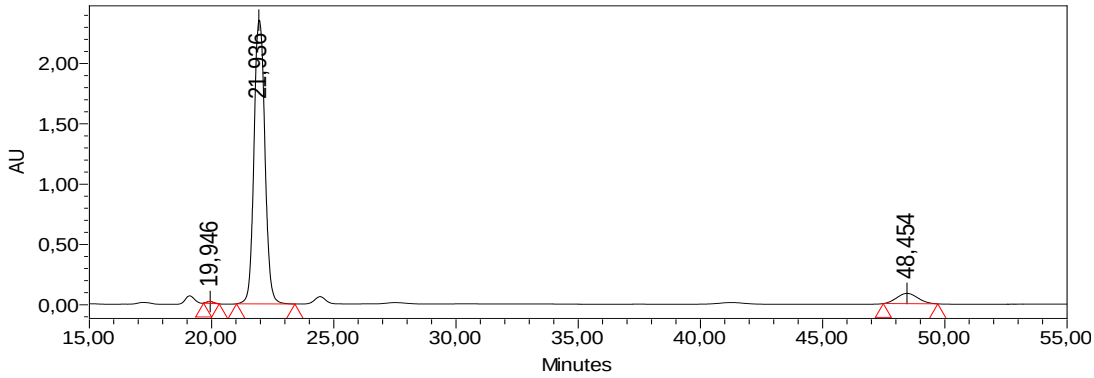
(*S*)-2-(Benzylthio)-1-(3-chlorophenyl)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (72Al)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 21.9 min (major.) and 48.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

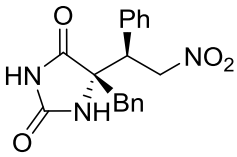


	Retention Time	% Area
1	20.280	46.58
2	21.559	3.57
3	22.151	3.62
4	48.894	46.23

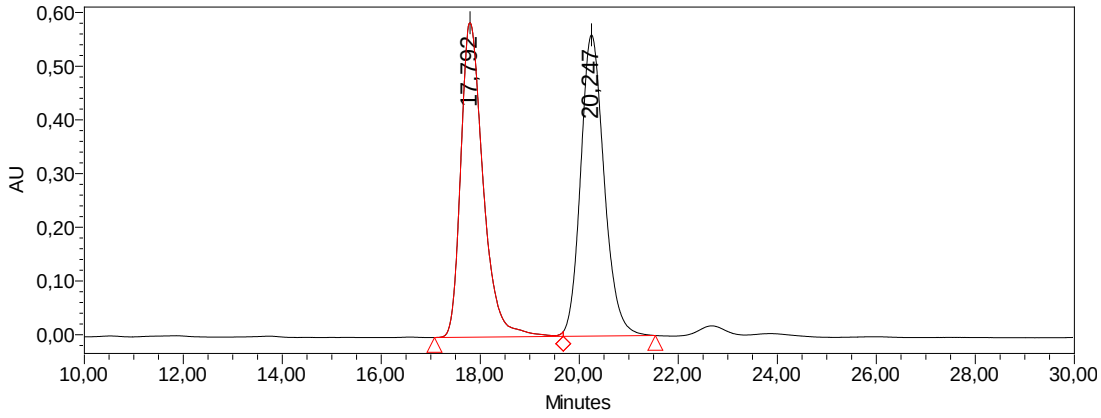


	Retention Time	% Area
1	19.946	0.41
2	21.936	93.06
3	48.454	6.53

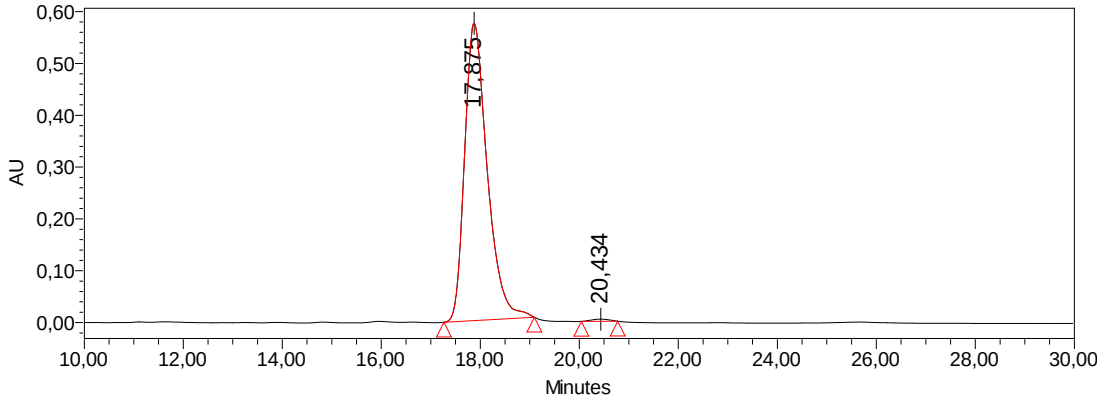
(*S*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (48)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate = 0.5 mL/min, retention times: 17.9 min (major.) and 20.4 min (min.). Processed Channel Descr.: PDA 210.0 nm).

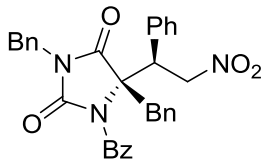


	Retention Time	% Area
1	17.792	49.88
2	20.247	50.12

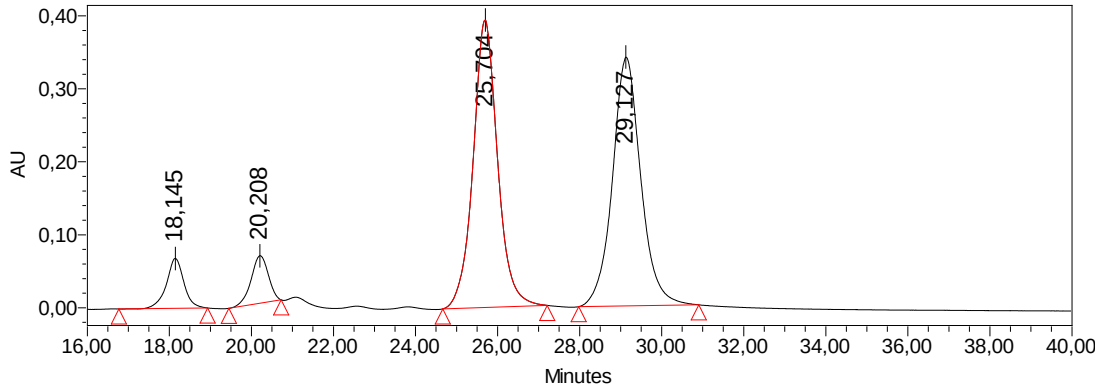


	Retention Time	% Area
1	17.875	99.43
2	20.434	0.57

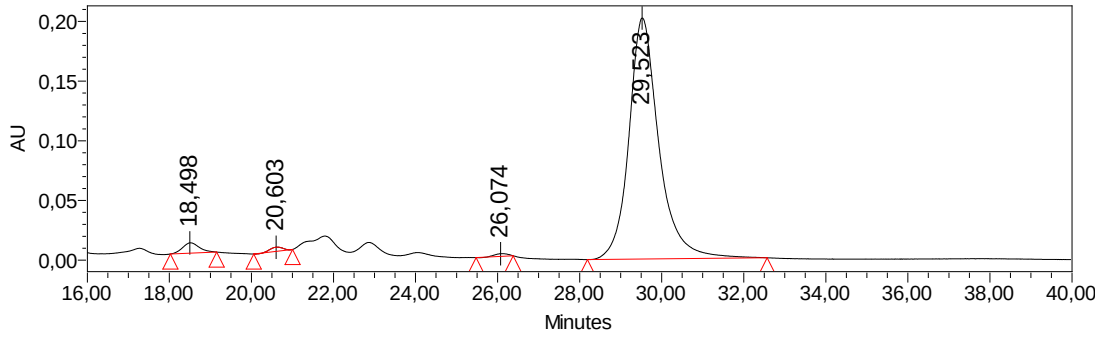
(*S*)-1-Benzoyl-3,5-dibenzyl-5-((*S*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (49)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 29.5 min (major.) and 26.1 min (min.). Processed Channel Descr.: PDA 210.0 nm).

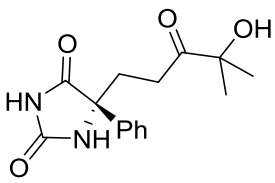


	Retention Time	% Area
1	18.145	5.54
2	20.208	5.21
3	25.704	44.55
4	29.127	44.69

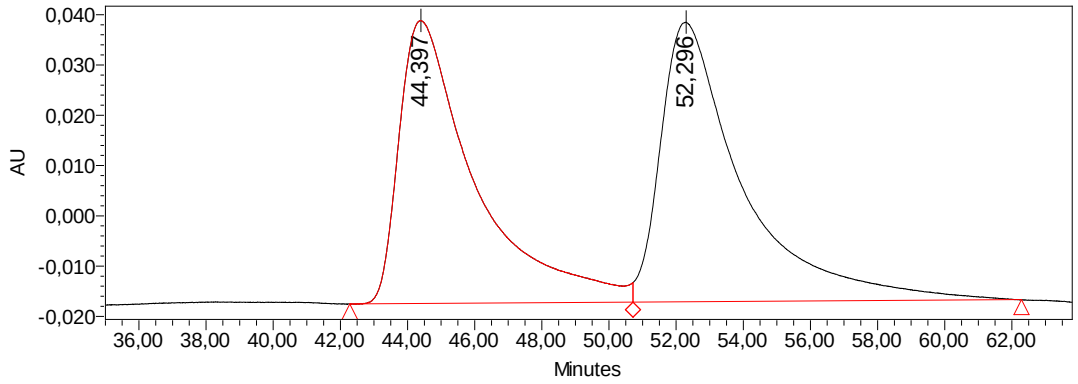


	Retention Time	% Area
1	18.498	2.31
2	20.603	0.73
3	26.074	0.52
4	29.523	96.44

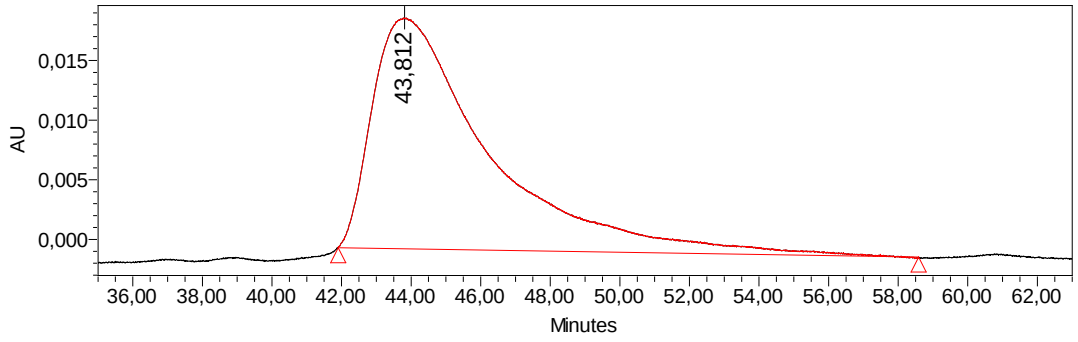
(*R*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-5-phenylimidazolidine-2,4-dione (50)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 44.4 min (major.). Processed Channel Descr.: PDA 210.0 nm).

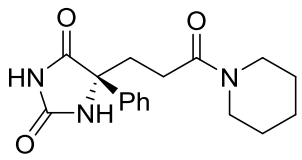


	Retention Time	% Area
1	44.397	48.61
2	52.296	51.39

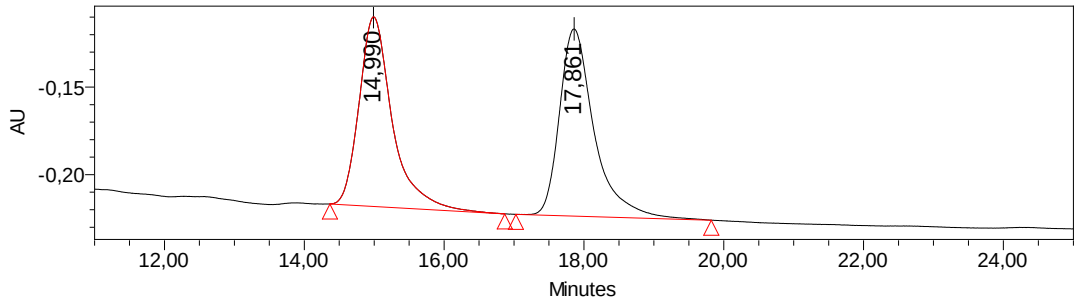


	Retention Time	% Area
1	43.812	100,00

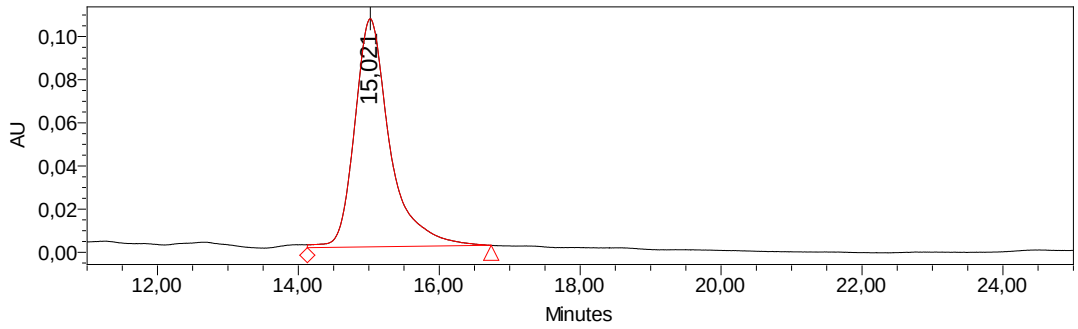
(*R*)-5-(3-Oxo-3-(piperidin-1-yl)propyl)-5-phenylimidazolidine-2,4-dione (52)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 50/50, flow rate = 0.5 mL/min, retention times: 15.0 min (major.). Processed Channel Descr.: PDA 210.0 nm).

