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Brønsted based catalyzed Michael additions for the production of heterocyclic compounds of biological interest

DOCTORAL THESIS

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ABBREVIATIONS AND ACRONYMS

Standard abbreviations and acronyms have been used as recommended in "Guidelines for authors" (*J. Org. Chem.,* January **2015**). Additionally, the following abbreviations and acronyms have been employed:

*	Chiral
AA	Amino acid
Alk.	Alkyl (group)
Ar.	Aryl (group)
Asp	Asparagine
B	base
BB	Brønsted base
BIOS	Biology Oriented Synthesis
Cat.	Catalyst
Conv.	Conversion
CtD	Complexity to diversity
DCC	*N,N'*-Dicyclohexylcarbodiimide
DIPEA	Diisopropylethylamine
DKP	Diketopiperazine
DMAP	4-(Dimethylamino)pyridine
DOS	Diversity oriented synthesis
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
EDCI	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide
Equiv.	Equivalent

EWG	Electron-withdrawing group
TOS	Target-oriented synthesis
HBTU	*N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HOBt	1-Hydroxybenztriazole
HTS	High-throughput screening
LFP	Lewis Frustrated Pairs
MLC	Metal-ligand cooperation
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
NBS	*N*-bromosuccinimide
ND	Not determined
NP	Natural product
NR	No reaction
NMM	4-Methylmorpholine
Phe	Phenylalanine
PG	Protecting group
PSSC	Protein Structure Similarity Clustering
Ref.	reference
SCONP	Structural Classification of Natural Products
TMS	Trimethyl silyl
Trp	Tryptophan
Val	Valine

CHAPTER 1

1. INTRODUCTION

Chirality[1] is defined as a property of certain three-dimensional objects, which was used for the first time by Lord Kelvin[2] in 1893: "I call any geometrical figure, or group of points, 'chiral', and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."

In 1812, Biot[3] observed that several organic compounds –including tartaric acid, sucrose, turpentine and camphor– deflect out of the plane polarized light and concluded that the 'optical activity' is a characteristic property of these type of products. In 1848, Luis Pasteur[4] associated this property to the asymmetric disposition of the atoms in a molecule and Kekulé proposed the tetravalence of carbon atoms.[5] A significant advance supposed the proposal of Le Bel and Van Hoff in 1874, in an independent way, the tetrahedral three-dimensioned disposition of the four substituents of a carbon atom generating two molecules of identical composition and constitution, but different spatial distribution of atoms, we call them enantiomers (Figure 1).[6]

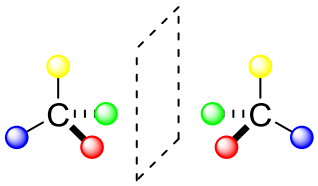


Figure 1. Both enantiomers of a chiral molecule containing a stereogenic carbon.

When enantiomers are in a chiral environment, their behavior can differ from one another, as happens in most biochemical processes. The consequence can be that the smell or the taste is completely different or that serious problems appear such in the case

[1] a) Riehl, J. P. *Mirror-Image Asymmetry: An Introduction to the Origin and Consequences of Chirality* (John Wiley & Sons, New Jersey) **2009**. b) Bentley, R. *Chirality* **2010**, *22*, 1-2.
[2] Lord Kelvin: C. J. Clay and Sons, *Baltimore Lectures on Molecular Dynamics and the Wave of Theory of Light* **1904**, Cambridge University Press Warehouse, London (UK).
[3] Biot, J. B. *Mem. Cl. Sci. Math. Phys. Inst. Imp. Fr.* **1812**, *13*, 1-371. b) Biot, J. B. *Bull. Soc. Philmomath. París*, **1815**, 190-192.
[4] a) Pasteur, L. *C. R. Acad. Sci. Paris* **1848**, *26*, 535-538. b) Pasteur, L. *Ann. de Chim. et de Phys.* **1848**, *24*, 442-459. c) Pasteur, L. *Ann. de Chim. et de Phys.* **1853**, *38*, 437-483. d) Vallery-Radot, R. *La vie de Pasteur* (Hachette et cie., Paris) **1900**.
[5] Kekulé, A. *Annals*. **1858**, *106*, 154.
[6] a) Le Bel, J. A. *Bull. Soc. Chim. Fr.* **1874**, *22*, 337-347. b) Van't Hoff, J. H. *Arch. Neerl. Sci. Exacles. Nat.* **1874**, *4*, 445-454.

of thalidomide.[7] After the scandal caused by the administration of this medicine and to avoid further undesired responses, pharmaceuticals-,[8] agricultural-,[9] food-chemistry and flavors,[10] fragrances[11] and new materials;[12] it was clear the necessity of synthesizing enantiomerically pure compounds.[13]

Obtaining enantiomerically enriched molecules through the formation of new carbon-carbon and carbon-heteroatom bonds can be performed using three approaches: *racemic resolution*,[14] by means of adequate physical or chemical methodologies; *chiral pool*,[15] using enantiopure natural products as substrates and; *asymmetric synthesis*,[16] the stereoselective conversion of prochiral compounds into chiral products using a chiral reagent, a chiral auxiliary,[17] a metallic center and a chiral ligand,[18] or a chiral catalyst.[19] In the last approaches, substoichiometric quantities of an enantiopure substance control both reactivity and selectivity.

[7] Stephens, T.; Brynner, R. *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine* (Perseus, Cambridge, MA) **2001**.

[8] a) Serafini, M.; Cargnin, S.; Massarotti, A.; Pirali, T.; Genazzani, A. A. *J. Med. Chem.* **2020**, *63*, 10170-10187. b) Coelho, M. M.; Fernandes, C.; Remião, F.; Tiritan, M. E. *Molecules* **2021**, *26*, 3113-3135.

[9] More than 30% of the registered pesticides in 2018 were chiral, but only 7% were commercialized as a pure enantiomer or stereo enriched mixture: de Albuquerque, N. C. P.; Carrão, D. B.; Habenschus, M. D.; Oliveira, A. R. M. *Pharm. Biomed. Anal.* **2018**, *147*, 89-109.

[10] a) Zawirska-Wojtasiak, R. *Acta Sci. Pol. Technol. Aliment.* **2006**, *5*, 21-36. b) Engel, K.-H. *J. Agric. Food Chem.* **2020**, *68*, 10265-10274.

[11] a) Heuberger, E.; Hongratanaworakit, T.; Böhm, C.; Weber, R.; Buchbauer, G. *Chem. Senses* **2001**, *26*, 281-292. b) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281-1290.

[12] a) Hodgkinson, I.; Wu, Q. H. *Adv. Mater.* **2001**, *13*, 889-897. b) Mallia, V. A.; Tamaoki, N. *Chem. Soc. Rev.* **2004**, *33*, 76-84.

[13] Thayler, A. N. Thayler, A. N. *Chem. Eng. News* **2007**, *9*, 105-110.

[14] For general reviews on resolution methods, see: a) Anderson, N. G. *Org. Proc. Res. Dep.* **2005**, *9*, 800-813. b) Synoradzki, L.; Bernás, U.; Ruśkowski, P. *Org. Prep. Proced. Inc.* **2008**, *40*, 163-200. For general reviews on the kinetic dynamic resolution, see: c) Matute, B. M. *An. Quim.* **2006**, *102*, 46-52. d) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*, **2011**, RSC, Cambridge.

[15] For reviews about chiral pools, see: a) Hanessian, S. *Pure Appl. Chem.* **1993**, *65*, 1189-1204. b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis* **1996**, Wiley-VCH. c) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II* **2003**, Wiley-VCH.

[16] For more information about asymmetric synthesis, see: a) Christmann, M.; Bräse, S. *Asymmetric Synthesis: The Essentials* **2007**, Wiley-VCH, New York. b) *Asymmetric Synthesis II: More Methods and Applications* Eds. Christmann, M.; Bräse, S. **2012**, Wiley-VCH, Weinheim, Germany. c) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis 2nd Edition* **2012**, Pergamon Press, Oxford.

[17] For a recent review, see: a) Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; de Rezende, D. C.; Diaz, M. A. N. *Chirality* **2019**, *31*, 776-812.

[18] For a review of chiral ligands, see: Fanourakis, A.; Docherty, P. J.; Chuentragool, P.; Phipps, R. J. *ACS Catal.* **2020**, *10*, 10672-10714.

[19] For more information on asymmetric catalysis, see: Akiyama, T.; Ojima, I. *Catalytic Asymmetric Synthesis, Fourth Edition* **2022**, Wiley-VCH, New York.

Asymmetric catalysis is nowadays the most convenient methodology for the synthesis of chiral molecules, since only small amount of expensive and/or less available chiral material is necessary. Specially, after the world community recognized the importance of asymmetric catalysis when in 2001 the Royal Swedish Academy of Sciences awarded the Nobel Prize in Chemistry to W. S. Knowles, R. Noyori and K. B. Sharpless for developing catalytic asymmetric hydrogenation and oxidation reactions.[20]

1.1. Organocatalysis

As a particular branch in the field of asymmetric catalysis, organocatalysis[21] has suffered an exponential growth in the last two decades. This methodology takes advantage of enantiopure organic compounds to generate new stereogenic units. Underlining the importance of this field, the Nobel Prize in Chemistry 2021 was awarded to Benjamin List and David MacMillan for their work in the synthesis of enantioenriched compounds using in the process small organic molecules (Figure 2).[22]

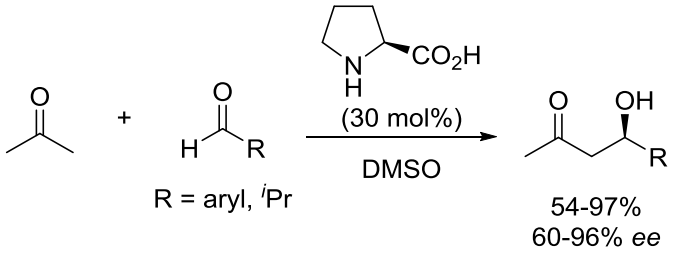
Figure 2. Benjamin List (left) and David W. C. MacMillan (right), Nobel Prize in Chemistry laureates in 2021.[23]

Even though the use of metal free compounds for the asymmetric synthesis of enantioenriched products, such as *Cinchona* alkaloid derived catalysts[24] and *L*-proline,[25]

[20] www.nobelprize.org/prizes/chemistry/2001/summary/.
[21] For recent reviews, see: a) Xiang, S.-H.; Tan, B. *Nat. Commun.* **2020**, *11*, 3786-3790. b) Lassaletta, J. M. *Nat. Commun.* **2020**, *11*, 3787-3791. c) Reyes, E.; Prieto, L.; Milelli, A. *Molecules* **2023**, *28*, 271-294.
[22] https://www.nobelprize.org/prizes/chemistry/2021/press-release/
[23] a) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396. b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
[24] a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22. b) Červinca, O.; Bělovský, O. *Collect. Czech. Chem. Commun.* **1965**, *30*, 2487-2491.
[25] 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.

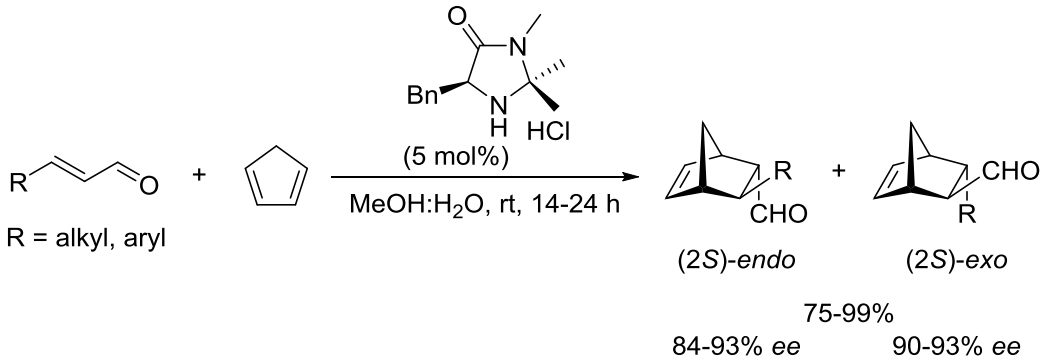
was already known, the value and potential of organocatalyzed reactions was not recognized until the aforementioned researchers published their seminal works.

List introduced the use of proline as catalyst for the direct asymmetric aldol reaction between acetone and aliphatic aldehydes, thus describing the first example of a non-metallic catalyst (nontoxic, inexpensive, and readily available in both enantiomeric forms) for the direct intermolecular asymmetric aldol reaction (Scheme 1).[23a]



Scheme 1. First organocatalyzed asymmetric aldol reaction.

On the other hand, MacMillan documented a new strategy for the first highly enantioselective amine-catalyzed Diels-Alder reaction, demonstrating that α,β-unsaturated aldehydes and amines can emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis, thereby providing a new platform for the design of organocatalytic processes. Significantly, this analysis reveals the attractive prospect that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metals (Scheme 2).[23b]



Scheme 2. First organocatalyzed Diels-Alder reaction.

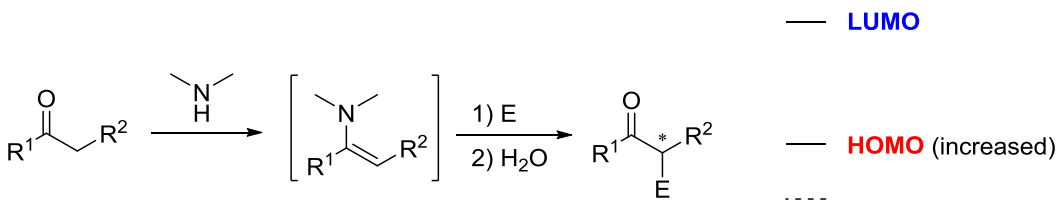
In the field of organocatalysis, usually a noteworthy classification is used, according to the interaction between the catalyst and the substrate.[26] On this basis, two major groups are considered: covalent and non-covalent catalysis.

1.1.1. Covalent catalysis

1.1.1.1. Aminocatalysis

The previous commented studies constituted the basis for the development of aminocatalysis through three novel activation modes under catalytic conditions:[27]

On one hand, the enamine formation rises the HOMO (highest occupied molecular orbital) energy of the system favoring the increment in nucleophilicity of the carbonyl compound (Scheme 3).[28]



Scheme 3. Aminocatalysis via enamine activation.

In 2006, the HOMO-activation concept was extended to the use of α,β-unsaturated aldehydes/ketones,[29] which after condensation with a chiral amine generate dienamine species capable of undergoing stereoselective α or γ-functionalization. In 2011, the HOMO-activation strategy was expanded to trienamines,[30] which are formed upon

[26] a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. For an alternative classification based on the acidic/base reactivity of the catalysts, see: b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724.

[27] For reviews about aminocatalysis, see: a) List, B. *Chem. Commun.* **2006**, 819-824. b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138-6171.

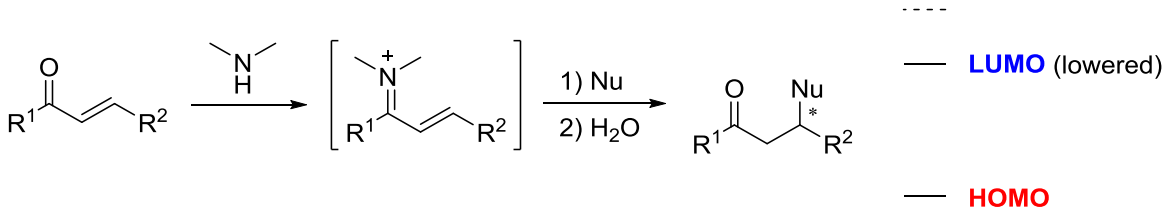
[28] For reviews about catalysis via enamine activation, see: a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001-2011. b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569. c) Pihko, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem.* **2010**, *291*, 29-75.

[29] For the first example of dienamine catalysis, see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973-12980.

[30] For the first example of trienamine catalysis, see: Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053-5061.

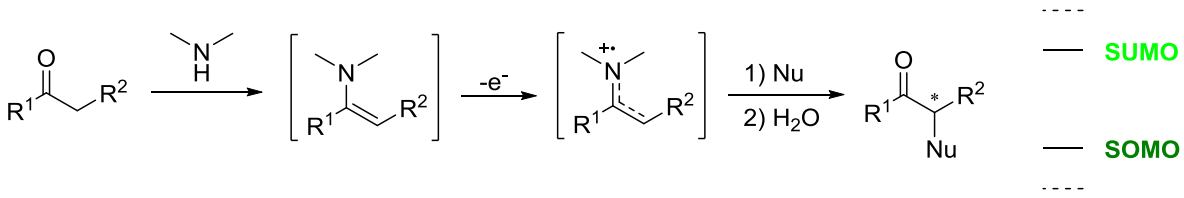
the condensation of an amine catalyst with dienals/dienones, that usually react at β,ε-positions.

On the other hand, the iminium ion formation lowers the LUMO (lowest unoccupied molecular orbital) energy of the system increasing the electrophility of the original carbonyl compound (Scheme 4).[31]



Scheme 4. Aminocatalysis via iminium ion activation.

Finally, the SOMO (singly occupied molecular orbital) activation mode, occurs when the enamine suffers one-electron oxidation rendering a radical cation. Now, this species can participate in the α-functionalization of carbonyl compounds (Scheme 5).[32]

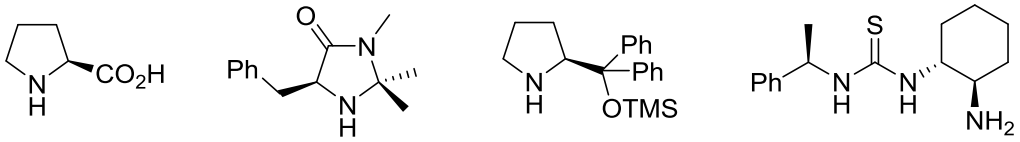


Scheme 5. Aminocatalysis via SOMO activation.

In Figure 3 are shown the most representative catalysts (primary and secondary amines) employed in aminocatalysis.

[31] For reviews about catalysis via iminium ion activation, see: a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica. Acta* **2006**, *39*, 79-87. b) Bartoli, G.; Melchiorre, P. *Synlett*, **2008**, *12*, 1759-1772. c) Brazier, J. B.; Tomkinson, N. C. O. *Top Cur. Chem.* **2010**, *291*, 281-347.

[32] For reviews about catalysis via SOMO-enamine activation, see: a) MacMillan, D. W. C.; Renden, S. *Asymmetric Synthesis II*. p. 87-94 (Eds.: Christmann, M.; Brase, S.), Wiley-VCH, Weinheim, **2012**. b) Mečiarová, M.; Tisovský, P.; Šebesta, R. *New J. Chem.* **2016**, *40*, 4855-4864.



List 2000[23a] **MacMillan** 2000[23b] **Hayashi-Jørgenssen** 2005[33a] **Tsogoeva** 2006[33b]

Figure 3. Pioneering catalysts used in aminocatalysis.[33]

1.1.1.2. Nucleophilic catalysis

Nucleophilic catalysis[34] constitutes an interesting strategy for the generation of new carbon-carbon bonds in an atom-economical mode. Commonly, the catalysts used to mediate this type of reactions contain in their structure a tertiary amine or phosphine[34a-c] (Figure 4a) or an *N*-heterocyclic carbene[34d,e] (Figure 4b) that acts as a nucleophile to trigger the reaction.

[33] a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215. b) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826-832.

[34] For reviews about nucleophilic catalysis, see: a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219-10220. b) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310-1311. c) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681. d) Enders, D.; Kalfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743-1745. e) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654-1655.

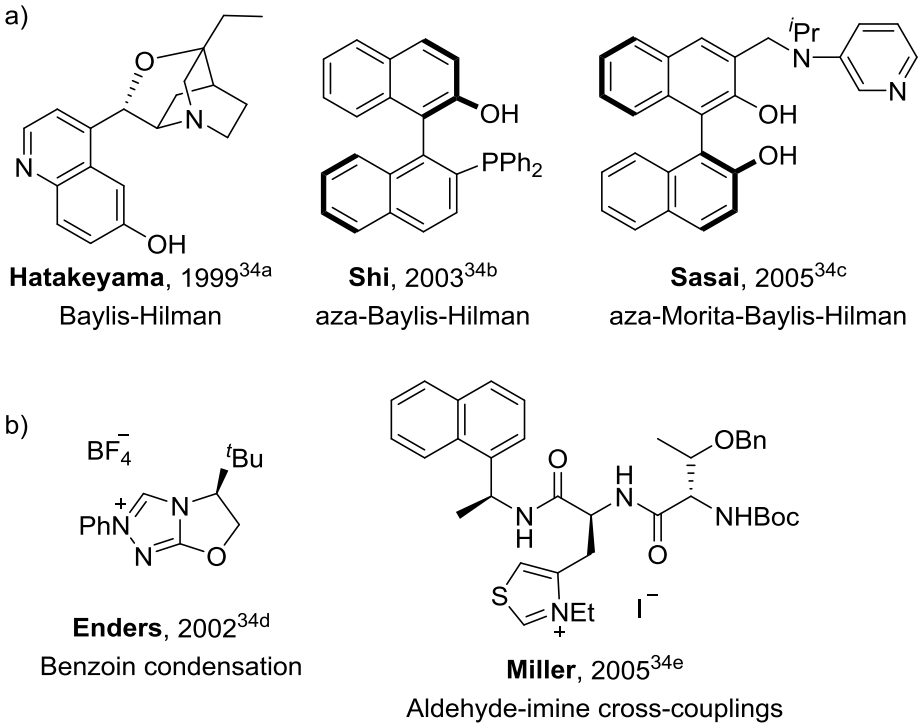
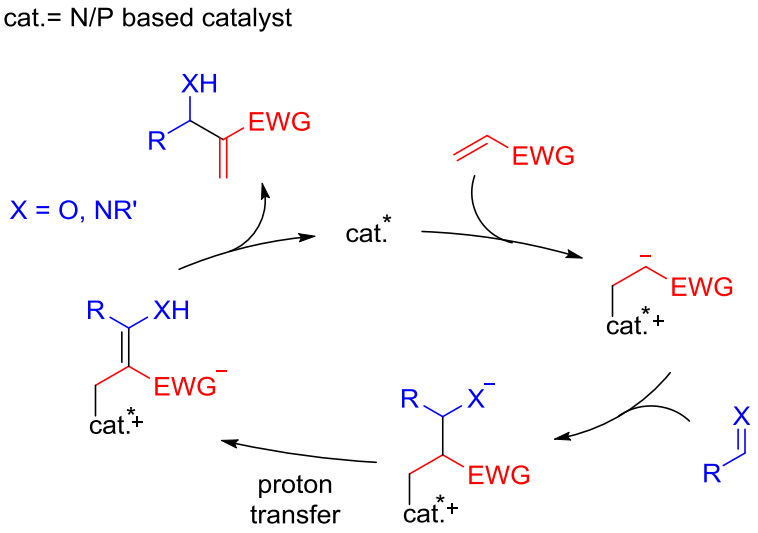


Figure 4. Representative catalysts for nucleophilic catalysis bearing a) tertiary amines or phosphines and b) *N*-heterocyclic carbenes.

The mechanism for the previously mentioned catalysts differs a little from one another although, in general terms, both systems involve the nucleophilic addition to the starting material creating a charged intermediate species with nucleophilic character that reacts with the corresponding reaction partner.

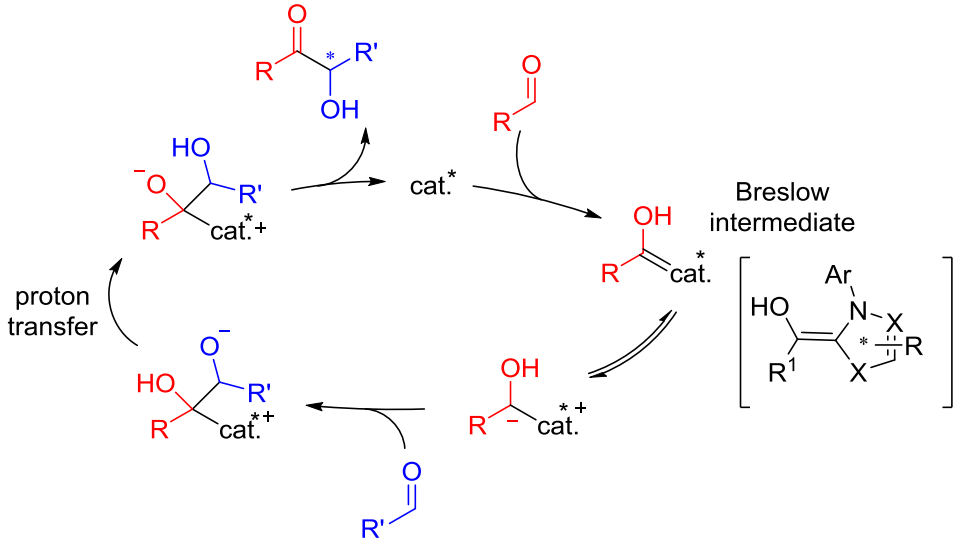
On the one hand, catalysts from the first group of Figure 4 react with α,β-unsaturated substrates to facilitate subsequent aldol or Mannich type reactions (Morita-Baylis-Hillman, MBH),[35] and Michael additions (Rauhut-Currier)[36] through the coupling between the α-position of the activated double bond and an electrophilic carbon (Scheme 6).

[35] For recent reviews about MBH reaction, see: a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659-6690. b) Hu, F.-L.; Shi, M. *Org. Chem. Front.* **2014**, *1*, 587-595. c) Pellissier, H. *Tetrahedron* **2017**, *73*, 2831-2861.
[36] For reviews about Rauhut-Currier reaction, see: a) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069-4084. b) Biswas, S.; Bania, N.; Pan, S. C. *Chem. Rec.* **2023**, e202200257.



Scheme 6. Catalytic cycle for N/P mediated nucleophilic catalysis.

On the other hand, nucleophilic catalysis can be mediated by heterocyclic carbenes[37] that are able to activate carbonylic compounds through the formation of the Breslow intermediate (Scheme 7).



Scheme 7. Catalytic cycle for *N*-heterocyclic carbenes mediated nucleophilic catalysis.

[37] a) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000. b) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522. b) Hopkinson, M. N.; Richter, C. Schedler, M.; Glorius, F. *Nature.* **2014**, *510*, 485-496.

1.1.2. Non-covalent catalysis

There are other catalytic strategies that do not need the catalyst to be covalently bonded to the substrates. The modes in which the catalyst may interact with the substrate through weak interactions, reminding the way enzymes catalyse reactions in biological environments, can be classified into three different categories: phase-transfer catalysis, Brønsted acid- and Brønsted base mediated catalysis.

1.1.2.1. Phase-transfer catalysis

The term "phase-transfer catalysis"[38] was introduced to explain the reaction of substances located at immiscible phases through the formation of an organic chiral ion-paired intermediate, combining the catalyst and the nucleophile (Cat^+ Nu^-). The PTC catalyst must fulfil with several requirements to be an efficient candidate. Its design should be able to generate the corresponding catalyst-substrate ion pair, be stable in basic conditions and possess the adequate solubility in the reaction medium.[39] Following these design patterns, several organocatalysts have been described (Figure 5).

[38] For general reviews about PTC, see: a) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312-4348. b) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367-5376. c) Patel, N.; Sood, R.; Bharatam, P. V. *Chem. Rev.* **2018**, *118*, 8770-8785.
[39] Satrio, J. A. B.; Doraiswamy, L. K. *Chem. Eng. J.* **2001**, *82*, 43-56.

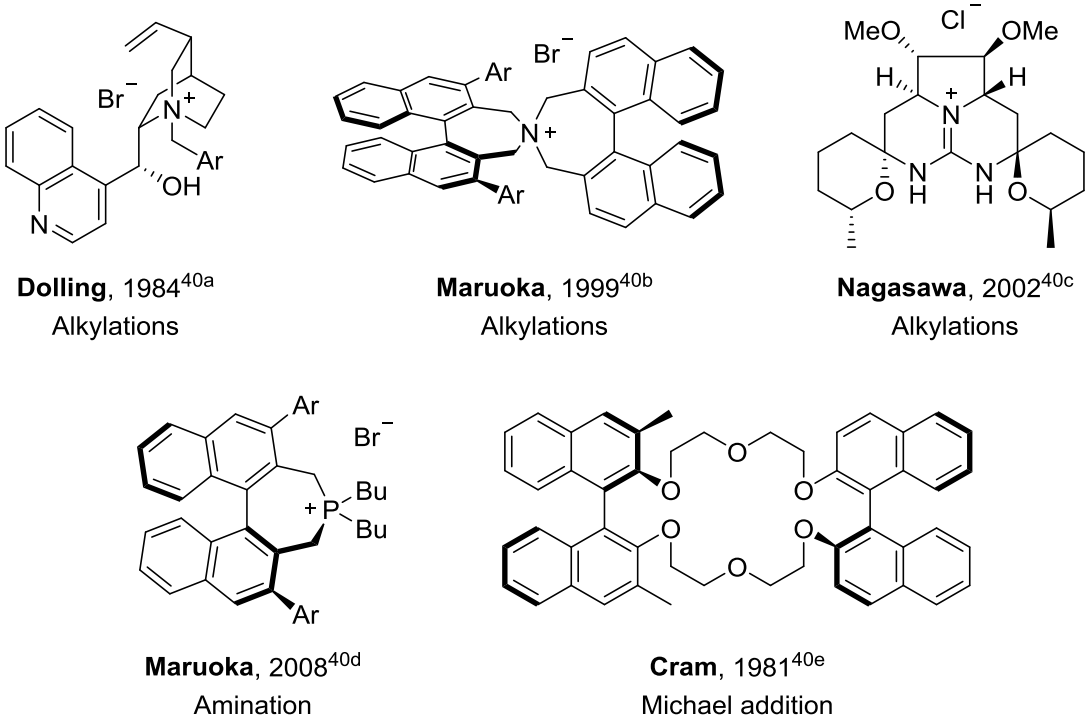
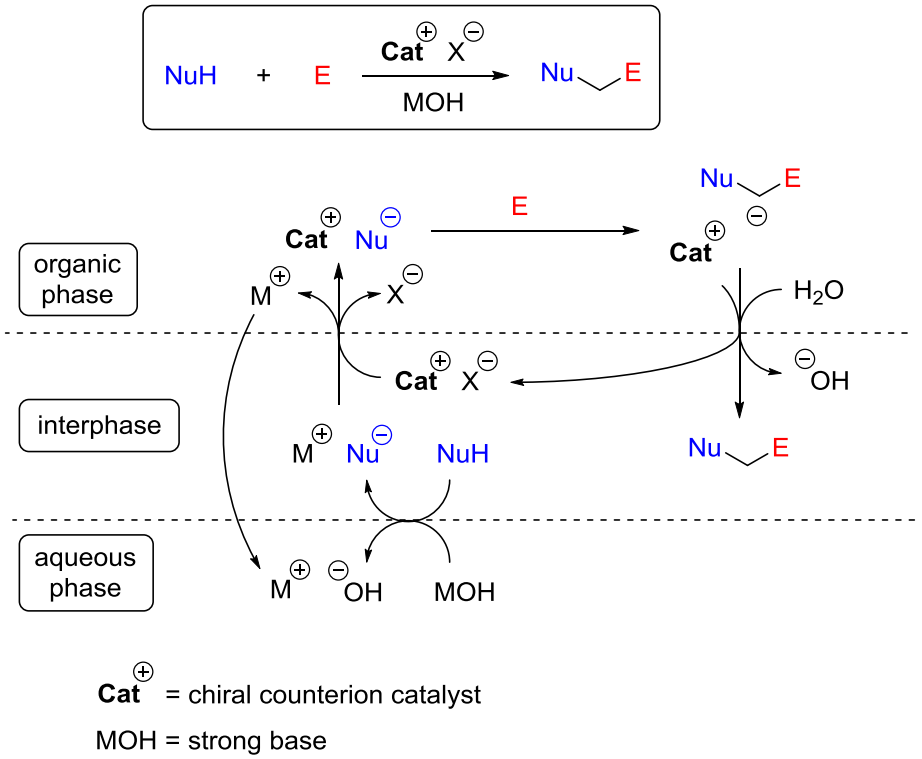


Figure 5. Representative catalysts used in PTC.[40]

The first step of a reaction under PTC conditions consists on the deprotonation of the nucleophile generally using aqueous metal hydroxides or carbonates. The nucleophile generated in the interphase suffers cation exchange with the chiral PTC catalyst to generate the more soluble chiral nucleophile ion-pair responsible of the stereochemical outcome of the reaction (Scheme 8).

[40] a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446-447. b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520. c) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2832-2834. d) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 9466-9468. e) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625-628.



Scheme 8. General mechanism of chiral PTC.

1.1.2.2. Brønsted acid catalysis

Chiral Brønsted acids can be classified into two subgroups: neutral acids, which are also called *H*-bonding catalysts; and stronger acids, generally referred to them as Brønsted acids.

Hydrogen-bonding catalysis[41] has emerged as a powerful tool for the enantioselective synthesis, relying on the use of small molecules bearing hydrogen-bond donor motifs in their structure. The activation mode is similar to the mechanism with metal Lewis acid catalysts, where the activation energy is lowered (the metal accepts electronic density) (Figure 6).

[41] For general reviews on *H*-bonding catalysis, see: a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743. b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516-532. c) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187-1198. d) Pihko, P. M. *Hydrogen Bonding in Organic Synthesis*, **2009**, Wiley-VCH, Weinheim, Germany. e) Sohtome, Y.; Nagasawa, K. *Synlett* **2010**, *1*, 1-22. f) Nishikawa, Y. *Tetrahedron Lett.* **2018**, *59*, 216-223.

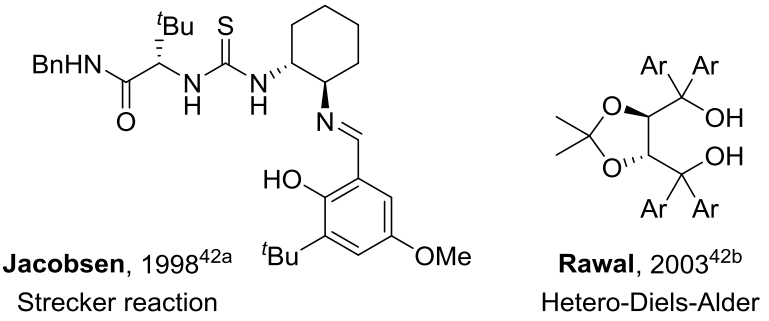


Figure 6. Pioneering catalysts used in *H*-bond catalysis.[42]

Brønsted acid catalysis[43] represents another important branch of asymmetric catalysis and the prototype, which chemists have been using as reference for the design of new catalysts, is BINOL-derived phosphoric acid introduced by Akiyama[44] and Terada[45] independently in 2004 (Figure 7). The bifunctional character of the catalyst displaying Lewis base and Brønsted acid activity at the same time enables the dual activation of the nucleophile and the electrophile. The axial chirality of the catalyst is usually transferred to the products as central chirality with high efficiency. [46]

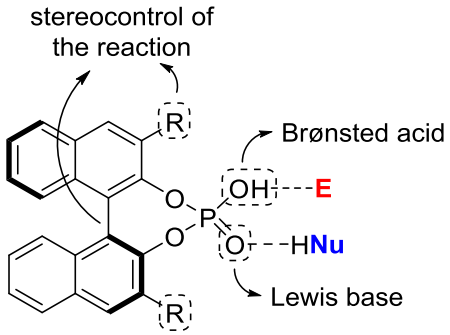


Figure 7. General aspects and activation mode of chiral phosphoric acids.

[42] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. b) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

[43] For general reviews about Brønsted acid catalysis, see: a) Cheon, C. H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043-3056. b) Greindl, J.; Hioe, J.; Sorgenfrei, N.; Morana, F.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 15965-15971. c) Min, C.; Seidel, D. *Chem. Soc. Rev.* **2017**, *46*, 5889-5902. d) Mitra, R.; Niemeyer, J. *ChemCatChem* **2018**, *10*, 1221-1234. e) Merad, J.; Lalli, C.; Bernadat, G.; Maury, J.; Masson, G. *Chem. Eur. J.* **2018**, *24*, 3925-3943.

[44] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568.

[45] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.

[46] For a review about computational studies on Brønsted acid catalysis, see: Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142-1158.

1.1.2.3. Brønsted base catalysis

Chiral Brønsted bases are a type of organocatalysts that promote the reaction via non-covalent interactions with the substrates.[47] According to the IUPAC, a Brønsted base (BB) can be defined as a molecular entity capable of accepting hydron (or proton) from an acid or the corresponding chemical species. From the perspective of organic transformations, proton transfer is often considered a key activation step of one of the reaction components that precedes the new bond creation in the coupling of reactants through the formation of a chiral ionic pair (Figure 8).

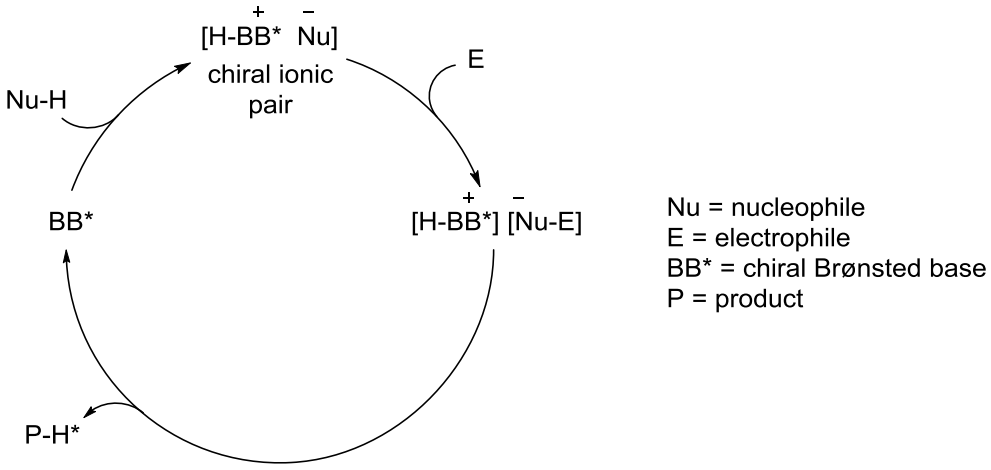


Figure 8. Catalytic cycle promoted by Brønsted bases.

Nitrogen-containing functionalities have been usually employed for the design and development of chiral BB catalysts, such as tertiary amines, guadinines,[48] amidines and imidazoles[49] (Figure 9).

[47] For reviews on organocatalytic reactions promoted by chiral Brønsted bases, see: a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985-3012. b) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570-5595. c) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632-653. d) Ting, A.; Gross, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem.* **2010**, *291*, 145-200. e) Maruoka, K. *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics: Science of Synthesis*; Thieme: Stuttgart, **2012**. f) Ting, A.; Schaus, S. E. *Chapter 13: Brønsted Bases*, **2013**, 343-363, Weinheim, Wiley-VCH. g) Teng, B.; Lim, W. C.; Tan, C.-H. *Synlett*, **2017**, *28*, 1272-1277.

[48] For reviews on guanidines in asymmetric synthesis, see: a) Ishikawa, T.; Isobe, T. *Chem. Eur. J.* **2002**, *8*, 553-557. b) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737-752. c) Leow, D.; Tan, C.-H. *Chem. Asian J.* **2009**, *4*, 488-507.

[49] For a review on imidazole catalysts in asymmetric synthesis, see: Zhang, Z.; Xie, F.; Jia, j.; Zhang, W. *J. Am. Chem. Soc.* **2010**, *132*, 15939-15941.

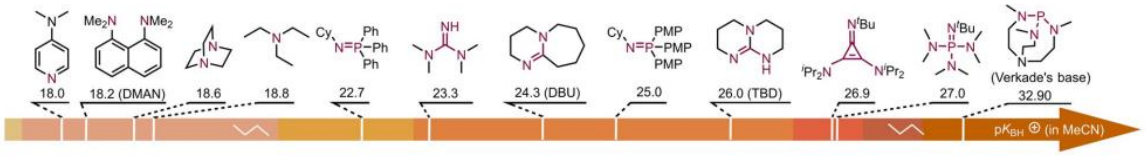


Figure 9. The basicity (pKBH + values in MeCN) of organobases,

As a result of the non-directional nature of the electrostatic interactions of the formed ionic complexes, it is difficult to predict the stereochemical course of the BB-catalyzed reactions. With the purpose to solve this issue, hydrogen-bond donor sites are included into the catalysts structure that would allow activating simultaneously both the pronucleophile and the electrophile in a more rigid transition state and, consequently, higher stereochemical results can be obtained (Figure 10).[50]

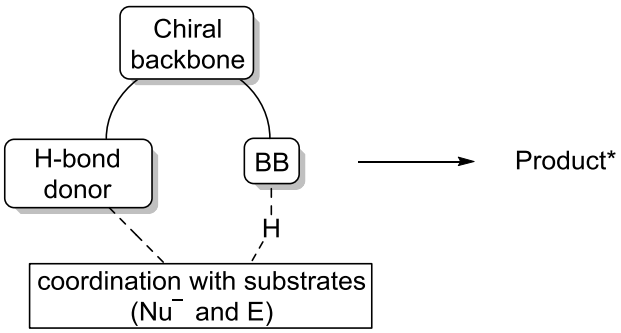


Figure 10. Activation mode of a bifunctional Brønsted base/H-donor catalyst.

A bifunctional organocatalyst follows a general structure design consisting on a modular functional H-bond donor moiety such as thiourea, urea, squaramide or sulfonamide attached to an amine (BB) that deprotonates de pronucleophile providing another anchoring point. Furthermore, a high-density substituent (R), such as CF_3 bearing aromatic rings, is usually present in the molecule to increase the acidity of the N-H groups (Figure 11a).

[50] Odagi, M.; Nagasawa, K. *Asian J. Org. Chem.* **2019**, *8*, 1766-1774.

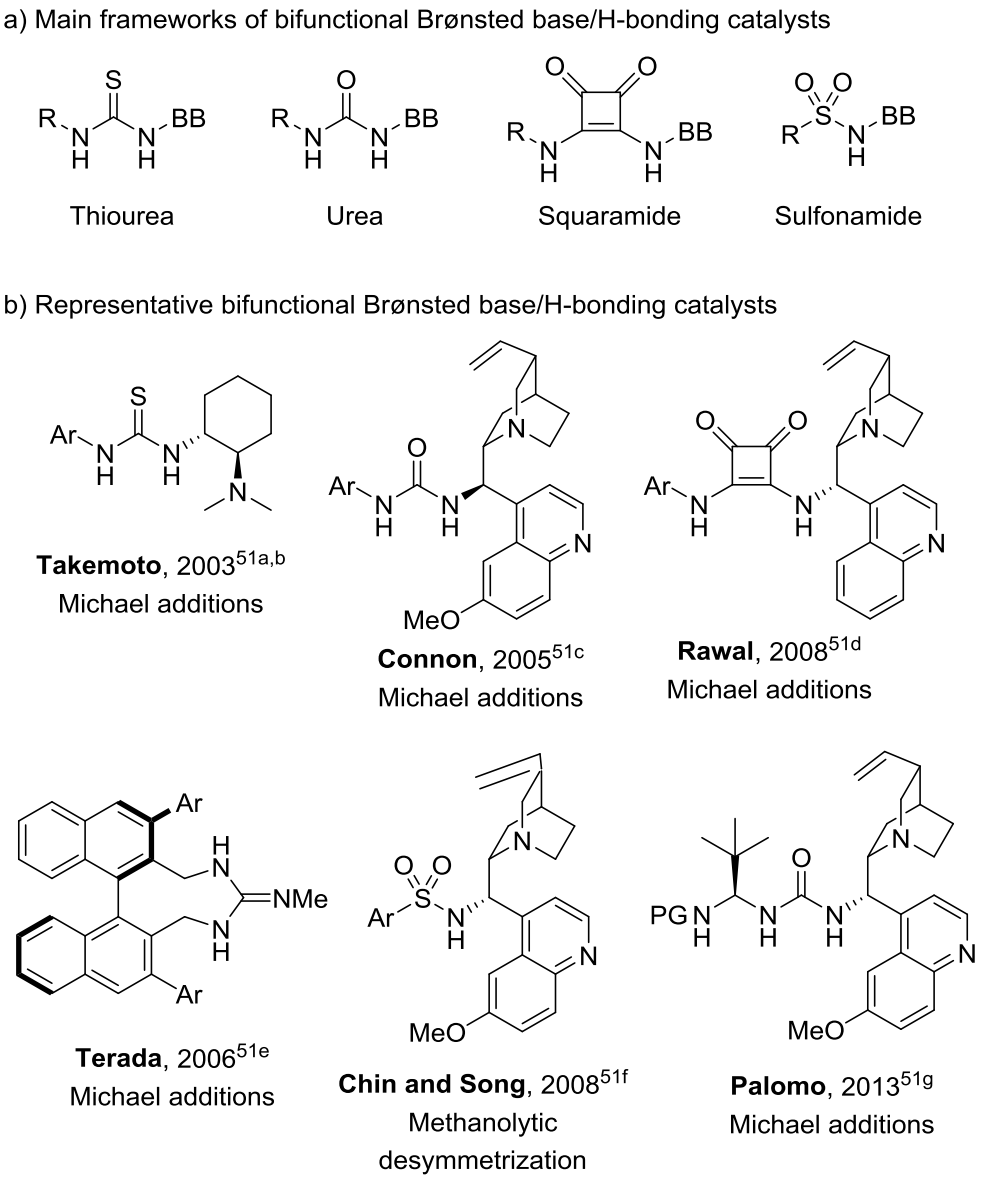


Figure 11. Structural features and representative examples of Brønsted base/H-bonding catalyst.[51]

The mechanism of bifunctional Brønsted base/H-bonding catalyzed Michael additions has been the subject of many studies since it was described for the first time by Takemoto in 2005.[53a,b] For the thiourea-catalyzed Michael addition of malonates to nitroalkenes, the authors proposed a mechanism (based on ^{1}H-NMR studies) that still remains unclear; it implies a trimolecular transition state complex where the nucleophile

[51] a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673. b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119-125. c) Mccooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed* **2005**, *44*, 6367–6370. d) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. f) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 7872-7875. g) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

is activated by deprotonation while the thiourea moiety activates the electrophile (Figure 12).

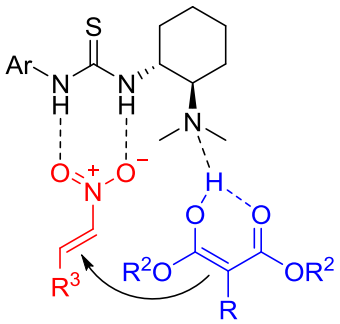


Figure 12. Transition state proposed by Takemotao for the enantioselctive Michael addition of malonates to nitroalkenes.

Later, Pápai,[52] Zhong[53] and Wang[54] contributed with their own proposals for analogous Michael reactions. Having in mind that slight modifications in the structure of the catalyst and the substrates could affect the reaction pathway, a general proposal is difficult to maintain. As a consequence, studies for particular transformation may provide dissimilar mechanisms.

More recently, organic compounds that incorporate metal elements, which do not interact directly with the substrate in the catalytic process,[55] have emerged as a new promising approach in asymmetric catalysis. In these chiral systems, nicknamed "organocatalysts in disguise",[56] where the central metal atom serves as structural anchorpoint and provides metal centrochirality, catalysis is mediated through the organic ligand sphere. Remarkably, this type of catalysts are air stable and compatible with non-inert atmosphere and the presence of water (Figure 13).[57]

[52] Hamza, A.; Schubert, G.; Soós, t.; Papai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.
[53] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682–2685.
[54] Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813–9825.
[55] For reviews about organocatalysts with metal centers, see: a) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. *Acc. Chem. Res.* **2014**, *47*, 2365-2377. b) Gong, L.; Chen, L.-A.; Meggers, E. *Angew. Chem. Int. Ed.* **2014**, *53*, 10868-10874.
[56] Larionov, V. A.; Feringa, B. L.; Belokon, Y. N. *Chem. Soc. Rev.* **2021**, *50*, 9715–9740.
[57] Ma, J.; Ding, X.; Hu, Y.; Huang, Y.; Gong, L.; Meggers, E. *Nat. Commun.* **2014**, *5*, 5531-5536.

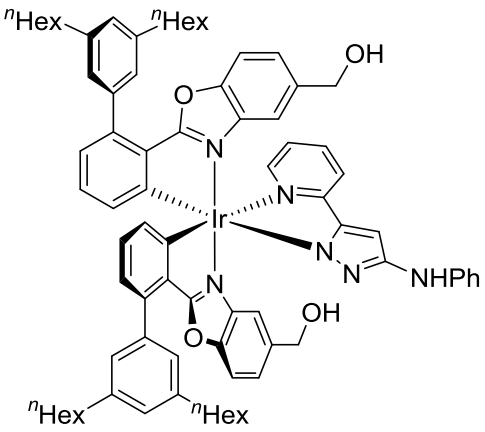
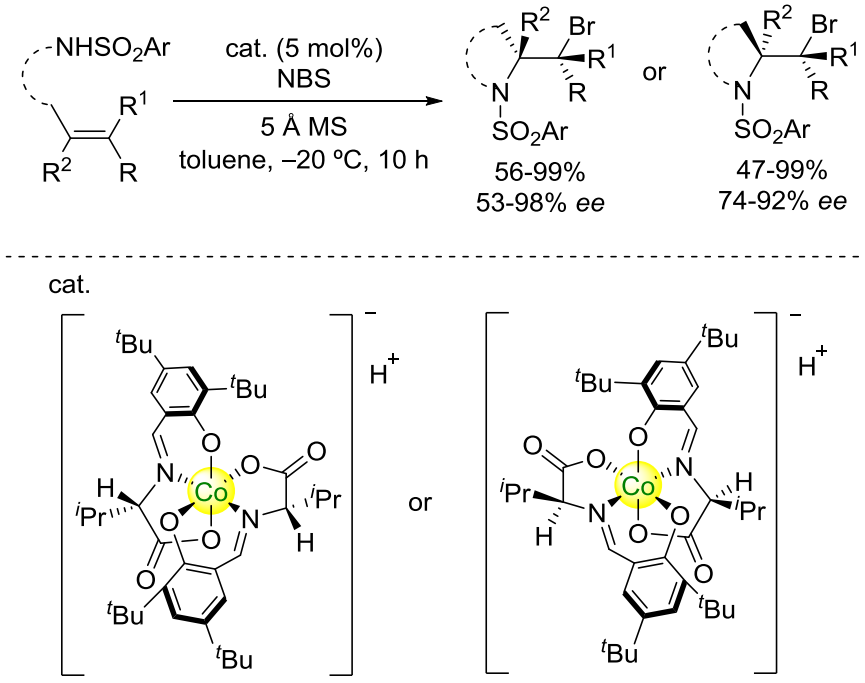


Figure 13. Chiral only-at-metal iridium(III) complex as bifunctional Brønsted base/hydrogen bond donor organocatalyst.

As a representative example, in 2017 the groups of Yu and Gong validated the use Brønsted acids of anionic chiral Co^{III} complexes as bifunctional phase-transfer catalysts (Scheme 9).[58] The diastereomeric chiral Co^{III}-templated Brønsted acids enabled a switch in the enantioselective bromoaminocyclization of olefins to afford the two enantiomers of the 2-substituted pyrrolidines with high stereoselectivities.



Scheme 9. Bromoaminocyclization with chiral cobalt(III) complex.

[58] Jiang, H.-J.; Liu, K.; Yu, J.; Zhang, L.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 11931-11935.

Although countless asymmetric procedures have been developed over the last decades for their application in the synthesis of new drug candidates, all of them are usually very specific and limited to a small group of molecules. The need to identify new and more general ones is becoming increasingly urgent. To complete this task, several strategies for the synthesis of bioactive compounds have been developed that also include organocatalytic methodologies, which are explained in the following sections with some distinctive examples.

1.2. Strategies for the synthesis of bioactive compounds

Drug design is aiming to invent and develop novel biologically active molecules in therapeutic areas. All known theoretical and experimental knowledge of the physiological targets is applied for developing such potential, but the synthesis of new bioactive compounds and drug scaffolds requires competitive strategies to access the entire chemical space. Overtaking classical total synthesis, which needs long reaction sequences and is focused in particular targets,[59] several fresh strategies have gained the attention of the chemical community owing to the easier and faster synthesis of collections based on natural products (NPs). Among them, *complexity to diversity*, *biology oriented synthesis* and *diversity oriented synthesis* come to the flare and are briefly summarized next.

1.2.1. Complexity to diversity methodology (CtD)

In the early 1990s, the advent of the high-throughput screening (HTS) boosted the production of large collections of low molecular weight compounds with high sp^2 character but soon the drug discovery industry found out that these planar compounds, lacking three-dimensionality and moderate functional diversity, did not always match the target drug structures specifically and, in consecuence, provoked secondary effects.[60] The

[59] Wessjohann, L. A.; Ruijter, E. *Natural Product Synthesis I* **2005**, Springer, Heidelberg.
[60] a) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565-8566. b) O'Shea, R.; Moser, H. E. *J. Med. Chem.* **2008**, *51*, 2871-2878. c) Silver, L. L. *Clin. Microbiol. Rev.* **2011**, *24*, 71-109. d) Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nat. Rev. Drug Discov.* **2007**, *6*, 29-40.

approach termed complexity-to-diversity (CtD)[61] is focused on the creation of structurally diverse compound libraries, populated by complex molecules through the manipulation of existing ring systems in readily available NPs. The chemical transformations, ring distortion reactions, directly alter the composition of the core ring and cause three-dimensionality (Figure 14).

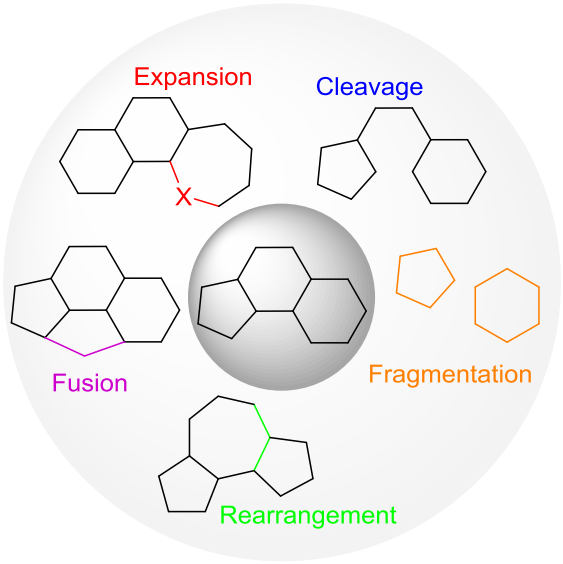
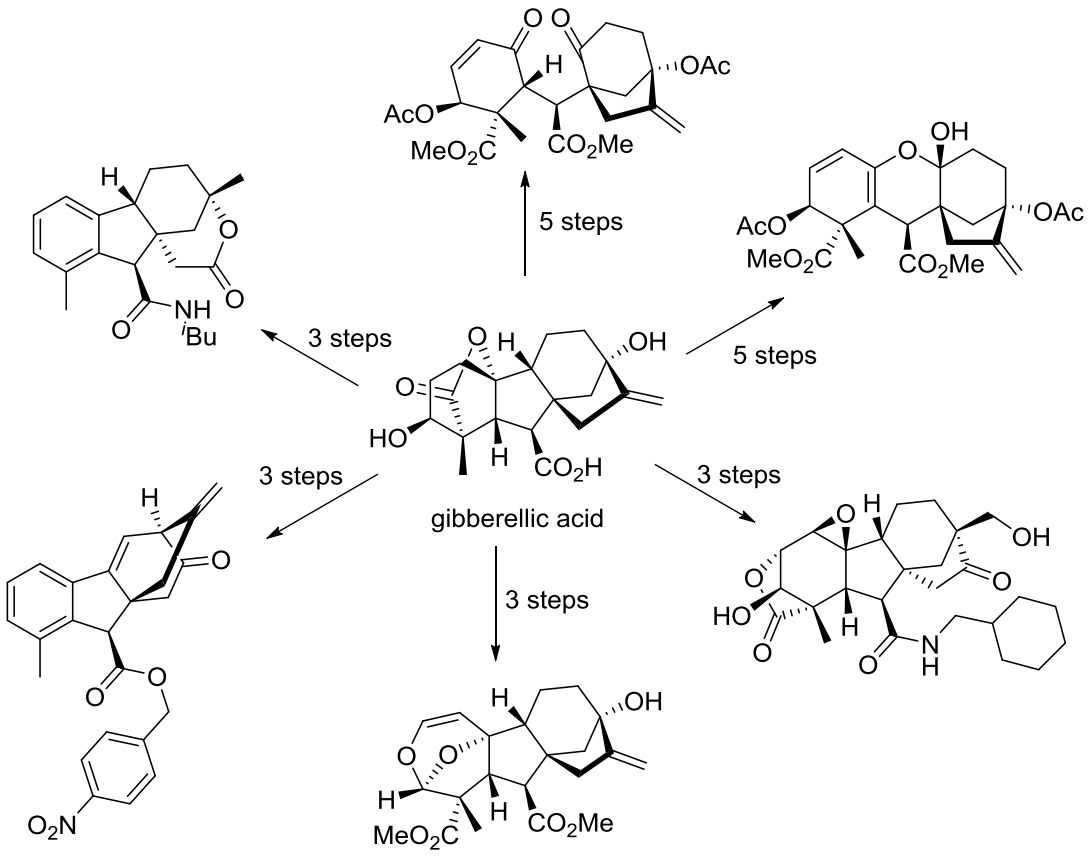


Figure 14. Ring distortion approaches for the synthesis of natural product derived libraries.

For instance, in 2013 Hergenrother and co-workers demonstrated the potential of gibberellic acid to enable several divergent transformations all across the ring system validating the use of this strategy for the synthesis of complex and diverse compounds (Scheme 10).[62]

[61] a) Rafferty, R. J.; Hicklin, R. W.; Maloof, K. A.; Hergenrother, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 220-224. b) Ciardiello, J. J.; Stewart, H. L.; Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. *Bioorg. Med. Chem.* **2017**, *25*, 2825-2843. c) Silva, D. G.; Emery, F. S. *Braz. J. Pharm. Sci.* **2018**, *54*, e01004. d) Srinivasulu, V.; Srikanth, G.; Khanfar, M. A.; Abu-Yousef, I. A.; Majdalawieh, A. F.; Mazitschek, R.; Setty, S. C.; Sebastian, A.; Al-Tel, T. H. *J. Org. Chem.* **2022**, *87*, 1377-1397.

[62] Huigens III, R. W.; Morrison, K. C.; Hicklin, R. W.; Flood Jr.; T. A.; Richter, M. F.; Hergenrother, P. J. *Nature Chem.* **2013**, *5*, 195-202.



Scheme 10. Transformation of gibberellic acid using the CtD methodology.

1.2.2. Biology Oriented Synthesis (BIOS)

The challenge of identifying a suitable compound class for the specific perturbation of one particular protein function is fundamental for the study of biological systems. The chemical space is very large and is unfeasible to investigate all the druglike population; one of the most followed procedures to complete this task regards the protein-ligand binding processes and the resulting biological activities for the development, growth and sustainability of the living systems.

The approach termed "biology oriented synthesis" is based on the structural similarity of bioactive molecules that may retain the chemical and biological characteristics of NPs and the receptors (usually proteins), and how they complement each other during the interaction.[63] Thus, new collections of NP-inspired compounds with

[63] a) Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. *Cell. Mol. Life Sci.* **2008**, *65*, 1186-1201. b) Waldmann, H. *Drugs Future* **2009**, *34*, 24-25. c) Wilk, W.; Zimmermann, T. J.; Kaiser, M.; Waldmann, H. *Biol. Chem.* **2010**, *391*, 491-497.

diverse substitution patterns around a common core scaffold can be described using the fragment-based compound desing (Figure 15).[64]

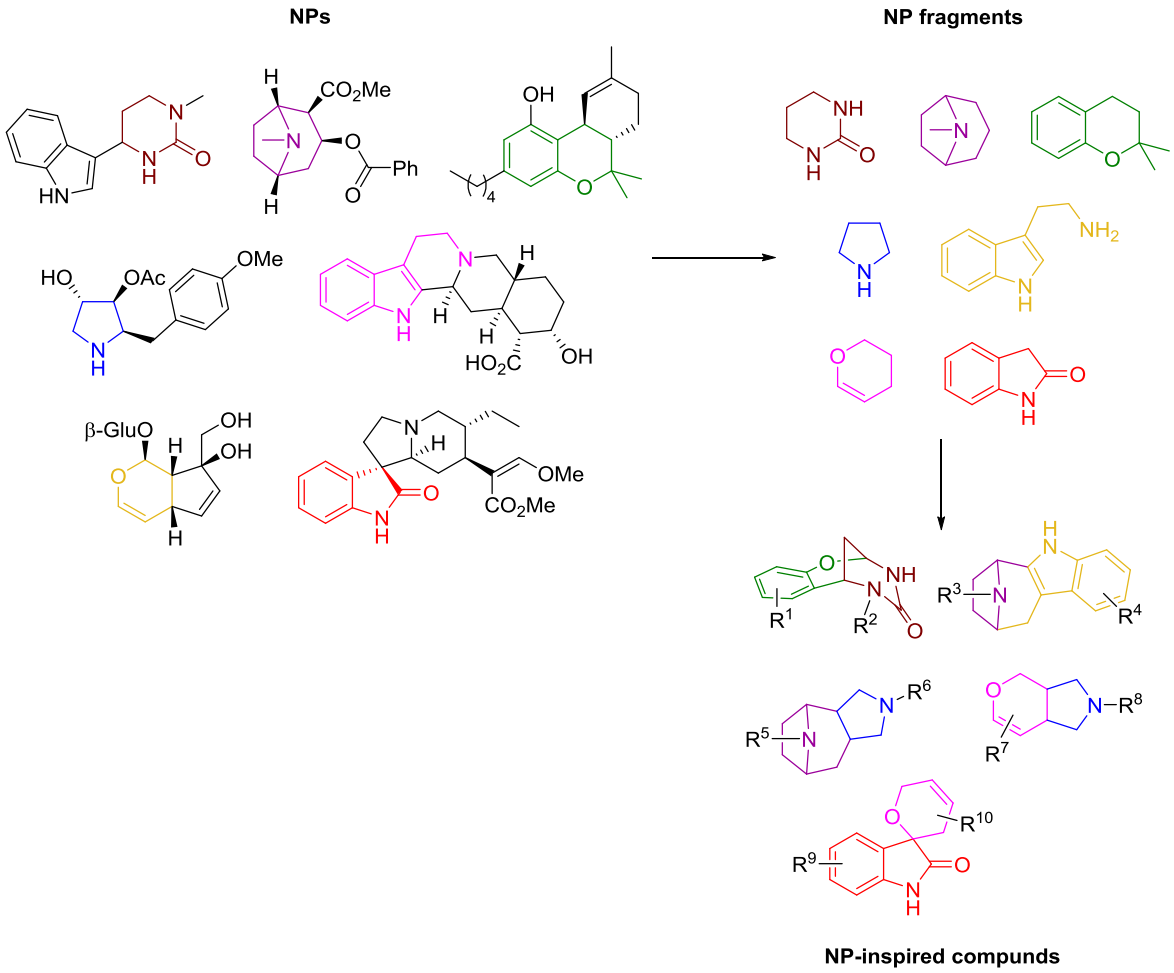


Figure 15. New approach for the design of biologically relevant compound collections.

The use of the BIOS methodology requires chemoinformatic analysis specially developed to chart the chemical space covered by NPs and their scaffold structures.[65] With that purpose, all known NPs were encoded in the Dictionary of Natural Products (DNP) database and classified, by reducing their structures to the simplest building blocks, in a hierarchical way in a tree analysis; the Structural Classification of Natural Products (SCONP). The organization of the scaffolds in charts allows navigating the chemical space in three sectors: *O*-heterocycles, carbocycles and *N*-heterocycles (Figure 16).[66]

[64] Erlanson, D. A.; Fesik, S. W.; Hubbard, R. E.; Jahnke, W.; Jhoti, H. *Nat. Rev. Drug Discov.* **2016**, *15*, 605-619.
[65] Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P. Waldmann, H. *Proc. Natl. acad. Sci. U.S.A.* **2005**, *102*, 17272-17277.
[66] a) Hattum, H.; Waldmann, H. *J. Am. Chem. Soc.* **2014**, *136*, 11853-11859.

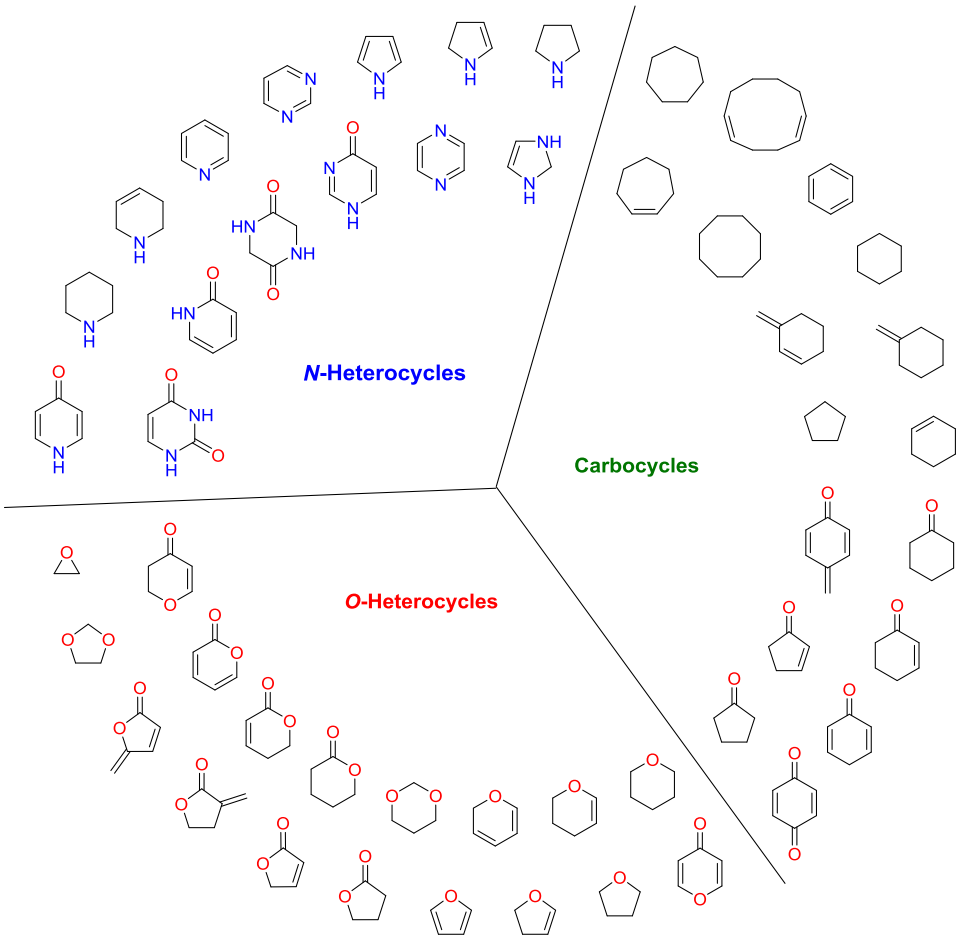


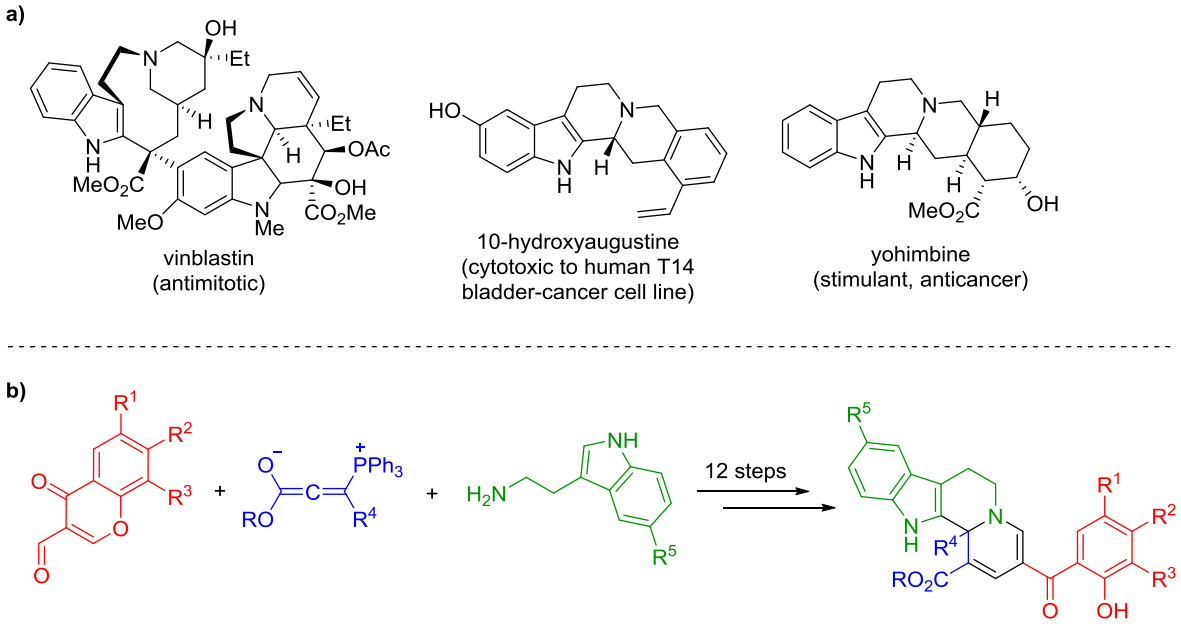
Figure 16. Tree-like graphical representation of natural product scaffolds.

The complementation between a small molecule and a protein through the binding site is crucial for desired results of a ligand-protein interaction. The three-dimensional backbone framework of this complex in the ligand-sensing binding site of the protein will determine the arrangement of interaction points in space. The similarities of the protein pockets make possible to group them in the Protein Structure Similarity Clustering (PSSC).[67] Combining both, SCONP and PSSC, provides new opportunities for the development of synthetic ways to obtain product libraries.

As an example, Waldmann and co-workers reported a cascade reaction of unprecedented length and efficiency, giving access to a structurally complex natural

[67] Kumar, K.; Wetzel, S.; Waldmann, H. Biology Oriented Synthesis and Diversity Oriented Synthesis in Compound Collection Development. In *The Practice of Medicinal Chemistry*; 3rd Ed. Academic Press, **2008**; 187–209.

product-inspired polycyclic compound collection starting from simple starting materials in a 12-step cascade reaction (Scheme 11).[68]



Scheme 11. a) Source of inspiration for indoloquinolizine compound collection. b) Cascade reaction for the natural product-inspired modulators of centrosome integrity.

1.2.3. Diversity oriented synthesis (DOS)

Traditionally, to generate a new target molecule in a linear and convergent way, the retrosynthetic plan makes use of the structure of known natural ligands; this method is called target-oriented synthesis.[69] However, when the intention is to synthesize a library of products the need of a different process is evident. DOS can give a solution to this issue transforming simple precursors to generate a library of complex molecular scaffolds with skeletal and stereochemical diversity (Figure 17).

[68] Dückert, H.; Pries, V.; Khedkar, V.; Menninger, S.; Bruss, H.; Bird, A. W.; Maliga, Z.; Brockmeyer, A.; Janning, P.; Hyman, A.; Grimme, S.; Schürmann, M.; Preut, H.; Hübel, K.; Ziegler, S.; Kumar, K.; Waldmann, H. *Nat. Chem. Biol.* **2012**, *8*, 179-184.

[69] a) Galloway, W. R. J. D.; Bender, A.; Welch, M.; Spring, D. R. *Chem. Commun.* **2009**, 2446-2462. b) Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobel, A.; Spring, D. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1194-1196.

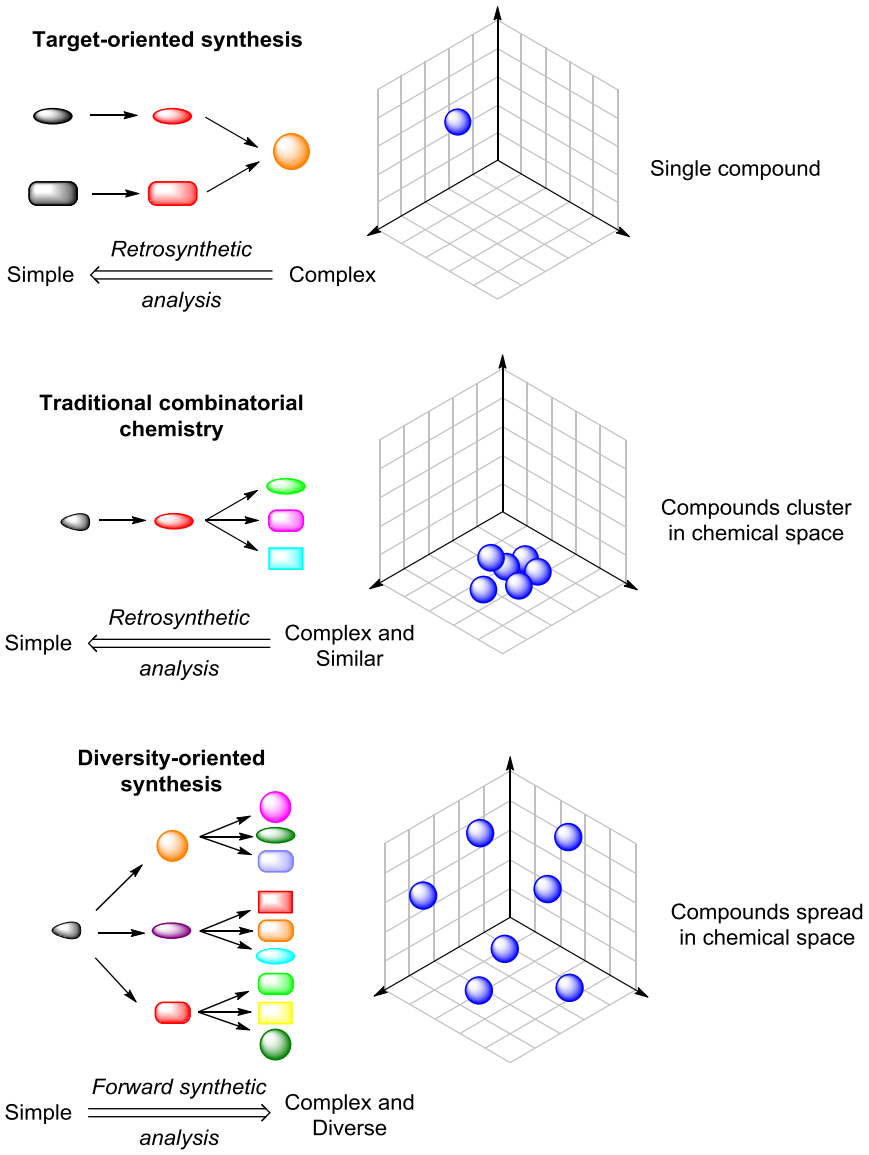


Figure 17. Comparison of synthetic strategies.[70]

The foundation of the "Diversity oriented synthesis" was underpinned by several technologies. The principal basis for DOS is solid-phase peptide synthesis, thanks to the facile purification of the desired products from the reagents and unwanted byproducts formed.[71] The other pillar is combinatorial synthesis which enables systematic mixing and matching of different building blocks.[72] From a qualitative point of view, "diversity" can be considered a spectrum that ranges from a TOS of a specific molecule to the synthesis

[70] Spandl, R. J.; Diáz-Gavilán, M.; O'Connell, K. M. G.; Thomas, G. L.; Spring, D. R. *Chem. Rec.* **2008**, *8*, 129-142

[71] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[72] a) Chen, J. K.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 953-969. b) Liu, D. R.; Schultz, P. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 37-54.

of all possible molecular entities covering the total chemical space. A combinatorial approach and a DOS will produce collections between the two extremes (Figure 18).[73]

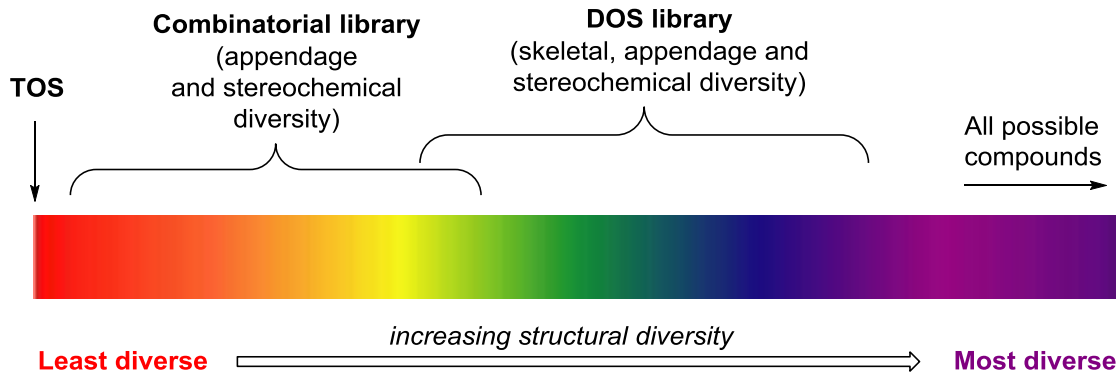


Figure 18. Molecular diversity spectrum.

In a DOS context, there are two mayor ways to obtain diversity: the reagent-based approach, using a common starting material and different reagents achieving the transformation of the target functional group and producing a collection of compounds with diverse skeletons; and the substrate-based approach, using different pre-encoded starting materials under the same reaction conditions (Figure 19).[74]

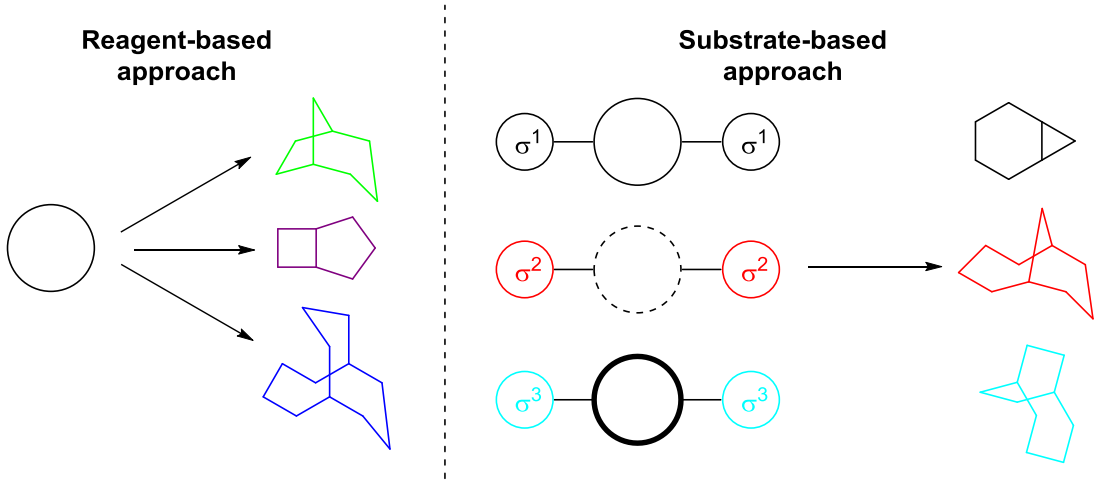


Figure 19. DOS approaches to scaffold diversity.

[73] a) Galloway, W. R. J. D.; Spring, D. R. *Expert Opin. Drug Discov.* **2009**, *4*, 467-472. b) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149-1158.
[74] Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613-618.

Another strategy, that can be classified in either one or another approach, is the build/couple/pair (B/C/P). First, the build phase affords the chiral building blocks with various functional groups that will be transformed in the next steps. Second, during the couple phase previously obtained scaffolds are joined performing intermolecular coupling reactions providing the basis for stereochemical diversity. And finally, the pair phase consist of intramolecular coupling reactions to join pairwise functional groups providing the basis for skeletal diversity (Figure 20).[75]

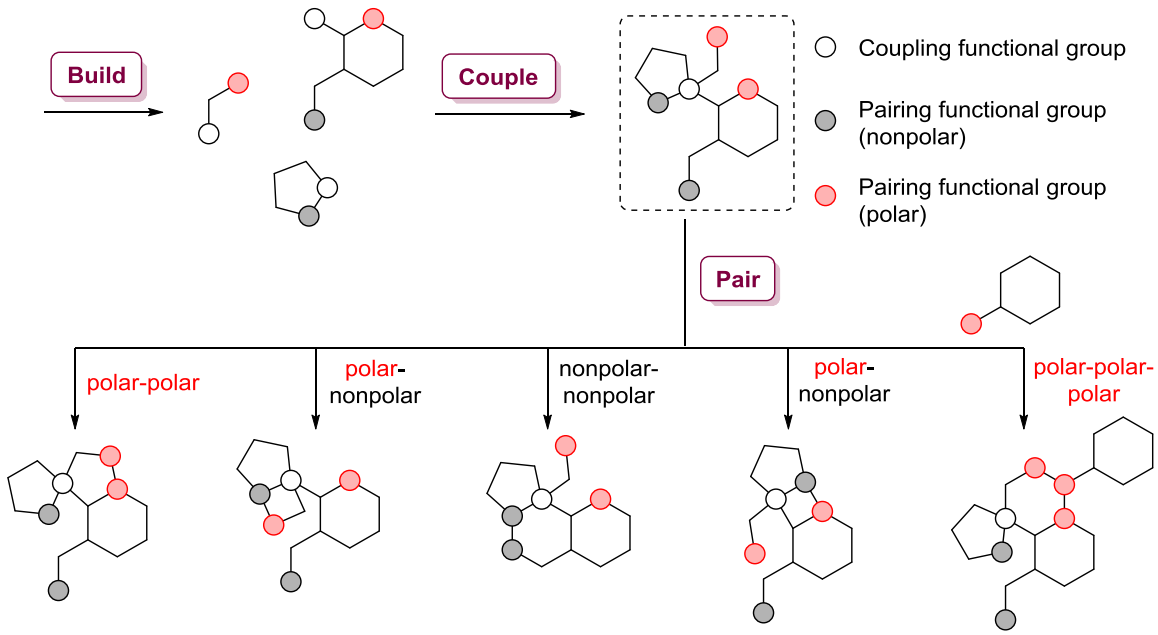


Figure 20. Generation of skeletal diversity with build/couple/pair strategy.

Since these novel NP-inspired templates would not be achievable by biosynthetic methods, they will receive the name of "pseudo-natural products" and they will provide access to unexplored areas of chemical space.[76]

Another feature to take into account is the descriptors of drug-likeness. Lipinski's Rule of Five (Ro5) continue to be a guiding principle for the design of drugs.[77] Nevertheless, after Ro5 other descriptors have been developed. Among them, the fraction of sp^3 hybridized carbon atoms, Fsp^3 (the number of sp^3 carbons/total carbon count), used to determine the carbon saturation of molecules and categorizes their spatial

[75] Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 48-56.
[76] Karageorgis, G.; Foley, D. J.; Laraia, L.; Waldmann, H. *Nat. chem.* **2020**, *12*, 227-235.
[77] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3-26.

structure. This factor demonstrates that as the saturation of a compound increases along with the total amount of present chiral centers, the clinical success rate goes up, too. The increased solubility and affinity for three-dimensional target proteins being the reason of the increment.[78]

1.3. Heterocycles and quaternary stereocenters

As mentioned in the previous sections, natural products have been explored and remain to be the main source of inspiration for the synthesis of new bioactive compounds and drug design.[79] It is known that the presence of heteroatoms in molecules brings new synthetic and biological values, mainly due to their strong coordination and adsorption properties.

Many of these bioactive molecules have heterocycles in their structure with the heteroatom attached to an α-C(sp^3) quaternary position of a carbonyl moiety (Figure 21). In the synthesis of these compounds, a mayor challenge, and one of the most attractive from a synthetic perspective, is the formation of quaternary stereocenters.[80] In addition to reactivity issues, caused by the steric repulsion between the substituents in a tertiary carbon, the usual need of harsh reaction conditions adds more difficulty to this ambitious task. For this reason, the design and development of new strategies for the generation of this heterocyclic scaffolds is of crucial interest.

[78] a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756. b) Wei, W.; Cherukupalli, S.; Jing, L.; Liu, X.; Zhang, P. *Drug Discov. Today* **2020**, *25*, 1839-1845.
[79] a) Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284-289. b) Koehn, F. E.; Carter, G. T. *Nature Rev. Drug Discov.* **2005**, *4*, 206-220.
[80] a) Bella, M.; Gasperi, T. *Synthesis.* **2009**, *10*, 1583-1614. b) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181-191. c) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740-751.

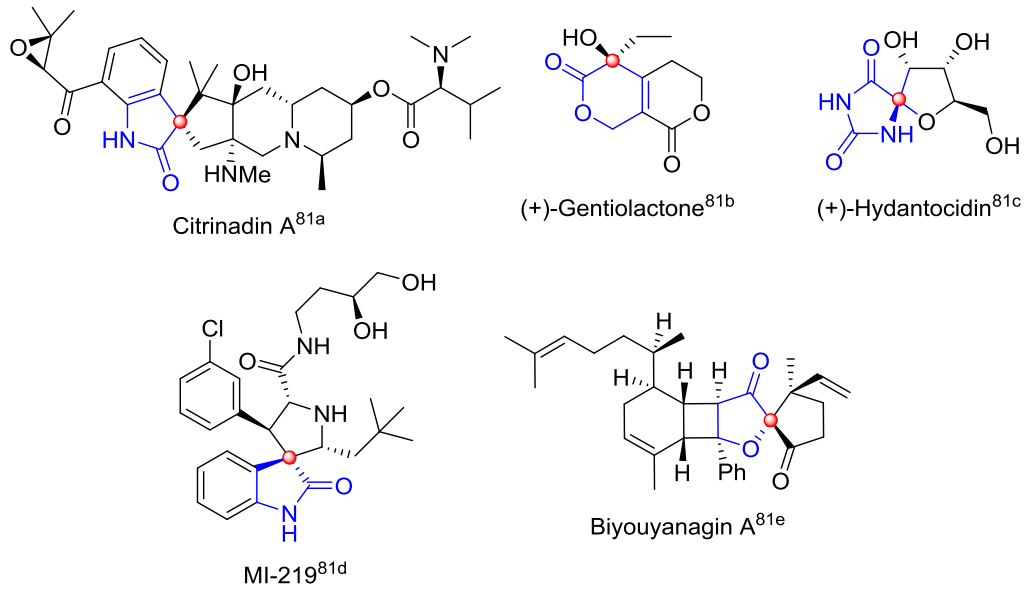


Figure 21. Selected examples of natural products with tetrasubstituted carbons in their heterocyclic structures.[81]

Recently, a simple procedure for obtaining these complex structures is being the addition of five-membered ring heterocycles to electrophiles under proton transfer conditions. The success of this development is the result of the confluence of two aspects intrinsic to these heterocycles: firstly, the easy generation of the chiral enolate due to the aromatic character of its enol tautomer (Scheme 12a) and, secondly, the fixed geometry of the resulting enolate due to its cyclic nature. We can find diverse structure cores that fulfil these requirements, among those we can outline 5*H*-oxazol-4-ones,[82] 5*H*-thiazol-4-ones, [83] rhodanines,[84] azlactones[85] and 4*H*-thiazol-5-ones[86] (Scheme 12b).

[81] a) Bian, Z.; Marvin, C. C.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 10886-10889. b) Kakuda, R.; Machida, K.; Yaoita, Y.; Kikuchi, M.; Kikuchi, M. *Chem. Pharm. Bull.* **2003**, *51*, 885-887. c) Mio, S.; Ichinose, R.; Goto, K.; Sugai, S. *Tetrahedron* **1991**, *47*, 2111-2120. d) Sun, S. H.; Zheng, M.; Ding, K.; Wang, S.; Sun, Y. *Anticancer Res.* **2010**, *30*, 3321-3331.

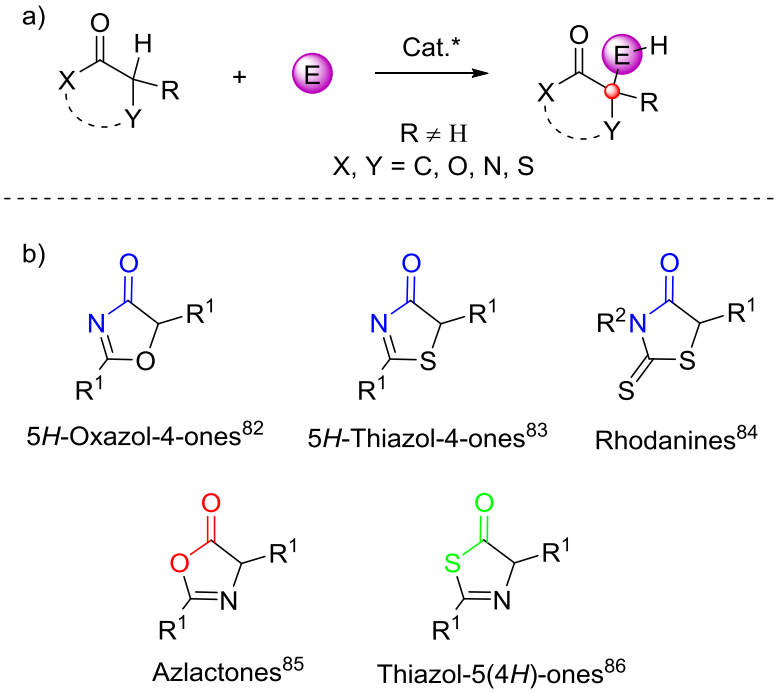
[82] For a recent review about the use of 5*H*-oxazol-4-ones in asymmetric synthesis, see: Jain, A.; Rana, N. K. *Adv. Synth. Catal.* **2021**, *363*, 3879-3912.

[83] For recent reviews about 5*H*-thiazol-4-ones, see: a) Zhu, B.; Qiu, S.; Li, J.; Coote, M. L.; Lee, R.; Jiang, Z. *Chem. Sci.* **2016**, *7*, 6060-6067. b) Mielgo, A.; Palomo, C. *Beilstein J. Org. Chem.* **2016**, *12*, 918-936. c) Huang, Q.; Cheng, Y.; Yuan, H.; Chang, X.; Li, P.; Li, W. *Org. Chem. Front.* **2018**, *5*, 3226-3230. d) Huang, A.; Guo, X.; Li, P.; Li, W. *Adv. Synth. Catal.* **2020**, *362*, 3542-3557.

[84] For recent reviews about rhodanines, see: a) Tomašić, T.; Mašič, L. P. *Expert Opin. Drug Discov.* **2012**, *7*, 549-560. b) Mousavi, S. M.; Zarei, M.; Hashemi, S. A.; Babapoor, A.; Amani, A. M. *Artif. Cells Nanomed. Biotechnol.* **2019**, *47*, 1132-1148.

[85] For reviews about oxazol-5(4*H*)-ones, see: a) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762. b) Hewlett, N. M.; Hupp, C. D.; Tepe, J. J. *Synth.* **2009**, *17*, 2825-2839. c) Piperno, A.; Scala, A.; Risitano, F.; Grassi, G. *Curr. Org. Chem.* **2014**, *18*, 2691-2710.

[86] For a recent review about 4*H*-thiazol-5-ones, see: Huang, A.; Guo, X.; Li, P.; Li, W. *Adv. Synth. Catal.* **2020**, *362*, 3542-3557.



Scheme 12. a) General representation of the formation of α-quaternary center. b) A selection of heterocyclic pronucleophiles employed in organocatalysis.

In contrast to the use and/or synthesis of 5-membered heterocycles, 6-membered heterocycles have been much less exploited within this strategy.[87] In none of the examples reported, the enolate with aromatic character is formed and all of the nucleophiles employed have very activated methyne groups (see chapter 3 for more information) (Figure 22).

[87] a) Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1-63. b) Gasperi, T.; Punzi, P.; Migliorini, A.; Tofani, D. *Curr. Org. Chem.* **2011**, *15*, 2098-21146.

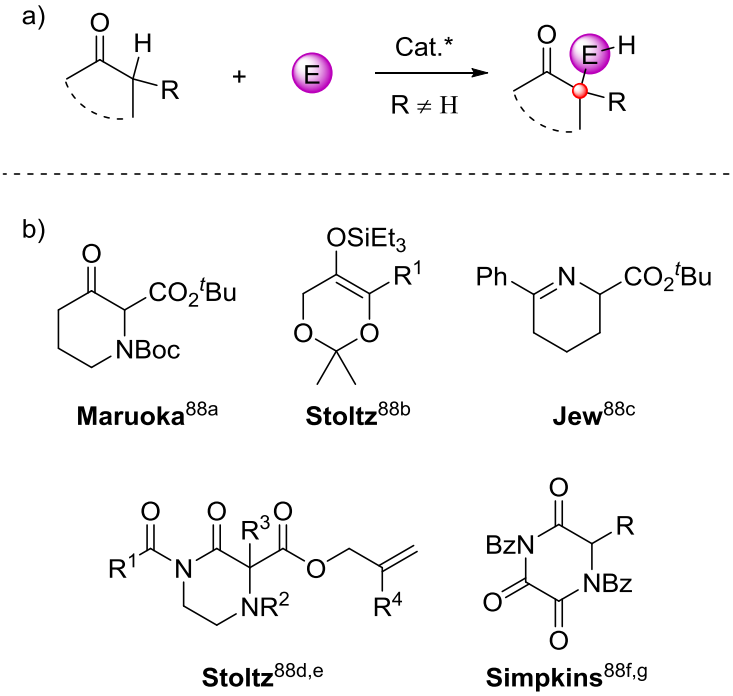


Figure 22. Examples of 6-member heterocycles in asymmetric catalysis.[88]

1.4. Asymmetric and catalytic Michael addition

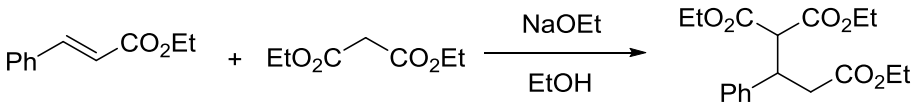
The first example of a carbon nucleophilic addition to an electron deficient double bond was published in 1883 by Komnenos, who noted the easy addition of the diethyl malonate anion to ethylidene malonate.[89] However, the investigations about the mechanistic process finally came to a conclusion in 1887, when Michael studied the addition of various soft nucleophiles, primarily malonates, to α,β-unsaturated systems (Scheme 13).[90] Since then, the transformation known as the Michael addition became one of the most versatile tools for the formation of carbon-carbon bonds and has been widely studied.[91]

[88] a) Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191-193. b) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 6873-6876. c) Kim, T.-S.; Lee, Y.-J.; Lee, K.; Jeong, B.-S.; Park, H.-G.; Jew, S.-S. *Synlett* **2009**, *4*, 671-674. d) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179-183. For an extension of the latter methodology, see: e) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082-1085. f) Cabanillas, A.; Davies, C. D.; Male, L.; Simpkins, N. S. *Chem. Sci.* **2015**, *6*, 1350-1354. g) Peczkowski, G. R.; Craven, P. G. E.; Stead, D.; Simpkins, N. S. *Chem. Commun.* **2019**, *55*, 4214-4217.

[89] Komnenos, T. *Liebigs Ann. Chem.* **1883**, 218, 145-169.

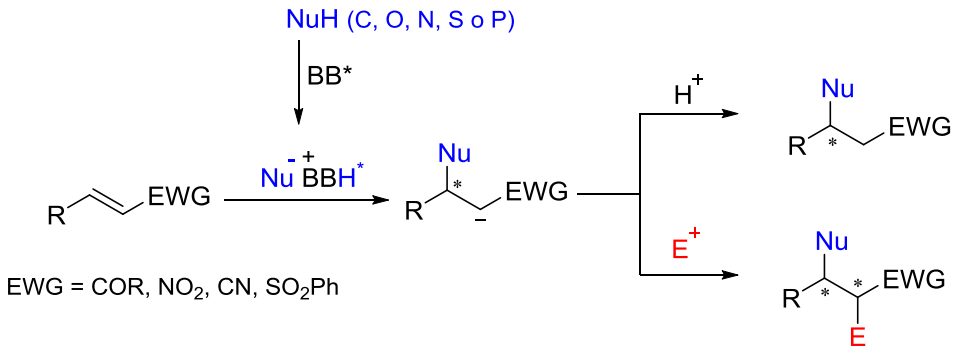
[90] a) Michael, A. *J. Prakt. Chem./Chem.-Ztg.* **1887**, 35, 349. b) Michael, A. *Am. Chem. J.* **1887**, 9, 115.

[91] For reviews on Michael reactions, see: a) Bergmann, E. D.; Ginsburg, D., Pappo, R. *Org. React*. **1959**, *10*, 179-556. b) Jung, M. E. in *Comprehensive Organic* Synthesis, Pergamon, Oxford, **1991**, 1-67. c) Little, R. D.;



Scheme 13. The first Michael adduct.

In general terms, the Michael addition refers to the addition of a nucleophile, generated after deprotonation of its precursor or pronucleophile, to the beta carbon of the α,β-unsaturated acceptor producing a carbanion intermediate which can be protonated or treated with another electrophile to provide the final addition product (Scheme 14). It is well established that "soft" nucleophiles prefer the 1,4- attack while "hard" nucleophiles, such as the organomagnesium and lithium reagents, prefer the 1,2-attack.



Scheme 14. General scheme for Michael reactions under proton transfer conditions.

Generally, Michael donors comprise carbon- and heteroatom- centered nucleophiles whereas Michael acceptors range from the most activated ones, e.g. nitoalkanes, to acceptors with related electron-withdrawing group such as carbonyls, nitriles, sulphones and azodicarboxylates, among others (Figure 23).

Masjedizadeh, M. R.; Wallquist, O.; Mcloughlin, J. I. *Org. React.* **1995**, *47*, 315-552. c) Yamaguchi, M.; Jacobsen, E. N.; Pfltz, A.; Yamamoto Y. *Comprehensive Asymmetric Catalysis* **1999**, Springer, Berlin 1121-1139 d) Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Progr. Polym. Sci*. **2006**, *31*, 487-531. e) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267-9331. f) Córdova, A. *Catalytic Asymmetric Conjugate Reactions* **2010**, Wiley-VCH, Weinheim. g) Thirumalaikumar, M. *Org. Prep. Proc. Int.* **2011**, *43*, 67-129. h) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, 42–53. i) Maharwald, R.; Scheffler, U. *Chem. Eur. J.* **2013**, *19*, 14346-14396. j) Reyes, E; Uria, U.; Vicario, J. L.; Carrillo, L. *Org. React.* **2016**, *90*, 1-898.

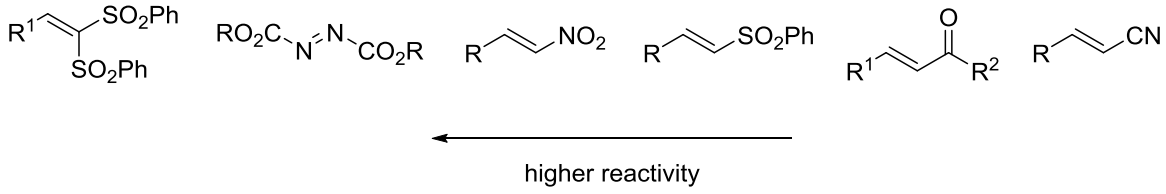
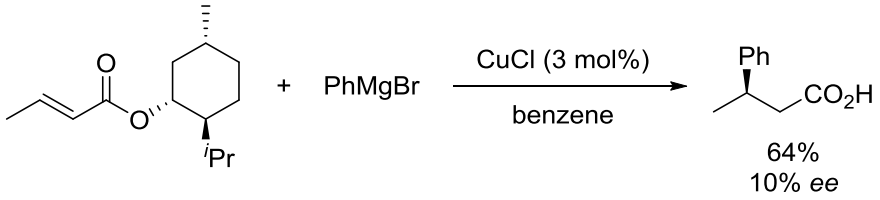


Figure 23. Typical Michael acceptors.

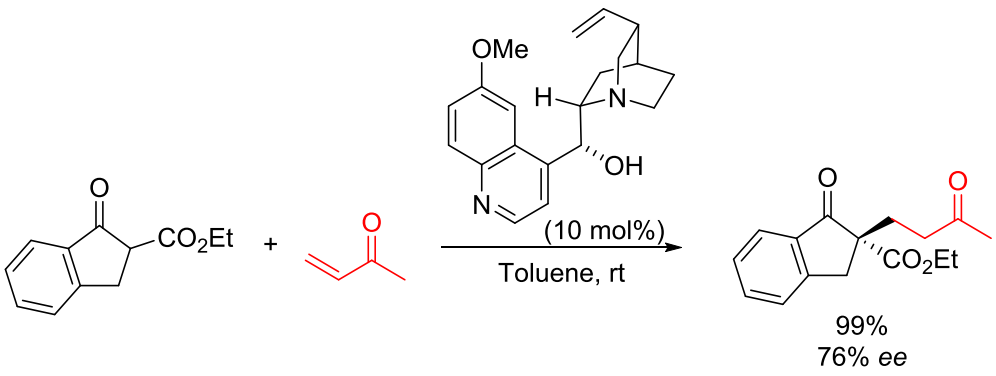
The first reported asymmetric Michael addition involved the use of copper catalysis to promote the conjugate addition of Grignard reagents to α,β-unsaturated esters (Scheme 15).[92] Even though the asymmetric induction was negligible, this transformation paved the way for future investigations.



Scheme 15. Asymmetric Michael addition under copper catalysis.

The first asymmetric Michael reaction promoted by the use of an organic catalyst was reported by Làngström and Bergeson in 1973.[93] The conjugate addition of β-keto esters to acrolein was performed using 2-hydroxymethylquinuclidine as catalyst, albeit the authors were not able to determine the enantioselectivity of the reaction. Two years later, Wynberg and Helder described the use of a *Cinchona* alkaloid as a chiral catalyst for the first time to produce the corresponding Michael adduct in almost cuantitative yield and moderate enantioselectivity (Scheme 16).[94,95]

[92] Inouye, Y.; Walborsky, H. M. *J. Org. Chem.* **1962**, *27*, 2706-2707.
[93] Làngström, B.; Bergeson, G. *Acta Chem. Scand*. **1973**, *27*, 3118.
[94] For the first work published on asymmetric induction Michael reaction by organic catalyst, see: Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057-4060.
[95] For later work see: a) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238-2244. For a review see: b) Wynberg, H. *Top. Sterochem*. **1986**, *16*, 87-129.



Scheme 16. First asymmetric Michael addition promoted by a Cinchona *alkaloid.*

Within this pioneer example, the bifuntional character exhibited by the catalyst was already pointed out (Figure 24); the OH group activates the methyl vinyl ketone through a H-bonding interaction whereas the quinuclidine basic moiety activates the 1,3-dicarbonyl pronucleophile. Despite the moderate enantioselectivities observed, those early studies revealed the importance of the OH group not only in the activation of the electrophile but also in the orientation of the substrates for taking control over the stereoselectivity, which was reduced when the hydroxyl group was protected.[96]

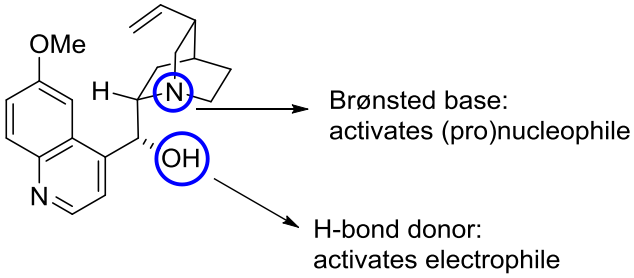


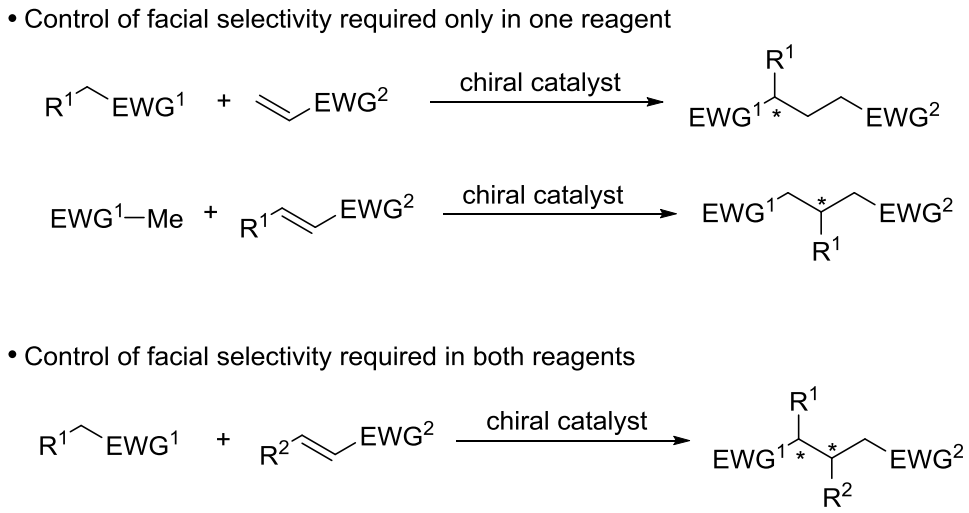
Figure 24. Bifunctional behaviour of *Cinchona* derived catalyst.

As mentioned previously, chirality and sterochemical control are of special relevance in the molecular design of compounds since governmental regulations on drug safety and efficacy have become stricter with regard to compounds that have chirality.[97] In asymmetric catalysis under proton transfer conditions, the entity that acts as catalyst

[96] For reviews on *Cinchona* alkaloids derivatives in asymmetric catalysis see: a) Marcelli, T. Marcelli, T. *Organocatalysis: Cinchona catalysts. Wiley Interdisciplinary Reviews: Computational Molecular Science*, **2011**, *1*, 142-152. b) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *8*, 1229-1279. c) Tian, S-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res*. **2004**, *37*, 621-631. d) Yoon, T. p.; Jacobsen, E. N. *Science* **2003**, *299*, 1691-1693.

[97] Brooks, W. H.; Guida, W. C.; Daniel, K. G. *Curr. Top. Med. Chem.* **2011**, *11*, 760-770.

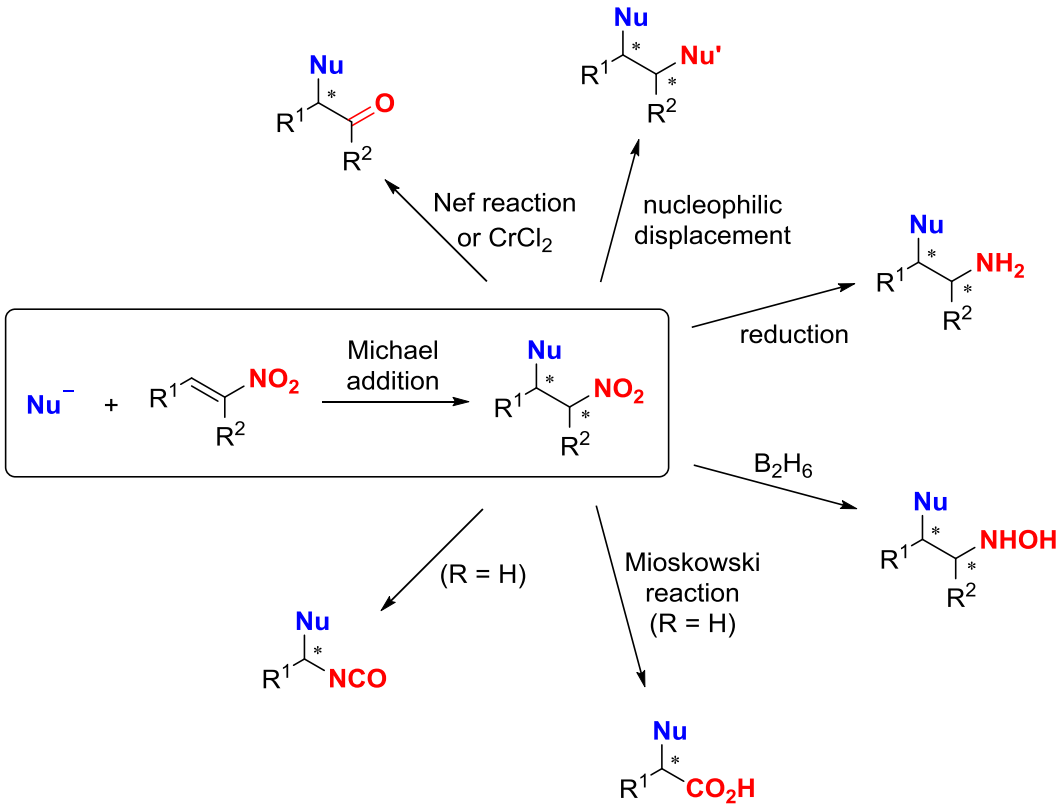
interacts with the substrates recognizing their prochirality and controlling the facial selectivity. In the case that both substrates are prochiral, the catalyst must dominate the arrangement among the substituents of the both substrates to control both the enantio- and the diastereoselectivity of the reaction (Scheme 17).



Scheme 17. Catalyst control of facial selectivity.

Among the Michael acceptors usually employed in carbon-carbon bond forming reactions, nitroalkenes result highly convenient counterparts not only in terms of reactivity[98] but in terms of chemical versatility. The ability of the nitro group to undergo different transformations makes it an ideal masking group for various functionalities, giving access to a wide range of molecules: carbonyl compounds;[99] carboxylic acids;[100] primary amines[101] or hydroxylamines[102] by reduction; nitrile oxides;[103] and even structures derived from its nucleophilic displacement[104] (Scheme 18).

[98] Seebach, D.; Colwin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1-18.
[99] For examples to obtain carbonyl compounds, see: through the Nef reaction, a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263-291. b) Pinnick, H. W. The Nef Reaction. *Org. React.* **1990**, *38*, 655-792. c) Ballini, R.; Petrini, M. *Adv. Synth. Catal.* **2015**, *357*, 2371-2402. Using Cr(II) salts: d) Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 3777-3778.
[100] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234-235.
[101] a) Barret, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733-5734. b) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608-5609. c) Goksu, H.; Sert, H.; Kilbas, B.; Fatih, S. *Curr. Org. Chem.* **2017**, *21*, 794-820.
[102] Feuer, H.; Bartlett, R. S.; Vincent, B. F.; Anderson, R. S. *J. Org. Chem.* **1965**, *30*, 2880-2882.
[103] Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.
[104] Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434.



Scheme 18. Chemical versatility of the nitro group.

1.5. Objectives

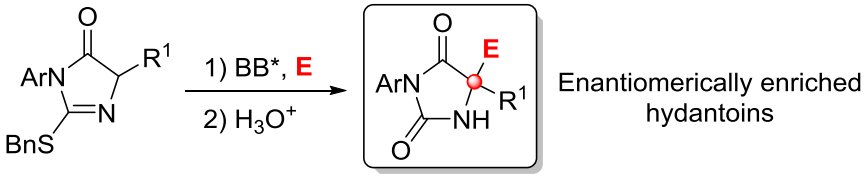
Precedents mentioned along the introduction chapter make clear the relevance of heterocyclic compounds. Apart from being interesting synthetic goals because of their biological and pharmaceutical properties, they can be used also as building blocks for the construction of complex targets.

These heterocycles are even more interesting when they have quaternary stereocenters in its structures and for that reason, it is the aim and a challenging objective for the chemical community to find new strategies for the stereoselective creation of tetrasubstituted carbon centers.

Based on these premises, we established the following main objectives for this Thesis:

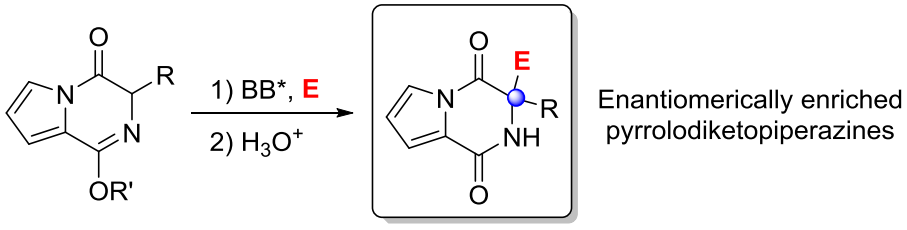
- **Objetive 1**: Following previous works from our laboratory, we decided to study the performance of N_3-aryl imidazolones as pronucleophiles in Michael

additions, under proton transfer conditions, promoted by chiral bifunctional Brønsted bases. The subsequent hydrolysis of the obtained adducts would allow the production of enantiomerically enriched hydantoins bearing quaternary stereocenters (Scheme 19).



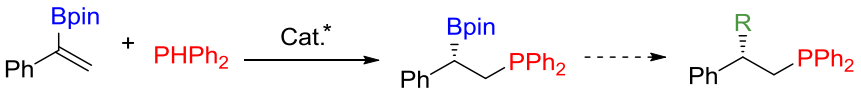
Scheme 19. Objective 1

- **Objetive 2**: Following with the idea of exploiting the propitious features of heterocycles in organocatalytic transformations, we decided to explore less studied 6-member heterocycles. In particular, the use of bicyclic acylpyrrol lactims, which have not been investigated previously as pronucleophiles, in Michael additions promoted by chiral bifunctional Brønsted bases. This catalytic approach would help to mitigate the lack methodologies towards the production of enantiomerically enriched pyrrolo diketopiperazines (Scheme 20).



Scheme 20. Objective 2.

In the last part of this PhD thesis, a short stay was carried out under the supervision of Prof. Suyzanna Harutyunyan in the Stratingh Institute for Chemistry of the University of Groningen in the Netherlands. The research project was focused on the synthesis of chiral phosphine boronates and the search of the possibilities for their application in organic transformation (Scheme 21).



Scheme 21. Abroad stay objetive.

CHAPTER 2

2. MICHAEL ADDITION OF 1*H*-IMIDAZOL-4(5*H*)-ONES TO NITROALKENES

2.1. Introduction

Hydantoins[105] or 2,4-imidazolidinediones constitute a family of nitrogen containing heterocycles, that are key functional components of biologically active small moieties found in commercialed drugs (Figure 25a) and natural products,[106] and also have been used as chiral organocatalysts,[107] auxiliaries[108] and ligands[109] (Figure 25b).

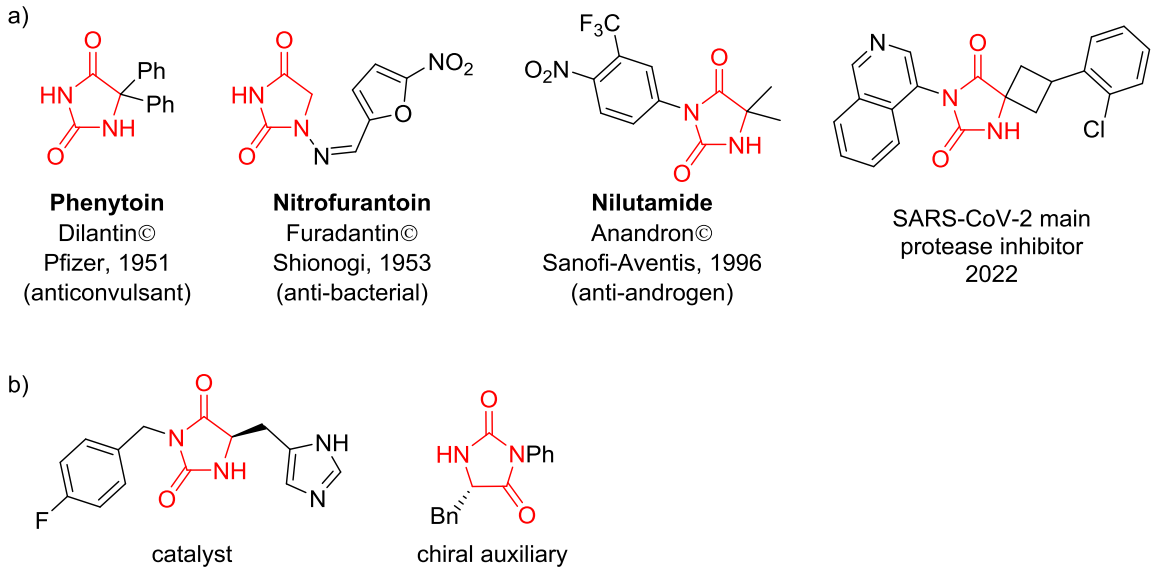


Figure 25. a) Representative examples of biologically active hydantoins. b) Examples of hydantoin based catalyst and chiral auxiliary.

[105] For reviews about hydantoins, see: a) Meusel, M. ; Gütschow, M. *Org. Prep. Prod. Int.* **2004**, *36*, 391-443. b) Konnert, L.; Lamaty, F.; Martinez, J.; Colacino, E. *Chem. Rev.* **2017**, *117*, 13757-13809. c) Cho, S.; Kim, S.-H.; Shin, D. *Eur. J. Med. Chem.* **2019**, *164*, 517-545.

[106] a) Wang, Q.; Tang, X.; Luo, X.; Voogd, N. J.; Li, P.; Li, G. *Org. Lett.* **2015**, *17*, 3458-3461. b) Lee, T. H.; Khan, Z.; Kim, S. Y.; Lee, K. R. *J. Nat. Prod.* **2019**, *82*, 3020-3024. c) Carlsson, J. et al. *J. Am. Chem. Soc.* **2022**, *144*, 2905-2920.

[107] Zhai, Z.; Chen, J.; Wang, H.; Zhang, Q. *Synth. Commun.* **2003**, *11*, 1873-1883.

[108] a) Yamaguchi, J.-I.; Harada, M.; Narushima, T.; Saitoh, A.; Nozaki, K.; Suyama, T. *Tetrahedron Lett.* **2005**, *46*, 6411-6415. b) Zhang, J.-S.; Lu, C.-F.; Chen, Z.-X.; Li, Y.; Yang, G.-C. *Tetrahedron: Asymmetry* **2012**, *23*, 72-75. c) Lu, G.-J.; Nie, J.-Q.; Chen, Z.-X.; Yang, G.-C.; Lu, C.-F. *Tetrahedron: Asymmetry* **2013**, *24*, 1331-1335. d) Metallinos, C.; John, J.; Zaifman, J.; Emberson, K. *Adv. Synth. Catal.* **2012**, *354*, 602-606.

[109] Oyaizu, K.; Ohtani, Y.; Shiozawa, A.; Sugawara, K.; Saito, T.; Yuasa, M. *Inorg. Chem.* **2005**, *44*, 6915-6917.

Structurally, these products can be viewed as masked α-amino acids, hence α-substituted hydantoins also serve as precursors to unnatural α-amino acid derivatives (Figure 26).[110]

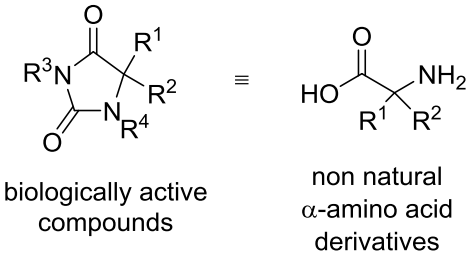
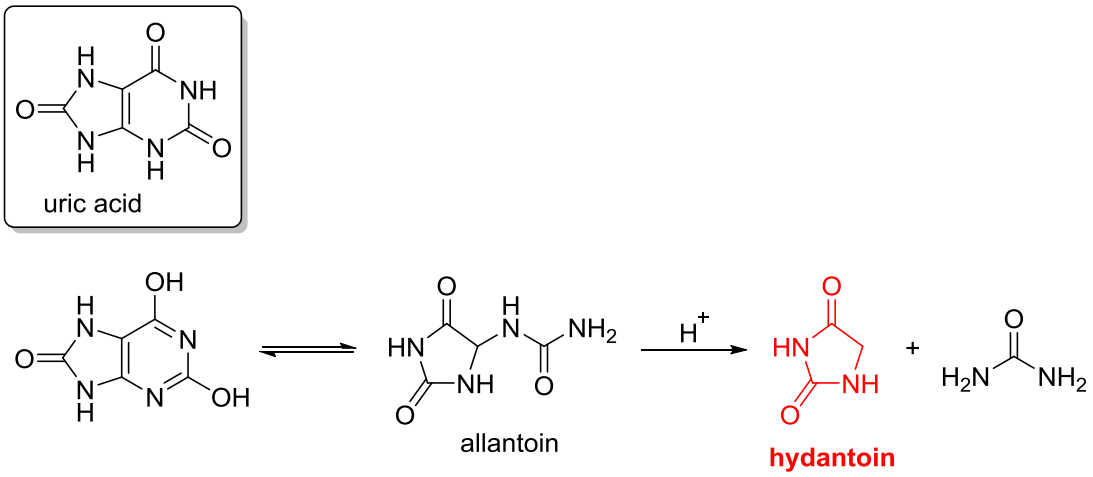


Figure 26. Hydantoins as possible equivalents of α-amino acids derivatives.

Given these diverse applications, it is not surprising that different synthetic methods have been developed to prepare hydantoins and it derivatives.

The discovery of the structure of hydantoin moiety was first made in 1861 by the German chemist Adolph von Baeyer in the course of his study of uric acid. The name is due to the fact that it was obtained through the **hyd**rogenolysis of all**antoin** (Scheme 22).[111]



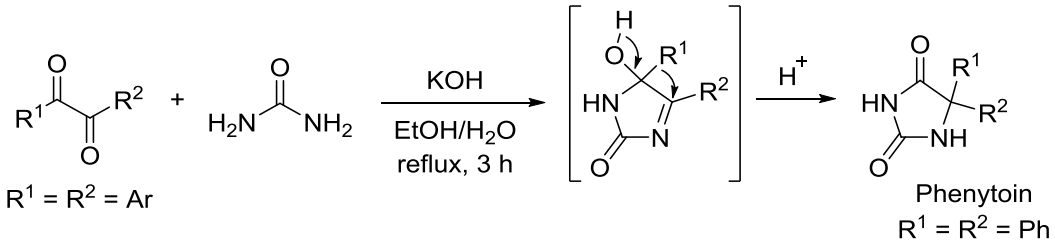
Scheme 22. Synthesis of hydantoin through the hydrogenolysis of allantoin.

[110] For a review on the stereoselective synthesis of α,α-disubstituted α-amino acids derivatives, see: a) Cativiela, C.; Ordóñez, M.; Viveros-Ceballos, J. L. *Tetrahedron* **2020**, *76*, 130875. For recent representative examples, see: b) Feskov, I. O.; Chernykh, A. V.; Kondratov, I. S.; Klyachina, M.; Daniliuc, C. G.; Haufe, G. *J. Org. Chem.* **2017**, *82*, 12863-12868. c) Costil, R.; Fernández-Nieto, F.; Atkinson, R. C.; Clayden, J. *Org. Biomol. Chem.* **2018**, *16*, 2757-2761. d) Correia, C. R.; Oliveira, V.; de Oliveira, J.; da Silva, V. S.; Khan, I. *Adv. Synth. Catal.* 10.1002/adsc.202000443.

[111] Baeyer, A. Ber. Dtsch. Chem. Ges. **1875**, *8*, 612-614.

Hydantoin nucleus can be synthesized following three general pathways.

One of the methodologies, the Biltz reaction, takes place through the formation of the ring involving the double condensation of an α-dicarbonyl compound. Then, under strong basic conditions, the hydroxy group of the hemiaminal is deprotonated followed by the transposition of the R^1 substituent to the adjacent carbon. This method was first applied for the synthesis of phenytoin (Scheme 23).[112]



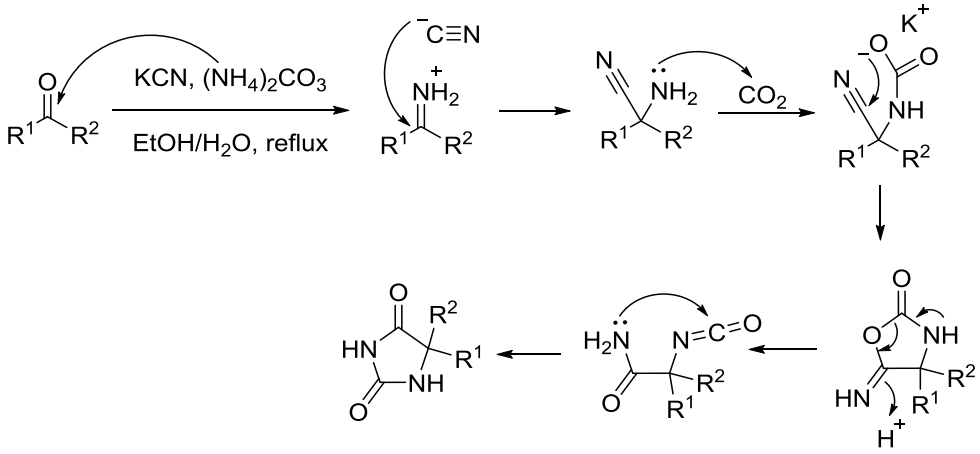
Scheme 23. Hydantoin synthesis by Biltz reaction.

The second general approach, the Bucherer-Bergs reaction, is a multicomponent reaction between a carbonyl compound (aldehydes or ketones), potassium cyanide and ammonium carbonate. [113] In the presence of the latter, the starting carbonyl compound becomes an imine intermediate, which is attacked by the cyanide. The released carbon dioxide, reacts with the newly formed amino nitrile. Subsequent cyclization and final rearrangement of the five-membered ring afforded targeted 5,5-disubstituted hydantoins (Scheme 24). Moreover, the need to use highly dangerous potassium cyanide, because it hydrolyses releasing hydrogen cyanide – a chemical asphyxiant that interferes with the body's ability to use oxygen – this means that the procedure has been little used.[114]

[112] a) Biltz, H. *Ber. Drsch. Chem Ges.* **1908***, 41*, 1379. For recent examples using the Biltz methodology to access hydantoins, see: b) Sachdev, D.; Dubey, A. *Catal. Commun.* **2010**, *11*, 1063-1067. c) Safari, J.; Naeimi, H.; Ghanbari, M. M.; Sabzi Fini, O. *Russ. J. Org. Chem.* **2009**, *45*, 477-479. d) Arani, N. M. ; Safari, J. *Ultrason. Sonochem.* **2011**, *18*, 640-643. For an example where the two substituents at α are different, see: Gbaguidi, F. A.; Kpoviessi, S. S. D.; Kapanda, C. N.; Muccioli, G. G.; Lambert, D. M.; Accrombessi, G. C.; Mansourou, M.; Poupaert, J. H. *Afr. J. Pure Appl. Chem.* **2011**, *5*, 168-175.

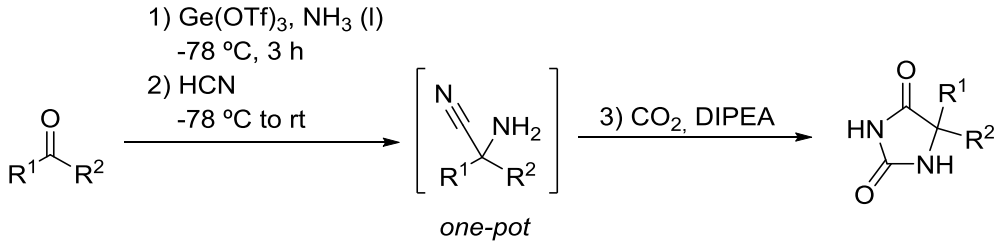
[113] a) Bucherer, H.T.; Lieb, V.A. *J. Prakt. Chem.* **1934**, *141*, 5-43. For recent examples using the Bucherer-Bergs methodology to access hydantoins, see: b) Montagne, C.; Shiers, J. J. Shipman, M. *Tetrahedron Lett.* **2006**, *47*, 9207-9209. c) Safari, J.; Javadian, L. *C. R. Chimie* **2013**, *16*, 1165-1171. d) Fesenko, A. A.; Shutalev, A. D. *Tetrahedron* **2020**, *76*, 131340.

[114] Hazardous substance fact sheet, potassium cyanide **1998**, NJDHSS.



Scheme 24. Hydantoin synthesis following Buchener-Bergs method.

On the other side, although the conversion of aminonitriles to hydantoins is easy to perform, in some cases, it is limited by the difficulty of isolating and purifying these starting materials. As a specific solution, in 2008, Conway and co-workers described a one-pot new strategy to obtain hydantoins from ketones or aldehydes without having to isolate the corresponding aminonitriles (Scheme 25).[115]

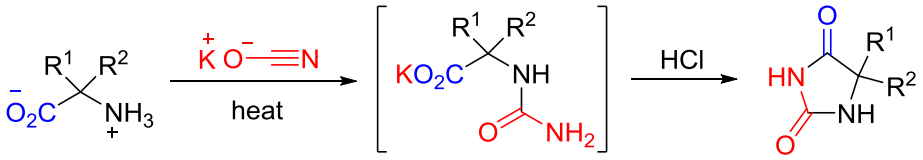


Scheme 25. One-pot synthesis of hydantoins from ketones and aldehydes.

In the last classical way, known as the Urech/Read synthesis, the hydantoins can be prepared through a two-step (condensation-cyclization) synthetic route from the corresponding zwitterionic amino acids and potassium cyanate under harsh reaction conditions (Scheme 26).[116]

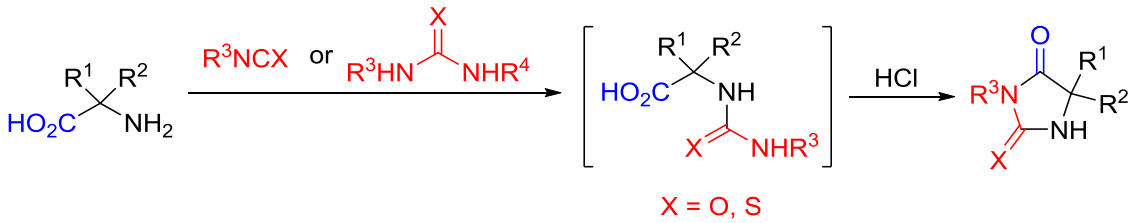
[115] a) Murray, R. G.; Whitehead, D. M.; Le Strat, F.; Conway, S. J. *Org. Biomol. Chem.* **2008**, *6*, 988-991. To see another examples to synthesize hydantoins starting from aminonitriles, see: b) Vukelić, S.; Koksch, B.; Seeberger, P. H.; Gilmore, K. *Chem. Eur. J.* **2016**, *22*, 13451-13454.

[116] Urech, F. *Jusfus. Liebigs. Ann. Chem.* **1873**, *165*, 99. The study of this reaction was extended to the use of α-aminonitriles by Read in 1922: b) Read, W. T. *J. Am. Chem. Soc.* **1922**, *44*, 1746-1755. For recent examples using the Urech/Read methodology to access hydantoins, see: c) Konnert, L.; Reneaud, B.; de Figueiredo, R.



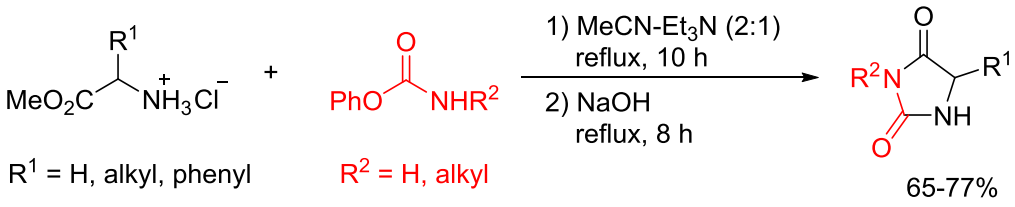
Scheme 26. Hydantoin synthesis using Urech/Read method.

Furthermore, this reaction can be extended to (thio)ureas and aryl and alkyl isocyanates (Scheme 27).[117] However, the isocyanates are often not commercially available and their synthesis requires the use of toxic or gaseous reagents.



Scheme 27. Synthesis of hydantoins from (thio)ureas and isocyanates.

In addition to the methodology presented above, the use of phenyl carbamates as equivalents of isocyanates or (thio)ureas was developed by Gill and co-workers in an efficient and practical procedure for the synthesis of hydantoins under mild reaction conditions using non-toxic reagents (Scheme 28).[118]



Scheme 28. Synthesis of hydantoins from phenyl carbamates.

M.; Campagne, J.-M.; Lamaty, F.; Martinez, J.; Colacino, E. *J. Org. Chem.* **2014**, *79*, 10132-10142. d) Konnert, L.; Dimassi, M.; Gonnet, L.; Lamaty, F.; Martinez, J.; Colacino, E. *RSC Advv.* **2016**, *6*, 36978-36986.

[117] a) Coghill, R. D.; Johnson, T. B. *J. Am. Chem. Soc.* **1925**, *47*, 184-193. b) Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1943**, *65*, 1013-1016. c) Blotny, G. *Synthesis* **1983**, *5*, 391-392. d) Gao, F.-F.; Li, Y.-X.; Zhang, S.-Q.; Zhang, G.-L. *Chem. Res. Chinese U.* **2006**, *22*, 593-597.

[118] a) Tanwar, D. K.; Ratan, A.; Gill, M. S. *Synlett*, **2017**, *28*, 2290. For examples of recent synthesis, see: cooperative catalysis (Lewis base/copper catalysis) b) Song, J.; Zhang, Z.-J.; Chen, S.-S.; Fan, T.; Gong, L.-Z. *J. Am. Chem. Soc.* **2018**, *140*, 3177-3180. Pd-catalyzed oxidative carbonilation: c) Voronov, A.; Botla, V.; Montanari, L.; Carfagna, C.; Mancuso, R.; Gabriele, B.; Maestri, G.; Motti, E.; Ca, N. D. *Chem. Commun.* **2022**, *58*, 294-297. Phase-transfer-catalyzed alkylation: d) Keenan, T.; Jean, A.; Arseniyadis, S. *ACS Org. Inorg. Au* **2022**, *2*, 312-317.

For the synthesis of optically active hydantoins the most straightforward procedure is the third one, but for that is compulsory to have the corresponding α-amino acids enantiomerically pure.[119] This issue is specially problematic for the case of 5,5-disubstituted hydantoins (quaternary α-amino acids).[120] The need of adquiring this type of products in its enantiopure form takes special importance since various clinical candidates based on the hydantoin skeleton have been reported. However, only very recently have been described practical syntheses of enantiomerically enriched quaternary hydantoins (Figure 27).

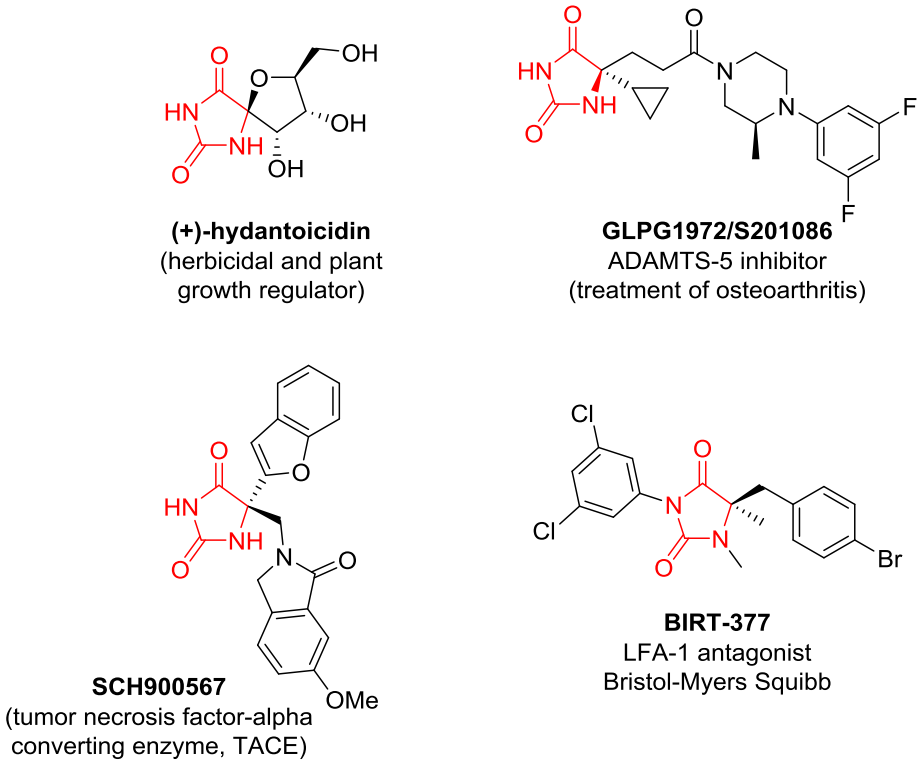


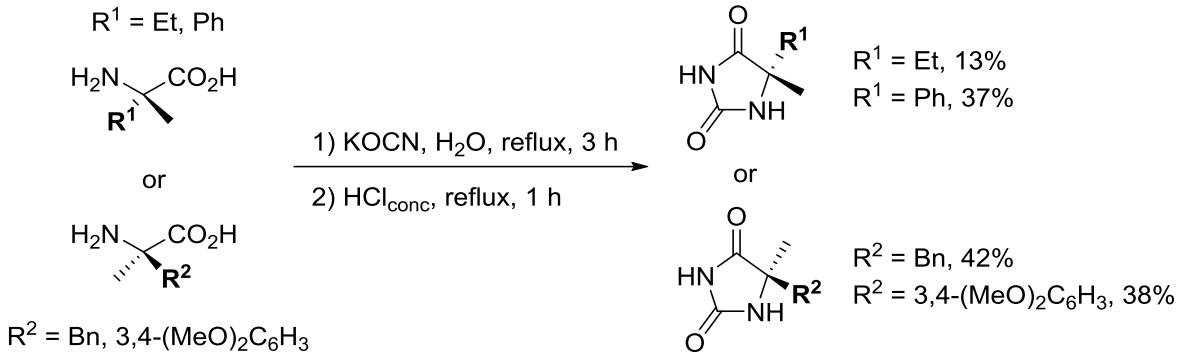
Figure 27. A selected group of chiral α-quaternary N^3-hydantoins.

