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Universidad del País Vasco

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CATALYTIC ASYMMETRIC SYNTHESIS OF α,α-DISUBSTITUTED α-THIO- AND α-AMINO ACID DERIVATIVES.

DOCTORAL THESIS

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Donostia-San Sebastián, 2016

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

DOCTORANDO/A DON **Julen Etxabe Telleria.**

TITULO DE LA TESIS: **Catalytic Asymmetric Synthesis of α,α-Disubstituted α-Thio- and α-Amino Acid Derivatives.**

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SUMMARY

The aim of this thesis has been the development of new pronucleophiles for organocatalytic reactions, leading to α,α-dialkyl α-thio- and α,α-dialkyl α-amino carboxylic acid derivatives, products that are of interest in biological and medicinal chemistry. To this end, we have developed 5*H*-thiazolones and 1*H*-imidazol-4(5*H*)-ones for the first time (Figure 1).

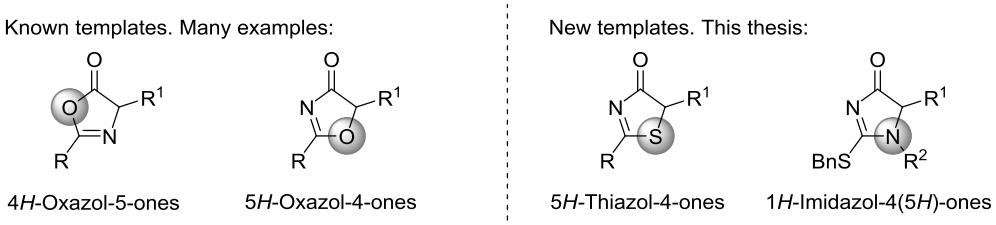
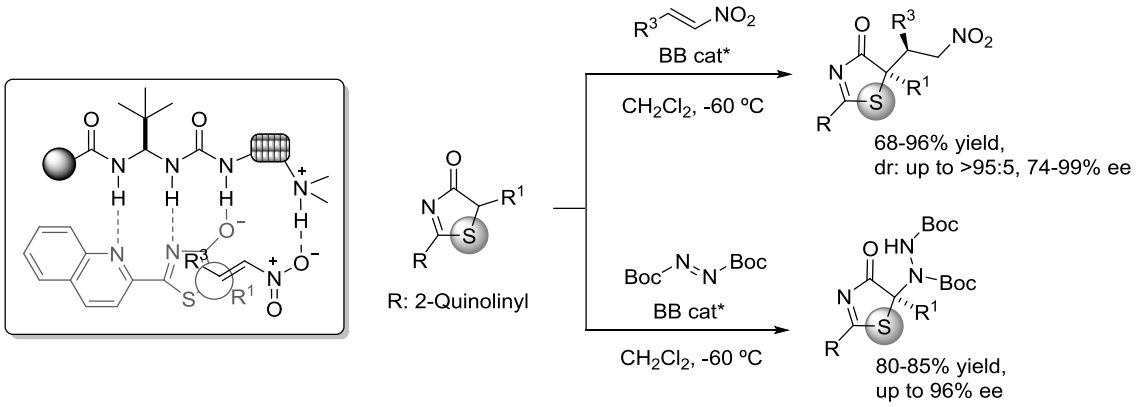


Figure 1.

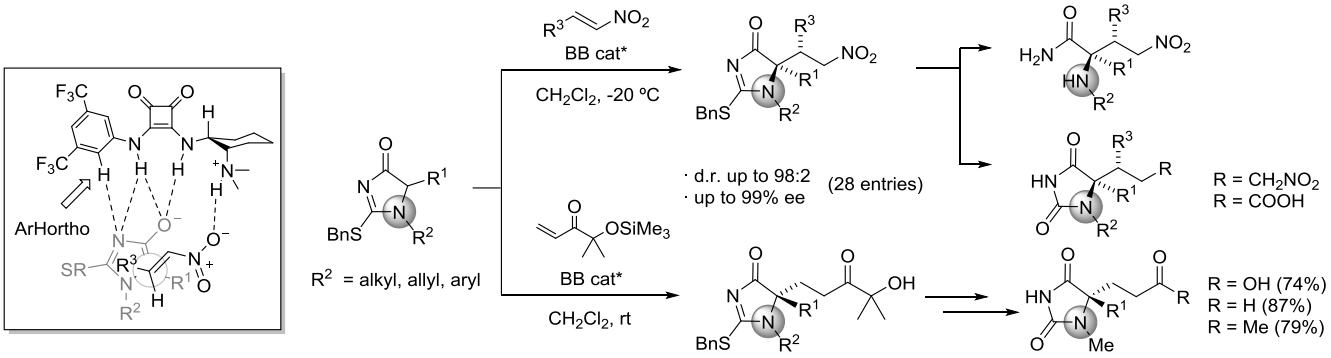
On one hand, 5*H*-thiazol-4-ones (sulfur equivalents of the widely employed 5*H*-oxazol-4-ones) were tested in the addition to nitroolefins and to azadicarboxylates using a new family of ureidopeptidic organocatalysts. Reactions performed with these catalysts gave the addition products with high yields and with excellent selectivities (up to >95:5 *dr* and 99% *ee*) (*ACIE* **2013**, *52*, 11846–11851).



Scheme 1.

On the other hand, 1*H*-imidazol-4(5*H*)-ones were synthesized and evaluated as novel pronucleophiles in conjugated reactions. These compounds not only allow highly efficient construction of tetrasubstituted stereogenic centers, as in the examples mentioned above, but unlike hitherto known templates provide direct access to *N*-substituted α-amino acid derivatives. Their addition to nitroolefins and to α-oxyenones (whose utility was first recognized by this group, *JACS* **2014**, *136*, 17869–17881) carried out with

bifunctional squaramide catalysts proceed with very good stereoselectivities (*ACIE* **2015**, *54*, 6883–6886), while the ureidopeptidic organocatalysts did not show such selectivity.



Scheme 2.

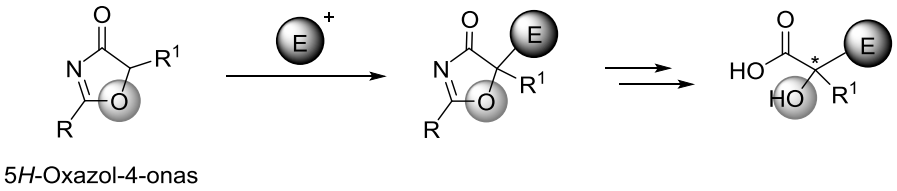
In conclusion, two new pronucleophiles were developed, as well as new bifunctional Brønsted base organocatalysts. Exploration of the properties of both heterocycles led to four successful reactions, providing access to a wide range of α,α-disubstituted α-mercaptocarboxylic and α,α-disubstituted α-amino acid derivatives, which presumably could be employed as building blocks for more complex structures.

RESUMEN

INTRODUCCIÓN

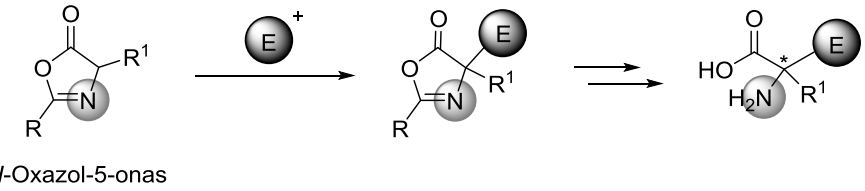
La búsqueda de nuevos pronucleófilos para la obtención de centros asimétricos tetrasustituidos utilizando organocatalizadores quirales ha sido objeto de intenso estudio en los últimos años.[1]

Por un lado, existe un gran número de ejemplos de reacciones organocatalíticas en la bibliografía para la formación de alcoholes terciarios.[2] Más concretamente, la obtención de derivados de α-hidroxiacidos α,α-disustituidos a través de 5*H*-oxazol-4-onas (Esquema 1) ha vivido un gran auge en la última década.[3]



Esquema 1

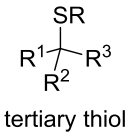
Por otro lado, se han hecho grandes esfuerzos para obtener metodologías que den lugar a compuestos α-aminocarboxílicos α,α-disustituidos,[4] siendo una de las más notables el empleo de 4*H*-oxazol-5-onas[5] como pronucleófilo (Esquema 2). Sin embargo, no existe un método generalizado que permita la obtención directa de la versión *N*-alquilada de estos compuestos,[6] lo que dificulta la síntesis estereoselectiva de moléculas de gran interés biológico (p. ej. hidantoínas *N*-sustituidas).[7]



[1] Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583–1614.
[2] a) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994. ; b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–388. ; c) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853–2873.
[3] a) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945. b) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.
[4] a) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260. b) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7.
[5] a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. b) Alba, A.-N. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720–734.
[6] a) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294–7. b) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chemie* **2015**, *127*, 181–185.
[7] Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391–443.

Esquema 2

Por otro lado, a pesar de su importancia, todavía no se ha desarrollado un procedimiento general para el acceso a tioles terciarios de configuración definida y, hasta la fecha, sólo se han podido obtener tioles terciarios ópticamente activos a través de unas pocas rutas sintéticas.[8] Esto es debido, principalmente, a que los compuestos sulfurados pueden interactuar con complejos metálicos, pudiendo desactivar el sistema catalítico.[9]

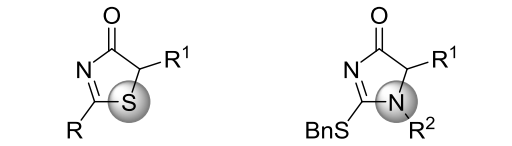


tertiary thiol

Figura 2

OBJETIVOS

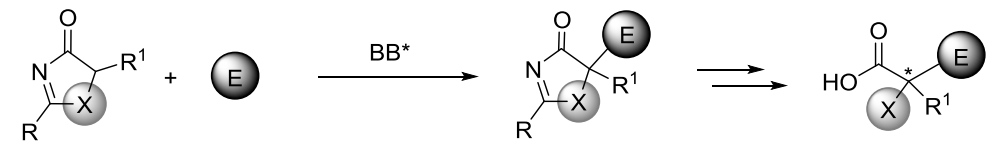
El objetivo de la presente tesis es el desarrollo de nuevos pronucleófilos para reacciones organocatalíticas que den lugar a derivados de ácidos α,α-dialquil α-thio y α-aminocarboxílicos. Así, con el fin de desarrollar este tipo de compuestos de interés biológico, se procederá a sintetizar por primera vez, 5*H*-tiazol-4-onas e 1*H*-imidazol-4(5*H*)-onas (Figura 3).



5*H*-Tiazol-4-onas 1*H*-Imidazol-4(5*H*)-onas

Figura 3

El segundo objetivo de este trabajo consistirá en el desarrollo de metodologías que permitan la adición conjugada de estos nuevo pronucleófilos a diferentes electrófilos (Esquema 3).



X = S ó NR2

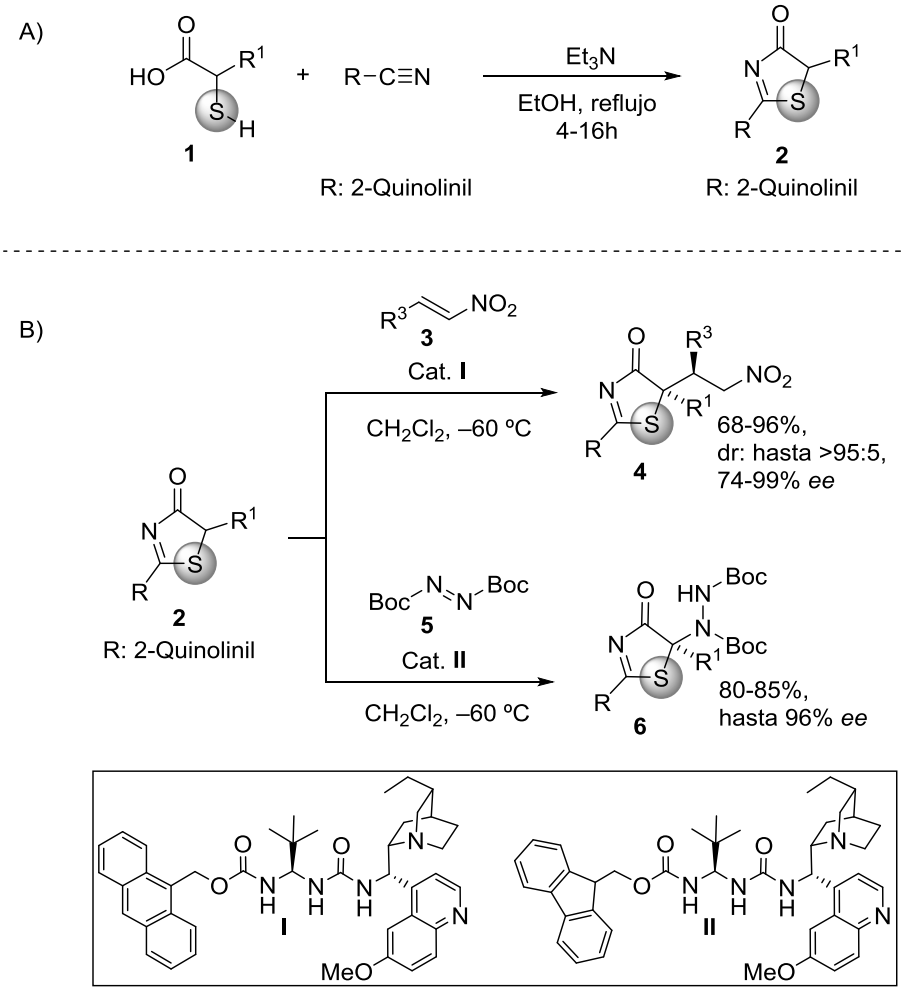
Esquema 3

[8] a) Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946–3949. b) Yu, F.; Hu, H.; Gu, X.; Ye, J. *Org. Lett.* **2012**, *14*, 2038–2041. c) Zhu, K.; Huang, H.; Wu, W.; Wei, Y.; Ye, J. *Chem. Commun.* **2013**, *49*, 2157–2159.

[9] a) J. Oudar & H. Wise, *Deactivation and Poisoning of Catalysts* (Marcel Dekker, Inc.) 1985. b) L. Louis Hegedus & Robert W. McCabe, *Catalyst Poisoning* (Marcel Dekker, Inc.) 1984.

RESULTADOS Y DISCUSIÓN

Por un lado, se sintetizaron de forma satisfactoria 5*H*-tiazol-4-onas **2** a partir de ácidos α-mercapto carboxílicos **1** (Esquema 4A) y se utilizaron por primera vez como pronucleófilos en la adición conjugada a nitroolefinas **3** y azadicarboxilatos **5**, empleando para ello una nueva familia de organocatalizadores ureidopeptídicos quirales desarrollados en el grupo de investigación. Las reacciones llevadas a cabo con este nuevo tipo de catalizador rindieron los productos deseados **4** y **6** con muy buen rendimiento y excelente estereoselectividad (del orden de >95:5 *dr* y 99% *ee*) (Esquema 4B).[10]



Esquema 4

El estado de transición propuesto para la adición de **2** a las nitroolefinas **3** es el representado en la Figura 4, pudiéndose observar el enlace de hidrógeno adicional entre el grupo aminal del catalizador y el nitrógeno presente en el anillo de quinolina de la tiazolona.

[10] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

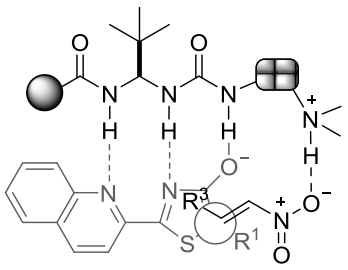
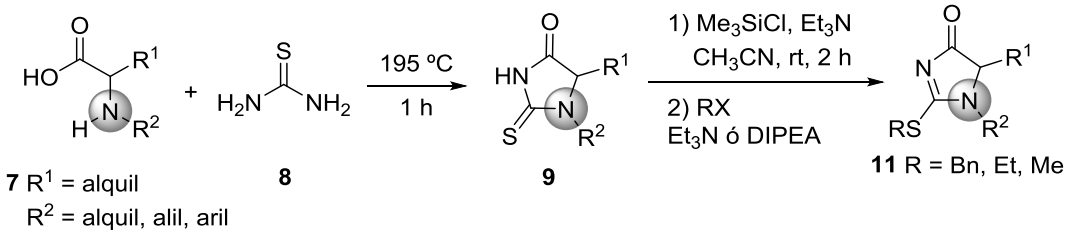


Figura 4

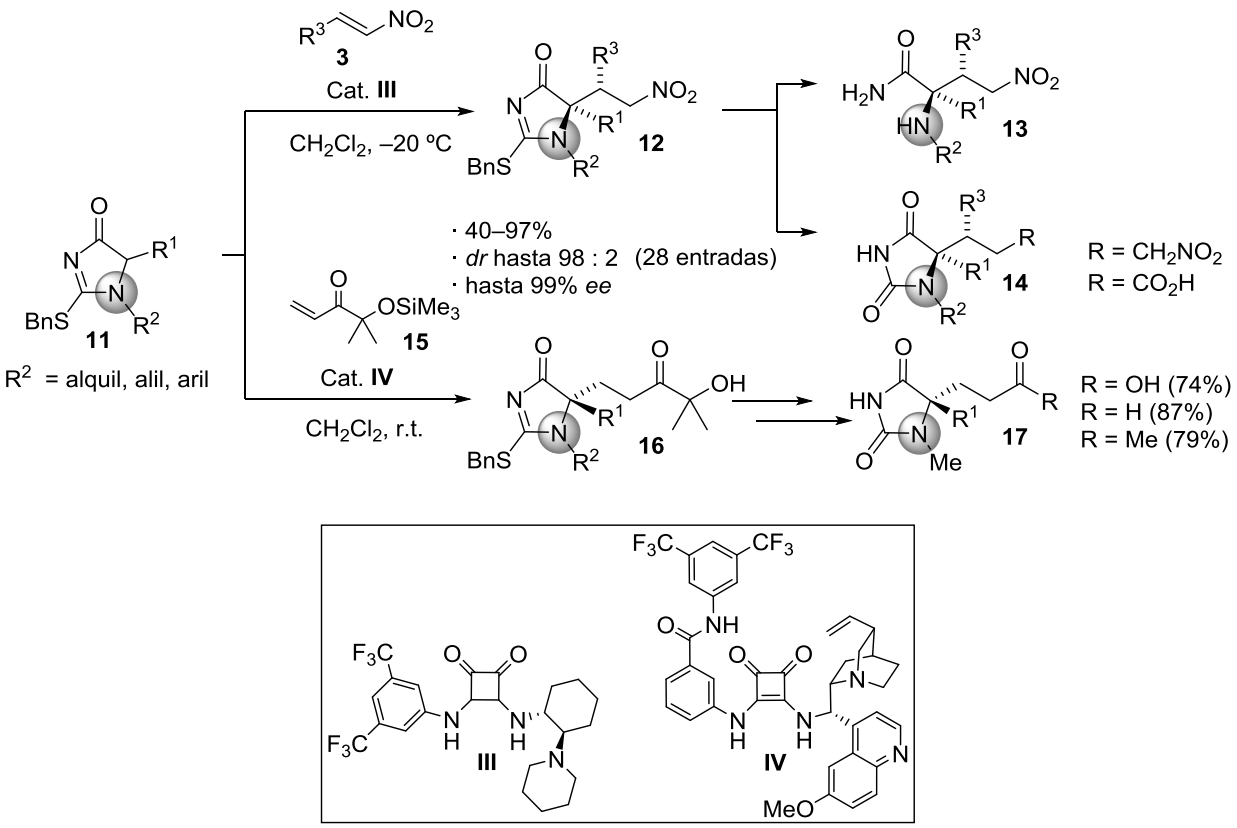
Por otro lado, la ciclación de aminoácidos *N*-sustituidos **7** con la tiourea **8** y la posterior bencilación selectiva de **9** dio lugar a 1*H*-imidazol-4(5*H*)-onas **11**. A diferencia de las 4*H*-oxazol-5-onas, estas nuevas estructuras permiten el acceso directo a derivados de α-aminoácidos *N*-sustituidos y portadores de centros estereogénicos tetrasustituidos (Esquema 5).



Esquema 5

La adición de **11** a nitroolefinas **3** y α'-oxienonas **15** (cuya utilidad sintética fue dada a conocer por este grupo de investigación)[11] se llevó a cabo mediante el uso de catalizadores bifuncionales tipo escuaramida, debido a la falta de selectividad de los organocatalizadores ureidopeptídicos, obteniéndose en ambos casos alto grado de estereocontrol (Esquema 6).[12]

[11] Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881.
[12] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886.



Esquema 6

Asimismo, se realizaron estudios de ^{1}H RMN para intentar entender la interacciones existentes entre el catalizador tipo escuaramida y los sustratos de reacción, llegando a la conclusión de que el modelo más adecuado para describir los excelentes resultados obtenidos era el que se ilustra en la Figura 5.

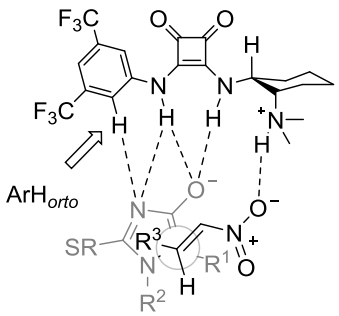


Figura 5

CONCLUSIONES

En conclusión, se han desarrollado dos nuevos pronucleófilos de forma eficaz, así como nuevos organocatalizadores bifuncionales de base de Brønsted. El estudio de las propiedades de ambos heterociclos concluyó con el desarrollo de cuatro reacciones exitosas que abren la puerta a un extenso abanico de derivados de ácidos α-tio y α-

aminocarboxílicos α,α-disustituidos, que en principio se podrían utilizar como *building blocks* de estructuras más complejas.

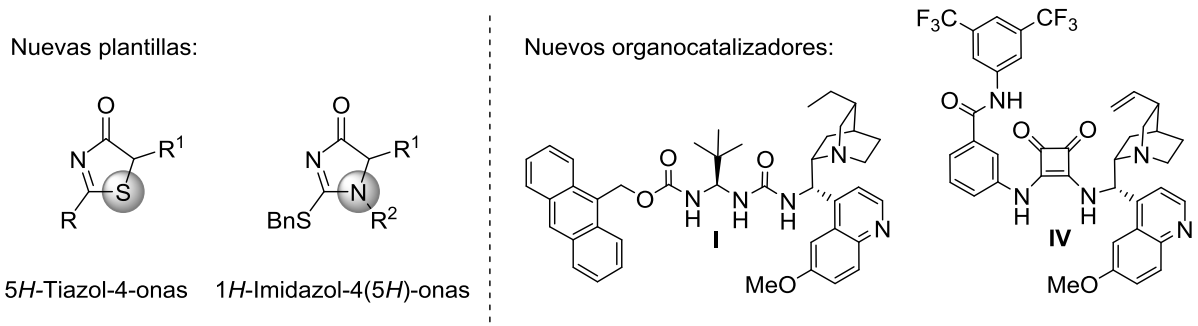


Figura 6

Abbreviations and acronyms

Ac	Acetyl (group)
ACDC	Asymmetric counteranion-directed catalysis
Ar	Aryl (group)
Å	Årmstrong
BB*	Chiral Brønsted base
Bn	Benzyl (group)
Boc	*tert*-Butyloxycarbonyl (group)
*i*Bu	Isobutyl (group)
*n*Bu	*n*-Butyl (group)
*s*Bu	*sec*-Butyl (group)
*t*Bu	*tert*-Butyl (group)
Cat.*	Chiral catalyst
Cbz	Benzyloxycarbonyl (group)
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl (group)
DBAD	Di-tert-butyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl (group)
Et_2O	Diethyl ether
EtOH	Ethanol
EWG	Electron withdrawing group
Fmoc	9-Fluorenylmethyloxycarbonyl
Hal	Halogen
ISOC	Intramolecular silyl nitronate-olefin cyclization
LDA	Lithium diisopropylamide
m-	*meta*-
MBH	Morita-Baylis-Hillman
Me	Methyl (group)
MeOH	Methanol
Mes	Mesityl (2,4,6-Me_3-C_6H_2-)

MOM	Methoxymethyl (CH_3OCH_2-)
MS	Molecular sieves
Ms	Mesyl ($MeSO_2$-)
MTBE	Methyl *tert*-butyl ether
NFSI	*N*-Fluorobenzenesulfonimide
o-	*ortho*-
p-	*para*-
PG	Protecting group
Ph	Phenyl (group)
PMP	*para*-Methoxyphenyl (4-MeO-C_6H_4-)
*n*Pr	*n*-Propyl (group)
*i*Pr	Isopropyl (group)
iPr_2O	Diisopropyl ether
PTC	Phase-transfer catalysis
quant.	Quantitative
ref.	Reference
r.t.	Room temperature
SOMO	Singly occupied molecular orbital
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBS	Tributyl silyl (group)
TFAA	Trifluoroacetic anhydride
TIPS	Triisopropylsilyl (group)
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMP	Tetramethylpiperidine
TMS	Trimethyl silyl (group)
*p*Tol	*para*-Tolyl (4-Me-C_6H_4-)
Ts	Tosyl (4-Me-C_6H_4-SO_2-)
*p*TSA	*para*-Toluenesulfonic acid

INDEX

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1. Organocatalysis

1.1.1. General considerations

Organocatalysis is commonly accepted as the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom. This strategy shows several significant advantages over conventional organometallic catalysis. For example, there are usually fewer toxicity issues associated with organocatalysis, although little is known about the toxicity of many organic catalysts.[13] Of particular importance is that most reactions are water and air tolerant, and are often easier to perform than those which require metals. These factors often affect metal catalyzed reactions, and provide a significant advantage in terms of operational simplicity. Moreover, reactions carried out with organic catalysts are often cheaper, as many enantiopure structures can often be derived from nature, which facilitates avoiding the use of expensive metals. By these means, usually both enantiomeric forms of the catalyst are readily available. Several comprehensive reviews and monographs have been published that give a full account of the organocatalysis area.[14]

Although it has not been long since MacMillan coined the term "organocatalysis" at the dawn of the twenty first century,[15] organic molecules have been used as catalysts from the very beginning of synthetic chemistry. The discovery of the first organocatalytic reaction is attributed to Justus von Liebig, who in 1860 accidentally found that the hydrolysis of dicyan to oxamide was accelerated by the presence of an aqueous solution of acetaldehyde (Scheme 1).[16]

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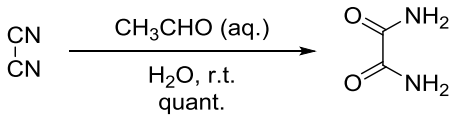
[13] For a study on the cytotoxicity of organocatalysts, see: Nachtergael, A.; Coulembier, O.; Dubois, P.; Helvenstein, M.; Duez, P.; Blankert, B.; Mespouille, L. *Biomacromolecules* **2015**, *16*, 507–514.

[14] a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175. c) List, B. *Adv. Synth. Catal.* **2004**, *346*, 1021. d) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T.; Dalko, P. I.; Moisan, L.; Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8–27. e) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331. f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660. g) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189. h) Bernardi, L.; Fochi, M.; Comes Franchini, M.; Ricci, A. *Org. Biomol. Chem.* **2012**, *10*, 2911–2922. i) Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346–14396. j) *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis* (A. Berkessel & H. Gröger ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2005. k) Enantioselective Organocatalysis (P. I. Dalko ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2007. l) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (P. I. Dalko ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2013.

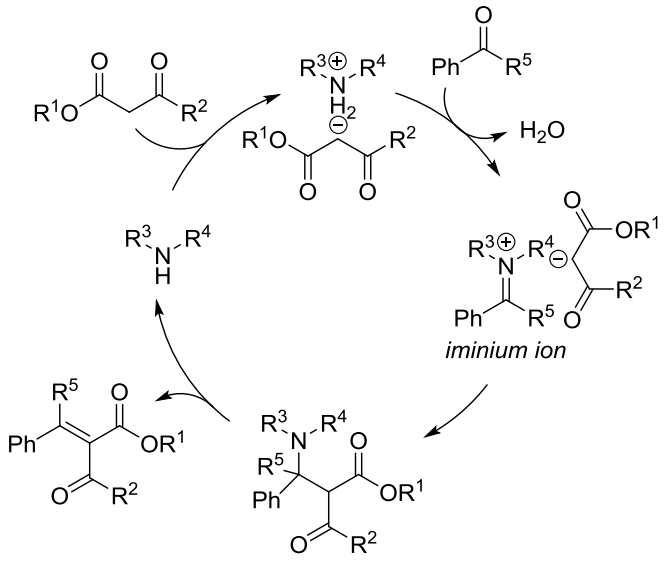
[15] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[16] von Liebig, J. *Ann. der Chemie und Pharm.* **1860**, *113*, 246–247.



Scheme 1.

Another milestone for modern organocatalysis can be found in the earliest works of Emil Knoevenagel. During his research, he found that primary and secondary amines, along with their salts, could catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones (Scheme 2).[17] Outstandingly, he also suggested the same intermediates that Weistheimer later proposed in his retro-aldolization studies.[18]



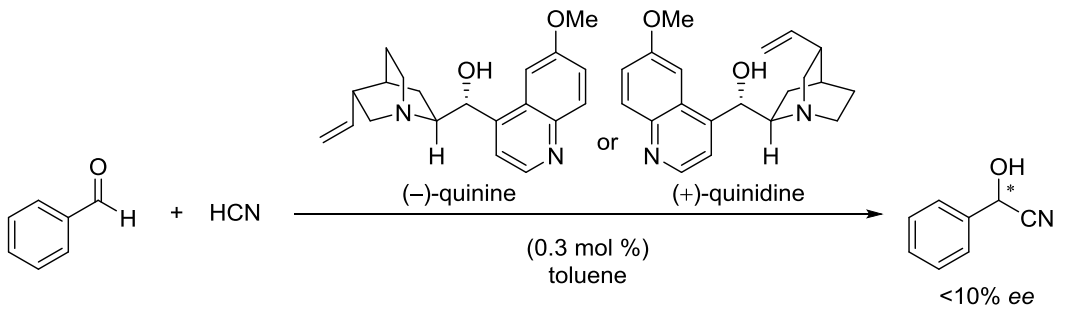
Scheme 2.

Concerning the utilization of organic Brønsted bases as catalysts, Bredig's work has to be mentioned, who in 1912 reported that the hydrocyanation of benzaldehyde is accelerated by the pseudoenantiomeric *Cinchona* alkaloids, quinine and quinidine, and that the resulting cyanohydrins are optically active and are of opposite configuration (Scheme 3). The enantiomeric excess of the resulting adducts did not surpass 10% *ee*, but the importance of this reaction is conceptually groundbreaking.[19]

[17] a) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 172–174. b) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 738–748. c) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2585–2595. d) Knoevenagel, E. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2596–2619. For a review on Knoevenagels's work, see: e) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734.

[18] Westheimer, F. H.; Cohen, H. *J. Am. Chem. Soc.* **1938**, *60*, 90–94.

[19] a) Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7–23. For a review about chiral Brønsted bases in asymmetric organocatalysis, see: b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653.

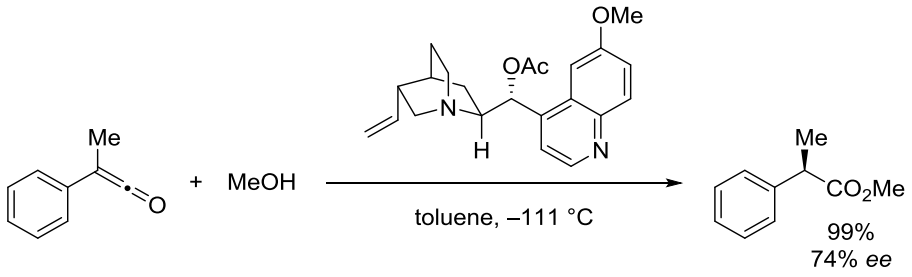


Entry	Cat.*	α (°)[a]
1	(–)-quinine	+0.23
2	(+)-quinidine	–0.27

[a] Measured in $CHCl_3$.

Scheme 3.

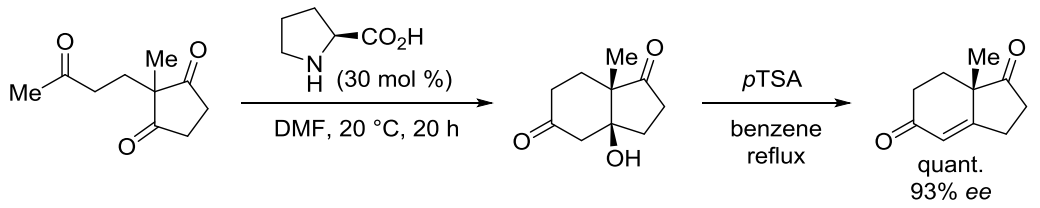
It was not until the late 1950s when Pracejus, following Bredig's work, developed the first reactions with synthetically useful enantioselectivities. He reported the addition of methanol to methyl phenyl ketene to afford (–)-α-phenyl methylpropionate in 74% *ee* by using *O*-acetyl quinine as catalyst (Scheme 4).[20]



Scheme 4.

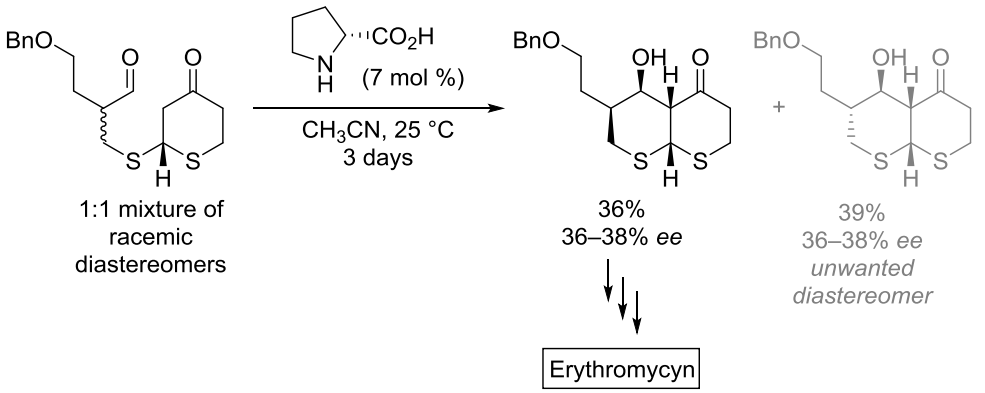
Another remarkable event in the history of organocatalysis was the employment of L-proline for the most efficient asymmetric Robinson annulation reported during the early 1970s.[21] The Hajos–Parrish–Eder–Sauer–Wiechert reaction (an intramolecular aldol reaction) allowed access to key intermediates for the synthesis of some natural products (Scheme 5), and offered a practical and enantioselective route to the Wieland–Miescher ketone.[22] It must not be forgotten, that this chemistry is based on the early studies of Langenbeck[23] and on the extensive research of Stork and co-workers on enamine chemistry.[24]

[20] Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.
[21] 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.
[22] 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.
[23] Langenbeck, W. *Justus Liebig's Ann. der Chemie* **1929**, *469*, 16–25.



Scheme 5.

In 1981, Woodward conducted an important example on iminium catalysis, which consisted on a D-proline-catalyzed deracemization of a thianone intermediate followed by an intramolecular aldol reaction (Scheme 6).[25] Although the outcome of this reaction was rather poor (36% *ee*), it led to the synthesis of erythromycin, hence its relevance.



Scheme 6.

The early 1980s meant the development of more general efficient asymmetric organocatalysts. Chiral diketopiperazines were synthesized by Inoue for Brønsted acid-catalyzed asymmetric hydrocyanation reactions,[26] and were subsequently employed by Lipton's group to perform an efficient hydrocyanation of aldimines.[27] Efficient phase-transfer reactions (ion-pairing catalysis) were first developed on the mid-1980s, when

[24] a) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029–2030. For some reviews on aminocatalysis, see: b) List, B. *Chem. Commun.* **2006**, 819–824. c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171. Reviews on diaryl prolinol silyl ether: d) Mielgo, A.; Palomo, C. *Chem. – An Asian J.* **2008**, *3*, 922–948. e) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264. f) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 13860–13874. For a review on chiral primary amines: g) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807–1821. For a review on amonocatalytic remote functionalization: h) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287–2300.

[25] Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213.

[26] a) Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229–230. b) Asada, S.; Kobayashi, Y.; Inoue, S. *Die Makromol. Chemie* **1985**, *186*, 1755–1762. c) Kobayashi, Y.; Asada, S.; Watanabe, I.; Hayashi, H.; Motoo, Y.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 893–895. d) Matthews, B.; Jackson, W.; Jayatilake, G.; Wilshire, C.; Jacobs, H. *Aust. J. Chem.* **1988**, *41*, 1697–1709.

[27] Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.

researchers at Merck reported the alkylation of substituted 2-phenyl-1-indanone systems with excellent enantioselectivity (up to 94% *ee*) in the presence of catalytic amounts of substituted *N*-benzylcinchoninium halides.[28] Mention should be made here of the *Cinchona* alkaloid-catalyzed cycloaddition reactions, described by Kagan,[29] as well as the earliest examples of the epoxidation of chalcones using polyamino acids under triphasic conditions, by Juliá and Colonna.[30] These examples are formally the first use of hydrogen-bonding catalysis in asymmetric synthesis (Figure 1).

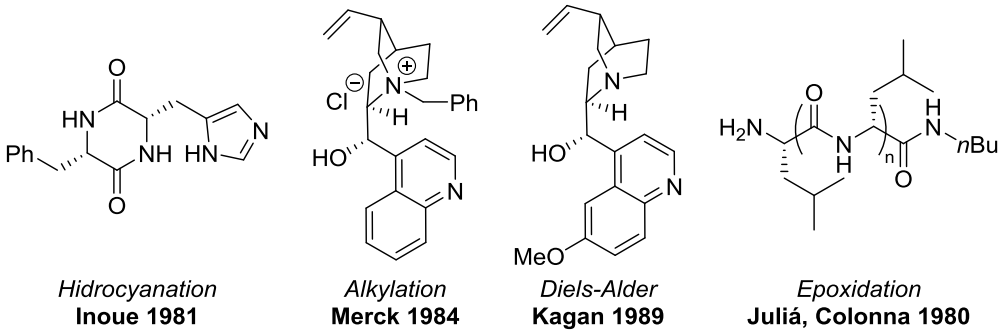
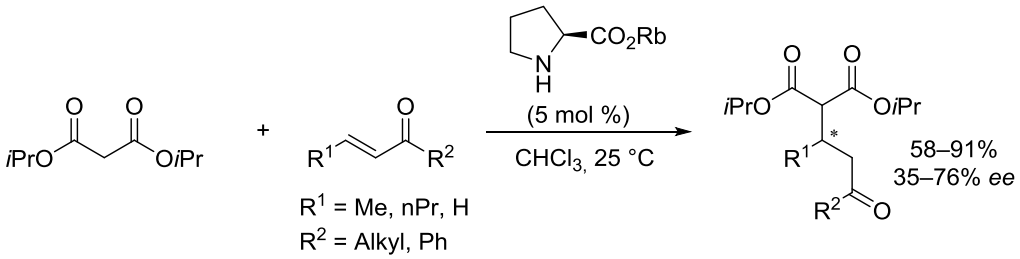


Figure 1.

In the 1990s, metallic salts of proline were employed as catalysts by Yamaguchi and Taguchi, in order to perform enantioselective Michael additions on enals (70–77% *ee*). Iminium ion activation was suggested in those cases (Scheme 9).[31]



Scheme 7.

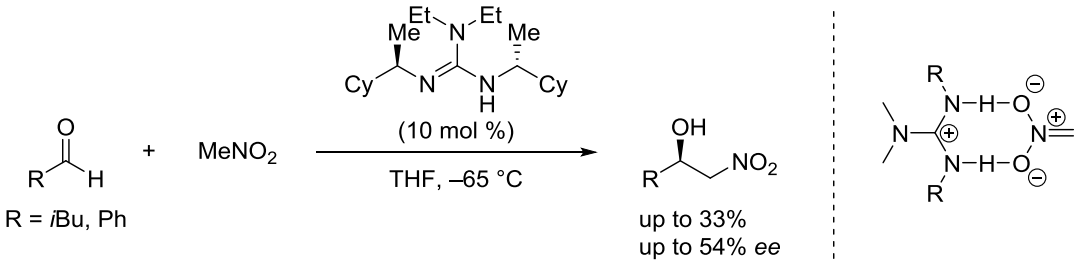
[28] a) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447. b) Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745–4752. For a review on io-pairing catalysis, see: c) Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.

[29] a) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403–7406. For a review on catalytic Diels-Alder reactions, see: b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019.

[30] a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929–931. b) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317–1324. For a mechanistic discussion of this reaction, see: c) Berkessel, A.; Gasch, N.; Glaubitz, K.; Koch, C. *Org. Lett.* **2001**, *3*, 3839–3842.

[31] a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed.* **1993**, *32*, 1176–1178. b) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805–8808. For a review on iminium ion-catalysis, see: c) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470. d) Brazier, J. B.; Tomkinson, N. C. O. *Top. Curr. Chem.* **2010**, *291*, 281–347.

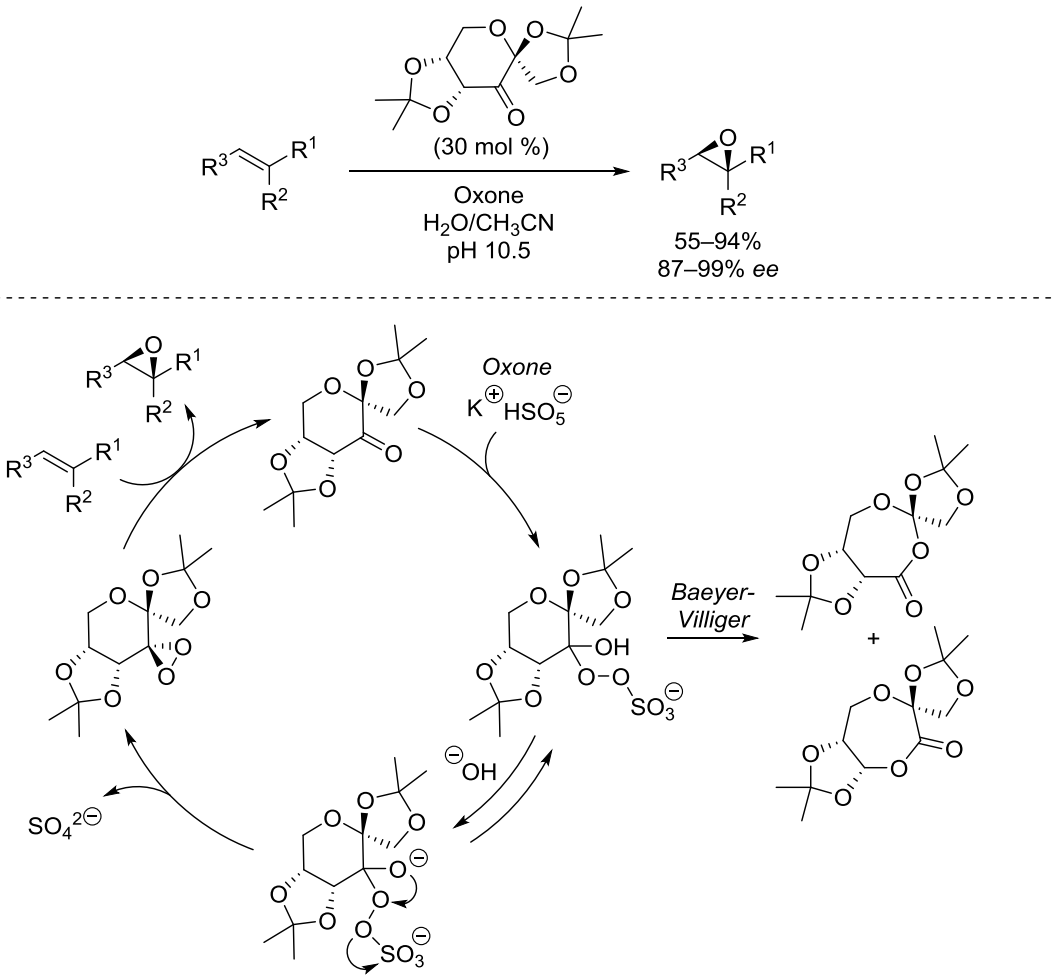
A pioneering report on using chiral guanidines for asymmetric organocatalysis appeared in 1994, when Nájera documented the Henry reaction of isopentenal and benzaldehyde with nitromethane using *C2*-symmetric guanidines as catalysts. The corresponding β-nitroalcohols were obtained with moderate yields and enantioselectivities (Scheme 8).[32]



Scheme 8.

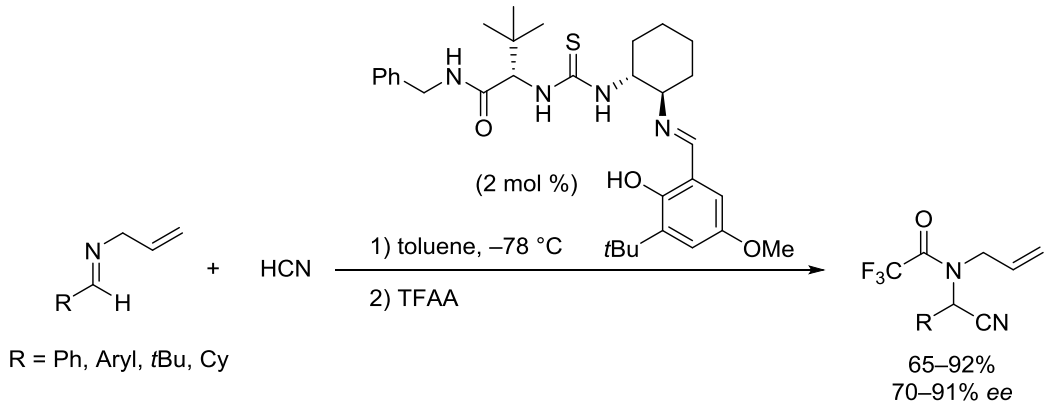
Later, in 1997, Shi made a great contribution to the field, reporting the asymmetric epoxidation of *trans*-olefins and trisubstituted alkenes by using a fructose-derived ketone as a catalyst and oxone as an oxidant. [33] pH was found to be an important factor for the epoxidation. On one hand, high pH accelerates autodecomposition of Oxone, so reactions with this reagent are usually carried out at pH 7–8. On the other hand, when this pH values were employed the catalyst decomposed rapidly, which made the authors think that a Baeyer-Villiger reaction could be the cause, as depicted in Scheme 9. Higher pH seemed to avoid this background reaction, so after optimization, pH 10.5 was chosen to be the most appropriate to perform the reaction. Actually, excellent enantioselectivities were achieved following this method (Scheme 9).

[32] a) Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393–1402. For a review on chiral guanidines, see: b) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488–507.
[33] Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.



Scheme 9.

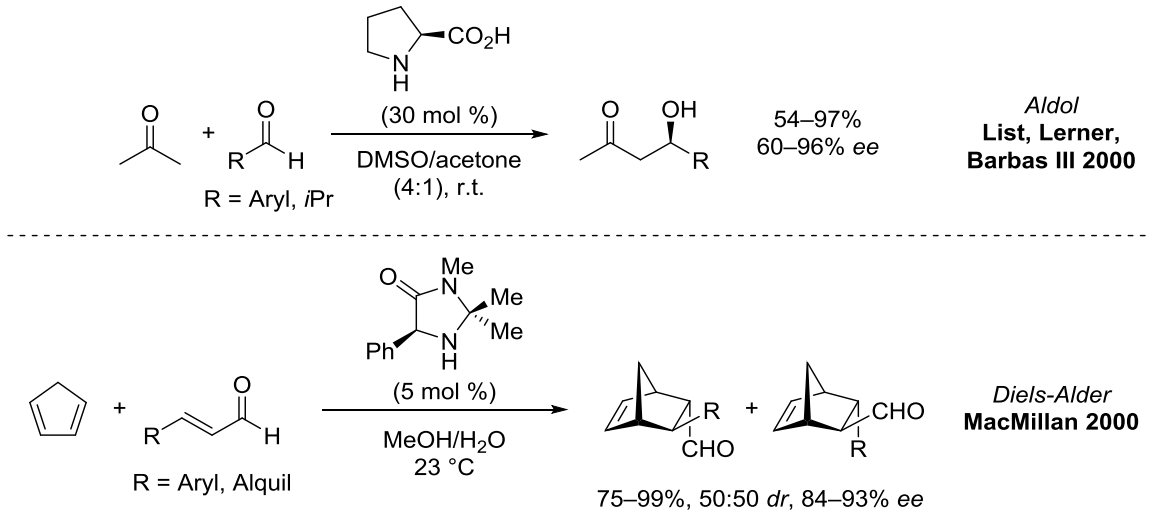
Also in this decade, mention should be made to the utilization of chiral thioureas as organocatalysts for the first time. In 1998, Jacobsen presented the chiral Brønsted acid-catalyzed hidrocyanation of aldimines. The Strecker reaction was carried out with peptide based thiourea derivatives (Scheme 10).[34]



Scheme 10.

[34] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902. For a review on asymmetric catalysis with peptides, see: b) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036–12041.

Unfortunately, the effect of these outstanding contributions was limited in the field of organic chemistry. The transition to the twenty first century breathed new life into this area, with the works of List, Lerner and Barbas III[35] in enamine chemistry and the works of MacMillan[15] in iminium chemistry paving the way (Scheme 11). Since 2000, the chemical community has reinforced its aim to develop new catalysts and methodologies that do not require the use of metals.[36]



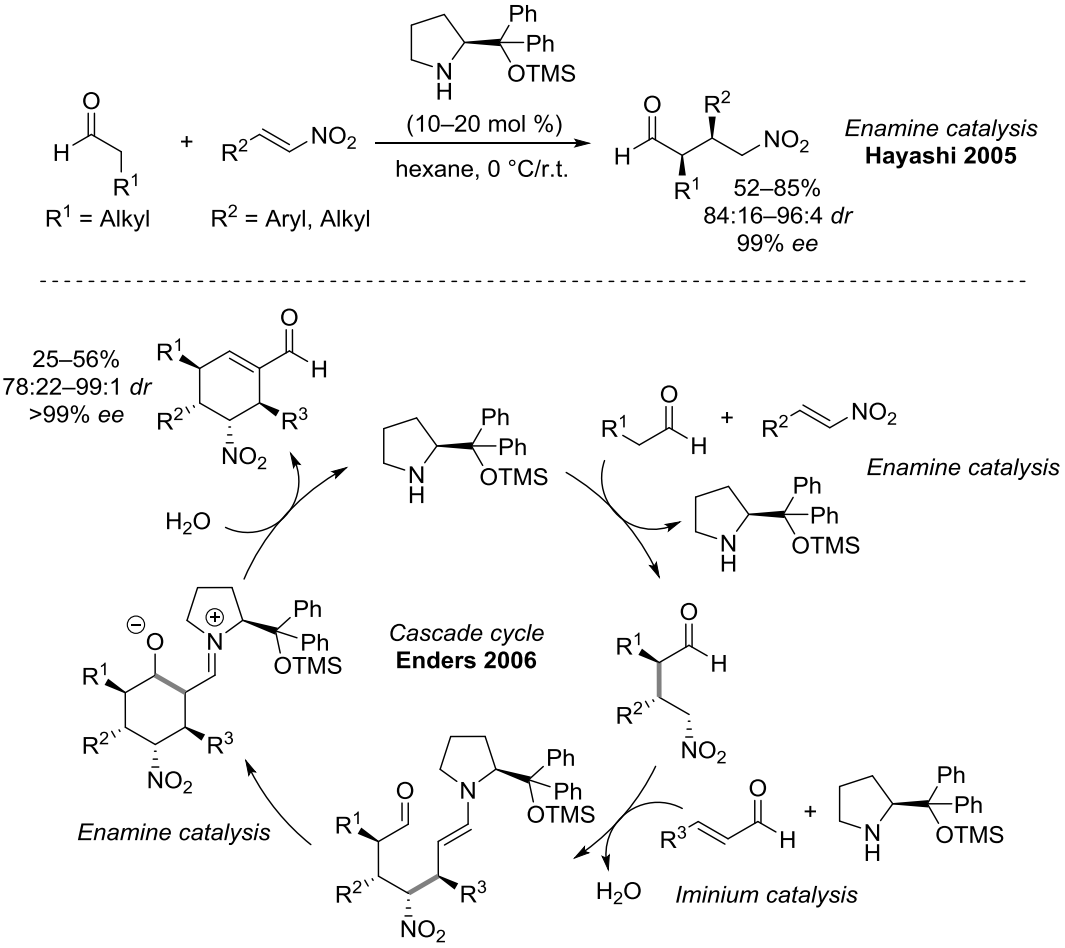
Scheme 11.

Due to the exponential growth in the number of these new strategies during the so-called "golden age" of organocatalysis in the 2000s, naming those which have meant significant achievements is not an easy task. However, some works that have supposed important developments must be highlighted.

The field of aminocatalysis has been particularly prolific. Apart from the pioneering results depicted above, noteworthy examples via iminium ion activation include: the Friedel-Krafts reaction to enals by MacMillan in 2001,[37] the reduction of enals by List[38] and MacMillan[39] in 2005, and the conjugated amination of enals by MacMillan in 2006.[40] Enamine activation also rendered groundbreaking examples, such as the α-oxidation of enolizable aldehydes using oxygen singlet by Córdova in 2004,[41] and the first Michael addition of aldehydes to nitroolefins by Hayashi in 2005 (Scheme 12).[42] Additionally, both activation modes have also been combined for the consecutive formation of multiple

[35] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[36] For an explanation of why the Hajos–Parrish–Eder–Sauer–Wiechert reaction remained an enigma until the 2000s, see: Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47.
[37] Paras, N. a; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
[38] Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110.
[39] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.
[40] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.
[41] Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915.
[42] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.

stereocentres, as in the case of the first iminium ion/enamine tandem reactions by List,[43] MacMillan[44] and Jørgensen[45] in 2005; and the multicomponent organocatalyzed Michael/Michael/aldol condensation by Enders in 2006 (Scheme 12).[46]



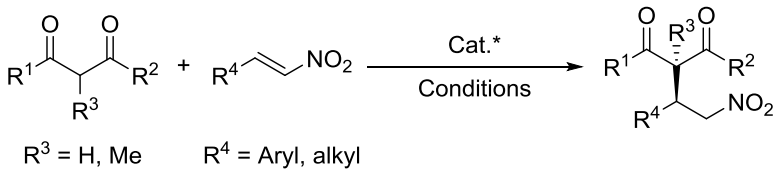
Scheme 12. Representative examples of enamine/iminium catalysis in the 2000's.

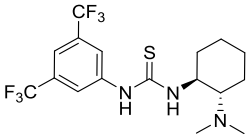
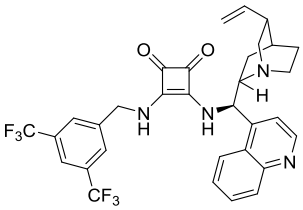
Non covalent activation modes have undergone a great growth during the last two decades.[47] Since the development of thiourea-Brønsted base bifunctional catalysts by Takemoto in 2003 (Table 1, entry 1),[48] and the Diels-Alder reaction catalyzed by TAD-

[43] Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.
[44] Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.
[45] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.
[46] 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.
[47] For leading reviews, see: a) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516–532. b) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, *2011*, 2209–2222.
[48] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

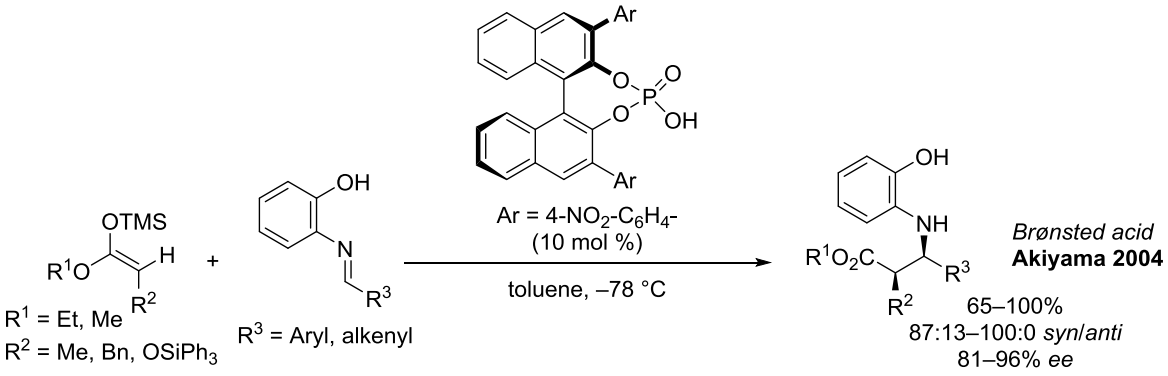
DOL reported by Rawal in 2003;[49] new H-bond donor moieties have appeared, as the squaramides by Rawal in 2008 (Table 1, entry 2).[50]

Table 1.



	Group	R^1	R^2	Catal.*	Conditions	Results
1	**Takemoto 2003**	$R^1 = R^2$ = OEt, OMe			(10 mol %) toluene, r.t.	74–95% 81–93% *ee*
2	**Rawal 2008**	$R^1 \neq R^2$ = Aryl, OAlkyl, Alkyl			(0.5 mol %) CH_2Cl_2, r.t.	65–97% 50:50–98:2 *dr* 88–97% *ee*

Brønsted acids in general, and chiral phosphoric acids in particular, have been widely employed since they discovery by Akiyama (Scheme 13) and Terada in 2004. [51]

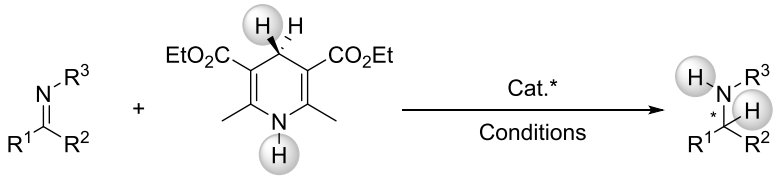


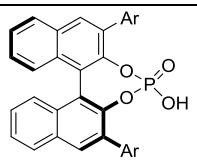
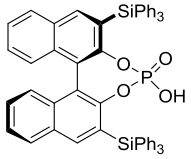
Scheme 13.

As a case in point, the enantioselective hydrogenation of double bonds reported by List and MacMillan in 2005 (Table 2).[52]

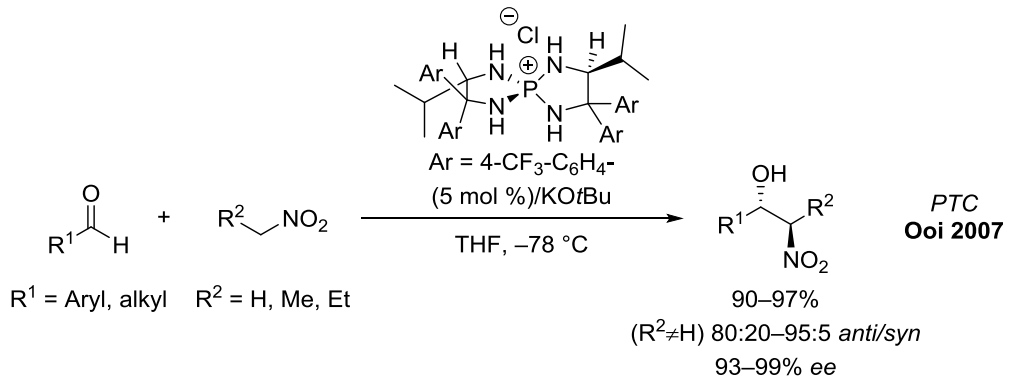
[49] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146–146.
[50] Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
[51] a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568. b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. For a leading phosphoric acids review, see: c) Terada, M. *Synthesis* **2010**, 1929–1982.

Table 2.



	Group	R^1	R^2	R^3	Cat.*	Conditions	Results
1	**List 2005**	Aryl, *i*Pr	Me	PMP	 Ar = 2,4,6-*i*Pr$_3$-C$_6$H$_2$- (1 mol %)	Toluene 35 °C	80–96% 80–92% *ee* (*S*)
2	**MacMillan 2006**	Aryl, Alkyl, Cy	Me, CH_2F	Aryl	 (10 mol %)	5Å MS benzene 40–50 °C	49–92% 81–97% *ee* (*R*)

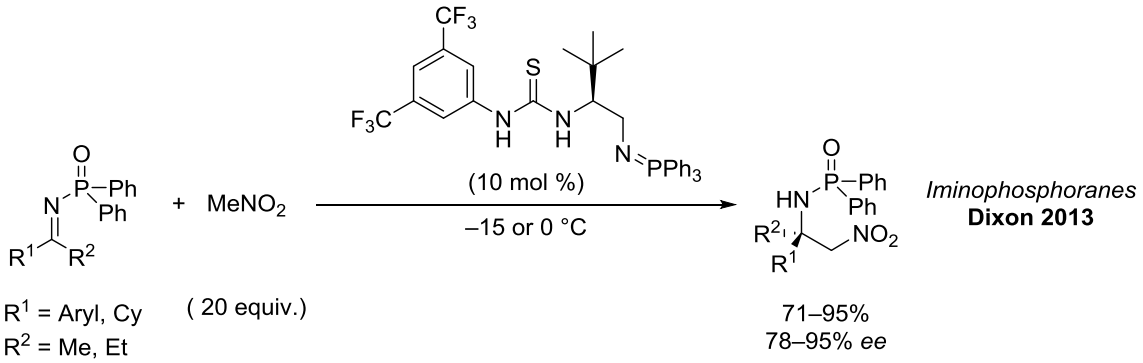
Other activation modes have been developed and explored with success during these years, including: the asymmetric counteranion-directed catalysis (ACDC) by List in 2006,[53] the phase-transfer catalysis employing chiral tetraaminophosphonium salts by Ooi in 2007 (Scheme 14),[54] and SOMO[55] and photoredox[56] catalysis developed by MacMillan in 2007 and 2008.



Scheme 14.

[52] a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427. b) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86. For a racemic version of the reaction, see: c) Rueping, M.; Azap, C.; Sugiono, E.; Theissmann, T. *Synlett* **2005**, 2367–2369.
[53] Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4195.
[54] Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393.
[55] Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.
[56] Nicewicz, D. a; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

Finally, new Brønsted superbases have been explored, as the bifunctional iminophosphoranes by Dixon in 2013.[57]



Scheme 15.

[57] a) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16348–16351. For the bifunctional iminophosphorane catalyzed enantioselective ketimine phospha-mannich reaction, see: b) Robertson, G.; Farley, A.; Dixon, D. *Synlett* **2015**, *27*, 21–24. For the bifunctional iminophosphorane catalyzed enantioselective sulfa-michael addition to unactivated α-substituted acrylate esters, see: c) Farley, A. J. M.; Sandford, C.; Dixon, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 15992–15995.

1.1.2. **Formation of quaternary stereocentres**

The properties of organic molecules are closely linked to their form. The shape of most of structurally complex molecules is directed by the three-dimensional orientation of the substituents of their stereogenic carbons. The chirality of biological macromolecules makes one enantiomer of a small molecule fit better than the other in its corresponding active binding site. In the last years, this task has become more and more important since the optical purity is now a strict requirement for the commercialization of new drugs and pharmaceutical products.[58] Therefore, the more stereoselective methodologies are available, the more efficiency could be achieved in the synthesis of such compounds.

The construction of quaternary stereocenters in complex molecules is one of the most challenging obstacles in asymmetric synthesis (Figure 2).[59]

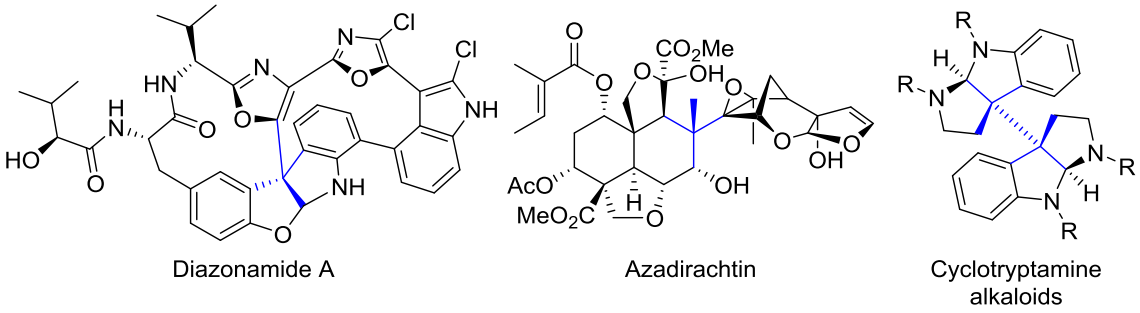


Figure 2. Selected examples where the construction of quaternary stereocenters was employed in the total synthesis of a natural product.[60]

The challenge is double here: first, the addition of the fourth and last substituent must be performed on a central atom that it is already hindered for the presence of other three lateral chains (is sterically congested). The second defiance is being able to obtain a single enantiomer of the product in this process, what obliges the catalyst to differentiate

[58] For the asymmetric synthesis of active pharmaceutical ingredients, see: Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
[59] For a review on the direct construction of vicinal all-carbon quaternary stereocenters in natural product synthesis, see: Long, R.; Huang, J.; Gong, J.; Yang, Z. *Nat. Prod. Rep.* **2015**, *32*, 1584–1601.
[60] Selected examples where the construction of quaternary stereocenters was employed in the total synthesis of a natural product: Diazonamide A: a) Nicolaou, K. C.; Bella, M.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3495–3499. b) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888–12896. c) Nicolaou, K. C.; Hao, J.; Reddy, M. V; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897–12906. d) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4961–4966. Azadirachtin: e) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7633–7635. Cyclotryptamine alkaloids: f) Steven, A.; Overman, L. E. *Angew. Chem. Int. Ed.* **2007**, *46*, 5488–5508.

the pre-existing appendages of the substrate. For these reasons, the asymmetric formation of quaternary stereocentres has been subject of intense scientific studies (Figure 3).[61]

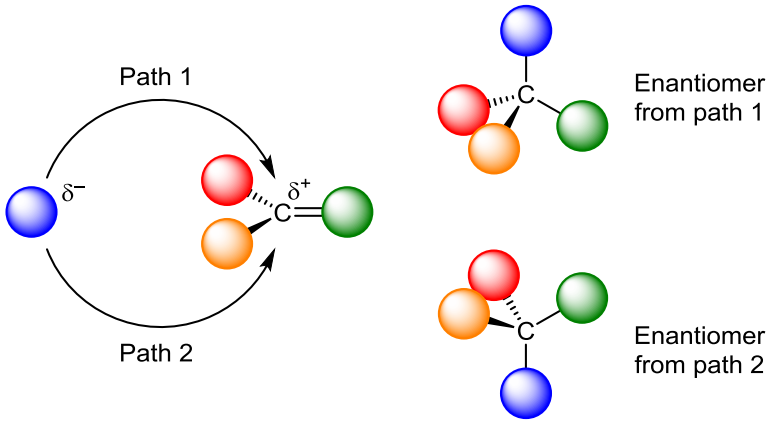
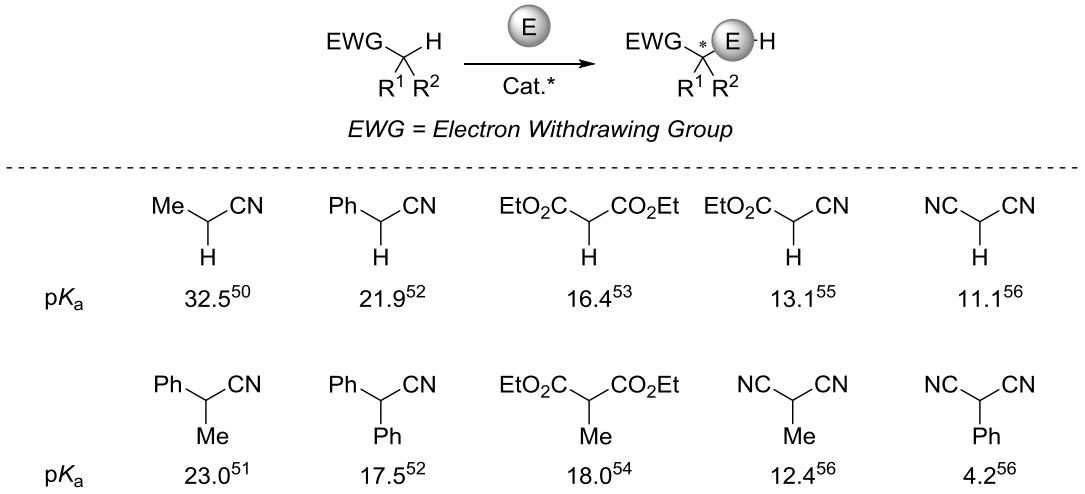


Figure 3.

1.1.3. **Importance of nucleophile design**

A common strategy for the formation of asymmetric *C*-*C* bonds involves the nucleophillic addition of carbanions to an electron deficient carbon, using a catalyst to promote not only bond formation but also stereocontrol (Scheme 16). To increase the reactivity of these substrates, the pronucleophillic α *C*(sp^3)–*H* functionality is often attached to electron withdrawing functional groups (EWG) that provide large reductions in pK_a at the desired deprotonation site (Scheme 16).[61n] This manoeuvre can also help the catalyst to distinguish between the two planar faces of both the nucleophile and the electrophile, rendering more enantioselectivity to the reaction.

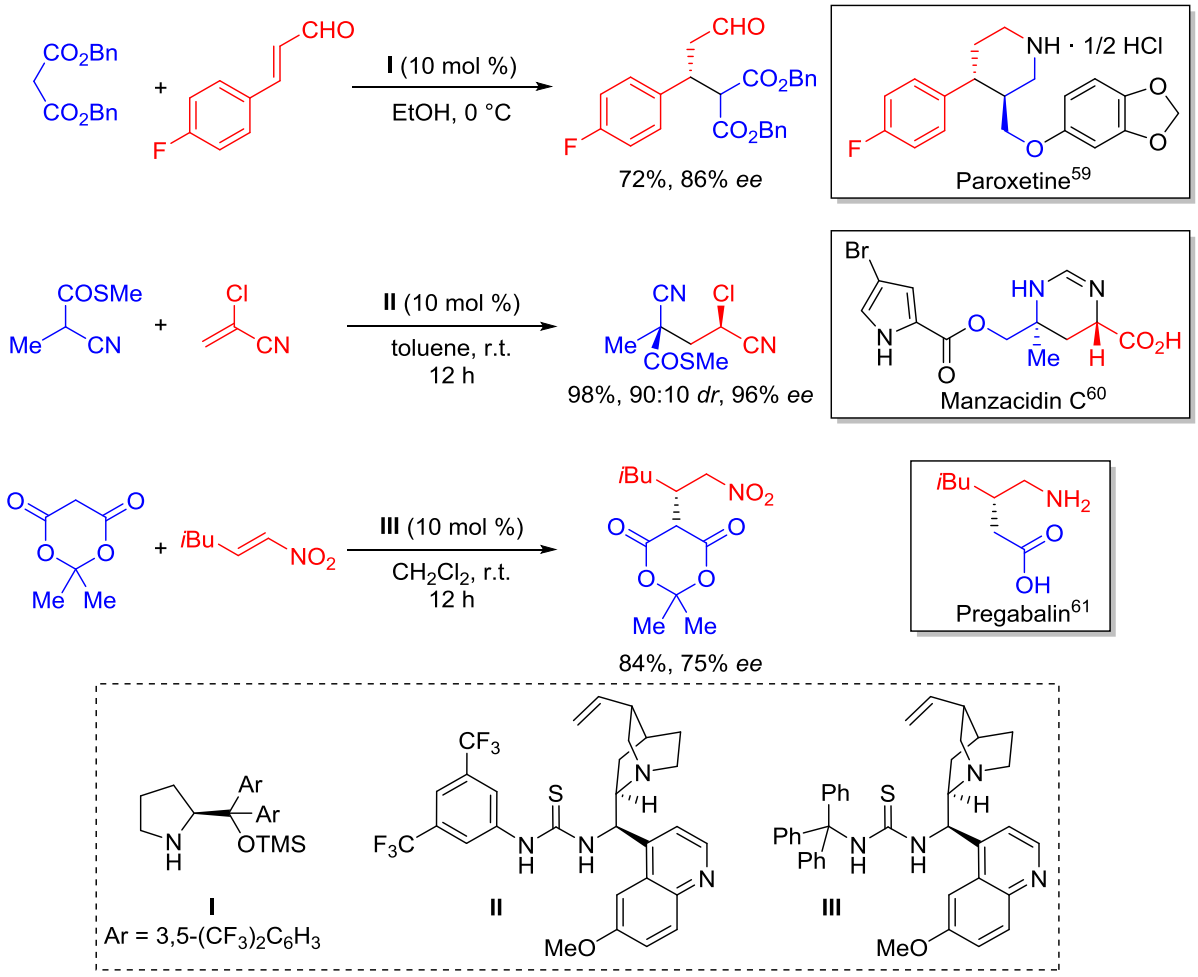
[61] For some selected reviews on the asymmetric formation of quaternary stereocentres, see: a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460. b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066. c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401. d) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597. e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. f) Ramon, D.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. g) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5363–5367. h) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 11943–11948. i) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (J. Christoffers & A. Baro ed., WILEY-VCH) 2005. j) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. k) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. l) Cozzi et al.m) Riant & Hannedouchen) Bella & Gasperio) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4597. p) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745–2759. q) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191.



Scheme 16. pK_a of several methylenes and methines measured in DMSO.

This strategy has shown plenty of notable examples in organocatalysis,[69] where the enantioselective transformation is accompanied by a thoughtful design of the nucleophile. This fact can help the chemist to elaborate the new adduct into desirable scaffolds, such as natural products or synthetically interesting structures (Scheme 17).[70]

[62] Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885–1886.
[63] Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209–223.
[64] 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.
[65] Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.
[66] Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.
[67] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.
[68] Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
[69] Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261–3288.
[70] For examples of organocatalytic synthesis of natural compounds, see: a) Marcia de Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575–2600. b) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138–1167. c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. For multiple examples of activated carbonyl compounds as nucleophiles in organocatalysis, see: ref. 61, page 8 and references herein.



Scheme 17. Selected examples of activated carbonyl compounds as nucleophiles as key steps in the total synthesis of natural products.

1.2. **Heterocyclic pronucleophiles**

1.2.1. **General considerations**

In literature, we can find a large number of examples of chiral natural products or bioactive substances with a heterocyclic core, where the heteroatom is attached to an α *C*(sp^3) position of a carbonyl moiety, as in a lactam or lactone. The complexity of their synthesis it is not to be underestimated, especially when the carbon in α position to the carbonyl group is tetrasubstituted.[70a-c] Below these lines are depicted few examples of

[71] Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305–4309.
[72] a) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768–769. The total synthesis could be completed following: b) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708–10709.
[73] Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. M. P. *Eur. J. Org. Chem.* **2009**, 1340–1351.

these biologically interesting compounds, whose total syntheses were reported at a given time.

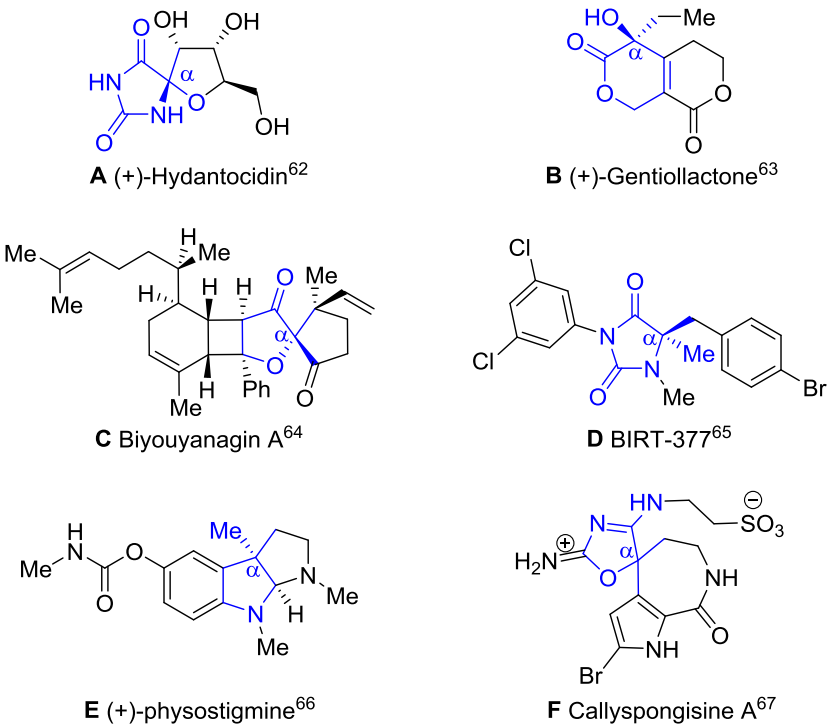


Figure 4.

A strategy for the generation of tetrasubstituted carbon stereocentres involves the use of heterocycles as pronucleophiles in reactions under proton transfer conditions (Scheme 18). Through the last decades, this task has been focusing the attention of sev-

[74] For the total synthesis of (+)-hydantocidin, see: a) Nakajima, N.; Matsumoto, M.; Kirihara, M.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1996**, *52*, 1177–1194. For previous syntheses, see: b) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S.; Sato, S. *Tetrahedron* **1991**, *47*, 2111–2120. c) Mio, S.; Shiraishi, M.; Sugai, S.; Haruyama, H.; Sato, S. *Tetrahedron* **1991**, *47*, 2121–2132. For references on herbicidal activity, see: d) Renard, A.; Lhomme, J.; Kotera, M. *J. Org. Chem.* **2002**, *67*, 1302–1307. e) Walter, M. W. *Nat. Prod. Rep.* **2002**, *19*, 278–291.

[75] For the total synthesis of (+)-gentiollactone, see: Kakuda, R.; Machida, K.; Yaoita, Y.; Kikuchi, M.; Kikuchi, M. *Chem. Pharm. Bull. (Tokyo).* **2003**, *51*, 885–887.

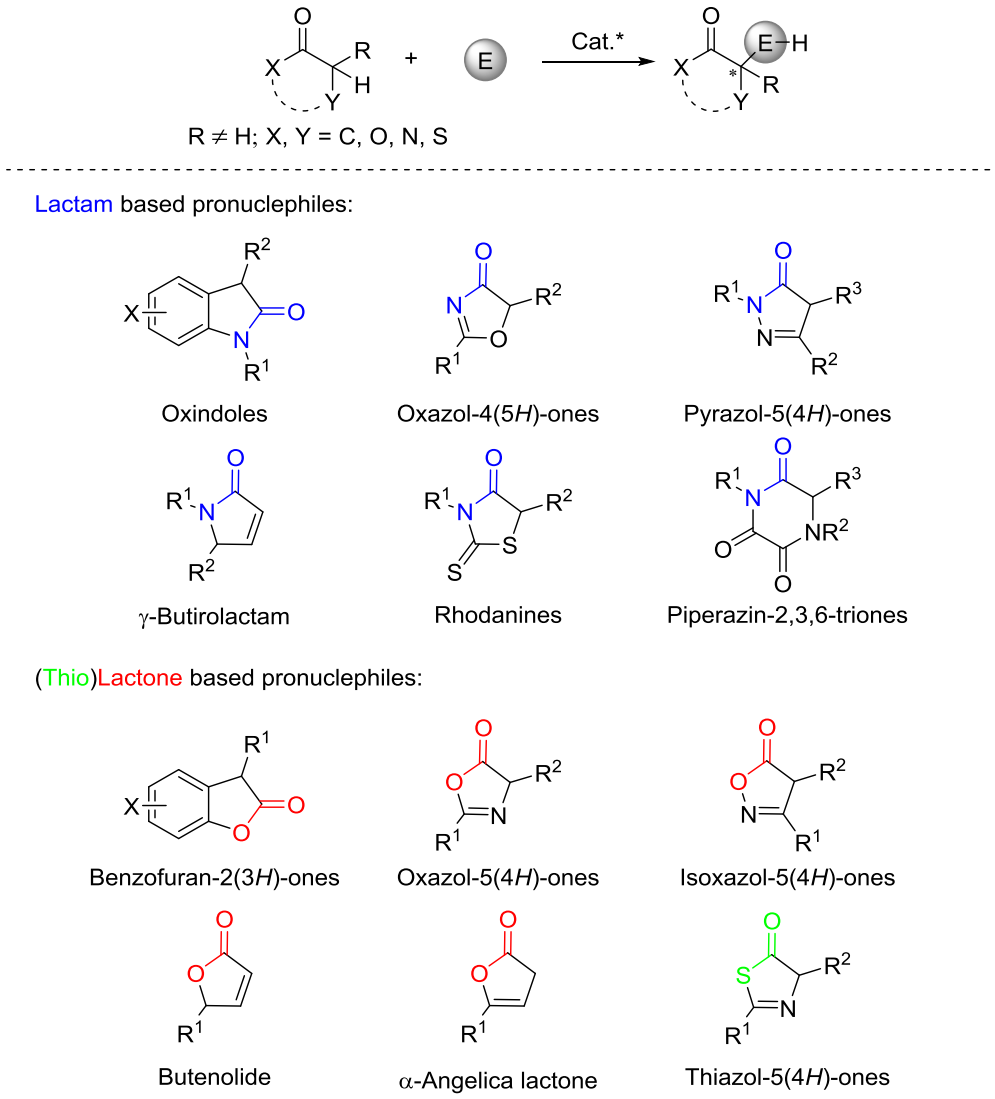
[76] For the aminocatalyzed synthesis of biyouyanagin A, see: a) Nicolaou, K. C.; Sarlah, D.; Shaw, D. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 4708–4711. For reference of its role as HIV replication inhibitor, see: b) Tanaka, N.; Okasaka, M.; Ishimaru, Y.; Takaishi, Y.; Sato, M.; Okamoto, M.; Oshikawa, T.; Ahmed, S. U.; Consentino, L. M.; Lee, K.-H. *Org. Lett.* **2005**, *7*, 2997–2999.

[77] For the aminocatalyzed synthesis of BIRT-377, see: Chowdari, N. S.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 867–870.

[78] For the synthesis of (+)-physostigmine employing oxindoles as pronucleophiles, see: a) Bui, T.; Syed, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759. For reference on its isolation from African Calabar bean *Physostigma venenosum*, see: b) Jobst, J.; Hesse, O. *Ann. der Chemie und Pharm.* **1864**, *129*, 115–121. For reference of its utility on the treatment of glaucoma, see: c) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053.

[79] For structural elucidation, see: Plisson, F.; Prasad, P.; Xiao, X.; Piggott, A. M.; Huang, X.; Khalil, Z.; Capon, R. J. *Org. Biomol. Chem.* **2014**, *12*, 1579–1584. Total synthesis is still unresolved.

eral research groups, but, to the best of our knowledge, all this information has not been gathered.



Scheme 18. Selection of heterocyclic pronucleophiles employed in organocatalysis

Must be noticed that in all cases depicted above (except for rhodanines and piperazin-2,3,6-triones), the deprotonation of the C(sp^3) in α position to the carbonyl moiety would lead to the formation of an aromatized enolate, thanks to the unsaturated C-heteroatom bonds inside the heterocycle or aromatic rings attached to it. This fact eases the mentioned deprotonation of this kind of pronucleophiles in comparison to all carbon cyclic ketones (Figure 5).

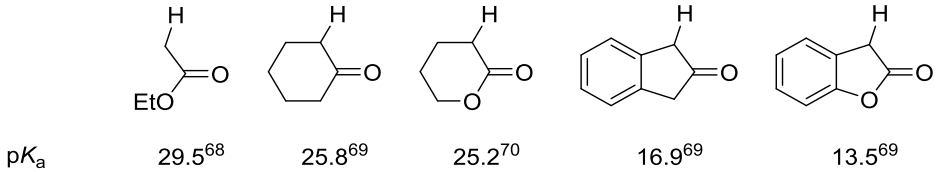
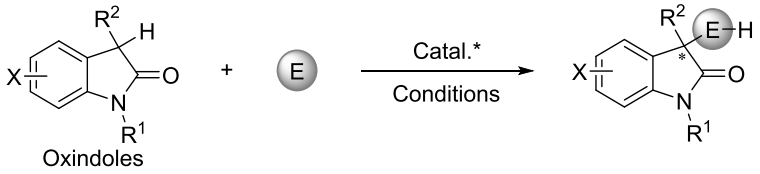


Figure 5. pKa of carbonylic compounds measured in DMSO.

1.2.2. **Lactam based pronucleophiles**

1.2.2.1. **Oxindoles (Indolin-2-ones)**

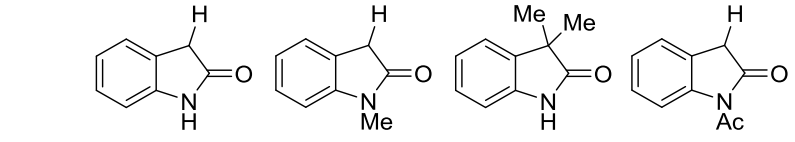
As previously has been said, C-3 disubstituted oxindoles are important frameworks that appear in plenty of biologically interesting compounds (Figure 4E).[83] Thus, the reactivity of oxindoles has been widely studied, including their role as pronucleophiles (Scheme 19).



Scheme 19.

Since the pK_a value of oxindole **A** is 18.2 (Figure 6), the values for 3-alkyl-substituted oxindoles may be expected to be higher, so they can require a strong base for deprotonation. The identical pK_a values of *N*-Me oxindole **B** and *N*-H 3,3-dimethyl oxindole **C** indicate that the ionization of oxindoles in organic solvents may occur readily at both nitrogen and carbon, suggesting potentially similar reactivity of nitrogen, oxygen and carbon in unsubstituted oxindoles.[84] Additionally, introducing an electron withdrawing group at C-3 or at N-1 positions could make the substrates more prone towards deprotonation, as can be seen in Figure 6D.

[80] Zhang, X. M.; Bordwell, F. G.; Van Der Puy, M.; Fried, H. E. *J. Org. Chem.* **1993**, *58*, 3060–3066.
[81] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.
[82] Arnett, E. M.; Harrelson, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809–812.
[83] For some reviews on the pharmacological interest of oxindoles, see: a) Rindhe, S. S.; Karale, B. K.; Gupta, R. C.; Rode, M. A. *Indian J. Pharm. Sci.* **2011**, *73*, 292–296. b) Rudrangi, S. R. S.; Bontha, V. K.; Manda, V. R.; Bethi, S. *Asian J. Res. Chem.* **2011**, *4*, 335–338.
[84] To see an example on *N*- and *O*- selectivity issues with *N*-unprotected oxindoles, see: Zhou, F.; Ding, M.; Liu, Y.-L.; Wang, C.-H.; Ji, C.-B.; Zhang, Y.-Y.; Zhou, J. *Adv. Synth. Catal.* **2011**, *353*, 2945–2952.

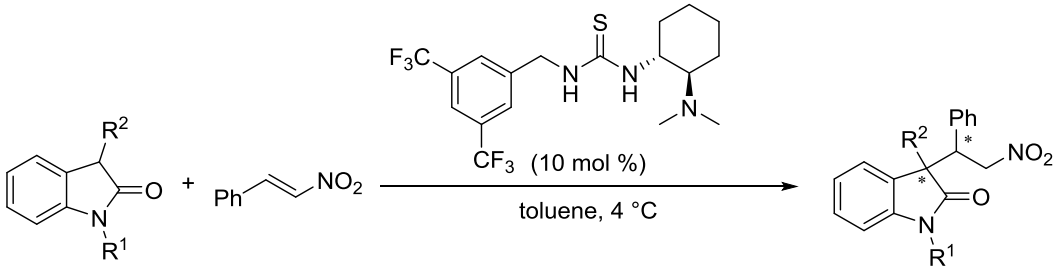


pK_a **A** 18.2[51] **B** 18.5[51] **C** 18.5[51] **D** 13.0[51]

Figure 6. pK_a of oxindoles measured in DMSO. [81]

Substitution of the NH moiety with protecting groups, e.g. Boc, also avoids the nucleophilic attack from it, while the bulky shielding that this group provides is found to be essential for the enantiofacial control in many cases (Table 3, entry 1 vs. 2). As a result, *N*-Boc protected 3-prochiral oxindoles have been much frequently used than unprotected ones for the asymmetric synthesis of 3,3-disubstituted oxindoles. In terms of reactivity, an electron withdrawing R^2 group, such as a phenyl moiety, is more effective, albeit in this instance no stereocontrol is produced, as should be noticed in Table 3 (entry 1 vs. 2).[85]

Table 3.



Entry	R^1	R^2	Time (h)	Yield (%)	*dr*	*ee* (%)
1	Me	Me	12	93	75:25	54
2	Boc	Me	12	94	90:10	74
3	Boc	Ph	2	99	50:50	0

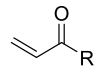
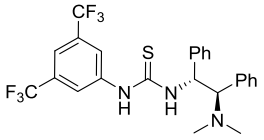
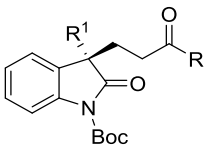
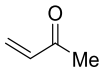
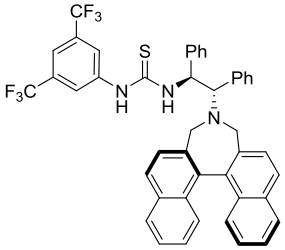
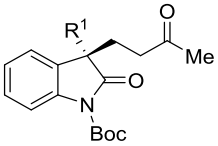
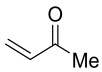
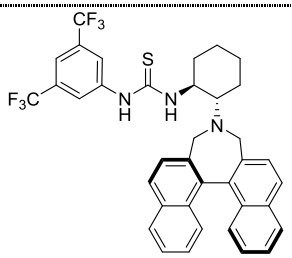
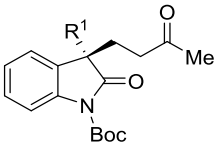
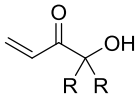
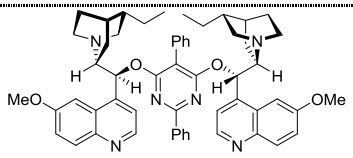
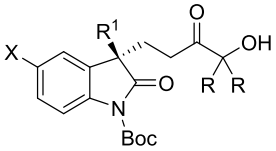
The conjugate addition of oxindoles to enones may serve to better illustrate the above observation (Table 4). While organocatalytic asymmetric Michael reaction of 3-aryl oxindoles has afforded excellent yields and enantioselectivities (entries 1–2),[86] the

[85] a) Li, X.; Zhang, B.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Adv. Synth. Catal.* **2010**, *352*, 416–424. For low reactivity of *N*-Boc 3-Me oxindole in comparison to *N*-Boc 3-aryl oxindoles when attempting Michael addition to nitrostyrene using ammonium salt PTC, see: b) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620–16621. For an example where the *N*-Boc group is not needed for good enantioselectivity, see: c) Ding, M.; Zhou, F.; Liu, Y.-L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Chem. Sci.* **2011**, *2*, 2035–2039.

[86] For the first addition of *N*-Boc 3-aryl oxindoles to enones with PTC, see: a) He, R.; Ding, C.; Maruoka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561. For the first addition *N*-Boc 3-aryl oxindoles to enones catalyzed by bifunctional Brønsted bases, see: b) Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 77–82. For the addition of *N*-Boc 3-aryl oxindoles to methyl vinyl ketone with bifunctional thioureas, see: c) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Molecules* **2012**, *17*, 7523–7532. For the addition of

examples developed for the Michael addition of 3-alkyl oxindoles to enones has showed several limitations (entries 1 and 3), except when benzylic substituent were tested in C-3 (entry 3).[87] Our group has recently addressed this problem employing α'-hydroxy enones as the electrophiles. The addition was catalyzed with dimeric Brønsted bases to render good yields and enantioselectivities (entry 4).[88]

Table 4. Examples for the reactivity difference of oxindoles regarding C-3 substitution.

	Electrophile	Cat.*	Product	R^1	Results	Ref.
1	 R = Me, Et, Ph	 (20 mol %)		Aryl	92–99% 46–82% *ee*	86b
				Me	90–99% 17–48% *ee*	
2		 (5 mol %)		Aryl	82–91% 81–91% *ee*	86c
3		 (5 mol %)		Benzylic	80–92% 91–97% *ee*	87
				Me, *i*Bu, allyl	76–85% 52–67% *ee*	
4	 R = Me, Bn	 (10–30 mol %)	 X = H, Me, MeO, F	Aryl	85–95%, 90–98% *ee*	88a
				Alkyl	76–92%, 78–96% *ee*	

N-Boc 3-aryl oxindoles to enals and enones with phosphonium salt PTC, see: d) Shirakawa, S.; Kasai, A.; Tokuda, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 2248–2252.

[87] For an organocatalytic asymmetric conjugate addition of 3-alkyl-substituted oxindoles to vinyl ketones, see: Lee, H.-J.; Kim, D.-Y. *Bull. Korean Chem. Soc.* **2012**, *33*, 3171–3172.

[88] a) Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2014**, *136*, 17869–17881. For a recent aminocatalyzed addition of 3-alkyl oxindoles to β-substituted enones, see: b) Wei, Y.; Wen, S.; Liu, Z.; Wu, X.; Zeng, B.; Ye, J. *Org. Lett.* **2015**, *17*, 2732–2735.

It is noteworthy that structural isomers of 3-substituted oxindoles as 2-substituted indolin-3-ones (Figure 7) have been much less employed as pronucleophiles. In fact, only one example, which describes an organocatalytic alkylation, has been reported to date.[89]

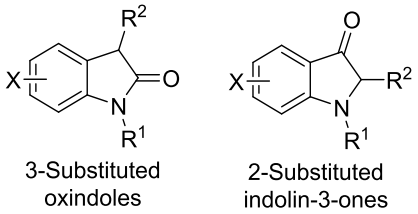


Figure 7.

Despite these different reactivity patterns, numerous examples concerning the use of oxindoles have hitherto been reported, which have been comprehensively reviewed several times and will not be further discussed here.[90]

1.2.2.2. **Oxazol-4(5*H*)-ones**

α,α-Disusbstituted α-hydroxy carboxylic acids, containing α tertiary hydroxy stereogenic centre and an easily modified carboxylic acid, are versatile and powerful intermediates that allow the formation of various chiral molecules with biological importance (Figure 8).[91] In this context, stereoselective construction of these valuable entities has attracted the interest of several research groups over the past few decades.[92] However, organocatalytic asymmetric variations have not been extensively studied.

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[89] For the organocatalytic asymmetric alkylation of 3-substituted indolin-3-ones employing PTC, see: Kawasaki, T.; Higuchi, K.; Masuda, K.; Koseki, T.; Hatori, M.; Sakamoto, M. *Heterocycles* **2007**, *73*, 641.

[90] For some recent reviews on the synthesis of 3,3-disubstituted oxindoles, see: a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. b) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. c) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343–356. For some recent reviews on the synthesis of 3,3'-spirooxindoles, see: d) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023–1052. e) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas III, C. F. *ACS Catal.* **2014**, *4*, 743–762. f) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. *Synlett* **2015**, *26*, 2491–2504.

[91] For a selected book on the topic, see: a) *α-Hydroxy Acids in Enantioselective Syntheses* (G. M. Coppola & H. F. Schuster ed., Wiley-VCH Verlag GmbH & Co. KGaA) 1997. For some references on the use of enantiopure α-hydroxy acids in the synthesis of biologically active compounds, see: b) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-Q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589–5599. (−)-Aphanorphine: c) Pansare, S. V.; Kulkarni, K. G. *RSC Adv.* **2013**, *3*, 19127–19134.

[92] Synthesis of asymmetric α-hydroxy acids by kinetic resolution: a) Moorlag, H.; Kellogg, R. M.; Kloosterman, M.; Kaptein, B.; Kamphuis, J.; Schoemaker, H. E. *J. Org. Chem.* **1990**, *55*, 5878–5881. b) Moorlag, H.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1991**, *2*, 705–720. c) O'Hagan, D.; Zaidi, N. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1111–1118. Synthesis of asymmetric α-hydroxy acids with chiral auxiliaries: d) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem. Int. Ed.* **2001**, *40*, 2906–2909. e) Ley, S. V; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608–3617.

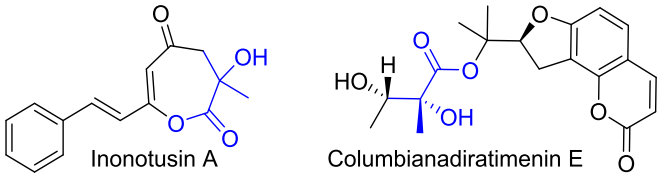


Figure 8. Selected examples of biologically active α,α-disubstituted α-hydroxy acids.[9394]

In 2004, Trost and co-workers introduced 5*H*-oxazol-4-ones as α-alkyl-α-hydroxy ester surrogates in a chiral disphosphomolibdenum catalyzed asymmetric allylic alkylation, leading to a convenient pathway to furnish asymmetric synthesis of α-hydroxy carboxylic acids.[95] Maruoka's group postulated a different substrate as α-hydroxy acid surrogate, oxazolidindione (Figure 9), but phase-transfer conditions and a strong base were required for deprotonation.[96]

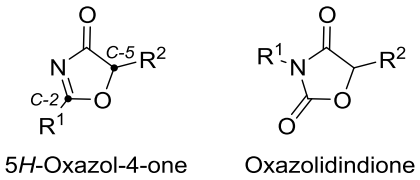
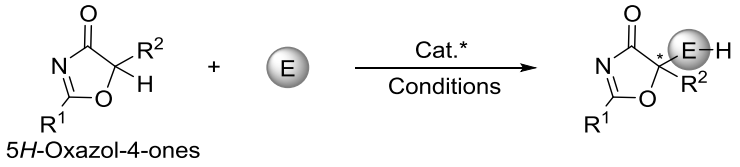


Figure 9.

5*H*-oxazol-4-ones have been utilized as pronucleophiles in a variety of metallic and organocatalytic asymmetric reactions, such as aldol,[97] Mannich[98] and sulfenylation reactions.[99] To the best of our knowledge, only 5-alkyl 2-aryl oxazol-4(5*H*)-ones have been employed for this kind of reactions, so in absence of any precedent, the reactivity of either 5-aryl or 2-alkyl oxazol-4(5*H*)-ones remains unknown (Scheme 20).[100]

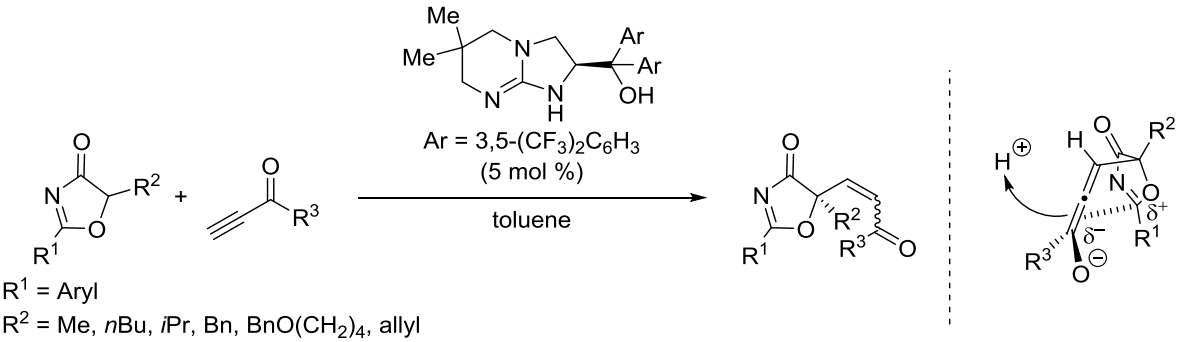
[93] Zan, L.; Qin, J.; Zhang, Y.; Yao, Y.; Bao, H.; Li, X. *Chem. Pharm. Bull. (Tokyo).* **2011**, *59*, 770–772.
[94] Zhang, Y.-B.; Li, W.; Yang, X.-W. *Phytochemistry* **2012**, *81*, 109–116.
[95] a) Trost et al. see ref. 3a page 7. For a recent allylic alkylation of 5*H*-oxazol-4-ones employing Ir catalysis, see: b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377–382. For a recent alkylation employing ammonium salt PTC, see: c) Duan, S.; Li, S.; Ye, X.; Du, N.-N.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 7770–7778.
[96] Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 3839–3842.
[97] For a chiral guanidine-catalyzed aldol reaction of 5*H*-oxazol-4-ones, see: a) Misaki et al.
[98] For a *syn*-Mannich addition to phosphoryl imines with Zn catalysis, see: a) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527. For a *syn*-Mannich addition to sulfonyl imines with bifunctional thioureas, see: b) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2013**, *355*, 1505–1511.
[99] For an example of 5*H*-oxazol-4-one sulfenylation with bifunctional squaramides, see: Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696–8702.
[100] For a study on the keto-enol tautomery of 2,5-diphenyl oxazol-4(5*H*)-ones, see: Jacobsen, N.; Philippides, A. *Aust. J. Chem.* **1985**, *38*, 1335–1338.



Scheme 20.

Conjugate addition to electron deficient double or triple bonds is the most used strategy with these pronucleophiles, although there are not many examples. In fact, the first precedent of a Michael reaction with oxazol-4(5*H*)-ones was performed on ynones by Misaki and Sugimura in 2011 (Table 5).[101] In 1,4-additions of this type, both the geometric control of the newly formed olefin and the enantiomeric control on the generated stereocentre, are the most significant challenges. While the enantioselectivity of the major diastereomer remained excellent in most of the cases, *Z*/*E* selectivity proved to be better when the electrophile was an ester or an amide (entries 1 and 4). The authors describe a stabilization of the charge between the electron enriched π orbital of the newly formed intermediate enolate and the electron deficient C-2 of the oxazolone to explain such results.

Table 5.

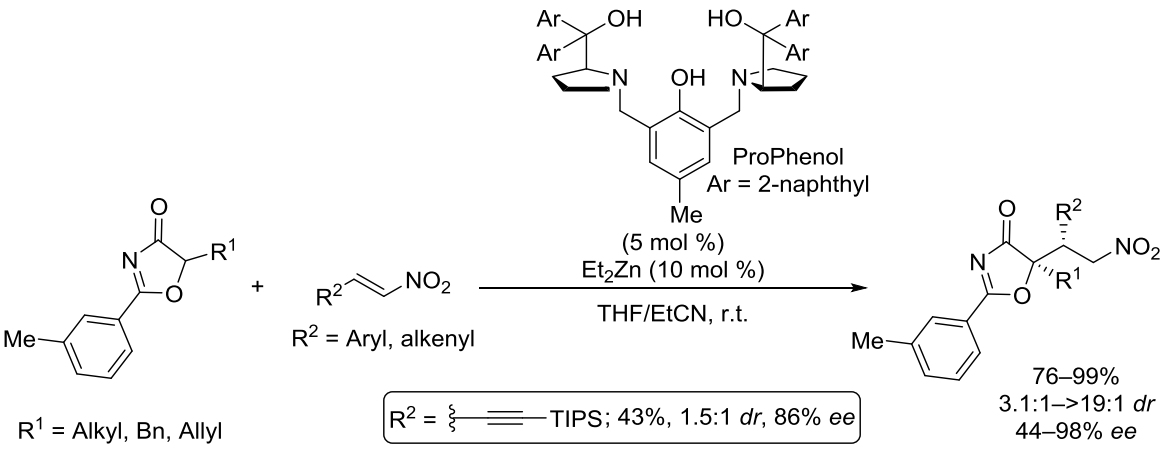


Entry	R^3	T (°C)	R^1	R^2	Yield (%)	*Z*/*E*	*ee* (%)
1	MeO	–40	Ph	Alkyl	66–77	96:4–99:1	84–93
2	*n*-heptyl	0	Ph	Me	77	44:56	91
3	$CH_3(CH_2)_{11}S$-	0	Ph	Me	88	76:24	38–91
4	*N*-Pyrrolidinyl	0	Ph	Alkyl	40–58	>99:1	94–99

Conjugate addition of 5*H*-oxazol-4- to nitroolefins was first reported by Trost and co-workers in 2012.[102] Using a chiral dinuclear Zn–ProPhenol complex, whose active structure was not described in the paper, good to excellent yields and diastereoselectivities were afforded, except for alkinyl-substituted nitroalkenes (Scheme 21). Enantioselec-

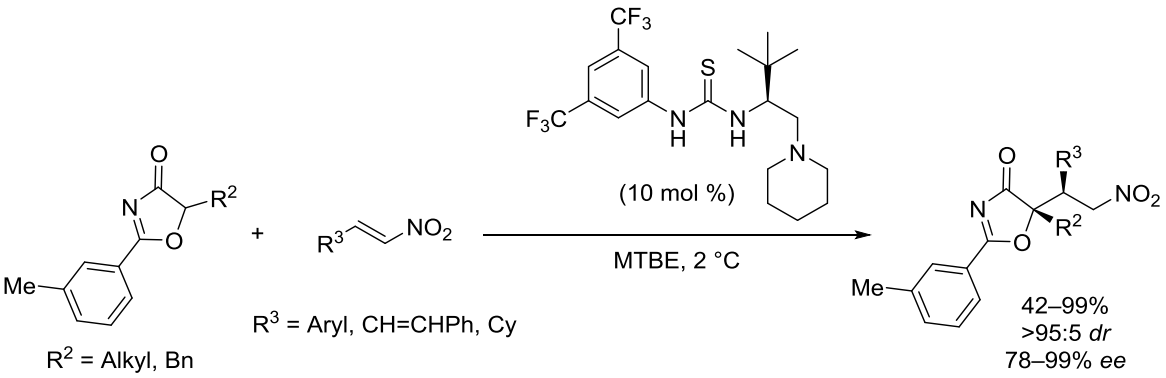
[101] For asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds, see: a) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, *133*, 5695–5697. b) Misaki, T.; Jin, N.; Kawano, K.; Sugimura, T. *Chem. Lett.* **2012**, *41*, 1675–1677.
[102] Trost, B. M.; Hirano, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 6480–6483.

tivities remained very good to excellent, except for β-aryl substituted nitroolefins in which the aromatic ring was *ortho* substituted (R^2 = *o*Tol, 1-napthyl, 2-F-C_6H_4-; 44–70% *ee*).



Scheme 21.

The organocatalytic version of this reaction was first developed by Jiang's research group,[103] who employed a thiourea-based bifunctional Brønsted base to perform the reaction affording excellent yields, diastereomeric ratios and enantioselectivities with aromatic and conjugated nitroalkenes (70–99%, >95:5 *dr*, 90–99% *ee*) (Scheme 22). It should be mentioned that a methyl group at the *meta* position of the phenyl ring of the 5*H*-oxazol-4-one was essential to obtain the aforementioned enantiocontrol. However, the method fails in obtaining such results with the only aliphatic nitroalkene tested (R^3 = Cy, 42%, >95:5 *dr*, 78% *ee*).

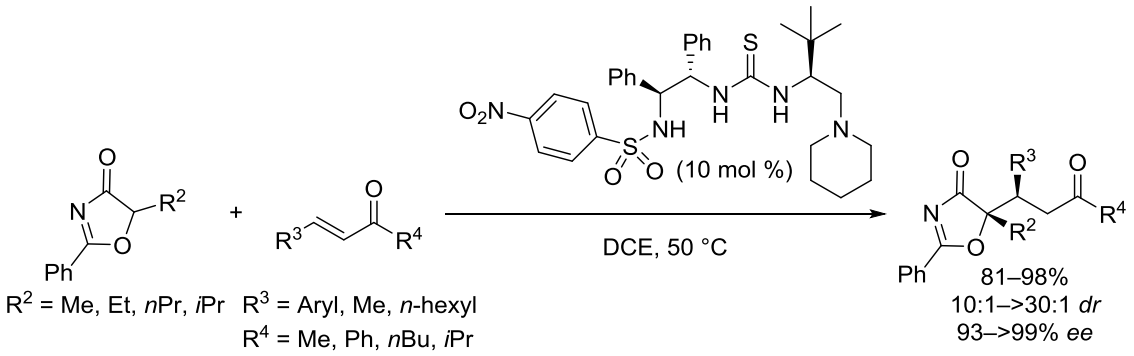


Scheme 22.

The asymmetric conjugate addition to enones is a better studied reaction. In this field, the work developed by Ye's group must be highlighted, who in 2012 developed the first example of this kind of reaction.[104] The addition was catalyzed by a thiourea-based

[103] Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358–2361.
[104] Huang, H.; Zhu, K.; Wu, W.; Jin, Z.; Ye, J. *Chem. Commun.* **2012**, *48*, 461–463.

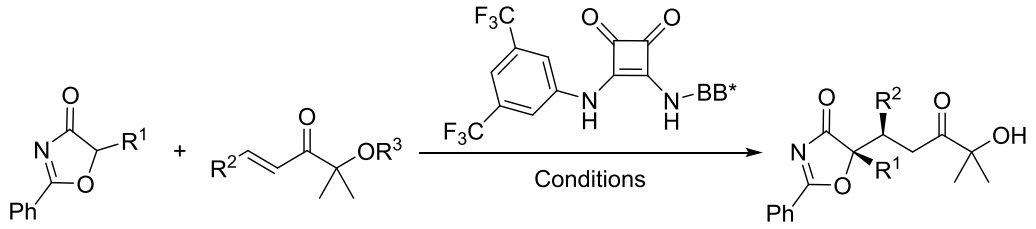
bifunctional Brønsted base, rendering excellent yields, *dr*'s and *ee*'s (Scheme 23). The results indicate that the additional acidic NH on the sulfonamide plays a significant role in this reaction.

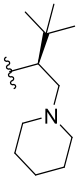
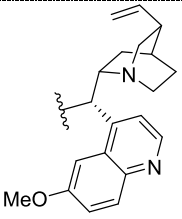


Scheme 23.

Recently, our group contributed to this field with another example, where the squaramide-based bifunctional Brønsted base catalyzed asymmetric Michael addition of 5*H*-oxazol-4-ones to both vinyl and β-substituted α'-silyloxy enones occurs.[88a] As can be seen in the results depicted in Table 6, the low reactivity of β-substituted enones requires an increase in the temperature, as well as changes in the catalyst, in order to obtain the same excellent enantiocontrol accomplished with unsubstituted ones.

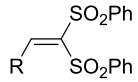
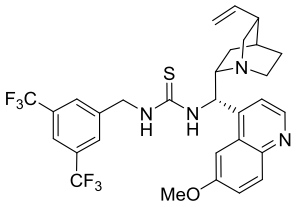
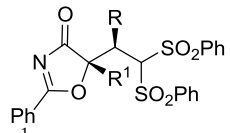
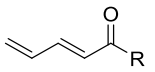
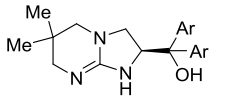
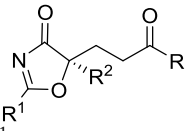
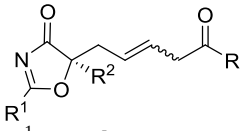
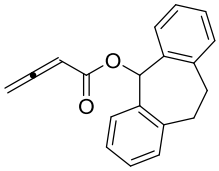
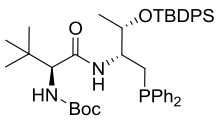
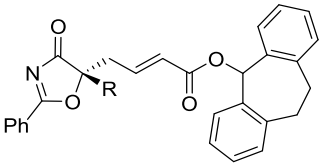
Table 6.



Entry	R^1	R^2	R^3	BB*	Conditions	Results
1	Me, Bn, *n*Pr, *n*-hexyl	H	$SiMe_3$		1) (20 mol %) CH_2Cl_2, r.t. 2) HF 48%, r.t.	73–86% 92–97% *ee*
2	*n*-hexyl, *i*Bu	Aryl	H		(10 mol %) DCE, 70 °C	67–86% 92:8–96:4 *dr* 95–99% *ee*

In addition to the above described electrophiles, other substrate acceptors have also been reported to react well with oxazolones under organocatalytic conditions: a thio-urea-based bifunctional Brønsted base catalyzed addition to vinyl sulfones,[105] a chiral guanidine catalyzed 1,4- and 1,6-addition to enones and dienones,[106] and a chiral phosphine catalyzed conjugate addition to ketenes[107], as depicted in Table 7.

Table 7. Reactions between oxazol-4-(5*H*)-ones and other Michael acceptors.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Aryl, H	 (10 mol %)	 R^1 = Me, Et, Bn, *n*Bu	64–99% >20:1 *dr* 81–>99% *ee*	105
2	 R = Aryl  R = Me, *n*Hex, Cy	 Ar = [3,5-$(CF_3)_2C_6H_3$]$_2$-C_6H_3 (5 mol %)	 R^1 = 3-Cl-5-MeC_6H_4 R^2 = Me, *n*Bu, *i*Pr, allyl  R^1 = 3-Cl-5-MeC_6H_4, 3-ClC_6H_4 R^2 = Me, allyl	55–96% 39–91% *ee* 34–77% 80:20 dr 93–99% *ee*	106
3		 (10 mol %)	 R = Alkyl, Bn	89–98% 81–97% *ee*	107

Given the above results, it seems to be clear that further examples on the use of 5*H*-oxazol-4-ones as precursors of tetrasubstituted hydroxy acids will appear in near the future.

[105] Liu, Q.; Qiao, B.; Chin, K. F.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 3777–3783.
[106] Morita, A.; Misaki, T.; Sugimura, T. *Tetrahedron Lett.* **2015**, *56*, 264–267.
[107] Wang, T.; Yu, Z.; Hoon, D. L.; Huang, K.-W.; Lan, Y.; Lu, Y. *Chem. Sci.* **2015**, *6*, 4912–4922.

1.2.2.3. **Pyrazolones (Pyrazolin-5(4*H*)-ones)**

The pyrazolone moiety is part of the core structure of various biologically active products or drugs (Figure 10),[108] but it is also employed in more industrial activities, as a dye[109] or anticorrosive, [110] for example.

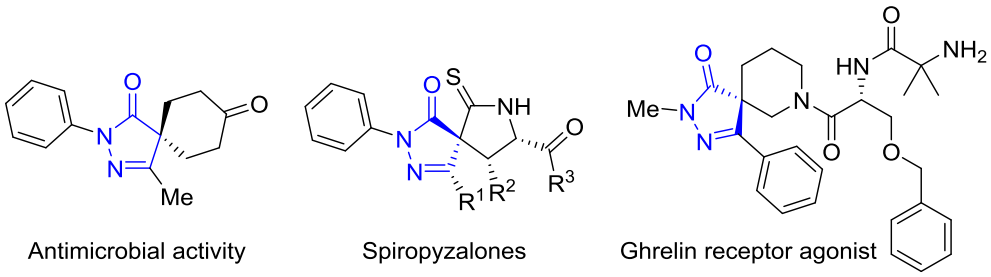


Figure 10. Selected examples of biologically active pyrazolone derivatives. [111112113]

Along the years, several approaches were developed for the synthesis of 4-substituted pyrazolin-5(4*H*)-ones,[114] but, despite their importance, these heterocycles had never been used as pronucleophiles to perform direct asymmetric addition reactions until this decade (Scheme 24). A structural feature of this heterocycle was reported in 2004 by Holzer and Alkorta's group,[115] who through ^{1}H NMR studies demonstrated that these compounds exist in equilibrium between three tautomeric forms in solution (Scheme 24). This observation explains the easy involvement of these heterocycles in direct reactions under proton transfer conditions.

---

[108] Antitumoral activity: a) Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; VanRens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; … Janusz, M. J. *J. Med. Chem.* **2004**, *47*, 2724–2727. Antiviral activity: b) Hadi, V.; Koh, Y.-H.; Sanchez, T. W.; Barrios, D.; Neamati, N.; Jung, K. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6854–6857.

[109] Li, Y.; Zhang, S.; Yang, J.; Jiang, S.; Li, Q. *Dyes Pigm.* **2008**, *76*, 508–514.

[110] Abdallah, M. *Mater. Chem. Phys.* **2003**, *82*, 786–792.

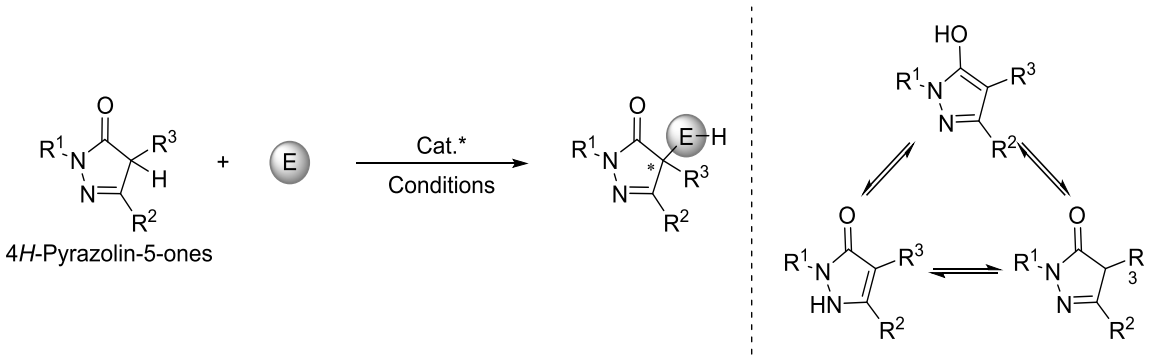
[111] Chande, M. S.; Barve, P. A.; Suryanarayan, V. *J. Heterocycl. Chem.* **2007**, *44*, 49–53.

[112] Liu, L.; Zhong, Y.; Zhang, P.; Jiang, X.; Wang, R. *J. Org. Chem.* **2012**, *77*, 10228–10234.

[113] A. V. Ambarkhane et al., *3-Spirocyclic piperidine derivatives as ghrelin receptor agonists* (US Patent 20120302540A1, November 29) 2012.

[114] For the synthesis of pyrazolinones from chromone derivatives, see: a) Ghosh, C. K.; Mukhopadhyay, K. K. *Synthesis* **1978**, 779–781. b) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G. *Tetrahedron Lett.* **1987**, *28*, 5165–5168. For the synthesis of pryazolinones from 4-hydroxycoumarins, see: c) Chantegrel, B.; Gelin, S. *Synthesis* **1985**, 548–550. For the synthesis of pyrazolinones via Pd-catalyzed carbonylation of 1,2-diaza-1,3-butadienes, see: d) Boeckman, R. K.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651–3653.

[115] Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R. M.; Pérez-Torralba, M.; Alkorta, I.; Elguero, J. *Tetrahedron* **2004**, *60*, 6791–6805.



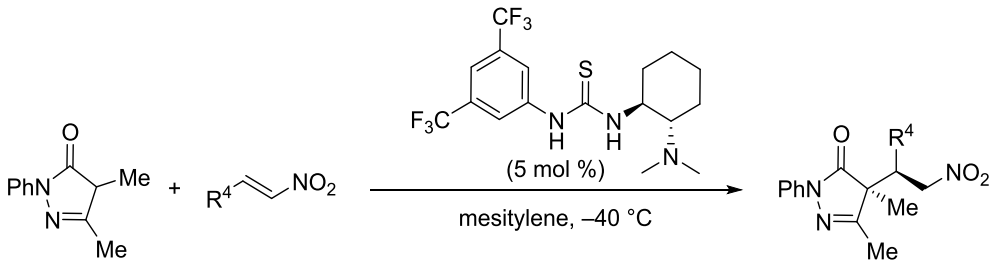
Scheme 24.

While Feng's research group carried out aminations,[116] and conjugate additions to 1,4-dicarbonyl but-2-enes[117] and ynones[118] under organometallic catalysis, the group of Rios performed pyrazolinone additions to enals employing iminium ion activation[119] and maleimides through bifunctional Brønsted base catalysis.[120] Organometallic strategies have also been employed to perform pyrazolone alkylations.[121]

The addition of 4-substituted pyrazolin-5(4*H*)-ones to nitroolefins employing Takemoto's catalyst has also been reported (0).[122] Aromatic nitroalkenes afforded excellent yields (entries 1–8), but aliphatic ones proved to be less effective (entries 9–10). Diastereocontrol was moderate at best, although enantiocontrol of the major diastereomer remained very good to excellent in every case.

[116] For a Gd catalyzed amination of pyrazolones, see: Yang, Z.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 596–599.
[117] For a Sc/Y catalyzed conjugate addition to 1,4-dicarbonyl but-2-enes, see: b) Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 4928–4932.
[118] For a Sc catalyzed conjugate addition to ynones, see: Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 2776–2779.
[119] For aminocatalyzed formation of spiropyrazolones with enals, see: a) Companyó, X.; Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953–6955. b) Alba, A.-N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, *2011*, 1318–1325. For a racemic S_N1 alkylation, see: c) Alba, A.-N. R.; Calbet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, 2053–2056.
[120] For a conjugate addition to maleimides with Takemoto's catalyst, see: Mazzanti, A.; Calbet, T.; Font-Bardia, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 1645–1652.
[121] For a Pd catalyzed allylic alkylation from other group, see: Tao, Z.-L.; Zhang, W.-Q.; Chen, D.-F.; Adele, A.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 9255–9258.
[122] a) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827–832. For a bifunctional squaramide catalyzed addition of 4-unsubstituted pyrazolones to nitroolefins, see: b) Li, J.-H.; Du, D.-M. *Org. Biomol. Chem.* **2013**, *11*, 6215. For a recent example of sequential bifunctional squaramide-silver catalyzed addition of 4-unsubstituted pyrazolones to nitroolefins, see: c) Hack, D.; Dürr, A. B.; Deckers, K.; Chauhan, P.; Seling, N.; Rübenach, L.; Mertens, L.; Raabe, G.; Schoenebeck, F.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 1797–1800.

Table 8. Representative examples of the Michael addition of pyrazolones to nitroolefins.



Entry	R^4	Time (h)	Yield (%)	*dr*	*ee* (%)[a]
1	4-ClC_6H_4-	24	96	30:70	92
2	4-$MeOC_6H_4$-	24	97	27:73	92
3	4-MeC_6H_4-	24	96	30:70	93
4	4-$NO_2C_6H_4$-	24	92	38:62	89
5	2-ClC_6H_4-	24	96	45:55	97
6	2-$MeOC_6H_4$-	20	86	32:68	97
7	2-$MeOC_6H_4$-	20	86	32:68	97
8	2-$NO_2C_6H_4$-	20	94	52:48	97
9	*i*Bu	90	65	46:54	92
10	Cy	90	44	39:61	86
11	1-naphthyl	24	91	29:71	92

[a] *ee* of the major diastereomer.

To date, while several metal catalyzed conjugate additions of 4-substituted pyrazolin-5(4*H*)-ones to enones have been developed,[117,118] organocatalytic approaches remain unexplored.

As far as we know, the majority of examples are based on conjugate additions, while other acceptors, such as aldehydes or imines, have to be yet explored.

1.2.2.4. **γ-Butirolactams**

α,β-Unsaturated γ-butyrolactam derivatives (5-substituted 3-pyrrolidin-2-ones) belong to a family of structurally diverse natural or non-natural compounds with remarkable biological activities which also signify their importance in organic chemistry (Figure 11).[123]

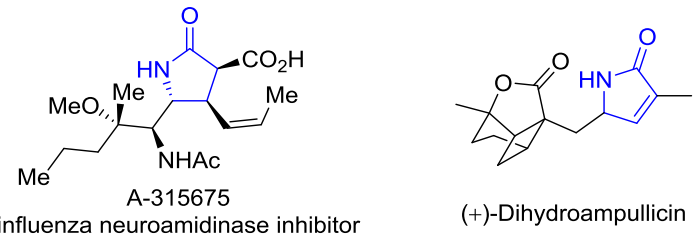
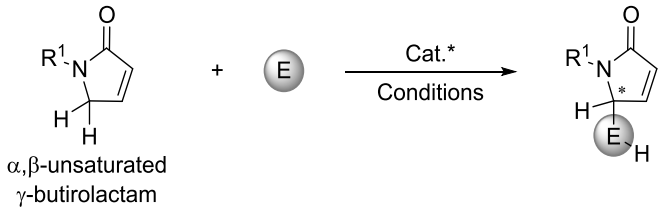


Figure 11. Selected examples natural and non-natural butirolactam derivatives.[124125]

It is remarkable, that α,β-unsaturated γ-butirolactams tend to undergo vinylogous activation and subsequent addition (Scheme 25). This distant addition allows the nucleophilic formation of tertiary carbon stereogenic centres, since, unlike in the previously described nucleophiles, the stereogenic carbon remains far from the carbonyl moiety, avoiding any possible racemization through keto-enol tautomerism.

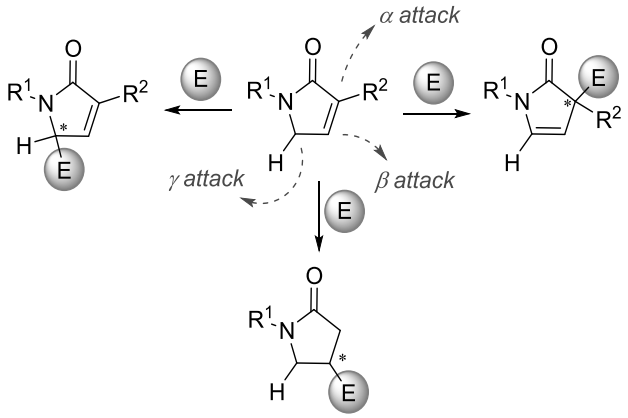


Scheme 25.

However, other reactivity patterns of α,β-unsaturated γ-butirolactams have also been explored (Scheme 26).[126] For instance, regarding α-reactivity, Morita-Baylis-Hillman additions to isatins,[127] aryl α-ketoesters[128] and tetrahydroisoquinolines[129] have been reported employing chiral thioureas and Brønsted bases. Among the reactions which

[123] a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670–2680. b) Cheng, Y.; Huang, Z.-T.; Wang, M.-X. *Curr. Org. Chem.* **2004**, *8*, 325–351.
[124] Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541–3551.
[125] a) Choi, E.; Lee, C.; Cho, M.; Seo, J. J.; Yang, J. S.; Oh, S. J.; Lee, K.; Park, S.-K.; Kim, H. M.; Kwon, H. J.; Han, G. *J. Med. Chem.* **2012**, *55*, 10766–10770. b) Lee, C.; Choi, E.; Cho, M.; Lee, B.; Oh, S. J.; Park, S.-K.; Lee, K.; Kim, H. M.; Han, G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4189–4192.
[126] For a thiourea catalyzed Diels-Alder reaction employing butirolactams, see: Jiang, X.; Liu, L.; Zhang, P.; Zhong, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2013**, *52*, 11329–11333.
[127] Duan, Z.; Zhang, Z.; Qian, P.; Han, J.; Pan, Y. *RSC Adv.* **2013**, *3*, 10127–10130.
[128] Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 3300–3302.
[129] Ma, Y.; Zhang, G.; Zhang, J.; Yang, D.; Wang, R. *Org. Lett.* **2014**, *16*, 5358–5361.

took advantage of β-reactivity of butirolactams, there are Cu catalyzed alkylations[130] and silylations,[131] and Rh catalyzed arylations.[132]

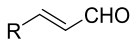
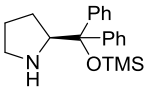
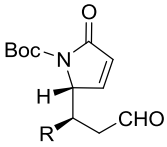
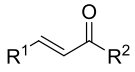
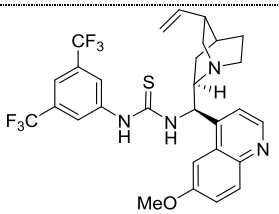
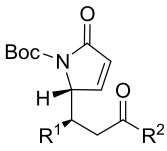
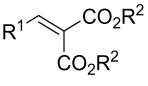
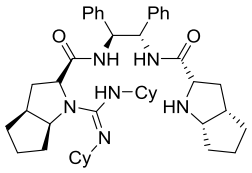
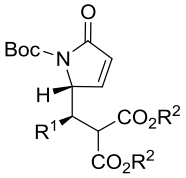
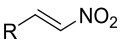
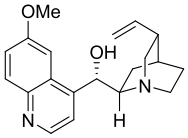
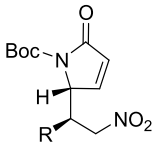
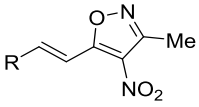
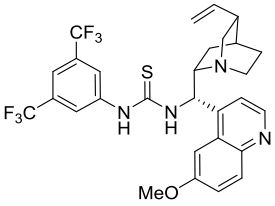
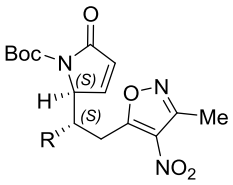
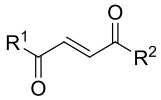
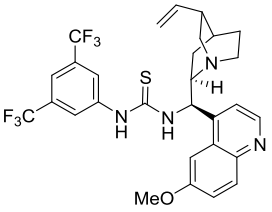
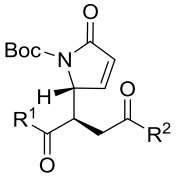
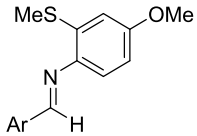
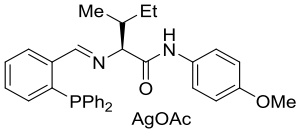
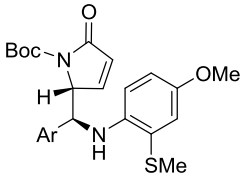


Scheme 26.

As mentioned above, these heterocycles have been mainly employed as vinylogous nucleophiles to perform Michael additions to form tertiary carbon stereocentres, as has been collected in various extensive reviews.[133] In Table 9 are depicted the most recent examples of this type of reactions, mostly involving Michael acceptors.[134]

[130] Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244–1245.
[131] Pace, V.; Rae, J. P.; Procter, D. J. *Org. Lett.* **2014**, *16*, 476–479.
[132] a) Shao, C.; Yu, H.-J.; Wu, N.-Y.; Tian, P.; Wang, R.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2011**, *13*, 788–791. b) Kuuloja, N.; Vaismaa, M.; Franzén, R. *Tetrahedron* **2012**, *68*, 2313–2318.
[133] For recent reviews on vinylogous reactions, see: a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154. b) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595–2615. c) Schneider, C.; Abels, F. *Org. Biomol. Chem.* **2014**, *12*, 3531–3543. d) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682–4698.
[134] a) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem. Eur. J.* **2010**, *16*, 10309–10312. b) Zhang, Y.; Shao, Y.-L.; Xu, H.-S.; Wang, W. *J. Org. Chem.* **2011**, *76*, 1472–1474. c) Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2012**, *48*, 5040–5042. d) Choudhury, A. R.; Mukherjee, S. *Org. Biomol. Chem.* **2012**, *10*, 7313–7320. e) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329–9331. f) Chen, Y.-R.; Das, U.; Liu, M.-H.; Lin, W. *J. Org. Chem.* **2015**, *80*, 1985–1992. g) Silverio, D. L.; Fu, P.; Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Tetrahedron Lett.* **2015**, *56*, 3489–3493.

Table 9. Selected examples of vinylogous addition of γ-butirolactams to unsaturated bonds.

	Electrophile	Cat.*	Product	Results	Ref.
1		 (20 mol %)	 R = Aryl, Me, Et	31–89% 1.1:1–>20:1 *dr* 79–99% *ee*	134a
2		 (10 mol %)	 R^1, R^2 = Aryl	73–95% 10:1–>30:1 *dr* 94–99% *ee*	134b
3		 (5 mol %)	 R^1 = Aryl, alkenyl, Cy R^2 = Et, Me, Bn	64–93% 81:19–95:5 *dr* 78–94% *ee*	134c
4		 (10 mol %)	 R = Aryl, Cy, *i*Bu, *i*Pr	64–93% >20:1 *dr* 60–89% *ee*	134d
5		 (10 mol %)	 R = Aryl	57–90% 1.3:1–19:1 *dr* 84–96% *ee*	134e
6		 (10 mol %)	 R^1 = OR, Aryl, Alkyl R^2 = Aryl, Alkyl	56–95% 10:1–>25:1 *dr* 83–99% *ee*	134f
7		 (5 mol %)		62–98% >98:2 *dr* 86–98% *ee*	134g

1.2.2.5. **Rhodanines (2-Thioxothiazolidin-4-ones)**

The rhodanine scaffold is found in many bioactive and pharmacologically interesting structures, showing antibacterial, antiviral, antimalarial, and antitumor activities (Figure 12).[135]

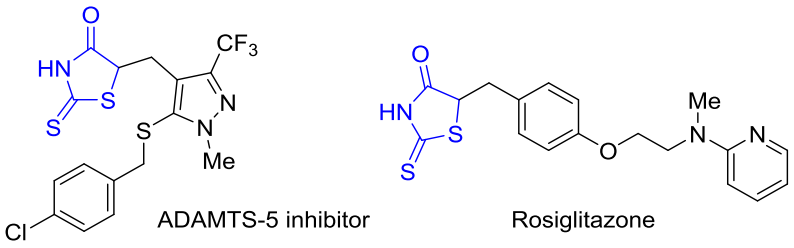
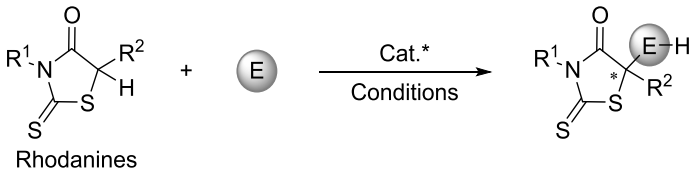


Figure 12. Selected examples of biologically active racemic rhodanine derivatives.[136][137]

It is demonstrated that in 5-monosubtituted 2-thioxothiazolidin-4-ones, like the ones depicted above, enolization can occur at the 5-position under physiological conditions, which makes difficult to maintain the sometimes essential configuration at this position.[138] To avoid this, work has been directed to the quaternization of the α C(sp^3) of 5-substituted rhodanines, mainly through reactions under proton transfer conditions (Scheme 27). These reactions will be more extensively discussed in the following chapter (page 76).



Scheme 27.

[135] 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.
[136] Gilbert, A. M.; Bursavich, M. G.; Lombardi, S.; Georgiadis, K. E.; Reifenberg, E.; Flannery, C. R.; Morris, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1189–1192.
[137] Kumar, B. R. P.; Nanjan, M. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1953–1956.
[138] Joshi, M.; Vargas, C.; Boisguerin, P.; Diehl, A.; Krause, G.; Schmieder, P.; Moelling, K.; Hagen, V.; Schade, M.; Oschkinat, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3790–3795.

1.2.2.6. **Triketopiperazines (Piperazin-2,3,6-triones)**

Diketopiperazines are privileged structures that can be found in the core of several commercial drugs or pharmaceutically interesting molecules (Figure 13). The extensive studies of the synthesis and medicinal chemistry of this scaffold and its occurrence in bioactive natural products have been described in comprehensive reviews.[139]

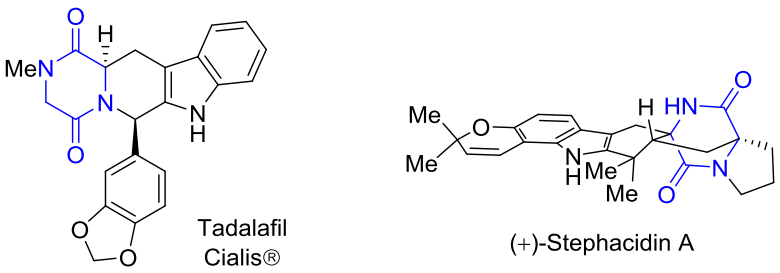
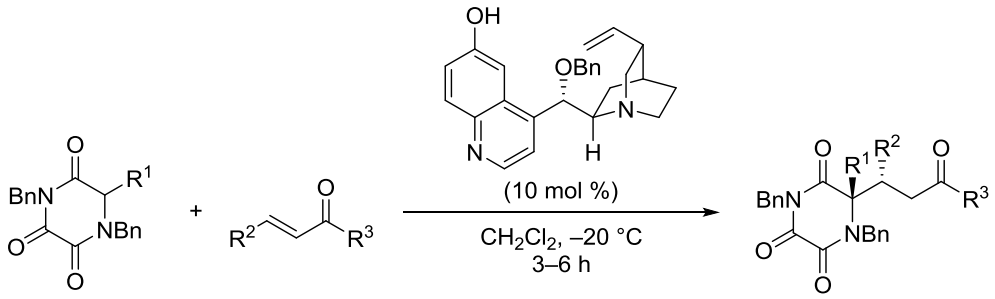


Figure 13. Selected examples of biologically active diketopiperazine derivatives.[140141]

Diverse strategies have been employed to gain access to structures bearing this heterocyclic core, including activated diketopiperazines as pronucleophiles in organocatalyzed reactions by Olenyuk and co-workers. However, total enantiocontrol of the reactions was not achieved.[142] The use of triketopiperazines as pronucleophiles is another strategy that recently provided a successful example of conjugate addition to enones and enals (Table 10).[143]

[139] a) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641–3716. b) González, J. F.; Ortín, I.; de la Cuesta, E.; Menéndez, J. C. *Chem. Soc. Rev.* **2012**, *41*, 6902–6915.
[140] Daugan, A.; Grondin, P.; Ruault, C.; Le Monnier de Gouville, A.-C.; Coste, H.; Linget, J. M.; Kirilovsky, J.; Hyafil, F.; Labaudinière, R. *J. Med. Chem.* **2003**, *46*, 4533–4542.
[141] a) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556–14557. b) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160–3174.
[142]For the sulfenylation of 5-alkoxycarbonyl diketopiperazines with quinine and moderate *ee*'s, see: a) Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742–2750. For diastereoselective alkylation of 5-alkoxycarbonyl diketopiperazines with *Cinchona* alkaloids, see: b) Dubey, R.; Olenyuk, B. *Tetrahedron Lett.* **2010**, *51*, 609–612.
[143] Cabanillas, A.; Davies, C. D.; Male, L.; Simpkins, N. S. *Chem. Sci.* **2015**, *6*, 1350–1354.

Table 10.



Entry	R^1	R^2	R^3	Yield (%)	*ee* (%)
1	CO_2Me	H	Me	99	98
2	CO_2Me	H	Et	90	94
3	CO_2Me	H	Cy	99	94
4	CO_2Me	H	Aryl	87–98	98
5	CO_2Me	H	H	99	92
6	H	H	Me	80	86
7	H	H	Et	86	92
8	H	H	Cy	99	80
9	H	H	4-$MeOC_6H_4$	93	76
10	H	Ph	Ph	98	98[a]
11	H	Ph	2-BrC_6H_4	91	76[a]

[a] Isolated as a single diastereomer.

However, the example depicted above only presents much activated 5-methyloxycarbonyl triketopiperazines (R^1 = CO_2Me) to form a quaternary stereocentre (entries 1–5) or 5-unsubstituted ones (R^1 = H) to form a tertiary one (two contiguous tertiary stereocentres if R^2 = Ph, entries 10–11). Yet, no examples involving aliphatic or aromatic R^1 substituents have been described and, with respect to the electrophile, no other examples have been reported to date.[142,143]

1.2.3. **Lactone based pronucleophiles**

1.2.3.1. **Benzofuranones (Benzofuran-2(3*H*)-ones)**

Benzofuran-2(3*H*)-ones are important building blocks that are found in a large variety of natural products, drugs and other biologically interesting structures. Additionaly, many of them feature a chiral quaternary stereocentre at the C-3 position of the heterocyclic ring. Thus, benzofuranones have been involved in several total syntheses, being Diazonamide A one of the most significants, as reported by Nicolaou and co-workers in 2002 (Figure 14).[59a]

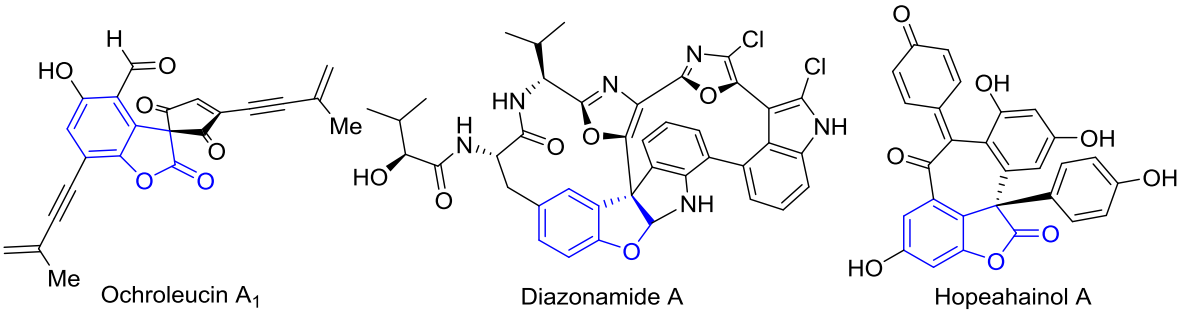
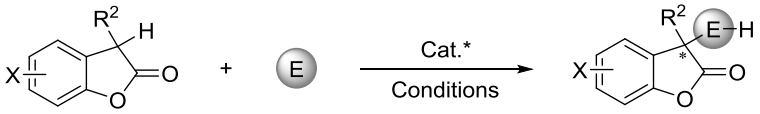


Figure 14. Selected examples of biologically active benzofuranone derivatives.[144][145]

The obvious structural similarities with oxindoles have prompted the utilization of benzofuranones as pronucleophiles in the same reactions that they were being tested in (Scheme 28).[146],[147]



Scheme 28.

The first example of the utilization of 3-substituted benzofuran-2(3*H*)-ones as pronucleophiles in a direct addition to obtain quaternary stereocentres was in the Michael addition to β-substituted enones reported by Cheng's group in 2010.[148] The reaction was catalyzed by a Takemoto's bifunctional catalyst derivative, obtaining high yields and excellent enantioselectivities, but moderate diastereoselectivity at best, when R^2 and R^3 were aromatic. No example employing 3-alkyl substituted benzofuranones was reported.

---

[144] Sontag, B.; Rüth, M.; Spiteller, P.; Arnold, N.; Steglich, W.; Reichert, M.; Bringmann, G. *Eur. J. Org. Chem.* **2006**, 1023–1033.

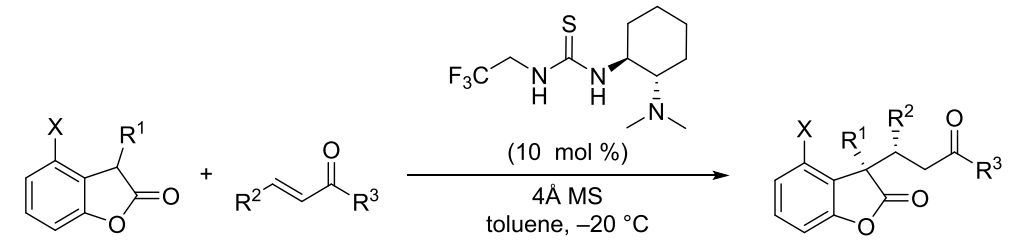
[145] Ge, H. M.; Zhu, C. H.; Shi, D. H.; Zhang, L. D.; Xie, D. Q.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem. Eur. J.* **2008**, *14*, 376–381.

[146] For a review regarding catalytic asymmetric synthesis of chiral benzofuranones, see: Li, Y.; Li, X.; Cheng, J.-P. *Adv. Synth. Catal.* **2014**, *356*, 1172–1198.

[147] For the conjugate addition of oxindoles and benzofuranones to cyclic enones employing iminium ion, Brønsted base catalysis, see: a) Pesciaioli, F.; Tian, X.; Bencivenni, G.; Bartoli, G.; Melchiorre, P. *Synlett* **2010**, 1704–1708. For the conjugate addition of oxindoles and benzofuranones to enals to obtain spirocyclic adduct via iminium ion, see: a) Companyó et al.ref 119a Page 29. b) Bergonzini, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 971–974. For the conjugate addition of 3-Se oxindoles and benzofuranones to nitroolefins mith squaramide-based bifunctional Brønsted bases, see: c) Marcos, V.; Alemán, J.; Garcia Ruano, J. L.; Marini, F.; Tiecco, M. *Org. Lett.* **2011**, *13*, 3052–3055. For the addition reaction of oxindoles and benzofuranones to Morita-Baylis-Hillman type carbonates with chiral phosphines, see: d) Wang, D.; Yang, Y.-L.; Jiang, J.-J.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 7158–7166. For the conjugated addition of oxindoles and benzofuranones to allenoates employing chiral phosphines, see: e) Chen, J.; Cai, Y.; Zhao, G. *Adv. Synth. Catal.* **2014**, *356*, 359–363. For the chiral guanidine catalyzed sulfenylation of 3-alkyl oxindoles and benzofuranones, see: f) Huang, L.; Li, J.; Zhao, Y.; Ye, X.; Liu, Y.; Yan, L.; Tan, C.-H.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 8933–8941.

[148] Li, X.; Xi, Z.; Luo, S.; Cheng, J. P. *Adv. Synth. Catal.* **2010**, *352*, 1097–1101.

However, early attempts to perform the addition on aliphatic vinyl ketones (R^2 = H, R^3 = Me or Et) were described, although no satisfactory results were obtained (Scheme 29).



X = H, Me
R^1 = Ph, 4-ClC_6H_4

R^2 = Aryl (H)
R^3 = Aryl (Me, Et)

R^2, R^3 = Aryl; 80–99%, 50:50–75:25 *dr,* 78–98% *ee*
(R^2 = H, R^3 = Me, Et; 82–95%, 7–27% *ee*)

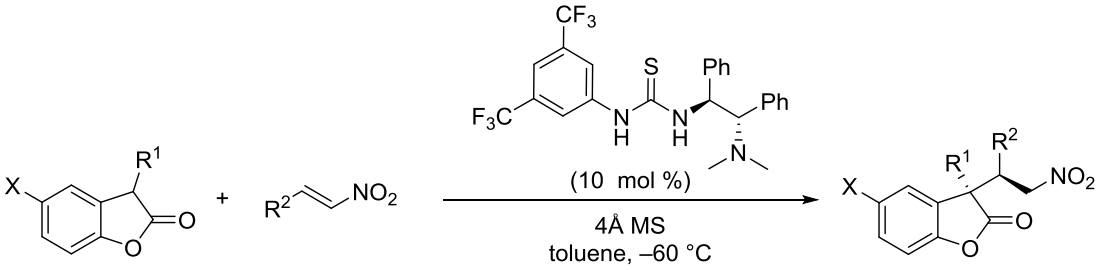
Scheme 29.

Since then, many other electrophiles have been employed to perform Michael additions,[149] including nitroolefins. In this field, the only example using 3-alkyl benzofuranones as pronucleophiles was also introduced by Cheng and co-workers in 2012.[150] As illustrated in Table 11, *ortho* substituted aromatic nitroolefins afforded the best stereoselectivities when 3-methyl benzofuranones were being used as Michael donors (entries 5–6). Surprisingly, the thiourea-based bifunctional Brønsted base catalyzed reaction worked quite well for aliphatic nitroolefins, despite their usual lack of reactivity (entries 8–9). Benzyl or aryl groups in C-3 did not affect the yields, but both diastereoselectivity and more pronouncedly enantioselectivity decreased (entries 10–11). Decrease of the electron density in the aromatic ring of the benzofuranone also resulted in an increase of *ee*, although *dr* was not improved (entries 13–14 vs. 11–12).

[149] For the conjugate addition of 3-aryl benzofuranones to maleimides with bifuntional thioureas, see: a) Li, X.; Hu, S.; Xi, Z.; Zhang, L.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 8697–8700. For the conjugate addition of 3-aryl benzofuranones to azadicarboxylates with PTC, see: b) Zhu, C. Le; Zhang, F. G.; Meng, W.; Nie, J.; Cahard, D.; Ma, J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 5869–5872. For the conjugate addition of 3-aryl benzofuranones to vinyl bis(sulfone)s with bifunctional thioureas, see: c) Li, X.; Zhang, Y. Y.; Xue, X. S.; Jin, J. L.; Tan, B. X.; Liu, C.; Dong, N.; Cheng, J. P. *Eur. J. Org. Chem.* **2012**, *2*, 1774–1782.

[150] Li, X.; Xue, X.-S.; Liu, C.; Wang, B.; Tan, B.-X.; Jin, J.-L.; Zhang, Y.-Y.; Dong, N.; Cheng, J.-P. *Org. Biomol. Chem.* **2012**, *10*, 413–420.

Table 11.



Entry	R^1	X	R^2	Yield (%)	*dr*	*ee* (%)
1	Me	H	Ph	96	80:20	66
2	Me	H	4-$MeOC_6H_4$	92	75:25	65
3	Me	H	4-ClC_6H_4	87	66:33	52
4	Me	H	3-$NO_2C_6H_4$	91	50:50	75/15
5	Me	H	2-ClC_6H_4	95	95:5	86
6	Me	H	2,6-$Cl_2C_6H_4$	87	92:8	91
7	Me	H	2-Naphthyl	85	75:25	77
8	Me	H	$PhCH_2CH_2$	90	95:5	85
9	Me	H	*i*Bu	88	94:6	82
10	Bn	H	Ph	91	50:50	84/65
11	Ph	H	Ph	95	80:20	55
12	Ph	Et	Ph	91	85:15	58
13	Ph	Cl	Ph	87	85:15	73
14	Ph	Br	Ph	98	86:14	77
15	4-ClC_6H_4	H	Ph	90	80:20	53

Despite their therapeutic and synthetic interest, and like in the case of oxindoles, structural isomers of 3-substituted benzofuran-2(3*H*)-ones like 2-alkyl substituted benzofuran-3(2*H*)-ones (Figure 15) have been much less employed as pronucleophiles in this kind of reactions. In fact, as far as we know, only one example has been described, that involves the use of nitroolefins as the acceptor partner.[151]

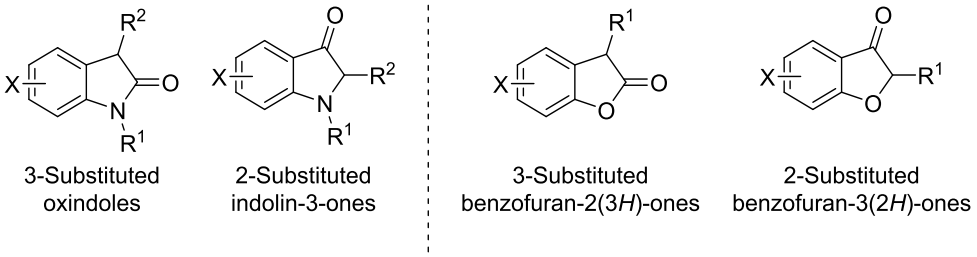


Figure 15.

[151] a) Zhang, Z.-P.; Dong, N.; Li, X.; Cheng, J.-P. *Org. Biomol. Chem.* **2015**, *13*, 9943–9947. For reactions employing benzofuran-3(2*H*)-ones with electron withdrawing groups in C-2 (R^1 = EWG), see: b) ref. 146 page 36.

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

Azlactones or 4*H*-oxazol-5-ones are one of the most synthetically versatile heterocycles, as it is demonstrated by some extensive reviews gathering the diverse purposes they have been employed for.[152] Plöchl and co-workers described the first synthesis of azlactones through a condensation reaction of benzaldehyde and hippuric acid in presence of acetic anhydride,[153] but it was Erlenmeyer who first established their correct structure and named them.[154] Azlactones contain multiple reactive sites that allow different possible modifications, making them excellent substrates for the synthesis of highly substituted heterocyclic scaffolds, as shown in Figure 16.

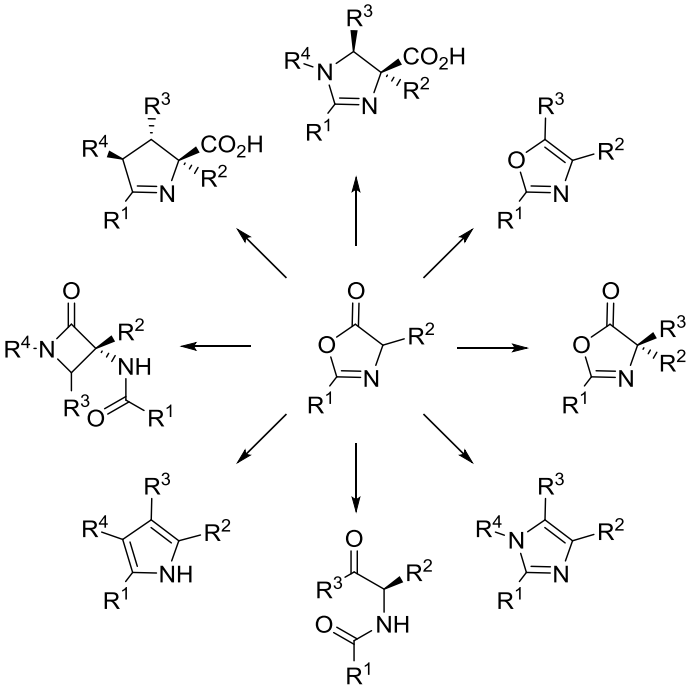
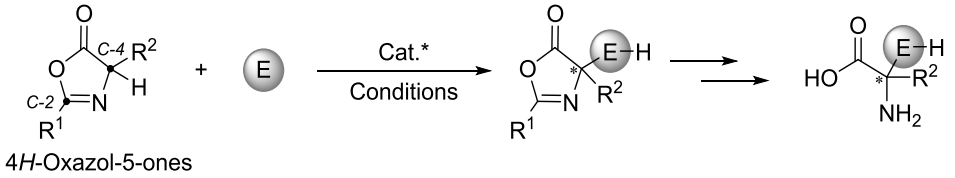


Figure 16. Diverse structures obtained from azlactones.

This multiple reactivity can be directed depending on the counterpart that is added to the reaction. The acidity of the α C(sp^3) in C-4 (pKa ≈ 9)[155] allows its facile deprotonation with mild Brønsted bases to obtain an enolate, that in presence of an electrophile would form a quaternary stereocentre contiguous to the carbonyl. This strategy has been broadly explored in several thorough reviews along the years, since it gives access to qua-

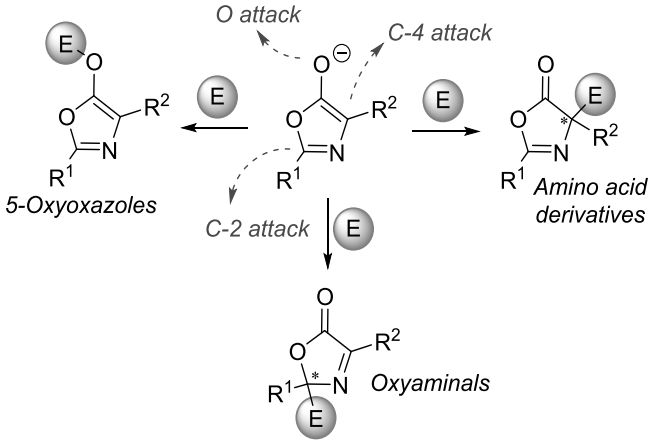
[152] For reviews on the diverse chemistry of azlactones, see: a) Fisk et al.b) Alba & Rios
[153] Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2815–2825.
[154] Erlenmeyer, E. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2036–2041.
[155] Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918–2922.

ternary natural or unnatural amino acid derivatives, which are highly requested building blocks or synthetic goals (Scheme 30).[156]



Scheme 30.

However, the presence of an electron withdrawing group or a proton at C-2 (R^1 = EWG or H) can alter this reactivity, making it possible for the aromatic enolate to perform nucleophilic attack from three different sites. This fact adds a regioselecitvity issue to solve in order to obtain the desired α,α-disubstituted α-amino acids, instead of an oxyaminal or an *O*-substituted oxazole (Scheme 31).



Scheme 31.

Whilst *O*- reactivity of these heterocycles has been extensively studied since the discovery of the rearrangement of *O*-acylated azlactones by Steglich and Höfle in 1970,[157] C-4 reactivity did not grab so much attention until Trost's research group reported the first Salen-Pd catalyzed α-allylation of azlactones in 1997.[158]

To date, a great number of examples involving azlactones as pronucleophiles for the synthesis of quaternary α-amino acids has been reported. These examples will be outlined later in chapter 3 (XXX).

[156] For some recent reviews on the stereoselective synthesis of quaternary α-amino acids employing azlactones among other strategies, see: a) Mosey, R. a.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762. b) Alba & Riossee ref. 152b page 38 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.

[157] Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, *11*, 4727–4730.

[158] 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. c) Zhou, H.; Yang, H.; Liu, M.; Xia, C.; Jiang, G. *Org. Lett.* **2014**, *16*, 5350–5353.

1.2.3.3. **Isoxazolinones (Isoxazol-5(4*H*)-ones)**

Cyclic five-membered oxime esters or isoxazolinones are currently involved in many biologically active species (Figure 17).[159] Along with this, these heterocycles are valuable building blocks of other heterocycles and β-amino acids.[160]

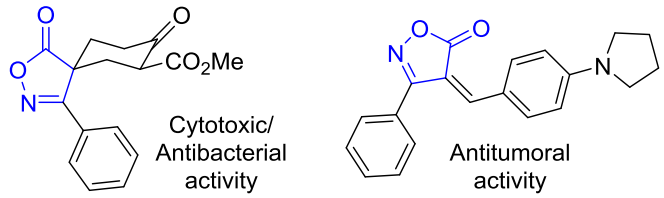
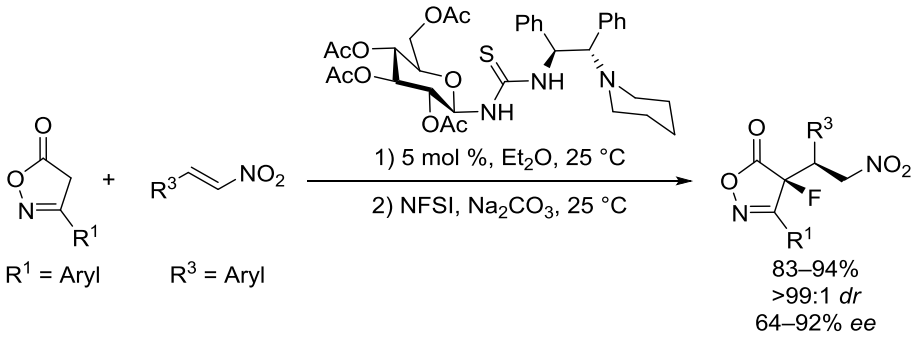


Figure 17. Selected examples of biologically active isoxazolinone derivatives.[161162]

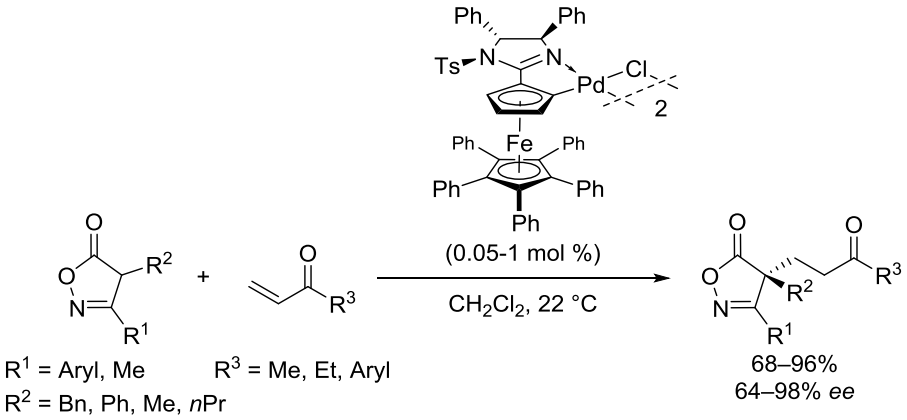
Despite their importance, there are only two examples of the use of isoxazolinones as pronucleophiles, which adds difficulty to a complete understanding of their reactivity. The first one was an organocatalytic Michael addition of isoxazol-5(4*H*)-ones developed by Ma's research group in 2013.[163] More specifically, it consisted of a one-pot sequential conjugate addition and dearomative fluorination of 3-aryl 4-unsubstituted isoxazolinones to aromatic nitroalkenes, catalyzed by a bifunctional amino-thiourea. Apart from the excellent yields and diastereo- and enantioselectivities, it is noteworthy that the authors were able to construct two contiguous stereogenic centres, especially a quaternary one from a methylene, in two sequential enantioselective steps (Scheme 32).



Scheme 32.

[159] Anti-obesity activity: a) Kafle, B.; Aher, N. G.; Khadka, D.; Park, H.; Cho, H. *Chem. Asian J.* **2011**, *6*, 2073–2079. Antitumoral activity: b) Ishioka, T.; Kubo, A.; Koiso, Y.; Nagasawa, K.; Itai, A.; Hashimoto, Y. *Bioorg. Med. Chem.* **2002**, *10*, 1555–1566.
[160] a) Batra, S.; Seth, M.; Bhaduri, A. P. *J. Chem. Res. Synop.* **1992**, 139. b) Batra, S.; Seth, M.; Bhaduri, A. P. *J. Chem. Res. Miniprint* **1992**, 1025.
[161] Chande, M. S.; Verma, R. S.; Barve, P. A.; Khanwelkar, R. R.; Vaidya, R. B.; Ajaikumar, K. B. *Eur. J. Med. Chem.* **2005**, *40*, 1143–1148.
[162] Ishioka, T.; Tanatani, A.; Nagasawa, K.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2655–2658.
[163] Meng, W.-T.; Zheng, Y.; Nie, J.; Xiong, H.-Y.; Ma, J.-A. *J. Org. Chem.* **2013**, *78*, 559–567.

The other example was an isoxazolinone addition to enones, which was recently described by Peters and co-workers.[164] This palladacycle-catalyzed Michael addition is the only example of 4-substituted isoxazol-5(4*H*)-ones as pronucleophiles reported to date (Scheme 33).



Scheme 33.

Thus, and to the best of our knowledge, no other electrophiles have been explored for the reaction with 4-substituted or unsubstituted isoxazol-5(4*H*)-ones.

1.2.3.4. **Butenolides**

γ,γ-Disubstituted butenolide skeletons represent a structural type of both synthetic and biological importance. A great number of biologically active natural products and pharmaceutically relevant molecules contain the special butenolide motif (Figure 18).[165]

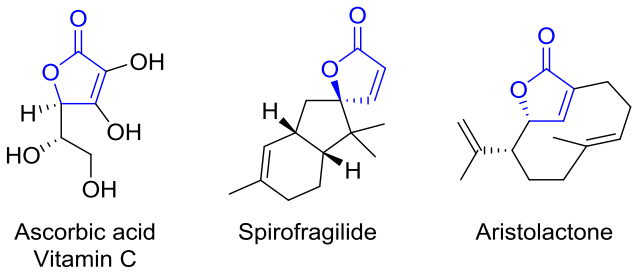
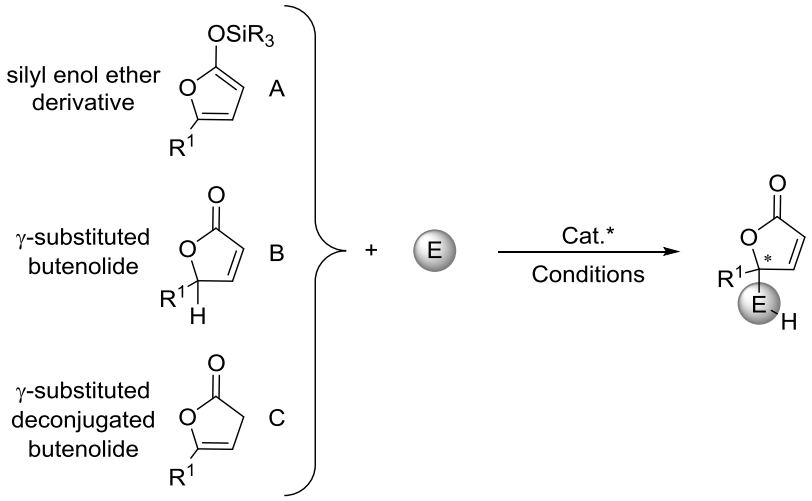


Figure 18. Selected natural products containing butenolide moiety.

[164] Hellmuth, T.; Frey, W.; Peters, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 2788–2791.

[165] For an early review on the importance of butenolides, see: a) Rao, Y. S. *Chem. Rev.* **1964**, *64*, 353–388. For a review on synthetic approaches to butenolide moiety, see: b) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287–315. Ascorbic acid: c) *Ascorbic Acid: Chemistry, Metabolism, and Uses* (P. A. Seib & B. M. Tolbert ed., American Chemical Society) 1982. Spirofragilide: d) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48. Aristolactone: e) Rueda, D.; Zaugg, J.; Quitschau, M.; Reich, E.; Hering, S.; Hamburger, M. *Planta Med.* **2012**, *78*, 207–210.

Many strategies have been used to access this structural motif, and different pro-nucleophiles have been employed for that purpose: such as silyl enol ether derivatives of γ-butenolide,[166] the butenolide itself,[167] and γ-substituted deconjugated butenolides (i.e. α-angelica lactone, when R^1 = Me), which upon reaction with an electrophile lead to γ,γ-disubstituted conjugated butenolide motifs (Scheme 34).[168]



Scheme 34.

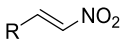
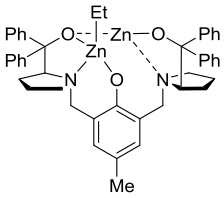
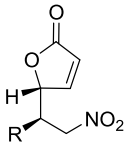
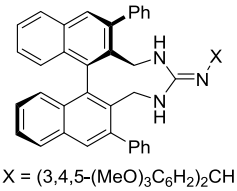
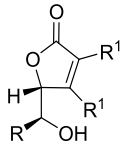
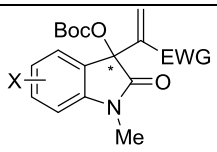
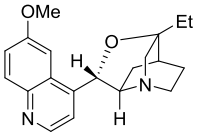
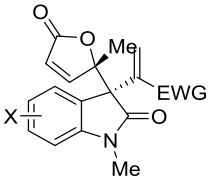
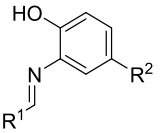
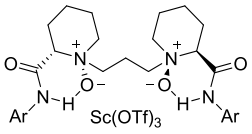
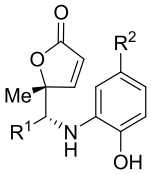
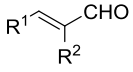
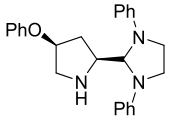
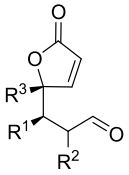
[166] See ref. 133 page 26.

[167] Some selected examples: For the Zn catalyzed vinylogous Michael addition to nitroalkenes, see: a) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572–4573. For the vinylogous aldol reaction catalyzed by a chiral guanidine, see: b) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1858–1861. For the vinylogous Michael reaction with nitroalkenes catalyzed by a chiral guanidine, see: c) Terada, M.; Ando, K. *Org. Lett.* **2011**, *13*, 2026–2029. For the vinylogous aldol reaction catalyzed by a thiourea-based bifunctional Brønsted base, see: d) Luo, J.; Wang, H.; Han, X.; Xu, L.-W.; Kwiatkowski, J.; Huang, K.-W.; Lu, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 1861–1864.

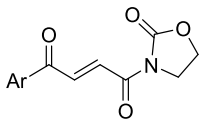
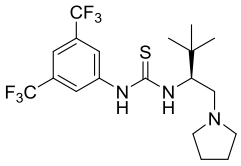
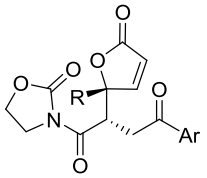
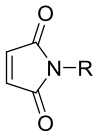
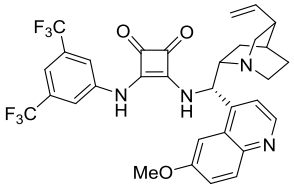
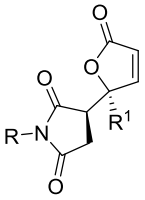
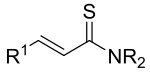
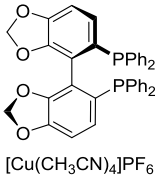
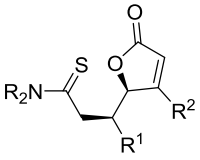
[168] For allylic substitution of α-angelica lactone employing dimeric Brønsted bases, see: a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720–723. For allylic substitution of α-angelica lactone employing chiral Brønsted bases, see: b) Huang, X.; Peng, J.; Dong, L.; Chen, Y.-C. *Chem. Commun.* **2012**, *48*, 2439. For the Sc catalyzed vinylogous Mannich reaction of α-angelica lactone, see: c) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 3056–3059. For the vinylogous Michael addition to enals catalyzed by a pyrrolidine derivative, see: d) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540–1543. For the vinylogous Michael addition to maleimides catalyzed by thiourea-based Brønsted bases, see: e) Manna, M. S.; Mukherjee, S. *Chem. Eur. J.* **2012**, *18*, 15277–15282. For the vinylogous Michael addition to enamides catalyzed by thiourea-based Brønsted bases, see: f) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 10069–10073. For the vinylogous Michael addition to nitroolefins catalyzed by thiourea-based Brønsted bases, see: g) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193–5195. For the vinylogous Michael addition to maleimides catalyzed by squaramide-based Brønsted bases, see: h) Guo, Y.-L.; Jia, L.-N.; Peng, L.; Qi, L.-W.; Zhou, J.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *RSC Adv.* **2013**, *3*, 16973–16976. For the Brønsted base catalyzed vinylogous Michael addition to acrylates, see: i) Das, U.; Chen, Y.-R.; Tsai, Y.-L.; Lin, W. *Chem. Eur. J.* **2013**, *19*, 7713–7717. For the vinylogous Michael addition to enones employing dual metal/organocatalysis, see: j) Yang, D.; Wang, L.; Zhao, D.; Han, F.; Zhang, B.; Wang, R. *Chem. Eur. J.* **2013**, *19*, 4691–4694. For the Cu catalyzed vinylogous Michael addition to thioamides, see: k) Yin, L.; Takada, H.; Lin, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 5327–5331.

In each case, the different tactics used have been mainly vinylogous additions, that have been thoroughly collected in several reviews.[169] Depicted in Table 12 are the diverse electrophiles employed to date for the additions of butenolides (entries 1–2 and 8), and α-angelica lactone derivatives (entries 3–7).

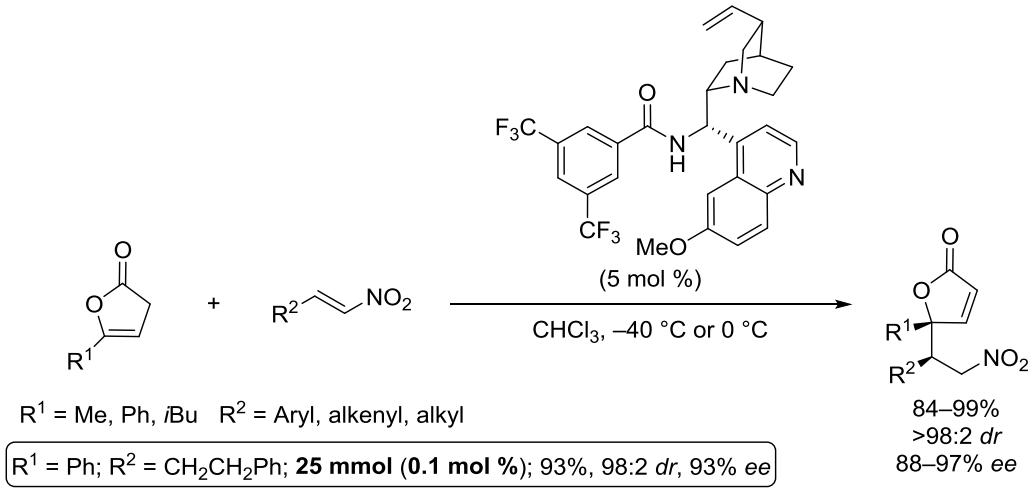
Table 12. Selected examples of vinylogous addition of butenolide equivalents to unsaturated bonds.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Aryl, Alkyl	 (10 mol %)	 R = Aryl, Alkyl	47–78% 3:1–20:1 *dr* 83–96% *ee*	167a
2	 R = Aryl	 X = (3,4,5-(MeO)$_3$C$_6$H$_2$)$_2$CH (5 mol %)	 R1 = Cl, Br	58–95% 85:15–91:9 *dr* 96–97% *ee*	167b
3	 EWG = CO_2Me, COMe X = H, Hal, F_3CO, Me	 (10 mol %)	 R^3 = Aryl, Me, Et	70–91% >95:5 *dr* 70–91% *ee*	168b
4	 R^1 = Aryl R^2 = H, Me, Cl	 Ar = 2,6-*i*Pr$_3$C$_6$H$_3$ (5 mol %)		58–90% 86:14–99:1 90–98	168c
5	 R^1 = Alkyl, aryl, H R^2 = H, Me	 (15 mol %)	 R^3 = Me, Et	60–95% 1:1–8:1 *dr* 88–96% *ee*	168d

[169] For a recent review on the synthesis of butenolides by direct vinylogous reactions, see: a) Yan, L.; Wu, X.; Liu, H.; Xie, L.; Jiang, Z. *Mini-Reviews Med. Chem.* **2013**, *13*, 845–853. For recent reviews on vinylogous reactions, see: b) ref. 134 page 26. For aminocatalytic remote functionalization strategies, see: c) Jiang et al.

6		 (1 mol %)	 R = Aryl, Alkyl	71–93% 16:1–99:1 *dr* 90–96% *ee*	168f
7	 R = Aryl, Me	 (1 mol %)	 R^1 = Aryl, Me	80–96% 44:56–82:18 *dr* 83–97% *ee*	168h
8	 R^1 = Alkyl, aryl; R^2 = Alkyl	 $[Cu(CH_3CN)_4]PF_6$ (5 mol %)	 R^2 = H, Me	78–98% 94–99% *ee*	168k

One of the most recent examples, described by Hatanaka and co-workers in 2015,[170] described the bifunctional benzamide-based bifunctional Brønsted base catalyzed vinylogous Michael addition of α-angelica lactones to nitroolefins, obtaining very good yields and excellent diastereo- and enantioselectivities (Scheme 35). An outstanding large scale test was performed, maintaining an excellent outcome even with very low catalyst loading.

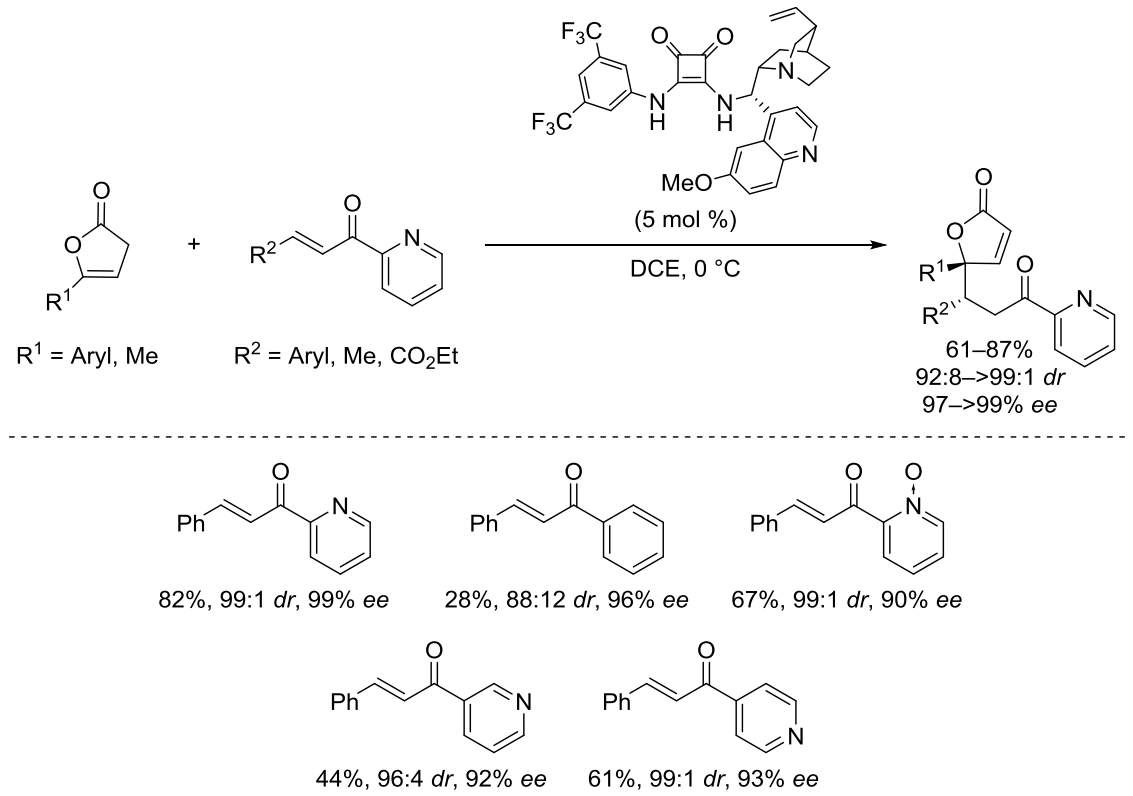


Scheme 35.

Another recent example concerns the Michael addition of deconjugated butenolides to 2-enoylpyridines reported by Xu and Yuan's research group.[171] The squaramide-

[170] Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026–3029.
[171] Wang, Z.-H.; Wu, Z.-J.; Huang, X.-Q.; Yue, D.-F.; You, Y.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Chem. Commun.* **2015**, *51*, 15835–15838.

based bifunctional Brønsted base catalyzed reaction occurred with good yield and excellent stereocontrol, although the reaction between 5-methyl substituted pronucleophile and β-methyl enone did not proceed ($R^1 = R^2 = Me$). The importance of the 2-pyridyl moiety was highlighted by performing several contrast experiments (Scheme 36).



Scheme 36.

1.2.4. **Thiolactone based pronucleophiles**

1.2.4.1. **Thiazol-5(4*H*)-ones**

As already has been proved, heterocyclic compounds have received considerable attention from many research groups, due to their utility in biological chemistry. Among them, five-membered rings containing two heteroatoms are the ones which show more prevalence, including the thiazole ring, which is present in numerous pharmaceutically interesting compounds (Figure 19).[172]

[172] For recent reviews on thiazol containing natural products, see: a) Davyt, D.; Serra, G. *Mar. Drugs* **2010**, *8*, 2755–2780. b) Gupta, V.; Kant, V. *Sci. Int.* **2013**, *1*, 253–260.

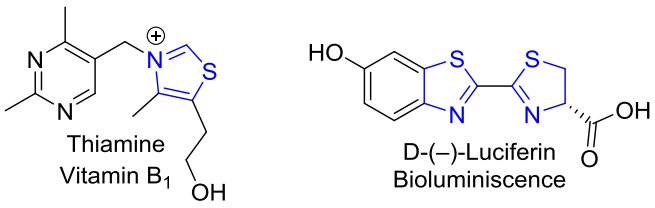
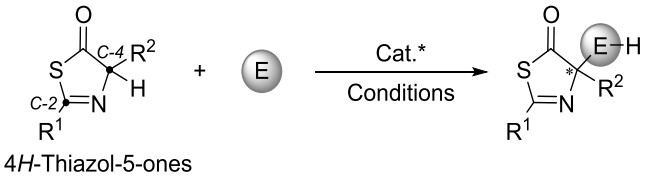


Figure 19. Selected examples of biologically meaningful thiazole derivatives.[173][174]

However, and despite their importance, the use of this kind of heterocycles as pro-nucleophiles to obtain chiral thiazole derivatives in an organocatalytic stereoselective manner has been limited to just a family of thiolactones, thiazol-5(4*H*)-ones (Scheme 37).



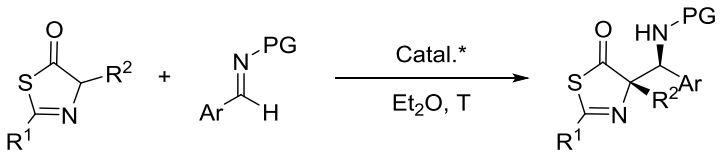
Scheme 37.

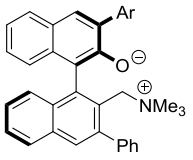
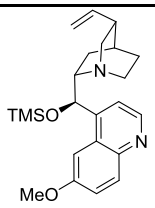
Taking into account the similarities between these compounds and azlactones (Page 43), regioselectivity (C-4/C-2) should also be an issue for them. For this reason, every research group avoided electron withdrawing moieties or hydrogen and only electron donating ones were located at C-2, in order to favour C-4 selectivity ($R^1 \neq$ EWG or H).

A case in point are the Mannich additions performed on *N*-protected aryl imines by Ooi's and Wang's groups, employing a chiral ammonium betaine and a silylated quinine derivative, respectively, as catalysts. Depicted in Table 13 are the results obtained with 4-activated 2-benzyloxy thiazol-5(4*H*)-ones by the former,[175] and with the less activated 4-alkyl 2-ethylthio thiazol-5(4*H*)-ones by the latter.[176] In every case, yields and diastereoselectivities were moderate to excellent, and enantioselectivity was very good or excellent.

[173] Williams, R. R.; Cline, J. K. *J. Am. Chem. Soc.* **1936**, *58*, 1504–1505.
[174] White, E. H.; McCapra, F.; Field, G. F.; McElroy, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 2402–2403.
[175] Uraguchi, D.; Koshimoto, K.; Ooi, T. *Chem. Commun.* **2010**, *46*, 300–302.
[176] Liu, X.; Deng, L.; Song, H.; Jia, H.; Wang, R. *Org. Lett.* **2011**, *13*, 1494–1497.

Table 13.

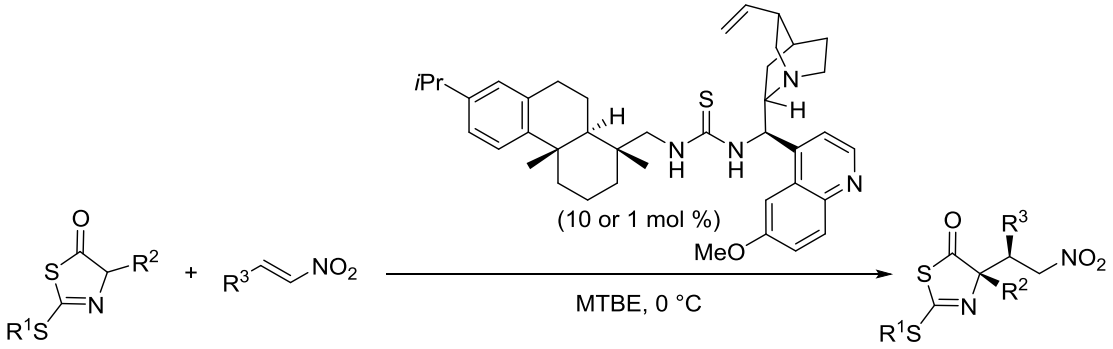


	R^1	R^2	PG	Cat.*	T (°C)	Results	Ref.
1	BnO	Ph, 4-ClC_6H_4, Bn	Boc	 Ar = *p*Tip-C_6H_4 Tip = 2,4,6-triisopropylphenyl	–40	88–97% 73:27–94:6 *dr* 92–99% *ee*	175
2	EtS	*i*Pr, *i*Bu	Ts		20	73–94% 75:25–>98:2 *dr* 80–>99% *ee*	176

The first example of organocatalyzed 1,4-addition of thiazol-5(4*H*)-ones to nitroolefins, developed by Wang and co-workers (Table 14).[177] The bifunctional thiourea-catalyzed reaction worked equally well with both electron enriched or deficient conjugated nitroalkenes, but the methodology was not robust enough to achieve such results with β-alkyl substituted nitroalkenes. Nitrodienes inverted the diastereoselectivity of the reaction, although moderate enantioselectivity was obtained for the major diastereomer (entry 4). Finally, it was demonstrated that changes in R^1 did not affect the outcome of the reaction much (entries 8–9).

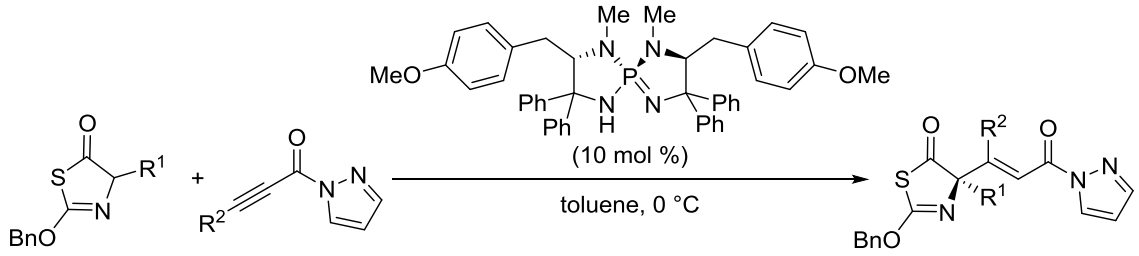
[177] Liu, X.; Song, H.; Chen, Q.; Li, W.; Yin, W.; Kai, M.; Wang, R. *Eur. J. Org. Chem.* **2012**, *5*, 6647–6655.

Table 14. Representative results of Michael addition of thiazolones to nitroolefins.



Entry	R^1	R^2	R^3	Yield (%)	*dr*	*ee* (%)
1	Et	*i*Pr	Ph	81	85:15	94
2	Et	*i*Pr	2-$NO_2C_6H_4$	84	91:9	96
3	Et	*i*Pr	4-$MeOC_6H_4$	75	89:11	91
4	Et	*i*Pr	(*E*)-PhCH=CH	66	20:80	97/70
5	Et	*i*Pr	Cy	–	–	–
6	Et	*i*Bu	2-$NO_2C_6H_4$	62	75:25	80
7	Et	*t*Bu	4-CNC_6H_4	68	90:10	84
8	Et	*i*Pr	4-CNC_6H_4	71	88:12	94
9	Bn	*i*Pr	4-CNC_6H_4	71	80:20	92

On another note, very recently, Ooi and co-workers reported a Michael addition to electron deficient alkynes under chiral iminophosphorane catalysis.[178] The reaction occurred with high *E*-selectivity and enantioselectivity in every case (Scheme 38).



Scheme 38.

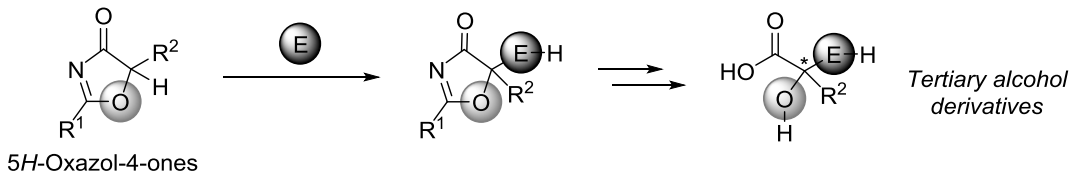
To date, no other electrophile (e.g. aldehydes, azodicarboxylates, etc.) has been employed for the reaction with thiazol-5(4*H*)-ones.

[178] Uraguchi, D.; Yamada, K.; Ooi, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 9954–9957.

1.3. **Working hypothesis and objectives**

Precedents mentioned in previous sections make clear the relevance of five-membered heterocycles containing two different heteroatoms. Sometimes their biological and pharmaceutical interest makes them important synthetic goals by themselves, but they can also be employed as building blocks to construct compounds of more structural complexity, that cannot be accessed in any other way. Thus, the development of new pronucleophiles for organocatalytic reactions that allow simpler synthetic pathways to carbonylic compounds with quaternary α-C(sp^3) moieties has been the aim of several research groups throughout decades.

In this field, oxazolones have attracted great part of the attention, since the compounds that can be accessed from them are of crucial interest in many purposes. On one hand, 5*H*-oxazol-4-ones make excellent precursors for tertiary alcohol derivatives, such as α,α-disubstituted α-hydroxy acid (Scheme 39).[179]



Scheme 39.

Attention on *N*,*O*-bearing templates has neglected the importance of other heterocycles, such the thiazole, which contain sulphur atoms in their structure. In fact, the number of stereoselective reactions that have been reported employing *S*-containing pronucleophiles is astonishingly smaller, comparing just to oxazolones. Five-membered *S*-containing carbonylic pronucleophiles are reduced to two: 4*H*-thiazol-5-ones[180] and rhodanines (Figure 20).[181]

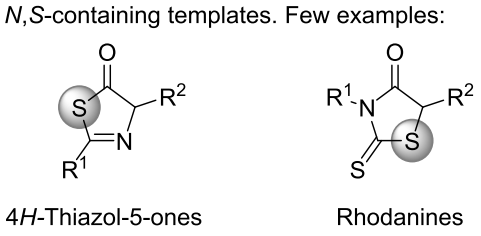
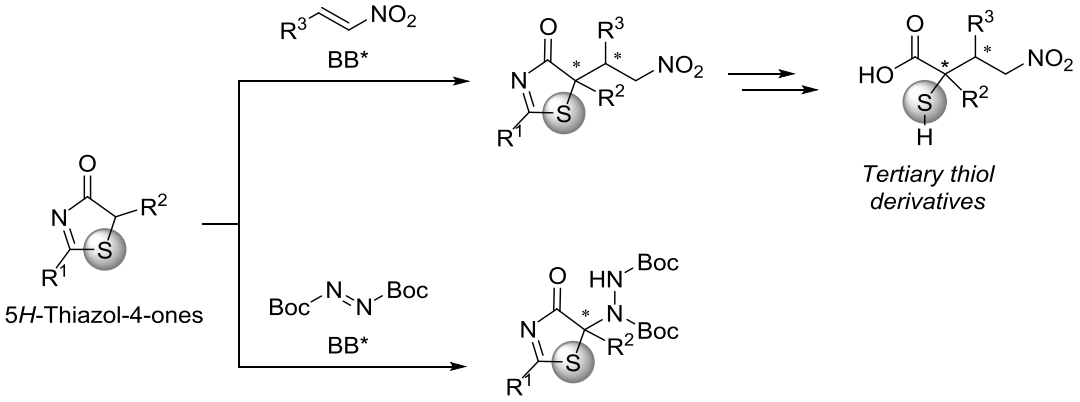


Figure 20.

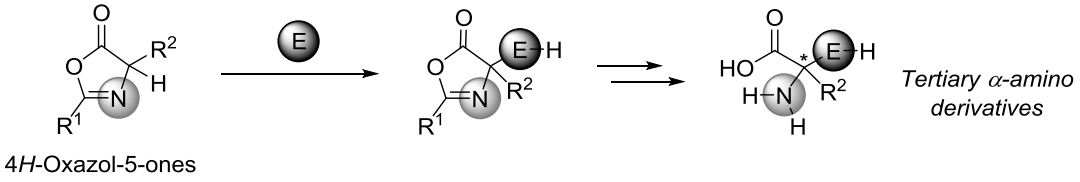
[179] For more information on oxazol-4(5*H*)-ones, see page 24.
[180] For more information on thiazol-5(4*H*)-ones, see page 49.
[181] For more information on rhodanines, see page 36.

Thus, the first objective of this work would be to synthesize 5*H*-thiazol-4-ones (as sulfur equivalents of 5*H*-oxazol-4-ones) for the first time and to test them as effective pronucleophiles for the addition to Michael acceptors employing bifunctional Brønsted bases, leading to α,α-dialkyl α-thiocarboxylic acid derivatives (Scheme 40).



Scheme 40.

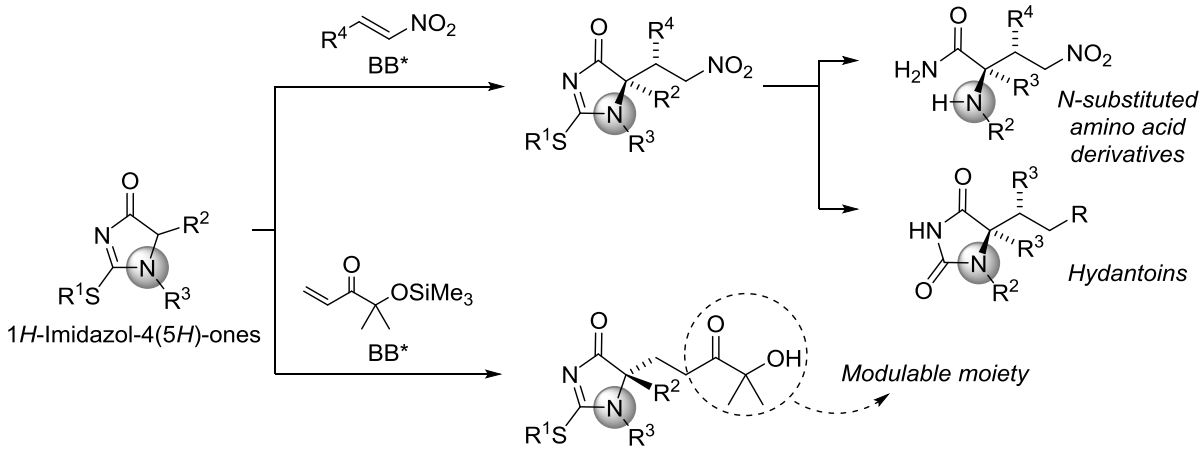
On the other hand, 4*H*-oxazol-5-ones have paved the way for the stereoselective formation of α,α-disubstituted α-amino acids, which explains the incredible growth that these pronucleophiles have suffered the last years (Scheme 41).[182]



Scheme 41.

Moved by this idea, the second goal of this work would be the synthesis of 2-alkylthio 1*H*-imidazol-4(5*H*)-ones, as synthetic equivalents to hydantoins, and to test them as effective pronucleophiles for the Michael addition to different electrophiles, including α'-oxy enones, whose utility was first recognized by our group.[183] It is noteworthy, that using these templates *N*-substituted quaternary amino acid derivatives would be obtained, instead of unsubstituted ones as with 4*H*-oxazol-5-ones (Scheme 39).

[182] For more information on oxazol-5(4*H*)-ones, see page 42.
[183] See ref. 88a page 16, and references herein.


BB*
BB*
1H-Imidazol-4(5H)-ones
N-substituted amino acid derivatives
Hydantoins
Modulable moiety

CHAPTER 2

CONSTRUCTION OF α,α-DISUBSTITUTED α-THIO ACID DERIVATIVES

2. CONSTRUCTION OF α,α-DISUBSTITUTED α-THIO ACID DERIVATIVES

2.1. Introduction

As it has been already explained in the previous chapter, tertiary thiols are an important moiety present in a great range of biologically active compounds. Thus, this structural motif has been employed widely for therapeutical and synthetic purposes. However, the construction of such compounds in an enantiopure manner, especially if comparing to secondary thiols, has been little explored.[184] The main strategies for the synthesis of tertiary thiols can be divided in two groups: the first one, which consists in the formation of a *C-S* bond, and the second, which consists in the creation of a *C-C* bond (Figure 21).

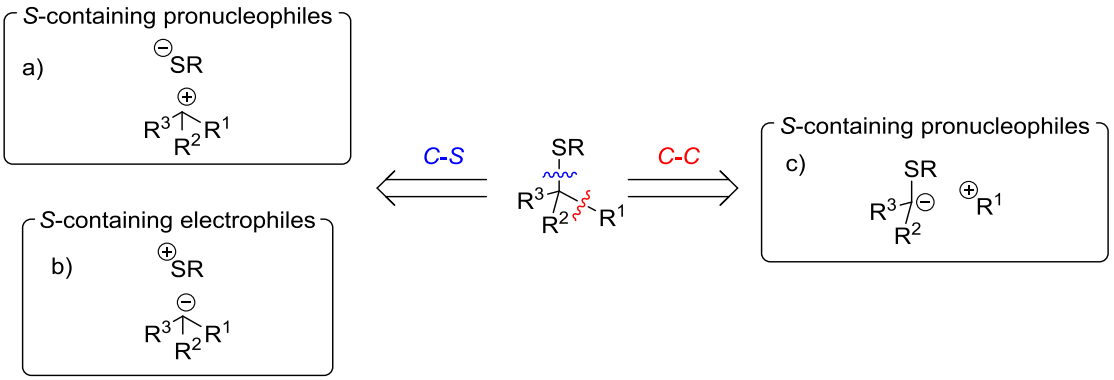


Figure 21. Strategies for the asymmetric synthesis of tertiary thiols.

2.1.1. Construction of tertiary thiols through *C-S* bond formation

In this section nucleophilic and electrophilic sulfenylation will be mainly discussed, along with few examples of sulfa-Michael reactions on electron deficient alkenes that have been also reported (Figure 22).

[184] For a review on the organocatalityc asymmetric synthesis of tertiary thiols, see: a) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem.* **2011**, *7*, 582–595. For a review on the organocatalytic formation of *C-S* bonds, see: b) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807–8864. For reviews on transition metal-catalyzed *C-S* bond formation, see: c) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596–1636. d) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051–2069. For leading books, see: e) *Organosulfur Chemistry in Asymmetric Synthesis* (T. Toru & C. Bolm ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2008. f) *C-X Bond Formation* (A. Vigalok ed., Springer Berlin Heidelberg) 2010.

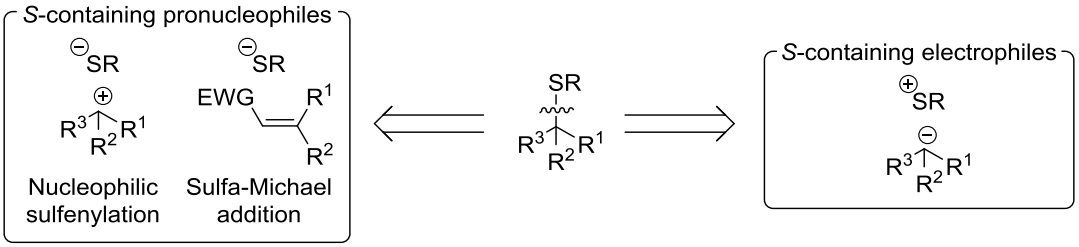
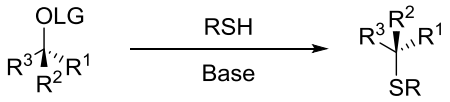


Figure 22. Strategies for the asymmetric synthesis of tertiary thiols through *C-S* bond formation.

2.1.1.1. **Nucleophilic sulfenylation**

These examples are based in most cases on the employment of optically pure tertiary alcohols, which, after proper transformation into a leaving group (LG), undergo a S_N2 displacement from a nucleophilic sulfur centre, providing tertiary thiol derivatives (Scheme 42).[185] The first example of such methodology was described by Effenberger's group in 1999, where a mesyl moiety was employed as a leaving group.[186] Subsequently, sulfones have been commonly chosen for this task.[187]



Scheme 42.