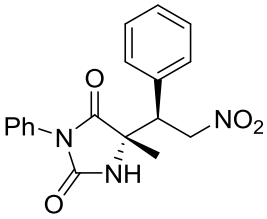


	Retention Time	% Area
1	14.990	49.26
2	17.861	50.74

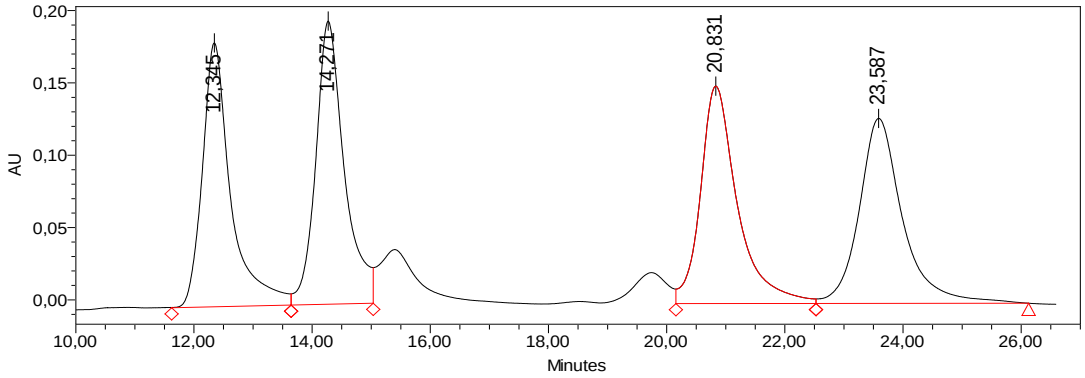


	Retention Time	% Area
1	15.021	100.00

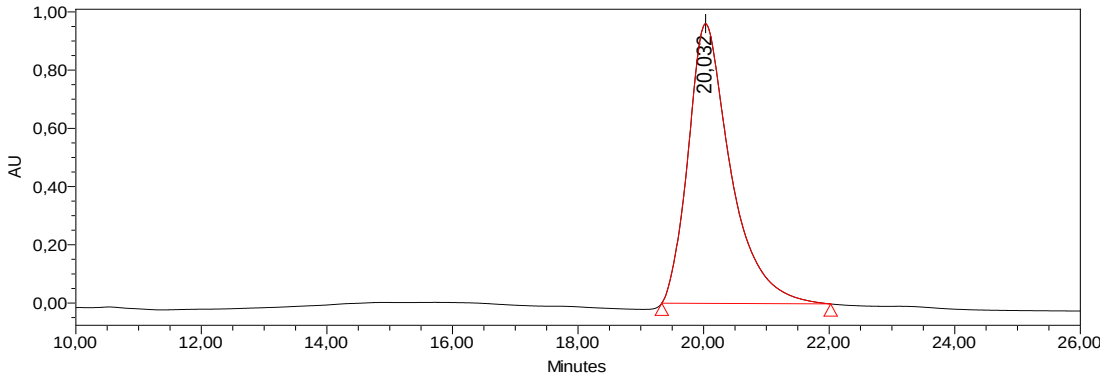
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (73)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 20.8 min (major.). Processed Channel Descr.: PDA 210.0 nm).

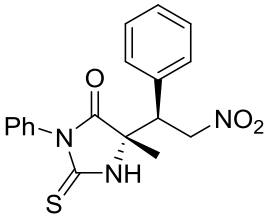


	Retention Time	% Area
1	12.345	23.67
2	14.271	25.54
3	20.831	25.40
4	23.587	25.38

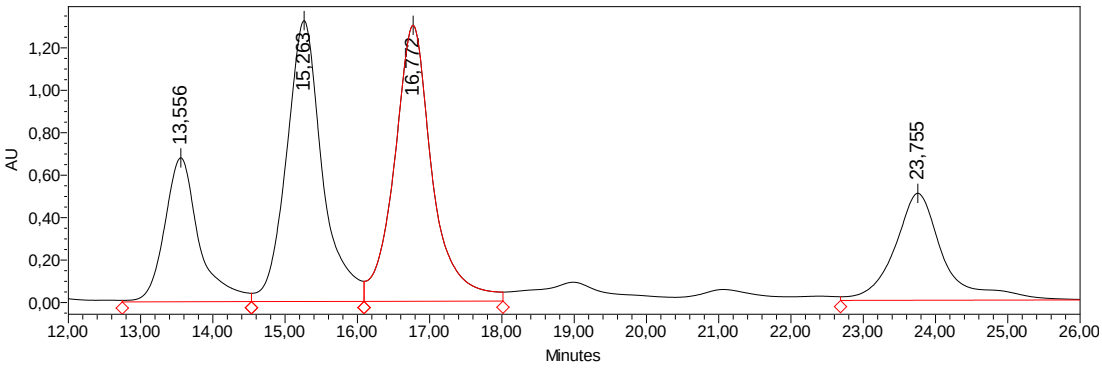


	Retention Time	% Area
1	20.032	100.00

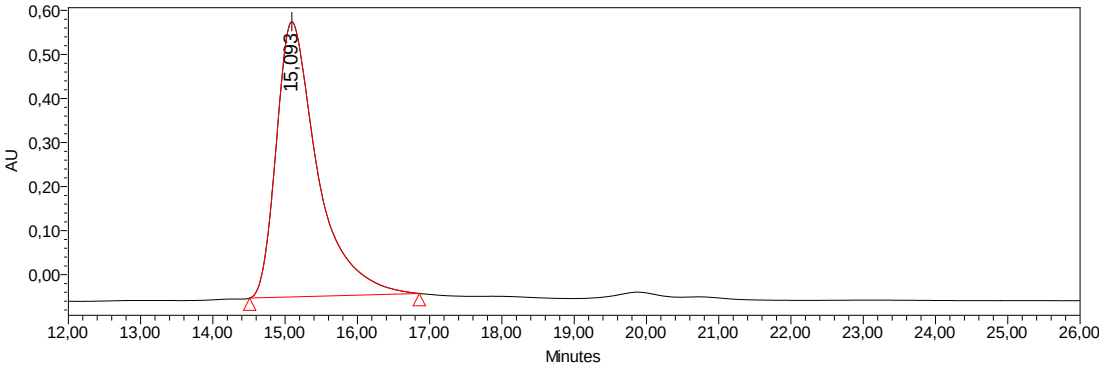
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenyl-2-thioxoimidazolidin-4-one (74)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate = 0.5 mL/min, retention times: 15.1 min (major.). Processed Channel Descr.: PDA 210.0 nm).

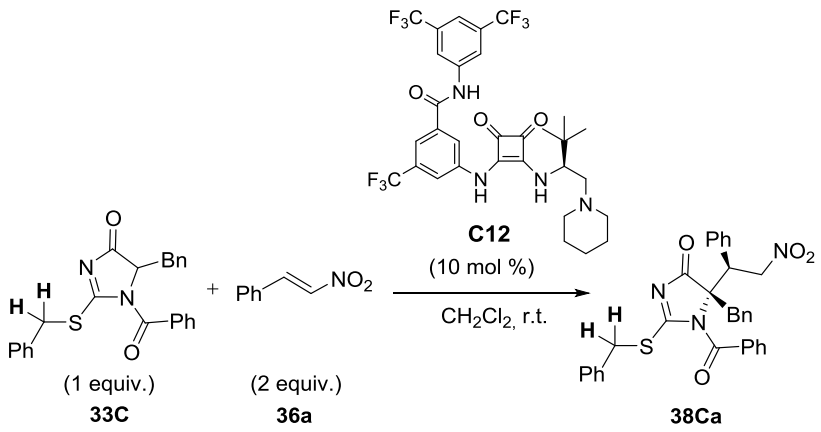


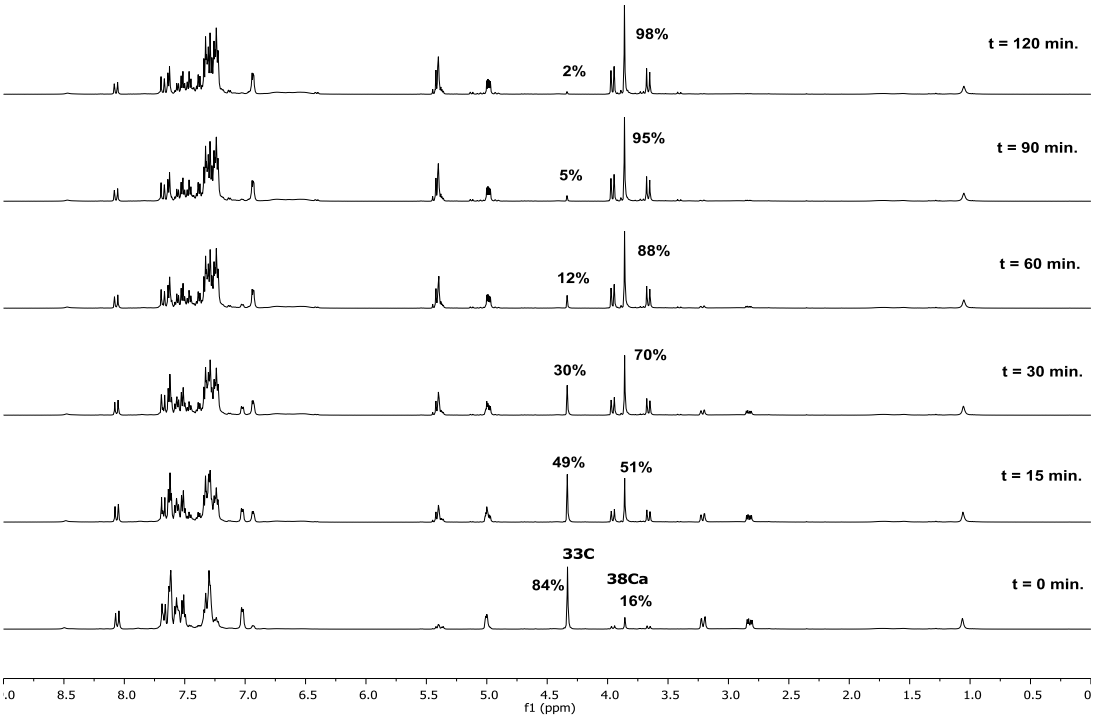
	Retention Time	% Area
1	13.556	16.06
2	15.263	32.65
3	16.772	34.18
4	23.755	17.11



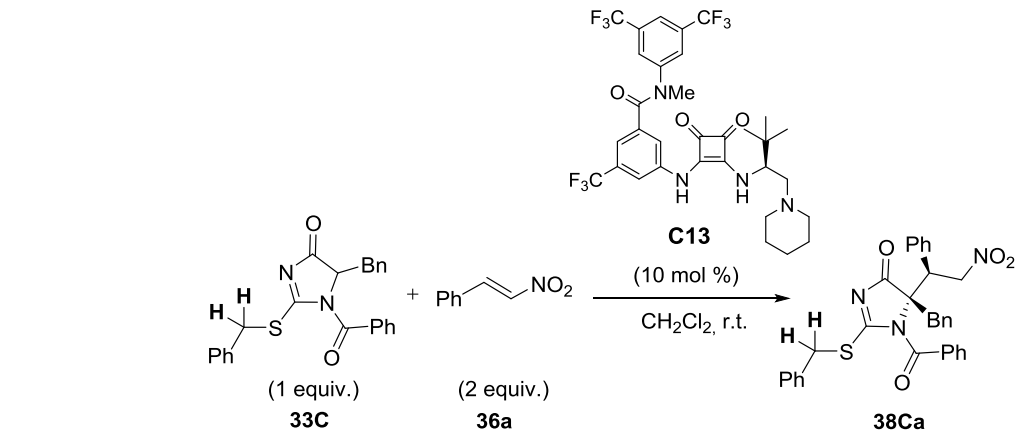
	Retention Time	% Area
1	15.093	100.00

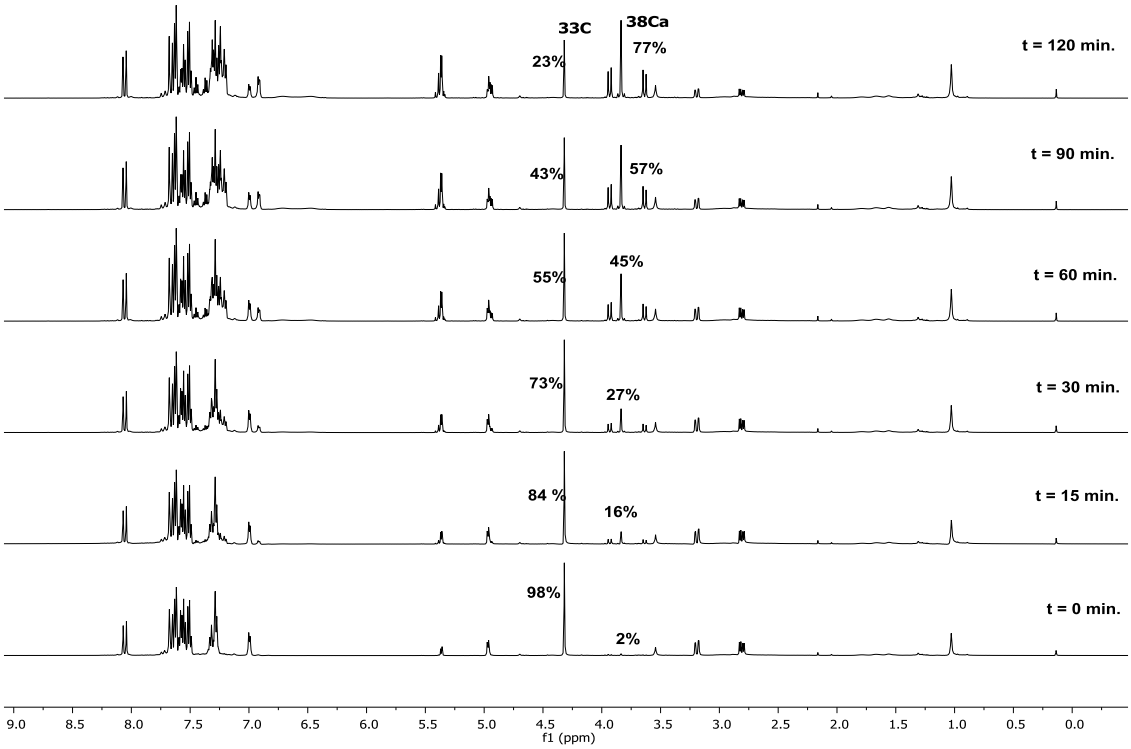
5.4.13. Kinetic studies





The reaction was performed in the NMR tube using 20 mg (1. eq., 0.05 mmol) of **33C**, 15 mg (2 eq, 0.1 mmol) of nitrostyrene **36a** and 10 mol % of catalyst **C12** (0.005 mmol, 3.46 mg) in 0.5 mL CD_2Cl_2. The reaction mixture was partially soluble and the measurements were made every 15 minutes.





The reaction was performed in the NMR tube using 20 mg (1. eq., 0.05 mmol) of **33C**, 15 mg (2 eq, 0.1 mmol) of nitrostyrene **36a** and 10 mol % of catalyst **C13** (0.005 mmol, 3.4 mg) in 0.5 mL CD_2Cl_2. The reaction mixture was completely soluble and the measurements were made every 15 minutes.

PUBLICATIONS

Asymmetric Catalysis

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Catalytic Enantioselective Synthesis of N,C$^{\alpha}$,C$^{\alpha}$-Trisubstituted α-Amino Acid Derivatives Using 1*H*-Imidazol-4(5*H*)-ones as Key Templates**

*Julen Etxabe, Joseba Izquierdo, Aitor Landa, Mikel Oiarbide, and Claudio Palomo**

Abstract: *1H-Imidazol-4(5H)-ones are introduced as novel nucleophilic α-amino acid equivalents in asymmetric synthesis. These compounds not only allow highly efficient construction of tetrasubstituted stereogenic centers, but unlike hitherto known templates, provide direct access to N-substituted (alkyl, allyl, aryl) α-amino acid derivatives.*

Because of the continuous interest in α,α-disubstituted (quaternary) α-amino acids,[1] many methods for their stereoselective preparation have been reported,[1,2] but catalytic approaches still remain underdeveloped.[2d–f,3] A major catalytic, enantioselective entry to quaternary NH α-amino acids consists of the α-functionalization of a nucleophilic template, for example, either an α-iminoester or azlactone, and subsequent hydrolysis (Figure 1a).[4] However, the majority of these methods are unable to afford the N-substituted analogues directly,[5] and an additional N-alkylation process is required.[6] This limitation is unfortunate since N-methyl (or superior N-alkyl) α-amino-acid-derived compounds are potential therapeutic candidates owing to their comparatively higher lipophilicity and membrane permeability.[7] We hypothesized that 1*H*-imidazol-4(5*H*)-ones might serve as appropriate templates for addressing this deficiency (Figure 1b): 1) the NR^2 group would be easily pre-installed, 2) base-catalyzed enolization appears suitable (aromatic enolate formation), and 3) unlike azlactones and related heterocycles, the new template would not present the Cα/Cγ selectivity complication.[8] However, this realization would require effective control of the stereochemistry of the C–C bond-forming step and, to the best of our knowledge, asymmetric reactions of 1*H*-imidazol-4(5*H*)-ones are unprecedented.

