Abbreviations and acronyms

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

Me	Methyl (group)
MeIm	1-Methylimidazole
MeOH	Methanol
Mes	Mesityl (2,4,6-Me_3-C_6H_2-)
MOC	Memory of chirality
MOM	Methoxymethyl (CH_3OCH_2-)
MS	Molecular sieves
Ms	Mesyl ($MeSO_2$-)
MTBE	Methyl *tert*-butyl ether
MVK	Methyl vinyl ketone
NFSI	*N*-Fluorobenzenesulfonimide
NR	No reaction
o-	*ortho*-
p-	*para*-
PG	Protecting group
Ph	Phenyl (group)
PMP	*para*-Methoxyphenyl (4-MeO-C_6H_4-)
*n*Pr	*n*-Propyl (group)
*i*Pr	Isopropyl (group)
iPr_2O	Diisopropyl ether
PTC	Phase-transfer catalysis
quant.	Quantitative
ref.	Reference
r.t.	Room temperature
SOMO	Singly occupied molecular orbital
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBS	Tributyl silyl (group)
TFAA	Trifluoroacetic anhydride
TIPS	Triisopropylsilyl (group)
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
TMP	Tetramethylpiperidine
TMS	Trimethyl silyl (group)
TMSCN	Trimethylsilyl cyanide
TMSO	3-(Trimethylsilyl)-2-oxazolidinone
*p*Tol	*para*-Tolyl (4-Me-C_6H_4-)
Ts	Tosyl (4-Me-C_6H_4-SO_2-)
*p*TSA	*para*-Toluenesulfonic acid
*	Chiral

INDEX

Chapter 1

INTRODUCTION

1. INTRODUCTION

1.1. Organocatalysis

1.1.1. General considerations

Organocatalysis is commonly accepted as the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom. This strategy shows several significant advantages over conventional organometallic catalysis. For example, there are usually fewer toxicity issues associated with organocatalysis, although little is known about the toxicity of many organic catalysts.[1] Of particular importance is that most reactions are water and air tolerant, and are often easier to perform than those which require metals. These factors often affect metal catalyzed reactions, and provide a significant advantage in terms of operational simplicity. Moreover, reactions carried out with organic catalysts are often cheaper, as many enantiopure structures can often be derived from nature, which facilitates avoiding the use of expensive metals. By these means, usually both enantiomeric forms of the catalyst are readily available. Several comprehensive reviews and monographs have been published that give a full account of the organocatalysis area.[2]

Although it has not been long since MacMillan coined the term "organocatalysis" at the dawn of the twenty first century,[3] organic molecules have been used as catalysts from the very beginning of synthetic chemistry. The discovery of the first organocatalytic reaction is attributed to Justus von Liebig, who in 1860 accidentally found that the hydrolysis of dicyan to oxamide was accelerated by the presence of an aqueous solution of acetaldehyde (Scheme 1).[4]

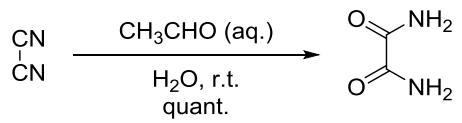
---

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

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

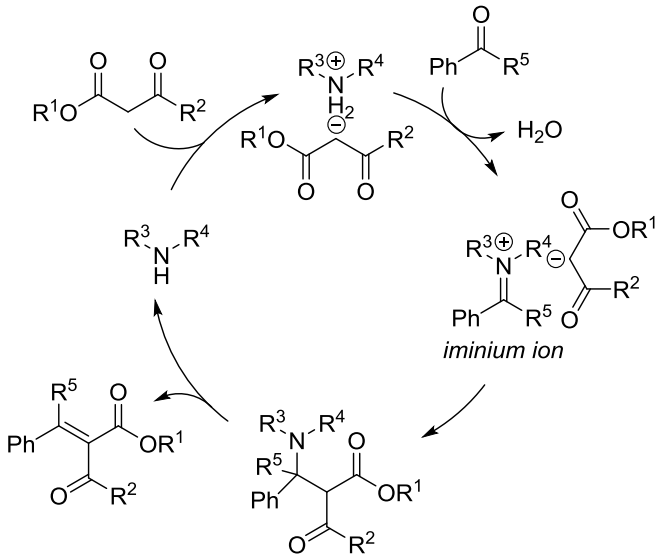
[3] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

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



Scheme 1.

Another milestone for modern organocatalysis can be found in the earliest works of Emil Knoevenagel. During his research, he found that primary and secondary amines, along with their salts, could catalyze the aldol condensation of β-ketoesters or malonates with aldehydes or ketones (Scheme 2).[5] Outstandingly, he also suggested the same intermediates that Weistheimer later proposed in his retro-aldolization studies.[6]



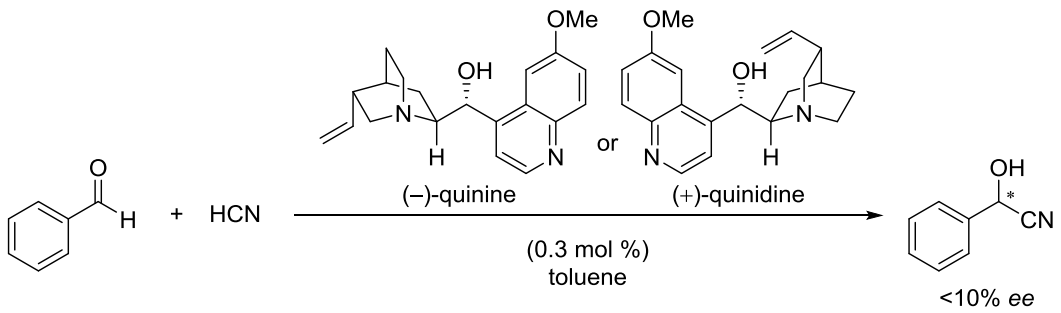
Scheme 2.

Concerning the utilization of organic Brønsted bases (BB) as catalysts, Bredig's work has to be mentioned, who in 1912 reported that the hydrocyanation of benzaldehyde is accelerated by the pseudoenantiomeric *Cinchona* alkaloids, quinine and quinidine, and that the resulting cyanohydrins are optically active and are of opposite configuration (Scheme 3). The enantiomeric excess of the resulting adducts did not surpass 10% *ee*, but the importance of this reaction is conceptually groundbreaking.[7]

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

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

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

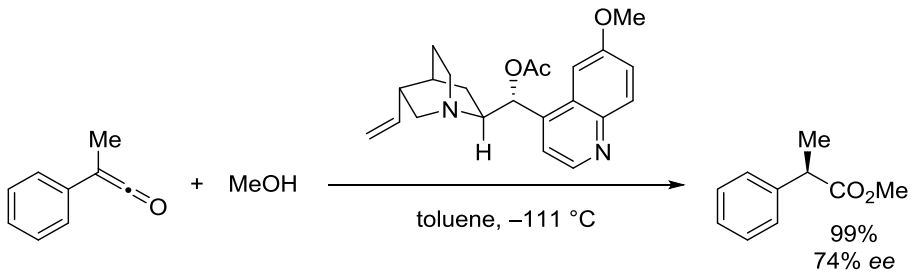


Entry	Cat.*	α (°)[a]
1	(−)-quinine	+0.23
2	(+)-quinidine	− 0.27

[a] Measured in $CHCl_3$.

Scheme 3.

It was not until the late 1950s when Pracejus, following Bredig's work, developed the first reactions with synthetically useful enantioselectivities. He reported the addition of methanol to methyl phenyl ketene to afford (−)-α-phenyl methylpropionate in 74% *ee* by using *O*-acetyl quinine as catalyst (Scheme 4).[8]

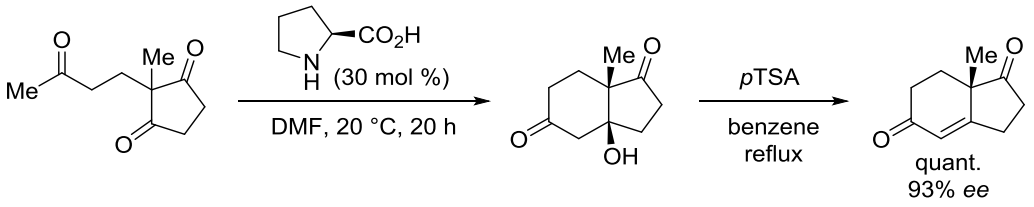


Scheme 4.

Another remarkable event in the history of organocatalysis was the employment of L-proline for the most efficient asymmetric Robinson annulation reported during the early 1970s.[9] The Hajos− Parrish− Eder− Sauer− Wiechert reaction (an intramolecular aldol reaction) allowed access to key intermediates for the synthesis of some natural products (Scheme 5), and offered a practical and enantioselective route to the Wieland− Miescher ketone.[10] It must not be forgotten, that this chemistry is based on the early studies of

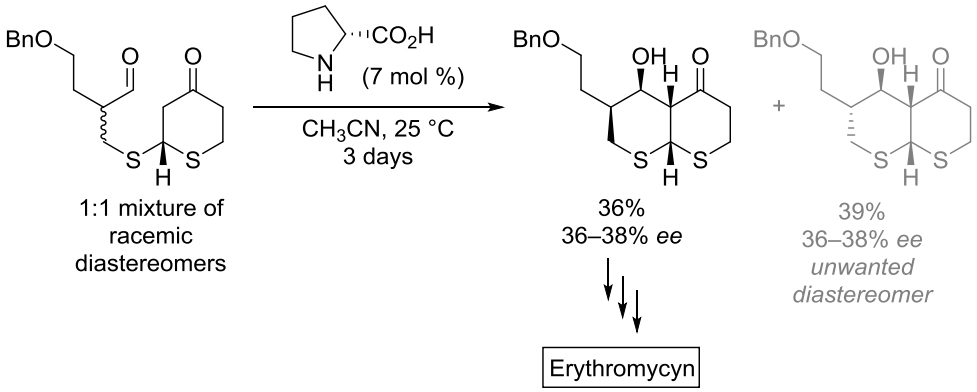
[8] Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22.
[9] a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
[10] a) Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215–2228. For a review concerning the utility of this ketone, see: b) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *23*, 337–356.

Langenbeck[11] and on the extensive research of Stork and co-workers on enamine chemistry.[12]



Scheme 5.

In 1981, Woodward conducted an important example on iminium catalysis, which consisted on a D-proline-catalyzed deracemization of a thianone intermediate followed by an intramolecular aldol reaction (Scheme 6).[13] Although the outcome of this reaction was rather poor (36% *ee*), it led to the synthesis of erythromycin, hence its relevance.



Scheme 6.

The early 1980s meant the development of more general efficient asymmetric organocatalysts. Chiral diketopiperazines were synthesized by Inoue for Brønsted acid (BA)-catalyzed asymmetric hydrocyanation reactions,[14] and were subsequently employed

[11] Langenbeck, W. *Justus Liebig's Ann. der Chemie* **1929**, *469*, 16–25.

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

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

[14] a) Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229–230. b) Asada, S.; Kobayashi, Y.; Inoue, S. *Die Makromol. Chemie* **1985**, *186*, 1755–1762. c) Kobayashi, Y.; Asada, S.; Watanabe, I.; Hayashi, H.;

by Lipton's group to perform an efficient hydrocyanation of aldimines.[15] Efficient phase-transfer reactions (ion-pairing catalysis) were first developed on the mid-1980s, when researchers at Merck reported the alkylation of substituted 2-phenyl-1-indanone systems with excellent enantioselectivity (up to 94% *ee*) in the presence of catalytic amounts of substituted *N*-benzylcinchoninium halides.[16] Mention should be made here of the *Cinchona* alkaloid-catalyzed cycloaddition reactions, described by Kagan,[17] as well as the earliest examples of the epoxidation of chalcones using polyamino acids under triphasic conditions, by Juliá and Colonna.[18] These examples are formally the first use of hydrogen-bonding catalysis in asymmetric synthesis (Figure 1).

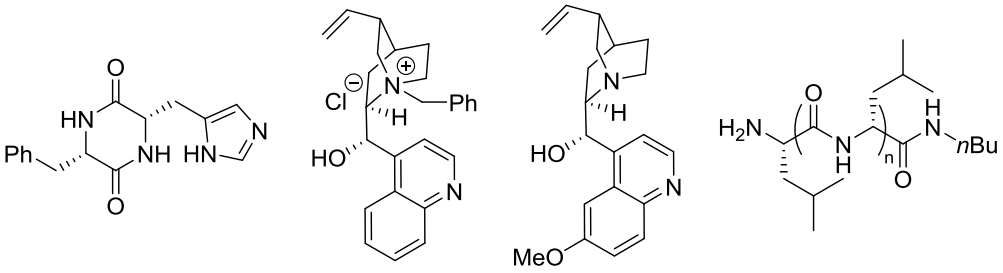


Figure 1.

In the 1990s, metallic salts of proline were employed as catalysts by Yamaguchi and Taguchi, in order to perform enantioselective Michael additions on enals (70– 77% *ee*). Iminium ion activation was suggested in those cases (Scheme 7).[19]

Motoo, Y.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 893–895. d) Matthews, B.; Jackson, W.; Jayatilake, G.; Wilshire, C.; Jacobs, H. *Aust. J. Chem.* **1988**, *41*, 1697–1709.

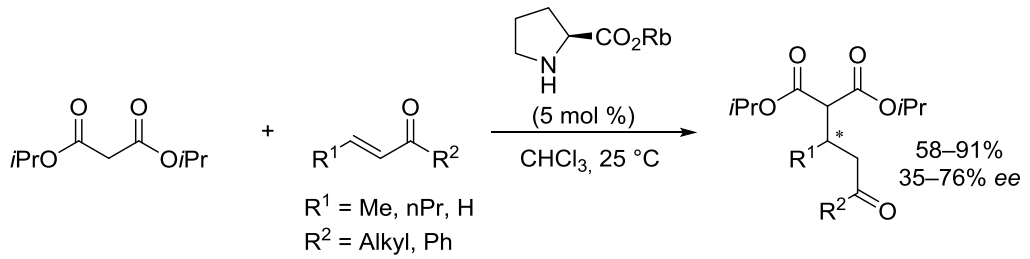
[15] Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.

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

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

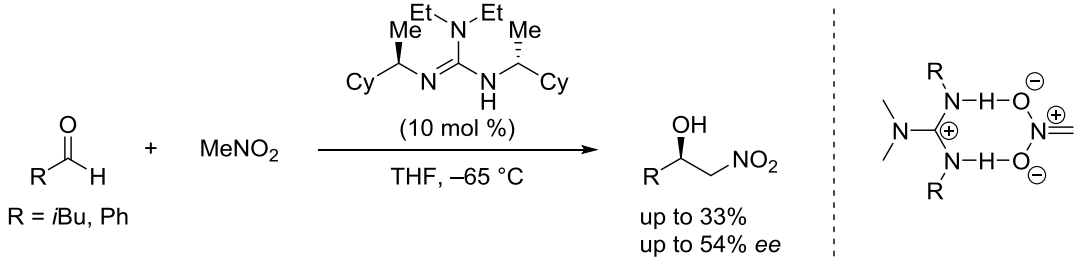
[18] a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929–931. b) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317–1324. For a mechanistic discussion of this reaction, see: c) Berkessel,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

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



Scheme 7.

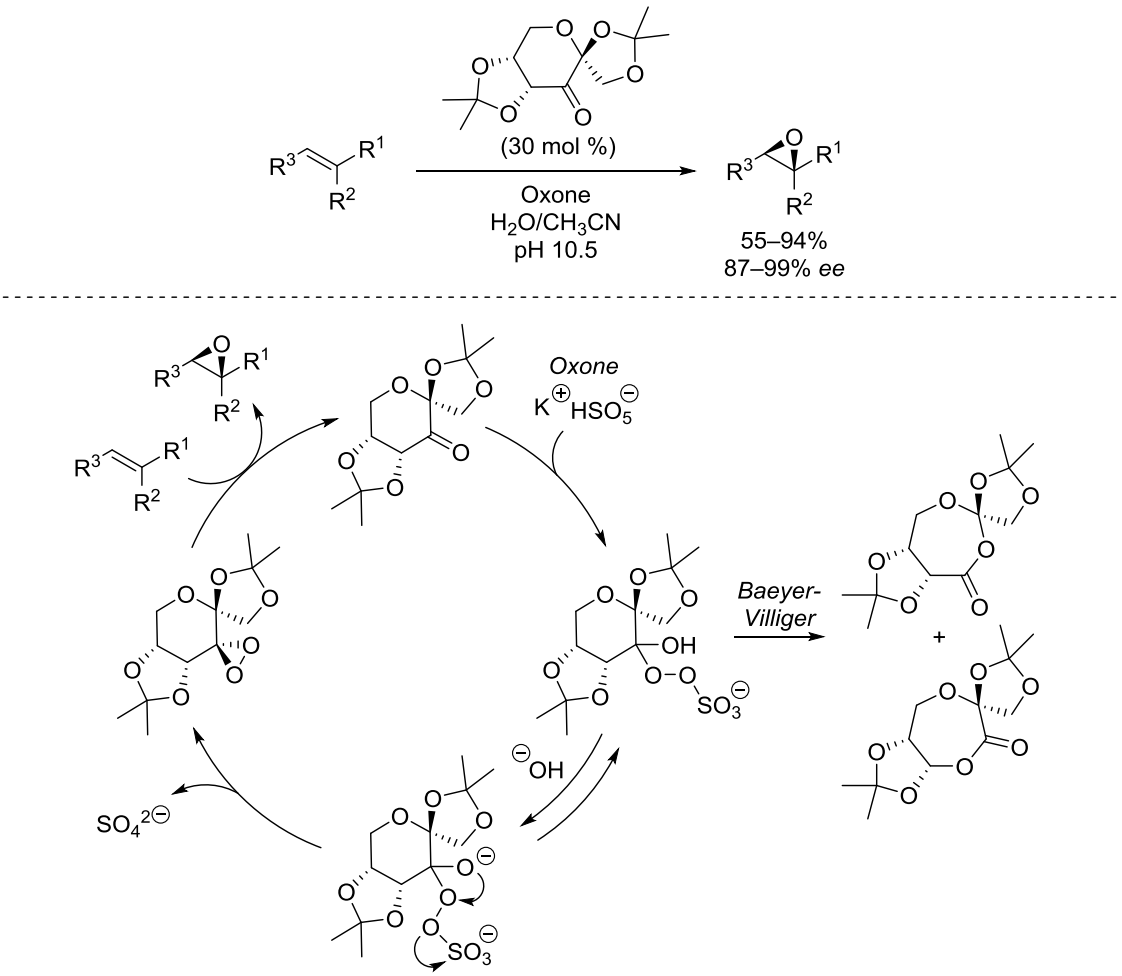
A pioneering report on using chiral guanidines for asymmetric organocatalysis appeared in 1994, when Nájera documented the Henry reaction of isopentenal and benzaldehyde with nitromethane using *C2*-symmetric guanidines as catalysts. The corresponding β-nitroalcohols were obtained with moderate yields and enantioselectivities (Scheme 8).[20]



Scheme 8.

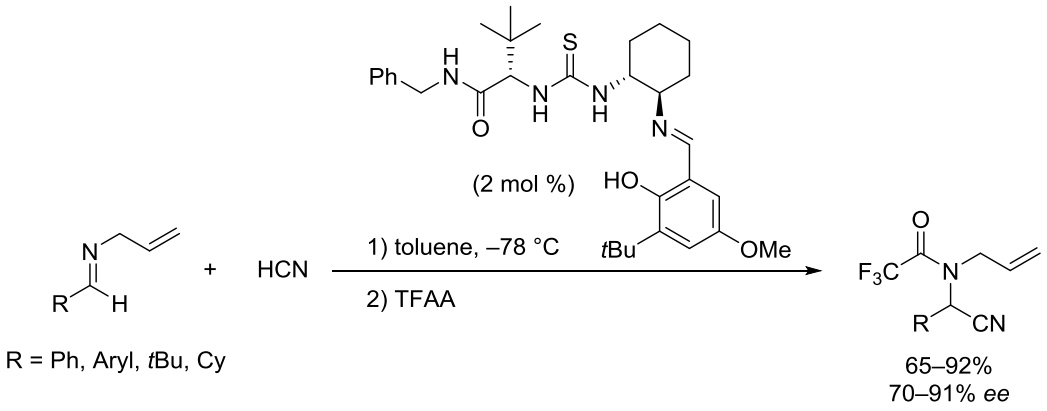
Later, in 1997, Shi made a great contribution to the field, reporting the asymmetric epoxidation of *trans*-olefins and trisubstituted alkenes by using a fructose-derived ketone as a catalyst and oxone as an oxidant. [21] The pH was found to be an important factor for the epoxidation. On one hand, high pH accelerates autodecomposition of Oxone, so reactions with this reagent are usually carried out at pH 7– 8. On the other hand, when this pH values were employed the catalyst decomposed rapidly, which made the authors think that a Baeyer-Villiger reaction could be the cause, as depicted in Scheme 9. Higher pH seemed to avoid this background reaction, so after optimization, pH 10.5 was chosen to be the most appropriate to perform the reaction. Actually, excellent enantioselectivities were achieved following this method (Scheme 9).

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



Scheme 9.

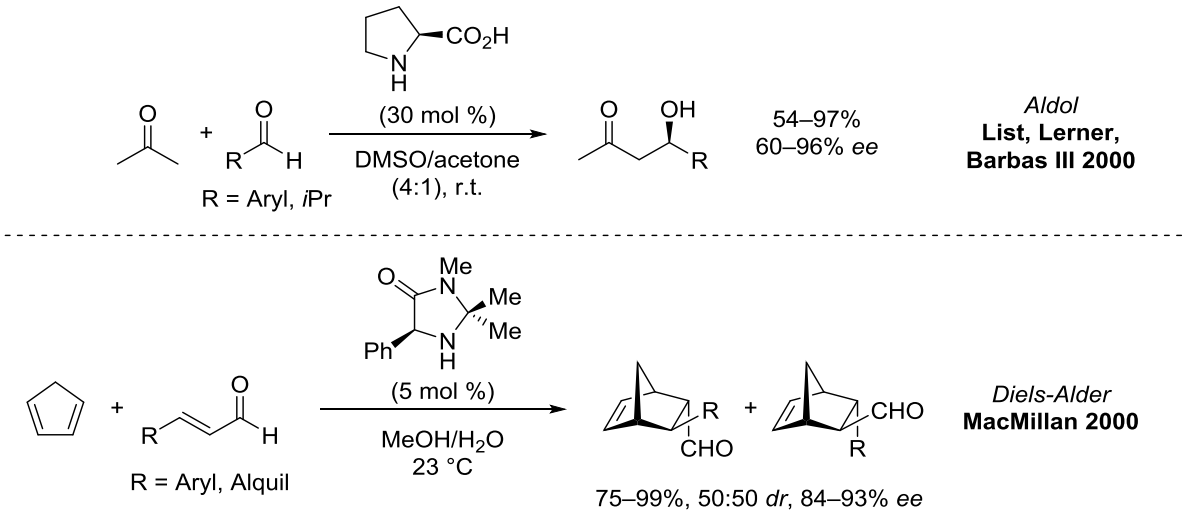
Also in this decade, mention should be made to the utilization of chiral thioureas as organocatalysts for the first time. In 1998, Jacobsen presented the chiral Brønsted acid-catalyzed hidrocyanation of aldimines. The Strecker reaction was carried out with peptide based thiourea derivatives (Scheme 10).[22]



Scheme 10.

[22] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

Unfortunately, the effect of these outstanding contributions was limited in the field of organic chemistry. The transition to the twenty first century breathed new life into this area, with the works of List, Lerner and Barbas III[23] in enamine chemistry and the works of MacMillan[3] in iminium chemistry paving the way (Scheme 11). Since 2000, the chemical community has reinforced its aim to develop new catalysts and methodologies that do not require the use of metals.[24]



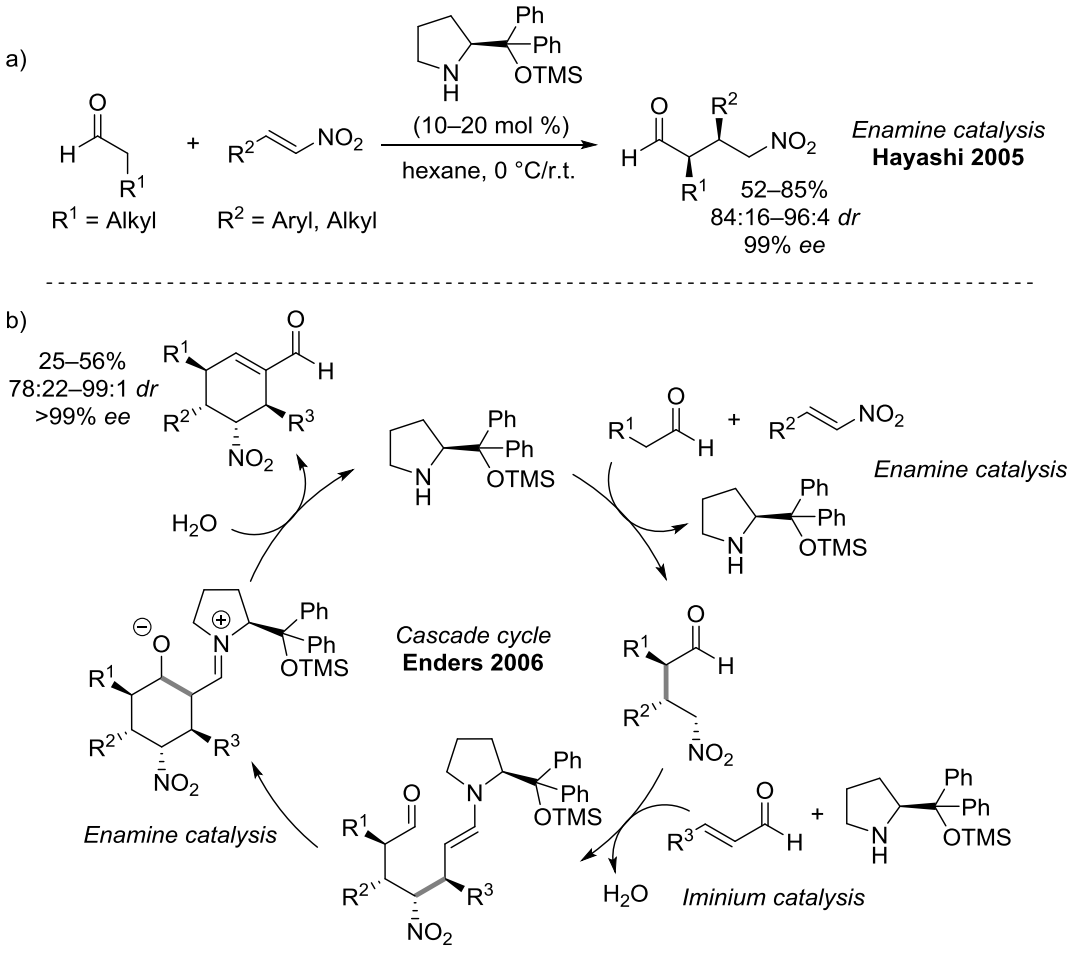
Scheme 11.

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

The field of aminocatalysis has been particularly prolific.[12] Apart from the pioneering results depicted above, noteworthy examples via iminium ion activation include: the Friedel-Krafts reaction to enals by MacMillan in 2001,[25] the reduction of enals by List[26] and MacMillan[27] in 2005, and the conjugated amination of enals by MacMillan in 2006.[28] Enamine activation also rendered groundbreaking examples, such as the α-oxidation of enolizable aldehydes using oxygen singlet by Córdova in 2004,[29] and the first Michael addition of aldehydes to nitroolefins by Hayashi in 2005 (Scheme

[23] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
[24] For a review on the rise of organocatalysis, see: a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308. For an explanation of why the Hajos– Parrish– Eder– Sauer– Wiechert reaction remained an enigma until the 2000s, see: b) Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47.
[25] Paras, N. a; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
[26] Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110.
[27] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.
[28] Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–9329.
[29] Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915.

12a).[30] Additionally, both activation modes have also been combined for the consecutive formation of multiple stereocentres, as in the case of the first iminium ion/enamine tandem reactions by List,[31] MacMillan[32] and Jørgensen[33] in 2005; and the multicomponent organocatalyzed Michael/Michael/aldol condensation by Enders in 2006 (Scheme 12b).[34]



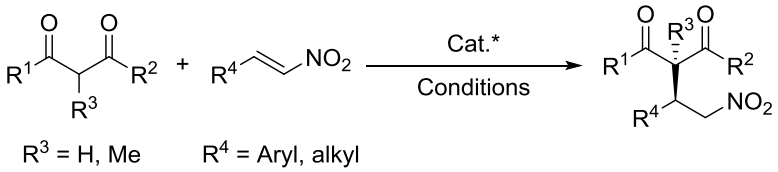
Scheme 12. Representative examples of enamine/iminium catalysis in the 2000's.

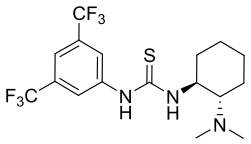
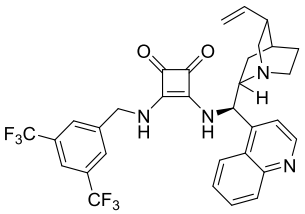
Non covalent activation modes have undergone a great growth during the last two decades.[35] Since the development of thiourea-Brønsted base bifunctional catalysts by

[30] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215.
[31] Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.
[32] Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.
[33] Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.
[34] a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863. For a review concerning multicomponent and sequential organocatalytic reactions, see: b) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712–7722. For a review on enantioselective organocatalyzed domino synthesis of six-membered carbocycles, see: c) Goudedranche, S.; Raimondi, W.; Bugaut, X.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Synthesis* **2013**, *45*, 1909–1930.
[35] For leading reviews, see: a) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516–532. b) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, *2011*, 2209–2222.

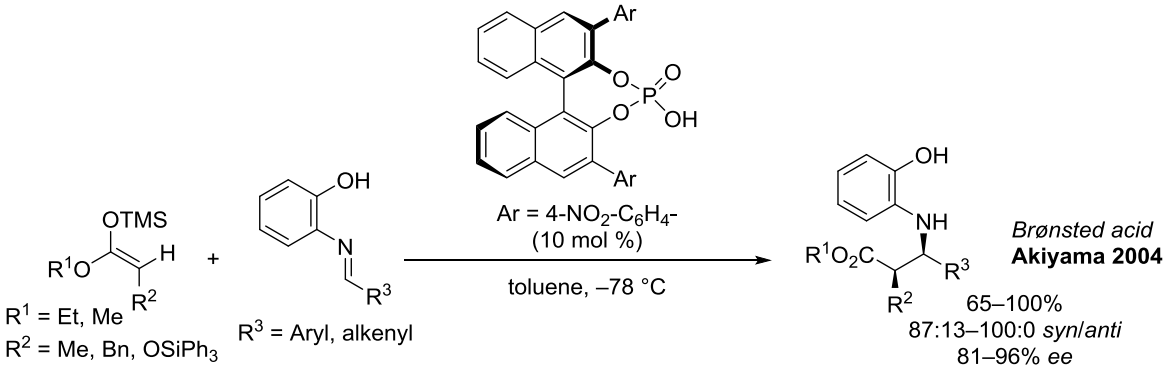
Takemoto in 2003 (Table 1, entry 1),[36] and the Diels-Alder reaction catalyzed by TADDOL reported by Rawal in 2003;[37] new *H*-bond donor moieties have appeared, as the squaramides by Rawal in 2008 (Table 1, entry 2).[38]

Table 1. First thiourea- and squaramide-based bifunctional Brønsted base catalysts.



	R^1	R^2	Catal.*	Conditions	Results	Ref.
1	$R^1 = R^2$ = OEt, OMe			(10 mol %) toluene, r.t.	74– 95% 81– 93% *ee*	36
2	$R^1 \neq R^2$ = Aryl, OAlkyl, Alkyl			(0.5 mol %) CH_2Cl_2, r.t.	65– 97% 50:50– 98:2 *dr* 88– 97% *ee*	38

Brønsted acids in general, and chiral phosphoric acids in particular, have been widely employed since they discovery by Akiyama (Scheme 13) and Terada in 2004. [39]

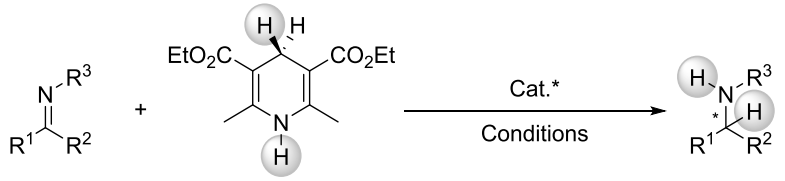


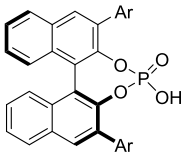
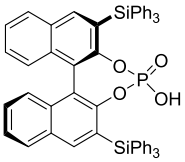
Scheme 13.

[36] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
[37] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146–146.
[38] a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417. For a leading review on squaramides, see: b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890–6899.
[39] a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568. b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. For a leading phosphoric acids review, see: c) Terada, M. *Synthesis* **2010**, 1929–1982.

As a case in point, the enantioselective hydrogenation of double bonds reported by List and MacMillan in 2005 (Table 2).[40]

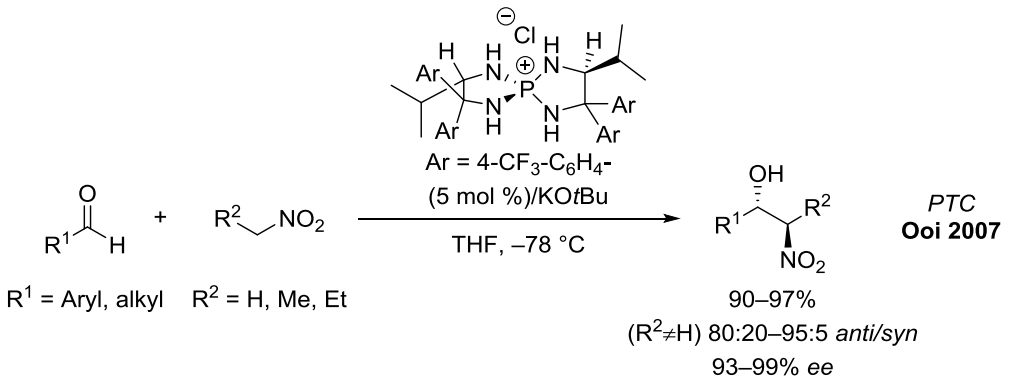
Table 2. Chiral phosphoric acid catalyzed enantioselective hydrogenation of imines.



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

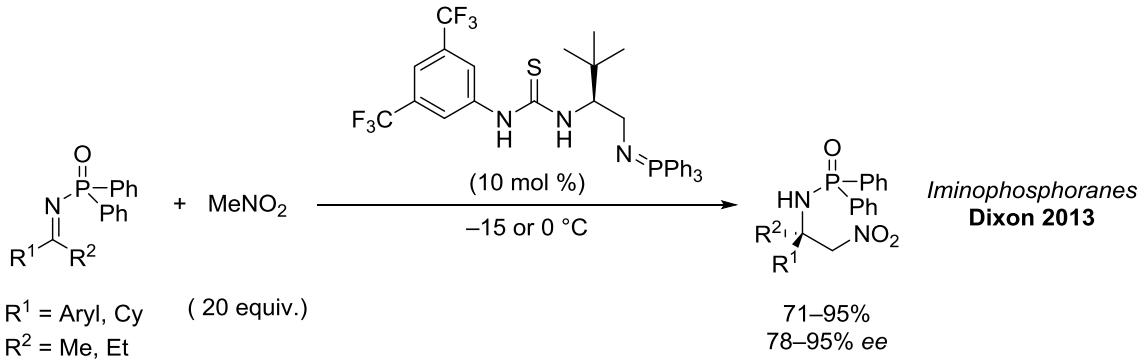
Other activation modes have been developed and explored with success during these years, including: the asymmetric counteranion-directed catalysis (ACDC) by List in 2006,[41] the phase-transfer catalysis employing chiral tetraaminophosphonium salts by Ooi in 2007 (Scheme 14),[42] and SOMO[43] and photoredox[44] catalysis developed by MacMillan in 2007 and 2008.

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



Scheme 14.

Finally, new Brønsted superbases have been explored, as the bifunctional iminophosphoranes by Dixon in 2013 (Scheme 15).[45]



Scheme 15.

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

1.1.2. **Formation of quaternary stereocentres**

The properties of organic molecules are closely linked to their form. The shape of most of structurally complex molecules is directed by the three-dimensional orientation of the substituents of their stereogenic carbons. The chirality of biological macromolecules makes one enantiomer of a small molecule fit better than the other in its corresponding active binding site. In the last years, this task has become more and more important since the optical purity is now a strict requirement for the commercialization of new drugs and pharmaceutical products.[46] Therefore, the more stereoselective methodologies are available, the more efficiency could be achieved in the synthesis of such compounds.

The construction of quaternary stereocenters in complex molecules is one of the most challenging obstacles in asymmetric synthesis (Figure 2).[47]

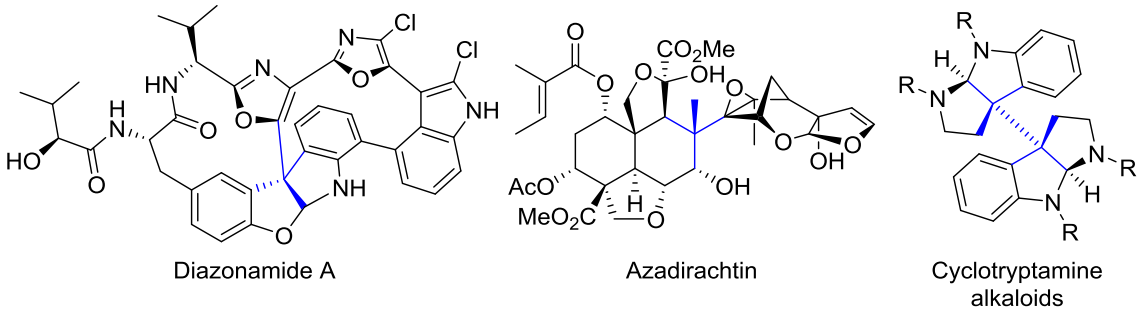


Figure 2. Selected examples where the construction of quaternary stereocenters was employed in the total synthesis of a natural product.[48]

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

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

the pre-existing appendages of the substrate. For these reasons, the asymmetric formation of quaternary stereocentres has been subject of intense scientific studies (Figure 3).[49]

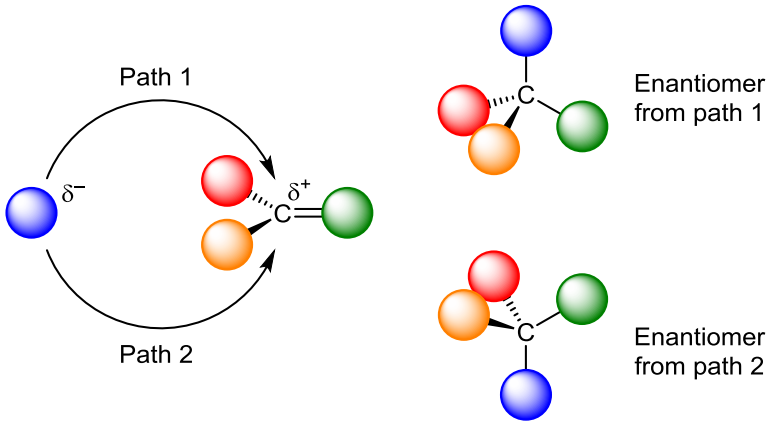
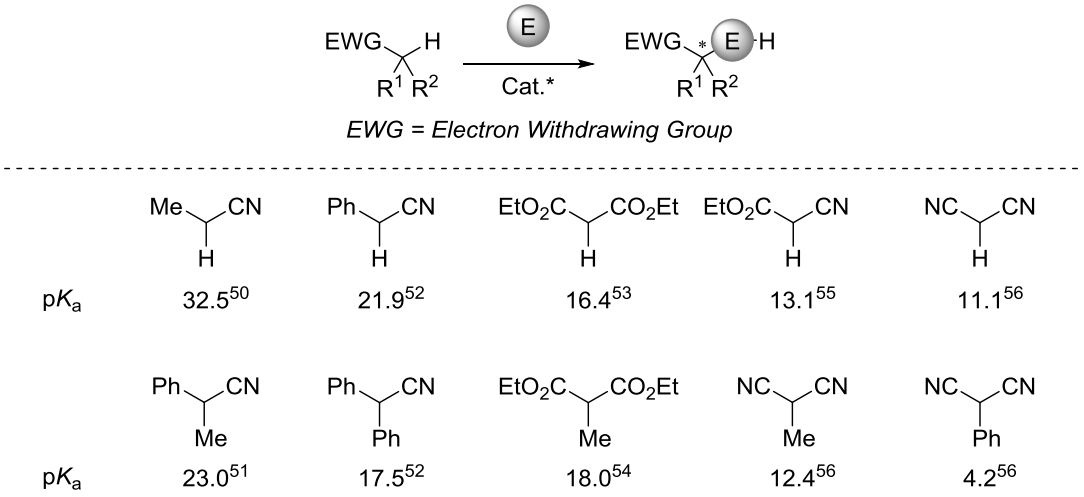


Figure 3.

1.1.3. **Importance of nucleophile design**

A common strategy for the formation of asymmetric *C–C* bonds involves the nucleophillic addition of carbanions to an electron deficient carbon system, using a catalyst to promote not only bond formation but also stereocontrol (Scheme 16). To increase the reactivity of these substrates, the pronucleophillic α *C*(sp^3)-*H* functionality is often attached to electron withdrawing functional groups (EWG) that provide large reductions in pK_a at the desired deprotonation site (Scheme 16).[49n] This manoeuvre can also help the catalyst to distinguish between the two planar faces of both the nucleophile, when it is an enolate or similar, and the electrophile, rendering more enantioselectivity to the reaction.

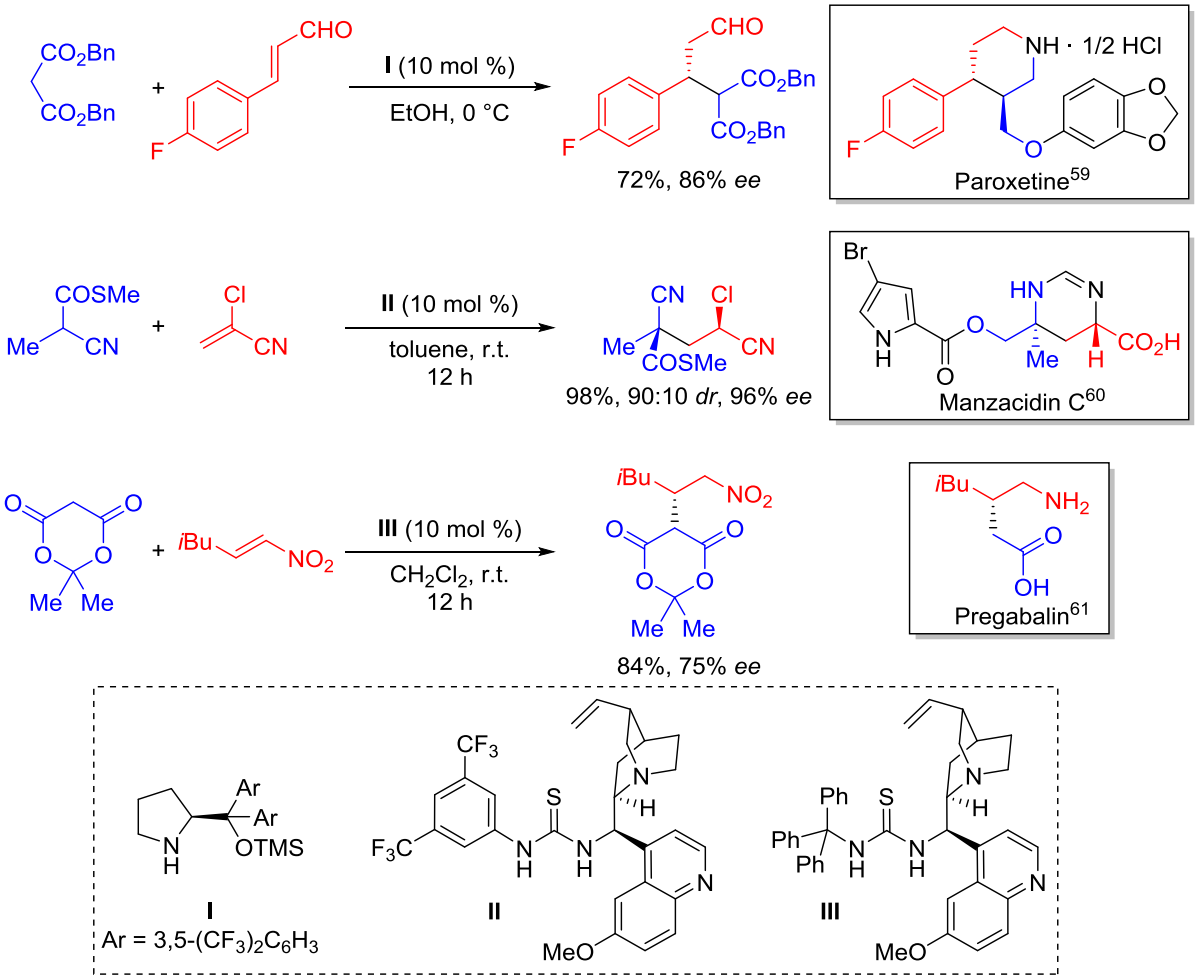
[49] For some selected reviews on the asymmetric formation of quaternary stereocentres, see: a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460. b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066. c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401. d) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597. e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. f) Ramon, D.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. g) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5363–5367. h) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 11943–11948. i) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (J. Christoffers & A. Baro ed., WILEY-VCH) 2005. j) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. k) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. l) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969–5994. m) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–388. n) Bella, M.; Gasperi, T. *Synthesis* **2009**, *2009*, 1583–1614. o) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4597. p) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745–2759. q) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–191.



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

This strategy has shown plenty of notable examples in organocatalysis,[57] where the enantioselective transformation is accompanied by a thoughtful design of the nucleophile. This fact can help the chemist to elaborate the new adduct into desirable scaffolds, such as natural products or synthetically interesting structures (Scheme 17).[58]

[50] Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885–1886.
[51] Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209–223.
[52] Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325.
[53] Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299–3305.
[54] Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.
[55] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331.
[56] Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
[57] Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, P. *Adv. Synth. Catal.* **2014**, *356*, 3261–3288.
[58] For examples of organocatalytic synthesis of natural compounds, see: a) Marcia de Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575–2600. b) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138–1167. c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. For multiple examples of activated carbonyl compounds as nucleophiles in organocatalysis, see: ref. 49, page 16 and references herein.



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

1.2. **Heterocyclic pronucleophiles**

1.2.1. **General considerations**

In literature, we can find a large number of examples of chiral natural products or bioactive substances with a heterocyclic core, where the heteroatom is attached to an α *C*(sp^3) position of a carbonyl moiety, as in a lactam or lactone. The complexity of their synthesis is not to be underestimated, especially when the carbon in α position to the carbonyl group is tetrasubstituted.[58a-c] Below these lines are depicted few examples of

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

these biologically interesting compounds, whose total syntheses have been eventually reported.

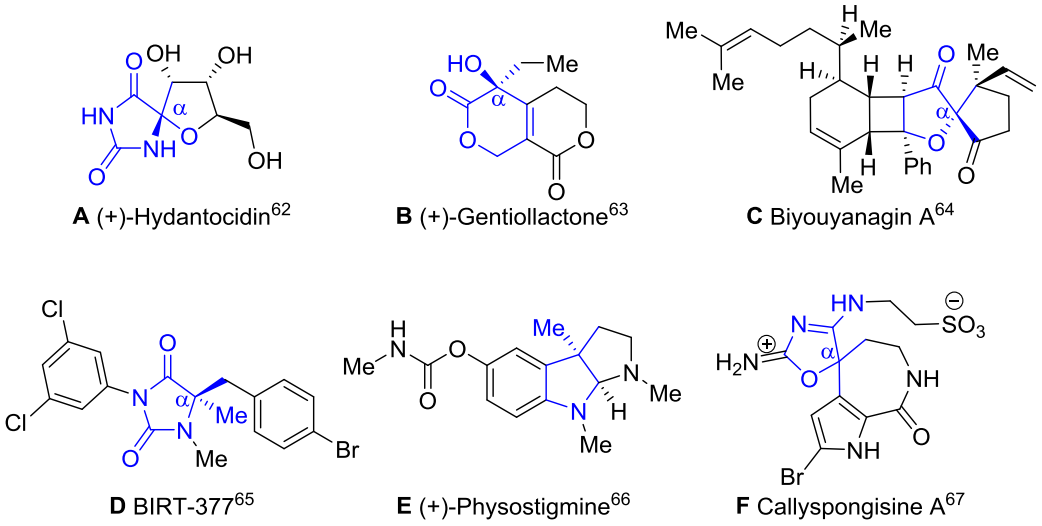


Figure 4. Biologically active compounds bearing a heterocyclic core.

A strategy for the generation of tetrasubstituted carbon stereocentres involves the use of heterocycles as pronucleophiles in reactions under proton transfer conditions (Scheme 18). Through the last decades, this task has been focusing the attention of several research groups and reviewed separately for each heterocycle, but, to the best of our knowledge, all this information has not been gathered.

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

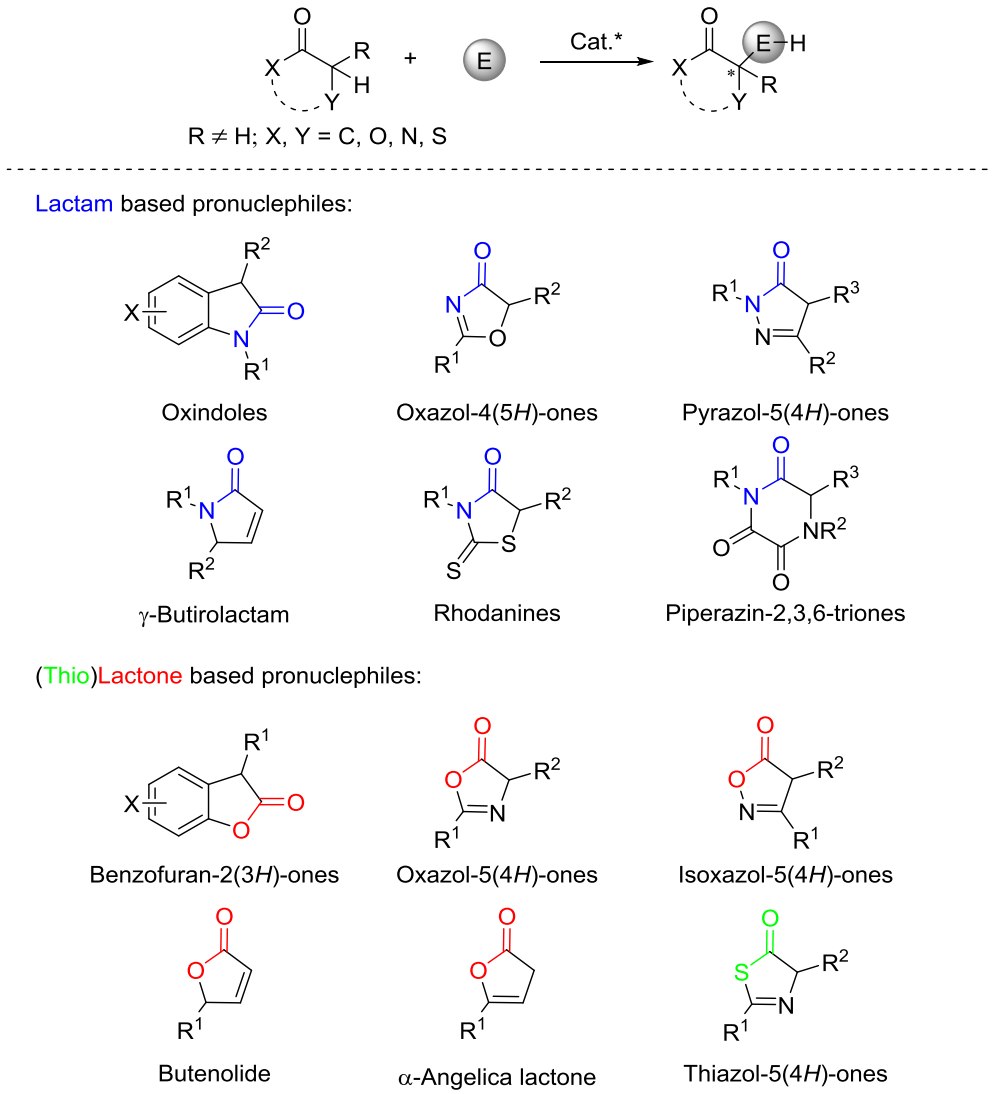
[63] For the total synthesis of (+)-gentiollactone, see: Kakuda, R.; Machida, K.; Yaoita, Y.; Kikuchi, M.; Kikuchi, M. *Chem. Pharm. Bull. (Tokyo).* **2003**, *51*, 885–887.

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

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

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

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



Scheme 18. Selection of heterocyclic pronucleophiles employed in organocatalysis.

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

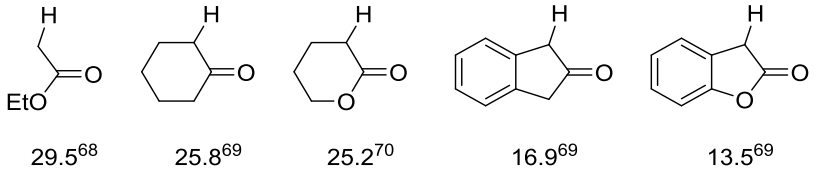
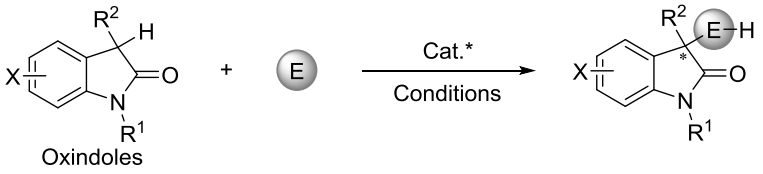


Figure 5. pK_a of carbonylic compounds measured in DMSO.

1.2.2. **Lactam based pronucleophiles**

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

As previously has been said, C-3 disubstituted oxindoles are important frameworks that appear in plenty of biologically interesting compounds (Figure 4E).[71] Thus, the reactivity of oxindoles has been widely studied, including their role as pronucleophiles (Scheme 19).



Scheme 19.

Since the pK_a value of oxindole **A** is 18.2 (Figure 6), the values for 3-alkyl-substituted oxindoles may be expected to be higher, so they require a strong base for deprotonation. The identical pK_a values of *N*-Me oxindole **B** and *N*-H 3,3-dimethyl oxindole **C** indicate that the ionization of oxindoles in organic solvents may occur readily at both nitrogen and carbon, suggesting potentially similar reactivity of nitrogen, oxygen and carbon in unsubstituted oxindoles.[72] Additionally, introducing an electron withdrawing group at C-3 or at N-1 positions could make the substrates more prone towards deprotonation, as can be seen in Figure 6D.

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

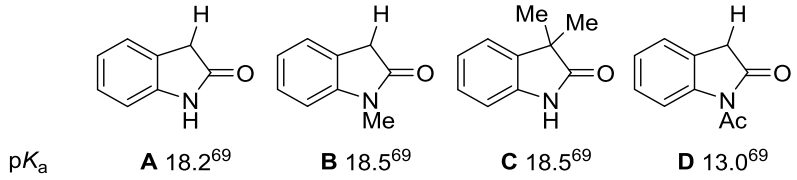
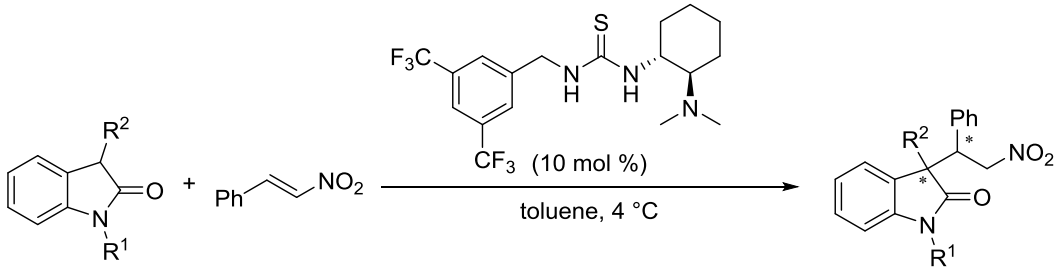


Figure 6. pK_a of oxindoles measured in DMSO.

Substitution of the *N* moiety with protecting groups, e.g. Boc, also avoids the nucleophilic attack from it, while the bulky shielding that this group provides is found to be essential for the enantiofacial control in many cases (Table 3, entry 1 vs. 2). As a result, *N*-Boc protected 3-prochiral oxindoles have been much frequently used than unprotected ones for the asymmetric synthesis of 3,3-disubstituted oxindoles. In terms of reactivity, an electron withdrawing R^2 group, such as a phenyl moiety, is more effective, albeit in this instance no stereocontrol is produced, as should be noticed in Table 3 (entry 2 vs. 3).[73]

Table 3. Examples for the reactivity difference of oxindoles regarding C-1/C-3 substitution.



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

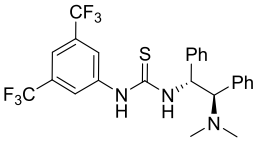
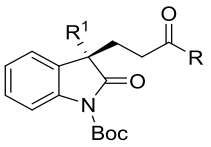
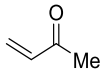
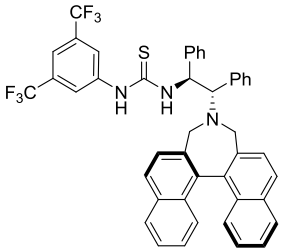
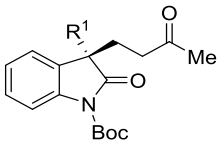
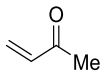
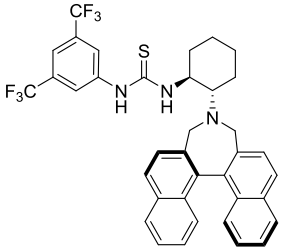
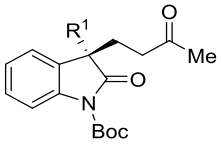
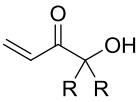
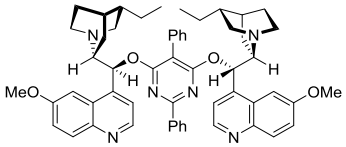
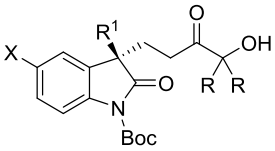
The conjugate addition of oxindoles to enones may serve to better illustrate the above observation (Table 4). While organocatalytic asymmetric Michael reaction of 3-aryl oxindoles has afforded excellent yields and enantioselectivities (entries 1– 2),[74] the

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

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

examples developed for the Michael addition of 3-alkyl oxindoles to enones has showed several limitations (entries 1 and 3), except when benzylic substituent were tested in C-3 (entry 3).[75] Our group has recently addressed this problem employing α'-hydroxy enones as the electrophiles. The addition was catalyzed with dimeric Brønsted bases to render good yields and enantioselectivities (entry 4).[76]

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

	Electrophile	Cat.*	Product	R^1	Results	Ref.
1	 R = Me, Et, Ph	 (20 mol %)		Aryl	92– 99% 46– 82% *ee*	74b
				Me	90– 99% 17– 48% *ee*	
2		 (5 mol %)		Aryl	82– 91% 81– 91% *ee*	74c
3		 (5 mol %)		Benzylic	80– 92% 91– 97% *ee*	75
				Me, *i*Bu, allyl	76– 85% 52– 67% *ee*	
4	 R = Me, Bn	 (10– 30 mol %)	 X = H, Me, MeO, F	Aryl	85–95%, 90–98% *ee*	76a
				Alkyl	76–92%, 78–96% *ee*	

It is noteworthy that structural isomers of 3-alkyl substituted oxindoles as 2-alkyl substituted indolin-3-ones have been much less employed as pronucleophiles ($R^2 \neq$ EWG

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

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

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

in Figure 7). In fact, only one example, which describes an organocatalytic alkylation, has been reported to date.[77]

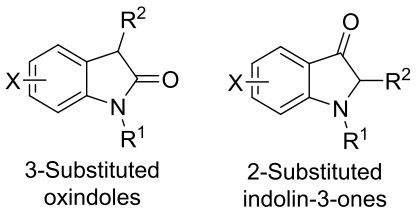


Figure 7.

Despite these different reactivity patterns, numerous examples concerning the use of oxindoles have hitherto been reported, which have been comprehensively reviewed several times and will not be further discussed here.[78]

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

α,α-Disubstituted α-hydroxy carboxylic acids, containing α tertiary hydroxy stereogenic centre and an easily modifiable carboxylic acid, are versatile and powerful intermediates that allow the formation of various chiral molecules with biological importance (Figure 8).[79] In this context, stereoselective synthesis of these valuable entities has attracted the interest of several research groups over the past few decades.[80] However, organocatalytic asymmetric methods have not been extensively studied.

[77] For the organocatalytic asymmetric alkylation of 2-alkyl substituted indolin-3-ones employing PTC, see: Kawasaki, T.; Higuchi, K.; Masuda, K.; Koseki, T.; Hatori, M.; Sakamoto, M. *Heterocycles* **2007**, *73*, 641.