In 1970, Yamada and co-workers described the synthesis of 5-tetrasubstituted hydantoins starting from chiral α-quaternary amino acids and following the Urech

[119] Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260.

[120] For works describing the synthesis of chiral α-terciary hydantoins starting from the Chiral Pool, see: a) Zhang, D.; Xing, X.; Cuny, G. D. *J. Org. Chem.* **2006**, *71*, 1750-1753. b) Liu, H.; Yang, Z.; Pan, Z. *Org. Lett.* **2014**, *16*, 5902-5905. c) Chen, Y.; Su, L.; Yang, X.; Pan, W.; Fang, H. *Tetrahedron* **2015**, *71*, 9234-9239. d) Declas, N.; Le Vaillant, F.; Waser, J. *Org. Lett.* **2019**, *21*, 524-528.

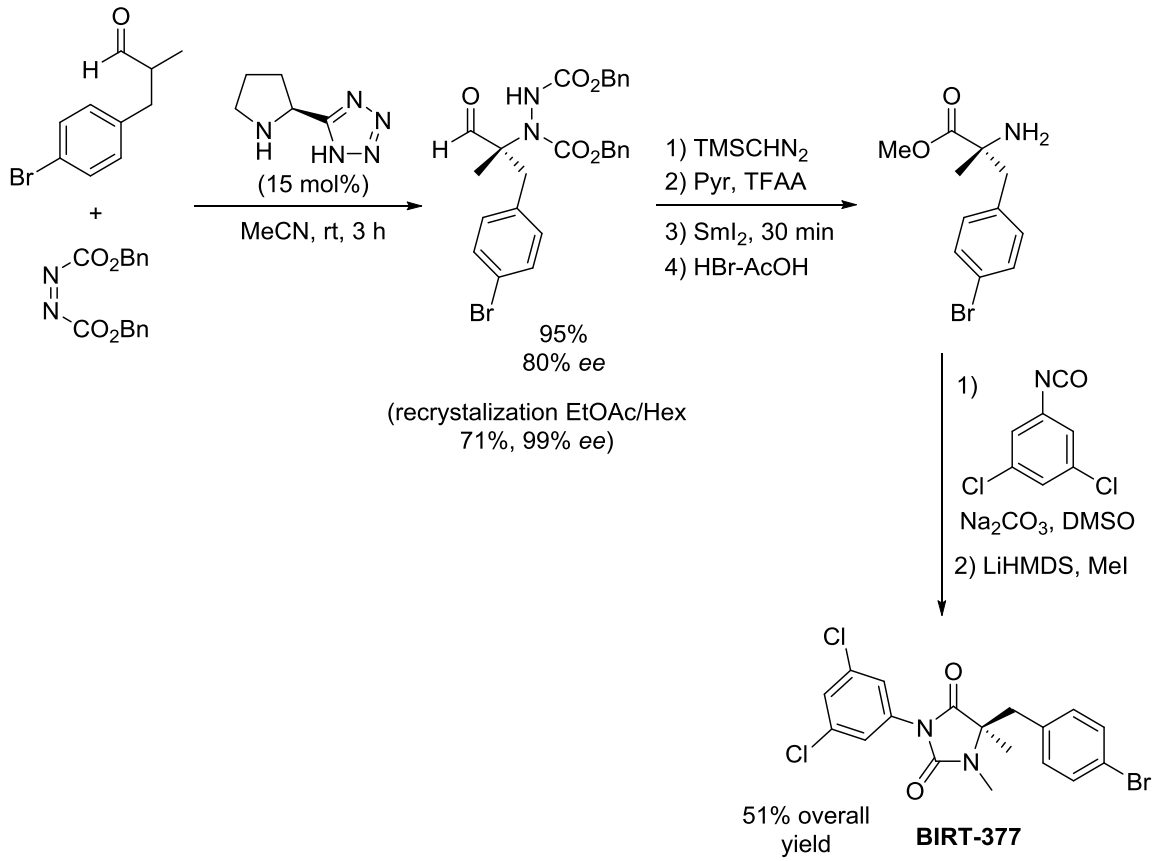
procedure. Unfortunately, the yields of the four examples that were described were very low (Scheme 29).[121]



Scheme 29. Synthesis of 5,5-disubstituted hydantoins starting from chiral quaternary amino acids.

Later, in 2005, Barbas III and co-workers reported the reaction of an α-terciary aldehyde, activated by a chiral proline-tetrazole organocatalyst, with dibenzylazadicarboxylate for the total synthesis of hydantoin BIRT-377. After two additional steps the final pharmaceutic product was obtained in an 51% overall yield (Scheme 30).[122]

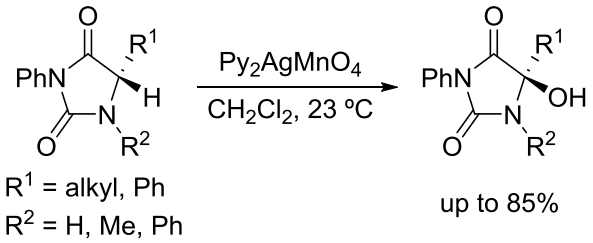
[121] Achiwa, K.; Terashima, S.; Mizuno, H.; Takamura, N.; Kitagawa, T.; Ishikawa, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1970**, *18*, 61-74.
[122] Chowdari, N. S.; Barbas III, C. F. *Org. Lett.* **2005**, *7*, 867-870.



Scheme 30. Synthesis of BIRT-377.

In a more recent job, the groups of Sigman and Movassaghi collaborated to study the hydroxylation of N^3-aryl hydantoins, with the bis(pyridine)silver(I) permanganate as the oxidant, providing excellent substrate variability with control over both the steric and electronic environment of the activated C-H bond subject to oxidation.[123] The transformation to the alcohol is stereospecific and stereoretentive suggesting that the oxygen is rapidly bounded after the proton abstraction (Scheme 31). The authors predicted that this method could provide a road map to synthetic design and application of late-stage oxidation reactions in complex synthesis and a strategic guide into mapping other site selective oxidation processes.

[123] Bischoff, A. J.; Nelson, B. M.; Niemeyer, Z. L.; Sigman, M. S. Movassaghi, M. *J. Am. Chem. Soc.* **2017**, *139*, 15539-15547.

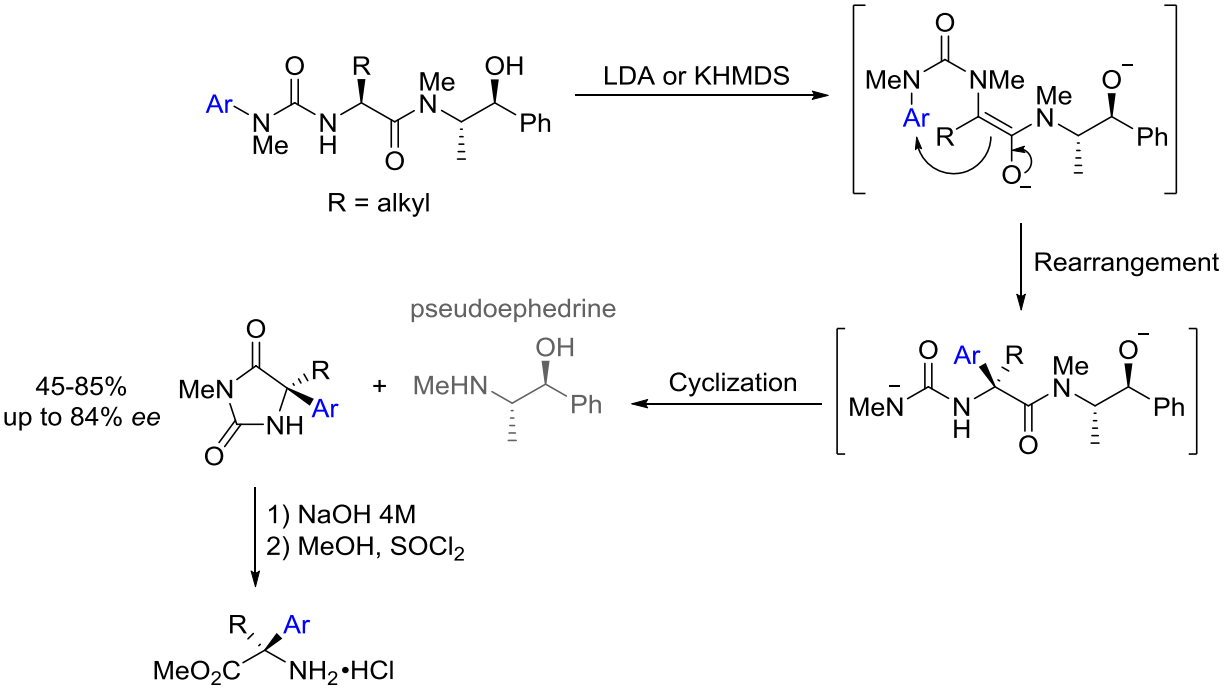


Scheme 31. Hydroxilation of hydantoins to afford the products with α-quaternary centerns.

As far as we know, until 2015, there was no examples to access optically active quaternary hydantoins involving new carbon-carbon bond forming reaction.

That year, Clayden's group reported a protocol for the obtention of quaternary hydantoins and compounds derived thereof. This procedure is based in a diastereoselective migration of the *N*-aryl group to the available α position of the amino acid on lithiated ureas. The N→C rearrangement is followed by the formation of the hydantoin by means of the cyclization of the ring with the concomitant expulsion of the pseudoephedrine chiral auxiliary. This method does not need the use of heavy metal catalysts or additives, and has better results with electron-rich rings and with amino acids containing saturated side chains. The hydrolysis of the hydantoins provided the corresponding α-tetrasubstituted amino acids, although the methodology is limited to the substrates in which the migrating group is aromatic (Scheme 32).[124]

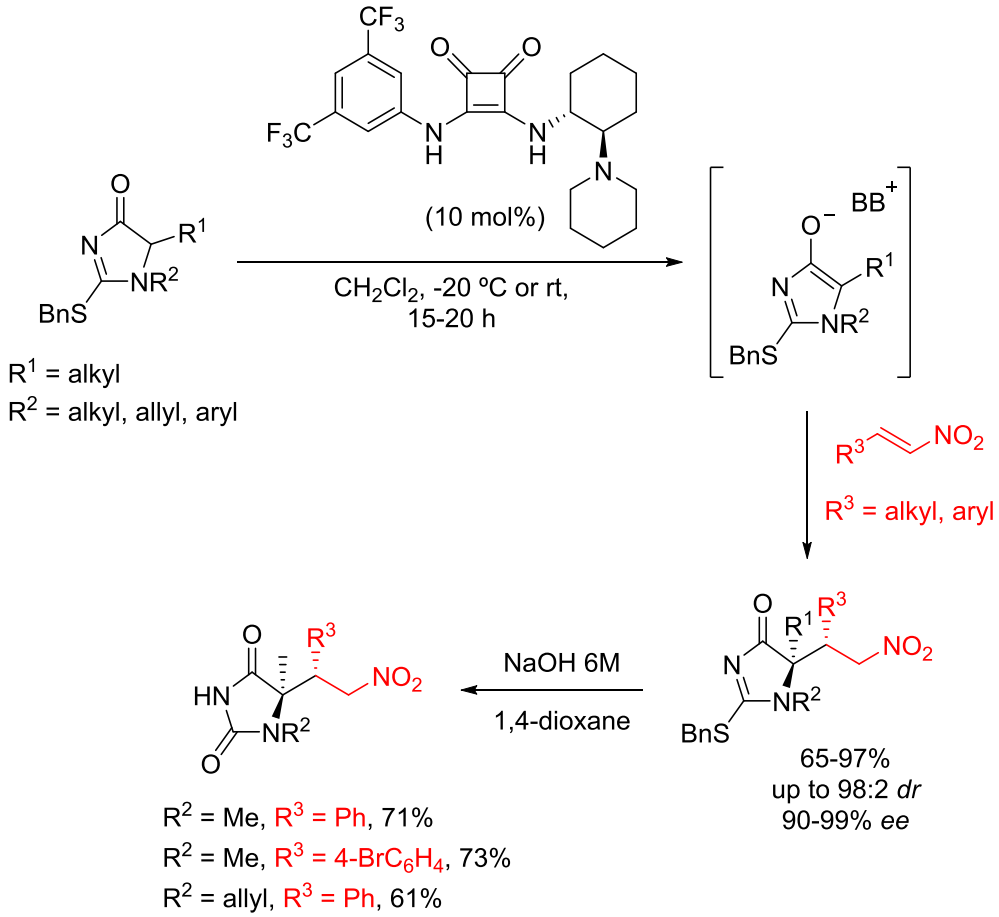
[124] a) Atkinson, R. C.; Fernández-Nieto, F.; Mas Rosello, J.; Clayden, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8961-8965. b) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757-10768. Another example via memory of chirality (MOC), see: c) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294-13297.



Scheme 32. Hydantoin formation by arylation.

At the same time, our group demonstrated that 2-thio-1*H*-imidazol-4(5*H*)-ones opens a spectra of new nucleophile candidates for the effective asymmetric construction of tetrasubstituted adducts. The subsequent elaboration of these gives access to an array of different N^1-alkyl quaternary α-amino acid derivatives and 5,5-disubstituted hydantoins (Scheme 33).[125] The effectiveness of the template to react under mild enolization conditions may be ascribed to the aromatic character of the transiently formed enolate.

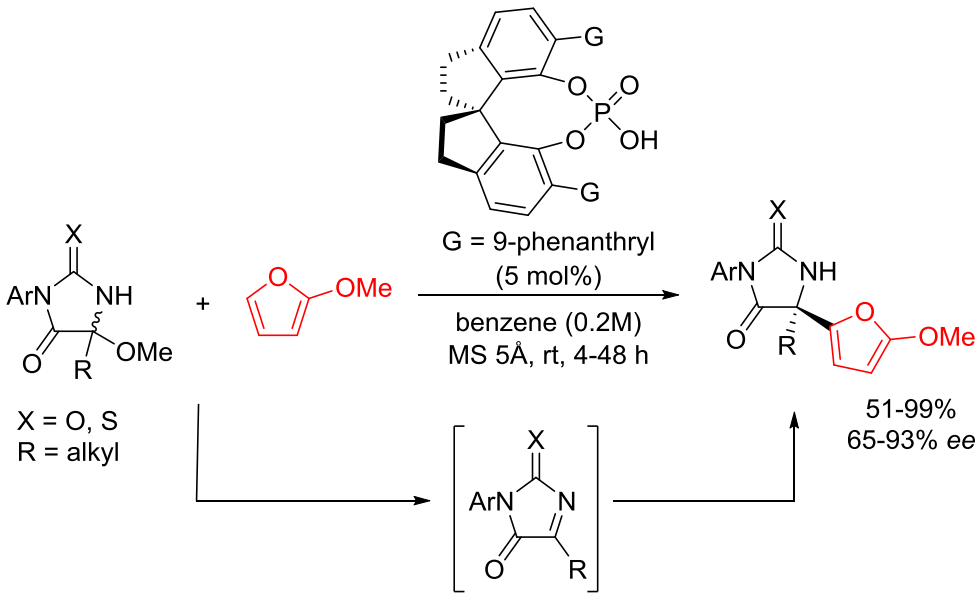
[125] Etxabe, J.; Izquierdo, J.; Landa, A.; Oiarbide, M.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 6883-6886.



Scheme 33. Synthesis of tetrasubstituted hydantoins.

A year later, Terada and co-workers described an asymmetric Friedel-Crafts-type addition of 2-methoxyfuran to *in situ* generated aliphatic ketimines under the influence of a chiral phosphoric acid catalyst. This reaction is a rare example involving ketimines possessing alkyl substituents, and is also an attractive method for the synthesis of (thio)hydantoin derivatives with a quaternary stereogenic center. The adducts were obtained in moderate to excellent yields and enantioselectivities (Scheme 34).[126]

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

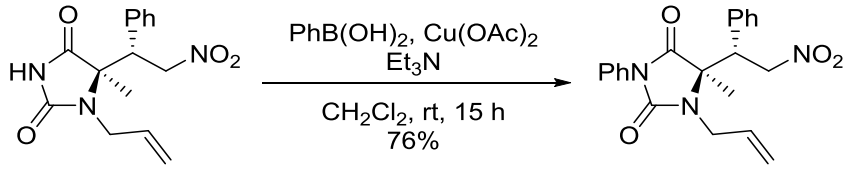


Scheme 34. Brønsted-acid catalysed Friedel-Crafts reaction.

2.2. Working hypothesis and synthetic plan

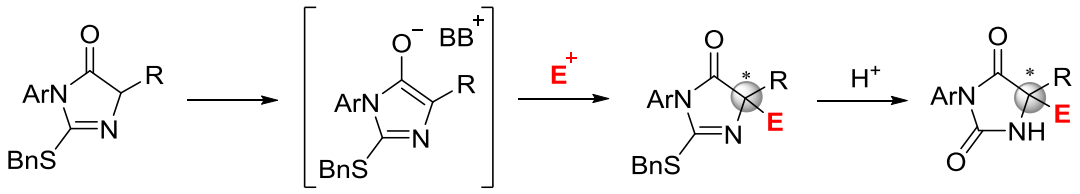
N^3-aryl α-tetrasubstituted hydantoin possessing heterocyclic core are interesting pharmacophores because of its interesting biological effects (see Figure 25 and 27). Taking into account and based on the antecedents recently described by our group referring to the asymmetric Michael addition of 1*H*-imidazol-4(5*H*)ones to nitroolefins and next transformation to quaternary hydantoins (above mentioned). Due to the few procedures for their synthesis, our preliminary objective was to develop a stereoselective method catalysed by Brønsted bases for the synthesis of the corresponding target hydantoins.

Julen Etxabe, during his PhD work, from our research group, performed the *N*^{3}-arylation of (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione using phenylboronic acid as the arylating agent and copper acetate as the metal catalyst (Scheme 35).



Scheme 35. *N*^{3}-arylation of chiral hydantoins with boronic acid and copper catalysis.

Based on the excellent results obtained with N^1-alkyl heterocycles and from a similar reasoning, it was envisaged that the related N^3-arylated heterocyclic system, would lead, in the presence of a base promoter, to the corresponding aromatic enolate. Moreover, in view of the structural similarities of enolates, their interaction with the protonated amine/squaramide catalyst might be equally productive in order to afford the addition adducts which, under acidic conditions, could generate the corresponding N^3-arylated α-tetrasubstituted hydantoins (Scheme 36).

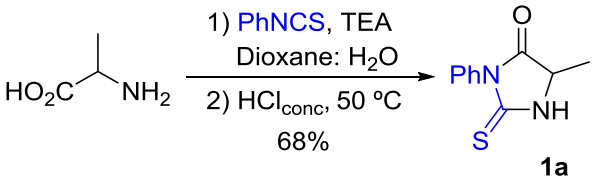


Scheme 36. Synthetic plan of N^3-asyl α-quaternary hydantoins.

2.3. Results and discussion

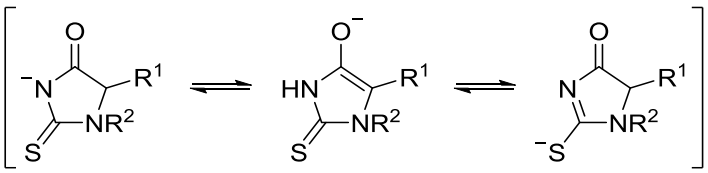
2.3.1. Preparation of N^3-phenyl template

The preparation of the N^3-phenyl thiohydantoin **1a** was performed following a stablished experimental procedure described in the Scheme 37,[127] that consists in the condensation of the *DL*-alanine with commercially available phenyl isothiocyanate and trimethylamine to obtain the corresponding thiohydantoin **1a** in 68% yield.



Scheme 37. Preparation of hydantoin **1a**.

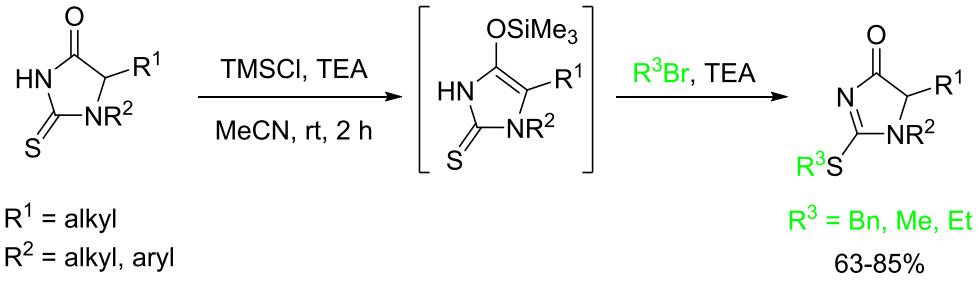
During the previous published work,[128] the alkylation of the sulphur atom supposed a challenge. The first attempts, using triethylamine as the base and benzyl bromide as the alkylating agent, afforded mixtures of *O*-benzyl and *O*,*S*-dibenzyl products. The lack of chemoselectivity could be a result of the electronic delocalization through the ring leading to a mixture of alkylated products (Scheme 38).



Scheme 38. Electronic delocalization through the ring.

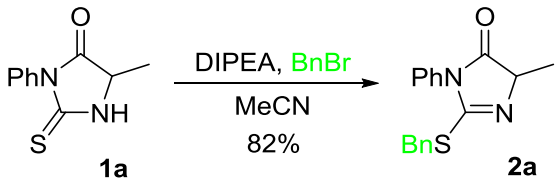
In order to confront this issue, the solution came along carrying out, first, with the silylation of the enolate and, second, the *S*-alkylation to produce the corresponding N^1-substituted templates in good yields (Scheme 39).

[127] Zhu, L.; Lu, C.; Chen, Z.; Yang, G.; Li, Y.; Nie, J. *Tetrahedron: Asymmetry* **2015**, *26*, 6–15.
[128] See reference 18.



Scheme 39. *S*-alkylation of N^1-substituted thiohydantoins.

In the case of the N^3-phenyl template **1a**, the electronic delocalization treatment with base is not possible and, as predicted, direct alkylation with benzyl bromide in the presence of diisopropyl ethyl amine yielded the corresponding imidazolone **2a** in 82% yield. The use of othe bases such as triethylamine produce **2a** in lower yields (Scheme 40).



Scheme 40. *S*-alkylation of N^3-substituted thiohydantoins.

2.3.2. Catalyst screening

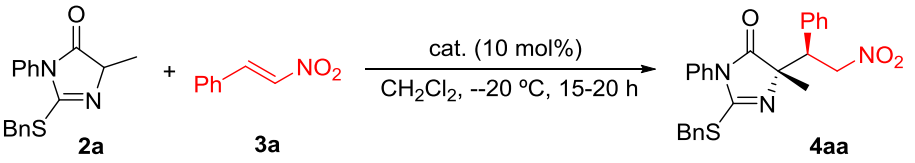
Once we had the starting substrate, we focused our attention in a preliminar study of the conjugate Michael addition of the imidazolone **2a** to nitrostyrene **3a** in the presence of Brønsted bases of different nature. According to the precedents and the adquired experienced in our group employing this family of organocatalysts, we focused in the most effective ones in the addition of activated methylenes to nitroalkenes: Brønsted bases/H-bonding type bifunctional catalysts. Taking into account this, we chose several squaramide- and thiourea-based bifunctional catalysts to carry out the reaction between imidazolone **2a** and nitrostyrene at –20 °C (Table 1).

At the beginning of the study, we tested squaramide type catalyst **C1**, which had turned out to be the best in the reaction between imidazolone N^1-alkylated substrates and different nitroalkenes. Even though the enantiomeric excess was maintained above

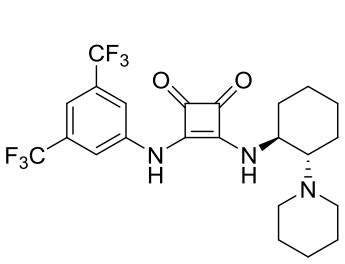
90%, the diastereomeric ratio was low. Then, we wondered what would be the effect of the tertiary amine stereoselectivity and tested catalysts **C2** and **C3** bearing a *Cinchone* derived tertiary amine. Diastereomeric ratio slightly increased with catalyst **C2** whereas catalyst **C3** afforded a lower asymmetric induction.

Nevertheless, the replacement of the typical Brønsted bases for a *tert*-leucine derived amino acid considerably improved the stereocontrol. Catalyst **C4** and the new one **C5**, designed by our research group, were tested under the same reaction conditions and **4aa** was produced as an almost single enantiomer (96:4 – 97:3 *dr* and 95 – 96% *ee*). Given the simplest structure of catalyst **C4**, we chose it as the most convenient to evaluate the scope of the reaction.

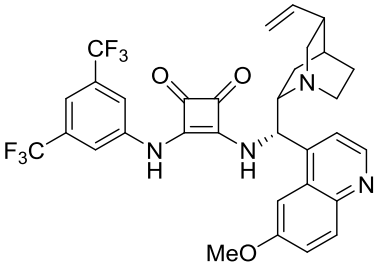
Table 1. Catalyst screening for the reaction of **2a** with nitrostyrene **3a**.[a]



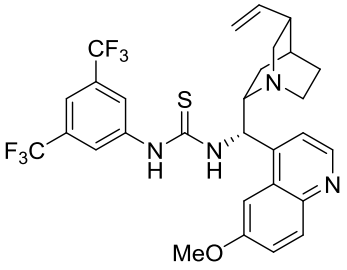
2a + **3a** → **4aa**



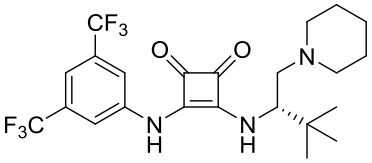
C1
95%, 62:38 *dr*, 94% *ee*



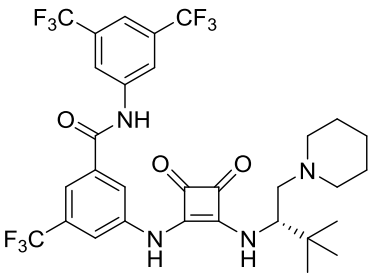
C2
99%, 83:17 *dr*, 88% *ee*



C3
99%, 60:40 *dr*, 75% *ee*



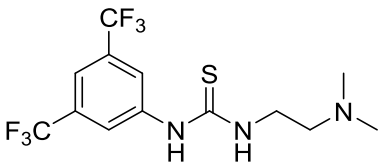
C4
99%, 97:3 *dr*, 96% *ee*



C5
95%, 96:4 *dr*, 95% *ee*

[a] The reactions were performed using 0.2 mmol of **2a**, 0.4 mmol of nitrostyrene **3a** and 10 mol% catalyst in 0.6 mL CH_2Cl_2. *ee* of major diastereoisomer was determined by ^{1}H-NMR and by chiral HPLC.

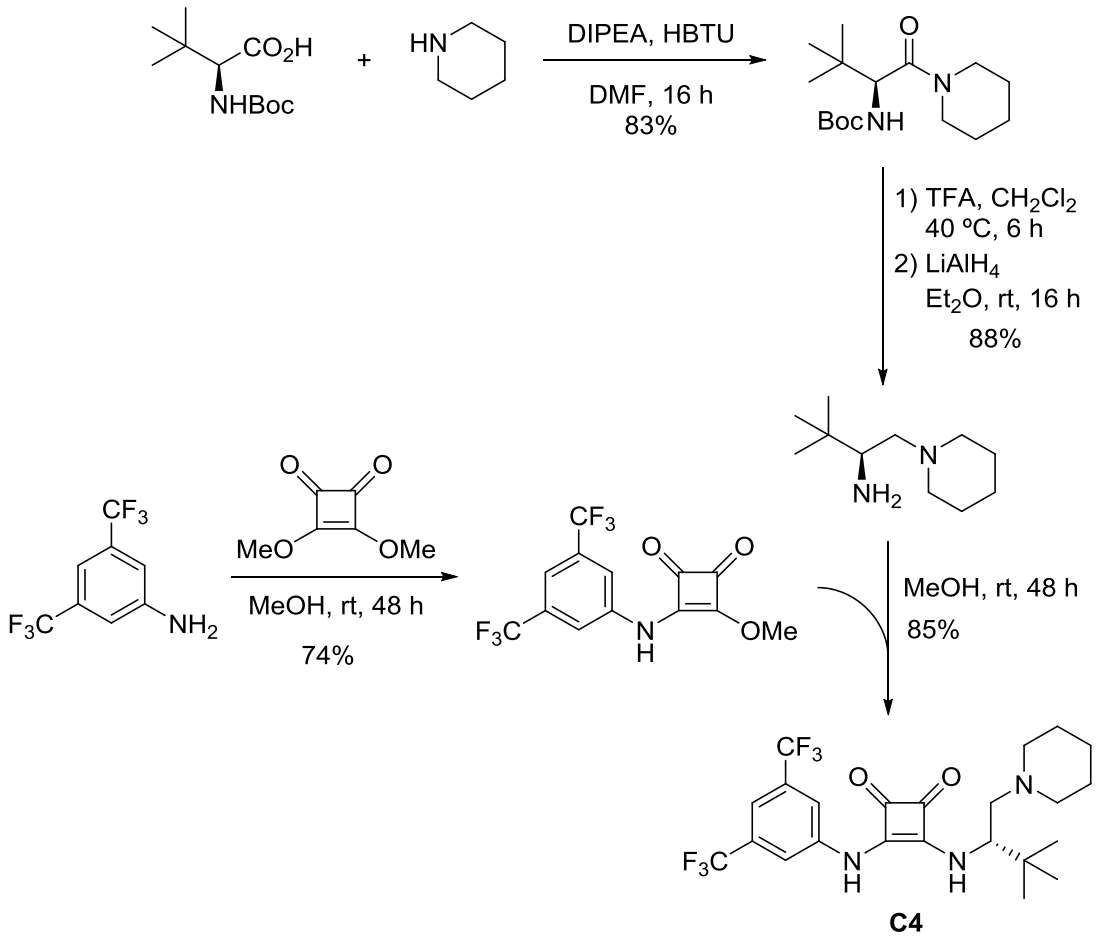
The racemic adducts were prepared according to the general procedure as for the asymmetric version described above using a 20 mol% of the achiral catalyst depicted in Figure 28.



C6

Figure 28. Achiral organocatalyst used in the racemic reaction.

The chosen catalyst **C4** was easily prepared following the synthetic pathway described in Scheme 41. On the one hand, the *N*-Boc-protected *tert*-leucine was coupled with piperidine in the presence of DIPEA and HBTU leading to the formation of amino amide intermediate in a 83% yield. After the deprotection with TFA, the amide was reduced with lithium aluminum hybride affording the diamine in 88% yield. In parallel, the electron deficient aniline was reacted with dimethyl squarate followed by the final coupling with the free amine led to organocatalyst **C4** in 85% yield.

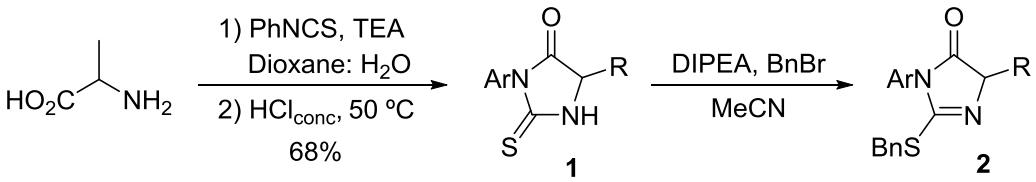


Scheme 41. Synthesis of catalyst **C4**, the catalyst selected for the study of the reaction scope.

2.3.3. Synthesis of imidazolone based pronecleophiles

Once we verified the screening results were good enough to continue with the project, we started the synthesis of the imidazolone based pronucleophiles **2**. As Table 2 shows, following the previous described protocol, the corresponding thiohydantoin **1** were obtained in moderate yields whereas the alkylation step to produce the pronucleophiles **2** turned out to be more efficient. An important note to underline is that this substrates, unlike the ones from the previous work (the N^1-alkylated compounds), are solids and stable for months at 0 °C.

Table 2. The benzylation of thiohydantoins.



Entry	R	Compound	Ar	Step 1 (%)[a]	Step 2 (%)[a]
1	Me	**2a**	Ph	68	82
2	Me	**2b**	4-MeC_6H_4	60	81
3	Me	**2c**	4-MeOC_6H_4	66	79
4	Me	**2d**	4-ClC_6H_4	64	83
5	Me	**2e**	3-ClC_6H_4	62	80
6	Bn	**2f**	Ph	72	79

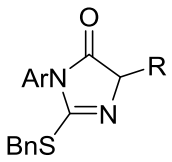
[a] The yield refers to the weight of the isolated product.

2.3.4. Reaction scope

At this point, we decided to proceed to study the reaction scope between *N*-aryl substrates **2** and nitrostyrenes **3** using the catalyst **C4** under the optimized conditions (Table 3). The addition tolerates different substitution patterns in the aromatic ring at the N^3 position of the pronucleophile and also in the aromatic system of the nitroalkene bearing both electron withdrawing and donating groups the results were equally maintained independently of the position they take on the ring (ortho, meta or para). In four of the examples described, a single diastereomer was obtained and the rest two afforded a ratio of 93:7. Regarding the enantioselectivity, almost all examples yielded the corresponding adducts with enantiomeric excesses greater than 90%. The only case where the *ee* was lower resulted adduct **4ec** (87%).

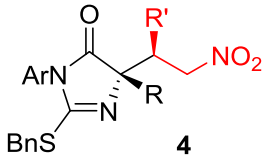
Table 3. Scope of the catalytic reaction of 1*H*-imidazol-5(4*H*)-ones **2** with nitroalkenes **3**.[a]

2a R = Me, Ar = Ph
2b R = Me, Ar = 4-Me-C_6H_4
2c R = Me, Ar = 4-MeO-C_6H_4
2d R = Me, Ar = 4-Cl-C_6H_4
2e R = Me, Ar = 3-Cl-C_6H_4
2f R = Bn, Ar = Ph



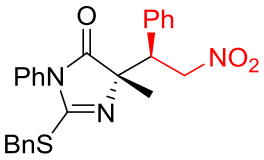
+

C4 (10 mol%)
CH_2Cl_2, –20 °C, 15-20 h

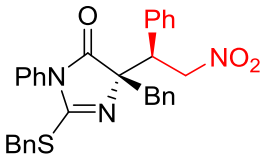


4

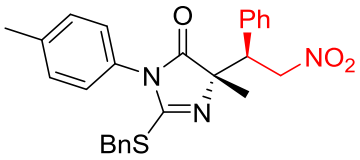
3a R' = Ph
3b R' = 2-Cl-C_6H_4
3c R' = 4-MeO-C_6H_4



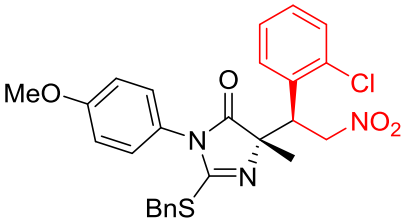
4aa
99%, 99:1 *dr*, 99% *ee*



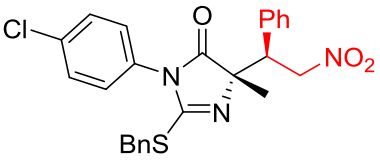
4fa
90%, 93:7 *dr*, 98% *ee*



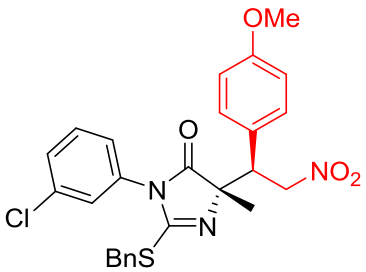
4ba
89%, 99:1 *dr*, 97% *ee*



4cb
91%, 99:1 *dr*, 93% *ee*



4da
90%, 99:1 *dr*, 94% *ee*



4ec
90%, 93:7 *dr*, 87% *ee*

[a] Reaction conditions: **2** (1 equiv., 0.2 mmol), **3** (2 equiv., 0.4 mmol) and **C4** (10 mol%) were stirred at --20 °C for 15-20 h in 0.6 mL of CH_2Cl_2. Diastereomeric ratio and *ee* of major diastereoisomer was determined by ^{1}H-NMR and by chiral HPLC.

In order to explain the stereochemical induction exerted by catalyst **C4**, we considered the dual activation proposed by Takemoto, and later by Papai and Zhong, and proposed a model in which the catalyst first deprotonates the pronucleophile at the α-position to the carbonyl, to generate the corresponding enolate which could be stabilized by H-bonding and π-interactions between the aromatic rings. At the same time, the protonated tertiary amine could activate and orientate the electrophile with both reagents approaching each other from *Si* faces (Figure 29).

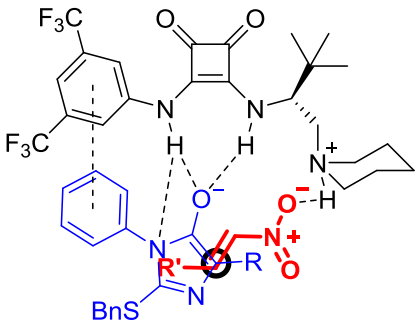
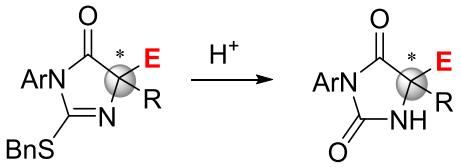


Figure 29. Proposed transition-state stereomodel.

2.3.5. Elaboration of adducts

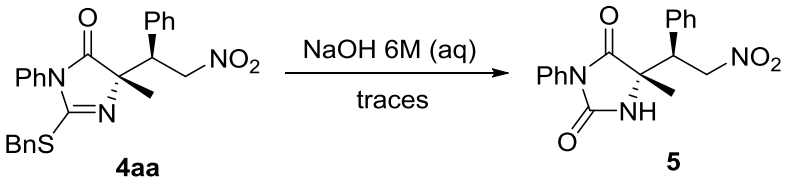
The next step of our work focused in the application of the developed methodology to the synthesis of chiral derivatives of 3-aryl-*N*-hydantoins 5,5-disubstituted with possible interest as complex molecules with biological activity (Scheme 42).



Scheme 42. Synthesis of hydantoin chiral derivatives.

Our first objective consisted in the transformation of the heterocycle to yield the corresponding hydantoin. Inicially, the hydrolysis of the starting material was carried out following the procedure described in our group for the displacement of the thioether phenylthio-4,5-dihydroimidazol-4-one **4aa** using NaOH.[129] However, under these reaction conditions all the product was consumed due to the retro-Michael reaction and only traces of the prodcut **5** were detected (Scheme 43).

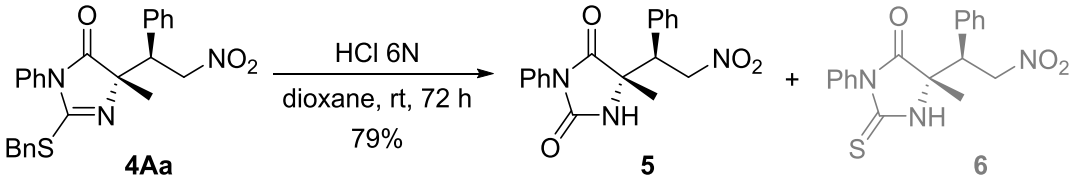
[129] See reference 125.



Scheme 43. Hydrolysis of **4aa**.

Next, the hydrolysis of the Michael adduct **4aa** was tried with acidic conditions, HCl 6N, dioxane as solvent and heating the reaction at reflux for 6 h. Under these reaction conditions, a 1:1 mixture of the hydantoin **5** and the thiohydantoin **6** was obtained. To control the regioselectivity, the reaction was repeated at room temperature and, fortunately, just hydantoin **5** was obtained without observing the presence of thiohydantoin **6** (Table 4).

Table 4. Hydrolysis of **4aa**.



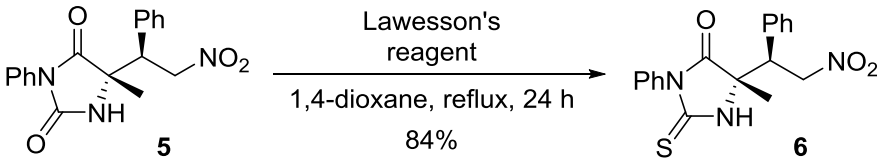
T (°C)	5	6
reflux	50	50
rt	100	-

[a] Ratio was determined by ^{1}H-NMR of the crude.

Facing this result, and due to the importance that thiohydantoins have as great biological active compounds,[130] we decided to study an approach to the synthesis of **6** following the procedure described by Jaehne[131] which consisted in the treatment of the hydantoin **5** with Lawesson's reagent in dry dioxane at reflux over 24 h (Scheme 44).

[130] a) Attanasi, O. A.; de Crescentini, L.; Filippone, P.; Giorgi, G.; Nicolini, S.; Perrulli F. R.; Santeusanio, S. *Tetrahedron* **2014**, *70*, 7336-7343. b) Mehra, V.; Singh, P.; Manhas N.; Kumar, V. *Synlett* **2014**, *25*, 1124-1126. c) Gosling, S.; Amri C. E.; Tatibouët, A. *Synthesis* **2014**, *46*, 1079-1084. d) Ceban, V.; Hands, K.; Meazza, M.; Light M. E.; Rios, R. *Tetrahedron Lett.*, **2013**, *54*, 7183-7187.

[131] Jaehne, G.; Stengelin, S.; Gossel, M.; Winkler, I.; Bigot, A.; Diu-Hercend, A. PCT Int. Appl. (2009), WO 2009097996 A1 20090813.



Scheme 44. Synthesis of thiohydantoin **6**.

Crystallization of the adduct **6** allowed the determination of its absolute and relative configuration by a single-crystal X-ray analysis (Figure 30), which was assumed for the rest of adducts on the basis of an uniform reaction mechanism.

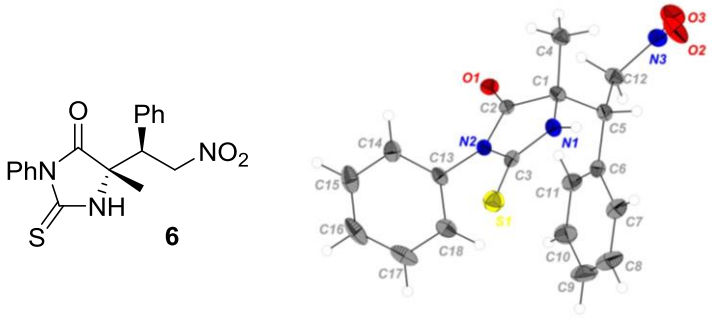
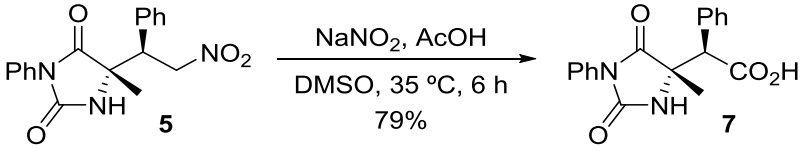


Figure 30. Structure of the compound **6** obtained by X rays.

Finally, using the versatility that the nitro group offers, we followed the procedure described by Mioskowski[132] to achieve the corresponding carboxylic acid **7** through acid hydrolysis with sodium nitrite and mild reaction conditions affording the product in 79% yield (Scheme 45).

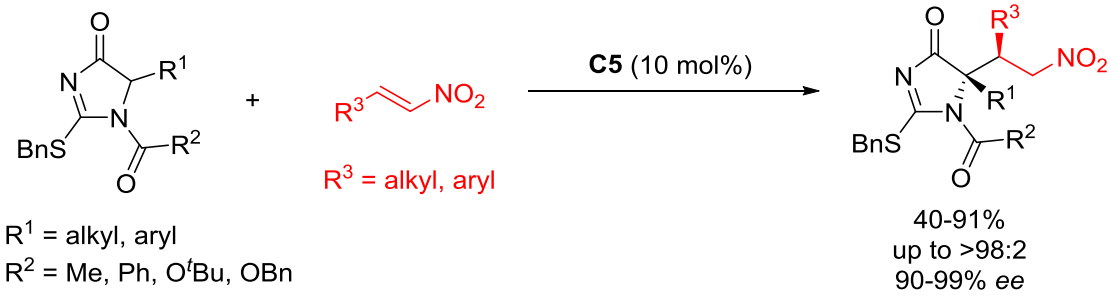


Scheme 45. Conversion of **5** to **7**.

During his PhD, Joseba Izquierdo, from our research group, performed the Michael addition of N^1-acyl imidazolones to nitroolefins and enones. No matter the substitution at the N^1 and at the α position of the imidazolone; the electron-rich, neutral or poor character of the aryl-substituted nitroolefins; and the alkyl or aromatic groups of the vinyl ketones, all of tested products showed to be excellent reaction partners affording the final

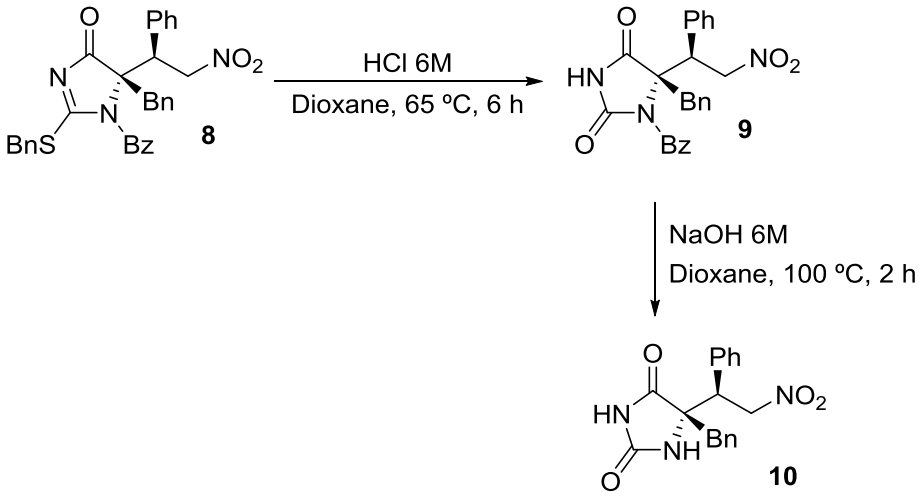
[132] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.***1997**, *62*, 234–235.

products in really good yields and almost perfect enantio- and diastereoselectivities (Scheme 46).



Scheme 46. Conjugate addition of N^1-acyl imidazolones to nitroalkenes.

In the same proyect, Dr. Izquierdo also studied the transformation potential of the imidazolone adducts (Scheme 47). Starting with the adduct **8**, treatment with HCl 6N heating at 65 °C gave rise to *N*-acyl hydantoin **9** and subsequently with NaOH 6M at 100 °C produced the final product, free hydantoin **10**.



Scheme 47. Elaboration of the adduct **8**.

CHAPTER 3

3. MICHAEL ADDITION OF ACYLPYRROL LACTIMS TO NITROOLEFINS. ACCESS TO CHIRAL PYRROLODIKETOPIPERAZINES

3.1. Introduction

The 2,5-diketopiperazine (2,5-DKP)[133] motif is spread over many disciplines of organic chemistry including natural products, synthesis, medicinal chemistry, synthetic methodology, etc. Organic molecules containing the 2,5-DKP constrained scaffold usually display important and interesting properties as a result of their structural rigidity and stability. In particular, 3,6-disubstituted 2,5-DKPs, the smallest cyclic peptides made up of two α-amino acid residues, offer an attractive solution to the longstanding peptide paradox in medicinal chemistry, i.e. high efficacy, selectivity and tolerability *versus* unstability, fast elimination and poor oral availability.[134] Indeed, the 2,5-DKP scaffold, which can mimic a preferential peptide conformation and avoid undesired physical and metabolic properties, is recurrent in synthetic products with biological activity (Figure 31).[135]

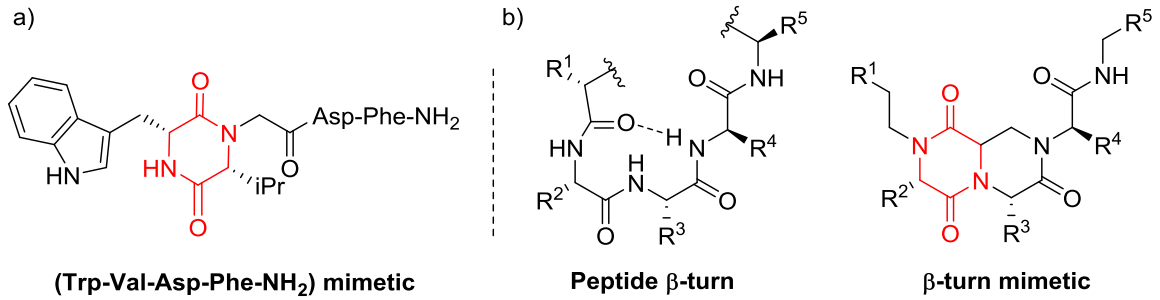


Figure 31. a) Mimicking tetrapeptide bioactive conformation. b) Mimicking protein secondary structure.

[133] For selected reviews on diketopiperazines, see: a) Borthwick, A. D. *Chem. Rev.* **2012**, *112*, 3641-3716. b) Mishra, A. K.; Choi, J.; Choi, S.-J.; Baek, K.-H. *Molecules* **2017**, *22*, 1796-1808. c) Zhao, K.; Xing, R.; Yan, X. *J. Pept. Sci.* **2021**, *113*, e24202. d) Bojarska, J.; Mieczkowski, A.; Ziora, Z. M.; Skwarczynski, M.; Toth, I.; Shalash, A. O.; Parang, K.; El-Mowafi, S. A.; Mohammed, E. H. M.; Elnagdy, S.; Alkhazindar, M.; Wolf, W. M. *Biomolecules* **2021**, *11*, 1515-1578. e) Balachandra, C.; Padhi, D.; Govindaraju, T. *Chem. Med. Chem*. **2021**, 2558-2587.

[134] Fosgerau, K; Hoffmann, T. *Drug Discovery Today* **2015**, *20*, 122-128.

[135] See for instance: a) de Tullio, P.; Delarge, J.; B. Pirotte. *Curr. Med. Chem*. **1999**, *6*, 433-455. b) Ressurreição, A. S. M.; Delatouche R.; Gennari, C.; Piarulli, U. *Eur. J. Org. Chem*. **2011**, *2*, 217-228.

Aditionally, the DKP moiety has the ability to easily bind to hydrogen-bond donor and acceptor sites improving the biological activities shown by the corresponding linear dipeptides.[136]

Isolation from natural sources is the main origin of biologically active 2,5-DKPs although synthetic methodologies, mainly based on classical condensation of chiral dipeptide precursors, are traditionally applied to produce the target DKPs (Figure 32).[137]

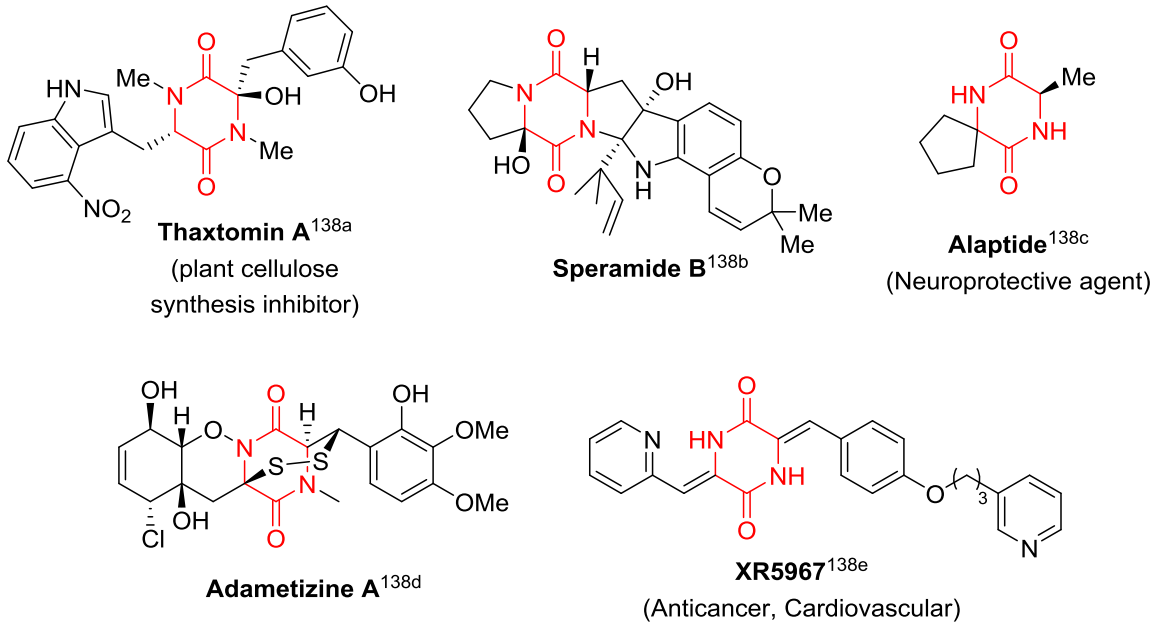


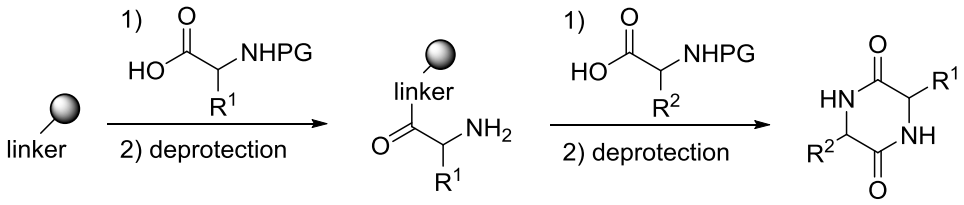
Figure 32. A small sampling of biologically active 2,5-DKPs.[138]

[136] a) Prasad, C. *Peptides* **1995**, *16*, 151-164. b) Chin, D. N.; Palmore, T. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 2115-2122. c) Donkor, I. O.; Sanders, M. L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2647–2649. d) Nam, N.-H.; Ye, G.; Sun, G.; Parang, K. *J. Med. Chem.* **2004**, *47*, 3131–3141. e) Kaur, N.; Zhou, B.; Breitbeil, F.; Hardy, K.; Kraft, K. S.; Trantcheva, I.; Phanstiel IV, O. *Mol. Pharm.* **2008**, *5*, 294-315. f) Ma, Y.-M.; Liang, X.-A.; Kong, Y. ; Jia, B. *J. Agric. Food Chem.* **2016**, *64*, 6659-6671. g) Yang, M.; Luo, J.; Zeng, Z.; Yang, L.; Xu, L.; Li, Y. *J. Mol. Graphics Modell.* **2019**, *89*, 178-191.

[137] For representative synthesis, see: a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953-11963. b) Horton, D.A.; Bourne, G. T.; Smythe, M. L. *Mol. Divers.* **2000**, *5*, 289-304. c) Dinsmore, C. J.; Benshore, D. C. *Tetrahedron* **2002**, *58*, 3297-3312. d) Richard, D. J.; Schiavi, B.; M. Joullie, M. M. *Proc. Nat. Acad. Sci*. **2004**, *102,* 11971-11976. e) Aboussafy, C. L.; Clive, D. L. J. *J. Org. Chem.* **2012**, *77*, 5125-5131.

[138] For selected examples of biologically active 2,5-DKPs, see a) King, R. R.; Calhoun, L. A. *Phytochemistry* **2009**, *70*, 833-841. b) Chang, Y.-W.; Yuan, C.-M.; Zhang, J.; Liu, S.; Cao, P.; Hua, H.-M.; Di, Y.-T.; Hao, X.-J. *Tetrahedron Lett.* **2016**, *57*, 4952-4955. c) Julinek, O.; Setnicka, V.; Rezacova, A.; Dohnal, J.; Vosatka, V.; Urbanova, M. *J. Pharma. Biomed. Anal*. **2010**, *53*, 958-961. d) Liu, Y.; Li, X.-M.; Meng, L.-H.; Jiang, W.-L.; Xu, G.-M.; Huang, C.-G.; Wang, B.-G. *J. Nat. Prod.* **2015**, *78*, 1294-1299. e) Brooks , T. D.; Wang, S. W.; Brünner, N.; Charlton, P. A. *Anticancer Drugs* **2004**, *15*, 7-44.

In addition to conventional methodologies, solid-phase synthesis has emerged as one of the most practical methods to obtain these cyclic structures and create combinatorial libraries. [139] The large supply of resins, protecting groups and cleavage types, provides highly efficient protocols in which the cyclization step is promoted by intramolecular aminolysis affording the free DKPs from the resin in a convenient way (Scheme 48).



Scheme 48. A solid-phase generic synthesis of 2,5-DKPs.

2,5-DKP scaffolds are also interesting candidates in organocatalysis. They have been employed in several asymmetric carbon-carbon bond-forming reactions acting at some instances as bifunctional catalysts, through covalent and non-covalent interactions (Figure 33).[140]

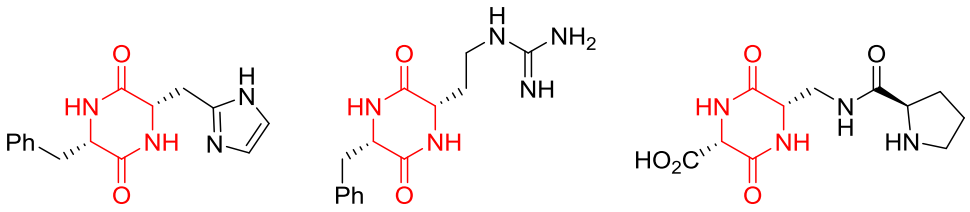


Figure 33. Representative examples of 2,5-DKPs employed as organocatalysts.

On the other hand, pyrrolodiketopiperazines and (dihydro)pyrrolopiperazinones constitute a particular subfamily of 2,5-DKPs in which the pyrrol and the (di)ketopyperazine rings are fusioned to raise a particular framework that appears within

[139] a) Wang, D.-X.; Liang, M.-T.; Tian, G.-J.; Lin, H.; Liu, H.-Q. *Tetrahedron Lett.* **2002**, *43*, 865-867. b) Li, W.-R.; Yang, J. H. *J. Comb. Chem.* **2002**, *4*, 106-108. c) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923-9932. c) Couladouros, E. A.; Magos, A. M. *Mol. Diversity*, **2005**, *9*, 111-121. For a review, see: d) Fischer, P. M. *J. Pept. Sci.* **2003**, *9*, 9-35 and references cited therein.

[140] For selected examples, see: a) Oku, J. I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229-230. a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911. b) Durini, M.; Sahr, F. A.; Kuhn, M.; Civera, M.; Gennari, C.; Piarulli, U. *Eur. J. Org. Chem.* **2011**, 5599-5607.

a wide range of bioactive natural products isolated from various sources as fungi, plants or sponges.[141] In contrast to classic DKPs, methods for the construction of these natural compounds remain somewhat limited, especially in the case of pyrrolodiketopiperazines, due probably to its relatively recent isolation. Furthermore, most synthetic efforts have been directed toward the preparation of representative members, isolated from natural sources, rather than designing effective catalytic processes to access pyrrolodiketopiperazine diversity (Figure 34).

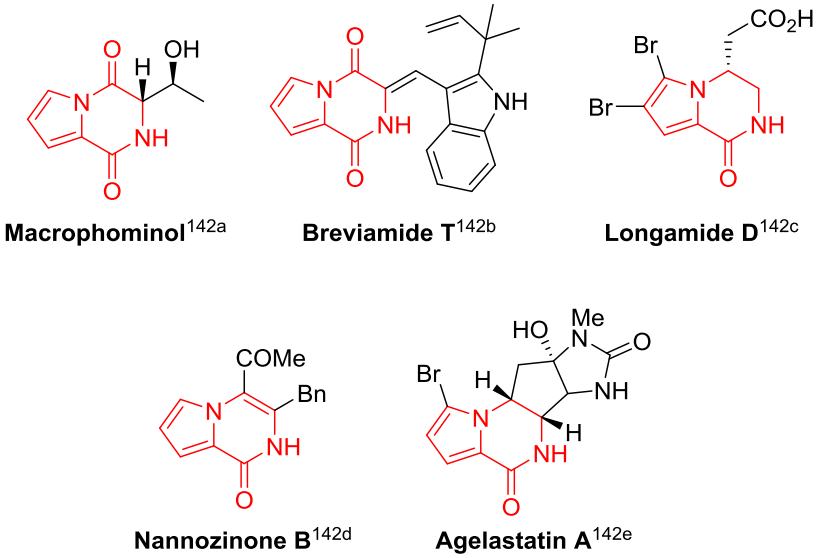


Figure 34. Selected pyrrolodiketopyperazines and pyrrolopyrazinone compounds with biological activity.[142]

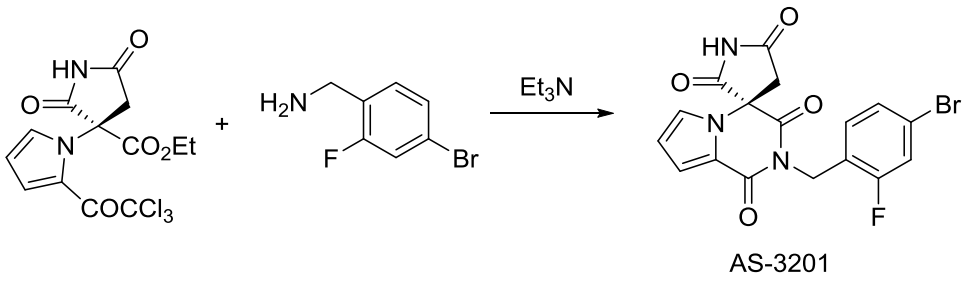
A pioneer example for the generation of structural diversity was described by Matsumoto and coworkers in 1998.[143] The authors described a protocol to produce a

[141] a) Rowan, D. D.; Hunt, M. B.; Gaynor, D. L. *J. Chem. Soc., Chem. Commun.* **1986**, 935-936. b) Miyashiro, J.; Woods, K. W.; Park, C. H.; Liu, X.; Shi, Y.; Johnson, E. F.; Bouska, J. J.; Olson, A. M.; Luo, Y.; Fry, E. H.; Giranda, V. L.; Penning, T. D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4050-4054. c) Shiokawa, Z.; Kashiwabara, E.; Yoshidome, D.; Fukase, K.; Inuki, S.; Fujimoto, Y. *ChemMedChem.* **2016**, *11*, 2682-2689. d) Winant, P.; Horsten, T.; Gil de Melo, S. M.; Emery, F.; Dehaen, W. *Organics* **2021**, *2*, 118-141.

[142] a) Trigos, A.; Reyna, S.; Matamoros, B. *Phytochemistry* **1995**, *40*, 1697-1698. b) Song, F.; Liu, X.; Guo, H.; Ren, B.; Chen, C.; Piggott, A. M.; Yu, K.; Gao, H.; Wang, Q.; Liu, M.; Liu, X.; Dai, H.; Zhang, L.; Capon, R. J. *Org. Lett.* **2012**, *14*, 4770-4773. c) Cafieri, F.; Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1999**, *61*, 122-125. d) Jansen, R.; Sood, S.; Mohr, K. I.; Kunze, B.; Irschik, H.; Stadler, M.; Müller, R. *J. Nat. Prod.* **2014**, *77*, 2545-2552. e) Hama, N.; Matsuda, T.; Sato, T.; Chida, N. *Org. Lett.* **2009**, *11*, 2687-2690.

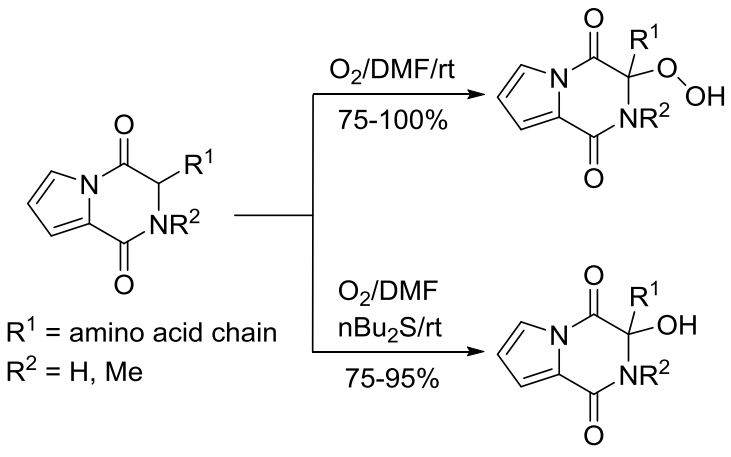
[143] a) Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Komiya, M.; Suzuki, K.; Matsumoto, J.-I. *J. Med. Chem.* **1998**, *41*, 4118-4129. b) Matsumoto, T.; Ono, Y.; Kurono, M.; Kuromiya, A.; Nakamura, K.; Bril, V. J. *Pharmacol Sci*, **2008**, 107, 231-237.

novel class of spirosuccinimide-fused pyrrolodiketopiperazines, amongst which compound AS-3201 (ranirestat) potently inhibited sorbitol accumulation in the sciatic nerve of the diabetic rats at low oral doses (Scheme 49). The enantiomerically enriched succinimide, employed in the ring closure by condensation with primary amines, was obtained by chemical resolution.



Scheme 49. Synthesis of the highly potent aldose reductase inhibitor AS-3201.

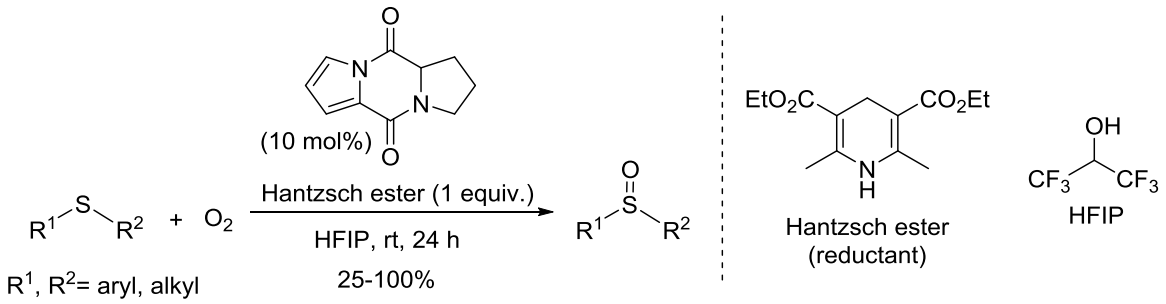
In the context of the construction of three-dimensional pyrrolodiketopiperazine scaffolds bearing tetrasubstituted stereocenters, Al-Mourabit and coworkers described the aerobic oxidation of α-amino acids acylated by pyrrole-carboxylic acid by the action of triplet dioxygen (Scheme 50).[144] The non-catalyzed direct oxidation is general and represents a very practical method for the selective preparation of chiral α-hydroperoxy- or α-hydroxy-α-amino acid derived pyrrolodiketopiperazines, although in its racemic version.



Scheme 50. Oxidation of pyrrolo 2,5-DKPs with O_2 in DMF.

[144] Tian, H.; Ermolenko, L.; Gabant, M.; Vergne, C.; Moriou, C.; Retailleau, P.; Al-Mourabit, A. *Adv. Synth. Catal.* **2011**, *353*, 1525-1533.

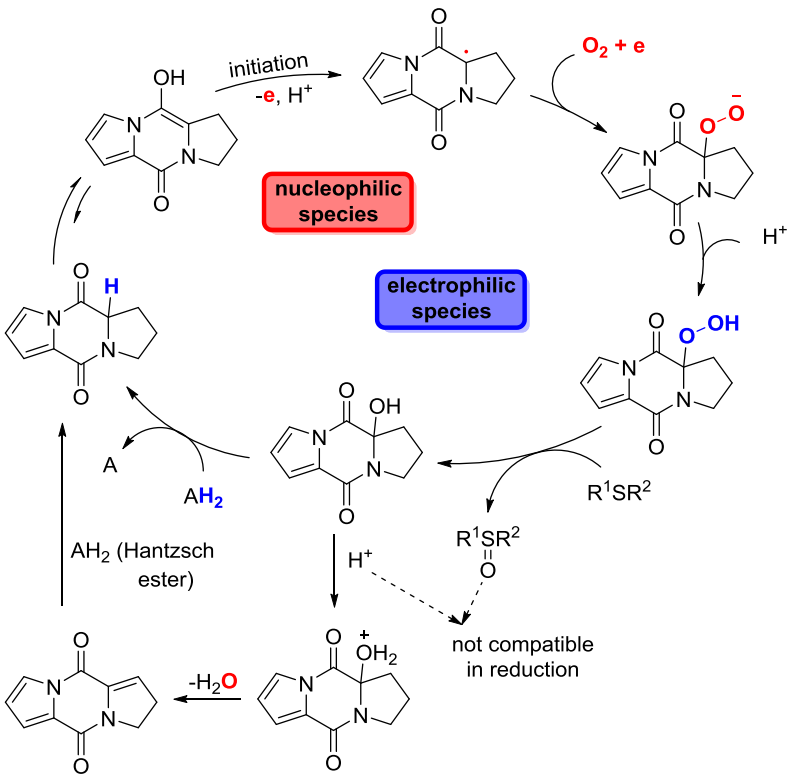
Recently, Zografos and co-workers have employed the ability of natural and non-natural dipeptides to act as activators of dioxygen in the absence of metallic catalysts to perform chemoselective aerobic oxidation processes.[145] The proline derived pyrrolodiketopiperazine shown in Scheme 51, serves as substochiometric mediator for the oxidation of sulphides, the epoxidation of alkenes and the oxidative coupling of phenols. In an unprecedented way, the dipeptide is able to catalyse the reduction of molecular dioxygen avoiding the use of light or radical initiators, representing the closest example to the way of action of cofactor independent monooxygenases.



Scheme 51. Pyrrolo DKP promoted aerobic oxidation of thiols.

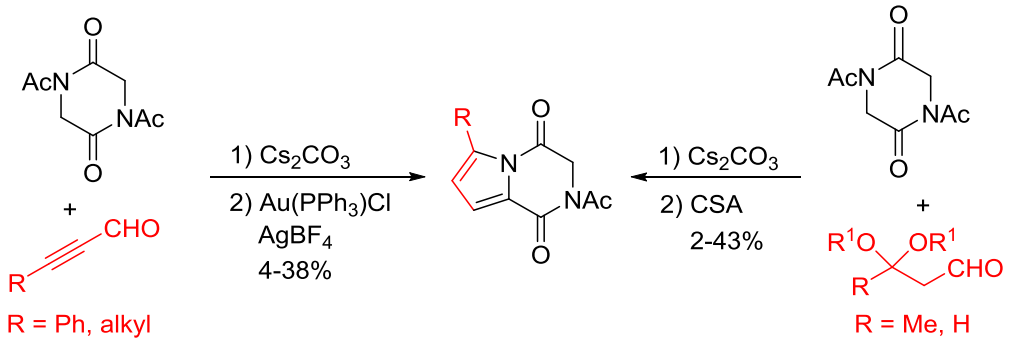
For the sulfoxidation cycle, the authors proposed a mechanism that starts by the removal of a proton and an electron from the enol form of the DKP. The resultant radical species is transferred to dioxygen, forming the corresponding peroxy anion, which is protonated to afford the hydroperoxide electrophilic species and reacts with the sulfide to produce the corresponding sulfoxide and the hydroxyl-DKP. The addition of the hydrogen-bonding mediator HFIP promotes hydroxyl cleavage and regenerates the catalyst in the presence of the appropriate reducing agent (Scheme 52).

[145] Petsi, M.; Zografos, A. L. *ACS Catal.* **2020**, *10*, 7093-7099.



Scheme 52. Proposed catalytic cycle for the aerobic oxidation of sulfides in the presence of pyrrolo DKP catalyst.

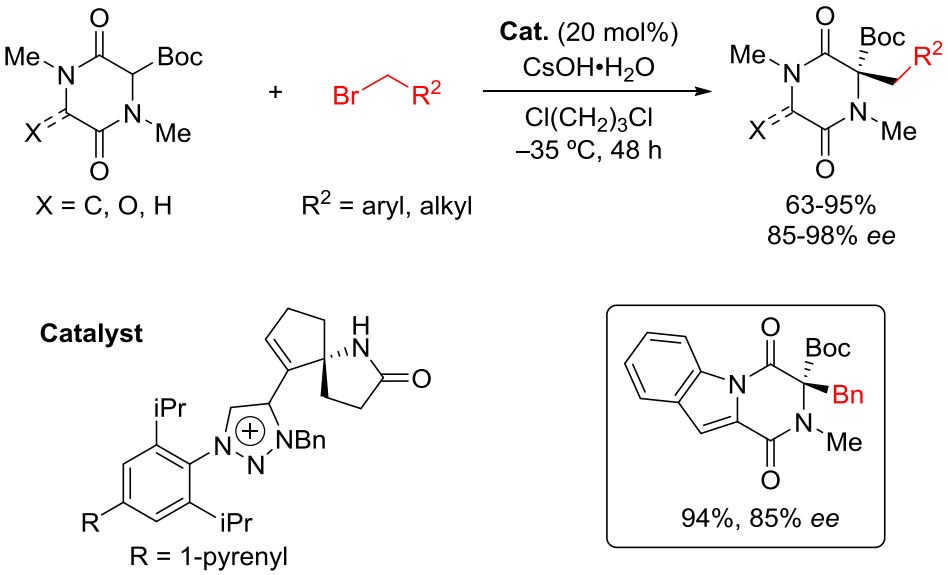
Also in 2020, the group of Scheerer developed a new two-step method for the annulation of a pyrrole ring to a diketopiperazine precursor (Scheme 53).[146] The sequence is initiated by the aldol condensation of a 2,5-DKP with either an alkynyl aldehyde or a 1,3-dicarbonyl derivative, followed by cyclization promoted by cationic gold complexes or protic acids, respectively.



Scheme 53. Synthesis of pyrrolo DKPs by construction of the pyrrole ring.

[146] Maisto, S. K; Leersnyder, A. P.; Pudner, G. L.; Scheerer, J. R. *J. Org. Chem*. **2020**, *85*, 9264–9271.

Last year, the groups of Zhang and Tu reported the use of chiral spirocyclic-amide-derived triazolium salts as PTC in the construction of 2,5-diketopiperazine motifs containing one or two tetrasubstituted carbon centers in high yields and excellent stereoselectivity (Scheme 54).[147] Only one indolediketopyperazine was prepared in this context, highlighting the low development of the field.



Scheme 54. Enantioselective monoalkylation of 2,5-DKP.

The lack of asymmetric methodologies for the preparation of pyrrolodiketopiperazines, in comparison to common DKPs, prompted us to develop an organocatalytic strategy that could address their synthesis focusing in two main issues: the challenging generation of tetrasubstituted stereocenters and the production of skeleton diversity in the heterocyclic scaffold.

[147] Yang, J.-S.; Lu, K.; Li, C.-X.; Zhao, Z.-H.; Zhang, X.-M.; Zhang, F.-M.; Tu, Y.Q. *Angew. Chem. Int. Ed.* **2022**, *61*, e202114129.

3.2. Our approximation

In the context of producing families of complex structure products, the pyrrolodiketopiperazine skeleton contains the adequate features to take part in CtD (complexity to diversity) and DOS (diversity-oriented synthesis) strategies and indeed comprises the design principles of pseudo NPs and connectivity patterns stablished to create collections for the modulation of many drug targets (Figure 35).

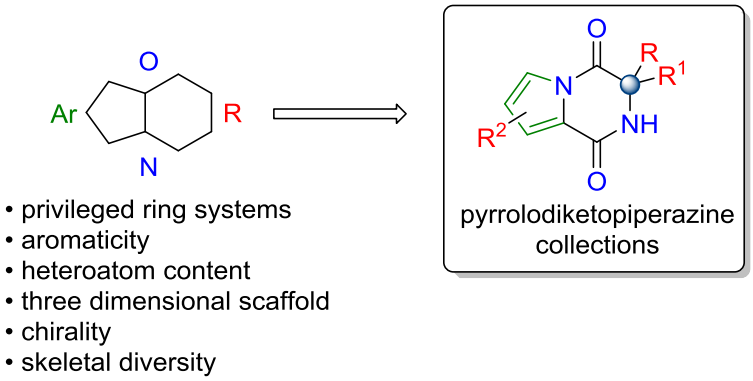
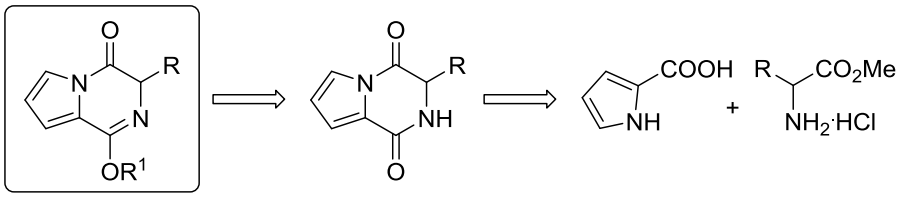


Figure 35. Principles and connectivity patterns for drug discovery that validate the pyrrolodiketopiperazine skeleton.

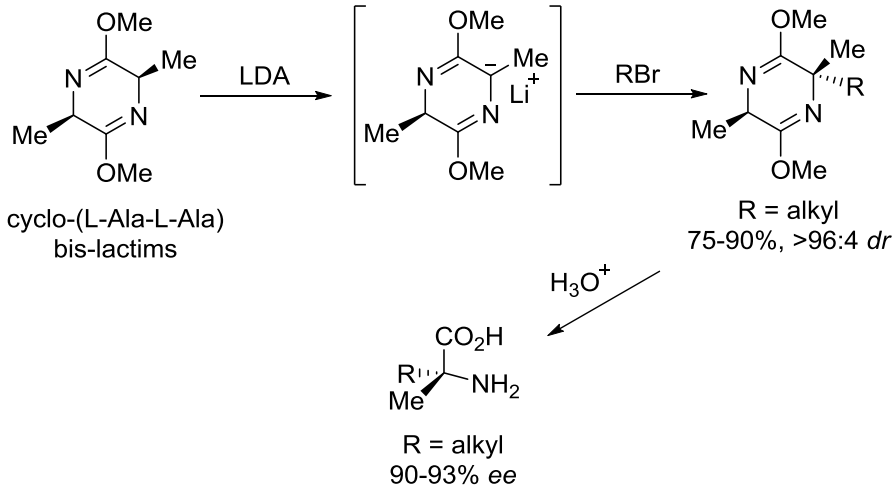
As mentioned in the introduction, there is an increasingly interest, along with catalyst design, for the identification of pronucleophiles that could act as privileged templates in Brønsted base catalyzed transformations. Thus, continuing with our interest in exploiting the propitious steric and electronics features of heterocyclic compounds, we focused our attention in the unexplored bicyclic acylpyrrol lactims (Scheme 55).



Scheme 55. Bicyclic acylpyrrol lactims from α-amino acids.

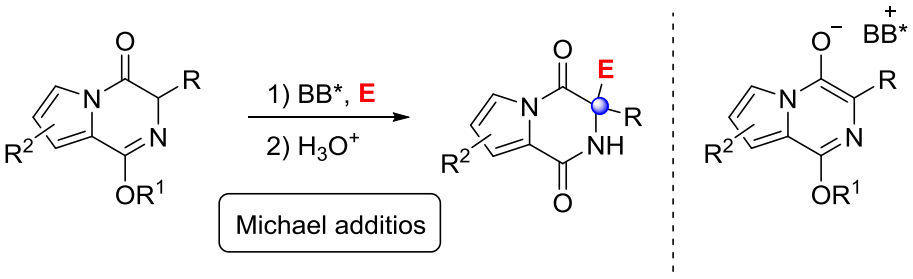
Bicyclic acylpyrrol lactims could be considered as Schöllkopf bis-lactims surrogates, except for the fact that the Schöllkopf bis-lactim ether requires stoichiometric amounts

of a strong base to generate the lithium carbanion that subsequently reacts with the electrophile (Scheme 56).[148]



Scheme 56. Enantioselective synthesis of α-methyl-α-aminocarboxylic acids.

In contrast, the suitability of these new pronucleophiles **13** toward deprotonation through the formation of pseudoaromatic enolates, would constitute a facile strategy for the creation of structural and stereochemical diversity from readily available α-amino acids. Thus, we envisaged developing a general asymmetric Brønsted-base catalyzed Michael addition of bicyclic acylpyrrol lactims **13** using different electrophiles to afford high skeleton diversity with chemical and stereochemical efficiency (Scheme 57).



Scheme 57. Main objective: Brønsted base catalyzed Michael additions toward chiral pyrrolo DKPs.

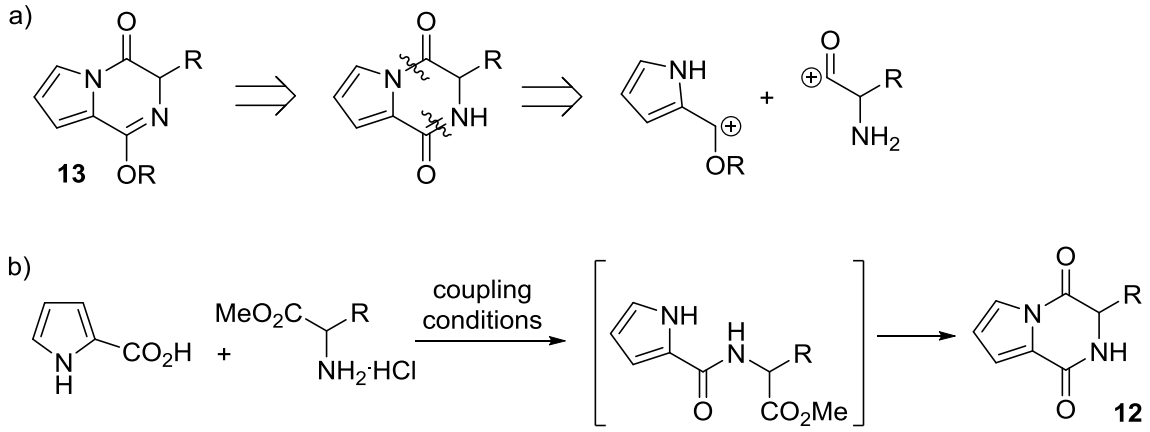
[148] a) Schöllkopf, U.; Hartwig, W.; Groth, U. *Angew. Chem. Int. Ed.* **1979**, *18*, 863-864. b) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed.* **1981**, *20*, 798-799. c) Schöllkopf, U. *Tetrahedron*, **1983**, *39*, 2085-209.

3.3. Results and discussion

3.3.1. Initial experiments and catalytic design

3.3.1.1. Synthesis of acylpyrrol lactims (pyrrolo[1,2-a]pyrazin-4(3H)-one)

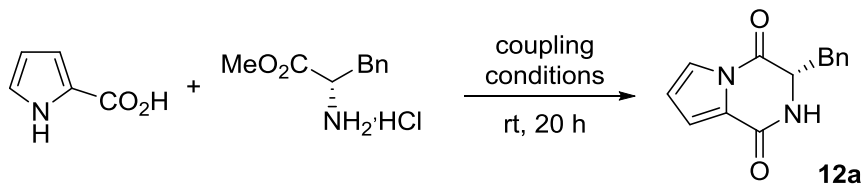
In order to address our goal, we first pursued an efficient protocol for the synthesis of bicyclic acylpyrrol lactims **13** (Scheme 58a). We envisioned that coupling of α-substituted amino acids with pyrrole-2-carboxylic acid could afford the corresponding amide, which could subsequently suffer intramolecular cyclization under basic conditions to produce **12** (Scheme 58b).



Scheme 58. a) Strategy for the construction of pyrrolo DKPs. b) Synthetic protocol.

Nevertheless, after testing some standard coupling conditions, using *L*-phenylalanine methyl ester, no conversion into the desired product **11a** was detected and the starting material was recovered (Table 5).

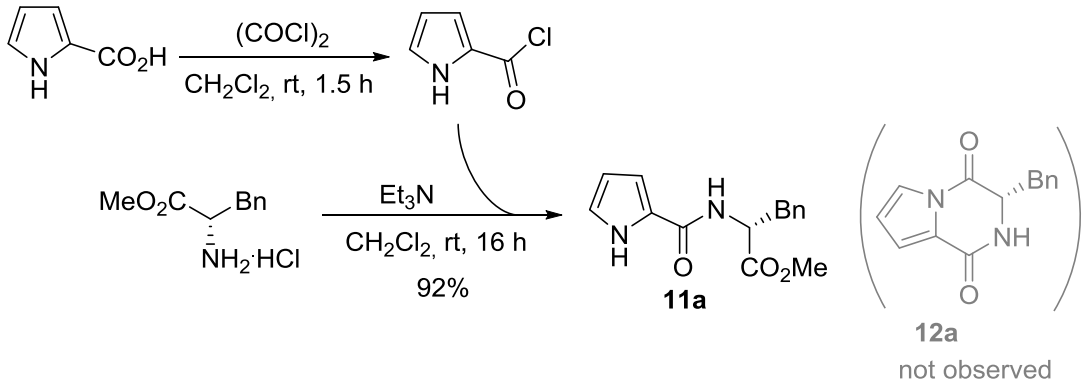
Table 5. Coupling attempts to produce **12a**.[a]



Solvent	Coupling reagent (equiv.)	Base (equiv.)	Additive (equiv.)	Conv. (%)
THF	DCC (1.5)	Et_3N (3)	HOBT (1.5)	NR

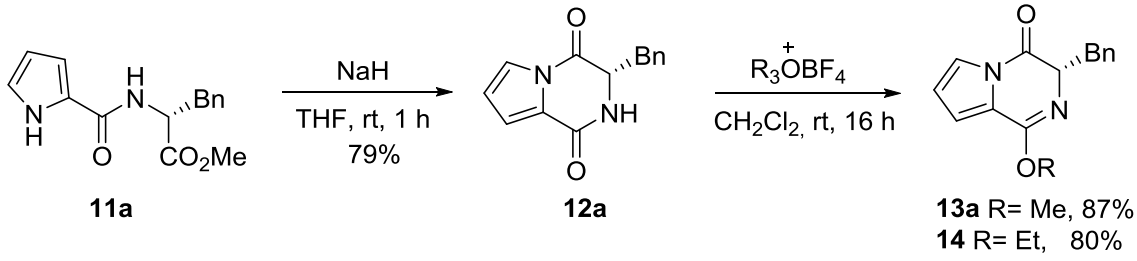
CH_2Cl_2	EDCI (1.3)	Et_3N (3)	DMAP (0.1)	NR
CH_2Cl_2	HBTU (1.1)	DIPEA (3.7)	-	NR

Alternatively, the acyl chloride produced the coupling adduct **11a** in high yield. Notwithstanding, contrary what we had expected, it was not possible to promote the *in situ* intramolecular cyclization, regardless the amount of base and the reaction temperature employed (Scheme 59).



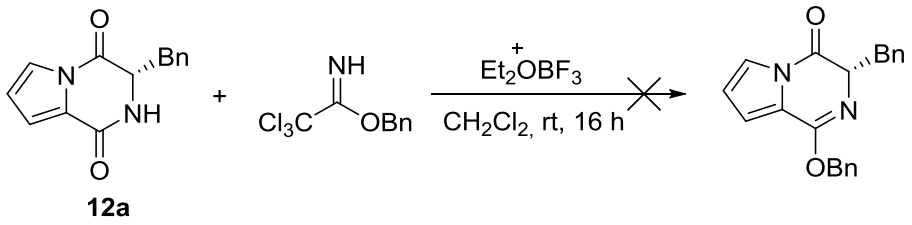
Scheme 59. Dipeptide formation.

Isolation of **11a** and treatment with a stronger base was required to promote the intramolecular reaction (Scheme 60). Finally, the *O*-alkylation of pyrrolo DKP **12a** was effected by reaction with trimethyl- or triethyloxonium tetrafluoroborate to produce the desired acylpyrrol lactims **13a** and **14** as single products in high yield.



Scheme 60. Cyclization and *O*-alkylation reactions to produce **13a** and **14**.

Attempts to prepare other lactimes, such as the analogous benzyloxy one, were unssuscesful regardless the methodoly employed (Scheme 61).[149]



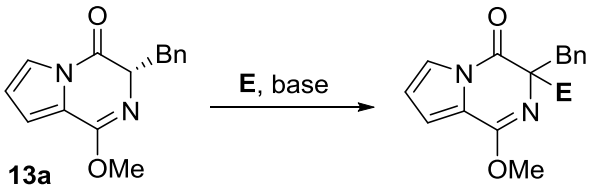
Scheme 61. Attempt to achieve the *O*-benzylated product.

3.3.1.2. Michael addition of acylpyrrol lactims under Brønsted base catalysis

In order to explore the suitability of these novel acylpyrrol lactims toward deprotonation under catalytic conditions, we studied their reaction with different Michael acceptors in the presence of substoichiometric amounts of Brønsted bases (Table 6). Typical activated olefins such as nitroalkenes, vinyl sulphones and α,β-unsaturated carboxyl and carbonyl compounds were chosen along with achiral amines with diverse basic strength.

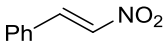
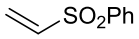
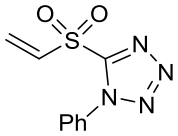
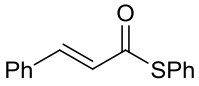
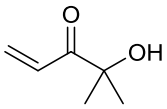
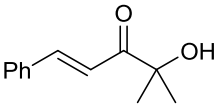
We were very gratified to confirm our hypothesis, since acylpyrrol lactim **13a** was able to react with all the Michael acceptors tested to produce the corresponding adducts. The stronger the base employed, the faster the reaction is over, being of special interest the efficiency of Et_3N since tertiary amines are the most recurrent fragment in chiral Brønsted bases.

Table 6. Preliminar Michael reactions of acylpyrrol lactim **13a** under Brønsted base catalysis.[a]



E	Base	T (°C)	t (h)	Conv. (%)[b]	Yield (%)[c]	*dr*[b]
	NEt_3	rt	16	>95	55	50:50

[149] Hutchby, M.; Sedgwick, A. C.; Bull, S. D. *Synthesis* **2016**, *48*, 2036-2049.

	DBU	0	30 min	>95	61	50:50
	NEt_3	rt	22	>95	71	-
	DBU	0	30 min	>95	79	-
	NEt_3	rt	40	90	70	-
	DBU	0	15 min	>95	74	-
	NEt_3	rt	22	>95	48	70:30
	DBU	0	30 min	>95	53	70:30
	TBD	0	30 min	>95	55	70:30
	MTBD	0	30 min	>95	52	70:30
	NEt_3	rt	16	>95	66	-
	NEt_3	rt	16	>95	71	1:1

[a] Reaction conditions: **13a** 0.1 mmol, **E** 1.5 equiv., 0.15 mmol in CH_2Cl_2 (0.3 mL). [b] Determined by ^{1}H-RMN spectroscopy. [c] Yields refer to isolated adducts.

In order to address the indispensable control over the stereoselectivity, we relied in the proven ability of chiral Brønsted bases linked to hydrogen bond donors to perform under proton transfer conditions. In a first approach, we chose a representative selection of bifunctional catalysts built from chiral tertiary amines derived from *Cinchona* alkaloids and unnatural cyclohexyl platforms linked to ureas, thioureas and squaramides as hydrogen bond donors: ureidoaminal type **C7**, squaramides **C1** and **C2**, and thioureas **C3** and **C8** were synthetized following described methodologies and assayed in the reactions previously shown (Figure 36).

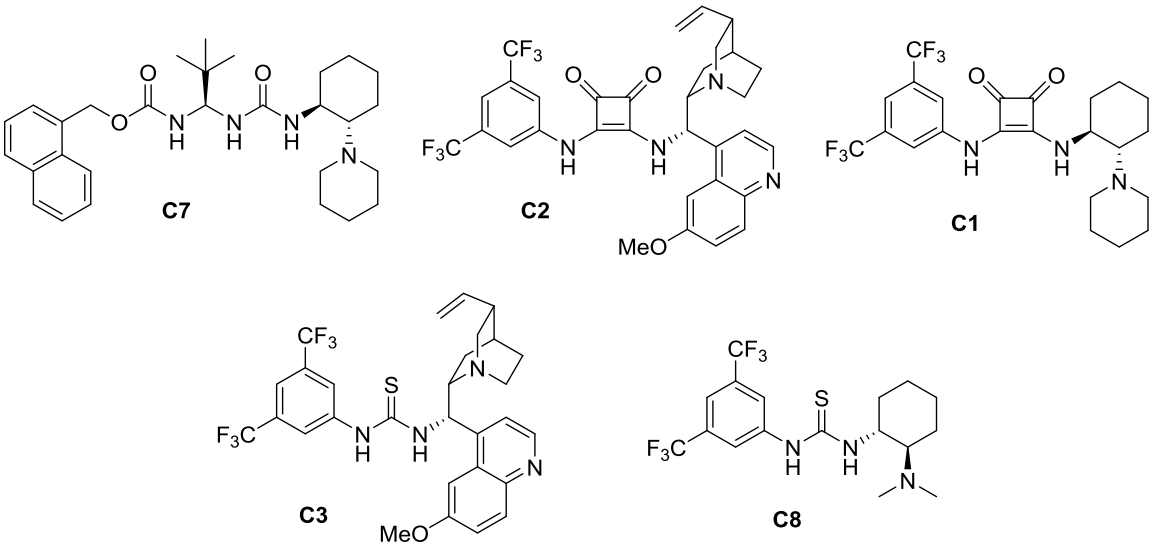
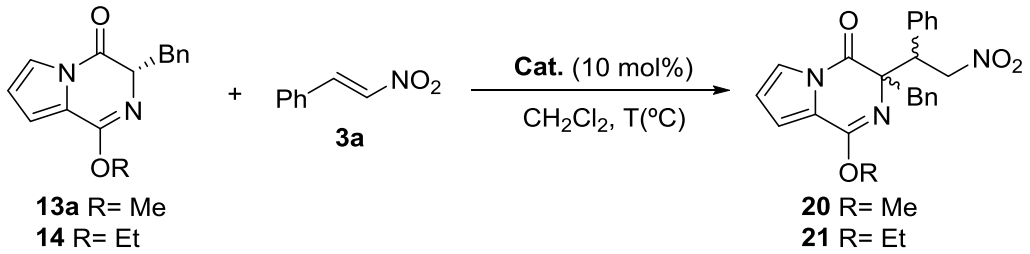


Figure 36. Selected bifunctional Brønsted bases

First, we evaluated the potential of these bifunctional Brønsted bases in the Michael addition of pyrrolo lactim **13a** and nitrostyrene (**3a**) (Table 7). Gratifingly, the catalysts tested afforded the desired Michael adduct **19a** in excellent yield and promising diastereo- and enantioselectivity, with the exception of squaramide **C2** that was not able to induce enantioselectivity regardless the high diastereoselectivity observed (entry 5). The effect of the reaction temperature in the asymmetric induction was studied with catalyst **C7.** As expected, decreasing temperature from 0 ºC to −20 ºC improved the distereometic ratio, whereas lower temperatures seemed to affect negatively the selectivity, probably due to solubility and aggregation effects (entries 1, 3-4). Additionally, pyrrolo lactim **14** displayed a similar behaviour (compare entries 1 and 2).

Table 7. Asymmetric Michael reaction of acylpyrrol lactims and nitrostyrene (**3a**).[a]



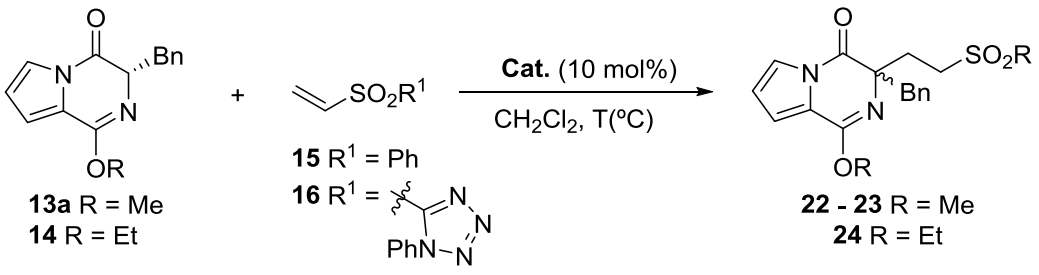
Entry	R	Cat	T (ºC)	t (h)	Conv. (%)	Yield (%)	*dr*	*ee* (%)
1	Me	**C7**	0	21	>95	86	90:10	79

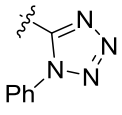
2	Et	**C7**	0	20	>95	83	92:8	76
3	Me	**C7**	−20	45	>95	87	94:6	80
4	Me	**C7**	−40	45	60	ND	85:15	ND
5	Me	**C2**	−20	20	>95	74	92:8	0
6	Me	**C1**	−20	20	>95	85	93:7	52
7	Me	**C3**	−20	20	>95	83	94:6	82
8	Me	**C8**	−20	20	>95	86	88:12	-68

[a] Reaction conditions: acylpyrrol lactime (0.1 mmol), nitrostyrene (1.5 equiv.) in CH_2Cl_2 (0.3 mL).

Next, we evaluated the reaction with the vinyl sulphones explored in the racemic version (Table 8). Very low transformations were obtained in the reaction with sulphone **15**, evidencing its low reactivity (entries 1 and 2). The most active 1-phenyl-5-(vinylsulfonyl)-1*H*-tetrazole **16** was able to produce the corresponding Michael adducts at 0 ºC under the action of catalysts **C7**, **C2** and **C1**, in reasonable reaction times (entries 3-4, and 6-7). Nevertheless, the enantioselectivity induced by these catalysts was negligible.

Table 8. Asymmetric Michael reaction of acylpyrrol lactims and vinyl sulphones.[a]



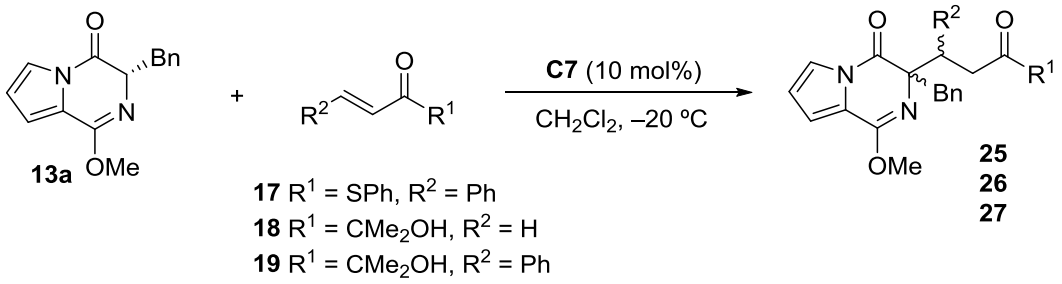
Entry	R	R^1	Cat.	T(ºC)	t(h)	Conv.(%)	Yield)%)	*ee(%)*
1	Me	Ph	**C7**	0	68	53	ND	ND
2	Me	Ph	**C2**	−20	47	14	ND	ND
3	Me		**C7**	0	20	>95	84	18
4	Et		**C7**	0	20	>95	80	9
5	Me		**C7**	−40	45	48	ND	ND

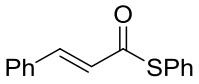
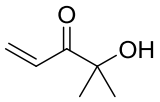
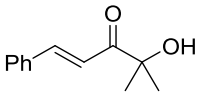
6	Me		**C2**	0	23	>95	86	0
7	Me		**C1**	0	22	>95	85	8

[a] Reaction conditions: acylpyrrol lactime (0.1 mmol), vinyl sulfone (1.5 equiv.) in CH_2Cl_2 (0.3 mL).

Finally, we evaluated the viability of the asymmetric Michael addition of pyrrolo lactim **13a** with the α,β-unsaturated carboxyl and carbonyl compounds, previously employed, in the presence of catalyst **C7** to evince the absence of transformation (entry 1) or the low asymmetric induction exerted (entries 2 y 3), respectively (Table 9).

Table 9. Asymmetric Michael reaction of acylpyrrol lactim **13a** and α,β-unsaturated carboxyl and carbonyl compounds.[a]



Entry	E	t (h)	Conv. (%)	Yield (%)	*dr*	*ee* (%)
1		20	0	-	-	-
2		22	>95	78	-	0
3		18	>95	75	50:50	ND

[a] Reaction conditions: acylpyrrol lactime (0.1 mmol), Michael acceptor (1.5 equiv.) in CH_2Cl_2 (0.3 mL).

In view of these results, we decided to concentrate on the search of a general asymmetric Brønsted-base catalyzed Michael addition of bicyclic acylpyrrol lactims to nitroalkenes to produce pyrrolo DKPs with high skeleton diversity and stereochemical efficiency. To achieve this goal, we first centered our efforts in the identification of the most appropriate catalyst. Among several possibilities, we selected the ureidoaminal-

derived Brønsted bases, developed by our group, as the catalyst prototype to improve the stereochemical outcome of the Michael reaction.[150] The main characteristics and implications of the use of this particular type of bifunctional Bronsted bases are disclosed in the following section.

3.3.1.3. Optimization of the catalyst for the Michael addition with nitroalkenes

The design of ureidoaminal-derived Brønsted bases was inspired by the observations made by Zhong,[151] Schreiner and co-workers[152] while evaluating the influence of the 3,5-bis(trifluoromethyl)phenyl group in certain coordination events. Based on exhaustive studies on NMR and IR spectroscopy, mass-spectrometry and DFT calculations, they concluded that the success of electronically deficient thioureas, as hydrogen bond donors, could be attributed to the participation of the *ortho* C–H in the aryl group as an extra H-bond donor group, during the electrophile activation event (0). The benefits of incorporating the 3,5-bis(trifluoromethyl)phenyl motif are also recognized in analogous bifunctional Brønsted bases built from squaramides (Figure 37).[153]

[150] For pioneering applications of ureidoaminal-type catalyst in asymmetric carbon-carbon bond forming reactions, see: a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846-11851. b) Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526-6531. c) Echave, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364-3368. d) Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J*. **2017**, *23*, 13332-13336. For a recent review, see: d) López, R.; Palomo, C. *Chem. Eur. J.* **2021**, *27*, 20-29.

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

[152] Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenter, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919-5927.

[153] Selected reviews for the use of squaramides: a) Alemán, J.; Parra, A.; Jørgensen, K. A. *Chem. Eur. J.* **2011**,*17*, 6890-6899. b) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330-2346. c) Marchetti, L. A.; Kumawat, L. K.; Mao, N.; Stephens, J. C.; Elmes, R. B. P. *Chem.* **2019**, *5*, 1398-1485. d) Popova, E. A.; Pronina, Y. A.; Davtian, A. V.; Nepochatyi, G. D.; Petrov, M. L.; Boitsov, V. M.; Stepakov, A. V. *Russ. J. Gen. Chem.* **2022**, *92*, 287-347.

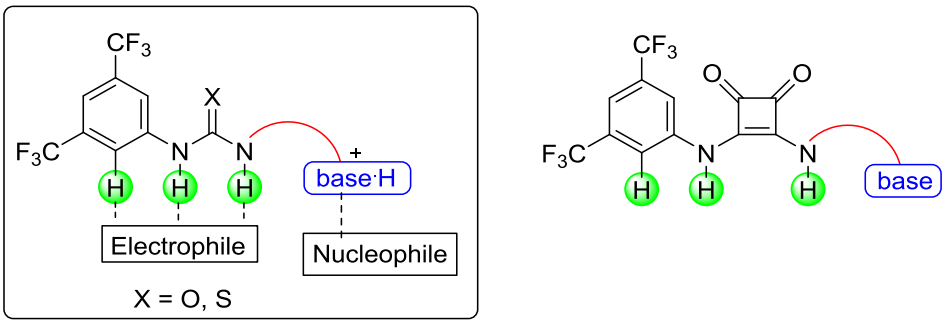


Figure 37. Structure of tipycal bifunctional Brønsted bases and a typical activation mode proposal for electron deficient thioureas.

Peptides, which are responsible for the high efficacy of biologically occurring events due to their conformational behaviour[154] and have the ability to fine tune reactivity and selectivity in several synthetic transformations,[155] were the second pillar for the design of these type of bifuntional catalysts (Figure 38). These compounds are distinguished by the presence of an *N*,*N*-diacyl aminal unit, in place of the bis(trifluoromethyl)-phenyl group, and a urea moiety as hydrogen bond donor, both in close proximity to an additional stereodirecting group. This type of structures closely resembles to ureidopeptides, which have been recognized for their ability to develop intermolecular hydrogen bond interactions.[156] The replacement of the α-amino acid terminus in ureidopeptides by a group bearing a tertiary amine results in novel bifunctional Brønsted base catalysts with several sites amenable for structural modification.

[154] Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292-296.
[155] Selected review: Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759-5812.
[156] a) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem. Eur. J.* **2000**, *6*, 2633-2643. b) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1893-1895. c) Myers, A. C.; Kowalski, J. A.; Lipton, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219-5222. d) Sureshbabu, V. V; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697-7705.

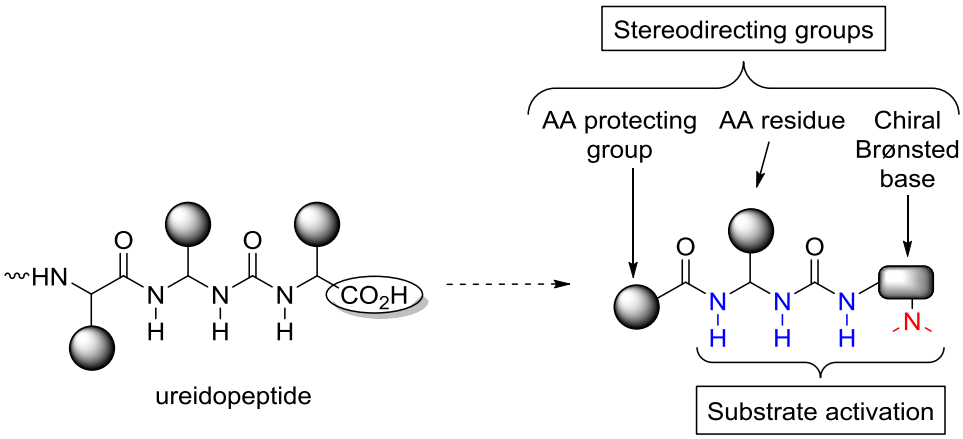
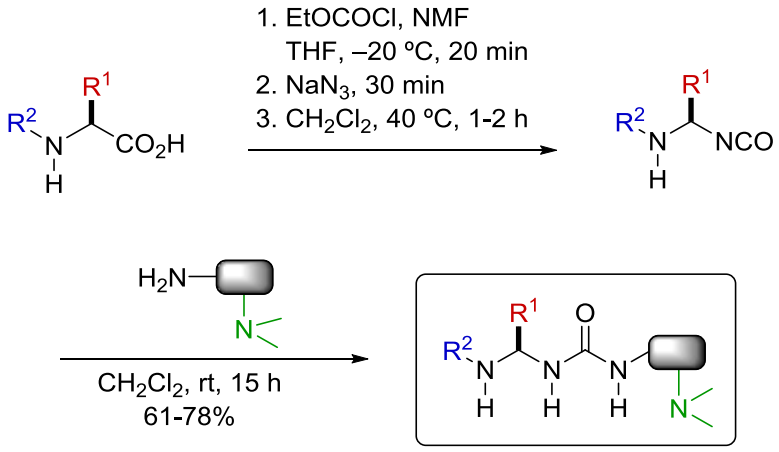


Figure 38. Design of ureidoaminal-derived Brønsted bases.

The first synthesis and subsequent optimization of these organocatalysts was conducted by Dr. Diosdado in our research group (Scheme 62).[157] The proposed general synthetic sequence involves carbamate protection of the α-amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base (Scheme 62). Hence, from a synthetic point of view, these structures can be easily tuned in several sites facilitating the modulation of catalyst properties.



Scheme 62. Synthesis of bifunctional ureidoaminal-derived Brønsted bases.

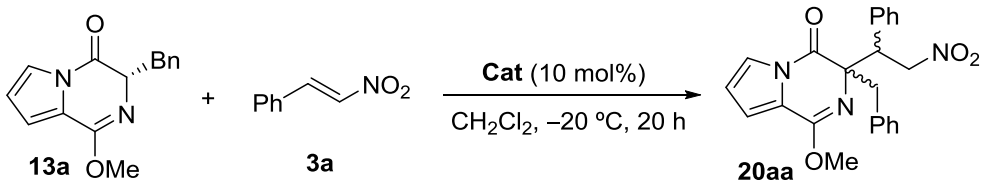
[157] Diosdado, S. Adición de Fosfonoacetatos, Malonatos y Sulfonilacetonitrilos a Iminas. Desarrollo de Bases de Brønsted Bifuncionales, Ureidopéptido-Cinchona. Ph.D. Thesis, University of the Basque Country, Donostia-San Sebastián, 2014.

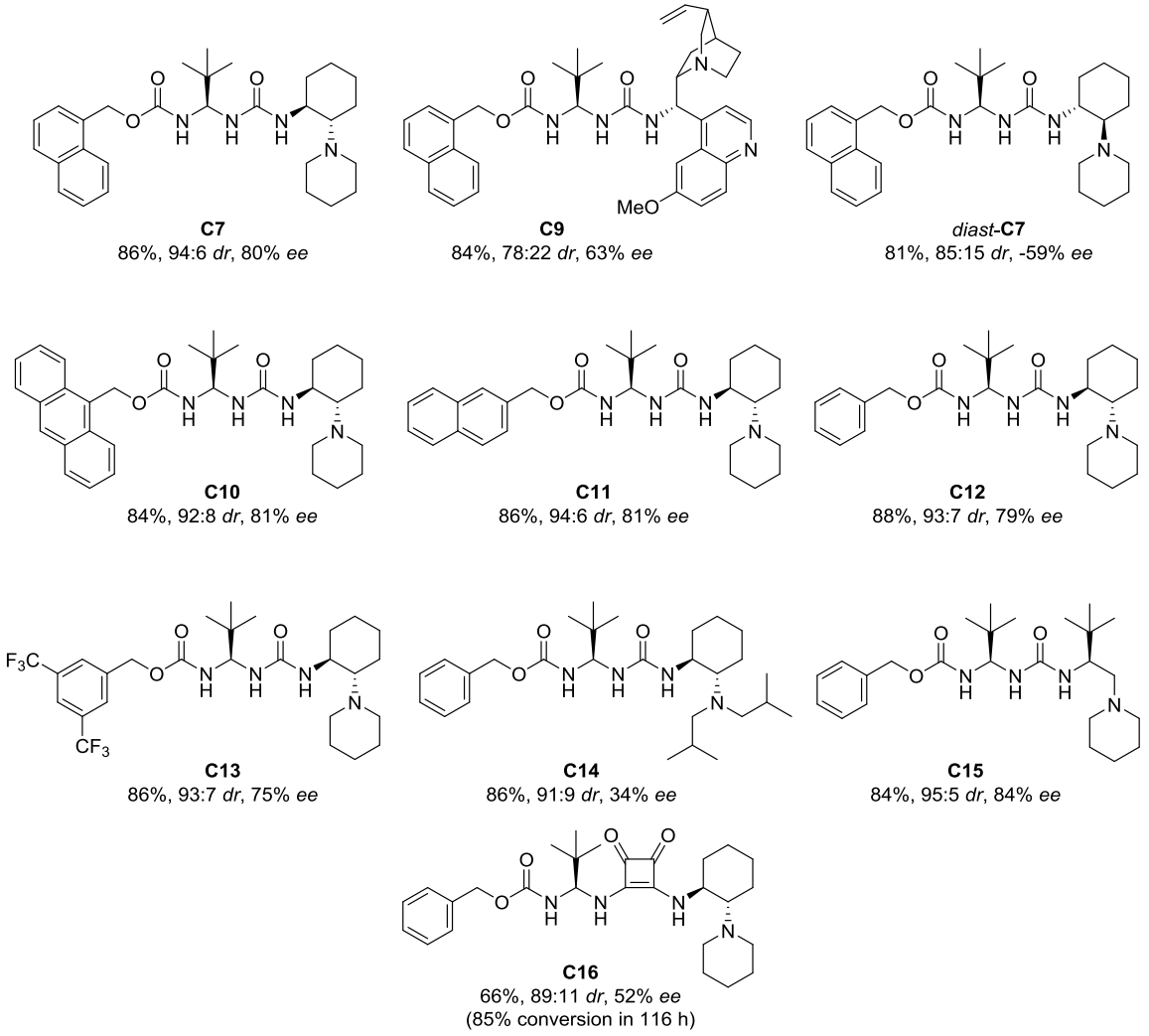
3.3.1.3.1. Ureidoaminal-derived Brønsted bases screening

Following the methodology described above, we synthetized several ureidoaminal-derived Brønsted bases to test them in the Michael reaction of bicyclic acylpyrrol lactims with nitroalkenes. Based on previous experience of the group, *tert*-leucine was selected to iniciate their preparation and variations were introduced in both the *tert*-leucine amine protecting group and the nature of the chiral scaffold bearing the tertiary amine.

As data in Table 10 show, it was gratifying to observe that after 20 hours of stirring at −20 ºC, all ureidoaminal-derived Brønsted bases provided complete conversion into the desired adduct **20aa**. Catalysts built up from carbamate protected *tert*-leucine and (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine (**C7**, **C10-C13**) provided adduct **20aa** with diastereomeric ratios greater than 92:8 and high enantioselectivities showing a negligible influence of the structure of the aromatic carbamate. In contrast, the replacement of the Brønsted base moiety in catalysts **C9**, *diast*-**C7** and **C14** provoked a noticeable reduction of the enantiomeric excess. The highest *ee* was achieved with catalyst **C15**, which incorporates the tertiary amine in a *tert*-leucine derived scaffold. The unexplored aminal-squaramide combination in catalysts **C16** induced a diminished reactivity and lower setereoselectivities probably motivated by its low solubility in the reaction conditions.

Table 10. Ureidoaminal-derived Brønsted base screening for the Michael addition of acylpyrrol lactim **13a** and nitrostyrene **3a**.[a]

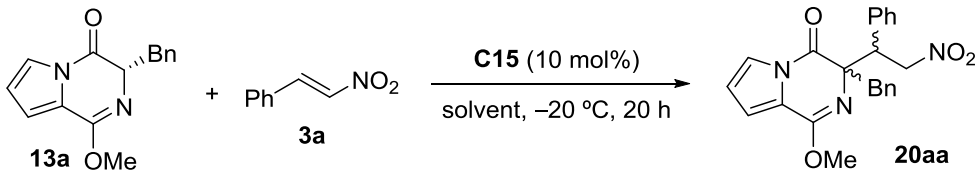




[a] Reaction conditions: **13a** (0.1 mmol), **3a** (1.5 equiv., 0.15 mmol) in CH_2Cl_2 (0.3 mL). *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC. The *ee* values were determined for the major diastereomer by chiral HPLC.

Among the catalyst tested, **C15** constitutes an unexplored variant of ureidoaminal-derived Brønsted bases with increased flexibility. Thus, we chose to investigate the effect of reaction conditions in the asymmetric induction exerted by this catalyst (Table 11). As data shown, the less polar the solvent, the highest the estereoselectivity observed; adduct **20aa** was obtained with good yield and excellent diastereoslectivity and enantioselectivity in toluene (entry 4). With these results in hand, we selected ureidoaminal-derived Brønsted base **C15** and toluene as a solvent to proceed with the study of the scope of the Michael reaction.

Table 11. Solvent screening for catalyst **C14**.[a]



Entry	Solvent	conv. (%)	Yield (%)	*dr*[b]	*ee* %[b]
1	CH_2Cl_2	>95	87	94:6	80
2	CH_3CN	>95	89	54:46	35
3	EtOAc	>95	83	95:5	70
4	toluene	>95	85	98:2	88
5	triflorotoluene	>95	84	96:4	84
6	*m*-xylene	>95	83	97:3	84

[a] The reactions were performed using 0.1 mmol of **13a**, 0.15 mmol of **3a**. [b] *dr* and *ee* of major diastereomer as determined by HPLC.

3.3.1.4. Approximation to the synhesis of thioureidoaminals

In the field of bifunctional organocatalysis, urea and thiourea subunits, together with squaramides, are recurrent moieties to stablish two directional H-bonds with the hydrogen bond acceptors. The H-bond donating tendency of a given donor group is in some way related to its protonic acidity. Noticeably, hydrogen bonding has been defined as a 'frozen' proton transfer from the donor to the acceptor[158] and the more advanced the proton transfer, the stronger the H-bond interaction. Thiourea is a much stronger acid than urea (pK_A = 21.1 and 26.9, respectively in DMSO),[159] and indeed its use exceeds the urea when designing organocatalysts.

On the other hand, the role played by oligoureas and ureidopeptides as peptidomimetics[160] can be modulated by the replacement of the oxygen atom of the urea motifs by the isoelectronical sulphur. This substitution usually results in an increased

[158] Steiner, T. *Angew. Chem., Int. Ed.*, **2002**, *41* , 48-76.
[159] Bordwell, F. G. *Acc. Chem. Res.*, **1988**, *21* , 456 -463.
[160] a) Lenci, E.; Trabocchi, A. *Chem. Soc. Rev.* **2020**, *49*, 3262-3277. b) Li Petri, G.; Di Martino, S.; De Rosa, M. *J. Med. Chem.* **2022**, *65*, 7438-7475.

activity, also observed in small molecules with biological and medicinal applications (Figure 39). [161]

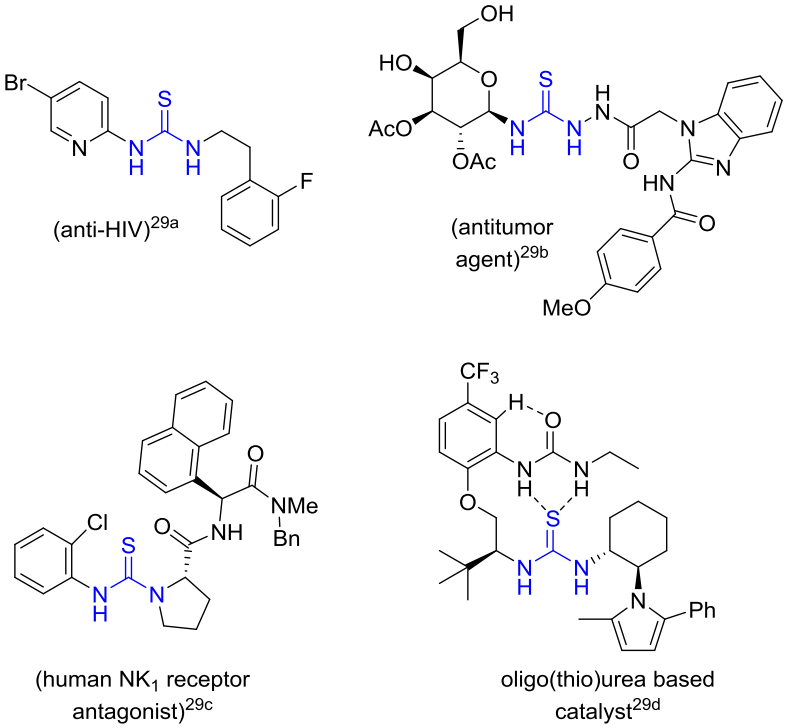
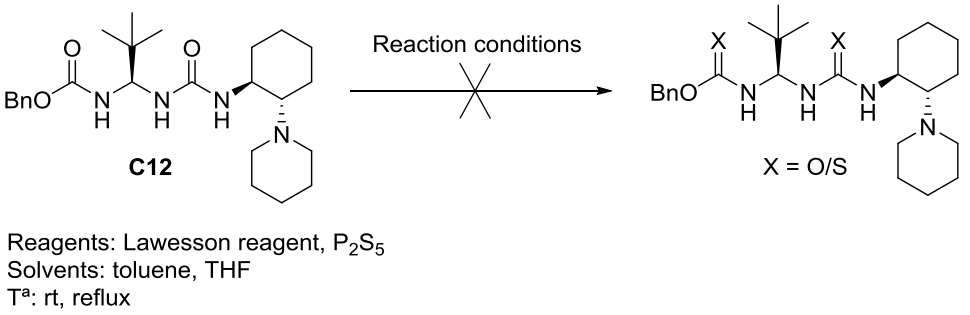


Figure 39. Representative examples of thiourea containing drugs and catalysts.

With these considerations, we decided to synthesize the isoelectronic ureidoaminal-derived catalysts containing sulphur and evaluate their performance in the Michael reaction with acylpyrrol lactims. Our first attempt consisted on the direct reaction of catalysts **C12** with thiation agents.[162] Nevertheless, no matter the reagent and the reaction conditions, the resulting crudes were complex mixtures in which the sulphur or sulphur/oxygen analogues could not be detected (Scheme 63).

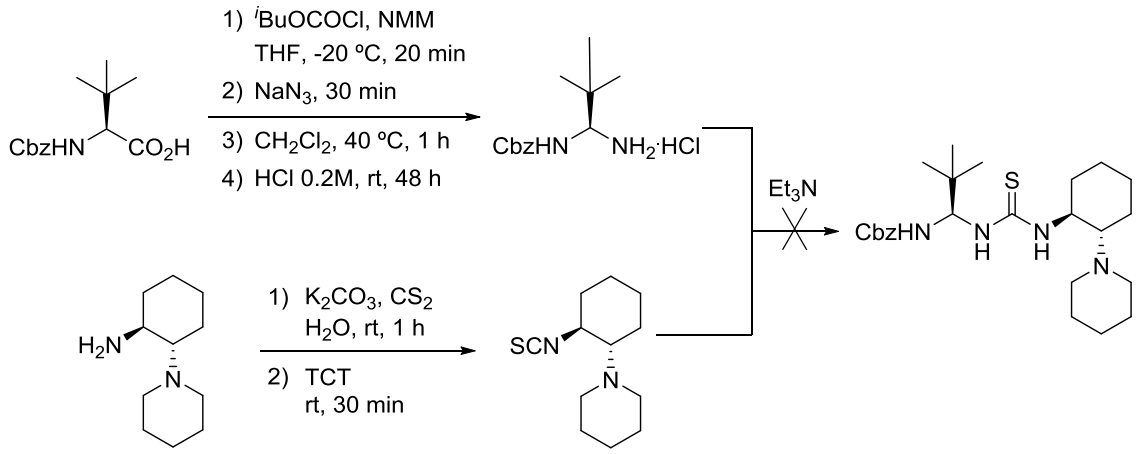
[161] a) Vig, R.; Mao, C.; Venkatachalam, T. K.; Tuel-Ahlgren, L.; Sudbeck, E. A.; Uckun, F. M. *Bioorg. Med. Chem.* **1998**, *6*, 1789-1797. b) Shusheng, Z.; Tianrong, Z.; Kun, C.; Youfeng, X.; Bo, Y. *Eur. J. Med. Chem.* **2008**, *43*, 2778-2783. c) Walpole, C.; Ko, S. Y.; Brown, M.; Beattie, D.; Campbell, E.; Dickenson, F.; Ewan, S.; Hughes, G. A.; Lemaire, M.; Lerpiniere, J.; Patel, S.; Urban, L. *J. Med. Chem.* **1998**, *41*, 3159-3173. d) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 7391-7394.

[162] a) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210-5278. b) Khatoon, H.; Abdulmalek, E. *Molecules* **2021**, *26*, 6937-6979.



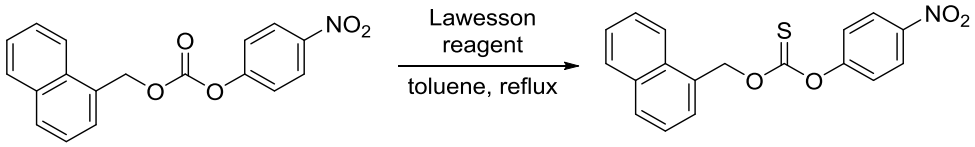
Scheme 63. Thiation attempt of catalyst **C11.**

Then, we decided to follow the same approach that we employed in the synthesis of hybrid catalyst **C16** (see experimental section). In this case, the generation *N*-Cbz protected *tert*-leucine derived isocyanate was followed by acidic treatment to generate the corresponding hydrochloric salt (Scheme 64). However, attempts to condensate the amine and the thioisocyanate, prepared from (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine, were unfruitful. We ascribed this negative result to the diminished reactivity of the thioisocyanate compared to the dimethyl squarate used in the preparation of catalyst **C16**.



Scheme 64. Second attempt for the synthesis of thioureidoaminals.

Our last attempt consisted in the synthesis of a thiocarbonate to generate the corresponding thiocarbamate protected α-amino acid (Scheme 65). The treatment of the carbonate with the Lawesson reagent produced a product compatible with the desired structure. Nevertheless, it was unstable and impossible to purify and characterize.

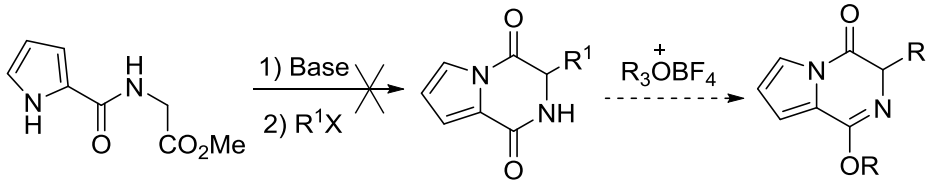


Scheme 65. Third attempt for the synthesis of thioureidoaminals.

At this point, we decided to continue with the generalization of the Michael addition of acylpyrrol lactims using catalyst **C15**, without excluding future attempts for the synthesis of thoureidoaminal based catalysts.

3.3.2. Scope of the Michael reaction of acylpyrrol lactims with nitroalkenes

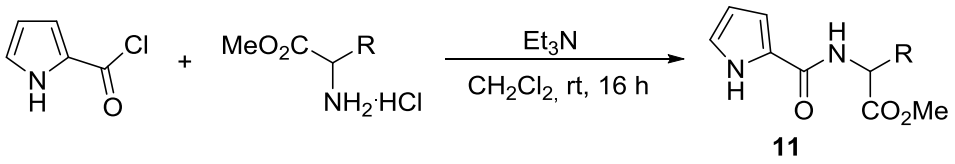
In order to explore the scope of the Michael reaction, an interesting option would consist in the preparation of the glycine derived pyrrolo DKP as a common intermediate followed by subsequent alkylation (Scheme 66). However, all attempts to promote cyclization of methyl acylpyrrol glycinate, prepared as in section 3.3.1.1., were unsuccessful. In the presence of different bases (NaH, Et_3N) complexed reaction mixtures were obtained and the desired pyrrolo DKP was not detected.



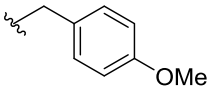
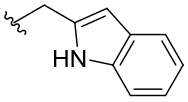
Scheme 66. Fisrt approach for the synthesis of acylpyrrol lactims.

After the disappointing attempts, we decided to follow the protocol previously stablished for the synthesis of **13a**. A representative selection of natural and synthetic α-aminoacids were subbmitted to reaction with the 2-pyrrol carbonyl chloride to produce the corresponding pyrrol amides **11** with good yields (Table 12).

Table 12. Synthesis of pyrrol amides.[a]



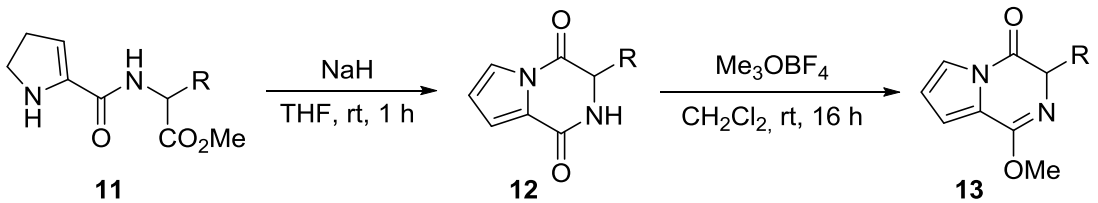
11

Entry	R	Amide	Yield (%)
1	Bn	**11a**	92
2	^{i}Bu	**11b**	84
3		**11c**	87
4	CH_2CH_2Ph	**11d**	89
5		**11e**	80
6	allyl	**11f**	85
7	^{n}hexyl	**11g**	70
8	Ph	**11h**	74

[a] The reactions were performed in 0.2 mL/mmol CH_2Cl_2 with 2 equivalents of the base.

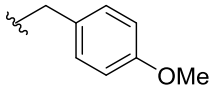
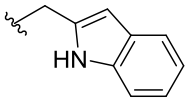
Next, the intramolecular cyclization of pyrrol amides **11** was effected in the presence of NaH, followed by *O*-alkylation to afford the corresponding acylpyrrol lactims **13** in good yields (Table 13).

Table 13. Intramolecular cyclization and cyclization toward pyrrolo DKPs **13**.



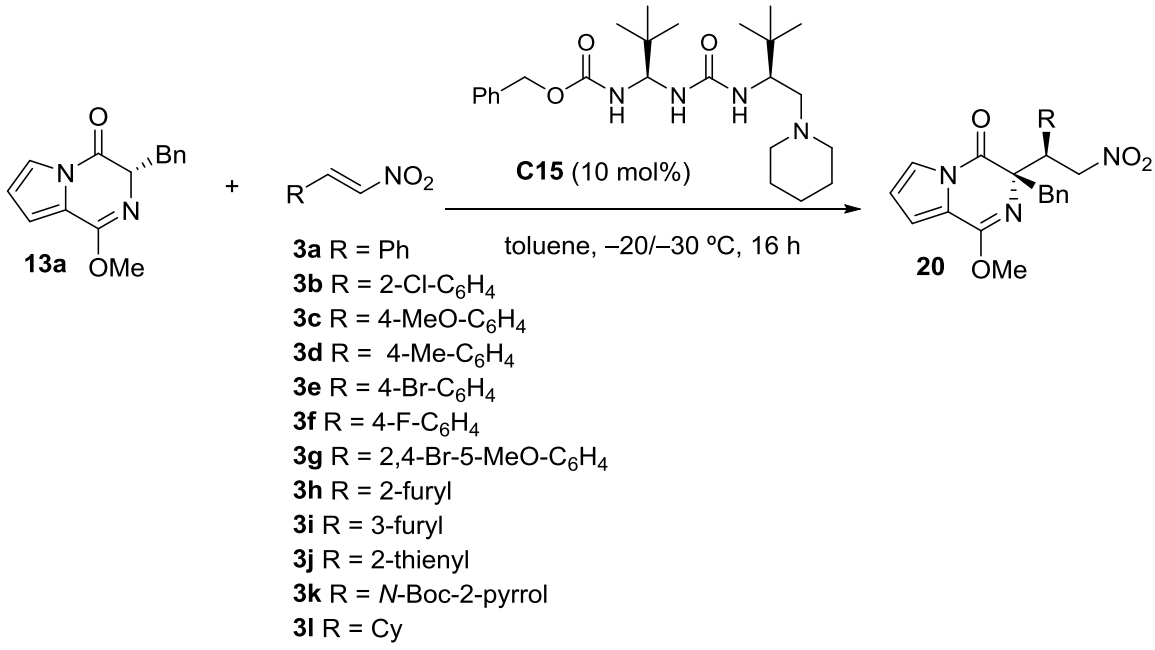
11 **12** **13**

Entry	R	Pyrrol DKP[a]	Yield (%)	Acylpyrrol lactim[b]	Yield (%)
1	Bn	**12a**	79	**13a**	87
2	^{i}Bu	**12b**	75	**13b**	82

3		**12c**	80	**13c**	77
4	CH_2CH_2Ph	**12d**	85	**13d**	71
5		**12e**	72	**13e**	88
6	allyl	**12f**	78	**13f**	88
7	^{n}hexyl	**12g**	80	**13g**	84
8	Ph	**12h**	71	**13h**	90

[a] The reactions were performed in 1 mL/mmol THF with 1.4 equivalents of the base. [b] The reactions were performed in 5 mL/mmol CH_2Cl_2 with 1.1 equivalents of the alkylating reagent.

With the reaction conditions optimized for the reaction of acylpyrrol lactim **13a** and nitrostyrene in the presence of **C15**, we first proceeded to examine the generality of the method with a selected variety of nitroalkenes (Scheme 67).

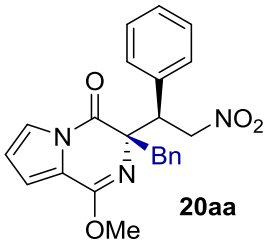


Scheme 67. Scope of the reaction between of acylpyrrol lactim **13a** and nitroalkenes **3**.

As results in Table 14 show, the methodology was compatible with aromatic nitroalkenes bearing electronwithdrawing groups in *para*- and *ortho*- positions. The corresponding adducts (**20aa**-**al**) were produced in high yield, excellent diastereoselectivity and good enantioselectivity. The introduction of electron donating groups in the aromatic ring provoked a slight decrease in diastereoselectivity (adducts **20ac** and **20ad**) but a marked reduction of the enantiomeric excess down to 65% in adduct **20ac**. Interestingly, the multiple substitution of the aromatic ring with electron-withdrawing and donating groups provided adduct **20ag** as a single diasteroisomer and good enantiomeric excess. The reaction with heteroaromatic substituted nitroalkenes also provided the corresponding adducts **20ah-aj** as single diasteoisomers and good enantioselectivities, with the exception of the pyrrolo *N*-Boc protected substituted one, which afforded adduct **20ak** with a poor enantiomeric excess. In addition, less reactive aliphatic nitroalkenes were compatible with the reaction conditions. For instance, adduct **20al** was produced as a pure diasteroisomer with 93% enantiomeric excess.

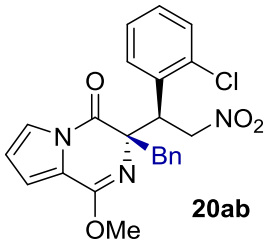
Table 14. Scope of the reaction between of acylpyrrol lactim **13a** and nitroalkenes **3**.

(a: –20 ºC; b: –30 ºC)



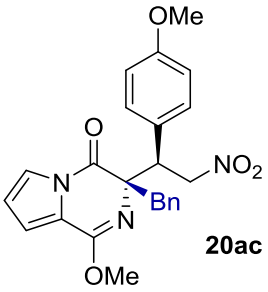
20aa

78%, *dr* 98:2, 88% *ee*[a] (1 mmol scale)



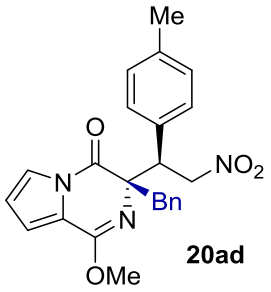
20ab

84%, *dr* >98:2, 86% *ee*[b]



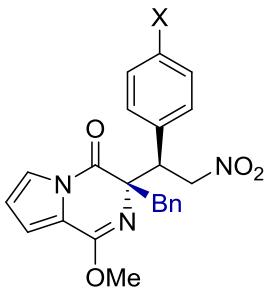
20ac

83%, *dr* 79:21, 65% *ee*[a]

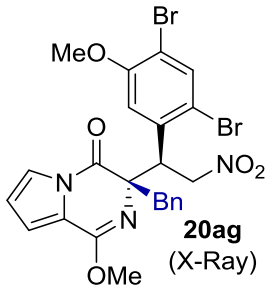


20ad

81%, *dr* 88:12, 82% *ee*[a]

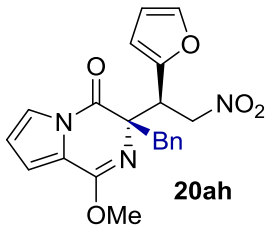


20ae X=Br 86%, *dr* 96:4, 85% *ee*[a]
20af X=F 90%, *dr* 97:3, 88% *ee*[b]



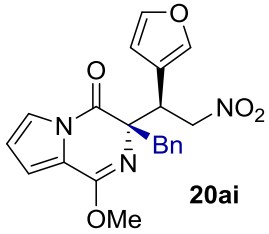
20ag (X-Ray)

86%, *dr* >98:2, 84% *ee*[b]



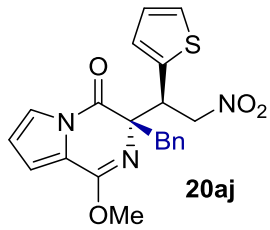
20ah

89%, *dr* >98:2, 98% *ee*[b]



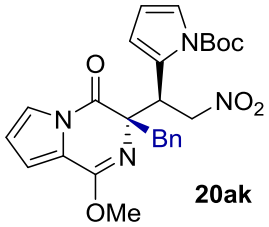
20ai

85%, *dr* >98:2, 91% *ee*[b]



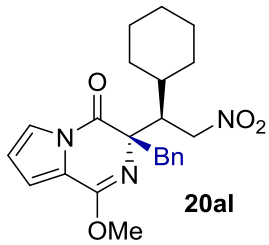
20aj

86%, *dr* >98:2, 89% *ee*[b]



20ak

80%, *dr* 93:7, 48% *ee*[b]



20al

85%, *dr* >98:2, 93% *ee*[a]

[a] Reaction conditions: **13** (0.1 mmol), **3** (0.15 mmol, 1.5 equiv.) in toluene (0.3 mL). *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC. The *ee* values were determined for the major diastereomer by chiral HPLC. [b] **3** (0.3 mmol, 3 equiv.) in toluene (1 mL).