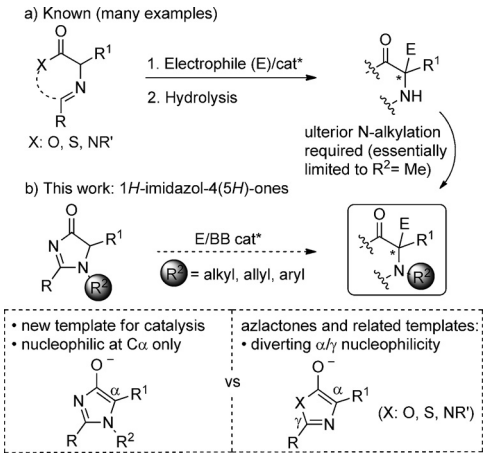
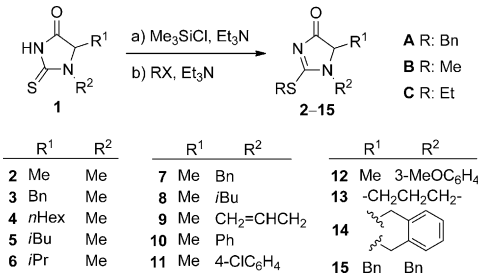


Figure 1. Enantioselective approaches to N,C$^{\alpha}$,C$^{\alpha}$-trisubstituted α-amino acid units. BB = Brønsted base.

For validation of the idea we selected the readily available 2-thio-1*H*-imidazol-4(5*H*)-ones **2**–**15** (Scheme 1)[9] whose base-catalyzed conjugate addition reaction[10] to nitroolefins[11] was evaluated first (Table 1). After examining several chiral Brønsted bases,[9] it was gratifying to find that by using the Rawal catalyst **C1**[12] the reactions of the N-methyl imidazolones **2A**–**6A** with nitroolefins (**16**) proceeded effectively in terms of yield and stereocontrol, regardless of the electron-neutral, electron-rich, and electron-poor character of either the β-aryl or heteroaryl substituent in **16** (entries 1–3 and 7–10). The reactions with β-alkyl-substituted nitroolefins (**16h**–**j**) using **C1** proceeded with poorer diastereocontrol, but it was improved by changing to the catalyst **C2**[13] (compare entries 4 and 6, 12 and 13, and 18 and 19), and the enantioselectivity for the major diastereomer was excellent in all the cases. The imidazolones **7A**–**12A**, bearing N-substituents other than methyl, for example, benzyl, allyl, isobutyl, phenyl, *p*-chlorophenyl, and *m*-methoxyphenyl,



Scheme 1. 1*H*-Imidazol-4(5*H*)-ones employed in this study.

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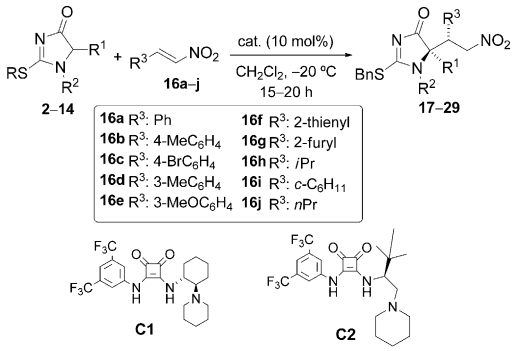
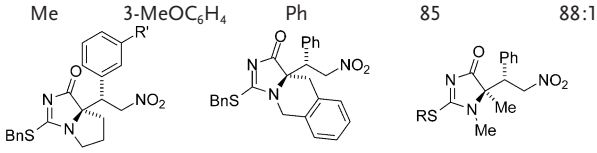
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501275.

Table 1: Catalytic reaction between imidazolones **2–14** and nitroolefins **16**.[a]



Entry	Prod.	R^1	R^2	R^3	Yield [%][b]	d.r. [%][c]	*ee* [%][d]
1	**17a**	Me	Me	Ph	97	93:7	99
2	**17b**	Me	Me	4-MeC_6H_4	91	90:10	96
3	**17c**	Me	Me	4-BrC_6H_4	82	94:6	98
4	**17h**	Me	Me	*i*Pr	66[e]	60:40	96
5					77[e,f]	50:50	−90
6					58[e,g]	80:20	−90
7	**18d**	Bn	Me	3-MeC_6H_4	82	92:8	95
8	**19a**	*n*Hex	Me	Ph	81	98:2	98
9	**20f**	*i*Bu	Me	2-thienyl	84	92:8	86
10	**21g**	*i*Pr	Me	2-furyl	75	93:7	92
11	**22a**	Me	Bn	Ph	85	98:2	98
12	**22i**	Me	Bn	*c*-C_6H_{11}	40[e]	75:25	94
13					40[e,f]	80:20	−90
14	**23a**	Me	*i*Bu	Ph	78	98:2	93
15	**24a**	Me	$CH_2CH{=}CH_2$	Ph	77	92:8	94
16					65[h]	90:10	95
17	**25a**	Me	Ph	Ph	65	93:7	92
18	**25j**	Me	Ph	*n*Pr	51[e]	50:50	94
19					51[e,g]	80:20	−90
20	**26b**	Me	4-ClC_6H_4	4-MeC_6H_4	83	98:2	98
21	**27a**	Me	3-$MeOC_6H_4$	Ph	85	88:12	95



R': H **28a** (83%) d.r.= 90:10, 94% *ee*
R': MeO **28e** (78%) d.r.= 87:13, 97% *ee*

29a (62%) d.r.= 98:2, 92% *ee*

R: Me **30a** (72%) d.r.= 92:8, 94% *ee*
R: Et **31a** (62%) d.r.= 90:10, 97% *ee*

[a] Reactions conducted on a 0.3 mmol scale in 0.5 mL CH_2Cl_2 (mol ratio of imidazolone/nitroolefin/**C1** catalyst 1:2:0.1) unless otherwise stated. [b] Yield of the isolated major diastereomer. [c] Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Reaction run at 50 °C in 1,2-dichloroethane. [f] Using *ent*-**C1**. [g] Using **C2**. [h] Reaction run at 4 mmol scale using 5 mol% catalyst (reaction time 30 h).

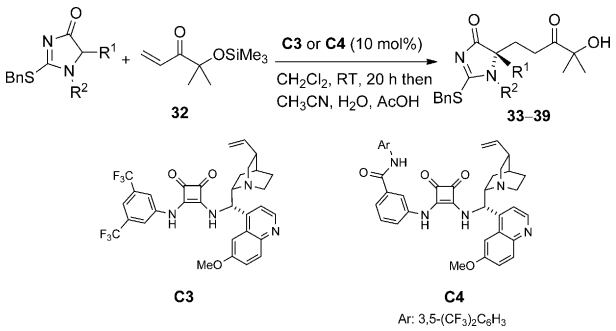
were all tolerated (entries 11–17, 20, and 21). Also bicyclic imidazolones, such as **13A** and **14A**, provided the corresponding adducts (**28a**, **28e**, **29a**) with equal effectiveness. These latter products represent quaternary proline and related derivatives which cannot be accessed directly through established catalytic methodologies.[14] Of practical interest, the catalyst loading may be reduced from 10 to 5 mol% without affecting the results (entry 15 versus 16). In contrast, the nature of the S-substituent group appears to have limited impact on stereoselectivity as results obtained from the imidazolones **2B** and **2C**, to produce **30a** and **31a**, respectively, are comparable to those obtained with **2A**.

In addition to these observations, it was also found that Michael acceptors, which are less reactive than nitroolefins, may participate in these reactions with equal effectiveness (Table 2). For example, the reaction of **2A** with the acrylate surrogate **32**,[15] promoted by catalyst **C1**, provided, after desilylation of the intermediate adduct, the product **33** in good yield (74%), albeit with moderate enantioselectivity (84% *ee*).[16] Improved selectivity (91% *ee*) was observed using **C2**, and even better selectivity was obtained with **C3**[17] (94% *ee*) and the new catalyst **C4** (96% *ee*, Table 2, entry 1). Under these latter conditions, the enone **32** also reacted efficiently with other imidazolones (entries 2–7).[18]

The chemical manipulation of adducts was briefly investigated to illustrate the synthetic potential of this approach (Scheme 2). Thus, nucleophilic displacement of the thioether group served to establish concise routes to various classes of heterocycles of interest in medicinal chemistry,[19] that is, imidazolidinones (**40**, **41**), 2-aryl imidazolones (**43**), 2-amino imidazolones (**44**), and hydantoins (**45–47**). Eventually, acid hydrolysis of **41** afforded the amino amide **42** with all the above reactions proceeding in good yields. Similarly, the hydantoins **48–50** could be obtained upon smooth hydrolysis of the corresponding adducts **33–35**. Further oxidative elaboration of the ketol moiety in these products[9,15] led to the corresponding carboxylic acids **51**/**52**, the aldehyde **53**, and ketone **54**. The present catalytic approach thus facilitates a novel entry for the rapid construction of functionalized 5,5-disubstituted hydantoins, a well-recognized scaffold for drug discovery.[20] Finally, the X-ray structure analyses of hydantoins **46** and **51** served to establish the configuration of the adducts.[21]

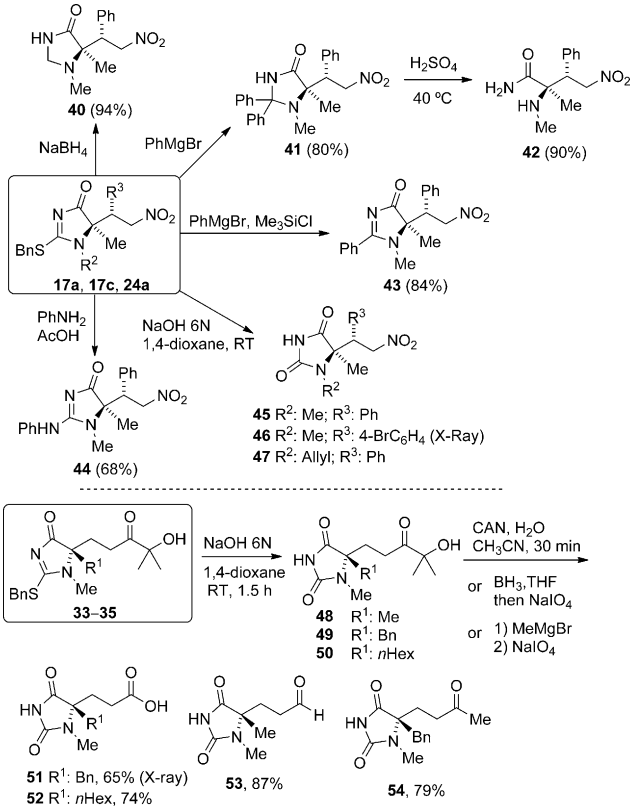
On the other hand, given that the new template allows direct access to N-substituted quaternary α-amino acid derivatives, additional ways for the elaboration of adducts can be envisaged in which the NR^2 moiety plays a strategic role. For instance (Scheme 3), from the common adduct **47**, the densely functionalized bi- (**55**) and tricyclic (**56**) compounds were prepared in two and four steps, respectively.[9]

Table 2: 1,4-Addition of 1*H*-imidazolo-4(5*H*)ones to the α′-silyloxy enone **32**.[a]

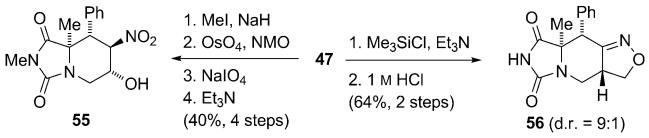


Entry	Imidazolone	R^1	R^2	Prod.	Yield [%][b]	*ee* [%][c]
1	**2A**	Me	Me	**33**	82	96[d]
2	**3A**	Bn	Me	**34**	75	96
3	**4A**	*n*Hex	Me	**35**	81	94
4	**5A**	*i*Bu	Me	**36**	71	96
5	**7A**	Me	Bn	**37**	78	96
6	**9A**	Me	CH_2=$CHCH_2$	**38**	77	94
7	**15A**	Bn	Bn	**39**	83	92

[a] Reactions conducted on a 0.3 mmol scale (mol ratio of imidazolone/enone/catalyst 1:2:0.1) using **C4** unless otherwise stated. Desilylation conducted in CH_3CN (1 mL), H_2O (0.5 mL), AcOH (0.3 mL). [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Using catalyst **C1**, −84% *ee*; using catalyst **C2**, 91% *ee*; using catalyst **C3**, 94% *ee*.



Scheme 2. Elaboration of the 2-thio-1*H*-imidazol-4(5*H*)-one moiety. CAN = ceric ammonium nitrate.



Scheme 3. New entries to functionalized polycyclic hydantoins. NMO = *N*-methyl-morpholine *N*-oxide.

The fidelity with which chirality is transferred in the above conjugate addition reactions may be explained by assuming the catalyst tightly bound to both the reactants in the TS, as shown in models A and B (Figure 2). It should be noted that

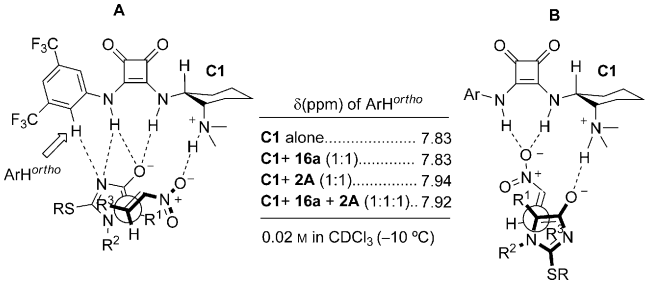


Figure 2. Plausible TS models and selected ^{1}H NMR data.

models similar to A and B, which define two major patterns for catalyst–substrate hydrogen bonding, have been previously proposed as heuristic or calculation-driven TS for related reactions involving bifunctional squaramide tertiary amine catalysis, and the prevalence of one over the other seems to be highly substrate-dependent.[15,22] As strong evidence in favor of model A, we found that the chemical shift of the *ortho*-ArH in **C1** is considerably affected ($\Delta\delta = +0.11$ ppm) by addition of 1 equivalent of **2A**, whereas it remains unaffected by addition of nitrostyrene (Figure 2 and see the Supporting Information). This observation also suggests that the polarized aromatic *ortho* protons in this type of catalysts contribute to TS stabilization.[23]

In summary, we have demonstrated for the first time that 2-thio-1*H*-imidazol-4(5*H*)-ones may serve as effective equivalents of N-substituted (alkyl, aryl, allyl) α-amino acids. Specifically, their base-catalyzed addition reaction to nitroolefins and enones to afford the corresponding quaternary α-amino acid derivatives can be carried out with very high diastereo- and enantiocontrol. Further elaboration of the thus obtained adducts opens straightforward access to an array of different N-substituted quaternary α-amino acid derivatives, including 5,5-disubstituted hydantoins and other complex N-heterocycles, in enantiomerically pure form. The scope of these imidazolones as new pronucleophiles against other acceptors, including C=X systems (1,2-addition), may be easily anticipated.