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

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

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

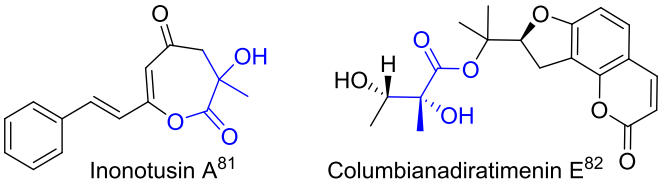


Figure 8. Selected examples of biologically active α,α-disubstituted α-hydroxy acids.

In 2004, Trost and co-workers introduced 5*H*-oxazol-4-ones as α-alkyl-α-hydroxy ester surrogates in a chiral disphosphomolibdenum catalyzed asymmetric allylic alkylation, leading to a convenient pathway to furnish asymmetric synthesis of α-hydroxy carboxylic acids.[83] Two years later, Maruoka's group postulated a different substrate as α-hydroxy acid surrogate, oxazolidindione (Figure 9), phase-transfer conditions and a strong base were required for deprotonation.[84]

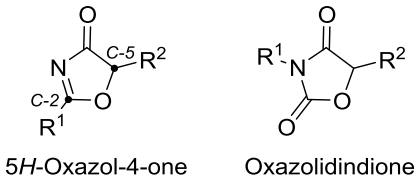
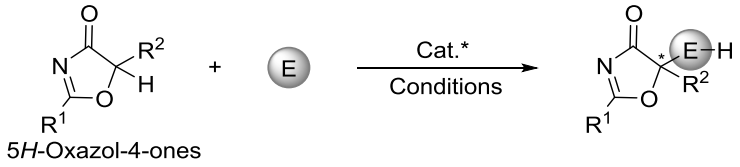


Figure 9.

5*H*-oxazol-4-ones have been utilized as pronucleophiles in a variety of metallic and organocatalytic asymmetric reactions, such as aldol,[85] Mannich[86] and sulfenylation reactions.[87] To the best of our knowledge, only 5-alkyl 2-aryl 5*H*-oxazol-4-ones have been employed for this kind of reactions, so in absence of any precedent, the reactivity of either 5-aryl or 2-alkyl 5*H*-oxazol-4-ones remains unknown (Scheme 20).[88]

---

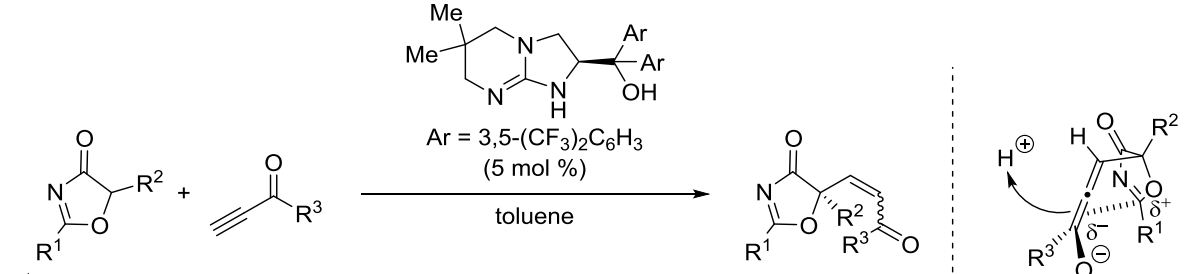
[81] Zan, L.; Qin, J.; Zhang, Y.; Yao, Y.; Bao, H.; Li, X. *Chem. Pharm. Bull. (Tokyo).* **2011**, *59*, 770–772.
[82] Zhang, Y.-B.; Li, W.; Yang, X.-W. *Phytochemistry* **2012**, *81*, 109–116.
[83] a) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944–1945. For a recent allylic alkylation of 5*H*-oxazol-4-ones employing Ir catalysis, see: b) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377–382. For a recent alkylation employing ammonium salt PTC, see: c) Duan, S.; Li, S.; Ye, X.; Du, N.-N.; Tan, C.-H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 7770–7778.
[84] Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 3839–3842.
[85] For a chiral guanidine-catalyzed aldol reaction of 5*H*-oxazol-4-ones, see: a) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287.
[86] For a *syn*-Mannich addition to phosphoryl imines with Zn catalysis, see: a) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7523–7527. For a *syn*-Mannich addition to sulfonyl imines with bifunctional thioureas, see: b) Han, Z.; Yang, W.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2013**, *355*, 1505–1511.
[87] For an example of 5*H*-oxazol-4-one sulfenylation with bifunctional squaramides, see: Xu, M.; Qiao, B.; Duan, S.; Liu, H.; Jiang, Z. *Tetrahedron* **2014**, *70*, 8696–8702.
[88] For a study on the keto-enol tautomery of 2,5-diphenyl oxazol-4(5*H*)-ones, see: Jacobsen, N.; Philippides, A. *Aust. J. Chem.* **1985**, *38*, 1335–1338.



Scheme 20.

Conjugate addition to electron deficient double or triple bonds is the most used strategy with these pronucleophiles, although there are not many examples. In fact, the first precedent of a Michael reaction with 5*H*-oxazol-4-ones was performed on ynones by Misaki and Sugimura in 2011 (Table 5).[89] In 1,4-additions of this type, both the geometric control of the newly formed olefin and the enantiomeric control on the generated stereocentre, are the most significant challenges. While the enantioselectivity of the major diastereomer remained excellent in most of the cases, *Z*/*E* selectivity proved to be better when the electrophile was an ester or an amide (entries 1 and 4). The authors describe a stabilization of the charge between the electron enriched π orbital of the newly formed intermediate enolate and the electron deficient C-2 of the oxazolone to explain such results.

Table 5. Representative results of guanidine-catalyzed addition of 5*H*-oxazol-4-ones to ynones.

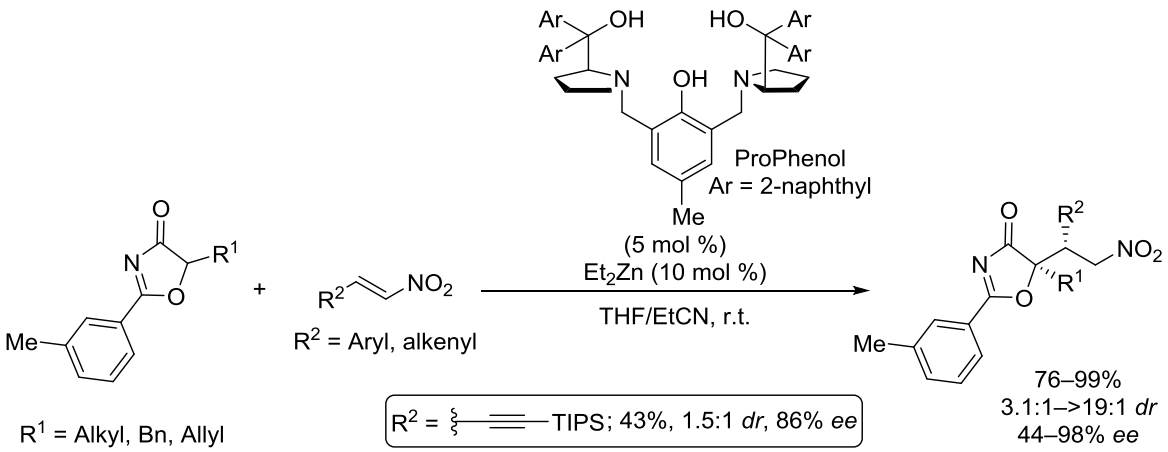


Entry	R^3	T (°C)	R^1	R^2	Yield (%)	*Z*/*E*	*ee* (%)
1	MeO	− 40	Ph	Alkyl	66− 77	96:4− 99:1	84− 93
2	*n*-heptyl	0	Ph	Me	77	44:56	91
3	$CH_3(CH_2)_{11}S$-	0	Ph	Me	88	76:24	38− 91
4	*N*-Pyrrolidinyl	0	Ph	Alkyl	40− 58	>99:1	94− 99

Conjugate addition of 5*H*-oxazol-4-ones to nitroolefins was first reported by Trost and co-workers in 2012.[90] Using a chiral dinuclear Zn− ProPhenol complex, whose active structure was not described in the paper, good to excellent yields and diastereoselectivities were afforded, except for alkynyl-substituted nitroalkenes (Scheme

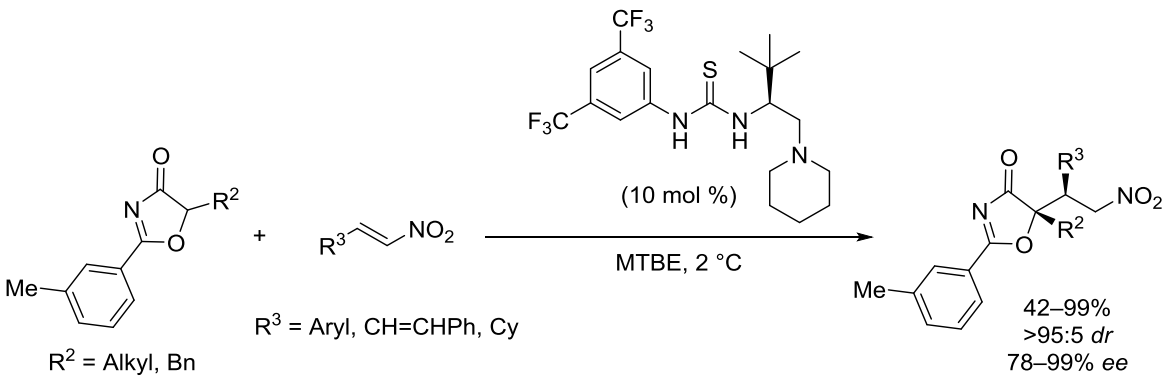
[89] For asymmetric 1,4-addition of 5*H*-oxazol-4-ones to alkynyl carbonyl compounds, see: a) Misaki, T.; Kawano, K.; Sugimura, T. *J. Am. Chem. Soc.* **2011**, *133*, 5695–5697. b) Misaki, T.; Jin, N.; Kawano, K.; Sugimura, T. *Chem. Lett.* **2012**, *41*, 1675–1677.
[90] Trost, B. M.; Hirano, K. *Angew.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

21). Enantioselectivities remained very good to excellent, except for β-aryl substituted nitroolefins in which the aromatic ring was *ortho* substituted (R^2 = *o*Tol, 1-napthyl, 2-F-C_6H_4-; 44– 70% *ee*). It should be mentioned that a *meta*-tolyl substituent at C-2 in the 5*H*-oxazol-4-one was essential to obtain the aforementioned enantiocontrol.



Scheme 21.

The organocatalytic version of this reaction was first developed by Jiang's research group,[91] who employed a thiourea-based bifunctional Brønsted base to perform the reaction affording excellent yields, diastereomeric ratios and enantioselectivities with aromatic and conjugated nitroalkenes (70– 99%, >95:5 *dr*, 90– 99% *ee*) (Scheme 22). However, the method fails in obtaining such results with the only aliphatic nitroalkene reported (R^3 = Cy, 42%, >95:5 *dr*, 78% *ee*).

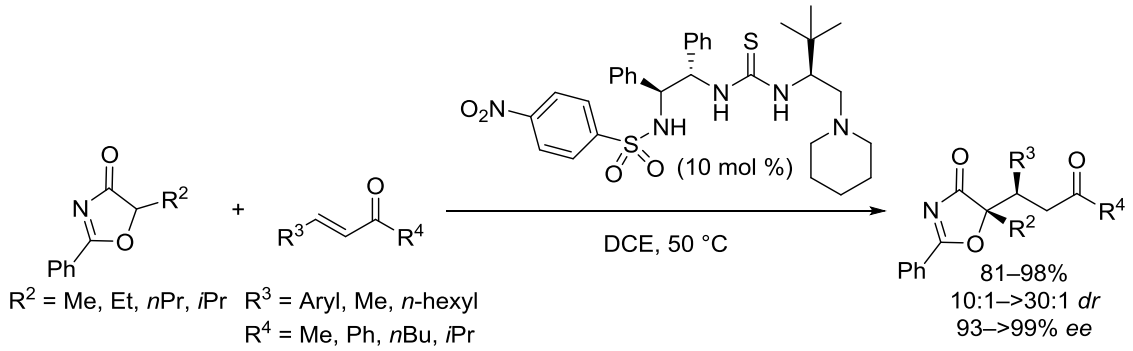


Scheme 22.

The asymmetric conjugate addition to enones is a better studied reaction. In this field, the work developed by Ye's group must be highlighted, who in 2012 developed the first example of this kind of reaction.[92] The addition was catalyzed by a thiourea-based bifunctional Brønsted base, rendering excellent yields, *dr*'s and *ee*'s (Scheme 23). The

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

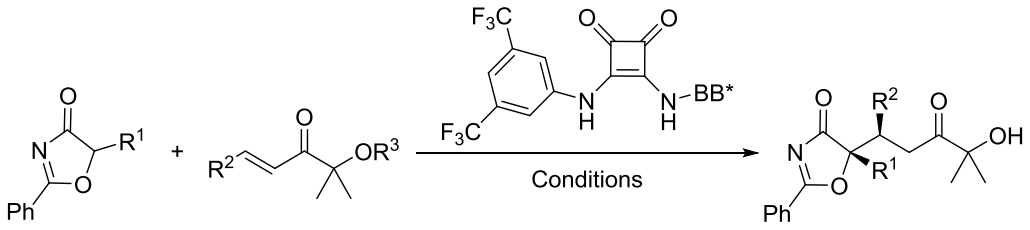
results indicate that the additional acidic *NH* on the sulfonamide catalyst plays a significant role in this reaction.

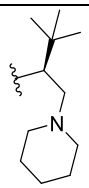
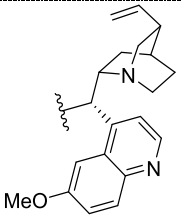


Scheme 23.

Recently, our group contributed to this field with another example, where the squaramide-based bifunctional Brønsted base catalyzed asymmetric Michael addition of 5*H*-oxazol-4-ones to both unsubstituted α'-silyloxyenones and β-substituted α'-silyloxyenones.[76a] As can be seen in the results depicted in Table 6, the low reactivity of β-substituted enones requires an increase in the temperature, as well as changes in the catalyst, in order to obtain the same excellent enantiocontrol accomplished with unsubstituted ones.

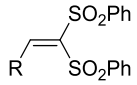
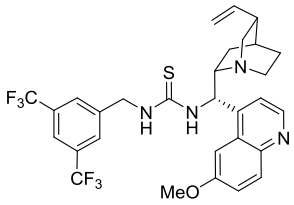
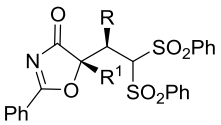
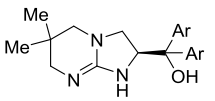
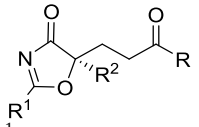
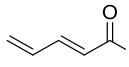
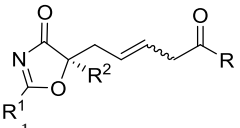
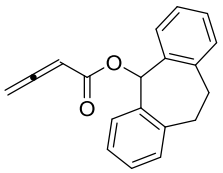
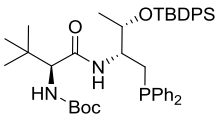
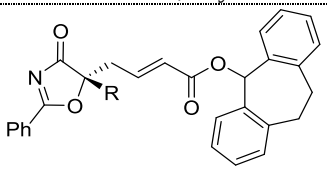
Table 6. Representative results of the squaramide-catalyzed addition of 5*H*-oxazol-4-ones to enones.



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

In addition to the above described electrophiles, other substrate acceptors have also been reported to react well with oxazolones under organocatalytic conditions: a thiourea-based bifunctional Brønsted base catalyzed addition to vinyl sulfones,[93] a chiral guanidine catalyzed 1,4- and 1,6-addition to enones and dienones,[94] and a chiral phosphine catalyzed conjugate addition to allenoates[95], as depicted in Table 7.

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

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Aryl, H	 (10 mol %)	 R^1 = Me, Et, Bn, *n*Bu	64– 99% >20:1 *dr* 81– >99% *ee*	93
2	 R = Aryl	 Ar = $[3,5\text{-}(CF_3)_2C_6H_3]_2\text{-}C_6H_3$ (5 mol %)	 R^1 = 3-Cl-5-MeC_6H_4 R^2 = Me, *n*Bu, *i*Pr, allyl	55– 96% 39– 91% *ee*	94
	 R = Me, *n*Hex, Cy		 R^1 = 3-Cl-5-MeC_6H_4, 3-ClC_6H_4 R^2 = Me, allyl	34– 77% 80:20 dr 93– 99% *ee*	
3		 (10 mol %)	 R = Alkyl, Bn	89– 98% 81– 97% *ee*	95

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

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

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

The pyrazolone moiety is part of the core structure of various biologically active products or drugs (Figure 10),[96] and it is also employed in industry, as a dye[97] or anticorrosive, [98] for example.

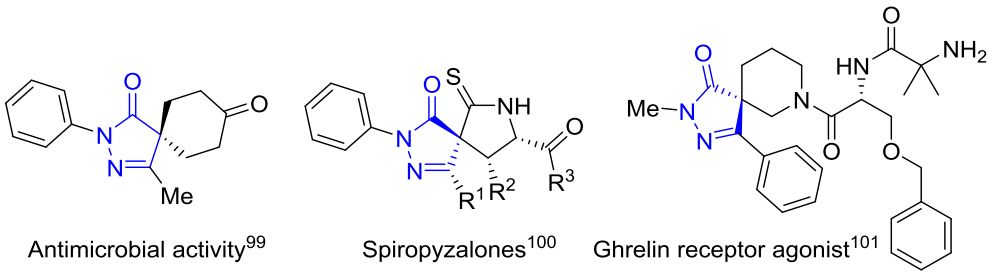
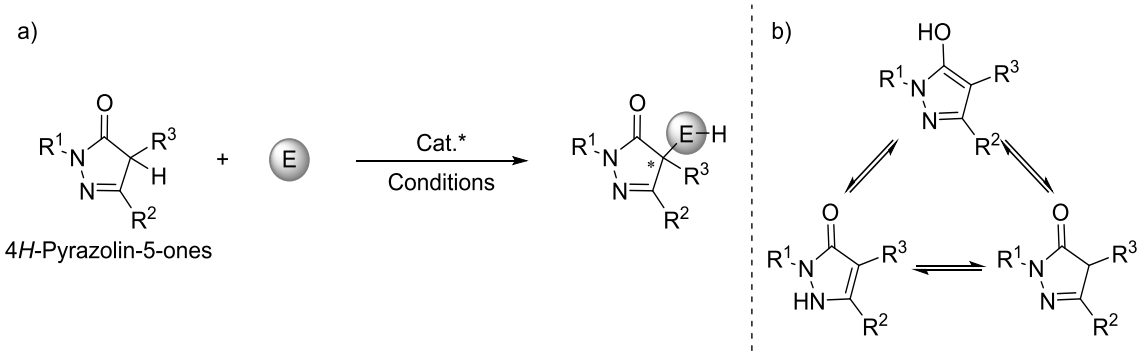


Figure 10. Selected examples of biologically active pyrazolone derivatives.

Along the years, several approaches were developed for the synthesis of 4-substituted 4*H*-pyrazolin-5-ones,[102] but, despite their importance, these heterocycles had never been used as pronucleophiles to perform direct asymmetric addition reactions until this decade (Scheme 24a). In 2004 Holzer and Alkorta's group,[103] who demonstrated through ^{1}H NMR studies that these compounds exist in equilibrium between three tautomeric forms in solution (Scheme 24b). This observation explains the easy involvement of these heterocycles in direct reactions under proton transfer conditions.

[96] Antitumoral activity: a) Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; VanRens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; … Janusz, M. J. *J. Med. Chem.* **2004**, *47*, 2724–2727. Antiviral activity: b) Hadi, V.; Koh, Y.-H.; Sanchez, T. W.; Barrios, D.; Neamati, N.; Jung, K. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6854–6857.
[97] Li, Y.; Zhang, S.; Yang, J.; Jiang, S.; Li, Q. *Dyes Pigm.* **2008**, *76*, 508–514.
[98] Abdallah, M. *Mater. Chem. Phys.* **2003**, *82*, 786–792.
[99] Chande, M. S.; Barve, P. A.; Suryanarayan, V. *J. Heterocycl. Chem.* **2007**, *44*, 49–53.
[100] Liu, L.; Zhong, Y.; Zhang, P.; Jiang, X.; Wang, R. *J. Org. Chem.* **2012**, *77*, 10228–10234.
[101] A. V. Ambarkhane et al., *3-Spirocyclic piperidine derivatives as ghrelin receptor agonists* (US Patent 20120302540A1, November 29) 2012.
[102] For the synthesis of pyrazolinones from chromone derivatives, see: a) Ghosh, C. K.; Mukhopadhyay, K. K. *Synthesis* **1978**, 779–781. b) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G. *Tetrahedron Lett.* **1987**, *28*, 5165–5168. For the synthesis of pryazolinones from 4-hydroxycoumarins, see: c) Chantegrel, B.; Gelin, S. *Synthesis* **1985**, 548–550. For the synthesis of pyrazolinones via Pd-catalyzed carbonylation of 1,2-diaza-1,3-butadienes, see: d) Boeckman, R. K.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651–3653.
[103] Holzer, W.; Kautsch, C.; Laggner, C.; Claramunt, R. M.; Pérez-Torralba, M.; Alkorta, I.; Elguero, J. *Tetrahedron* **2004**, *60*, 6791–6805.



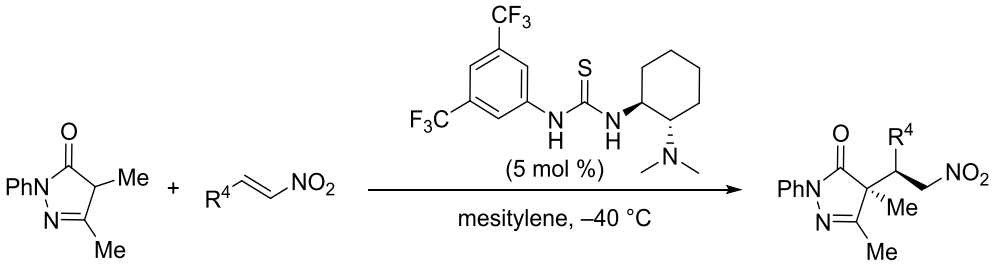
Scheme 24.

While Feng's research group carried out aminations,[104] and conjugate additions to 1,4-dicarbonyl but-2-enes[105] and ynones[106] under organometallic catalysis, the group of Rios performed pyrazolinone additions to enals employing iminium ion activation[107] and maleimides through bifunctional Brønsted base catalysis.[108] Organometallic strategies have also been employed to perform pyrazolone alkylations.[109]

The addition of 4-substituted 4*H*-pyrazolin-5-ones to nitroolefins employing Takemoto's catalyst has also been reported (Table 8).[110] Aromatic nitroalkenes afforded excellent yields (entries 1– 8), but aliphatic ones proved to be less effective (entries 9– 10). Diastereocontrol was moderate at best, although enantiocontrol of the major diastereomer remained very good to excellent in every case.

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

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



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

[a] *ee* of the major diastereomer.

To date, while several metal catalyzed conjugate additions of 4-substituted 4*H*-pyrazolin-5-ones to enones have been developed,[105,106] organocatalytic approaches remain unexplored.

As far as we know, the majority of examples are based on conjugate additions, while other reactions, such as 1,2-additions to aldehydes or imines, have to be yet explored.

1.2.2.4. γ-Butirolactams

α,β-Unsaturated γ-butyrolactam derivatives (5-substituted 3-pyrrolidin-2-ones) belong to a family of structurally diverse natural or non-natural compounds with remarkable biological activities which also signify their importance in organic chemistry (Figure 11).[111]

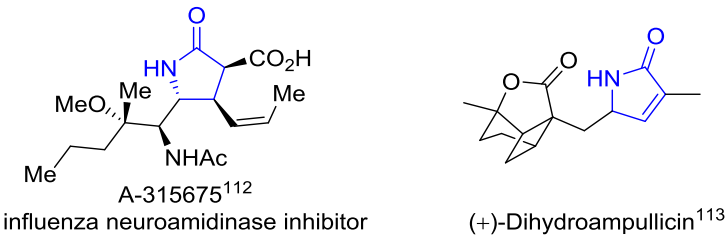
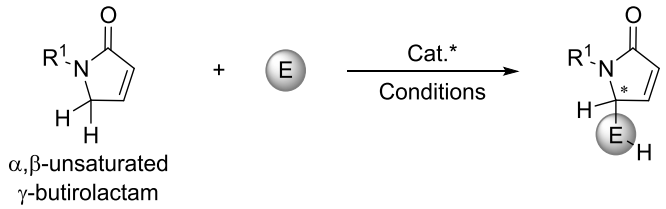


Figure 11. Selected examples natural and non-natural butirolactam derivatives.

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

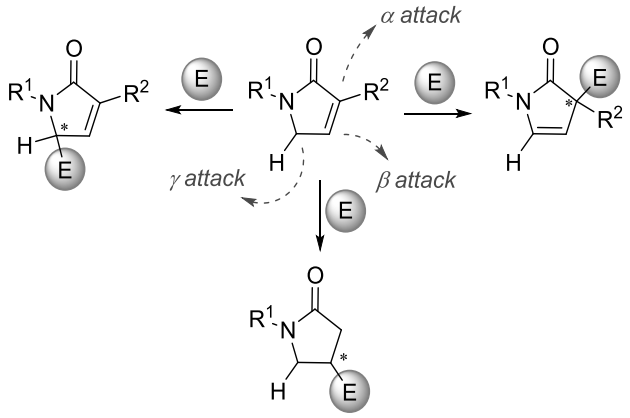


Scheme 25.

However, other reactivity patterns of α,β-unsaturated γ-butirolactams have also been explored (Scheme 26).[114] For instance, regarding α-reactivity, Morita-Baylis-Hillman additions to isatins,[115] aryl α-ketoesters[116] and tetrahydroisoquinolines[117] have been reported employing chiral thioureas and Brønsted bases. Among the reactions which

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

took advantage of β-reactivity of butirolactams, there are Cu catalyzed alkylations[118] and silylations,[119] and Rh catalyzed arylations.[120]

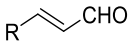
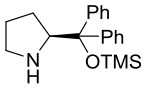
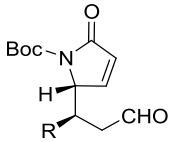
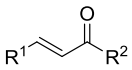
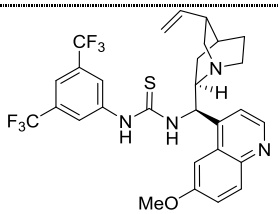
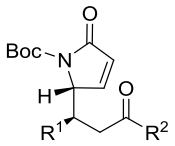
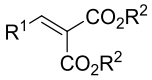
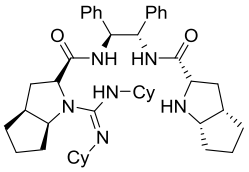
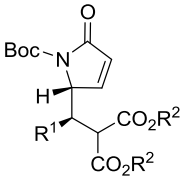
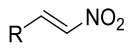
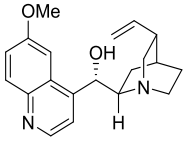
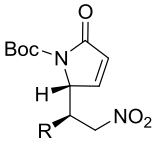
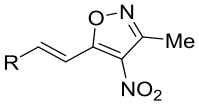
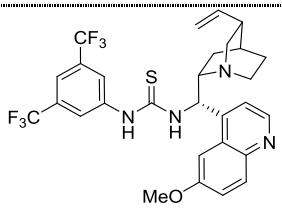
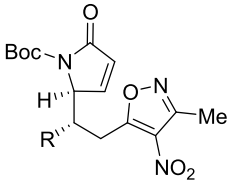
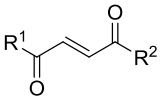
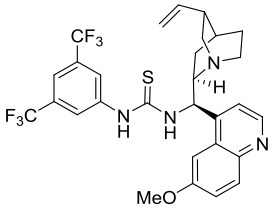
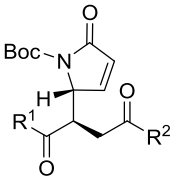
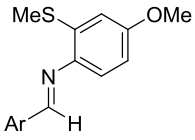
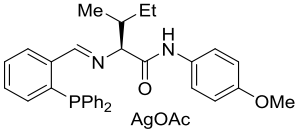
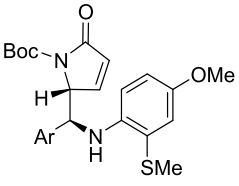


Scheme 26.

As mentioned above, these heterocycles have been mainly employed as vinylogous nucleophiles to perform Michael additions to form tertiary carbon stereocentres, as has been collected in various extensive reviews.[121] In Table 9 are depicted the most recent examples of this type of reactions, mostly involving Michael acceptors.[122]

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

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

	Electrophile	Cat.*	Product	Results	Ref.
1		 (20 mol %)	 R = Aryl, Me, Et	31– 89% 1.1:1– >20:1 *dr* 79– 99% *ee*	122a
2		 (10 mol %)	 R^1, R^2 = Aryl	73– 95% 10:1– >30:1 *dr* 94– 99% *ee*	122b
3		 (5 mol %)	 R^1 = Aryl, alkenyl, Cy R^2 = Et, Me, Bn	64– 93% 81:19– 95:5 *dr* 78– 94% *ee*	122c
4		 (10 mol %)	 R = Aryl, Cy, *i*Bu, *i*Pr	64– 93% >20:1 *dr* 60– 89% *ee*	122d
5		 (10 mol %)	 R = Aryl	57– 90% 1.3:1– 19:1 *dr* 84– 96% *ee*	122e
6		 (10 mol %)	 R^1 = OR, Aryl, Alkyl R^2 = Aryl, Alkyl	56– 95% 10:1– >25:1 *dr* 83– 99% *ee*	122f
7		 (5 mol %)		62– 98% >98:2 *dr* 86– 98% *ee*	122g

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

The rhodanine scaffold is found in many bioactive and pharmacologically interesting structures, showing antibacterial, antiviral, antimalarial, and antitumor activities (Figure 12).[123]

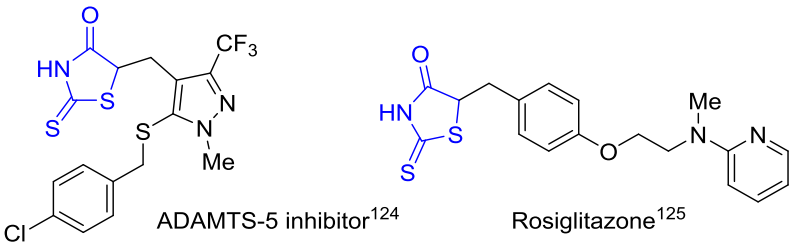
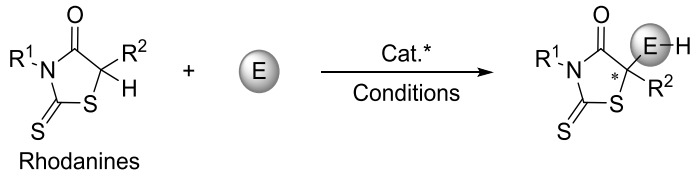


Figure 12. Selected examples of biologically active racemic rhodanine derivatives.

It is demonstrated that in 5-monosubtituted 2-thioxothiazolidin-4-ones, like the ones depicted above, enolization can occur at the 5-position under physiological conditions, which makes difficult to maintain the sometimes essential configuration at this position.[126] To avoid this, work has been directed to the quaternization of the α *C*(sp^3) of 5-substituted rhodanines, mainly through reactions under proton transfer conditions (Scheme 27). These reactions will be more extensively discussed in the following chapter (page 77).



Scheme 27.

[123] For reviews, see: a) Lesyk, R.; Zimenkovsky, B. *Curr. Org. Chem.* **2004**, *8*, 1547–1577. b) Tomasic, T.; Masic, L. *Curr. Med. Chem.* **2009**, *16*, 1596–1629.
[124] Gilbert, A. M.; Bursavich, M. G.; Lombardi, S.; Georgiadis, K. E.; Reifenberg, E.; Flannery, C. R.; Morris, E. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1189–1192.
[125] Kumar, B. R. P.; Nanjan, M. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1953–1956.
[126] Joshi, M.; Vargas, C.; Boisguerin, P.; Diehl, A.; Krause, G.; Schmieder, P.; Moelling, K.; Hagen, V.; Schade, M.; Oschkinat, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3790–3795.

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

Diketopiperazines are privileged structures that can be found in the core of several commercial drugs or pharmaceutically interesting molecules (Figure 13). The extensive studies of the synthesis and medicinal chemistry of this scaffold and its occurrence in bioactive natural products have been described in comprehensive reviews.[127]

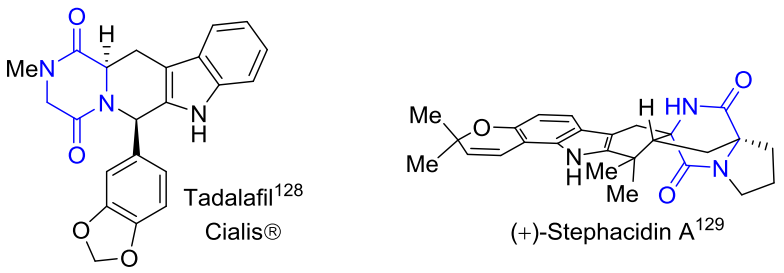
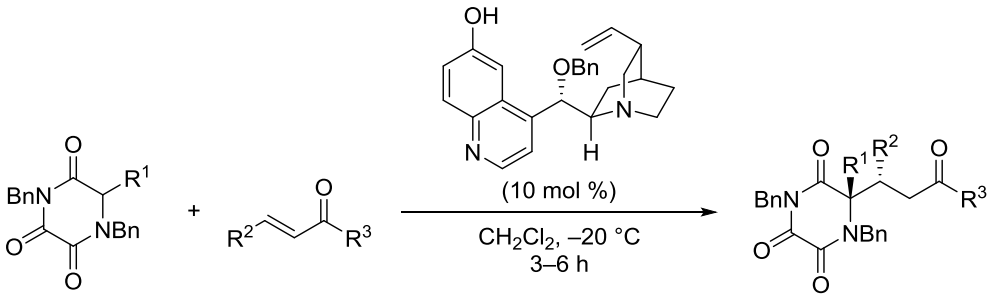


Figure 13. Selected examples of biologically active diketopiperazine derivatives.

Diverse strategies have been employed to gain access to structures bearing this heterocyclic core, including activated diketopiperazines as pronucleophiles in organocatalyzed reactions by Olenyuk and co-workers. However, total enantiocontrol of the reactions was not achieved.[130] The use of triketopiperazines as pronucleophiles is another strategy that recently provided a successful example of conjugate addition to enones and enals (Table 10).[131]

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

Table 10. Representative results for the Brønsted base-catalyzed addition of triketopiperazines to enones.



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

[a] Isolated as a single diastereomer.

However, the example depicted above only presents much activated 5-methyloxycarbonyl triketopiperazines (R^1 = CO_2Me) to form a quaternary stereocentre (entries 1– 5) or 5-unsubstituted ones (R^1 = H) to form a tertiary one (two contiguous tertiary stereocentres if R^2 = Ph, entries 10– 11). Yet, no examples involving aliphatic or aromatic R^1 substituents have been described and, with respect to the electrophile, no other examples have been reported to date.[130,131]

1.2.3. **Lactone based pronucleophiles**

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

3*H*-Benzofuran-2-ones are important building blocks that are found in a large variety of natural products, drugs and other biologically interesting structures. Additionaly, many of them feature a chiral quaternary stereocentre at the C-3 position of the heterocyclic ring. Thus, benzofuranones have been involved in several total syntheses, being Diazonamide A one of the most significants, as reported by Nicolaou and co-workers in 2002 (Figure 14).[47a]

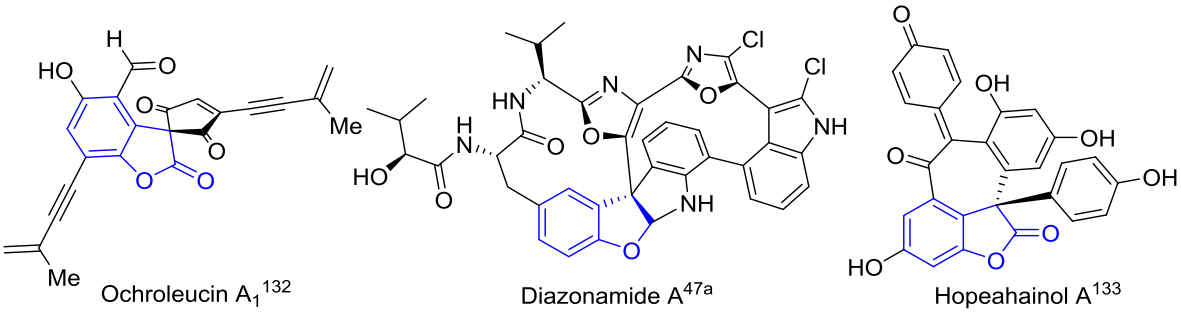
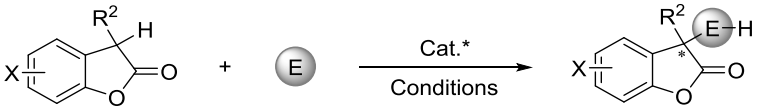


Figure 14. Selected examples of biologically active benzofuranone derivatives.

The obvious structural similarities with oxindoles have prompted the utilization of benzofuranones as pronucleophiles (Scheme 28).[134],[135]



Scheme 28.

The first example of the utilization of 3-substituted 3*H*-benzofuran-2-ones as pronucleophiles in a direct addition to obtain quaternary stereocentres was in the Michael addition to β-substituted enones reported by Cheng's group in 2010.[136] The reaction was catalyzed by an analog Takemoto's bifunctional catalyst, obtaining high yields and excellent enantioselectivities, but moderate diastereoselectivity at best, when R^2 and R^3 were aromatic. No example employing 3-alkyl substituted benzofuranones was reported. However, early attempts to perform the addition on aliphatic vinyl ketones (R^2 = H, R^3 = Me or Et) were described, although no satisfactory results were obtained (Scheme 29).

---

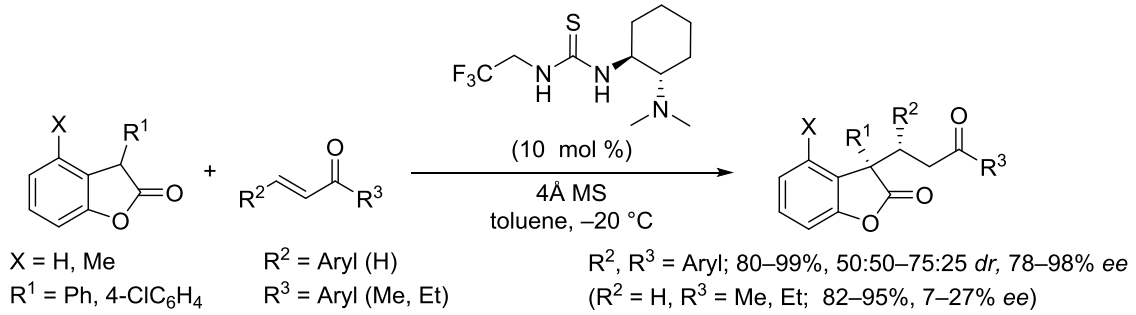
[132] Sontag, B.; Rüth, M.; Spiteller, P.; Arnold, N.; Steglich, W.; Reichert, M.; Bringmann, G. *Eur. J. Org. Chem.* **2006**, 1023–1033.

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

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

[135] For the conjugate addition of oxindoles and benzofuranones to cyclic enones employing iminium ion, Brønsted base catalysis, see: a) Pesciaioli, F.; Tian, X.; Bencivenni, G.; Bartoli, G.; Melchiorre, P. *Synlett* **2010**, 1704–1708. For the conjugate addition of oxindoles and benzofuranones to enals to obtain spirocyclic adduct via iminium ion, see: a) Companyó et al.ref 107a Page 29. b) Bergonzini, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 971–974. For the conjugate addition of 3-Se oxindoles and benzofuranones to nitroolefins mith squaramide-based bifunctional Brønsted bases, see: c) , J.; Garcia Ruano, J. L.; Marini, F.; Tiecco, M. *Org. Lett.* **2011**, *13*, 3052–3055. For the addition reaction of oxindoles and benzofuranones to Morita-Baylis-Hillman type carbonates with chiral phosphines, see: d) Wang, D.; Yang, Y.-L.; Jiang, J.-J.; Shi, M. *Org. Biomol. Chem.* **2012**, *10*, 7158–7166. For the conjugated addition of oxindoles and benzofuranones to allenoates employing chiral phosphines, see: e) Chen, J.; Cai, Y.; Zhao, G. *Adv. Synth. Catal.* **2014**, *356*, 359–363. For the chiral guanidine catalyzed sulfenylation of 3-alkyl oxindoles and benzofuranones, see: f) Huang, L.; Li, J.; Zhao, Y.; Ye, X.; Liu, Y.; Yan, L.; Tan, C.-H.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 8933–8941.

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



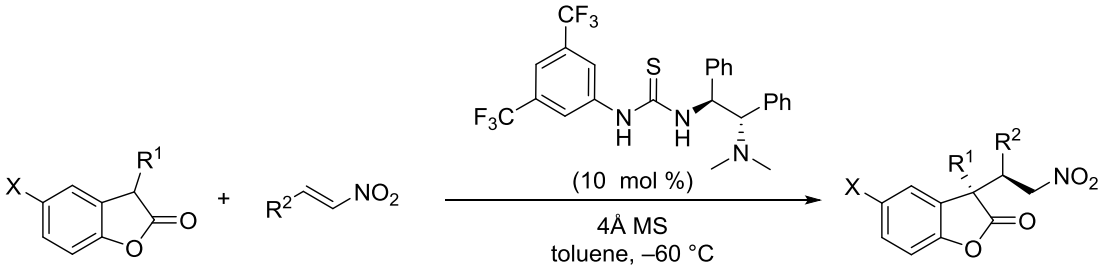
Scheme 29.

Since then, many other electrophiles have been employed to perform Michael additions with benzofuranone,[137] including nitroolefins. In this field, the only example using 3-alkyl benzofuranones as pronucleophiles was also introduced by Cheng and co-workers in 2012.[138] As illustrated in Table 11, *ortho* substituted aromatic nitroolefins afforded the best stereoselectivities when 3-methyl benzofuranones were used as Michael donors (entries 5− 6). Surprisingly, the thiourea-based bifunctional Brønsted base catalyzed reaction worked quite well for aliphatic nitroolefins, despite their usual lack of reactivity (entries 8− 9). Benzyl or aryl groups in C-3 did not affect the yields, but both diastereoselectivity and more pronouncedly enantioselectivity decreased (entries 10− 11). Decrease of the electron density in the aromatic ring of the benzofuranone also resulted in an increase of *ee*, although *dr* was not improved (entries 13− 14 vs. 11− 12).

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

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

Table 11. Representative results of the Michael addition of benzofuranones to nitroolefins.



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

Despite their therapeutic and synthetic interest, and like in the case of oxindoles, structural isomers of 3-substituted 3*H*-benzofuran-2-ones like 2-alkyl substituted 2*H*-benzofuran-3-ones (Figure 15) have been much less employed as pronucleophiles in this kind of reactions. In fact, as far as we know, only one example has been described, that involves the use of nitroolefins as the acceptor partner.[139]

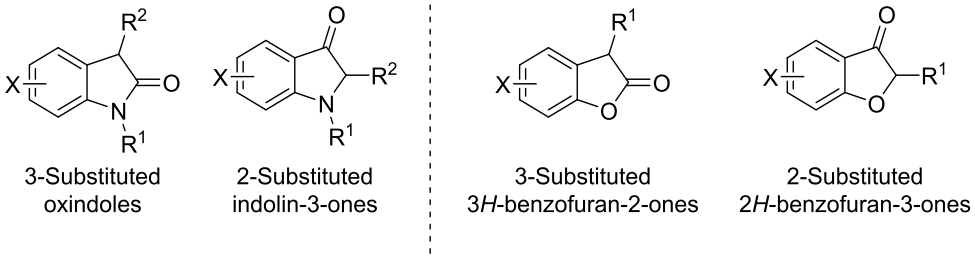


Figure 15.

[139] a) Zhang, Z.-P.; Dong, N.; Li, X.; Cheng, J.-P. *Org. Biomol. Chem.* **2015**, *13*, 9943–9947. For reactions employing 2*H*-benzofuran-3-ones with electron withdrawing groups in C-2 (R^1 = EWG), see: b) ref. 134 page 36.

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

Azlactones or 4*H*-oxazol-5-ones are one of the most synthetically versatile heterocycles, and extensive reviews have covered the subjet.[140] Plöchl and co-workers described the first synthesis of azlactones through a condensation reaction of benzaldehyde and hippuric acid in presence of acetic anhydride,[141] but it was Erlenmeyer who first established their correct structure and named them.[142] Azlactones are masked forms of α-amino acids that contain multiple reactive sites that allow different possible modifications, making them excellent substrates for the synthesis of highly substituted heterocyclic scaffolds, as shown in Figure 16.

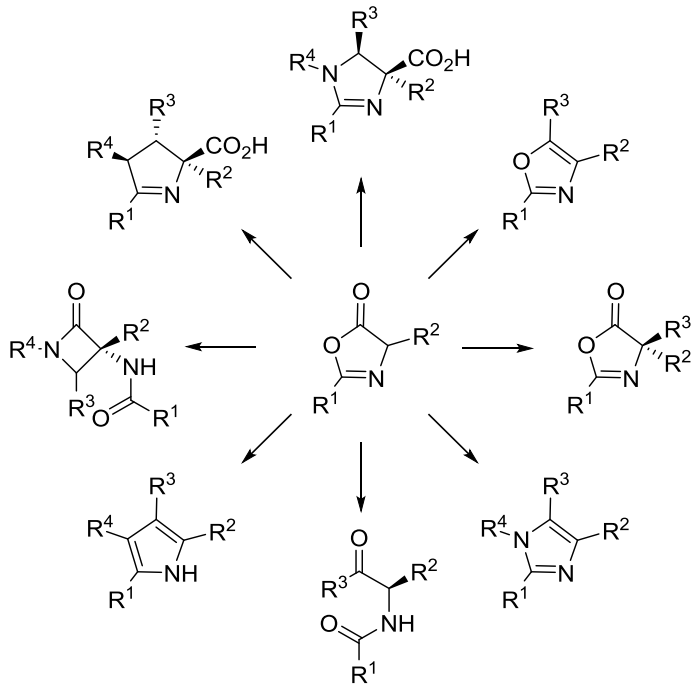
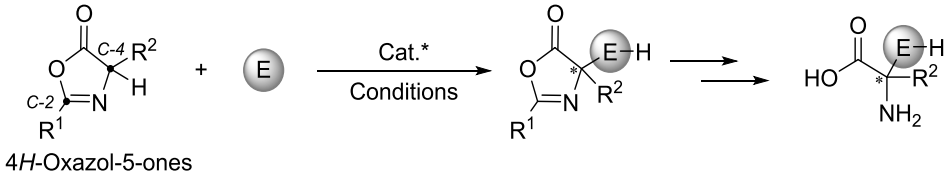


Figure 16. Diverse structures obtained from azlactones.

This multiple reactivity can be directed depending on the counterpart that is added to the reaction. The acidity of the 4-substituted azlactone (pKa ≈ 9)[143] allows its facile deprotonation with mild Brønsted bases to obtain an enolate, that in presence of an electrophile would form a quaternary stereocentre contiguous to the carbonyl. This strategy has been broadly explored in several thorough reviews along the years, since it

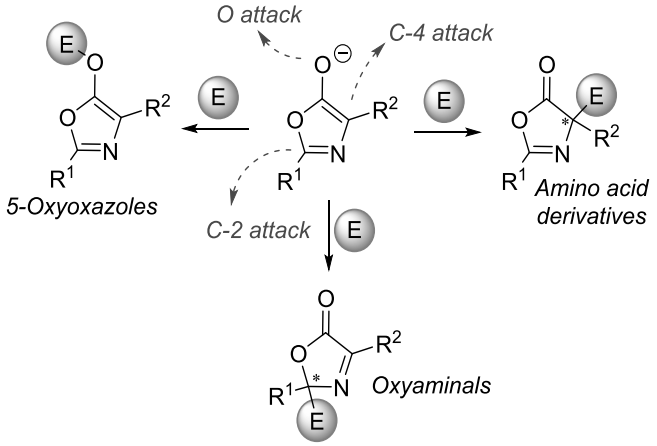
[140] For reviews on the diverse chemistry of azlactones, see: a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. b) Alba, A.-N. R.; Rios, R. *Chem. Asian J.* **2011**, *6*, 720–734.
[141] Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2815–2825.
[142] Erlenmeyer, E. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2036–2041.
[143] Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918–2922.

gives access to quaternary natural or unnatural amino acid derivatives, which are highly requested building blocks or synthetic goals (Scheme 30).[144]



Scheme 30.

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



Scheme 31.

Whilst *O*- reactivity of these heterocycles has been extensively studied since the discovery of the rearrangement of *O*-acylated azlactones by Steglich and Höfle in 1970,[145] C-4 reactivity did not grab so much attention until Trost's research group reported the first Salen-Pd catalyzed α-allylation of azlactones in 1997.[146]

To date, a great number of examples involving azlactones as pronucleophiles for the synthesis of quaternary α-amino acids have been reported. These examples will be outlined later in chapter 3 (page 127).

---

[144] For some recent reviews on the stereoselective synthesis of quaternary α-amino acids employing azlactones among other strategies, see: a) Mosey, R. a.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755–2762. b) Alba & Riossee ref. 140b page 38 c) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234–1260. d) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1–7.

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

[146] a) Trost, B. M.; Ariza, X. *Angew. Chem. Int. Ed.* **1997**, *36*, 2635–2637. For later examples of Pd catalyzed alkylation of azlactones, see: b) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, *134*, 5778–5781. c) Zhou, H.; Yang, H.; Liu, M.; Xia, C.; Jiang, G. *Org. Lett.* **2014**, *16*, 5350–5353.

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

Cyclic five-membered oxime esters or isoxazolinones are involved in many biologically active species (Figure 17).[147] Along with this, these heterocycles are valuable building blocks of other heterocycles and β-amino acids.[148]

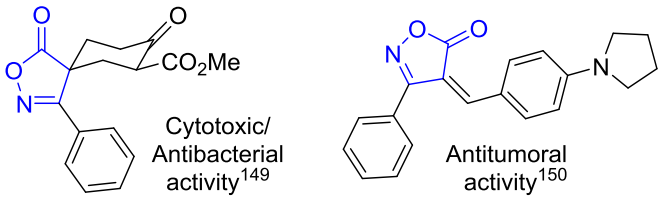
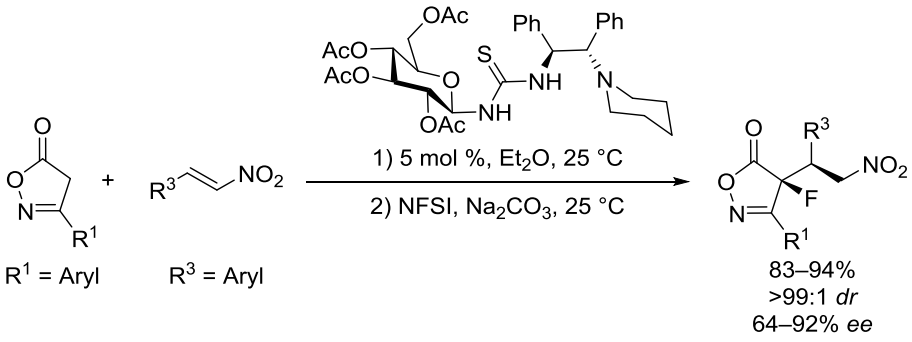


Figure 17. Selected examples of biologically active isoxazolinone derivatives.

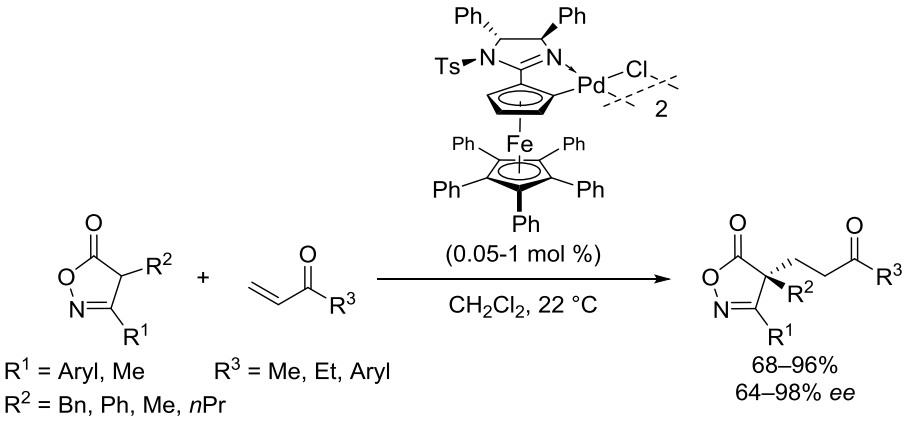
Despite their importance, there are only two examples of the use of isoxazolinones as pronucleophiles, which adds difficulty to a complete understanding of their reactivity. The first one was an organocatalytic Michael addition of 4*H*-isoxazol-5-ones developed by Ma's research group in 2013.[151] More specifically, it consisted of a one-pot sequential conjugate addition to aromatic nitroalkenes and fluorination of 3-aryl 4-unsubstituted isoxazolinones, catalyzed by a bifunctional amino-thiourea. Apart from the excellent yields and diastereo- and enantioselectivities, it is noteworthy that the authors were able to construct two contiguous stereogenic centres, especially a quaternary one from a methylene, in two sequential enantioselective steps (Scheme 32).



Scheme 32.

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

The other example was an isoxazolinone addition to enones, which was recently described by Peters and co-workers.[152] This palladacycle-catalyzed Michael addition is the only example of 4-substituted 4*H*-isoxazol-5-ones as pronucleophiles reported to date (Scheme 33).



Scheme 33.

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

1.2.3.4. **Butenolides**

γ-Substituted butenolide skeletons represent a structural type of both synthetic and biological importance. A great number of biologically active natural products and pharmaceutically relevant molecules contain the special butenolide motif (Figure 18).[153]

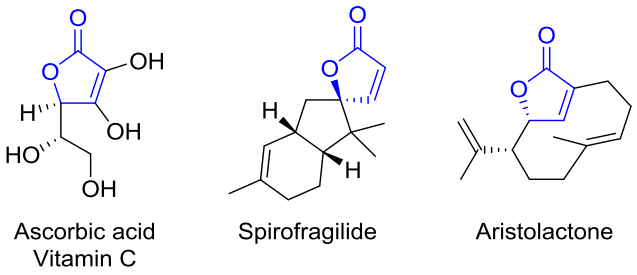
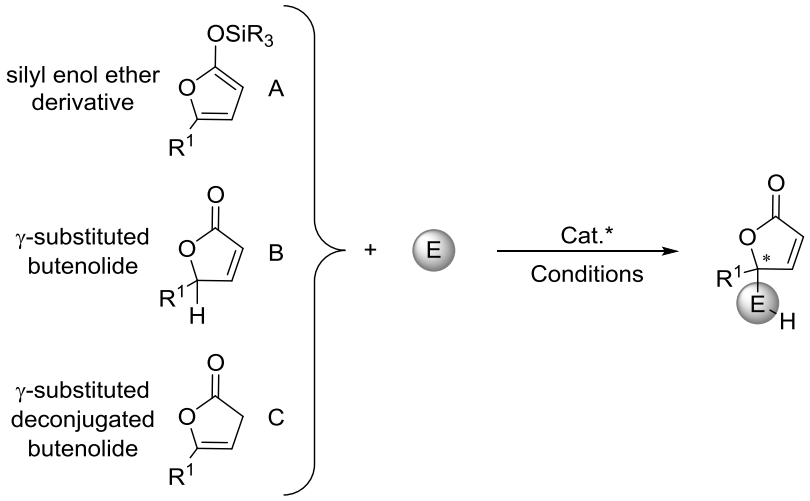


Figure 18. Selected natural products containing butenolide moiety.

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

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

Many strategies have been used to access this structural motif, and different pronucleophiles have been employed for that purpose: such as silyl enol ether derivatives of γ-butenolide,[154] the butenolide itself,[155] and γ-substituted deconjugated butenolides (i.e. α-angelica lactone, when R^1 = Me), which upon reaction with an electrophile lead to γ,γ-disubstituted conjugated butenolide motifs (Scheme 34).[156]



Scheme 34.

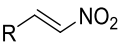
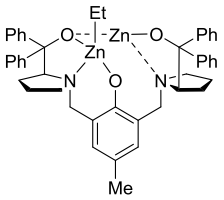
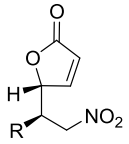
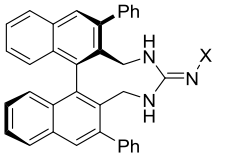
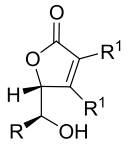
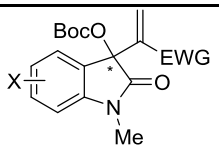
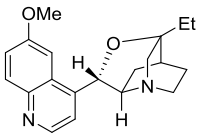
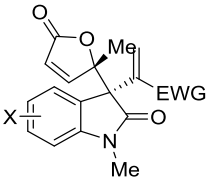
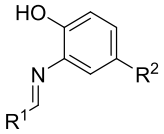
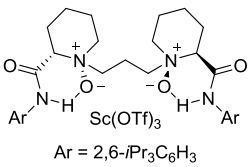
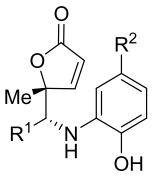
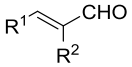
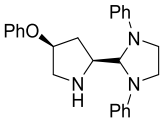
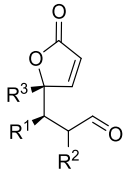
[154] See ref. 121 page 26.

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

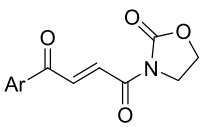
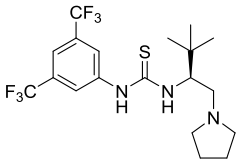
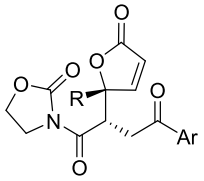
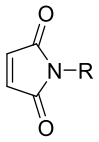
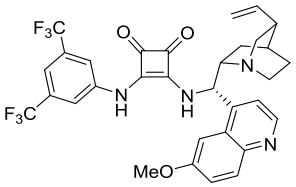
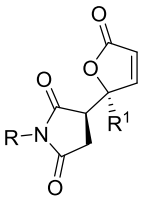
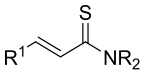
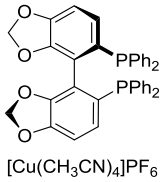
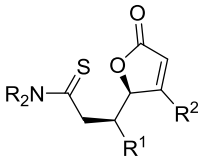
[156] For allylic substitution of α-angelica lactone employing dimeric Brønsted bases, see: a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720–723. For allylic substitution of α-angelica lactone employing chiral Brønsted bases, see: b) Huang,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

In each case, the different tactics used have been mainly vinylogous additions, that have been thoroughly collected in several reviews.[157] Depicted in Table 12 are the diverse electrophiles employed to date for the additions of butenolides (entries 1– 2 and 8), and α-angelica lactone derivatives (entries 3– 7).

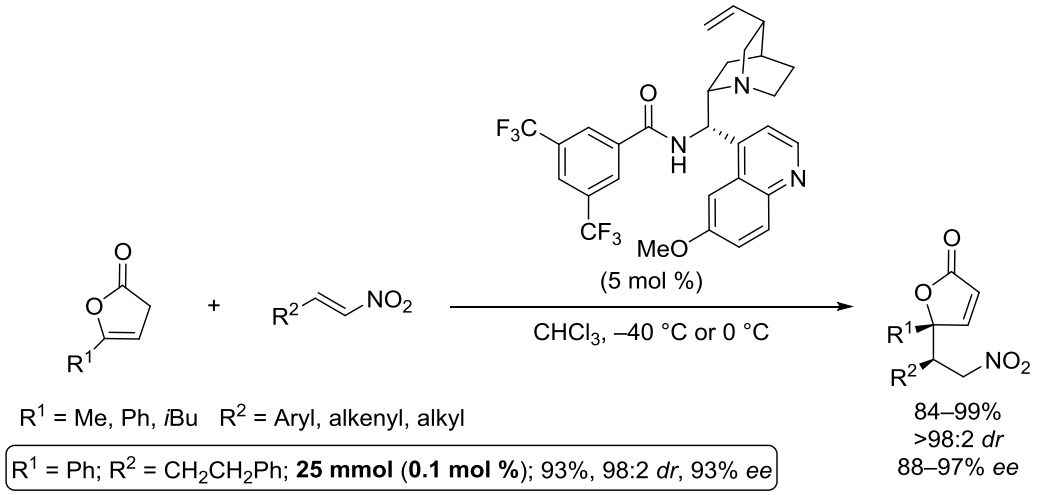
Table 12. Selected examples of vinylogous addition of butenolide equivalents to unsaturated bonds.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Aryl, Alkyl	 (10 mol %)	 R = Aryl, Alkyl	47– 78% 3:1– 20:1 *dr* 83– 96% *ee*	155a
2	 R = Aryl	 X = (3,4,5-(MeO)$_3$C$_6$H$_2$)$_2$CH (5 mol %)	 R1 = Cl, Br	58– 95% 85:15– 91:9 *dr* 96– 97% *ee*	155b
3	 EWG = CO_2Me, COMe X = H, Hal, F_3CO, Me	 (10 mol %)	 R^3 = Aryl, Me, Et	70– 91% >95:5 *dr* 70– 91% *ee*	156b
4	 R^1 = Aryl R^2 = H, Me, Cl	 Ar = 2,6-*i*Pr$_3$C$_6$H$_3$ (5 mol %)		58– 90% 86:14– 99:1 90– 98	156c
5	 R^1 = Alkyl, aryl, H R^2 = H, Me	 (15 mol %)	 R^3 = Me, Et	60– 95% 1:1– 8:1 *dr* 88– 96% *ee*	156d

[157] For a recent review on the synthesis of butenolides by direct vinylogous reactions, see: a) Yan, L.; Wu, X.; Liu, H.; Xie, L.; Jiang, Z. *Mini-Reviews Med. Chem.* **2013**, *13*, 845–853. For recent reviews on vinylogous reactions, see: b) ref. 122 page 26. For aminocatalytic remote functionalization strategies, see: c) Jiang et al. see ref. 12h page 7.