However, other tactics have also been employed for this purpose, such as the use of phosphinites as leaving groups by Mukaiyama and co-workers,[188] the Mitsunobu reaction by La Clair's research group,[189] the stereocontrolled ring opening of epoxides de-

[185] This displacement represents a considerable synthetic challenge due to the sterically hindered nature of the stereogenic centre.

[186] For the sulfenylation of a cyanohydrins with thioaetic acid, see: a) Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775.

[187] For the intramolecular sulfenylation of an isatin derivative in presence of pyridine, employing Ms as leaving group, in the total synthesis of spirobrassinin, see: a) Monde, K.; Taniguchi, T.; Miura, N.; Nishimura, S.-I.; Harada, N.; Dukor, R. K.; Nafie, L. A. *Tetrahedron Lett.* **2003**, *44*, 6017–6020. For the synthesis of tertiary thiols from α-aryl-α-hydroxy esters employing Ms as leaving group, see: b) Weaver, J.; Morris, D.; Tunge, J. *Synlett* **2010**, 470–474. For the use of hindered cyclic sulfamidates as precursors of α-mercapto β-amino acids, see: c) Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M. *J. Org. Chem.* **2006**, *71*, 1692–1695. For the synthesis of AMG 221 employing this strategy, see: d) Caille, S.; Cui, S.; Hwang, T.-L.; Wang, X.; Faul, M. M. *J. Org. Chem.* **2009**, *74*, 3833–3842.

[188] a) Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 638–639. b) Ikegai, K.; Pluempanupat, W.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 780–790. For extension of this work using phenoxydiphenyl phosphine and azide derivatives as oxidants, see: c) Kuroda, K.; Hayashi, Y.; Mukaiyama, T. *Chem. Lett.* **2008**, *37*, 592–593. d) Kuroda, K.; Maruyama, Y. *Bull. Chem. Soc. Jpn.* **2009**, *392*, 381–392. e) Mukaiyama, T.; Kuroda, K.; Maruyama, Y. *Heterocycles* **2010**, *80*, 63–82.

[189] La Clair, J. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2769–2773.

scribed by Rodríguez and co-workers,[190] and the S_N2 displacement of chiral tertiary chlorides by Shibatomi and Jacobsen.[191]

Summarizing, despite nucleophilic sulfenylation is a suitable strategy for the synthesis of tertiary thiol derivatives, this strategy invariably needs prior construction of enantiopure tertiary alcohol precursor.[192]

2.1.1.2. **Sulfa-Michael addition**

Michael addition of sulfur-containing nucleophiles to β,β-disubstituted electron deficient alkenes is other alternative to produce chiral tertiary thiols. However, this approach generally exhibits some problems, such as, low reactivity due to steric concerns, low π-facial stereoselectivity and a possible equilibration of the stereisomers through an addition/elimination mechanism.

In this field, our research group was able to perform an unprecedent intramolecular sulfa-Michael addition to β,β-disubstituted *N*-enoyl oxazolidin-2-thiones. In every case, the chiral auxiliary (i.e. oxazolidin-2-thione) acted as both, intramolecular sulfur donor reagent and stereodirecting group. The reaction may be promoted by Lewis acids (LA),[193] and/or a Brønsted acid (BA).[194] It is believed that the process occurs through the transition state depicted in Table 15 and by assuming a preferential reaction of sulfur on the *Si* face of the enoyl β carbon atom with no interference of the *i*Pr group.

[190] a) López, I.; Rodríguez, S.; Izquierdo, J.; González, F. V *J. Org. Chem.* **2007**, *72*, 6614–6617. For a practical application of this protocol in the total synthesis of (+)-BE-52440A, see: b) Tatsuta, K.; Suzuki, Y.; Toriumi, T.; Furuya, Y.; Hosokawa, S. *Tetrahedron Lett.* **2007**, *48*, 8018–8021.

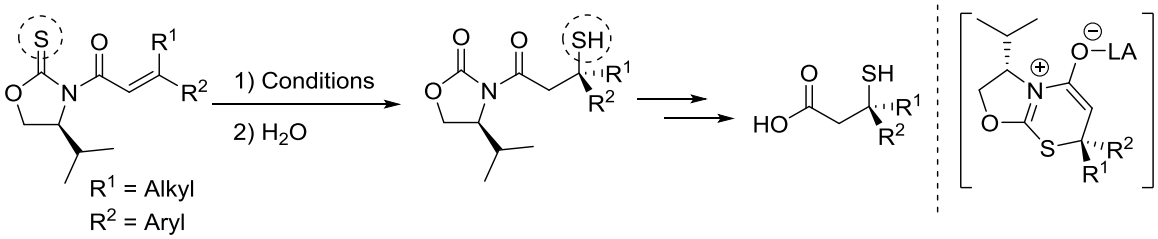
[191] a) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836–9839. b) Liu, R. Y.; Wasa, M.; Jacobsen, E. N. *Tetrahedron Lett.* **2015**, *56*, 3428–3430.

[192] For a recent example of the Brønsted acid catalyzed asymmetric formation of a tertiary thiol from an achiral tertiary alcohol, see: Suć, J.; Dokli, I.; Gredičak, M. *Chem. Commun.* **2016**, DOI: 10.1039/C5CC08813E.

[193] For intramolecular sulfenylation assisted by tin chloride to obtain secondary thiols, see: a) Palomo, C.; Oiarbide, M.; Dias, F.; Ortiz, A.; Linden, A. *J. Am. Chem. Soc.* **2001**, *123*, 5602–5603. For intramolecular sulfenylation assisted by boron to obtain tertiary thiols, see: b) Palomo, C.; Oiarbide, M.; Dias, F.; López, R.; Linden, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3307–3310.

[194] For intramolecular sulfenylation assisted by Brønsted bases to obtain tertiary thiols, see: a) Palomo, C.; Oiarbide, M.; López, R.; González, P. B.; Gómez-Bengoa, E.; Saá, J. M.; Linden, A. *J. Am. Chem. Soc.* **2006**, *128*, 15236–15247.

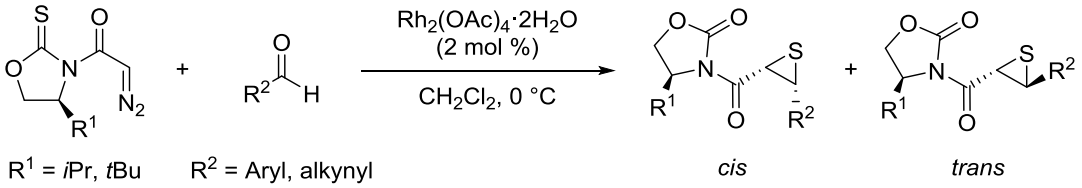
Table 15.



Entry	R^1	R^2	LA or BA	Results	Ref.
1	H	Me, Et, *i*Pr, Aryl	$SnCl_4$ (2 equiv.)	70–80% 75:25–98:2 *dr*	193a
2	Me, Et, *n*Bu	Aryl	$BF_3{\cdot}Et_2O$ (2 equiv.)	65–83% 52:48–99:1 *dr*	193b
3	Me, *n*Bu	Aryl	TFA (2 equiv.)	59–83% 33:67–1:99 *dr*	194

Some years later, our group came up with an additional application of this methodology to obtain thioepoxides.[195] The rhodium catalyzed reaction between *N*-(diazoacetyl)oxazolidin-2-thiones and aldehydes to afford thiiranes occurred with moderate yields and good to excellent diastereoselectivities (Table 16).

Table 16.

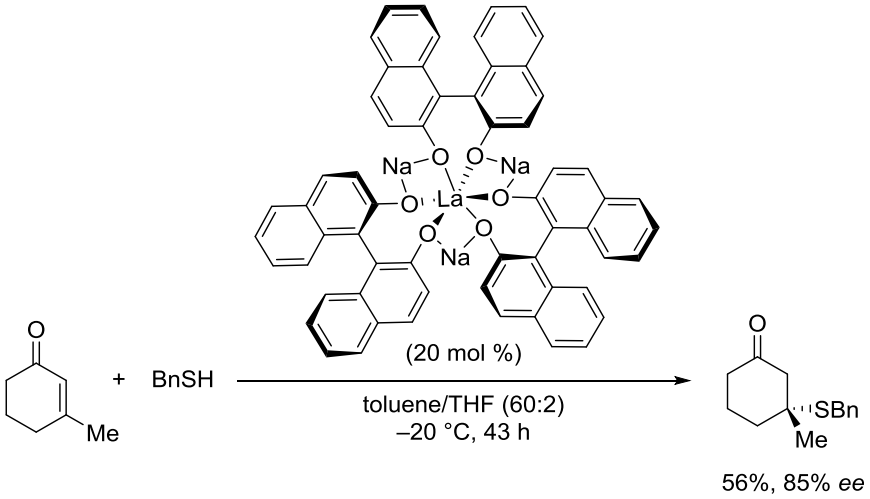


Entry	R^1	R^2	Yield (%)	*cis/trans*
1	*i*Pr	Ph	65	93:7
2	*i*Pr	4-MeC_6H_4	60	82:18
3	*i*Pr	4-$MeOC_6H_4$	61	1:99
4	*i*Pr	PhC≡C	65	72:28
5	*t*Bu	PhC≡C	75	83:17
6	*i*Pr	3-furyl	n.d.	62:38
7	*t*Bu	3-furyl	70	83:17
8	*i*Pr	3-pyridyl	0	-

Apart from this, as far as we know and until the development of this thesis work, only three examples in literature describe the asymmetric formation of tertiary thiol derivatives. These examples include the first sulfa-Michael additions developed by Shi-

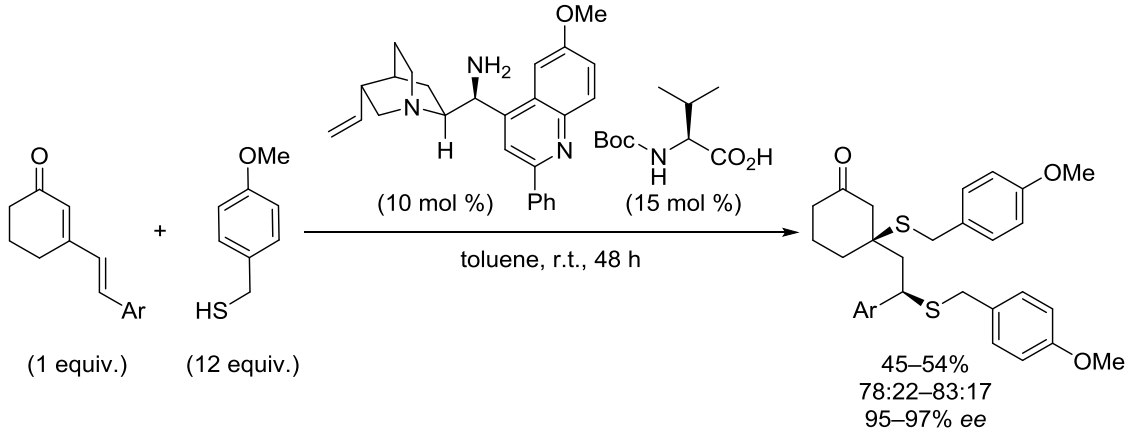
[195] Cano, I.; Gómez-Bengoa, E.; Landa, A.; Maestro, M.; Mielgo, A.; Olaizola, I.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 10856–10860.

basaki's research group in the late 1990's.[196] Their work consisted in the conjugate addition of benzyl thiol to cyclic enones, catalyzed by heterobimetallic complexes. In the addition to 3-methylcyclohex-2-en-1-one, yield was moderate and enantioselectivity was not excellent, although this was the first catalytic enantioselective formation of a tertiary thiol derivative (Scheme 43).



Scheme 43.

Cyclic enones were also chosen by Melchiorre and co-workers to perform sulfa-Michael additions, employing benzylic thiols as nucleophiles in a vinylogous iminium ion activation of cyclic dienones.[197] Despite their initial idea of executing only a 1,6-addition on the dienone, they realized that employing a great excess of the thiol enabled them to perfom a further 1,4-addition, accessing tertiary thioethers in moderate yield, good diastereoselectivity and excellent enantioselectivity (Scheme 44).

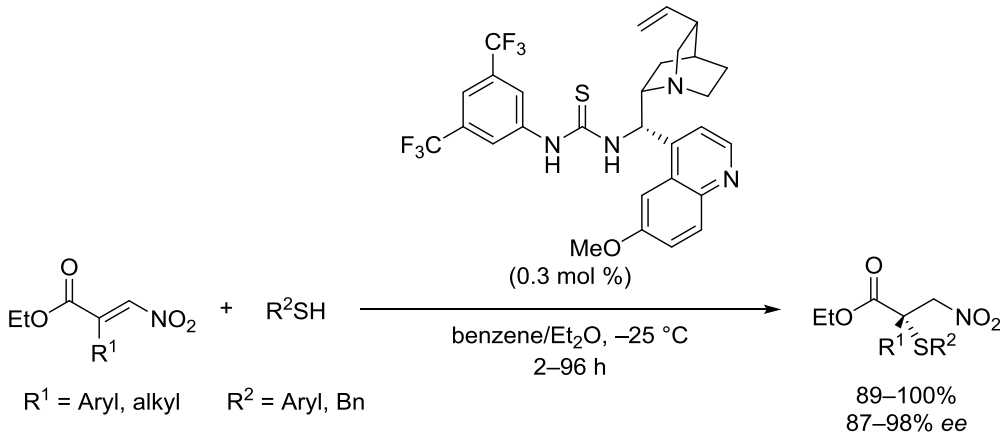


Scheme 44.

[196] a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043–4044. For an application of this methodology to perform a catalytic kinetic resolution, see: b) Emori, E.; Iida, T.; Shibasaki, M. *J. Org. Chem.* **1999**, *64*, 5318–5320.

[197] Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 6439–6442.

An outstanding illustration of this sulfenylation strategy was described by Xiao and co-workers in 2009.[198] Their research focused on the organocatalyzed addition of various thiols to β,β-disubstituted nitroalkenes bearing an electron withdrawing group (i.e. ethoxy carbonyl), in order to overcome their usual lack of reactivity. A thiourea-based bifunctional Brønsted base was chosen as catalyst, and it rendered excellent yield and enantioselectivity, even with extremely low catalytic loadings (Scheme 45).

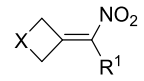
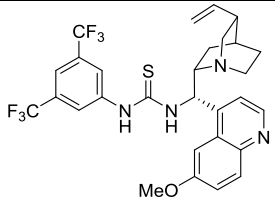
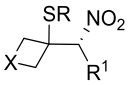
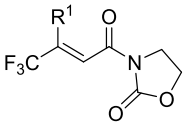
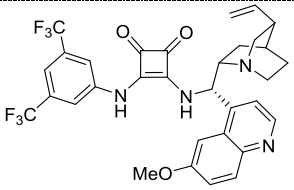
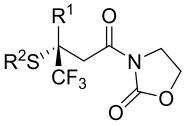
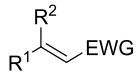
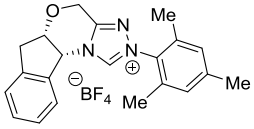
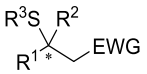


Scheme 45.

It is remarkable that between 2009 and 2014 no example of an enantioselective sulfa-Michael addition was reported.[199] Only recently, three more approaches for the sulfa-Michael addition to β,β-disubstituted Michael acceptors have appeared. However, as Table 17 illustrates, these approaches require highly activated electrophiles, which is usually restricted to few electron deficient alkenes. [200] It is noteworthy that the example in entry 1 incorporates a strained ring to increase the reactivity of the nitroalkene, instead of using electron withdrawing groups as in entries 2–3.

[198] Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946–3949.
[199] For a racemic sulfa-Michael addition to β,β-disubstituted nitroolefins, see: a) Xu, C.; Xu, J. *Amino Acids* **2011**, *41*, 195–203. For a diastereoselective sulfa-Michael addition to nitroolefins leading to secondary thiols, see: b) Chen, N.; Xu, J. *Tetrahedron* **2012**, *68*, 2513–2522.
[200] For the catalytic addition of thioacids to trisubstituted nitroolefins, see: a) Phelan, J. P.; Patel, E. J.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 11329–11332. For recent examples of sulfa-Michael additions to CF_3-bearing conjugate olefins, see: b) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292–1300. c) Chen, J.; Meng, S.; Wang, L.; Tang, H.; Huang, Y. *Chem. Sci.* **2015**, *6*, 4184–4189.

Table 17. Recent examples of enantioselective sulfa-Michael additions to electron deficient systems.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R^1 = Me, Et, *i*Pr, Bn X = O, NBoc	 (5 mol %)	 R = Ac, COPh	72–96% 86–96% *ee*	200a
2	 R^1 = Aryl, alkyl	 (10 mol %)	 R^2 = Alkyl, Bn	80–9% 93–99% *ee*	200b
3	 R^1 = CF_3, H R^2 = Aryl, alkyl EWG = NO_2, ketone	 (10 mol %)	 R^3 = Alkyl, Bn	56–99% 70–98% *ee*	200c

2.1.1.3. **Electrophilic sulfenylation**

Asymmetric electrophilic sulfenylation is a widely investigated strategy for the organocatalytic asymmetric α-sulfenylation of carbonyl compounds, leading mainly to secondary thiols.[201,184b] Concerning to the synthesis of tertiary thiols,[184a] chiral auxiliaries[202] and metal catalysis[203] have been employed, although recently, Brønsted base catalysis has been the tactic of choice in most examples.

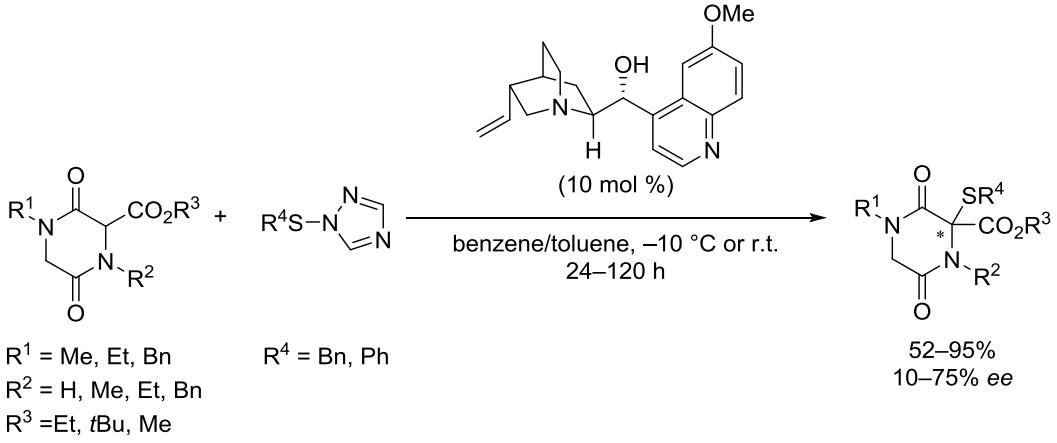
The first organocatalyzed versions of electrophilic sulfenylation involved the utilization of α-substituted β-dicarbonyl compounds as pronucleophiles, employing either

[201] a) *Comprehensive Enantioselective Organocatalysis* (P. I. Dalko ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2013. For the organocatalytic direct asymmetric α-heterofunctionalization of aldehydes and ketones, see: b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. c) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. For the transition metal catalyzed enantioselective α-heterofunctionalization of carbonyl compounds, see: d) Smith, A. M. R.; Hii, K. K. M. *Chem. Rev.* **2011**, *111*, 1637–1656. For a review on α,α-diaryl prolinol mediated reactions including electrophilic sulfenylation, see: e) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821.

[202] a) Ohata, K.; Terashima, S. *Tetrahedron Lett.* **2006**, *47*, 2787–2791. b) Ohata, K.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4070–4074.

[203] For the Ti catalyzed α-sulfenylation of β-ketoesters, see: a) Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041–4043. b) Srisailam, S. K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2603–2607. c) Jereb, M.; Togni, A. *Chem. Eur. J.* **2007**, *13*, 9384–9392. For the Se catalyzed sulfenylation of non carbonylic olefins, see: d) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308–15311.

secondary or tertiary amines to catalyze the reaction.[204] This strategy included the first organocatalyzed α-sulfenylation performed on 5-alkoxycarbonyl diketopiperazinones, as reported by Olenyuk in 2009 (Scheme 46).[205]



Scheme 46.

In 2012, almost simultaneously, three groups described the first examples using oxindoles as pronucleophiles. Feng and co-workers presented a Sc catalyzed sulfenylation of *N*-H oxindoles with *N*-(phenylthio) phthalimide (Table 18, entry 1),[206] while the other groups reported organocatalyzed versions of the reaction: Enders and co-workers used a squaramide based bifunctional Brønsted base (Table 18, entry 2),[207] and Cheng's group used quinidine (Table 18, entry 3).[208] The adducts obtained presented *S* configuration in the three cases. Later, opposite configuration of the adducts was achieved by Maruoka, employing a phosphonium salt for PTC (Table 18, entry 4),[209] and by Rueping, using $(DHQD)_2PYR$ (Table 18, entry 5).[210]

[204] For the pioneering sulfenylation of β-dicarbonyl compounds, including lactones and lactams, employing Brønsted bases, see: a) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 5689–5694. For the sulfenylation of β-ketoesters with prolinol derivatives, see: b) Fang, L.; Lin, A.; Hu, H.; Zhu, C. *Chem. Eur. J.* **2009**, *15*, 7039–7043. For the sulfenylation of β-ketophosphonates with prolinol derivatives, see: c) Lin, A.; Fang, L.; Zhu, X.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal.* **2011**, *353*, 545–549. For an enantioselective trifluoromethylsulfenylation of β-ketoesters catalyzed by quinidine, see: d) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12856–12859.

[205] For the sulfenylation of 5-alkoxycarbonyl diketopiperazines with quinine and moderate *ee*'s, see: a) Polaske et al.ref. 142a page 38.

[206] Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2012**, *14*, 2726–2729.

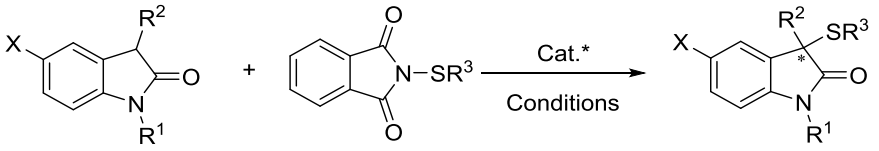
[207] Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2012**, *18*, 11531–11535.

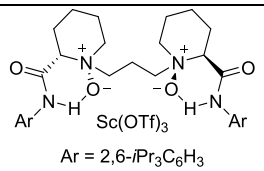
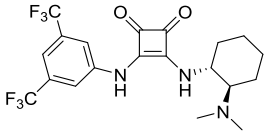
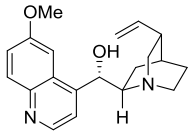
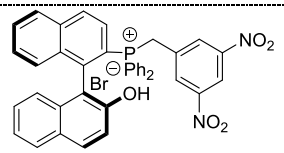
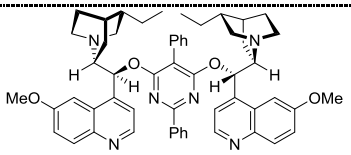
[208] Li, X.; Liu, C.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2012**, *14*, 4374–4377.

[209] Shirakawa et al. see ref. 86d page 23.

[210] a) Rueping, M.; Liu, X.; Bootwicha, T.; Pluta, R.; Merkens, C. *Chem. Commun.* **2014**, *50*, 2508–2511. For an example with Ag species as SCF_3 source and the same catalyst, see: b) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett.* **2014**, *16*, 2192–2195.

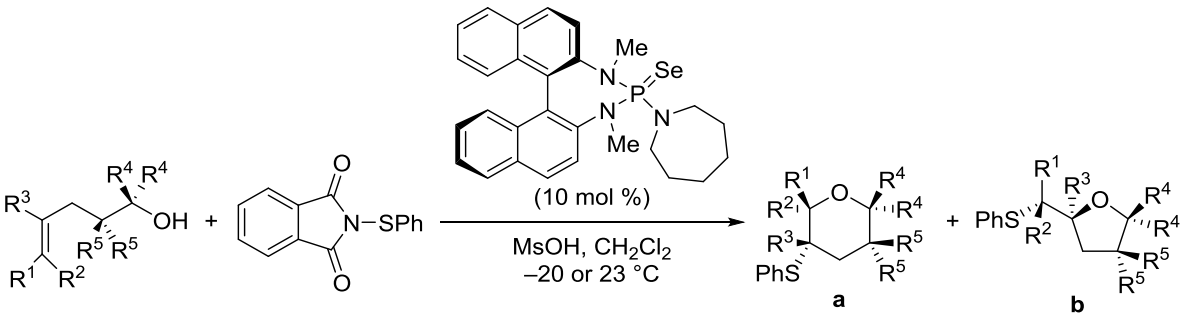
Table 18. α-Sulfenylation of oxindoles with *N*-thio phthalimides.



	R^1	R^2	R^3	Cat.*	Conditions	Results	Ref.
1	H	Alkyl, Aryl	Ph	 Ar = 2,6-*i*Pr$_3$C$_6$H$_3$ (5 mol %)	4Å MS CH_2Cl_2 35 °C	82–98% 87–99% *ee* (*S*)	206
2	Boc	Alkyl, Aryl	Aryl, Bn	 (5 mol %)	CH_3Cl r.t. or 50 °C	86–98% 85–96% *ee* (*S*)	207
3	Boc	Alkyl, Aryl	Aryl	 (10 mol %)	CH_2Cl_2, –78 °C	83–99% 72–99% *ee* (*S*)	208
4	Boc	*p*Tol	3-FC$_6$H$_4$	 (1 mol %)	H_2O/*o*-xylene 0 °C	93% 61–80% *ee* (*R*)	209
5	Boc	Aryl	CF_3	 (10 mol %)	THF 0 or –30 °C	50–96% 82–96% *ee* (*R*)	210a

Noteworthy is the strategy developed by Denmark and co-workers in 2011, when this group described the first oxysulfenylation of unactivated double bonds.[211] The reaction was catalyzed by a BINAM-based phosphoramide derivative, a Brønsted acid was employed as additive and *N*-thio phthalimide was used as electrophilic sulfur source, obtaining strongly substituent dependant results. Then, this strategy was adapted to perform carbosulfenylations.[212]

[211] Denmark et al. see ref. 203 page 66.
[212] a) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419–6422. b) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140–171.



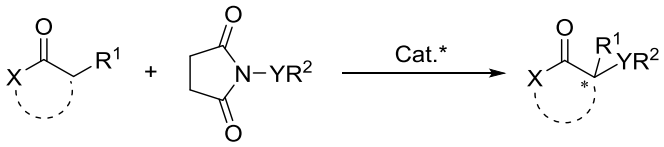
Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	a/b	*ee* (%)
1	Ph	H	H	H	H	80	49:1	82
2	Ph	H	H	H	Me	94	19:1	84
3	Ph	H	H	Me	H	84	13:1	84
4	H	H	Ph	H	H	85	1:99	24
5	H	H	H	H	H	72	1:50	66
6	Ph	H	Me	H	H	24	18:1	20
7	Ph	Me	H	H	H	82	17:1	40

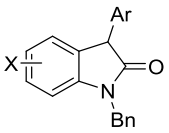
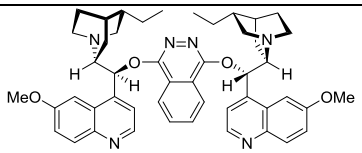
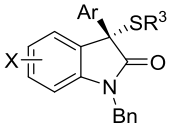
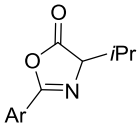
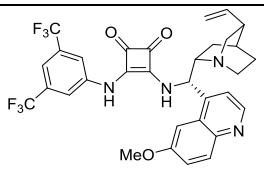
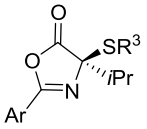
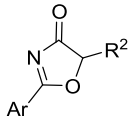
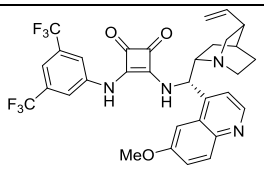
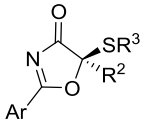
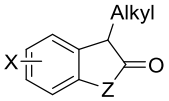
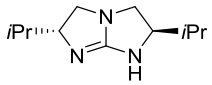
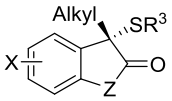
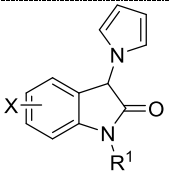
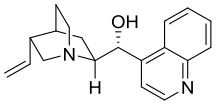
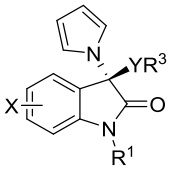
Scheme 47.

In 2012, *N*-(alkylthio) succinimide was employed for the first time for the sulfenylation of *N*-Bn 3-aryl oxindoles catalyzed by dimeric Brønsted bases, as part of Jiang's research work (Table 19, entry 1),[213] who also reported α-sulfenylation reactions of other heterocyclic pronucleophiles, such as azlactones (Table 19, entry 2),[214] 5*H*-oxazol-4-ones (Table 19, entry 3)[215] and both oxindoles and benzofuranones (Table 19, entry 4).[216] Very recently, Yuan and co-workers took advantage of the same sulphur source to sulfenylate *N*-alkyl 3-pyrrolyl oxindoles for the first time, reporting, additionaly, the first selenenylation of oxindoles (Table 19, entry 5).[217]

[213] Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670–4673.
[214] Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672–675.
[215] Xu et al. see ref. 99 page 26.
[216] Huang et al. see ref. 147f page 40.
[217] a) You, Y.; Wu, Z.-J.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 8470–8477. For another recent example of catalytic asymmetric sulfenylation of structurally diverse dithioketals employin *N*-thio succinimides, see: b) Liao, K.; Zhou, F.; Yu, J.-S.; Gao, W.-M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255–16258.

Table 19. α-Sulfenylation of heterocycles with *N*-heteroatom succinimides.



	Nu	YR^2	Cat.*	Product	Results	Ref.
1		SAryl SAlkyl	 (5–10 mol %)		68–98% 85–95% *ee*	213
2		SAlkyl SAryl	 (5 mol %)		43–94% 40–93% *ee*	214
3		SAlkyl SAryl	 (10 mol %)		51–97% 64–94% *ee*	215
4	 Z = O, NMe	SAlkyl	 (10–20 mol %)	 Z = O, NMe	65–99% 86–98% *ee*	216
5		SAryl SePh	 (10 mol %)		72–98% 50–99% *ee*	217

Taking into account the information mentioned during this section, it is clear that electrophilic sulfenylation has been a much more explored strategy than any other for the catalytic asymmetric construction *C*-*S* bonds, although this strategy commonly requires pronucleophiles with relatively acidic carbons.

2.1.2. **Construction of tertiary thiols through *C-C* bond formation**

The asymmetric construction of *C-C* bonds employing sulfur-containing substrates is a much less explored strategy to build tertiary thiol derivatives. To the best of our knowledge, there are no examples of this type of reactions using *S*-containing electrophiles (Figure 23a),[218] which limits this tactic to reactions carried out with *S*-bearing pronucleophiles and appropriate electrophiles (Figure 23b). Pioneering examples based on the utilization of enantiopure starting materials, and more recent examples in the field of asymmetric catalysis, will be discussed in this section.

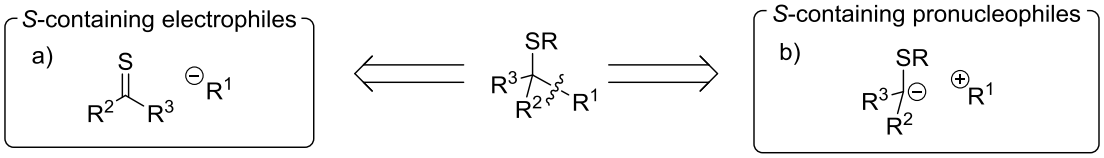


Figure 23.

2.1.2.1. **Stoichiometric asymmetric *C-C* bond formation**

The first asymmetric synthesis of a tertiary thiol using this approach came from the hand of Kellogg and co-workers in 1987,[219] applying the self-reproduction of chirality developed by Seebach in 1984 (Scheme 48).[220] The strategy consisted on reacting an enantiopure α-mercapto acid with pivalaldehyde to obtain a *cis*/*trans* mixture of 1,3-oxathiolan-4-ones. After separation, the major diastereomer was employed to form an enolate, which then reacted with different electrophiles. Stereocontrol was given by the *tert*-butyl group. Different electrophiles led to various reaction types, such as alkylation, Michael addition and aldol reaction. Very good to excellent yields and diastereoselectivity was achieved in alkylations and Michael reactions, while aldol reaction showed moderate yields and very poor diastereoselectivity when aldehydes were employed. Acetone, however, rendered excellent diastereoselectivity. Acidic hydrolysis of the adducts produced the desired enantioenriched tertiary thiols. The synthesis of thioactomycin, starting from (2*S*)-thiolactic acid, illustrates the utility of this methodology.[221]

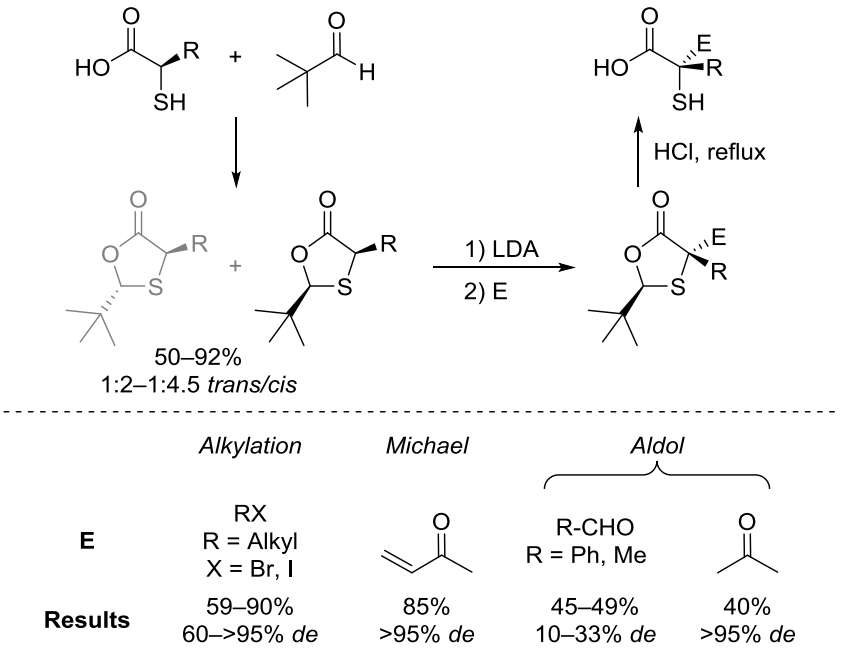
---

[218] Thioaldehydes and many thioketones are very reactive towards dimer, trimer or oligomer formation; often need to be generated *in situ*. For the asymmetric organocatalytic thio-Diels-Alder reactions via trienamine catalysis, see: a) Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200–5207. For the Cu-catalyzed thio-Diels-Alder reaction between dithioesters and 2,3-dimethyl-1,3-butadiene, see: b) Dentel, H.; Chataigner, I.; Le Cavelier, F.; Gulea, M. *Tetrahedron Lett.* **2010**, *51*, 6014–6017.

[219] Strijtveen, B.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 5039–5054.

[220] Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.

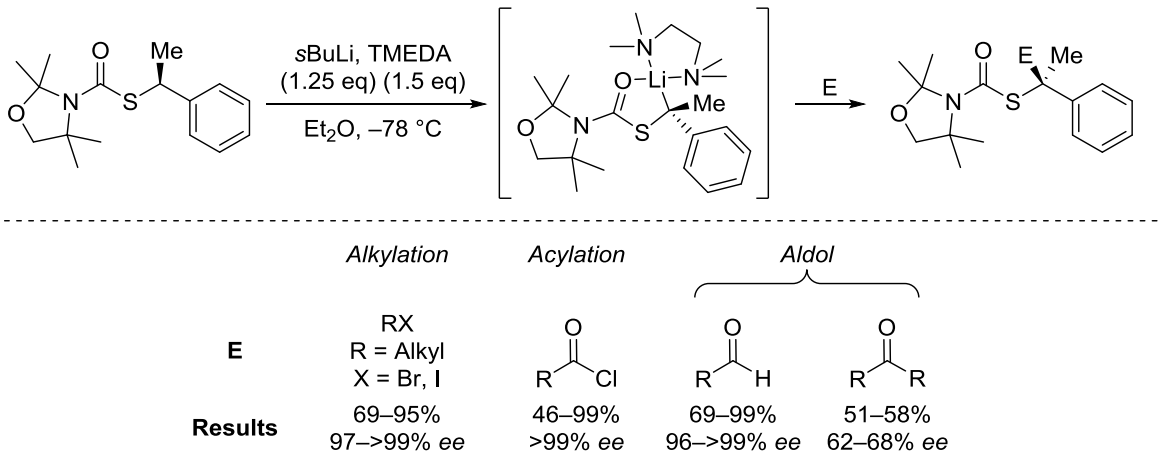
[221] McFadden, J. M.; Frehywot, G. L.; Townsend, C. A. *Org. Lett.* **2002**, *4*, 3859–3862.



Scheme 48.

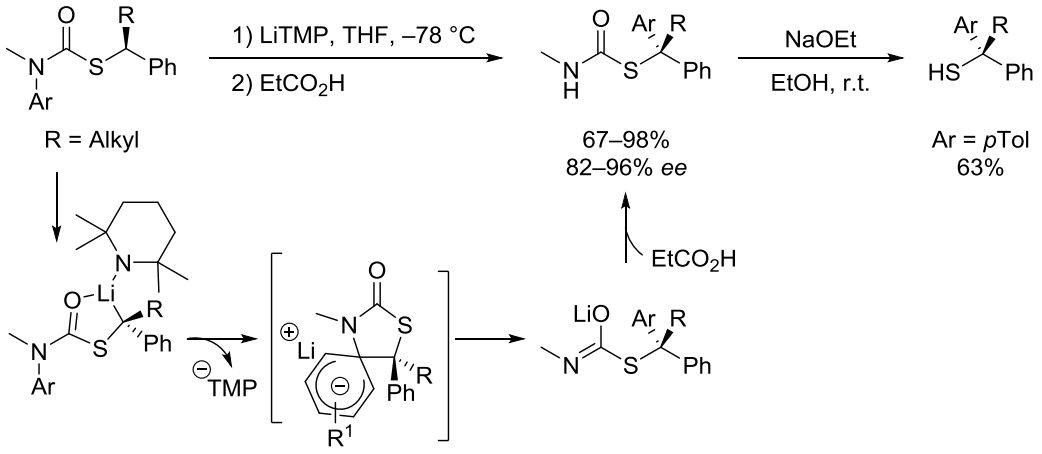
Enantioselective approaches to the asymmetric synthesis of tertiary thiol derivatives through *C-C* bond formation remained unexplored until 1997, when Hoppe and coworkers described several reactions using enantiopure benzylic thiocarbamates as substrates.[222] Electrophilic substitution occurred through a configurationally stable lithiated intermediate, affording the corresponding adducts in high yields and stereoselectivity, except for the ketones (Scheme 49).

[222] a) Hoppe, D.; Kaiser, B.; Stratmann, O.; Fröhlich, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 2784–2786. For an extesion of the scope, see: b) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D.; Frohlich, R.; Meyer, O.; Hoppe, D. *Chem. Eur. J.* **2001**, *7*, 423–435. For the extension of the methodology to cyclohexenyl thiocarbamates, see: b) Marr, F.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **1999**, *1*, 2081–2083. c) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217–4220. d) Marr, F.; Fröhlich, R.; Wibbeling, B.; Diedrich, C.; Hoppe, D. *Eur. J. Org. Chem.* **2002**, 2970–2988. For the application of this alkylation methodology: For the synthesis of α-quaternary carboxylic acids and α-quaternary primary alcohols, see: e) Arpin, A.; Manthorpe, J. M.; Gleason, J. L. *Org. Lett.* **2006**, *8*, 1359–1362. For the synthesis of β-amino acids and β-amino alcohols, see: f) Tiong, E. A.; Gleason, J. L. *Org. Lett.* **2009**, *11*, 1725–1728.



Scheme 49.

A particular aryl rearrangement of lithiated thiocarbamates was reported by Clayden's research group in 2011, as an efficient protocol to access tertiary thiols.[223] The intramolecular migration of the *N*-aryl moiety proceeded with retention of configuration, which enabled the access to enantioenriched tertiary thiols by treatment of the obtained adducts with sodium ethoxide, under mild conditions (Scheme 50).



Scheme 50.

2.1.2.2. **Catalytic asymmetric *C-C* bond formation**

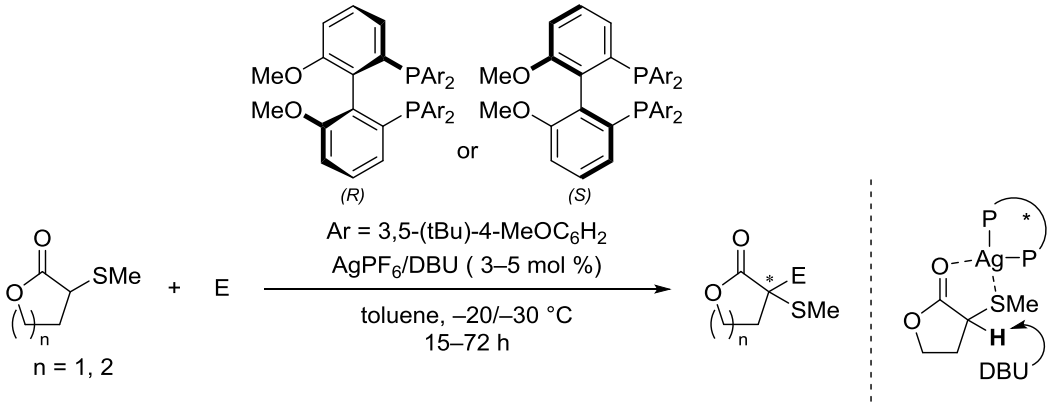
The employment of catalyst for the asymmetric formation of tertiary thiols through the formation of *C-C* bonds is a relatively new strategy. In this section the nature of the pronucleophiles employed will be the element of choice to classify and discuss the examples in literature.

[223] MacLellan, P.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3395.

2.1.2.2.1. Pronucleophiles bearing a sulfur substituent

The first example of catalytic asymmetric tertiary thiol derivative formation using a sulfur-bearing pronucleophile was developed by Shibasaki and co-workers in 2012. α-Sulfanyl lactones were chosen to perform aldol and Mannich type reactions through Lewis acid catalysis, employing a biphep-type ligand and a Brønsted base. Their first approach consisted on the addition of sulfanyl lactones to aldehydes, which occurred with moderate to excellent yield, and excellent stereocontrol (Table 20, entry 1).[224] The success of the methodology was explained by the authors as a result of a cooperative catalytic system between silver and the sulfanyl moiety, which enabled an easier deprotonation of the lactone with DBU, even in presence of highly enolizable aldehydes. A posterior attempt of addition to *N*-Boc-aldimines proceeded with similar results, employing the same substrates and catalytic system (Table 20, entry 2).[225]

Table 20.



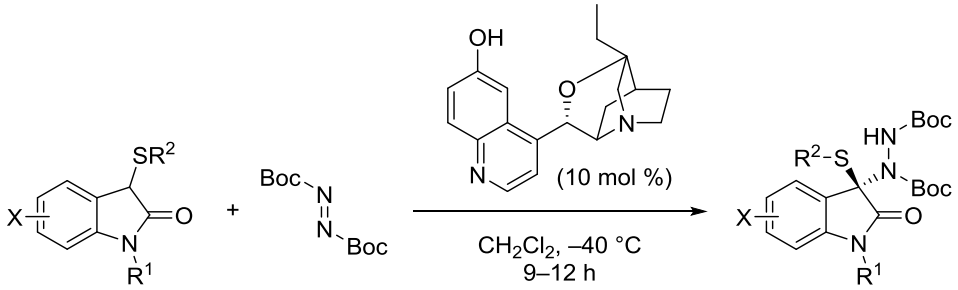
Entry	E	Ligand	Product	Results	Ref.
1	R = Alkyl	(*R*)		50–93% 90:10–95:5 *dr* 96–99% *ee*	224
2	R = Aryl, alkyl	(*S*)		42–94% 86:14–95:5 *dr* 82–99% *ee*	225

Besides this lactone based pronucleophiles, there are some particular examples of 3-thiooxindoles involved in organocatalyzed reactions in the same role. Zhou's research group described the first example of this strategy in 2013,[226] based on the deprotonation

[224] Takechi, S.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4218–4222.
[225] Takechi, S.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 2632–2635.
[226] a) Zhou, F.; Zeng, X.-P.; Wang, C.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 2022–2024. For a recent example of the sulfenylation of this structures, see: ref. 217b page 9

of 3-thiooxindoles and subsequent reaction with electrophilic di-*tert*-butyl azodicarboxylate employing a chiral Brønsted base. Good to excellent yields and stereocontrol were achieved in the formation of 3,3-disubstituted oxindoles featuring two heteroatoms in C3 when aromatic substituents were placed in the sulfur atom (Table 21).

Table 21.

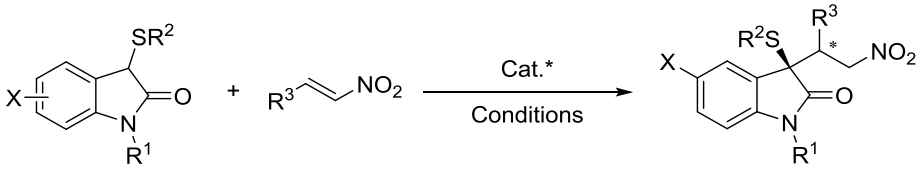


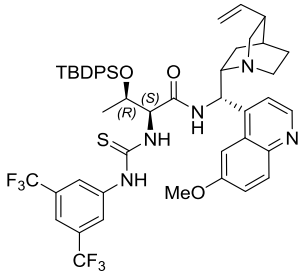
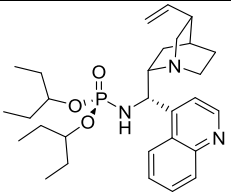
Entry	X	R^1	R^2	Yield (%)	*ee* (%)
1	H, Hal, Me, Et, MeO	H	2-Naphthyl	68–98	83–94
2	H	Me	2-Naphthyl	96	82
3	H	Bn	2-Naphthyl	92	79
4	H	H	Ph	97	90
5	H	H	Bn	88	56
6	H	H	Allyl	82	47

However, only two examples have been reported employing 3-thiooxindoles as pronucleophiles to form *C-C* bonds, both consisting on conjugate addition to nitroolefins. Both research groups reported the use of bifunctional *Cinchona* alkaloid-based organocatalysts with remarkably low loadings. While Lu chose a thiourea as H bond donor, affording very good to excellent yield and stereocontrol (Table 22, entry 1),[227] Zhou and coworkers leant towards a phosphoramide as an activating moiety, which also rendered excellent enantioselectivity but more modest diastereoselectivity and yields (Table 22, entry 2).[228] In both cases, beneficial effect of the presence of molecular sieves for the stereocontrol was reported.

[227] Dou, X.; Zhou, B.; Yao, W.; Zhong, F.; Jiang, C.; Lu, Y. *Org. Lett.* **2013**, *15*, 4920–4923.
[228] Gao, W.-M.; Yu, J.-S.; Zhao, Y.-L.; Liu, Y.-L.; Zhou, F.; Wu, H.-H.; Zhou, J. *Chem. Commun.* **2014**, *50*, 15179–15182.

Table 22.



Entry	Cat.*	Conditions	Results	Ref.
1	 (1 mol %)	4Å MS toluene, r.t.	81–99% 85:15–95:5 *dr* 79–99% *ee* (*R*)	227
2	 (1–5 mol %)	5Å MS Et_2O, –20 °C	80–99% 80:20–89:11 *dr* 91–98% *ee* (*S*)	228

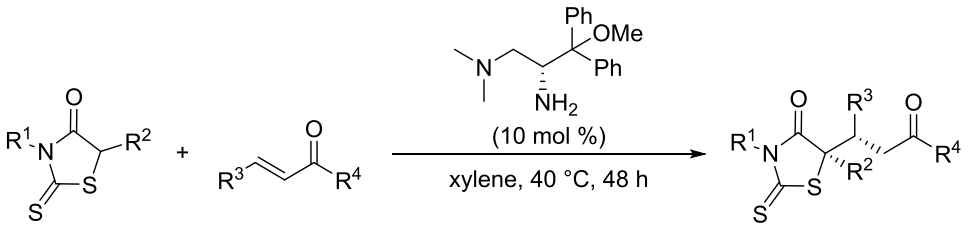
2.1.2.2.2. Sulfur-containing heterocyclic pronucleophiles

The use of rhodanines, heterocycles mentioned in the introductory part of this work (page 37), is a complementary strategy to obtain tertiary thiols.

Recently, Ye and co-workers introduced the first organocatalyzed Michael addition of rhodanines to β-substituted enones (Table 23).[229] The catalyst of choice was a bulky chiral diamine, which consisted of a primary amine (for iminium ion activation of the electrophile) and a Brønsted base (to deprotonate the pronucleophile). Due to the low reactivity of the electrophile the reaction should be heated and reaction times elongated, but diastereo- and enantioselectivity remained excellent with conjugated enones (entries 1–7). Branched substituent in C-5 (entry 8) and β-aliphatic enones (entries 9–10) rendered lower yields and enantioselectivities, although they kept moderately good.

[229] a) Yu, F.; Hu, H.; Gu, X.; Ye, J. *Org. Lett.* **2012**, *14*, 2038–2041. For the enantioselective synthesis of spirorhodanines through aminocatalyzed Michael/Michael/aldol cascade addition of 5-unsubstituted rhodanines to enals, see: b) Géant, P.-Y.; Urban, M.; Remeš, M.; Císařová, I.; Veselý, J. *Eur. J. Org. Chem.* **2013**, *2013*, 7979–7988.

Table 23. Representative results of the Michael reaction of rhodanines with enones by Ye et al.[229a]

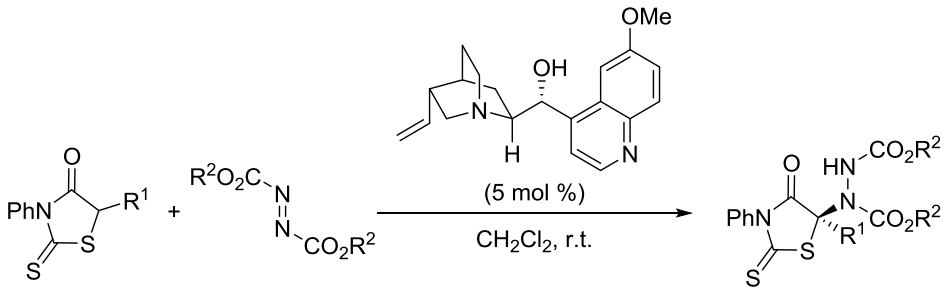


Entry	R^1	R^2	R^3	R^4	Yield (%)	*dr*	*ee* (%)
1	Ph	Me	Ph	Me	95	99:1	96
2	Ph	Me	(*E*)-PhCH=CH	Me	83	93:7	96
3	*i*Pr	Me	Ph	Me	97	99:1	90
4	Bn	Me	Ph	Me	94	98:2	95
5	4-$MeOC_6H_4$	Me	Ph	Me	98	99:1	96
6	Ph	Me	Ph	*i*Pr	82	99:1	95
7	Ph	Et	Ph	Me	91	98:2	97
8	Ph	*i*Pr	Ph	Me	68	93:7	71
9	Ph	Me	Me	Me	64	95:5	80
10	Ph	Me	$PhCH_2CH_2$	Me	60	97:3	87

Reactivity of 5-aryl rhodanines (R^2 = Ar in Table 23) was not studied in the previous case, but it was in an organocatalytic enantioselective α-amination of 5-substituted rhodanines with diethyl azodicarboxylate (DEAD) developed by Wang in 2014 (Table 24).[230] The quinine-catalyzed reaction proceeded with excellent yield in every case, and the increase in time that can be noticed with hindered and less activated substrates (entries 4–7) is more probably due to the bulkiness of the groups rather than to any electronic effect, although this may be the reason for the loss of enantiocontrol when R^2 = Ph (entry 7). Regarding electrophile reactivity, while diisopropyl azodicarboxylate (DIAD) afforded a product with marginally lowered enantioselectivity (entry 8), a dramatic decrease in enantiomeric excess was observed when di-*tert*-butyl azodicarboxylate (DBAD) was used (entry 9).

[230] Zhang, H.; Wang, B.; Cui, L.; Li, Y.; Qu, J.; Song, Y. *Org. Biomol. Chem.* **2014**, *12*, 9097–9100.

Table 24. Representative results of α-amination of rhodanines by Wang et al.[230]



Entry	R^1	R^2	Time (h)	Yield (%)	*ee* (%)
1	Me	Et	9	99	95
2	Allyl	Et	9	90	94
3	Bn	Et	10	98	94
4	*n*Bu	Et	23	98	94
5	Et	Et	25	95	96
6	Ph	Et	33	91	81
7	*i*Pr	Et	55	99	91[a]
8	Me	*i*Pr	-	99	93
9	Me	kBu	-	99	47

[a]Performed at –60 °C for 37 h, then –40 °C for 18 h

To date, as far as we know, other electrophiles have not been employed in reactions with rhodanines.

Several examples of asymmetric synthesis of tertiary thiols or derivatives through *C-C* bond formation have been disclosed in this section. Different reactions have been applied for that, but, as it is noticeable, this strategy has been scarcely explored, and no general protocol has been reported. Additionally, the obtained adducts are in most cases thioethers, whose deprotection to free thiol cannot be neglected. Therefore, the development of new strategies for this purpose is highly sought after.

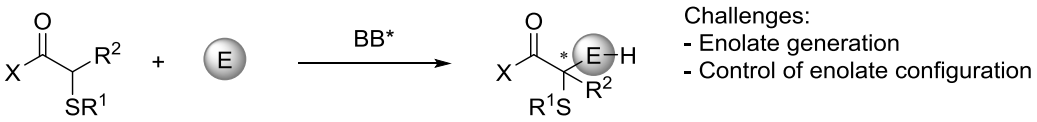
2.2. **Michael addition of 5*H*-thiazol-4-ones to nitroolefins**

2.2.1. **Working hypothesis and synthetic plan**

As mentioned above, there are few methodologies for the catalytic enantioselective synthesis of tertiary thiol derivatives, probably due to the inherent difficulty associated to the asymmetric construction of quaternary stereocentres.[231] Connected to the previous efforts of our research group directed towards the stereoselective synthesis of organosulfur compounds, such as β,β-disubstituted β-mercaptocarboxylic acids[232] and thiiranes,[233] our attention focused on the catalytic asymmetric synthesis of α,α-disubstituted α-mecaptocarboxylic acids.

Taking into account the previous strategies employed for the synthesis of tertiary thiols, the possible disconnections to access these compounds involve a *C-S* or a *C-C* bond formation. Within the possibilities concerning a *C-S* bond construction, nucleophilic sulfenylation is readily discounted, since it is limited to enantiopure electrophilic substrates. Another alternative would consist in a sulfa-Michael addition to a β,β-disubstituted Michael acceptor, which present several drawbacks, due to their low reactivity, low π-facial stereoselectivity and equilibration of stereoisomers through an addition/elimination mechanism, as has been mentioned in previous sections. Finally, a third alternative regarding this strategy would be electrophilic sulfenylation, but this strategy has already been much explored, and the electrophilic sulfur reagents present a low atom-economy issue.

On the other hand, concerning the asymmetric formation of *C-C* bonds, only the employment of sulfur-containing pronucleophiles to perform additions on suitable electrophiles seems to be viable, since the reaction of nucleophiles with thioketones has been already dismissed in the introduction of this chapter. With this in mind, our investigation was concentrated on the tactic depicted in Scheme 51, an organocatalytic protocol for the reaction of sulfur-containing pronucleophiles with appropriate electrophiles using a chiral Brønsted base as catalyst.

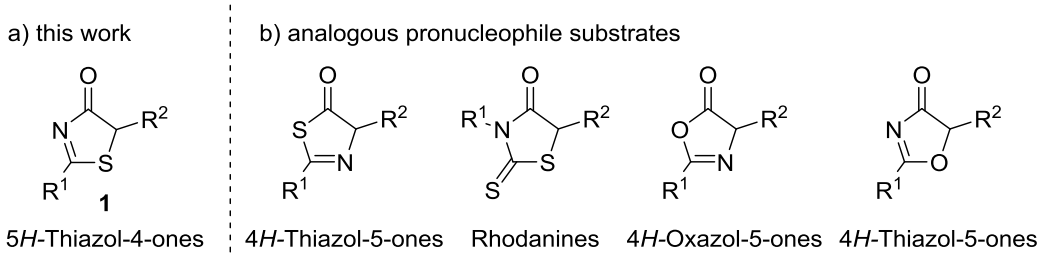


Scheme 51. Working hypothesis for stereoselective synthesis of α,α-disubstituted α-thiofunctionalized carboxylic acid derivatives.

[231] see ref. 60 page 16
[232] ref. 193 and 194a page 3.
[233] ref. 194b page 3.

At this point, there were three main challenges. First, the selection of the appropriate substrates to take part in the reaction; second, to find the adequate conditions to form the enolate; and third, the control over it, in order to achieve configurational uniformity in the produced adducts.

A comprehensive literature search led us to select 5*H*-thiazol-4-ones **1** (Scheme 52a), a sulfur-containing heterocycle that had been never used as a pronucleophile, unlike the closely related 4*H*-thiazol-5-ones and rhodanines, and also structurally related 5*H*-oxazol-4-ones and 4*H*-oxazol-5-ones (azlactones) (Scheme 52b).



Scheme 52.

An interesting aspect of this template was reported in 2011 by Weiß, Beckert and Fabian's group,[234] who through a ^{1}H NMR study demonstrated that in solution these compounds exist in equilibrium between two tautomeric forms (Figure 24).

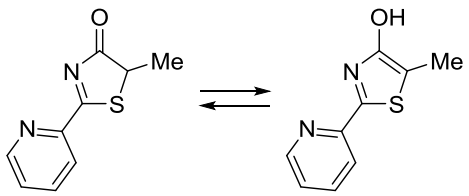
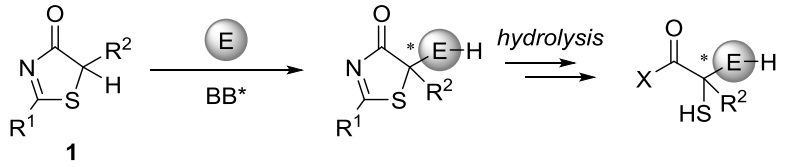


Figure 24. Tautomeric forms of 5*H*-thiazol-4-ones in solution.

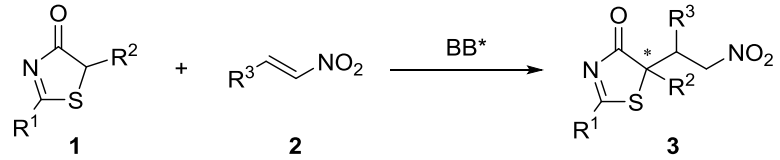
This particular property, along with the cyclic nature of these compounds, would fix the geometry of the generated enolate through aromatization, facilitating the addition of these heterocycles to different electrophiles in a stereocontroled manner (Scheme 53). Hydrolysis of the resulting adduct would additionally provide access to α,α-disubstituted α-mercaptocarboxylic acids with a free thiol moiety, unlike most of the known protocols, which only gain access to thioether, requiring an additional and not so trivial step.

[234] Täuscher, E.; Weiß, D.; Beckert, R.; Fabian, J.; Assumpção, A.; Görls, H. *Tetrahedron Lett.* **2011**, *52*, 2292–2294.



Scheme 53. General reaction of 5*H*-thiazol-4-ones with electrophiles and hydrolysis of the corrensponding adduct.

On this basis, 5*H*-thiazol-4-ones were chosen as pronucleophiles, and in a first instance nitroolefins were chosen as electrophiles.[235] This Michael acceptor added a diastereoselectivity issue to the previous challenges, due to the formation of two contiguous stereocentres during the reaction (Scheme 54).



Scheme 54. Proposed reaction for the first investigation.

Another feature is that the substituent R^1 could be modified in order to help stereocontrol.

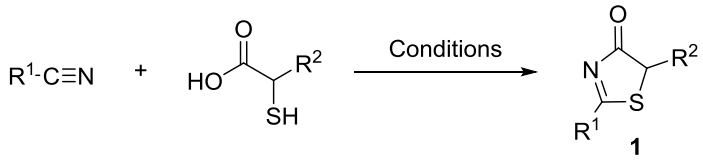
2.2.2. **Results and discussion**

2.2.2.1. **Synthesis of 5*H*-thiazol-4-ones**

First, we proceeded to the synthesis of the substrates that were going to be employed in the reaction. The selected strategy consisted in the cyclization of α-monosubstituted α-mercaptocarboxylic acids with the corresponding aromatic nitrile (Scheme 55). The experimental procedure for this task was slightly different depending on the starting materials.[236]

[235] For reviews on conjugate additions to nitroolefins, see: a) Aitken, L.; Arezki, N.; Dell'Isola, A.; Cobb, A. *Synthesis* **2013**, *45*, 2627–2648. b) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601. c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.

[236] Not every α-mercaptocarboxylic acid was commercially available, but they could be readily prepared from the corresponding α-bromocarboxylic acid trough a nucleophilic S_N2 sulfenylation with potassium thioacetate. For more information see Experimental Section.



R^2 = Me; **Procedure A:** pyridine (20 mol %), 120 °C, 4 h
R^2 = Et, *n*Hex, Bn; **Procedure B:** Et_3N (5 equiv.), EtOH, reflux, 4–16 h

Scheme 55. Synthesis of 5*H*-thiazol-4-ones.

Thus, this synthetic strategy allowed us rapid access to a variety of 5*H*-thiazol-4-ones, making the optimization of the reaction faster and more efficient.

Once with the substrates of the initially proposed reaction in hand, and regarding the strong catalyst-substrate dependence of Brønsted base-catalyzed direct asymmetric *C-C* bond forming reactions, catalyst design was thought to be the best strategy to address our goal.

2.2.2.2. **Catalyst design**

The 3,5-bis(trifluoromethyl)phenyl group present in most of (thio)urea-based bifunctional Brønsted bases, is a key structural motif that has commonly been using for hydrogen-bond catalysis since it was first introduced by Schreiner and Wittkopp in 2002.[237] Later, Zhong[238] and Schreiner,[239] as a result of an exhaustive study based on NMR- and IR- spectroscopy, mass-spectrometry and DFT calculations, suggested that the success of this family of catalysts may be a consequence of the participation of three contiguous *H*-bond donors. Thus, both *N-H* bonds of the (thio)urea moiety and the aromatic ortho *C-H* bond of the aforementioned aryl group, would participate in the activation of the electrophile (Figure 25).[240]

[237] a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. c) M. Kotice & P. R. Schreiner, *Hydrogen Bonding in Organic Synthesis* (P. M. Pihko ed., Wiley-VCH) 2009. pages 141–351.
[238] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682–2685.
[239] Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919–5927.
[240] For a review on recent advances in asymmetric organocatalysis mediated by multiple hydrogen-bonding donors, see: Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

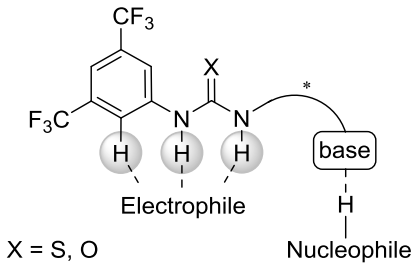


Figure 25. Previous known designs

On the other hand, over the last years several significant synthetic transformations have been performed thanks to the efficacy of synthetic peptides for the fine-tuning of reactivity and selectivity.[241] In this context, ureidopeptides (Figure 26), which are peptidomimetics where an amide bond has been replaced by a urea moiety, have been fully recognized for their ability to develop hydrogen bonds.[242] On this basis, our research group considered that the replacement of the α-amino acid *C*-terminus of the ureidopeptide by a chiral Brønsted base should provide a new family of bifunctional catalysts, with several modulable sites for the fine-tuning of the catalyst's properties. Thus, the Brønsted base, the stereodirecting group of the aminal moiety, and the protecting group on *N*-terminus would be prompt to modification (Figure 26). The new N,N'-diacyl aminal unit and the urea moiety would provide three contiguous hydrogen bond donors in close proximity to a stereodirecting group, unlike the 3,5-bis(trifluoromethyl)phenyl group-bearing catalysts, increasing the number of coordination patterns with the substrates and controlling their spatial conformation.

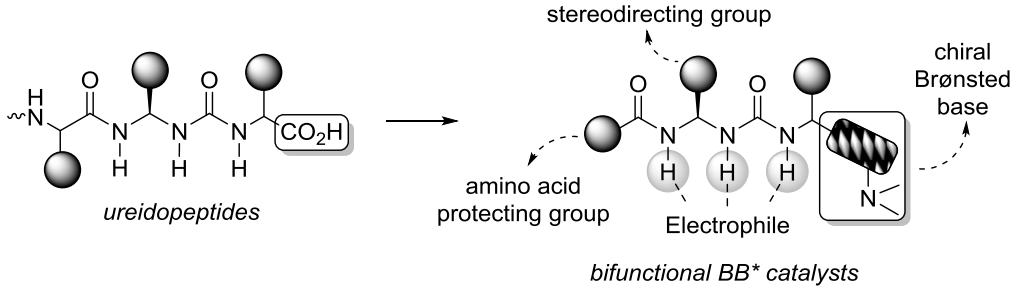
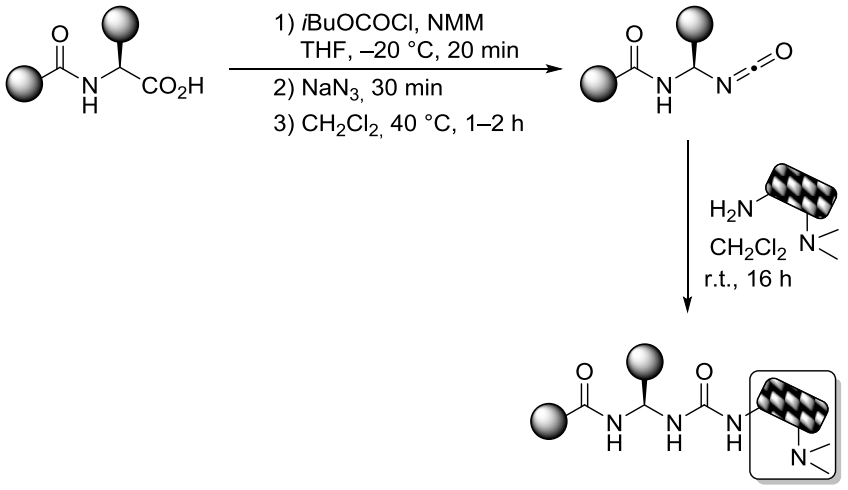


Figure 26. New design for ureidopeptide-based Brønsted bases.

[241] For asymmetric catalysis mediated by peptides, see: a) Wennemers see ref 34 page 10. b) Davie, E. a C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. c) Fanelli Roberto & Piarulli Umberto, *Oligopeptides as Modular Organocatalytic Scaffolds* (P. I. Dalko ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2013.

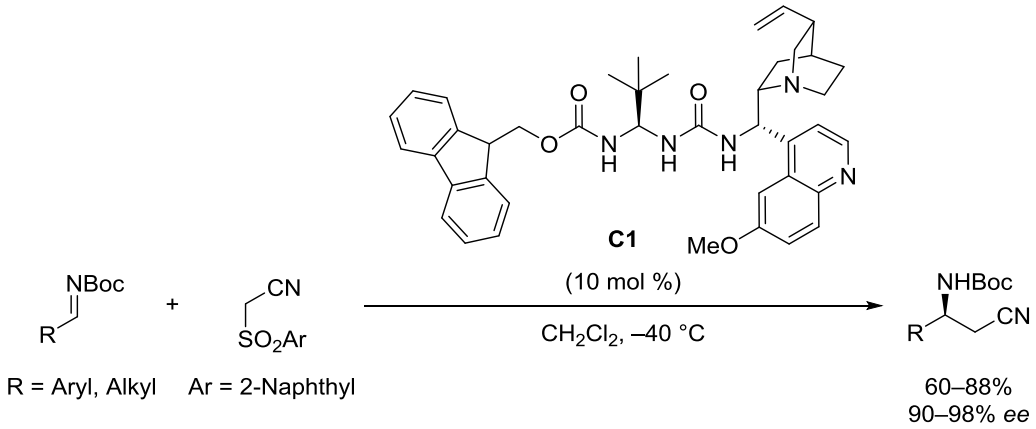
[242] a) Sureshbabu, V. V; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705. b) Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222. c) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1893–1895. d) Semetey, V.; Hemmerlin, C.; Didierjean, C.; Schaffner, A.-P.; Giner, A. G.; Aubry, A.; Briand, J.-P.; Marraud, M.; Guichard, G. *Org. Lett.* **2001**, *3*, 3843–3846.

So, as part of a more general research project, our group focused on this new catalyst design with the aim of checking the efficiency of these new catalysts in different transformations. The proposed general synthetic sequence for these catalysts is outlined in Scheme 56, and involves carbamate protection of the amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base.



Scheme 56. Ureidopeptide-based bifunctional Brønsted base catalyst preparation.

The first synthesis and subsequent optimization of these catalysts was developed by Diosdado from our research group in another context,[243] who found that catalysts bearing the *tert*-butyl moiety were the most efficient (Scheme 57).

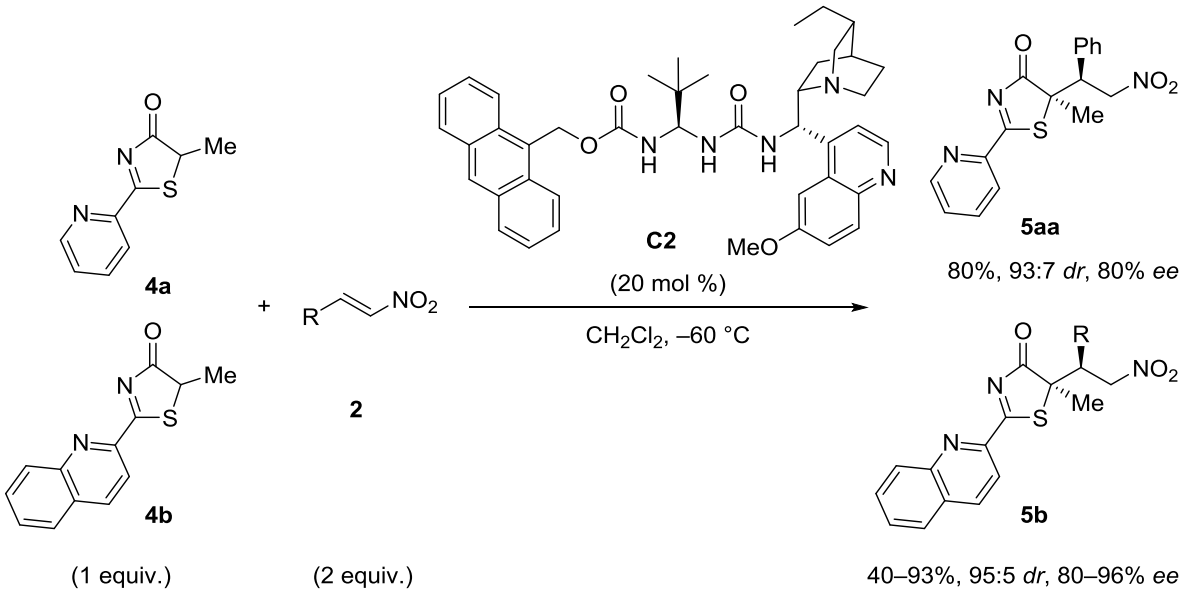


Scheme 57.

Olaizola during her PhD work,[244] synthesized several catalysts of this family and tested them in the reaction of 5-methyl-2-pyridyl thiazol-4(5*H*)-one **4a** and 5-methyl-2-

[243] Saioa Diosdado, PhD. Dissertation, UPV/EHU, 2014. http://www.ehu.eus/es/web/gicas/tesiak
[244] Yurre Olaizola, PhD. Dissertation, UPV/EHU, 2015. http://www.ehu.eus/es/web/gicas/tesiak

quinolinyl thiazol-4(5*H*)-one **4b** and nitroolefins. This study revealed that the latter produced the best results and that increasing the aromaticity of the protecting group of the aminal moiety induced a greater stereocontrol over the reaction. Thus, she found, as illustrated in Scheme 58, that the addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **4b** to nitroalkenes **2** (2 equiv.) in presence of catalyst **C2** (20 mol %) at –60 °C in dichloromethane provided product **5** with excellent results independently or the R substituent.



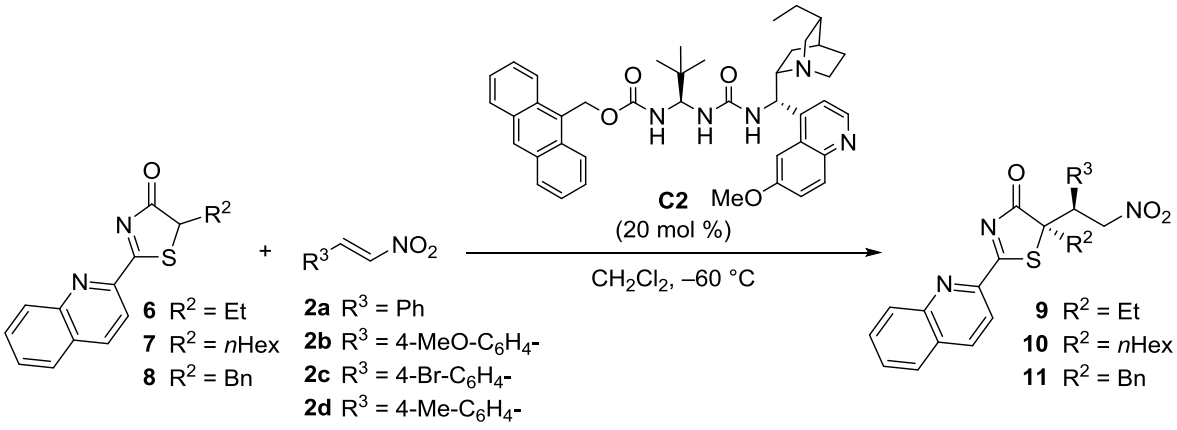
Scheme 58. Optimal conditions for the Michael addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **4** to nitroolefins **2**.

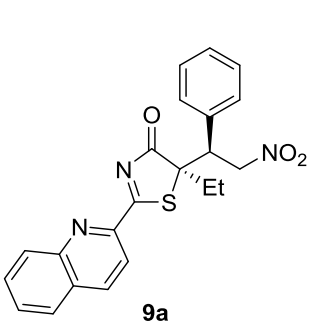
2.2.2.3. **Reaction scope**

Given the observations noted above, we then focused on the scope of the reaction with the aim of evaluating the generality of this asymmetric route respect to the thiazolone component.[245] In order to investigate the generality of the reaction regarding the substituent at C-5 of the thiazolone, thiazolones **6**–**8** were synthesized and tested (Table 25). Employing the same reaction conditions previously mentioned (i.e. 20 mol % of catalyst **C2** loading in dichloromethane at –60 °C), successful Michael addition of 5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **6** to nitroolefins was achieved. Furthermore, excellent diastereo- and stereoselectivities were obtained, probably due to the greater steric hindrance generated by the 5-alkyl group. However, these bulky substituents could have supposed an important drawback for the chemical reactivity of the thiazolones, but the excellent yields and stereocontrol rendered with larger groups dispelled all concerns.

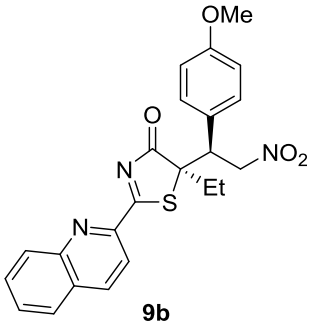
[245] a) Diosdado et al. see ref. 10 page 9. b) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Synfacts* **2013**, *9*, 1346–1346.

Table 25. Scope of 2-(quinolin-2-yl)thiazol-4(5*H*)-ones **6**–**8** for the conjugate addition to nitroolefins **2**.

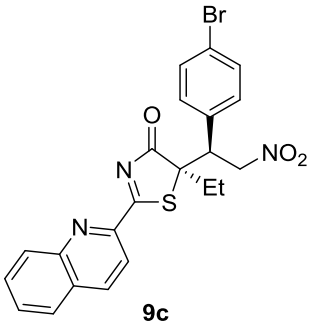




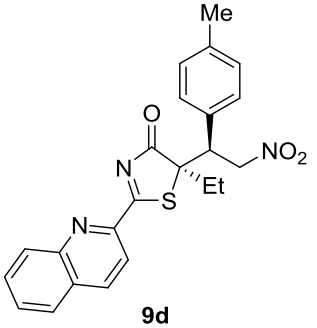
9a
95%, >95:5 *dr*, 97% *ee*



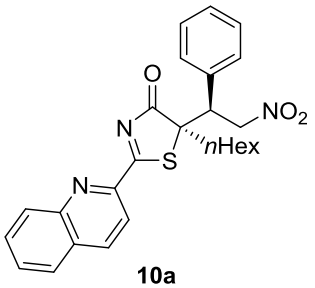
9b
95%, >95:5 *dr*, 97% *ee*



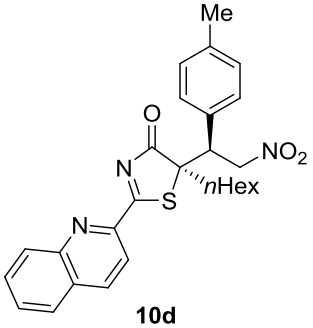
9c
81%, >95:5 *dr*, 97% *ee*



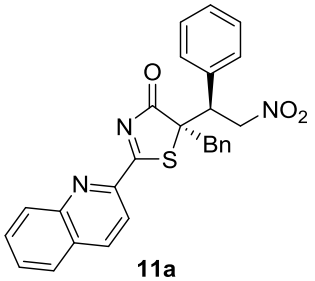
9d
87%, >95:5 *dr*, 91(94)% *ee*



10a
96%, >95:5 *dr*, 92% *ee*



10d
96%, >95:5 *dr*, 98% *ee*

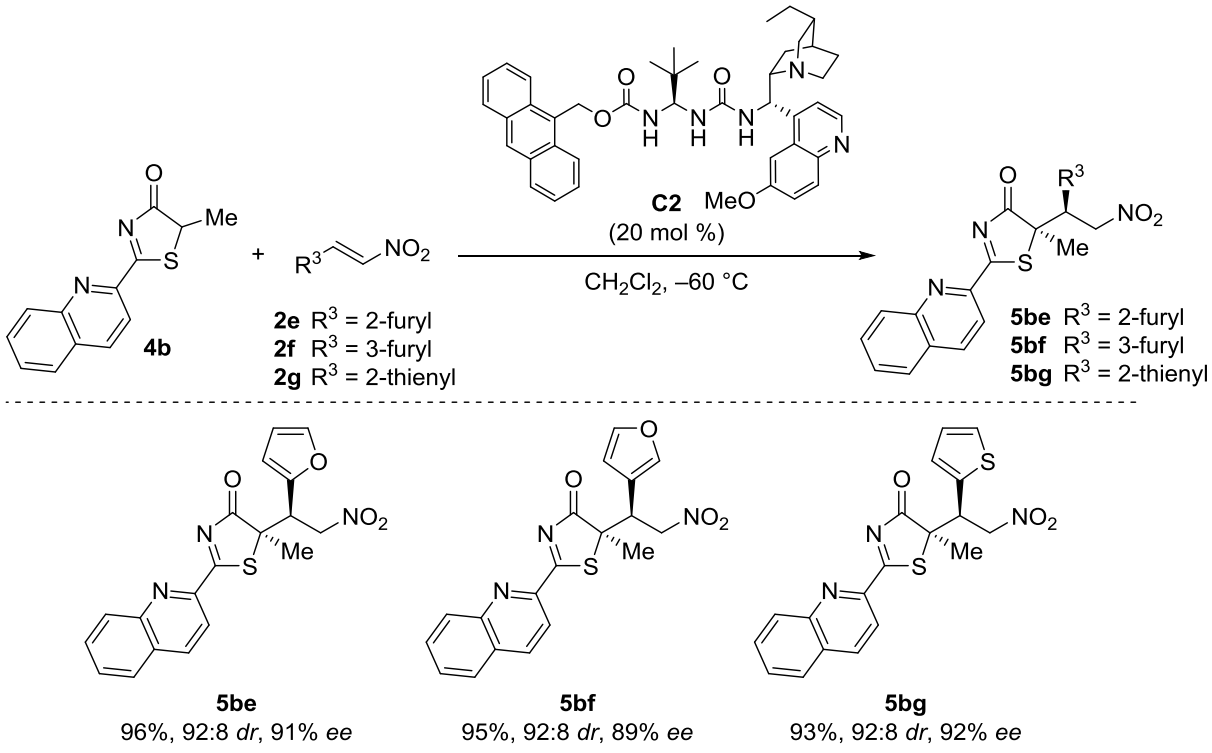


11a
90%, >95:5 *dr*, 92(99)% *ee*

[a] Reaction conditions: **6**–**8** (0.3 mmol), **2** (0.6 mmol, 2 equiv.), catalyst **C2** (20 mol %), –60 °C in CH_2Cl_2 (0.6 mL). Yields correspond to the isolated major isomer after column chromatography. *dr*'s determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. *ee*'s determined by HPLC analysis on a chiral stationary phase. Data within parentheses were obtained after crystallization from diethyl ether.

At this point, and to complete Olaizola's work with β-aromatic nitroolefins,[244] we proceeded to evaluate β-heteroaryl substituted nitroalkenes, in order to confirm the robustness of our protocol. Results obtained are gathered in Table 26. The reaction worked as fine as it did with regular all-carbon aromatic nitroolefins, rendering excellent yields in every case. Diastereomeric ratios remained above 90:10, and enantioselectivities also proved to be excellent, especially with 2-furyl and 2-thienyl moieties, whereas it lowered some points when the 3-furyl moiety was tested (89% *ee*).

Table 26. Scope of the Michael addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **4b** to heteroaromatic nitroolefins **2n**–**p**.



[a] Reaction conditions: **4b** (0.3 mmol), **2e**–**g** (0.6 mmol, 2 equiv.), catalyst **C2** (20 mol %), –60 °C in CH_2Cl_2 (0.6 mL). Yields correspond to the isolated major isomer after column chromatography. *dr*'s determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. *ee*'s determined by HPLC analysis on a chiral stationary phase.

An interesting aspect of this methodology to synthesize tertiary thiol derivatives is the general crystallinity of both starting substrates, thiazolones **4b** and **6**–**8** and most of nitroolefins, a property which is readily translated to the resulting products **5b** and **9**–**11**. This attractive characteristic provided the opportunity of crystallizing the adducts; thus, as mentioned before, a single crystallization from diethyl ether produced products with increased enantiomeric purity. Moreover, an unambiguous determination of the absolute configuration of the corresponding adducts was performed by a single-crystal X-ray analysis of **5bc** (Figure 27) and by assuming a uniform reaction mechanism.

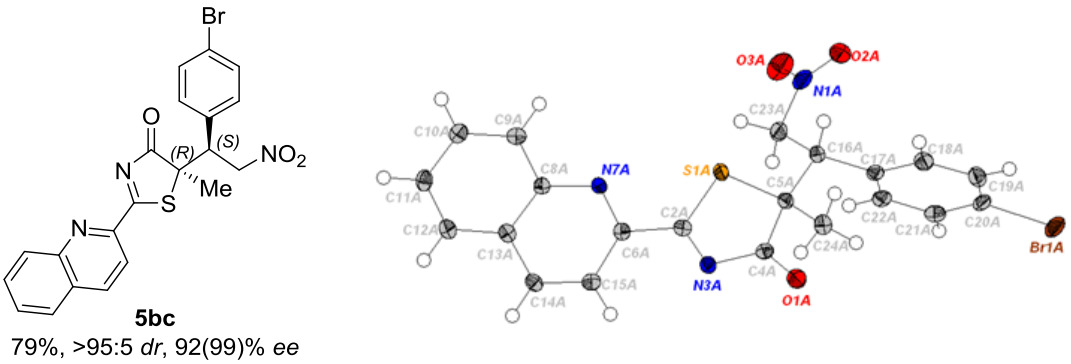
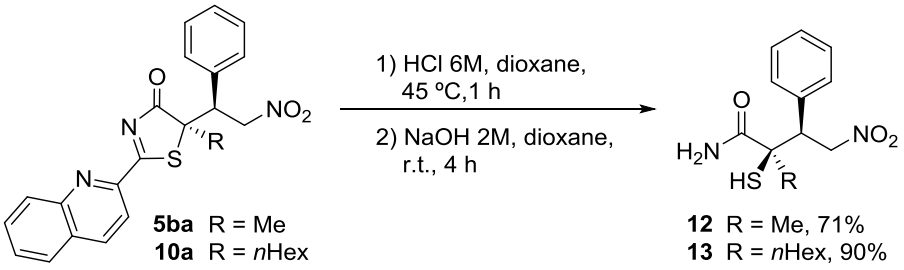


Figure 27. ORTEP diagram of compound **5c**.

2.2.2.4. **Elaboration of adducts**

One of the first objectives of this project was to develop a methodology to obtain free tertiary thiols stereoselectively. We were happy to find that adducts **5ba** and **10a** could be transformed into the corresponding α,α-disubstituted α-mercapto carboxylic acid derivatives **12** and **13**, by simple ring opening in acid medium, followed by saponification of the resulting thioester, both under mild conditions, illustrating thus the utility of our procedure (Scheme 59). As it has been shown in the introduction of this chapter, the majority of the methodologies for the preparation of organosulfur compounds generally afford aryl or alkyl thioethers. Interestingly, our approach provides a quick entry to mercapto compounds with the thiol group in its free form.

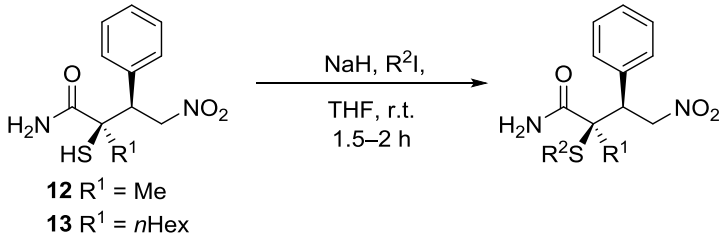


Scheme 59. Transformation of adduct **5a** and **10a** into α,α-disubstituted α-mercapto carboxylic acid derivatives **12** and **13**.

Next, we wondered whether these adducts could be *S*-alkylated without affecting the nitro group. Apart from steric constraints it is known that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[246] Satisfactorily, treating the adduct **12** with different halides in the presence of sodium hydride the corresponding *S*-alkylated products were produced in 75–93% yield and leaving untouched the nitro group (Table 27).

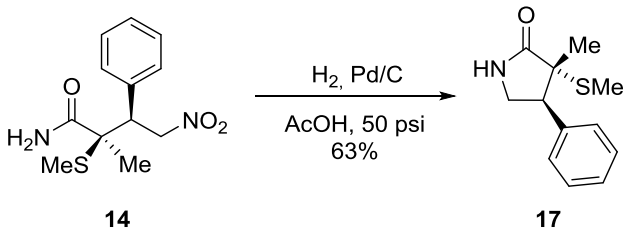
[246] Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612–615. and references therein.

Table 27. *S*-Alkylation of α,α-disubstituted α-mercapto carboxylic acid derivatives **12–13**.



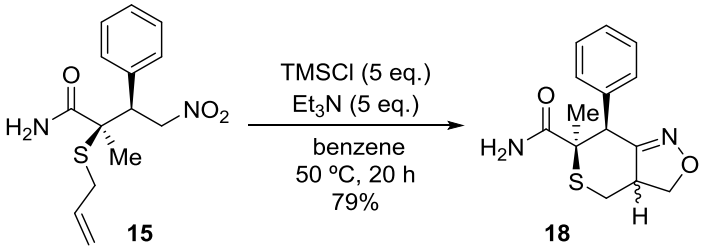
Entry	R^1	R^2	Product	Yield (%)
1	Me	Me	**14**	75
2	Me	Allyl	**15**	93
3	*n*Hex	Allyl	**16**	91

Starting from these thioether derivatives, different cyclic structures were readily available. On one hand, exposure to elemental hydrogen over palladium on charcoal under a 50 psi atmosphere enabled reduction of the nitro group of adduct **14** to the amino function, thus leading to γ-lactams (Scheme 60).



Scheme 60.

On the other hand, a 1,3-dipolar cycloaddition of the allylic adduct **15** through a intramolecular silyl nitronate-olefin cyclization (ISOC)[247] gave access to isoxazoline **18** (Scheme 61). Nevertheless, and despite the importance of these heterocycles, a 1.4:1 diastereomeric mixture was obtained.



Scheme 61.

[247] For a leading books on stereoselective intramolecular 1,3-dipolar cycloadditions, see: a) Hassner, A.; Namboothiri, I. N. N. *Top. Curr. Chem.* **2001**, *216*, 1–49. b) I. N. N. Namboothiri & N. Rastogi, *Synthesis of Heterocycles via Cycloadditions I* (A. Hassner ed., Springer Berlin Heidelberg) 2008. For a leading book on the utility of nitro group in organic synthesis, see: c) Noboru Ono, *The Nitro Group in Organic Synthesis* (H. Feuer ed., John Wiley & Sons, Inc.) 2001.

2.2.2.5. **Mechanistic proposal**

The mechanistic proposals regarding the interactions between the catalyst and the substrates in Michael additions of 1,3-dicarbonylic compounds to nitroolefins differ depending on the research group. Takemoto and co-workers proposed the mechanistic model A in 2005 (Figure 28),[248] based on ^{1}H NMR studies. Their model suggested that the malonate was coordinated to the protonated tertiary amine and that the nitroalkene was bind to the thiourea moiety through *NH*-bonds with its oxygens. In 2006, Pápai did an exhaustive DFT study considering Takemoto's model (Figure 28, Model B),[249] and the calculations showed that model B was energetically more favoured than model A. Thus, this model has been generally assumed to be the most accurate to explain the way of action of these bifunctional catalysts in this kind of reactions. Moreover, Zhong's research group reported in 2010 a similar model to B (Figure 28, Model C), on the basis of ^{1}H NMR and DFT studies.[238]

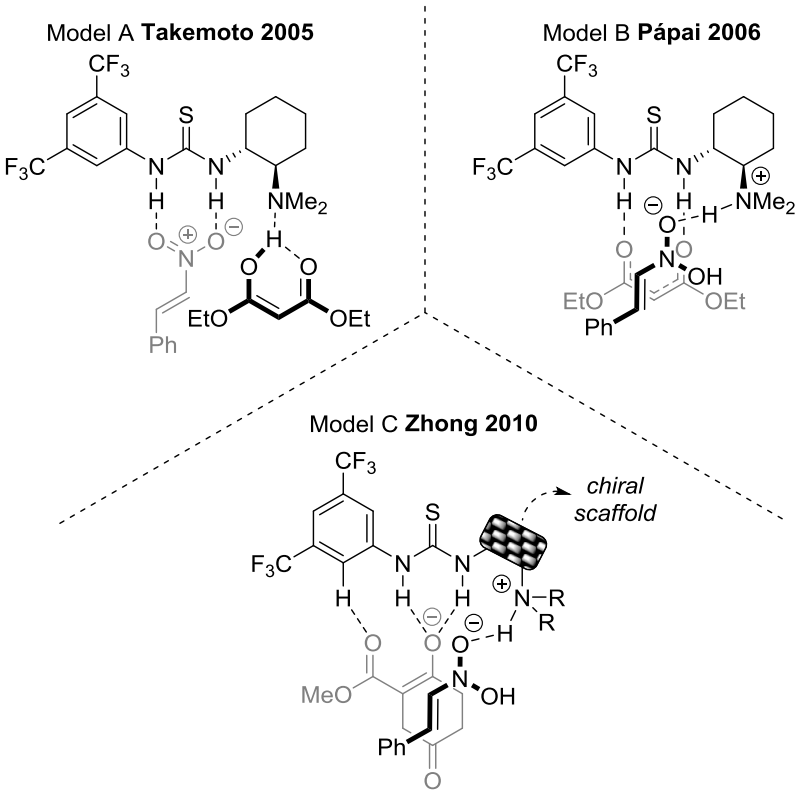


Figure 28. Proposed dual activation models for the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes promoted by thiourea-based bifunctional Brønsted bases.

[248] a) Takemoto catalyst see ref. 48 page 12. For a mechanistic proposal, see: b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
[249] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

Taking into account the aforementioned models, we propose the model depicted in Figure 29 for our reaction, where both the nitroolefin and the thiazolone are activated by the ureidopeptide-base catalyst. The electrophile would be coordinated to the Brønsted base, already protonated after the formation of the enolate in the thiazolone; whereas the urea moiety would coordinate to the thiazolone, through the nitrogen and oxygen atoms present in the heterocycle. A third coordination site in the quinolinyl group of the nucleophile would be possible, thanks to the aminal moiety in the catalyst, what would enhance the fixation of the transition state, thus providing better stereocontrol during the reaction.

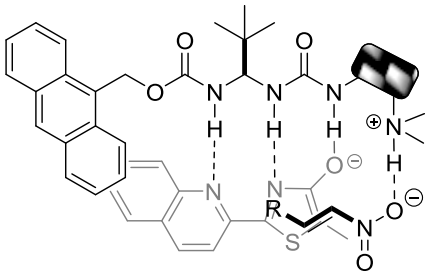
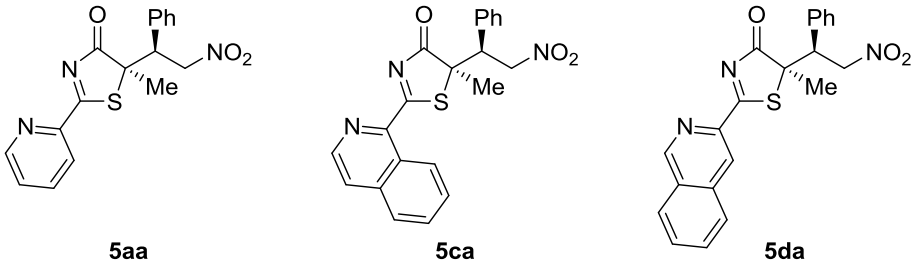


Figure 29. Proposed model for reaction activation.

Some support of this assumption was provided from the reaction of 5-methyl-2-(pyridin-2-yl)thiazol-4(5*H*)-one **4a**, 2-(isoquinolin-1-yl)-5-methylthiazol-4(5*H*)-one **4c** and 2-(isoquinolin-3-yl)-5-methylthiazol-4(5*H*)-one **4d** with nitrostyrene **2a** affording products **5aa**, **5ca** and **5da**, respectively, with worse results mainly in terms of enantioselectivity (Figure 30). The obtained results suggest that the increased aromaticity (respect to the 2-pyridyl derivative) and the spatial conformation adopted by the 2-quinolinyl group may assist to some sort of π–π stacking with the carbamate protecting group and the aromatic moiety of the nitroalkene, opposed to its isomers 1-isoquinolinyl and 3-isoquinolinyl derivatives. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation remains to be clarified.



5aa
80%, 93:7 *dr*, 80% *ee*

5ca
95%, 86:14 *dr*, 22% *ee*

5da
90%, 91:9 *dr*, 80% *ee*

Figure 30.

In general, these catalysts were solids and Diosdado[243] obtained a single-crystal of **C1** that was analyzed by X-ray revealing that in the solid state the *N–H* groups, in the *N,N´*-diacyl aminal and the urea moiety, are oriented in the same direction and that neither of them display any apparent tendency to develop intramolecular hydrogen bonds (Figure 31), being therefore accessible for coordination with the substrates. Nevertheless, in solution this orientation could differ.

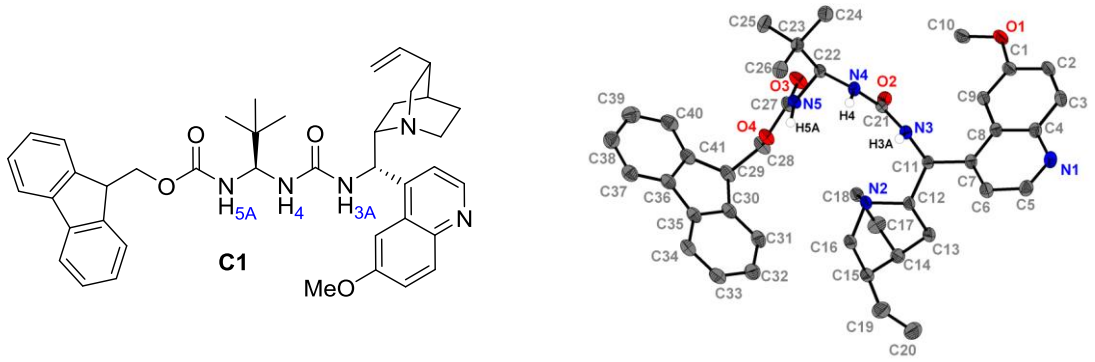


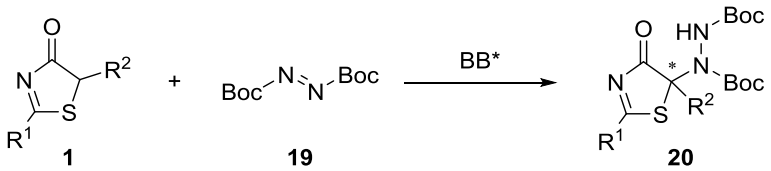
Figure 31. ORTEP diagram of compound **C1**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

2.3. **Electrophilic α-amination of 5*H*-thiazol-4-ones**

2.3.1. **Working hypothesis and synthetic plan**

Given that good results regarding reactivity and stereoselectivity were afforded in the Michael addition of 5*H*-thiazol-4-ones to nitroolefins catalyzed by new ureidopeptide-based Brønsted bases developed in our group, and, taking into account that these catalysts offer the opportunity of multiple *H*-bond interactions, we suspected that they might be suitable to coordinate to other Michael acceptors.

On this basis, di-*tert*-butyl azodicarboxilate (DBAD) **19** was chosen as electrophile, what would gain access to quaternary α-mercapto α-amino acid derivatives, a much seeked structure, as has been mentioned in previous sections. The reaction with this would led to the formation of only one stereocentre, eliminating the previous diastereoselectivity problem (Scheme 62).



Scheme 62. Proposed reaction for the first investigation.

2.3.2. **Results and discussion**

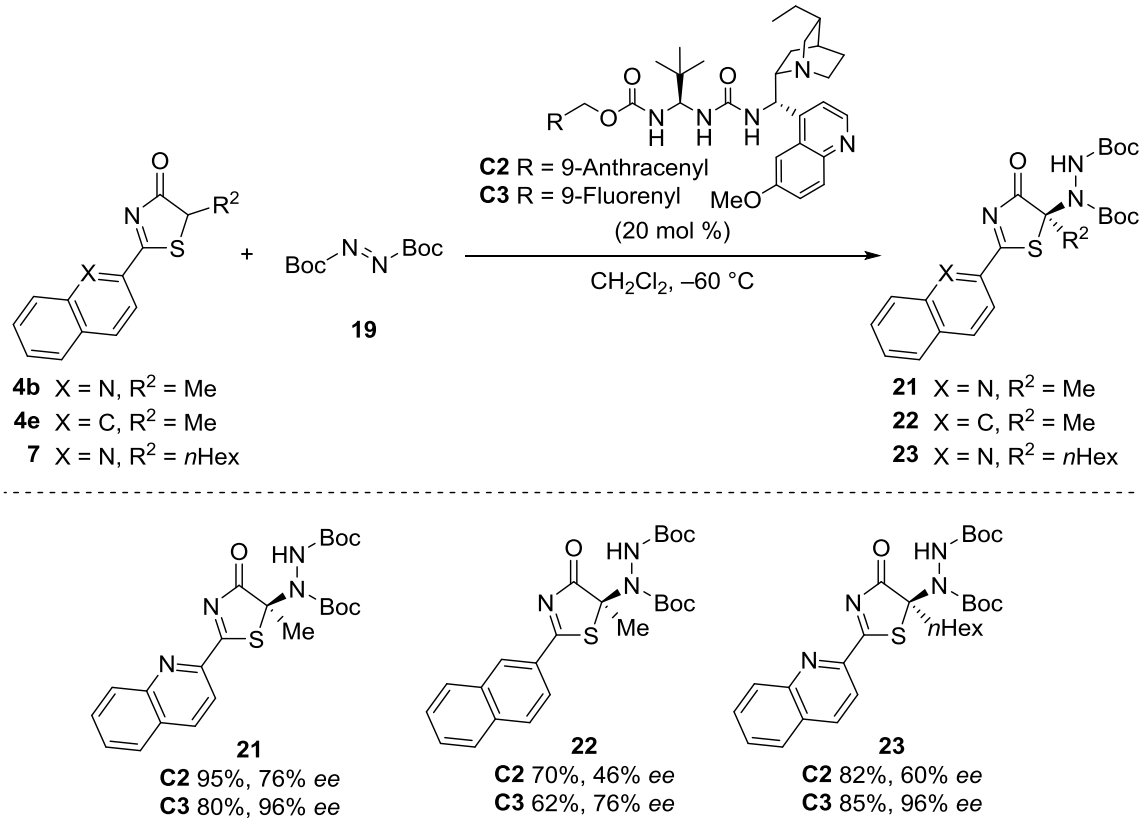
2.3.2.1. **Catalyst and thiazolone screening**

The consistency of the results regarding chemical reactivity and stereoselectivity in the Michael addition of 5*H*-thiazol-4-ones to nitroolefins suggested that the protocol developed by our group was robust enough to perform further additions. Therefore, when time had come to start evaluating reaction conditions for the α-amination, our first thought was to check the conjugate addition employing those optimized for the reaction with nitroalkenes. At least a starting point would thereby be established.

Our study thus began with the addition of the 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **4b** to DBAD **19** in dichloromethane at –60 °C in presence of catalyst **C2** (Table 28). Although the stereocontrol was far from being excellent, the obtained yield exceeded our first expectations, encouraging us to the consecution of this project. At this point, in order to confirm the previously observed data, we performed the electrophilic amination on two representative thiazolones: 5-hexyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **7** and 5-methyl-2-naphthyl-thiazol-4(5*H*)-one **4e**. To our delight, the naphthyl derivative rendered lower yield and a poor stereoselectivity, validating our hypothesis of a three NH-bond stabilized intermediate. On the other hand, the results of the 5-hexyl derivative remained closer to those of **4b**, although far from excellence.

In view of these results, we resolved to test a catalyst with a different protecting group in the aminal moiety, choosing fluorenylmethyloxycarbonyl (Fmoc) as a readily available and bulky substituent. Fortunately, this strategy worked out, obtaining the results depicted in Table 28. This time, the 2-quinolinyl derived thiazolones afforded excellent enantioselectivities, but while adduct **23** was produced in similar yield than with catalyst **C2**, the yield of adduct **21** lowered. The results rendered by 2-naphthyl derivative adduct **22** reinforced our aforementioned thesis, since both the yield and the enantioselectivity were much lower than those of 2-quinolinyl derivatives.

Table 28. Screening of thiazolones and catalyst for the stereoselective electrophilic α-amination.

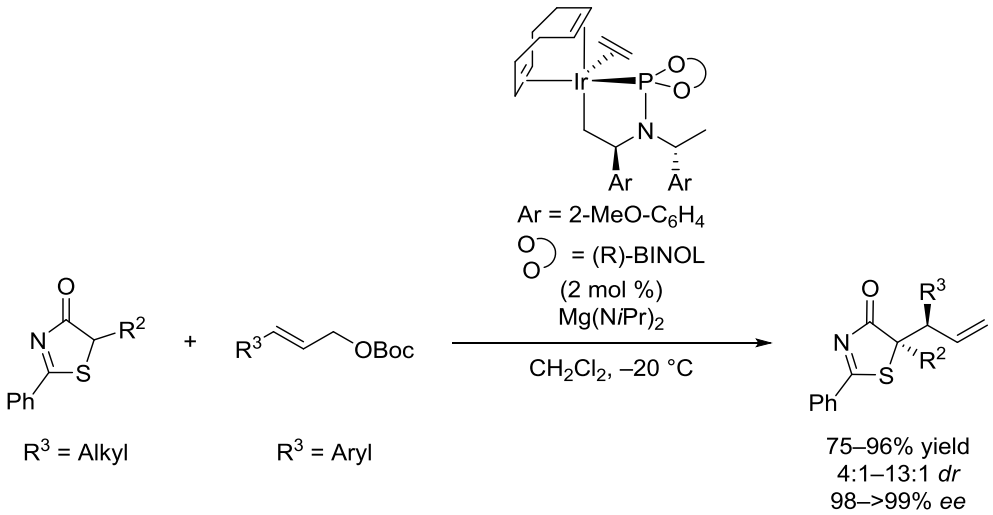


[a] Reaction conditions: **4b**, **7** and **23** (0.3 mmol), **21** (0.6 mmol, 2 equiv.), catalyst (20 mol %), –60 °C in CH_2Cl_2 (0.6 mL). Yields correspond to the isolated major isomer after column chromatography. *ee*'s determined by HPLC analysis on a chiral stationary phase.

The configuration of the adducts depicted in Table 28 was established assuming a uniform reaction mechanism respect to the addition to nitroolefins, assumption supported by the results obtained regarding the importance of a nitrogen atom in the 2-aryl group of the thiazolone.

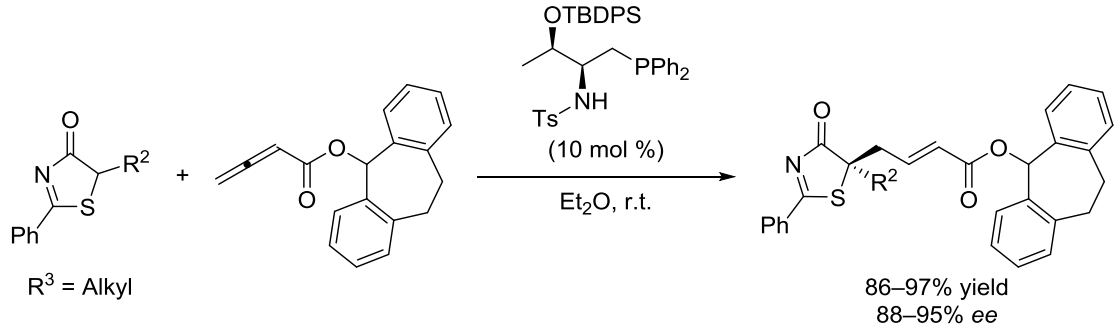
After our work, two papers concerning the use of 5*H*-thiazol-4-ones in catalytic asymmetric synthesis appeared. On the one hand, Hartwig and co-workers reported the Ir-catalyzed allylation of thiazolones, affording good to excellent yields and diastereoselectivities and excellent enantioselectivities (Scheme 63).[250]

[250] Chen & Hartwig see ref. 95b page 26.



Scheme 63.

On the other hand, Lan and Lu's research group described the conjugate addition of thiazolones to allenoates, with excellent yields and enantiocontrol, employing chiral phosphines as catalysts (Scheme 64).[251]



Scheme 64.

[251] Wang et al. see ref. 107 page 30.

CHAPTER 3

CONSTRUCTION OF *N*,C^{α},C^{α}-TRISUBSTITUTED α-AMINO ACID DERIVATIVES

3. CONSTRUCTION OF *N*,C^{α},C^{α}-TRISUBSTITUTED α-AMINO ACID DERIVATIVES

3.1. Introduction

3.1.1. General considerations

The essential role of naturally occurring α-amino acids as building blocks of peptides and proteins, has led to the development of various synthetic strategies for their preparation.[252] The flexible nature of peptides and proteins allows them to adopt several conformations in solution, but their diverse biological properties are commonly triggered by few of them. The introduction of different functional groups into the structure of amino acids can alter their conformation and, thus, their biological properties; a much seeked goal that has led numerous research groups to the synthesis of various non-proteinogenic α-amino acids.[253] Apart from their biological interest, α-amino acids have also been employed as chirality source for chemical catalysis and synthesis.[254]

Quaternary α-amino acids are stereochemically rigid building blocks that can be employed, among others uses, to synthesize novel unnatural peptides and proteins with unusual biological properties, such as helix-inducing potential[255] or enhanced resistance against chemical and enzymatic hydrolysis,[256] probably due to the absence of conforma-

[252] For selected reviews on the synthesis of α-amino acids, see: a) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. b) Martens, J. *ChemCatChem* **2010**, *2*, 379–381. c) Luo, Y.-C.; Zhang, H.-H.; Wang, Y.; Xu, P.-F. *Acc. Chem. Res.* **2010**, *43*, 1317–1330. d) Jakubowska, A.; Kulig, K. *Curr. Org. Synth.* **2013**, *10*, 547–563. e) Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. *Amino Acids* **2013**, *45*, 1017–1033. f) Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. *Amino Acids* **2014**, *46*, 2047–2073. For leading books on the topic, see: g) R. M. Williams, *Synthesis of Optically Active α-Amino Acids* (Pergamon, Oxford) 1989. h) *Asymmetric Synthesis and Application of α-Amino Acids* (V. A. Soloshonok & K. Izawa ed., American Chemical Society, Washington DC) 2009.

[253] For several reviews on the synthesis of unnatural α-amino acids, see: a) Michaux, J.; Niel, G.; Campagne, J.-M. *Chem. Soc. Rev.* **2009**, *38*, 2093–2116. b) Tarui, A.; Sato, K.; Omote, M.; Kumadaki, I.; Ando, A. *Adv. Synth. Catal.* **2010**, *352*, 2733–2744. c) Johansson, H.; Pedersen, D. S. *Eur. J. Org. Chem.* **2012**, 4267–4281. d) Popkov, A.; Elsinga, P. *Curr. Org. Chem.* **2013**, *17*, 2127–2137. e) Kotha, S.; Goyal, D.; Chavan, A. S. *J. Org. Chem.* **2013**, *78*, 12288–12313. f) Kotha, S.; Bandarugattu, V. B.; Krishna, N. G. *Tetrahedron* **2014**, *70*, 5361–5384. For leading book on the topic, see: g) J. Vidal, *Amino Acids, Peptides and Proteins in Organic Chemistry* (A. B. Hughes ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2009. h) M. Ikunaka & K. Maruoka, *Asymmetric Catalysis on Industrial Scale* (H.-U. Blaser & H.-J. Federsel ed., Wiley-VCH Verlag GmbH & Co. KGaA 2nd ed.) 2010.

[254] For an application in the synthesis of heterocycles, see: a) Singh, P.; Samanta, K.; Das, S. K.; Panda, G. *Org. Biomol. Chem.* **2014**, *12*, 6297–6339. For their use as chiral auxiliaries, see: b) W. Maison, *Comprehensive Chirality* (E. M. Carreira & K. Yamamoto ed., Elsevier B.V., Amsterdam) 2012. For an application in the synthesis of biodegradable polymers, see: c) Sun, H.; Meng, F.; Dias, A. A.; Hendriks, M.; Feijen, J.; Zhong, Z. *Biomacromolecules* **2011**, *12*, 1937–1955.

[255] For a review on the design of folded peptides, see: Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.

[256] For some review on the biological properties of quaternary α-amino acids, see: a) Crisma, M.; Valle, G.; Bonora, G. M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternall, F.; Hardy, P. M.; Maia, H. L. S. *Biopolymers*

tional freedom caused by the steric constraint.[257] Quaternary α-amino acids can also be found in some natural products acting as antibiotics.[258]

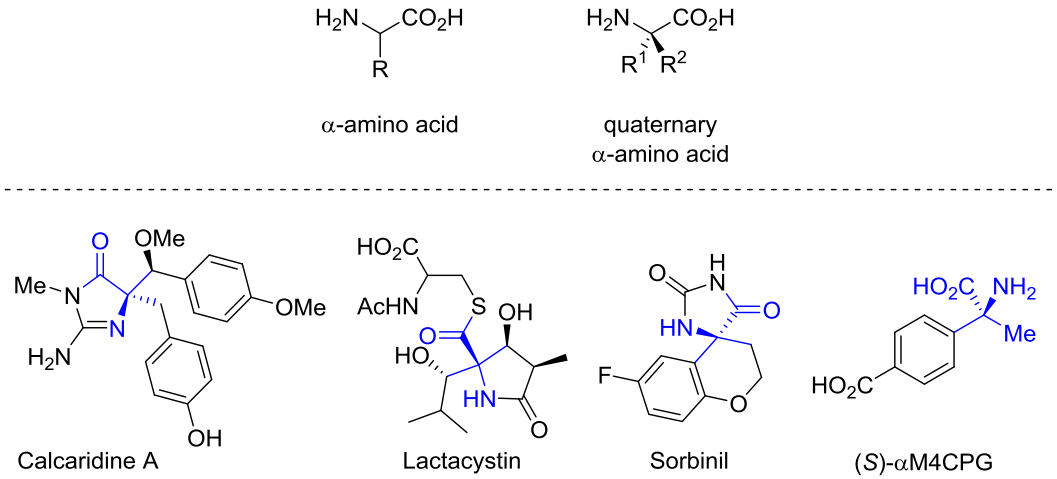


Figure 32. i) General structures of both α-amino acids and quaternary α-amino acids (α,α-disubstituted α-amino acids). ii) Biologically active quaternary α-amino acid derivatives.[257a,c]

3.1.2. **Strategies for the synthesis of α,α-disubstituted α-amino acid derivatives**

The methods described for the synthesis of enantioenriched α,α-disubstituted α-amino acid derivatives comprise several different strategies, including several non catalytic methods.[259] Due to the importance of the topic and the extensive variety of synthetic methods, only stereoselective approaches will be discussed in this chapter, and more par-

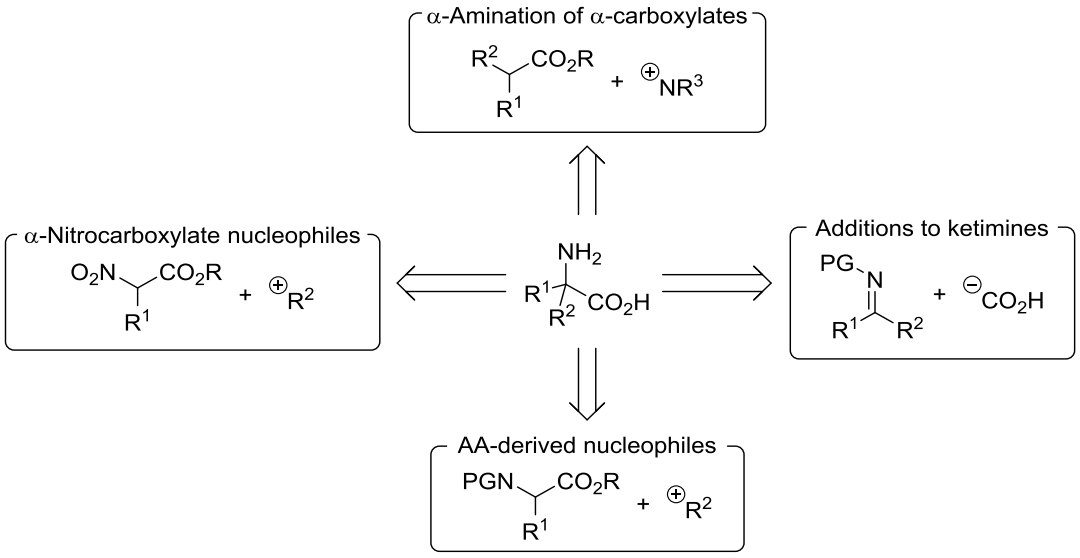
1991, *31*, 637–641. b) Gante, J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1699–1720. c) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048–12054. d) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. *Synlett* **2006**, *2006*, 1295–1310. e) Tanaka, M. *Chem. Pharm. Bull. (Tokyo).* **2007**, *55*, 349–358.

[257] For selected reviews on the synthesis of quaternary α-amino acids, see: a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, *2005*, 5127–5143. b) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430. c) Tanaka, M. *Chem. Pharm. Bull. (Tokyo).* **2007**, *55*, 349–358. c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623. d) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63. e) Soloshonok, V.; Sorochinsky, A. *Synthesis* **2010**, 2319–2344. f) Baer, K.; Dückers, N.; Hummel, W.; Gröger, H. *ChemCatChem* **2010**, *2*, 939–942. g) Bera & Namboothirih) Metz & Kozlowski

[258] a) Kende, A. S.; Liu, K.; Jos Brands, K. M. *J. Am. Chem. Soc.* **1995**, *117*, 10597–10598. b) Yano, H.; Nakanishi, S.; Ikuina, Y.; Ando, K.; Yoshida, M.; Saitoh, Y.; Matsuda, Y. *J. Antibiot. (Tokyo).* **1997**, *50*, 992–997. c) Becker, D.; Kiess, M.; Brückner, H. *Liebigs Ann.* **1997**, *1997*, 767–772. d) *Peptaibiotics: Fungal Peptides Containing α-Dialkyl α-Amino Acids* (C. Toniolo & H. Bruckner ed., Wiley-VCH) 2009.

[259] For a review on the Self-Regeneration of Stereocentres (SRS), see: a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708–2748. For a recent example employing SRS to synthesize quaternary prolines, see: b) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*, 432–435. For a review on Memory of Chirality (MOC), see: c) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16. For an example of MOC of tertiary aromatic amides, see: d) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711–10718. For a recent example of the synthesis of β-hydroxy quaternary α-amino acids through MOC, see: e) Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Lett.* **2014**, *16*, 788–791.

ticularly, direct catalytic asymmetric tactics. Depicted in Scheme 1 are the possible disconnections used for this purpose.

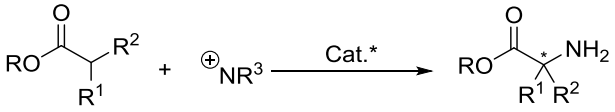


Scheme 65. Strategies for the direct asymmetric synthesis of α,α-disubstituted α-amino acid derivatives.

Following sections will gather examples corresponding to these strategies until the beginning of this thesis work.

3.1.2.1. **Electrophilic α-amination of tertiary α-carboxylates**

Electrophilic amination of α-carboxylic acid derivatives is probably one of the simplest approaches for the formation of α,α-disubstituted α-amino acid derivatives (Scheme 66), although it is relatively uncommon due to the shortage of suitable electrophilic nitrogen sources, being azodicarboxylates the usual choice.

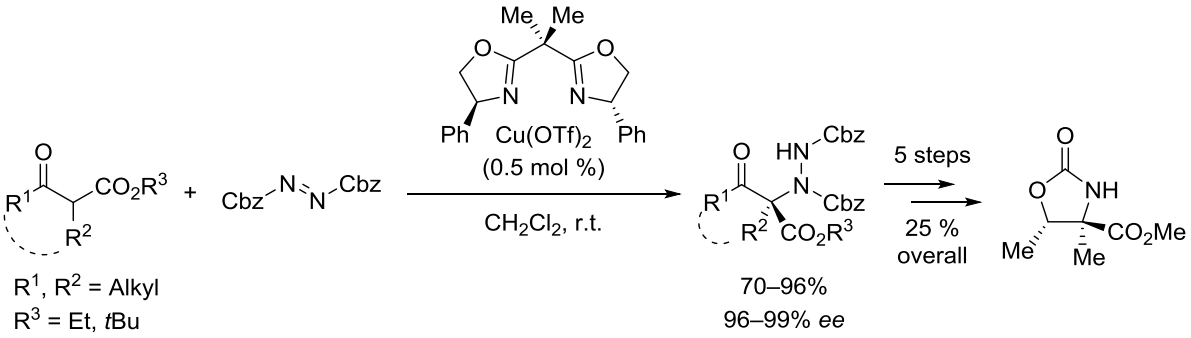


Scheme 66.

Direct α-amination of α-substituted β-ketoesters was first reported by Jørgensen's research group, employing a chiral copper bisoxazoline complex as catalyst.[260] Very good to excellent yields and excellent enantioselectivities were obtained with both acyclic and cyclic substrates and dibenzyl azodicarboxylate (Scheme 67). Employing this method,

[260] a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1367–1369. For a recent polymer supported Cu-catalyzed α-amination of β-ketoesters, see: b) Torres, M.; Maisse-François, A.; Bellemin-Laponnaz, S. *ChemCatChem* **2013**, *5*, 3078–3085. For a recent Eu catalyzed α-amination of β-ketoesters, see: c) Pericas, À.; Shafir, A.; Vallribera, A. *Org. Lett.* **2013**, *15*, 1448–1451.

optically active β-hydroxy-α-amino acid derivatives were accessed, although 5 steps were required rendering a 25% overall yield.



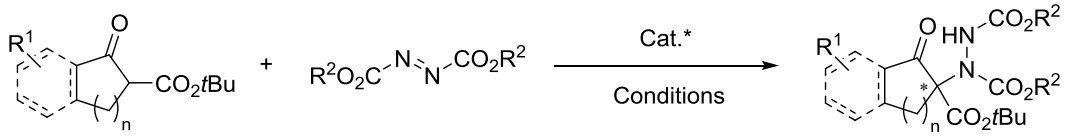
Scheme 67.

Although Jørgensen also reported the first organocatalytic approach to the α-amination of β-ketoesters using a bifunctional *Cinchona* alkaloid catalyst (Table 29, entry 1),[261] it is noteworthy the work developed on this topic by Maruoka's research group using phase-transfer conditions.[262] The first example they reported employed an axially chiral phosphonium bromide as catalyst and stoichiometric quantities of KH_2PO_4 as a base, rendering moderate to excellent yields and enantioselectivities (entry 2). Few years later, they found that the reaction could also be catalyzed under similar reaction conditions by a chiral ammonium salt catalyst and catalytic amounts of KH_2PO_4, obtaining comparable results regarding chemical and stereochemical performance (entry 3).

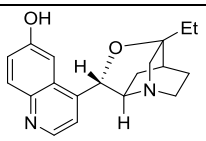
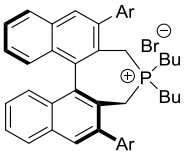
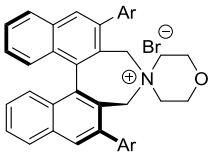
[261] Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.

[262] a) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9466–9468. b) Lan, Q.; Wang, X.; He, R.; Ding, C.; Maruoka, K. *Tetrahedron Lett.* **2009**, *50*, 3280–3282. For a recent α-amination of β-ketoesters employing immobilized bifunctional thioureas, see: Kasaplar, P.; Ozkal, E.; Rodríguez-Escrich, C.; Pericàs, M. A. *Green Chem.* **2015**, *17*, 3122–3129.

Table 29. Asymmetric α-amination of β-ketoesters.



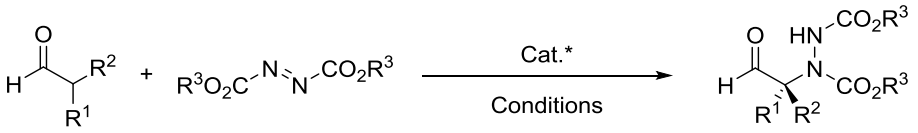
R^1 = Cl, OMe
n = 1,2

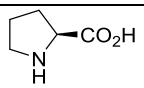
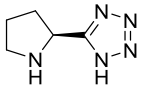
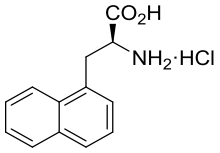
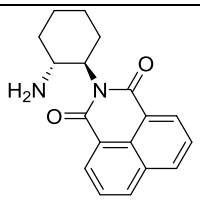
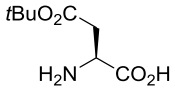
Entry	R^2	Cat.*	Conditions	Results	Ref.
1	*t*Bu	 (5 mol %)	toluene –50 to 0 °C	86–99% 83–90% *ee* (*R*)	261
2	*t*Bu	 Ar = 3,5-$(CF_3)_2$-C_6H_3 (3 mol %)	K_2HPO_4 (1–5 equiv.) toluene –40 to –20 °C	42–99% 77–95% *ee* (*S*)	262a
3	Et	 Ar = 3,5-(3,5-(*t*Bu)$_2$-C_6H_3)$_2$-C_6H (3 mol %)	K_2HPO_4 or K_2CO_3 (0.3 equiv.) toluene –40 to 0 °C	95–99% 76–97% *ee* (*S*)	262b

In 2003, Bräse and co-workers described,[263] using enamine activation, the proline-catalyzed α-amination of α,α-disubstituted aldehydes but using 50 mol % catalyst loading and with moderate results (Table 30, entry 1). Few years later, Barbas III employed this strategy in the synthesis of BIRT-377 in a much more efficient way, obtaining 99% *ee* upon crystallization (entry 2).[264] α-Amination of aldehydes has been revisited several times, by Wang and co-workers (entries 3–4)[265] and by Kokoto's group (entry 5),[266] changing the catalyst or lowering catalyst loading, in order to obtain better results in a more efficient way. However, both yield and *ee*'s are strongly substituent dependant.

[263] Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448–2449.
[264] Chowdari & Barbas III see ref. 77 page 20.
[265] a) Fu, J.-Y.; Yang, Q.-C.; Wang, Q.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2011**, *76*, 4661–4664. b) Fu, J.-Y.; Wang, Q.-L.; Peng, L.; Gui, Y.-Y.; Xu, X.-Y.; Wang, L.-X. *Chirality* **2013**, *25*, 668–672.
[266] Theodorou, A.; Papadopoulos, G. N.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 5438–5443.

Table 30. Aminocatalyzed α-amination of aldehydes employing azodicarboxilates.

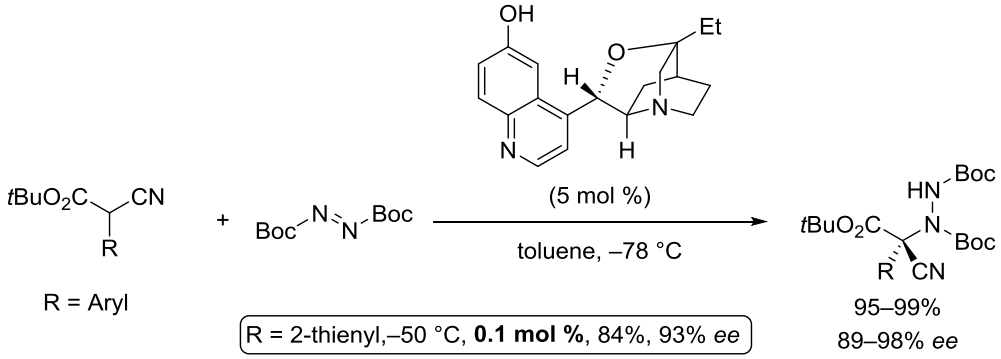


	R^1	R^2	R^3	Cat.*	Conditions	Results	Ref.
1	Alkyl	Alkyl, Aryl	Et, *t*Bu	 (50 mol %)	CH_2Cl_2, r.t.	17–99% 4–86% *ee*	263
2	4-Br-C_6H_4-CH_2	Me	Bn	 (15 mol %)	CH_3CN, r.t.	95% 80% *ee*	264
3	Alkyl	Alkyl, Aryl	Et, *i*Pr, *t*Bu	 (20 mol %)	THF, 0 °C	29–99% 85–97% *ee*	265a
4	Me	Aryl, *n*Pr	Et, *i*Pr, *t*Bu, Bn	 (10 mol %)	TFA (10 mol %) DCE, 25 °C	38–99% 57–97% *ee*	265b
5	Aryl, Alkyl	Me, Et	*t*Bu	 (20 mol %)	THF, 0 °C	72–98% 50–99% *ee*	266

α-Amination of α-cyanocarboxylic compounds has also rendered excellent examples of quaternary α-amino acid synthesis. The versatility of the nitrile moiety allows its transformation into different functional groups, but its presence in the final adduct can also be of interest. Case in point is the amination of α-aryl *tert*-butyl cyanoacetates developed by Jørgensen's group in 2004.[267] The β-isocupreidine-catalyzed reaction afforded excellent yields and stereocontrol in every case, even employing low catalyst loadings (down to 0.1 mol %, Scheme 68). The extremely low temperatures employed to maintain

[267] For the asymmetric α-amination of α-cyanoketones employing thiourea-based bifunctional Brønsted bases, see: a) Kim, S.; Lee, J.; Kim, D. *Synlett* **2008**, 2659–2662. For the asymmetric α-amination of α-cyanothioacetates employing chiral guanidines, see: b) Terada, M.; Tsushima, D.; Nakano, M. *Adv. Synth. Catal.* **2009**, *351*, 2817–2821. For the asymmetric α-amination of 1,3-dicarbonyl compounds and α-cyanoacetates BINOL–quinine–squaramide catalysts, see: c) Gao, Y.; Liu, B.; Zhou, H.-B.; Wang, W.; Dong, C. *RSC Adv.* **2015**, *5*, 24392–24398.

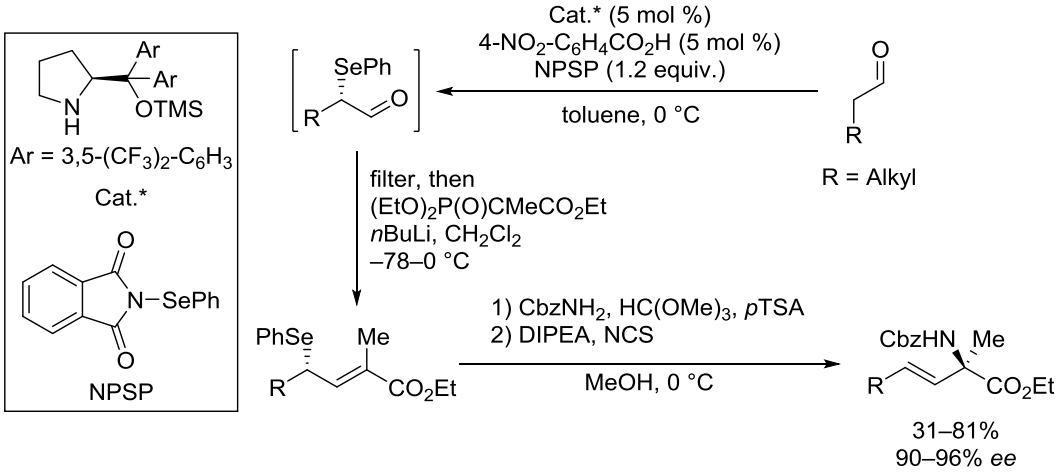
stereocontrol on the reaction was due to the reactivity of the substrate, caused by the strong acidity of the α C(sp^3) of the cyanoacetate.



Scheme 68.

Other nucleophiles used for these transformations include α-substituted α-nitroacetates,[268] α-fluoro β-ketoesters,[269] and α-acyl acrylates.[270]

However, there are other routes to perform an α-amination, as Armstrong and co-workers reported in 2011.[271] Their tactic relied on the asymmetric α-selenenylation of aldehydes to form an enolate umpolung equivalent. After olefination employing a Wittig reagent, a stereoselective nucleophilic amination of the allylic selenide, followed by a [2,3]-sigmatropic rearrangement afforded the desired aminoesters in good yields and excellent enantioselectivities (Scheme 69).

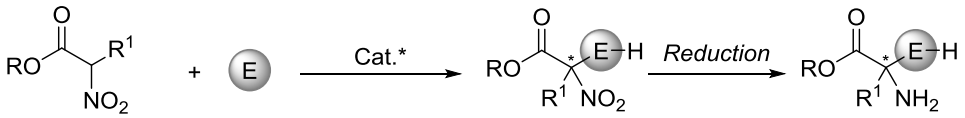


Scheme 69.

[268] Ji, C.-B.; Liu, Y.-L.; Zhao, X.-L.; Guo, Y.-L.; Wang, H.-Y.; Zhou, J. *Org. Biomol. Chem.* **2012**, *10*, 1158–1161.
[269] Han, X.; Zhong, F.; Lu, Y. *Adv. Synth. Catal.* **2010**, *352*, 2778–2782.
[270] De Fusco, C.; Fuoco, T.; Croce, G.; Lattanzi, A. *Org. Lett.* **2012**, *14*, 4078–4081.
[271] Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2011**, *13*, 1040–1043.

3.1.2.2. **α-Nitrocarboxylate-derived nucleophiles for *C-C* bond formation**

Addition of α-nitrocarboxylates to different electrophiles is a well known strategy for the construction of α,α-disubstituted α-amino acid derivatives, since the reduction of the nitro moiety gives access to amino functional groups (Scheme 70).



Scheme 70.

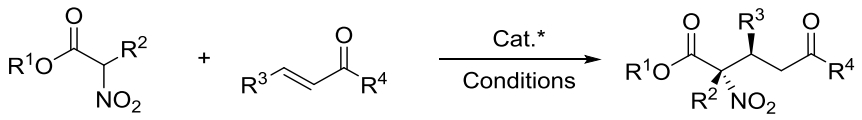
The classification of the examples described in this section is based on the transformation performed.

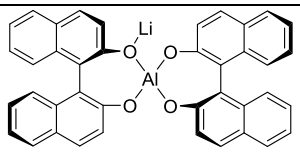
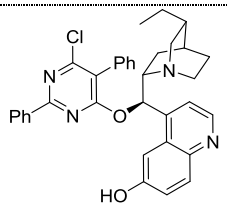
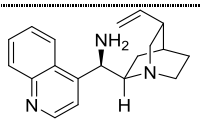
3.1.2.2.1. Michael addition

In 1997, Feringa's research group reported the first conjugate addition of α-nitroesters to α,β-unsaturated ketones in presence of a Lewis acid,[272] affording moderate yields and enantioselectivities at best (Table 31, entry 1). The first organocatalytic version came in hand of Snider and co-workers,[273] who employed the conjugate addition of ethyl 2-nitropropanoate to methyl vinyl ketone as a key step in the total synthesis of natural produc (+)-NP25302, although no wider scope was explored (entry 2). Some years later, Zhao's group described the Michael addition of α-fluoro α-nitroacetates to β-substituted enones,[274] affording very good yields and excellent enantioselectivities, but moderate diastereoselectivities (entry 3).

[272] Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403–3413.
[273] Duvall, J. R.; Wu, F.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579–8590.
[274] Cui, H.-F.; Li, P.; Wang, X.-W.; Chai, Z.; Yang, Y.-Q.; Cai, Y.-P.; Zhu, S.-Z.; Zhao, G. *Tetrahedron* **2011**, *67*, 312–317.

Table 31. Michael addition of α-nitroacetates to enones.

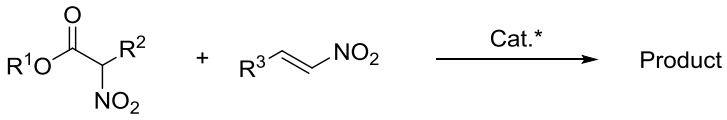


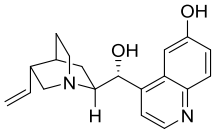
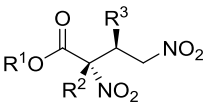
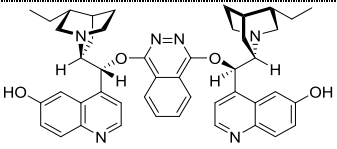
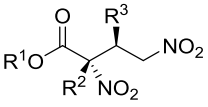
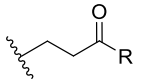
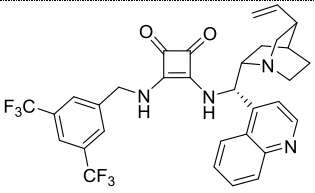
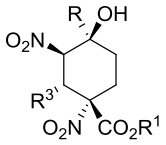
	R^1	R^2	R^3	R^4	Cat.*	Conditions	Results	Ref.
1	Alkyl	Me, Et	H	Me, Et, Ph	 (10 mol %)	THF:H_2O (85:15) –65 °C	81–86% 33–80% *ee* (R^4 = Ph, 5% *ee*)	272
2	Et	Me	H	Me		CH_2Cl_2 –20 °C	90% 90% *ee*	273
3	Et	F	Alkyl, Aryl	Me	 (10 mol %)	4-NO_2-$C_6H_4CO_2H$ (10 mol %) toluene, r.t.	75–95% 1.2:1–2.4:1 *dr* 93–99% *ee*	274

The first conjugate addition of α-nitroesters to nitroolefins was reported by Deng and co-workers in 2005, employing crupeine as catalyst, which rendered good yields and excellent diastereo- and enantioselectivities (Table 32, entry 1).[275] In 2013, Lin's research group used a dimeric version of the catalyst (i.e. *de*-Me-DHQ)$_2$PHAL), which allowed them to lower the catalyst loading without compromising the outcome (entry 2).[276] Also using nitroalkenes and nitroacetates, Carrillo and Vicario's group described an effective synthesis of densely substituted cyclohexanes through a Michael-Henry tandem sequence (entry 3).[277]

[275] Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108.
[276] Li, Y.-Z.; Li, F.; Tian, P.; Lin, G.-Q. *Eur. J. Org. Chem.* **2013**, *2013*, 1558–1565.
[277] Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627–3648.

Table 32. Michael addition of α-nitroacetates to nitroolefins.

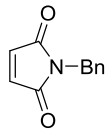
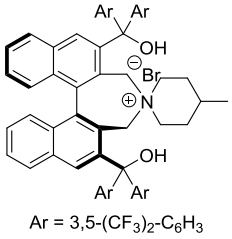
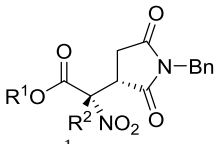
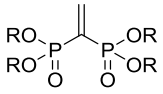
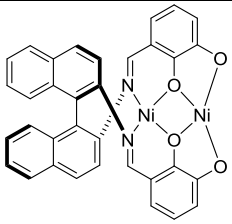
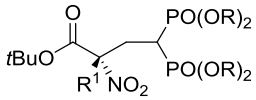
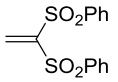
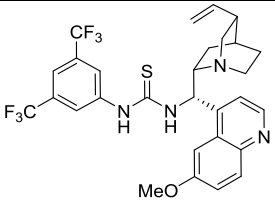
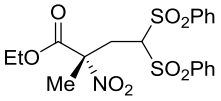
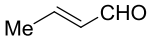
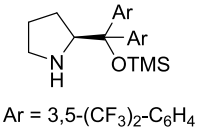
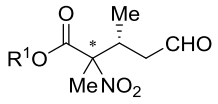
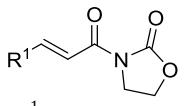
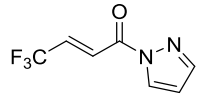
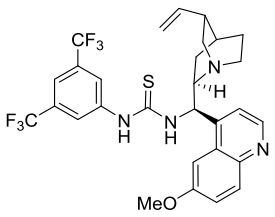
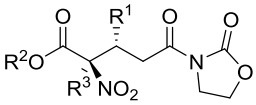
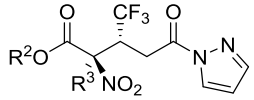


	R^1	R^2	R^3	Cat.*	Product	Results	Ref.
1	Et	Me, Et	Alkyl, Aryl	 (15 mol %)		77–78% 92:8–95:5 *dr* 92–96% *ee*	275
2	Et	Me, Et	Alkyl, Aryl	 (1 mol %)		71–99% 89:11–99:1 *dr* 94–98% *ee*	276
3	Et, Me	 R = Me, Et	Aryl	 (2–2.5 mol %)		91–98% 1:6–1:19 *dr* 96–99% *ee*	277

The high reactivity of these nucleophiles has prompted the development of methodologies for their asymmetric addition to several electrophiles (Table 33), such as maleimides (entry 1),[278] *gem*-bisphosphonates (entry 2),[279] 1,1-bis(sulfonyl)ethylenes (entry 3),[280] di-*tert*-butyl azodicarboxylate (entry 4),[281] enals (entry 5),[282] and enamides (entry 6).[283] Sulfenylation of nitroacetates employing L-proline derived catalysts as H-bond acceptors has also been reported (entry 7).[284]

[278] Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557–10559.
[279] Kato, Y.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Synlett* **2009**, 1635–1638.
[280] Quintard, A.; Alexakis, A. *Org. Biomol. Chem.* **2011**, *9*, 1407–1418.
[281] Ji et al. see ref. 268 page 106.
[282] Han, M.-Y.; Zhang, Y.; Wang, H.-Z.; An, W.-K.; Ma, B.-C.; Zhang, Y.; Wang, W. *Adv. Synth. Catal.* **2012**, *354*, 2635–2640.
[283] Wen, L.; Yin, L.; Shen, Q.; Lu, L. *ACS Catal.* **2013**, *3*, 502–506.
[284] Fang, L.; Lin, A.; Shi, Y.; Cheng, Y.; Zhu, C. *Tetrahedron Lett.* **2014**, *55*, 387–389.

Table 33. Diverse electrophiles employed with α-nitroacetates as nucleophiles.

	Electrophile	Cat.*	Product	Results	Ref.
1		 Ar = 3,5-$(CF_3)_2$-C_6H_3 (3 mol %)	 R^1 = Me, Et R^2 = Alkyl, Bn	42–92% 10:1–20:1 *dr* 83–91% *ee*	278
2	 R = Et, allyl, Bn	 (10 mol %)	 R^1 = Alkyl	65–94% 76–93% *ee*	279
3		 (20 mol %)		100% (conv.) 28% *ee*	280
5		 Ar = 3,5-$(CF_3)_2$-C_6H_4 (10 mol %)		44% 1:1.3 *dr* 82/88% *ee*	282
6	 R^1 = CF_3, C_2F_5 	 (10 mol %)	 R^2, R^3 = Me, Et  R^2, R^3 = Me, Et	71–93% >50:1 *dr* 89–92% *ee* 71–83% 4.4:1–10:1 *dr* 80–90% *ee*	283

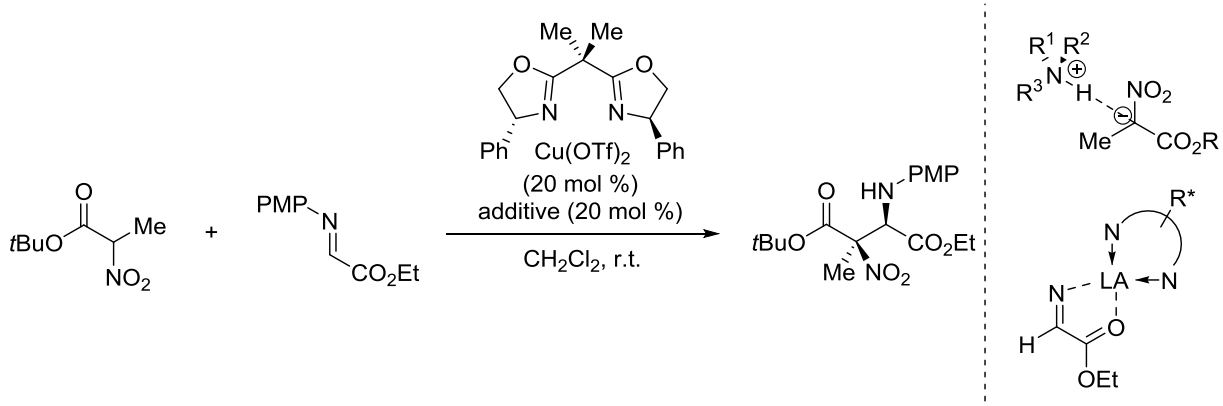
3.1.2.2.2. Mannich reaction

The first enantioselective Mannich reaction of a nitroester with an imine was described by Jørgensen and co-workers in 2005 using synergetic catalysis.[285] The reaction

[285] a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364. For a review on combinig transition metal catalysis and organocatalysis, see: b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755. For a review on synergistic catalysis, see: c) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633–658. For a review on dual activation in organocatalysis, see: d) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, *23*, 490–508.

was performed in presence of a Cu catalyst and an organocatalyst (Table 34). Results suggested that the enantiocontrol was induced by both catalysts, although diastereoselectivity was not much affected by *Cinchona* alkaloid changes.

Table 34. Effect of the additive in the Cu-catalyzed Mannich addition of nitroacetates to iminoesters.

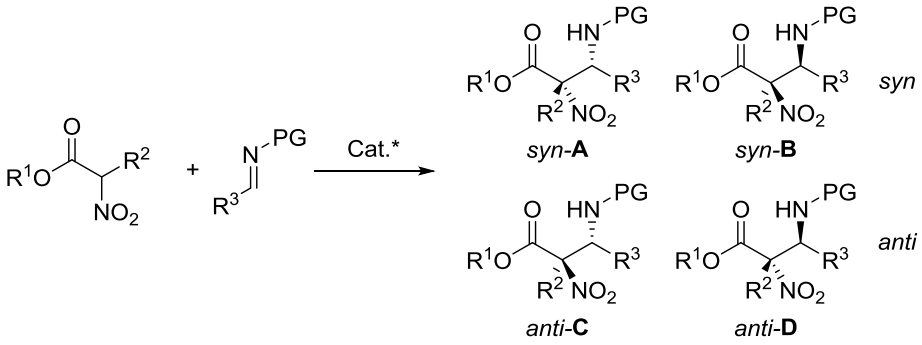


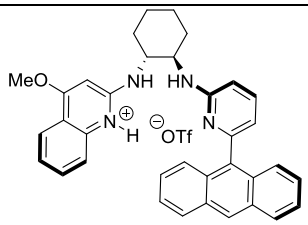
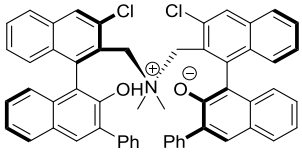
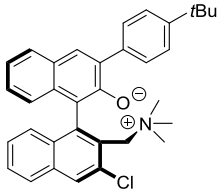
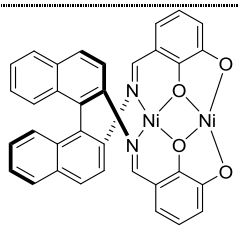
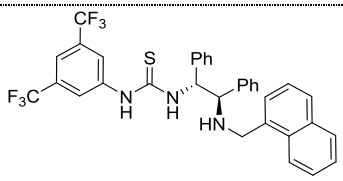
Entry	Additive	Yield (%)	*dr*	*ee* (%)
1	Et_3N	90	2:1	80/82
2	quinine	90	14:1	98
3	quinidine	80	8.5:1	96
4	cinchonine	76	7:1	94
5	hydroquinine	90	8:1	95
6	hydrocinchonine	90	7:1	93

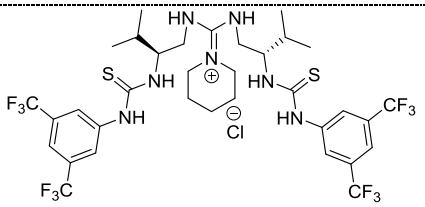
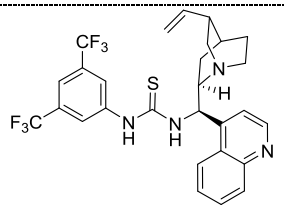
Following this pioneering work, several methodologies have been developed in order to synthesize all four possible diastereomers. Efforts reported by Johnston with a bifunctional chiral proton complex,[286] Ooi with phase-transfer catalysis,[287] Shibasaki with a homodinuclear Ni catalyst,[288] Chen with a bifunctional thiourea catalyst,[289] Dong with a guanidinium-based catalyst,[290] and Miao with a bifunctional thiourea catalyst,[291] are depicted in Table 35.

[286] Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867.
[287] a) Uraguchi, D.; Koshimoto, K.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879. b) Uraguchi, D.; Koshimoto, K.; Sanada, C.; Ooi, T. *Tetrahedron: Asymmetry* **2010**, *21*, 1189–1190.
[288] Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171.
[289] Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 8094–8097.
[290] Han, B.; Huang, W.; Xu, Z. R.; Dong, X. P. *Chinese Chem. Lett.* **2011**, *22*, 923–926.
[291] Fan, W.; Kong, S.; Cai, Y.; Wu, G.; Miao, Z. *Org. Biomol. Chem.* **2013**, *11*, 3223–3229.

Table 35. Mannich reactions employing α-nitroacetates as pronucleophiles.



	R^1	R^2	R^3	PG	Cat.*	Prod.	Results	Ref.
1	Aryl	Alkyl	Aryl	Boc	 (5 mol %)	*syn*-A	59–88% 5:1–20:1 *dr* 94–98% *ee*	286
2	*t*Bu	Me, Et	Alkyl, aryl	Boc	 (1 mol %)	*syn*-B	91–99% 2:1–5:1 *dr* 91–99% *ee*	287
3	*t*Bu	Me, Et	Alkyl, aryl	Boc	 (1 mol %)	*syn*-B	95–99% 2:1–6:1 *dr* 90–96% *ee*	287
4	*t*Bu	Alkyl	Alkyl, aryl	Boc	 (5–10 mol %)	*anti*-C	67–96% 86:14–97:3 *dr* 91–99% *ee*	288
5	Me	Me, *i*Pr, Bn	Aryl	Boc	 (10 mol %)	*anti*-D	38–86% 4:1–7:1 *dr* 91–96% *ee*	289

6	Et	Me, *i*Pr, Bn	Aryl	Boc	 (5 mol %)	*anti*-D	40–80% 3:1–8:1 *dr* 91–96% *ee*	290
7	Me	Me, Et	Aryl	$PO(OEt)_2$	 (5 mol %)	*anti*-D	65–86% 4:1–7:1 *dr* 91–96% *ee*	291

3.1.2.2.3. Aldol reaction

Despite the similarity of the product of the aldol reaction of α-nitroesters with the α-amino acid with natural α-amino acid Serine (Figure 33), this approach has not been as much explored as Mannich reaction has been. In fact, as far as we know, there are only two examples in literature, which describe the hydroxymethylation of nitroesters. This may be due to the facility by which these adducts can undergo retro-aldol reactions, this reason also explains why only formaldehyde has been used to date as acceptor.

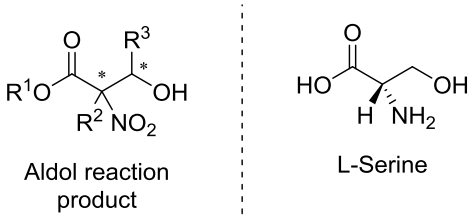
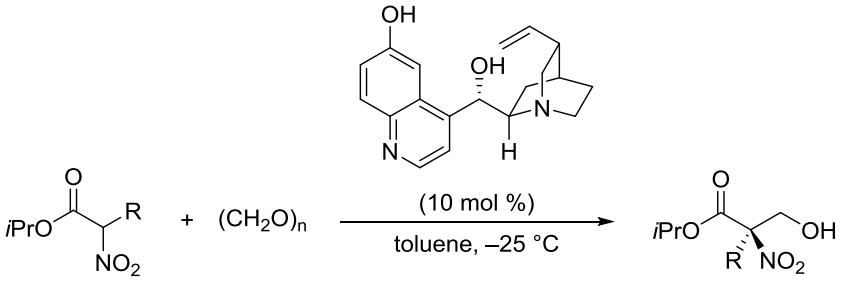


Figure 33.

The first example of an aldol reaction employing nitroacetates as pronucleophiles was reported by Zhou and co-workers,[292] who presented the addition of isopropyl α-nitroesters to paraformaldehyde (Table 36). In presence of cupreidine, the reaction afforded good yields and moderate enantioselectivities with alkyl substituents (entries 1–5), but poor stereocontrol when R = Ph (entry 6). The long reaction times are a consequence of the low temperatures, needed for the stereocontrol of the reaction.

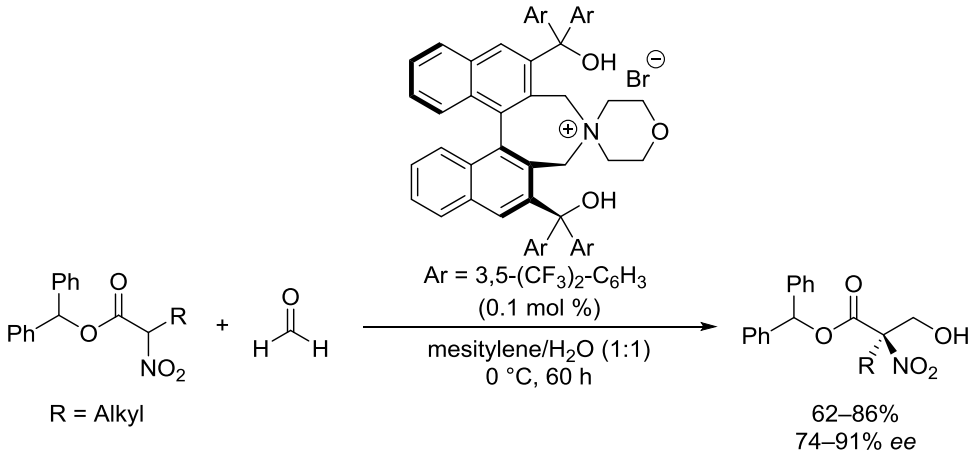
[292] Ji, C.-B.; Liu, Y.-L.; Cao, Z.-Y.; Zhang, Y.-Y.; Zhou, J. *Tetrahedron Lett.* **2011**, *52*, 6118–6121.

Table 36.



Entry	R	Time (days)	Yield (%)	*ee* (%)
1	Me	6	83	60
2	Et	6	80	64
3	*n*Bu	6	77	71
4	*i*Bu	6	72	51
5	$CyCH_2$	6	89	52
6	Ph	7	82	25

In 2012, Maruoka's research group reported a phase-transfer catalyzed formylation of benzyl α-nitroesters, employing an aqueous solution of formaldehyde.[293] As illustrated in Scheme 71, an astonishingly low catalyst loading (0.1 mol %) was enough to induce very good to excellent enantioselectivities in the aldol reaction.



Scheme 71.

To date, no other aldehyde has been tested for the reaction with nitroesters, and successful methodologies for asymmetric aldol reaction with aryl substituted α-nitroacetate substrates remain unexplored.

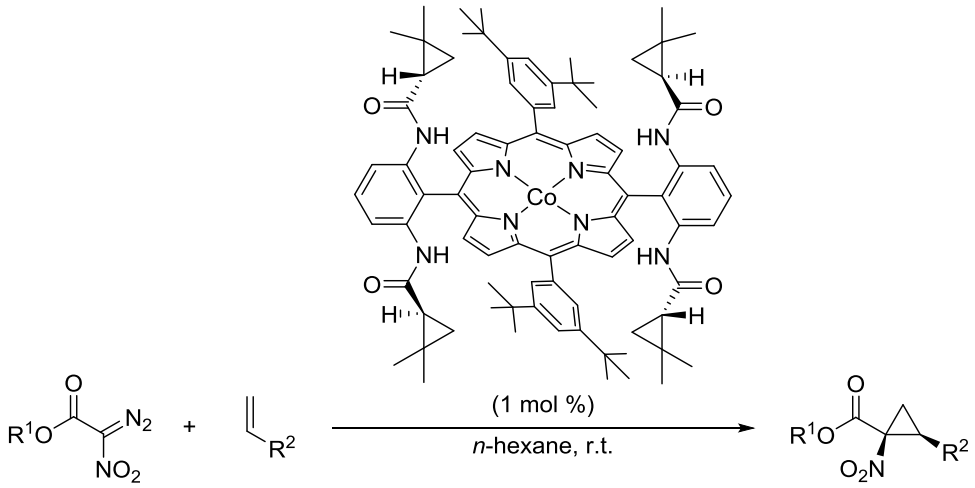
[293] Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem.* **2012**, *10*, 5753–5755.

3.1.2.2.4. Metal-catalyzed substitutions

This strategy has not received much attention comparing to the aforementioned, but, anyway, two noteworthy examples have been reported in literature.

In 2008, Zhang and co-workers described the *Z*-selective cyclopropanation of olefins with α-nitrodiazo acetates, employing a chiral porphiryn-Co^{II} complex as catalyst (Table 37).[294] The reaction rendered cyclopropanated quaternary α-amino acid derivatives in excellent diastereo- and enantioselectivities in the case of aryl and alkyl olefins (entries 1–2), but poor diastereoselectivity and just good enantioselectivity in the case of acrylates and vinyl amides (entries 3–5).

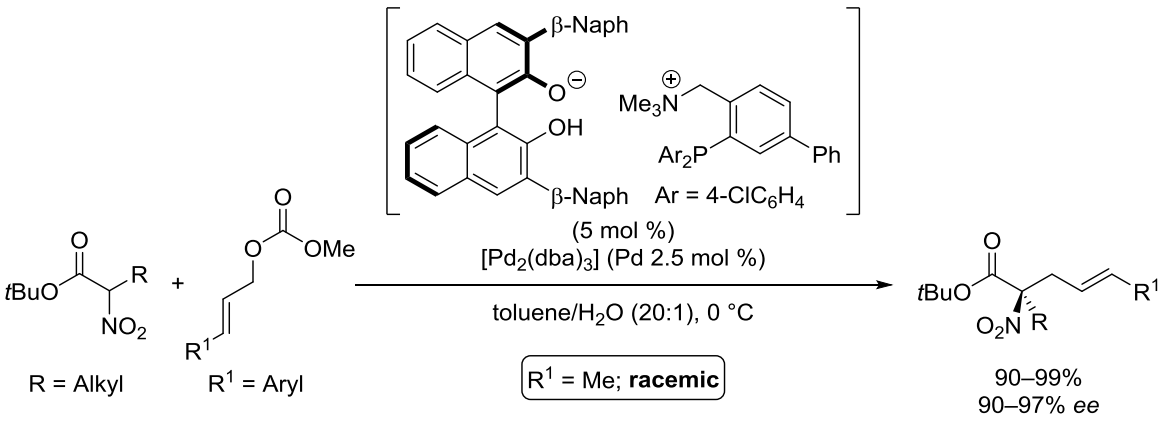
Table 37.



Entry	R^1	R^2	Yield (%)	*Z*/*E*	*ee* (%)
1	Et, *t*Bu	Aryl	51–93	90:10–99:1	82–95
2	*t*Bu	Alkyl	43–45	92:8	80–86
3	Et	CO_2Me	42	53:47	88
4	Et	CO_2Et	62	56:44	88
5	Et	NMe_2	92	63:37	75

An interesting example of Pd-catalyzed nitroacetate allylation was described by Ooi's research group in 2012,[295] where the enantiocontrol was induced by a chiral binaphtholate anion paired with an achiral cationic ammonium-phosphine hybrid ligand (Scheme 72). Allylation of γ-substituted allylic carbonates occurred in excellent yields and enantioselectivities, although no enantiocontrol was obtained when methyl allyl carbonate was tested.

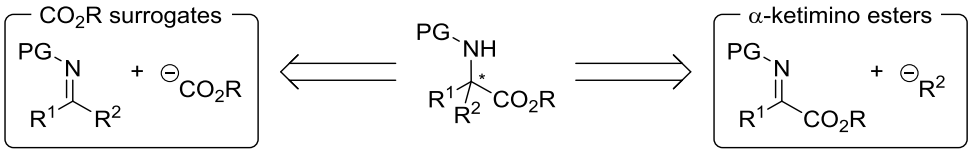
[294] Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8460–8463.
[295] Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *Nat. Chem.* **2012**, *4*, 473–477.



Scheme 72.

3.1.2.3. **Nucleophillic additions to ketimines**

Another well known strategy for the asymmetric construction of α,α-disubstituted α-amino acid derivatives is the addition of different nucleophiles to ketimines. Two different approaches can be employed for this purpose: First, the asymmetric nucleophilic addition of carboxylate anion surrogates (e.g. cyanide) which upon simple transformations could lead to the desired carboxylic acid moiety. The second would involve the asymmetric addition of a given nucleophile to an α-substituted α-ketiminoester, affording the desired amino acid derivative in a direct manner Scheme 73.



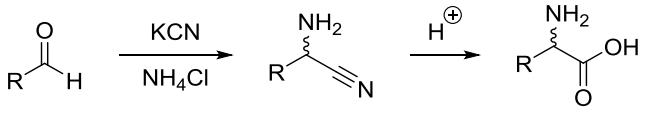
Scheme 73.

3.1.2.3.1. Addition of carboxylate surrogates to ketimines

One of the most known reactions in organic chemistry belongs to this section. The Strecker reaction,[296] or cyanation of imines, is a widely used strategy for the obtention of α-amino acids, especially employing aldimines (Scheme 74).[297]

[296] a) Strecker, A. *Ann. der Chemie und Pharm.* **1850**, *75*, 27–45. b) Strecker, A. *Ann. der Chemie und Pharm.* **1854**, *91*, 349–351.

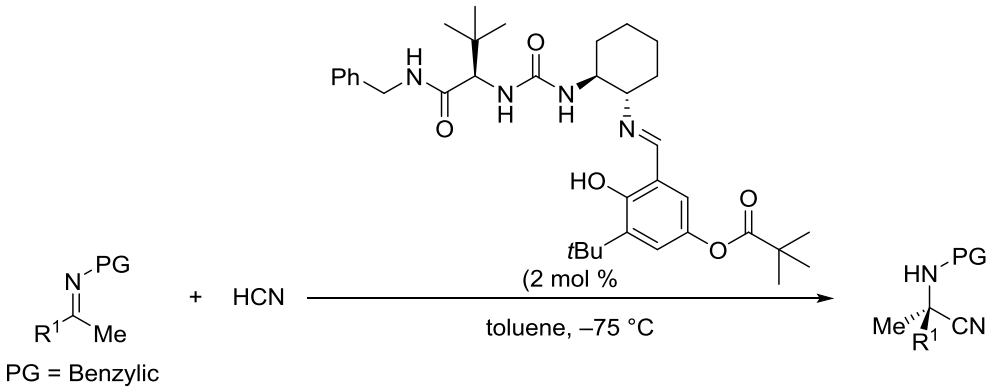
[297] For recent reviews on the asymmetric Strecker reaction, see: a) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947–6983. b) Cai, X. H.; Xie, B. *Arkivoc* **2014**, 205–248. For a leading book on the topic, see: c) Masakatsu Shibasaki et al., *The Catalytic Asymmetric Strecker Reaction* (John Wiley & Sons, Inc.) 2008. For a study on the Strecker reaction mechanism, see: d) Zhang, G.-W.; Zheng, D.-H.; Nie, J.; Wang, T.; Ma, J.-A. *Org. Biomol. Chem.* **2010**, *8*, 1399–1405.



Scheme 74. Scheme of the original Strecker reaction.

Thus, there are fewer successful reports for the more hindered ketimines, presumably due to competitive enamine formation in the case of aliphatic imines. The first Strecker reaction with ketimines was perfomed by Jacobsen employing a urea-Schiff base catalyst (Table 38).[298] Aryl ketimines rendered excellent yields and enantioselectivities, generally, except for the ketimine bearing the *ortho*-bromo aryl substituent (entry 2). Aliphatic but bulky substituent tert-butyl group afforded excellent yield but moderately good enantioselectivity (entry 3). Additionally, extremely dangerous cyanhydric acid was employed, a strategy nowadays avoided by most of research groups.

Table 38. Hydrocyanation of ketimines using cyanhydric acid.



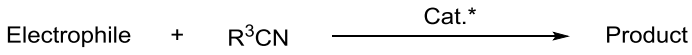
Entry	R^1	Yield (%)	*ee* (%)
1	Aryl	97–99	88–95
2	2-Br-C_6H_4	45	42
3	*t*Bu	98	70

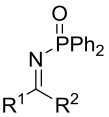
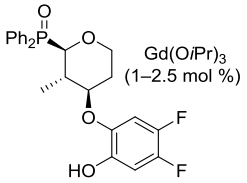
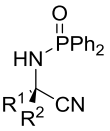
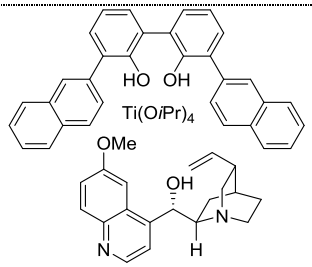
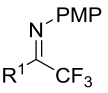
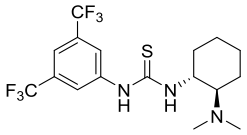
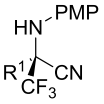
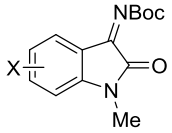
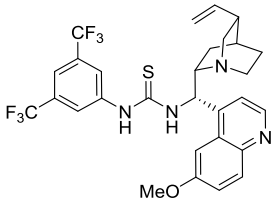
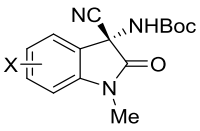
The other examples depicted in Table 39 are the most recent examples of cyanation of ketimines reported to date, employing TMSCN (trimethylsilyl cyanide) as cyanide source in all cases (entries 2–5).[299]

[298] Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867–870.

[299] a) Shibasaki, M.; Kanai, M. *Org. Biomol. Chem.* **2007**, *5*, 2027–2039. b) Wang, J.; Wang, W.; Li, W.; Hu, X.; Shen, K.; Tan, C.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 11642–11659. c) Enders, D.; Gottfried, K.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 3147–3152. d) Wang, D.; Liang, J.; Feng, J.; Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548–558. For a recent example of hidrocyanation employing chiral inductors, see: e) Netz, I.; Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2015**, *80*, 6864–6869.

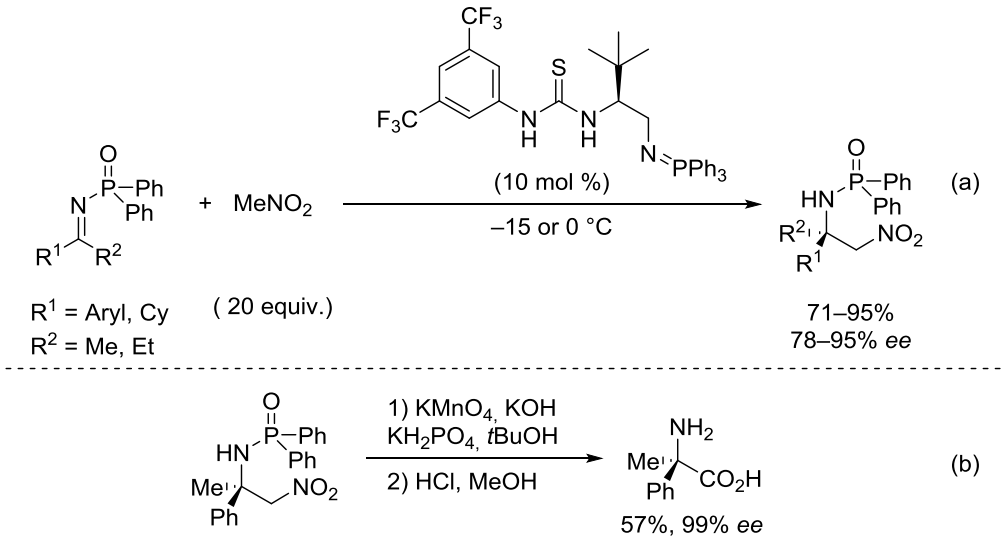
Table 39.



	Electrophile	R^3	Cat.*	Prod.	Results	Ref.
1	 R^1 = Alkyl, Aryl R^2 = Me, Et	TMS	 (2–5 mol %)		73–99% 74–99% *ee*	299a
2	 R^1 = Alkyl, Aryl R^2 = Alkyl, Aryl PG = Ts	TMS, CO_2Et	 (10 mol %)		95–99% 8–99% *ee*	299b
3	 R^1 = Alkyl, Aryl	TMS	 (5 mol %)		5–27 days 83–95% 25–99% *ee*	299c
4	 X = Br, F, Cl, Me, OMe, OCF_3, NO_2	TMS	 (10 mol %)		60–98% 78–98% *ee*	299d

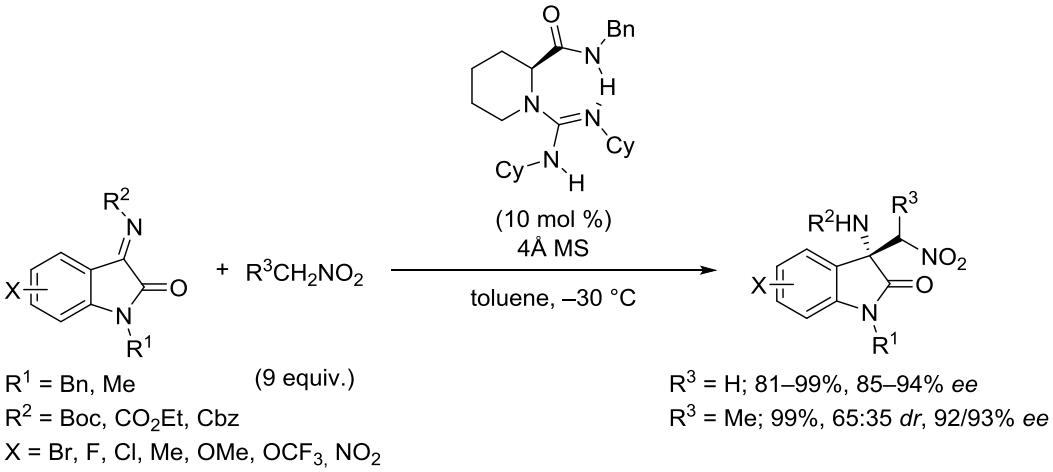
Recently, Dixon and co-workers reported a new strategy to obtain α,α-disubstituted α-aminoacids.[300] Through addition of nitromethane to ketimines and employing bifunctional thiourea-based iminophosphorane catalysts (Scheme 75, equation a), very good to excellent yields and enantioselectivities were achieved, and amino acid derivatives were obtained after oxidative Nef reaction and subsequent *N*-deprotection (equation b).

[300] Núñez et al.see ref. 57 page 15.



Scheme 75.

To date, there is only another example in literature using this strategy, a chiral bifunctional guanidine-catalyzed enantioselective aza-Henry reaction of isatin-derived ketimines reported by Liu and Feng's group.[301] The reaction afforded very good to excellent yields and enatioselectivities in every case, although when nitroethane was tested the diastereoselectivity of the reaction was only moderate (Scheme 76).



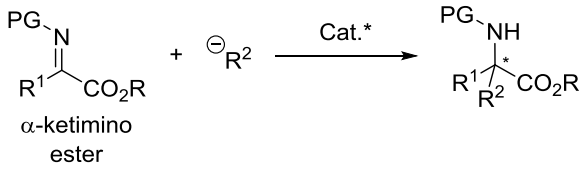
Scheme 76.

The results discussed above highlight the main limitations of the synthesis of quaternary amino acid derivatives via carboxylate addition to ketimines, namely the need of electron withdrawing groups in the ketimine, in order to increase its electrophilicity, or the use of strongly basic catalysts and great amounts of the nucleophile to increase the reactivity of the system.

[301] Fang, B.; Liu, X.; Zhao, J.; Tang, Y.; Lin, L.; Feng, X. *J. Org. Chem.* **2015**, *80*, 3332–3338.

3.1.2.3.2. Nucleophillic additions to α-ketimino esters

A variation of the strategy described above involves employing α-ketimino esters as acceptors for nucleophillic additions. As mentioned before, these acceptors are greatly activated by the effect of the electron withdrawing ester moiety. Thus, numerous examples concerning the use of α-ketimino esters through the reaction depicted in Scheme 77 have hitherto been reported, which have been comprehensively reviewed several times and will not be further discussed here.[302]



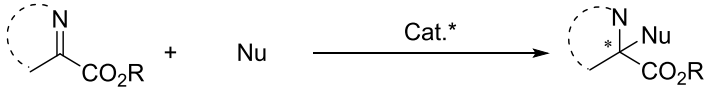
Scheme 77.

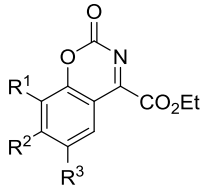
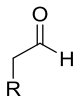
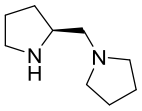
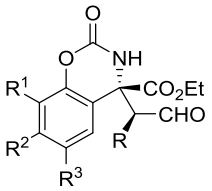
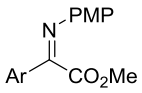
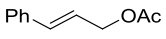
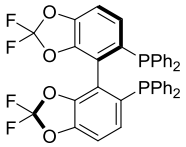
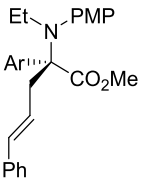
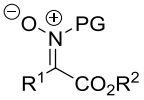
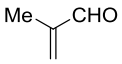
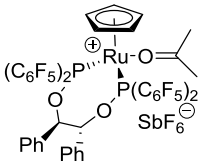
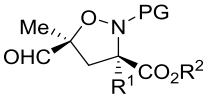
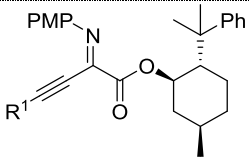
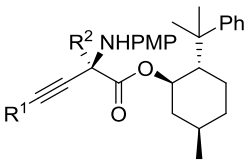
However, this strategy is still fully competitive, and new methodologies and variations are developed constantly. Table 40 illustrates the first example of the Mannich addition to α-ketimino esters reported by Jørgensen and co-workers in 2004, which occurred through enamine activation (entry 1), and the most recent examples involving ketimino esters reported from 2014 to date.[303]

[302] For reviews on the topic, see: ref. 257 page 101.

[303] a) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476–4478. b) Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2014**, *16*, 1948–1951. c) Selim, K. B.; Martel, A.; Laurent, M. Y.; Lhoste, J.; Py, S.; Dujardin, G. *J. Org. Chem.* **2014**, *79*, 3414–3426. For the diastereoselective alkyl addition to β,γ-alkynyl-α-imino esters with zinc complexes, see: d) Hatano, M.; Yamashita, K.; Mizuno, M.; Ito, O.; Ishihara, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 2707–2711. For a racemic Brønsted acid–catalyzed Friedel–Crafts reaction of indoles to α-ketimino esters, see: e) Yang, J.-H.; Lou, Q.-X.; Chen, Y.-X.; Tang, K.-K. *Synth. Commun.* **2015**, *45*, 1887–1892.

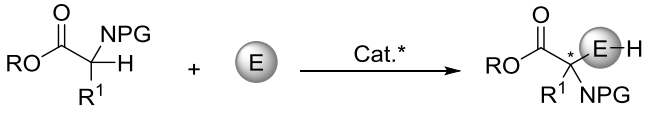
Table 40.



	Ketimine	Nu	Cat.*	Prod.	Results	Ref.
1	 R^1, R^2, R^3 = H, Me, OMe R^2 = Me	 R = Alkyl	 (5 mol %)		45–98% 4:1–20:1 42–95% *ee*	303a
2		1) EtMgBr 2) 	$[\eta\text{-}C_3H_5PdCl]_2$ (7.5 mol %)  (4.9 mol %)		72–89% 74–92% *ee*	303b
3	 R^1 = Me, Et, *n*Pr R^2 = Me, Et, *t*Bu PG = Bn, Me		 (10 mol %)		42–99% 70:30–99:1 *endo/exo* 79–92% *ee*	303c
4	 R^1 = TBS, Ph	R^2MgCl R^2 = Alkyl	$ZnCl_2$ (1.1 equiv) $TMSCH_2MgCl$ (2.2 equiv)		60–98% >99:1 *dr*	303d

3.1.2.4. **Amino acid-derived nucleophiles for *C-C* bond formation**

The most employed strategy for the synthesis of α,α-disubstituted α-amino acid derivative synthesis is the use of α-monosubstituted α-amino acids or surrogates as nucleophiles (Scheme 78).



Scheme 78.

In this section, we will focus on the main nucleophile types used for this task, which are Schiff bases,[304] α-(iso)cyano acetates and azlactones.

3.1.2.4.1. Schiff bases

It is more than two decades since a quaternary centre was first generated from a Schiff base derived from the *tert*-butyl ester of alanine (Figure 34), employing phase-transfer catalysis.[305]

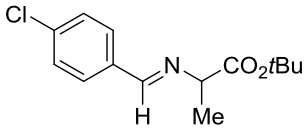


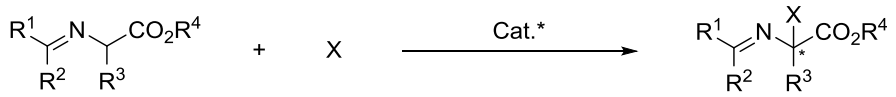
Figure 34. Alanine Schiff base.

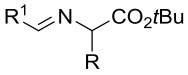
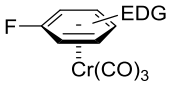
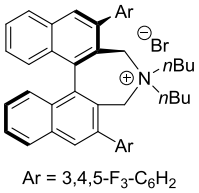
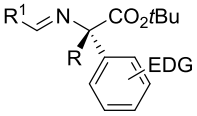
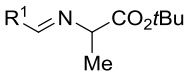
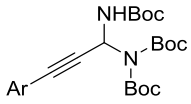
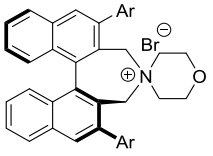
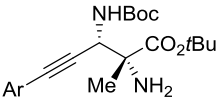
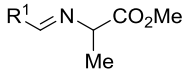
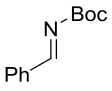
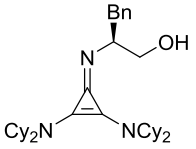
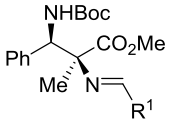
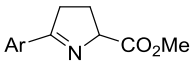
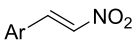
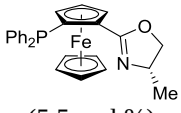
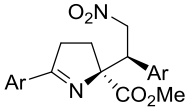
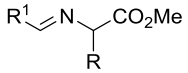
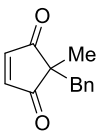
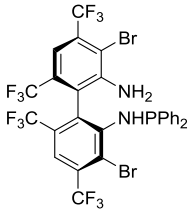
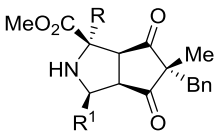
Ever since, numerous examples employing this strategy have appeared, and have been extensively gathered in several reviews.[306] For years, PTC has been the tactic of choice to perform asymmetric alkylations on this substrates, being Maruoka's group one of the most prolific in this field.[307] Additionally, the most recent example of Schiff base PTC arylation reaction belongs to the same research group (Table 41, entry 1).[308] The other most recent reactions performed with Schiff bases to date are a PTC catalyzed *syn*-Mannich type reaction by Maruoka (entry 2),[309] a thiourea-based Brønsted base catalyzed

[304] For a review on Hugo Schiff and Schiff bases, see: Tidwell, T. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 1016–1020.
[305] O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591–594.
[306] For reviews on the topic, see: ref. 257 page 101.
[307] For examples of PTC alkylation of Schiff bases employing different alkylating agents, see: a) Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900–4904. b) Maruoka, K. *Chem. Rec.* **2010**, *10*, 254–259. c) Maruoka, K. *Pure Appl. Chem.* **2012**, *84*, 1575–1585. d) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. *Asian J. Org. Chem.* **2014**, *3*, 433–436.
[308] Shirakawa, S.; Yamamoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 838–840.
[309] Kano, T.; Kobayashi, R.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 8471–8474.

syn-Mannich reaction (entry 3),[310] a Cu/Ag catalyzed Michael reaction (entry 5),[311] and a Ag catalyzed 1,3-dipolar cycloaddition (entry 5).[312] It is remarkable, that when Schiff bases are used for the formation of α,α-disubstituted α-amino acid derivatives, a simple hydrolysis of the azomethine group gives access to the free amino moiety, as shown in entry 2.

Table 41.



	Schiff base	X	Cat.*	Prod.	Results	Ref.
1	 R^1 = 4-ClC_6H_4 R = Alkyl	 EDG = H, Me, OMe, OEt, SMe, NMe_2	 Ar = 3,4,5-F_3-C_6H_2 (10 mol %)		51–78% 88–99% *ee*	308
2	 R^1 = 2-thienyl	1)  2) HCl, EtOAc, r.t.	 Ar = 3,5-(3,5-$(CF_3)_2$-$C_6H_3)_2$-C_6H (5 mol %)		50–70% >20:1 *dr* 90–91% *ee*	309
3	 R^1 = 4-ClC_6H_4		 (20 mol %)		94% 64:36 *dr* 63/44% *ee*	310
4			CuOAc (or AgOAc) (5 mol %)  (5.5 mol %)		69–86% 74:26–92:8 *syn/anti* 94–99% *ee* (1:99 *anti* with AgOAc)	311
5	 R^1 = Aryl R = Me, Bn		 AgOAc/L (5 mol %)		88–93% >20:1 *dr* 94–99% *ee*	312

[310] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799–11802.
[311] Koizumi, A.; Kimura, M.; Arai, Y.; Tokoro, Y.; Fukuzawa, S. *J. Org. Chem.* **2015**, *80*, 10883–10891.
[312] Liu, H.-C.; Liu, K.; Xue, Z.-Y.; He, Z.-L.; Wang, C.-J. *Org. Lett.* **2015**, *17*, 5440–5443.

3.1.2.4.2. α-(Iso)cyanoacetates

Other commonly used nucleophiles to access α-amino acid derivatives are the structural isomers α-isocyanoacetates and α-cyanoacetates (Figure 35).

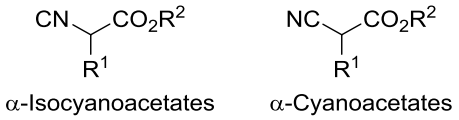
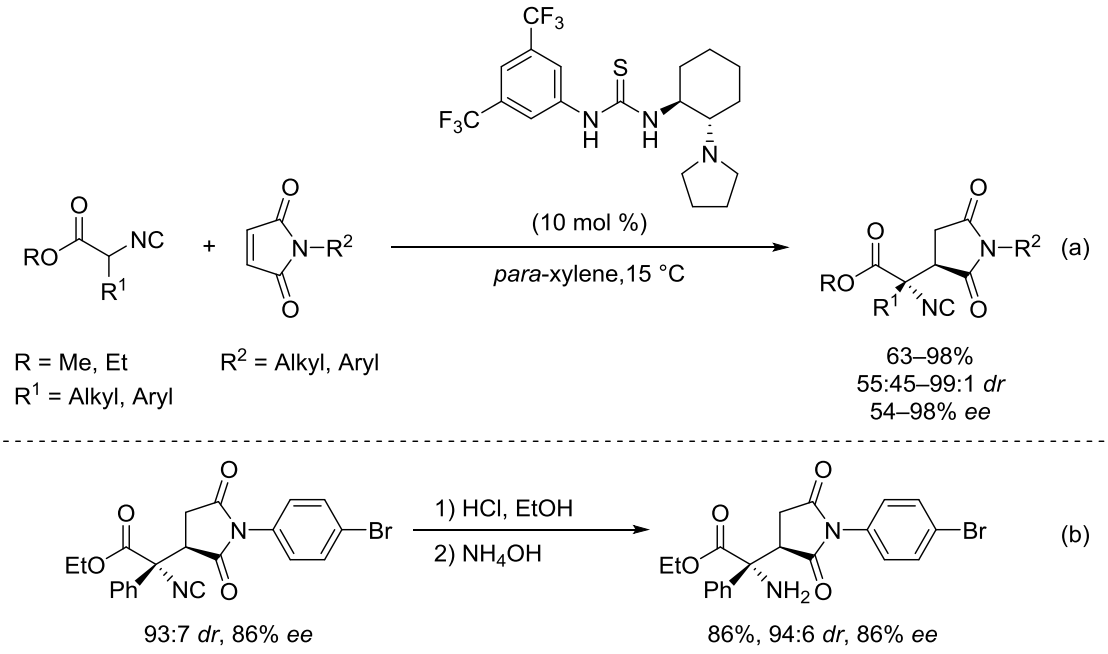


Figure 35.

In contrast to Schiff bases, it was not until 2012 when the research group of Wang and Xu introduced α-isocyanoacetates as amino acid surrogates for the enantioselective synthesis of quaternary α-amino acids.[313] Michael addition to maleimides was performed in presence of a thiourea-based Brønsted base catalyst, affording the conjugate adducts in good to excellent yields, and diastereo- and enantioselectivity (Scheme 79, equation a). Additionally, acidic hydrolysis of one of the adducts provided the quaternary α-amino ester in very good yield and with retention of stereochemistry (equation b).

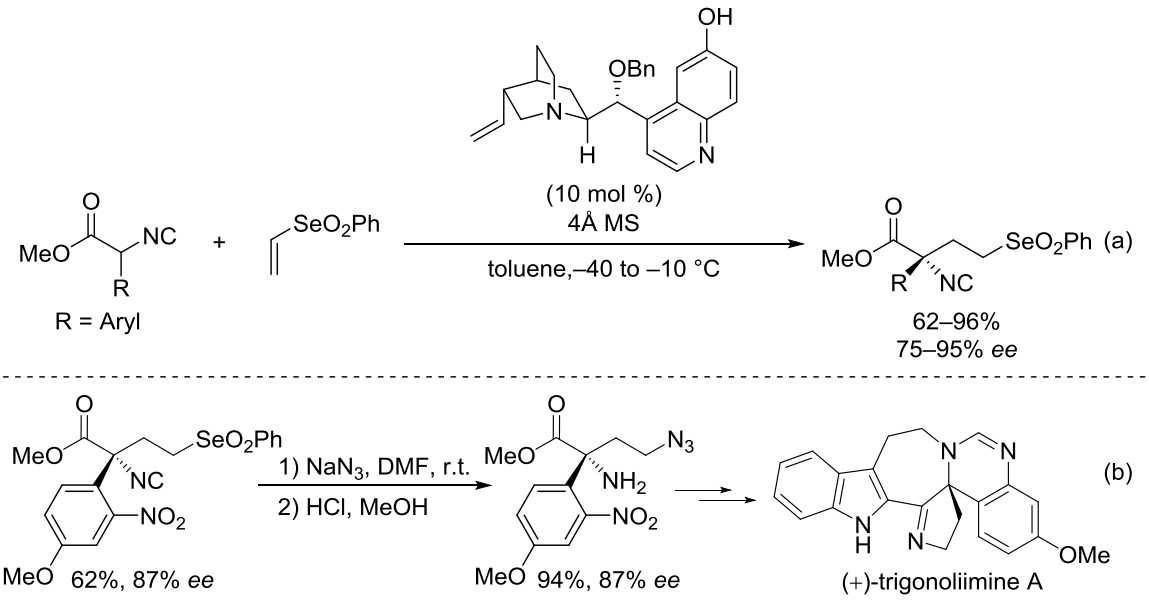


Scheme 79.

Zhou and co-workers reported the highly enantioselective Michael addition of α-aryl α-isocyanoacetates to phenyl vinyl selenone in 2013.[314] The Brønsted base-catalyzed reaction rendered the desired adducts in good to excellent yields and enantioselectivities

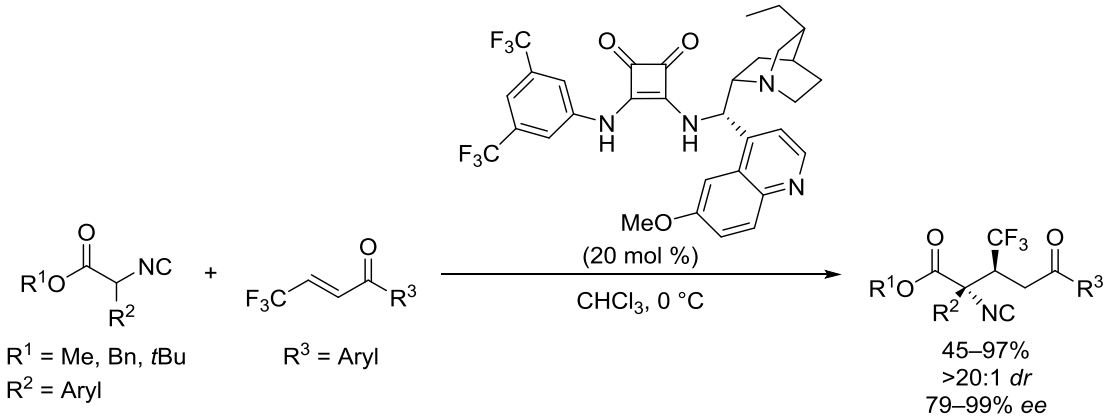
[313] a) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947–2953. For the squaramide-catalyzed version of the reaction, see: b) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**, *69*, 10763–10771.
[314] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.

(Scheme 80, equation a). Simple elaboration of the product afforded the quaternary α-amino ester needed as building block for the synthesis of (+)-trigonoliimine A (equation b).



Scheme 80.

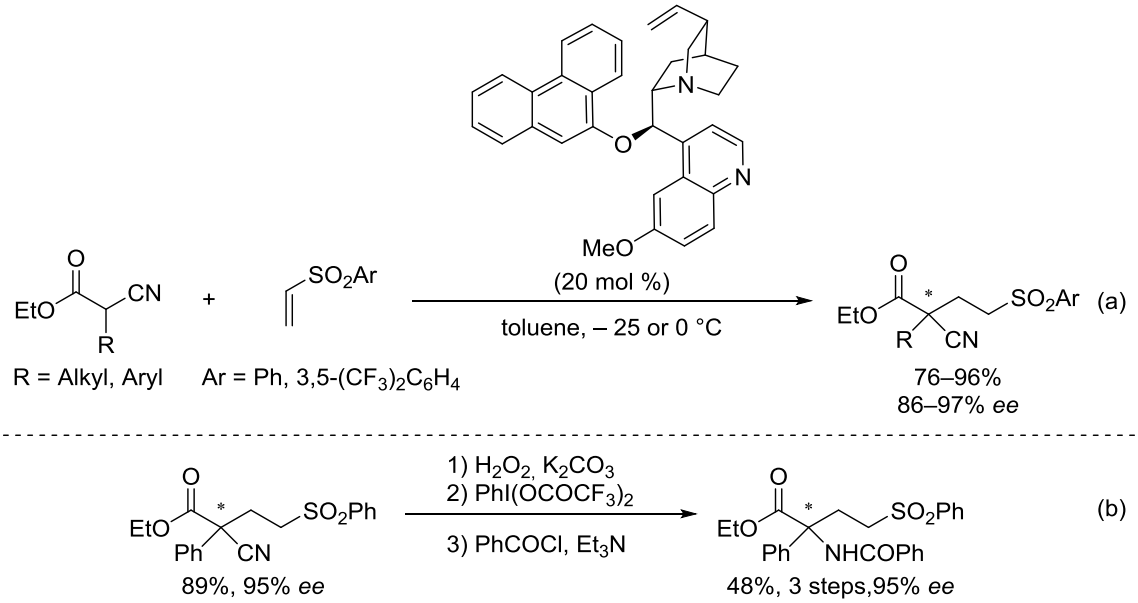
To date, just another example of the use of isocyanoacetates as pronucleophiles has been reported,[315] which consist in the squaramide-catalyzed asymmetric Michael addition of α-isocyanoacetates to enones (Scheme 81). Moderate to excellent yield and enantioselectivities and excellent diastereoselectivities were obtained with α-aryl cyanoacetates and aryl substituted β-trifluoromethylated enones, but no reaction occurred when α-alkyl cyanoacetates or alkyl substituted β-trifluoromethylated enones were employed.



Scheme 81.

[315] Zhao, M.-X.; Zhu, H.-K.; Dai, T.-L.; Shi, M. *J. Org. Chem.* **2015**, *80*, 11330–11338.

Despite α-cyanoacetates have commonly used to access β-amino acids,[316] they can also be employed to obtain quaternary α-amino acids, as it was reported by Deng's research group in 2005.[317] They described the conjugate addition of ethyl cyanoacetates to vinyl sulfones catalyzed by *Cinchona* alkaloids, affording the reaction adduct in very good to excellent yields and enantioselectivities (Scheme 82, equation a)). Elaboration of these products led to enantiopure quaternary α-amino acids, although the process required three steps, and the overall yield was significantly lowered (equation b).



Scheme 82.

3.1.2.4.3. Azlactones

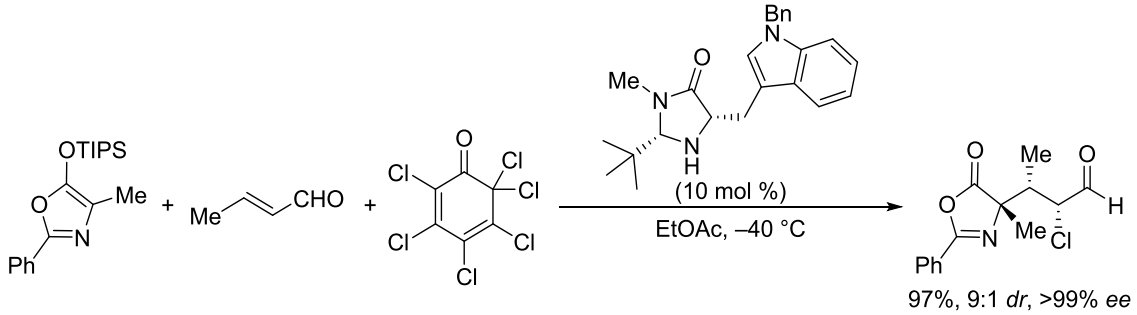
The use of azlactones or 4*H*-oxazol-5-ones, already mentioned in the introductory part of this work (page 43), is a complementary strategy to obtain α,α-disubstituted α-amino acids.

The first example of the utilization of these kind of heterocycles as C-4 selective pronucleophiles in organocatalysis came from MacMillan and co-workers in 2005, who described only one example of iminium-enamine cascade Michael addition/chlorination

[316] For the use of α-cyanoacetates for the synthesis of β-amino acids, see: Liu, T.-Y.; Li, R.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Eur. J.* **2007**, *13*, 319–327. and references therein.

[317] a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949. For previously mentioned examples of the asymmetric α-amination of cyanoacetates, see: b) see ref. 267 page 5 and reference therein. For a recent example of diastereoselective Pd-catalyzed allylic alkylation of α-cyanoacetates, see: c) Trost, B. M.; Mahapatra, S.; Hansen, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6032–6036. For an early example of Rh catalyzed Michael addition of cyanoacetates to obtain quaternary α-amino acids, see: d) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439–4454.

of a preactivated azlactone as silylenol ether to crotonaldehyde, employing an imidazolidinone as catalyst (Scheme 83).[318]



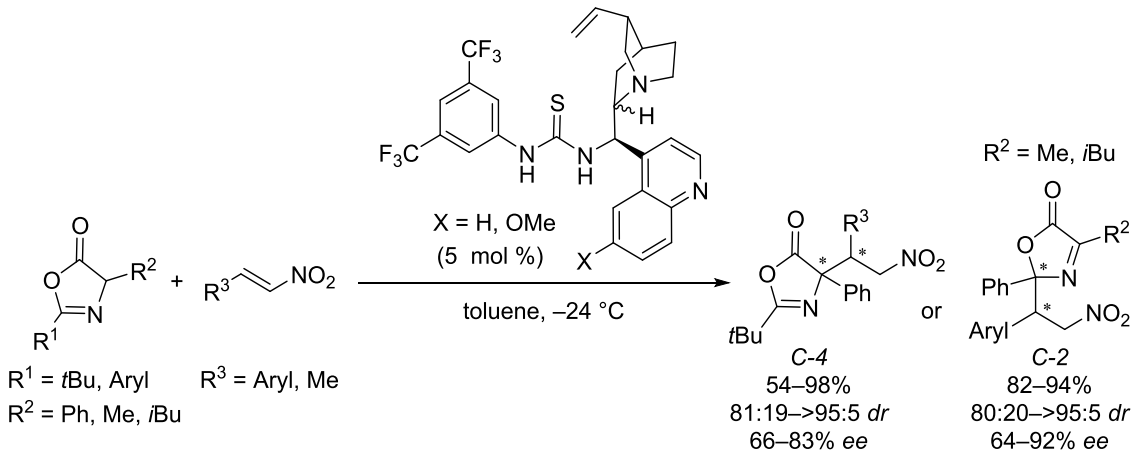
Scheme 83. Example of indirect Michael reaction of azlactones with enals.

In addition to this example, the first successful methodology for the direct Michael addition of azlactones to enals was developed again by Jørgensen's research group, using iminium ion activation, who observed only C-4 addition in every case.[319] Soon after, the same group reported the first oxazol-4(5*H*)-one addition to nitroolefins, where regiochemistry of the reaction was rationalized.[320] Generally, the relative nucleophilicities of these two positions were greatly affected by several factors, including substituents on the azlactone ring, particularly R^1, electrophiles, catalysts, and reaction conditions. As depicted in Scheme 84, aryl substituents at C-2 favoured attack from this carbon, while hindered and electron donating aliphatic ones (i.e. *tert*-butyl) directed C-4 attack (entries 1–2 vs. 3–4). Nevertheless, thiourea-based bifunctional Brønsted bases conducted the Michael reaction with good to excellent yields, very good diastereoselectivity and moderate to very good enantioselectivity in both cases.

[318] Huang et al.ref. 44 page 12. For the opposite strategy where azlactones are used ad electrophiles, see: b) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032–9036.

[319] a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037. For subsequent examples of Michael addition of azlactones to enals using iminium ion activation, see: b) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian J.* **2009**, *4*, 246–249. c) Companyó et al.ref 119a page 32. d) Dell'Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063–8070.

[320] a) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958–10966. For a regio- and diastereoselective C-4 Michael addition of azlactones to nitroolefins with triethylamine, 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 only example of Michael addition of dioxolanes to nitroolefins with bifunctional thioureas, see: c) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107–2110.



Entry	R^1	R^2	R^3	Regioselectivity	Yield (%)	*dr*	*ee* (%)
1	Ph	*i*Bu	Ph	C-2	93	80:20	65
2	Ph	Me	Ph	C-2	82	93:7	66
3	*t*Bu	Ph	Ph	C-4	65	>95:5	83
4	*t*Bu	Ph	Me	C-4	88	95:5	66

Scheme 84. Represenative examples of Michael addition of azlactones to nitroolefins.