Keywords: amino acids · asymmetric catalysis · Michael additions · organocatalysis · synthetic methods

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Base-Catalyzed Asymmetric α-Functionalization of 2-(Cyanomethyl)azaarene *N*-Oxides Leading to Quaternary Stereocenters

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Supporting Information

ABSTRACT: A simple, new strategy for the direct asymmetric α-functionalization of 2-alkyl azaarenes is described. Specifically, a Brønsted base catalyzed conjugate addition of substituted 2-cyanomethylpyridine (and pyrazine) *N*-oxides to acrylate equivalents to afford hitherto elusive 2-*tert*-alkyl azaaryl adducts with high enantioselectivity (up to 94% *ee*) is realized. Extension of the method to the α-amination reaction by using azodicarboxylate esters as electrophiles is also demonstrated. Key for success is the *N*-oxide functionality of substrates that acts as a removable activating and stereodirecting group. A bifunctional Brønsted base catalyst bearing a squaramide with an attached bulky silyl group is also disclosed.

Ortho-substituted pyridines, and more generally azaarenes, are widespread structural motifs,[1] with the congeners that are chiral by virtue of an α-stereogenic *o*-substituent constituting a relevant subset. Several catalytic approaches have recently been reported for the enantioselective synthesis of such chiral units via α-deprotonation of the corresponding 2-alkylazaarene (Figure 1a).[2] With simple 2-alkylazaarenes (R: H, alkyl, etc.), substrate activation requires a (super)stoichiometric strong base (LiHMDS),[3] thus compromising practicality. Milder conditions have been developed for the α-functionalization of preactivated substrates, i.e. those with electron-withdrawing substituents (EWG) in either the azaarene ring (*p*-nitroazaarenes, polyheteroarenes) or the Cα (α-ester, amide, electron-deficient aryl) or both (strategy 2).[4,5] In these cases, α-stereogenic 2-substituted azaarenes can be produced with high enantioselectivities by means of a chiral Pd(II),[4a] Ni(II),[4b] or amine[5] catalyst and no base, or only a catalytic weak base, being added. However, none of these methods address the generation of a quaternary α-stereocenter,[6] an issue of general importance in organic synthesis,[7] and of particular significance to the present context given the interest in 1,1-diaryl quaternary compounds as potential pharmacophores.[8] Here we describe an enantioselective α-functionalization of *o*-substituted azaarenes that is complementary to the known procedures in several aspects: (i) successfully affords hitherto elusive all-carbon quaternary stereocenters, (ii) relies on a Brønsted base activation strategy using newly designed chiral bifunctional organocatalysts, and (iii) uses azaarene *N*-oxides, more specifically substituted 2-cyanomethyl azaarene *N*-oxides,[9] as enabling substrates (Figure 1b).

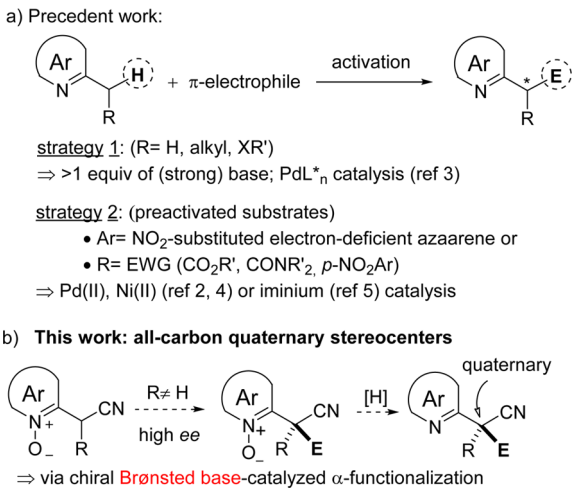

Figure 1. Enantioselective routes to *o*-substituted azaarenes.

Two key elements that make 2-cyanomethyl azaarene *N*-oxides perfect substrate candidates *a priori* are their relatively high CH Brønsted acidity as compared to most alkylazaarenes[10] and the presence of the N → O group as a potentially coordinating site for catalyst binding.[11] Considering this, one might expect that bifunctional chiral Brønsted bases[12] would suffice for an effective α-deprotonation and subsequent stereoselective bond formation. As far as we know azaarene *N*-oxides have not been investigated within the context of asymmetric C(sp^3)−H functionalizations.[13,14]

At the outset, we studied the behavior of 2-cyanoalkylpyridine **1** under Brønsted base catalysis conditions and selected as a reaction partner enone **2**, an acrylate surrogate well suited for organocatalytic conjugate additions.[15] As data in Scheme 1 show, the reactions in the presence of typical cinchona-based bifunctional Brønsted base catalysts **C1**−**C3**[16] were sluggish, with low conversion after an extended reaction time (96 h) at room temperature and poor enantioselectivity. The reactivity increased substantially when the corresponding *N*-oxide[17] **4a** was employed instead (Scheme 2). Thus, conversions of ∼70% were reached after 2 days at ambient temperature, almost complete at 40 °C, but with yet suboptimal enantioselectivity (75% *ee* with **C3**). After some additional screening,[18] we tested the new

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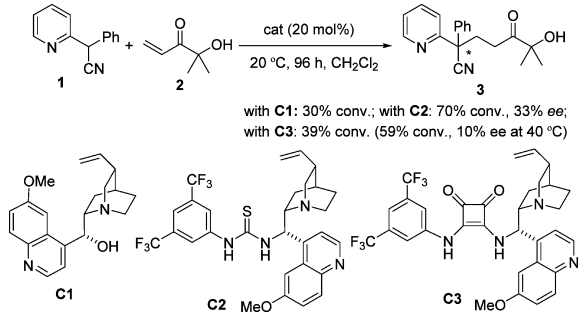
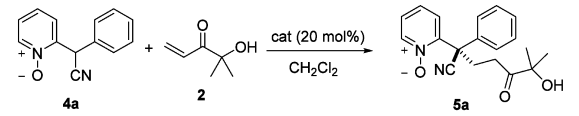
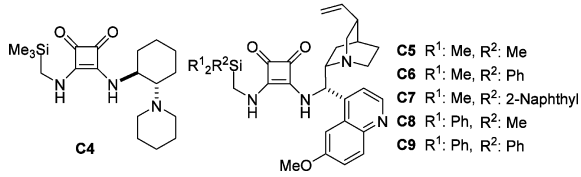
Scheme 1. Difficulties in the Brønsted Base Catalyzed Reaction of 2-Cyanomethylpyridine 1



Scheme 2. Catalyst Screening for the Reaction of 2-Cyanomethylpyridine *N*-Oxide 4a and Enone 2



cat.	conditions	conv. (%)	*ee* (%)	cat.	conditions	conv. (%)	*ee* (%)
C1	20 °C, 48 h	72	22	**C5**	40 °C, 20 h	100	90
C2	20 °C, 40 h	60	17	**C6**	20 °C, 64 h	100	92
C3	40 °C, 48 h	92	75	**C7**	40 °C, 24 h	100	84
C3	20 °C, 48 h	72	88	**C8**	40 °C, 24 h	100	85
C4	40 °C, 96 h	83	58	**C9**	20 °C, 64 h	100	81

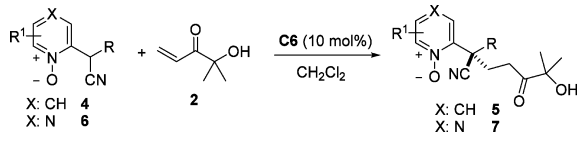


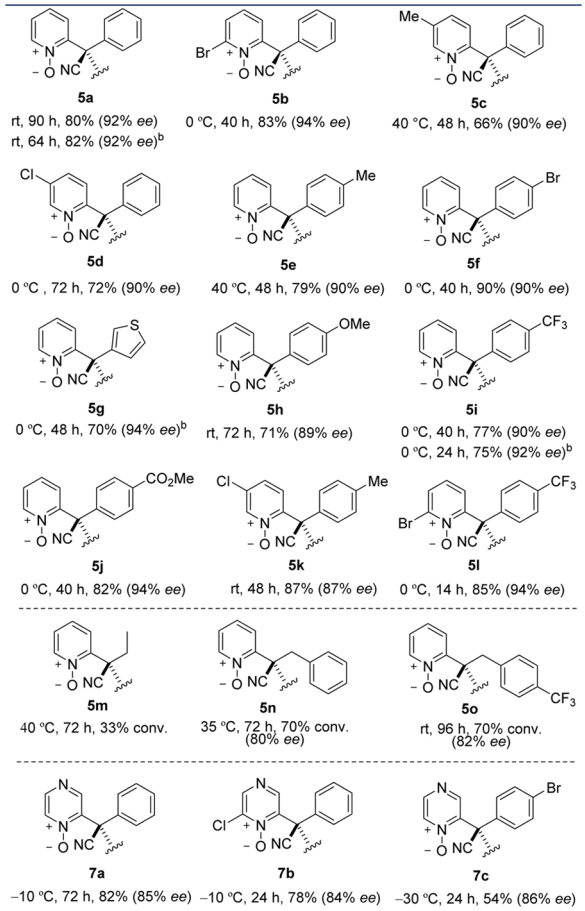
squaramide catalysts[19] **C4**–**C9**, which show as a novel feature a R_4Si site that might play a steric function or even participate in some specific *N*–*O* → *Si* interaction.[20] Gratifyingly, we observed that while catalyst **C4** performed poorly, the reaction between **4a** and **2** catalyzed by **C5** and **C6** led to the highest selectivity (90% and 92% *ee*, respectively) in dichloromethane at temperatures in the range 20–40 °C.

Catalyst **C6** was thus selected to explore the scope of the reaction with a range of 2-cyanomethyl azaarene *N*-oxides (Table 1). It was found that under these conditions the reaction tolerated well pyridine *N*-oxides **4** with both electron-releasing and -withdrawing groups attached at different positions of the pyridine ring. Similarly, substrates bearing both electron-rich and -poor aryl substituents at C*α* were equally effective in providing the corresponding addition adducts **5** in generally very good yield and high enantioselectivity. Nonetheless, the method was less tolerant with the corresponding *α*-alkyl substituted 2-(cyanomethyl)azaarene *N*-oxides **4** (R = alkyl, products **5m**–**o**). Then it was proven that variation of the azaarene system did not apparently affect the reaction course, as the corresponding 2-cyanomethylpyrazines **6** added efficiently to **2** to afford the quaternary 1,1′-diaryls **7a**–**c** in good yields. In these latter cases somewhat lower enantioselectivity was obtained, although they were still acceptable considering the challenge posed by these types of targets.[9]

It was subsequently proven that these 2-cyanomethylpyridine *N*-oxides may also work as enabling substrates for stereoselective *α*-heterofunctionalization reactions under conditions similar to those mentioned above. For example, the pyridine *N*-oxide **4a** reacted with di(*tert*-butyl) azodicarboxylate **8** in the presence of

Table 1. Scope of the Reaction of *α*-Substituted 2-(Cyanomethyl)azaarene *N*-Oxides with 2 Catalyzed by C6[a]





[a]Reactions conducted on a 0.2 mmol scale in 1 mL of CH_2Cl_2 (molar ratio of **4** or **6**/**2**/catalyst 1:3:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase. [b]20 mol % **C6** was used.

10 mol % **C8** to afford *α*-aminated adduct **10a** in 90% isolated yield and 81% *ee*. The same reaction using catalyst **C9** led to product with 90% *ee*. The scope of this *α*-amination process using either di(*tert*-butyl) or dibenzyl azodicarboxylate **8** or **9** as the amination reagent was briefly investigated for a range of 2-cyanoalkylpyridine *N*-oxides. As data collected in Table 2 show, reactions proceeded successfully to give products **10** and **11** in good yields and *ee*'s, with catalyst **C9** providing the best results for most of the entries. Once again, the parent pyridine **1** proved to be less efficient for these transformations. For instance, the reaction of **1** and di(*tert*-butyl) azodicarboxylate **8** in the presence of 10 mol % catalyst **C8** proceeded to a limited extent of 30% conversion after 15 h at 0 °C.

The detailed mechanism of these catalytic transformations as well as the precise role played by each element involved remains unclear. However, data in Figure 2 indicate that the *N*-oxide group and its *ortho*-relationship to the cyanoalkyl substituent are key for optimal reaction outcome.[21] As a general trend, for the three positional isomers *ortho*, *meta*, and *para*, the corresponding pyridine *N*-oxide was more reactive than the parent pyridine in

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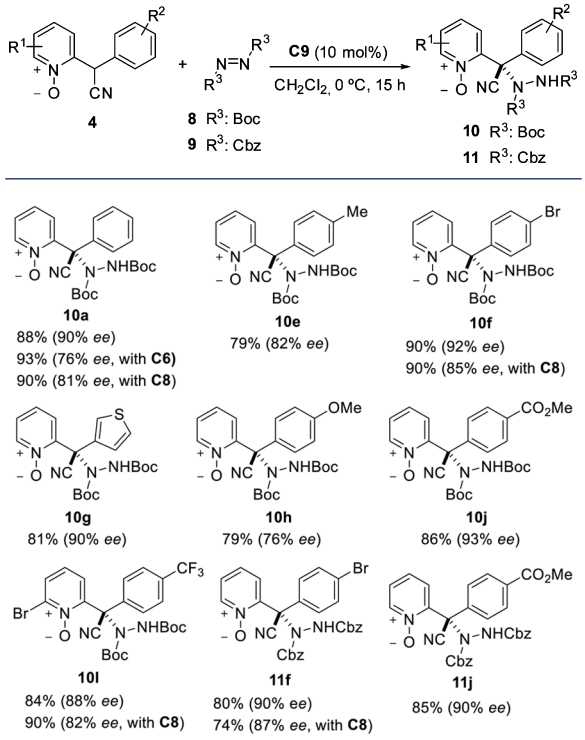
Table 2. α-Amination Reaction of 4[a]



[a]Reactions conducted on a 0.2 mmol scale in 1 mL of CH_2Cl_2 at 0 °C (molar ratio of **4**/**8** or **9**/catalyst 1:1.5:0.1). Yields of isolated product. Enantioselectivity determined by HPLC analysis using a chiral stationary phase.

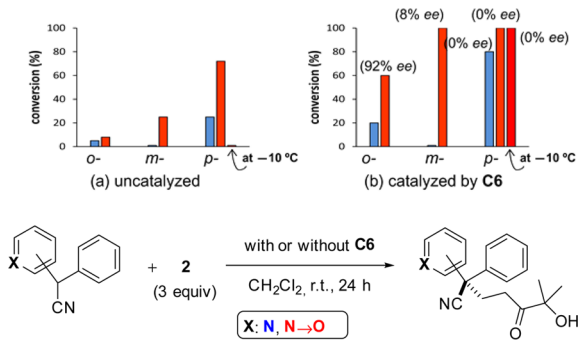
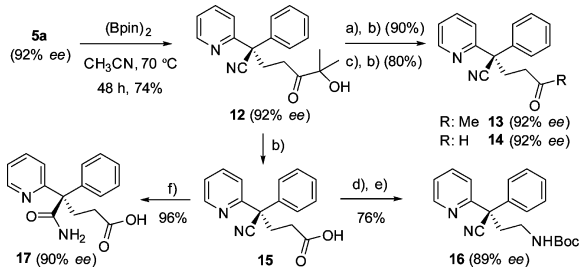


Figure 2. Conversion after 24 h for the reactions of **2** with *o*-, *m*-, and *p*-substituted cyanoalkylpyridines and pyridine *N*-oxides.

both the catalyzed and uncatalyzed reactions. In fact, among the six experiments involving cyanoalkylpyridines, only that using *p*-cyanoalkylpyridine in the presence of **C6** provided practical conversion after 24 h, leading to a racemic product. Equally important is the position of the *N*-oxide group relative to the cyanoalkyl substituent on the ring. Among the three cyanoalkylpyridine *N*-oxides, the *meta* and *para* isomers proved to be inherently more reactive than the *ortho* isomer, also in the presence of catalyst **C6**, although both led to essentially a racemic product. In contrast, the *ortho* isomer led to 92% *ee*.