6		 (1 mol %)	 R = Aryl, Alkyl	71– 93% 16:1– 99:1 *dr* 90– 96% *ee*	156f
7	 R = Aryl, Me	 (1 mol %)	 R^1 = Aryl, Me	80– 96% 44:56– 82:18 *dr* 83– 97% *ee*	156h
8	 R^1 = Alkyl, aryl; R^2 = Alkyl	 $[Cu(CH_3CN)_4]PF_6$ (5 mol %)	 R^2 = H, Me	78– 98% 94– 99% *ee*	156k

One of the most recent examples, described by Hatanaka and co-workers in 2015,[158] described the benzamide-based bifunctional Brønsted base catalyzed vinylogous Michael addition of α-angelica lactones to nitroolefins, obtaining very good yields and excellent diastereo- and enantioselectivities (Scheme 35). A large scale reaction was performed, maintaining an excellent outcome even with very low catalyst loading.

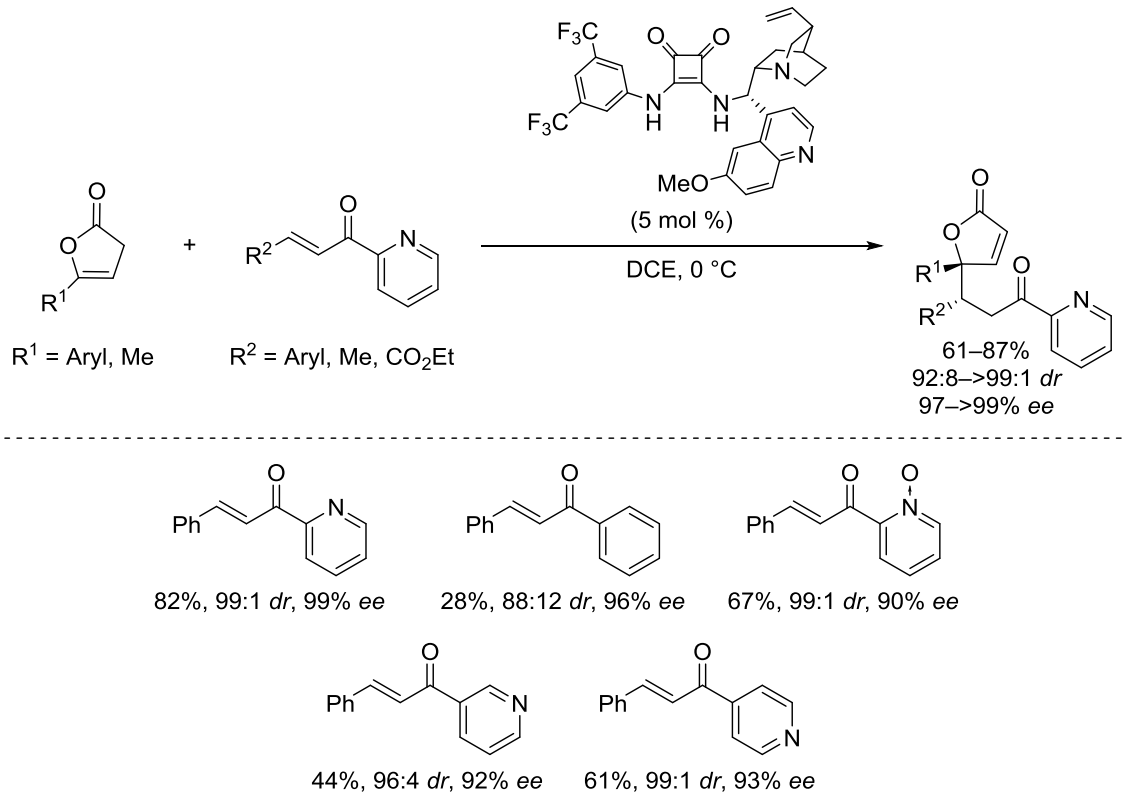


Scheme 35.

Another recent example concerns the Michael addition of deconjugated butenolides to 2-enoylpyridines reported by Xu and Yuan's research group.[159] The squaramide-based bifunctional Brønsted base catalyzed reaction occurred with good yield

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

and excellent stereocontrol, although the reaction between 5-methyl substituted pronucleophile and β-methyl enone did not proceed (R^1,R^2 = Me). The importance of the 2-pyridyl moiety was highlighted by performing several control experiments (Scheme 36).



Scheme 36.

1.2.4. **Thiolactone based pronucleophiles**

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

As already has been proved, heterocyclic compounds have received considerable attention from many research groups, due to their utility in biological chemistry. Among them, five-membered rings containing two heteroatoms are the ones which show more prevalence, including the thiazole ring, which is present in numerous pharmaceutically interesting compounds (Figure 19).[160]

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

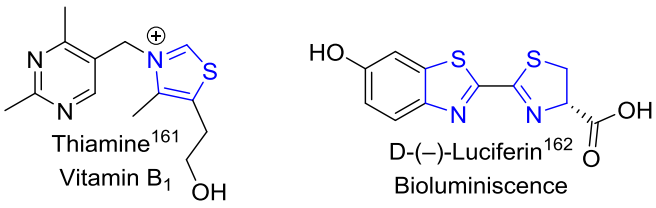
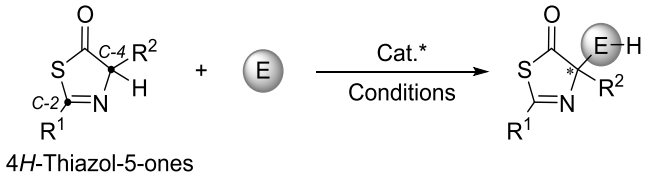


Figure 19. Selected examples of biologically meaningful thiazole derivatives.

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



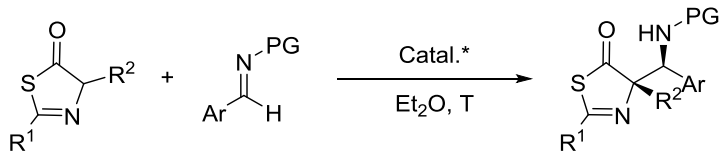
Scheme 37.

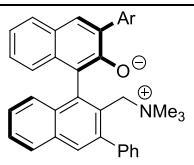
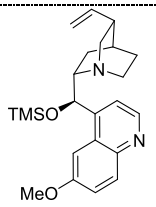
Taking into account the similarities between these compounds and azlactones (page 42), C-4/C-2 regioselectivity should also be an issue for them. For this reason, thiazolones with electron withdrawing moieties or hydrogen at C-2 are avoided in order to favour C-4 selectivity ($R^1 \neq$ EWG or H).

A case in point are the Mannich additions performed with *N*-Boc or *N*-Ts aryl imines by Ooi's and Wang's groups, employing a chiral ammonium betaine and a silylated quinine derivative, respectively, as catalysts. Depicted in Table 13 are the results obtained with more activated 4-aryl and 4-benzyl 2-benzyloxy 4*H*-thiazol-5-ones by the former (entry 1),[163] and with the less activated 4-alkyl 2-ethylthio 4*H*-thiazol-5-ones by the latter (entry 2).[164] In every case, yields and diastereoselectivities were from moderate to excellent, and enantioselectivity was very good or excellent.

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

Table 13. Organocatalytic Mannich reactions of 4*H*-thiazol-5-ones.

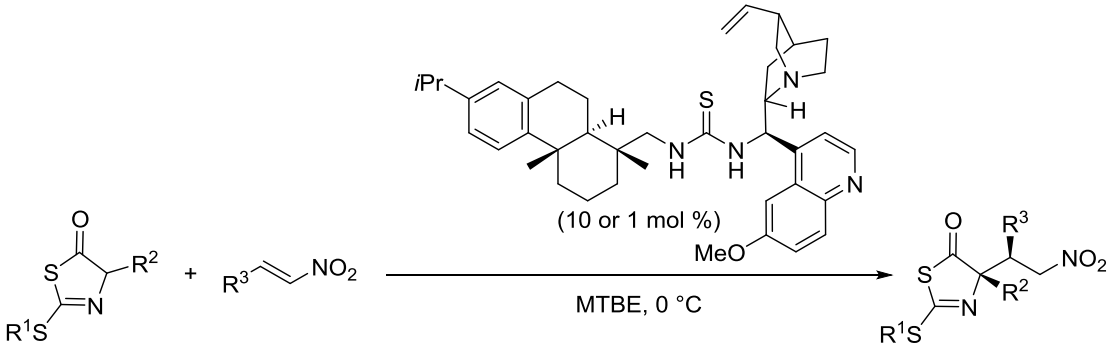


	R^1	R^2	PG	Cat.*	T (°C)	Results	Ref.
1	BnO	Ph, 4-ClC_6H_4, Bn	Boc	 Ar = *p*Tip-C_6H_4 Tip = 2,4,6-triisopropylphenyl	– 40	88– 97% 73:27– 94:6 *dr* 92– 99% *ee*	163
2	EtS	*i*Pr, *i*Bu	Ts		20	73– 94% 75:25– >98:2 *dr* 80– >99% *ee*	164

The first example of organocatalyzed 1,4-addition of 4*H*-thiazol-5-ones to nitroolefins, was developed by Wang and co-workers (Table 14).[165] The bifunctional thiourea-catalyzed reaction worked equally well with nitroalkenes bearing either electron enriched or deficient aryl substituents, but the methodology was not robust enough to achieve such results with β-alkyl substituted nitroalkenes (entry 4). Nitrodienes inverted the diastereoselectivity of the reaction, although moderate enantioselectivity was obtained for the major diastereomer (entry 5). Finally, it was demonstrated that changing R^1 from Et to Bn did not affect the outcome of the reaction much (entries 8– 9).

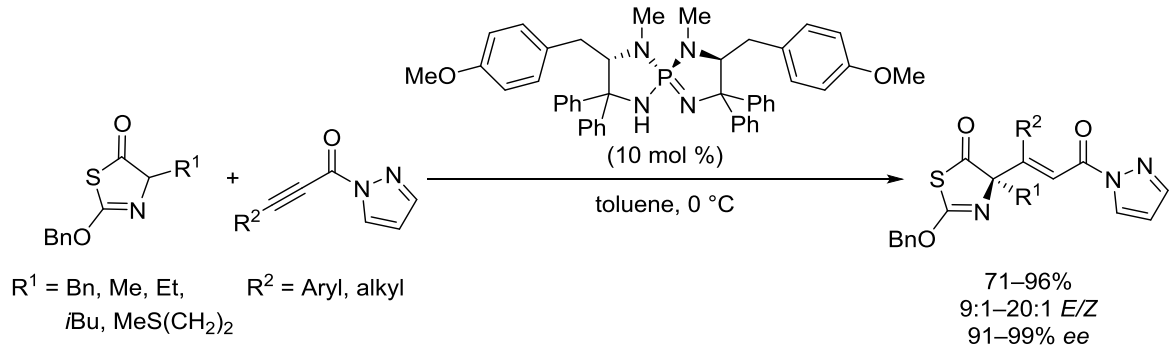
[165] Liu, X.; Song, H.; Chen, Q.; Li, W.; Yin, W.; Kai, M.; Wang, R. *Eur. J. Org. Chem.* **2012**, *5*, 6647–6655.

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



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

On another note, very recently, Ooi and co-workers reported a Michael addition of thiazolones to electron deficient alkynes under chiral iminophosphorane catalysis.[166] The reaction occurred with high *E*-selectivity and enantioselectivity in every case (Scheme 38).



Scheme 38.

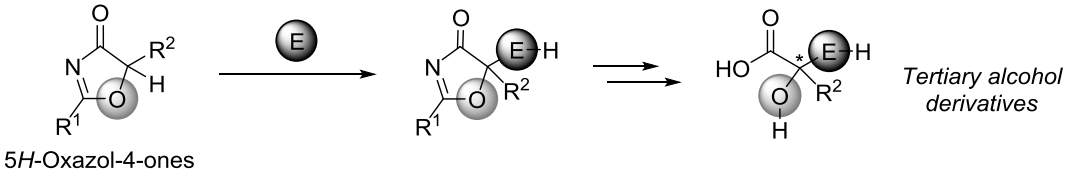
To date, no other electrophile (e.g. aldehydes, azodicarboxylates, etc.) has been employed for the reaction with 4*H*-thiazol-5-ones.

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

1.3. **Working hypothesis and objectives**

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

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



Scheme 39.

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

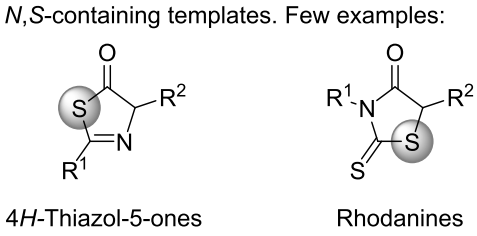
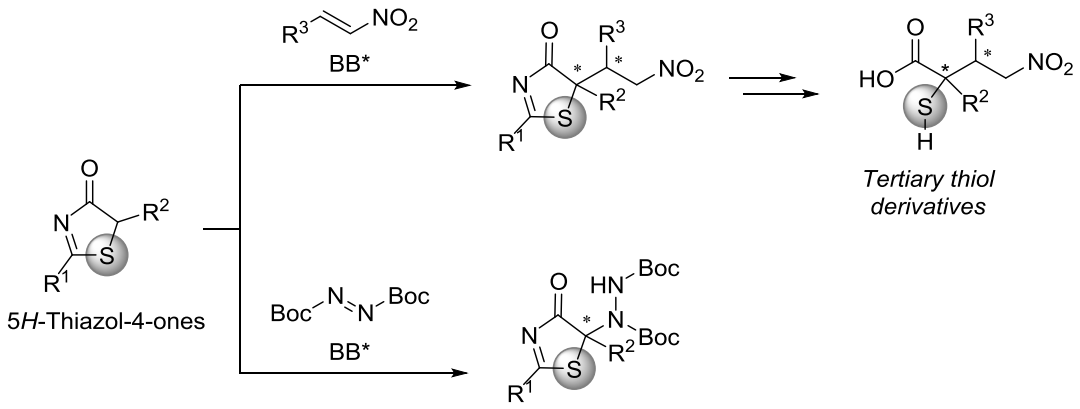


Figure 20.

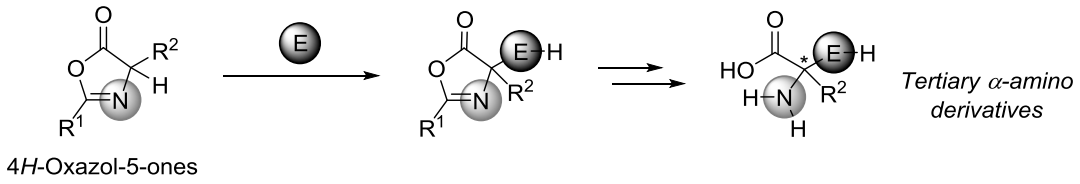
Thus, the first objective of this work would be to synthesize 5*H*-thiazol-4-ones (as sulfur equivalents of 5*H*-oxazol-4-ones) for the first time and to test them as

pronucleophiles for the addition to Michael acceptors employing bifunctional Brønsted bases, leading to α,α-dialkyl α-thiocarboxylic acid derivatives (Scheme 40).



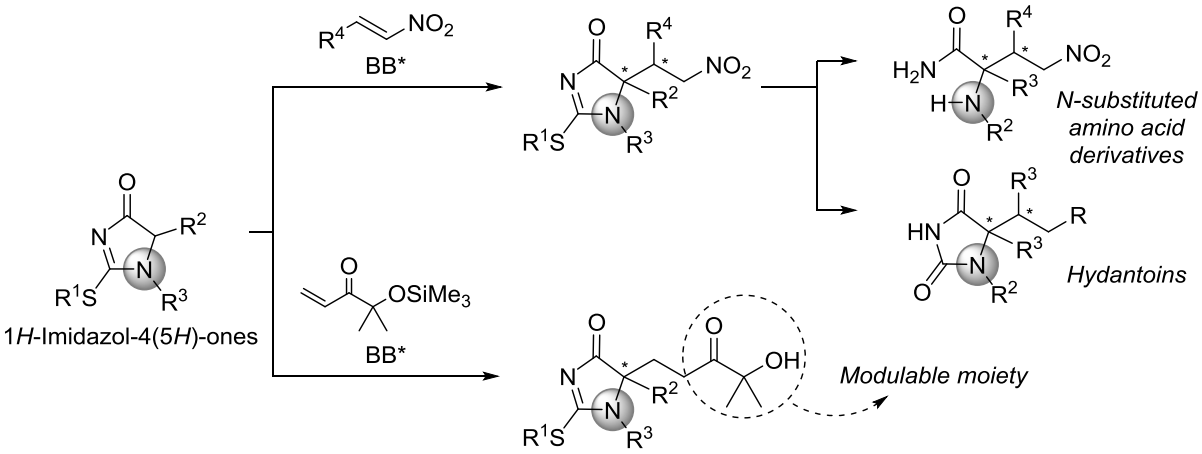
Scheme 40.

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



Scheme 41.

Moved by this idea, the second goal of this work would be the synthesis of 2-alkylthio 1*H*-imidazol-4(5*H*)-ones, as synthetic equivalents of hydantoins, and to test them as effective pronucleophiles for the Michael addition to different electrophiles, including α'-oxy enones, whose utility was first recognized by our group. It is noteworthy, that using these templates *N*-substituted quaternary amino acid derivatives would be obtained, instead of unsubstituted ones as with 4*H*-oxazol-5-ones (Scheme 42).


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

Scheme 42.

Chapter 2

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

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

2.1. Introduction

As it has been already explained in the previous chapter, tertiary thiols are in a wide range of biologically active compounds. Thus, this structural motif has been employed widely for therapeutical and synthetic purposes. However, the synthesis of such compounds in an enantiopure manner has been little explored, as compared with the secondary thiol.[167]

The main strategies for the synthesis of tertiary thiols can be divided in two groups: (i) methods based on *C–S* bond formation, and (ii) methods based on *C–C* bond formation (Figure 21).

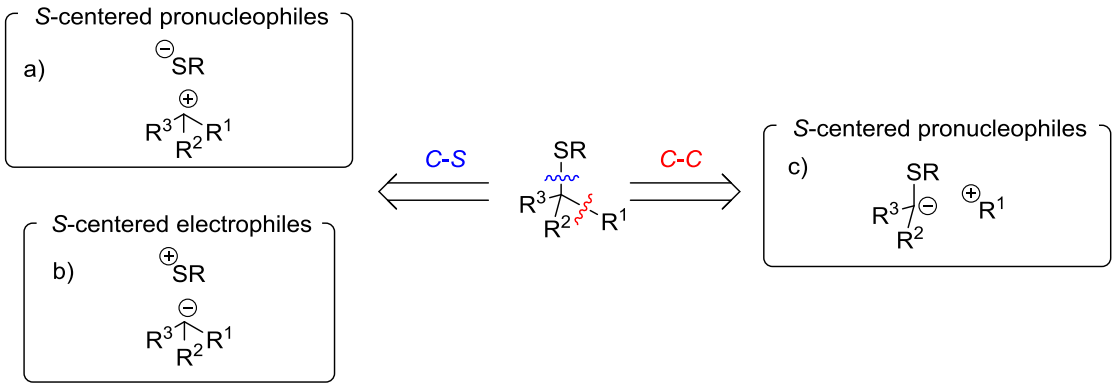


Figure 21. Strategies for the asymmetric synthesis of tertiary thiols.

2.1.1. Synthesis of tertiary thiols through *C–S* bond formation

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

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

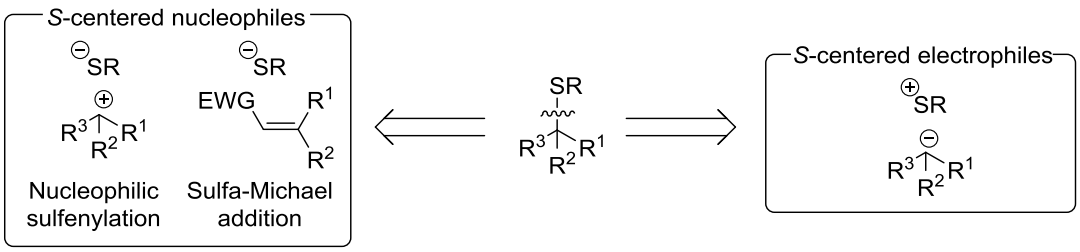
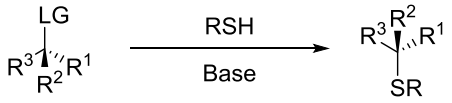


Figure 22. Strategies for the asymmetric synthesis of tertiary thiols through *C–S* bond formation.

2.1.1.1. **Nucleophilic sulfenylation**

This strategy is based in most cases on the employment of optically pure tertiary alcohols, which, after proper transformation into a leaving group (LG), undergo a S_N2 displacement from a nucleophilic sulfur reagent (Scheme 43). This displacement process is not free of complication because of the steric constraint of the electrophilic carbon. The first example of such methodology was described by Effenberger's group in 1999, and the mesyl was employed as a leaving group.[168] Subsequently, sulfonates have been commonly chosen for this task.[169]



Scheme 43.

Other tactics for the activation of the OH as leaving group include the use of phosphinites by Mukaiyama and co-workers,[170] the Mitsunobu reaction by La Clair's research group.[171] In addition, the stereocontrolled ring opening of epoxides described by

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

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

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

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

Rodríguez and co-workers,[172] and the S_N2 displacement of chiral tertiary chlorides by Shibatomi and Jacobsen are other approaches to the synthesis of tertiary *C–S* systems.[173]

One important aspect of all these methods is that enantiopure tertiary alcohols are required. Therefore, their synthesis would be the actual problem, and the only requirement for the displacement reaction is to be stereospecific.[174]

2.1.1.2. **Sulfa-Michael addition**

Michael addition of sulfur-centered nucleophiles to *gem*-disubstituted electron deficient alkenes is another way to produce chiral tertiary thiol derivatives. This approach has to face some problems, mainly the low reactivity of the sterically congested acceptor, the difficulties in controlling π-facial selectivity, and reaction reversibility that can led to equilibration of the stereisomers through an addition/elimination mechanism.

In this context, our research group described a unique intramolecular formal sulfa-Michael addition to β-monosubstituted and β,β-disubstituted *N*-enoyl oxazolidin-2-thiones (Table 15). In this transformation, the chiral auxiliary (i.e. oxazolidin-2-thione) acts as both, intramolecular sulfur donor reagent and stereodirecting group. The reaction may be promoted by either Lewis acids (LA) (entries 1 and 2),[175] or Brønsted acid (entry 3)[176] and is believed to occur through the intermediate depicted in Table 15.

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

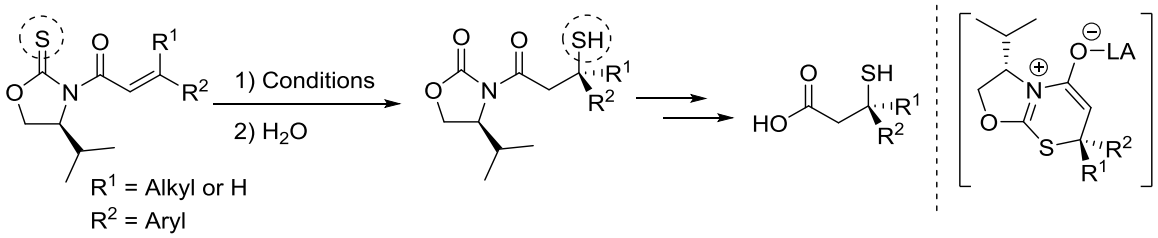
[173] a) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836–9839. b) Liu, R. Y.; Wasa, M.; Jacobsen, E. N. *Tetrahedron Lett.* **2015**, *56*, 3428–3430.

[174] For a recent example of the Brønsted acid catalyzed asymmetric formation of a tertiary thiol from an achiral tertiary alcohol, see: Suć, J.; Dokli, I.; Gredičak, M. *Chem. Commun.* **2016**, *52*, 2071–2074.

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

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

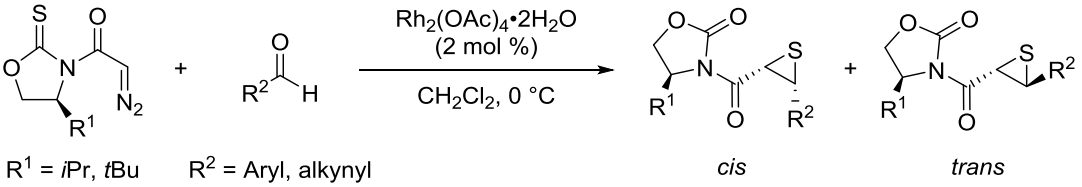
Table 15. Intramolecular formal sulfa-Michael reactions reported by our research group.



Entry	R^1	R^2	LA or BA	Results	Ref.
1	H	Me, Et, *i*Pr, Aryl	$SnCl_4$ (2 equiv.)	70– 80% 75:25– 98:2 *dr*	175a
2	Me, Et, *n*Bu	Aryl	$BF_3{\cdot}Et_2O$ (2 equiv.)	65– 83% 52:48– 99:1 *dr*	175b
3	Me, *n*Bu	Aryl	TFA (2 equiv.)	59– 83% 33:67– 1:99 *dr*	176

More recently, our group came up with an additional application of this methodology to obtain thioepoxides.[177] The rhodium catalyzed reaction between *N*-(diazoacetyl)oxazolidin-2-thiones and aldehydes to afford the corresponding α,β-thiiranes occurred with moderate yields and good to excellent diastereoselectivities (Table 16).

Table 16. Thioepoxide formation through intramolecular sulfur rearrangement.

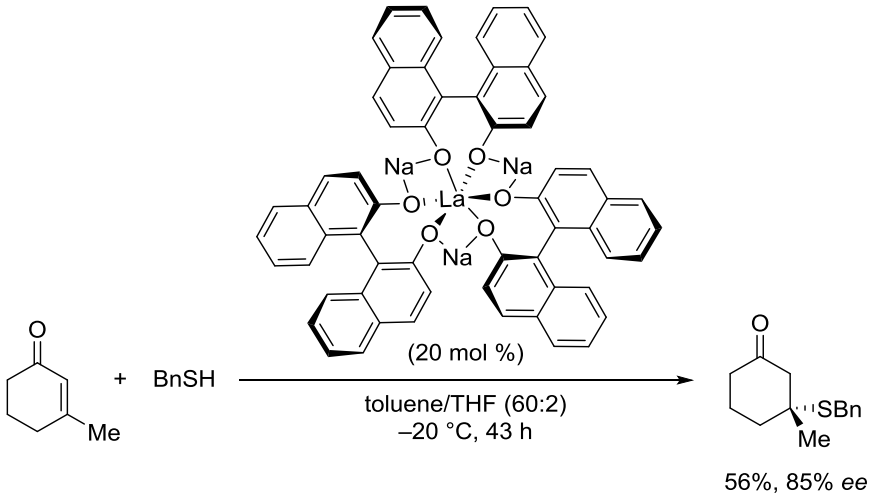


Entry	R^1	R^2	Yield (%)	*cis/trans*
1	*i*Pr	Ph	65	93:7
2	*i*Pr	4-MeC_6H_4	60	82:18
3	*i*Pr	4-$MeOC_6H_4$	61	1:99
4	*i*Pr	PhC≡C	65	72:28
5	*t*Bu	PhC≡C	75	83:17
6	*i*Pr	3-furyl	n.d.	62:38
7	*t*Bu	3-furyl	70	83:17
8	*i*Pr	3-pyridyl	NR	-

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

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

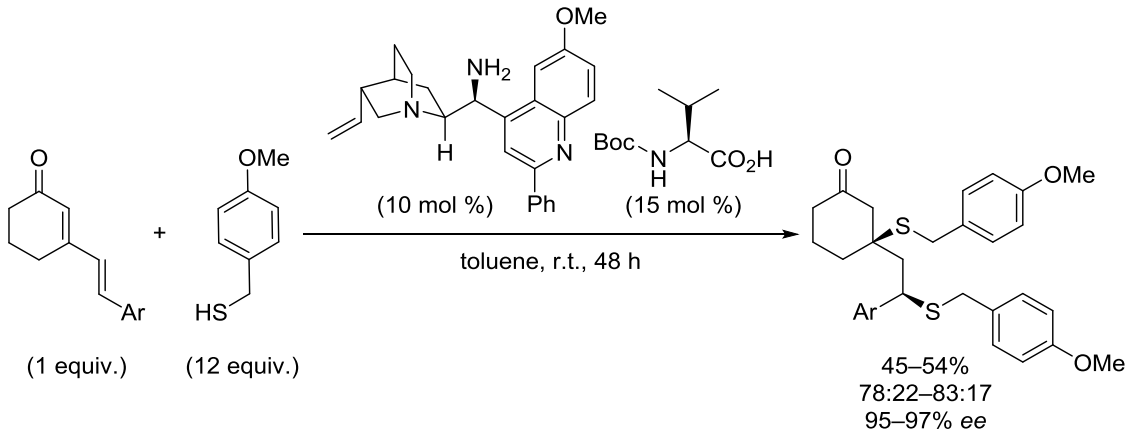
research group in the late 1990's, which was the first catalytic enantioselective formation of a tertiary thiol derivative reported.[178] The method consisted in the conjugate addition of benzyl thiol to cyclic enones, catalyzed by heterobimetallic complexes which are believed to work as bifunctional Lewis acid/Brønsted base catalysts. In some cases, particularly the addition to 3-methylcyclohex-2-en-1-one, yield was moderate and enantioselectivity was not excellent (Scheme 44).



Scheme 44.

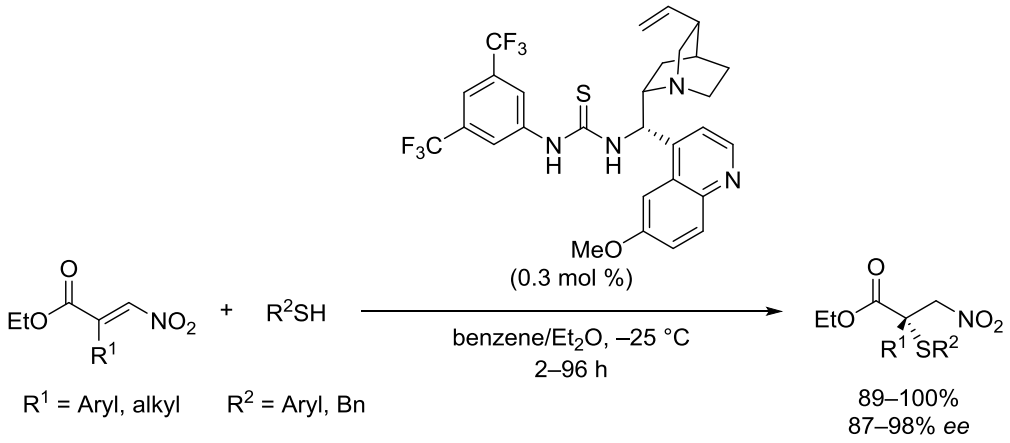
In another development, Melchiorre and co-workers described the sulfa-Michael addition of benzylic thiols to cyclic enones using a vinylogous iminium ion activation strategy.[179] Despite their initial idea of executing only a 1,6-addition on the dienone (which was achieved with excellent stereocontrol), they realized that employing a great excess of the thiol enabled them to perfom a further 1,4-addition, accessing tertiary thioethers in moderate yield, good diastereoselectivity and excellent enantioselectivity for the major diastereomer (Scheme 45).

[178] a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043–4044. For an application of this methodology to perform a catalytic kinetic resolution, see: b) Emori, E.; Iida, T.; Shibasaki, M. *J. Org. Chem.* **1999**, *64*, 5318–5320.
[179] Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 6439–6442.



Scheme 45.

Using a different approach, based on the concurrent activation of the donor and the acceptor reagents by a difunctional Brønsted base organocatalyst, Xiao and co-workers described an outstanding example of this sulfenylation strategy in 2009.[180] Their research focused on the organocatalyzed addition of various thiols to β,β-disubstituted nitroalkenes bearing an electron withdrawing group (i.e. ethoxy carbonyl), in order to overcome the usual lack of reactivity of the *gem*-substituted nitroalkenes. A thiourea-based bifunctional Brønsted base was found to be the most appropriate catalyst, rendering excellent yields and enantioselectivities, even with extremely low catalytic loadings (Scheme 46).



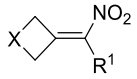
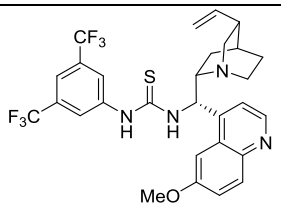
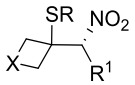
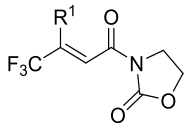
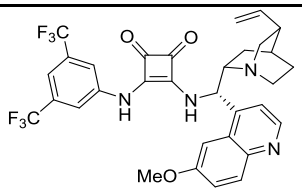
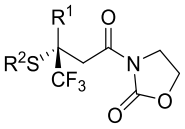
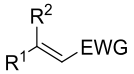
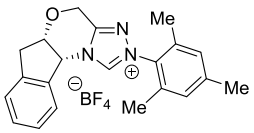
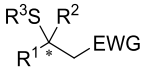
Scheme 46.

It is remarkable that between 2009 and 2014 essentially no examples of enantioselective sulfa-Michael addition were reported.[181] Only recently, three more approaches for the sulfa-Michael addition to β,β-disubstituted Michael acceptors have

[180] Lu, H.-H.; Zhang, F.-G.; Meng, X.-G.; Duan, S.-W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 3946–3949.
[181] For a racemic sulfa-Michael addition to β,β-disubstituted nitroolefins, see: a) Xu, C.; Xu, J. *Amino Acids* **2011**, *41*, 195–203. For a diastereoselective sulfa-Michael addition to nitroolefins leading to secondary thiols, see: b) Chen, N.; Xu, J. *Tetrahedron* **2012**, *68*, 2513–2522.

appeared. However, as Table 17 illustrates, these approaches require highly activated electrophiles, which is usually restricted to few electron deficient alkenes. [182] These usually involve alkenes bearing two electron withdrawing substituens or, as in entry 1, alkenes geminally bounded to a strained 4-membered ring.

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

	Electrophile	Cat.*	Product	Results	Ref.
1	 R^1 = Me, Et, *i*Pr, Bn X = O, NBoc	 (5 mol %)	 R = Ac, COPh	72– 96% 86– 96% *ee*	182a
2	 R^1 = Aryl, alkyl	 (10 mol %)	 R^2 = Alkyl, Bn	80– 9% 93– 99% *ee*	182b
3	 R^1 = CF_3, H R^2 = Aryl, alkyl EWG = NO_2, ketone	 (10 mol %)	 R^3 = Alkyl, Bn	56– 99% 70– 98% *ee*	182c

2.1.1.3. **Electrophilic sulfenylation**

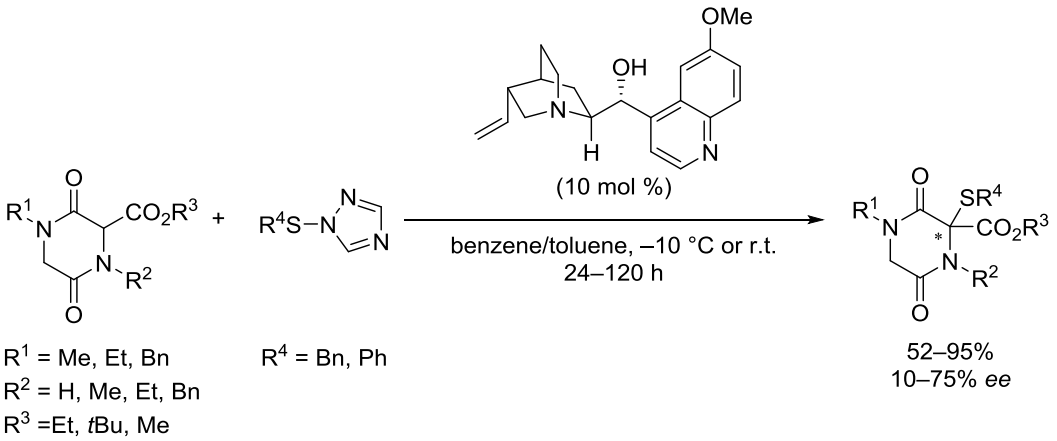
Asymmetric electrophilic α-sulfenylation of carbonyl compounds via organocatalysis has been widely investigated, particularly for the synthesis of secondary thiols.[183,167b] Asymmetric synthesis of tertiary thiols,[167a] has been accomplished by using

[182] For the catalytic addition of thioacids to trisubstituted nitroolefins, see: a) Phelan, J. P.; Patel, E. J.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 11329–11332. For recent examples of sulfa-Michael additions to CF_3-bearing conjugate olefins, see: b) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292–1300. c) Chen, J.; Meng, S.; Wang, L.; Tang, H.; Huang, Y. *Chem. Sci.* **2015**, *6*, 4184–4189.

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

chiral auxiliaries[184] and metal catalysis[185] mainly, and more recently, by using Brønsted base catalysis as well.

The first organocatalyzed electrophilic carbonyl α-sulfenylation involved α-substituted β-dicarbonyl compounds as pronucleophiles and secondary or tertiary amines as catalysts.[186] This strategy includes the first organocatalyzed α-sulfenylation performed on 5-alkoxycarbonyl diketopiperazinones using sulfanyl triazoles as the source of electrophilic sulfur, as reported by Olenyuk in 2009 (Scheme 47).[130a]



Scheme 47.

In 2012, three groups almost simultaneously described the first examples using oxindoles as pronucleophiles (Table 18). Feng and co-workers presented a Sc(III) catalyzed sulfenylation of *N*-H oxindoles with *N*-(phenylthio) phthalimide (entry 1).[187] Enders and co-workers used a squaramide based bifunctional Brønsted base for similar reactions employing *N*-Boc oxindoles (entry 2),[188] and Cheng's group used quinidine (entry 3).[189] The obtained adducts presented *S* configuration in the three cases. Later, sulfenylated adducts with opposite configuration were obtained by Maruoka, employing a

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

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

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

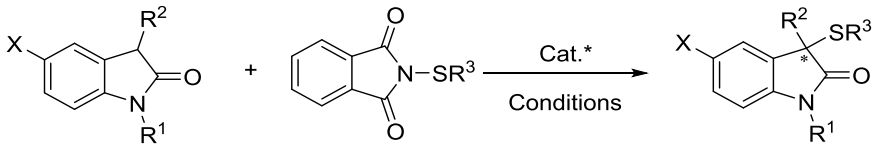
[187] Cai, Y.; Li, J.; Chen, W.; Xie, M.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2012**, *14*, 2726–2729.

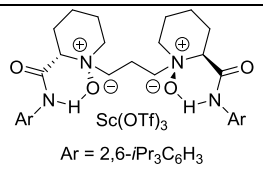
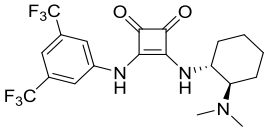
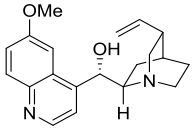
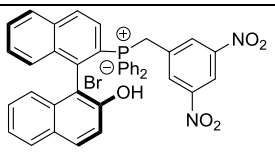
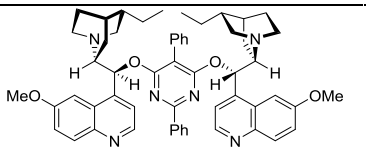
[188] Wang, C.; Yang, X.; Loh, C. C. J.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2012**, *18*, 11531–11535.

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

phosphonium salt as phase-transfer catalyst (entry 4),[190] and by Rueping, using $(DHQD)_2PYR$ as catalyst (entry 5).[191]

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



	R^1	R^2	R^3	Cat.*	Conditions	Results	Ref.
1	H	Alkyl, Aryl	Ph	 Ar = 2,6-*i*Pr$_3$C$_6$H$_3$ (5 mol %)	4Å MS CH_2Cl_2 35 °C	82– 98% 87– 99% *ee* (*S*)	187
2	Boc	Alkyl, Aryl	Aryl, Bn	 (5 mol %)	CH_3Cl r.t. or 50 °C	86– 98% 85– 96% *ee* (*S*)	188
3	Boc	Alkyl, Aryl	Aryl	 (10 mol %)	CH_2Cl_2, – 78 °C	83– 99% 72– 99% *ee* (*S*)	189
4	Boc	*p*Tol	3-FC_6H_4	 (1 mol %)	H_2O/*o*-xylene 0 °C	93% 61– 80% *ee* (*R*)	190
5	Boc	Aryl	CF_3	 (10 mol %)	THF 0 or – 30 °C	50– 96% 82– 96% *ee* (*R*)	191a

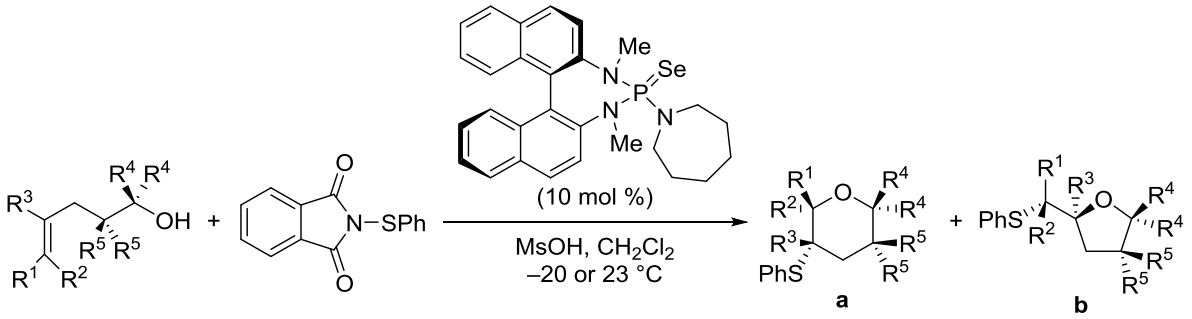
In 2011, Denmark and co-workers developed an original oxysulfenylation of unactivated double bonds leading to α-sulfenylated cyclic ethers (Table 19).[185] The reaction was catalyzed by a BINAM-based selenophosphoramide in the presence of Brønsted acid and using *N*-thio phthalimide as electrophilic sulfur source. Yields, and,

[190] Shirakawa et al. see ref. 74d page 23.

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

especially, selectivities, were highly substrate dependant. Then, this strategy was adapted to perform carbosulfenylations.[192]

Table 19. Representative results of the phosphoramide-catalyzed oxysulfenylation of double bonds.

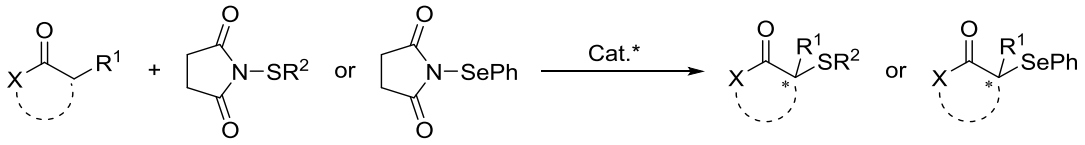


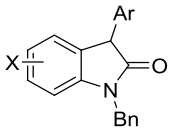
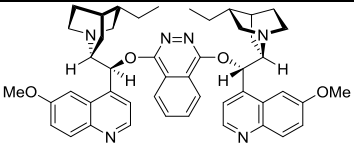
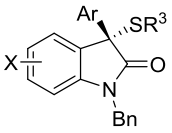
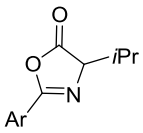
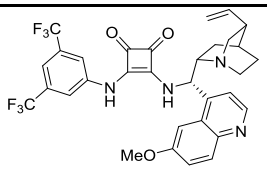
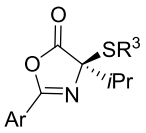
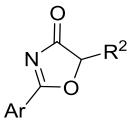
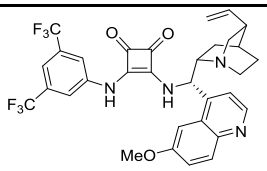
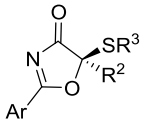
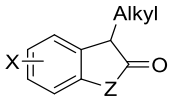
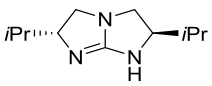
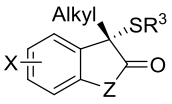
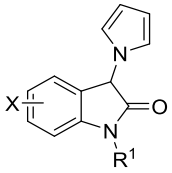
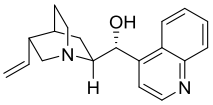
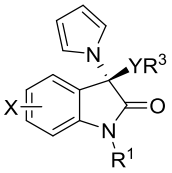
Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	a/b	*ee* (%)
1	Ph	H	H	H	H	80	49:1	82
2	Ph	H	H	H	Me	94	19:1	84
3	Ph	H	H	Me	H	84	13:1	84
4	H	H	Ph	H	H	85	1:99	24
5	H	H	H	H	H	72	1:50	66
6	Ph	H	Me	H	H	24	18:1	20
7	Ph	Me	H	H	H	82	17:1	40

In 2012 and the subsequent years, the group of Jiang reported the α-sulfenylation of several carbonyl pronucleophiles, i.e. *N*-Bn 3-aryl oxindoles (Table 20, entry 1),[193] azlactones (entry 2),[194] 5*H*-oxazol-4-ones (entry 3)[195] and benzofuranones (entry 4),[196] using as catalyst mono- and bifunctional Brønsted bases. Using same strategy, very recently Yuan and co-workers reported the first α-selenylation of oxindoles (entry 5).[197]

[192] a) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419–6422. b) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140–171.
[193] Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670–4673.
[194] Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672–675.
[195] Xu et al. see ref. 87 page 26.
[196] Huang et al. see ref. 135f page 40.
[197] a) You, Y.; Wu, Z.-J.; Wang, Z.-H.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 8470–8477. For another recent example of catalytic asymmetric sulfenylation of structurally diverse dithioketals employin *N*-thio succinimides, see: b) Liao, K.; Zhou, F.; Yu, J.-S.; Gao, W.-M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255–16258.

Table 20. α-Sulfenylation(selenylation) of heterocycles with *N*-heteroatom succinimides.



	Substrate	SR^2/SePh	Cat.*	Product	Results	Ref.
1		SAryl SAlkyl	 (5– 10 mol %)		68– 98% 85– 95% *ee*	193
2		SAlkyl SAryl	 (5 mol %)		43– 94% 40– 93% *ee*	194
3		SAlkyl SAryl	 (10 mol %)		51– 97% 64– 94% *ee*	195
4	 Z = O, NMe	SAlkyl	 (10– 20 mol %)	 Z = O, NMe	65– 99% 86– 98% *ee*	196
5		SAryl SePh	 (10 mol %)		72– 98% 50– 99% *ee*	197

As a corollary, it is clear that electrophilic sulfenylation has been the most widely employed strategy for the catalytic asymmetric construction of *C–S* bonds. Usually this strategy requires relatively acidic carbonyl pronucleophiles.

2.1.2. **Synthesis of tertiary thiols through *C–C* bond formation**

Tertiary thiol derivatives can be prepared stereoselectively by the asymmetric construction of a *C–C* bond adjacent to sulfur by employing sulfur-containing nucleophiles (Figure 23a). To the best of our knowledge, the complementary approach using *S*-containing electrophiles remains unexplored as yet (Figure 23b).[198] Pioneering examples corresponding to approach a) based on the utilization of enantiopure starting materials will be discussed in this section, as well as more recent examples based on asymmetric catalysis.

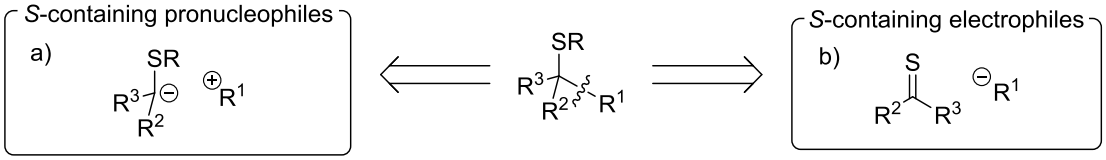


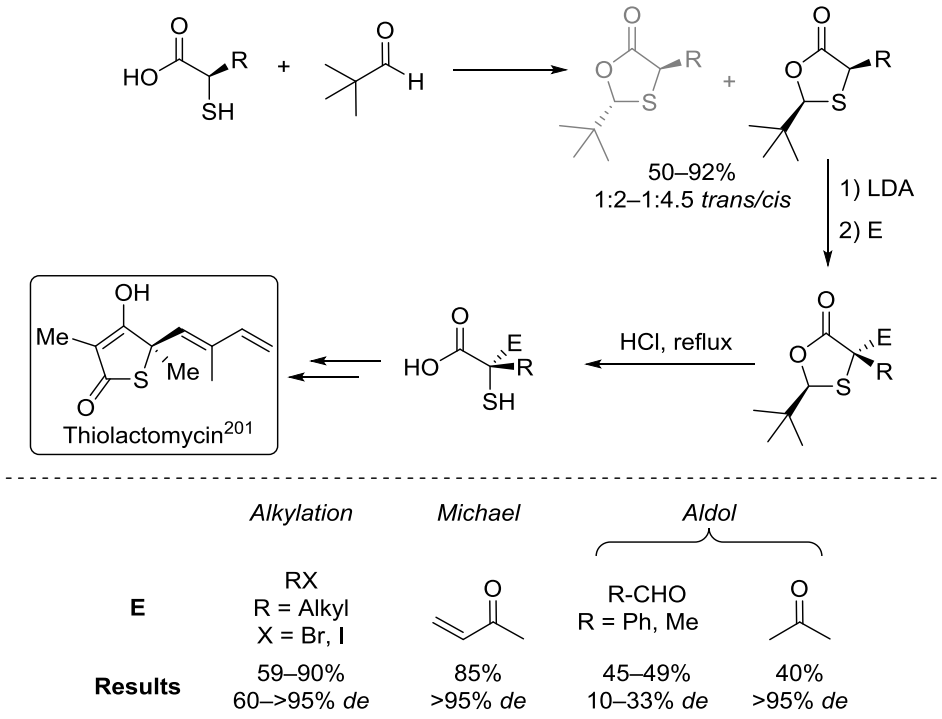
Figure 23.

2.1.2.1. **Stoichiometric asymmetric reactions**

The first asymmetric synthesis of a tertiary thiol using this approach came from the hand of Kellogg and co-workers in 1987,[199] and is based on the self-reproduction of chirality method developed by Seebach in 1984.[200] The route starts by reacting an enantiopure α-mercapto acid with pivalaldehyde to obtain a *cis*/*trans* mixture of 1,3-oxathiolan-4-ones (Scheme 48). After separation, the major diastereomer was employed to form an enolate, which then reacted with different electrophiles. The electrophile approaches the intermediate enolate through the face opposite to *tert*-butyl group. Different electrophiles can be used, leading to various reaction types, such as alkylation, Michael addition and aldol reaction. Very good to excellent yields and diastereoselectivities were achieved in alkylations and Michael reactions, while aldol reaction showed moderate yields and very poor diastereoselectivity when aldehydes were employed. Acetone, however, rendered excellent diastereoselectivity. Acidic hydrolysis of the adducts produced the desired enantioenriched tertiary thiols. The synthesis of

[198] Thioaldehydes and many thioketones are very reactive towards dimer, trimer or oligomer formation, and often need to be generated *in situ*. For an asymmetric organocatalytic thio-Diels-Alder reaction via trienamine catalysis, see: a) Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200–5207. For the Cu-catalyzed thio-Diels-Alder reaction between dithioesters and 2,3-dimethyl-1,3-butadiene, see: b) Dentel, H.; Chataigner, I.; Le Cavelier, F.; Gulea, M. *Tetrahedron Lett.* **2010**, *51*, 6014–6017.
[199] Strijtveen, B.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 5039–5054.
[200] Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.

thiolactomycin, starting from (2*S*)-thiolactic acid, illustrates the utility of this methodology.[201]

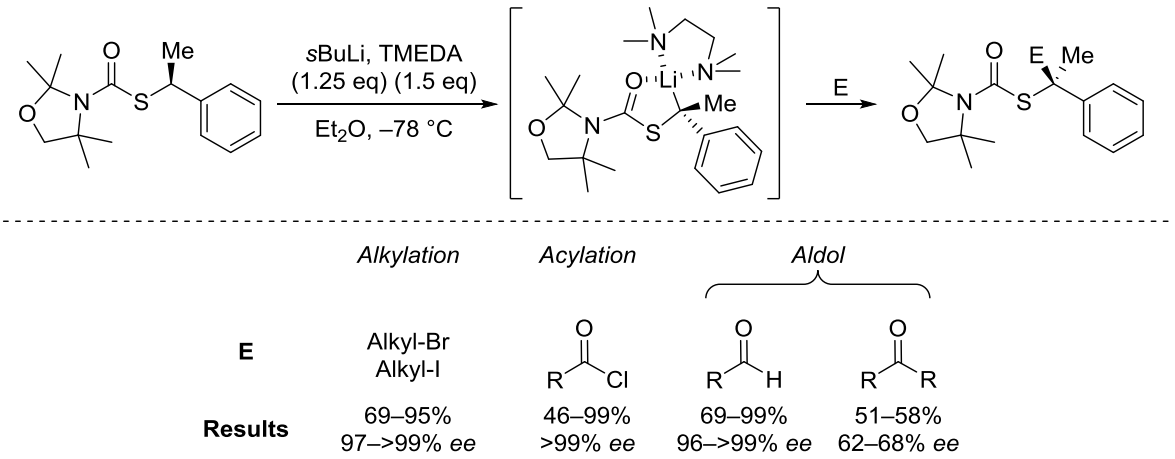


Scheme 48.

The asymmetric synthesis of tertiary thiol derivatives through an enantioselective *C–C* bond formation remained unexplored until 1997. In this year Hoppe and co-workers described the stereospecific reactions of enantiopure benzylic thiocarbamates with several electrophilic reagents via trapping of configurationally stable lithiated intermediate.[202] The corresponding adducts were formed in high yields and stereoselectivity, except for ketones, and the reaction proceeded with retention/inversion of configuration (Scheme 49).

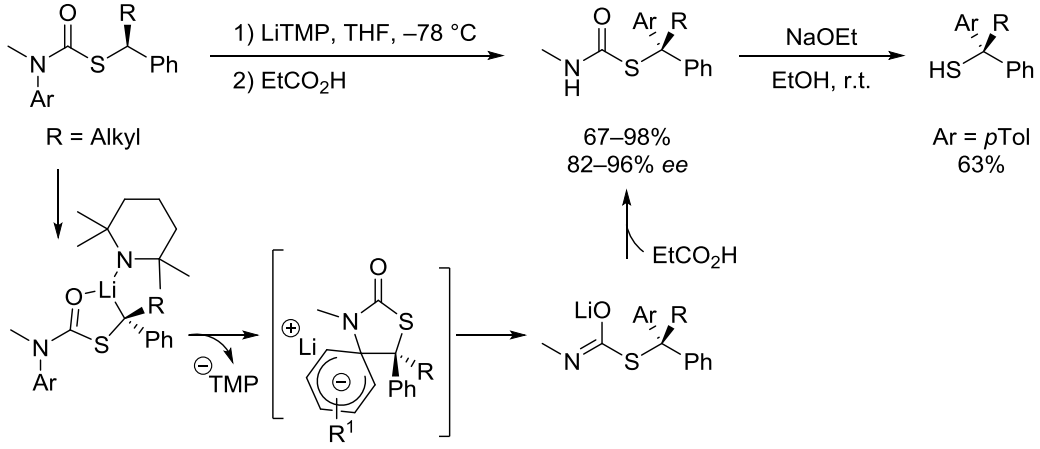
[201] McFadden, J. M.; Frehywot, G. L.; Townsend, C. A. *Org. Lett.* **2002**, *4*, 3859–3862.

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



Scheme 49.

A similar, but intramolecular, stereospecific lithium anion trapping was reported by Clayden's research group in 2011 as an efficient protocol to access tertiary thiols.[203] The intramolecular migration of the *N*-aryl moiety from *N* to *C* proceeded with retention of configuration, which enabled the access to enantioenriched tertiary thiols by ulterior treatment of the obtained adducts with sodium ethoxide at room temperature (Scheme 50).



Scheme 50.

2.1.2.2. **Catalytic asymmetric reactions**

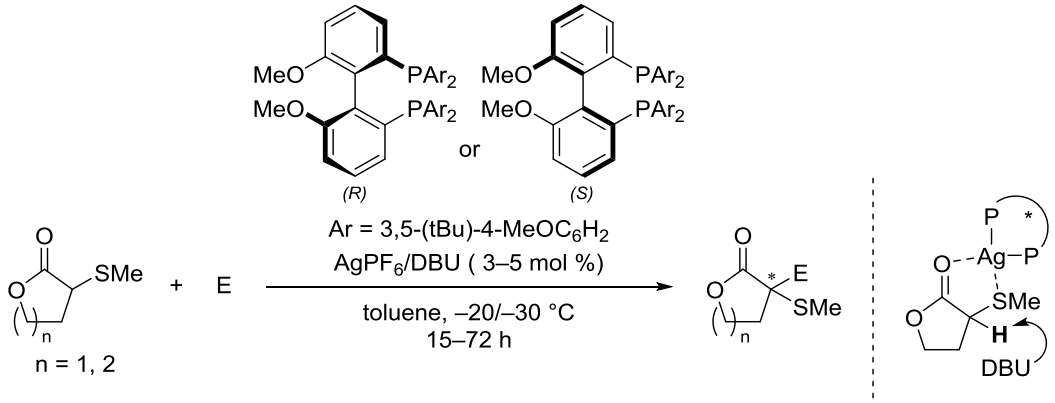
The asymmetric synthesis of tertiary thiols through the catalyst-controlled formation of *C–C* bonds, has been introduced more recently. In this section the most relevant examples described in literature will be discussed according to the nature of the pronucleophiles employed.

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

2.1.2.2.1. Nucleophilic addition reactions with S-containing C-pronucleophiles

The first example of catalytic asymmetric tertiary thiol derivative formation using a sulfur-bearing pronucleophile was developed by Shibasaki and co-workers in 2012 (Table 21). Thus, Ag-catalyzed aldol and Mannich type reactions of α-sulfanyl lactones took place employing a biphep-type ligand and in the presence of 3–5 mol % of DBU, with moderate to excellent yield, and excellent stereocontrol.[204] The success of the methodology was explained by the authors as a result of a cooperative catalytic system: silver would coordinate to both C=O, enabling an easier deprotonation of the lactone with DBU, even in presence of highly enolizable aldehydes or *N*-Boc-aldimines.

Table 21. Ag-catalyzed aldol and Mannich reaction of sulfanyl lactones.



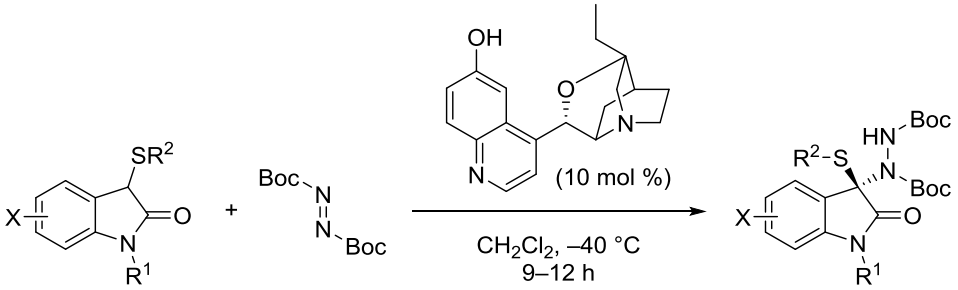
Entry	E	Ligand	Product	Results	Ref.
1	R = Alkyl	(*R*)		50– 93% 90:10– 95:5 *dr* 96– 99% *ee*	204a
2	R = Aryl, alkyl	(*S*)		42– 94% 86:14– 95:5 *dr* 82– 99% *ee*	204b

Soon later, Zhou's research group described the Brønsted base-catalyzed α-amination of 3-thiooxindoles with di-*tert*-butyl azodicarboxylate.[205] Good to excellent yields and stereocontrol were achieved in the formation of the 3,3-heterodisubstituted oxindole adducts when reactions started from arylthioethers (R^2 = Ar, Table 22).