During the last decade, multiple examples of organocatalyzed Mannich,[321] aldol,[322] and conjugate additions[323] of azlactones have been reported employing different electrophiles and activation modes, obtaining both C-4 and C-2 selectivities.[324] Table 42

[321] For the C-4 selective anti-Mannich reaction of 2-aryl azlactones with aliphatic imines employing chiral betaines, see: a) Zhang, W.-Q.; Cheng, L.-F.; Yu, J.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 4085–4088. For the C-4 selective syn-Mannich reaction of azlactones with *N*-tosyl imines employing chiral phosphate-Ag, see: b) Shi, S.-H.; Huang, F.-P.; Zhu, P.; Dong, Z.-W.; Hui, X.-P. *Org. Lett.* **2012**, *14*, 2010–2013. For the C-4 selective anti-Mannich reaction of azlactones with *N*-mesyl imines employing chiral phosphines, see: c) Ávila, E. P.; Justo, R. M. S.; Gonçalves, V. P.; Pereira, A. A.; Diniz, R.; Amarante, G. W. *J. Org. Chem.* **2015**, *80*, 590–594. For the C-4 selective syn-Mannich reaction of azlactones with *N*-sulfenyl imines employing thiourea-based bifunctional Brønsed bases, see: d) Žabka, M.; Malastová, A.; Šebesta, R. *RSC Adv.* **2015**, *5*, 12890–12893.

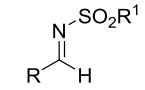
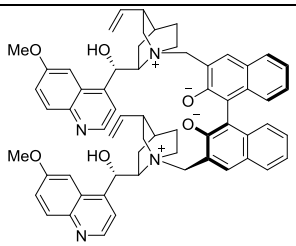
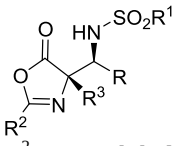
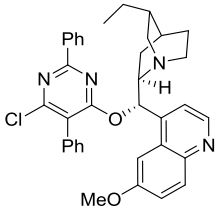
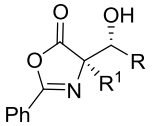
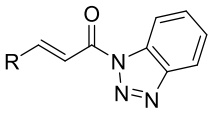
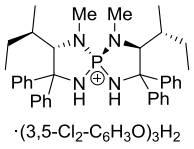
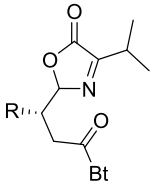
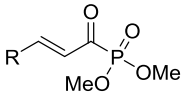
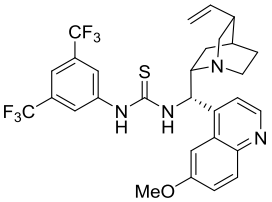
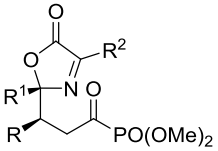
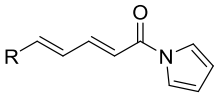
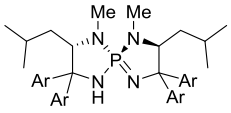
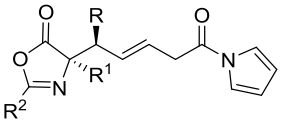
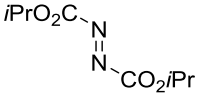
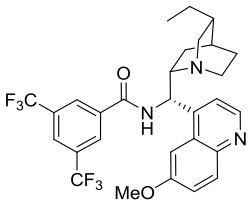
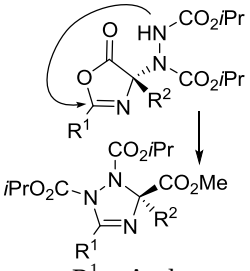
[322] For the Brønsted base catalyzed C-4 selective aldol reaction of 2-phenyl azlactones to aliphatic aldehydes, see: b) Zheng, Y.; Deng, L. *Chem. Sci.* **2015**, *6*, 6510–6514.

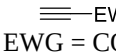
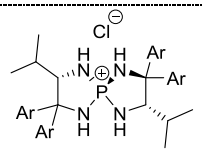
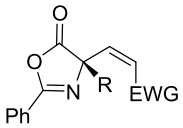
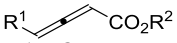
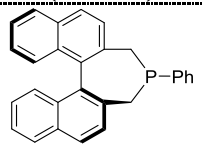
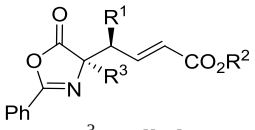
[323] For an oustanding C-2 selective Michael addition of 2-unsubstituted azlactones to α,β-unsaturated acylbenzotriazoles employing phosphonium ion PTC, see: a) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120–123. For the C-2 selective Michael addition of 2-aryl azlactones to α,β-unsaturated acyl phosphonates with bifunctional thioureas, see: b) Jiang, H.; Paixão, M. W.; Monge, D.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 2775–2783. For the C-4 selective 1,6- and 1,8-additions of 2-aryl azlactones to dienyl and trienyl acylpyrroles with chiral triaminoiminophosphoranes, see: c) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370–19373. For the C-4 selective Michael addition/aromatization of azlactones to azodicarboxylates to obtain pyrazolones, see: d) Geng, Z.-C.; Chen, X.; Zhang, J.-X.; Li, N.; Chen, J.; Huang, X.-F.; Zhang, S.-Y.; Tao, J.-C.; Wang, X.-W. *Eur. J. Org. Chem.* **2013**, 4738–4743. For the C-4 selective Michael addition of 2-aryl azlactones to electron-deficient triple bonds with iminophosphoranes, see: e) Uraguchi, D.; Ueki, Y.; Sugiyama, A.; Ooi, T. *Chem. Sci.* **2013**, *4*, 1308–1311. For a recent phosphine catalyzed C-4 selective Michael addition of 2-*tert*-butyl azlactones to allenoates, see: f) Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438–9442.

[324] For a recent example of conjugate addition of azlactones to allenoates with C-4/C-2 selectivity, see: Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265–271.

shows the most common substrate acceptors employed in conjugate additions with azlactones.

Table 42. Diverse electrophiles employed with azlactones as nucleophiles.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Alkyl R^1 = 4-*i*PrC_6H_4	 (10 mol %)	 R^2 = 2-naphthyl R^3 = Alkyl	76–99% 2:1–7:1 *dr* 96–99% *ee*	321a
2	 R = Alkyl	 (15 mol %)	 R^1 = Alkyl	83–98% 91:9–98:2 *anti/syn* 88–95% *ee*	322
3	 R = Aryl, alkyl	 ·(3,5-Cl_2-$C_6H_3O)_3H_2$ (1 mol %)	 R = Aryl, alkyl	90–98% >20:1 *dr* 93–98% *ee*	323a
4	 R = Alkyl	 (10 mol %)	 R^1 = Aryl R^2 = *i*Bu, *i*Pr	50–79% 82–99% *ee*	323b
5	 R = Alkyl, Aryl, (*E*)-R-CH_2=CH_2	 Ar = 4-FC_6H_4 (5 mol %)	 R^1 = Alkyl R^2 = 2,6-$(MeO)_2C_6H_3$	84–99% >20:1 *dr* 90–98% *ee*	323c
6		 (10 mol %)	 R^1 = Aryl R^2 = Alkyl	42–95% 81–93% *ee*	323d

7	 EWG = CO_2Me, CN	 Ar = pCF_3-C_6H_4 (5 mol %)	 R = Aryl, Bn, *i*Bu	78–95% 1:10–1:20 *E/Z* 56–90% *ee*	323e
8	 R^1, R^2 = Alkyl, alkenyl	 (5 mol %)	 R^3 = Alkyl	83–98% 91:9–98:2 *anti/syn* 88–95% *ee*	323f

Organocatalytic asymmetric Michael addition to enones, however, was not developed until 2013.[325] Table 43 below gathers all examples reported to date.

Amarante's research group presented the first organocatalytic version of the reaction, and, although the catalyst was racemic, excellent diastereocontrol was gained.[326] Total enantiocontrol was achieved by Wang and co-workers, employing β-substituted enones with a strong inductive electron withdrawing group (i.e. trichloromethyl), in order to compensate the low reactivity that this electrophiles usually show.[327] Almost simultaneously, our group developed the squaramide-catalyzed addition of azlactones to α'-silyloxy enones to obtain highly malleable adducts with excellent enantioselectivities.[328] Recently, Wang and co-workers demonstrated that a hydroxy group in the *ortho* position of the β-aryl group of chalcones could direct the azlactone addition to take place just with C-2 selectivity.[329]

[325] For several examples of successful Michael addition of azlactones to enones employing bispalladacycles, by Peters and co-workers, see: a) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* **2010**, *132*, 12222–12225. b) Weber, M.; Frey, W.; Peters, R. *Chem. Eur. J.* **2013**, *19*, 8342–8351. and references therein.

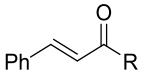
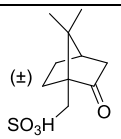
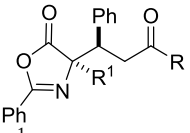
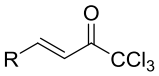
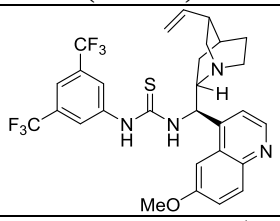
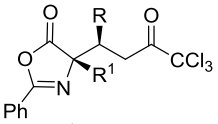
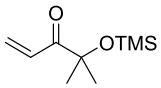
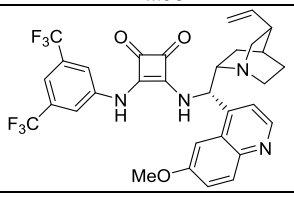
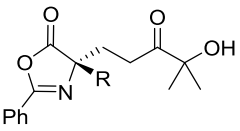
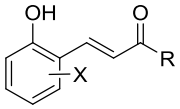
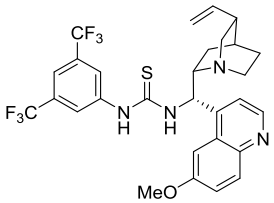
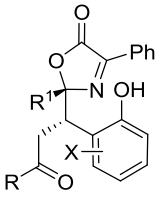
[326] a) Ávila, E. P.; de Mello, A. C.; Diniz, R.; Amarante, G. W. *Eur. J. Org. Chem.* **2013**, *2013*, 1881–1883. For a Mannich addition of 2-phenyl azlactones to aryl imines performed by the same group, see: b) Ávila et al.

[327] Zhang, J.; Liu, X.; Wu, C.; Zhang, P.; Chen, J.; Wang, R. *Eur. J. Org. Chem.* **2014**, *32*, 7104–7108.

[328] Badiola et al.see ref. 88 page 24.

[329] Zhang, S.-Y.; Ruan, G.-Y.; Geng, Z.-C.; Li, N.-K.; Lv, M.; Wang, Y.; Wang, X.-W. *Org. Biomol. Chem.* **2015**, *13*, 5698–5709.

Table 43. Michael addition of azlactones to enones. (R^1, R^2, R^3 = Alkyl, Aryl; X = H, Me, MeO, Cl)

	Electrophile	Catalyst	Product	Results	Ref.
1	 R = Alkyl	 (7 mol %)	 R^1 = Me, Bn, *i*Bu	53–80% >20:1 *dr*	326a
2	 R = Aryl, Me		 R^1 = Alkyl	58–85% 2:1–20:1 *dr* 63–99% *ee*	327
3			 R = Ph, *i*Pr, *i*Bu, Bn	71–77% 88–92% *ee*	328
4	 R = Aryl X = Cl, Me, MeO, H		 R^1 = Aryl, *t*Bu	54–99% >20:1 *dr* 72–99% *ee*	329

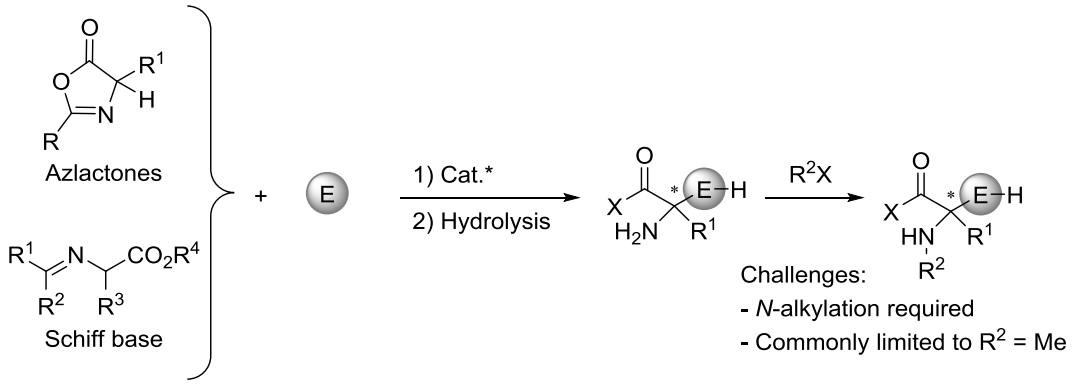
3.2. **Michael addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins**

3.2.1. **Working hypothesis and synthetic plan**

The continuous interest in quaternary α-amino acids (page 100) has prompted the apparition of many methods for their stereoselective preparation, although catalytic approaches still remain underdeveloped.[330] As mentioned in the introduction of this chapter, one of the most employed strategies to access quaternary *NH* α-amino acids consists in the α-functionalization of a nucleophilic template, e.g. Schiff base or azlactone, and subsequent hydrolysis (Scheme 85).[331] However, the majority of these methods are unable to afford the *N*-substituted analogues directly,[332] and an additional *N*–alkylation process is required.[333] This represents a major drawback, since *N*- alkyl α-amino acid-derived com-

[330] For reviews on the topic, see: ref. 257 page 2.
[331] Fisk et al.see ref. 5a page 7.
[332] For rare examples, see: ref. 6 page 7.
[333] For the synthetic preparation of *N*-methyl α-amino acids, see: Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2004**, *104*, 5823–5846.

pounds are potential therapeutic candidates due to their comparatively higher lipophilicity and membrane permeability.'[334]



Scheme 85.

Thus, we thought that 1*H*-imidazol-4(5*H*)-ones might serve as appropriate templates for addressing this deficiency (Figure 36a). First, because the *N*R^2 group would be easily pre-installed; second, base-catalyzed enolization appeared to be suitable due to the aromaticity of the formed enolate; and finally, unlike azlactones and related heterocycles, the new template would not present the C-4/C-2 regioselectivity issue (Figure 36b, for more information, see page 126).

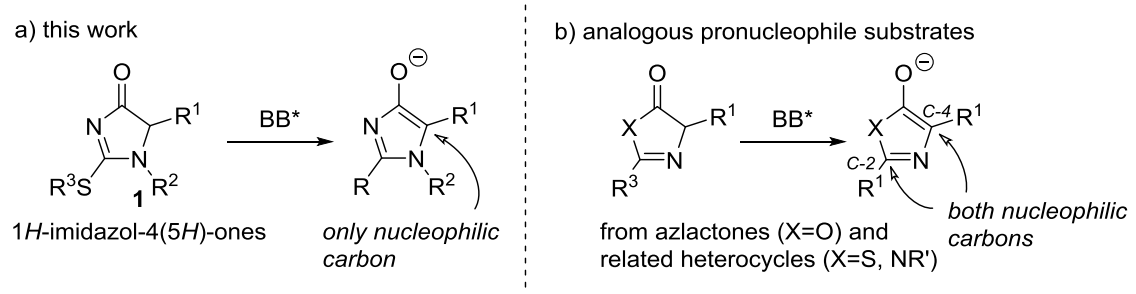


Figure 36.

Additionally, 1*H*-imidazol-4(5*H*)-ones are synthetic analogues to hydantoins, heterocycles of great therapeutical and biological interest.[335]

[334] For a recent application in medicinal chemistry and biochemistry, see: a) Kawakami, T.; Sasaki, T.; Reid, P. C.; Murakami, H. *Chem. Sci.* **2014**, *5*, 887–893. For a leading book on the subject, see: b) J. Deska, *Amino Acids, Peptides and Proteins in Organic Chemistry* (A. B. Hughes ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2010.

[335] For a review on the importance of hydantoins and their synthesis, see: a) Meusel & Gütschowand references therein. For a recent synthesis of aryl hydantoins, see: b) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8961–8965.

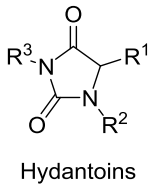
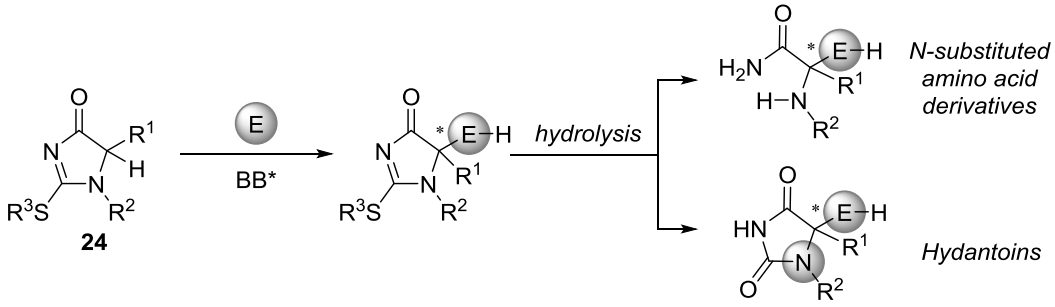


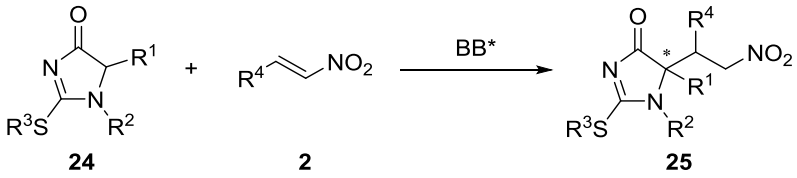
Figure 37.

Fulfilling this hypothesis would require effective control of the stereochemistry of the *C*-*C* bond-forming step and, as far as we knew, asymmetric reactions of 1*H*-imidazol-4(5*H*)-ones were unprecedented at the time of initiation of the work presented herein.



Scheme 86. General reaction of 1*H*-imidazol-4(5*H*)-ones with electrophiles and hydrolysis of the corrensponding adduct.

On this basis, 1*H*-imidazol-4(5*H*)-ones were chosen as pronucleophiles, and in a first instance nitroolefins were chosen as electrophiles.[336] This Michael acceptor added a diastereoselectivity issue to the previous challenges, due to the formation of two contiguous stereocentres during the reaction (Scheme 54).



Scheme 87. Proposed reaction for the first investigation.

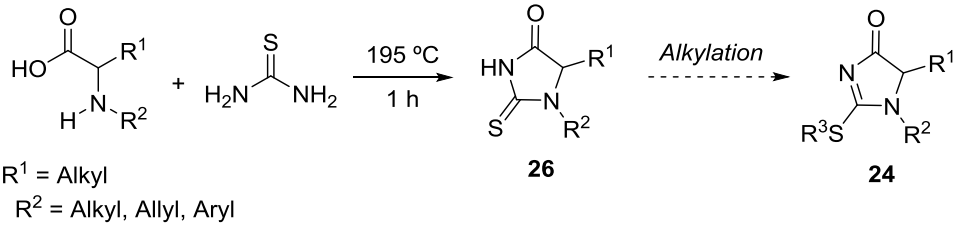
3.2.2. **Results and discussion**

3.2.2.1. **Synthesis of 1*H*-imidazol-4(5*H*)-ones**

First, we envisioned that the cyclization of *N*-substituted α-monosubstituted α-amino acids with thiourea followed by an *S*-alkylation of the formed thiohydantoin could

[336] For reviews on conjugate additions to nitroolefins, see: ref. 235 page 81.

yield the desired 1*H*-imidazol-4(5*H*)-ones (Scheme 88). The thiohydantoin derivatives were produced by heating a mixture of thiourea and an α-amino acid, which offered the advantages of simplicity, low cost, easy work-up and scalability.[337]

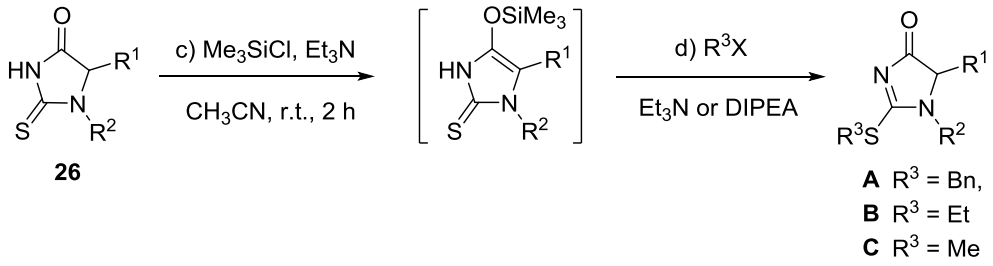


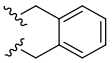
Scheme 88.

Nevertheless, the alkylation of thiohydantoins presented quite a challenge. First attempts using benzyl bromide and triethylamine afforded *O*-benzyl or *O,S*-dibenzyl products, due to the greater reactivity of enolate respect to the thiocarbonyl moiety. Well aware of this potential pitfall, the problem was promptly solved including a previous step, which consisted in the silylation of the carbonyl group (taking advantage of the *O*-*Si* affinity) and subsequent *S*-alkylation of the thiocarbonyl group, as shown in Table 44. It should be stressed that the yields reported in Table 44 correspond to two one-pot reaction steps, and are not optimized.

[337] Wang, Z. D.; Sheikh, S. O.; Zhang, Y. *Molecules* **2006**, *11*, 739–750.

Table 44.



Entry		R^1	R^2	R^3	Base	Yield (%)
1	**27A**	Me	Me	Bn	Et_3N	82
2	**28A**	Me	Bn	Bn	Et_3N	84
3	**29A**	Me	*i*Bu	Bn	Et_3N	73
4	**30A**	Me	Allyl	Bn	Et_3N	66
5	**31A**	Me	Ph	Bn	Et_3N	68
6	**32A**	Me	4-ClC_6H_4	Bn	Et_3N	83
7	**33A**	Me	3-$MeOC_6H_4$	Bn	Et_3N	85
8	**34A**	Bn	Me	Bn	Et_3N	74
9	**35A**	*n*Hex	Me	Bn	Et_3N	68
10	**36A**	*i*Bu	Me	Bn	Et_3N	71
11	**37A**	*i*Pr	Me	Bn	Et_3N	68
12	**38A**	-$CH_2CH_2CH_2$-		Bn	Et_3N	87
13	**39A**			Bn	Et_3N	78
14	**40A**	Bn	Bn	Bn	Et_3N	79
15	**27B**	Me	Me	Me	DIPEA	63
16	**27C**	Me	Me	Et	DIPEA	67

Once with the substrates of the initially proposed reaction in hand, we proceeded to test several Brønsted base catalysts in order to achieve successful direct asymmetric *C*-*C* bond forming reactions.

3.2.2.2. **Catalyst screening**

In order to check the validity of the initial hypothesis (Scheme 86), several classical Brønsted bases were evaluated for the reaction of the readily available 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** with the nitroolefin **2a** (Table 46). At the beginning of the study, some representative *Cinchona* alkaloids were explored, quinine, and $(DHQ)_2PYR$ in dichloromethane at –20 °C. The stereochemical output was disappointing when quinine was employed, affording moderate diastereo- and enantioselectivities (67%, 30:70 *dr*, 58% *ee*), while $(DHQ)_2PYR$ did not catalyze the reaction.

After these discouraging results, thiourea-based bifunctional catalyst **C5** was tested in the reaction. However, as illustrated in Table 46, although very good diastereoselectivity was achieved, the catalyst rendered only moderate enantioselectivity (90:10 *dr*, 70% *ee*). It is remarkable, that while triethylamine and quinine tend to afford one diastereomer pre-eminently, those catalysts bearing a H-bond donor moiety favoured the opposite one. This problem was addressed by employing thiourea-based achiral catalyst **C4** to obtain the racemic version of the adducts.

Ureidopeptidic catalysts **C2** and **C3**, employed in the previous project did not contribute to the improvement of stereoselectivity, and they afforded even worst diastereoselectivities. At this point, in view of the obtained results, we decided to abandon this family of catalyst and focus on new H-bond donor moieties.

Thus, and taking Rawal's pioneering work on squaramides as reference,[338] we tested squaramide-based catalysts **C6–8** in the reaction under the same conditions. Quinine-based **C6** encouraged our quest, affording the reaction product in excellent yield and promising diastereo- and enantioselectivity (99%, 90:10 *dr*, 86% *ee*). Effect of the temperature was then evaluated, although lowering it only rendered worse general behavior (Table 45, entries 1–2), and increasing it lowered the diastereoseelctivity but did not affect enantioselectivity (entries 4–5).

Table 45. Temperature screening for the addition of **27A** to **2a** in presence of **C6**.[a]

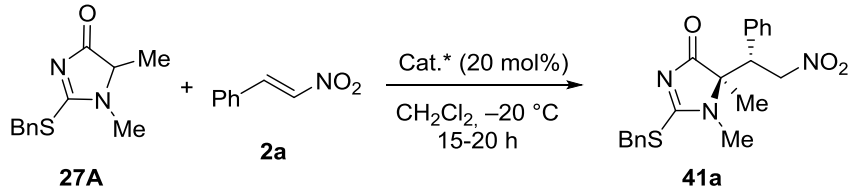
Entry	T (ºC)	Time (h)	Conv. (%)[b]	*dr*[b]	*ee* (%)[c]
1	–40	20	60	80:20	72
2	–30	20	95	80:20	80
3	–20	16	100	90:10	86
4	–10	15	100	85:15	86
5	0	15	100	80:20	86

[a] Reaction conditions: **27A** (1 eq, 0.3 mmol), **2a** (2 eq., 0.6 mmol), **C6** (20 mol%) were stirred at room temperature for stated time in CH_2Cl_2. [b] Determined by ^{1}H-NMR analysis of the crude mixture. [c] Determined by HPLC for the major. diastereomer: IA Hex/*i*Pr/EtOH 85:14:1 f=0.5 mL/min,

Next, after replacing the 9-*epi*-9-amino-9-deoxyquinine group in **C6** with the 1,2-diaminocyclohexane scaffold the selectivity was improved (93:7 *dr*, >95% *ee*). For catalyst **C8**, where the 3,3-dimethylbutane-1,2-diamine scaffold was inserted, no significant changes in the outcome of the reaction was found in comparison to **C7** (90:10 *dr*, –95% *ee*), albeit the configuration of the adduct was opposite to that obtained with the latter.

[338] a) Malerich et al.For a review on the synthesis and physical properties of squaramides, see: b) Ian Storer, R.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346.

Table 46. Catalyst screening for 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **1** addition to *trans*-*β*-nitrostyrene **2a**. [a-b]



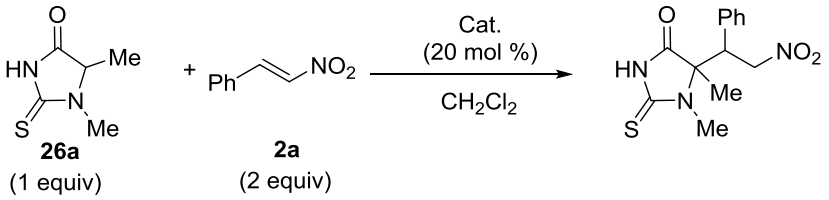
Et_3N –20 °C, 20 h 95%, 1:99 *dr*	**C4** 99%, 90:10 *dr*	
$(DHQ)_2PYR$ No Reaction	Quinine 67%, 30:70 *dr*, 58% *ee*[b]	**C5** 88%, 90:10 *dr*, 70% *ee*[b]
C2 –40 ºC, 44 h 53%[c], 81:19 *dr*, 46% *ee*	**C3** –20 °C, 22 h 82%, 72:28 *dr*, 40% *ee*	**C3-Me** –60 °C, 46 h 55%[c], 87:13 *dr*, 0% ee
C6 99%, 90:10 *dr*, 86% *ee*[b]	**C7** 99%, 93:7 *dr*, >95% *ee*	**C8** 91%, 90:10 *dr*, >95% *ee*[b]

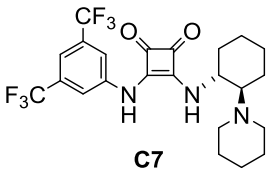
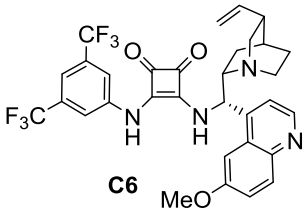
[a] Reaction conditions: **27A** (1 eq, 0.3 mmol), **2a** (2 equiv, 0.6 mmol), catalyst (10 mol %) were stirred at –20 °C temperature for 15-20 h in CH_2Cl_2. Diastereomeric ratio was determined by ^1H NMR analysis of the crude mixture. *ee*'s determined by HPLC for the major diastereomer: column IA eluting with Hex/iPr/EtOH 85:14:1 f=0.5 mL/min. [b] The enantiomer of **41a** was obtained. [c] Reaction stopped after 24 h.

Thus, the optimal reaction conditions for the addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** with the nitroolefin **2a** (2 equiv.) included the presence of catalyst **C7** or **C8** (20 mol %) at –20 °C in dichloromethane.

It is noteworthy that in order to proof the need of S-alkylated substrates, Michael addition of thiohydantoin **26** to nitrostyrene **2a** was performed. Squaramide derivatives **C7** and **C8** did not catalyze the reaction at –20 °C, and although reaction partially occurred when temperature raised to 0 °C, no diastereoselectivity was achieved (50:50 *dr*).

Table 47. Thiohydantoin addition to nitrostyrene.



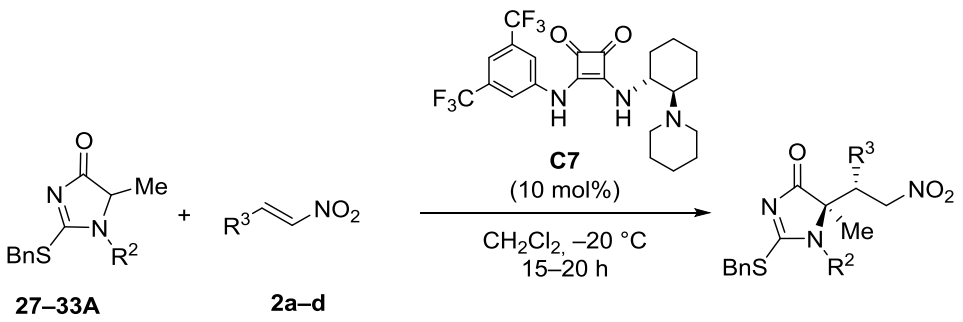
Et_3N	 **C7**	 **C6**
–20 °C, 20 h, 95%, *dr* 60 : 40	–20 °C, 20 h, *no reaction*	–20 °C, 20 h, *no reaction*
0 °C, 20 h, 95%, *dr* 50 : 50	0 °C, 48 h, 76%, *dr* 50 : 50, 10 *ee*	0 °C, 48 h, 81%, *dr* 50 : 50, 76 *ee*

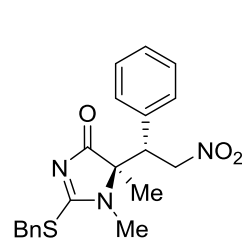
Reaction conditions: **26a** (1 eq, 0.2 mmol), **2a** (2 eq., 0.4 mmol), catalyst (20 mol %) were stirred at stated temperature for stated time in CH_2Cl_2. Conversions and *dr* determined by ^{1}H-NMR analysis of the crude mixture.

3.2.2.3. **Reaction scope**

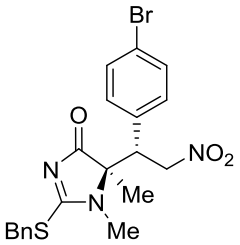
With the optimized conditions for the catalystic diastereo- and enatioselective Michael addition reaction at hand, the scope and limitation of the system were investigated (Table 48). The reactions of *N*-methyl imidazolones **27A–33A** with nitroolefins **2a–d** proceeded with excellent yields and stereocontrol with 10 mol % catalyst loading, regardless of the electron neutral, rich or poor character of the β-aryl substituent in the nitroalkene (Table 48). Imidazolones **27A–33A** bearing *N*-substituents other than methyl, e.g. benzyl, allyl, isobutyl, phenyl, and *para*-chlorophenyl were all well tolerated although in the case of *N*-(*meta*-methoxyphenyl) imidazolone worse diastereoselectivity was rendered, probably due to the steric hindrance. It is remarkable, that the catalyst loading could be reduced from 10 mol% to 5 mol% in the escalated reaction of the *N*-allyl imidazolone, without affecting the results essentially (Adduct **44a**, 65%, 90:10 *dr*; 95% *ee*).

Table 48. Catalyst screening for 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **1** addition to *trans*-*β*-nitrostyrene **2a**. [a-d]

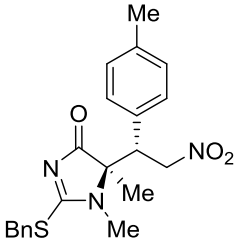




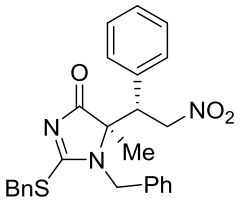
41a
97%, 93:7 *dr*; 99% *ee*



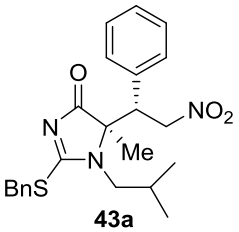
41c
82%, 94:6 *dr*; 98% *ee*



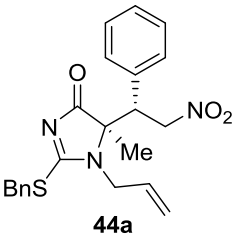
41d
91%, 90:10 *dr;* 96% *ee*



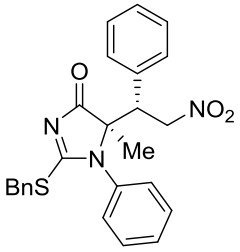
42a
85%, 98:2 *dr*; 98% *ee*



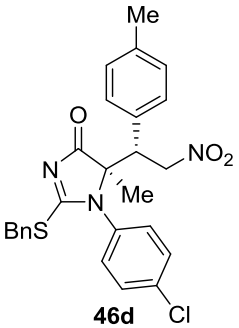
43a
78%, 98:2 *dr*; 93% *ee*



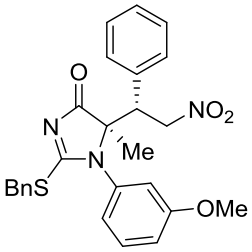
44a
77%, 92:8 *dr*; 94% *ee*
65%, 90:10 *dr*; 95% *ee*[e]



45a
65%, 93:7 *dr*; 92% *ee*



46d
83%, 98:2 *dr*; 98% *ee*

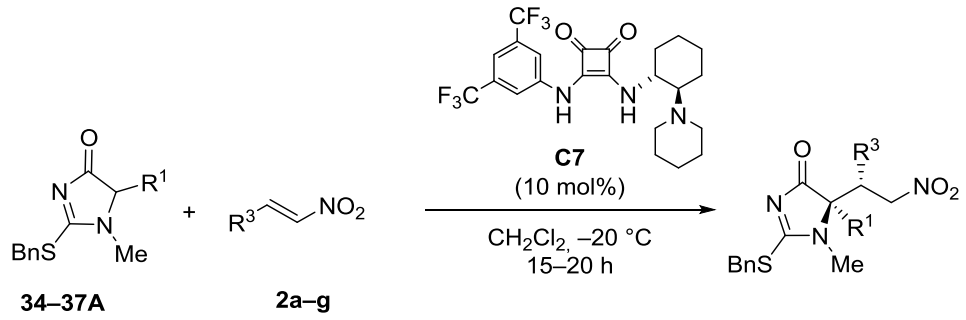


47a
85%, 88:12 *dr*; 95% *ee*

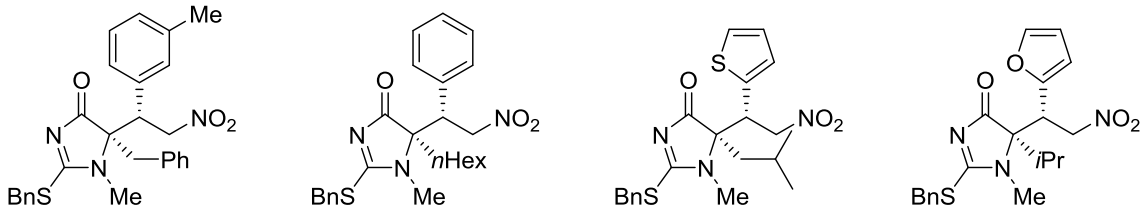
[a] Reactions performed on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio nitroolefin/imidazolone/catalyst 2:1:0.1) at –20 °C. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC. [e] Reaction run at 4 mmol scale using 5 mol % catalyst loading (reaction time 30 h)

Imidazolones bearing substituents different than methyl in R^1 also work well, without compromising the yield or the stereocontrol of the reaction, although when β-heteroaryl substituted nitroolefins were evaluated enantioselectivity lowered (Table 49).

Table 49. [a-d].



34–37A **2a–g**

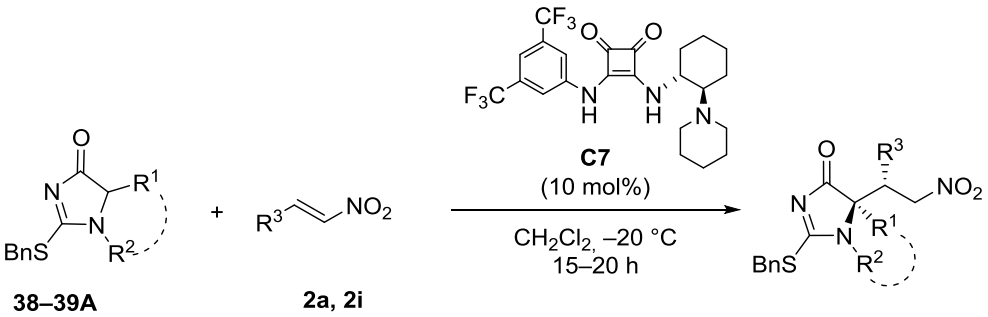


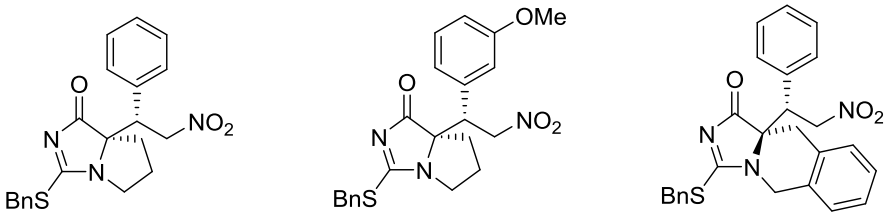
48h	**49a**	**50g**	**51e**
82%, 92:8 *dr*; 95% *ee*	81%, 98:2 *dr;* 98% *ee*	84%, 92:8 *dr*; 86% *ee*	75%, 93:7 *dr*; 92% *ee*

[a] Reactions performed on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio nitroolefin/imidazolone/catalyst 2:1:0.1) at –20 °C. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

Cyclic imidazolones **38A** and **39A** were also evaluated for the Michael addition to nitroolefins **2a** and **2i**. Nitrostyrene **2a** afforded very good yields and diastereoselectivity and excellent enantioselectivity in its reaction with proline-derived imidazolone **38A**, although when nitroalkene **2i** was employed both yield and diastereoselectivity lowered. Tricyclic imidazolone **39A** rendered excellecent stereocontrol of the reaction, although the yield got compromised.

Table 50. .[a-d]





52a
83%, 90:10 *dr*; 94% *ee*

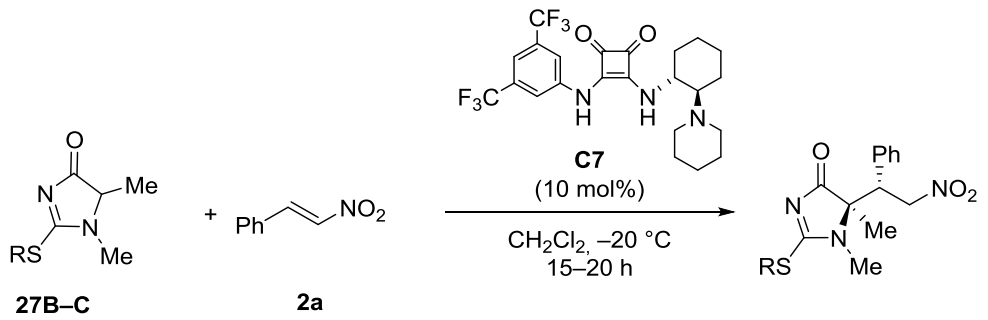
52i
78%, 87:13 *dr;* 97% *ee*

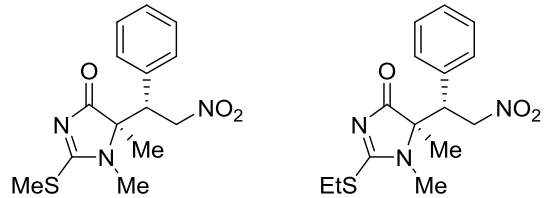
53a
62%, 98:2 *dr*; 92% *ee*

[a] Reactions performed on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio nitroolefin/imidazolone/catalyst 2:1:0.1) at –20 °C. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

In order to evaluate if the *S*-substituent would affect the reaction outcome apart from enhancing the diastereoselectivity, *S*-methyl and *S*-ethyl derivatives were tested in the Michael reaction with nitrostyrene, obtaining similar results to that obtained with the *S*-benzyl equivalent (Table 51).

Table 51. .[a-d]





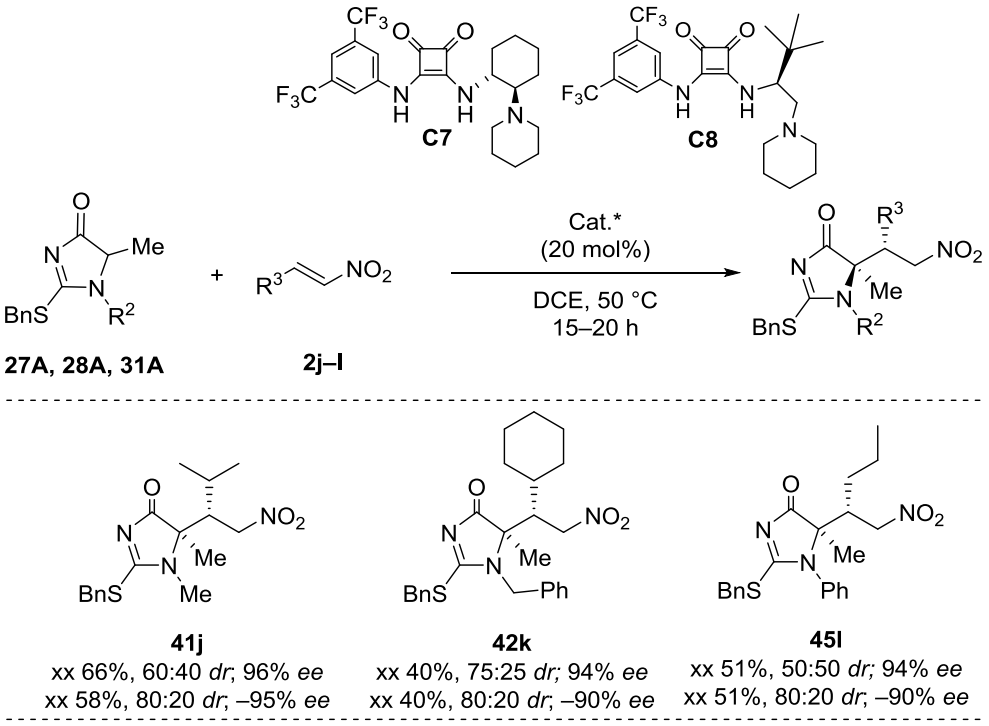
54a
83%, 90:10 *dr*; 94% *ee*

55a
78%, 87:13 *dr;* 97% *ee*

[a] Reactions performed on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio nitroolefin/imidazolone/catalyst 2:1:0.1) at –20 ºC. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

The reactions with β-alkyl substituted nitroolefins **16h**–**j** using catalyst **C7** proceeded with worse diastereocontrol, so a little screening of the reaction conditions was performed. Increasing nitroolefin equivalents and temperature to 50 °C, and by changing to catalyst **C8**[13] the diastereoselectivities increased although enantioselectivity was merely compromised, remaining excellent in every case.

Table 52. Conjugate addition of imidazolones **27A**, **28A** and **31A** to nitroolefins **2j–l** promoted by catalysts **C7** and **C8**.[a-d]

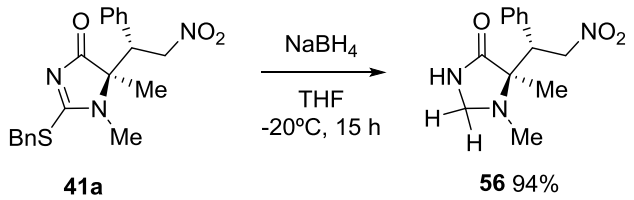


[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of DCE (mol ratio nitro olefin/imidazolone/catalyst 3:1:0.2) at 50 ºC. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

3.2.2.4. **Elaboration of adducts**

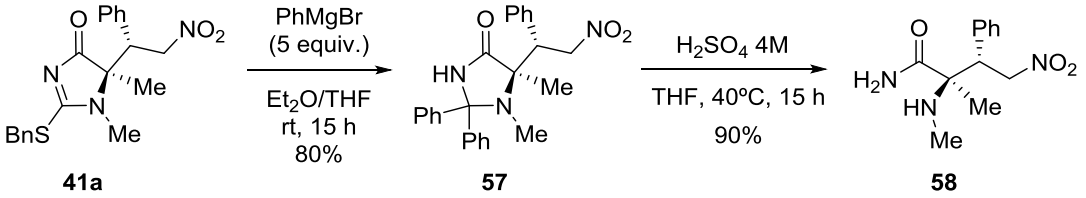
The chemical manipulation of adducts was briefly investigated to illustrate the synthetic potential of this approach (Scheme 3). Thus, nucleophilic displacement of the thioether group served to establish concise routes to various classes of heterocycles of interest in medicinal chemistry.[339] Reduction of the thioether moiety employing sodium borohydride afforded imidazolidinone **56** in 94% yield (Scheme 89).

[339] a) Arshad, N.; Hashim, J.; Kappe, C. O. *J. Org. Chem.* **2009**, *74*, 5118–5121. b) Bepary, S.; Youn, I. K.; Lim, H.-J.; Lee, G. H. *Eur. J. Org. Chem.* **2012**, 2542–2548. c) Konnert, L.; Reneaud, B.; de Figueiredo, R. M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, *79*, 10132–10142.



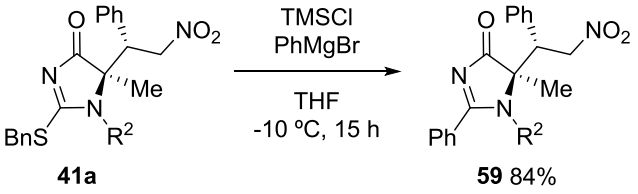
Scheme 89.

Treatment with an excess of phenyl magnesium bromide at room temperature rendered the gem-diarylated adduct **57** in 80% yield, which upon acidic hydrolysis was transformed into quaternary α-amino amide **58** in excellent yield (Scheme 90).[340]



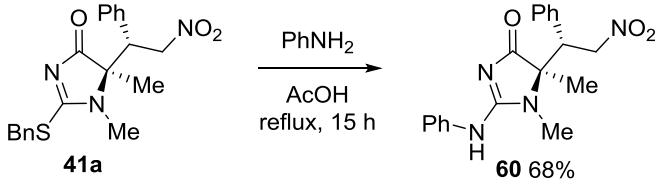
Scheme 90.

Arylation could be controlled lowering the Grignard reagent equivalents and the temperature, and using trimethylsilyl chloride to accelerate the reaction. Monoarylated adduct was obtained in 84% yield (Scheme 91).



Scheme 91.

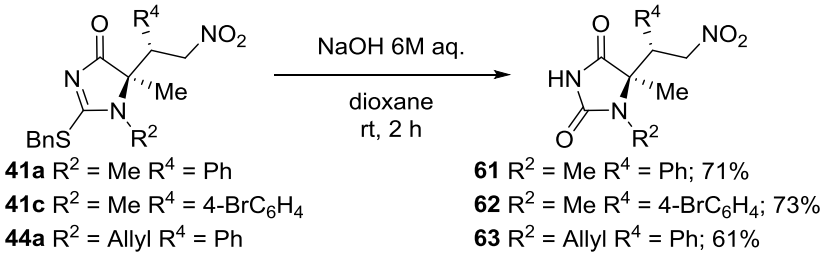
Aminohydantoin **60** was also accessed by treatment of the reaction adduct with aniline and acetic acid, with a moderately good yield (Scheme 92).[341]



Scheme 92.

[340] Pangerl, M.; Hughes, C. C.; Trauner, D. *Tetrahedron* **2010**, *66*, 6626–6631.
[341] Adapted from: Godlewskim, M. et al. PCT Int. Appl. (WO9823595), June 4, 1998.

Basic hydrolysis of the thioether moiety under mild conditions led to the much desired hydantoins **61–63** in good yields and with retention of the enantiopurity. To the bet of our knowledge this constitutes a novel access to this important class of compounds.[342]



Scheme 93.

Crystallization of adduct **62** allowed the determination of its absolute configuration by a single-crystal X-ray analysis (Figure 27), which was extrapolated to the other adducts by assuming a uniform reaction mechanism.

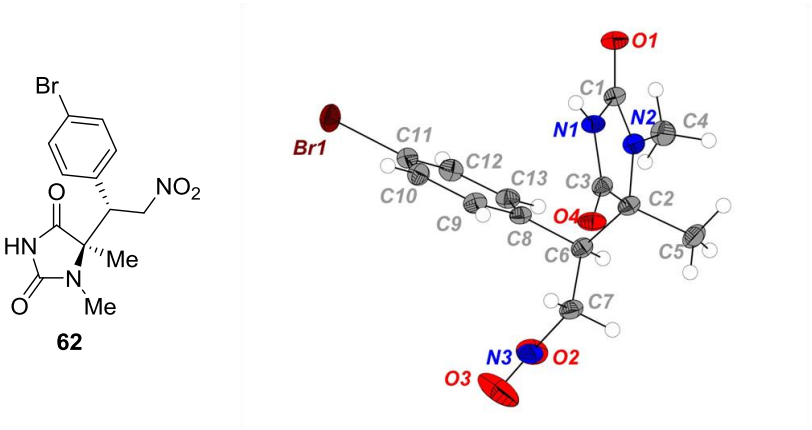
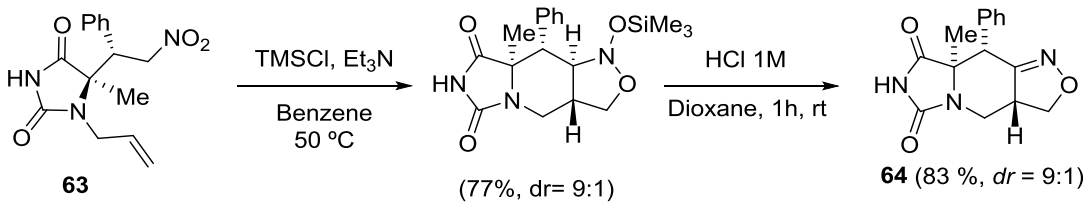


Figure 38. ORTEP diagram of compound **62**.

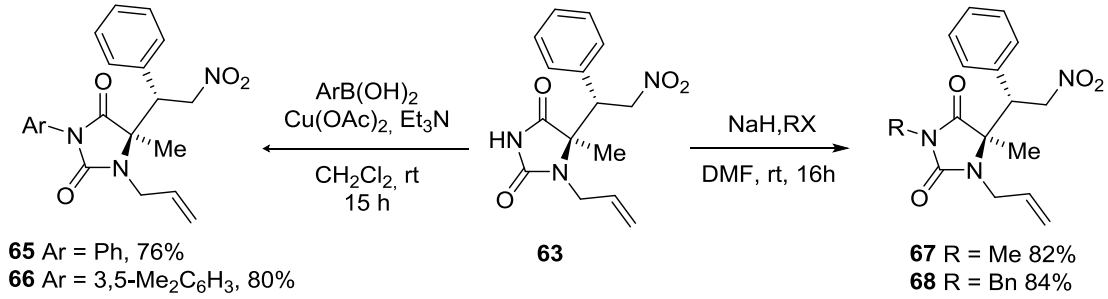
Izquierdo from our research group performed an intramolecular silyl-nitronate olefin cycloaddition (ISOC) of *N*-allyl hydantoin adduct **63** using trimethylsilyl chloride and subsequent acid hydrolysis afforded isoxazoline **64** in very good yield and diastereoselectivity (Scheme 94).[343,344]



Scheme 94.

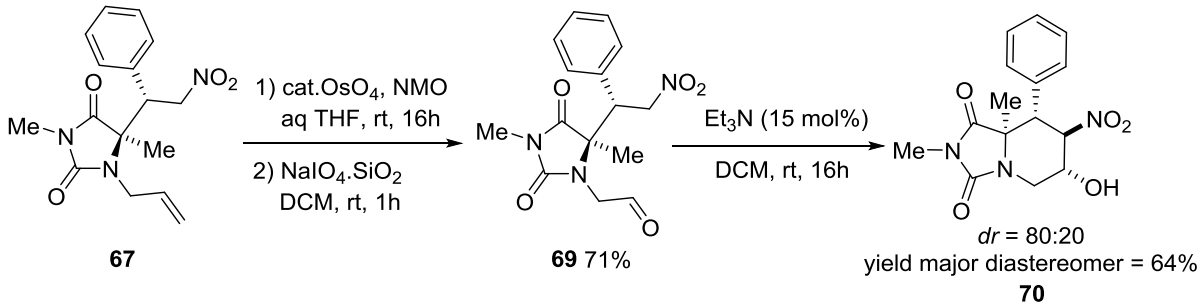
[342] see ref. 335 page 34.
[343] Joseba Izquierdo, PhD student, UPV/EHU.
[344] see ref. 247 page 89.

N-allyl hydantoin adduct **63** could also be N-alkylated or N-arylated using standard procedures. For example, alkylation was achieved employing sodium hydride as a base and alkyl halides,[345] while arylation required boronic acids and copper catalysis, although under mild conditions (Scheme 95).[346]



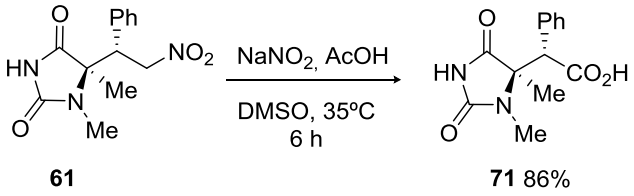
Scheme 95.

Oxidation of the *N*-allyl moiety to the diol and subsequent oxidation with sodium periodate was performed by Izquierdo, to access aldehyde **69**, which under basic conditions underwent an internal Henry cyclization with good diastereoselctivity and yield (Scheme 96).[343,347]



Scheme 96.

Finally, carboxylic acid derivative **71** was afforded from **61** by treatment with sodium nitrite and acetic acid in DMSO (Scheme 97).



Scheme 97.

[345] Adapted from Owen, D. A. et al From U. S., 6566384, 20 May 2003.
[346] Chan, D. M. .; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
[347] Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396–9414.

3.2.2.5. **Mechanistic proposal**

The description of a reaction model which would accurately explain the outcome of the reaction was our next concern.

The difference of the results obtained when thioureas or squaramides were employed, made clear that the H-bond donor moiety of the catalyst was indeed involved in the process. Jørgensen and Alemán, in their review on the squaramides and their importance for bifunctional organocatalysis,[348] highlighted that one of the most significant difference between thioureas and squaramides is the relative distance and spacing between the two N-H groups that can be found in their structures. Takemoto's[349] and Rawal's[350] groups calculated the distances for *N*,*N*'-dimethylthiourea and *N*,*N*'-dimethylsquaramide (Scheme 3 b) to be approximately 2.13Å and approximately 2.72Å, respectively. Moreover, the constrained structure of the cyclobutenedione ring of the squaramide induces a convergent orientation of the N-H groups, bending each bond by approximately by 6°.

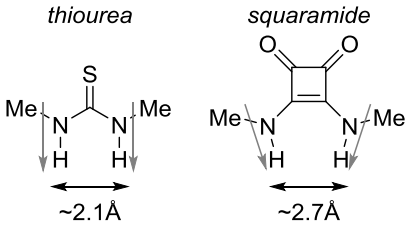


Figure 39. H-bond spacing distances in *N*,*N*'-dimethylthiourea and *N*,*N*'-dimethylsquaramide.

Following the reaction model proposed for the reaction with 5*H*-thiazol-4-ones (page xx), the enolate formed after deprotonation of the 1*H*-imidazol-4(5*H*)-one should be interacting with the H-bond donor moiety, which in view of the results, happened to occur with greater affinity with squaramides than with thioureas.

To support this assumption, ^{1}H NMR studies were carried out in order to establish the possible interactions between the catalyst and the substrates. ^{1}H NMR spectra of each of the following compounds in $CDCl_3$ at –10 °C (0.02 M) were recorded: (i) nitrostyrene **2a**, (ii) 1*H*-imidazol-4(5*H*)-one **27A** and (iii) catalyst **C7**. Sub-sequently, ^{1}H NMR spectra of the following mixtures were recorded under the same conditions (0.02 M in $CDCl_3$ at –10 °C): (iv) **C7**/**27A** (1:1 mixture), (v) **C7**/**2a** (1:1 mixture), and (vi) **C7**/**2a** (1:1 mixture) + 1 equivalent **27A**. The aromatic portion of the spectra (i) to (vi) are depicted below. Note the downfield shift of proton H_A of catalyst **C7** upon addition of imidazolone **27A**, regardless of the presence (vi) or absence (iv) of nitrostyrene.

[348] Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899.
[349] Okino et al. see ref. 248 page 90.
[350] see ref. 338a page 34.

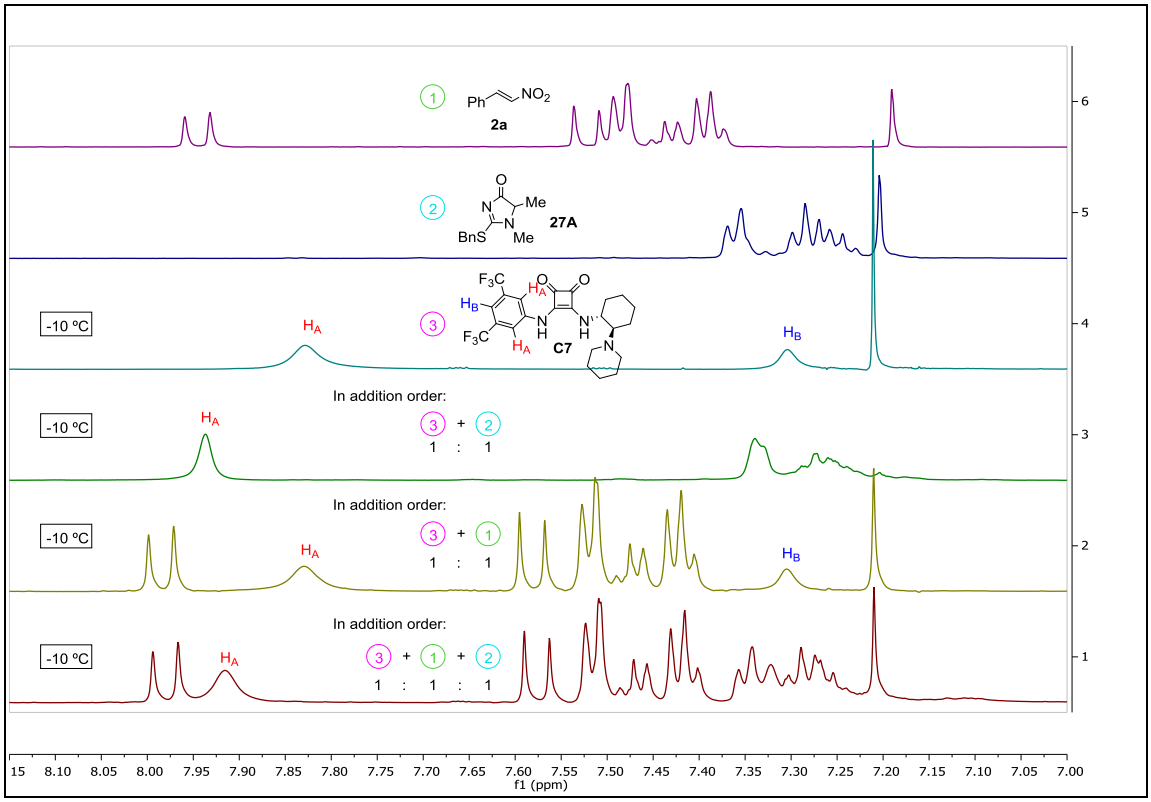


Figure 40. ^{1}H NMR spectra (aromatic portion) of pure samples of compounds **C7**, **27A** and **2a** (0.02 M in $CDCl_3$ at –10 °C) and some of their mixtures.

With these results in hand, we propose the the model depicted in Figure 41 for our reaction, where both the 1*H*-imidazol-4(5*H*)-one and the nitroolefin are activated by the catalyst. The deprotonated nucleophile would be fixed in space by H-bonds with the squaramide and the *ortho* aromatic proton of the 3,5-bistrifuoromethylphenyl moiety as the ^{1}H NMR studies suggested, while the nitroolefin would be directed by the protonated Brønsted base.

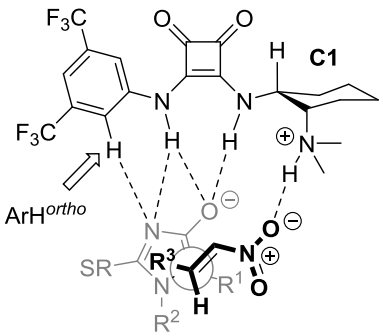


Figure 41.

3.3. **Michael addition of 1*H*-imidazol-4(5*H*)-ones to α'-oxyenones**

3.3.1. **Working hypothesis and synthetic plan**

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 squaramides as catalysts, and seeing the synthetic possibilities that these heterocycles bear, we decided to test our pronucleophiles with a different electrophile.

At this point, our research group was concurrently working in a new electrophile template (Figure 42a), which would act as an acrylate surrogate (Figure 42b).[351] The advantage of this electrophile is thought to derive from the increased reactivity provided by intramolecular interactions between the carbonyl and the extra hydroxy or silyloxy group.

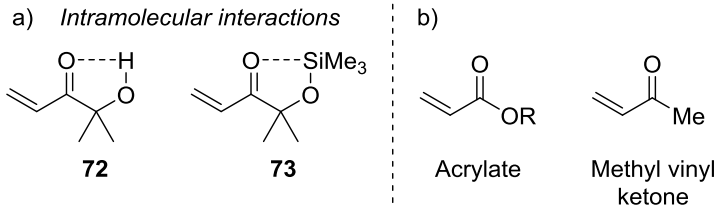
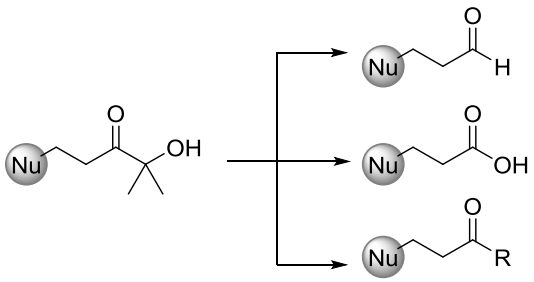


Figure 42. α'-Oxyenones as more reactive acrylate surrogates.

Additionally, the interest on this family of Michael acceptors comes from the synthetic potential of their reaction adducts, since several functional groups can be accessed by simple elaboration (Scheme 98).



Scheme 98. Easily accessible functional groups from α'-oxyenones.

On this basis, we chose α'-oxyenone **xx** to test it as electrophile with 1*H*-imidazol-4(5*H*)-ones, which would led to quaternary α-amino acids derivatives, including hydantoins. The adducts would bear only a stereocentre, eliminating the previous diastereose-

[351] For previous work of our group employing hydroxyenones, see: Badiola et al. ref. xx page xx. and references therein.

lectivity problem, although the less reactivity of the acceptor could imply a challenge (Scheme 62).

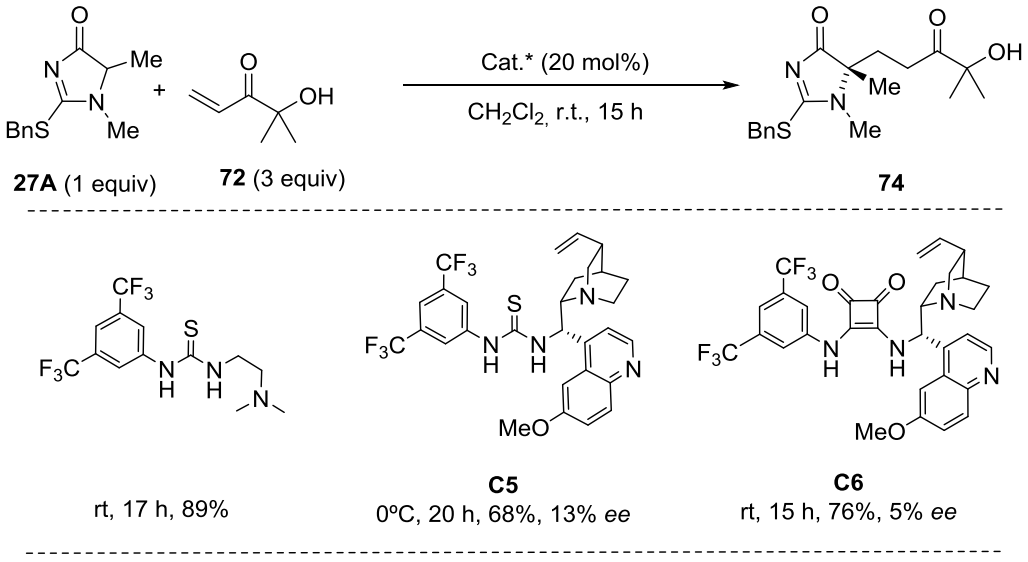
Scheme 99. Proposed reaction for the first investigation.

3.3.2. **Results and discussion**

3.3.2.1. **Screening of conditions**

Our study began with the evaluation of several Brønsted bases for the addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** to α'-hrydoxyenone **72** (Table 53). First, thiourea-based catalyst **C5** was tested for the reaction in dichloromethane at 0 °C with a 20 mol % catalyst loading, rendering good yield but very poor enantioselectivity. Squaramide based catalyst **C6** rendered better yield, but similarly poor enantioselectivity.

Table 53. Catalyst screening for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** to α'-hrydoxyenone **74**.

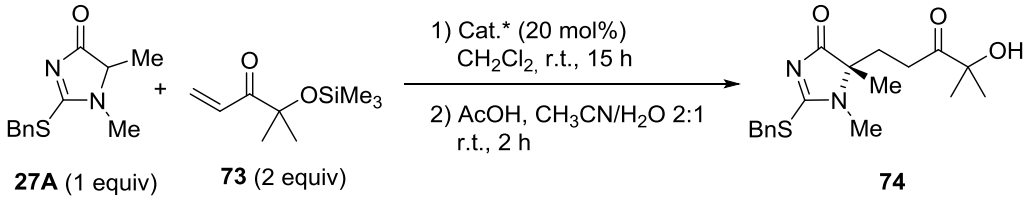


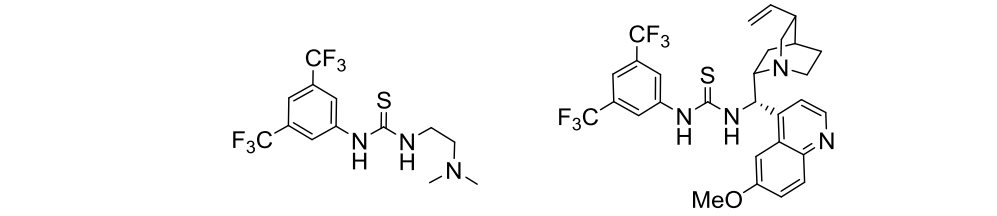
[a] Reaction conditions: **27A** (1 equiv, 0.3 mmol), **72** (3 equiv, 0.9 mmol), catalyst (20 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.3 mmol scale. *ee*'s determined by HPLC: IC Hex/iPr 40:60 f=0.5 mL/min.

Then silylated equivalent of the hydroxyenone, i.e. 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **73**, was tested, in the hope that the bulky TMS moi-

ety would increase the stereocontrol. Thiourea based catalyst **C5** rendered equally poor *ee* value (12% *ee*). However, when squaramide-based catalysts **C6–C8**, which afforded the best results concerning the addition of nitroalkenes, were evaluated for this reaction, a significant increase of the stereocontrol was observed, being the quinine derivative **C6** the most promising (94% *ee*).

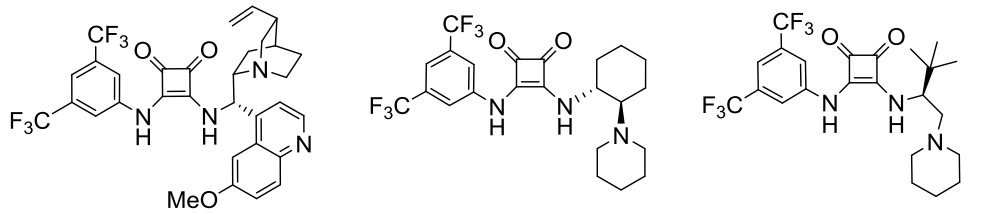
Table 54. Catalyst screening for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** to α'-silyloxyenone **73**.





C4
rt, 17 h, 89%

C5
0ºC, 20 h, 88%, 12% *ee*



C6
rt, 15 h, 75%, 94% *ee*

C7
rt, 15 h, 74%, –84% *ee*[b]

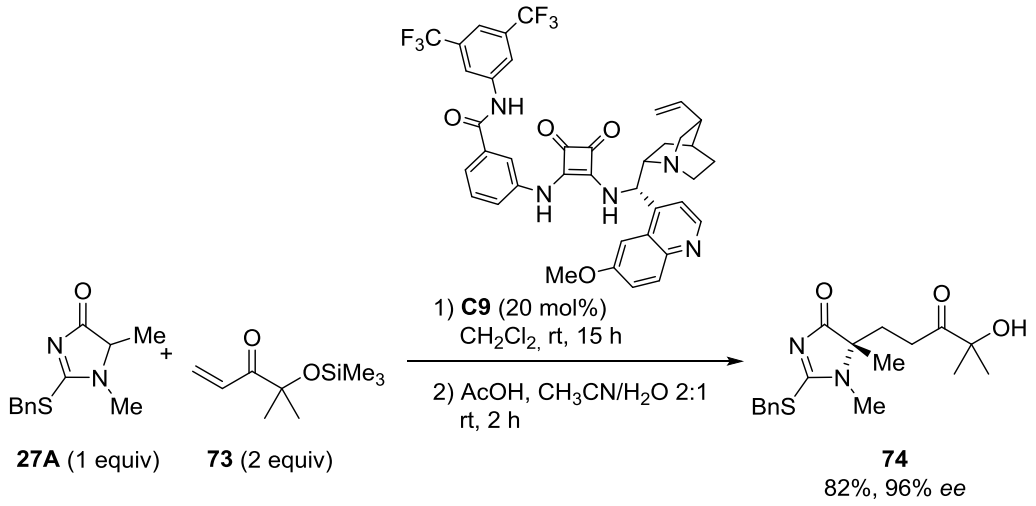
C8
rt, 15 h, 80%, 91% *ee*

[a] Reaction conditions: **27A** (1 equiv, 0.3 mmol), **73** (2 equiv, 0.6 mmol), catalyst (10 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.3 mmol scale. *ee*'s determined by HPLC: IC Hex/iPr 40:60 f=0.5 mL/min. [b] The enantiomer of **74** was obtained.

At this point, despite the good results, we decided to focus in a way to improve both the yield and the enantiocontrol of the reaction, and increasing the interactions between the catalyst and the substrate was the chosen strategy. Based on the β-turn structures found in peptides,[352] we designed and synthesized catalyst **C9** in the hope that a possible intramolecular H-bond would increase the electrophillicity of the squaramide moiety, and, thus, enhance the stereoselectivity of the reaction. However, and although

[352] For a study on the conformation and biological activity of cyclic peptides, see: a) Kessler, H. *Angew. Chem. Int. Ed.* **1982**, *21*, 512–523. For a recent enantioselective azlactone ring opening using an oligopeptide bearing a β-hairpin-like secondary structure as catalyst, see: Metrano, A. J.; Miller, S. J. *J. Org. Chem.* **2014**, *79*, 1542–1554.

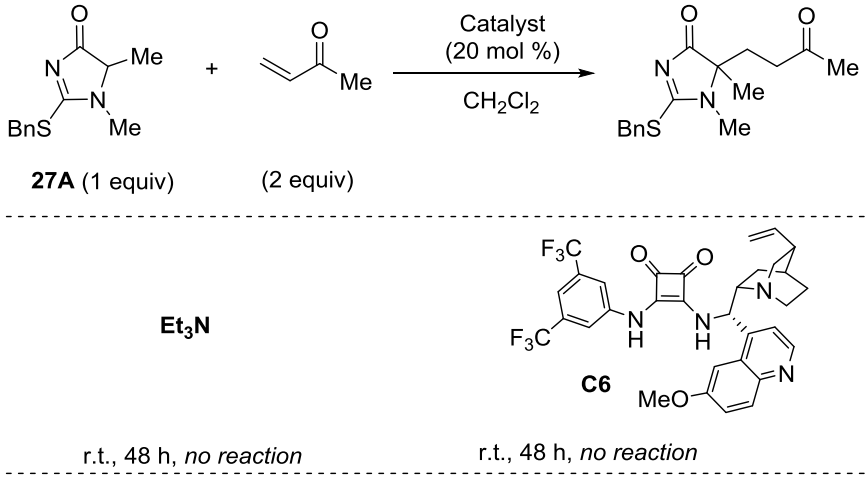
the data suggested that the amidic NH next to the 3,5-bis(trofluoromethyl)phenyl moiety had some kind of interaction that diminished its mobility, an intramolecular H bond remains unconfirmed.[353] Fortunately, the new catalyst design worked out and excellent enantioselectivity was achieved, concluding that the optimal conditions for the asymmetric Michael addition were the ones illustrated in Scheme 100.



Scheme 100. Optimal conditions for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **27A** to oxyenone **73**.

It is remarkable that when Michael addition of imidazolone **27A** to methyl vinyl ketone was tested, no conversion was obtained neither with achiral nor with chiral catalysts.

Table 55. 2-(Benzylthio)-1,5-dimethyl-1,5-dihydro-1*H*-imidazol-4(5*H)*-one **27A** addition to methyl vinyl ketone.



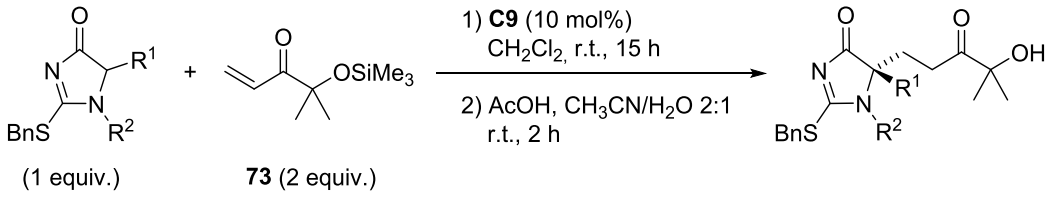
Reaction conditions: **27A** (1 eq, 0.2 mmol), MVK (2 eq., 0.4 mmol), catalyst (20 mol %) were stirred at stated temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. Conversions and *dr* determined by ^{1}H-NMR analysis of the crude mixture.

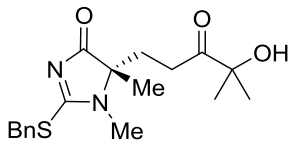
[353] For the study of the temperature gradients through ^{1}H NMR chemical shifts of N-H signals of **C9**, see Experimental Section.

3.3.2.2. **Reaction scope**

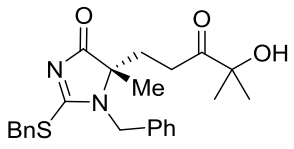
Once with the optimal conditions in hand, we then started to check the generality of the method, testing different imidazolones for the addition to silyloxyenone **73**. It is noteworthy, that after a successful trial, catalyst loading was lowered to 10 mol % without compromising the outcome of the reaction (Table 56). Different substituents in both R^1 and R^2 were well tolerated, affording very good yields in every case. Even bulkier substituents rendered excellent enantioselectivities in the reaction, proving the robustness of our methodology.

Table 56. Conjugate addition of imidazolones **27–40** to 4-methyl-4-((trimethylsilyl)-oxy)pent-1-en-3-one **73** promoted by catalyst **C9**.[a]

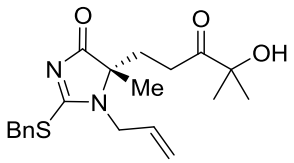




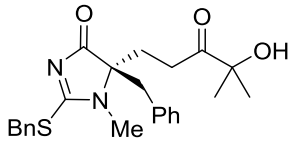
74
82%, 96% *ee*



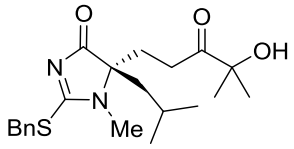
75
78%, 96% *ee*



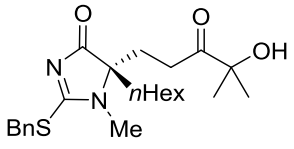
76
77%, 94% *ee*



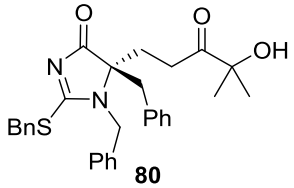
77
75%, 96% *ee*



78
71%, 96% *ee*



79
81%, 94% *ee*

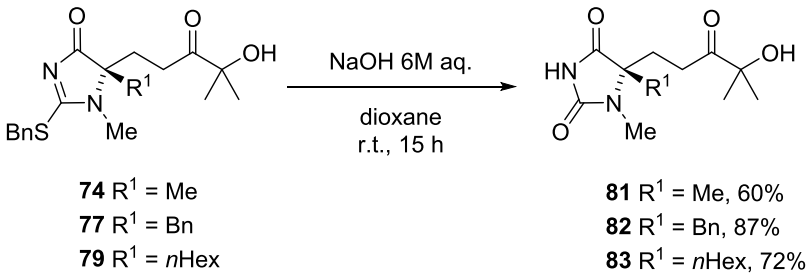


80
83%, 92% *ee*

Reaction conditions: **27–40** (1 eq, 0.3 mmol), **73** (2 eq., 0.6 mmol), catalyst (10 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. [a] *ee*'s determined by HPLC.

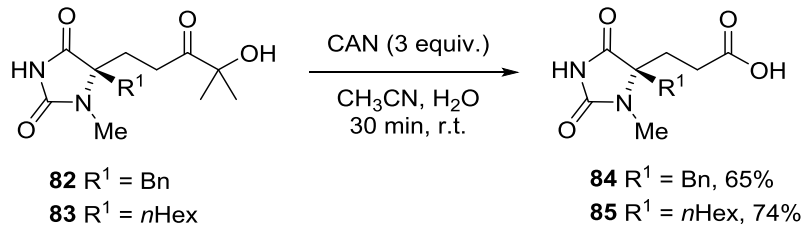
3.3.2.3. **Elaboration of adducts**

The next aspect that we explored was the elaboration of the reaction products, taking advantage of the high modulability of the oxyenone moiety. First, basic hydrolysis of the thioether group in the imidazolone afforded the corresponding more stable hydantoins in very good yields (Scheme 101).



Scheme 101.

Subsequent oxidative cleavage of the ketol moiety in adducts **82–83** employing cerium ammonium nitrate afforded carboxylic acids **84–85** in very good yields.[354]



Scheme 102.

Fortunately, the cristallinity of compound **84** allowed obtaining monocrystals, and in order to establish the absolute configuration of the compound a single-crystal X-ray analysis was performed (Figure 43). Configuration of the rest of adducts was thus established by assuming the uniformity of the rection mechanism.

[354] Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

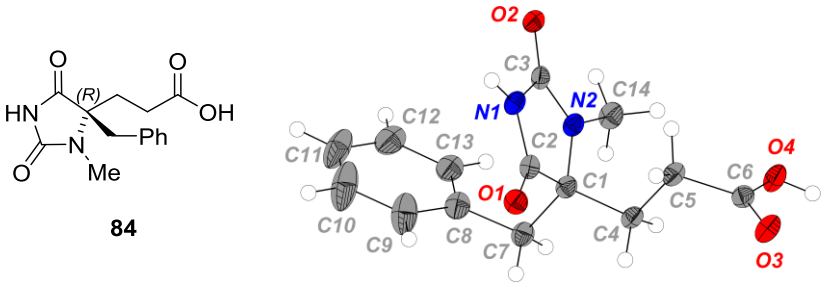
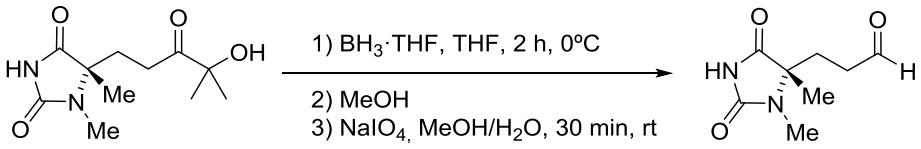


Figure 43. ORTEP diagram of compound **84**.

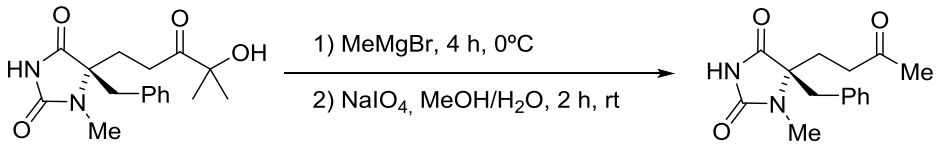
Aldehyde derivative **86** was obtained straightly from **81** through reduction of the carbonyl moiety and subsequent oxidation of the resulting diol using sodium periodate in very good yield (Scheme 103).



81 **86** 87%

Scheme 103.

On the other hand, ketone **87** required the nucleophilic methylation of **81** prior to oxidation employing sodium periodate (Scheme 104).



81 **87**

Scheme 104.

In view of the synthetic value of the reaction adducts of 1*H*-imidazol-4(5*H*)-ones, and their suitability for the generation of *N*-substituted quaternary α-amino acid derivatives, further studies for the addition of these pronucleophiles to different acceptors are currently being developed in our research group.

CHAPTER 4

CONCLUSIONS

4. CONCLUSIONS

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

5*H*-Thiazol-4-ones have demonstrated their utility as efficient reagents for the asymmetric synthesis of α,α-disubstituted α-mercapto carboxylic acid derivatives. Thiazolones add to nitroolefins in the presence of ureidopeptidic bifunctional Brønsted base catalysts in high stereoselectivity to give adducts that after mild hydrolysis provide tertiary thiols for which few synthetic protocols exist. Likewise, the addition of 5*H*-thiazol-4-ones to di-*tert*-butyl azodicarboxylate has provided access to quaternary α-mercapto α-amino acid derivatives, and has acted as a proof of concept for the proposed reaction model.

1*H*-Imidazol-4(5*H*)-ones have proved to be excellent substrates for the direct organocatalytic asymmetric synthesis of *N*-substituted α,α-disubstituted α-amino acid derivatives, whose direct preparation has commonly been restricted to rare examples. The Michael addition of imidazolones to nitroolefins occurs with great stereocontrol in presence of squaramide-based bifunctional Brønsted base catalysts, and elaboration of the adducts has provided a variety of heterocycles, including hydantoins, which are a family of great biological interest. Enantioselective addition of 1*H*-imidazol-4(5*H*)-ones to α'-silyloxyenone has been achieved, in presence of a novel squaramide based catalyst with a suspected intramolecular H-bond, although this point remains unconfirmed. However, taking advantage of the high modulability of the adducts, several useful transformations have been carried out.

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. $(DHQ)_2PYR$ 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 100 mL of water (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**

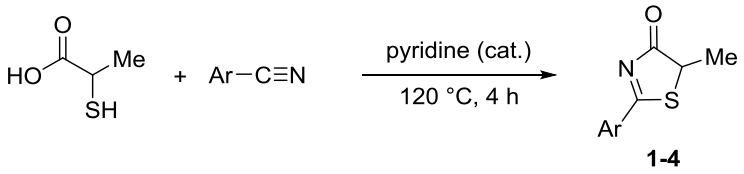
Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg·cm^2·g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degree Celsius (°C).

5.2. **Experimental section of chapter 2**

5.2.1. **General procedure for the synthesis of 5*H*-thiazol-4-ones 4a–e and 6–8**

5.2.1.1. **General procedure for the synthesis of 5*H*-thiazol-4-ones**

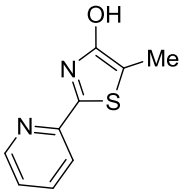
5.2.1.1.1. General procedure A:[355]



1-4

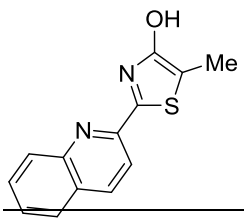
In an inert atmosphere, the corresponding carbonitrile (1 equiv.) was treated with the corresponding α-mercaptocarboxylic acid (1 equiv.) and pyridine (20 mol %). The mixture was stirred for 4 h at 120 °C. During this time, a yellow mass was formed which was collected by filtration and washed with methanol, diethyl ether or diisopropyl ether.[356]

5-Methyl-2-(pyridin-2-yl)thiazol-4-ol (4a)



The title compound **4a** was prepared from pyridine-2-carbonitrile (1.1 g, 10 mmol) and mercaptolactic acid (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with methanol. Yellow solid; yield: 1.4 g, 7.3 mmol, 73%. m.p. = 209–210 °C. ^{1}H NMR (300 MHz, DMSO), δ: 10.34 (s, 1H), 8.58–8.49 (m, 1H), 7.96–7.84 (m, 2H), 7.39 (ddd, *J* = 6.8, 4.8, 1.9 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (300 MHz, DMSO), δ: 159.1, 158.7, 150.6, 149.5, 137.5, 124.2, 117.9, 105.8, 9.3. HRMS: $C_9H_8N_2OS$ $[M+H]^+$ calcd.: 193.0436, found: 193.0439.

5-Methyl-2-(quinolin-2-yl)thiazol-4-ol (4b)

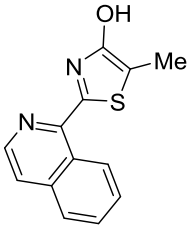


The title compound **4b** was prepared from quinoline-2-carbonitrile (1.5 g, 10 mmol) and mercaptolactic acid (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with diethyl ether. Yellow solid; yield: 2.2 g, 9.1 mmol, 91%. m.p. = 232-

[355] U. W. Grummt, D. Weiss, E. Birckner, R. Beckert, *J. Phys. Chem. A.* **2007**, *111*, 1104-1110.
[356] Keto-enol-tautomerism established by ^{1}H-NMR using $CDCl_3$ as solvent. Using DMSO-d_6 only the enol form was detected.

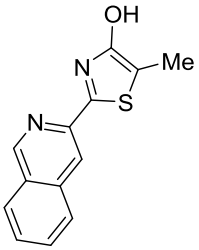
234 °C. ^{1}H NMR (300 MHz, DMSO), δ: 9.59 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 6.97 (t, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.3, 158.8, 150.6, 147.1, 137.5, 130.4, 128.5, 128.0, 127.9, 126.9, 116.6, 107.2, 9.4. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0592, found: 243.0597.

2-(isoquinolin-1-yl)-5-methylthiazol-4-ol (4c)



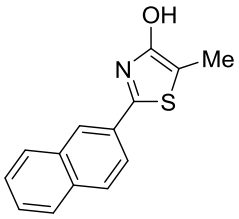
The title compound **4c** was prepared from isoquinoline-1-carbonitrile (1.5 g, 10 mmol) according to the general procedure, the solid was washed with diethyl ether. Yellow solid, yield: 1.50 g, 6.2 mmol, 62%. m. p. 207–29 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 – 9.48 (m, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 8.06 – 7.59 (m, 4H), 2.41 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ: 160.43, 152.17, 151.98, 142.67, 135.65, 129.84, 132.72, 128.39, 125.68, 124.34, 115.27, 101.42, 8.98. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0593, found: 243.0598.

2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (4d)



The title compound **4d** was prepared from isoquinoline-3-carbonitrile (1.5 g, 10 mmol) according to the general procedure, the solid was washed with diethyl ether. Yellow solid, yield: 1.77 g, 7.3 mmol, 73%. m. p. 212–214 °C. ^{1}H NMR (300 MHz, DMSO) δ: 10.33 (s, 1H), 9.27 (s, 1H), 8.30 (s, 1H), 8.08 (dd, *J* = 14.2, 8.0 Hz, 2H), 7.78 (ddd, *J* = 9.3, 5.9, 1.8 Hz, 1H), 7.70 – 7.61 (m, 1H), 2.25 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ: 159.33, 154.15, 152.63, 144.61, 135.65, 131.32, 130.74, 128.39, 127.88, 127.43, 113.64, 105.35, 9.37. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0593, found: 243.0592.

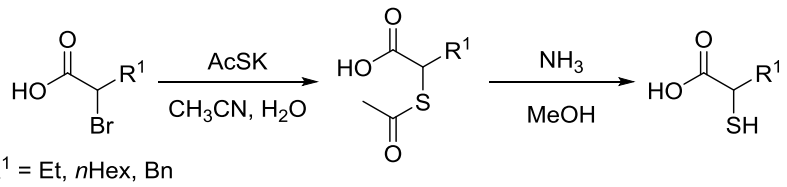
5-Methyl-2-(naphthalen-2-yl)thiazol-4-ol (4e)



The title compound **4e** was prepared from 2-naphthonitrile (1.5 g, 10 mmol) and mercaptolactic acid (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with diethyl ether. Yellow solid; yield: 1.2 g, 5.0 mmol, 50%. m.p. = 229–230 °C. ^{1}H NMR (300 MHz, DMSO), δ: 10.35 (s, 1H), 8.33 (s, 1H), 8.07–7.87 (m, 4H), 7.61– 7.49 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.0, 158.2, 133.2, 132.9, 130.8, 128.8, 128.4, 127.7, 126.9, 123.6, 122.7, 103.0, 9.2. UPLC-DAD-QTOF: $C_{14}H_{12}NOS$ $[M+H]^+$ calcd.: 242.0640, found: 242.0637.

5.2.1.1.2. General procedure B:[357]

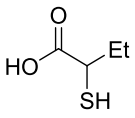
5.2.1.1.2.1. General procedure for the synthesis of α-mercaptocarboxylic acids[358]



R^1 = Et, *n*Hex, Bn

To a solution of the corresponding α-bromocarboxylic acid (25 mmol, 1 equiv.) in 60 mL of anhydrous CH_3CN was added a solution of potassium thioacetate (50 mmol, 2 equiv.) in water (15 mL), and the mixture was stirred for 3 h. The organic solvent was evaporated and the mixture was diluted with water and washed with CH_2Cl_2. The aqueous phase was acidified with concentrated hydrochloric acid, extracted with CH_2Cl_2 (3 × 25 mL), dried over $MgSO_4$ and concentrated to afford the α-(acetylthio)carboxylic acid as an off white solid in quantitative yield. Subsequently, the solid was dissolved in MeOH (15 mL) at 0 °C and ammonia (7N in MeOH, 27 mL, 7.5 equiv.) was added to the solution. The mixture was allowed to warm up to room temperature and stirred for 1 h. The organic solvent was then completely evaporated under reduced pressure and the residue was dissolved in a saturated aqueous solution of $NaHCO_3$. The solution was washed with EtOAc, the aqueous phase was acidified with concentrated hydrochloric acid and extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford the corresponding α-mercaptocarboxylic acids as orange oils, which were used as such without further purification.

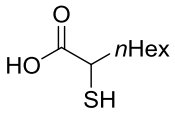
2-Mercaptobutanoic acid



The title compound was prepared from 2-bromobutanoic acid (2.66 mL, 25 mmol) according to the general procedure. Orange oil; yield: 2.99 g, 24.91 mmol, 99%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.29 (dt, *J* = 9.0, 7.3 Hz, 1H), 2.07 (d, *J* = 9.1 Hz, 1H), 2.03–1.89 (m, 1H), 1.87–1.70 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H).

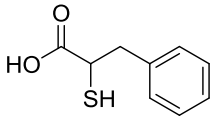
2-Mercaptooctanoic acid

[357] S. Barzen, C. B. Rödl, A. Lill, D. Steinhilber, H. Stark, B. Hofmann, *Bioorg. Med. Chem.* **2012**, *20*, 3575-3583.
[358] Adapted from: J. E. Shaffer, S. A. Thomson, *US Patent* 5.087.631 Feb 11, **1992**.



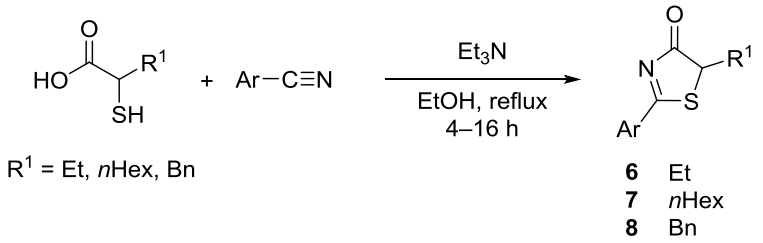
The title compound was prepared from 2-bromooctanoic acid (4.43 mL, 25 mmol) according to the general procedure. Orange oil; yield: 4.92 g, 25 mmol, 100%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.35 (dt, *J* = 8.9, 7.4 Hz, 1H), 2.17 (s, 1H), 2.03–1.83 (m, 1H), 1.83–1.63 (m, 1H), 1.54–1.22 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).

2-Mercapto-3-phenylpropanoic acid



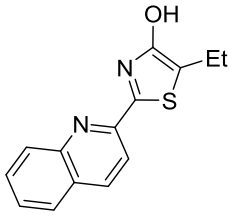
The title compound was prepared from 2-bromo-3-phenylpropanoic acid (5.73 g, 25 mmol) according to the general procedure. Orange oil; yield: 4.49 g, 24.65 mmol, 99%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.25–7.03 (m, 5H), 3.55 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.21 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.82 (dd, *J* = 13.8, 8.1 Hz, 1H).

*5.2.1.1.2.2. General procedure for the synthesis of 5H-thiazol-4-ones **6–8***[359]



The corresponding carbonitrile (1 eq., 10 mmol) was refluxed with mercaptolactic acid (1 eq., 10 mmol) and triethylamine (5 eq., 50 mmol) in ethanol (20 mL) in an inert atmosphere. The mixture was stirred at 110 °C and the reaction was monitored by TLC. After reaction completion, the reaction mixture was evaporated under reduced pressure and the resulting solid was washed with diisopropyl ether.[360]

5-Ethyl-2-(quinolin-2-yl)thiazol-4-ol (6)

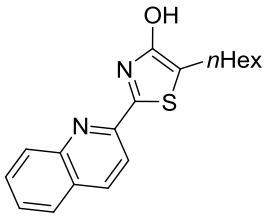


The title compound **6** was prepared from quinoline-2-carbonitrile (0.77 g, 5 mmol) and 2-mercaptobutanoic acid (0.6 g, 5 mmol) according to the general procedure B. The resulting solid was washed with diisopropyl ether. Green solid; yield: 1.1 g, 4.35 mmol, 87%. m.p. = 100–104 °C. ^{1}H NMR (300 MHz, DMSO), δ: 8.44 (d, *J* = 8.6 Hz, 1H), 8.11 (t, *J* = 8.2 Hz, 1H), 8.05–7.86 (m, 2H), 7.79 (dd, *J* = 13.6, 6.5 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz,

[359] Adapted from: J. E. Shaffer, S. A. Thomson, *US Patent* 5.087.631 Feb 11, **1992**.
[360] Keto-enol-tautomerism can be detected in chloroform by ^{1}H-NMR analysis.

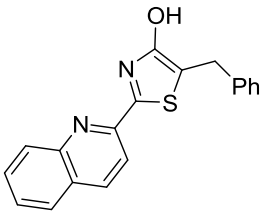
3H). ^{13}C NMR (75 MHz, DMSO), δ: 158.5, 150.6, 147.1, 138.4, 137.5, 131.5, 130.4, 129.5, 129.1, 128.4, 128.3, 128.0, 127.9, 126.9, 123.8, 116.6, 114.8, 17.7, 15.6. HRMS: $C_{14}H_{13}N_2OS$ $[M+H]^+$ calcd.: 257.0759, found: 257.0749.

5-Hexyl-2-(quinolin-2-yl)thiazol-4-ol (7)



The title compound **7** was prepared from quinoline-2-carbonitrile (1.17 g, 7.6 mmol) and 2-mercaptooctanoic acid (1.3 g, 7.6 mmol) according to the general procedure B. The resulting solid was washed with diisopropyl ether. Yellow solid; yield: 1.3 g, 4.25 mmol, 85%. m.p. = 120–123 °C. ^{1}H NMR (300 MHz, DMSO), δ: 8.45 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 9.3 Hz, 2H), 7.82–7.74 (m, 1H), 7.65–7.57 (m, 1H), 2.68 (t, *J* = 7.4 Hz, 2H), 1.67–1.53 (m, 2H), 1.41–1.18 (m, 6H), 0.85 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 159.0, 158.9, 150.6, 147.1, 137.5, 130.4, 128.4, 128.1, 127.9, 126.9, 116.6, 113.0, 30.9, 30.5, 28.1, 24.0, 22.0, 13.9. HRMS: $C_{18}H_{21}N_2OS$ $[M+H]^+$ calcd.: 313.1375, found: 313.1373.

5-Benzyl-2-(quinolin-2-yl)thiazol-4-ol (8)



The title compound **8** was prepared from quinoline-2-carbonitrile (0.67 g, 4.4 mmol) and 2-mercapto-3-phenylpropanoic acid (0.8 g, 4.4 mmol) according to the general procedure B. The resulting solid was washed with diisopropyl ether. Green solid; yield: 1.1 g, 3.4 mmol, 78%. m.p. = 200–203 °C. ^{1}H NMR (300 MHz, DMSO), δ: 8.46 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.04–7.91 (m, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.38–7.28 (m, 3H), 7.24 (d, *J* = 3.5 Hz, 1H), 4.04 (s, 2H). ^{13}C NMR (75 MHz, DMSO), δ: 160.1, 159.0, 150.5, 147.1, 140.4, 137.5, 130.4, 128.5, 128.5, 128.3, 128.0, 127.0, 126.3, 116.5, 112.1, 30.1. HRMS: $C_{19}H_{15}N_2OS$ $[M+H]^+$ calcd.: 319.0905, found: 319.0909.

5.2.2. General procedure for the synthesis of nitroalkenes 2f and 2j–l

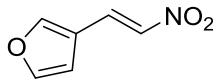
Nitroalkenes **2a–e** and **2g–i** are commercially available and were purchased from commercial suppliers.

5.2.2.1. General procedure A[362]

To a solution of the corresponding aldehyde (1 equiv., 10 mmol) and nitromethane (1 equiv., 0.5 mL, 10 mmol) in ethanol (2.5 mL) at 0 ºC an aqueous NaOH 1M solution

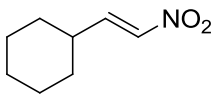
(1 equiv., 1 mL, 10 mmol) was added. After 10 min under vigorous stirring the reaction mixture became yellow. Then acetic acid (1 equiv., 0.6 mL, 10 mmol) was added and the aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the corresponding nitro alcohol, which was dissolved in dichloromethane (10 mL) and cooled at 0 ºC. Then trifluoroacetic acid anhydride (1 equiv., 0.8 mL, 10 mol) and triethylamine (4 equiv., 5.5 mL, 40 mmol) were added dropwise. The reaction mixture was stirred for 1 h at 0 ºC, quenched with water (10 mL), extracted with dichloromethane (3 x 20 mL) and washed with HCl 1M (2 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the pure product.

Synthesis of (*E*)-3-(2-nitrovinyl)furan 2f



The title compound was prepared from 3-furaldehyde (1 equiv., 0.82 mL, 10 mmol) following the general procedure. Yellow solid, yield: 0.77 g, 5.5 mmol, 55%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.77 (d, *J* = 13.5 Hz, 1H), 7.59 (dd, *J* = 3.5, 0.5 Hz, 1H), 7.59 (dd, *J* = 3.5, 0.5 Hz, 1H), 7.50 (d, *J* = 13 Hz, 1H), 6.89 (d, *J* = 3.5 Hz, 1H), 6.57 (dd, *J* = 3.5, 1.5 Hz, 1H).

Synthesis of (*E*)-(2-nitrovinyl)cyclohexane 2k



The title compound was prepared from cyclohexanecarboxaldehyde (1 equiv., 1.2 mL, 10 mmol) following the general procedure. Yellow oil, yield: 0.74 g, 4.8 mmol, 48%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.26–7.17 (m, 1H), 6.93 (dd, *J* = 13.5, 1.3 Hz, 1H), 2.36–2.15 (m, 1H), 1.90–1.64 (m, 4H), 1.45–1.09 (m, 6H).

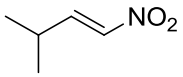
5.2.2.2. General procedure B[361]

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 ºC, followed by dropwise addition of 10N NaOH solution (1.05 equiv., 201 mL, 21 mmol). The resulting mixture was stirred at 0 ºC 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 ºC for 1 hour, then extracted with dichloromethane (3 x 50 mL), dried over $MgSO_4$, filtered, and the solvent evaporated

[361] Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem*. **1985**, *63*, 2354–2361.

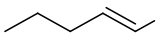
under reduced pressure. The residue was purified by flash column chromatography on silica gel.

3-Methyl-1-nitrobut-1-ene 2j[362]



The title compound **2j** was prepared from isobutyraldehyde (1.8 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 1.0 g, 9.1 mmol, 46%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.31–7.18 (m, 1H), 6.94 (dd, *J* = 13.5, 1.4 Hz, 1H), 2.67–2.50 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 6H).

1-Nitropent-1-ene 2l[362]



The title compound **2l** was prepared from butyraldehyde (1.8 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 1.2 g, 10.4 mmol, 52%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35–7.19 (m, 1H), 6.98 (dt, *J* = 13.4, 1.4 Hz, 1H), 2.34–2.16 (m, 2H), 1.67–1.46 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

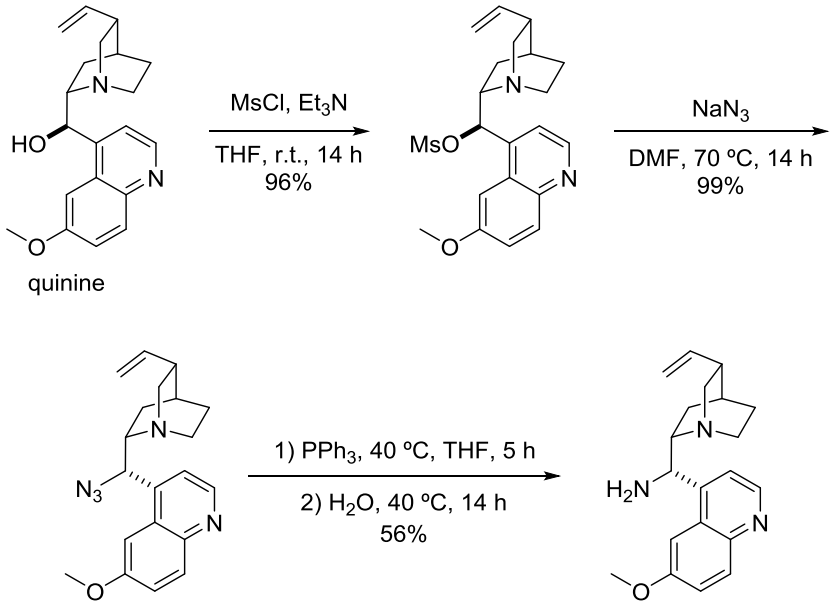
[362] Adapted from: Lucet, D.; Sabell,e S.; Kostelitz, O.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **1999**, 2583–2591.

5.2.3. **General procedure for the synthesis of catalysts**

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

5.2.3.1. **Preparation of 9-epi *Cinchona*-based amines**

5.2.3.1.1. Preparation of 9-amino-(9-deoxy)epiquinine[363]



1st step:[364] 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 ºC 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:[365] The crude mesylated product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 ºC and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 ºC for 16 h and after this

[363] Adapted from: Brunner, H.; Büegler, J.; Nuber, B. *Tetrahedron: Asymmetry*, **1995**, *6*, 1699–1702.

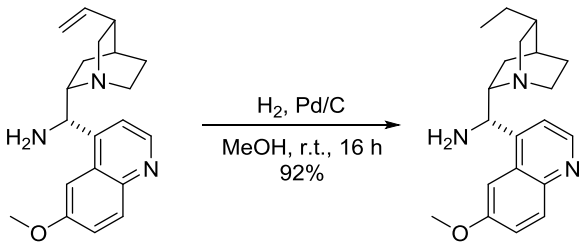
[364] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

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

time the reaction was quenched with water (80 mL) and then ethyl acetate (150 mL) was added. The organic layer was separated and washed with saturated NaCl thoroughly (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude azide derived product in quantitative yield which was used in the next step without further purification.

3rd step:[365] 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 ºC and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 ºC. 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 ºC 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).

5.2.3.1.2. Preparation of 9-amino-(9-deoxy)epihydroquinine[366]



10% Palladium on carbon (10% w/w, 0.32 g) was added to a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 3.2 g, 10 mmol) in methanol (10 mL). The reaction mixture was stirred overnight under H_2 atmosphere, and then was filtered over celite and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*hydroquinine as a yellow viscous oil. Yield: 3.0 g, 9.2 mmol, 92%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, CD_3OD), δ: 8.69 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.69 (brs, 1H), 7.61 (d, *J* = 4.7 Hz, 1H,), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.00 (s, 3H), 3.36–3.24 (m, 1H), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H), 3.16 (q, *J* = 10.7 Hz, 1H), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz,

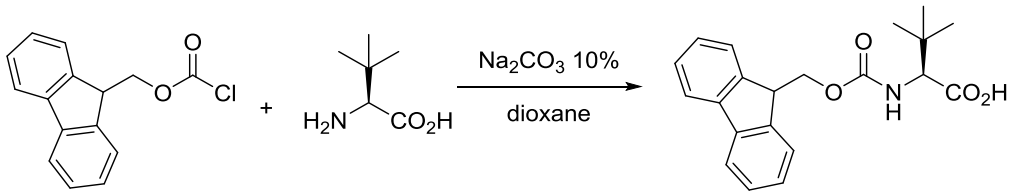
[366] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

1H), 1.62–1.58 (m, 1H), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.58–1.47 (m, 4H), 1.37–1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

5.2.3.2. **Ureidopeptide-like Brønsted base catalysts C1–C3**

5.2.3.2.1. Preparation of N-protected α-amino acids

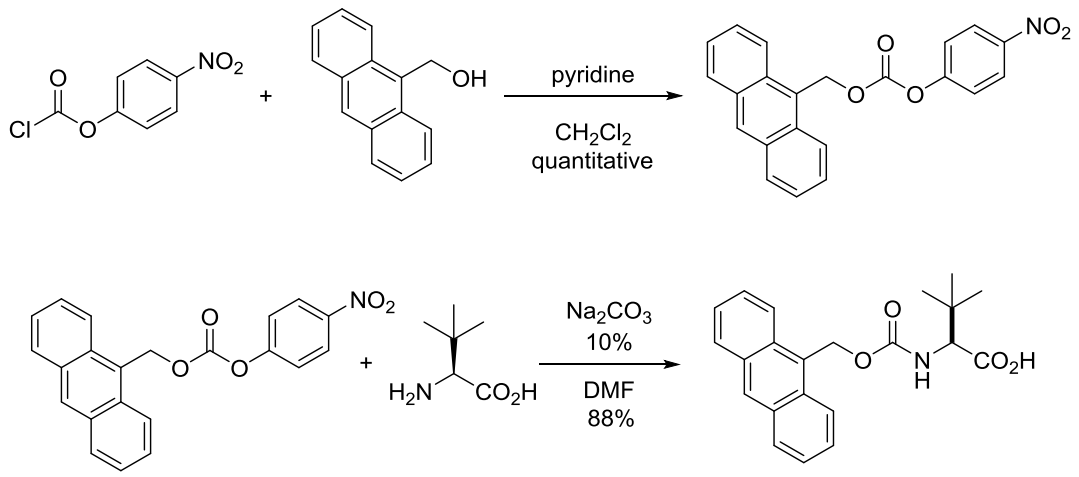
((9*H*-Fluoren-9-ylmethoxy)carbonyl)-*L*-*tert*-leucine[367]



To a stirred solution of *L*-*tert*-leucine (1.31 g, 10 mmol, 1 equiv.) in 10% aqueous Na_2CO_3 (26 mL), and dioxane (10 mL) was slowly added at 0 ºC a solution of (9*H*-fluoren-9-yl)methyl carbonochloridate (2.6 g, 10 mmol, 1 equiv.) in dioxane (30 mL). The mixture was stirred at the same temperature for 1 h and then allowed to warm to room temperature. The solution was subsequently stirred overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL). The combined extracts were dried over $MgSO_4$, filtered off and the solvent evaporated under reduced pressure to afford the corresponding *N*-protected α-amino acids. White solid, yield: 3.4 g, 9.5 mmol, 95%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, MeOD), δ: 7.78 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 6.7 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (dt, *J* = 7.5, 1.0 Hz, 2H), 4.39–4.33 (m, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.05 (brs, 1H), 3.66 (s, 1H), 1.03 (s, 9H).

[367] Pan, S. C.; Zhou, J.; List, B. *Angew. Chem. Int. Ed*. **2007**, *46*, 612–614.

((Anthracen-9-ylmethoxy)carbonyl)-*L-tert*-leucine[368]



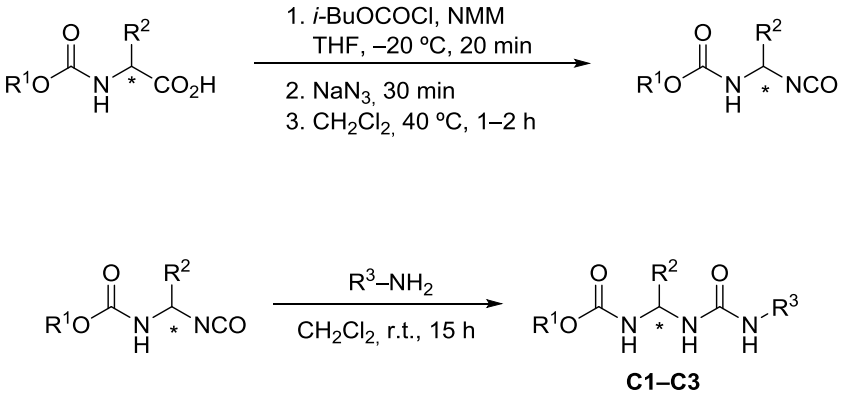
To a stirred solution of *p*-nitrophenylchloroformate (1.1 equiv. 2.2 g, 11 mmol) in dichloromethane (13.6 mL) was added pyridine (1.1 equiv., 0.9 mL, 11 mmol). The white slurry was cooled to 0 ºC, and anthracen-9-ylmethanol (1 equiv., 10 mmol) was added in several portions to keep the temperature at 0 ºC. After completion of the addition, the yellow mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and subsequently washed with 1 N HCl (20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

To a stirred solution of *L-tert*-leucine (1 equiv. 10 mmol) in 10% aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0 ºC a solution of the corresponding 4-nitrophenyl carbonate (1 equiv., 10 mmol) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 h and then allowed to warm to room temperature and subsequently stirred at the same temperature overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to afford the corresponding *N*-protected α-amino acid.

White solid, yield: 3.2 g, 8.8 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.65–7.54 (m, 2H), 7.53–7.46 (m, 2H), 6.18 (q, *J* = 12.1 Hz, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.28 (d, *J* = 10.2 Hz, 1H), 1.01 (s, 9H).

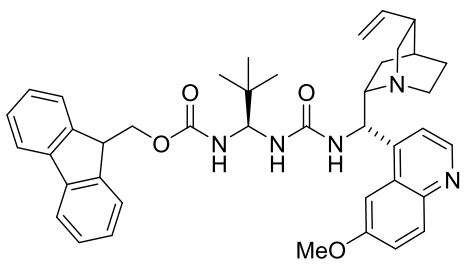
[368] Lan, P.; Porco Jr., J. A.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660–669.

5.2.3.2.1.1. Preparation of α-amino acid derived isocyanates and coupling with 9-epi Cinchona-based amines [369]



To a cooled solution of the corresponding *N*-protected α-amino acid (5 mmol, 1 equiv.) in dry THF (20 mL) were added isobutyl chloroformate (1 equiv., 0.65 mL, 5 mmol), and *N*-methylmorpholine (1 equiv., 0.6 mL, 5 mmol) and the mixture was stirred at –20 ºC for 20 min. Then, a suspension of NaN_3 (1.5 equiv., 0.48 g in 5 mL of H_2O, 7.5 mmol) was added and the reaction mixture was stirred at the same temperature. After 30 min, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, and concentrated under vacuum to give a yellow oil which was redissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 ºC under nitrogen for 1–2 h. The reaction was monitored by IR analysis until disappearance of the isocyanate band. After completion, the corresponding amine was added (0.7 equiv., 3.5 mmol) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (eluting with dichloromethane → dichloromethane/ methanol 80/20) or on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the desired catalysts **C1–C3**.

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

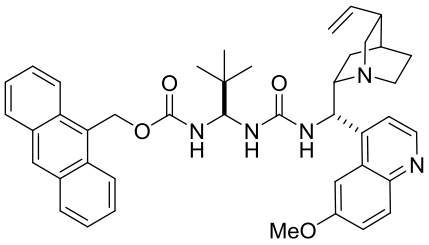


The title compound **C1** was prepared from Fmoc-*L*-*tert*-leucine (1.8 g, 5 mmol) and 9-amino-(9-deoxy)epiquinine (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.67 g, 2.5 mmol, 71%. $[\alpha]_D^{25}$= –16.2 (c = 1.00, CH_2Cl_2).

[369] Adapted from: Suresh Babu, V. V.; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705.

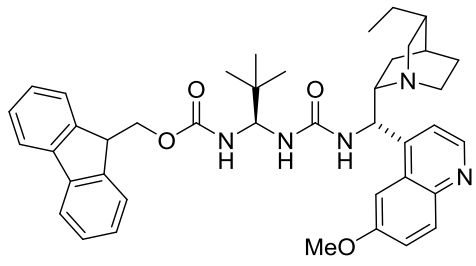
^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.63 (d, *J* = 4.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.83–7.72 (m, 3H), 7.62–7.55 (m, 2H), 7.47–7.31 (m, 7H), 6.41–6.26 (bs, 1H), 5.84–5.69 (m, 1H), 5.40–5.25 (m, 1H), 5.09–5.05 (bs, 1H), 5.07–4.95 (m, 3H), 4.47–4.41 (m, 1H), 4.35–4.30 (m, 1H), 4.26–4.11 (m, 1H), 3.97 (s, 3H), 3.32–3.24 (m, 2H), 3.17–3.02 (m, 1H), 2.81–2.69 (m, 2H), 2.36–2.25 (m, 1H), 1.66–157 (m, 3H), 1.48–1.38 (m, 1H), 0.92 (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 158.2, 157.8, 156.8, 147.9, 146.3, 145.1, 144.3, 144.1, 141.8, 141.7, 132.00, 128.9, 128.1, 127.5, 125.5, 122.0, 120.4, 114.9, 102.5, 67.4, 67.1, 60.8, 56.8, 56.3, 56.0, 47.6, 41.4, 39.9, 35.8, 28.3, 27.9, 26.5, 25.8. UPLC-DAD-QTOF: $C_{41}H_{48}N_5O_4$ $[M+H]^+$ calcd: 674.3726, found: 674.3726.

Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate C2



The title compound **C2** was prepared from anthracen-9-ylmethoxycarbonyl-*L-tert*-leucine (1.8 g, 5 mmol) and 9-amino-(9-deoxy)epiquinine (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.78 g, 2.6 mmol, 74%. $[\alpha]_D^{25}$= –2.7 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.61–8.22 (m, 4H), 8.12–7.93 (m, 3H), 7.82–7.67 (m, 1H), 7.61–7.32 (m, 5H), 7.19–7.11 (m, 1H), 6.51–6.32 (bs, 1H), 6.24–6.00 (m, 2H), 5.89–5.68 (m, 1H), 5.12–4.93 (m, 3H), 4.92–4.74 (bs, 1H), 3.96 (s, 3H), 3.39–2.98 (m, 3H), 2.97–2.56 (m, 2H), 2.46–2.22 (m, 2H), 1.92–1.54 (m, 4H), 1.45–1.29 (m, 1H), 0.86 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.7, 157.5, 156.5, 147.4, 144.5, 141.3, 131.4, 131.2, 130.8, 128.9, 128.5, 126.5, 125.0, 123.9, 121.6, 118.5, 114.4, 101.9, 66.7, 66.4, 59.2, 55.6, 55.2, 46.2, 40.7, 39.4, 35.2, 27.7, 27.2, 25.8, 25.1. UPLC-DAD-QTOF: $C_{42}H_{48}N_5O_4$ $[M+H]^+$ calcd: 686.3706, found: 686.3716.

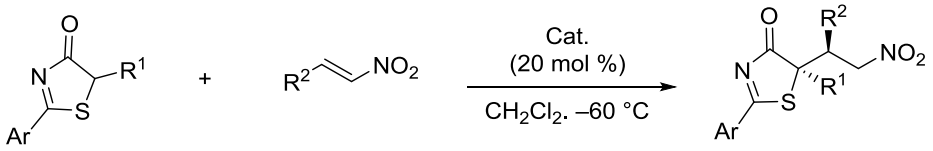
(9H-Fluoren-9-yl)methyl (*S*)-1-(3-((*S*)-((*2S,4S,8R*)-8-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropylcarbamate C3



The title compound **C3** was prepared from Fmoc-*L-tert*-leucine (1.8 g, 5 mmol) and 9-amino-(9-deoxy)epihydroquinine (1.1 g, 3.5 mmol) according to the general procedure. according to the general procedure. White solid; yield: 1.02 g, 1.5 mmol, 50%.$[\alpha]_D^{25}$= -25.7 (*c*= 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.54 (s, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.71 (dd, *J* = 10.5, 4.9 Hz, 2H), 7.54 (s, 2H), 7.46–7.10 (m, 6H), 6.42 (s, 1H), 5.38 (dd, *J* = 31.6, 22.4 Hz, 2H), 4.98 (s, 1H), 4.49–4.02 (m, 3H), 4.02–3.75 (m, 3H), 3.07 (dd, *J* = 48.9, 8.1 Hz, 3H), 2.64

(s, 1H), 2.39 (dd, *J* = 29.2, 18.6 Hz, 1H), 2.09–1.94 (m, 1H), 1.68–1.32 (m, 4H), 1.32–1.06 (m, 4H), 1.03–0.57 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.7, 157.5, 156.3, 147.4, 144.6, 143.8, 143.7, 141.2, 141.2, 131.5, 128.5, 127.6, 127.0, 127.0, 125.0, 121.5, 119.9, 102.0, 66.8, 66.5, 60.3, 57.5, 55.5, 47.1, 40.9, 37.2, 35.4, 28.5, 27.4, 25.8, 25.3, 25.1, 14.1, 11.9. UPLC-DAD-QTOF: $C_{41}H_{50}N_5O_4$ $[M+H]^+$calcd: 676.3863, found: 676.3861.

5.2.4. **General procedure for the asymmetric conjugate addition of 5*H*-thiazol-4-ones to nitroolefins**



4a–e, 6–8 **2a–f** **5a–e, 9–11**

5.2.4.1. **Asymmetric reaction**

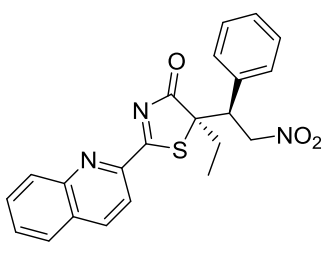
To a mixture of the corresponding thiazolone (1 equiv., 0.3 mmol) and the nitroolefin (0.6 mmol, 2.0 equiv.), in dichloromethane (0.6 mL) cooled to –60 °C the catalyst was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (monitored by ^{1}H NMR). The reaction mixture was directly purified by flash column chromatography on silica gel without previous workup to afford the expected adducts.

5.2.4.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using triethylamine (20 mol %) as the catalyst at –20 °C.

5.2.4.3. **Characterization data for compounds 5a–e and 9–11**

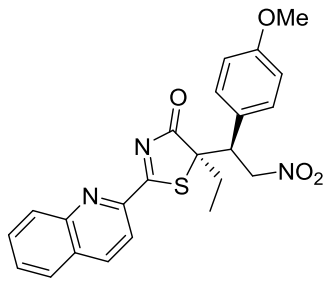
(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9a)



The title compound **9a** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**6**) (77 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 116 mg,

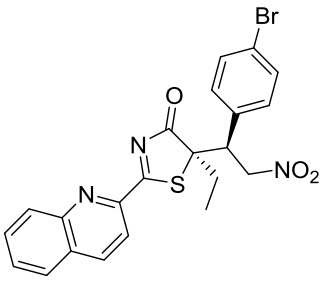
0.285 mmol, 95 %. $[\alpha]_D^{25}$= –221.9 (*c*= 1.00, 97% *ee*, CH_2Cl_2). m.p. 89-92 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.24 (dt, *J* = 14.3, 8.5 Hz, 3H), 7.85 (ddd, *J* = 11.6, 9.8, 4.8 Hz, 2H), 7.71 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.08 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.93 (dd, *J* = 13.1, 11.0 Hz, 1H), 4.21 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.35–2.05 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.8, 194.4, 149.5, 148.7, 138.5, 134.0, 132.6, 131.9, 131.7, 131.4, 130.6, 128.8, 124.0, 120.6, 72.0, 51.2, 30.9, 9.9.UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 406.1225, found: 406.1235. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 32.1 min (min.) and 38.6 min (major.)).

(*R*)-5-Ethyl-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9b)



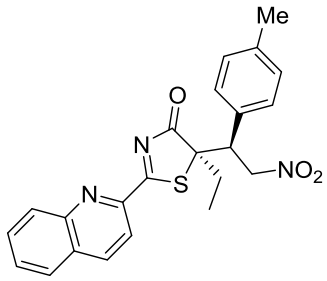
The title compound **9b** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**6**) (77 mg, 0.3 mmol) and 4-methoxy-nitrostyrene (**2b**) (108 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 122 mg, 0.28 mmol, 95%. $[\alpha]_D^{25}$= –270.0 (*c*= 0.6, 97% *ee*, CH_2Cl_2). m.p. 85–87 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.31–8.15 (m, 3H), 7.93–7.79 (m, 2H), 7.69 (ddd, *J* = 13.5, 7.3, 3.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.07 (dd, *J* = 12.9, 4.6 Hz, 1H), 4.93 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.19 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.68 (s, 3H), 2.34–2.03 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.4, 194.4, 160.2, 149.3, 148.4, 138.0, 131.3, 131.0, 130.10, 128.5, 126.5, 120.2, 115.1, 114.5, 72.3, 55.7, 50.8, 30.3, 9.7. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_4S$ $[M+H]^+$ calcd.: 436.1331, found: 436.1327. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 30.3 min (min.) and 33.0 min (major.)).

(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9c)



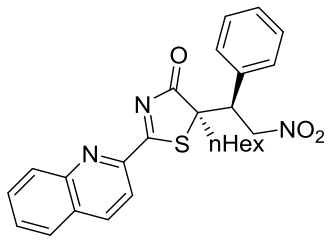
The title compound **9c** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**6**) (77 mg, 0.3 mmol) and 4-bromo-nitrostyrene (**2c**) (137 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 117 mg, 0.24 mmol, 81%. $[\alpha]_D^{25}$= –233.3 (*c*= 1.00, 97% *ee*, CH_2Cl_2). m.p. 91–93 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.24 (dt, *J* = 14.3, 8.5 Hz, 3H), 7.85 (ddd, *J* = 11.6, 9.8, 4.8 Hz, 2H), 7.74–7.57 (m, 1H), 7.29 (dd, *J* = 24.5, 8.6 Hz, 4H), 5.08 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.93 (dd, *J* = 13.1, 11.0 Hz, 1H), 4.21 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.35–2.05 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.8, 194.4, 149.5, 148.7, 138.5, 134.0, 132.6, 131.9, 131.7, 131.4, 130.6, 128.8, 124.0, 120.6, 72.0, 51.2, 30.9, 9.9. UPLC-DAD-QTOF: $C_{22}H_{19}BrN_3O_3S$ $[M+H]^+$ calcd.: 484.0331, found: 484.0341. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 26.6 min (min.) and 29.8 min (major.)).

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9d)



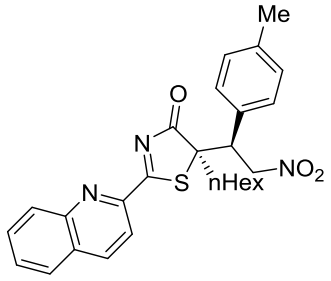
The title compound **9d** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**6**) (77 mg, 0.3 mmol) and 4-methyl-nitrostyrene (**2d**) (98 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 109 mg, 0.26 mmol, 87%. $[\alpha]_D^{25}$= –251.5 (*c*= 0.35, 94% *ee*, CH_2Cl_2). m.p. 93–95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.18 (m, 3H), 7.93–7.80 (m, 2H), 7.74–7.66 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.11 (dd, *J* = 13.0, 4.6 Hz, 1H), 5.05–4.90 (m, 1H), 4.19 (dt, *J* = 16.5, 8.2 Hz, 1H), 2.27 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (dd, *J* = 13.8, 7.2 Hz, 1H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.5, 194.4, 149.5, 148.5, 139.2, 138.1, 131.8, 131.4, 131.2, 131.1, 130.5, 130.2, 129.9, 129.9, 128.6, 120.3, 72.3, 51.2, 30.3, 21.8, 9.8. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 420.1382, found: 420.1391. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 32.4 min (min.) and 36.4 min (major.)).

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (10a)



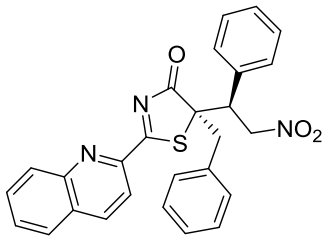
The title compound **10a** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**7**) (94 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 133 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= –165.3.0 (*c*= 0.98, 92% *ee*, CH_2Cl_2). m.p. 72–74 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.13 (m, 3H), 7.95–7.76 (m, 2H), 7.75–7.63 (m, 1H), 7.37 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.19 (dd, *J* = 5.0, 1.8 Hz, 3H), 5.06 (ddd, *J* = 23.9, 13.1, 7.7 Hz, 2H), 4.23 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.12 (ddt, *J* = 16.9, 5.7, 4.0 Hz, 2H), 1.50–1.08 (m, 8H), 0.81 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.5, 194.5, 149.5, 148.5, 138.2, 134.8, 131.5, 131.2, 131.1, 130.3, 130.1, 129.4, 129.2, 128.6, 120.3, 71.5, 51.8, 37.3, 32.2, 29.9, 25.4, 23.2, 14.7. UPLC-DAD-QTOF: $C_{26}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 462.1851, found: 462.1850. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 39.1 min (min.) and 47.4 min (major.)).

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (10d)



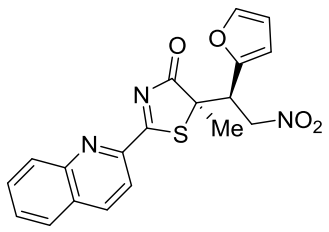
The title compound **10d** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**7**) (94 mg, 0.3 mmol) and 4-methyl-nitrostyrene (**2d**) (98 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 140 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= –185.6 (*c*= 0.99, 98% *ee*, CH_2Cl_2). m.p. 75–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.25 (dt, *J* = 8.5, 6.9 Hz, 3H), 7.95–7.80 (m, 2H), 7.75–7.67 (m, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 13.0, 4.6 Hz, 1H), 5.00 (dd, *J* = 13.0, 10.9 Hz, 1H), 4.21 (dd, *J* = 10.9, 4.6 Hz, 1H), 2.30–2.17 (m, 4H), 2.07 (ddd, *J* = 16.2, 11.9, 5.8 Hz, 1H), 1.47–1.12 (m, 8H), 0.84 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.4, 194.5, 149.4, 148.4, 139.1, 138.0, 131.6, 131.4, 131.1, 131.0, 130.2, 129.9, 129.8, 128.5, 120.3, 71.5, 51.4, 37.2, 32.1, 29.8, 25.2, 23.1, 21.7, 14.6. UPLC-DAD-QTOF: $C_{27}H_{30}N_3O_3S$ $[M+H]^+$ calcd.: 476.2008, found: 476.2013. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 40.7 min (min.) and 47.7 min (major.)).

(*R*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (11a)



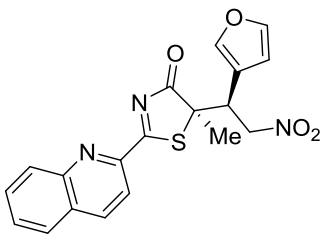
The title compound **11a** was prepared from 5-benzyl-2-(quinolin-2-yl)thiazol-4-ol (**8**) (95 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 126 mg, 0.27 mmol, 90%. $[\alpha]_D^{25}$= -95.5 (*c*= 0.54, 99% *ee*, CH_2Cl_2). m.p. 189–194 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.19 (dd, *J* = 18.4, 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 11.0, 8.4 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.49–7.39 (m, 2H), 7.31–7.06 (m, 8H), 5.25–4.97 (m, 2H), 4.39 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.64–3.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.7, 193.8, 149.1, 148.3, 137.8, 134.9, 134.3, 131.4, 131.2, 131.1, 130.9, 130.2, 130.0, 129.8, 129.4, 129.2, 128.9, 128.6, 128.4, 128.2, 120.0, 78.0, 77.8, 77.6, 77.2, 77.2, 71.9, 51.36, 43.4. UPLC-DAD-QTOF: $C_{27}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 468.1382, found: 468.1391. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 24.1 min (major.) and 27.8 min (min.)).

(*R*)-5-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5be)



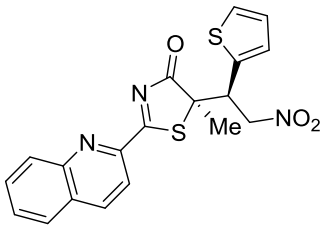
The title compound **5be** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**4b**) (72.7 mg, 0.3 mmol) and 2-(2-nitrovinyl)furan (**2e**) (83 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 110 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= -73.3 (*c*= 0.5, 91% *ee*, CH_2Cl_2). m.p. 89–91 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.33 (s, 2H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.82 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.32 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.38–6.22 (m, 2H), 5.30–5.16 (m, 1H), 4.98 (dd, *J* = 13.4, 10.5 Hz, 1H), 4.33 (dd, *J* = 10.5, 4.1 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.3, 194.8, 149.6, 149.3, 148.3, 143.5, 138.1, 131.3, 131.0, 130.1, 128.4, 120.1, 111.2, 110.5, 74.4, 64.9, 44.9, 23.9. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_4S$ $[M+H]^+$ calcd.: 382.0862, found: 382.0871. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 46.2 min (major.) and 51.2 min (min.)).

(*R*)-5-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bf)



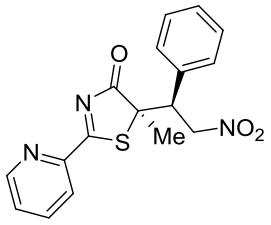
The title compound **5bf** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**4b**) (72.7 mg, 0.3 mmol) and 3-(2-nitrovinyl)furan (**2f**) (83 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 109 mg, 0.285 mmol, 95%. $[\alpha]_D^{25}$= –161.7 (*c*= 1.00, 89% *ee*, CH_2Cl_2). m.p. 166–169 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.18 (m, 3H), 7.91 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.83 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.41 (s, 1H), 7.24 (t, *J* = 1.6 Hz, 1H), 6.43 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.05 (dd, *J* = 12.7, 4.3 Hz, 1H), 4.76 (dd, *J* = 12.7, 10.8 Hz, 1H), 4.19 (dd, *J* = 10.8, 4.3 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.2, 195.3, 149.4, 148.5, 144.0, 142.4, 138.2, 131.5, 131.1, 130.3, 128.6, 120.3, 119.7, 110.5, 65.6, 43.2, 24.6. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_4S$ $[M+H]^+$ calcd.: 382.0862, found: 382.0866. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 48.7 min (major.) and 56.2 min (min.)).

(*R*)-5-Methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bg)



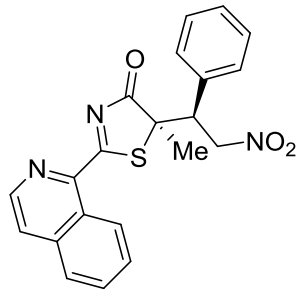
The title compound **5bg** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**4b**) (72.7 mg, 0.3 mmol) and 2-(2-nitrovinyl)thiophene (**2g**) (93 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 111 mg, 0.28 mmol, 93%. $[\alpha]_D^{25}$= –244.7 (*c*= 1.00, 92% *ee*, CH_2Cl_2). m.p. 173-176 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.20 (m, 3H), 7.91 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.84 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.75–7.66 (m, 1H), 7.15 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.06 (dt, *J* = 7.1, 3.6 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.24–5.11 (m, 1H), 4.85 (dd, *J* = 12.9, 10.6 Hz, 1H), 4.54 (dt, *J* = 10.6, 5.3 Hz, 1H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 193.8, 148.3, 147.4, 137.1, 135.8, 130.4, 130.1, 129.2, 128.3, 127.4, 126.3, 125.8, 119.2, 64.6, 53.0, 46.2, 23.7. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_3S_2$ $[M+H]^+$ calcd.: 398.0633, found: 398.0634. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 61.6 min (min.) and 75.6 min (major.)).

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(pyridin-2-yl)thiazol-4(5*H*)-one (5aa)



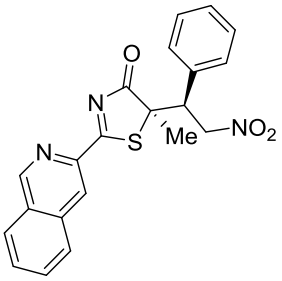
The title compound **5aa** was prepared from 5-methyl-2-(pyridin-2-yl)thiazol-4-ol (**4a**) (57.7 mg, 0.3 mmol) and nitrostyrene (**2a**) (89.4 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 81.9 mg, 0.24 mmol, 80%. $[\alpha]_D^{25}$= -58.2 (*c*= 1.00, 80% *ee*, CH_2Cl_2). m.p. 185–186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.73 (d, *J* = 4.2 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.35–7.28 (m, 2H), 7.28–7.14 (m, 3H), 5.15 (dd, *J* = 13.2, 4.7 Hz, 1H), 4.94 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 4.7 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.8, 194.1, 150.0, 148.8, 137.3, 134.2, 129.0, 128.7, 128.7, 128.5, 123.7, 75.9, 65.1, 50.2, 23.9. HRMS: $C_{17}H_{15}N_3O_3S$ $[M+H]^+$ calcd.: 342.0912, found: 342.0909. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 42.8 min (min.) and 47.2 min (major.)).

(*R*)-2-(isoquinolin-3-yl)-5-methyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)thiazol-4(5*H*)-one (5ca)



The title compound **5ca** was prepared from 2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (**5c**) (72.7 mg, 0.3 mmol) and 4-methyl-*β*-nitrostyrene (**2a**) (98 mg, 0.6 mmol) according to the general procedure. The title compound was obtained as a 86:14 mixture of isomers. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 112 mg, 0.29 mmol, 95 %. m.p. 106–108 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 8.69 (s, 1H), 8.11 – 8.04 (m, 1H), 8.00 – 7.92 (m, 2H), 7.85 – 7.76 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.18 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.94 (dt, *J* = 11.0, 8.1 Hz, 1H), 4.18 (dt, *J* = 10.9, 5.6 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.4, 195.1, 153.9, 143.5, 139.5, 136.1, 132.8, 132.3, 132.0, 131.8, 130.9, 130.3, 129.9, 129.0, 123.9, 66.4, 51.0, 22.1. UPLC-DAD-QTOF: $C_{21}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1071. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.7 min (mayor.) and 25.2 min (min.). Processed Channel Descr.: PDA 260.0 nm).

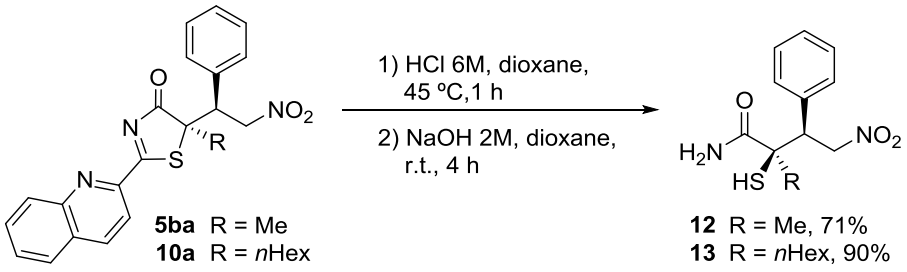
(*R*)-2-(isoquinolin-3-yl)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-5-methylthiazol-4(5H)-one (5da)



The title compound **5da** was prepared from 2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (**5d**) (72.7 mg, 0.3 mmol) and nitrostyrene (**2a**) (137 mg, 0.6 mmol) according to the general procedure. The title compound was obtained as a 91:9 mixture of isomers. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 106 mg, 0.27 mmol, 90 %. m.p. 101–103 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (d, *J* = 3.4 Hz, 1H), 8.69 (s, 1H), 8.12 – 8.05 (m, 1H), 7.99 (dd, *J* = 8.9, 4.6 Hz, 1H), 7.87 – 7.76 (m, 3H), 7.39 – 7.31 (m, 2H), 7.24 (dt, *J* = 9.0, 2.2 Hz, 2H), 5.14 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.92 (dd, *J* = 13.2, 11.0 Hz, 1H), 4.19 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.6, 195.0, 154.1, 143.4, 136.3, 134.4, 133.1, 133.0, 132.1, 131.9, 130.2, 129.2, 124.4, 124.3, 66.1, 51.0, 25.5. UPLC-DAD-QTOF: $C_{21}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1073. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 36.6 min (mayor.) and 42.3 min (min.). Processed Channel Descr.: PDA 260.0 nm).

5.2.5. **Elaboration of adducts**

5.2.5.1. **Hydrolysis of adducts 5ba and 10**



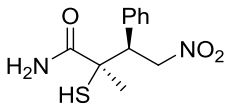
5ba R = Me
10a R = *n*Hex

12 R = Me, 71%
13 R = *n*Hex, 90%

The reaction adduct (1 mmol, 1 equiv.) was dissolved in a mixture of dioxane (5 mL) and HCl 6N (1.84 mL, 11.04 mmol, 12 equiv.). The resulting solution was heated at 45 °C for 1 h. After this period the cooled reaction mixture was treated at 0 °C with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane 1/1).

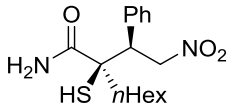
The obtained product was dissolved in 1 mL of dioxane at 0 °C, and a 2 M aqueous solution of NaOH (0.8 mL, 1.60 mmol, 2.5 eq.,) was added dropwise. The resulting mixture was stirred at room temperature for 4 h and afterwards the reaction was quenched with 2 M aq. $NaHSO_4$. The combined organic phases were washed with an aqueous solution of saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the pure product which was used as such in the next step.

(*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide (12)



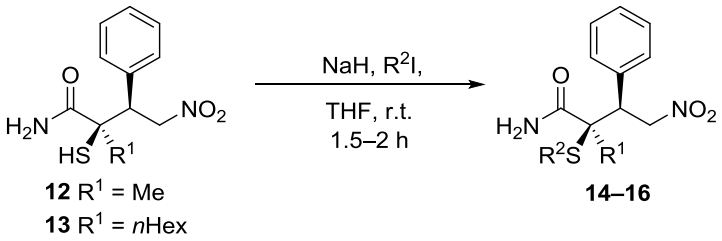
Yield: 335.4 mg, 0.82 mmol, 71%. $[\alpha]_D^{25}$= +2.9 (*c*= 1.00, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35–7.28 (m, 5H), 6.42–6.31 (m, 1H), 5.52–5.41 (m, 1H), 5.14–5.05 (m, 2H), 4.22 (dd, *J* = 8.8, 6.1 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 175.3, 135.4, 129.1, 128.6, 128.4, 77.0, 54.0, 52.0, 26.9. UPLC-DAD-QTOF: $C_{11}H_{14}N_2O_3S$ $[M+H]^+$ calcd.: 254.0725, found: 254.0721. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 33.2 min (major.) and 48.6 min (min.)).

(*R*)-2-mercapto-2-((S)-2-nitro-1-phenylethyl)octanamide (13)



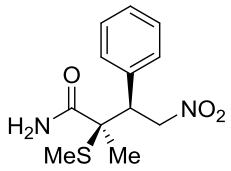
Yellow oil; yield: 58.2 mg, 0.22 mmol, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (dd, *J* = 12.5, 5.2 Hz, 5H), 6.58 (s, 1H), 6.16 (s, 1H), 5.15 – 4.88 (m, 1H), 4.40 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 2.13 (d, *J* = 17.6 Hz, 2H), 1.73 – 1.49 (m, 1H), 1.51 – 1.03 (m, 8H), 1.01 – 0.71 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9, 136.0, 130.2, 129.6, 129.4, 129.2, 129.0, 67.9, 61.1, 51.4, 40.2, 32.3, 30.5, 30.1, 29.8, 26.2, 23.3, 15.0, 14.8.UPLC-DAD-QTOF: $C_{10}H_{12}N_2O_3S$ $[M+H]^+$ calcd.: 240.0569, found: 240.0571.

5.2.5.2. ***S*-Alkylation of α-mercapto carboxylic acid derivatives 12–13**



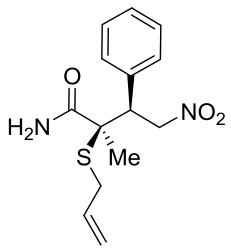
To a solution of the corresponding amide (0.24 mmol, 1 equiv.) in dry THF (1mL) under argon atmosphere was added NaH 60% in mineral oil (11 mg, 0.29 mmol, 1.2 equiv.). The mixture was cooled to 0 ºC and then the corresponding alkyl halide (1.2 equiv) was added. The mixture was stirred at room temperature for 2h and then quenched with 2 M aq. $NaHSO_4$. The organic layer was separated and washed with an aqueous solution of saturated $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with ethyl acetate/hexane 1/1).

(*2R,3S*)-2-Methyl-2-(methylthio)-4-nitro-3-phenylbutanamide (14)



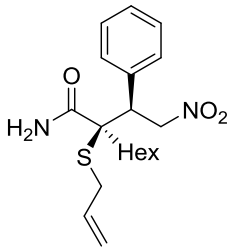
The title compound **14** was prepared from (*2R,3S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide (**12**) (61 mg, 0.24 mmol) and MeI (18 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 58.2 mg, 0.22 mmol, 90%. $[\alpha]_D^{25}$= -14.2 (*c*= 1.00, 93% ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.27 (m, 5H), 6.69–6.49 (m, 1H), 5.56–5.36 (m, 1H), 5.13–5.00 (m, 2H), 3.99 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.10 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.4, 134.99, 130.0, 128.5, 127.9, 94.6, 77.0, 55.7, 51.2, 21.4, 12.4. UPLC-DAD-QTOF: $C_{12}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 269.0882, found: 269.0885.

(*2R,3S*)-2-(Allylthio)-2-methyl-4-nitro-3-phenylbutanamide (15)



The title compound **15** was prepared from (*2R,3S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide (**12**) (61 mg, 0.24 mmol) and allyl iodide (27 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 65.7 mg, 0.22 mmol, 93%. $[\alpha]_D^{25}$= -2.2 (*c*= 0.5, 93% ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36–7.27 (m, 5H), 6.63–6.48 (m, 1H), 5.56–5.41 (m, 1H), 5.29–4.98 (m, 4H), 3.99 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.34–3.11 (m, 2H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 174.2, 134.9, 132.8, 129.4, 128.6, 128.6, 119.0, 77.0, 56.6, 51.8, 33.2, 22.4. UPLC-DAD-QTOF: $C_{14}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 295.1116, found: 295.1118.

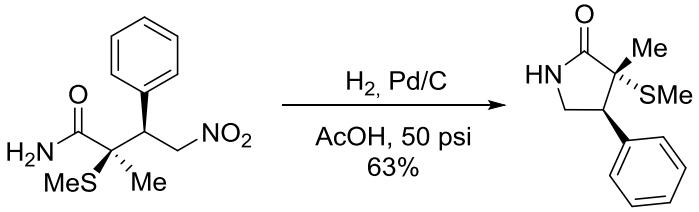
(*R*)-2-(Allylthio)-2-((*S*)-2-nitro-1-phenylethyl)octanamide (16)



The title compound **16** was prepared from (*R*)-2-mercapto-2-((S)-2-nitro-1-phenylethyl)octanamide (**13**) (78 mg, 0.24 mmol) and allyl iodide (27 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 80 mg, 0.22 mmol, 91%. $[\alpha]_D^{25}$= –9.1 (*c*= 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.13 (m, 5H), 6.30 (s, 1H), 5.83 (ddt, *J* = 14.2, 10.0, 7.1 Hz, 2H), 5.32 – 4.96 (m, 3H), 3.99 (dt, *J* = 19.6, 9.8 Hz, 1H), 3.27 – 3.04 (m, 2H), 1.79 – 1.44 (m, 4H), 1.27 (d, *J* = 12.0 Hz, 7H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.2, 135.3, 132.6, 129.4, 128.5, 128.4, 118.9, 78.0, 61.0, 49.8, 34.9, 33.2, 31.6, 29.7, 29.4, 24.7, 22.5, 14.0. UPLC-DAD-QTOF: $C_{19}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 365.1899, found: 365.1912.

5.2.5.3. **Reduction of the nitro group in 14: formation of γ-lactam 17**

(*3R,4S*)-3-Methyl-3-(methylthio)-4-phenylpyrrolidin-2-one (17)

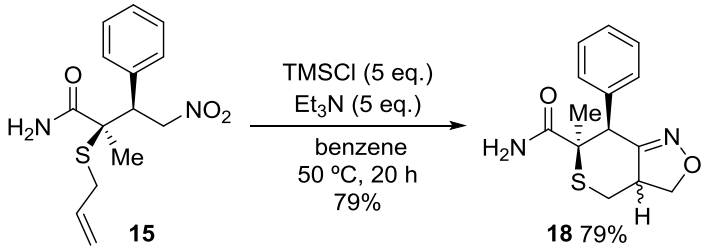


14 **17**

10% Palladium on carbon (15 mg) was added to a solution of (*2R,3S*)-2-methyl-2-(methylthio)-4-nitro-3-phenylbutanamide **14** (32 mg, 0.12 mmol) in acetic acid (5.0 mL). The reaction vessel was evacuated and back-filled with hydrogen (3x) and afterwards the reaction mixture was stirred under hydrogen atmosphere (50 psi) at room temperature overnight. The reaction mixture was filtered over celite, concentrated, and a saturated aqueous sodium carbonate solution was added. The mixture was extracted with dichloromethane (3x 10mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20 to 50/50) to give the title compound as a colourless oil. Yield: 16 mg, 0.076 mmol, 63%. $[\alpha]_D^{25}$= 0.82 (*c*= 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.34–7.23 (m, 5H), 6.45 (bs, 1H), 3.89 (m, 1H), 3.56 (m, 1H), 3.42 (s, 1H), 2.22 (s, 3H), 1.04 (s, *3*H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 177.2, 139.0, 129.4, 128.6, 128.3, 127.9, 127.5, 52.0, 50.4, 45.2, 18.4, 12.4. UPLC-DAD-QTOF: $C_{12}H_{16}NOS$ $[M+H]^+$ calcd.: 222.0953, found: 222.0964.

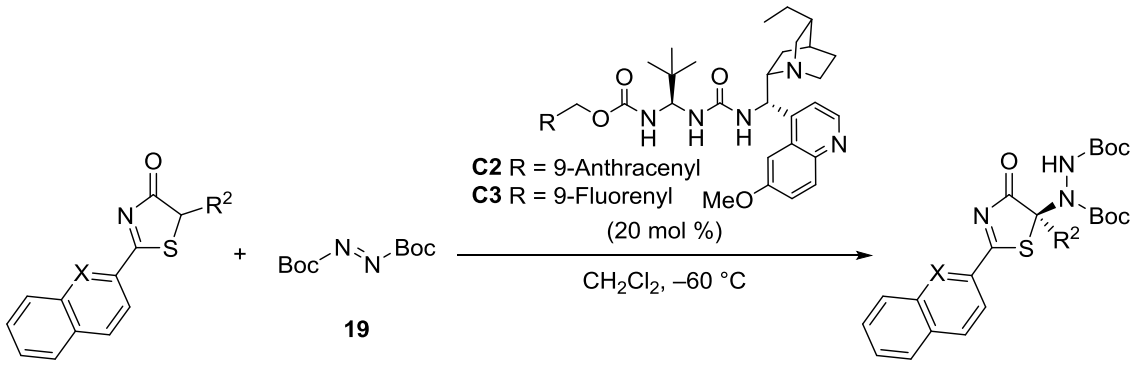
5.2.5.4. **1,3-Dipolar cyloaddition of 15**

(*6R,7S*)-6-Methyl-7-phenyl-3a,4,6,7-tetrahydro-3H-thiopyrano[4,3-c]isoxazole-6-carboxamide (18)



To a solution of nitroalkane **15** (1 eq., 70 mg, 0.24 mmol) in 1.5 mL of C_6H_6 under Ar atmosphere were added Et_3N (5 eq., 165 µl, 1.2 mmol) and freshly distilled TMSCl (4 eq., 121 µl, 0.96 mmol). After the addition was complete the mixture was warmed to 50°C and stirred for 20 h. Afterwards, the reaction mixture was cooled to 0ºC and treated with 1.5 mL of HCl 2M. The acidic mixture was stirred for 20 min at room temperature and then was washed with water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate 80/20 to 50/50, Hexane:AcOEt). Yield: 52 mg, 0.19 mmol, 79%. (dr 1.4:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.72–7.27 (m, 5H), 5.39 (bs, 2H), 5.23 (bs, 2H), 4.66 (t, *J* = 9.0 Hz, 1H) (Major), 4.44 (t, *J* = 9.0 Hz, 1H) (Minor), 4.35 (s, 1H), 3.96-3.82 (m), 3.64-3.48 (m), 3.04-2.87 (m), 1.82 (s, 3H) (Minor), 1.41 (s, 3H) (Minor). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.1 (Major), 173.1 (Minor), 159.6 (Major), 158.2 (Minor), 137.0 (Minor), 134.2 (Major), 130.5, 128.9, 128.4, 128.3, 128.0, 127.5, 73.3 (Major), 73.0 (Minor), 55.9 (Major), 55.1 (Minor), 49.0 (Major), 48.5 (Minor), 44.8 (Minor), 30.8 (Major), 30.2 (Minor), 27.3 (Minor), 22.7 (Major). UPLC-DAD-QTOF: $C_{14}H_{16}N_2O_2S$ $[M+H]^+$ calcd.: 277.1011, found: 277.1013.

5.2.6. **General procedure for the asymmetric conjugate addition of 5*H*-thiazol-4-ones to di-*tert*-butyl azodicarboxylate**



4b X = N, R^2 = Me
4e X = C, R^2 = Me
7 X = N, R^2 = *n*Hex

21 X = N, R^2 = Me
22 X = C, R^2 = Me
23 X = N, R^2 = *n*Hex

5.2.6.1. **Asymmetric reaction**

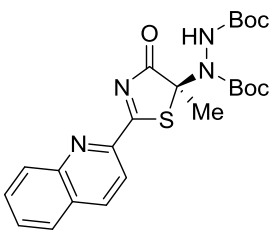
To a mixture of the corresponding thiazolone (0.3 mmol, 1 equiv.) and di-*tert*-butyl azodicarboxylate (0.6 mmol, 2 equiv.) in dichloromethane (0.6 mL) at –60 °C the catalyst was added. The resulting suspension was stirred at –60 °C, until the signals of the thiazolone had disappeared (monitored by *1*H NMR). The reaction mixture was purified by flash column chromatography on silica gel without treatment to afford the expected adducts.

5.2.6.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using triethylamine (20 mol %) as the catalyst at –20 °C.

5.2.6.3. **Characterization data for compounds 24–25**

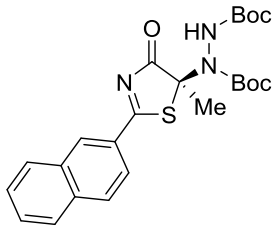
(*S*)-Di-*tert*-butyl 1-(5-methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (21)



The title compound **21** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**4b**) (74 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) 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 give the title compound as a yellow solid. Yield: 113.4 mg, 0.24 mmol, 80%. $[\alpha]_D^{25}$= +72.3 (*c*= 1.00, 96% *ee*, CH_2Cl_2). m.p.

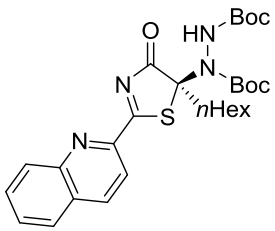
110–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 8.3 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.86–7.74 (m, 1H), 7.74–7.58 (m, 1H), 6.70 (s, 1H), 1.82 (s, 3H), 1.53 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.2, 155.9, 152.8, 149.9, 147.9, 137.3, 130.7, 130.6, 129.3, 127.9, 119.6, 83.5, 82.4, 79.3, 28.3, 28.1, 25.9. UPLC-DAD-QTOF: $C_{23}H_{29}N_4O_5S$ $[M+H]^+$calcd.: 473.1859, found: 473.1866. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 21.9 min (min.) and 72.3 min (major.)).

(*S*)-Di-*tert*-butyl 1-(5-methyl-2-(naphthalen-2-yl)-4-oxo-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (22)



The title compound **22** was prepared from 5-methyl-2-(naphthalen-2-yl)thiazol-4-ol (**4e**) (72 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) 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 give the title compound as a yellow solid. Yield: 99 mg, 0.21 mmol, 70%. $[\alpha]_D^{25}$= +118.1 (*c*= 1.00, 74% *ee*, CH_2Cl_2). m.p. 120–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.75 (d, *J* = 12.9 Hz, 1H), 8.20 (dd, *J* = 18.8, 8.5 Hz, 1H), 7.95 (dd, *J* = 17.6, 8.2 Hz, 3H), 7.63 (dt, *J* = 14.7, 6.8 Hz, 2H), 6.81 (s, 1H), 1.88 (s, 3H), 1.56 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 194.8, 190.4, 156.0, 152.6, 136.7, 132.6, 130.8, 130.1, 129.9, 129.3, 128.8, 128.0, 127.3, 124.2, 82.5, 80.6, 28.3, 28.0, 26.2. UPLC-DAD-QTOF: $C_{24}H_{30}N_3O_5S$ $[M+H]^+$calcd.: 472.1906, found: 472.1920. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 24.4 min (min.) and 62.0 min (major.)).

(*S*)-Di-*tert*-butyl 1-(5-hexyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (23)

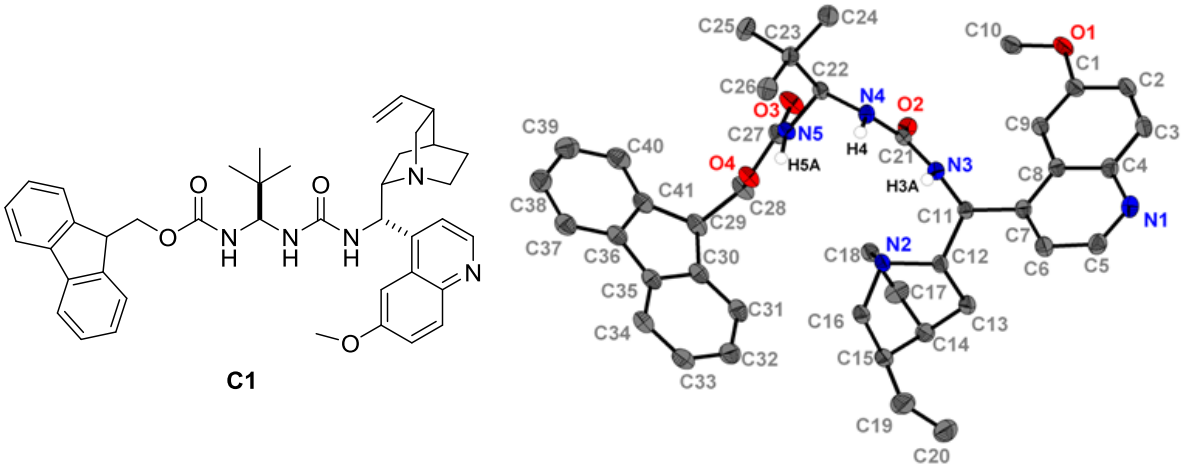


The title compound **23** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**7**) (94 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 138 mg, 0.26 mmol, 85%. $[\alpha]_D^{25}$= +67.8 (*c*= 1.00, 96% *ee*, CH_2Cl_2). m.p. 64–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.41 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H),

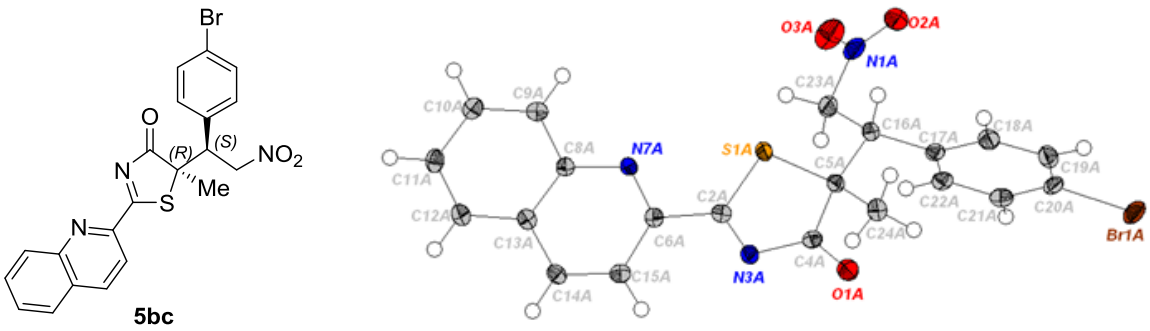
7.65 (s, 1H), 6.68 (s, 1H), 2.09 (s, 2H), 1.52 (s, 9H), 1.45 (s, 8H), 1.35 (s, 9H), 0.79 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$), δ 197.3, 190.8, 155.9, 152.9, 149.9, 147.9, 137.6, 137.2, 130.7, 130.5, 130.1, 129.6, 129.2, 127.8, 119.7, 83.4, 83.2, 82.3, 60.5, 54.0, 37.9, 31.8, 31.5, 29.4, 29.3, 28.3, 28.1, 22.7, 22.6, 14.3, 14.0. UPLC-DAD-QTOF: $C_{28}H_{39}N_4O_5S$ $[M+H]^+$calcd.: 543.2641, found: 543.2642.. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 14.8 min (min.) and 36.0 min (major.)).

5.2.7. **X-Ray Analysis: ORTEP diagrams of compounds C1 and 5bc.**

CCDC-930440 contains the supplementary crystallographic data for the structural analysis of **C1**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

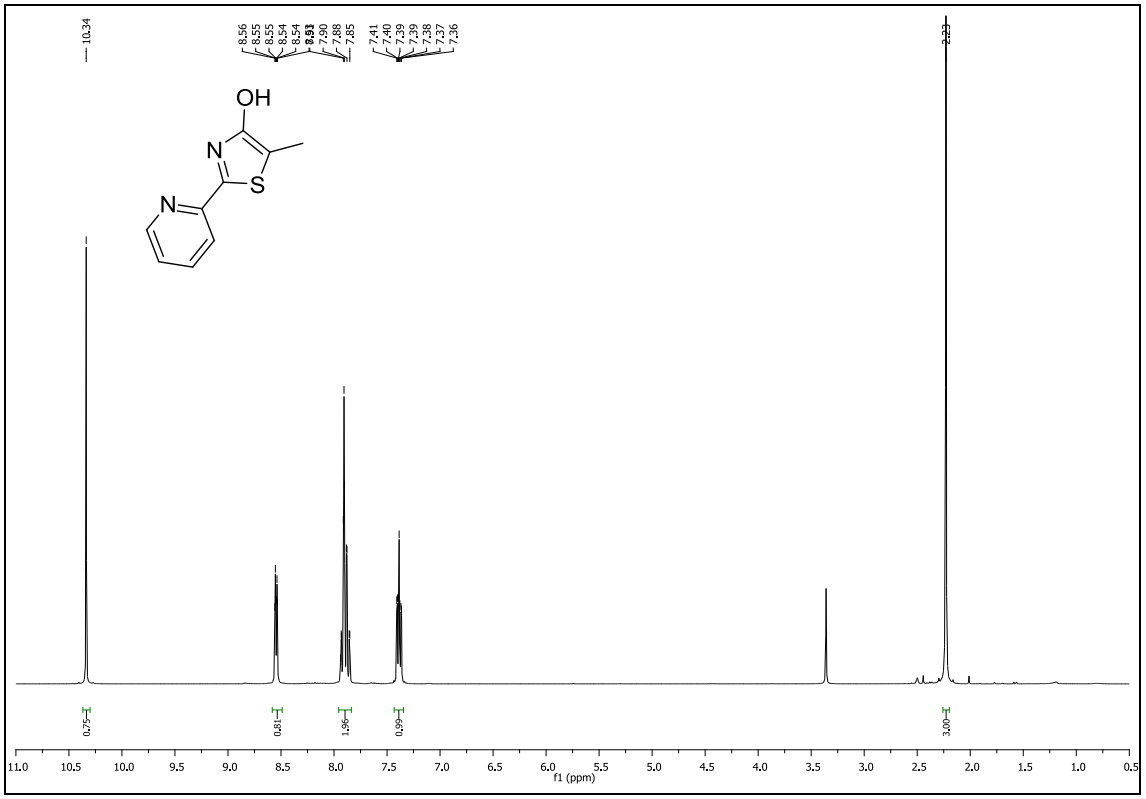


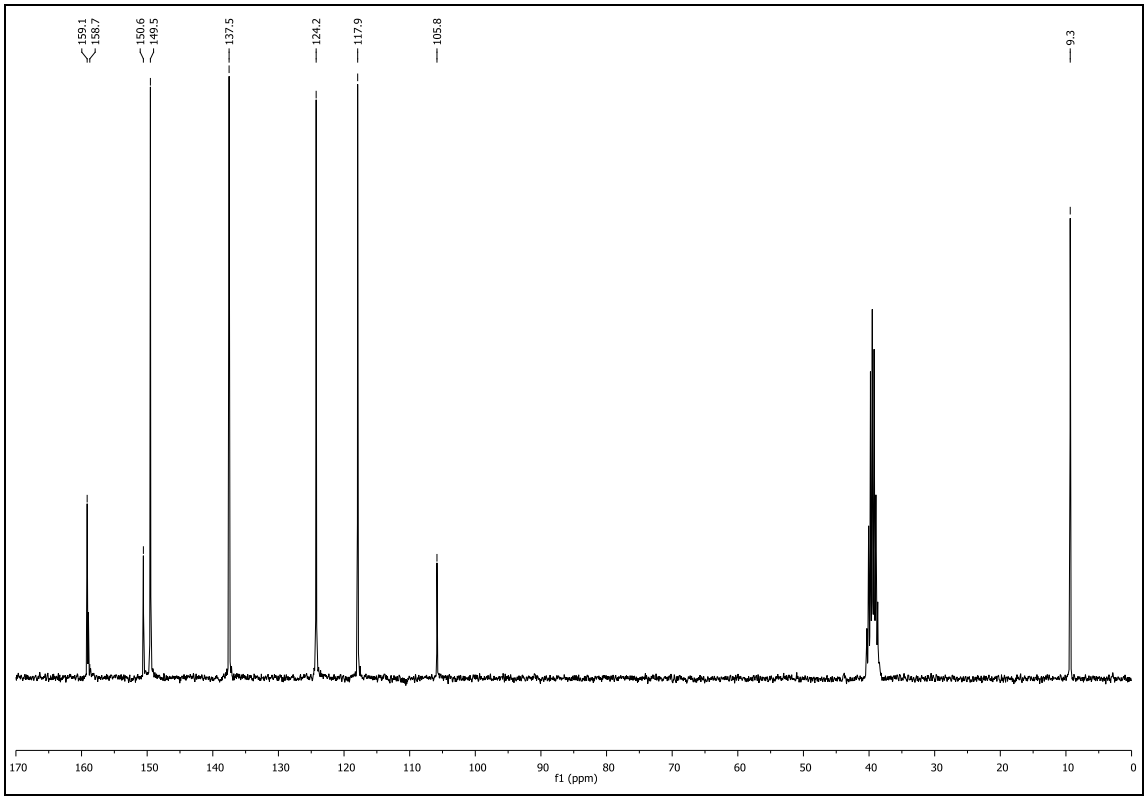
CCDC-947275 contains the supplementary crystallographic data for the structural analysis of **5bc**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



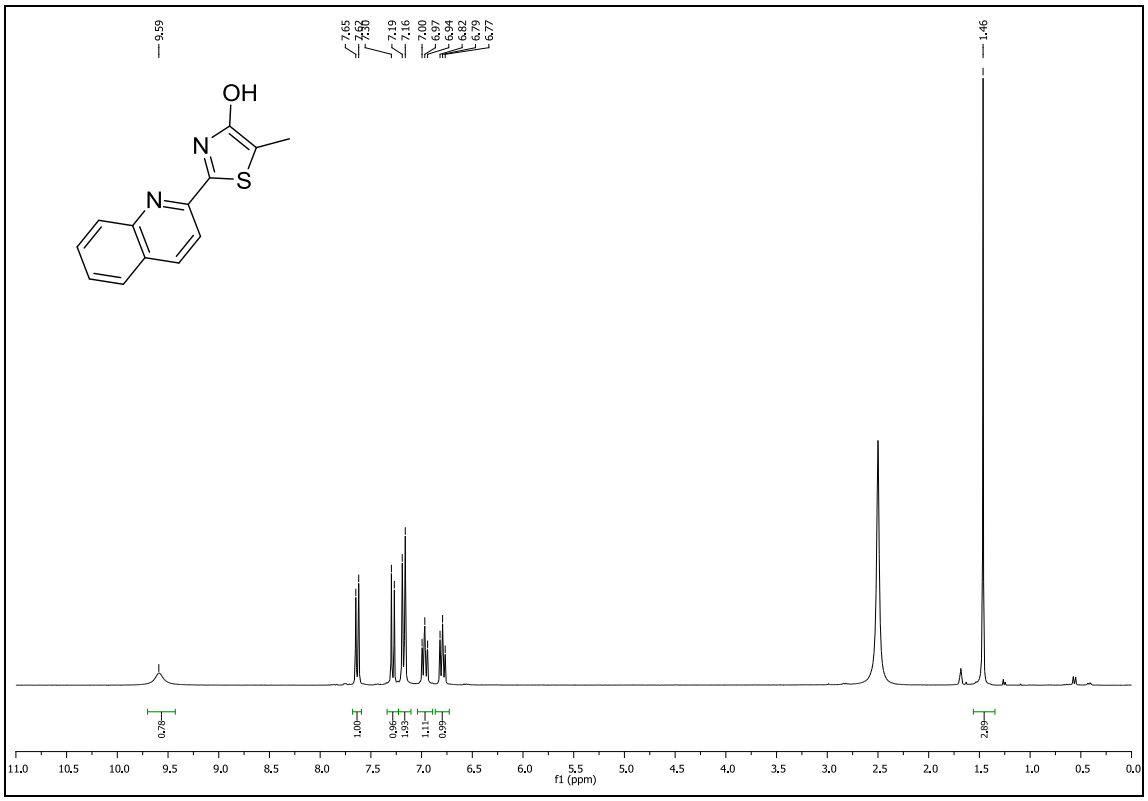
5.2.8. **Representative NMR spectra**

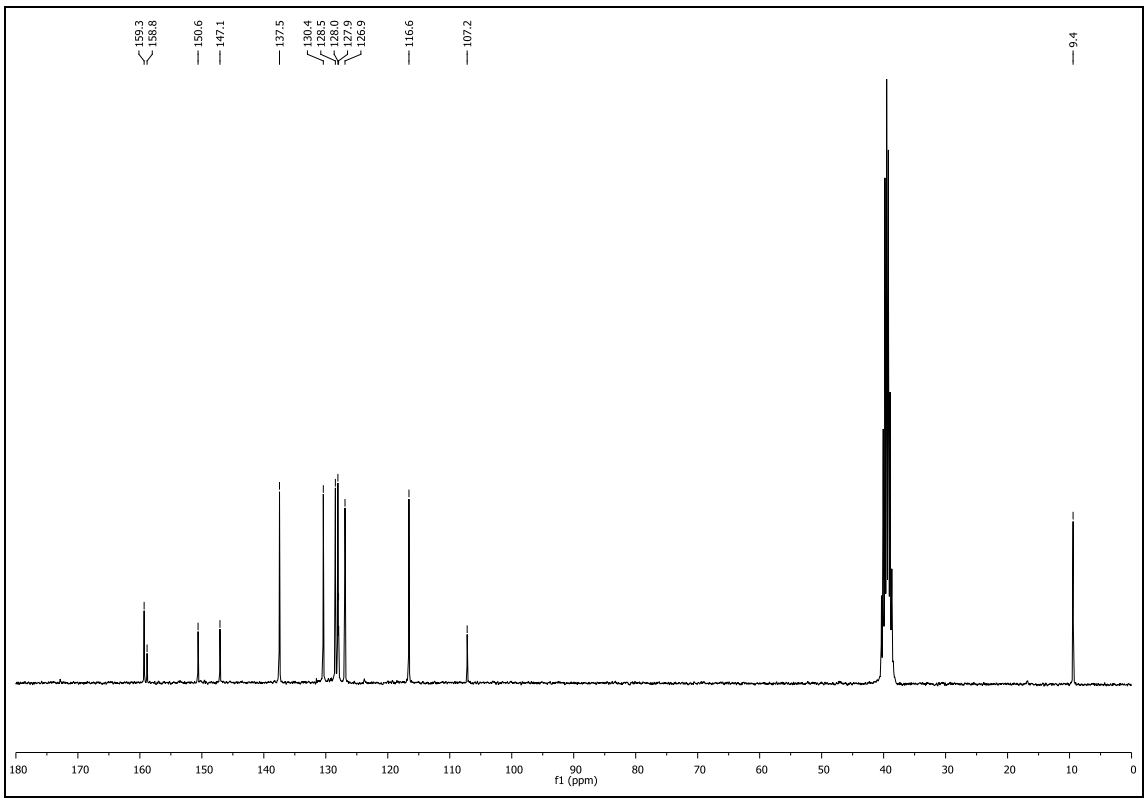
5-Methyl-2-(pyridin-2-yl)thiazol-4-ol (4a)



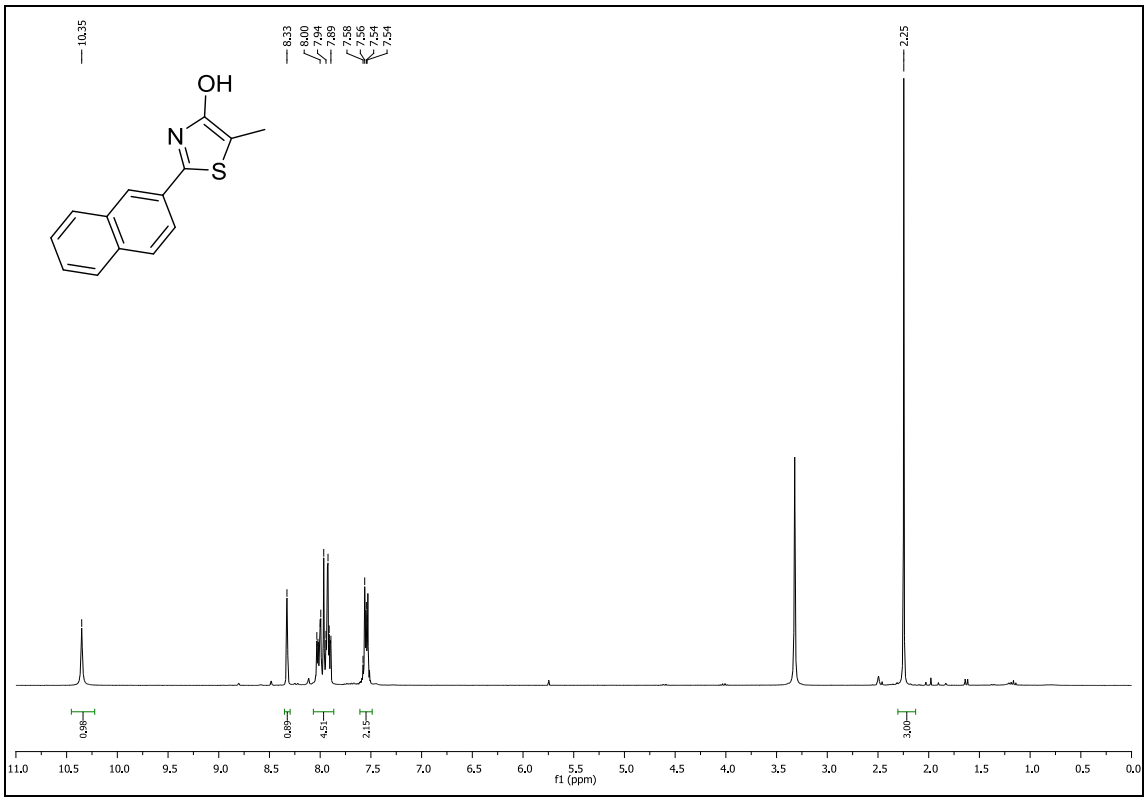


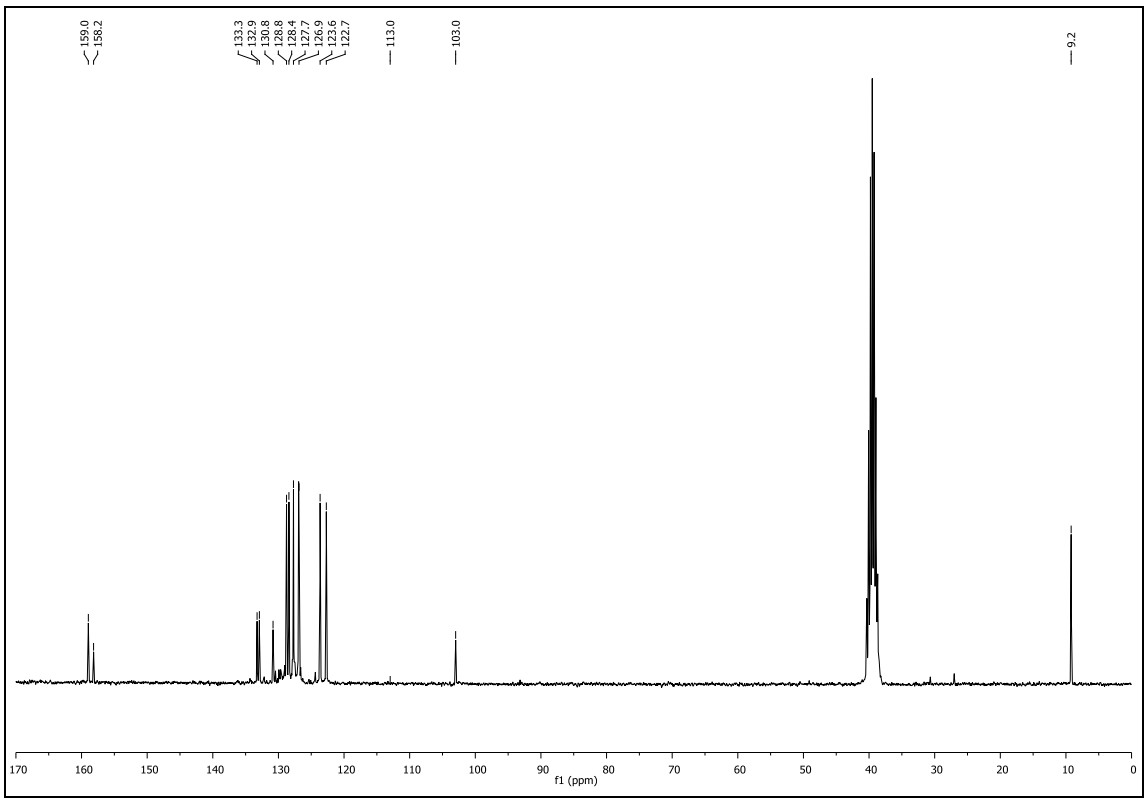
5-Methyl-2-(quinolin-2-yl)thiazol-4-ol (4b)



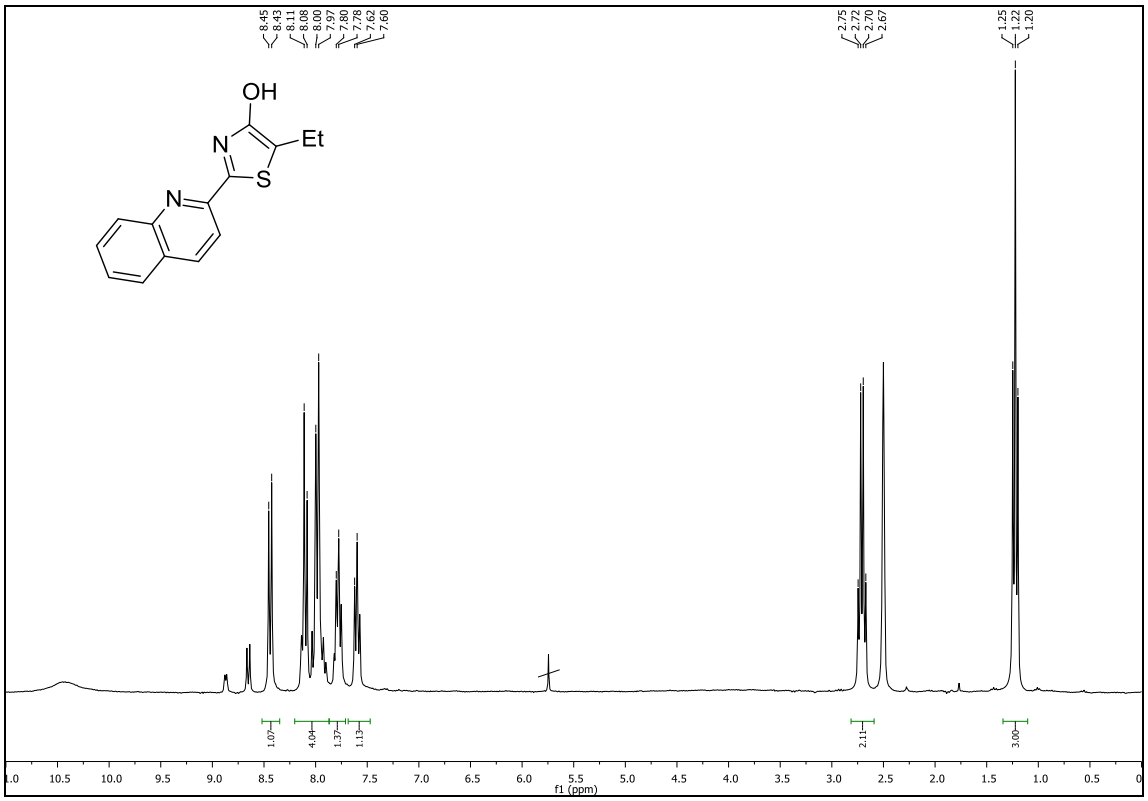


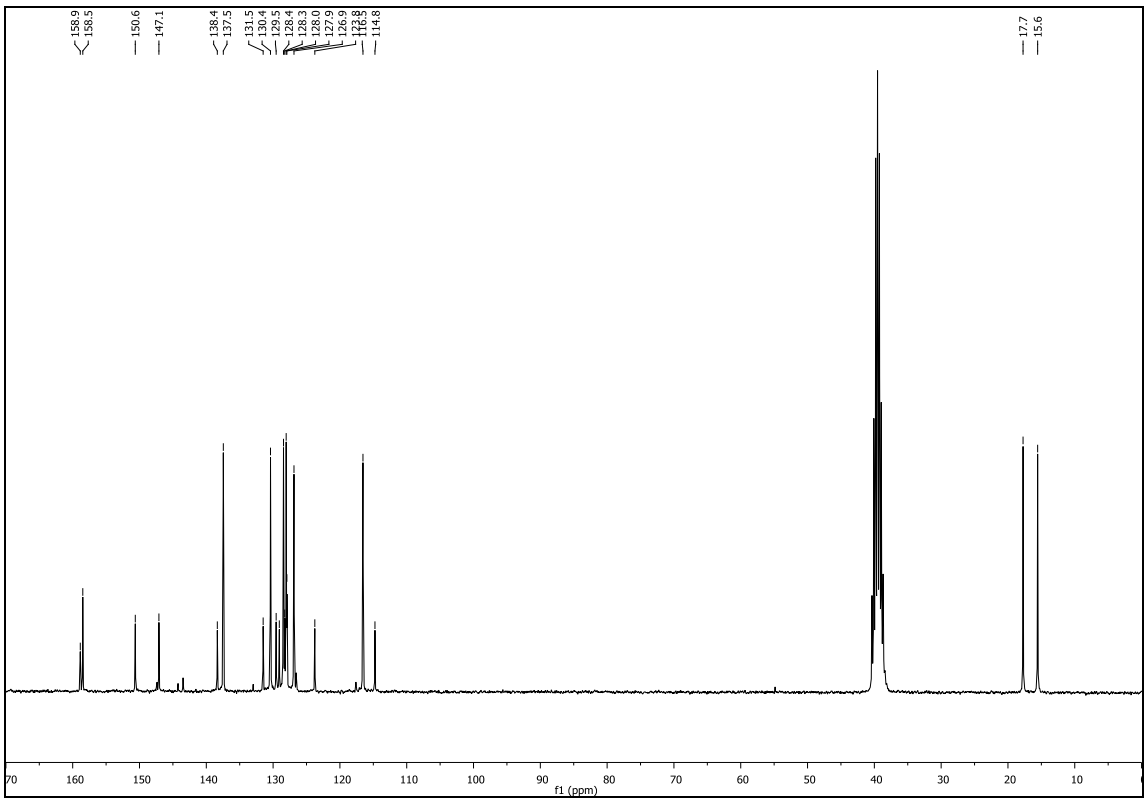
5-Methyl-2-(naphthalen-2-yl)thiazol-4-ol (4e)



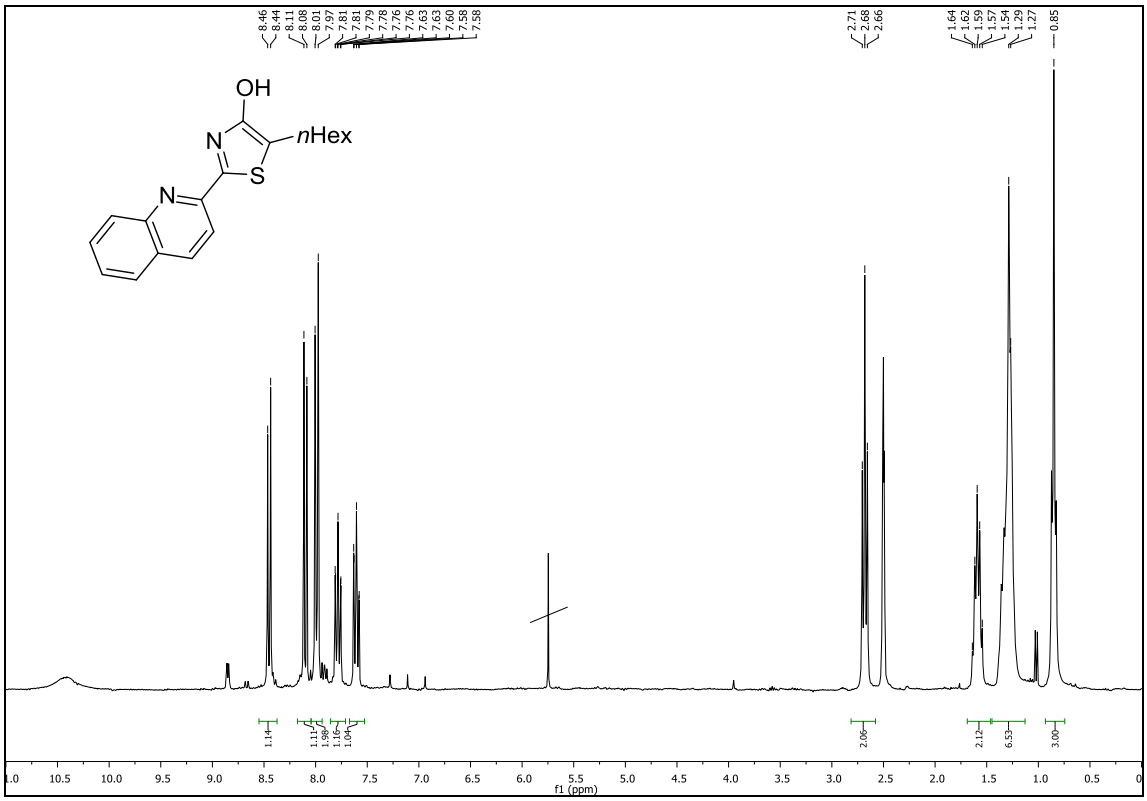


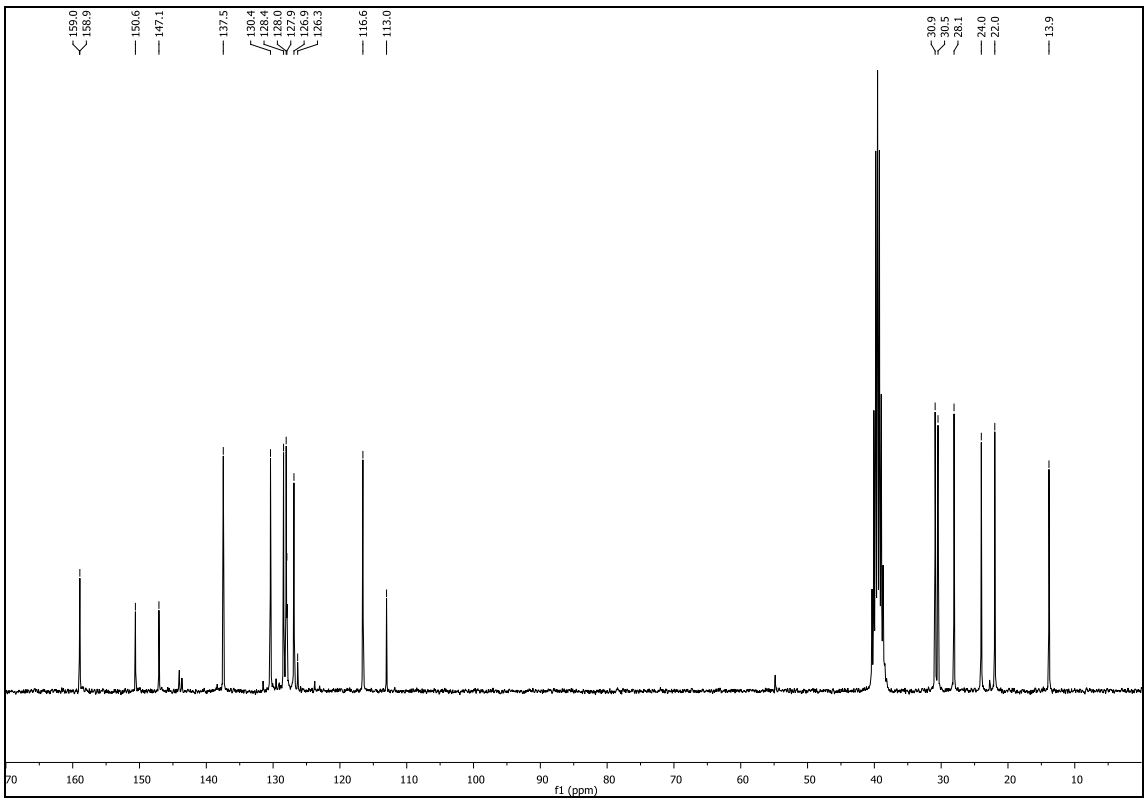
5-Ethyl-2-(quinolin-2-yl)thiazol-4-ol (6)



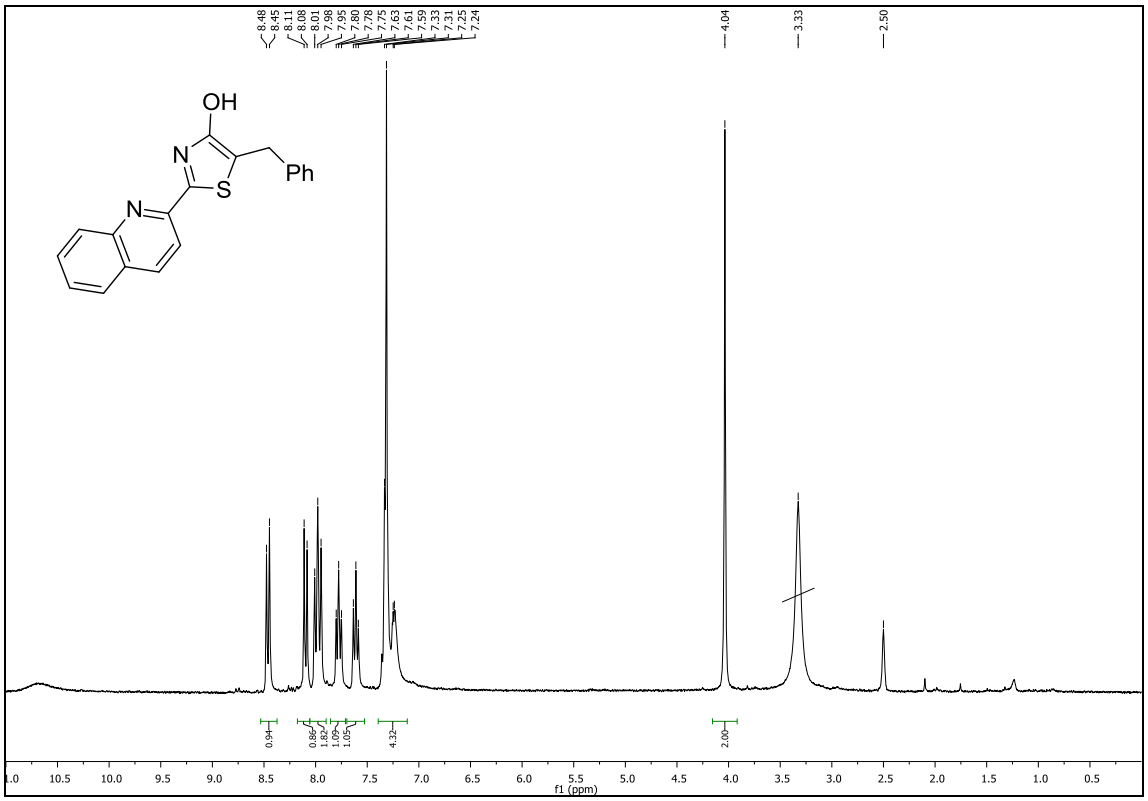


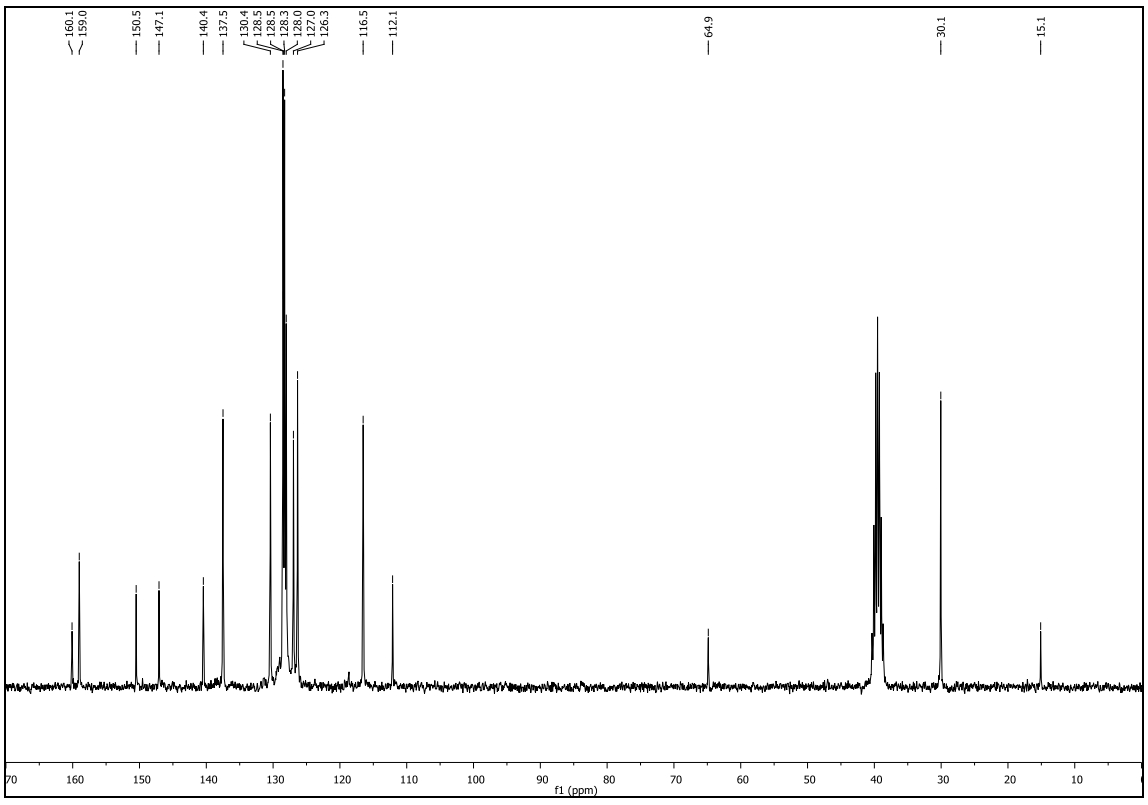
5-Hexyl-2-(quinolin-2-yl)thiazol-4-ol (7)



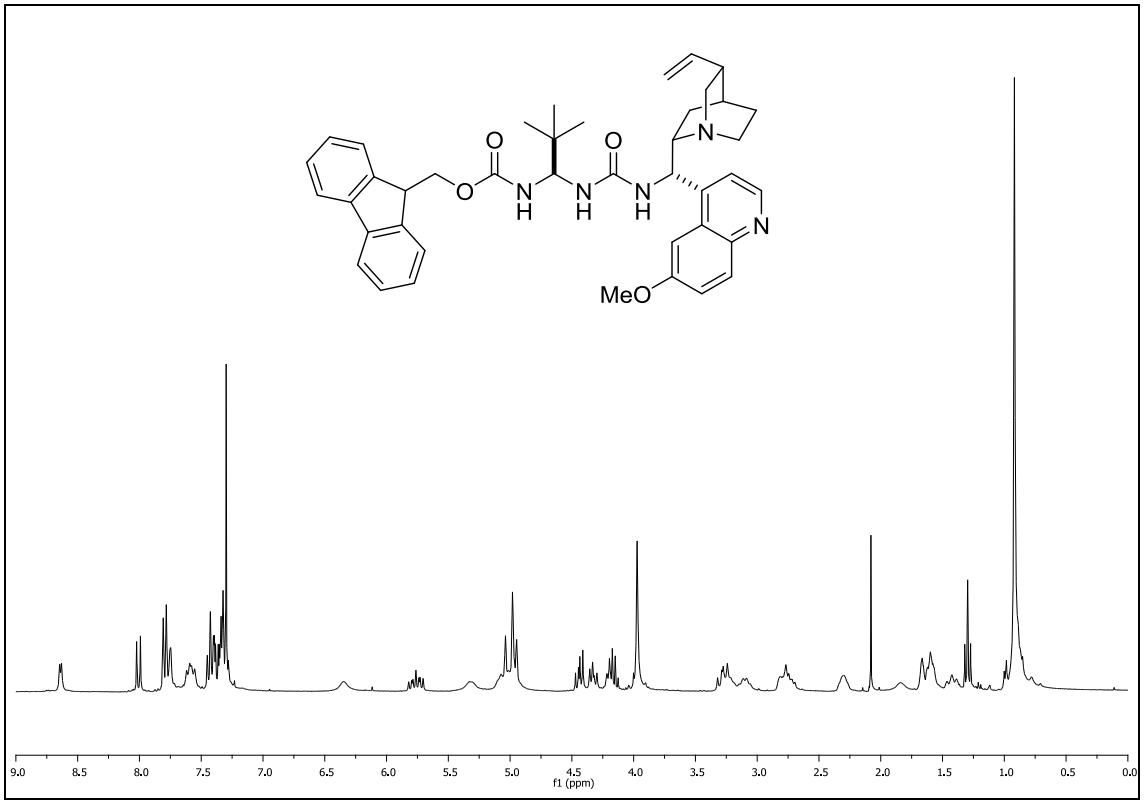


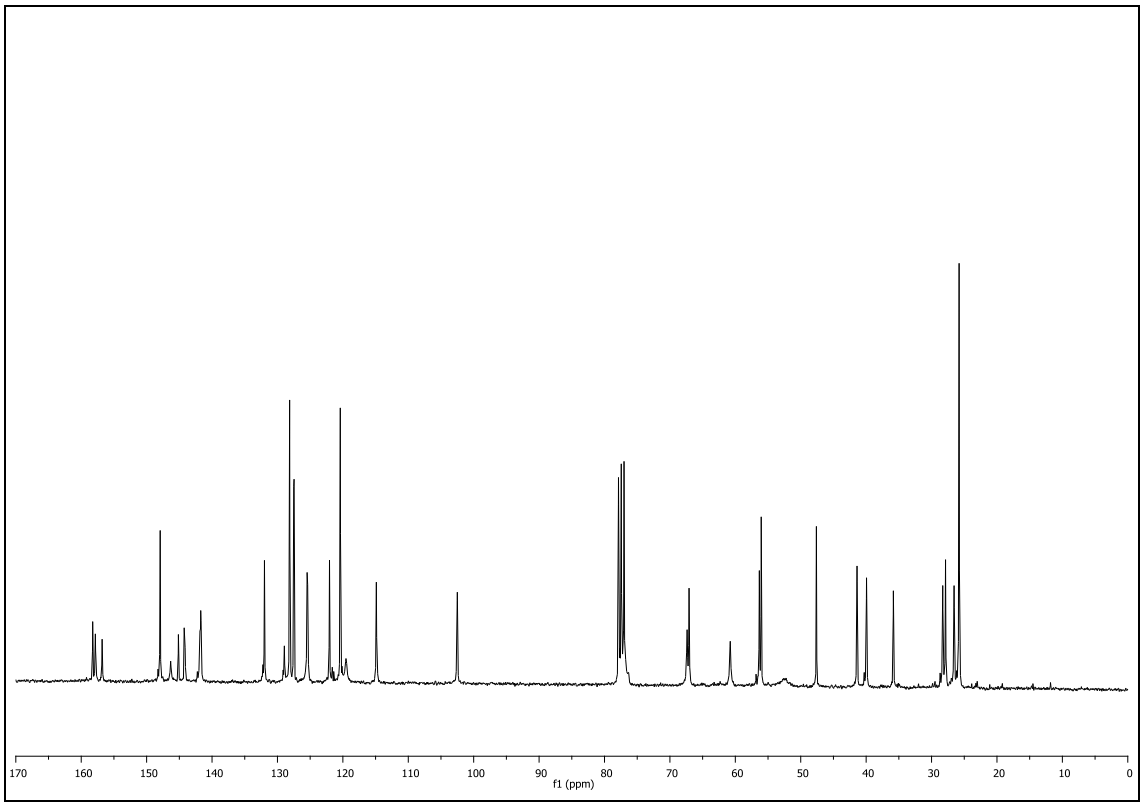
5-Benzyl-2-(quinolin-2-yl)thiazol-4-ol (8)