Adducts obtained from these catalytic transformations can be modified in several ways. For instance, reduction of the *N*-oxide group on adduct **5a** by treatment with $(Bpin)_2$[22] afforded pyridine **12** in 74% isolated yield and unaltered enantioselectivity (92% *ee*, Scheme 3). Furthermore, elaboration of the ketol moiety in adducts by applying well established protocols allows

Scheme 3. Elaboration of 5a into Quaternary 1,1′-Diaryls[a]



[a]Reagents and conditions: (a) MeMgBr, 0 °C, 6 h; (b) $NaIO_4$, $MeOH/H_2O$, rt, 1 h; (c) BH_3·THF, THF, 0 °C, 2 h, then MeOH; (d) Et_3N, DPPA, toluene, 80 °C, 2 h; (e) ^tBuOH, 50 °C, 16 h; (f) H_2SO_4 (conc.), rt, overnight.

the corresponding ketone (**13**), aldehyde (**14**), or carboxylic acid (**15**) product to be furnished from a common single intermediate and with formation of acetone as the only organic waste. These results are of particular interest in that the direct conjugate addition of azaarene *N*-oxide **4** to simple enones, i.e. methyl vinyl ketone, or unsaturated esters, i.e. methyl acrylate, did not work under the present catalytic conditions. In addition, the reaction of **4** with acrolein afforded the corresponding 1,4-addition adduct, but with a poor 15% *ee*. Another illustration of the synthetic versatility of adducts is shown by transformation of the nitrile carboxylic acid **15** into the protected amine **16** and amide **17**, respectively. On the other hand, the configuration of adducts **5a** and **10a** was established by single crystal X-ray analysis,[23] and for the remaining adducts it was assigned by assuming a uniform reaction mechanism.

In summary, a mild and highly enantioselective carbo- and hetero-α-functionalization of 2-cyanomethylazaarene *N*-oxides is developed as the first direct and asymmetric entry to α-quaternary alkylazaarenes. The *N*-oxide group plays a strategic role as a removable activating and stereodirecting element in conjunction with newly designed bifunctional squaramide-Brønsted base catalysts bearing a bulky silyl group. While the specific role played by the silyl group during catalysis is not clear yet,[24] its easy variation makes this new subclass of squaramides very attractive for further asymmetric transformations under proton transfer conditions. Work to address these issues is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13385.

Crystallographic data for **5a** (CIF)
Crystallographic data for a **10a** derivative (CIF)
Experimental details, NMR spectra, HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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(21) Unlike the *meta* and *para* isomers, the ^{1}H NMR spectrum of the *ortho* isomer shows significant changes when recorded in the absence or the presence of 1 mol equiv of **C6**, respectively. For details, see the SI.

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(24) In a preliminary prospect, these Brønsted bases proved to be efficient catalysts in reactions involving *C*-nucleophiles other than azaarene *N*-oxides. For example, the reaction of *tert*-butyl phenylcyanoacetate with **2** promoted by **C6** led to the corresponding Michael addition product with 94% *ee*. See the SI for details.

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Enantioselective Synthesis of 5,5-Disubstituted Hydantoins by Brønsted Base/H-Bond Catalyst Assisted Michael Reactions of a Design Template

Joseba Izquierdo, Julen Etxabe, Eider Duñabeitia, Aitor Landa, Mikel Oiarbide,* and Claudio Palomo*[a]

Abstract: A new method for the enantioselective synthesis of 5,5-disubstituted (quaternary) hydantoins was developed on the basis of an organocatalytic Michael reaction approach involving the use of 2-benzylthio-3,5-dihydroimidazol-4-ones as key hydantoin surrogates. The method is general with respect to the substitution pattern at the hydantoin N^1 (alkyl, aryl, acyl), N^3 (aryl), and C^5 (linear/branched alkyl, aryl) positions and affords essentially single diastereomeric products with enantioselectivities higher than 95% *ee* in most cases. Among the bifunctional Brønsted base/H-bond catalysts examined, a known squaramide–tertiary amine catalyst and a newly prepared squaramide–tertiary amine catalyst provide the highest selectivity so far with either nitroolefins or vinyl ketones as the acceptor components. Kinetic measurements support a first-order rate dependence on both reaction partners, the donor template and the Michael acceptor, whereas competitive ^{1}H NMR spectroscopy experiments reveal the high ability of the template for catalyst binding.

Introduction

Hydantoins (2,4-imidazolidinediones) constitute a family of nitrogen heterocycles that are present in natural products[1] and comprise a variety of pharmaceutical uses.[2] In particular, 5-substituted and 5,5-disubstituted hydantoins are important medicinal compounds.[3] Examples include the anticonvulsant phenytoin, used for the treatment of epilepsy and cardiac arrhythmia;[4] compounds with antidepressant[5] and antiviral[6] activity; inhibitors of platelet aggregation,[7] human aldose reductase,[8] and human leukocyte elastase;[9] and antagonists for use in Hedgehog pathway-dependent malignancies.[10] On the other hand, hydantoins are also interesting from a purely chemical point of view.[11] 5-Substituted hydantoins have been employed in the context of molecular recognition,[12] as chiral auxiliaries in organic synthesis,[13] and as constituents of optically active polymers[14] and metal complexes.[15] Structurally, they can be viewed as masked α-amino acids, and as such, 5-substituted hydantoins also serve as precursors to unnatural α-amino acid derivatives.[16]

Although alternative routes from ketones or α-dicarbonyl compounds exist,[11] the main synthetic route to 5-substituted hydantoins starts from the corresponding α-amino acid derivatives,[17] which are condensed with an isocyanate or equivalent with the assistance of some highly reactive coupling reagent (Figure 1).[18] Whereas this route is, in principle, simple and straightforward, its realization depends on the availability of the corresponding α-amino acid precursors in enantiomerically pure form. This is a serious problem, especially if 5,5-disubstituted (quaternary) hydantoins are targeted.[19]

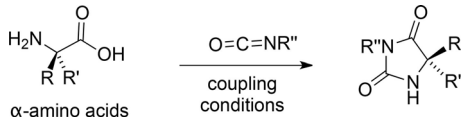

Figure 1. Conventional synthesis of optically active 5,5-disubstituted hydantoins from the chiral pool.

Only very recently have practical syntheses of enantiomerically enriched quaternary hydantoins involving new carbon–carbon bond-forming reactions been reported. Clayden developed an elegant protocol to access quaternary hydantoins and compounds derived thereof with good diastereoselectivity on the basis of a substrate-controlled anionic aryl group N→C rearrangement on lithiated ureas[20] (Figure 2a). On the other hand, Terada recently reported a chiral phosphoric acid catalyzed Friedel–Crafts-type addition of 2-methoxyfuran to in situ generated ketimines (Figure 2b).[21] Despite these significant advances, the scope of available optically active quaternary hydantoins continues to be rather narrow and is essentially restricted to some particular 5-aryl-substituted subfamilies.

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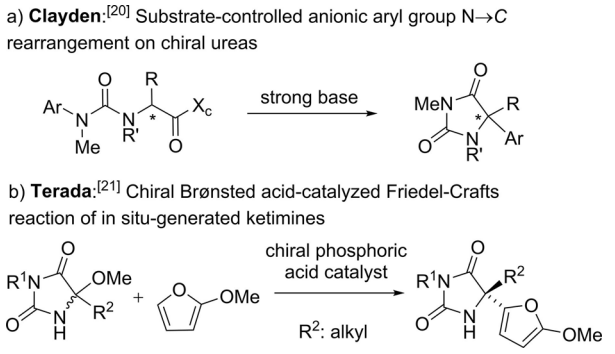


Figure 2. Advances in the asymmetric synthesis of 5,5-disubstituted hydantoins involving C–C bond construction.

Recently, we found[22a] that heterocycles **I** could react smoothly with some Michael acceptors (i.e., nitroolefins and an acrylate equivalent) triggered by bifunctional Brønsted base/H-bond catalysts, thus serving, via the intermediate hydantoin, as *N*-substituted α-amino acids surrogates. Herein, we present a full study on the ability not only of **I** but also of related heterocycles **II** and **III** to engage in bifunctional Brønsted base/H-bond catalyzed highly enantioselective Michael reactions with some selected acceptors, including simple vinyl ketones. This work, which discloses newly prepared and active squaramide–tertiary amine catalyst **C3**, represents the first catalyst-controlled, enantioselective, and broad-scope method for the synthesis of 5,5-disubstituted (quaternary) hydantoins with a variety of substitution patterns at N^1, N^3, and C^5 (Figure 3).

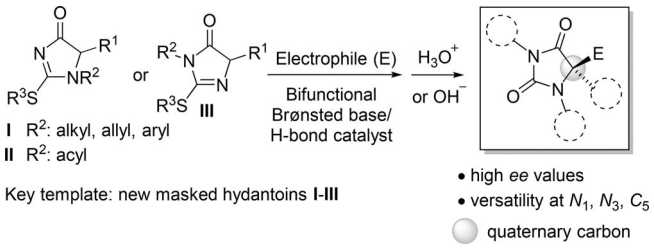
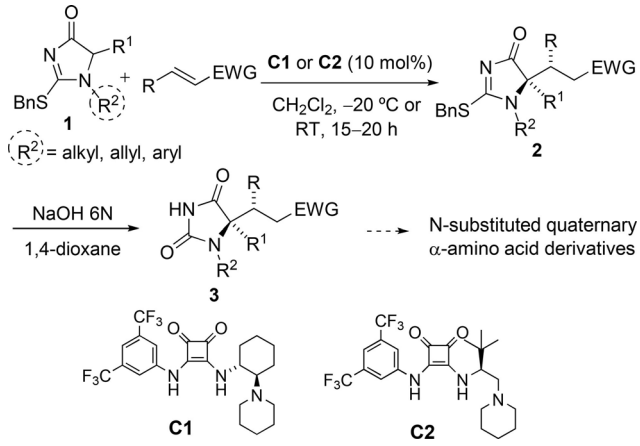


Figure 3. Template-based catalytic enantioselective synthesis of diversely substituted quaternary hydantoins.

Results and Discussion

Background and working plan

We recently communicated a novel, highly enantioselective approach for the synthesis of *N*-substituted α-amino acid derivatives via corresponding enantioenriched 1,5,5-trisubstituted hydantoins **3** (Scheme 1).[22] A distinguishing feature of this sequence is that the synthesis of hydantoins **3** no longer relies on the availability of the precursor α-amino acid in enantiopure form; instead, **3** is prepared through a Brønsted base catalyzed conjugate addition[23,24] of racemic dihydroimidazolones **1**, followed by basic hydrolysis of resulting Michael adduct **2**. The **1**→**2** transformation serves to install a second substituent at C^5 of the heterocycle and creates a new tetrasubstituted



Scheme 1. Our preliminary finding.[22a]

carbon stereocenter adjacent to a tertiary one with high diastereo- and enantioselectivity. To the best of our knowledge, methods for that goal have not yet been described.[11] During these preliminary studies, we found that the squaramide–tertiary amine catalysts pioneered by Rawal,[25] such as **C1**, efficiently promoted the addition reaction of **1** to aromatic nitroolefins under very smooth conditions (CH_2Cl_2 at $-20\,^{\circ}C$) to afford corresponding adducts **3** (EWG = NO_2) in diastereomeric ratios typically higher than 9:1 with excellent enantioselectivity. In some instances, particularly with aliphatic nitroolefins (R = alkyl), catalyst **C1** led to modest diastereoselectivities, but using **C2**[26] instead, both the diastereo- and the enantioselectivity were high. Importantly, this system tolerated a range of dihydroimidazolones **1** with varying substituents at N^1 (R^2 = alkyl, allyl, aryl) and C^5 (R^1 = linear and branched alkyl groups), including bicyclic dihydroimidazoles [R^1,R^2 = $(CH_2)_3$]. One of the problems of using template **1**, or in general structures **I** (R^2 = alkyl or aryl), is their limited thermal stability, as they partially decompose upon storage at room temperature for several hours or during standard silica gel chromatographic purification, making storage in the freezer at $-40\,^{\circ}C$ necessary.

Given the simplicity and the high selectivity of the method and the mild reaction conditions involved, we sought to investigate the behavior of related heterocyclic systems **II** and **III**. If successful, a broad-scope approach for the enantioselective synthesis of diversely 1,3,5-substituted hydantoins would be at hand. The effectiveness of template **I** to react under the above soft enolization conditions may be ascribed to the aromatic character of transiently formed enolate **I′** (Figure 4). By similar reasoning, it was envisaged that, in the presence of a base promoter, related heterocyclic systems **II** (N^1-acyl) and **III** would lead to corresponding aromatic enolates **II′** and **III′**. Moreover, in view of the structural similarities of the three enolates, their interaction with the protonated amine–squaramide catalyst might be equally productive in affording the Michael-addition adducts.

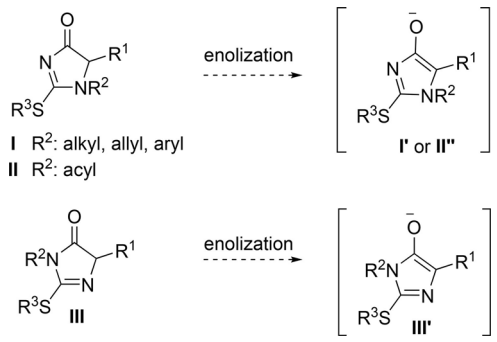
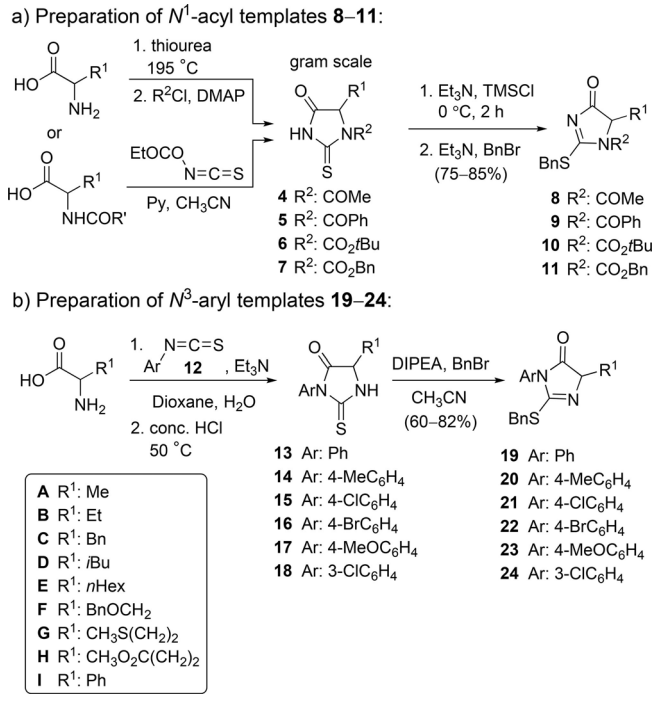


Figure 4. Enolization of templates leading to enolates with aromatic character.