The absolute configuration of adduct **20ag** was determined by single-crystal X-ray analysis (Figure 40). Furthermore, its recrystallization from methylene chloride increased

the enantiomeric excess of **20ag** up to 97%. The absolute configuration of the rest of Michael adducts was established by assuming the uniformity of the reaction mechanism.

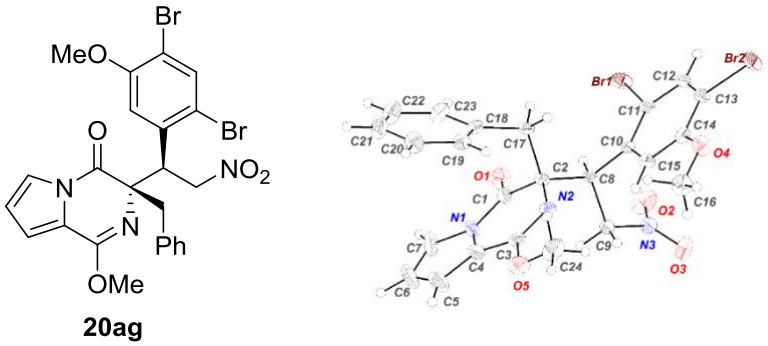
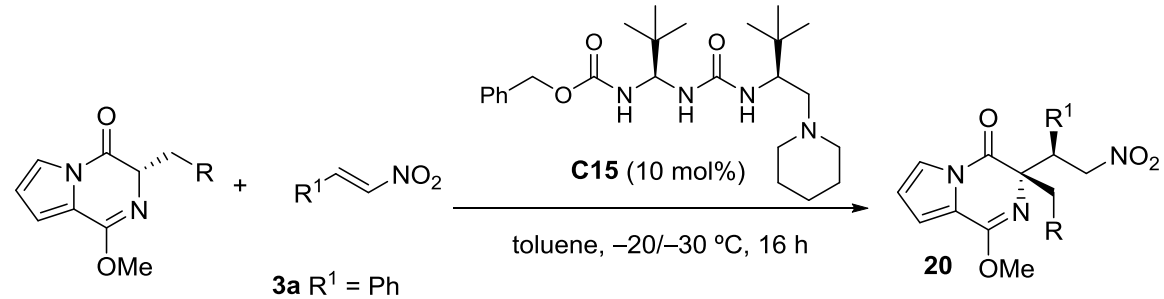


Figure 40. ORTEP diagram for compound **20ag**.

To verify the robustness of the protocol, we continued testing the method with acylpyrrol lactims **13b**, **13c** and **13e** derived from *L*-leucine, *O*-methyl-*L*-tyrosine and *L*-tryptophan, respectively (Scheme 68).



13b R = ^{i}Pr
13c R = PMP
13e R = 1*H*-indole

3a R^1 = Ph
3e R^1 = 4-Br-C_6H_4
3h R^1 = 2-furyl
3j R^1 = 2-thienyl
3l R^1 = Cy

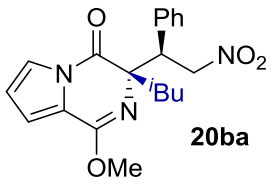
Scheme 68. Scope of the reaction between acylpyrrol lactims **13b**, **13c** and **13e** and nitroalkenes **3**.

The methodology with these new pronucleophiles proved to be as efficient as in the case of the acylpyrrol lactim **13a** derived from *L*-phenylalanine, in the reaction with aromatic nitroalkenes, affording the corresponding adducts in excellent yields and diastereomeric ratios above 96:4 in all cases and from good to excellent enantioselectivities (Table 15). The use of the acylpyrrol lactim derived from *L*-tryptophan constituted an exception. The presence of an extra coordinating group impaired enantioselectivity, presumably by the formation of energetically closer diastereomeric

transition states. In addition, the reaction between acylpyrrol lactims **13b** and **13c** with less reactive aliphatic nitroalkenes was not observed.

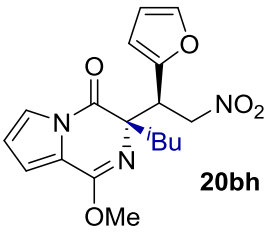
Table 15. Scope of the reaction between acylpyrrol lactims **13b**, **13c** and **13e** and nitroalkenes **3**.

(a: –20 ºC; b: –30 ºC, c: rt)



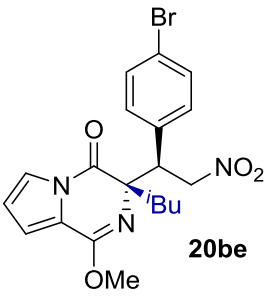
20ba

84%, *dr* 96:4, 89% *ee*[a]



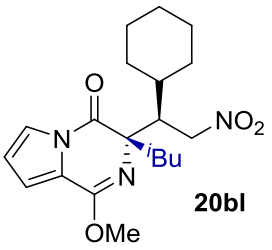
20bh

87%, *dr* >98:2, 72% *ee*[b]



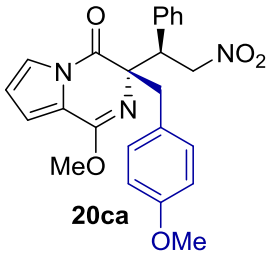
20be

82%, *dr* 96:4, 89% *ee*[a]



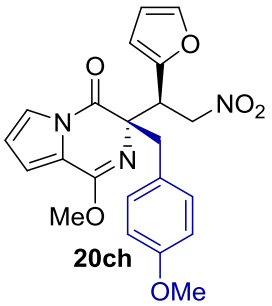
20bl

NR[c]



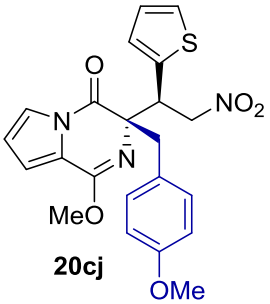
20ca

88%, *dr* >98:2, 84% *ee*[a]



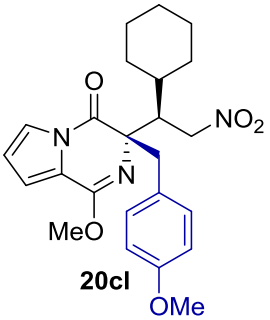
20ch

90%, *dr* >98:2, 70% *ee*[a]



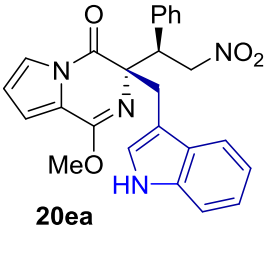
20cj

88%, *dr* >98:2, 77% *ee*[a]



20cl

NR[c]

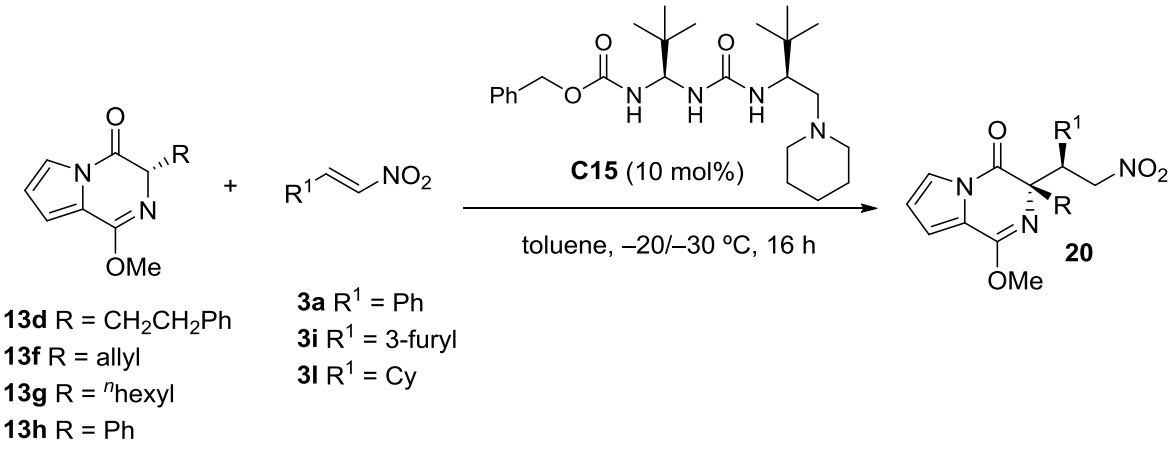


20ea

85%, *dr* >98:2, 48% *ee*[b]

[a] Reaction conditions: **13** (0.1 mmol), **3** (0.15 mmol, 1.5 equiv.) in toluene (0.3 mL). *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC. The *ee* values were determined for the major diastereomer by chiral HPLC. [b] **3** (0.3 mmol, 3 equiv.) in toluene (1 mL).

Finally, we completed the reaction scope by using acylpyrrol lactims **13d**, **13f**, **13g** and **13h** derived from synthetic α-aminoacids (Scheme 69).

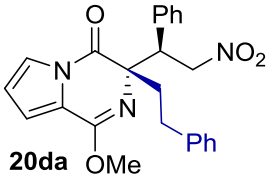


Scheme 69. Scope of the reaction between acylpyrrol lactims **13d**, **13f**, **13g** and **13h** and nitroalkenes **3**.

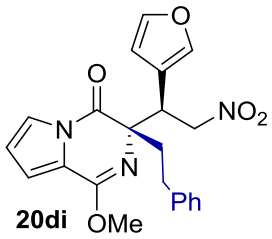
In general, the methodology was compatible with these new substitutions in the pronucleophile to produce the Michael adducts with excellent diastereoselectivities and good enantioselectivities. Nevertheless, the combination of acylpyrrol lactim **13h** with aromatic nitroalkanes had a negative impact in the stereoselectivity. The pronounced planar character of both pronucleophile and electrophile might difficult face discrimination during the carbon-carbon bond forming event. On the other hand, aliphatic acylpyrrol lactim **13g** performed well although adduct **20gl** was unstable and resulted impossible to characterize (Table 16).

Table 16. Scope of the reaction between acylpyrrol lactims **13d**, **13f**, **13g** and **13h** and nitroalkenes **3**.

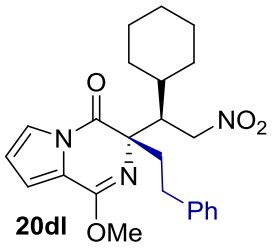
(a: –20 ºC; b: –30 ºC)



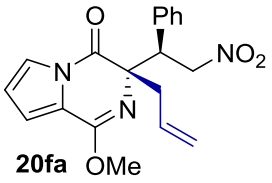
84%, *dr* 94:6, 84% *ee*[b]



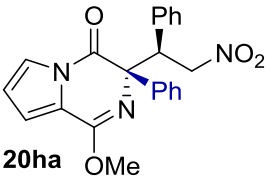
85%, *dr* 97:3, 92% *ee*[b]



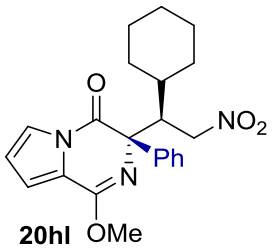
84%, *dr* >98:2, 93% *ee*[b]



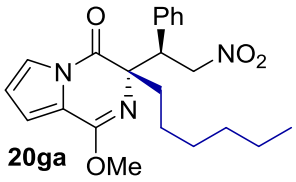
84%, *dr* 96:4, 85% *ee*[b]



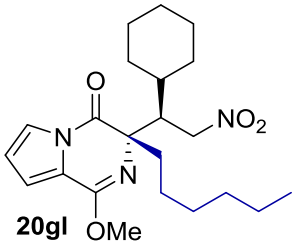
82%, *dr* 63:37, 24% *ee*[b]



92%, *dr* >98:2, 72% *ee*[b]



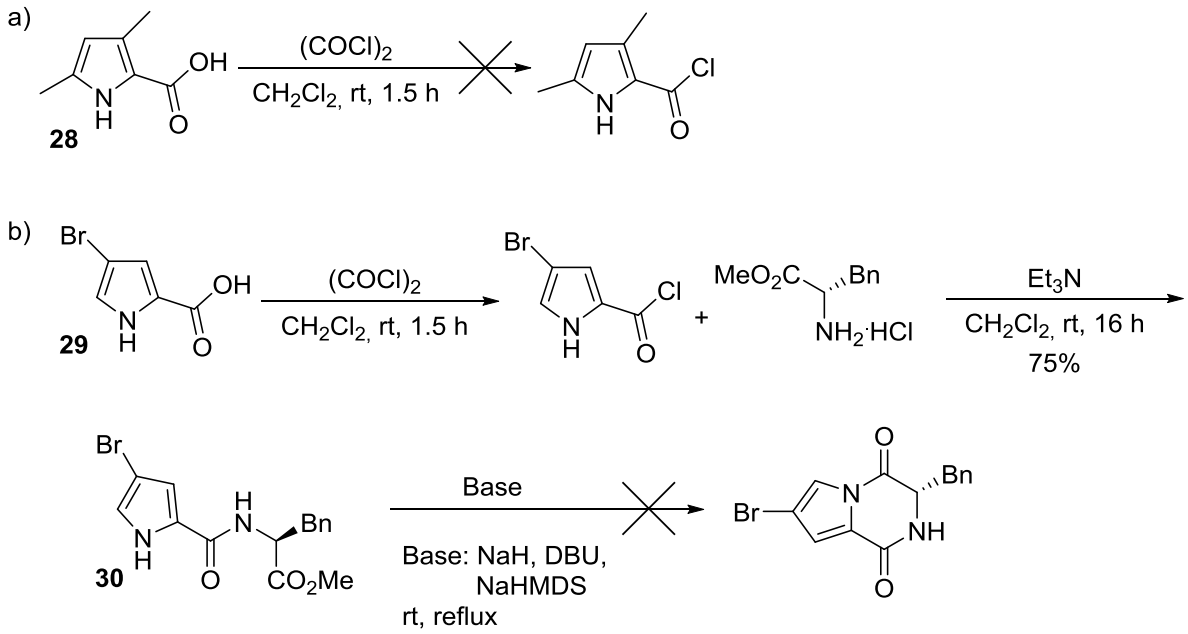
89%, *dr* 95:5, 75% *ee*[b]



decomposed

[a] Reaction conditions: **13** (0.1 mmol), **3** (0.15 mmol, 1.5 equiv.) in toluene (0.3 mL). *dr* values were determined by ^{1}H-RMN and corroborated by chiral HPLC. The *ee* values were determined for the major diastereomer by chiral HPLC. [b] **3** (0.3 mmol, 3 equiv.) in toluene (1 mL).

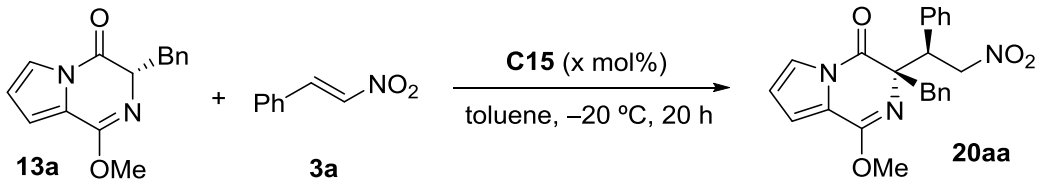
In order to improve the generality of the Michael reaction and, as a consequence, the skeleton diversity of the pyrrolodiketopiperazines pursued, we tried to modify the pyrrol ring in the starting pronucleophiles. With this porpoise, we selected 3,5-dimethyl pyrrol 2-carboxylic acid **28** and 4-bromo pyrrol 2-carboxylic acid **29** and followed the stablished synthetic protocol. To our disappointment, **28** could not be converted in the corresponding acyl chloride. Under classical reaction conditions, only polymerization was observed (Scheme 70a). On the other hand, the acyl chloride was efficiently transformed in the corresponding pyrrol amide **30** but all attempts to promote the intramolecular cyclization were fruitless (Scheme 70b).



Scheme 70. Attempts to produce acylpyrrol lactims substituted at pyrrol.

Regarding the asymmetric induction exerted by the ureidoaminal-derived catalysts, it is known that for certain bifunctional Brønsted bases, self-aggregation[163] may cause reactivity and stereoselectivity to be strongly dependent on the concentration and the temperature at which the transformations are carried out. Nonetheless, we verified that neither the concentration (referred to **13a**) nor the catalyst loading affected the asymmetric induction in the reaction between **13a** and **3a**. (Table 17).

Table 17. Impact of concentration and catalyst loading on stereoselectivity.



Entry	13a, M	C15 (x mol%)	t (h)	*dr*	*ee*
1	0.05	10	20	96:4	88

[163] For early examples of the aggregation of urea and thiourea-based bifunctional organocatalysts in solid state, see: a) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898-1900. b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807-811. In solution, see: c) Tárkányi, G.; Király, P.; Varga, S.; Vakulya, B.; Soós, T. *Chem. Eur. J.* **2008**, *14*, 6078-6086. d) Jang, H. B.; Rho, H. S.; Oh, J. S.; Nam, E. H.; Park, S. E.; Bae, H. Y.; Song, C. E. *Org. Biomol. Chem.* **2010**, *8*, 3918-3922.

2	0.1	10	20	98:2	88
3	0.3	10	20	98:2	88
4	0.3	5	20	96:4	85
5	0.3	20	20	98:2	89

13a: 0.1 mmol, **3a**: 1.5 equiv.

With these experimental results, it might be argued that, at the conditions in which the Michael addition is performed, the catalyst appears as monomeric species in solution and only one molecule of catalyst would be involved in the stereodeterminig step. According to the diastereo- and enantioselectivities observed, the capacity of the catalyst **C15** to produce mainly the adduct with the *S,S* configuration might be consistent with the generation of a tight transition state, through multiple hydrogen bonding interactions, in which the *Si* face of the bicycle approaches the *Si* face of the nitro alkane (Figure 41).

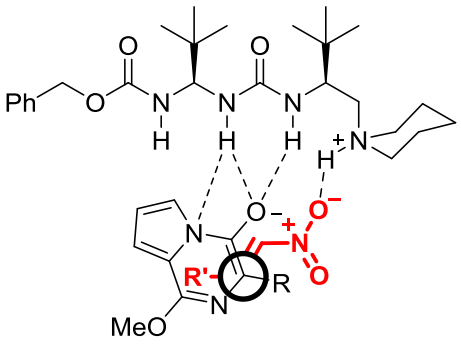


Figure 41. Proposed model to explain stereoselectivity.

Some computational studies were carried out by my PhD director Dr. Rosa López where we could see that ureidoaminal-derived catalyst **C15** seems more flexible than some congeners previously described by us. Nevertheless, the asymmetric induction exerted, over the kinetically produced adducts, could be related to the prevalence of a major conformer of catalyst **C15** rather than to the increased steric demand at the stereogenic centers. Indeed, the most stable conformation computed for **C15** in toluene

shows how the *tert*-butyl groups, located at both sides of the urea moiety, tend to separate to minimize steric interactions (Figure 42).

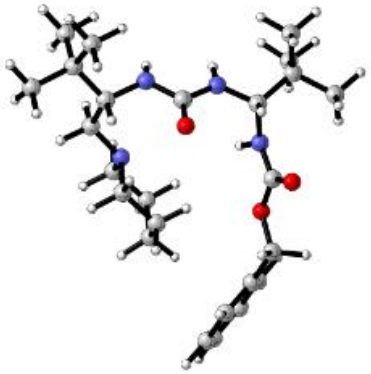
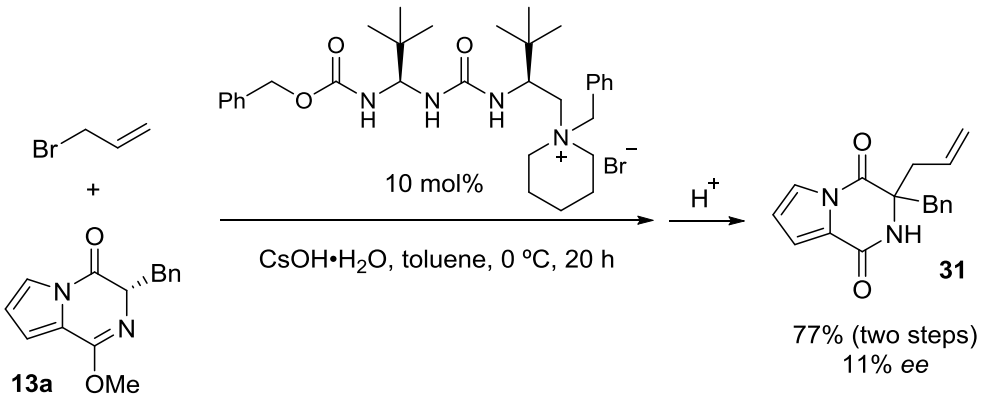


Figure 42. Most stable computed conformation of **C15** in toluene.

Once we proved the ability of bicyclic acylpyrrol lactims **13** to perform as pronucleophiles in Michael additions, promoted by bifunctional Brønsted bases, we decided to explore briefly other transformations and open new possibilities in the use of this novel pronucleophiles. With this objective in mind, we chose the alkylation of bicyclic acylpyrrol lactims **13a** under phase transfer conditions as reaction model. We confirmed the viability of the reaction using TBAB for its racemic version and prepared a chiral PTC catalyst based on our ureidoaminal-derived Brønsted bases (Scheme 71). Although the asymmetric induction observed was very poor, we believe the alkylation with bicyclic acylpyrrol lactims **13a** might be promising and the reaction optimization is underway.

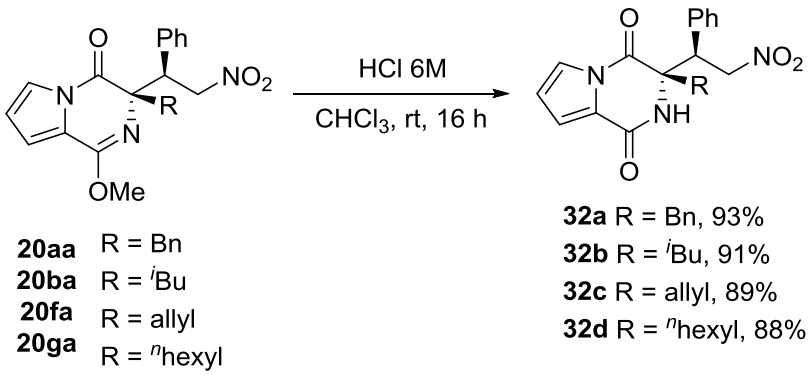


Scheme 71. PTC alkylation of acylpyrrol lactim **13a**.

At this point, we decided to concentrate in the manipulation of the Michael adducts to prove the validity of our organocatalytic methodology in producing the chiral pyrrolodiketopiperazines that were the main objective of this project. This particular transformation and others are disclosed in the following section.

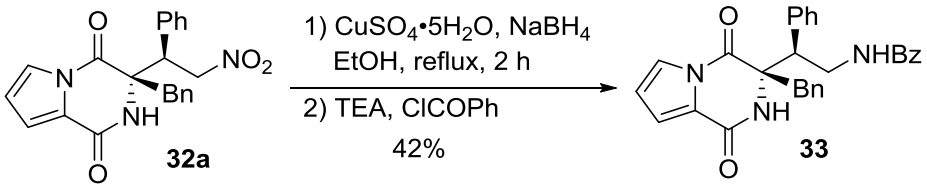
3.3.3. Michael adducts transformations

We confirmed that adducts **20** were efficiently converted into the target pyrrolodiketopiperazines **32**, under acidic conditions (Scheme 72). Other reagents, such as $HSiCl_3$, DIPEA or bromine also yielded the pyrrolo DKPs in a clean manner.



Scheme 72. Obtention of chiral pyrrolodiletopyperazines.

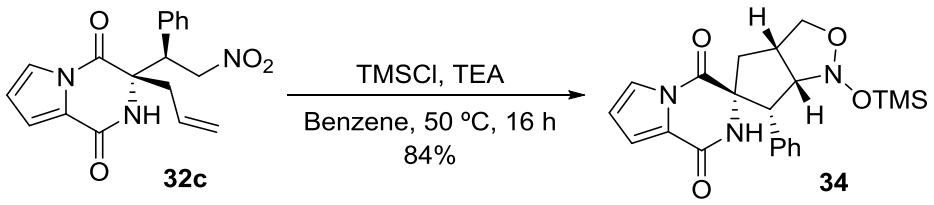
Additionally, pyrrolodiketopiperazines **33** may be adequate platforms to access more diversity by exploiting the orthogonal properties of the functional groups installed in the core. For example, the reduction of the nitro group in **32a**, followed by protection, afforded the corresponding protected primary amine **33** (Scheme 73).[164]



Scheme 73. Reduction of pyrrolo DKP **32a**.

[164] Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246-4247.

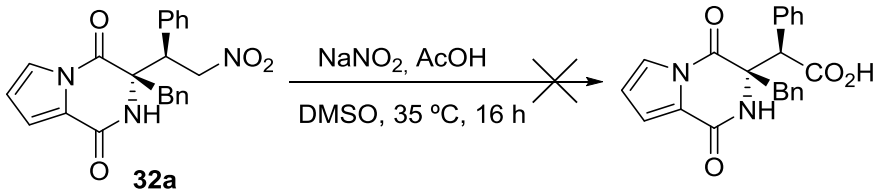
Continuing with the chemical versatility of the nitro group, the intramolecular silyl-nitronate olefin cycloaddition (ISOC)[165] of the Michael adduct **32c**, in the presence of trimethylsilyl chloride and trimethylamine, produced the spiro compound **34** as a single diastereomer in very good yield (Scheme 74).



Scheme 74. Synthesis of spiro compound **34**.

The configuration of the new stereogenic centers was determined by NOESY experiments based on the two carbon centers known previously by single-crystal X-ray analysis of the starting material **32c** (see Experimental Section).

Attempts to transform the nitro group into the corresponding carboxylic acid under Nef conditions[166] were unproductive and the starting material was systematically recovered (Scheme 75).

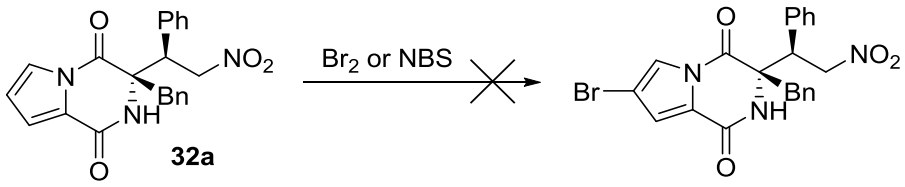


Scheme 75. Unsuccessful Nef reaction.

To continue with our efforts to modify the pyrrol ring we performed several tests to bromate it with different halogenating agents. Anyway, our aim found no satisfying

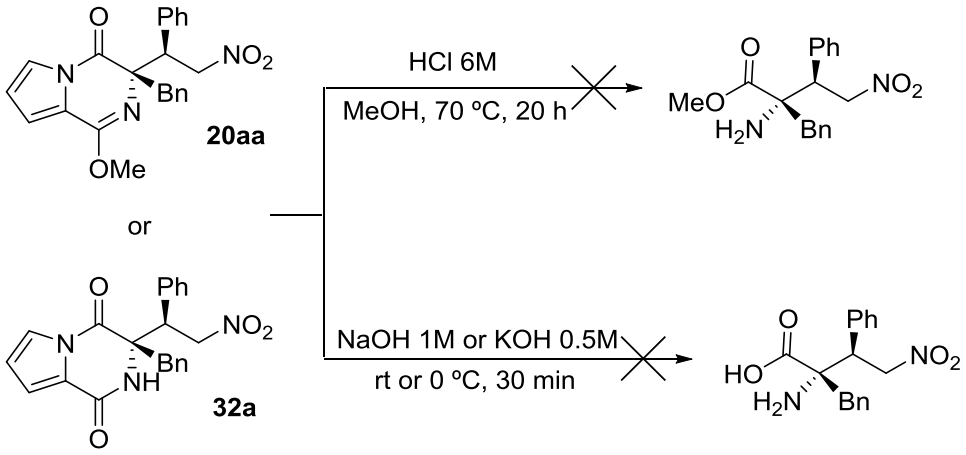
[165] Hassner, A.; Friedman, O.; Dehaen, W. *Liebigs Ann./Recueil* **1997**, 587-594.
[166] Nef, J. U. *Justus Liebigs Ann. Chem.* **1984**, *280*, 263-291. b) Varma, R. S.; Varma, M.; Kabalka, G. W. *Tetrahedron Lett.* **1985**, *26*, 3777-3778. c) Pinnick, H. W. *Organic Reactions*, Wiley, **1990**, 655-792. d) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017-1047.

results even at high temperatures and the substrate was recovered without any alteration (Scheme 76).



Scheme 76. Attempt to modify the pyrrol ring.

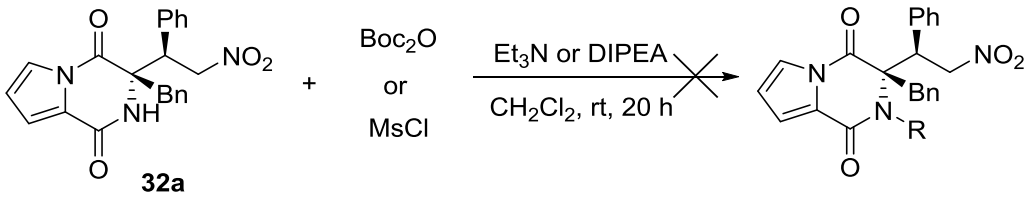
In order to prove that these novel compounds could behave as Schöllkopf bislactim surrogates, we tried to hydrolyse the Michael adducts to produce tetrasubstituted α-aminoacids and offer a catalytic alternative to the Schöllkopf bislactim methodology. It was very disappointing to find out that classical acid treatment did not alter the starting material whereas the use of basic conditions produced complex mixtures, regardless the temperature employed. (Scheme 77).



Scheme 77. Attempts to hydrolyze pyrrolo DKPs.

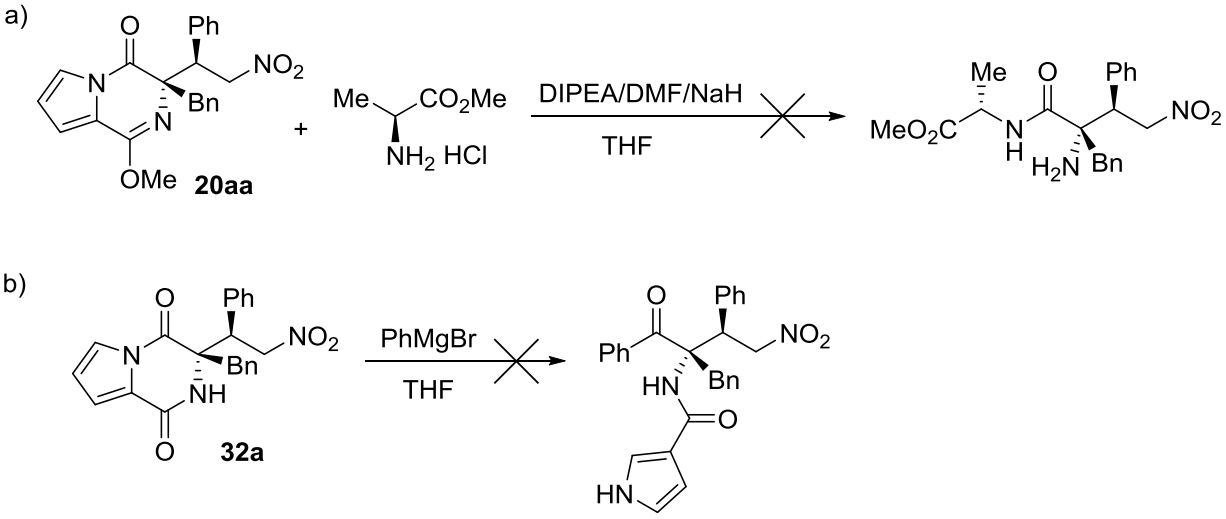
We tried to activate the cycle to make it prone to opening by protecting the amide but all attempts resulted disappointing and the starting material was recovered (Scheme 78).[167]

[167] Nakamura, K.; Kanao, T.; Uesugi, T.; Hara, T.; Sato, T.; Kawakami, T.; Aimoto, S. *J. Pept. Sci.* **2009**, *15*, 731-737.



Scheme 78. Attempts to protect pyrrolo DKP **32a**.

To demonstrate the suitability of the Michael adducts to serve as masked quaternary α-amino acids, we also tried to effect the opening by reaction with α-amino acids but the transformation was not observed in any of the conditions assayed (Scheme 79a). The use of Grignard reagents did not provide bicyclic opening neither and the starting material was recovered (Scheme 79b).



Scheme 79. Further attempts to open pyrrolo DKPs.

CHAPTER 4

4. EXPLORATION OF BORONATES VERSATILITY TO ACCESS CHIRAL PHOSPHINES

This part of the work has been carried out in the group of Prof. Syuzanna Harutyunyan at the Stratingh Institute for Chemistry of the University of Groningen (The Netherlands) during a 4-months internship.

4.1. Introduction

Phosphorus atom is one of the most abundant non-metallic elements in the Earth's crust and plays a significant role in the growth of living organisms. Among phosphorus-containing materials, chiral phosphines stand out due to their application in organometallic chemistry,[168] organocatalysis,[169] chemical biology[170] and the production of pharmaceuticals and agrochemicals.[171]

In the field of asymmetric catalysis, chiral phosphines display an important role since it is possible to take advantage of their steric and electronic properties to induce chirality.[172] Although their chirality usually comes from their carbon backbones, P-stereogenetic phosphines have also proved to be highly efficient in numerous catalytic processes[173] (Figure 43).

[168] a) *Comprehensive Asymmetric Catalysis*, Vols. 1-3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**. b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3069.
[169] Ni, H.; Chan, W.-L.; Lu, Y. *Chem. Rev.* **2018**, *118*, 9344-9411.
[170] a) Elliott, H. A.; O'Connor, G. A. *Soil Biol. Biochem.* **2007**, *39*, 1318-1327. b) McGrath, J. W.; Chin, J. P.; Quinn, J. P. *Nat. Rev. microbial.* **2013**, *11*, 412-419.
[171] a) Chirality in Agrochemicals (Ed.: N. Kurihara, J. Miyamoto), Wiley, Chichester, **1998**, pp. 85-139. b) Cheng-ye, Y. *Youji Huaxue* **2001**, *21*, 862-868.
[172] a) *Phosphorous Ligands in Asymmetric Catalysis,* Vol. 3 (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**, pp. 211-1233. b) Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis (Eds.: P. C. J. Kamer, P. W. N. M. van Leeuwen), Wiley, Hoboken, **2012**
[173] a) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25-90. b) Dutartre, M.; Bayardon, J.; Jugé, S. *Chem. Soc. Rev.* **2016**, *45*, 5771-5794.

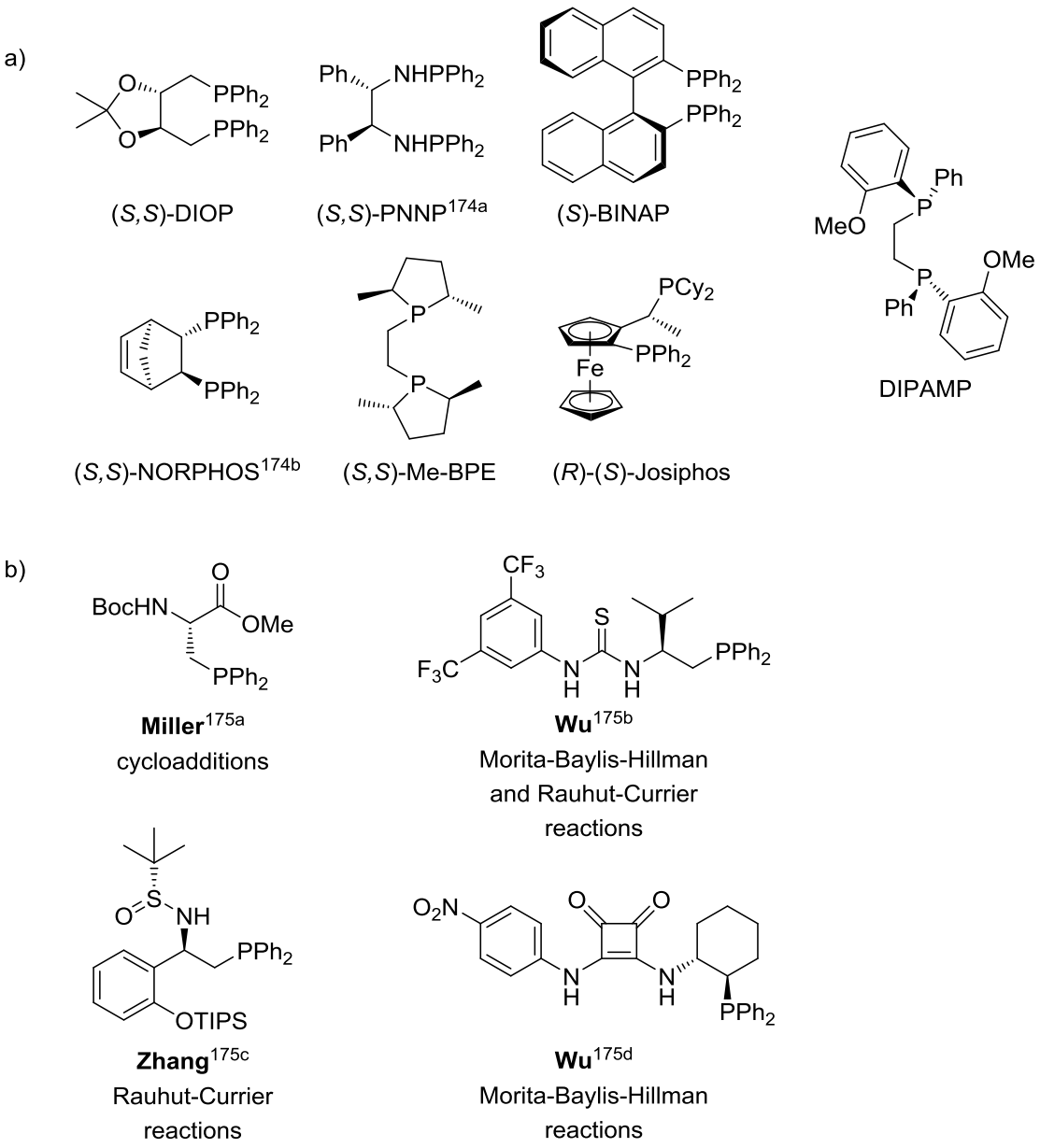


Figure 43. Selected examples of chiral phosphorus based a) ligands[174] and b) nucleophilic organocatalysts.[175]

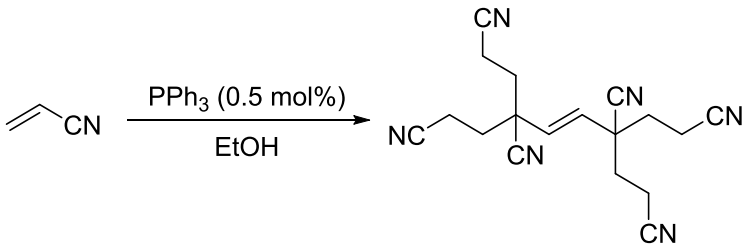
Since Horner's discovery of phosphonium zwitterion species,[176] nucleophilic phosphine catalysis has emerged as a powerful strategy for constructing functionalized structures that have important applications. Taking a look back to the 60s, three major discoveries settled the reference points in phosphine catalysis.

[174] a) Fiorini, M.; Giongo, G. M. *J. Mol. Catal.* **1979**, *5*, 303-310. b) Brunner, H.; Pieronczyk, W. *Angew. Chem.* **1979**, *91*, 655-656.

[175] a) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988-10989. b) Gong, J.-J.; Yuan, K.; Wu, X.-Y. *Tetrahedron: Asymmetry* **2009**, *20*, 2117-2120. c) Su, X.; Zhou, W.; Li, Y.; Zhang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 6874-6877. d) Qian, J.-Y.; Wang, C.-C.; Sha, F.; Wu, X.-Y. *RSC Adv.* **2012**, *2*, 6042-6048.

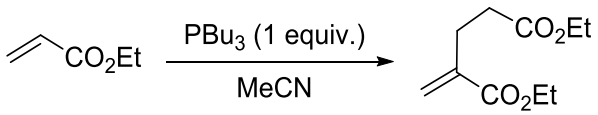
[176] Horner, L.; Jurgeleit, W.; Klupfel, K. *Liebigs Ann. Chem*. **1955**, *591*, 108-117.

The first carbon-carbon bond forming reaction catalyzed by triphenylphosphine was published by Price in 1962.[177] The hexamerization of acrylonitrile was efficiently achieved in the presence of ethanol, or other alcohols, which were required to avoid the polymer to be amorphous (Scheme 80).



Scheme 80. Polymerization of acrylonitrile.

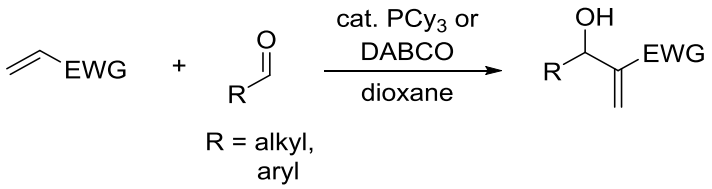
A year later, Rauhut and Currier reported the phosphine-catalyzed dimerization of electron-deficient alkenes.[178] Originally, the reaction described the dimerization of ethyl acrylate to yield the ethyl diester of 2-methylene-glutaric acid with stoichiometric amount of triphenylphosphine in acetonitrile (Scheme 81).[179]



Scheme 81. Rauhut-Currier reaction of ethyl acrylate.

In 1968, Morita and co-workers[180] disclosed the tricyclohexyl phosphine catalysed reaction of activated alkenes and non-enolizable aldehydes and, four years later, Baylis and Hilman[181] reported the same reaction using DABCO as catalyst (Scheme 82). For that reason, the transformation is known as Morita-Baylis-Hilman reaction (MBH)[182] and addresses substrate reactivity and regioselectivity issues more efficiently than the Rauhut Currier reaction.

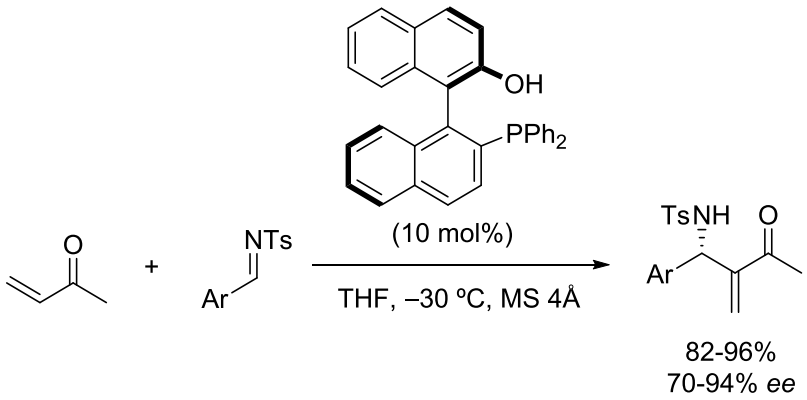
[177] Takashina, N.; Price, C. C. A. *J. Am. Chem. Soc.* **1962**, *84*, 489-491.
[178] Rauhut, M. M.; Currier, H. U.S. Patent 3 074 999, 1958. *Chem. Abstr.* **1963**, *58*, 66109.
[179] For reviews about Rauhut-Currier reaction, see: a) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069-4084. b) Biswas, S.; Bania, N.; Pan, S. C. *Chem. Rec.* **2023**, e202200257.
[180] Morita, K.-I.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815-2815.
[181] Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
[182] For recent reviews about MBH reaction, see: a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659-6690. b) Pellissier, H. *Tetrahedron* **2017**, *73*, 2831-2861.



Scheme 82. Morita-Baylis-Hillman reaction.

These transformations encouraged the discovery of countless efficient phosphine catalyzed transformations including catalytic versions of traditionally phosphine oxide-promoted reactions such as Wittig, Mitsunobu, and Staudinger reactions.[183] The following examples illustrate the potential and interest in the field, nowadays.

As a pioneering example, in 2003, Shi introduced a chiral phosphine Lewis base for the asymmetric aza-MBH reaction between methyl vinyl ketone and *N*-sulfonated imines producing the corresponding products in high yields and with excellent stereocontrol (Scheme 83).[184]

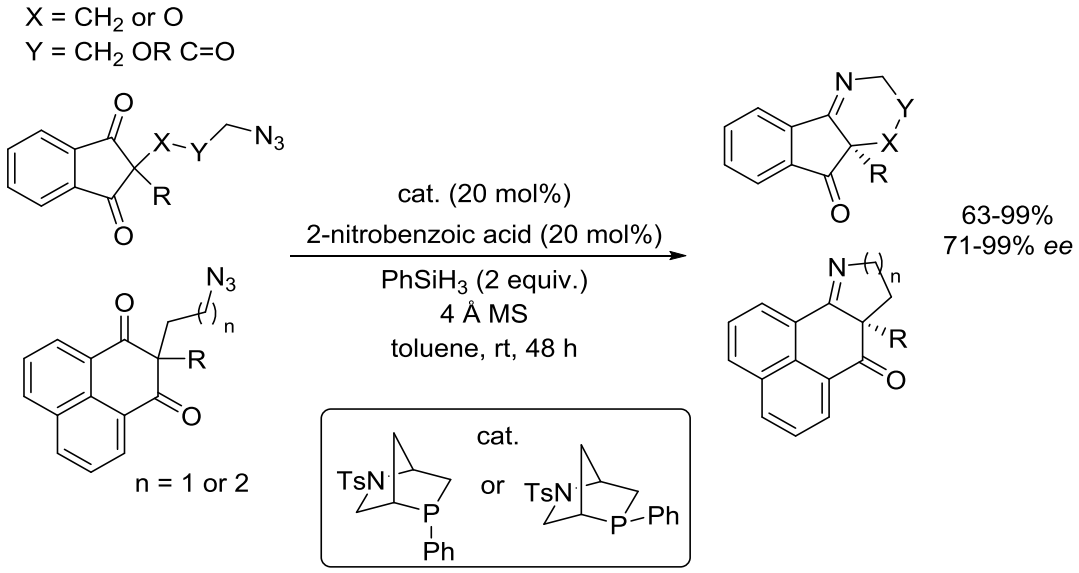


Scheme 83. Phosphine catalysed asymmetric aza-MBH reaction.

In 2019, the group of Kwon reported the first catalytic and asymmetric Staudinger-aza-Wittig reaction for the desymmetrization of ketones.[185] The transformation, promoted by a chiral phosphine at phosphorous and a Brønsted acid, provided five- and

[183] a) Guo, H.; Fan,Y. C.; Sun, Z.; Wu, Y.; Kwon, O. *Chem. Rev.* **2018**, *118*, 10049-10293. b) Xie, C.; Smaligo, A. J.; Song, X.-R.; Kwon, O. *ACS Cent. Sci.* **2021**, *7*, 536-558.
[184] See reference 34b.
[185] Cai, L.; Zhang, K.; Chen, S.; Lepage, R. J.; Houk, K. N.; Krenske, E. H.; Kwon, O. *J. Am. Chem. Soc.* **2019**, *141*, 9537-9542.

six-membered nitrogen heterocycles featuring a quaternary stereocenter in moderate to good yields and enantioslectivities (Scheme 84).



Scheme 84. Staudinger-aza-Wittig asymmetric reaction.

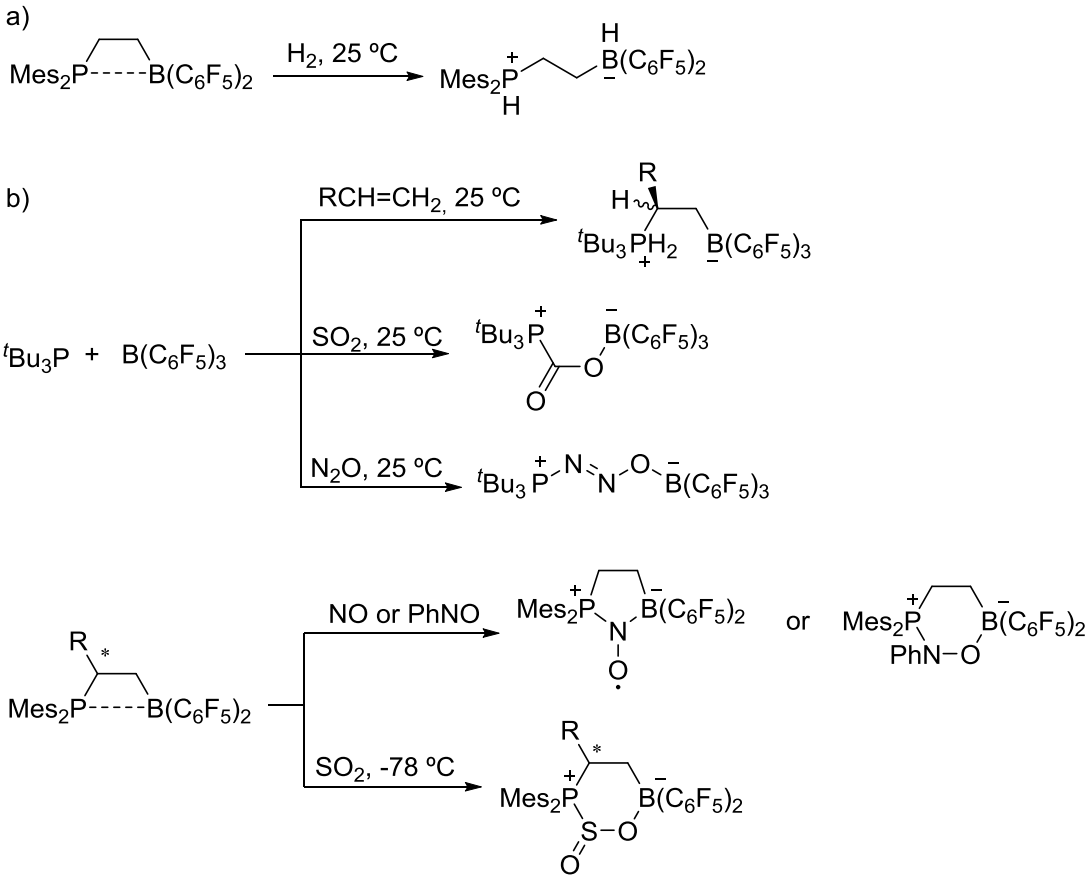
On the other hand, phosphorus-containing materials have encounter application in the chemistry of Lewis Frustrated Pairs (LFP); a seminal strategy in which Lewis acids and bases that are sterically prevented from forming classical Lewis acid–base adducts have Lewis acidity and basicity available for interaction with a third molecule.[186] In 1959, Halpern provided insight and foreshadowed the basis of FLPs with these words:

"to be effective, the two functional groups must be so disposed that they can interact simultaneously with a hydrogen molecule, but at the same time are prevented from interacting with (neutralizing) each other."[187]

The most striking finding from FLP chemistry was the discovery that FLPs can activate H_2, thus toppling the existing dogma that metals are required for such activation. As a pioneering example, the subtle balance of steric and electronics of the phosphorous/boron intramolecular FLP shown in Scheme xx,[188] enabled rapidly and

[186] a) Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124-1126. b) Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2007**, *129*, 1880-1881. c) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 2, 306–316.
[187] Halpern, J. *J. Phys. Chem.* **1959**, *63*, 398-403.
[188] Spies, P.; Schwendemann, S.; Lange, S.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 7543-7546.

reversibly H_2 activation and promoted the hydrogenation reaction of unsaturated bonds of bulky imines and enamines (Scheme 85a). Since this pioneering example described by Erker and co-workers, several examples of small molecules activation have been reported (Scheme xxb) alkene,[189] CO_2,[190] N_2O,[191] NO[192] and SO_2.[193]



Scheme 85. a) Transfer of the H^+/H^- pair under mild conditions. b) Small molecule activation by FLP.

[189] McCahill, J. S. J.; Welch, G. C.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 4968-4971.
[190] Mömming, C. M.; Otten, E.; Kehr, G.; Frölich, R.; Grimme, S.; Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 6643-6646.
[191] Otten, E.; Neu, R. C.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 9918-9919.
[192] Cardenas, A. J. P.; Culotta, B. J.; Warren, T. H.; Grimme, S.; Stute, A.; Frölich, R.; Kehr, G.; Erker, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 7567-7571.
[193] Sajid, M.; Klose, A.; Birkmann, B.; Liang, L.; Schimer, B.; Wiegand, T.; Eckert, H.; Lough, A. J.; Frölich, R.; Daniliuc, C. G.; Grimme, S.;Kehr, G.; Erker, G. *Chem. Sci.* **2013**, *4*, 213-219.

In addition to their good fruition in intramolecular FLP chemistry, phosphine boranes/boronates combinations also perform well as ligands in metal catalysed transformations and as organocatalysts (Figure 44).[194,195]

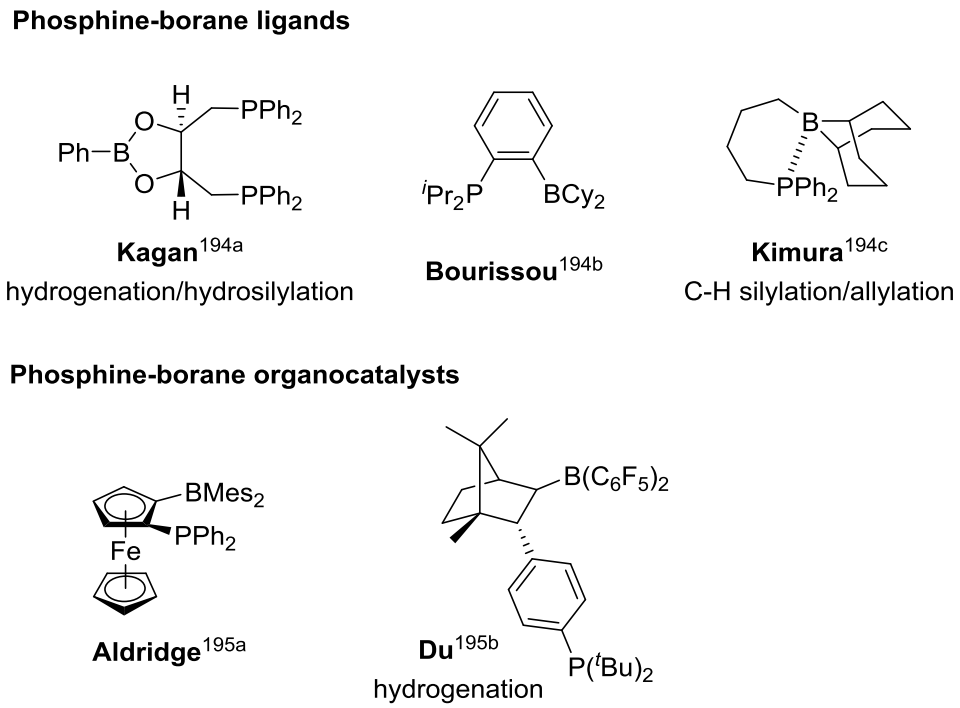


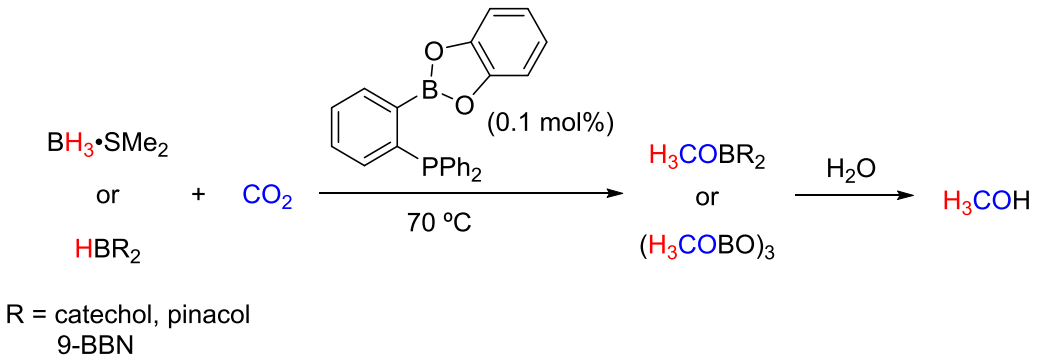
Figure 44. Selected phosphine-borane compounds used as ligands or organocatalysts.

A remarkable example of their potential is the reduction of carbon dioxide to methanol in a metal-free system, described by Maron and Fontain's research groups in 2013 (Scheme 86).[196] The organocatalyts shown in Scheme xx, acted as an ambiphilic metal-free system for the reduction of carbon dioxide in presence of hydroboranes to generate exclusively CH_3OBR_2 or $(CH_3OBO)_3$, which could be readily hydrolyzed to methanol.

[194] For selected phosphine-borane based ligands, see: a) Boerner, A.; Ward, J.; Kortus, K.; Kagan, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2219-2228. b) Boerner, A.; Ward, J.; Kortus, K.; Kagan, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2219-2228. c) Shimizu, A.; Hirata, G.; Onodera, G.; Kimura, M. *Adv. Synth. Catal.* **2018**, *360*, 1954-1960.

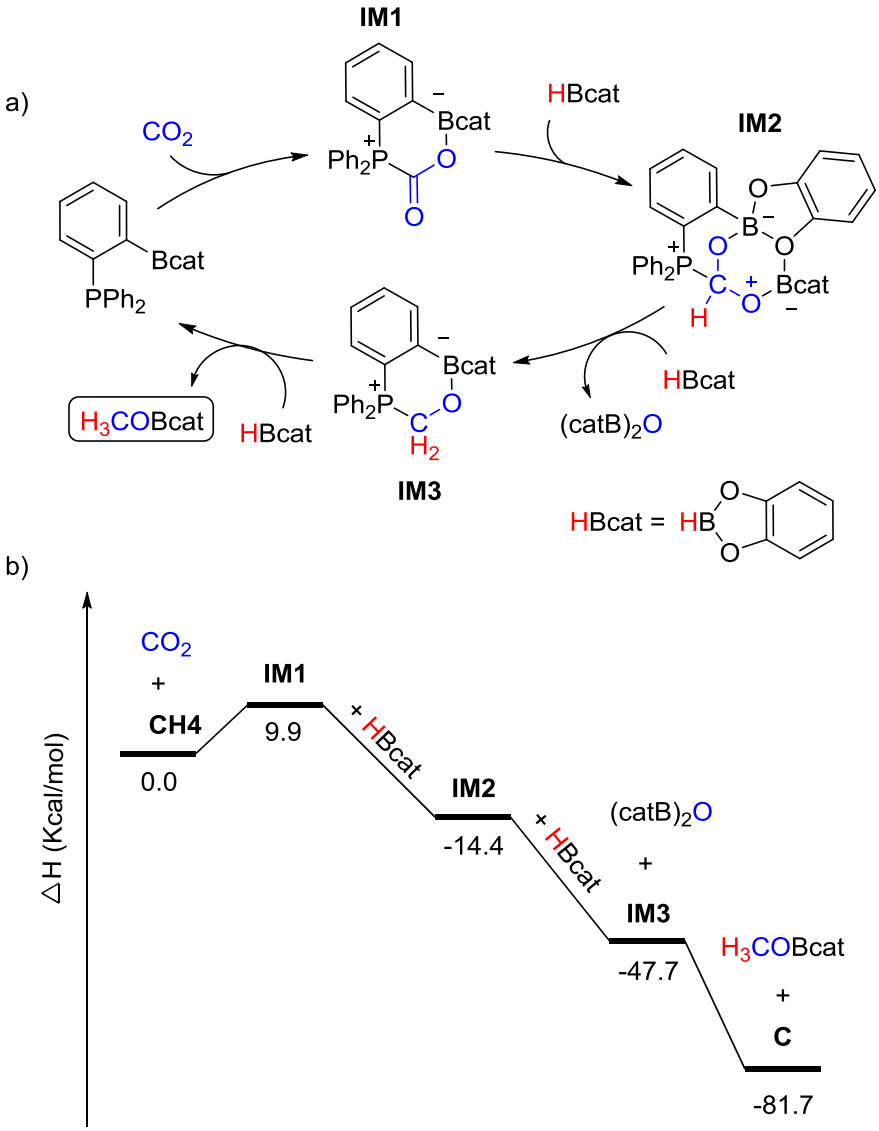
[195] For selected phosphine-borane based organocatalysts, see: a) Siewert, I.; Vidovic, D.; Aldridge, S. *J. Organomet. Chem.* **2011**, *696*, 2528-2532. b) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959-6964.

[196] Courtemanche, M.-A.; Légaré, M.-A.; Maron, L.; Fontaine, F.-G. *J. Am. Chem. Soc.* **2013**, *135*, 9326-9329.



Scheme 16. Reduction of CO_2 to methanol using hydroboranes.

As experimental results suggest, the coordination of the CO_2 leading to **IM1** is disfavoured although the activation of this small molecule makes the attack of the HBcat possible, yielding the species **IM2**. A second HBcat intercedes to exchange a proton atom for the previously attached Bcat taking an oxygen to afford catBOBcat and **IM3**. The third and last catecholborane involved in the reduction of CO_2 regenerates the catalyst and the reduced product (Scheme 87). The overall process is highly favoured once the activation has taken place.

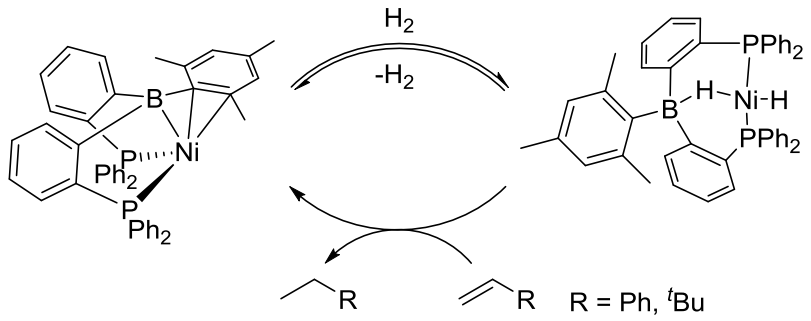


Scheme 87. a) Catalytic cycle of the reduction of CO_2. b) Enthalpy profile for the reduction of CO_2 by phosphine borane organocatalyst and catecholborane.

The advent of phosphine boranes as a new class of ambiphilic ligands has provided straightforward access to M→B interactions. The presence of a Lewis acid in the first coordination sphere of a transition metal may offers very interesting possibilities.[197] In 2012, Peters and co-workers reinforced this idea with their milestone work in the field of catalysis (Scheme 88).[198] The diphosphine borane nickel complex adopted a pyramidal geometry with η^3-BCC coordination with an ideal balance between stability and reactivity that facilitated rapid and reversible H_2 activation. Interestingly, when the Mes group at B

[197] Devillard, M.; Bouhadir, G.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 730-732.
[198] Harman, H.; Peters, J. C.M. *J. Am. Chem. Soc.* **2012**, *134*, 5080-5082.

by is replaced by a phenyl ring, the nickel complex features strong η^2-BC coordination and does not react with H_2 even under forcing conditions.

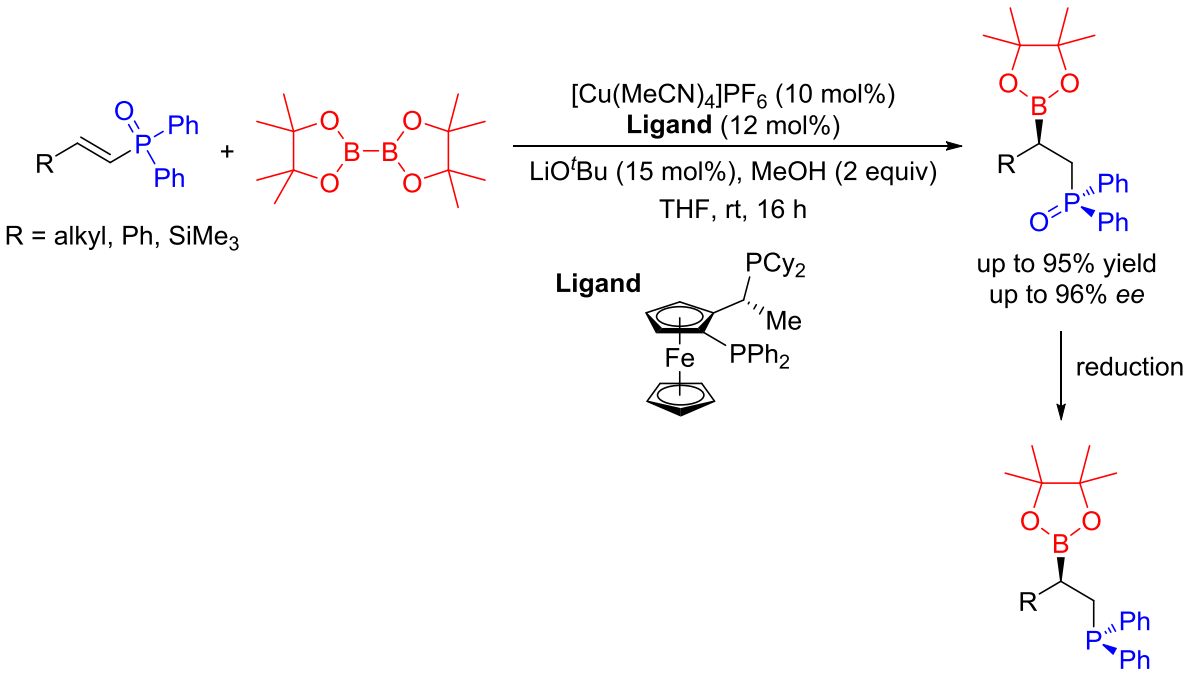


Scheme 88. Activation of H_2 by a diphosphine borane nickel complex and application to catalytic hydrogenation.

Notwithstanding the interesting properties of phosphorous-boron containing compounds, a single example for their catalytic synthesis has been described (Scheme 89).[199] Feringa and co-workers developed an asymmetric β-boration of α,β-unsaturated phosphine oxides to produce chiral ambiphilic phosphine oxides/phosphine boronates with high enantiomeric excess under mild conditions. The methodology, using copper(I) in the presence of (*R,S*)-Josiphos, showed a broad structural scope and functional group

[199] Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867-7871.

tolerance. Additionally, the stereospecific transformation to new optically active products and subsequent elaborations demonstrate the synthetic versatility of these compounds.



Scheme 89. Catalytic and asymmetric synthesis of phosphine boronates.

4.2. Group precedents

In this context, the Harutyunyan group has been working on hydrophosphination reactions making use of manganese (Figure 45), an earth-abundant transition metal with low toxicity, towards more sustainable homogeneous catalytic transformations.[200] Catalytic asymmetric hydrophosphination[201] is a highly attractive pathway and one of the most straightforward approaches for the generation of optically active P- or C-chiral phosphines.[202]

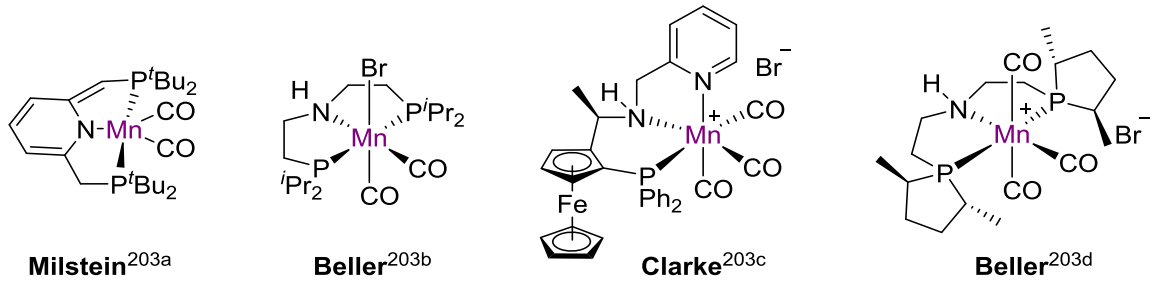


Figure 45. Mn(I) based complexes used in (de)hydrogenations.[203]

In 2021, the Harutyunyan group demonstrated that chiral Mn(I) catalyst is able to activate H-P bonds, being the metal-ligand cooperation (MLC) the basis for the activation.[204] This type of activation, unprecedented in catalysis by the time the work was

[200] a) Klein Gebbink, R. J. M.; Moret, M. E., Eds. *Non-Noble Metal Catalysis: Molecular Approaches and Reactions*; Wiley-VCH: Weinheim, **2019**. b) Bullock, R. M., Ed. *Catalysis without Precious Metals*; Wiley-VCH: Weinheim, **2010**. c) Mukherjee, A.; Milstein, D. *ACS Catal.* **2018**, *8*, 11435-11469. d) The limits for Mn in pharmaceuticals are 250 ppm relative to less than 10 ppm for all precious metal catalysts: Guideline on Specification Limits for Residues of Metal Catalystsor Metal Reagents; Report HMP/SWP/4446/2000; European Medicines Agency, **2008**. e) Hayler, J. D.; Leahy, D. K.; Simmons, E. M. Organometallics **2019**, *38*, 36-46.

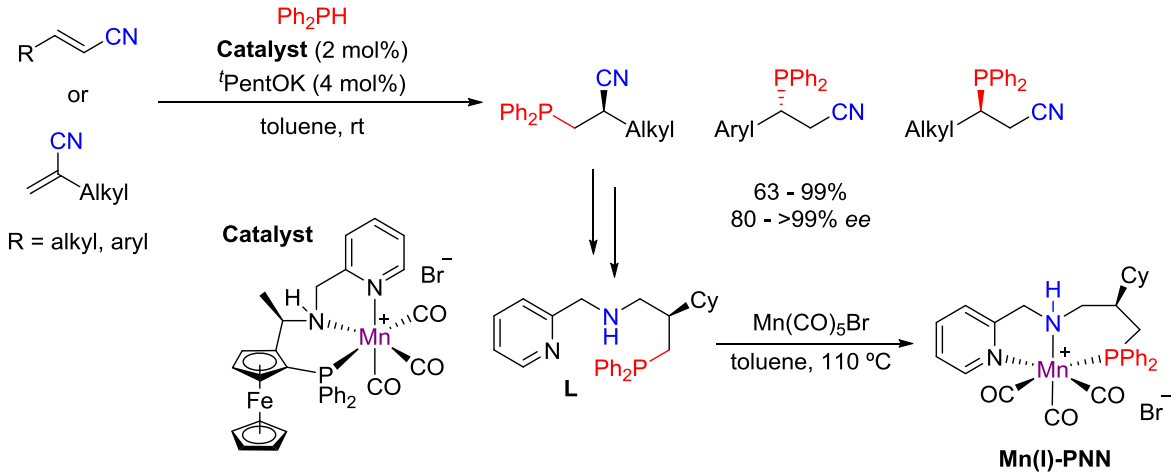
[201] For a recent review on catalytic hydrophosphination, see: Lau, S.; Hood, T. M.; Webster, R. L. *ACS Catal.* **2022**, *12*, 10939-10949.

[202] a) Zhao, D.; Wang, R. *Chem. Soc. Rev*. **2012**, *41*, 2095-2108. b) Pullarkat, S. A. *Synthesis* **2016**, *48*, 493-503. c) Chew, R. J.; Leung, P.-H. *Chem. Rec*. **2016**, *16*, 141-158. d) Li, Y.-B.; Tian, H.; Yin, L. *J. Am. Chem. Soc.* **2020**, *142*, 20098-20106. e) Liu, X.-T.; Han, X.-Y.; Wu, Y.; Sun, Y.-Y.; Gao, L.; Huang, Z.; Zhang, Q.-W. *J. Am. Chem. Soc.* **2021**, *143*, 11309-11316.

[203] a) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J. W.; David, Y. B.; Jalapa, N. A. E.; Milstein, D. *J. Am. Chem. Soc.* **2016**, *138*, 4298-4301. b) Elangovan, S.; Topf, C.; Fischer, S.; Jiao, H.; Spannenberg, A.; Baumann, W.; Ludwig, R.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2016**, *138*, 8809-8814. c) Widegren, M. B.; Harkness, G. J.; Slawin, A. M. Z.; Cordes, D. B.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 5825-5828. d) Garbe, M.; Junge, K.; Walker, S.; Wei, Z.; Jiao, H.; Spannenberg, A.; Bachmann, S.; Scalone, M.; Beller, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11237-11241.

[204] Pérez, J. M.; Postolache, R.; Castiñeira Reis, M.; Sinnema, E. G.; Vargová, D.; de Vries, F.; Otten, E.; Ge, L.; Harutyunyan, S. H. *J. Am. Chem. Soc.* **2021**, *143*, 20071-20076.

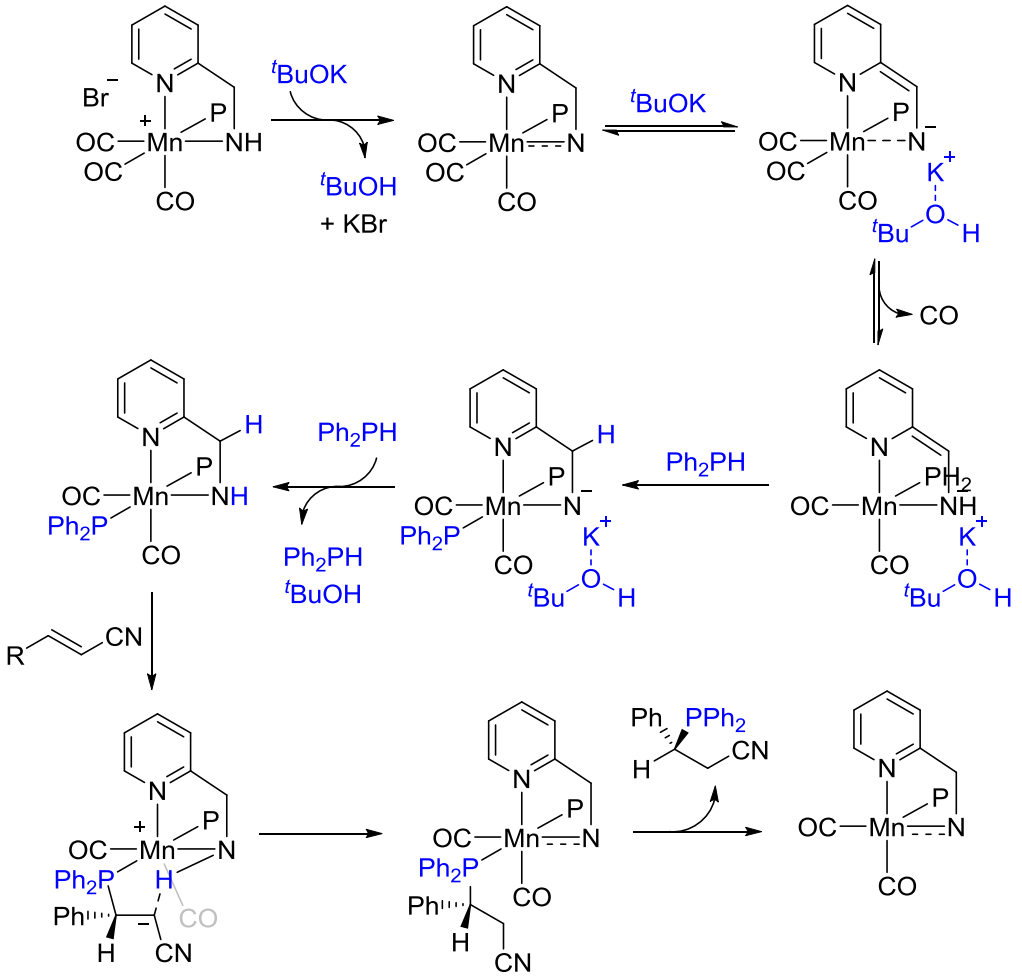
published, enabled the enantioselective hydrophosphination of internal and terminal α,β-unsaturated nitriles (Scheme 90). In order to show the potential applications of the methodology, the appropriate adduct was transformed into the ligand **L** to obtain the complex **Mn(I)-PNN** that was found to be efficient for hydrophosphination and transfer hydrogenation reactions.[205]



Scheme 90. Hydrophosphination of acrylonitriles and application of the adducts.

In (de)hydrophosphinations catalyzed by manganese complexes, the ligand takes part in the catalytic cycle playing an important role in the process. It was proven by computational studies that the base acts twice in the Mn(I) complex: first, deprotonating the amino group and second leading to the dearomatization of the pyridine ring, after of which the catalyst is ready to trigger the reaction. Now, the conjugate addition can proceed through both faces (top and bottom) of the nitrile, providing opposite configurations. Experimentally, just the *R*-product was obtained meaning that the reaction occurs from different faces when it comes to aromatic or aliphatic substrates (Scheme 91).

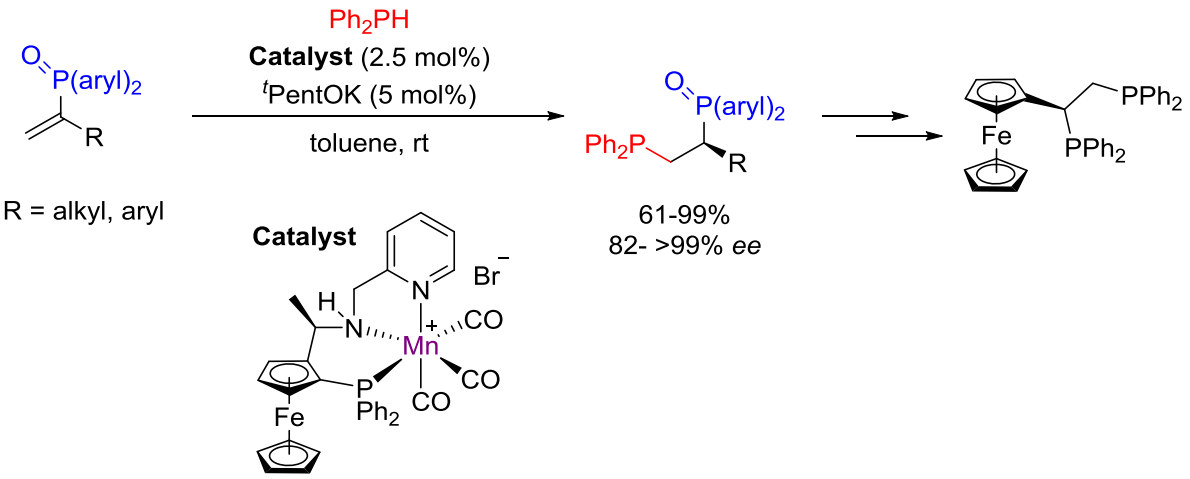
[205] a) Erken, C.; Kaithal, A.; Sen, S.; Weyhermüller, T.; Hölscher, M.; Werlé, C.; Leitner, W. *Nat. Commun.* **2018**, *9*, 4521-4529. b) Gorgas, N.; Kirchner, K. *Acc. Chem. Res.* **2018**, *51*, 1558-1569. c) Wang, Y.; Zhu, L.; Shao, Z.; Li, G.; Lan, Y.; Liu, Q. *J. Am. Chem. Soc.* **2019**, *141*, 17337-17349.



Scheme 91. Activation of Mn(I) complex by base and asymmetric hydrophosphination.

In 2022, the same group developed the first Mn(I) catalysed enantioselective strategy for the hydrophosphination of α,β-unsaturated phosphine oxides to obtain, after a two-step sequence, enantiopure 1,2-bisphosphine ligands, which found application in copper catalysed hydrophosphination reactions (Scheme 92).[206]

[206] Ge, L.; Harutyunyan, S. R. *Chem. Sci.* **2022**, *13*, 1307-1312.

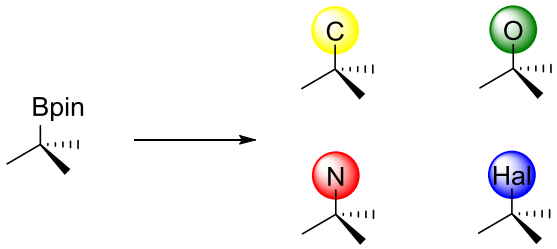


Scheme 92. Mn(I)-catalyzed asymmetric hydrophosphination of α,β-unsaturated phosphine oxides.

4.3. Objetives

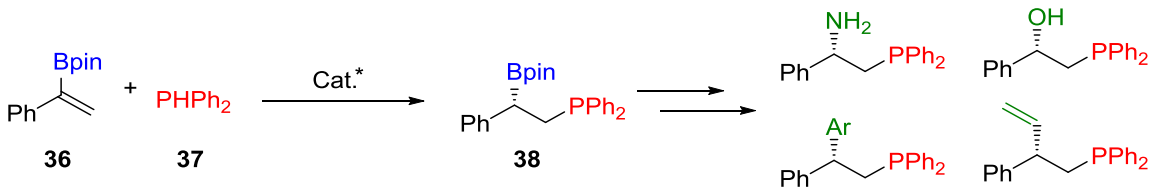
As disclosed in the introduction of this chapter, despite the promising reactivity, beneficial properties and applications that chiral phosphine boronates may display, there is just a single example for their preparation using catalytic asymmetric methodologies (see Scheme 89).

Furthermore, organoboron compounds are configurationally stable molecules, and consequently, can be transformed to a variety of different functional groups thanks to its capacity to undergo stereospecific elaborations to form new C-O, C-N, C-C and C-Hal bonds and providing access to a broad array of products (Scheme 93).[207]



Scheme 93.

Taking advantage of the knowledge previously acquired in the group, the goal of the work carried out during the internship was to develop an asymmetric procedure for the synthesis of chiral phosphine boronates and use them to access β-functionalized chiral phosphines. In particular, the large scale preparation of (*S*)-diphenyl(2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phosphane **38** to explore its chemical versatility toward the production of a phosphine based products library (Scheme 94).



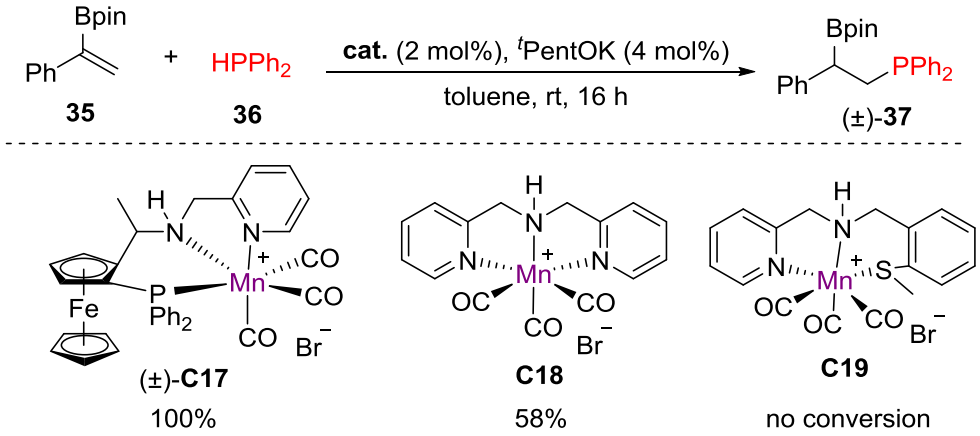
Scheme 94. Main goal of the research work during the intership.

[207] Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494.

4.4. Results and discussion

For a preliminary study on the hydrophosphination of boronic esters, we decided to explore the racemic reaction between 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2 dioxaborolane **35** and diphenylphosphine **36**. To evaluate the viability of the reaction, we chose three Mn(I) based catalysts **C17** – **C19**, available in the laboratory, and ran the reactions at 0.1 mmol scale employing 2 mol% of the metal complex and 4 mol% of the strong base, as optimal conditions stablished in previous reactions (Table 17).[208]

Table 17. Screening of catalyst.

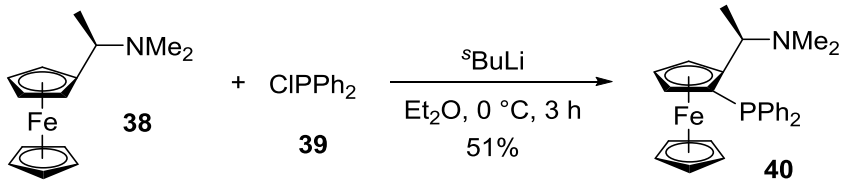


As expected, based on those previous works, Clarke's racemic catalyst **C17** promoted full conversion after 16 hours at room temperature. Catalyst **C18** provided 58% conversion into **37** whereas **C19** did not promote the reaction despite extending the reaction time. Since **C18** is easier to synthesize, we decide to increase the catalyst loading up to 4 mol% to complete the reaction and produce enough quantities of racemic **37** to check its chemical versatility.

For the exploration of the asymmetric version, we chose enantiomerically pure Clarke's catalyst **C20**, which was prepared following described procedures (Scheme 95). The first step was the phosphination of the Ugi's amine **38** to produce **40** with a moderate yield, probably due to partial oxidation of the chlorodiphenylphosphine.[209]

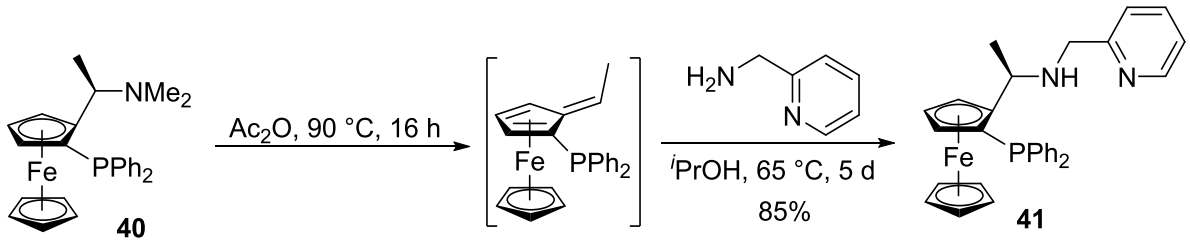
[208] See references 204 and 206.

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



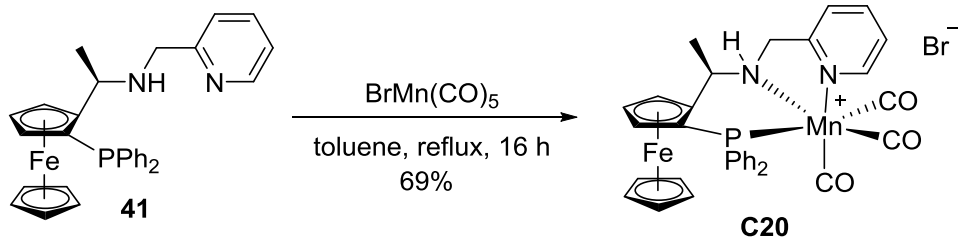
Scheme 95. Ugi's amine phosphination.

Next, nucleophilic substitution with complete retention of configuration produced the ferrocenyl ligand **41** in high yield (Scheme 96). Stereochemical and kinetic evidences support an SN_1 mechanism via a configurationally stable ferrocenylethenyl intermediate.[210]



Scheme 96. Synthesis of PNN based ligand.

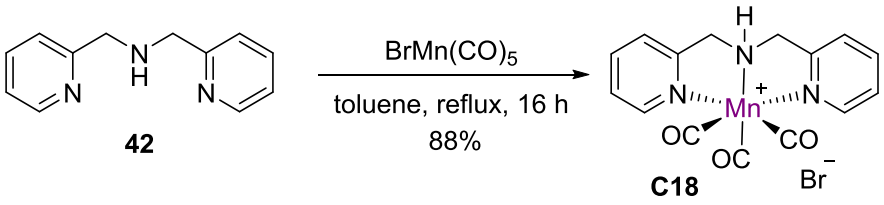
The chiral complex Mn(I)complex **C20** was finally prepared in 69% yield following the procedure described by Clarke[36] (Scheme 97).



Scheme 97. Complexation of the ligand with manganese.

On the other hand, the achiral Mn(I)complex **C18** was prepared with high yield in a single step by combining di-(2-picolyl)amine **42** and bromopentacarbonylmanganese(I) (Scheme 98) and the racemic hydrophosphination reaction also scaled up to 2 mmol.[36]

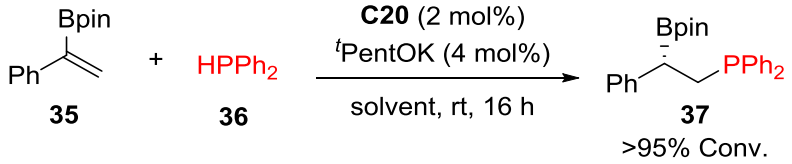
[210] Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem*. **1972**, *37*, 3052-3058.



Scheme 98. Synthesis of the Mn(I)-complex **C18**.

Once enantiomerically pure **C20** was prepared, we evaluate the asymmetric hydrophosphination (Table 18). As expected, total conversion into the desired phosphine boronate **37** was observed at room temperature after 16 hours. Gratifingly, the enantiomeric excess was excellent regardless the solvent employed: 94% and 96% in toluene and THF, respectively. Then, the reaction was scaled up to 2 mmol and the yield and the enantiomeric excess were maintained.

Table 18. Solvent screening of the hydrophosphination of boronate **36**.[a]



solvent	*ee* (%)	yield (%)
toluene	94	99
THF	96	99

[a] Reaction conditions: boronate (0.1 mmol), phosphine (1.0 equiv.) in toluene (1 mL).

In the following section the reactions conducted to explore the synthetic applications of phosphine boronate **37** are presented.

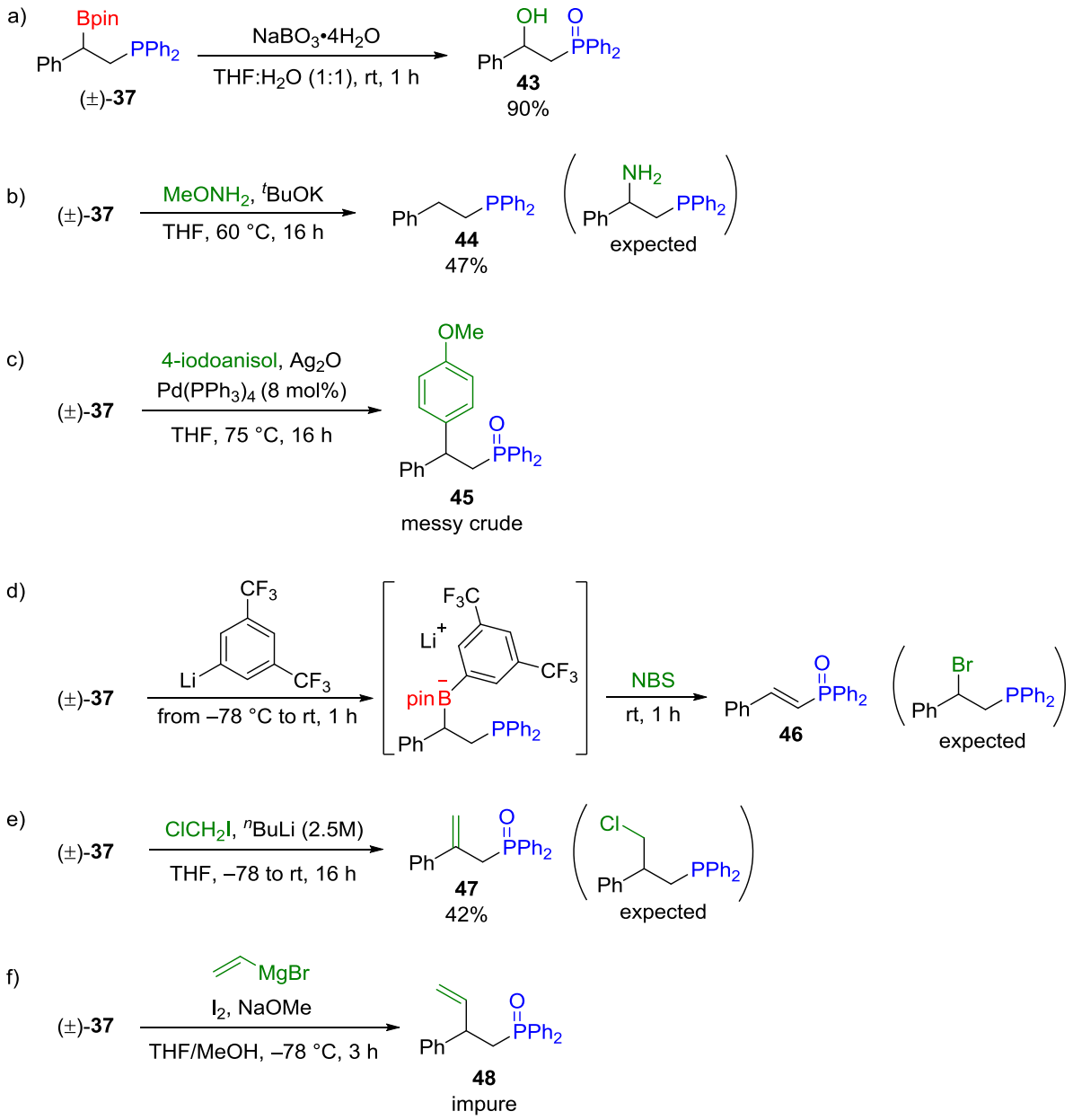
4.4.1. Chemical versatility of adduct 38

4.4.1.1. Non-protected phosphine

Preliminary attempts to modify racemic (±)-**37** were carried out with the naked phosphine boronic ester. In a first attempt, the adduct (±)-**37** was reacted with sodium

perborate tetrahydrate[211] to produce the desired hydroxylated product **43** in good yield thought the phosphine was also oxidized (Scheme 99a). In a second reaction, the phosphine boronate was treated with methoxyamine and potassium *tert*-butoxide[212] in order to install the amine group but, on the contrary, phenethyldiphenylphosphane **44** was formed instead (Scheme 99b). Attempts to arylate[213] (±)-**37** afforded complex mixtures in which the oxidation of the phosphine was detected by ^{31}P-NMR (Scheme 99c). The reaction of the *in-situ* formed (3,5-bis(trifluoromethyl)phenyl)lithium boronate complex with NBS[214] was also disappointing since elimination was produced instead of bromination (Scheme 99d). β-Elimination was also observed when (±)-**37** was treated with chloroiodomethane[215] in the presence of a strong base (Scheme 99e). Finally, treatment with vinylmagnesium[216] provided the desired oxidized product **48** but there was another impurity that we we were not able to identify (Scheme 99f).

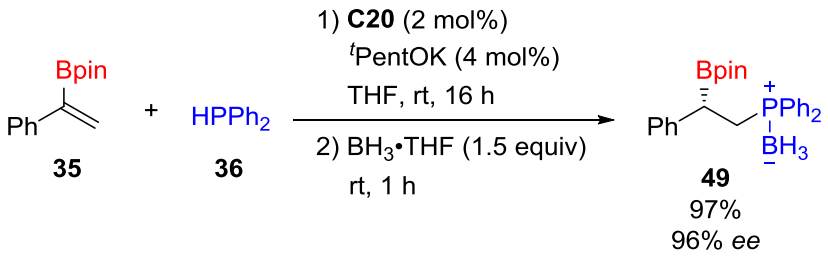
[211] Lee, J.-E.; Yun, J. *Angew. Chem. Int. Ed.* **2007**, *47*, 145-147.
[212] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451.
[213] Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024-5025.
[214] Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794-16797.
[215] Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687-1689.
[216] Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760-3763.



Scheme 99. Attempts to transform phosphine boronate (±)-**37**.

4.4.1.2. Borane-protected phosphine

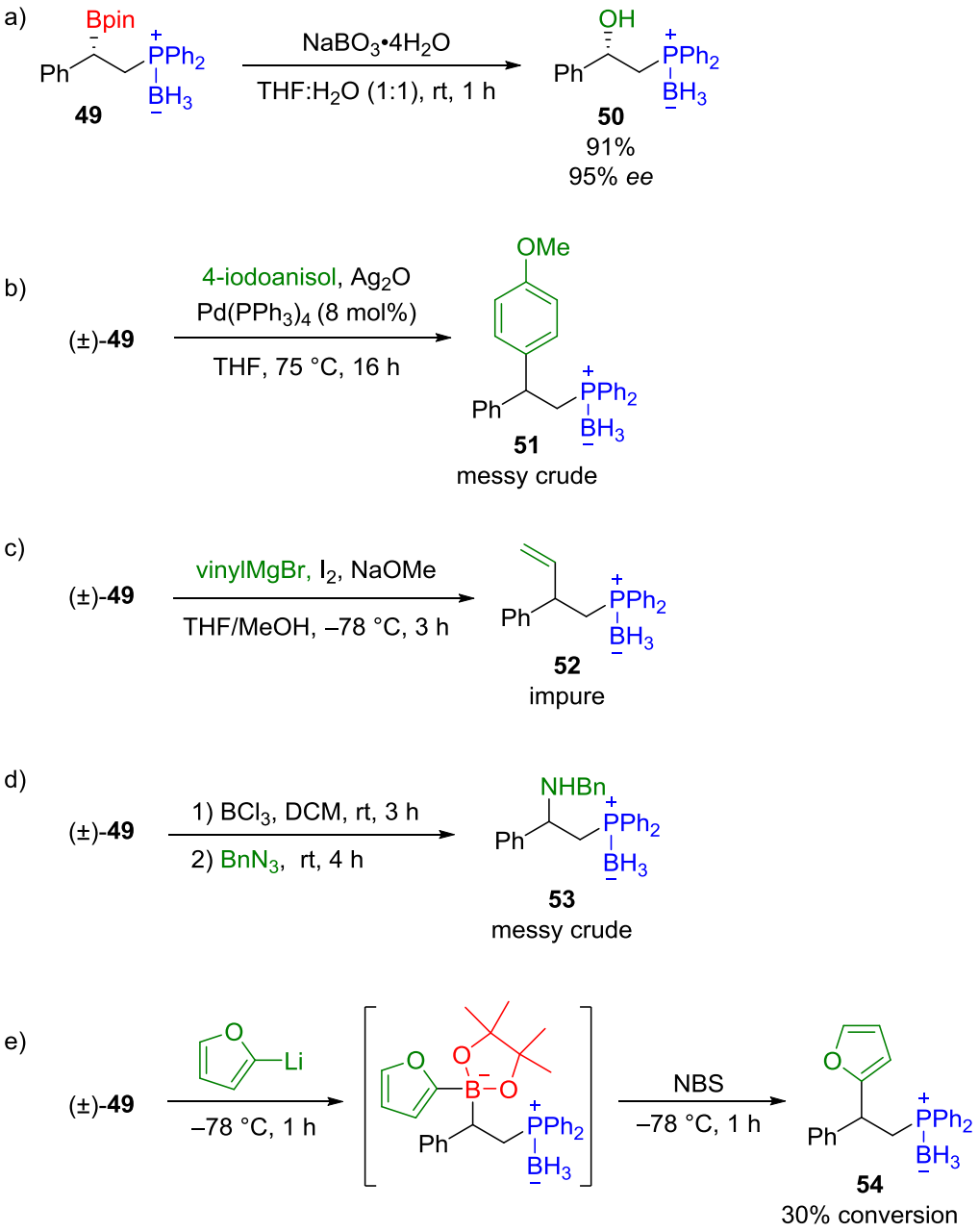
Being aware of the difficulties to obtain phosphine derivatives and their easy oxidation, we decided to react enantiomerically enriched **37** with BH_3·THF to generate the corresponding protected adduct **49**, which was obtained in excellent yield and enantiomeric excess (Scheme 100).



Scheme 100. Asymmetric hydrophosphination and protection of the phosphine.

Using the protected phosphine **49**, the oxidation reaction afforded the desired alcohol **50** with excellent yield and with practically the same enantiomeric excess as the starting material (Scheme 101a). The arylation reaction (Scheme 101b) and the treatment with vinylmagnesium bromide (Scheme 101c) afforded similar results as those for phosphine boronate (±)-**37**. Attempts to produce amines, this time by treatment with boron trichloride and benzyl azide[217] were also unfruitful (Scheme 101d). Finally, adduct (±)-**49** was partially converted into **54** by treatment with 2-furyllithium.[218] Nevertheless, the low conversion could not be improved neither by extending reaction times nor increasing 2-furyllithium excess up to 2 equivalents (Scheme 101e).

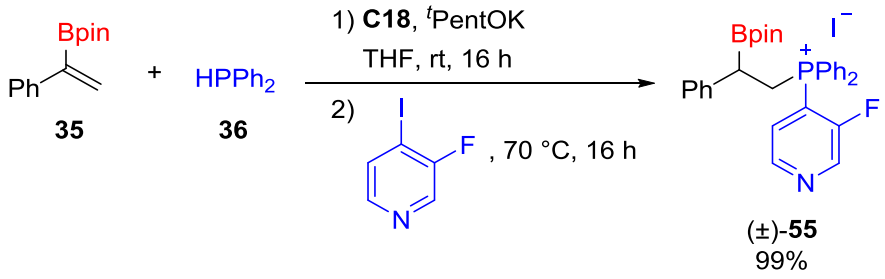
[217] Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2863-2863.
[218] Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082-1096.



Scheme 101. Attempts to transform protected phosphine boronate **49**.

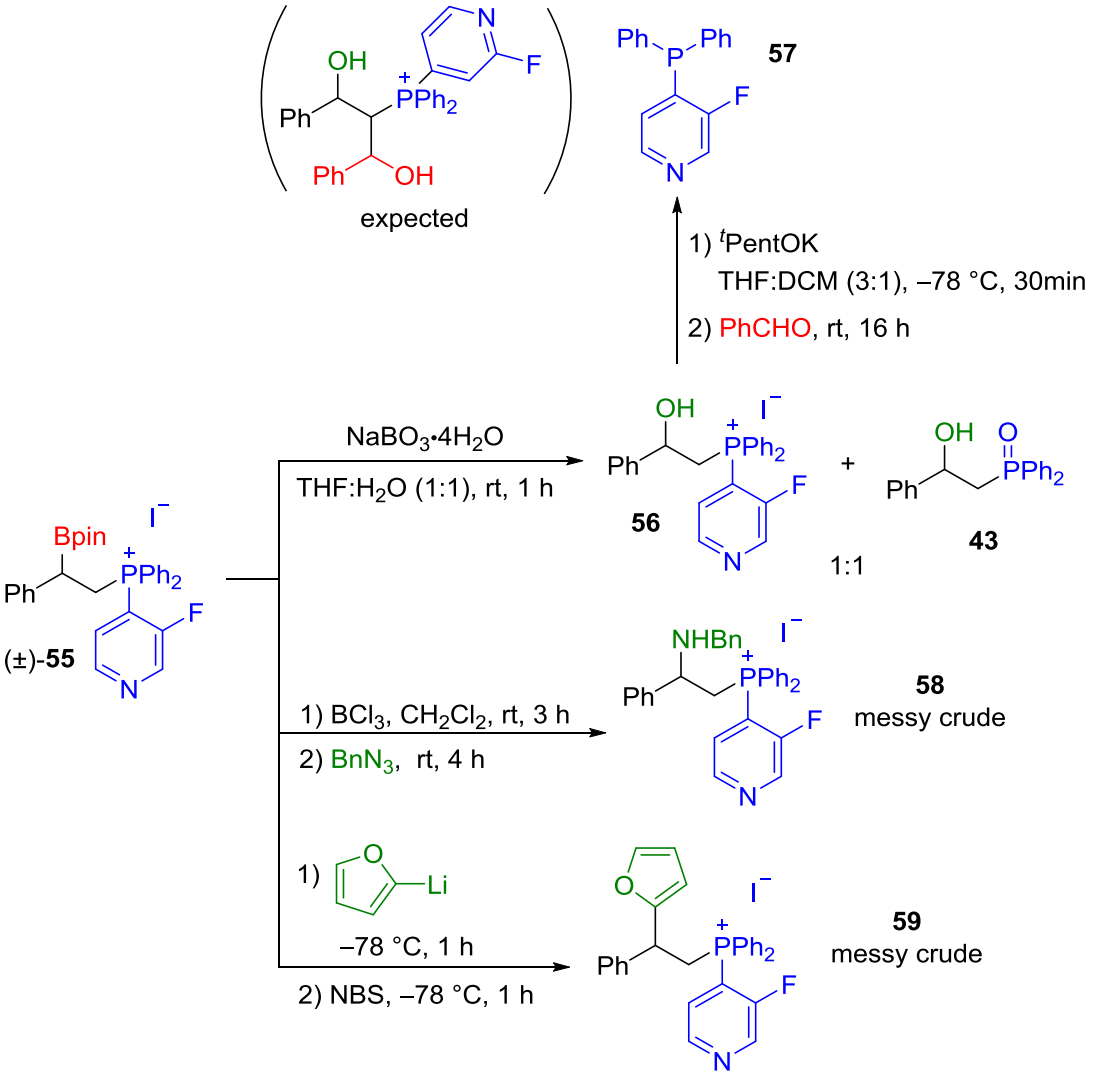
4.4.1.3. Phosphonium salt

As the last alternative during my internship, we decided explore the behaviour of the phosphonium salt (±)-**55**, which was synthesized in quantitative yield (Scheme 102).



Scheme 102.

In this case, the boronate oxidation afforded a 1:1 mixture of the phosphine oxide **43** and the desired product **56** (Scheme 103a). The crude, without any purification, was directly reacted with potassium *tert*-pentoxide and benzaldehyde but the 4-(diphenylphosphaneyl)-3-fluoropyridine **57** was obtained instead of the desire β-hydroxy phosphine. Likewise, the amination reaction and the treatment with 2-furyllithium produced messy reaction crudes (Scheme 103b and c).


expected
57
1) tPentOK
THF:DCM (3:1), –78 °C, 30min
2) PhCHO, rt, 16 h
NaBO3•4H2O
THF:H2O (1:1), rt, 1 h
56
43
1:1
(±)-55
1) BCl3, CH2Cl2, rt, 3 h
2) BnN3, rt, 4 h
58
messy crude
1)
–78 °C, 1 h
2) NBS, –78 °C, 1 h
59
messy crude

Scheme 103.

CHAPTER 5

5. CONCLUSIONS

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

3-aryl-1*H*-imidazol-4(5*H*)-ones have demonstrated to be the perfect key 5,5-disubtituted hydantoin surrogates in enantioselective Michael reaction to nitrostyrenes, efficiently performed by a squaramide-based *tert*-leucine derived BB catalyst. The Michael adducts elaboration has given access to a wide library of chiral derivatives of (thio)hydantoins, which could be used directly as biologically active compounds or as scaffolds for the synthesis of more complex structures.

Pyrrolodiketopiperazines have been employed for the first time in BB catalysed reactions for the construction of chiral α-tetrasubstituted structures, via direct carbon-carbon bond forming reactions mediated by an ureidoaminal-based tertiary amine that afforded high skeleton diversity with chemical and stereochemical efficiency. The use of (hetero)aryl nitroolefins, and even less reactive alkylic nitroalkenes, were well-tolerated and yielded the desired products with excellent results in terms of reactivity and enantioselectivity. Furthermore, the synthetized product library could provide a variety of new candidates to enter drug discovery programs.

Finally, as part of an international internship at the Stratingh Institute for Chemistry of the University of Groningen (The Netherlands) under the supervision of Prof. Syuzanna Harutyunyan, hydrophosphination of 4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2 dioxaborolane catalyzed by a Mn(I) complex in a large scale has been developed. The phosphine adduct has been used (naked or protected) as the subject of study to test in different stereoselective reactions.

CHAPTER 6

6. EXPERIMENTAL SECTION

6.1. Material and general techniques

6.1.1. General experimental

All non-aqueous reactions were performed under argon atmosphere in flame dried glassware with efficient magnetic stirring. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

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

Organic layers washed with aqueous phases were dried over $MgSO_4$ and filtered through cotton. Organic solvents were evaporated under reduced pressure using rotavapors Büchi R-100, R-200 and R-210, the latter equipped with a Büchi V-700 vacuum pump and a Büchi V-850 vacuum controller, appropriate for the evaporation of solvents when products were volatile compounds. For the complete removal of solvents vacuum pump Telstar Top-3 (≈ 0.5 mmHg) was employed.

6.1.2. Reagents, solvents and products

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

When anhydrous solvents were required, they were dried following stablished protocols.[219] Dichloromethane and acetonitrile were dried over CaH_2. Toluene was dried over magnesium. *N,N*-dimethylformamide and dimethyl sulfoxide were dried over molecular sieves (3Å). Tetrahydrofuran was distilled over sodium/benzophenone. Analytical reagent grade MeOH was used without further drying. Triethylamine, DBU

[219] Armanego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 3rd Edition Butterworth-Heinemann, Oxford, **1988**.

and *N,N*-diisopropylamine were purified by distillation. After purification, catalysts were basified with aqueous saturated $NaHCO_3$ before usage.

6.1.3. Chromatography

Reactions and flash chromatographic columns were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light, Fisher Biolock lamp VL-4LC, λ = 254 and 365 nm. 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 as stationary phase and a suitable mixture of solvents (typically hexane:ethyl acetate, dichloromethane:hexane or dichloromethane:methanol) as eluent. In some particular cases non-acidic silica gel was used (specified in each case), which was prepared by mixing silica gel with a saturated aqueous solution of sodium bicarbonate (300 mL of solution for 100 g of silica gel) during 24 h. After filtration, the residual water was evaporated in an oven at 80 °C during 72 h.

6.1.4. Melting points

Melting points were determined in open capillaries in a Stuart SHP3 melting point apparatus microscope and were uncorrected.

6.1.5. Mass spectra

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

6.1.6. NMR spectra

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. The chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 7.26), $(CD_3)_2CO$ (δ = 2.05) and CD_3OD (δ = 3.31) for ^{1}H NMR and relative to the central resonances of $CDCl_3$ (δ = 77.0), $(CD_3)_2CO$ (δ = 206.3) and CD_3OD (δ = 49.2) for ^{13}C NMR. 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, doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), doublet of quartets (dq), quartet of doublets (qd), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), doublet of triplet of doublets (dtd), triplet of doublet of doublets (tdd). Coupling constants (*J*) are reported in Hertz (Hz). MestrReNova Mnova 11.0.4 program was used to process and edit the registered spectra.

6.1.7. Determination of enantiomeric excesses

Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC) performed on a Waters 600-E (equipped with Photodiode Array Detector Waters 2996 and 2998) (column and solvent conditions are given with the compound).

6.1.8. 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).

6.1.9. X-Ray diffraction analysis

The X-ray diffraction analysis experiments were conducted in the General Research Service (SGIKer) of the University of the Basque Country (UPV/EHU) using a SuperNova, Single source at offset/far, Atlas diffractometer. The crystal was kept at

149.93(16) K during data collection. Using Olex2,[220] the structure was solved with the ShelXT[221] structure solution program using Intrinsic Phasing and refined with the ShelXL[222] refinement package using Least Squares minimisation.

6.1.10. Infrared spectra

Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as a thin film.

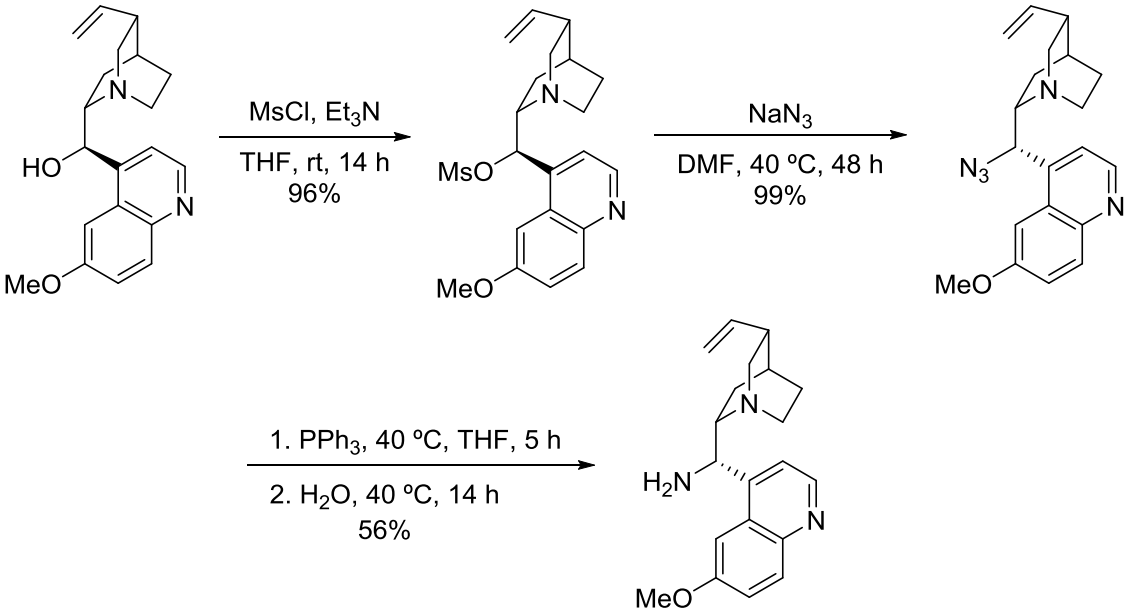
[220] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. **2009**, J. Appl. Cryst. 42, 339-341.
[221] Sheldrick, G.M. **2015**. Acta Cryst. A71, 3-8.
[222] Sheldrick, G.M. **2015**. Acta Cryst. C71, 3-8.

6.2. Preparation of catalysts

All new bifunctional catalysts employed in this Thesis include a chiral amine as Brønsted-base fragment. The synthesis of these amines is first described in the following section. The rest of catalyst employed in the screening were prepared as previously described: catalysts **C1**,[223] **C2**,[224] **C3**,[225] **C6**,[226] **C9**[226] and **C10**[226] or purchased from commercial suppliers: catalyst **C13**.

6.2.1. Preparation of chiral amines

6.2.1.1. 9-amino-(9-deoxy)epiquinine[227]



Step 1:[228] A mixture of quinine (16.2 g, 50 mmol, 1 equiv.) and Et_3N (25.1 mL, 180 mmol, 3.6 equiv.) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (7.0 mL, 90 mmol, 1.8 equiv.) was added dropwise. The mixture was stirred 14 hours at room temperature. The reaction was quenched with water (40 mL) and then the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (40 mL)

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

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

[225] Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967-1969.

[226] Vera, S.; Vázquez, A.; Rodriguez, R.; del Pozo, S.; Urruzuno, I.; de Cózar, A.; Mielgo, A.; Palomo C. *J. Org. Chem.* **2021**, *86, 7757-7772.*

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

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

and washed successively with water (30 mL) and saturated $NaHCO_3$ (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford the crude mesylate in 96% yield (19.3 g), which was used in the next step without further purification.

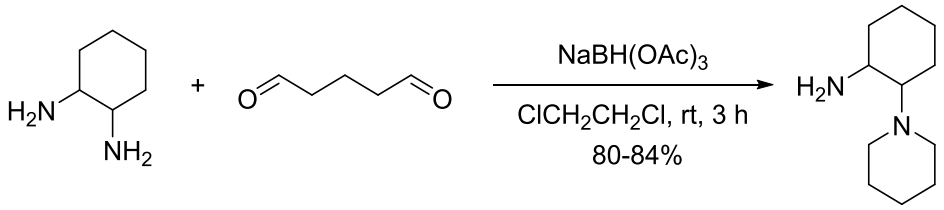
Step 2:[229] The crude product (19.3 g, 48 mmol, 1 equiv.) was dissolved in DMF (150mL). The solution was cooled to 0 °C and NaN_3 (6.2 g, 96 mmol, 2 equiv.) was added portionwise. The reaction mixture was stirred at 40 °C for 48 hours and then was quenched with water (80 mL) and EtOAc (150 mL) was added. The organic layer was separated and washed with saturated NaCl (5 x 60 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtain the crude product in quantitative yield (16.8 g), which was used in the next step without further purification.

Step 3:[229] The crude product was dissolved in THF (250 mL) and PPh_3 (12.6 g, 48 mmol, 1 equiv.) was added. The reaction mixture was heated at 40 °C and stirred until the gas evolution ceased (aprox. 5 hours). Then, water (8 mL) was added and the mixture was stirred overnight at 40 °C. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 (150 mL). HCl 6 M (250 mL) was added and the aqueous phase was separated and washed with CH_2Cl_2 (2 x 100 mL). Then the aqueous layer was cooled to 0 °C and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with CH_2Cl_2 (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: 56% (8.7 g, 26.9 mmol). ^{1}H NMR was consistent with that previously reported.[230] ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.75 (d, *J* = 4.6 Hz, 1H), 7.36 – 8.05 (m, 4H), 5.79 – 5.75 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02 – 3.34 (m, 3H), 2.75 – 2.77 (m, 2H), 2.27 – 2.24 (m, 1H), 2.08 (s, 2H), 1.26 – 1.63 (m, 4H), 0.80 – 0.78 (m, 1H).

[229] Adapted from: Sudermeier, U.; Döbler, C.; Mehlretter, G. M.; Baumann, W. *Chirality*, **2003**, *15*, 127-134.

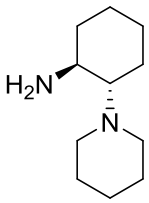
[230] He, W.; Liu, P.; Zhang, B. L.; Sun, X. L.; Zhang, S. Y. *Appl. Organometal. Chem.* **2006**, *20*, 328-334.

6.2.1.2. (1S,2S)- and (1R,2R)-2-(piperidin-1-yl)cyclohexan-1-amine



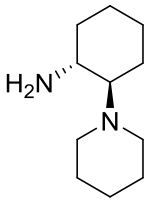
Glutaraldehyde (50 wt % H_2O, 0.93 mL, 5.1 mmol, 1.05 equiv.) was added dropwise to a mixture of the 1,2-diaminocyclohexane (0.56 g, 4.9 mmol, 1.0 equiv.) and $NaBH(OAc)_3$ (4.16 g, 19.6 mmol, 4.0 equiv.) in $ClCH_2CH_2Cl$ (30 mL) at room temperature. The mixture was stirred at room temperature for 3 hours, and quenched with NaOH 6.0 M (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice (2 x 15 mL). The organic layers were combined and washed with brine (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the diamine.

(1*S*,2*S*)-2-(Piperidin-1-yl)cyclohexan-1-amine[231]



The title compound was prepared following the general procedure starting from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane. Brown oil. Yield: 80% (0.715 g, 3.92 mmol). Spectral data were in agreement with the data described in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.71 – 2.51 (m, 3H), 2.40 – 2.19 (m, 2H), 1.87 – 1.59 (m, 5H), 1.60 – 1.35 (m, 6H), 1.25 – 0.99 (m, 4H).

(1*R*,2*R*)-2-(Piperidin-1-yl)cyclohexan-1-amine[232]

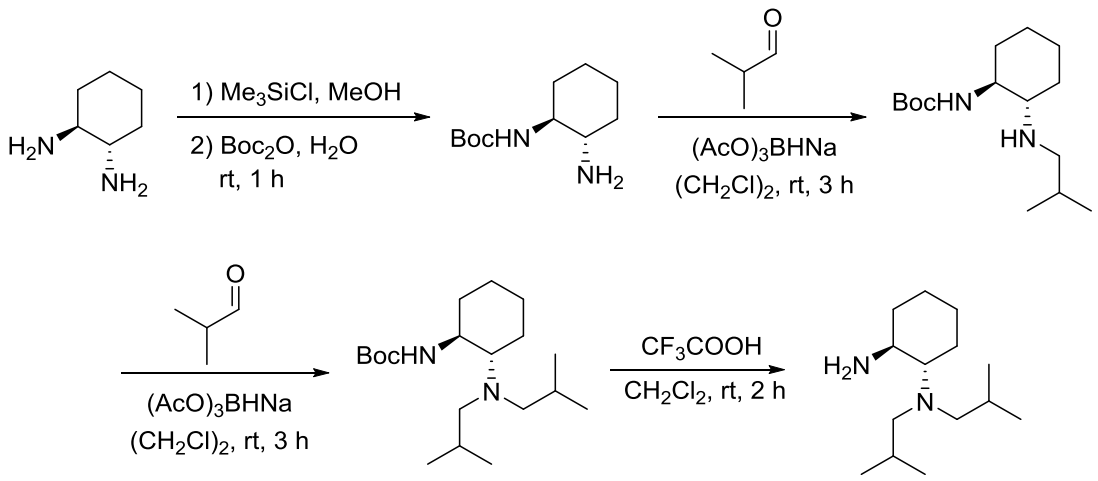


The title compound was prepared following the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane. Yellow liquid. Yield: 84% (0.750 g, 4.12 mmol). Spectral data were in agreement with the data described in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.87 – 2.68 (m, 1H), 2.67 – 2.49 (m, 3H), 2.41 – 2.19 (m, 2H), 2.16 – 1.92 (m, 2H), 1.88 – 1.34 (m, 8H), 1.31 – 0.97 (m, 4H).

[231] Gonzalez-Sabin, J.; Gotor, V.; Rebolledo, F. *Chem. Eur. J.* **2004**, 10, 5788-5794.

[232] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153-156.

6.2.1.3. (1S,2S)-N1,N1-diisobutylcyclohexane-1,2-diamine



Step 1:[233] To the (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (1.14 g, 10 mmol, 1 equiv.) was added MeOH (12 mL) at 0 °C under stirring, followed by the dropwise addition of freshly distilled Me_3SiCl (1.27 mL, 10 mmol, 1 equiv.). A white precipitate appeared at the bottom of the flask. Then the mixture was allowed to warm up to room temperature and water (1 mL), followed by Boc_2O (1 equiv.) in MeOH (3 mL), was added. The mixture was stirred at room temperature for 1 hour, diluted with water and the aqueous layer washed with Et_2O (2 x 50 mL). The aqueous layer was adjusted to pH > 12 with NaOH 2N and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and the evaporation of the solvents under vacuum gave the corresponding monoprotected diamine which was used in the next step without further purification. White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.49 (brs, 1H), 3.13 (d, J = 6.2 Hz, 1 H), 2.33 (ddd, J = 10.4, 3.8, 3.8 Hz, 1H), 1.98 (m, 2H), 1.70 (m, 2H), 1.45 (s, 9H), 1.28 (m, 2H), 1.12 (m, 2H).

Step 2 and step 3: The protected diamine (1.71 g, 8 mmol, 1 equiv.) and sodium $NaBH(OAc)_3$ (3.39, 16 mmol, 2 equiv.) were dissolved in $ClCH_2CH_2Cl$ (23 mL) and isobutyraldehyde (0.77 mL, 8.4 mmol, 1.05 equiv.) was added dropwise at 0 °C. After 3 h the reaction was quenched with NaOH 6N and extracted with CH_2Cl_2 (4 x 25 mL). The organic layers were dried over $MgSO_4$, filtrated and evaporated under vacuum. The crude mixture was purified by a flash column chromatography (eluting with Hex/EtOAc

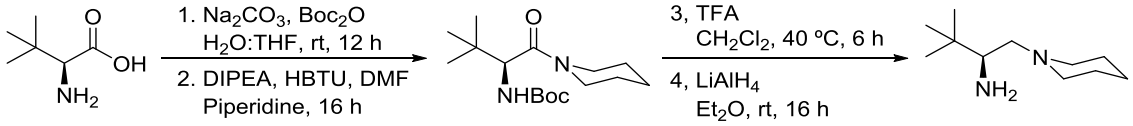
[233] Servín, F. A.; Romero, J. A.; Aguirre, G.; Grotjahn, D.; Somanathan, R.; Chávez, D. *J. Mex. Chem. Soc.* **2017**, *61*, 23-27.

80/20). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.57 (s, 1H), 3.36 – 3.19 (m, 1H), 2.53 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.30 (dd, *J* = 11.2, 6.6 Hz, 1H), 2.21 (td, *J* = 10.1, 3.9 Hz, 1H), 1.79 – 1.61 (m, 4H), 1.59 – 1.50 (m, 4H), 1.47 (s, 9H), 1.24 – 1.08 (m, 3H), 0.92 (d, *J* = 6.6 Hz, 6H).

Step 2 was repeated to provide the diprotected diamine, which was was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.43 (s, 1H), 3.15 (tt, *J* = 10.6, 3.5 Hz, 1H), 2.80 – 2.47 (m, 3H), 2.31 – 2.15 (m, 3H), 1.93 – 1.83 (m, 1H), 1.83 – 1.75 (m, 2H), 1.66 (dt, *J* = 9.9, 3.3 Hz, 3H), 1.44 (s, 9H), 0.92 (d, *J* = 6.5 Hz, 6H), 0.86 (d, *J* = 6.6 Hz, 6H).

Step 4: The previously obtained diamine (1.14 g, 3.5 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (8 mL) and CF_3COOH (2 mL) and stirred at room temperature for 2 h. The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40%), dried over $MgSO_4$, filtrated and evaporated under vacuum to afford the desired product as a yellow oil. Yield: 0.697 g, 3.1 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.62 – 2.51 (m, 1H), 2.28 – 2.15 (m, 2H), 2.02 (dd, *J* = 12.7, 10.0 Hz, 3H), 1.79 – 1.61 (m, 9H), 1.26 – 1.02 (m, 5H), 0.92 (d, *J* = 6.5 Hz, 6H), 0.84 (d, *J* = 6.7 Hz, 4H).

6.2.1.4. Preparation of (S)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine[234]



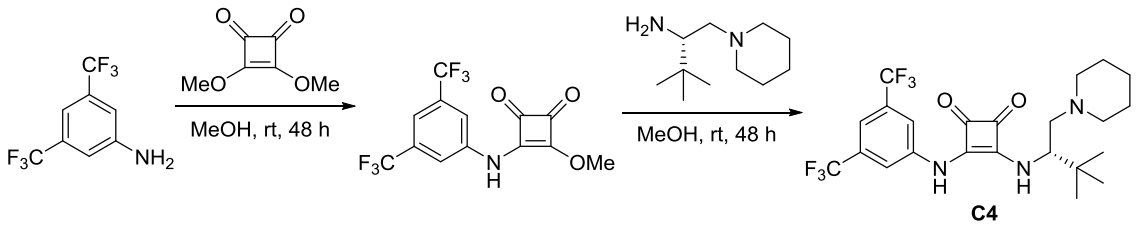
Steps 1 and 2: Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3 g, 15 mmol, 1.5 equiv.) were added to a solution of *t*-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) and THF (5 mL) at 0 °C. After stirring for 12 hours at room temperature, HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was redissolved in dry DMF (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 g, 15 mmol, 1,5 equiv.)

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

were added. After stirring for 1 hour, 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 combined, washed with a HCl 1 M and brine (20 mL), dried over $MgSO_4$ and 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 the corresponding *t*-leucine derivative 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, CDCl3) 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).

Steps 3 and 4: The previous compound (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and CF_3COOH (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane/ EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40%), dried over $MgSO_4$ and the solvent was removed under reduced pressure to produce the aminoamide as a yellow oil. The aminoamide was then dissolved in dry Et_2O (10 mL) and added dropwise over a suspension of $LiAlH_4$ (0.879 g, 24 mmol, 3 equiv.) in Et_2O (40 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 hours. The reaction was quenched adding water (1.2 mL), NaOH 15% (1,2 mL) and water (3.6 mL) at 0 °C. The resulting suspension was filtered and the liquid was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ 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. 1H 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).

6.2.2. Preparation of squaramide-based C4[235]



Step 1: To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (710 mg, 5.0 mmol, 1 equiv.) in MeOH (25 mL) was added the amine (5.0 mmol, 1 equiv.) and the reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vaccum to give the squaric ester monoamide. Yield: 1.3 g, 3.7 mmol, 74 %. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

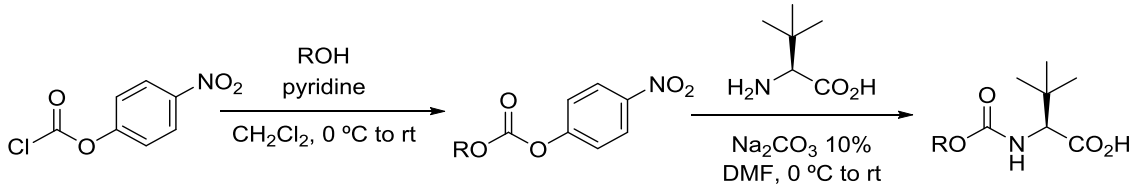
Step 2: To a suspension of the squaric ester monoamide (1.3 g, 7.0 mmol, 1 equiv.) in MeOH (35 mL), the chiral Brønsted base (2.40 g, 7.0 mmol, 1 equiv.) was added and the reaction mixture was stirred at room temperature for 48 hours. The solvent was evaporated and the oil residue was purified by silica flash column chromatography (eluting with CH_2Cl_2/MeOH 95:5) to afford the pure catalyst. Yield: 2.9 g, 5.9 mmol, 84%. All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, CDCl3) δ 10.09 (s, 1H), 8.08 (s, 2H), 7.64 (s, 1H), 4.07 – 3.93 (m, 1H), 2.49 – 2.04 (m, 5H), 1.51 – 1.22 (m, 6H), 0.93 (s, 9H).

6.2.3. Preparation of ureidoaminal-derived Brønsted base catalysts

The catalysts were prepared by coupling the previously described chiral amines with *L-tert*-leucine derived isocyanates. The preparation of no commercially available *N*-protected *L*-tert-leucines is described first.

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

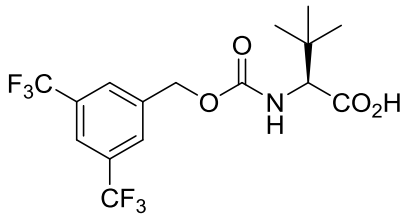
6.2.3.1. Preparation of N-protected L-tert-leucine



Step 1: Pyridine (0.9 mL, 11 mmol, 1.1 equiv.) was added to a stirred solution of *p*-nitrophenyl chloroformate (2.2 g, 11 mmol, 1.1 equiv.) in CH_2Cl_2 (13.6 mL). The white slurry was cooled to 0 ºC and the corresponding alcohol (10 mmol, 1 equiv.) was slowly added at the same temperature. Then, the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with HCl 1M (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentred under reduced pressure. The residue was used in the next step without further purification.

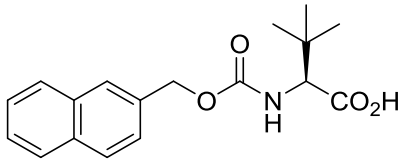
Step 2: To a stirred solution of *L*-tert-leucine (1.31 g, 10 mmol, 1 equiv.) in 10% Na_2CO_3 (26 mL), and DMF (10 mL), a solution of the corresponding carbonate (10 mmol, 1 equiv.) in DMF (30 mL) was slowly added at 0 ºC. The mixture was stirred at the same temperature for 1 hour and at room temperature for 16 hours.The reaction mixture was poured into water (100 mL) and washed with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (5 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to produce the corresponding *N*-protected L-tert-leucine.

(*S*)-2-((((3,5-Bis(trifluoromethyl)benzyl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid[236]



The title compound was prepared from 3,5-bis(trifluoromethyl)benzyl alcohol (2.44 g, 10 mmol) according to the general procedure. Removal of the remaining fenol was not possible by column chromatography, so after the work up described in the general procedure, the crude was dissolved in Et_2O (20 mL) and basified with NaOH 20%. The aqueous phase was washed with Et_2O (3 x 20 mL), acidified with concentrated HCl and extracted with EtOAc (3 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to afford the acid as a white solid. Yield: 91% (3.65 g, 9.1 mmol). All spectroscopic data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.80 (s, 2H), 5.56 (d, *J* = 9.6 Hz, 1H), 5.36 –5.09 (m, 2H), 4.20 (d, *J* = 9.6 Hz, 1H), 1.03 (s, 9H).

(*S*)-3,3-Dimethyl-2-(((naphthalen-2-ylmethoxy)carbonyl)amino)butanoic acid[237]



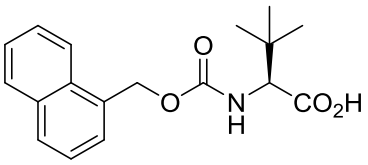
The title compound was prepared from 2-naphthalenemethanol (1.58 g, 10 mmol) according to the general procedure. Removal of the remaining fenol was not possible by column chromatography. After the work up described in the general procedure, the crude was dissolved in Et_2O (30 mL) and basified with saturate $NaHCO_3$ (1 x 20 mL). The aqueous phase was washed with Et_2O (3 x 20 mL), acidified with concentrated HCl and extracted with EtOAc (3 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to afford the acid as a white solid. Yield 48% (1.5 g, 4.8 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.74 (m, 4H), 7.58 – 7.36(m, 3H), 5.47 (d, *J* = 9.4 Hz, 1H), 5.30 (s, 2H), 4.26 (d, *J* = 9.6 Hz, 1H), 1.04 (s, 9H).

(S)-3,3-Dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino)butanoic acid[238]

[236] Bastida, I.; San Segundo, M.; López, R.; Palomo, C. *Chem. Eur. J.* **2017**, *23*, 13332-13336.

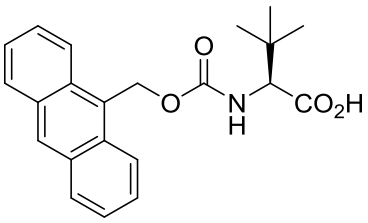
[237] Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew.Chem. Int. Ed.* **2013**, *52*, 11846-11851.

[238] Vera, S.; Vázquez, A.; Rodriguez, R.; del Pozo, S.; Urruzuno, I.; de Cózar, A.; Mielgo, A.; Palomo C. *J. Org. Chem.* **2021**, *86, 7757-7772.*



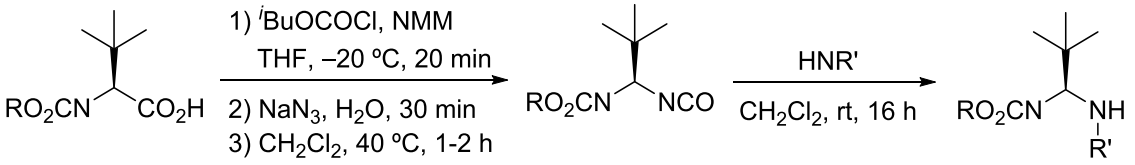
The title compound was prepared from 1-naphthalenemethanol (1.58 g, 10 mmol) according to the general procedure. Purification by column chromatography (Hex/EtOAc, 80/20) afforded the product as a white solid. Yield: 88% (2.8 g, 8.8 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.10 (s,1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 8.8 Hz, 2H), 7.49 (dt, *J* = 27.2, 7.3 Hz, 4H), 5.60 (q, *J* = 12.3 Hz, 2H), 5.40 (d, *J* = 9.5 Hz, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 1.02 (s, 9H).

Anthracen-9-ylmethyl (S)-(1-amino-2,2-dimethylpropyl)carbamate[239]



The title compound was prepared from 9-anthracenemethanol (1.58 g, 10 mmol) according to the general procedure. Purification by column chromatography (Hex/EtOAc, 80/20) afforded the product as a white solid. Yield: 88% (2.8 g, 8.8 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 8.38 (d, J = 8.9, 2H), 8.03 (d, J = 8.4, 2H), 7.54 (dt, J = 15.0, 7.0, 4H), 6.18 (q, J = 12.1, 2H), 5.24 (d, J = 9.5, 1H), 4.28 (d, J = 9.4, 1H), 1.01 (s, 9H).

6.2.3.2. L-tert-leucine derived isocyanate generation and coupling with chiral amines[237]



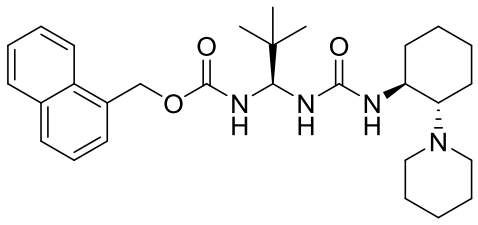
To a cooled solution of the corresponding *N*-protected α-amino acid (5 mmol, 1 equiv.) in dry THF (20 mL), isobutyl chloroformate (0.65 mL, 5 mmol, 1 equiv.) and *N*-methylmorpholine (0.6 mL, 5 mmol, 1 equiv.) were added at –20 °C. The mixture was stirred at the same temperature for 20 min. Then, a suspension of NaN_3 (0.48 g, 7.5mmol, 1.5 equiv.) in 5 mL of H_2O was added and the reaction mixture stirred at the same temperature for 30 min. The organic layer was separated, evaporated and the

[239] Echave, H.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3364-3368.

residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was stirred at 40 °C under nitrogen for 1-2 hours. The reaction was monitored by IR analysis until disappearance of the azide band (from azide $\lambda = 2136\ cm^{-1}$ to isocyanate $\lambda = 2239\ cm^{-1}$).

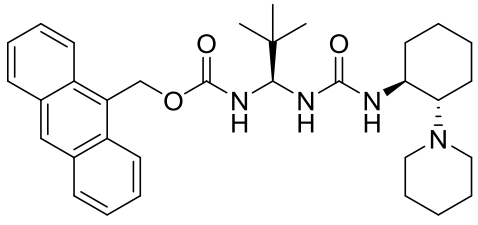
After complete isocyanate generation, the corresponding amine was added (3.5 mmol, 0.7 equiv.) and the reaction mixture was stirred for 16 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on non-acidic silica gel to afford the desired catalysts.

Naphthalen-1-ylmethyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1- yl)cyclohexyl) ureido)propyl)carbamate (C7)[238]



Prepared according to the general procedure starting from (*S*)-3,3-dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino)butanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 60% (1.42 g, 3 mmol). $[\alpha]_D^{25}$ = -5.9 (c=1, CH_2Cl_2). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (500 MHz, DMSO-d_6, 70 °C) δ: 8.32 – 8.27 (m, 1H), 8.21 – 8.18 (m, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.77 (m, 3H), 7.76 – 7.69 (m, 1H), 7.19 (br s, 1H), 6.16 (d, *J* = 9.1 Hz, 1H), 6.00 – 5.95 (m, 1H), 5.75 (q, 2H), 5.39 (t, *J* = 9.2 Hz, 1H), 3.63 (br s, *J* = 6.7, 5.6 Hz, 1H), 2.85 (br s, 2H), 2.60 (br s, 2H), 2.43 (s, 1H), 2.28 (d, *J* = 12.5 Hz, 1H), 2.04 (d, *J* = 11.0 Hz, 1H), 1.94 (d, *J* = 11.4 Hz, 1H), 1.82 (d, *J* = 10.1 Hz, 1H), 1.74 – 1.66 (m, 5H), 1.64 – 1.53 (m, 3H), 1.47 – 1.36 (m, 3H), 1.12 (s, 9H).