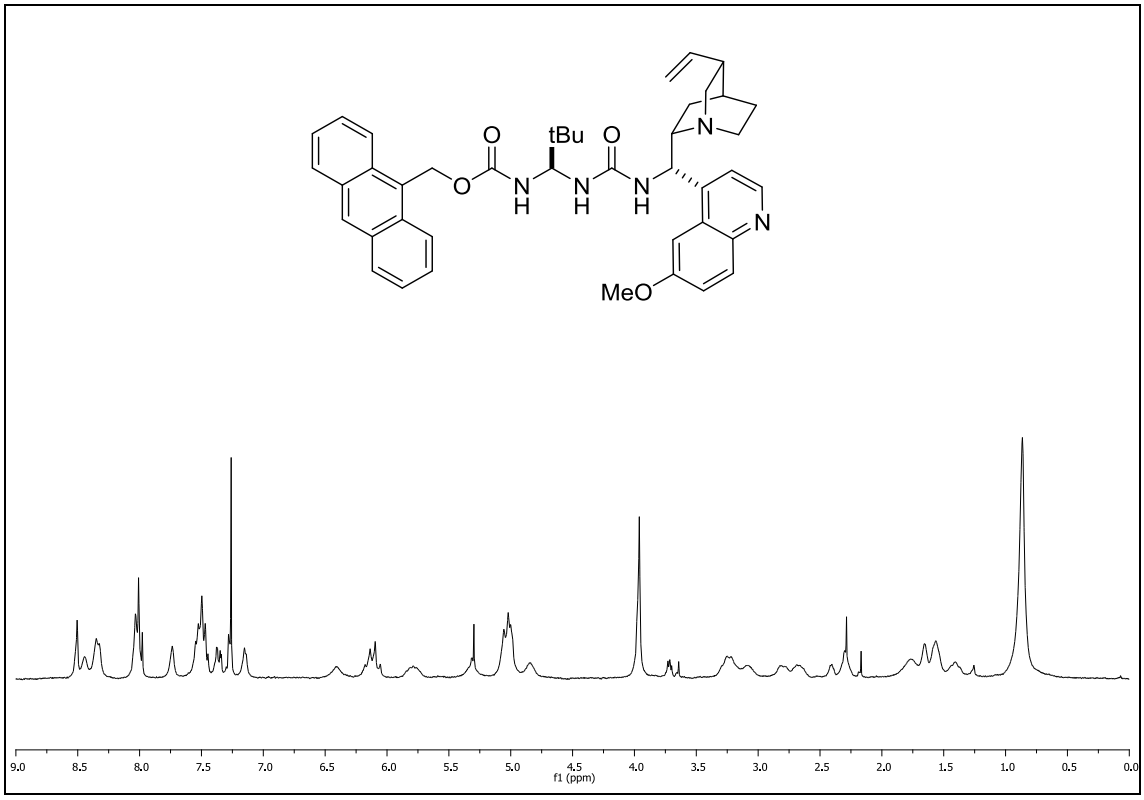


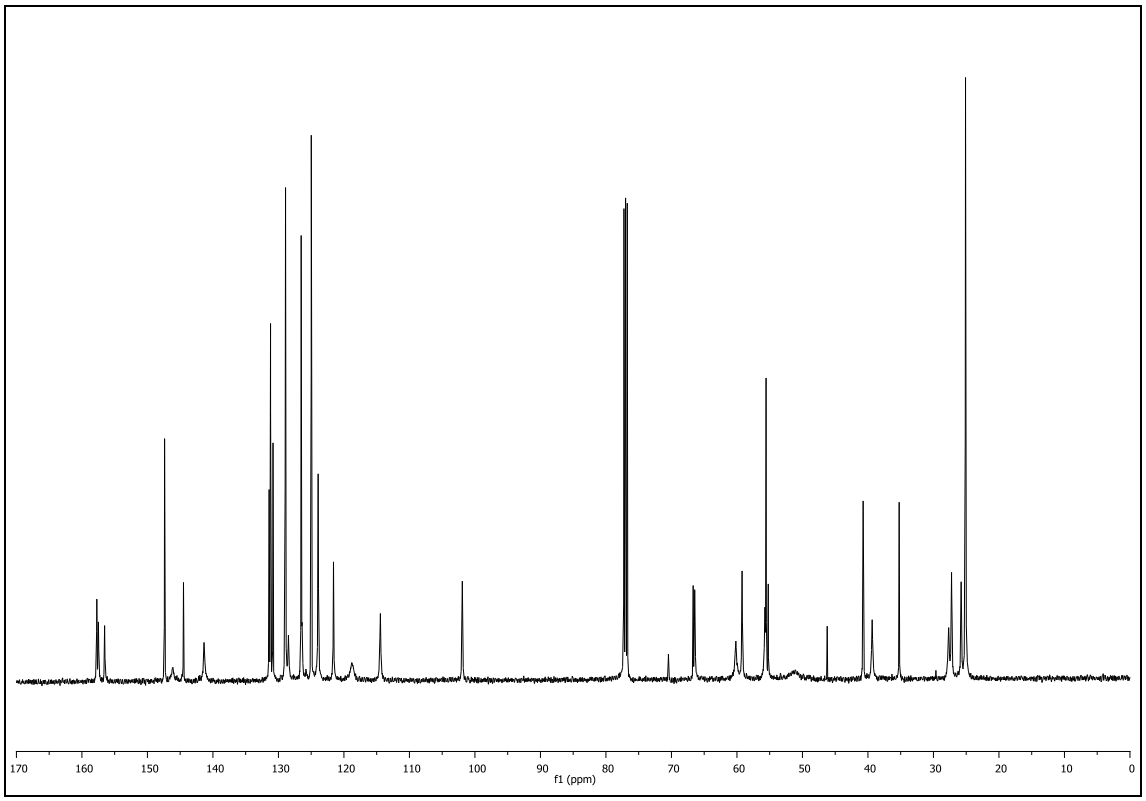
(9*H*-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C1)



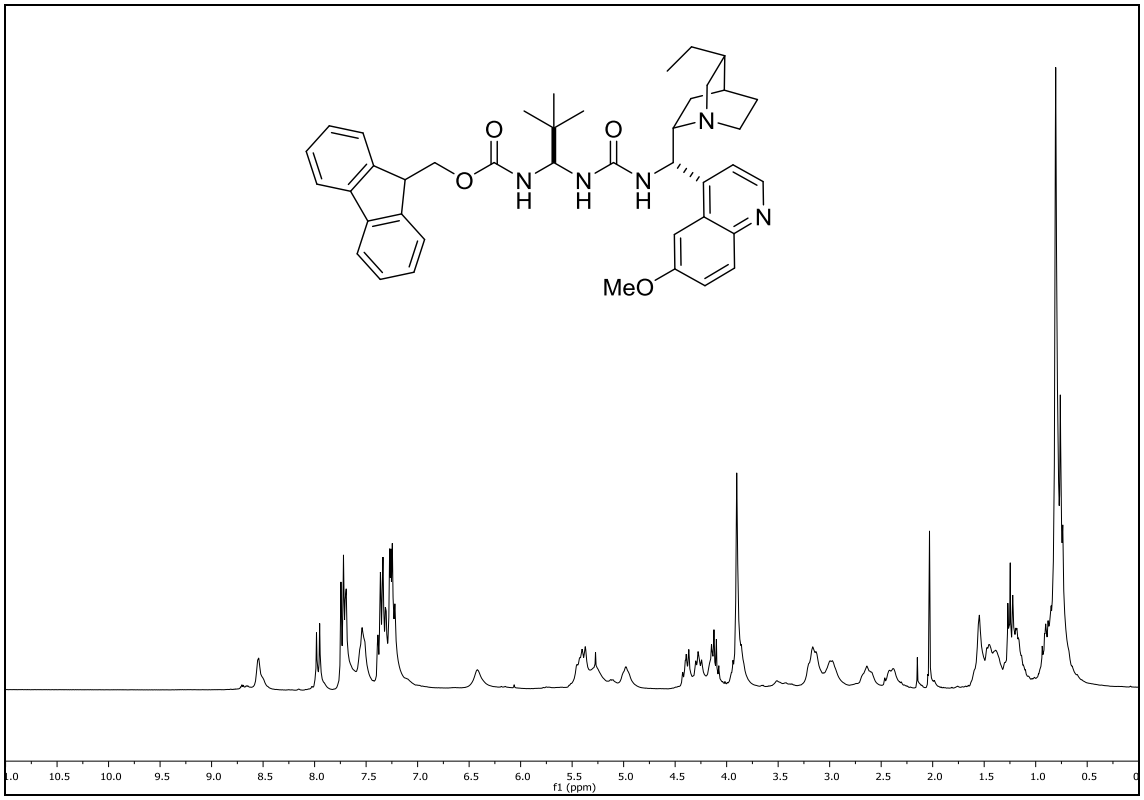


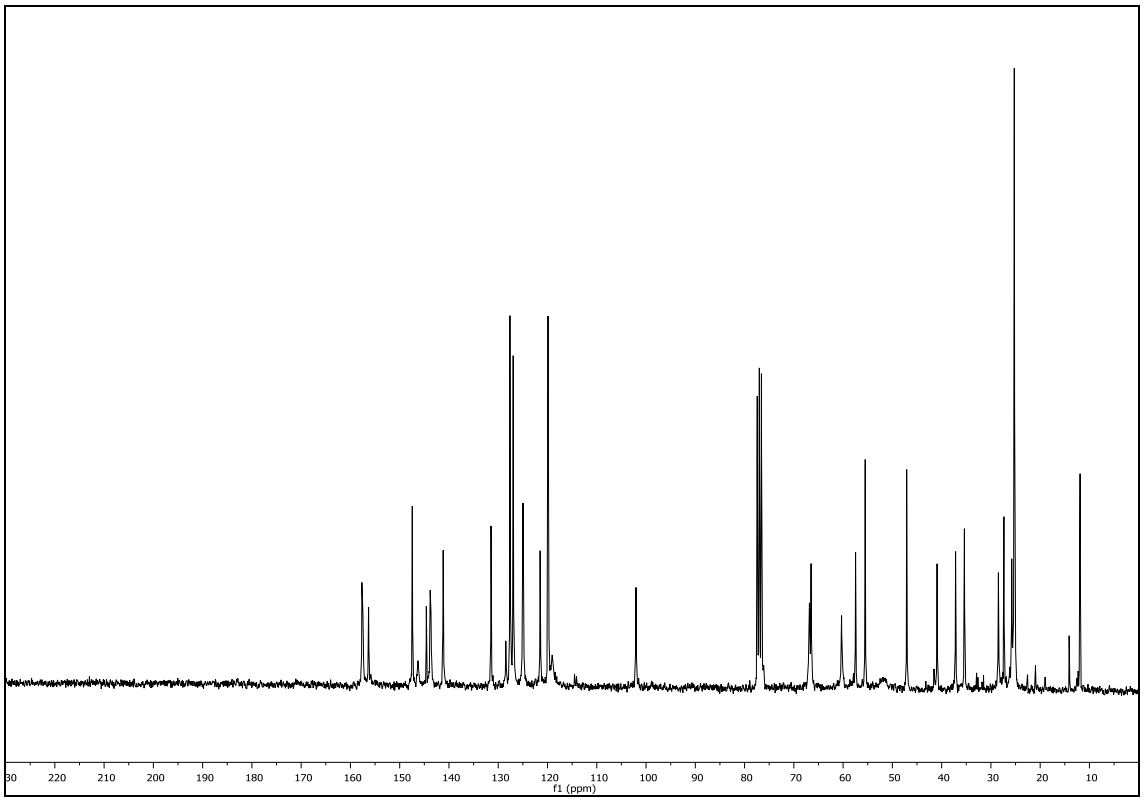
Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C2)



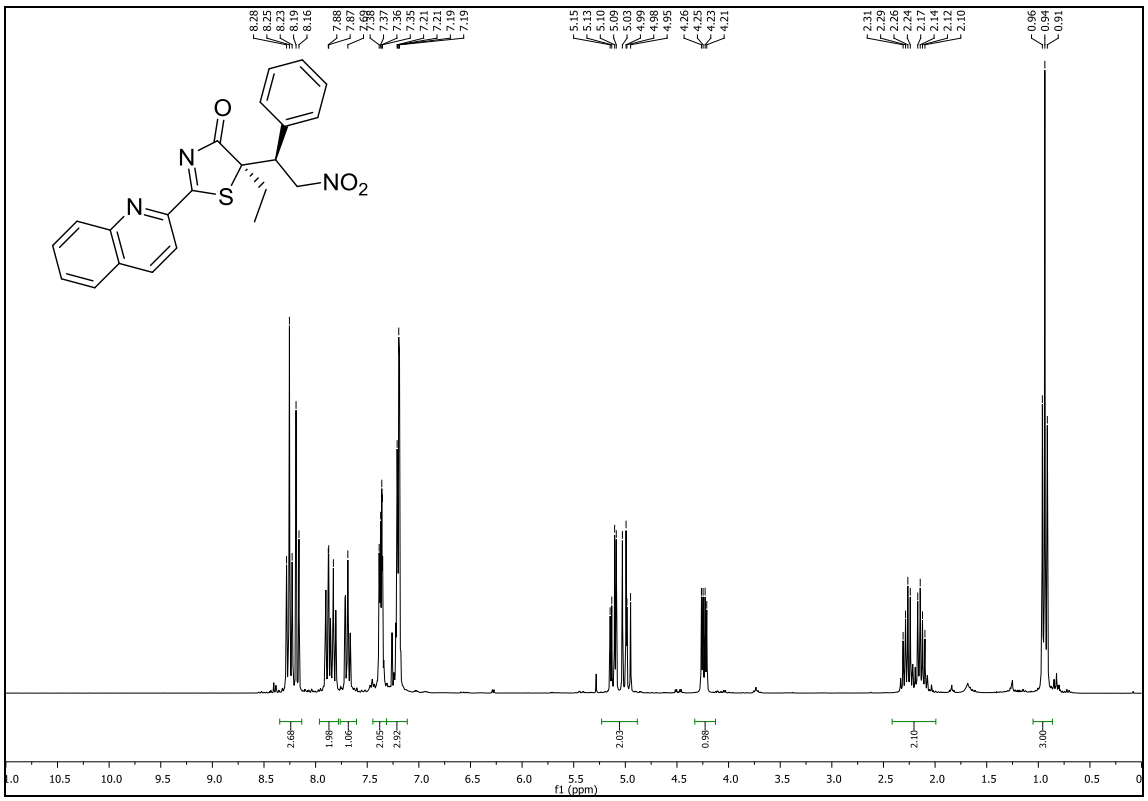


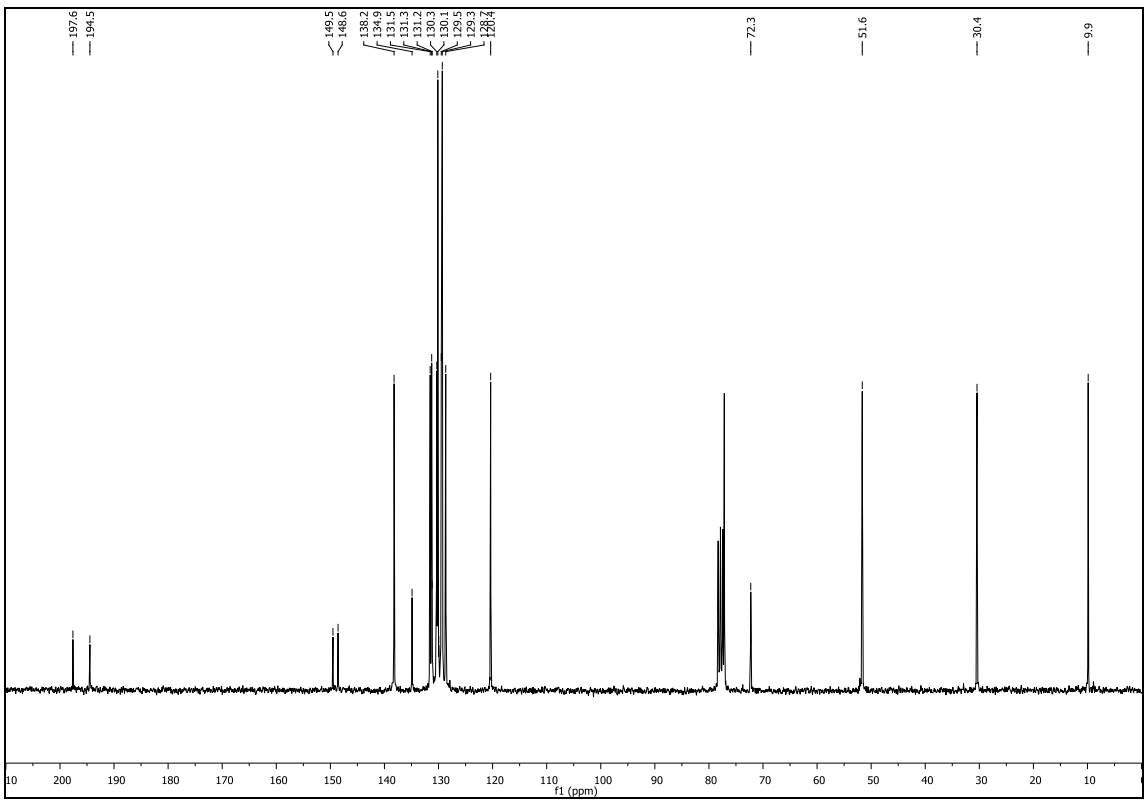
(9*H*-Fluoren-9-yl)methyl (*S*)-1-(3-((*S*)-((*2S,4S,8R*)-8-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropylcarbamate (C3)



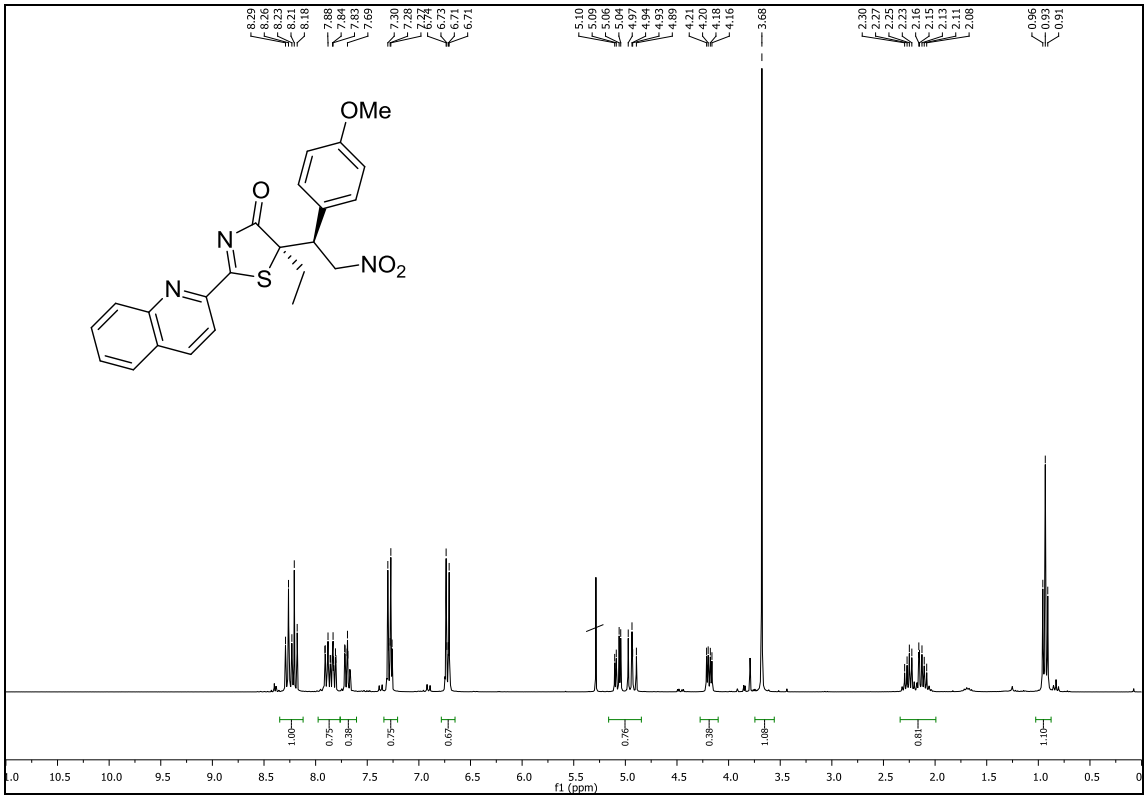


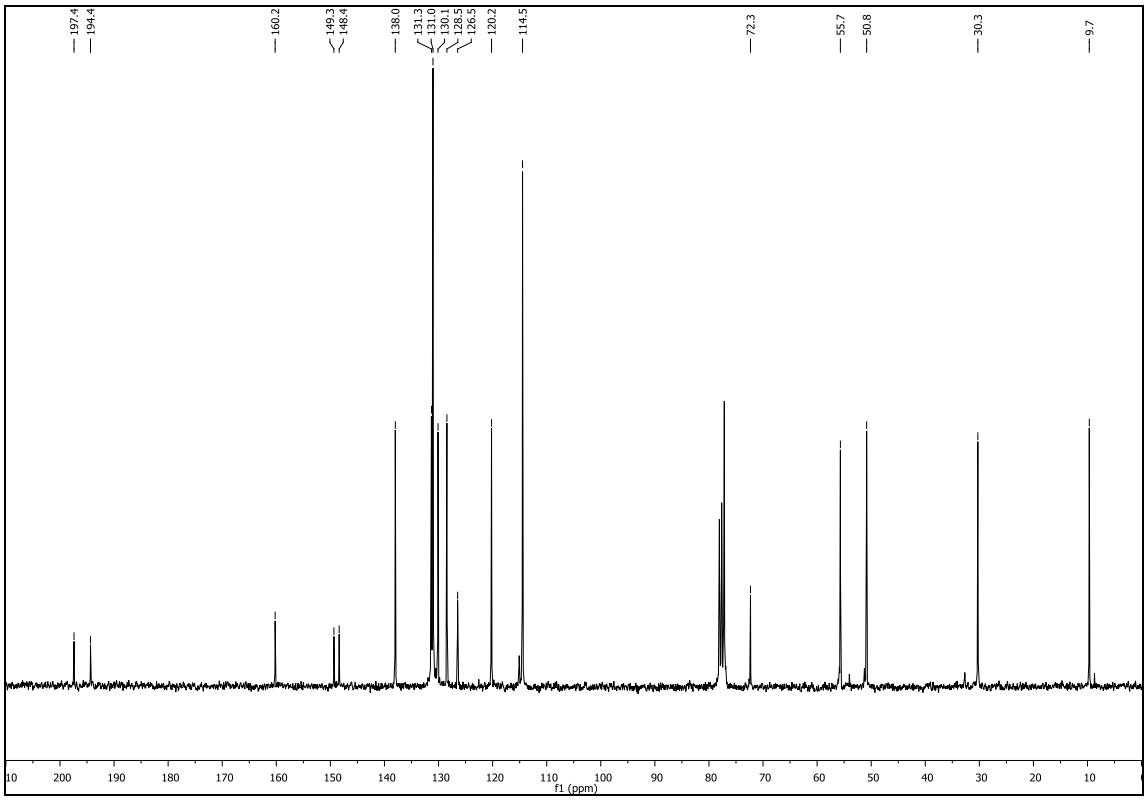
(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9a)



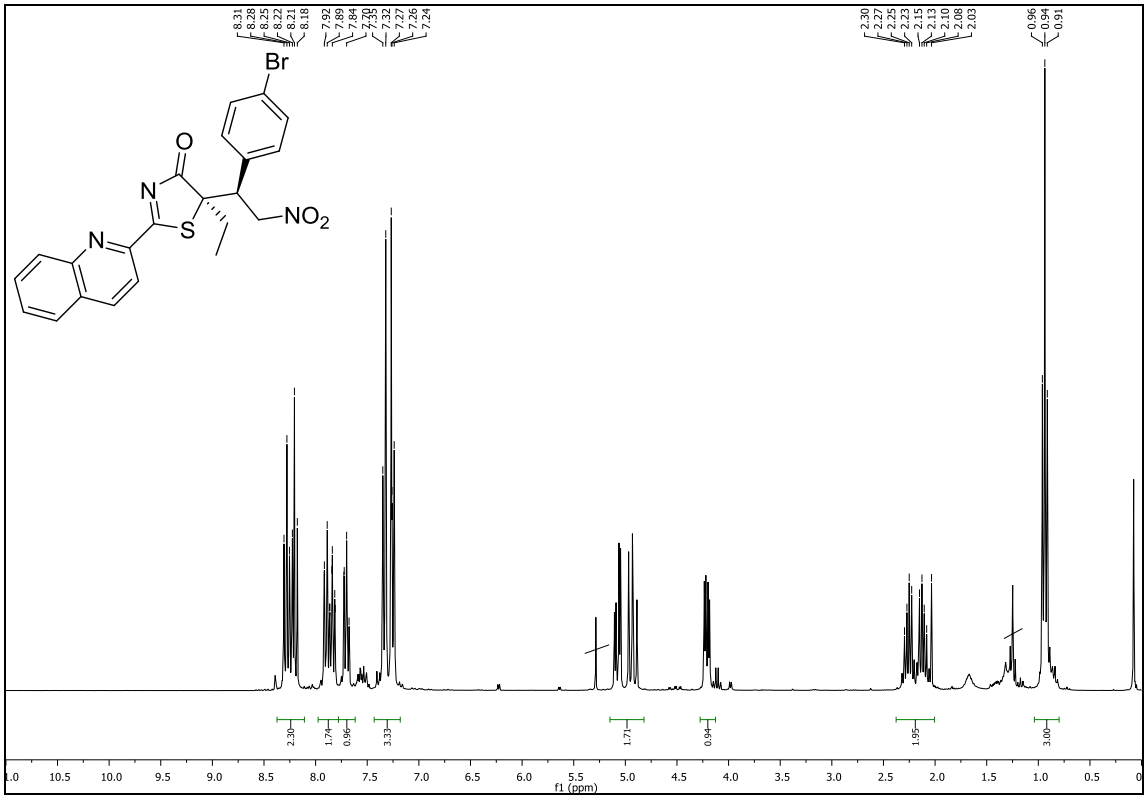


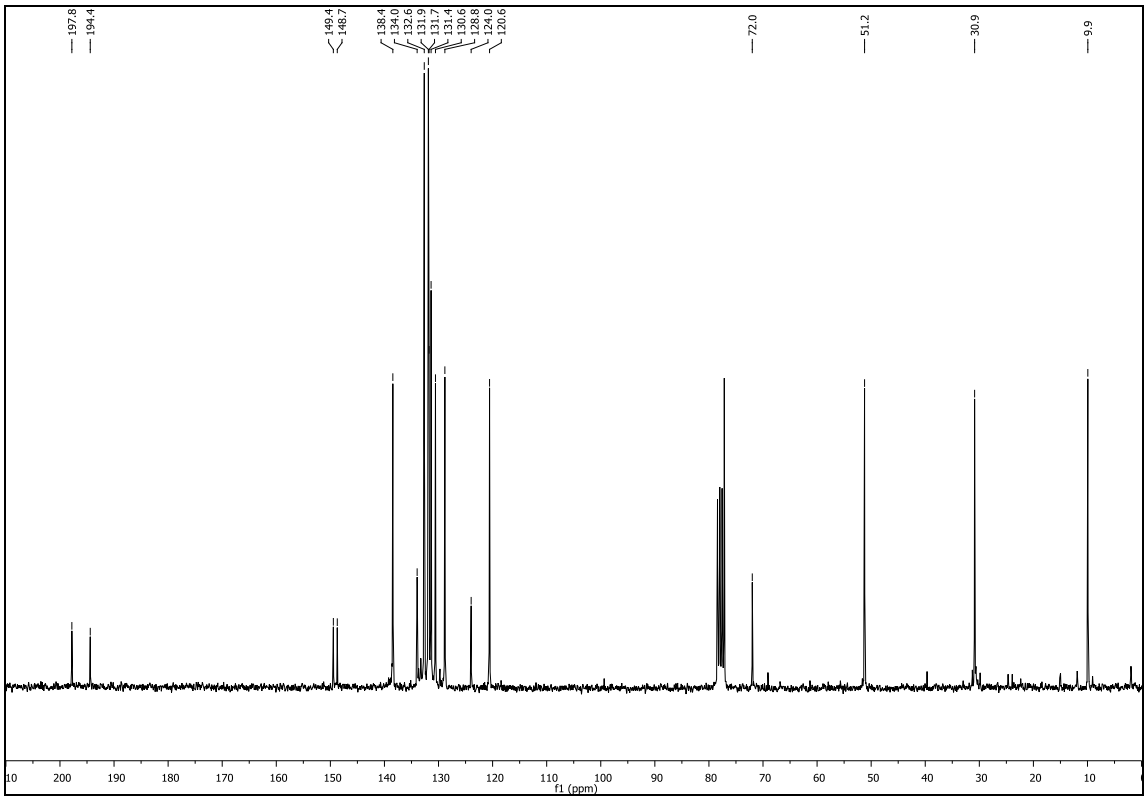
(*R*)-5-Ethyl-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9b)



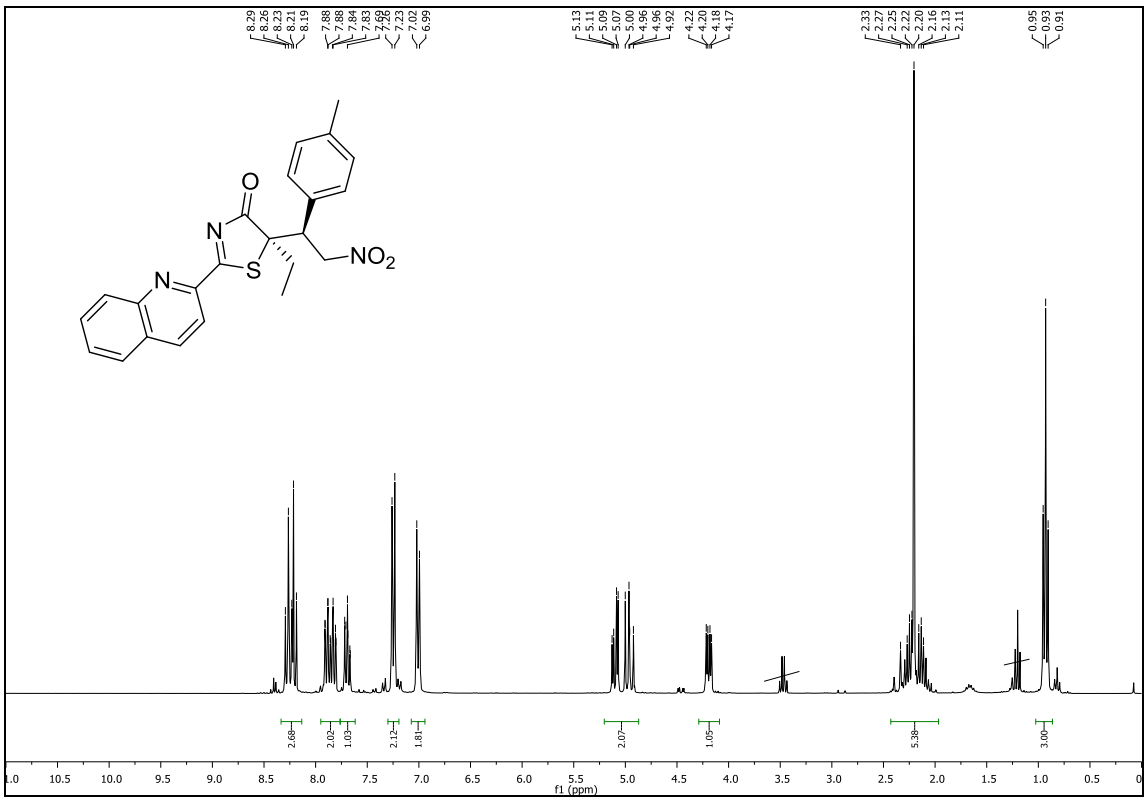


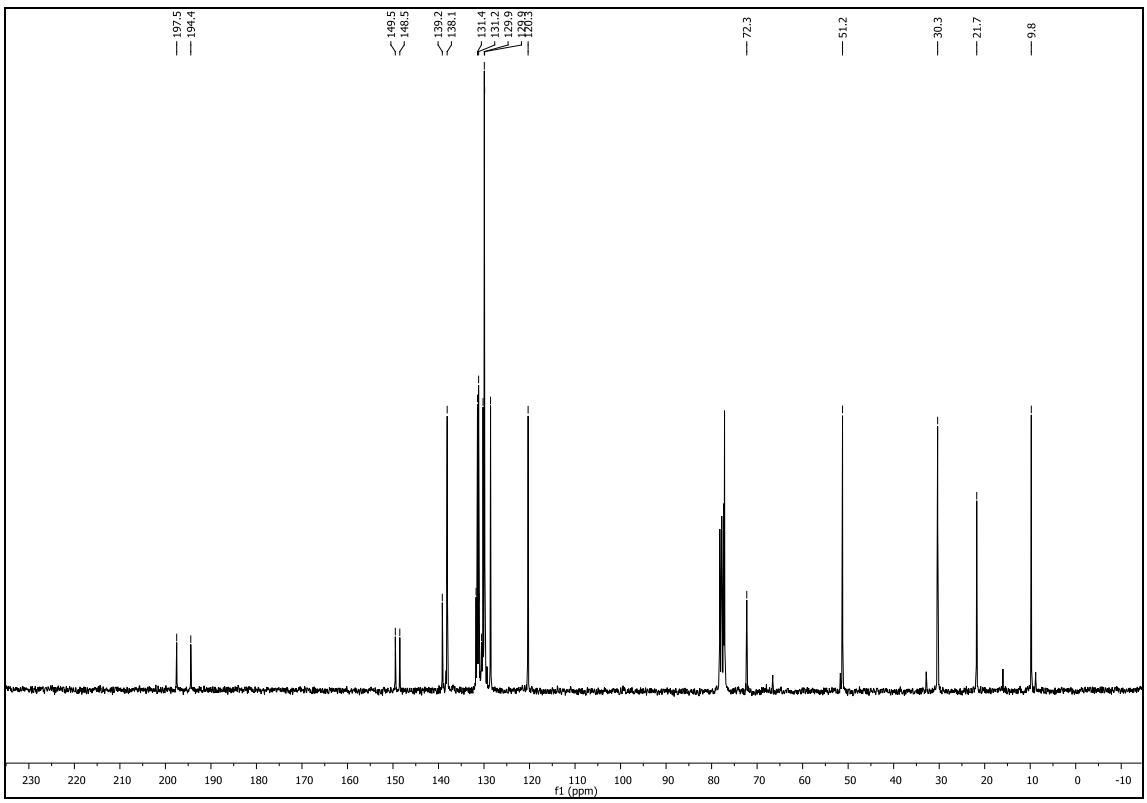
(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9c)



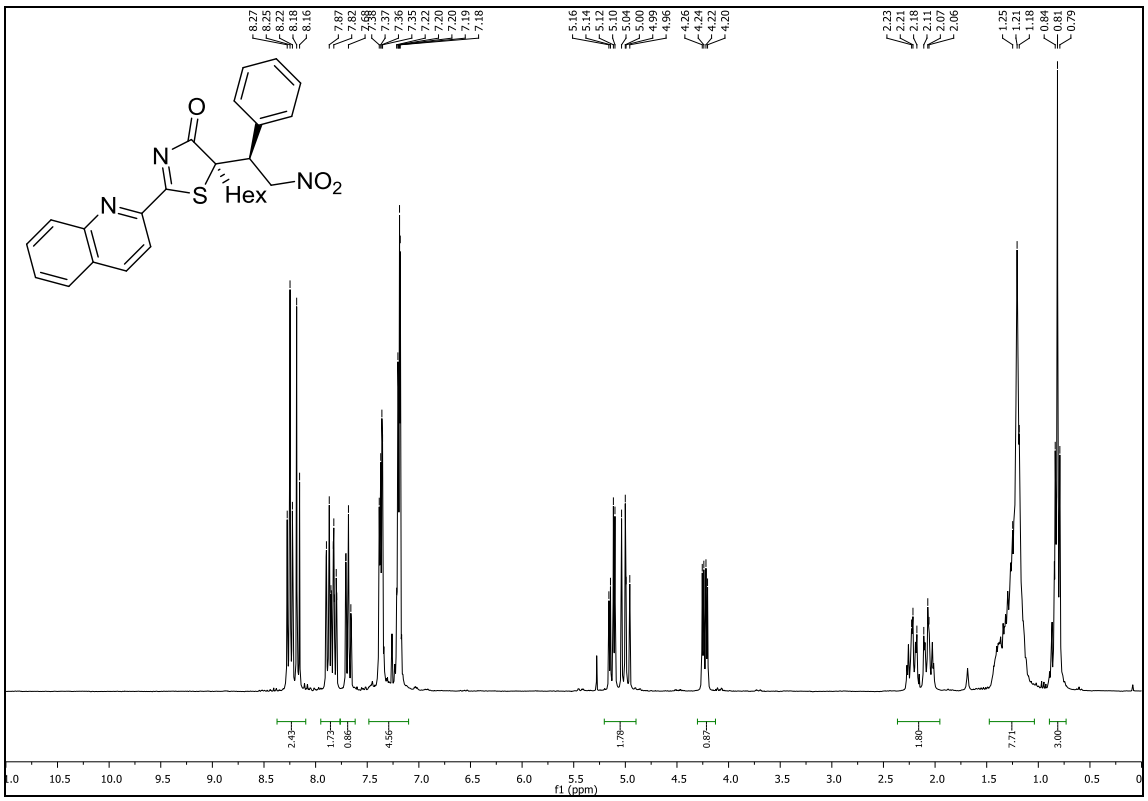


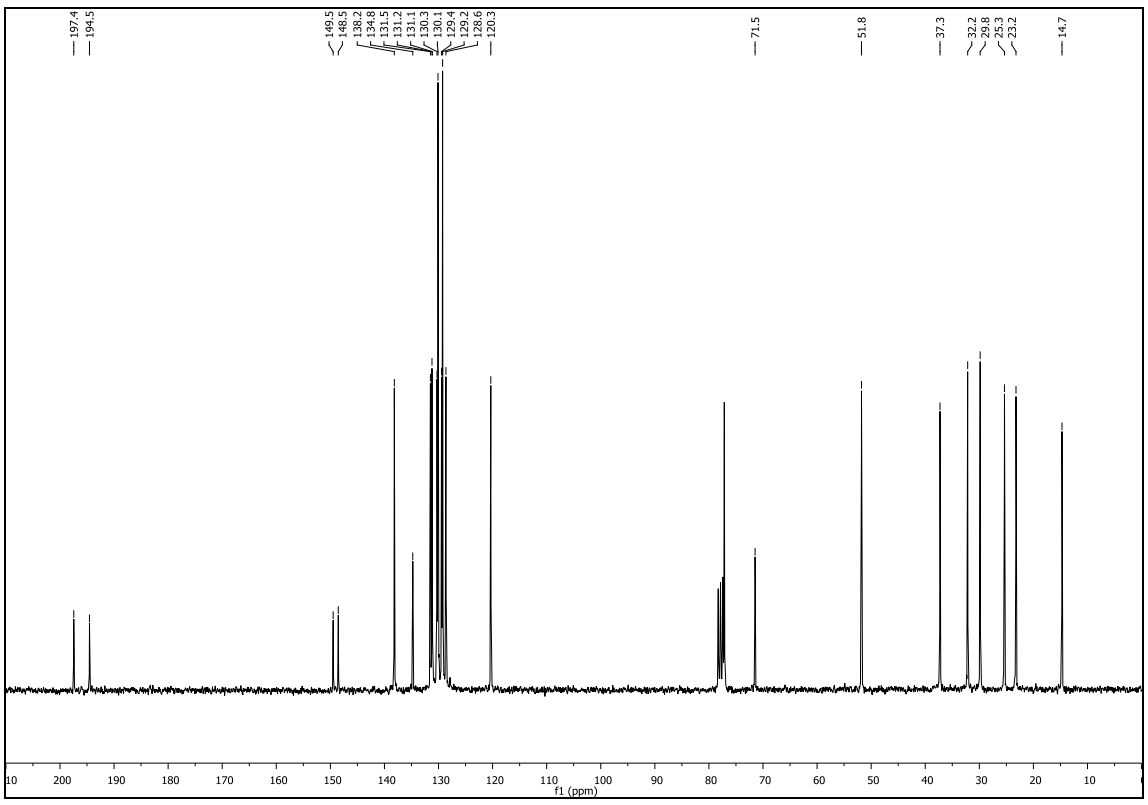
(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9d)



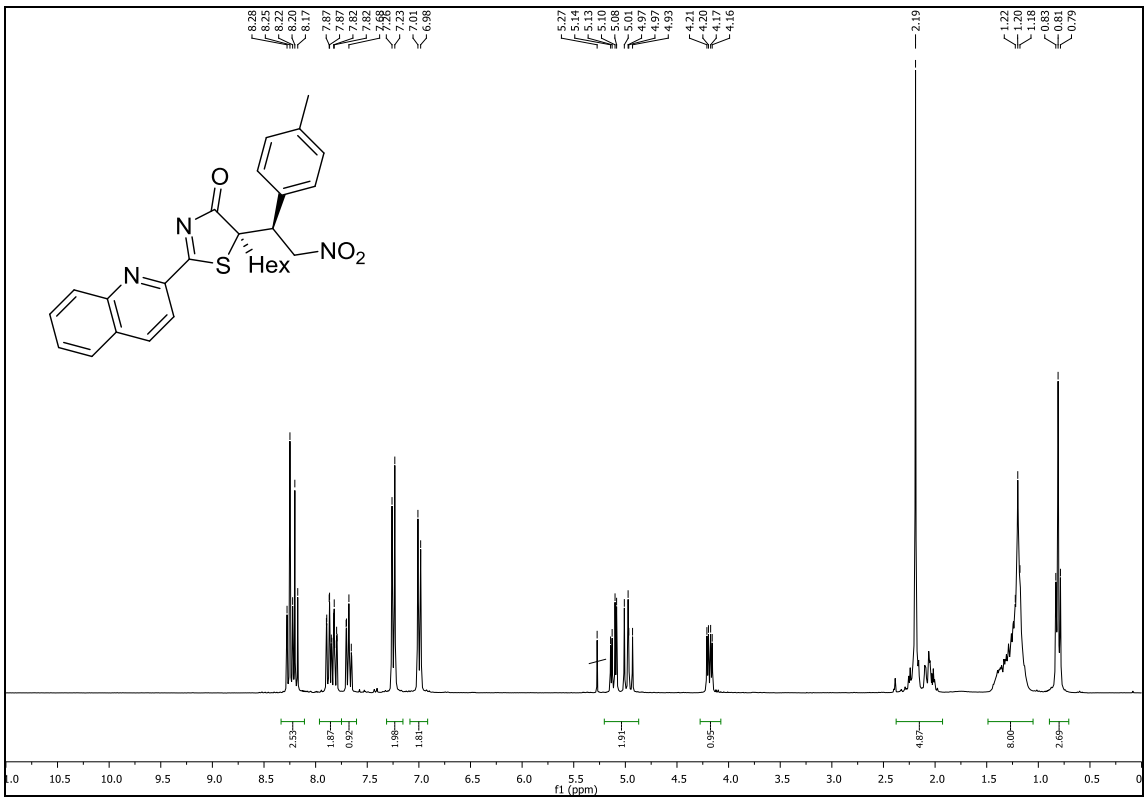


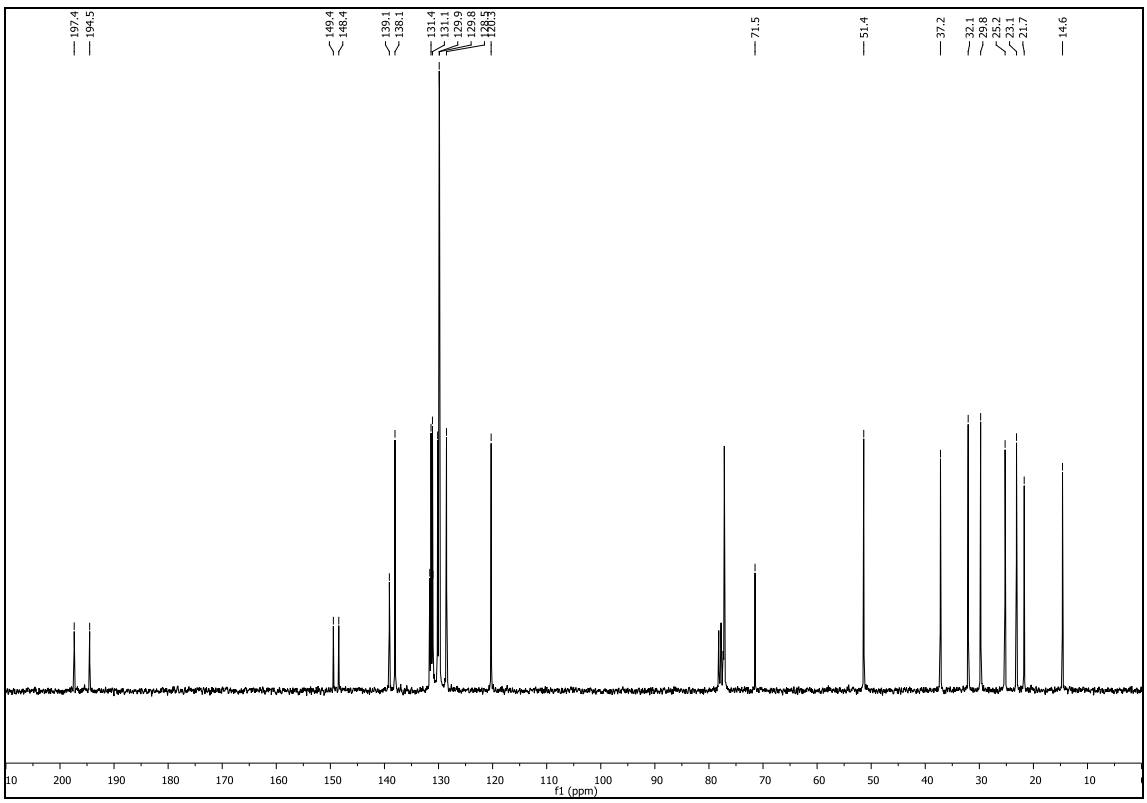
(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (10a)



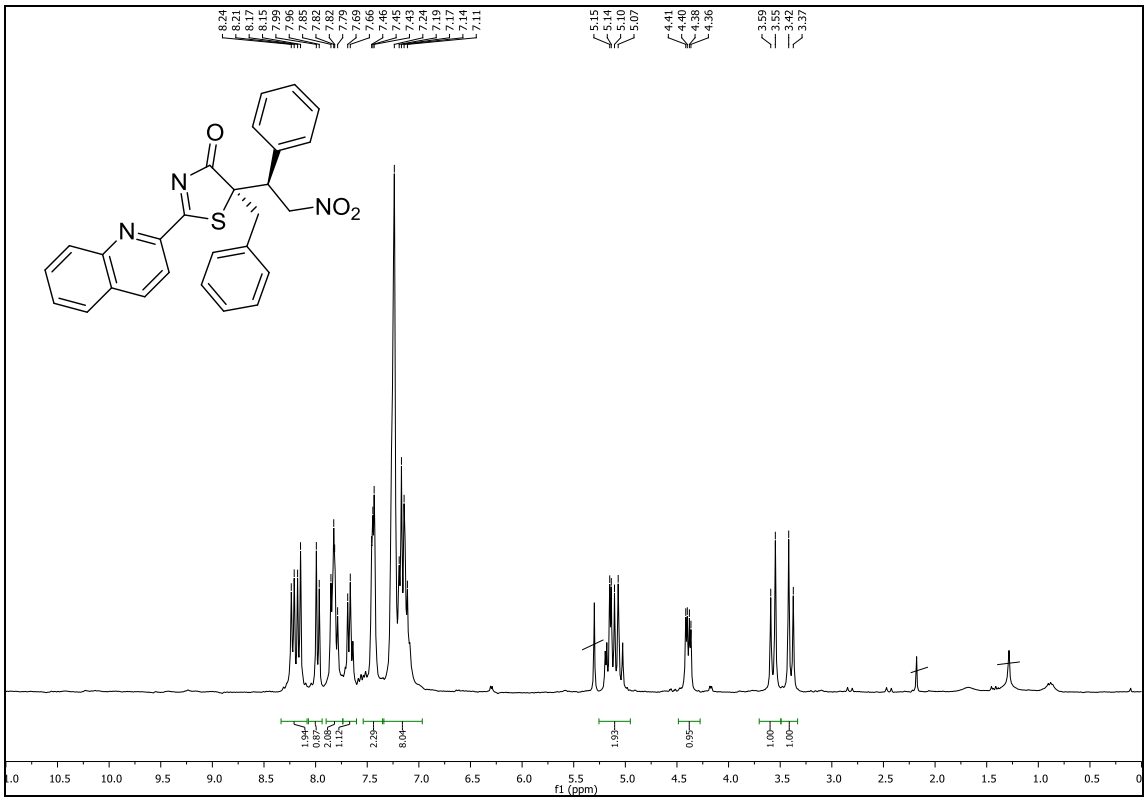


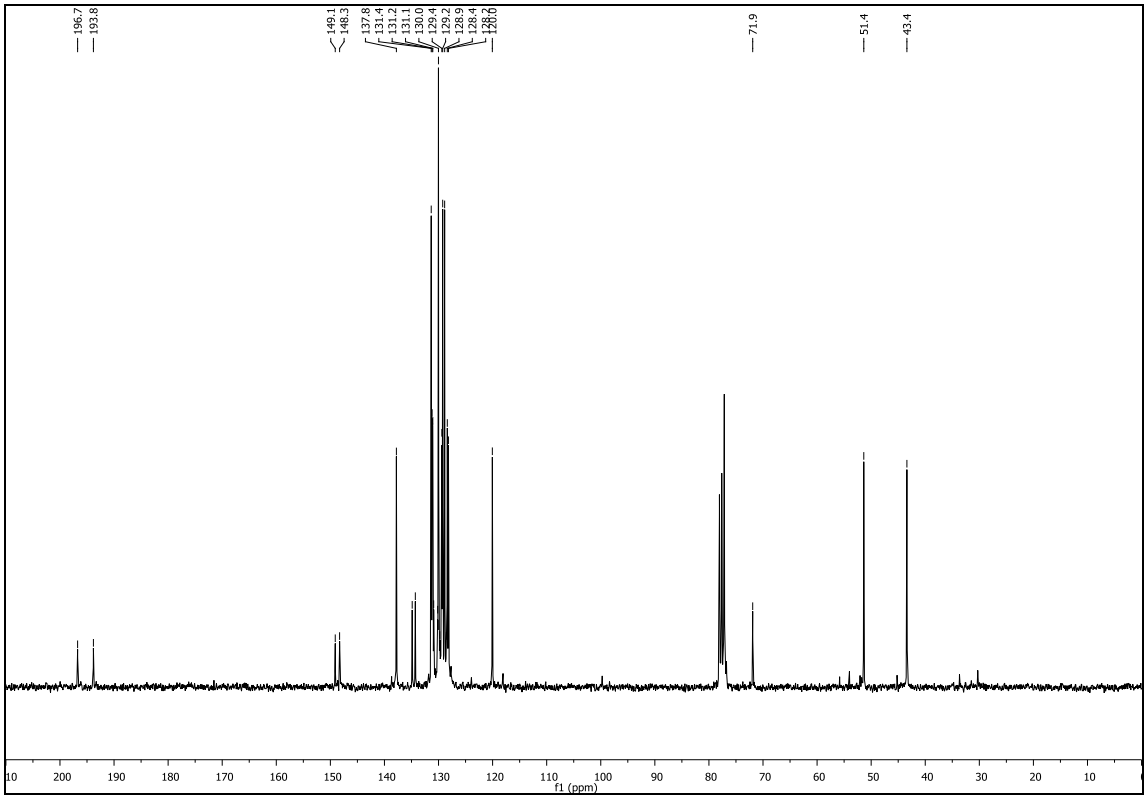
(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5H)-one (10d)



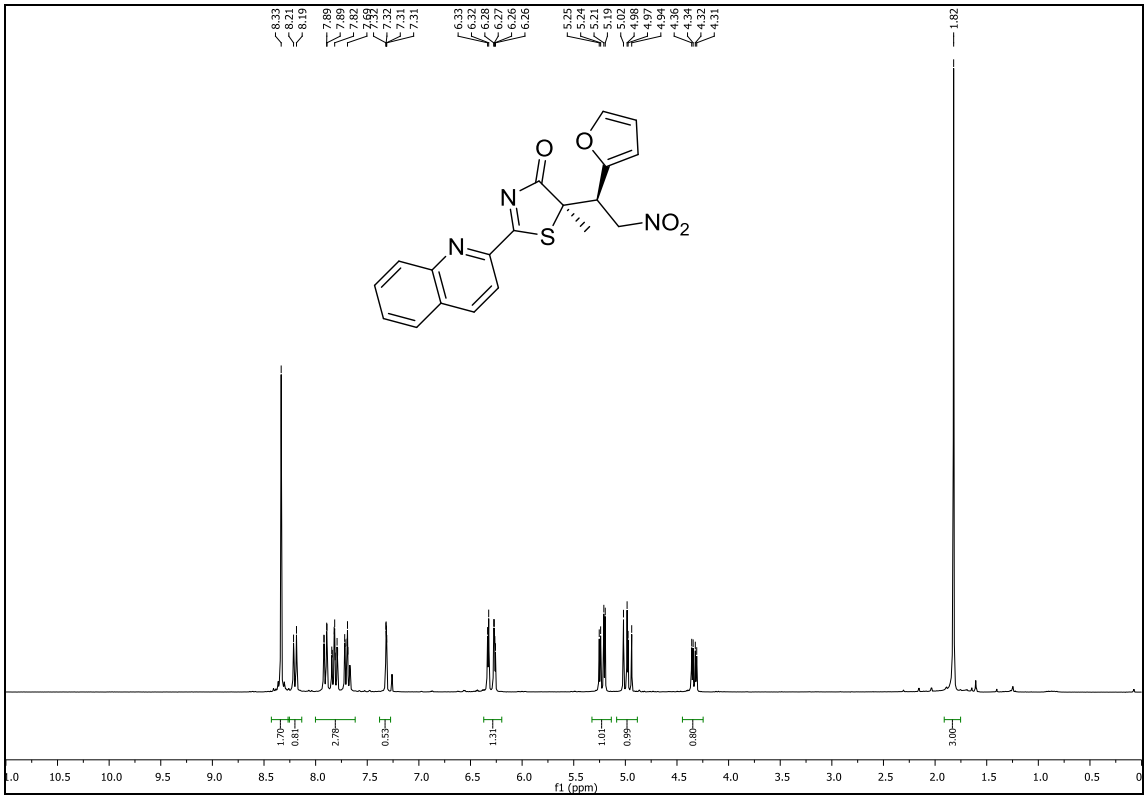


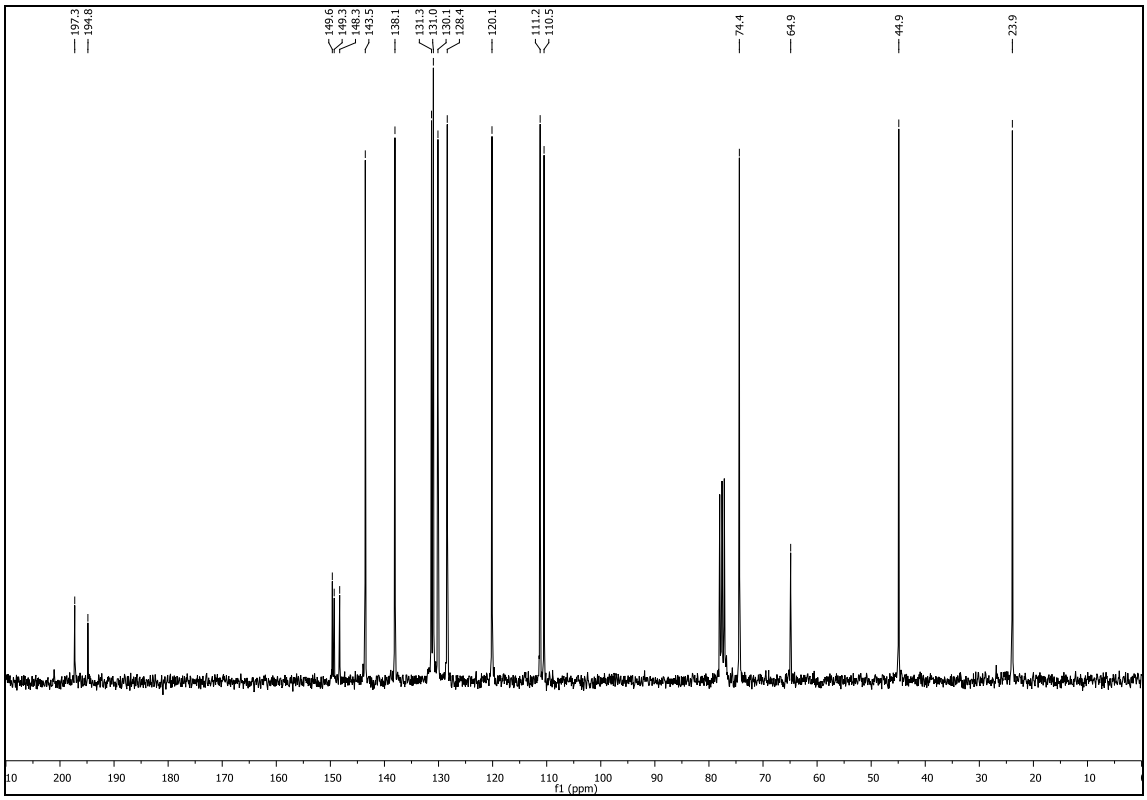
(*R*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5H)-one (11a)



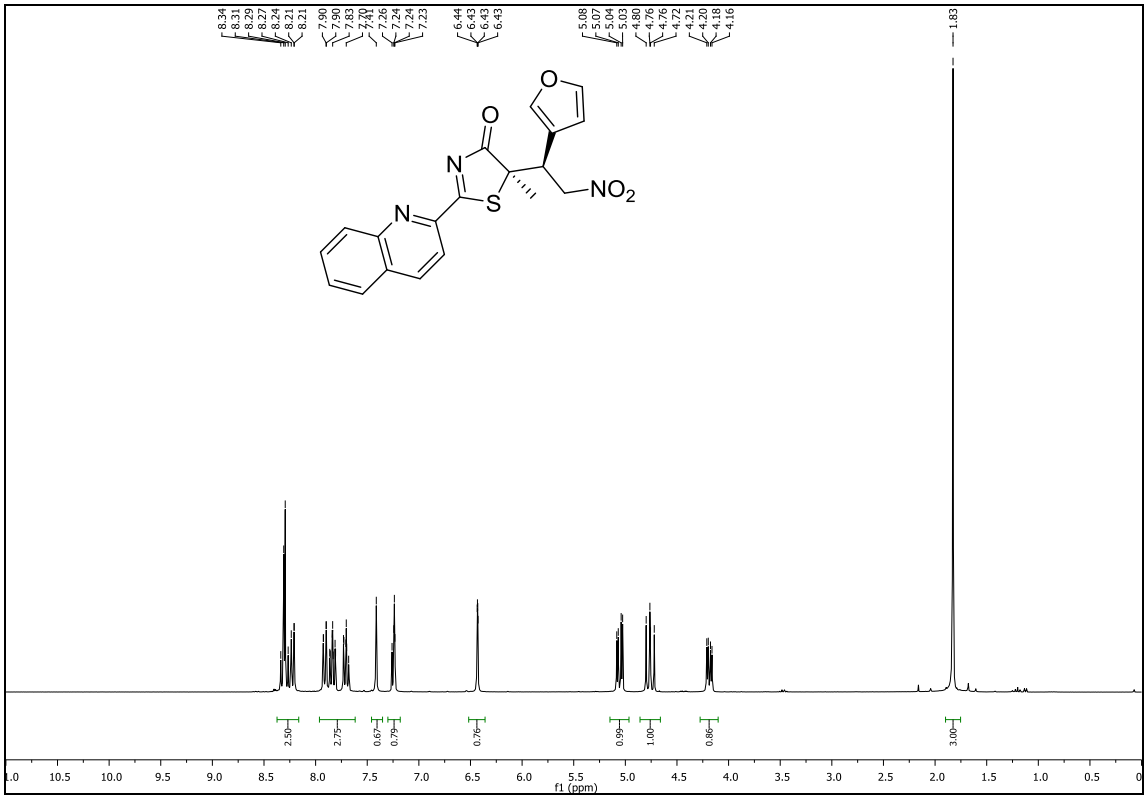


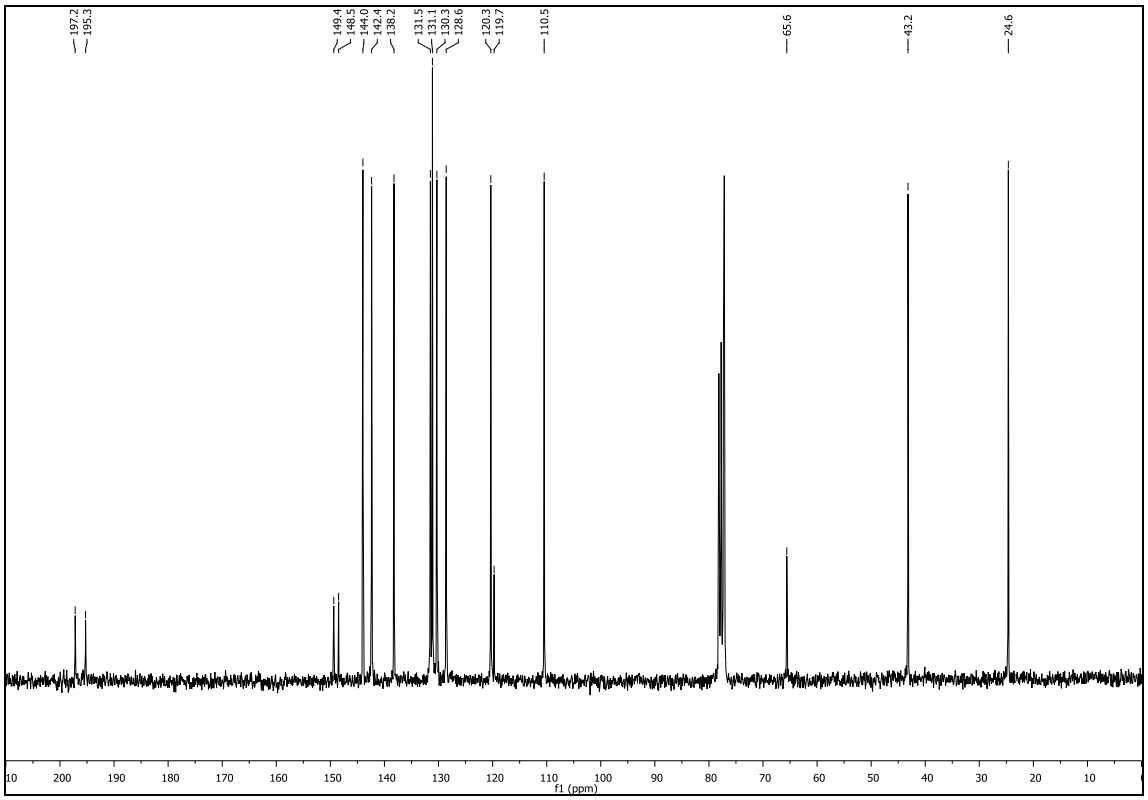
(*R*)-5-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5be)



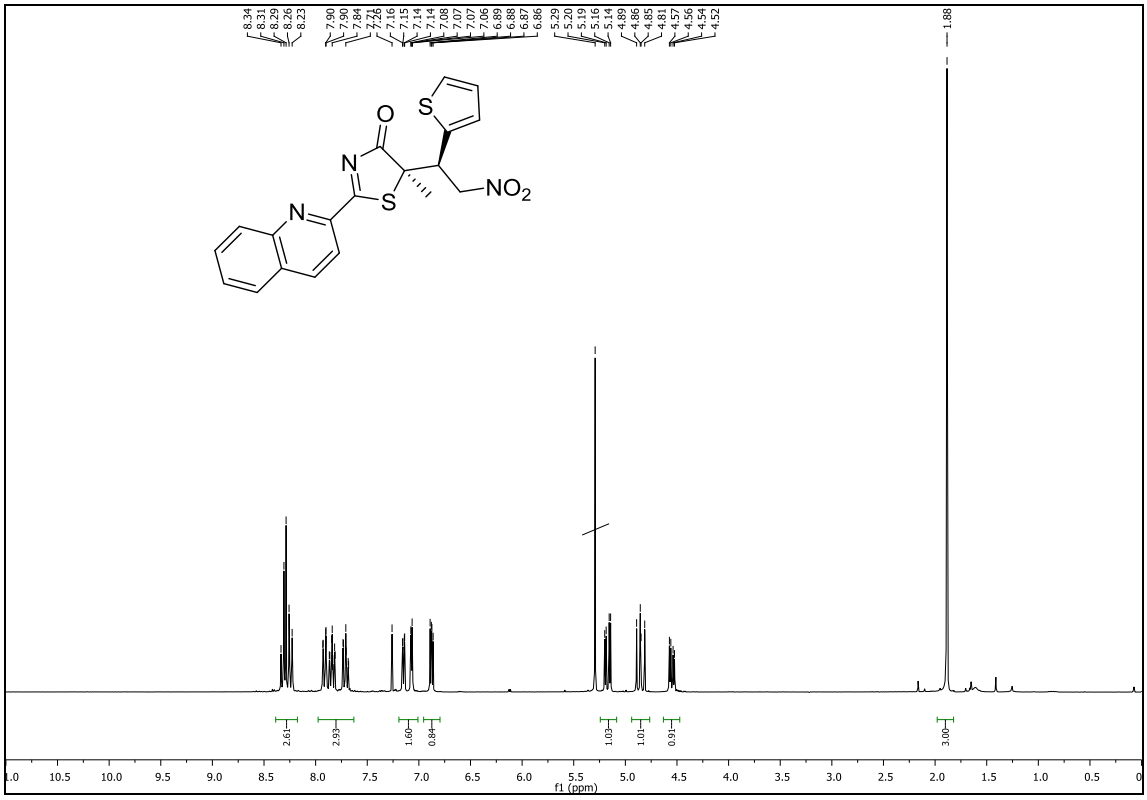


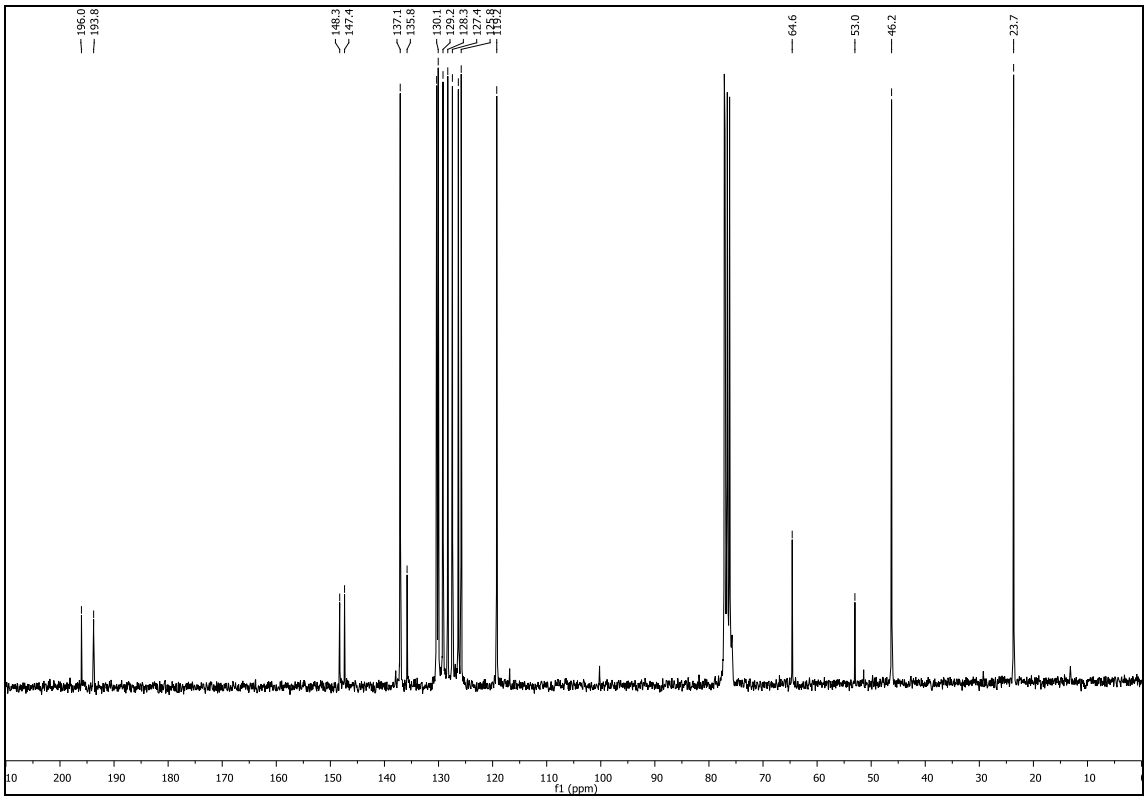
(*R*)-5-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bf)



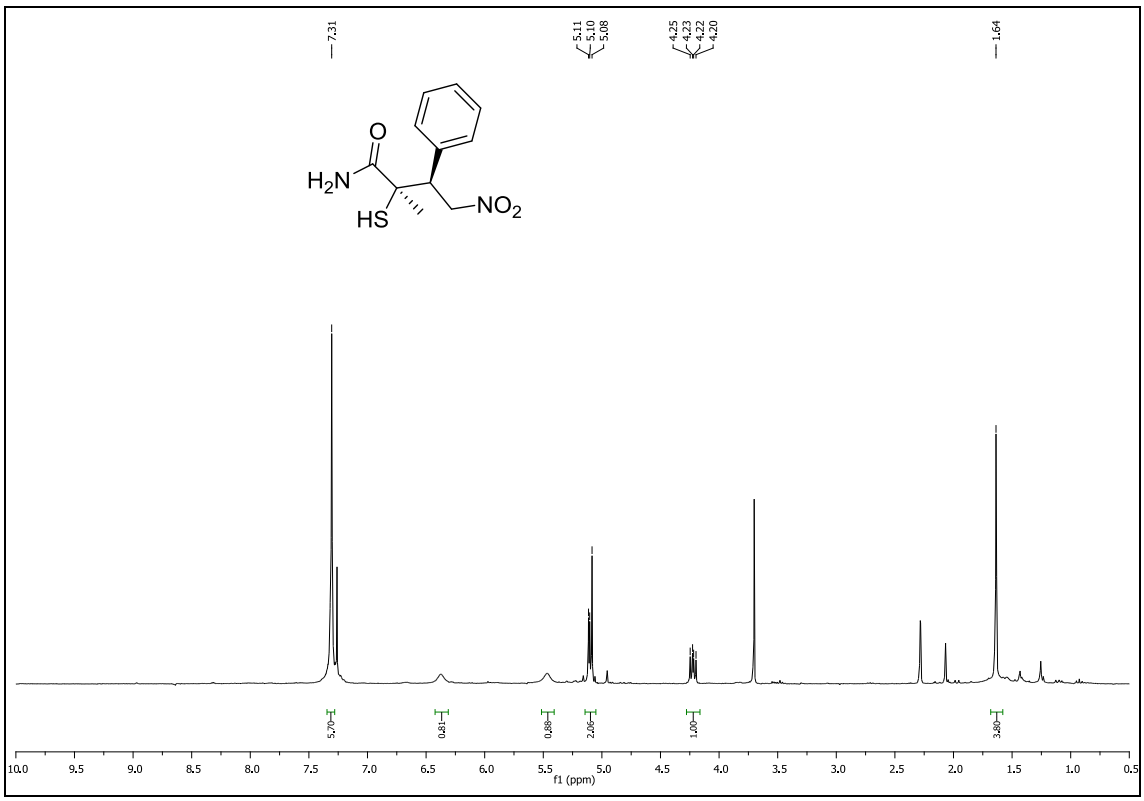


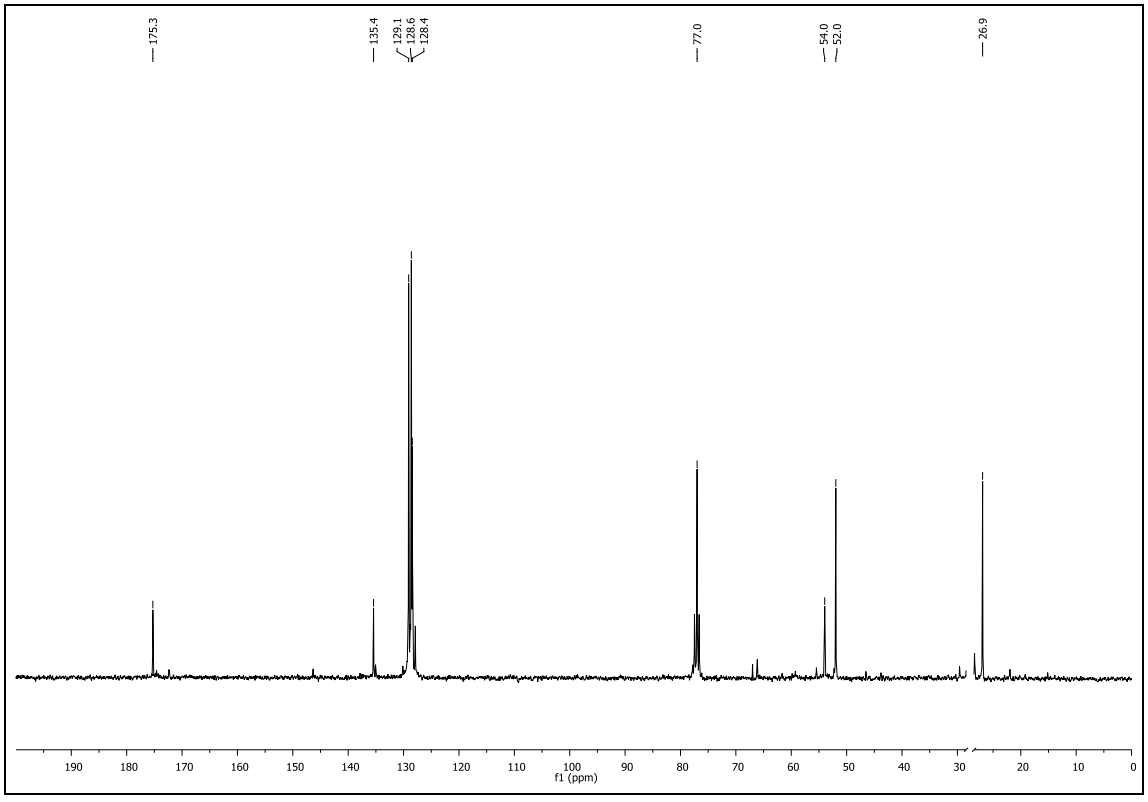
(*R*)-5-Methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bg)



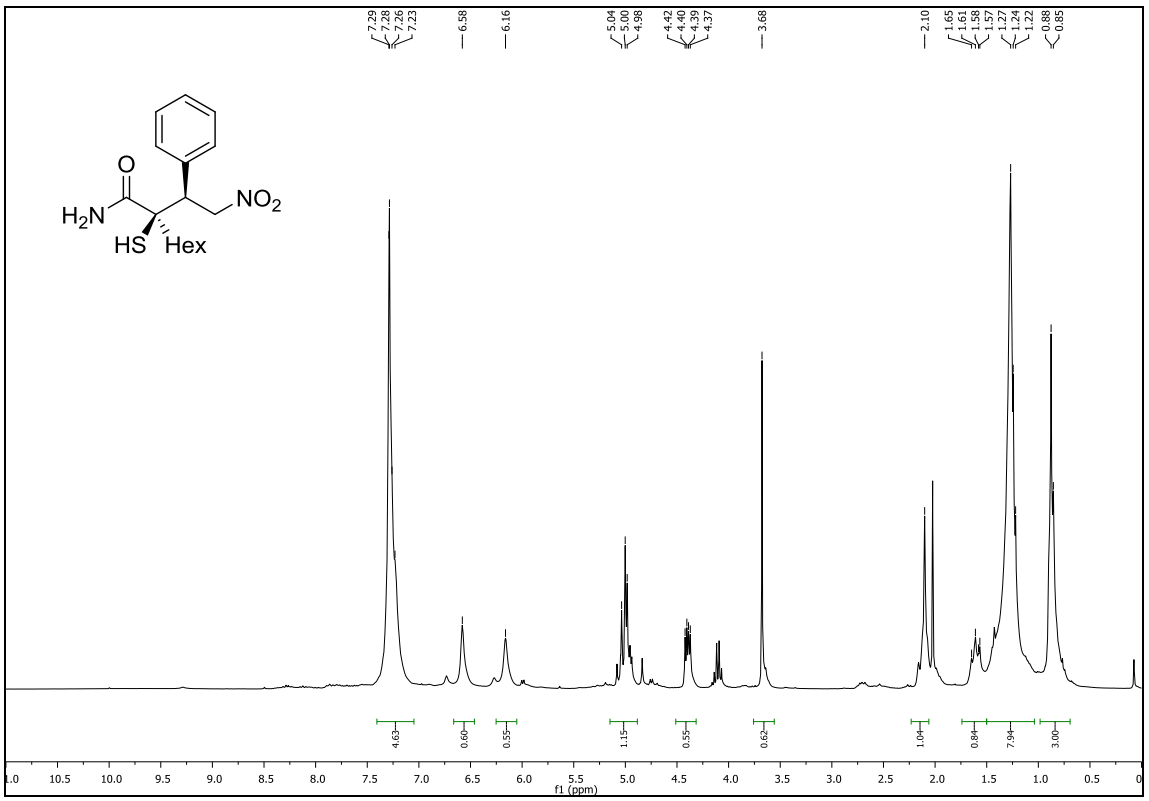


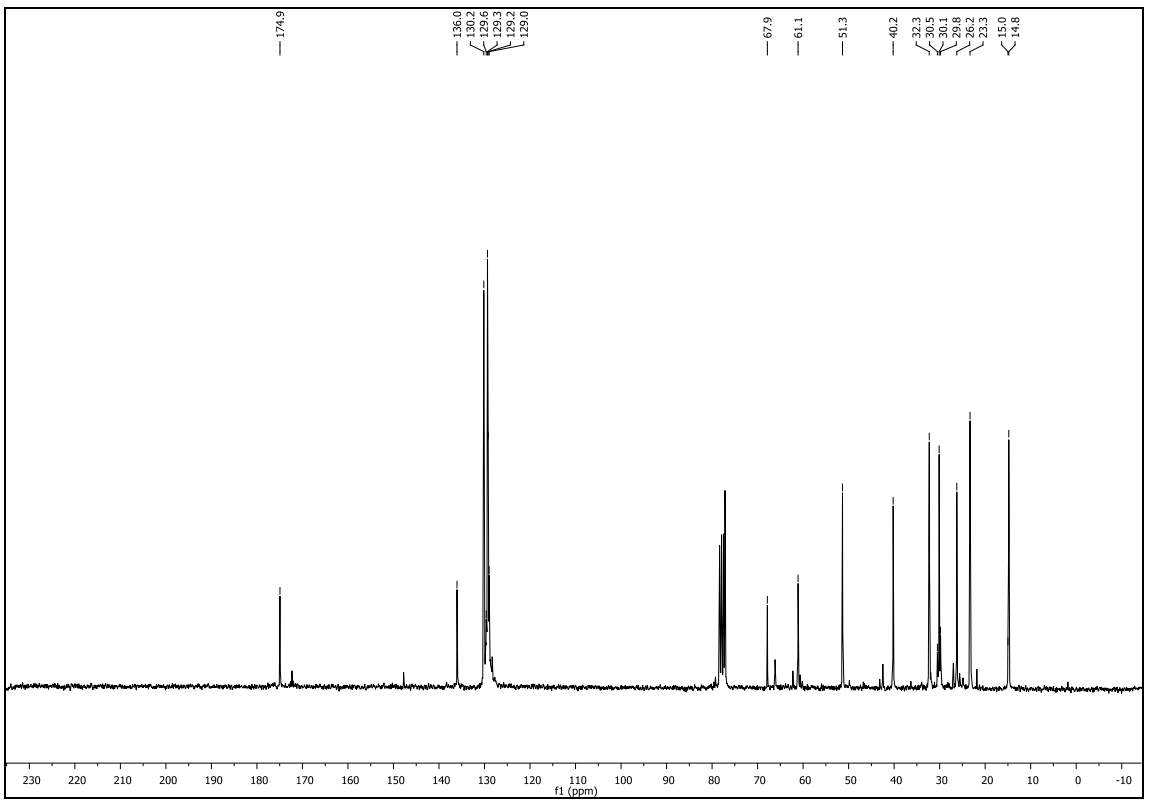
(*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide (12)



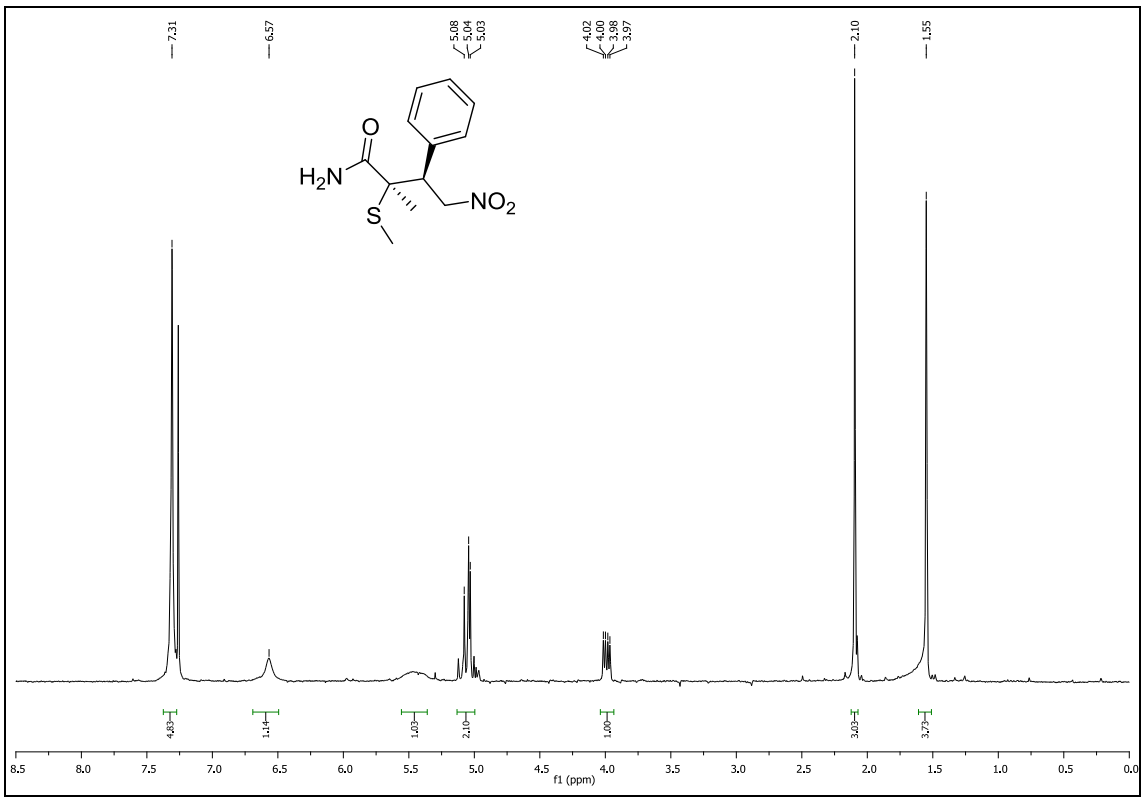


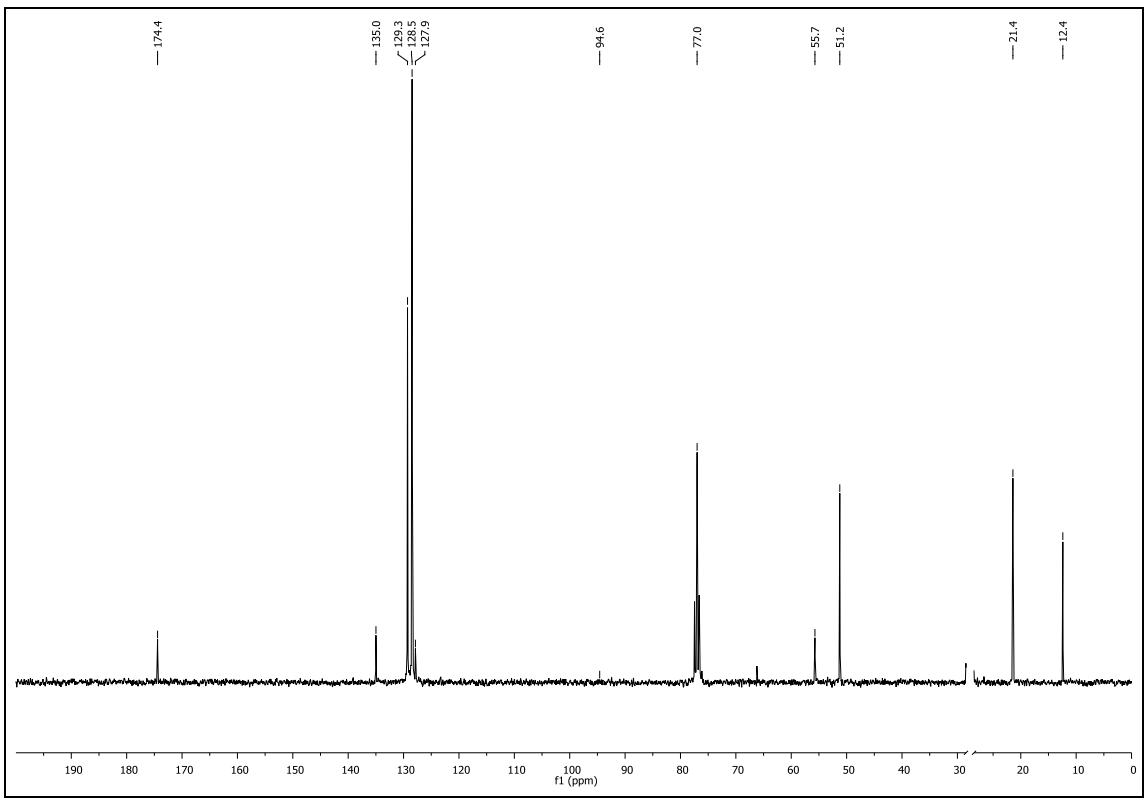
(*R*)-2-mercapto-2-((S)-2-nitro-1-phenylethyl)octanamide (13)



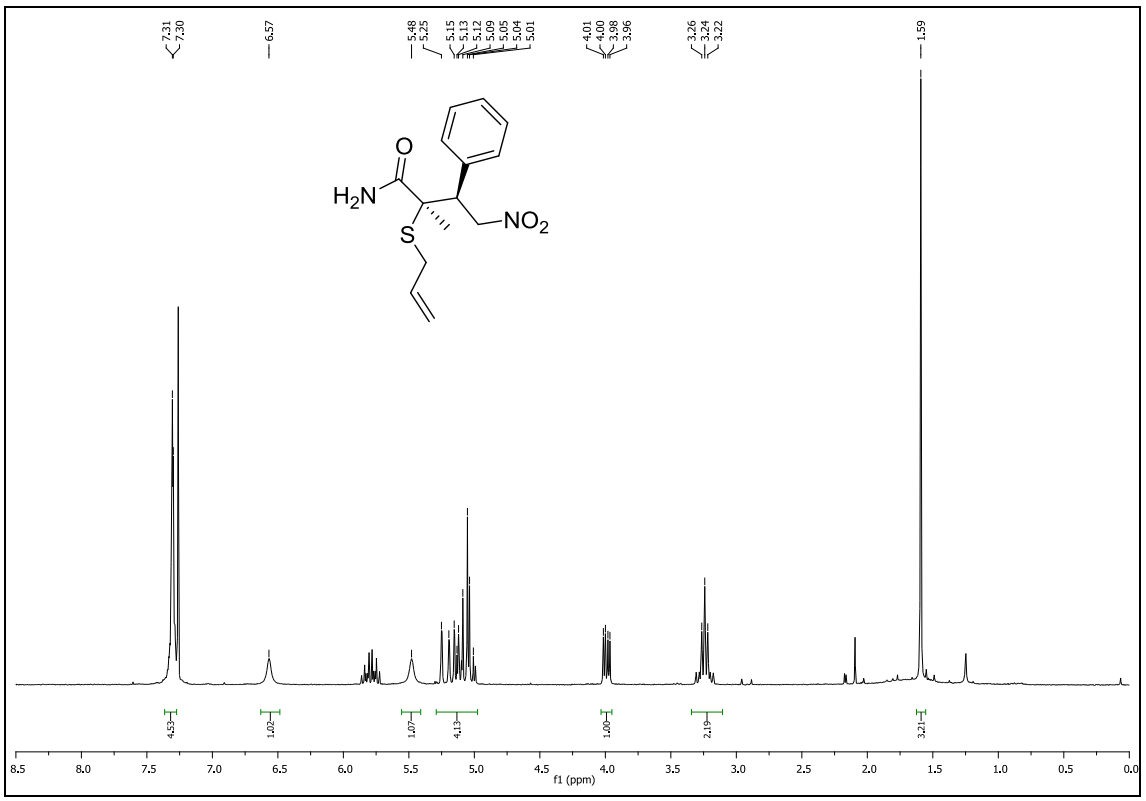


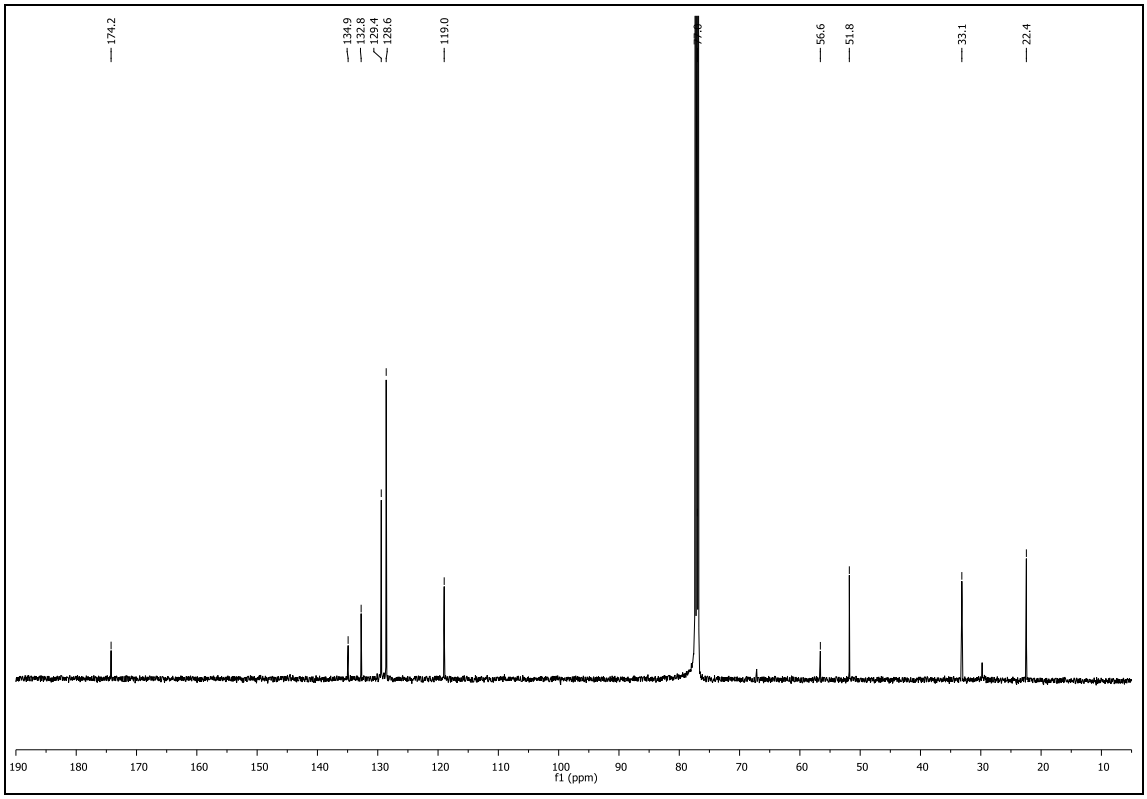
(*2R,3S*)-2-Methyl-2-(methylthio)-4-nitro-3-phenylbutanamide (14)



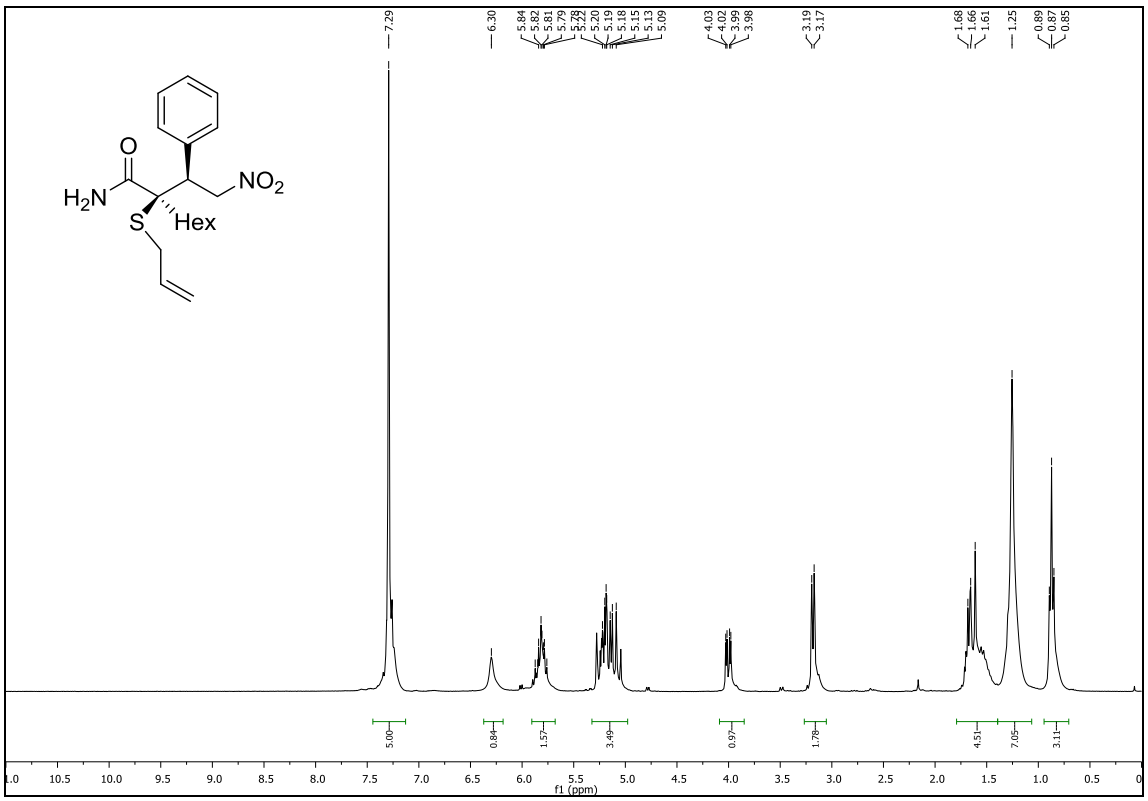


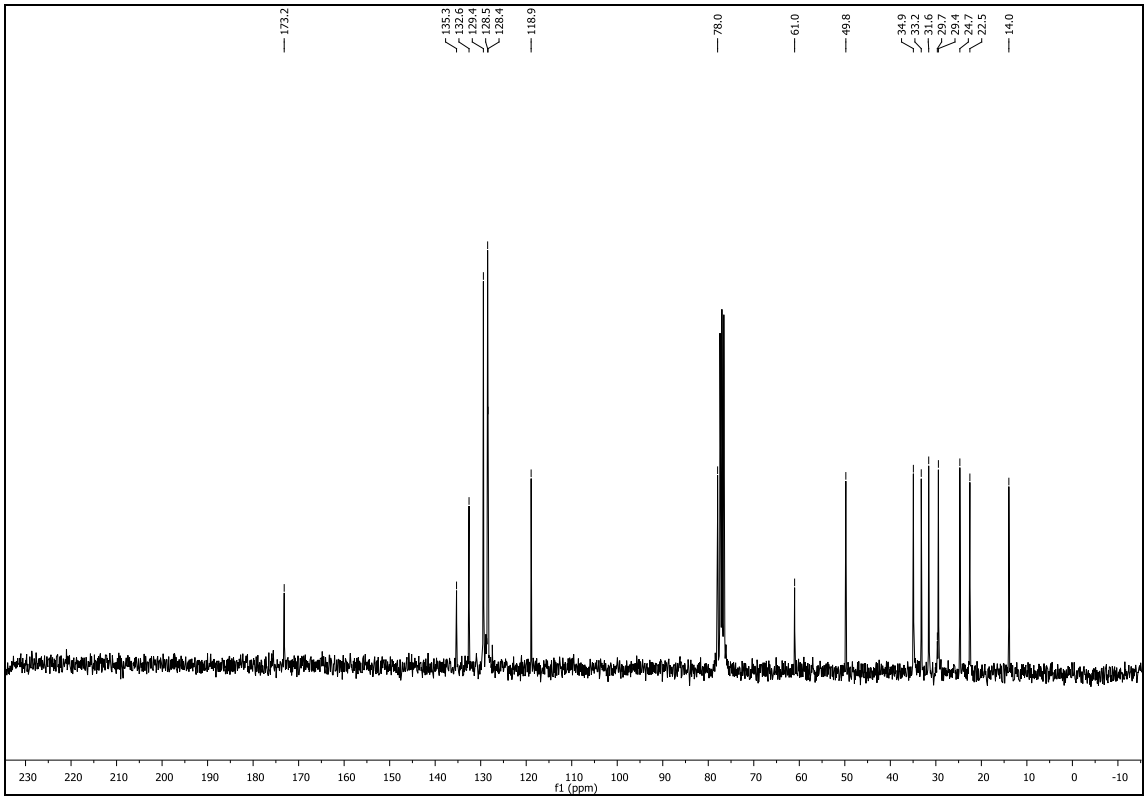
(*2R,3S*)-2-(Allylthio)-2-methyl-4-nitro-3-phenylbutanamide (15)



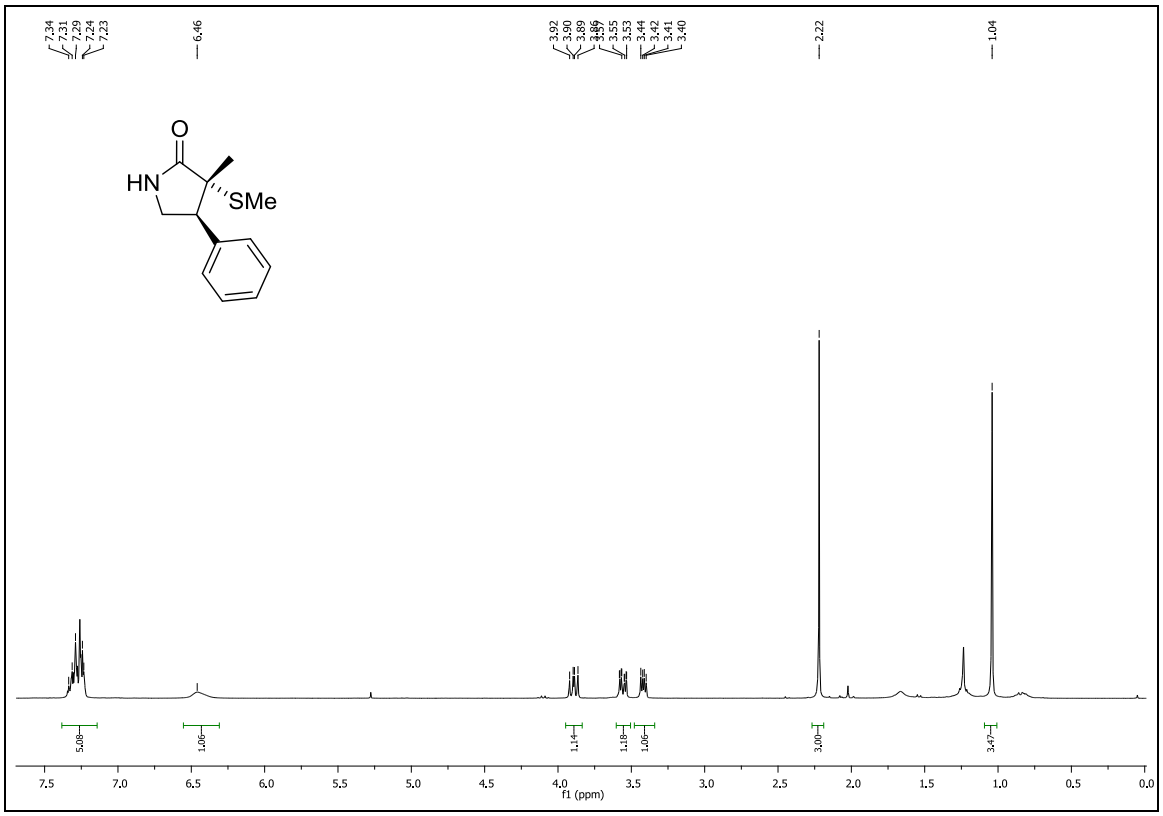


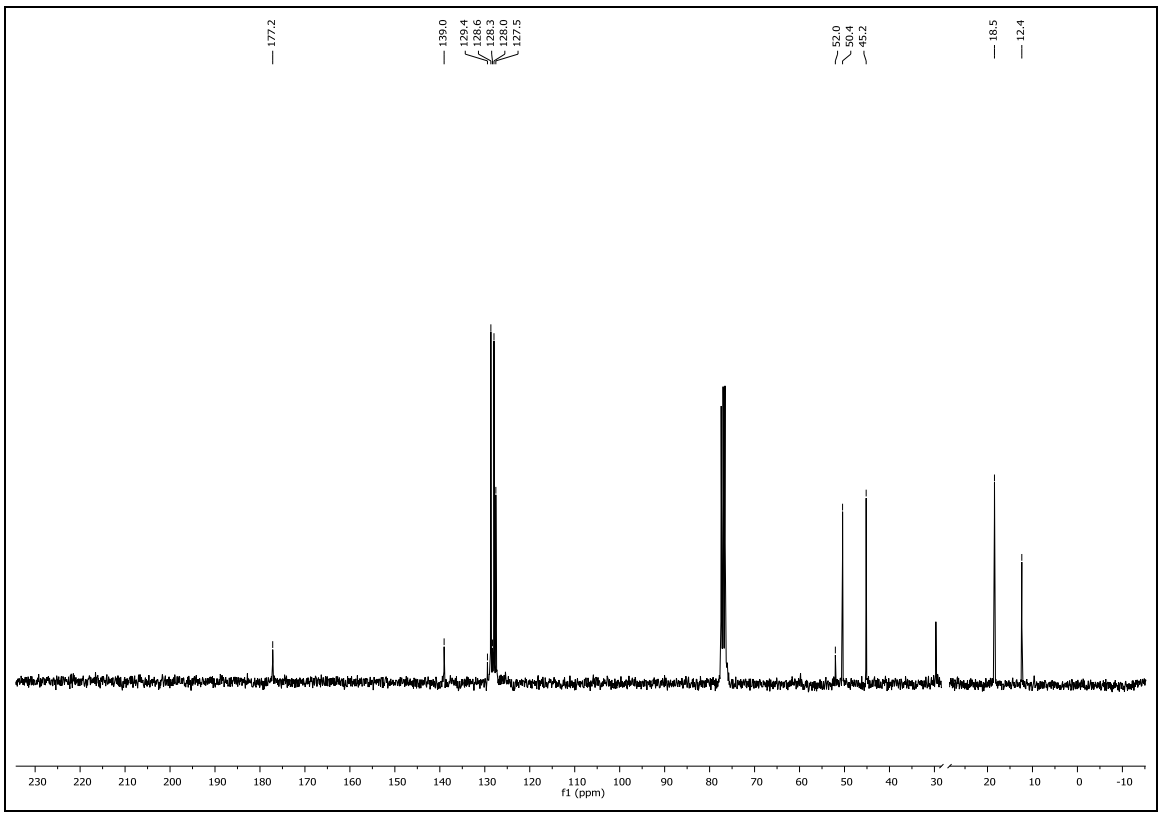
(*R*)-2-(Allylthio)-2-((*S*)-2-nitro-1-phenylethyl)octanamide (16)



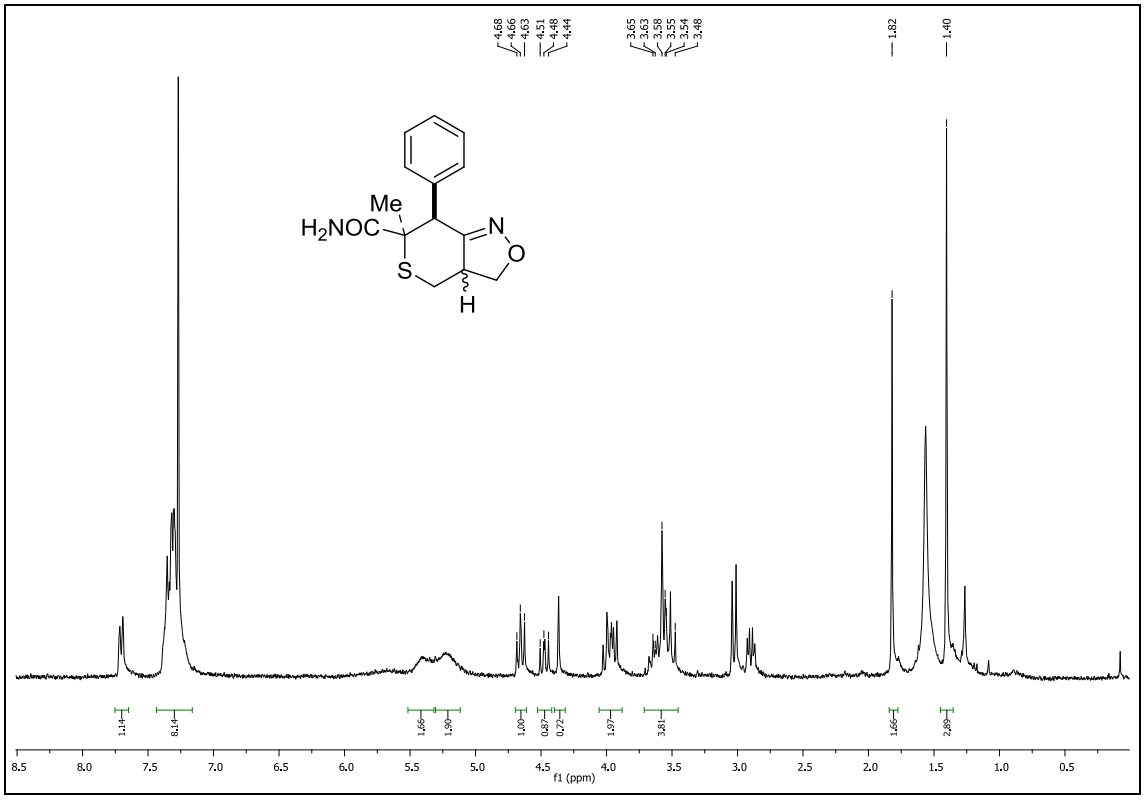


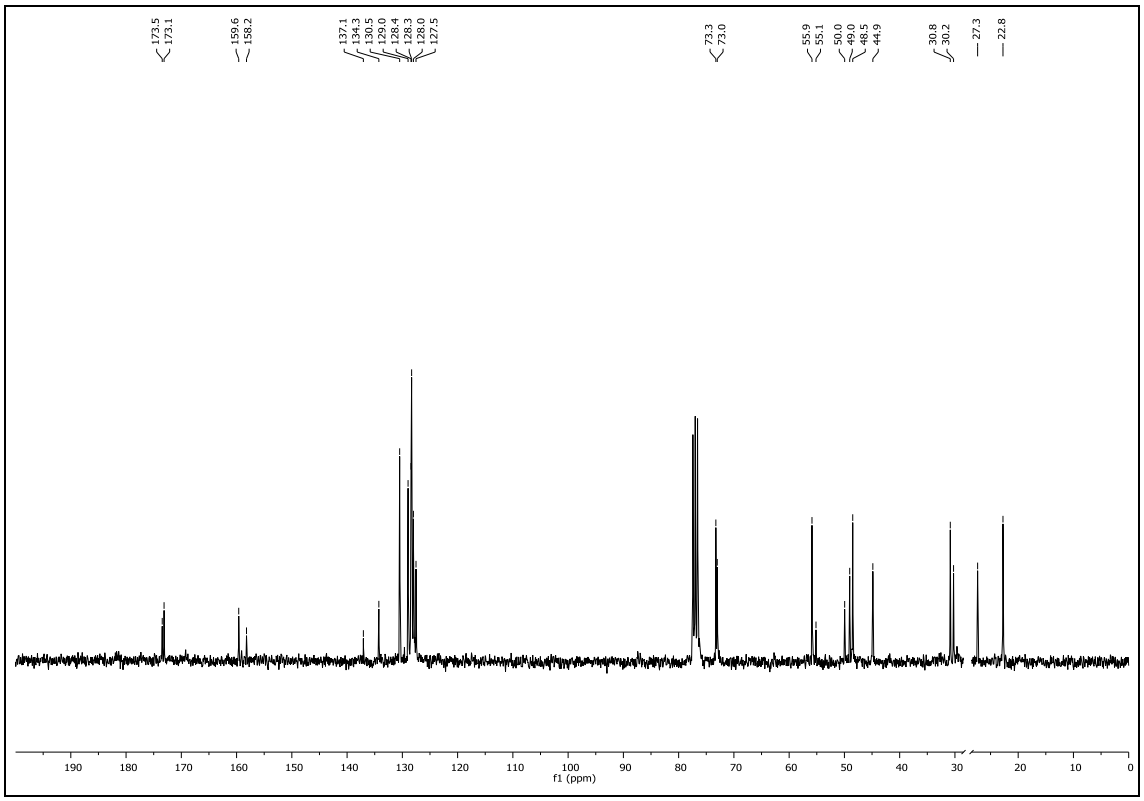
(*3R,4S*)-3-Methyl-3-(methylthio)-4-phenylpyrrolidin-2-one (17)



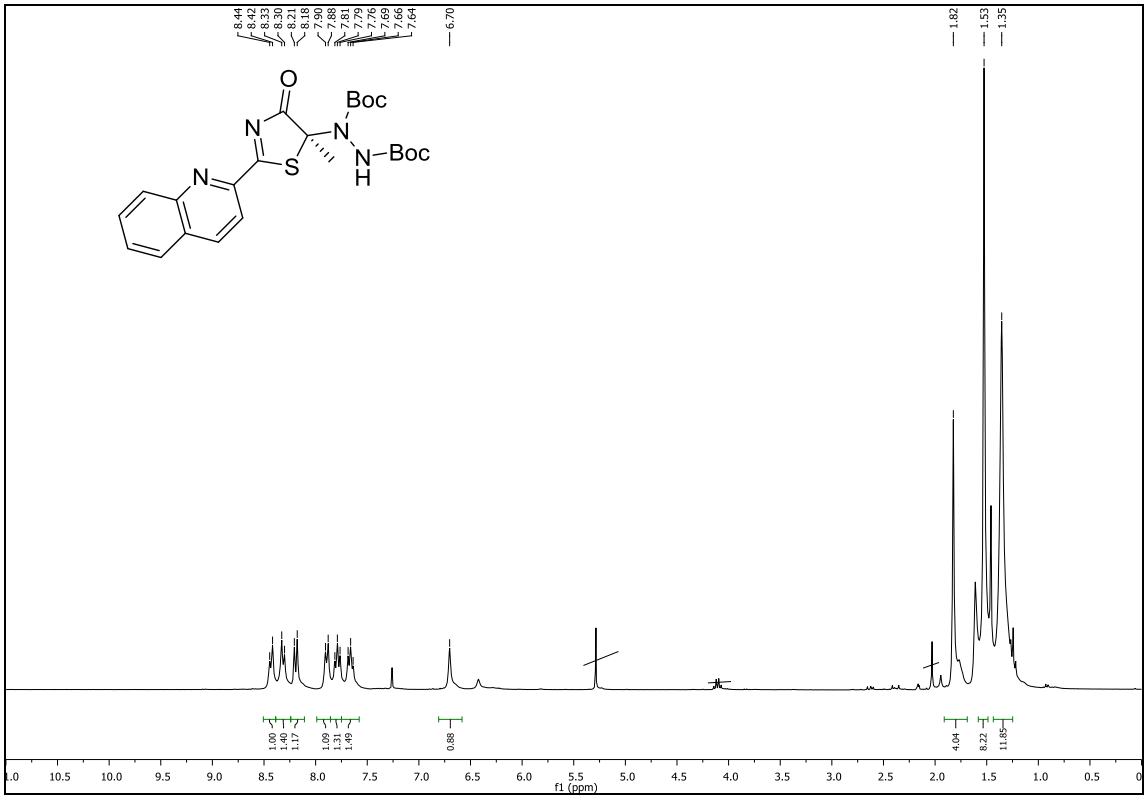


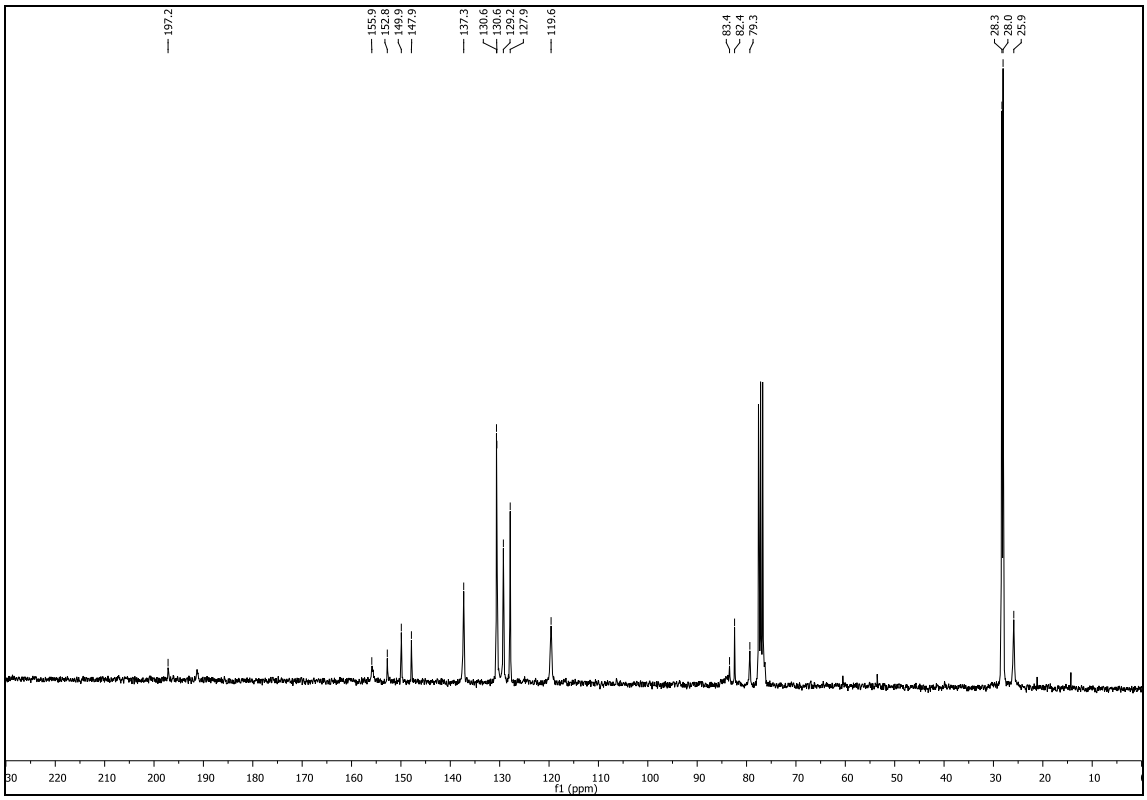
(*6R,7S*)-6-Methyl-7-phenyl-3a,4,6,7-tetrahydro-3H-thiopyrano[4,3-c]isoxazole-6-carboxamide (18)



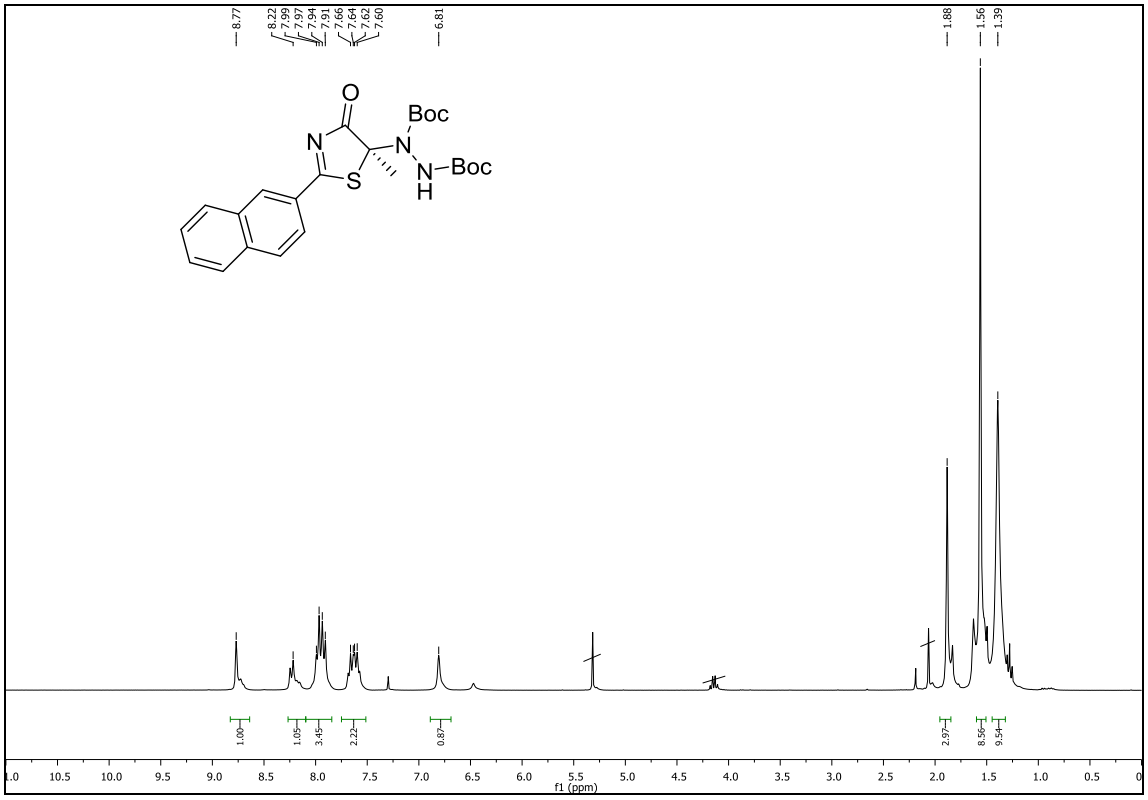


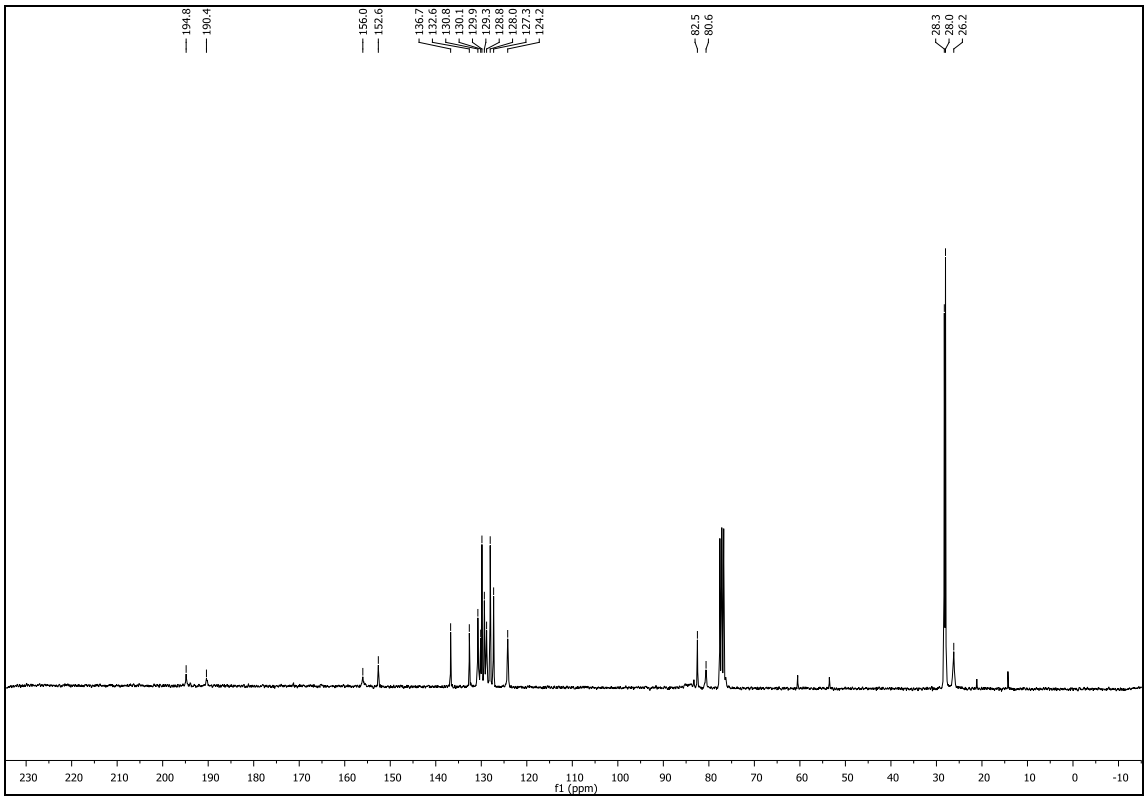
(*S*)-Di-*tert*-butyl 1-(5-methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (21)



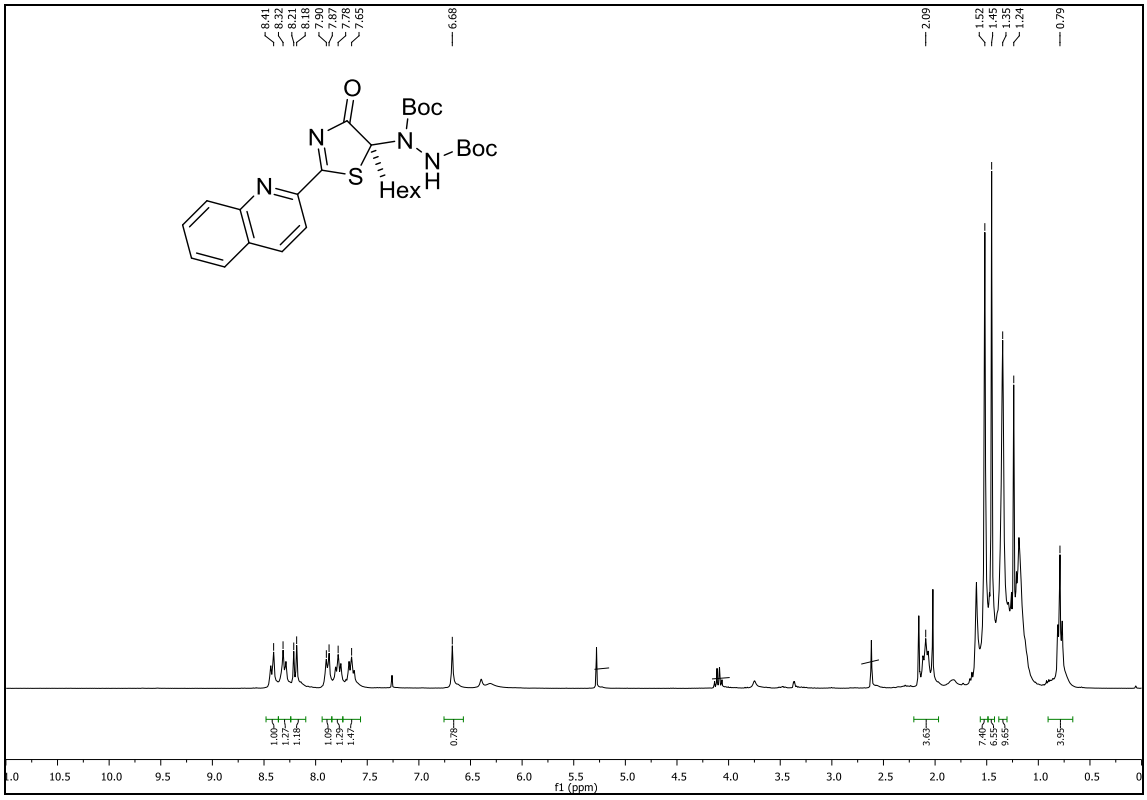


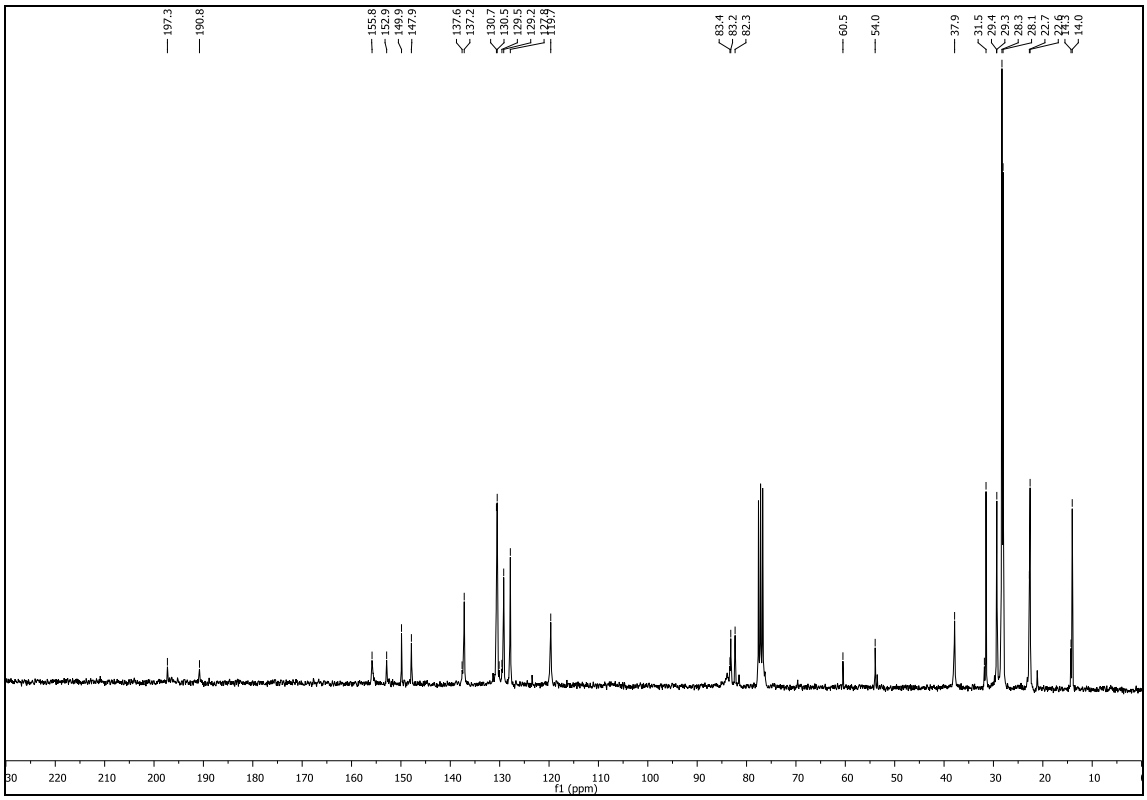
(*S*)-Di-*tert*-butyl 1-(5-methyl-2-(naphthalen-2-yl)-4-oxo-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (22)





(*S*)-Di-*tert*-butyl 1-(5-hexyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (23)





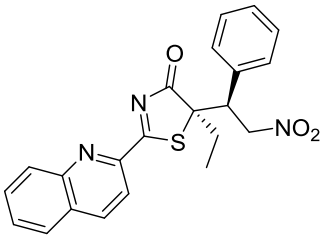
5.2.9. **HPLC chromatograms**

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9a)

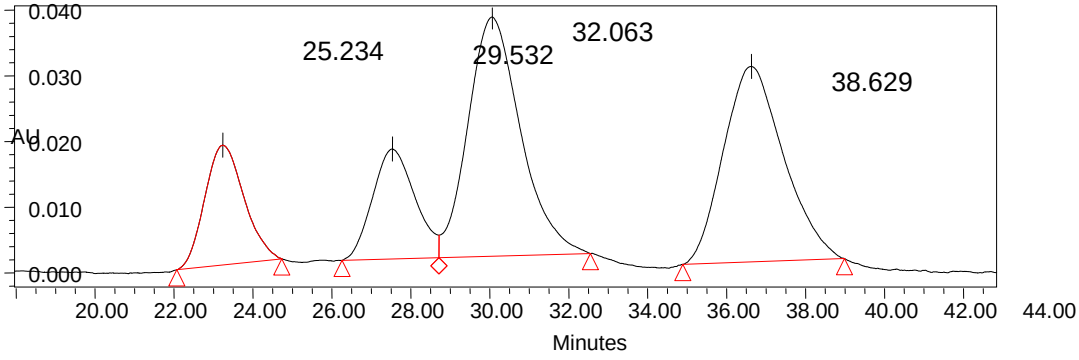
Daicel Chiralpak IA, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

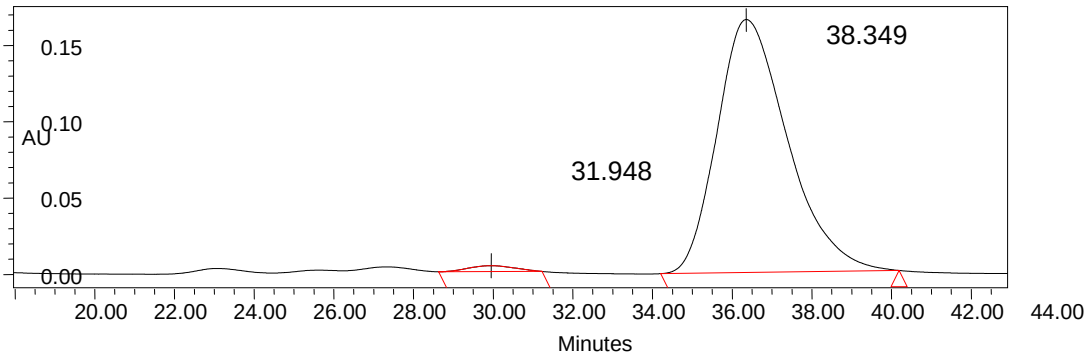


Rac-**9a**



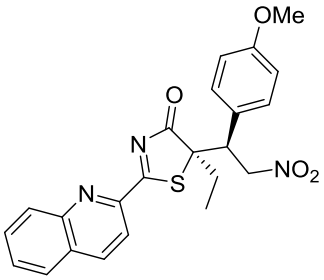
	Retention Time	% Area
1	25.234	13.95
2	29.532	13.85
3	32.063	37.40
4	38.629	34.80

9a



	Retention Time	% Area
1	31.948	1.52
2	38.349	98.48

(*R*)-5-Ethyl-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9b)

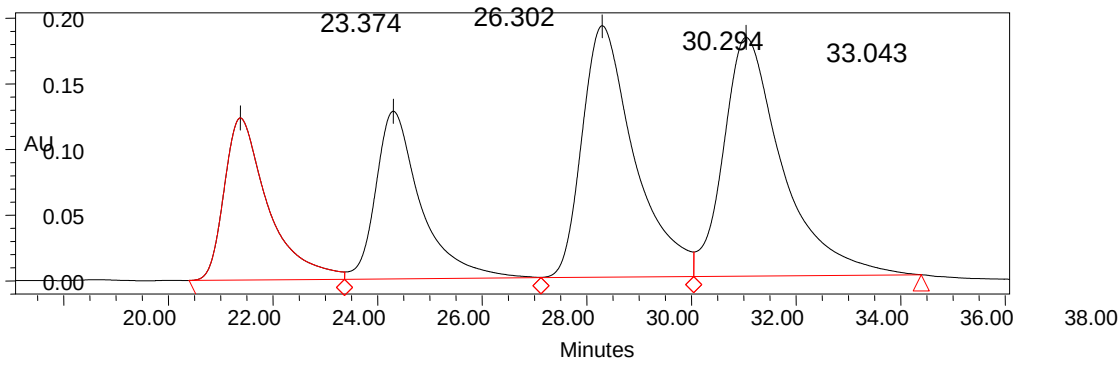


Daicel Chiralpak IA, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

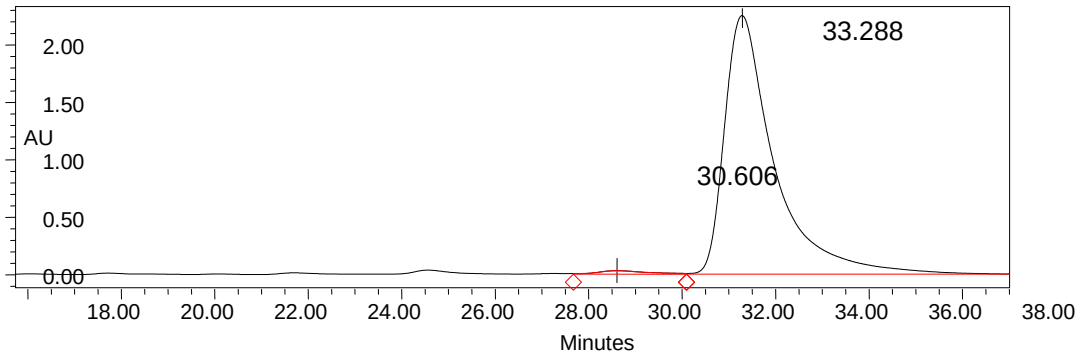
Processed Channel Descr.: PDA 260.0 nm.

Rac-**9b**



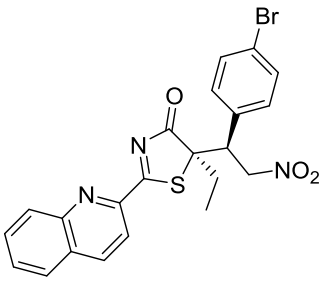
	Retention Time	% Area
1	23.374	17.04
2	26.302	18.02
3	30.294	31.34
4	33.043	33.60

9b



	Retention Time	% Area
1	30.606	1.34
2	33.288	98.66

(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9c)

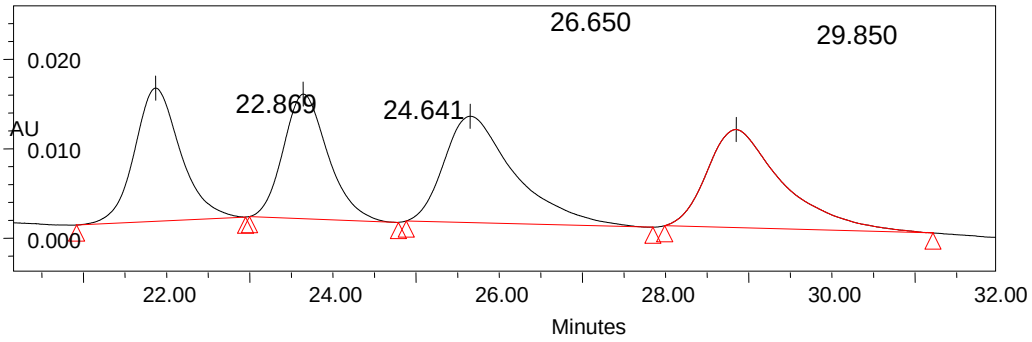


Daicel Chiralpak IB, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

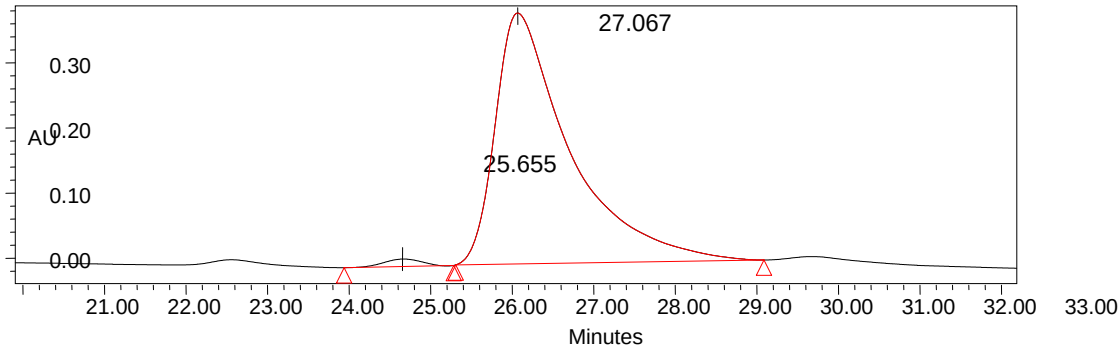
Processed Channel Descr.: PDA 260.0 nm.

Rac-**9c**



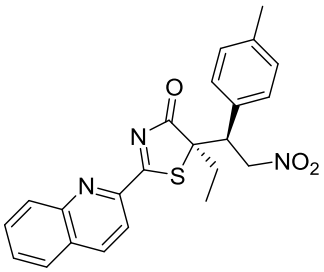
	Retention Time	% Area
1	22.869	23.05
2	24.641	20.90
3	26.650	28.10
4	29.850	27.95

9c



	Retention Time	% Area
1	25.655	1.46
2	27.067	98.54

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (9d)

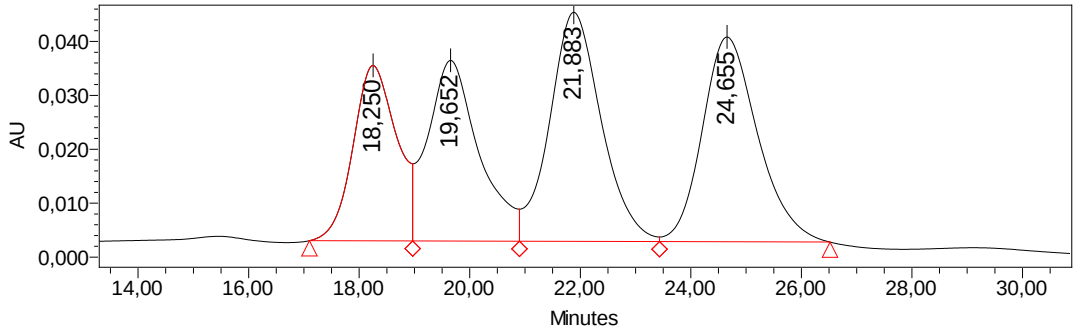


Daicel Chiralpak IA, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

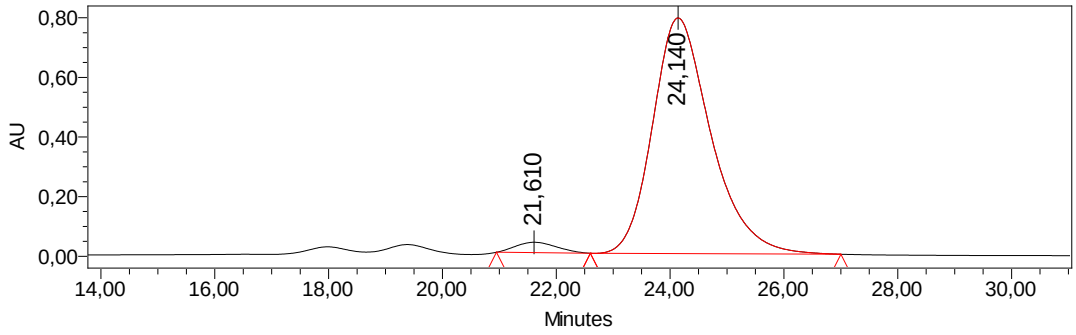
Processed Channel Descr.: PDA 260.0 nm.

Rac-**9d**



	Retention Time	% Area
1	18,250	19,04
2	19,652	23,22
3	21,883	29,44
4	24,655	28,31

9d



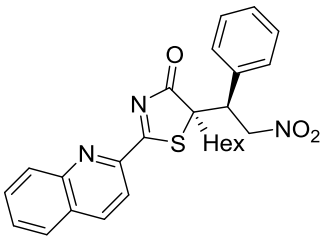
	Retention Time	% Area
1	21,610	3,00
2	24,140	97,00

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (10a)

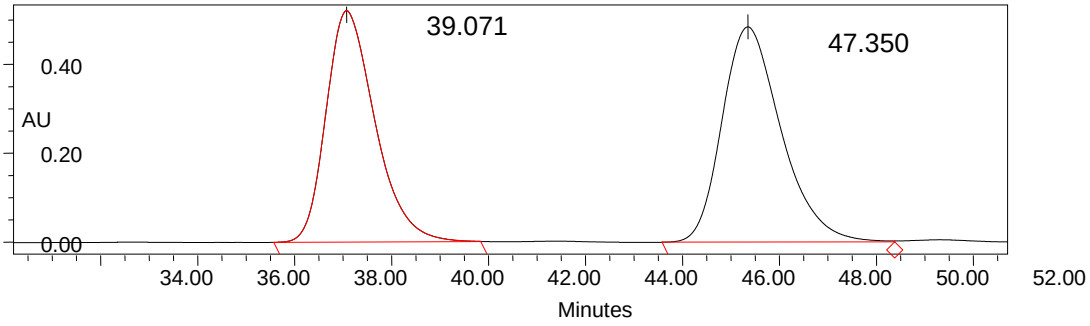
Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

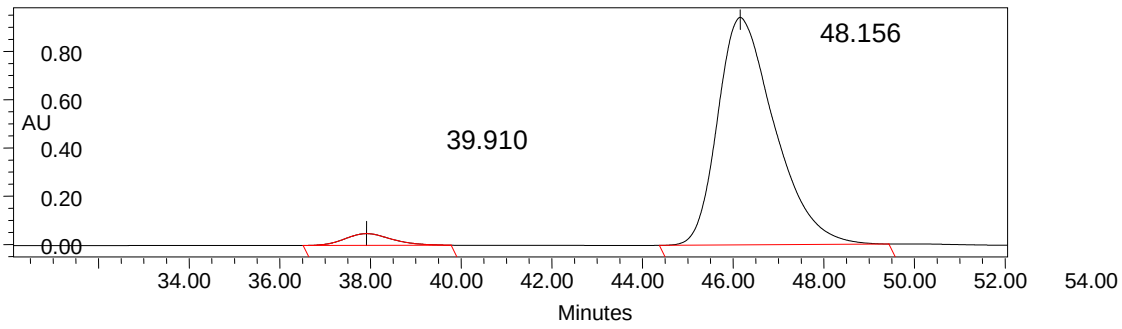


Rac-**10a**



	Retention Time	% Area
1	39.071	47.10
2	47.350	52.90

10a



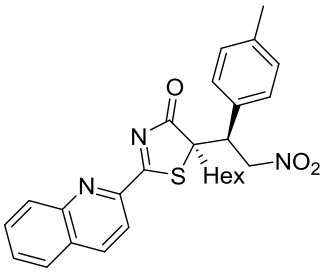
	Retention Time	% Area
1	39.910	4.06
2	48.156	95.94

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (10d)

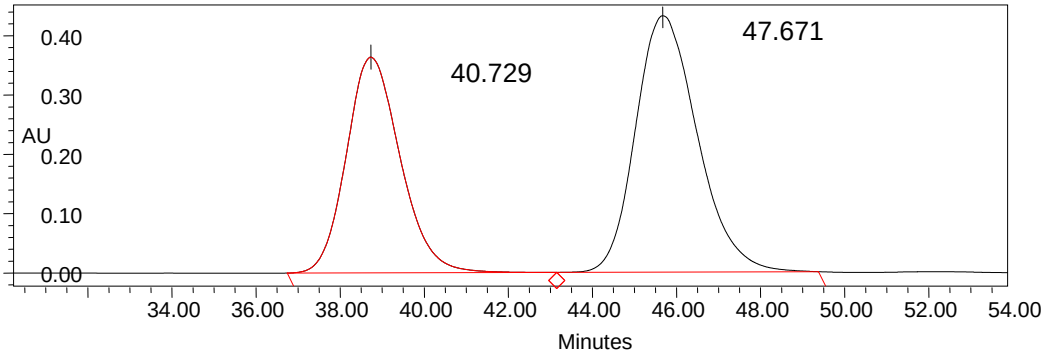
Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

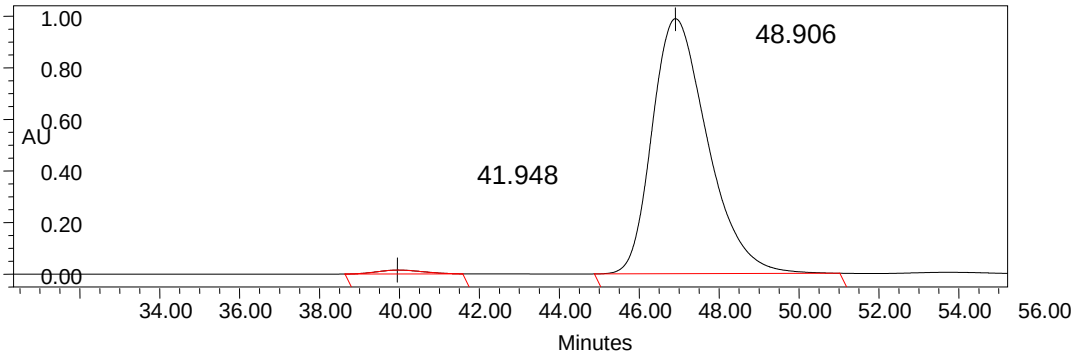


Rac-**10d**



	Retention Time	% Area
1	40.729	42.32
2	47.671	57.68

10d



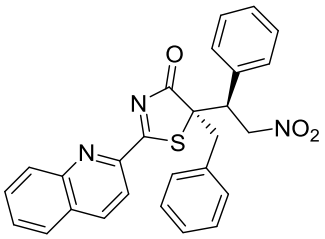
	Retention Time	% Area
1	41.948	1.25
2	48.906	98.75

(*R*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5H)-one (11a)

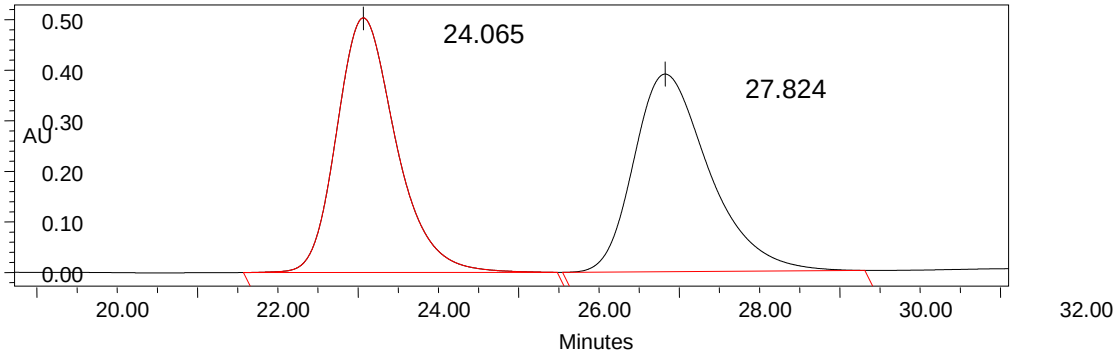
Daicel Chiralpak IC, hexane/isopropanol 50/50

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

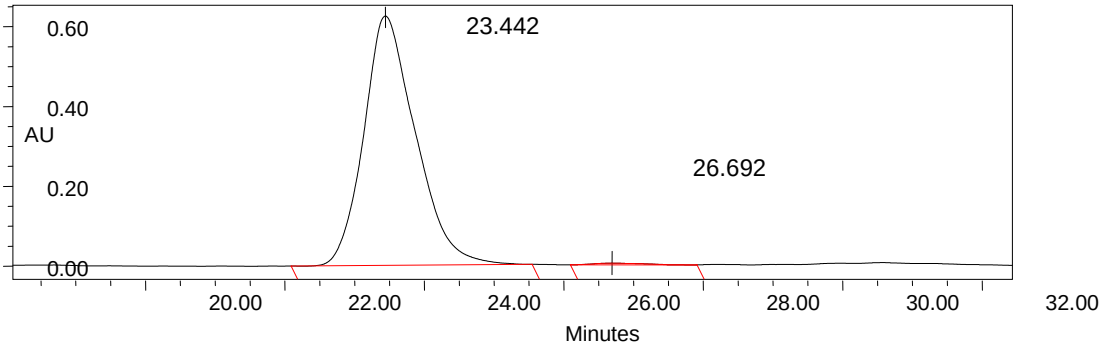


Rac-**11a**



	Retention Time	% Area
1	24.065	50.45
2	27.824	49.55

21



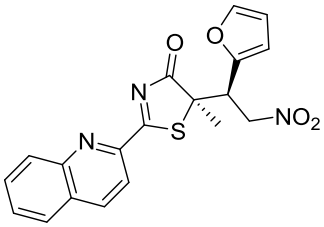
	Retention Time	% Area
1	23.442	99.38
2	26.692	0.62

(*R*)-5-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5H)-one (5be)

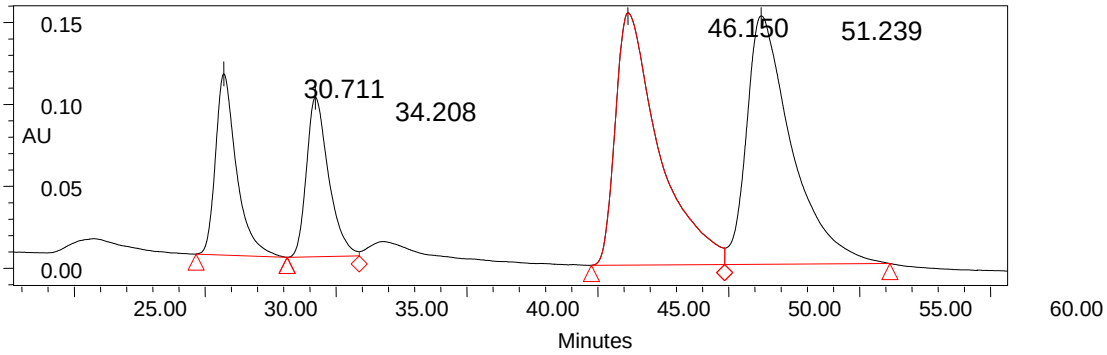
Daicel Chiralpak IB, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

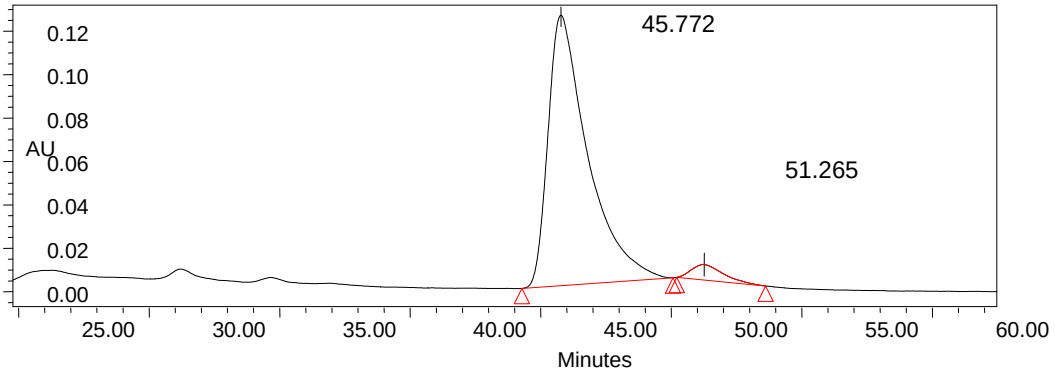


Rac-**5be**



	Retention Time	% Area
1	30.711	12.90
2	34.208	11.97
3	46.150	37.24
4	51.239	37.88

5be



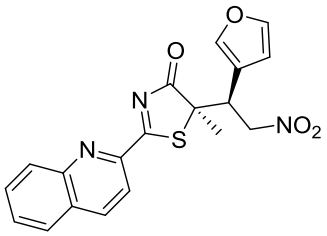
	Retention Time	% Area
1	45.772	95.65
2	51.265	4.35

(*R*)-5-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bf)

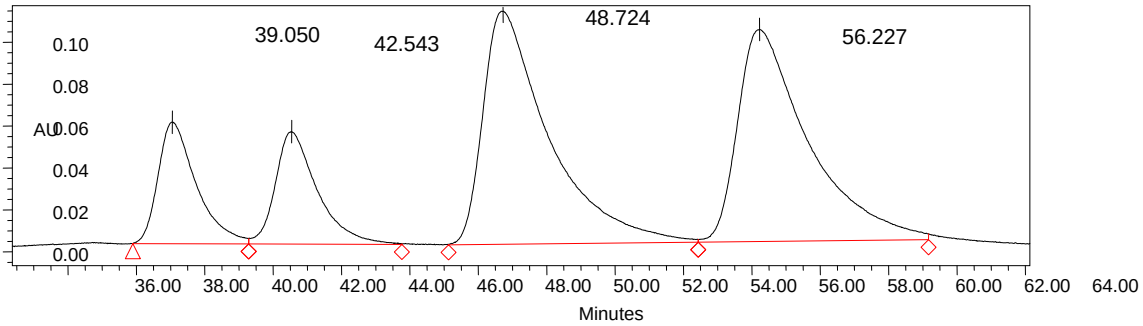
Daicel Chiralpak IB, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

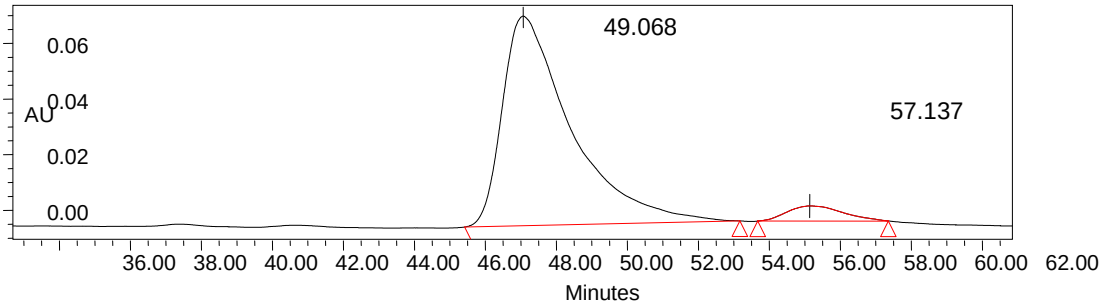


Rac-**5bf**



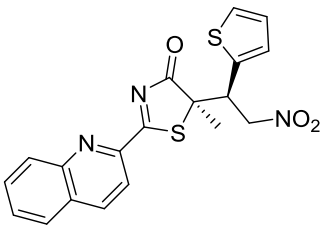
	Retention Time	% Area
1	39.050	11.73
2	42.543	11.87
3	48.724	38.63
4	56.227	37.76

5bf



	Retention Time	% Area
1	49.068	94.44
2	57.137	5.56

(*R*)-5-Methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (5bg)

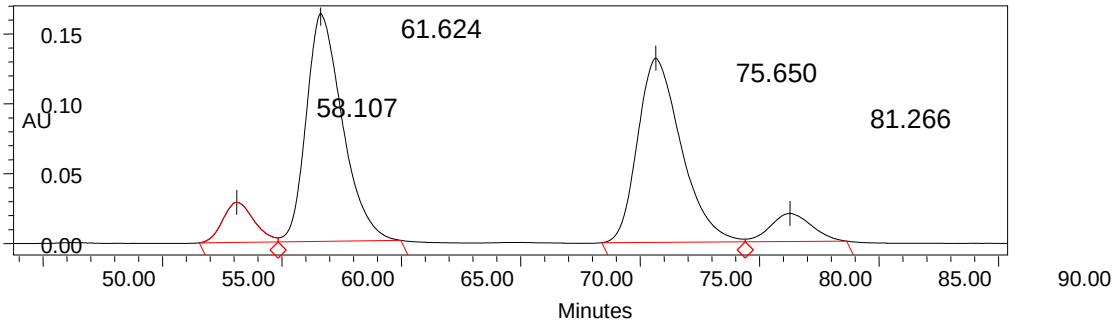


Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

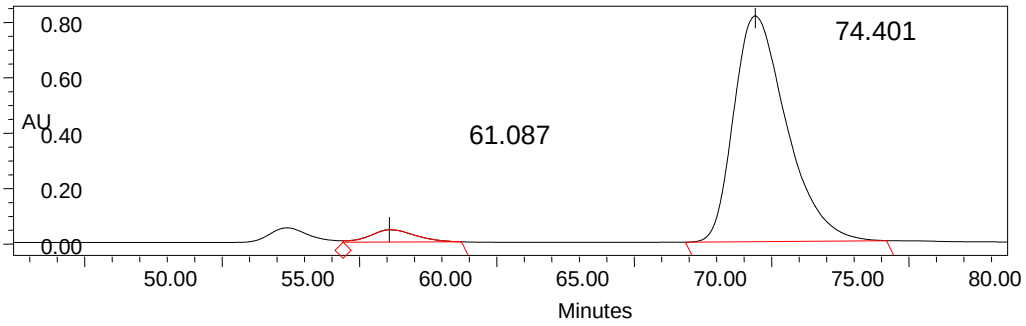
Processed Channel Descr.: PDA 260.0 nm.

Rac-**5bg**



	Retention Time	% Area
1	58.107	6.70
2	61.624	44.06
3	75.650	43.07
4	81.266	6.18

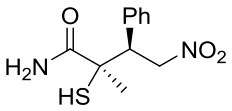
5bg



	Retention Time	% Area
1	61.087	4.36
2	74.401	95.64

(*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide (12)

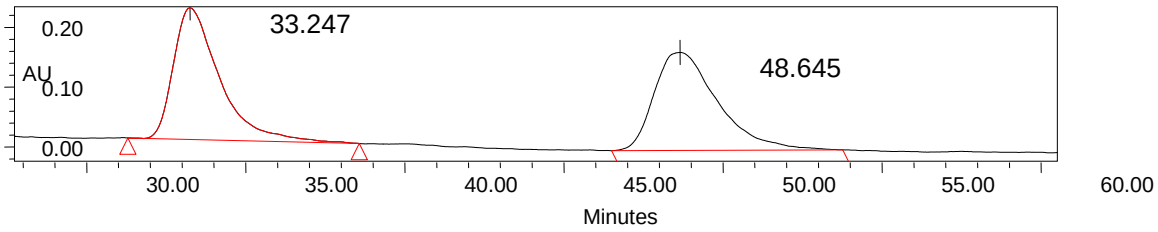
Daicel Chiralpak OD-H, hexane/isopropanol 80/20



flow rate= 0.5 mL/min,

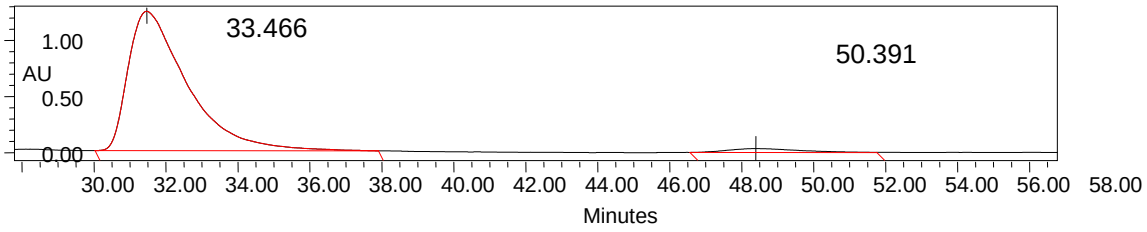
Processed Channel Descr.: PDA 210.0 nm.

Rac-**12**



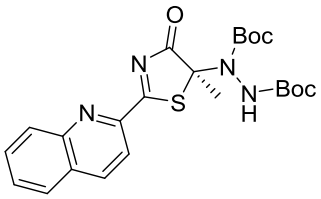
	Retention Time	% Area
1	33.247	49.51
2	48.645	50.49

12



	Retention Time	% Area
1	33.466	96.64
2	50.391	3.36

(*S*)-Di-*tert*-butyl 1-(5-methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (21)

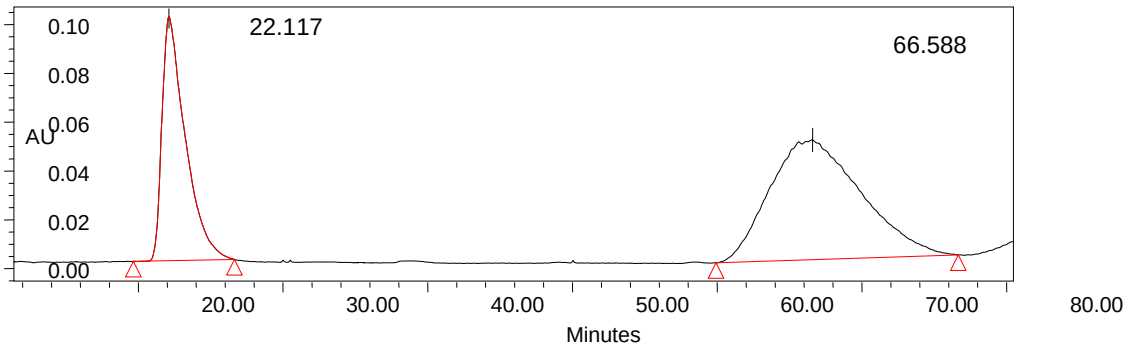


Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

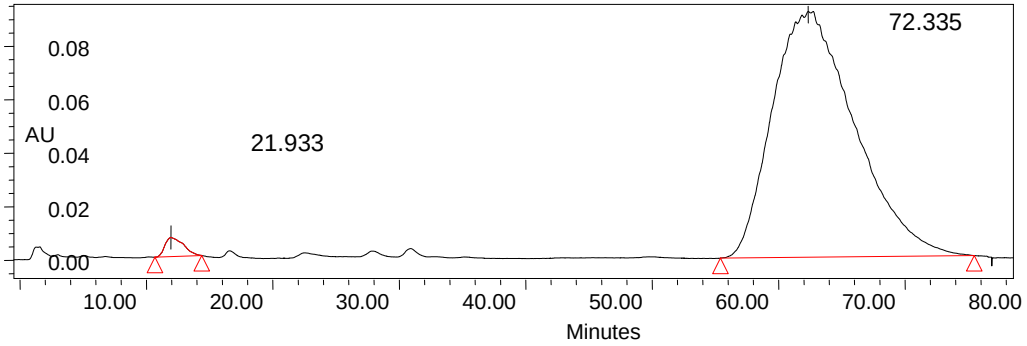
Processed Channel Descr.: PDA 262.0 nm.

Rac-21



	Retention Time	% Area
1	22.117	34.15
2	66.588	65.85

21



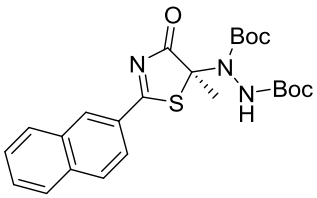
	Retention Time	% Area
1	21.933	1.71
2	72.335	98.29

(*S*)-Di-*tert*-butyl 1-(5-methyl-2-(naphthalen-2-yl)-4-oxo-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (22)

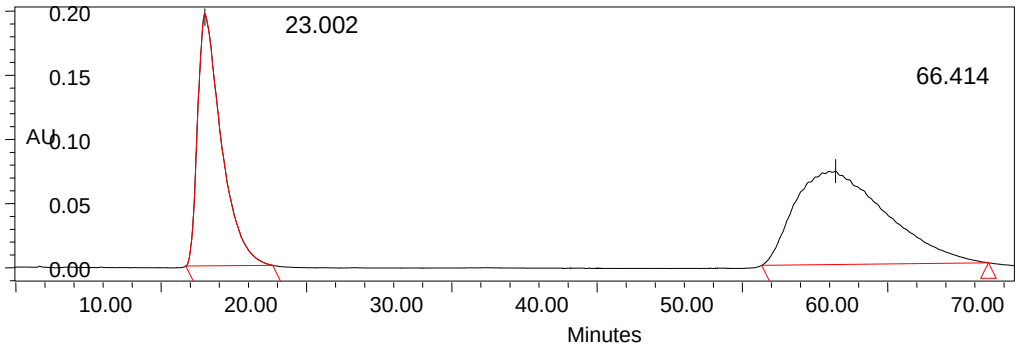
Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 262.0 nm.

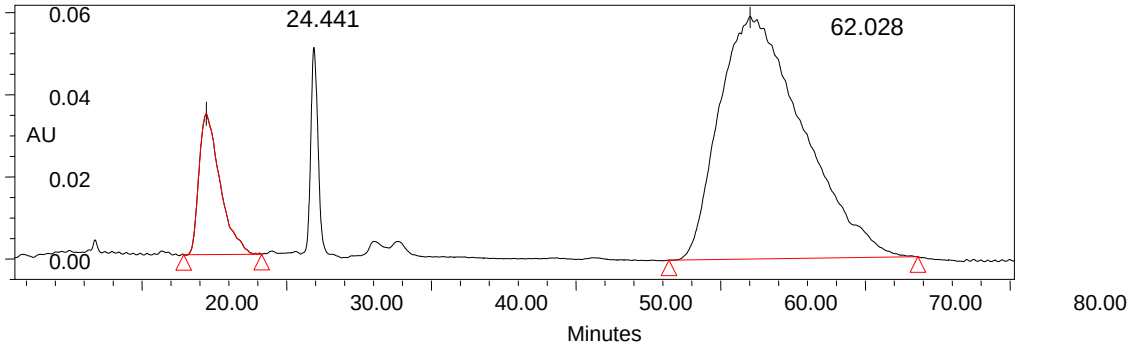


Rac-22



	Retention Time	% Area
1	23.002	41.08
2	66.414	58.92

22



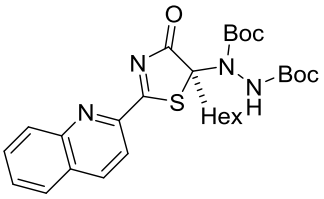
	Retention Time	% Area
1	24.441	12.74
2	62.028	87.26

(*S*)-Di-*tert*-butyl 1-(5-hexyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (23)

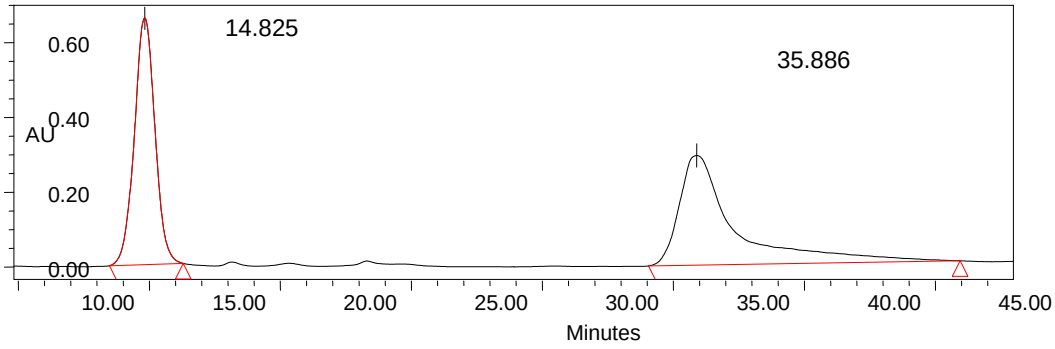
Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 262.0 nm.

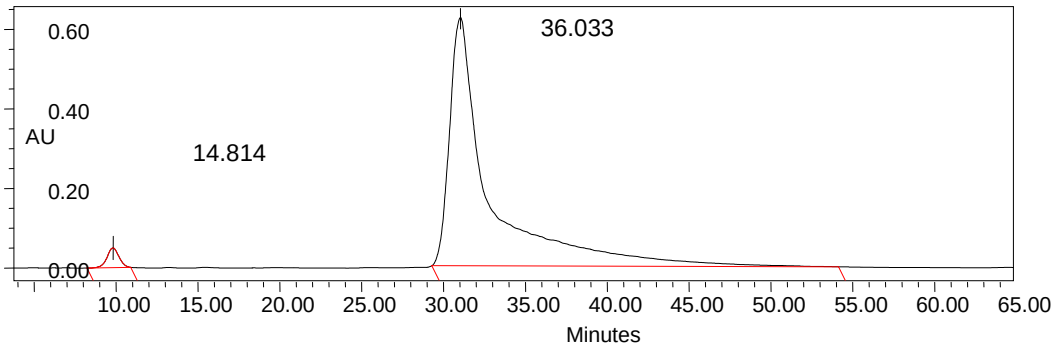


Rac-23



	Retention Time	% Area
1	14.825	45.42
2	35.886	54.58

23



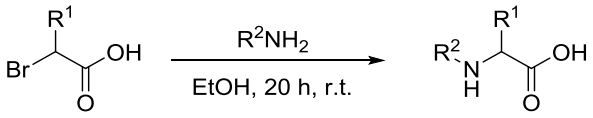
	Retention Time	% Area
1	14.814	2.33
2	36.033	97.67

5.3. **Experimental section of chapter 3**

5.3.1. **General procedure for the synthesis of 1*H*-imidazol-4(5*H*)-ones 27–40.**

5.3.1.1. **Preparation of *N*-substituted amino acids and amino esters.**

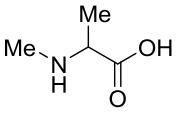
5.3.1.1.1. Procedure for the synthesis of N-methyl amino acids.[370]



R^1 = Me, Bn, *n*Hex, *i*Bu, *i*Pr
R^2 = Me, *i*Bu

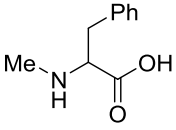
Methylamine (33% wt in EtOH, 20 mL, 160 mmol, 4 equiv.) was added to a stirred solution of the corresponding α-bromocarboxylic acid (40 mmol, 1 equiv.) in ethanol (24 mL) at 0 °C. The cooling bath was removed and the reaction was stirred at room temperature for 48 hours. The reaction mixture was evaporated under reduced pressure and the residue was crushed with acetone. If the acetone was not enough to obtain a proper solid, some drops of methanol were added, in order to solve any excess of the starting materials. Filtration of the suspension afforded the corresponding *N*-methyl α-amino acid as a white solid.

_N_-Methyl alanine



The title compound was prepared from 2-bromopropanoic acid (4.6 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 2.78 g, 27 mmol, 90 %. m.p. = 315–317°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.64 (q, *J* = 7.2 Hz, 1H), 2.72 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H).

_N_-Methyl phenylalanine

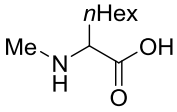


The title compound was prepared from 2-bromo-3-phenylpropanoic acid (9.2 g, 40 mmol) and methylamine (33% wt in EtOH, 20 mL, 160 mmol) according to the general procedure. Yield: 3.93 g, 22 mmol, 55 %. m.p. = 252–254°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.50 – 7.25 (m,

[370] Adapted from: I. J. Collins, J. C. Hannam, T. Harrison, A. Madin, M. P. Ridgill, *GB Patent* 4.728 Oct 31, **2003**.

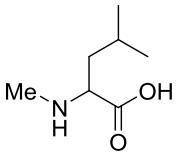
5H), 3.88 (t, *J* = 6.3 Hz, 1H), 3.25 (d, *J* = 6.3 Hz, 2H), 2.70 (s, 3H).

2-(Methylamino)octanoic acid



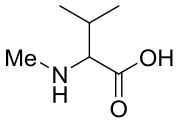
The title compound was prepared from 2-bromooctanoic acid (8.93 g, 40 mmol) and methylamine (33% wt in EtOH, 20 mL, 160 mmol) according to the general procedure. Yield: 5.84 g, 33.7 mmol, 84 %. m.p. = 246–250°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.59 (t, *J* = 5.8 Hz, 1H), 2.72 (s, 3H), 1.98 – 1.78 (m, 2H), 1.49 – 1.19 (m, 8H), 1.00 – 0.78 (m, 3H).

***N*-Methyl leucine**



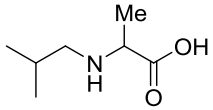
The title compound was prepared from 2-bromo-4-methylpentanoic acid (5.85 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 3.84 g, 26.43 mmol, 88 %. m.p. = 300–305°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.59 (t, *J* = 6.7 Hz, 1H), 2.72 (s, 3H), 1.72 (qd, *J* = 12.9, 10.9, 6.7 Hz, 3H), 0.98 (d, *J* = 4.3 Hz, 6H).

***N*-Methyl valine**



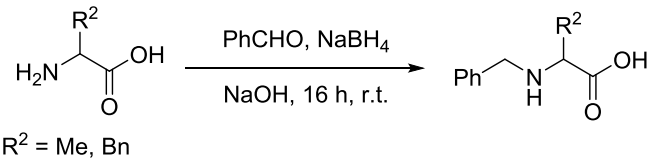
The title compound was prepared from 2-bromo-3-methylbutanoic acid (5.43 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 2.91 g, 22.2 mmol, 74 %. m.p. = 302–307°C. ^{1}H NMR (300 MHz, D_2O+CF_3CO_2D) δ: 3.59–3.54 (m, 1H), 2.64–2.60 (m, 3H), 2.18–2.14 (m, 1H), 0.96–0.84 (m, 6H).

***N*-Isobutyl alanine**



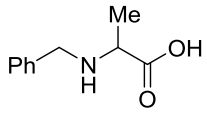
The title compound was prepared from 2-bromopropanoic acid (2.78 ml, 30 mmol) and 2-methylpropan-1-amine (5.96 ml, 60 mmol) according to the general procedure. The crude material was purified by crushing the reaction crude with acetone to afford the title compound as a white solid. Yield: 3.48 g, 24 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.68 (q, *J* = 9, 9 Hz, 1H), 2.96-2.83 (m, 2H), 2.10-1.96 (m, 1H), 1.51 (d, *J* = 6 Hz, 3H), 1.02 (dd, *J* = 3, 3 Hz 1H).

5.3.1.1.2. Procedure for the synthesis of N-benzyl amino acids.[371]



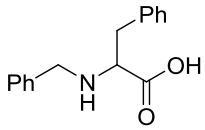
Benzaldehyde (5.09 mL, 50.0 mmol) was added to a vigorously stirred solution of the amino acid (50.0 mmol) in aqueous NaOH (2 M, 25 mL). The emulsion was stirred for 30 min before the mixture was cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The mixture was allowed to warm to room temperature, then stirred for a further hour before a second equivalent of benzaldehyde (5.09 mL, 50.0 mmol) was added. The slurry was stirred vigorously for 30 min, cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The white mixture was stirred for a further 2 h then diluted with H_2O (30 mL) and washed with dichloromethane (2 × 30 mL). Hydrochloric acid (1 M) was added until neutral pH was obtained and the resulting white precipitate was collected by filtration, washed with water (2 × 10 mL) and then acetone (2 × 10 mL) to give the *N*-benzyl amino acid as a white powder.

_N_-Benzyl alanine



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. Yield: 4.57 g, 25.4 mmol, 51 %. m.p. = 270–272°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.51 (s, 5H), 4.25 (dd, *J* = 13.0, 4.2 Hz, 2H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H).

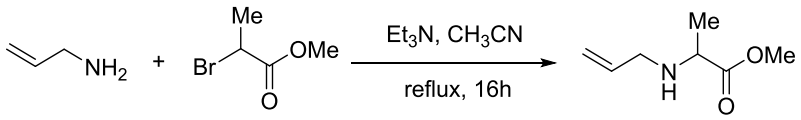
_N_-Benzyl phenylalanine



The title compound was prepared from phenylalanine (8.26 g, 50 mmol) according to the general procedure. Yield: 6.4 g, 25 mmol, 50 %. m.p. = 230–233°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.45–6.99 (m, 10H), 3.58 (dd, *J* = 41.9, 12.6 Hz, 2H), 3.27 (t, *J* = 6.9 Hz, 1H), 2.83 (dd, *J* = 6.7, 2.4 Hz, 2H).

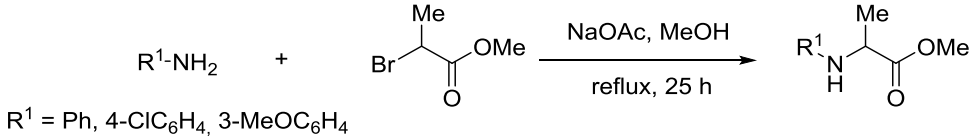
[371] P. Dzygiel, T. B. Reeve, U. Piarulli, M. Krupicka, I. Tvaroska, C. Gennari *Eur. J. Org. Chem.* **2008**, *7*, 1253–1264.

5.3.1.1.3. Synthesis of methyl N-allyl alaninate.[372]



A solution of allylamine (7.7 g, 135 mmol, 1 equiv) and Et_3N (13.6 g, 135 mmol, 1 equiv) in CH_3CN (100 mL) was added to methyl 2-bromopropanoate (26.4 g, 135 mmol) and the mixture was heated under reflux. After 16 h saturated $NaHCO_3$ (100 mL) was added and the mixture was extracted with ethyl acetate (450 mL), dried over $MgSO_4$, filtered and the solvents evaporated under reduced pressure. Purification by silica gel column chromatography, eluting with hexane/ethyl acetate (3:2), gave the aminoester as a colourless oil. Yield: 15.89 g, 111 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.95 – 5.75 (m, 1H), 5.21 – 5.05 (m, 2H), 3.72 (d, *J* = 0.6 Hz, 3H), 3.37 (q, *J* = 7.0 Hz, 1H), 3.30 – 3.08 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H).

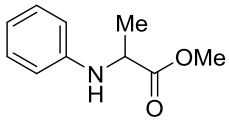
5.3.1.1.4. Synthesis of methyl N-aryl alaninate.[373]



R^1 = Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$

A solution of the corresponding aniline (9.2 mL, 100 mmol, 1 equiv.), sodium acetate (8.3 g, 100 mmol, 1 equiv.) and methyl 2-bromopropanoate (11.16 mL, 100 mmol, 1 equiv) in methanol (3 mL) was heated under reflux for 25 h. After being cooled to room temperature, the mixture was diluted with water (40 mL) and extracted with diethyl ether (2 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to afford the aminoester as a yellow oil.

Methyl *N*-phenyl alaninate

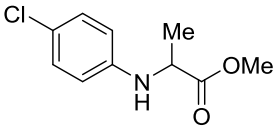


The title compound was prepared from methyl 2-bromopropanoate (11.16 mL, 100 mmol) and aniline (9.2 mL, 100 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 10 g, 56 mmol, 56 %. ^{1}H NMR

[372] Adapted from: I. Coldham, B. C. Dobson, S. R. Fletcher and A. I. Franklin *Eur. J. Org. Chem.* **2007**, *16*, 2676–2686.
[373] Adapted from: D. Kato, K. Miyamoto, H. Ohta *Tetrahedron: Asymmetry* **2004**, *15*, 2965–2973.

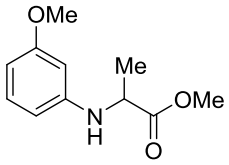
(300 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.82 – 6.72 (m, 1H), 6.62 (dd, *J* = 8.7, 1.1 Hz, 2H), 4.17 (q, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H).

Methyl *N*-(4-chlorophenyl)alaninate



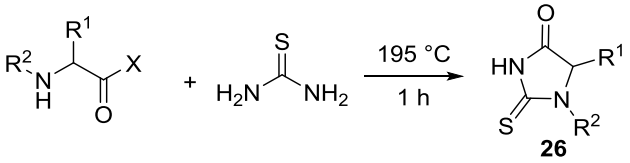
The title compound was prepared from methyl 2-bromopropanoate (3.30 ml, 30 mmol) and 4-chloroaniline (3.84 g, 30 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 5.36 g, 25.2 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13-7.10 (m, 2H), 6.54-6.51 (m, 2H), 4.13-4.09 (m, 2H), 3.73 (s, 3H), 1.46 (d, *J* = 9 Hz, 3H).

Methyl *N*-(3-methoxyphenyl)alaninate



The title compound was prepared from 2-bromo-3-methylbutanoic acid (5.43 g, 30 mmol) and 3-methoxyaniline (3.37 ml, 30 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 4.64 g, 22.2 mmol, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.08 (t, *J* = 8.1 Hz, 1H), 6.31 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 6.22 (ddd, *J* = 8.0, 2.3, 0.9 Hz, 1H), 6.16 (t, *J* = 2.3 Hz, 1H), 4.15 (t, *J* = 4.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H).

5.3.1.2. General procedure for the synthesis of thiohydantoins 26.[374]



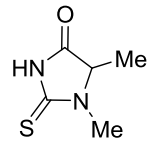
R^1 = Me, Bn, *n*Hex, *i*Bu, *i*Pr
R^2 = Me, Bn, allyl, *i*Bu, Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$
X = OH, OMe

A mixture of the corresponding *N*-substituted amino acid or their methyl ester (1 equiv) and thiourea (3 equiv) was placed in a flask and heated under stirring. When the oil bath 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. The reaction mixture was kept at this temperature for an ad-

[374]Adapted from: Z. D. Wang , S. O. Sheikh and Y. Zhang *Molecules* **2006**, *11*, 739–750.

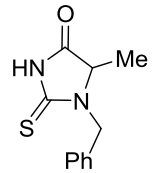
ditional hour. The flask was then allowed to cool down to room temperature and ethyl acetate was added. A white precipitate formed, which was filtered off. The mother liquid was then evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 70:30) to afford the title compound as a white solid.

1,5-Dimethyl-2-thioxoimidazolidin-4-one



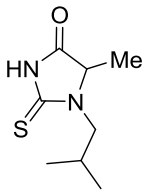
The title compound was prepared from *N*-methyl alanine (1.03 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.29 g, 9 mmol, 90 %. m.p. = 151–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 3.25 (s, 3H), 1.52 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 174.7, 61.7, 32.1, 15.3. UPLC-DAD-QTOF: $C_5H_9N_2OS$ $[M+H]^+$ calcd.: 145.0436, found: 145.0430.

1-Benzyl-5-methyl-2-thioxoimidazolidin-4-one



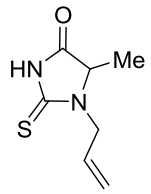
The title compound was prepared from *N*-benzyl alanine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.20 g, 6.5 mmol, 65 %. m.p. = 140–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.97 (s, 1H), 7.49 – 7.21 (m, 4H), 5.03 (dd, *J* = 377.3, 15.1 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.0, 134.8, 129.2, 128.6, 128.2, 58.5, 48.0, 15.0. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0751.

1-Isobutyl-5-methyl-2-thioxoimidazolidin-4-one



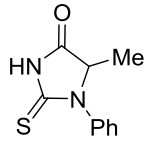
The title compound was prepared from *N*-isobutyl alanine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. (Column chromatography on silica gel eluting with hexane/ethyl acetate, 80:20) Yield: 1.47 g, 7.9 mmol, 79 %. m.p. = 84–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 4.13 (q, *J* = 6Hz, 1H), 4.05-3.97 (m, 1H), 3.05 (dd, *J* = 6Hz, 1H), 2.09-1.99 (m, 1H), 1.44 (d, *J* = 9 Hz, 2H), 0.95 (d, *J* = 6 Hz, 3H), 0.88 (d, *J* = 9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.8, 59.2, 51.0, 27.1, 20.3, 19.8, 14.8. UPLC-DAD-QTOF: $C_8H_{15}N_2OS$ $[M+H]^+$ calcd.: 187.0905, found: 187.0893.

1-Allyl-5-methyl-2-thioxoimidazolidin-4-one



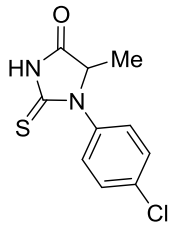
The title compound was prepared from methyl *N*-allyl alaninate (1.43 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.31 g, 7.7 mmol, 77 %. m.p. = 109–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 5.90 – 5.68 (m, 1H), 5.41 – 5.19 (m, 2H), 4.83 (dd, *J* = 15.5, 4.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 3.99 – 3.83 (m, 1H), 1.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 174.8, 131.1, 120.3, 59.5, 47.5, 15.5. UPLC-DAD-QTOF: $C_7H_{11}N_2OS$ $[M+H]^+$ calcd.: 171.0592, found: 171.0597

5-Methyl-1-phenyl-2-thioxoimidazolidin-4-one



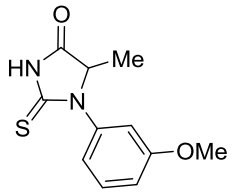
The title compound was prepared from methyl *N*-phenyl alaninate (1.79 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.73 g, 8.4 mmol, 84 %. m.p. = 188–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 7.53 – 7.33 (m, 5H), 4.60 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.1, 136.7, 130.0, 129.1, 127.3, 122.7, 63.0, 16.1. UPLC-DAD-QTOF: $C_{10}H_{11}N_2OS$ $[M+H]^+$ calcd.: 207.0592, found: 207.0593.

1-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from methyl (4-chlorophenyl)alaninate (2.13 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 2.05 g, 8.5 mmol, 85 %. m.p. = 170–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.01 (s, 1H), 7.47-7.35 (m, 4H), 4.57 (q, *J* = 6, 9 Hz, 1H), 1.43 (d, *J* = 9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.0, 173.1, 134.7, 134.4, 129.9, 128.2, 62.4, 15.7. UPLC-DAD-QTOF: $C_{10}H_{10}ClN_2OS$ $[M+H]^+$ calcd.: 241.0202, found: 241.0193.

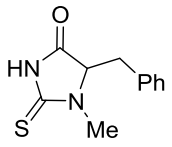
1-(3-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from methyl (3-methoxyphenyl)alaninate (2.09 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. (Column chromatography on silica gel eluting with hexane/ethyl acetate, 2:1) Yield: 1.89 g, 8 mmol, 80 %. m.p. = 145–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (s, 1H), 7.41-7.35 (t, J = 9 Hz, 1H), 7.01-6.91 (m, 3H), 4.57 (q, J = 9 Hz, 1H), 3.83 (s, 3H), 1.44 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.7, 173.2, 160.4, 137.7,

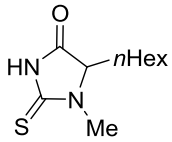
130.4, 118.7, 114.2, 113.6, 62.6, 56.7, 15.7. UPLC-DAD-QTOF: $C_{11}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 237.0698, found: 237.0684.

5-Benzyl-1-methyl-2-thioxoimidazolidin-4-one



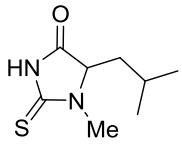
The title compound was prepared from *N*-methyl phenylalanine (1.79 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.85 g, 8.4 mmol, 84 %. m.p. = 130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.39 – 7.07 (m, 6H), 4.31 (t, *J* = 4.8 Hz, 1H), 3.41 – 3.16 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 172.4, 133.8, 129.4, 129.3, 129.2, 129.1, 127.9, 66.6, 63.0, 35.7. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0751.

5-Hexyl-1-methyl-2-thioxoimidazolidin-4-one



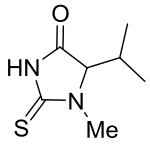
The title compound was prepared from 2-(methylamino)octanoic acid (1.73 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.73 g, 8.1 mmol, 81 %. m.p. = 79–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.40 (s, 1H), 4.08 (dd, *J* = 5.7, 3.6 Hz, 1H), 3.20 (s, 3H), 1.91 (ddd, *J* = 27.8, 7.8, 2.7 Hz, 2H), 1.25 (d, *J* = 5.4 Hz, 8H), 0.91 – 0.71 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.13, 174.28, 65.74, 32.12, 31.89, 29.34, 29.27, 23.44, 22.94, 14.45. UPLC-DAD-QTOF: $C_{10}H_{19}N_2OS$ $[M+H]^+$ calcd.: 215.1213, found: 215.1209.

5-Isobutyl-1-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from *N*-methyl leucine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.47 g, 7.9 mmol, 79 %. m.p. = 125–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 4.05 (t, *J* = 5.9 Hz, 1H), 3.24 (s, 3H), 1.99 – 1.85 (m, 1H), 1.84 – 1.74 (m, 1H), 0.98 (d, *J* = 0.7 Hz, 1H), 0.96 (d, *J* = 6.5 Hz, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 173.8, 64.1, 38.1, 32.2, 24.2, 23.1, 22.6. UPLC-DAD-QTOF: $C_8H_{15}N_2OS$ $[M+H]^+$ calcd.: 187.0905, found: 187.0908.

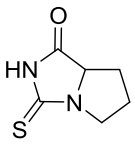
5-isoPropyl-1-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from *N*-methyl valine (1.31 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.20 g, 7 mmol, 70 %. m.p. = 137–140 °C. ^{1}H NMR (300 MHz,$CDCl_3$) δ: 8.87 (s, 1H), 3.91 (dd, *J* = 3.4, 0.7 Hz, 1H), 3.24 (s, 3H), 2.32 (ddt, *J* =

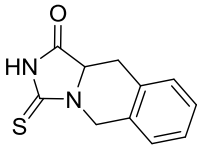
10.4, 7.0, 3.4 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.2, 173.0, 70.4, 32.8, 30.0, 17.5, 16.8. UPLC-DAD-QTOF: $C_7H_{13}N_2OS$ $[M+H]^+$ calcd.: 173.0749, found: 173.0750.

3-Thioxohexahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one



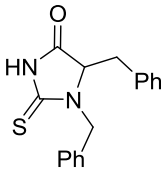
The title compound was prepared from proline (1.15 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 968 mg, 6.2 mmol, 62 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (s, 1H), 4.28 (dd, *J* = 10.4, 6.7 Hz, 1H), 3.94 (dt, *J* = 11.6, 8.1 Hz, 1H), 3.52 (ddd, *J* = 12.0, 8.7, 3.5 Hz, 1H), 2.42 – 2.05 (m, 3H), 1.79 (dd, *J* = 11.4, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 186.9, 175.6, 67.4, 48.4, 27.6, 27.0. UPLC-DAD-QTOF: $C_6H_9N_2OS$ $[M+H]^+$ calcd.: 157.0436, found: 157.0434.

3-Thioxo-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5*H*)-one



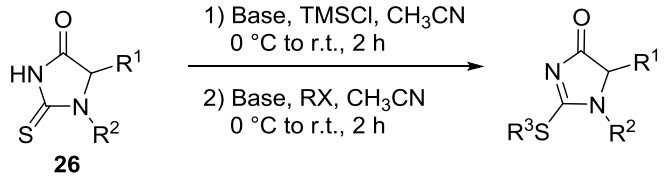
The title compound was prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.77 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, from 70:30 to 50:50). Yellow solid. Yield: 1.62 g, 7.4 mmol, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.44 – 7.11 (m, 4H), 5.42 (d, *J* = 17.2 Hz, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 4.26 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.32 (dd, *J* = 15.6, 4.7 Hz, 1H), 3.12 – 2.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.5, 173.7, 131.2, 130.6, 129.9, 128.2, 128.0, 127.3, 59.5, 46.1, 31.2. UPLC-DAD-QTOF: $C_{11}H_{11}N_2OS$ $[M+H]^+$ calcd.: 219.0592, found: 219.0595.

1,5-Dibenzyl-2-thioxoimidazolidin-4-one



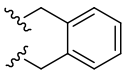
The title compound was prepared from *N*-benzyl phenylalanine (2.55 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 2.63 g, 8.9 mmol, 89 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.22 (s, 1H), 7.50 – 6.93 (m, 10H), 5.79 (d, *J* = 15.0 Hz, 1H), 4.26 – 4.05 (m, 2H), 3.19 (ddd, *J* = 27.7, 14.5, 4.7 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.0, 173.3, 134.4, 133.92, 129.0, 128.7, 128.6, 128.1, 128.1, 127.4, 62.8, 47.9, 35.1.. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1056, found: 297.1062.

5.3.1.3. General procedure for the synthesis of 1*H*-imidazol-4(5*H*)-ones 27–40



26

	R^1	R^2
27	Me	Me
28	Me	Bn
29	Me	*i*Bu
30	Me	Allyl
31	Me	Ph
32	Me	4-ClC_6H_4
33	Me	3-$MeOC_6H_4$

	R^1	R^2
34	Bn	Me
35	*n*Hex	Me
36	*i*Bu	Me
37	*i*Pr	Me
38	-$CH_2CH_2CH_2$-	
39		
40	Bn	Bn

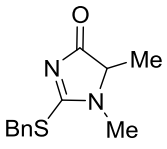
A R^3: Bn
B R^3: Me
C R^3: Et

METHOD A: A solution of the corresponding thiohydantoin **26** (5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with freshly distilled triethylamine (0.84 mL, 6 mmol, 1.2 equiv.) and, after 5 min at 0 °C, freshly distilled TMSCl (0.99 mL, 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. The solution was cooled to 0 °C and freshly distilled triethylamine (2.8 mL, 20 mmol, 4 equiv.) and benzyl bromide (1.19 mL, 10 mmol, 2 equiv.) were added. The mixture was then warmed up to room temperature and monitored by TLC (hexane/ethyl acetate, 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 $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography.

METHOD B: A solution of the corresponding thiohydantoin (453 mg, 5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with DIPEA (distilled, 1.05 mL, 6 mmol, 1.2 equiv.) and, after 5 min at 0 °C, freshly distilled TMSCl (0.99 mL, 6 mmol, 1.2 equiv.) was added. The reaction mixture was warmed up to room temperature and stirred for 2 hours. The solution was cooled to 0 °C and DIPEA (distilled, 3.48 mL, 24 mmol, 4 equiv.) and the corresponding iodide (10 mmol, 2 equiv) were added. The mixture was then warmed up to room temperature and monitored by TLC (hexane/ethyl acetate, 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 $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography.

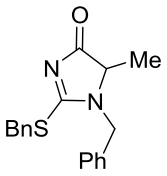
(**Note:** Imidazolones **27–40** decompose over time and should be stored in a refrigerator under argon atmosphere (at –30 °C they are stable for at least 1 month)).

2-(Benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (27A)



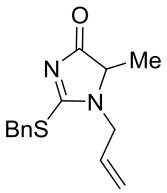
The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 576 mg, 2.46 mmol, 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.13 (m, 5H), 4.49 (s, 2H), 3.82 (q, *J* = 7.3 Hz, 1H), 2.98 (s, 3H), 1.37 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.3, 183.3, 135.5, 128.9, 128.4, 127.6, 62.6, 36.3, 30.6, 14.5. UPLC-DAD-QTOF: $C_{12}H_{15}N_2OS$ $[M+H]^+$ calcd.: 235.0905, found: 235.0910.

1-Benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (28A)



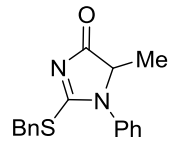
The title compound was prepared from 1-benzyl-5-methyl-2-thioxoimidazolidin-4-one (1.10 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Yellow oil. Yield: 1.3 g, 4.2 mmol, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.10 (m, 15H), 4.75 (d, *J* = 15.9 Hz, 1H), 4.68 (d, *J* = 1.5 Hz, 1H), 4.61 (s, 2H), 4.54 (d, *J* = 4.7 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.39 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.8, 183.9, 135.7, 134.5, 129.4, 128.8, 128.1, 127.6, 60.9, 48.7, 37.2, 15.2. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1231.

1-Allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (30A)



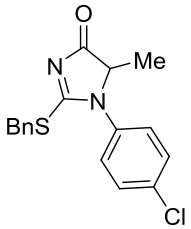
The title compound was prepared from 1-allyl-5-methyl-2-thioxoimidazolidin-4-one (851 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 859 mg, 3.30 mmol, 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 – 6.88 (m, 5H), 5.63 – 5.38 (m, 1H), 5.14 – 4.83 (m, 2H), 4.33 (s, 2H), 4.00 – 3.58 (m, 3H), 1.18 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 184.1, 136.0, 131.1, 129.6, 129.2, 128.4, 119.8, 61.5, 47.6, 37.3, 15.6. UPLC-DAD-QTOF: $C_{14}H_{17}N_2OS$ $[M+H]^+$ calcd.: 261.,1056, found: 261.1053.