Preparation of substrates

The preparation of *N*-acyl templates **8**–**11** was performed by the sequence described in Scheme 2a. Racemic hydantoins **4**–**7**, prepared in bulk quantities through classic condensation reactions of the corresponding free or *N*-acyl amino acids and suitable reagents,[27–29] were first silylated with trimethylchlorosilane and triethylamine and were then treated with benzyl bromide to afford, after aqueous workup, desired N^1-acyl 2-benzylthioimidazolones **8**–**11**. Notably, at this point, these compounds turned out to be solids and were comparatively more stable than corresponding *N*-alkyl and *N*-aryl compounds **I**. For instance, compounds **8**–**11** were perfectly stable at room temperature for several days. On the other hand, the preparation of N^3-aryl templates **19**–**24** (Scheme 2b) started with the condensation of the respective amino acid with phenyl(aryl) isothiocyanate **12** and triethylamine to yield thiohydantoins **13**–**18**. Each one was *S*-benzylated by treatment with benzyl bromide and *N*,*N*-diisopropylethylamine (DIPEA) to yield **19**–**24**, which were also found to be bench-stable compounds.

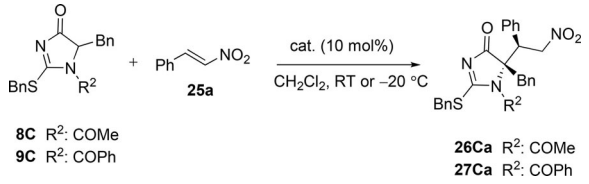


Scheme 2. Preparation of N^1-acyl- and N^3-aryl-2-benzylthio-3,5-dihydroimidazol-4-ones. DMAP = 4-(dimethylamino)pyridine, Py = pyridine, *n*-Hex = *n*-hexyl.

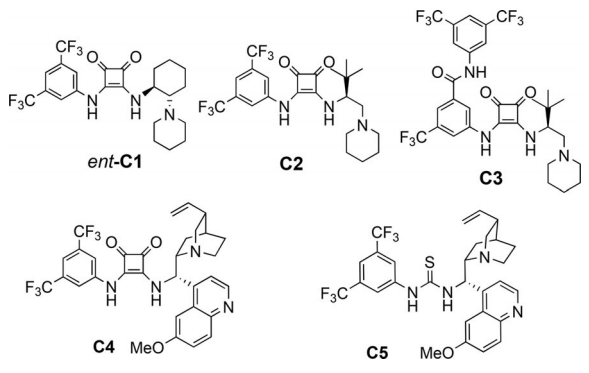
Reactions of N^1-acyl-2-thiobenzyl-3,5-dihydroimidazol-5-ones

To assess the viability of these substrates, their behavior towards nitroolefins under the same conditions as those previously reported for *N*-alkyl/aryl congeners **1** was evaluated. Gratifyingly, as the brief screening in Table 1 shows, the reaction of *N*-acetyl **8C** with nitrostyrene **25a** to afford adduct **26Ca** proceeded at room temperature in the presence of various bifunctional Brønsted base catalysts with remarkable selectivity, whereas reactivity was more catalyst dependent. For instance, both catalysts **C1** and **C2** were able to afford adduct **26Ca** as a 97:3 mixture of diastereomers in very high (but opposite) enantioselectivity, although no full conversion could be reached in either case after 24 h (Table 1, entries 1 and 5). As

Table 1. Catalyst screening for the reaction of **8C**/**9C** with nitrostyrene **25a** (R = Ph).[a]



Entry	Catalyst	R^2	T [°C]	t [h]	Conversion [%]	d.r.	*ee* [%]
1	**C1**	COMe	RT	24	80	97:3	−98
2	*ent*-**C1**	COMe	RT	24	80	97:3	98
3	*ent*-**C1**	COPh	RT	16	>98	>98:2	98
4	*ent*-**C1**	COPh	−20	96	NR	–	–
5	**C2**	COMe	RT	24	50	97:3	98
6	**C2**	COPh	RT	16	>98	>98:2	97
7	**C2**	COPh	−20	96	65	>98:2	98
8	**C3**	COMe	RT	16	90	98:2	99
9	**C3**	COPh	RT	4	>98	98:2	99
10	**C3**	COPh	−20	48	>98	>98:2	98
11	**C4**	COMe	RT	16	95	90:10	99
12	**C5**	COMe	RT	16	60	80:20	90

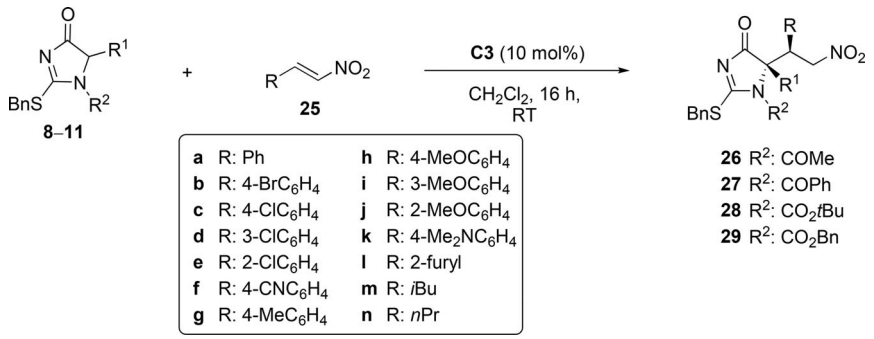


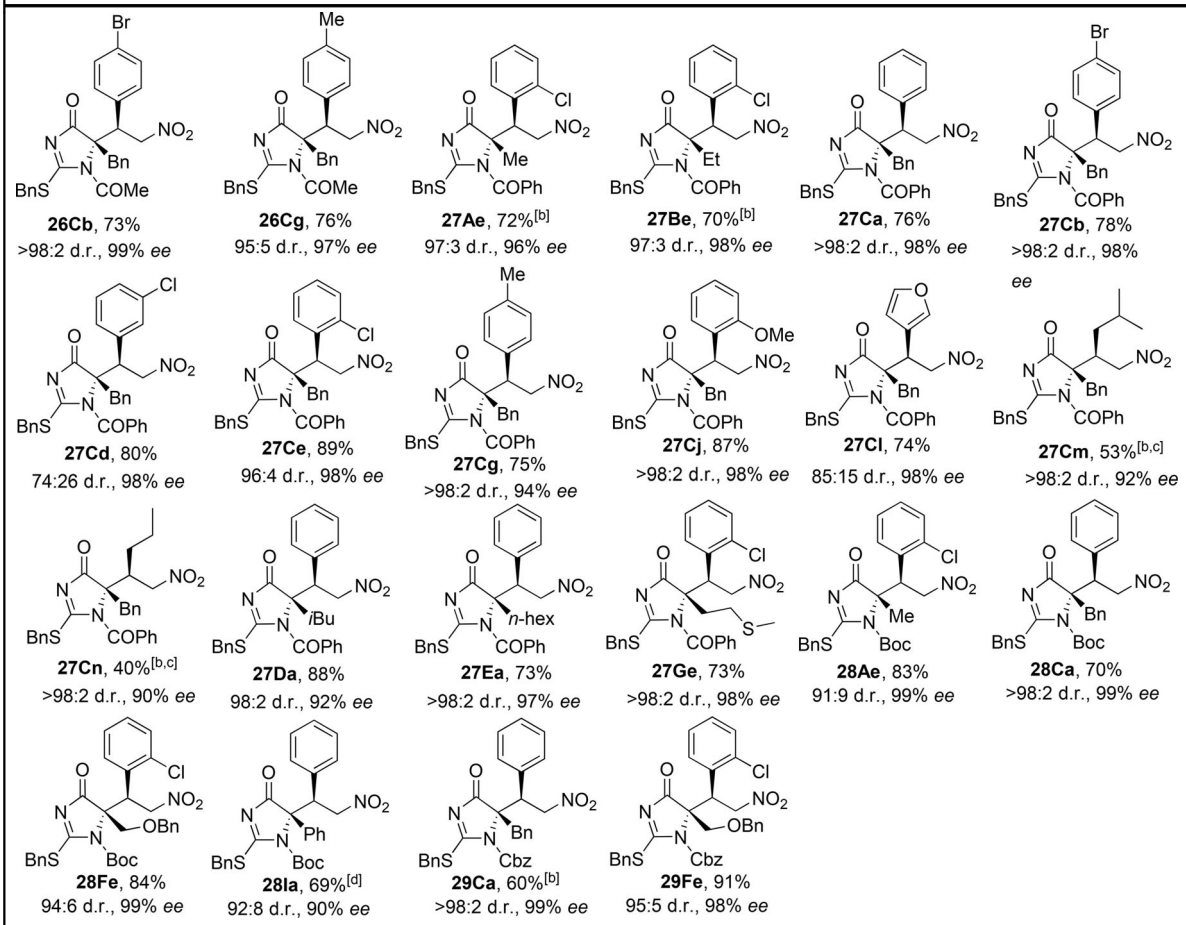
[a] The reactions were performed by using **8C**/**9C** (0.3 mmol), nitrostyrene (0.6 mmol), and catalyst (10 mol%) in CH_2Cl_2 (0.6 mL). The *ee* values of the major diastereomers were determined by HPLC. NR = no reaction.

expected, catalyst *ent*-**C1** (Table 1, entry 2) afforded the same enantiomer as **C2** with reproducible reactivity and selectivity compared to **C1** and was employed from this point on.

Newly developed catalyst **C3**[30] was more active and essentially led to full conversion after 24 h (90% conversion after 16 h) with nearly the same degree of diastereo- and enantiocontrol (Table 1, entry 8). Regardless of the catalyst employed, *N*-benzoyl analogue **9C** proved to be more reactive than *N*-acetyl derivative **8C** and upon reaction with nitrostyrene afforded corresponding adduct **27Ca**, again, with essentially perfect diastereo- and enantioselectivity (Table 1, entries 3, 6, and 9). This same order of catalyst activity, namely, *ent*-**C1** < **C2** < **C3**, was observed at subzero temperatures, despite the fact that *ent*-**C1** was perfectly soluble, whereas both **C2** and **C3** were only partially soluble. Thus, whereas *ent*-**C1** was completely inactive at −20 °C, **C2** (Table 1, entry 7) and especially catalyst **C3** (Table 1, entry 10), promoted the reaction between **9C** and nitrostyrene at that temperature to afford compound **27Ca** with very high stereoselectivity. It was also observed that cinchona-based squaramide catalyst **C4**[31] was equally active,

Table 2. Scope of the reaction of N^1-acyl-2-benzylthio-3,5-dihydroimidazol-4-ones **8**–**11** with nitroalkenes **25**.[a]





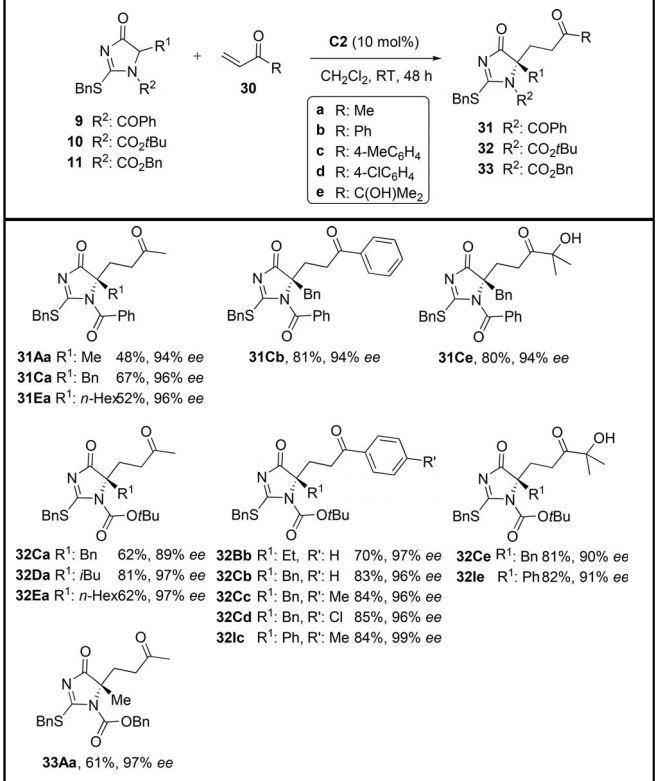
[a] Reaction conditions: a mixture of dihydroimidazolone **8**–**11** (0.2 mmol, 1 equiv), nitroolefin **25** (0.4 mmol, 2 equiv), and **C3** (10 mol%) in CH_2Cl_2 (1.0 mL) was stirred at 20 °C for 16 h unless otherwise stated. Diastereomeric ratios and *ee* values were determined by HPLC. [b] Reaction was run for 48 h. [c] Reaction was performed in deoxygenated DME at 50 °C by using nitroalkene (5 equiv) and catalyst (20 mol%). [d] Reaction was run for 72 h.

albeit less selective (d.r. 90:10; Table 1, entry 11), whereas corresponding thiourea analogue **C5**[32] was both less active and less selective (Table 1, entry 12). In turn, quinine and hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2PYR$] were completely ineffective catalysts for this reaction. With these initial results in hand, the scope of the reaction was explored by using catalyst **C3**, although *ent*-**C1** and **C2** could be employed with almost equal effectiveness. As the data in Table 2 show, the reactions were performed at room temperature and worked uniformly well for *N*-acyl heterocycles **8**/**9** bearing a variety of substituents at the C^5 position of the heterocycle (benzyl, short and long linear alkyl, branched alkyl, heteroalkyl). A range of 5,5-disubstituted cycloadducts **26**/**27** were isolated in very high yields and enantioselectivities, and with dr values generally $\geq$94:6; adduct **27Cd** (d.r. 74:26) was an exception. The reactions involving more problematic aliphatic nitroolefins also proceeded with very good diastereo- and enantioselectivity (adducts **27Cm** and **27Cn**). However, these latter substrates were comparatively less reactive than their aromatic congeners and required 5 equivalents of the nitroalkene and 20 mol% catalyst in 1,2-dimethoxyethane (DME) at 50 °C for practical reaction conversions. Under these conditions, deoxygenated solvent was optimal to prevent the α-hydroxylation reaction. Dihydroimidazolone templates with *N*-*tert*-butoxycarbonyl (*N*-Boc) and *N*-benzyloxycarbonyl (*N*-Cbz) groups (i.e., compounds **10** and **11**) were also competent substrates for this reaction and afforded adducts **28** and **29** with essentially perfect stereoselectivity in good yields. As formation of product **28la** in 69% yield and high selectivity proves, the method is also suitable for templates with an aryl group at the C^5 position. Notably, in some instances and with extended reaction times the formation of small amounts ($\approx$5%) of overaddition of the initially formed adduct to a second molecule of nitroolefin was observed. Adjusting the reaction time was generally enough to minimize or even cancel this undesired side reaction.