[204] For the addition to aliphatic aldehydes, see: a) Takechi, S.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4218–4222. For the addition to *N*-Boc-aldimines, see: b) Takechi, S.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 2632–2635.

[205] a) Zhou, F.; Zeng, X.-P.; Wang, C.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 2022–2024. For a recent example of the sulfenylation of this structures, see: ref. 197b page 9

Table 22. Electrophilic α-amination of 3-thiooxindoles catalyzed by a Brønsted base.

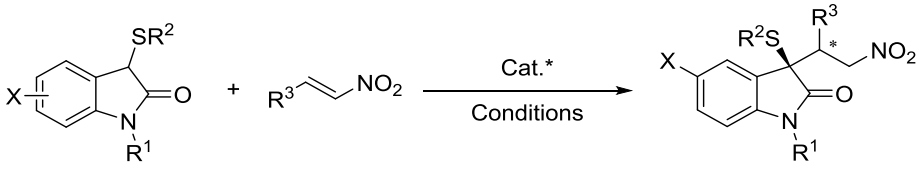


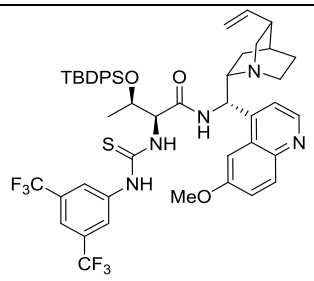
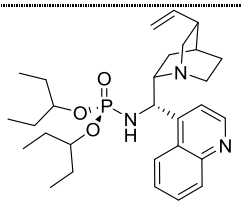
Entry	X	R^1	R^2	Yield (%)	*ee* (%)
1	H, Hal, Me, Et, MeO	H	2-Naphthyl	68– 98	83– 94
2	H	Me	2-Naphthyl	96	82
3	H	Bn	2-Naphthyl	92	79
4	H	H	Ph	97	90
5	H	H	Bn	88	56
6	H	H	Allyl	82	47

In another variation, also using 3-thiooxindoles as *C*-(pro)nucleophiles, the groups of Lu and Zhou, respectively, reported the bifunctional BB-catalyzed conjugate addition to nitroolefins. While Lu used a thiourea as *H*-bond donor, affording very good to excellent yield and stereocontrol (Table 23, entry 1),[206] Zhou and co-workers employed a phosphoramide as *H*-bond donor unit, which also rendered excellent enantioselectivity and yields, but more modest diastereoselectivity in some instances (entry 2).[207] In both cases, a beneficial effect of molecular sieves on the stereocontrol was observed.

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

Table 23. Bifunctional Brønsted base-catalyzed addition of 3-thiooxindoles to nitroolefins.



Entry	Cat.*	Conditions	Results	Ref.
1	 (1 mol %)	4Å MS toluene, r.t.	81– 99% 85:15– 95:5 *dr* 79– 99% *ee* (*R*)	206
2	 (1– 5 mol %)	5Å MS Et_2O, – 20 °C	80– 99% 80:20– 89:11 *dr* 91– 98% *ee* (*S*)	207

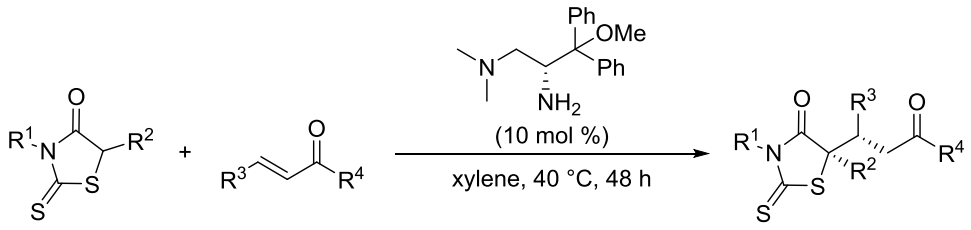
2.1.2.2.2. Heterocyclic C-(pro)nucleophiles with an inner S atom

As mentioned in Introduction (page 36), rhodanines are easy to prepare, stable compounds that can be conveniently activated by treatment with BB catalysts to react with the corresponding electrophile.

Recently, Ye and co-workers introduced the first organocatalyzed Michael addition of rhodanines to β-substituted enones (Table 24).[208] The catalyst of choice was a bulky chiral tertiary/primary diamine, designed to effect concurrent substrate activation (iminium ion activation of the enone and deprotonation of the rhodanine). The reactions required heating and elongated times to proceed, but diastereo- and enantioselectivity were excellent with conjugated enones (entries 1– 7). Branched substituent in C-5 of rhodanine (entry 8) and β-aliphatic enones (entries 9– 10) rendered lower yields and enantioselectivities, although still acceptable. Authors did not describe examples involving rhodanines with an aryl substituent at C-5 (R^2 = Ar).

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

Table 24. Representative results of the Michael reaction of rhodanines with enones by Ye et al.

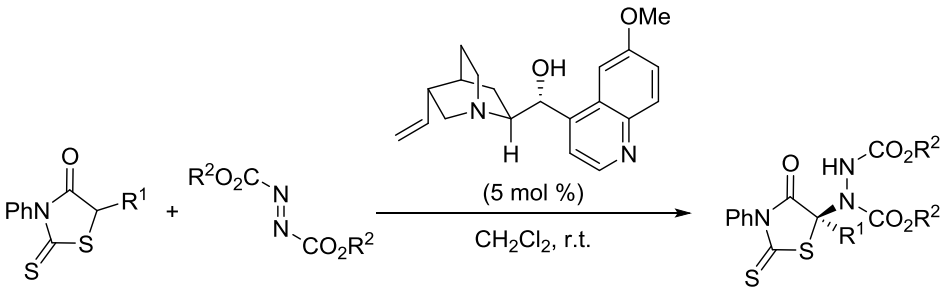


Entry	R^1	R^2	R^3	R^4	Yield (%)	*dr*	*ee* (%)
1	Ph	Me	Ph	Me	95	99:1	96
2	Ph	Me	(*E*)-PhCH=CH	Me	83	93:7	96
3	*i*Pr	Me	Ph	Me	97	99:1	90
4	Bn	Me	Ph	Me	94	98:2	95
5	4-$MeOC_6H_4$	Me	Ph	Me	98	99:1	96
6	Ph	Me	Ph	*i*Pr	82	99:1	95
7	Ph	Et	Ph	Me	91	98:2	97
8	Ph	*i*Pr	Ph	Me	68	93:7	71
9	Ph	Me	Me	Me	64	95:5	80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

Rhodanines have also been studied as C-(pro)nucleophiles in organocatalyzed α-amination reactions. Thus, Wang in 2014 reported the quinine-catalyzed reaction of 5-substituted rhodanines with diethyl azodicarboxylate (DEAD) (Table 25).[209] The addition proceeded with excellent yield in every case, although an increase in time can be noticed with hindered and less activated substrates (entries 4– 7) Regarding electrophile reactivity, while diisopropyl azodicarboxylate (DIAD) afforded a product with essentially the same *ee* (entry 8), a dramatic decrease in enantiomeric excess was observed when di-*tert*-butyl azodicarboxylate (DBAD) was used (entry 9).

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

Table 25. Representative results of α-amination of rhodanines by Wang et al.



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

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

As far as we know, catalytic asymmetric reactions of rhodanines with electrophiles other than enones or diazocompounds have not been reported.

As conclusion for this section, there are several examples of asymmetric synthesis of tertiary thiols or derivatives through *C–C* bond formation. However, this approach has been developed to a lesser extent than others. Additionally, the obtained adducts are in most cases thioethers, whose deprotection to free thiol is not trivial. Therefore, the development of new strategies for this purpose is highly sought after.

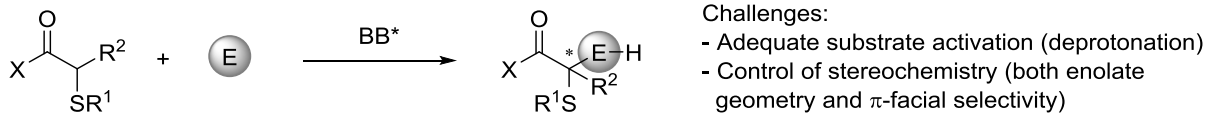
2.2. **Michael addition of 5*H*-thiazol-4-ones to nitroolefins**

2.2.1. **Working hypothesis and synthetic plan**

As mentioned above, there are few methodologies for the catalytic enantioselective synthesis of tertiary thiol derivatives, probably due to the inherent difficulty associated to the asymmetric construction of quaternary stereocentres (page 15). Connected to the previous efforts of our research group directed towards the stereoselective synthesis of organosulfur compounds, such as β,β-disubstituted β-mercaptocarboxylic acids (ref. 175 and 176a page 63) and thiiranes (ref. 177 page 64), our attention focused on the catalytic asymmetric synthesis of α,α-disubstituted α-mecaptocarboxylic acids.

Taking into account the previous strategies employed for the synthesis of tertiary thiols, the possible disconnections to access these compounds involve a *C–S* or a *C–C* bond formation. Within the possibilities concerning a *C–S* bond construction, nucleophilic sulfenylation is readily discounted, since it is limited to enantiopure electrophilic substrates. Another alternative would consist in a sulfa-Michael addition to a β,β-disubstituted Michael acceptor, which presents several drawbacks, due to the low reactivity of the acceptors and the potential equilibration of stereoisomers through an addition/elimination mechanism, as it has been mentioned in previous sections. Finally, an electrophilic sulfenylation is also feasible, but this approach has already been much explored, and reactions are far from the goal of atom-economy since an important mass-fragment of the electrophilic sulfur reagent is lost.

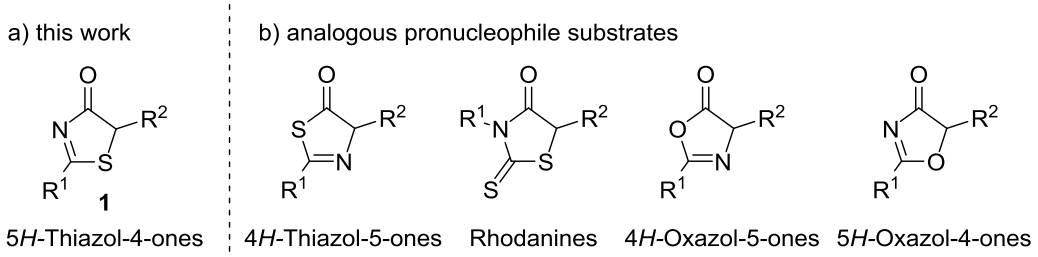
On the other hand, concerning the asymmetric formation of *C–C* bonds, out of the two complementart approaches, namely the reaction of S-containing C-nucleophile with an electrophile, and the addition reaction of a nucleophile to a thioketone, this latter approach seems umpractical due to the inherent constrains already discussed in the introduction of this chapter (ref. 198 page 72). With this in mind, our investigation was concentrated on the tactic depicted in Scheme 51, that is the development of an organocatalytic reaction of sulfur-containing (pro)nucleophiles with appropriate electrophiles using a chiral Brønsted base as catalyst.



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

At this point, there were three main challenges. First, the selection of the appropriate *S*-containing substrates to take part in the reaction; second, to find the adequate catalysts and conditions for appropriate substrate activation (deprotonation); and third, the control of the reaction stereochemistry, which implies control of both enolate geometry and its facial seelctivity, in order to achieve configurational uniformity in the produced adducts.

Because of some inherent properties (see below) we selected 5*H*-thiazol-4-ones **1** (Scheme 52a) as good potential candidates for being employed as *S*-containing pronucleophiles. This sulfur-containing heterocycle had never been used as a pronucleophile, unlike the closely related 4*H*-thiazol-5-ones, rhodanines, and also structurally related 5*H*-oxazol-4-ones and 4*H*-oxazol-5-ones (azlactones) (Scheme 52b).



Scheme 52.

An interesting aspect of this *S*-heterocycle was reported in 2011 by Weiß, Beckert and Fabian's group,[210] who demonstrated that in solution these compounds exist in equilibrium between two tautomeric forms with the particularity that the enolic form fulfils the criteria of aromaticity (Figure 24).

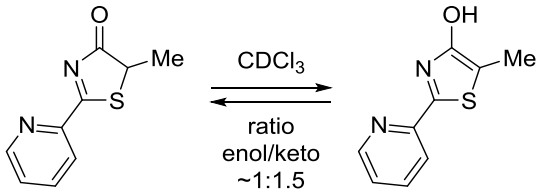
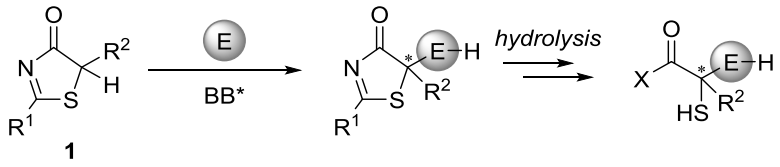


Figure 24. Tautomeric forms of 5*H*-thiazol-4-ones in solution.

In addition, the cyclic nature of the enol/evolving enolate guarantees its configurational integrity, also facilitating the addition process. Finally, hydrolysis of the resulting adduct would provide access to α,α-disubstituted α-mercaptocarboxylic acids with a free thiol moiety (Scheme 53), unlike most of known protocols which give access

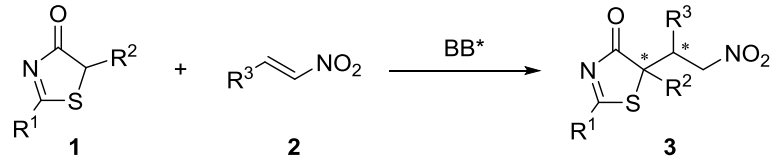
[210] Täuscher, E.; Weiß, D.; Beckert, R.; Fabian, J.; Assumpção, A.; Görls, H. *Tetrahedron Lett.* **2011**, *52*, 2292–2294.

to thioethers, requiring an additional, and not so trivial, step. Another feature is that the substituent R^1 could be modified, thus helping for the best substrate tunning.



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

On this basis, 5*H*-thiazol-4-ones were chosen as pronucleophiles, and in a first instance nitroolefins were chosen as electrophiles, in part due to their high reactivity and also because they are prone towards *H*-bond activation.[211] This Michael acceptor added a diastereoselectivity issue to the previous challenges, due to the formation of two contiguous stereocentres during the reaction (Scheme 54). Obviously, for the most general cases (R3 ≠ H), control of the relative configuration of the newly generated contiguous stereocentres would be an additional issue.



Scheme 54. Proposed reaction for the first investigation.

2.2.2. **Results and discussion**

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

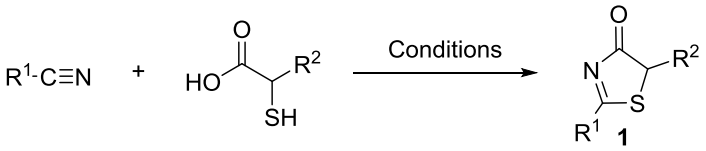
First, the synthesis of the *S*-containing substrates was addressed. Following a reported procedure[212] thiazolones were prepared by treatment of α-monosubstituted α-mercaptocarboxylic acids with the corresponding aromatic nitrile (Table 26). Thiazolones bearing an R^2 substituent different from Me, were prepared employing a different experimental procedure.[213]

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

[212] Grummt, U.-W.; Weiss, D.; Birckner, E.; Beckert, R. *J. Phys. Chem. A* **2007**, *111*, 1104–1110.

[213] a) Barzen, S.; Rödl, C. B.; Lill, A.; Steinhilber, D.; Stark, H.; Hofmann, B. *Bioorg. Med. Chem.* **2012**, *20*, 3575–3583. Not every α-mercaptocarboxylic acid was commercially available, but they could be readily

Table 26. Synthesis of 5*H*-thiazol-4-ones.



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

Entry		R^1	R^2	Procedure	Yield (%)
1	**1a**	2-pyridyl	Me	A	73
2	**1b**	2-quinolinyl	Me	A	91
3	**1c**	2-quinolinyl	Et	B	87
4	**1d**	2-quinolinyl	*n*Hex	B	85
5	**1e**	2-quinolinyl	Bn	B	78
6	**1f**	1-isoquinolinyl	Me	A	62
7	**1g**	3-isoquinolinyl	Me	A	73
8	**1h**	2-naphthyl	Me	A	50

Thus, this synthetic strategy allowed us rapid access to a variety of 5*H*-thiazol-4-ones. Once with the substrates of the initially proposed reaction in hand, and regarding the strong catalyst-substrate dependence of Brønsted base-catalyzed direct asymmetric *C–C* bond forming reactions, catalyst design was thought to be the best strategy to address our goal.

2.2.2.2. **Catalyst design**

The 3,5-bis(trifluoromethyl)phenyl group attached to *N* in most of (thio)urea-based bifunctional Brønsted bases, is a key structural motif to modulate de *H*-bond donor capability of the (thio)urea since it was first introduced by Schreiner and Wittkopp in 2002.[214] Later, Zhong[215] and Schreiner,[216] as a result of an exhaustive study based on NMR- and IR- spectroscopy, mass-spectrometry and DFT calculations, suggested that the success of this family of catalysts may be a consequence of the participation of three contiguous *H*-bond donors. Thus, both *N-H* bonds of the (thio)urea moiety and the aromatic ortho *C-H* bond of the aforementioned aryl group, would participate in the activation of the electrophile (Figure 25).[217]

prepared from the corresponding α-bromocarboxylic acid trough a nucleophilic S_N2 sulfenylation with potassium thioacetate. For more information see Experimental Section.

[214] a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187–1198. c) M. Kotice & P. R. Schreiner, *Hydrogen Bonding in Organic Synthesis* (P. M. Pihko ed., Wiley-VCH) 2009. pages 141– 351.

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

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

[217] For a review on recent advances in asymmetric organocatalysis mediated by multiple hydrogen-bonding donors, see: Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185–1197.

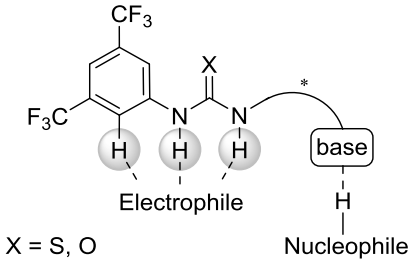


Figure 25. Previous known designs.

On the other hand, synthetic peptides have demonstrated over the last years their efficacy for the fine-tuning of reactivity and selectivity of several significant synthetic transformations.[218] In this context, ureidopeptides (Figure 26), which are peptidomimetics where an amide bond has been replaced by a urea moiety, have been fully recognized for their ability to develop hydrogen bonds.[219] On this basis, our research group considered that the replacement of the α-amino acid *C*-terminus of the ureidopeptide by a chiral Brønsted base should provide a new family of bifunctional catalysts, with several modulable sites for the fine-tuning of the catalyst's properties. Thus, the Brønsted base, the stereodirecting group of the aminal moiety, and the protecting group on *N*-terminus would be prompt to modification (Figure 26). The new *N*,*N*'-diacyl aminal unit and the urea moiety would provide three contiguous hydrogen bond donors in close proximity to a stereodirecting group, unlike the 3,5-bis(trifluoromethyl)phenyl group-bearing catalysts, increasing the number of coordination patterns with the substrates and controlling their spatial conformation.

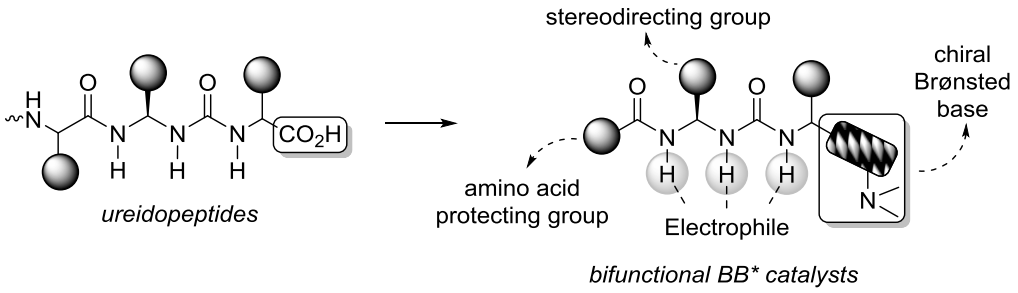
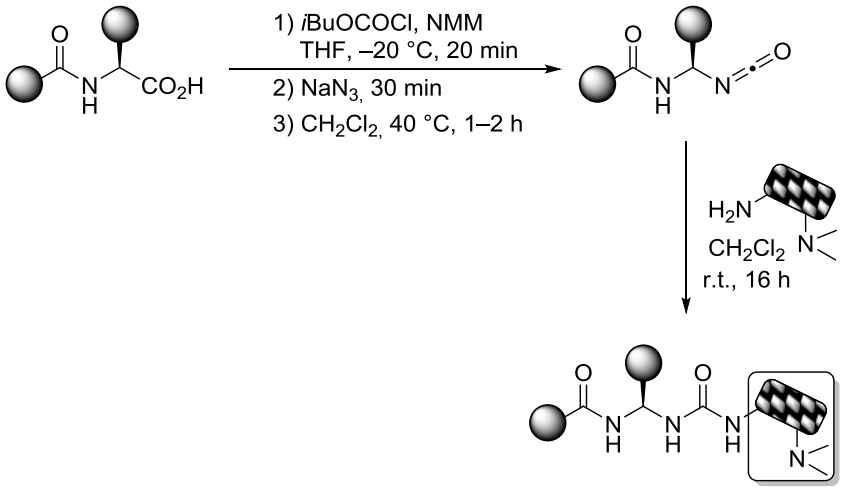


Figure 26. New design for ureidopeptide-based Brønsted bases.

[218] For asymmetric catalysis mediated by peptides, see: a) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036–12041. b) Davie, E. a C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. c) Fanelli Roberto & Piarulli Umberto, *Oligopeptides as Modular Organocatalytic Scaffolds* (P. I. Dalko ed., Wiley-VCH Verlag GmbH & Co. KGaA) 2013.

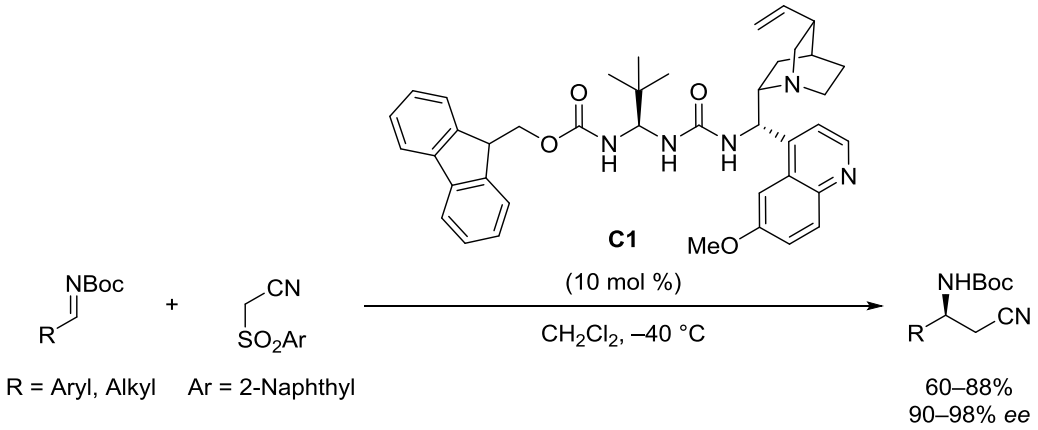
[219] a) Sureshbabu, V. V; Patil, B. S.; Venkataramanarao, R. *J. Org. Chem.* **2006**, *71*, 7697–7705. b) Myers, A. C.; Kowalski, J. A.; Lipton, M. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219–5222. c) Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G.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

So, as part of a more general research project, our group focused on this new catalyst design with the aim of checking the efficiency of these new catalysts in different transformations. The proposed general synthetic sequence for these catalysts is outlined in Scheme 55, and involves carbamate protection of the amino acid, followed by Curtius rearrangement and coupling of the resulting isocyanate with the primary amino group of the corresponding Brønsted base.



Scheme 55. Ureidopeptide-based bifunctional Brønsted base catalyst preparation.

The first synthesis and subsequent optimization of these catalysts was developed by Diosdado from our research group in another context,[220] who found that catalysts bearing the *tert*-butyl moiety were the most efficient (Scheme 56).

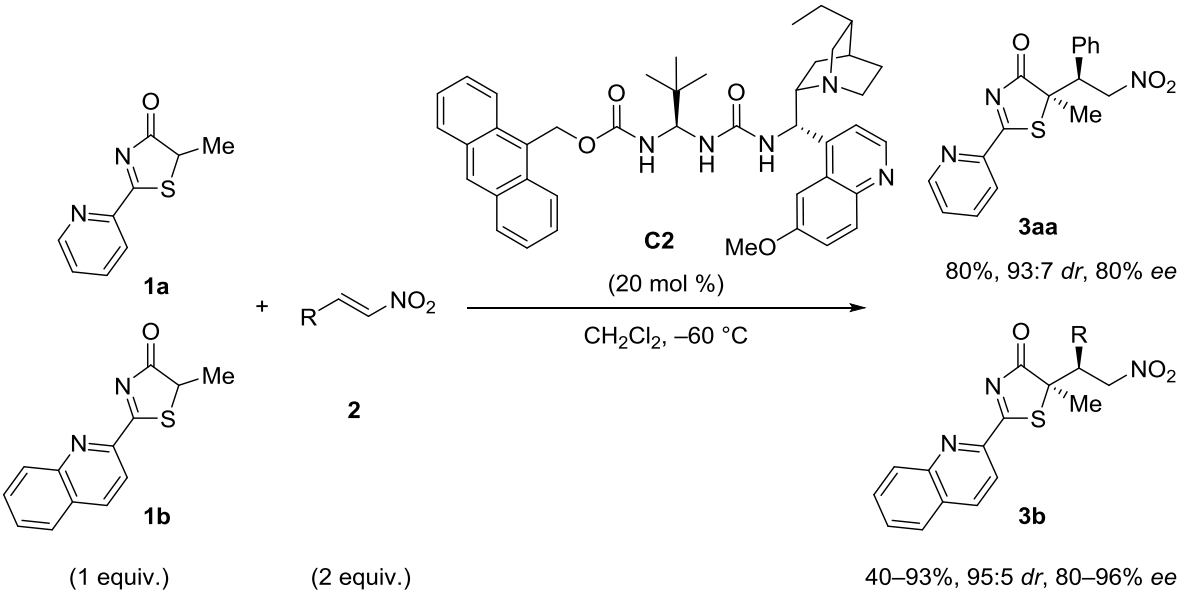


Scheme 56.

Olaizola during her PhD work,[221] synthesized several catalysts of this family and tested them in the reaction of 5-methyl-2-pyridyl thiazol-4(5*H*)-one **1a** and 5-methyl-2-

[220] Diosdado, S.; López, R.; Palomo, C. *Chem. Eur. J.* **2014**, *20*, 6526–6531.
[221] Yurre Olaizola, PhD. Dissertation, UPV/EHU, 2015. http://www.ehu.eus/es/web/gicas/tesiak

quinolinyl thiazol-4(5*H*)-one **1b** and nitroolefins. This study revealed that the latter produced the best results and that increasing the aromaticity of the protecting group of the aminal moiety induced a greater stereocontrol over the reaction. Thus, she found, as illustrated in Scheme 57, that the addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **1b** to nitroalkenes **2** (2 equiv.) in presence of catalyst **C2** (20 mol %) at − 60 °C in dichloromethane provided product **3** with excellent results independently of the R substituent.



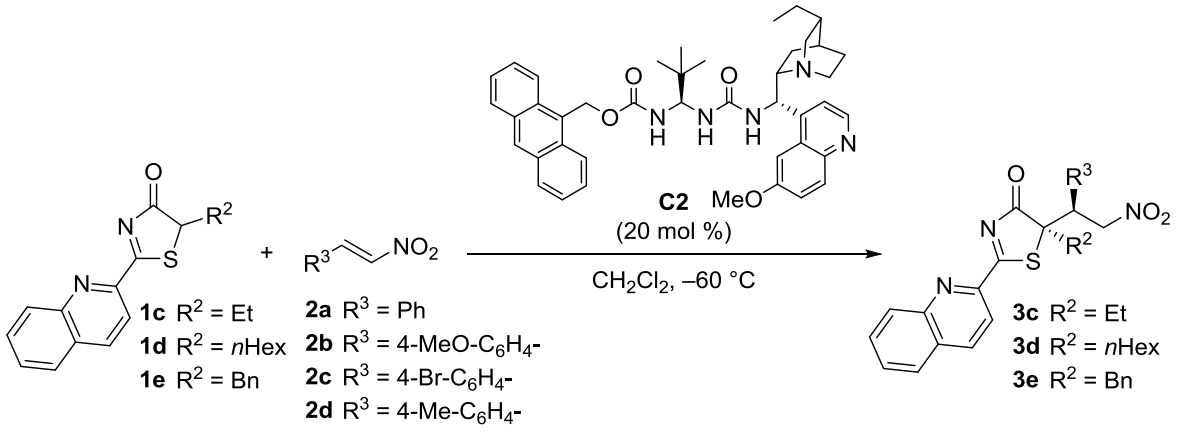
Scheme 57. Optimal conditions for the Michael addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **1b** to nitroolefins **2**.

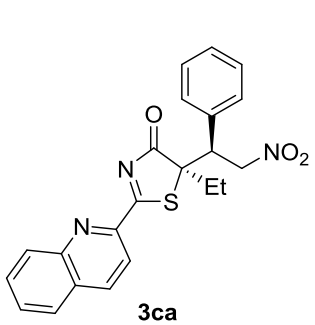
2.2.2.3. **Reaction scope**

Given the observations noted above, we then focused on the scope of the reaction with the aim of evaluating the generality of this asymmetric route respect to the thiazolone component.[222] In order to investigate the generality of the reaction regarding the substituent at C-5 of the thiazolone, thiazolones **1c– e** were synthesized and tested (Table 27). Employing the same reaction conditions previously mentioned (i.e. 20 mol % of catalyst **C2** loading in dichloromethane at − 60 °C), successful Michael addition of 5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **1c** to nitroolefins **2a**–**d** was achieved. Furthermore, excellent diastereo- and stereoselectivities were obtained, probably due to the greater steric hindrance generated by the 5-alkyl group with respect to the 5-methyl moiety in **1b**. The bulkiness of these larger substituents in C-5 did not affect the reactivity of thiazolones, rendering very good to excellent yield in every case.

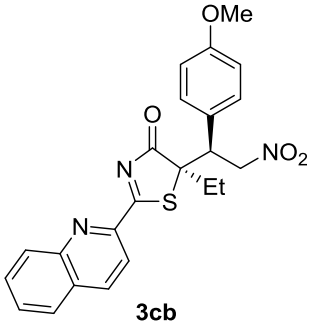
[222] a) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851. b) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Synfacts* **2013**, *9*, 1346–1346.

Table 27. Scope of 2-(quinolin-2-yl)thiazol-4(5*H*)-ones **1c– e** for the conjugate addition to nitroolefins **2**.

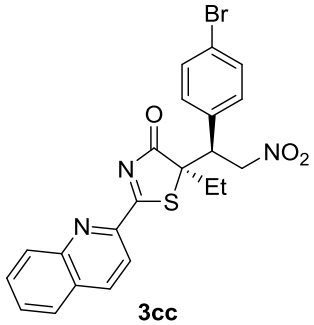




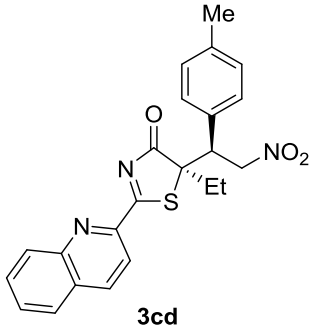
3ca
95%, >95:5 *dr*, 97% *ee*



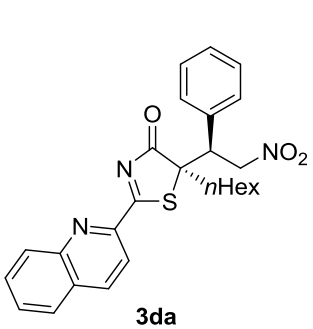
3cb
95%, >95:5 *dr*, 97% *ee*



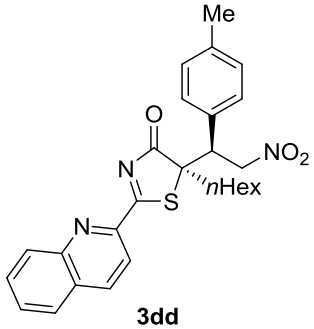
3cc
81%, >95:5 *dr*, 97% *ee*



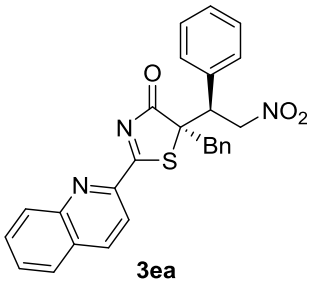
3cd
87%, >95:5 *dr*, 91(94)% *ee*



3da
96%, >95:5 *dr*, 92% *ee*



3dd
96%, >95:5 *dr*, 98% *ee*

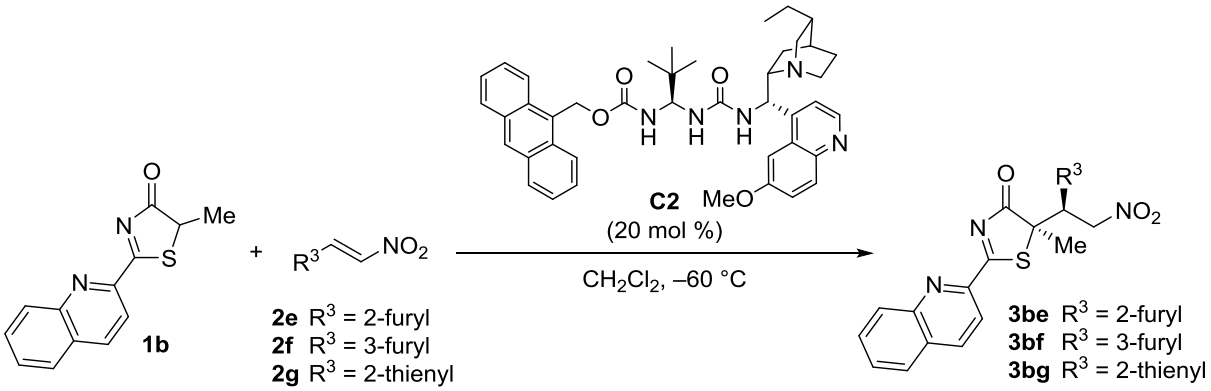


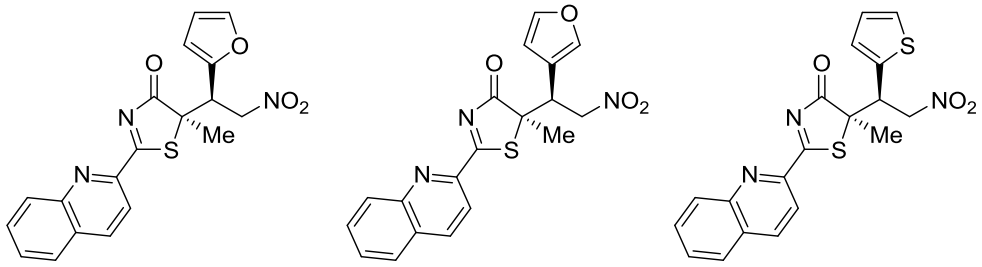
3ea
90%, >95:5 *dr*, 92(99)% *ee*

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

At this point, and to complete Olaizola's work with β-aromatic nitroolefins,[221] we proceeded to evaluate β-heteroaryl substituted nitroalkenes, in order to confirm the robustness of our protocol. Results obtained are gathered in Table 28. The reaction worked as fine as it did with regular all-carbon aromatic nitroolefins, rendering excellent yields in every case. Diastereomeric ratios remained above 90:10, and enantioselectivities also proved to be very good, especially with 2-furyl and 2-thienyl moieties, whereas it lowered some points when the 3-furyl moiety was tested (89% *ee*).

Table 28. Scope of the Michael addition of 5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one **1b** to heteroaromatic nitroolefins **2e**– **g**.





3be 96%, 92:8 *dr*, 91% *ee*

3bf 95%, 92:8 *dr*, 89% *ee*

3bg 93%, 92:8 *dr*, 92% *ee*

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

An interesting aspect of this methodology to synthesize tertiary thiol derivatives is the general crystallinity of both starting substrates, thiazolones **1a**–**e** and most of nitroolefins, a property which is readily translated to the resulting products **3a**–**e**. This attractive characteristic provided the opportunity of crystallizing the adducts; thus, as mentioned before, a single crystallization from diethyl ether produced products with increased enantiomeric purity. Moreover, an unambiguous determination of the absolute configuration of the corresponding adducts was performed by a single-crystal X-ray analysis of **3bc** (Figure 27) and by assuming a uniform reaction mechanism.

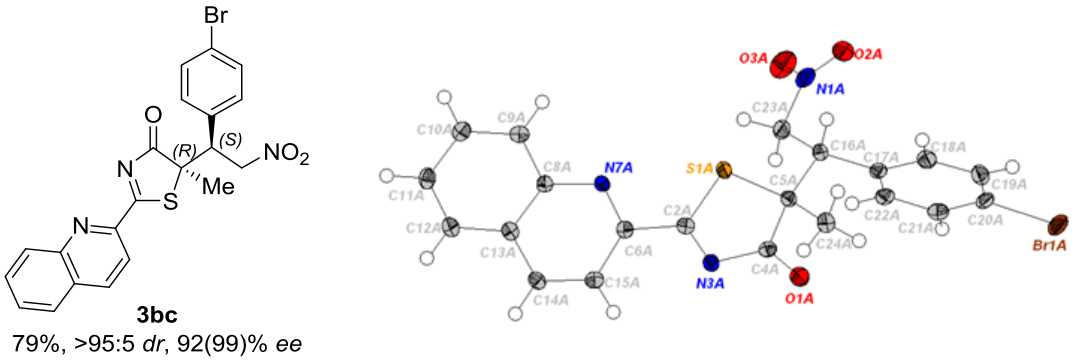
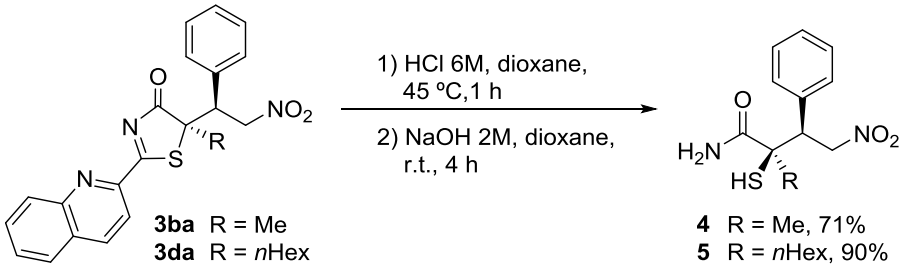


Figure 27. ORTEP diagram of compound **3bc**.

2.2.2.4. **Elaboration of adducts**

One of the first objectives of this project was to develop a methodology to obtain free tertiary thiols stereoselectively. We were happy to find that adducts **3ba** and **3da** could be transformed into the corresponding α,α-disubstituted α-mercapto carboxylic amides **4** and **5**, by simple ring opening in acid medium, followed by saponification of the resulting thioester, both under mild conditions, illustrating thus the utility of our procedure (Scheme 58). As it has been shown in the introduction of this chapter, the majority of the methodologies for the preparation of organosulfur compounds generally afford aryl or alkyl thioethers. Interestingly, our approach provides a quick entry to mercapto compounds with the thiol group in its free form.

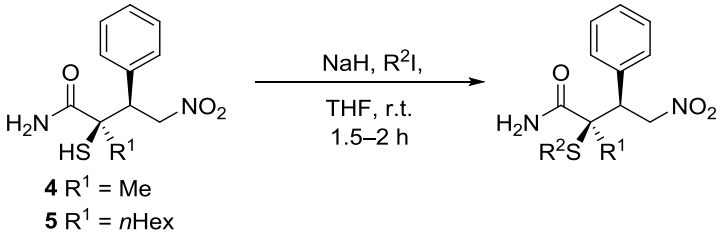


Scheme 58. Transformation of adduct **3ba** and **3da** into α,α-disubstituted α-mercapto carboxylic acid derivatives **4** and **5**.

Next, we wondered whether these adducts could be *S*-alkylated without affecting the nitro group. Apart from steric constraints it is known that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[223] Satisfactorily, treating adducts **4** and **5** with different halides in the presence of sodium hydride the corresponding *S*-alkylated products were produced in 75– 93% yield, leaving the nitro group untouched (Table 29).

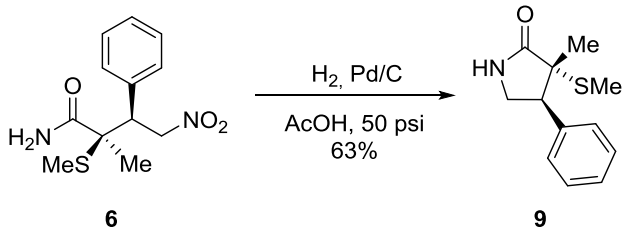
[223] Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612–615. and references therein.

Table 29. *S*-Alkylation of α,α-disubstituted α-mercapto carboxylic acid derivatives **4**–**5**.



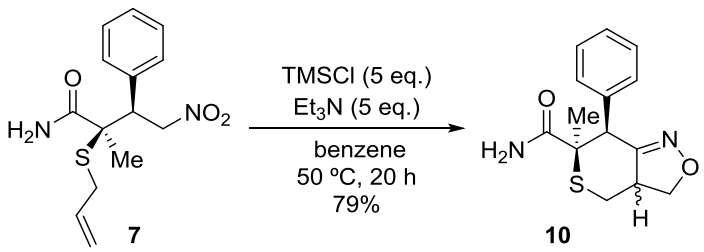
Entry	R^1	R^2	Product	Yield (%)
1	Me	Me	**6**	75
2	Me	Allyl	**7**	93
3	*n*Hex	Allyl	**8**	91

Starting from these thioether derivatives, different cyclic structures were readily available. On the one hand, exposure of adduct **6** to hydrogen over palladium on charcoal under a 50 psi atmosphere enabled reduction of the nitro group to the amino function, followed by spontaneous cyclisation to γ-lactams (Scheme 59).



Scheme 59.

On the other hand, a 1,3-dipolar cycloaddition of the allylic adduct **7** through a intramolecular silyl nitronate-olefin cyclization (ISOC)[224] gave access to isoxazoline **10** (Scheme 60), albeit in a poor 1.4:1 diastereomeric ratio.



Scheme 60.

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

2.2.2.5. **Mechanistic proposal**

Up to three different activation models have been proposed in the literature with regard to the Michael additions of 1,3-dicarbonylic compounds to nitroolefins. Takemoto and co-workers proposed the mechanistic model A in 2005 (Figure 28),[225] based on ^{1}H NMR studies. Their model suggested that the malonate was coordinated to the protonated tertiary amine and that the nitroalkene was bind to the thiourea moiety through *NH*-bonds with its oxygens. In 2006, Pápai did an exhaustive DFT study considering Takemoto's model (Figure 28, Model B),[226] and the calculations showed that model B was energetically more favoured than model A. Thus, this model has been generally assumed to be the most accurate to explain the way of action of these bifunctional catalysts in these kind of reactions. Moreover, Zhong's research group reported in 2010 a similar model to B (Figure 28, Model C), on the basis of ^{1}H NMR and DFT studies.[215]

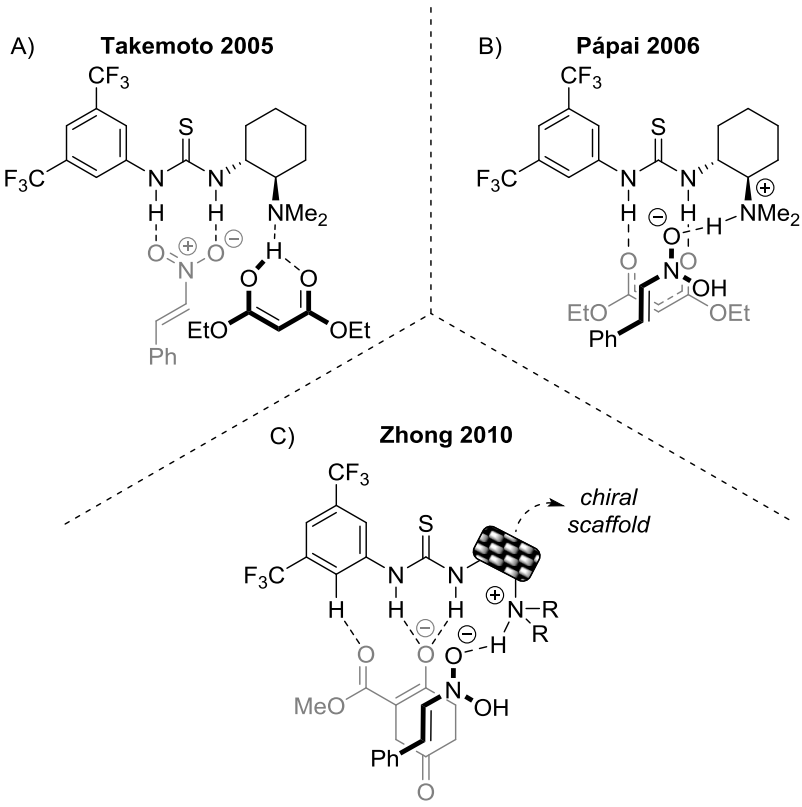


Figure 28. Proposed dual activation models for the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes promoted by thiourea-based bifunctional Brønsted bases.

[225] For the first report of Takemoto's catalyst, see a) ref. 36 page 12. For a mechanistic proposal, see: b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
[226] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

Taking into account the aforementioned models, we propose the model depicted in Figure 29 for our reaction, where both the nitroolefin and the thiazolone are activated by the ureidopeptide-base catalyst. The electrophile would be coordinated to the protonated quinuclidine, whereas the urea moiety would coordinate to the thiazolone enolate, through the nitrogen and oxygen atoms present in the heterocycle. A third coordination site would be possible between the quinolinyl group of the nucleophile and the aminal moiety in the catalyst, what would further stabilize the transition state.

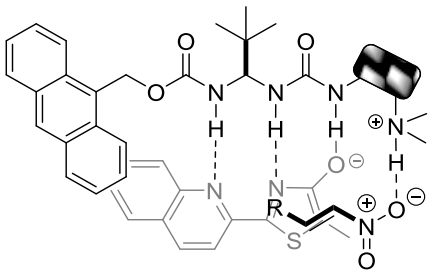
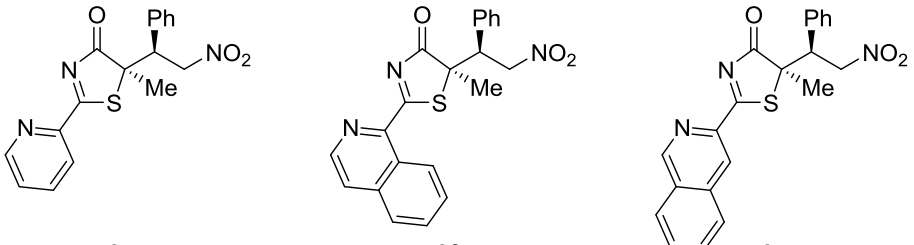


Figure 29. Proposed model for reaction activation.

Some support of the model depicted in Figure 29 was provided from the reaction of 2-(pyridin-2-yl)thiazolone **1a**, 2-(isoquinolin-1-yl)-thiazolone **1f** and 2-(isoquinolin-3-yl)-thiazolone **1g** with nitrostyrene **2a** affording products **3aa**, **3fa** and **3ga**, respectively, with worse results mainly in terms of enantioselectivity (Figure 30). The obtained results suggest that the increased aromaticity (respect to the 2-pyridyl derivative) and better superposition between the 2-quinolinyl group and the carbamate protecting group may assist to some sort of $\pi-\pi$ stacking, opposed to its isomers 1-isoquinolinyl and 3-isoquinolinyl derivatives. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation remains to be clarified.



3aa
80%, 93:7 *dr*, 80% *ee*

3fa
95%, 86:14 *dr*, 22% *ee*

3ga
90%, 91:9 *dr*, 80% *ee*

Figure 30.

In general, these catalysts were solids and Diosdado[220] obtained a single-crystal of **C1** that was analyzed by X-ray revealing that in the solid state the $N-H$ groups, in the *N,N´*-diacyl aminal and the urea moiety, are oriented in the same direction and that

neither of them display any apparent tendency to develop intramolecular hydrogen bonds (Figure 31), being therefore accessible for coordination with the substrates. Nevertheless, in solution this orientation could differ.

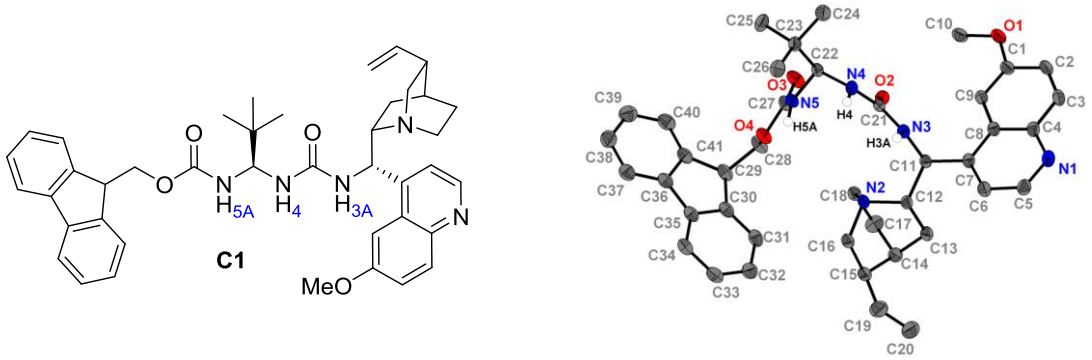


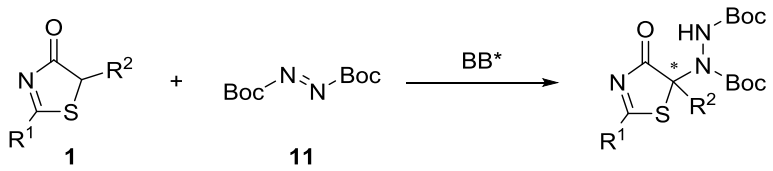
Figure 31. ORTEP diagram of compound **C1**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

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

2.3.1. **Working hypothesis and synthetic plan**

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

On this basis, di-*tert*-butyl azodicarboxilate (DBAD) **11** was chosen as electrophile, what would gain access to quaternary α-mercapto α-amino acid derivatives, a much seeked structure, as has been mentioned in previous sections. The reaction with this would led to the formation of only one stereocentre, thus being diastereoselectivity no longer an issue (Scheme 61).



Scheme 61. Proposed reaction for the first investigation.

2.3.2. **Results and discussion**

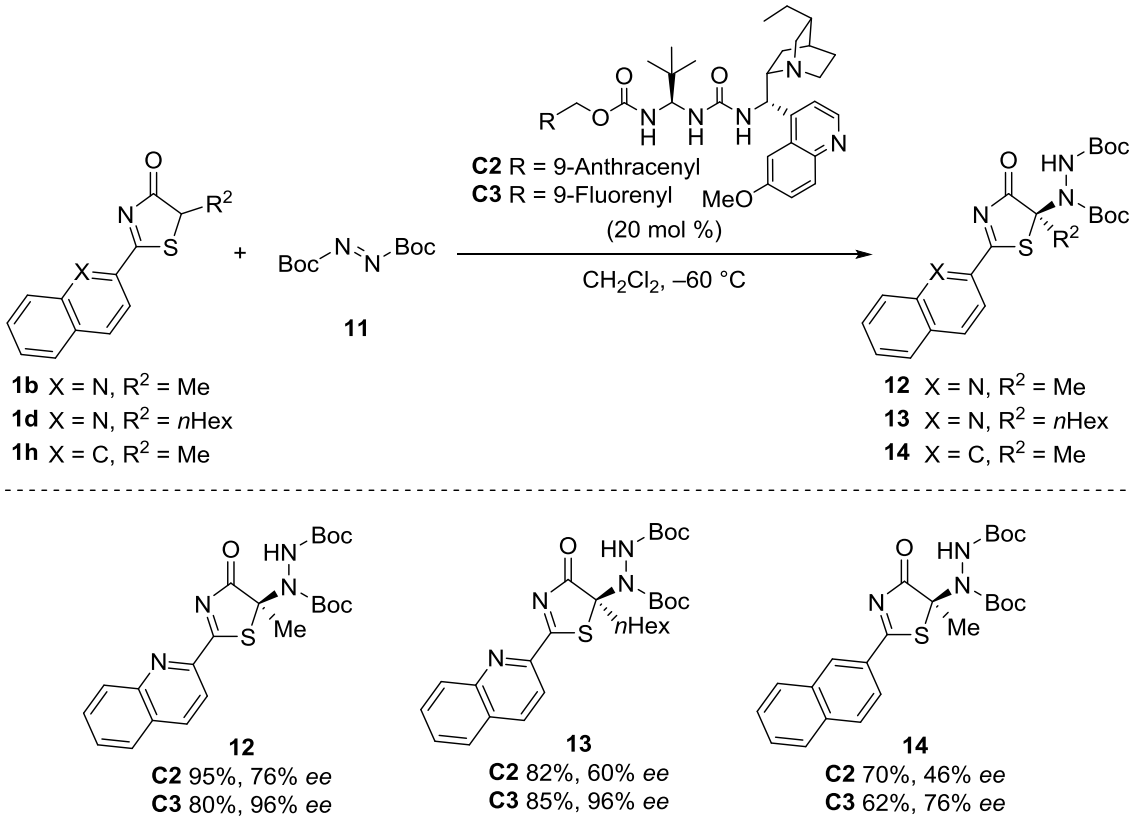
2.3.2.1. **Catalyst and thiazolone screening**

At the outset we selected for the amination reaction the conditions previously optimized for the Michael reaction with nitroolefins.

Our study thus began with the addition of the 2-(quinolin-2-yl)thiazolone **1b** to DBAD **11** in dichloromethane at − 60 °C in presence of catalyst **C2** (Table 30). Although the stereocontrol was far from being excellent, the obtained yield exceeded our first expectations, encouraging us to the consecution of this project. At this point, in order to confirm the previously observed data, we performed the electrophilic amination on two representative thiazolones: 5-hexyl-2-(quinolin-2-yl)thiazolone **1d** and 5-methyl-2-naphthyl-thiazolone **1h**. To our delight, the naphthyl derivative rendered lower yield and a poor stereoselectivity, validating our hypothesis of a three *NH*-bond stabilized intermediate. On the other hand, the outcome of the reaction with the 5-hexyl derivative **1d** remained similar to those of **1b**, although far from excellence.

In view of these results, we resolved to test a catalyst with a different group attached to the aminal moiety, and choose fluorenylmethyloxycarbonyl (Fmoc) as a readily available and bulky substituent. Fortunately, this strategy worked out, obtaining the results depicted in Table 30. This time, the 2-quinolinyl derived thiazolones afforded excellent enantioselectivities, but while adduct **13** was produced in similar yield than with catalyst **C2**, the yield of adduct **12** lowered. The low yield and the enantioselectivity rendered by 2-naphthyl derivative adduct **14** reinforced our aforementioned thesis of a three *NH*-bond stabilized intermediate.

Table 30. Screening of thiazolones and catalyst for the stereoselective electrophilic α-amination.

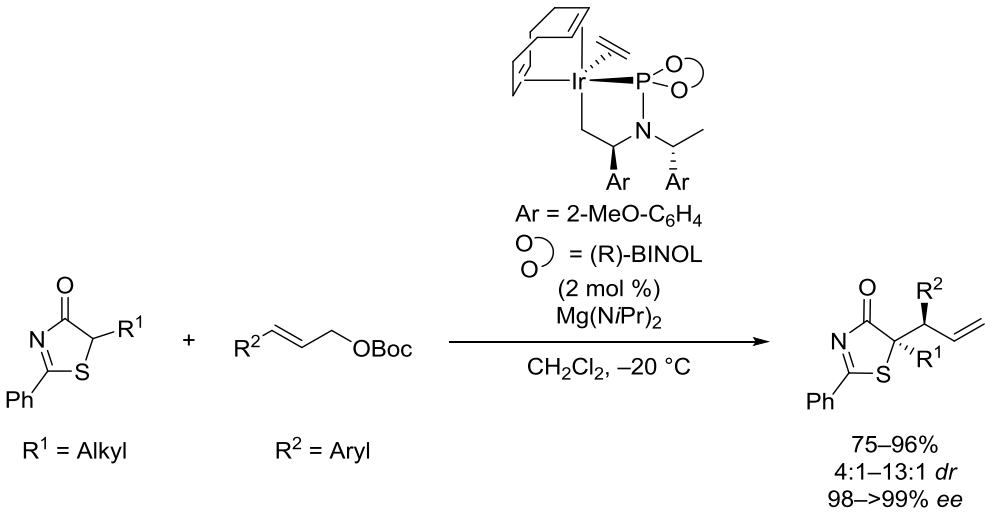


[a] Reaction conditions: **1b**, **1d** and **1h** (0.3 mmol), **11** (0.6 mmol, 2 equiv.), catalyst (20 mol %), – 60 °C in CH_2Cl_2 (0.6 mL). Yields correspond to the isolated major isomer after column chromatography. *ee*'s determined by HPLC analysis on a chiral stationary phase.

The configuration of the adducts depicted in Table 30 was induced by assuming a uniform reaction mechanism respect to that proposed for the addition of thiazolones to nitroolefins, assumption supported by the results obtained suggesting a intermediate-stabilizing third *H*-bond between the 2-quinolinyl moiety in **1b** and **1d** and the catalyst.

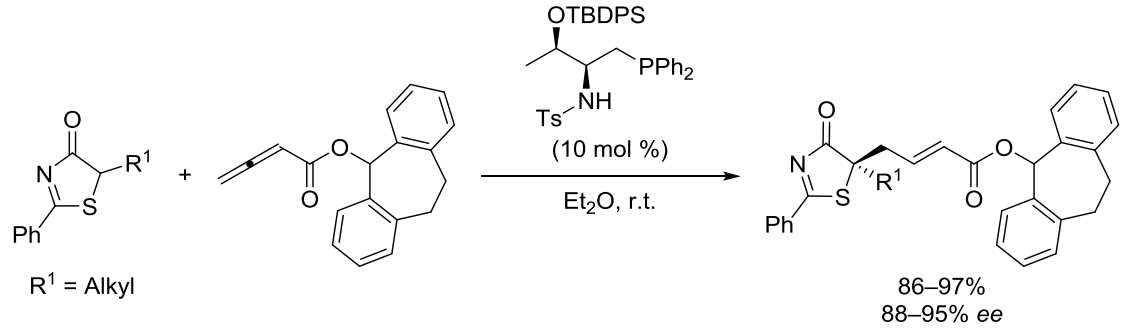
After our work, two papers concerning the use of 5*H*-thiazol-4-ones in catalytic asymmetric synthesis appeared. On the one hand, Hartwig and co-workers reported the Ir-catalyzed allylation of thiazolones, affording good to excellent yields and diastereoselectivities and excellent enantioselectivities (Scheme 62).[227]

[227] Chen & Hartwig see ref. 83b page 26.



Scheme 62.

On the other hand, Lan and Lu's research group described the conjugate addition of thiazolones to allenoates, with excellent yields and enantiocontrol, employing chiral phosphines as catalysts (Scheme 63).[228]



Scheme 63.

[228] Wang et al. see ref. 95 page 29.