2-(Benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (31A)



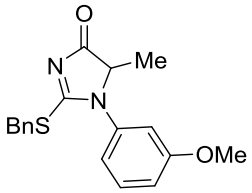
The title compound was prepared from 5-methyl-1-phenyl-2-thioxoimidazolidin-4-one (1.03 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.01 g, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.14 (m, 10H), 4.57 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, MeOD) δ: 190.7, 184.9, 137.1, 136.5, 130.9, 130.2, 130.1, 130.0, 129.7, 128.9, 127.7, 65.3, 37.5, 15.6. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1062, found: 297.1064.

2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (32A)



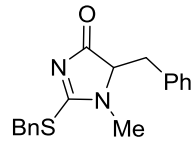
The title compound was prepared from 1-(4-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1.20 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. White solid. Yield: 1.36 g, 4.15 mmol, 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.17 (m, 9H), 4.53 (s, 2H), 4.35 (q, *J* = 6 Hz, 1H), 1.40 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.8, 183.4, 135.4, 134.7, 134.1, 130.2, 129.3, 128.9, 128.1, 127.8, 63.9, 37.3, 15.6. UPLC-DAD-QTOF: $C_{17}H_{16}ClN_2OS$ $[M+H]^+$ calcd.: 331.0672, found: 331.0675.

2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (33A)



The title compound was prepared from 1-(3-methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (1.17 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 1.38 g, 4.25 mmol, 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.23 (m, 6H), 6.94-6.75 (m, 3H), 4.53 (s, 2H), 4.37 (q, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 1.41 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.6, 182.8, 160.1, 136.1, 135.3, 130.2, 128.9, 128.3, 127.5, 117.8, 113.6, 111.8, 63.4, 55.2, 36.7, 15.1.

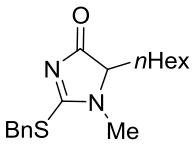
5-Benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (34A)



The title compound was prepared from 5-benzyl-1-methyl-2-thioxoimidazolidin-4-one (1.10 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 25:75. Yellow oil. Yield: 1.15 g, 3.7 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 6.85 (m, 10H), 4.39 (dd, *J* = 13.1 Hz, 2H), 4.09 (t, *J* = 5.2 Hz, 1H), 3.15 (dd, *J* = 28.0,

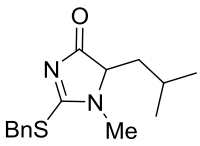
5.2 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.8, 184.0, 135.4, 134.7, 128.5, 128.0, 127.2, 126.6, 67.7, 35.9, 35.4, 31.4. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1226.

2-(Benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (35A)



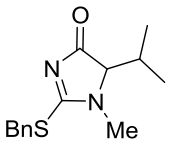
The title compound was prepared from 5-hexyl-1-methyl-2-thioxoimidazolidin-4-one (1.07 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.03 g, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.04 (m, 5H), 4.47 (s, 2H), 3.82 (dd, *J* = 5.5, 3.9 Hz, 1H), 2.96 (s, 3H), 1.96 – 1.66 (m, 2H), 1.36 – 0.98 (m, 8H), 0.90 – 0.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.1, 184.3, 136.2, 129.5, 129.1, 128.2, 67.4, 37.0, 31.8, 31.4, 29.3, 29.2, 23.6, 22.8, 14.3. UPLC-DAD-QTOF: $C_{17}H_{25}N_2OS$ $[M+H]^+$ calcd.: 305.1682, found: 305.1684.

2-(Benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (36A)



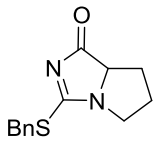
The title compound was prepared from 5-isobutyl-1-methyl-2-thioxoimidazolidin-4-one (0.93 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 25:75. Colourless oil. Yield: 661 mg, 3.55 mmol, 71%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.17 (m, 5H), 4.66 – 4.43 (m, 2H), 3.01 (s, 3H), 2.00 – 1.65 (m, 2H), 1.52 – 1.34 (m, 1H), 0.85 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.0, 185.6, 135.8, 129.9, 129.4, 128.6, 90.5, 43.7, 36.8, 28.7, 24.2, 24.1, 23.9. UPLC-DAD-QTOF: $C_{15}H_{21}N_2OS$ $[M+H]^+$ calcd.: 277.1369, found: 277.1371.

2-(Benzylthio)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (37A)



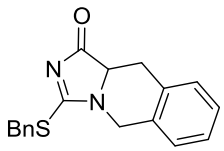
The title compound was prepared from 5-isopropyl-1-methyl-2-thioxoimidazolidin-4-one (861 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 892 mg, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.01 (m, 5H), 4.54 (s, 2H), 3.74 (d, *J* = 3.2 Hz, 1H), 3.05 (s, 3H), 2.28 (td, *J* = 7.0, 3.2 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.4, 184.8, 136.4, 129.7, 129.4, 128.5, 72.4, 37.4, 32.3, 29.9, 17.8, 17.3. UPLC-DAD-QTOF: $C_{14}H_{19}N_2OS$ $[M+H]^+$ calcd.: 263.1218, found: 263.1225.

3-(Benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (38A)



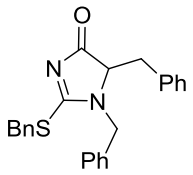
The title compound was prepared from 3-thioxohexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (781 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.07 g, 4.35 mmol, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.11 (m, 5H), 4.62 – 4.38 (m, 2H), 4.15 (t, *J* = 8.3 Hz, 1H), 3.54 – 3.19 (m, 2H), 2.30 – 1.95 (m, 3H), 1.68 (ddd, *J* = 12.2, 9.9, 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.7, 188.2, 135.2, 128.4, 128.1, 127.2, 68.2, 53.2, 47.4, 35.9, 27.5, 25.4. UPLC-DAD-QTOF: $C_{13}H_{15}N_2OS$ $[M+H]^+$ calcd.: 247.0905, found: 247.0909.

3-(Benzylthio)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (39A)



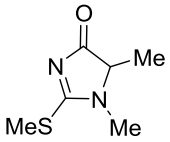
The title compound was prepared from 3-thioxo-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (1.09 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Yellow oil. Yield: 1.2 g, 3.9 mmol, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.00 (m, 9H), 4.72 (s, 2H), 4.66 (dd, *J* = 144.9, 16.4 Hz, 1H), 4.55 (s, 2H), 3.27 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.7, 183.8, 135.5, 130.8, 130.6, 129.9, 129.9, 129.4, 128.6, 128.2, 127.7, 126.9, 126.6, 85.5, 44.7, 37.0, 36.9. UPLC-DAD-QTOF: $C_{18}H_{17}N_2OS$ $[M+H]^+$ calcd.: 309.1062, found: 309.1060.

1,5-Dibenzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (40A)



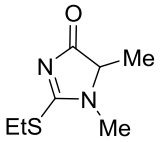
The title compound was prepared from 1,5-dibenzyl-2-thioxoimidazolidin-4-one (1.48 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Yellow oil. Yield: 1.53 g, 3.95 mmol, 79%. (10% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 6.75 (m, 15H), 4.66 (d, *J* = 15.9 Hz, 1H), 4.60 – 4.37 (m, 2H), 4.17 (d, *J* = 15.9 Hz, 1H), 4.05 (dd, *J* = 6.2, 4.5 Hz, 1H), 3.15 (dd, *J* = 42.0, 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 184.5, 135.6, 135.2, 133.9, 128.9, 128.5, 127.6, 127.2, 65.1, 48.9, 36.6, 36.1. UPLC-DAD-QTOF: $C_{24}H_{23}N_2OS$ $[M+H]^+$ calcd.: 387.1526, found: 387.1521.

1,5-Dimethyl-2-(methylthio)-1*H*-imidazol-4(5*H*)-one (27B)


2B

The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) and iodomethane (0.62 mL, 10 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil, stored at –30 °C. Yield: 498 mg, 3.15 mmol, 63%. (13% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (q, *J* = 7.2 Hz, 1H), 3.07 (s, 3H), 2.66 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H). UPLC-DAD-QTOF: $C_6H_{11}N_2OS$ $[M+H]^+$ calcd.: 159.0592, found: 159.0589.

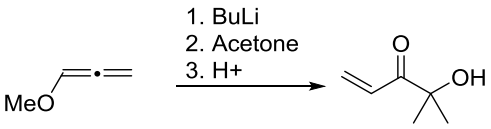
2-(Ethylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (27C)


2C

The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) and iodoethane (0.80 mL, 10 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil, stored at –30 °C. Yield: 577 mg, 3.35 mmol, 67%. (15% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (q, *J* = 7.2 Hz, 1H), 3.28 – 3.14 (m, 2H), 3.01 (s, 3H), 1.45 – 1.29 (m, 5H). UPLC-DAD-QTOF: $C_7H_{13}N_2OS$ $[M+H]^+$ calcd.: 173.0749, found: 173.0747.

5.3.2. General procedure for the synthesis of α'-silyloxy enone 73.

5.3.2.1. General procedure for the synthesis of α'-hydroxy enone 72.[375]

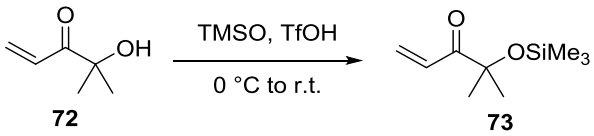


To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at –40 °C, *n*BuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at –40 °C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid (5.65 g) (82%) that was employed in the next step without further purification.

[375] C. Palomo, M. Oiarbide, J. García, A. González, E. Arceo *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

The material from previous step (2-methyl-3-methoxy-3,4-pentadien-2-ol, 5.65 g, 44 mmol) was added dropwise to 5% aq. H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 × 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid (4.42 g) (88%). ^{1}H NMR ($CDCl_3$) δ: 6.73 (dd, 1H, CH, J= 9.5 Hz, J'= 16.8 Hz), 6.50 (dd, 1H, HCH, J= 2.2 Hz, J'= 16.8 Hz), 5.82 (dd, 1H, HCH, J= 2.2 Hz, J'= 10.3 Hz), 1.38 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 202.3, 131.1, 128.8, 75.4, 26.1. IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O).

5.3.2.2. General procedure for the synthesis of 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (73). [376]



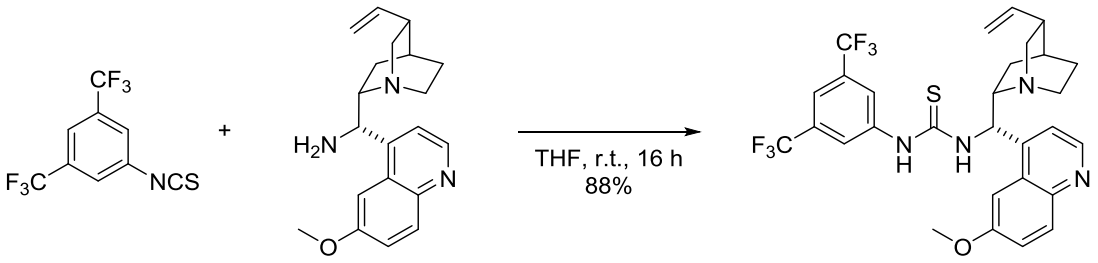
72 **73**

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 (**79**) as a colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) 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).

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

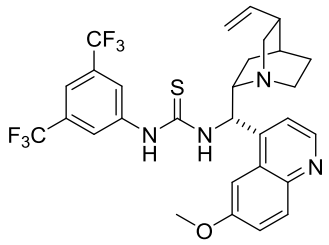
5.3.3. **General procedure for the synthesis of catalysts**

5.3.3.1. **Thiourea containing Brønsted base catalyst C5**[366]



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 ºC, 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 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.

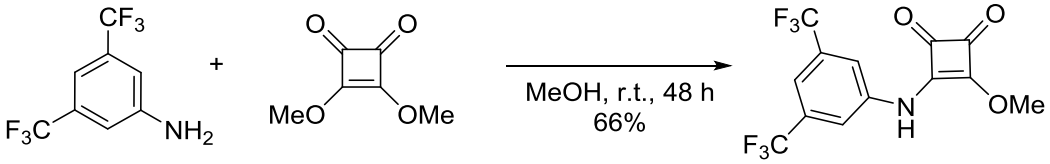
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea C5



White solid, yield: 2.6 g, 4.4 mmol, 88%. m. p. 123–125 ºC. 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).

5.3.3.2. **Squaramide-based Brønsted base catalysts C6-C8**

5.3.3.2.1. Preparation of squaric ester monoamine[377]

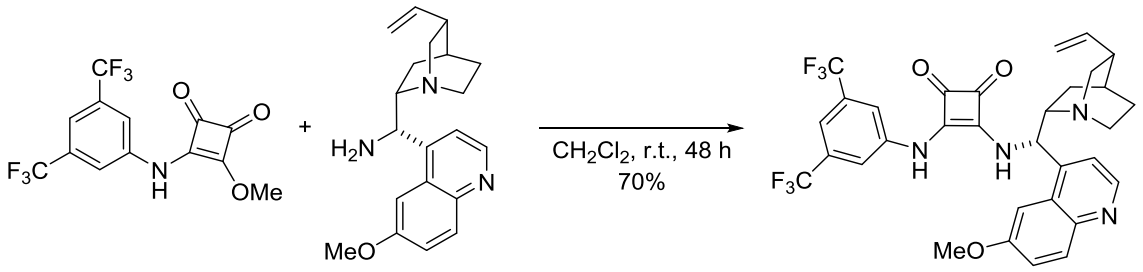


To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 1.42 g, 10 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1 equiv., 1.56 mL, 10 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vacuum to give title compound as a white solid. Yield: 2.25 g, 6.6 mmol, 66%. m. p. 179–181 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

*5.3.3.2.2. Preparation of catalysts **C6–C8.***

*5.3.3.2.2.1. Preparation of catalyst **C6***

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 C6[377]

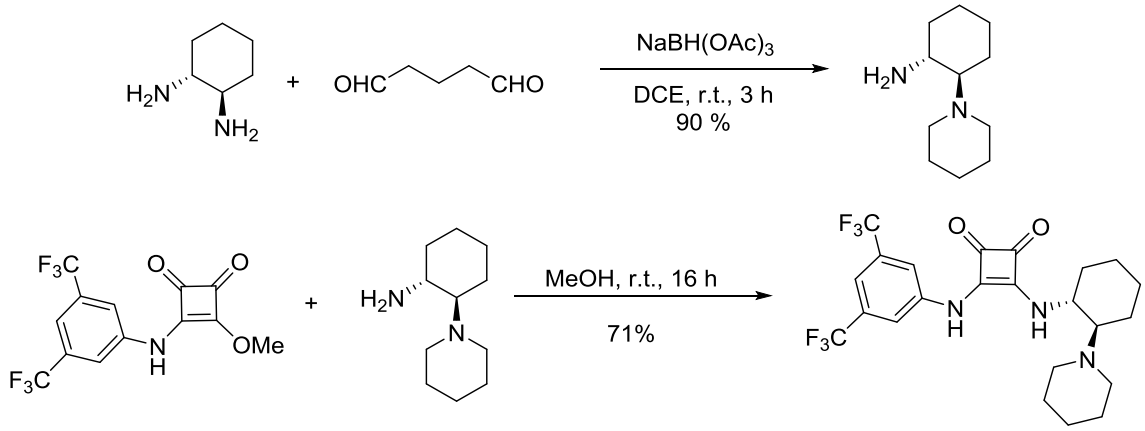


To a solution of squaric ester monoamide prepared as above (1 equiv., 2.25 g, 6.6 mmol) in dichloromethane (33 mL), 9-amino-(9-deoxy)*epi*quinine (1 equiv., 2.13 g, 6.6 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford **C6** as white solid. Yield: 2.91 g, 4.6 mmol, 70%. m. p. 224–225 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 9.88 (brs, 1H), 8.80 (d, *J*

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

= 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).

*5.3.3.2.2.2. Preparation of catalyst **C7***[378]



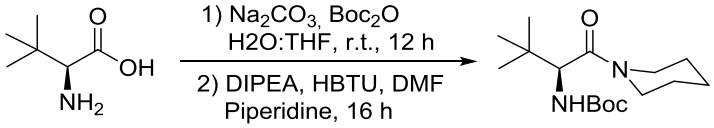
Aqueous glutaraldehyde (50%, 1.0 mL) was added dropwise into a mixture of $NaBH(OAc)_3$(4.24g, 20.0 mmol) and (1S,2S)-1,2-diaminocyclohexane 9 (570 mg, 5.0 mmol) in dichloroetane (30 mL) at room temperature. The resulting mixture was stirred at room temperature for 3h, and then quenched with aqueous 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 CH2Cl2 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).

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

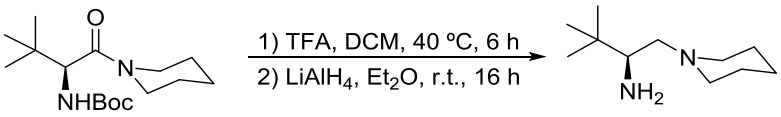
*5.3.3.2.2.3. Preparation of catalyst **C8***

Step 1) Protection of the amine and amide formation[379]



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

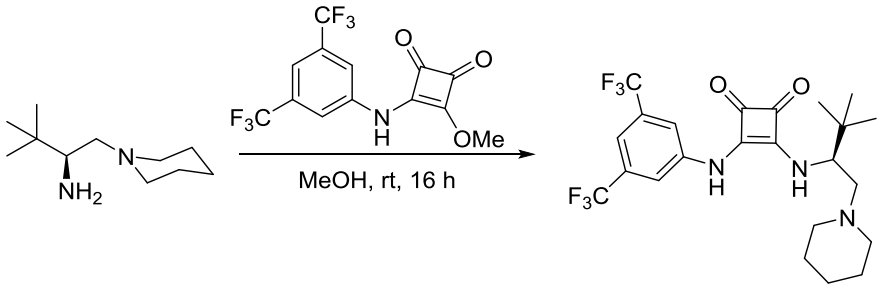


Previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane/ EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40%), dried over MgSO4 and the solvent was 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

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

of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 oC 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 oC. 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) Formation of catalyst C8[380]

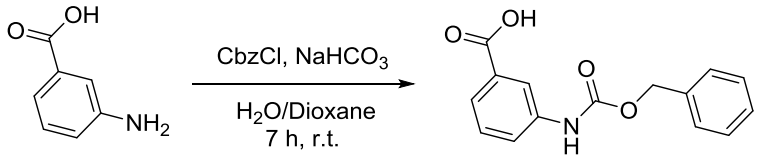


To a solution of the diamine (780 mg, 4,6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4,6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure **C8** 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.

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

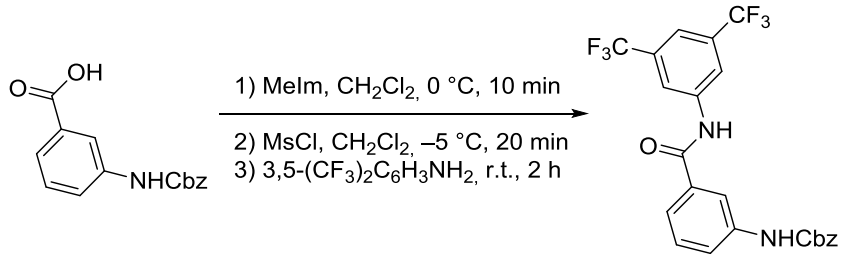
5.3.3.3. **Synthesis of catalyst C9.**

3-(((Benzyloxy)carbonyl)amino)benzoic acid[381]



To a solution of 3-aminobenzoic acid (5 g, 36.3 mmol, 1.1 equiv.) an $NaHCO_3$ (2.0 equiv.) in water (150 mL) was added a solution of benzyl chloroformate (4.7 mL, 33 mmol, 1 equiv.) in 1,4-dioxane (150 mL). The reaction mixture was stirred for seven hours at room temperature before the volatiles were evaporated. The residue was distributed between ethyl acetate and water and the layers were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with brine. The solution was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was crushed with diethyl ether to afford the title product as a white solid. Yield: 7.8 g, 28.7 mmol, 87%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.01 (s, 1H), 8.29 (s, 1H), 7.81 (ddd, J = 8.2, 2.4, 1.1 Hz, 1H), 7.70 (ddd, J = 7.7, 1.6, 1.1 Hz, 1H), 7.54 – 7.22 (m, 5H), 5.19 (s, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ: 167.7, 154.4, 140.4, 137.7, 132.4, 129.8, 129.3, 128.9, 128.9, 124.6, 123.3, 120.2, 67.0. UPLC-DAD-QTOF: $C_{15}H_{14}NO4$ $[M+H]^+$ calcd.: 272.0923, found: 272.0925.

Benzyl (3-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)phenyl)carbamate[382]

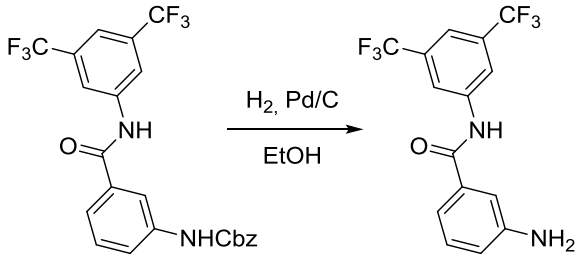


1-Methylimidazole (2.2 mL, 27.6 mmol, 2.5 equiv.) was added to a slurry of the protected 3-aminobenzoic acid (3 g, 11 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.3 mL, 16.5 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) was added to the mixture under –5 °C. After the mixture was stirred under that temperature for 20 min, 3,5-bis(trifluoromethyl)aniline (1.72 mL, 11 mmol, 1 equiv) was added. Then the mixture was stirred at room temperature for 2 h. H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved with ethyl acetate (100

[381] S. Ansorge et al. US Pat. Appl. Publ., 20120028995, 02 Feb **2012**.
[382] Adapted from: L. Mao, Z. Wang, Y. Li, X. Han and W. Zhou *Synlett* **2011**, *1*, 129–133.

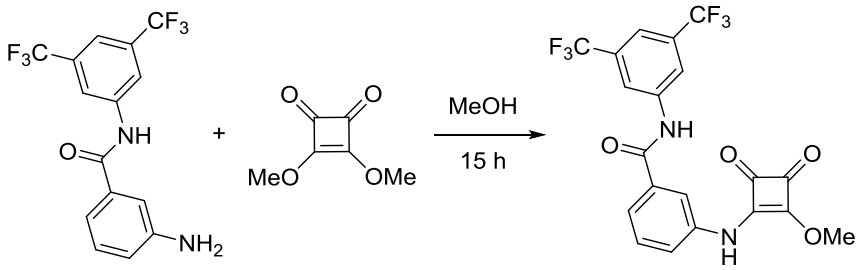
mL). The organic layer was washed with brine (3 × 50 mL) and dried with anhydrous MgSO4. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title product as a white solid. Yield: 3.43 g, 7.1 mmol, 65%. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.43 (s, 2H), 8.09 (s, 1H), 7.81 – 7.57 (m, 4H), 7.57 – 7.28 (m, 5H), 5.24 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ: 168.9, 155.8, 142.2, 140.8, 138.0, 136.3, 133.20 (q, *J* = 33.2 Hz), 132.8, 130.3, 129.5, 129.2, 129.1, 125.8, 123.5, 123.1, 121.3, 119.0, 117.9, 67.8. UPLC-DAD-QTOF: $C_{23}H_{17}F_6N_2O_3$ $[M+H]^+$ calcd.: 483.1143, found: 483.1146.

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



To a solution of the protected aniline (3.22 g, 6.68 mmol) in EtOH (15 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 20h. After that the solution was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product. Yield: 1.34 g, 3.85 mmol, 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 2H), 7.68 (s, 1H), 7.25 (dd, *J* = 4.7, 1.0 Hz, 3H), 7.01 – 6.87 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 169.7, 149.6, 142.3, 136.3, 133.13 (q, *J* = 33.2 Hz), 130.4, 125.8, 123.7, 121.3, 119.9, 117.6, 115.0. UPLC-DAD-QTOF: $C_{15}H_{11}F_6N_2O$ $[M+H]^+$ calcd.: 349.0776, found: 349.0779.

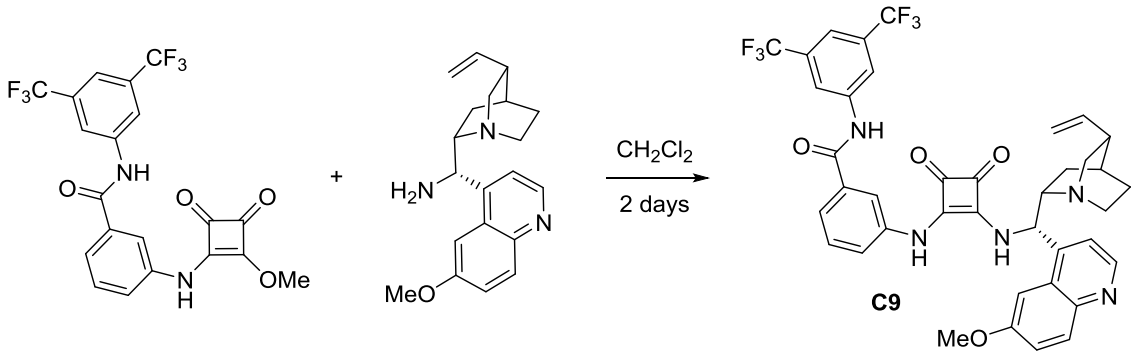
***N*-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide**[383]



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

To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (481 mg, 3.38 mmol, 1 equiv.) in MeOH (10 mL) was added the free aniline (1.3 g, 3.72 mmol, 1.1 equiv.) at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated and washed with MeOH. Obtained white solid was dried in vacuo to give the title product as a white solid. Yield: 1.49 g, 3.24 mmol, 96%. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 10.25 (s, 1H), 9.99 (s, 1H), 8.55 (s, 2H), 8.08 (s, 1H), 7.89 – 7.64 (m, 3H), 7.64 – 7.46 (m, 1H), 4.47 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 184.2, 179.1, 169.3, 165.8, 141.0, 138.5, 135.0, 130.69 (q, J = 32.8 Hz), 129.3, 126.5, 124.4, 123.2, 122.9, 122.2, 119.9, 119.2, 116.5, 60.7. UPLC-DAD-QTOF: $C_{20}H_{13}F_6N_2O_4$ $[M+H]^+$ calcd.: 459.0780, found: 459.0778.

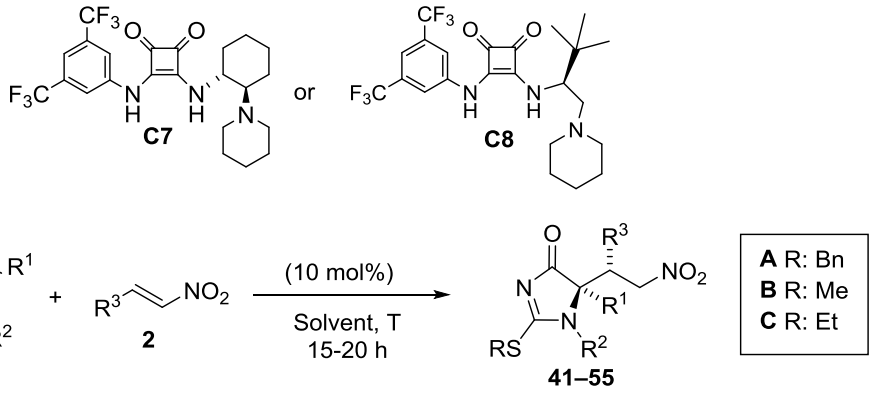
_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C9)[384]

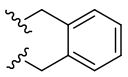


To a suspension of the squarate (252 g, 0.55 mmol, 1 equiv.) in CH_2CL_2 (4 mL) was added (*R*,*R*)-9-deoxy-9-epiaminoquinine (194 mg, 0.6 mmol, 1.1 equiv.) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was filtrated and washed with diethyl ether to give pure catalyst **C4**. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 9.24 (s, 1H), 8.13 (d, J = 4.6 Hz, 1H), 7.81 (s, 2H), 7.55 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.21 – 6.67 (m, 8H), 5.48 – 5.16 (m, 2H), 4.46 – 4.19 (m, 2H), 3.29 (s, 3H), 2.89 – 2.58 (m, 3H), 2.15 – 1.90 (m, 2H), 1.61 (s, 1H), 1.08 – 0.65 (m, 4H), -0.02 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 184.3, 180.0, 168.3, 165.9, 163.5, 157.9, 147.8, 144.4, 143.2, 142.2, 141.1, 139.2, 135.2, 131.5, 130.9, 130.5, 129.6, 127.5, 125.1, 121.8, 119.8, 117.7, 116.4, 114.2, 101.6, 59.0, 56.1, 55.7, 53.8, 48.6, 27.4, 26.1. UPLC-DAD-QTOF: $C_{39}H_{34}F_6N_5O_4$ $[M+H]^+$ calcd.: 750.2515, found: 750.2515.

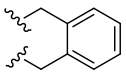
[384] Adapted from: W. Yang and D.-M. Du *Org. Lett.* **2010**, *12*, 5450–5453.

5.3.4. **General procedure for the asymmetric conjugate addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins**



	R^1	R^2
27	Me	Me
28	Me	Bn
29	Me	*i*Bu
30	Me	Allyl
31	Me	Ph
32	Me	4-ClC_6H_4
33	Me	3-$MeOC_6H_4$
34	Bn	Me
35	*n*Hex	Me
36	*i*Bu	Me
37	*i*Pr	Me
38	-$CH_2CH_2CH_2$-	
39		

a R^3 = Ph
c R^3 = 4-BrC_6H_4
d R^3 = 4-MeC_6H_4
e R^3 = 2-furyl
g R^3 = 2-thienyl
h R^3 = 3-MeC_6H_4
i R^3 = 3-$MeOC_6H_4$
j R^3 = *i*Pr
k R^3 = Cy
l R^3 = *n*Pr

	R^1	R^2	
41	Me	Me	
42	Me	Bn	
43	Me	*i*Bu	
44	Me	Allyl	
45	Me	Ph	
46	Me	4-ClC_6H_4	
47	Me	3-$MeOC_6H_4$	
48	Bn	Me	
49	*n*Hex	Me	
50	*i*Bu	Me	
51	*i*Pr	Me	
52	-$CH_2CH_2CH_2$-		
53			
54	Me	Me	R: Me
55	Me	Me	R: Et

5.3.4.1. **Asymmetric reaction**

For aromatic nitroalkenes: To a solution of the corresponding imidazolone (0.3 mmol, 1 equiv) and the corresponding aromatic nitroalkene (2.0 equiv, 0.6 mmol) in dichloromethane (0.75 mL) at -20 °C the catalyst (0.03 mmol, 10 mol %) was added. The resulting solution was stirred at the same temperature until consumption of the imidazolone (monitored by ^{1}H NMR). The reaction mixture was then directly purified by flash column chromatography (eluting with hexane/ethyl acetate, 70:30) to afford the title compound as a colourless oil.

For aliphatic nitroalkenes: A solution of the corresponding imidazolone (0.3 mmol, 1 equiv), the corresponding aliphatic nitroalkene (0.9 mmol, 3 equiv) and the catalyst (0.06 mmol, 20 mol %) in 1,2-dichloroethane (0.5 mL) was heated up to 50 °C. The solution was stirred at the same temperature until consumption of the imidazolone (moni-

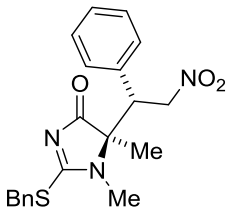
tored by ^{1}H NMR). The reaction mixture was then directly purified by flash column chromatography (eluting with hexane/ethyl acetate) to afford the title compound as a colourless oil.

5.3.4.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using **C4** (20 mol %) as the catalyst at –20 °C.

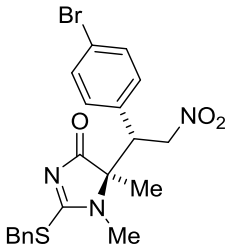
5.3.4.3. **Characterization data for compounds 41–55**

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (41a)



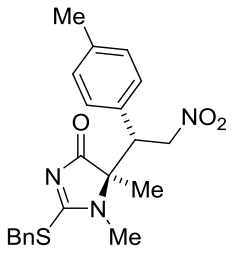
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27A**) (70.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 111 mg, 0.29 mmol, 97 %. (diastereomeric mixture 93:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.08 (m, 10H), 5.20 (dd, *J* = 13.7, 10.3 Hz, 1H), 5.03 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.46 (d, *J* = 13.4 Hz, 1H), 4.28 (d, *J* = 13.4 Hz, 1H), 3.81 (dd, *J* = 10.3, 4.3 Hz, 1H), 2.92 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.5, 183.5, 135.4, 128.6, 128.4, 128.3, 128.2, 127.4, 127.4, 74.9, 70.7, 48.7, 35.7, 28.7, 20.0. UPLC-DAD-QTOF: $C_{20}H_{21}N_3O_3S$ $[M+H]^+$ calcd.: 384.1382, found: 384.1385.

(*R*)-2-(Benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (41c)



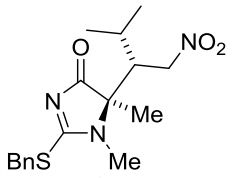
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27A**) (70.5 mg, 0.3 mmol) and (*E*)-1-bromo-4-(2-nitrovinyl)benzene (**2c**) (136.8 mg, 0.6 mmol) according to procedure A. Yield: 114 mg, 0.24 mmol, 82 %. (diastereomeric mixture 94:6). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.14 (m, 7H), 7.07 – 7.00 (m, 2H), 5.25 – 4.89 (m, 2H), 4.38 (dd, *J* = 59.5, 13.5 Hz, 2H), 3.77 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.92 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 184.8, 136.0, 133.7, 132.6, 131.8, 129.9, 129.5, 129.4, 128.6, 123.4, 75.7, 71.2, 49.4, 37.0, 29.5, 21.1. UPLC-DAD-QTOF: $C_{20}H_{21}BrN_3O_3S$ $[M+H]^+$ calcd.: 462.0487, found: 462.0487.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (41d)



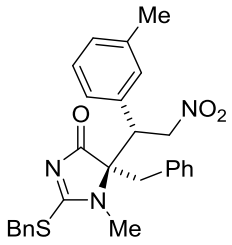
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27A**) (70.5 mg, 0.3 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2d**) (97.5 mg, 0.6 mmol) according to procedure A. Yield: 108 mg, 0.27 mmol, 91 %. (diastereomeric mixture 90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.10 (m, 5H), 7.03 (d, *J* = 0.9 Hz, 4H), 5.21 – 4.88 (m, 2H), 4.37 (dd, *J* = 56.9, 13.3 Hz, 2H), 3.76 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.89 (s, 3H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.4, 184.4, 138.9, 136.2, 131.4, 130.0, 129.5, 129.2, 128.4, 128.0, 76.1, 71.4, 49.7, 36.8, 29.5, 21.6, 21.1.UPLC-DAD-QTOF: $C_{21}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 398.1538, found: 398.1537.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-3-methyl-1-nitrobutan-2-yl)-1*H*-imidazol-4(5*H*)-one (41j)



The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27A**) (70.5 mg, 0.3 mmol) and (*E*)-3-methyl-1-nitrobut-1-ene (**2j**) (103.5 mg, 0.9 mmol) according to procedure B. Yield: 60.8 mg, 0.17 mmol, 58 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.14 (m, 5H), 5.29 (dd, *J* = 15.0, 5.9 Hz, 1H), 4.67 – 4.47 (m, 2H), 4.39 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.97 (s, 3H), 2.69 (ddd, *J* = 6.0, 4.1, 2.1 Hz, 1H), 1.63 – 1.49 (m, 1H), 1.38 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.1, 183.9, 129.7, 129.4, 128.6, 71.3, 47.7, 37.2, 29.0, 27.2, 23.2, 21.7, 17.5. UPLC-DAD-QTOF: $C_{17}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 350.1538, found: 350.1548.

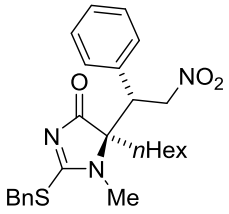
(*R*)-5-Benzyl-2-(benzylthio)-1-methyl-5-((*R*)-2-nitro-1-(*m*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (48h)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (**34A**) (93 mg, 0.3 mmol) and (*E*)-1-methyl-3-(2-nitrovinyl)benzene (**2h**) (97.9 mg, 0.6 mmol) according to procedure A. Yield: 117 mg, 0.24 mmol, 82 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 – 6.95 (m, 14H), 5.31 – 5.13 (m, 2H), 4.19 (s, 2H), 3.93 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 3.04 (d, *J* = 13.7 Hz, 1H), 2.82 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.1, 184.9, 138.6, 135.9, 134.3, 133.2, 129.6, 129.4, 128.9, 128.9,

128.7, 128.7, 127.8, 127.7, 125.0, 76.2, 76.1, 49.7, 40.8, 36.1, 30.3, 21.5. UPLC-DAD-QTOF: $C_{27}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 474.1851, found: 474.1856.

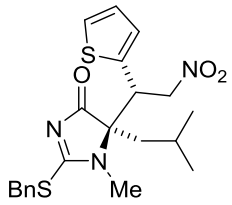
(*R*)-2-(Benzylthio)-5-hexyl-1-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (49a)



19a

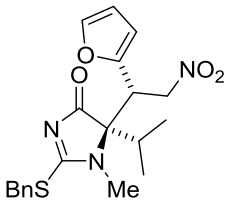
The title compound was prepared from 2-(benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**35A**) (91.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 90:10. Yield: 110.1 mg, 0.24 mmol, 81 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.15 (m, 10H), 5.23-5.03 (m, 2H), 4.37 (dd, *J* = 12, 15 Hz, 2H), 3.78 (dd, *J* = 3,6 Hz, 1H), 2.86 (s, 3H), 2.16-2.03 (m, 1H), 1.82-1.72 (m, 1H), 1.29-1.22 (m, 8H), 0.90-0.85 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.3, 184.5, 135.9, 134.3, 129.0, 128.9, 128.7, 127.9, 127.9, 75.7, 75.1, 49.1, 36.3, 34.0, 31.5, 29.0, 3.5, 22.5, 14.1. UPLC-DAD-QTOF: $C_{25}H_{32}N_3O_3S$ $[M+H]^+$ calcd.: 454.2164, found: 454.2161.

(*R*)-2-(Benzylthio)-5-isobutyl-1-methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-imidazol-4(5*H*)-one (50g)



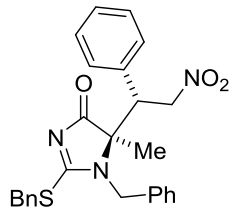
The title compound was prepared from 2-(benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**36A**) (82.9 mg, 0.3 mmol) and (*E*)-2-(2-nitrovinyl)thiophene (**2g**) (93 mg, 0.6 mmol) according to procedure A. Yield: 109 mg, 0.25 mmol, 84 %. (diastereomeric mixture 92:8)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.18 (m, 5H), 7.12 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 3.8, 1.2 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.24 – 4.92 (m, 2H), 4.40 (dd, *J* = 23.8, 13.6 Hz, 2H), 4.03 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.95 (s, 3H), 1.98 (dd, *J* = 14.2, 7.6 Hz, 1H), 1.74 (dd, *J* = 14.2, 4.6 Hz, 1H), 1.40 (ddd, *J* = 6.6, 3.9, 1.5 Hz, 1H), 0.95 – 0.73 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.6, 185.2, 136.4, 135.7, 129.6, 129.2, 128.4, 127.8, 126.9, 125.7, 76.6, 75.1, 45.0, 42.6, 36.8, 30.1, 25.4, 24.5, 23.6. UPLC-DAD-QTOF: $C_{21}H_{26}N_3O_3S_2$ $[M+H]^+$ calcd.: 432.1416, found: 432.1426.

(*R*)-2-(Benzylthio)-5-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (51e)



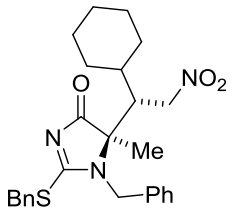
The title compound was prepared from 2-(benzylthio)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**37A**) (78.7 mg, 0.3 mmol) and (*E*)-2-(2-nitrovinyl)furan (**2e**) (85.5 mg, 0.6 mmol) according to procedure A. Yield: 90 mg, 0.23 mmol, 75 %. (diastereomeric mixture 93:7)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.16 (m, 6H), 6.34 – 6.20 (m, 2H), 5.07 (dd, *J* = 13.6, 11.6 Hz, 1H), 4.63 (dd, *J* = 13.6, 3.4 Hz, 1H), 4.46 (dd, *J* = 15.2, 13.6 Hz, 2H), 4.33 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.98 (s, 3H), 2.25 – 2.11 (m, 1H), 1.04 (dd, *J* = 6.9, 6.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.0, 185.8, 148.6, 143.2, 136.2, 129.7, 129.3, 128.6, 111.4, 110.0, 74.1, 40.3, 37.3, 32.5, 31.6, 17.1, 17.0. UPLC-DAD-QTOF: $C_{20}H_{24}N_3O_4S$ $[M+H]^+$ calcd.: 402.1488, found: 402.1497.

(*R*)-1-Benzyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (42a)



The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**28A**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 117 mg, 0.26 mmol, 85 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.05 (m, 15H), 5.19 (dd, *J* = 13.7, 10.2 Hz, 1H), 5.02 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.50 (s, 2H), 4.46 (d, *J* = 13.4 Hz, 1H), 4.24 (d, *J* = 13.4 Hz, 1H), 3.94 (dd, *J* = 10.2, 4.3 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.2, 185.3, 135.9, 135.2, 134.4, 129.5, 129.5, 129.4, 129.2, 129.2, 128.9, 128.4, 127.7, 76.1, 72.3, 50.1, 48.2, 37.3, 22.4. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 460.1695, found: 460.1711.

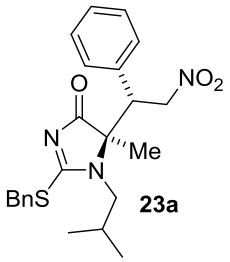
(*R*)-1-Benzyl-2-(benzylthio)-5-((*R*)-1-cyclohexyl-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (42k)



The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**28A**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)cyclohexane (**2k**) (139.5 mg, 0.9 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 90:10. Yield: 55.9 mg, 0.12 mmol, 40 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.21 (m, 10H), 5.21 (dd, *J* = 15.0, 6.7 Hz, 1H), 4.77 (d, *J* = 13.3 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 2H), 4.51 (d, *J* = 13.3 Hz, 1H), 4.29 (dd, *J* = 15.0, 3.7 Hz, 1H), 2.57 (dq, *J* = 5.5, 2.4, 1.9 Hz, 1H), 1.79 – 1.48 (m, 5H), 1.32 (s, 3H), 1.09 – 0.82 (m, 4H), 0.69 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.3,

184.6, 136.3, 135.2, 129.8, 129.7, 129.7, 129.6, 129.4, 129.4, 129.2, 129.2, 129.0, 128.9, 128.6, 127.9, 72.1, 70.8, 48.5, 48.2, 37.6, 37.5, 33.0, 28.4, 27.3, 27.0, 26.4, 22.3. UPLC-DAD-QTOF: $C_{26}H_{32}N_3O_3S$ $[M+H]^+$ calcd.: 466.2164, found: 466.2170.

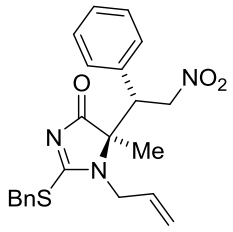
(*R*)-2-(Benzylthio)-1-isobutyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (43a)



23a

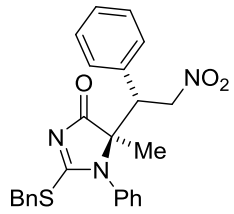
The title compound was prepared from 2-(benzylthio)-1-isobutyl-5-methyl-1*H*-imidazol-4(5*H*)-one (**29A**) (82.7 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Yield: 99 mg, 0.23 mmol, 78 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.14 (m, 10 H), 5.21– 5.00 (m, 2H), 4.34 (dd, J = 12 Hz, 1H), 4.24 (dd, J = 12 Hz, 1H), 3.85 (dd, J = 6, 3 Hz, 1H), 3.13 (dd, *J* = 6Hz, 1H), 2.99 (dd, *J* = 9 Hz, 1H), 2.13-2.02 (m, 1H), 1.62 (s, 3H), 0.90 (dd, J = 3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.5, 185.0, 135.3, 133.8, 129.1, 128.7, 128.0, 127.9, 75.7, 72.0, 52.0, 49.5, 37.0, 28.5, 22.1, 20.6. UPLC-DAD-QTOF: $C_{23}H_{27}N_3O_3S$ $[M+H]^+$ calcd.: 426.1851, found: 426.1866.

(*R*)-1-Allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (44a)



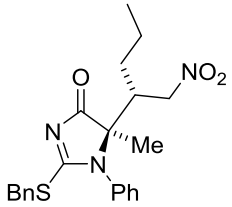
The title compound was prepared from 1-allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**30A**) (78 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 94.6 mg, 0.23 mmol, 77 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.04 (m, 10H), 5.66 (dd, *J* = 16.6, 10.7 Hz, 1H), 5.33 – 5.11 (m, 3H), 5.03 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.43 (d, *J* = 13.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.01 – 3.72 (m, 3H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.1, 184.8, 136.0, 134.5, 131.6, 129.5, 129.3, 129.2, 128.4, 128.3, 120.3, 76.0, 72.2, 49.9, 46.8, 37.1, 22.2. UPLC-DAD-QTOF: $C_{22}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 410.1538, found: 410.1558.

(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (45a)



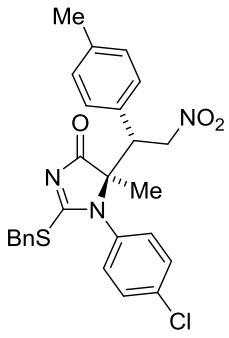
The title compound was prepared from 2-(benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (**31A**) (88.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 86.9 mg, 0.195 mmol, 65 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 – 6.81 (m, 15H), 5.21 – 4.85 (m, 2H), 4.52 (d, *J* = 13.3 Hz, 1H), 4.29 (d, *J* = 13.2 Hz, 1H), 3.66 (dd, *J* = 10.4, 4.2 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 185.6, 135.6, 134.7, 134.1, 130.0, 129.7, 129.2, 129.0, 128.9, 128.8, 128.8, 128.8, 128.0, 72.3, 50.5, 44.2, 37.0, 24.2. UPLC-DAD-QTOF: $C_{25}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 446.1538, found: 446.1553.

(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-1-nitropentan-2-yl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (45l)



The title compound was prepared from 2-(benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (**31A**) (88.5 mg, 0.3 mmol) and (*E*)-1-nitropent-1-ene (**2l**) (139.5 mg, 0.6 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 80:20. Yield: 63 mg, 0.15 mmol, 51 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 – 7.09 (m, 10H), 5.19 (dd, *J* = 14.7, 6.6 Hz, 1H), 4.61 – 4.41 (m, 2H), 4.35 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.58 – 2.47 (m, 1H), 1.69 – 1.57 (m, 1H), 1.44 (s, 3H), 1.34 – 1.19 (m, 3H), 0.94 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl^3$) δ: 188.9, 185.2, 135.4, 133.9, 130.5, 130.4, 130.3, 129.3, 129.3, 128.9, 128.1, 128.1, 74.3, 72.5, 41.8, 37.1, 30.1, 21.1, 20.3, 14.2. UPLC-DAD-QTOF: $C_{22}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 412.1695, found: 412.1709.

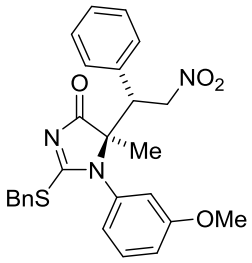
(*R*)-2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (46d)



The title compound was prepared from 2-(benzylthio)-1-(4-chlorophenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (**32A**) (99 mg, 0.3 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2d**) (97.5 mg, 0.6 mmol) according to procedure A. Yield: 123 mg, 0.24 mmol, 83 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.32 (m, 2H), 7.30-7.21 (m, 5H), 7.07– 7.05 (m, 2H), 6.98-6.93 (m, 2H), 6.83-6.78 (m, 2H), 5.11-4.94 (m, 2H), 4.53 (dd, *J* = 12 Hz, 1H), 4.30 (d, *J* = 15 Hz, 1H), 3.57 (dd, J = 3, 6 Hz, 1H), 2.33 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.8, 185.5, 138.9, 136.2, 135.6, 132.5, 131.5,

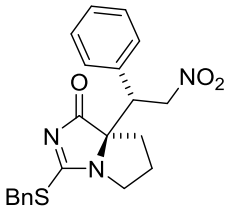
130.3, 130.0 129.7, 129.2, 128.9, 128.5, 128.1, 72.3, 50.3, 37.0. 24.3, 21.3 UPLC-DAD-QTOF: $C_{26}H_{24}ClN_3O_3S$ $[M+H]^+$ calcd.: 494.1305, found: 494.1309.

(*R*)-2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (47a)



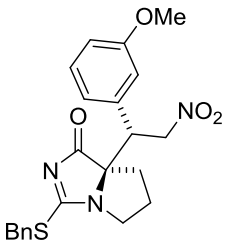
The title compound was prepared from 2-(benzylthio)-1-(3-methoxyphenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (**33A**) (97.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Yield: 122 mg, 0.23 mmol, 85 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.22 (m, 9 H), 7.16– 7.12 (m, 2H), 6.99-6.95 (m, 1H), 6.56-6.52 (m, 1H), 6.37-6.35 (m, 1H), 5.18-4.99 (m, 2H), 4.53 (d, *J* = 15 Hz, 1H), 4.32 (d, J = 12 Hz, 1H), 3.75 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 185.5, 160.2, 135.6, 160.2, 135.6, 135.0, 134.8, 130.4, 129.2, 128.9, 128.8, 127.9, 120.6, 115.4, 114.7, 77.2, 72.3, 55.5, 50.5, 37.0, 24.2. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4S$ $[M+H]^+$ calcd.: 476.1644, found: 476.1649.

(*R*)-3-(benzylthio)-7a-((*R*)-2-nitro-1-phenylethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (52a)



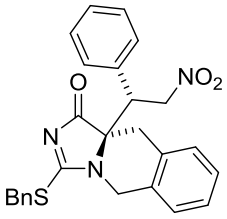
The title compound was prepared from 3-(benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**38A**) (73.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 99 mg, 0.23 mmol, 83 %. (diastereomeric mixture 90:10)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.12 (m, 9H), 5.09 (dd, *J* = 13.5, 11.4 Hz, 1H), 4.78 (dd, *J* = 13.5, 3.9 Hz, 1H), 4.42 (dd, *J* = 13.2, 8.9 Hz, 2H), 3.87 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.63 – 3.44 (m, 1H), 3.17 – 2.99 (m, 1H), 2.10 – 1.93 (m, 2H), 1.89 – 1.52 (m, 2H).^{13}C NMR (75 MHz, CDCl3) δ:194.2, 190.5, 135.8, 134.8, 129.5, 129.4, 129.4, 129.3, 129.2, 129.1, 128.6, 79.1, 75.9, 50.2, 49.7, 37.5, 30.8, 27.1. UPLC-DAD-QTOF: $C_{21}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 396.1382, found: 396.1395.

(*R*)-3-(Benzylthio)-7a-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (52i)



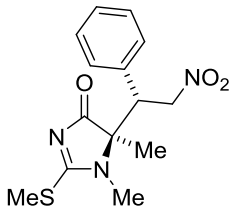
The title compound was prepared from 3-(benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**38A**) (73.5 mg, 0.3 mmol) and (*E*)-1-methoxy-3-(2-nitrovinyl) benzene (**2i**) (108 mg, 0.6 mmol) according to procedure A. Yield: 99.6 mg, 0.23 mmol, 78 %. (diastereomeric mixture 87:13). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33– 7.21 (m, 6H), 6.87-6.79 (m, 3H), 5.08-4.99 (m, 1H), 4.76 (dd, *J* = 6, 9 Hz, 1H), 4.45 (q, *J* = 12, 15 Hz, 2H), 3.78 (s, 3H), 3.59-3.51 (m, 1H), 3.16-3.07 (m, 1H), 2.09-1.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.0, 190.1, 159.8, 136.0, 130.0, 129.2, 128.2, 115.1, 113.8, 78.7, 75.6, 55.4, 50.0, 49.3, 37.2, 30.4, 26.6. UPLC-DAD-QTOF: $C_{22}H_{23}N_3O_4S$ $[M+H]^+$ calcd.: 426.1488, found: 426.1491.

(*R*)-3-(Benzylthio)-10a-((*R*)-2-nitro-1-phenylethyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (53a)



The title compound was prepared from 3-(benzylthio)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (**39A**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 85 mg, 0.19 mmol, 62 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 6.97 (m, 14H), 5.30 – 5.09 (m, 2H), 4.68 (d, *J* = 16.6 Hz, 1H), 4.50 (d, *J* = 13.4 Hz, 1H), 4.39 (s, 1H), 4.35 (d, *J* = 13.3 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.27 (d, *J* = 16.5 Hz, 1H), 3.09 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 189.3, 184.0, 135.9, 135.0, 130.7, 129.9, 129.6, 129.4, 129.3, 129.2, 129.1, 128.8, 128.4, 128.4, 128.0, 126.7, 76.1, 68.6, 46.8, 45.4, 36.8, 35.0, 30.1. UPLC-DAD-QTOF: $C_{26}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 458.1538, found: 458.1541.

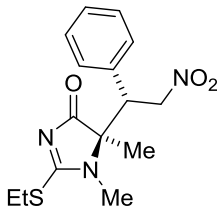
(*R*)-1,5-Dimethyl-2-(methylthio)-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (54a)



The title compound was prepared from 1,5-dimethyl-2-(methylthio)-1*H*-imidazol-4(5*H*)-one (**27B**) (48 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.4 mmol) according to procedure A. Yield: 66.3 mg, 0.21 mmol, 72 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29-7.15 (m, 5H), 5.23-5.15 (m, 1H), 5.04-4.98 (m, 1H), 3.80 (dd, J = 3, 3 Hz, 1H), 2.48 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 185.0, 134.3, 129.7, 129.0, 128.9, 127.9, 75.6, 71.0,

49.7, 29.2, 20.8, 14.7. UPLC-DAD-QTOF: $C_{14}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 308.1069, found: 308.1072.

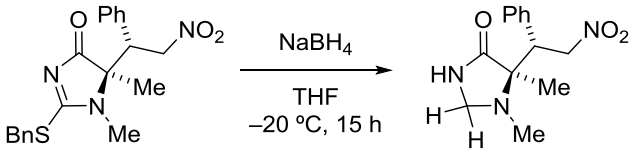
(*R*)-2-(Ethylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (55a)



The title compound was prepared from 2-(ethylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27C**) (51 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 59.8 mg, 0.19 mmol, 62 %. (diastereomeric mixture 90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.10 (m, 5H), 5.20 (dd, *J* = 13.7, 10.3 Hz, 1H), 5.01 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.79 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.24 – 3.06 (m, 1H), 3.06 – 2.90 (m, 1H), 2.92 (s, 3H), 1.54 (s, 3H), 1.17 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1, 184.5, 134.2, 129.7, 129.0, 128.9, 128.8, 128.8, 127.8, 75.5, 70.6, 49.6, 29.1, 26.9, 20.6, 15.1. UPLC-DAD-QTOF: $C_{15}H_{20}N_3O_3S$ $[M+H]^+$ calcd.: 322.1225, found: 322.1223.

5.3.5. **Elaboration of adducts 41a, 41c, 44a.**

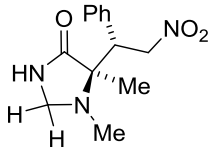
5.3.5.1. **Synthesis of imidazolidinone 56.**



41a **56**

To a solution of **41a** (52 mg, 0.14 mmol, 1 equiv.) in THF (0.7 mL) at –20 °C under inert atmosphere was added sodium borohydride (11 mg, 0.28 mmol, 2 equiv.). The reaction mixture was stirred for 15 h at the same temperature and afterwards quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 50:50).

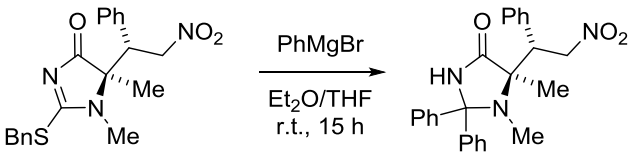
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidin-4-one (56)



Yield: 35 mg, 0.13 mmol, 94 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 – 7.17 (m, 6H), 5.21 (dd, *J* = 13.4, 11.1 Hz, 1H), 4.71 (dd, *J* = 13.4, 4.3 Hz, 1H), 4.26 (dd, *J* = 4.5, 0.9 Hz, 1H), 3.86 – 3.70 (m, 2H), 2.17

(s, 3H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.2, 136.2, 130.1, 128.9, 65.8, 65.3, 50.6, 35.7, 16.5. UPLC-DAD-QTOF: $C_{13}H_{18}N_3O_3$ $[M+H]^+$ calcd.: 264.1348, found: 264.1350.

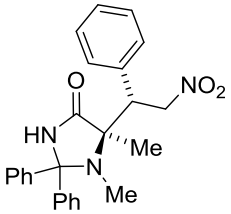
5.3.5.2. **Synthesis of *gem*-diarylated adduct 57.**



41a **57**

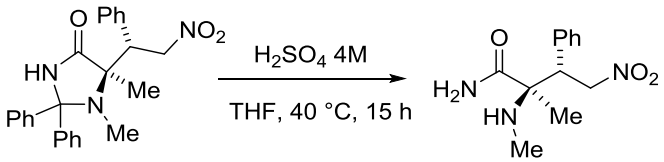
To a solution of **41a** (76 mg, 0.2 mmol, 1 equiv.) in THF (1 mL) at 0 °C under inert atmosphere was added phenylmagnesium bromide (1M in Et_2O, 0.6 mL, 1 mmol, 5 equiv.). The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 50:50).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2,2-diphenylimidazolidin-4-one (57)



Yield: 66 mg, 0.16 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (s, 1H), 7.49 – 6.57 (m, 17H), 5.25 (dd, *J* = 13.5, 11.3 Hz, 1H), 4.71 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.76 (dd, *J* = 11.3, 3.6 Hz, 1H), 2.05 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.4, 142.4, 140.9, 137.5, 129.8, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 126.9, 120.7, 115.5, 82.8, 77.2, 66.8, 52.1, 29.7, 20.0. UPLC-DAD-QTOF: $C_{25}H_{26}N_3O_3$ $[M+H]^+$ calcd.: 416.1974, found: 416.1974.

5.3.5.3. **Synthesis of amino amide (58).**[385]



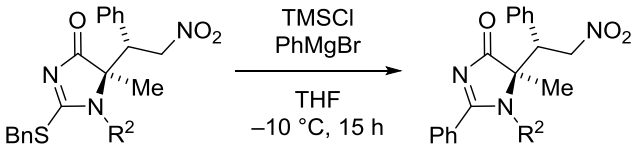
57 **58**

To a solution of 1-methyl-2,2-diphenylimidazolidin-4-one **57** (41.5 mg, 0.10 mmol) in 0.5 mL THF at 0 °C was added dropwise an aqueous solution of H_2SO_4 4M (0.5

[385] M. Pangerl, C. C. Hughes and D. Trauner *Tetrahedron* **2010**, *66*, 6626–6631.

mL). The resulting mixture was stirred at 40 °C 16 h and afterwards the reaction was quenched with an aqueous solution of NaOH 1M (2.0 mL). The mixture was diluted with saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2 × 15mL). The combined extracts were washed with brine (20 mL) and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluent: hexane:ethyl acetate 7:1 to ethyl acetate). Yield: 22.6 mg, 0.09 mmol, 90 %. $[\alpha]_D^{25}$= +14.0 (*c*= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.25 (m, 5H), 6.96 (s, 1H), 5.34 (dd, *J* = 13.6, 11.1 Hz, 2H), 4.98 (dd, *J* = 13.6, 3.5 Hz, 1H), 3.79 (dd, *J* = 11.1, 3.5 Hz, 1H), 2.37 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 136.1, 129.2, 129.1, 128.5, 78.2, 64.1, 50.1, 29.1, 21.3. UPLC-DAD-QTOF: $C_{12}H_{18}N_3O_3$ $[M+H]^+$ calcd.: 252.1348, found: 252.1350.

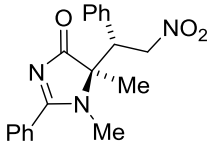
5.3.5.4. **Synthesis of monoarilation adduct 59.**



41a **59**

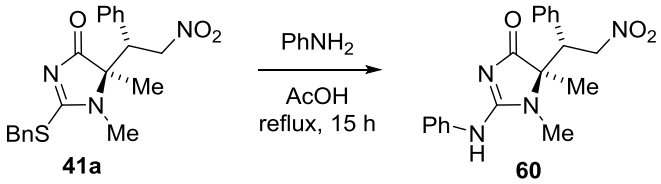
To a solution of **41a** (0.2 mmol, 1 equiv.) in THF (1 mL) at –10 °C under inert atmosphere was added TMSCl (24 µL, 0.1 mmol, 1 equiv.) and phenylmagnesium bromide (1M in THF, 0.6 mL, 0.6 mmol, 3 equiv.). The reaction mixture was stirred for 15 h at –10 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 0:100).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-phenyl-1*H*-imidazol-4(5*H*)-one (59)



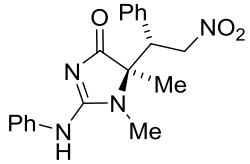
Yield: 57.3 mg, 0.17 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 – 7.00 (m, 10H), 5.33 – 5.03 (m, 2H), 3.91 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.08 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.0, 180.0, 134.4, 132.1, 129.1, 129.1, 128.7, 128.5, 127.8, 118.3, 75.5, 69.3, 50.0, 30.5, 20.8. UPLC-DAD-QTOF: $C_{19}H_{20}N_3O_3$ $[M+H]^+$ calcd.: 338.1505, found: 338.1510.

5.3.5.5. **Synthesis of aminohydantoin 60.**[386]



To a solution of **41a** (38 mg, 0.1 mmol, 1 equiv.) in glacial acetic acid (0.5 mL) under inert atmosphere was added aniline (0.10 mL, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred under reflux for 16 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with ethyl acetate (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 0:100).

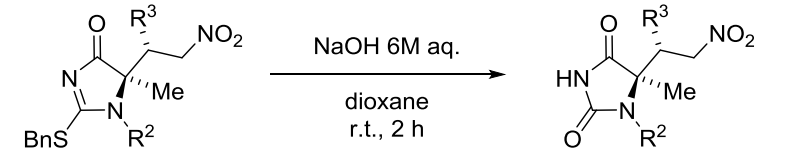
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-(phenylamino)-1*H*-imidazol-4(5*H*)-one (60)



Yield: 24 mg, 0.07 mmol, 68 %. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.40 – 7.00 (m, 10H), 5.28 (dd, *J* = 13.5, 11.2 Hz, 1H), 5.10 (dd, *J* = 13.5, 4.3 Hz, 1H), 3.96 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.04 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ: 191.4, 168.0, 136.6, 130.5, 129.7, 129.5, 129.4, 126.5, 124.7, 76.5, 70.7, 50.4, 27.7, 20.5. UPLC-DAD-QTOF: $C_{19}H_{21}N_4O_3$ $[M+H]^+$ calcd.: 353.1614, found: 353.1610.

[386] Adapted from: Godlewskim, M. et al. PCT Int. Appl. (WO9823595), June 4, 1998.

5.3.5.6. **Synthesis of hydantoins 61, 62 and 63.**

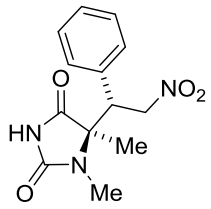


41a R^2: Me R^3: Ph
41c R^2: Me R^3: 4-BrC_6H_4
44a R^2: Allyl R^3: Ph

61 R^2: Me R^3: Ph
62 R^2: Me R^3: 4-BrC_6H_4
63 R^2: Allyl R^3: Ph

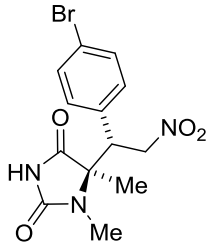
The corresponding adduct **41a**, **41c**, **44a** (1 equiv.) was dissolved dioxane (5 mL) and cooled to 0 °C. NaOH 6M (11 equiv.) was added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After this period the solution was treated at 0 °C with a saturated aqueous solution of NH_4Cl. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane, from 70:30 to 50:50).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (61)



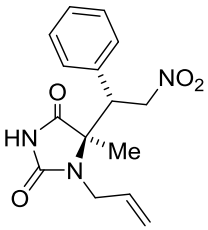
The title compound was prepared from (*R*)-2-(benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (**41a**) (410 mg, 1.07 mmol) according to the general procedure. White foam. Yield: 211 mg, 0.76 mmol, 71 %. $[\alpha]_D^{25}$= +26.8 (*c*= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.34 – 7.25 (m, 3H), 7.18 – 7.10 (m, 2H), 5.16 (dd, *J* = 13.7, 10.2 Hz, 1H), 4.97 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.87 (dd, *J* = 10.2, 4.7 Hz, 1H), 2.86 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 154.9, 134.3, 129.7, 129.6, 128.3, 76.1, 67.6, 49.3, 25.4, 20.9. UPLC-DAD-QTOF: $C_{13}H_{16}N_3O_4$ $[M+H]^+$ calcd.: 278.1141, found: 278.1143.

(*R*)-5-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)-1,5-dimethylimidazolidine-2,4-dione (62)



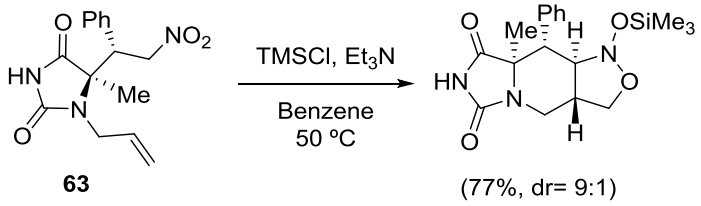
The title compound was prepared from (*R*)-2-(benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**41c**) (197 mg, 0.43 mmol) according to the general procedure. White solid. Yield: 112 mg, 0.31 mmol, 73 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.14 (dd, *J* = 13.8, 10.4 Hz, 1H), 4.93 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.84 (dd, *J* = 10.4, 4.6 Hz, 1H), 2.87 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 179.6, 175.4, 133.0, 132.8, 129.9, 123.7, 75.1, 70.4, 48.7, 29.9, 20.4. UPLC-DAD-QTOF: $C_{13}H_{13}BrN_3O_4$ $[M+H]^+$ calcd.: 354.0089, found: 354.0087.

(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (63)



The title compound was prepared from (*R*)-1-allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (**44a**) (54 mg, 0.13 mmol) according to the general procedure. White foam. Yield: 24 mg, 0.08 mmol, 61 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.37 – 7.04 (m, 5H), 5.94 – 5.71 (m, 1H), 5.32 – 5.07 (m, 3H), 4.96 (dd, *J* = 13.7, 4.7 Hz, 1H), 4.10 (dd, *J* = 16.0, 5.3 Hz, 1H), 3.90 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.65 (dd, *J* = 16.0, 6.9 Hz, 1H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 155.1, 134.2, 133.4, 129.6, 129.6, 128.5, 119.1, 76.1, 68.4, 49.5, 43.3, 22.3. UPLC-DAD-QTOF: $C_{15}H_{18}N_3O_4$ $[M+H]^+$ calcd.: 304.1297, found: 304.1306.

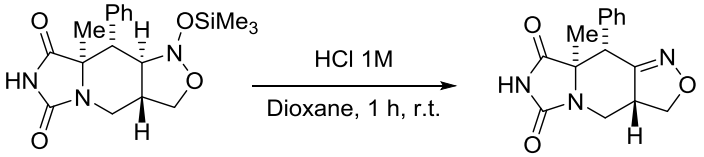
5.3.5.7. **Intramolecular silyl nitronate olefin cycloaddition (ISOC) of 64.**



63 (77%, dr= 9:1)

To a solution of hydantoin **63** (101 mg, 0.33 mmol, 1 equiv.) in benzene (2.5 mL) under inert atmosphere were added freshly distilled Et_3N (280 µL, 2 mmol, 6 equiv.) and freshly distilled TMSCl (213 µL, 1.67 mmol, 5 equiv.). After addition was complete the mixture was warmed to 50 °C and stirred for 48 h. Afterwards, the reaction mixture was cooled to 0 °C, quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate 80:20 to 50:50) to yield the corresponding *N*-trimethylsilyloxyisoxazoline. Yield: 95 mg, 0.25 mmol, 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 7.33-7.16 (m, 5H), 4.64-4.60 (m, 1H), 4.35-4.30 (m, 1H), 3.73-3.53 (m , 2H), 3.17 (d, *J* = 12 Hz, 1H), 2.96-2.87 (m, 2H), 1.34 (s, 3H), -0.29 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.2, 154.6, 134.1, 130.4, 12.2, 127.9, 73.4, 70.4, 64.4, 49.8, 42.2, 39.6, 16.7, -1.0. UPLC-DAD-QTOF: $C_{18}H_{26}N_3O_4Si$ $[M+H]^+$ calcd.: 376.1693, found: 376.1689.

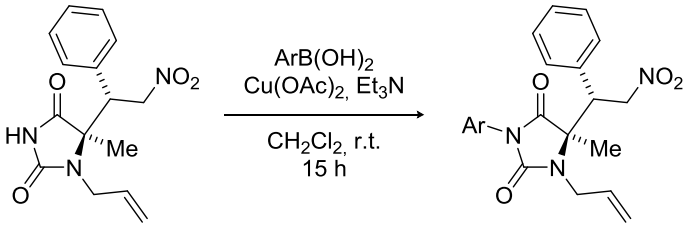
5.3.5.8. **Synthesis of isoxazoline 64.**



(*dr* = 9:1) **64** (83 %, *dr* = 9:1)

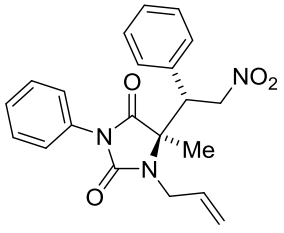
A solution of the *N*-trimethylsilyloxyisoxazoline (95 mg, 0.25 mmol, 1 equiv.) in dioxane (1 mL) was cooled to 0 °C and then treated with 10% aqueous HCl. The reaction mixture was stirred for 1 h at rt and afterwards poured into water and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by short plug of silica gel (eluent: 80:20 to 0:100, hexane/ethyl acetate). Yield: 59 mg, 0.21 mmol, 83%. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 9.70 (s, 1H), 7.57 – 7.11 (m, 5H), 4.63 – 4.46 (m, 2H), 4.16 (d, *J* = 1.3 Hz, 1H), 3.99 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.58 (ddd, *J* = 10.6, 7.4, 1.3 Hz, 1H), 3.11 (dd, *J* = 13.3, 10.9 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 174.5, 157.3, 154.2, 132.7, 128.5, 128.0, 72.0, 65.4, 51.0, 48.4, 40.7, 16.9. UPLC-DAD-QTOF: $C_{15}H_{16}N_3O_3$ $[M+H]^+$ calcd.: 286.1189, found: 286.1192.

5.3.5.9. ***N*-Arylation of hydantoin 63.**[387]



A slurry of (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**63** from big scale reaction *dr* 9:1, table 1, entry 15) (30 mg, 0.1 mmol, 1 equiv.), arylboronic acid (0.2 mmol, 2 equiv.), $Cu(OAc)_2$ (18 mg, 0.1 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 15 h. The progress of the reaction was monitored by TLC. The products were isolated from the crude reaction mixture by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20).

(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (65)

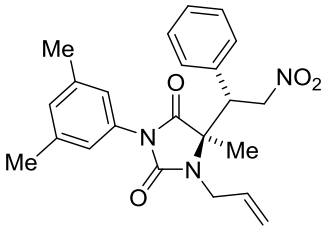


The title compound was prepared from (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**63**) (30 mg, 0.1 mmol) and phenyl boronic acid (24 mg, 0.2 mmol, 2 equiv) according to the general procedure. Yellow oil. Yield: 29 mg, 0.08 mmol, 76 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.27 (m, 7H), 7.19 – 7.13 (m, 2H), 7.03 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.99 – 5.83 (m, 1H), 5.40 – 5.16 (m, 3H), 5.03 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.28 (dd, *J* = 15.8, 5.4

[387] D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters *Tetrahedron Letters* **1998**, *39*, 2933-2936.

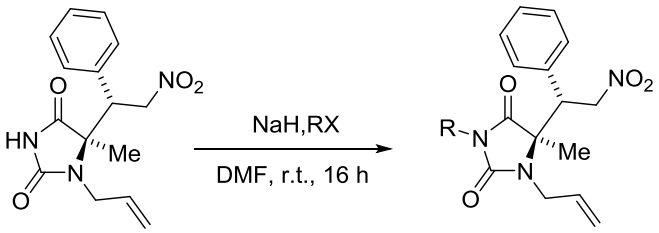
Hz, 1H), 4.01 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.87 – 3.76 (m, 1H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.2, 153.8, 133.1, 129.2, 129.2, 129.2, 129.1, 129.0, 128.5, 128.2, 126.0, 118.9, 75.5, 66.5, 49.0, 43.2, 21.6. UPLC-DAD-QTOF: $C_{21}H_{22}N_3O_4$ $[M+H]^+$ calcd.: 380.1610, found: 380.1612.

(*R*)-1-Allyl-3-(3,5-dimethylphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (66)



The title compound was prepared from (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**63**) (30 mg, 0.1 mmol) and 3,5-dimethylphenyl boronic acid (30 mg, 0.2 mmol, 2 equiv) according to the general procedure. Yellow oil. Yield: 32.6 mg, 0.08 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.29 (m, 3H), 7.20 – 7.13 (m, 2H), 6.97 (s, 1H), 6.58 (s, 2H), 6.00 – 5.84 (m, 1H), 5.40 – 5.15 (m, 3H), 5.03 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.34 – 4.22 (m, 1H), 4.00 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.81 (dd, *J* = 15.8, 7.0 Hz, 1H), 2.29 (s, 6H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8, 154.5, 139.4, 133.6, 130.9, 129.6, 129.6, 128.7, 124.4, 119.3, 76.0, 66.9, 49.4, 43.7, 22.1, 21.7. UPLC-DAD-QTOF: $C_{23}H_{26}N_3O_4$ $[M+H]^+$ calcd.: 408.1923, found: 408.1921.

5.3.5.10. *N*-Alkylation of hydantoin 63.[388]

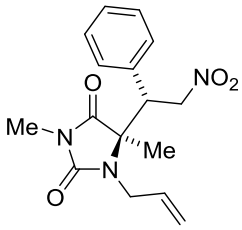


Sodium hydride (60% dispersion in mineral oil, 38.4 mg, 1 mmol, 1 equiv.) was added to a solution of (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**63** from big scale reaction *dr* 9:1, table 1, entry 15) (303 mg, 1.0 mmol, 1 equiv.) in DMF (4 mL) at 0 °C. The mixture was stirred for 30 min, then the corresponding alkyl halide (1.2 mmol, 1.2 equiv.) was added dropwise. The cooling bath was removed and the reaction was stirred at room temperature for 16 h. The mixture was added to water (20 mL) and extracted with Et_2O. The organic layer was dried with anhyd.

[388] Adapted from Owen, David Alan et al From U. S., 6566384, 20 May 2003

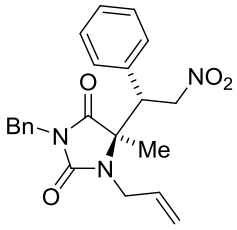
$MgSO_4$, evaporated and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20).

(*R*)-1-Allyl-3,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (67)



The title compound was prepared adding iodomethane (74.1 µL, 1.2 mmol, 1.2 equiv.) according to the general procedure. Colourless oil. Yield: 259 mg, 0.82 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.27 (m, 3H), 7.09-7.06 (m, 2H), 5.89-5.77 (m, 1H), 5.33-5.13 (m, 3H), 5.01-4.95 (m, 1H), 4.21-4.13 (m, 1H), 3.93-3.88 (m, 1H), 3.76-3.67 (m, 1H), 2.79 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.3, 154.8, 133.8, 133.2, 129.4, 128.9, 128.8, 128.6, 127.8, 118.2, 75.4, 66.6, 48.8, 42.7, 24.4, 21.1. UPLC-DAD-QTOF: $C_{16}H_{20}N_3O_4$ $[M+H]^+$ calcd.: 318.1454, found: 318.1451.

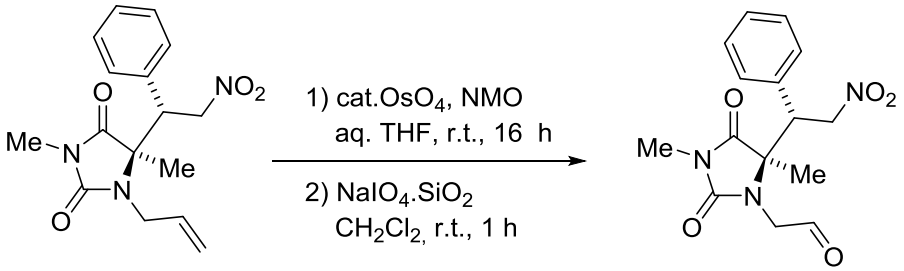
(*R*)-1-Allyl-3-benzyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (68)



The title compound was prepared adding benzyl bromide (142.8 µL, 1.2 mmol, 1.2 equiv.) according to the general procedure. Yellow oil. Yield: 330 mg, 0.84 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 7.16-7.10 (m, 1H), 6.99-6.87 (m, 4H), 5.91-5.78 (m, 1H), 5.33-5.21 (m, 2H), 5.11 (dd, *J* = 9, 12 Hz, 1H), 4.97 (dd, *J* = 3, 6 Hz, 1H), 4.50 (d, 2H), 4.16-4.08 (m, 1H), 3.88 (dd, *J* = 6,3 Hz, 1H), 3.68-3.65 (m, 1H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 154.8, 135.3, 133.6, 133.3, 129.6, 129.2, 129.0, 128.8, 128.5, 128.1, 127.8, 118.6, 76.0, 66.3, 49.2, 43.1, 42.7, 22.2. UPLC-DAD-QTOF: $C_{22}H_{24}N_3O_4$ $[M+H]^+$ calcd.: 394.1767, found: 394.1762.

5.3.5.11. **Intramolecular Henry reaction.**

5.3.5.11.1. Synthesis of aldehyde.[389]



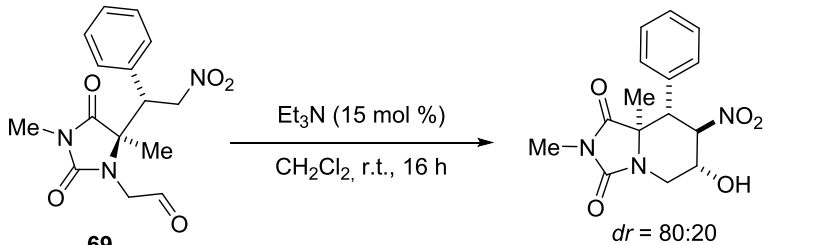
67 **69**

Step 1-Synthesis of the diol: OsO_4 (2.5 wt% in 2-methyl-2-propanol, 175.7 mg , 0.0164 mmol, 0.02 equiv.) and 4-methylmorpholine *N*-oxide (125 mg, 1.1 mmol, 1.3 equiv.) were added to a solution of hydantoin **67** (0.82 mmol, 1 equiv.) in THF (6 mL) and H_2O (2 mL) at room temperature. The mixture was stirred for 16 h, then a solution of $NaHSO_3$ in H_2O 40% w/v (2.3 mL, 9 mmol, 11 equiv.) was added and the resulting mixture was stirred for 10 min. The mixture was diluted with 20 mL of brine and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50 to 0:100) to afford the diol as white foam (Yield: 0.7 mmol, 86 %).

Step 2-Synthesis of the aldehyde: $NaIO_4$ supported on silica gel (1.5 g, 1.4 mmol, 2.0 equiv.) was added to a solution of previously prepared diol (1 equiv., 0.7 mmol) in DCM (10 mL). The suspension was stirred at room temperature for 1 h. The reaction mixture was filtrated through a sintered glass funnel and the filtrate was concentrated to afford the aldehyde **69** as white foam used in the next step without purification (Yield: 0.5 mmol, 71 %).

[389] Adapted from: R. L. Danheiser et al. *J. Org. Chem.* **2013**, *78*, 9396-9414.

5.3.5.11.2. Intramolecular cyclization.



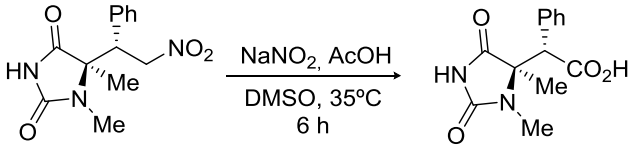
69

dr = 80:20
yield major diastereomer = 64%

70

To a solution of aldehyde **69** (97 mg, 0.3 mmol, 1 equiv.) in 1.5 mL of DCM was added Et_3N (6.3 µL, 0.045 mmol, 0.15 equiv.). The reaction mixture was stirred for 16 h at room temperature and white precipitate was generated. Then, the organic layer was concentrated under reduced pressure and the crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate: 70:30 to 50:50,) to afford the desired product as white solid. Yield: 61 mg, 0.19 mmol, 64 % (major. diasteroisomer) $[\alpha]_D^{25}$= +1.71 (*c*= 2, Acetone, major. diastereomer). ^{1}H NMR (300 MHz, Acetone-d_6) δ: 7.31-7.30 (m, 5H), 5.47 (dd, *J* = 6, 6 Hz, 1H), 4.36 (dd, J = 3, 3 Hz, 1H), 4.19-4.13 (m, 1H), 3.65 (d, *J* = 6Hz, 1H), 3.07 (dd, J = 6, 6 Hz, 1H), 2.95 (s, 3H), 2.83 (s, 1H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 174.1, 155.6, 134.2, 129.4, 129.0, 92.1, 70.7, 63.2, 52.1, 41.9, 25.5, 16.8. UPLC-DAD-QTOF: $C_{15}H_{18}N_3O_5$ $[M+H]^+$ calcd.: 320.1246, found: 320.1245.

5.3.5.12. **Synthesis of carboxylic acid 71.**

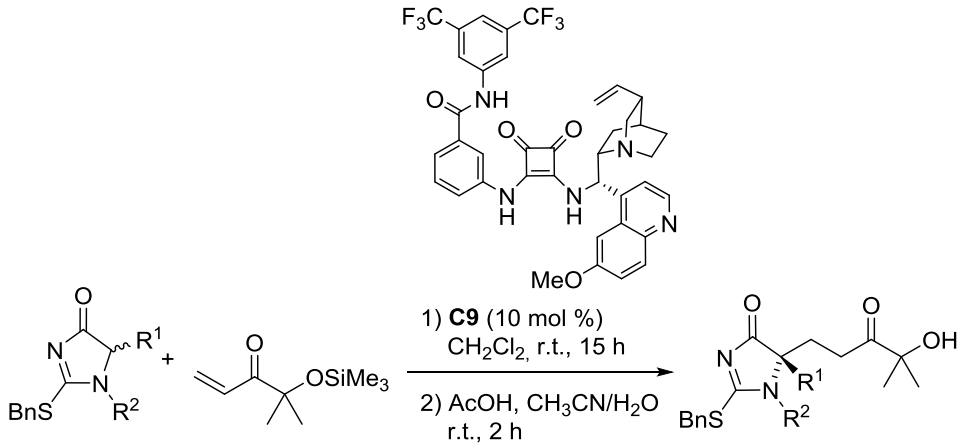


61 **71**

A solution of the nitroalkane N (0.19 mmol, 51mg), 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 35ºc for 6h. After this period the reaction mixture was treated with HCl 1N (5 mL) and the product was extracted from the aq. phase with Et_2O (4 x 5mL). The combined organic phases were dried with anhyd. $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was washed with Et_2O giving the pure product *S*-((2*R*,3*S*)-1-amino-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl) **71** as white solid. Yield 43 mg, 0.164 mmol (86 %). $[\alpha]_D^{25}$= +15.8 (*c*= 0.50, MeOH). m.p. 230–232 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.34 (m, 5H), 4.09 (s, 1H), 2.56 (s, 3H), 1.49 (s, 3H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 178.9, 173.2, 158.9, 134.8, 131.3, 129.5, 129.3, 68.0, 57.2, 26.9, 20.8. UPLC-DAD-QTOF: $C_{13}H_{14}N_2O_4$ $[M+H]^+$ calcd.: 263.1032, found: 263.1034.

5.3.6. **General procedure for the asymmetric conjugate addition of 1*H*-imidazol-4(5*H*)-ones to α'-silyloxyenone 73.**



73

27A R^1 = Me, R^2 = Me
28A R^1 = Me, R^2 = Bn
30A R^1 = Me, R^2 = Allyl
34A R^1 = Bn, R^2 = Me
35A R^1 = *n*Hex, R^2 = Me
36A R^1 = *i*Bu, R^2 = Me
40A R^1 = Bn, R^2 = Bn

74 R^1 = Me, R^2 = Me
75 R^1 = Bn, R^2 = Me
76 R^1 = *n*Hex, R^2 = Me
77 R^1 = *i*Bu, R^2 = Me
78 R^1 = Me, R^2 = Bn
79 R^1 = Me, R^2 = Allyl
80 R^1 = Bn, R^2 = Bn

5.3.6.1. **Asymmetric reaction**

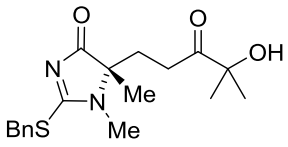
To a solution of the corresponding imidazolone (0.2 mmol, 1 equiv.) and the 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **73** (0.6 mmol, 3 equiv.) in dichloromethane (0.5 mL) at room temperature catalyst **C9** (10 mol %) was added. The resulting solution was stirred at the same temperature until consumption of the imidazolone (monitored by ^{1}H NMR). The reaction mixture was then quenched with an aqueous solution of HCl (0.1 M) and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The reaction crude was then solved in an acetonitrile/water 2:1 mixture (1.5 mL) and acetic acid (0.3 mL, 5 mmol, 25 equiv.) was added to the solution. Desilylation was monitored by TLC. After reaction termination, the solution was treated with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with dichloromethane and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with hexane/ethyl acetate, 70:30).

5.3.6.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using **C4** (20 mol %) as the catalyst at room temperature.

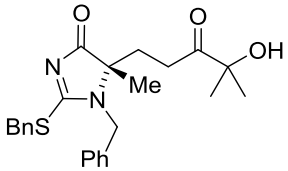
5.3.6.3. **Characterization data for compounds 74–80**

(*S*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (74)



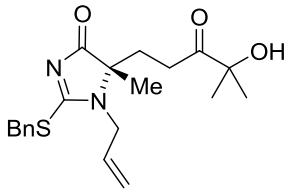
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**27A**) (47 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 56 mg, 0.16 mmol, 82 %. $[\alpha]_D^{25}$= +9.0 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.20 (m, 5H), 4.55 (dd, *J* = 3.5 Hz, 2H), 2.93 (s, 3H), 2.57 – 2.40 (m, 1H), 2.36 – 2.22 (m, 1H), 2.20 – 1.92 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.9, 189.7, 183.2, 135.4, 129.0, 128.6, 127.8, 69.6, 36.3, 29.6, 29.4, 28.4, 28.4, 26.2, 21.2. UPLC-DAD-QTOF: $C_{18}H_{25}N_2O_3S$ $[M+H]^+$ calcd.: 349.1586, found: 349.1582.

(*S*)-1-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (75)



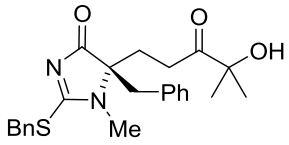
The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**28A**) (62.1 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 66.2 mg, 0.16 mmol, 78 %. $[\alpha]_D^{25}$= –4.2 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 6.98 (m, 10H), 4.34 (dd, *J* = 13.3 Hz, 2H), 3.24 (d, *J* = 14.1 Hz, 1H), 2.93 (s, 3H), 2.88 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.49 (m, 1H), 2.36 – 2.11 (m, 3H), 1.29 (d, *J* = 13.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 189.24, 184.5, 136.2, 134.2, 129.6, 129.3, 129.1, 128.8, 128.7, 128.2, 127.7, 75.5, 42.0, 36.5, 30.3, 29.3, 28.7, 26.8, 26.8. UPLC-DAD-QTOF: $C_{24}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 425.1899, found: 425.1899.

(*S*)-1-Allyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (76)



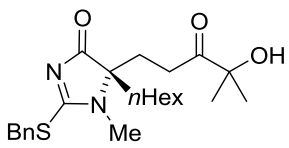
The title compound was prepared from 1-allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**30A**) (52.1 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 57.7 mg, 0.15 mmol, 77 %. $[\alpha]_D^{25}$= +10.5 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.19 (m, 5H), 5.84 – 5.62 (m, 1H), 5.34 – 5.18 (m, 2H), 4.56 (dd, *J* = 13.2, 9.4 Hz, 2H), 3.99 – 3.88 (m, 2H), 3.51 (s, 1H), 2.49 (ddd, *J* = 18.2, 8.9, 6.2 Hz, 1H), 2.35 – 1.91 (m, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.3, 189.9, 183.6, 135.7, 131.5, 129.4, 129.0, 128.2, 120.1, 116.6, 70.5, 42.6, 37.0, 29.8, 29.5, 26.7, 22.6. UPLC-DAD-QTOF: $C_{20}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 375.1742, found: 375.1753.

(*R*)-5-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (77)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (**34A**) (62 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Yellow solid. Yield: 64 mg, 0.15 mmol, 75 %. $[\alpha]_D^{25}$= +20.2 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 6.95 (m, 10H), 4.48 – 4.15 (m, 2H), 3.23 (d, *J* = 14.0 Hz, 1H), 2.93 (s, 3H), 2.88 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.50 (m, 1H), 2.36 – 2.09 (m, 3H), 1.29 (d, *J* = 13.0 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 189.0, 184.3, 135.9, 134.0, 129.7, 129.3, 129.1, 127.9, 127.4, 127.4, 75.2, 41.7, 36.3, 30.0, 29.5, 28.45, 26.6, 26.5. UPLC-DAD-QTOF: $C_{24}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 425.1899, found: 425.1899.

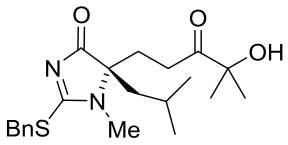
(*S*)-2-(Benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (78)



The title compound was prepared from 2-(benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**35A**) (60.9 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 67.8 mg, 0.16 mmol, 81 %. $[\alpha]_D^{25}$= +3.1 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.16 (m, 5H), 4.55 (s, 2H), 2.89 (s, 3H), 2.58 – 2.40 (m, 1H), 2.32 – 2.17 (m, 1H), 2.13 – 1.92 (m, 2H), 1.93 – 1.76 (m, 1H), 1.69 – 1.53 (m, 1H), 1.32 – 1.07 (m, 15H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.8, 190.0,

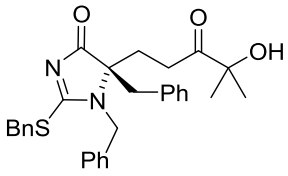
184.4, 136.4, 129.7, 129.4, 128.6, 74.5, 37.1, 35.8, 32.1, 30.3, 29.5, 29.3, 28.9, 27.0, 23.7, 23.0, 14.6. UPLC-DAD-QTOF: $C_{23}H_{35}N_2O_3S$ $[M+H]^+$ calcd.: 419.2363, found: 419.2361.

(*R*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (79)



The title compound was prepared from 2-(benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**36A**) (55.3 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 55.5 mg, 0.14 mmol, 71 %. $[\alpha]_D^{25}$= +12.3 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.17 (m, 5H), 4.55 (s, 2H), 2.89 (s, 3H), 2.45 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.33 – 2.13 (m, 1H), 2.00 (ddd, *J* = 12.9, 8.5, 5.5 Hz, 2H), 1.81 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.59 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.48 – 1.35 (m, 1H), 1.27 (d, *J* = 14.3 Hz, 6H), 0.82 (dd, *J* = 9.8, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.5, 189.7, 183.8, 136.1, 129.3, 128.9, 128.1, 73.4, 43.7, 36.6, 29.8, 29.5, 29.1, 26.6, 24.6, 23.8, 23.5. UPLC-DAD-QTOF: $C_{21}H_{31}N_2O_3S$ $[M+H]^+$ calcd.: 391.2055, found: 391.2060.

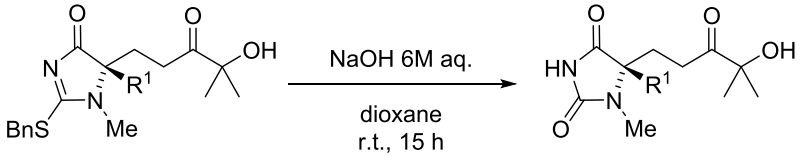
(*R*)-1,5-Dibenzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (79)



The title compound was prepared from 1,5-dibenzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (**40A**) (77.3 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**73**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 83.1 mg, 0.17 mmol, 83 %. $[\alpha]_D^{25}$= +1.28 (*c*= 1.00, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 – 6.92 (m, 15H), 4.55 (dd, *J* = 15.9 Hz, 2H), 4.39 (dd, *J* = 13.3 Hz, 2H), 3.19 (dd, *J* = 14.9 Hz, 2H), 2.45 – 2.29 (m, 1H), 2.13 – 1.95 (m, 2H), 1.90 – 1.74 (m, 1H), 1.19 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.2, 189.1, 185.3, 135.8, 129.9, 129.7, 129.6, 129.3, 129.2, 129.0, 129.0, 128.4, 128.0, 49.0, 42.8, 37.5, 30.0, 29.8, 27.3, 27.0. UPLC-DAD-QTOF: $C_{30}H_{33}N_2O_3S$ $[M+H]^+$ calcd.: 501.2206, found: 501.2210.

5.3.7. **Elaboration of adducts 74–79.**

5.3.7.1. **Synthesis of hydantoins 81–83.**

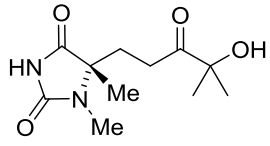


74 R^1 = Me
77 R^1 = Bn
79 R^1 = *n*Hex

81 R^1 = Me, 60%
82 R^1 = Bn, 87%
83 R^1 = *n*Hex, 72%

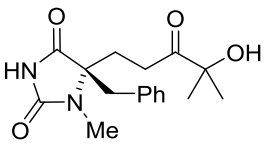
The corresponding adduct **74–79** (361.1 mg, 0.92 mmol, 1 equiv.) was dissolved in dioxane (5 mL) and cooled to 0 °C. NaOH 6M (1.84 mL, 11.04 mmol, 12 equiv.) was added at 0°C and the reaction mixture was stirred at room temperature for 15 h. After this period the solution was treated at 0 °C with a saturated aqueous solution of NH_4Cl. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with hexane/ethyl acetate, from 70:30 to 0:100).

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylimidazolidine-2,4-dione (81)



The title compound was prepared from (*S*)-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**74**) (172 mg, 0.5 mmol) according to the general procedure. Colourless oil. Yield: 73.1 mg, 0.3 mmol, 60 %. $[\alpha]_D^{25}$= –6.46 (*c*= 1.00, 99 % *ee*, MeOH). ^{1}H NMR (300 MHz, MeOD) δ: 2.84 (s, 3H), 2.68 – 2.48 (m, 2H), 2.20 – 1.89 (m, 2H), 1.45 (s, 3H), 1.30 (s, 6H). ^{13}C NMR (75 MHz, MeOD) δ: 215.4, 179.1, 157.8, 77.8, 66.7, 31.3, 29.5, 26.7, 24.6, 21.7. UPLC-DAD-QTOF: $C_{11}H_{19}N_2O_4$ $[M+H]^+$ calcd.: 243.1339, found: 243.1343.

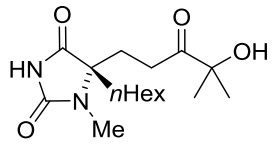
(*R*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (82)



The title compound was prepared from (*R*)-5-benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (**77**) (352.0 mg, 0.7 mmol) according to the general procedure. White foam. Yield: 193 mg, 0.61 mmol, 87%. $[\alpha]_D^{25}$= +0.6 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.15 (s, 1H), 7.26 – 6.90 (m, 5H), 4.04 (s, 1H), 2.94 (dd, *J* = 33.7, 14.3 Hz, 2H), 2.78 (s, 3H), 2.63 – 2.31 (m, 2H), 2.14 – 2.02 (m, 2H), 1.23 (d, *J* = 2.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$)

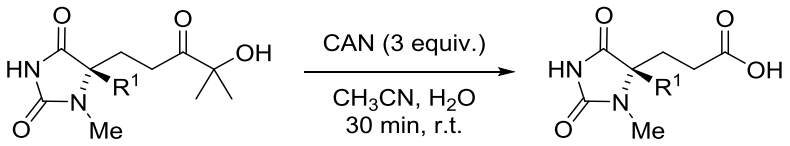
δ: 213.7, 175.5, 156.2, 133.8, 129.6, 128.7, 127.7, 77.2, 70.3, 40.7, 29.9, 28.2, 26.5, 25.1. UPLC-DAD-QTOF: $C_{17}H_{23}N_2O_4$ $[M+H]^+$ calcd.: 319.1658, found: 319.1666.

(*S*)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (83)



The title compound was prepared from (*S*)-2-(benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (**79**) (418.6 mg, 1 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30. White foam. Yield: 225 mg, 0.72 mmol, 72%. $[\alpha]_D^{25}$= +4.4 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 3.63 (s, 1H), 2.76 (s, 3H), 2.58 – 2.37 (m, 1H), 2.13 – 1.95 (m, 1H), 1.92 – 1.75 (m, 1H), 1.63 (s, 1H), 1.43 – 1.00 (m, 16H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 176.2, 156.6, 69.5, 35.2, 32.0, 30.1, 29.4, 28.9, 27.1, 27.0, 24.9, 23.6, 23.0, 14.5. UPLC-DAD-QTOF: $C_{16}H_{29}N_2O_4$ $[M+H]^+$ calcd.: 313.2122, found: 313.2127.

5.3.7.2. **Synthesis of carboxylic acids 84–85.**[390]



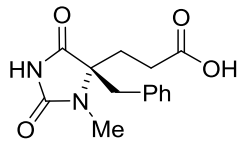
82 R^1 = Bn
83 R^1 = *n*Hex

84 R^1 = Bn, 65%
85 R^1 = *n*Hex, 74%

To a solution of the corresponding α'-hydroxy ketone **82–83** (1 mmol) in acetonitrile (12 mL) at 0 °C was added dropwise a solution of cerium(IV)ammonium nitrate (CAN) (1.64 g, 3 mmol, 3 equiv.) in water (6 mL) and the mixture was stirred at the same temperature for 30 minutes. Then water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered and the solvent evaporated to afford the corresponding carboxylic acid. 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 white solid.

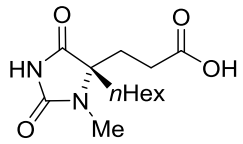
[390] [CSL STYLE ERROR: reference with no printed form.]

(*R*)-3-(4-Benzyl-3-methyl-2,5-dioxoimidazolidin-4-yl)propanoic acid (84)



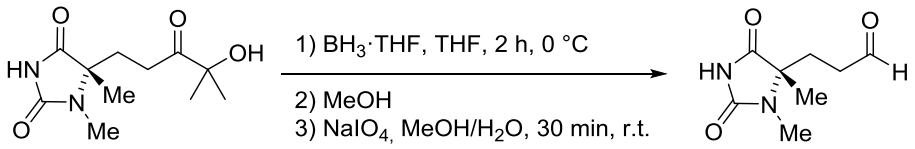
The title compound was prepared from (*R*)-5-benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (**82**) (107.0 mg, 0.34 mmol) according to the general procedure. White solid. Yield: 61 mg, 0.22 mmol, 65%. $[\alpha]_D^{25}$= +0.6 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.36 – 7.01 (m, 5H), 3.04 (dd, *J* = 47.9, 13.3 Hz, 2H), 2.92 (s, 3H), 2.42 – 2.16 (m, 4H). ^{13}C NMR (75 MHz, MeOD) δ: 177.5, 175.5, 158.0, 135.6, 130.7, 129.4, 128.3, 71.8, 41.2, 30.5, 29.3, 25.4. UPLC-DAD-QTOF: $C_{14}H_{17}N_2O_4$ $[M+H]^+$ calcd.: 277.1188, found: 277.1185.

(*S*)-3-(4-Hexyl-3-methyl-2,5-dioxoimidazolidin-4-yl)propanoic acid (85)



The title compound was prepared from (*S*)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (**83**) (62.0 mg, 0.2 mmol) according to the general procedure. White solid.Yield: 40.5 mg, 0.15 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (s, 1H), 2.79 (s, 3H), 2.46 – 1.97 (m, 2H), 1.84 (d, *J* = 2.5 Hz, 1H), 1.75 – 1.51 (m, 1H), 1.28 (d, *J* = 14.7 Hz, 10H), 1.01 – 0.76 (m, 3H).^{13}C NMR (75 MHz, MeOD) δ: 176.4, 175.9, 156.8, 69.5, 35.0, 31.8, 30.0, 29.3, 28.7, 24.8, 23.4, 22.9, 14.4. UPLC-DAD-QTOF: $C_{13}H_{23}N_2O_4$ $[M+H]^+$ calcd.: 271.1652, found: 271.1658.

5.3.7.3. **Synthesis of aldehyde 86.**

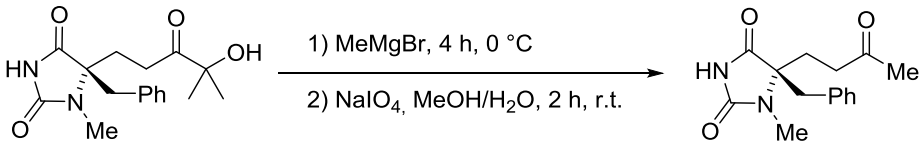


81 **86**

BH_3·THF complex (1M in THF, 0.6 mL, 0.6 mmol, 2 equiv.) was added to a solution of (*S*)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylimidazolidine-2,4-dione (**81**) (74 mg, 0.3 mmol, 1 equiv.) in dry THF (2 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. The reaction was monitored by TLC (hexane/ethyl acetate, 1:1). After reaction completion, MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were evaporated under reduced pressure and the residue thus obtained was solved in MeOH (2 mL) again. A suspension of sodium periodate $NaIO_4$ (320 mg, 1.5 mmol, 5 equiv.) in water (1 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 30 min and solvents were evaporated under reduced pressure. Water (6 mL) was added to the crude product and the resulting mixture was extracted with ethyl

acetate (3 × 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 (hexane/ethyl acetate, 80:20 to 0:100) affording title product **86** as a white solid. Yield: 48 mg, 0.26 mmol, 87%. $[\alpha]_D^{25}$= –1.83 (*c*= 1.00, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 8.40 (s, 1H), 2.82 (s, 3H), 2.51 – 2.25 (m, 2H), 2.18 – 1.95 (m, 2H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.7, 175.9, 155.2, 65.2, 38.1, 27.0, 24.5, 21.5. UPLC-DAD-QTOF: $C_8H_{13}N_2O_3$ $[M+H]^+$ calcd.: 185.0921, found: 185.0919.

5.3.7.4. **Synthesis of ketone 87.**



81 **87**

MeMgBr (3M in Et_2O, 0.5 mmol, 5 equiv.) was added to a solution of α-hydroxy ketone **81** (107 mg, 0.34 mmol, 1 equiv.) 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 × 15 mL). The solvents were evaporated under reduced pressure and the residue thus obtained was solved in MeOH (1.8 mL). A suspension of sodium periodate $NaIO_4$ (321 mg, 1.5 mmol, 5 equiv.) in water (0.9 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 30 min and solvents were evaporated under reduced pressure. Water (9 mL) was added to the crude product and the resulting mixture was extracted with ethyl acetate (3 × 9 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, affording directly the pure product **87** without the need for further purification. Yield: 74 mg, 0.27 mmol, 79%. $[\alpha]_D^{25}$= +23.1 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.31 – 7.00 (m, 5H), 3.04 (dd, *J* = 44.6, 14.3 Hz, 2H), 2.91 (s, 3H), 2.52 – 2.27 (m, 1H), 2.26 – 2.19 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.3, 174.8, 155.4, 133.7, 129.6, 128.8, 127.7, 70.2, 40.7, 37.3, 30.3, 28.1, 25.1.UPLC-DAD-QTOF: $C_{15}H_{19}N_2O_3$ $[M+H]^+$ calcd.: 275.1390, found: 275.1396.

5.3.8. ^{1}H NMR studies.

^{1}H NMR spectra of each of the following compounds in $CDCl_3$ at –10 °C (0.02 M) were recorded: (i) nitrostyrene **2a**, (ii) 1*H*-imidazol-4(5*H*)-one **27A** and (iii) catalyst **C7**. Sub-sequently, ^{1}H NMR spectra of the following mixtures were recorded under the same conditions (0.02 M in $CDCl_3$ at –10 °C): (iv) **C7**/**27A** (1:1 mixture), (v) **C7**/**2a** (1:1 mixture), and (vi) **C7**/**2a** (1:1 mixture) + 1 equivalent **27A**. The aromatic portion of the spectra (i) to (vi) are depicted below. Note the downfield shift of proton H_A of catalyst **C7** upon addition of imidazolone **27A**, regardless of the presence (vi) or absence (iv) of nitrostyrene.

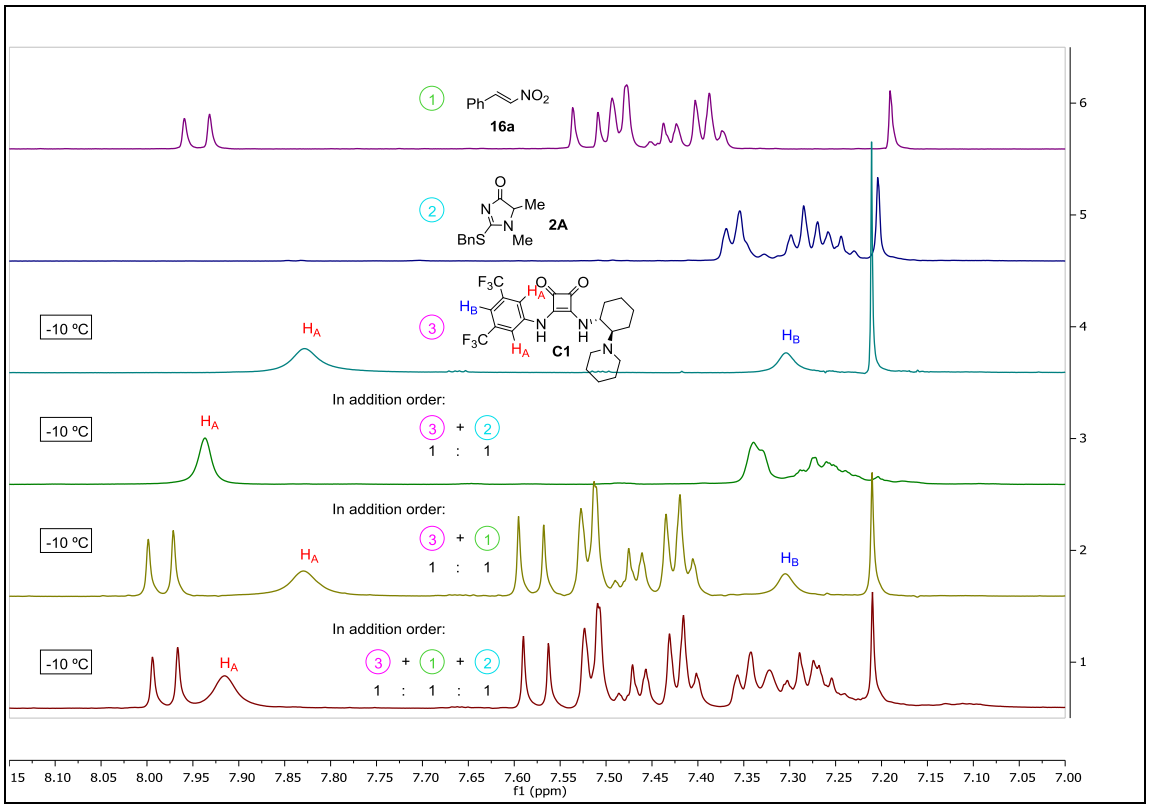
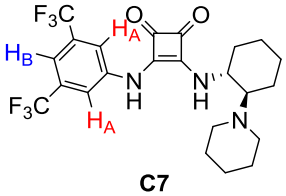
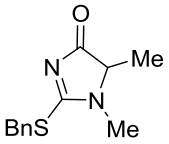


Figure 44. 1H NMR spectra (aromatic portion) of pure samples of compounds **C7**, **27A** and **2a** (0.02 M in CDCl3 at –10 °C) and some of their mixtures.

In an independent study, the ^{1}H NMR spectra of catalyst **C7** (0.02 M in $CDCl_3$ at –10 °C) were recorded in the presence of increasing amounts of 1*H*-imidazol-4(5*H*)-one **27A** (increments of 0.25 equivalent until saturation), and the chemical shift of the aromatic ortho protons H_A was monitored.



C7



27A

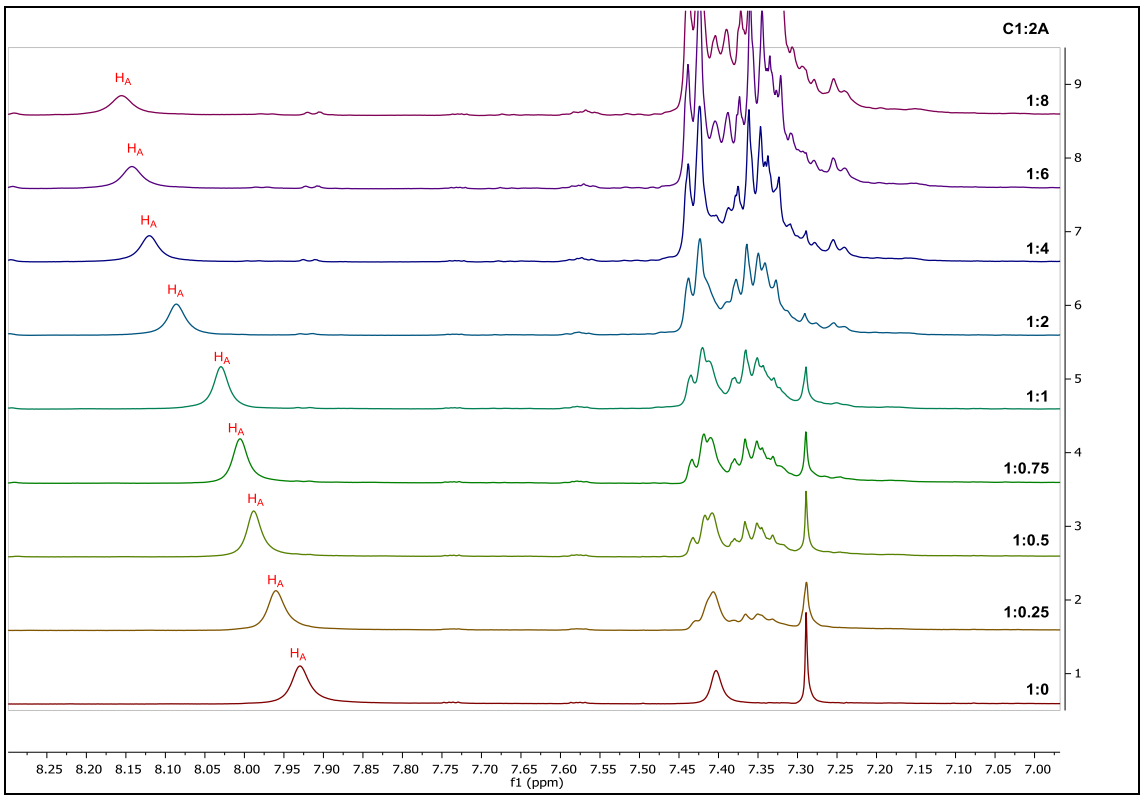
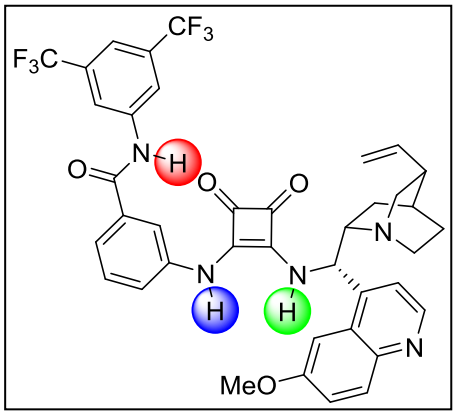
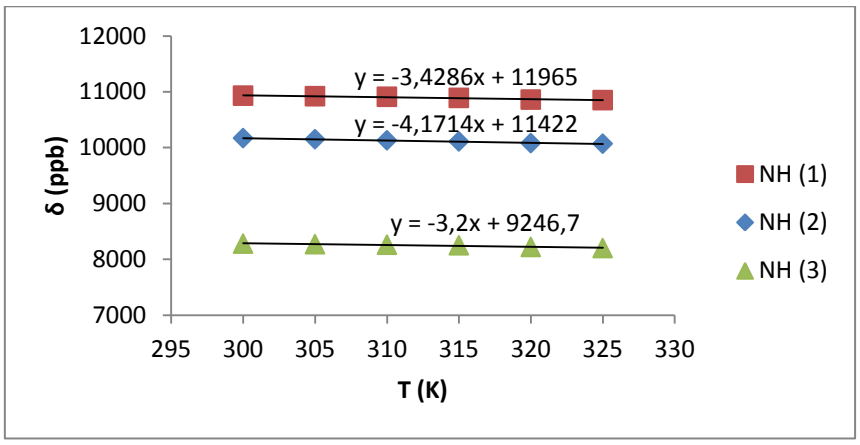


Figure 45. ^{1}H NMR spectra (aromatic portion) of **C7** (0.02 M) in the presence of vari-able amounts (from none to 8 equivalents) of **27A** (recorded in $CDCl_3$ at –10 °C).

A study was performed measuring the temperature gradient of the NH protons of catalyst **C9** (0.02 M in $CDCl_3$) Measurement were made from 300 to 330 K, calculating their thermal coefficient in 10 K intervals. Values closer to $\Delta\delta/\Delta T(H^N) = -2.0$ are indicative of intramolecular H bond. Values above $\Delta\delta/\Delta T(H^N) = -4.0$ indicate that no H bond is occurring.[391] The values obtained for **C9** indicate that there is a weak H bond, although not strong enough to be intramolecular.

	δ (ppb)		
T (K)	**NH (1)**	**NH (2)**	**NH (3)**
300	10930	10170	8280
305	10920	10150	8270
310	10910	10130	8260
315	10890	10110	8250
320	10860	10080	8220
325	10850	10070	8200

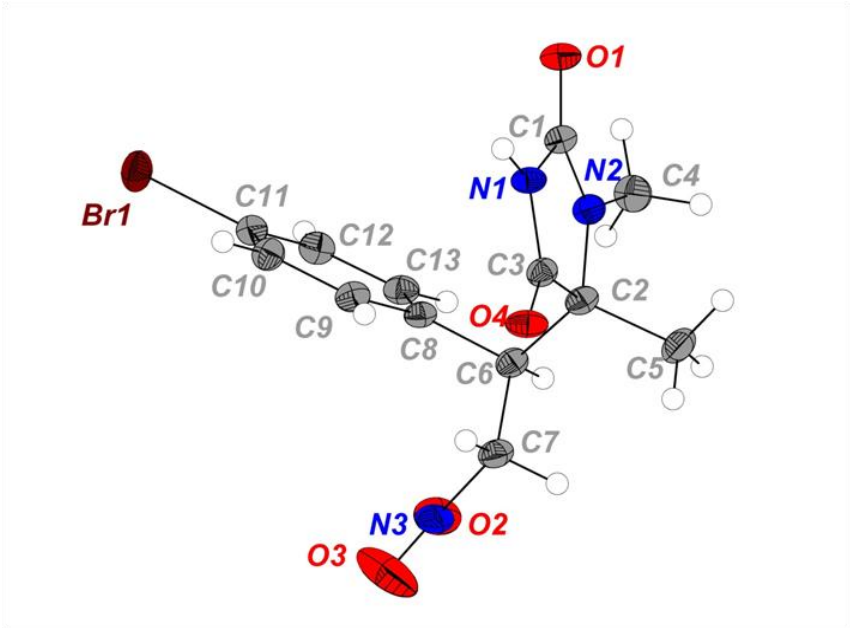


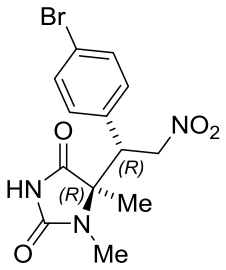


[391] Kessler

5.3.9. **X-Ray Analysis: ORTEP diagrams of compounds 62 and 84.**

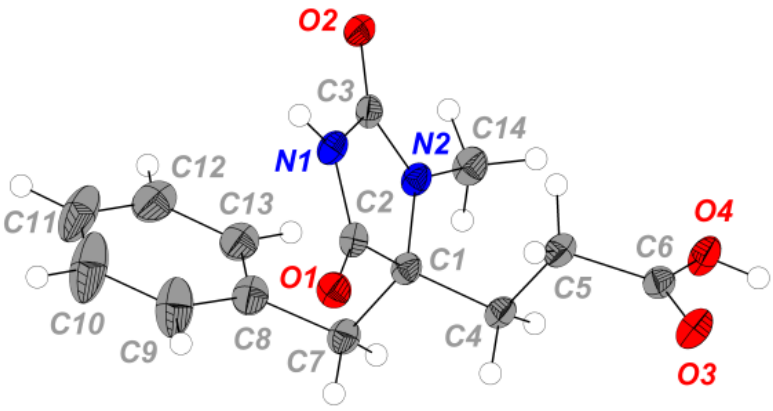
CCDC-1044978 contains the supplementary crystallographic data for the structural analysis of **62**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

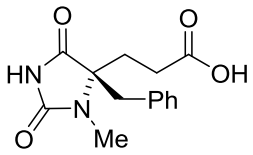




62

CCDC-1044937 contains the supplementary crystallographic data for the structural analysis of **84**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

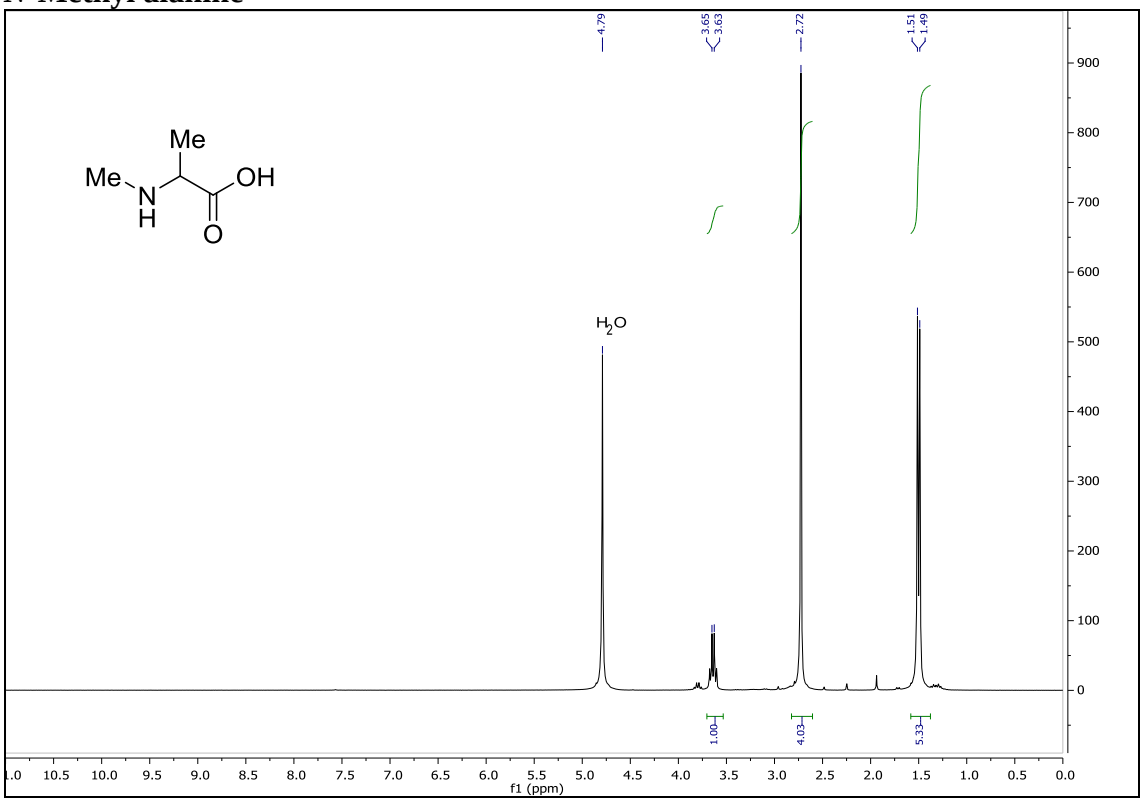




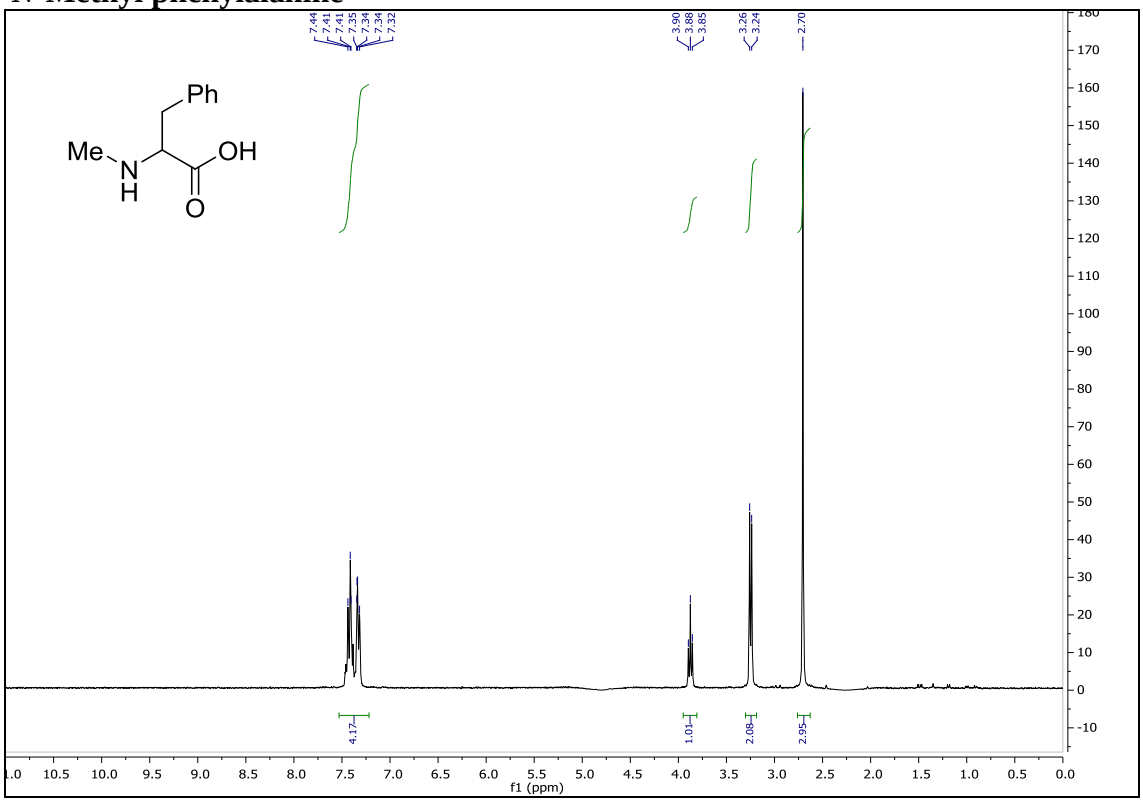
84

5.3.10. Representative NMR spectra

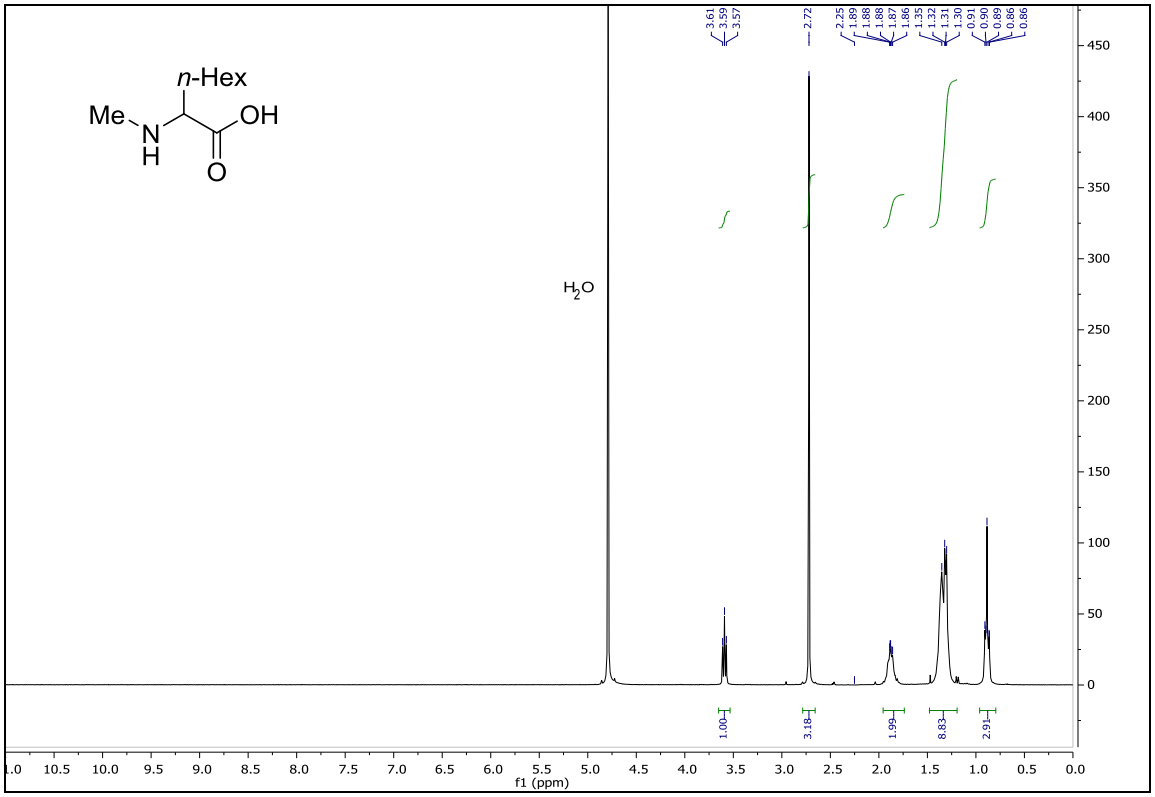
N-Methyl alanine



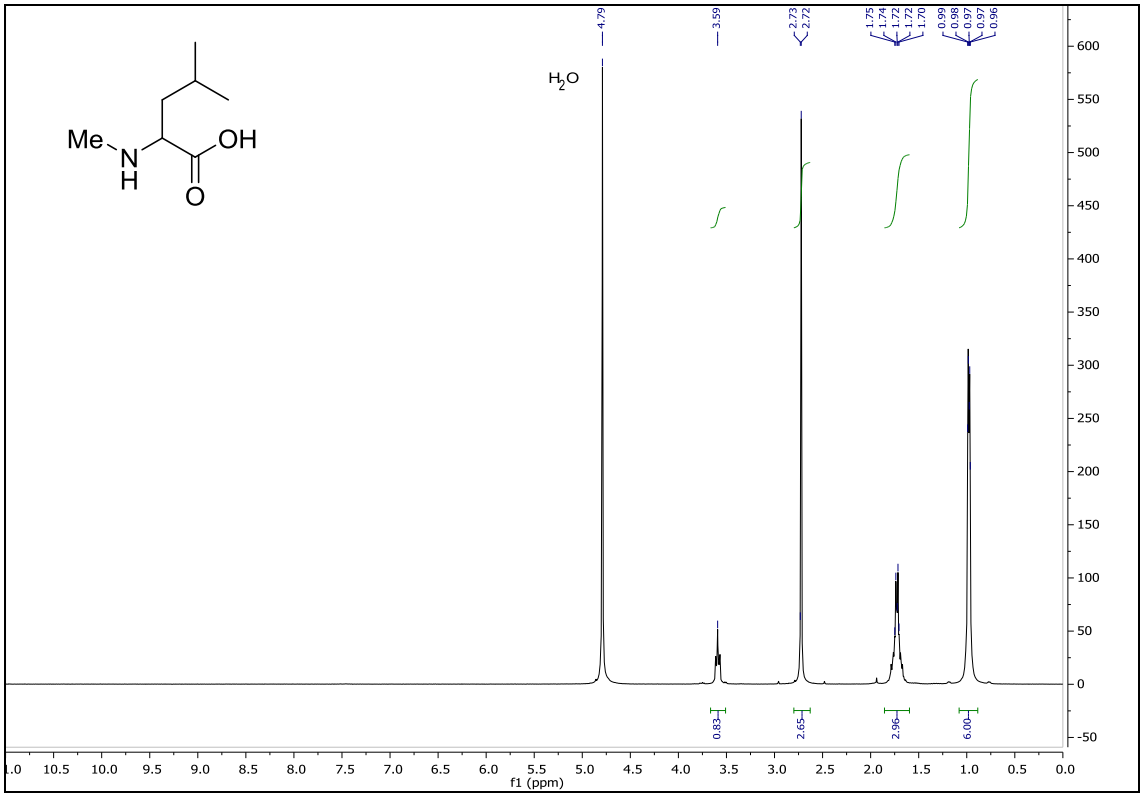
N-Methyl phenylalanine



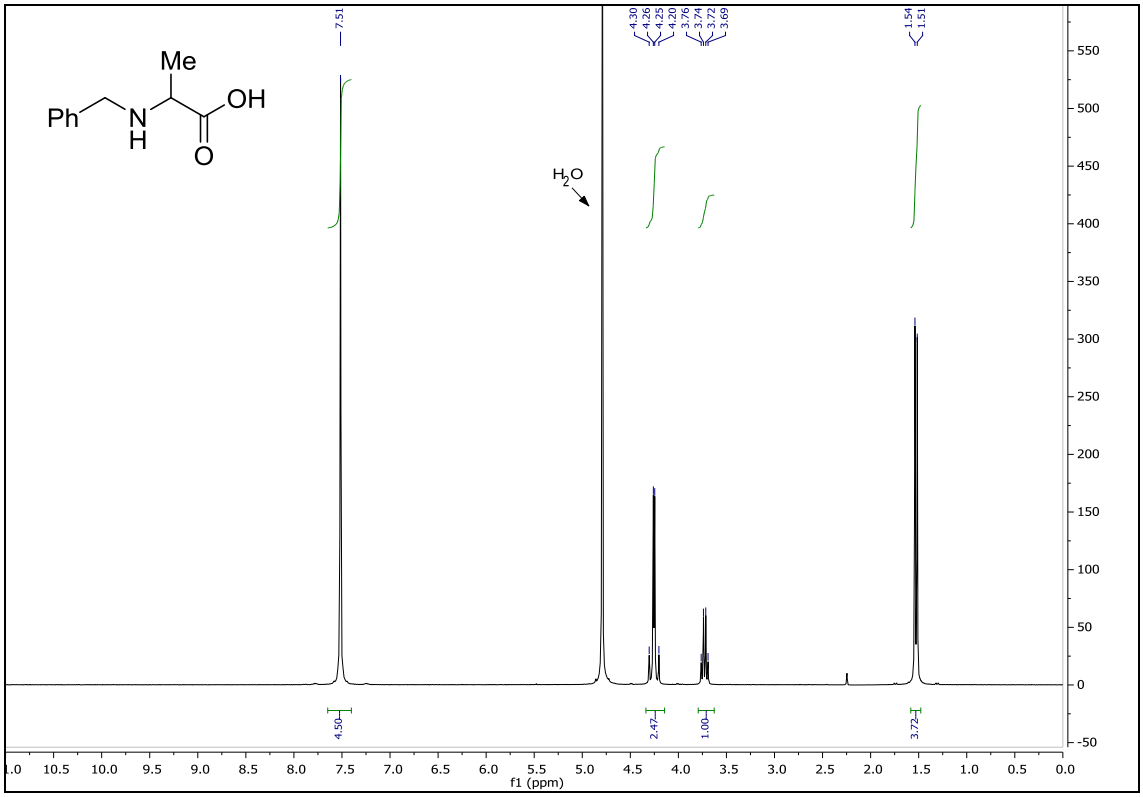
2-(Methylamino)octanoic acid



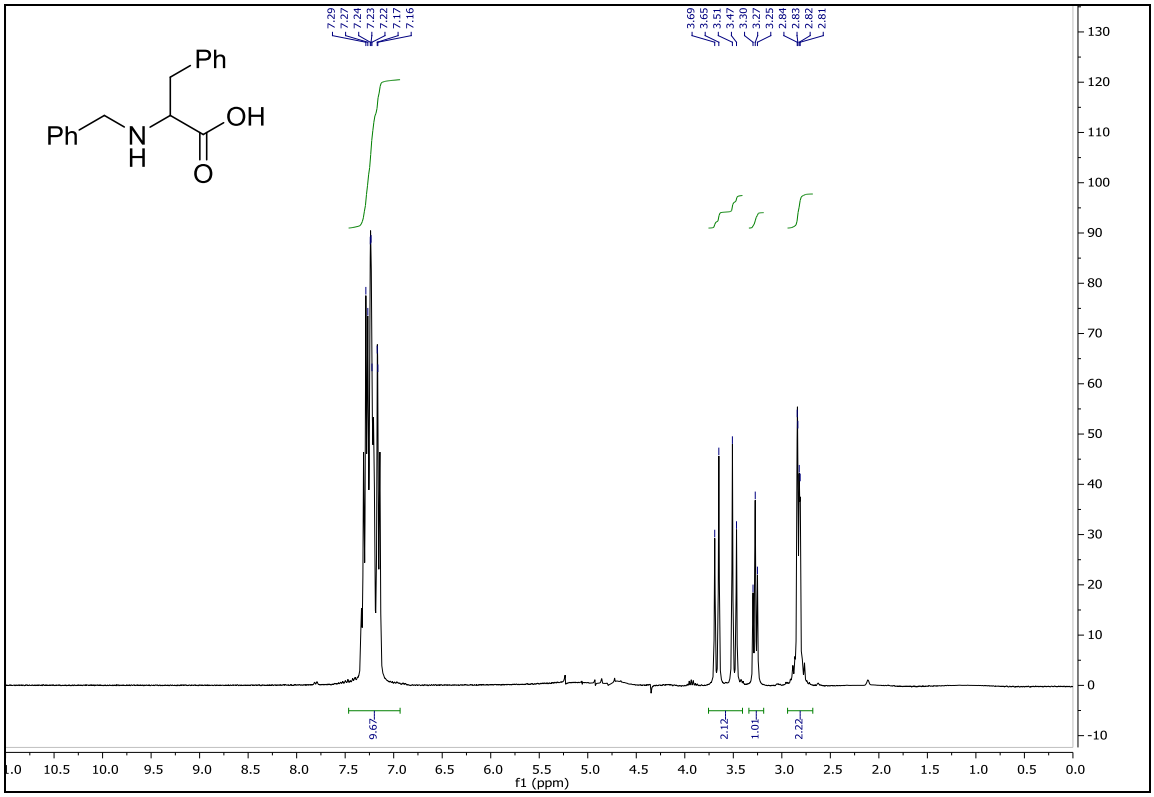
N-Methyl leucine



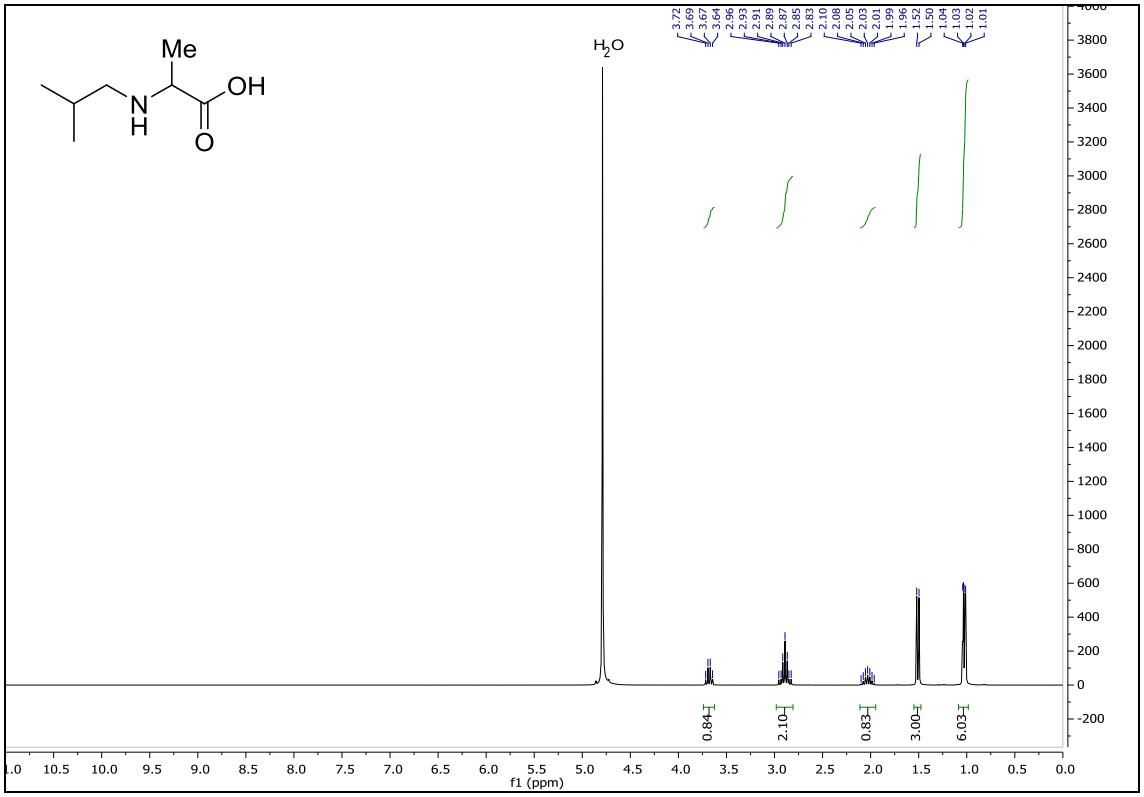
N-Benzyl alanine



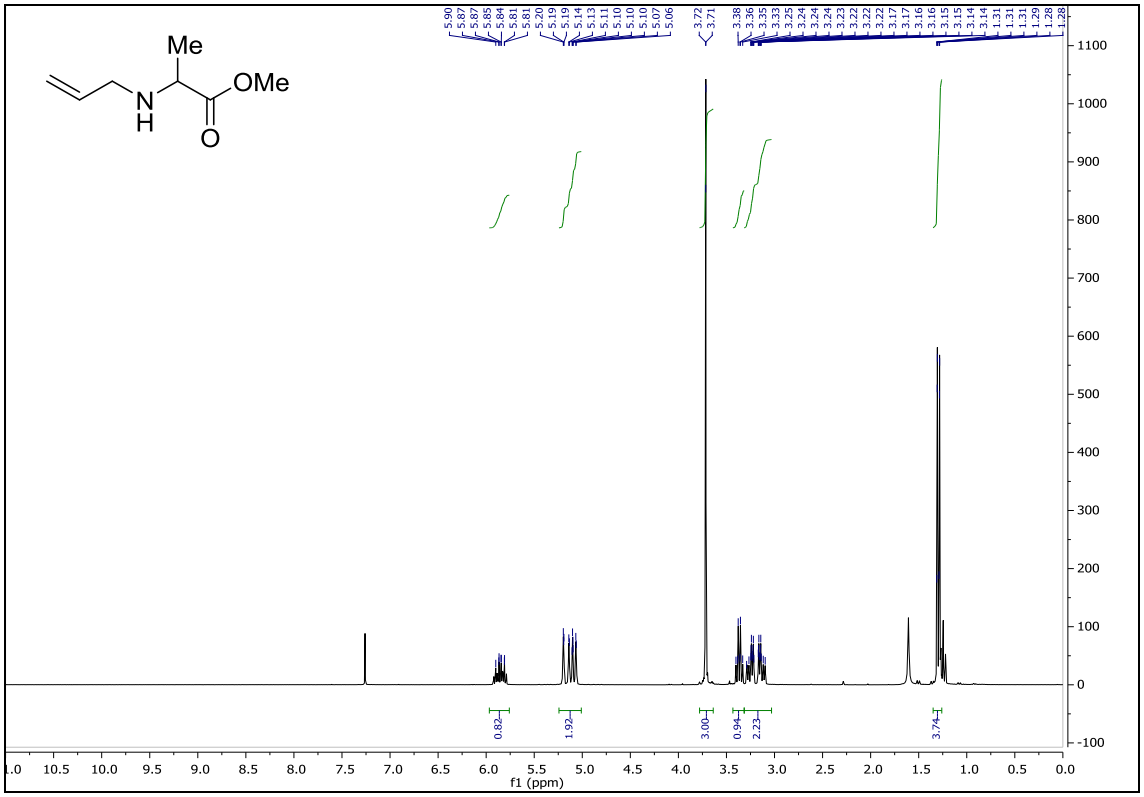
N-Benzyl phenylalanine



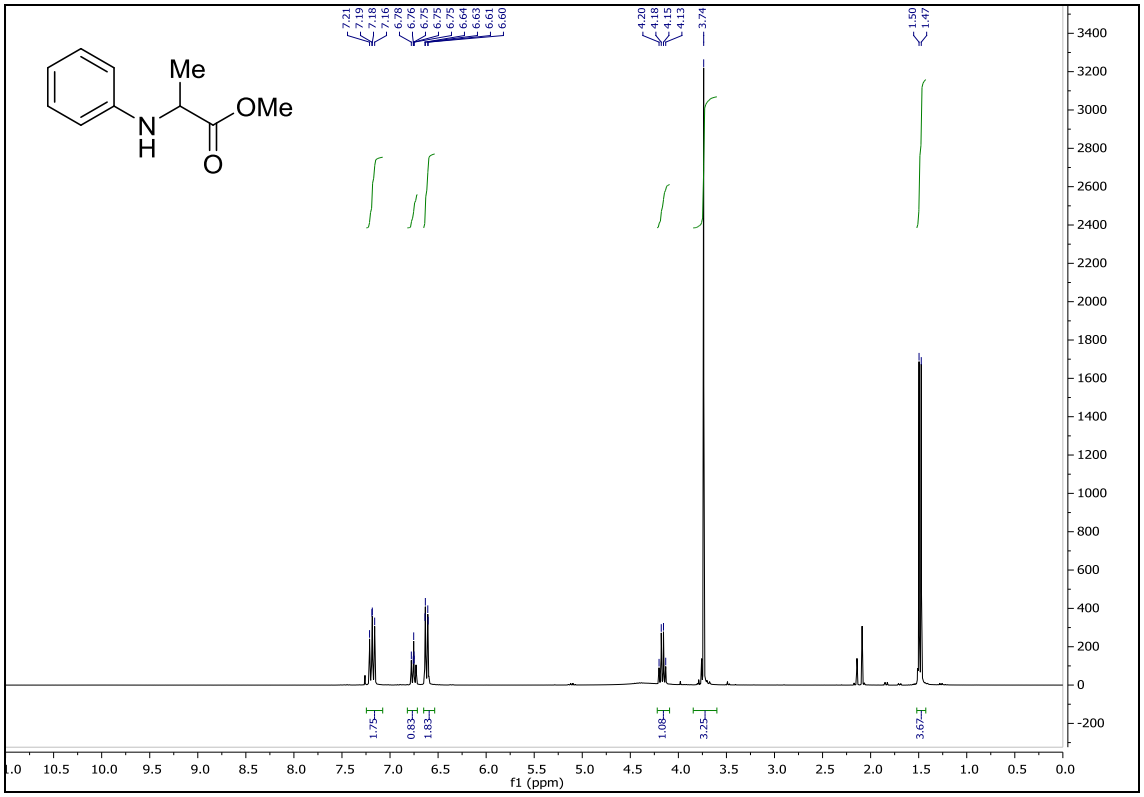
Isobutylalanine



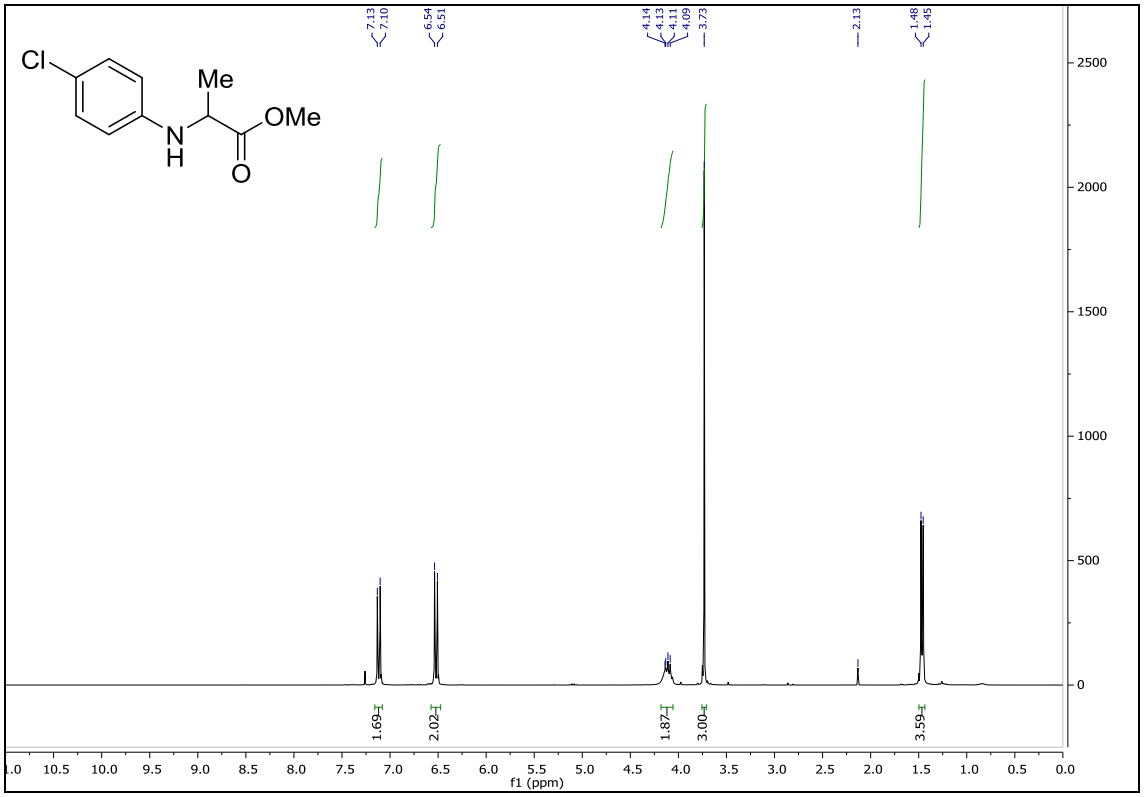
Methyl *N*-allyl alaninate



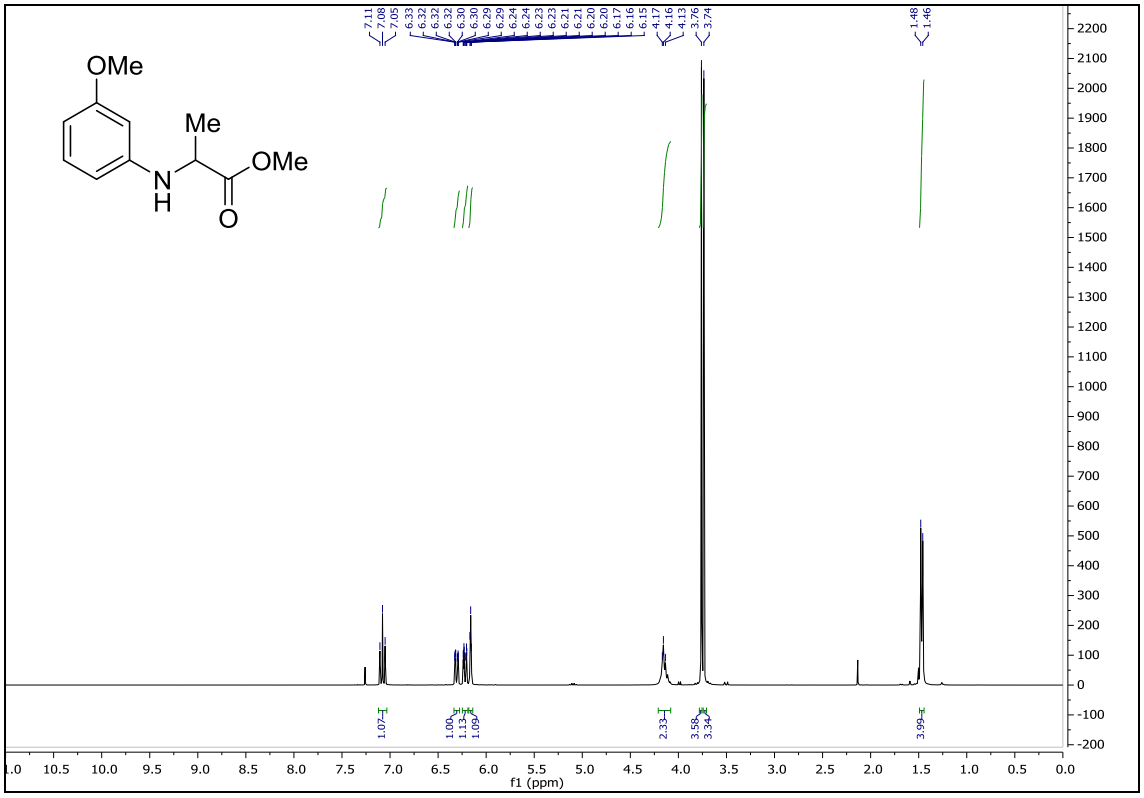
Methyl *N*-phenyl alaninate



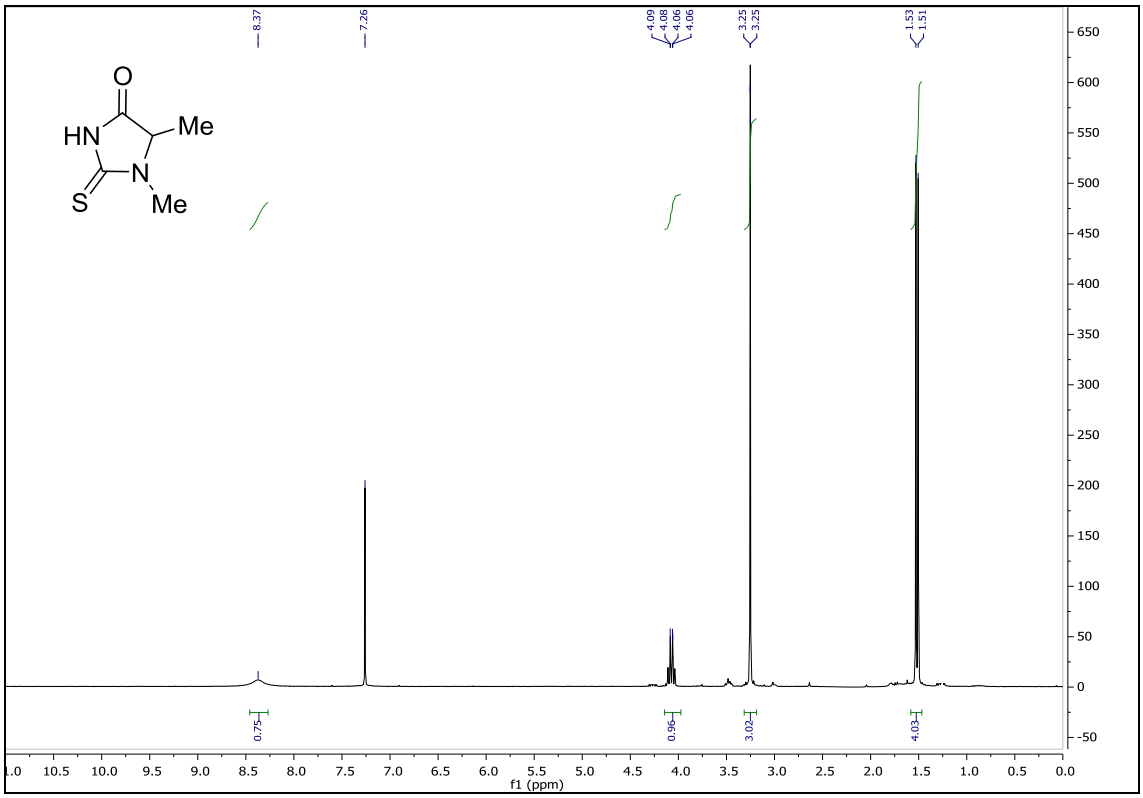
Methyl (4-chlorophenyl)alaninate

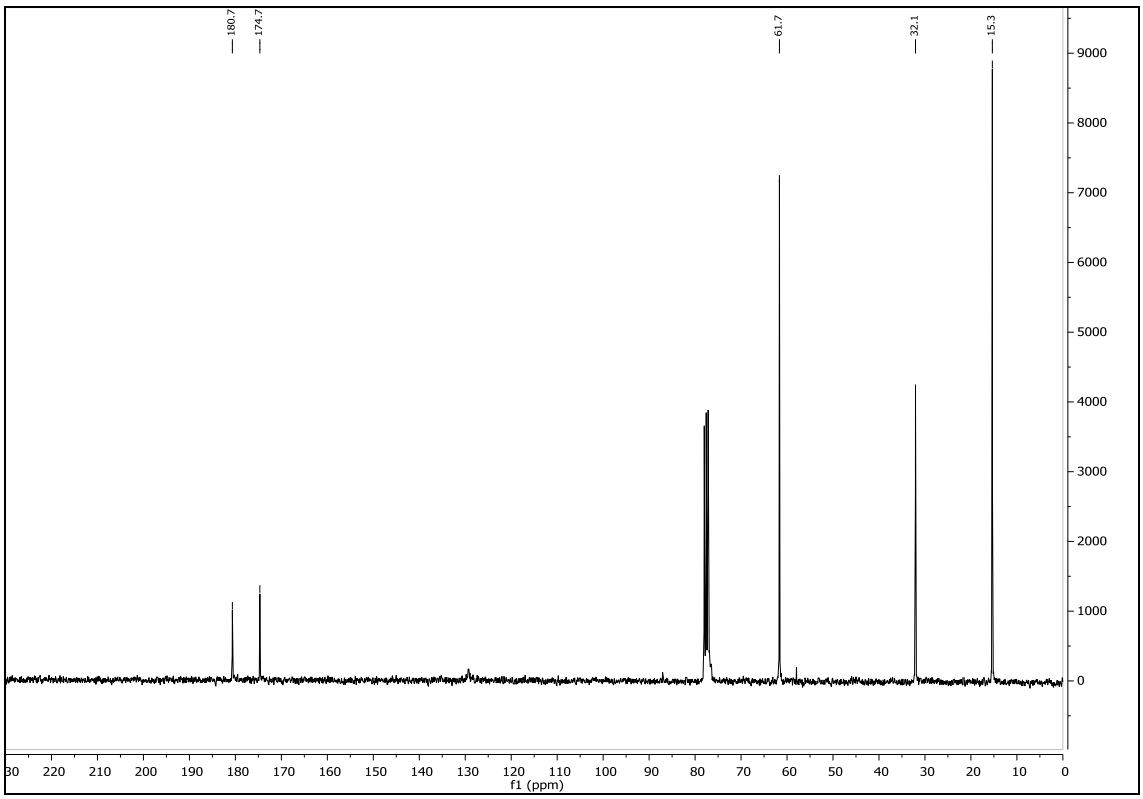


Methyl (3-methoxyphenyl)alaninate

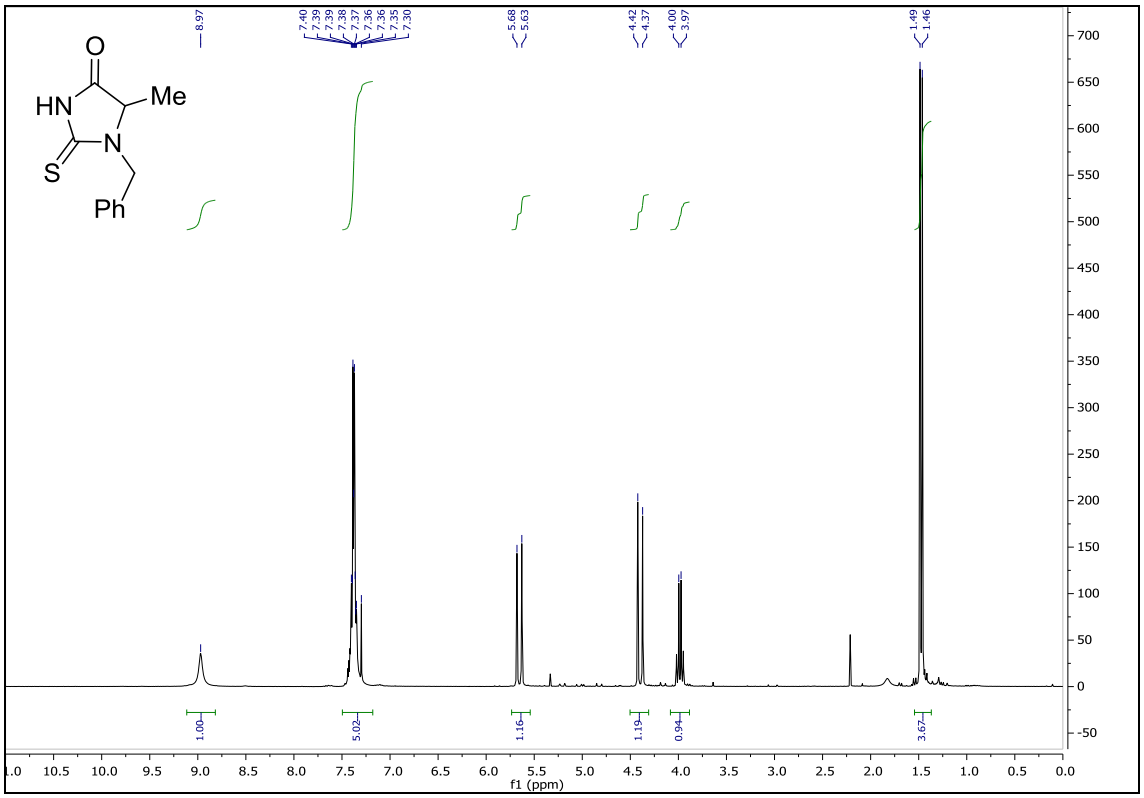


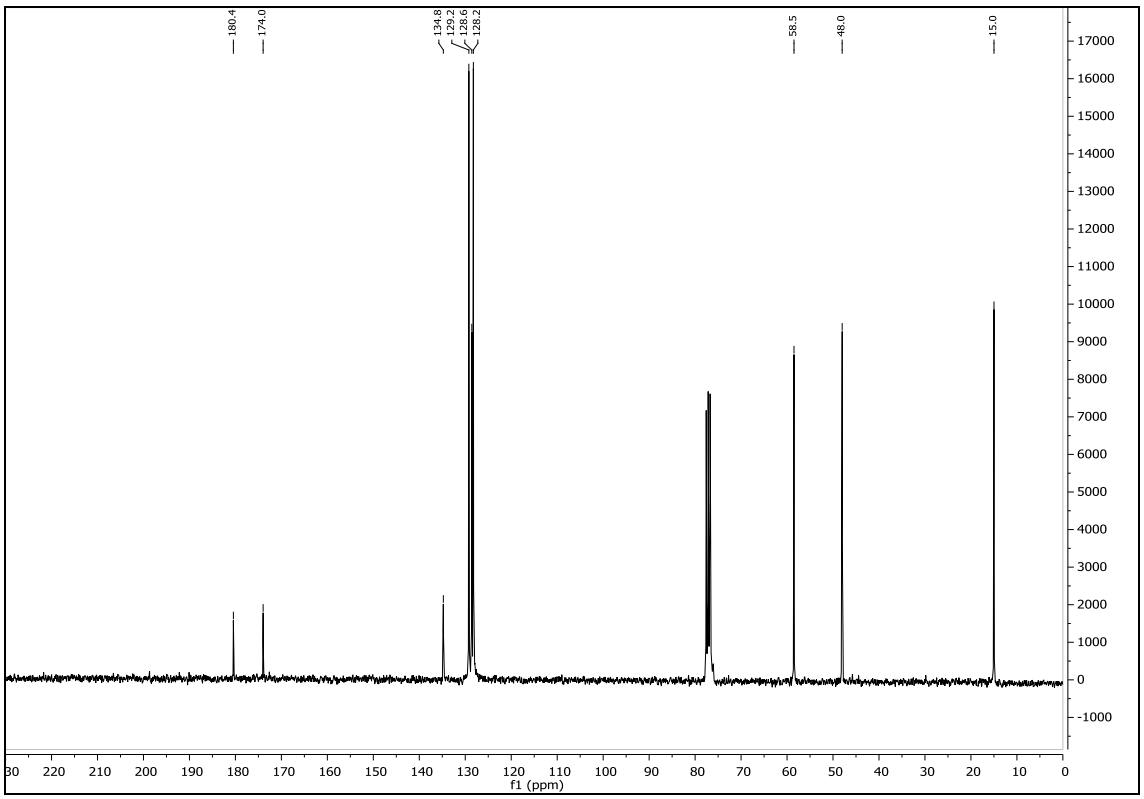
1,5-Dimethyl-2-thioxoimidazolidin-4-one



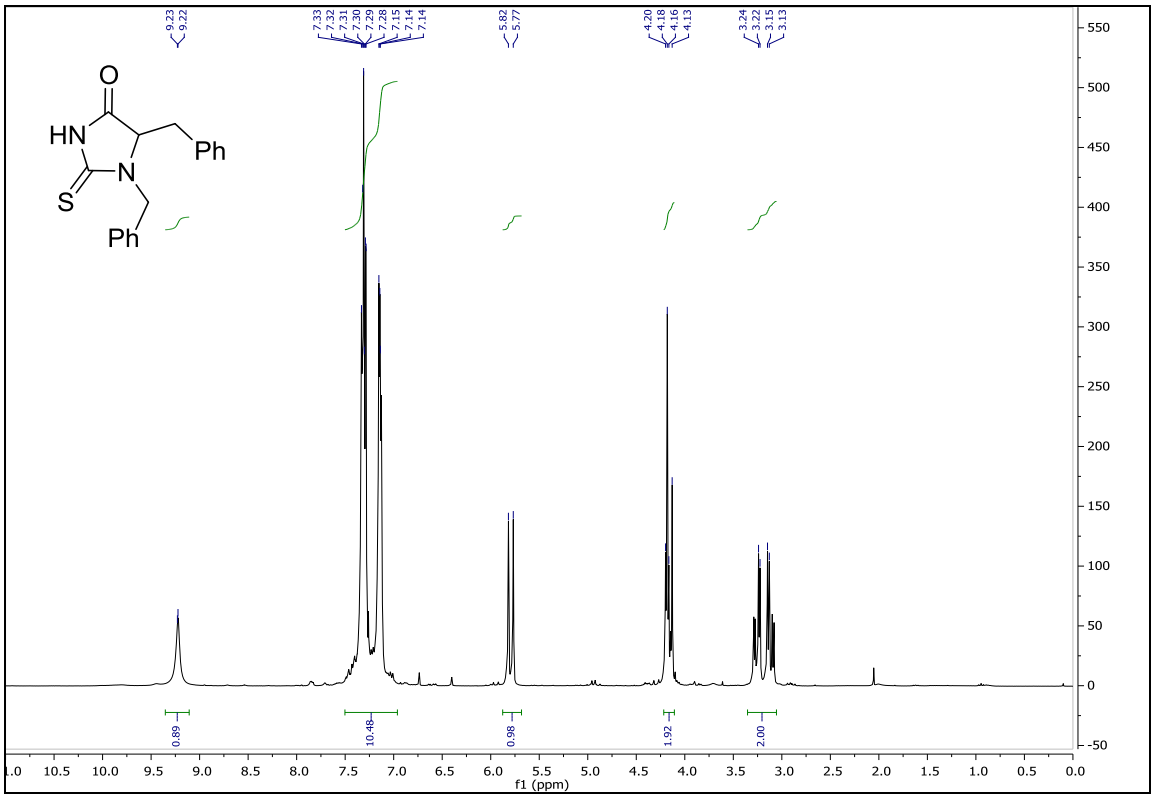


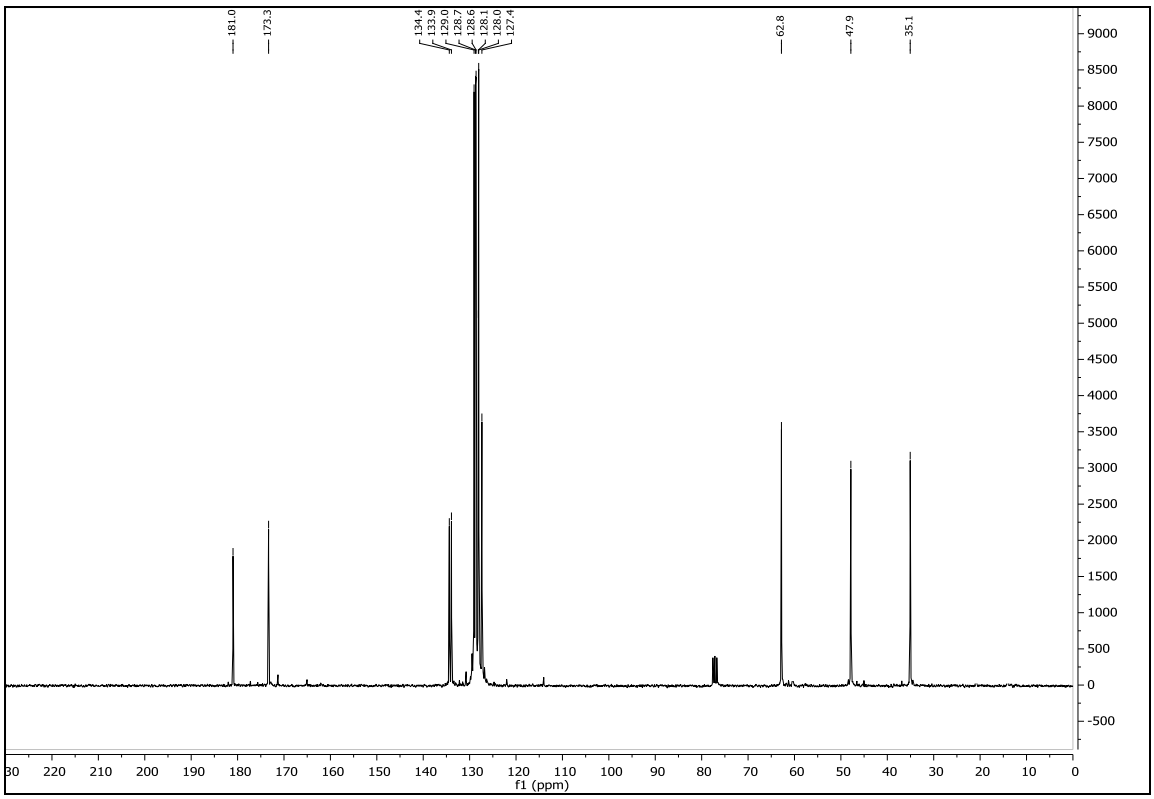
1-Benzyl-5-methyl-2-thioxoimidazolidin-4-one



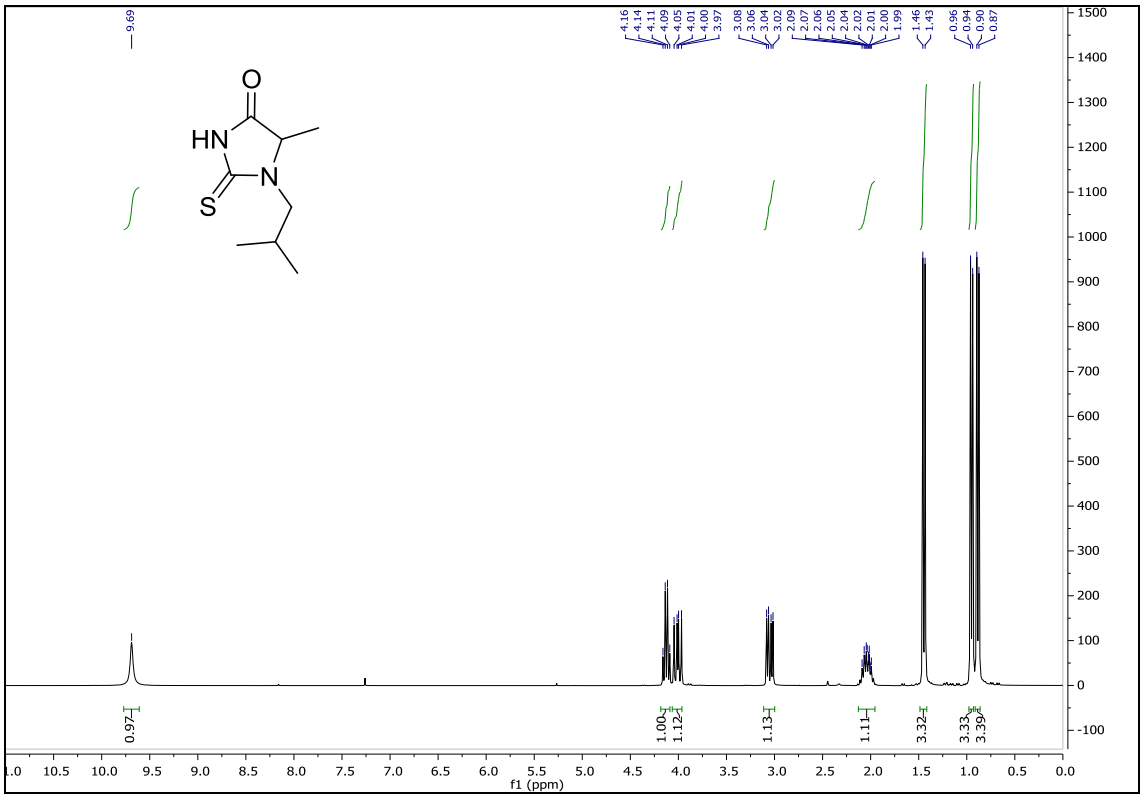


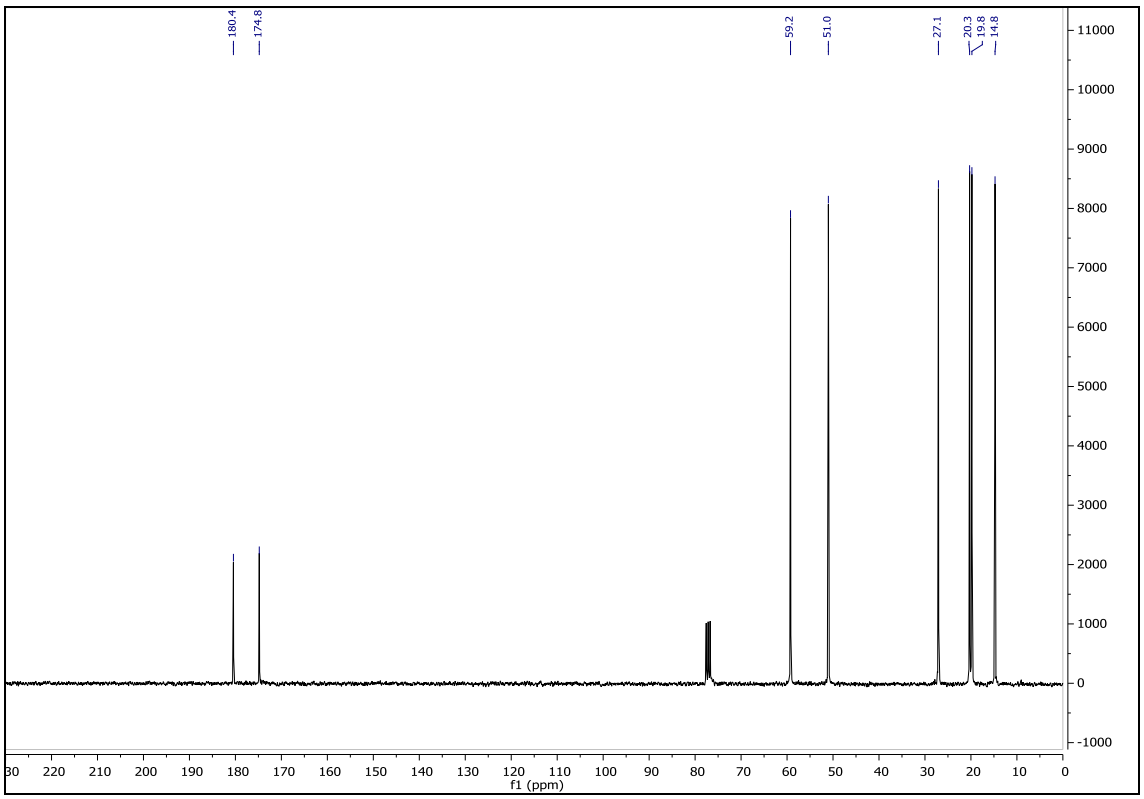
1,5-Dibenzyl-2-thioxoimidazolidin-4-one



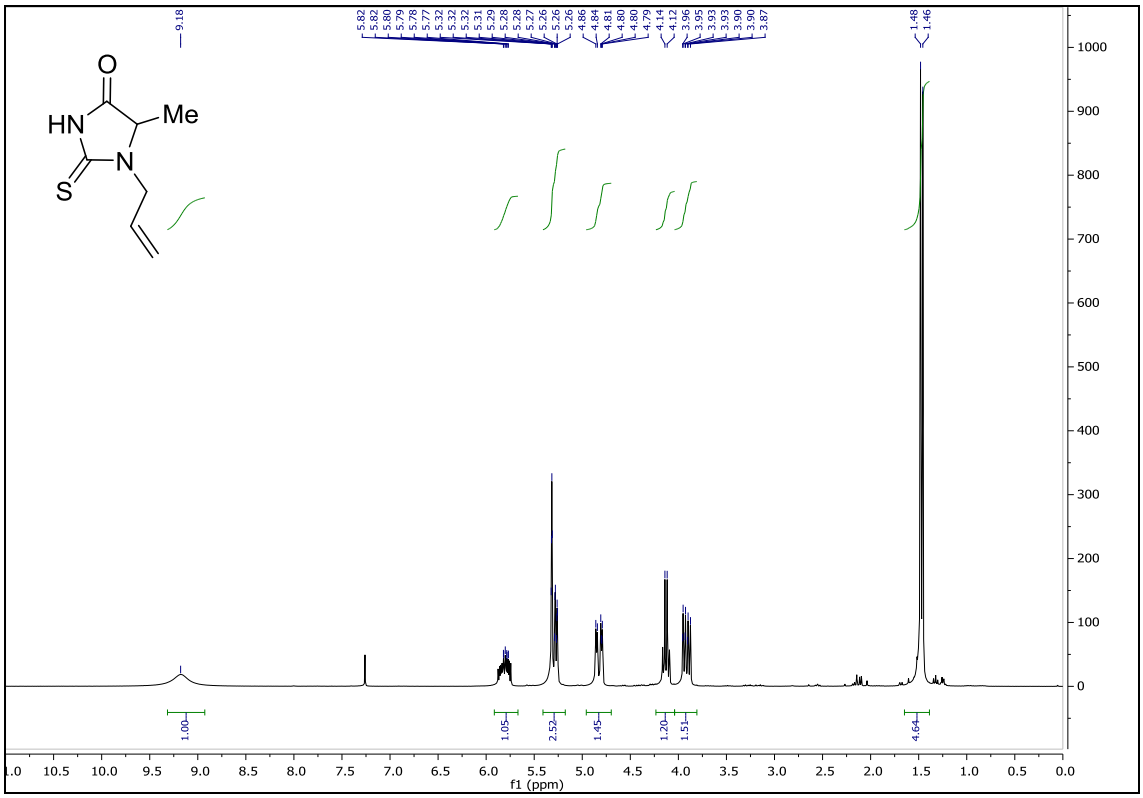


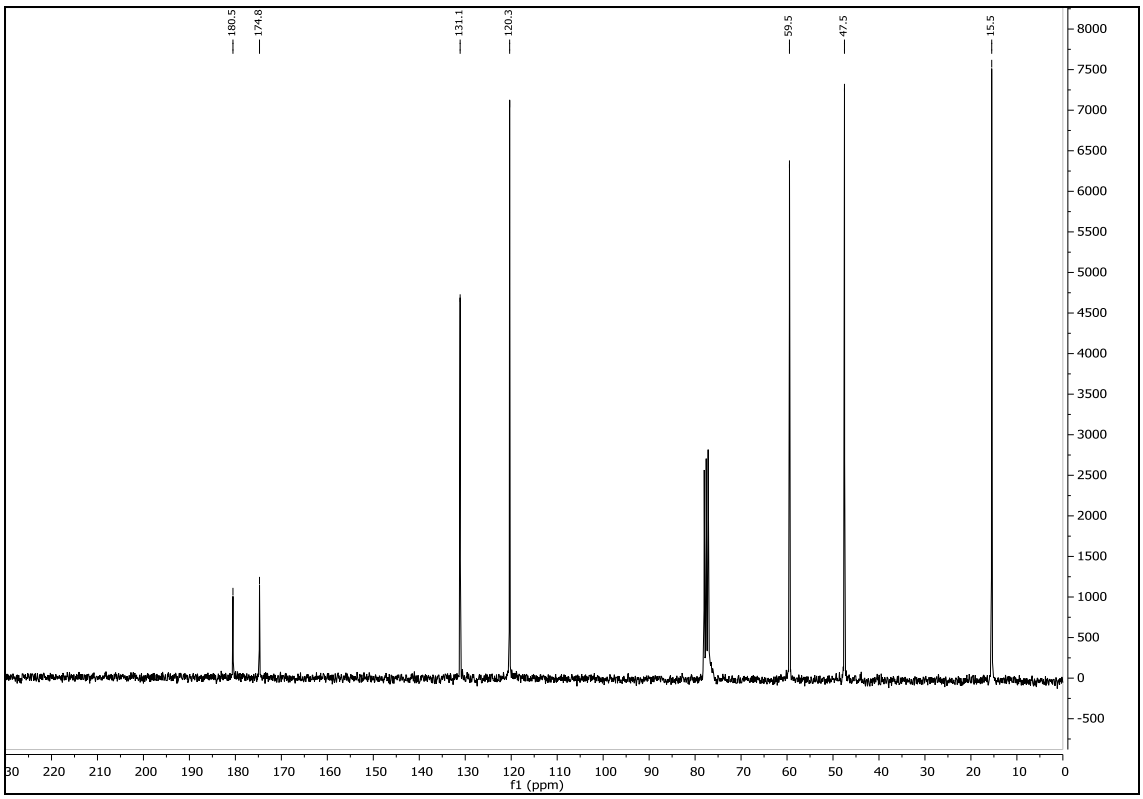
1-Isobutyl-5-methyl-2-thioxoimidazolidin-4-one



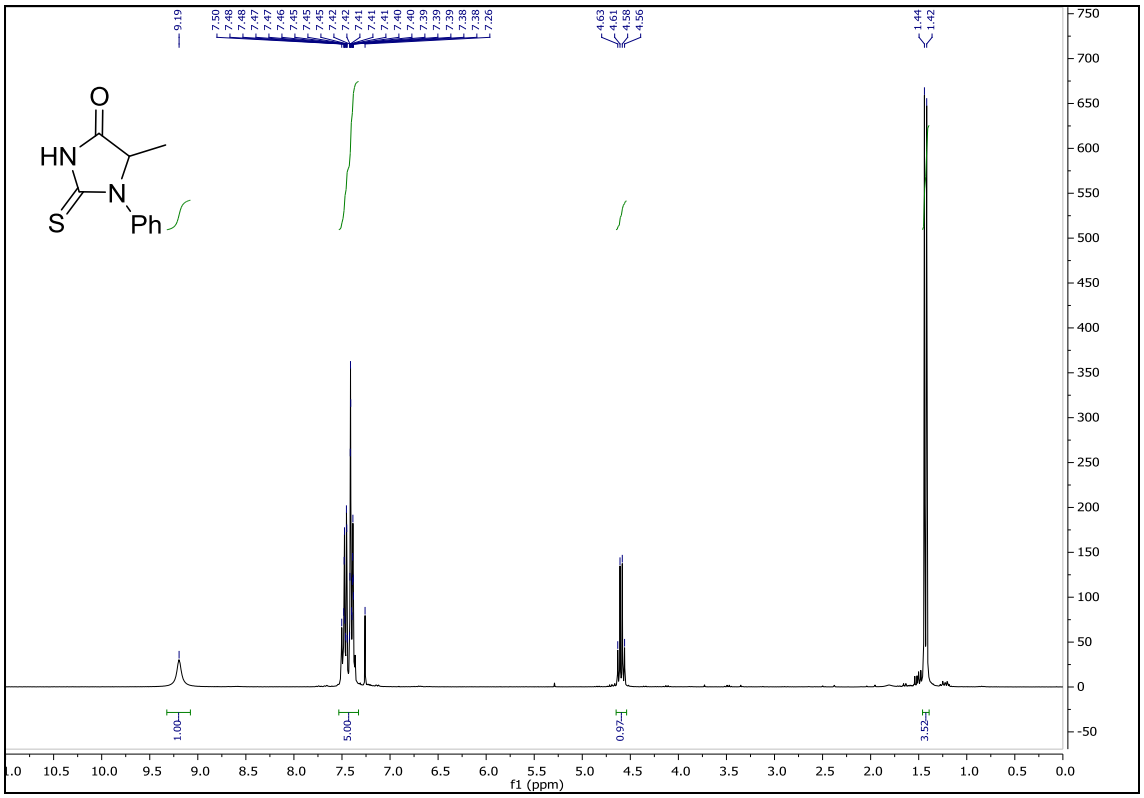


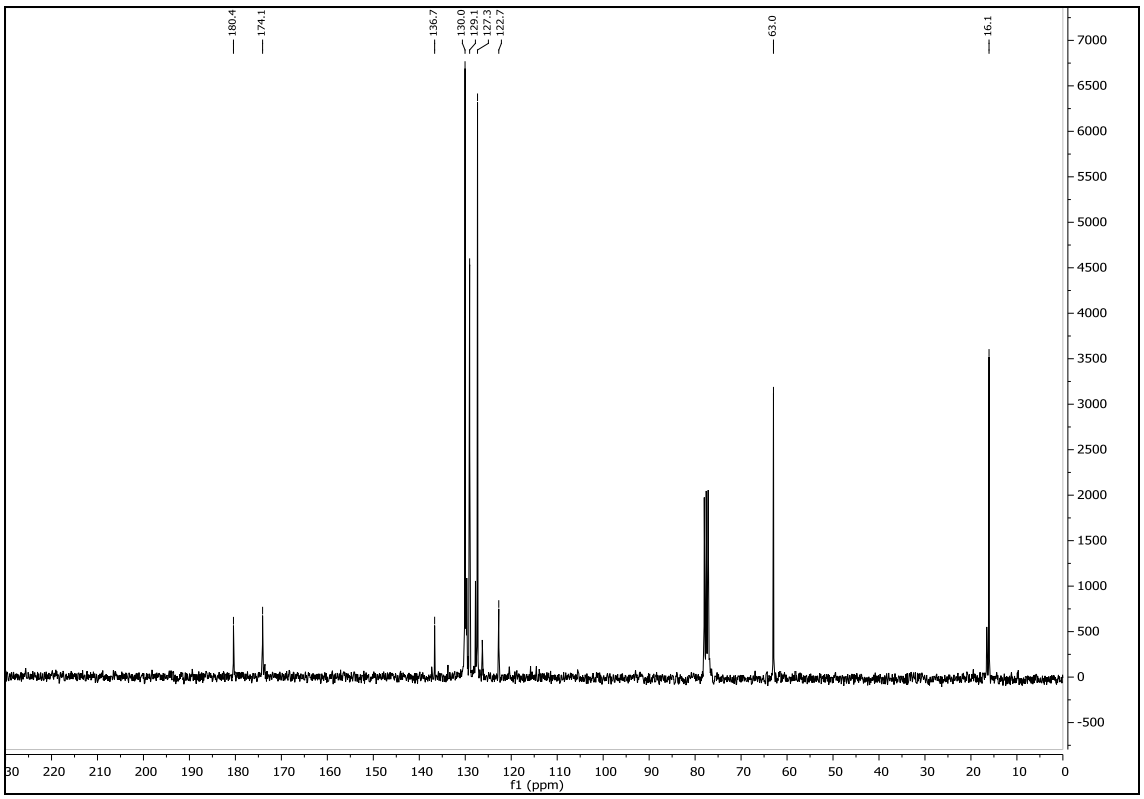
1-Allyl-5-methyl-2-thioxoimidazolidin-4-one



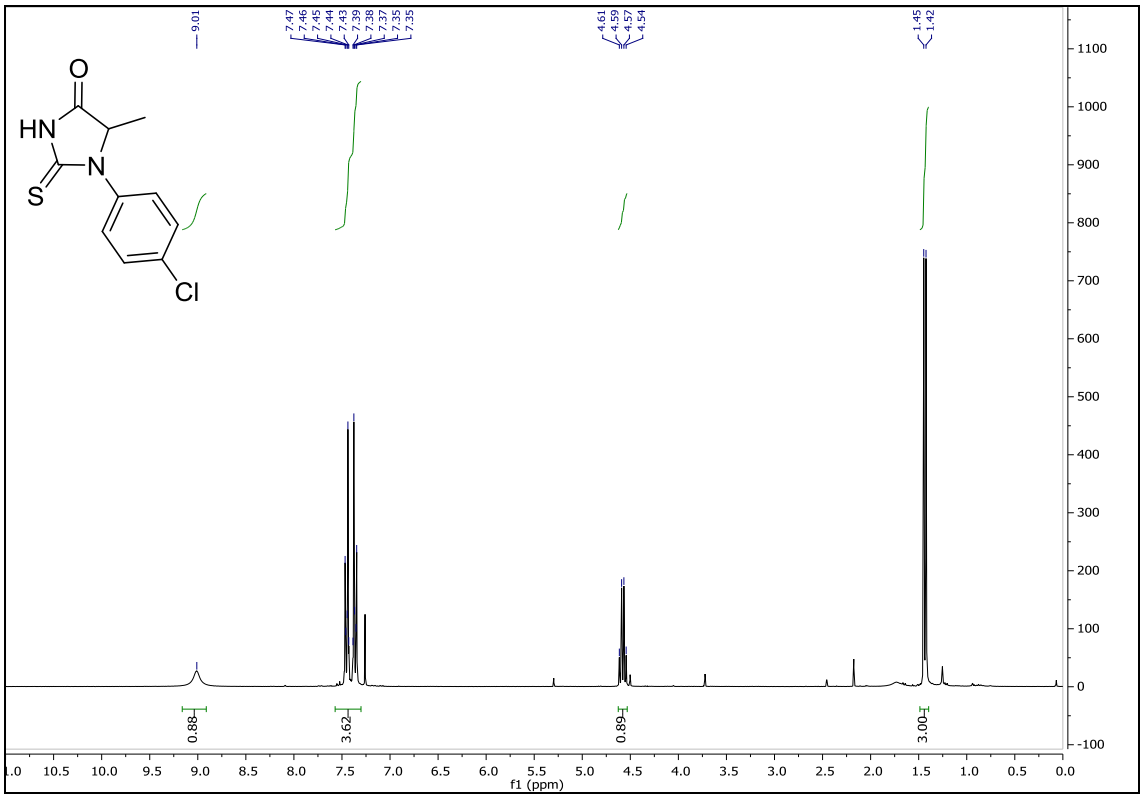


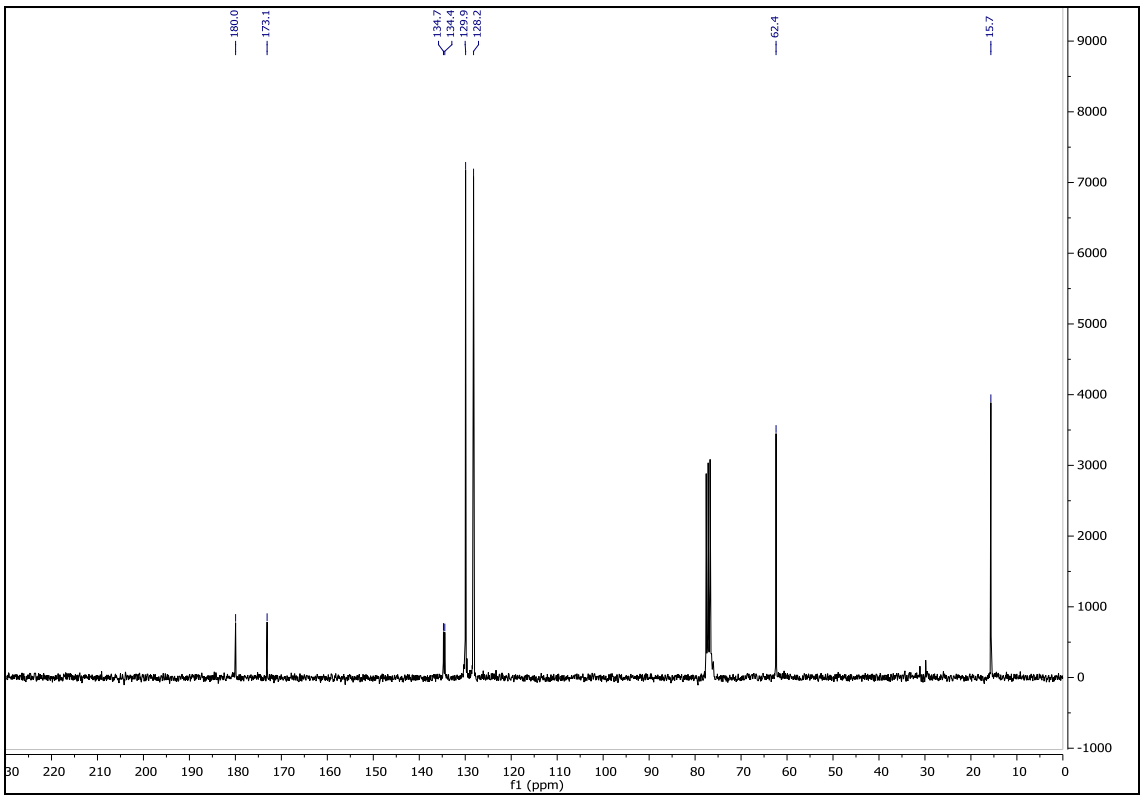
5-Methyl-1-phenyl-2-thioxoimidazolidin-4-one



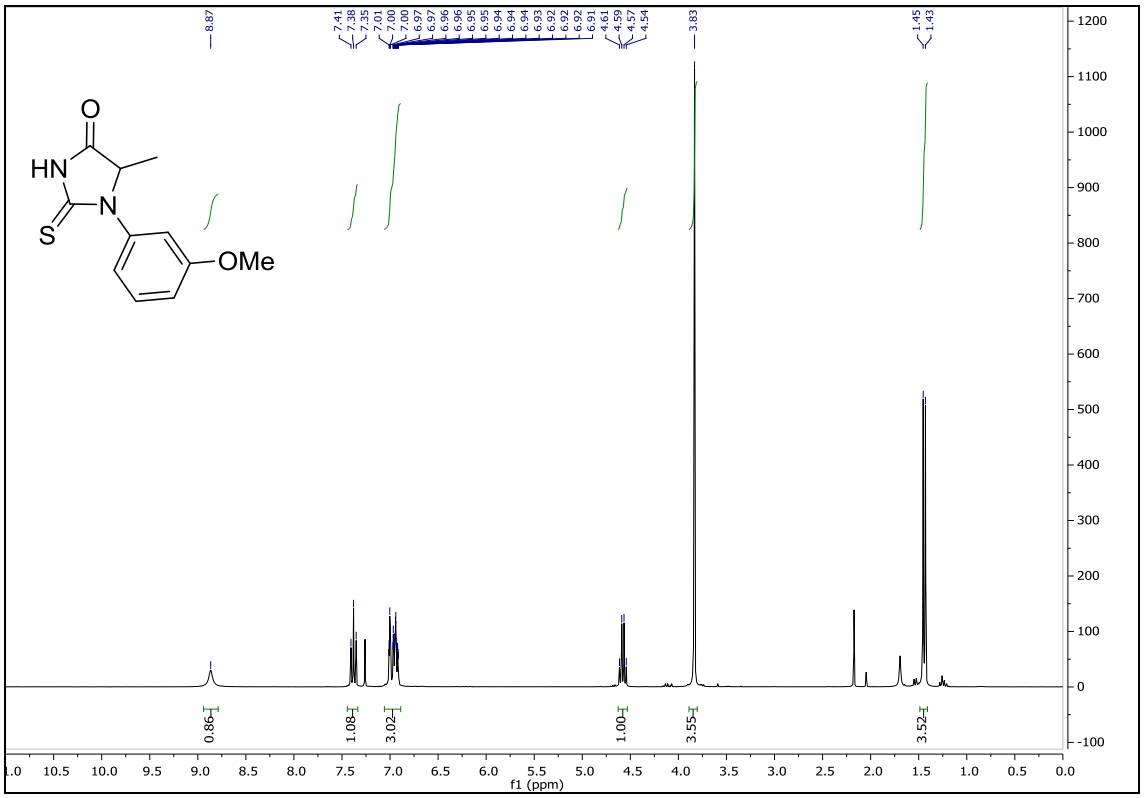


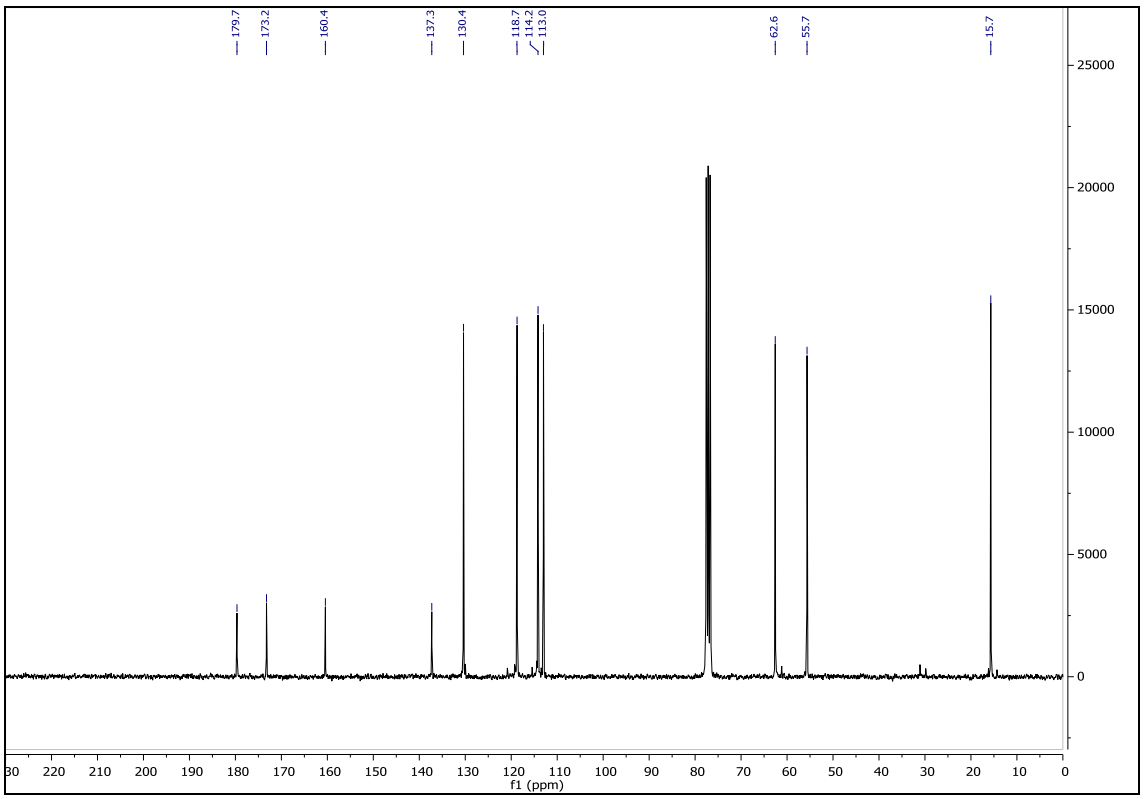
1-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one