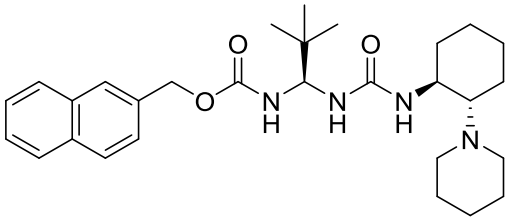
Anthracen-9-ylmethyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C10)[238]



Prepared according to the general procedure starting from anthracen-9-ylmethyl (*S*)-(1-amino-2,2-dimethylpropyl)carbamate (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 58% (1.58 g, 2.9 mmol). $[\alpha]_D^{25}$ = -6.7 (c=1, CH_2Cl_2). All the spectroscopic data

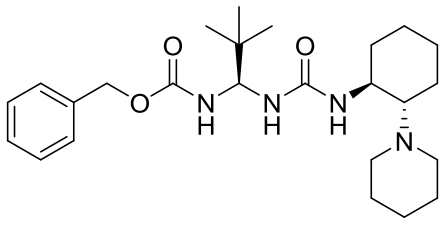
were coincident withthose previously reported. ^{1}H NMR (500 MHz, DMSO-d_6, 70 ^{o}C) δ: 8.67 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.12 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.59 (ddd, *J* = 8.6, 6.5, 1.5 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.04 (q, *J* = 11.5, 10.9 Hz, 3H), 5.79 (s, 1H), 5.16 (s, 1H), 2.54 (s, 1H), 2.28 (s, 1H), 2.01 – 1.95 (m, 1H), 1.79 – 1.72 (m, 1H), 1.69 – 1.63 (m, 2H), 1.56 – 1.50 (m, 1H), 1.39 (s, 5H), 1.28 – 1.22 (m, 3H), 1.19 – 1.07 (m, 4H), 0.82 (s, 9H).

Naphthalen-2-ylmethyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C11)[11]



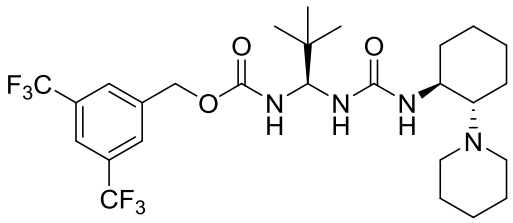
Prepared according to the general procedure starting from (*S*)-3,3-dimethyl-2-(((naphthalen-2-ylmethoxy)carbonyl)amino) butanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 70/30). White solid. Yield: 61% (1.06 g, 2.14 mmol). $[\alpha]_D^{25}$ = -24.2 (c=1, CH_2Cl_2). All the spectroscopic data were coincident withthose previously reported. ^{1}H NMR (500 MHz, DMSO-d_6, 70 ºC) δ: 7.99 – 7.80 (m, 4H), 7.65 – 7.41 (m, 3H), 6.88 (s, 1H), 5.91 (d, *J* = 9.2 Hz, 1H), 5.69 (d, *J* = 6.3 Hz, 1H), 5.21 (s, 2H), 5.15 (t, *J* = 9.2 Hz, 1H), 3.48 – 3.31 (m, 1H), 2.60 – 2.55 (m, 2H), 2.39 – 2.27 (m, 2H), 2.24 – 2.11 (m, 1H), 2.09 – 2.03 (m, 1H), 1.82 – 1.74 (m, 1H), 1.72 – 1.64 (m, 1H), 1.64 – 1.52 (m, 1H), 1.52 – 1.39 (m, 4H), 1.39 – 1.25 (m, 3H), 1.24 – 1.12 (m, 3H), 0.91 (s, 9H).

Benzyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C12)



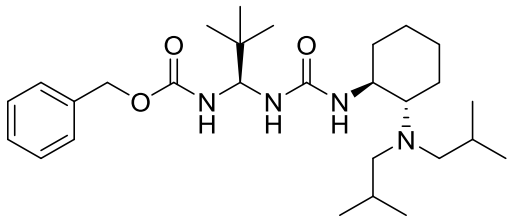
Prepared according to the general procedure starting from (*S*)-2-(((benzyloxy)carbonyl)amino)-3,3-dimethylbutanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 80/20). White solid. Yield: 62% (1.38 g, 3.1 mmol). $[\alpha]_D^{25}$ = – 21.3 (c=1, CH_2Cl_2). m.p.= 146-150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 – 7.16 (m, 5H), 6.41 – 5.92 (m, 2H), 5.79 – 5.31 (m, 1H), 5.05 (q, *J* = 12.3 Hz, 4H), 3.53 (s, 1H), 2.78 – 2.54 (m, 2H), 2.47 – 2.29 (m, 1H), 2.25 – 2.12 (m, 1H), 1.87 – 1.69 (m, 3H), 1.66 – 1.45 (m, 5H), 1.40 – 1.30 (m, 2H), 1.29 – 1.09 (m, 4H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 156.4, 136.6, 128.4, 128.0, 68.1, 66.9, 66.6, 53.5, 49.7, 35.6, 33.8, 25.7, 25.6, 25.4, 24.8, 23.7. UPLC-DAD-QTOF: $C_{25}H_{41}N_4O_3$ [M+H]+ calcd.: 445.3179, found: 445.3181.

3,5-Bis(trifluoromethyl)benzyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C13)



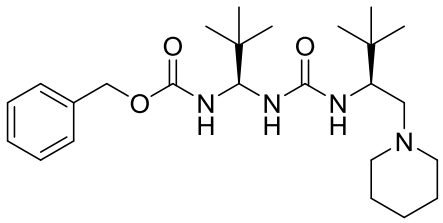
Prepared according to the general procedure starting from (*S*)-2-((((3,5-Bis(trifluoromethyl) benzyl)oxy)carbonyl)amino)-3,3-dimethylbutanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 80/20). White solid. Yield: 58% (1.68 g, 2.8 mmol). m.p.= 291-294 °C. $[\alpha]_D^{25}$ = –3.50 (c=1, CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6, 70 °C) δ: 8.05 (s, 2H), 7.96 (s, 1H), 7.05 (s, 1H), 5.94 (d, *J* = 9.1 Hz, 1H), 5.70 (d, *J* = 6.2 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.13 (t, *J* = 9.1 Hz, 1H), 3.39 (s, 1H), 2.59 (br s, 2H), 2.34 (br s, 2H), 2.19 (d, *J* = 10.3 Hz, 1H), 2.05 (d, *J* = 12.6 Hz, 1H), 1.78 (s, 1H), 1.71 (d, *J* = 8.5 Hz, 1H), 1.58 (d, *J* = 10.1 Hz, 1H), 1.46 (s, 4H), 1.32 (d, *J* = 11.7 Hz, 3H), 1.22 – 1.13 (m, 3H), 0.90 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.7, 156.3, 140.2, 133.1, 132.6, 132.2, 131.8, 128.3, 125.6, 122.4, 122.0, 77.9, 68.8, 67.7, 65.4, 63.7, 36.3, 35.4, 34.5, 30.3, 27.1, 26.3, 26.2, 26.1, 25.9, 25.3, 24.2. UPLC-DAD-QTOF: $C_{25}H_{41}N_4O_3$ [M+H]+ calcd.: 581.2921, found: 581.2923.

Benzyl ((*S*)-1-(3-((1*S*,2*S*)-2-(diisobutylamino)cyclohexyl)ureido)-2,2-dimethylpropyl)carbamate (C14)



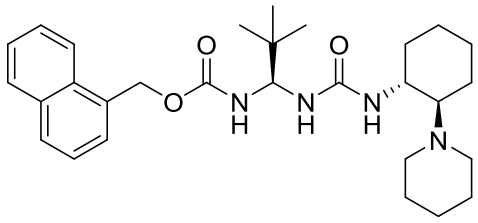
Prepared according to the general procedure starting from (*S*)-2-(((benzyloxy)carbonyl) amino)-3,3-dimethylbutanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 68% (1.66 g, 3.4 mmol). m.p.= 175–177 °C. $[\alpha]_D^{23}$ = –31.6 (*c*=1, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.38 – 7.20 (m, 5H), 5.98 (d, *J* = 9.4 Hz, 1H), 5.59 (d, *J* = 7.1 Hz, 1H), 5.11 – 4.93 (m, 3H), 2.30 – 2.20 (m, 1H), 2.12 (d, *J* = 7.1 Hz, 4H), 1.88 (d, *J* = 11.8 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.70 – 1.63 (m, 1H), 1.56 (td, *J* = 12.9, 12.4, 6.2 Hz, 3H), 1.17 – 1.00 (m, 3H), 0.84 (s, 9H), 0.80 (dd, *J* = 8.6, 6.6 Hz, 12H). ^{13}C NMR (75 MHz, DMSO) δ: 156.6, 155.7, 137.3, 128.3, 127.7, 127.7, 65.1, 63.0, 59.2, 50.4, 35.8, 34.5, 26.7, 25.7, 25.5, 25.4, 24.8, 21.0, 20.7. UPLC-DAD-QTOF: $C_{28}H_{49}N_4O_3$ [M+H]+ calcd.: 489.3805, found: 489.3812.

Benzyl ((*S*)-1-(3-((*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (C15)



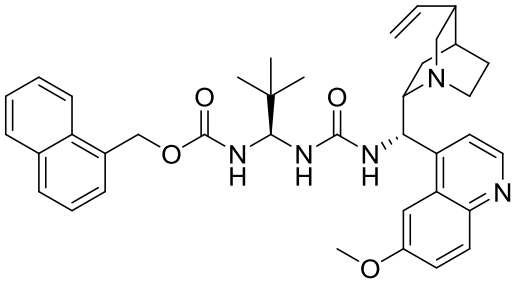
Prepared according to the general procedure starting from (*S*)-2-(((benzyloxy)carbonyl) amino)-3,3-dimethylbutanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 70% (1.56 g, 3.5 mmol). m.p.= 162–164 °C. $[\alpha]_D^{23}$ = –2.9 (*c*=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.25 (m, 5H), 5.83 (s, 1H), 5.67 – 5.42 (m, 1H), 5.09 (s, 3H), 3.84 – 3.46 (m, 1H), 2.56 – 2.39 (m, 3H), 2.36 – 2.18 (m, 3H), 1.61 – 1.44 (m, 4H), 1.38 (q, *J* = 5.7 Hz, 2H), 0.97 (s, 9H), 0.89 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.5, 156.7, 136.4, 128.5, 128.5, 128.1, 128.0, 128.0, 127.9, 66.9, 66.9, 60.2, 54.7, 54.6, 35.9, 35.8, 34.8, 34.5, 27.1, 26.7, 26.1, 25.7, 25.6, 24.4. UPLC-DAD-QTOF: $C_{25}H_{43}N_4O_3$ [M+H]+ calcd.: 447.3335, found: 447.3339.

Naphthalen-1-ylmethyl ((*S*)-2,2-dimethyl-1-(3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (diast-C7)



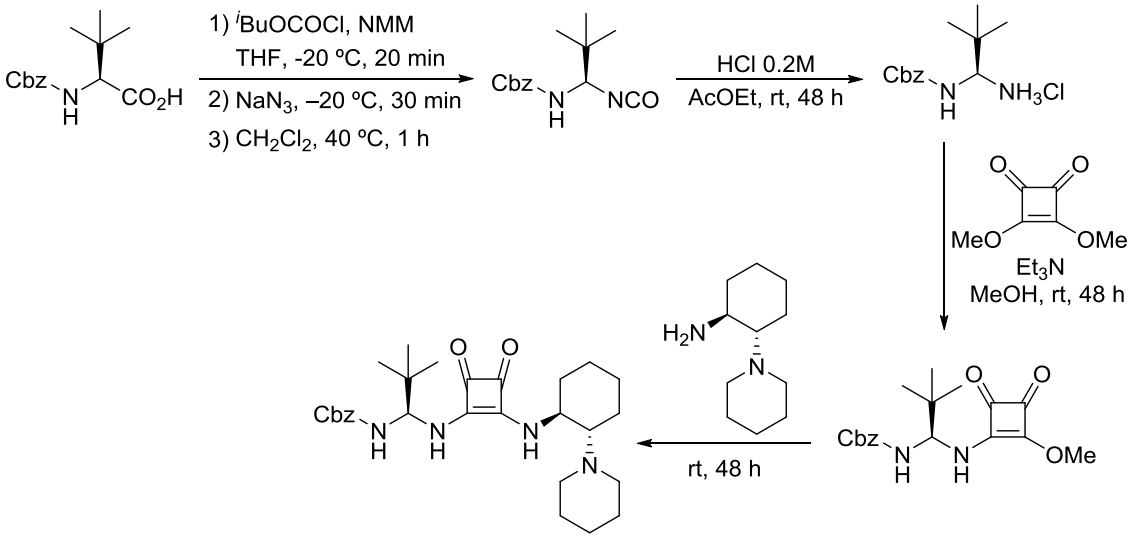
Prepared according to the general procedure starting from (*S*)-3,3-dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino) butanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 63% (1.56 g, 3.15 mmol). m.p.= 169-174 °C. $[\alpha]_D^{23}$ = 13.8 (*c*=0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.82 (d, *J* = 7.9 Hz, 2H), 7.70 – 7.60 (m, 3H), 7.38 – 7.18 (m, 7H), 7.01 (s, 1H), 6.62 (s, 1H), 5.41 – 5.25 (m, 2H), 3.58 (s, 1H), 3.10 (s, 3H), 2.92 (s, 1H), 1.95 – 1.85 (m, 1H), 1.80 – 1.41 (m, 6H), 1.37 – 0.98 (m, 6H), 0.74 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD) δ: 159.4, 158.1, 135.1, 133.5, 132.7, 129.9, 129.6, 127.8, 127.4, 126.9, 126.2, 124.6, 69.4, 66.9, 65.8, 53.2, 37.0, 34.5, 25.9, 25.5, 25.0, 24.5, 24.2, 23.0. UPLC-DAD-QTOF: $C_{25}H_{41}N_4O_3$ [M+H]+ calcd.: 495.3330, found: 495.3342.

Naphthalen-1-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 (C9)



Prepared according to the general procedure starting from (*S*)-3,3-dimethyl-2-(((naphthalen-1-ylmethoxy)carbonyl)amino) butanoic acid (5 mmol). Purified by column chromatography by non-acid silica gel (eluting with Hex/EtOAc 90/10). White solid. Yield: 65% (2.07 g, 3.25 mmol). m.p.= 163–171 °C. $[\alpha]_D^{23}$ = 21.76 (*c*=0.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.35 (s, 1H), 8.04 (dd, *J* = 6.6, 3.0 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.00 (s, 1H), 6.66 (s, 1H), 5.71 (td, *J* = 17.0, 13.8, 8.5 Hz, 2H), 5.64 – 5.42 (m, 4H), 5.38 (brs, 1H), 5.10 – 4.95 (m, 4H), 3.92 (s, 3H), 3.38 – 2.99 (m, 3H), 2.89 – 2.76 (m, 1H), 2.47 (s, 1H), 1.64 – 1.34 (m, 4H), 0.80 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 157.7, 156.5, 147.5, 144.7, 133.8, 132.1, 131.8, 131.6, 129.4, 128.8, 128.6, 127.8, 126.7, 126.1, 125.4, 123.9, 121.9, 118.8, 115.2, 102.1, 66.9, 65.1, 60.1, 55.8, 55.5, 41.0, 38.8, 35.4, 29.8, 27.2, 25.8, 25.4. UPLC-DAD-QTOF: $C_{38}H_{46}N_5O_4$ [M+H]+ calcd.: 636.3550, found: 636.3551.

6.2.3.3. Preparation of hybrid catalyst C16



Step 1: 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 (0.65 mL, 5 mmol, 1 equiv.) and *N*-methylmorpholine (0.6 mL, 5 mmol, 1 equiv.) at −20 °C and the

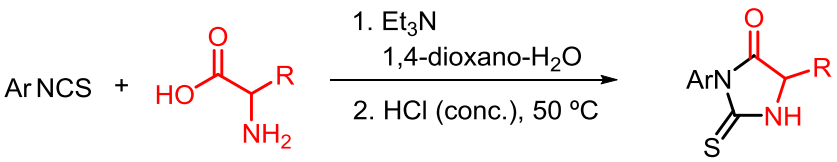
mixture was stirred for 20 minutes. Then, a suspension of NaN_3 (0.48 g, 7.5 mmol, 1.5 equiv., in 5 mL of H_2O) was added and the reaction mixture was stirred at the same temperature. After 30 minutes, the organic layer was separated, evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), and washed with water (15 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil which was dissolved in dry CH_2Cl_2 (10 mL). The resulting solution was heated at 40 °C under nitrogen for 1-2 hours. The reaction was monitored by infrared analysis until disappearance of the isocyanate band. After completion, HCl 0.2M was added (5 mL/1 mmol) and the reaction mixture was stirred at room temperature for 48 hours. The solvents were evaporated under reduced pressure to afford the corresponding salt which was used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 9.2, 3H), 7.41 – 7.30 (m, 5H), 5.13 (s, 2H), 4.64 – 4.54 (m, 1H), 0.97 (s, 9H).

Step 2: To a solution of the amine hydrochloride (5.46 g, 2 mmol, 1 equiv.) and triethylamine (0.84 mL, 6 mmol, 3 equiv.) in MeOH (5 mL/1 mmol), 3,4-dimethoxy-3-cyclobutane-1,2-dione (2.84 g, 2 mmol, 1 equiv.) was added and the reaction mixture was stirred at room temperature for 48 hours. Subsequently, the (1*S*,2*S*)-2-(piperidin-1-yl)cyclohexan-1-amine was added (0.36 g, 2 mmol, 1 equiv.). The suspension was stirred at room temperature for another 48 hours. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel (eluting from 98/2 to 96/4 CH_2Cl_2/MeOH). Yield: 42%, 2 steps (1.04 g, 2.1 mmol). White solid. m.p.= 181–183 ºC. $[\alpha]_D^{23}$ = 31.5 (*c*=0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 – 7.84 (m, 1H), 7.74 – 7.62 (m, 1H), 7.34 (s, 5H), 5.39 (s, 1H), 5.04 (s, 2H), 3.88 – 3.77 (m, 1H), 2.59 (t, *J* = 8.3 Hz, 2H), 2.32 – 2.19 (m, 3H), 2.00 (d, *J* = 10.4 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.75 – 1.60 (m, 2H), 1.43 – 1.12 (m, 11H), 0.92 (s, 9H). ^{13}C NMR (75 MHz, DMSO) δ: 182.5, 181.4, 167.7, 167.2, 155.5, 136.8, 128.3, 127.9, 69.0, 68.3, 65.6, 53.8, 49.2, 35.8, 34.4, 29.0, 26.2, 25.0, 24.8, 24.6, 24.5, 23.6. UPLC-DAD-QTOF: $C_{28}H_{41}N_4O_4$ $[M+H]^+$ calcd.: 497.3128, found: 497.3133.

6.3. Experimental section for Chapter 2

6.3.1. Synthesis of starting materials

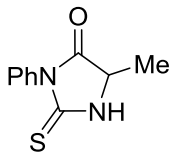
6.3.1.1. Synthesis of thiohydantoins 1



1a R = Me, Ar = Ph
1b R = Me, Ar = 4-Me-C_6H_4
1c R = Me, Ar = 4-MeO-C_6H_4
1d R = Me, Ar = 4-Cl-C_6H_4
1e R = Me, Ar = 3-Cl-C_6H_4
1f R = Bn, Ar = Ph

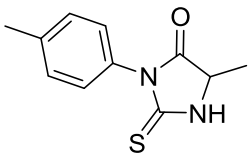
The corresponding amino acid (50 mmol, 1.0 equiv) was added to a solution of phenyl isothiocyanate (5.92 mL, 50 mmol, 1.0 equiv) in 1,4-dioxane–H_2O (120 mL, 1:1, v/v) and cooled to 0 °C. Then Et_3N (14.0 mL, 100 mmol, 2.0 equiv) was slowly added and the solution was stirred for 1 h, followed by the addition of concentrated HCl (12.50 mL, 150 mmol, 3.0 equiv) at 0 °C until the pH was approximately 2. The reaction mixture was stirred for another 12 h at 50 °C, and the precipitate formed was filtered and dried to afford the desired compound.

5-Methyl-3-phenyl-2-thioxoimidazolidin-4-one (1a)



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. White solid. Yield: 6.99 g, 33.86 mmol, 68% (two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 7.54–7.31 (m, 5H), 4.35 (q, *J* = 7.0 Hz, 1H), 1.60 (d, *J* = 7.0 Hz, 4H).

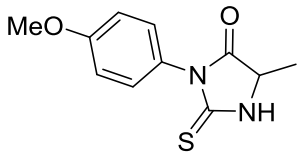
5-Methyl-2-thioxo-3-(p-tolyl)imidazolidin-4-one (1b)



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a yellow solid. Yield: 6.60 g, 30

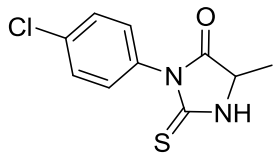
mmol, 60%. m. p. 184-186 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (s, 1H), 7.65 – 6.94 (m, 4H), 4.31 (q, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.9, 174.4, 139.6, 130.0, 130.0, 128.1, 55.6, 21.4, 17.1. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0753.

3-(4-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (1c)



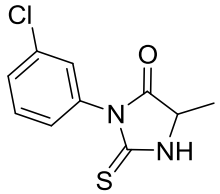
The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. Yield: 7.79 g, 33 mmol, 66%. m. p. 182-185 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.47 (s, 1H), 7.22 – 7.15 (m, 2H), 7.04 – 6.97 (m, 2H), 4.46 – 4.36 (m, 1H), 3.78 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ: 182.5, 175.2, 159.1, 130.0, 126.0, 113.9, 55.4, 55.0, 16.3. UPLC-DAD-QTOF: $C_{11}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 237.0698, found: 237.0700.

3-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1d)



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a white solid. Yield: 7.68 g, 32 mmol, 64%. m. p. 202-206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.58 (s, 1H), 7.59 – 7.53 (m, 2H), 7.38 – 7.32 (m, 2H), 4.45 (q, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ: 181.7, 174.8, 133.2, 132.4, 130.8, 128.8, 55.2, 16.1. UPLC-DAD-QTOF: $C_{10}H_{10}N_2OSCl$ $[M+H]^+$ calcd.: 241.0202, found: 241.0196.

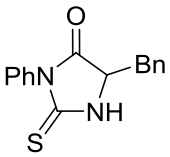
3-(3-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1e)



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. The resulting crude was purified by silica gel flash column chromatography (hexane/ethyl acetate, 90:10 to 70:30) to obtain the desired product as a yellow solid. Yield: 7.44 g, 31 mmol, 62%. m. p. 169-171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.56 – 7.22 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 1H), 1.61 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ:

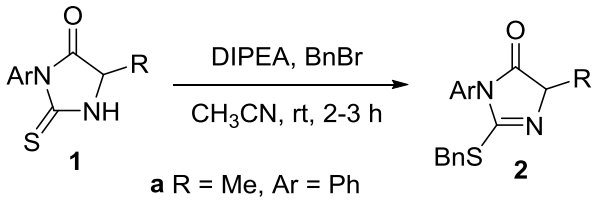
183.1, 173.8, 134.8, 133.7, 130.2, 129.7, 128.8, 126.7, 55.6, 17.1. UPLC-DAD-QTOF: $C_{10}H_{10}N_2OSCl$ $[M+H]^+$ calcd.: 241.0202, found: 241.0205.

5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (1f)



The title compound was prepared from phenylalanine (8.25 g, 50 mmol) according to the general procedure. White solid. Yield: 10.15 g, 36 mmol, 72%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49-7.25 (m, 8H), 7.10– 7.07 (m, 2H), 4.53 (dd, *J* = 7.9, 3.9 Hz, 1H), 3.39 – 3.33 (m, 1H), 3.13 – 3.06 (m, 1H).

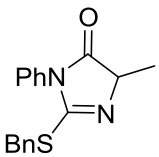
6.3.1.2. S-alkylation of thiohydantoins 1



a R = Me, Ar = Ph
b R = Me, Ar = 4-Me-C_6H_4
c R = Me, Ar = 4-MeO-C_6H_4
d R = Me, Ar = 4-Cl-C_6H_4
e R = Me, Ar = 3-Cl-C_6H_4
f R = Bn, Ar = Ph

A solution of the corresponding thiohydantoin **1** (5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with freshly distilled DIPEA (20 mmol, 4 equiv.) and benzyl bromide (1.19 mL, 10 mmol, 2 equiv.), unless stated otherwise. The mixture was then warmed up to room temperature and monitored by TLC (Hex/EtOAc, 50:50). After reaction completion (2–3 h), the reaction mixture was diluted with CH_2Cl_2 and washed with water. The clear yellow solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography to obtain the desired product.

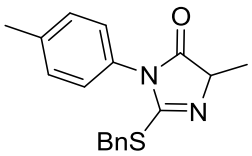
2-(Benzylthio)-5-methyl-3-phenyl-3,5-dihydro-4*H*-imidazol-4-one (2a)



The title compound was prepared from 5-methyl-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.03 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the

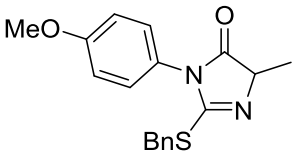
title compound as a white solid. Yield: 4.1 mmol, 1.21 g, 82%. m. p. 113-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51-7.30 (m, 10H), 4.42 (s, 1H), 4.37 (q, 1.61 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.7, 161.2, 135.8, 132.3, 129.5, 129.3, 129.1, 128.7, 127.8, 127.4, 64.9, 34.9, 17.2. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1062, found: 297.1079.

2-(Benzylthio)-5-methyl-3-(*p*-tolyl)-3,5-dihydro-4*H*-imidazol-4-one (2b)



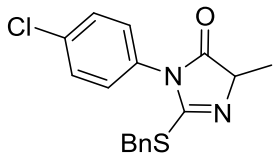
The title compound was prepared from 5-methyl-2-thioxo-3-(*p*-tolyl)imidazolidin-4-one (5 mmol, 1.10 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a yellow solid. Yield: 4.0 mmol, 1.25 g, 81%. m. p. 78-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.05 (m, 9H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 2.41 (s, 3H), 1.59 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.6, 139.4, 135.9, 130.2, 129.6, 129.3, 128.7, 127.8, 127.2, 65.0, 34.9, 21.3, 17.2. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1236.

2-(Benzylthio)-3-(4-methoxyphenyl)-5-methyl-3,5-dihydro-4*H*-imidazol-4-one (2c)



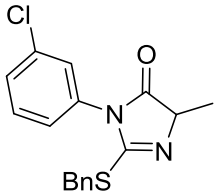
The title compound was prepared from 3-(4-methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.18 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a yellow solid. Yield: 3.9 mmol, 1.29 g, 79%. m. p. 94-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.15 (m, 2H), 7.06 – 6.81 (m, 2H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 1.59 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.7, 160.0, 135.8, 129.2, 128.7, 128.6, 127.7, 124.6, 114.6, 114.5, 64.8, 55.4, 34.7, 17.1. UPLC-DAD-QTOF: $C_{18}H_{19}N_2O_2S$ $[M+H]^+$ calcd.: 327.1167, found: 327.1178.

2-(Benzylthio)-3-(4-chlorophenyl)-5-methyl-3,5-dihydro-4*H*-imidazol-4-one (2d)



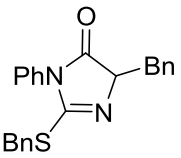
The title compound was prepared from 3-(4-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.20 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a white solid. Yield: 4.1 mmol, 1.37 g, 83%. m. p. 133-135 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 – 6.75 (m, 9H), 4.40 (s, 2H), 4.34 (q, *J* = 7.5 Hz, 1H), 1.57 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.7, 135.8, 135.2, 130.8, 129.8, 129.3, 128.8, 128.7, 128.0, 65.0, 35.0, 17.2. UPLC-DAD-QTOF: $C_{17}H_{16}N_2OSCl$ $[M+H]^+$ calcd.: 331.0672, found: 331.0675.

2-(Benzylthio)-3-(3-chlorophenyl)-5-methyl-3,5-dihydro-4*H*-imidazol-4-one (2e)



The title compound was prepared from 3-(3-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (5 mmol, 1.20 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a yellow oil. Yield: 4.0 mmol, 1.32 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.03 (m, 9H), 4.41 (s, 2H), 4.35 (q, *J* = 7.5 Hz, 1H), 1.58 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.4, 160.5, 135.7, 135.0, 133.4, 130.4, 129.4, 129.3, 128.8, 127.9, 127.6, 125.5, 64.9, 35.0, 17.1. UPLC-DAD-QTOF: $C_{17}H_{16}N_2OSCl$ $[M+H]^+$ calcd.: 331.0672, found: 331.0676.

5-Benzyl-2-(benzylthio)-3-phenyl-3,5-dihydro-4*H*-imidazol-4-one (2f)

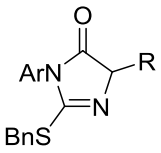


The title compound was prepared from 5-benzyl-3-phenyl-2-thioxoimidazolidin-4-one (5 mmol, 1.41 g) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20) to afford the title compound as a colourless oil; yield: 3.9 mmol, 1.47 g, 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.18 (m, 13H), 7.09 – 6.75 (m, 2H), 4.74 – 4.57 (m, 1H), 4.52 – 4.33 (m, 2H), 3.46 (dd, *J* = 13.5, 4.5 Hz, 1H), 3.30 (dd, *J* = 13.5, 5.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.2, 161.6, 136.1, 135.6, 132.0, 130.0, 129.3, 129.2, 129.1, 128.6, 128.0,

127.7, 127.3, 126.9, 69.7, 37.5, 34.6. UPLC-DAD-QTOF: $C_{23}H_{20}N_2OS$ $[M+H]^+$ calcd.: 373.1375, found: 373.1388.

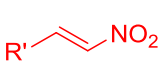
6.3.2. Conjugate addition of N^3-aryl imidazolones to nitroolefins

2a R = Me, Ar = Ph
2b R = Me, Ar = 4-Me-C_6H_4
2c R = Me, Ar = 4-MeO-C_6H_4
2d R = Me, Ar = 4-Cl-C_6H_4
2e R = Me, Ar = 3-Cl-C_6H_4
2f R = Bn, Ar = Ph

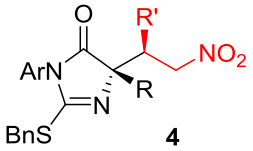


+

3a R' = Ph
3b R' = 2-Cl-C_6H_4
3c R' = 4-MeO-C_6H_4



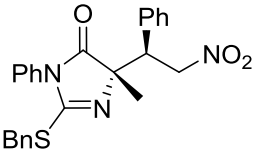
C4 (10 mol%)
CH_2Cl_2, -20 ºC, 15-20 h



4

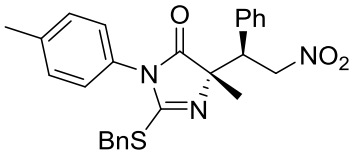
To a solution of the corresponding imidazolone **2** (1 equiv., 0.2 mmol) and nitroalkene **3** (2.0 equiv., 0.4 mmol) in dichlorometane (0.6 mL) the catalyst was added at -20 °C. The resulting mixture was stirred until consumption of the imidazolone (monitored by 1H-NMR). Afterwards, the reaction was directly submitted to flash column chromatography on silica gel to afford the corresponding adducts.

(*S*)-2-(Benzylthio)-5-methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenyl-3,5-dihydro-4*H*-imidazol-4-one (4aa)



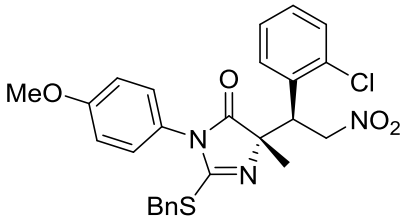
The title compound was prepared from 2-(benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one **2a** (0.2 mmol, 59.2 mg) and (*E*)-(2-nitrovinyl)benzene **3a** (0.4 mmol, 60 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 97:3 mixture of diastereomers (colourless oil). Yield: 0.20 mmol, 88.1 mg, 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.02 (m, 15H), 4.89 (dd, *J* = 13.1, 10.1 Hz, 1H), 4.73 (dd, *J* = 13.1, 5.3 Hz, 1H), 4.43 – 4.25 (m, 2H), 4.05 (dd, *J* = 10.1, 5.3 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 161.0, 135.9, 135.2, 131.8, 129.6, 129.5, 129.2, 129.2, 128.8, 128.5, 128.4, 127.9, 127.3, 75.6, 73.1, 50.1, 34.9, 22.7. UPLC-DAD-QTOF: $C_{25}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 446.1538, found: 446.1545.

(*S*)-2-(Benzylthio)-5-methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-3,5-dihydro-4*H*-imidazol-4-one (4ba)



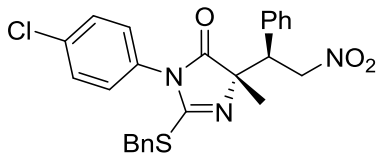
The title compound was prepared from 2-(benzylthio)-4-methyl-1-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one **2b** (0.2 mmol, 62.0 mg) and (*E*)-(2-nitrovinyl)benzene **3a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 93:7 mixture of diastereomers (yellow oil). Yield: 0.18 mmol, 81.7 mg, 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.21 (m, 11H), 6.99 – 6.88 (m, 2H), 4.89 (dd, *J* = 13.1, 10.2 Hz, 1H), 4.73 (dd, *J* = 13.1, 5.2 Hz, 1H), 4.45 – 4.27 (m, 2H), 4.04 (dd, *J* = 10.2, 5.2 Hz, 1H), 2.39 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.9, 161.2, 139.7, 136.0, 135.2, 130.2, 129.2, 129.1, 129.0, 128.7, 128.4, 128.3, 127.9, 127.1, 50.1, 34.8, 22.7, 21.3. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 460.1695, found: 460.1700.

(*S*)-2-(Benzylthio)-5-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-5-methyl-3,5-dihydro-4*H*-imidazol-4-one (4cb)



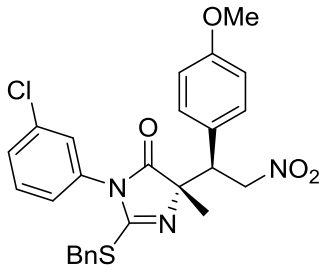
The title compound was prepared from 2-(benzylthio)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **2c** (0.2 mmol, 65.2 mg) and (*E*)-1-chloro-2-(2-nitrovinyl)benzene **3b** (0.4 mmol, 73.2 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.18 mmol, 92.6 mg, 91%. $[\alpha]_D^{25}$= –32.62 (*c* = 0.82, >98:2 dr, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.23 (m, 8H), 7.07 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.90 – 4.62 (m, 1H), 4.36 (s, 2H), 3.84 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 161.9, 160.3, 136.3, 135.9, 133.6, 130.1, 129.3, 129.0, 128.8, 128.6, 127.9, 126.0, 124.2, 114.9, 75.4, 73.2, 55.6, 44.8, 34.8, 22.4. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4SCl$ $[M+H]^+$ calcd.: 510.1254, found: 510.1254.

(*S*)-2-(Benzylthio)-3-(4-chlorophenyl)-5-methyl-5-((*S*)-2-nitro-1-phenylethyl)-3,5-dihydro-4*H*-imidazol-4-one (4da)



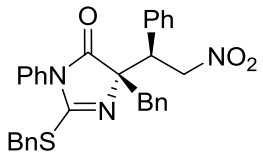
The title compound was prepared from 2-(benzylthio)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **2d** (0.2 mmol, 66.0 mg) and (*E*)-(2-nitrovinyl)benzene **3a** (0.4 mmol, 60.0 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a colourless oil. Yield: 0.18 mmol, 86.2 mg, 90%. $[\alpha]_D^{25}$= –12.73 (*c* = 0.97, >98:2 dr, 94% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.22 (m, 12H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.94 – 4.68 (m, 2H), 4.35 (d, *J* = 2.5 Hz, 2H), 4.03 (dd, *J* = 9.8, 5.6 Hz, 1H), 1.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.4, 135.8, 135.5, 135.1, 130.2, 129.8, 129.2, 128.8, 128.5, 128.5, 128.4, 128.0, 75.5, 73.1, 50.0, 34.9, 22.6. UPLC-DAD-QTOF: $C_{25}H_{23}N_3O_3SCl$ $[M+H]^+$ calcd.: 480.1149, found: 480.1156.

(*S*)-2-(Benzylthio)-3-(3-chlorophenyl)-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-5-methyl-3,5-dihydro-4*H*-imidazol-4-one (4ec)



The title compound was prepared from 2-(benzylthio)-1-(3-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one **2e** (0.2 mmol, 66.0 mg) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **3c** (0.4 mmol, 71.6 mg) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a yellow oil. Yield: 0.18 mmol, 91.6 mg, 90%. $[\alpha]_D^{25}$= –20.30 (*c* = 0.60, >98:2 dr, 87% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 6.82 (m, 13H), 4.89 – 4.65 (m, 2H), 4.36 (d, *J* = 2.3 Hz, 2H), 3.97 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.83 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.6, 160.2, 159.6, 135.8, 135.1, 132.9, 130.5, 130.3, 129.7, 129.2, 128.8, 128.0, 127.6, 126.9, 125.5, 75.7, 73.4, 55.4, 49.4, 35.0, 22.6. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4SCl$ $[M+H]^+$ calcd.: 510.1254, found: 510.1264.

(S)-5-benzyl-2-(benzylthio)-5-((S)-2-nitro-1-phenylethyl)-3-phenyl-3,5-dihydro-4H-imidazol-4-one (4fa)

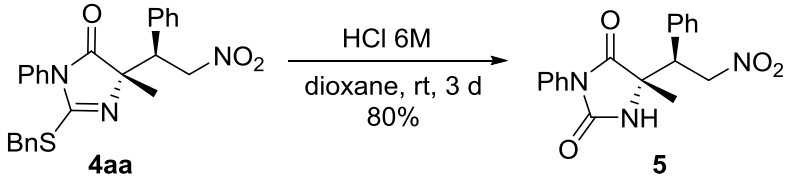


The title compound was prepared from 4-benzyl-2-(benzylthio)-1-phenyl-1*H*-imidazol-5(4*H*)-one **19C** (0.2 mmol, 74.4 mg) and (*E*)-(2-nitrovinyl)benzene **25a** (0.4 mmol, 60.0 mg) according to the

general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with Hex/EtOAc 90:10 to 80:20) to give the title compound as a 91:9 mixture of diastereomers (colourless oil). Yield: 0.18 mmol, 93.8 mg, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 – 7.07 (m, 16H), 7.10 – 6.91 (m, 2H), 6.61 – 6.35 (m, 2H), 4.90 – 4.52 (m, 2H), 4.36 (d, *J* = 1.3 Hz, 2H), 4.19 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 2.83 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 161.6, 136.3, 135.6, 134.2, 131.5, 130.6, 130.5, 129.6, 129.5, 129.4, 129.2, 128.8, 128.7, 128.5, 128.0, 127.9, 127.3, 127.2, 76.5, 49.5, 42.5, 34.8. UPLC-DAD-QTOF: $C_{31}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 522.1851, found: 522.1848.

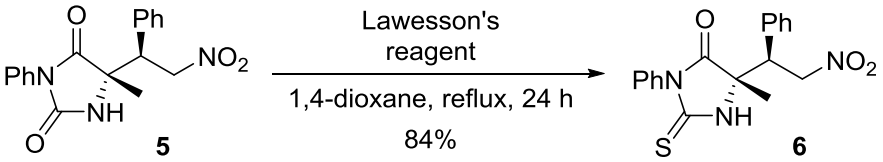
6.3.3. Chemical elaboration of adducts

6.3.3.1. Hydrolysis of product 4aa



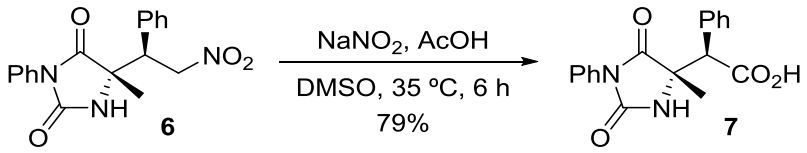
Adduct **4aa** (445 mg, 1.0 mmol, 1 equiv.) was dissolved in 1,4-dioxane (5 mL). The solution was cooled to 0 °C and an aqueous solution of HCl 6M (1.9 mL, 11 mmol, 11 equiv.) was added. The reaction mixture was stirred at room temperature for 3 days. Then, the reaction mixture was cooled to 0 °C, and a saturated solution of $NaHCO_3$ was added until basic pH was obtained. The aqueous layer was extracted with CH_2Cl_2 (2 x 5mL) and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 0:100) to obtain the desired product as a white solid. Yield: 271 mg, 0.80 mmol, 80%. m. p. 169-172 ^{o}C. $[\alpha]_D^{25}$= -23.55 (*c* = 0.60, >98:2 dr, 99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 – 7.03 (m, 10H), 6.74 (s, 1H), 5.31 – 4.63 (m, 2H), 3.98 (dd, *J* = 10.4, 5.0 Hz, 1H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, Acetone) δ: 182.9, 175.9, 135.3, 134.3, 129.9, 129.7, 129.6, 129.6, 129.5, 75.6, 66.8, 51.1, 22.2. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_4$ $[M+H]^+$ calcd.: 340.1297, found: 340.1304.

6.3.3.2. Synthesis of thiohydantoin 6



A suspension of hydantoin **5** (0.5 mmol) and Lawesson's reagent (202.2 mg, 0.5 mmol) in 2.3 mL of dry dioxane was refluxed for 24 h. The mixture was then concentrated, and the residue was submitted to flash chromatography on silica gel, eluent Hex:EtOAc (80:20 to 50:50) to afford **6** as a white solid. Yield: 149 mg, 0.42 mmol, 84%. m. p. 235-237 ^{o}C. $[\alpha]_D^{25}$= –29.01 (*c* = 1.00, >98:2 dr, 99% *ee*. ^{1}H NMR (300 MHz, Acetone) δ: 9.51 (s, 1H), 7.46 – 7.36 (m, 8H), 7.07 – 7.00 (m, 2H), 5.38 – 5.24 (m, 2H), 4.12 (dd, *J* = 9.8, 6.2 Hz, 1H), 1.74 (s, 4H).^{13}C NMR (75 MHz, Acetone) δ: 182.80, 175.81, 135.25, 134.20, 129.76, 129.62, 129.57, 129.48, 129.45, 129.41, 75.47, 66.76, 50.98, 22.15. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 356.1069, found: 356.1069.

6.3.3.3. Conversion of 5 to 7



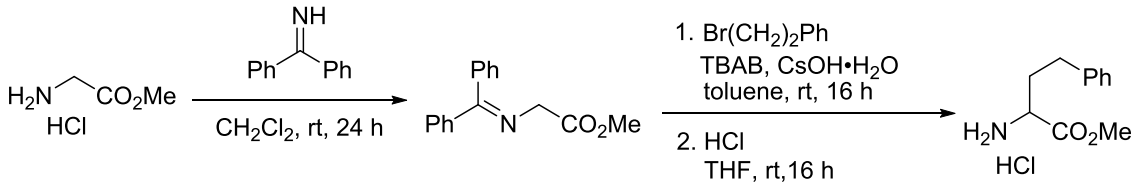
A solution of **6** (0.19 mmol, 64 mg), sodium nitrite (3 equiv., 0.55 mmol, 34 mg) and acetic acid (10 equiv., 1.9 mmol, 120 µL) in DMSO (0.5 mL) was stirred at 35 ^{o}C for 6 h. After this period, the reaction mixture was quenched with HCl 1N (5 mL) and the product was extracted with Et_2O (4 x 5 mL). The combined organic phases were dried with anhyd. $MgSO_4$ and filtered. Evaporation of the solvent under reduced pressure and ulterior washing of the solid with Et_2O gave essentially pure **7** as orange foam. Yield: 48.6 mg, 0.15 mmol, 79%. $[\alpha]_D^{25}$= –32.99 (CH_2Cl_2). >98:2 dr, 99% *ee*. ^{1}H NMR (300 MHz, Acetone) δ: 7.51 – 7.33 (m, 10H), 7.24 (s, 1H), 4.23 (s, 1H), 2.57 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, Acetone) δ: 206.3, 176.7, 172.5, 156.6, 135.2, 134.0, 131.1, 129.4, 129.4, 128.8, 128.4, 127.6, 62.6, 56.9, 24.0. UPLC-DAD-QTOF: $C_{18}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 325.1183, found: 325.1190.

6.4. Experimental section for Chapter 3

6.4.1. Synthesis of starting materials

Acyl pyrrol lactims **1** were synthesized following the general procedure described below starting from commercially available α-amino acids, except in the case of the 2-amino-4-phenylbutanoic acid, which was prepared as follows.

6.4.1.1. Synthesis of non-natural amino acid



Step 1:[240] A solution of benzophenone imine (1.81 g, 10 mmol, 1 equiv.), glycine methyl ester hydrochloride (10 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) was stirred for 24 hours at room termperature, filtrated and the organic solvent was evaporated *in vacuo*. The crude product was purified by a flash column chromatography (eluting with Hex/EtOAc 80/20) to afford the desired imine as a white solid (2.33 g, 9.2 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 – 7.63 (m, 2H), 7.54 – 7.45 (m, 3H), 7.44 – 7.32 (m, 3H), 7.24 – 7.18 (m, 2H), 4.24 (s, 2H), 3.77 (s, 3H).

Step 2:[241] To a solution of the imine (2.03 g, 8.00 mmol) in toluene (32 mL) were added a catalytic amount of TBAB (1.16 g, 2.4 mmol, 0.3 equiv.), cesium hydroxide monohydrate (1.48 g, 8.8 mmol, 1.1 equiv.) and (2-bromoethyl)benzene (1.1 mL, 8.00 mmol, 1 equiv.). The reaction mixture was left to stir overnight at room temperature, then the solvent was evaporated under vacuum and the crude was purified by flash column chromatography (eluting with Hex/EtOAc 80/20) affording the desired product (2.18 g, 6.09 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.49

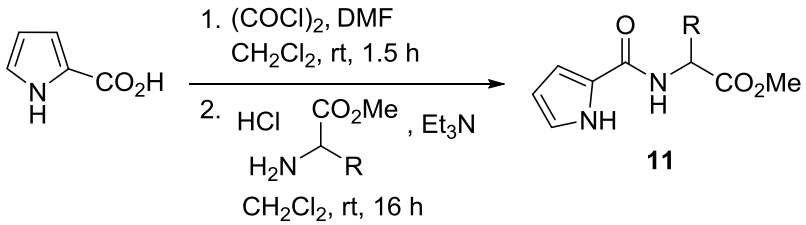
[240] Zhang, H.; Syed, S.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 708-711.

[241] Adapted from: Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.

– 7.32 (m, 8H), 7.27 – 7.12 (m, 5H), 4.16 (dd, *J* = 7.6, 5.5 Hz, 1H), 3.73 (s, 3H), 2.62 (dddd, *J* = 35.0, 13.8, 9.8, 6.4 Hz, 2H), 2.28 (dddd, *J* = 14.2, 9.6, 7.8, 3.7 Hz, 2H).

Step 3:[242] To a solution of the α-substituted imine (1.89 g, 5.3 mmol) in THF (7 mL) was added HCl 1M (7 mL) and the reaction was stirred overnight at room temperature. The solvent was evaporated and the crude was used in the next step without further purification (1.2 g, 5.3 mmol, quantitative). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.34 –7.09 (m, 5H), 4.04 (t, *J*= 6.4 Hz, 1H), 3.79 (s, 3H), 2.90 –2.58 (m, 2H), 2.35–1.95 (m, 2H).

6.4.1.2. Acylation of α-amino acids[243]



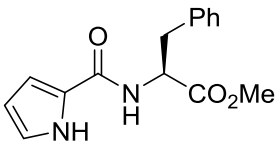
11

To a mixture of pyrrole-2-carboxylic acid (1.11 g, 10.0 mmol, 1 equiv.) was added oxalyl chloride (1.3 mL, 15 mmol, 1.5 equiv.) at 0 °C and the mixture was left stirring at room temperature for 1.5 hours. Then, the solvent was evaporated.

To a solution of the corresponding α-amino methyl ester hydrochloride (10.0 mmol, 1 equiv.) in dry CH_2Cl_2 (40 mL) at 0 °C, was added Et_3N (20 mmol, 2 equiv.) followed by a solution of the acyl chloride in CH_2Cl_2 (10 mL). After stirring overnight, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with HCl 1M, $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated, concentrated and purified by flash chromatography (eluting with Hexane/EtOAc 70/30).

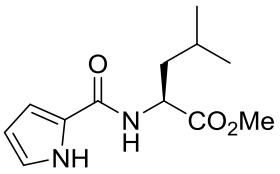
Methyl (1*H*-pyrrole-2-carbonyl)-*L*-phenylalaninate (11a)

[242] Genêt, J.-P.; Jugé, S.; Ruiz Montès, J.; Gaudin, J.-M. *J. Chem. Soc. Chem. Commun.* **1988**, 718-719.
[243] Tian, H.; Ermolenko, L.; Gabant, M.; Vergne, C.; Moriou, C.; Retailleau, P.; Al-Mourabit, L. *Adv. Synth. Catal.* **2011**, *353*, 1525-1533.



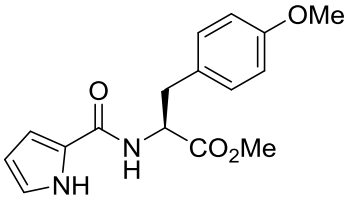
The title compound was prepared following the general procedure starting from *L*-phenylalanine methyl ester hydrochloride (2.5 g, 9.2 mmol, 92%). All the spectroscopic data were coincident withthose previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.26 (s, 1H), 7.31–7.20 (m, 3H), 7.13 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.93 (td, *J* = 2.7, 1.3 Hz, 1H), 6.53 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.26 (s, 1H), 6.23 (dt, *J* = 3.8, 2.6 Hz, 1H) 5.05 (td, *J* = 7.8 and 5.7 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 5.7, 1.4 Hz, 2H).

Methyl (1*H*-pyrrole-2-carbonyl)-*L*-leucinate (11b)



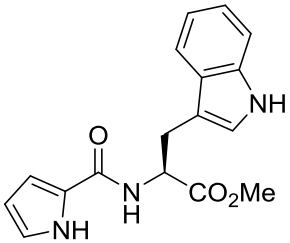
The title compound was prepared following the general procedure starting from *L*-leucine methyl ester hydrochloride (2.0 g, 8.4 mmol, 84%). All the spectroscopic data were coincident withthose previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.37 (s, 1H), 6.93 (td, *J* = 2.7, 1.3 Hz, 1H), 6.63 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.25 (dt, *J* = 3.8, 2.6 Hz, 1H), 6.2 (brs, *J* = 8.6 Hz, 1H), 4.81 (td, *J* = 8.7, 5.2 Hz, 1H), 3.76 (s, 3H), 1.79 – 1.62 (m, 3H), 0.97 (dd, *J* = 6.1, 4.9 Hz, 6H).

Methyl (*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrole-2-carboxamido)propanoate (11c)



The title compound was prepared following the general procedure starting from *L*-tyrosine methyl ester hydrochloride (2.6 g, 8.7 mmol, 87%). All the spectroscopic data were coincident withthose previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 7.08 – 7.00 (m, 2H), 6.93 (td, *J* = 2.7, 1.3 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.54 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.25 (ddt, *J* = 11.3, 3.8, 2.6 Hz, 2H), 5.00 (dt, *J* = 7.9, 5.5 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.15 (d, *J* = 5.5 Hz, 2H).

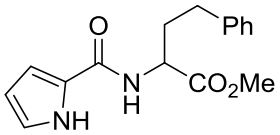
Methyl (1*H*-pyrrole-2-carbonyl)-*L*-tryptophanate (11d)



The title compound was prepared following the general procedure starting with the *L*-tryptophan methyl ester hydrochloride (2.49 g, 8.0 mmol, 80%). All the spectroscopic data were coincident withthose previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.27 (s, 1H), 8.09 (s, 1H), 7.59 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.40 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.14 (td, *J* = 7.6, 7.1, 1.1 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.94

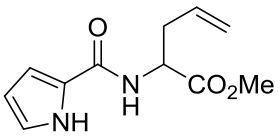
(ddd, *J* = 4.0, 2.5, 1.3 Hz, 1H), 6.44 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.37 (d, *J* = 7.9 Hz, 1H), 6.22 (dt, *J* = 3.9, 2.6 Hz, 1H), 5.13 (dt, *J* = 8.1, 5.2 Hz, 1H), 3.72 (s, 3H), 3.43 (t, *J* = 4.9 Hz, 1H).

Methyl 4-phenyl-2-(1*H*-pyrrole-2-carboxamido)butanoate (11e)



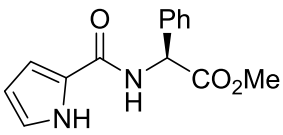
The title compound was prepared following the general procedure starting from *D,L*-homophenyl alanine methyl ester hydrochloride (2.6 g, 8.9 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 7.35 – 7.24 (m, 2H), 7.22 (td, *J* = 6.2, 1.6 Hz, 2H), 6.94 (q, *J* = 1.4 Hz, 1H), 6.61 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.25 (dt, *J* = 3.8, 2.6 Hz, 1H), 4.87 (td, *J* = 7.7, 5.1 Hz, 1H), 3.77 (s, 3H), 2.79 – 2.69 (m, 2H), 2.40 – 2.22 (m, 1H), 2.21 – 2.07 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.1, 161.0, 140.8, 128.7, 128.6, 126.4, 125.4, 122.2, 110.0, 52.6, 52.0, 34.2, 31.9. UPLC-DAD-QTOF: $C_{16}H_{19}N_2O_3$ [M+H]+ calcd.: 287.1390, found: 287.1388.

Methyl 2-(1*H*-pyrrole-2-carboxamido)pent-4-enoate (11f)



The title compound was prepared following the general procedure starting with the *D,L*-allylglycine methyl ester hydrochloride (1.9 g, 8.5 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.67 (s, 1H), 6.93 (td, *J* = 2.7, 1.3 Hz, 1H), 6.62 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 6.25 (dt, *J* = 3.8, 2.6 Hz, 1H), 5.74 (ddt, *J* = 17.1, 9.7, 7.2 Hz, 1H), 5.23 – 5.14 (m, 1H), 5.13 (dt, *J* = 2.3, 1.2 Hz, 1H), 4.84 (dt, *J* = 7.9, 5.8 Hz, 1H), 3.78 (s, 3H), 2.64 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.7, 161.2, 132.4, 125.1, 122.4, 119.0, 110.3, 109.5, 52.4, 51.7, 36.5. UPLC-DAD-QTOF: $C_{11}H_{15}N_2O_3$ [M+H]+ calcd.: 223.1077, found: 223.1080.

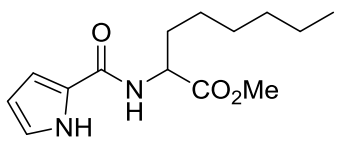
Methyl (*S*)-2-phenyl-2-(1*H*-pyrrole-2-carboxamido)acetate (11g)



The title compound was prepared following the general procedure starting from *L*-phenylglycine methyl ester hydrochloride (1.9 g, 7.4 mmol, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.67 (s, 1H), 7.48 – 7.29 (m, 5H), 6.93 – 6.81 (m, 2H), 6.69 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.23 (ddt, *J* = 7.3, 3.5, 2.5 Hz, 1H), 5.73 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H). ^{13}C NMR (75

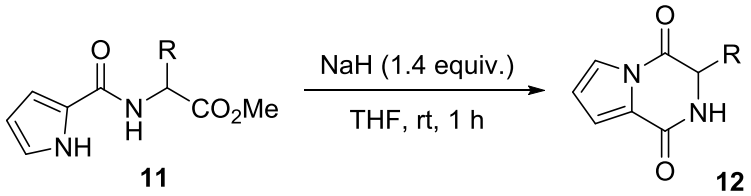
MHz, $CDCl_3$) δ: 171.6, 160.5, 136.8, 129.1, 128.7, 127.4, 125.2, 122.3, 110.1, 110.0, 56.5, 53.0. UPLC-DAD-QTOF: $C_{14}H_{15}N_2O_3$ [M+H]+ calcd.: 259.1077, found: 259.1085.

Methyl 2-(1*H*-pyrrole-2-carboxamido)octanoate (11h)



The title compound was prepared following the general procedure starting from methyl *D,L*-2-aminooctanoate hydrochloride (1.9 g, 7.0 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 6.93 (td, *J* = 2.7, 1.3 Hz, 1H), 6.64 (ddd, *J* = 3.8, 2.5, 1.3 Hz, 1H), 6.30 (d, *J* = 8.3 Hz, 1H), 6.25 (dt, *J* = 3.7, 2.6 Hz, 1H), 4.76 (td, *J* = 7.7, 5.4 Hz, 1H), 3.77 (s, 3H), 1.91 (dq, *J* = 15.0, 4.9 Hz, 1H), 1.84 – 1.65 (m, 1H), 1.45 – 1.19 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.7, 161.3, 125.2, 122.3, 110.4, 109.5, 52.3, 52.2, 32.4, 31.5, 28.8, 25.4, 22.5, 14.0. UPLC-DAD-QTOF: $C_{14}H_{23}N_2O_3$ [M+H]+ calcd.: 267.1703, found: 266.1699.

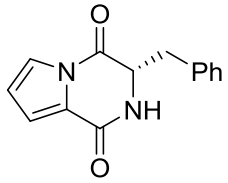
6.4.1.3. Cyclization of pyrrol esters[243]



11 **12**

The corresponding methyl ester (5 mmol, 1 equiv.) was dissolved in degassed anhydrous THF (50 mL) and cooled to 0 °C. Sodium hydride (7 mmol, 1.4 equiv.) was added and the mixture was stirred at 0 °C for five minutes and then at room temperature for 1 hour. After reaction completion, the mixture was poured into acetate buffer pH 3.8 (30 mL) and quickly extracted with AcOEt. The organic layer was dried over $MgSO_4$, the solvent was evaporated and the residue was dried under vacuum. The compound was stored and used without further purification.

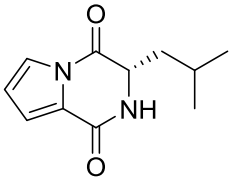
(*S*)-3-Benzyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12a)



The title compound was prepared following the general procedure starting with the methyl (1*H*-pyrrole-2-carbonyl)-*L*-phenylalaninate (0.95 g, 3.95 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.38–7.21 (m, 5H), 7.08 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.51 (t, *J* = 3.4 Hz, 1H),

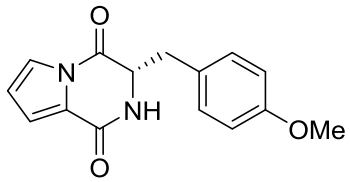
5.63 (s, 1H), 4.60 (ddd, *J* = 9.6, 3.6, 2.1 Hz, 1H), 3.55 (dd, *J* = 13.7, 3.6 Hz, 1H), 3.02 (dd, *J* = 13.7, 9.6 Hz, 1H).

(*S*)-3-Isobutyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12b)



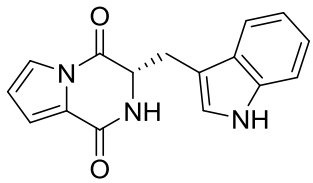
The title compound was prepared following the general procedure starting with the methyl (1*H*-pyrrole-2-carbonyl)-*L*-leucinate (0.77 g, 3.75 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.14 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.53 (t, *J* = 3.3 Hz, 1H), 5.99 (s, 1H), 4.42 (ddd, *J* = 8.8, 4.2, 2.1 Hz, 1H), 1.99 – 1.77 (m, 3H), 0.99 (t, *J* = 6.2 Hz, 8H).

(*S*)-3-(4-Methoxybenzyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12c)



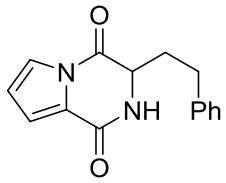
The title compound was prepared following the general procedure starting with the methyl (*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrole-2-carboxamido) propanoate (1.08 g, 4.0 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.19 – 7.08 (m, 2H), 7.07 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.91 – 6.80 (m, 2H), 6.50 (t, *J* = 3.3 Hz, 1H), 5.78 (s, 1H), 4.55 (ddd, *J* = 9.2, 3.8, 2.1 Hz, 1H), 3.45 (dd, *J* = 13.8, 3.7 Hz, 1H), 2.99 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.04 (s, 3H).

(*S*)-3-((1*H*-Indol-3-yl)methyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12d)



The title compound was prepared following the general procedure starting with the methyl (1*H*-pyrrole-2-carbonyl)-*L*-tryptophanate (1.01 g, 3.6 mmol, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (s, 1H), 7.63 (ddd, *J* = 8.0, 1.3, 0.8 Hz, 1H), 7.51 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.26 – 7.12 (m, 2H), 7.06 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.47 (t, *J* = 3.3 Hz, 1H), 5.87 (s, 1H), 4.68 (ddd, *J* = 9.6, 3.5, 2.0 Hz, 1H), 3.72 (ddd, *J* = 14.4, 3.5, 0.9 Hz, 1H), 3.22 (dd, *J* = 14.4, 9.6 Hz, 1H).

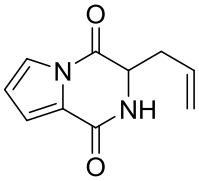
3-Phenethyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12e)



The title compound was prepared following the general procedure starting with the methyl 4-phenyl-2-(1*H*-pyrrole-2-carboxamido)butanoate (1.08 g, 4.25 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.34 – 7.24 (m, 1H), 7.24 – 7.11 (m, 5H), 6.53

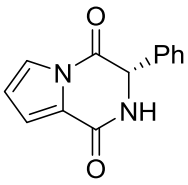
(t, *J* = 3.4 Hz, 1H), 5.88 (s, 1H) 4.44 (td, *J* = 5.5, 2.0 Hz, 1H), 2.84 – 2.72 (m, 2H), 2.40 – 2.31 (m, 2H).

3-Allyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12f)



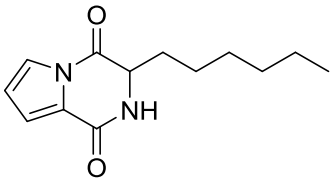
The title compound was prepared following the general procedure starting with the methyl 2-(1*H*-pyrrole-2-carboxamido)pent-4-enoate (0.74 g, 3.9 mmol, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.15 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.54 (t, *J* = 3.3 Hz, 1H), 5.26 (d, *J* = 10.7 Hz, 2H), 4.50 – 4.40 (m, 1H), 2.99 – 2.85 (m, 2H).

(*S*)-3-Phenyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12g)



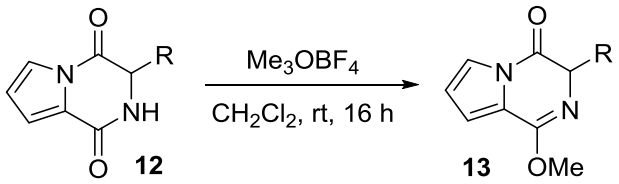
The title compound was prepared following the general procedure starting with the methyl (*S*)-2-phenyl-2-(1*H*-pyrrole-2-carboxamido)acetate (0.90 g, 4.0 mmol, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.44 – 7.31 (m, 5H), 7.23 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.55 (t, *J* = 3.3 Hz, 1H), 5.46 (d, *J* = 2.1 Hz, 1H).

3-Hexyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12h)



The title compound was prepared following the general procedure starting with the methyl 2-(1*H*-pyrrole-2-carboxamido)octanoate (0.84 g, 3.6 mmol, 71 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.14 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.53 (t, *J* = 3.3 Hz, 1H), 6.19 (s, 1H), 4.43 (t, *J* = 5.3 Hz, 1H), 1.74 (dt, *J* = 14.9, 5.2 Hz, 2H), 1.38 – 1.23 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H).

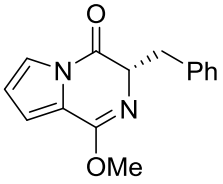
6.4.1.4. Preparation of pyrrol lactims 13



To a well-stirred solution of the corresponding diketopiperazine (3 mmol, 1 equiv.) in CH_2Cl_2 (15 mL), trimethyloxonium tetrafluoroborate (3.3 mmol, 1.1 equiv.) was added in one portion. The reaction mixture was stirred at room temperature overnight.

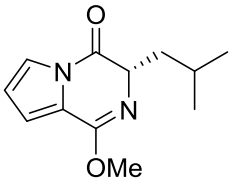
After reaction completion, the reaction mixture was quenched with a saturated aqueous sodium carbonate solution and extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluting with Hex/EtOAc 90/10).

(*S*)-3-Benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13a)



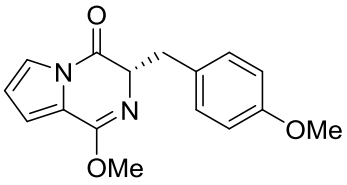
The title compound was prepared following the general procedure starting with the (*S*)-3-benzyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.661 g, 2.6 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.33 – 7.22 (m, 5H), 6.55 (dd, *J* = 3.3, 1.4 Hz, 1H), 6.45 (t, *J* = 3.3 Hz, 1H), 4.90 (t, *J* = 5.3 Hz, 1H), 3.99 (s, 3H), 3.48 (t, *J* = 5.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 152.8, 136.2, 129.7, 128.0, 126.8, 122.7, 117.6, 114.7, 112.2, 63.2, 52.9, 41.0. UPLC-DAD-QTOF: $C_{15}H_{16}N_2O_2$ [M+H]+ calcd.: 255.1134, found: 255.1141.

(*S*)-3-Isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13b)



The title compound was prepared following the general procedure starting with the (*S*)-3-isobutyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.551 g, 2.5 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 3.2, 1.3 Hz, 1H), 6.65 – 6.56 (m, 1H), 6.44 (dd, *J* = 3.7, 2.8 Hz, 1H), 4.47 (dd, *J* = 8.8, 4.9 Hz, 2H), 3.86 (s, 3H), 2.12 – 1.83 (m, 2H), 1.67 (ddd, *J* = 13.1, 8.8, 5.5 Hz, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 152.5, 123.3, 118.4, 115.2, 112.6, 61.3, 53.4, 45.1, 25.5, 23.7, 22.6. UPLC-DAD-QTOF: $C_{12}H_{18}N_2O_2$ [M+H]+ calcd.: 221.1290, found: 221.1295.

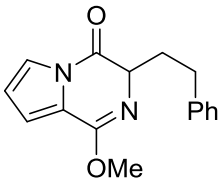
(*S*)-1-Methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13c)



The title compound was prepared following the general procedure starting with the (*S*)-3-(4-methoxybenzyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.654 g, 2.3 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.10 – 6.99 (m, 2H), 6.44 (ddd, *J* = 3.4, 1.5, 0.6 Hz, 1H), 6.32 (t, *J* = 3.3 Hz, 1H), 4.74 (t, *J* = 5.2 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.31 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.6, 158.5,

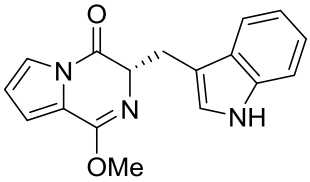
152.7, 130.6, 128.2, 122.7, 117.4, 114.6, 113.4, 112.1, 63.3, 55.1, 52.8, 40.0. UPLC-DAD-QTOF: $C_{16}H_{17}N_2O_3$ [M+H]+ calcd.: 285.1239, found: 285.1239.

1-Methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13d)



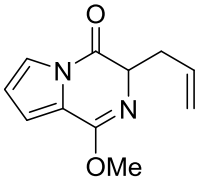
The title compound was prepared following the general procedure starting with the 3-phenethyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.698 g, 2.6 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.32 – 7.11 (m, 5H), 6.64 (ddd, *J* = 3.4, 1.4, 0.6 Hz, 1H), 6.44 (t, *J* = 3.3 Hz, 1H), 4.48 (dd, *J* = 7.4, 4.7 Hz, 1H), 3.91 (s, 3H), 2.88 – 2.65 (m, 2H), 2.44 (dddd, *J* = 13.8, 9.1, 7.1, 4.8 Hz, 1H), 2.23 (dddd, *J* = 13.4, 9.1, 7.4, 6.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 152.5, 141.2, 128.7, 128.4, 126.1, 122.8, 117.9, 114.8, 112.3, 61.3, 52.9, 36.6, 31.6. UPLC-DAD-QTOF: $C_{16}H_{17}N_2O_2$ [M+H]+ calcd.: 269.1290, found: 269.1293.

(*S*)-3-((1*H*-Indol-3-yl)methyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13e)



The title compound was prepared following the general procedure starting with the (*S*)-3-((1*H*-indol-3-yl)methyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.616 g, 2.1 mmol, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.70 (dq, *J* = 7.2, 0.8 Hz, 1H), 7.36 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.11 (dtd, *J* = 14.0, 7.0, 1.4 Hz, 2H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.38 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.26 (t, *J* = 3.3 Hz, 1H), 4.85 (t, *J* = 5.0 Hz, 1H), 3.86 (s, 3H), 3.59 (dt, *J* = 4.9, 0.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 152.8, 135.9, 128.0, 123.0, 122.8, 121.9, 119.5, 119.3, 117.5, 114.5, 112.0, 110.9, 110.6, 63.4, 60.5, 52.8, 30.8. UPLC-DAD-QTOF: $C_{17}H_{16}N_3O_2$ [M+H]+ calcd.: 294.1243, found: 294.1242.

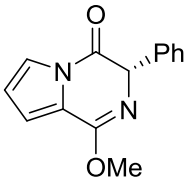
3-Allyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13f)



The title compound was prepared following the general procedure starting with the 3-allyl-2,3-dihydropyrrolo[1,2-a]pyrazine-1,4-dione (0.531 g, 2.6 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (dd, *J* = 3.2, 1.4 Hz, 1H), 6.58 (ddt, *J* = 3.5, 1.3, 0.6 Hz, 1H), 6.40 (td, *J* = 3.3, 0.9 Hz, 1H), 5.64 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.08 (ddd, *J* = 17.2, 2.2, 1.1 Hz, 1H), 4.98 (ddt, *J* = 10.2, 2.0, 1.0 Hz, 1H), 4.53 (t, *J* = 5.6 Hz, 1H), 3.84 (s, 3H), 2.88 – 2.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$)

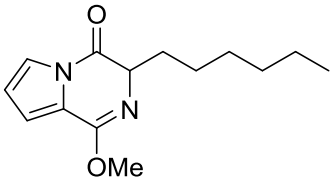
δ: 169.6, 152.7, 132.6, 122.8, 118.8, 117.8, 117.7, 114.8, 112.3, 62.0, 52.9, 39.2. UPLC-DAD-QTOF: $C_{11}H_{13}N_2O_2$ [M+H]+ calcd.: 205.0977, found: 205.0978.

(*S*)-1-Methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13g)



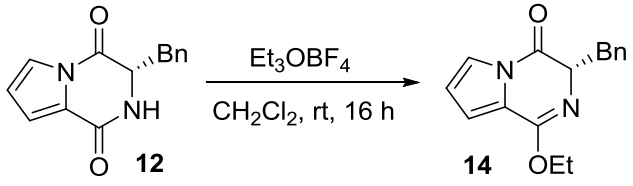
The title compound was prepared following the general procedure starting with the 3-phenyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.649 g, 2.7 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.48 – 7.29 (m, 5H), 6.76 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.47 (td, *J* = 3.3, 1.6 Hz, 1H), 5.64 (s, 1H), 3.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 152.9, 137.1, 128.2, 127.6, 127.0, 122.1, 118.1, 114.4, 112.5, 65.3, 52.6. UPLC-DAD-QTOF: $C_{14}H_{13}N_2O_2$ [M+H]+ calcd.: 241.0977, found: 241.0979.

3-Hexyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13h)



The title compound was prepared following the general procedure starting with the 3-hexyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (0.621 g, 2.5 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dt, *J* = 3.2, 1.7 Hz, 1H), 6.52 (dq, *J* = 3.3, 1.6 Hz, 1H), 6.39 – 6.32 (m, 1H), 4.39 (ddd, *J* = 6.8, 4.8, 1.8 Hz, 1H), 3.78 (s, 3H), 1.99 (ddd, *J* = 14.4, 7.1, 4.0 Hz, 1H), 1.91 – 1.77 (m, 1H), 1.36 – 1.14 (m, 8H), 0.78 (td, *J* = 6.9, 6.3, 2.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 152.2, 122.7, 117.5, 114.5, 112.0, 62.0, 52.6, 35.2, 31.6, 29.0, 24.9, 22.5, 14.0. UPLC-DAD-QTOF: $C_{14}H_{21}N_2O_2$ [M+H]+ calcd.: 249.1603, found: 249.1607.

6.4.1.5. Preparation of pyrrol lactim 14

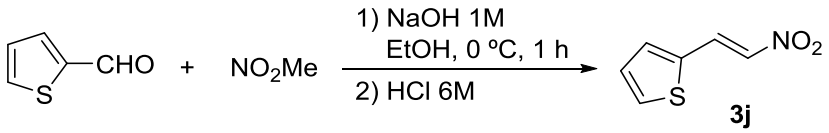


To a well-stirred solution of the corresponding diketopiperazine (3 mmol, 1 equiv.) in CH_2Cl_2 (15 mL), triethyloxonium tetrafluoroborate (3.3 mmol, 1.1 equiv.) was added in one portion. The reaction mixture was stirred at room temperature overnight. After reaction completion, the reaction mixture was quenched with a saturated aqueous sodium carbonate solution and extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and

concentrated under reduced pressure. The crude product was purified by flash column chromatography (eluting with Hex/EtOAc 90/10). Yield: 610 mg, 2.4 mmol, 80%. %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.17 – 7.11 (m, 5H), 6.44 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.30 (td, *J* = 3.3, 1.2 Hz, 1H), 4.76 (t, *J* = 5.3 Hz, 1H), 4.37 – 4.25 (m, 2H), 3.35 (dd, *J* = 5.4, 3.3 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.6, 152.3, 136.3, 129.6, 127.9, 126.66, 122.9, 117.4, 114.5, 112.0, 63.1, 61.2, 40.8, 14.4. UPLC-DAD-QTOF: $C_{15}H_{14}N_2O_2$ [M+H]+ calcd.: 255.1128, found: 255.1134.

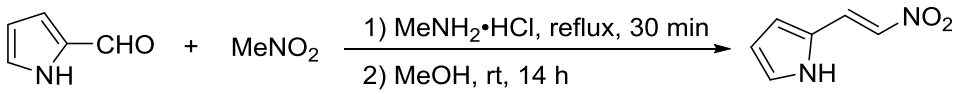
6.4.2. Preparation of the nitroolefins

6.4.2.1. Synthesis of the (E)-2-(2-nitrovinyl)thiophene 3j[244]



To a solution of the 2-thiophenecarboxaldehyde (10 mmol, 1 equiv.) and nitromethane (10 mmol, 1 equiv.) in methanol (2.5 mL) at 0 °C, an aqueous solution of NaOH 1M (5 mL) was added. After 1 hour under vigorous stirring, the reaction mixture became yellow. Then hydrochloride acid 6M (20 mL) was added and the aqueous layer 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. The crude was purified by flash column chromatography on silica gel eluting 95:5 Hex:EtOAc to afford the product as a yellow solid (1.35 g, 8.7 mmol, 87%). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 13.5 Hz, 1H), 7.57 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.15 (dd, *J* = 5.1, 3.7 Hz, 1H).

6.4.2.2. Synthesis of (E)-2-(2-nitrovinyl)-1H-pyrrole[245]

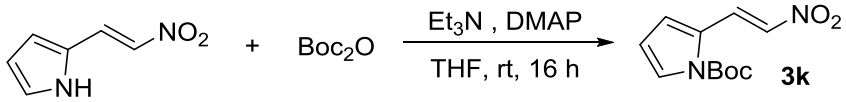


[244] Bourguinon, J.; Lenard, G.; Queguiner, G. *Can. J. Chem.* **1985**, *63*, 2354-2361.

[245] Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160-3172.

1*H*-pyrrole-2-carbaldehyde (10 mmol, 1 equiv.) was dissolved in dry methanol (30 mL) in the presence of molecular sieves. Nitromethane (20 mmol, 2 equiv.), methylamine hydrochloride (10.5 mmol, 1.05 equiv.) and sodium acetate (10.5 mmol, 1.05 equiv.) were added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography eluting 80:20 Hex:EtOAc to yield the product in 78% as a yellow solid. All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (s, 1H), 7.95 (d, *J* = 13.4 Hz, 1H), 7.41 (d, *J* = 13.4 Hz, 1H), 7.12 (s, 1H), 6.81 (d, *J* = 3.8 Hz, 1H), 6.41 (t, *J* = 3.3 Hz, 1H).

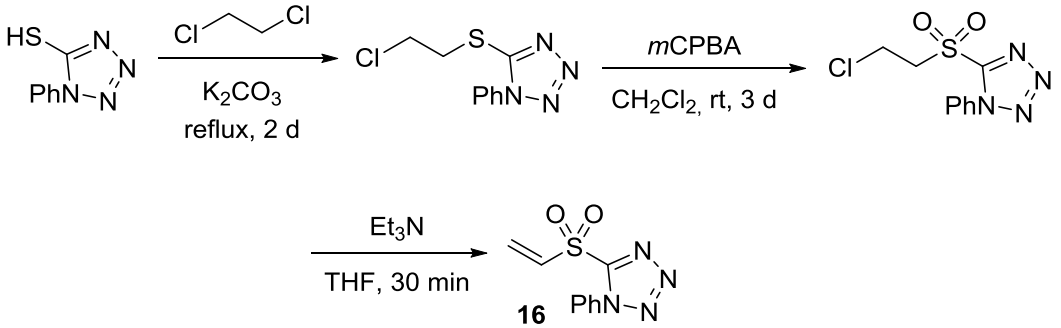
6.4.2.3. Synthesis of tert-butyl (E)-2-(2-nitrovinyl)-1H-pyrrole-1-carboxylate 3k[246]



2-(2-nitrovinyl)-1H-pyrrole (5 mmol, 1 equiv.) was dissolved in THF (20 mL). di-*tert*-butyl dicarbonate (6 mmol, 1.2 equiv.), triethylamine (6 mmol, 1.2 equiv.) and DMAP (0.5 mmol, 0.1 equiv.) were added subsequently. The reaction mixture was stirred for 16 h at room temperature, the solvent was removed under reduced pressure and the crude product was purified by flash column chromatography eluting 90:10 to 80:20 Hex:EtOAc to afford the product as a yellow solid. Yield: 80% (0.953 g, 4 mmol). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 13.6 Hz, 1H), 7.54 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.47 (d, *J* = 13.5 Hz, 1H), 6.88 – 6.77 (m, 1H), 6.37 – 6.25 (m, 1H), 1.55 (s, 9H).

[246] Neuhaus, J. D.; Angyal, R.; Maulide, N. *J. Org. Chem.* **2018**, *83*, 2479-2485..

6.4.3. Preparation of 1-phenyl-5-(vinylsulfonyl)-1*H*-tetrazole 16[247]



Step 1: 1,2-dichloroethane (45 mL) was added to 1-phenyl-1*H*-tetrazole-5-thiol (8.90 g, 50 mmol) followed by K_2CO_3 (17.3 g, 125 mmol, 2.5 equiv.). The suspension was stirred and heated under reflux during 2 days. After cooling to room temperature, water was added and the mixture was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 5-(2-chloroethylthio)-1-phenyl-1Htetrazole as a pale yellow solid that was used in the next step without previous purification.

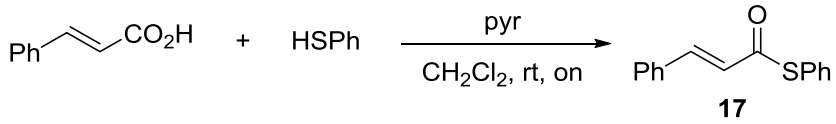
Step 2: The crude compound (8.2 g, 34 mmol) was dissolved in CH_2Cl_2 (40 mL) and a solution of *meta*-chloroperbenzoic acid (14.7 g, 85 mmol, 2.5 equiv.) in CH_2Cl_2 (40 mL) was added. The reaction mixture was stirred at room temperature for 3 days, whereupon it was filtered. The filtrate was transferred into a separatory funnel, washed with 100 mL of a 40% w/v $NaHSO_3$ solution, a sat. $NaHCO_3$ solution (2 x 100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum to afford the product which was used in the next step without previous purification.

Step 3: The obtained crude was dissolved in THF (30 mL) and triethylamine (7.1 ml, 51 mmol, 1.5 equiv.) was added dropwise. The clear solution turned to a clouded suspension which was stirred for 30 min. Solid triethlyamine hydrochloride was filtered and the solvent removed under reduced pressure. The residue was purified by flash

[247] Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.-H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S. *Science* **2018**, *360*, 75-80.

column chromatography (Hex/EtOAc, 4:1) to afford the compound **16** as a white solid. All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72-7.57 (m, 5H), 7.14 (dd, *J* = 10.0, 16,5 Hz, 1H), 6.67 (d, *J* = 16,5 Hz, 1H), 6.49 (d, *J* = 10 Hz, 1H).

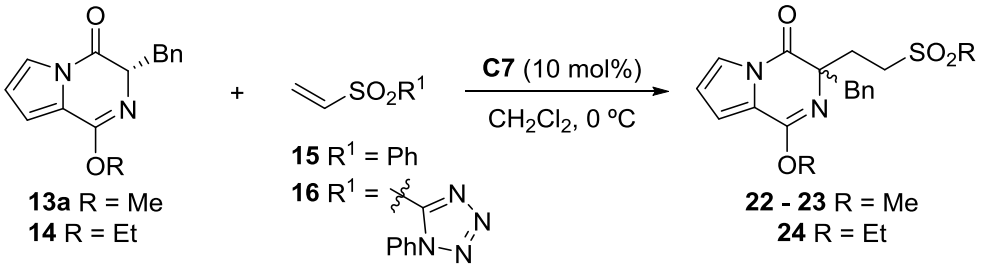
6.4.4. Preparation of α,β-thioesther 17[248]



17

Thiol (1.0 mL, 10 mmol, 1.0 equiv) and pyridine (10 mmol, 1.0 equiv) were dissolved in methylene chloride (50 mL), and cooled to 5 ºC. The acyl chloride (1.4 mL, 10 mmol, 1.0 equiv) was added by syringe over 5 min. The resulting suspension was stirred at 5 ºC for an additional 5 min, and then stirred at room temperature overnight. The progress of the reaction was monitored by TLC. The reaction was quenched by adding water (40 mL). The aqueous phase was separated and extracted with methylene chloride (40 mL x 2), and the combined organic extracts were dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash column chromatography on silica gel to afford the desired thioester. All the spectroscopic data were coincident with those previously reported.[249] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 15.8 Hz, 1H), 7.43 – 7.06 (m, 10H), 6.66 (d, *J* = 15.8 Hz, 1H).

6.4.5. Michael addition of 1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-ones 13a-14 to vinyl sulfones 15-16

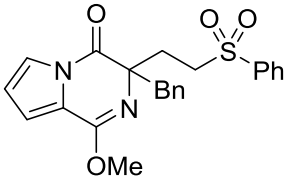


To a solution of pyrrol lactim **13a** (0.1 mmol, 1 equiv.) and the corresponding vinyl sulfone **15-16** (0.15 mmol, 1.5 equiv.) in methylenechloride (0.3 mL) catalyst **C7**

[248] Adapted from: Ichiishi, N.; Malapit, C. A.; Woźniak, Ł.; Sanford, M. S. *Org. Lett.* **2018**, *20*, 44-47.
[249] Zhong, P.; Xiong, Z.-X.; Huang, X. *Synth. Commun.* **2000**, *30*, 2793-2800.

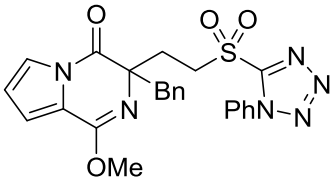
(0.01 mmol) was added at 0 °C. The resulting mixture was stirred until consumption of the starting material at the same temperature (typically 16 h). The solvent was eliminated and the crude was purified by flash column chromatograph on silica gel to afford the expected adducts.

3-Benzyl-1-methoxy-3-(2-(phenylsulfonyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (22)



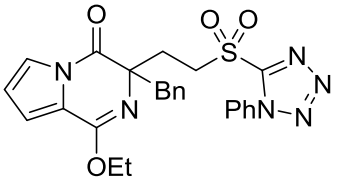
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** and vinyl sulfone **15** according to the general procedure. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.17 – 8.10 (m, 2H), 7.95 – 7.87 (m, 1H), 7.81 (dd, *J* = 8.3, 6.6 Hz, 2H), 7.50 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.26 (dd, *J* = 4.9, 1.8 Hz, 3H), 7.17 – 7.06 (m, 2H), 6.48 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.44 (t, *J* = 3.3 Hz, 1H), 4.07 (s, 3H), 3.47 (d, *J* = 12.6 Hz, 1H), 3.41 – 3.16 (m, 3H), 2.80 (ddd, *J* = 12.9, 11.9, 5.0 Hz, 1H), 2.60 (td, *J* = 12.3, 4.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 153.1, 138.9, 134.4, 133.9, 129.7, 129.5, 128.2, 127.8, 127.2, 122.4, 117.6, 115.1, 112.4, 68.2, 53.1, 52.2, 47.7, 33.4. UPLC-DAD-QTOF: $C_{23}H_{22}N_2O_4S$ [M+H]+ calcd.: 422.1300, found: 422.1303.

3-Benzyl-1-methoxy-3-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (23)



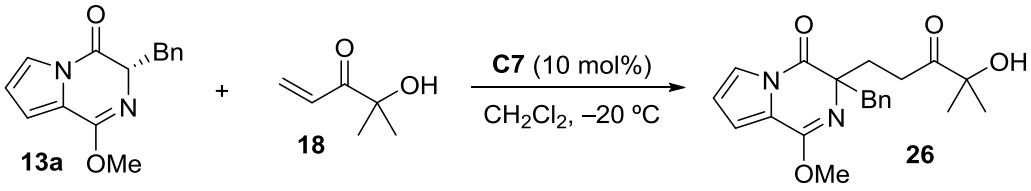
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** and vinyl sulfone **16** according to the general procedure. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 41 mg, 0.084 mmol, 84%. 18% *ee.* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90 – 7.84 (m, 2H), 7.83 – 7.74 (m, 3H), 7.50 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.29 – 7.20 (m, 3H), 7.16 – 7.09 (m, 2H), 6.48 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.44 (t, *J* = 3.3 Hz, 1H), 4.11 (s, 3H), 4.02 (ddd, *J* = 14.3, 11.7, 4.5 Hz, 1H), 3.88 (ddd, *J* = 14.3, 11.9, 4.9 Hz, 1H), 3.51 (d, *J* = 12.6 Hz, 1H), 3.27 (d, *J* = 12.6 Hz, 1H), 3.02 (ddd, *J* = 13.1, 11.6, 4.9 Hz, 1H), 2.80 (ddd, *J* = 13.0, 11.8, 4.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 153.5, 153.4, 134.1, 133.1, 131.6, 129.8, 129.7, 127.9, 127.3, 125.28, 122.4, 117.8, 115.2, 112.7, 68.0, 53.3, 52.4, 47.7, 32.3. UPLC-DAD-QTOF: $C_{24}H_{22}N_6O_4S$ [M+H]+ calcd.: 490.1423, found: 490.1318.

3-Benzyl-1-ethoxy-3-(2-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (24)



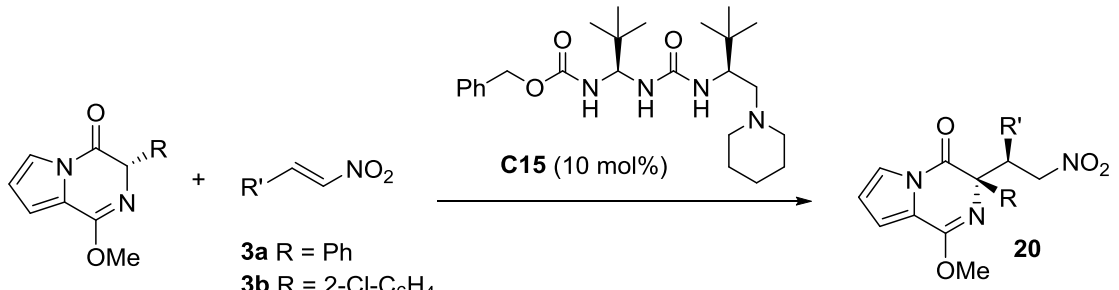
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **14** and vinyl sulfone **16** according to the general procedure. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 40 mg, 0.080 mmol, 80%. 9% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 – 7.53 (m, 5H), 7.31 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.06 (dd, *J* = 4.9, 1.8 Hz, 3H), 6.93 (dd, *J* = 6.7, 2.9 Hz, 2H), 6.31 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.25 (t, *J* = 3.3 Hz, 1H), 4.37 (qd, *J* = 7.1, 3.1 Hz, 2H), 3.82 (ddd, *J* = 14.3, 11.7, 4.4 Hz, 1H), 3.67 (ddd, *J* = 14.3, 12.0, 4.8 Hz, 1H), 3.32 (d, *J* = 12.6 Hz, 1H), 3.07 (d, *J* = 12.6 Hz, 1H), 2.82 (ddd, *J* = 12.8, 11.9, 4.8 Hz, 1H), 2.59 (td, *J* = 12.3, 4.4 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H). UPLC-DAD-QTOF: $C_{25}H_{24}N_6O_4S$ [M+H]+ calcd.: 504.1580, found: 504.1582.

6.4.6. Michael addition of 1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one 13a to 4-hydroxy-4-methylpent-1-en-3-one 18



To a solution of pyrrol lactim **13a** (0.1 mmol, 1 equiv.) and the α-hydroxy enone **18** (0.15 mmol, 1.5 equiv.) in methylenechloride (0.3 mL) catalyst **C7** (0.01 mmol) was added at –20 °C. The resulting mixture was stirred until consumption of the starting material at the same temperature (typically 16 h). The solvent was eliminated and the crude was purified by flash column chromatograph on silica gel to afford the expected adduct. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange foam. 29 mg, 0.078 mmol, 78%. 0% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (dd, *J* = 3.1, 1.5 Hz, 1H), 7.07 – 7.02 (m, 3H), 6.98 – 6.92 (m, 2H), 6.28 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.25 (t, *J* = 3.3 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 1H), 3.32 (d, *J* = 12.6 Hz, 1H), 3.07 (d, *J* = 12.6 Hz, 1H), 2.68 – 2.48 (m, 1H), 2.50 – 2.40 (m, 2H), 2.41 – 2.26 (m, 1H), 1.30 (d, *J* = 3.5 Hz, 6H). UPLC-DAD-QTOF: $C_{25}H_{24}N_6O_4S$ [M+H]+ calcd.: 368.1736, found: 368.1735.

6.4.7. Michael reaction of 1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-ones 13-14 to nitroalkenes 3

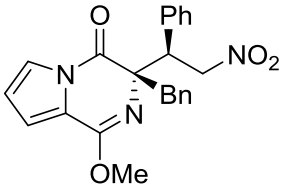


13a R = Bn
13b R = ^{i}Bu
13c R = PMP
13e R = 1*H*-indole
13d R = CH2CH2Ph
13f R = allyl
13g R = ^{n}hexyl
13h R = Ph
14 R = Bn (Et instead of Me)

3a R = Ph
3b R = 2-Cl-C_6H_4
3c R = 4-MeO-C_6H_4
3d R = 4-Me-C_6H_4
3e R = 4-Br-C_6H_4
3f R = 4-F-C_6H_4
3g R = 2,4-Br-5-MeO-C_6H_4
3h R = 2-furyl
3i R = 3-furyl
3j R = 2-thienyl
3k R = *N*-Boc-2-pyrrol
3l R = Cy

To a solution of the corresponding pyrrol lactim **13** (0.1 mmol, 1 equiv.) and nitroalkene **3** (0.3 mmol, 3.0 equiv.) in toluene (1 mL) catalyst **C15** (0.01 mmol) was added at the indicated temperature. The resulting mixture was stirred until consumption of the starting material (typically 16 h). The solvent was eliminated and the crude was purified by flash column chromatograph on silica gel to afford the expected adducts **20**.

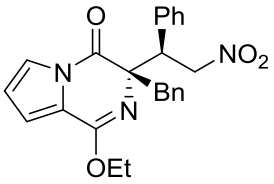
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aa)



The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at –20 ºC at 1 mmol scale. The crude material was purified by flash column chromatography eluting 1:1 Hexane:CH_2Cl_2. Colourless solid. Yield: 315 mg, 0.78 mmol, 78%. m.p. 118-123 °C. $[\alpha]_D^{21}$= +34.9 (c=1, CH_2Cl_2). *dr* 98:2, 88% *ee.* ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.40 – 7.30 (m, 4H), 6.99 (dd, *J* = 5.0, 2.0 Hz, 3H), 6.82 (dd, *J* = 6.4, 3.1 Hz, 2H), 6.21 (d, *J* = 2.3 Hz, 2H), 4.83 (dd, *J* = 12.4, 10.4 Hz, 1H), 4.61 – 4.43 (m, 2H), 3.98 (s, 3H), 3.21 (d, *J* = 12.5 Hz, 1H), 2.66 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 153.2, 135.4, 134.1, 130.0,

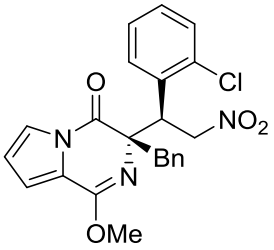
129.7, 128.5, 128.4, 127.8, 127.1, 122.0, 117.8, 115.2, 112.5, 77.5, 71.0, 53.2, 51.5, 46.6. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_4$ [M+H]+ calcd.: 404.1610, found: 404.1613.

(*S*)-3-Benzyl-1-ethoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (21)



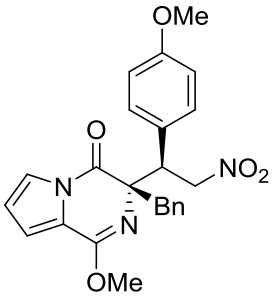
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **14** according to the general procedure at 0 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 315 mg, 0.78 mmol, 78%. m.p. 118-123 °C. $[\alpha]_D^{21}$= +34.9 (c=1, CH_2Cl_2). *dr* 92:8, 76% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.52 (m, 2H), 7.39 – 7.30 (m, 4H), 6.98 (dd, *J* = 5.0, 2.0 Hz, 3H), 6.86 – 6.76 (m, 2H), 6.23 – 6.18 (m, 2H), 4.81 (dd, *J* = 12.2, 10.3 Hz, 1H), 4.57 – 4.38 (m, 4H), 3.18 (d, *J* = 12.5 Hz, 1H), 2.62 (d, *J* = 12.5 Hz, 1H), 1.45 (t, *J* = 7.1 Hz, 3H). UPLC-DAD-QTOF: $C_{24}H_{23}N_3O_4$ [M+H]+ calcd.: 417.1689, found: 417.1687.

(*S*)-3-Benzyl-3-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ab)



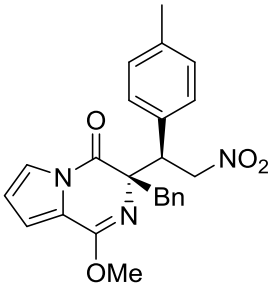
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 37 mg, 0.084 mmol, 84%. m.p.= 156–159 °C. $[\alpha]_D^{21}$= +54.7 (c=1, CH_2Cl_2). *dr* >98:2, 86% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 – 7.75 (m, 1H), 7.50 – 7.44 (m, 1H), 7.39 – 7.31 (m, 1H), 7.28 (ddd, *J* = 6.5, 3.7, 2.1 Hz, 2H), 7.01 – 6.96 (m, 3H), 6.80 (dd, *J* = 7.2, 2.3 Hz, 2H), 6.22 (dd, *J* = 2.5, 0.7 Hz, 2H), 5.42 (dd, J = 10.7, 4.6 Hz, 1H), 4.76 (dd, *J* = 13.1, 10.9 Hz, 1H), 4.54 (ddd, *J* = 13.1, 4.6, 0.7 Hz, 1H), 3.97 (s, 3H), 3.40 (d, *J* = 12.5 Hz, 1H), 2.61 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5, 153.4, 136.7, 133.8, 133.6, 130.1, 129.8, 129.7, 129.4, 127.8, 127.2, 126.8, 121.9, 117.9, 115.2, 112.6, 77.1, 71.3, 53.2, 45.5, 45.4. UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_5$ [M+H]+ calcd.: 438.1221, found: 438.1221.

(*S*)-3-Benzyl-1-methoxy-3-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ac)



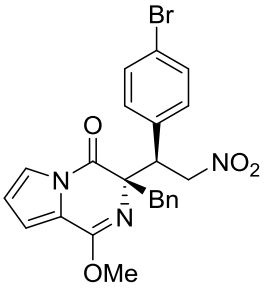
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 36 mg, 0.083 mmol, 83%. *dr* 79:21, 65% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 – 7.46 (m, 2H), 7.32 (t, *J* = 2.3 Hz, 1H), 7.08 – 6.94 (m, 3H), 6.91 – 6.85 (m, 2H), 6.81 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.21 (dd, *J* = 4.4, 2.9 Hz, 2H), 4.76 (dd, *J* = 12.1, 10.5 Hz, 1H), 4.56 – 4.38 (m, 2H), 3.97 (s, 3H), 3.80 (s, 3H), 3.17 (d, *J* = 12.5 Hz, 1H), 2.66 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 159.6, 153.2, 134.2, 131.1, 129.7, 127.8, 127.2, 127.1, 117.8, 115.1, 113.9, 112.4, 77.7, 71.2, 55.4, 53.2, 50.9, 46.6. UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_5$ [M+H]+ calcd.: 434.1716, found: 434.1718.

(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ad)



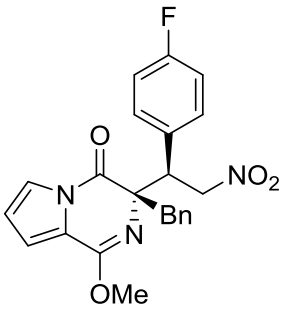
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 34 mg, 0.081 mmol, 81%. *dr* 88:12, 82% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 (d, *J* = 7.7 Hz, 2H), 7.38 – 7.30 (m, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.05 – 6.96 (m, 3H), 6.81 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.28 – 6.17 (m, 2H), 4.86 – 4.71 (m, 1H), 4.56 – 4.41 (m, 2H), 3.98 (s, 3H), 3.19 (d, *J* = 12.5 Hz, 1H), 2.66 (d, *J* = 12.5 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 153.2, 138.1, 134.2, 132.3, 129.9, 129.7, 129.2, 127.8, 127.1, 117.7, 115.1, 112.4, 77.6, 71.0, 53.2, 51.2, 46.6, 21.3. UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_4$ [M+H]+ calcd.: 418.1767, found: 418.1765.

(*S*)-3-Benzyl-3-((*S*)-1-(*4*-bromophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ae)



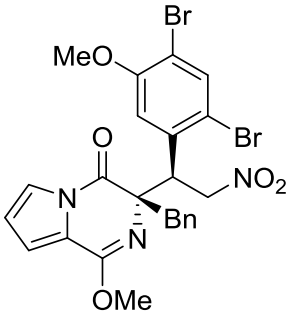
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 42 mg, 0.086 mmol, 86%. m.p.= 66-69 °C. $[\alpha]_D^{21}$= +38.7 (c=1, CH_2Cl_2). *dr* 96:4, 85% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (d, *J* = 2.2 Hz, 4H), 7.32 (dd, *J* = 2.8, 1.9 Hz, 1H), 7.09 – 6.91 (m, 3H), 6.83 – 6.75 (m, 2H), 6.25 – 6.20 (m, 2H), 4.82 – 4.69 (m, 1H), 4.54 – 4.43 (m, 2H), 3.96 (s, 3H), 3.16 (d, *J* = 12.4 Hz, 1H), 2.61 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 153.5, 134.5, 133.7, 131.7, 129.6, 127.9, 127.3, 122.7, 121.9, 117.9, 115.3, 112.8, 77.3, 70.8, 53.2, 50.9, 46.7. UPLC-DAD-QTOF: $C_{23}H_{21}N_3O_4Br$ [M+H]+ calcd.: 482.0715, found: 482.0719.

(*S*)-3-Benzyl-3-((*S*)-1-(*4*-fluorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20af)



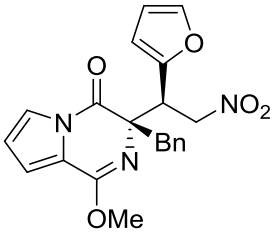
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 38 mg, 0.09 mmol, 90%. m.p. 47-50 °C. $[\alpha]_D^{21}$= +36.2 (c=1, CH_2Cl_2). *dr* 97:3, 88% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 (ddd, *J* = 8.5, 5.2, 2.6 Hz, 2H), 7.32 (t, *J* = 2.4 Hz, 1H), 7.09 – 6.95 (m, 5H), 6.83 – 6.77 (m, 2H), 6.21 (d, *J* = 2.3 Hz, 2H), 4.85 – 4.70 (m, 1H), 4.55 – 4.45 (m, 2H), 3.97 (s, 3H), 3.18 (d, *J* = 12.5 Hz, 1H), 2.62 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 164.5, 161.2, 153.4, 133.9, 131.7, 131.6, 129.7, 127.9, 127.2, 121.9, 117.8, 115.6, 115.4, 115.3, 112.7, 77.5, 70.9, 53.2, 50.8, 46.6. UPLC-DAD-QTOF: $C_{23}H_{21}N_3O_4F$ [M+H]+ calcd.: 422.1516, found: 422.1513.

(*S*)-3-Benzyl-3-((*S*)-1-(2,4-dibromo-5-methoxyphenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ag)



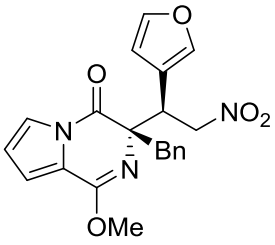
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 51 mg, 0.086 mmol, 86%. m.p. 200-203 °C. $[\alpha]_D^{21}$= +47.8(c=1, CH_2Cl_2). *dr* >98:2, 84% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (s, 1H), 7.45 (d, *J* = 2.6 Hz, 2H), 7.39 – 7.31 (m, 1H), 7.04 – 6.94 (m, 3H), 6.79 (dd, *J* = 7.3, 2.3 Hz, 2H), 6.23 (d, *J* = 2.4 Hz, 2H), 5.34 (dd, *J* = 10.6, 4.7 Hz, 1H), 4.72 (dd, *J* = 13.0, 10.6 Hz, 1H), 4.53 (dd, *J* = 13.0, 4.7 Hz, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.37 (d, *J* = 12.5 Hz, 1H), 2.63 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 155.4, 153.6, 136.8, 135.7, 133.4, 129.7, 127.8, 127.3, 121.8, 118.4, 118.0, 115.4, 113.0, 112.7, 77.2, 71.3, 56.5, 53.1, 48.2, 45.6. UPLC-DAD-QTOF: $C_{24}H_{22}N_3O_5Br_2$ [M+H]+ calcd.: 589.9926, found: 589.9927.

(*S*)-3-Benzyl-3-((*S*)-1-(furan-2-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ah)



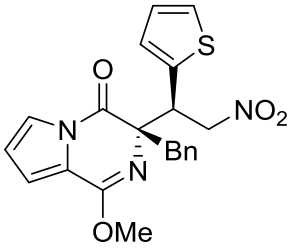
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange solid. Yield: 35 mg, 0.89 mmol, 89%. m.p.= 99–102 °C. $[\alpha]_D^{21}$= +31.5 (c=1, CH_2Cl_2). *dr* >98:2, 98% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (td, *J* = 1.9, 1.0 Hz, 2H), 7.05 – 7.00 (m, 3H), 6.92 – 6.86 (m, 2H), 6.40 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.24 – 6.21 (m, 2H), 4.83 (dd, *J* = 12.2, 9.9 Hz, 1H), 4.65 – 4.53 (m, 2H), 3.91 (s, 3H), 3.37 (d, *J* = 12.5 Hz, 1H), 2.85 (d, *J* = 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2, 153.2, 149.8, 142.6, 134.0, 129.9, 127.9, 127.2, 122.1, 117.8, 115.2, 112.5, 110.6, 109.9, 75.6, 70.6, 53.1, 46.1, 45.8. UPLC-DAD-QTOF: $C_{21}H_{20}N_3O_5$ [M+H]+ calcd.: 394.1403, found: 394.1403.

(*S*)-3-Benzyl-3-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ai)



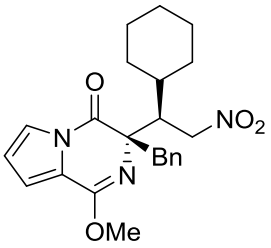
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange solid. Yield: 33 mg, 0.085 mmol, 85%. m.p.= 124–127 °C. $[\alpha]_D^{21}$= +48.1 (c=1, CH_2Cl_2). *dr* >98:2, 91% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.32 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.04 – 6.98 (m, 3H), 6.83 (dd, *J* = 6.3, 2.7 Hz, 2H), 6.68 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.28 – 6.17 (m, 2H), 4.62 – 4.32 (m, 3H), 3.97 (s, 3H), 3.16 (d, *J* = 12.7 Hz, 1H), 2.89 (d, J = 12.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 153.6, 143.3, 142.3, 134.0, 129.7, 127.8, 127.2, 122.0, 119.6, 117.8, 115.3, 112.6, 110.8, 77.8, 70.7, 53.2, 46.5, 43.1. UPLC-DAD-QTOF: $C_{21}H_{20}N_3O_5$ [M+H]+ calcd.: 394.1403, found: 394.1405.

(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aj)



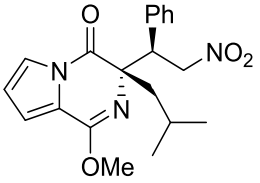
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **1a** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange solid. Yield: 35 mg, 0.086 mmol, 86%. m.p. 49-53 °C. $[\alpha]_D^{21}$= +41.6 (c=1, CH_2Cl_2). *dr* >98:2, 89% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.29 (m, 2H), 7.18 (dd, *J* = 3.4, 1.4 Hz, 1H), 7.04 – 6.97 (m, 4H), 6.82 (dq, *J* = 4.4, 1.9 Hz, 2H), 6.24 (td, *J* = 3.3, 1.7 Hz, 2H), 4.89 (dd, *J* = 10.4, 4.1 Hz, 1H), 4.56 (ddd, *J* = 12.1, 10.6, 1.5 Hz, 1H), 4.37 (ddd, *J* = 12.2, 4.2, 1.6 Hz, 1H), 4.06 (s, 3H), 3.17 (dd, *J* = 12.6, 1.6 Hz, 1H), 2.88 (dd, *J* = 12.6, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5, 153.8, 137.0, 133.8, 129.8, 129.6, 127.8, 127.3, 127.2, 126.3, 122.0, 117.9, 115.3, 112.8, 79.2, 70.6, 53.9, 47.9, 46.5. UPLC-DAD-QTOF: $C_{21}H_{20}N_3O_4S$ [M+H]+ calcd.: 410.1175, found: 410.1173.

(*S*)-3-Benzyl-3-((*S*)-1-cyclohexyl-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ak)



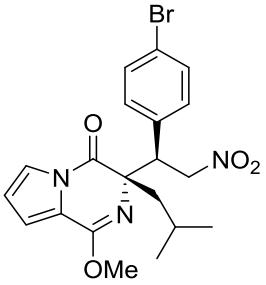
The title compound was prepared starting from (*S*)-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13a** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colorless oil. Yield: 35 mg, 0.085 mmol, 85%. $[\alpha]_D^{21}$= +11.9 (c=1, CH_2Cl_2). *dr* >98:2, 93% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (dd, *J* = 3.3, 1.6 Hz, 1H), 7.02 (q, *J* = 3.0 Hz, 3H), 6.95 – 6.86 (m, 2H), 6.28 – 6.16 (m, 2H), 4.78 (dd, *J* = 13.9, 5.0 Hz, 1H), 4.59 (ddd, *J* = 14.0, 6.3, 2.0 Hz, 1H), 3.89 (s, 3H), 3.38 (d, *J* = 12.2 Hz, 1H), 3.16 (d, *J* = 12.3 Hz, 1H), 1.94 (ddd, *J* = 14.5, 7.1, 2.9 Hz, 1H), 1.81 – 1.60 (m, 5H), 1.32 – 0.95 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 152.9, 134.2, 129.9, 127.8, 127.2, 122.1, 117.6, 115.0, 112.2, 74.5, 70.9, 53.1, 51.2, 46.0, 38.1, 33.0, 28.4, 27.1, 26.7, 26.2. UPLC-DAD-QTOF: $C_{23}H_{28}N_3O_4$ [M+H]+ calcd.: 410.2080, found: 410.2074.

(*S*)-3-Isobutyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ba)



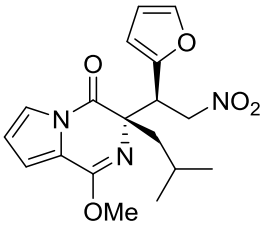
The title compound was prepared starting from (*S*)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13b** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colorless solid. Yield: 31 mg, 0.084 mmol, 84%. *dr* 96:4, 89% *ee* (determined in the corresponding pyrrolopyrazinones **33b**) . ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (dq, *J* = 3.1, 1.6 Hz, 1H), 7.20 – 7.15 (m, 5H), 6.45 – 6.35 (m, 2H), 4.93 (dd, *J* = 12.9, 11.3 Hz, 1H), 4.83 – 4.71 (m, 1H), 4.06 (dt, *J* = 11.0, 3.6 Hz, 1H), 3.89 (s, 3H), 2.09 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.76 (dd, *J* = 13.1, 4.7 Hz, 1H), 1.60 – 1.41 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.59 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 152.5, 134.7, 129.2, 128.3, 128.1, 122.1, 117.9, 115.4, 112.7, 76.5, 69.8, 53.9, 53.1, 48.0, 24.9, 24.4, 22.8. The complete characterization of the adduct was made for the final pyrrolopyrazinones **4ba** (see section 6.4.8.1.).

(*S*)-3-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20bb)



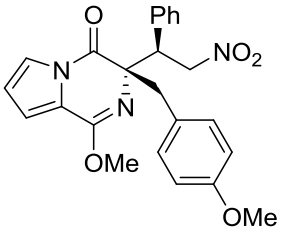
The title compound was prepared starting from (*S*)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13b** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange oil. Yield: 37 mg, 0.082 mmol, 82%. $[\alpha]_D^{21}$= -71.5 (c=1, CH_2Cl_2). *dr* 96:4, 89% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (dt, *J* = 3.2, 0.7 Hz, 1H), 6.49 (dq, *J* = 3.4, 0.9 Hz, 1H), 6.42 (td, *J* = 3.3, 0.8 Hz, 1H), 4.84 (dd, *J* = 13.1, 11.4 Hz, 1H), 4.67 (dd, *J* = 13.1, 4.2 Hz, 1H), 4.05 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.89 (s, 3H), 2.03 (dd, *J* = 13.2, 7.4 Hz, 1H), 1.68 (dd, *J* = 13.1, 5.0 Hz, 1H), 1.45 (ddd, *J* = 13.2, 9.3, 6.0 Hz, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.59 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8, 153.1, 134.4, 131.8, 131.4, 122.9, 122.4, 118.5, 116.1, 113.6, 78.0, 70.1, 53.6, 53.6, 48.6, 25.2, 24.8, 23.3. UPLC-DAD-QTOF: $C_{20}H_{23}N_3O_4Br$ [M+H]+ calcd.: 448.0872, found: 448.0873.

(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20bf)



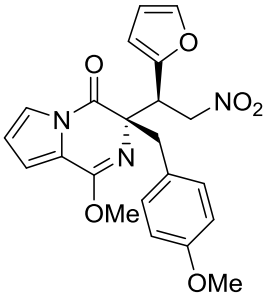
The title compound was prepared starting from (*S*)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13b** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange solid. Yield: 31 mg, 0.087 mmol, 87%. m.p.= 104–108 °C. $[\alpha]_D^{21}$= -80.3 (c=1, CH_2Cl_2). *dr* >98:2, 72% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (dt, *J* = 3.2, 1.3 Hz, 1H), 7.10 (dt, *J* = 1.8, 0.9 Hz, 1H), 6.49 (dt, *J* = 3.4, 1.2 Hz, 1H), 6.40 (td, *J* = 3.3, 0.9 Hz, 1H), 6.19 – 6.13 (m, 1H), 6.13 – 6.10 (m, 1H), 4.97 – 4.77 (m, 2H), 4.11 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.86 (s, 3H), 2.21 – 2.10 (m, 1H), 1.90 – 1.81 (m, 1H), 1.66 – 1.48 (m, 1H), 0.86 (dd, *J* = 6.7, 0.9 Hz, 3H), 0.62 (dd, *J* = 6.6, 0.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 152.7, 149.0, 142.5, 122.1, 118.2, 115.2, 112.7, 110.4, 109.9, 74.8, 69.0. UPLC-DAD-QTOF: $C_{18}H_{22}N_3O_5$ [M+H]+ calcd.: 360.1559, found: 360.1560.

(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ca)



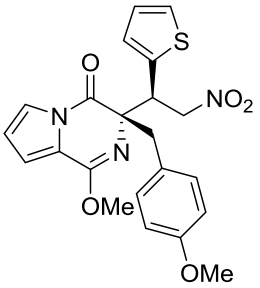
The title compound was prepared starting from (*S*)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13c** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colorless oil. Yield: 38 mg, 0.088 mmol, 88%. $[\alpha]_D^{21}$= +46.1 (c=1, CH_2Cl_2). *dr* >98:2, 84% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.52 (m, 2H), 6.79 – 6.67 (m, 2H), 6.58 – 6.46 (m, 2H), 6.27 – 6.17 (m, 2H), 4.82 (dd, *J* = 12.6, 10.7 Hz, 1H), 4.55 (dd, *J* = 12.7, 4.5 Hz, 1H), 4.46 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.97 (s, 3H), 3.64 (s, 3H), 3.16 (d, *J* = 12.7 Hz, 1H), 2.60 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 158.8, 153.2, 135.4, 130.7, 130.0, 128.5, 128.4, 126.1, 122.0, 117.8, 115.2, 113.3, 112.5, 77.5, 71.1, 55.2, 53.2, 51.5, 45.8. UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_5$ [M+H]+ calcd.: 434.1716, found: 434.1718.

(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20cf)



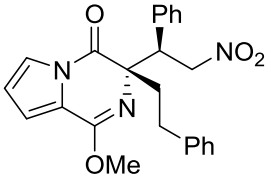
The title compound was prepared starting from (*S*)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13c** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Pale yellow oil. Yield: 39 mg, 0.090 mmol, 90%. $[\alpha]_D^{21}$= +47.5 (c=1, CH_2Cl_2). *dr* >98:2, 79% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 3.1, 1.6 Hz, 1H), 7.31 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.82 (dd, *J* = 9.0, 2.3 Hz, 2H), 6.59 – 6.54 (m, 2H), 6.38 (d, *J* = 3.1 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.27 – 6.22 (m, 2H), 4.82 (dd, *J* = 12.9, 10.7 Hz, 1H), 4.61 (dd, *J* = 13.0, 4.2 Hz, 1H), 4.53 (dd, *J* = 10.7, 4.2 Hz, 1H), 3.90 (s, 3H), 3.66 (s, 3H), 3.32 (d, *J* = 12.7 Hz, 1H), 2.80 (d, *J* = 12.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 158.8, 153.2, 149.8, 142.6, 130.9, 126.1, 122.1, 117.8, 115.2, 113.4, 112.5, 110.6, 109.8, 75.6, 70.6, 55.2, 53.1, 46.0, 44.9. UPLC-DAD-QTOF: $C_{22}H_{22}N_3O_6$ [M+H]+ calcd.: 424.1503, found: 424.1511.

(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ch)



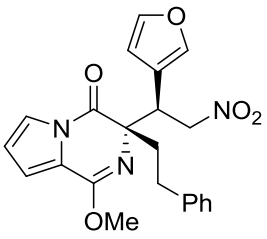
The title compound was prepared starting from (*S*)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13c** according to the general procedure at −20 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 39 mg, 0.088 mmol, 88%. m.p. 134-137 °C. $[\alpha]_D^{21}$= +42.2 (c=1, CH_2Cl_2). *dr* >98:2, 77% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (dt, *J* = 4.1, 1.0 Hz, 2H), 7.17 (dd, *J* = 3.5, 1.3 Hz, 1H), 6.99 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.74 (dd, *J* = 9.2, 2.6 Hz, 2H), 6.53 (dt, *J* = 9.3, 2.7 Hz, 2H), 6.28 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.24 (t, *J* = 3.3 Hz, 1H), 4.86 (dd, *J* = 10.5, 4.2 Hz, 1H), 4.55 (dd, *J* = 12.2, 10.5 Hz, 1H), 4.36 (dd, *J* = 12.2, 4.2 Hz, 1H), 4.05 (s, 3H), 3.65 (s, 3H), 3.12 (d, *J* = 12.9 Hz, 1H), 2.82 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 158.9, 153.7, 137.1, 130.6, 129.7, 127.2, 126.2, 125.9, 122.1, 117.9, 115.3, 113.3, 112.8, 79.2, 70.7, 55.3, 53.9, 47.8, 45.7. UPLC-DAD-QTOF: $C_{22}H_{22}N_3O_5S$ [M+H]+ calcd.: 440.1275, found: 440.1284.

(*S*)-1-Methoxy-3-((*S*)-2-nitro-1-phenylethyl)-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20da)



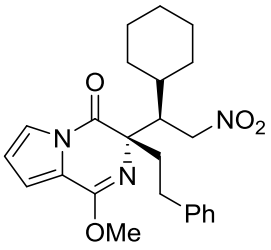
The title compound was prepared starting from 1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13d** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Yield: 35 mg, 0.084 mmol, 84%. m.p. 46-50 °C. $[\alpha]_D^{21}$= -10.6 (c=1, CH_2Cl_2). *dr* 94:6, 84% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.10 (m, 6H), 7.01 – 6.91 (m, 2H), 6.52 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.42 (t, *J* = 3.3 Hz, 1H), 4.86 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.66 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.20 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.93 (s, 3H), 2.45 – 2.16 (m, 4H), 2.01 – 1.87 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 153.1, 140.4, 134.9, 129.5, 128.5, 128.4, 128.4, 128.3, 122.2, 118.1, 115.5, 113.1, 76.9, 70.0, 53.3, 52.4, 41.5, 30.4. UPLC-DAD-QTOF: $C_{24}H_{24}N_3O_4$ [M+H]+ calcd.: 418.1767, found: 418.1763.

(*S*)-3-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20dg)



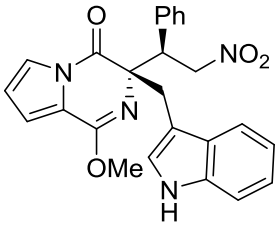
The title compound was prepared starting from 1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13d** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange oil. Yield: 35 mg, 0.085 mmol, 85%. $[\alpha]_D^{21}$= -5.56 (c=1, CH_2Cl_2). *dr* 97:3, 92% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 3.2, 1.4 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.30 (t, *J* = 1.7 Hz, 1H), 7.17 (tdd, *J* = 8.4, 6.3, 4.8 Hz, 3H), 7.01 – 6.94 (m, 2H), 6.63 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.49 – 6.43 (m, 2H), 4.58 (dd, *J* = 12.4, 10.9 Hz, 1H), 4.45 (dd, *J* = 12.4, 4.3 Hz, 1H), 4.21 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.95 (s, 3H), 2.45 – 2.18 (m, 4H), 2.03 (td, *J* = 12.1, 7.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 153.4, 143.2, 142.0, 140.3, 128.5, 128.4, 126.3, 122.2, 119.2, 118.3, 115.6, 113.4, 110.3, 77.3, 69.6, 53.3, 43.8, 41.6, 30.2. UPLC-DAD-QTOF: $C_{22}H_{22}N_3O_5$ [M+H]+ calcd.: 408.1559, found: 408.1558.

(*S*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20di)



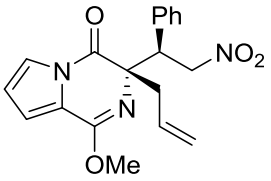
The title compound was prepared starting from 1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13d** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Yellow oil. Yield: 36 mg, 0.084 mmol, 84%. $[\alpha]_D^{21}$= +17.6 (c=1, CH_2Cl_2). *dr* >98:2, 93% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.27 – 7.13 (m, 3H), 7.09 – 7.02 (m, 2H), 6.67 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.48 (t, *J* = 3.3 Hz, 1H), 4.67 (dd, *J* = 13.9, 5.3 Hz, 1H), 4.49 (dd, *J* = 13.9, 6.2 Hz, 1H), 3.89 (s, 3H), 2.98 (td, *J* = 5.8, 2.1 Hz, 1H), 2.52 – 2.33 (m, 2H), 2.31 – 2.12 (m, 2H), 1.85 – 1.65 (m, 2H), 1.60 (q, *J* = 4.3 Hz, 4H), 1.23 – 0.81 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.7, 153.0, 140.7, 128.6, 128.5, 126.3, 122.3, 118.2, 115.5, 113.0, 74.0, 69.7, 53.2, 51.2, 41.5, 37.6, 33.2, 30.3, 28.3, 27.1, 26.6, 26.2. UPLC-DAD-QTOF: $C_{24}H_{30}N_3O_4$ [M+H]+ calcd.: 424.2236, found: 424.2231.

(*S*)-3-((1*H*-Indol-3-yl)methyl)-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ea)



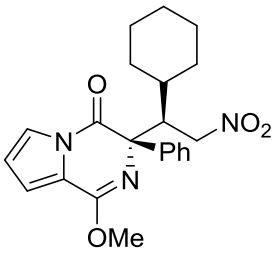
The title compound was prepared starting from (*S*)-3-((1*H*-indol-3-yl)methyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13e** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Orange foam. Yield: 38 mg, 0.085 mmol, 85%. *dr* > 98:2, 48% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.65 – 7.59 (m, 2H), 7.45 – 7.31 (m, 4H), 7.19 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.13 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.10 – 6.96 (m, 2H), 6.66 (d, *J* = 2.5 Hz, 1H), 6.13 – 6.07 (m, 2H), 4.85 (dd, *J* = 13.6, 11.6 Hz, 1H), 4.57 (ddd, *J* = 11.7, 8.3, 4.5 Hz, 2H), 3.91 (s, 3H), 3.61 (dd, *J* = 7.6, 5.8 Hz, 1H), 3.42 (d, *J* = 13.5 Hz, 1H), 2.88 (d, *J* = 13.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 153.1, 135.7, 135.6, 128.5, 128.4, 122.9, 122.0, 119.3, 119.3, 117.7, 114.7, 112.0, 110.8, 108.9, 77.7, 71.3, 53.0, 51.3, 36.7. UPLC-DAD-QTOF: $C_{25}H_{23}N_4O_4$ [M+H]+ calcd.: 443.1719, found: 443.1714.

(*S*)-3-Allyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20fa)



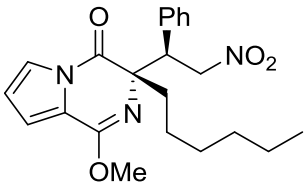
The title compound was prepared starting from 3-allyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13f** according to the general procedure at −30 °C. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 30 mg, 0.084 mmol, 84%, m.p.= 116–122 °C. $[\alpha]_D^{21}$= -17.9 (c=1, CH_2Cl_2), *dr* 96:4, 85% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (dt, *J* = 3.1, 1.3 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.27 (dd, *J* = 4.5, 2.4 Hz, 3H), 6.54 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.43 (dd, *J* = 3.9, 2.7 Hz, 1H), 5.43 – 5.27 (m, 1H), 5.02 – 4.86 (m, 2H), 4.81 (dd, *J* = 12.8, 10.8 Hz, 1H), 4.56 (ddd, *J* = 12.8, 4.6, 1.2 Hz, 1H), 4.27 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.94 (s, 3H), 2.64 (dd, *J* = 12.8, 8.1 Hz, 1H), 2.25 (ddt, *J* = 12.9, 6.8, 1.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 153.1, 135.1, 130.6, 129.8, 128.4, 122.2, 120.3, 118.1, 115.5, 113.0, 77.0, 70.1, 53.3, 51.4, 44.6. UPLC-DAD-QTOF: $C_{19}H_{20}N_3O_4$ [M+H]+ calcd.: 354.1454, found: 354.1461.

(*R*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20gi)



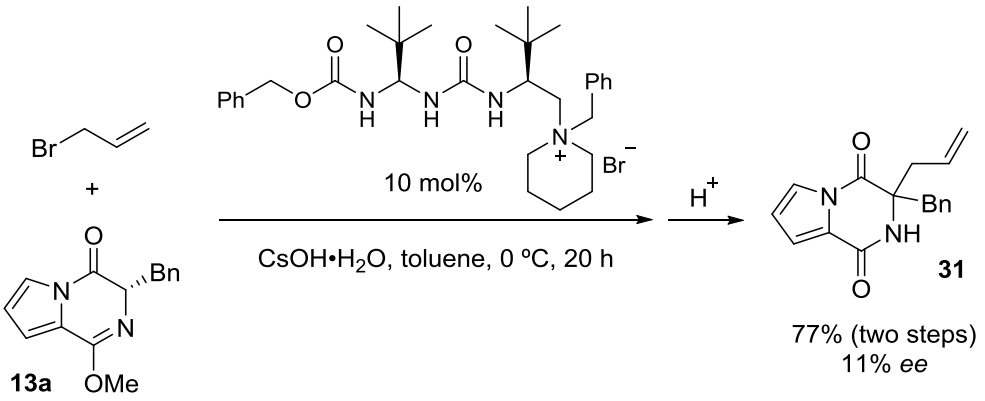
The title compound was prepared starting from (*S*)-1-methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one **13g** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless solid. Yield: 36 mg, 0.092 mmol, 92%. m.p.= 153–154 °C. $[\alpha]_D^{21}$= +17.6 (c=1, CH_2Cl_2). *dr* >98:2, 72% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.54 (m, 2H), 7.43 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.39 – 7.25 (m, 3H), 6.65 (dd, *J* = 3.4, 1.4 Hz, 1H), 6.42 (t, *J* = 3.3 Hz, 1H), 4.54 (dd, *J* = 14.4, 7.7 Hz, 1H), 4.29 (dd, *J* = 14.4, 3.5 Hz, 1H), 4.04 (s, 3H), 3.76 (dt, *J* = 7.7, 3.3 Hz, 1H), 1.80 – 1.52 (m, 5H), 1.46 – 1.31 (m, 1H), 1.18 – 1.02 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.1, 153.3, 138.8, 129.0, 128.9, 126.8, 121.9, 119.2, 115.1, 113.1, 74.9, 73.4, 53.3, 51.0, 40.8, 33.6, 29.5, 27.1, 26.7, 26.1. UPLC-DAD-QTOF: $C_{22}H_{26}N_3O_4$ [M+H]+ calcd.: 396.1923, found: 396.1916.

(*S*)-3-Hexyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ha)



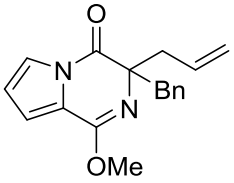
The title compound was prepared starting from **13h** according to the general procedure at −30 ºC. The crude material was purified by flash column chromatography eluting 1:1 Hex:CH_2Cl_2. Colourless foam. Yield: 35 mg, 0.089 mmol, 89%. *dr* 92:8, 75% *ee* (determined in the corresponding pyrrolopyrazinones **33d**). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.07 (dd, *J* = 3.5, 2.5 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.42 (t, *J* = 3.3 Hz, 1H), 4.84 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.62 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.18 (dd, *J* = 10.8, 4.5 Hz, 1H), 3.92 (s, 3H), 2.01 (ddd, *J* = 12.7, 11.5, 4.6 Hz, 1H), 2.01 (ddd, *J* = 12.7, 11.5, 4.6 Hz, 1H), 1.63 – 1.46 (m, 1H), 1.31 – 1.05 (m, 8H), 0.79 (t, *J* = 6.9 Hz, 3H). The complete characterization of the adduct was made for the final pyrrolopyrazinones **33d** (see section 6.4.8.1.).

6.4.8. Alkylation of 1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one 13a



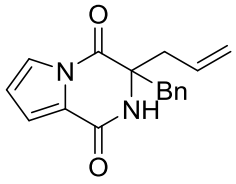
To a solution of the pyrrol lactim **13a** (25.4 g, 0.1 mmol) in toluene (0.3 mL) were added a catalytic amount of ureidopeptide-based PTC (6.3 mg, 0.01 mmol, 0.1 equiv.), cesium hydroxide monohydrate (16.8 mg, 0.11 mmol, 1.1 equiv.) and allyl bromide (8.6 µL, 0.1 mmol, 1 equiv.). The reaction mixture was left to stir overnight at room temperature, then the solvent was evaporated under vacuum and the crude was purified by flash column chromatography (eluting with Hex/EtOAc 80/20) affording the desired product. Treatment the adduct with acid gave the hydrolysis yielding the pyrrolo DKP **31** (22 mg, 0.077 mmol, 77%, two steps).

3-Allyl-3-benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one



^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.14 – 6.98 (m, 5H), 6.30 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.25 (t, *J* = 3.3 Hz, 1H), 5.57 (dddd, *J* = 17.1, 10.1, 7.6, 6.9 Hz, 1H), 5.11 (ddt, *J* = 17.1, 2.4, 1.3 Hz, 1H), 4.97 (ddt, *J* = 10.1, 1.9, 0.9 Hz, 1H), 3.89 (s, 3H), 3.38 (d, *J* = 12.7 Hz, 1H), 3.09 (d, *J* = 12.8 Hz, 1H), 2.95 (dd, *J* = 13.1, 7.7 Hz, 1H), 2.69 (dd, *J* = 13.1, 6.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 152.2, 135.7, 132.5, 130.8, 130.0, 127.8, 126.8, 119.2, 117.3, 114.7, 111.6, 69.9, 52.9, 47.1, 45.6. UPLC-DAD-QTOF: $C_{18}H_{20}N_2O_2$ [M+H]+ calcd.: 295.1441, found: 295.1442.

3-Allyl-3-benzyl-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (31)

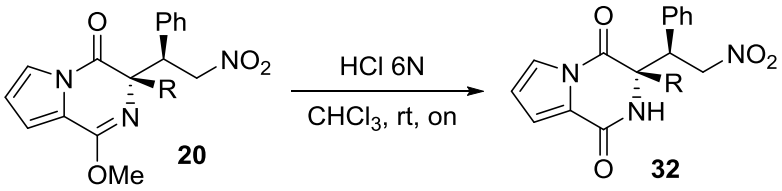


Colourless solid. Yield: 34 mg, 0.088 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.21 – 7.08 (m, 5H), 6.86 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.77 (s, 1H), 6.36 (t, *J* = 3.3 Hz, 1H), 5.71 (ddt, *J* = 17.2, 10.1, 7.3 Hz, 1H), 5.29 – 5.10 (m, 2H), 3.35 (d, *J* = 13.4 Hz, 1H), 3.06 (d, *J* = 13.4 Hz,

1H), 2.96 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.60 (dd, *J* = 13.8, 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.4, 157.4, 133.6, 130.3, 130.2, 128.6, 127.8, 125.3, 121.8, 119.4, 118.2, 115.5, 66.8, 47.2, 44.4. UPLC-DAD-QTOF: $C_{17}H_{17}N_2O_2$ [M+H]+ calcd.: 281.1285, found: 281.1283.

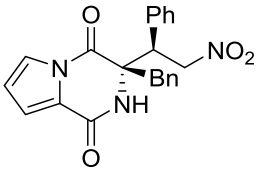
6.4.9. Chemical elaboration of adducts

6.4.8.1. Preparation of chiral pyrrolo DKP



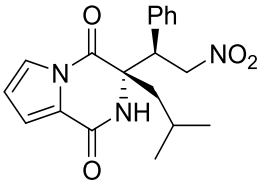
To a solution of the corresponding Michael adducts **20** (0.07-0.5 mmol) in $CHCl_3$ (1 mL) was added HCl 6N (1 mL) and the reaction mixture was stirred overnight at room temperature. Then, it was diluted with CH_2Cl_2 and water, extracted with CH_2Cl_2 (3 x 25 mL), dried over $MgSO_4$, filtrated and concentrated under vacuum to produce pure diketopyrrolo piperazines **32**.

(*S*)-3-Benzyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32a)



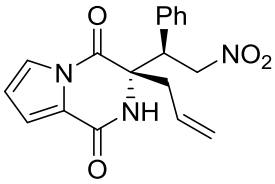
Colourless solid. Yield: 181 mg, 0.46 mmol, 93%. m.p.= 136-138 °C. $[\alpha]_D^{21}$= -9.31 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (s, 1H), 7.41 (dd, *J* = 3.3, 1.6 Hz, 1H), 7.37 – 7.25 (m, 4H), 7.14 – 7.09 (m, 2H), 7.06 – 7.00 (m, 2H), 6.70 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.33 (t, *J* = 3.3 Hz, 1H), 5.14 (dd, *J* = 13.3, 11.1 Hz, 1H), 4.89 (dd, *J* = 13.3, 4.3 Hz, 1H), 4.38 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 2.83 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7, 157.3, 133.0, 132.7, 130.1, 129.3, 129.3, 129.2, 128.5, 127.9, 124.6, 119.4, 118.9, 116.1, 75.8, 68.6, 52.3, 46.2. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_4$ [M+H]+ calcd.: 390.1454, found: 390.1452.

(*S*)-3-Isobutyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32b)



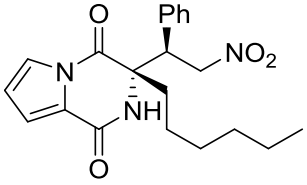
Colorless solid. Yield: 25 mg, 0.071 mmol, 71% (from **13b**). m.p.= 71-74 °C. $[\alpha]_D^{21}$= -62.3 (c=1, CH_2Cl_2). *dr* 96:4, 89% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 – 7.76 (m, 1H), 7.48 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.26 – 7.05 (m, 5H), 6.86 (dd, *J* = 3.3, 1.3 Hz, 1H), 6.43 (t, *J* = 3.3 Hz, 1H), 5.09 (t, *J* = 12.5 Hz, 1H), 4.95 – 4.86 (m, 1H), 4.00 (dd, *J* = 11.1, 4.5 Hz, 1H), 2.31 – 2.22 (m, 1H), 1.81 – 1.63 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1, 157.4, 132.9, 129.1, 128.8, 128.8, 124.7, 119.5, 118.9, 116.2, 75.2, 67.4, 54.9, 46.6, 29.8, 25.2, 24.0, 22.7. UPLC-DAD-QTOF: $C_{19}H_{22}N_3O_4$ [M+H]+ calcd.: 356.1610, found: 356.1602; $C_{19}H_{21}N_3O_4Na$ [M+Na]+ calcd.: 378.1430, found: 378.1423.

(*S*)-3-Allyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32c)



Colourless solid. Yield: 153 mg, 0.45 mmol, 90%. m.p.= 140-143 °C. $[\alpha]_D^{21}$= -7.53 (c=1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.28 – 7.24 (m, 2H), 7.03 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.53 (t, *J* = 3.4 Hz, 1H), 6.11 (s, 1H), 5.57 (dddd, *J* = 16.9, 10.1, 7.7, 6.9 Hz, 1H), 5.23 – 5.12 (m, 2H), 5.03 (dd, *J* = 13.3, 11.0 Hz, 1H), 4.74 (dd, *J* = 13.3, 4.5 Hz, 1H), 4.20 (dd, *J* = 10.9, 4.5 Hz, 1H), 2.89 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.32 (dd, *J* = 13.7, 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 157.2, 132.8, 129.3, 129.2, 129.1, 128.9, 124.8, 122.6, 119.7, 119.2, 116.3, 75.3, 67.4, 52.4, 43.6. UPLC-DAD-QTOF: $C_{22}H_{20}N_3O_4$ [M+H]+ calcd.: 340.1292, found: 340.1290.