Chapter 3

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

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

3.1. Introduction

3.1.1. General considerations

The essential role of naturally occurring α-amino acids as building blocks of peptides and proteins, has led to the development of various synthetic strategies for their preparation.[229] The flexible nature of peptides and proteins allows them to adopt several conformations in solution, but only few of them are responsible for their diverse biological properties. Minute modifications of the structure of the parent amino acids can alter the conformational bias of the peptides derived thereof and, thus, their biological properties; a much seeked goal that has led numerous research groups to investigate the synthesis of non-proteinogenic α-amino acids.[230] Apart from their biological interest, α-amino acids constitute a primary source of chiral non racemic starting material for use in chemical catalysis and synthesis.[231]

Quaternary α-amino acids are configurationally rigid building blocks that can be employed, among others uses, to synthesize novel unnatural peptides and proteins with unusual biological properties. For example, peptides incorporating quaternary α-amino

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

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

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

acid units in their structure have been reported to increase helix-inducing potential[232] or enhance resistance against chemical and enzymatic hydrolysis,[233] probably due to the absence of conformational freedom caused by the steric constraint.[234] Quaternary α-amino acids can also be found in some natural products acting as antibiotics.[235]

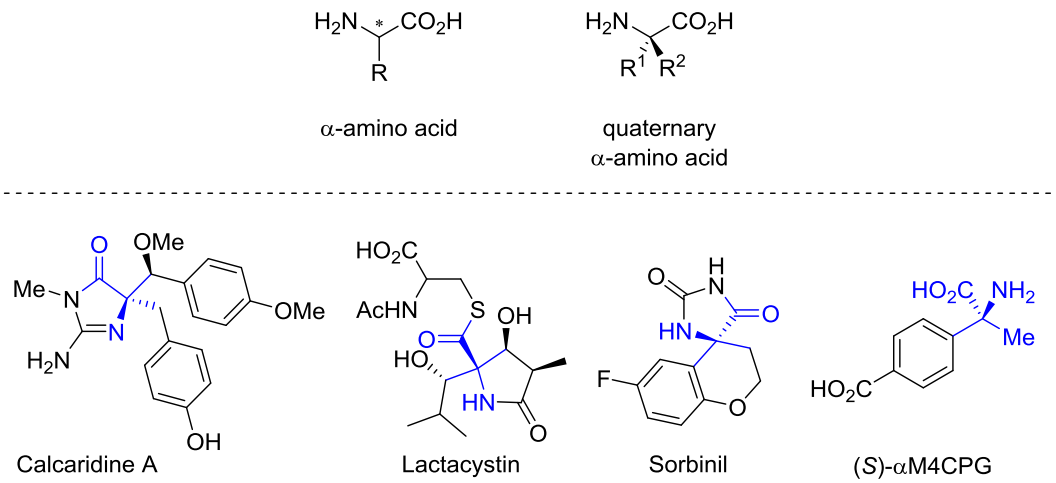


Figure 32. General structures of both simple and quaternary α-amino acids, and examples of biologically active compounds bearing a quaternary α-amino acid core.[234a,c]

3.1.2. **Synthesis of α,α-disubstituted α-amino acid derivatives**

A number of approaches have been explored for the stereoselctive synthesis of α,α-disubstituted α-amino acid derivatives. These include stoichiometric methods based on the chiral pool or the use of chiral auxiliaries, which will not be discussed here and the reader is refered to extensive reviews on the matter.[234,236] Methods based on the

[232] For a reviews on the design of folded peptides, see: a) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152. For a review on synthetic foldamers, see: b) Guichard, G.; Huc, I. *Chem. Commun.* **2011**, *47*, 5933–5941.

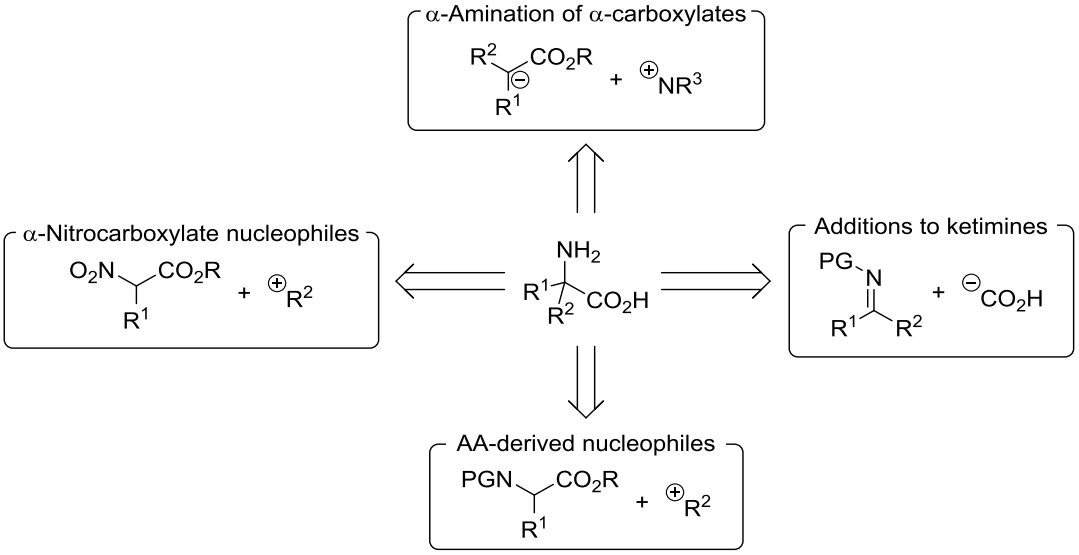
[233] For some review on the biological properties of quaternary α-amino acids, see: a) Crisma, M.; Valle, G.; Bonora, G. M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternall, F.; Hardy, P. M.; Maia, H. L. S. *Biopolymers* **1991**, *31*, 637–641. b) Gante, J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1699–1720. c) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048–12054. d) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. *Synlett* **2006**, *2006*, 1295–1310. e) Tanaka, M. *Chem. Pharm. Bull. (Tokyo).* **2007**, *55*, 349–358.

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

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

[236] For a review on the Self-Regeneration of Stereocentres (SRS), see: a) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708–2748. For a recent example employing SRS to synthesize quaternary prolines, see: b) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*,

participation of a chiral catalyst as the reaction controller are definitely more attractive and atom-economic. Here, direct catalytic asymmetric methods will be discussed only. Depicted in Scheme 1 are major disconnections used for this purpose.

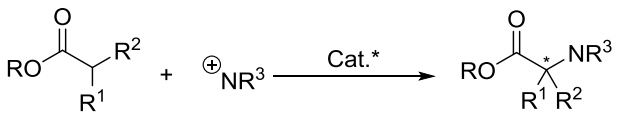


Scheme 64. Strategies for the direct catalytic asymmetric synthesis of α,α-disubstituted α-amino acid derivatives.

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

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

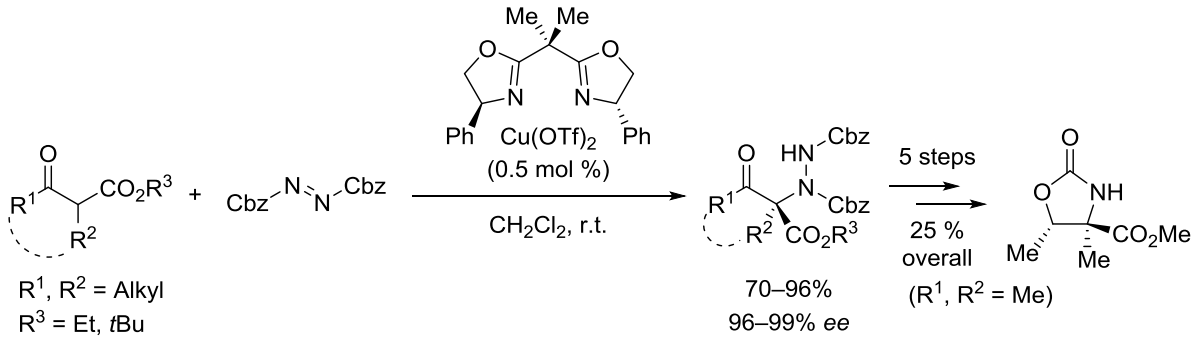
Electrophilic amination of α-substituted carboxylic acid derivatives is probably one of the simplest approaches for the formation of α,α-disubstituted α-amino acid derivatives (Scheme 65). However, the approach is relatively uncommon due to the shortage of suitable electrophilic nitrogen sources, being azodicarboxylates the usual choice.



Scheme 65.

432–435. For a review on Memory of Chirality (MOC), see: c) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16. For an example of MOC of tertiary aromatic amides, see: d) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711–10718. For a recent example of the synthesis of β-hydroxy quaternary α-amino acids through MOC, see: e) Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Lett.* **2014**, *16*, 788–791.

Direct α-amination of α-substituted β-ketoesters was first reported by Jørgensen's research group, employing a chiral copper bisoxazoline complex as catalyst.[237] Very good to excellent yields and excellent enantioselectivities were obtained with both acyclic and cyclic substrates using dibenzyl azodicarboxylate as the amination reagent (Scheme 66). Employing this method, optically active β-hydroxy-α-amino acid derivatives were accessed, although 5 additional steps were required with a 25% overall yield.



Scheme 66.

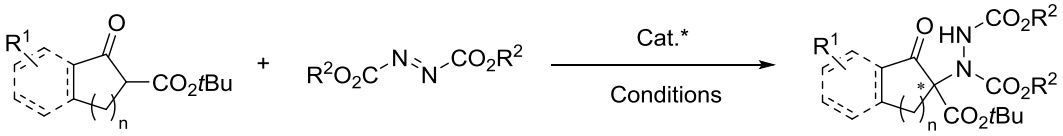
The first organocatalytic approach to the α-amination of β-ketoesters was also reported by Jørgensen using a bifunctional *Cinchona* alkaloid catalyst (Table 31, entry 1).[238] Later on Maruoka's research group reported an alternative approach using phase-transfer conditions involving an axially chiral phosphonium bromide as catalyst and stoichiometric quantities of KH_2PO_4 as a base, and rendering moderate to excellent yields and enantioselectivities (entry 2).[239] Few years later, the same group found that the reaction could also be catalyzed under similar reaction conditions by a chiral ammonium salt catalyst and catalytic amounts of KH_2PO_4, obtaining comparable chemical and stereochemical efficiency (entry 3).

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

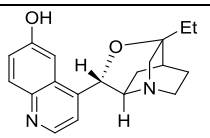
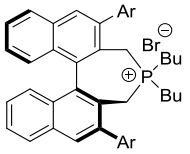
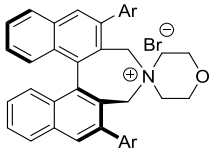
[238] Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.

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

Table 31. Asymmetric α-amination of β-ketoesters.



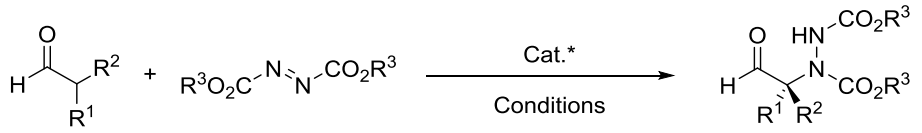
R^1 = Cl, OMe
n = 1,2

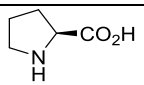
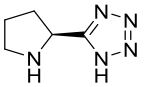
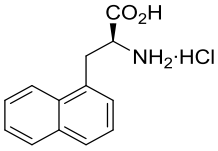
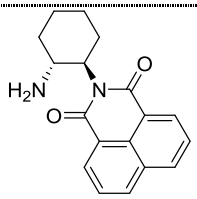
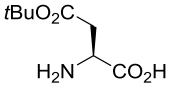
Entry	R^2	Cat.*	Conditions	Results	Ref.
1	*t*Bu	 (5 mol %)	toluene – 50 to 0 °C	86– 99% 83– 90% *ee* (*R*)	238
2	*t*Bu	 Ar = 3,5-$(CF_3)_2$-C_6H_3 (3 mol %)	K_2HPO_4 (1– 5 equiv.) toluene – 40 to – 20 °C	42– 99% 77– 95% *ee* (*S*)	239a
3	Et	 Ar = 3,5-(3,5-(*t*Bu)$_2$-C_6H_3)$_2$-C_6H (3 mol %)	K_2HPO_4 or K_2CO_3 (0.3 equiv.) toluene – 40 to 0 °C	95– 99% 76– 97% *ee* (*S*)	239b

In 2003, Bräse and co-workers described,[240] using enamine activation, the proline-catalyzed α-amination of α,α-disubstituted aldehydes, although 50 mol % catalyst loading was needed to afford moderate results (Table 32, entry 1). Few years later, Barbas III employed this strategy in the synthesis of BIRT-377, a cell adhesion inhibitor, in a much more efficient way, obtaining a product of 99% *ee* upon crystallization (entry 2).[241] α-Amination of aldehydes has been revised several times, among others by Wang and co-workers (entries 3– 4)[242] and by Kokoto's group (entry 5),[243] who used a different catalyst or lower catalyst loading in order to increase efficiency. However, both yield and *ee*'s are strongly substituent dependant.

[240] Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun.* **2003**, 2448–2449.
[241] Chowdari & Barbas III see ref. 65 page 20.
[242] a) Fu, J.-Y.; Yang, Q.-C.; Wang, Q.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2011**, *76*, 4661–4664. b) Fu, J.-Y.; Wang, Q.-L.; Peng, L.; Gui, Y.-Y.; Xu, X.-Y.; Wang, L.-X. *Chirality* **2013**, *25*, 668–672.
[243] Theodorou, A.; Papadopoulos, G. N.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 5438–5443.

Table 32. Aminocatalyzed α-amination of aldehydes employing azodicarboxilates.

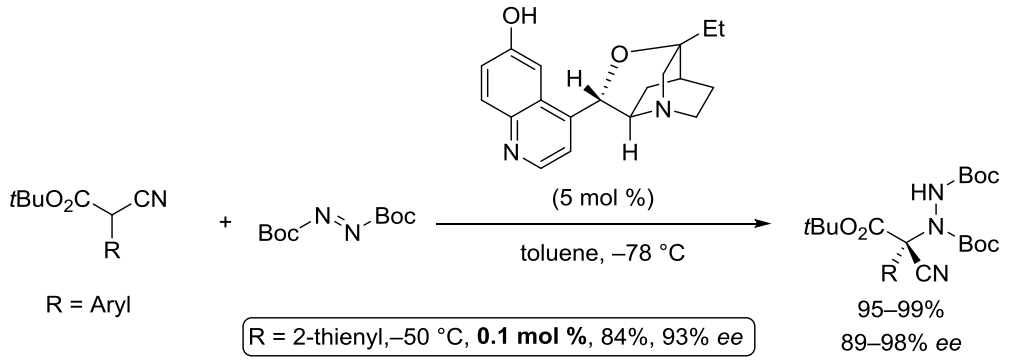


	R^1	R^2	R^3	Cat.*	Conditions	Results	Ref.
1	Alkyl	Alkyl, Aryl	Et, *t*Bu	 (50 mol %)	CH_2Cl_2, r.t.	17–99% 4–86% *ee*	240
2	4-Br-C_6H_4-CH_2	Me	Bn	 (15 mol %)	CH_3CN, r.t.	95% 80% *ee*	241
3	Alkyl	Alkyl, Aryl	Et, *i*Pr, *t*Bu	 (20 mol %)	THF, 0 °C	29– 99% 85– 97% *ee*	242a
4	Me	Aryl, *n*Pr	Et, *i*Pr, *t*Bu, Bn	 (10 mol %)	TFA (10 mol %) DCE, 25 °C	38–99% 57–97% *ee*	242b
5	Aryl, Alkyl	Me, Et	*t*Bu	 (20 mol %)	THF, 0 °C	72–98% 50–99% *ee*	243

The α-amination of α-cyanocarboxylic compounds has also been explored for the synthesis of quaternary α-amino acids. The versatility of the nitrile moiety allows its transformation into different functional groups, but its presence in the final adduct can also be of interest. Case in point is the β-isocupreidine-catalyzed amination of α-aryl *tert*-butyl cyanoacetates developed by Jørgensen's group in 2004,[244] which afforded the corresponding adducts in excellent yields and stereocontrol in every case, even employing low catalyst loadings (down to 0.1 mol %, Scheme 67). The extremely low temperature

[244] a) Saaby et al. see ref. 238 page 106. For the asymmetric α-amination of α-cyanoketones employing thiourea-based bifunctional Brønsted bases, see: b) Kim, S.; Lee, J.; Kim, D. *Synlett* **2008**, 2659–2662. For the asymmetric α-amination of α-cyanothioacetates employing chiral guanidines, see: c) Terada, M.; Tsushima, D.; Nakano, M. *Adv. Synth. Catal.* **2009**, *351*, 2817–2821. For the asymmetric α-amination of 1,3-dicarbonyl compounds and α-cyanoacetates by catalysis with BINOL–quinine–squaramide catalysts, see: d) Gao, Y.; Liu, B.; Zhou, H.-B.; Wang, W.; Dong, C. *RSC Adv.* **2015**, *5*, 24392–24398.

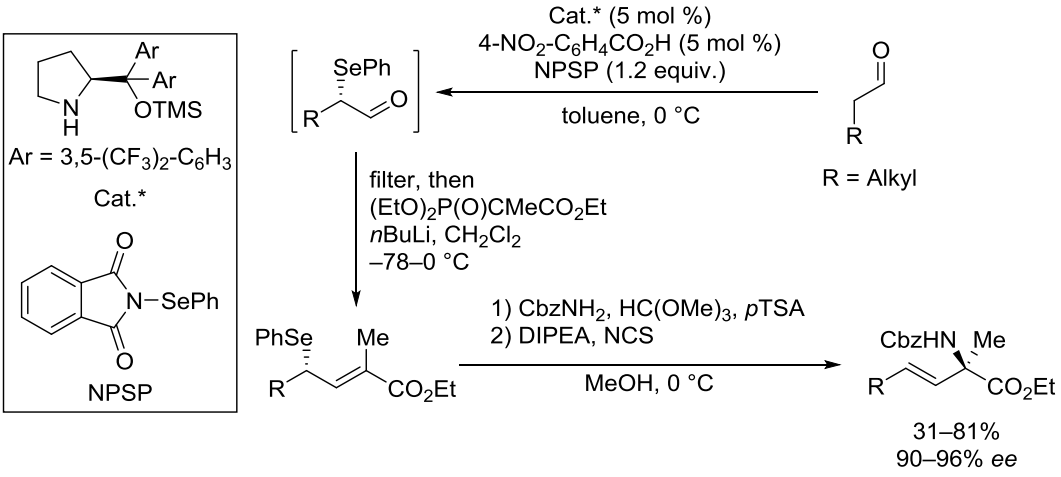
employed to maintain stereocontrol on the reaction was due to the reactivity of the substrate, caused by the strong acidity of the α *C*(sp^3) of the cyanoacetate.



Scheme 67.

Other active methylenes used as (pro)nucleophiles in these transformations include α-substituted α-nitroacetates,[245] α-fluoro β-ketoesters,[246] and α-acyl acrylates.[247]

Although the majority of α-amination protocols use electrophilic amination reagents, recently Armstrong and co-workers reported a reversal tactic to prepare α-allyl quaternary α-amino acids.[248] First, aldehydes were submitted to asymmetric α-selenenylation and then a Wittig olefination produced the corresponding α-selenoxy α,β-unsaturated ester. Final treatment with benzyl carbamate followed by a [2,3]-sigmatropic rearrangement afforded the desired aminoesters from moderate to good yields and excellent enantioselectivities (Scheme 68).

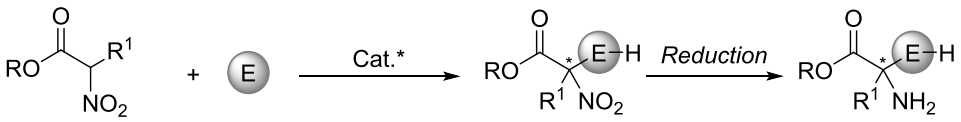


Scheme 68.

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

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

Addition of α-nitrocarboxylates to different electrophiles is a well known strategy for the synthesis of α,α-disubstituted α-amino acid derivatives. Not only α-nitroesters have a very active methylene group but also the reduction of the nitro moiety gives access to amino function (Scheme 69).



Scheme 69.

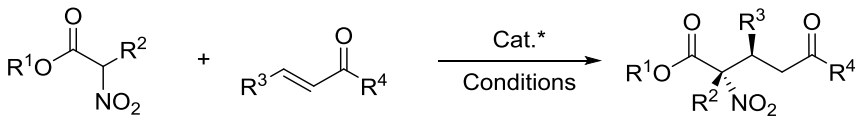
The classification of the examples described in this section is based on the type of electrophile, and thus, type of reaction.

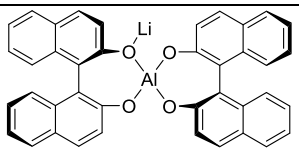
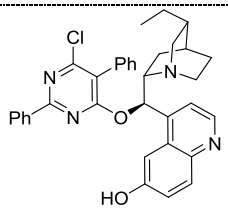
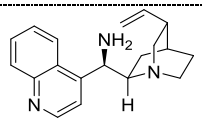
3.1.2.2.1. Michael addition

In 1997, Feringa's research group reported the first conjugate addition of α-nitroesters to α,β-unsaturated ketones in presence of a Lewis acid,[249] affording 1,4-addition adducts in good yields and enantioselectivities from low to moderate (Table 33, entry 1). The first organocatalytic version came in hand of Snider and co-workers,[250] who carried out the conjugate addition of ethyl 2-nitropropanoate to methyl vinyl ketone as a key step in the total synthesis of natural produc (+)-NP25302, although no wider scope was explored (entry 2). Some years later, Zhao's group described the Michael addition of α-fluoro α-nitroacetates to β-substituted enones,[251] affording α,α-disubstituted nitroacetates in very good yields and enantioselectivities, but poor diastereoselectivities (entry 3).

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

Table 33. Michael addition of α-nitroacetates to enones.

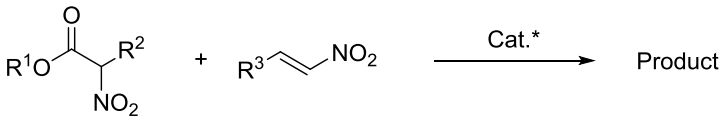


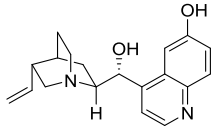
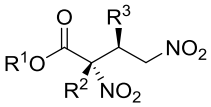
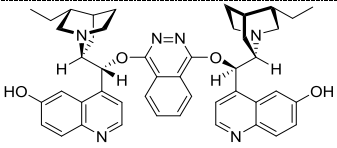
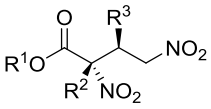
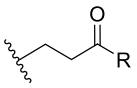
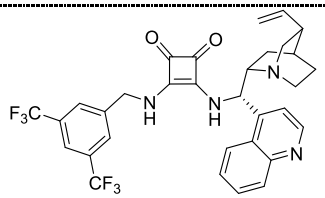
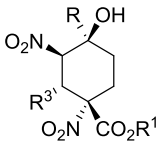
	R^1	R^2	R^3	R^4	Cat.*	Conditions	Results	Ref.
1	Alkyl	Me, Et	H	Me, Et, Ph	 (10 mol %)	THF:H_2O (85:15) – 65 °C	81– 86% 33– 80% *ee* (R^4 = Ph, 5% *ee*)	249
2	Et	Me	H	Me		CH_2Cl_2 – 20 °C	90% 90% *ee*	250
3	Et	F	Alkyl, Aryl	Me	 (10 mol %)	4-NO_2-$C_6H_4CO_2H$ (10 mol %) toluene, r.t.	75– 95% 1.2:1– 2.4:1 *dr* 93– 99% *ee*	251

The first catalytic and asymmetric direct conjugate addition of α-nitroesters to nitroolefins was reported by Deng and co-workers in 2005.[252] Employing crupeine as catalyst, the addition adducts were obtained in good yields and excellent diastereo- and enantioselectivities (Table 34, entry 1). In 2013, Lin's research group used a dimeric version of the catalyst (i.e. *de*-Me-DHQ)$_2$PHAL), which allowed them to lower the catalyst loading without compromising the outcome (entry 2).[253] Also using nitroalkenes and nitroacetates, Carrillo and Vicario's group described an effective synthesis of densely substituted cyclohexanes through a Michael-Henry tandem sequence (entry 3).[254]

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

Table 34. Michael addition of α-nitroacetates to nitroolefins.

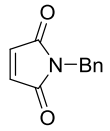
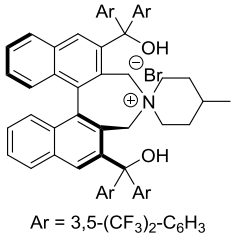
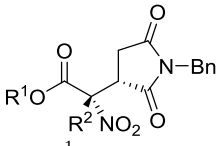
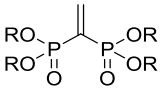
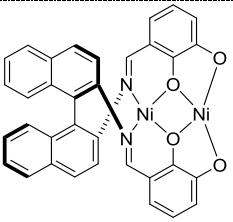
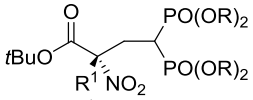
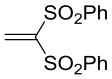
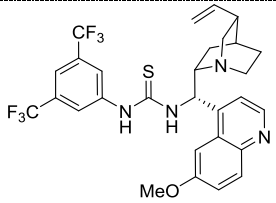
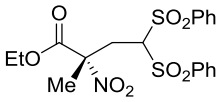
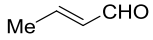
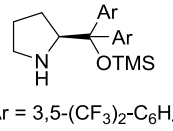
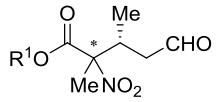
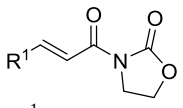
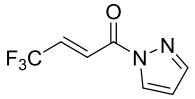
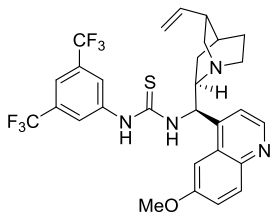
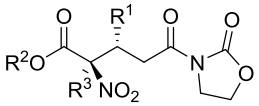
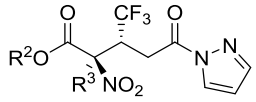


	R^1	R^2	R^3	Cat.*	Product	Results	Ref.
1	Et	Me, Et	Alkyl, Aryl	 (15 mol %)		77– 78% 92:8– 95:5 *dr* 92– 96% *ee*	252
2	Et	Me, Et	Alkyl, Aryl	 (1 mol %)		71– 99% 89:11– 99:1 *dr* 94– 98% *ee*	253
3	Et, Me	 R = Me, Et	Aryl	 (2– 2.5 mol %)		91– 98% 1:6– 1:19 *dr* 96– 99% *ee*	254

The high reactivity of α-nitroesters as (pro)nucleophiles has prompted the development of methodologies for their asymmetric addition to several electrophiles other than nitroolefins (Table 35), such as maleimides (entry 1),[255] *gem*-bisphosphonates (entry 2),[256] 1,1-bis(sulfonyl)ethylenes (entry 3),[257] enals (entry 4),[258] and enamides (entry 5).[259]

[255] Shirakawa, S.; Terao, S. J.; He, R.; Maruoka, K. *Chem. Commun.* **2011**, *47*, 10557–10559.
[256] Kato, Y.; Chen, Z.; Matsunaga, S.; Shibasaki, M. *Synlett* **2009**, 1635–1638.
[257] Quintard, A.; Alexakis, A. *Org. Biomol. Chem.* **2011**, *9*, 1407–1418.
[258] Han, M.-Y.; Zhang, Y.; Wang, H.-Z.; An, W.-K.; Ma, B.-C.; Zhang, Y.; Wang, W. *Adv. Synth. Catal.* **2012**, *354*, 2635–2640.
[259] Wen, L.; Yin, L.; Shen, Q.; Lu, L. *ACS Catal.* **2013**, *3*, 502–506.

Table 35. Diverse electrophiles employed with α-nitroacetates as nucleophiles.

	Electrophile	Cat.*	Product	Results	Ref.
1		 Ar = 3,5-$(CF_3)_2$-C_6H_3 (3 mol %)	 R^1 = Me, Et R^2 = Alkyl, Bn	42– 92% 10:1– 20:1 *dr* 83– 91% *ee*	255
2	 R = Et, allyl, Bn	 (10 mol %)	 R^1 = Alkyl	65– 94% 76– 93% *ee*	256
3		 (20 mol %)		100% (conv.) 28% *ee*	257
4		 Ar = 3,5-$(CF_3)_2$-C_6H_4 (10 mol %)		44% 1:1.3 *dr* 82/88% *ee*	258
5	 R^1 = CF_3, C_2F_5 	 (10 mol %)	 R^2, R^3 = Me, Et  R^2, R^3 = Me, Et	71– 93% >50:1 *dr* 89– 92% *ee* 71– 83% 4.4:1– 10:1 *dr* 80– 90% *ee*	259

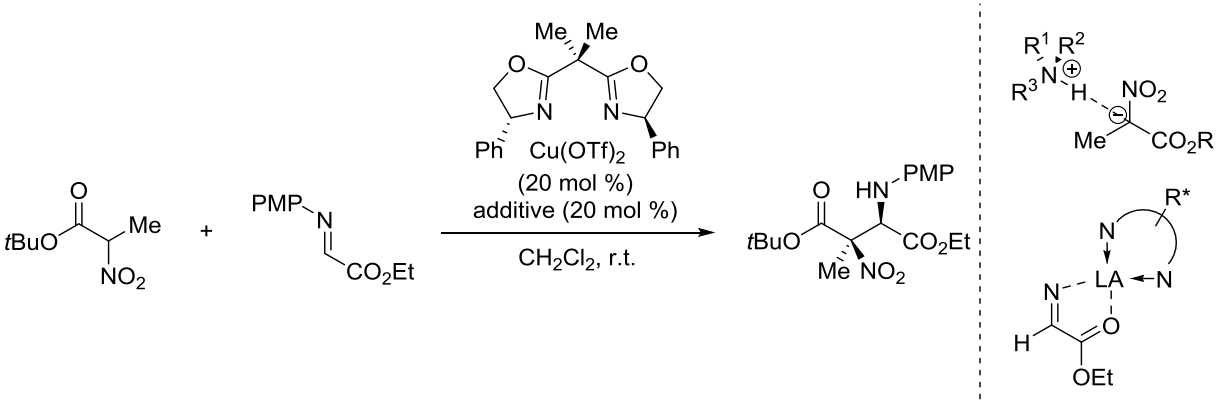
3.1.2.2.2. Mannich reaction

The first enantioselective Mannich reaction of a nitroester with an imine was described by Jørgensen and co-workers in 2005 using synergistic catalysis.[260] The

[260] a) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364. For a review on combining transition metal catalysis and organocatalysis, see: b) Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337–1378. For a review on synergistic catalysis, see: c) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633–658. For a review on dual activation in organocatalysis, see: d) Lu, L.-Q.; An, X.-L.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2012**, *23*, 490–508.

reaction was performed in presence of a chiral Cu catalyst and a Brønsted base (20 mol % each) (Table 36). Results suggested that the enantiocontrol was induced by both catalysts, although neither diastereoselectivity nor enantioselectivity was much affected by changing the *Cinchona* alkaloid of choice.

Table 36. Effect of the additive in the Cu-catalyzed Mannich addition of nitroacetates to iminoesters.

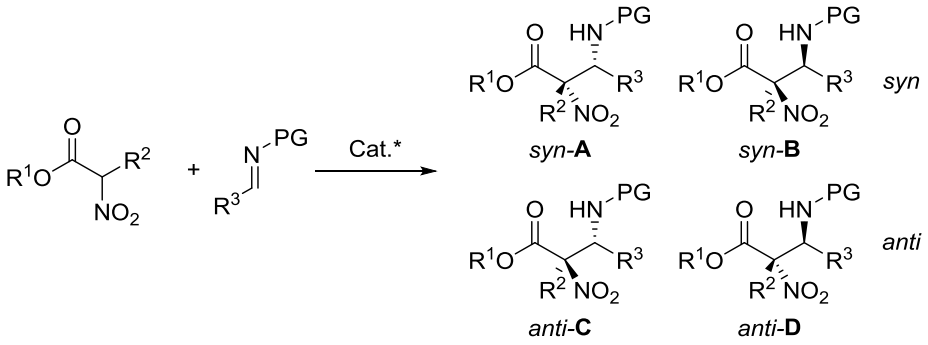


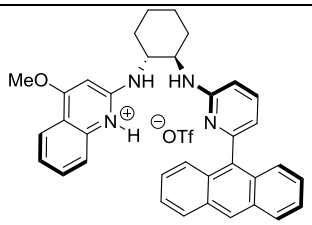
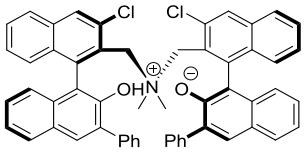
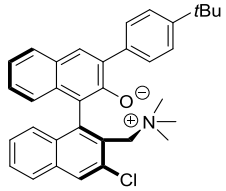
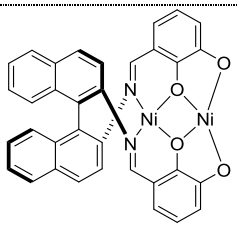
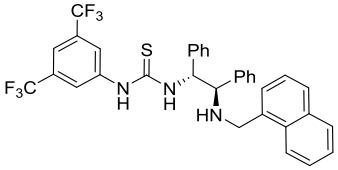
Entry	Additive	Yield (%)	*dr*	*ee* (%)
1	Et_3N	90	2:1	80/82
2	quinine	90	14:1	98
3	quinidine	80	8.5:1	96
4	cinchonine	76	7:1	94
5	hydroquinine	90	8:1	95
6	hydrocinchonine	90	7:1	93

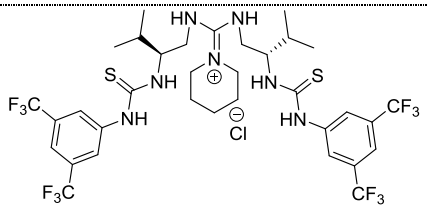
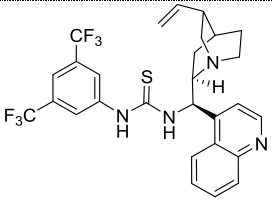
Following this pioneering work, several methodologies have been developed in order to synthesize all four possible diastereomers. Efforts reported by Johnston with a bifunctional chiral proton complex (entry 1),[261] Ooi with phase-transfer catalysis (entries 2 and 3),[262] Shibasaki with a homodinuclear Ni(II) catalyst (entry 4),[263] Chen with a bifunctional secondary amine thiourea catalyst (entry 5),[264] Dong with a guanidinium-based catalyst (entry 6),[265] and Miao with a bifunctional tertiary amine thiourea catalyst (entry 7),[266] are depicted in Table 37.

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

Table 37. Mannich reactions employing α-nitroacetates as pronucleophiles.



	R^1	R^2	R^3	PG	Cat.*	Prod.	Results	Ref.
1	Aryl	Alkyl	Aryl	Boc	 (5 mol %)	*syn*-A	59– 88% 5:1– 20:1 *dr* 94– 98% *ee*	261
2	*t*Bu	Me, Et	Alkyl, aryl	Boc	 (1 mol %)	*syn*-B	91– 99% 2:1– 5:1 *dr* 91– 99% *ee*	262a
3	*t*Bu	Me, Et	Alkyl, aryl	Boc	 (1 mol %)	*syn*-B	95– 99% 2:1– 6:1 *dr* 90– 96% *ee*	262b
4	*t*Bu	Alkyl	Alkyl, aryl	Boc	 (5–10 mol %)	*anti*-C	67– 96% 86:14– 97:3 *dr* 91– 99% *ee*	263
5	Me	Me, *i*Pr, Bn	Aryl	Boc	 (10 mol %)	*anti*-D	38– 86% 4:1– 7:1 *dr* 91– 96% *ee*	264

6	Et	Me, *i*Pr, Bn	Aryl	Boc	 (5 mol %)	*anti*-D	40– 80% 3:1– 8:1 *dr* 91– 96% *ee*	265
7	Me	Me, Et	Aryl	$PO(OEt)_2$	 (5 mol %)	*anti*-D	65– 86% 4:1– 7:1 *dr* 91– 96% *ee*	266

3.1.2.2.3. Aldol reaction

The product of an aldol reaction of α-nitroesters with an aldehyde resembles very much the natural α-amino acid Serine (Figure 33), and such this approach may serve to access serine analogs. However, this approach has not been as much explored as Mannich reaction above. As far as we know, there are only two examples in literature, both involving formaldehyde, which describe the hydroxymethylation of nitroesters. This may be due to the facility by which the resulting adducts can undergo retro-aldol reactions.

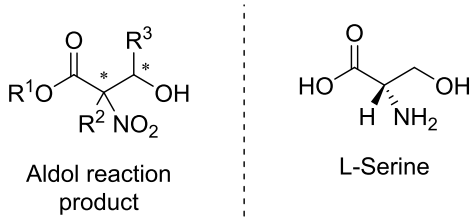
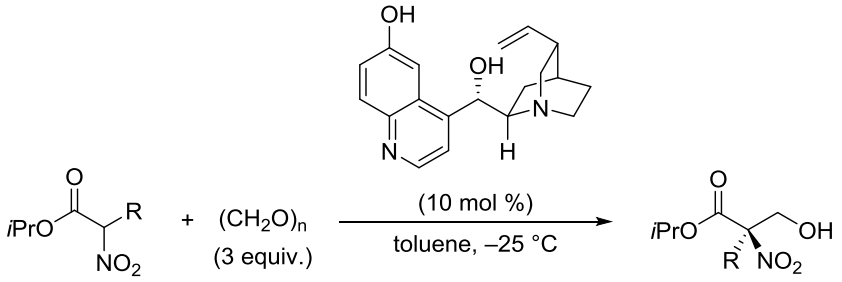


Figure 33.

The first example of an aldol reaction employing nitroacetates as pronucleophiles was reported by Zhou and co-workers,[267] who presented the addition of isopropyl α-nitroesters to paraformaldehyde (Table 38). In presence of cupreidine, the reaction afforded good yields and moderate enantioselectivities with alkyl substituents (entries 1– 5), but poor stereocontrol when R = Ph (entry 6). The long reaction times are a consequence of the low temperatures, needed for the stereocontrol of the reaction.

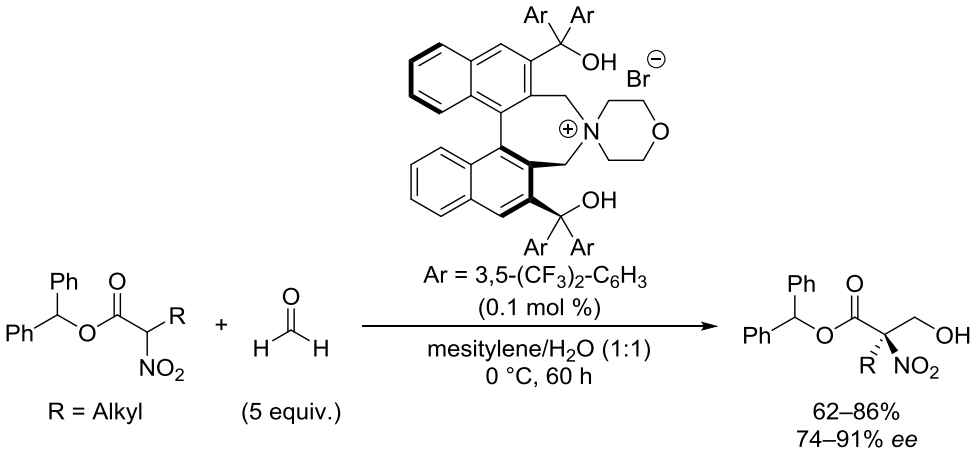
[267] Ji, C.-B.; Liu, Y.-L.; Cao, Z.-Y.; Zhang, Y.-Y.; Zhou, J. *Tetrahedron Lett.* **2011**, *52*, 6118–6121.

Table 38. Cupreidine-catalyzed hydroformylation of α-nitroacetates.



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

In 2012, Maruoka's research group reported a phase-transfer catalyzed formylation of benzyl α-nitroesters, employing an aqueous solution of formaldehyde.[268] As illustrated in Scheme 70, a very low catalyst loading (0.1 mol %) was enough to promote the aldol reaction and induce very good to excellent enantioselectivities.



Scheme 70.

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

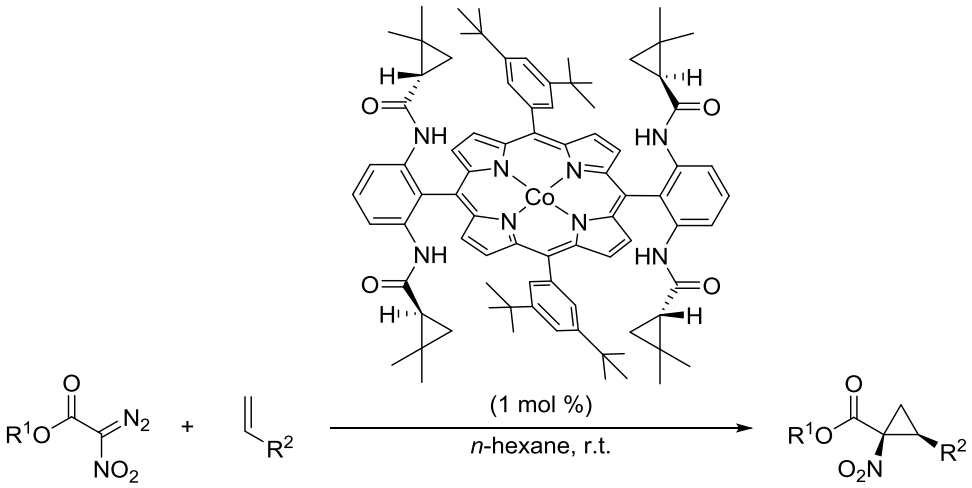
[268] Shirakawa, S.; Ota, K.; Terao, S. J.; Maruoka, K. *Org. Biomol. Chem.* **2012**, *10*, 5753–5755.

3.1.2.2.4. Metal-catalyzed substitutions

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

In 2008, Zhang and co-workers described the *Z*-selective cyclopropanation of olefins with α-nitro diazoacetates, employing a chiral porphiryn-Co^{II} complex as catalyst (Table 39).[269] The reaction rendered cyclopropanated quaternary α-nitroesters in excellent diastereo- and enantioselectivities in the case of aryl and alkyl olefins (entries 1– 2), but poor diastereoselectivity and just good enantioselectivity in the case of acrylates and vinyl amides (entries 3– 5).

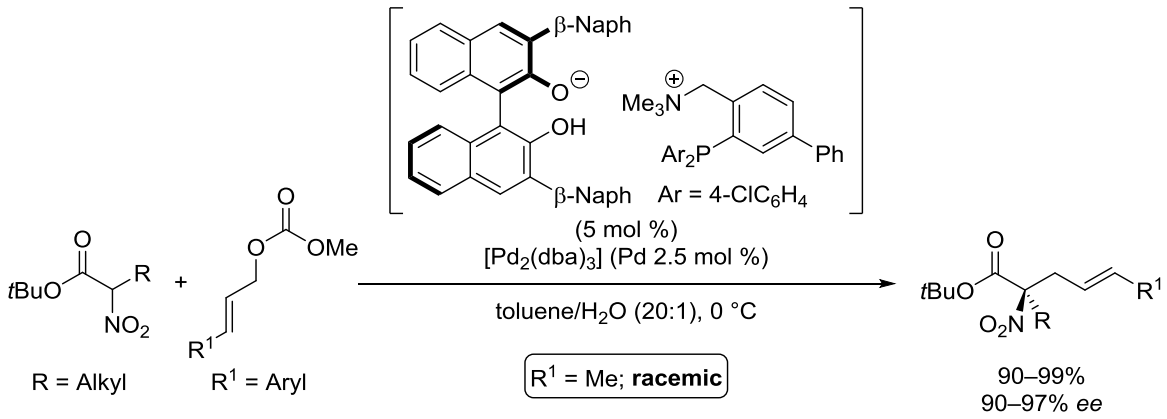
Table 39. Co-catalyzed cyclopropanation of α-nitro diazoacetates.



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

An interesting example of Pd-catalyzed nitroacetate allylation was described by Ooi's research group in 2012,[270] where the enantiocontrol was achieved by a chiral binaphtholate anion paired with an achiral cationic ammonium-phosphine hybrid ligand (Scheme 71). Allylation with γ-substituted allylic carbonates occurred in excellent yields and enantioselectivities, although no enantiocontrol was obtained when methyl allyl carbonate was tested.

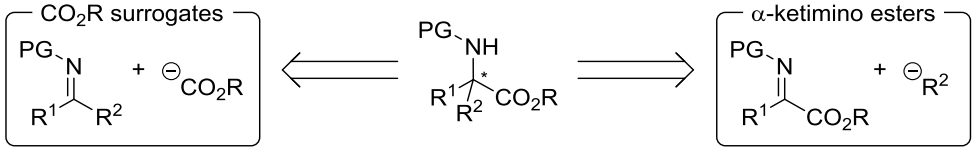
[269] Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8460–8463.
[270] Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *Nat. Chem.* **2012**, *4*, 473–477.



Scheme 71.

3.1.2.3. **Nucleophillic additions to ketimines**

Another well known strategy for the asymmetric synthesis of α,α-disubstituted α-amino acid derivatives is the addition of different nucleophiles to ketimines. Two different approaches can be employed for this purpose: First, the asymmetric nucleophilic addition of carboxylate anion surrogates (e.g. cyanide) which upon simple transformations could lead to the desired carboxylic acid moiety. The second would involve the asymmetric addition of a *C*-nucleophile to an α-ketiminoester, affording the desired amino acid derivative in a direct manner Scheme 72.



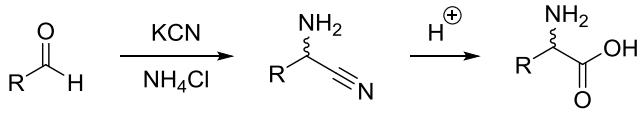
Scheme 72.

3.1.2.3.1. Addition of carboxylate surrogates to ketimines

One of the most known reactions in organic chemistry belongs to this section. The Strecker reaction,[271] or cyanation of imines, is a widely used strategy for the obtention of α-amino acids, especially employing aldimines (Scheme 73).[272]

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

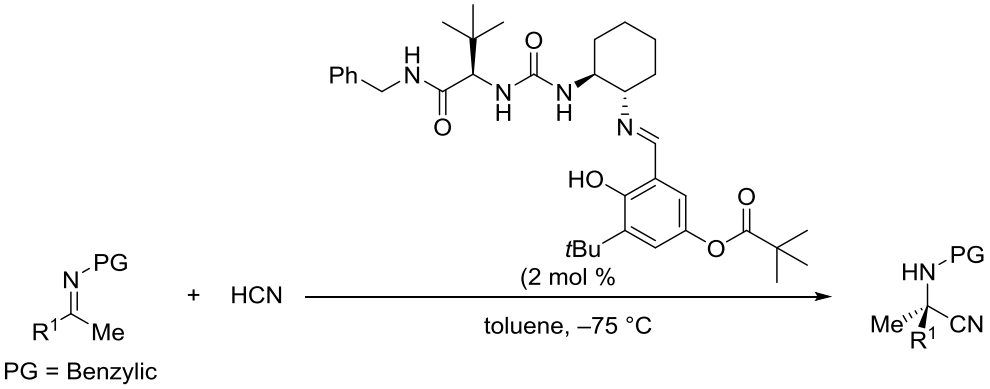
[272] For recent reviews on the asymmetric Strecker reaction, see: a) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947–6983. b) Cai, X. H.; Xie, B. *Arkivoc* **2014**, 205–248. For a leading book on the topic, see: c) Masakatsu Shibasaki et al., *The Catalytic Asymmetric Strecker Reaction*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



Scheme 73. Scheme of the original Strecker reaction.

Ketimines have been less exploited in part because of their attenuated reactivity as compared with aldimines, and also because their tendency to tautomerize to the corresponding enamine, in the case of aliphatic imines. The first asymmetric catalytic Strecker reaction with ketimines was perfomed by Jacobsen employing a urea-Schiff base catalyst (Table 40).[273] Aryl ketimines rendered excellent yields and enantioselectivities, except for the ketimine bearing an *ortho*-bromo aryl substituent (entry 2). *tert*-Butyl substituted ketimine also afforded excellent yield but moderate enantioselectivity (entry 3). Additionally, extremely dangerous cyanhydric acid was employed, a strategy nowadays avoided by most of research groups.

Table 40. Hydrocyanation of ketimines using cyanhydric acid.



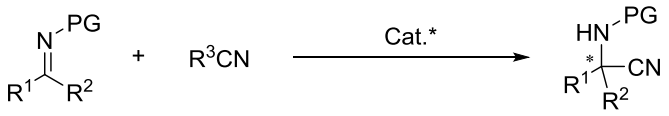
Entry	R^1	Yield (%)	*ee* (%)
1	Aryl	97– 99	88– 95
2	2-Br-C_6H_4	45	42
3	*t*Bu	98	70

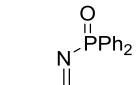
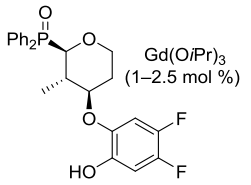
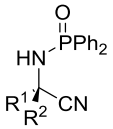
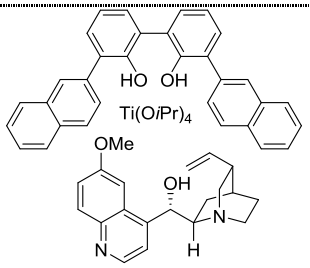
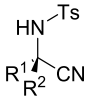
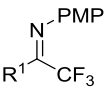
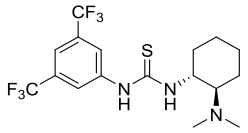
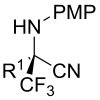
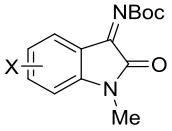
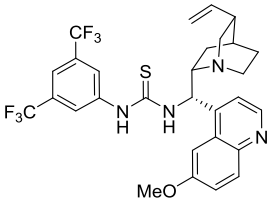
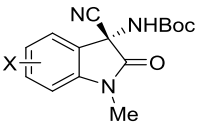
The other examples depicted in Table 41 are the most recent examples of cyanation of *N*-activated ketimines reported to date, employing TMSCN (trimethylsilyl cyanide) as cyanide source in all cases.[274]

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

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

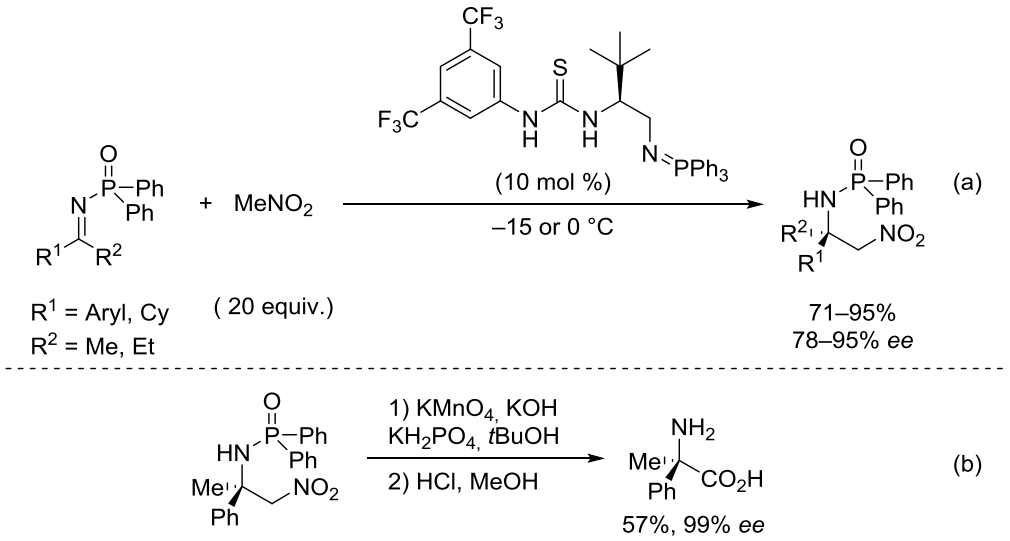
Table 41. Hydroacyanation of activated ketimines employing other cyanide sources than HCN.



	Electrophile	R^3	Cat.*	Prod.	Results	Ref.
1	 R^1 = Alkyl, Aryl R^2 = Me, Et	TMS	 (2– 5 mol %)		73–99% 74–99% *ee*	274a
2	 R^1 = Alkyl, Aryl R^2 = Alkyl, Aryl PG = Ts	TMS, CO_2Et	 (10 mol %)		95–99% 8–99% *ee*	274b
3	 R^1 = Alkyl, Aryl	TMS	 (5 mol %)		5–27 days 83–95% 25–99% *ee*	274c
4	 X = Br, F, Cl, Me, OMe, OCF_3, NO_2	TMS	 (10 mol %)		60–98% 78–98% *ee*	274d

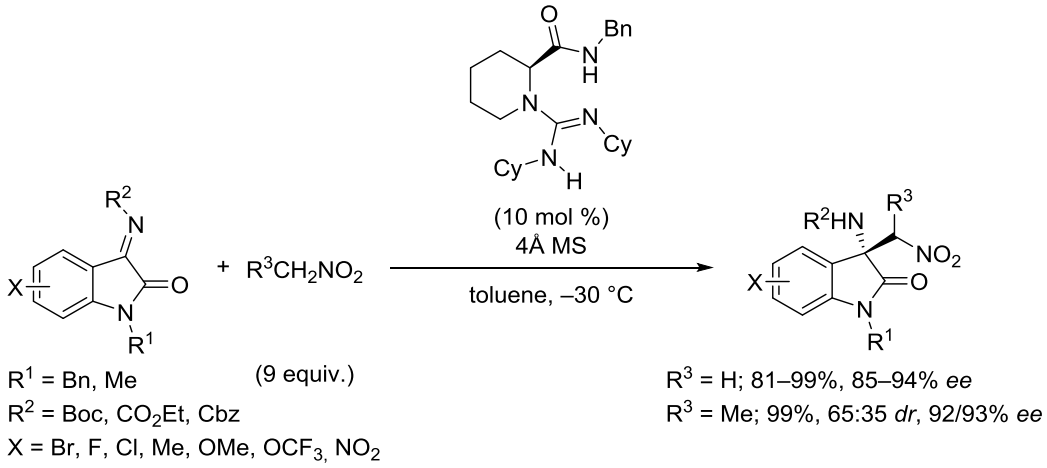
Recently, Dixon and co-workers reported a new strategy to obtain α,α-disubstituted α-aminoacids based on a bifunctional thiourea-based iminophosphorane catalyst and the use of nitromethane as an anionic carboxylate equivalent.[275] Thus the addition of nitromethane to ketimines under these conditions (Scheme 74, equation a), took place with very good to excellent yields and enantioselectivities, and subsequent Nef reaction afforded the target quaternary α-amino acid (equation b).

[275] Núñez et al.see ref. 45 page 15.



Scheme 74.

To date, there is only another example in literature using this strategy, a chiral bifunctional guanidine-catalyzed enantioselective aza-Henry reaction of isatin-derived ketimines reported by Liu and Feng's group.[276] The reaction afforded very good to excellent yields and enatioselectivities, although when nitroethane was tested instead of nitromethane low diastereoselectivity was attained (Scheme 75).



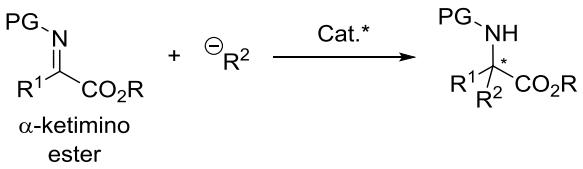
Scheme 75.

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

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

3.1.2.3.2. Nucleophillic additions to α-ketimino esters

A variation of the strategy described above involves the addition of *C*-nucleophiles to α-ketimino esters. As mentioned before, these acceptors are greatly activated by the effect of the electron withdrawing ester moiety. Thus, numerous examples concerning the use of α-ketimino esters through the reaction depicted in Scheme 76 have hitherto been reported, which have been comprehensively reviewed several times and will not be further discussed here.[277]



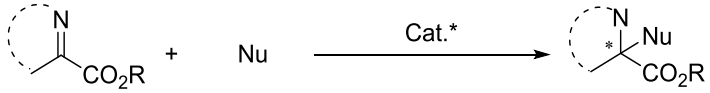
Scheme 76.

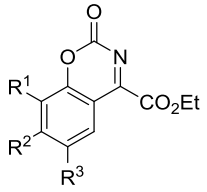
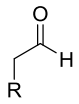
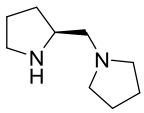
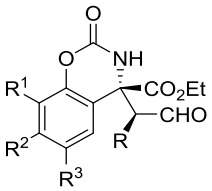
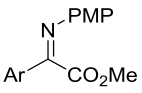
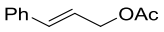
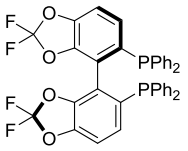
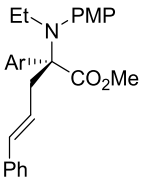
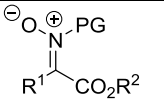
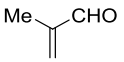
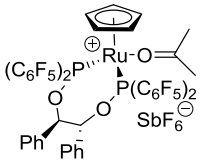
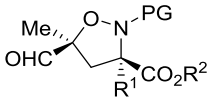
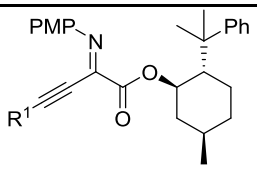
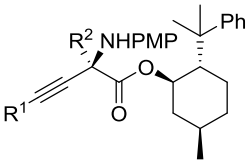
However, this strategy is still fully competitive, and new methodologies and variations are developed constantly. Table 42 collects selected examples that include a Mannich reaction reported by Jørgensen and co-workers in 2004, which occurred through enamine activation (entry 1), and the most recent examples involving ketimino esters reported from 2014 to date.[278]

[277] For reviews on the topic, see: ref. 234 page 101.

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

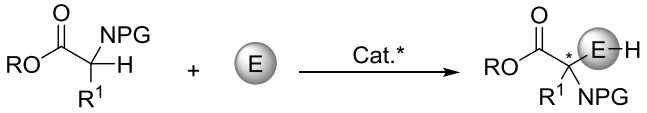
Table 42. Most recent examples of additions to ketiminoesters.



	Ketimine	Nu	Cat.*	Prod.	Results	Ref.
1	 R^1, R^2, R^3 = H, Me, OMe; R^2 = Me	 R = Alkyl	 (5 mol %)		45–98% 4:1– 20:1 42–95% *ee*	278a
2		1) EtMgBr 2) 	[η-$C_3H_5PdCl]_2$ (7.5 mol %)  (4.9 mol %)		72–89% 74–92% *ee*	278b
3	 R^1 = Me, Et, *n*Pr; R^2 = Me, Et, *t*Bu; PG = Bn, Me		 (10 mol %)		42–99% 70:30– 99:1 *endo/exo* 79–92% *ee*	278c
4	 R^1 = TBS, Ph	R^2MgCl R^2 = Alkyl	$ZnCl_2$ (1.1 equiv) $TMSCH_2MgCl$ (2.2 equiv)		60–98% >99:1 *dr*	278d

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

Probably the most commonly employed strategy for the asymmetric synthesis of α,α-disubstituted α-amino acid derivatives is the electrophilic α-alkylation of α-monosubstituted α-amino surrogates (Scheme 77).



Scheme 77.

In the following, precedents in literature have been cathegorized according to the type of (pro)nucleophile α-amino acid surrogate employed, namely α-amino acid derived Schiff bases,[279] α-(iso)cyano acetates and azlactones.

3.1.2.4.1. Schiff bases

It is more than two decades since the first report dealing with the asymmetric creation of a quaternary centre from a Schiff base derived from the *tert*-butyl ester of alanine (Figure 34), employing phase-transfer catalysis (PTC).[280]

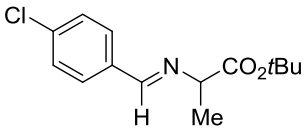


Figure 34. Alanine Schiff base.

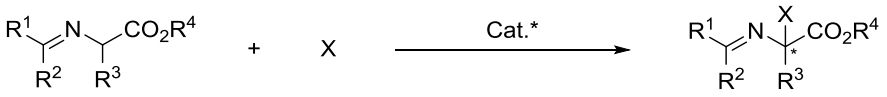
Ever since the pioneering work on the subject by the laboratory of O'Donnell, among others, numerous examples employing this strategy have appeared, and have been extensively gathered in several reviews.[281] Also in recent years, PTC has amply applied to perform asymmetric alkylations on this substrates, being Maruoka's group one of the most prolific.[282] Apart from α-alkylation, other asymmetric transformations of α-amino acid-derived Schiff bases under PTC conditions include arylation (Table 43, entry 1)[283]

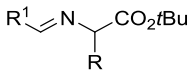
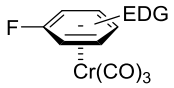
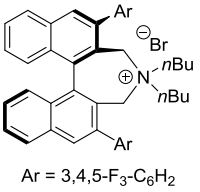
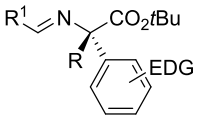
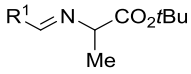
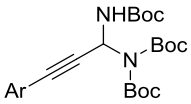
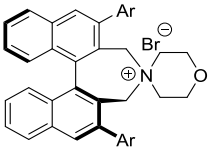
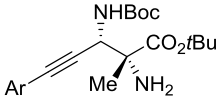
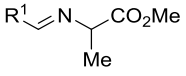
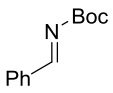
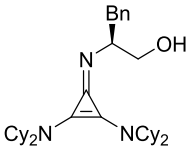
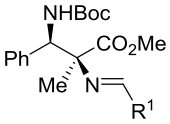
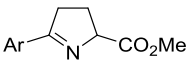
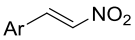
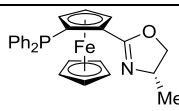
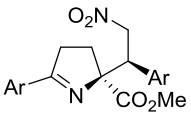
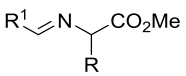
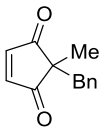
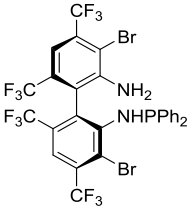
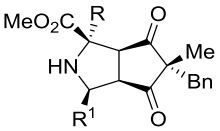
---

[279] For a review on Hugo Schiff and Schiff bases, see: Tidwell, T. T. *Angew. Chem. Int. Ed.* **2008**, *47*, 1016–1020.
[280] O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591–594.
[281] For reviews on the topic, see: ref. 234 page 101.
[282] For examples of PTC alkylation of Schiff bases employing different alkylating agents, see: a) Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900–4904. b) Maruoka, K. *Chem. Rec.* **2010**, *10*, 254–259. c) Maruoka, K. *Pure Appl. Chem.* **2012**, *84*, 1575–1585. d) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. *Asian J. Org. Chem.* **2014**, *3*, 433–436.
[283] Shirakawa, S.; Yamamoto, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 838–840.

and Mannich-type reaction (entry 2).[284] In addition, a cyclopropenimine-catalyzed *syn*-Mannich reaction (entry 3),[285] a Cu/Ag catalyzed Michael reaction (entry 5),[286] and a Ag(I) catalyzed 1,3-dipolar cycloaddition (entry 5)[287] have also been reported. One interesting common aspect to all these methods employing amino acid-derived Schiff bases is that simple hydrolysis on adducts frees the α-amino acids or esters.