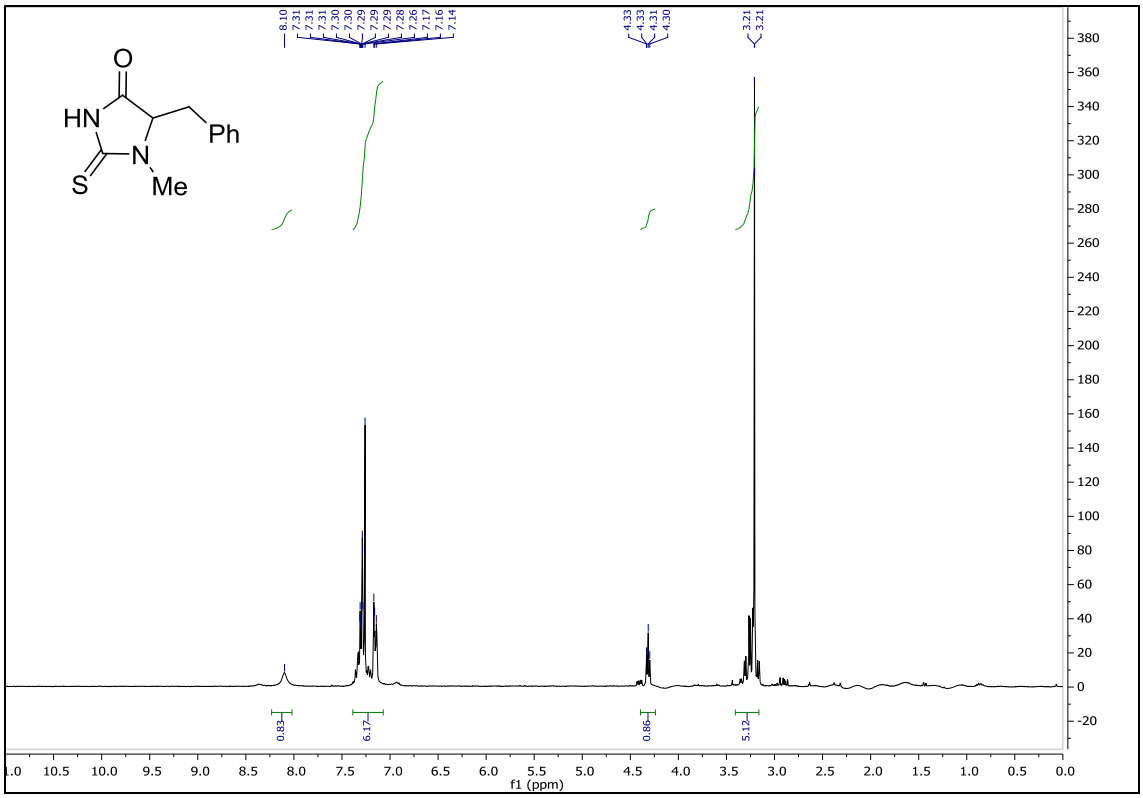


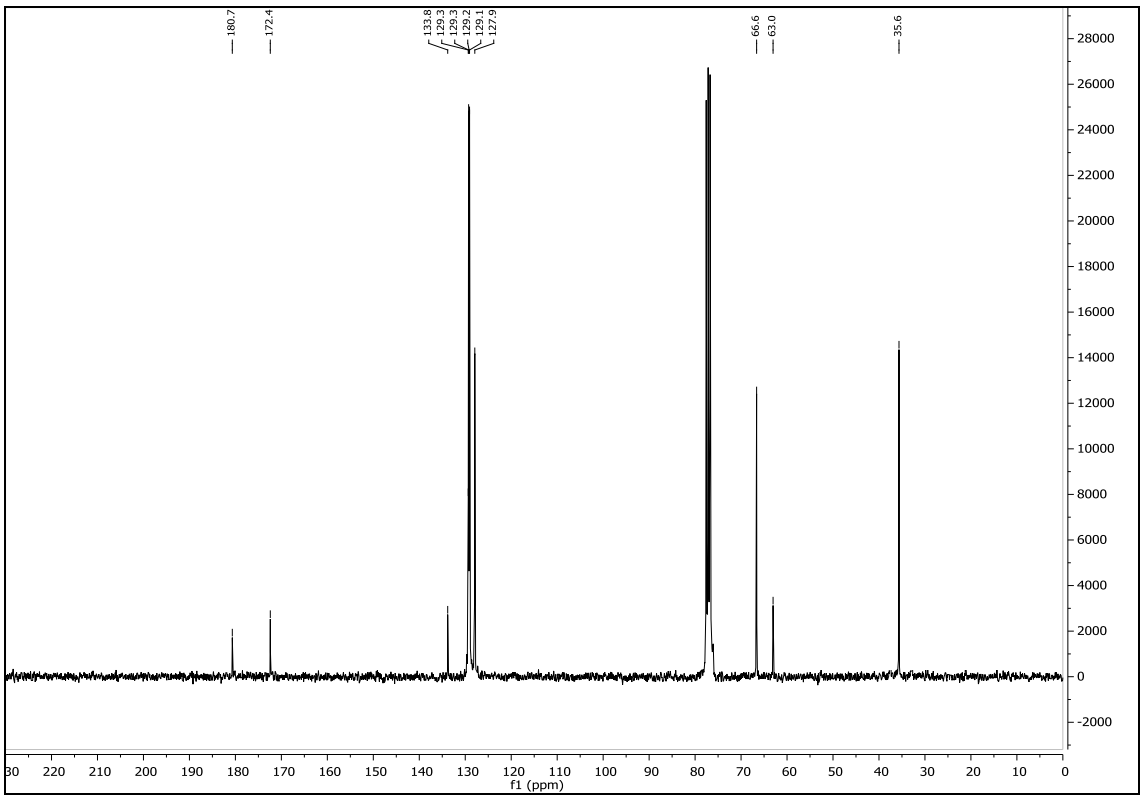
1-(3-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one



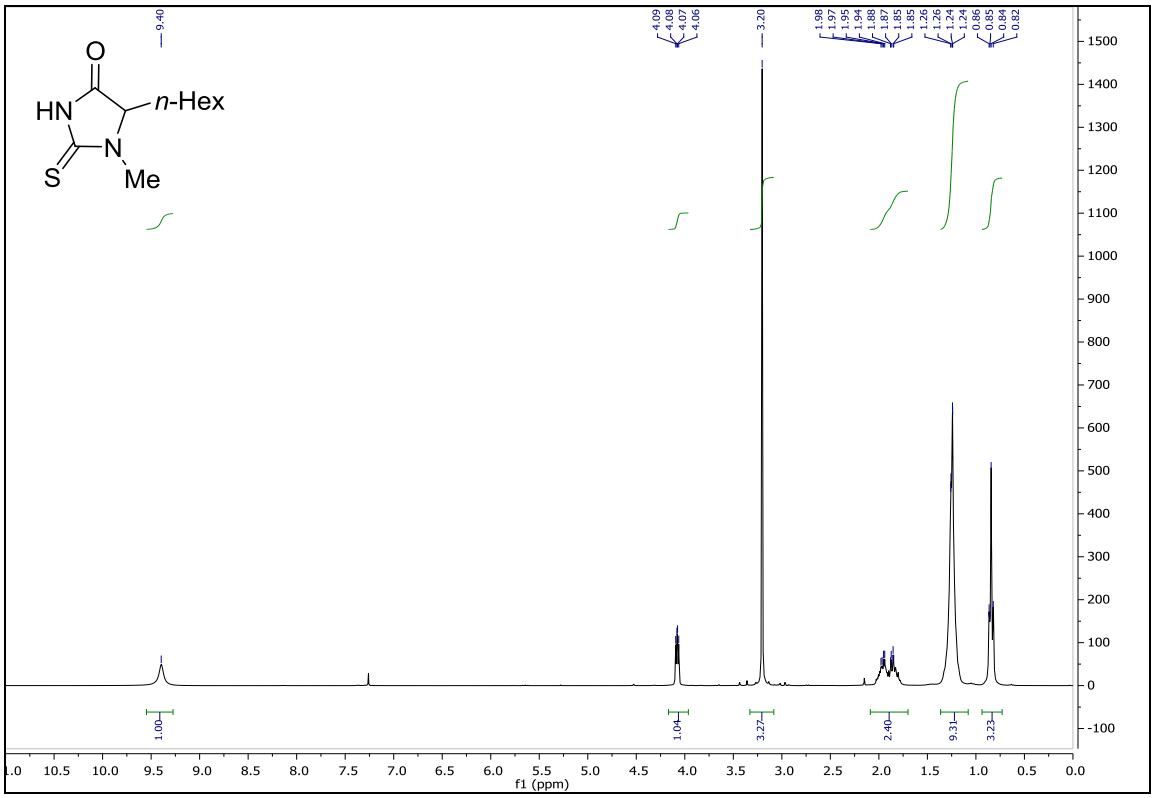


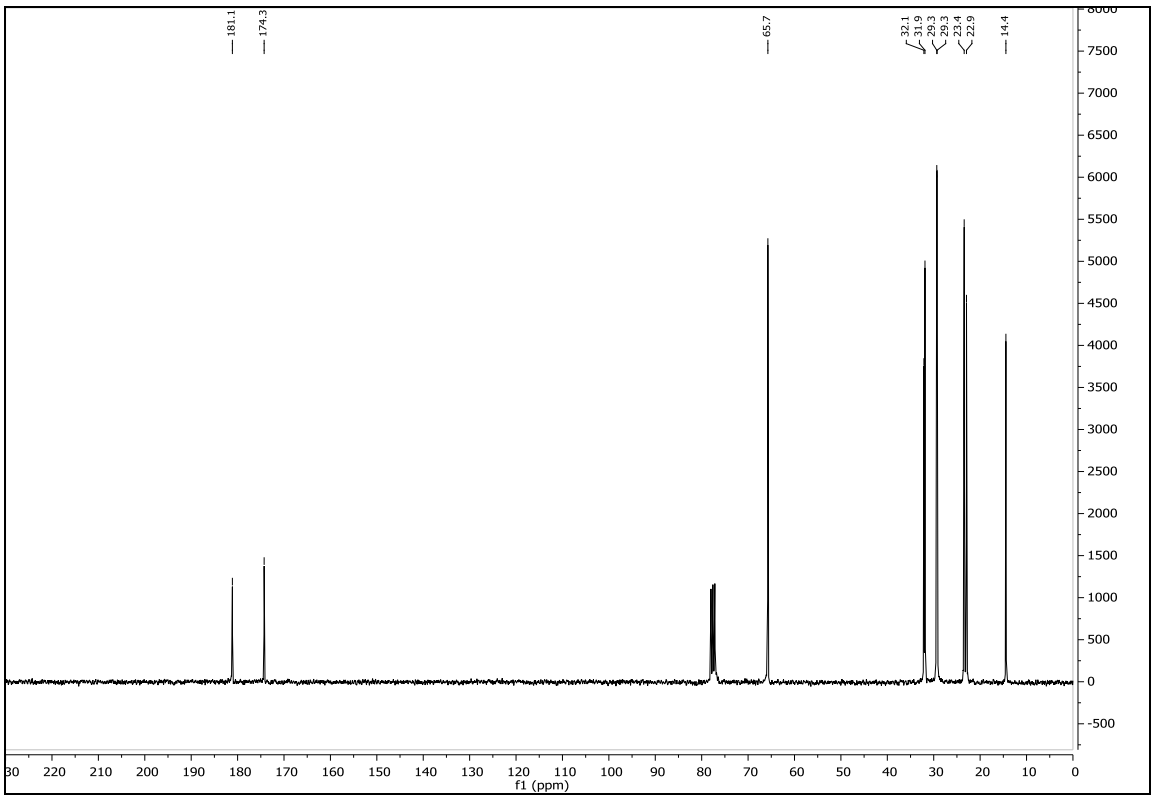
5-Benzyl-1-methyl-2-thioxoimidazolidin-4-one



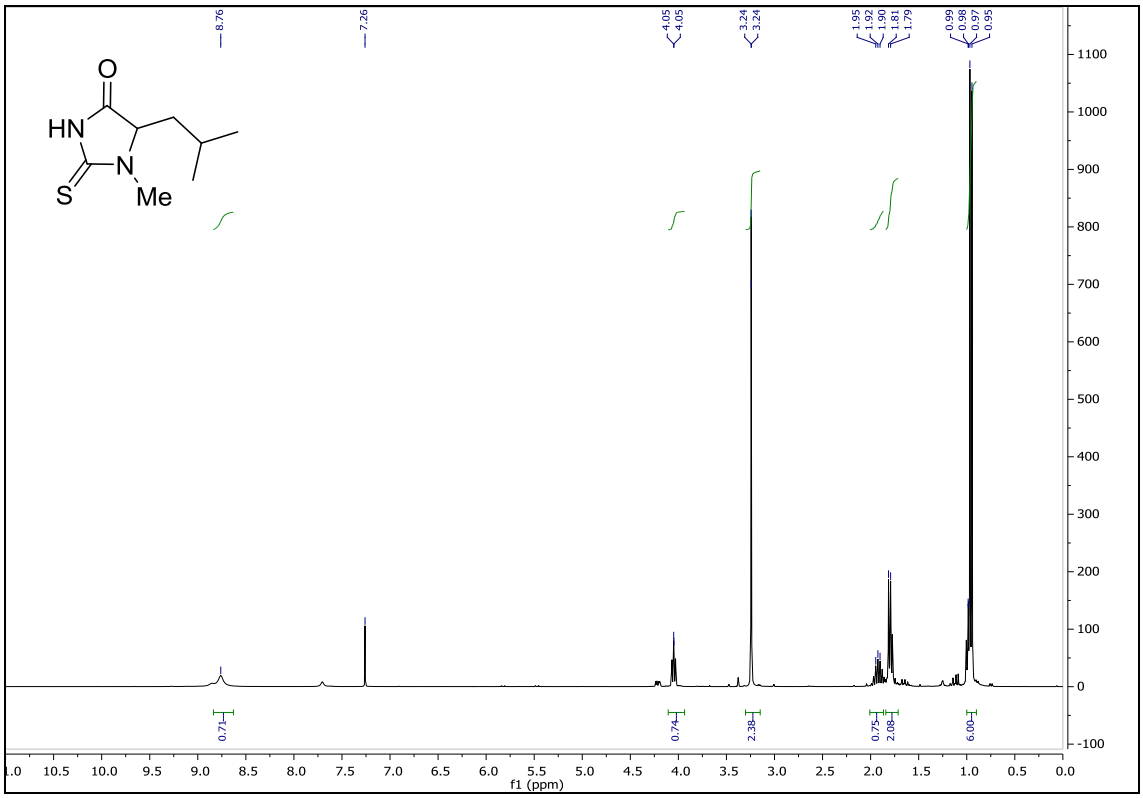


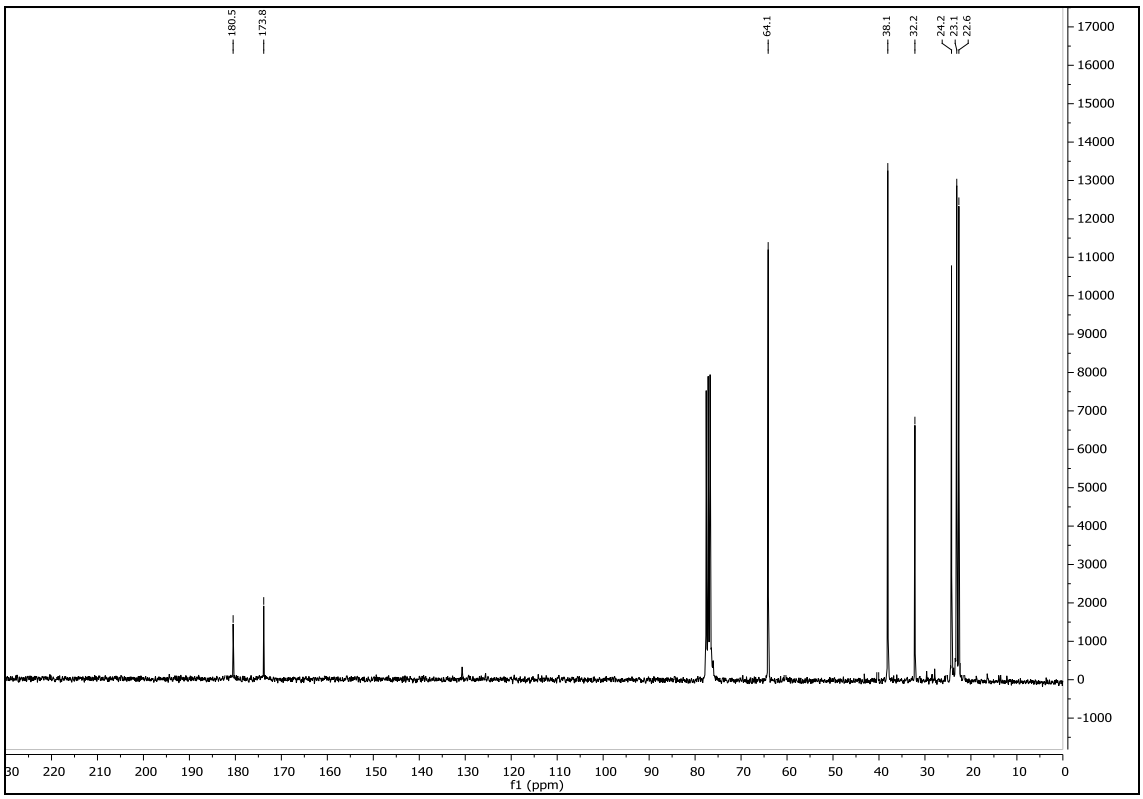
5-Hexyl-1-methyl-2-thioxoimidazolidin-4-one



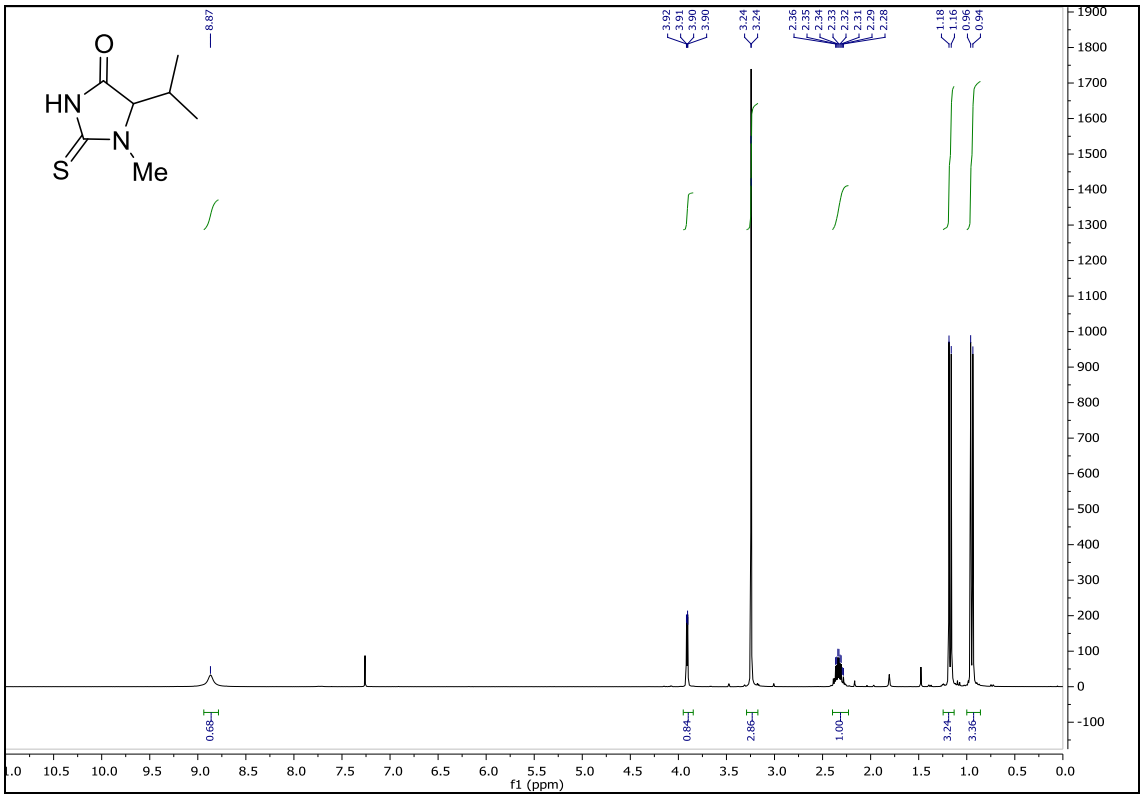


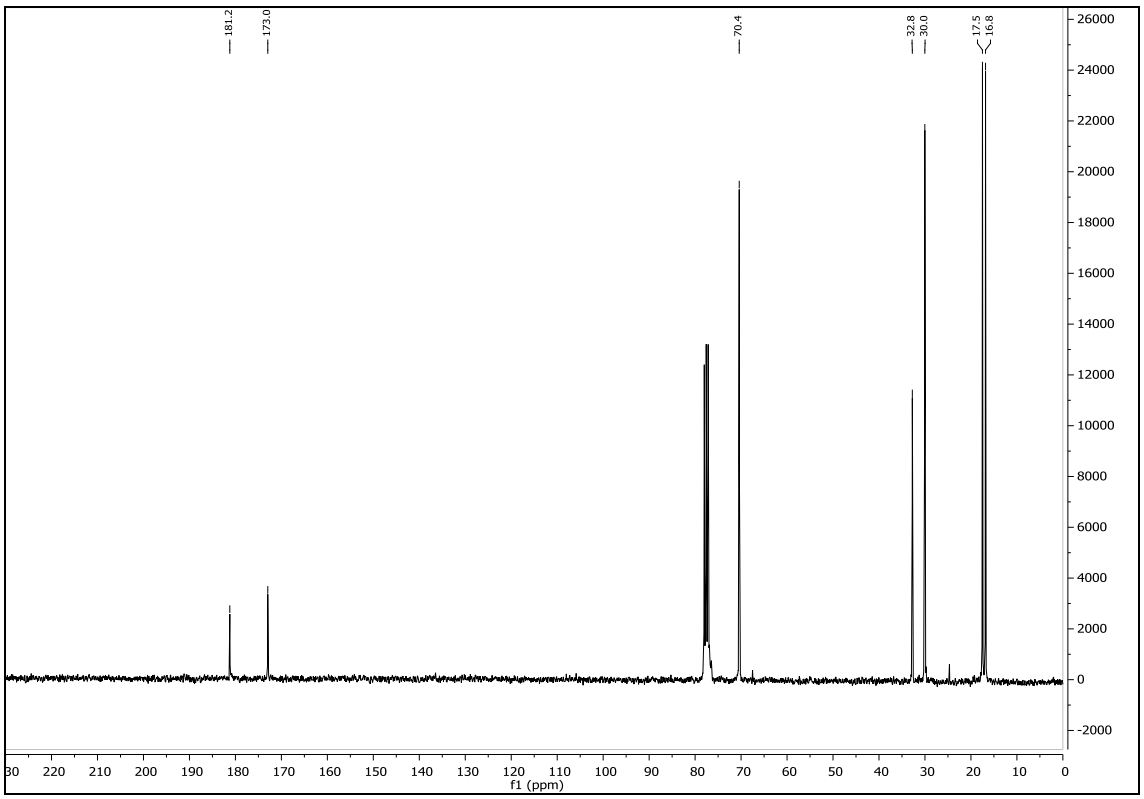
5-Isobutyl-1-methyl-2-thioxoimidazolidin-4-one



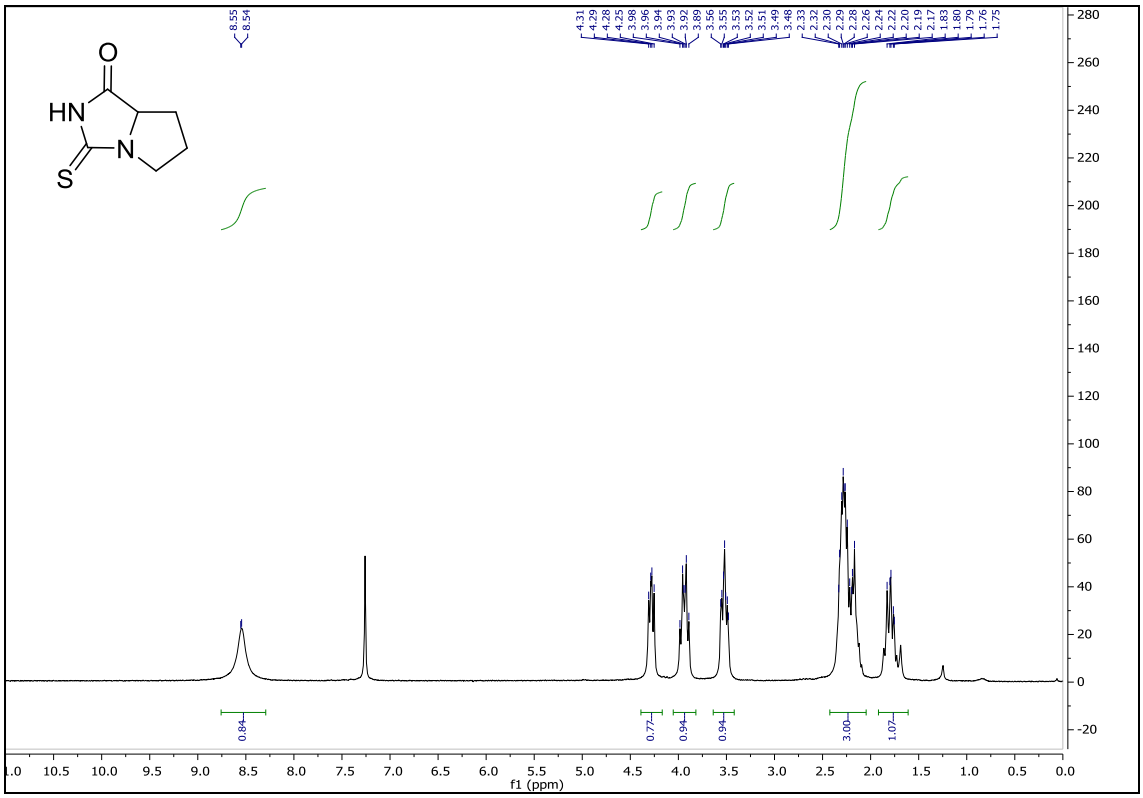


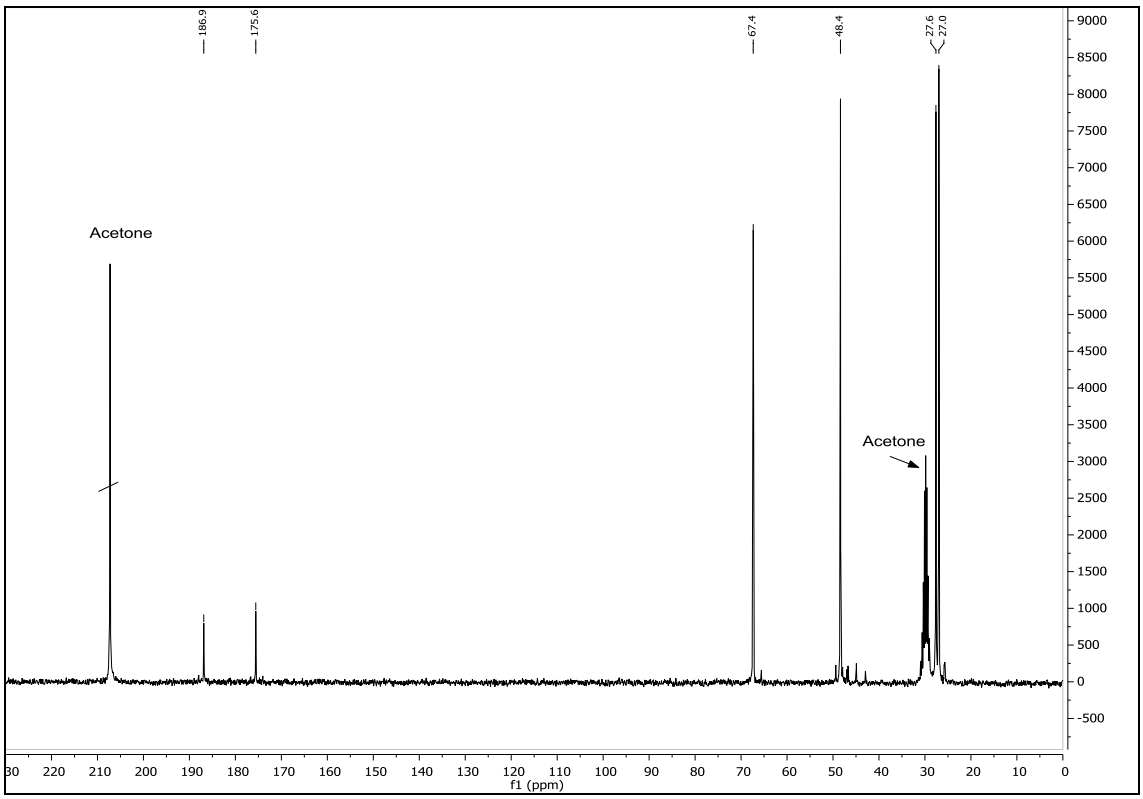
5-Isopropyl-1-methyl-2-thioxoimidazolidin-4-one



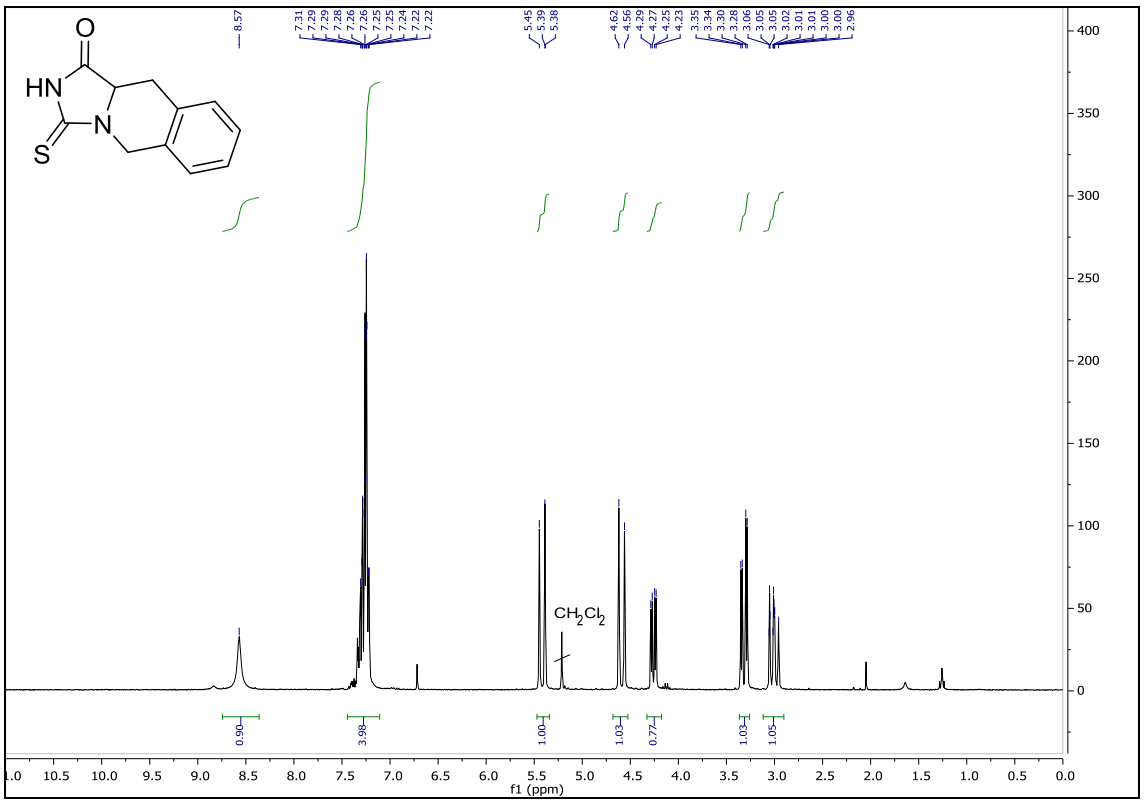


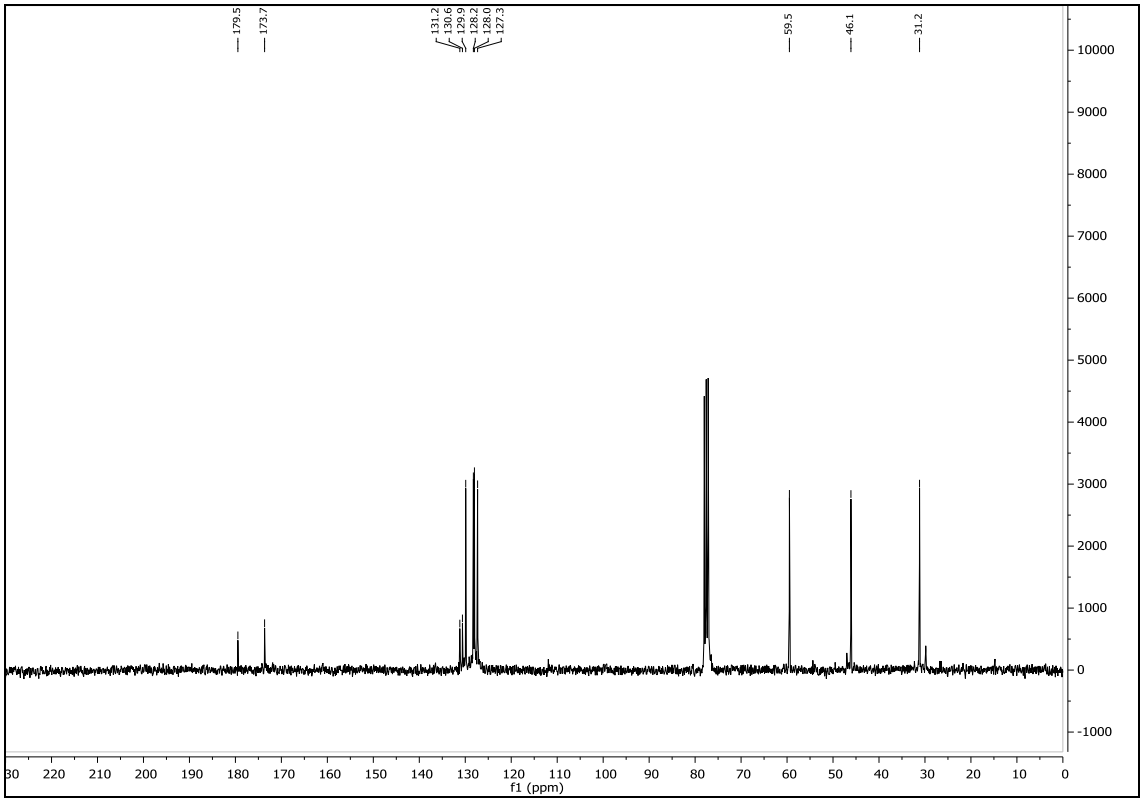
3-Thioxohexahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one



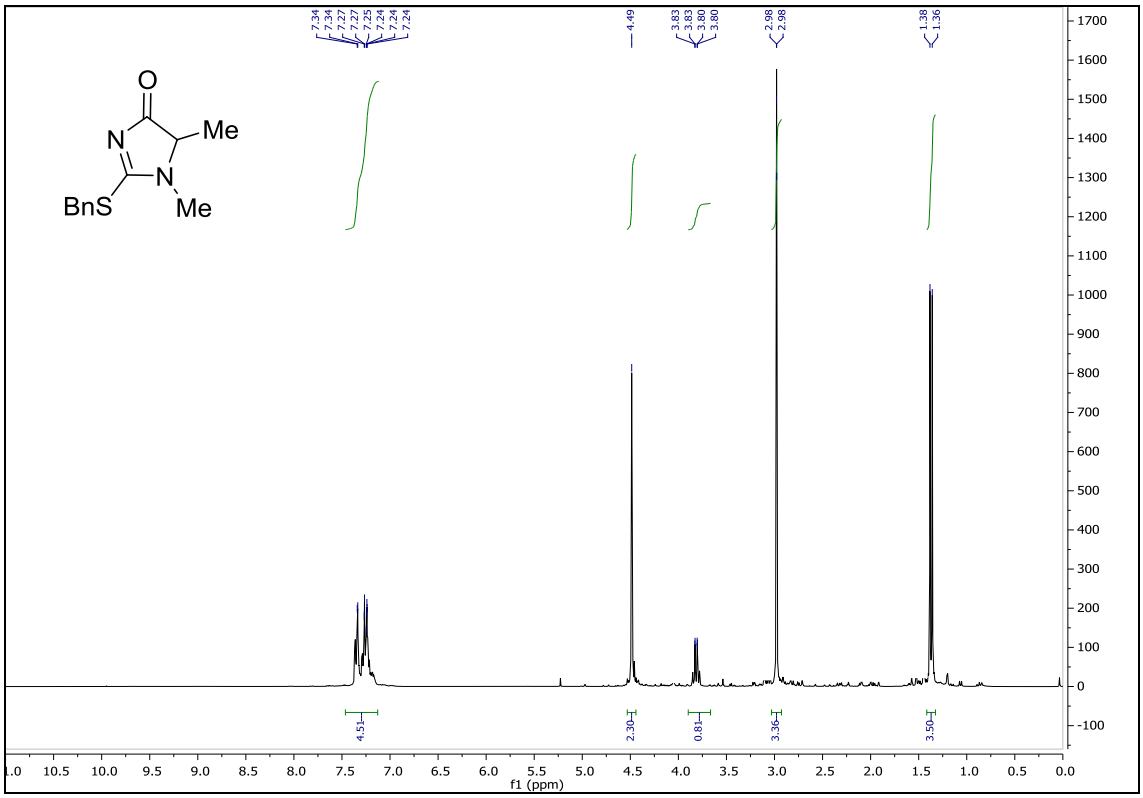


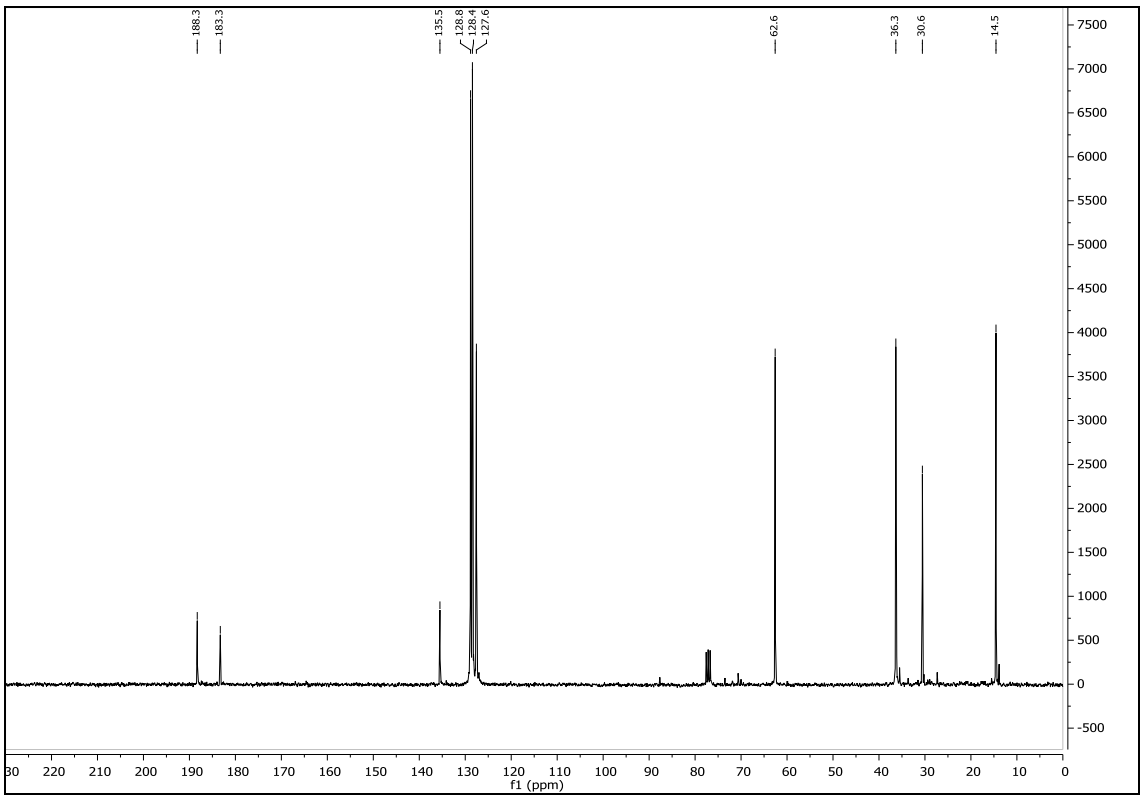
3-Thioxo-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5*H*)-one



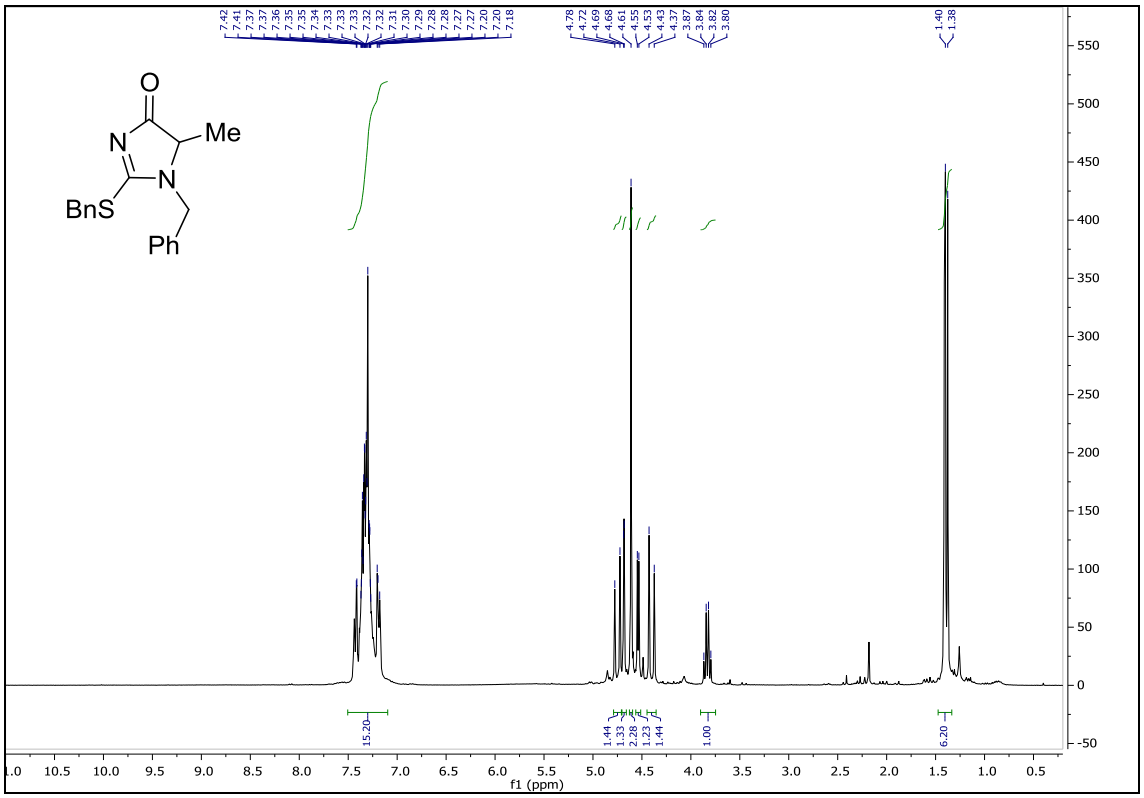


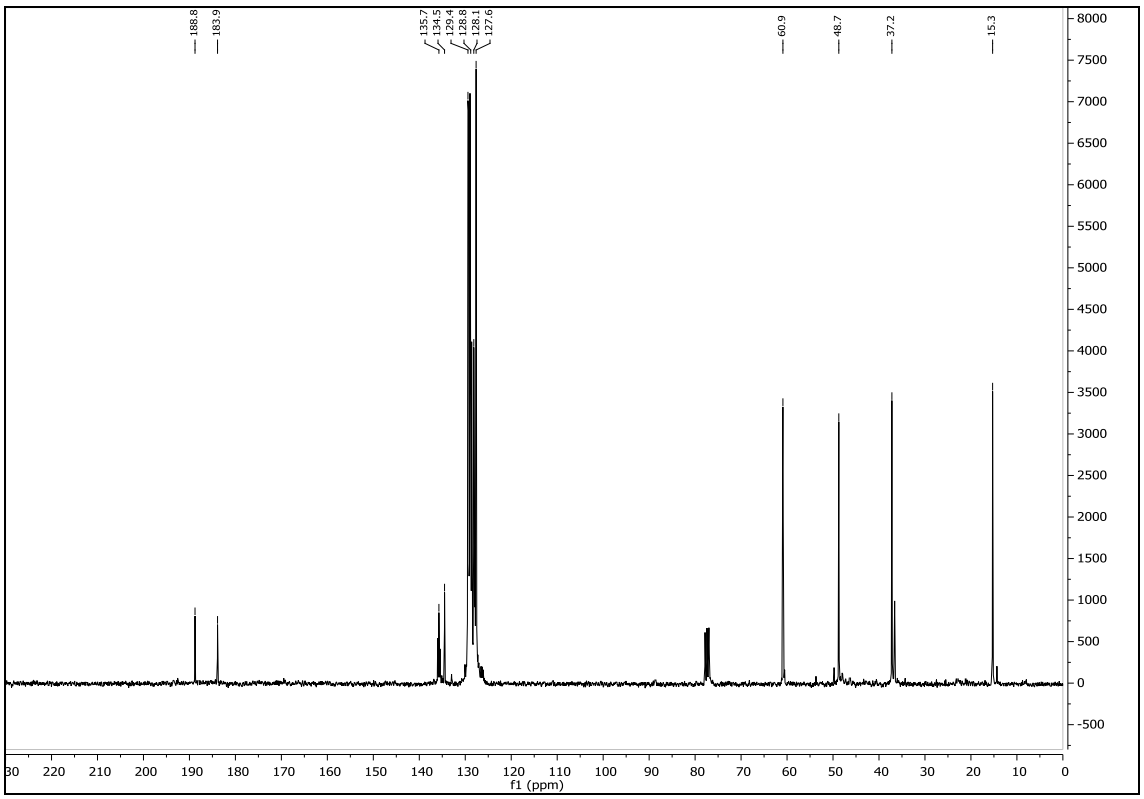
2-(Benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (27A)



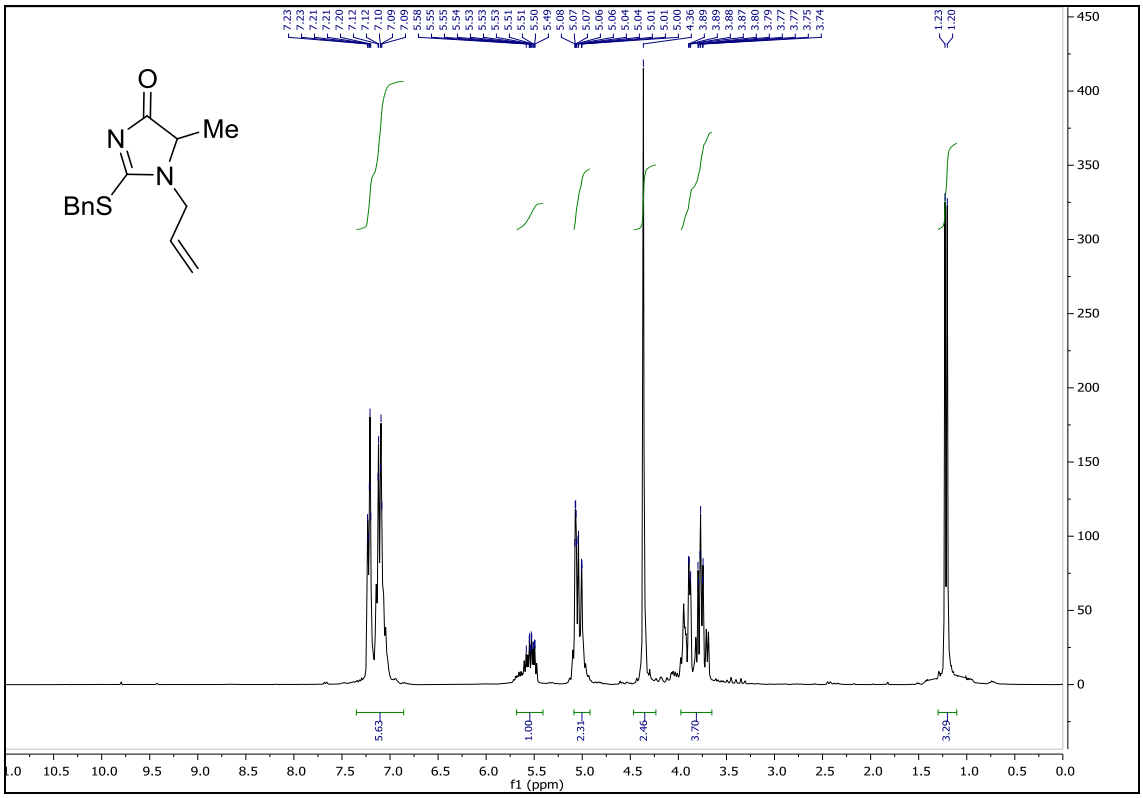


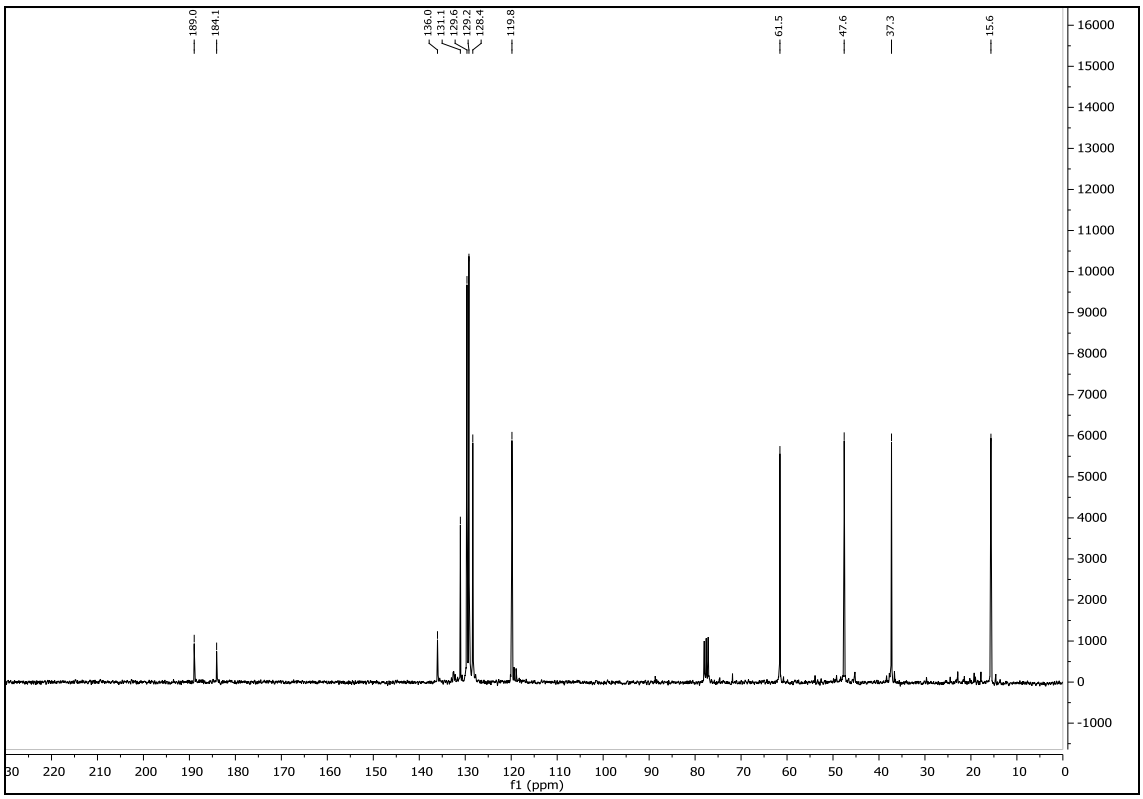
1-Benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (28A)



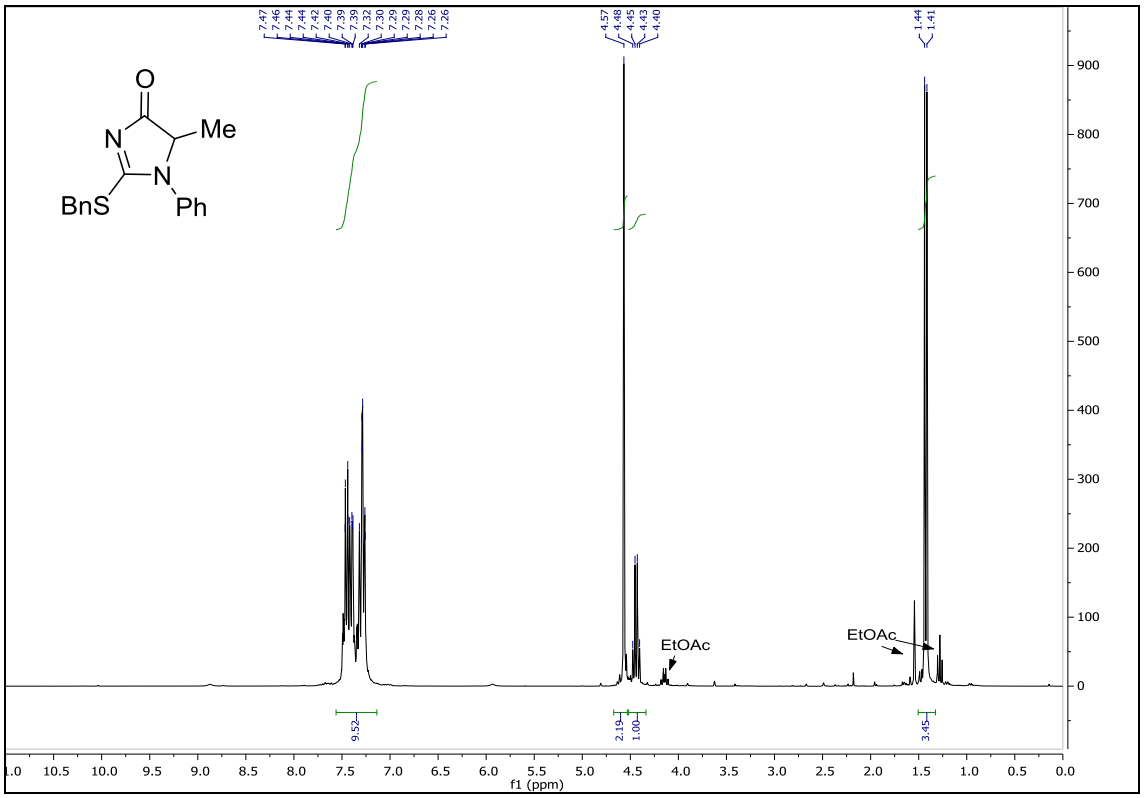


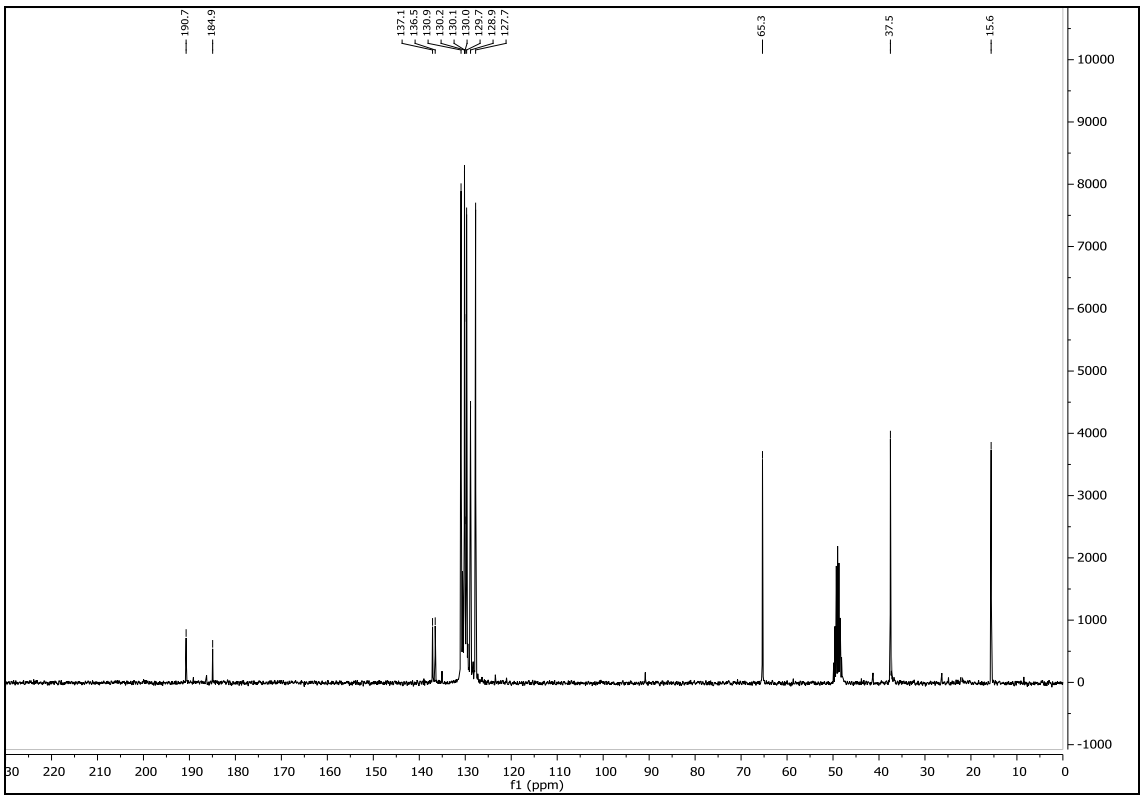
1-Allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (30A)



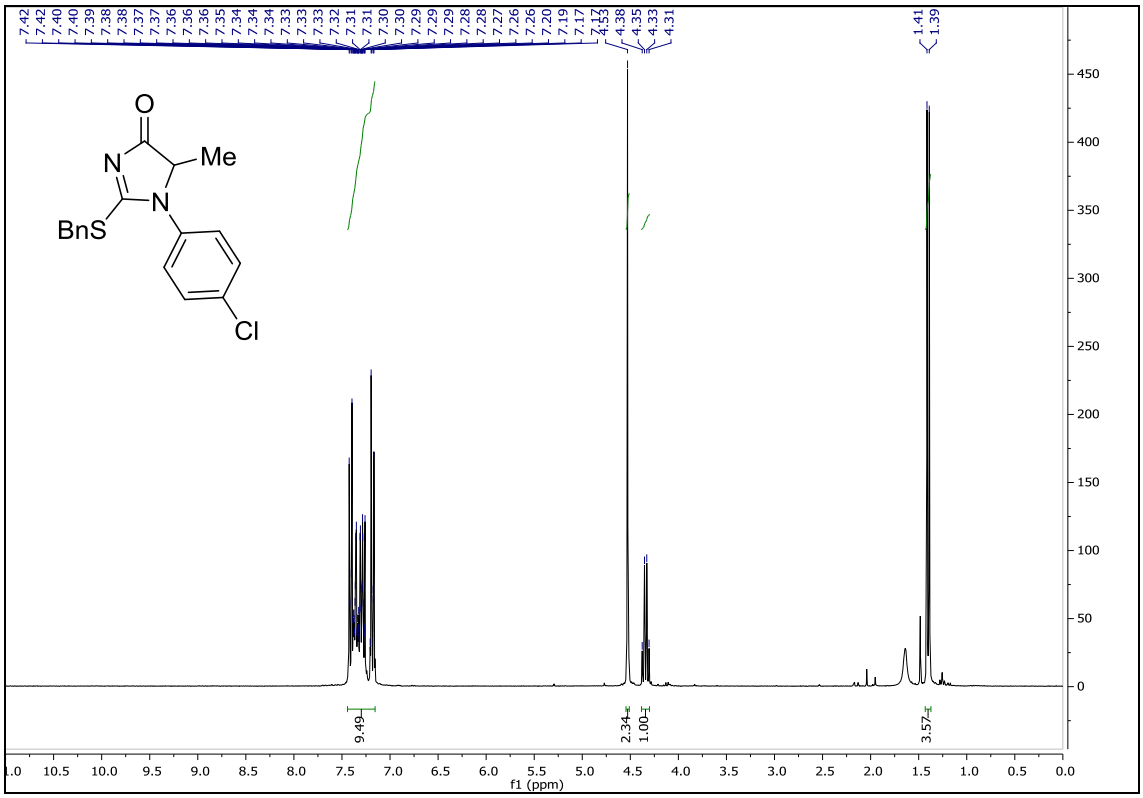


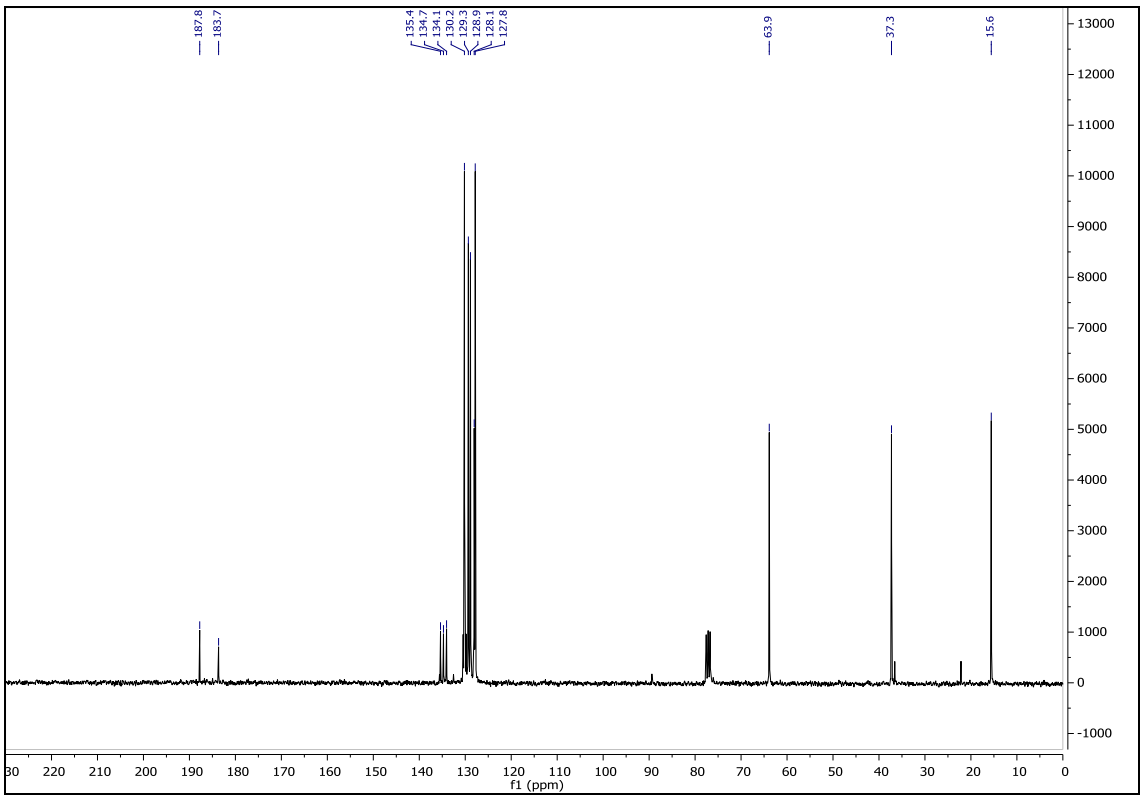
2-(Benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (31A)



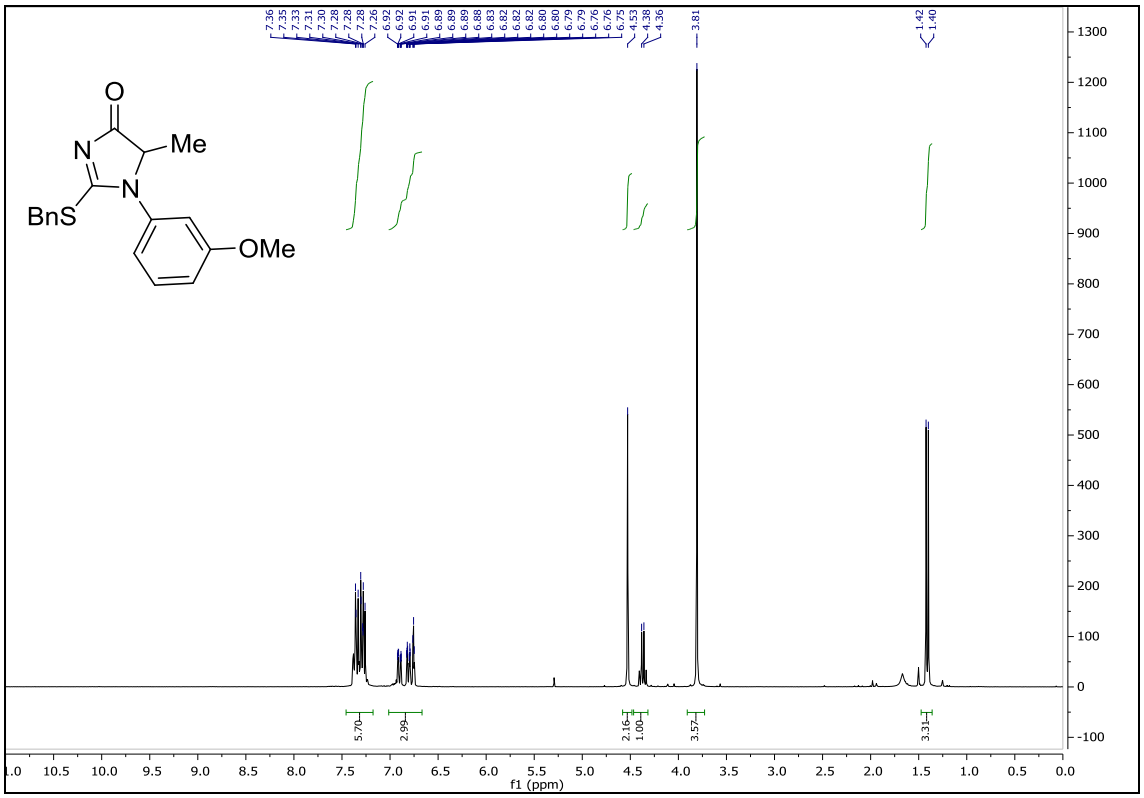


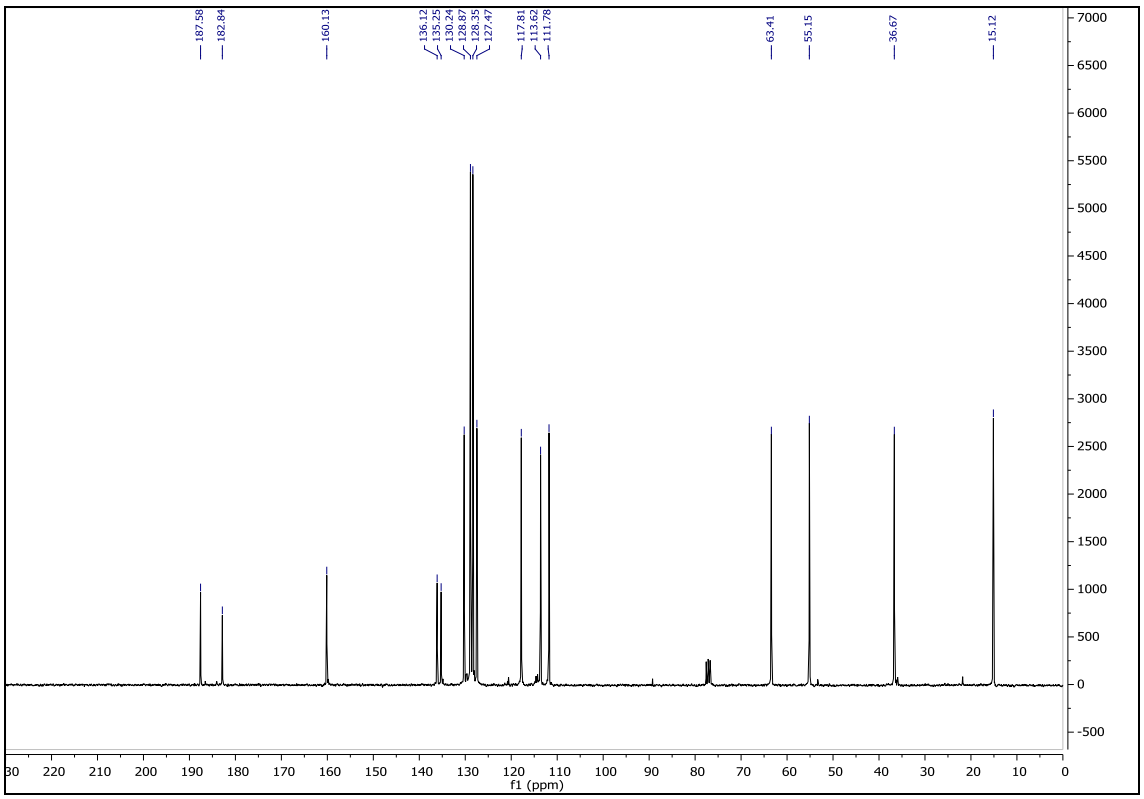
2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (32A)



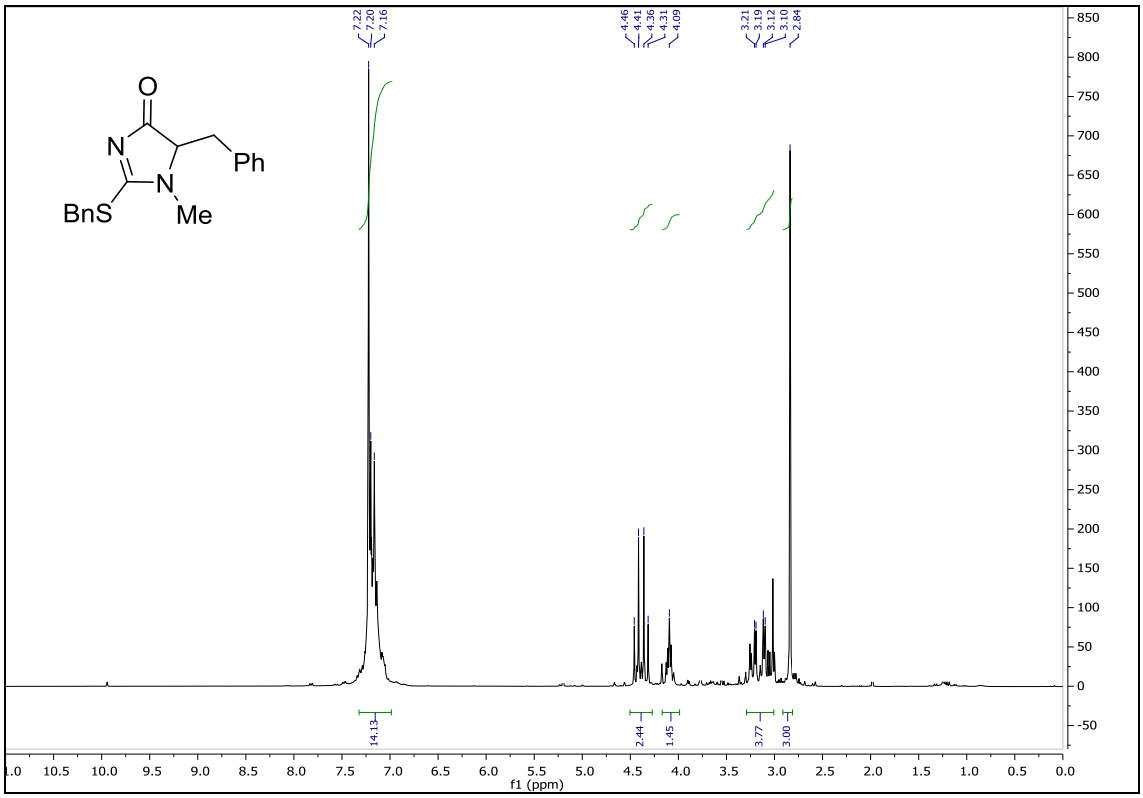


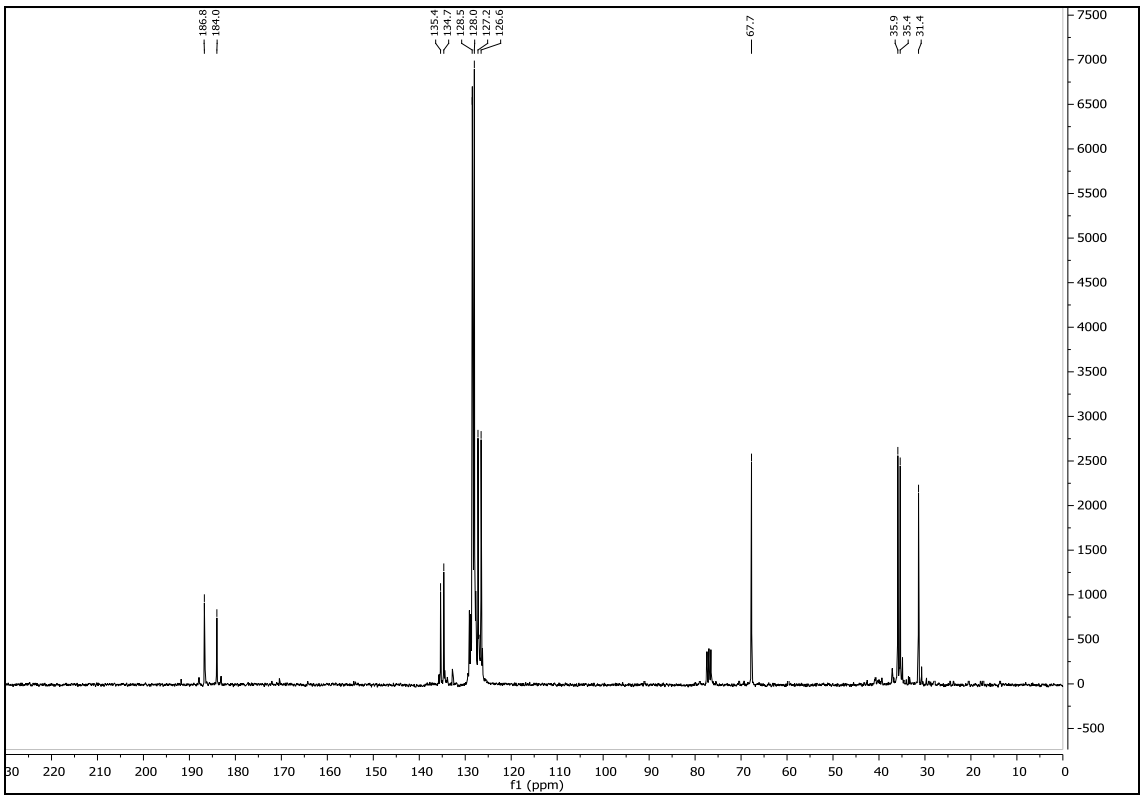
2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (33A)



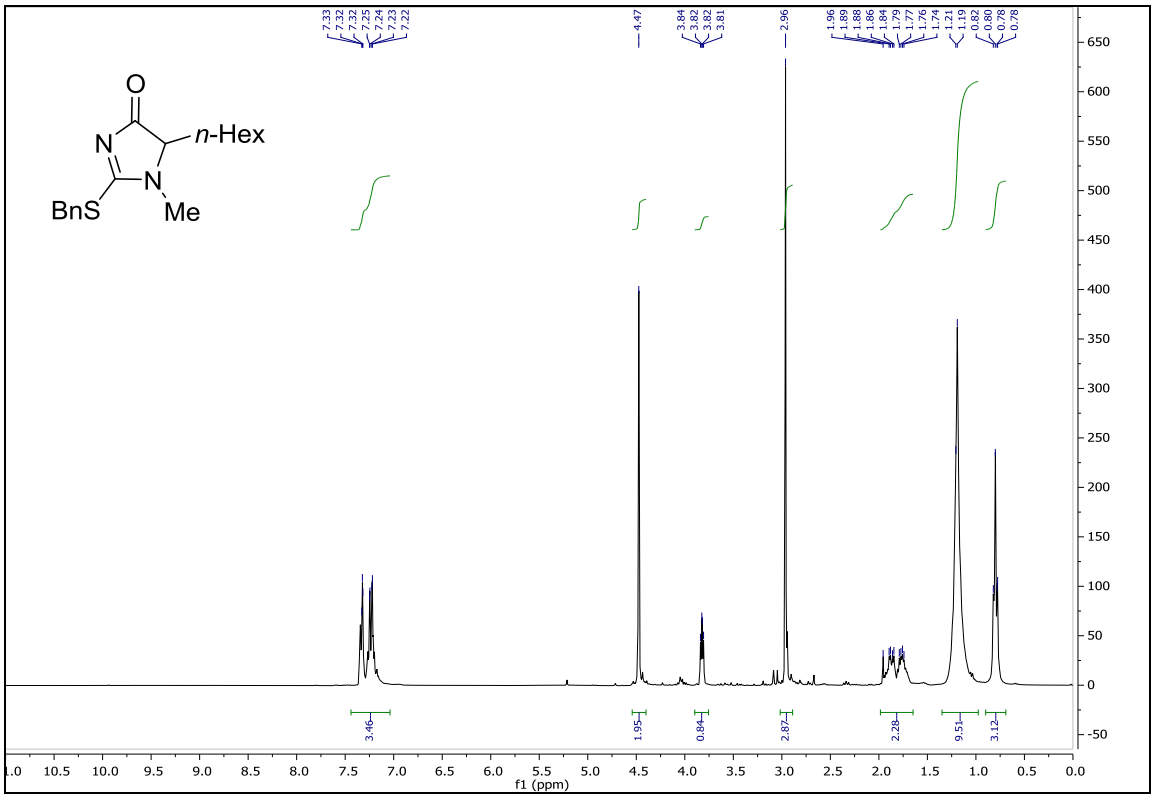


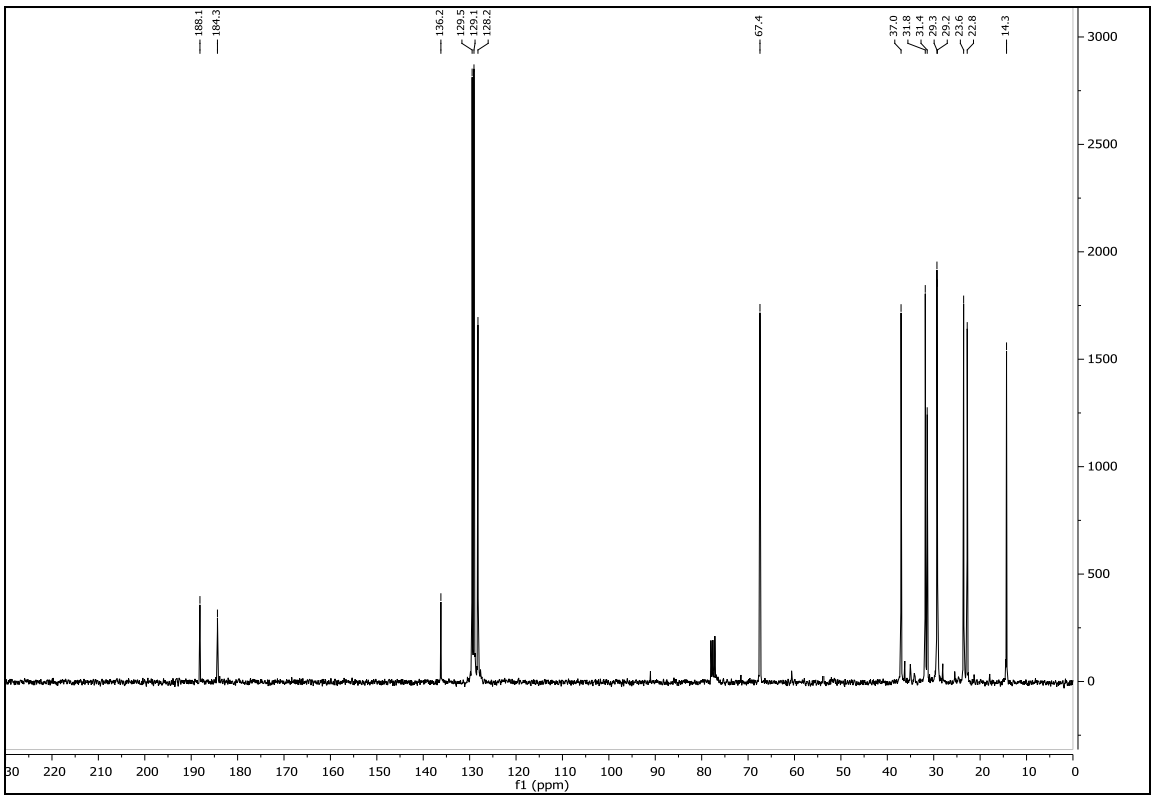
5-Benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (34A)



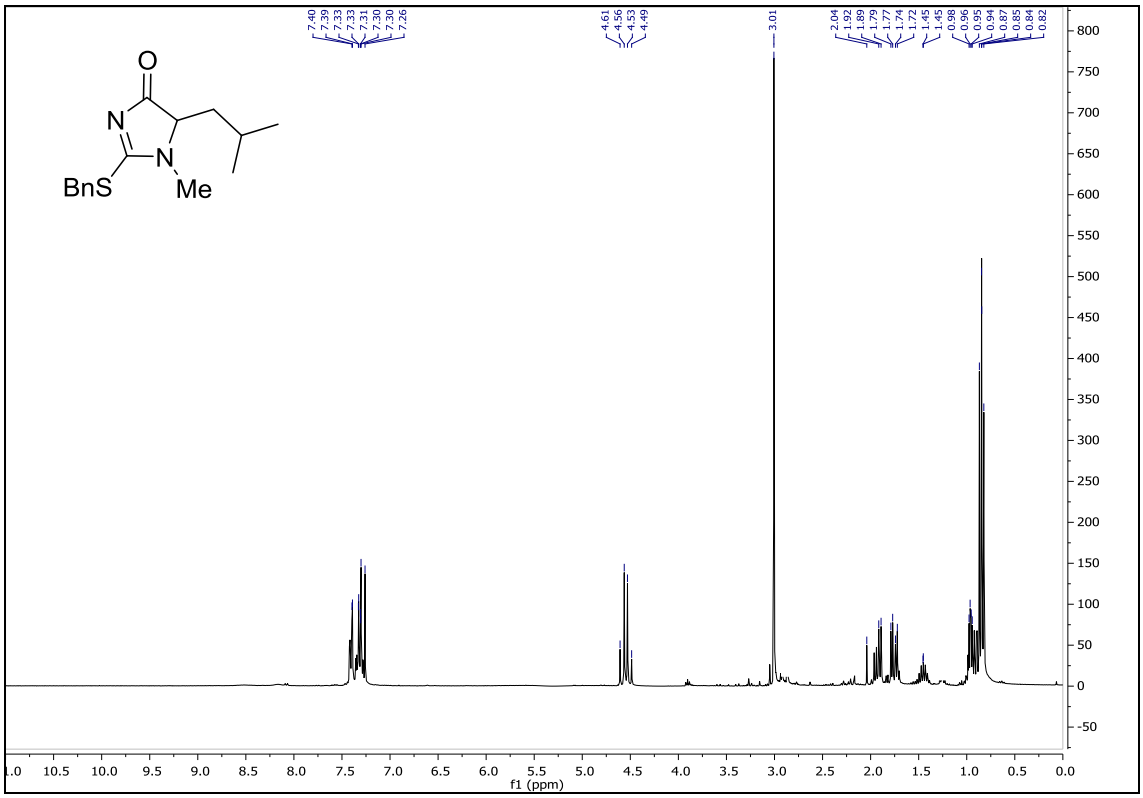


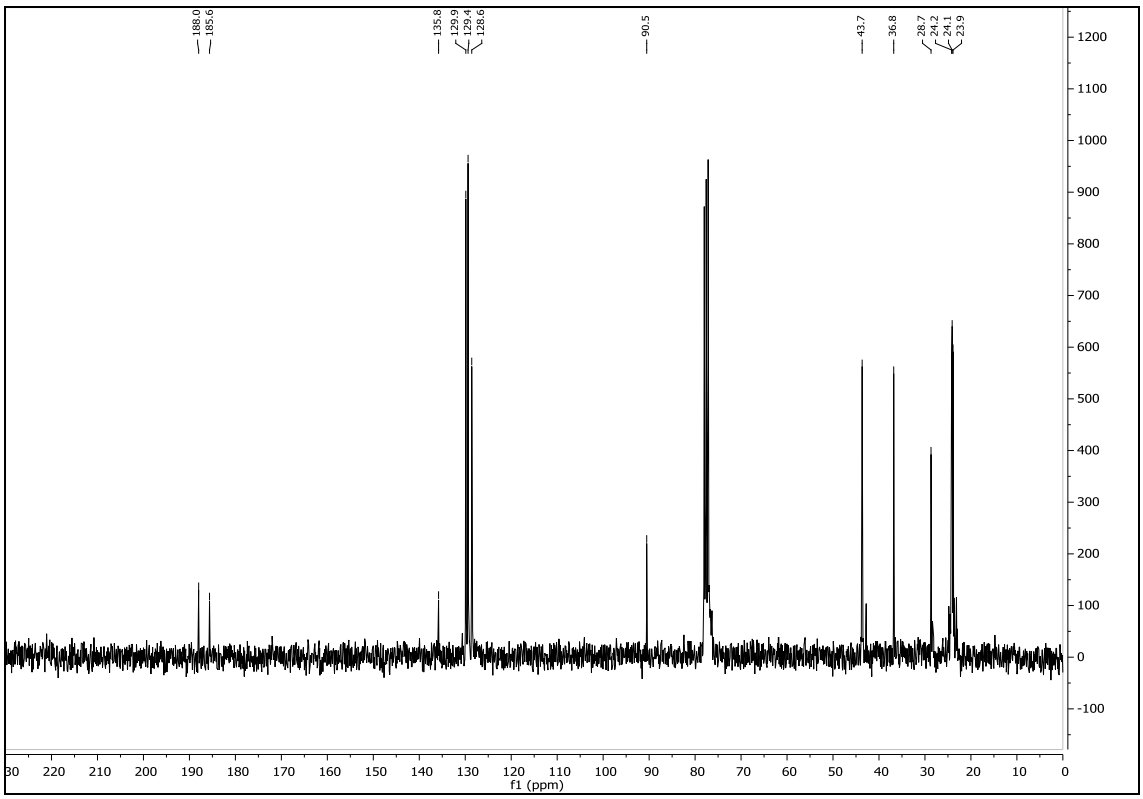
2-(Benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (35A)



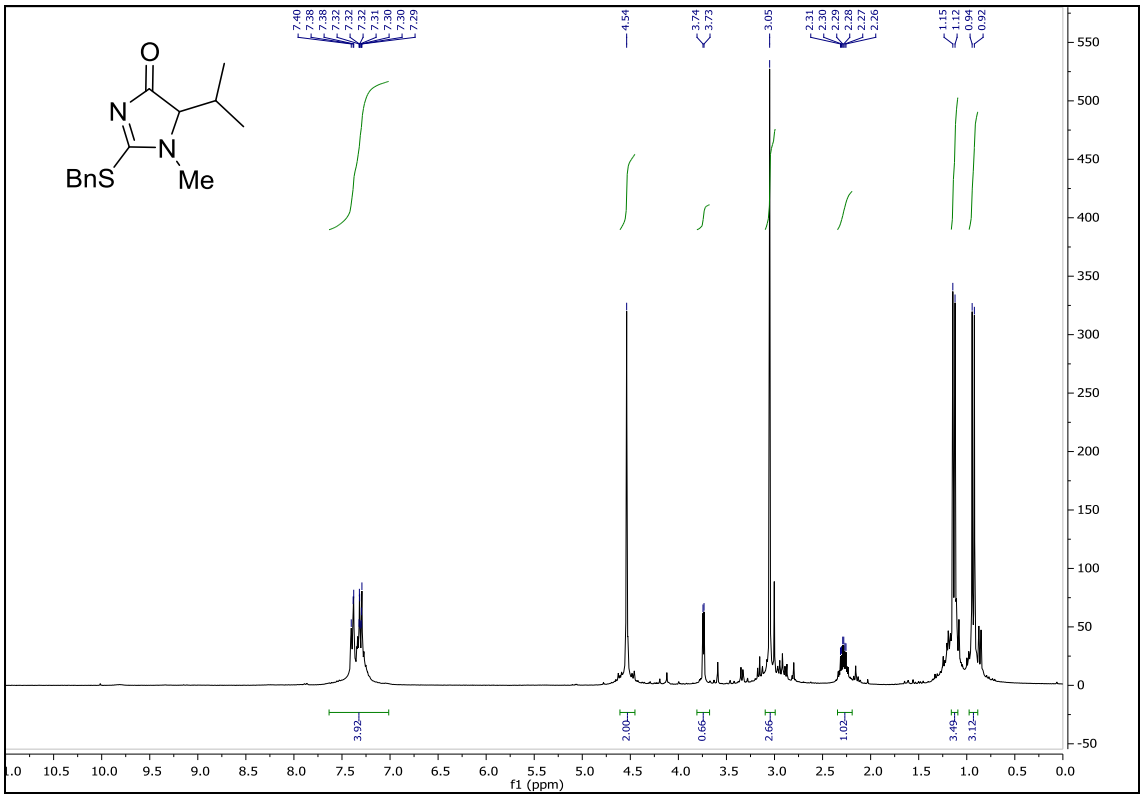


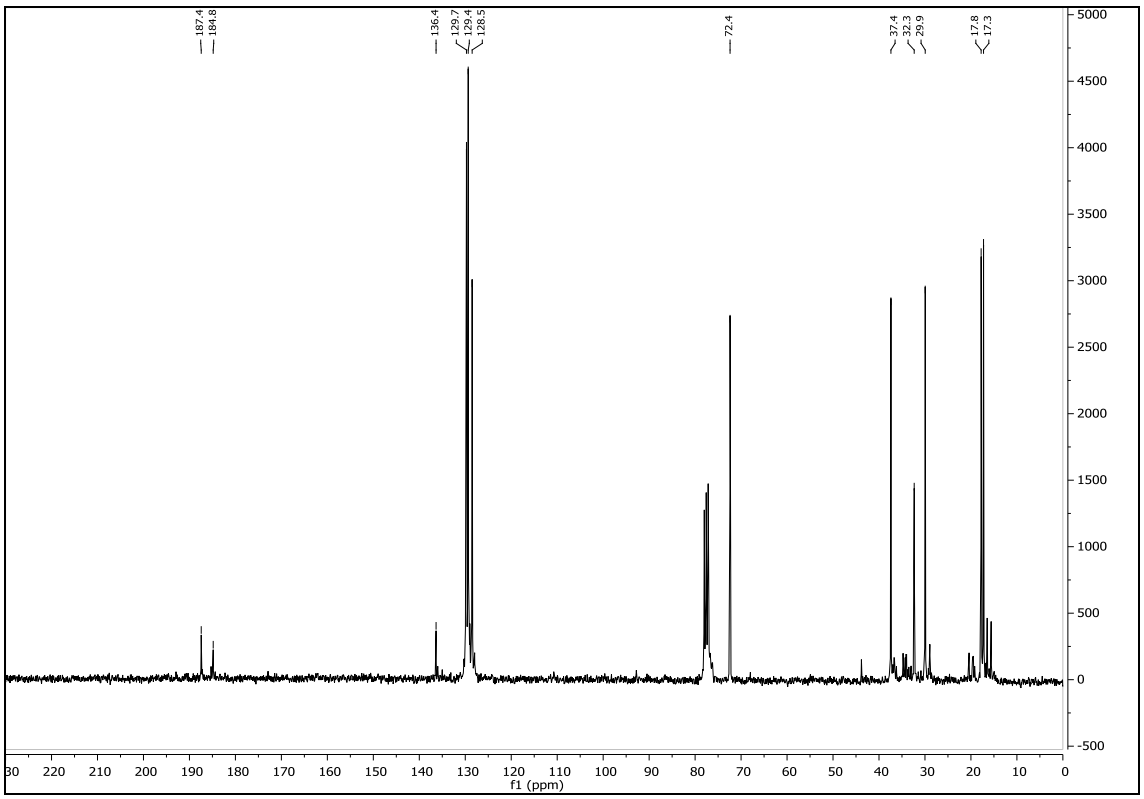
2-(Benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (36A)



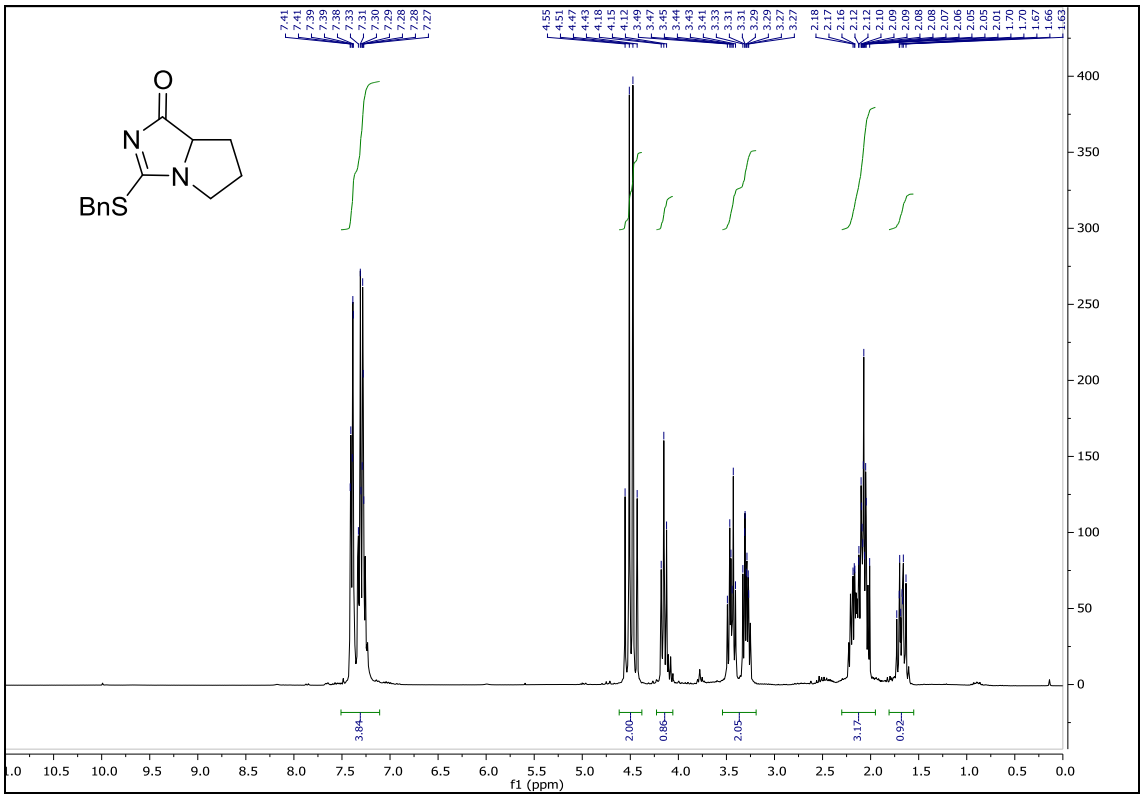


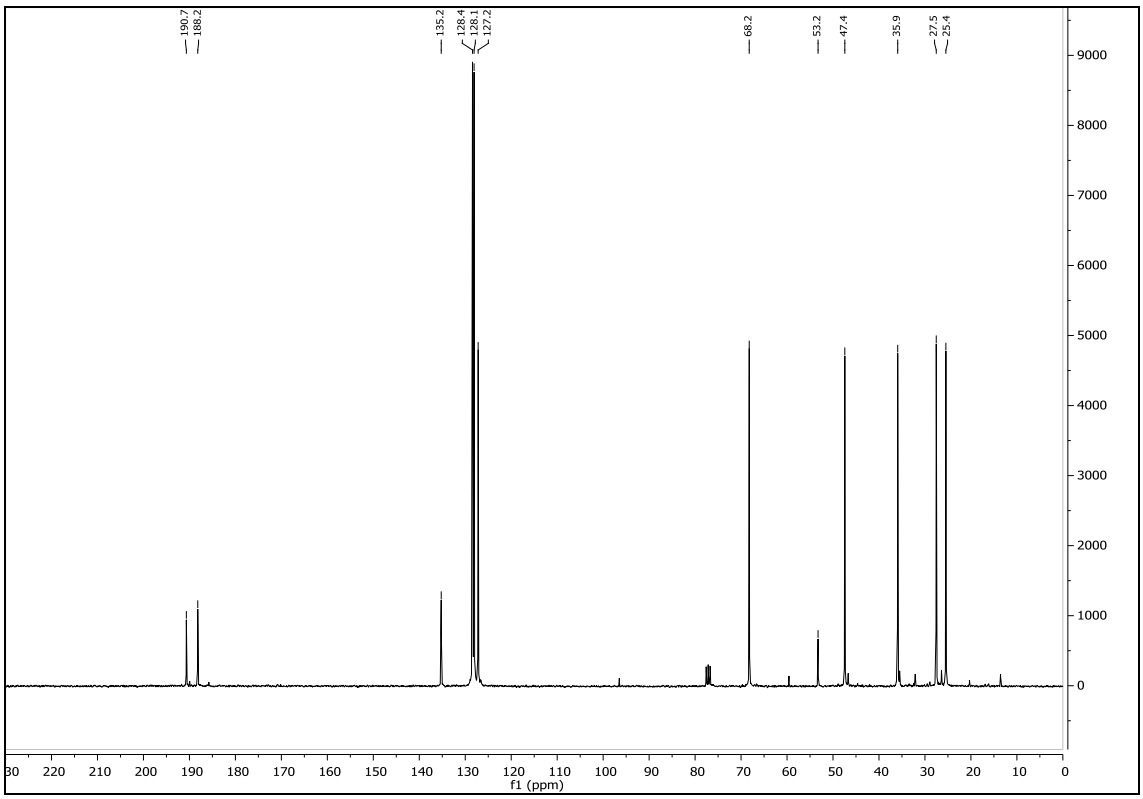
2-(Benzylthio)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (37A)



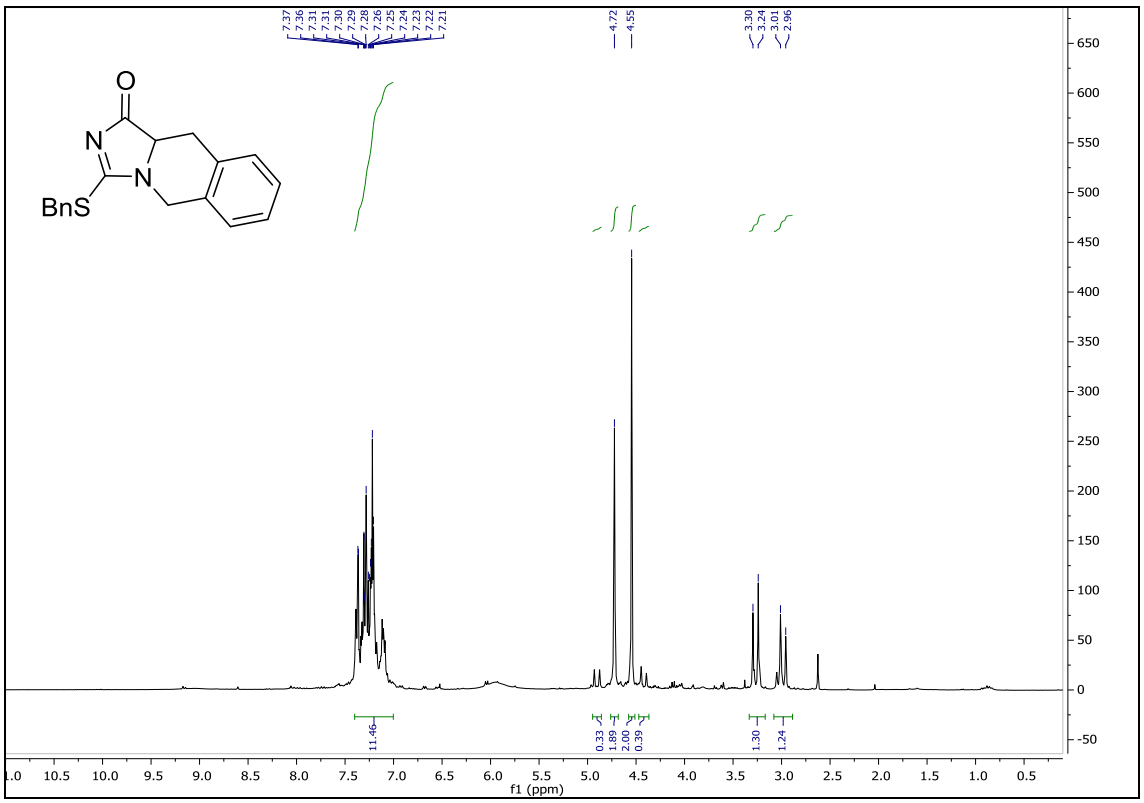


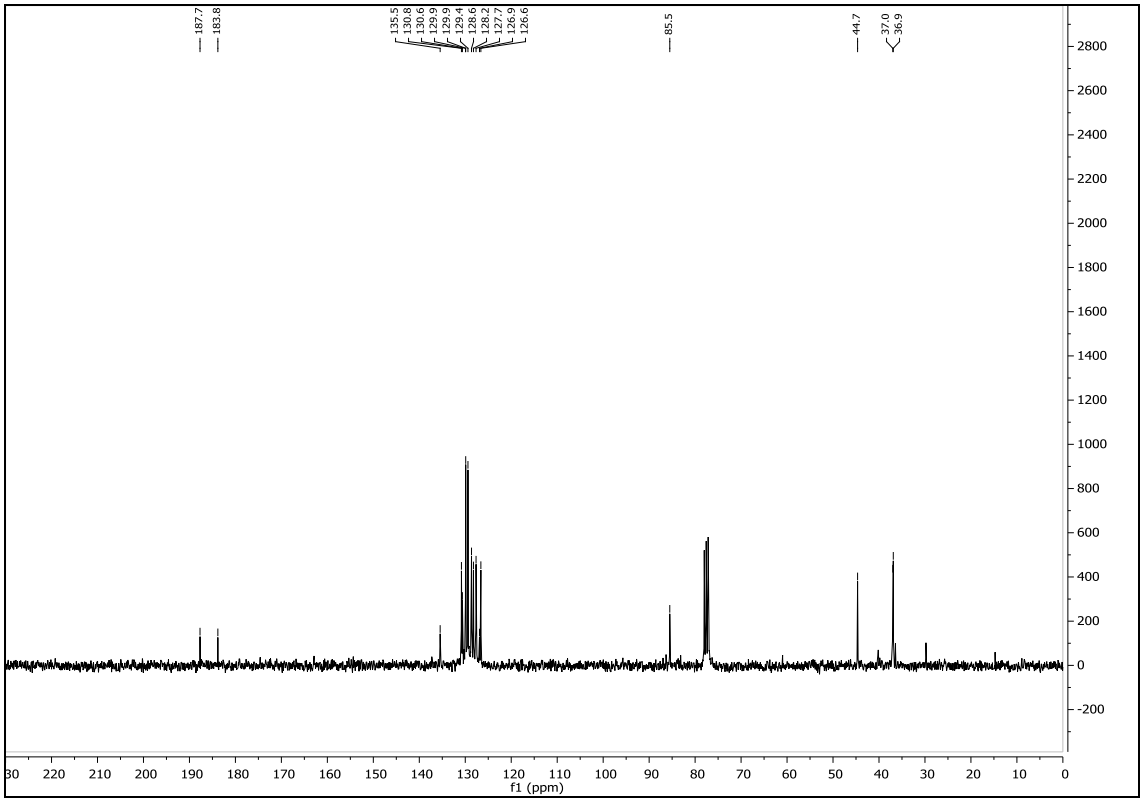
3-(Benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one (38A)



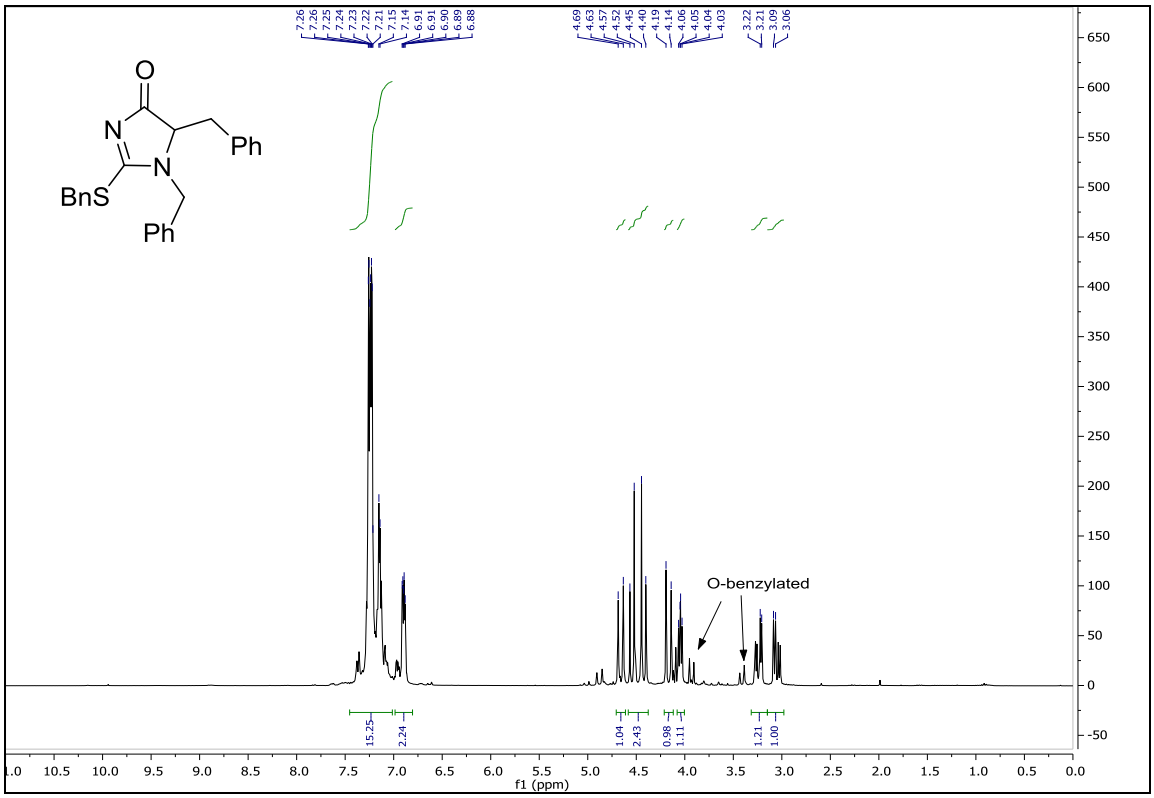


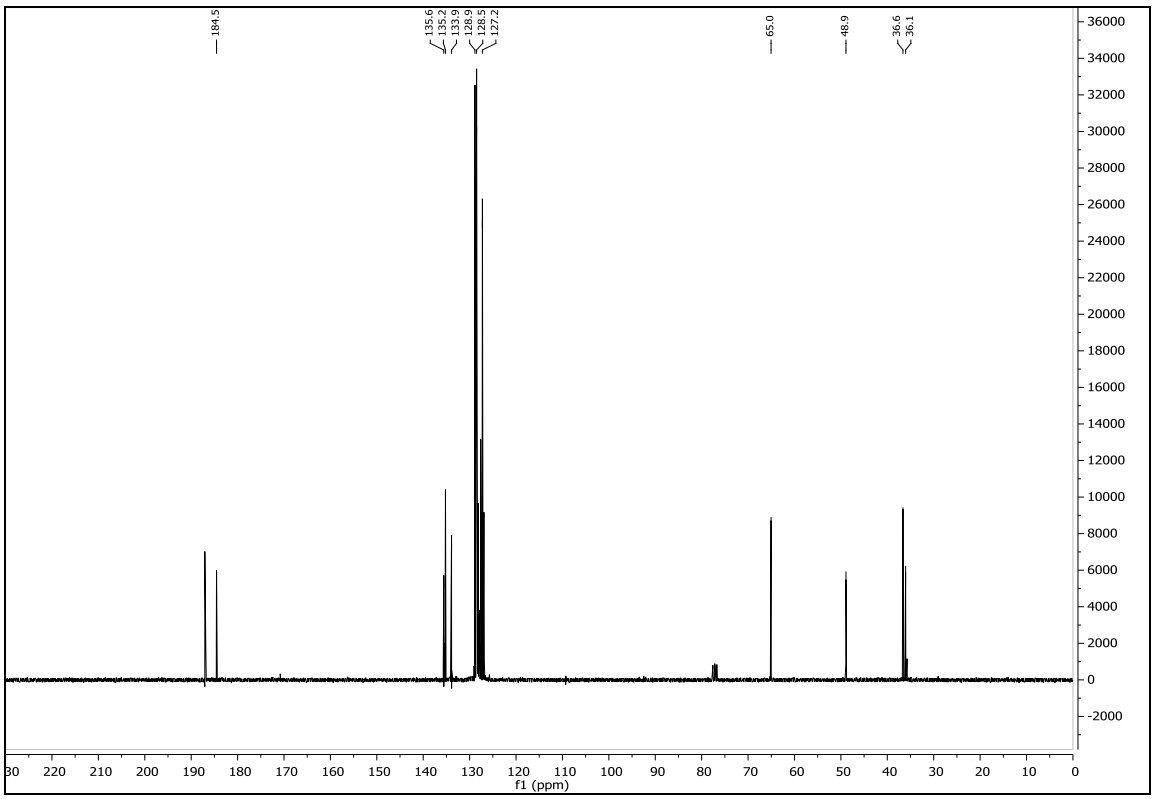
3-(Benzylthio)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (39A)



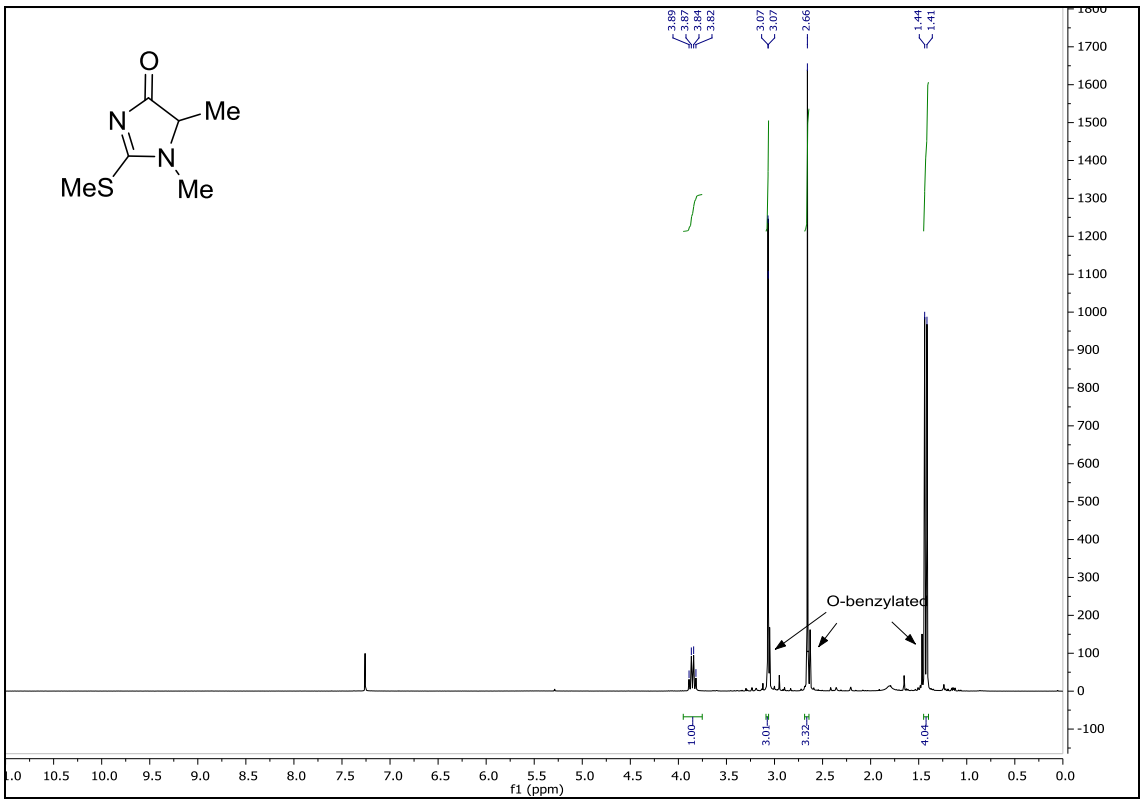


1,5-Dibenzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (40A)

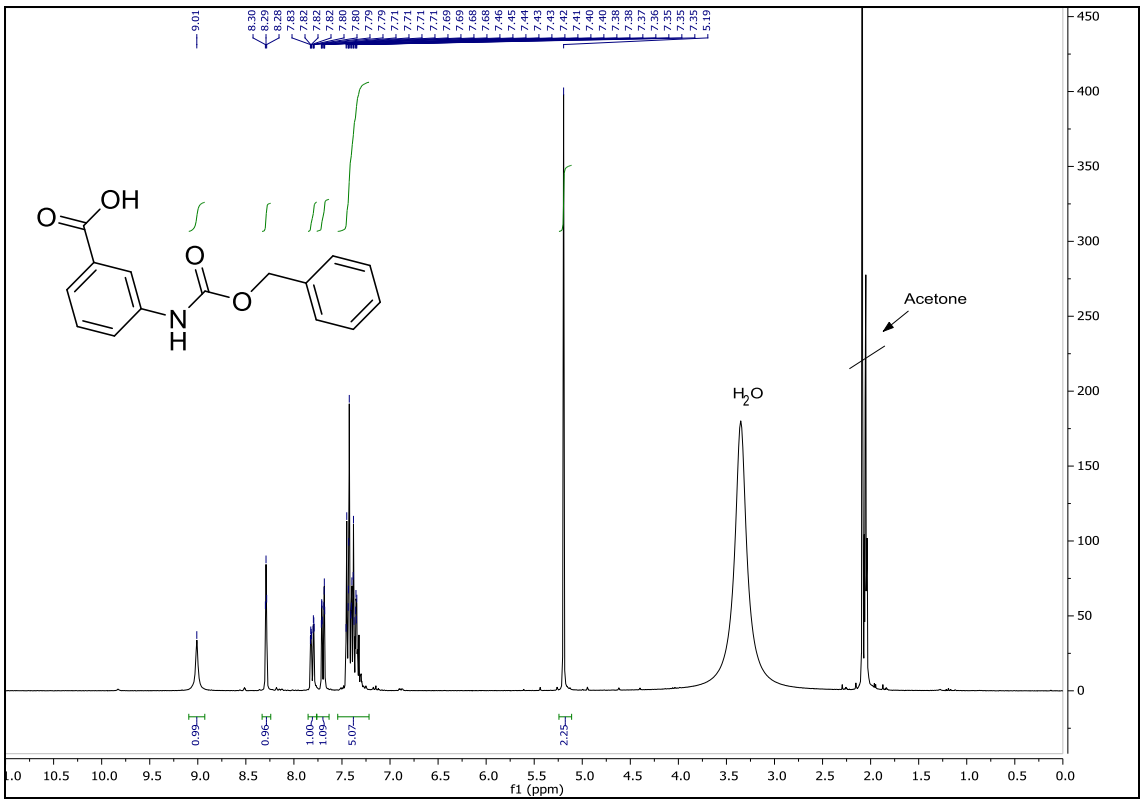


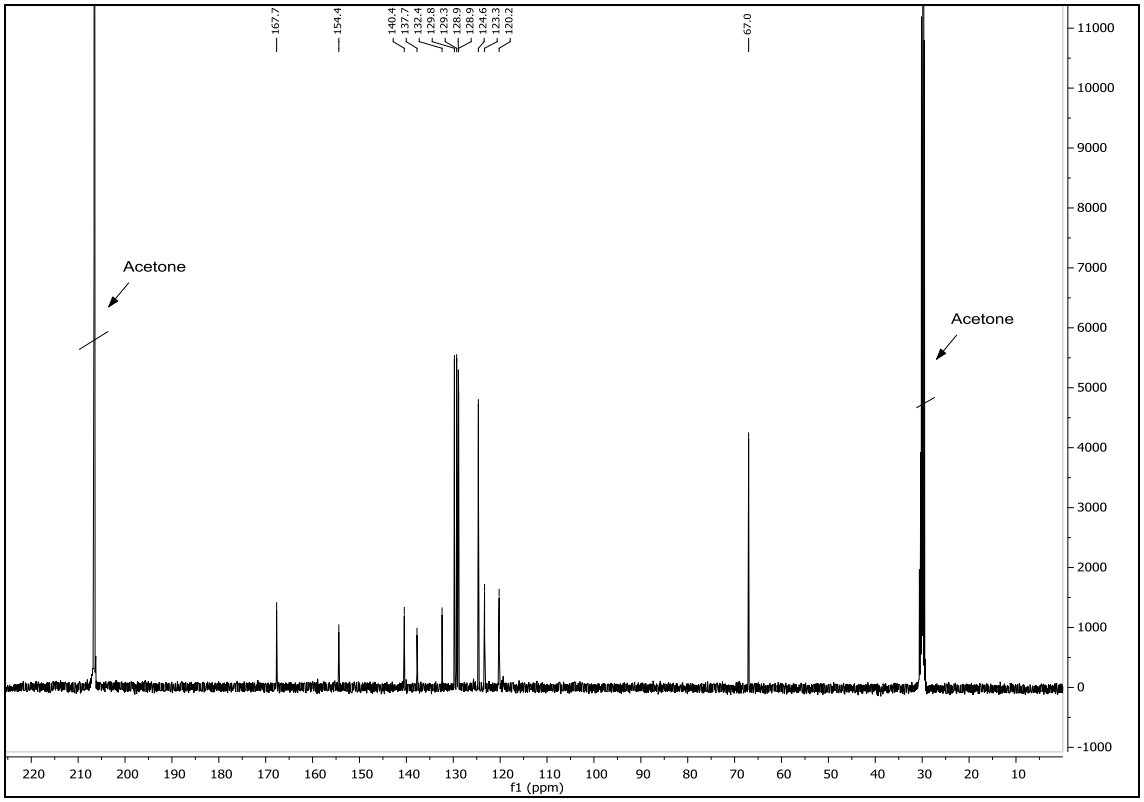


1,5-Dimethyl-2-(methylthio)-1*H*-imidazol-4(5*H*)-one (27B)

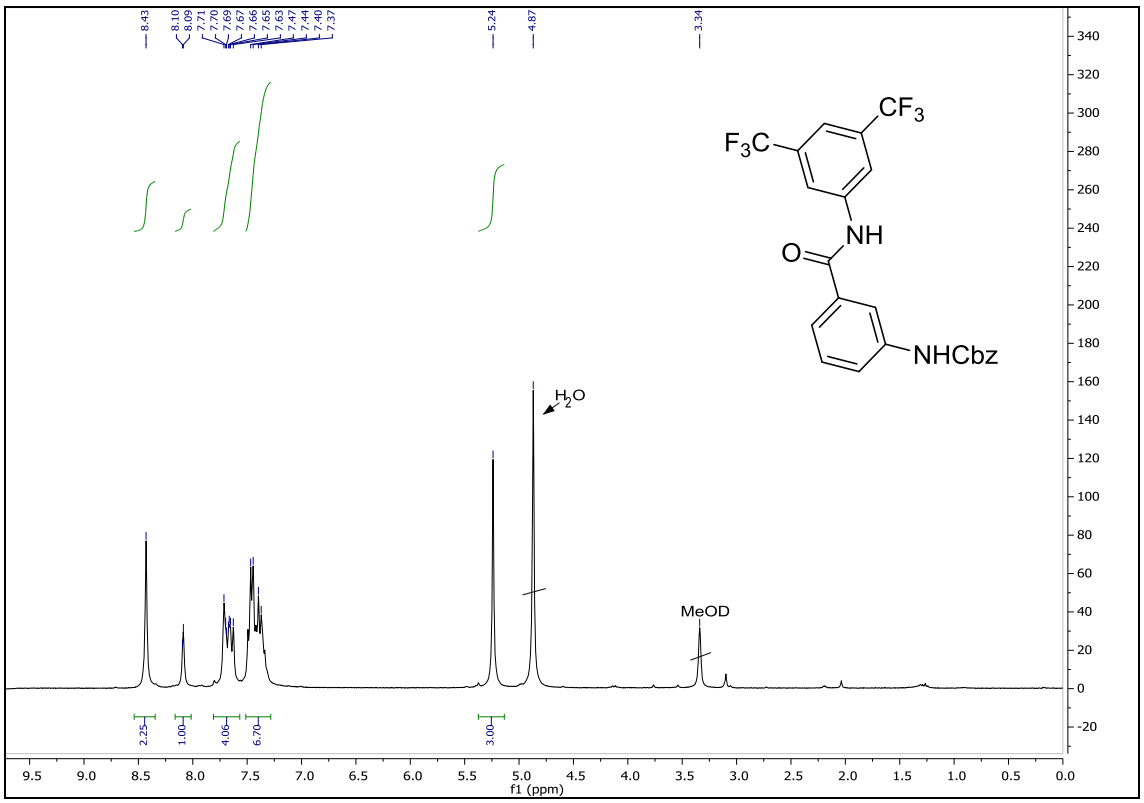


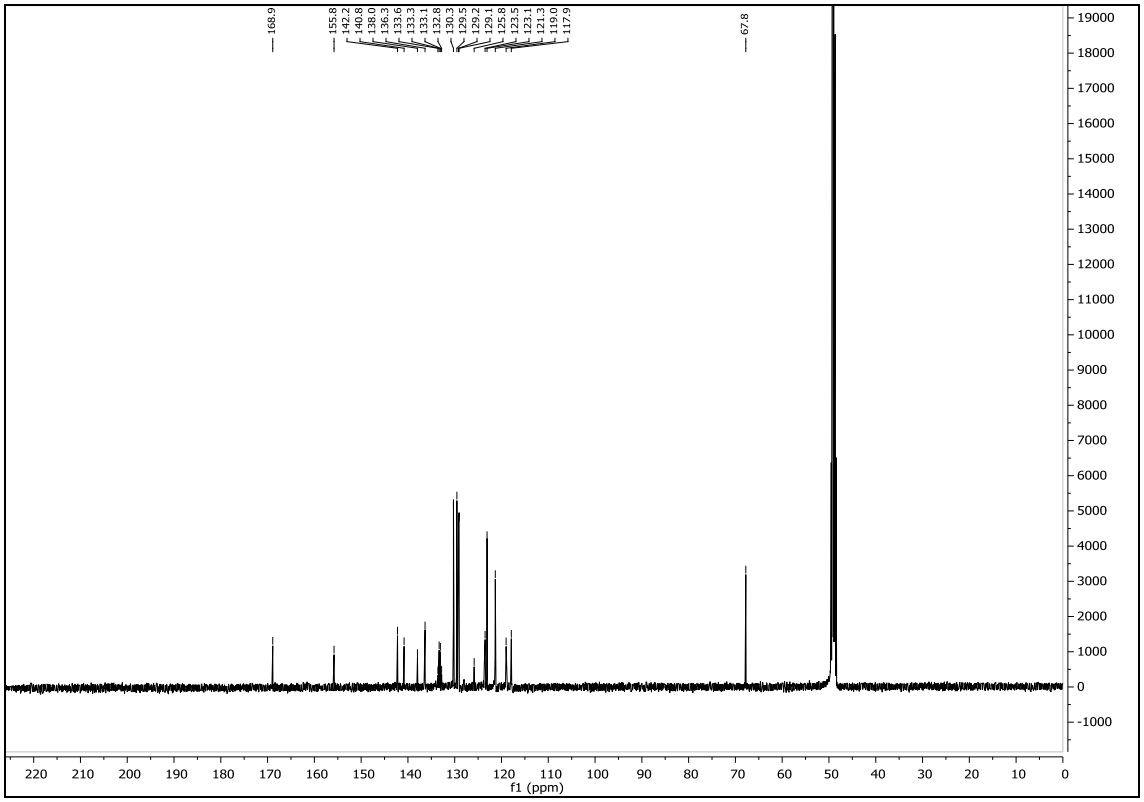
3-(((Benzyloxy)carbonyl)amino)benzoic acid



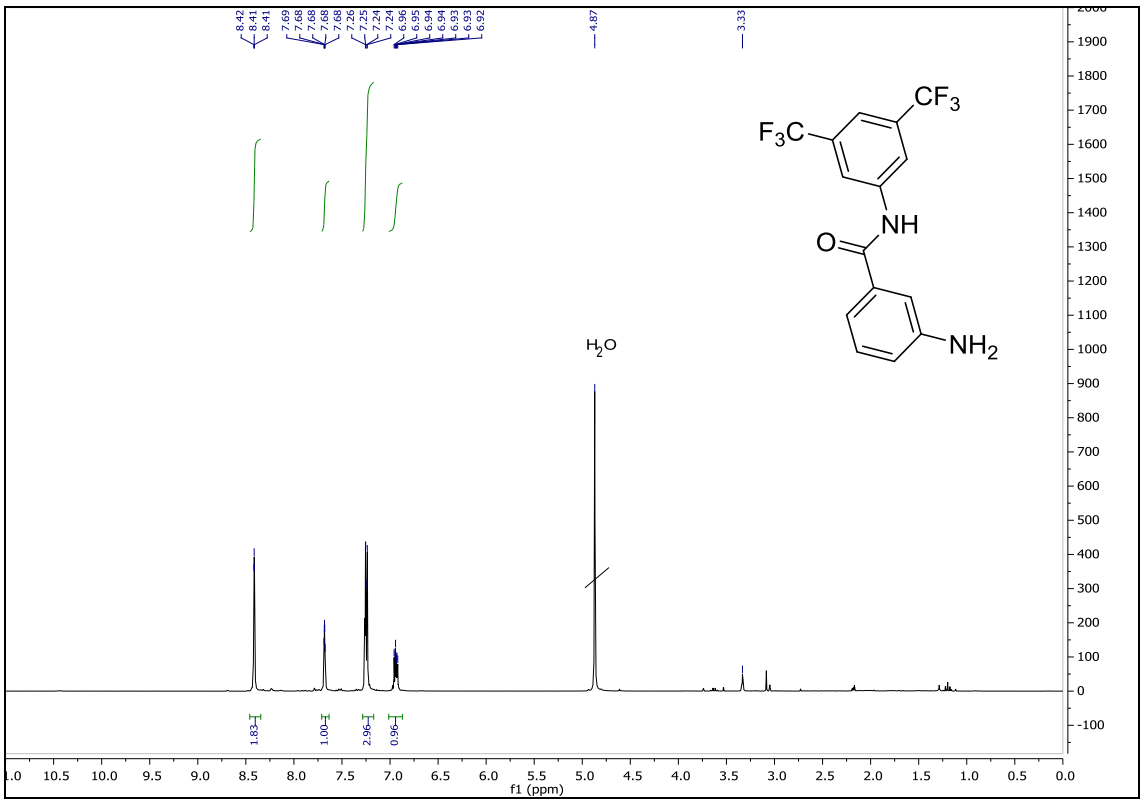


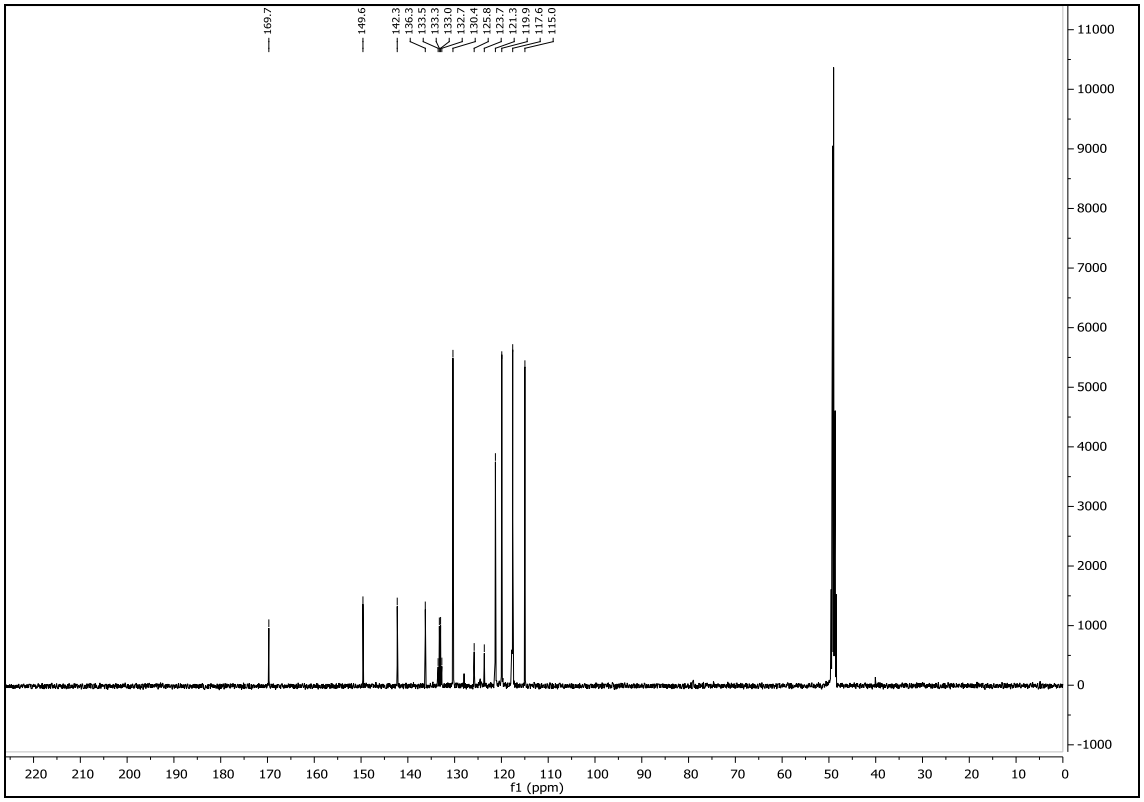
Benzyl (3-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)phenyl)carbamate



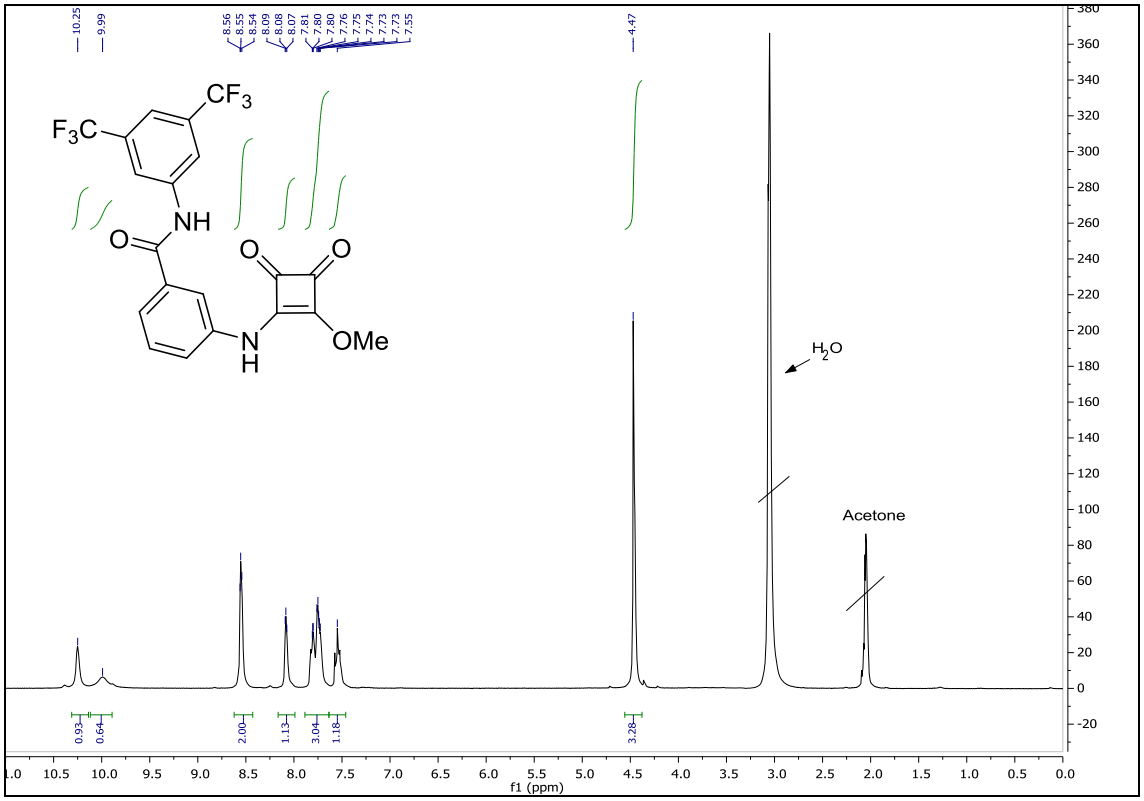


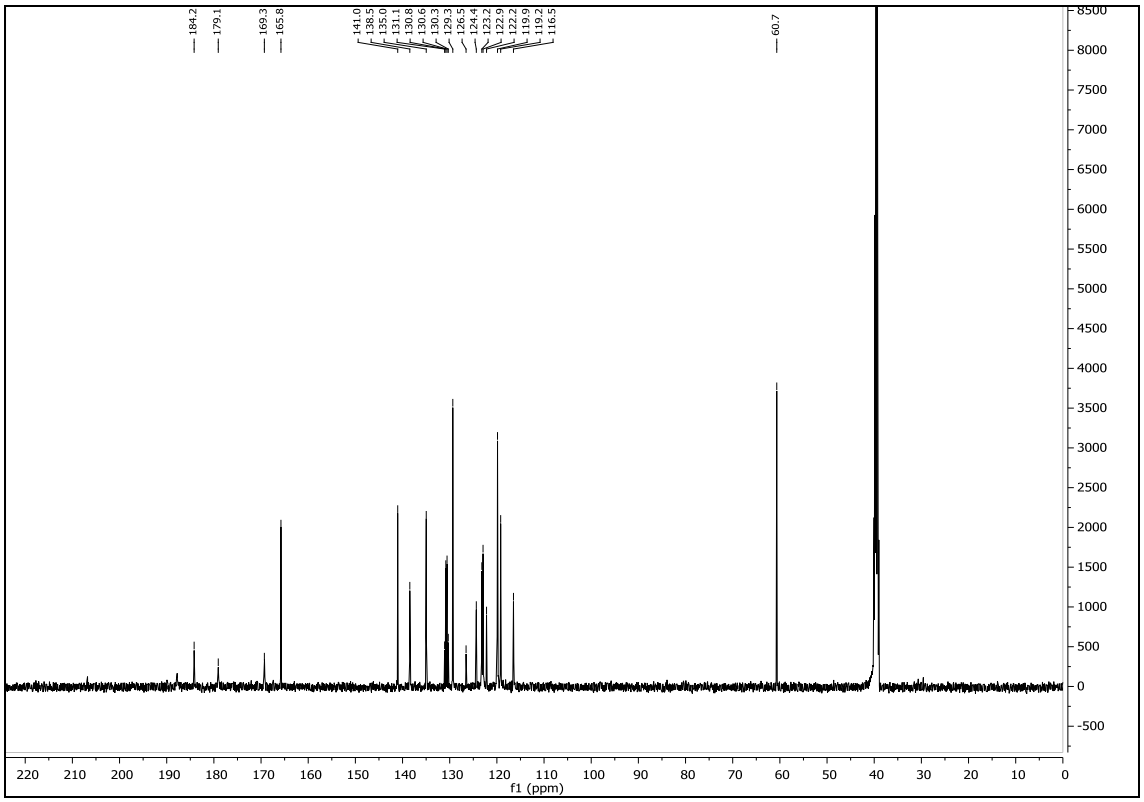
3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)benzamide



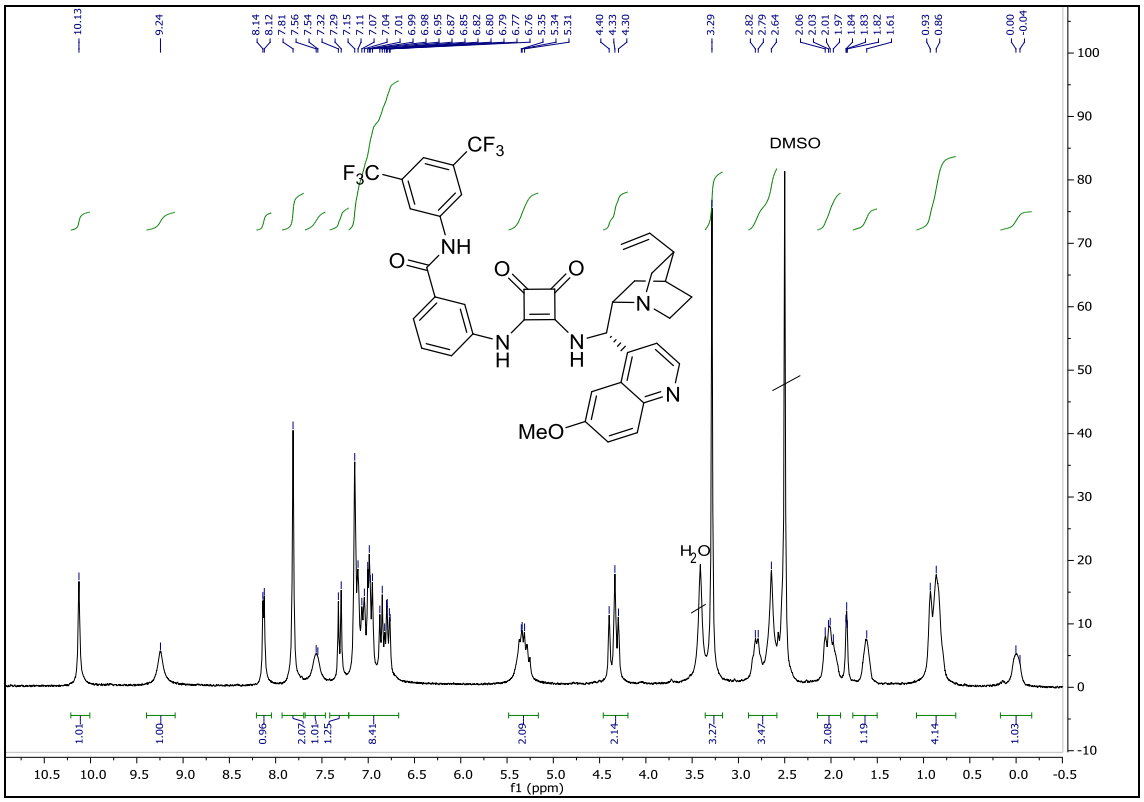


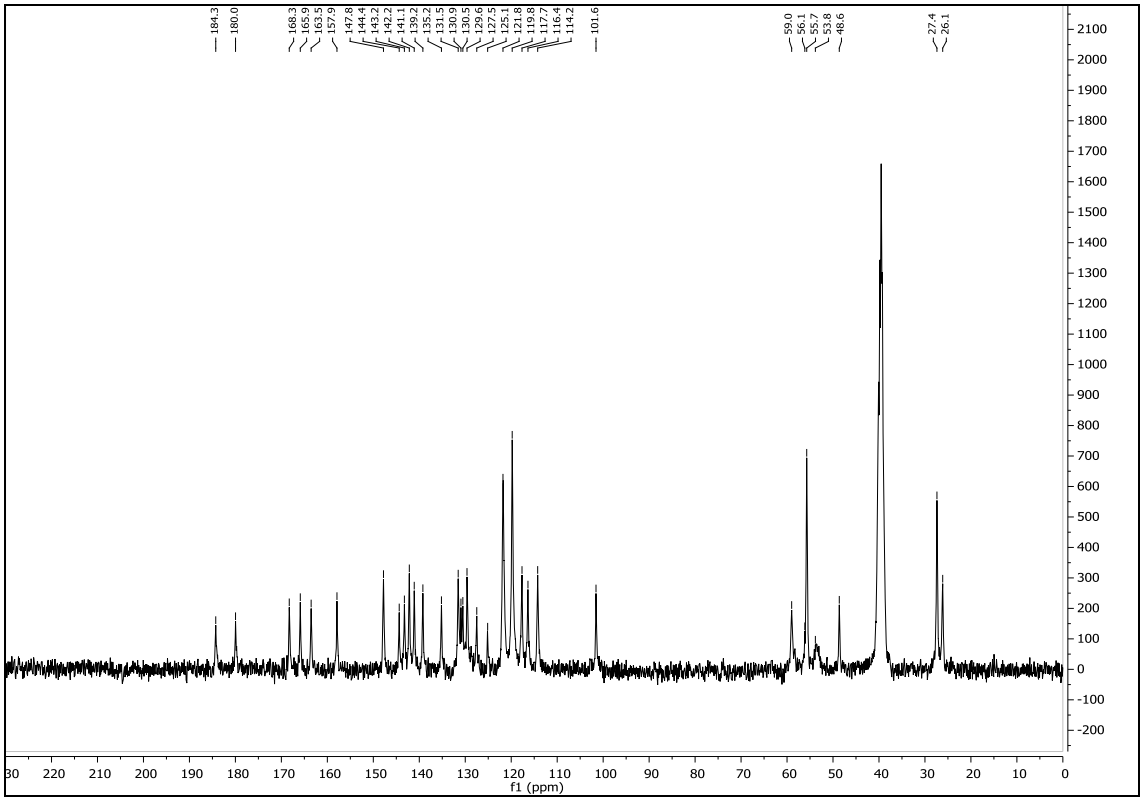
_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide



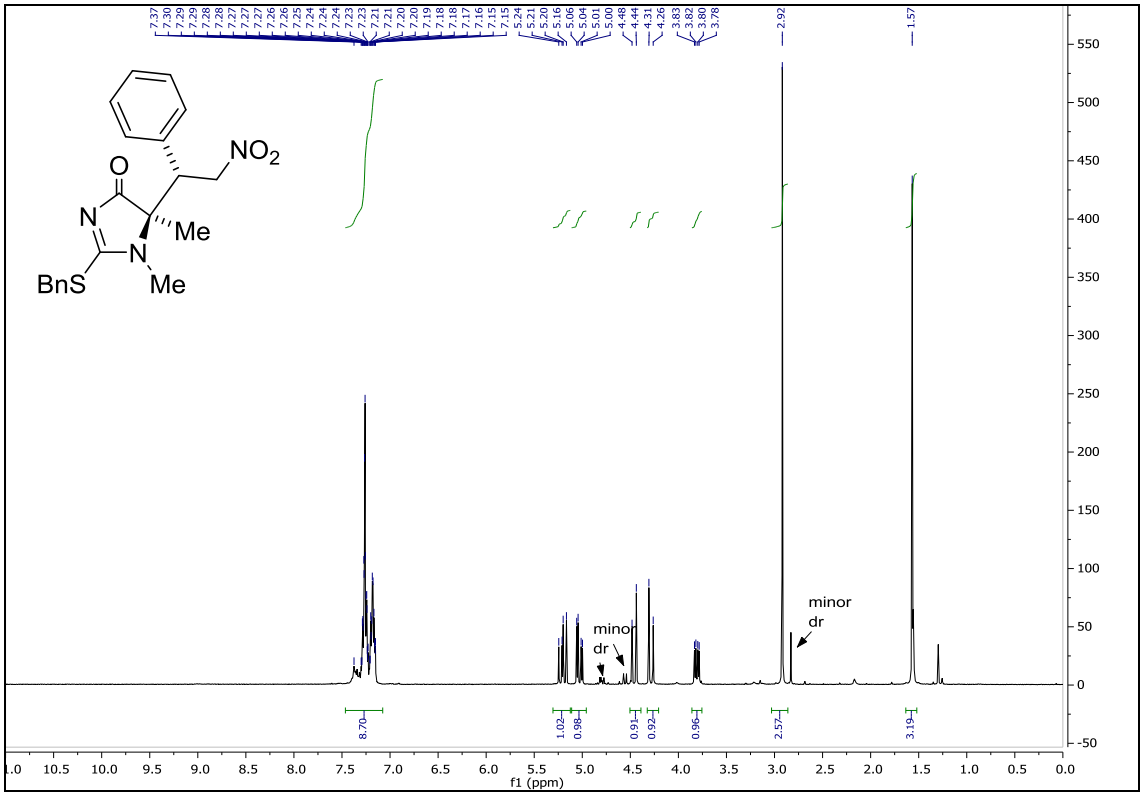


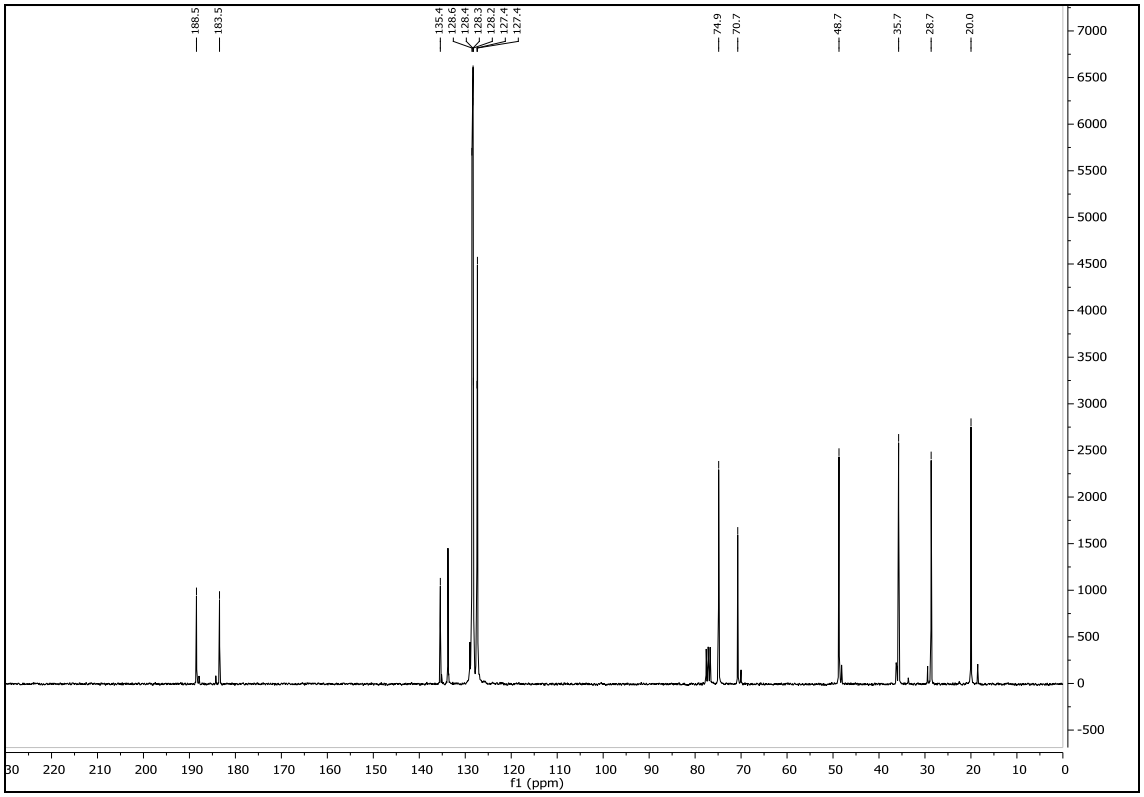
_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C9)



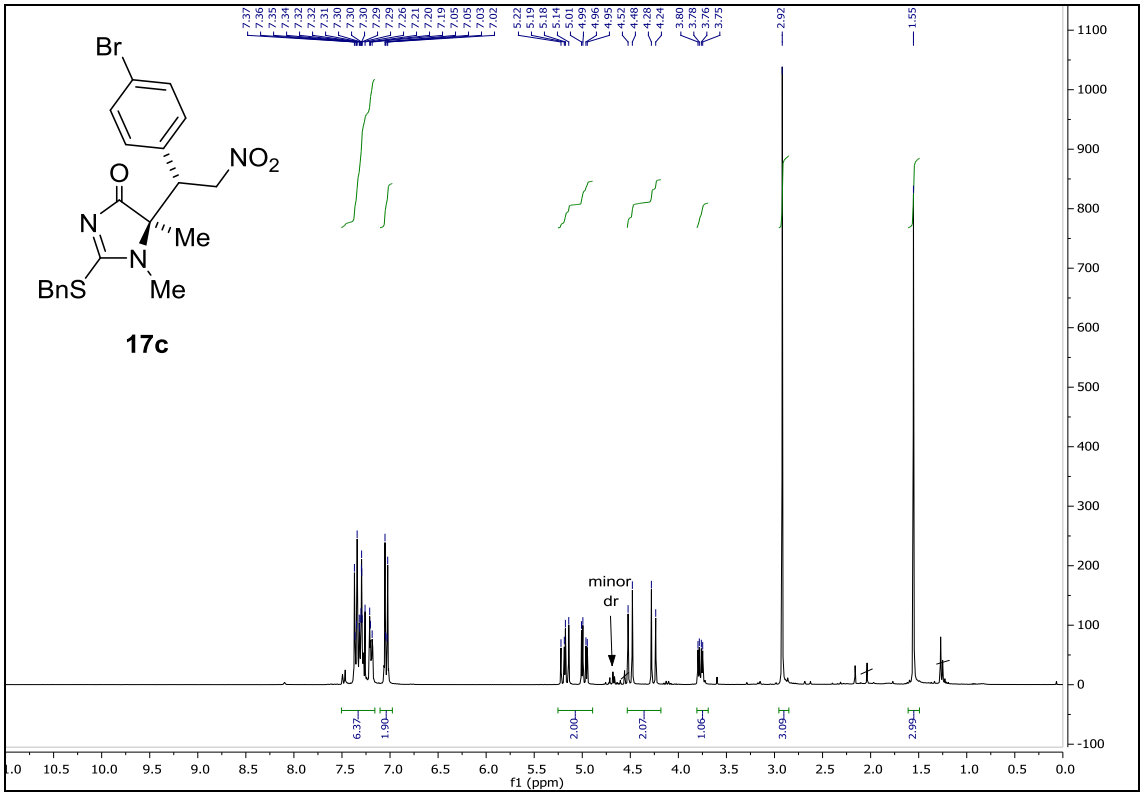


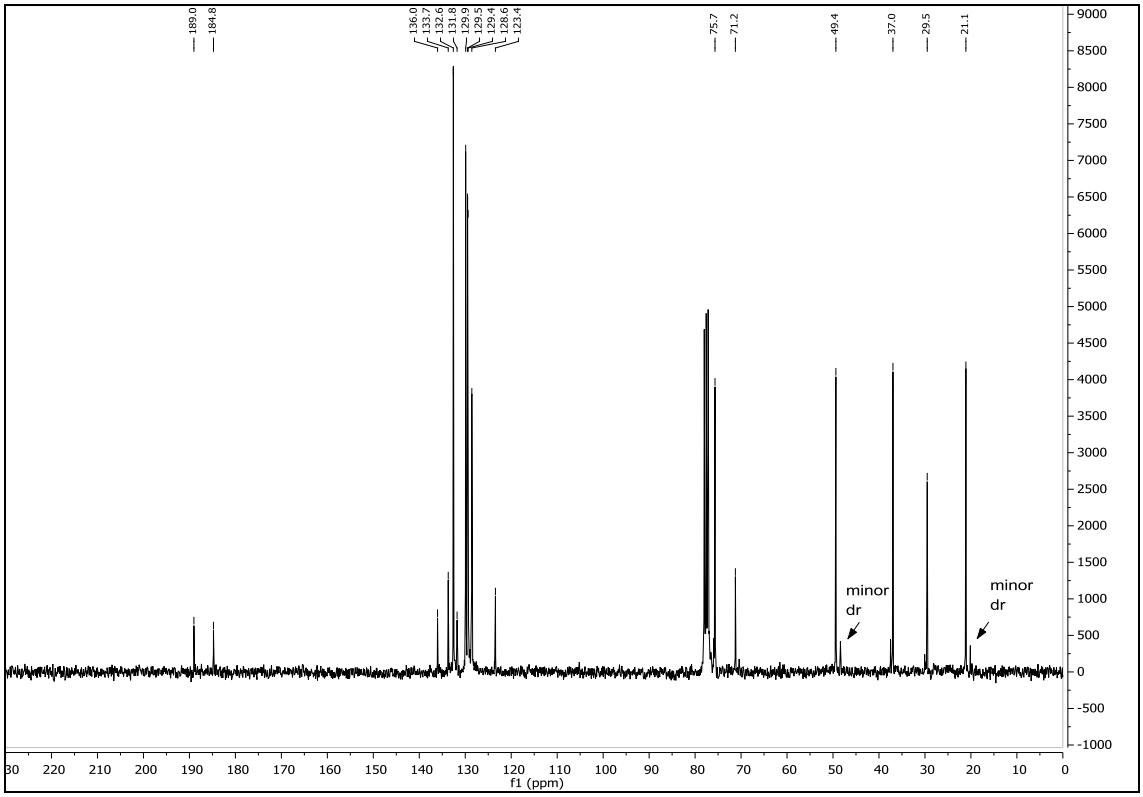
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (41a)



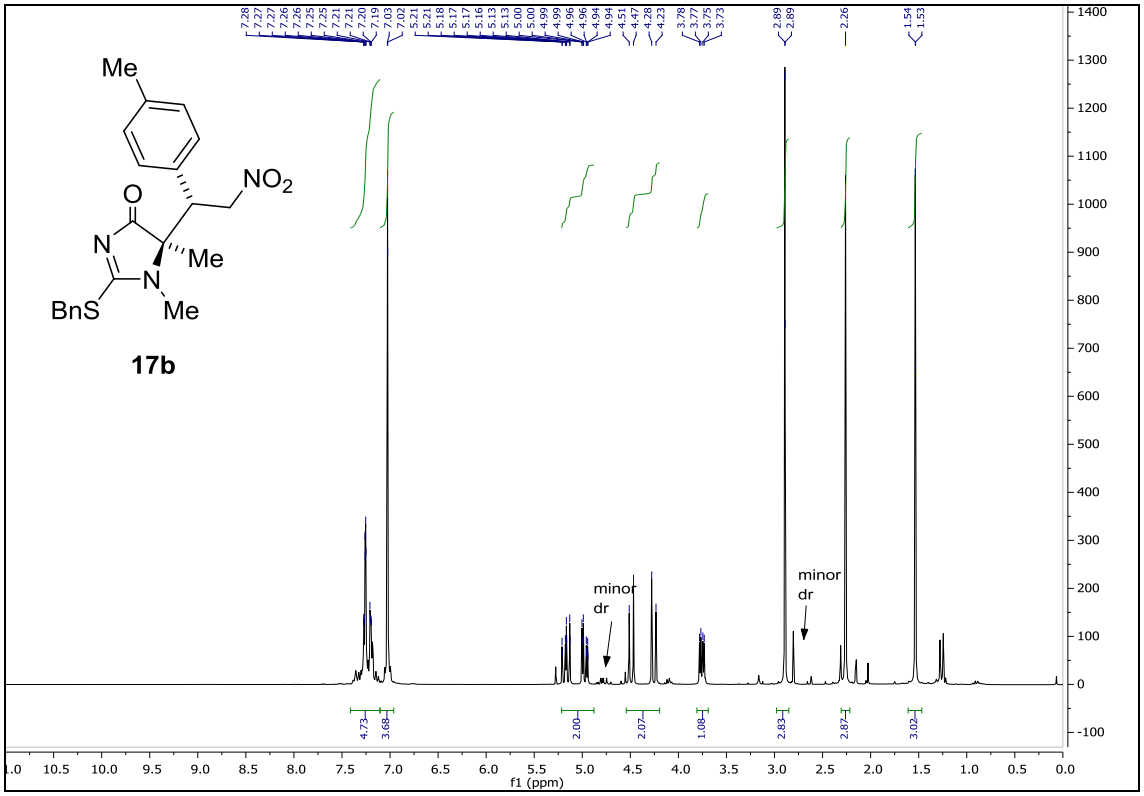


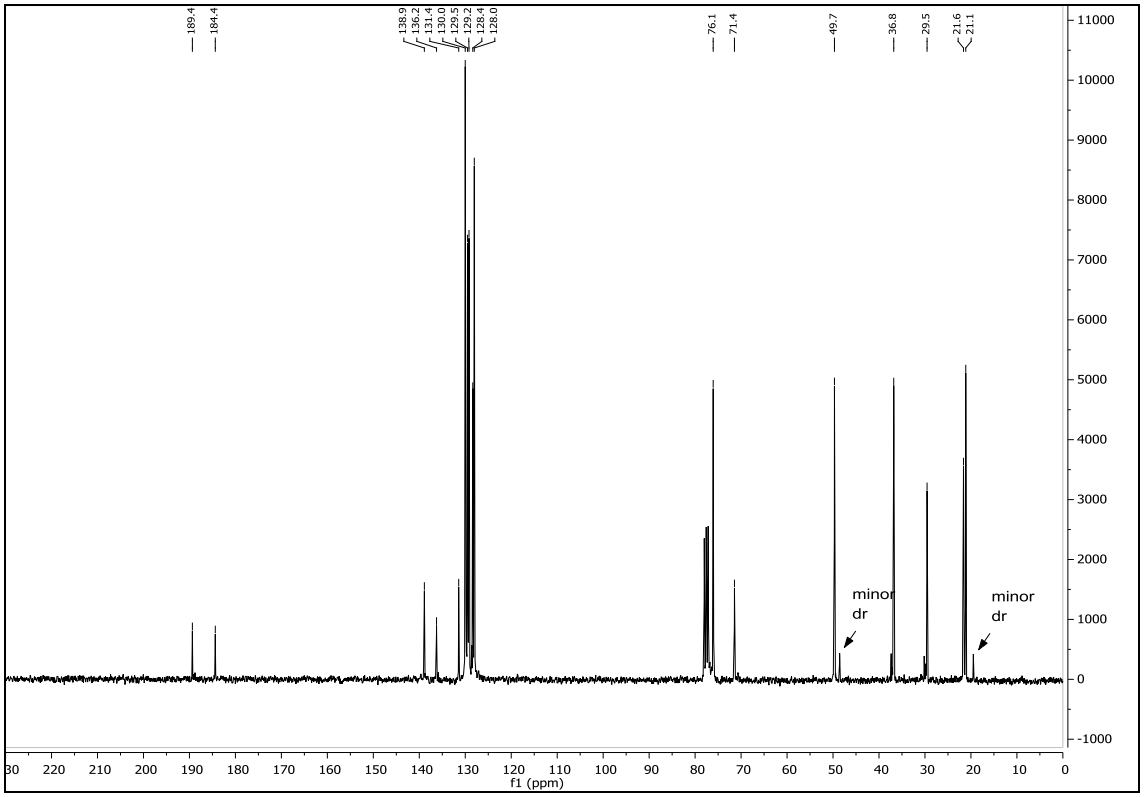
(*R*)-2-(Benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (41c)



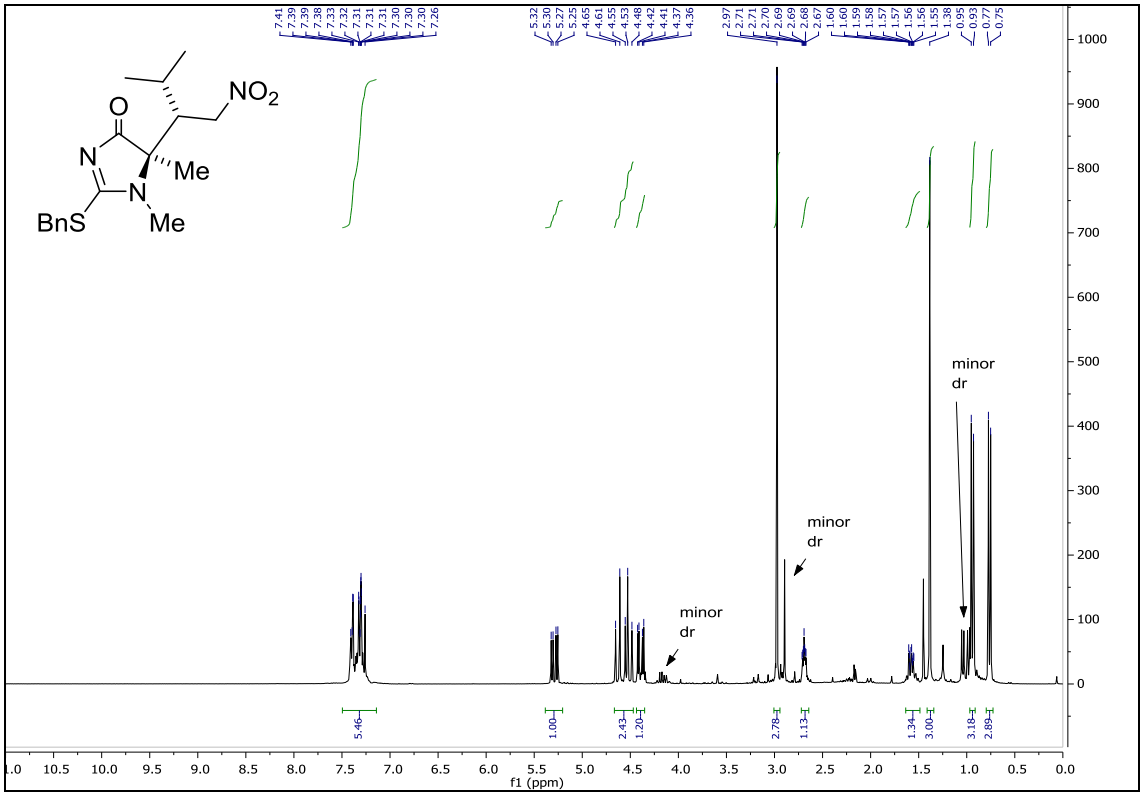


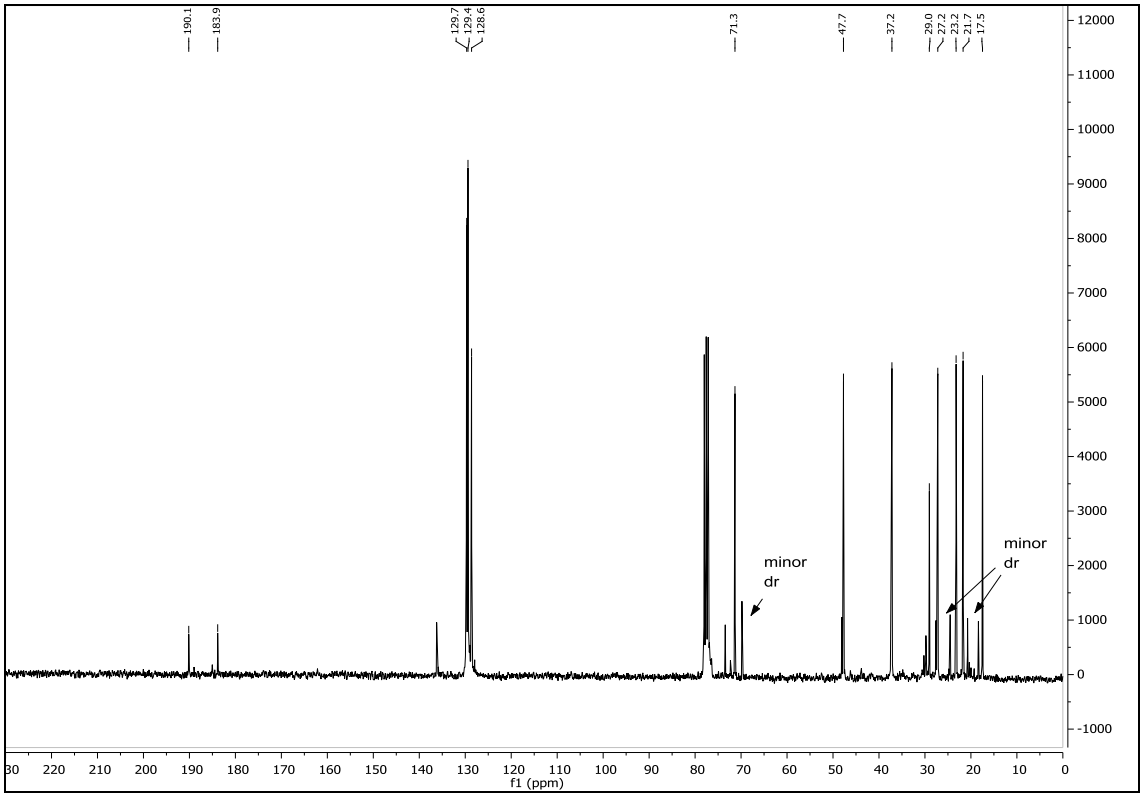
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (41d)



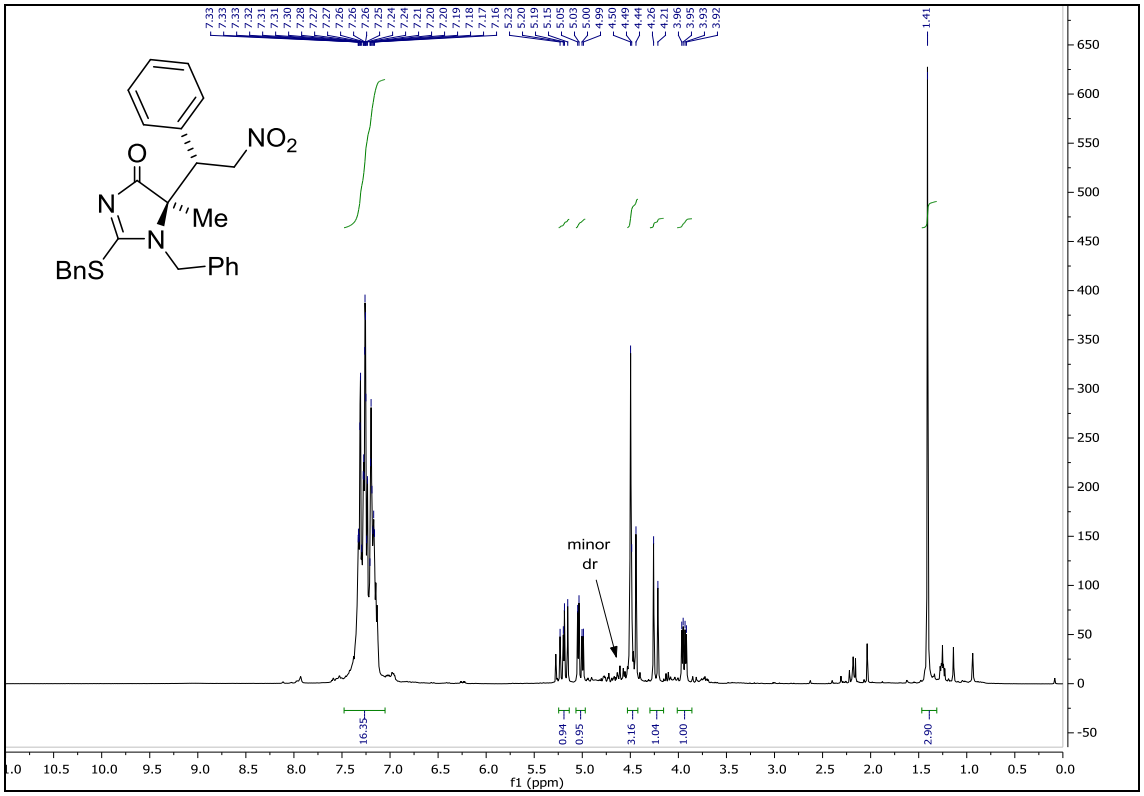


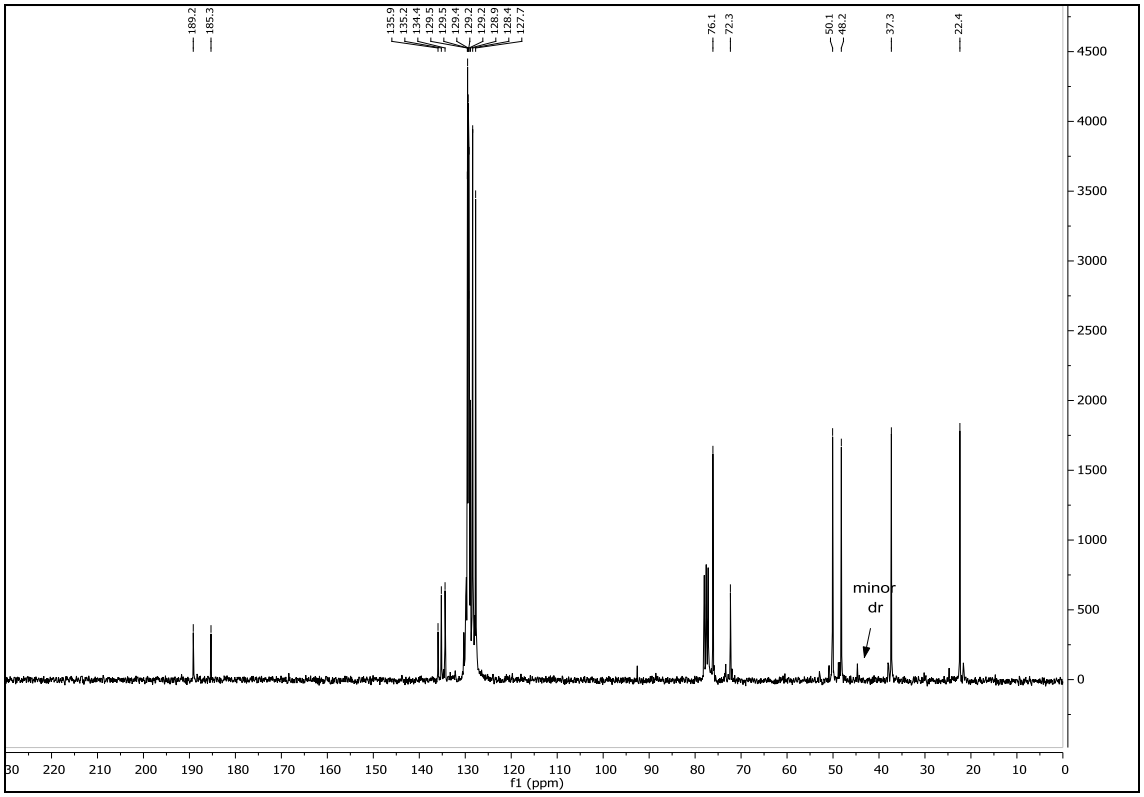
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-3-methyl-1-nitrobutan-2-yl)-1*H*-imidazol-4(5*H*)-one (41h)



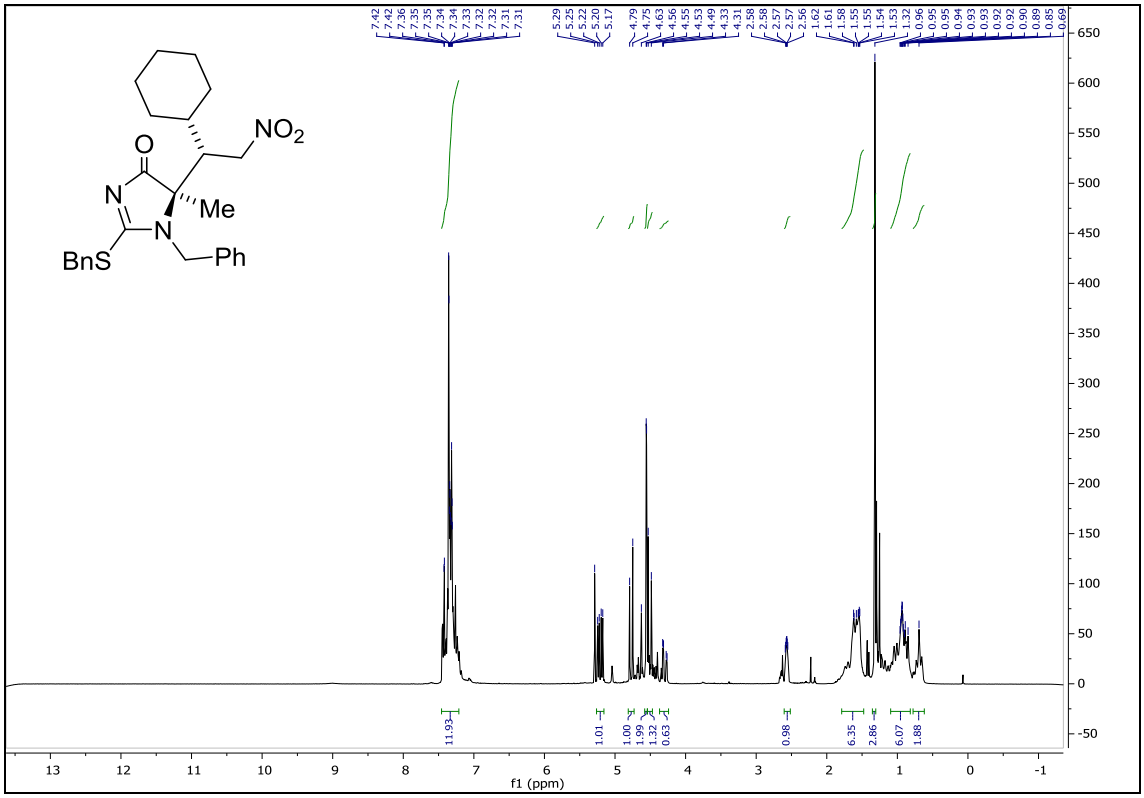


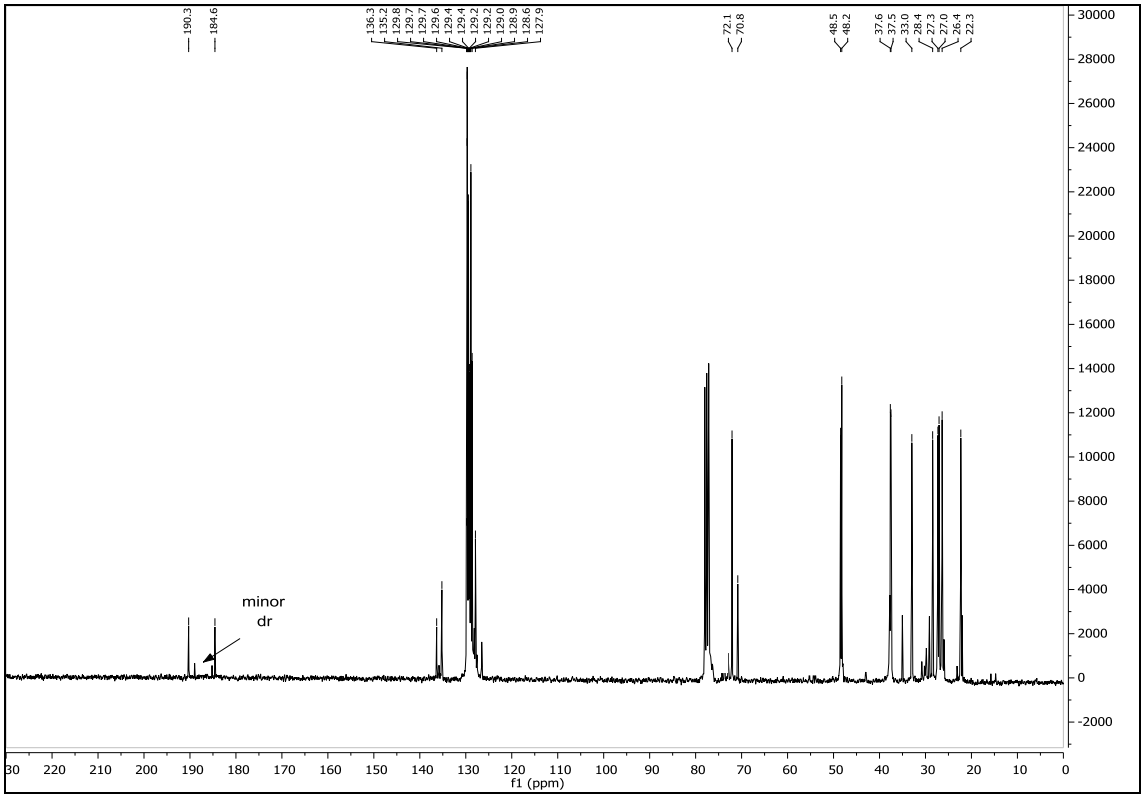
(*R*)-1-Benzyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (42a)



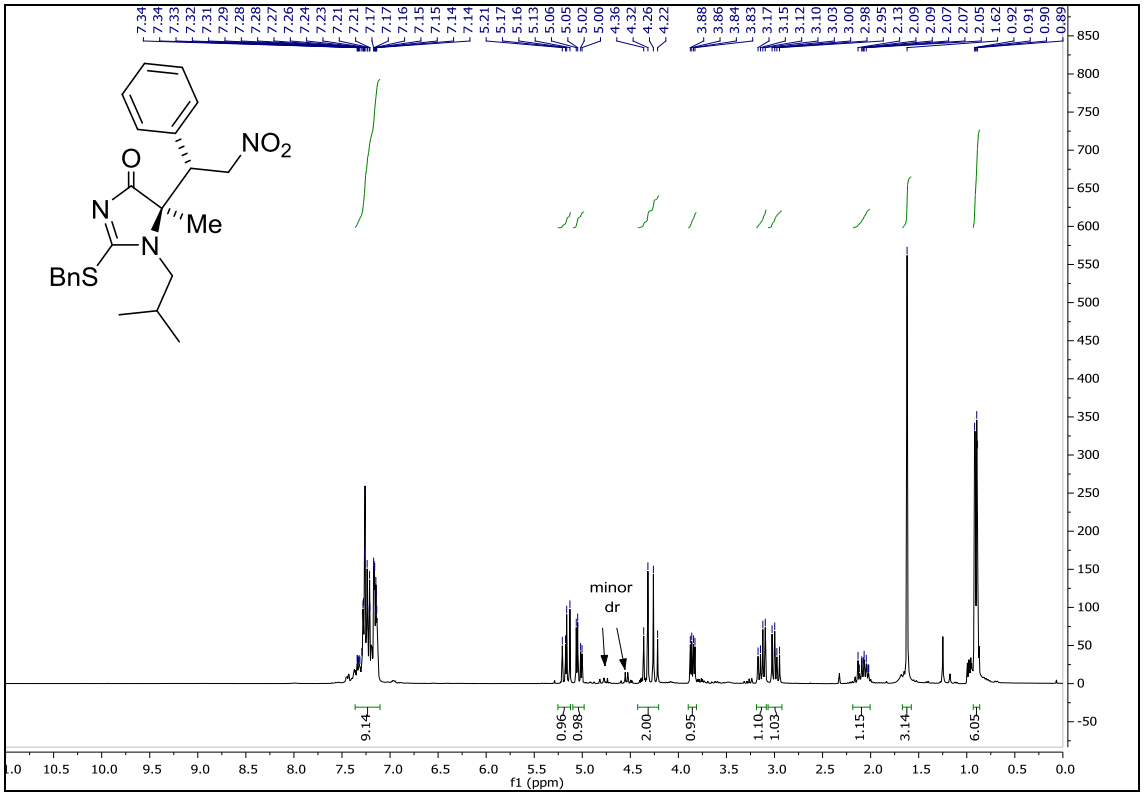


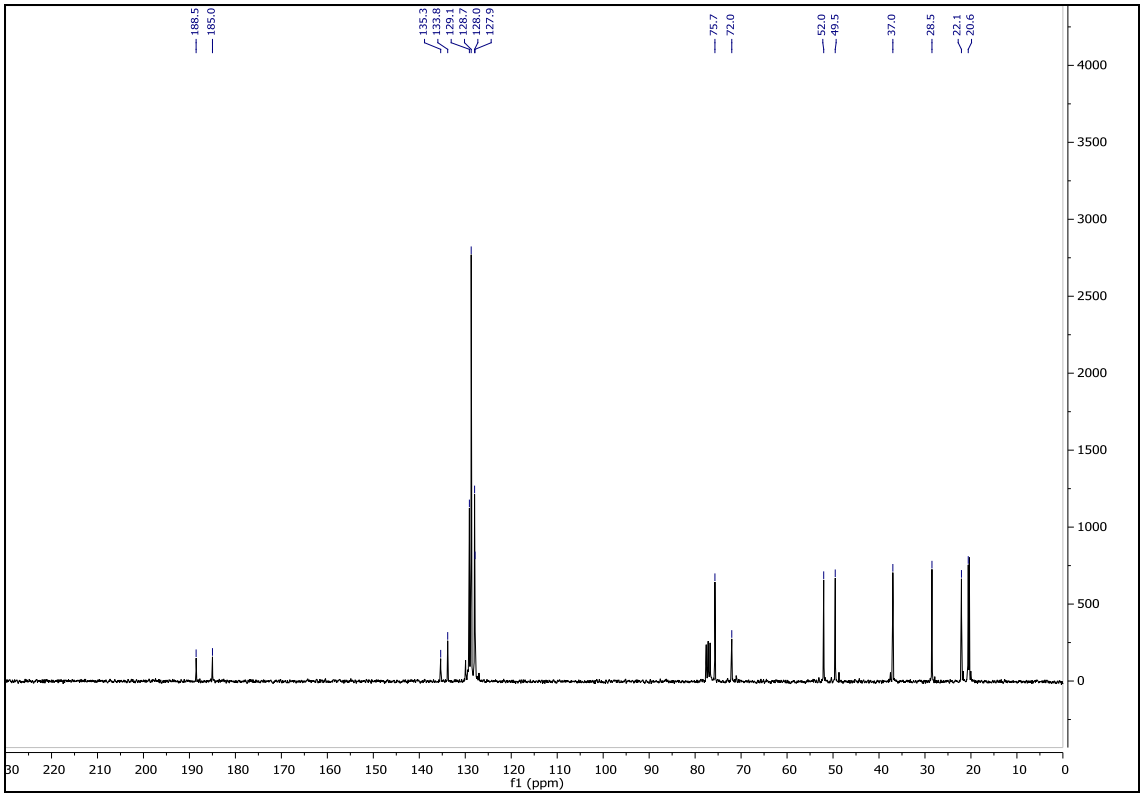
(*R*)-1-Benzyl-2-(benzylthio)-5-((*R*)-1-cyclohexyl-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (42k)



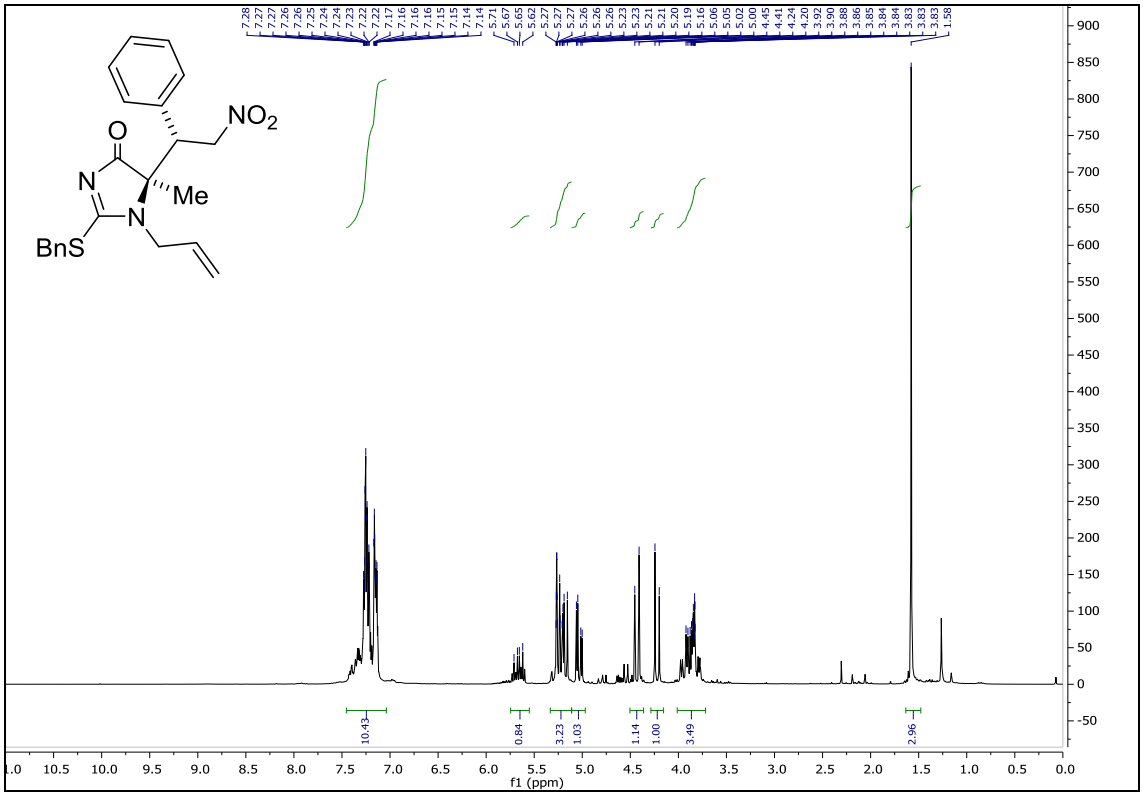


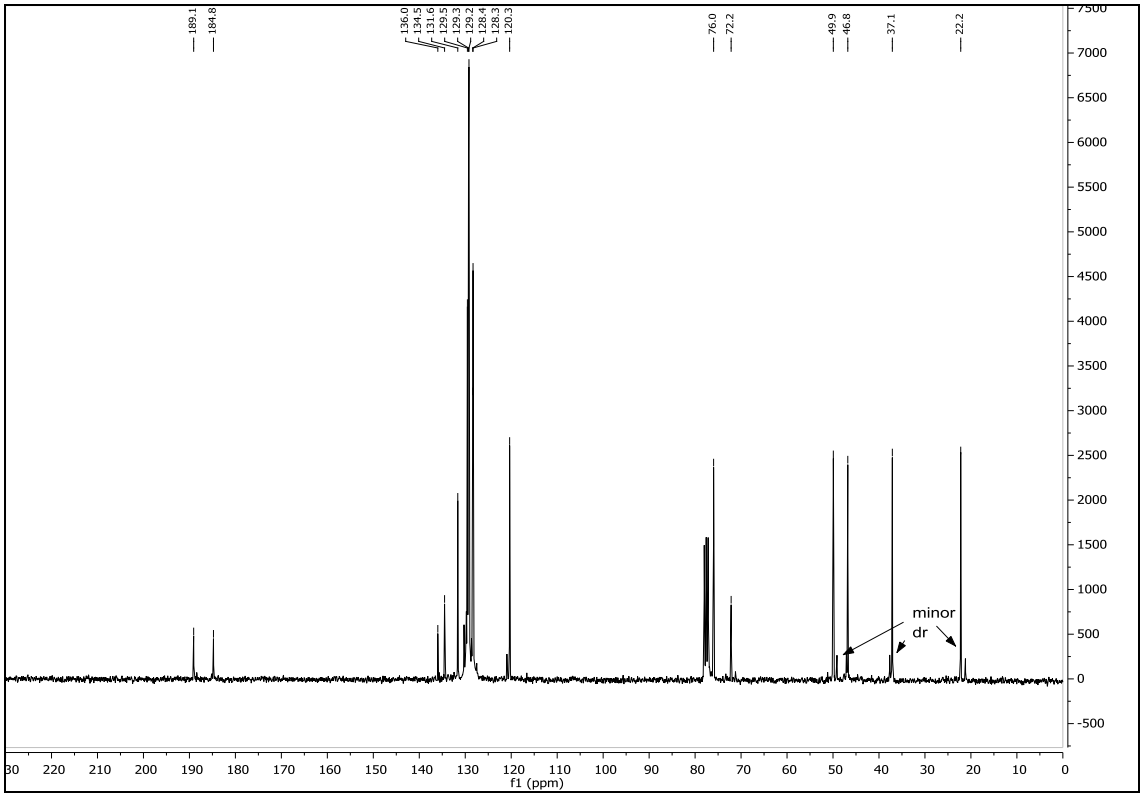
(*R*)-2-(Benzylthio)-1-isobutyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (43a)



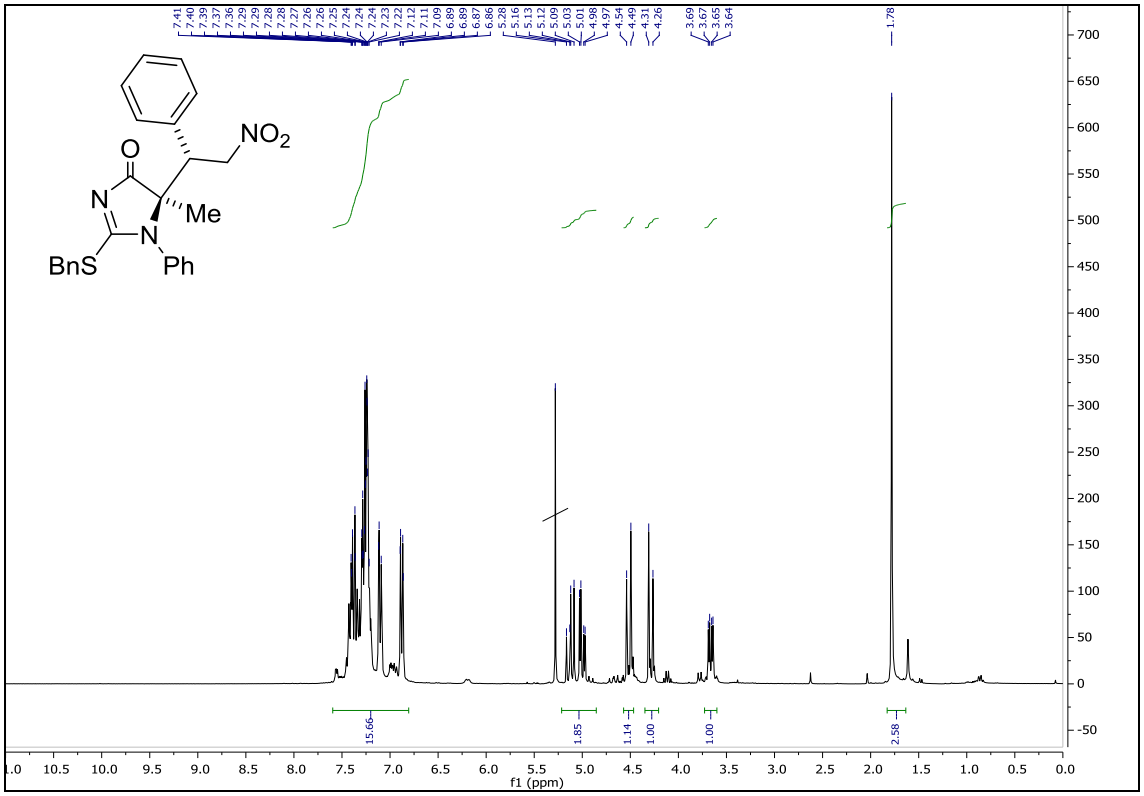


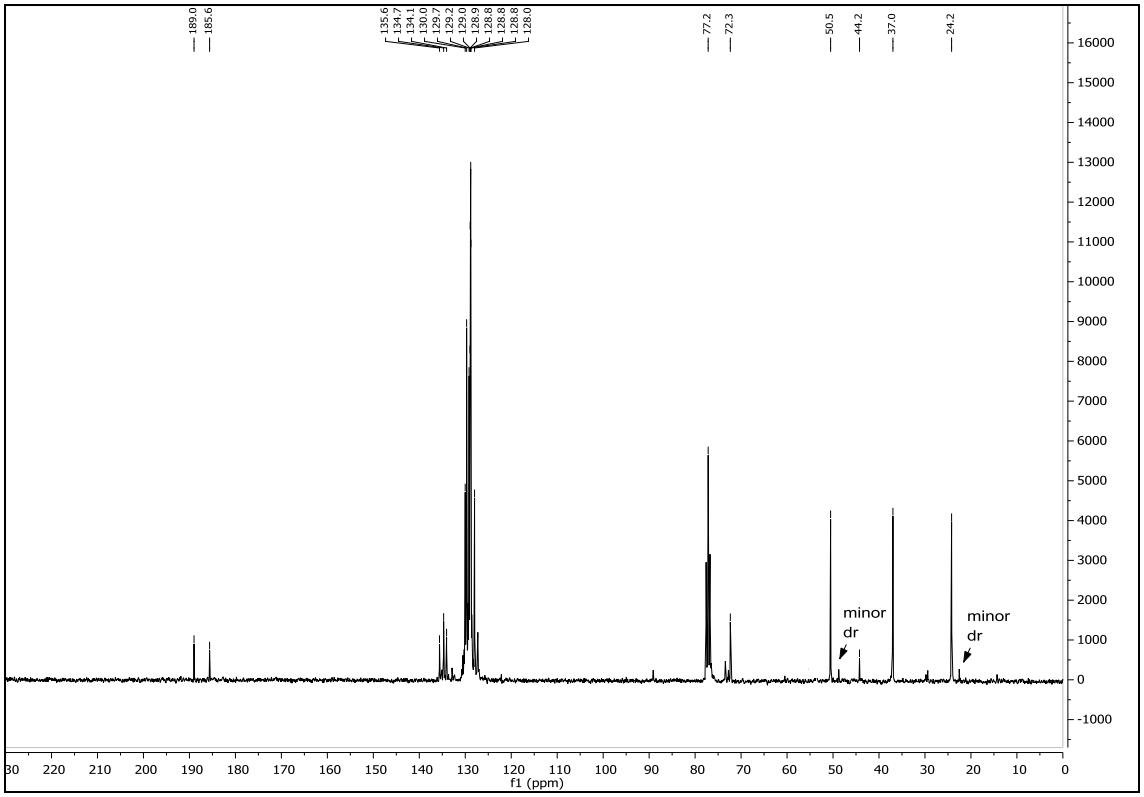
(*R*)-1-Allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (44a)



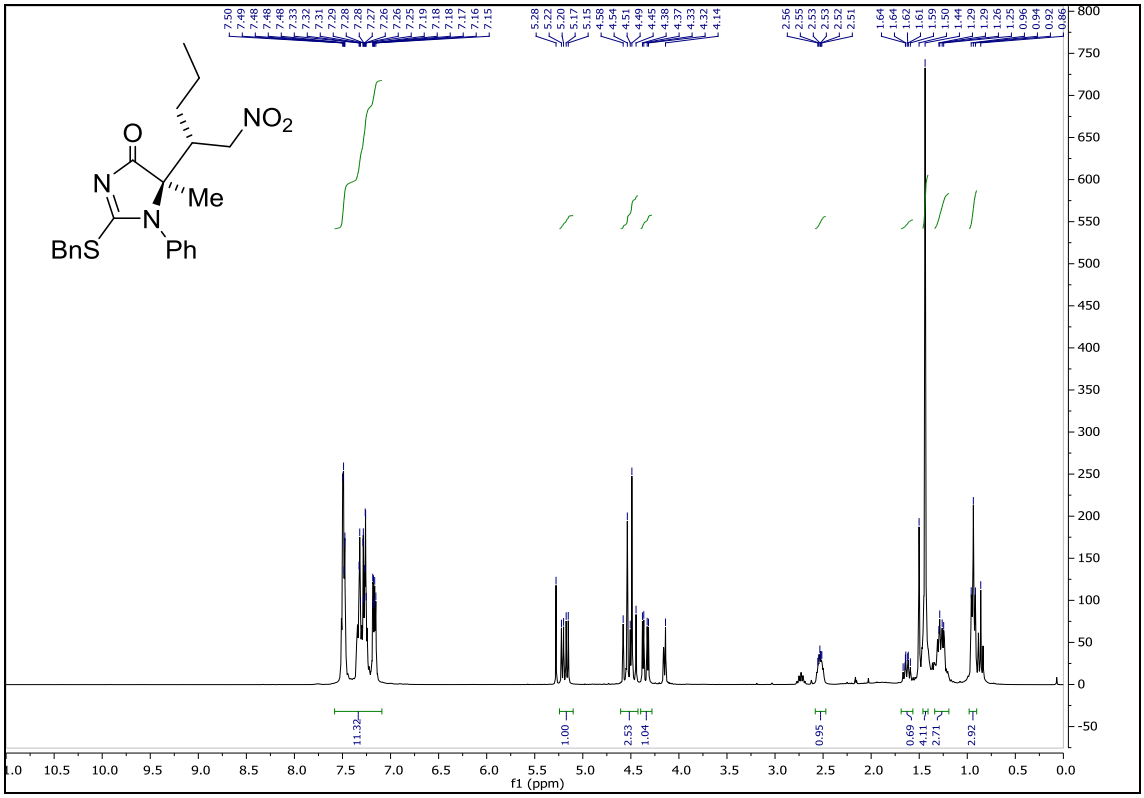


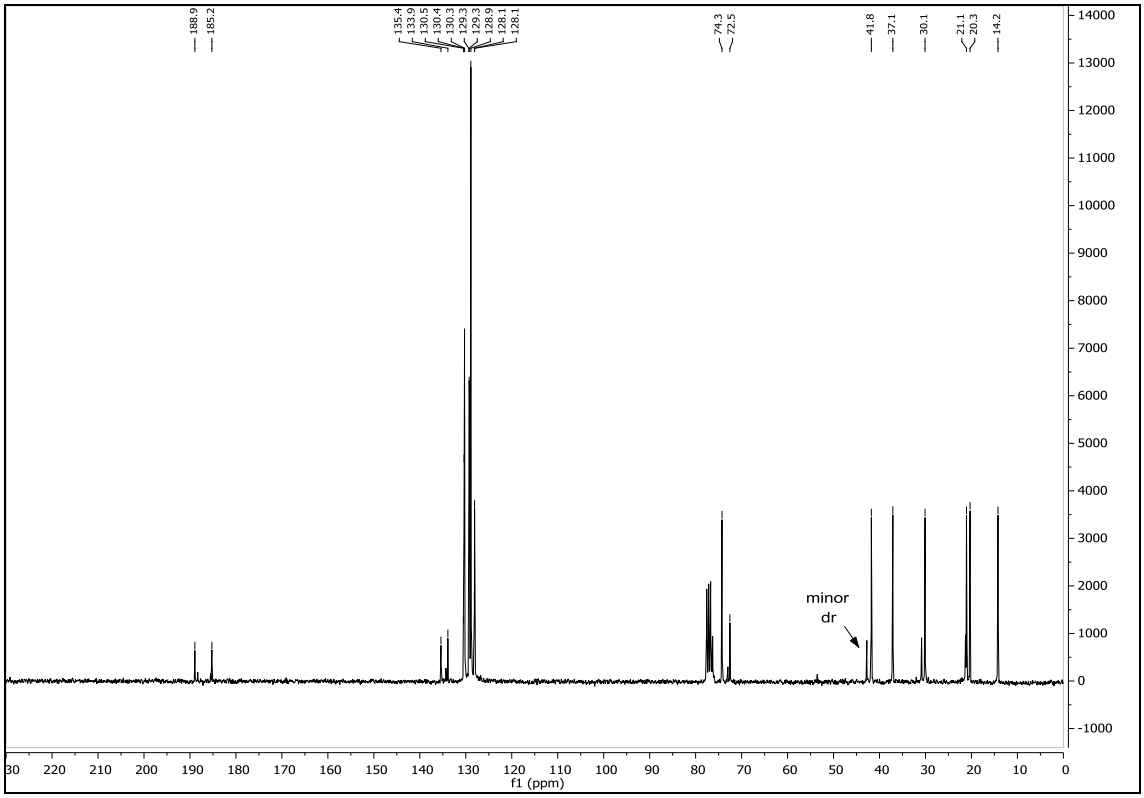
(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (45a)