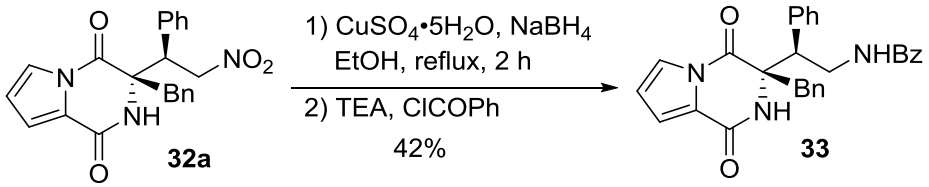
***(S)*-3-Hexyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32d)**



Colourless solid. Yield: 34 mg, 0.088 mmol, 88%. m.p.= 60-65 °C. $[\alpha]_D^{21}$= -37.6. (c=1, CH_2Cl_2). *dr* 92:8, 75% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.49 (s, 1H), 7.35 – 7.17 (m, 5H), 6.95 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.50 (t, *J* = 3.3 Hz, 1H), 5.07 (dd, *J* = 13.3, 10.9 Hz, 1H), 4.84 (dd, *J* = 13.5, 4.6 Hz, 1H), 4.11 (dd, *J* = 10.9, 4.5 Hz, 1H), 2.34 – 2.18 (m, 1H), 1.63 (td, *J* = 12.9, 12.5, 3.8 Hz, 1H), 1.36 – 1.04 (m, 8H), 0.80 (d, *J* = 7.1 Hz, 3H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 166.0, 157.3, 133.0, 129.5, 129.2, 129.1, 128.8, 127.2, 124.8, 119.6, 119.1, 116.3, 75.4, 67.9, 53.3, 39.2, 31.5, 29.0, 23.9, 22.5, 14.0. UPLC-DAD-QTOF: $C_{21}H_{26}N_3O_4$ [M+H]+ calcd.: 384.1923, found: 384.1923. $C_{21}H_{25}N_3O_4Na$ [M+Na]+ calcd.: 406.1743, found: 406.1738.

6.4.8.2. Reduction of the nitro in 32a and protection of the primary amine



Step 1:[250] The diketopiperazine **4aa** (0.1 mmol) was dissolved in ethanol (0.5 mL) and a solution of $CuSO_4$ (0.5 mL, 2M aqueous solution, 10 mol %) was added. After the reaction mixture was cooled to 0 °C, $NaBH_4$ (0.5 mmol, 5 equiv.) was added portionwise and the reaction mixture was stirred at reflux. After 2 hours the reaction mixture was diluted with EtOAc and the organic layer washed with water, dried over $MgSO_4$, filtrated and evaporated under vacuum. The crude was used in the next step without any purification.

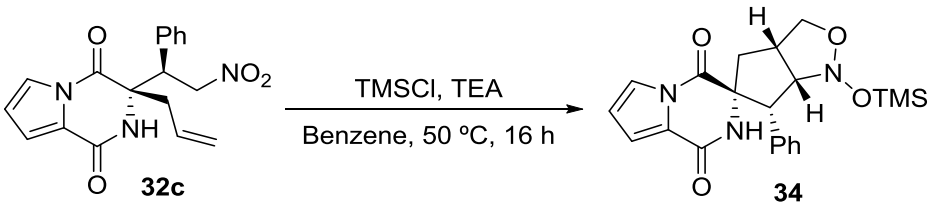
Step 2:[251] To a solution of the resulting amine (0.1 mmol) and Et_3N (0.11 mmol, 1.1 equiv.) in CH_2Cl_2 (1 mL) was added benzoyl chloride (1.1 equiv.) dropwise and the reaction was left stirring overnight. The reaction was quenched with water and extracted with CH_2Cl_2, dried over $MgSO_4$, filtrated and evaporated under vacuum. The crude product was purified by flash column chromatography (eluting with Hexane/EtOAc 95/5 to 70/30) to afford an orange foam. $[\alpha]_D^{21}$= -21.76 (c=1, CH_2Cl_2). Yield: 19.5 mg, 0.042 mmol, 42% (2 steps).

***N*-((*S*)-2-((*S*)-3-benzyl-1,4-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-yl)-2-phenylethyl)benzamide (33).** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 8.07 – 7.99 (m, 3H), 7.61 – 7.49 (m, 1H), 7.38 (td, *J* = 7.4, 4.7 Hz, 2H), 7.32 – 7.18 (m, 7H), 7.15 – 7.03 (m,

[250] Yoo, S.-E.; Lee, S.-H. *Synlett* **1990**, 419-420.
[251] Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246-4247.

2H), 6.76 (td, *J* = 2.7, 1.2 Hz, 1H), 6.17 (dq, *J* = 2.7, 1.5 Hz, 1H), 5.97 (q, *J* = 2.7 Hz, 1H), 5.90 (s, 1H), 3.95 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.78 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.72 (d, *J* = 7.6 Hz, 1H), 3.34 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 163.9, 161.0, 138.1, 134.7, 134.5, 133.5, 131.0, 130.5, 130.2, 128.8, 128.7, 128.6, 128.5, 128.5, 127.7, 126.6, 125.1, 122.2, 110.2, 109.8, 63.1, 53.0, 46.5, 42.1. UPLC-DAD-QTOF: $C_{29}H_{26}N_3O_3$ [M+H]+ calcd.: 464.1969, found: 464. 1969. $C_{29}H_{25}N_3O_3Na$ [M+Na]+ calcd.: 486.1788, found: 486.1796.

6.4.9.3. Preparation of spiro compound 6 by intramolecular silyl nitronate olefin cycloaddition (ISOC) of 4fa.[252]



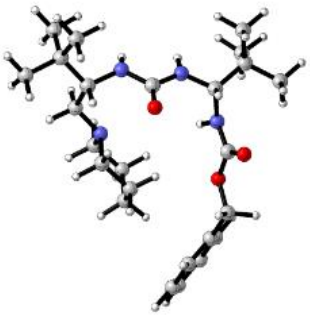
To a solution of the pyrrolo diketopiperazine **32c** (102 mg, 0.3 mmol, 1 equiv.) in benzene (2.5 mL) under inert atmosphere were added freshly distilled Et_3N (0.250 mL, 1.8 mmol, 6 equiv.) and freshly distilled TMSCl (0.190 mL, 1.5 mmol, 5 equiv.). After addition was complete the mixture was warmed to 50 °C and stirred for 16 hours. Afterwards, the reaction mixture was cooled 0 °C, quenched with water (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combination of organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with Hexane/EtOAc 50/50 to 20/80) to produce the corresponding *N*-trimethylsilyloxyisoxazoline **34**. Yield: 104 mg, 0.25 mmol, 84%. m.p.= 151-154 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 – 7.95 (m, 1H), 7.28 (dd, *J* = 3.2, 1.5 Hz, 1H), 7.21 – 7.07 (m, 5H), 6.83 (dd, *J* = 3.5, 1.4 Hz, 1H), 6.26 (t, *J* = 3.3 Hz, 1H), 4.65 (dd, *J* = 10.3, 8.4 Hz, 1H), 4.49 (dd, *J* = 8.6, 7.0 Hz, 1H), 3.83 (dd, *J* = 8.5, 1.4 Hz, 1H), 3.70 (dt, *J* = 15.8, 8.0 Hz, 1H), 3.27 (dd, *J* = 10.3, 1.8 Hz, 1H), 2.87 (dd, *J* = 13.4, 9.0 Hz, 1H), 1.97 (ddd, *J* = 13.7, 8.5, 1.7 Hz, 1H), -0.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.7, 157.7, 134.0, 128.6, 128.1, 128.0, 125.0, 119.1, 118.3, 115.5, 82.6, 73.4, 73.0, 60.9, 44.3, 41.9, -0.7.

[252] Hassner, A.; Friedman, O.; Dehaen, W. *Liebigs Ann./Recueil* **1997**, 587-594.

UPLC-DAD-QTOF: $C_{29}H_{26}N_3O_3$ [M+H]+ calcd.: 412.1687, found: 412.1697. $C_{29}H_{25}N_3O_3Na$ [M+Na]+ calcd.: 434.1507, found: 434.1516.

6.4.10. Theoretical calculations

Catalyst **C15** structure was optimized using density functional theory (DFT) as implemented in Gaussian 16,[253] with B3LYP[254] as functional and 6-311G(d,p) as basis set, introducing solvation factors with the IEF-PCM[255] method (toluene as solvent). The stationary point of **C15** was characterized by frequency calculations, verifying that it did not contain any imaginary frequency. The electronic energy of the minimized structure was -1423.174659 Hartrees.



Standard orientation

Center Atomic Atomic Coordinates (Angstroms)

[253] Gaussian 16, Revision A.03, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2016.**

[254] a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* 1988, **37**, 785-789; b) A. D. Becke, *J. Chem. Phys*. 1993, **98**, 5648-5652; c) W. Khon, A. D. Becke, G. R. Parr, *J. Phys. Chem*. 1996, **100**, 12974-12980.

[255] a) E. Cances, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, **1997**, *107*, 3032-3041; b) M.Cossi, V. Barone, B. Mennucci and J. Tomasi, *Chem. Phys. Lett.*, **1998**, *286*, 253-260; c) J. Tomasi, B. Mennucci and E. Cances, *J. Mol.Struc.: THEOCHEM*, **1999**, *464*, 211-226.

Number	Number	Type	X	Y	Z
1	8	0	2.504933	-1.210033	-0.255259
2	6	0	1.534376	-2.068396	-0.670827
3	8	0	1.562579	-2.670517	-1.723543
4	7	0	0.559801	-2.156093	0.275593
5	1	0	0.595491	-1.470901	1.015444
6	6	0	-0.764903	-2.710653	-0.047809
7	1	0	-0.803137	-2.788325	-1.134651
8	6	0	-0.985307	-4.125426	0.558637
9	6	0	-2.342582	-4.664173	0.074027
10	6	0	-0.947236	-4.086025	2.096787
11	6	0	0.136337	-5.050252	0.053766
12	1	0	-3.170929	-4.039219	0.414556
13	1	0	-2.377793	-4.701765	-1.018730
14	1	0	-2.502512	-5.677975	0.451238
15	1	0	-1.782356	-3.520685	2.524037
16	1	0	-1.017390	-5.100143	2.498745
17	1	0	-0.011815	-3.648263	2.455018
18	1	0	0.188034	-5.047954	-1.037018
19	1	0	1.109964	-4.733241	0.432304

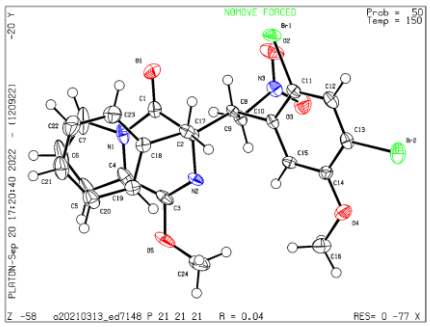
20	1	0	-0.044582	-6.073937	0.392845
21	7	0	-1.794117	-1.785973	0.363710
22	1	0	-2.131190	-1.846530	1.310948
23	7	0	-3.025901	0.167156	0.185510
24	1	0	-3.182406	0.041275	1.175210
25	6	0	3.597218	-1.004481	-1.181551
26	1	0	4.166277	-1.935629	-1.260435
27	1	0	3.196051	-0.769748	-2.168292
28	6	0	4.439895	0.119097	-0.645139
29	6	0	4.955492	0.055436	0.653570
30	6	0	4.707435	1.242952	-1.427159
31	6	0	5.719547	1.101340	1.161616
32	1	0	4.738071	-0.810376	1.268891
33	6	0	5.480395	2.289004	-0.923794
34	1	0	4.298968	1.306843	-2.429965
35	6	0	5.984923	2.221736	0.372417
36	1	0	6.108223	1.045142	2.172239
37	1	0	5.677032	3.158964	-1.540021
38	1	0	6.578741	3.037673	0.768537

39	6	0	-2.089671	-0.663871	-0.389732
40	6	0	-4.694012	1.918212	-0.427033
41	6	0	-5.431969	1.828757	0.921372
42	6	0	-5.344635	0.938910	-1.422476
43	6	0	-4.828539	3.346324	-0.989778
44	1	0	-4.236208	3.466360	-1.902247
45	1	0	-5.873128	3.552588	-1.239838
46	1	0	-4.506834	4.105968	-0.274005
47	1	0	-4.859659	0.998033	-2.401395
48	1	0	-5.262798	-0.090905	-1.070532
49	1	0	-6.404380	1.176702	-1.553584
50	1	0	-5.388947	0.816500	1.333929
51	1	0	-5.022076	2.521865	1.661010
52	1	0	-6.488307	2.079340	0.788910
53	8	0	-1.597698	-0.476612	-1.494285
54	6	0	-2.355815	2.491371	0.598841
55	1	0	-2.754352	2.454791	1.617951
56	1	0	-2.474140	3.530111	0.249987
57	6	0	-0.230835	2.444191	-0.581367

58	6	0	-0.281964	2.704704	1.827664
59	6	0	1.219389	1.965446	-0.535822
60	1	0	-0.257674	3.538644	-0.758444
61	1	0	-0.739151	1.956627	-1.412988
62	6	0	1.162542	2.216616	1.954155
63	1	0	-0.285010	3.812309	1.770091
64	1	0	-0.851757	2.430599	2.721125
65	6	0	1.956107	2.528441	0.681934
66	1	0	1.725779	2.254879	-1.461707
67	1	0	1.227133	0.874031	-0.493494
68	1	0	1.627894	2.679282	2.830537
69	1	0	1.156296	1.133090	2.121722
70	1	0	2.965925	2.118958	0.743868
71	1	0	2.055861	3.616987	0.578094
72	7	0	-0.944779	2.114267	0.660974
73	1	0	-2.771435	1.547766	-1.296833
74	6	0	-3.186074	1.541084	-0.288778

6.4.11. X-Ray Crystallographic data of 3ae

Solvent System: Dichloromethane/*n*-Hexane; Crystallization Method: Slow evaporation of the solvent at room temperature.



X-ray structure of **20ag** with 50% thermal ellipsoids probability

Crystal data and structure refinement for 3ae: CCDC 2210448

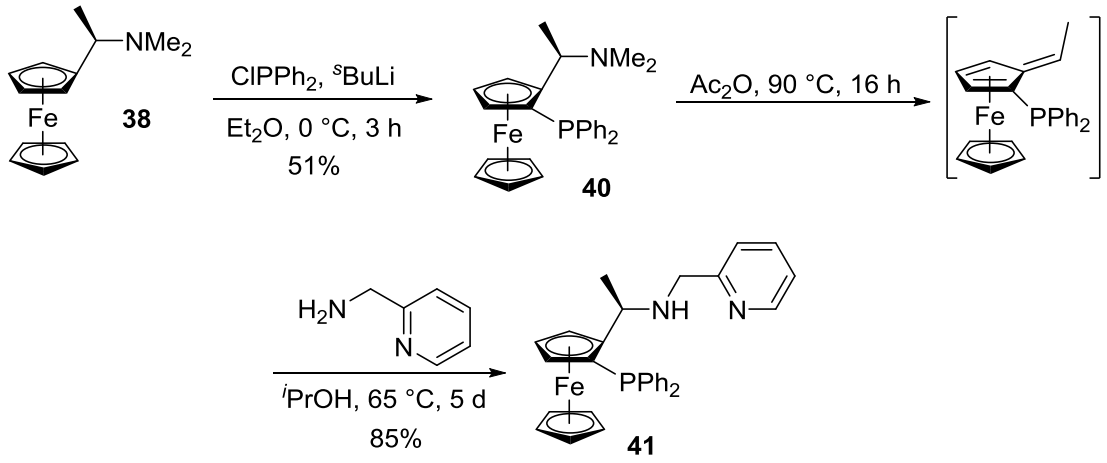
Empirical formula	$C_{24}H_{21}Br_2N_3O_5$
Formula weight	591.26
Temperature/K	149.93(16)
Crystal system	orthorhombic
Space group	P212121
a/Å	9.91489(13)
b/Å	14.37037(19)
c/Å	16.7111(2)
α/°	90.0
β/°	90.0
γ/°	90.0
Volume/Å$_3$	2381.01(5)
Z	4
ρ_{calc}g/cm$_3$	1.649
μ/mm^{-1}	4.672
F(000)	1184.0
Crystal size/mm$_3$	0.477 × 0.214 × 0.139
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.114 to 137.962
Index ranges	-12 ≤ h ≤ 12, -17 ≤ k ≤ 17, -17 ≤ l ≤ 20
Reflections collected	21755
Independent reflections	4409 [Rint = 0.0520, Rsigma = 0.0371]
Data/restraints/parameters	4409/0/309
Goodness-of-fit on	F2 1.077
Final R indexes [I>=2 σ (I)]	R_1 = 0.0393, wR_2 = 0.0977
Final R indexes [all data]	R_1 = 0.0417, wR_2 = 0.0995
Largest diff. peak/hole /	e Å^{-3} 0.44/-0.52
Flack parameter	-0.042(13)
Bijvoet Pairs Covarage	100%

Hooft y -0.044(9)
P3 false ≤10^{-99}

6.5. Experimental section of Chapter 4

6.5.1. Synthesis of Mn(I) complexes

6.5.1.1. Preparation of the ligand

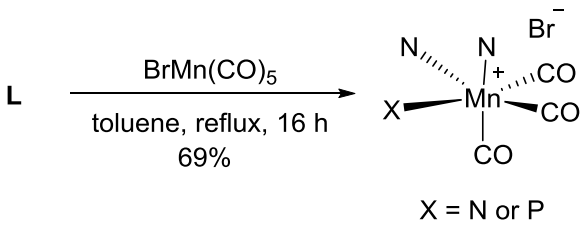


Step 1: To a solution of (*R*)-(+)-*N,N*-dimethyl-1-ferrocenylethylamine **38** (771 mg, 3 mmol) in 5 mL of dry ether at 0 °C *sec*-butyllithium 1.4M (2.7 mL, 3.75 mmol, 1.25 equiv.) and chlorodiphenylphosphine **39** (1.1 mL, 6 mmol, 2 equiv.) in 2 mL of ether were slowly added. The mixture was stirred at the same temperature for 3 h. Then, sodium bicarbonate was added with cooling in an ice-bath. The layers were separated and the aqueous phase was extracted with ether (2 x 10 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, filtrated and concentrated under reduced pressure to afford a red oil. The crude product was purified by flash column chromatography eluting Hex:EtOAc 4:1.

Step 2: To the (S_c, R_p)-N,N-dimethyl-1-[2-(diphenylphosphino)ferrocenyl] ethylamine (209 mg, 0.47 mmol) was added degassed acetic anhydride (152 µL, 1.59 mmol, 3.4 equiv.). The reaction mixture was heated to 90 °C and the solution eventually became homogeneous. The mixture was held at the reaction temperature overnight. The solution was cooled to room temperature and isopropanol (0.55 mL) was added. To

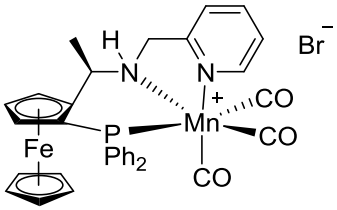
this solution, 2-picolylamine (0.98 mL, 9.55 mmol, 20 equiv.) in isopropanol (0.3 mL) was added and the reaction mixture was heated at 65 °C for 5 days, under argon atmosphere. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography (EtOAc:Hexane, 50:50, Et_3N deactivated silica) to give an orange oil (214 mg, 0.4 mmol, 85%). All the spectroscopic data were coincident with those previously reported. ^{1}H NMR ($CDCl_3$) δ: 8.31 (d, *J* = 4.9, 1H), 7.59-7.48 (m, 2H), 7.43-7.26 (m, 5H), 7.26-7.21 (m, 2H), 7.18-7.11 (m, 3H), 7.03-6.94 (m, 1H), 6.55 (d, *J* = 7.8, 1H), 4.55 (brs, 1H), 4.32 (t, *J* = 2.5, 1H), 4.26-4.17 (m, 1H), 4.02 (s, 5H), 3.83 (s, 1H), 3.64 (d, *J* = 2.1, 2H) and 1.57 (d, J = 6.0, 3H).

6.5.1.2. Complexation with Mn(I)



The ligand (0.3 mmol, 1.2 equiv.) was added to pentacarbonylbromomanganese(I) (69 mg, 0.25 mmol, 1.0 equiv.) at ambient temperature. Dry toluene (5 mL) was added and the mixture was heated to reflux and kept at that temperature for 16 h. The mixture was cooled to ambient temperature and concentrated to dryness. The crude material was dissolved in methylene chloride, filtered to remove insoluble material and the product precipitated by addition of *n*-hexane, collected by filtration and washed with *n*-hexane and to give the desired product.

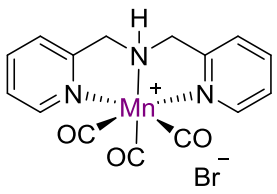
Manganese complex C20



The title compound was synthesized starting from *N*-2-Picolyl (S_c, R_p)-1-(-2-diphenylphosphino) ferrocenylethylamine (160 mg, 0.3 mmol, 1.2 equiv.). Orange powder. Yield: 203 mg, 0.28 mmol, 69%. All the spectroscopic data were coincident with those previously reported. ^{1}H NMR (600 MHz, Acetone-d_6) δ: 8.50 (brs, 1H), 8.02 (m, 2H), 7.79-7.28 (m, 4H), 6.97 (m, 4H), 6.77 (m, 3H),

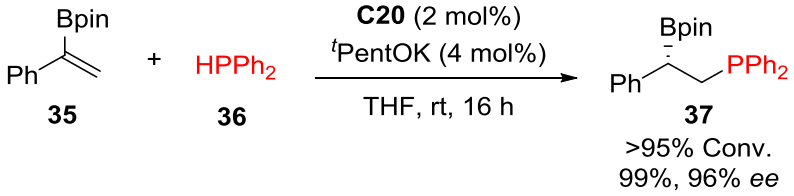
5.57 (brs, 1H), 4.97 (brs, 1H), 4.80 (brs, 1H), 4.58 (brs, 1H), 4.48 (brs, 1H), 4.30 (m, 1H), 3.85 (brs, 5H), 3.72 (m, 1H), 1.78 (brs, 3H).

Manganese complex C18



The title compound was synthesized starting from di-(2-picolyl)amine **42** (54 µL, 0.3 mmol, 1.2 equiv.). Yellow powder. Yield: 110 mg, 0.26 mmol, 88%.

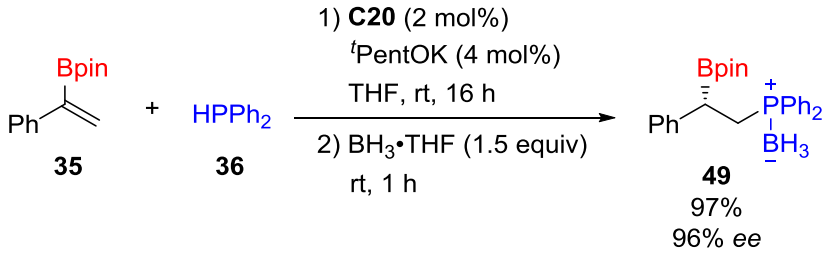
6.5.2. Hydrophosphination reaction



In the glovebox, in an oven-dried 4 mL vial equipped with a magnetic stirring bar, the (R_C, S_P)-Clarke catalyst (2 mol%, 1.5 mg) was added and it was dissolved in 1 mL of dry, deoxygenated toluene and stirred for 5 min. Then, a commercially available solution of ^{t}PentOK (1.7 M solution in toluene, 4 mol%) was added and the mixture was stirred for 1 min. When toluene is used as solvent and tPentOK as base, a color change of the solution from yellow to dark red is observed. This color change is indicative of the catalyst activation. After 5 min stirring, the α,β-unsaturated boronic ester (0.1 mmol, 1.0 equiv) was added at once, followed by the addition of Ph_2PH (17 µL, 0.1 mmol, 1.0 equiv.). The reaction was monitored by analysing aliquots of the reaction mixture by ^{1}H NMR and ^{31}P NMR spectroscopy. Upon reaction completion, EtOAc (2 mL) was added to the reaction and the resulting mixture was filtered through a plug of alumina in order to remove the catalyst.

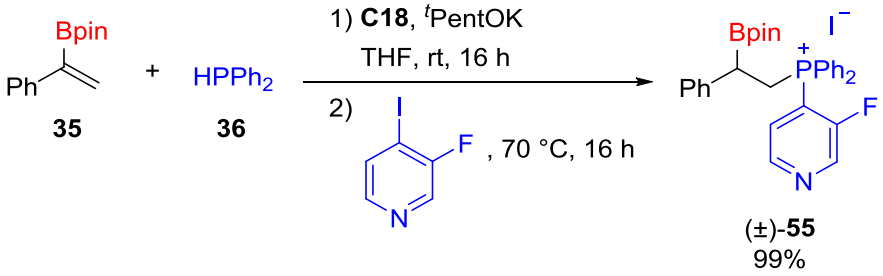
6.5.3. Phosphine protection

6.5.3.1. Synthesis of borane-protected phosphine



Inside the glovebox, once the asymmetric hydrophosphination is over, the reaction mixture is moved to an oven dried Schlenk tube equipped with septum and stirring bar, is taken out of the glovebox and connected to the nitrogen line. BH_3-THF (1M solution in THF, 3 mL, 3 mmol, 1.5 equiv.) was then added. The reaction mixture was stirred for 1 h and the solvent was removed in vacuo. Flash column chromatography (Hex/AcOEt 9:1) afforded **49** (588 mg,1.94 mmol 97%).

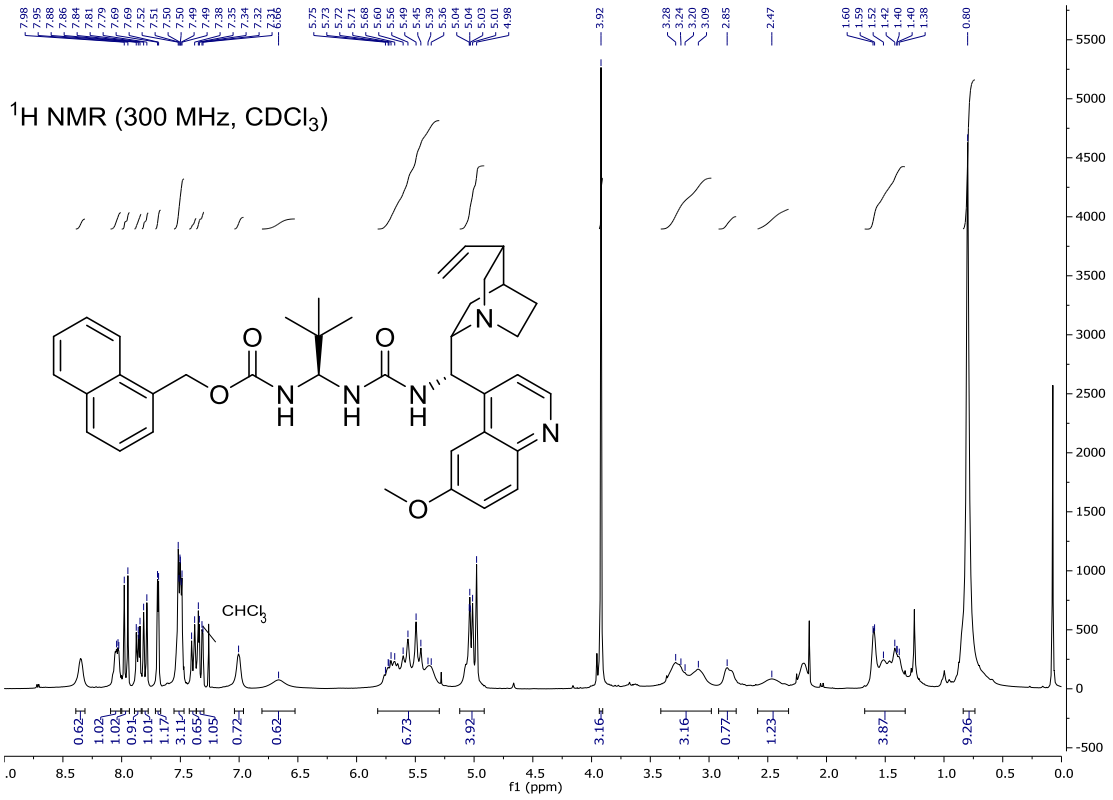
6.5.3.2. Protection as phosphonium salt

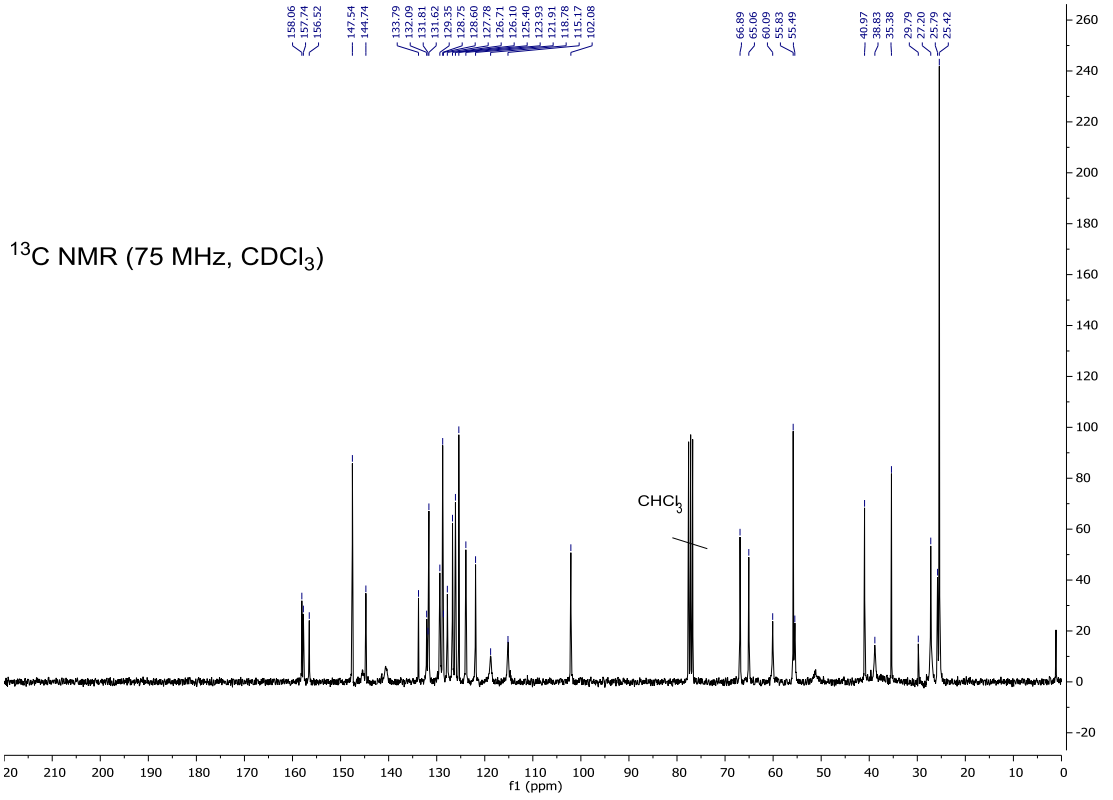


Inside the glovebox, once the asymmetric hydrophosphination is over, the reaction mixture is moved to an oven dried Schlenk tube equipped with septum and stirring bar, taken out of the glovebox and connected to the nitrogen line. BH_3-THF (446 mL, 2 mmol, 1.0 equiv.) was then added. The reaction mixture was stirred overnight at 70 °C and the solvent was removed in vacuo. Flash column chromatography (Hex/AcOEt 9:1) afforded **55** (588 mg,1.94 mmol 97%).

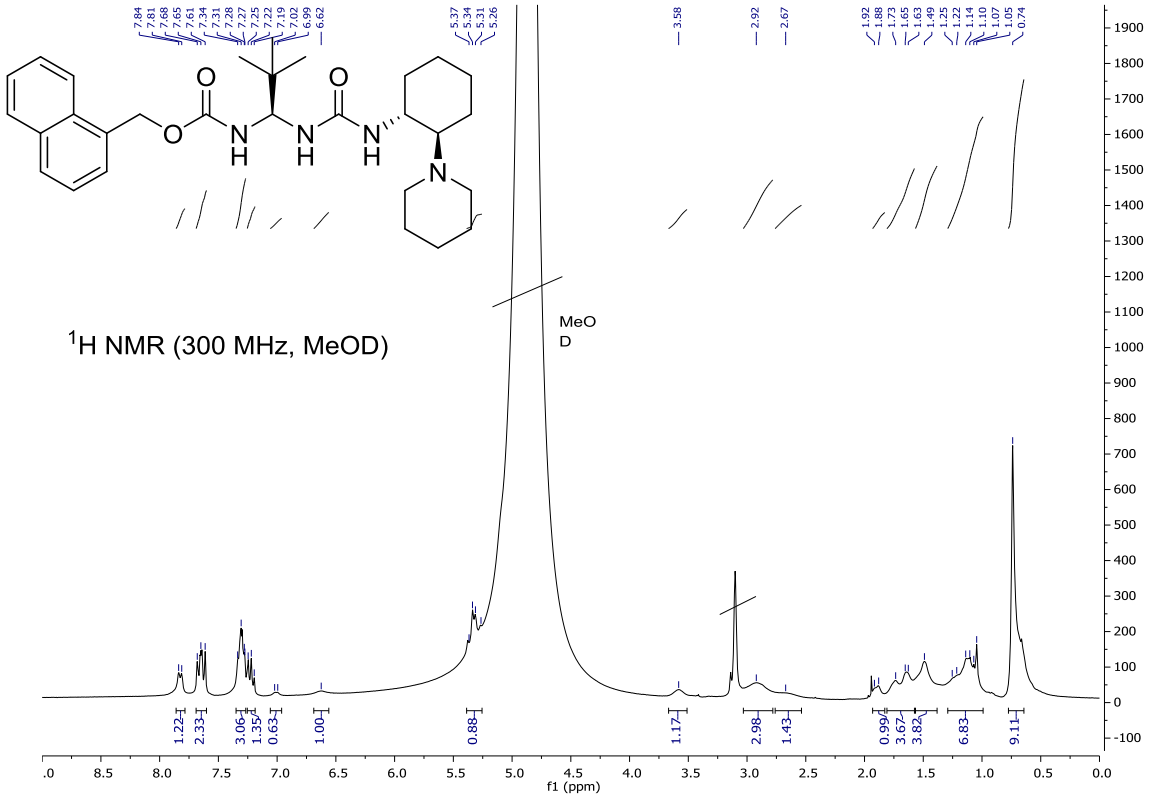
6.6. Representative NMR spectra

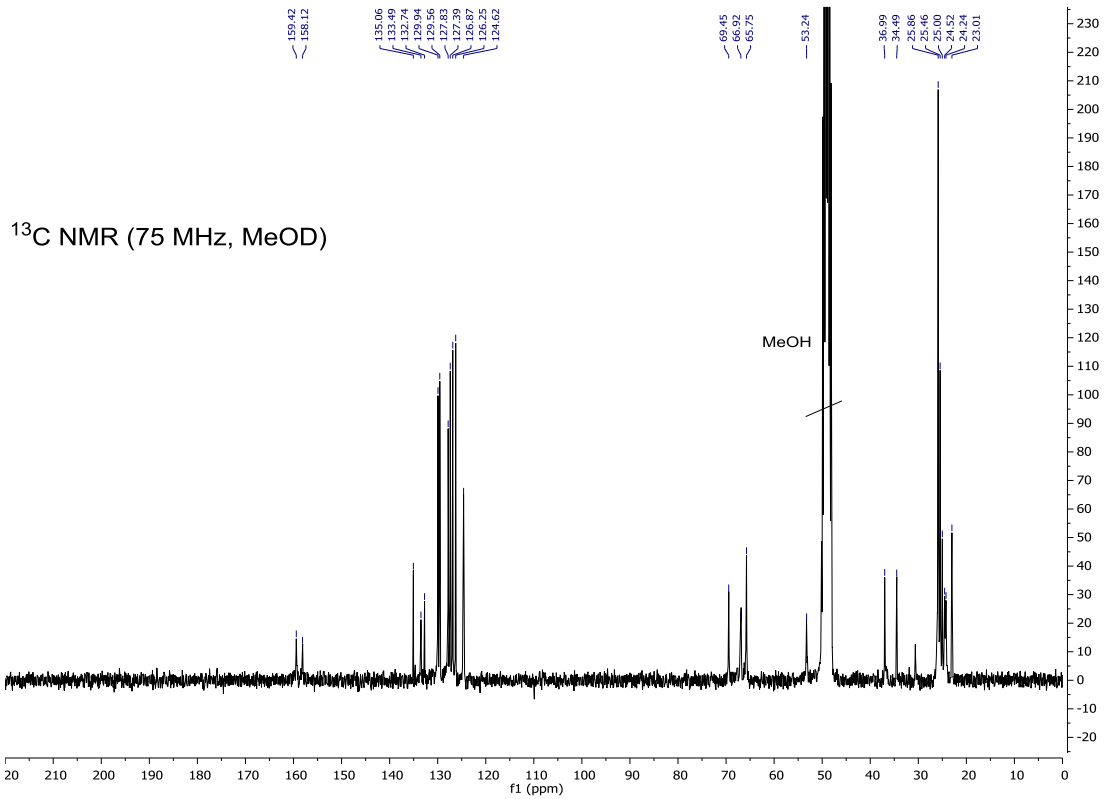
Naphthalen-1-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C9)



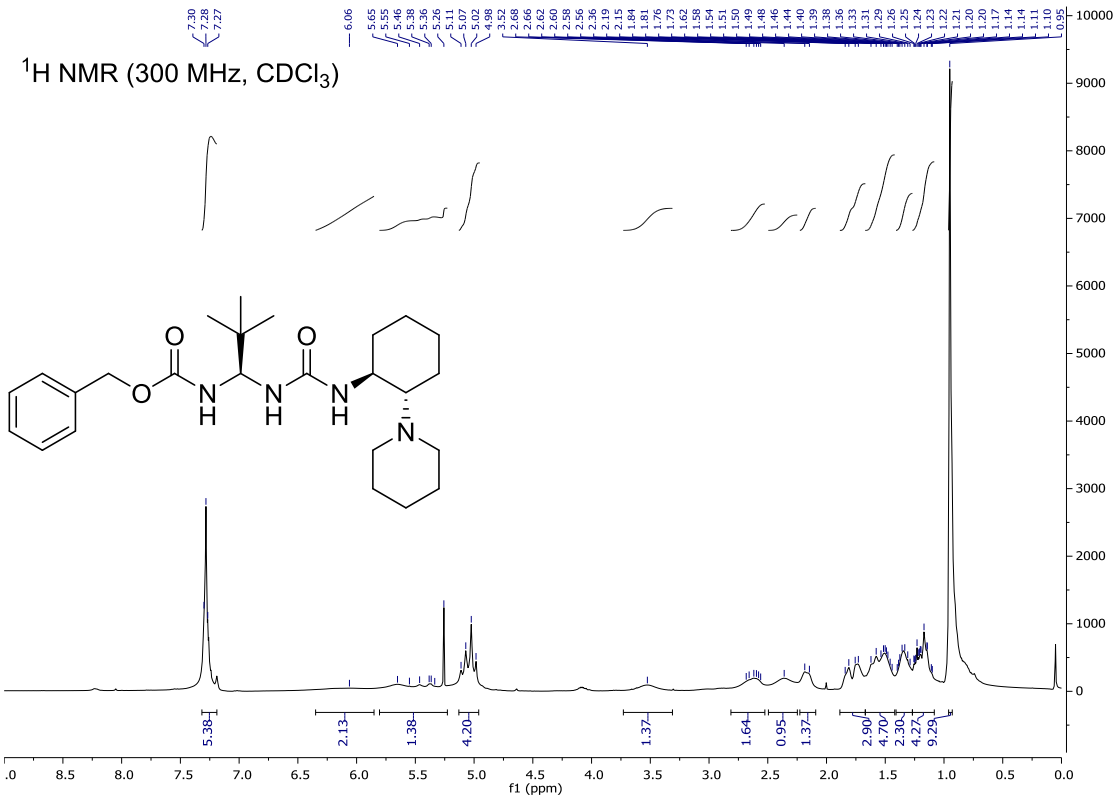


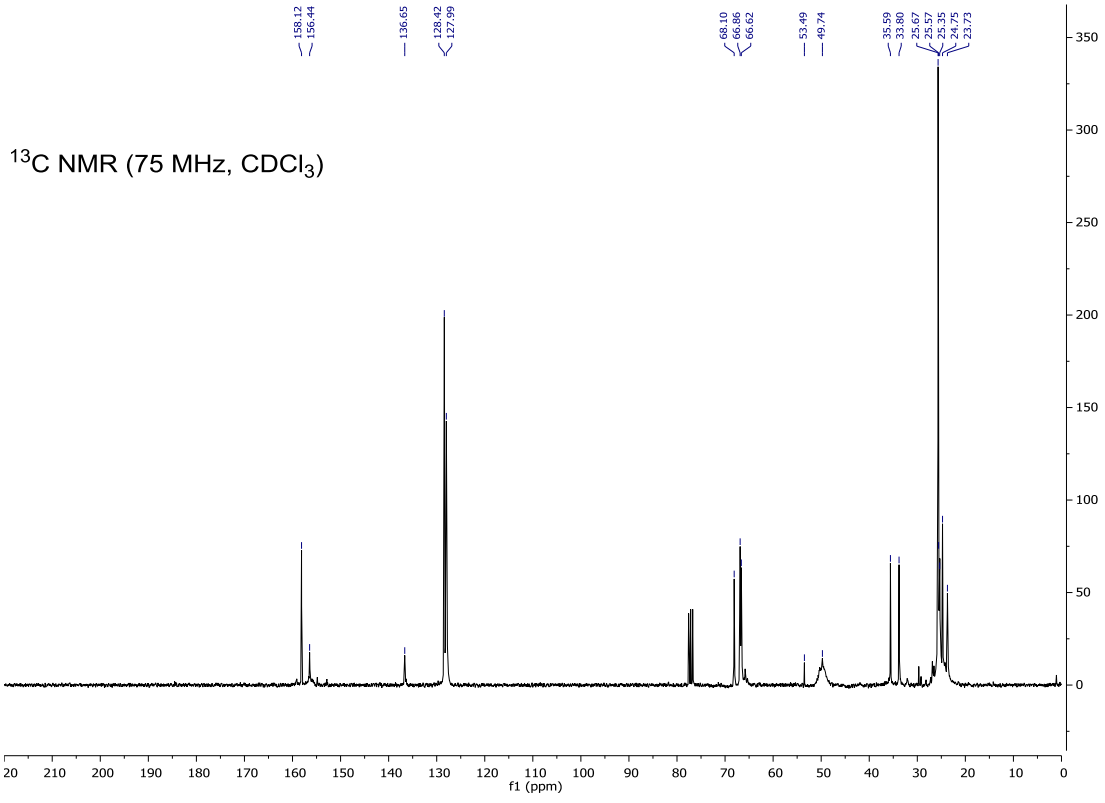
Naphthalen-1-ylmethyl ((*S*)-2,2-dimethyl-1-(3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (*diast*-C7)





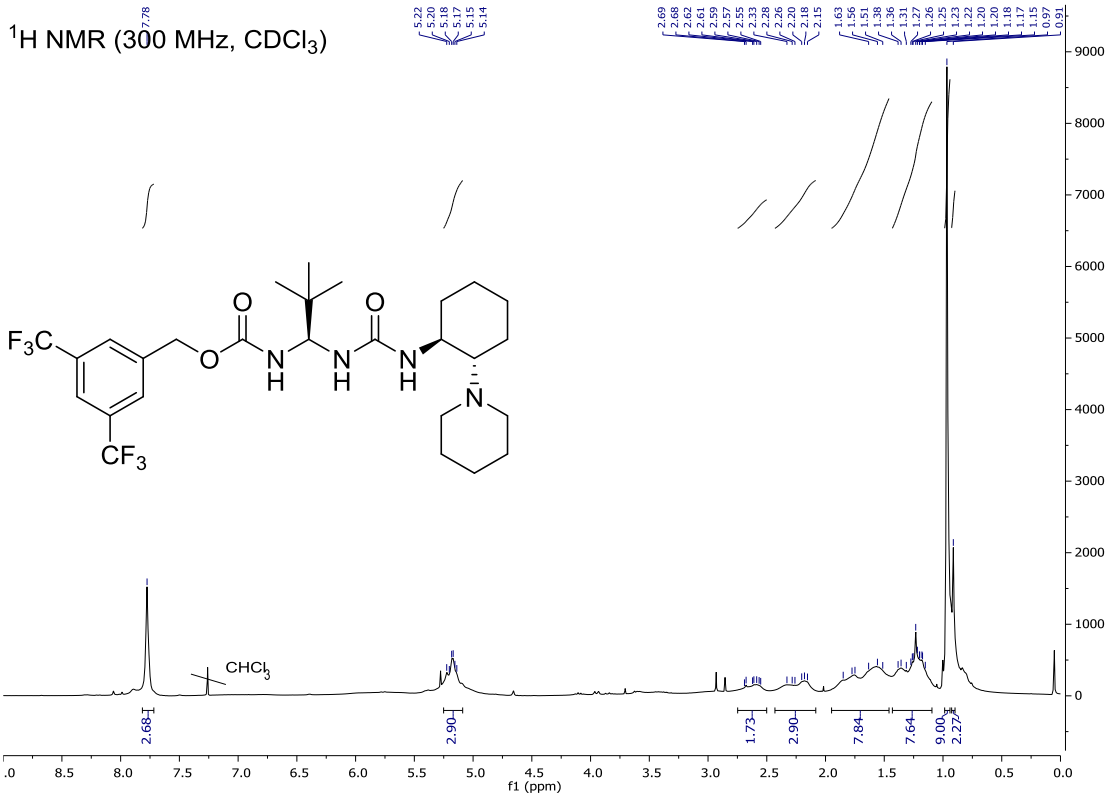
Benzyl ((*S*)-2,2-dimethyl-1-(3-((1*S*,2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C12)



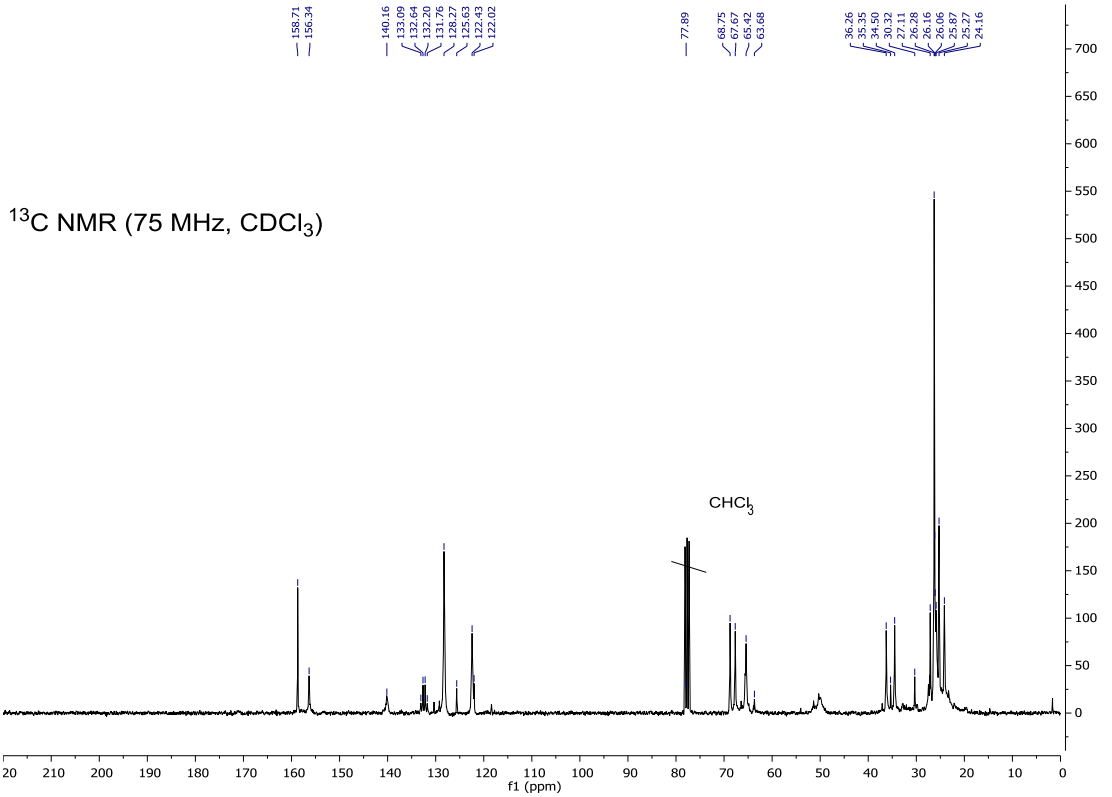


3,5-Bis(trifluoromethyl)benzyl ((1*S*)-2,2-dimethyl-1-(3-((2*S*)-2-(piperidin-1-yl)cyclohexyl)ureido)propyl)carbamate (C13)

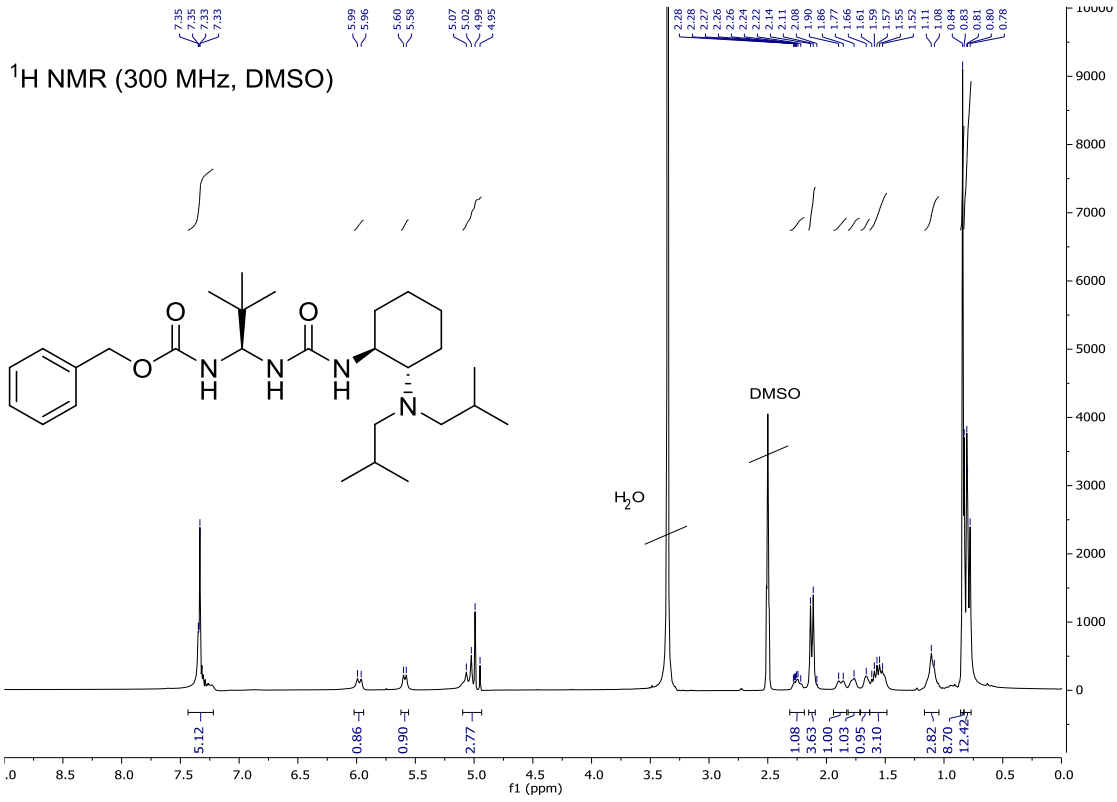
^{1}H NMR (300 MHz, $CDCl_3$)

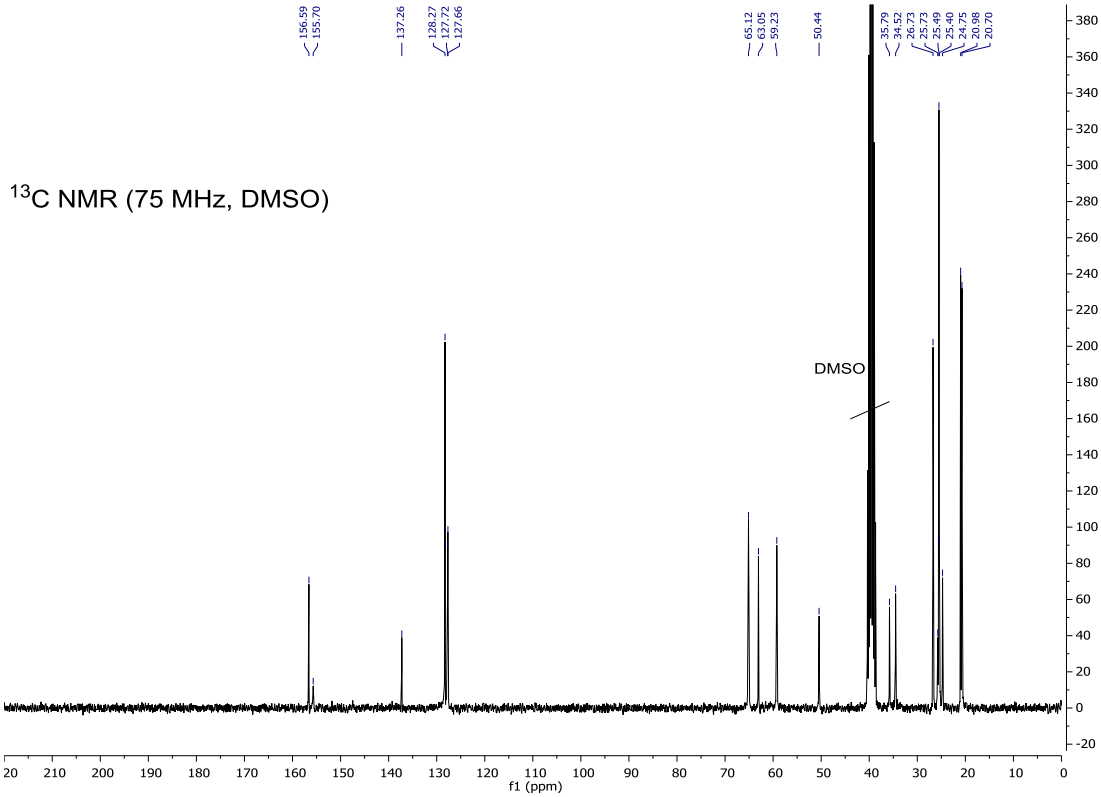


^{13}C NMR (75 MHz, $CDCl_3$)

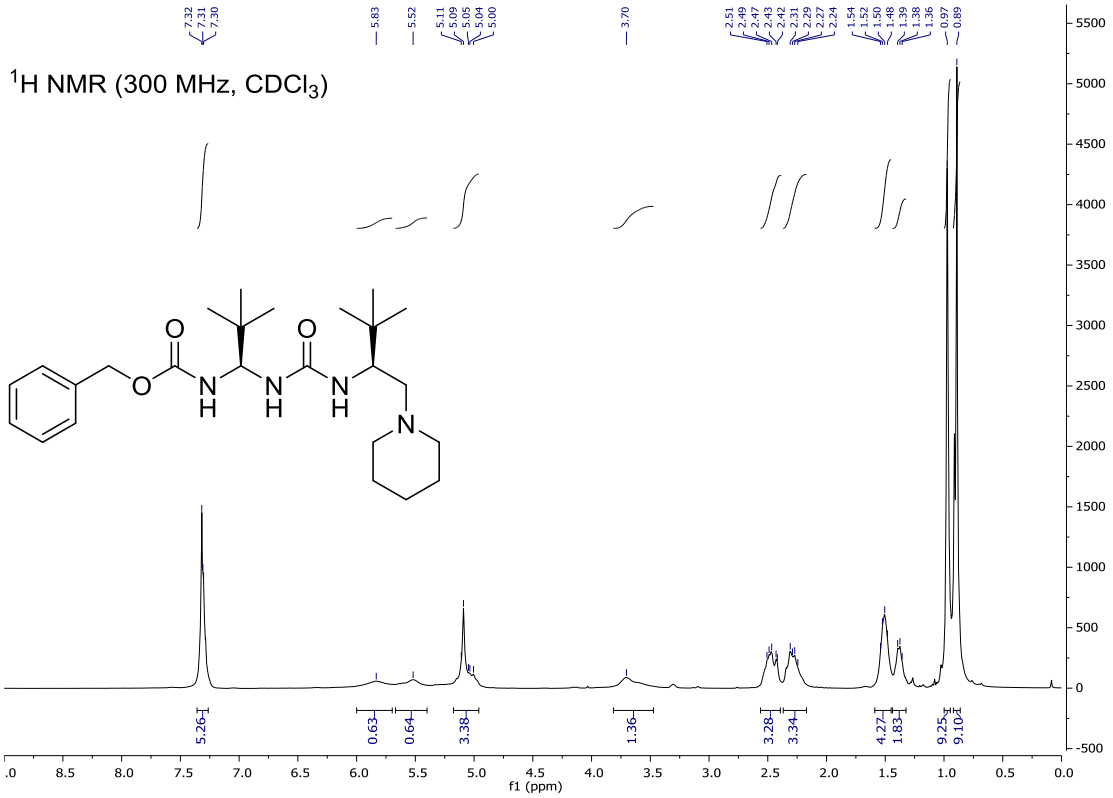


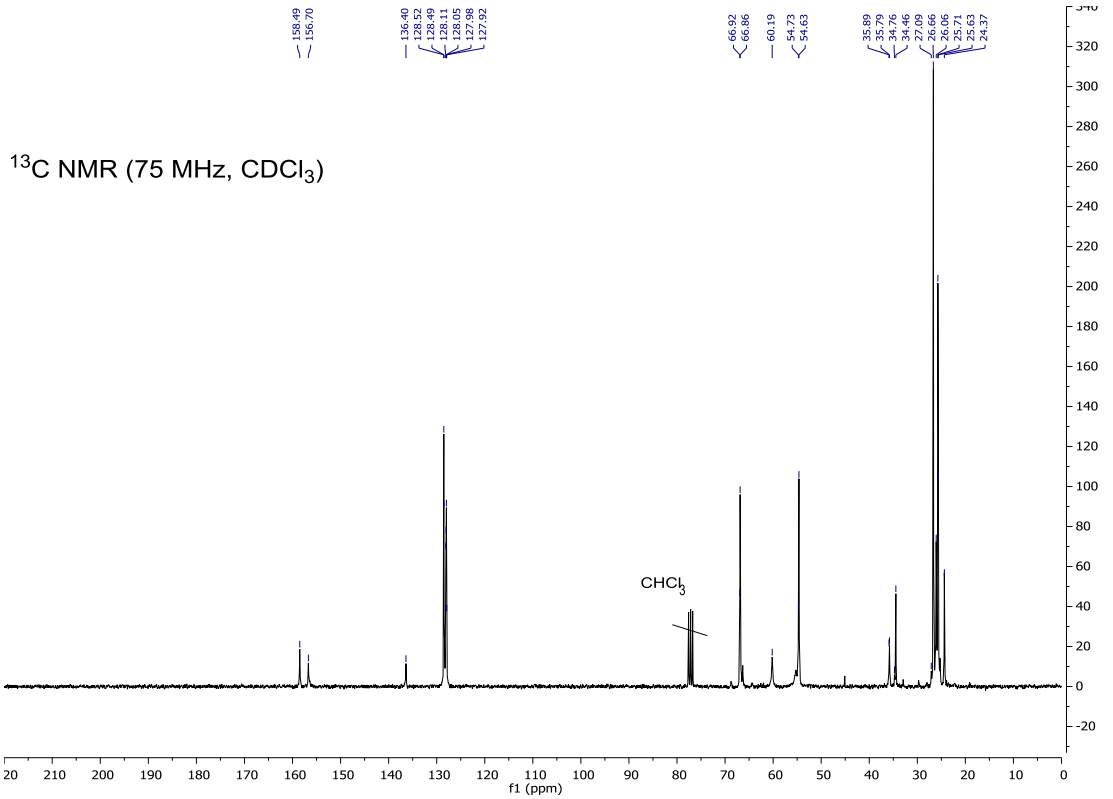
Benzyl ((*S*)-1-(3-((1*S*,2*S*)-2-(diisobutylamino)cyclohexyl)ureido)-2,2-dimethylpropyl)carbamate (C14)



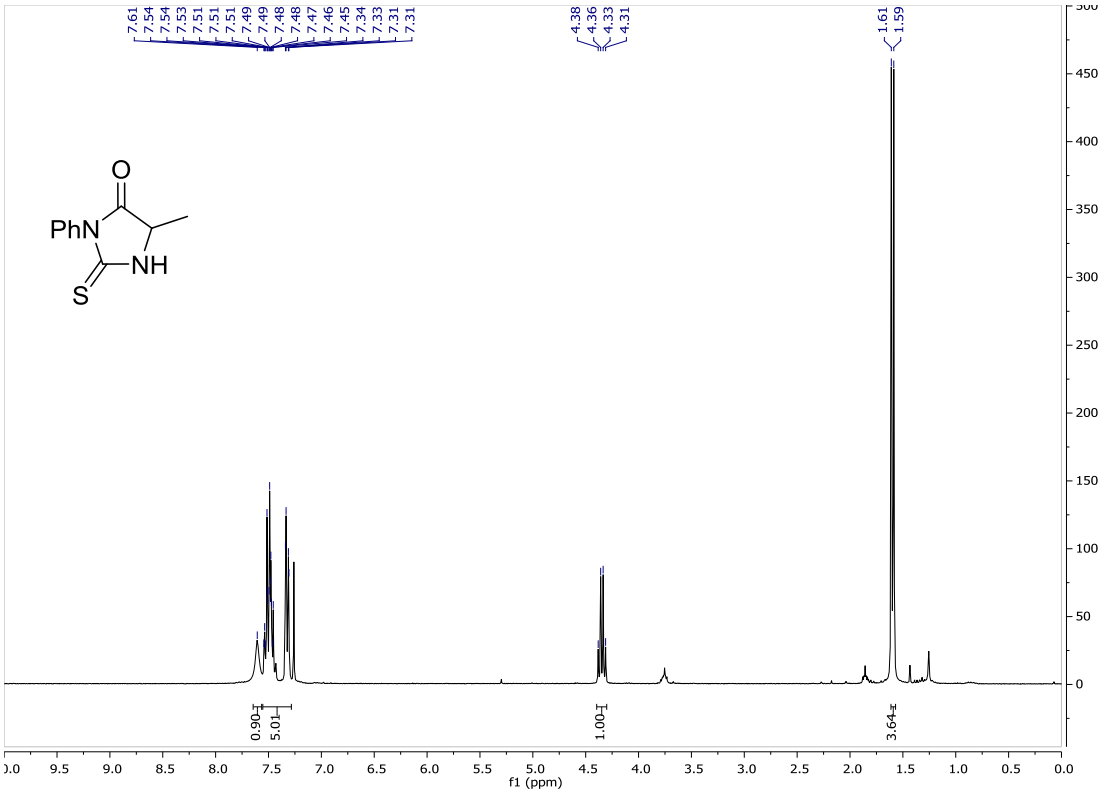


Benzyl ((*S*)-1-(3-((*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)ureido)-2,2-dimethylpropyl)carbamate (C15)

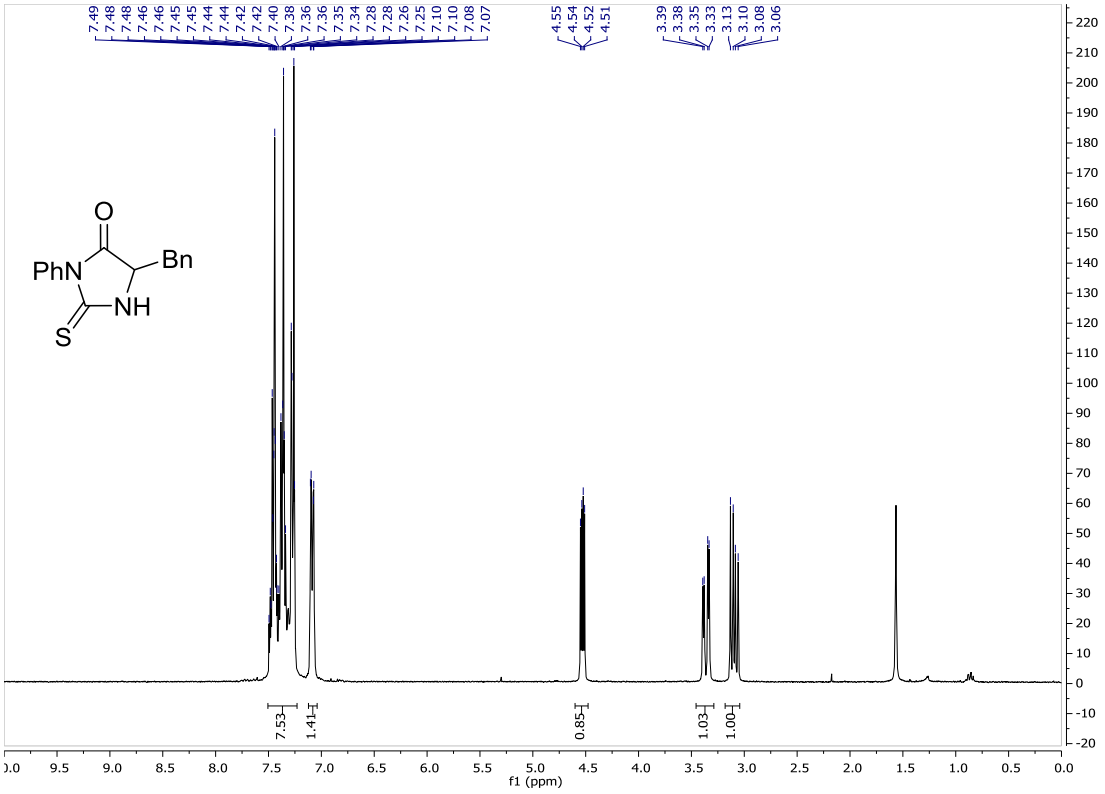




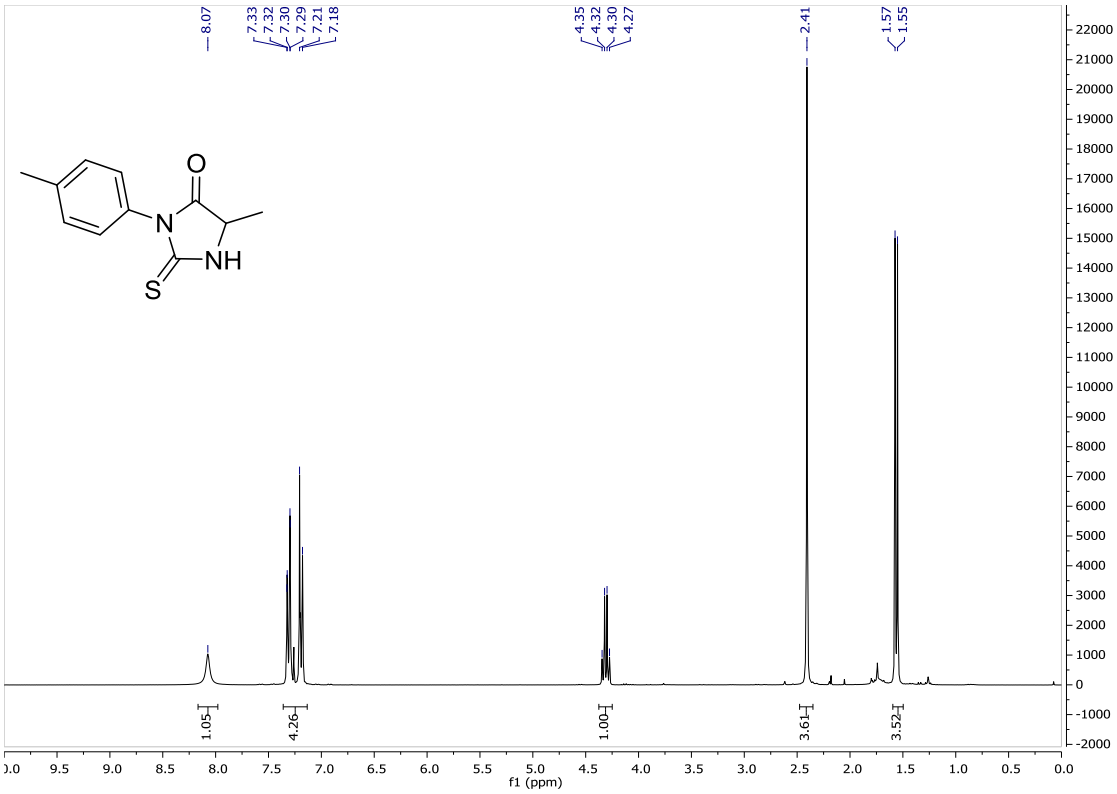
5-Methyl-3-phenyl-2-thioxoimidazolidin-4-one (1a)

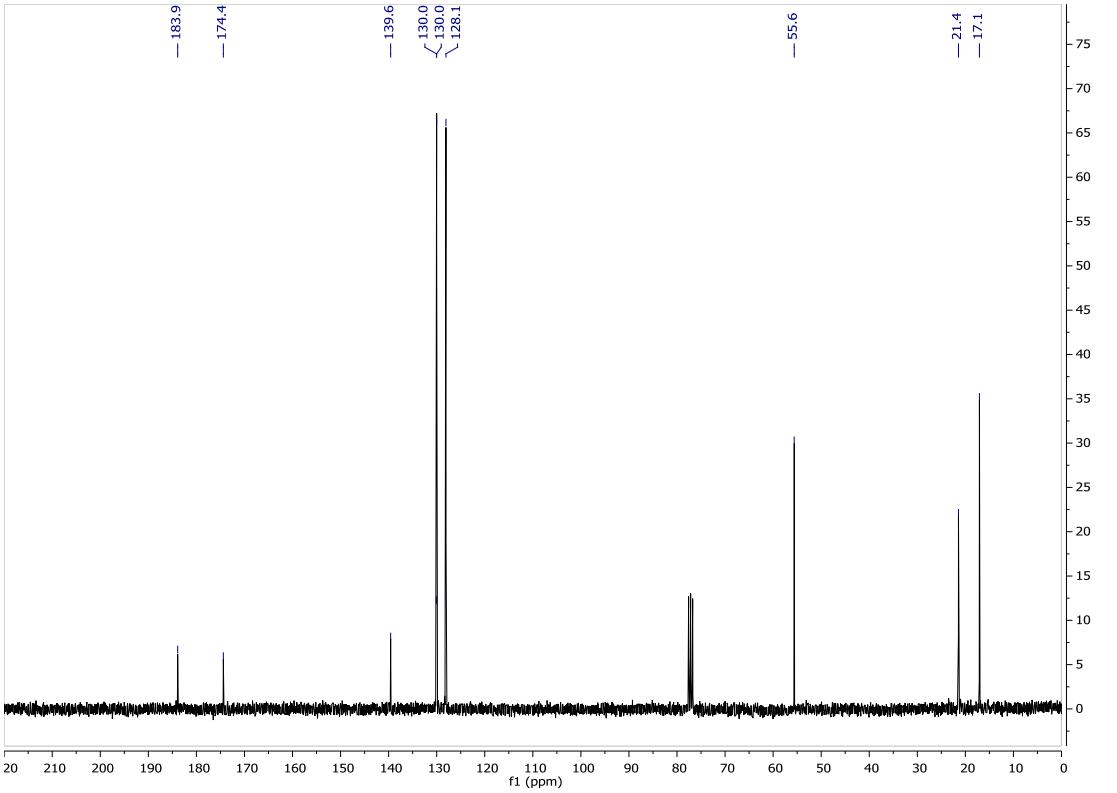


5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one (1f)

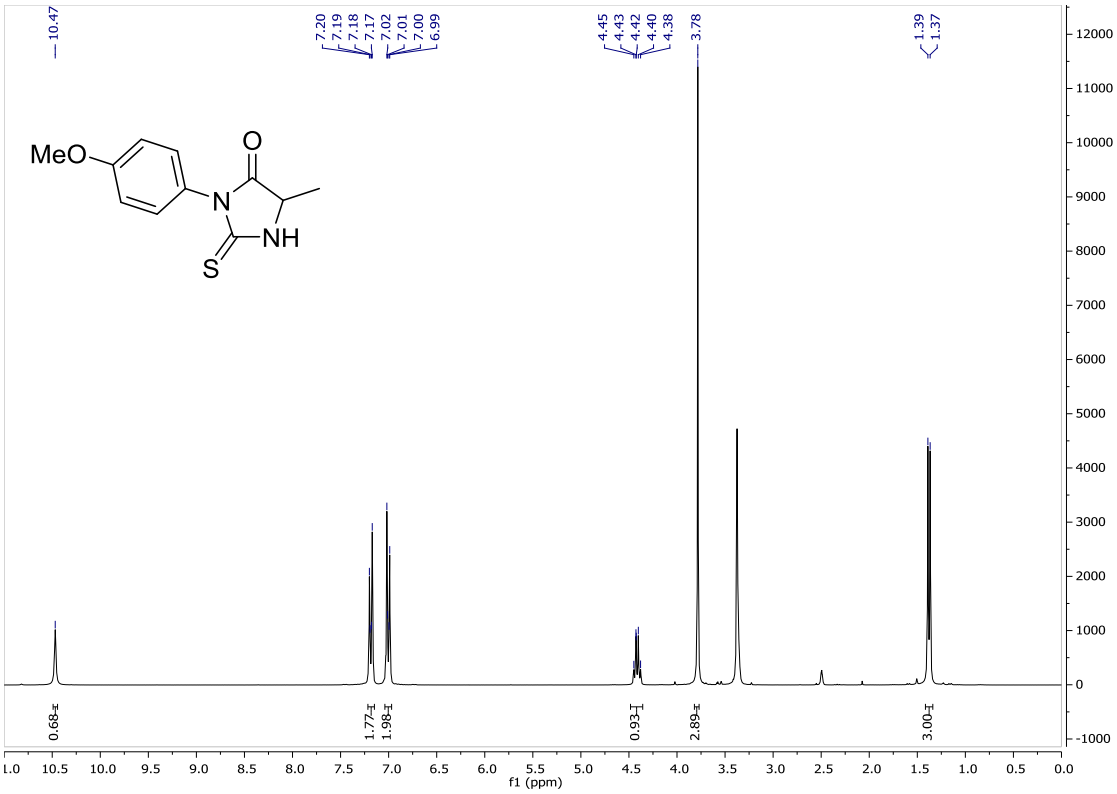


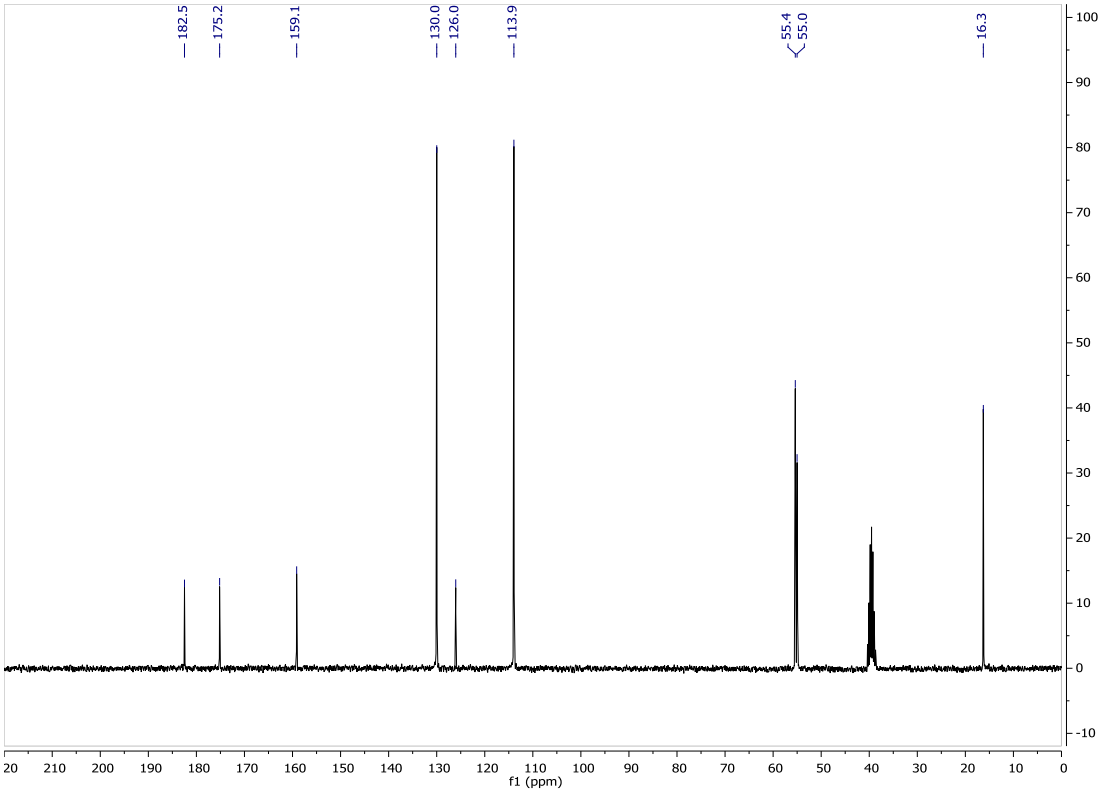
5-Methyl-2-thioxo-3-(p-tolyl)imidazolidin-4-one (1b)



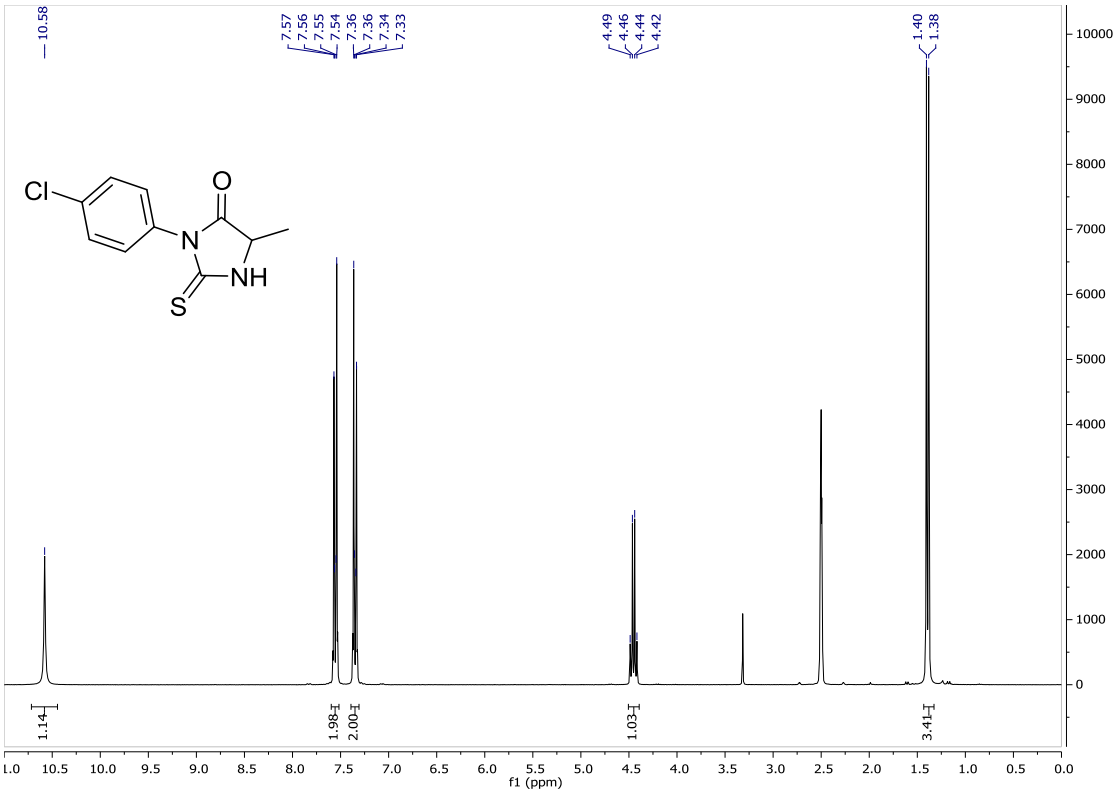


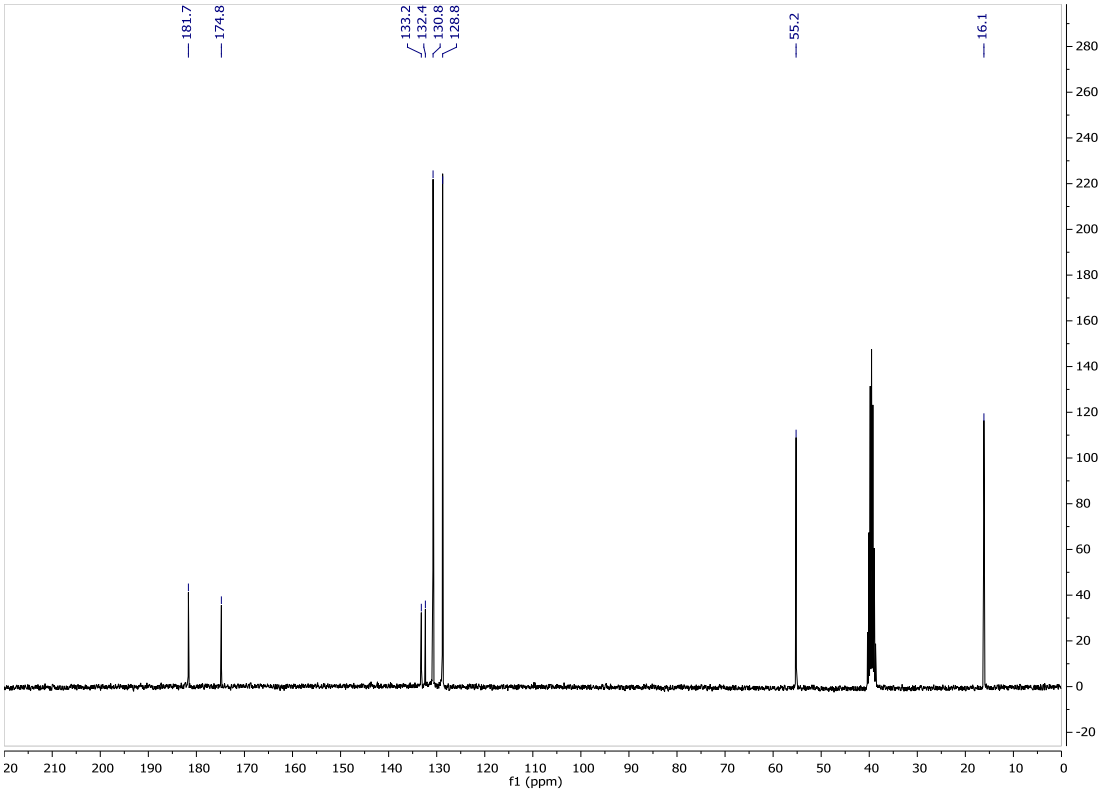
3-(4-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (1c)



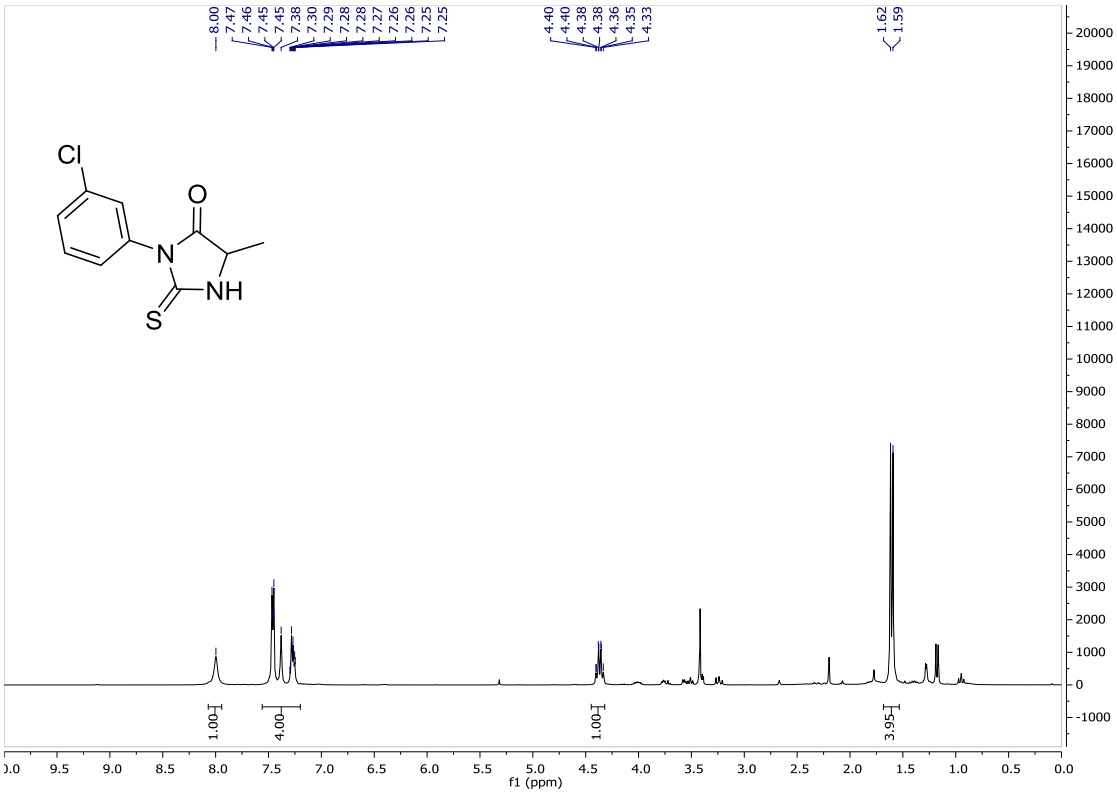


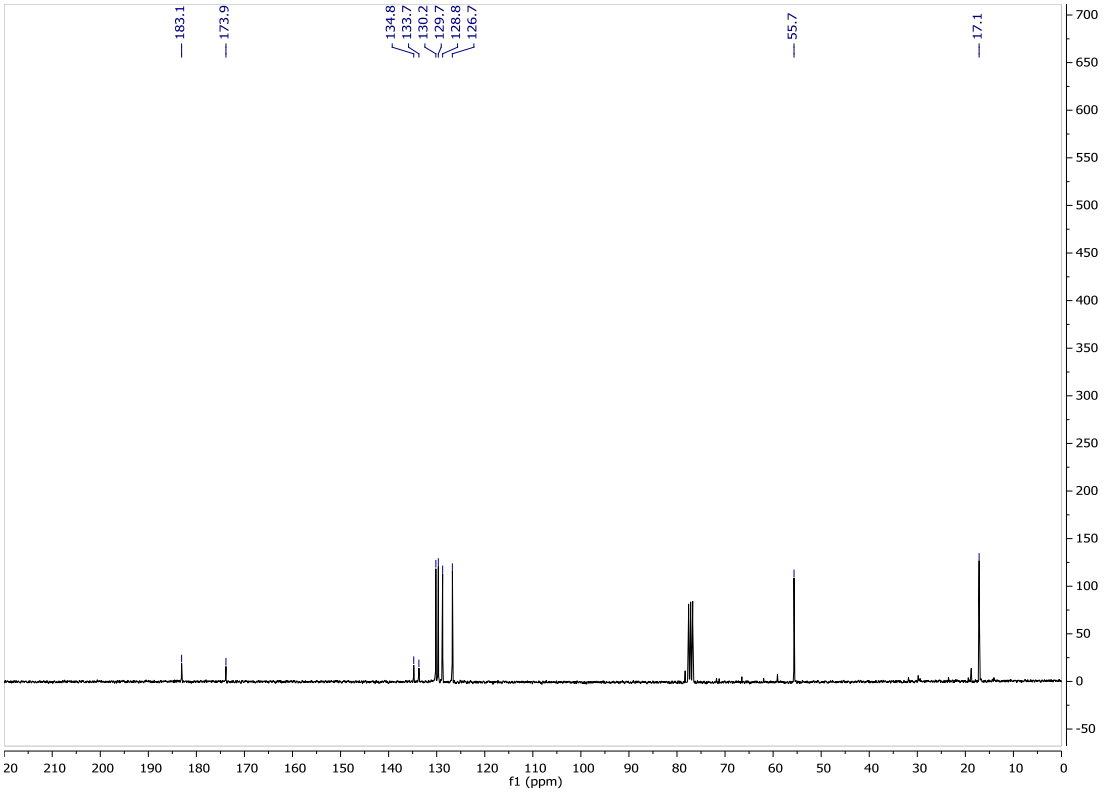
3-(4-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1d)



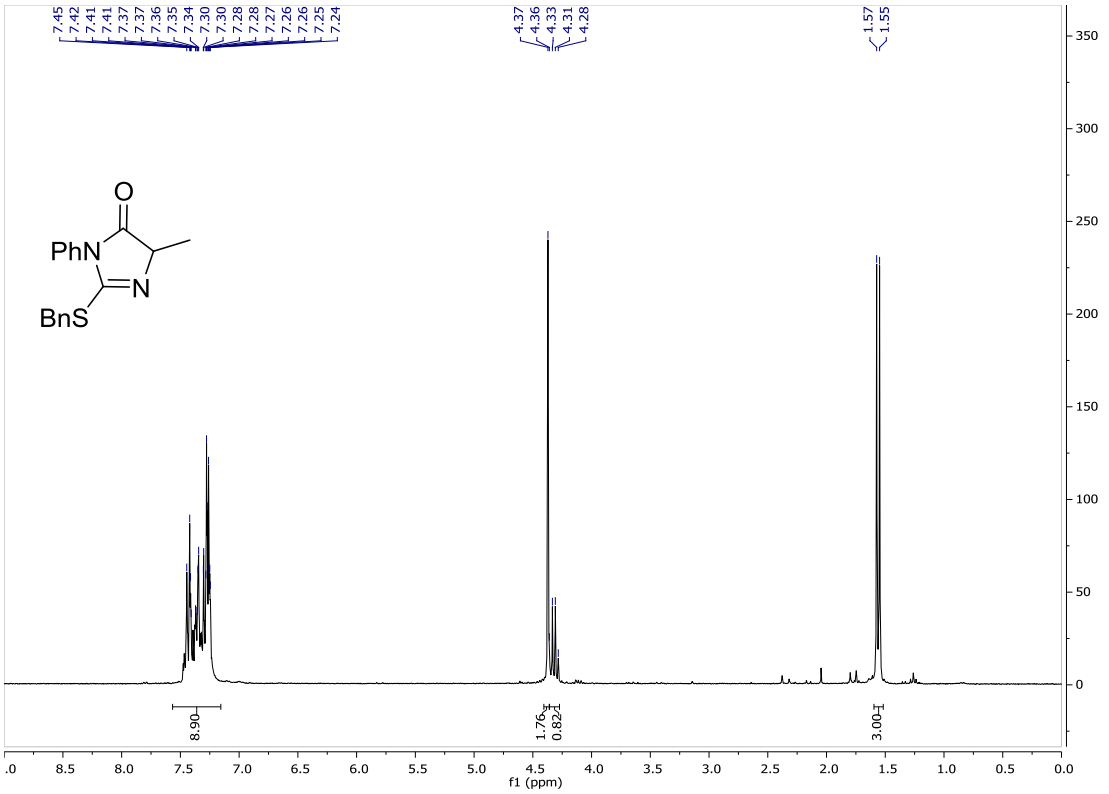


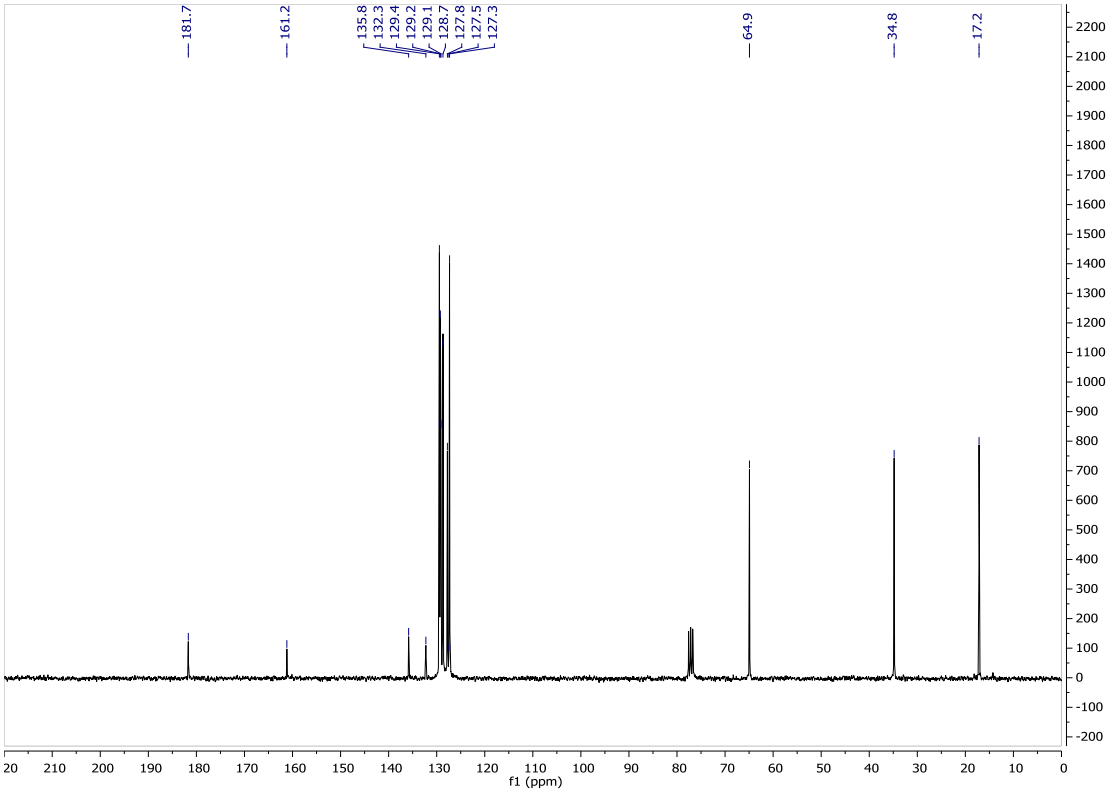
3-(3-Chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1e)



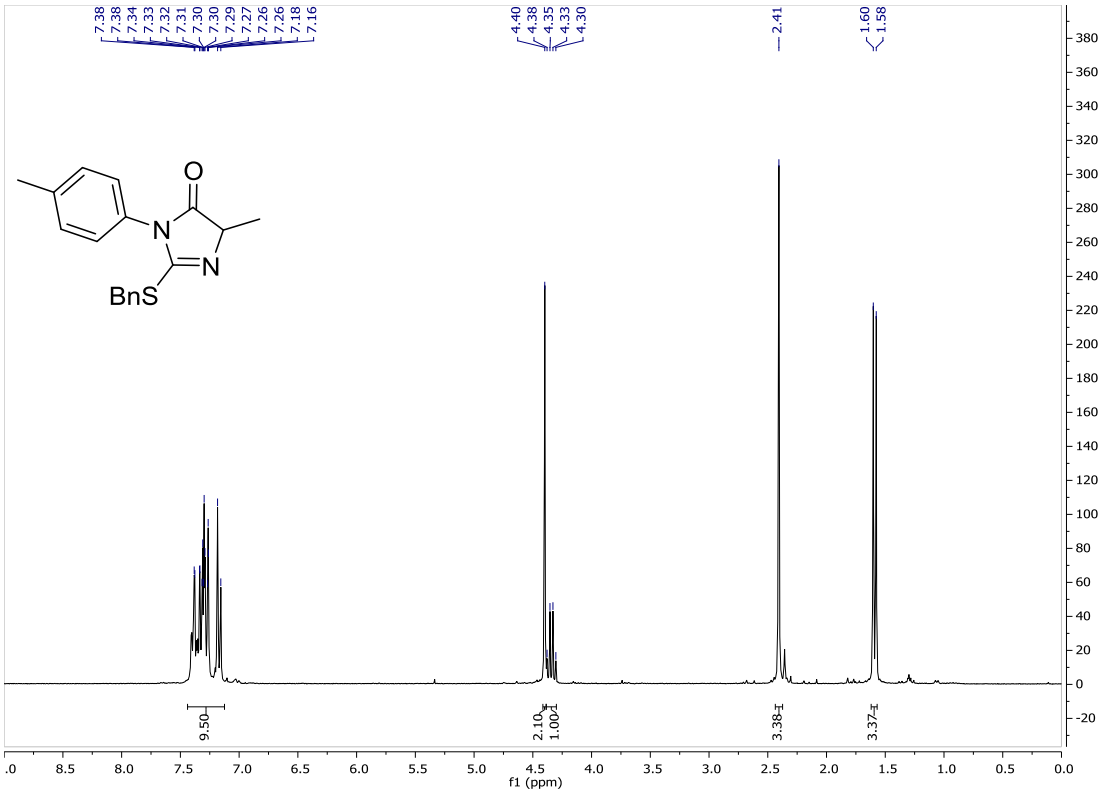


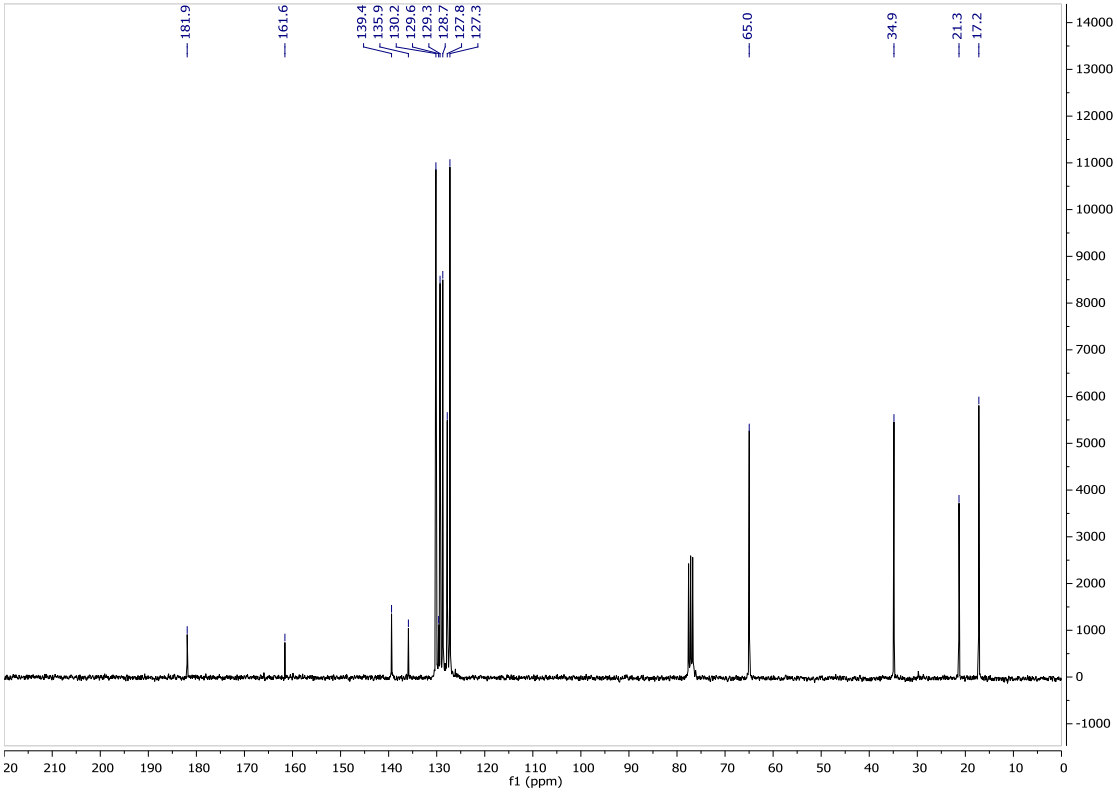
2-(Benzylthio)-4-methyl-1-phenyl-1*H*-imidazol-5(4*H*)-one (2a)



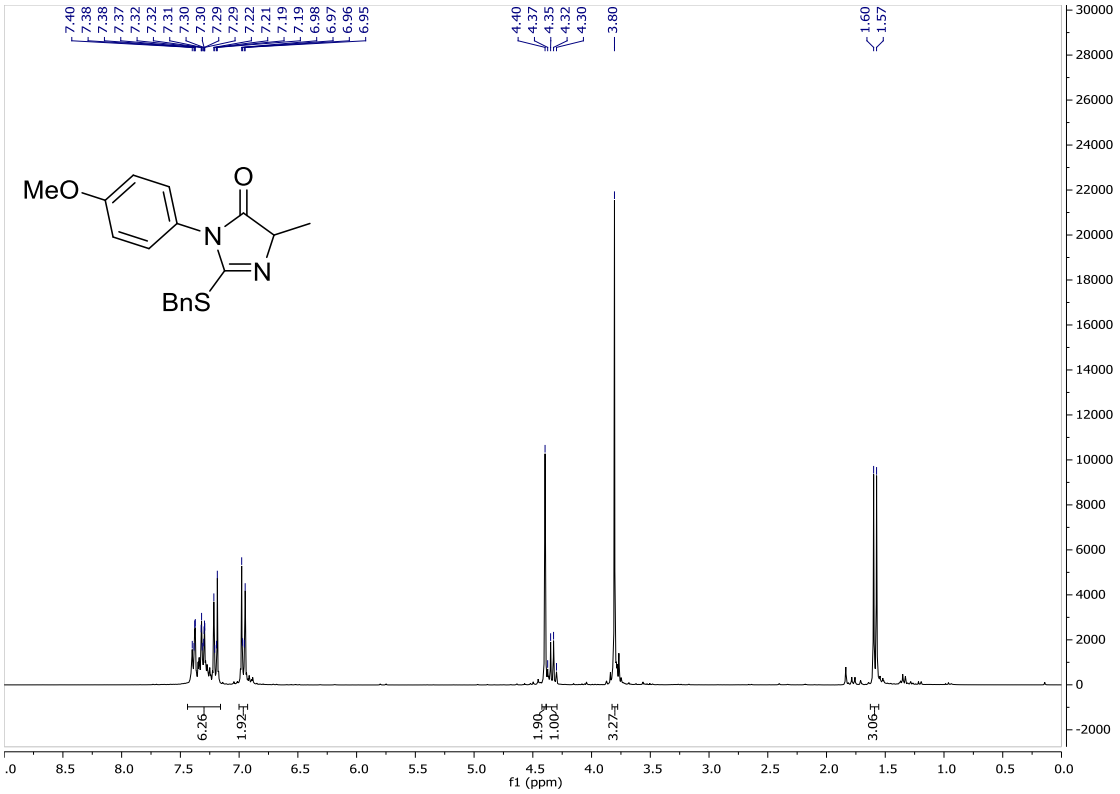


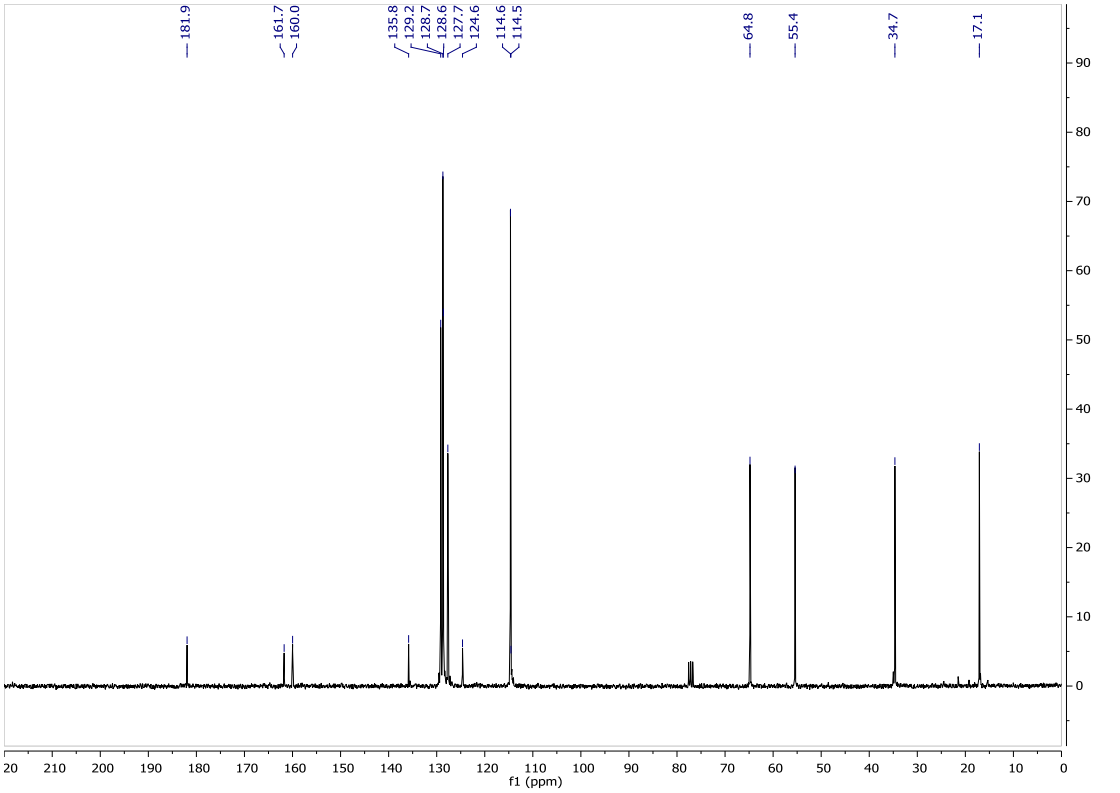
2-(Benzylthio)-4-methyl-1-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (2b)



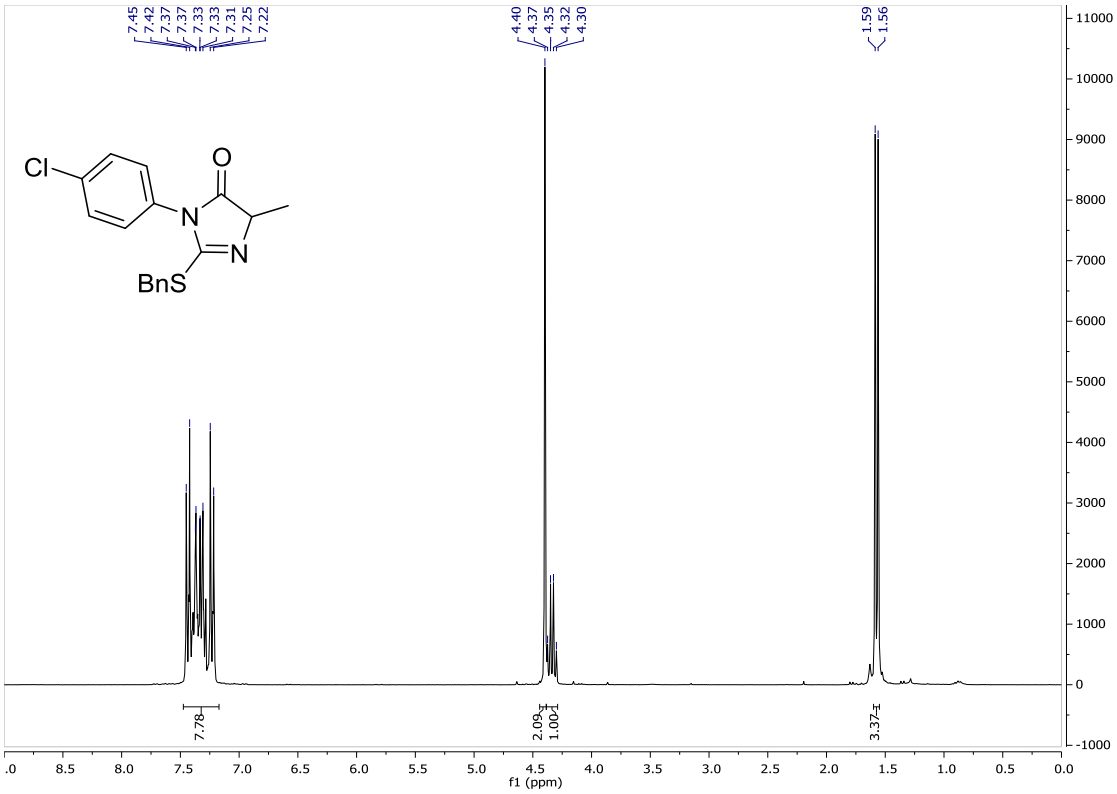


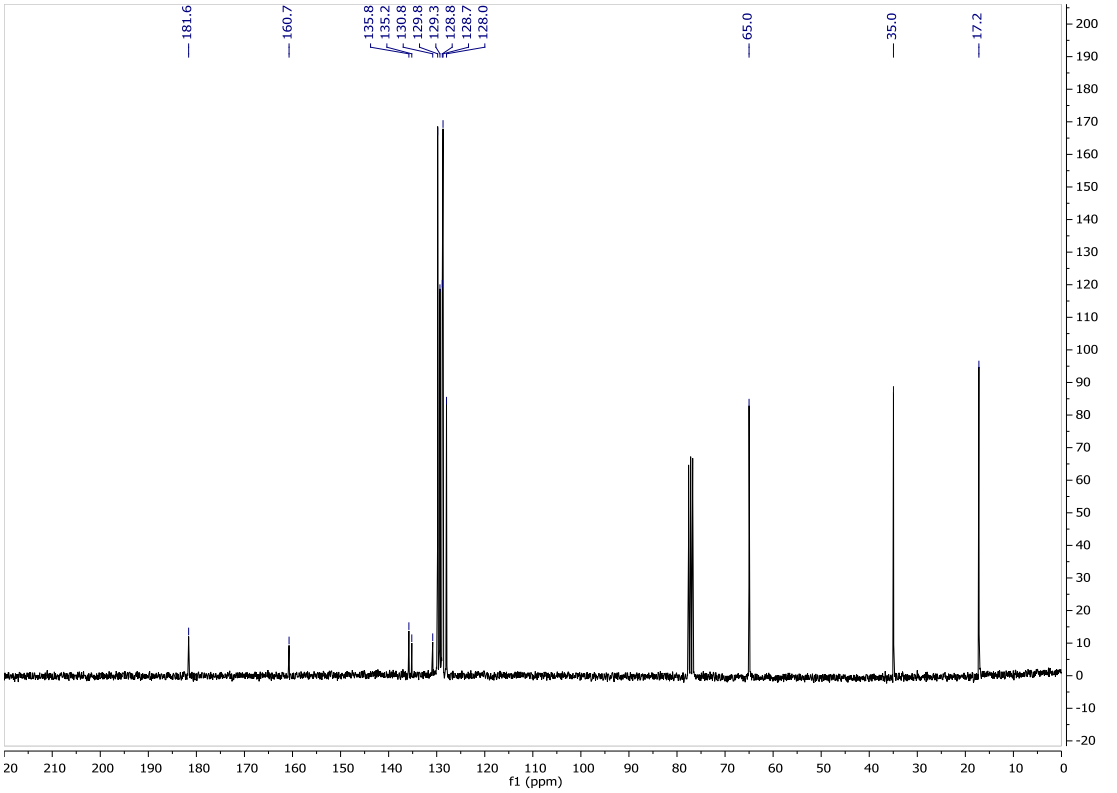
2-(Benzylthio)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (2c)



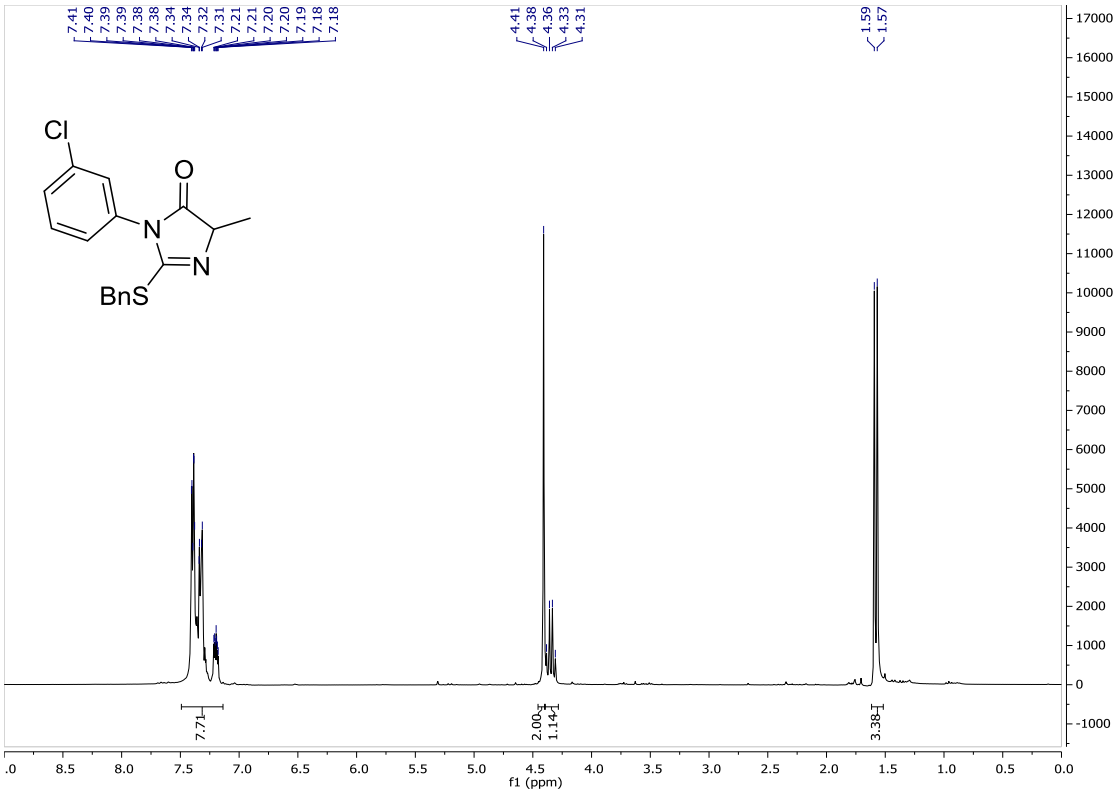


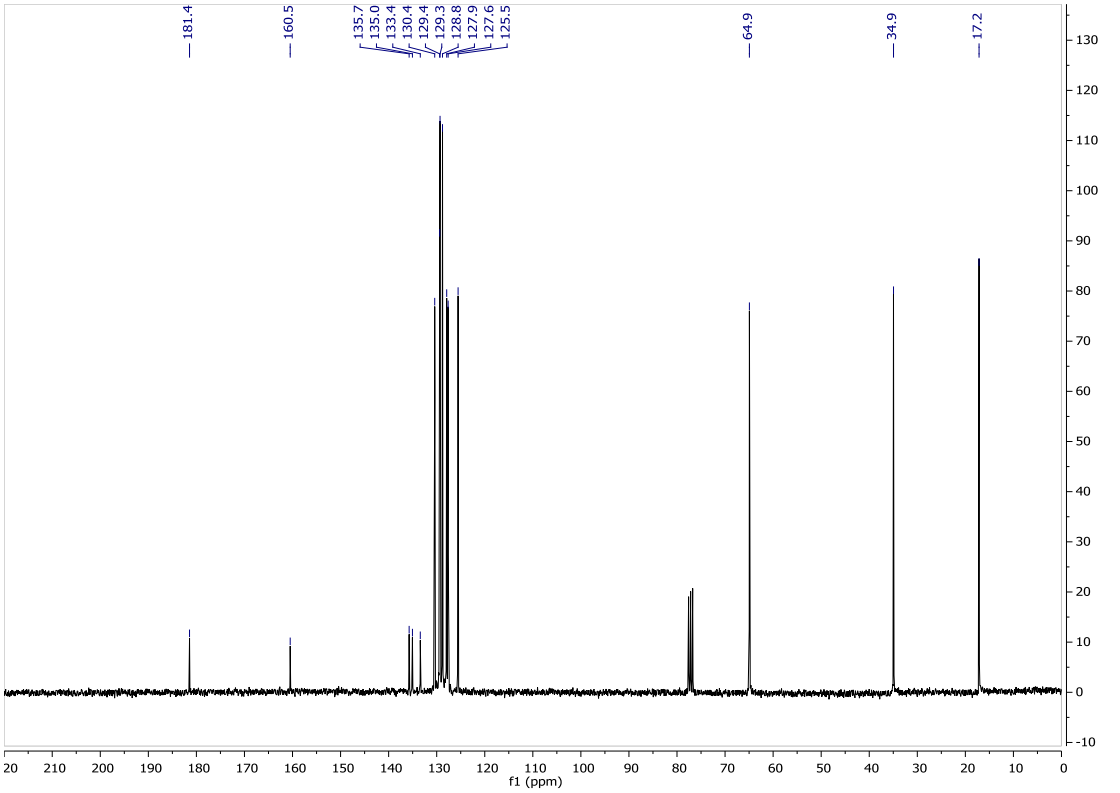
2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (2d)



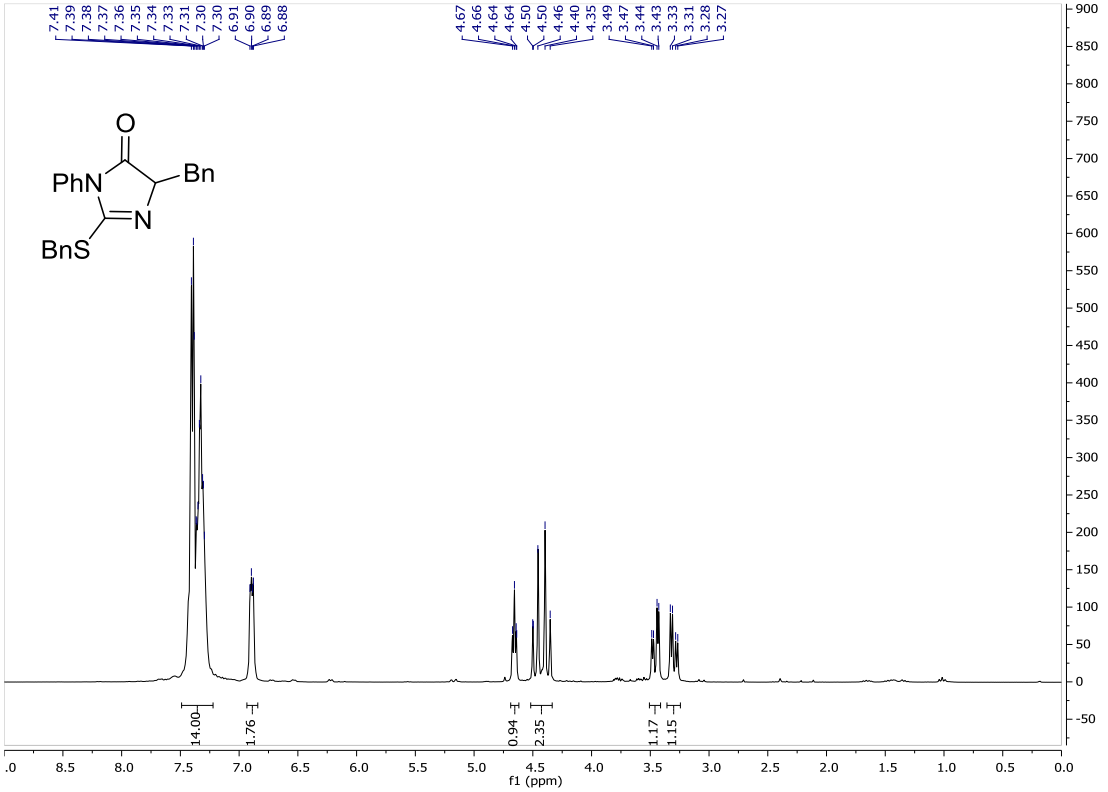


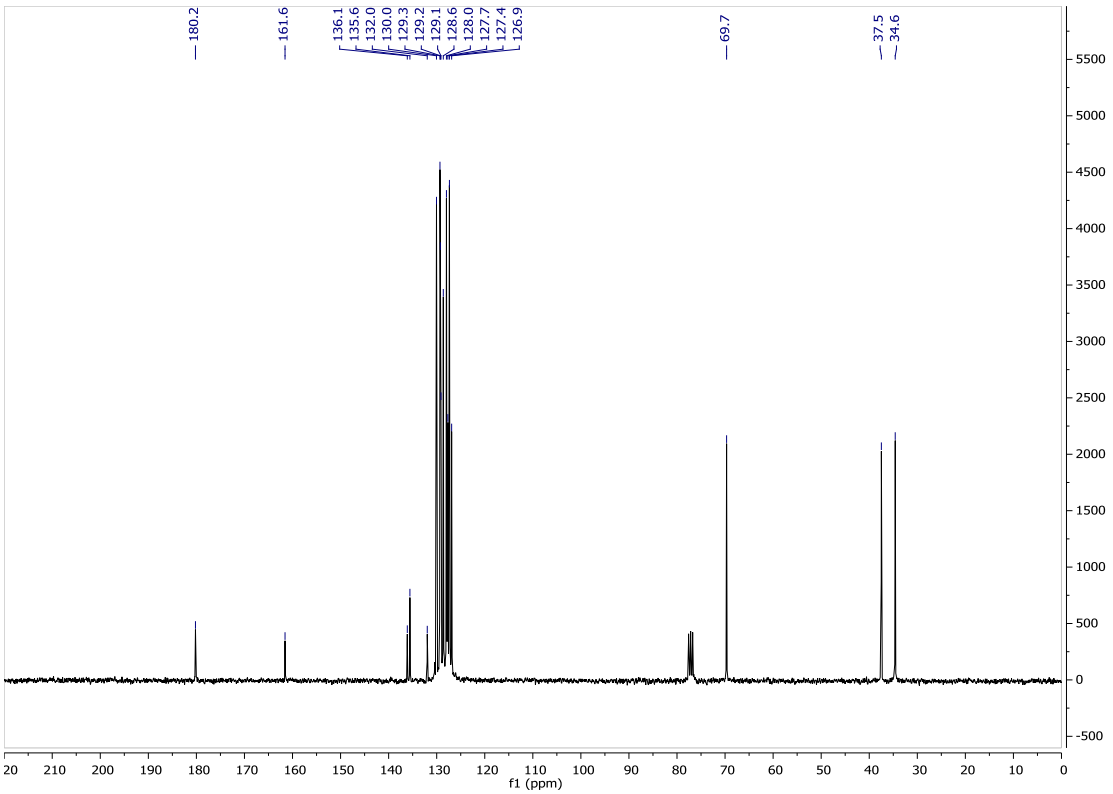
2-(Benzylthio)-1-(3-chlorophenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (2e)



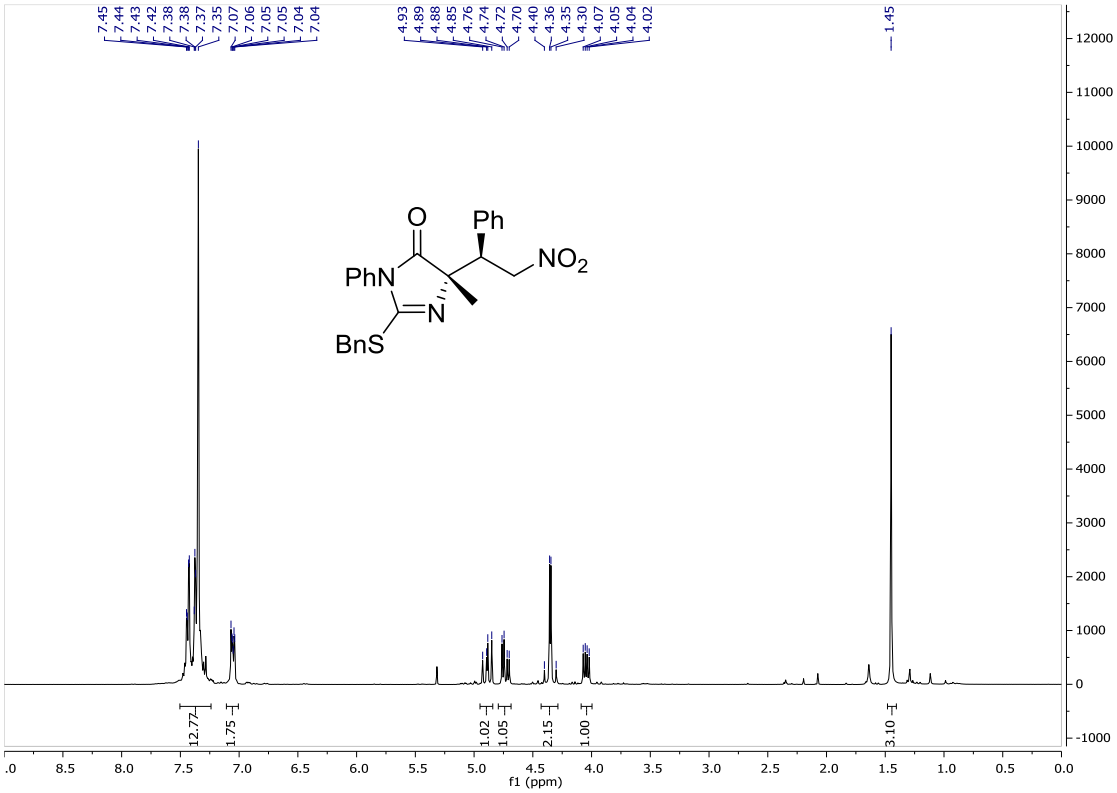


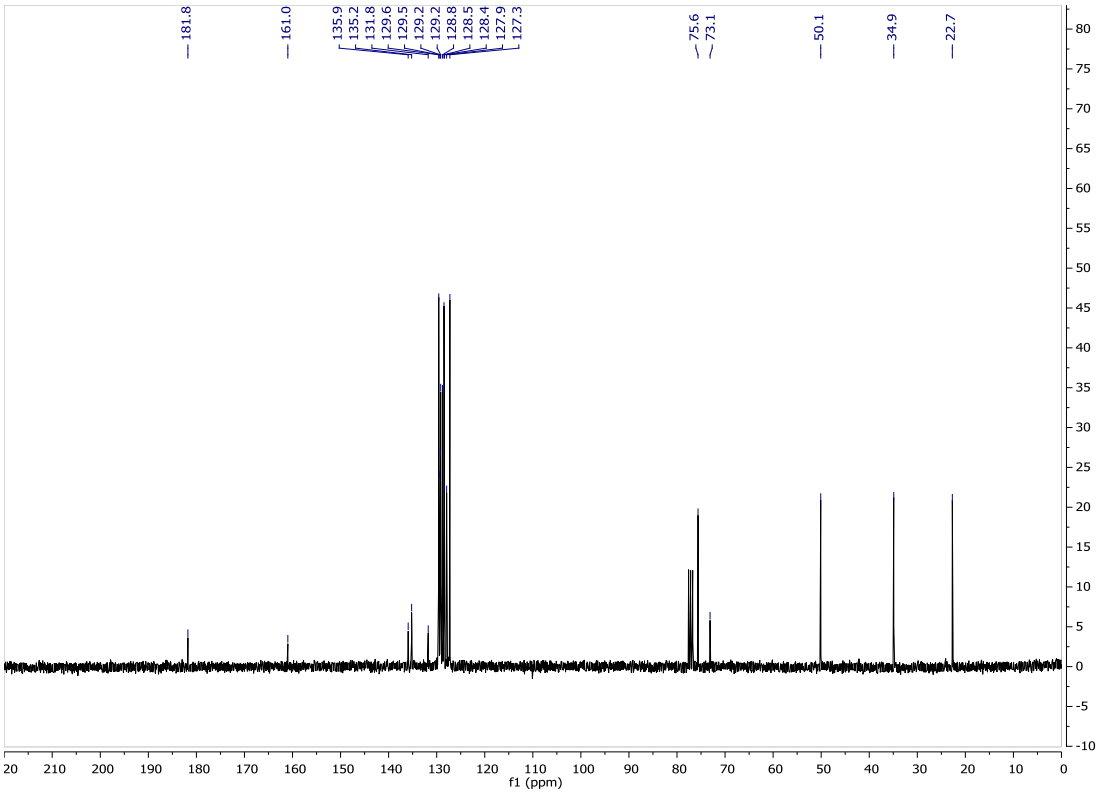
4-Benzyl-2-(benzylthio)-1-phenyl-1*H*-imidazol-5(4*H*)-one (2f)



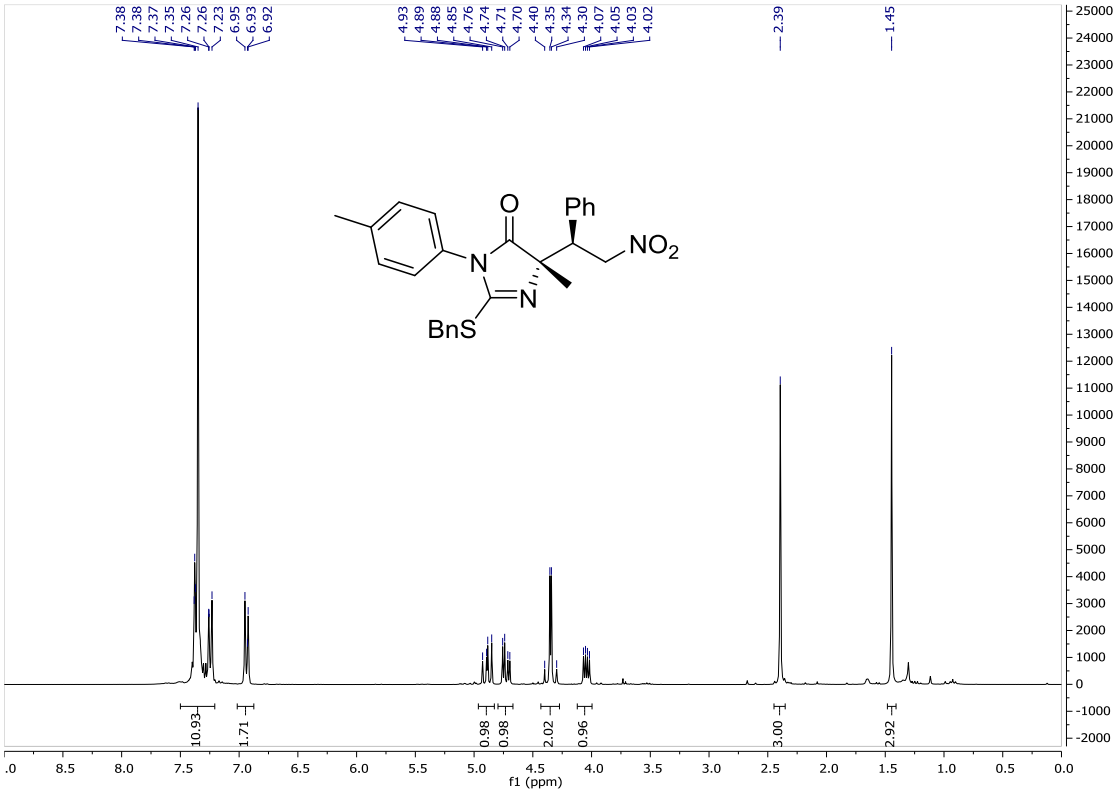


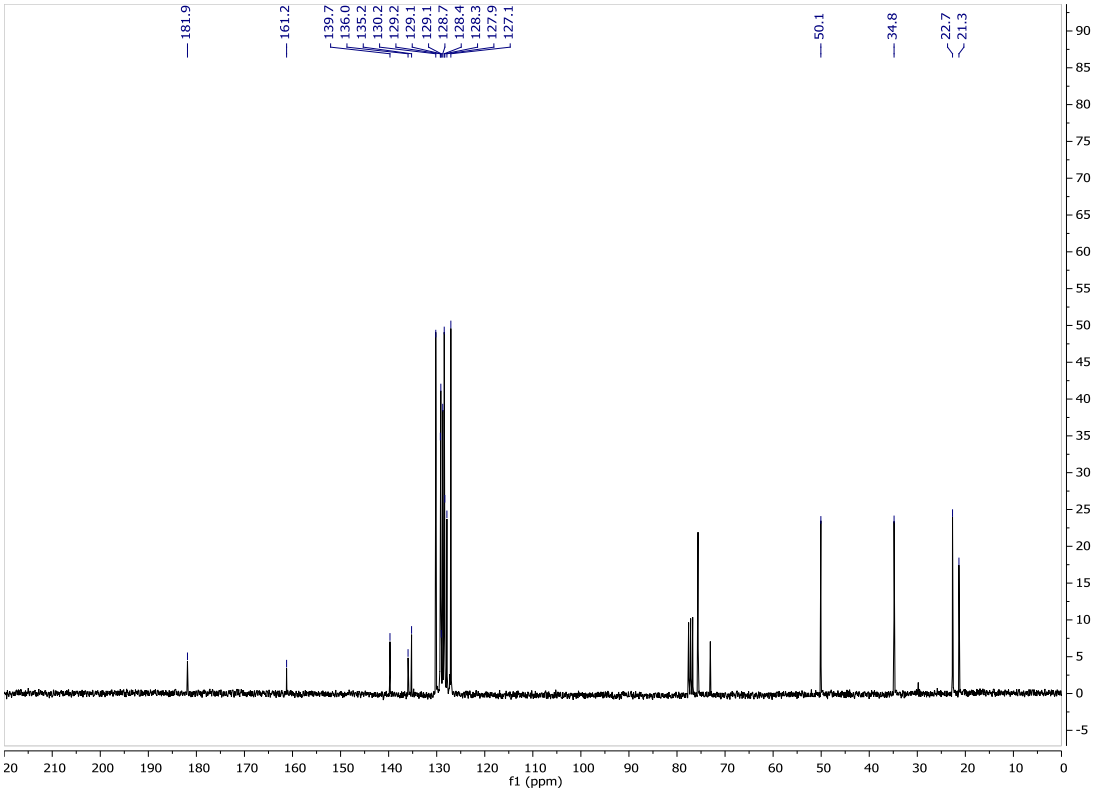
(*S*)-2-(Benzylthio)-4-methyl-4-((S)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (4aa)



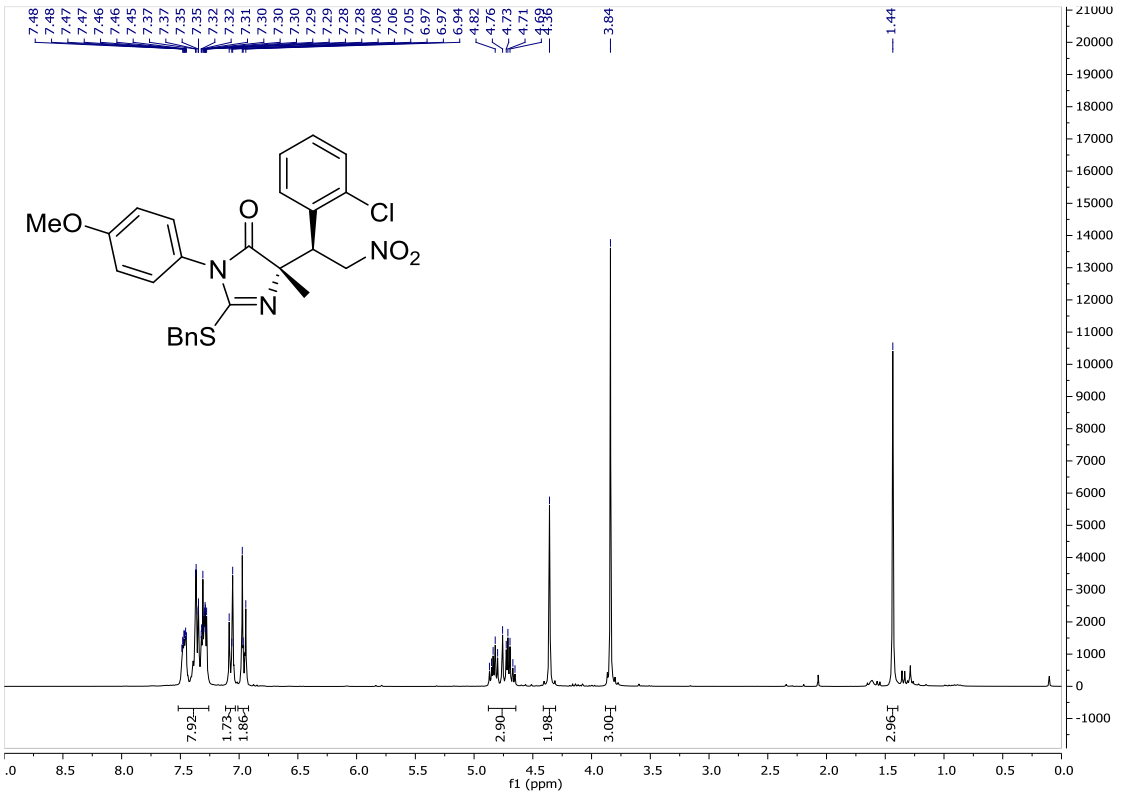


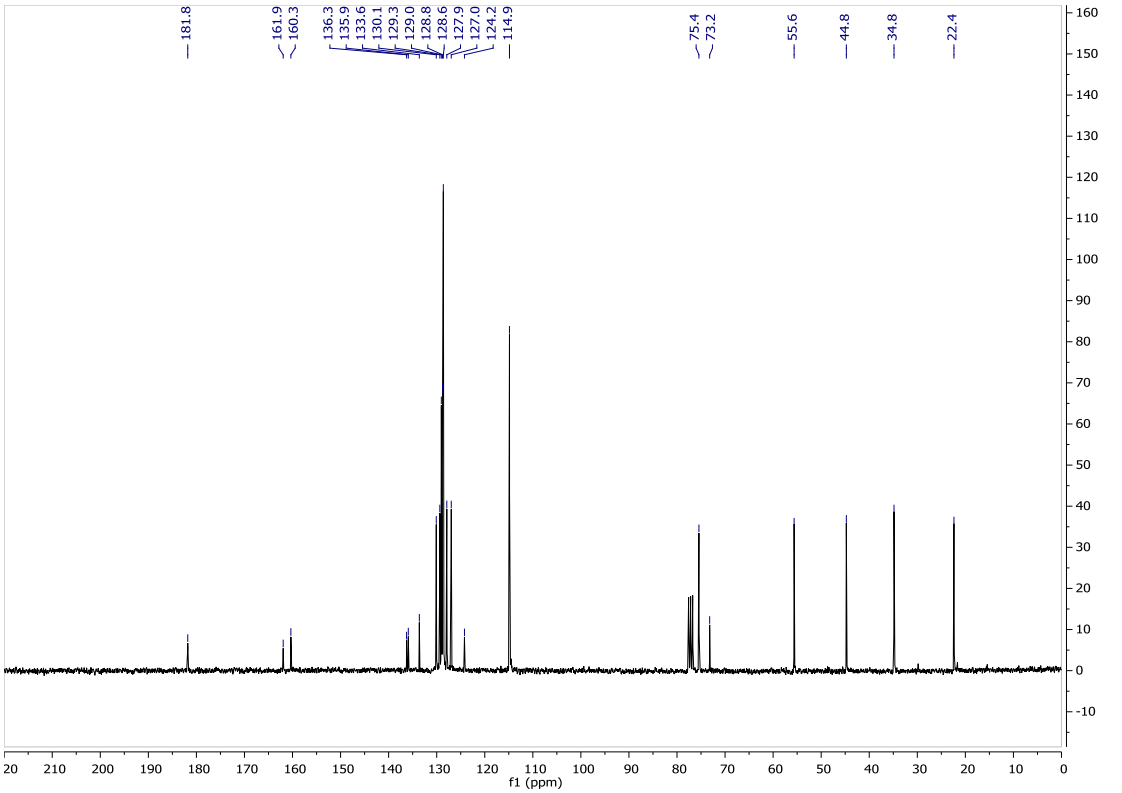
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (4ba)