Table 43. Most recent addition and substitution reactions of α-substituted Schiff bases.



	Schiff base	X	Cat.*	Prod.	Results	Ref.
1	 R^1 = 4-ClC_6H_4 R = Alkyl	 EDG = H, Me, OMe, OEt, SMe, NMe_2	 Ar = 3,4,5-F_3-C_6H_2 (10 mol %)		51–78% 88–99% *ee*	283
2	 R^1 = 2-thienyl	1)  2) HCl, EtOAc, r.t.	 Ar = 3,5-(3,5-$(CF_3)_2$-$C_6H_3)_2$-C_6H (5 mol %)		50–70% >20:1 *dr* 90–91% *ee*	284
3	 R^1 = 4-ClC_6H_4		 (20 mol %)		94% 64:36 *dr* 63/44% *ee*	285
4			 (5.5 mol %) CuOAc (or AgOAc) (5 mol %)		69–86% 74:26– 92:8 *syn/anti* 94– 99% *ee* (1:99 *anti* with AgOAc)	286
5	 R^1 = Aryl R = Me, Bn		 AgOAc/L (5 mol %)		88–93% >20:1 *dr* 94–99% *ee*	287

[284] Kano, T.; Kobayashi, R.; Maruoka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 8471–8474.
[285] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799–11802.
[286] Koizumi, A.; Kimura, M.; Arai, Y.; Tokoro, Y.; Fukuzawa, S. *J. Org. Chem.* **2015**, *80*, 10883–10891.
[287] Liu, H.-C.; Liu, K.; Xue, Z.-Y.; He, Z.-L.; Wang, C.-J. *Org. Lett.* **2015**, *17*, 5440–5443.

3.1.2.4.2. α-(Iso)cyanoacetates

Other commonly used nucleophilic α-amino acid surrogates are α-isocyanoacetates and α-cyanoacetates, which are structural isomers (Figure 35).

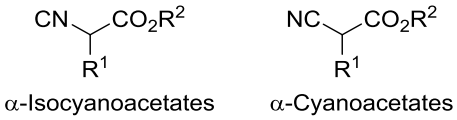
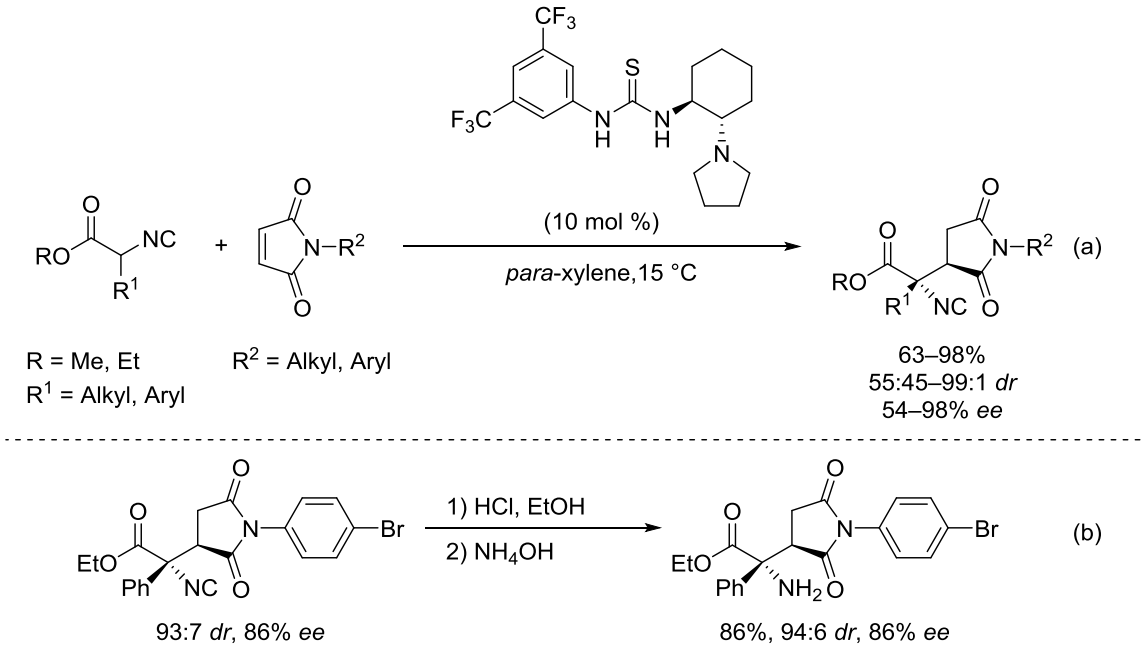


Figure 35.

In 2012, the research group of Wang and Xu introduced α-isocyanoacetates as amino acid surrogates for the enantioselective synthesis of quaternary α-amino acids.[288] Michael addition to maleimides was performed in the presence of a thiourea-based Brønsted base catalyst, affording the addition adducts in good to excellent yields, and diastereo- and enantioselectivity (Scheme 78, equation a). Additionally, acidic hydrolysis of the isonitrile group on one of the adducts provided the quaternary α-amino ester in very good yield and with retention of stereochemistry (equation b).

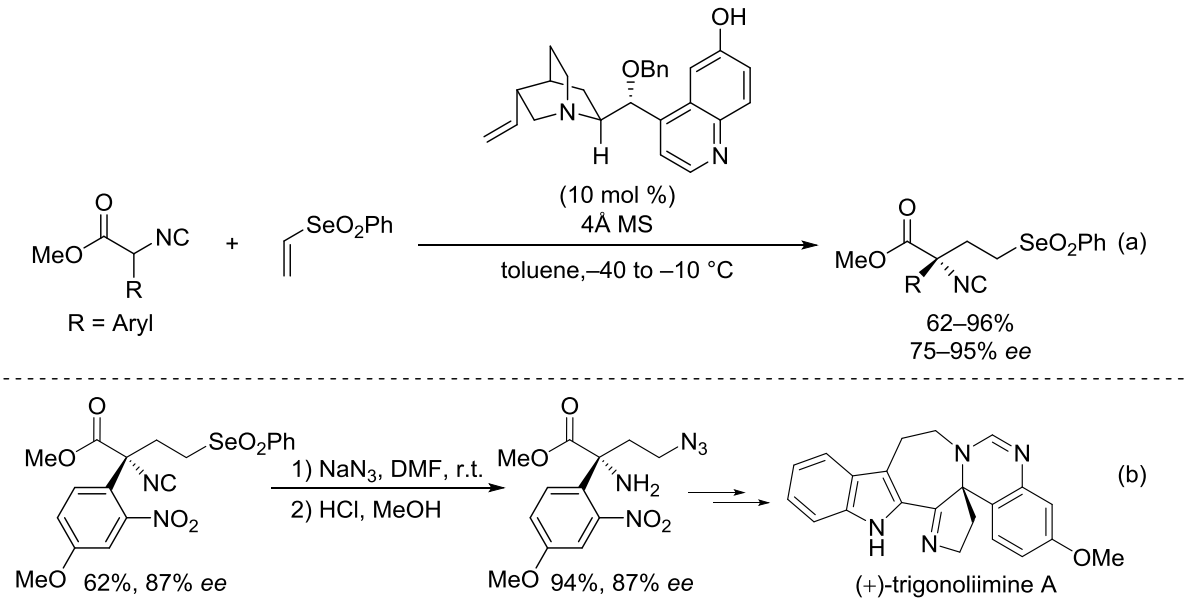


Scheme 78.

Later on, Zhou and co-workers reported the Brønsted base-catalyzed highly enantioselective Michael addition of α-aryl α-isocyanoacetates to phenyl vinyl

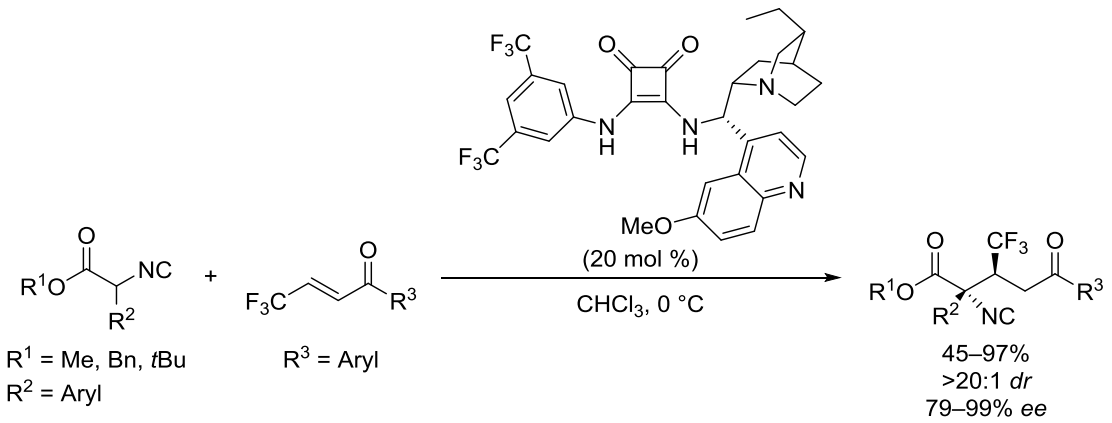
[288] a) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Jia, L.-N.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *J. Org. Chem.* **2012**, *77*, 2947–2953. For the squaramide-catalyzed version of the reaction, see: b) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**, *69*, 10763–10771.

selenone.[289] The reaction rendered the desired adducts in good to excellent yields and enantioselectivities (Scheme 79, equation a). Elaboration of the product afforded the azide-bearing quaternary α-amino ester needed as building block for the synthesis of (+)-trigonoliimine A (equation b).



Scheme 79.

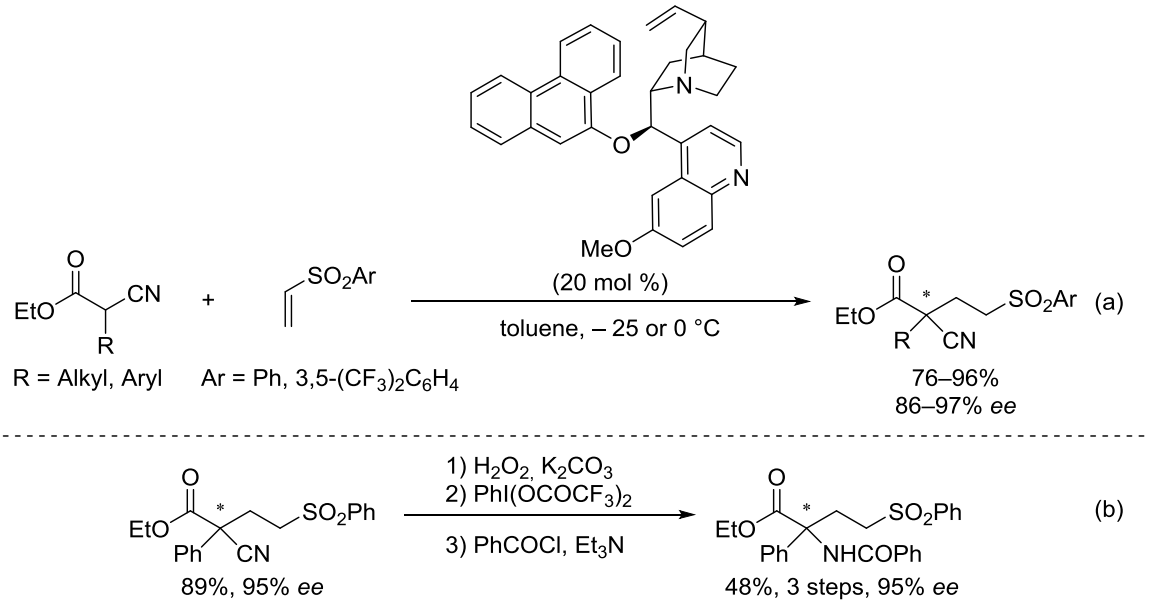
To date, just another example of the use of isocyanoacetates as pronucleophiles has been reported,[290] which consist in the squaramide/tertiary amine-catalyzed asymmetric Michael addition of α-isocyanoacetates to β-trifluoromethylated enones (Scheme 80). Moderate to excellent yield and enantioselectivities and excellent diastereoselectivities were obtained with α-aryl cyanoacetates and aryl substituted enones, but no reaction occurred when α-alkyl cyanoacetates or alkyl substituted β-trifluoromethylated enones were employed (R^2 = alkyl or R^3 = alkyl).



Scheme 80.

[289] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12714–12718.
[290] Zhao, M.-X.; Zhu, H.-K.; Dai, T.-L.; Shi, M. *J. Org. Chem.* **2015**, *80*, 11330–11338.

α-Cyanoacetates have been commonly used to access β-amino acids through hydrolysis of the nitrile group.[291] However, they can also be employed to obtain quaternary α-amino acids through an alternative transformation of the nitrile into amine via Curtius rearrangement. For instance, Deng's research group described the conjugate addition of ethyl cyanoacetates to vinyl sulfones catalyzed by *Cinchona* alkaloids,[292] affording the reaction adduct in very good to excellent yields and enantioselectivities (Scheme 81, equation a). Elaboration of these products led to enantiopure quaternary α-amino acids, although the process required three steps, and the overall yield was moderate (equation b).



Scheme 81.

3.1.2.4.3. Azlactones

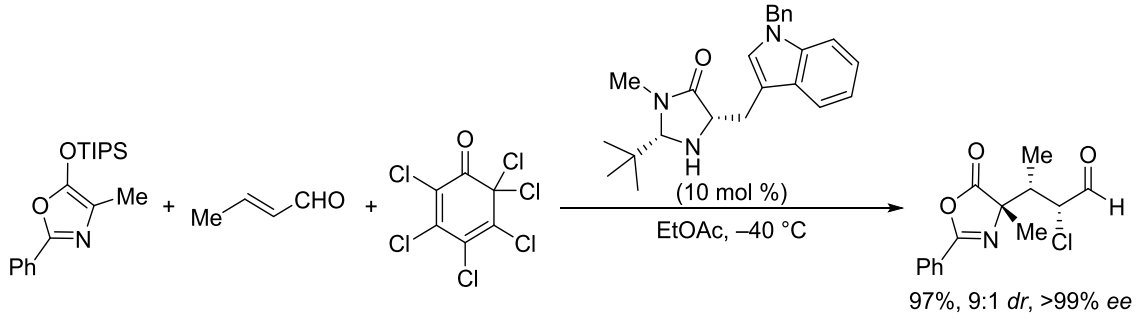
Azlactones, or 4*H*-oxazol-5-ones (page 42), formally are protected forms of α-amino acids and they have also been used as (pro)nucleophiles in electrophilic α-alkylations in a complementary strategy to obtain α,α-disubstituted α-amino acids.

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

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

[292] a) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949. For previously mentioned examples of the asymmetric α-amination of cyanoacetates, see: b) see ref. 244 page 5 and reference therein. For a recent example of diastereoselective Pd-catalyzed allylic alkylation of α-cyanoacetates, see: c) Trost, B. M.; Mahapatra, S.; Hansen, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6032–6036. For an early example of Rh catalyzed Michael addition of cyanoacetates to obtain quaternary α-amino acids, see: d) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439–4454.

involving a preactivated azlactone in the form of silylenol ether, crotonaldehyde, and a chlorinating reagent (Scheme 82).[293]



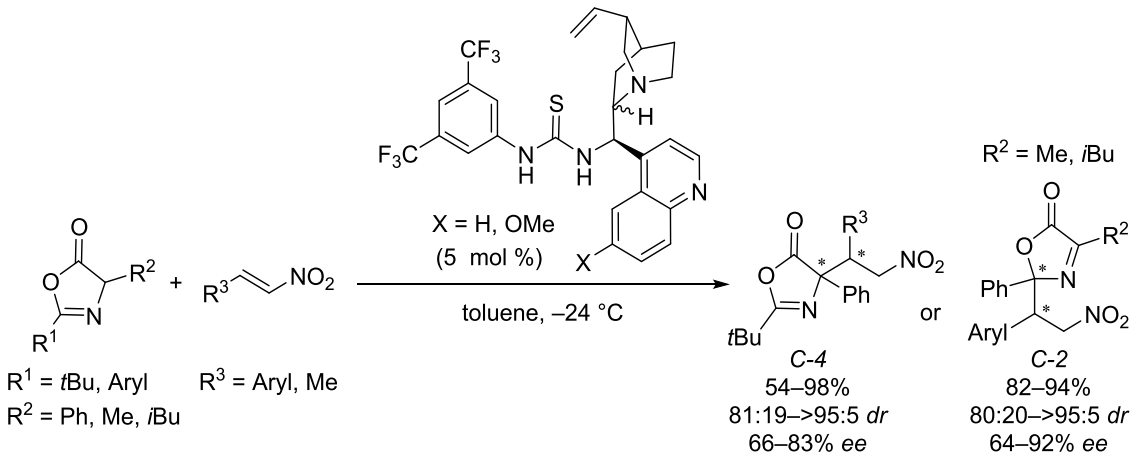
Scheme 82. Example of indirect Michael reaction of azlactones with enals.

A successful iminium ion mediated direct Michael addition of azlactones to enals was developed by Jørgensen's research group, who observed that addition exclusively occurred at the C-4 addition of the azlactone in every case.[294] Soon after, the same group reported the first 4*H*-oxazol-5-one addition to nitroolefins, where regiochemistry of the reaction was rationalized.[295] Generally, the relative nucleophilicities of these two positions were greatly affected by several factors, including substituents on the azlactone ring, particularly substituents in C-2 position, electrophiles, catalysts, and reaction conditions. As depicted in Scheme 83, aryl substituents at C-2 favoured attack from this carbon, while hindered aliphatic ones (i.e. *t*Bu) directed C-4 attack (entries 1− 2 vs. 3− 4). Nevertheless, thiourea-based bifunctional Brønsted bases conducted the Michael reaction with good to excellent yields, very good diastereoselectivity and moderate to very good enantioselectivity in both cases. It is remarkable that acidic hydrolysis upon mild conditions of the C-4 reaction adducts led to *N*-protected quaternary α-amino acids in excellent yields.

[293] Huang et al.ref. 32 page 12. For a strategy where azlactones are used as electrophiles, see: b) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032–9036.

[294] a) , J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037. For subsequent examples of Michael addition of azlactones to enals using iminium ion activation, see: b) Hayashi, Y.; Obi, K.; Ohta, Y.; Okamura, D.; Ishikawa, H. *Chem. Asian J.* **2009**, *4*, 246–249. c) Companyó et al.ref 107a page 32. d) Dell'Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063–8070.

[295] a) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 10958–10966. For a regio- and diastereoselective C-4 Michael addition of azlactones to nitroolefins with triethylamine, see: b) Balaguer, A.-N.; Companyó, X.; Calvet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2009**, 199–203. For an only example of Michael addition of dioxolanes to nitroolefins with bifunctional thioureas, see: c) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107–2110.



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

Scheme 83. Represenative examples of Michael addition of azlactones to nitroolefins.

During the last decade, multiple examples of organocatalyzed Mannich,[296] aldol,[297] and conjugate additions[298] of azlactones have been reported employing different electrophiles and activation modes, obtaining both C-4 and C-2 selectivities.[299] Table 44

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

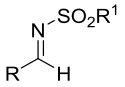
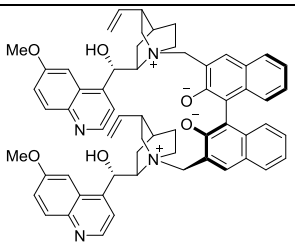
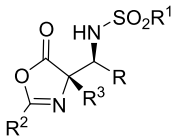
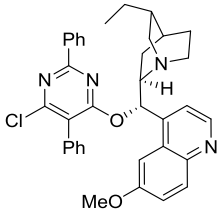
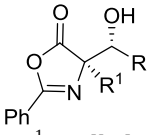
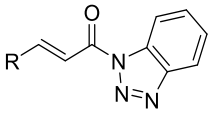
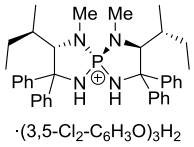
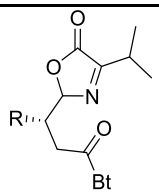
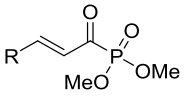
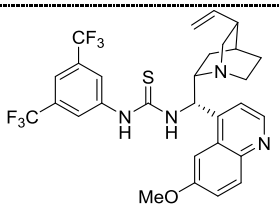
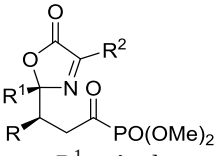
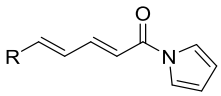
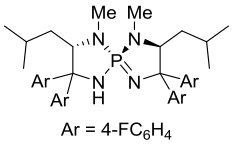
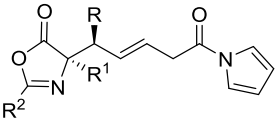
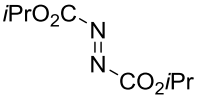
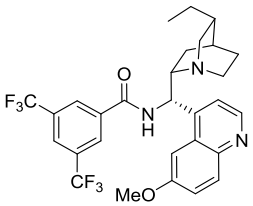
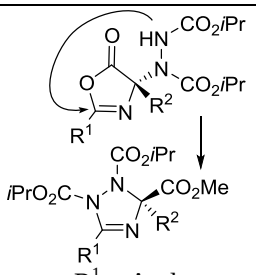
[297] For the Brønsted base catalyzed C-4 selective aldol reaction of 2-phenyl azlactones to aliphatic aldehydes, see: b) Zheng, Y.; Deng, L. *Chem. Sci.* **2015**, *6*, 6510–6514.

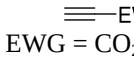
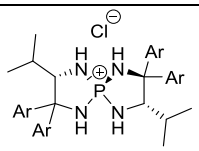
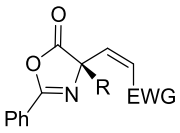
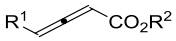
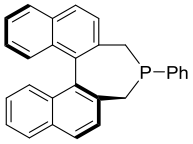
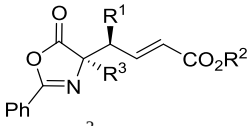
[298] For a C-2 selective Michael addition of 2-unsubstituted azlactones to α,β-unsaturated acylbenzotriazoles employing phosphonium ion PTC, see: a) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120–123. For the C-2 selective Michael addition of 2-aryl azlactones to α,β-unsaturated acyl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

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

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

Table 44. Diverse electrophiles employed with azlactones as nucleophiles.

	Electrophile	Cat.*	Product	Results	Ref.
1	 R = Alkyl R^1 = 4-*i*PrC_6H_4	 (10 mol %)	 R^2 = 2-naphthyl R^3 = Alkyl	76– 99% 2:1– 7:1 *dr* 96– 99% *ee*	296a
2	 R = Alkyl	 (15 mol %)	 R^1 = Alkyl	83– 98% 91:9– 98:2 *anti/syn* 88– 95% *ee*	297
3	 R = Aryl, alkyl	 ·(3,5-Cl_2-$C_6H_3O)_3H_2$ (1 mol %)	 R = Aryl, alkyl	90– 98% >20:1 *dr* 93– 98% *ee*	298a
4	 R = Alkyl	 (10 mol %)	 R^1 = Aryl R^2 = *i*Bu, *i*Pr	50– 79% 82– 99% *ee*	298b
5	 R = Alkyl, Aryl, (*E*)-R-CH_2=CH_2	 Ar = 4-FC_6H_4 (5 mol %)	 R^1 = Alkyl R^2 = 2,6-$(MeO)_2C_6H_3$	84– 99% >20:1 *dr* 90– 98% *ee*	298c
6		 (10 mol %)	 R^1 = Aryl R^2 = Alkyl	42– 95% 81– 93% *ee*	298d

7	 EWG = CO_2Me, CN	 Ar = *p*CF_3-C_6H_4 (5 mol %)	 R = Aryl, Bn, *i*Bu	78– 95% 1:10– 1:20 *E/Z* 56– 90% *ee*	298e
8	 R^1, R^2 = Alkyl, alkenyl	 (5 mol %)	 R^3 = Alkyl	83– 98% 91:9– 98:2 *anti/syn* 88– 95% *ee*	298f

Organocatalytic asymmetric Michael addition to enones, however, was not developed until 2013.[300] Table 45 below gathers all examples reported to date.

Amarante's research group presented the first organocatalytic version of the reaction, and, although the catalyst was racemic, excellent diastereocontrol was gained (entry 1).[301] Total enantiocontrol was achieved by Wang and co-workers, employing β-trichloromethyl substituted enones as specific substrates (entry 2).[302] Almost simultaneously, our group developed the squaramide/tertiary amine-catalyzed addition of azlactones to α'-silyloxy enones to obtain with excellent enantioselectivities ketol adducts easily convertible into carboxylic acids, aldehydes or ketones (entry 3).[303] Recently, Wang and co-workers demonstrated that chalcones with *ortho*-hydroxyaryl substituents at C^{β} could direct the azlactone addition to take place just with C-2 selectivity (entry 4).[304]

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

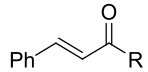
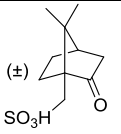
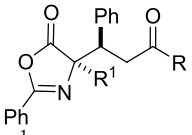
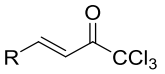
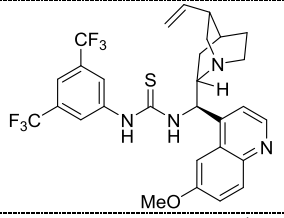
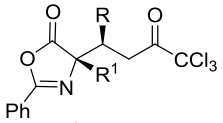
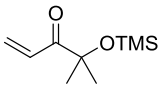
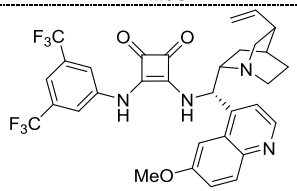
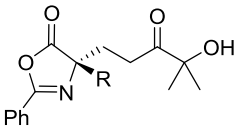
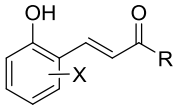
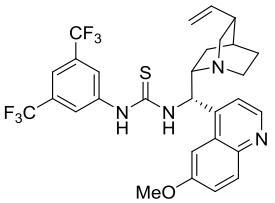
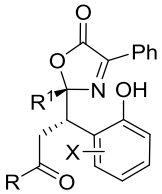
[301] a) Ávila, E. P.; de Mello, A. C.; Diniz, R.; Amarante, G. W. *Eur. J. Org. Chem.* **2013**, *2013*, 1881–1883. For a Mannich addition of 2-phenyl azlactones to aryl imines performed by the same group, see: b) Ávila et al. ref. 296 page 128.

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

[303] Badiola et al. see ref. 76a page 24.

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

Table 45. Michael addition of azlactones to enones. (R^1, R^2, R^3 = Alkyl, Aryl; X = H, Me, MeO, Cl)

	Electrophile	Catalyst	Product	Results	Ref.
1	 R = Alkyl	 (7 mol %)	 R^1 = Me, Bn, *i*Bu	53– 80% >20:1 *dr*	301a
2	 R = Aryl, Me		 R^1 = Alkyl	58– 85% 2:1– 20:1 *dr* 63– 99% *ee*	302
3			 R = Ph, *i*Pr, *i*Bu, Bn	71– 77% 88– 92% *ee*	303
4	 R = Aryl X = Cl, Me, MeO, H		 R^1 = Aryl, *t*Bu	54– 99% >20:1 *dr* 72– 99% *ee*	304

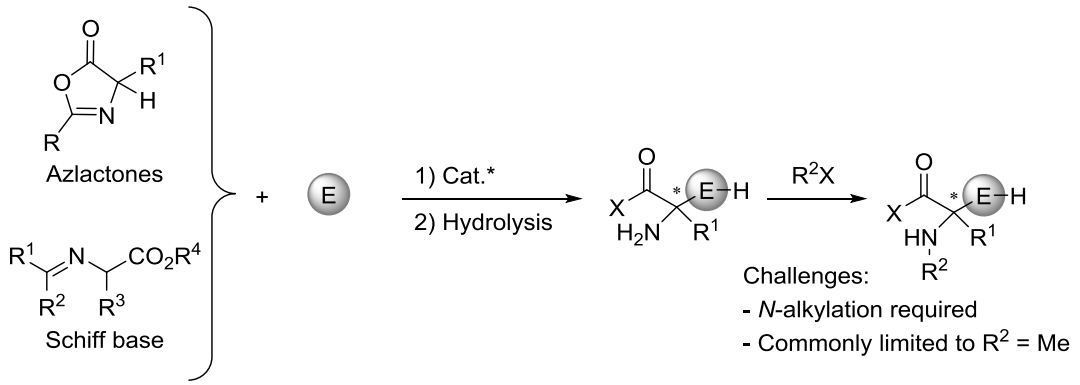
3.2. **Michael addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins**

3.2.1. **Working hypothesis and synthetic plan**

The continuous interest in quaternary α-amino acids (page 101) has prompted the apparition of many methods for their stereoselective preparation, although robust and truly general and efficient catalytic approaches are still demanded.[305] As mentioned in the introduction of this chapter, one of the most employed strategies to access quaternary *NH* α-amino acids consists in the α-functionalization of a nucleophilic α-amino acid surrogate or template, e.g. Schiff base or azlactone, and subsequent hydrolysis (Scheme 84).[306] However, the majority of these methods are unable to afford the *N*-substituted analogues directly,[307] and an additional *N*-alkylation process is required.[308] This represents a major

[305] For reviews on the topic, see: ref. 234 page 2.
[306] Fisk et al. see ref. 140a page 42.
[307] For rare examples, see: a) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294–13297. b) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 179–183. ref. **¡Error! Marcador no definido.** page 7.
[308] For the synthetic preparation of *N*-methyl α-amino acids, see: Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2004**, *104*, 5823–5846.

drawback, since *N*-alkyl α-amino acid-derived compounds are potential therapeutic candidates due to their comparatively higher lipophilicity and membrane permeability as compared to the parent free amino derivatives.[309]



Scheme 84.

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

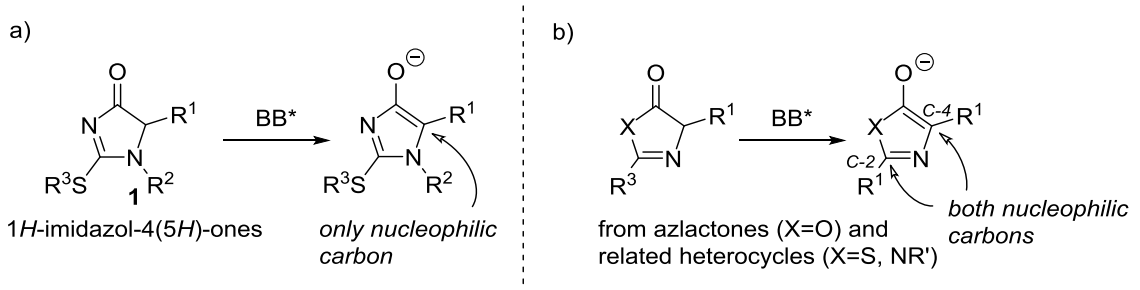
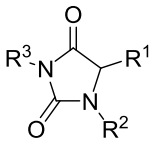


Figure 36. Comparison of 1*H*-imidazol-4(5*H*)-ones and analogous heterocycles previously documented.

Additionally, 1*H*-imidazol-4(5*H*)-ones are synthetic analogues to hydantoins (Figure 37), these latter heterocycles of great therapeutical and biological interest.[310]

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

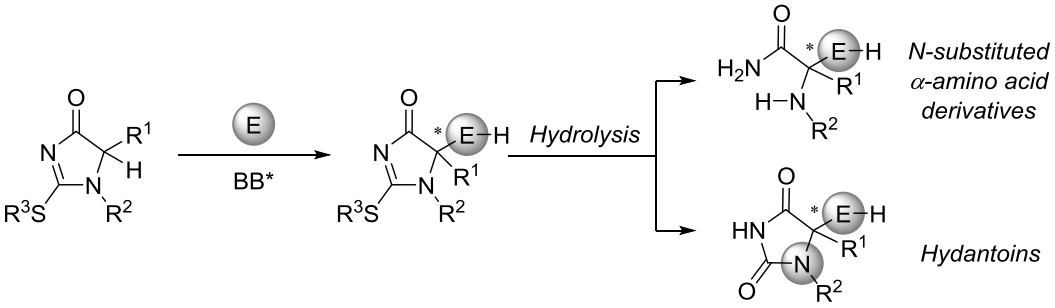
[310] For a review on the importance of hydantoins and their synthesis, see: a) Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int.* **2004**, *36*, 391–443. and references therein. For a recent synthesis of aryl hydantoins, see: b) Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8961–8965.



Hydantoins

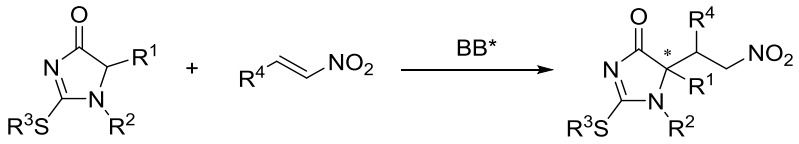
Figure 37.

For this hypothesis to be fulfilled effective control of the stereochemistry of the *C–C* bond-forming step would be required. In this respect, as far as we know, asymmetric reactions of 1*H*-imidazol-4(5*H*)-ones were unprecedented at the time of initiation of the work presented herein.



Scheme 85. General reaction of 1*H*-imidazol-4(5*H*)-ones with electrophiles and hydrolysis of the correnspondingadduct.

On this basis, 1*H*-imidazol-4(5*H*)-ones were chosen as pronucleophiles, and in a first instance nitroolefins were chosen as electrophiles. During the reaction two contiguous stereocentres would be created and thus control of the diastereoselectivity did constitute another issue (Scheme 54).



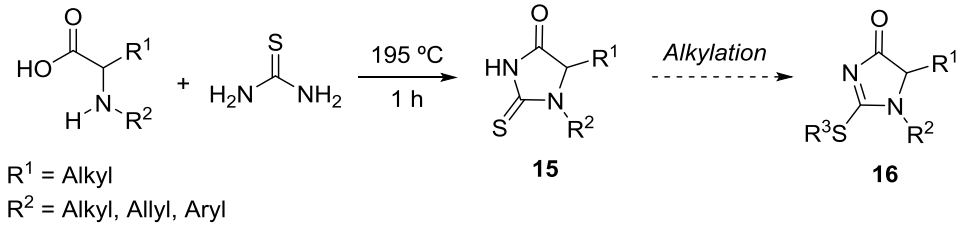
Scheme 86. Proposed reaction for the first investigation.

3.2.2. **Results and discussion**

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

First, we envisioned that the cyclization of *N*-substituted α-monosubstituted α-amino acids with thiourea followed by an *S*-alkylation of the formed thiohydantoins **15** could yield the desired 1*H*-imidazol-4(5*H*)-ones **16** (Scheme 87). Actually, the

thiohydantoins **15** were produced by heating a mixture of thiourea and the corresponding α-amino acid, a method that offered the advantages of simplicity, low cost, easy work-up and scalability.[311]

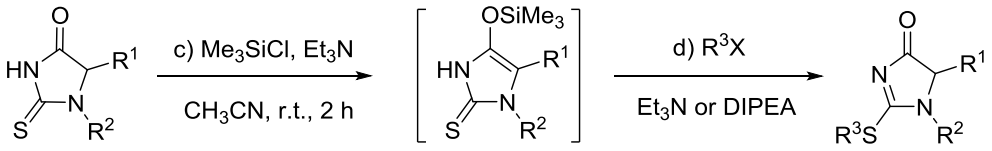


Scheme 87.

Nevertheless, the alkylation of thiohydantoins **15** presented quite a challenge. First attempts using benzyl bromide and triethylamine afforded a mixture of *O*-benzyl and *O*,*S*-dibenzyl products, clearly showing that chemoslective *S*-alkylation of these adducts is not trivial under this basic conditions. Well aware of this potential pitfall, the problem was solved by including a previous and selective *O*-silylation step, which consisted in the silylation of the carbonyl group (taking advantage of the *O*-*Si* affinity). In this way, the subsequent *S*-alkylation could be clearly accomplished under standard conditions (R^3X/Et_3N), as shown in Table 46. It should be stressed that the yields reported in Table 46 correspond to two one-pot reaction steps, and are not fully optimized.

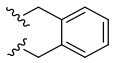
[311] Wang, Z. D.; Sheikh, S. O.; Zhang, Y. *Molecules* **2006**, *11*, 739–750.

Table 46.



15

16 R^3 = Bn,
17 R^3 = Me
18 R^3 = Et

Entry		R^1	R^2	R^3	Base	Yield (%)
1	**16a**	Me	Me	Bn	Et_3N	82
2	**16b**	Me	Bn	Bn	Et_3N	84
3	**16c**	Me	*i*Bu	Bn	Et_3N	73
4	**16d**	Me	Allyl	Bn	Et_3N	66
5	**16e**	Me	Ph	Bn	Et_3N	68
6	**16f**	Me	4-ClC_6H_4	Bn	Et_3N	83
7	**16g**	Me	3-$MeOC_6H_4$	Bn	Et_3N	85
8	**16h**	Bn	Me	Bn	Et_3N	74
9	**16i**	*n*Hex	Me	Bn	Et_3N	68
10	**16j**	*i*Bu	Me	Bn	Et_3N	71
11	**16k**	*i*Pr	Me	Bn	Et_3N	68
12	**16l**	-$CH_2CH_2CH_2$-		Bn	Et_3N	87
13	**16m**			Bn	Et_3N	78
14	**16n**	Bn	Bn	Bn	Et_3N	79
15	**17a**	Me	Me	Me	DIPEA	63
16	**18a**	Me	Me	Et	DIPEA	67

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

3.2.2.2. **Catalyst screening**

In order to check the validity of the initial hypothesis (Scheme 85), several Brønsted bases were evaluated as catalyst for the reaction of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** with nitroolefin **2a** (Table 48). At the beginning of the study, some representative bases derived from *Cinchona* alkaloids were explored, including quinine, and $(DHQ)_2PYR$, in dichloromethane at − 20 °C. The stereochemical outcome was disappointing when quinine was employed, affording moderate diastereo- and enantioselectivities (67%, 30:70 *dr*, 58% *ee*), while $(DHQ)_2PYR$ did not catalyze the reaction.

After these discouraging results, thiourea-based bifunctional catalyst **C5** was tested in the reaction. However, as illustrated in Table 48, although very good diastereoselectivity was achieved, the catalyst rendered only moderate enantioselectivity (90:10 *dr*, 70% *ee*). It is remarkable, that while quinine and especially triethylamine tend to afford one diastereomer pre-eminently, bifunctional catalysts bearing a *H*-bond donor moiety favoured the opposite one. This problem was addressed by employing thiourea-based achiral catalyst **C4** to obtain the racemic version of the adducts.

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

Thus, and taking Rawal's pioneering work on squaramides as reference,[312] we tested squaramide-based catalysts **C6**– **8** in the reaction under the same conditions. Quinine-based **C6** encouraged our quest, affording the expected adducts in excellent yield and promising diastereo- and enantioselectivity (99%, 90:10 *dr*, 86% *ee*). Effect of the temperature was then evaluated, but unfortunatey neither lower nor higher temperatures provided any benefit. Thus temperatures below − 20 °C rendered incomplete reactions and lower selectivities (Table 47, entries 1– 2), while increasing it lowered the diastereoselectivity (entries 4– 5).

Table 47. Temperature screening for the addition of **16a** to **2a** in presence of **C6**.[a]

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

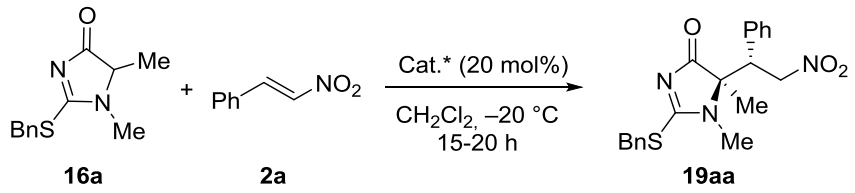
[a] Reaction conditions: **16a** (1 eq, 0.3 mmol), **2a** (2 eq., 0.6 mmol), **C6** (20 mol%) were stirred at room temperature for stated time in CH_2Cl_2. [b] Determined by ^{1}H-NMR analysis of the crude mixture. [c] Determined by HPLC for the major. diastereomer: IA Hex/*i*Pr/EtOH 85:14:1 f=0.5 mL/min,

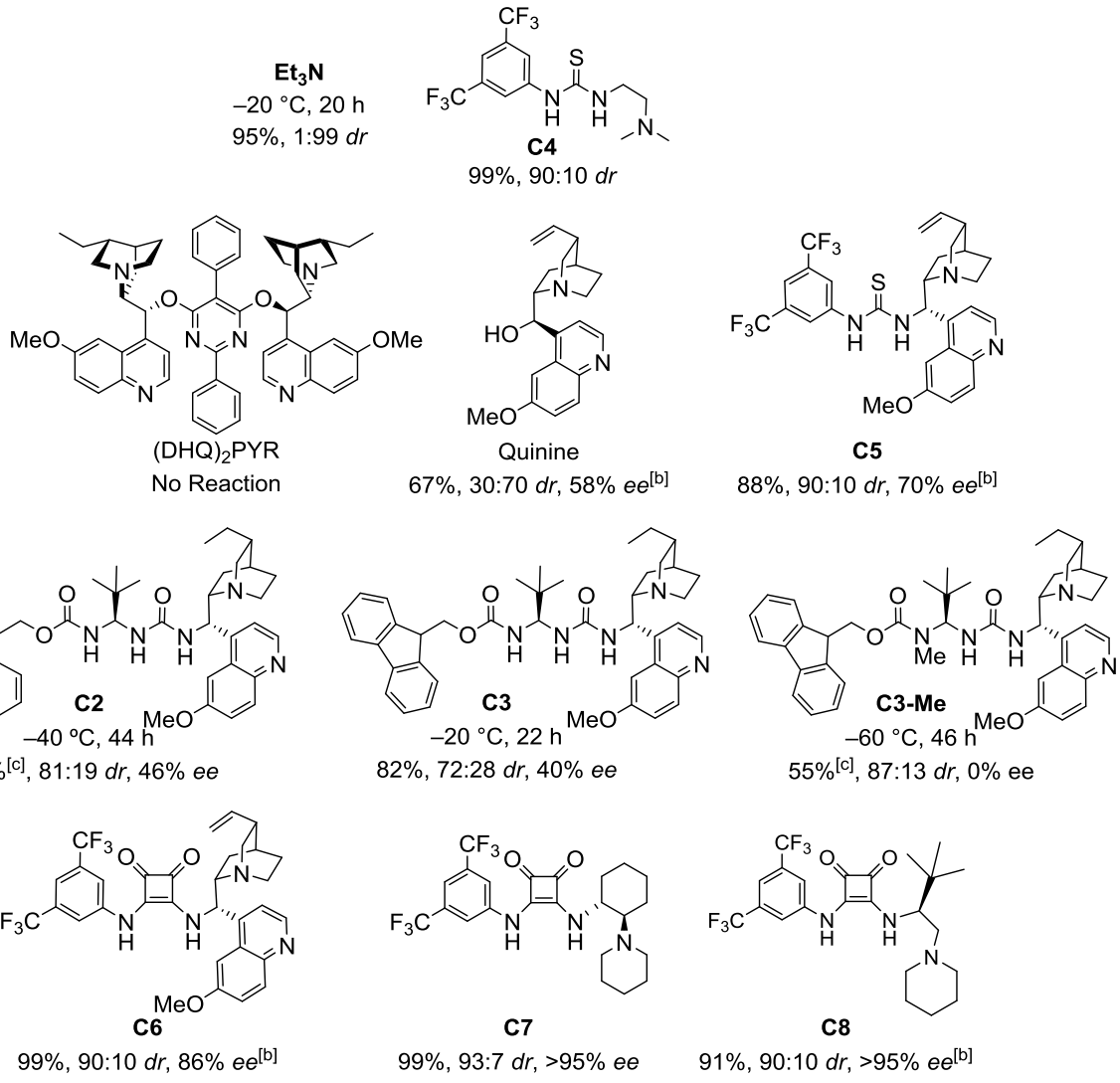
Next, after replacing the 9-*epi*-9-amino-9-deoxyquinine group in **C6** with the 1,2-diaminocyclohexane scaffold the selectivity was improved (**C7**, 93:7 *dr*, >95% *ee*). For catalyst **C8**, where the 3,3-dimethylbutane-1,2-diamine scaffold was inserted, no significant changes in the outcome of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

[312] a) Malerich et al. see ref. 38 page 12. For a review on the synthesis and physical properties of squaramides, see: b) Ian Storer, R.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330–2346.

dr, – 95% *ee*), albeit the configuration of the adduct was opposite to that obtained with the latter.

Table 48. Catalyst screening for 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** addition to *trans*-*β*-nitrostyrene **2a**. [a-b]



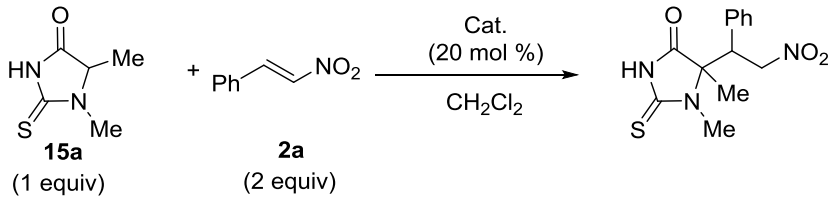


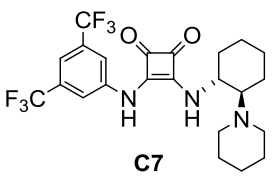
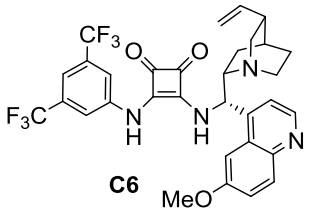
[a] Reaction conditions: **16a** (1 eq, 0.3 mmol), **2a** (2 equiv, 0.6 mmol), catalyst (10 mol %) were stirred at – 20 °C temperature for 15-20 h in CH_2Cl_2. Diastereomeric ratio was determined by ^1H NMR analysis of the crude mixture. *ee*'s determined by HPLC for the major diastereomer: column IA eluting with Hex/iPr/EtOH 85:14:1 f=0.5 mL/min. [b] The enantiomer of **19aa** was obtained. [c] Reaction stopped after 24 h.

Thus, the optimal reaction conditions for the addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** to the nitroolefin **2a** (2 equiv.) included the presence of catalyst **C7** or **C8** (20 mol %) at − 20 °C in dichloromethane.

It should be noted that the attempted Michael addition of thiohydantoin **15a** to nitrostyrene **2a** in the presence of 20 mol % squaramide derivatives **C7** and **C8** did not proceed at all at − 20 °C, and although reaction partially occurred when temperature rose to 0 °C, no diastereoselectivity was achieved (Table 49).

Table 49. Attempted reaction of thiohydantoin with nitrostyrene **2a**.



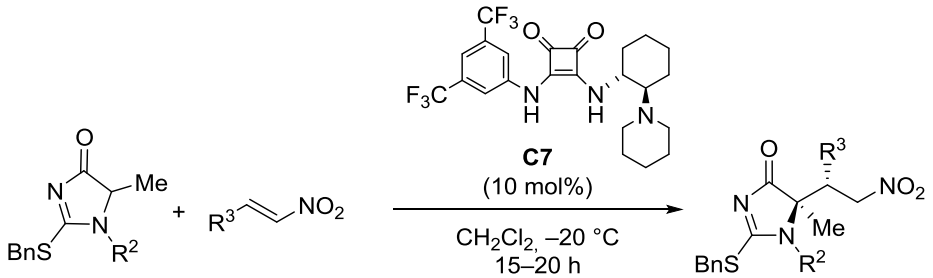
Et_3N	 **C7**	 **C6**
–20 °C, 20 h, 95%, 60:40 *dr* 0 °C, 20 h, 95%, 50:50 *dr*	–20 °C, 20 h, *no reaction* 0 °C, 48 h, 76%, 50:50 *dr*, 10% *ee*	–20 °C, 20 h, *no reaction* 0 °C, 48 h, 81%, 50:50 *dr*, 76% *ee*

Reaction conditions: **15a** (1 eq, 0.2 mmol), **2a** (2 eq., 0.4 mmol), catalyst (20 mol %) were stirred at stated temperature for stated time in CH_2Cl_2. Conversions and *dr* determined by ^{1}H-NMR analysis of the crude mixture.

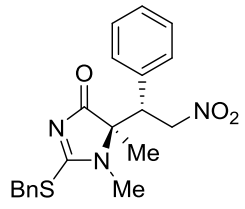
3.2.2.3. **Reaction scope**

With the best conditions found for the catalytic diastereo- and enatioselective Michael addition reaction in hand, the scope and limitation of the system were investigated (Table 50). The reactions of *N*-methyl imidazolone **16a** with nitroolefins **2a**–**d** proceeded with excellent yields and stereocontrol with 10 mol % catalyst loading, regardless of the electron neutral, rich or poor character of the β-aryl substituent in the nitroalkene (compounds **19aa**, **19ac** and **19ad**). Imidazolones **16b**–**g** bearing *N*-substituents other than methyl, e.g. benzyl, allyl, isobutyl, phenyl, and *para*-chlorophenyl were all well tolerated although in the case of *N*-(*meta*-methoxyphenyl) imidazolone worse diastereoselectivity was obtained, probably due to the steric effects. It is remarkable, that the catalyst loading could be reduced from 10 mol% to 5 mol% in the reaction of the *N*-allyl imidazolone carried out at 4 mmol scale, without affecting the results essentially (Adduct **19da**, 65%, 90:10 *dr*; 95% *ee*).

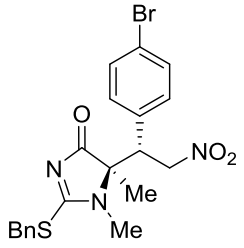
Table 50. Michael addition of 5-methyl-1*H*-imidazol-4(5*H*)-ones **16a**–**g** to nitroolefins **2a**–**d**.[a-d]



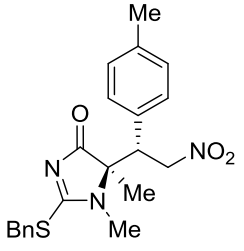
16a R^2 = Me **2a** R^3 = Ph
16b R^2 = Bn **2c** R^3 = 4-BrC_6H_4
16c R^2 = *i*Bu **2d** R^3 = 4-MeC_6H_4
16d R^2 = Allyl
16e R^2 = Ph
16f R^2 = 4-ClC_6H_4
16g R^2 = 3-MeOC_6H_4



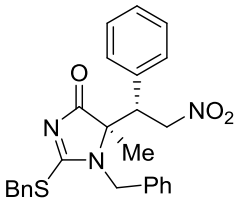
19aa
97%, 93:7 *dr*; 99% *ee*



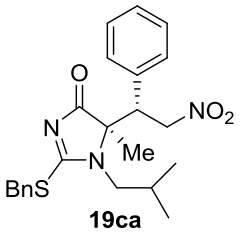
19ac
82%, 94:6 *dr*; 98% *ee*



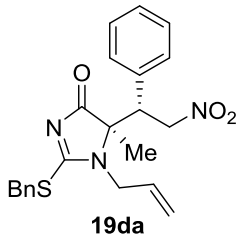
19ad
91%, 90:10 *dr;* 96% *ee*



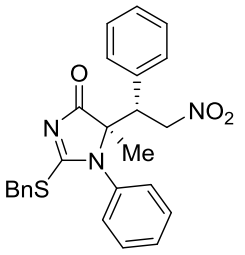
19ba
85%, 98:2 *dr*; 98% *ee*



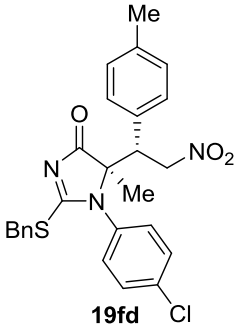
19ca
78%, 98:2 *dr*; 93% *ee*



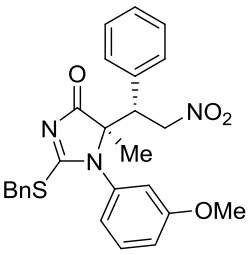
19da
77%, 92:8 *dr*; 94% *ee*
65%, 90:10 *dr*; 95% *ee*[e]



19ea
65%, 93:7 *dr*; 92% *ee*



19fd
83%, 98:2 *dr*; 98% *ee*

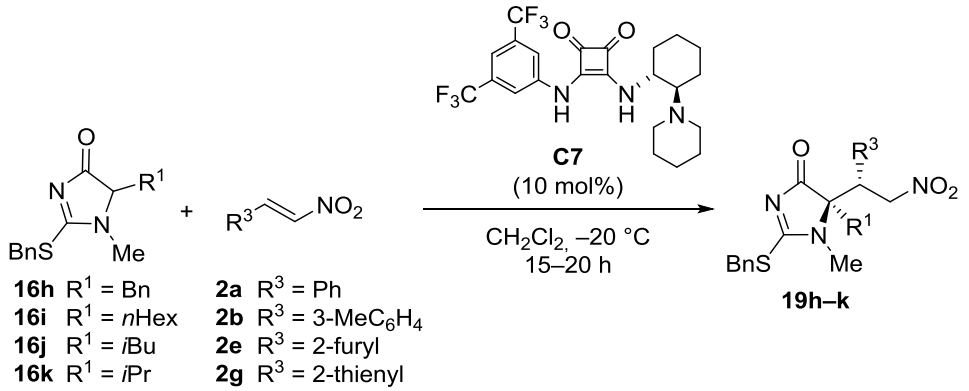


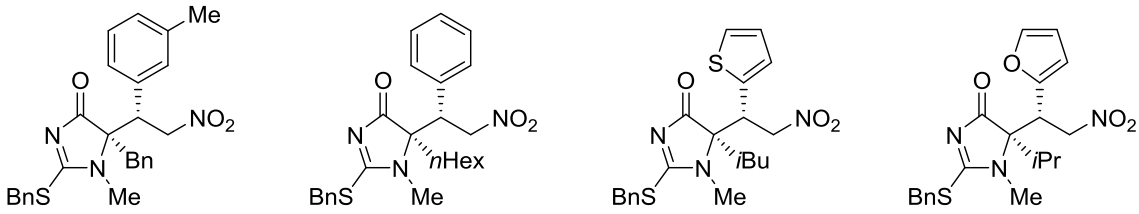
19ga
85%, 88:12 *dr*; 95% *ee*

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

Imidazolones bearing R^1 substituents different than methyl also worked well, without compromising the yield or the stereocontrol of the reaction. However, when β-heteroaryl substituted nitroolefins were involved enantioselectivity lowered (Table 51).

Table 51. Michael addition of 1-methyl-1*H*-imidazol-4(5*H*)-ones **16h**–**k** to nitroolefins **2a**–**g**. [a-d].

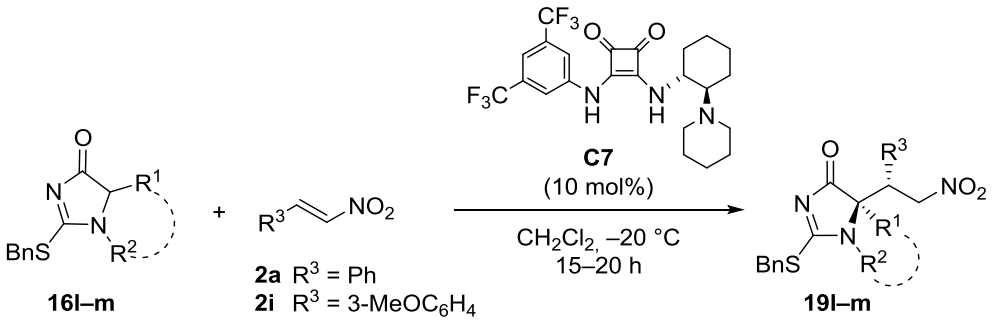


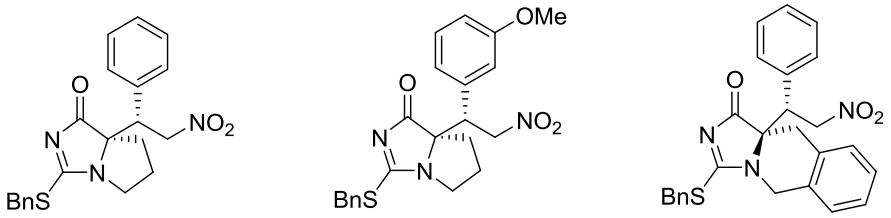


[a] Reactions performed on a 0.2 mmol scale in 0.5 mL of CH_2Cl_2 (mol ratio nitroolefin/imidazolone/catalyst 2:1:0.1) at − 20 °C. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

Cyclic imidazolones **16l** and **16m** were also competent substrates for the Michael addition to nitroolefins **2a** and **2i**. Thus, nitrostyrene **2a** afforded very good yields and diastereoselectivity and excellent enantioselectivity in its reaction with proline-derived imidazolone **16l**, although when nitroalkene **2i** was employed both yield and diastereoselectivity lowered. Tricyclic imidazolone **16m** rendered excellent stereocontrol of the reaction, and acceptable yield considering the complexity of the resulting product.

Table 52. Michael addition of cyclic 1*H*-imidazol-4(5*H*)-ones **16l**–**m** to nitroolefins **2a**–**i**.[a-d]





19la
83%, 90:10 *dr*; 94% *ee*

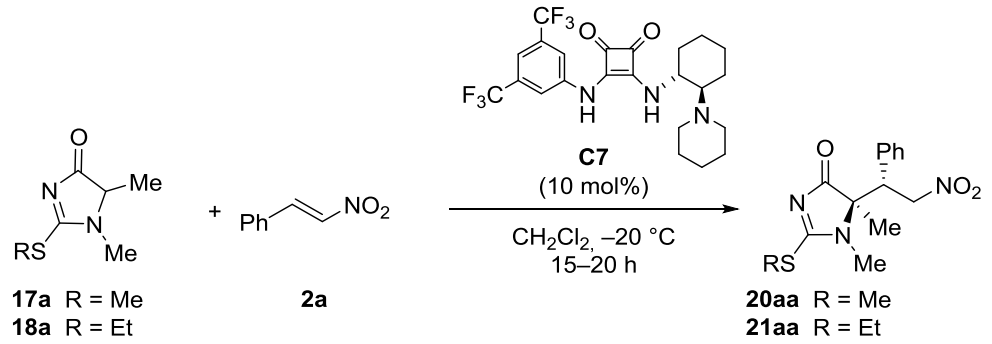
19li
78%, 87:13 *dr;* 97% *ee*

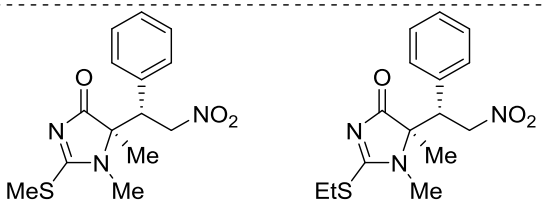
19ma
62%, 98:2 *dr*; 92% *ee*

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

In order to evaluate the influence of the *S*-substituent of imidazolones on the reaction outcome, *S*-methyl and *S*-ethyl derivatives **17a** and **18a** were prepared and tested in the Michael reaction with nitrostyrene, observing no significant differences as compared with the *S*-benzyl equivalent (Table 53).