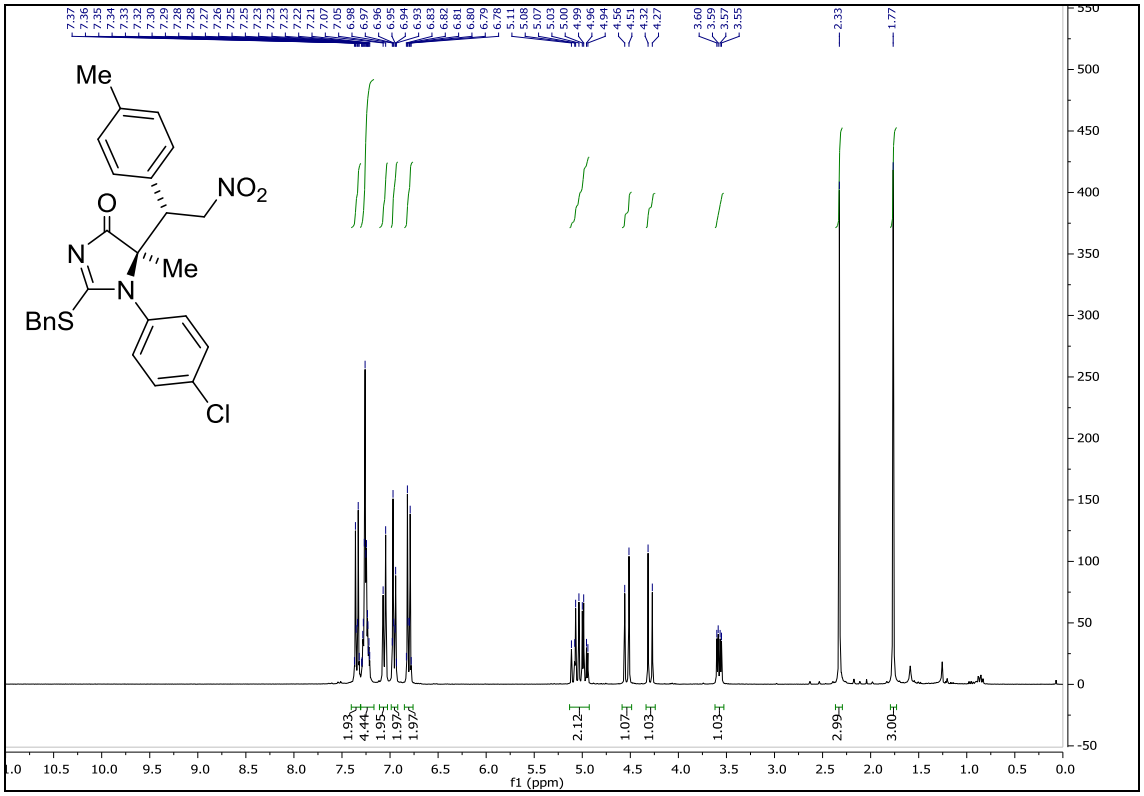


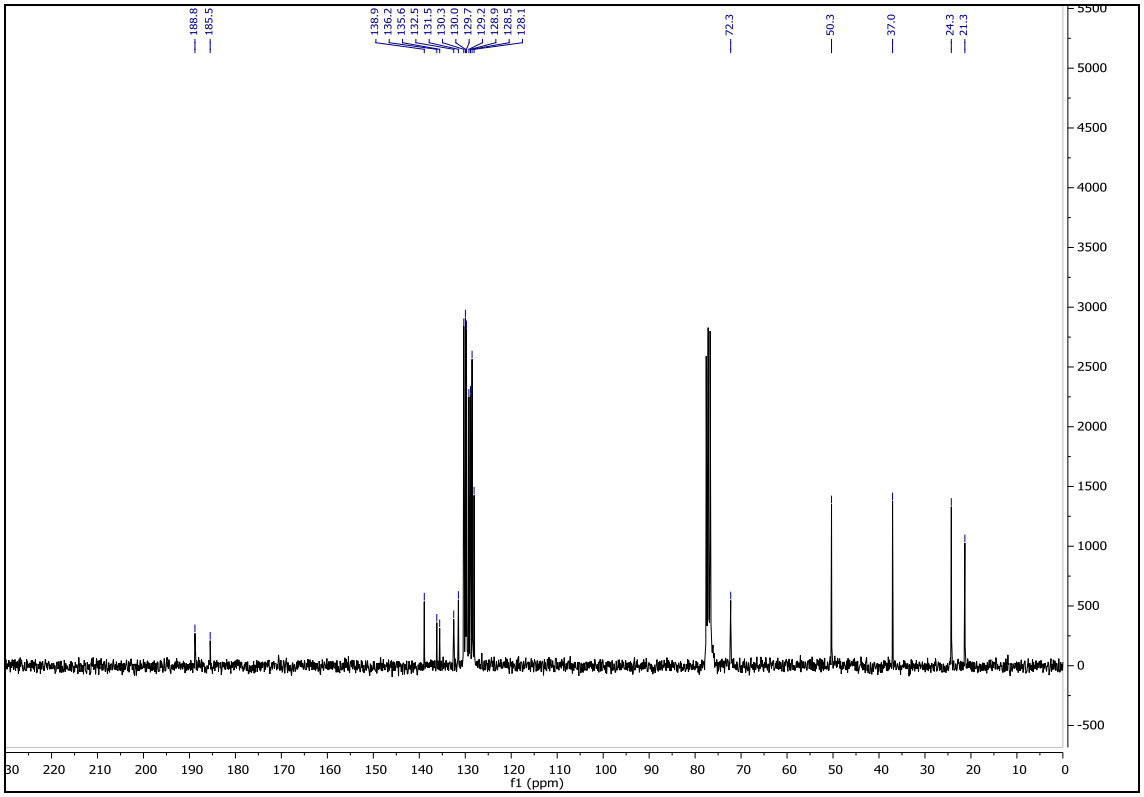
(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-1-nitropentan-2-yl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (45l)



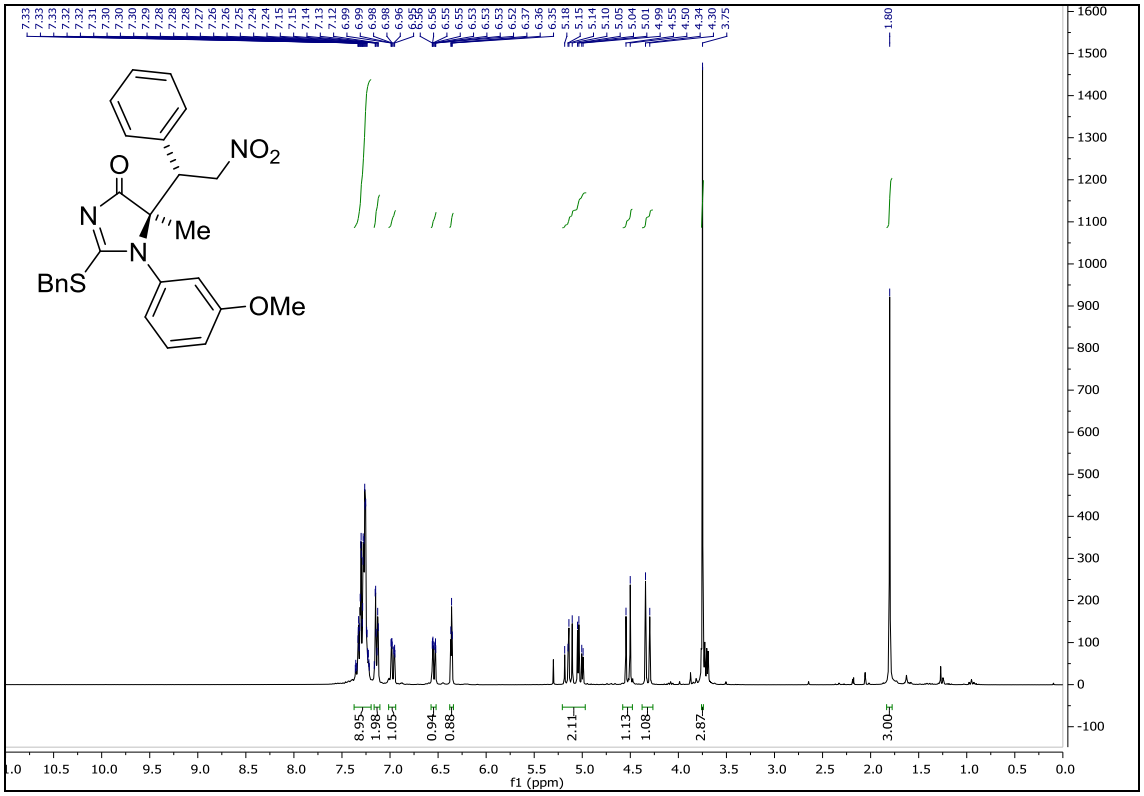


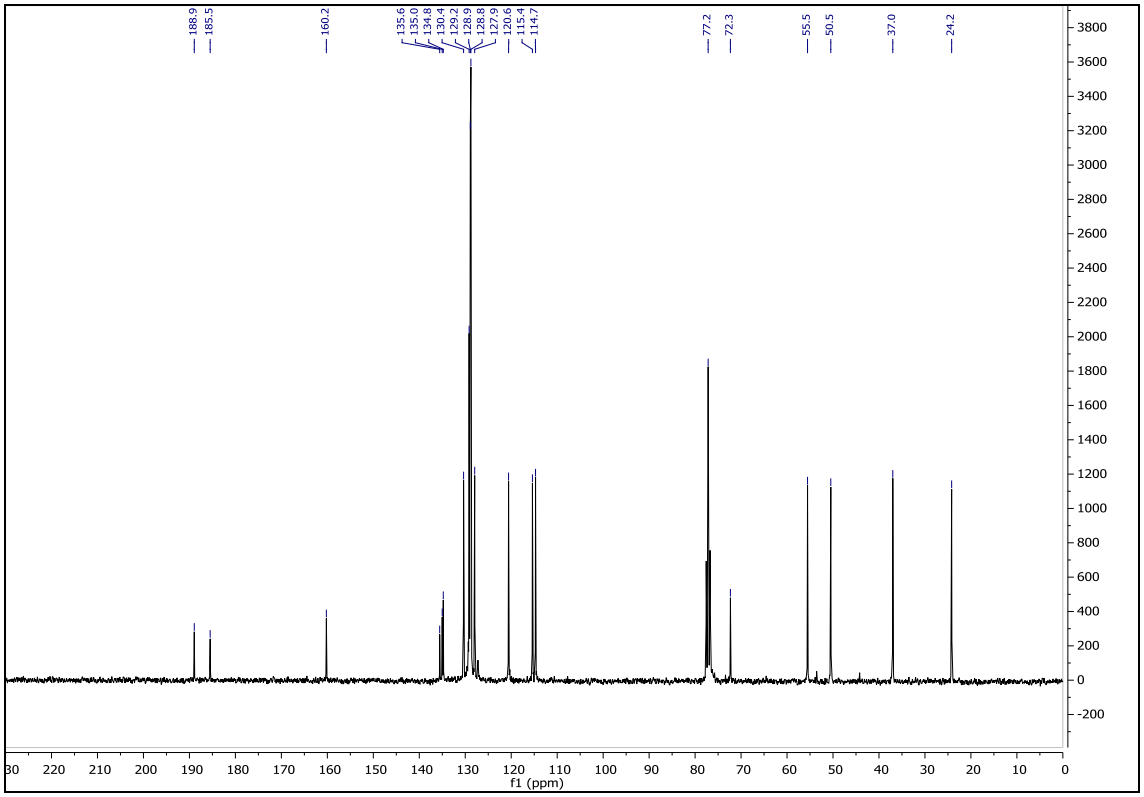
(*R*)-2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (46d)



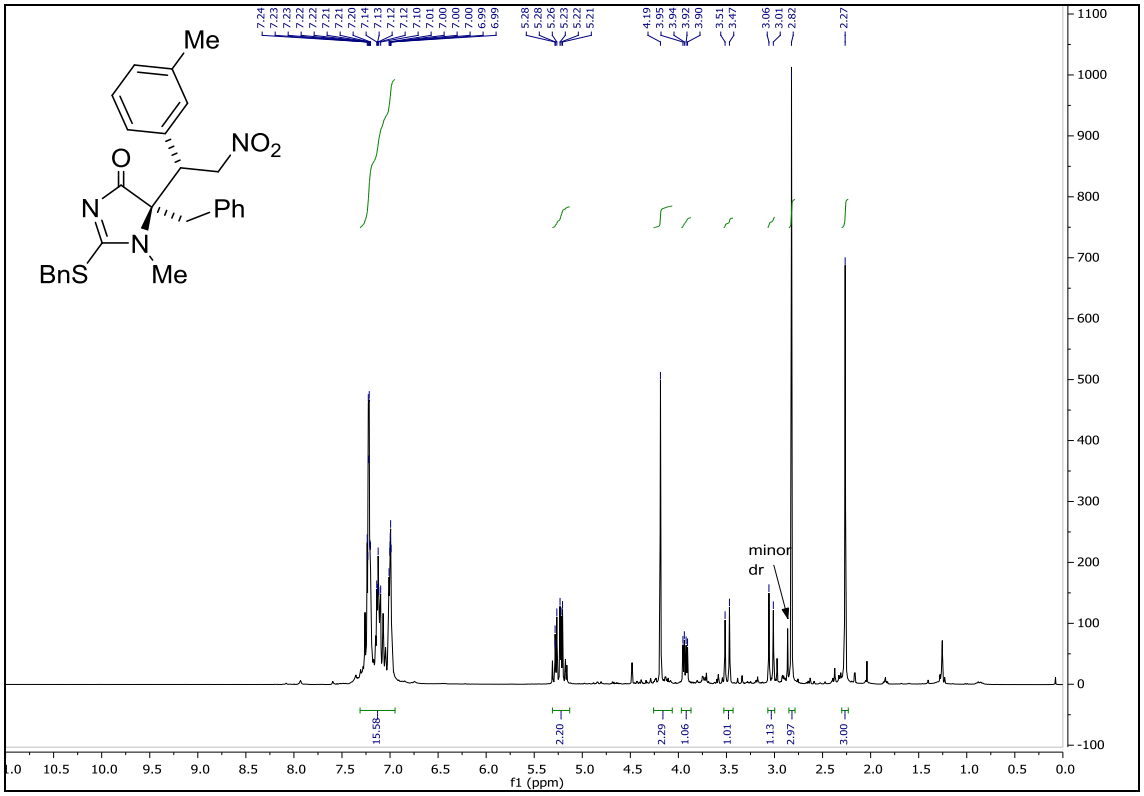


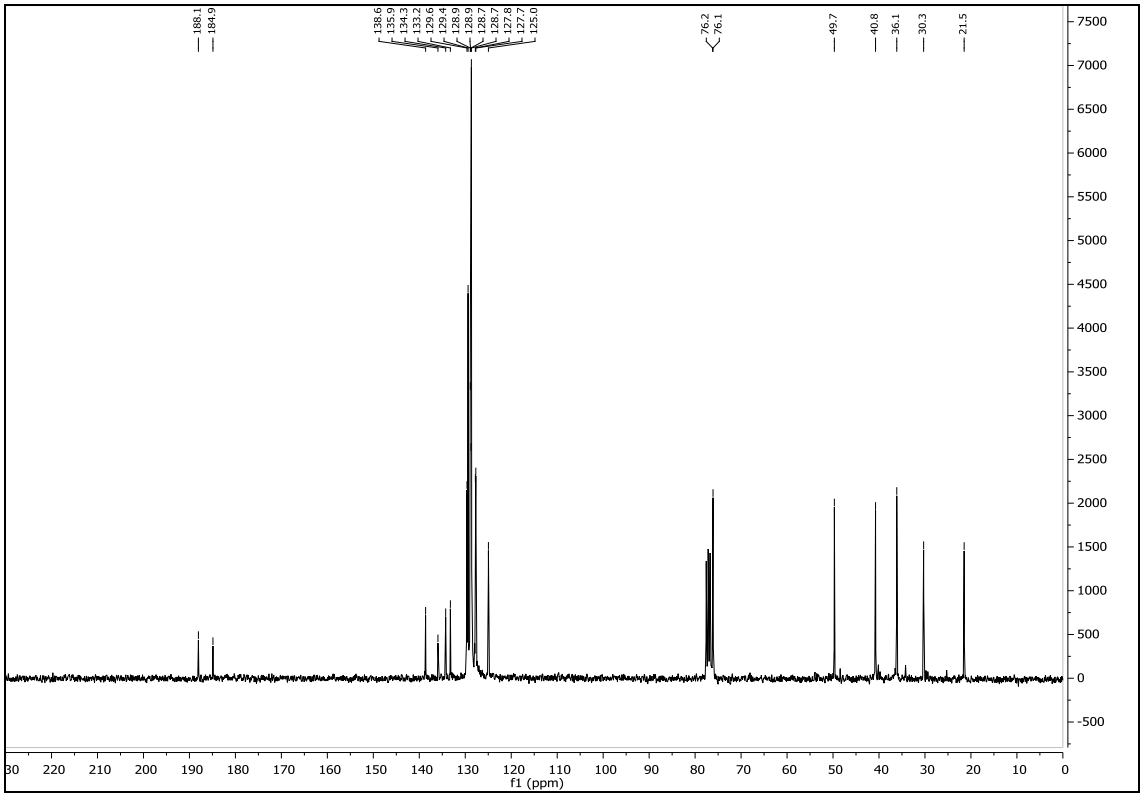
(*R*)-2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (47a)



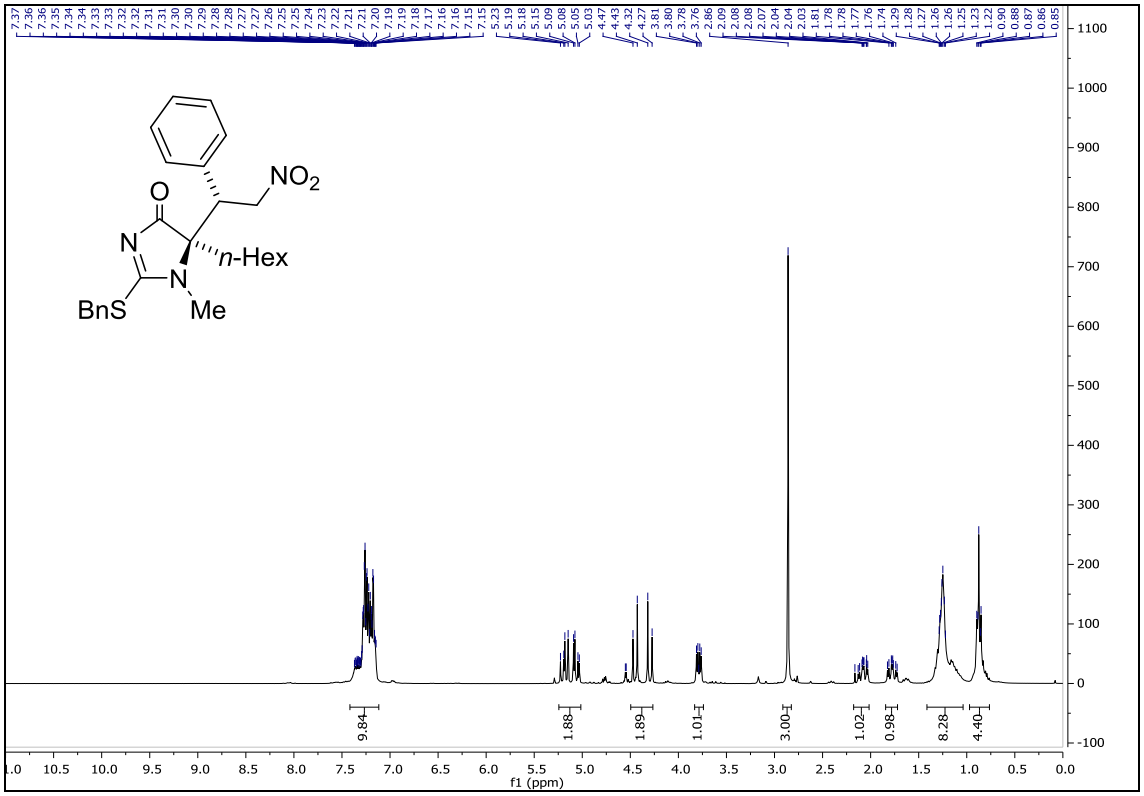


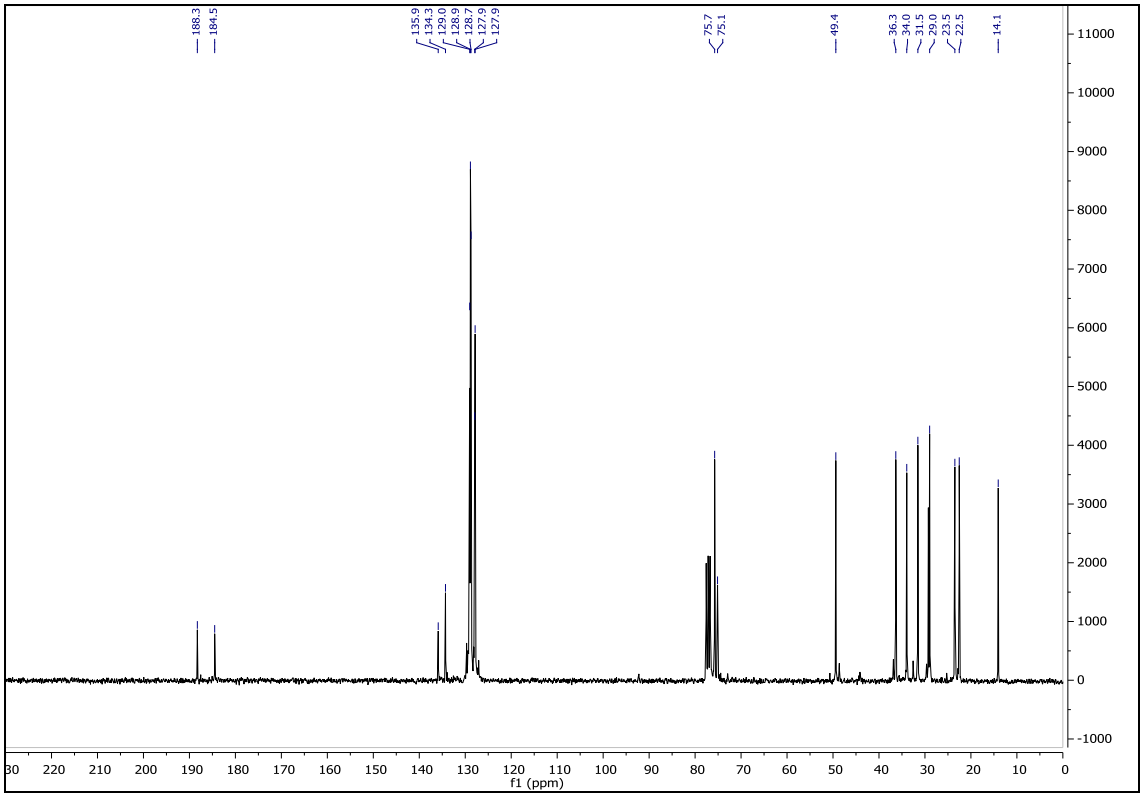
(*R*)-5-Benzyl-2-(benzylthio)-1-methyl-5-((*R*)-2-nitro-1-(*m*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (48h)



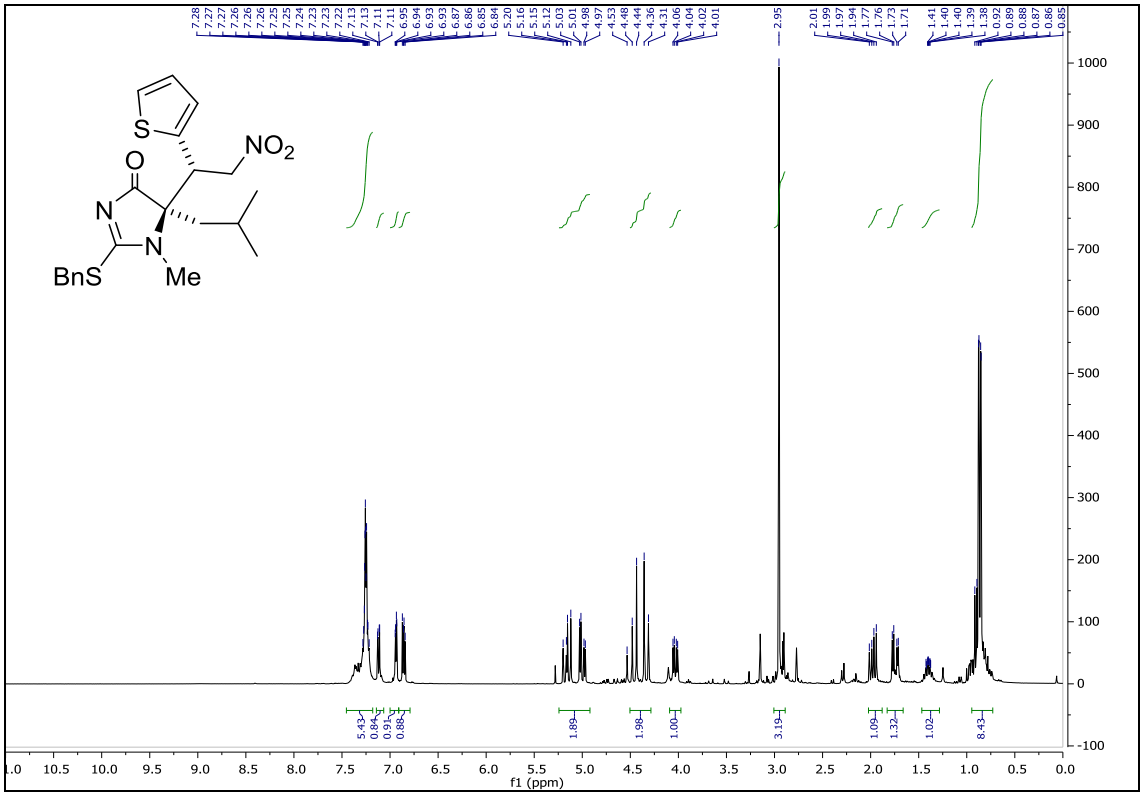


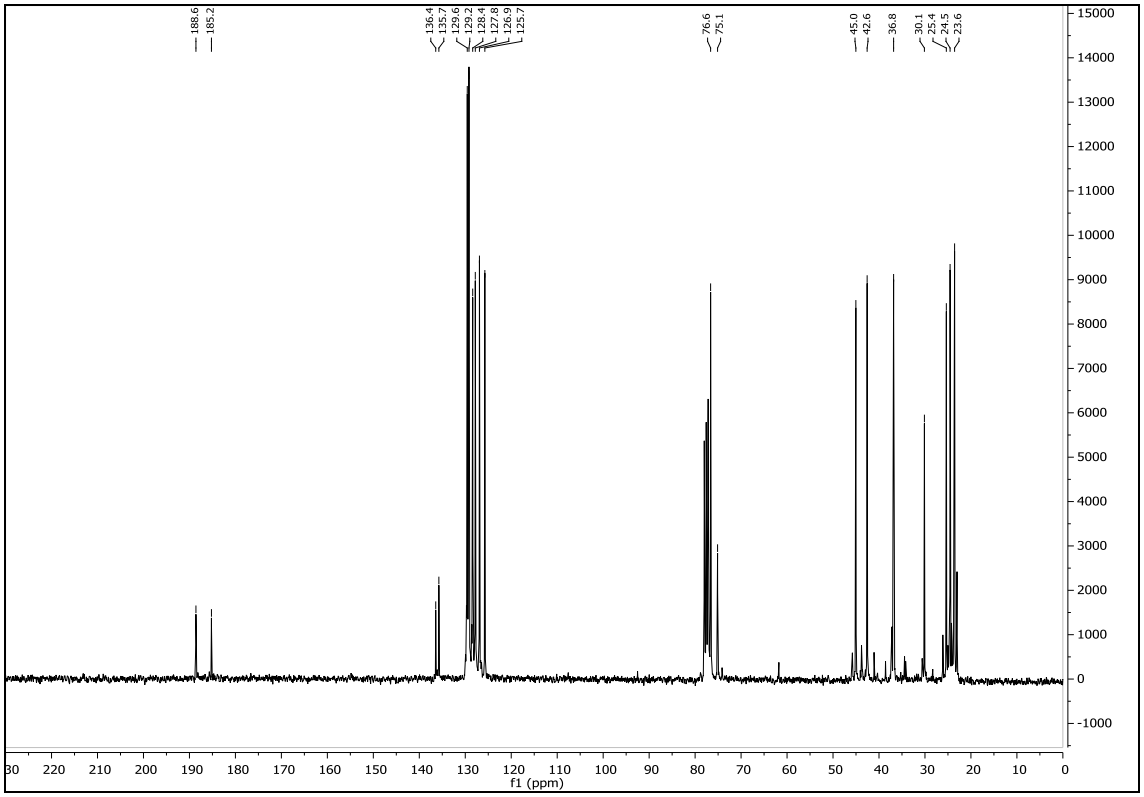
(*R*)-2-(Benzylthio)-5-hexyl-1-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (49a)



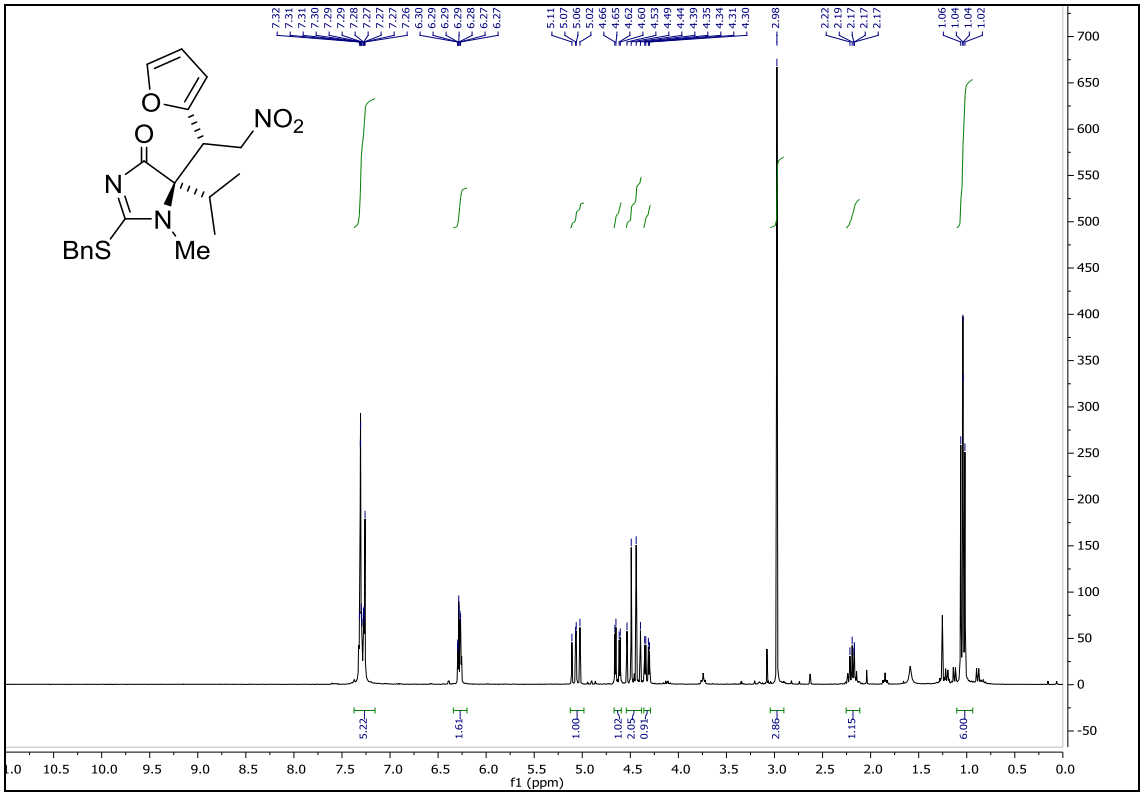


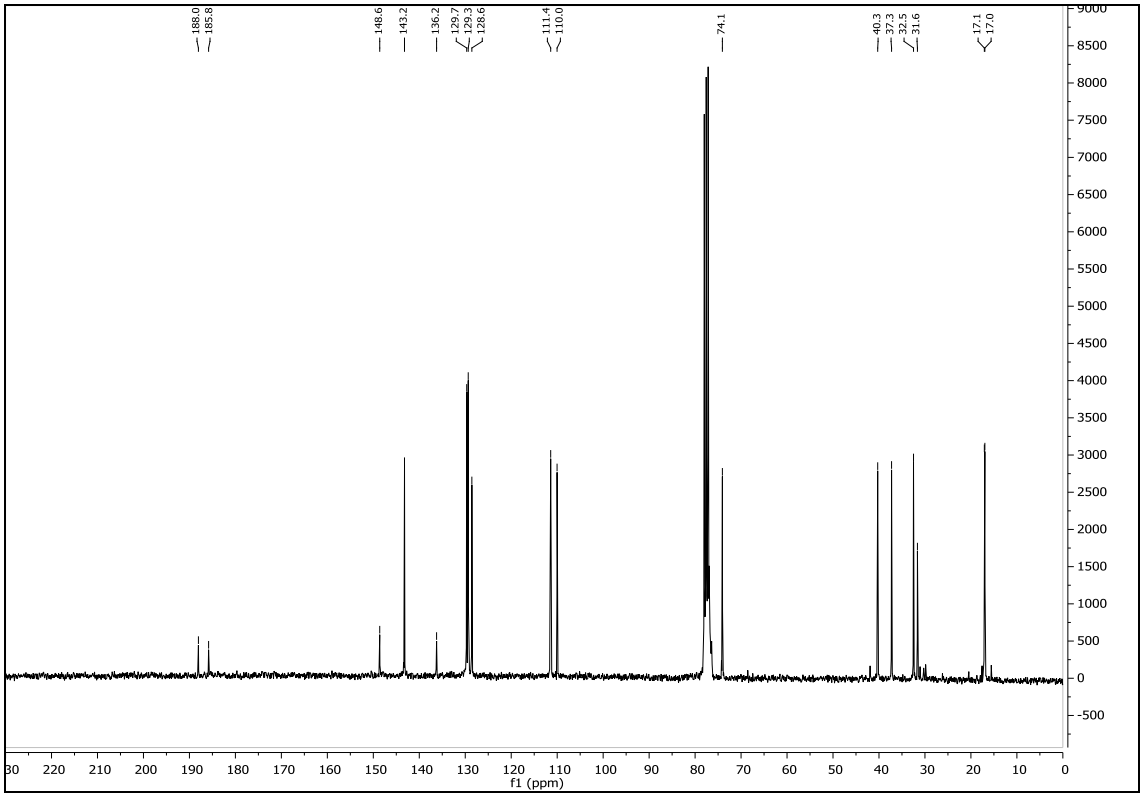
(*R*)-2-(Benzylthio)-5-isobutyl-1-methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-imidazol-4(5*H*)-one (50g)



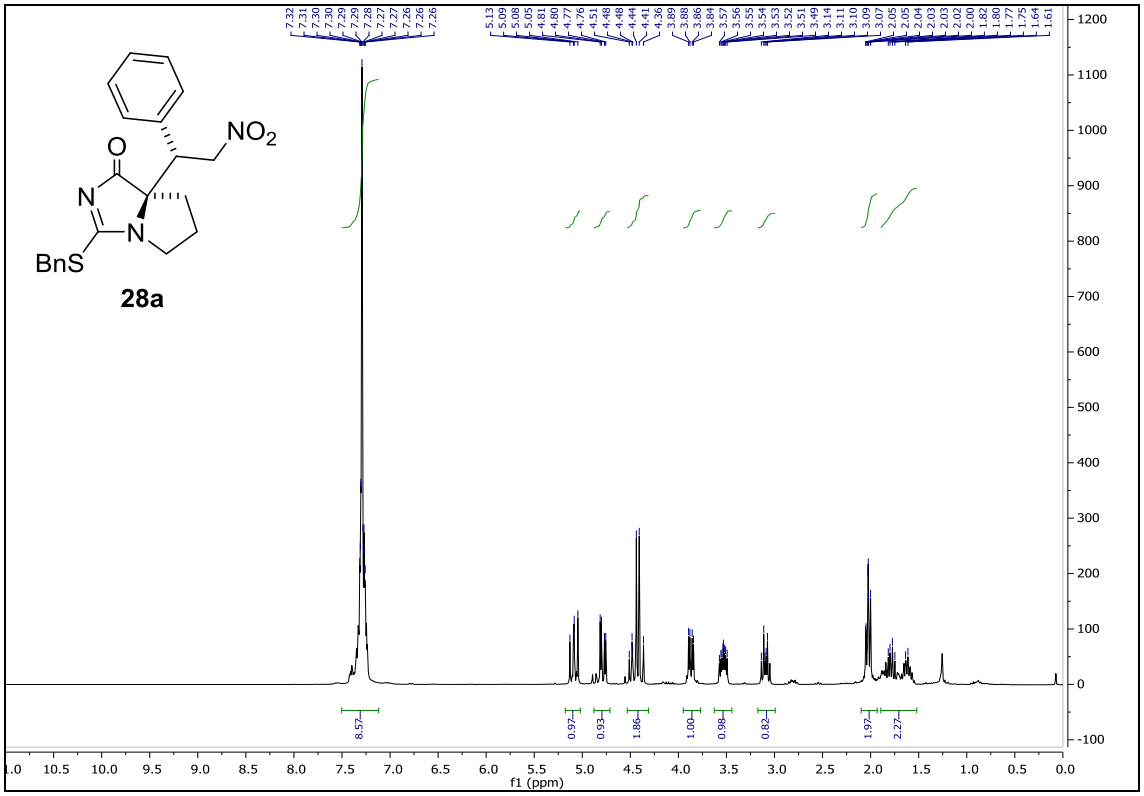


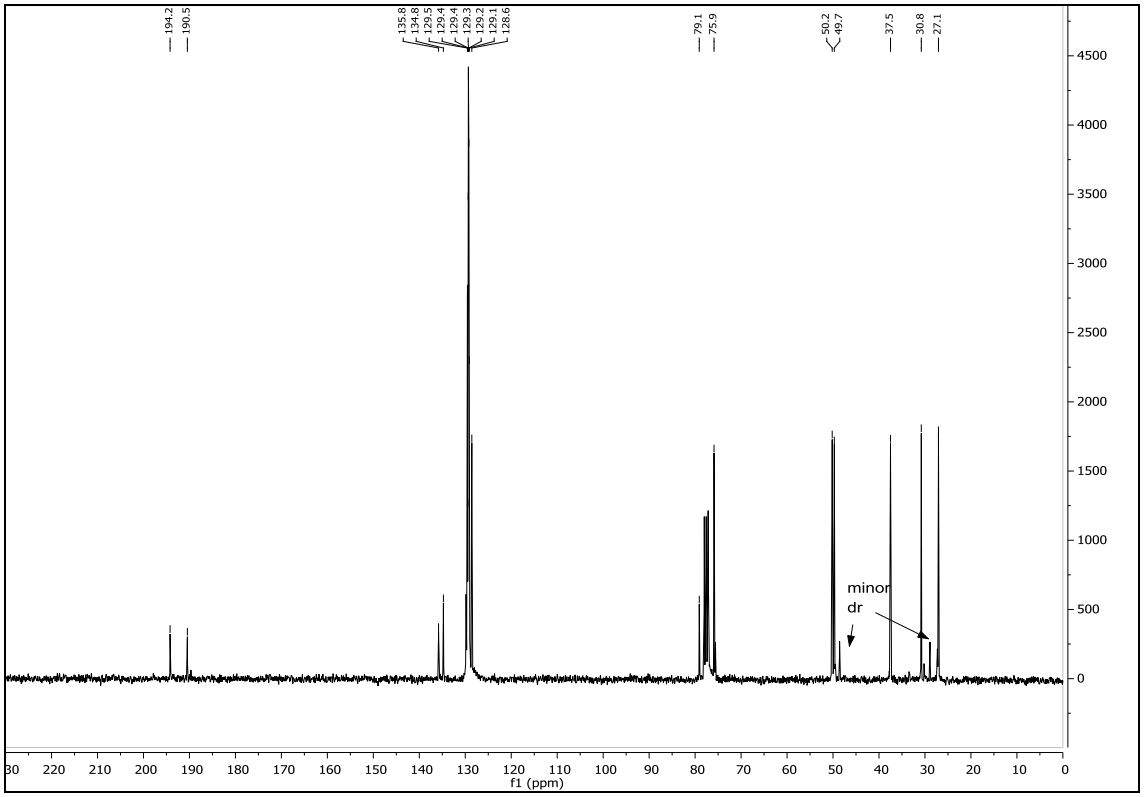
(*R*)-2-(Benzylthio)-5-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (51e)



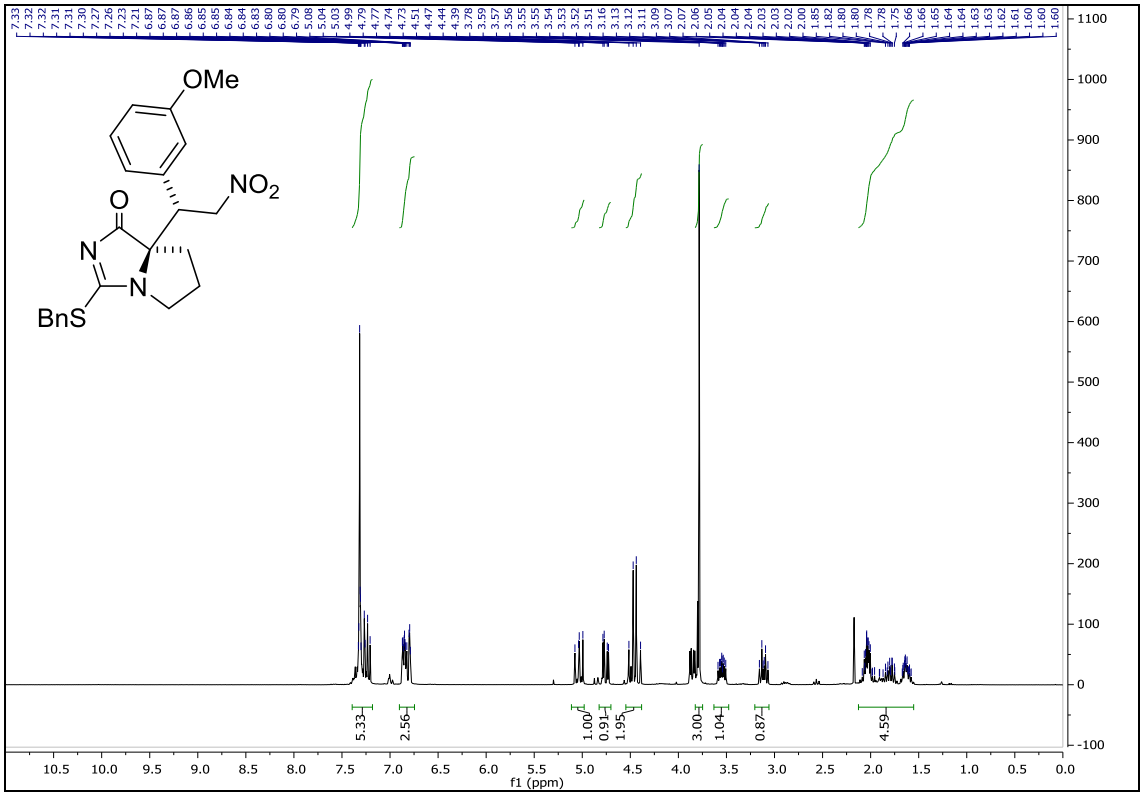


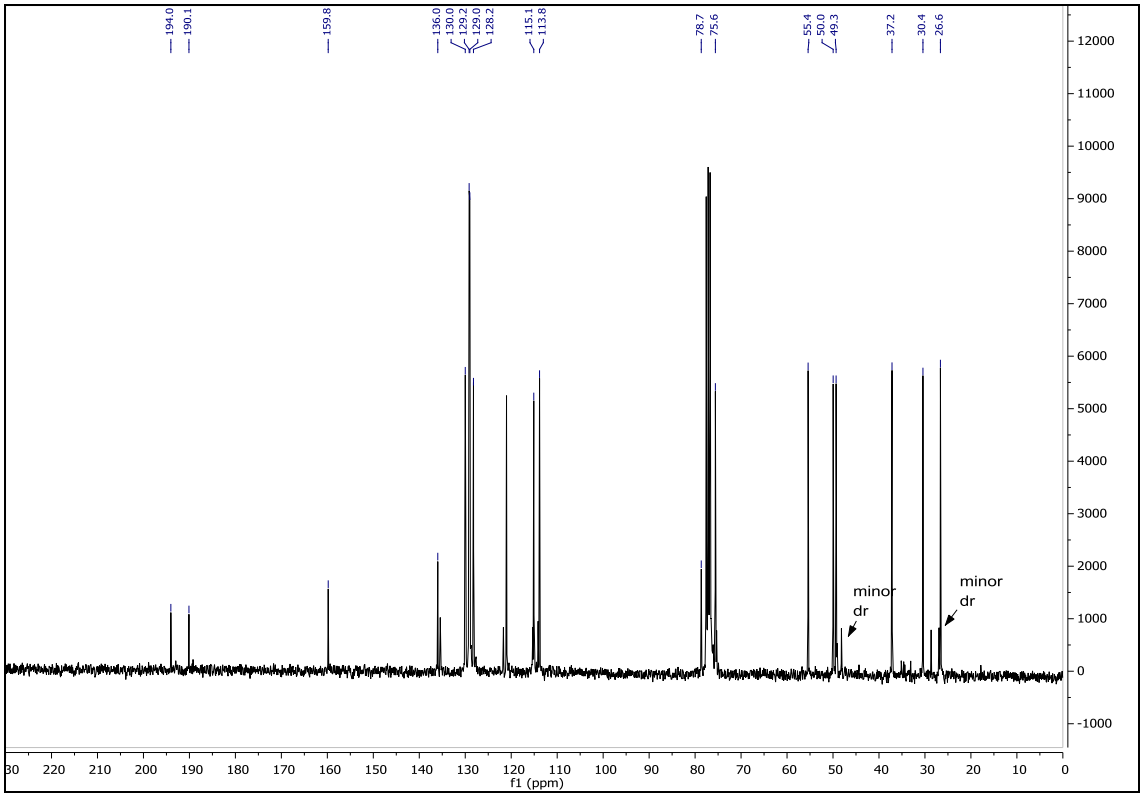
(*R*)-3-(Benzylthio)-7a-((*R*)-2-nitro-1-phenylethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (52a)



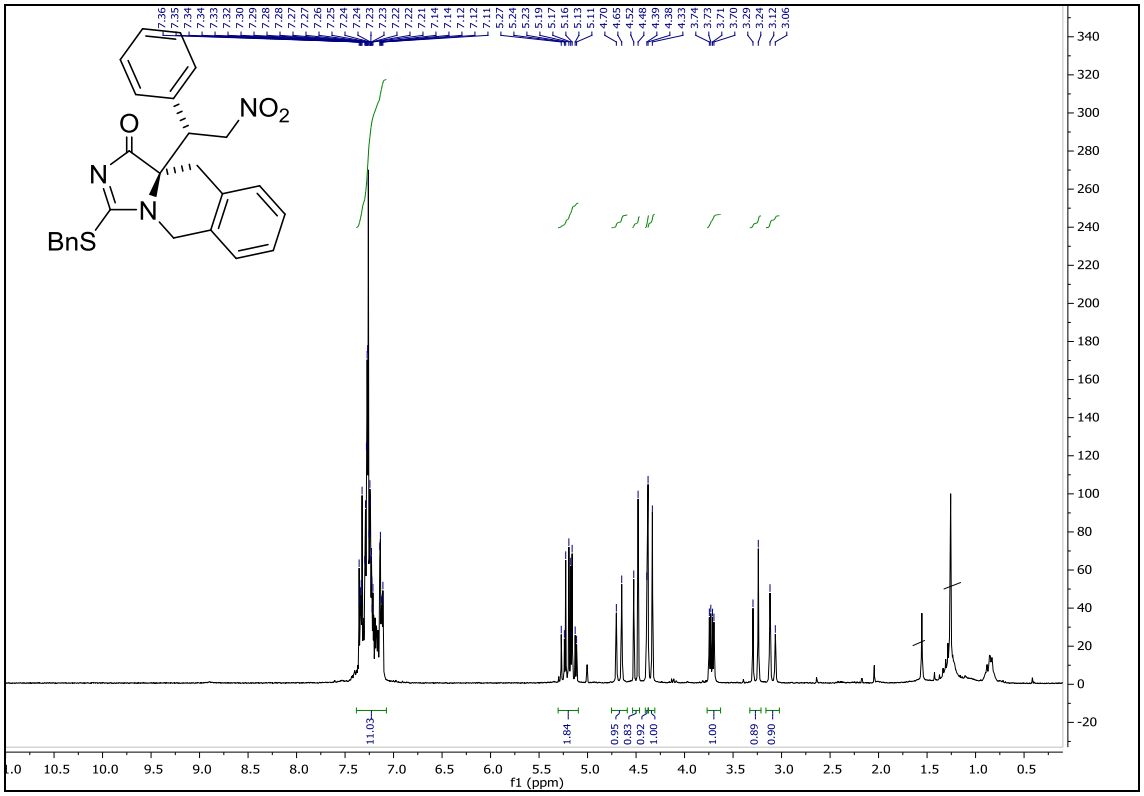


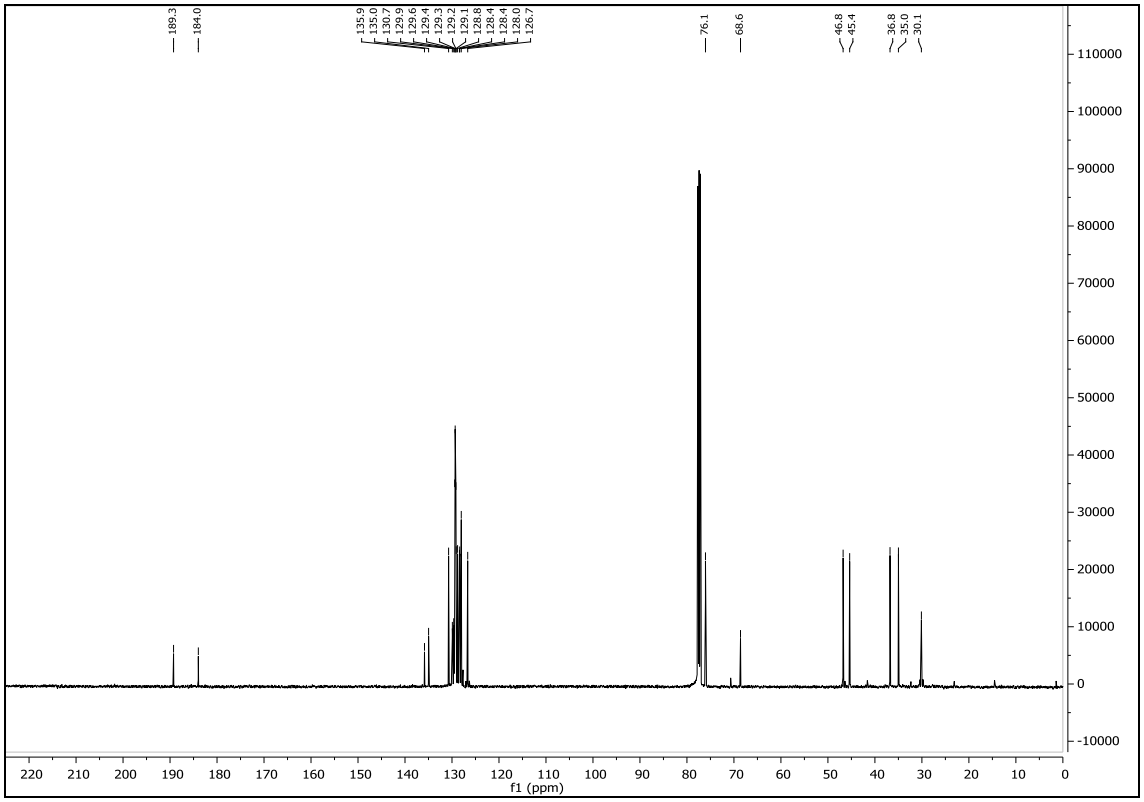
(*R*)-3-(Benzylthio)-7a-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one (52i)



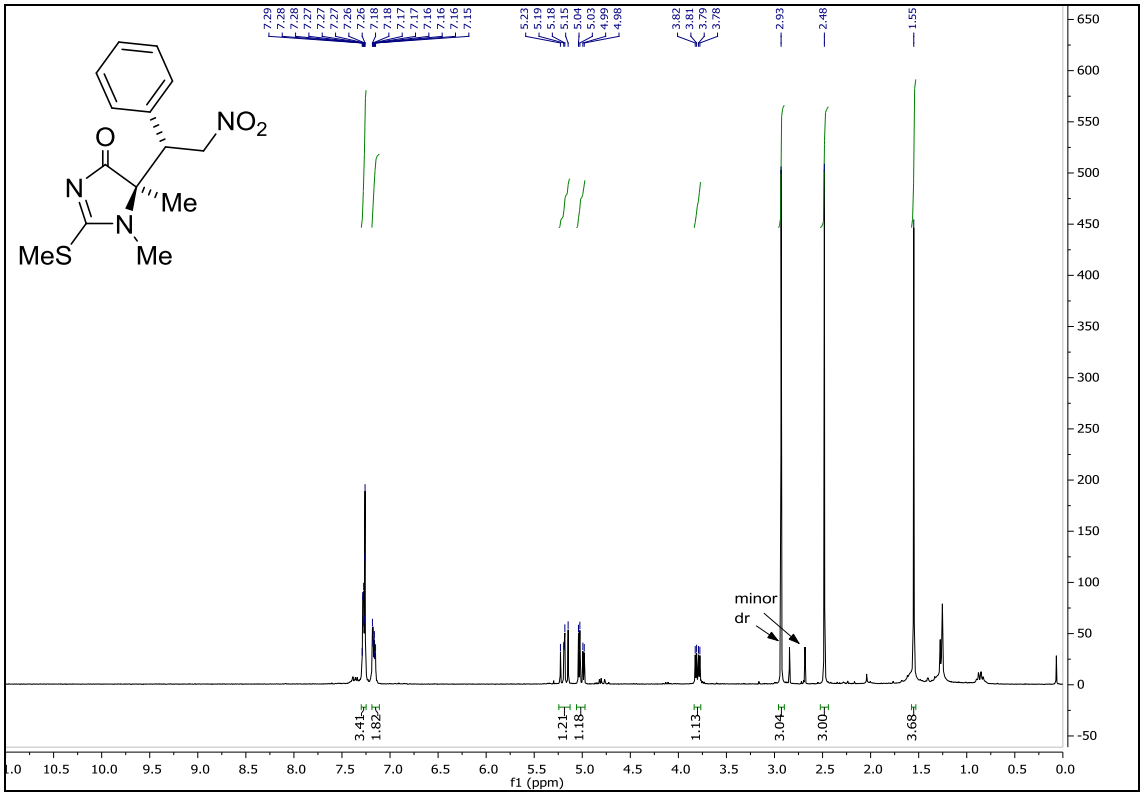


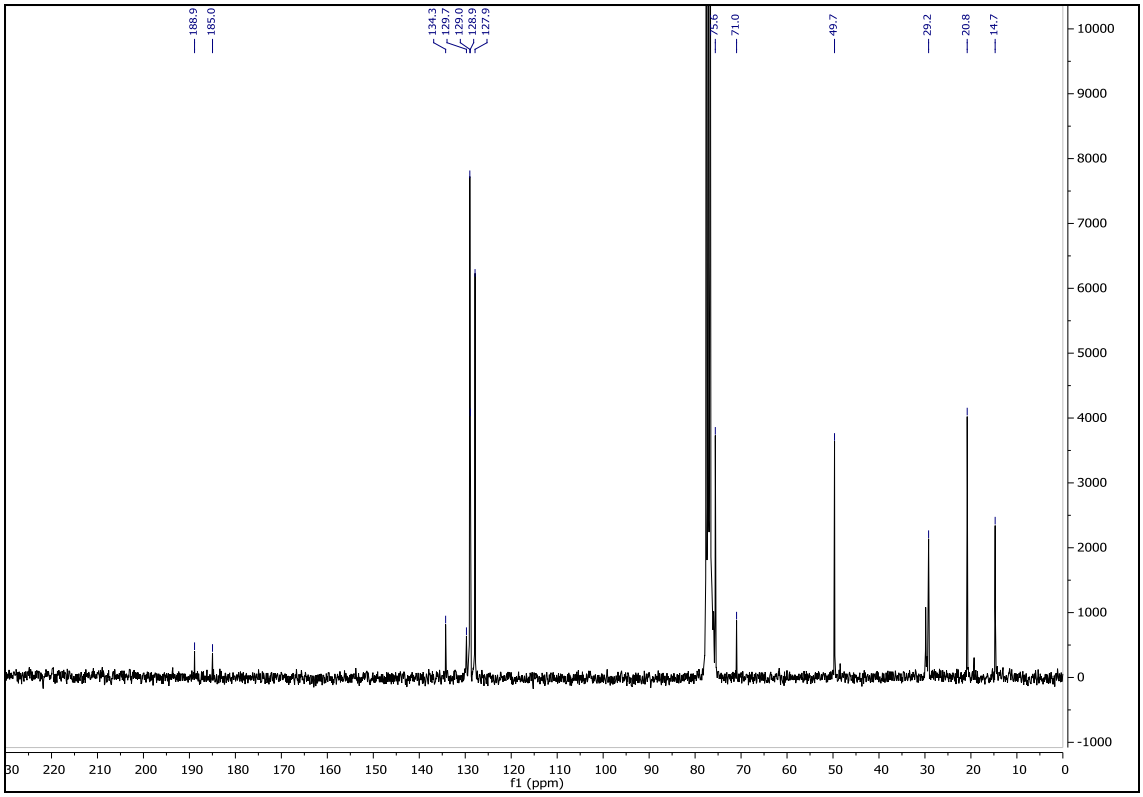
(*R*)-3-(Benzylthio)-10a-((*R*)-2-nitro-1-phenylethyl)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (53a)



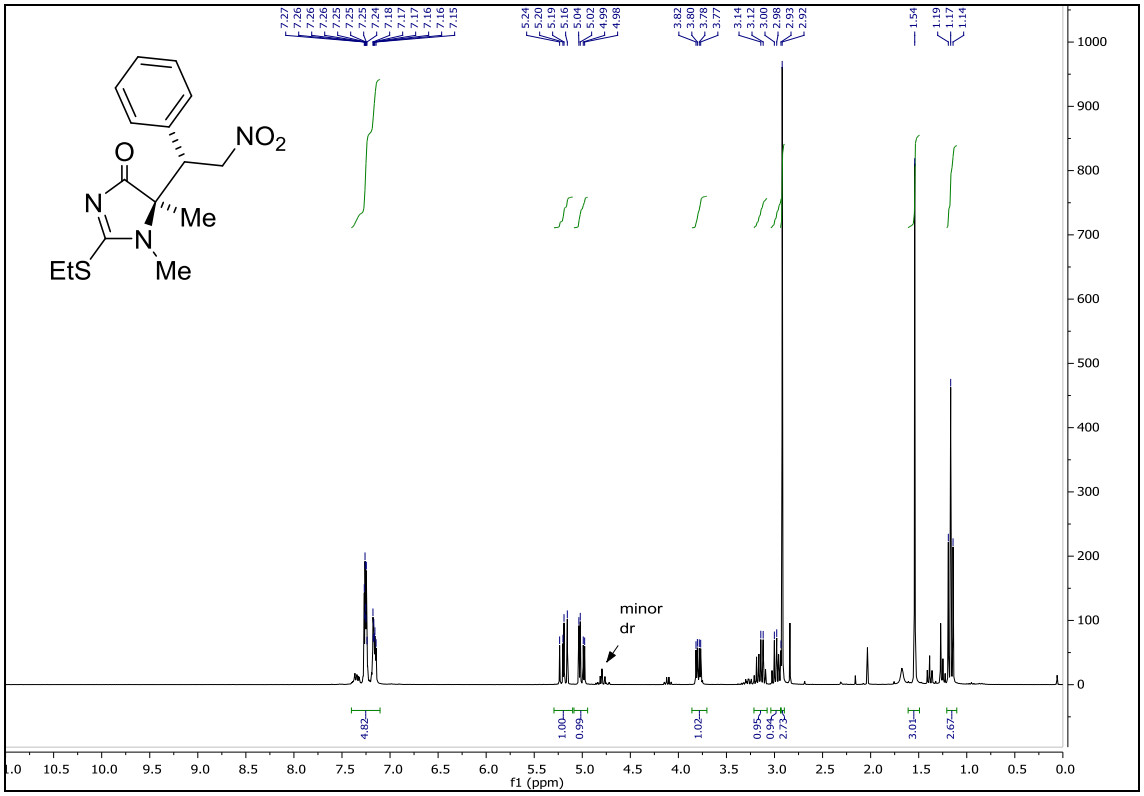


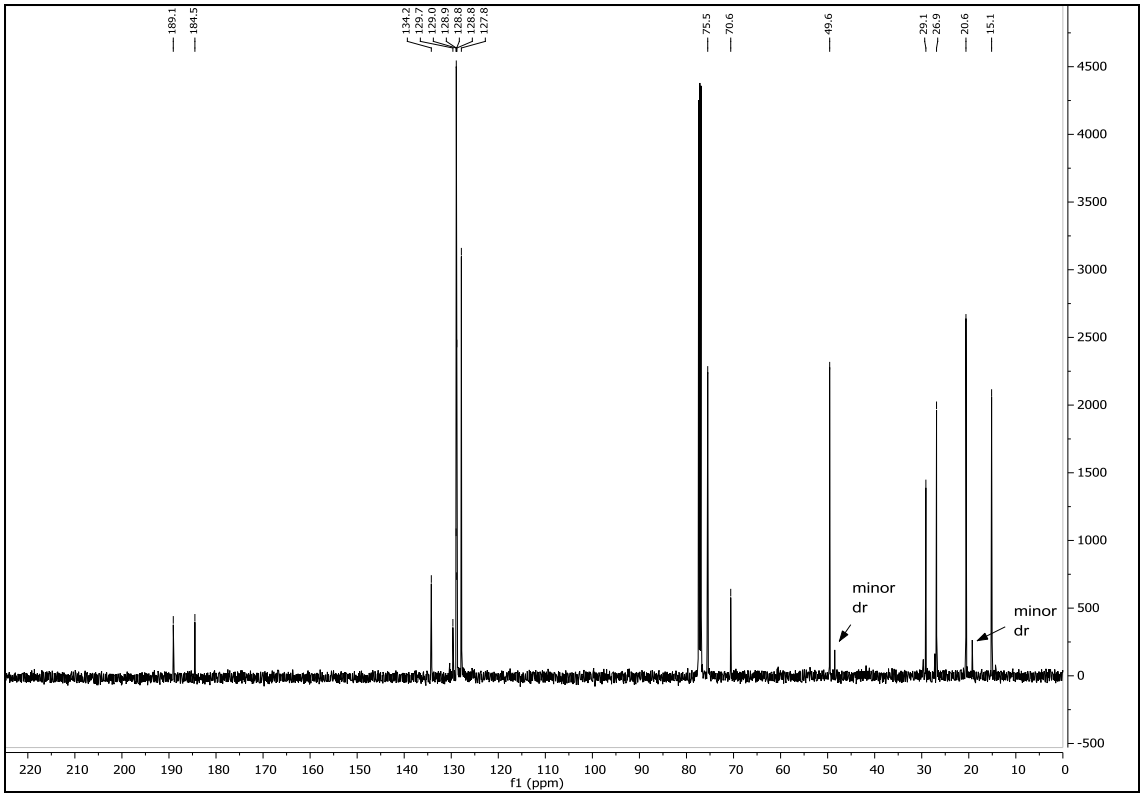
(*R*)-1,5-Dimethyl-2-(methylthio)-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (54a)



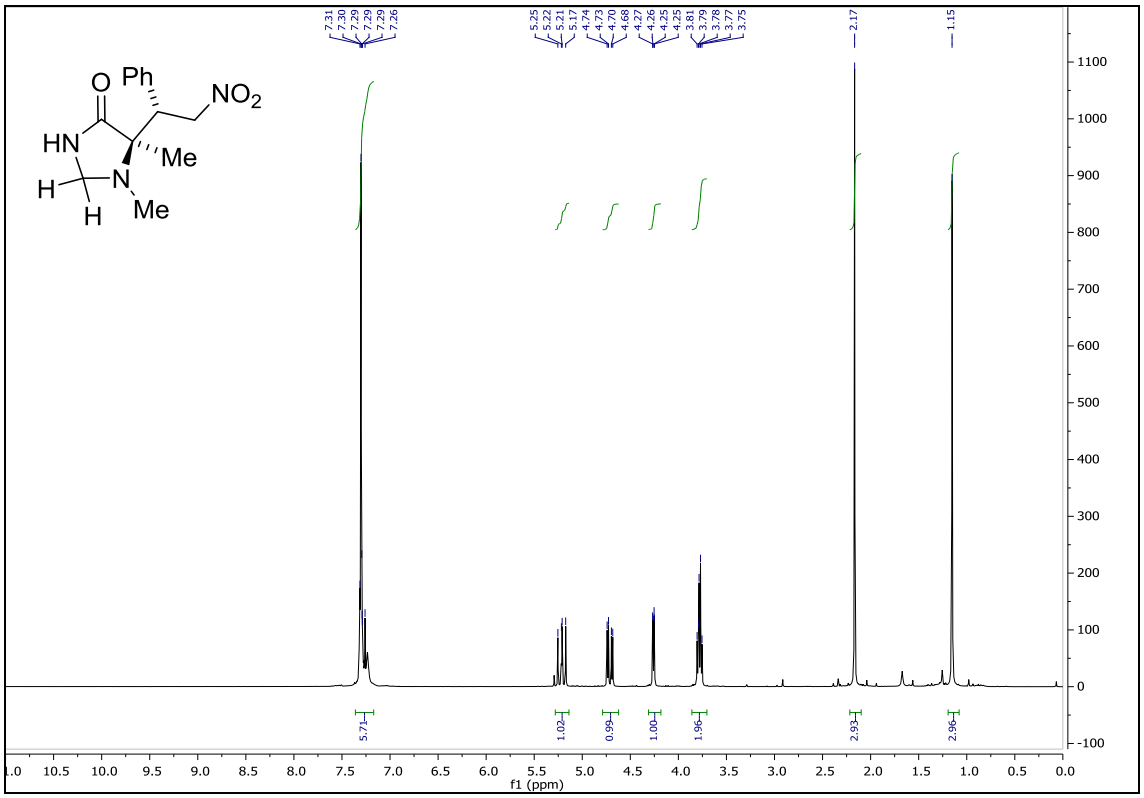


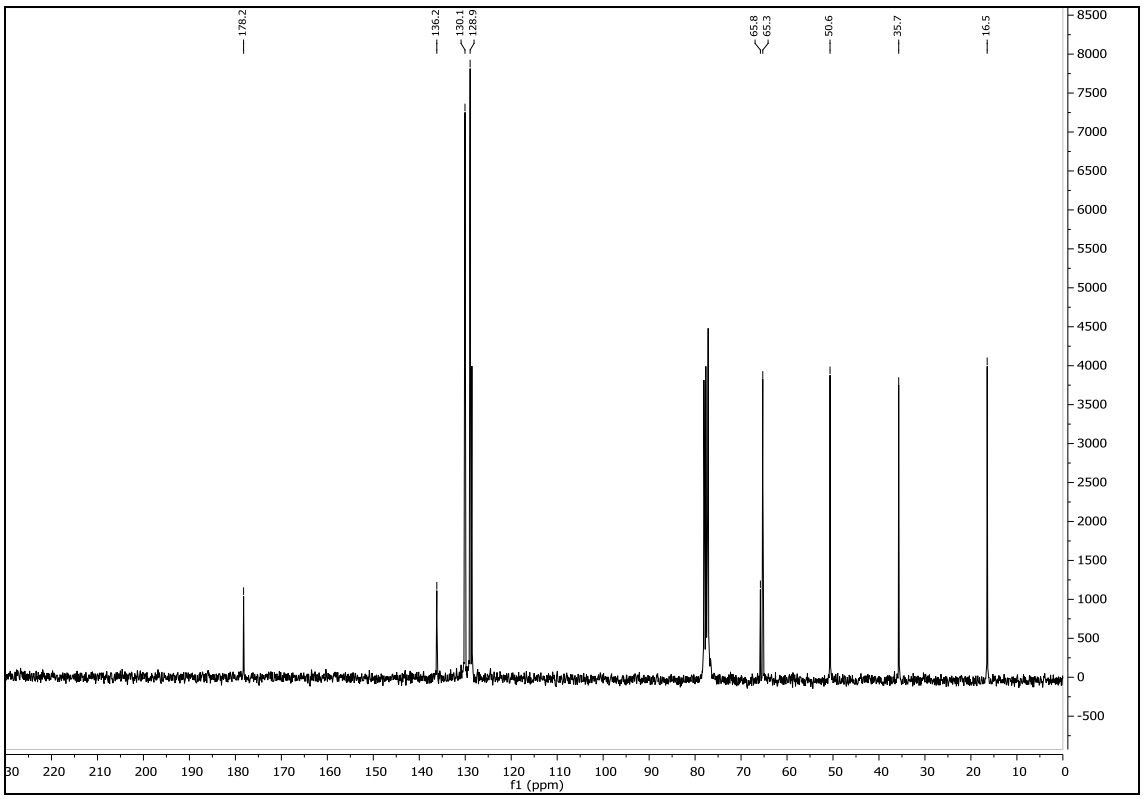
(*R*)-2-(Ethylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (55a)



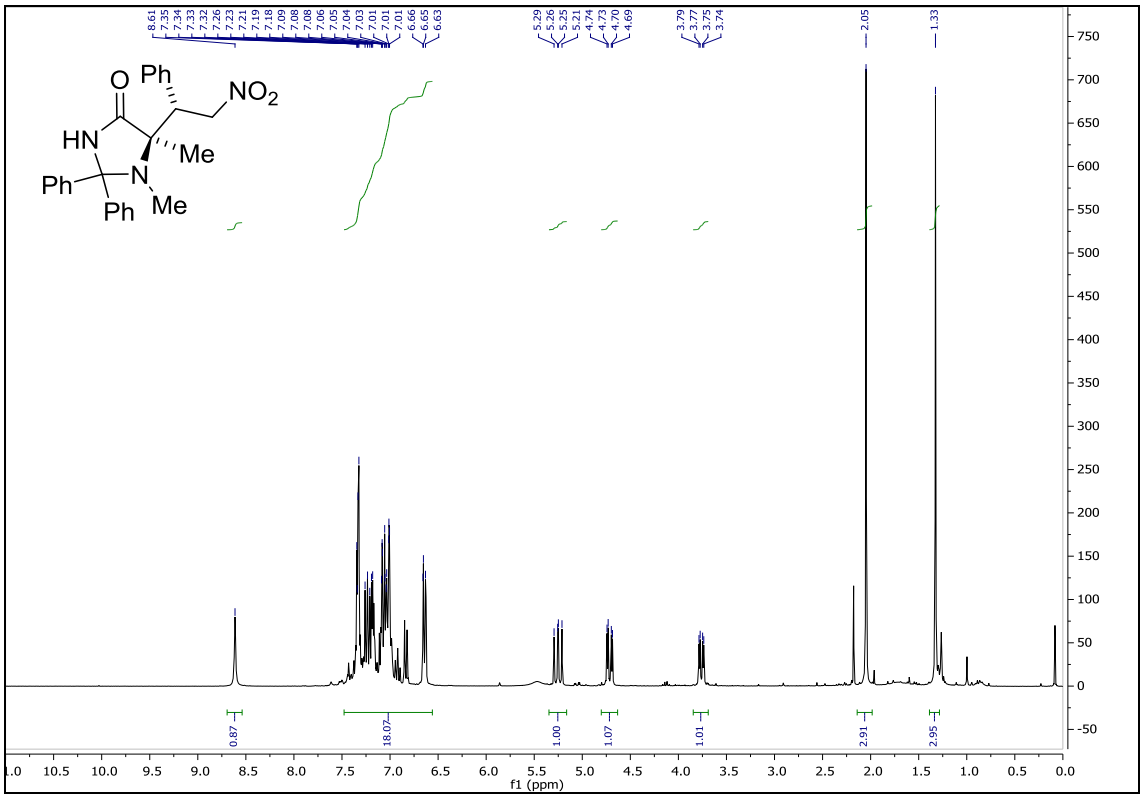


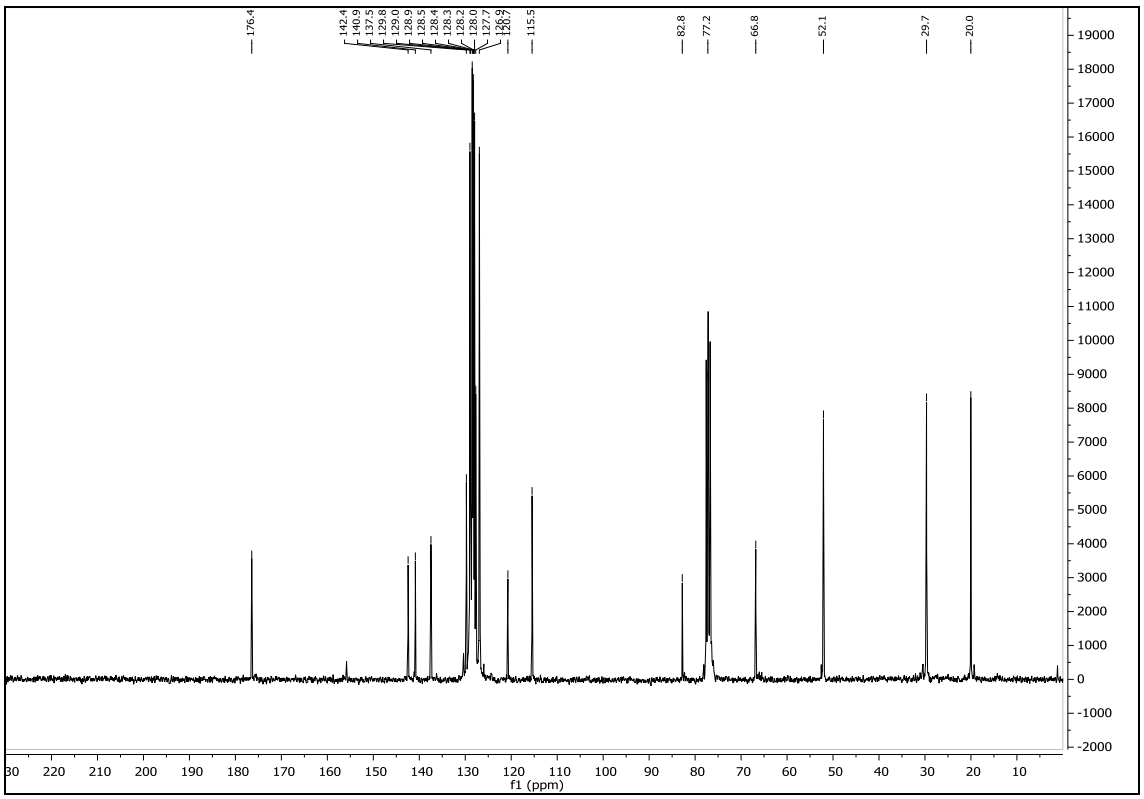
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidin-4-one (56)



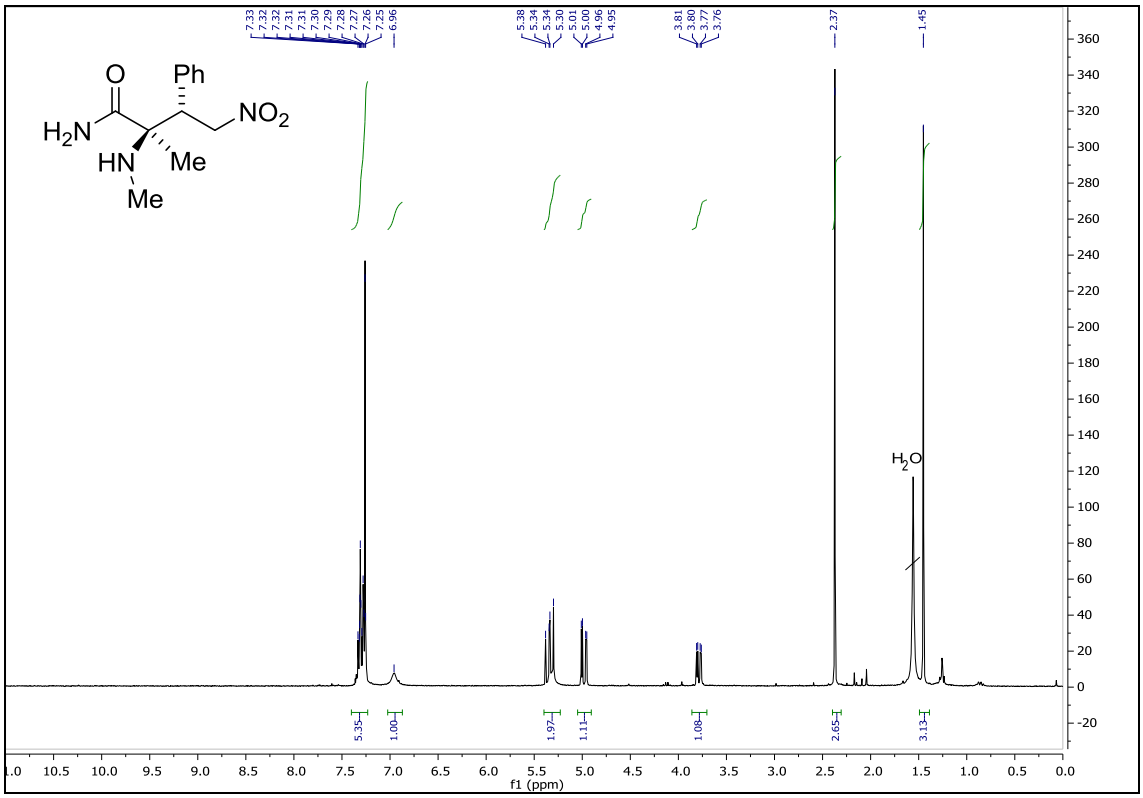


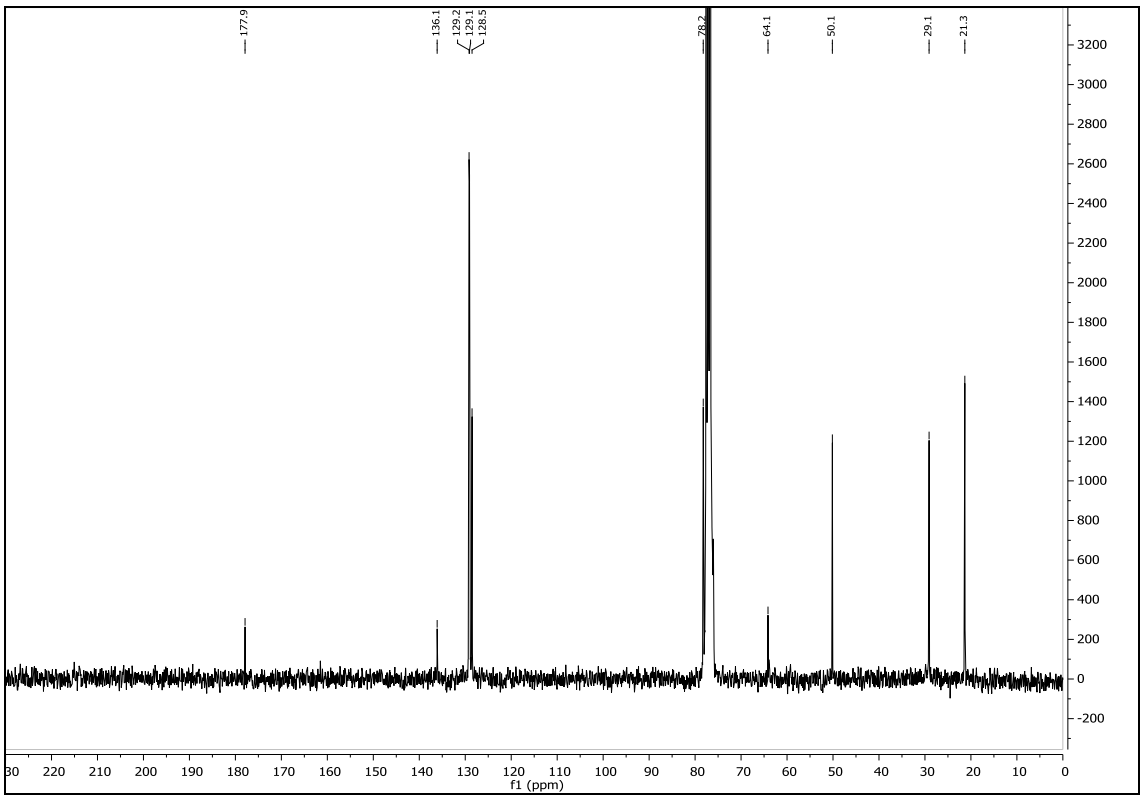
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2,2-diphenylimidazolidin-4-one (57)



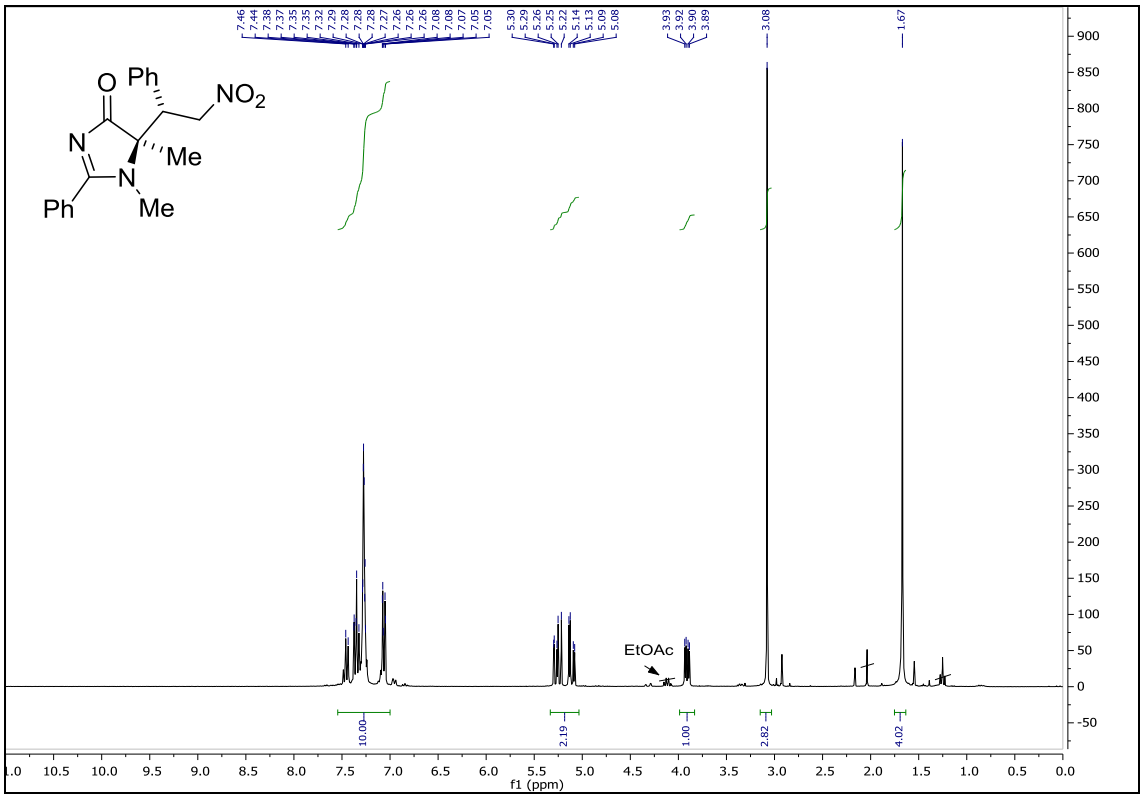


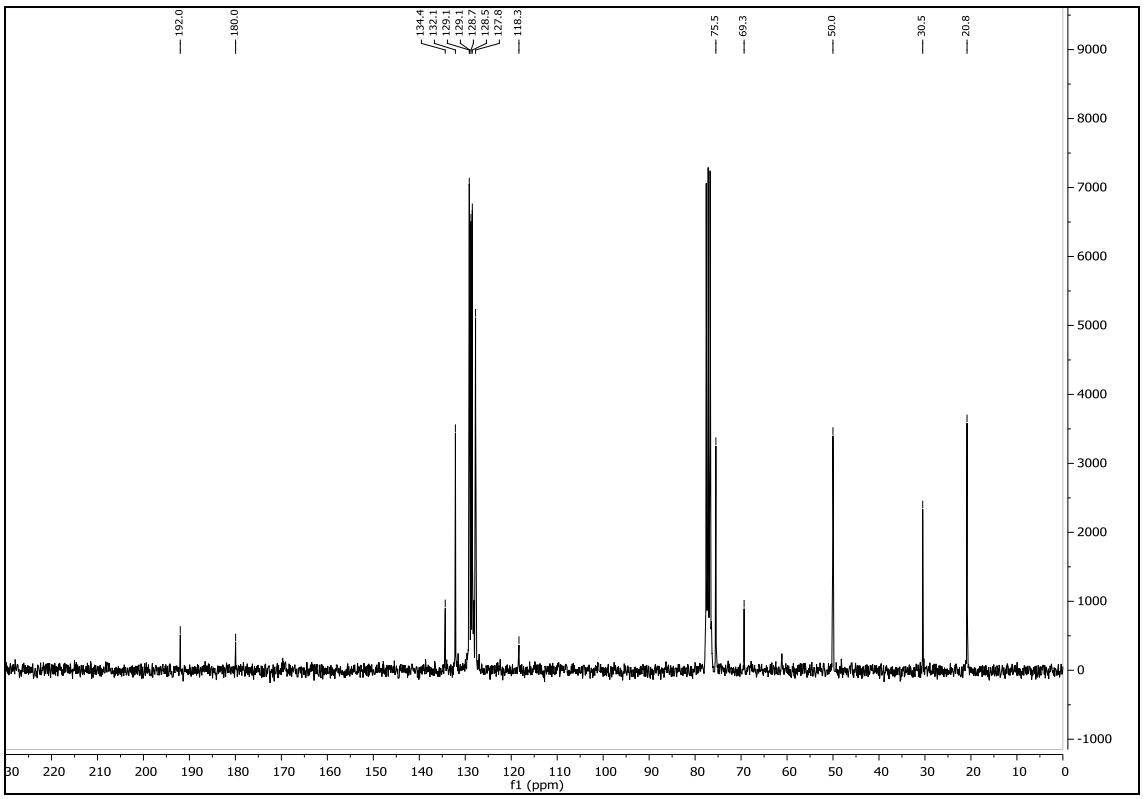
(2*R*,3*R*)-2-Methyl-2-(methylamino)-4-nitro-3-phenylbutanamide (58)



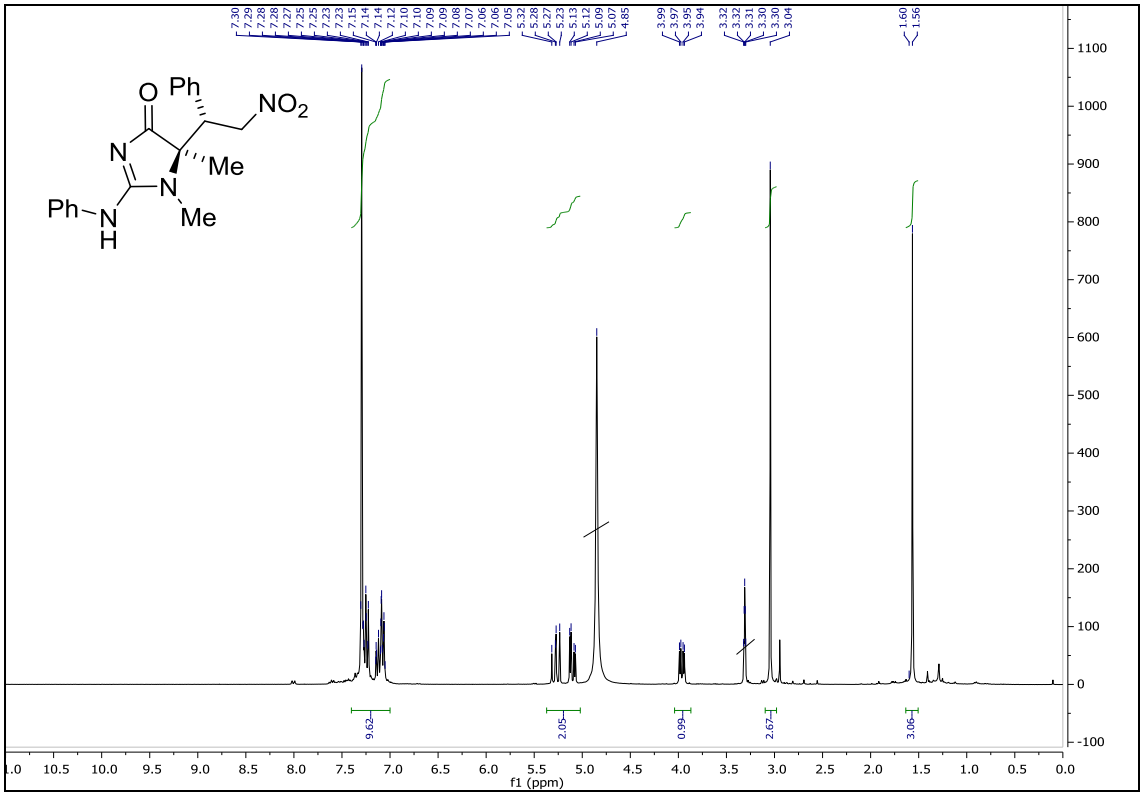


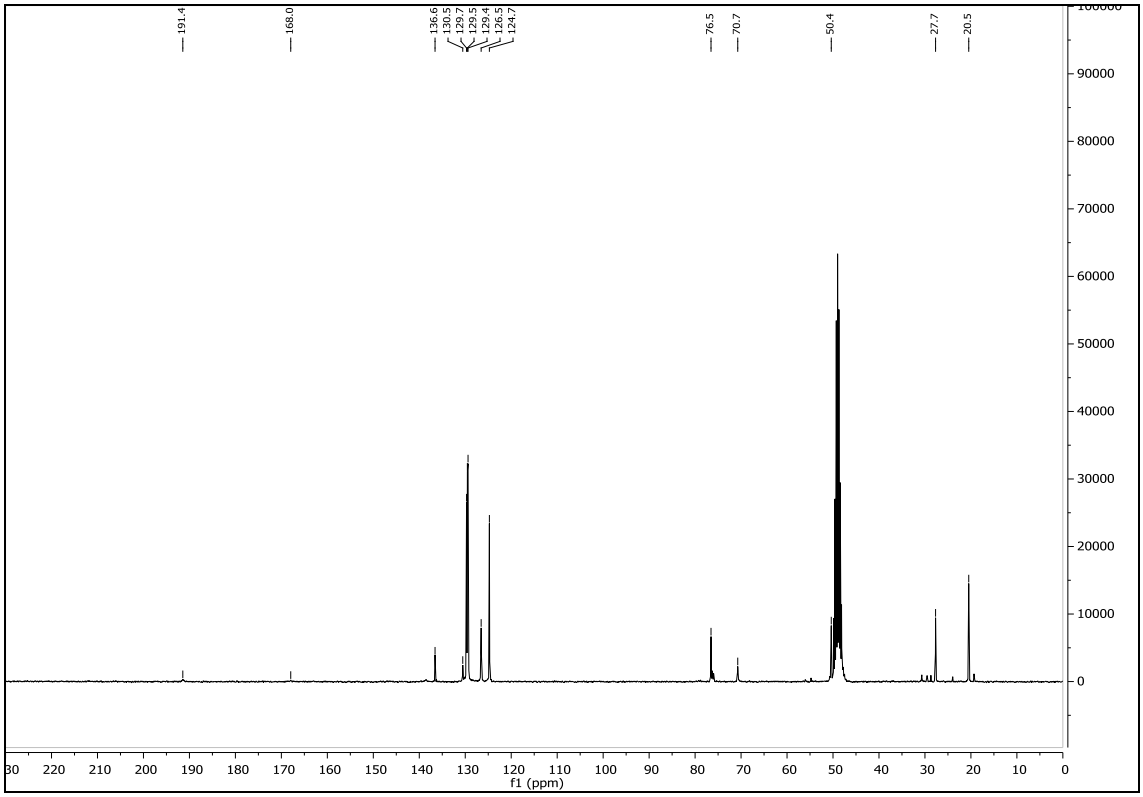
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-phenyl-1*H*-imidazol-4(5*H*)-one (59)



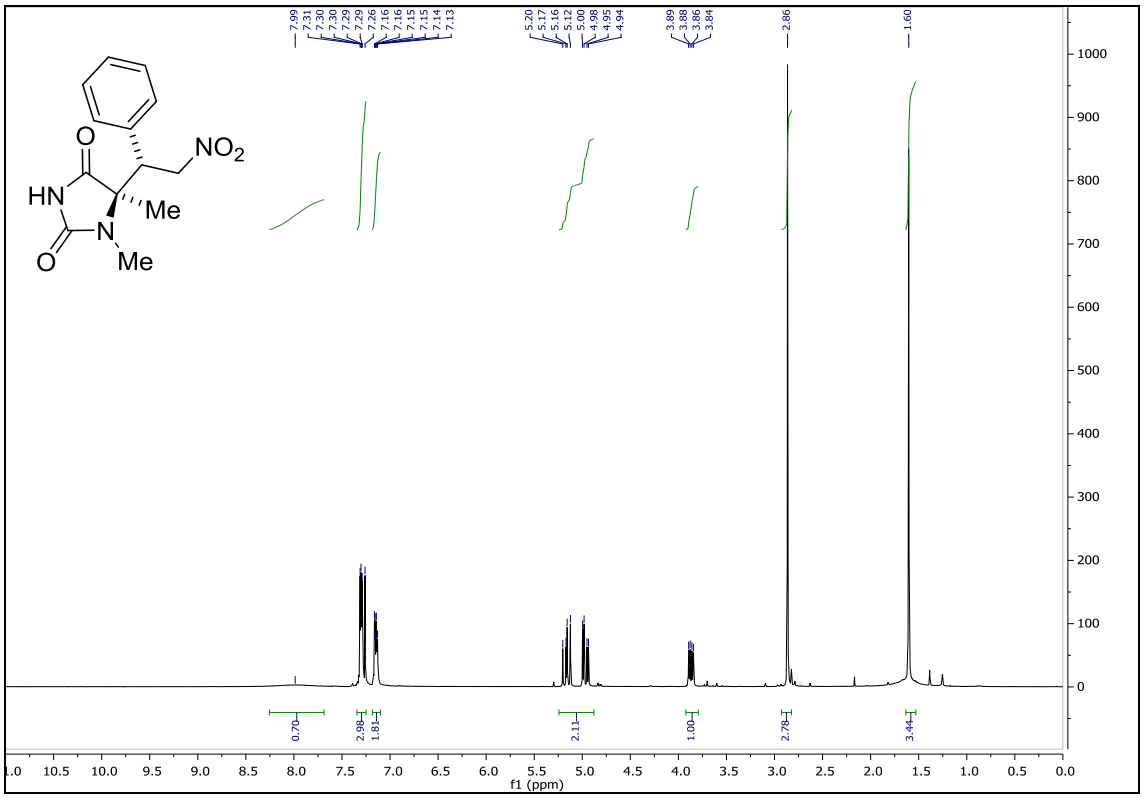


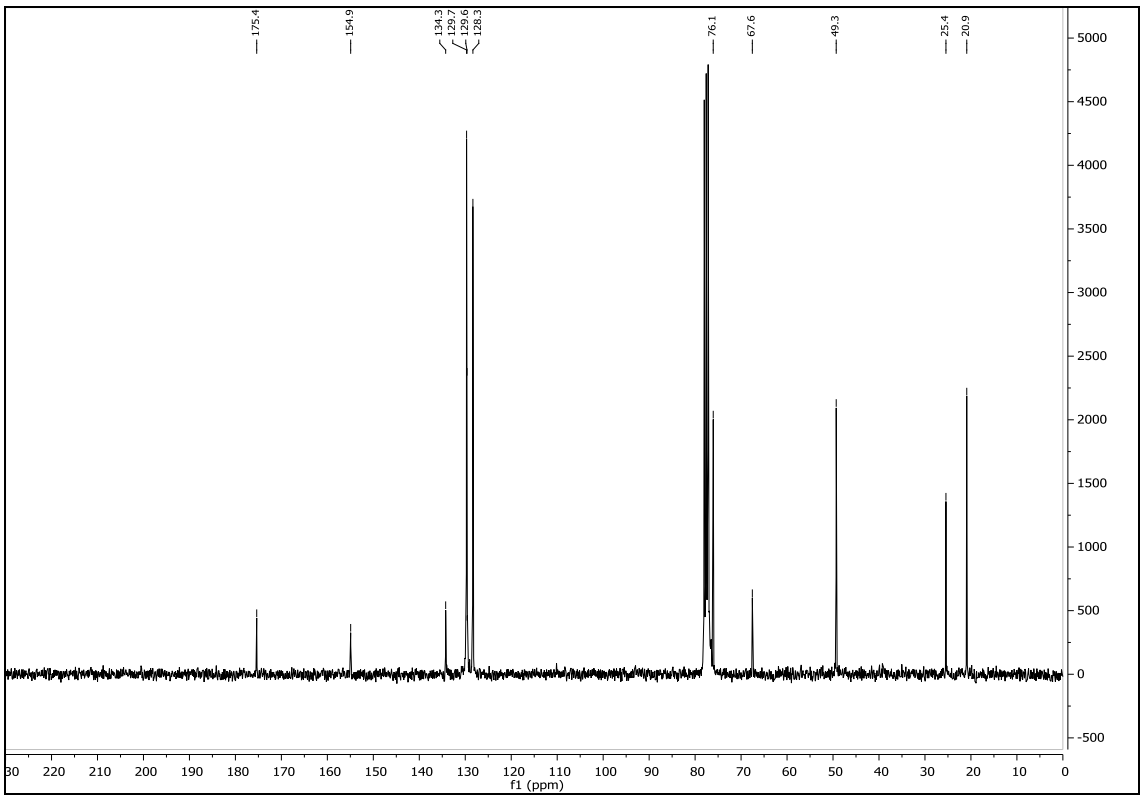
(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-(phenylamino)-1*H*-imidazol-4(5*H*)-one (60)



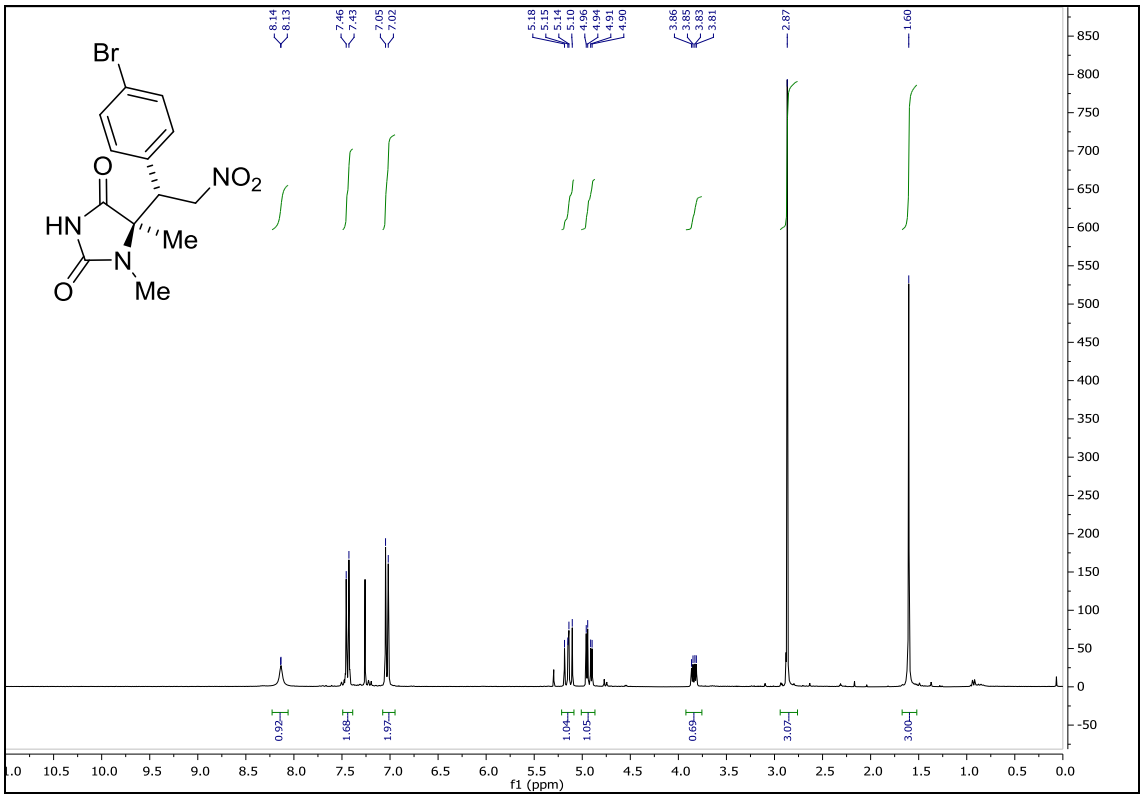


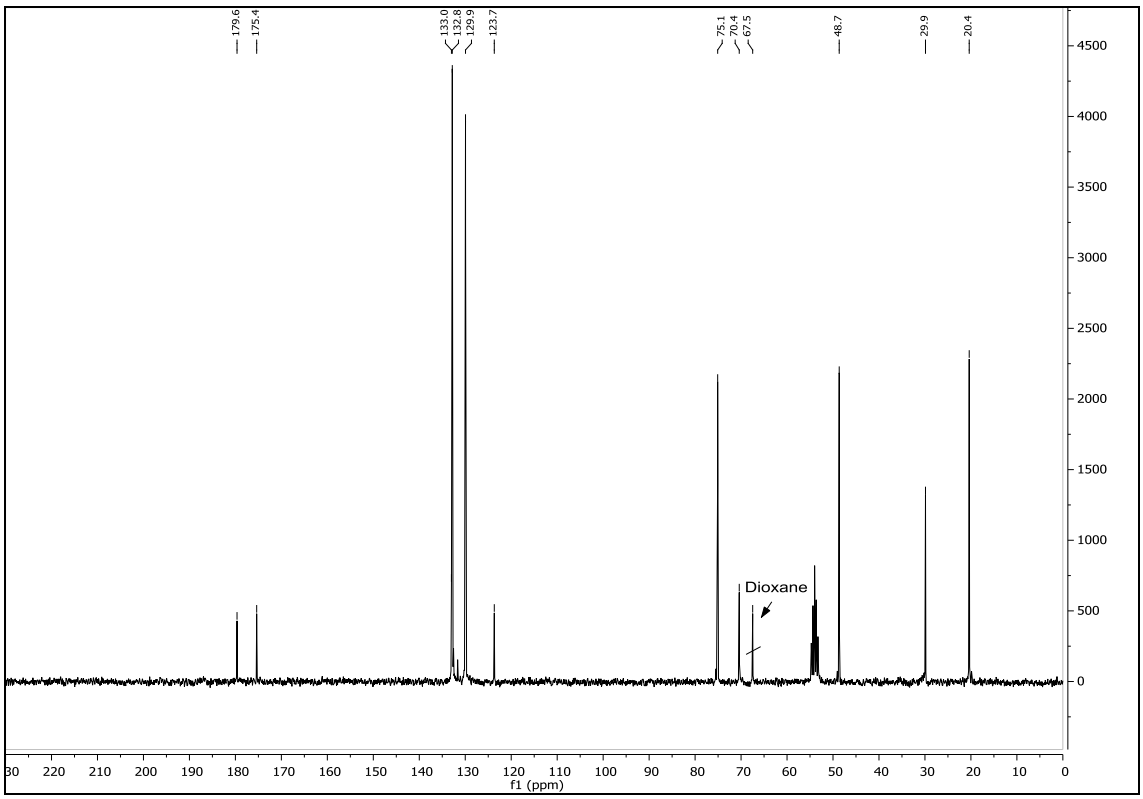
(*R*)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (61)



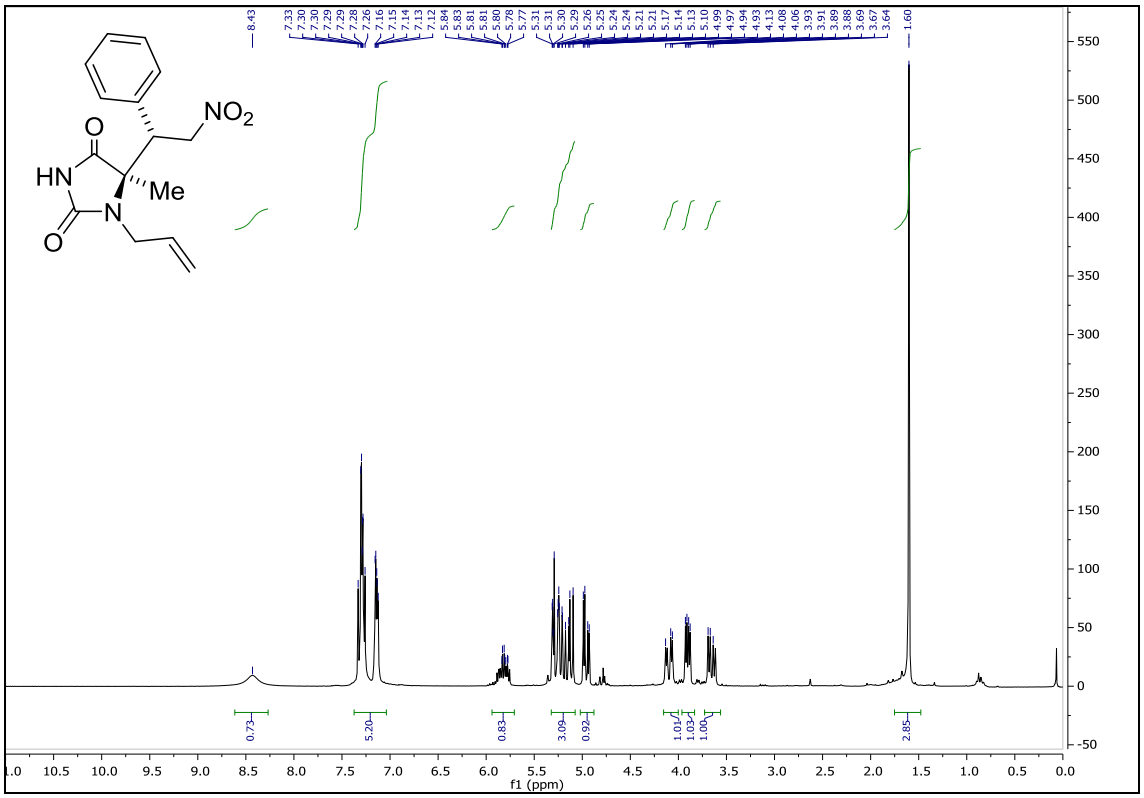


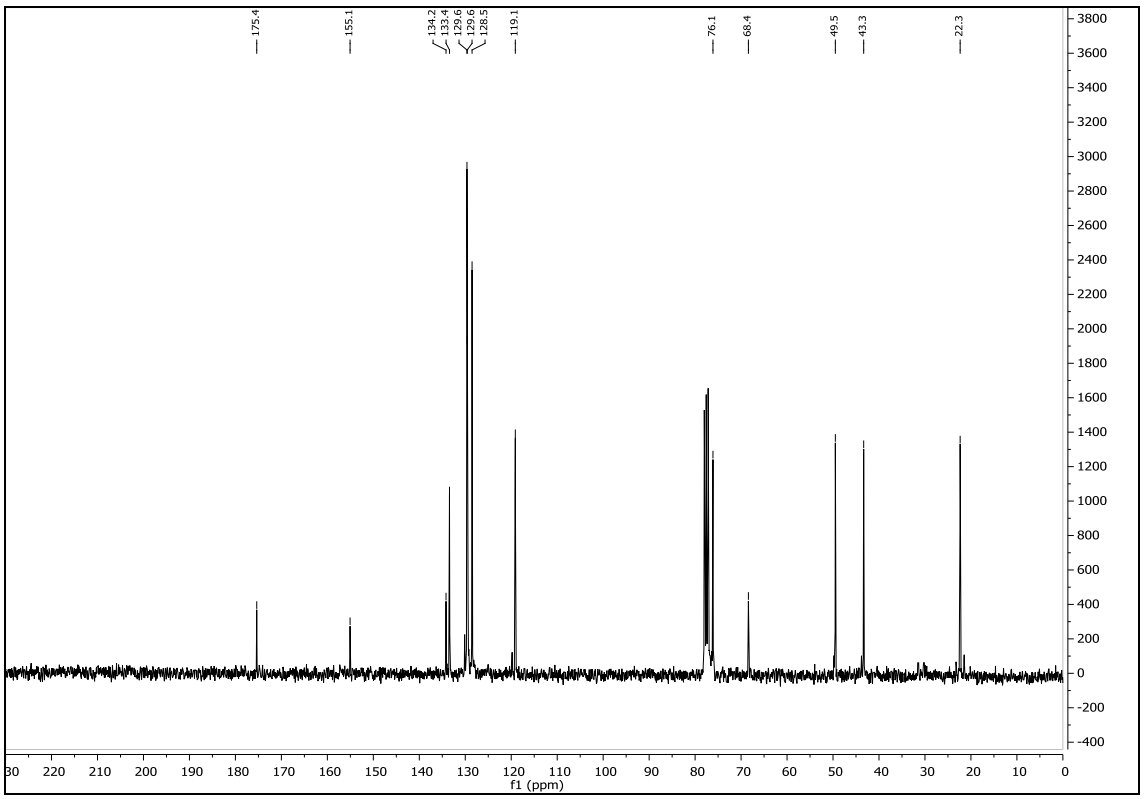
(*R*)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethylimidazolidine-2,4-dione (62)



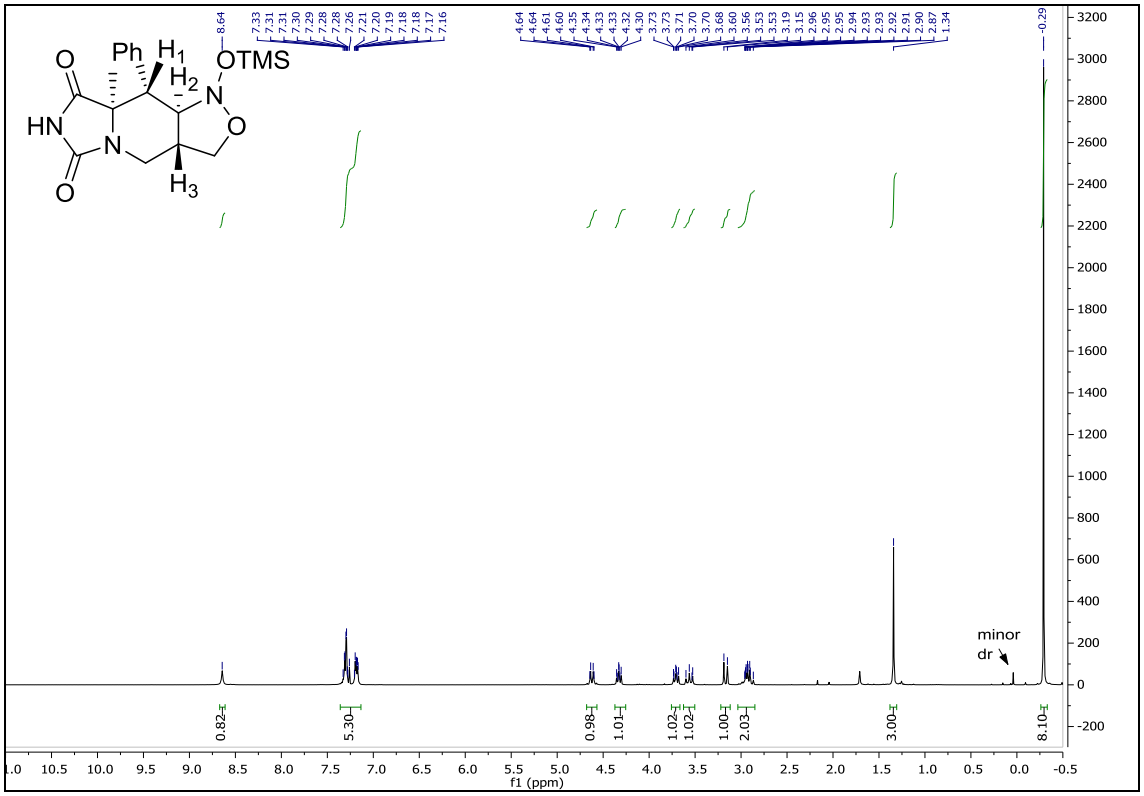


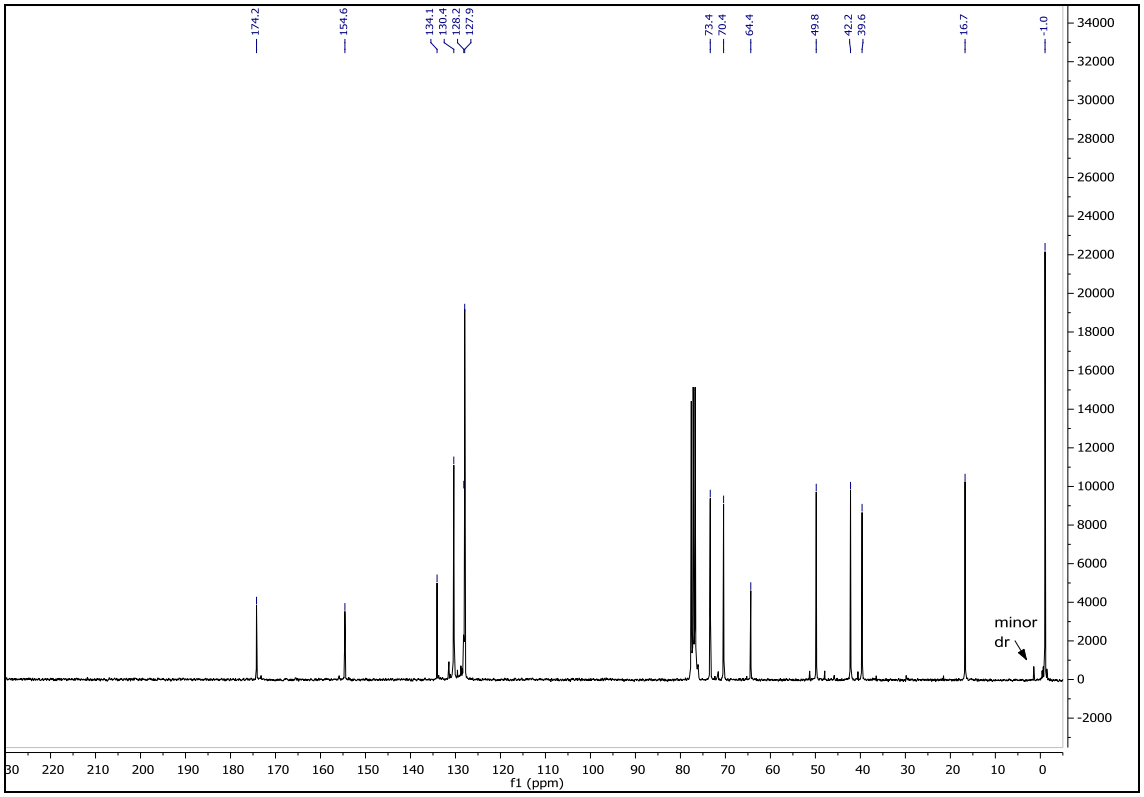
(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (63)

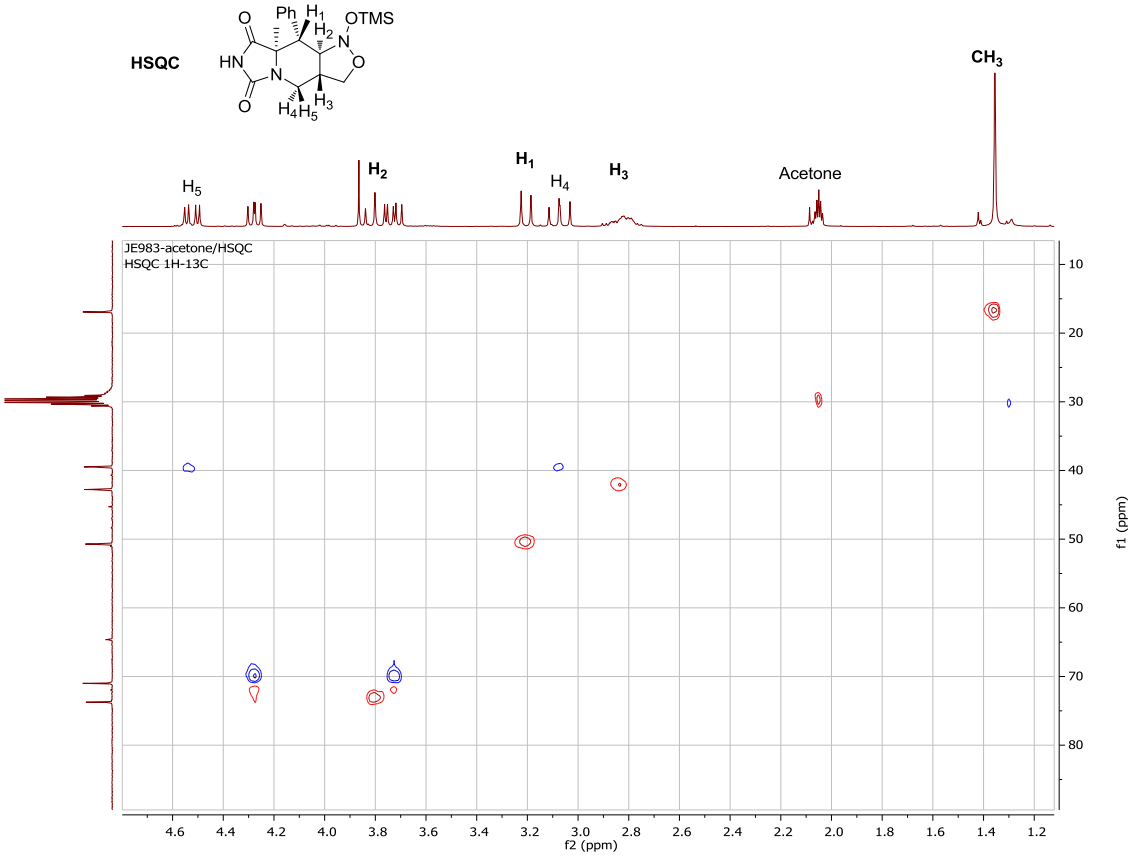




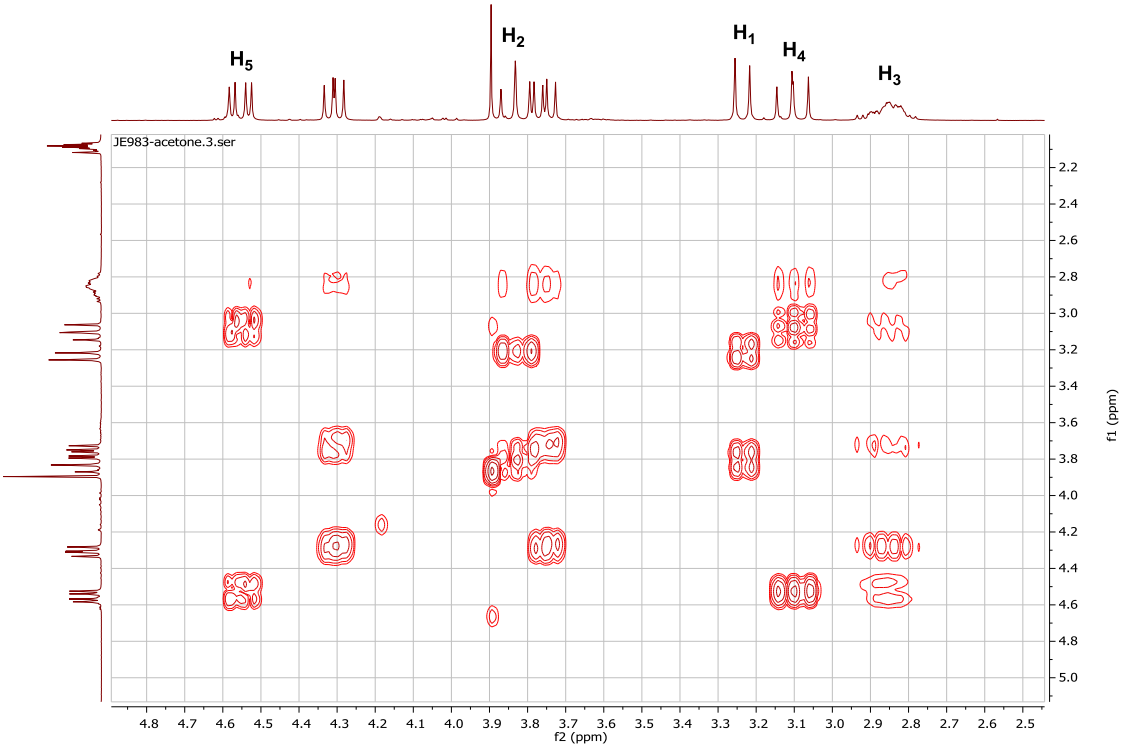
(3a*R*,8a*R*,9*R*,9a*R*)-8a-Methyl-9-phenyl-1-((trimethylsilyl)oxy)hexahydro-3*H*,6*H*-imidazo[1,5-a]isoxazolo[3,4-d]pyridine-6,8(7*H*)-dione



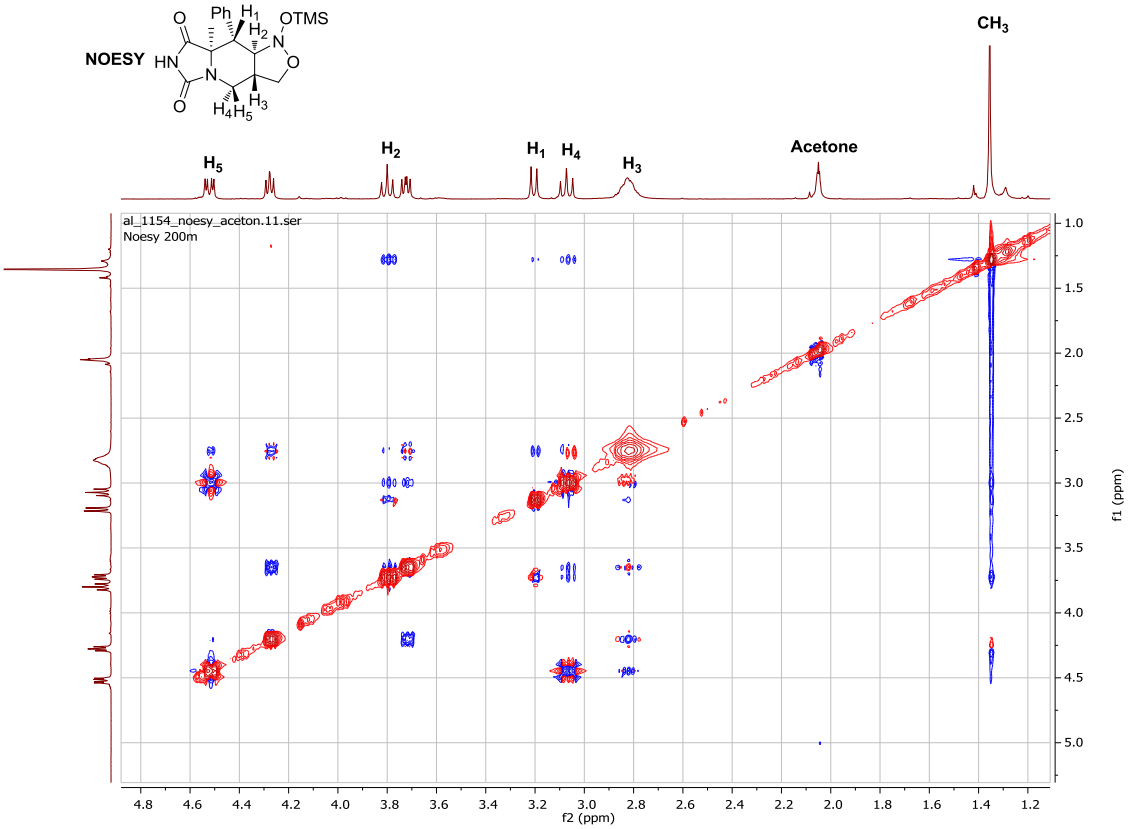



HSQC
Ph
H1
H2
OTMS
HN
N
O
O
O
H4H5
H3
CH3
H5
H2
H1
H4
H3
Acetone
JE983-acetone/HSQC
HSQC 1H-13C
f2 (ppm)
f1 (ppm)

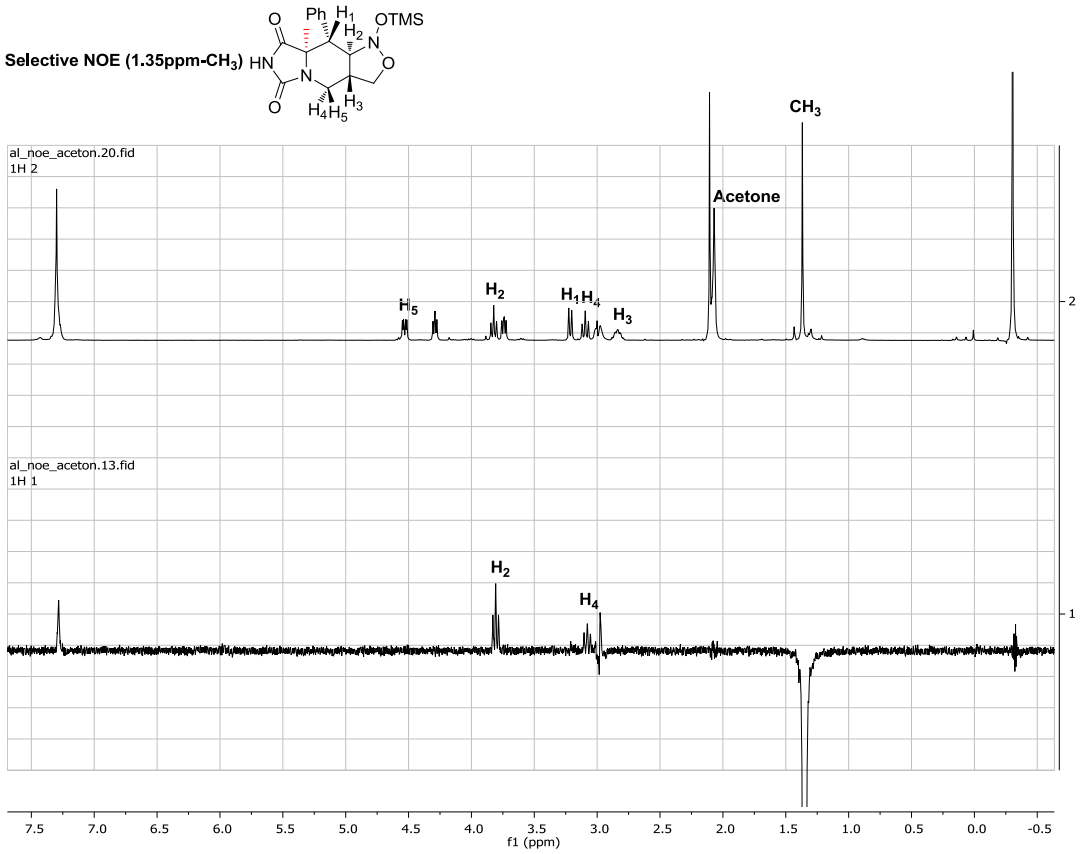
COSY


H5
H2
H1
H4
H3
JE983-acetone.3.ser
f2 (ppm)
f1 (ppm)

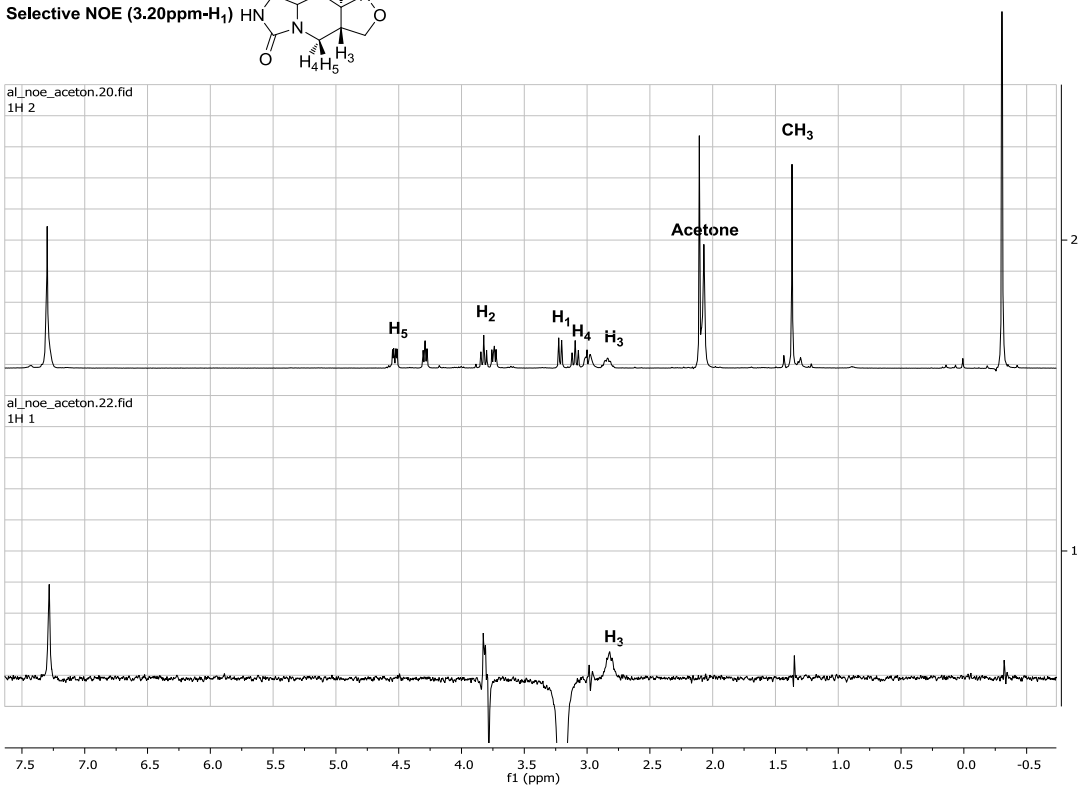
NOESY


CH3
H5
H2
H1
H4
H3
Acetone
al_1154_noesy_aceton.11.ser
Noesy 200m
f2 (ppm)
f1 (ppm)

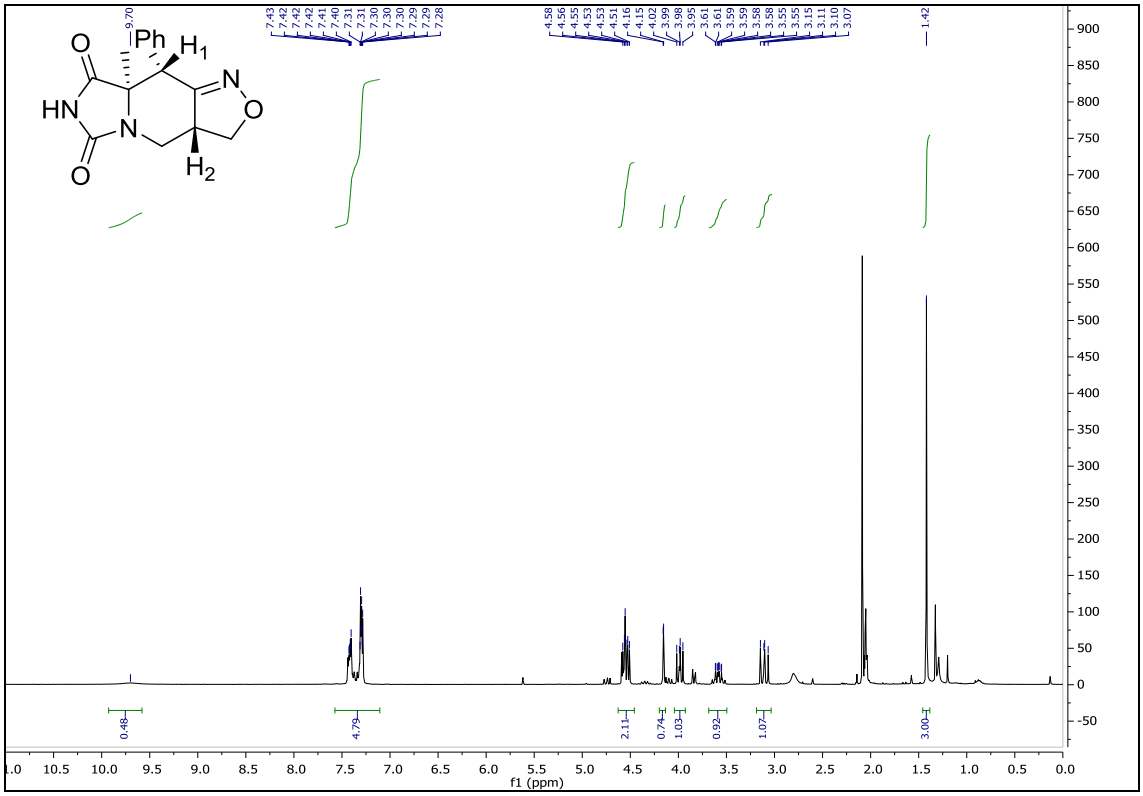
Selective NOE (1.35ppm-CH_3)

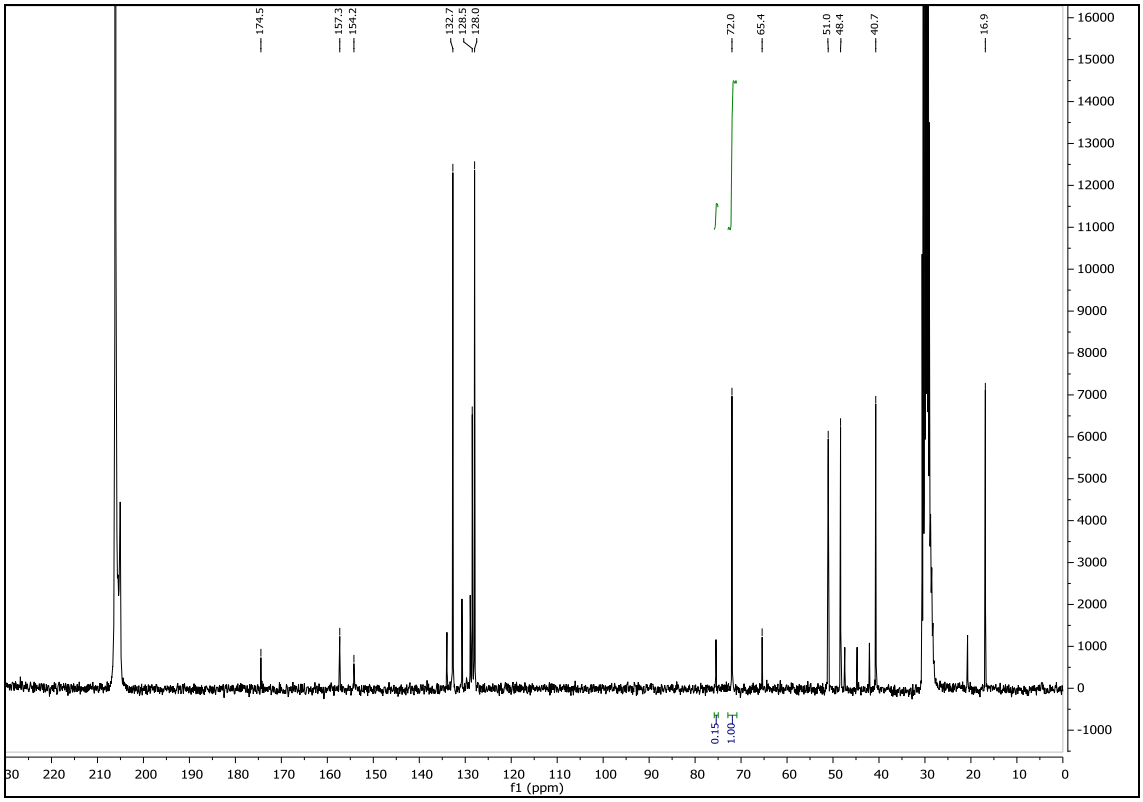


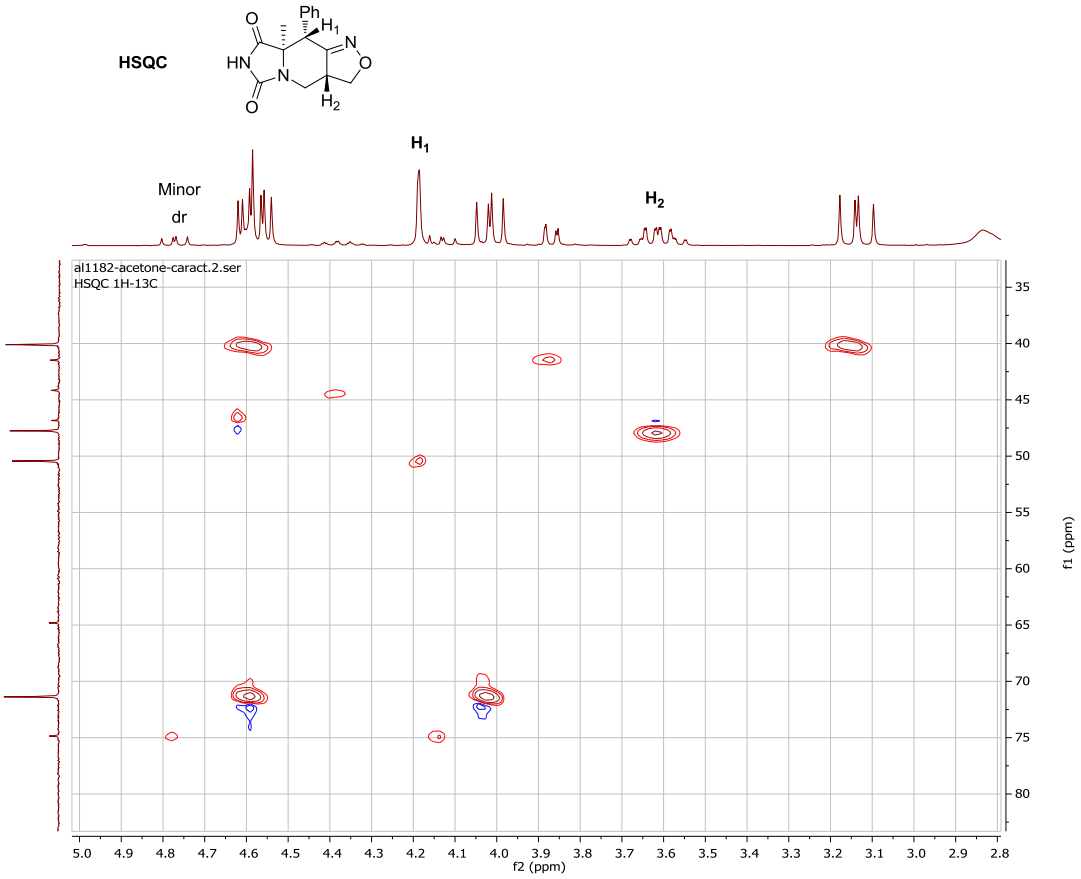
Selective NOE (3.20ppm-H_1)



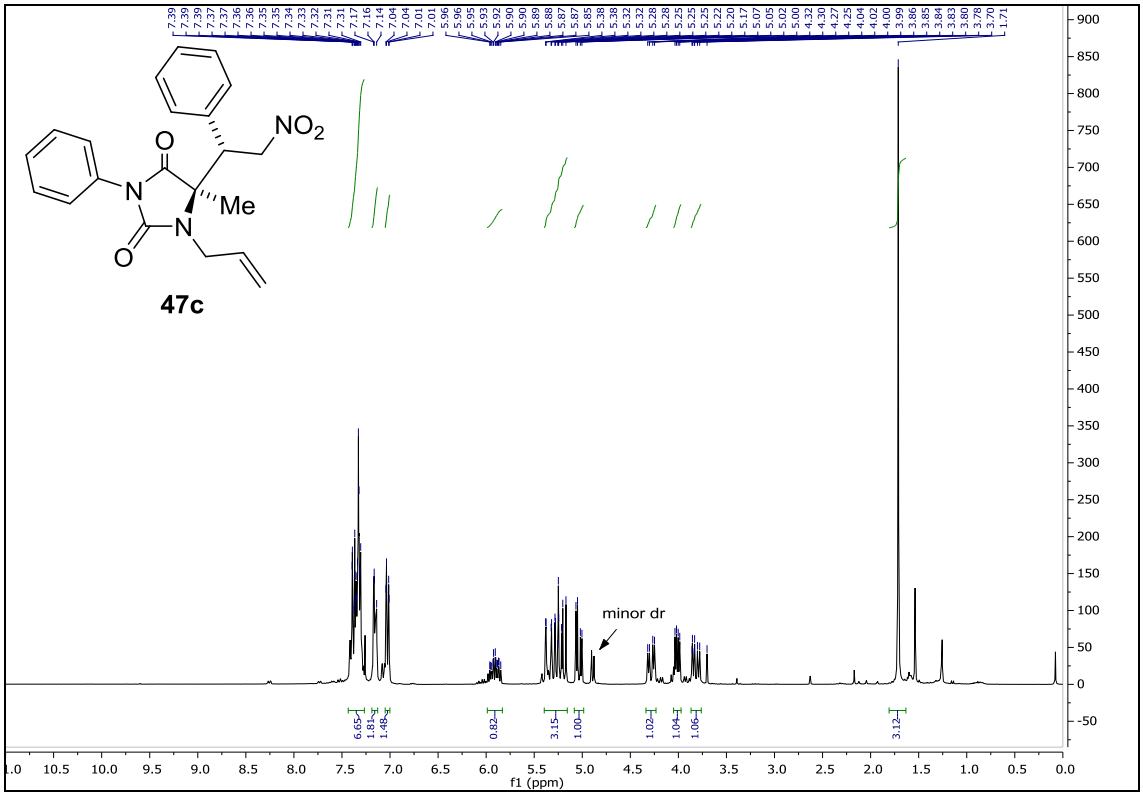
(3a*R*,8a*R*,9*S*)-8a-Methyl-9-phenyl-3a,4,8a,9-tetrahydro-3*H*,6*H*-imidazo[1,5-a]isoxazolo[3,4-d]pyridine-6,8(7*H*)-dione (64)

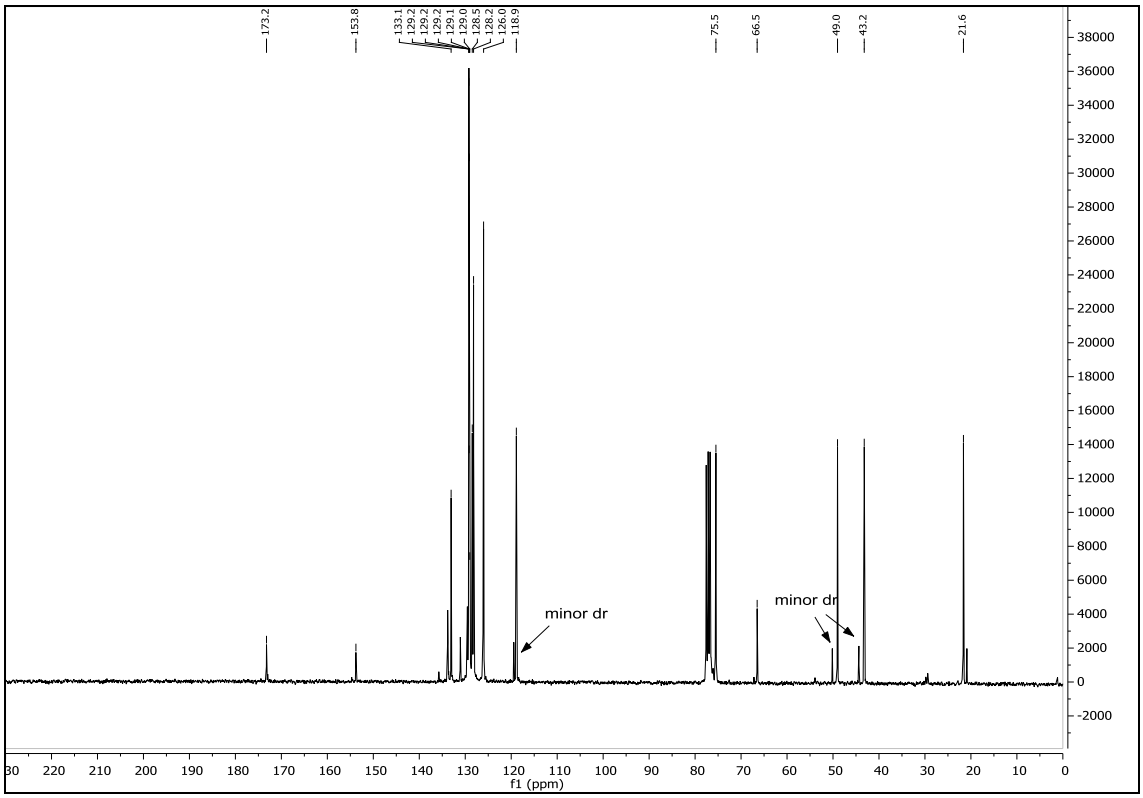




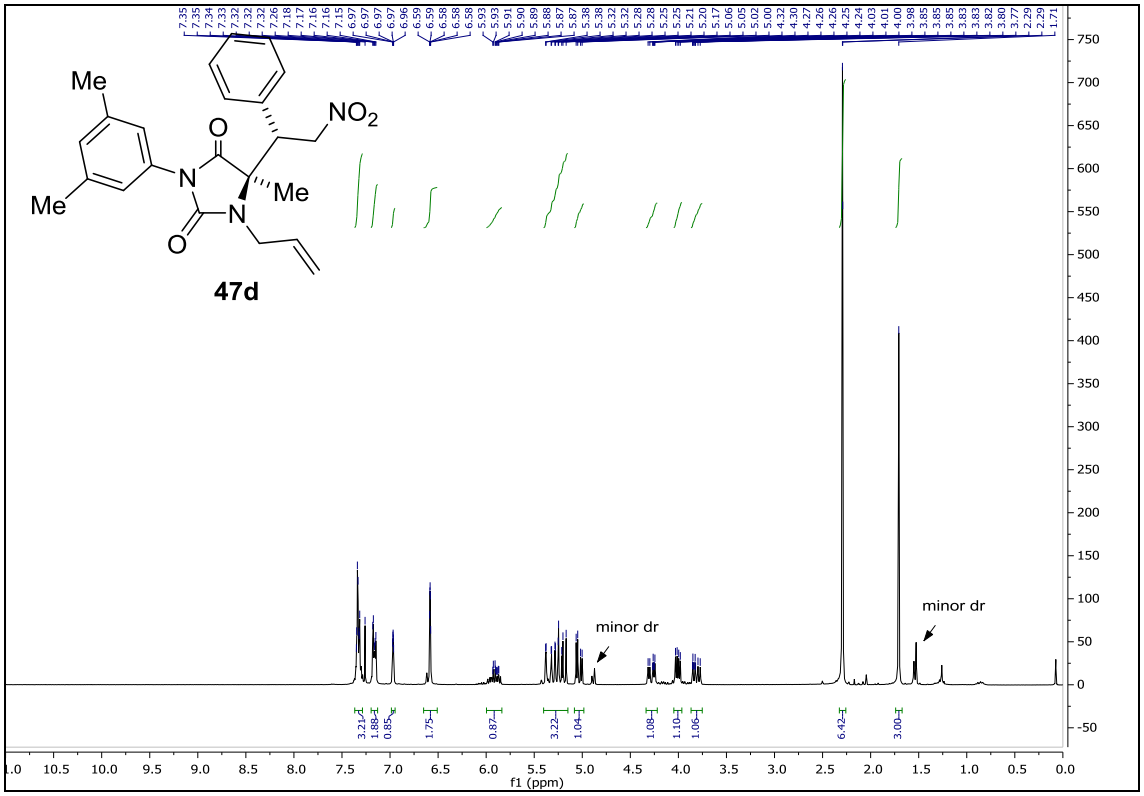

HSQC
Ph
H1
N
O
HN
N
O
O
H2
H1
Minor
dr
H2
al1182-acetone-caract.2.ser
HSQC 1H-13C
35
40
45
50
55
60
65
70
75
80
f1 (ppm)
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
f2 (ppm)

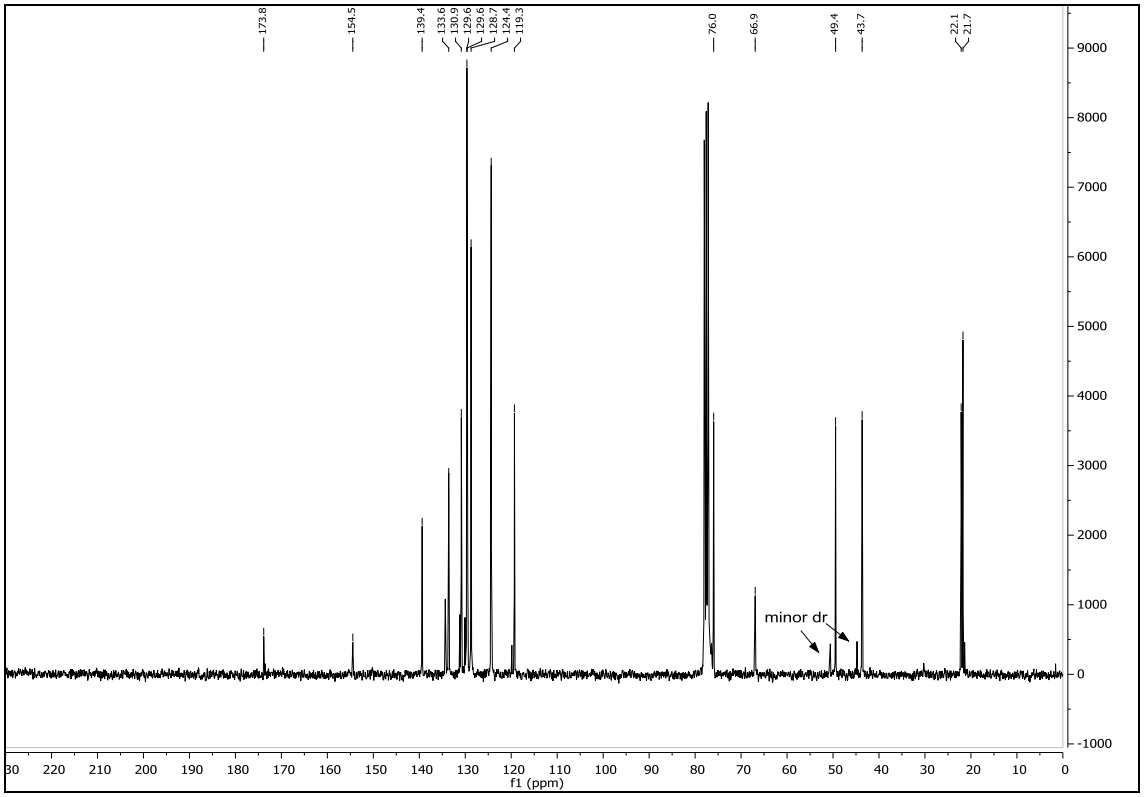
(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (65)



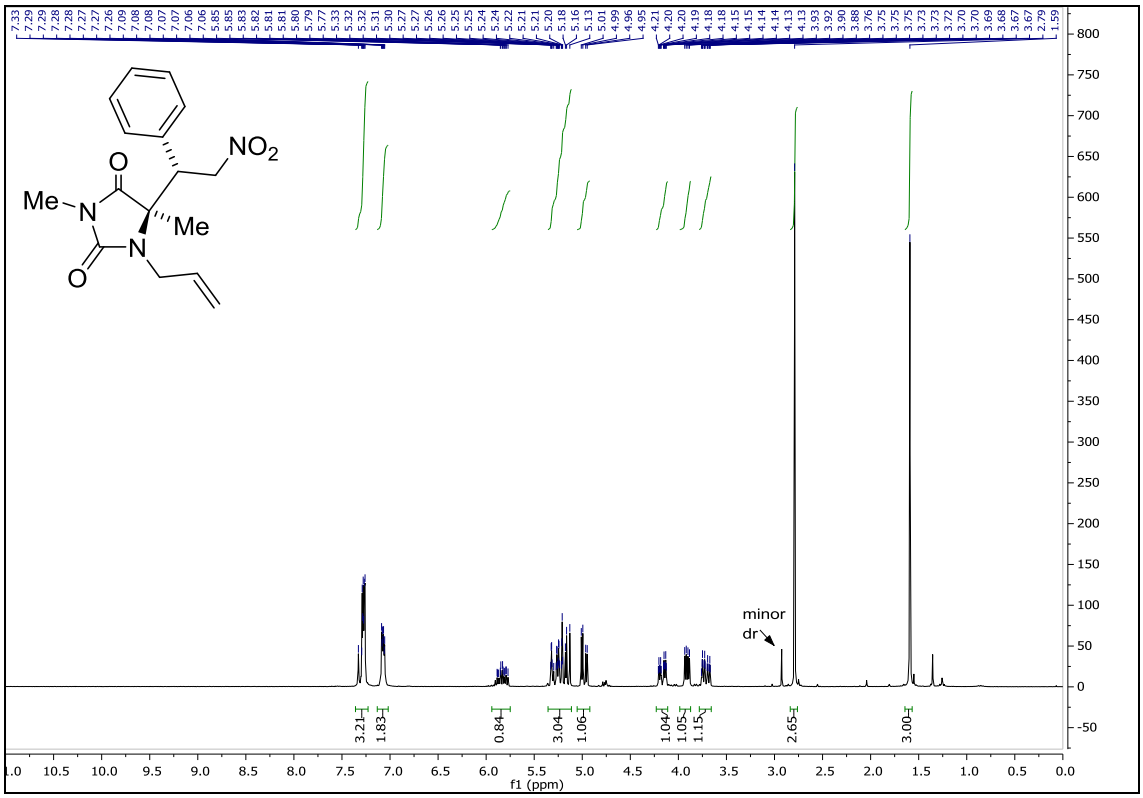


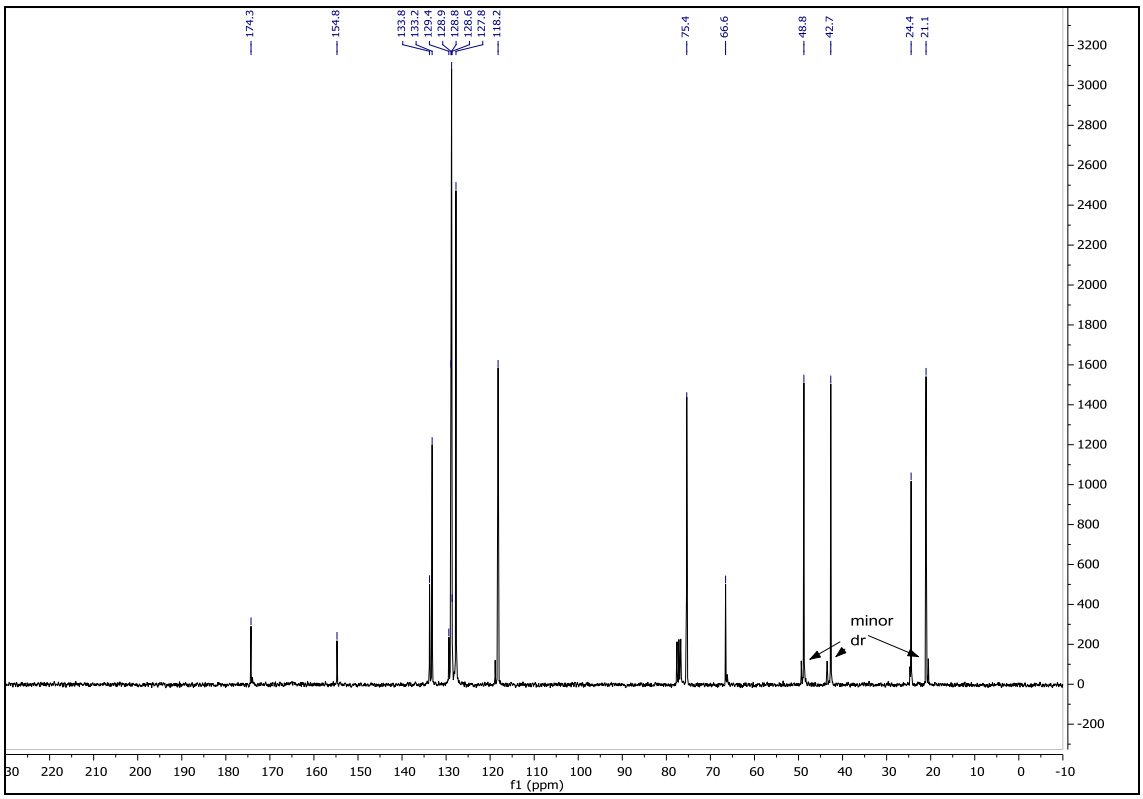
(*R*)-1-Allyl-3-(3,5-dimethylphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (66)



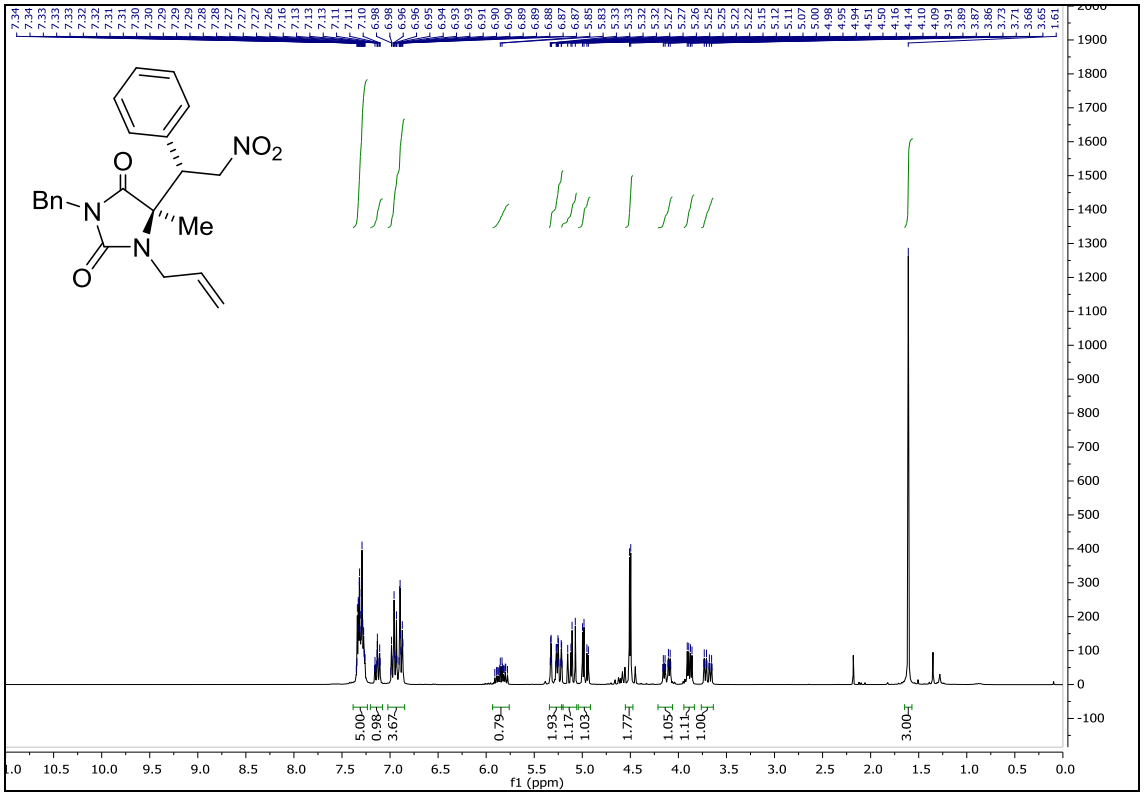


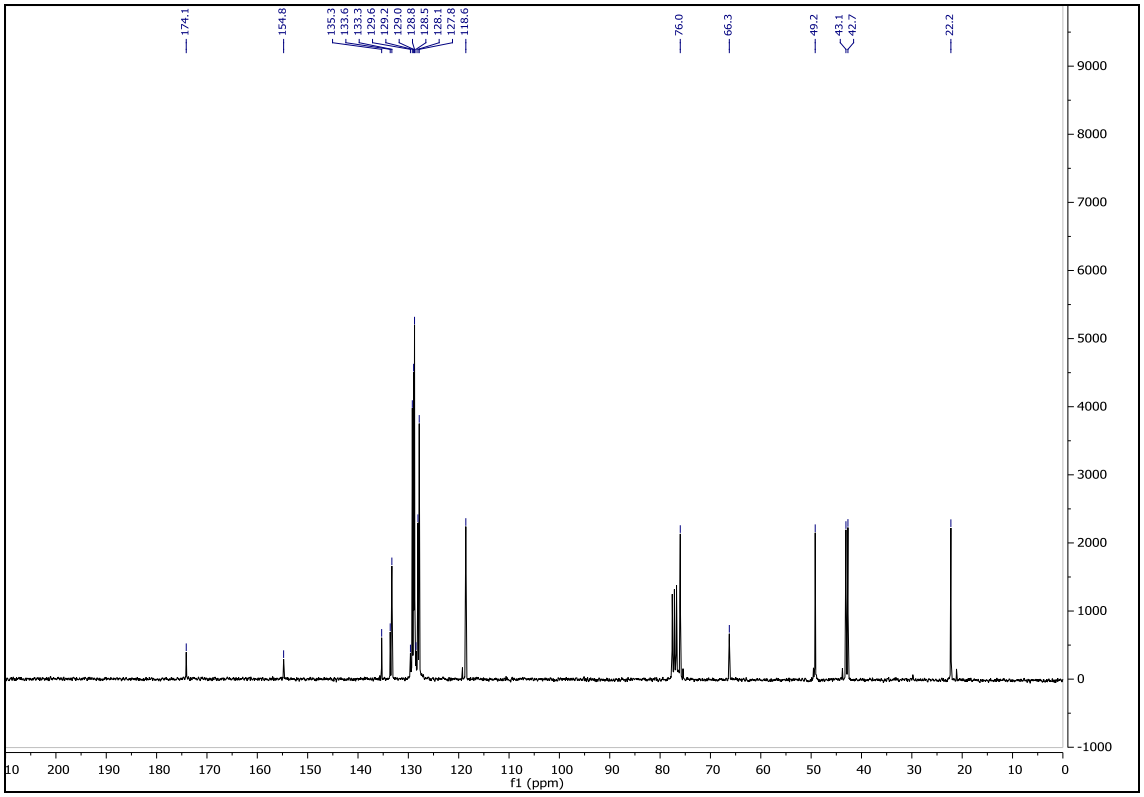
(*R*)-1-Allyl-3,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (67)



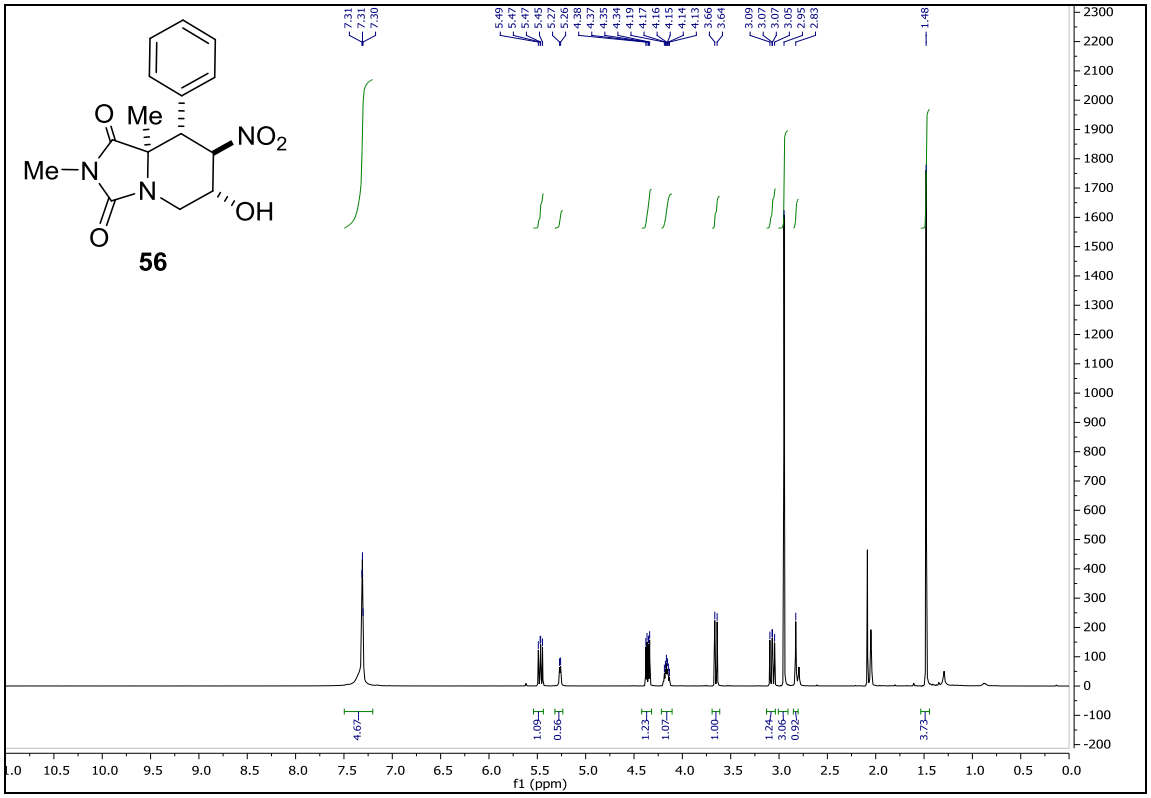


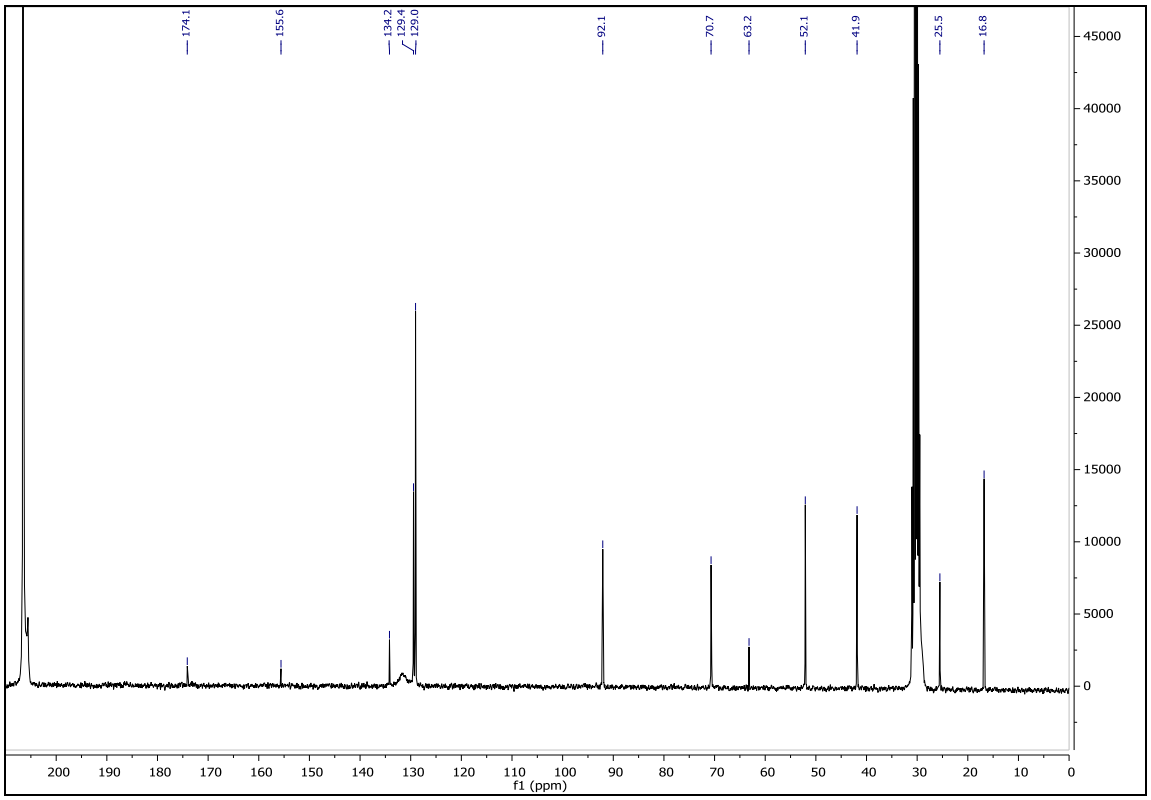
(*R*)-1-Allyl-3-benzyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (68)

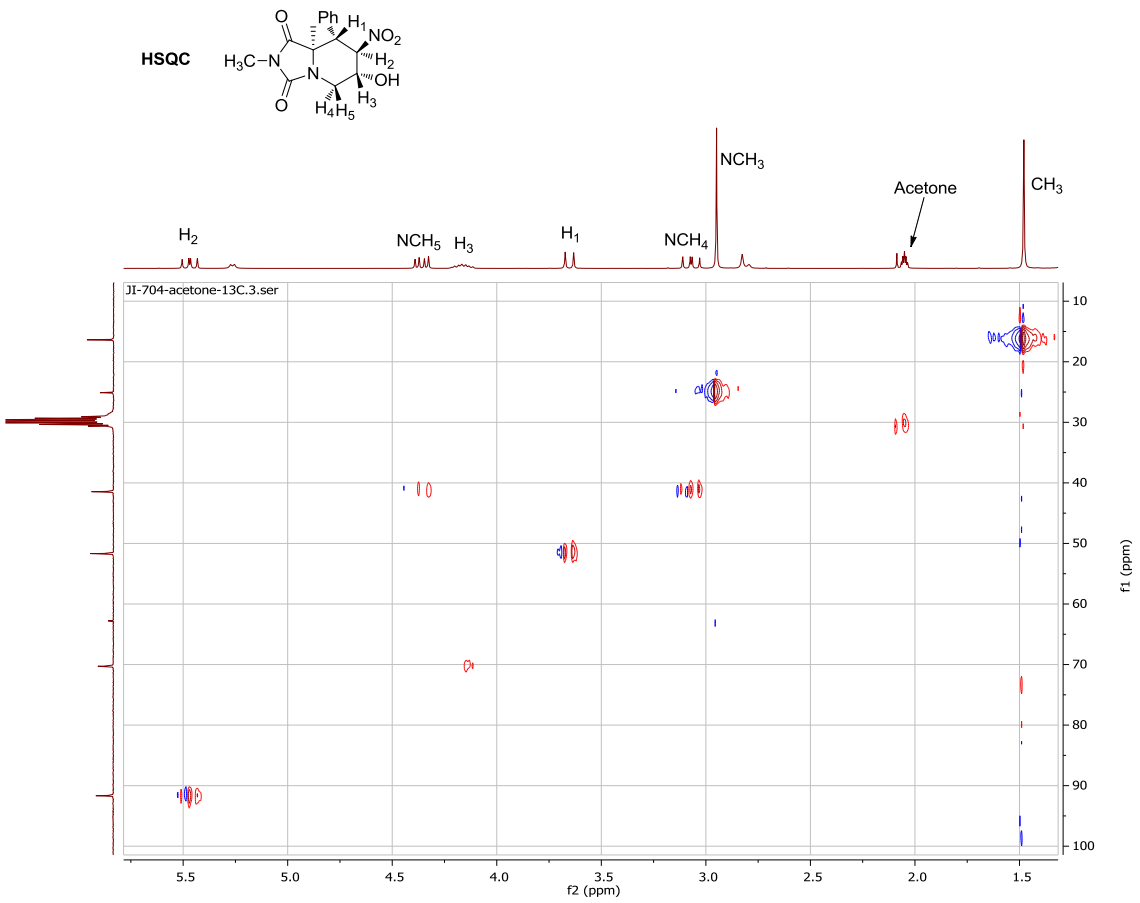




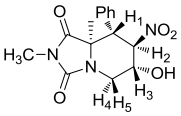
(6*R*,7*R*,8*R*,8a*R*)-6-Hydroxy-2,8a-dimethyl-7-nitro-8-phenyltetrahydroimidazo[1,5-a]pyridine-1,3(2*H*,5*H*)-dione (70)

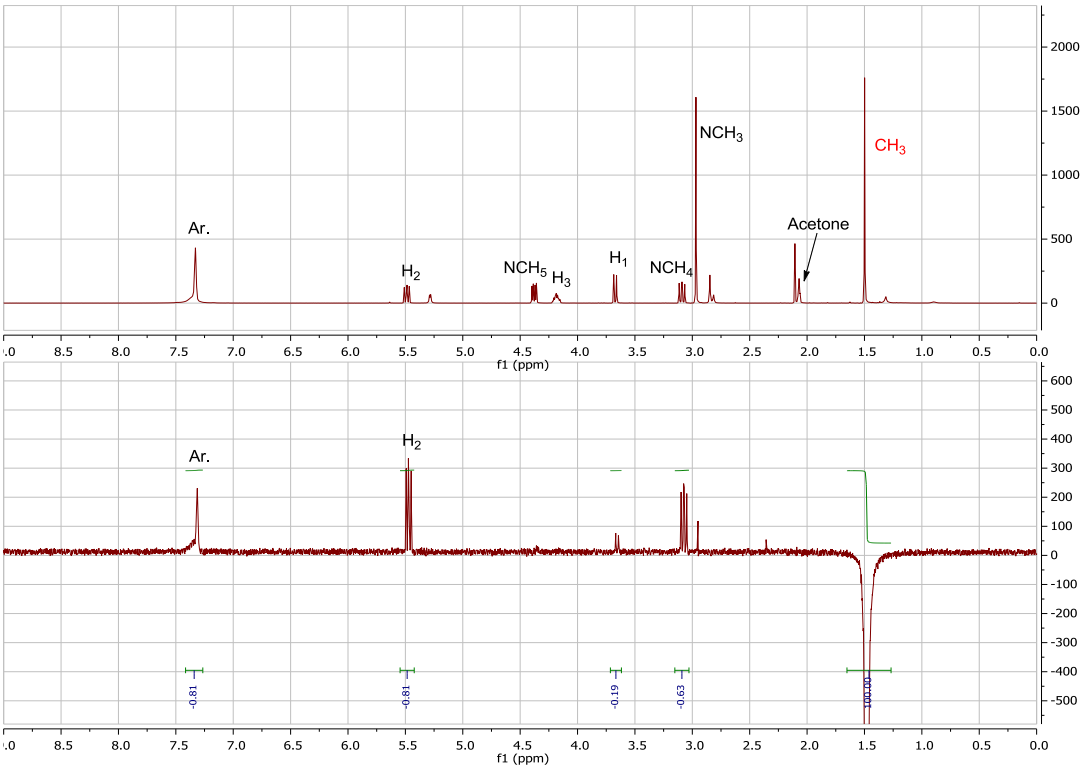




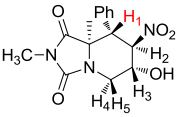

HSQC
Ph
H1
NO2
H3C–N
H2
OH
H3
H4H5
NCH3
Acetone
CH3
H2
NCH5
H3
H1
NCH4
JI-704-acetone-13C.3.ser
f2 (ppm)
f1 (ppm)

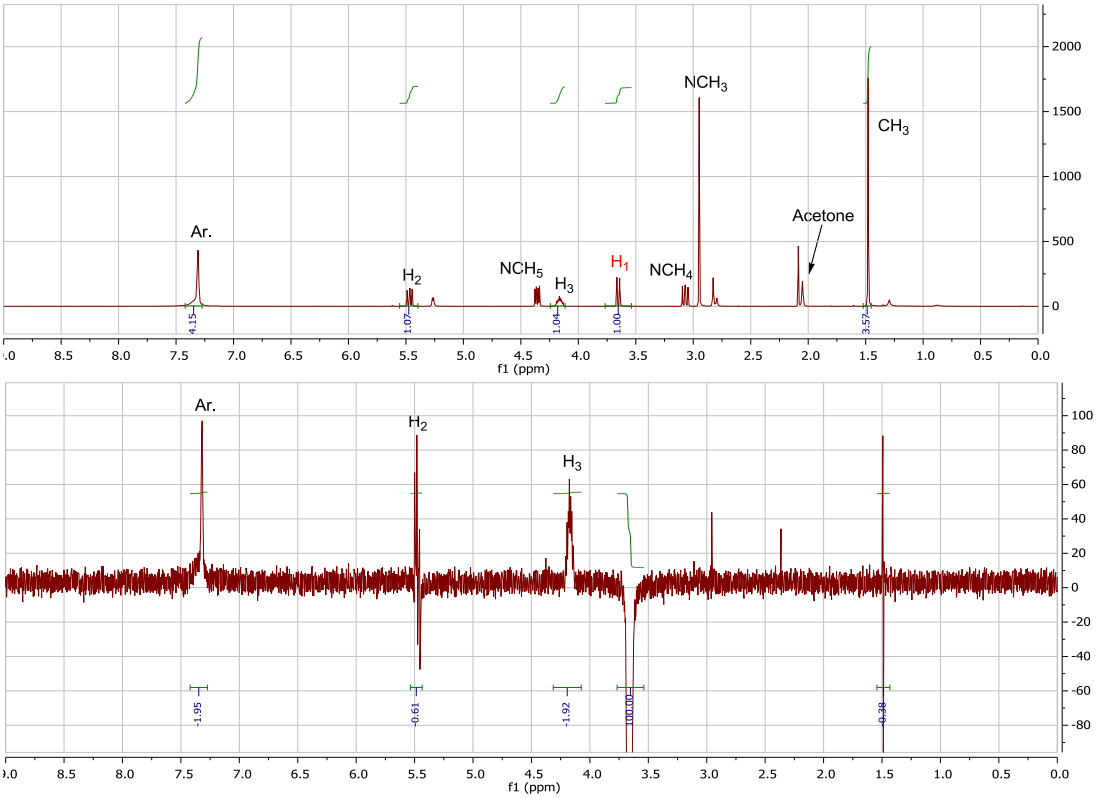
Selective NOE (1.50ppm-CH_3)



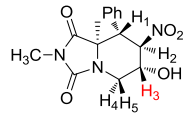


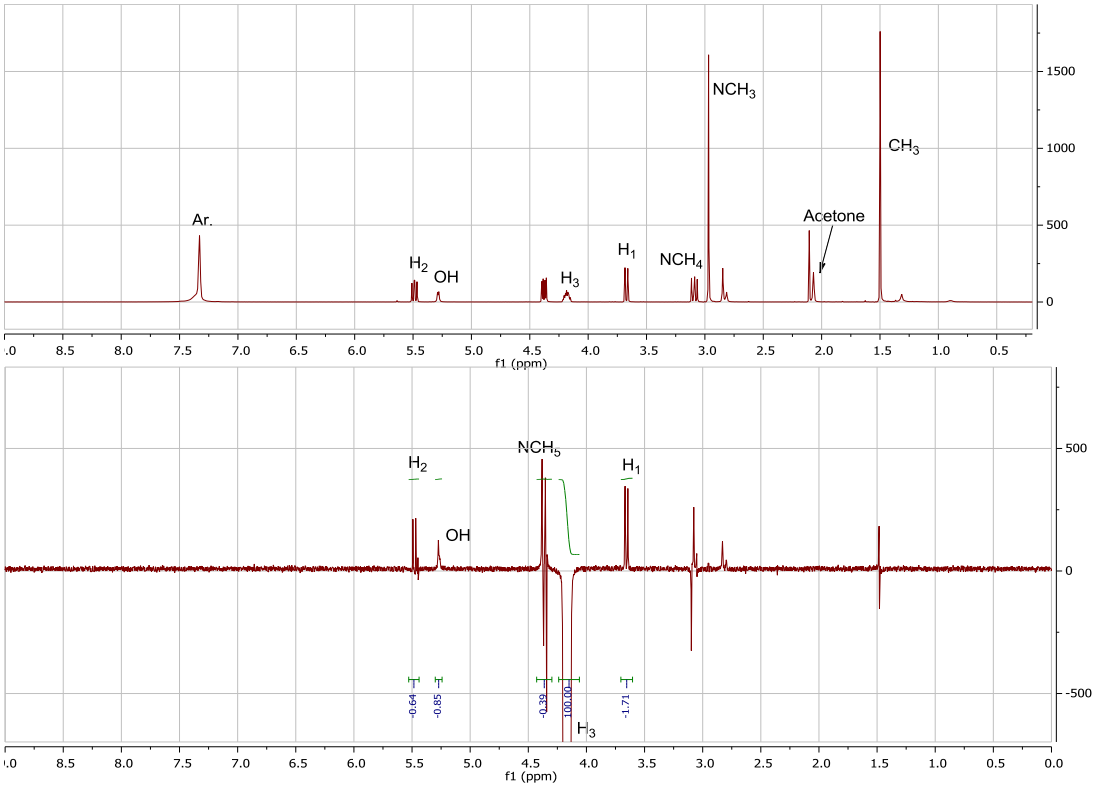
Selective NOE (3.65ppm-H_1)



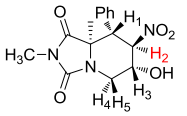


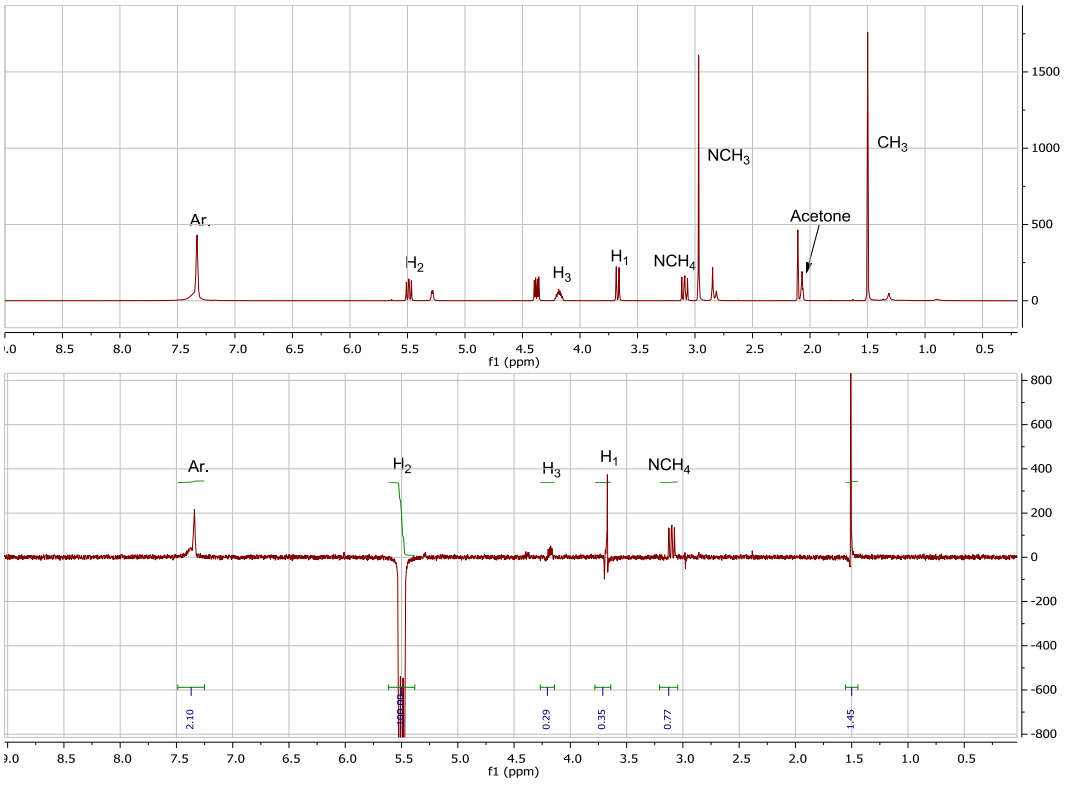
Selective NOE (4.18ppm-H_3)



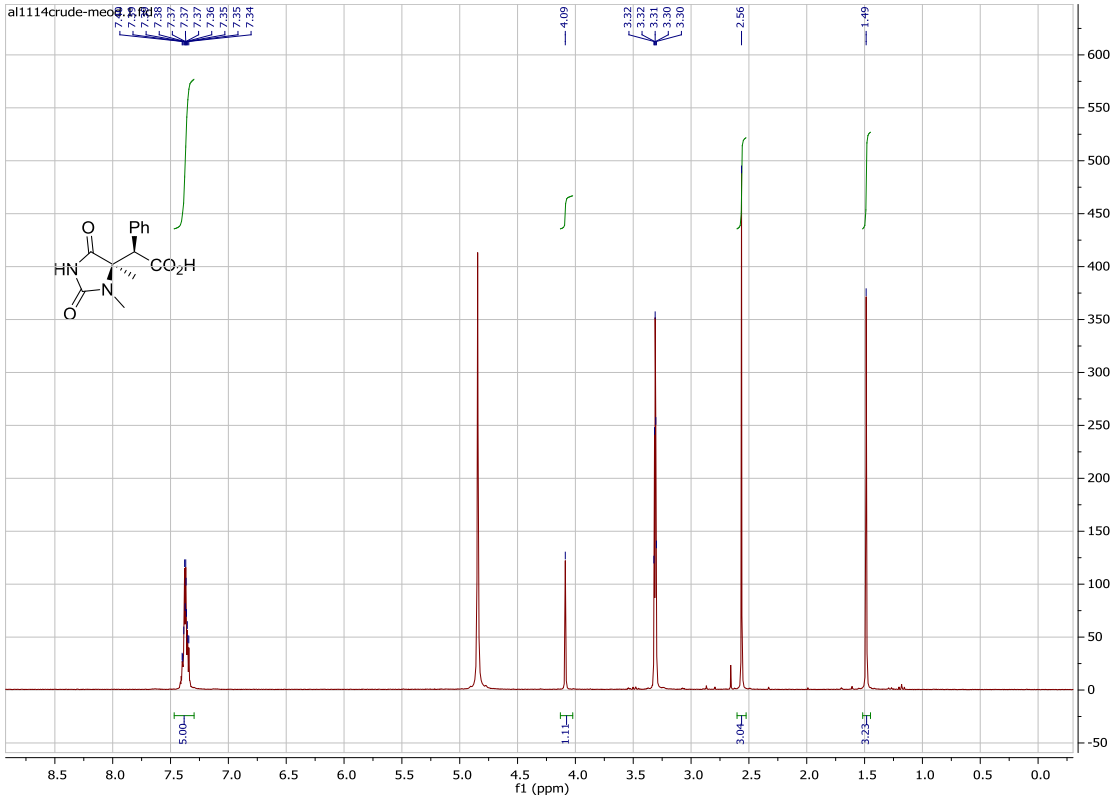


Selective NOE (5.5ppm-H_2)

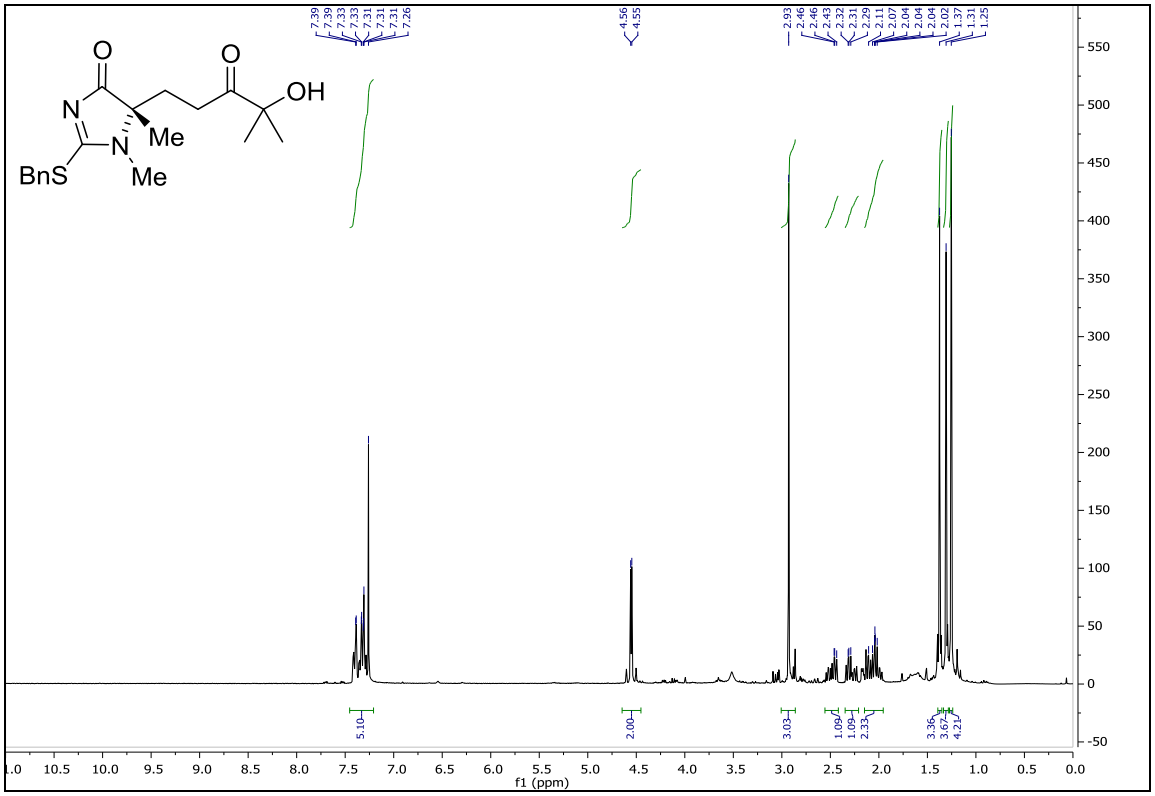


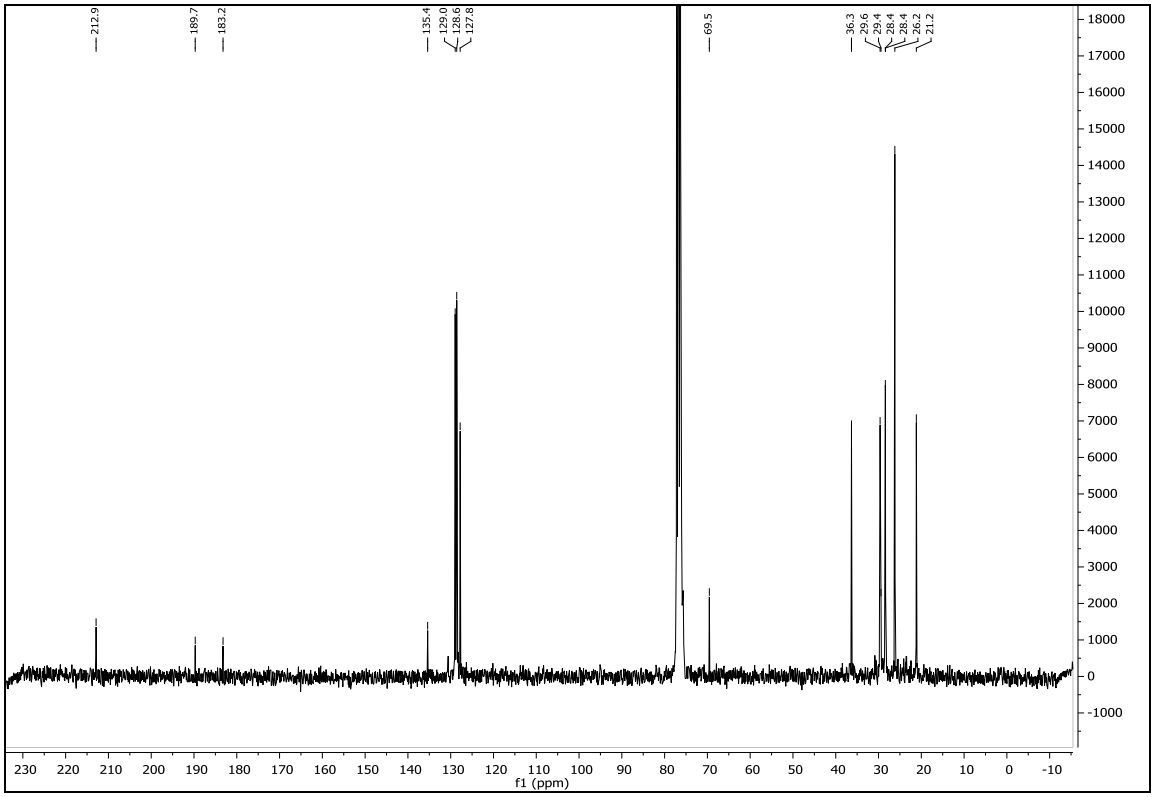


S-((2*R*,3*S*)-1-amino-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl) (71)

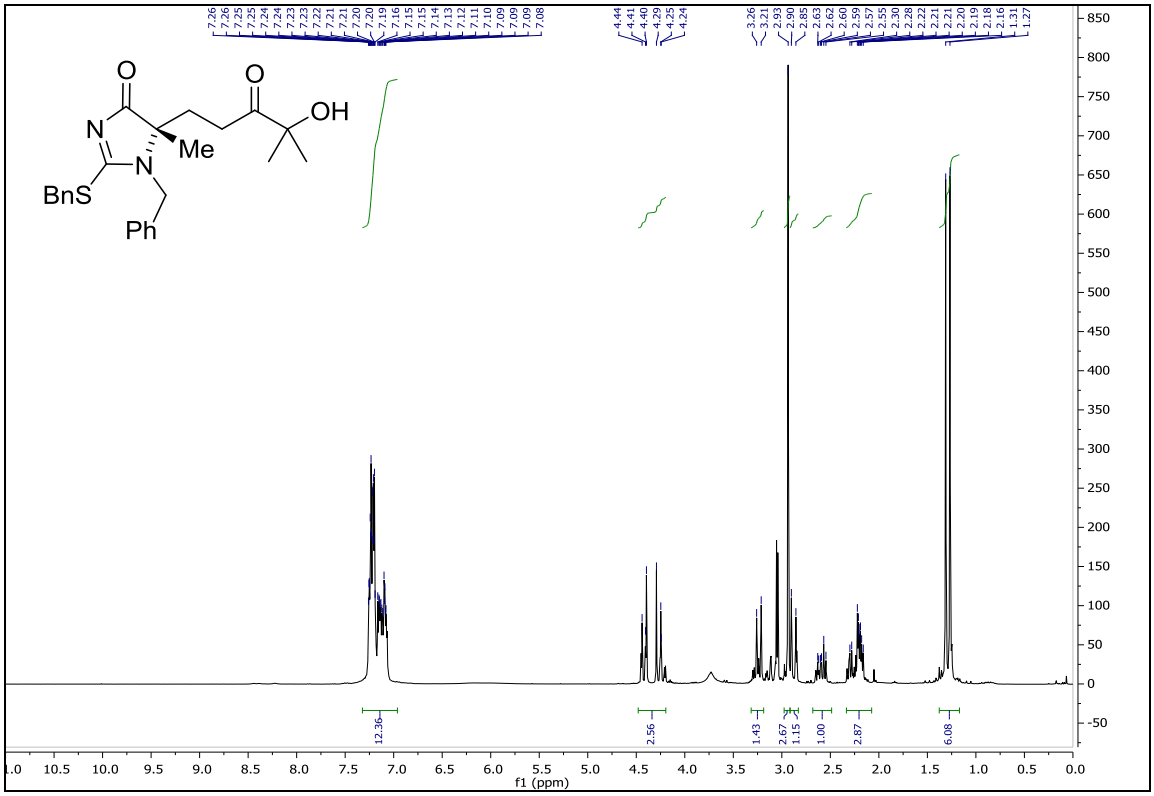


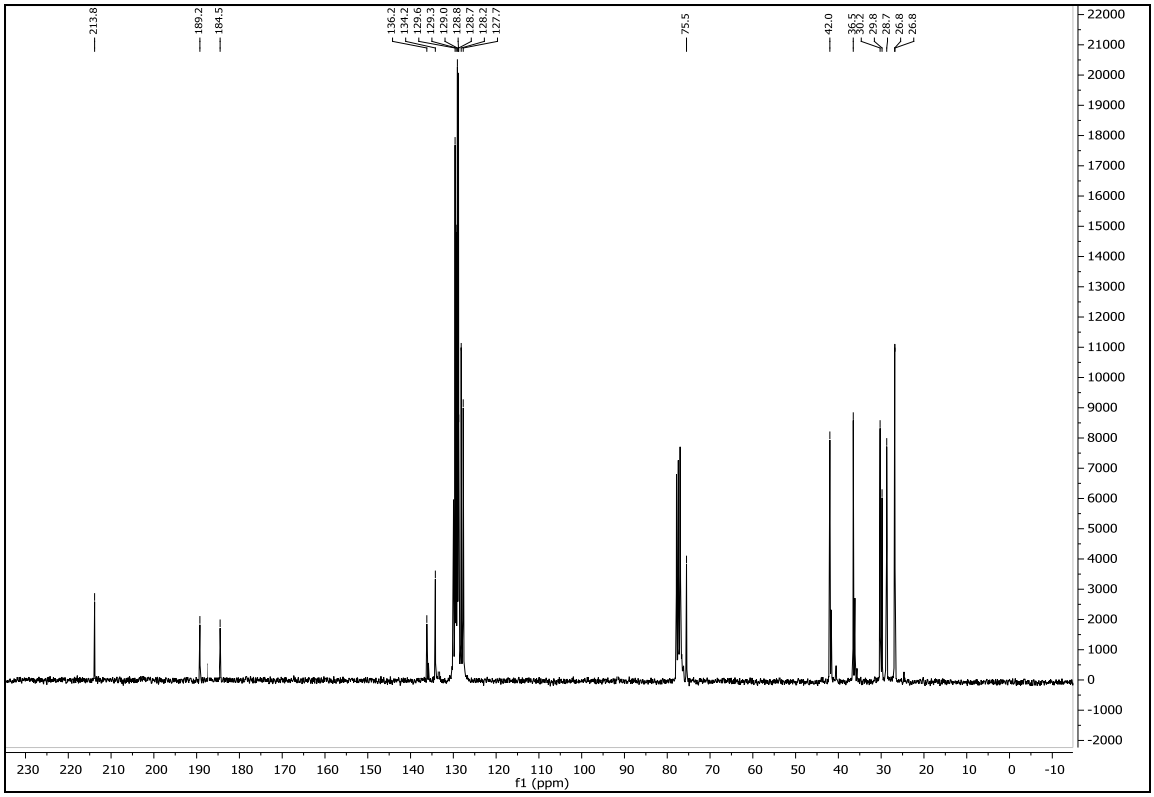
(*S*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (74)