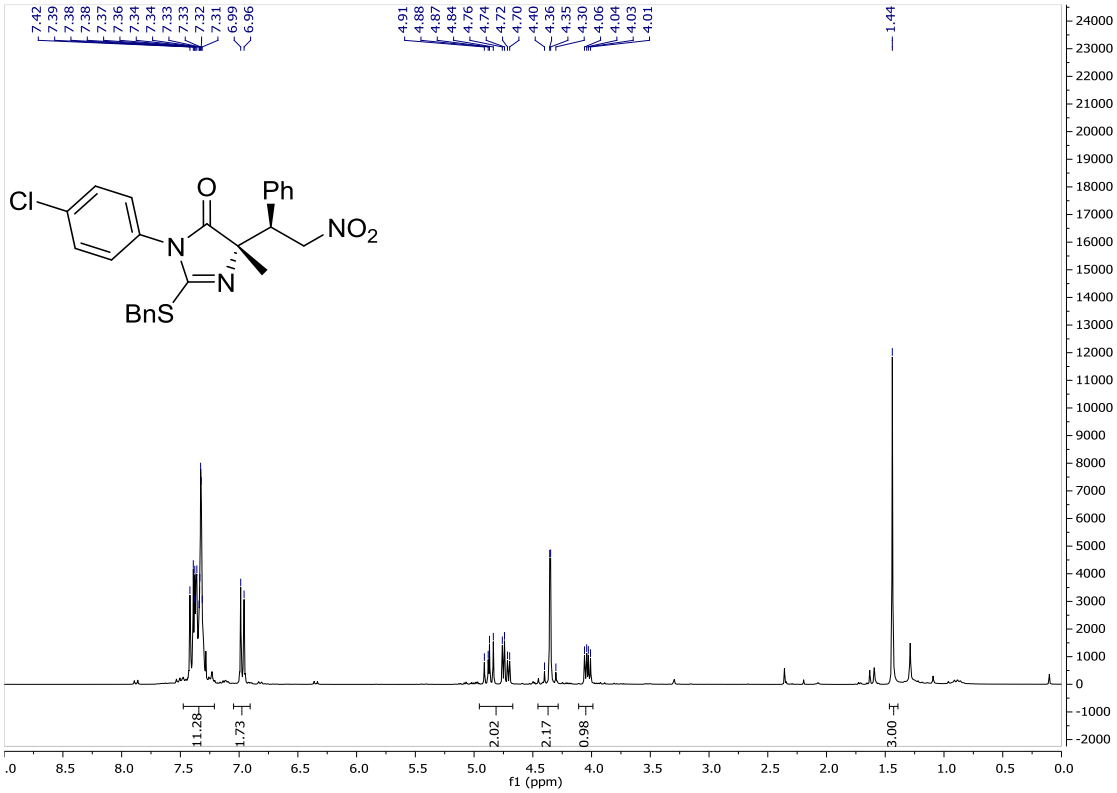


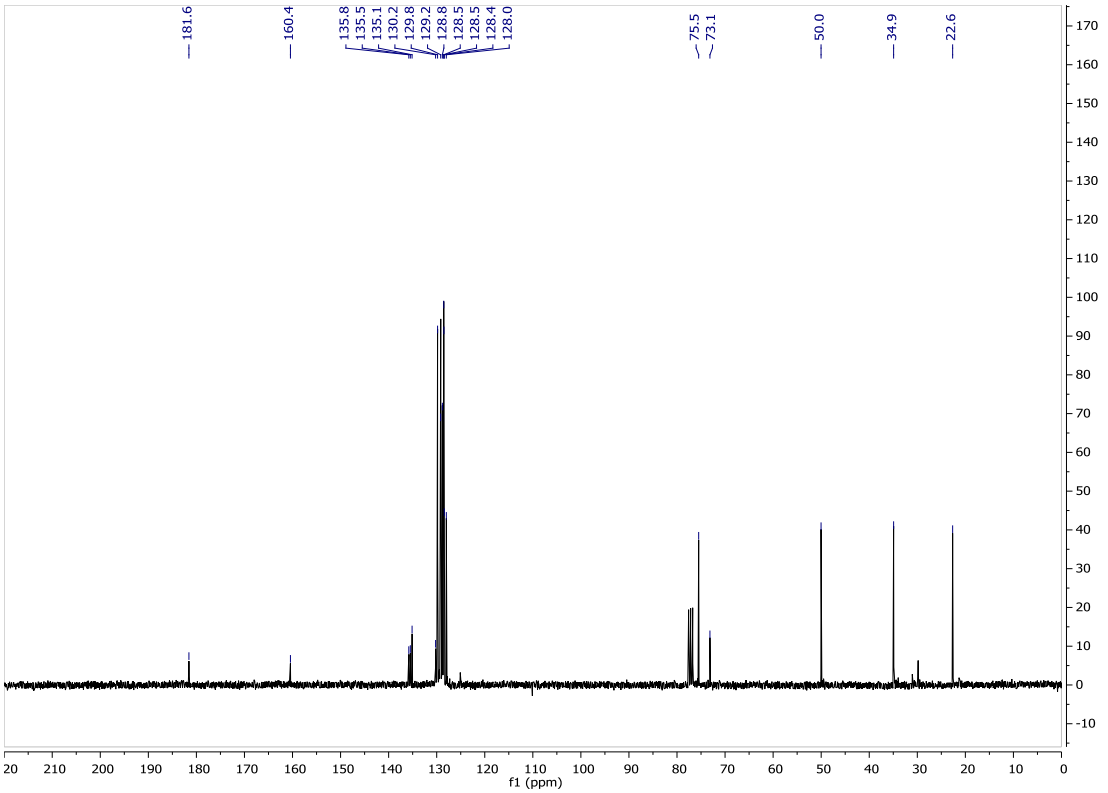
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (4cb)



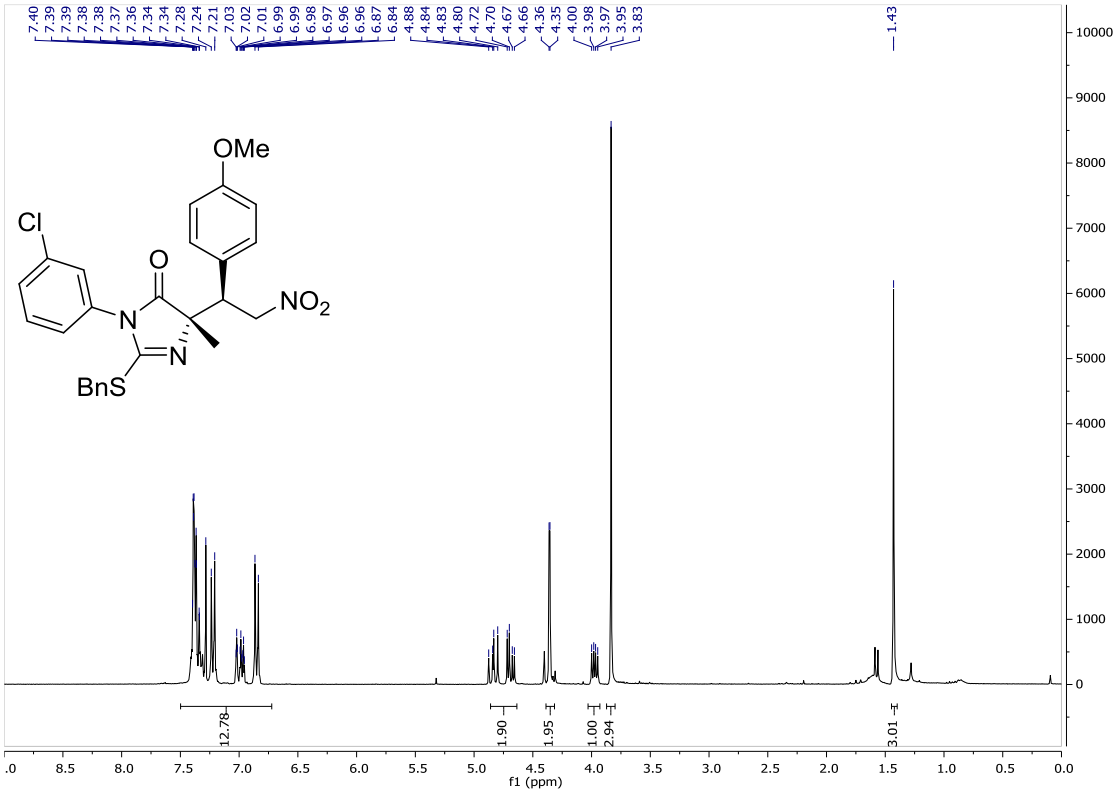


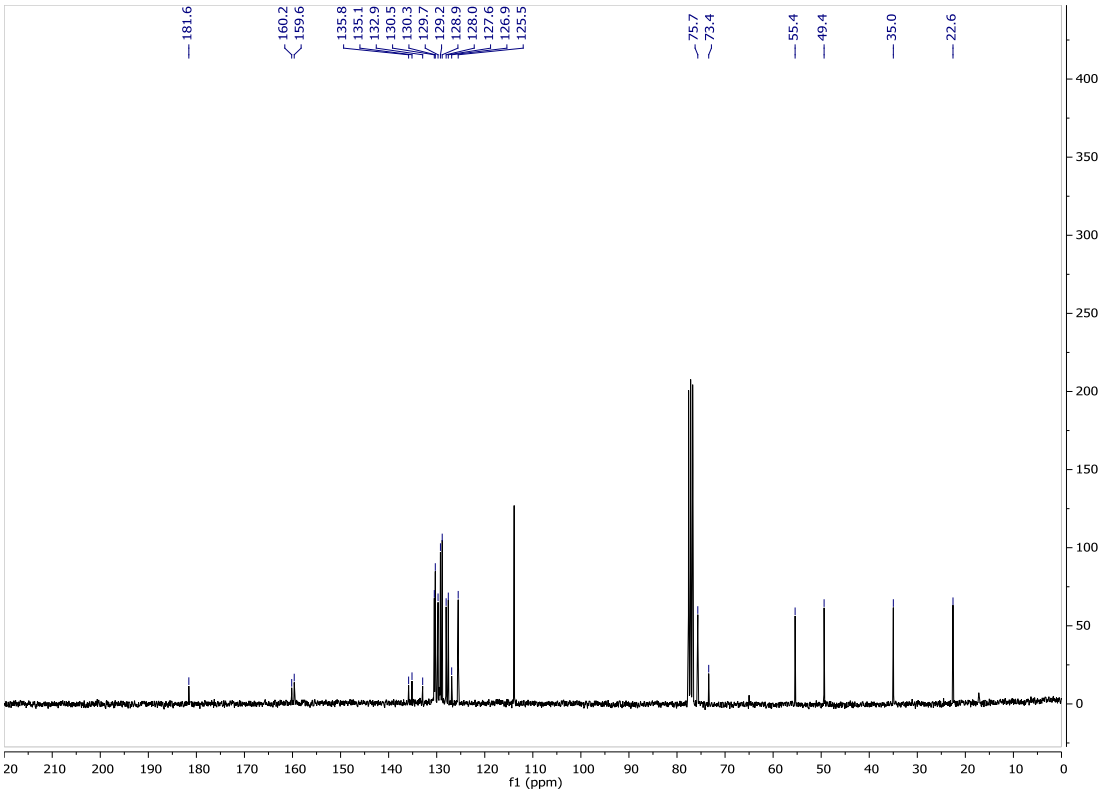
(*S*)-2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (4da)



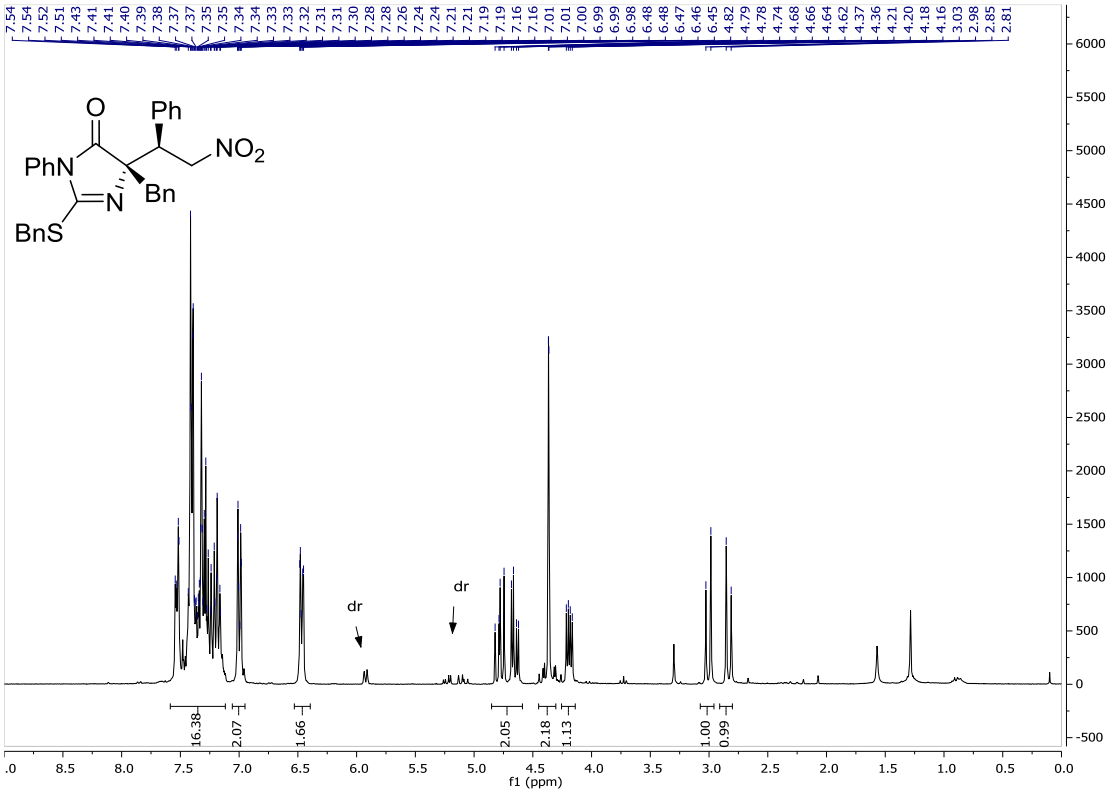


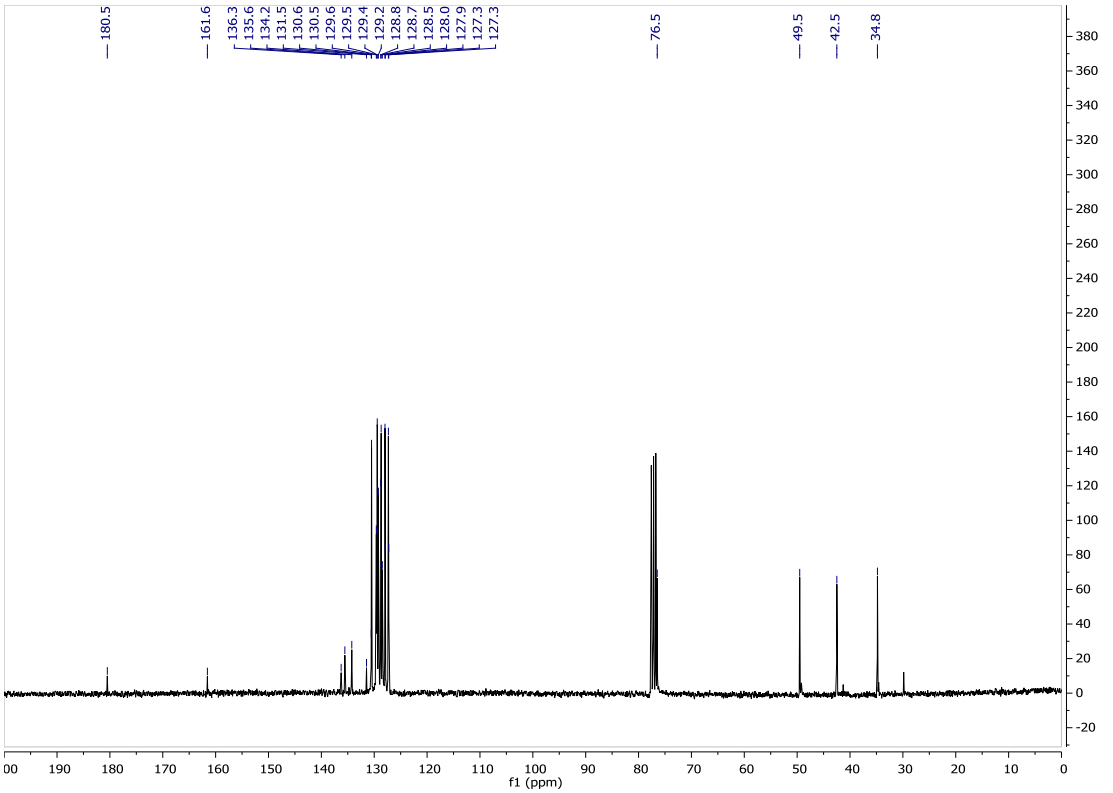
(*S*)-2-(Benzylthio)-1-(3-chlorophenyl)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (4ec)



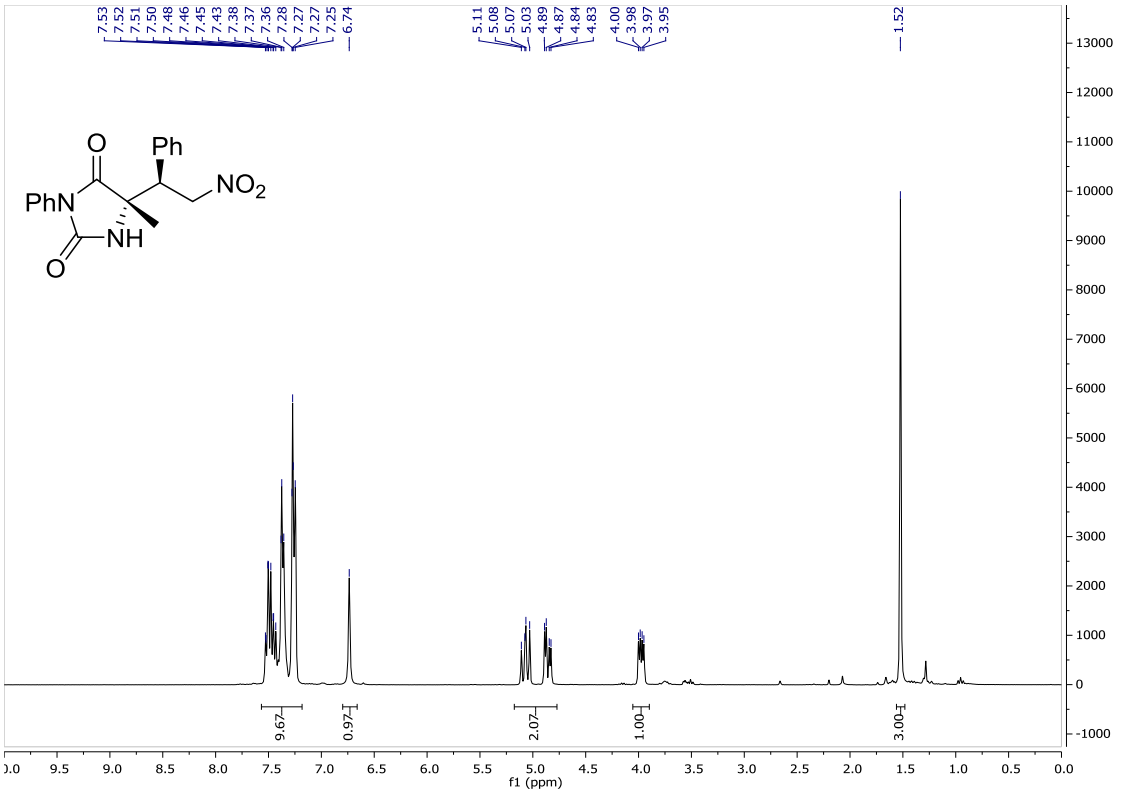


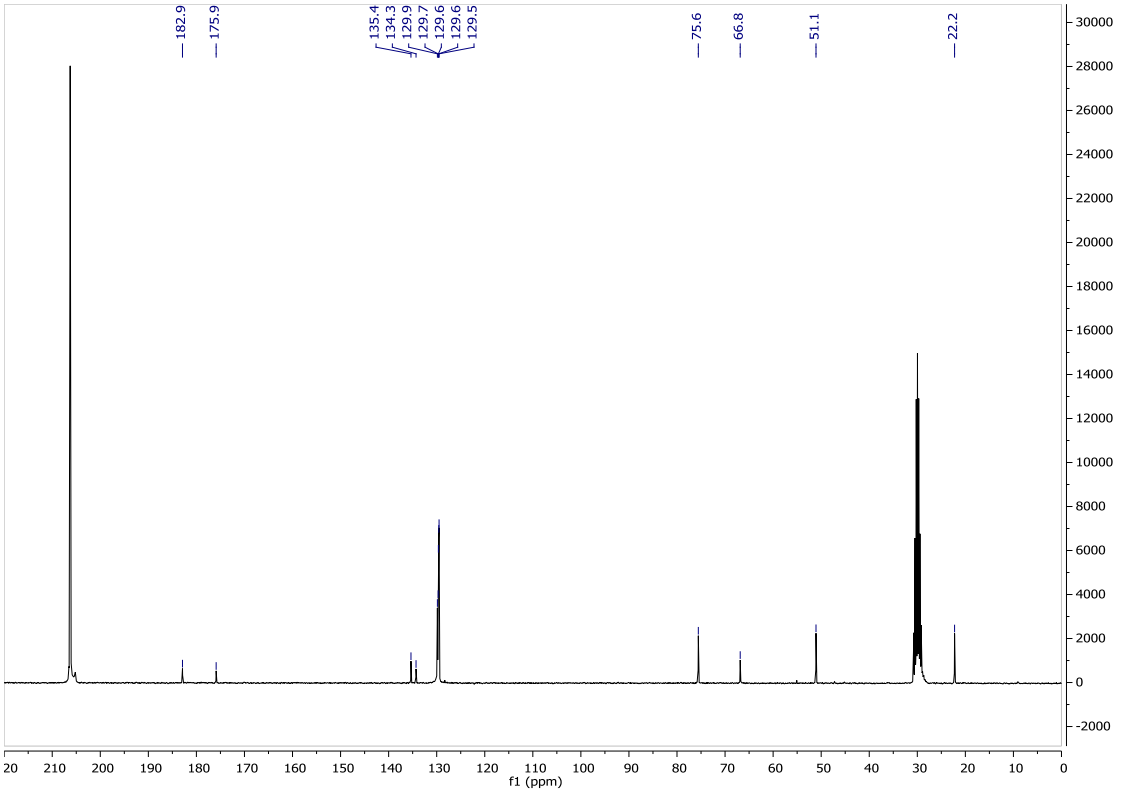
(*S*)-4-Benzyl-2-(benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (4fa)



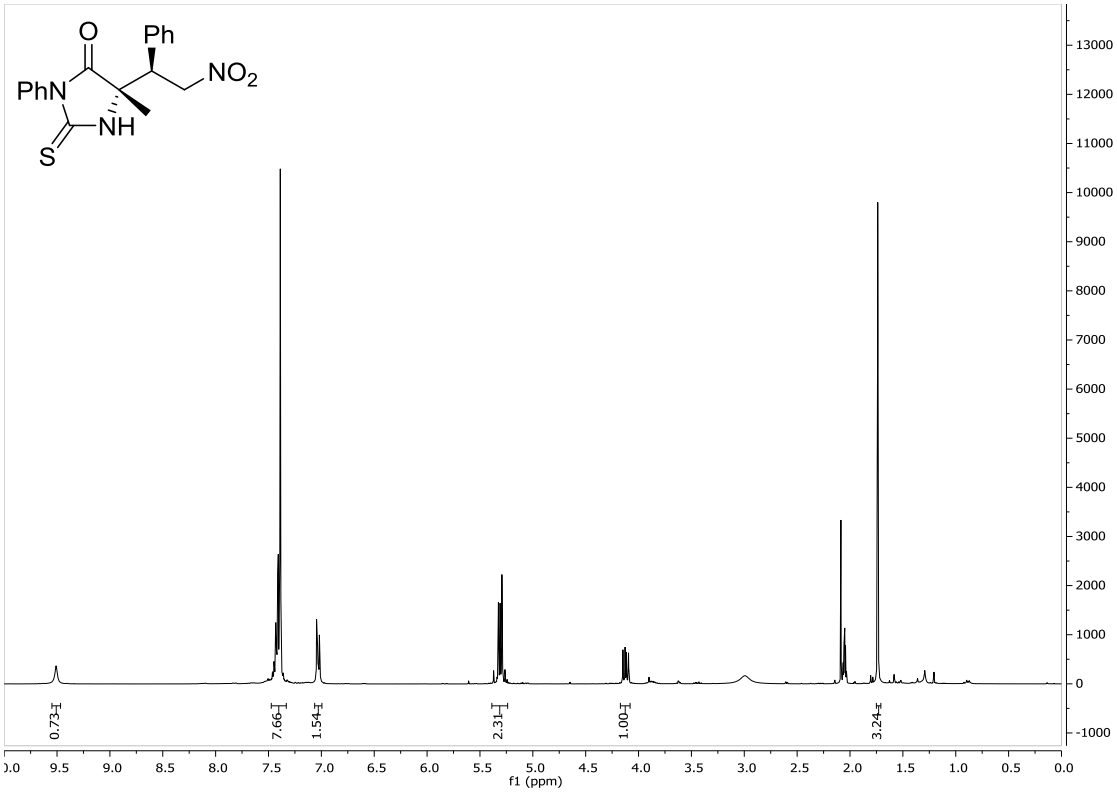


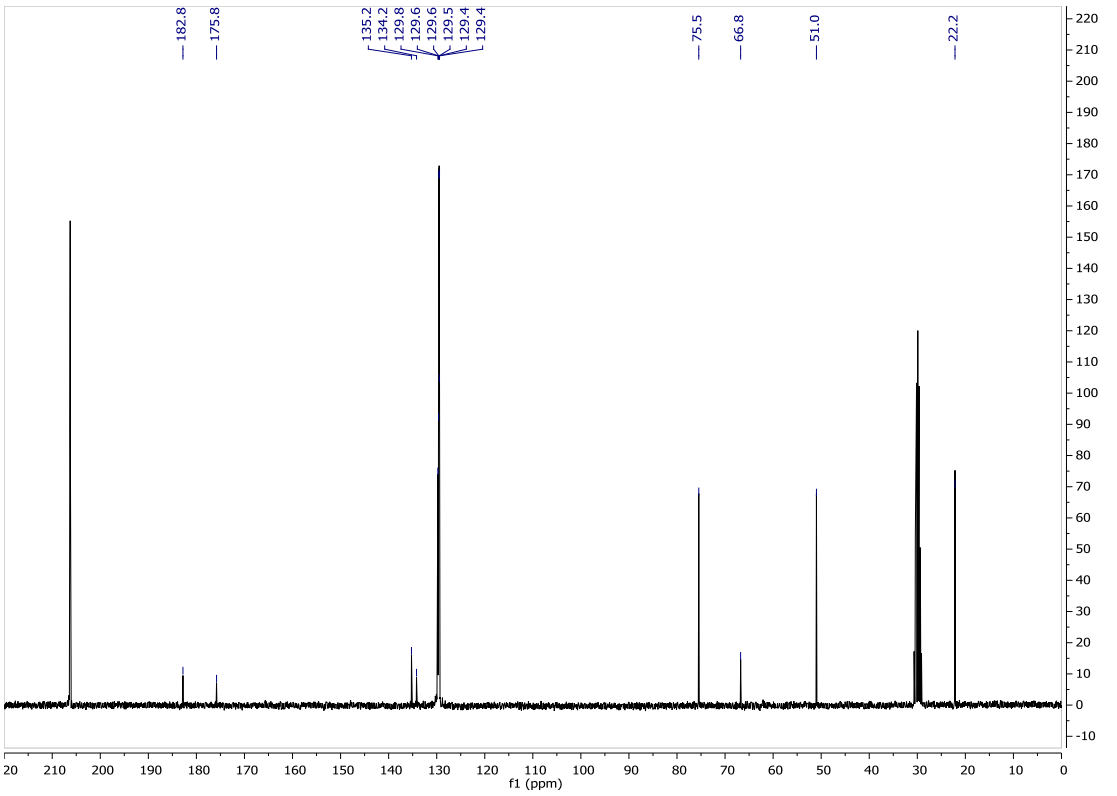
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (5)



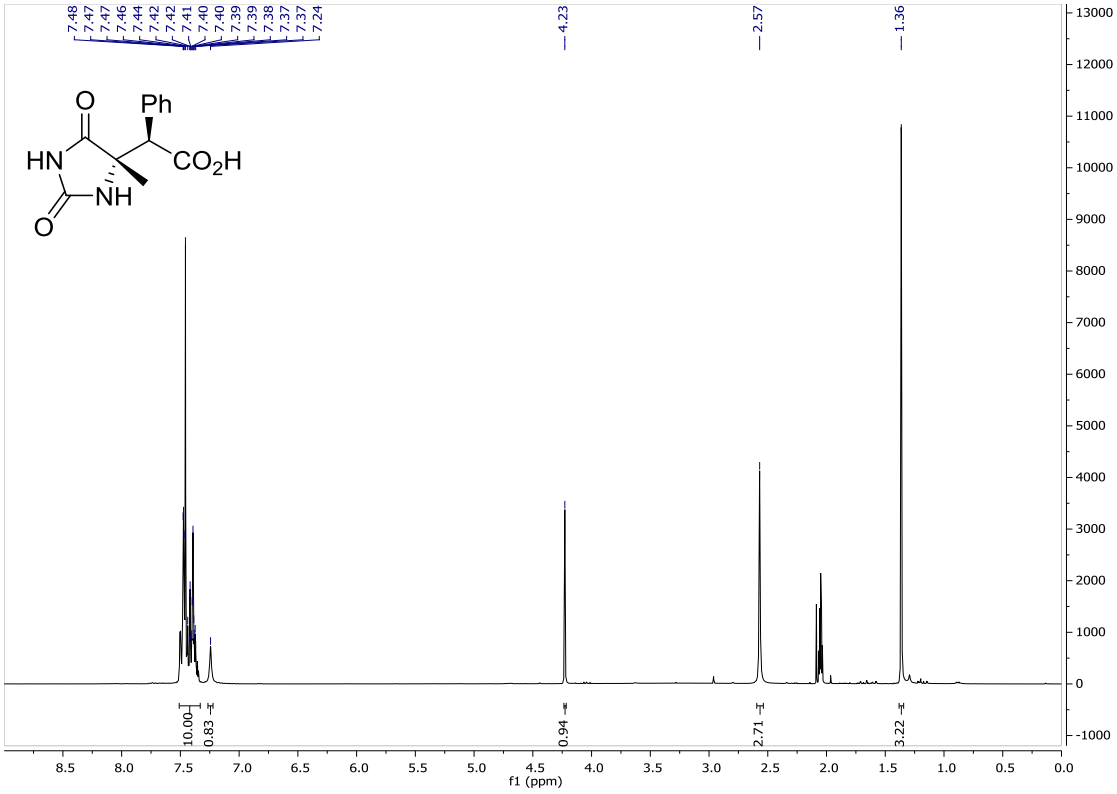


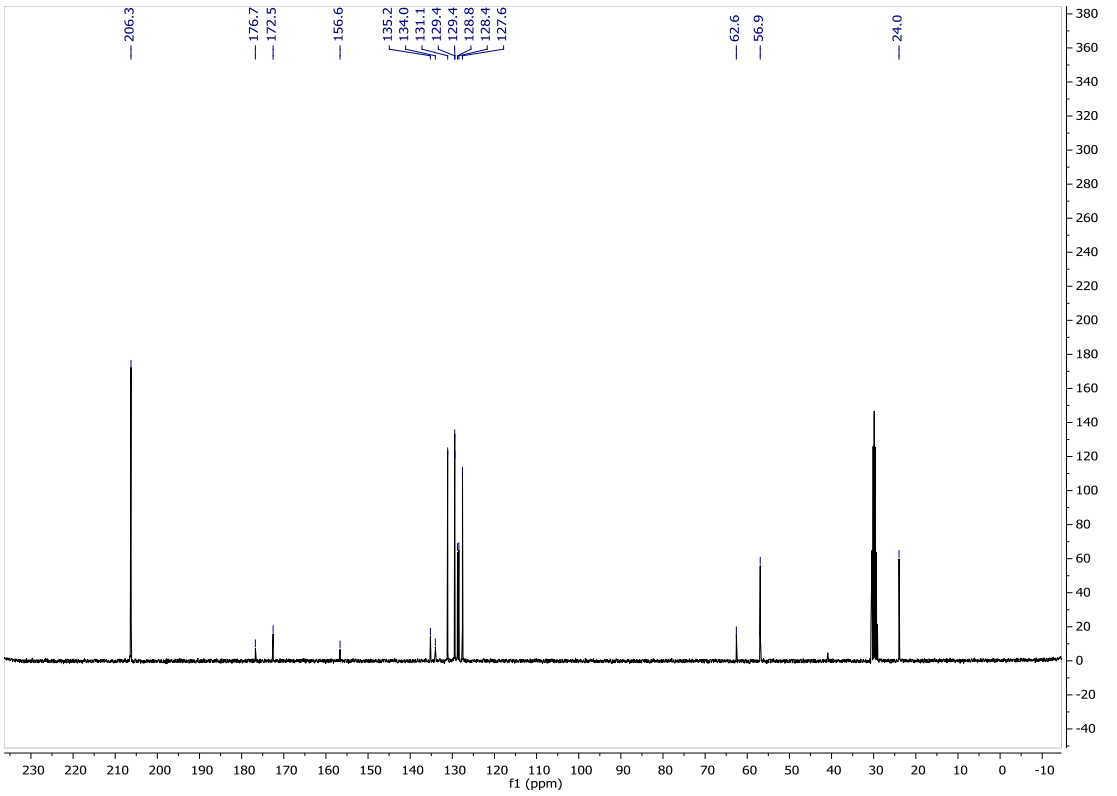
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenyl-2-thioxoimidazolidin-4-one (6)



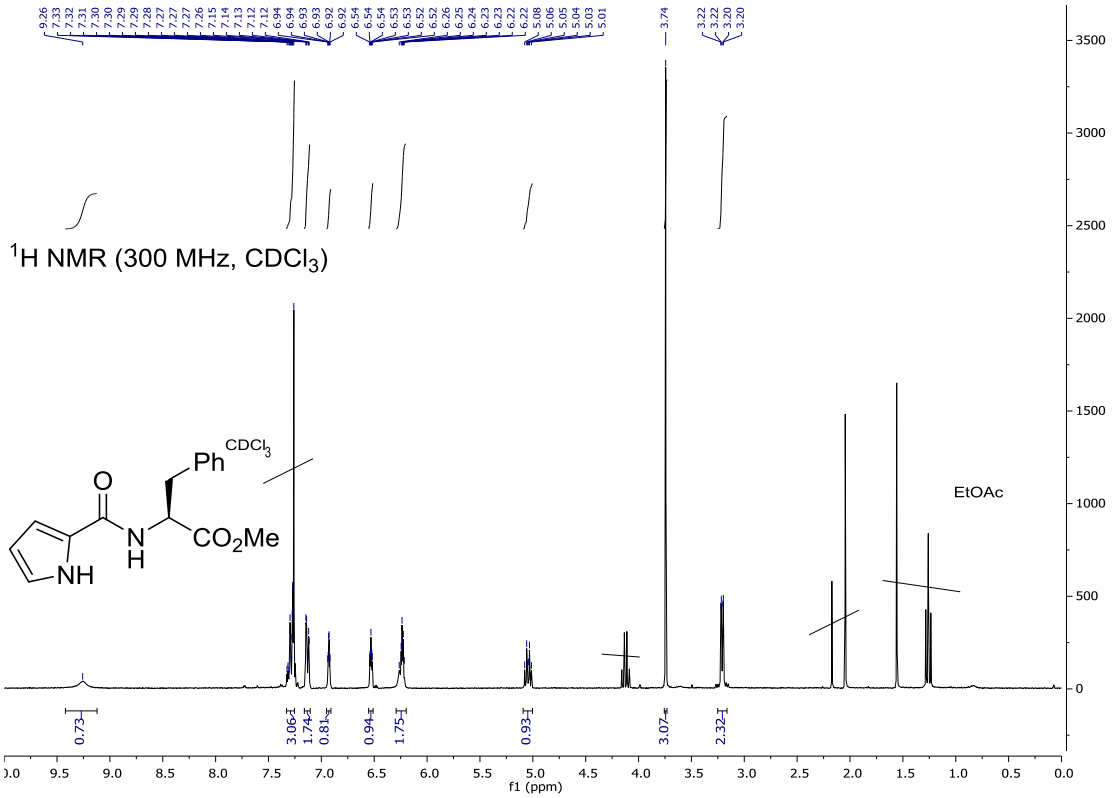


(*R*)-2-((*S*)-4-Methyl-2,5-dioxo-1-phenylimidazolidin-4-yl)-2-phenylacetic acid (7)

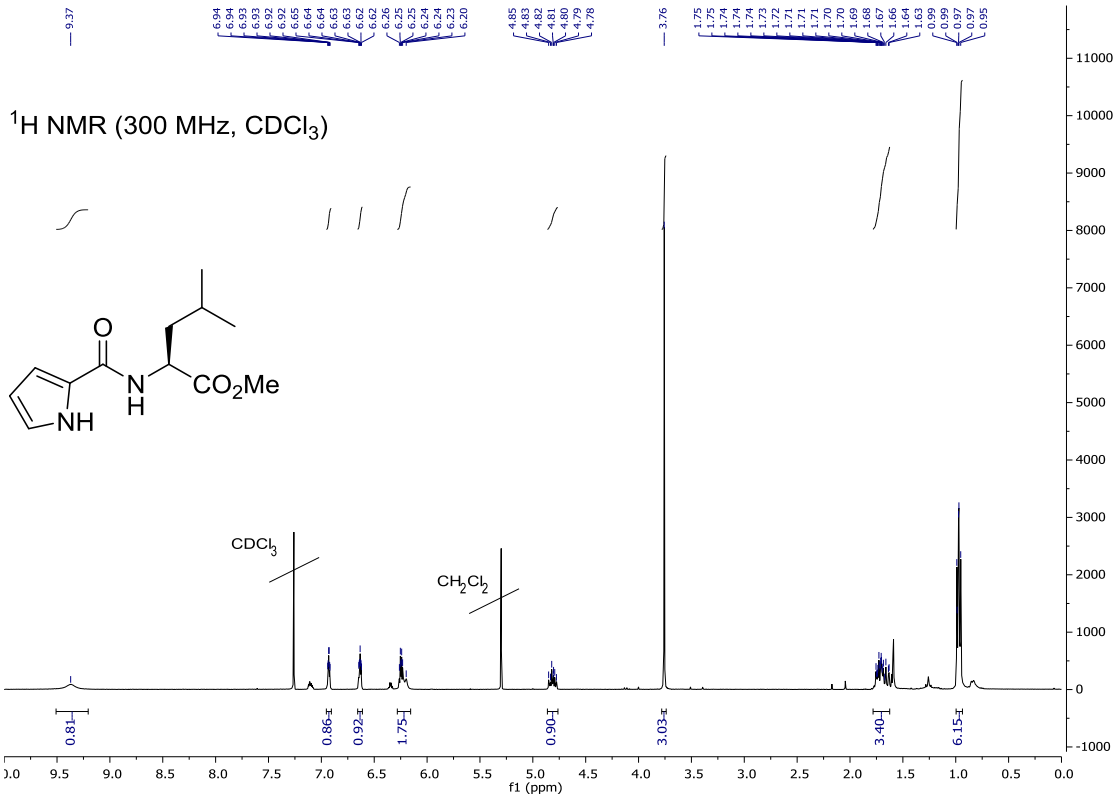




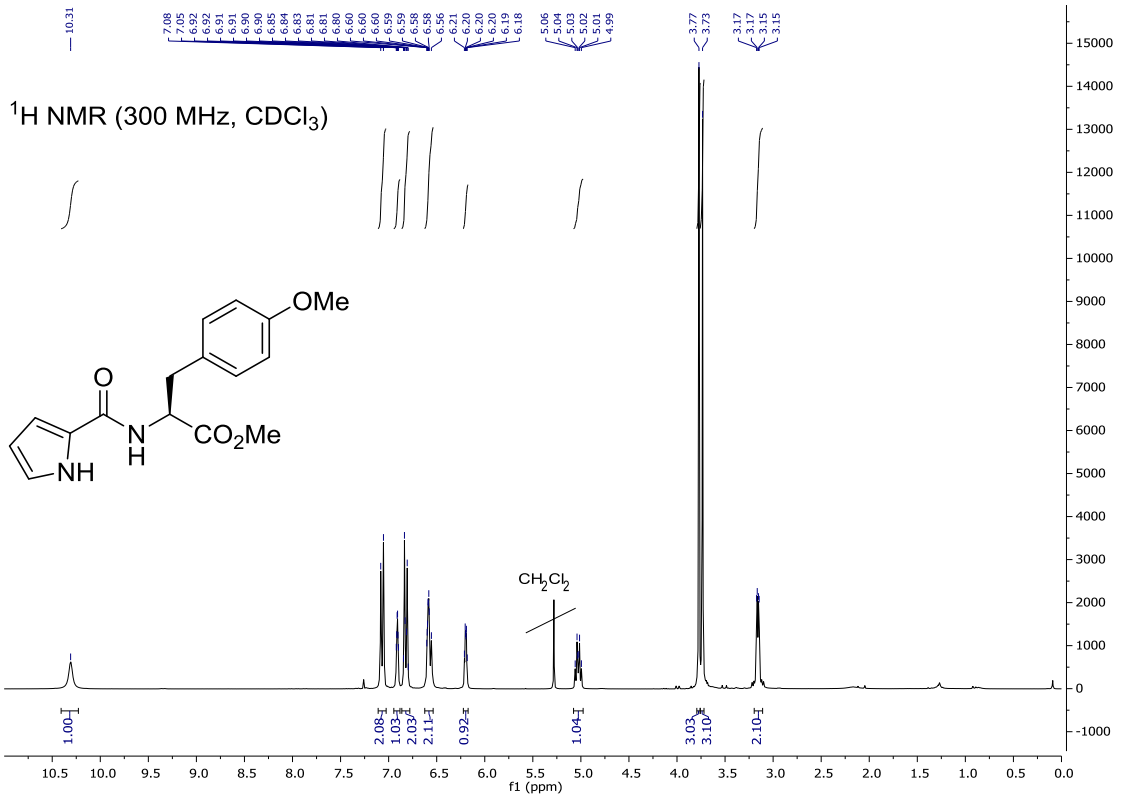
Methyl (1*H*-pyrrole-2-carbonyl)-*L*-phenylalaninate (11a)



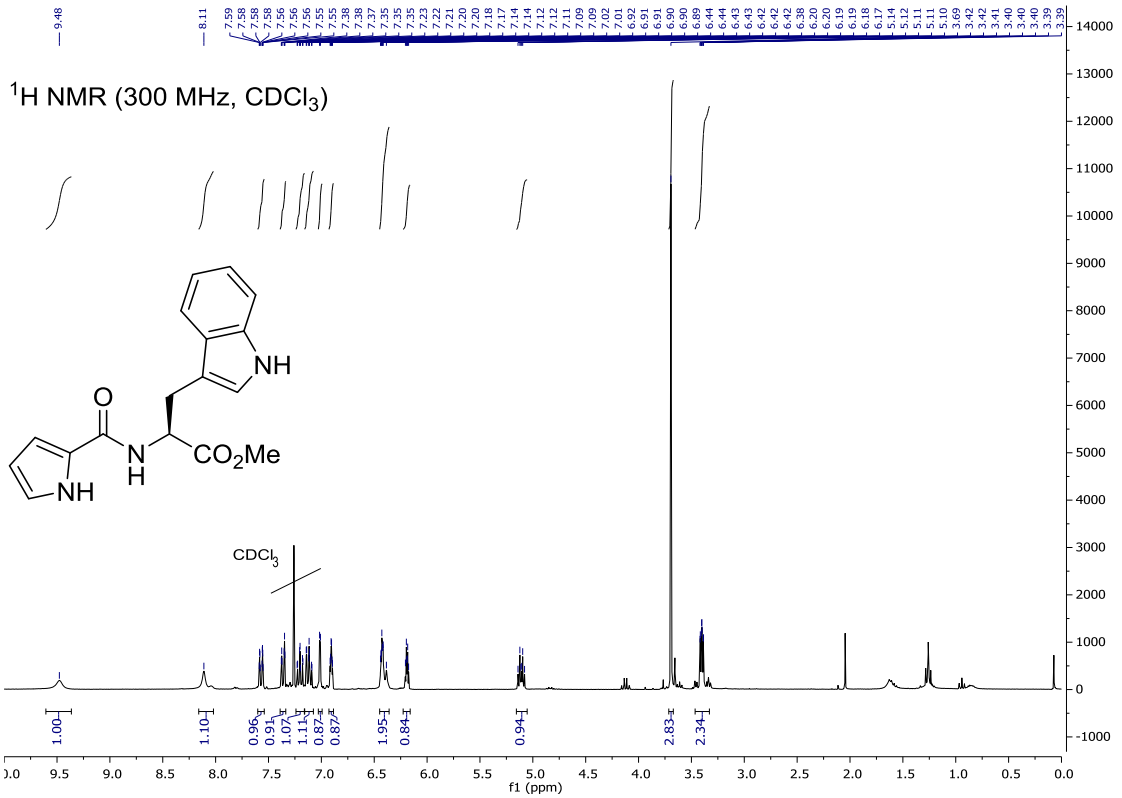
Methyl (1*H*-pyrrole-2-carbonyl)-*L*-leucinate (11b)



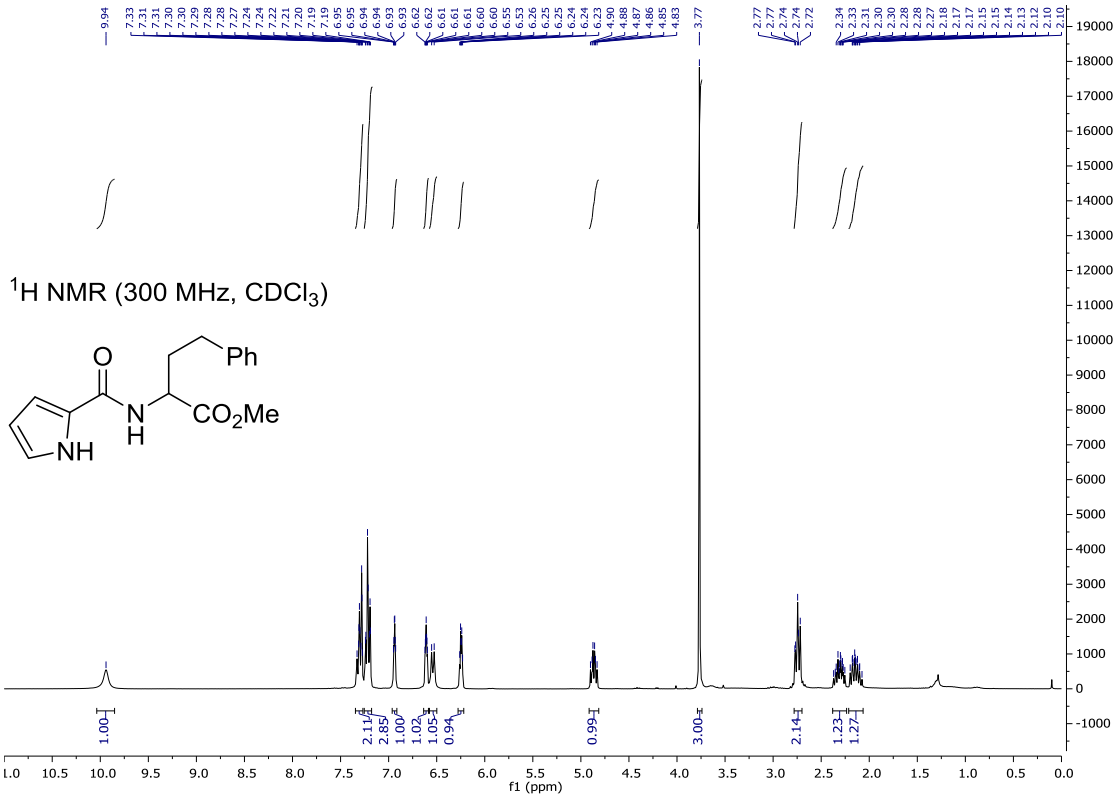
Methyl (*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrole-2-carboxamido)propanoate (11c)

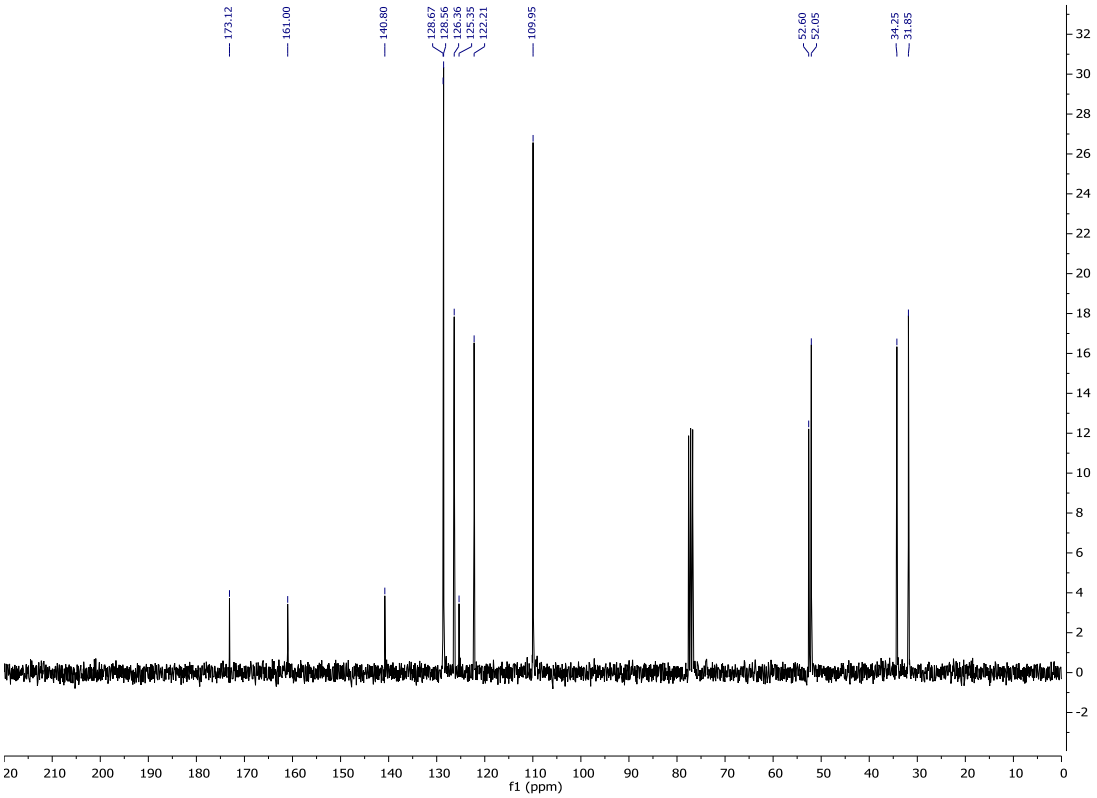


Methyl (1*H*-pyrrole-2-carbonyl)-*L*-tryptophanate (11e)

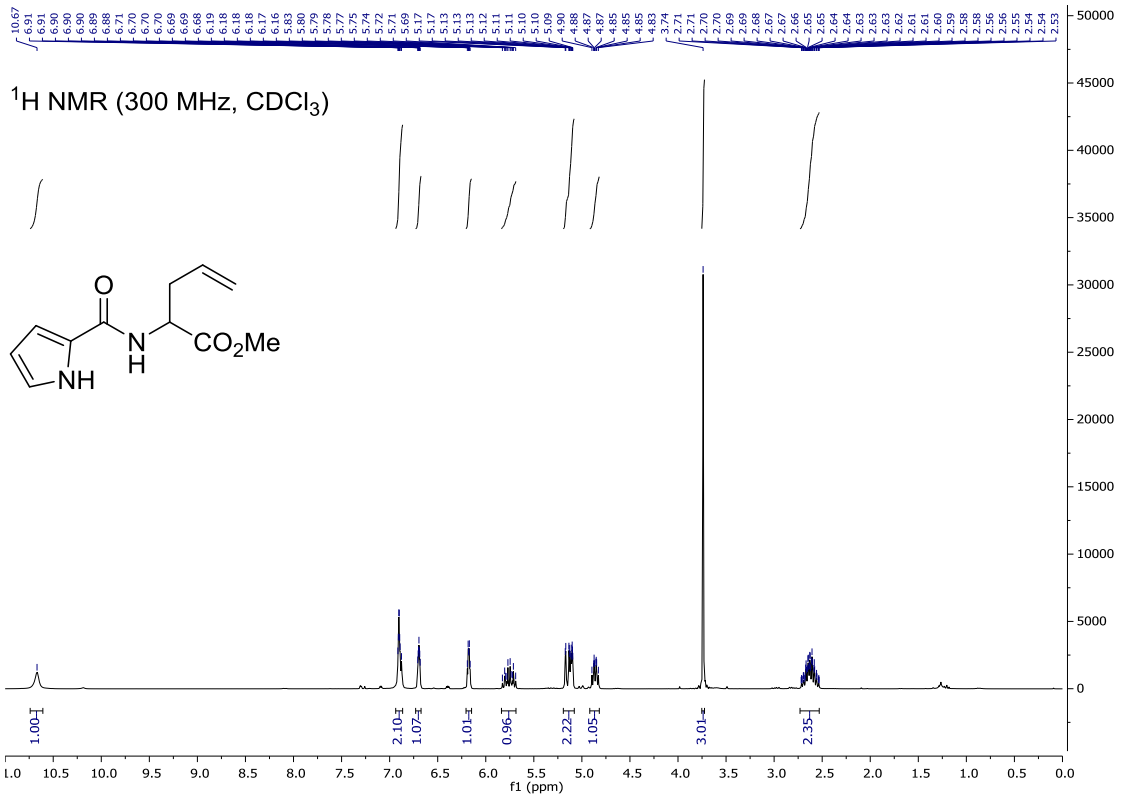


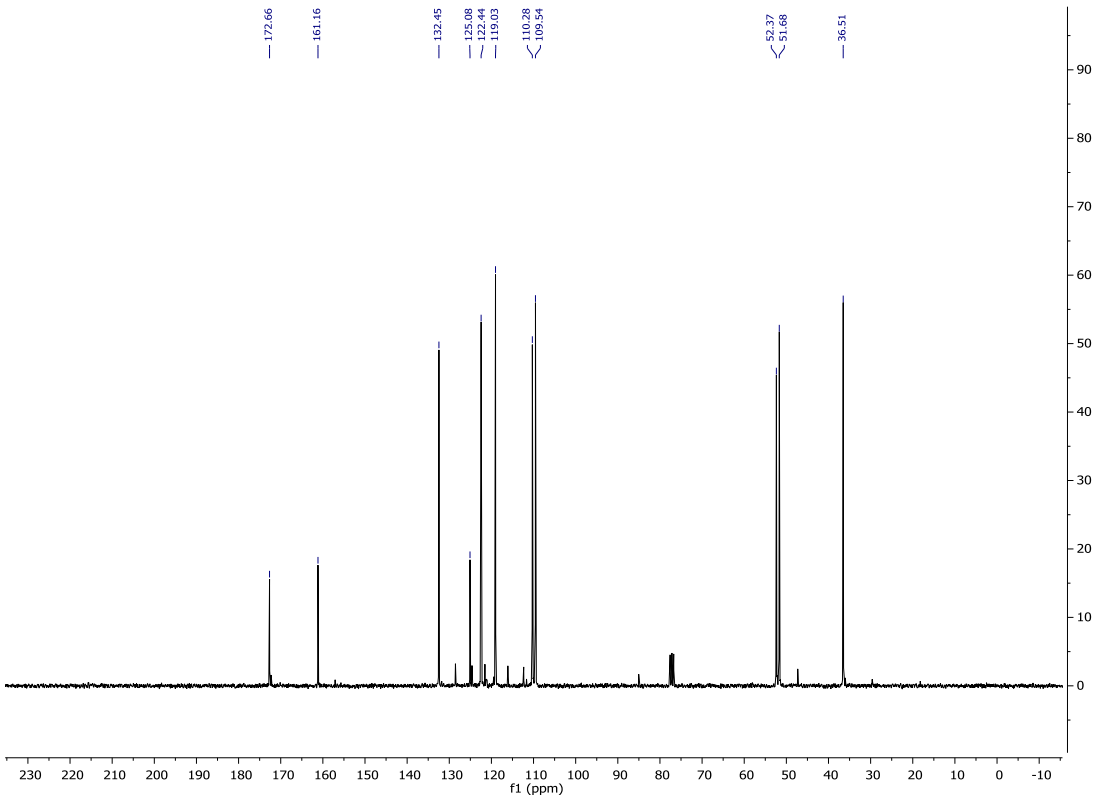
Methyl 4-phenyl-2-(1*H*-pyrrole-2-carboxamido)butanoate (11d)



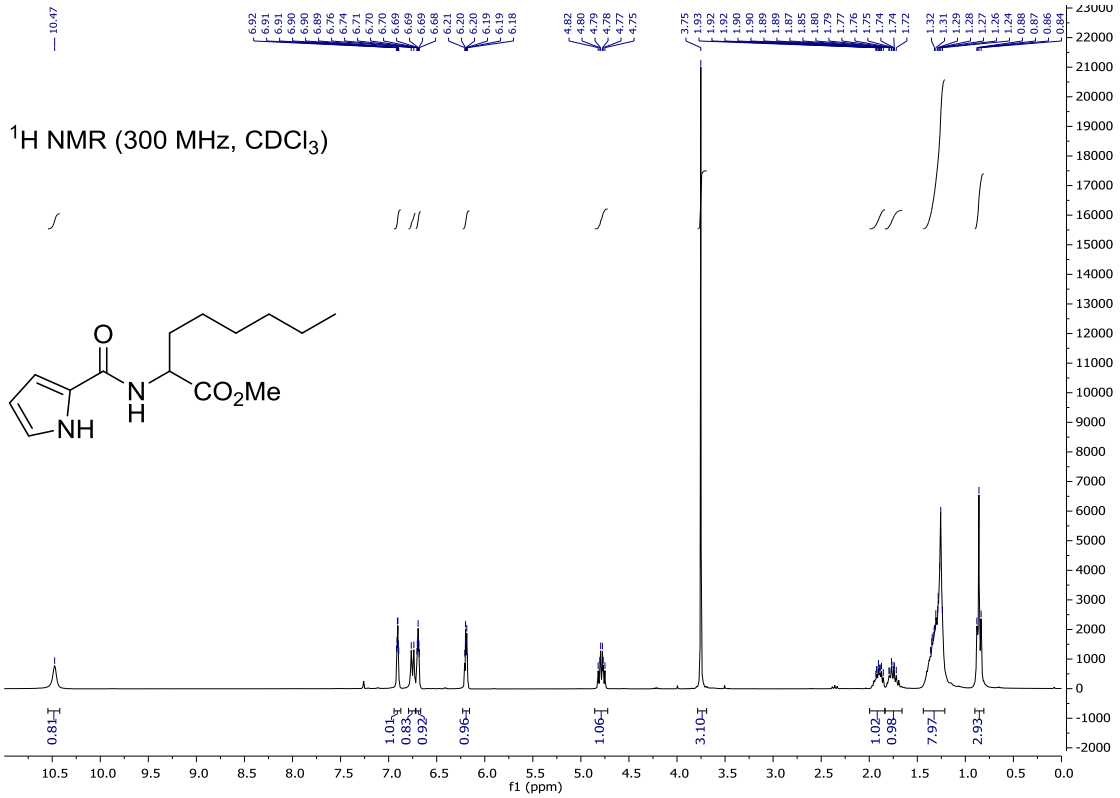


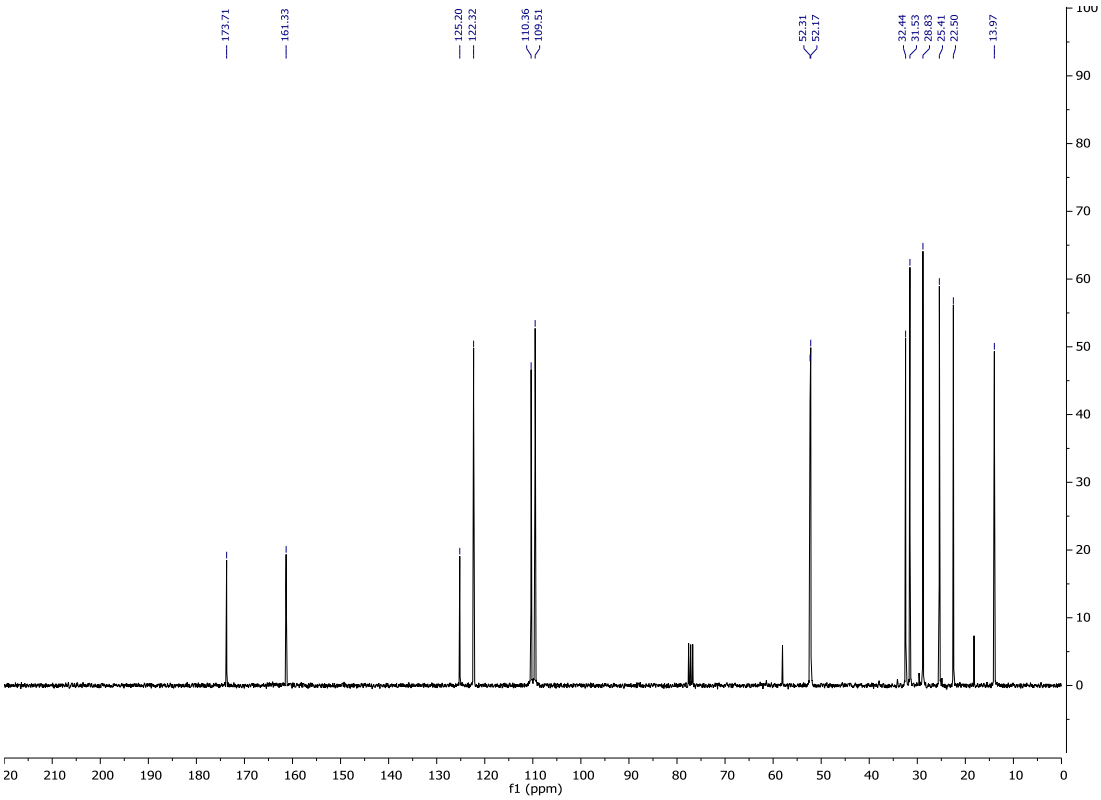
Methyl 2-(1*H*-pyrrole-2-carboxamido)pent-4-enoate (11f)



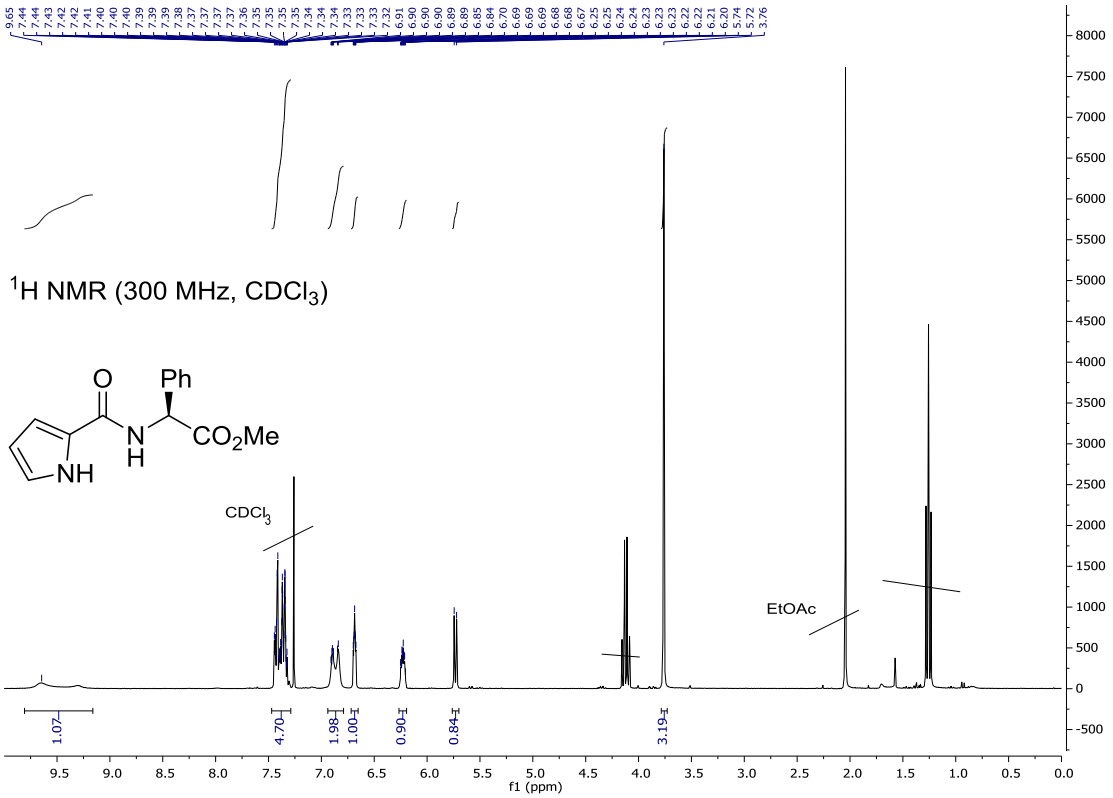


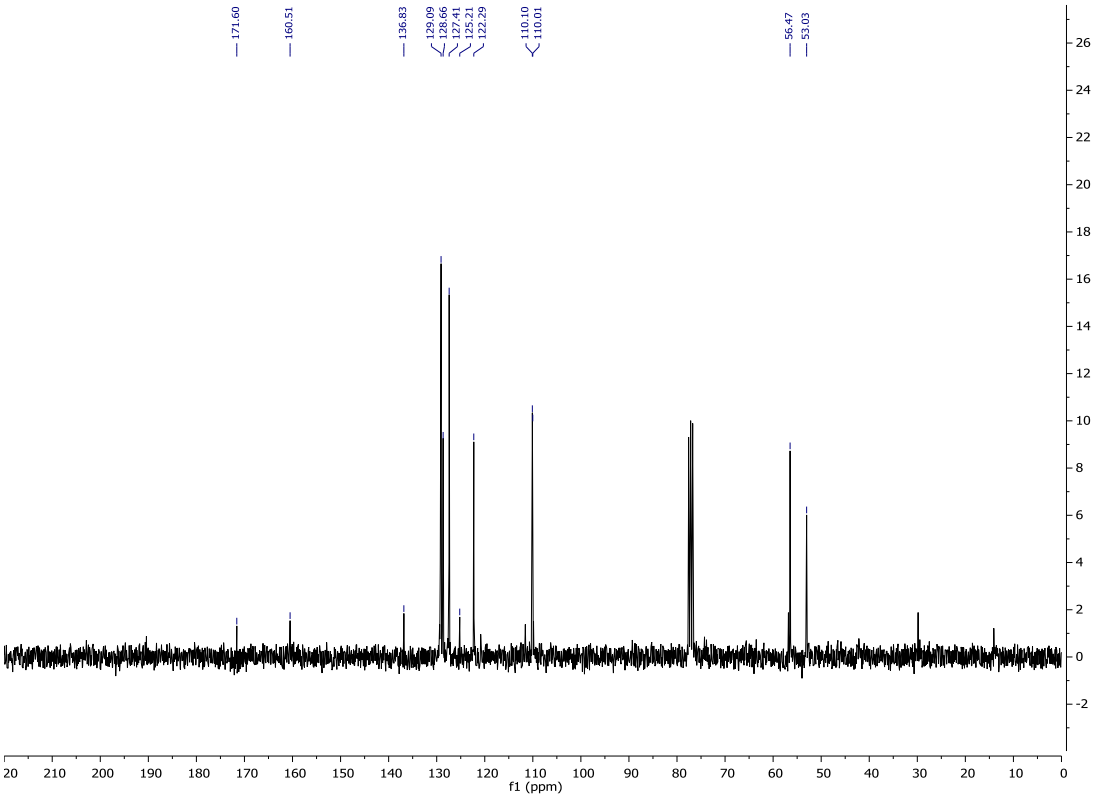
Methyl 2-(1*H*-pyrrole-2-carboxamido)octanoate (11g)



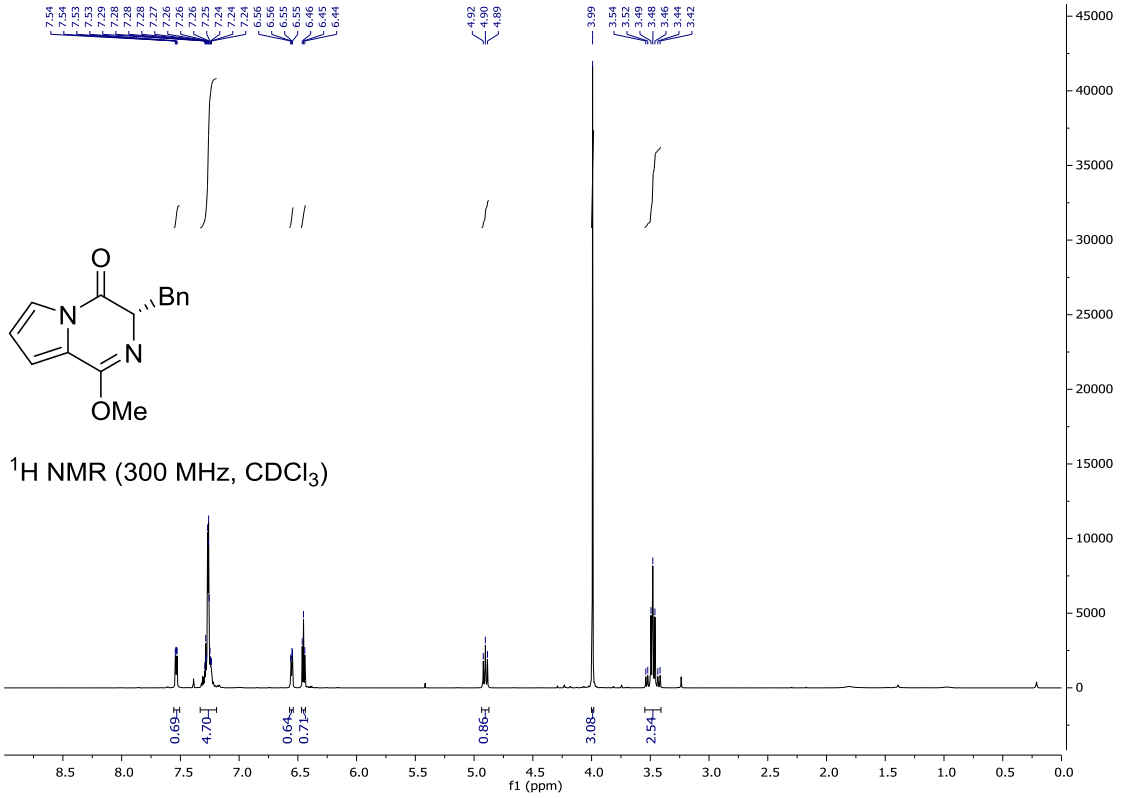


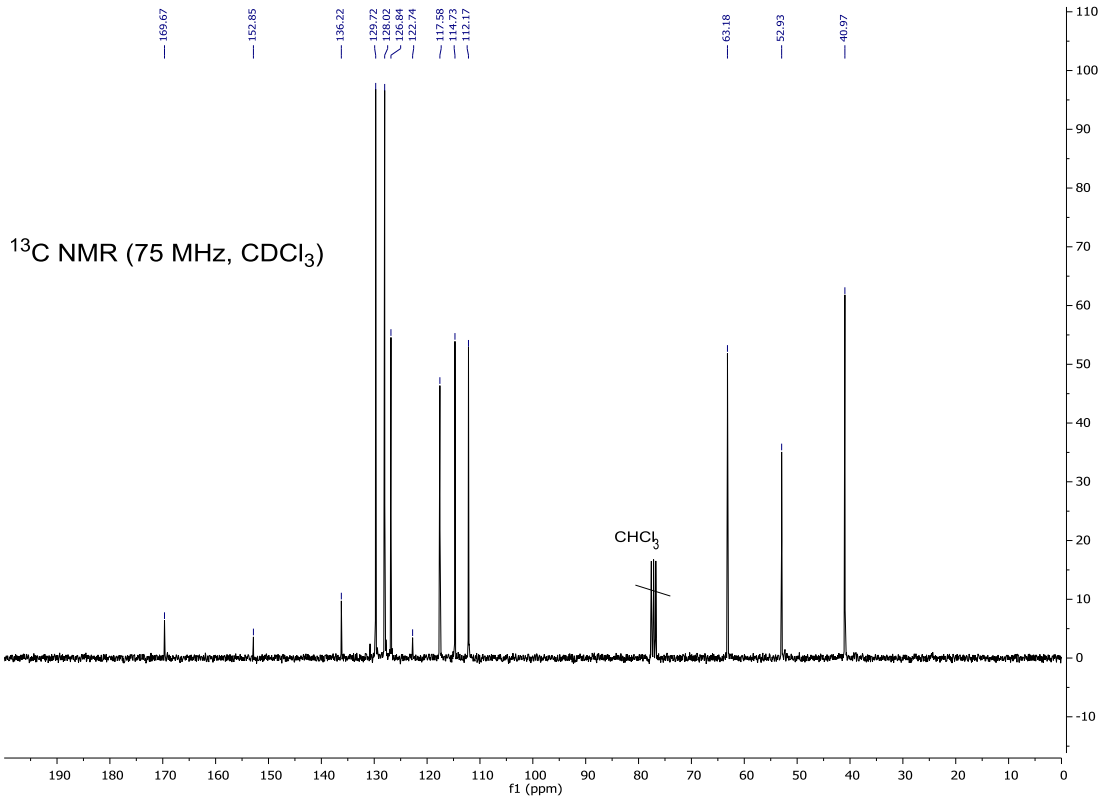
Methyl (*S*)-2-phenyl-2-(1*H*-pyrrole-2-carboxamido)acetate (11h)



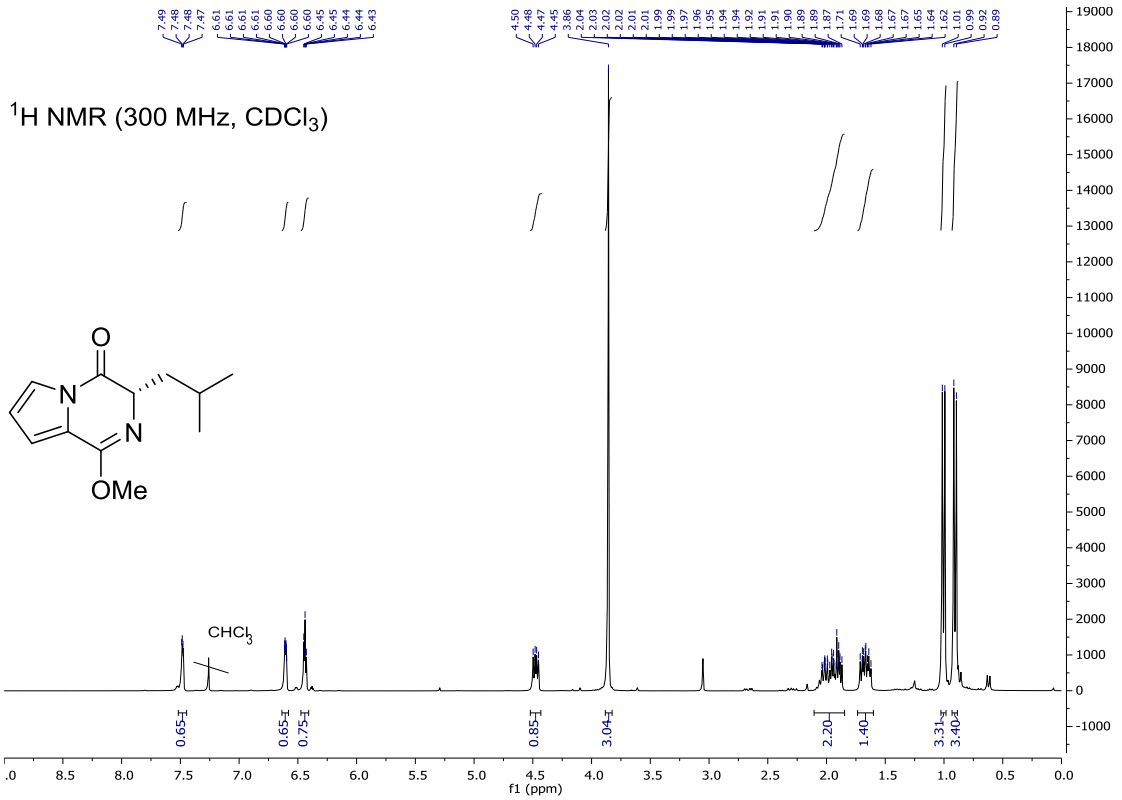


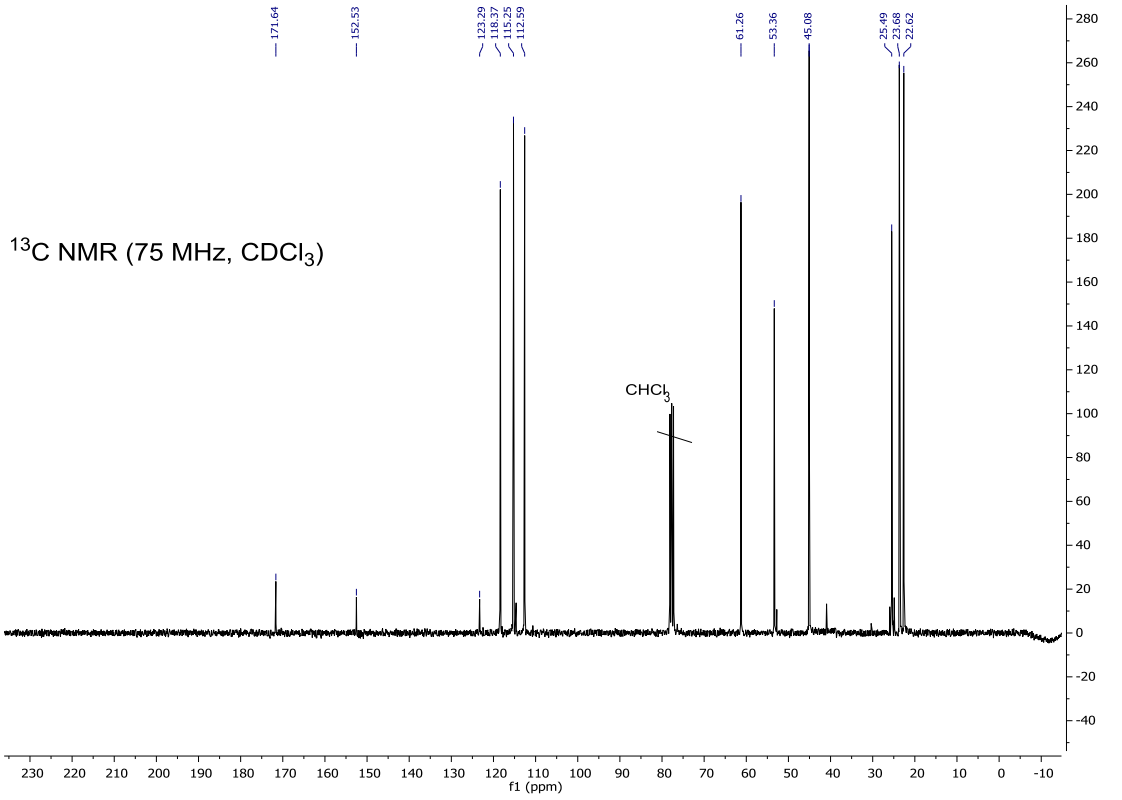
(*S*)-3-Benzyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13a)



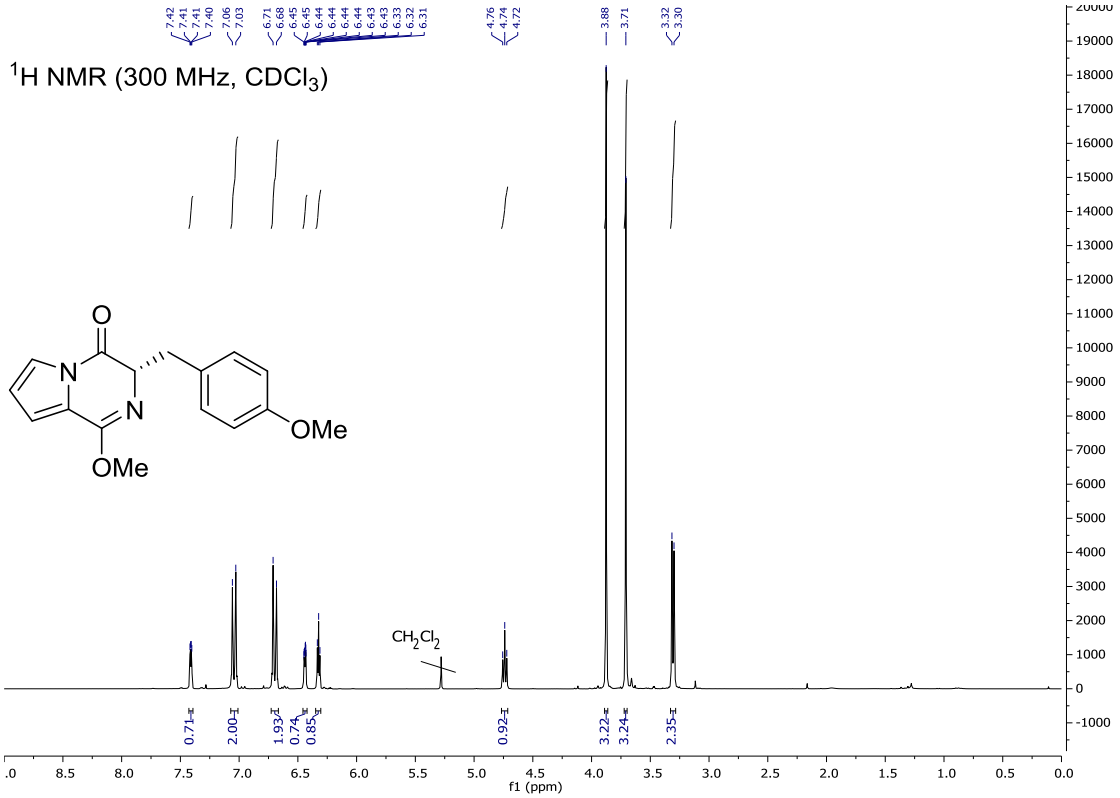


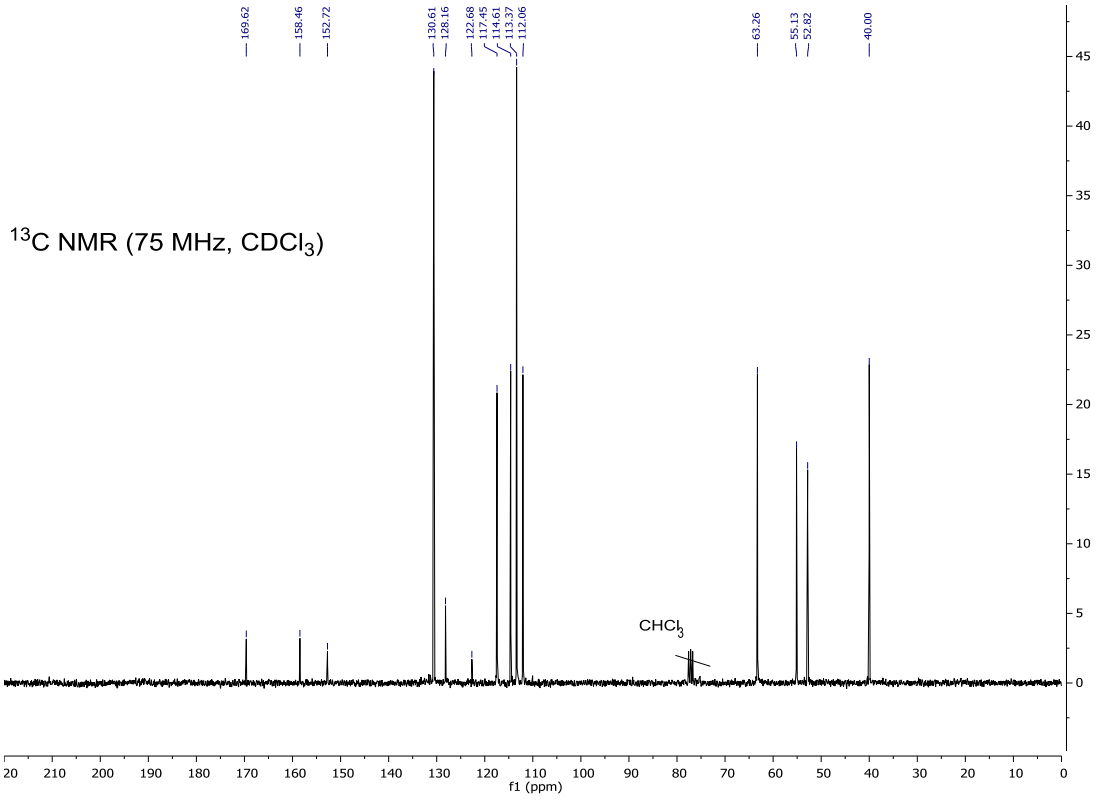
(*S*)-3-Isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13b)



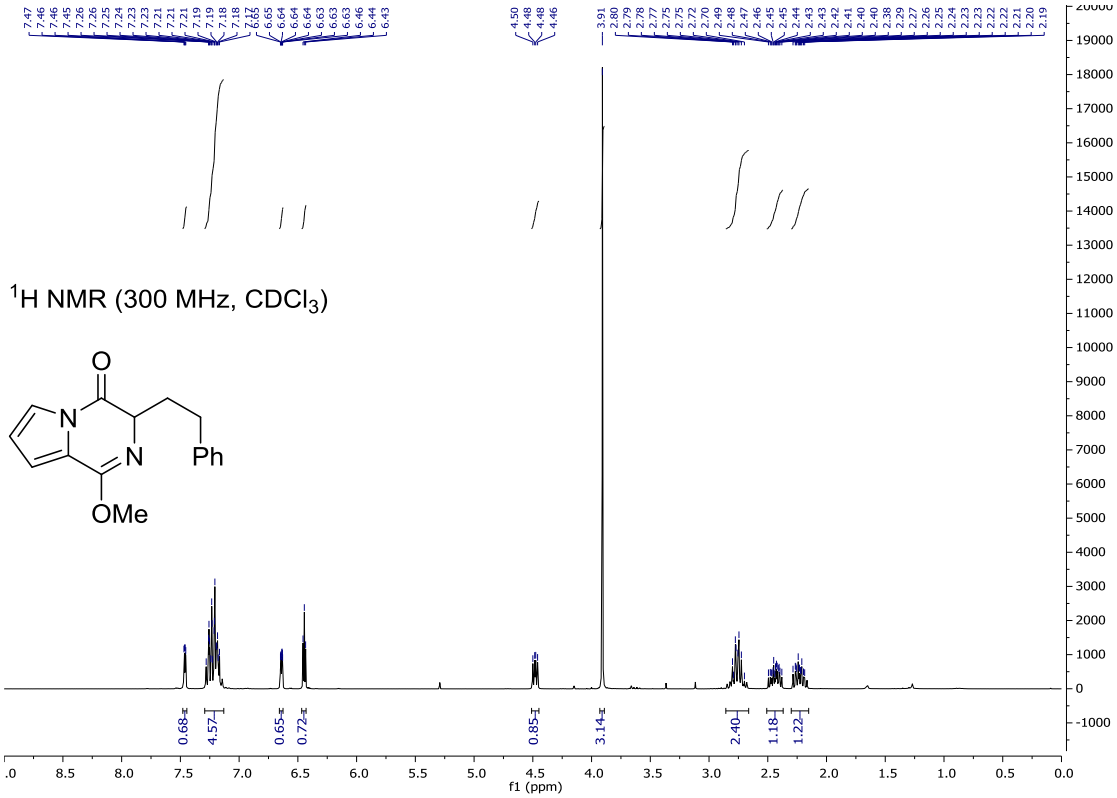


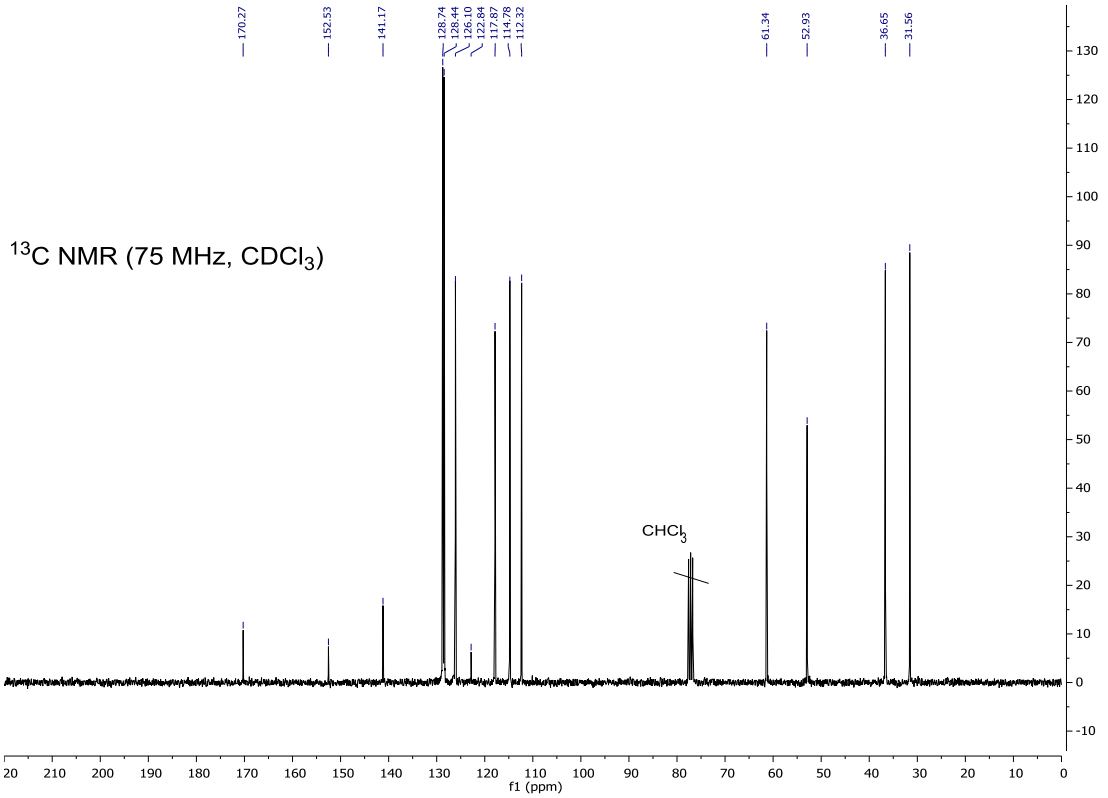
(*S*)-1-Methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13c)



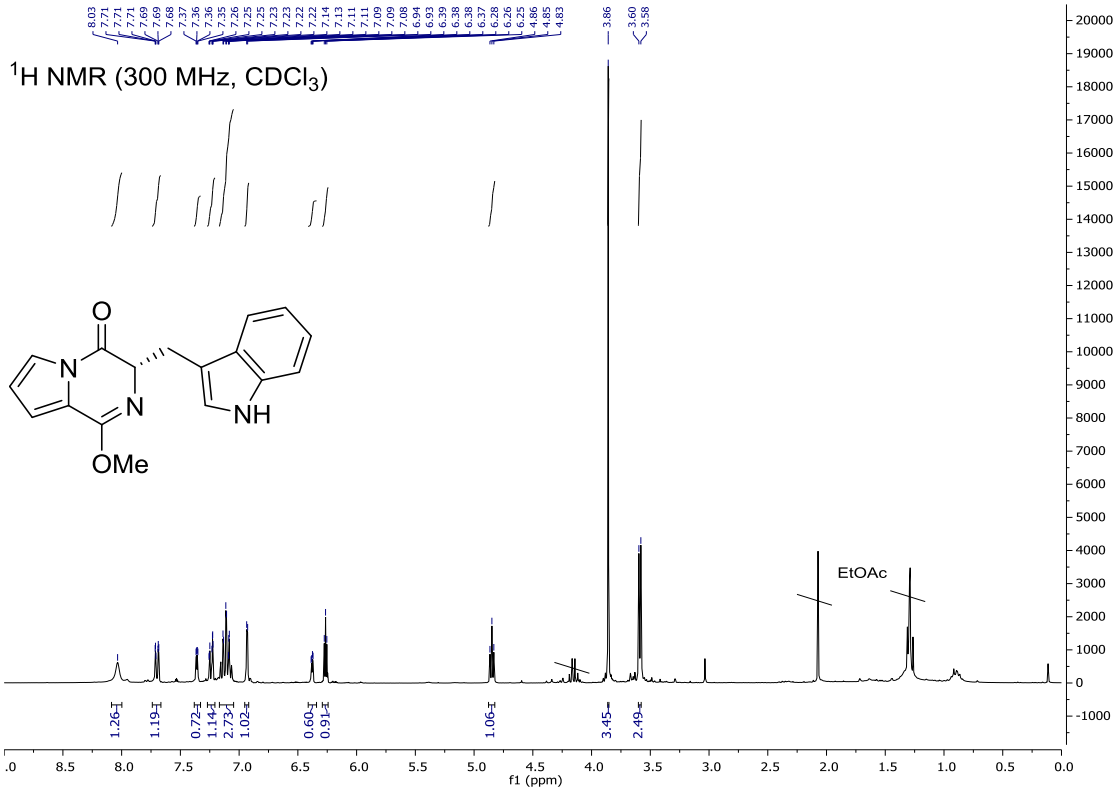


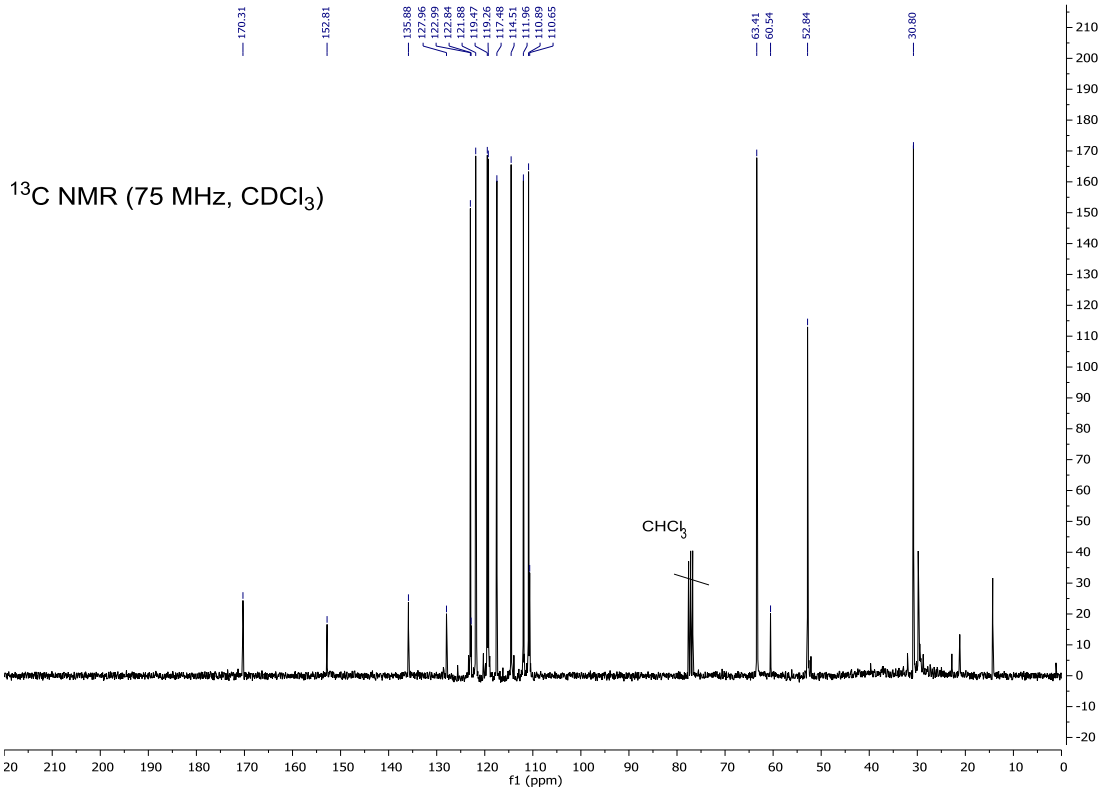
1-Methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13d)



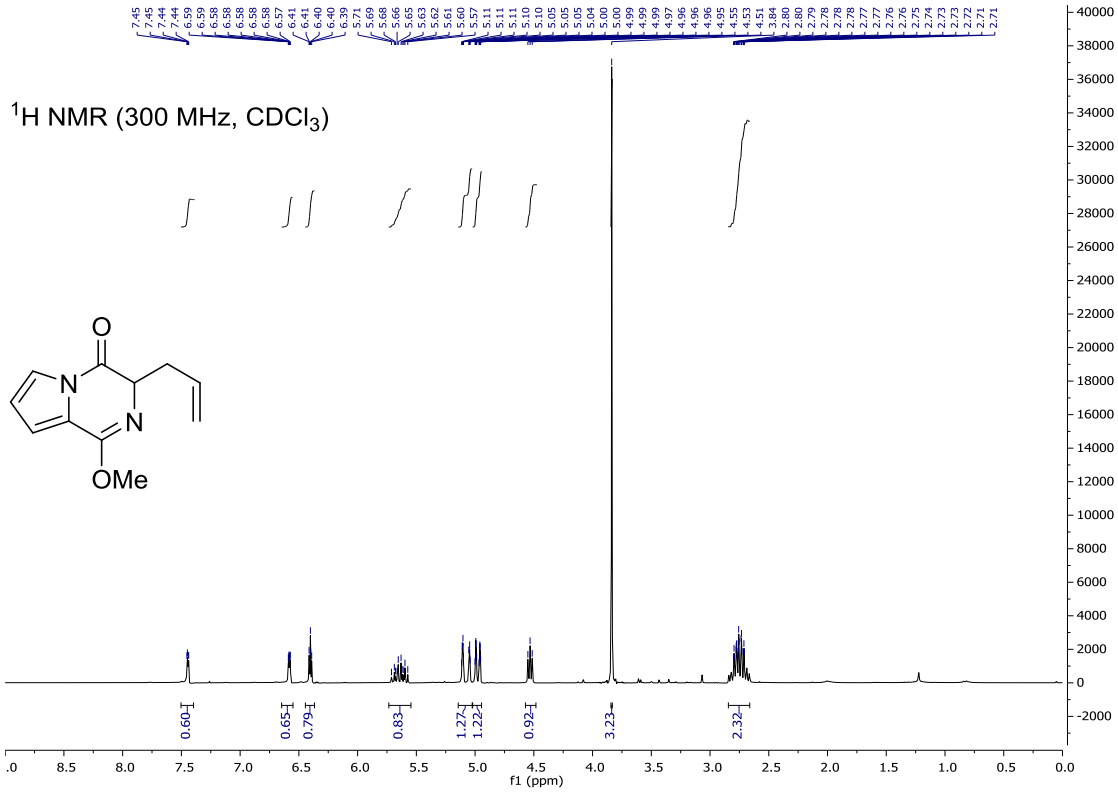


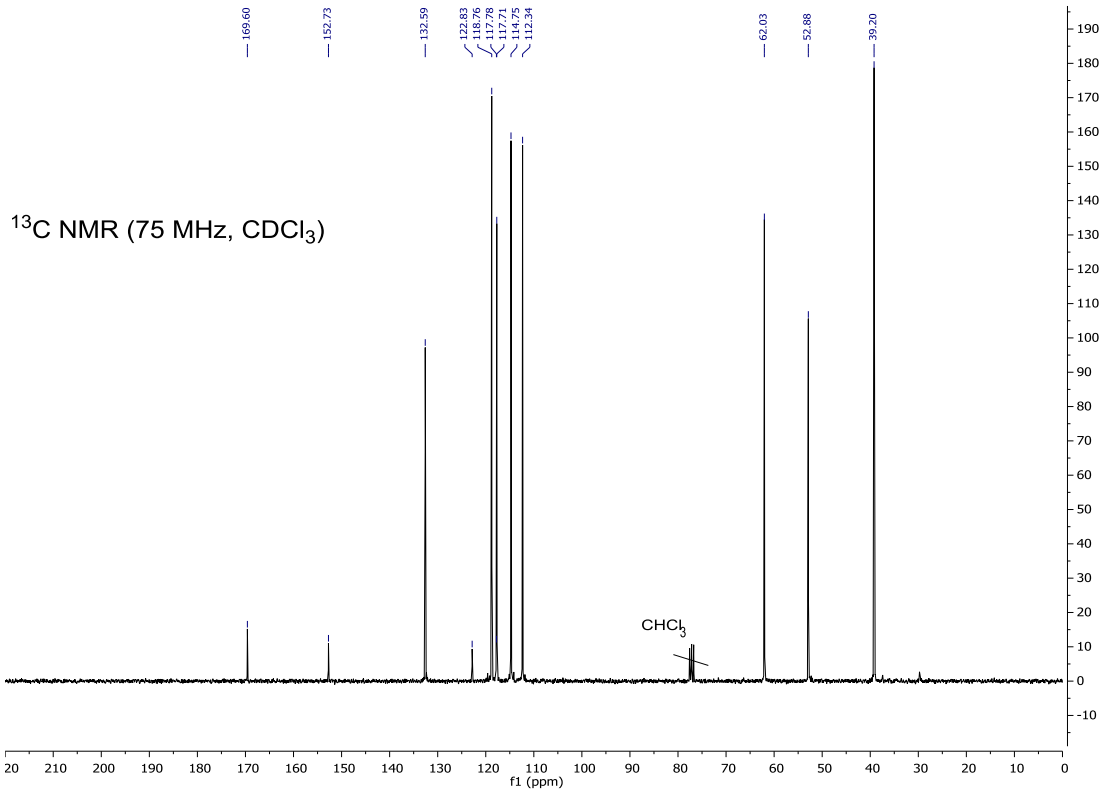
(*S*)-3-((1*H*-Indol-3-yl)methyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13e)



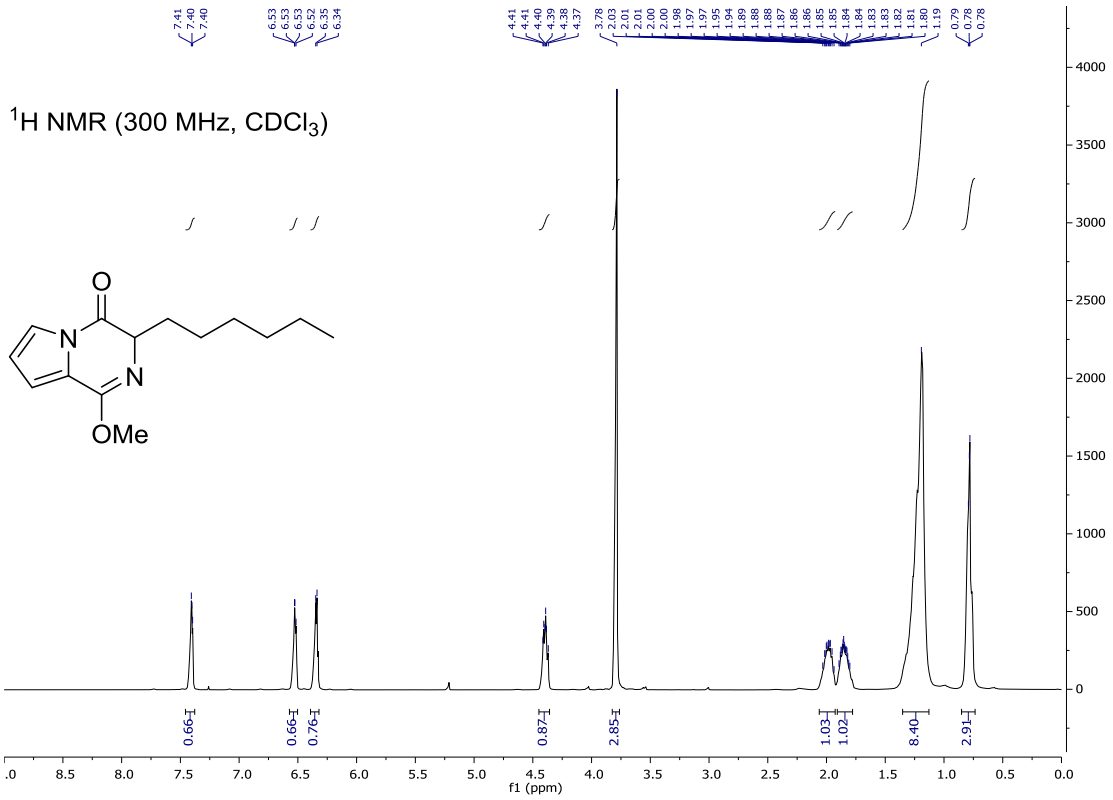


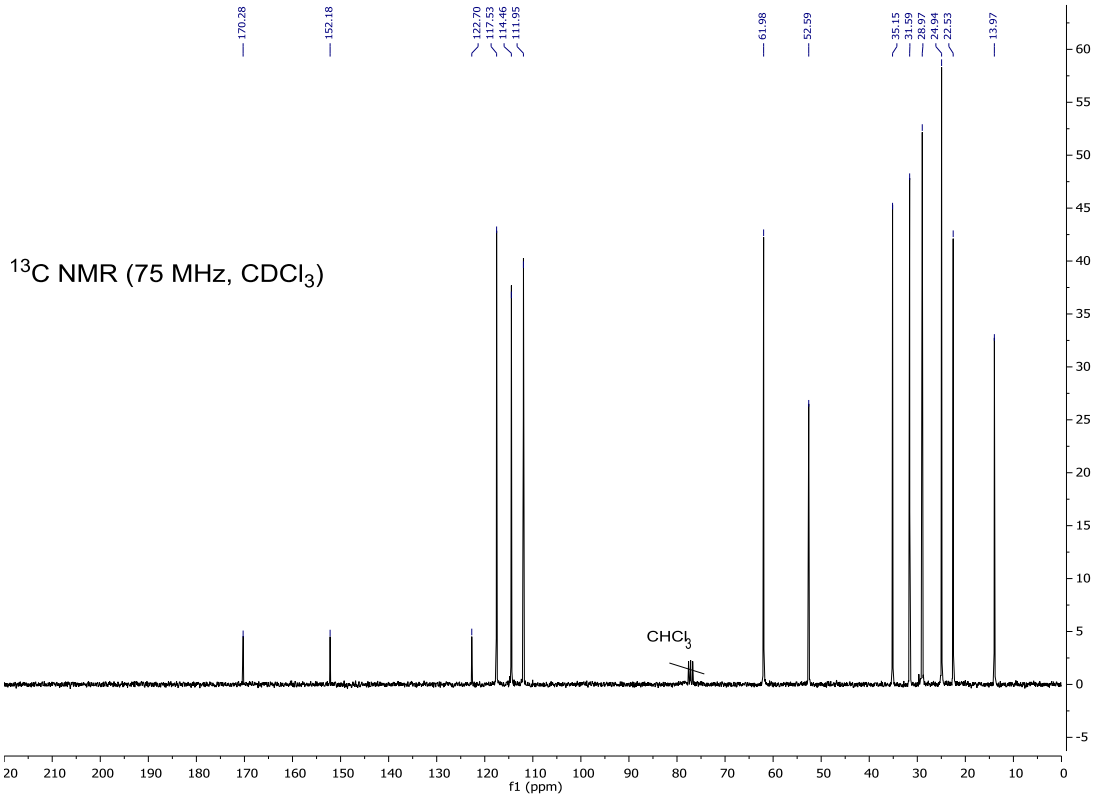
3-Allyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13f)



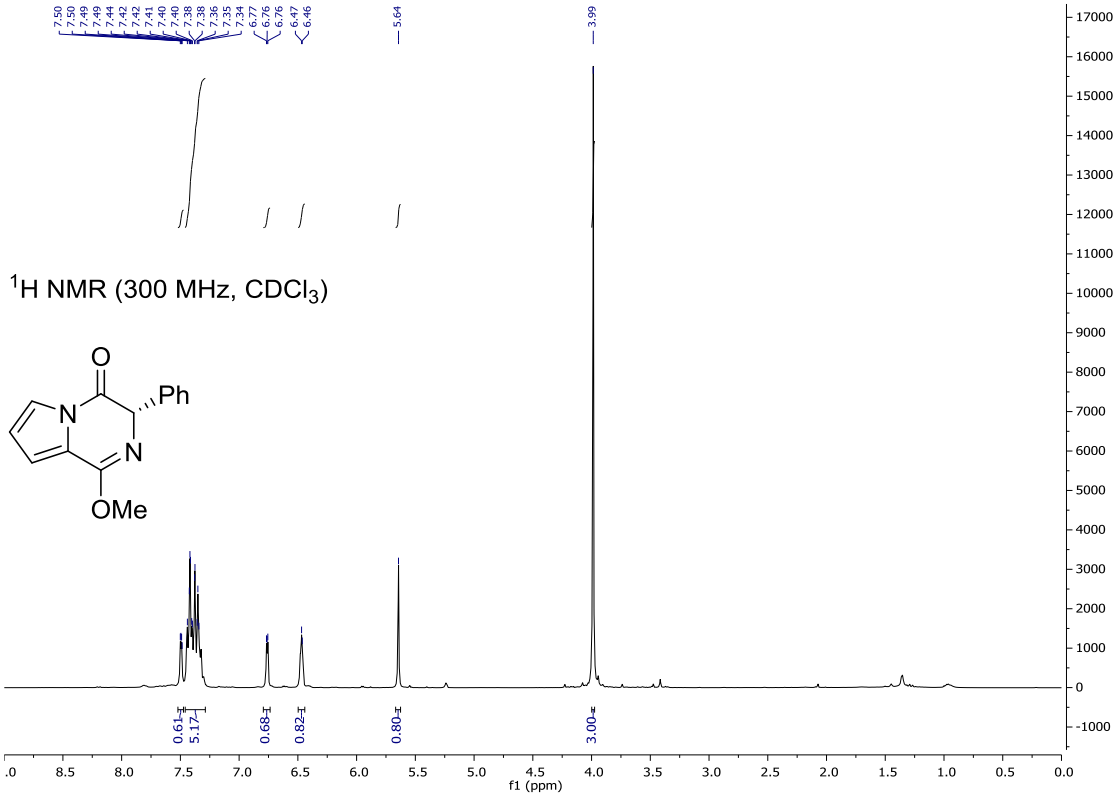


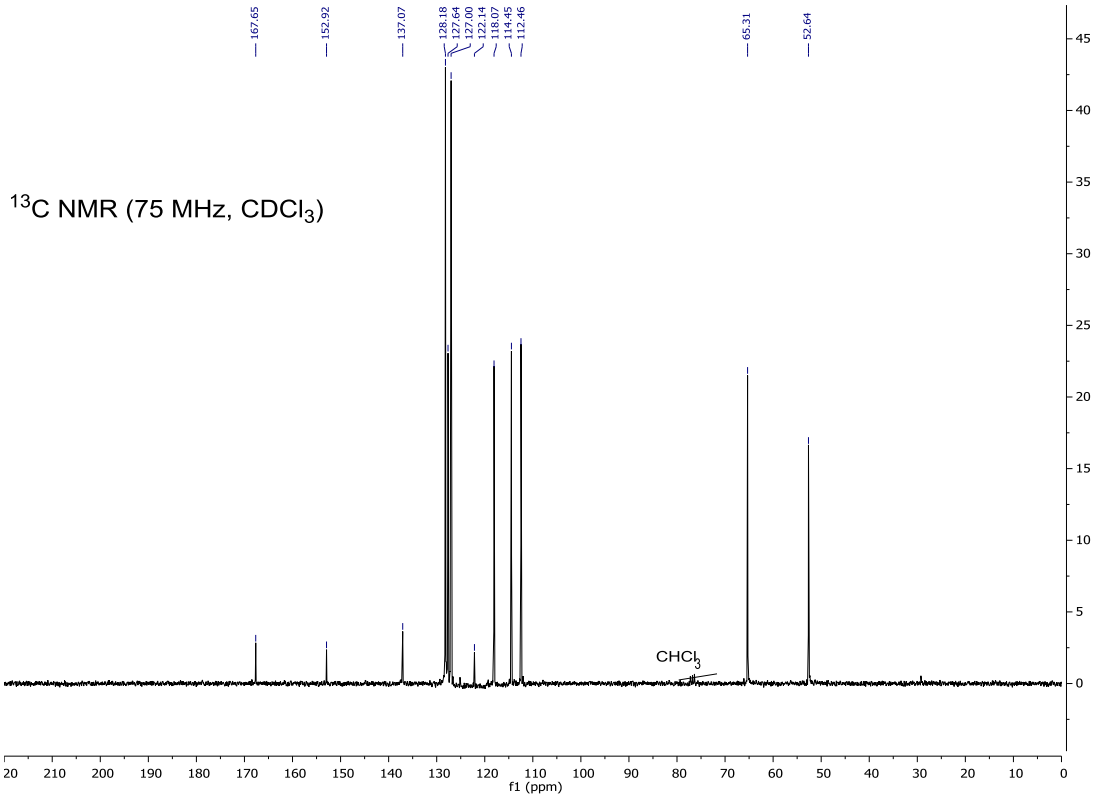
3-Hexyl-1-methoxypyrrolo[1,2-a]pyrazin-4(3H)-one (13g)



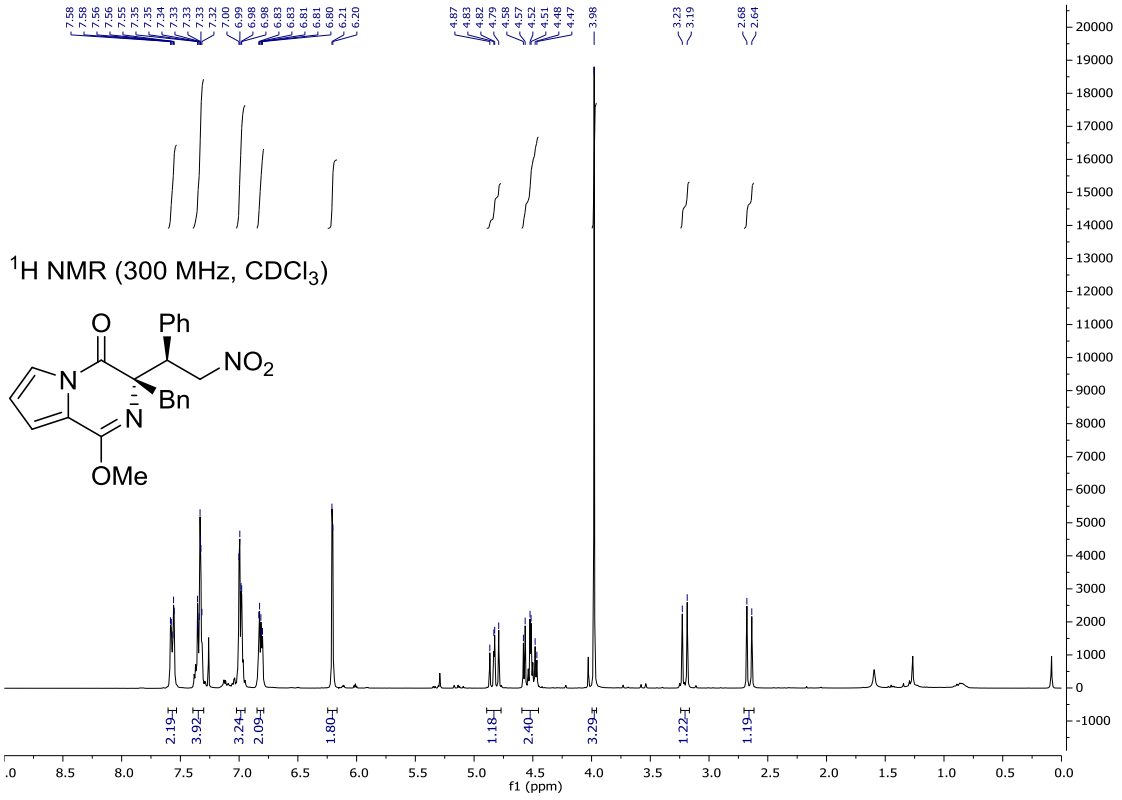


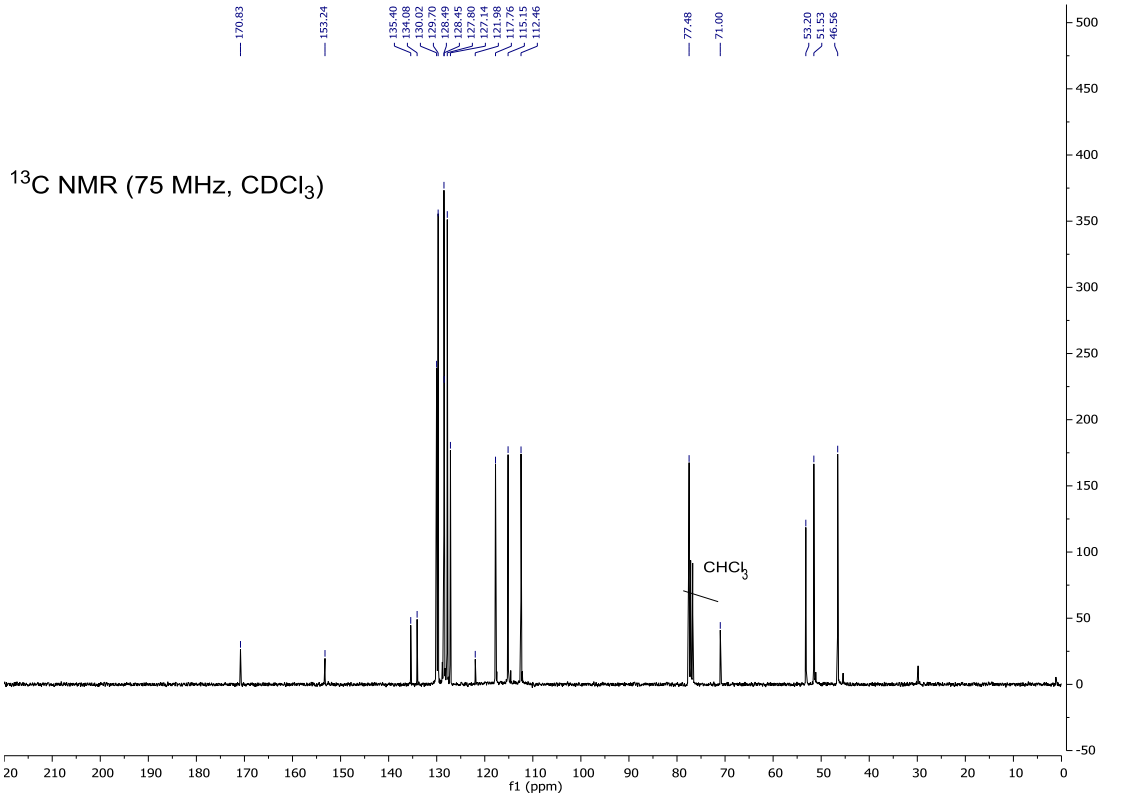
(*S*)-1-Methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (13h)



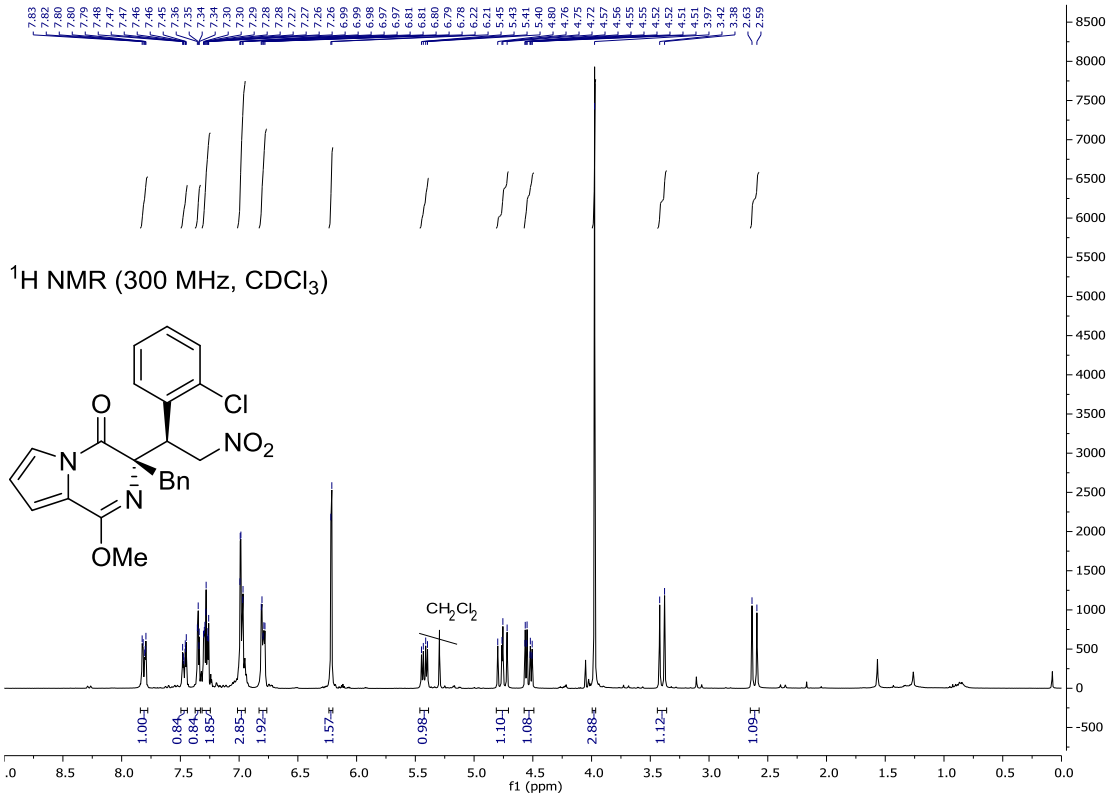


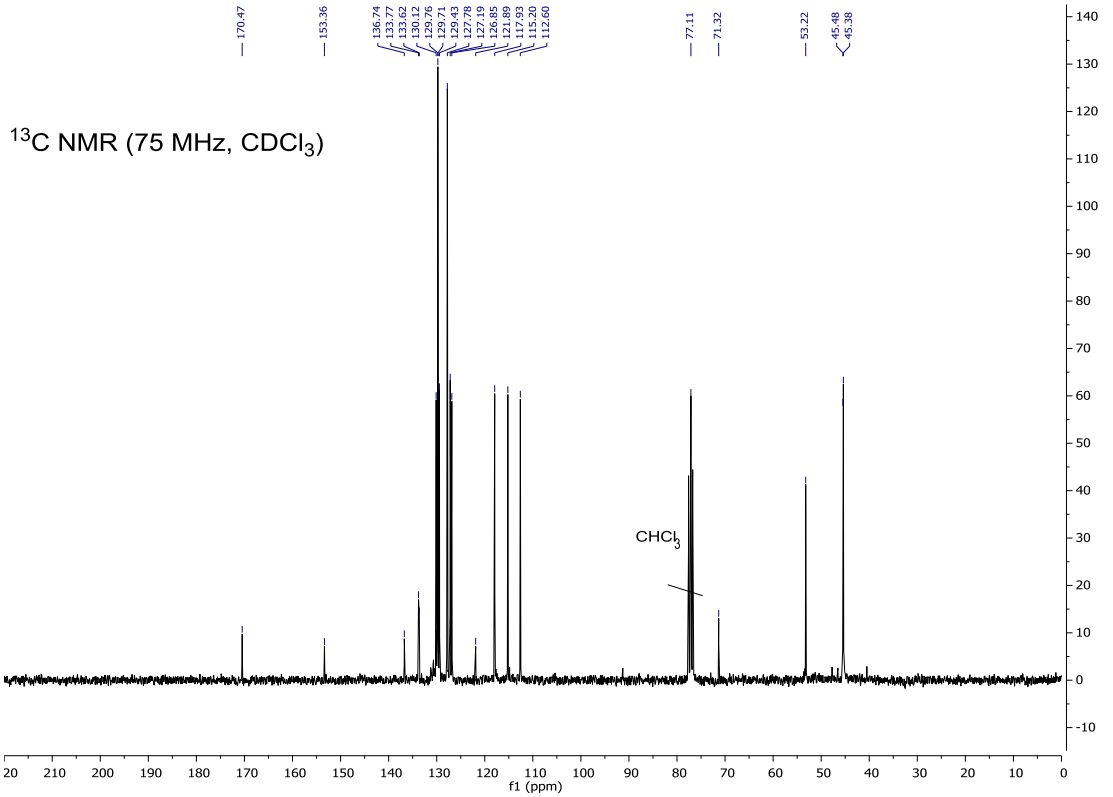
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aa)



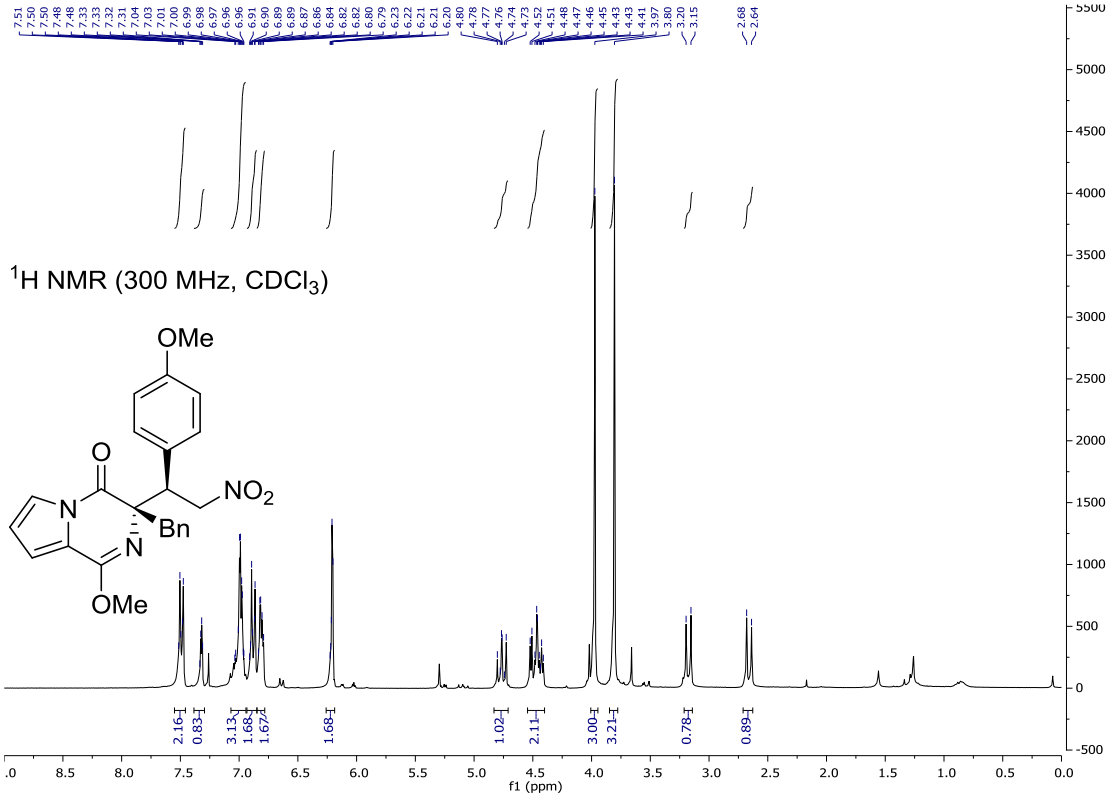


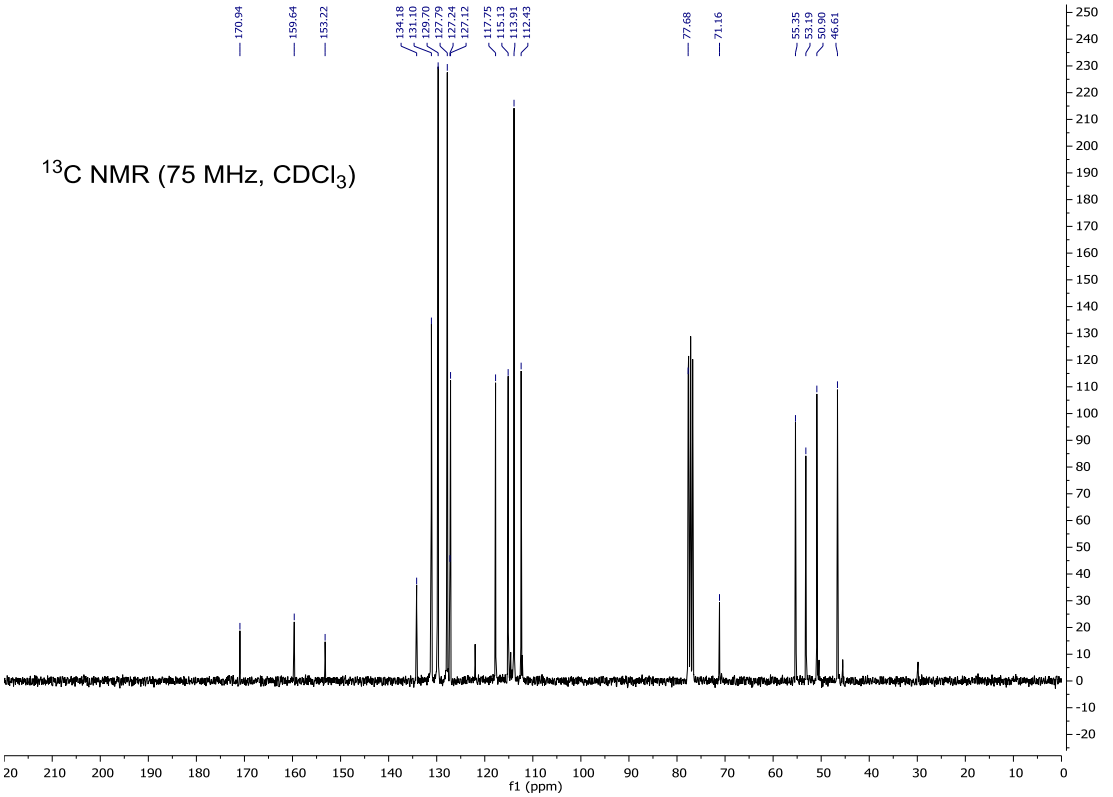
(*S*)-3-Benzyl-3-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ab)



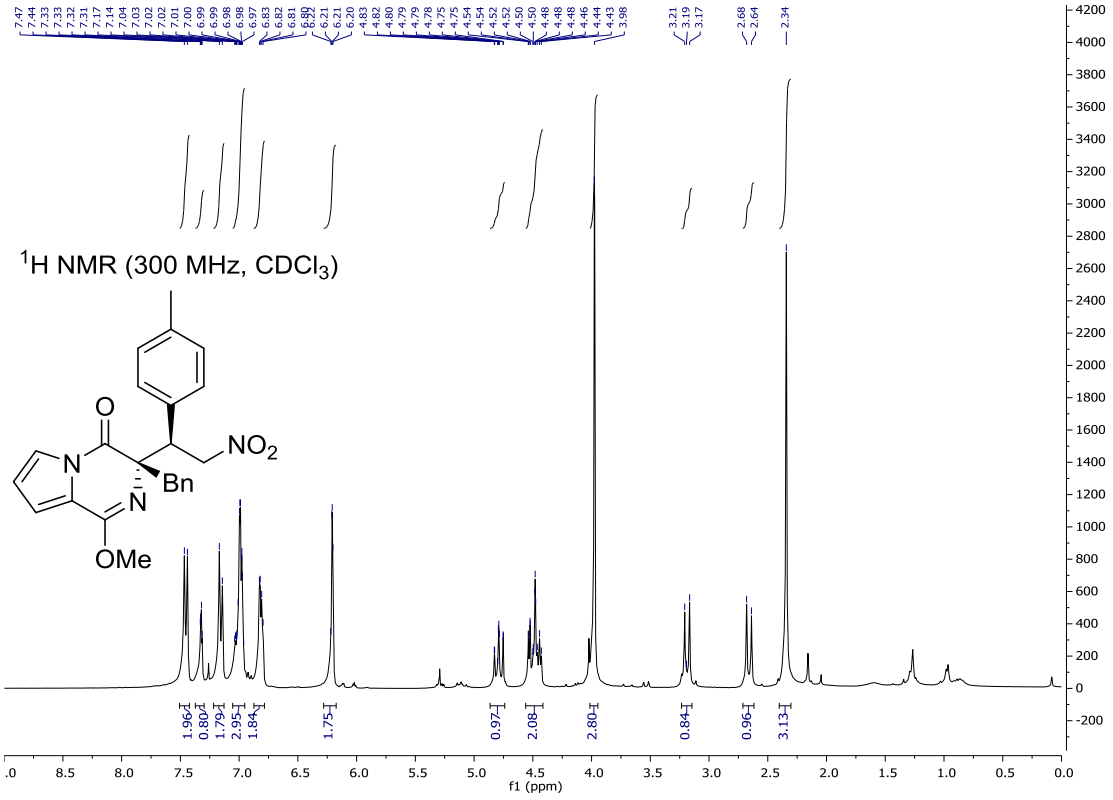


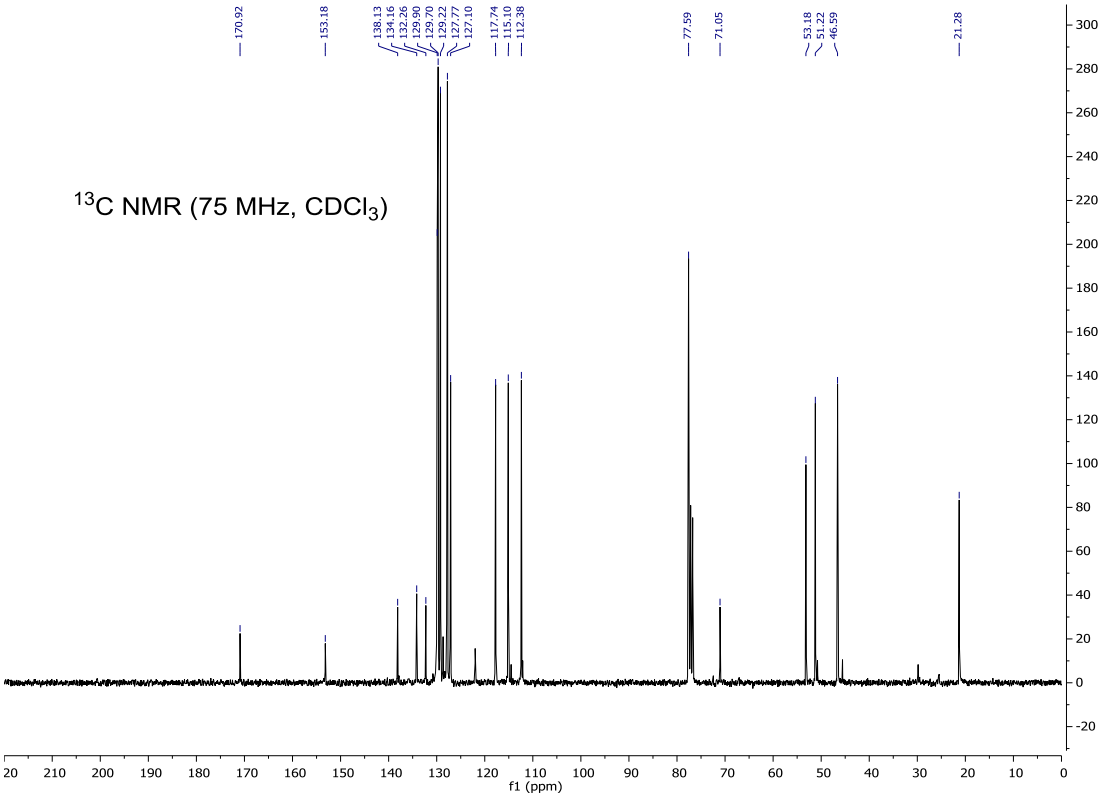
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ac)