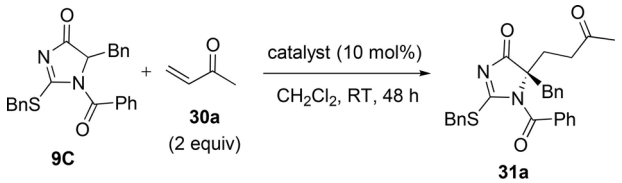
At this stage, the efficacy of this catalytic system against simple vinyl ketones, a less active but yet relevant Michael acceptor category, was explored. Initial screening of catalysts for the reaction of **9C** with methyl vinyl ketone (**30a**) as a representative reaction model (Scheme 3) showed a trend in catalyst activity and selectivity similar to that observed with nitroalkenes. Thus, *ent*-**C1** promoted the addition of **9C** to **30a**, although the reaction progressed slowly and with suboptimal enantioselectivity. In contrast, catalyst **C3** and, especially, catalyst **C2** were comparatively more active (reaction conversions after 48 h at room temperature: 70 and 85%, respectively) and led to *ee* values of 95 and 96%, respectively.

Then, the reactions of **9**, **10**, and **11** with vinyl ketones **30** were explored by using **C2** as the catalyst. As the data in Table 3 show, independent of the substitution pattern, vinyl ketones **30a**–**d** were all equally competent reaction partners and gave rise to respective Michael adducts **31**–**33** in generally good yields and selectivities. However, intrinsically less-reactive Michael acceptors, such as α,β-unsaturated esters and, in particular, acrylates, were not competent reaction partners. Nonetheless, this deficiency may be surmounted in part by using α-hydroxy enone **30e**, an acrylate equivalent (see below) that is very easy to prepare from acetone or commercially available 3-hydroxy-3-methyl-2-butanone in two steps.[33] Thus, adducts such as **31Ce**, **32Ce**, and **32Ie** were obtained in good yields and selectivities and, as will be shown later, could be converted into the corresponding carboxylic acid products through conventional ketol cleavage.

Table 3. Reaction of *N*-acyl-2-benzylthioimidazolones **9**–**11** with vinyl ketones **30**.[a]



[a] The reactions were performed by using **9**–**11** (0.3 mmol), vinyl ketone **30** (0.6 mmol), and catalyst **C2** (10 mol%) in CH_2Cl_2 (0.6 mL). The *ee* values were determined by HPLC.



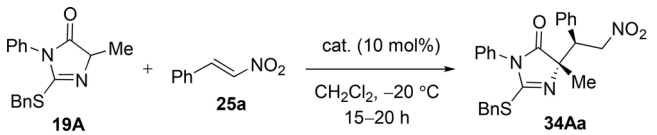
Catalyst	conv. [%]	*ee* [%]
ent-**C1**	50	72
C2	85	96
C3	70	95

Scheme 3. Catalyst screening for the reaction of **9C** with methyl vinyl ketone (**30a**).

Reactions of N^3-aryl-2-thiobenzyl-3,5-dihydroimidazol-4-ones 19–24 with nitroolefins

In all of the examples shown, masked hydantoins of type **I/II** were used exclusively. Accordingly, the hydrolysis of the isothiourea moiety of the resulting adducts would deliver a route to N^3-unsubstituted hydantoins (see below). To develop a similar catalytic approach useful for the synthesis of the complementary N^3-protected N^1-unsubstituted hydantoins, we next studied the behavior of 2-benzylthiodihydroimidazolones **19**–**24**. Although it was expected that these compounds would also provide extended pseudoaromatic enolate species **III**′ upon enolization in the presence of a bifunctional Brønsted base catalyst (Figure 4), whether or not these latter would react as efficiently as **I**′/**II**′ remained unanswered. To begin the study, the reaction of **19A** with β-nitrostyrene **25a** was performed in the presence of a base catalyst. As the results in Scheme 4 show for the title reaction, catalyst *ent*-**C1** was able to promote the formation of the contiguous quaternary and tertiary carbon stereocenters of **34Aa** in good yield with moderate diastereoselectivity (62:38) and very high enantioselectivity for the major isomer. Under such smooth reaction conditions, among the catalyst examined, catalysts **C2** and **C3** were both, once again, the best in affording product **34Aa** in nearly quantitative yield with diastereoselectivities higher than 95:5 and excellent enantioselectivities (96 and 95% *ee*, respectively, for the almost-exclusive diastereomer).

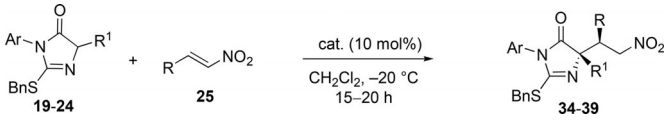
With catalyst **C2** selected for further reaction development, the robustness of the method with respect to structural variation of both reactants was explored (Table 4). As the data illustrate (Table 4, entries 1–11), aryl-substituted nitroolefins **25a**–**k** with either electron-rich, electron-neutral, or electron-poor character were equally competent reaction partners and upon reaction with **19A** afforded corresponding adducts **34A** in very good yields with nearly perfect diastereo- and enantioselectivity in most cases. During this substrate screening, catalyst **C3** was found to be less efficient than **C2**, as the inferior diastereoselectivity attained for products **34Ag** and **34Ah** indicated (Table 4, entries 7/6 vs. 9/8). Variation of the R^1 substituent of the imidazolidinone substrate did not have any appreciable impact on the reaction outcome. Thus, not only methyl but also benzyl (Table 4, entries 12 and 13) and other alkyl (Table 4, entry 14) and functionalized chains (Table 4, entries 15 and 16) were tolerated at the substrate C^5 position without affecting the reaction efficiency or selectivity. On the other hand, N^3-aryl substrates **20**–**24** bearing aryl groups other than phenyl also



(*ent*-**C1**) 95%, d.r. 62:38, 94% *ee*
(**C2**) 99%, d.r. 97:3, 96% *ee*
(**C3**) 95%, d.r. 96:4, 95% *ee*
(**C4**) 99%, d.r. 83:17, 88% *ee*
(**C5**) 99%, d.r. 60:40, 75% *ee*

Scheme 4. Catalyst screening for the reaction of **19A** with nitrostyrene.

Table 4. Scope of the catalytic reaction of N^3-substituted 2-benzylthio-3,5-dihydroimidazol-4-ones with nitroolefins.[a]

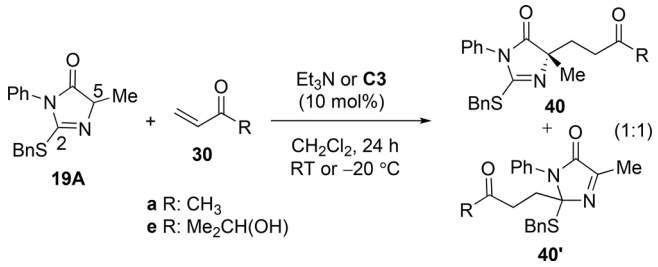


Entry	Ar	R^1	R	Product	Catalyst	Yield [%]	d.r.	*ee* [%]
1	Ph	Me	4-BrC_6H_4	**34Ab**	**C2**	95	>98:2	99
2	Ph	Me	4-ClC_6H_4	**34Ac**	**C2**	94	>98:2	99
3	Ph	Me	3-ClC_6H_4	**34Ad**	**C2**	86	>98:2	99
4	Ph	Me	2-ClC_6H_4	**34Ae**	**C2**	90	>98:2	99
5	Ph	Me	4-NCC_6H_4	**34Af**	**C2**	88	>98:2	96
6	Ph	Me	4-MeC_6H_4	**34Ag**	**C2**	87	>98:2	97
7	Ph	Me	4-MeC_6H_4	**34Ag**	**C3**	83	84:16	96
8	Ph	Me	4-$MeOC_6H_4$	**34Ah**	**C2**	85	95:5	90
9	Ph	Me	4-$MeOC_6H_4$	**34Ah**	**C3**	86	70:30	90
10	Ph	Me	3-$MeOC_6H_4$	**34Ai**	**C2**	94	>98:2	98
11	Ph	Me	4-$Me_2NC_6H_4$	**34Ak**	**C2**	92	>98:2	99
12	Ph	Bn	Ph	**34Ca**	**C2**	90	93:7	98
13	Ph	Bn	Ph	**34Ca**	**C3**	92	91:9	99
14	Ph	$(CH_3)_2CHCH_2$	Ph	**34Da**	**C2**	90	>98:2	99
15	Ph	$MeSCH_2CH_2$	Ph	**34Ga**	**C2**	85	>98:2	86
16	Ph	$MeO_2CCH_2CH_2$	Ph	**34Ha**	**C2**	90	>98:2	99
17	4-MeC_6H_4	Me	Ph	**35Aa**	**C2**	89	93:7	97
18	4-ClC_6H_4	Me	Ph	**36Aa**	**C2**	90	>98:2	94
19	4-BrC_6H_4	Me	Ph	**37Aa**	**C2**	86	>98:2	99
20	4-$MeOC_6H_4$	Me	2-ClC_6H_4	**38Ae**	**C2**	91	>98:2	94
21	3-ClC_6H_4	Me	4-$MeOC_6H_4$	**39Ah**	**C2**	90	>98:2	87

[a] Reaction conditions: a mixture of **19**–**24** (0.3 mmol, 1 equiv), **25** (0.6 mmol, 2 equiv), and catalyst (10 mol%) in CH_2Cl_2 (0.6 mL) was stirred at −20 °C for 15–20 h. Diastereomeric ratios and *ee* values of the major diastereomers were determined by HPLC.

participated in this reaction satisfactorily (Table 4, entries 17–21).

Vinyl ketones were also competent electrophilic partners in the reactions of N^3-substituted 2-benzylthioimidazolones **19**–**24**. However, in contrast to that observed with nitroalkenes, the reactions involving vinyl ketones followed two divergent pathways: one producing 5-addition products **40** and one producing 3-addition products **40′** (Scheme 5). The configuration

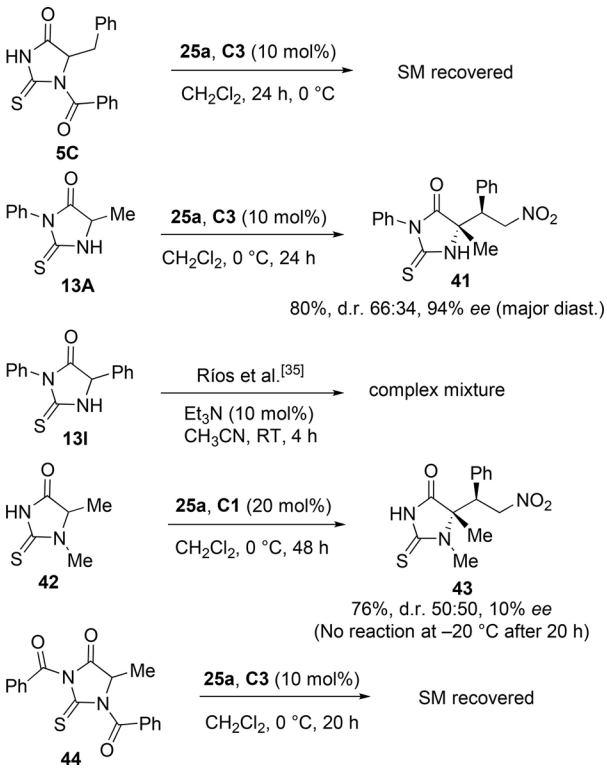


Scheme 5. Reaction of 2-benzylthiodihydroimidazolones **19A** with vinyl ketones **30a** and **30e**.

of products **40′** was not determined and that of products **40** was assigned by assuming a uniform reaction mechanism. Attempts to favor either reaction pathway were unsuccessful, and regardless of the catalyst and reaction temperature, an essentially equimolar ratio of either product was formed for the studied cases (Scheme 5). Similar observations were previously reported in Brønsted base catalyzed addition reactions involving azlactones as the nucleophiles.[34]

Control experiments using the related thiohydantoins

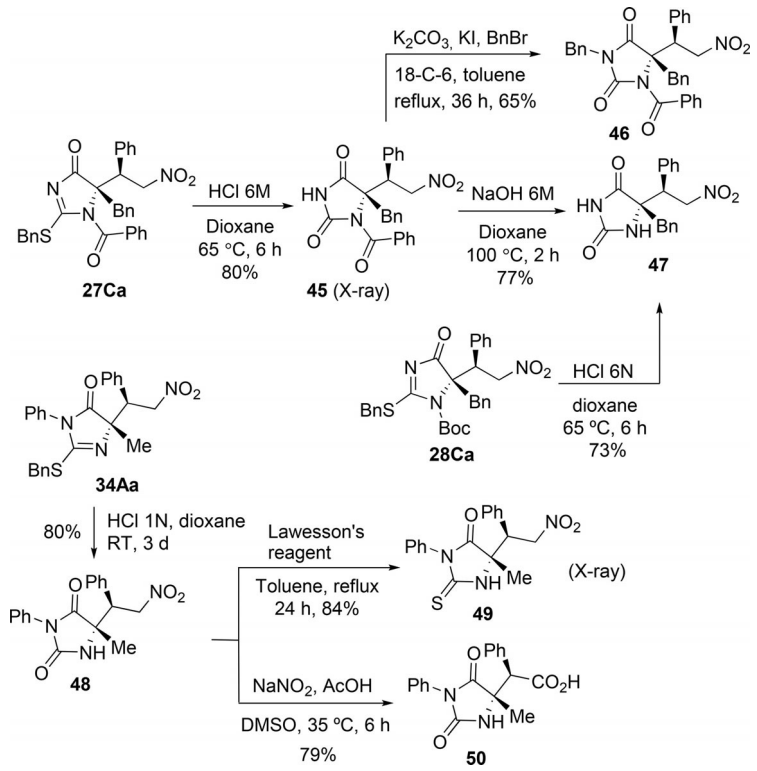
To put the reactivity and, particularly, the selectivity profiles of templates **I**–**III** into context under the present soft enolization conditions, the behavior of **5C**, **13A**, **42**, and **44**, four parent thiohydantoins with comparable substitution patterns at N^1 and N^3, was explored (Scheme 6). Initial control experiments showed that, in contrast to templates **I**–**III** (see above), none of these four thiohydantoins reacted at all with nitrostyrene **25a** in the presence of catalyst **C3** at low temperature (experiments performed at −20 °C). This lack of reactivity was most evident in the case of thiohydantoin **5C**, which remained unchanged even after stirring the mixture for 24 h at 0 °C. We ascribe the comparatively higher reactivity of templates **I**–**III** to their tendency to undergo enolization owing to the aromatic character of the resulting enol/enolate intermediate species. At higher temperatures (0 °C), N^3-phenylthiohydantoin **13A** reacted with nitrostyrene **25a** in the presence of catalyst **C3**, but product **41** was obtained as a 1.9:1 mixture of diastereomers. Similarly, N^1-methylthiohydantoin **42** also reacted with nitrostyrene **25a** at 0 °C but, again, led to a roughly equimolecular mixture of diastereomers with marginal enantioselection. In turn, Rios[35] reported that upon treatment with nitrostyrene at room temperature **13I** gave a complex mixture. Finally, *N*,*N*-dibenzoyl derivative **44** was completely unreactive under these conditions.



Scheme 6. Reactivity profile of the related thiohydantoins **5C**, **13A**, **13I**, **42**, and **44**. SM = starting material.