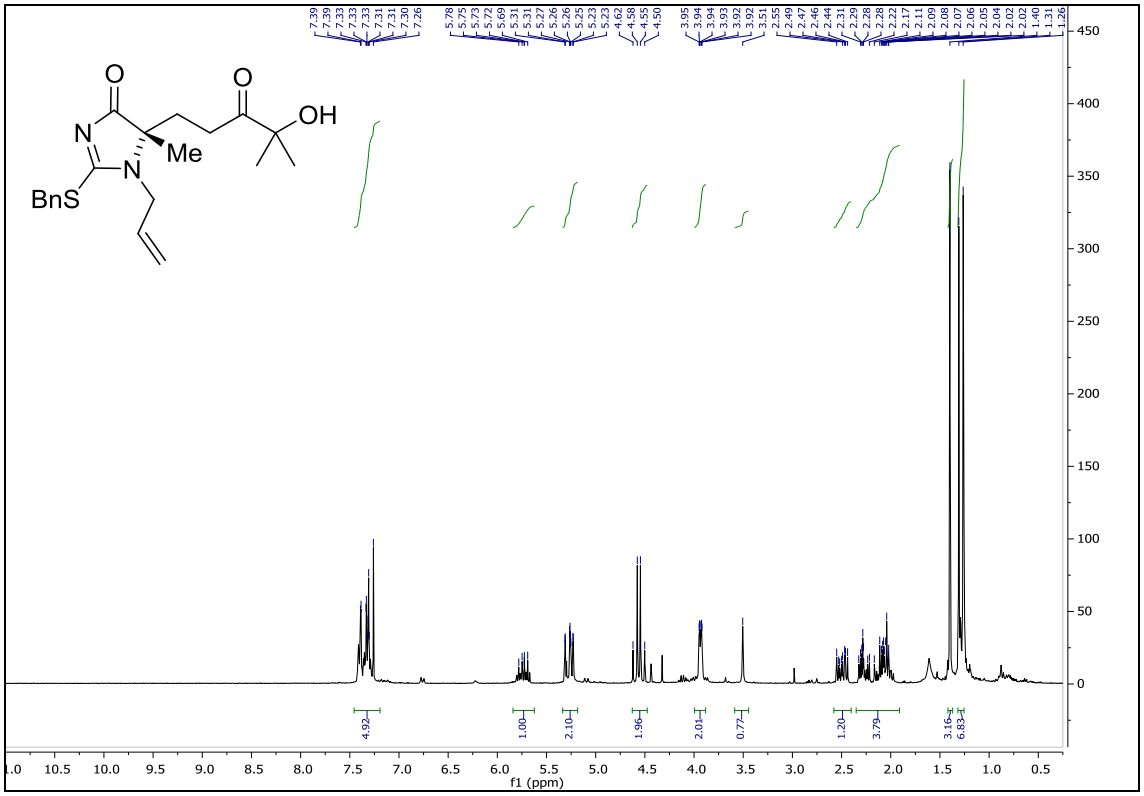


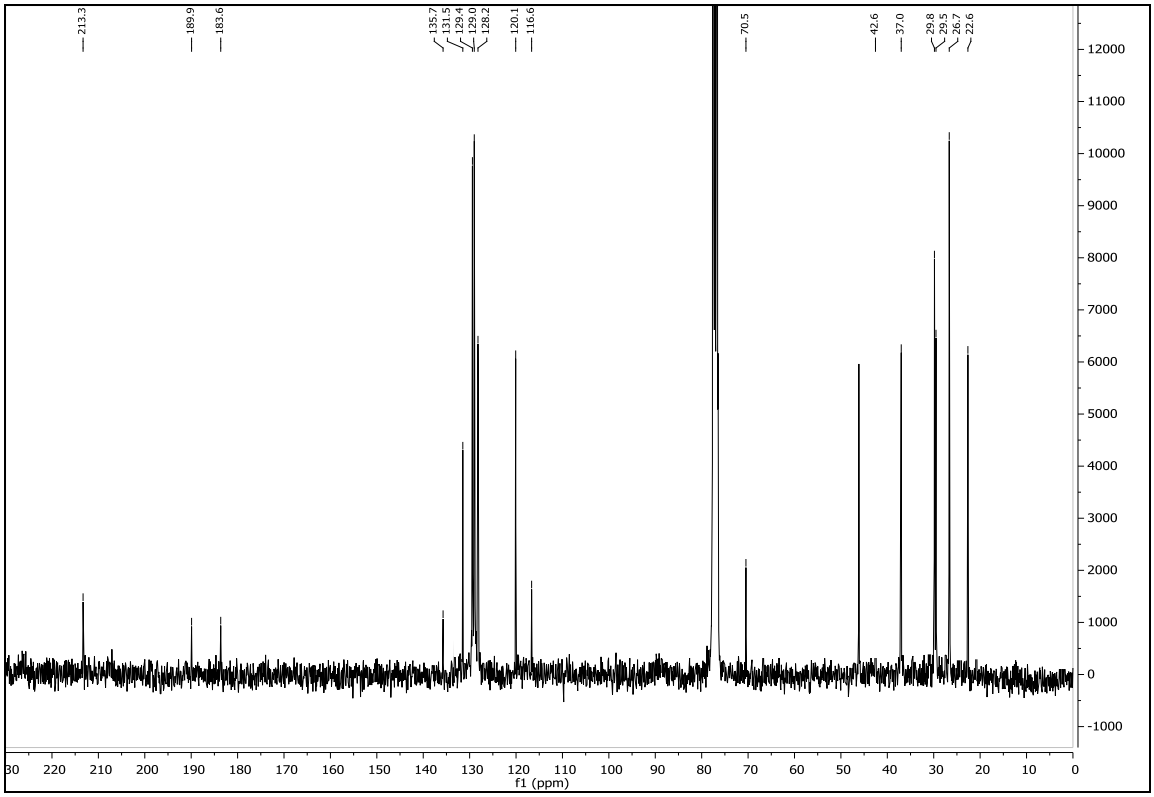
(*S*)-1-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (75)



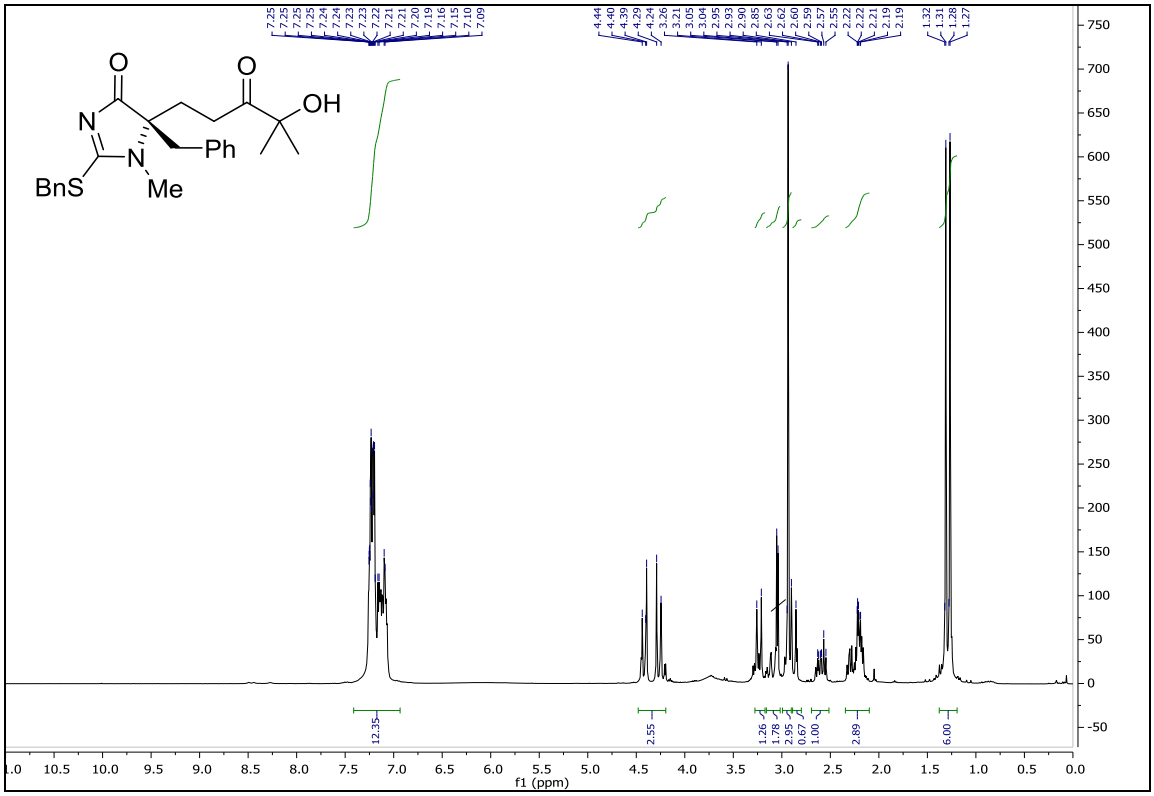


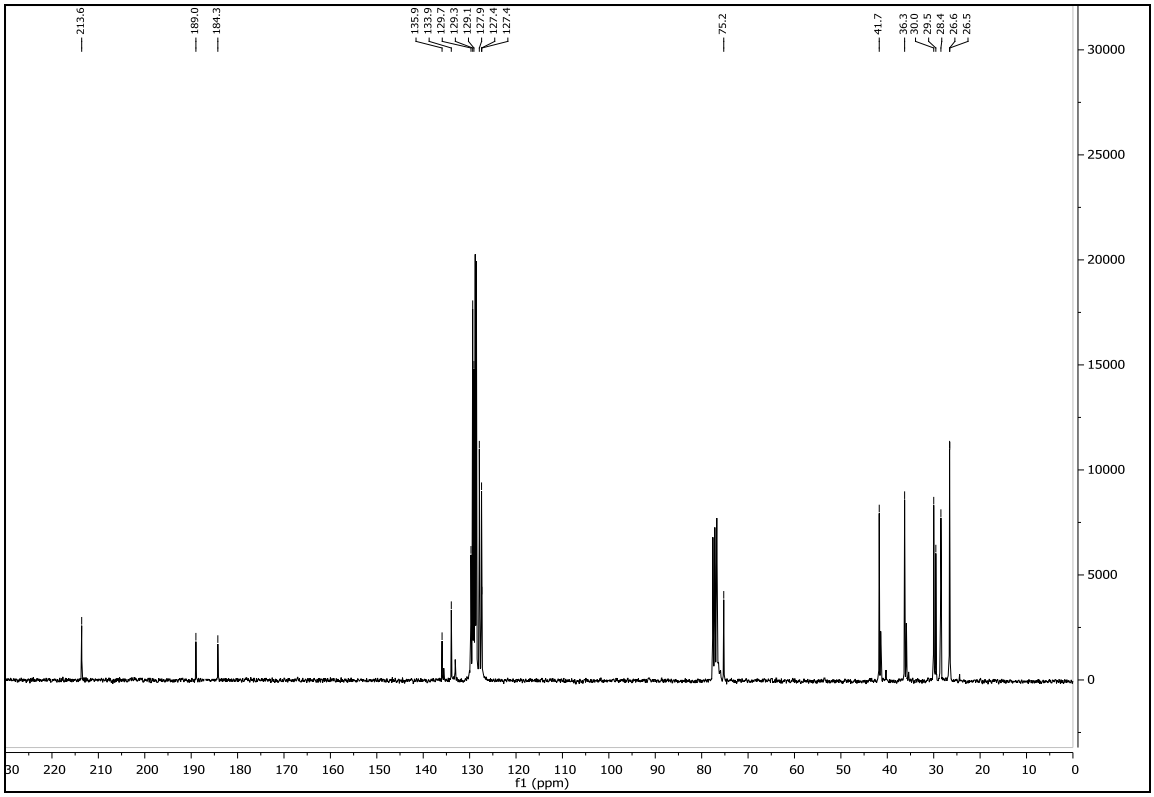
(*S*)-1-Allyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (76)



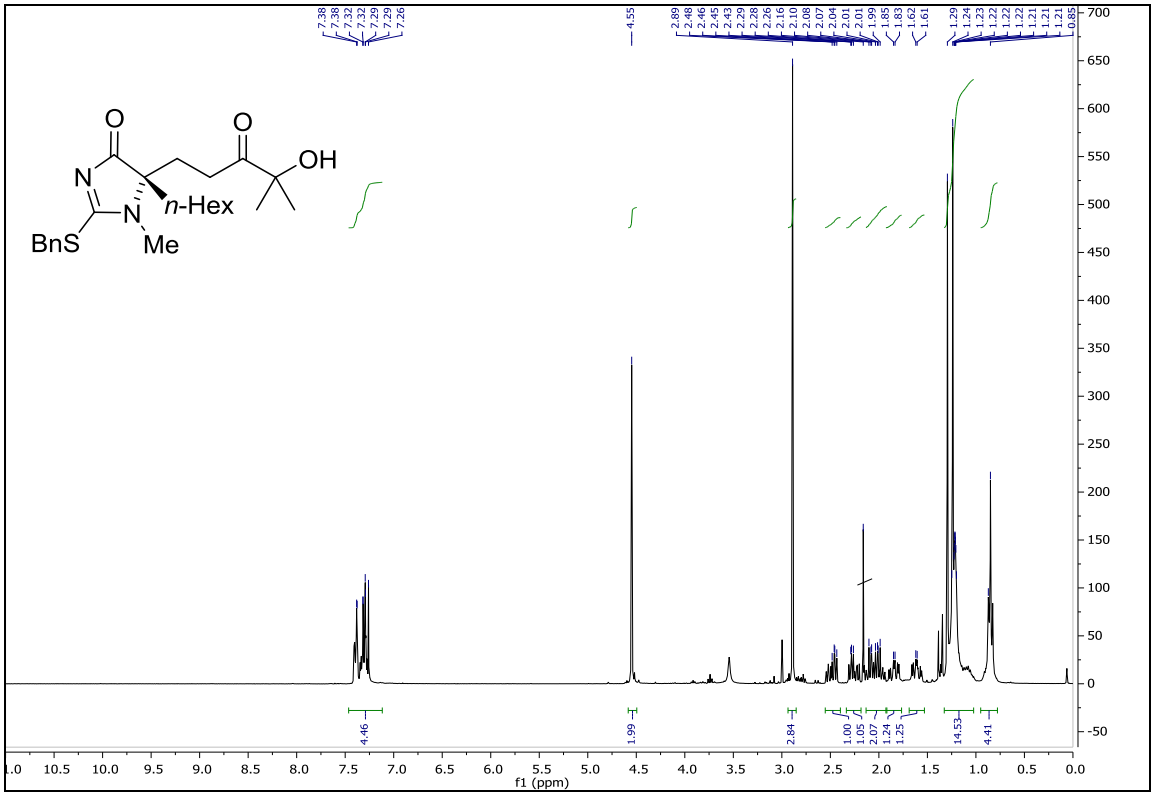


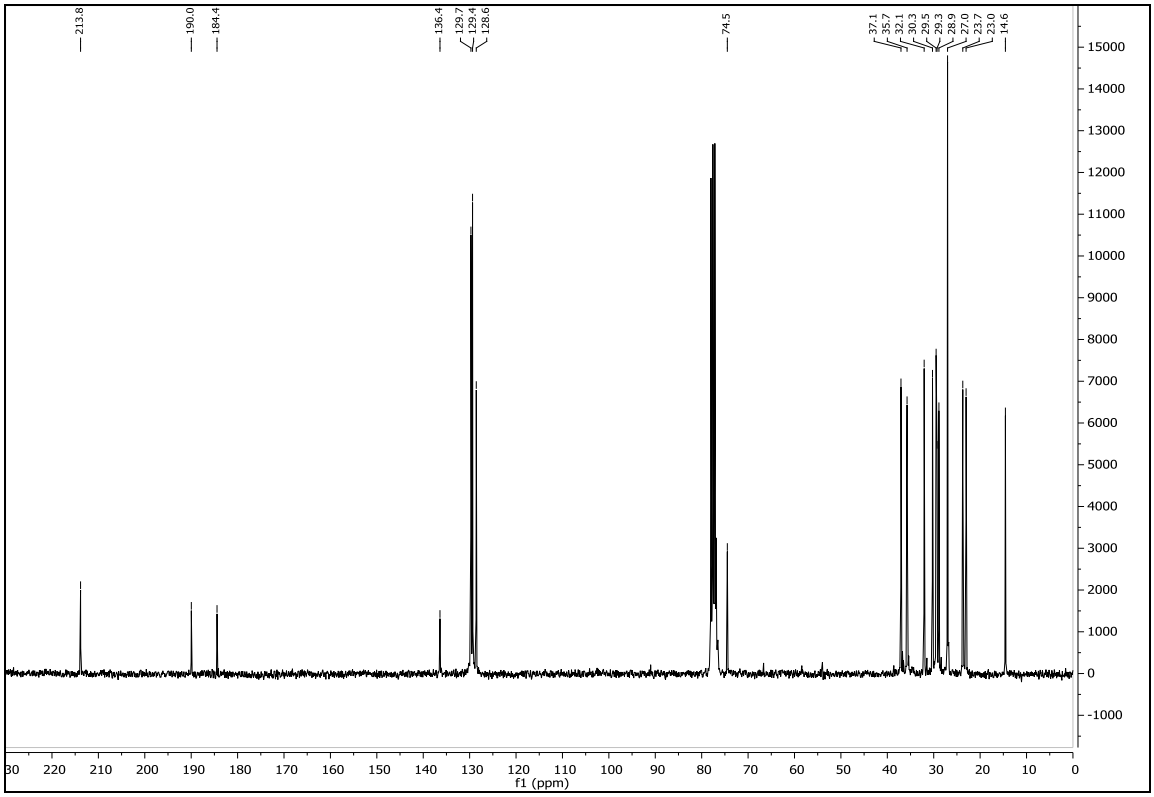
(*R*)-5-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (77)



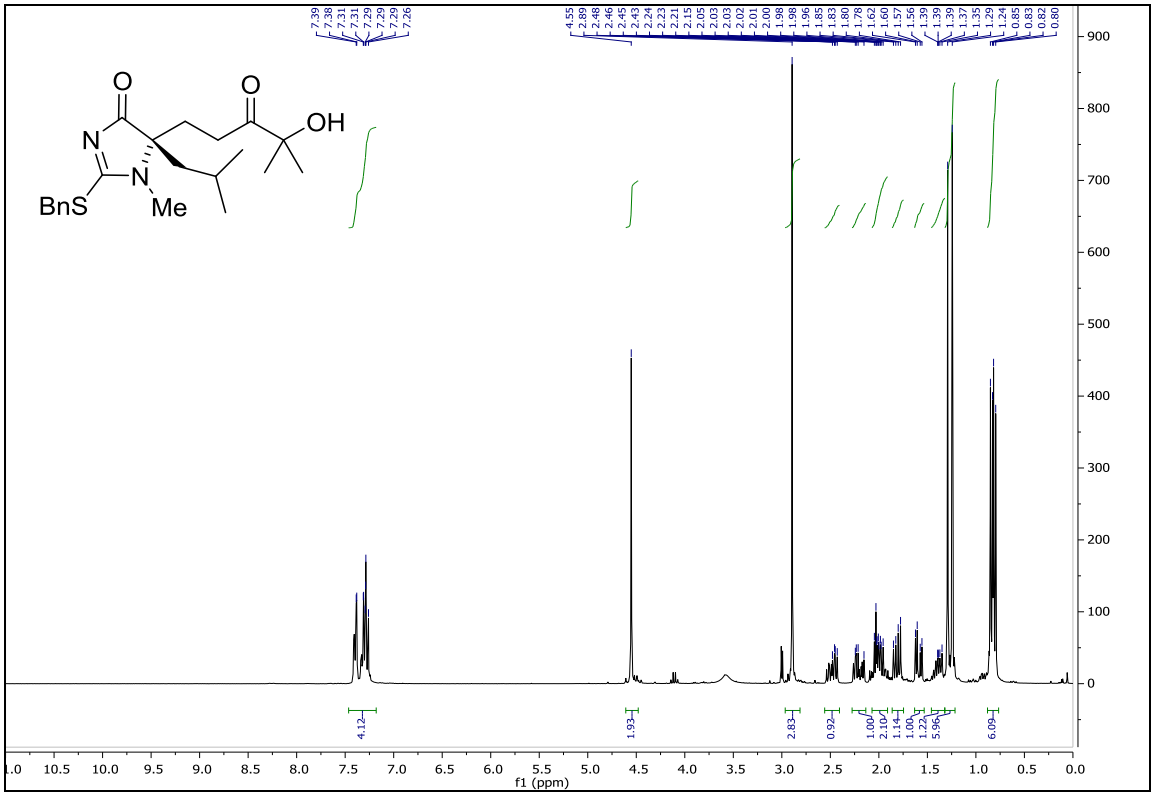


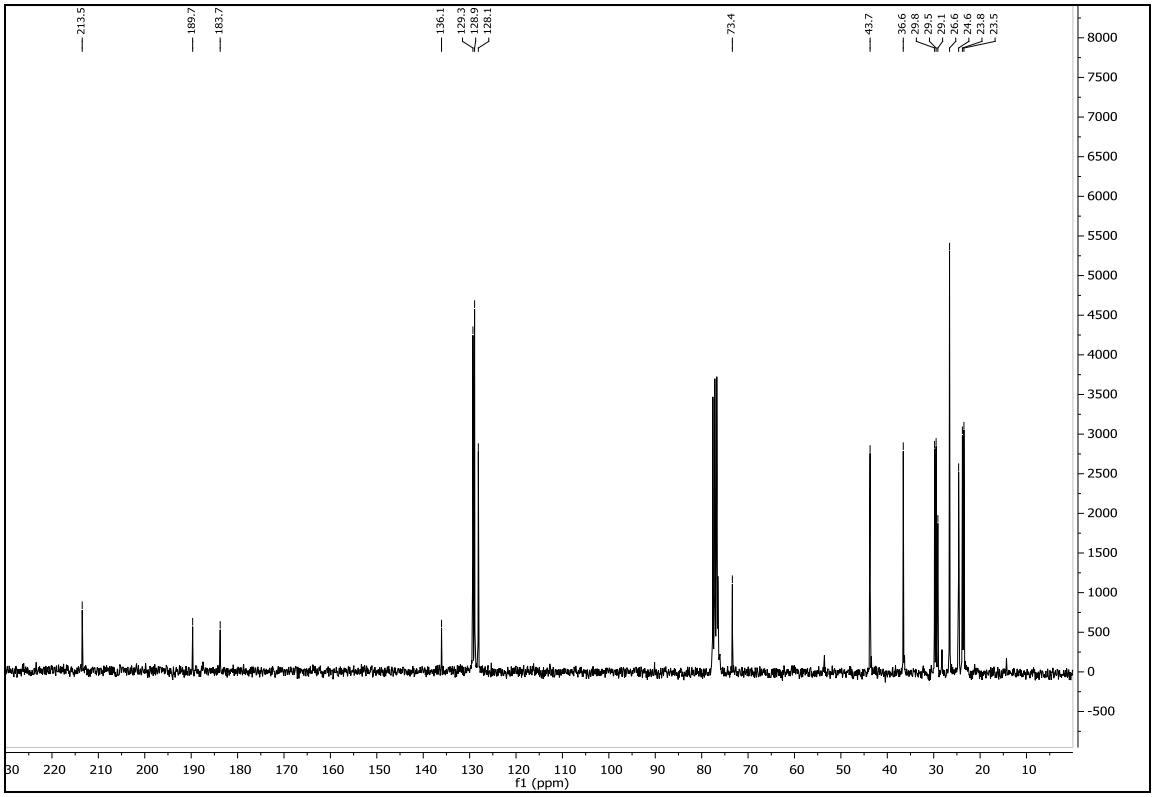
(*S*)-2-(Benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (78)



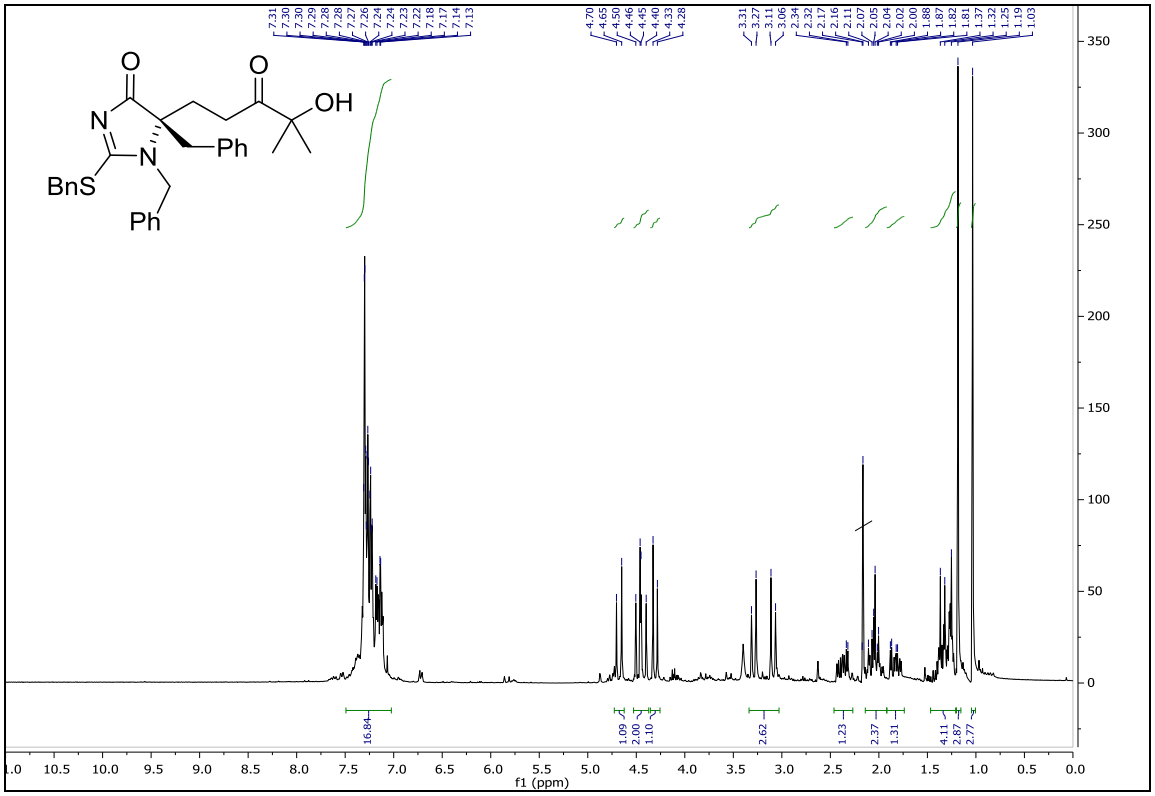


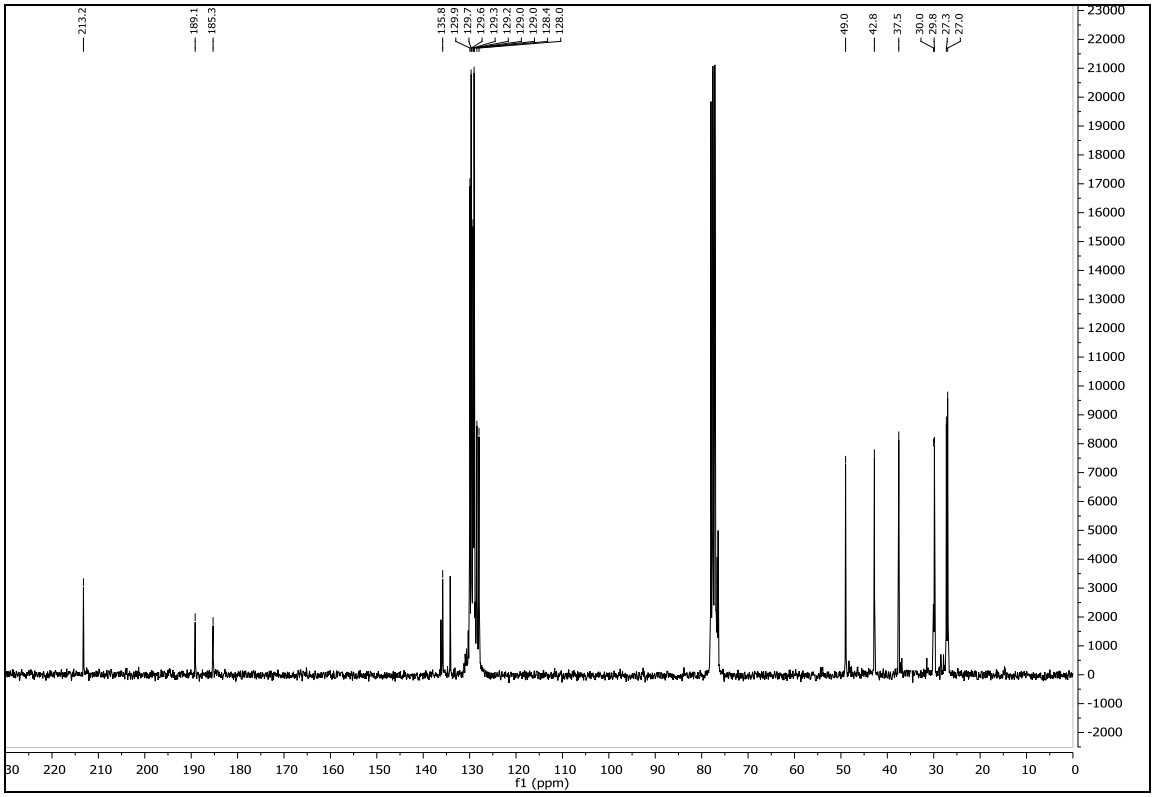
(*R*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (79)



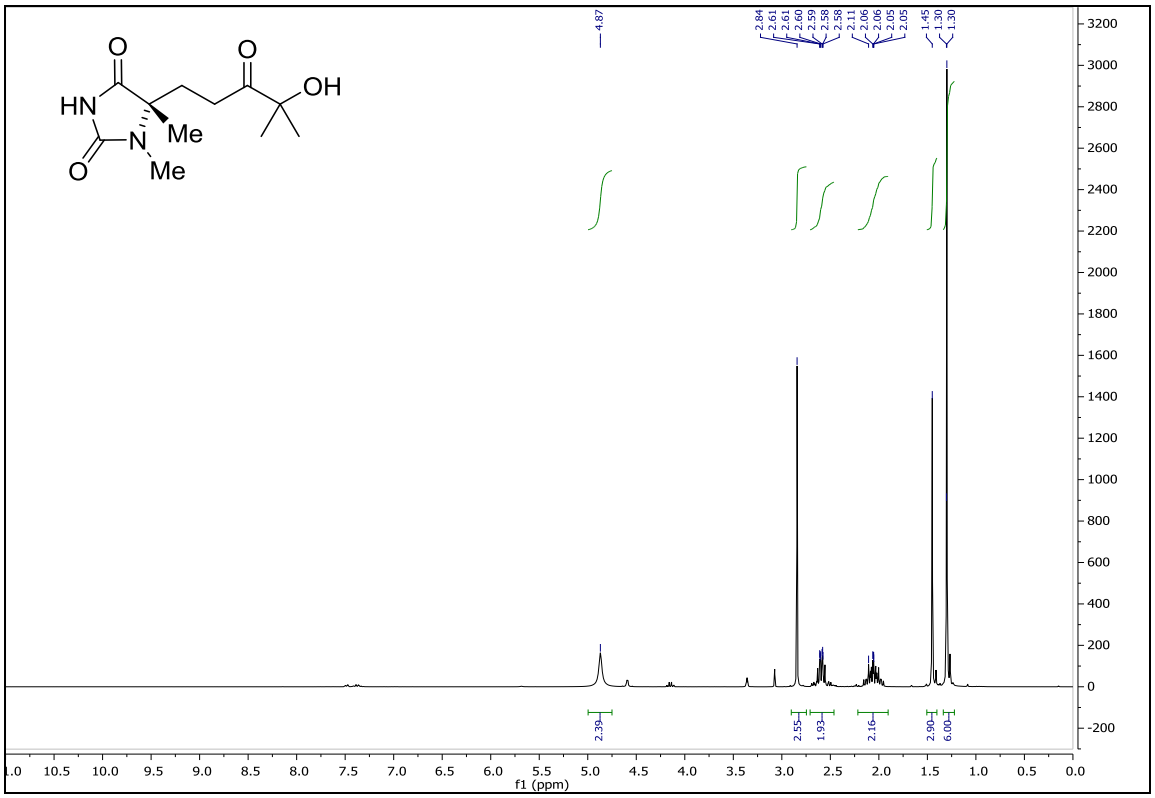


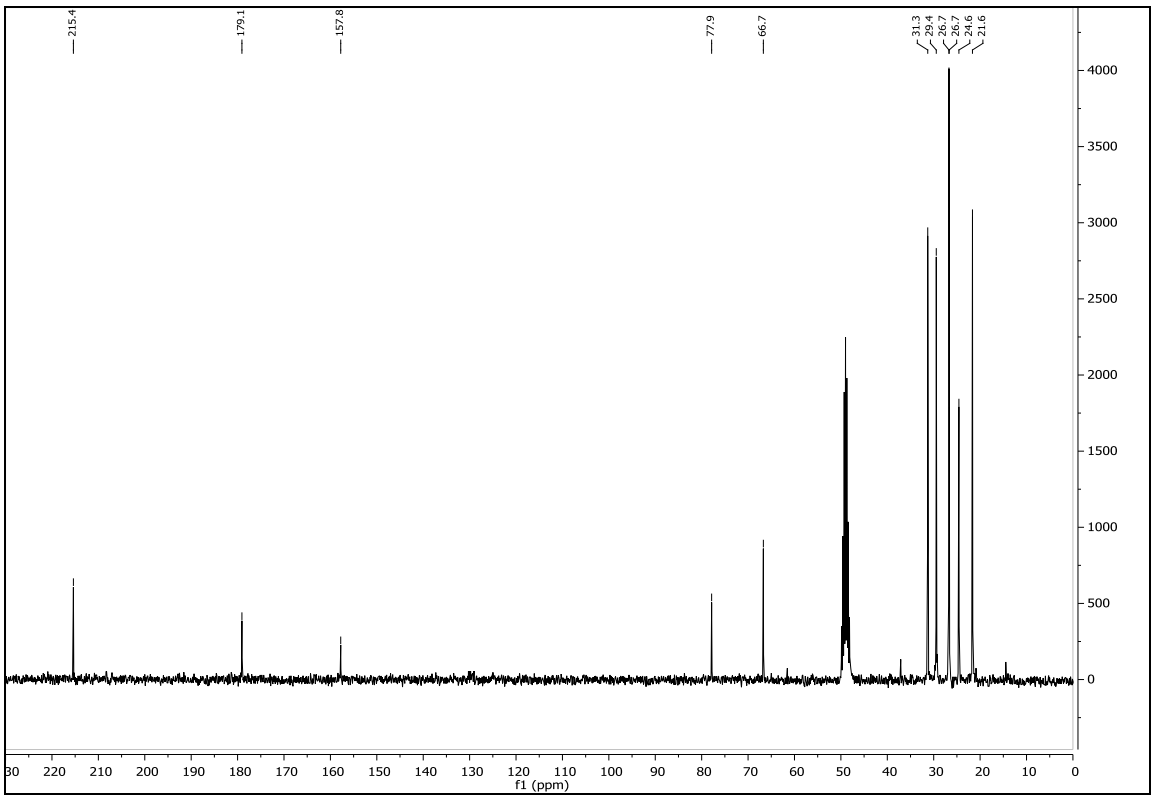
(*R*)-1,5-Dibenzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)- 1*H*-imidazol-4(5*H*)-one (80)



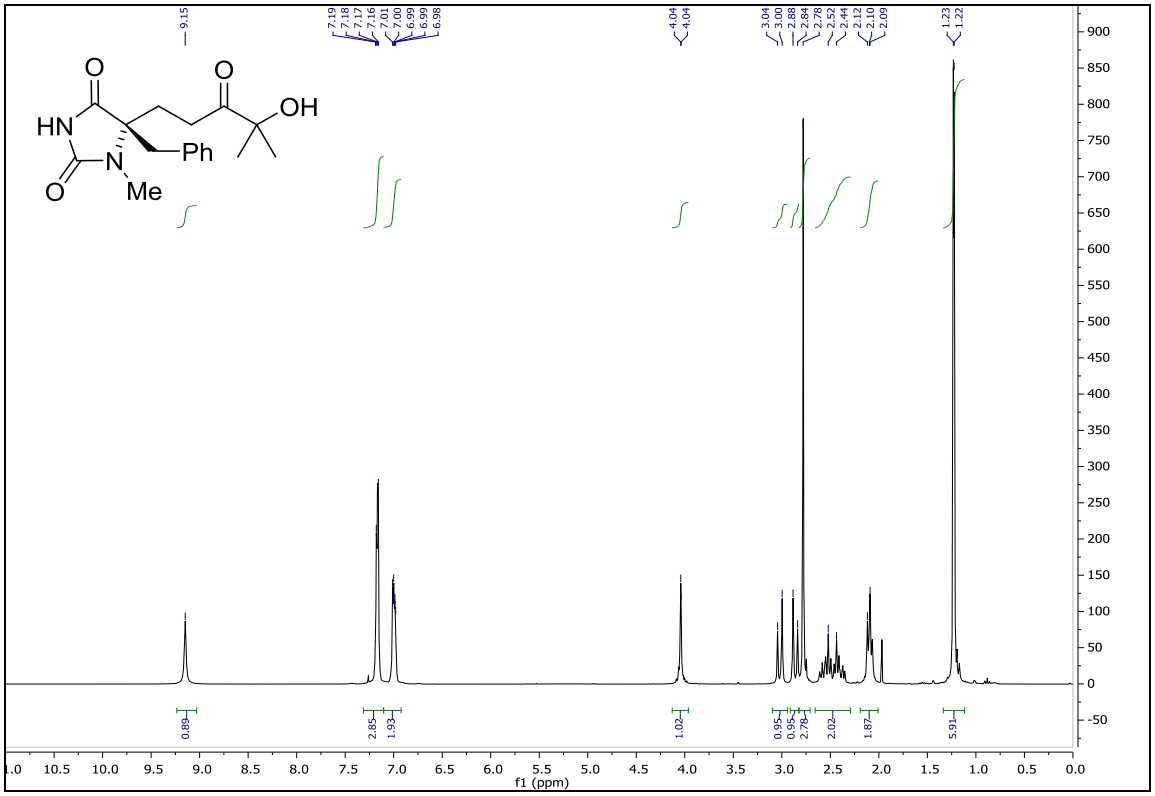


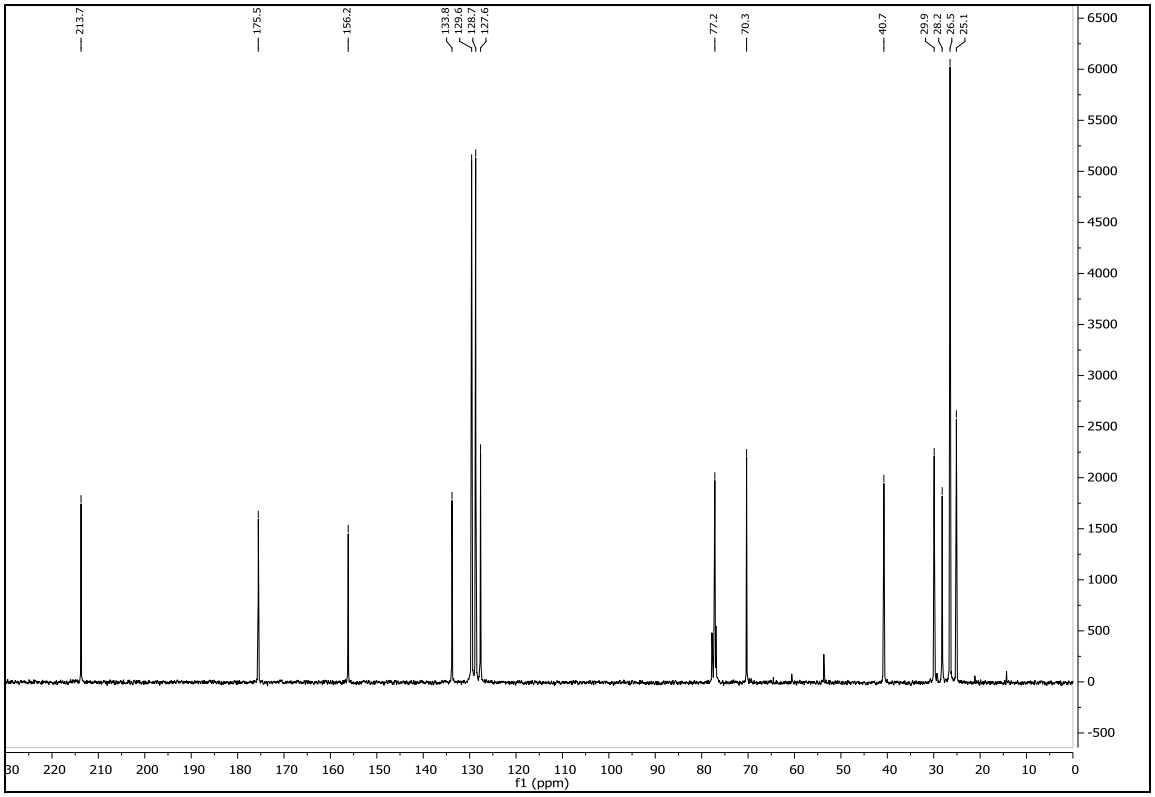
(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylimidazolidine-2,4-dione (81)



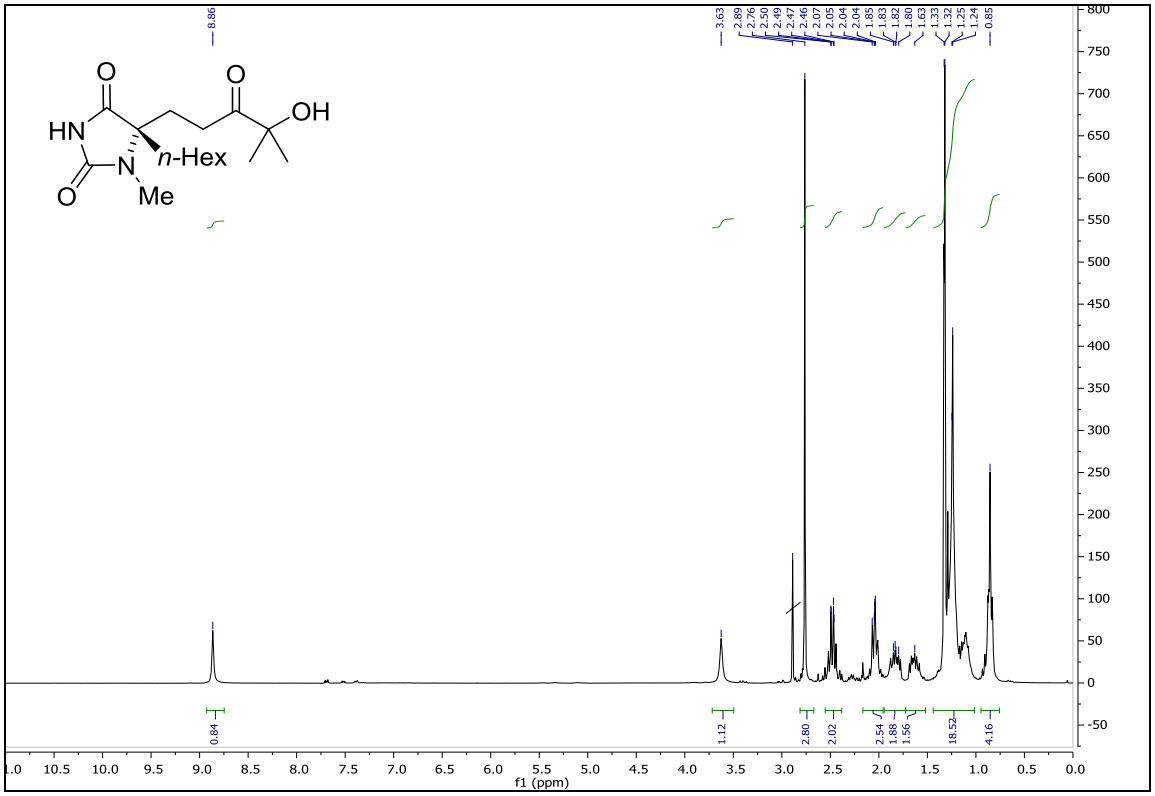


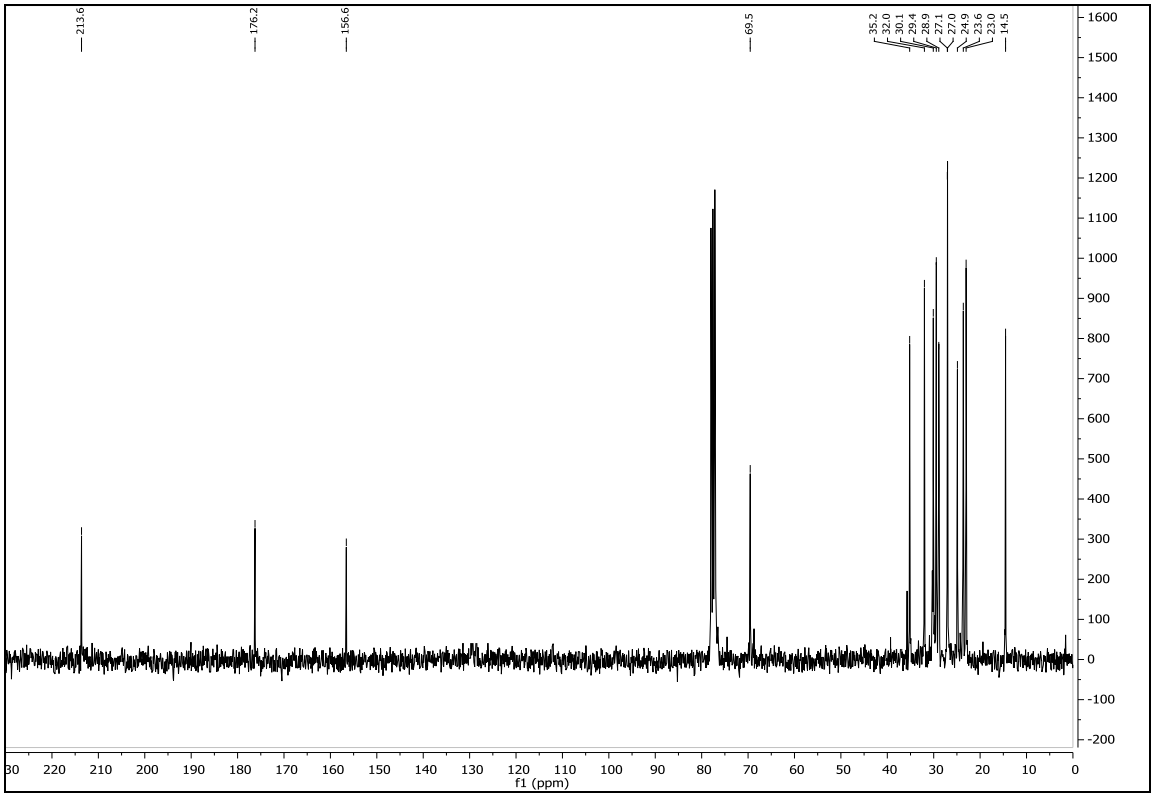
(*R*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (82)



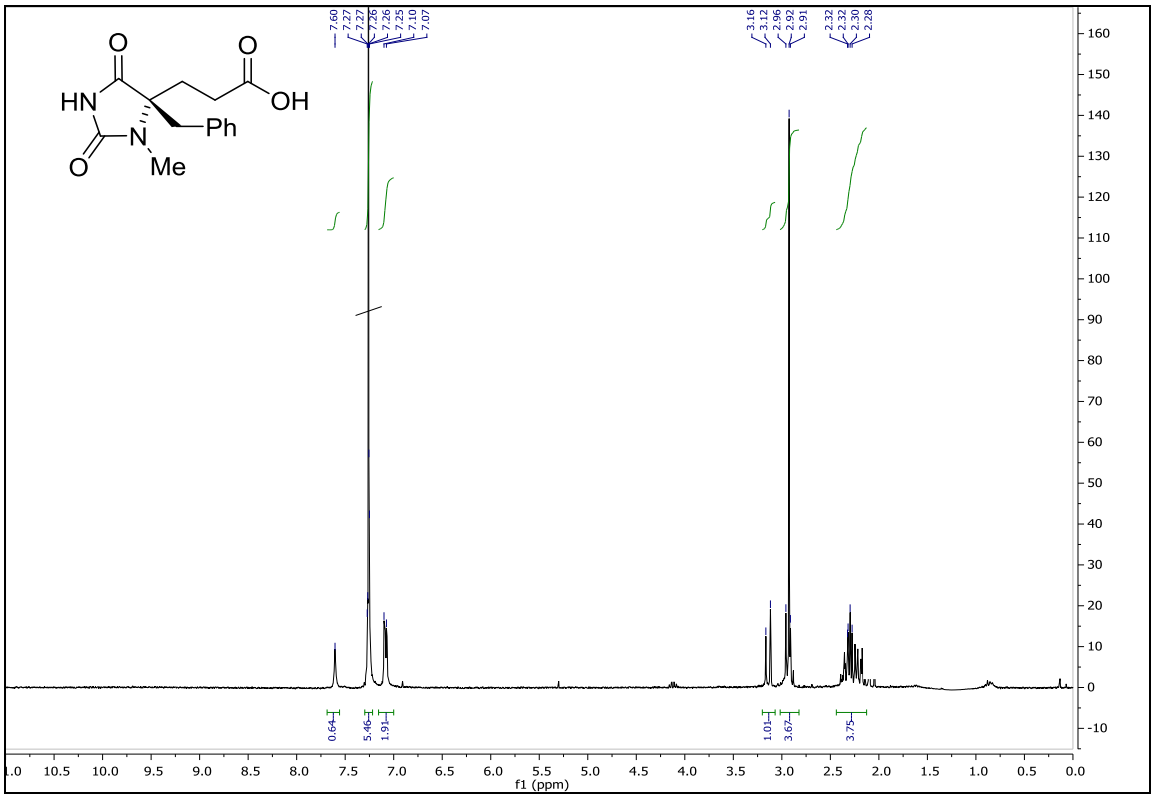


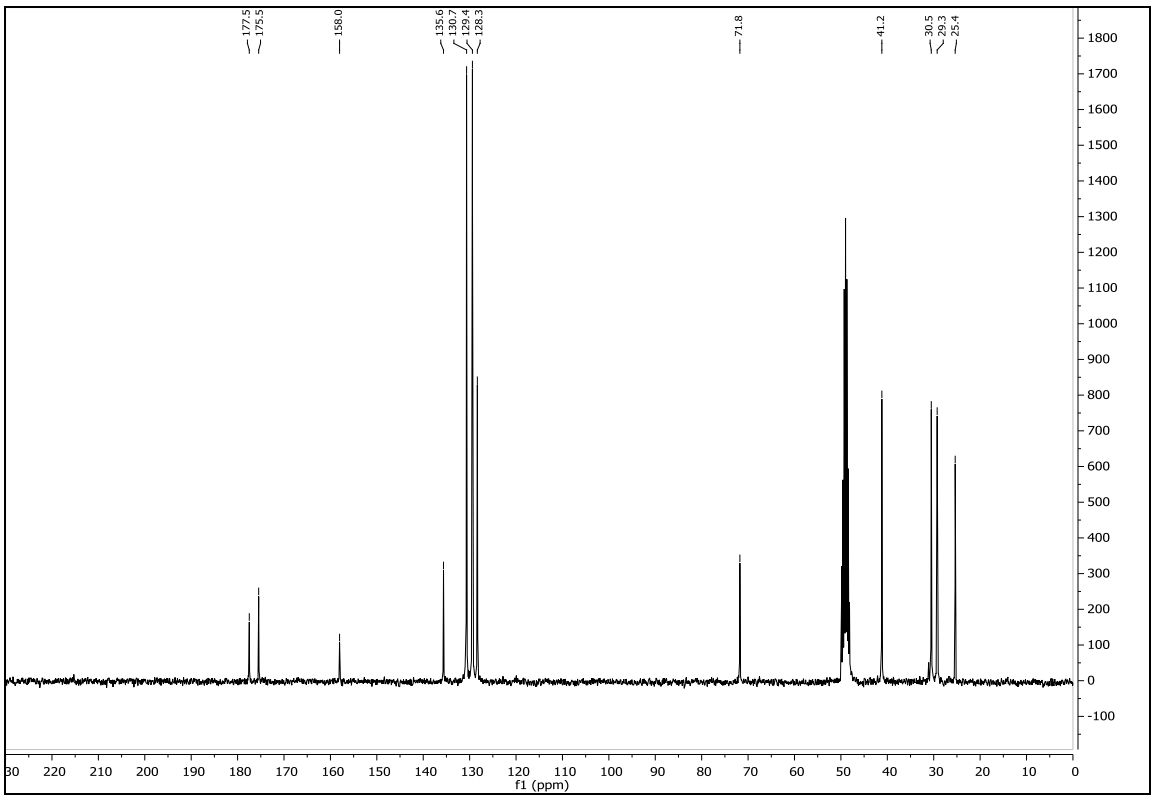
(*S*)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (83)



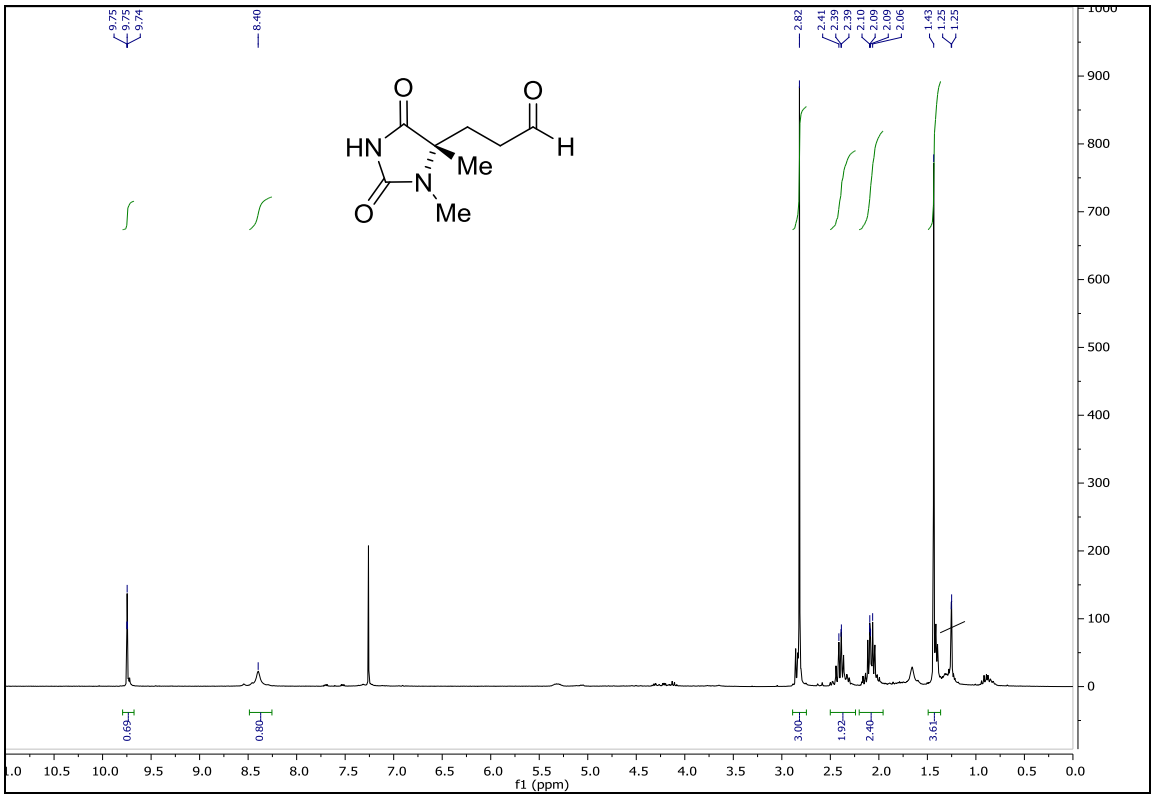


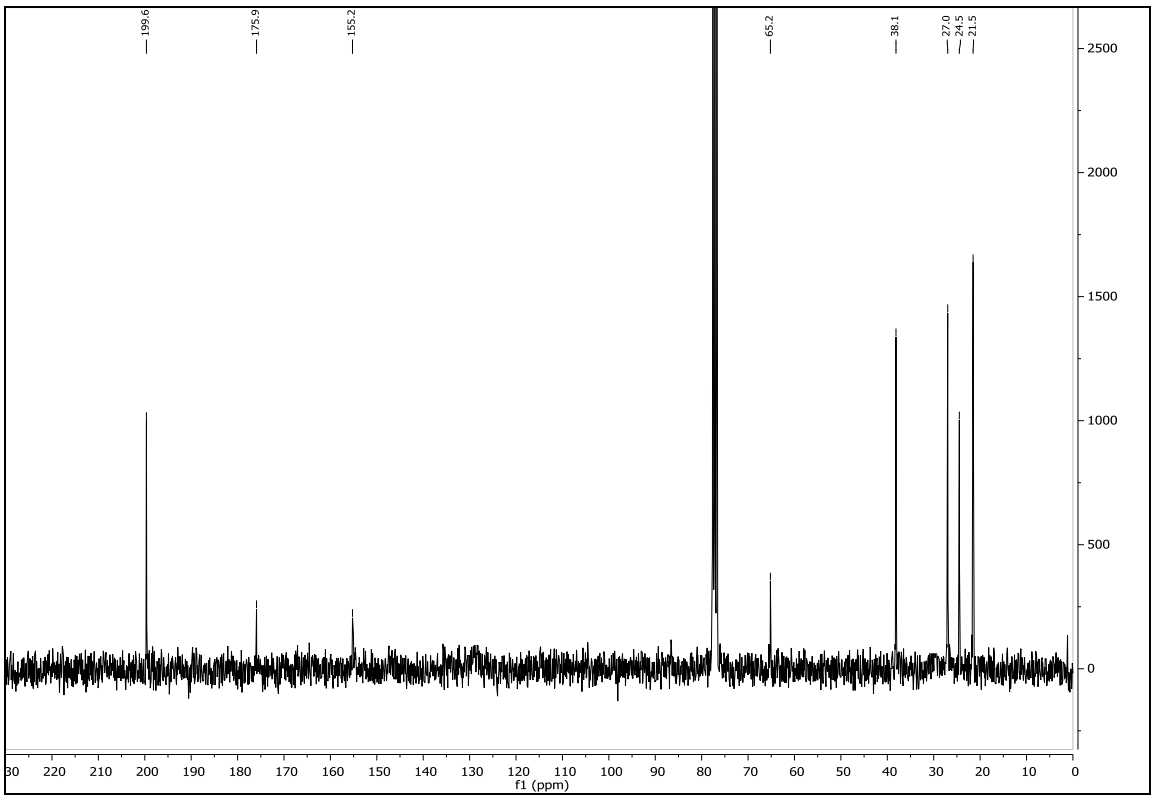
(*R*)-3-(4-Benzyl-3-methyl-2,5-dioxoimidazolidin-4-yl)propanoic acid (84)



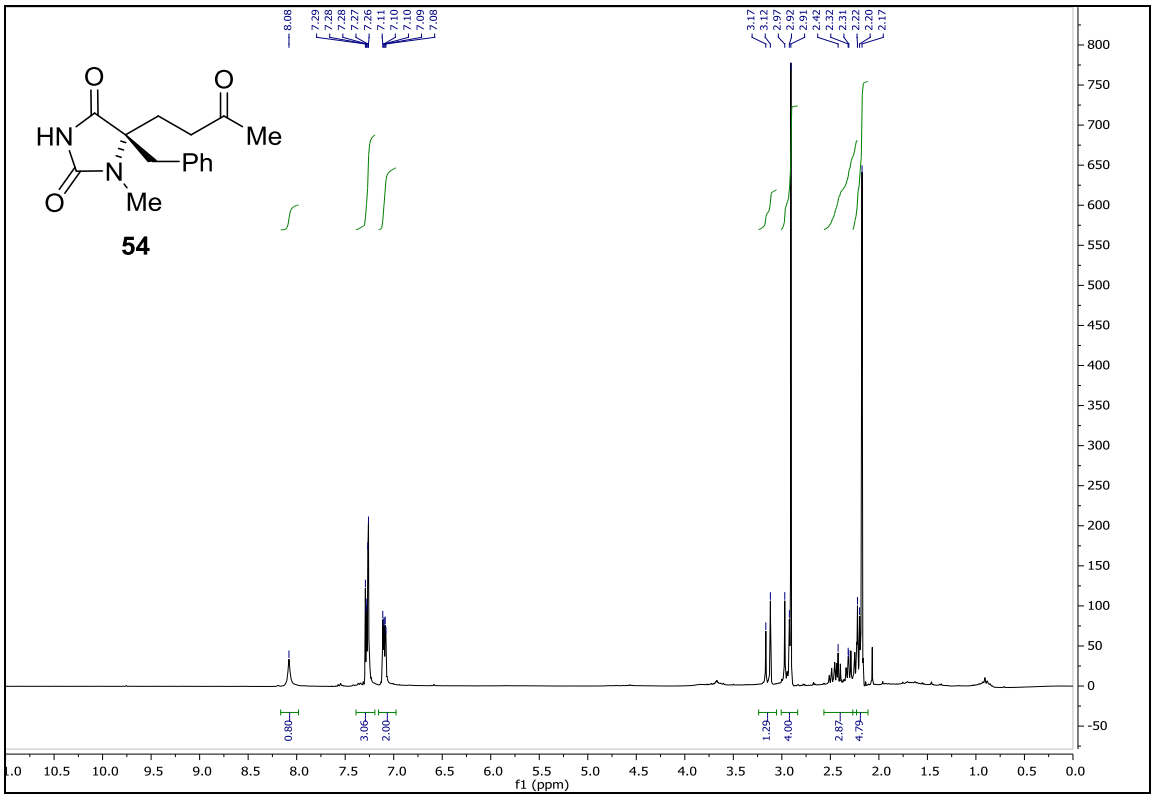


(*S*)-3-(3,4-Dimethyl-2,5-dioxoimidazolidin-4-yl)propanal (86)

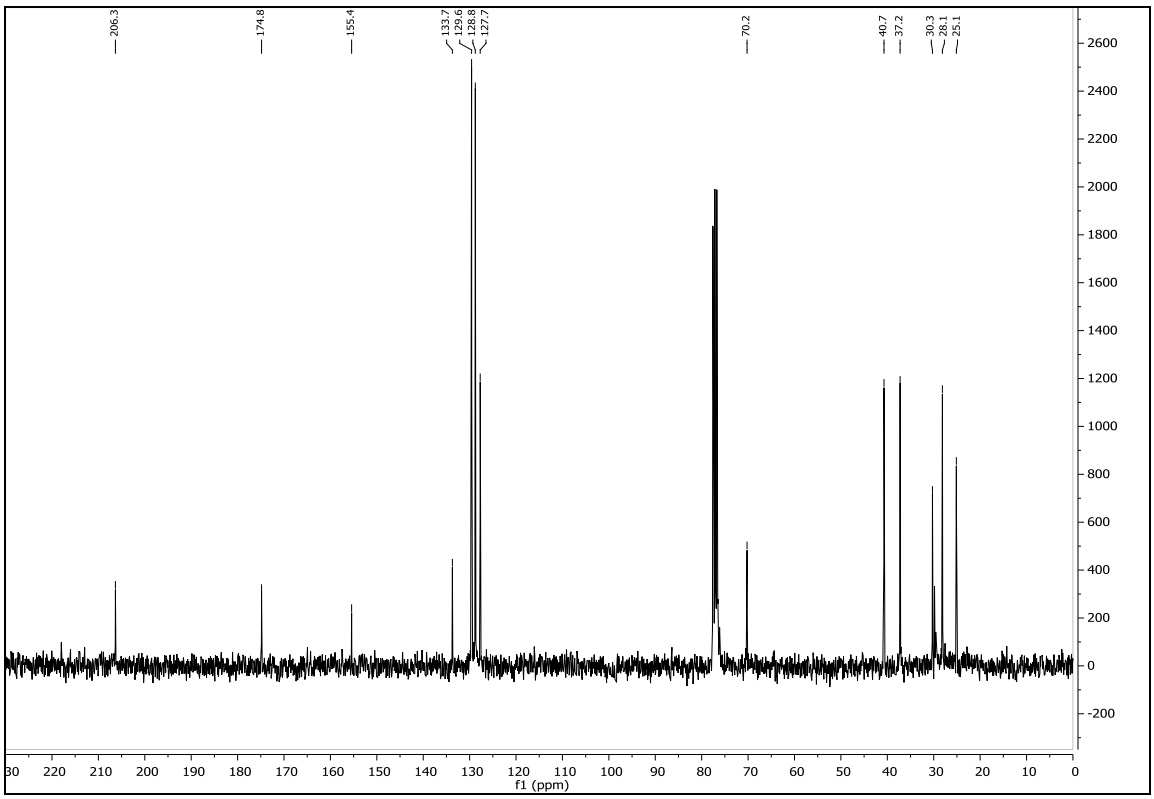




(*R*)-5-Benzyl-1-methyl-5-(3-oxobutyl)imidazolidine-2,4-dione (87)

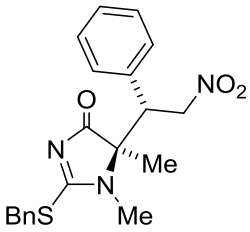


54

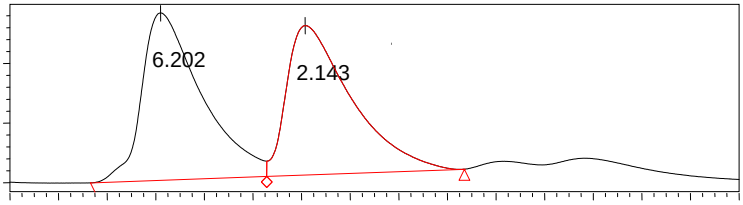


5.3.11. HPLC chromatograms

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (41a)

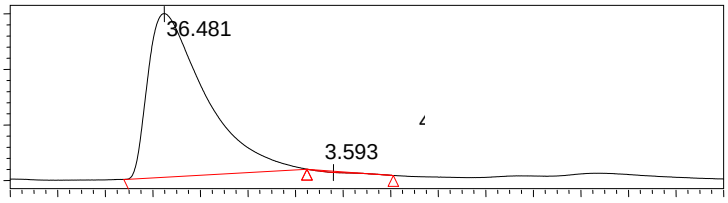


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 36.5 min (major.) and 45.6 min (min.). Processed Channel Descr.: PDA 239.0 nm).



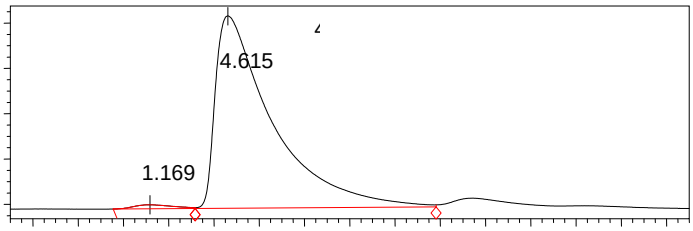
	Retention Time	% Area
1	36.202	50.99
2	42.143	49.01

Using Cat. C7



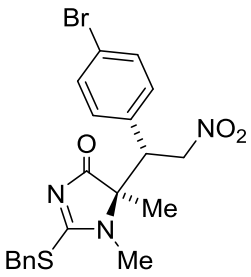
	Retention Time	% Area
1	36.481	99.57
2	43.593	0.43

Using Cat. C8

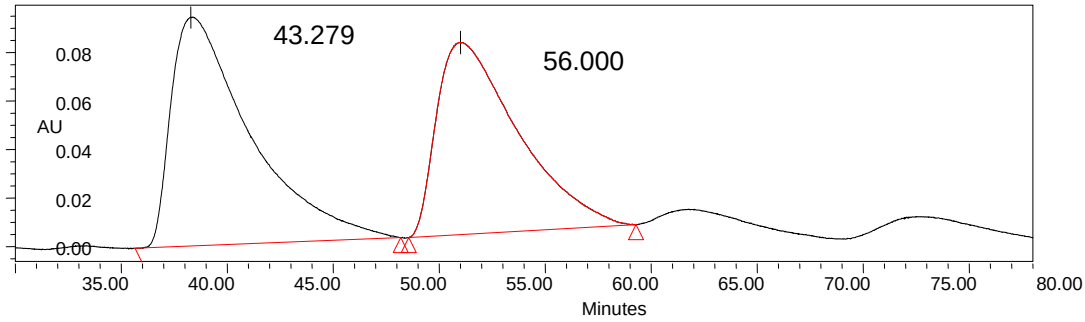


	Retention Time	% Area
1	41.169	1.39
2	44.615	98.61

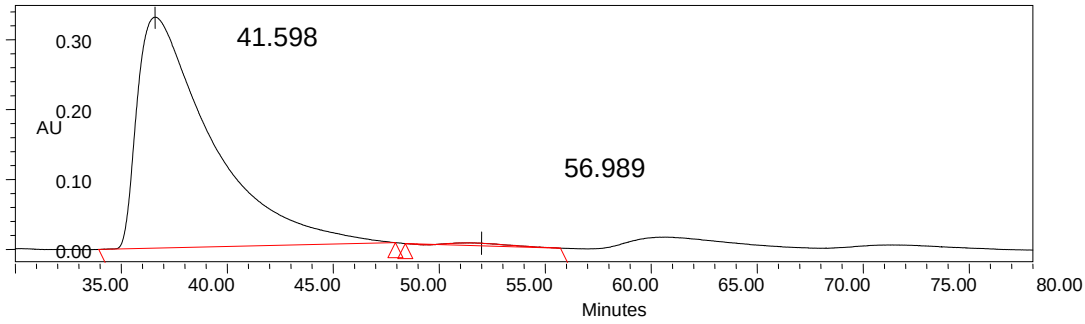
(*R*)-2-(Benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (41c)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 41.6 min (major.) and 57.0 min (min.). Processed Channel Descr.: PDA 210.0 nm).

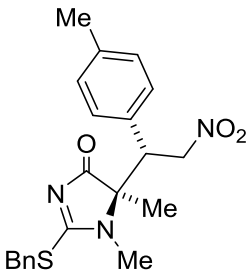


	Retention Time	% Area
1	43.279	53.71
2	56.000	46.29

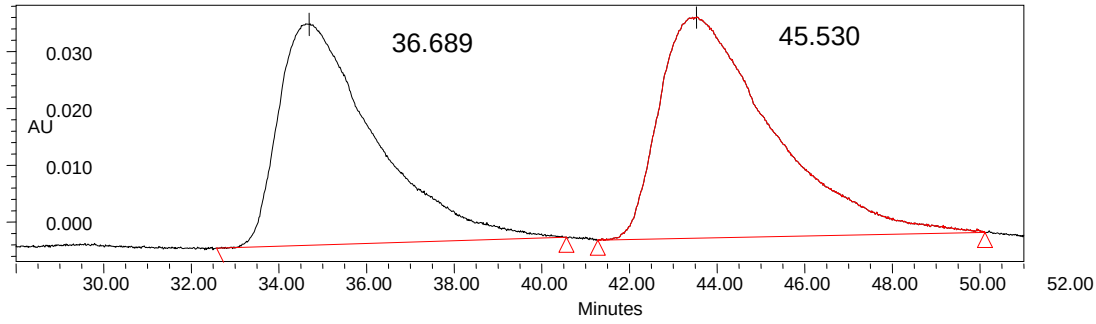


	Retention Time	% Area
1	41.598	99.12
2	56.989	0.88

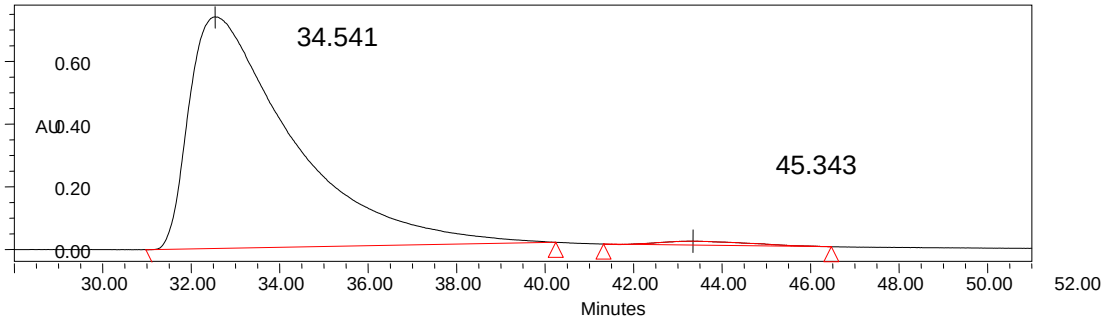
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (41d)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 34.5 min (major.) and 45.3 min (min.). Processed Channel Descr.: PDA 239.0 nm).

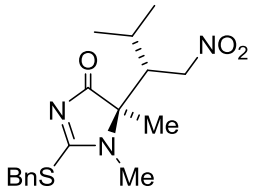


	Retention Time	% Area
1	36.689	46.17
2	45.530	53.83

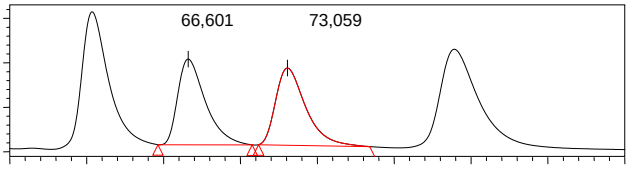


	Retention Time	% Area
1	34.541	98.55
2	45.343	1.45

(S)-2-(Benzylthio)-1,5-dimethyl-5-((*S*)-3-methyl-1-nitrobutan-2-yl)-1*H*-imidazol-4(5*H*)-one (41j)

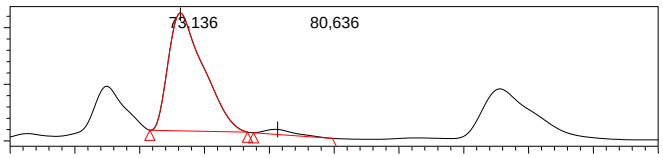


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 68.9 min (min.) and 75.3 min (major.). Processed Channel Descr.: PDA 254.0 nm).



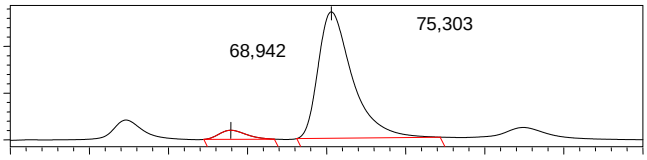
	Retention Time	% Area
1	66.601	50.49
2	73.059	49.51

Using Cat. C7



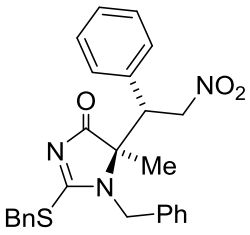
	Retention Time	% Area
1	73.136	96.56
2	80.636	3.44

Using Cat. C8

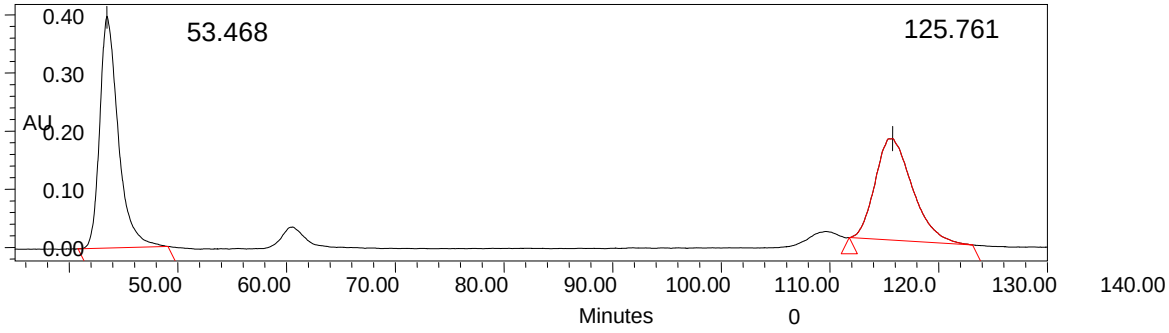


	Retention Time	% Area
1	68.942	5.36
2	75.303	94.64

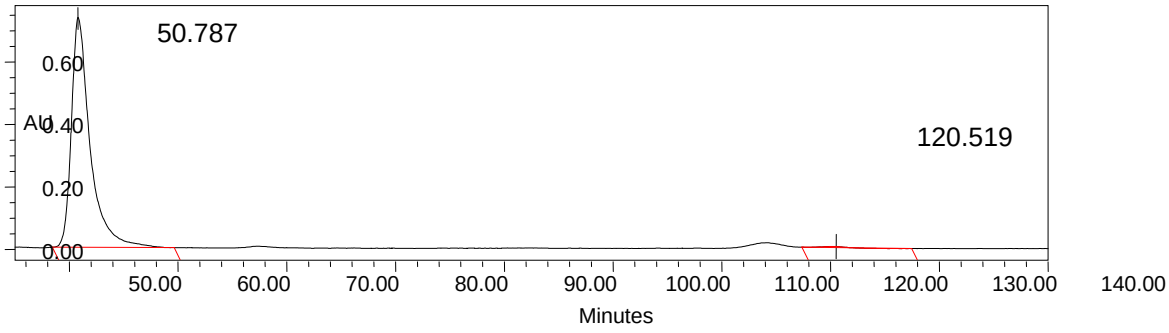
(*R*)-1-Benzyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (42a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 50.8 min (major.) and 120.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

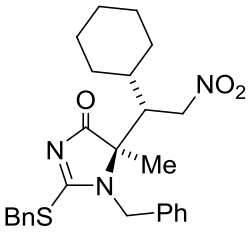


	Retention Time	% Area
1	53.468	53.05
2	125.761	46.95

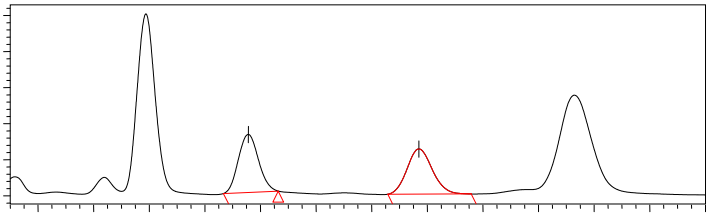


	Retention Time	% Area
1	50.787	99.72
2	125.362	0.28

(*S*)-1-Benzyl-2-(benzylthio)-5-((*S*)-1-cyclohexyl-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (42k)

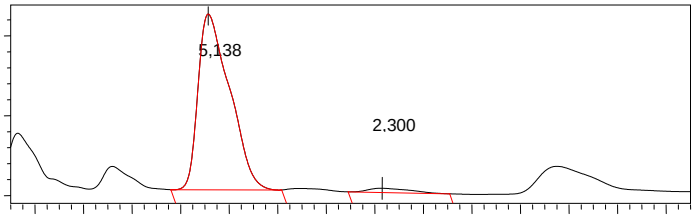


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.5 min (min.) and 29.7 min (major.). Processed Channel Descr.: PDA 254.0 nm).



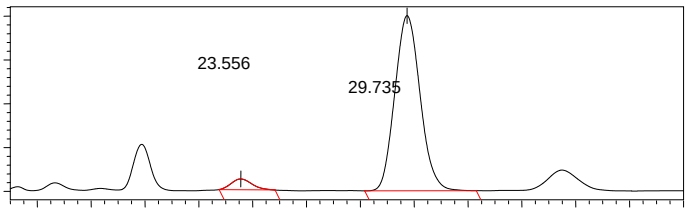
	Retention Time	% Area
1	23.563	50.52
2	29.693	49.48

Using Cat. C7



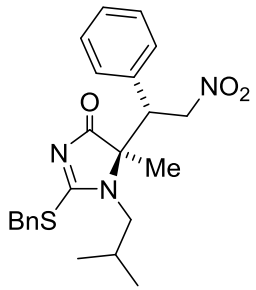
	Retention Time	% Area
1	25.138	96.89
2	32.300	3.11

Using Cat. C8

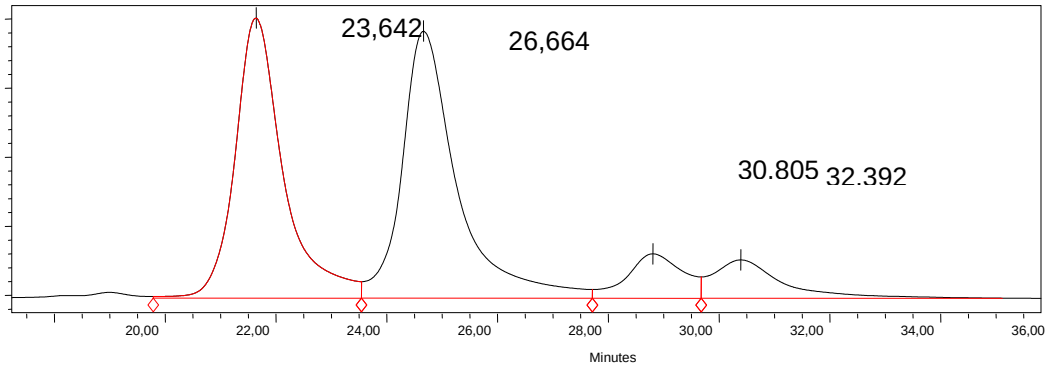


	Retention Time	% Area
1	23.556	4.80
2	29.735	95.20

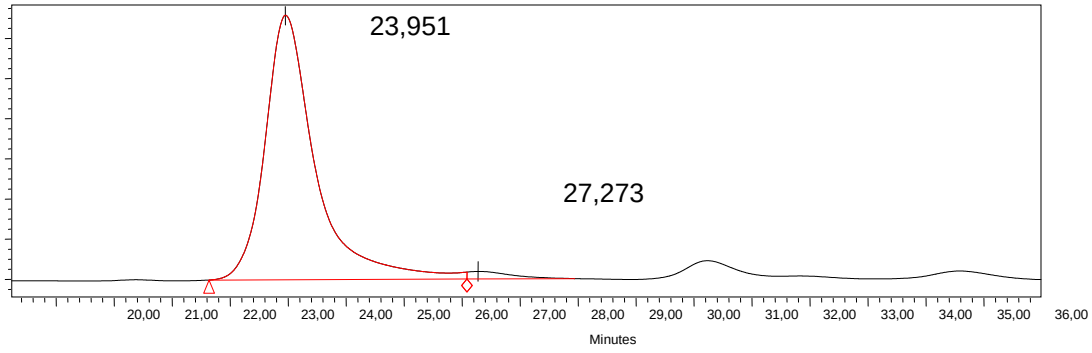
(R)-2-(benzylthio)-1-isobutyl-5-methyl-5-((R)-2-nitro-1-phenylethyl)- 1*H*-imidazol-4(5*H*)-one (43a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 24.0 min (major.) and 27.3 min (min.). Processed Channel Descr.: PDA 209.8 nm).

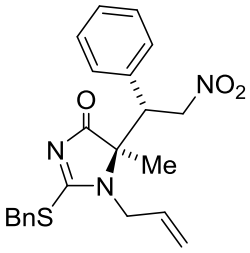


	Retention Time	% Area
1	23.642	41.15
2	26.664	44.04

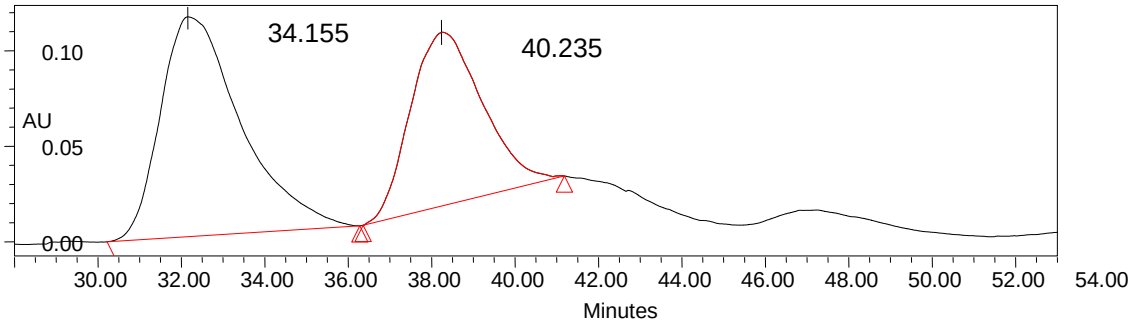


	Retention Time	% Area
1	23.956	96.26
2	27.295	3.74

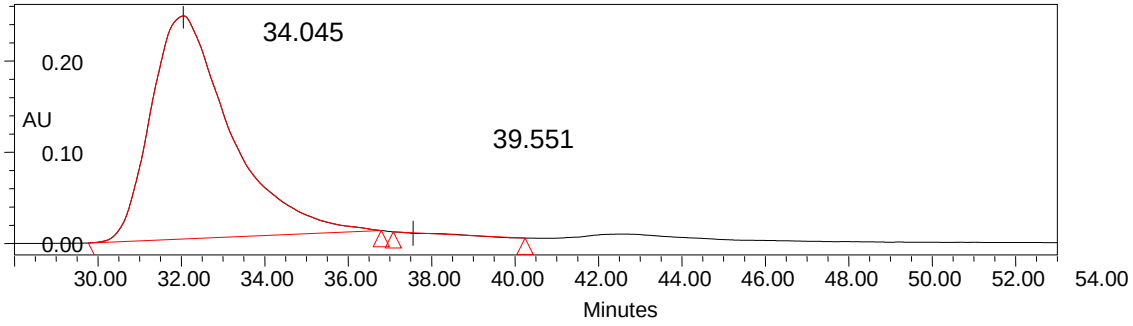
(*R*)-1-Allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (44a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 34.0 min (major.) and 39.6 min (min.). Processed Channel Descr.: PDA 242.0 nm).

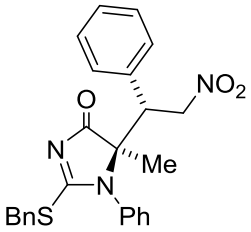


	Retention Time	% Area
1	34.155	58.62
2	40.235	41.38

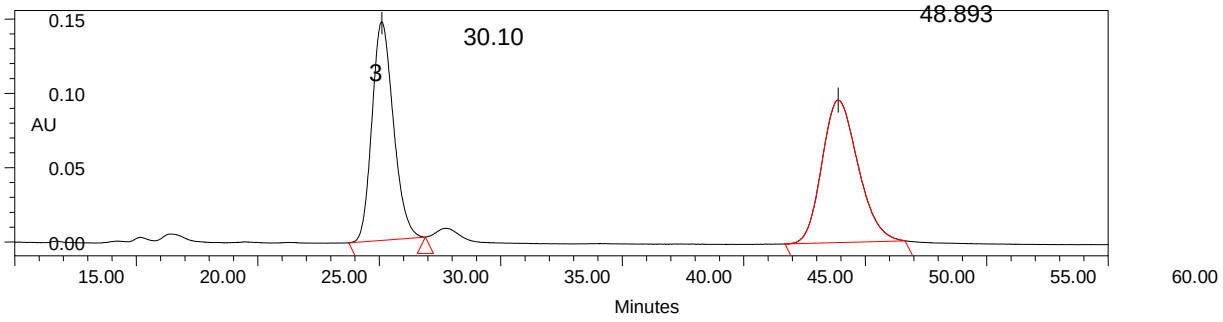


	Retention Time	% Area
1	34.045	99.84
2	39.551	0.16

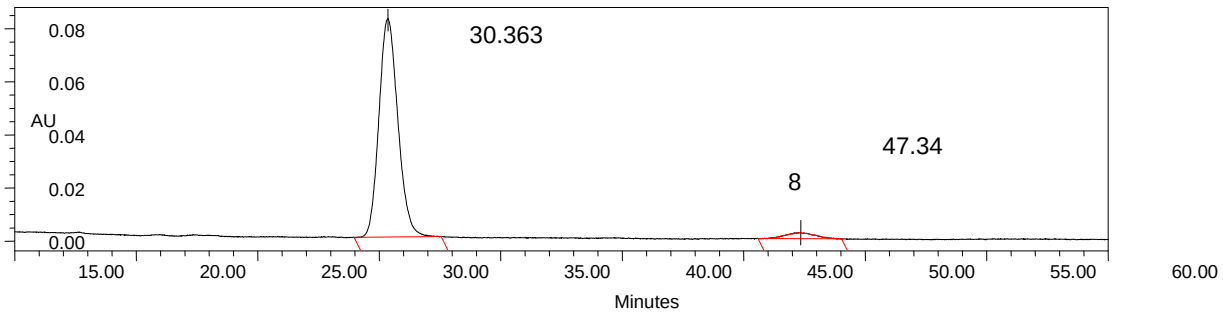
(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (45a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 30.4 min (major.) and 47.3 min (min.). Processed Channel Descr.: PDA 250.0 nm).

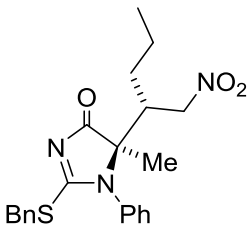


	Retention Time	% Area
1	30.103	47.67
2	48.893	52.33

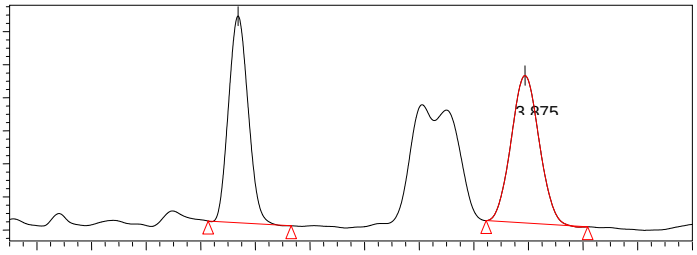


	Retention Time	% Area
1	30.363	95.89
2	47.348	4.11

(*S*)-2-(Benzylthio)-5-methyl-5-((*S*)-1-nitropentan-2-yl)-1-phenyl-1H-imidazol-4(5H)-one (45l)

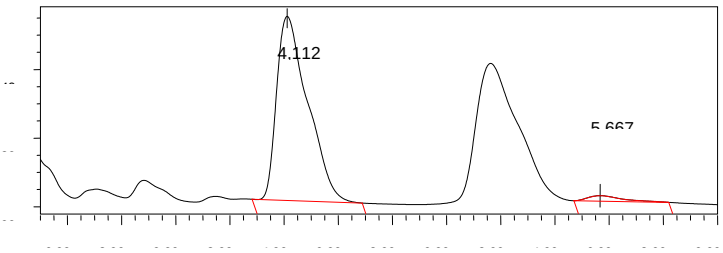


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.2 min (min.) and 33.6 min (major.). Processed Channel Descr.: PDA 247.0 nm).



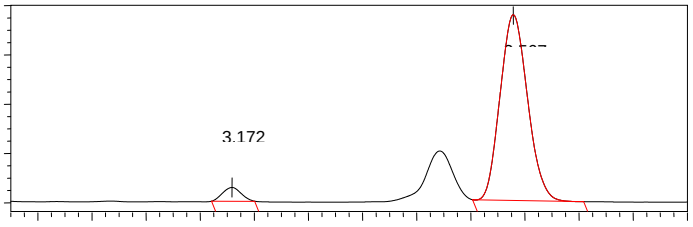
	Retention Time	% Area
1	23.364	49.49
2	33.875	50.51

Using Cat. C7



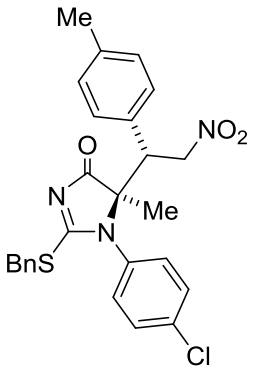
	Retention Time	% Area
1	24.112	96.79
2	35.667	3.21

Using Cat. C8

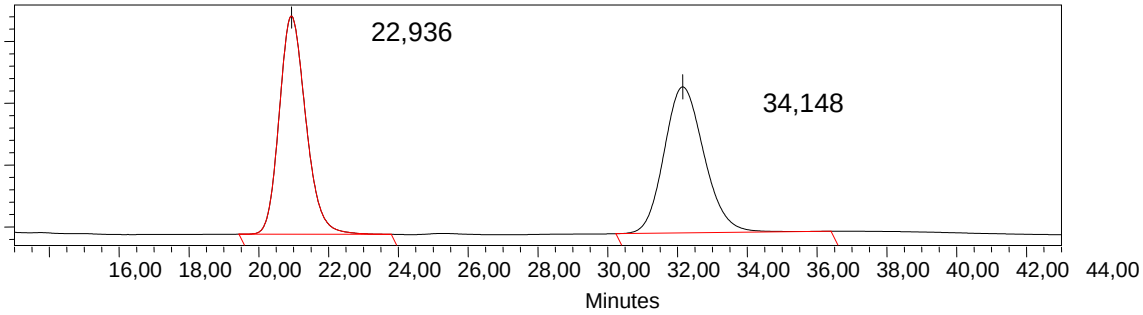


	Retention Time	% Area
1	23.172	4.71
2	33.567	95.29

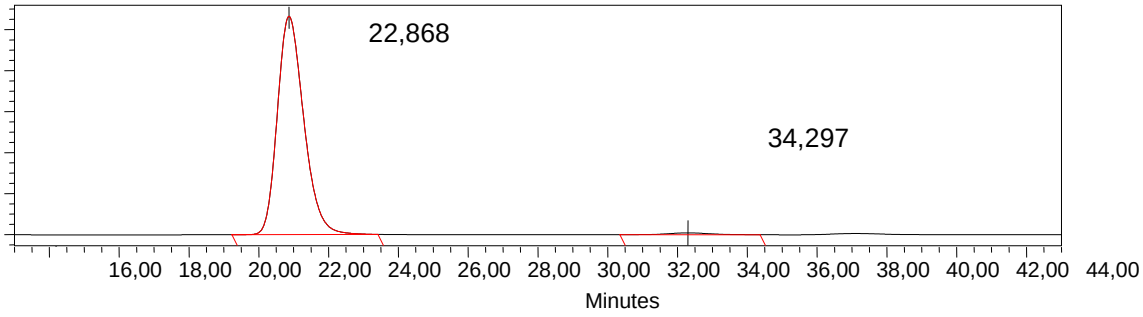
(*R*)-2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (46d)



The denantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 22.9 min (major.) and 34.3 min (min.). Processed Channel Descr.: PDA 255.2 nm).

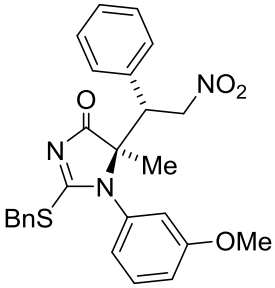


	Retention Time	% Area
1	22.936	49.96
2	34.148	50.04

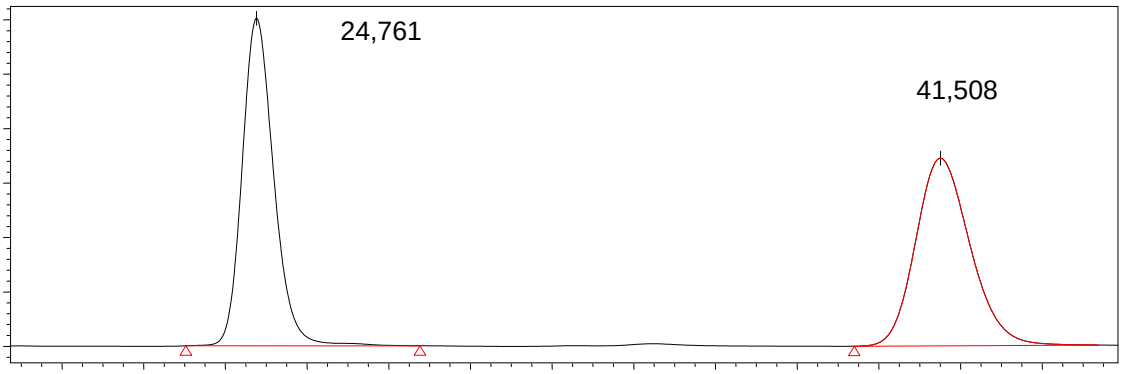


	Retention Time	% Area
1	22.868	98.70
2	34.297	1.30

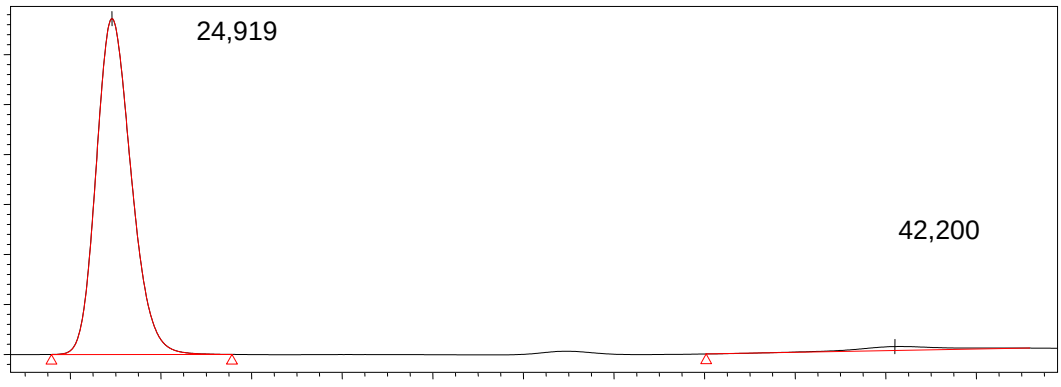
(*R*)-2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (47a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 25.0 min (major.) and 35.0 min (min.). Processed Channel Descr.: PDA 255.2 nm).

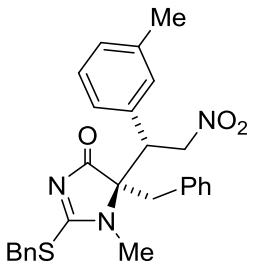


	Retention Time	% Area
1	24.761	50.34
2	41.508	49.66

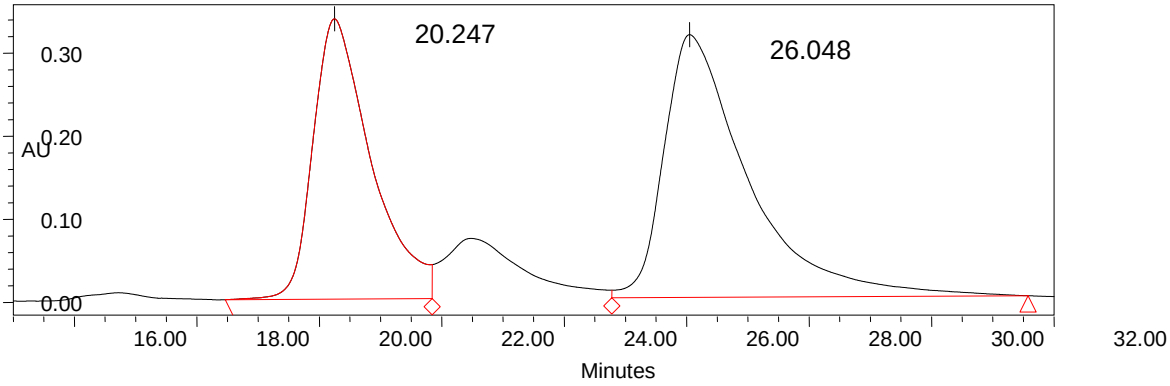


	Retention Time	% Area
1	24.919	97.63
2	42.200	2.37

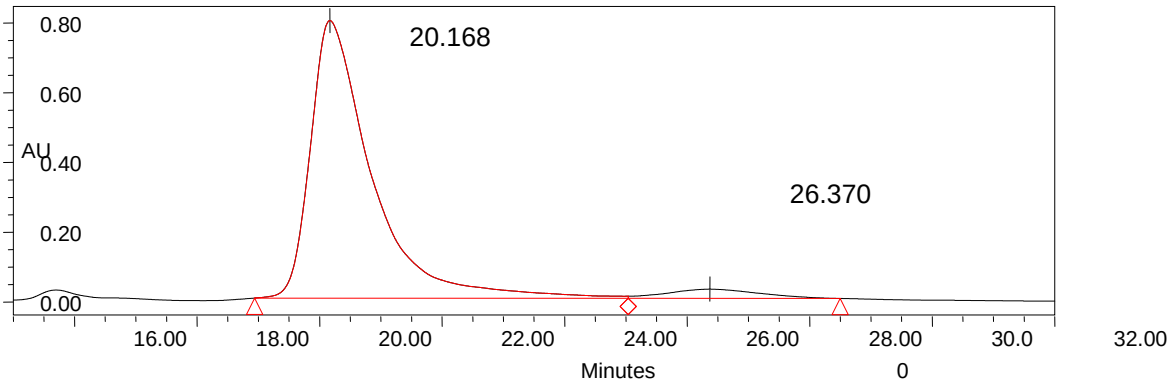
(*R*)-5-Benzyl-2-(benzylthio)-1-methyl-5-((*R*)-2-nitro-1-(*m*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (48h)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 20.2 min (major.) and 26.4 min (min.). Processed Channel Descr.: PDA 242.0 nm).

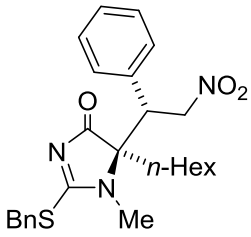


	Retention Time	% Area
1	20.247	42.50
2	26.048	57.50

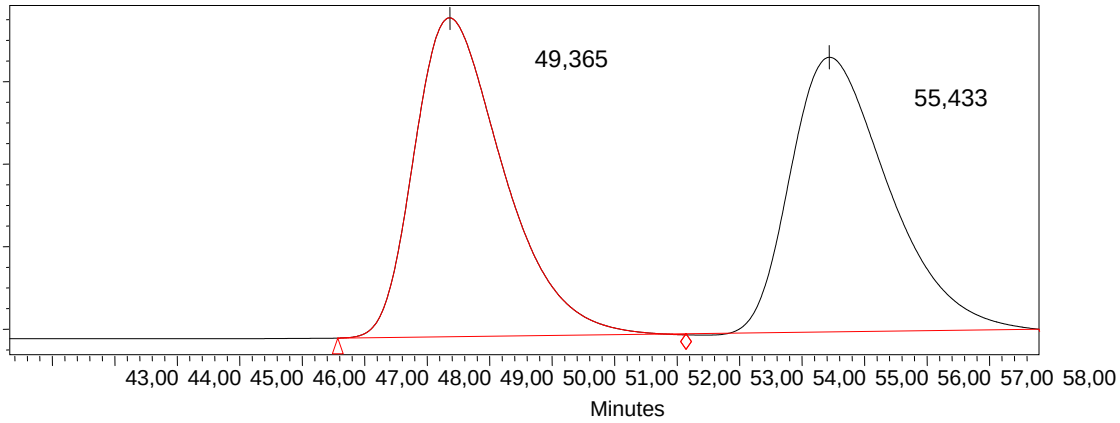


	Retention Time	% Area
1	20.168	95.25
2	26.370	4.75

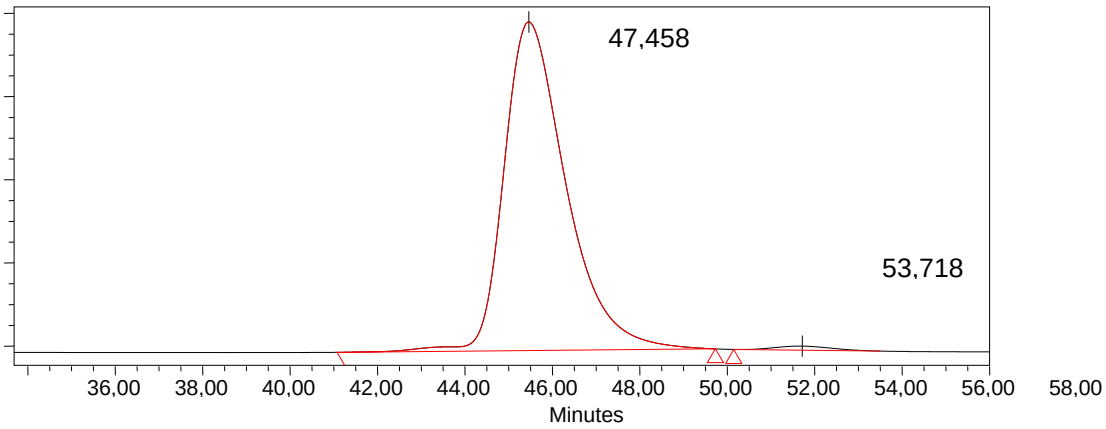
(*R*)-2-(benzylthio)-5-hexyl-1-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (49a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 47.5 min (major.) and 53.7 min (min.). Processed Channel Descr.: PDA 254 nm).

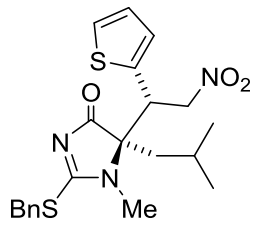


	Retention Time	% Area
1	49.365	50.33
2	55.433	49.67

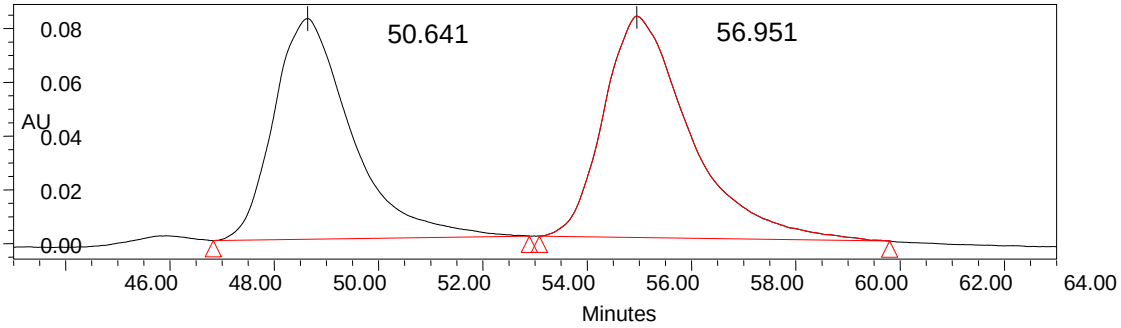


	Retention Time	% Area
1	47.458	98.27
2	53.718	1.73

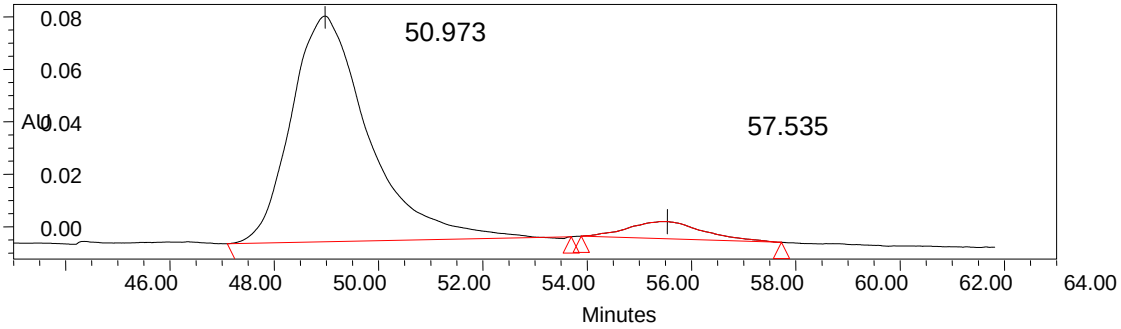
(*R*)-2-(Benzylthio)-5-isobutyl-1-methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-imidazol-4(5*H*)-one (50g)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 50.9 min (major.) and 57.5 min (min.). Processed Channel Descr.: PDA 239.0 nm).

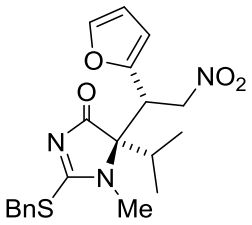


	Retention Time	% Area
1	50.641	47.28
2	56.951	52.72

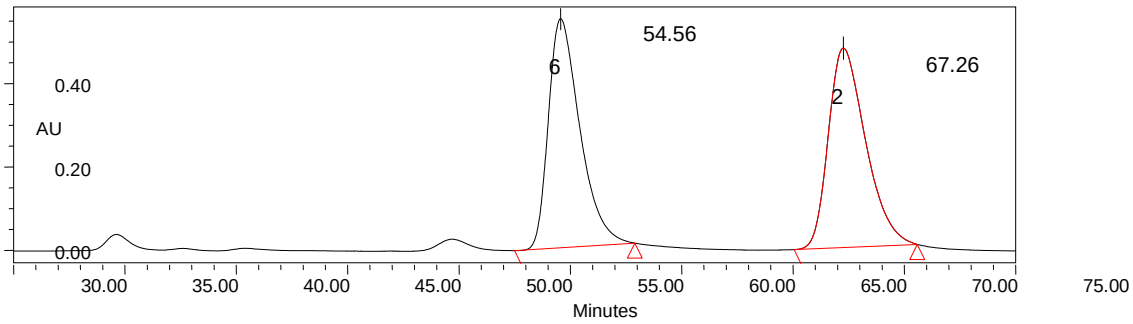


	Retention Time	% Area
1	50.973	93.16
2	57.535	6.84

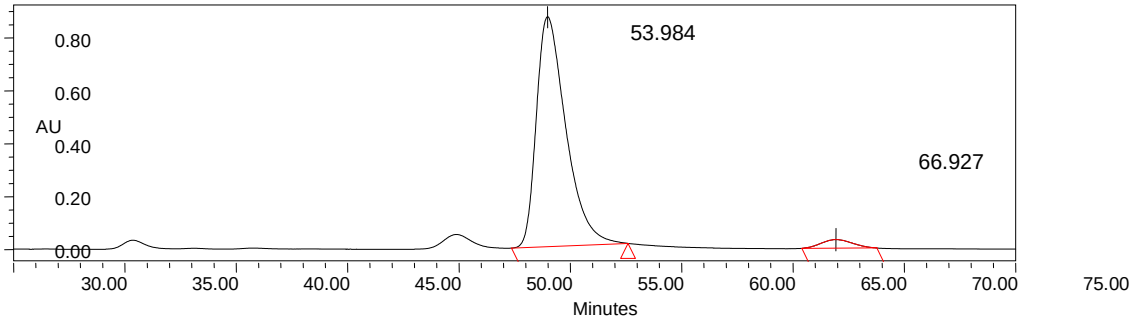
(*R*)-2-(Benzylthio)-5-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (51e)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 66.9 min (min.). Processed Channel Descr.: PDA 249.0 nm).

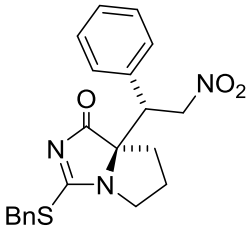


	Retention Time	% Area
1	54.566	49.29
2	67.262	50.71

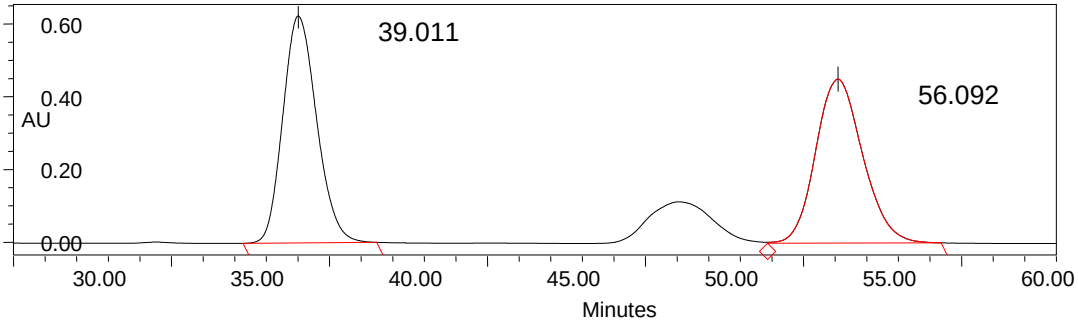


	Retention Time	% Area
1	53.984	96.22
2	66.927	3.78

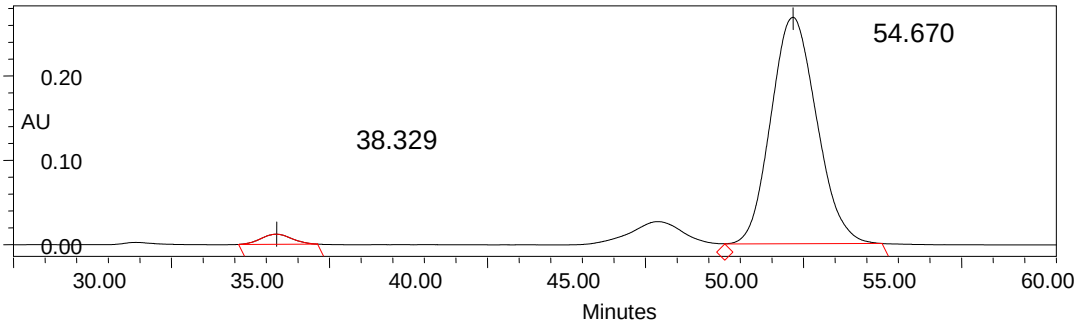
(*R*)-3-(benzylthio)-7a-((*R*)-2-nitro-1-phenylethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (52a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 38.3 min (min.) and 54.7 min (major.). Processed Channel Descr.: PDA 242.0 nm).

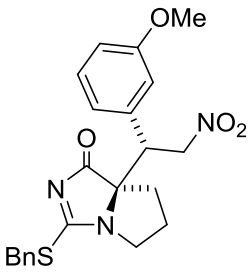


	Retention Time	% Area
1	39.011	49.95
2	56.092	50.05

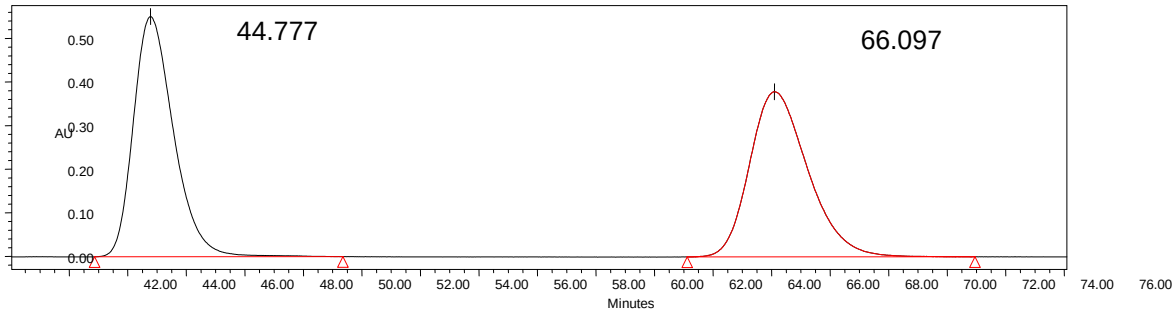


	Retention Time	% Area
1	38.329	2.91
2	54.670	97.09

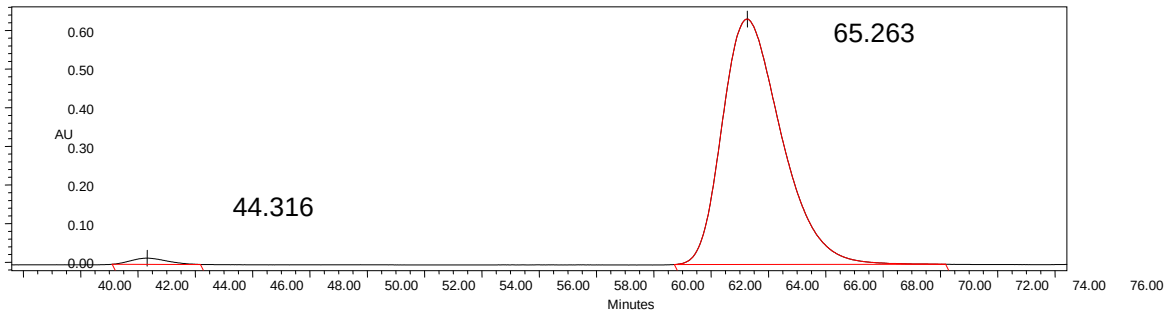
(*R*)-3-(Benzylthio)-7a-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one (52i)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 44.3 min (minor.) and 65.3 min (major.). Processed Channel Descr.: PDA 255.2 nm).

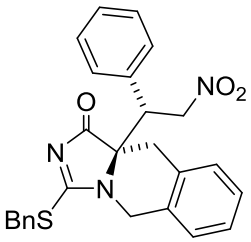


	Retention Time	% Area
1	44.777	50.10
2	66.097	49.90

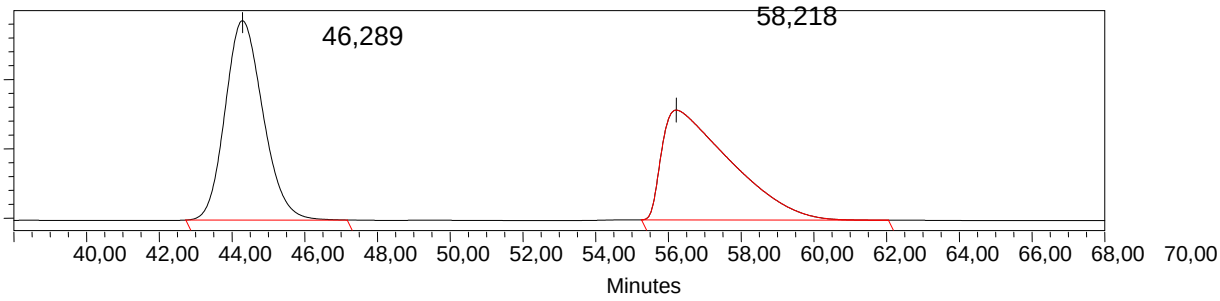


	Retention Time	% Area
1	44.316	1.48
2	65.263	98.52

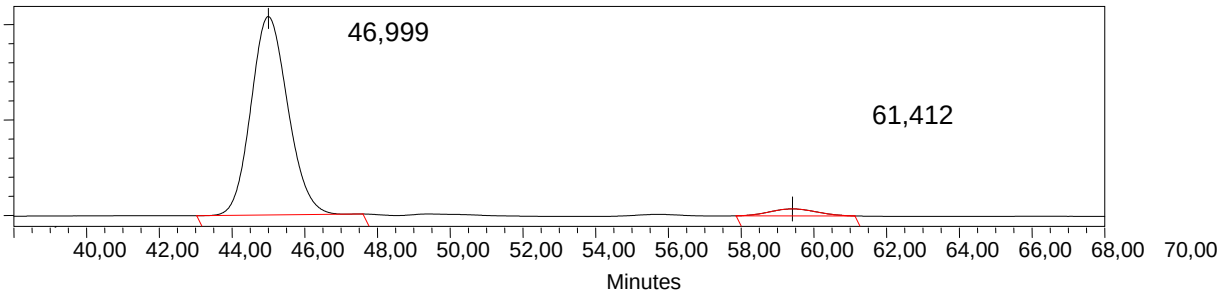
(*R*)-3-(Benzylthio)-10a-((*R*)-2-nitro-1-phenylethyl)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (53a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 47.0 min (major.) and 61.4 min (min.). Processed Channel Descr.: PDA 255.2 nm).

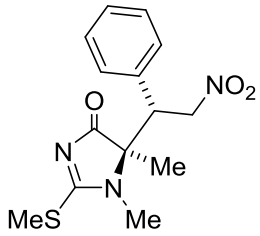


	Retention Time	% Area
1	46.289	50.09
2	58.218	49.91

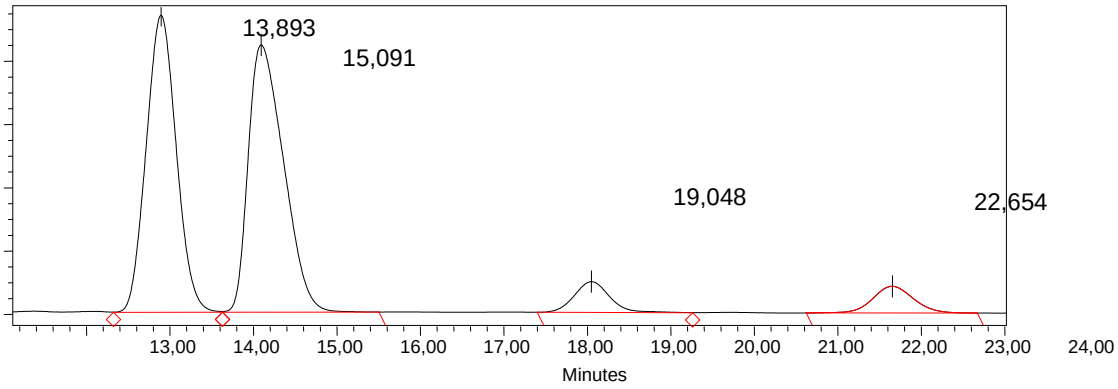


	Retention Time	% Area
1	46.999	95.71
2	61.412	4.29

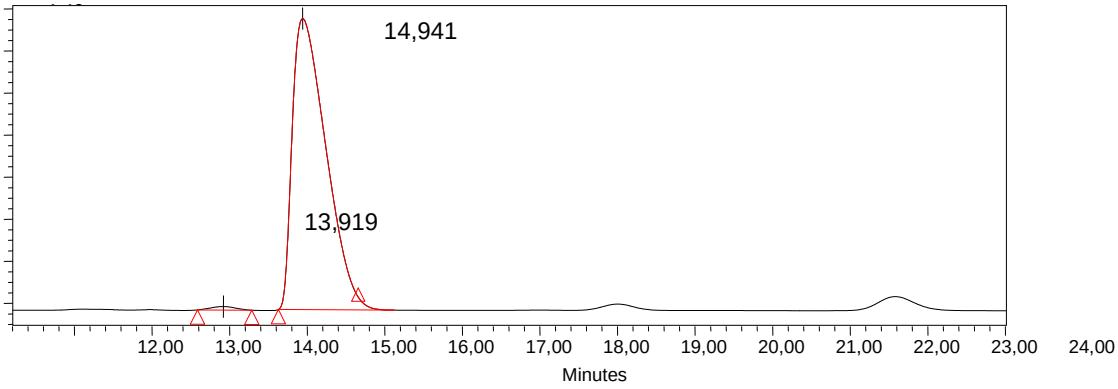
(*R*)-1,5-dimethyl-2-(methylthio)-5-((R)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (54a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate= 0.5 mL/min, retention times: 13.9 min (min.) and 14.9 min (major.). Processed Channel Descr.: PDA 254 nm).

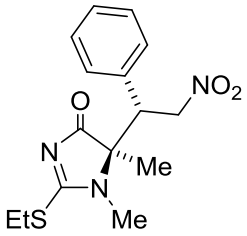


	Retention Time	% Area
1	13.893	48.70
2	15.091	51.30

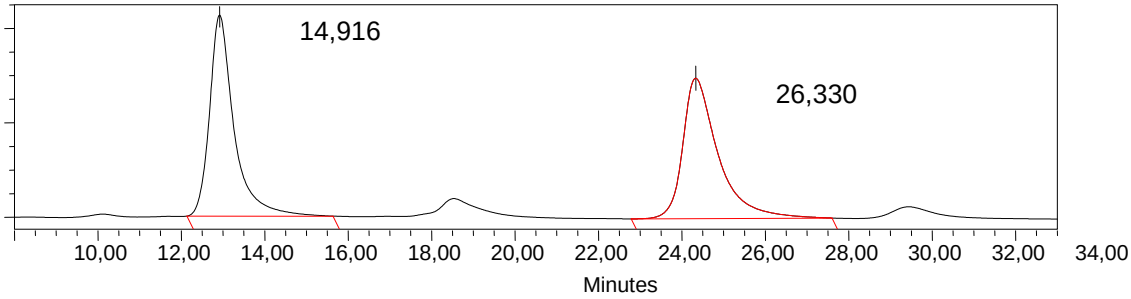


	Retention Time	% Area
1	13.919	0.77
2	14.941	99.23

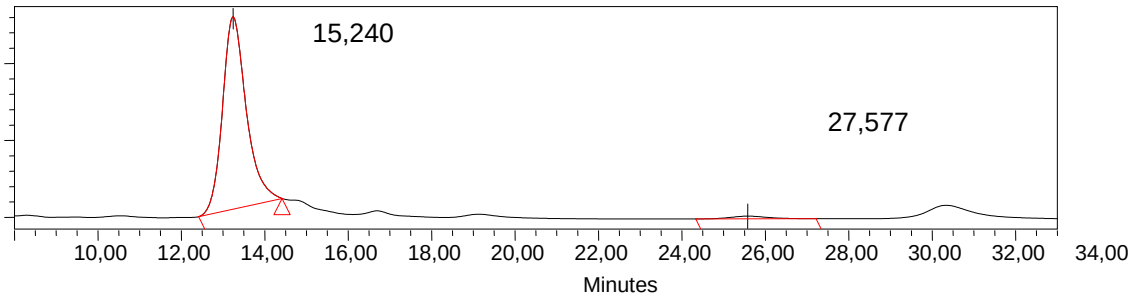
(*R*)-2-(Ethylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (55a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 15.2 min (major.) and 27.6 min (min.). Processed Channel Descr.: PDA 254 nm).

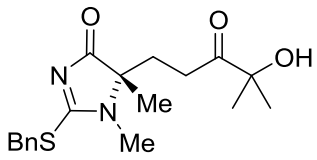


	Retention Time	% Area
1	14.916	49.79
2	26.330	50.21

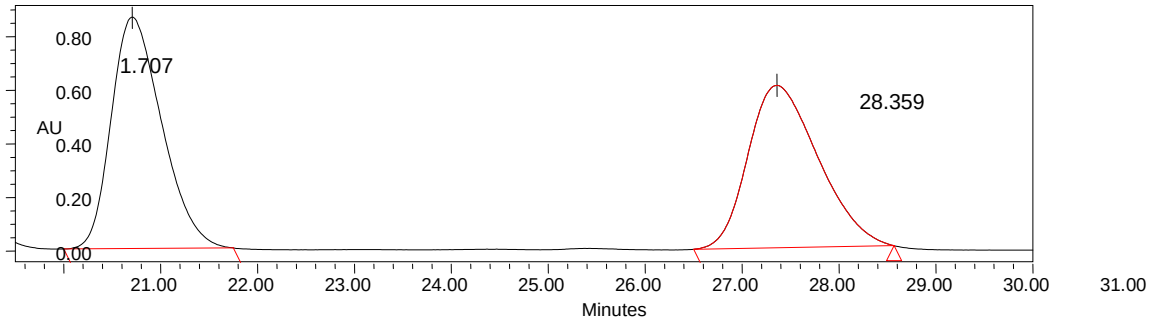


	Retention Time	% Area
1	15.240	97.82
2	27.577	2.18

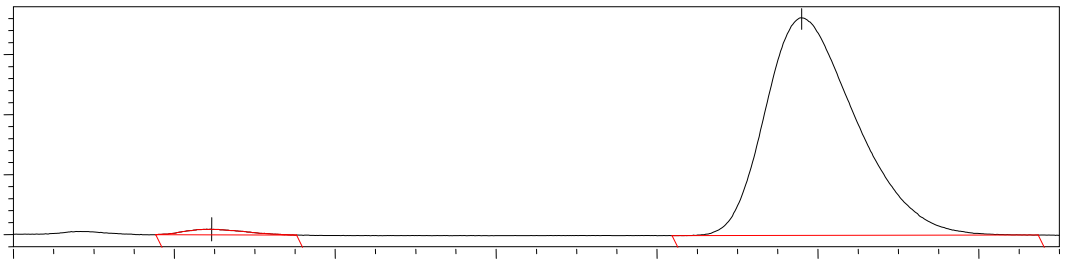
(*S*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1H-imidazol-4(5*H*)-one (74)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 20.5 min (min.) and 27.8 min (major.). Processed Channel Descr.: PDA 238.0 nm).

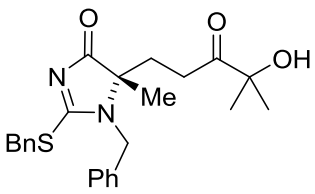


	Retention Time	% Area
1	21.707	50.65
2	28.359	49.35

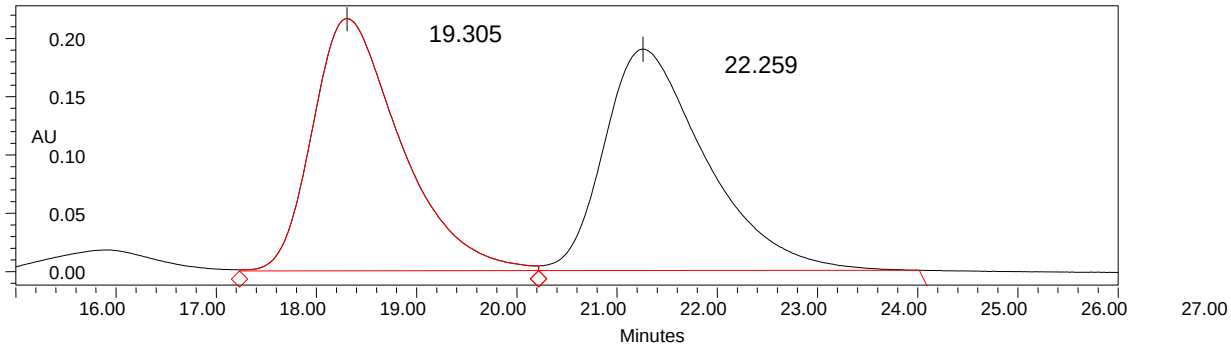


	Retention Time	% Area
1	20.463	1.68
2	27.795	98.32

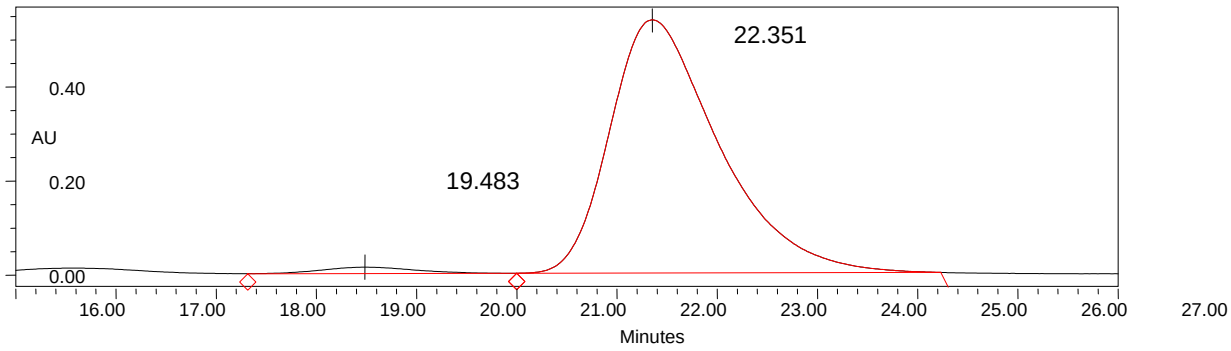
(*S*)-1-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (75)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 19.5 min (min.) and 22.4 min (major.). Processed Channel Descr.: PDA 240.0 nm).

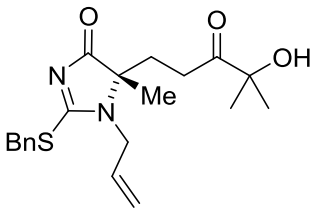


	Retention Time	% Area
1	19.305	49.76
2	22.259	50.24

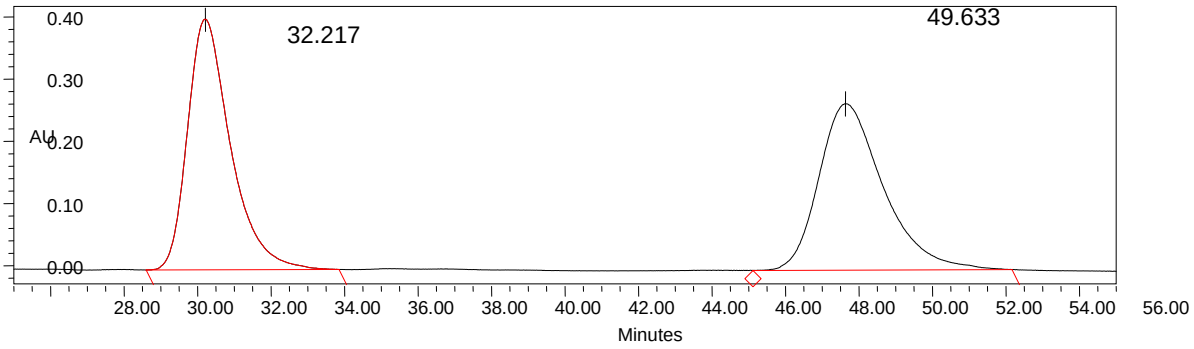


	Retention Time	% Area
1	19.483	2.15
2	22.351	97.85

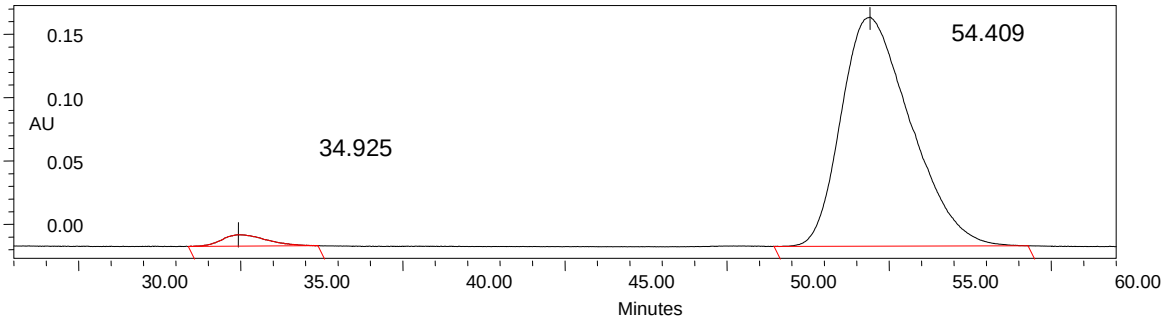
(*S*)-1-Allyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (76)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 34.9 min (min.) and 54.4 min (major.). Processed Channel Descr.: PDA 239.0 nm).

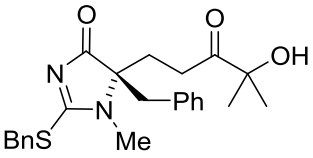


	Retention Time	% Area
1	32.217	50.17
2	49.633	49.83

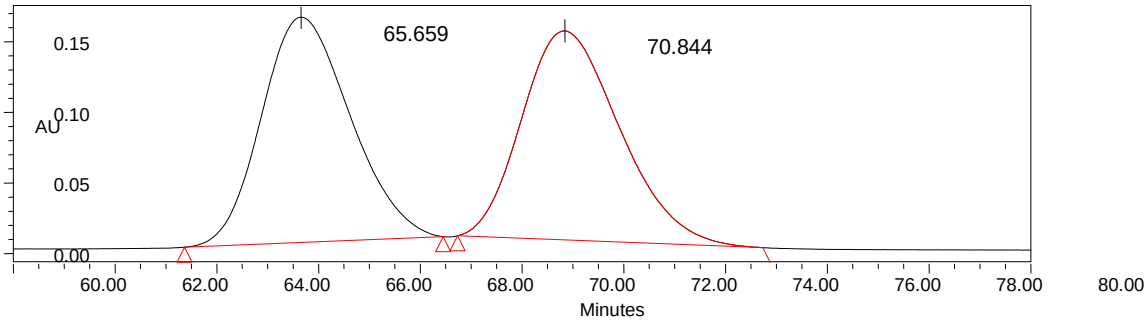


	Retention Time	% Area
1	34.925	3.07
2	54.409	96.93

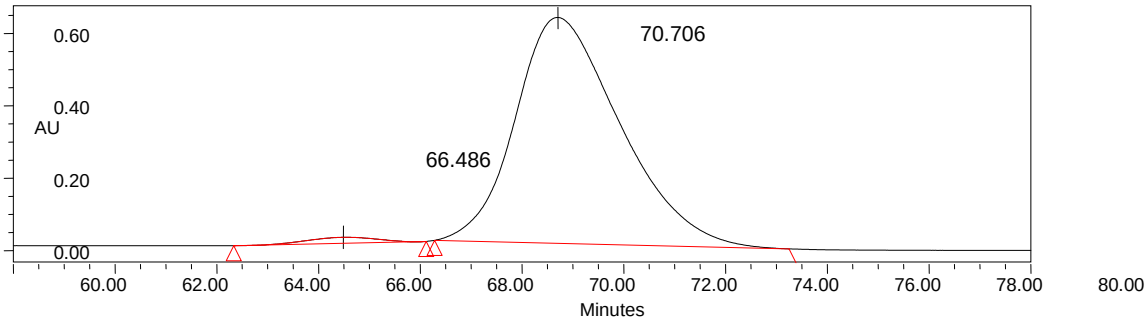
(*R*)-5-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (77)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 66.5 min (min.) and 70.7 min (major.). Processed Channel Descr.: PDA 239.0 nm).

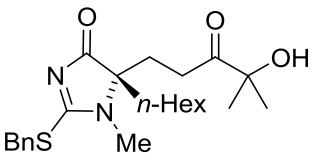


	Retention Time	% Area
1	65.659	49.44
2	70.844	50.56

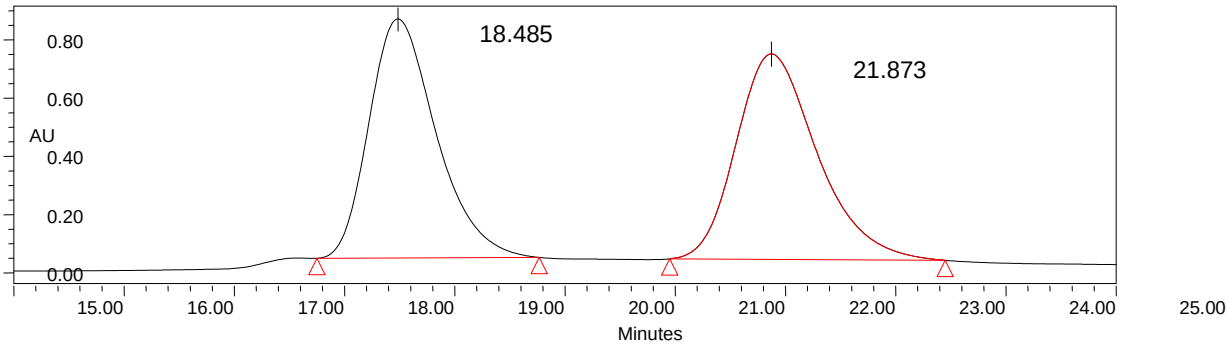


	Retention Time	% Area
1	66.486	1.69
2	70.706	98.31

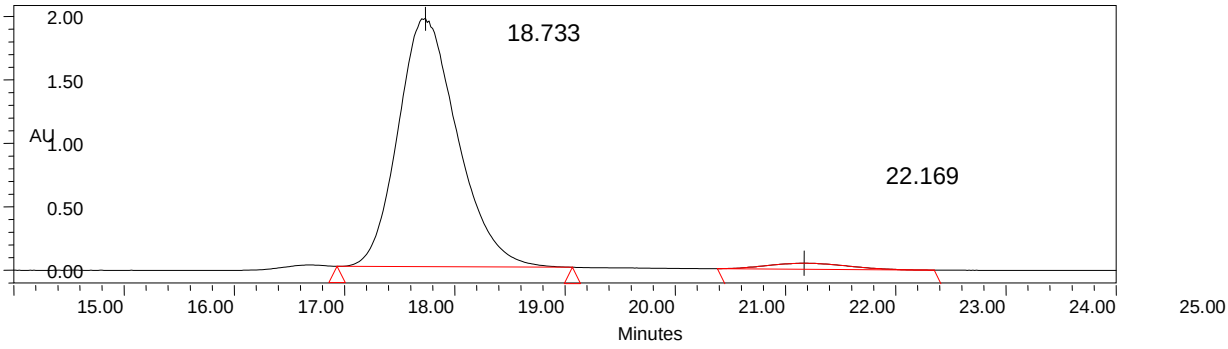
(*S*)-2-(Benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (78)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 18.8 min (major.) and 22.2 min (min.). Processed Channel Descr.: PDA 238.0 nm).

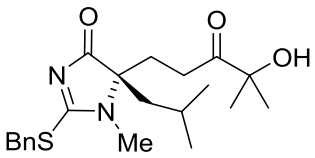


	Retention Time	% Area
1	18.485	49.04
2	21.873	50.96

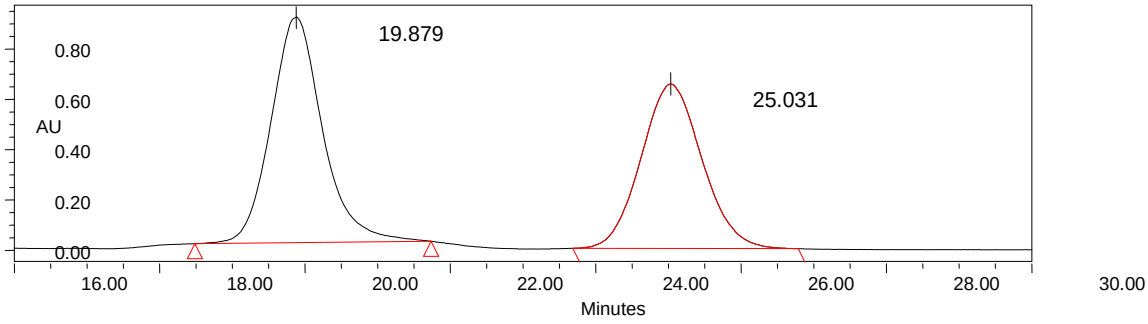


	Retention Time	% Area
1	18.733	96.81
2	22.169	3.19

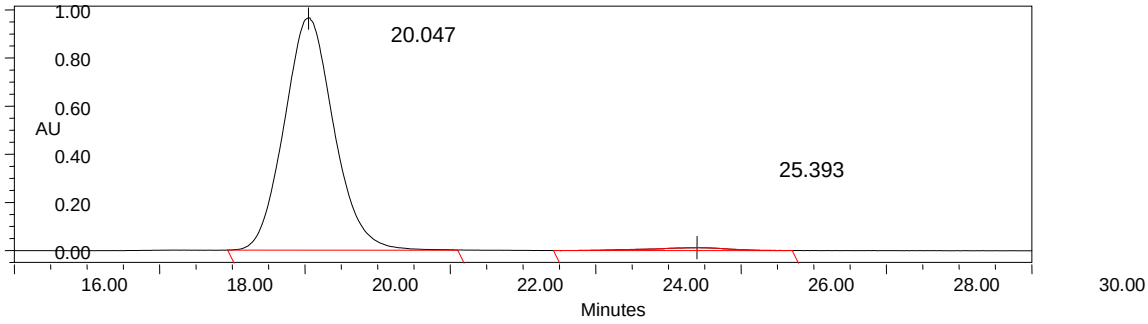
(*R*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (79)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 20.0 min (major.) and 25.4 min (min.). Processed Channel Descr.: PDA 236.0 nm).

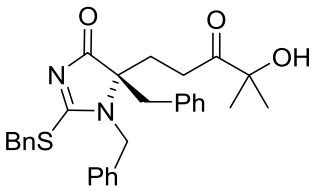


	Retention Time	% Area
1	19.879	53.69
2	25.031	46.31

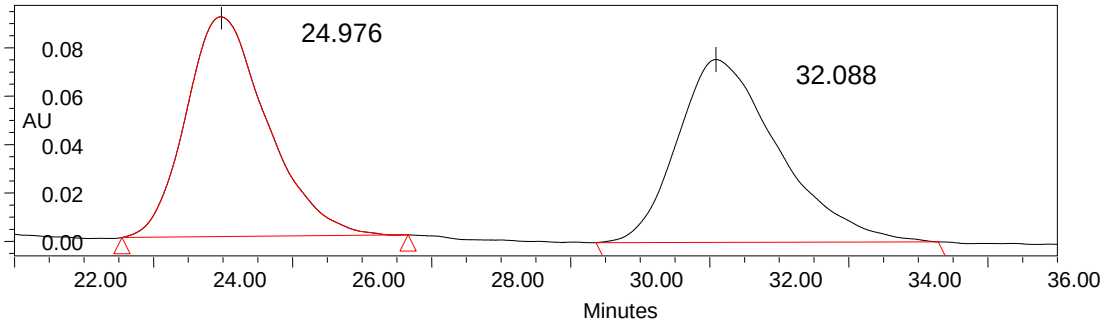


	Retention Time	% Area
1	20.047	98.06
2	25.393	1.94

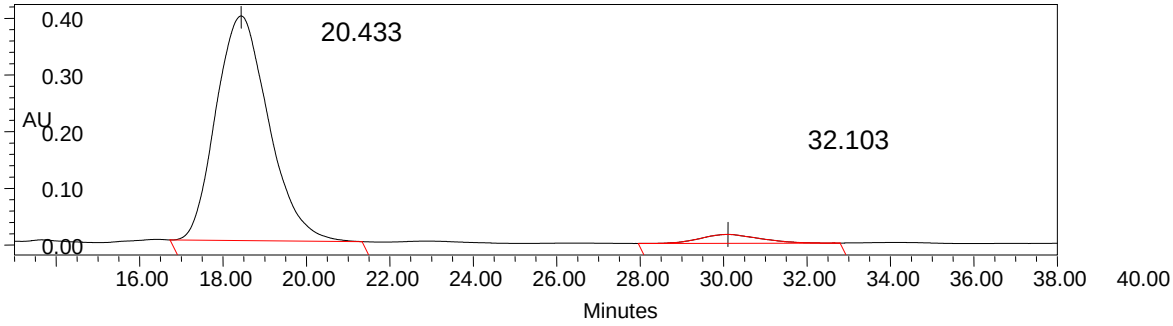
(*R*)-1,5-Dibenzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)- 1*H*-imidazol-4(5*H*)-one (80)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 20.4 min (major.) and 32.1 min (min.). Processed Channel Descr.: PDA 210.0 nm).



	Retention Time	% Area
1	24.976	49.16
2	32.088	50.84



	Retention Time	% Area
1	20.433	95.80
2	32.103	4.20

PUBLICATIONS

Organocatalysis

DOI: 10.1002/anie.201305644

Catalytic Enantioselective Synthesis of Tertiary Thiols From 5*H*-Thiazol-4-ones and Nitroolefins: Bifunctional Ureidopeptide-Based Brønsted Base Catalysis**

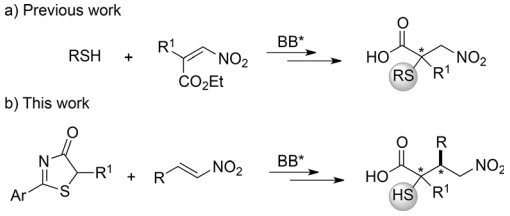
*Saioa Diosdado, Julen Etxabe, Joseba Izquierdo, Aitor Landa, Antonia Mielgo, Iurre Olaizola, Rosa López, and Claudio Palomo**

Dedicated to Professor Carmen Nájera

The direct catalytic reaction between an enolizable carbonyl compound and an electrophile under proton-transfer conditions has emerged as a challenging versatile transformation in organic synthesis.[1] Over the last years several chiral Brønsted bases have been developed to promote this transformation diastereo- and enantioselectively.[2] However, successful examples are mostly limited to 1,3-dicarbonyl compounds and acidic carbon analogues as the pronucleophilic reaction partners. 5*H*-Thiazol-4-ones, in contrast, have been well known for a long time and have found several applications in pharmaceutical and medicinal chemistry.[3] Although structurally related to 5*H*-oxazol-4-ones[4] and 4*H*-oxazol-5-ones (azlactones),[5] 5*H*-thiazol-4-ones have, as far as we know, been never been used in asymmetric synthesis in spite of the fact that they may be easily deprotonated[6] and in spite of the importance of thiols and organosulfur compounds in organic synthesis[7] and chemical biology.[8] In this context, whilst chiral secondary thiol derivatives have been the subject of most investigations, tertiary thiols have remained mostly unexplored owing to the insufficient catalytic enantioselective methodology for their preparation in optically pure form.[9]

The most general synthesis of organosulfur compounds involves reaction of a sulfur nucleophile with an electron-deficient π-olefin acceptor.[10] By using this approach Zhang and co-workers[11] reported an efficient catalytic asymmetric synthesis of tertiary thiols using chiral Brønsted bases and β-substituted β-ethoxycarbonyl nitroalkene acceptors. Conversely, tertiary thiols may be produced through conjugate additions of sulfur-based carbon pronucleophiles.[12] For instance, using rhodanines as carbon pronucleophiles and iminium catalysis, Ye and co-workers[13] have recently reported the conjugate addition and the Diels–Alder reaction to α,β-unsaturated ketones and 2,4-dienals, respectively. Tertiary thiols have also been accessed through enantioselective α-sulfenylation of aldehydes,[14a] 1,3-dicarbonyl compounds,[14b] β-keto phosphonates,[14c] and 3-substituted oxindoles.[14d–g] Other methods include thiofunctionalization of unactivated alkenes,[15a] amination of 3-thiooxindoles,[15b] and the aldol[15c] and Mannich[15d] reactions of α-sulfanyl lactones. Accordingly, whilst many methodologies for the enantioselective synthesis of secondary thiols exist, approaches for the asymmetric synthesis of tertiary thiols are clearly necessary to help fill this important gap in organic chemistry. The inherent difficulty associated with the stereoselective construction of quaternary stereogenic centers is probably the reason for the limited number of studies.[16] In connection with our efforts directed towards the asymmetric synthesis of organosulfur compounds, that is, β,β-disubstituted β-mercapto carboxylic acids[17a,b] and thiiranes,[17c] we focused on the enantioselective generation of a tetrasubstituted carbon atom at the α position of α-mercapto carboxylic acids.[18] We report herein the first highly diastereo- and enantioselective direct Michael addition of 5*H*-thiazol-4-ones to nitroolefins (Scheme 1) and it provides a quick entry to functionalized tertiary thiols. To this end, design and synthesis of ureidopeptide-based Brønsted bases, a novel subfamily of organic catalysts, are also documented for the first time.

We began our study by evaluating several Brønsted bases for the reaction of the readily available thiazolone **1**[19] with the nitroolefin **5a** (R = Ph; Scheme 2).[20] Initially, the reaction was explored using several representative cinchona alkaloids such as quinine, 9-epi-quinine, quinidine, and $(DHQ)_2PYR$ in CH_2Cl_2 at −60 °C. In every case the product



Scheme 1. Organocatalytic Michael approaches to α,α-disubstituted α-mercapto carboxylic acids mediated by chiral Brønsted bases (BB*). a) Asymmetric construction of C–S bond. b) Asymmetric construction of C–C bond.

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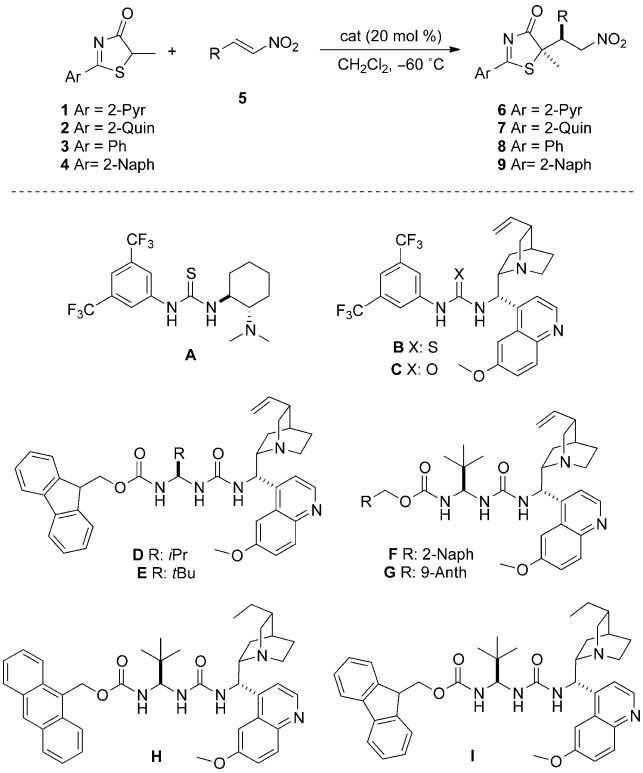
[**] Support has been provided by the University of the Basque Country UPV/EHU (UFI QOSYC 11/22), Basque Government (GV grant No IT-291-07 and SAIOTEK 2012), and Ministerio de Ciencia e Innovación (MICINN, Grant CTQ2010-21263-C02), Spain. S.D., J.E., and I.O. thank MEC. We also thank SGIker (UPV/EHU) for providing NMR, HRMS, X-ray, and computational resources. We also thank S. Vera and M. Zalacain for their help with catalyst preparation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305644.



Scheme 2. Conjugate addition of 5-methyl 5*H*-thiazol-4-ones to nitro olefins promoted by chiral Brønsted bases.

6a (R = Ph) was obtained but with disappointing chemical and stereochemical results (12–40% *ee*).[21] Next, on the basis of the pioneering studies of Takemoto and co-workers, and subsequent seminal works by the groups of Jacobsen, Connon, Dixon, and Soós on bifunctional (urea)thiourea-tertiary amine catalysts,[22] we examined the catalysts **A**–**C**. However, as the results in Table 1 show **A** led to almost racemic **6a** (entry 1), whilst no improvement was essentially observed with either **B** or **C** (entries 2 and 3).

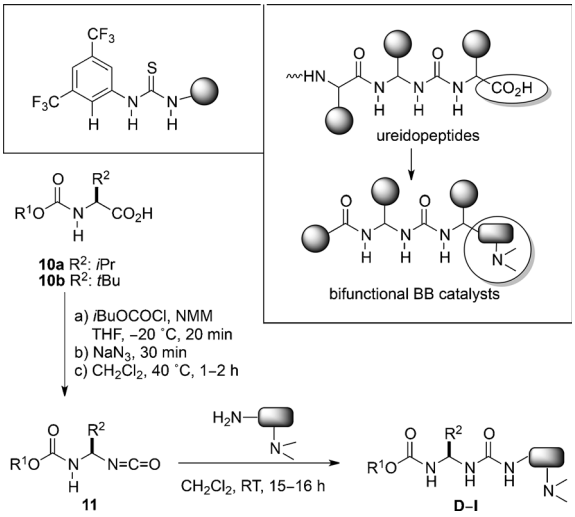
At this stage and in view of these results we focused on catalyst design. Like the catalysts **A**–**C**, most thiourea (urea)

Table 1: Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-ones **1**–**4** to nitrostyrene **5a** (R = Ph).[a]

Entry	Comp.	Cat.	Prod. (R=Ph)	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1**	**A**	**6a**	48	53	83:17	20
2	**1**	**B**	**6a**	20	53	60:40	35
3	**1**	**C**	**6a**	20	48	54:46	40
4	**1**	**D**	**6a**	20	88	91:9	40
5	**1**	**E**	**6a**	20	92	95:5	66
6	**1**	**F**	**6a**	20	90	94:6	70
7	**1**	**G**	**6a**	20	86	90:10	78
8	**1**	**H**	**6a**	20	80	93:7	80
9	**2**	**H**	**7a**	20	93	95:5	96
10	**3**	**H**	**8a**	20	65	85:15	55
11	**4**	**H**	**9a**	20	55	75:25	68

[a] Reactions conducted at −60 °C on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2). [b] Yield of the isolated major isomer. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

based Brønsted bases known to date display the 3,5-bis(trifluoromethyl)phenyl group, a structural motif which was introduced first by Schreiner and Wittkopp in 2002 for hydrogen-bond catalysis.[23] Recently, Schreiner and co-workers suggested that the success of these catalysts may be attributed in part to the participation of both N–H bonds of the thiourea unit and the *ortho* C–H bond of the aryl group during the substrate activation event.[24] Based on this observation and given the proved efficacy of synthetic peptides for fine-tuning of reactivity and selectivity of several significant synthetic transformations[25] we wondered whether the urea derivatives **D**–**I** might be more appropriate catalysts for promoting the above reaction. These products display, as new features, the presence of an N,N′-diacyl aminal unit in place of the bis(trifluoromethyl)phenyl group, and an urea moiety as hydrogen-bond donors, and both are in close proximity to an additional stereodirecting group. This type of structure closely resembles ureidopeptides (Scheme 3), which



Scheme 3. Ureidopeptide-based Brønsted bases: Catalyst preparation. NMM = *N*-methylmorpholine, THF = tetrahydrofuran.

have been recognized for their ability to develop hydrogen-bond interactions.[26] It was expected that the replacement of the α-amino acid terminus by an amino cinchona moiety in ureidopeptides should result in new bifunctional Brønsted base catalysts with several sites amenable for structural modification.

Although, several different classes of ureidopeptide-based catalysts may be made readily accessible from the available pools of both α-amino acids (or peptides) and primary-tertiary diamines, we intended first to take advantage of the tunable aminal moiety for catalyst optimization. To the best of our knowledge this family of ureidopeptide-based Brønsted base catalysts have not been previously reported. Thus, starting from valine and the *tert*-leucine derivatives **10a** and **10b**, the catalysts **D**–**I** were easily prepared by reaction of the respective intermediate isocyanates **11**[26b] with 9-epi-9-amino-9-deoxyquinine or 9-epi-9-amino-9-deoxyhydroquinine in yields within the 70–80% range for the latter step (Scheme 3). A single-crystal X-ray analysis of **E** (Figure 1)

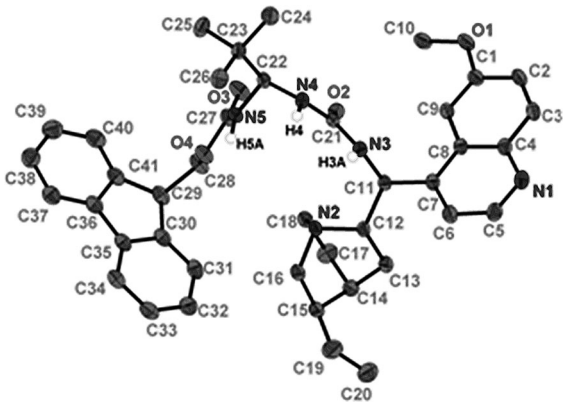


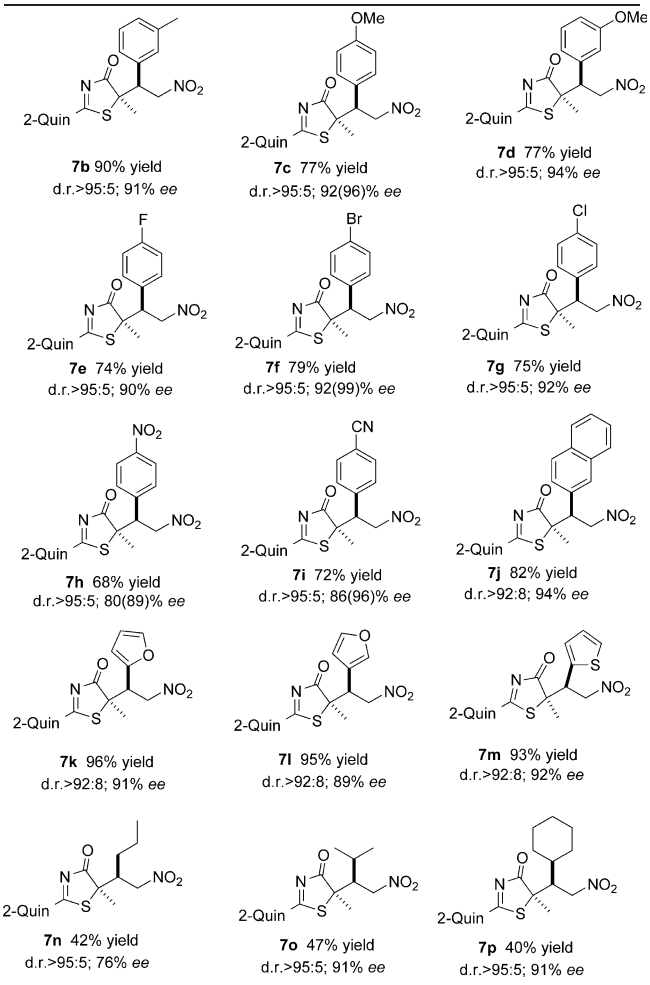
Figure 1. ORTEP representation for **E**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

shows that N-H groups, in the N,N′-diacyl aminal and the urea moiety, are oriented in the same direction and that neither of them display any apparent tendency to develop intramolecular hydrogen bonds.[21]

Experiments with these catalysts revealed an improvement in diastereoselectivity. Also, by increasing the size of the aminal substituent from isopropyl to *tert*-butyl (catalysts **D** and **E**), enantioselectivity increased up to 66%, but was still insufficient (Table 1, entries 4 and 5). Further improvements in the reaction selectivity were observed with the catalysts **F** and **G** (entries 6 and 7) and the best result was produced with the catalyst **H**, which provided the product **6a** in 80% yield and 80% *ee* (entry 8). In subsequent experiments it was found that by using the quinoline-derived thiazolone **2** and catalyst **H** the corresponding product **7a** (entry 9) was produced in 93% yield as a 95:5 mixture of diastereomers with 96% *ee* for the major isomer. In contrast, using the thiazolones **3** and **4**, the corresponding addition products **8a** and **9a** (entries 10 and 11) were formed in lower diastereomeric ratios and *ee* values, results which seem to indicate that the pyridine and quinoline nitrogen atoms of the thiazolones **1** and **2** play a significant role in reaction stereocontrol. A representative selection of nitroolefins was evaluated to establish the generality of this asymmetric route to tertiary thiols. As the data in Table 2 shows, nitroolefins bearing β-aryl substituents with either electron-donating or electron-withdrawing groups are almost equally tolerated, thus giving the corresponding adducts with good diastereomeric ratios, typically greater than 95:5 and *ee* values of up to 96%. For example, performing the reaction with the substrates **5b, 5c**, and **5d**, led to the corresponding products **7b, 7c**, and **7d** as single diastereomers with *ee* values within the 91–94% range. The nitroolefins **5e**, **5f**, and **5g** with inductively electron-withdrawing fluoro, bromo, and chloro substituents, respectively, also provided excellent chemical and stereochemical results, whereas the nitrostyrenes **5h** and **5i** bearing mesomeric electron-withdrawing substituents gave the corresponding **7h** and **7i** with slightly reduced enantioselectivities. The method also works with nitroolefins having heteroaromatic β-substituents such as for **5k, 5l**, and **5m** to afford adducts **7k, 7l**, and **7m**, respectively, with good yields and stereoselectivities. Even the recalcitrant β-alkyl-substituted nitroolefins participate in this reaction to give the desired adducts essentially as single diastereomers, albeit in modest chemical yield (typically 40%). The unbranched aliphatic nitroolefin **5n** led to the product **7n** with a modest 76% *ee*, whereas the branched aliphatic substrates **5o** and **5p** provided **7o** and **7p**, respectively, in 91% *ee*. In this study we have employed 20 mol% of catalyst but it is worth mentioning that reactions using 10 mol% of the catalyst proceeded equally well without compromising either selectivity or chemical yield (Table 2 and see the Experimental Section).

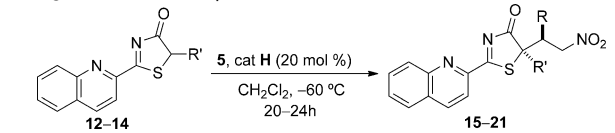
Thiazolones with short, large, and branched alkyl chains, also participate in this reaction (Table 3), and in all cases good to excellent yields were observed and the products were obtained with high enantioselectivity. The 5-ethylthiazolone **12**, for example, afforded the products **15–18**, essentially as

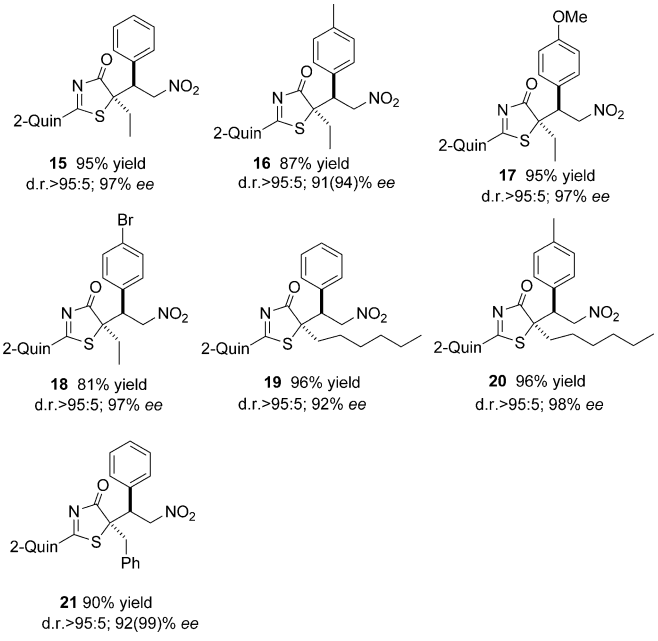
Table 2: Conjugate addition of the thiazolone **2** to nitroolefins **5** promoted by catalyst **H**.[a–d]



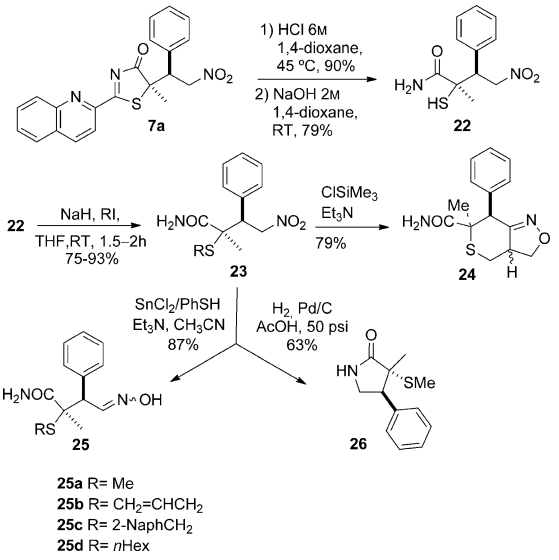
[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2) at −60°C for 20-24 h. [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^{1}H NMR (300 MHz) spectroscopy on the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Data within parentheses were obtained after crystallization from diethyl ether or diisopropyl ether. By using a 10 mol% catalyst loading, essentially the same results for **7c**, **7f**, and **7o** were attained.

Table 3: Thiazolone scope.[a–d]





[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroalkene/thiazolone/catalyst 2:1:0.2). [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase.



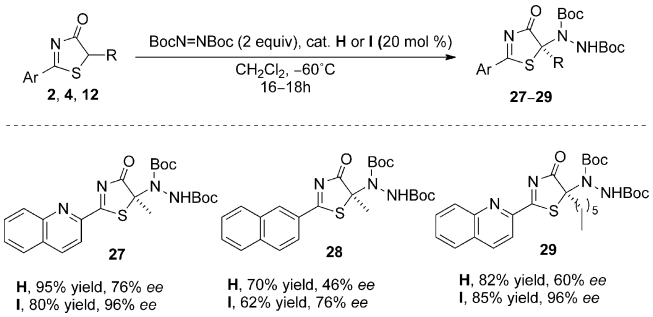
Scheme 4. Elaboration of adducts to α,α-disubstituted α-mercapto carboxylic acid derivatives.

sole diastereomers with excellent yields and 91–97% *ee*. Similarly, the hexyl (**13**) and benzyl (**14**) thiazolones, provided adducts **19, 20**, and **21** in very good yields, and diastereo- and enantioselectivities.

A practical aspect of the present methodology is the general crystallinity of the starting susbtrates, the thiazolones **2** and **12–14** and nitroolefin **5**, a property which is readily transformed into the resulting products **7** and **15–21**. Thus, a single crystallization, generally from diethyl ether or diisopropyl ether, provided products with increased enantiomeric purity. The absolute configuration of the adducts was established by a single-crystal X-ray analysis of **7 f**[21] and by assuming a uniform reaction mechanism.

Transformation of the adduct **7a** into the α,α-disubstituted α-mercapto carboxylic acid derivative **22**, by simple ring opening under mild acid conditions and subsequent saponification of the resulting thioester intermediate, illustrates the utility of the method. Thus, unlike the majority of procedures for the preparation of organosulfur compounds which generally give aryl or alkyl thioethers,[9–15] our method provides a quick entry to mercapto compounds with the thiol group in its free form (Scheme 4). Therefore, the question that we examined next was to establish whether these adducts could be S alkylated without affecting the nitro group. Besides steric constraints, there is the fact that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[27] Gratifyingly, treatment of the adduct **22** with a series of halides in the presence of sodium hydride furnished the corresponding S-alkylated adducts **23** in 75–93% yields. Therefore, our approach also provides rapid access to a variety of thioether derivatives from a single common intermediate, a practical aspect that facilitates access to more elaborated products as exemplified in the formation of the tetrahydrothiopyran-fused isoxazoline **24** from **23b**. In contrast, oximes such as **25c**, may also be obtained in good yields by treatment of the respective thioether adduct with a $SnCl_2$/PhSH/Et_3N system,[28] whilst exposure to H_2 over Pd on charcoal under 50 psi enabled reduction of the nitro group to the amino function, thus leading to γ lactams.

Concerning the mechanism of these reactions,[29] we believe that the quinoline nitrogen atom of these thiazolone substrates could interact through a hydrogen bond with one of the three accessible N-H protons of the catalyst, likely with one of the aminal moieties, thereby providing a well-ordered transition state during the reaction. This assumption nicely accounts for the better behavior of quinolyl thiazolone substrates versus the 2-naphthyl thiazolone **4**. Further support for this assumption was provided from the amination reaction of the thiazolones **2**, **4**, and **12** with *tert*-butylazodicarboxylate (Scheme 5). Whilst in this case enantiocontrol proceeded better with **I** rather than with **H**, thiazolones bearing the quinoline moiety (**2** and **12**) furnished once again a better stereochemical outcome than the 2-naphthyl thiazolone **4**. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation[30] remains to be clarified. Whereas the above assumption appears reasonable for enolate ions having additional Lewis basic functionality, there is evidence from this laboratory that this structural element in the pronucleophile is not a prerequisite for catalyst efficiency and that these bifunctional ureidopeptide-based Brønsted bases are advantageous for a variety of transformations which are currently under study.[31]



Scheme 5. Catalytic enantioselective α-amination of thiazolones. Boc = *tert*-butoxycarbonyl.

In summary, we have realized the first direct catalytic Michael reaction of α-mercapto carboxylate surrogates with nitroolefins involving the construction of a fully substituted α-carbon atom. The method demonstrates the efficacy of 5*H*-thiazol-4-ones as a new class of S-carrying pronucleophiles providing α,α-disubstituted α-mercapto carboxylic acid derivatives with good yields and high diastereo- and enantioselectivities and, consequently, the method contributes to broadening the currently limited methodology available for the catalytic enantioselective synthesis of tertiary thiols. From an intuitive design we have introduced for the first time a new family of Brønsted base catalysts whose architecture can be easily modified by simply choosing the appropriate α-amino-acid-derived (or peptide) isocyanate and a survey of naturally or synthetically primary/tertiary diamines. Since strong substrate dependence is quite common in reactions promoted by Brønsted bases we believe these new catalysts may help to address this challenging issue.

Experimental Section

The catalyst **H** (67.6 mg, 0.1 mmol, 10 mol %) was added to a mixture of 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**2**) (242.3 mg, 1.0 mmol, 1 equiv) and nitrostyrene **5a** (298.3 mg, 2.0 mmol, 2 equiv) in dichloromethane (2.0 mL) cooled to −60 °C. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (16 h; monitored by ^{1}H NMR spectroscopy wherein there was disappearance of the methyl signal at $\delta = 1.46$ ppm). The crude reaction mixture was directly purified by flash column chromatography on silica gel (eluting with dichloromethane) to give adduct **7a** as a yellow solid. Yield: 364 mg, 93 %.

7a: $[\alpha]_D^{25} = -100.5$ ($c = 1.00$, 96 % *ee*, CH_2Cl_2). m.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.16 (m, 3H), 7.95–7.78 (m, 2H), 7.76–7.64 (m, 1H), 7.43–7.32 (m, 2H), 7.31–7.12 (m, 3H), 5.19 (dd, $J = 13.2$, 4.6 Hz, 1H), 5.00 (dd, $J = 13.2$, 10.7 Hz, 1H), 4.22 (dd, $J = 10.7$, 4.6 Hz, 1H), 1.85 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.9$, 194.2, 148.7, 147.7, 137.4, 134.2, 134.2, 130.7, 130.4, 130.4, 129.5, 129.0, 128.7, 128.5, 127.8, 76.0, 65.1, 50.3, 24.0 ppm. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1065. The enantiomeric purity of the major diastereomer was found to be 96 % (98 % *ee* after crystallization from diethyl ether) and was determined by HPLC analysis [Daicel Chiralpak AD-H, *n*-hexane/isopropanol/ethanol 85:14:1, flow rate = 0.5 mL min^{-1}, retention times: 45.5 min (minor) and 57.2 min (major)].

Received: July 1, 2013
Published online: September 17, 2013

Keywords: Brønsted bases · organocatalysis · peptides · sulfur heterocycles · synthetic methods

[1] N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4856 – 4868; *Angew. Chem. Int. Ed.* **2011**, *50*, 4760 – 4772.
[2] a) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145 – 200; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; c) "Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics": *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**.
[3] a) N. A. Khalil, E. M. Ahmed, H. B. El-Nassan, *Med. Chem. Res.* **2013**, *22*, 1021 – 1027; b) U. V. Grummt, D. Weiss, E. Birckner, R. Beckert, *J. Phys. Chem. A* **2007**, *111*, 1104 – 1110; c) M. M. Véniant, C. Hale, R. W. Hungate, K. Gahm, M. G. Emery, J. Jona, S. Joseph, J. Adams, A. Hague, G. Moniz et al., *J. Med. Chem.* **2010**, *53*, 4481 – 4487.
[4] 5*H*-oxazol-4-ones for the synthesis of α,α-branched α-hydroxy acids. Metal catalysis: a) B. M. Trost, K. Dogra, M. Franzin, *J. Am. Chem. Soc.* **2004**, *126*, 1944 – 1945; b) D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem.* **2012**, *124*, 7641 – 7645; *Angew. Chem. Int. Ed.* **2012**, *51*, 7523 – 7527; c) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin, X. Feng, *Angew. Chem.* **2012**, *124*, 2830 – 2833; *Angew. Chem. Int. Ed.* **2012**, *51*, 2776 – 2779; d) B. M. Trost, K. Hirano, *Angew. Chem.* **2012**, *124*, 6586 – 6589; *Angew. Chem. Int. Ed.* **2012**, *51*, 6480 – 6483; organocatalysis: e) T. Misaki, G. Takimotoa, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286 – 6287; f) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695 – 5697; g) B. Quiau, Y. An, Q. Liu, W. Yang, H. Liu, J. Shen, L. Yan, Z. Jiang, *Org. Lett.* **2013**, *15*, 2358 – 2361; h) H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461 – 463; i) Z. Han, W. Yang, C.-H. Tan, Z. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 1505 – 1511.
[5] Reviews: a) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720 – 734; b) R. A. Mosey, J. S. Fisk, J. T. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755 – 2762; for the sulfur analogs of azlactones, see: c) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300 – 302; d) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876 – 879; e) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, *13*, 1494 – 1497; f) X. Liu, H. Song, Q. Chen, W. Li, W. Yin, M. Kai, R. Wang, *Eur. J. Org. Chem.* **2012**, 6647 – 6655.
[6] E. Täuscher, D. Weib, R. Beckert, J. Fabian, A. Assumpçao, H. Görls, *Tetrahedron Lett.* **2011**, *52*, 2292 – 2294.
[7] a) P. Metzner, A. Thuillier, *Sulfur Reagents in Organic Synthesis* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. S. Rees), Academic Press, **1995**; b) *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**.
[8] L. K. Moran, J. M. Gutteridge, G. J. Quinlan, *Curr. Med. Chem.* **2011**, *18*, 763 – 772.
[9] Review: J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582 – 595.
[10] Review of sulfa-Michael reaction: D. E. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959 – 980.
[11] H. H. Lu, F. G. Zhang, X. G. Meng, S. W. Duan, W. J. Xiao, *Org. Lett.* **2009**, *11*, 3946 – 3949.
[12] Diastereoselective methods: a) B. Strijtveen, R. M. Kellogg, *Tetrahedron* **1987**, *43*, 5039 – 5054; b) J. M. McFadden, G.-L. Frehynot, C. A. Townsend, *Org. Lett.* **2002**, *4*, 3859 – 3862; c) R. Alibés, P. Bayón, P. De March, M. Figueredo, J. Font, G. Marjanet, *Org. Lett.* **2006**, *8*, 1617 – 1620; d) E. A. Tiong, J. L. Gleason, *Org. Lett.* **2009**, *11*, 1725 – 1728.
[13] a) F. Yu, H. Hu, X. Gu, J. Ye, *Org. Lett.* **2012**, *14*, 2038 – 2041; b) K. Zhu, H. Huang, W. Wu, Y. Wei, J. Ye, *Chem. Commun.* **2013**, *49*, 2157 – 2159.

[14] a) M. Marigo, T. C. Wabnitz, D. Filenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804 – 807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797; b) S. Sobhani, D. Fielenbach, M. Marigo, T. C. Wabnitz, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 5689 – 5694; c) A. Ling, L. Fang, X. Zhu, C. Zhu, Y. Chen, *Adv. Synth. Catal.* **2011**, *353*, 545 – 549; d) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2012**, *14*, 2726 – 2729; e) X. Li, C. Liu, X.-S. Xua, J.-P. Cheng, *Org. Lett.* **2012**, *14*, 4374 – 4377; f) Z. Hang, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan, Z. Jiang, *Org. Lett.* **2012**, *14*, 4670 – 4673; g) C. Wang, X. Yang, C. C. J. Loh, G. Raabe, D. Enders, *Chem. Eur. J.* **2012**, *18*, 11531 – 11535.

[15] a) S. E. Denmark, D. J. P. Kornfilt, T. Vogler, *J. Am. Chem. Soc.* **2011**, *133*, 15308 – 15311; b) F. Zhou, X. P. Zeng, C. Wang, X. L. Zhao, J. Zhou, *Chem. Commun.* **2013**, *49*, 2022 – 2024; c) S. Takechi, S. Yasuda, N. Kunagai, M. Shibasaki, *Angew. Chem.* **2012**, *124*, 4294 – 4298; *Angew. Chem. Int. Ed.* **2012**, *51*, 4218 – 4222; d) S. Takechi, N. Kumagai, M. Shibasaki, *Org. Lett.* **2013**, *15*, 2632 – 2635.

[16] Recent reviews: a) M. Bella, T. Casperi, *Synthesis* **2009**, 1583 – 1614; b) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295 – 7306; c) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[17] a) C. Palomo, M. Oiarbide, F. Dias, R. López, A. Linden, *Angew. Chem.* **2004**, *116*, 3369 – 3372; *Angew. Chem. Int. Ed.* **2004**, *43*, 3307 – 3310; b) C. Palomo, M. Oiarbide, R. López, P. B. González, E. Gómez-Bengoa, J. M. Saá, A. Linden, *J. Am. Chem. Soc.* **2006**, *128*, 15236 – 15247; c) I. Cano, E. Gómez-Bengoa, A. Landa, M. Maestro, A. Mielgo, I. Olaizola, M. Oiarbide, C. Palomo, *Angew. Chem.* **2012**, *124*, 11014 – 11018; *Angew. Chem. Int. Ed.* **2012**, *51*, 10856 – 10860.

[18] Interest in α-mercapto carboxylic acids also stems from their general use as precursors of 4-thiazolidinones and 2,4-thiazolidinediones, which are key scaffolds for drug design and pharmaceutical agents, see: a) M. Abhinit, M. Ghodke, N. A. Pratima, *Int. J. Pharm. Pharm. Sci.* **2009**, *1*, 47 – 64; b) A. Verma, S. K. Saraf, *Eur. J. Med. Chem.* **2008**, *43*, 897 – 905; c) S. P. Singh, S. S. Parmar, K. R. Raman, V. I. Stenberg, *Chem. Rev.* **1981**, *81*, 175 – 203.

[19] U. W. Grummt, D. Weiss, E. Birckner, R. Beckert, *J. Phys. Chem. A* **2007**, *111*, 1104 – 1110.

[20] For a review on conjugate additions to nitroolefins, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; for reviews on organocatalytic asymmetric conjugate additions, see: b) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; d) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; e) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065 – 2092; f) *Organocatalytic Enantioselective Conjugate Addition Reactions* (Eds.: J. L. Vicario, D. Badía, L. Carrillo, E. Reyes), RSC, Cambridge, **2010**; g) *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, Weinheim, **2010**.

[21] CCDC 947275 (**E**) and 930440 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

[22] a) O. Tomotaka, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 – 12673; b) H. Miyabe, T. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785 – 795; c) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964 – 8965; d) S. H. McCooey, S. Connon, *Angew. Chem.* **2005**, *117*, 6525 – 6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367 – 6370; e) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481 – 4483; f) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967 – 1969; for recent reviews on (thio)urea-tertiary amines, see: g) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418 – 5427; h) W. Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298 – 1310; i) H. B. Jang, J. S. Oh, C. E. Song in Ref. [2c], pp. 119–168; j) T. Inokuma, Y. Takemoto in Ref. [2c], pp. 437–497.

[23] a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217 – 220; b) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187 – 1198; c) M. Kotice, P. R. Schreiner in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 141 – 351.

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

[25] a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759 – 5812; b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036 – 12041.

[26] a) V. Semetey, D. Rognan, C. Hemmerlin, R. Graff, J. P. Briand, M. Marraud, G. Guichard, *Angew. Chem.* **2002**, *114*, 1973 – 1975; *Angew. Chem. Int. Ed.* **2002**, *41*, 1893 – 1895; b) V. V. Sureshbabu, B. S. Patil, R. Venkataramanarao, *J. Org. Chem.* **2006**, *71*, 7697 – 7705; c) A. C. Myers, J. A. Kowalski, M. A. Lipton, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219 – 5222; d) V. Semetey, C. Hemmerlin, C. Didierjean, A. P. Schaffner, A. G. Giner, A. Aubry, J. P. Briand, M. Marraud, G. Guichard, *Org. Lett.* **2001**, *3*, 3843 – 3846.

[27] C. Czekelius, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 618 – 621; *Angew. Chem. Int. Ed.* **2005**, *44*, 612 – 615, and references therein.

[28] a) M. Bartra, P. Romea, F. Urpí, J. Vilarrasa, *Tetrahedron* **1990**, *46*, 587 – 594; b) C. C. Hughes, D. Trauner, *Angew. Chem.* **2002**, *114*, 4738 – 4741; *Angew. Chem. Int. Ed.* **2002**, *41*, 4556 – 4559.

[29] For mechanistic details on Michael reactions with nitroolefins and thiourea-tertiary amine catalysts, see: a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151 – 13160; b) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682 – 2685. Also, see Ref. [22a,b].

[30] At present no conclusive results are attained from computational studies. The flexibility of the rather large catalyst **H** requires an extensive number of reaction modes to be examined. For related work, see: E. Gómez-Bengoa, A. Linden, R. López, I. Mugica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955 – 7966.

[31] An illustrative example is the Mannich reaction of 2-naphthalenesulphonyl acetonitrile with N-Boc imines to afford β-amino nitriles, a reaction which is promoted by catalyst **E** in good chemical yields and *ee* values up to 94%. Full details of this reaction as well as the application of these Brønsted bases to other transformations will be published soon. For some further information see the Supporting Information.

Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201501275
German Edition: DOI: 10.1002/ange.201501275

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.

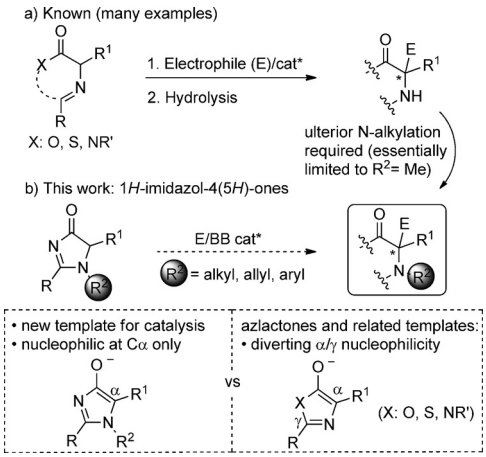
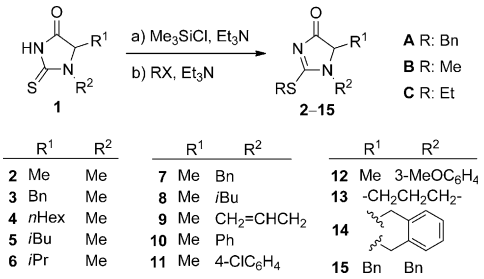


Figure 1. Enantioselective approaches to N,C$^{\alpha}$,C$^{\alpha}$-trisubstituted α-amino acid units. BB = Brønsted base.

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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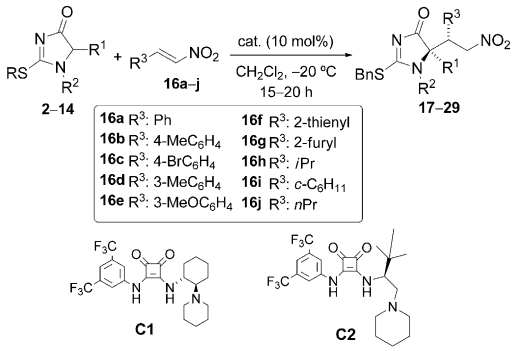
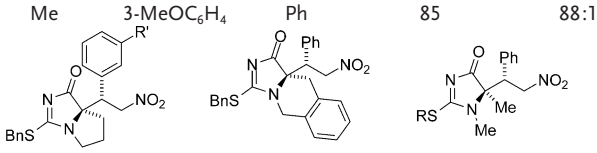
[**] Financial support was provided by the University of the Basque Country UPV/EHU (UFI 11/22), Basque Government (Grant No IT-628-13 and Saiotek 2014), and Ministerio de Economía y Competitividad (MEC, Grant CTQ2013-47925-C2-1-P), Spain. J.E. thanks MEC and J.I. thanks UPV/EHU for Fellowships. We also thank SGIker (UPV/EHU) for providing NMR, HRMS, and X-Ray resources.

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).

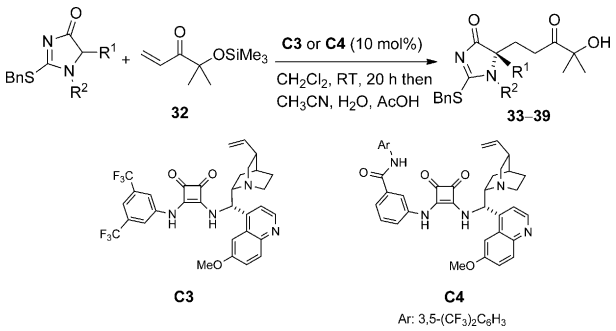
were all tolerated (entries 11–17, 20, and 21). Also bicyclic imidazolones, such as **13A** and **14A**, provided the corresponding adducts (**28a**, **28e**, **29a**) with equal effectiveness. These latter products represent quaternary proline and related derivatives which cannot be accessed directly 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]

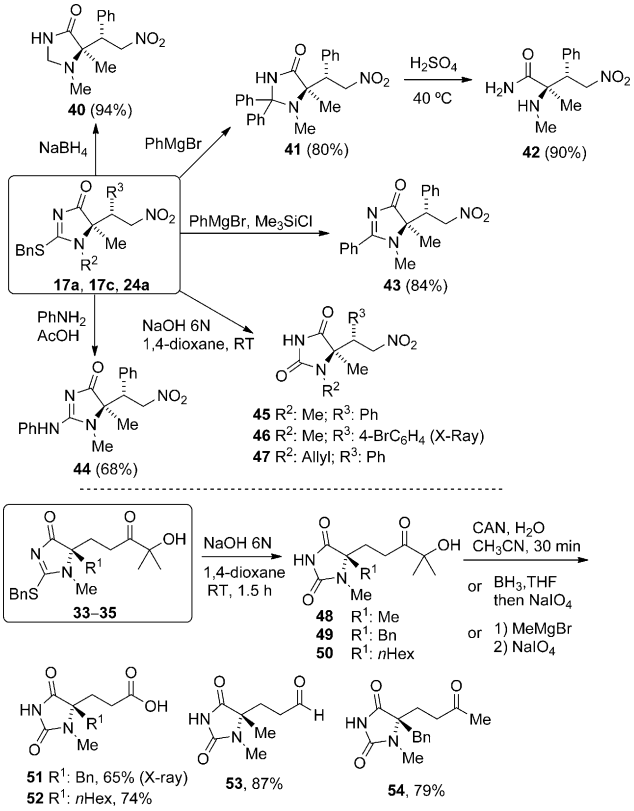
On the other hand, given that the new template allows direct access to N-substituted quaternary α-amino acid derivatives, additional ways for the elaboration of adducts can be envisaged in which the NR^2 moiety plays a strategic role. For instance (Scheme 3), from the common adduct **47**, the densely 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]

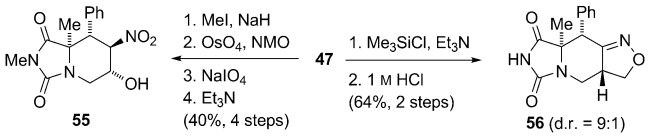


Entry	Imidazolone	R^1	R^2	Prod.	Yield [%][b]	*ee* [%][c]
1	**2A**	Me	Me	**33**	82	96[d]
2	**3A**	Bn	Me	**34**	75	96
3	**4A**	*n*Hex	Me	**35**	81	94
4	**5A**	*i*Bu	Me	**36**	71	96
5	**7A**	Me	Bn	**37**	78	96
6	**9A**	Me	CH_2=$CHCH_2$	**38**	77	94
7	**15A**	Bn	Bn	**39**	83	92

[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

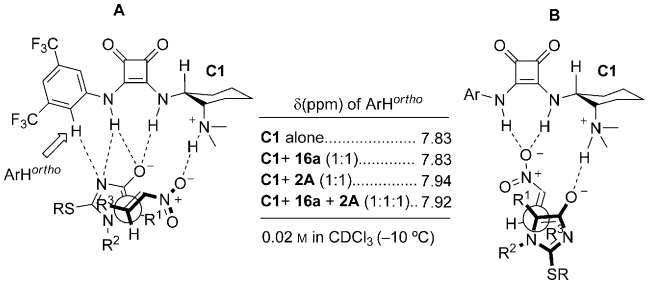


Figure 2. Plausible TS models and selected ^{1}H NMR data.

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

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 6883–6886
Angew. Chem. **2015**, *127*, 6987–6990

[1] *Amino Acids, Peptides and Proteins in Organic Chemistry, Vols. 1&2* (Ed.: A. B. Hughes), Wiley-VCH, Weinheim, **2009**.
[2] a) C. Cativiela, M. D. Díaz de Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569 – 623; b) C. Cativiela, M. Ordoñez, *Tetrahedron: Asymmetry* **2009**, *20*, 1 – 63; c) Y. Ohfune, T. Shinada, *Eur. J. Org. Chem.* **2005**, 5127 – 5143; d) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406 – 430; e) R. A. Monsey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755 – 2762; f) K. Bera, I. N. N. Namboothiri, *Asian J. Org. Chem.* **2014**, *3*, 1234 – 1260.
[3] a) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584 – 4671; b) A. E. Metz, M. C. Kozlowski, *J. Org. Chem.* **2015**, *80*, 1 – 7.
[4] a) J. S. Fisk, R. A. Monsey, J. J. Tepe, *Chem. Soc. Rev.* **2007**, *36*, 1432 – 1440; b) Reference [2e]; c) A.-N. R. Alba, R. Ríos, *Chem. Asian J.* **2011**, *6*, 720 – 734; d) A. J. Metrano, S. J. Miller, *J. Org. Chem.* **2014**, *79*, 1542 – 1554, and references therein.
[5] For rare examples, see: a) K. Tomohara, T. Yoshimura, R. Hyakutake, P. Yang, T. Kawabata, *J. Am. Chem. Soc.* **2013**, *135*, 13294 – 13297. For a recent Pd-catalyzed asymmetric synthesis of α-allyl α-alkyl piperazine-2-ones, see: b) K. M. Korch, C. Eidamshaus, D. C. Behenna, S. Nam, D. Horne, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2015**, *54*, 179 – 183; *Angew. Chem.* **2015**, *127*, 181 – 185.
[6] Synthetic preparation of N-methyl α-amino acids: L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823 – 5846.
[7] Review: a) L. Aurelio, A. B. Hughes in *Amino Acids, Peptides and Proteins in Organic Chemistry*, *Vols. 1&2* (Ed.: A. B. Hughes), Wiley-VCH, Weinheim, **2009**, pp. 245 – 290. Recent application in medicinal chemistry and biochemistry: b) T. Kawakami, T. Sasaki, P. C. Reid, H. Murakami, *Chem. Sci.* **2014**, *5*, 887 – 893, and references therein.
[8] For further information, see: a) J. Alemán, A. Milelli, S. Cabrera, E. Reyes, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 10958 – 10966; b) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775 – 2783; c) A. N. Balaguer, X. Companyo, T. Calvet, M. Font-Bardia, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2009**, 199 – 203. Also, see Ref. [4c].
[9] See the Supporting Information for details.
[10] Recent reviews on organocatalytic asymmetric Michael reactions: a) J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions*, RSC Publishing, Cambridge, **2010**; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; c) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365.
[11] Reviews on conjugate additions to nitroolefins: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; b) D. Roca-López, D. Sádaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2562 – 2601; c) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, 2627 – 2628.
[12] a) J. P. Malerich, K. Hagihara, V. R. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416 – 14417; b) Y. Zhu, J. P. Malerich, V. R. Rawal, *Angew. Chem. Int. Ed.* **2010**, *49*, 153 – 156; *Angew. Chem.* **2010**, *122*, 157 – 160. For reviews on squaramide catalysis, see: c) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330 – 2346; d) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890 – 6899. For a recent review on Brønsted-base-catalyzed asymmetric reactions, see: e) "Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics": *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**.
[13] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953 – 957.
[14] For the synthesis of this class of quaternary amino acids, Seebach's "self regeneration of stereocenters" methodology is the most convenient approach, but it requires prior construction of the corresponding enantiomerically pure α-amino acid. For details, see: a) D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708 – 2748; *Angew. Chem.* **1996**, *108*, 2881 – 2921. For a review on the stereoselective synthesis of quaternary proline analogues, see: b) M. I. Calaza, C. Cativiela, *Eur. J. Org. Chem.* **2008**, 3427 – 3448.
[15] E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2014**, *136*, 17869 – 17881.
[16] Under these reaction conditions, simple unsaturated esters and ketones work sluggish.
[17] W. Yang, D.-M. Du, *Org. Lett.* **2010**, *12*, 5450 – 5453.
[18] Although premature, the high reactivity profile of, and the consistently high levels of enantiocontrol imparted by, catalyst **C4** might be ascribed to its ability to form an intramolecular CONH···O=C H-bond. For design strategies to enhance hydrogen-bond donor catalysis, see: T. J. Auvil, A. G. Schafer, A. E. Mattson, *Eur. J. Org. Chem.* **2014**, 2633 – 2646.
[19] a) N. Arshad, J. Hashim, C. O. Kappe, *J. Org. Chem.* **2009**, *74*, 5118 – 5121; b) S. Bepary, I. K. Youn, H.-J. Lim, G. H. Lee, *Eur. J. Org. Chem.* **2012**, 2542 – 2548; c) L. Konnert, B. Reneaud, R. Marcia de Figueiredo, J.-M. Campagne, F. Lamaty, J. Martinez, E. Colacino, *J. Org. Chem.* **2014**, *79*, 10132 – 10142.
[20] M. Meusel, M. Gütschow, *Org. Prep. Proc. Int.* **2004**, *36*, 391 – 443.
[21] CCDC 1044978 (**46**) and 1044937 (**51**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[22] a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631 – 5639; For proposals involving bifunctional amine – thiourea catalysts, see: b) W. Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298 – 1310.
[23] a) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682 – 2685; b) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther, P. R. Schreiner, *Eur. J. Org. Chem.* **2012**, 5919 – 5927; c) D. Bastida, Y. Liu, X. Tian, E. Escudero-Adán, P. Melchiorre, *Org. Lett.* **2013**, *15*, 220 – 223.

Received: February 11, 2015
Revised: March 24, 2015
Published online: April 23, 2015