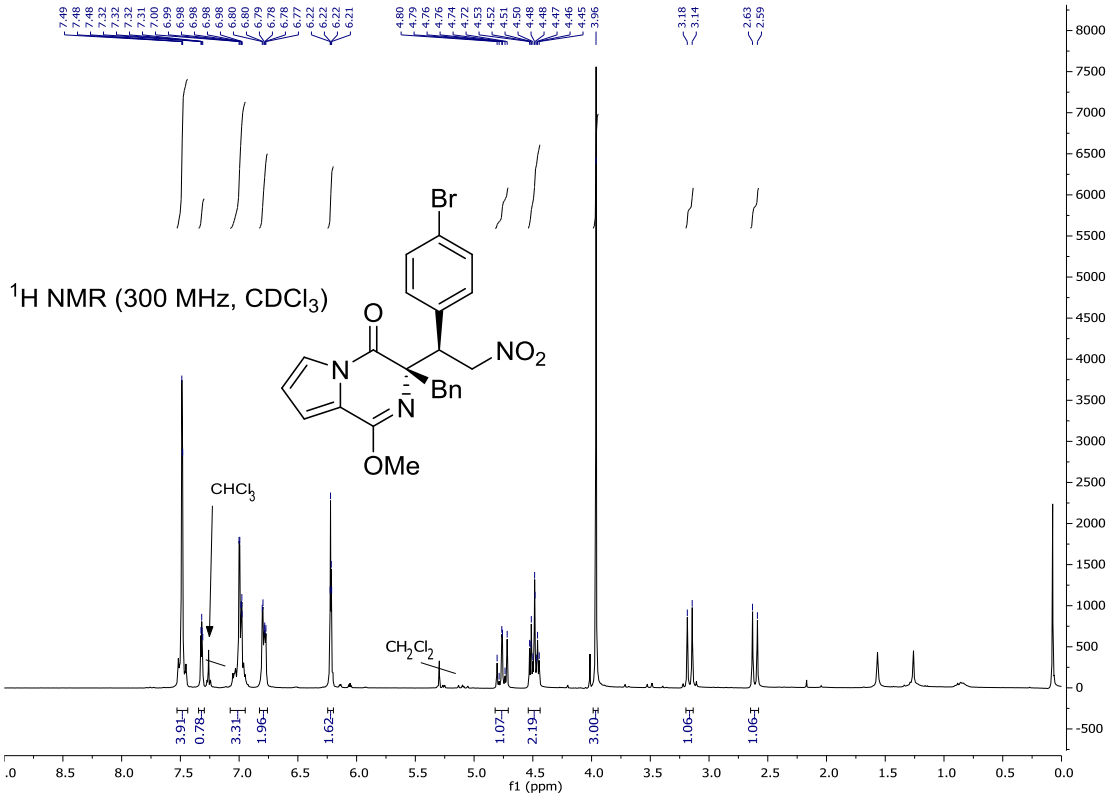


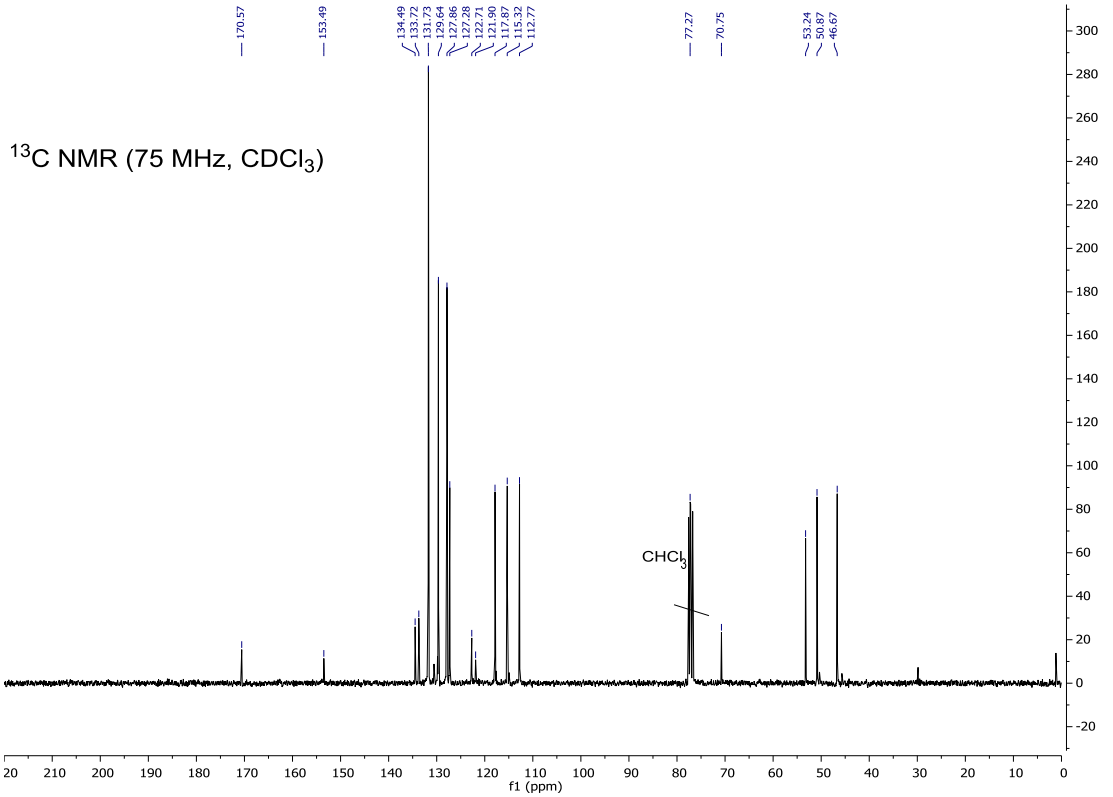
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ad)



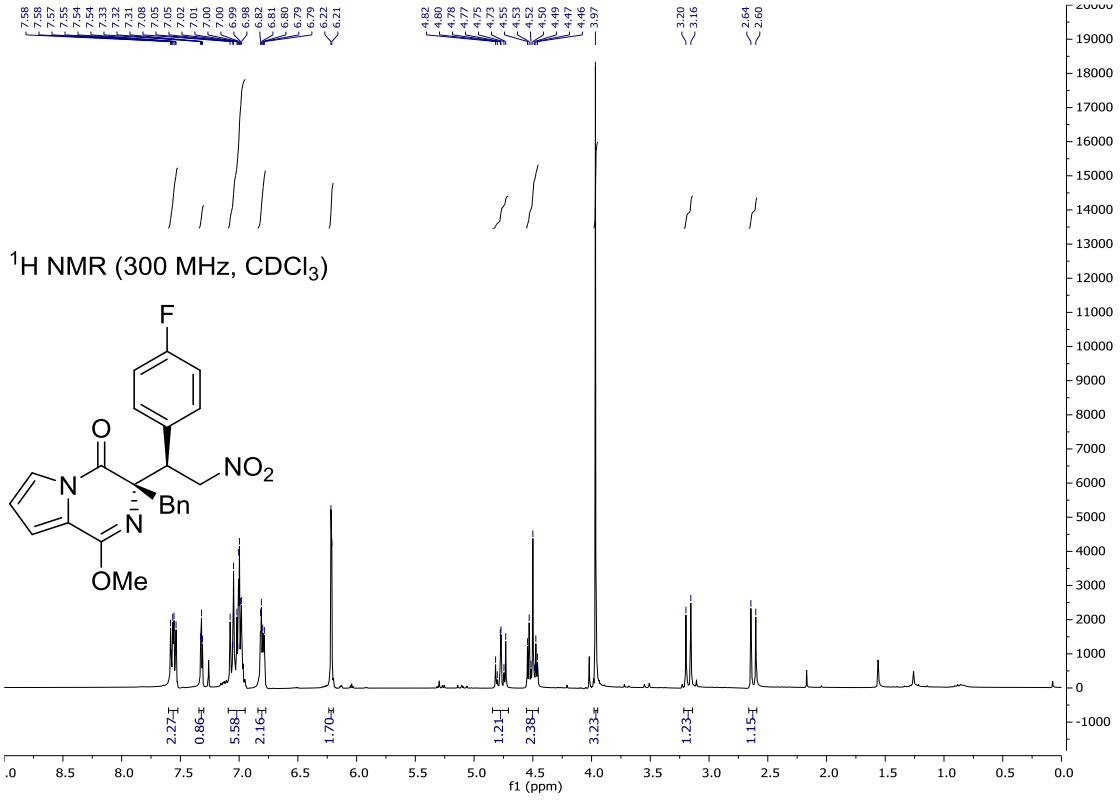


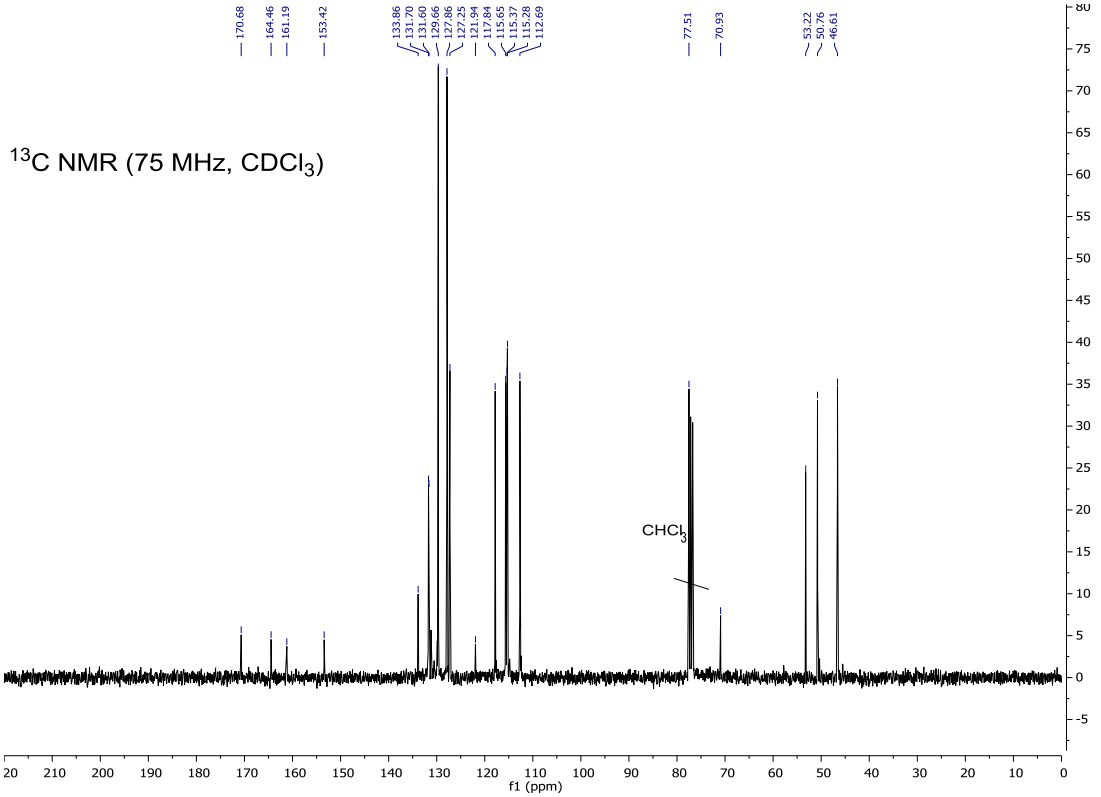
(*S*)-3-Benzyl-3-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ae)



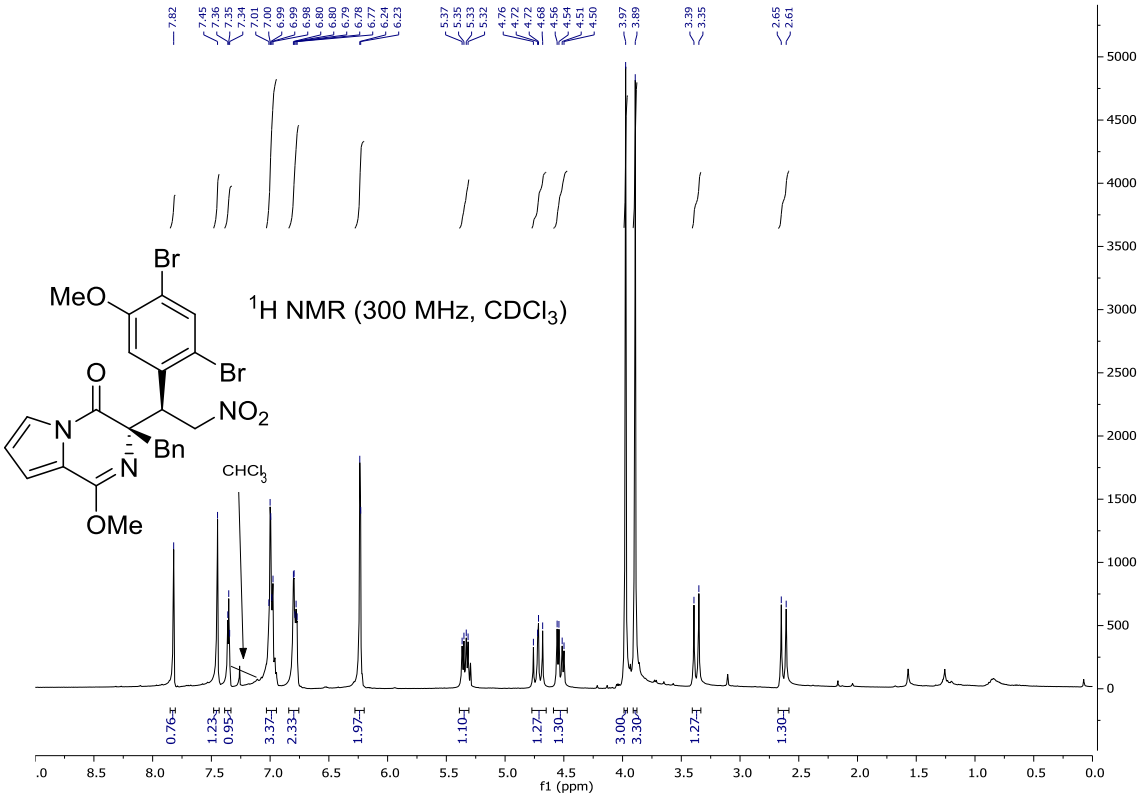


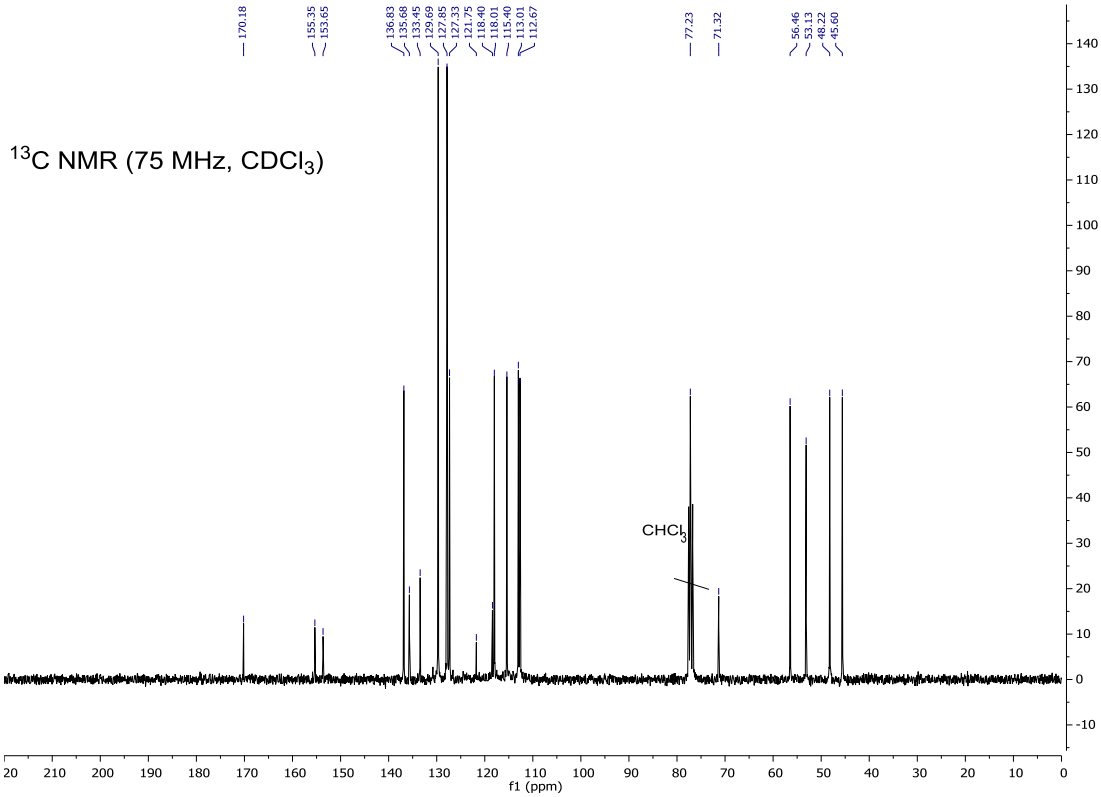
(*S*)-3-Benzyl-3-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20af)



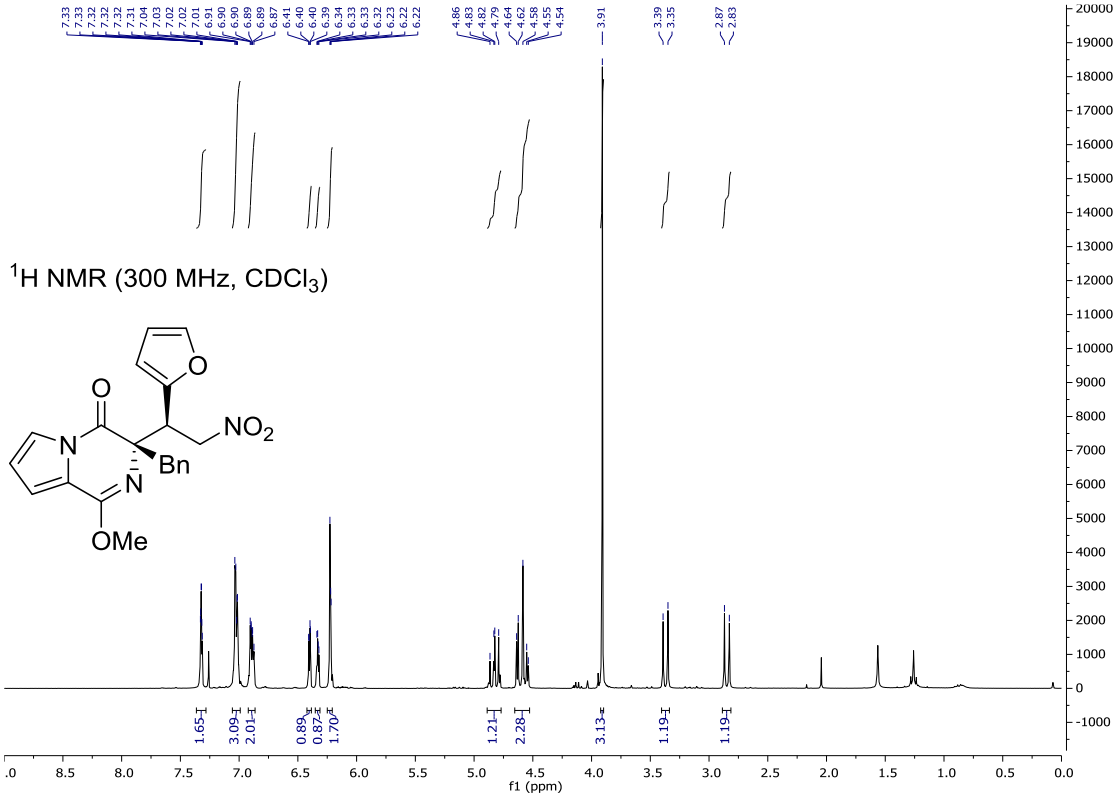


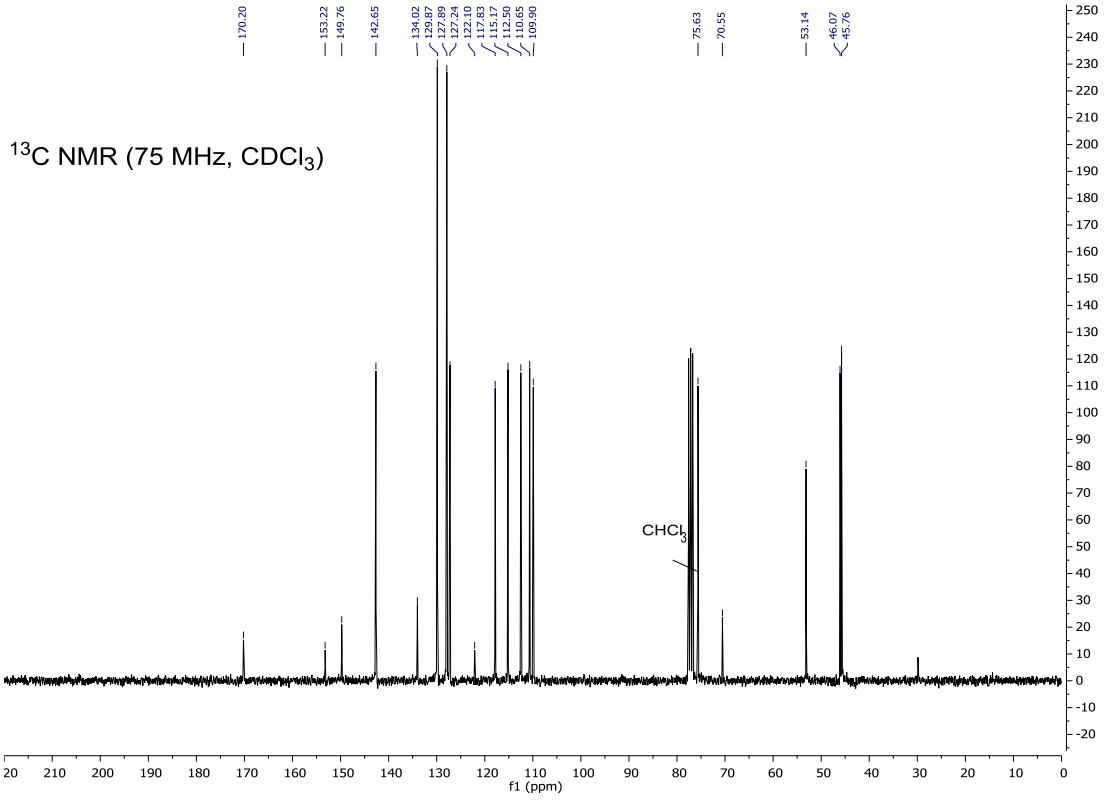
(*S*)-3-Benzyl-3-((*S*)-1-(2,4-dibromo-5-methoxyphenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ag)



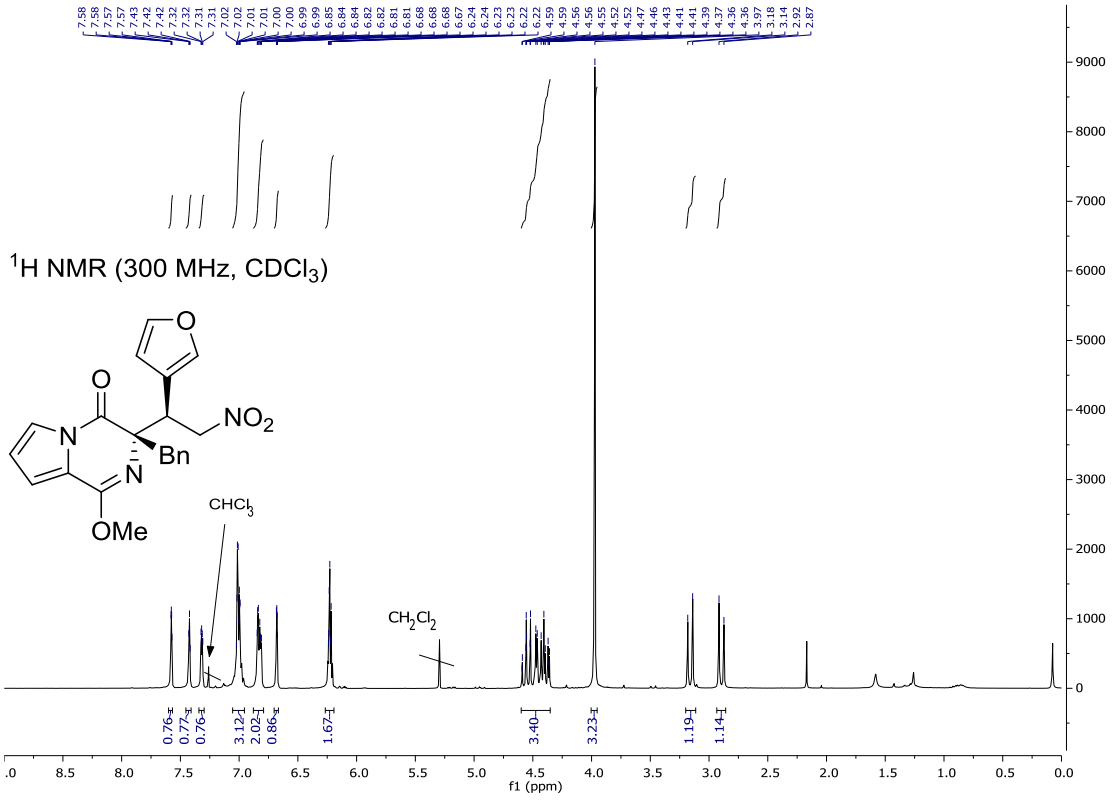


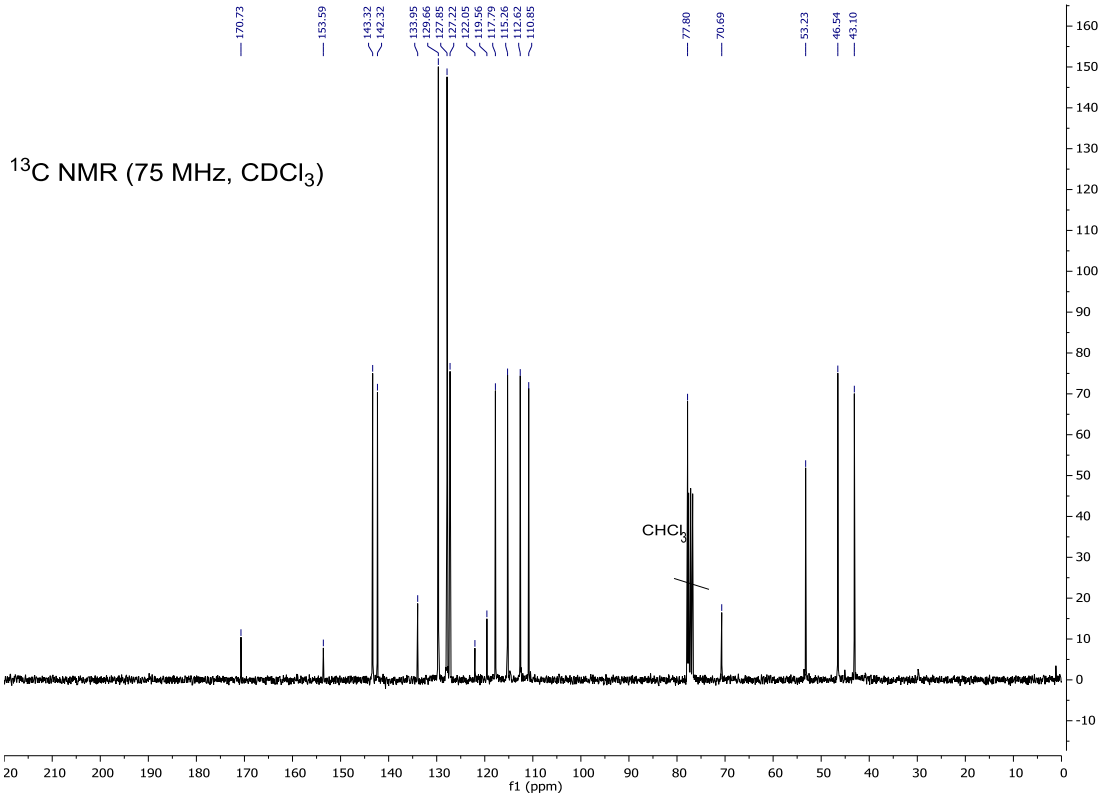
(*S*)-3-Benzyl-3-((*S*)-1-(furan-2-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ah)



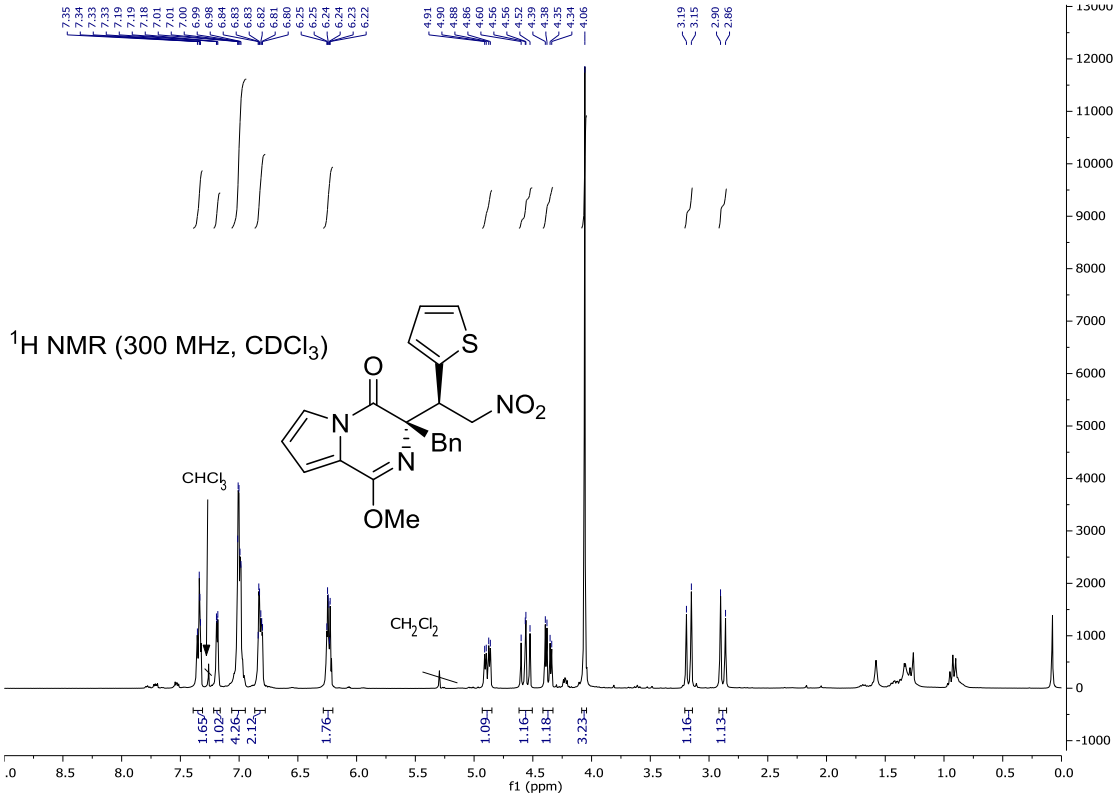


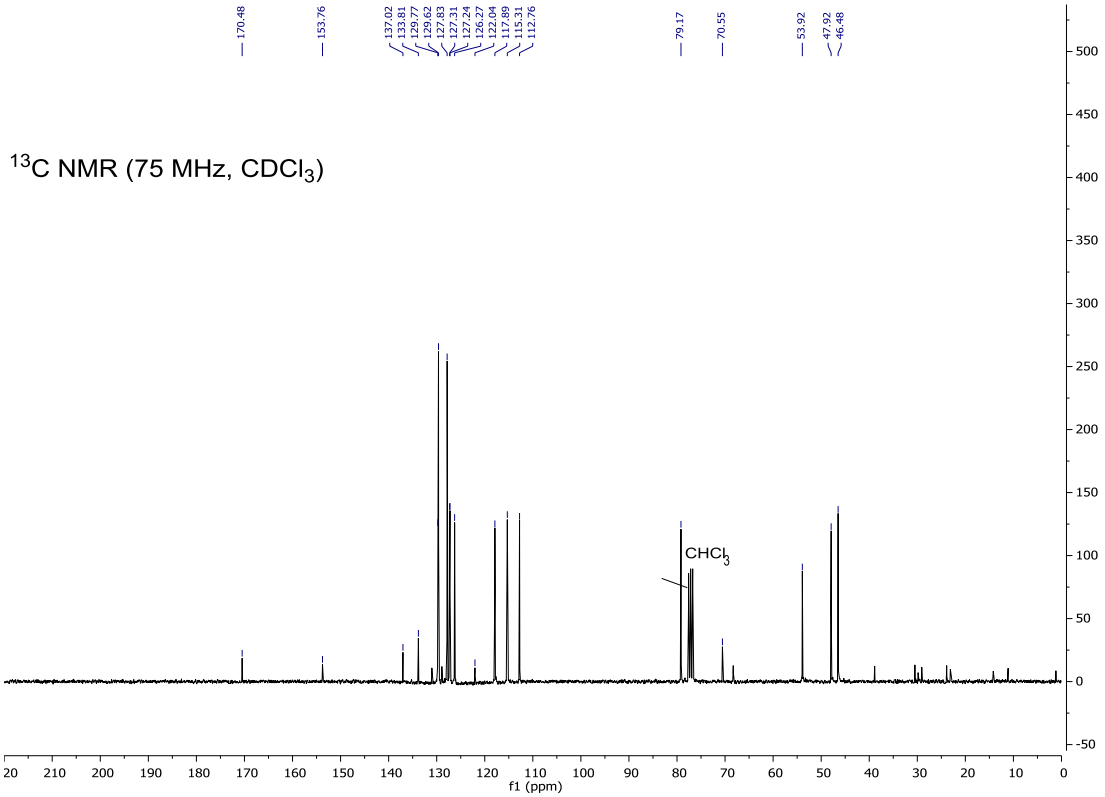
(*S*)-3-Benzyl-3-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ai)



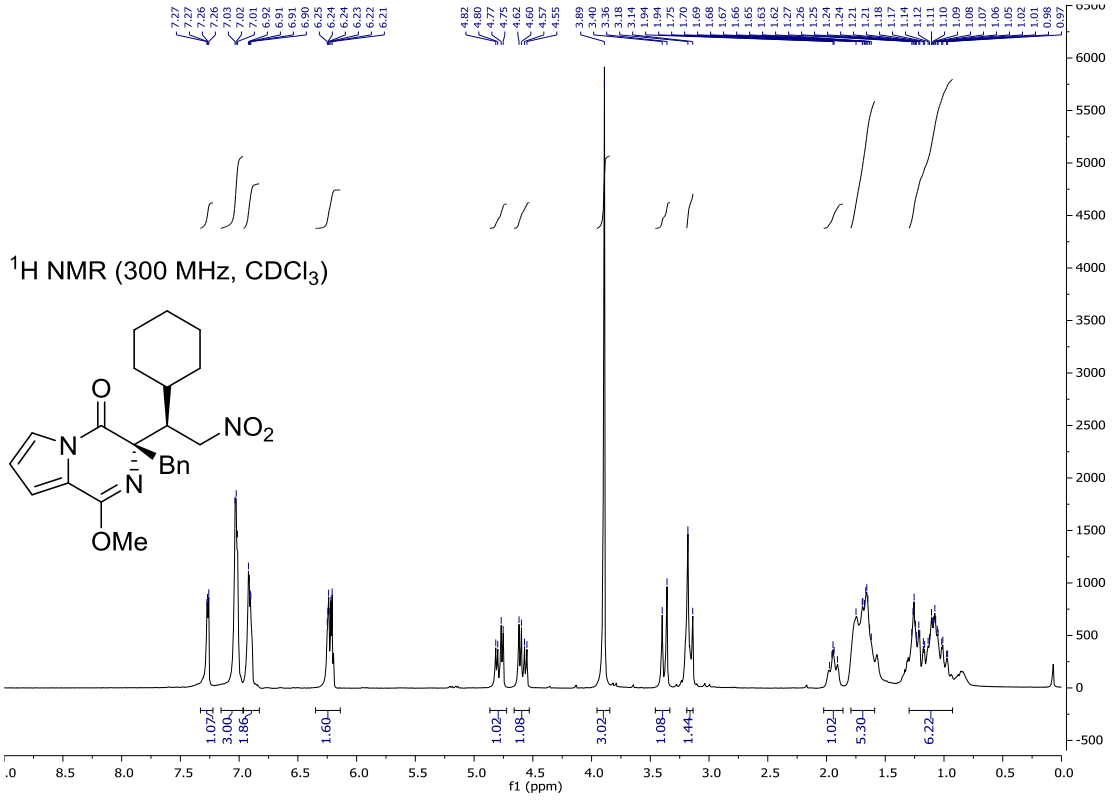


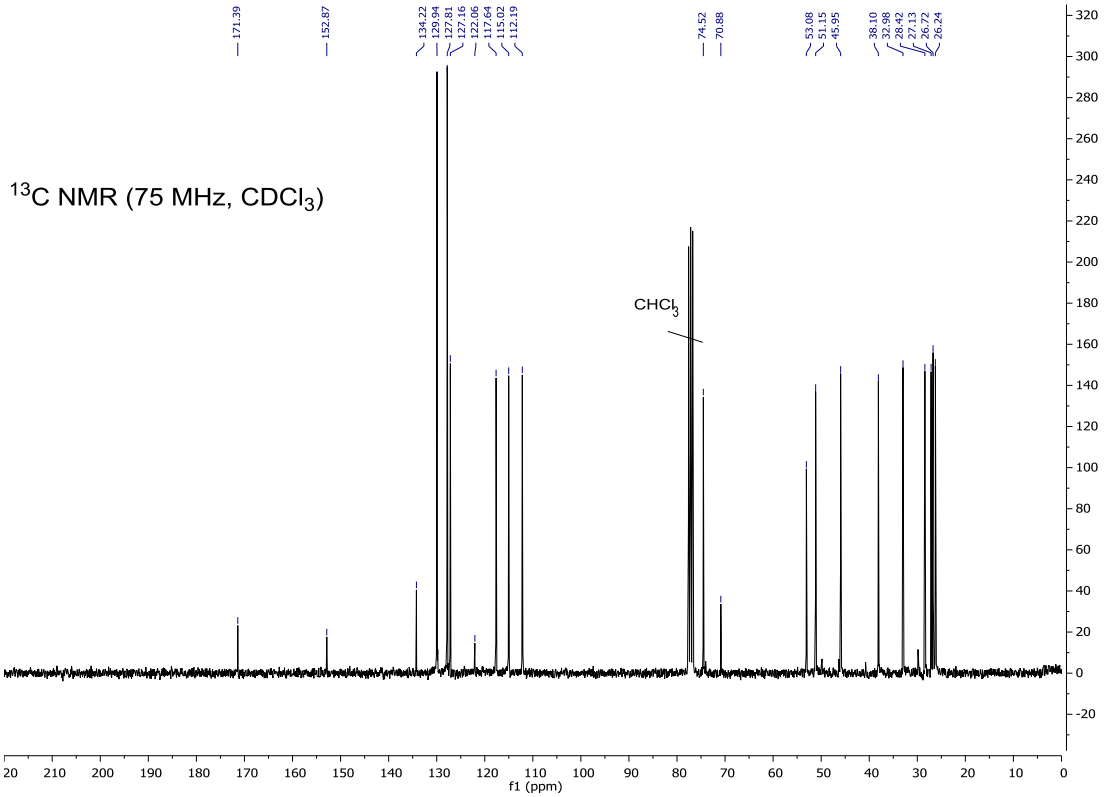
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aj)



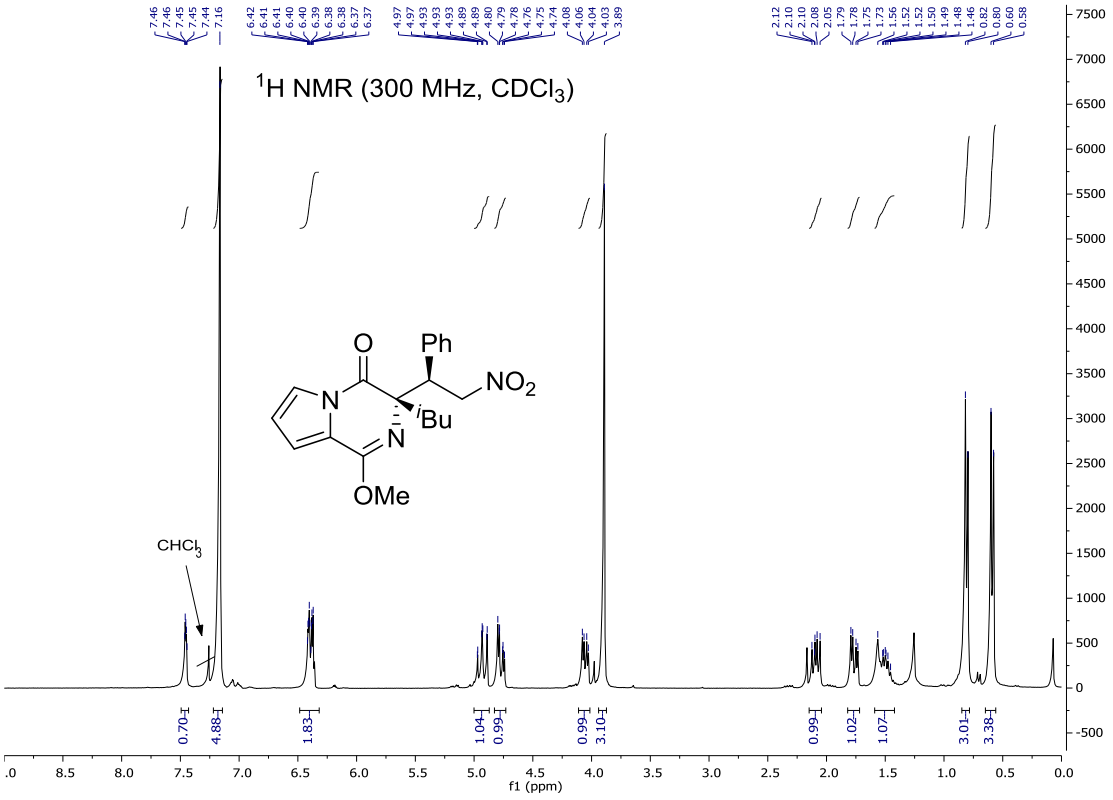


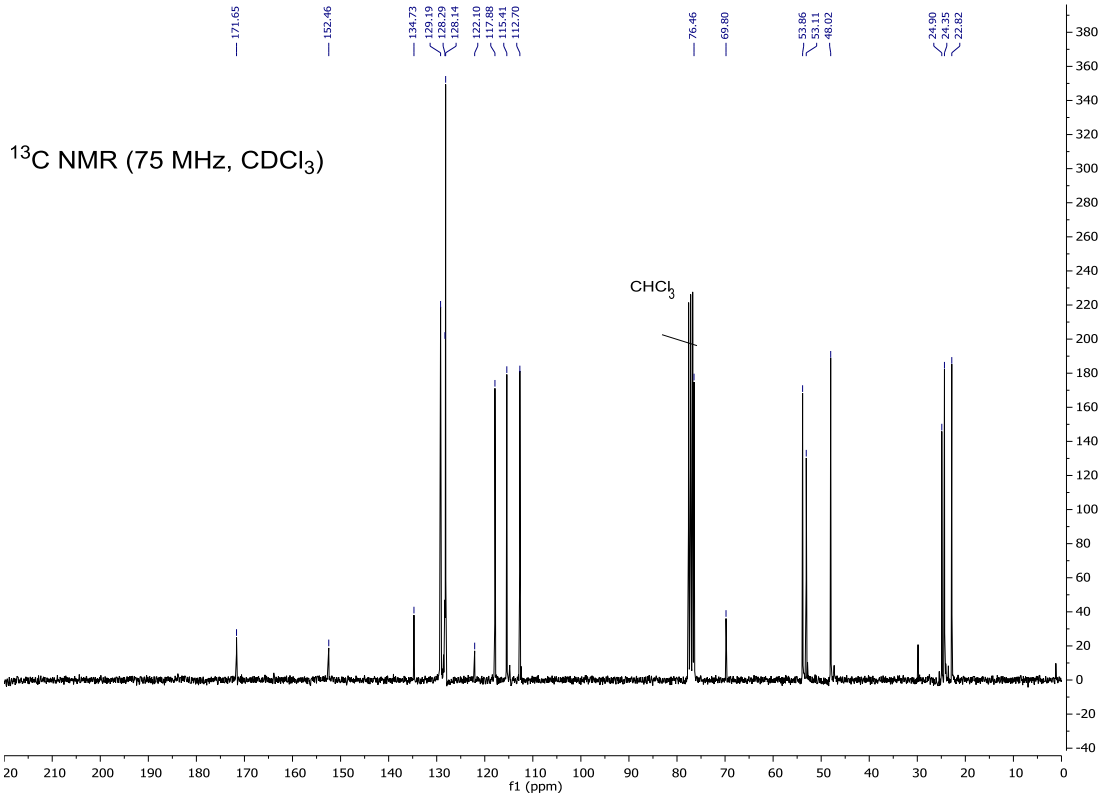
(*S*)-3-Benzyl-3-((*S*)-1-cyclohexyl-2-nitroethyl)-1-methoxypyrrolo[1,2-a]pyrazin-4(3H)-one (20al)



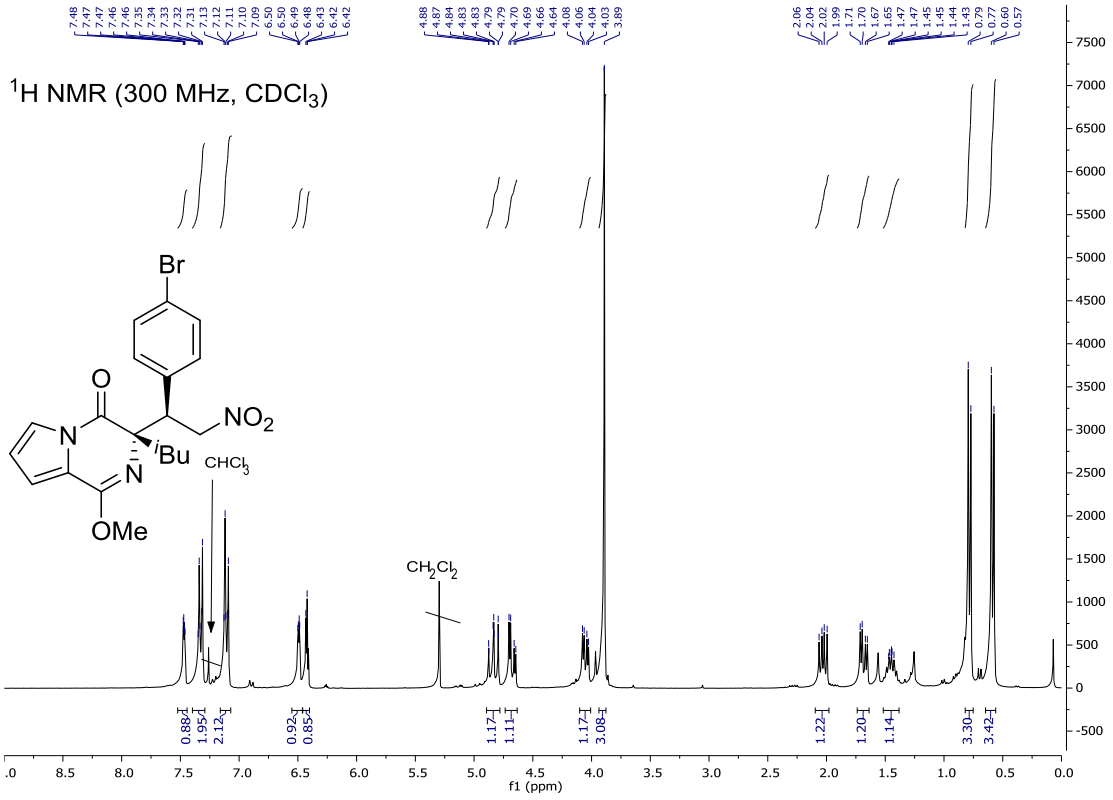


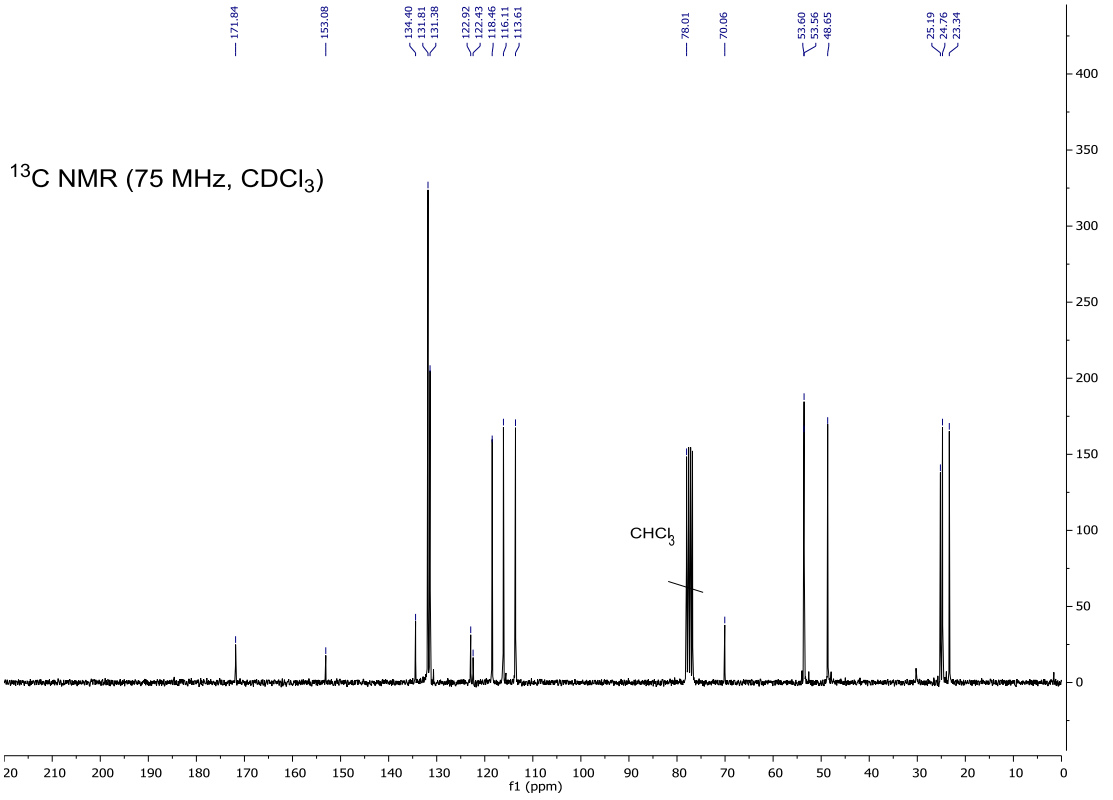
(*S*)-3-Isobutyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ba)



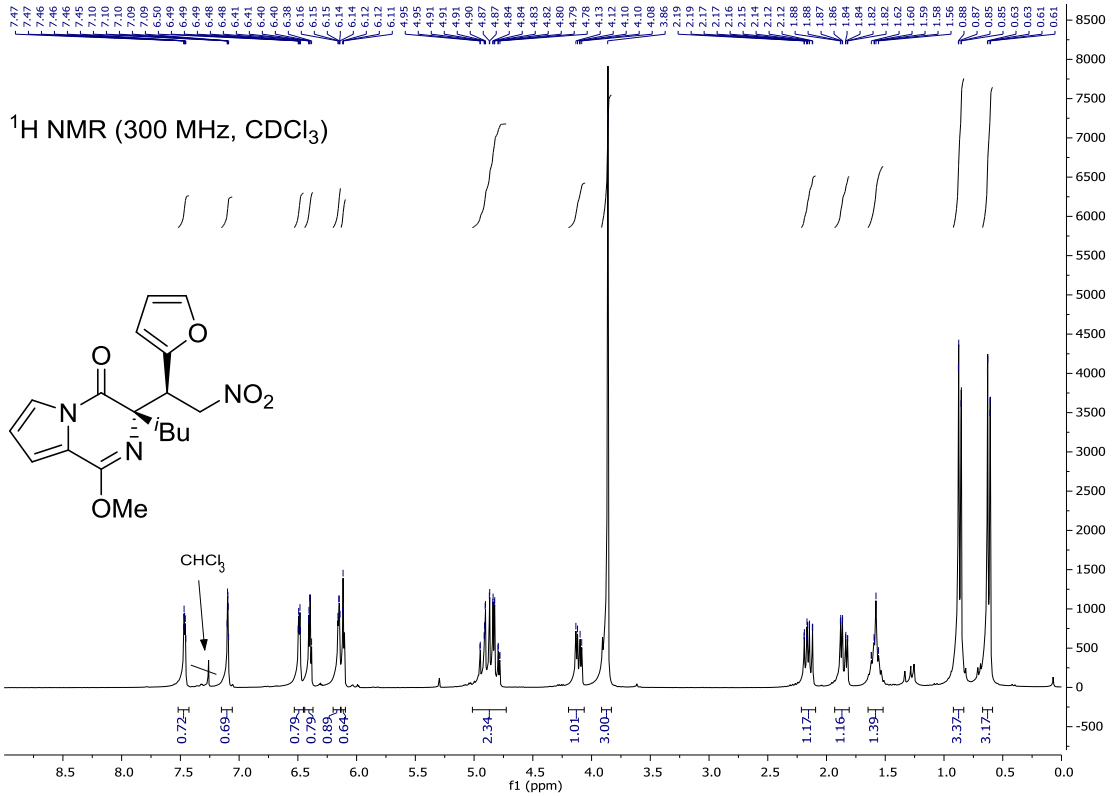


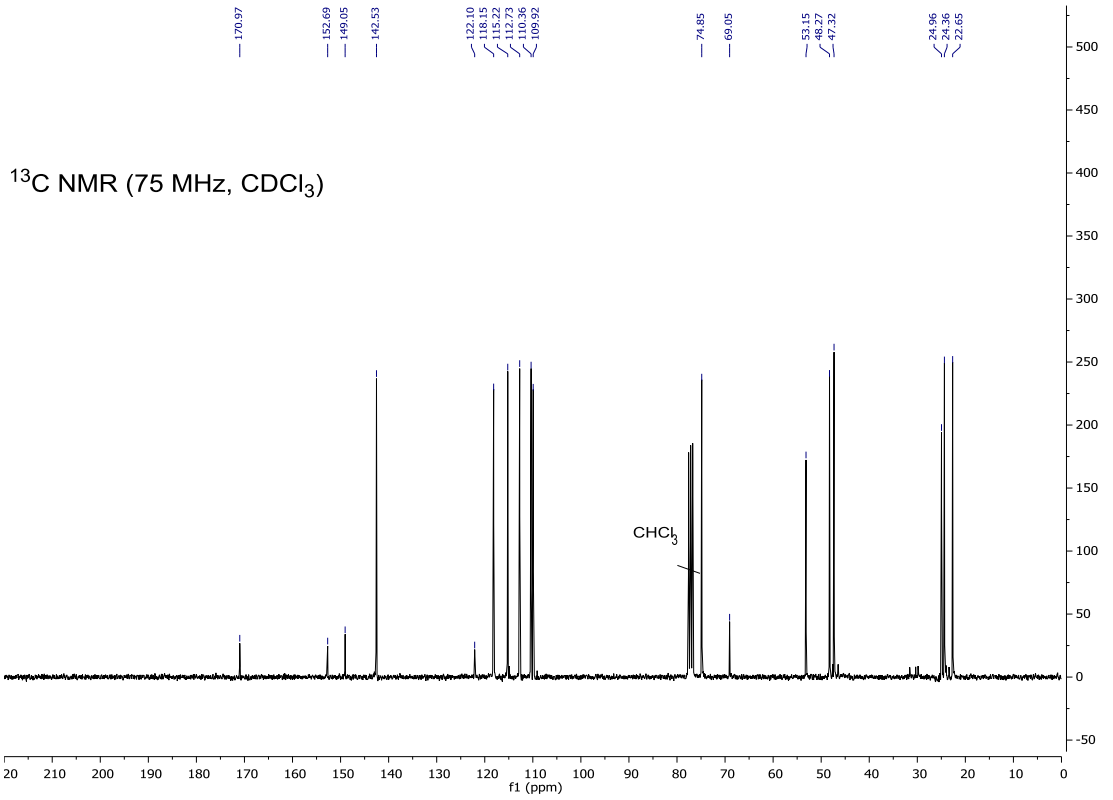
(*S*)-3-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20be)



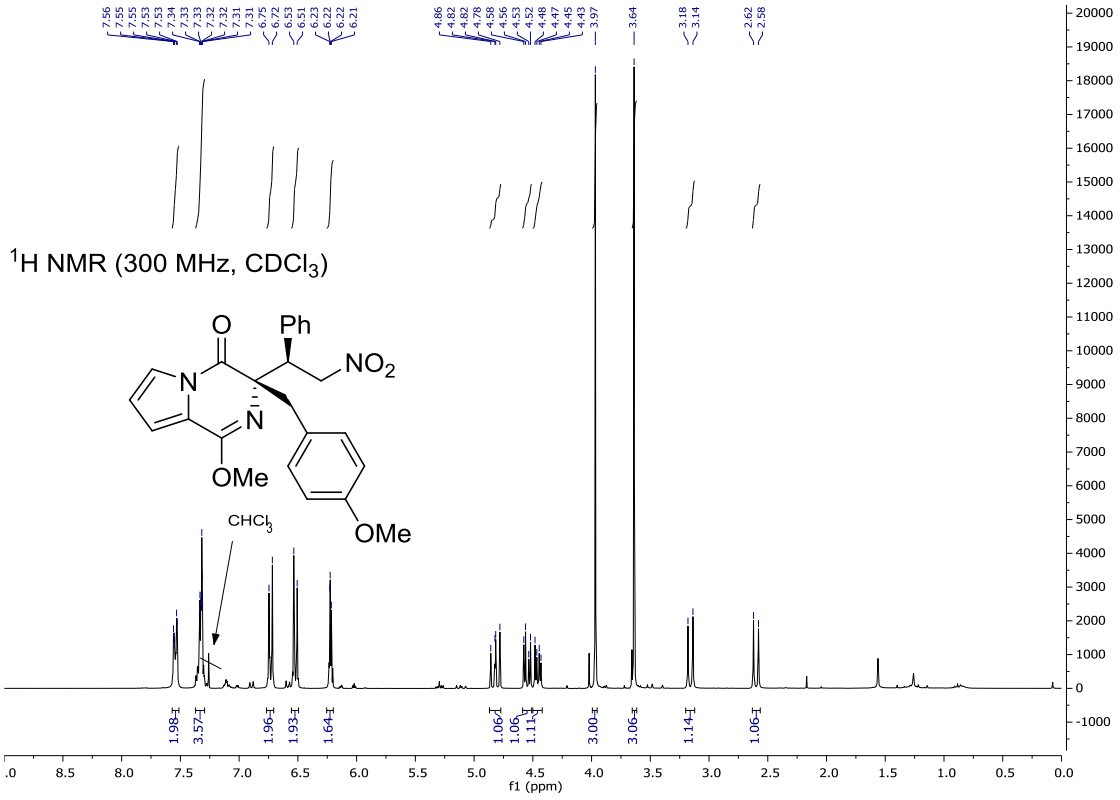


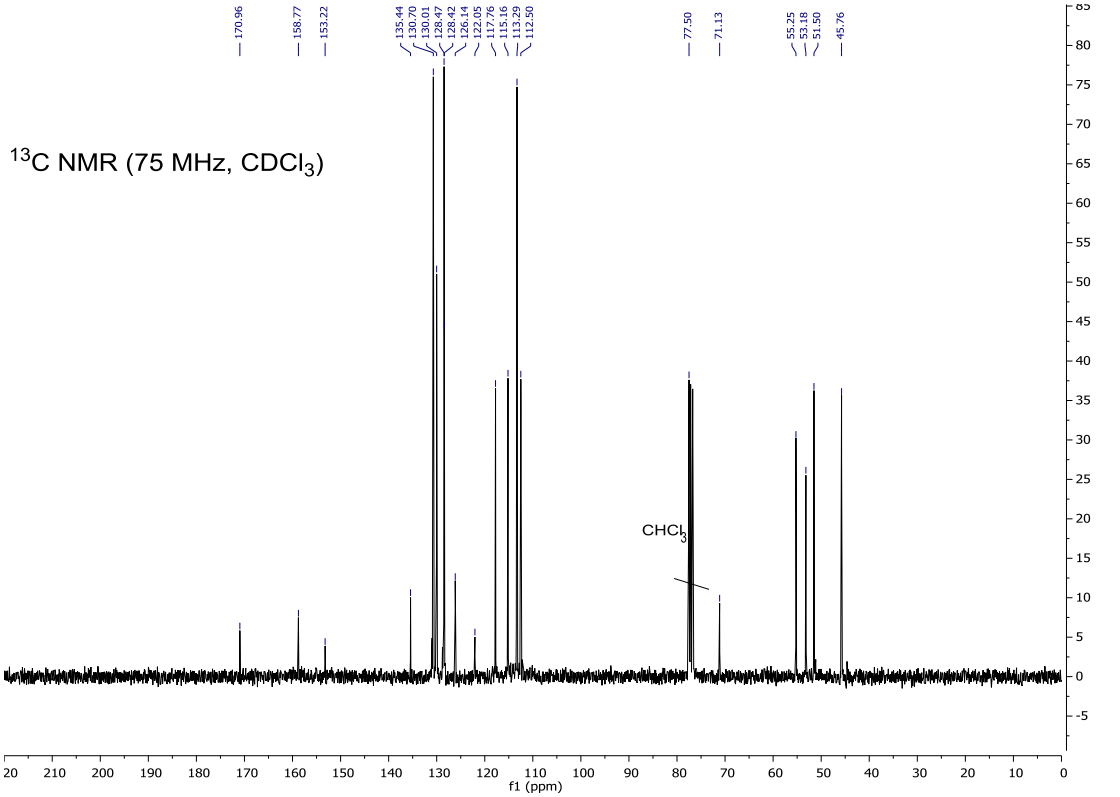
(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20bh)



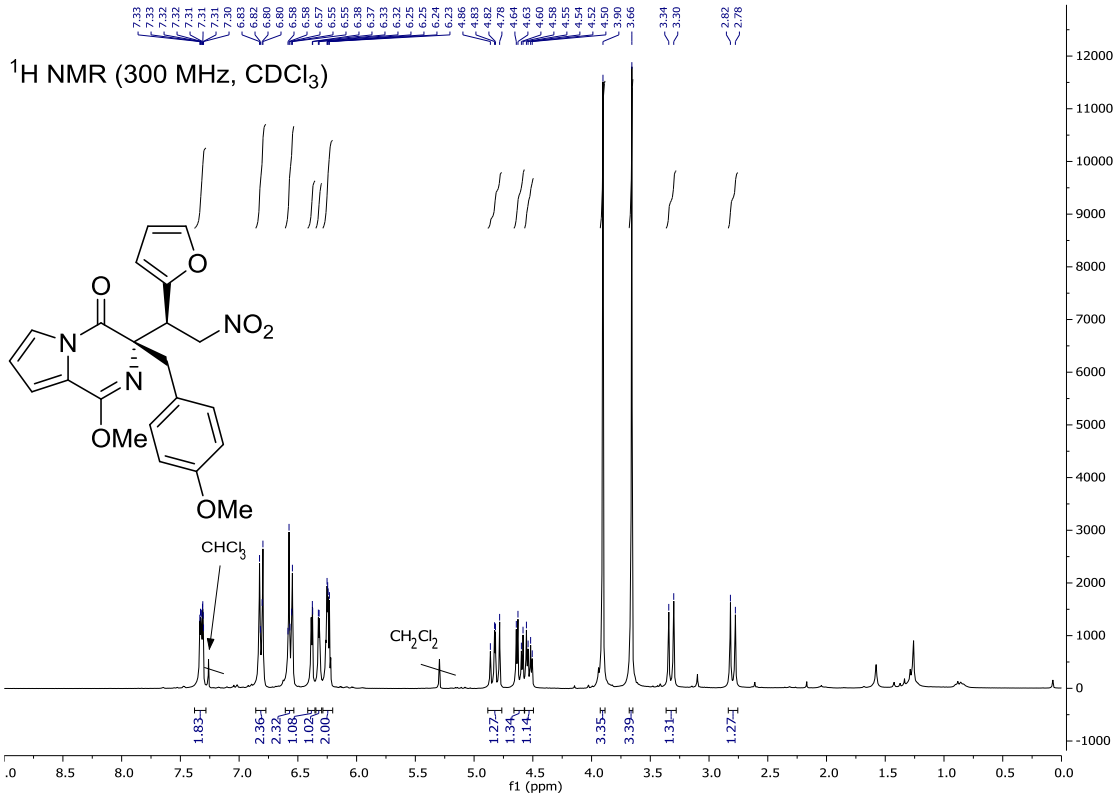


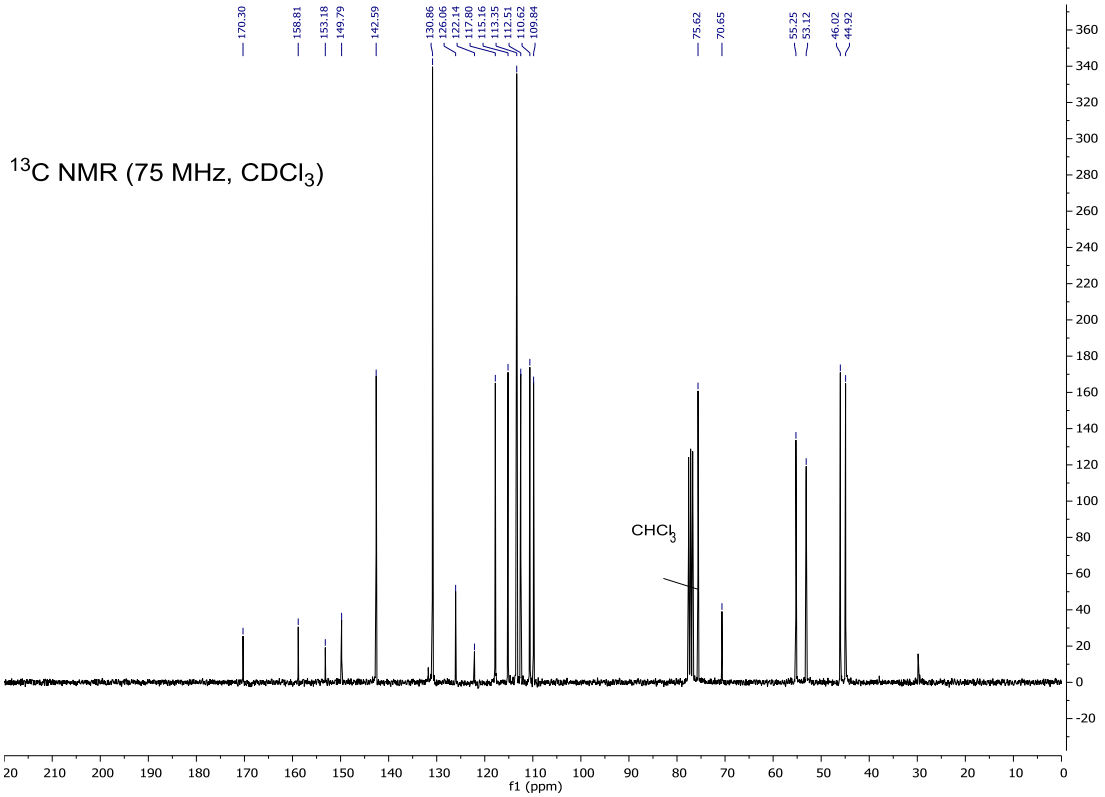
(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ca)



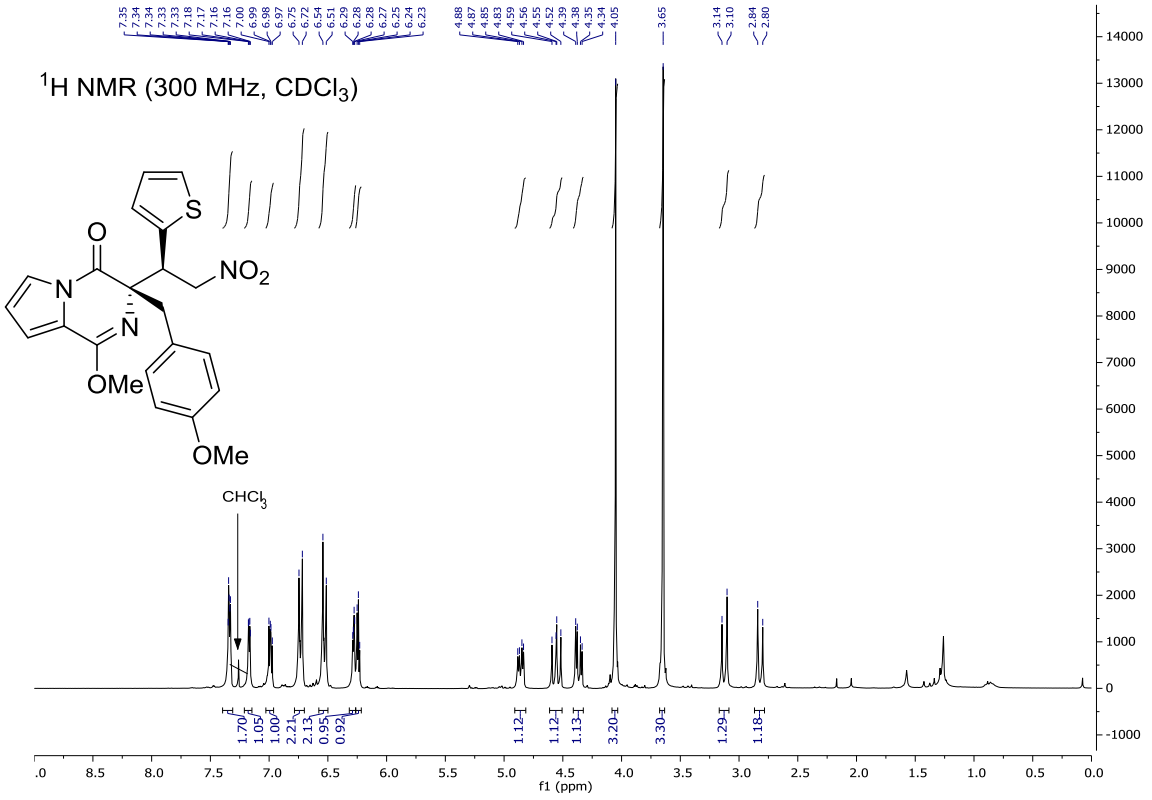


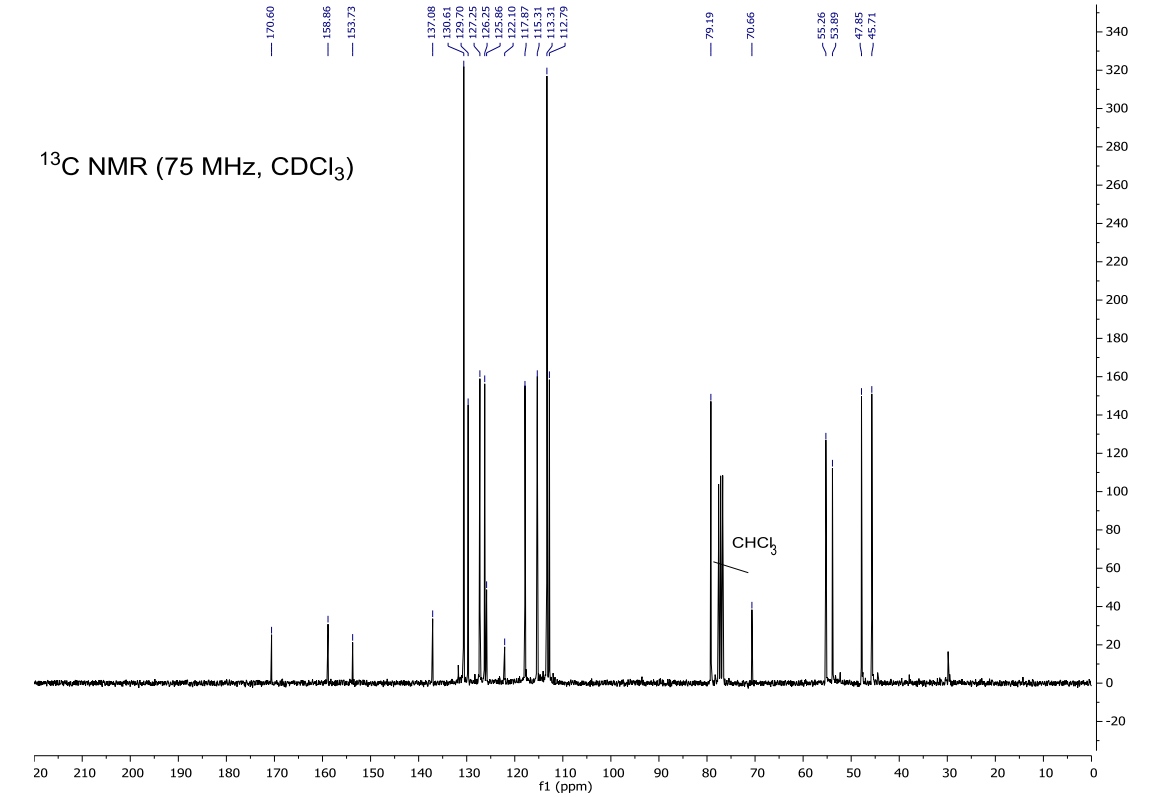
(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ch)



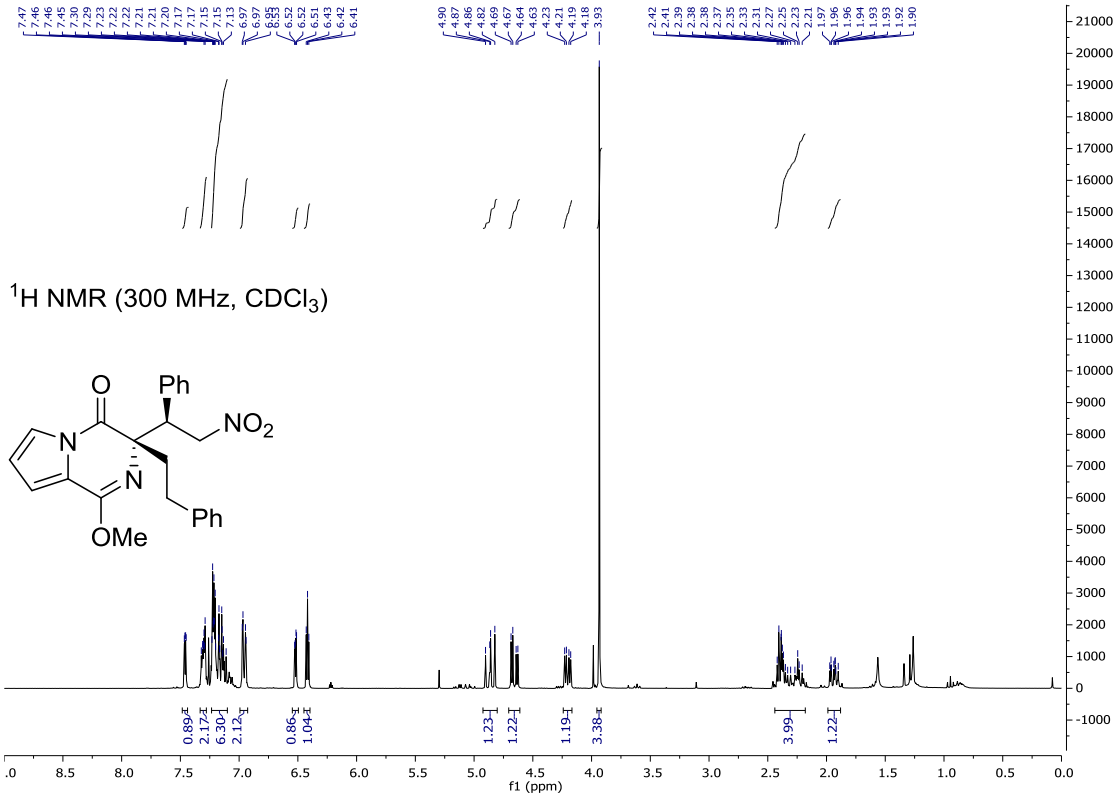


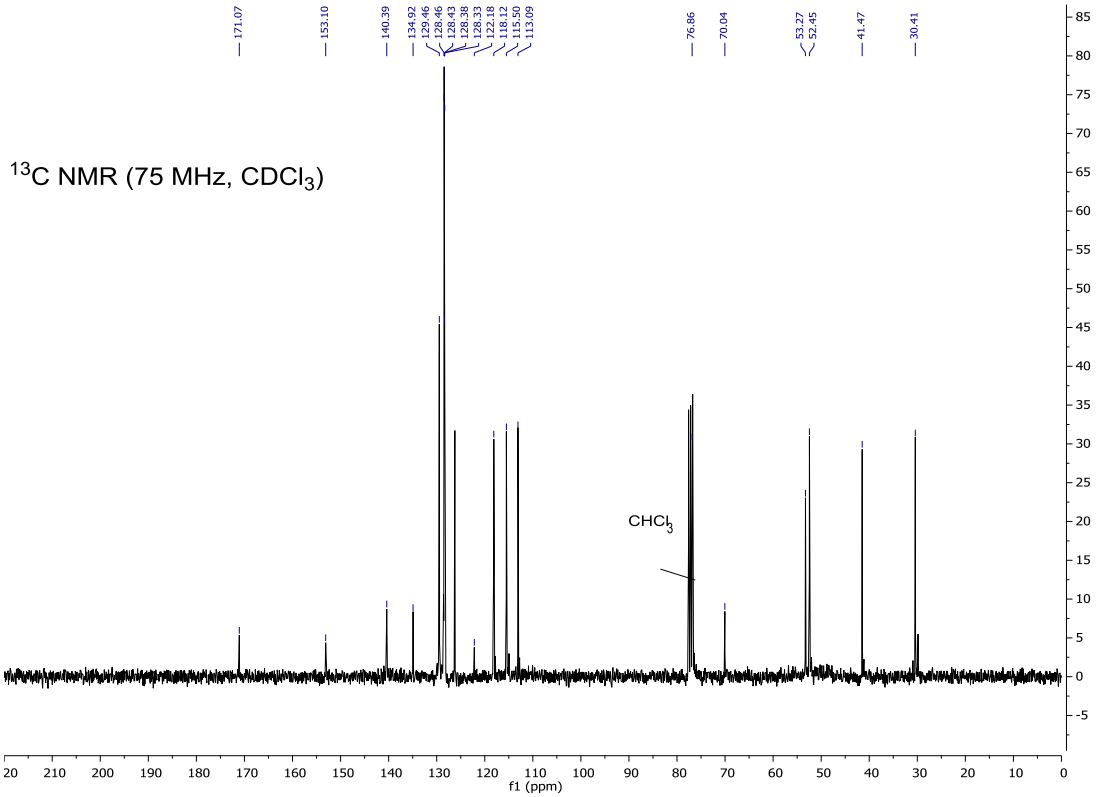
(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20cj)



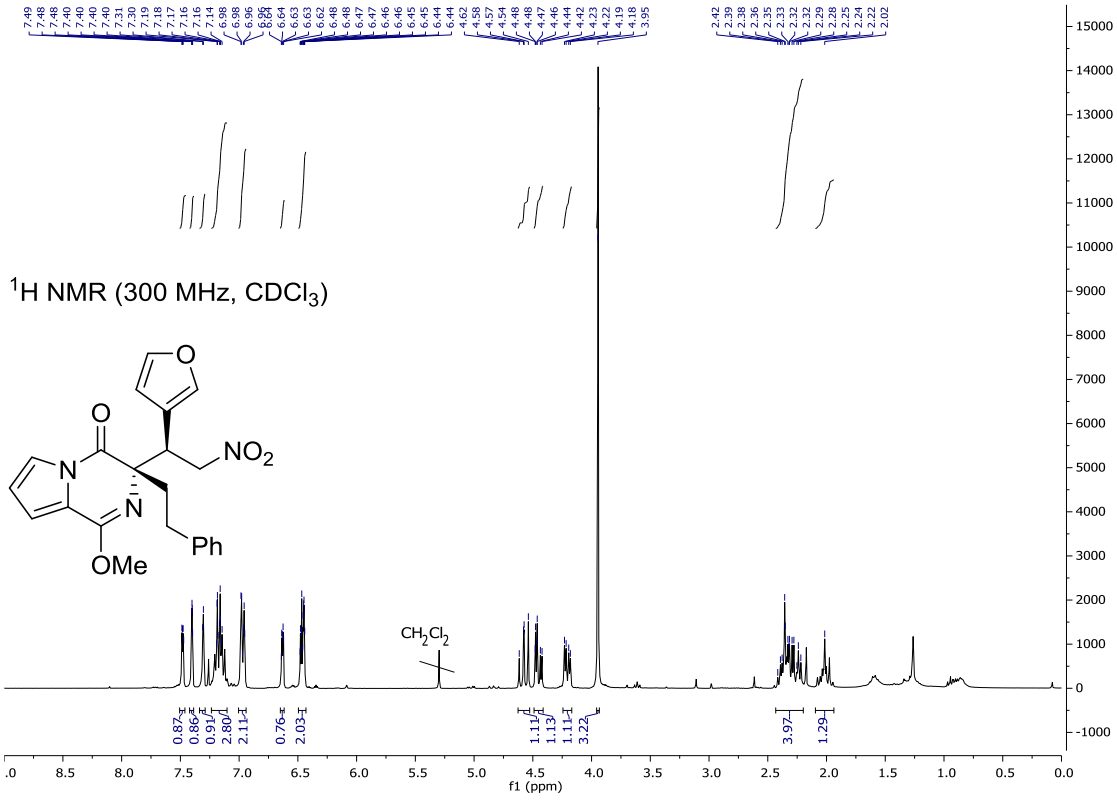


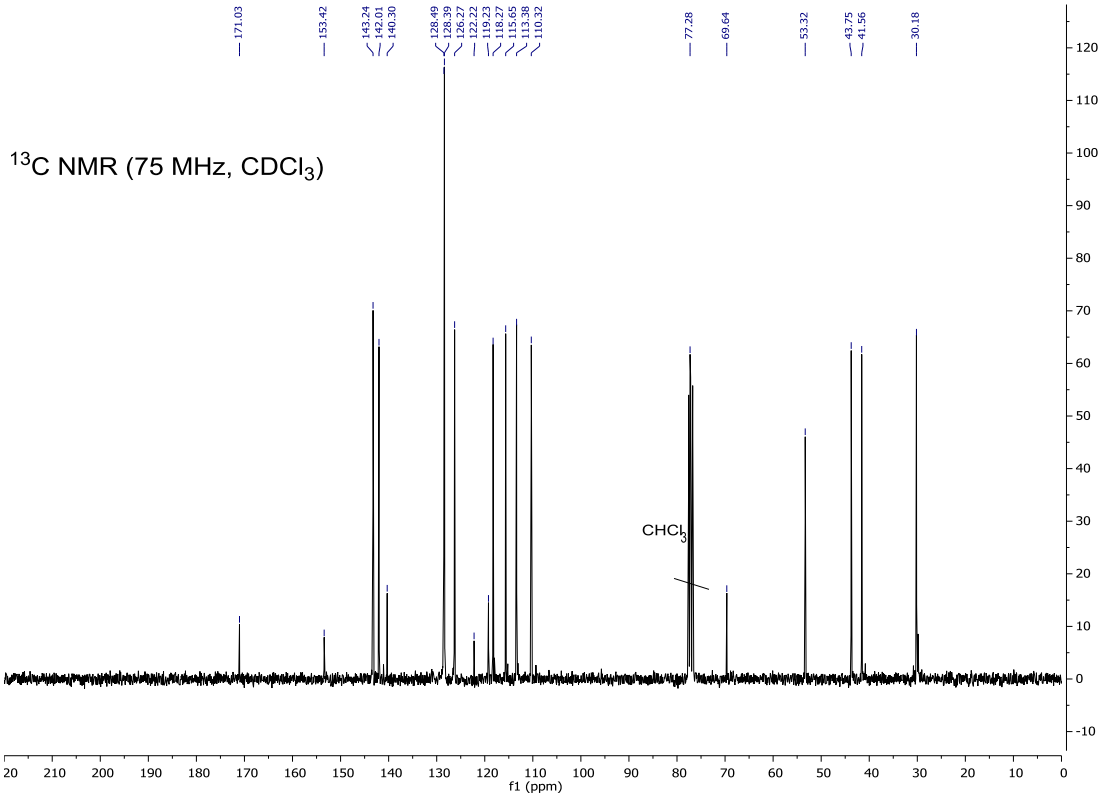
(*S*)-1-Methoxy-3-((*S*)-2-nitro-1-phenylethyl)-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20da)



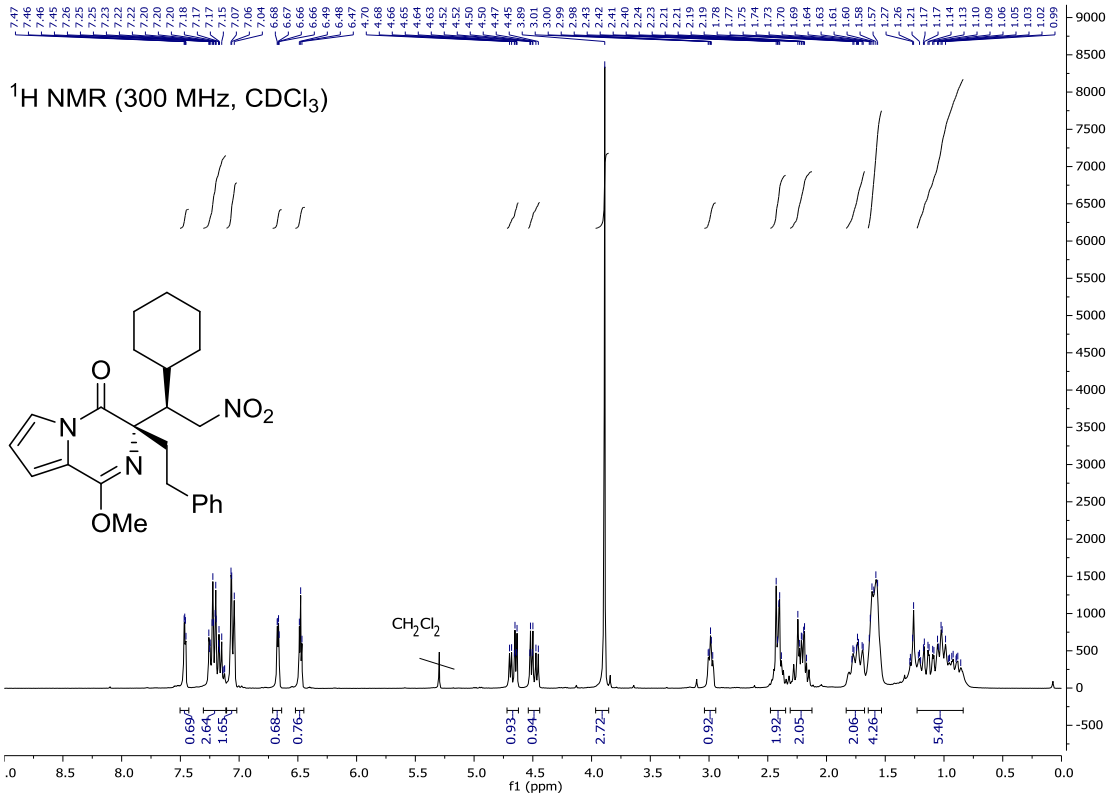


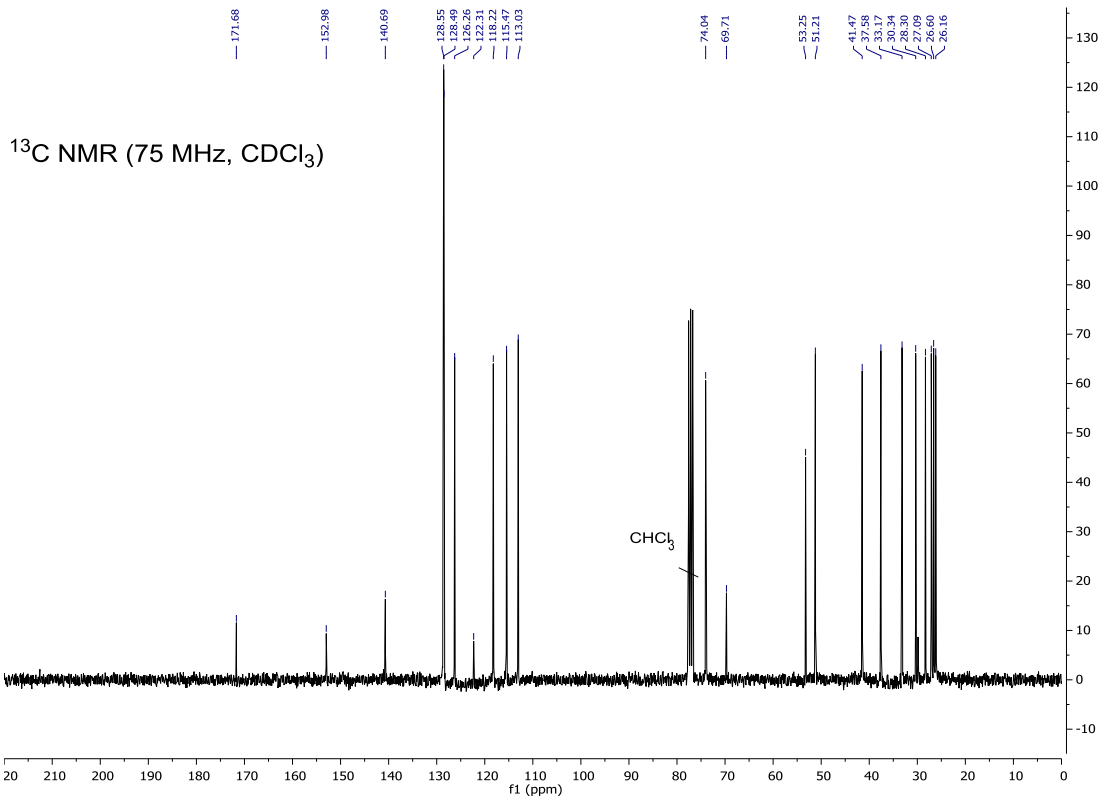
(*S*)-3-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20di)



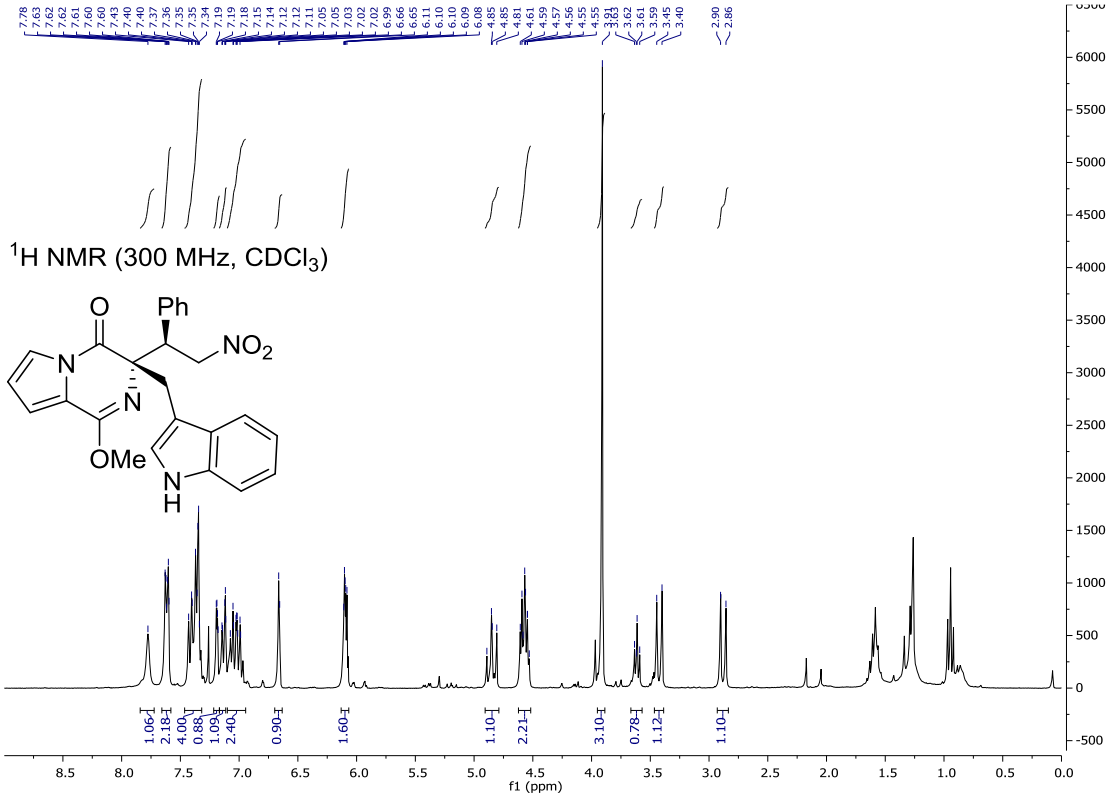


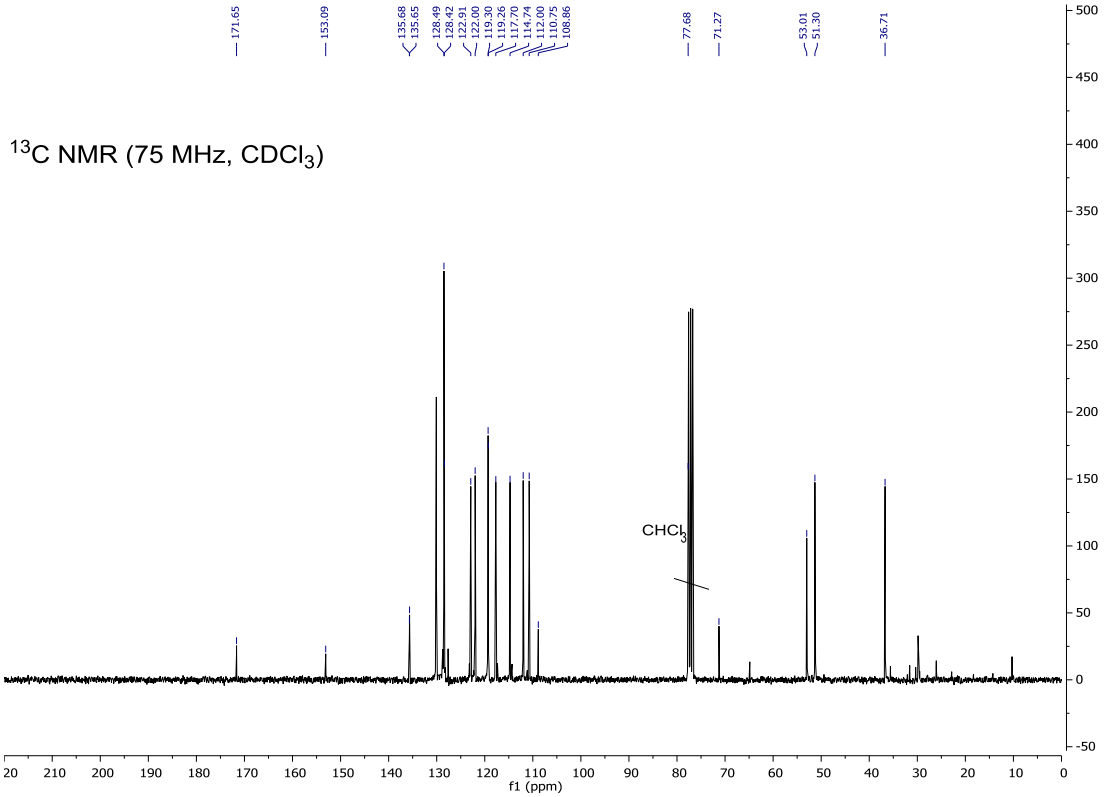
(*S*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20dl)



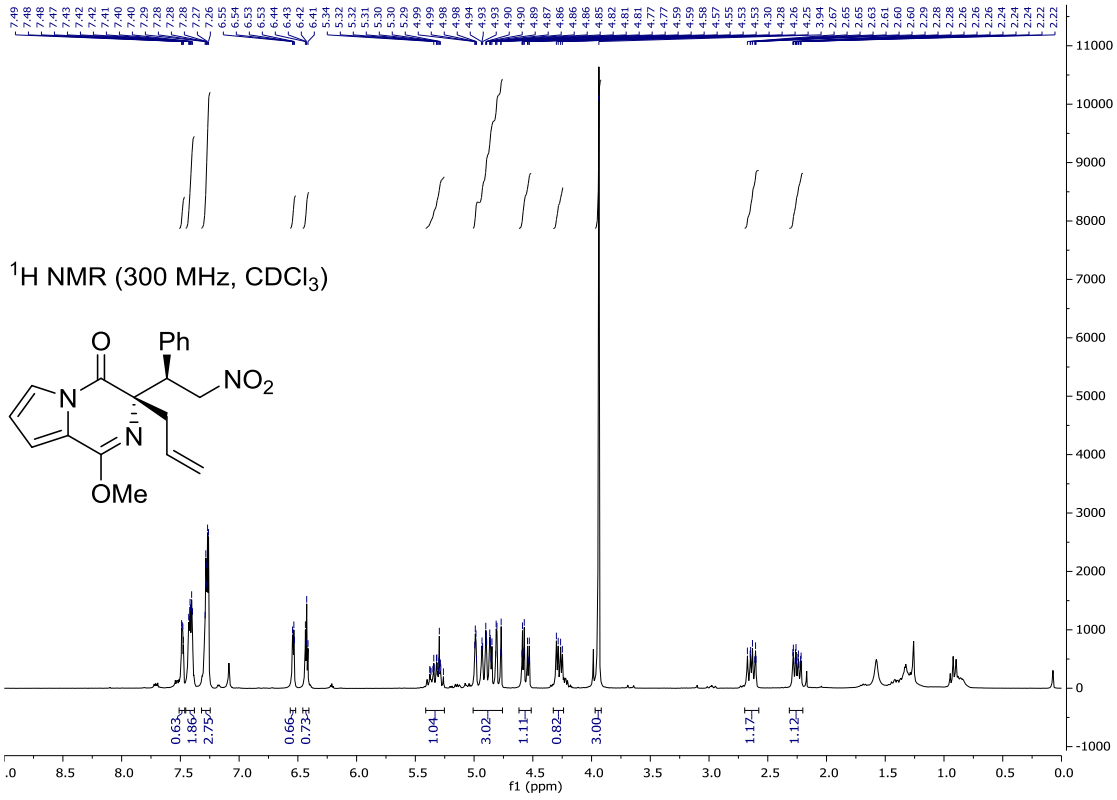


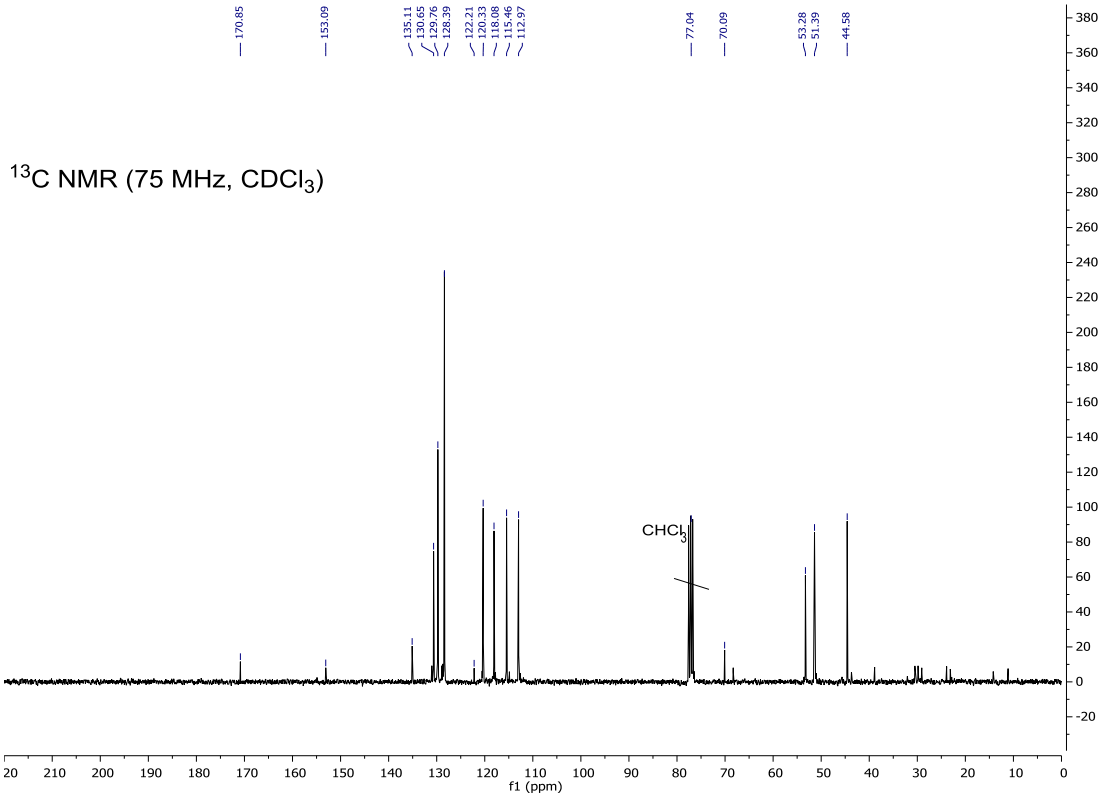
(*S*)-3-((1*H*-Indol-3-yl)methyl)-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ea)



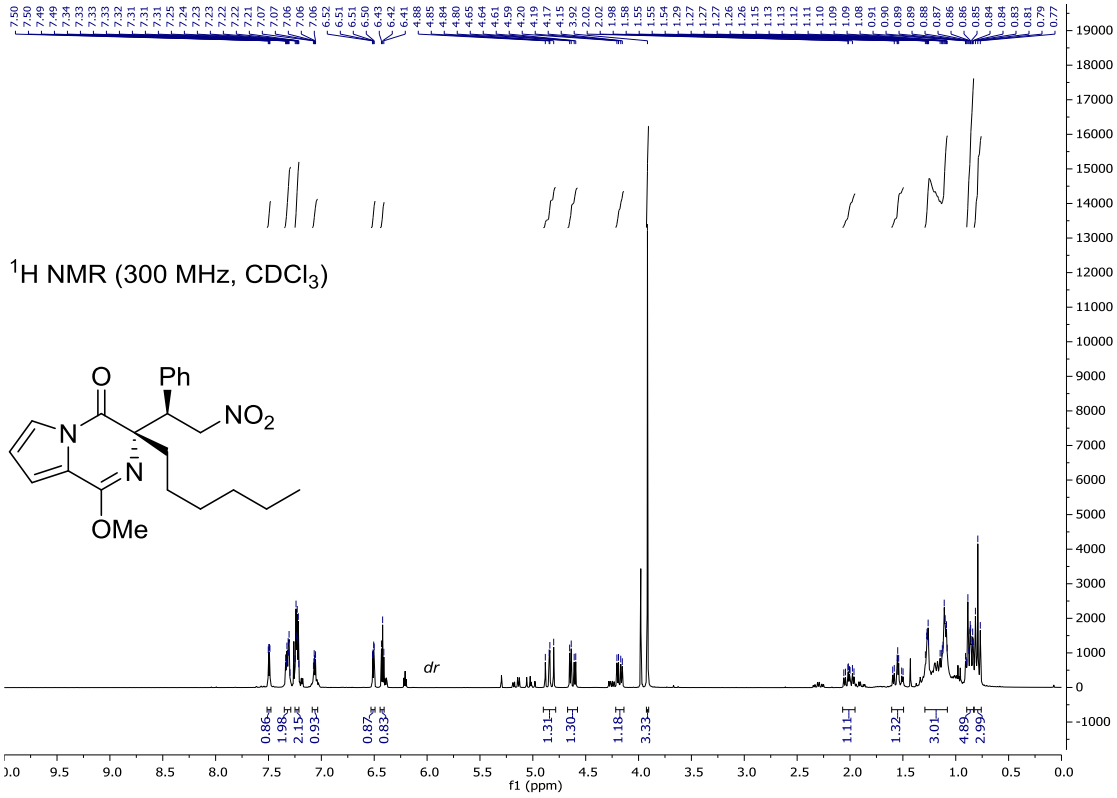


(*S*)-3-Allyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20fa)

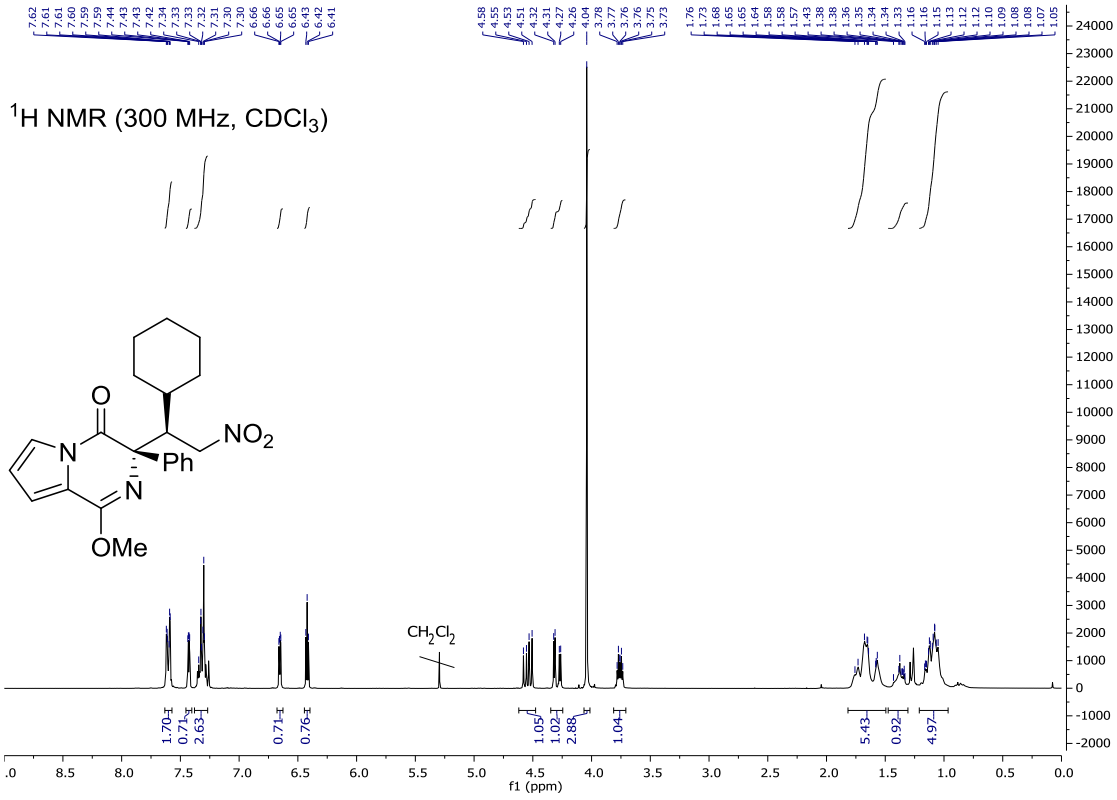


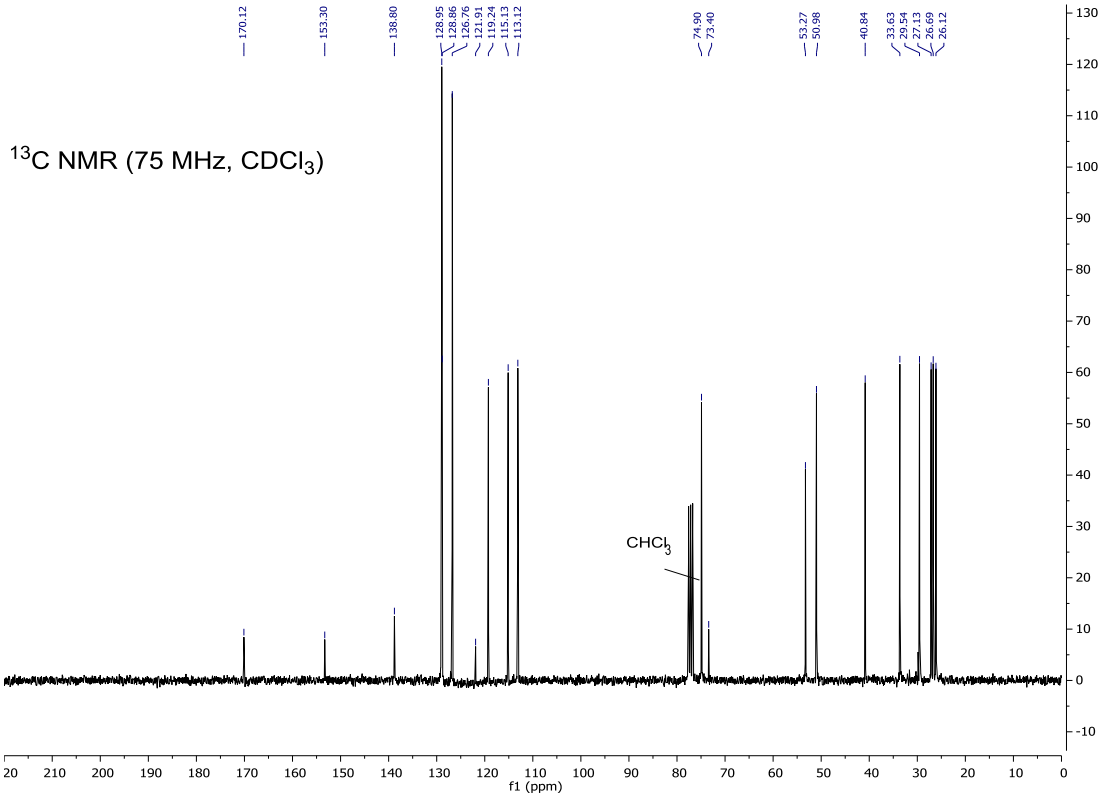


(*S*)-3-Hexyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ga)

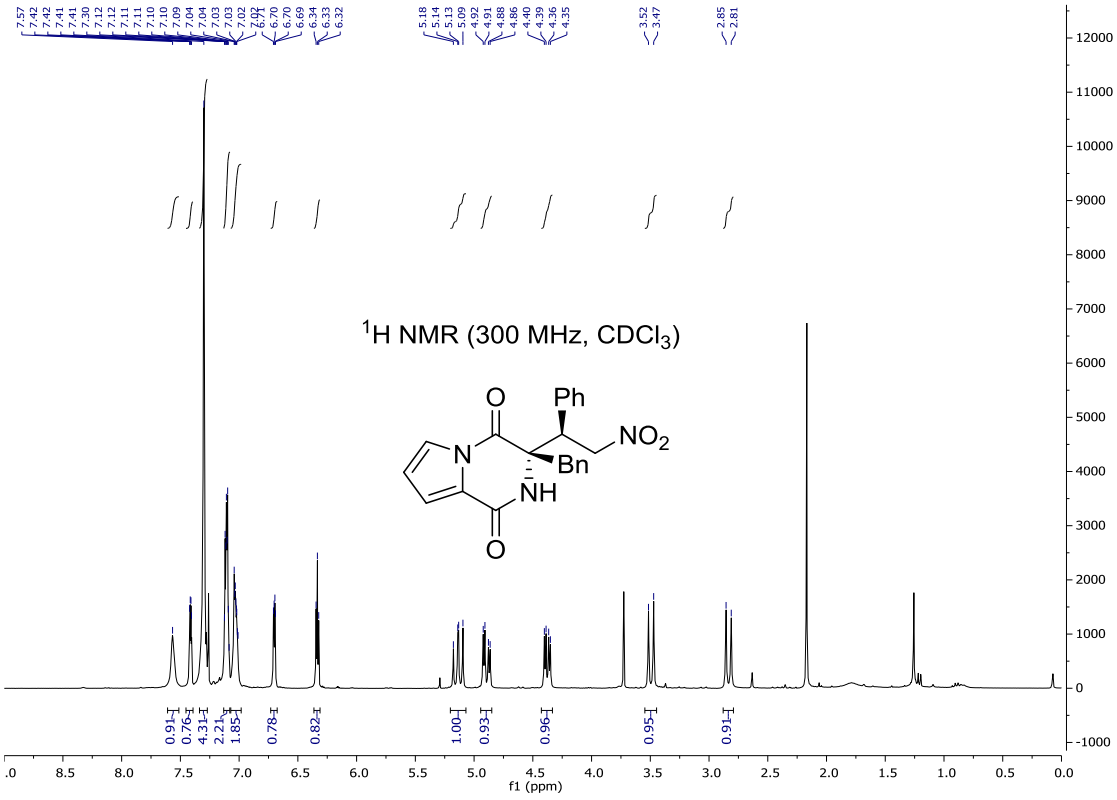


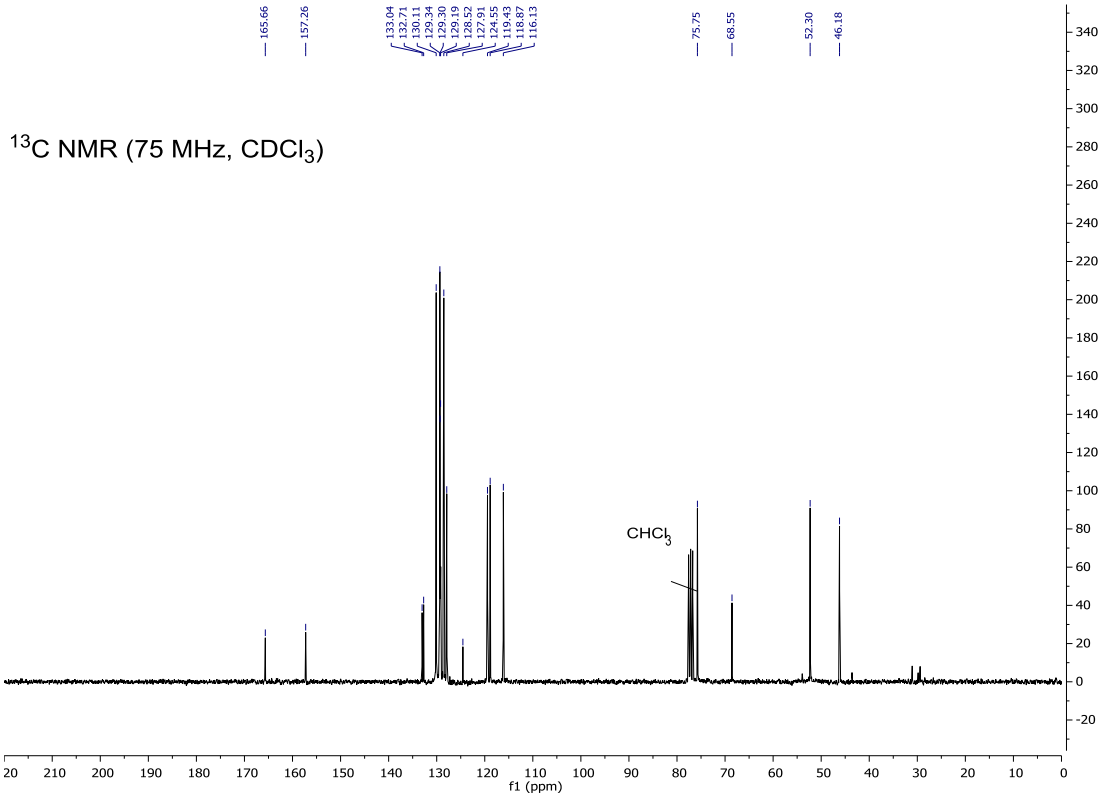
(*R*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20hl)



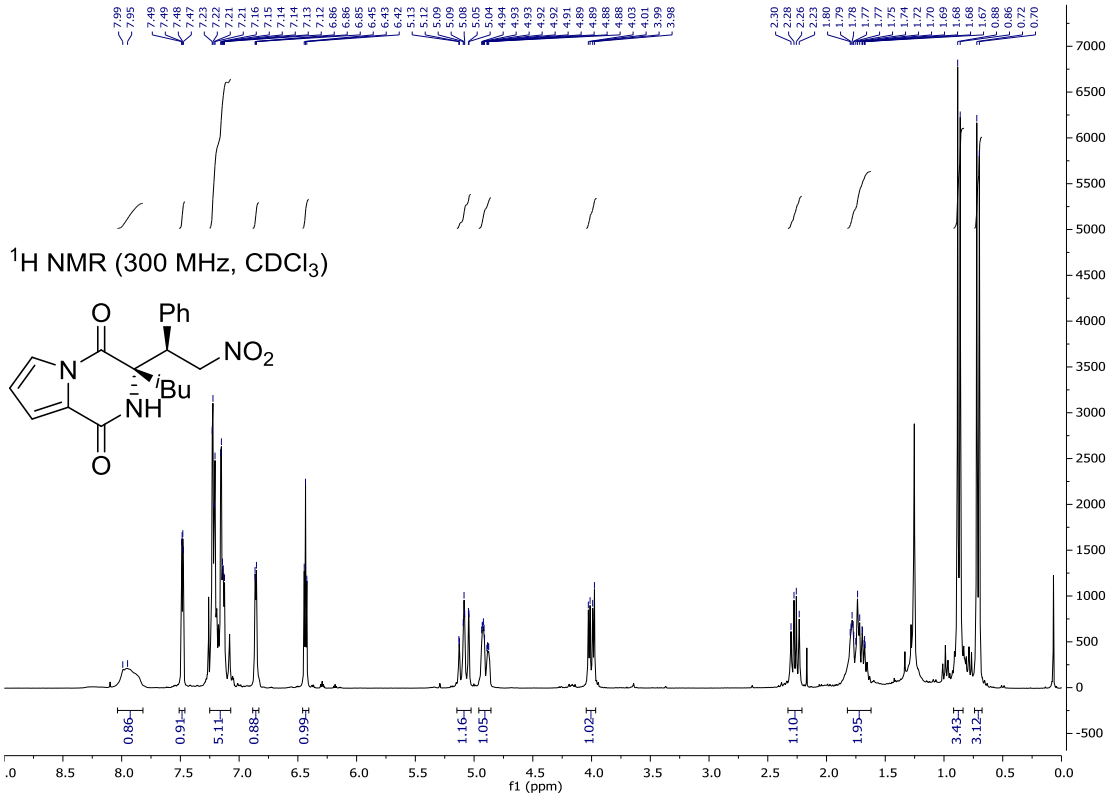


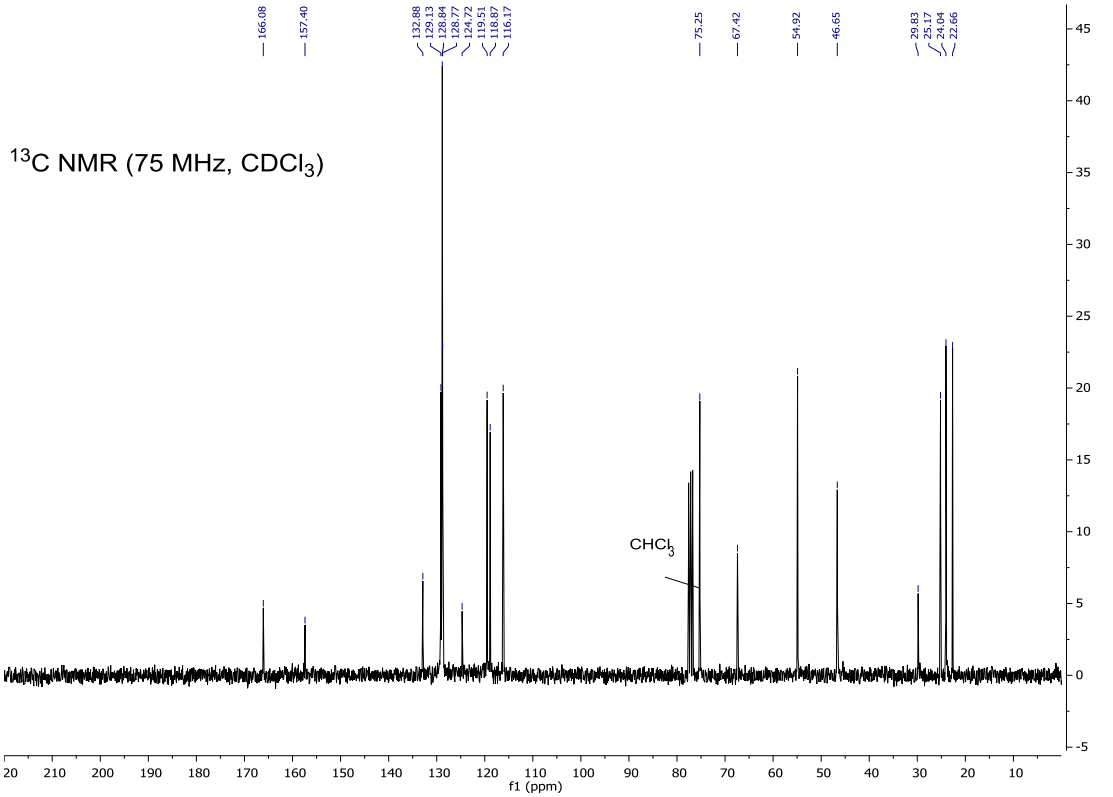
(*S*)-3-Benzyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32a)



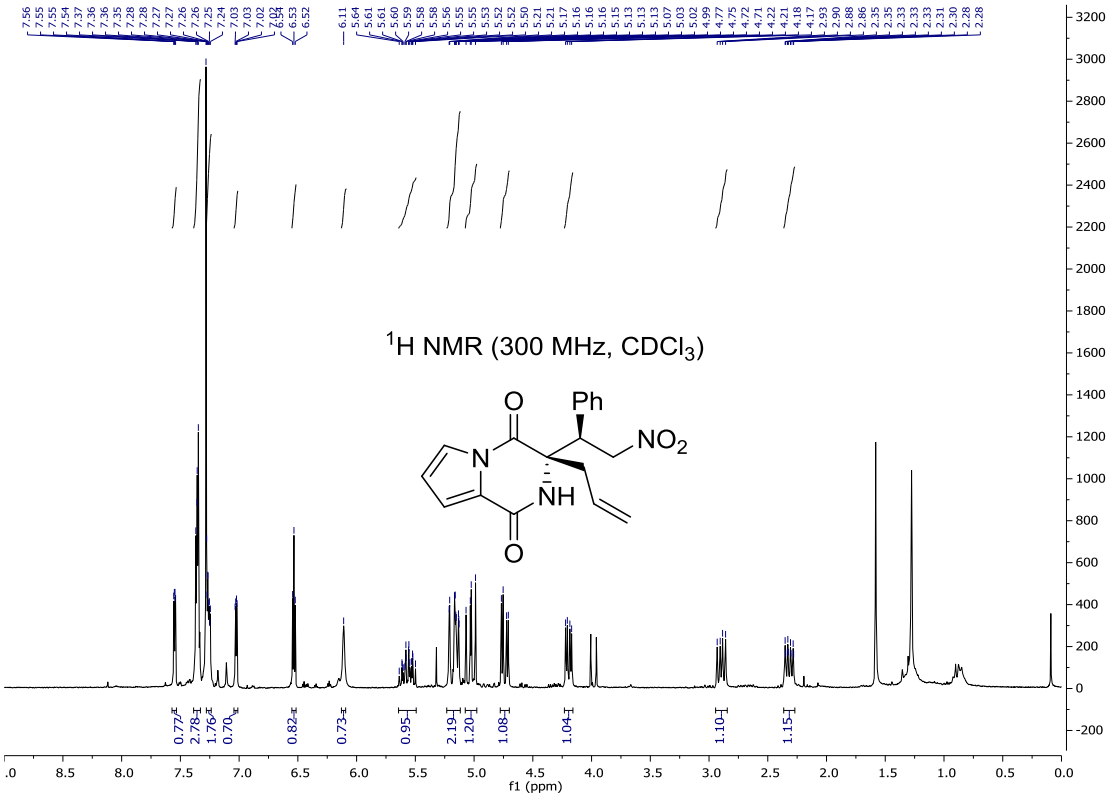


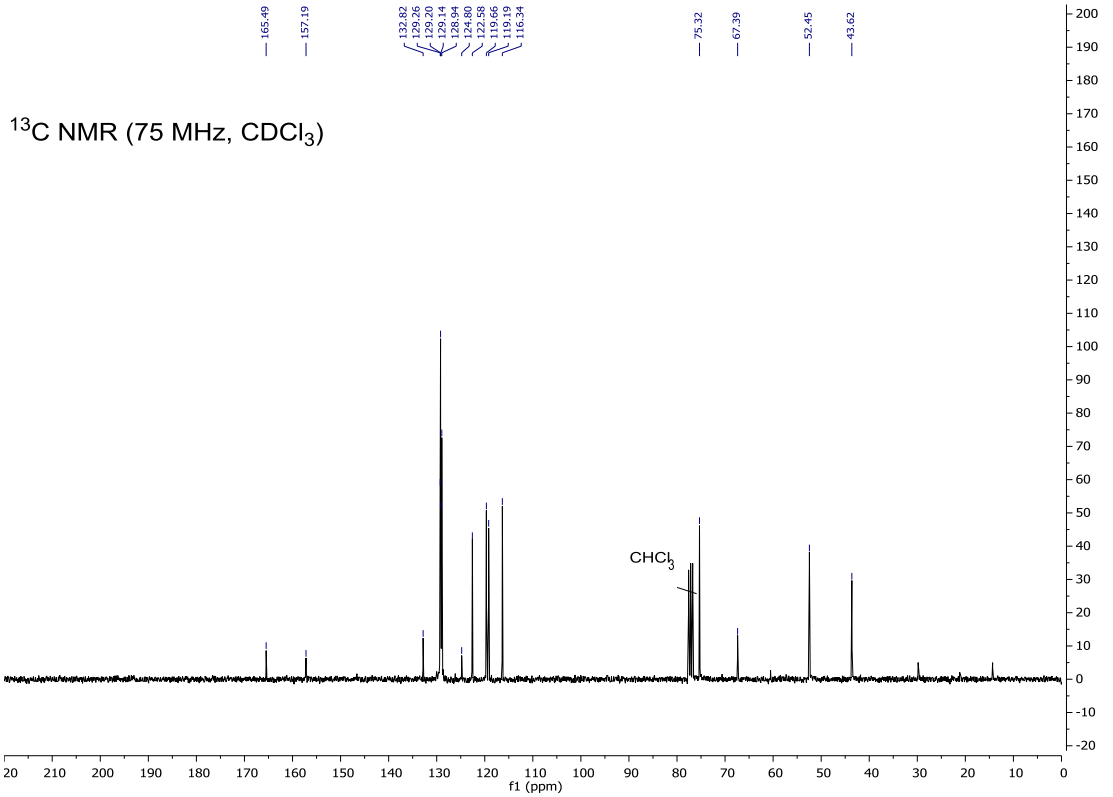
(*S*)-3-Isobutyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32b)



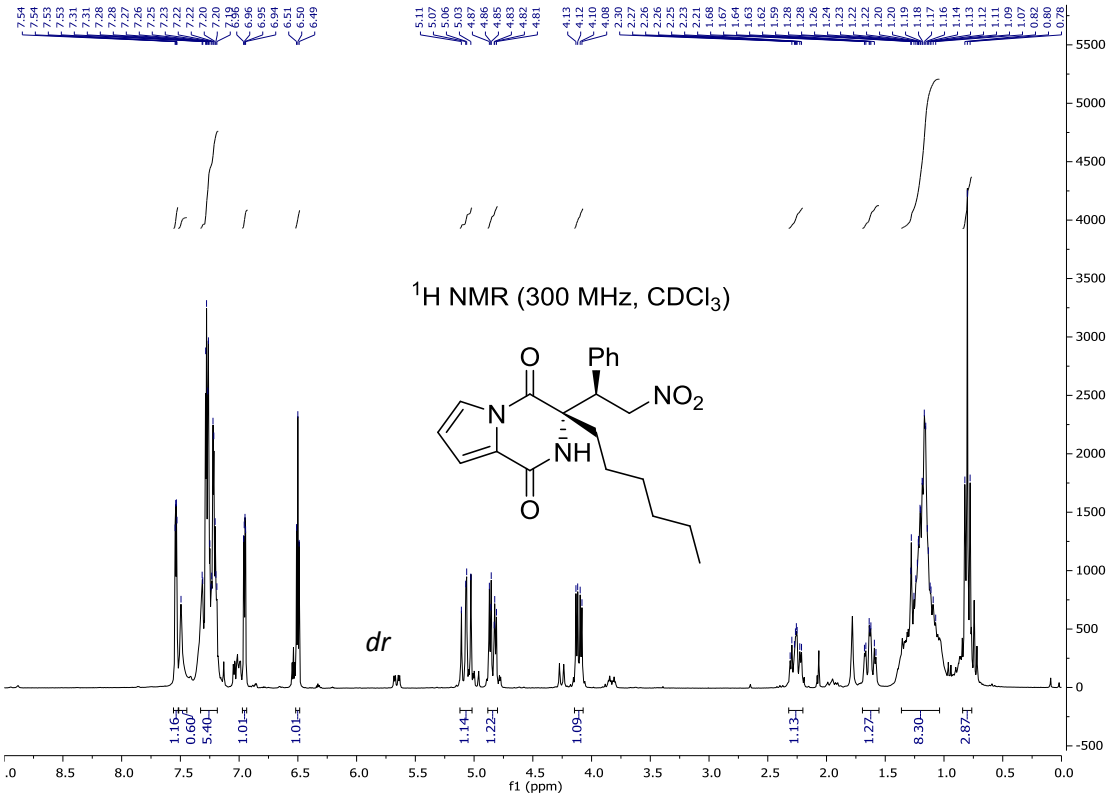


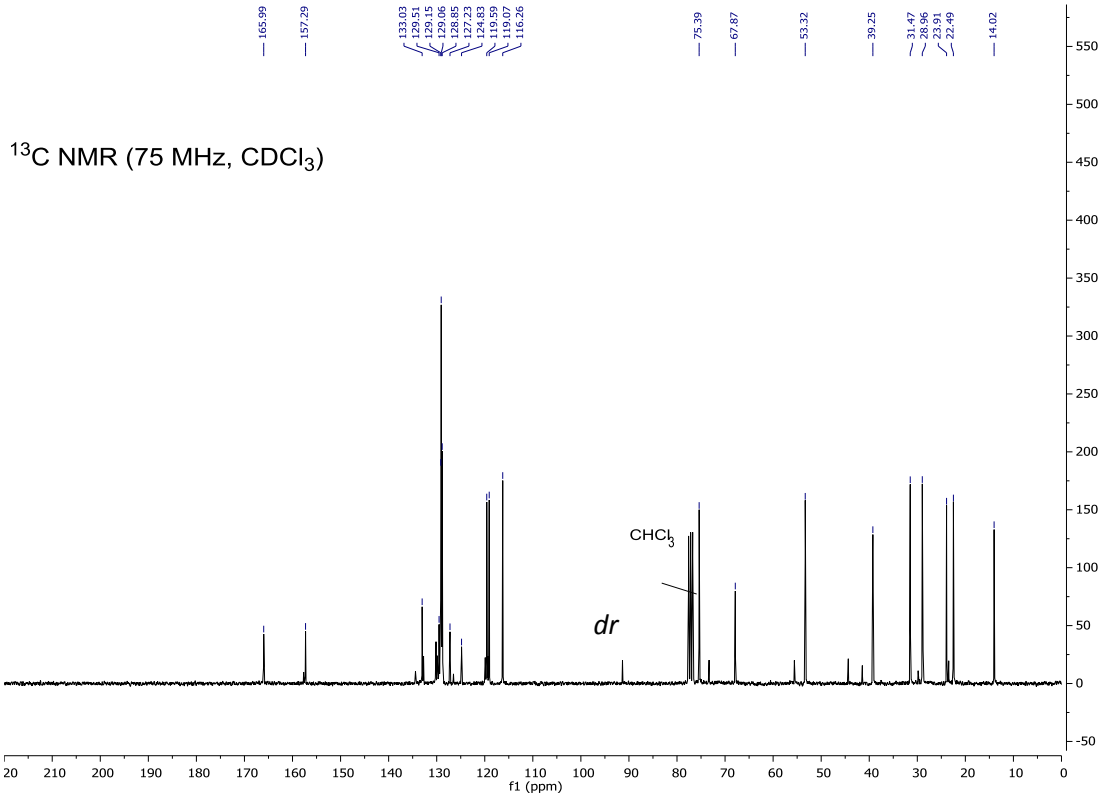
(*S*)-3-allyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32c)



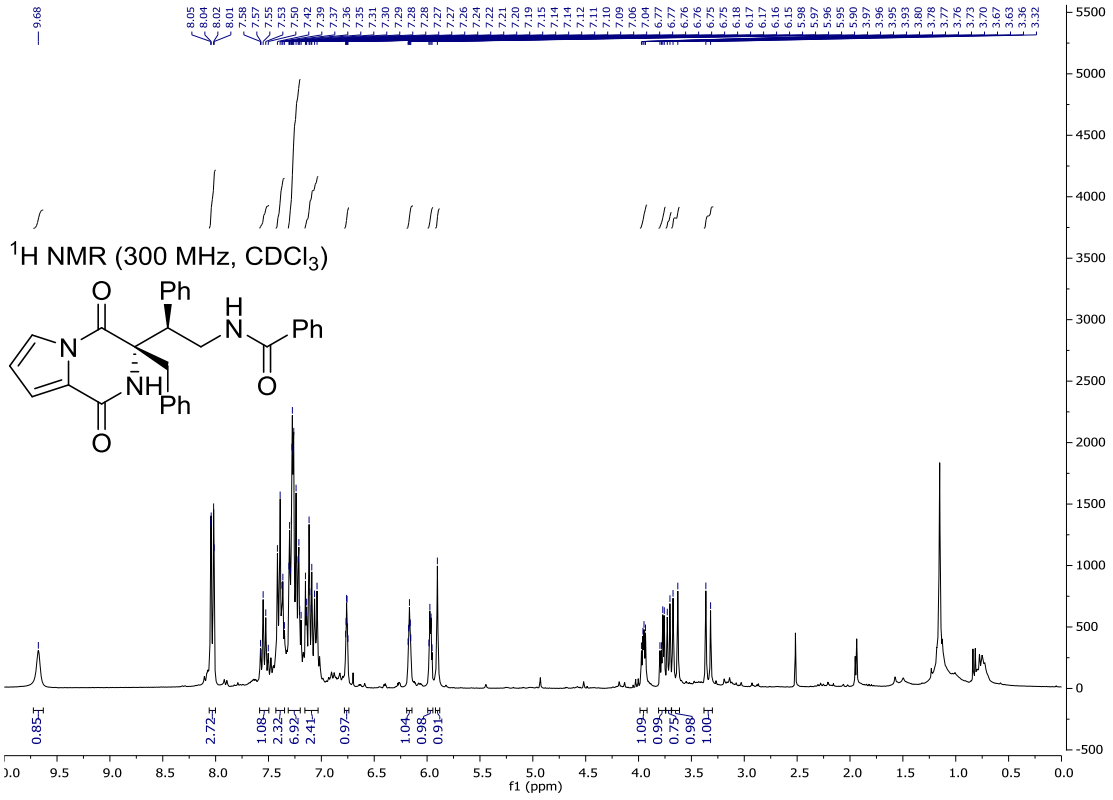


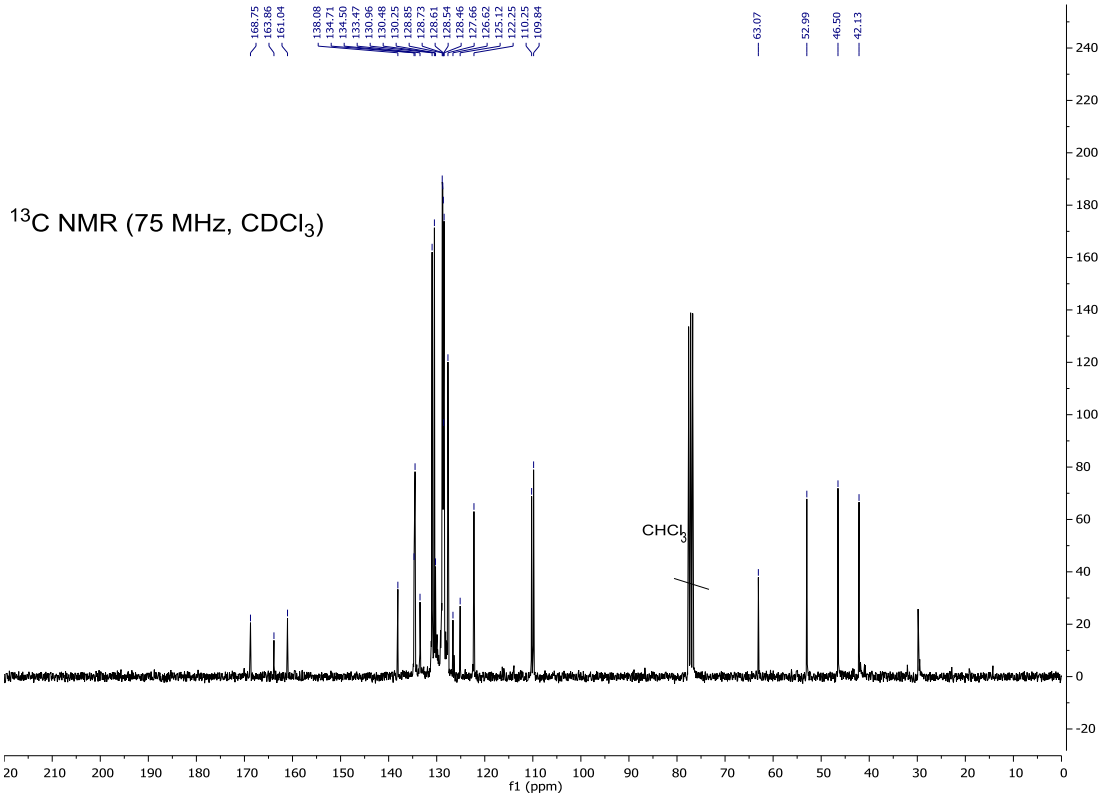
(*S*)-3-Hexyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (32d)