Hydrolysis of adducts into 5,5-disubstituted hydantoins

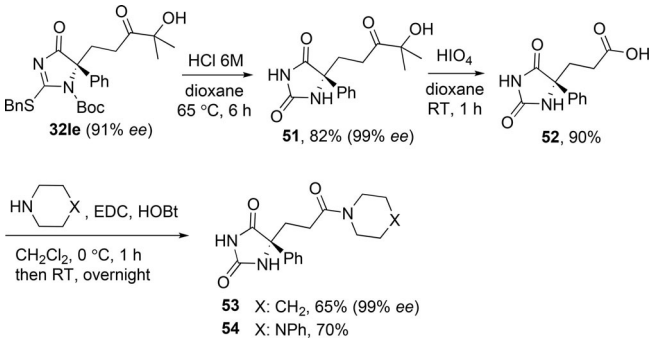
Removal of the benzylthio adjuvant from adducts obtained through these series of catalytic conjugate addition reactions could be performed by hydrolysis under various convenient conditions. As shown in Scheme 7, treatment of N^1-benzoyl adduct **27Ca** with 6 M HCl in dioxane at 65 °C for 6 h gave rise to corresponding *N*-acylhydantoin **45** in 80% yield. Subsequent treatment of **45** with 6 M NaOH at 100 °C produced free hydantoin **47** in 77% yield. On the other hand, the same acid hydrolytic conditions applied to *N*-Boc adduct **28Ca** induced concomitant deprotection of the Boc group to afford hydantoin **47**. Interestingly, alkylation of the imide nitrogen atom in product **45** under standard Williamson conditions allowed access to corresponding *N*-benzyl adduct **46** in good yield. In turn, hydrolysis of 2-phenylthio-4,5-dihydroimidazol-4-one **34Aa** to respective hydantoin **48** could be performed by treatment with 1 M HCl at room temperature. Temperature control of this reaction was important for clean hydrolysis. The same reaction performed under more forcing conditions (65 °C) led to a 1:1 mixture of compound **48** and thio analogue **49**. In any event, resulting adduct **48** could be fully converted into thiohydantoin analogue **49** by applying Lawesson's reagent, which served to establish the compound identity and configuration by X-ray analysis. On the other hand, Nef-type oxidation of the nitro group in **48** under Mioskowski conditions[36] proceeded smoothly to furnish carboxylic acid **50** in 79% yield. The configurational integrity of the adducts was not affected during all



Scheme 7. Hydrolysis of cycloadducts to 5,5-disubstituted hydantoins and further elaboration. 18-C-6 = 18-crown-6.

of these transformations, and the final products were obtained as essentially single enantiomers (≥99% *ee*).

Scheme 8 shows a specific application to the synthesis of pharmacologically active constituents based on a three-step sequence. Both amides **53** and **54** have been reported to present significant inhibitory activity as ADAMTS (A disintegrin and metalloproteinase) inhibitors.[37] Starting from adduct **32 le** (Table 2, 82%, 91% *ee*), acid hydrolysis of the *S*-benzylisothiourea moiety in dioxane at 65 °C, followed by ketol oxidative scission with HIO_4, provided carboxylic acid **52** in 74% yield over two steps. Final coupling of acid **52** with piperidine and *N*-phenylpiperazine by using *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide/1-hydroxybenzotriazole (EDC/HOBt) coupling reagent led to amides **53** and **54** in 65 and 70% yield, respectively. These examples show that the adducts can be manipulated easily, with minimum production of waste organic materials (e.g., acetone is obtained as a byproduct in the **51**→**52** transformation) and, most important, with preserved configurational integrity.



Scheme 8. Synthesis of ADAMTS (A disintegrin and metalloproteinase) inhibitors **53** and **54**.

Mechanistic insight

Several experiments were performed to obtain insight into the reaction mechanism. In a first set of experiments (Figure 5), the conversion for the reaction between **10 C** and **25 a** was measured as a function of time, maintaining the concentration of **25 a** pseudoconstant (15 equiv) in the presence of 10 mol% catalyst **C3**. A plot of $-\ln([\mathbf{10C}]/[\mathbf{10C}]_0)$ versus time gave a straight line ($R^2 = 0.996$), which indicated first-order dependence in the nucleophile.

The reaction order in the electrophilic component was determined similarly by measuring the reaction conversion as a function of time at a pseudoconstant concentration of nucleophile **10 C** (15 mol equiv) in the presence of 10 mol% catalyst **C3**. In this instance, a plot of $\ln([\mathbf{25a}]/[\mathbf{25a}]_0)$ versus time again afforded a straight line ($R^2 = 0.9815$), indicating first-order reaction with respect to the acceptor component. Unfortunately, the reaction order in the catalyst could not be determined by this means owing to the limited solubility of the catalyst.

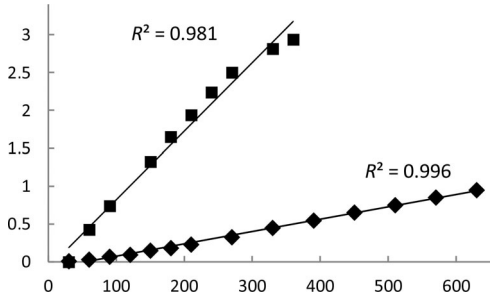


Figure 5. Plot of reaction conversion versus time for the **C3**-catalyzed reaction between **10 C** and **25 a** with pseudoconstant concentrations of **25 a** (◆) and **10 C** (■).

On the other hand, the collective experimental data shown in Tables 1–4 reveal the unique reactivity profile of templates **I**–**III**, in contrast to the variable results attained with the parent thiohydantoins (see Scheme 6). An interesting aspect of this high reactivity is that it appears quite general regardless of the catalyst employed, and therefore, it should be ascribed to an inherent feature of the template design. As shown in the Introductory section (Figure 4), the pseudoaromatic character of enol forms **I**′–**III**′ would facilitate the enolization process, but this effect alone would not necessarily justify the subsequent reactivity against the electrophilic acceptor. To obtain additional insight into this aspect, and more specifically with regard to

the affinity of the templates for these type of bifunctional catalysts, we performed competitive ^{1}H NMR spectroscopy experiments involving template **9C**, nitroolefin **25a**, and catalyst *ent*-**C1** (Figure 6). Catalyst *ent*-**C1** was chosen because of its complete solubility in halogenated solvents, as noted above. As a comparison of spectra 1, 2, and 4 shows (Figure 6), admixing **25a** and *ent*-**C1** caused a slight downfield shift in the olefinic H^c/H^d protons of **25a** along with an upfield shift in H^a and H^b of *ent*-**C1**, quite significant ($\Delta\delta \approx 0.1$ ppm) in the former case, clearly indicating some degree of molecular recognition between nitrostyrene **25a** and the catalyst. In turn, variation of the chemical shifts upon admixing template **9C** and the catalyst (compare spectra 2, 3, and 5 in Figure 6) seemed to be less pronounced, with only a slight downfield shift in H^b. However, spectrum 6, in which both substrates **25a** and **9C** must compete for best catalyst binding, reveals that the molecular affinity between **9C** and *ent*-**C1** is relatively high. Indeed, the chemical shift pattern of *ent*-**C1** in spectrum 6, in particular the chemical shifts of both H^a and H^b, remained essentially the same as that in spectrum 5 and distinct from that in spectrum 4. These observations reinforce the idea that the new hydantoin template upon enolization would remain tightly bound to the catalyst during the key C–C bond-forming event, allowing efficient transfer of chiral information.

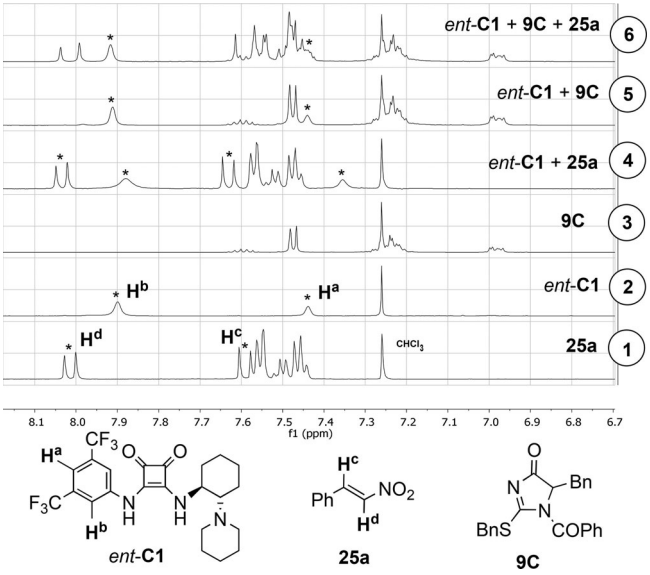


Figure 6. Insets of the ^{1}H NMR spectra corresponding to individual samples of **9C**, **25a**, and *ent*-**C1** and three 1:1 combinations of them taken in $CDCl_3$ at room temperature (concentration ≈ 0.1 M).

To obtain more insight into the structural/functional requirements of these catalysts for optimal activity and selectivity, the performances of catalyst **C3**, featuring a free NH amide, and its *N*-Me derivative were compared. As the conversion profiles in Figure 7 show for the reaction between **9C** and **25a**, catalyst **C3** was significantly more active than its *N*-methylated form. For instance, with **C3** the reaction conversion was over 70% after 30 min at room temperature (over 90% after 1 h), whereas with **C3**-NMe the conversion barely reached 27% after 30 min (45% after 1 h). Although erosion of the stereoselectivity was less important (**C3**, d.r. 98:2, 99% *ee*, Table 1, entry 9; **C3**-NMe, dr > 98:2, 90% *ee*), the difference in catalyst activities is significant, especially considering that, unlike **C3**, **C3**-NMe is completely soluble, and this may be attributable to the ability of the free amide in **C3** to form additional H-bonds. Although the number of individual H-bonding interactions within the substrate–catalyst complex in the transition state and their precise orientation remain unknown, on the basis of previous studies on related catalytic systems,[38] simultaneous activation of both reactants as in stereomodels **A**/**A**′ (Figure 8) may be proposed tentatively for reactions catalyzed by **C3**. The free amide NH group would be H-bonded internally, as in **A**, to assist catalyst preorganization or intermolecularly, as in **A**′, to fix better one of the approaching reactants. Similar models are conceivable for the remaining templates and catalysts in which the approaching trajectory of both reactants correctly explains the observed configuration, both relative and absolute, of the adducts.

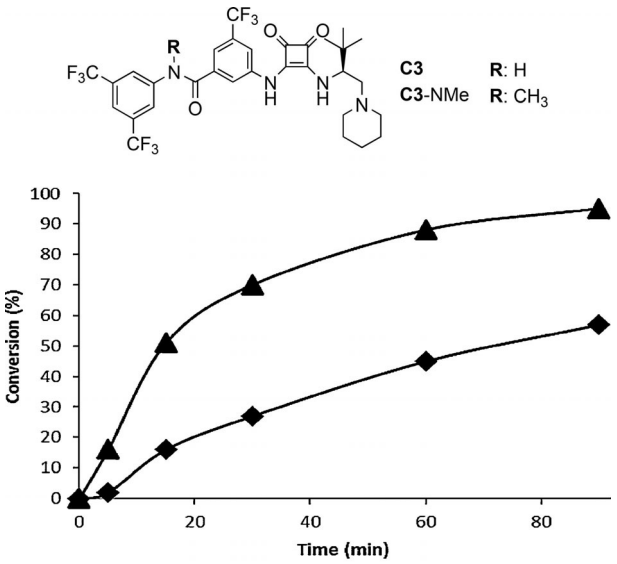


Figure 7. Conversions for the reaction between **9C** and **25a** catalyzed by **C3** (▲) and its *N*-Me derivative (◆) under standard conditions.

Conclusions

A new, quick entry to the enantioselective synthesis of 5,5-disubstituted hydantoins was developed on the basis of an organocatalytic Michael reaction approach by using easy-to-prepare and easy-to-handle 2-benzylthiodihydroimidazol-4-ones as key hydantoin surrogates. The method was found to be general with respect to the substitution pattern at the N^1 (alkyl, aryl, acyl), N^3 (aryl), and C^5 (linear/branched alkyl, aryl) positions of the resulting hydantoins and afforded essentially single diastereomeric products with enantioselectivities higher than 95% *ee* in most cases. These hydantoin surrogates were demonstrated to be clearly superior to the parent thiohydantoins, which were inefficient in terms of reactivity and/or selectivity under similar catalytic conditions. Among the catalysts examined, **C2**

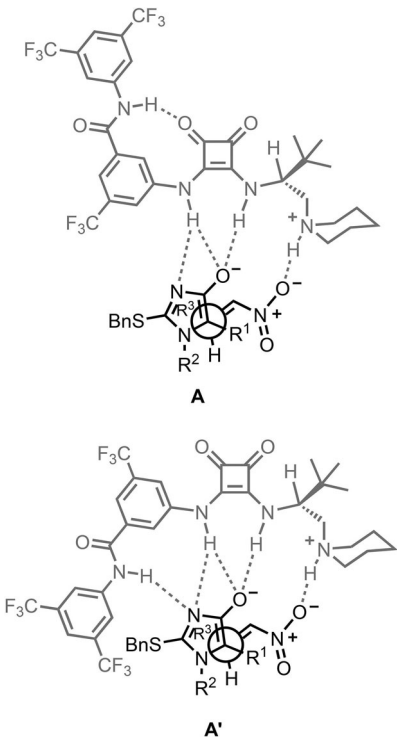


Figure 8. Plausible transition-state stereomodels for the **C3**-catalyzed reaction between template **II** and nitroolefins.

and newly prepared squaramide–tertiary amine catalyst **C3** provided the highest selectivity in the reactions with either nitroolefins or vinyl ketones as the acceptor components. One designing advantage of **C3** is its adaptability to particular reaction needs owing to easy modification of the carboxamide unit. Kinetic studies of these catalytic Michael reactions support a first-order rate dependence on both the donor and acceptor reactants. On the other hand, ^{1}H NMR spectroscopy monitoring of mixtures of donor template, acceptor, and catalyst suggested that the good reactivity and high fidelity of chirality transfer with these templates was bound to the unique capacity of the benzylthiodihydroimidazolone system to bind the catalyst. As the adducts obtained through the present method may display a tetrasubstituted stereogenic center adjacent to a tertiary one and can be chemically manipulated in many ways, new perspectives are opened in the field of hydantoin chemistry. The potential of this method was illustrated with an expeditious synthesis of ADAMTS (A disintegrin and metalloproteinase) inhibitors **53** and **54**. Further applications of templates **I**–**III** as pronucleophiles in related catalytic settings can be foreseen.

Experimental Section

For a detailed description of the experimental procedures (preparation of templates, catalytic enantioselective reactions, transformations of adducts, kinetic measurements), characterization of the compounds, and spectroscopic/chromatographic information, see the Supporting Information.

CCDC 1581118 (**45**) and 1581122 (**49**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amino acids · asymmetric catalysis · Brønsted bases · chirality · hydantoins

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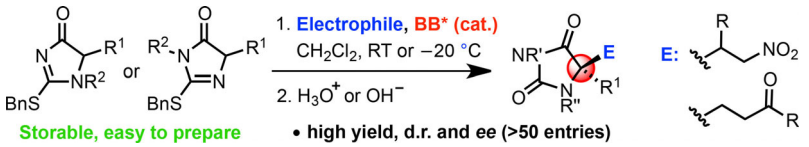
FULL PAPER

Asymmetric Synthesis

J. Izquierdo, J. Etxabe, E. Duñabeitia, A. Landa, M. Oiarbide, C. Palomo**

■■ – ■■

Enantioselective Synthesis of 5,5-Disubstituted Hydantoins by Brønsted Base/H-Bond Catalyst Assisted Michael Reactions of a Design Template



Hydantoins made easy: A general, catalytic, and asymmetric procedure to access 5,5-disubstituted (quaternary) hydantoins is developed by relying on the Brønsted base (BB*)-catalyzed enantioselective C-functionalization of a design dihydroimidazolone template with Michael acceptors.