Table 53. Michael addition of 1*H*-imidazol-4(5*H*)-ones **17a**–**18a** addition to nitrostyrene **2a**.[a-d]





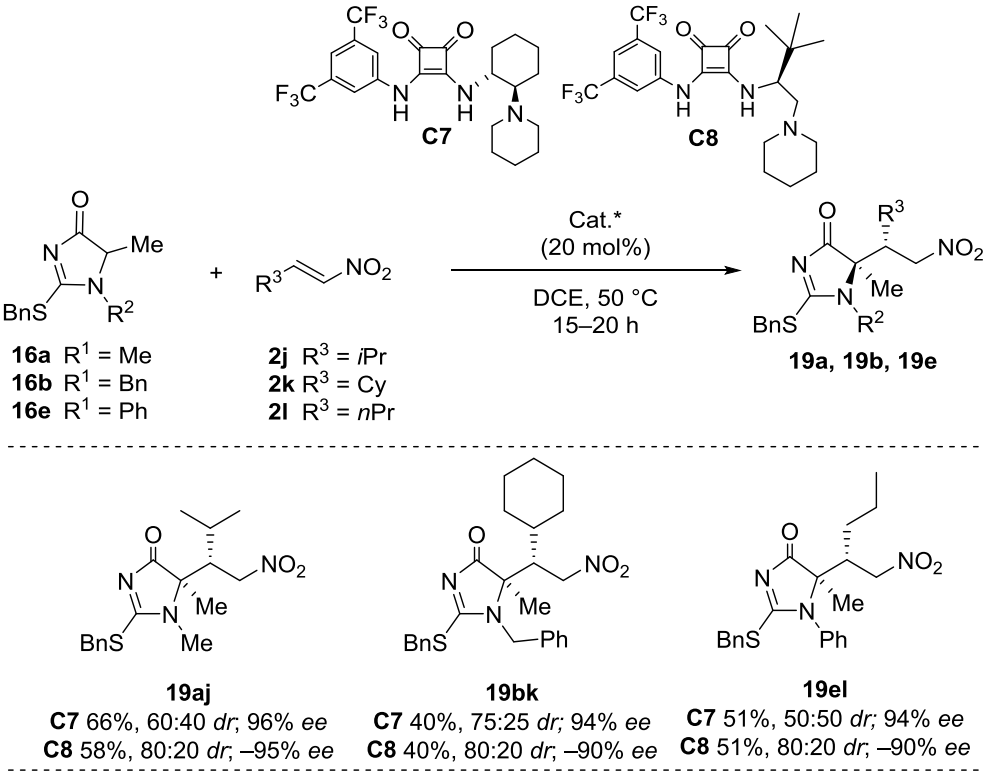
20aa
83%, 90:10 *dr*; 94% *ee*

21aa
78%, 87:13 *dr;* 97% *ee*

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

The reactions with β-alkyl substituted nitroolefins **2j–l** using catalyst **C7** proceeded with worse diastereocontrol, so a little screening of the reaction conditions was performed. Increasing nitroolefin loading to 3 equivalents and temperature to 50 °C, and by changing to catalyst **C8**[13] the diastereoselectivities increased substantially.

Table 54. Conjugate addition of imidazolones **16a**–**e** to nitroolefins **2j**–**l** promoted by **C7** and **C8**.[a-d]

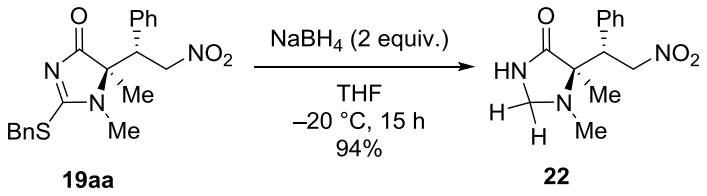


[a] Reactions conducted on a 0.2 mmol scale in 0.5 mL of DCE (mol ratio nitro olefin/imidazolone/catalyst 3:1:0.2) at 50 ºC. [b] Yields refer to the isolated major isomer. [c] *dr*'s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] *ee*'s determined by chiral HPLC.

3.2.2.4. **Elaboration of adducts**

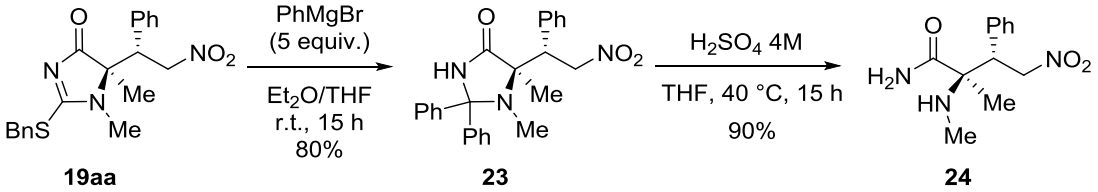
The chemical manipulation of adducts was investigated to illustrate the synthetic potential of this approach. Thus, nucleophilic displacement of the thioether group served to establish concise routes to various classes of heterocycles of interest in medicinal chemistry.[313] For example, reduction of the thioether moiety employing sodium borohydride afforded imidazolidinone **22** in 94% yield (Scheme 88).

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



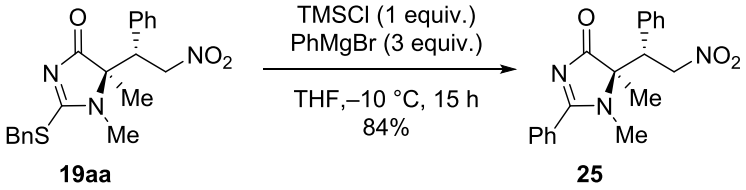
Scheme 88.

Treatment of **19aa** with an excess of phenyl magnesium bromide at room temperature rendered the *gem*-diarylated adduct **23** in 80% yield, which upon acidic hydrolysis was transformed into the quaternary α-amino amide **24** in excellent yield (Scheme 89).[314]



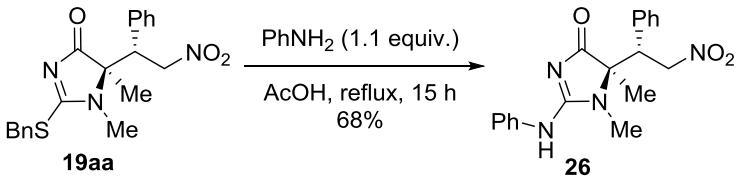
Scheme 89.

Monoarylation could be controlled by lowering the equivalents of Grignard reagent used and the temperature, and using trimethylsilyl chloride as an additive to accelerate the reaction. Monoarylated adduct was obtained in 84% yield (Scheme 90).



Scheme 90.

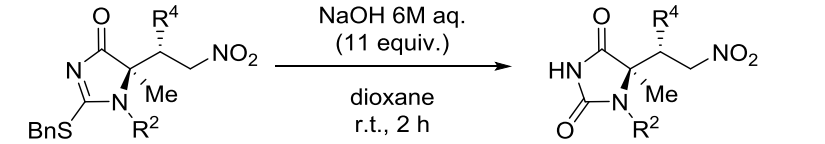
On the other hand, aminohydantoin **26** was also accessed with a moderately good yield from **19aa** by treatment with aniline and acetic acid (Scheme 91).[315]



Scheme 91.

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

Basic hydrolysis of the thioether moiety under mild conditions led to hydantoins **27**–**29** in good yields and with retention of the enantiopurity (Scheme 92). To the best of our knowledge this constitutes a novel access to this important class of compounds (see ref. 310 page 133).



19aa R^2 = Me R^4 = Ph
19ac R^2 = Me R^4 = 4-BrC_6H_4
19da R^2 = Allyl R^4 = Ph

27 R^2 = Me R^4 = Ph; 71%
28 R^2 = Me R^4 = 4-BrC_6H_4; 73%
29 R^2 = Allyl R^4 = Ph; 61%

Scheme 92.

Crystallization of adduct **28** allowed the determination of its absolute configuration by a single-crystal X-ray analysis (Figure 38), which was extrapolated to the other adducts by assuming a uniform reaction mechanism.

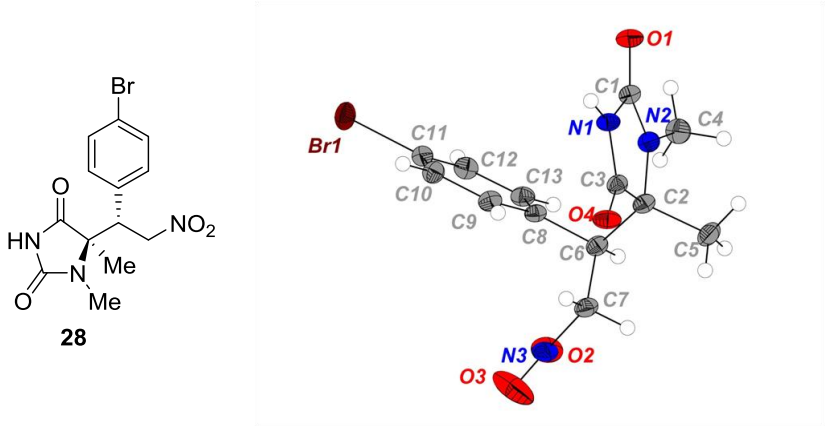
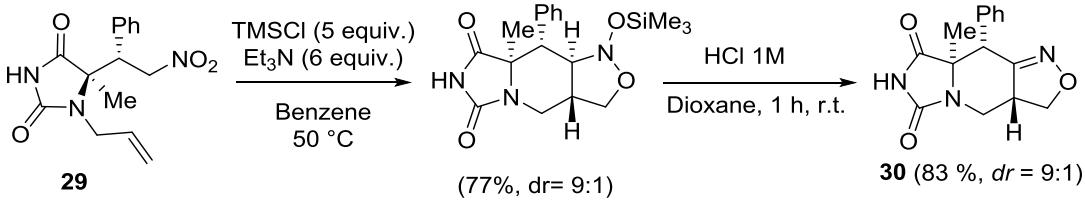


Figure 38. ORTEP diagram of compound **28**.

J. Izquierdo from our research group and in the context of his PhD research performed an intramolecular silyl-nitronate olefin cycloaddition (ISOC) on *N*-allyl hydantoin adduct **29** using trimethylsilyl chloride and subsequent acid hydrolysis afforded isoxazoline **30** in very good yield and diastereoselectivity (Scheme 93, fo a similar reaction, see ref. 224 page 90).



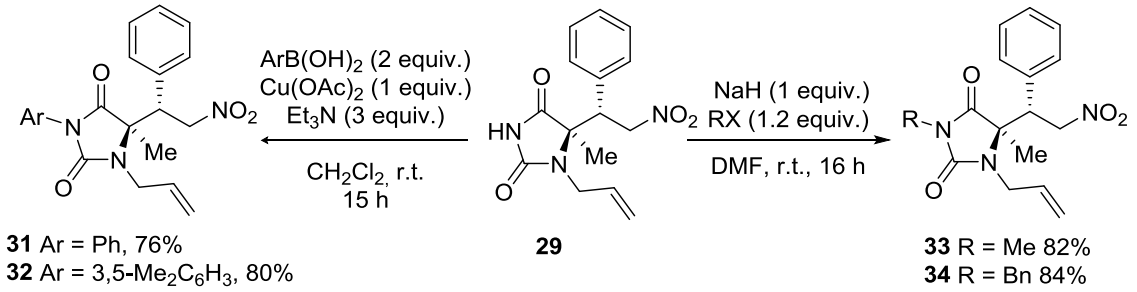
29

(77%, dr= 9:1)

30 (83 %, *dr* = 9:1)

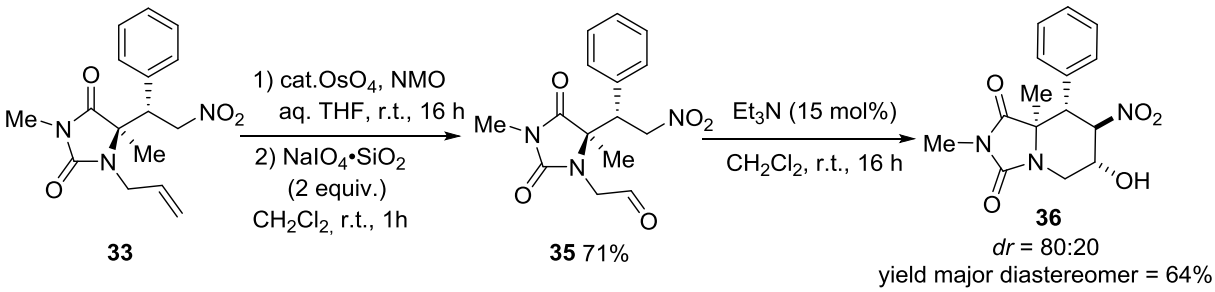
Scheme 93.

N-allyl hydantoin adduct **29** could be *N*-arylated or *N*-alkylated using standard procedures. For example, alkylation was achieved employing sodium hydride as a base and alkyl halides,[316] while arylation required boronic acids and copper catalysis, under mild conditions (Scheme 94).[317]



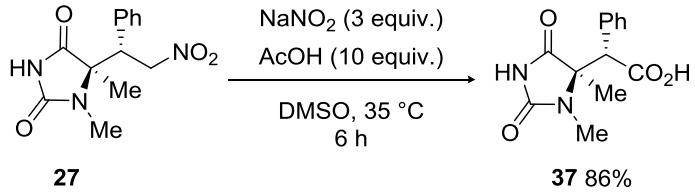
Scheme 94.

Dihydroxylation of the *N*-allyl moiety and subsequent oxidation of the resulting diol with sodium periodate was performed by Izquierdo, to access aldehyde **35**, which under basic conditions underwent an internal Henry cyclization with good diastereoselectivity and yield (Scheme 95).[318]



Scheme 95.

Finally, carboxylic acid derivative **37** was afforded from **27** via Nef oxidation by treatment with sodium nitrite and acetic acid in DMSO (Scheme 96).[319]



Scheme 96.

[316] Adapted from Owen, D. A. et al From U. S., 6566384, 20 May 2003.
[317] Chan, D. M. .; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
[318] Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396–9414.
[319] Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529–1532.

3.2.2.5. **Mechanistic proposal**

The description of a reaction model which would explain the outcome of the Michael addition of imidazolone to nitroolfins was our next concern.

The difference of the results obtained when thioureas or squaramides were employed as catalysts, made clear that the *H*-bond donor moiety of the catalyst was indeed involved in the process. Alemán and co-workers, in their review on the squaramides and their importance for bifunctional organocatalysis (ref. 38b page 12), highlighted that one of the most significant difference between thioureas and squaramides as *H*-bond donors is the distance between the two *N–H* groups and their relative orientation. Takemoto's[320] and Rawal's[321] groups theoretically calculated the distances for *N*,*N*'-dimethylthiourea and *N*,*N*'-dimethylsquaramide (Figure 39) to be approximately 2.13 Å and approximately 2.72 Å, respectively. Moreover, the constrained structure of the cyclobutenedione ring of the squaramide induces a convergent orientation of the *N–H* groups, bending each bond by approximately by 6°.

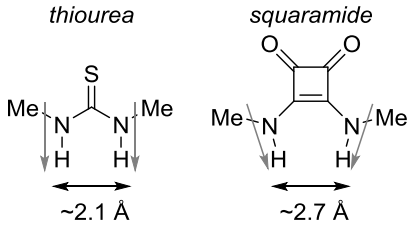


Figure 39. *H*-bond spacing distances in *N*,*N*'-dimethylthiourea and *N*,*N*'-dimethylsquaramide.

Following the reaction model proposed for the reaction with 5*H*-thiazol-4-ones (Figure 29, page 92), the enolate formed after deprotonation of the 1*H*-imidazol-4(5*H*)-one should be interacting with the *H*-bond donor moiety, which in view of the results, occurred with greater affinity with squaramides than with thioureas.

In order to have some clues about how both substrates interact with the catalyst, a series of NMR experiments were recorded (Figure 40). The top three spectra correspond, respectively, to equimolar samples of **C7**+**16a**, **C7**+**2a**, and **C7**+**2a**+**16a**. Note the downfield shift of proton H_A of catalyst **C7** upon addition of imidazolone **16a** (compare spectra 3 and 4). In contrast, no apparent change is operating in either spectra of **C7** or **2a** upon admixture of both components (compare spectra 1, 3 and 5). Finally, when the spectrum of the ternary mixture **C7**+**2a**+**16a** was recorded, H_A appeared deshielded again. These observations suggested that the interaction between **C7**/**16a** involved H_A.

[320] Okino et al. see ref. 225 page 91.
[321] see ref. 312a page 139.

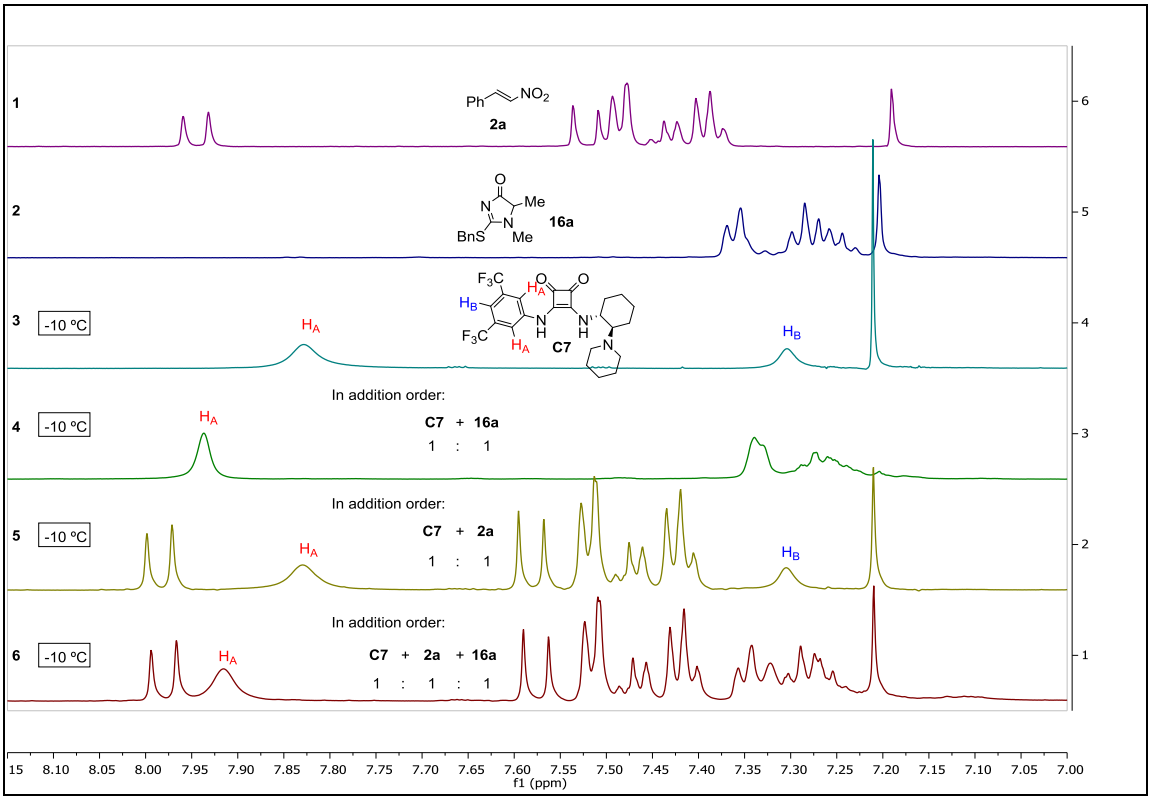


Figure 40. ^{1}H NMR spectra (aromatic portion) of catalyst **C7**, and substrates **16a** and **2a** (top) and some of their equimolar mixtures (bottom) (0.02 M in $CDCl_3$ at –10 °C).

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

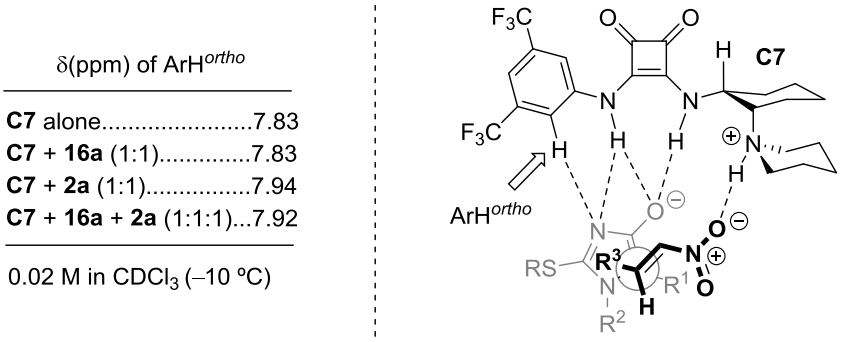


Figure 41. Empirical ^{1}H NMR data recorded and proposed reaction model for the **C7** catalyzed Michael addition of imidazolones to nitroolefins.

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

3.3.1. **Working hypothesis and synthetic plan**

Given the excellent results regarding both the reactivity and stereocontrol afforded in the Michael addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins using bifunctional squaramide-based Brønsted bases as catalysts, and seeing the synthetic possibilities that these heterocycles bear, we decided to extent this methodology to other relevant electrophiles, in particular α,β-unsaturated carbonyl compounds.

Our research group have introduced α'-oxyenones **38**/**39** (Figure 42a) as efficient acrylate surrogates (Figure 42b) in a series of metal-catalyzed conjugate additions and cycloadditions.[322] Concurrently to the development of this Thesis, work in our laboratory was in progress in order to verify the effectiveness of this template in the context of organocatalysis, and more specifically BB-catalyzed conjugate additions. So as part of these studies we investigated the reaction of our imidazolones with enones **38** and **39** in the presence of a Brønsted base catalyst. The hope was that while typical enones (and unsaturated esters) are less reactive (and therefore less prone towards BB-triggered activation), the unique reactivity demonstrated by these α'-oxyenones could facilitate our goal.

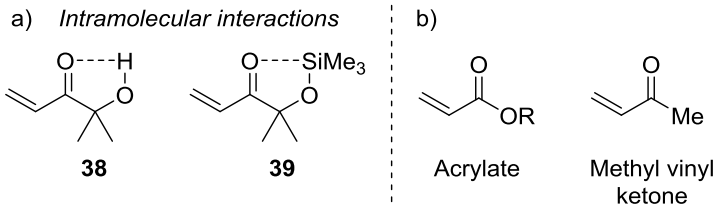
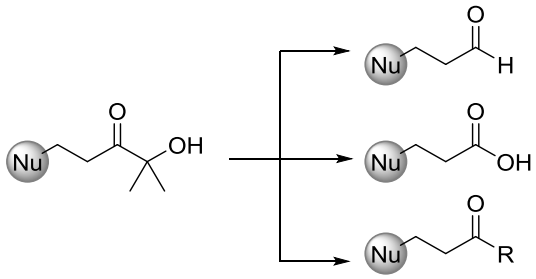


Figure 42. α'-Oxyenones as more reactive acrylate surrogates.

Additionally, the interest on this family of Michael acceptors comes from the synthetic potential of their reaction adducts, since several functional groups can be accessed by simple elaboration (Scheme 97).



Scheme 97. Easily accessible functional groups from α'-oxyenones.

[322] For previous work of our group employing hydroxyenones, see: Badiola et al. see ref. 76a page 24 and references therein.

On this basis, we chose α'-oxyenones **38**–**39** to test them as electrophiles with 1*H*-imidazol-4(5*H*)-ones, which would led to quaternary α-amino acids derivatives, including hydantoins. The adducts would bear only a stereocentre, eliminating the previous diastereoselectivity problem, although the less reactivity of the acceptor could imply a challenge (Scheme 61).

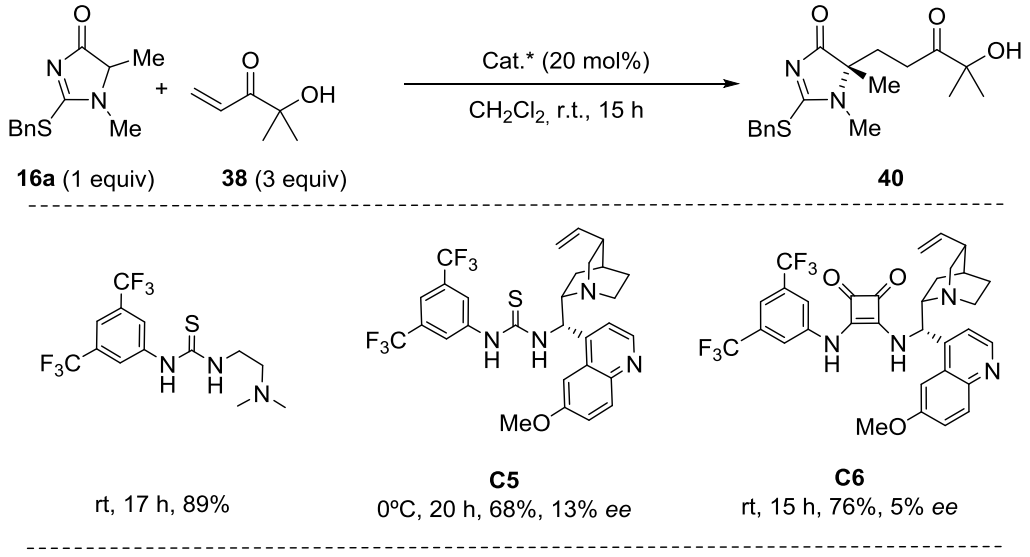
Scheme 98. Proposed reaction for the first investigation.

3.3.2. **Results and discussion**

3.3.2.1. **Screening of conditions**

Our study began with the evaluation of several Brønsted bases for the addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** to α'-hydroxyenone **38** (Table 55). First, thiourea-based catalyst **C5** was tested for the reaction in dichloromethane at 0 °C with a 20 mol % catalyst loading, rendering good yield but very poor enantioselectivity. Squaramide based catalyst **C6** rendered better yield, but similarly poor enantioselectivity.

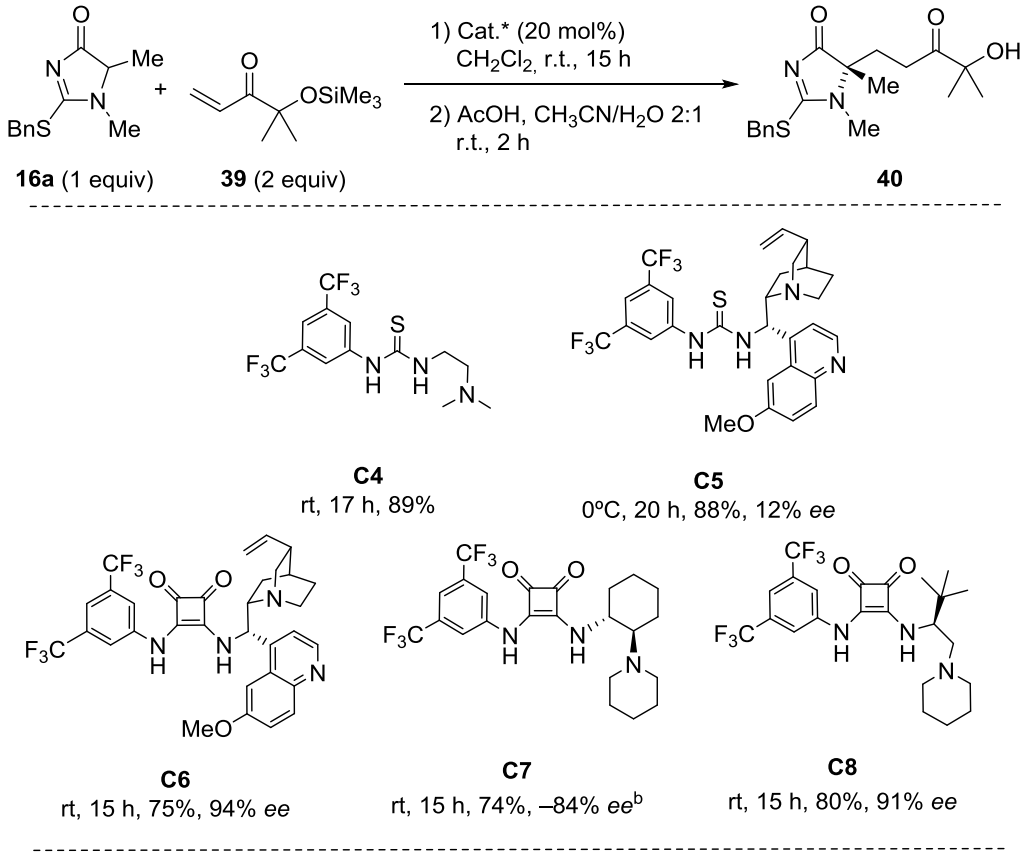
Table 55. Catalyst screening for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** to α'-hydroxyenone **38**.



[a] Reaction conditions: **16a** (1 equiv, 0.3 mmol), **38** (3 equiv, 0.9 mmol), catalyst (20 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.3 mmol scale. *ee*'s determined by HPLC: IC Hex/iPr 40:60 f=0.5 mL/min.

Then, the α'-silylated enone **39** was tested (Table 56), in the hope that the bulky TMS moiety would increase the stereocontrol. Thiourea-based catalyst **C5** rendered equally poor *ee* value (12% *ee*). However, when squaramide-based catalysts **C6**–**C8**, which afforded the best results concerning the addition of nitroalkenes, were evaluated for this reaction, a significant increase of the stereocontrol was observed, being the quinine derivative **C6** the most promising (94% *ee*).

Table 56. Catalyst screening for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** to α'-silyloxyenone **39**.

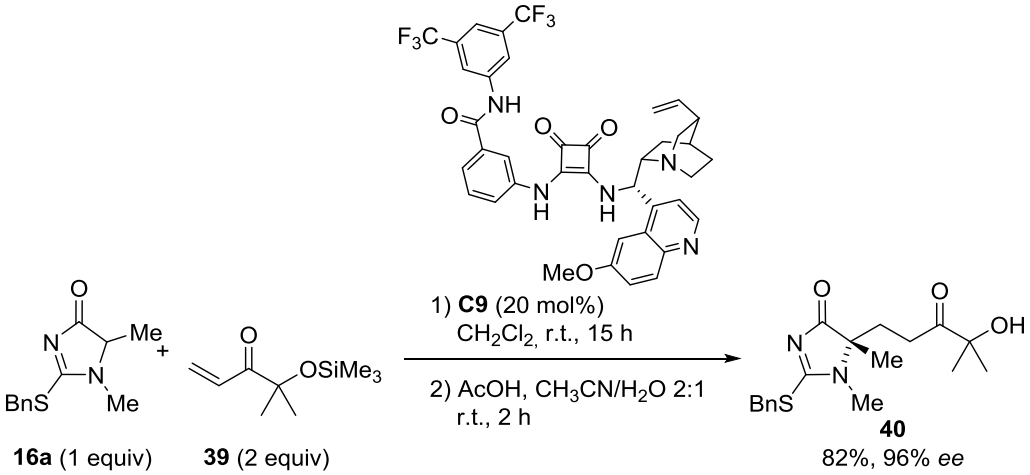


[a] Reaction conditions: **16a** (1 equiv, 0.3 mmol), **39** (2 equiv, 0.6 mmol), catalyst (10 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.3 mmol scale. *ee*'s determined by HPLC: IC Hex/iPr 40:60 f=0.5 mL/min. [b] The enantiomer of **40** was obtained.

At this point, we designed the new catalyst **C9** bearing an additional amide group which could, through internal *H*-bond resembling β-turn structures in peptides,[323] rigidify the catalyst's structure and increase *H*-bond donor ability of squaramide. It should be noted that attempts to confirm the conformational feature of this novel catalyst, and

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

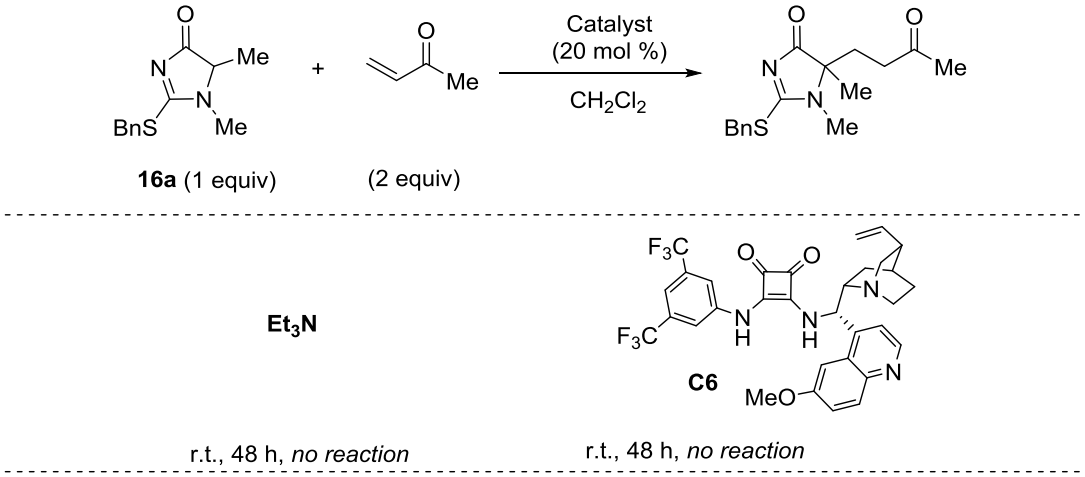
particularly the prevalence of any intramolecular H-bond, remain unsuccessful so far.[324] In any case, it was gratifying to observe that the new catalyst worked out remarkably well and provided the expected addition product in excellent enantioselectivity (Scheme 99).



Scheme 99. Optimal conditions for the Michael addition of 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one **16a** to oxyenone **73**.

On the other hand, the importance of our acceptor template was evident when other unsaturated carbonyl systems were evaluated. For example, the Michael addition of imidazolone **16a** to methyl vinyl ketone (MVK) did not work at all, regardless of the type of both achiral or chiral catalysts (Table 57).

Table 57. Unsuccesful attempts to react **16a** with methyl vinyl ketone.



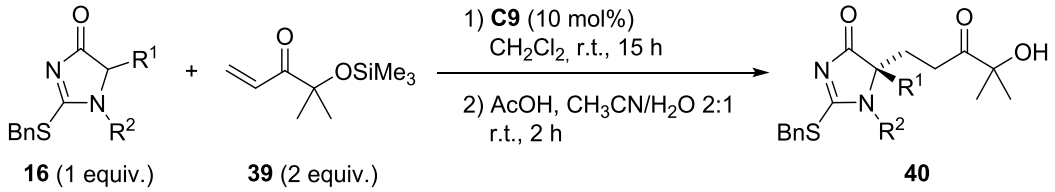
Reaction conditions: **16a** (1 eq, 0.2 mmol), MVK (2 eq., 0.4 mmol), catalyst (20 mol %) were stirred at stated temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. Conversions and *dr* determined by ^{1}H-NMR analysis of the crude mixture.

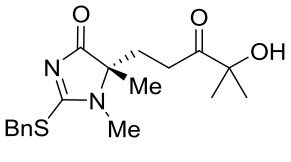
[324] For the study of the temperature gradients through ^{1}H NMR chemical shifts of *N–H* signals of **C9**, see Experimental Section.

3.3.2.2. **Reaction scope**

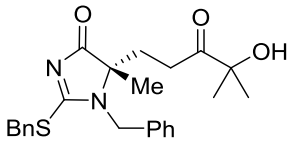
With all this screening in hand, the scope of the reaction with regard to the substitution at C-5 and N-1 of the imidazolones was studied under the conditions above, namely catalyst **C9** (20 mol %) in dichloromethane at room temperature (Table 58). During this study it was eventually found that catalyst loading could be reduced to 10 mol % without compromising the outcome of the reaction. Different substituents in both R^1 and R^2 were well tolerated, affording very good yields in every case. Even bulkier substituents rendered excellent enantioselectivities in the reaction, proving the robustness of our methodology.

Table 58. Conjugate addition of imidazolones **16** to α'-silyloxyenone **39** promoted by catalyst **C9**.[a]

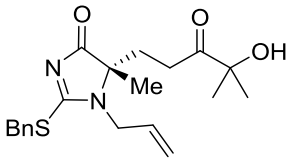




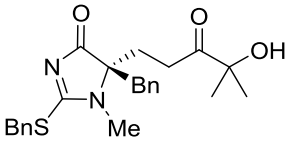
40a
82%, 96% *ee*



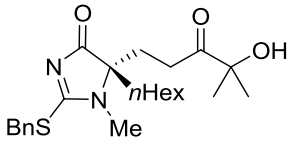
40b
78%, 96% *ee*



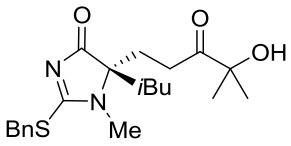
40d
77%, 94% *ee*



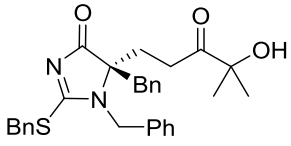
40h
75%, 96% *ee*



40i
81%, 94% *ee*



40j
71%, 96% *ee*

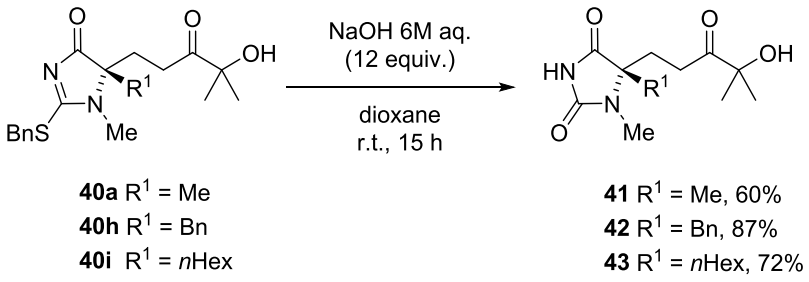


40n
83%, 92% *ee*

Reaction conditions: **16** (1 eq, 0.3 mmol), **39** (2 eq., 0.6 mmol), **C9** (10 mol%) were stirred at room temperature for stated time in CH_2Cl_2. The reactions were performed on a 0.2 mmol scale. [a] *ee*'s determined by HPLC.

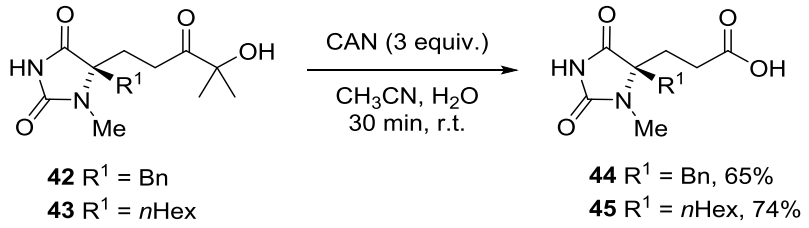
3.3.2.3. **Elaboration of adducts**

The next aspect that we addressed was the elaboration of the reaction adducts. In principle, both sites the imidazolone ring and the ketol moiety could be transformed in several ways. In a first instance, basic hydrolysis of the thioether group in the imidazolone afforded the corresponding hydantoins in very good yields (Scheme 100).



Scheme 100.

Subsequently the potential of the ketol to overcome different oxidative cleavages was exploited. Thus, treatment of adducts **42**–**43** with cerium ammonium nitrate afforded carboxylic acids **44**–**45** with good yields, with acetone being the only major organic side product formed.[325]



Scheme 101.

The cristallinity of compound **44** allowed good enough crystals for single-crystal X-ray analysis, and thus to establish the absolute configuration of the compound (Figure 43). Configuration of the remaining adducts was assigned by assuming a uniform reaction mechanism.

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

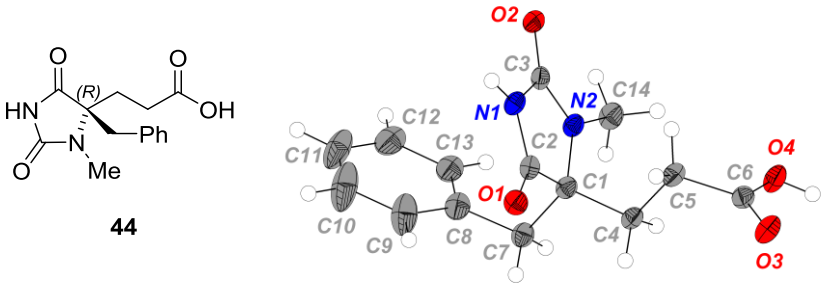
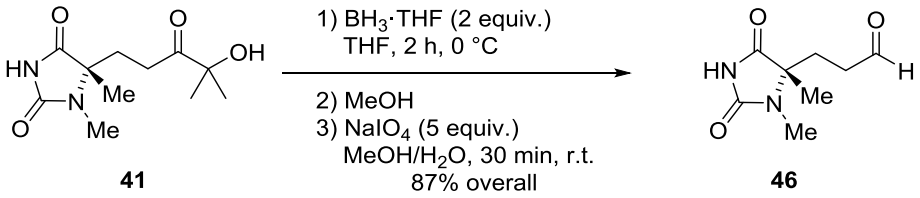


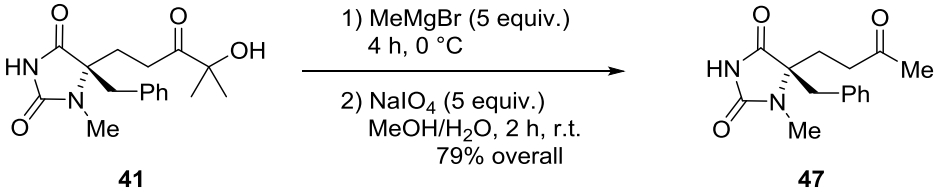
Figure 43. ORTEP diagram of compound **44**.

As an alternative illustration of the synthetic value of adducts obtained, aldehyde **46** was obtained in two steps from **41** through reduction of the carbonyl moiety and subsequent oxidation of the resulting diol using sodium periodate rendering an excellent overall yield (Scheme 102).



Scheme 102.

On the other hand, methylation of **41** and subsequent oxidation employing sodium periodate gave place to hydantoin-ketone **47** (Scheme 103).



Scheme 103.

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

Chapter 4

CONCLUSIONS

4. **CONCLUSIONS**

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

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

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

Chapter 5

EXPERIMENTAL SECTION

5. EXPERIMENTAL SECTION

5.1. Materials and general techniques

5.1.1. General experimental

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

5.1.2. Solvents and reagents

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

5.1.3. Chromatography

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with a dipping solution of potassium permanganate (1 g) in 100 mL of water (limited lifetime), followed by heating. Chromatographic purification was performed on ROCC 60 silica gel 40-63 μm.

5.1.4. Melting points

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

5.1.5. Mass spectra

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

5.1.6. **Infrared spectra**

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

5.1.7. **NMR spectra**

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

5.1.8. **Determination of enantiomeric excesses**

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

5.1.9. **Optical rotations**

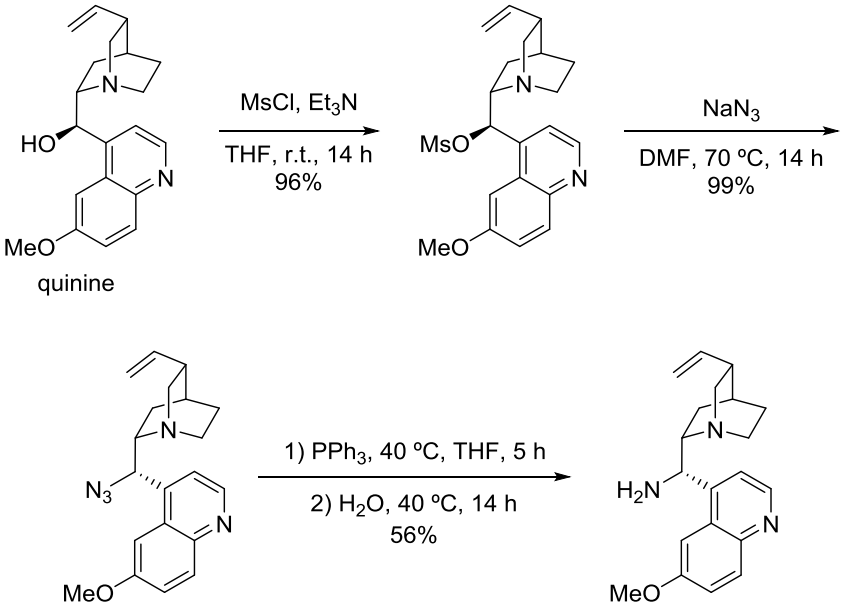
Optical rotations were recorded using a Jasco P-2000 polarimeter; specific rotation (SR) ($[\alpha]_D$) are reported in 10^{-1} deg·cm^2·g^{-1}; concentrations (*c*) are quoted in g/100 mL; *D* refers to the D-line of sodium (589 nm); temperatures (*T*) are given in degree Celsius (°C).

5.2. General procedure for the synthesis of catalysts

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

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

5.2.1.1. Preparation of 9-amino-(9-deoxy)epiquinine[326]



1st step:[327] A mixture of quinine (1 equiv., 16.2 g, 50 mmol) and triethylamine (3.6 equiv., 25.1 mL, 180 mmol) in dry THF (250 mL) was cooled to 0 ºC and then methanesulfonyl chloride (1.8 equiv., 7.0 mL, 90 mmol) was added dropwise. The mixture was stirred overnight at room temperature. The reaction was quenched with water (40 mL) and then THF was removed under vacuum. The residue was dissolved in dichloromethane (40 mL) and washed with water (30 mL) and saturated sodium bicarbonate (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentred under vacuum to afford crude mesylated product with 96% yield, which was used in the next step without further purification.

2nd step:[328] The crude mesylated product (1 equiv., 19.3 g, 48 mmol) was dissolved in DMF (150 mL). The solution was cooled to 0 ºC and NaN_3 (2 equiv., 6.2 g, 96 mmol) was added portionwise. The mixture was stirred at 70 ºC for 16 h and after this

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

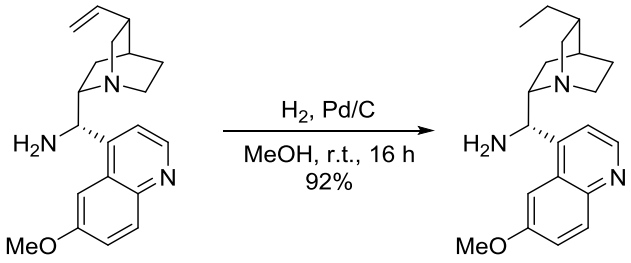
[327] Adapted from: Zielinska-Blajet, M.; Kucharska, M.; Skarzewski, J. *Synthesis*, **2006**, *7*, 4383–4387.

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

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

3rd step:[328] The azide derived crude product was dissolved in THF (250 mL) and PPh_3 (1 equiv., 12.6 g, 48 mmol) was added. The reaction mixture was heated to 40 ºC and stirred until the gas evolution ceased (~5 h). Then H_2O (8 mL) was added and the mixture was stirred overnight at 40 ºC. The solvent was removed under vacuum and the residue was dissolved in dichloromethane (150 mL). HCl 6M (250 mL) was added and the aqueous phase was separated and washed with dichloromethane (2 x 100 mL). Then the aqueous layer was cooled to 0 ºC and basified until pH > 10 with NaOH 40%. The aqueous phase was then extracted with dichloromethane (3 x 150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 9-amino-(9-deoxy)*epi*quinine as a yellow viscous oil. Yield: 8.7 g, 26.9 mmol, 56%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.75 (d, *J* = 4.6 Hz, 1H), 7.36–8.05 (m, 4H), 5.79 (m, 1H), 4.97 (m, 2H), 4.57 (d, *J* = 10.4 Hz, 1H), 3.97 (s, 3H), 3.02–3.34 (m, 3H), 2.77 (m, 2H), 2.27 (m, 1H), 2.08 (s, 2H), 1.26–1.63 (m, 4H), 0.80 (m, 1H).

5.2.1.2. **Preparation of 9-amino-(9-deoxy)epihydroquinine**[329]



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

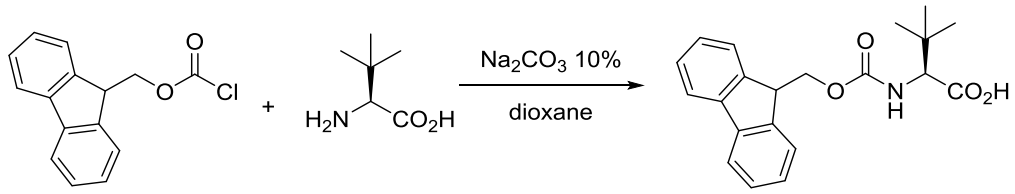
[329] Adapted from: Vakulya, B.; Varga, S.; Csámpai, A. Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.

4.7, 2.3 Hz, 1H), 1.62–1.58 (m, 1H), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H), 1.58–1.47 (m, 4H), 1.37–1.34 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H).

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

5.2.2.1. **Preparation of *N*-protected α-amino acids**

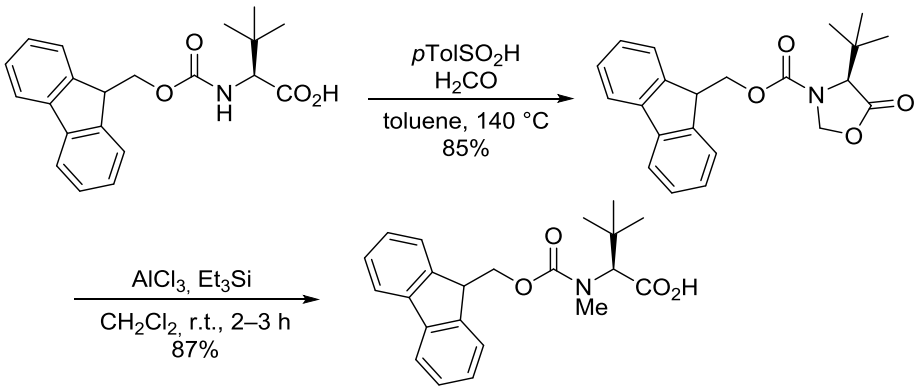
((9*H*-Fluoren-9-ylmethoxy)carbonyl)-L-*tert*-leucine[330]



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

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

(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-3,3-dimethylbutanoic acid[331]

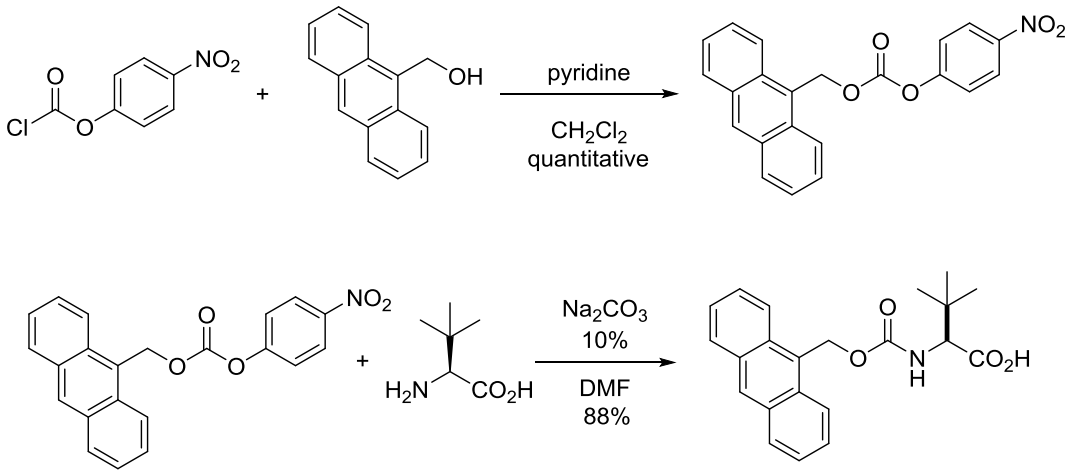


In a dean-stark, paraformaldehyde (2 g, 66.6 mmol, 6.6 equiv.) and *para*-toluenesulfinic acid (0.2 g, 1 mmol, 0.1 equiv.) were added to a solution of *N*-Fmoc-tert-leucine (3.53 g, 10 mmol, 1 equiv.) in toluene (200 mL). The reaction mixture was stirred at 140 °C. Afetr 14 h the reaction was cooled, washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), the organic layer dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatografy (hexane/EtOAc 90:10) to afford the desired product. Yield: 3.1 g (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 7.5, 2H), 7.58 (d, *J* = 7.5, 2H), 7.46 (t, J = 7.5, 2H), 7.37 (t, *J* = 7.4, 2H), 5.63–5.35 (m, 2H), 5.00 (d, *J* = 5.2, 1H), 4.84–4.61 (m, 2H), 4.27 (t, *J* = 4.9, 1H), 0.92 (s, 9H).

Triethylsilyl ether (3.1 mL, 20 mmol, 2 equiv.) was added over a solution of the product obtained in the previous step (3.65g, 10 mmol, 1 equiv.) and $AlCl_3$ (2.7 g, 20 mmol, 2 equiv.) in CH_2Cl_2 (200 mmol) under N_2 atmosphere. The reaction mixture was stirred at room temperature. After 2–3 h the mixture was diluted with CH_2Cl_2 (200 mL) and washed with a 1M HCl solution (20 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatografy (hexane/EtOAc 90:10) to afford the title product as a colorless oil. Yield: 3.2 g (87%);^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 7.5, 2H), 7.63 (d, *J* = 7.0, 2H), 7.44 (t, *J* = 7.4, 2H), 7.35 (t, *J* = 7.3, 2H), 4.78 (s, 1H), 4.52 (t, *J* = 6.3, 2H), 4.31 (s, 1H), 3.02 (d, *J* = 12.0, 3H), 1.15 (s, 9H).

[331] Zhang, S.; Govender, T.; Norstroem, T.; Arvidsson, P.I. *J. Org. Chem.* **2005**, *70*, 6918– 6920.

((Anthracen-9-ylmethoxy)carbonyl)-*L*-*tert*-leucine[332]

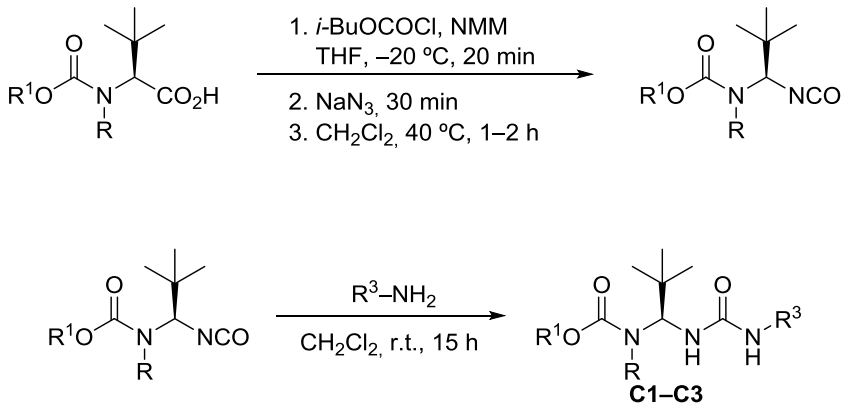


To a stirred solution of *p*-nitrophenylchloroformate (1.1 equiv. 2.2 g, 11 mmol) in dichloromethane (13.6 mL) was added pyridine (1.1 equiv., 0.9 mL, 11 mmol). The white slurry was cooled to 0 ºC, and anthracen-9-ylmethanol (1 equiv., 10 mmol) was added in several portions to keep the temperature at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

To a stirred solution of *L*-*tert*-leucine (1 equiv. 10 mmol) in 10% aqueous Na_2CO_3 (26 mL), and dimethylformamide (10 mL) was slowly added at 0 ºC a solution of the corresponding 4-nitrophenyl carbonate (1 equiv., 10 mmol) in dimethylformamide (30 mL). The mixture was stirred in an ice bath for 1 h and then allowed to warm to room temperature and subsequently stirred at the same temperature overnight, poured into H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was cooled in an ice bath and acidified with concentrated HCl, followed by extraction with EtOAc (3 x 50 mL) and washed with brine (5 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to afford the corresponding *N*-protected α-amino acid. White solid, yield: 3.2 g, 8.8 mmol, 88%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.65–7.54 (m, 2H), 7.53–7.46 (m, 2H), 6.18 (q, *J* = 12.1 Hz, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.28 (d, *J* = 10.2 Hz, 1H), 1.01 (s, 9H).

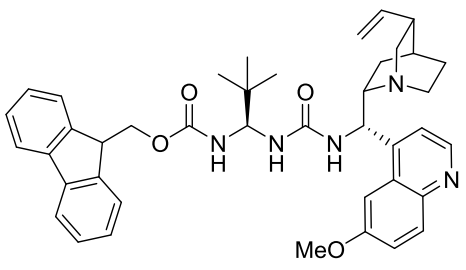
[332] Lan, P.; Porco Jr., J. A.; South, M. S.; Parlow, J. J. *J. Comb. Chem.* **2003**, *5*, 660–669.

5.2.2.2. **Preparation of catalysts C1–C3** [333]



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

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

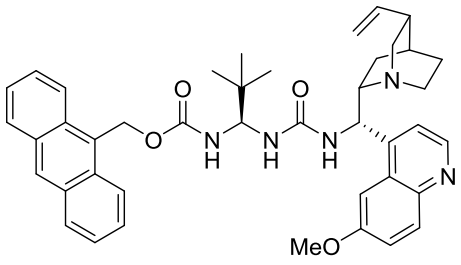


The title compound **C1** was prepared from Fmoc-*L-tert*-leucine (1.8 g, 5 mmol) and 9-amino-(9-deoxy)epiquinine (1.1 g, 3.5 mmol) according to the general procedure. White solid, yield: 1.67 g, 2.5 mmol, 71%. $[\alpha]_D^{25}$= –16.2 (c = 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.63 (d, *J* = 4.4

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

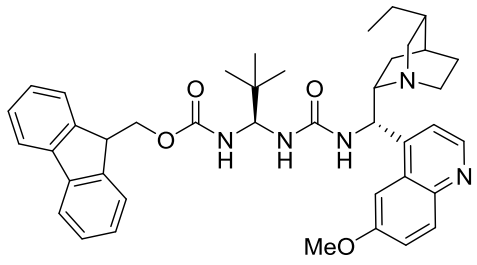
Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.83–7.72 (m, 3H), 7.62–7.55 (m, 2H), 7.47–7.31 (m, 7H), 6.41–6.26 (bs, 1H), 5.84–5.69 (m, 1H), 5.40–5.25 (m, 1H), 5.09–5.05 (bs, 1H), 5.07–4.95 (m, 3H), 4.47–4.41 (m, 1H), 4.35–4.30 (m, 1H), 4.26–4.11 (m, 1H), 3.97 (s, 3H), 3.32–3.24 (m, 2H), 3.17–3.02 (m, 1H), 2.81–2.69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

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



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

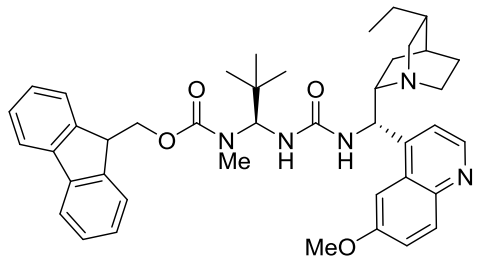
(9*H*-Fluoren-9-yl)methyl (*S*)-1-(3-((*S*)-((*2S,4S,8R*)-8-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropylcarbamate C3



The title compound **C3** was prepared from Fmoc-*L-tert*-leucine (1.8 g, 5 mmol) and 9-amino-(9-deoxy)epihydroquinine (1.1 g, 3.5 mmol) according to the general procedure. according to the general procedure. White solid; yield: 1.02 g, 1.5 mmol, 50%. $[\alpha]_D^{25}$= -25.7 (*c*= 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.54 (s, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.71 (dd, *J* = 10.5, 4.9 Hz, 2H), 7.54 (s, 2H), 7.46–7.10 (m, 6H), 6.42 (s, 1H), 5.38 (dd, *J* = 31.6, 22.4 Hz,

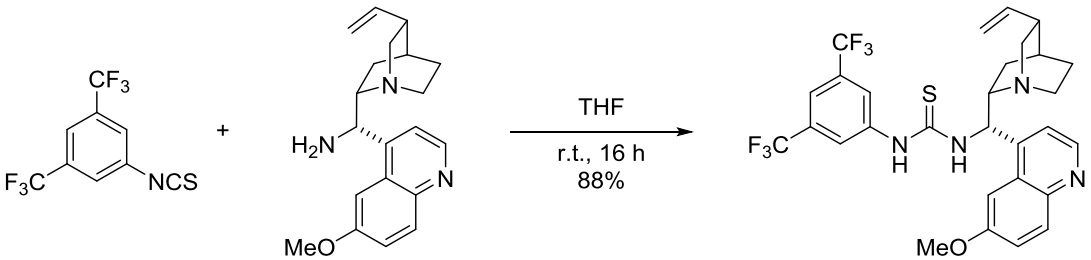
2H), 4.98 (s, 1H), 4.49–4.02 (m, 3H), 4.02–3.75 (m, 3H), 3.07 (dd, *J* = 48.9, 8.1 Hz, 3H), 2.64 (s, 1H), 2.39 (dd, *J* = 29.2, 18.6 Hz, 1H), 2.09–1.94 (m, 1H), 1.68–1.32 (m, 4H), 1.32–1.06 (m, 4H), 1.03–0.57 (m, 13H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 157.7, 157.5, 156.3, 147.4, 144.6, 143.8, 143.7, 141.2, 141.2, 131.5, 128.5, 127.6, 127.0, 127.0, 125.0, 121.5, 119.9, 102.0, 66.8, 66.5, 60.3, 57.5, 55.5, 47.1, 40.9, 37.2, 35.4, 28.5, 27.4, 25.8, 25.3, 25.1, 14.1, 11.9. UPLC-DAD-QTOF: $C_{41}H_{50}N_5O_4$ $[M+H]^+$calcd: 676.3863, found: 676.3861.

(9*H*-fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)(methyl)carbamate C3-Me



The title compound **C3-Me** was prepared from *N*-methyl Fmoc-*L*-*tert*-leucine (1.9 g, 5 mmol) and 9-amino-(9-deoxy)epihydroquinine (1.1 g, 3.5 mmol) according to the general procedure. according to the general procedure. White solid, yield: 2.1 g, 60%. $[\alpha]_D^{25}$= – 13.85 (c=1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.68 (s, 1H), 8.04 (d, *J* = 9.1, 1H), 7.77 (dd, *J* = 5.0, 13.5, 3H), 7.64–7.59 (m, 2H), 7.46–7.30 (m, 7H), 5.98 (bs, 1H), 5.85–5.67 (m, 1H), 5.29–5.18 (m, 2H), 4.99 (dd, *J* = 9.0, 13.7, 3H), 4.49–4.31 (m, 2H), 4.23 (t, *J* = 6.4, 1H), 3.98 (s, 3H), 3.27 (dd, *J* = 10.1, 13.8, 1H), 3.21–3.14 (m, 1H), 3.09 (dd, *J* = 9.3, 17.6, 1H), 2.82–2.66 (m, 5H), 2.29 (s, 1H), 1.60 (s, 2H), 1.44 (d, *J* = 13.0, 1H), 0.90 (s, 10H); 13C NMR (75 MHz, CDCl3) δ 158.2, 157.7, 147.9, 146.3, 145.2, 144.4, 144.3, 141.8, 141.7, 132.1, 128.8, 128.1, 127.4, 125.4, 122.0, 120.4, 114.8, 102.4, 67.7, 60.6, 56.3, 56.0, 47.6, 41.3, 39.9, 36.8, 30.1, 28.3, 27.8, 26.9, 26.5; UPLC-DAD-QTOF: $C_{42}H_{50}N_5O_4$ $[M+H]^+$ calcd.: 688.3863; found: 688.3880.