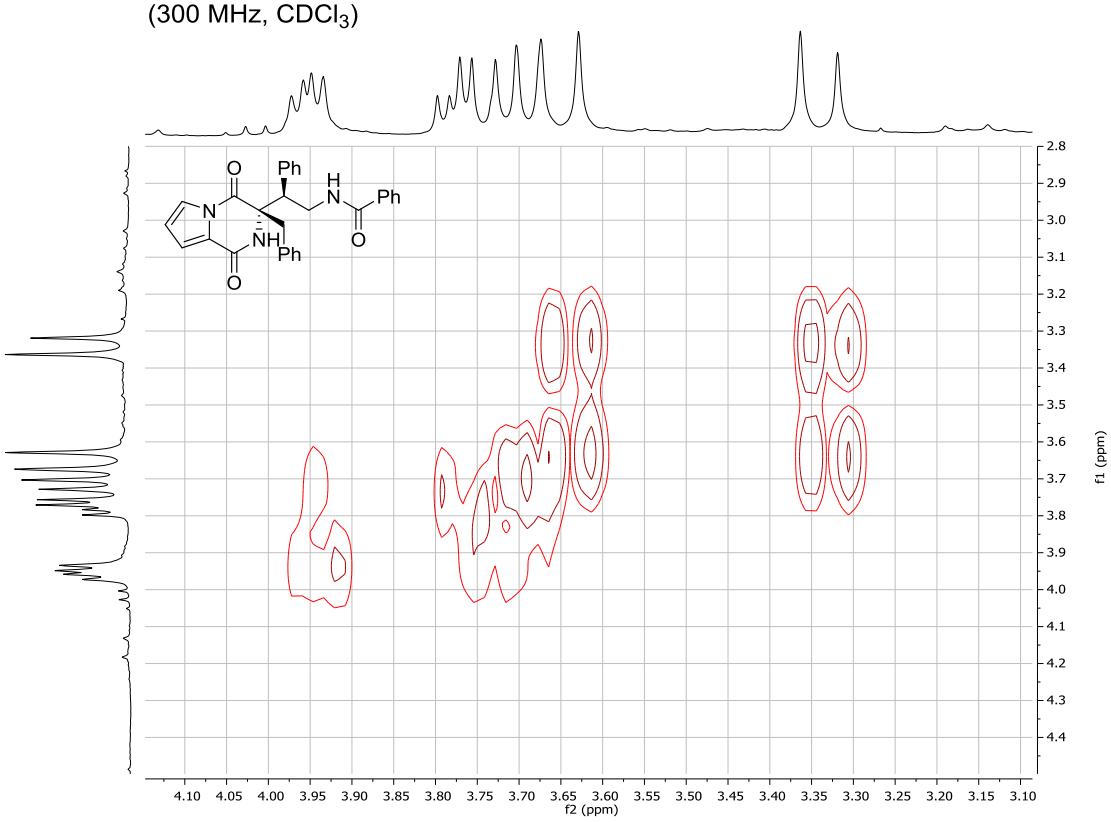
_N_-((_R_)-2-((_S_)-3-Benzyl-1,4-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-_a_]pyrazin-3-yl)-2-phenylethyl)benzamide (33)





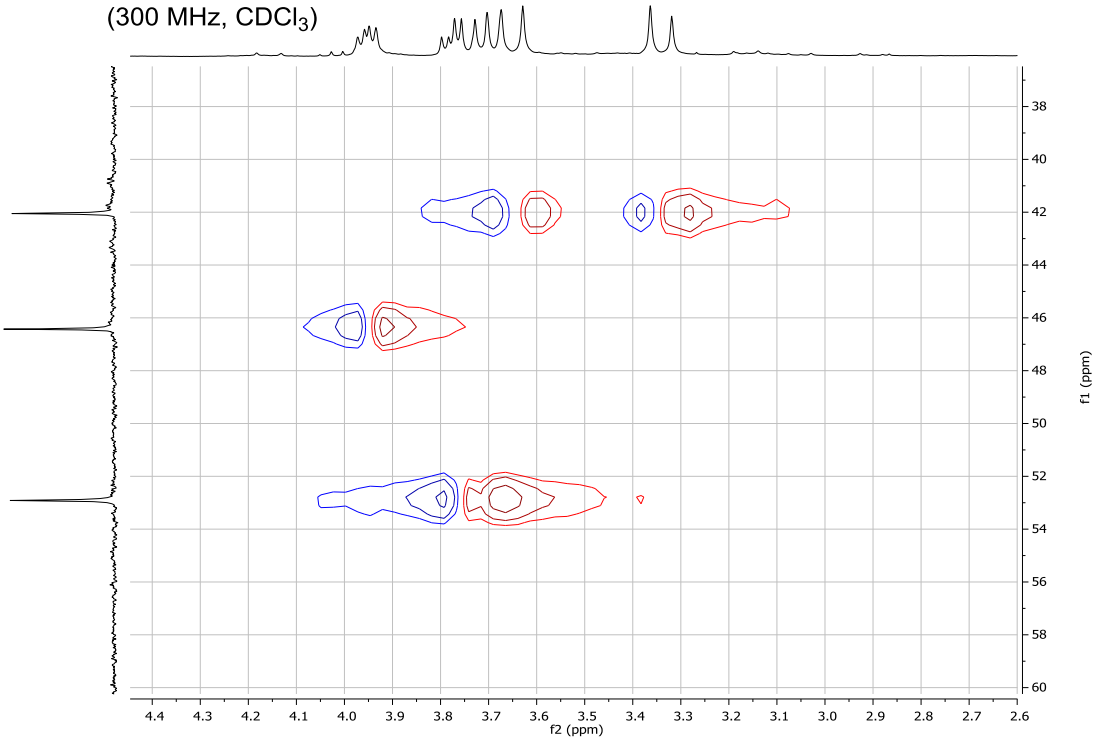
COSY

(300 MHz, $CDCl_3$)

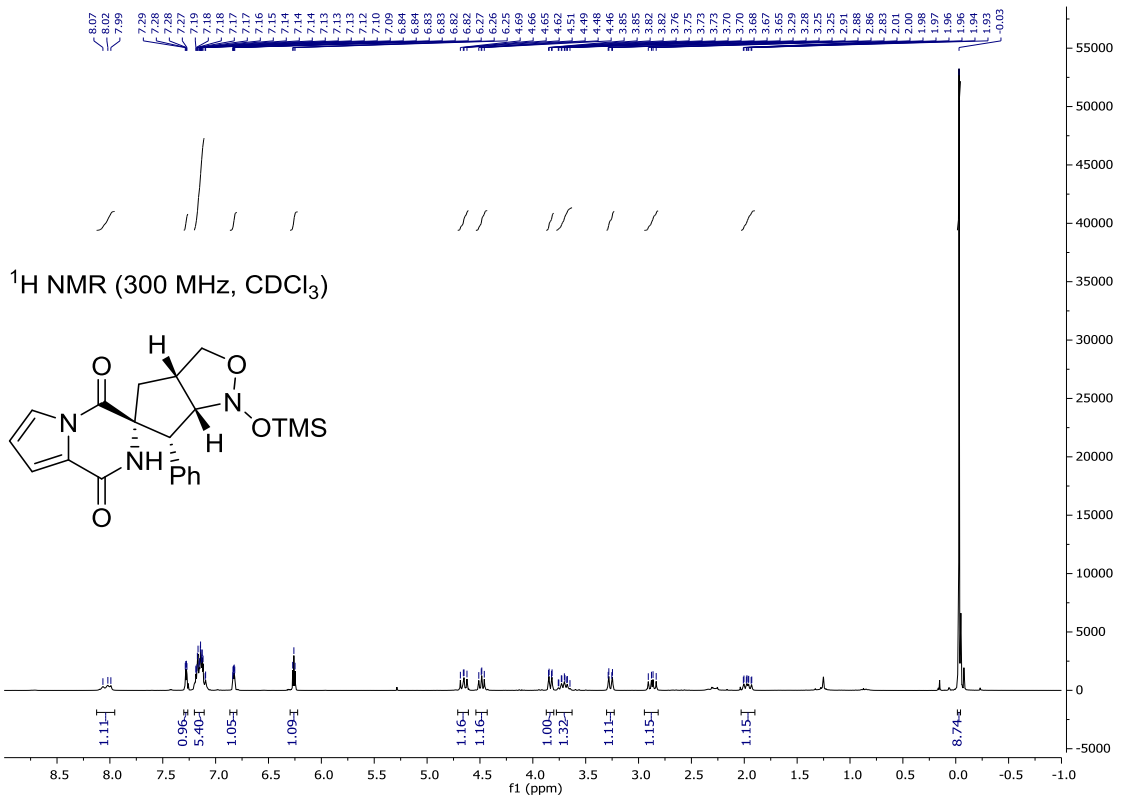


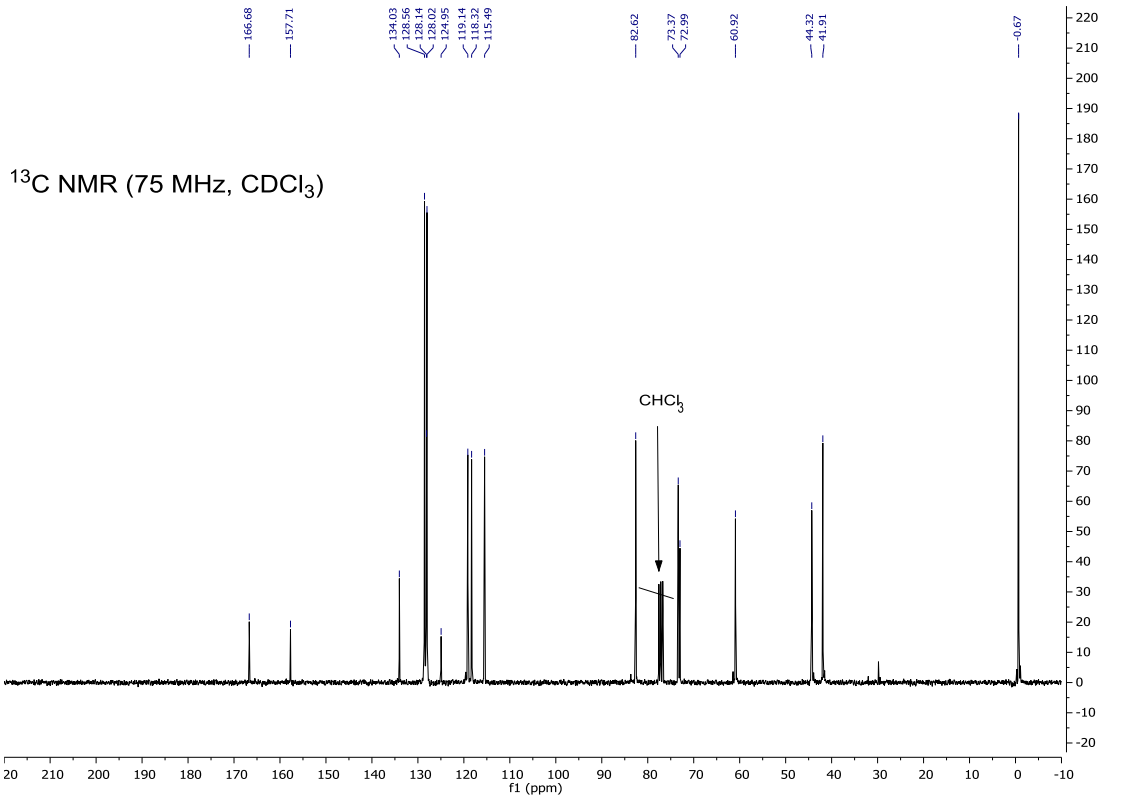
HSQC

(300 MHz, $CDCl_3$)

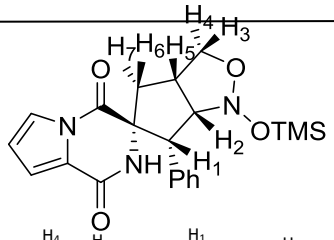


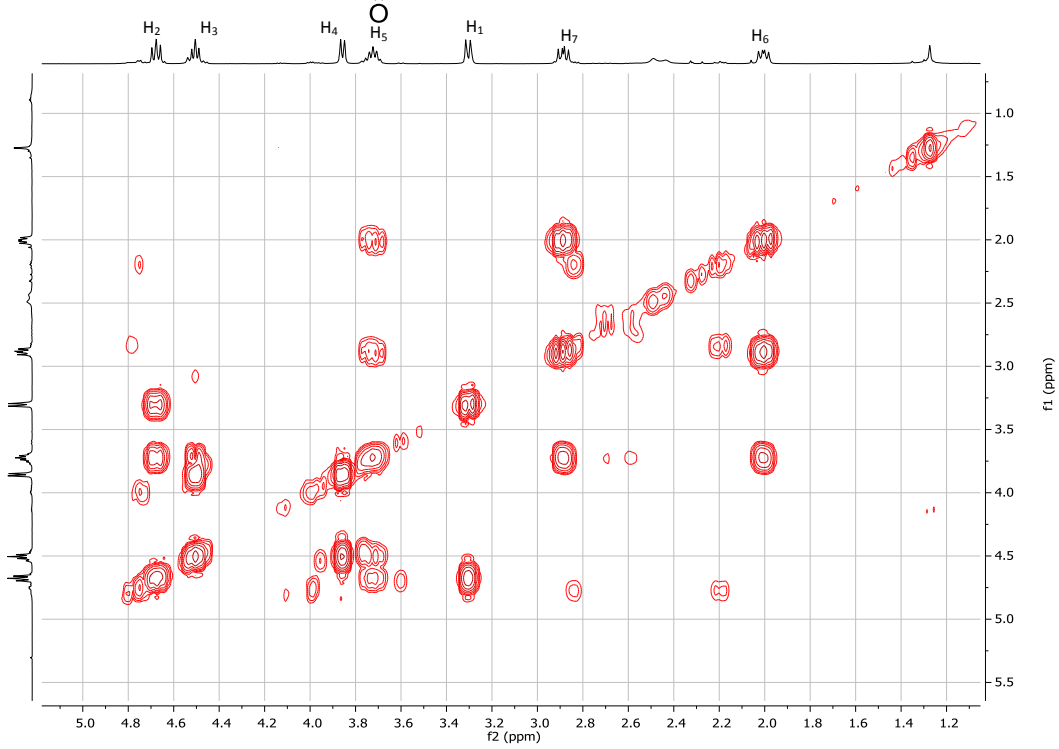
(3a*S*,5*R*,6*S*,6a*R*)-6-phenyl-1-((trimethylsilyl)oxy)-3a,4,6,6a-tetrahydro-1*H*,3*H*,4'*H*-spiro[cyclopenta[*c*]isoxazole-5,3'-pyrrolo[1,2-*a*]pyrazine]-1',4'(2'*H*)-dione (34)



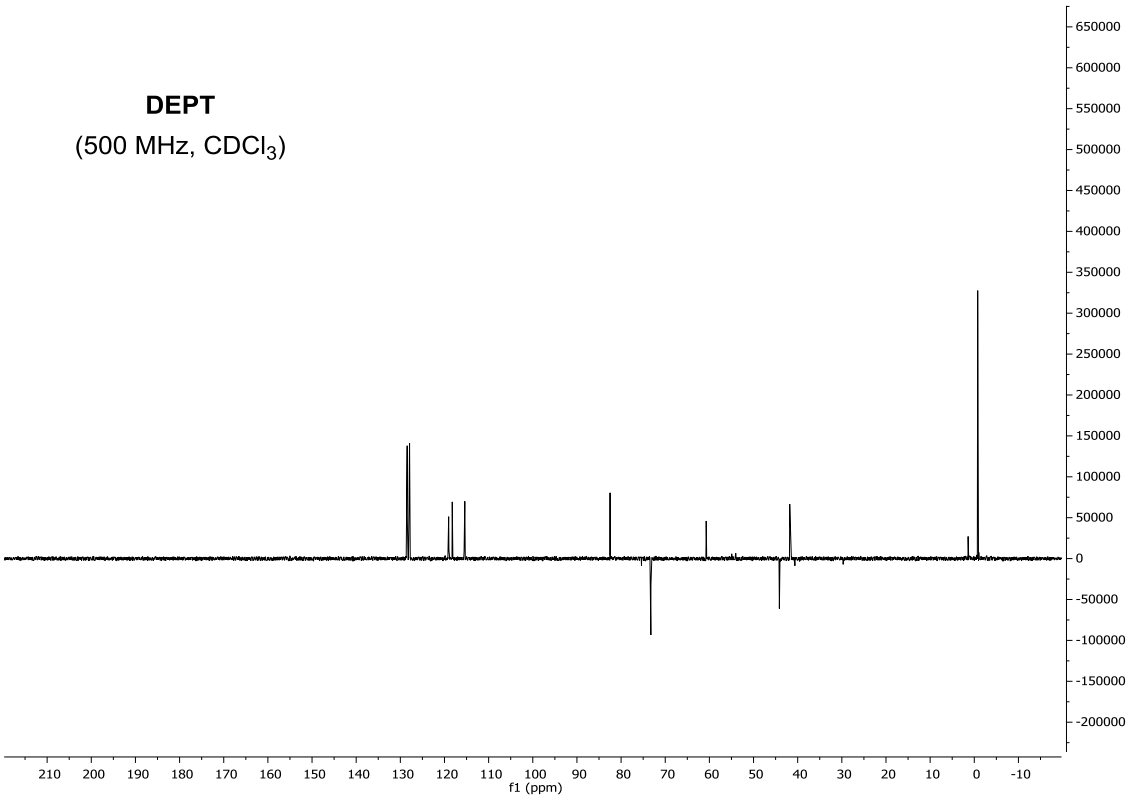


COSY
(500 MHz, $CDCl_3$)



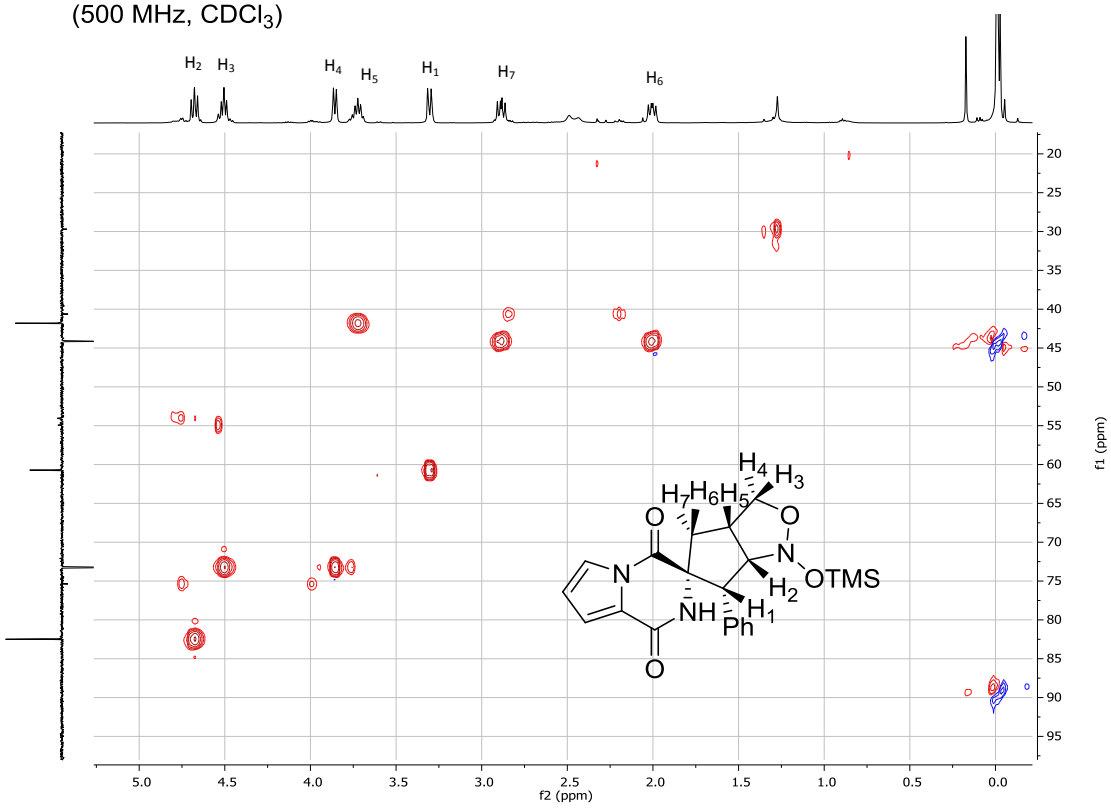


DEPT
(500 MHz, $CDCl_3$)



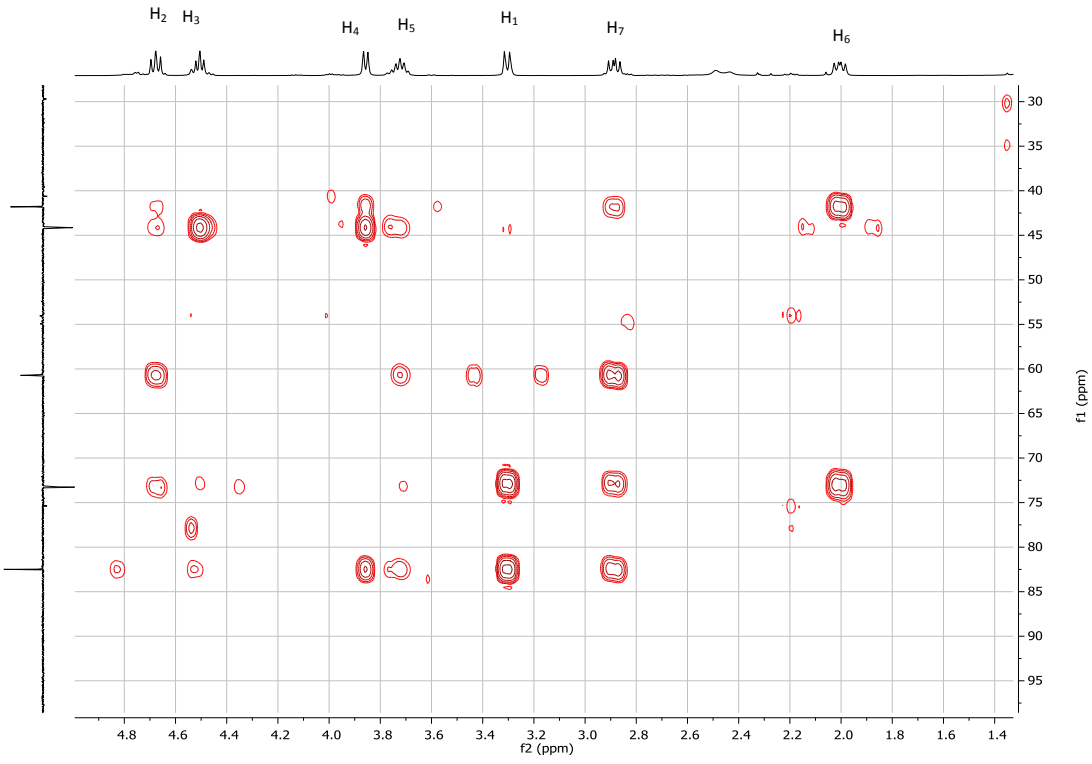
HSQC

(500 MHz, $CDCl_3$)



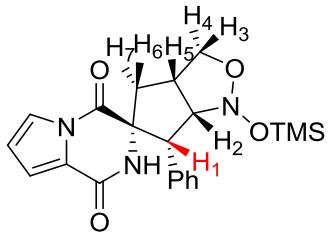
HMBC

(500 MHz, $CDCl_3$)



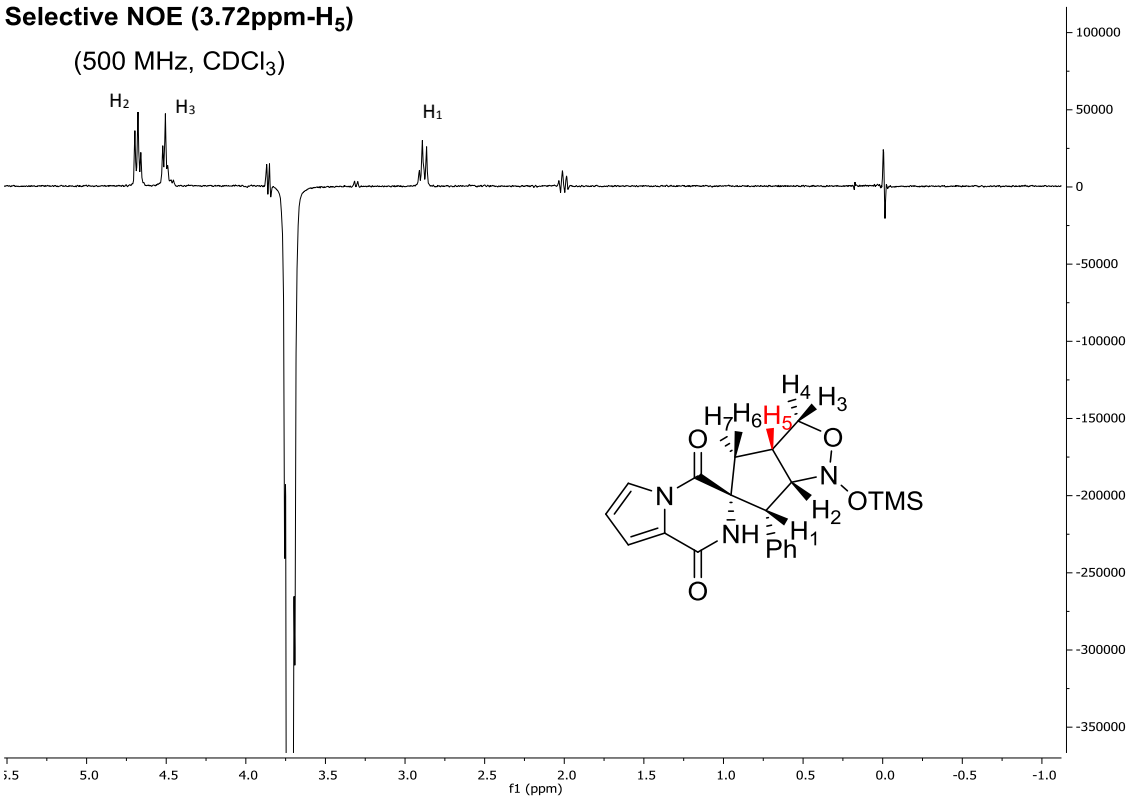
Selective NOE (3.28ppm-H_1)

(500 MHz, $CDCl_3$)



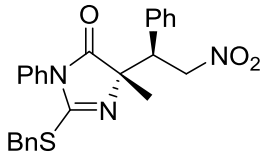
Selective NOE (3.72ppm-H_5)

(500 MHz, $CDCl_3$)

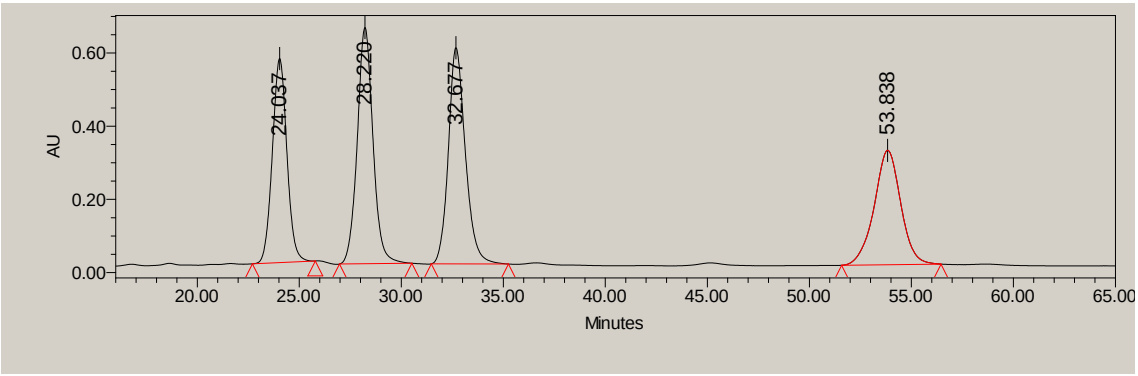


6.7. HPLC chromatograms

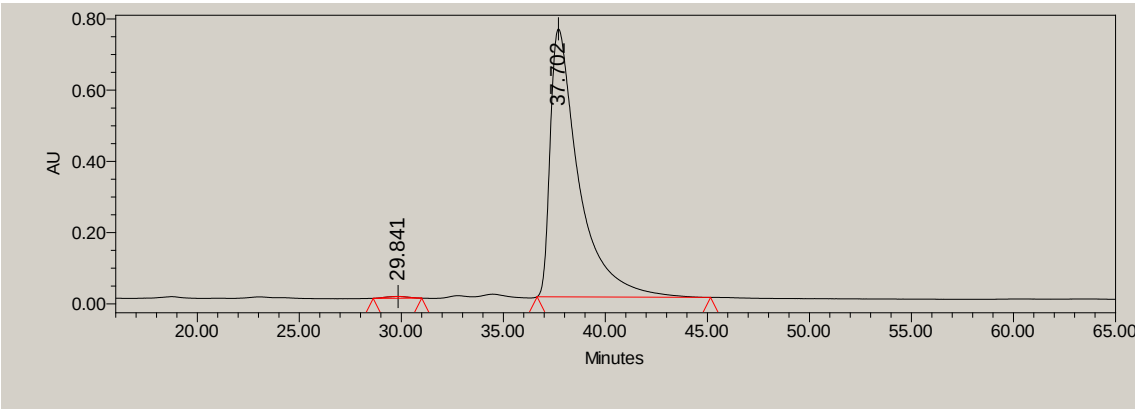
(*S*)-2-(Benzylthio)-4-methyl-4-((S)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (4aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 95/5, flow rate= 0.5 mL/min, retention times: 37.3 min (major.). Processed Channel Descr.: PDA 210.0 nm).

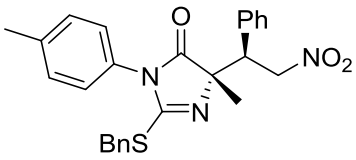


	Retention time	% Area
1	24,037	22,62
2	28,202	27,42
3	32,677	27,77
4	53,838	20,14

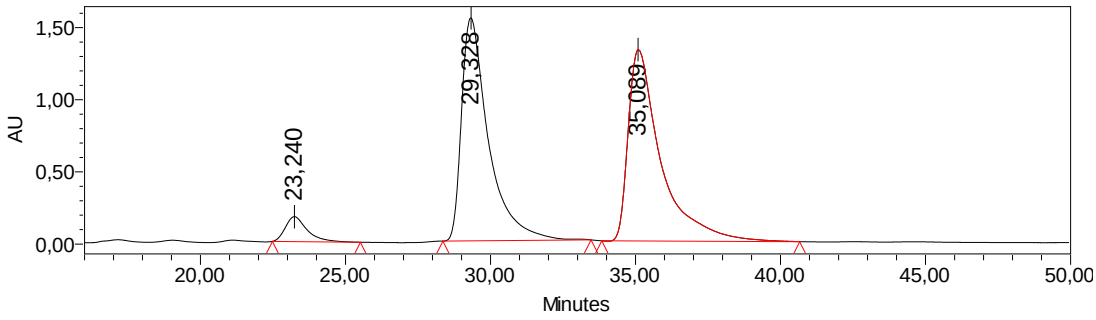


	Retention time	% Area
1	29,841	0,52
2	37,702	99,48

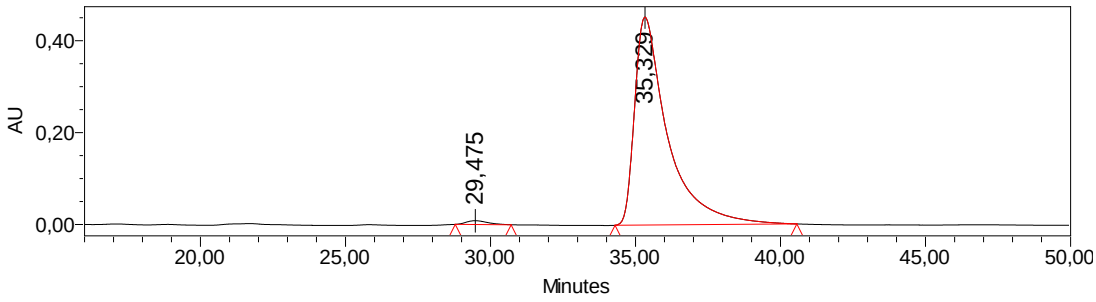
(*S*)-2-(Benzylthio)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-3-(*p*-tolyl)-1*H*-imidazol-5(4*H*)-one (4ba)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90/10, flow rate= 0.5 mL/min, retention times: 35.3 min (major.) and 29.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

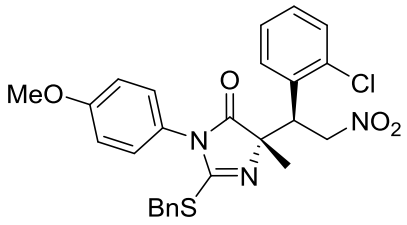


	Retention time	% Area
1	23,240	4,26
2	29,326	47,03
3	35,089	48,71

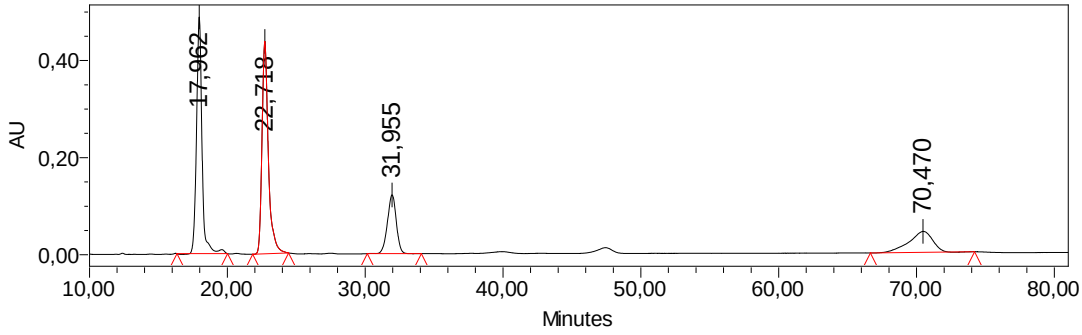


	Retention time	% Area
1	29,475	1,18
2	35,329	98,82

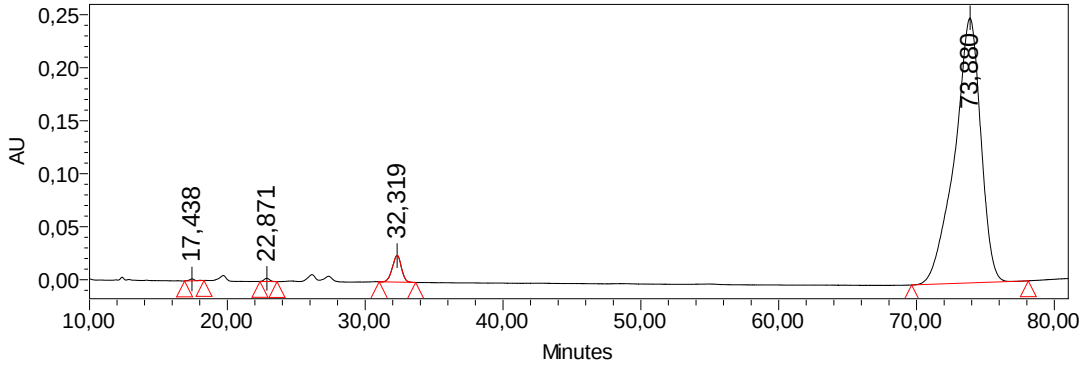
(*S*)-2-(Benzylthio)-4-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-(4-methoxyphenyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (4cb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 73.9 min (major.) and 32.3 min (min.). Processed Channel Descr.: PDA 210.0 nm).

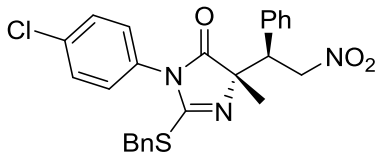


	Retention time	% Area
1	17,962	35,53
2	22,718	36,56
3	31,955	14,16
4	70,470	13,76

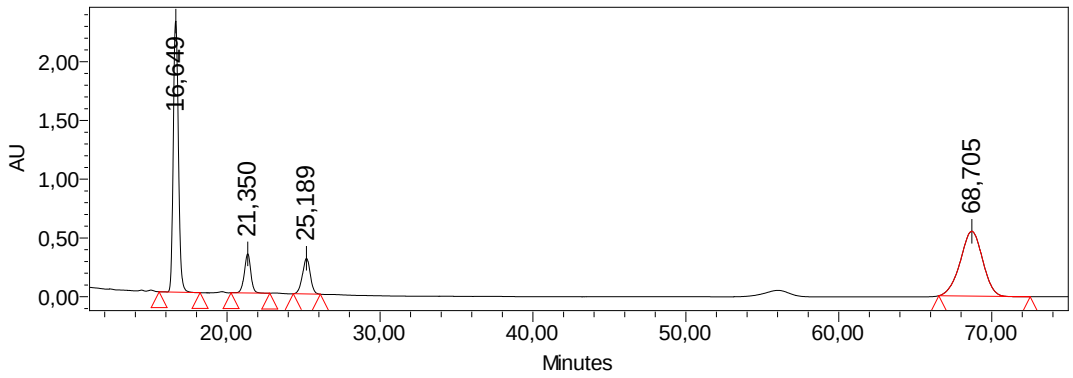


	Retention time	% Area
1	17,438	0,13
2	22,871	0,24
3	32,319	3,35
4	73,880	96,28

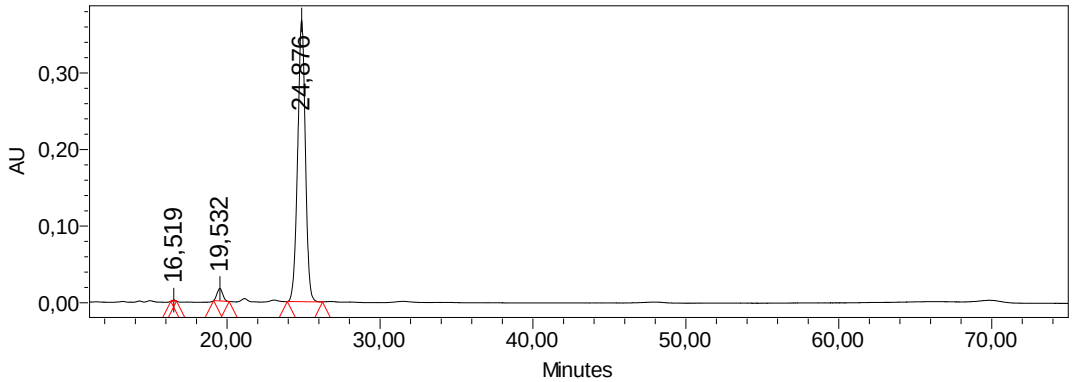
(*S*)-2-(Benzylthio)-1-(4-chlorophenyl)-4-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-imidazol-5(4*H*)-one (4da)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 24.9 min (major.) and 19.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

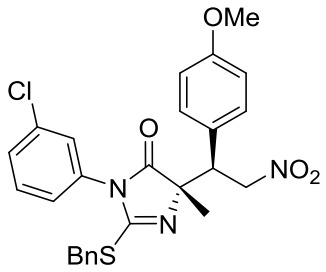


	Retention time	% Area
1	16,649	41,22
2	21,350	7,48
3	25,189	8,35
4	68,705	42.96

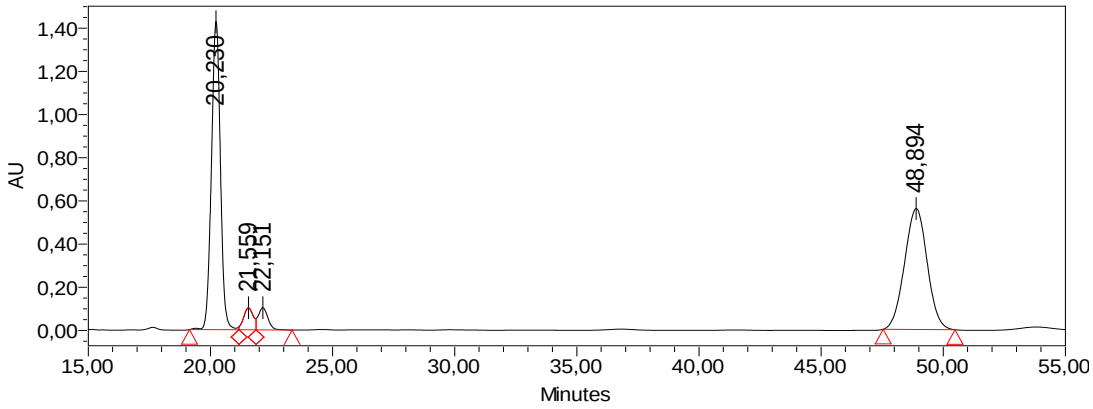


	Retention time	% Area
1	16,519	0,16
2	19,532	3,14
3	24,876	96,70

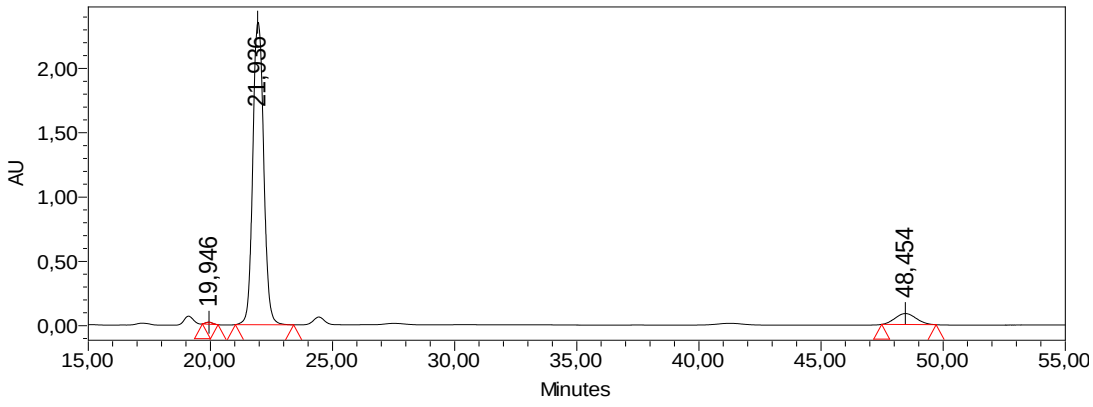
(*S*)-2-(Benzylthio)-1-(3-chlorophenyl)-4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-methyl-1*H*-imidazol-5(4*H*)-one (4ec)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 21.9 min (major.) and 48.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

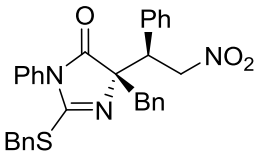


	Retention time	% Area
1	20,280	46,58
2	21,559	3,57
3	22,151	3,62
4	48,894	46,23

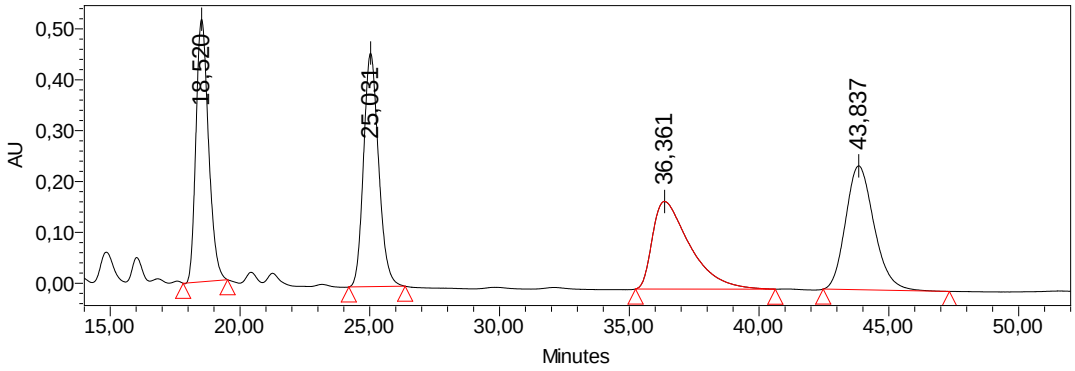


	Retention time	% Area
1	19.946	0,41
2	21,936	93,06
3	48,454	6,53

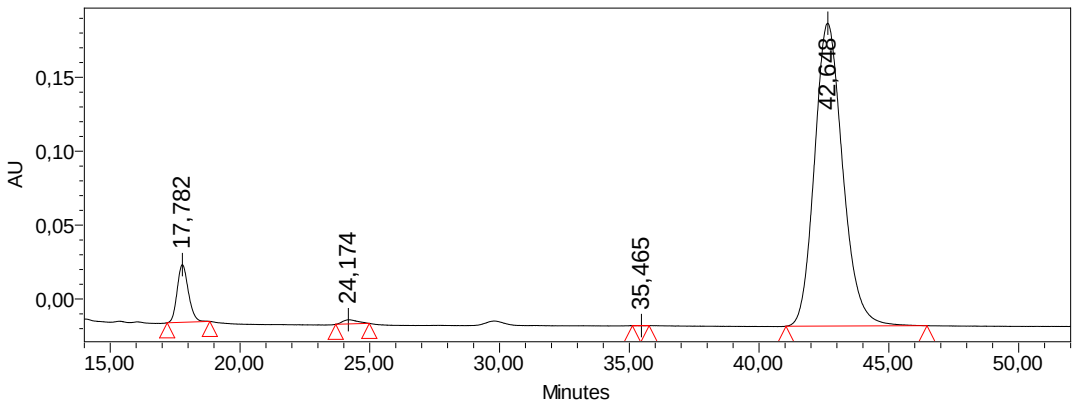
(*S*)-4-Benzyl-2-(benzylthio)-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-5(4*H*)-one (4fa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 70/30, flow rate= 0.5 mL/min, retention times: 42.6 min (major.) and 24.2 min (min.). Processed Channel Descr.: PDA 210.0 nm).

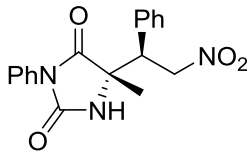


	Retention time	% Area
1	18,520	25,93
2	25,031	24,03
3	36,361	25,77
4	43,837	24,26

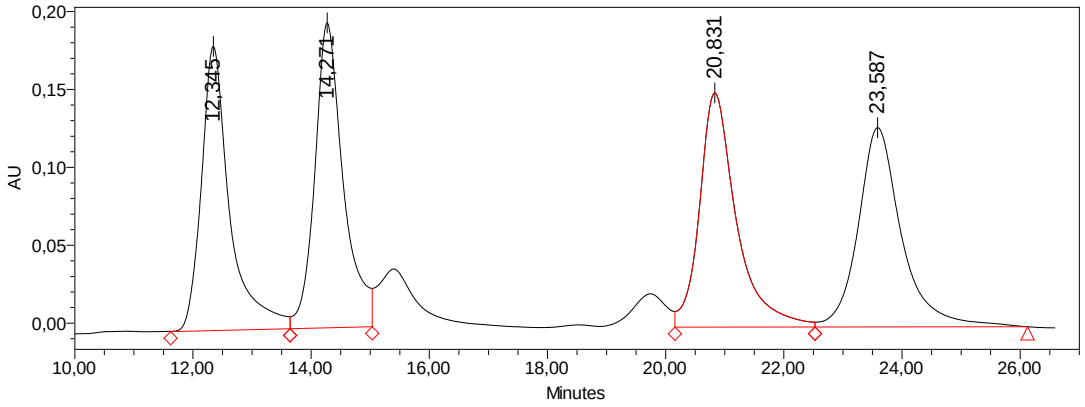


	Retention time	% Area
1	17,782	6,98
2	24,174	0,68
3	35,465	0,01
4	42,648	92,32

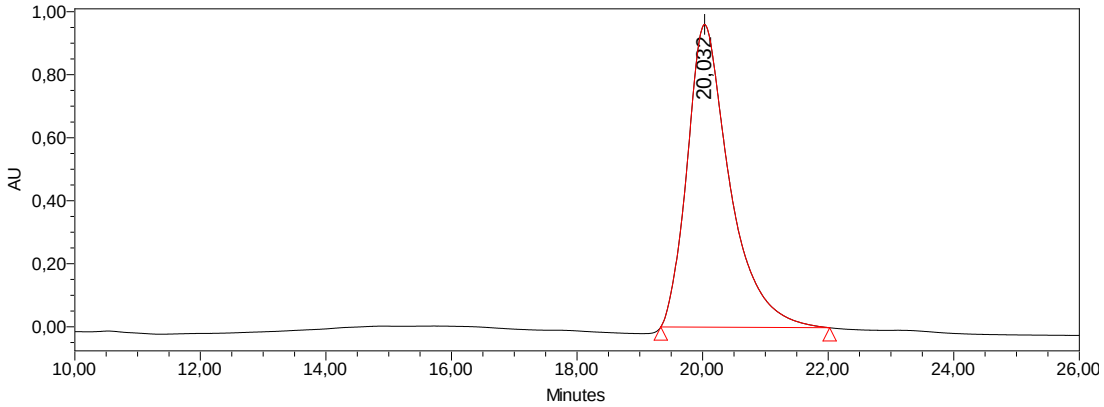
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (5)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 20.8 min (major.). Processed Channel Descr.: PDA 210.0 nm).

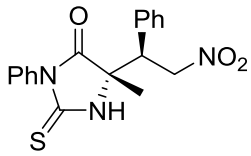


	Retention time	% Area
1	12,345	23,67
2	14,271	25,54
3	20,831	25,40
4	23,587	25,38

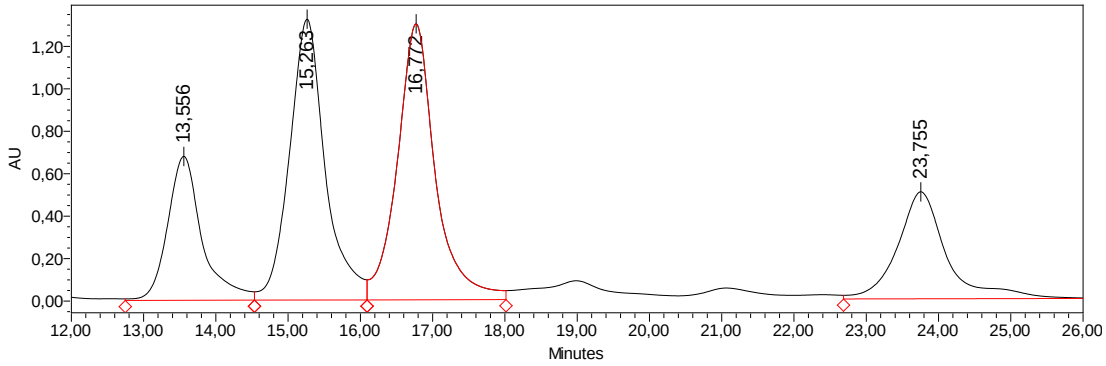


	Retention time	% Area
1	20,032	100,00

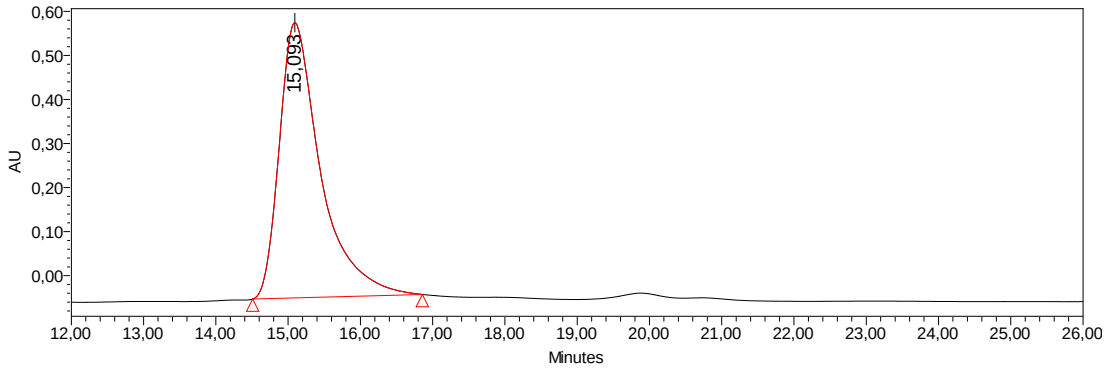
(*S*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-3-phenyl-2-thioxoimidazolidin-4-one (6)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 15.1 min (major.). Processed Channel Descr.: PDA 210.0 nm).

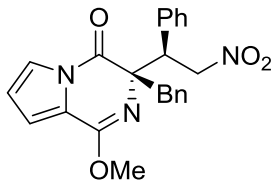


	Retention time	% Area
1	13,556	16,06
2	15,263	32,65
3	16,772	34,18
4	23,755	17,11

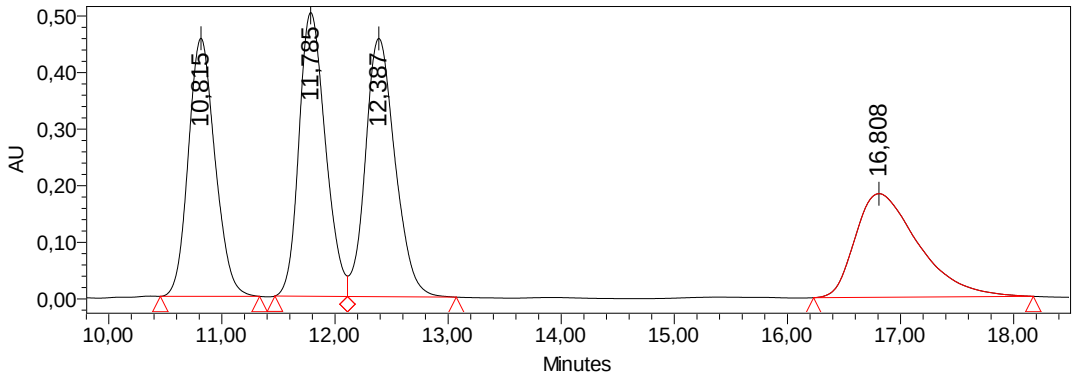


	Retention time	% Area
1	15.093	100,00

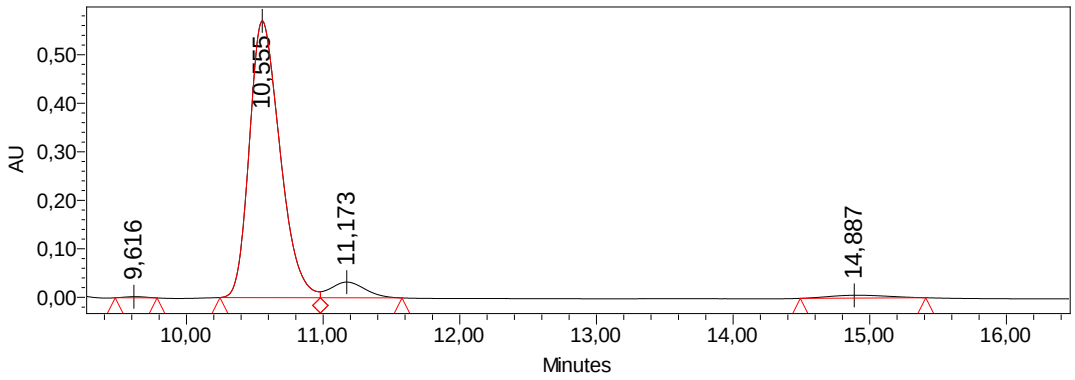
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID, hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 10.8 min (anti), 11.8 min (syn, major.), 12.4 min (syn, minor.) and 16.8 min (anti). Processed chanel Descr.: PDA 210.0 nm).

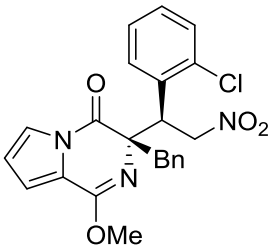


	Retention time	% Area
1	10,815	24,06
2	11,785	26,22
3	12,387	26,79
4	16,808	22,94

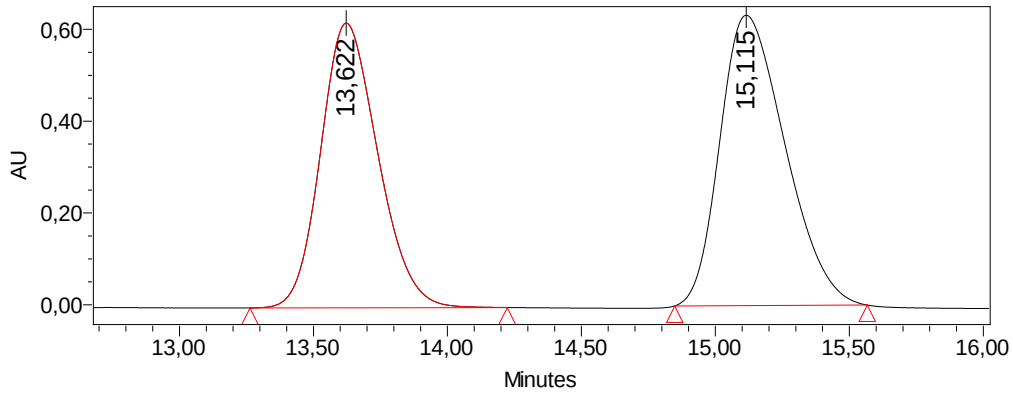


	Retention time	% Area
1	9,616	0,28
2	10,555	91,95
3	11,173	5,93
4	14,887	1,84

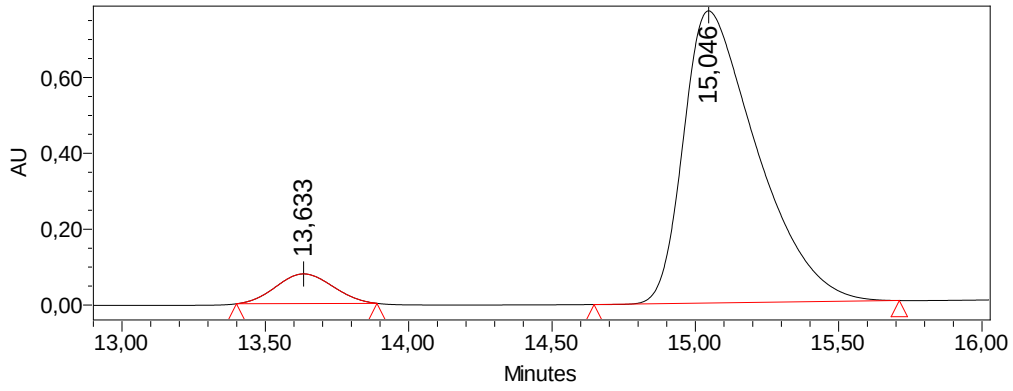
(*S*)-3-Benzyl-3-((*S*)-1-(2-chlorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ab)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 13.6 min (minor.) and 15.1 min (major.) Processed chanel Descr.: PDA 210.0 nm).

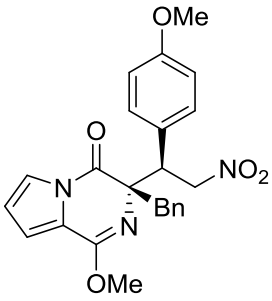


	Retention time	% Area
1	13,622	46,23
2	15,115	53,77

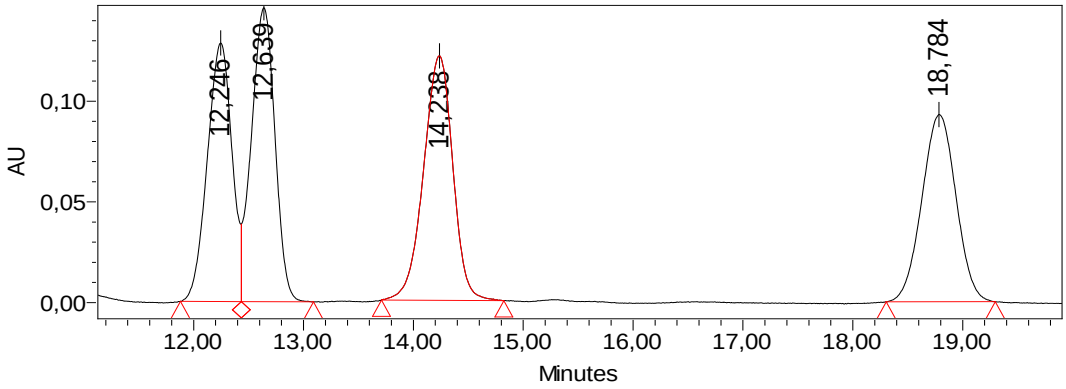


	Retention time	% Area
1	13,633	7,28
2	15,046	92,72

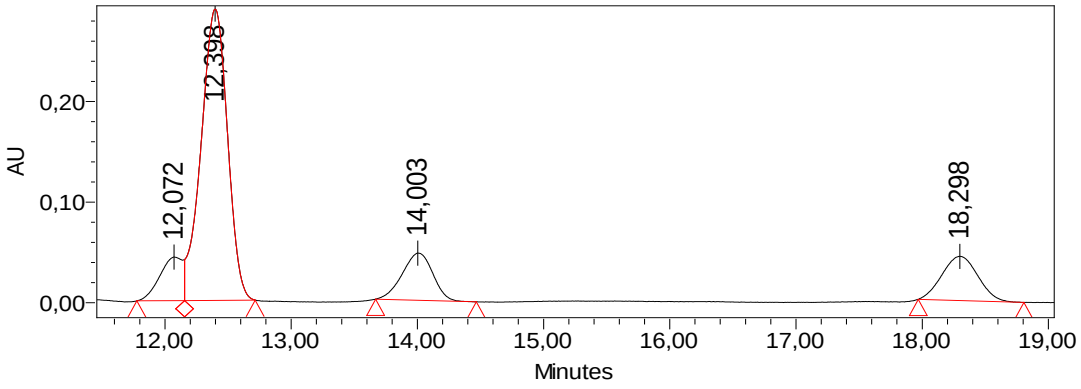
(S)-3-Benzyl-1-methoxy-3-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ac)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3, hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 12.2 min (anti), 12.6 min (syn, major.), 14.2 min (syn, minor.) and 18.8 min (anti). Processed chanel Descr.: PDA 210.0 nm).

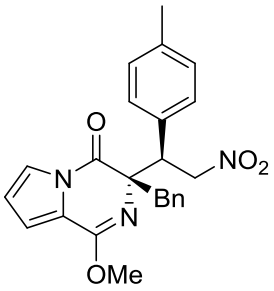


	Retention time	% Area
1	12,246	23,75
2	12,639	25,76
3	14,238	26,66
4	18,784	23,83

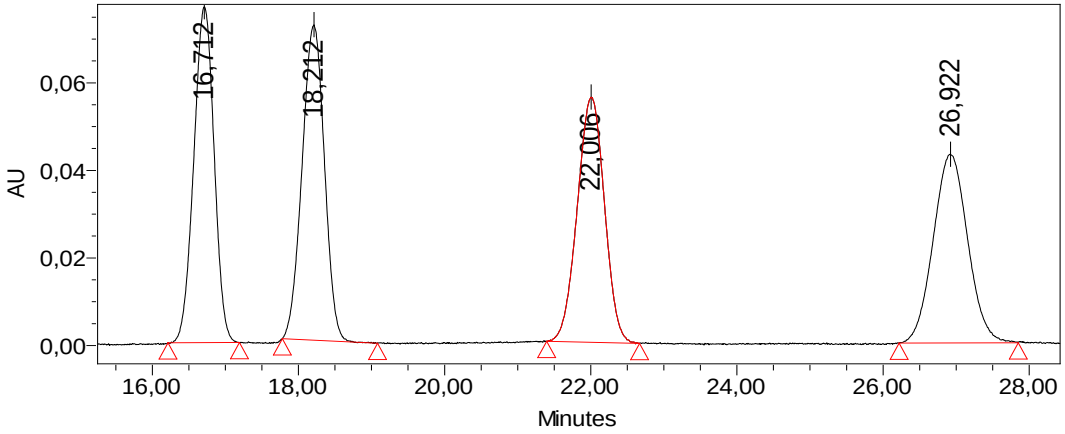


	Retention time	% Area
1	12,072	8,56
2	12,398	65,61
3	14,003	12,30
4	18,298	13,53

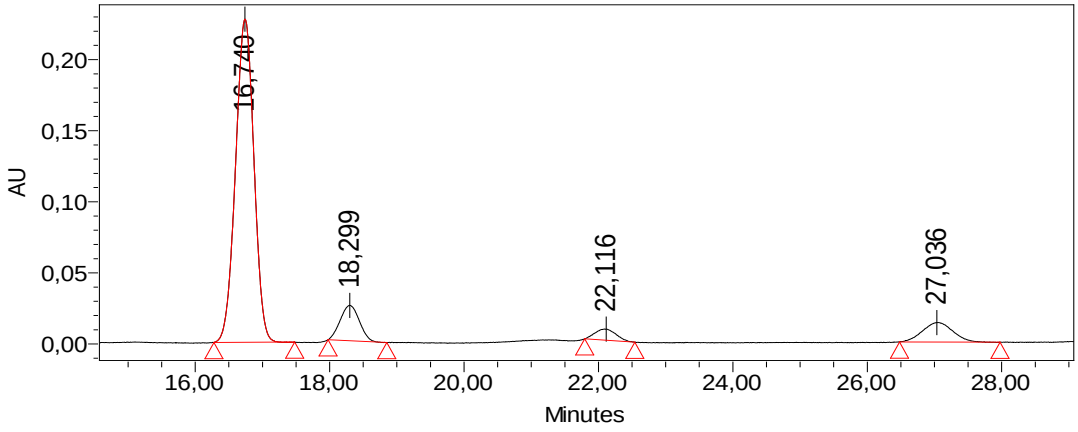
(S)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ad)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3, hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 16.7 min (syn, major.), 18.2 min (syn, minor.), 22.0 min (anti) and 26.9 min (anti). Processed chanel Descr.: PDA 210.0 nm).

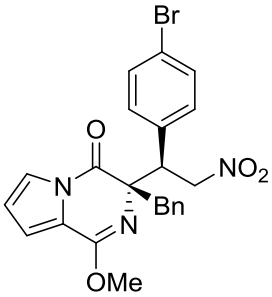


	Retention time	% Area
1	16,712	25,25
2	18,212	26,04
3	22,006	24,64
4	26,922	24,07

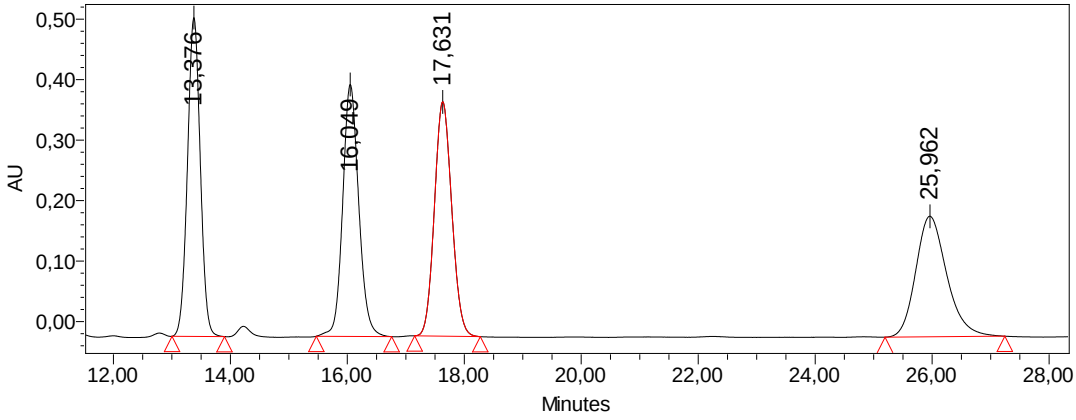


	Retention time	% Area
1	16,740	79,88
2	18,299	9,07
3	22,116	3,10
4	27,036	7,94

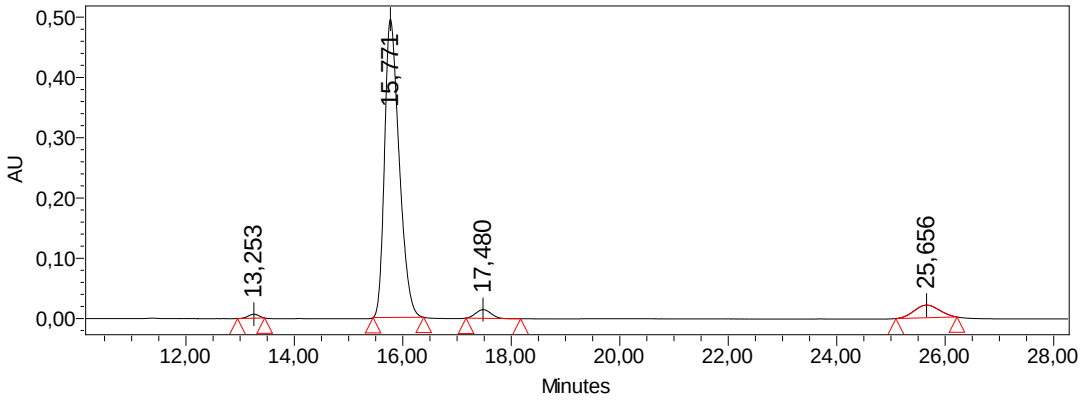
(*S*)-3-Benzyl-3-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ae)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3, hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 13.4 min (anti), 16.0 min (syn, major.), 17.6 min (anti) and 26.0 min (syn, minor.). Processed chanel Descr.: PDA 210.0 nm).

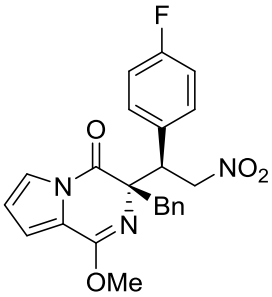


	Retention time	% Area
1	13,376	25,65
2	16,049	25,37
3	17,631	25,53
4	25,962	23,45

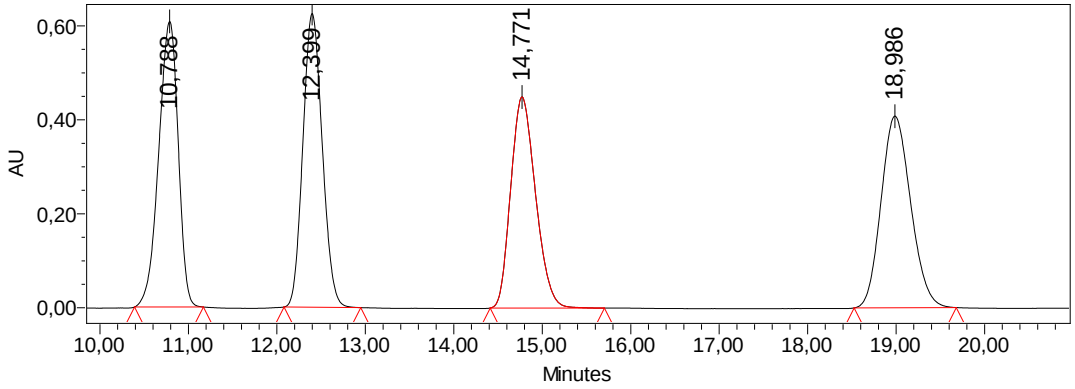


	Retention time	% Area
1	13,253	0,90
2	15,771	89,80
3	17,480	2,73
4	25,656	6,57

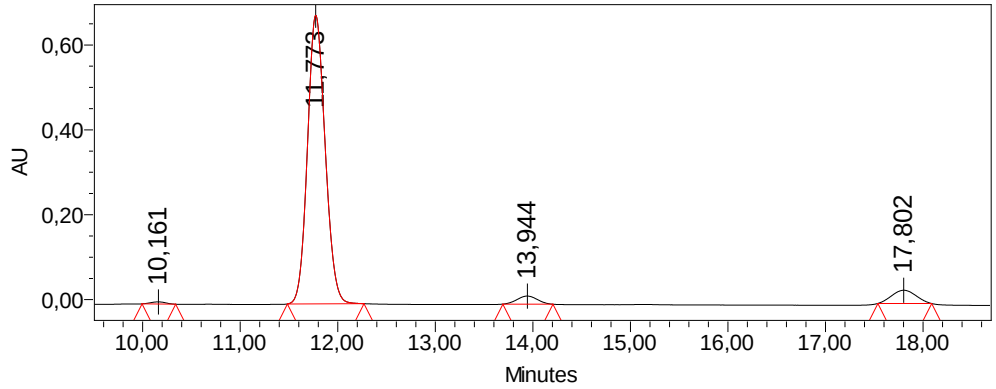
(*S*)-3-Benzyl-3-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20af)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 10.8 min (anti), 12.4 min (syn, major.), 14.7 min (anti) and 19.0 min (syn, minor.). Processed chanel Descr.: PDA 210.0 nm).

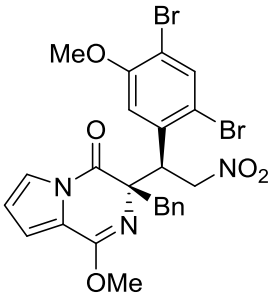


	Retention time	% Area
1	10,788	25,10
2	12,399	25,67
3	14,771	23,61
4	18,986	25,62

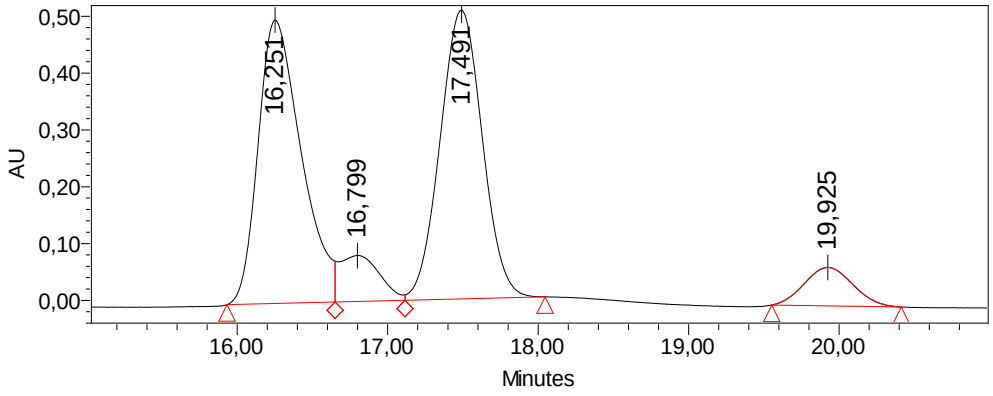


	Retention time	% Area
1	10,161	0,56
2	11,773	90,86
3	13,944	2,90
4	17,802	5,68

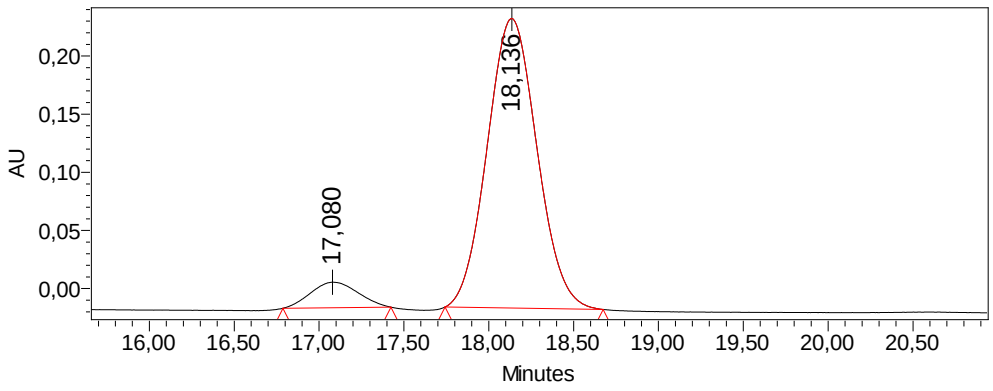
(*S*)-3-Benzyl-3-((*S*)-1-(2,4-dibromo-5-methoxyphenyl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ag)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 16.2 min (syn, minor.) 16.8 min (anti), 17.5 (syn, mayor. and 19.9 min (anti). Processed chanel Descr.: PDA 210.0 nm).

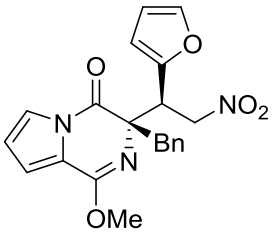


	Retention time	% Area
1	16,251	43,41
2	16,799	6,61
3	17,491	43,35
4	19,925	6,64

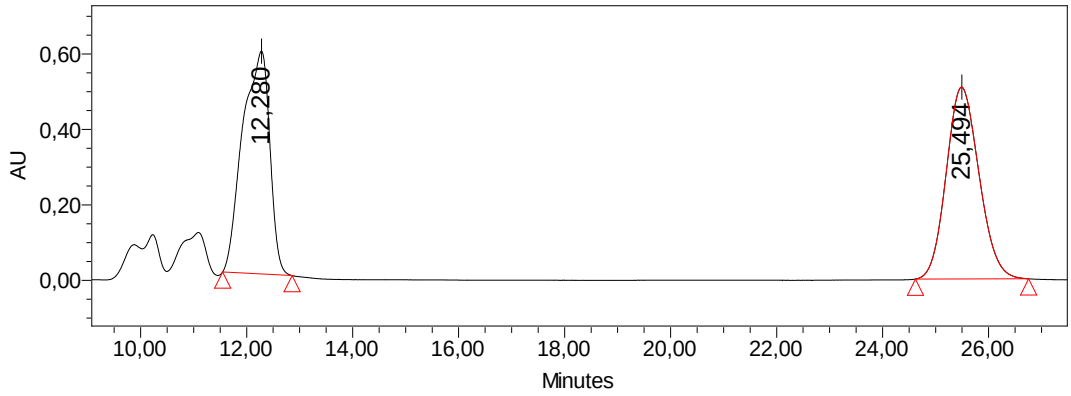


	Retention time	% Area
1	17,080	7,72
2	18,136	92,28

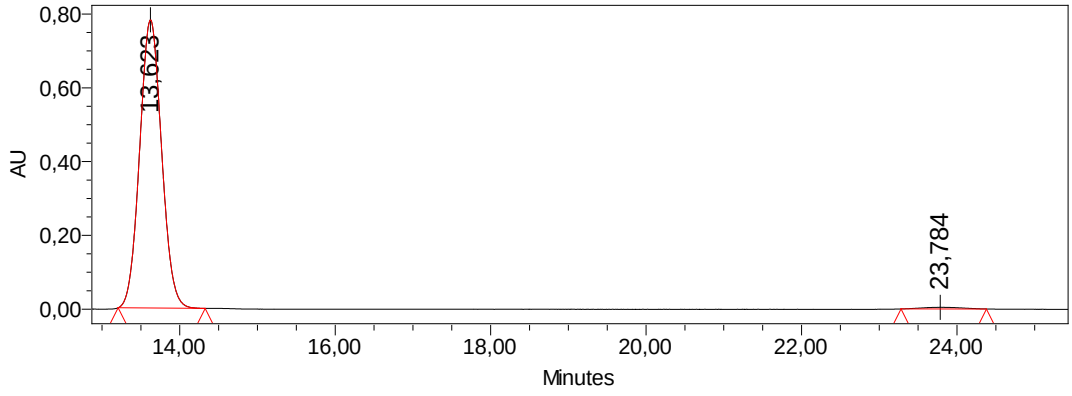
(*S*)-3-Benzyl-3-((*S*)-1-(furan-2-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ah)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 12.3 min (major.) and 25.5 min (minor.). Processed chanel Descr.: PDA 210.0 nm).

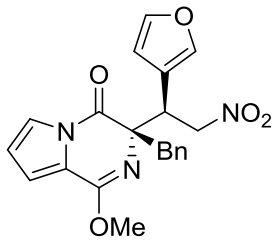


	Retention time	% Area
1	12,280	48,95
2	25,494	51,05

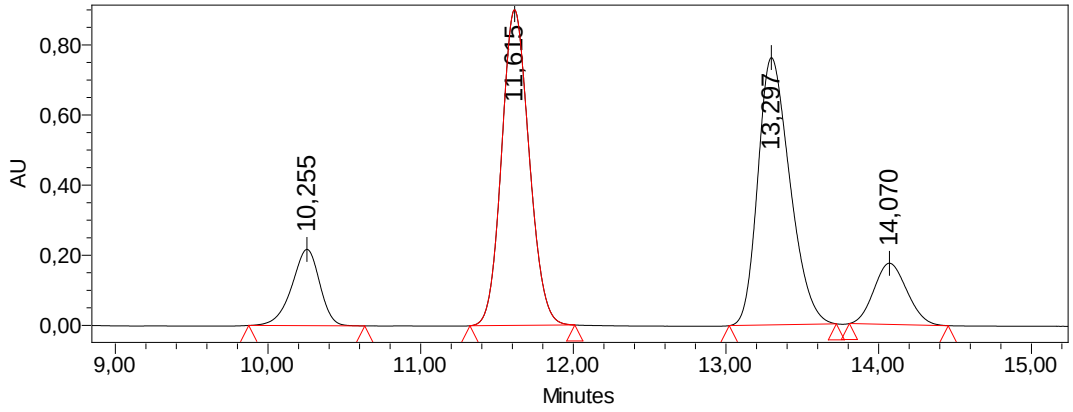


	Retention time	% Area
1	13,623	98,98
2	23,784	1,02

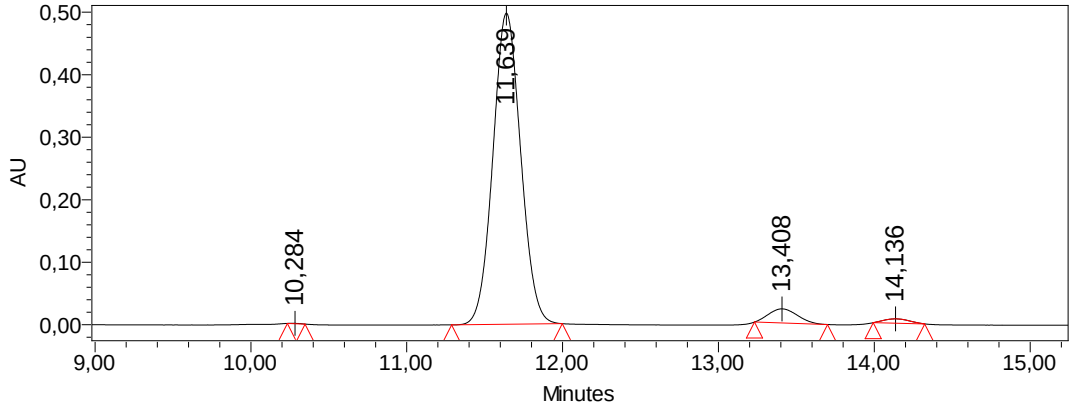
(*S*)-3-Benzyl-3-((*S*)-1-(furan-3-yl)-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ai)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 10.3 min (anti), 11.6 min (syn, major.) and 13.3 min (syn, minor.) and 14.1 min (anti). Processed chanel Descr.: PDA 210.0 nm).

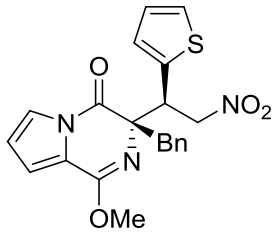


	Retention time	% Area
1	10,255	9,98
2	11,615	40,58
3	13,297	40,00
4	14,070	9,43

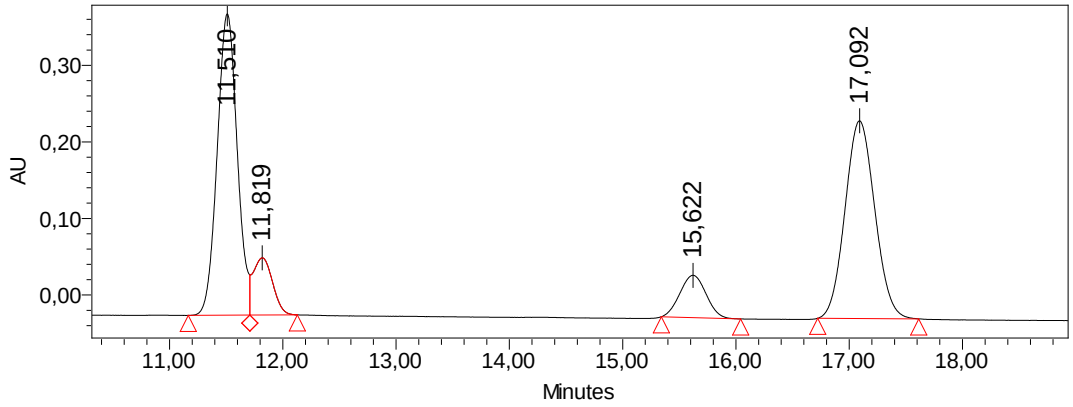


	Retention time	% Area
1	10,284	0,04
2	11,639	94,31
3	13,408	4,45
4	14,136	1,20

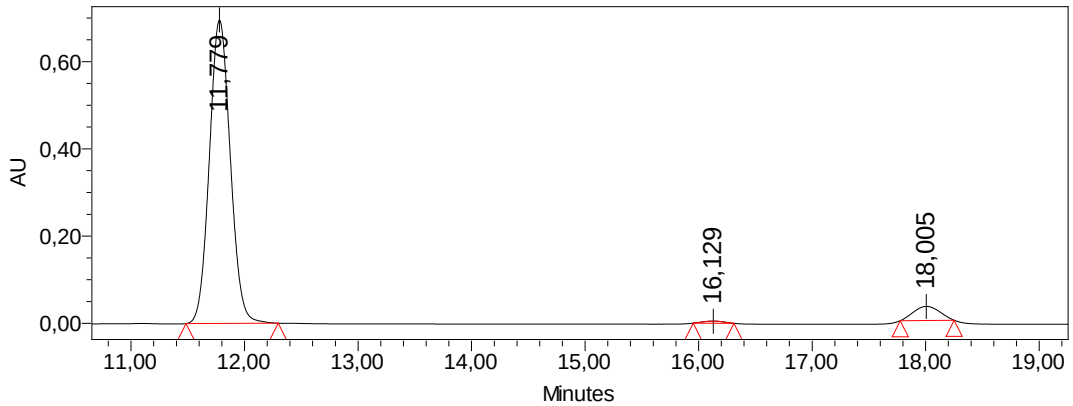
(*S*)-3-Benzyl-1-methoxy-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20aj)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 11.5 min (syn, major.), 11.8 min (anti), 15.6 min (anti) and 17.1 min (syn, minor.). Processed chanel Descr.: PDA 210.0 nm).

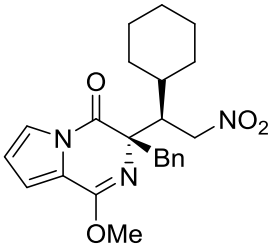


	Retention time	% Area
1	11,510	42,64
2	11,819	7,93
3	15,622	7,82
4	17,092	41,61

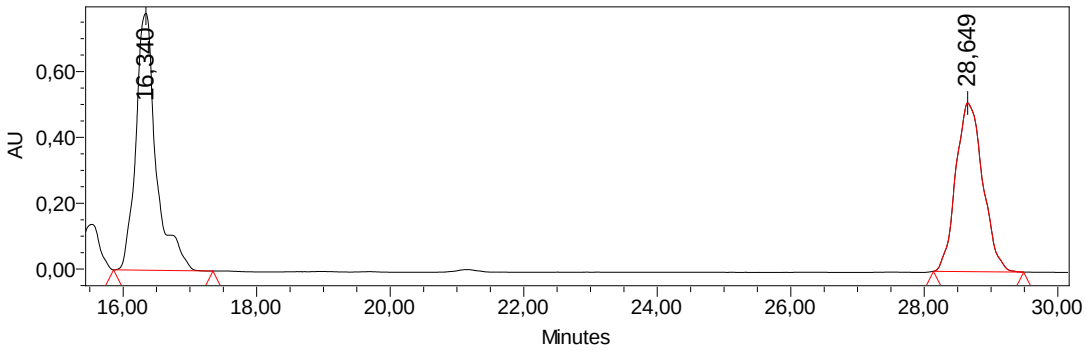


	Retention time	% Area
1	11,779	93,92
2	16,129	0,64
3	18,005	5,44

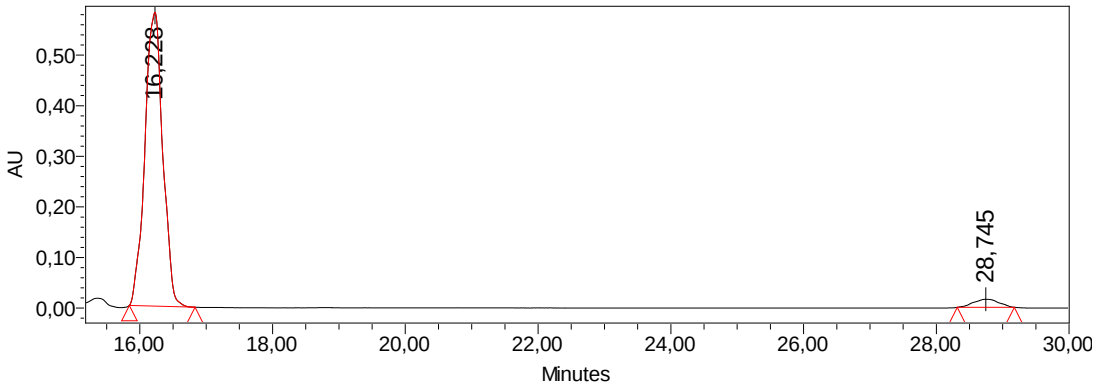
(*S*)-3-Benzyl-3-((*S*)-1-cyclohexyl-2-nitroethyl)-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20al)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 16.2 min (major.) and 28.7 min (min.). Processed chanel Descr.: PDA 210.0 nm).

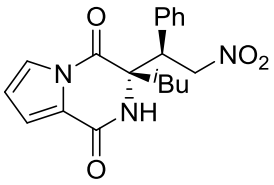


	Retention time	% Area
1	16,340	53,31
2	28,649	46,69

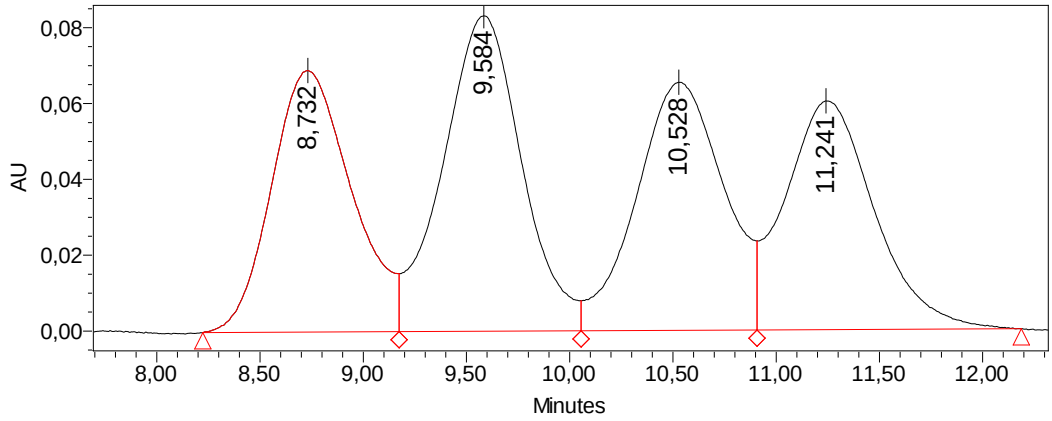


	Retention time	% Area
1	16,228	96,47
2	28,745	3,53

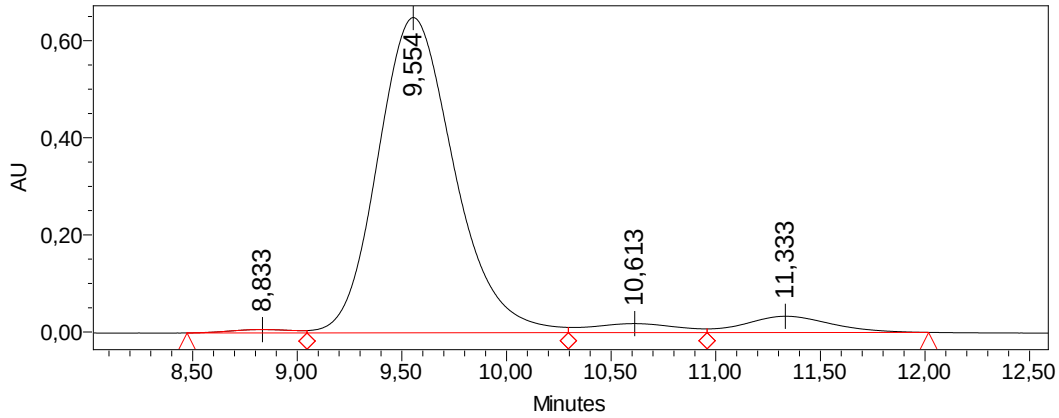
(*S*)-3-Isobutyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (3ba)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 8.7 min (anti), 9.6 min (syn, major.), 10.5 min (anti) and 11.2 min (syn, minor.). Processed chanel Descr.: PDA 210.0 nm).

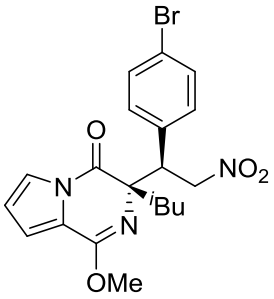


	Retention time	% Area
1	8,732	23,82
2	9,584	28,29
3	10,528	24,67
4	11,241	23,22

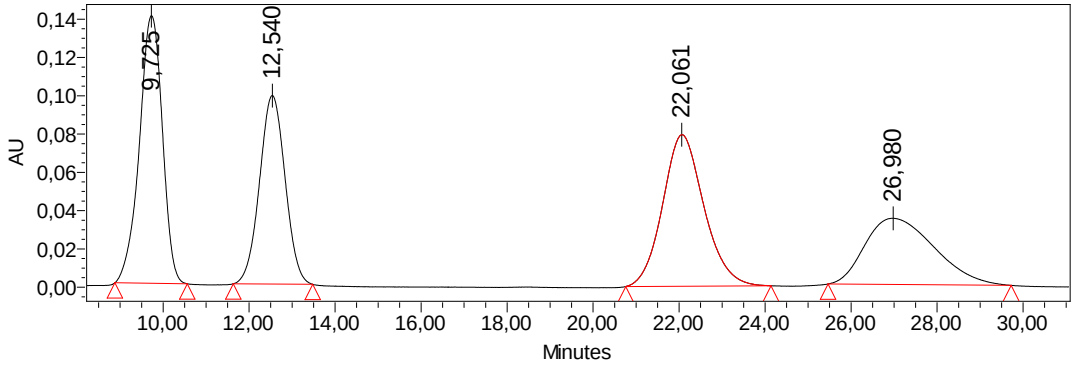


	Retention time	% Area
1	8,833	0,80
2	9,554	90,96
3	10,613	2,99
4	11,333	5,26

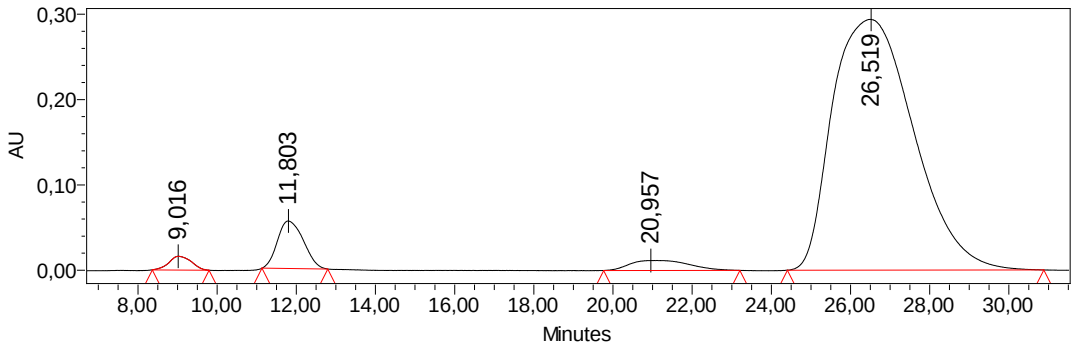
(*S*)-3-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20be)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H), hexane/isopropanol 98/2, flow rate = 1 mL/min, retention times: 9.7 min (anti), 12.5 min (syn, minor.), 22.1 min (anti) and 27.0 min (syn, major.) Processed chanel Descr.: PDA 210.0 nm).

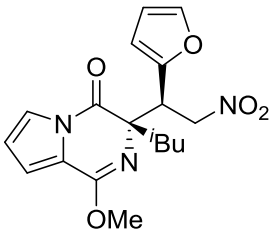


	Retention time	% Area
1	9,725	28,22
2	12,540	22,08
3	22,061	28,66
4	26,980	21,04

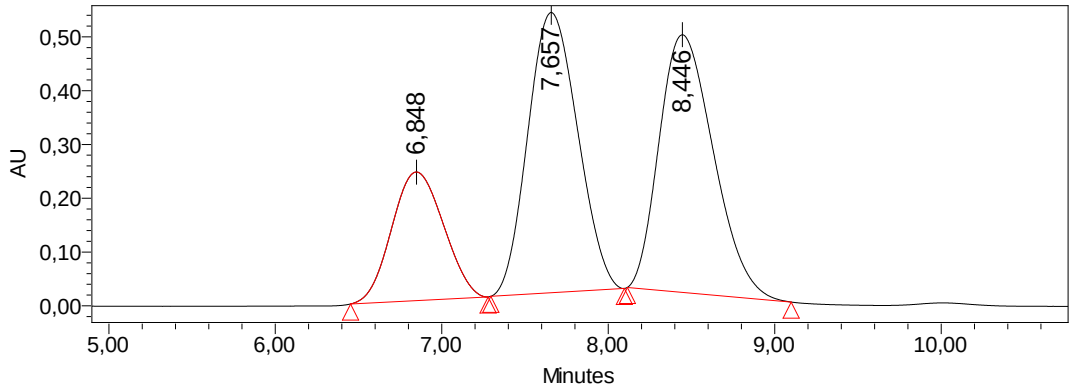


	Retention time	% Area
1	9,016	1,37
2	11,803	5,46
3	20,957	2,63
4	26,519	90,54

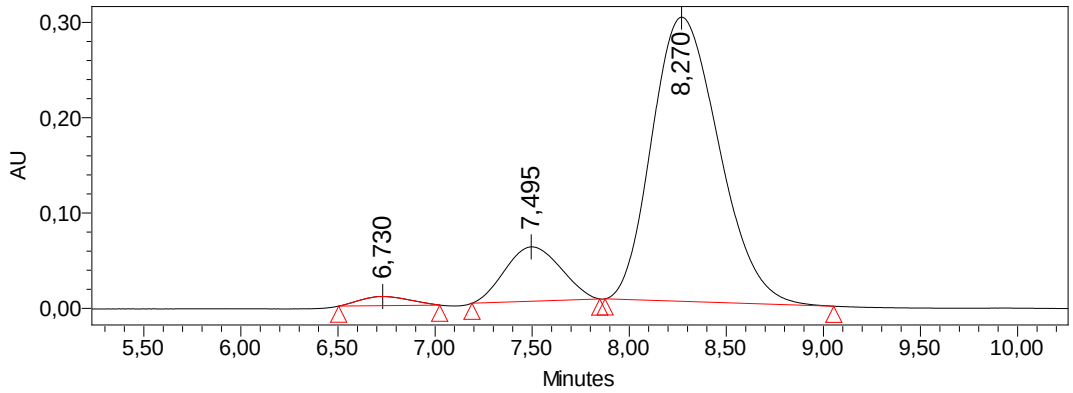
(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-3-isobutyl-1-methoxypyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20bh)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H), hexane/isopropanol 98/2, flow rate = 1 mL/min, retention times: 6.8 min (anti), 7.6 min (syn, minor.), 8.4 min (syn, major.). Processed chanel Descr.: PDA 210.0 nm).

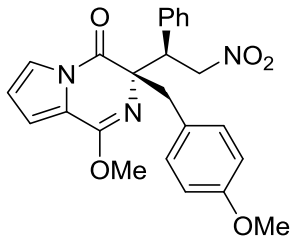


	Retention time	% Area
1	6,848	19,22
2	7,657	40,32
3	8,446	40,46

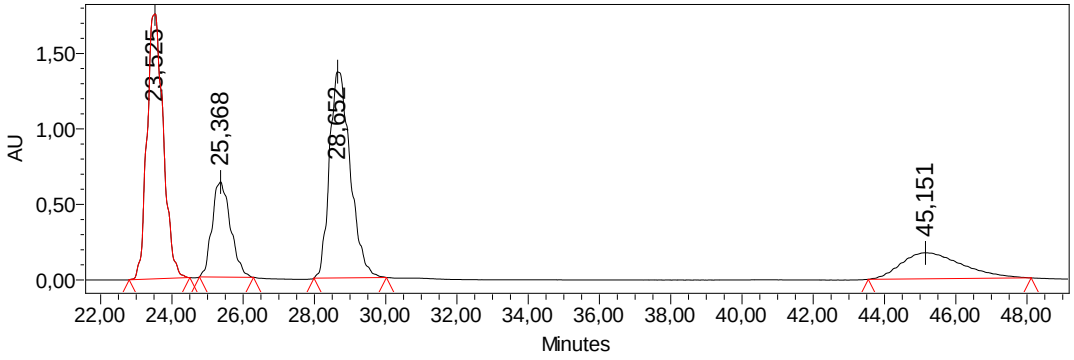


	Retention time	% Area
1	6,730	2,00
2	7,495	13,44
3	8,270	84,56

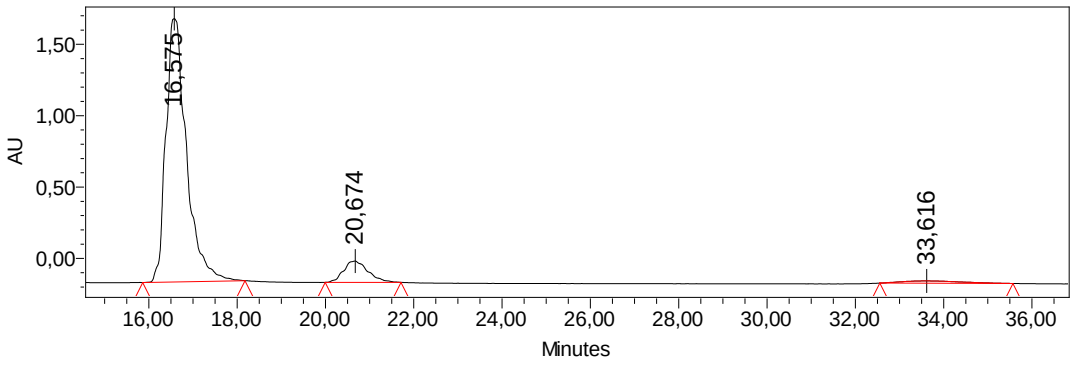
(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 23.5 min (syn, major.), 25.4 min (anti), 28.6 min (syn, minor.) and 45.2 min (anti). Processed chanel Descr.: PDA 210.0 nm).

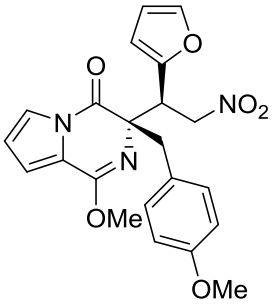


	Retention time	% Area
1	23,525	36,07
2	25,368	14,71
3	28,652	35,89
4	45,151	13,34

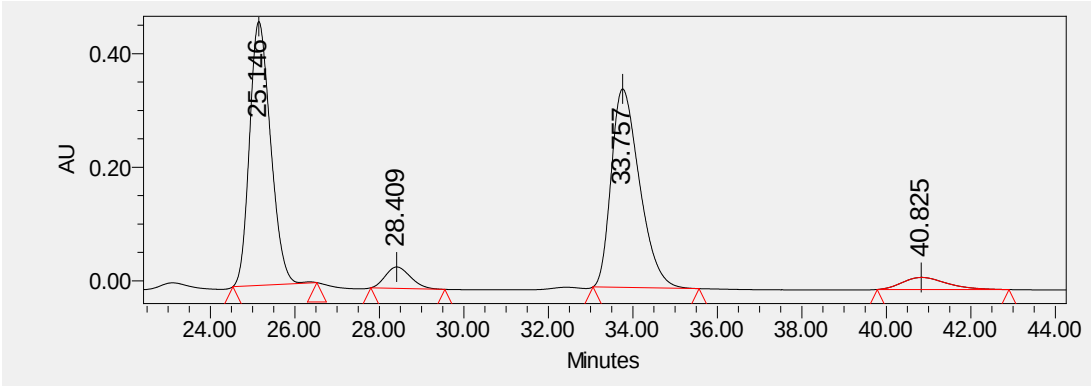


	Retention time	% Area
1	16,575	89,12
2	20,674	8,62
3	33,616	2,26

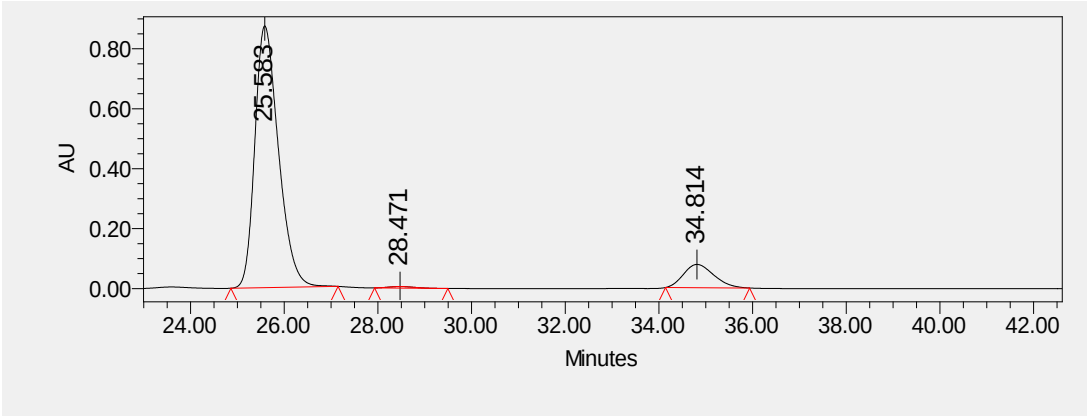
(*S*)-3-((*S*)-1-(Furan-2-yl)-2-nitroethyl)-1-methoxy-3-(4-methoxybenzyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ch)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID), hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 25.1 min (syn, major.), 28.4 min (anti), 33.8 min (syn, minor.) and 40.8 min (anti). Processed chanel Descr.: PDA 210.0 nm).

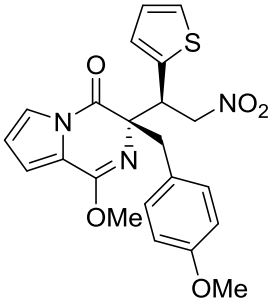


	Retention time	% Area
1	25.146	45.35
2	28.409	4.38
3	33.757	45.87
4	40.825	4.40

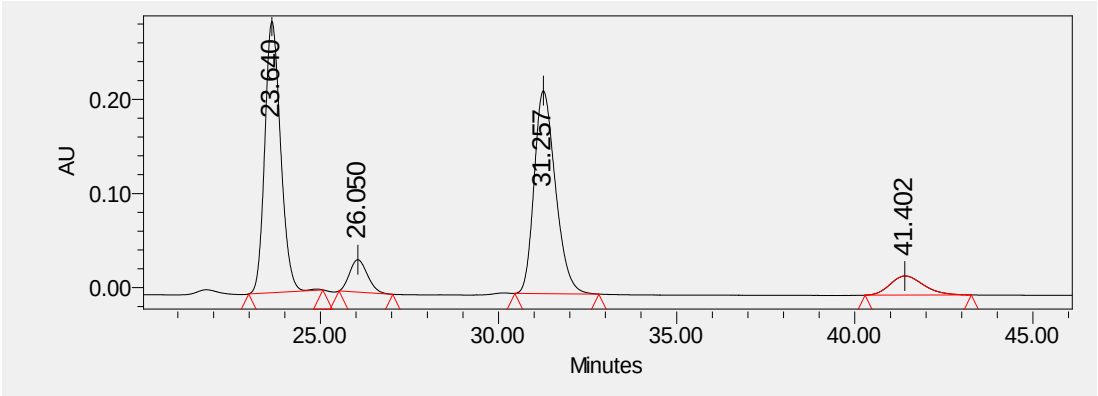


	Retention time	% Area
1	25.583	89.23
2	28.471	0.58
3	34.814	10.20

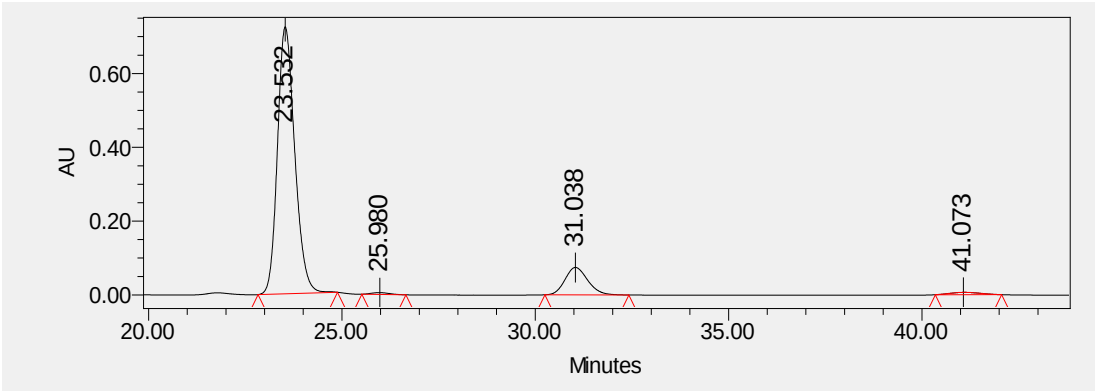
(*S*)-1-Methoxy-3-(4-methoxybenzyl)-3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20cj)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak ID), hexane/isopropanol 90/10, flow rate = 0.5 mL/min, retention times: 23.6 min (syn, major.), 26.0 min (anti), 31.2 min (syn, minor.) and 41.4 min (anti). Processed chanel Descr.: PDA 210.0 nm).

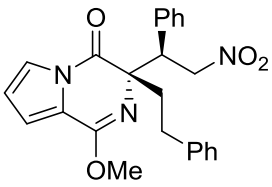


	Retention time	% Area
1	23.640	43.65
2	26.050	5.89
3	31.257	43.96
4	41.402	6.50

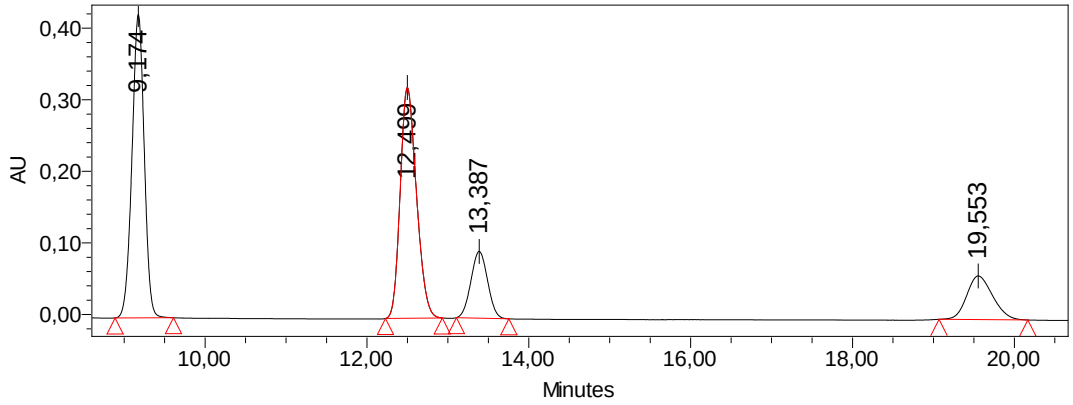


	Retention time	% Area
1	23.532	86.38
2	25.980	0.62
3	31.038	11.67
4	41.073	1.33

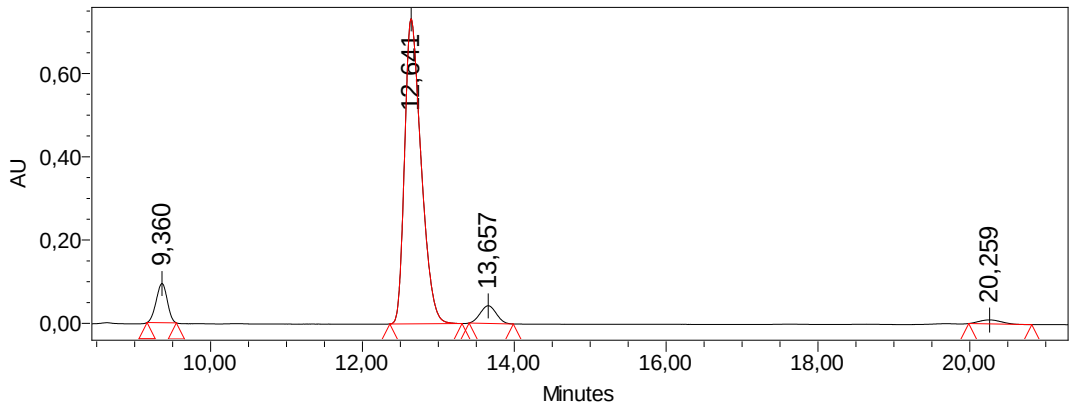
(*S*)-1-Methoxy-3-((*S*)-2-nitro-1-phenylethyl)-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20da)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 9.2 min (syn, minor.), 12.5 min (syn, major.), 13.4 min (anti) and 19.6 min (anti). Processed chanel Descr.: PDA 210.0 nm).

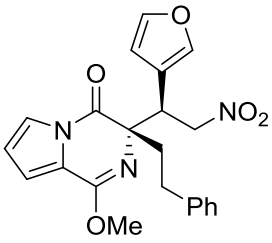


	Retention time	% Area
1	9,174	38,35
2	12,499	38,49
3	13,387	11,50
4	19,553	11,66

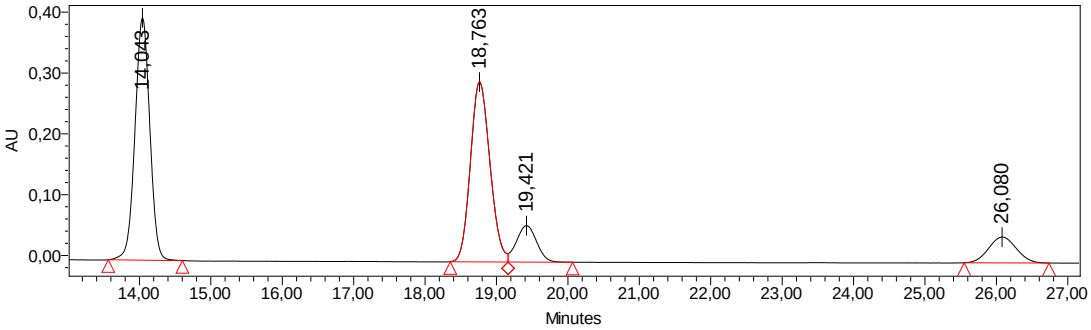


	Retention time	% Area
1	9,360	7,40
2	12,641	86,26
3	13,657	4,84
4	20,259	1,50

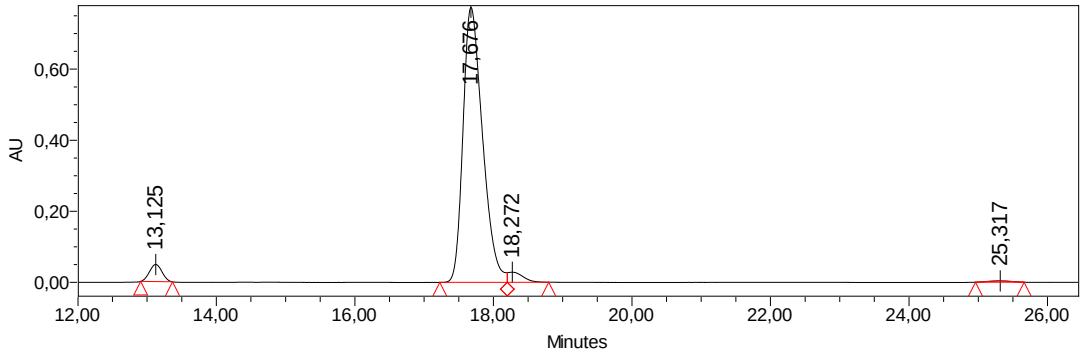
(*S*)-3-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20di)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 14.0 min (syn, minor.), 18.8 min (syn, major.), 19.4 min (anti) and 26.1 min (anti). Processed chanel Descr.: PDA 210.0 nm).

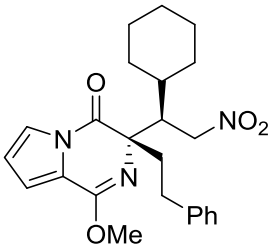


	Retention time	% Area
1	14,043	41,98
2	18,763	41,09
3	19,421	8,57
4	26,080	8,36

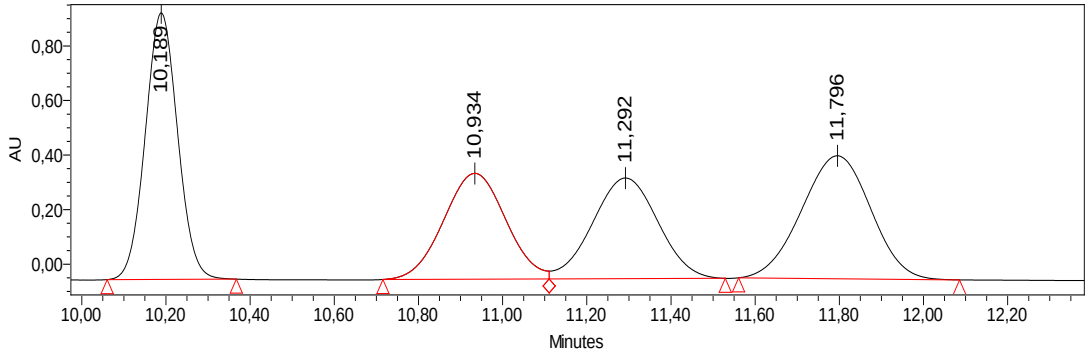


	Retention time	% Area
1	13,125	3,73
2	17,676	93,13
3	18,272	2,62
4	25,317	0,52

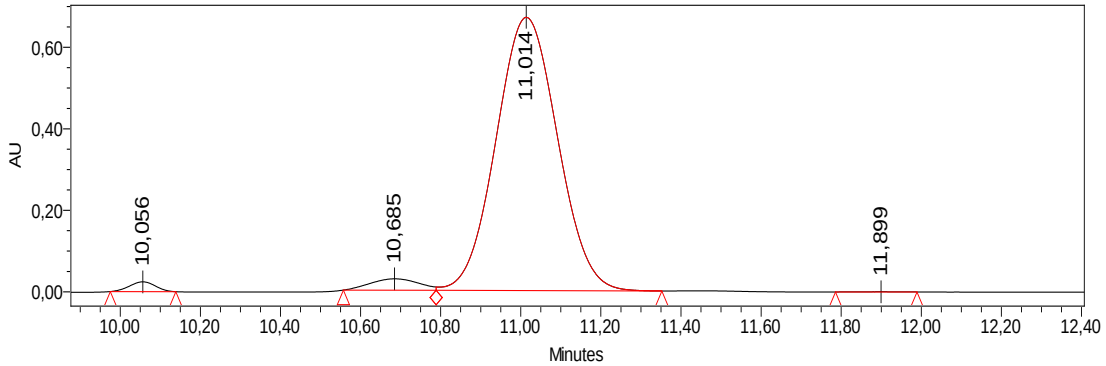
(*S*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenethylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20dl)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 10.2 min (anti), 10.9 min (syn, minor.), 11.3 min (syn, major.) and 11.8 min (anti). Processed chanel Descr.: PDA 210.0 nm).

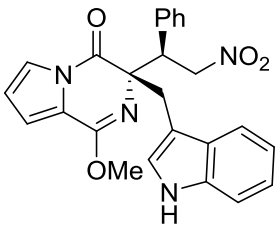


	Retention time	% Area
1	10,189	28,47
2	10,934	21,72
3	11,292	21,71
4	11,796	28,09

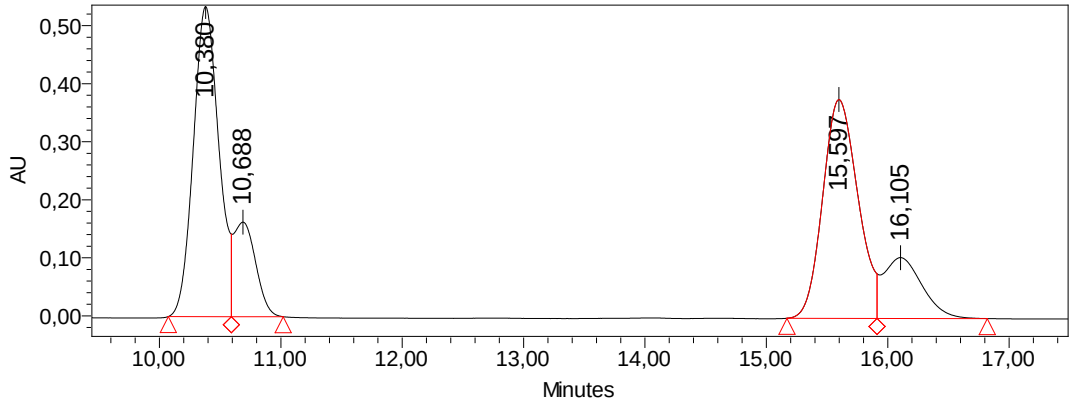


	Retention time	% Area
1	10,056	1,44
2	10,685	3,14
3	11,014	95,38
4	11,899	0,04

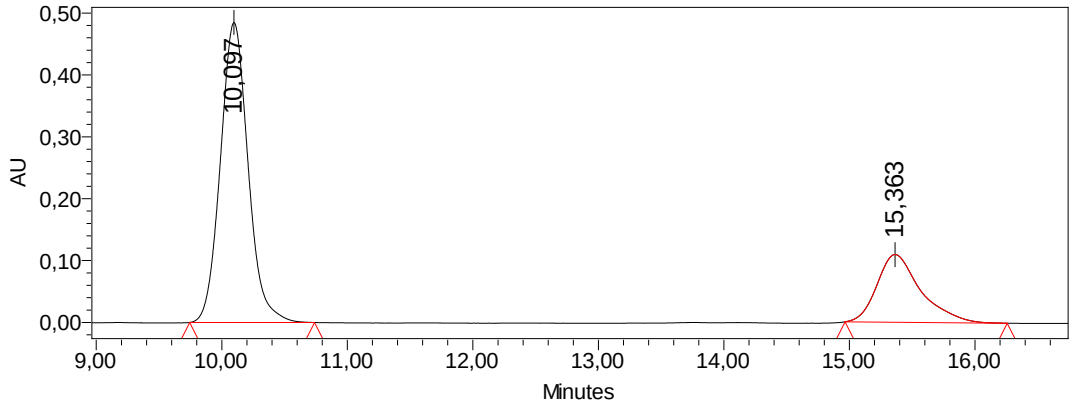
(*S*)-3-((1*H*-Indol-3-yl)methyl)-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20ea)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 80/20, flow rate = 1 mL/min, retention times: 10.4 min (syn, major.), 10.7 min (anti), 15.6 min (syn, minor.) and 16.1 min (anti). Processed chanel Descr.: PDA 210.0 nm).

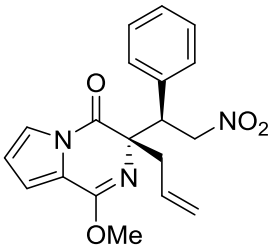


	Retention time	% Area
1	10,380	39,30
2	10,688	10,51
3	15,597	38,33
4	16,105	11,86

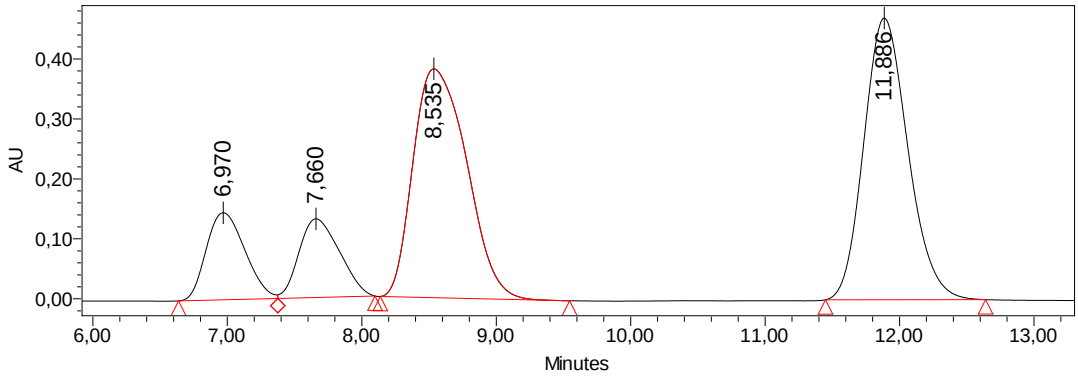


	Retention time	% Area
1	10,097	73,80
2	15,363	26,20

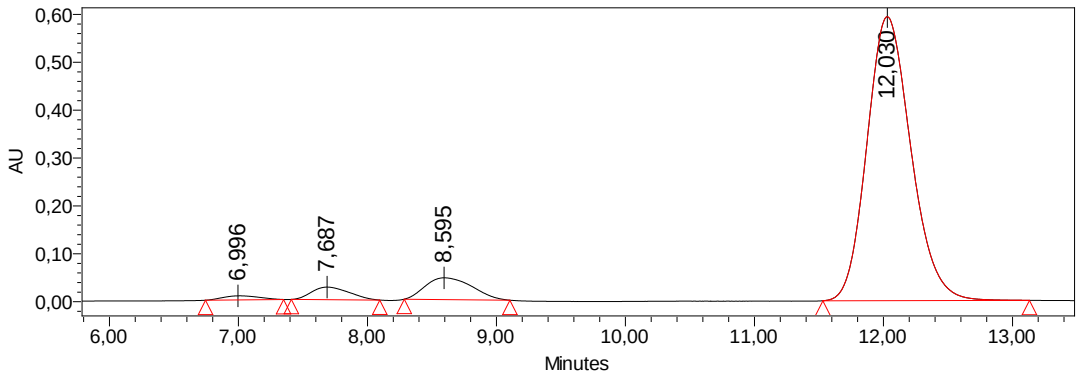
(*S*)-3-Allyl-1-methoxy-3-((*S*)-2-nitro-1-phenylethyl)pyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (3fa)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OD-H), hexane/isopropanol 90/10, flow rate = 1 mL/min, retention times: 7.0 min (anti), 7.7 min (anti), 8.5 min (syn, minor.) and 11.9 min (syn, major.). Processed chanel Descr.: PDA 210.0 nm).

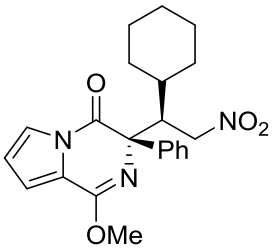


	Retention time	% Area
1	6,970	10,75
2	7,660	10,17
3	8,535	39,28
4	11,886	39,79

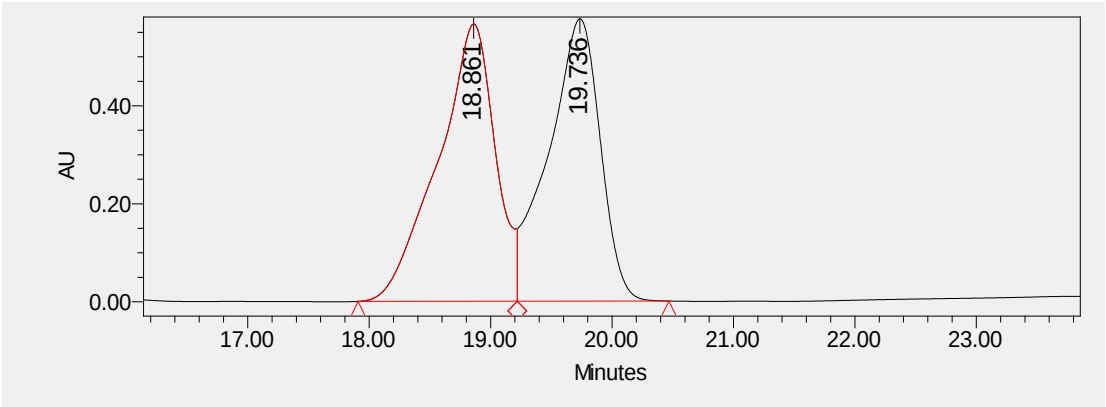


	Retention time	% Area
1	6,996	1,04
2	7,687	3,33
3	8,595	7,22
4	12,030	88,40

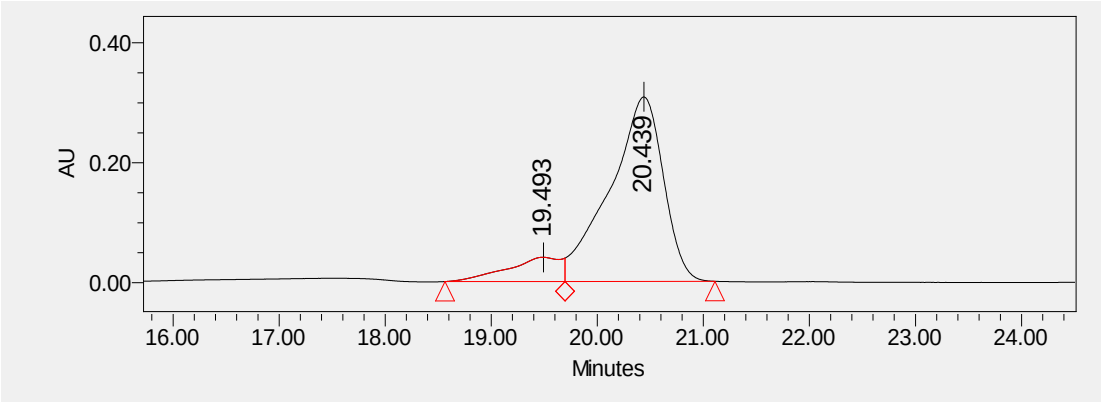
(*R*)-3-((*S*)-1-Cyclohexyl-2-nitroethyl)-1-methoxy-3-phenylpyrrolo[1,2-*a*]pyrazin-4(3*H*)-one (20hl)



The enantiomeric purity was determined by HPLC analysis (Lux amylose-3), hexane/isopropanol 98/2, flow rate = 0.5 mL/min, retention times: 18.9 min (major.) and 19.7 min (minor.). Processed chanel Descr.: PDA 210.0 nm).

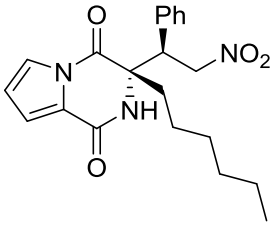


	Retention time	% Area
1	18.861	52.01
2	19.736	47.99

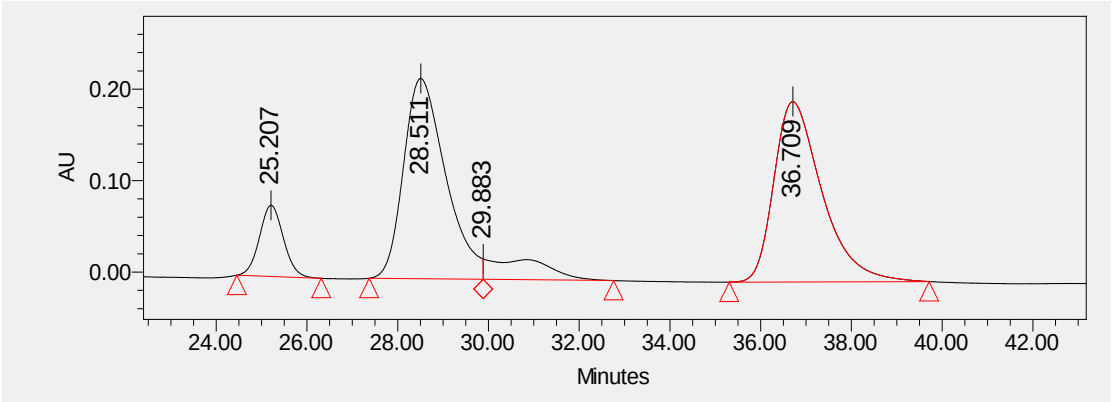


	Retention time	% Area
1	19.493	11.68
2	20.439	88.32

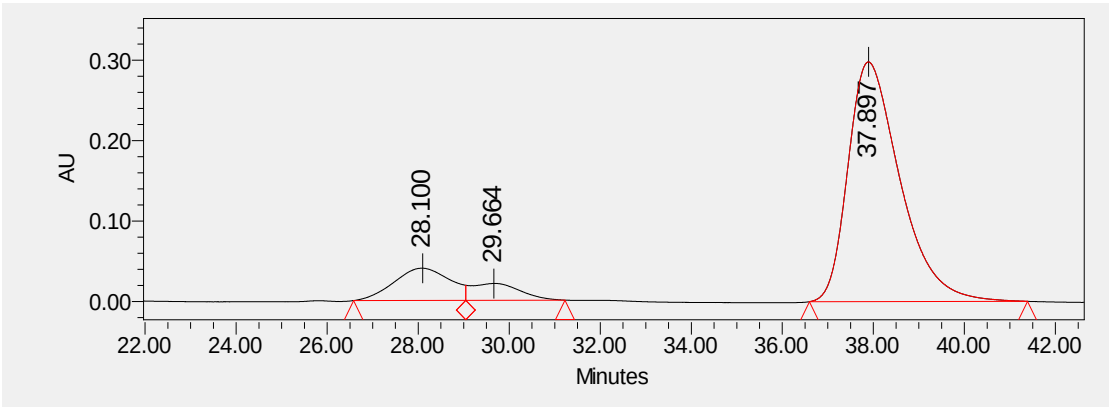
(*S*)-3-Hexyl-3-((*S*)-2-nitro-1-phenylethyl)-2,3-dihydropyrrolo[1,2-*a*]pyrazine-1,4-dione (33d)



The enantiomeric purity was determined by HPLC analysis (Lux cellulose-5), hexane/isopropanol 95/5, flow rate = 0.5 mL/min, retention times: 25.2 min (anti), 28.5 min (syn, minor.), 29.9 min (anti) and 36.7 min (syn, major.). Processed chanel Descr.: PDA 210.0 nm).



	Retention time	% Area
1	25.207	8.53
2	28.511	42.08
3	29.883	6.14
4	36.709	43.25



	Retention time	% Area
1	28.100	11.93
2	29.664	5.44
3	37.897	82.63