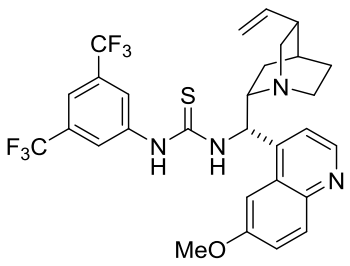
5.2.3. **Thiourea containing Brønsted base catalyst C5**[329]



To a solution of 9-amino-(9-deoxy)*epi*quinine (1 equiv., 1.6 g, 5 mmol) in dry THF (7.5 mL) at 0 ºC, a solution of bis(trifluomethyl)phenyl isothiocyanate (1.1 equiv., 1.5 g, 5.5 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The

residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford the title compound.

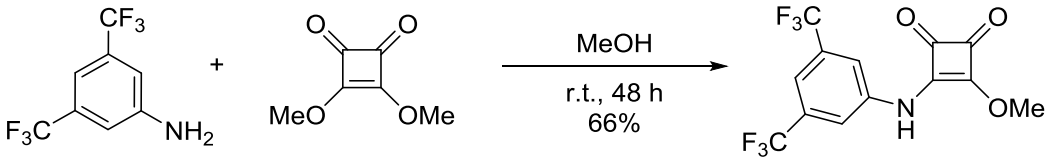
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea C5



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

5.2.4. **Squaramide-based Brønsted base catalysts C6-C8**

5.2.4.1. **Preparation of squaric ester monoamine**[334]



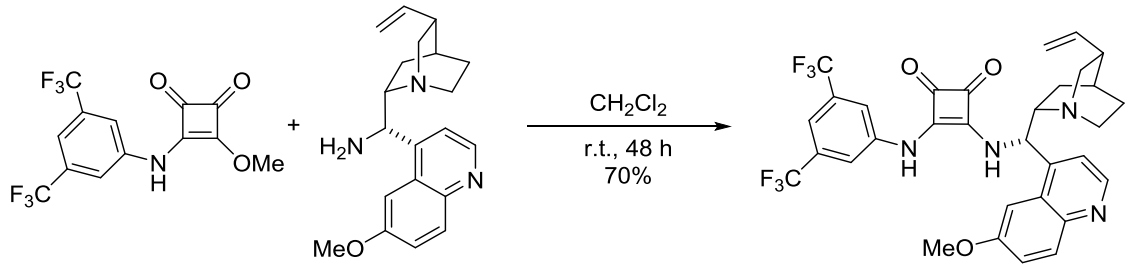
To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (1 equiv., 1.42 g, 10 mmol) in MeOH (20 mL) was added 3,5-bis(trifluoromethyl)aniline (1 equiv., 1.56 mL, 10 mmol). The reaction mixture was stirred at room temperature for 48 h. The formed precipitate was filtered and dried under vacuum to give title compound as a white solid. Yield: 2.25 g, 6.6 mmol, 66%. m.p. = 179–181 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 11.18 (s, 1H), 8.04 (s, 2H), 7.78 (s, 1H), 4.41 (s, 3H).

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

5.2.4.2. **Preparation of catalysts C6–C8.**

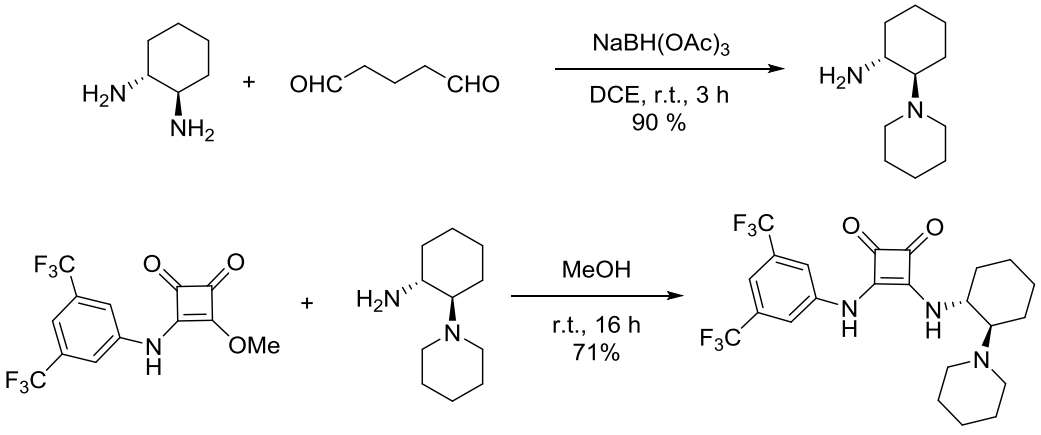
*5.2.4.2.1. Preparation of catalyst **C6***

3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (C6)[334]



To a solution of squaric ester monoamide prepared as above (1 equiv., 2.25 g, 6.6 mmol) in dichloromethane (33 mL), 9-amino-(9-deoxy)*epi*quinine (1 equiv., 2.13 g, 6.6 mmol) was added. The reaction mixture was stirred for 48 h at room temperature, the solvent evaporated, and the residue was purified by flash column chromatography on non acid silica gel (eluting with hexane/ ethyl acetate 80/20 → ethyl acetate) to afford **C6** as white solid. Yield: 2.91 g, 4.6 mmol, 70%. m.p. = 224–225 ºC. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, DMSO), δ: 9.88 (brs, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.36 (brs, 1H), 8.04–7.86 (m, 3H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.67 (d, *J* = 4.5 Hz, 1H), 7.58 (s, 1H), 7.47 (d, *J* = 6.8 Hz, 1H), 6.19–5.73 (m, 2H), 5.13–4.92 (m, 2H), 3.95 (s, 3H), 3.52–3.42 (m, 1H), 3.30–3.25 (m, 1H), 2.77–2.58 (m, 2H), 2.35–2.20 (m, 1H), 1.60–1.47 (m, 4H), 0.66 (m, 1H).

*5.2.4.2.2. Preparation of catalyst **C7**[335]*



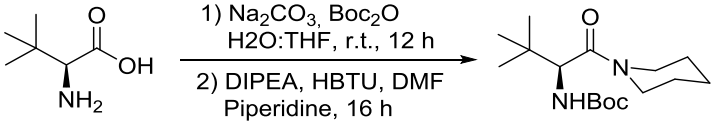
[335] Yang, W.; Du, D-M *Adv. Synth. Catal.* **2011**, *353*, 1241–1246.

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

To a solution of the crude amine (273 mg, 1.5 mmol) in 5 mL CH_2Cl_2 was added squaric ester monoamine (271 mg, 1.0 mmol). The reaction was stirred at room temperature for 24 h. Then the mixture was concentrated and purified by basic silica gel column chromatography (using CH2Cl2 as eluant) to afford the desired product VII as a pale yellow solid (347 mg, 71% yield). m.p. 134−136 °C, $[\alpha]_D^{25}$ = +150.3 (c = 0.62, CH_2Cl_2). All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (s, 2H), 7.42 (s, 1H), 4.00 (s, 1H), 2.62 (br s, 2H), 2.35−2.27 (m, 3H), 2.18−2.16 (m, 1H), 1.89−1.87 (m, 1H), 1.78 (d, J = 10.5 Hz, 1H), 1.70 (d, J = 11.0 Hz, 1H), 1.40−1.12 (m, 10H).

*5.2.4.2.3. Preparation of catalyst **C8***

Step 1) Protection of the amine and amide formation[336]

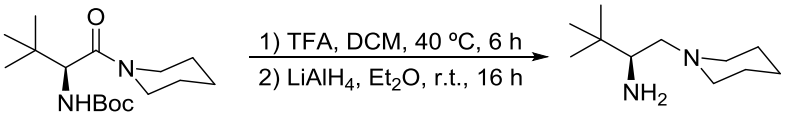


Na_2CO_3 (2.12 g, 20 mmol, 2 equiv.) and Boc_2O (3.3g, 15 mmol, 1.5 equiv.) were added to a solution of t-leucine (1.31 g, 10 mmol, 1 equiv.) in water (20 mL) and THF (5 mL) at 0 °C. After stirring for 12 h at room temperature HCl (10 %) was added until pH 2 and the mixture was extracted with EtOAc (3 x 30 mL). The aqueous phases were united and washed with brine (50 mL) and dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was then redissolved in dry DMF dissolution (20 mL) and DIPEA (2.58 g, 20 mmol, 2 equiv.) and HBTU (5.7 gm 15 mmol, 1,5 equiv.) were added. After stirring for 1 h piperidine (0.94 g, 11 mmol, 1.1 equiv.) was added and the mixture was stirred for further 16 h. The reaction was quenched adding HCl 1 M (20 mL) and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were united and washed with a HCl 1 M and brine (20 mL) and

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

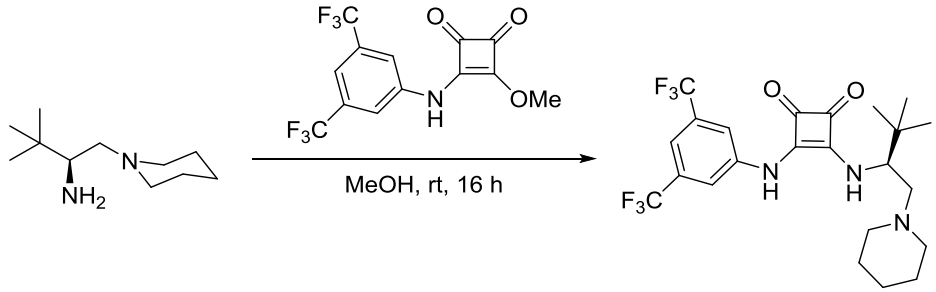
dried over $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 85/15) to afford tert-butyl (*S*)-(3,3-dimethyl-1-oxo-1-(piperidin-1-yl)butan-2-yl)carbamate as a white solid. Yield: 2.5 g, 8.3 mmol, 83%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$) δ= 0.98 (s, 9H), 1.43 (s, 9H), 1.52 – 1.62 (m, 6H), 3.46 – 3.69 (m, 4 H), 4.54 (d, J = 9.7 Hz, 1H), 5.38 (d, J = 9.6 Hz, 1H).

Step 2) Deprotection and reduction



Previously obtained amide (2.5 g, 8 mmol, 1 equiv.) was dissolved in a mixture of CH_2Cl_2 (8 mL) and trifluoroacetic acid (2 mL) and stirred at 40 °C until no more starting material was observed by TLC (eluting with hexane/ EtOAc 70/30). The solvent was then removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (10 mL). The solution was washed with NaOH (40%), dried over MgSO4 and the solvent was removed under reduced pressure obtaining the aminoamide as a yellow oil. The aminoamide was then dissolved in dry diethyl ether (10 mL) and was added dropwaise over a suspension of lithium aluminiumhydride (879 mg, 24 mmol, 3 equiv.) in diethyl ether (40 mL) at 0 oC under nitrogen atmosphere. The mixture was stirred at the same temperature for some minutes and afterwards it was stirred at room temperature for 16 h. The reaction was quenched adding water (1.2 mL), NaOH 15% (1,2 mL) and water (3.6 mL) at 0 oC. The result was filtered and the liquid was extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over MgSO4 and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ EtOAc 1/1) to afford (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine as yellow oil. Yield: 1.16 g, 6.8 mmol, 92%. All spectroscopic data were identical to those reported in the literature. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.66 (dd, J = 11.0, 2.5 Hz, 1H), 2.52 (d, J = 12.3 Hz, 4H), 2.28 (dd, J = 12.3, 2.8 Hz, 3H), 2.13 (dd, J = 12.1, 11.2 Hz, 1H), 1.61-1.53 (m, 4H), 1.44 – 1.42 (m, 2H), 0.90 (s, 9H).

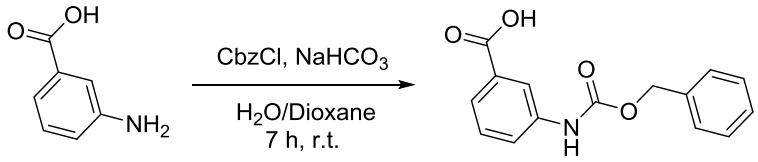
Step 3) Formation of catalyst C8[337]



To a solution of the diamine (780 mg, 4,6 mmol, 1 equiv.) in methanol (30 mL) the squaric ester monoamide obtained above (1.56 g, 4,6 mmol, 1 equiv.) was added and the mixture was stirred until complete disappearance of the starting amide as monitored by TLC (16 h). The white precipitate was filtered and washed with CH_2Cl_2 to afford essentially pure **C8** as a white solid. m.p. 246– 248 °C. Yield: 1.29 g, 2.6 mmol, 59%. All spectroscopic data were identical to those reported in the literature.

5.2.4.3. **Synthesis of catalyst C9.**

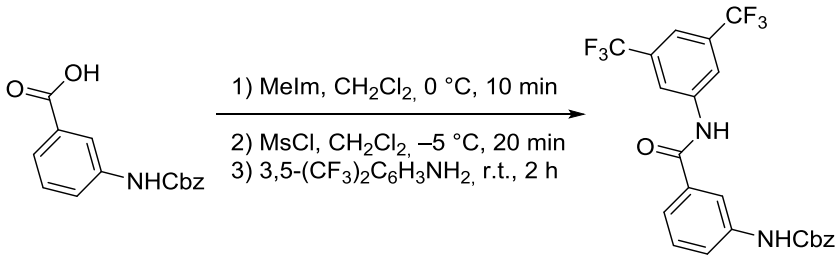
3-(((Benzyloxy)carbonyl)amino)benzoic acid[338]



To a solution of 3-aminobenzoic acid (5 g, 36.3 mmol, 1.1 equiv.) an $NaHCO_3$ (2.0 equiv.) in water (150 mL) was added a solution of benzyl chloroformate (4.7 mL, 33 mmol, 1 equiv.) in 1,4-dioxane (150 mL). The reaction mixture was stirred for seven hours at room temperature before the volatiles were evaporated. The residue was distributed between ethyl acetate and water and the layers were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic phases were washed with brine. The solution was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was crushed with diethyl ether to afford the title product as a white solid. Yield: 7.8 g, 28.7 mmol, 87%. ^{1}H NMR (300 MHz, Acetone-d_6) δ 9.01 (s, 1H), 8.29 (s, 1H), 7.81 (ddd, J = 8.2, 2.4, 1.1 Hz, 1H), 7.70 (ddd, J = 7.7, 1.6, 1.1 Hz, 1H), 7.54 – 7.22 (m, 5H), 5.19 (s, 2H). ^{13}C NMR (126 MHz, Acetone-d_6) δ: 167.7, 154.4, 140.4, 137.7, 132.4, 129.8, 129.3, 128.9, 128.9, 124.6, 123.3, 120.2, 67.0. UPLC-DAD-QTOF: $C_{15}H_{14}NO4$ $[M+H]^+$ calcd.: 272.0923, found: 272.0925.

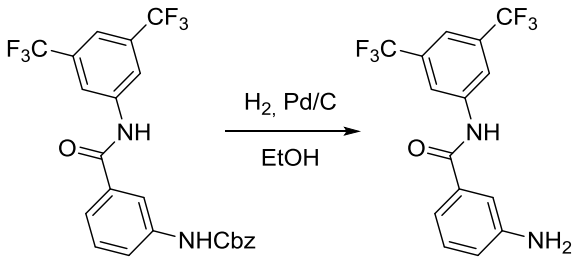
[337] K. Hu, A. Lu, Y. Wang, Z. Zhou, C. Tang, *Tetrahedron: Asymmetry* **2013**, *24*, 953–957.
[338] S. Ansorge et al. US Pat. Appl. Publ., 20120028995, 02 Feb **2012**.

Benzyl (3-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)phenyl)carbamate[339]



1-Methylimidazole (2.2 mL, 27.6 mmol, 2.5 equiv.) was added to a slurry of the protected 3-aminobenzoic acid (3 g, 11 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) at 0 °C, and the mixture was stirred for 10 min. MsCl (1.3 mL, 16.5 mmol, 1.5 equiv) in CH_2Cl_2 (1 mL) was added to the mixture under –5 °C. After the mixture was stirred under that temperature for 20 min, 3,5-bis(trifluoromethyl)aniline (1.72 mL, 11 mmol, 1 equiv) was added. Then the mixture was stirred at room temperature for 2 h. H_2O (100 mL) was added to the mixture and a solid precipitated, which was solved with ethyl acetate (100 mL). The organic layer was washed with brine (3 × 50 mL) and dried with anhydrous MgSO4. The solvent was evaporated under reduced pressure and the crude was crushed with diethyl ether to afford the title product as a white solid. Yield: 3.43 g, 7.1 mmol, 65%. ^{1}H NMR (300 MHz, CD_3OD) δ: 8.43 (s, 2H), 8.09 (s, 1H), 7.81 – 7.57 (m, 4H), 7.57 – 7.28 (m, 5H), 5.24 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ: 168.9, 155.8, 142.2, 140.8, 138.0, 136.3, 133.20 (q, J = 33.2 Hz), 132.8, 130.3, 129.5, 129.2, 129.1, 125.8, 123.5, 123.1, 121.3, 119.0, 117.9, 67.8. UPLC-DAD-QTOF: $C_{23}H_{17}F_6N_2O_3$ $[M+H]^+$ calcd.: 483.1143, found: 483.1146.

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

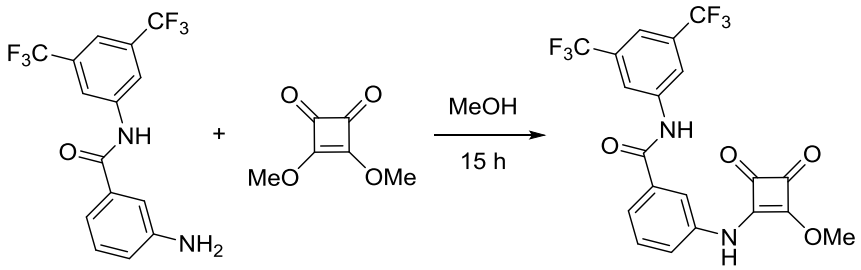


To a solution of the protected aniline (3.22 g, 6.68 mmol) in EtOH (15 mL) under inert atmosphere, Pd/C was added (Pd 10% in activated carbon, 10% in weight). The reaction mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 20h. After that the solution was filtered over celite and the filtrate was concentrated under reduced pressure to afford the hydrogenated product. Yield: 1.34 g, 3.85 mmol, 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.41 (s, 2H), 7.68 (s, 1H), 7.25 (dd, J = 4.7, 1.0 Hz, 3H), 7.01

[339] Adapted from: L. Mao, Z. Wang, Y. Li, X. Han and W. Zhou *Synlett* **2011**, *1*, 129–133.

– 6.87 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD) δ 169.7, 149.6, 142.3, 136.3, 133.13 (q, *J* = 33.2 Hz), 130.4, 125.8, 123.7, 121.3, 119.9, 117.6, 115.0. UPLC-DAD-QTOF: $C_{15}H_{11}F_6N_2O$ $[M+H]^+$ calcd.: 349.0776, found: 349.0779.

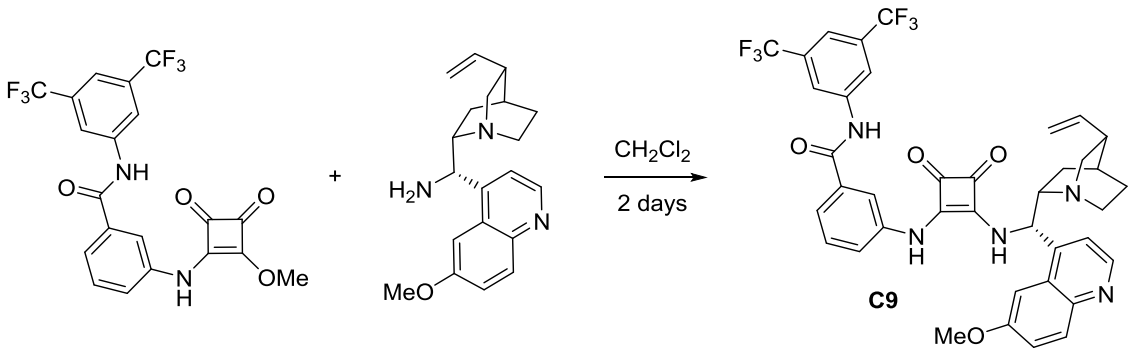
_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide[340]



To a solution of 3,4-dimethoxy-3-cyclobutane-1,2-dione (481 mg, 3.38 mmol, 1 equiv.) in MeOH (10 mL) was added the free aniline (1.3 g, 3.72 mmol, 1.1 equiv.) at room temperature. The mixture was stirred at room temperature for 15 h. The white precipitate was filtrated and washed with MeOH. Obtained white solid was dried in vacuo to give the title product as a white solid. Yield: 1.49 g, 3.24 mmol, 96%. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 10.25 (s, 1H), 9.99 (s, 1H), 8.55 (s, 2H), 8.08 (s, 1H), 7.89 – 7.64 (m, 3H), 7.64 – 7.46 (m, 1H), 4.47 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 184.2, 179.1, 169.3, 165.8, 141.0, 138.5, 135.0, 130.69 (q, *J* = 32.8 Hz), 129.3, 126.5, 124.4, 123.2, 122.9, 122.2, 119.9, 119.2, 116.5, 60.7. UPLC-DAD-QTOF: $C_{20}H_{13}F_6N_2O_4$ $[M+H]^+$ calcd.: 459.0780, found: 459.0778.

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

_N_-(3,5-Bis(trifluoromethyl)phenyl)-3-((2-(((_S_)-(6-methoxyquinolin-4-yl)((1_S_,2_S_,4_S_,5_R_)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide (C9)[341]

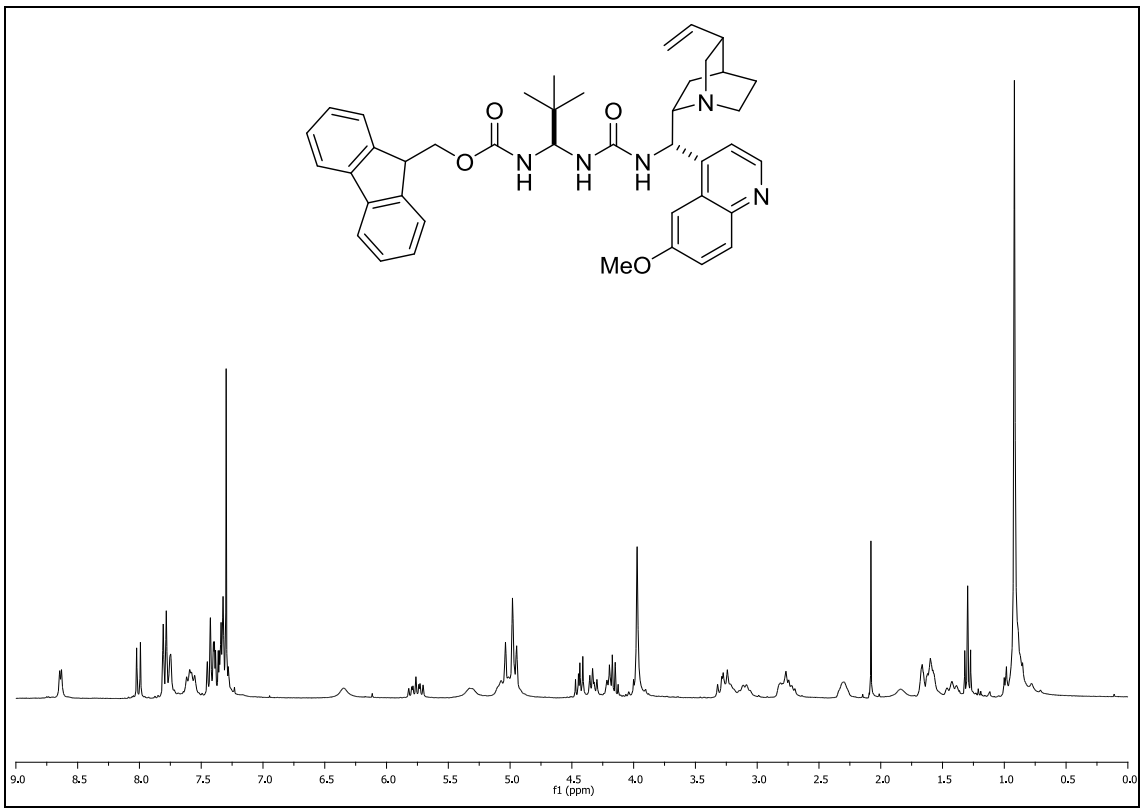


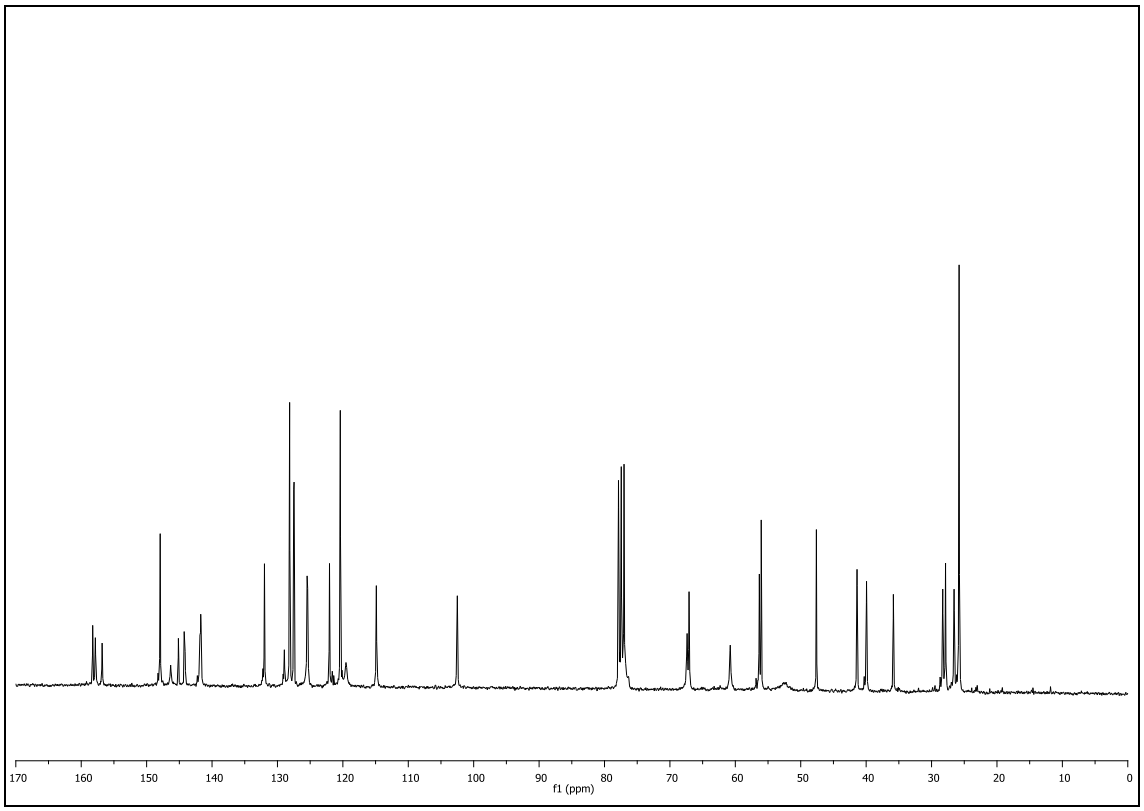
To a suspension of the squarate (252 g, 0.55 mmol, 1 equiv.) in CH_2CL_2 (4 mL) was added (*R*,*R*)-9-deoxy-9-epiaminoquinine (194 mg, 0.6 mmol, 1.1 equiv.) at room temperature. The reaction mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was filtrated and washed with diethyl ether to give pure catalyst **C4**. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.13 (s, 1H), 9.24 (s, 1H), 8.13 (d, J = 4.6 Hz, 1H), 7.81 (s, 2H), 7.55 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.21 – 6.67 (m, 8H), 5.48 – 5.16 (m, 2H), 4.46 – 4.19 (m, 2H), 3.29 (s, 3H), 2.89 – 2.58 (m, 3H), 2.15 – 1.90 (m, 2H), 1.61 (s, 1H), 1.08 – 0.65 (m, 4H), -0.02 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 184.3, 180.0, 168.3, 165.9, 163.5, 157.9, 147.8, 144.4, 143.2, 142.2, 141.1, 139.2, 135.2, 131.5, 130.9, 130.5, 129.6, 127.5, 125.1, 121.8, 119.8, 117.7, 116.4, 114.2, 101.6, 59.0, 56.1, 55.7, 53.8, 48.6, 27.4, 26.1. UPLC-DAD-QTOF: $C_{39}H_{34}F_6N_5O_4$ $[M+H]^+$ calcd.: 750.2515, found: 750.2515.

[341] Adapted from: W. Yang and D.-M. Du *Org. Lett.* **2010**, *12*, 5450–5453.

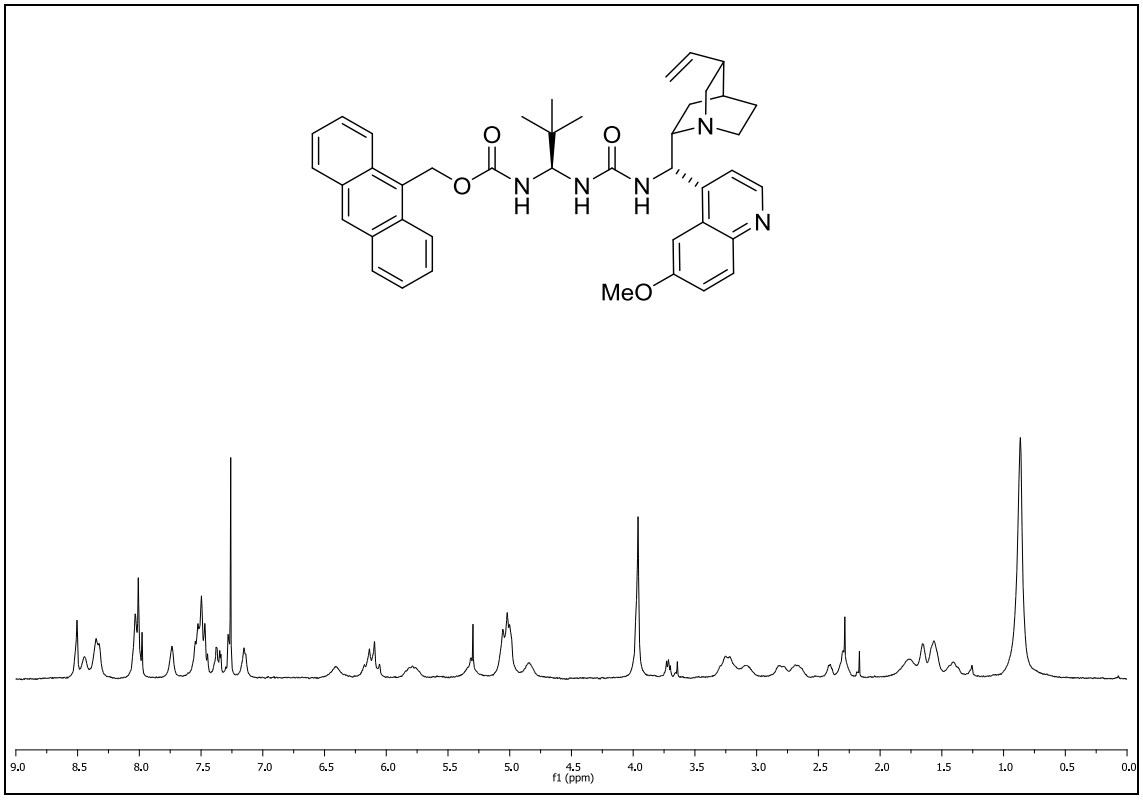
5.2.5. **Representative NMR spectra**

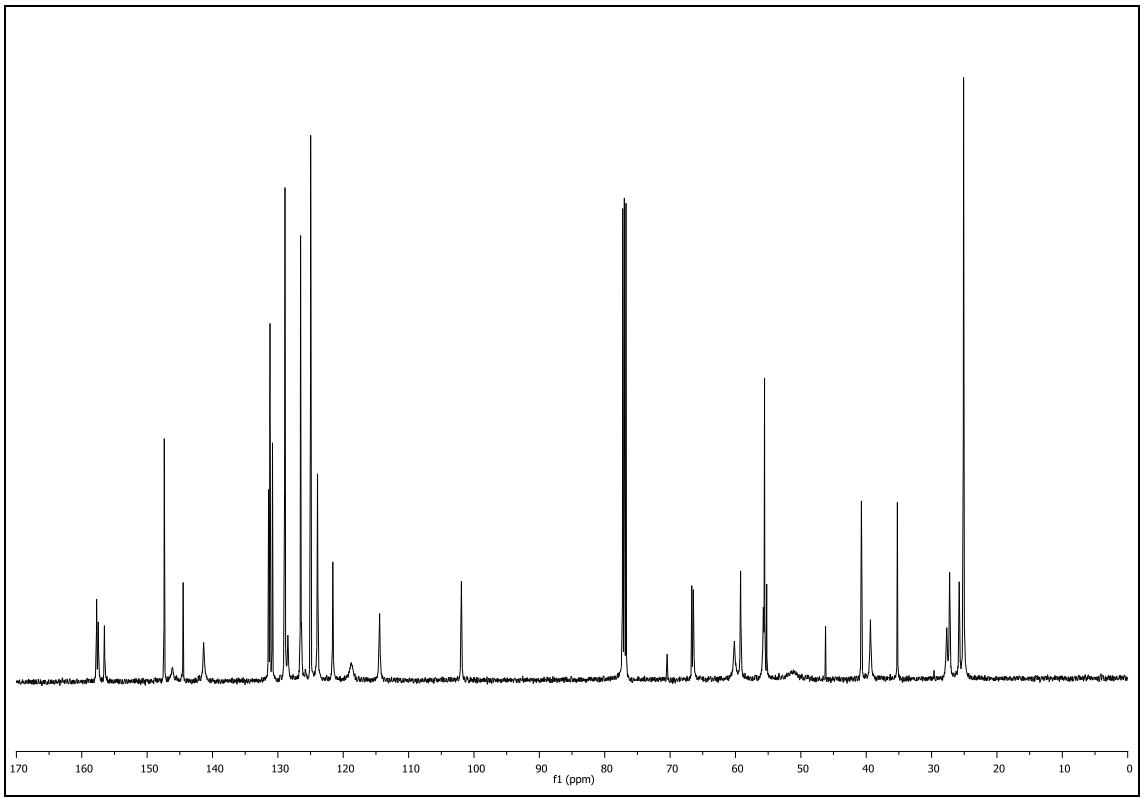
(9*H*-Fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C1)



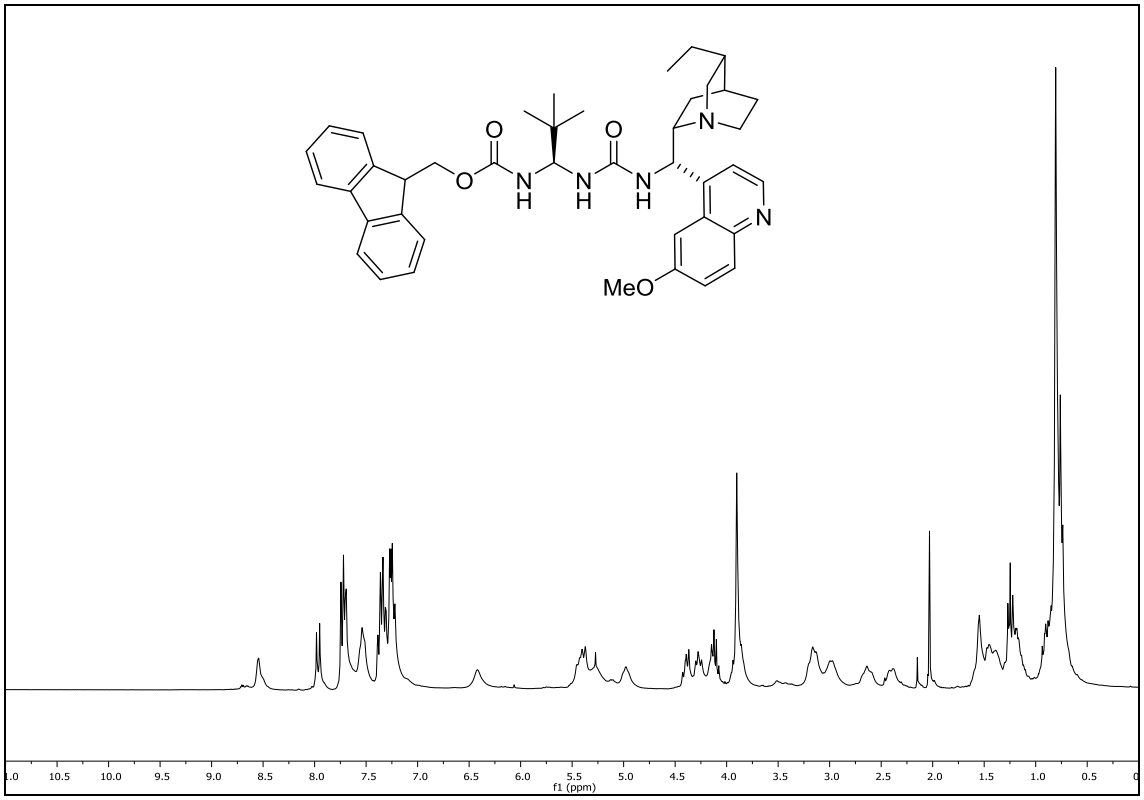


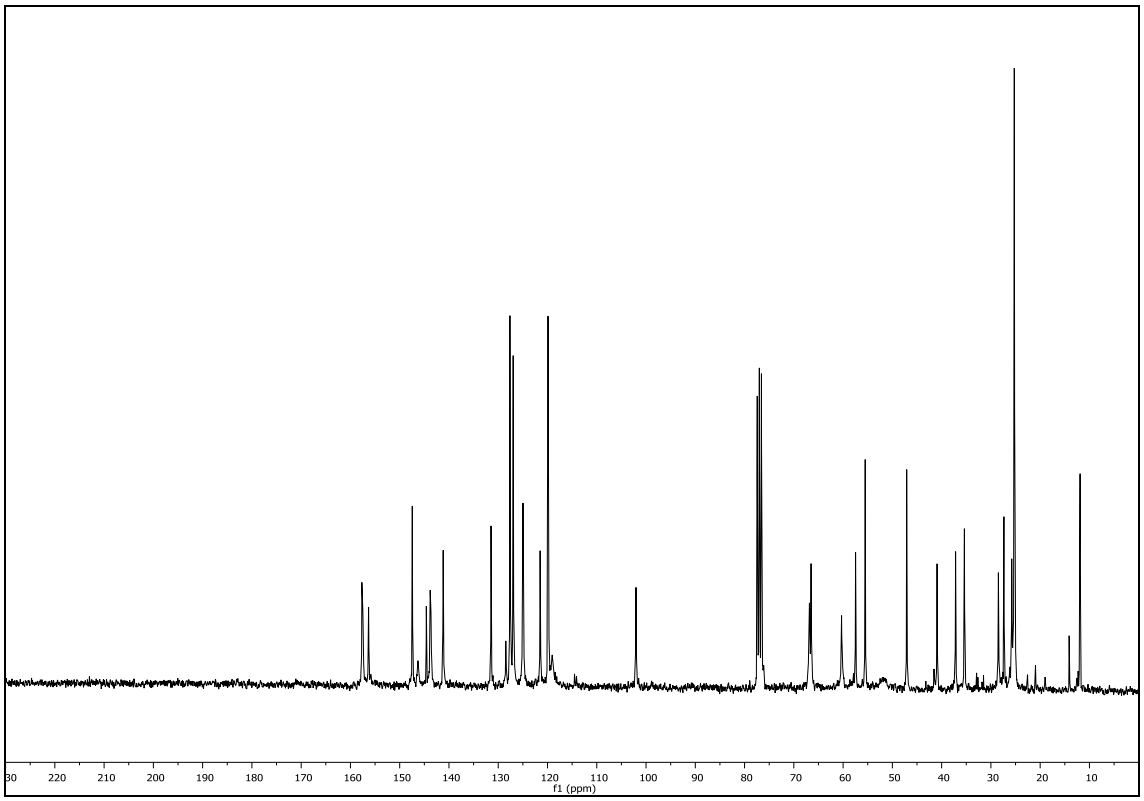
Anthracen-9-ylmethyl ((*S*)-1-(3-((*S*)-(6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)ureido)-2,2-dimethylpropyl)carbamate (C2)



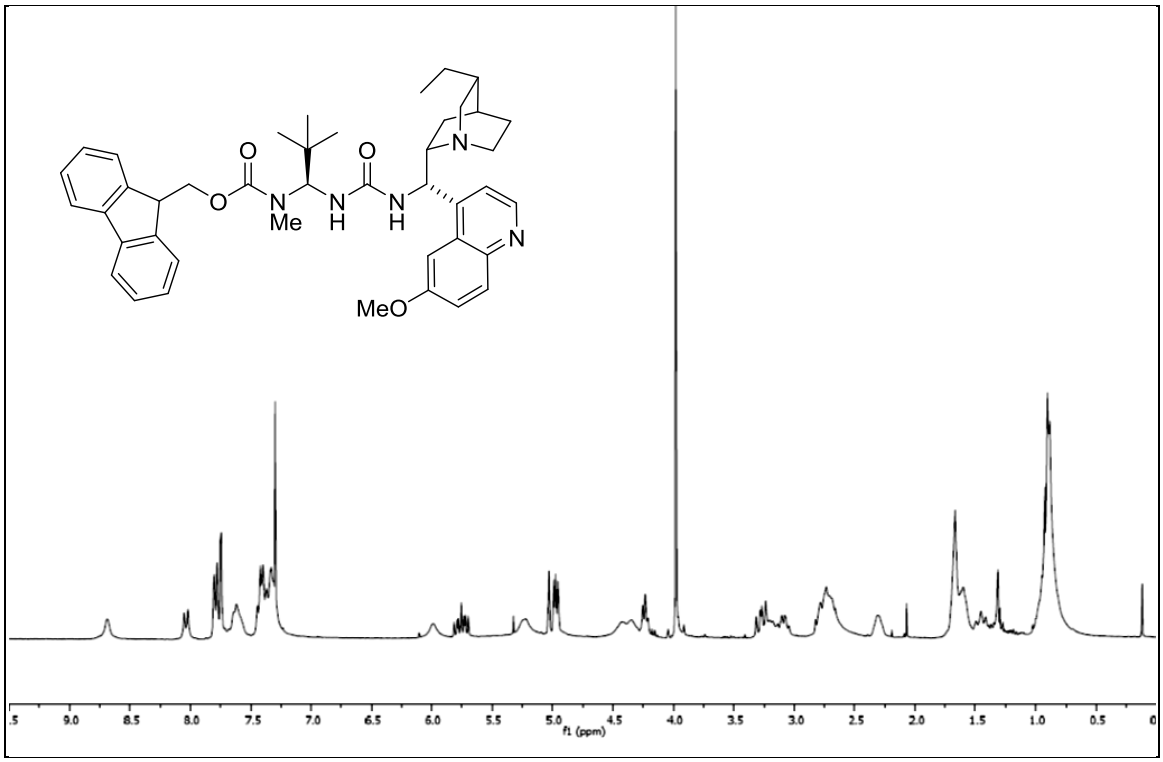


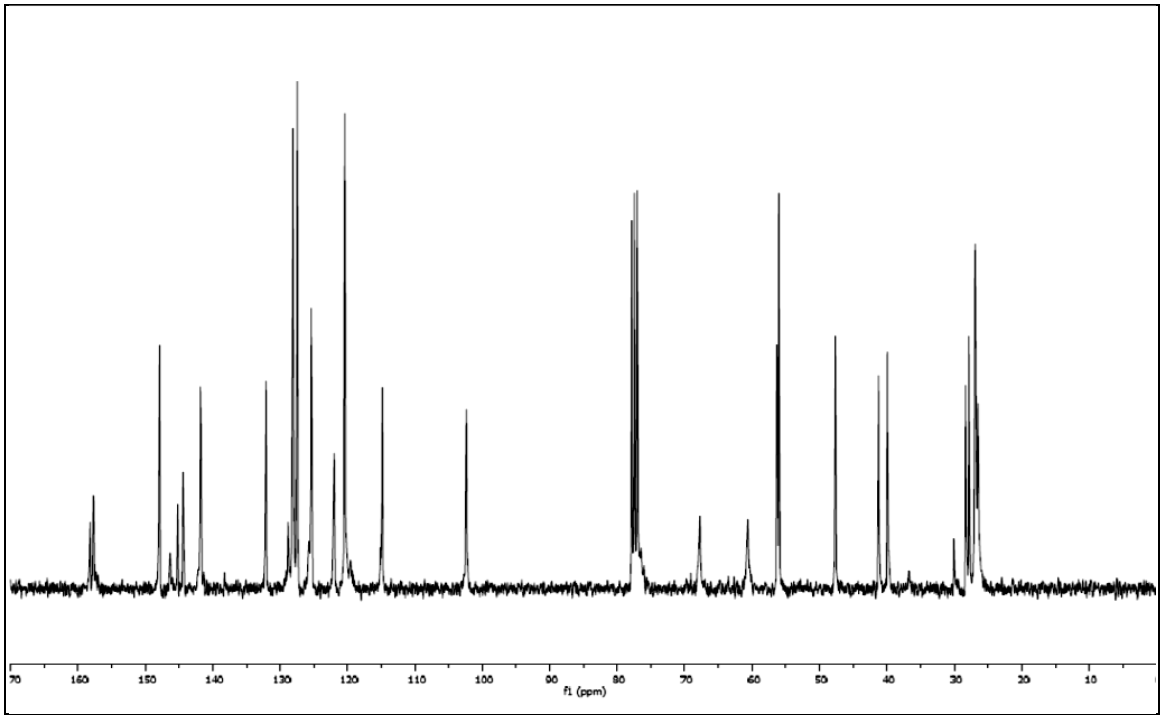
(9*H*-Fluoren-9-yl)methyl (*S*)-1-(3-((*S*)-((*2S,4S,8R*)-8-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropylcarbamate (C3)



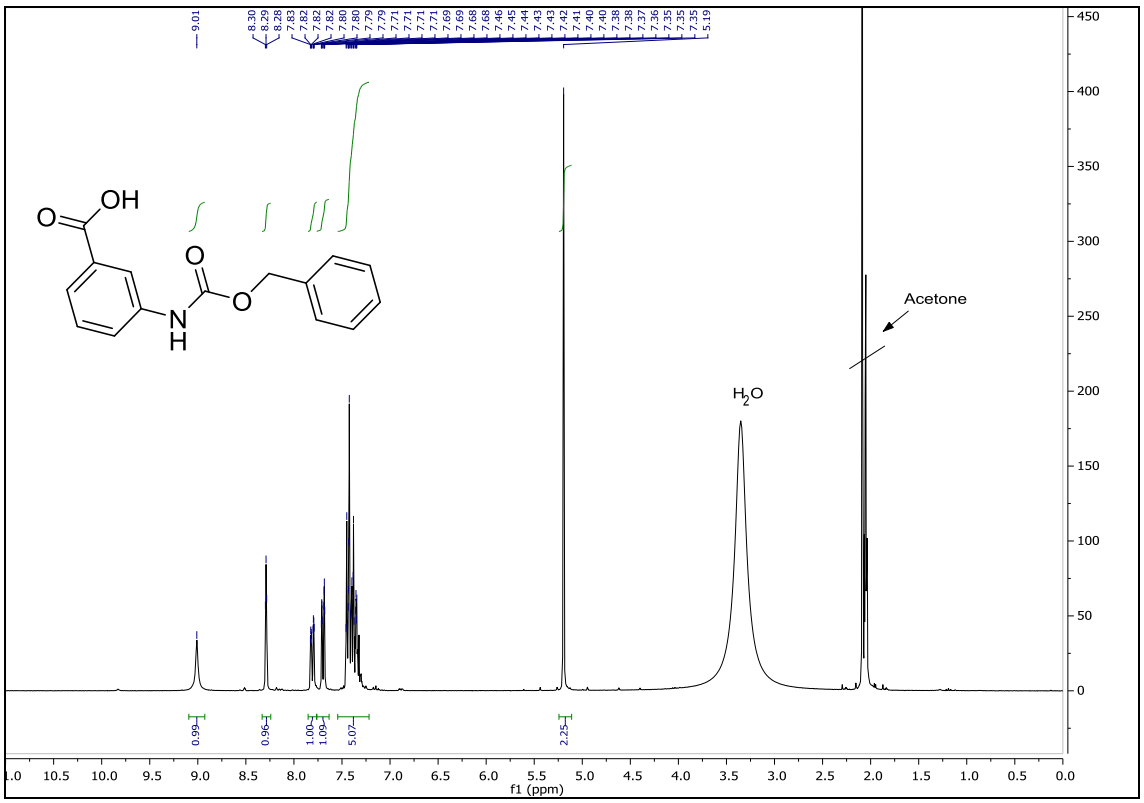


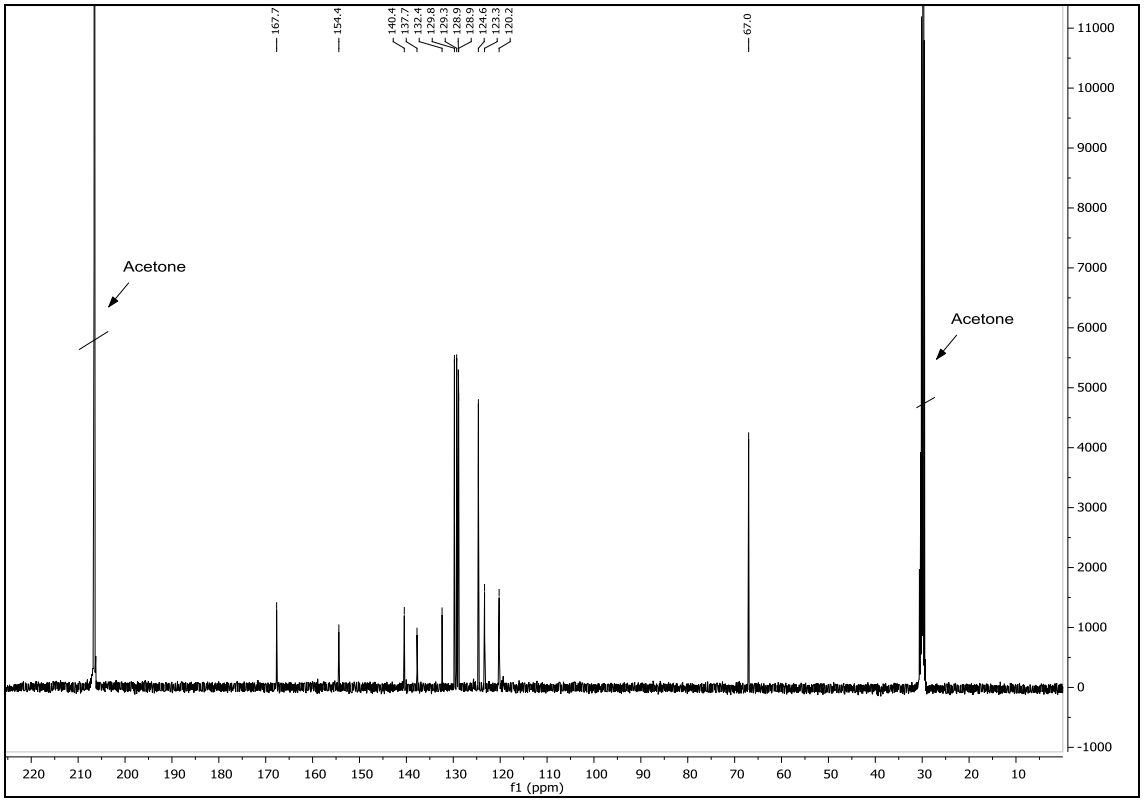
(9*H*-fluoren-9-yl)methyl ((*S*)-1-(3-((*S*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)ureido)-2,2-dimethylpropyl)(methyl)carbamate (C3-Me)



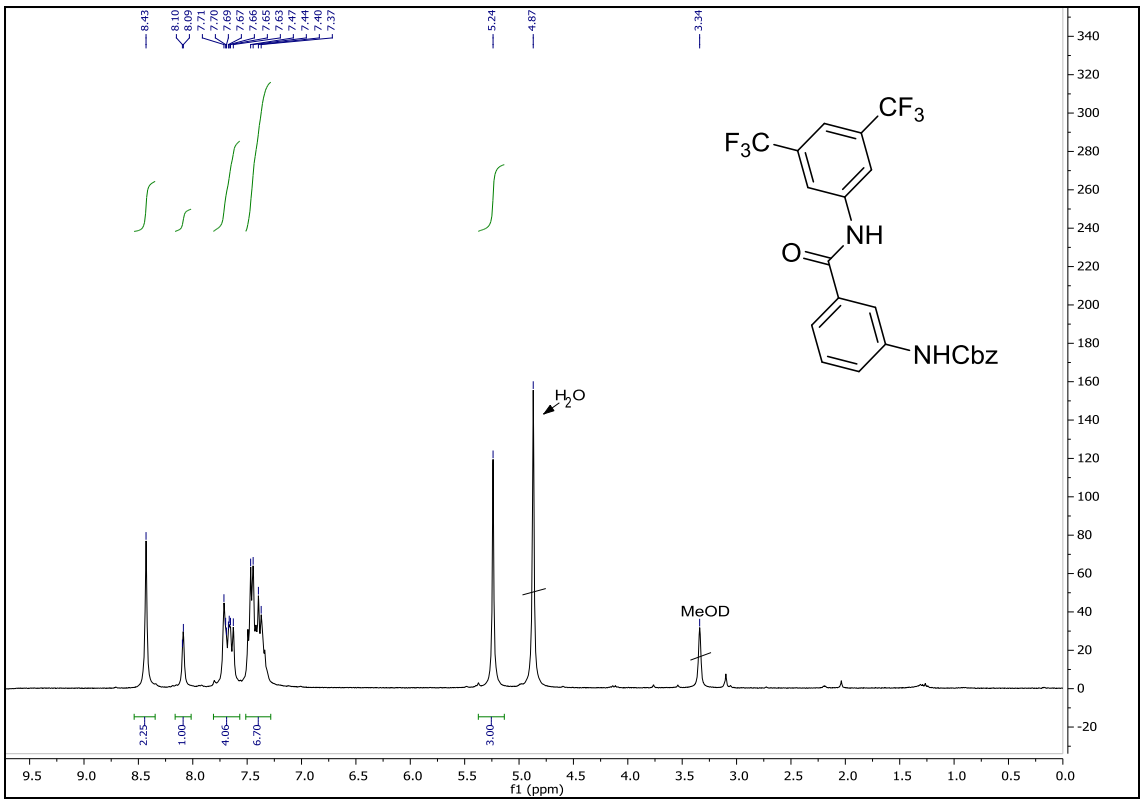


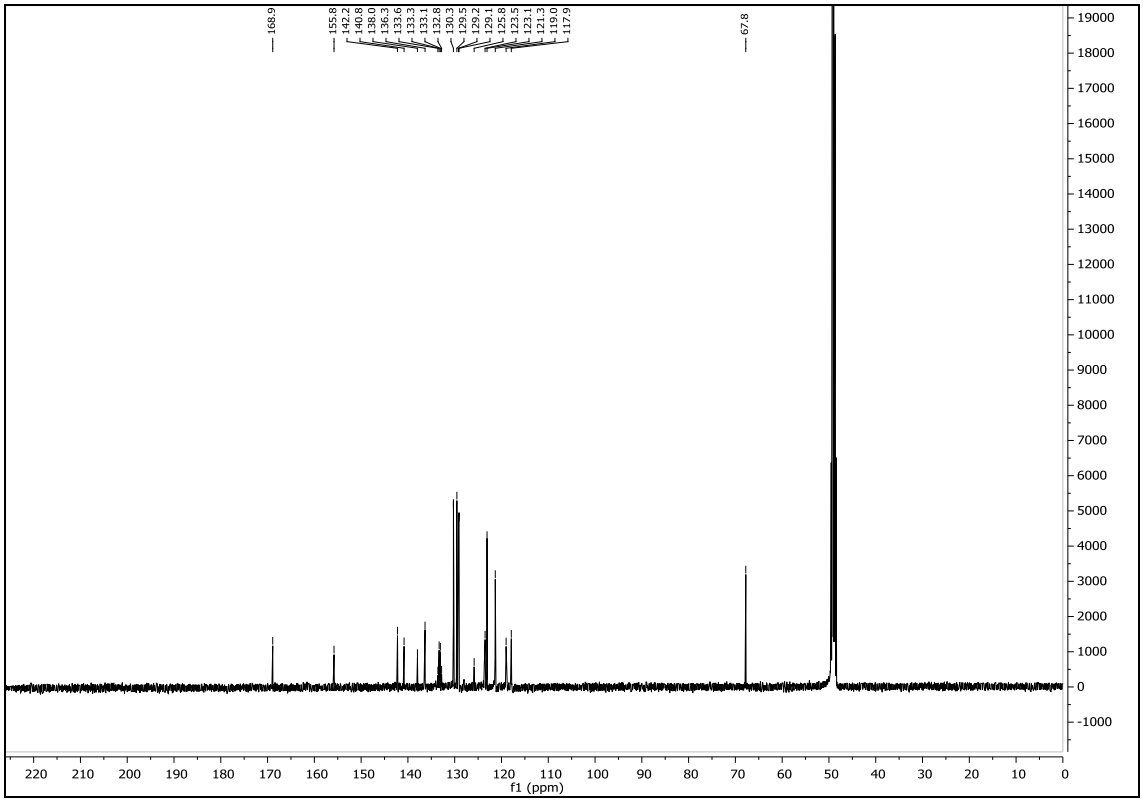
3-(((Benzyloxy)carbonyl)amino)benzoic acid



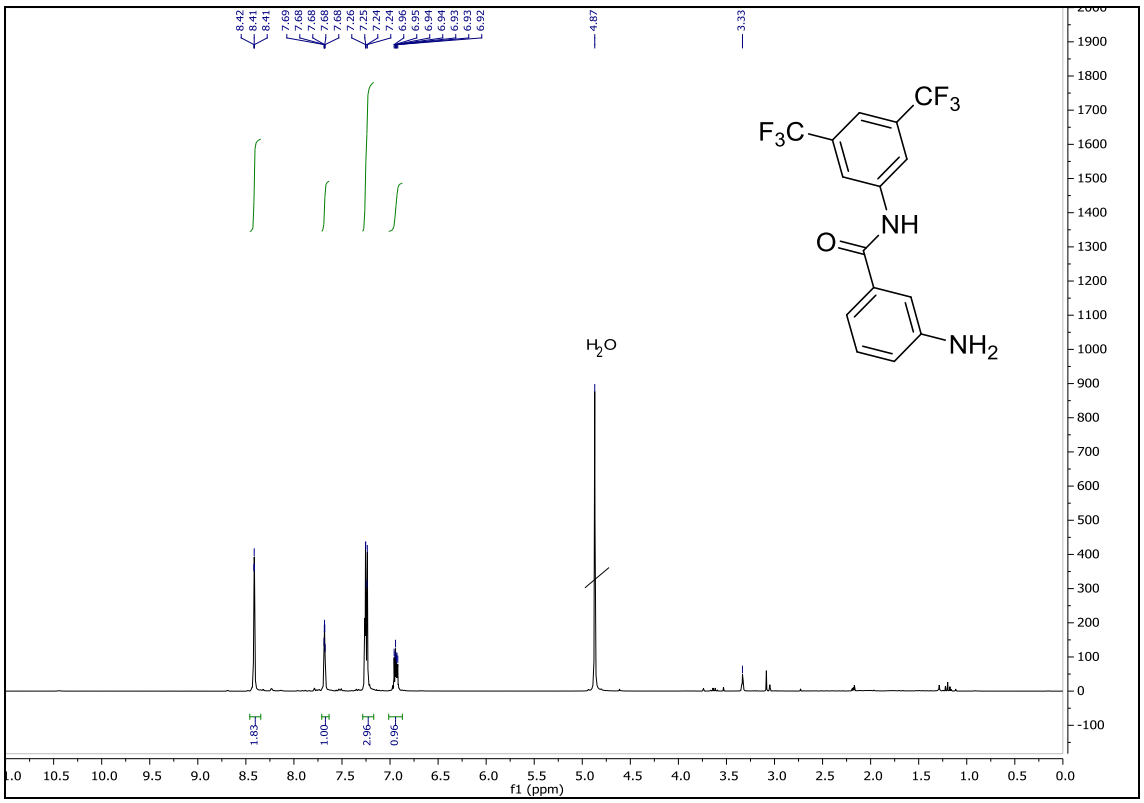


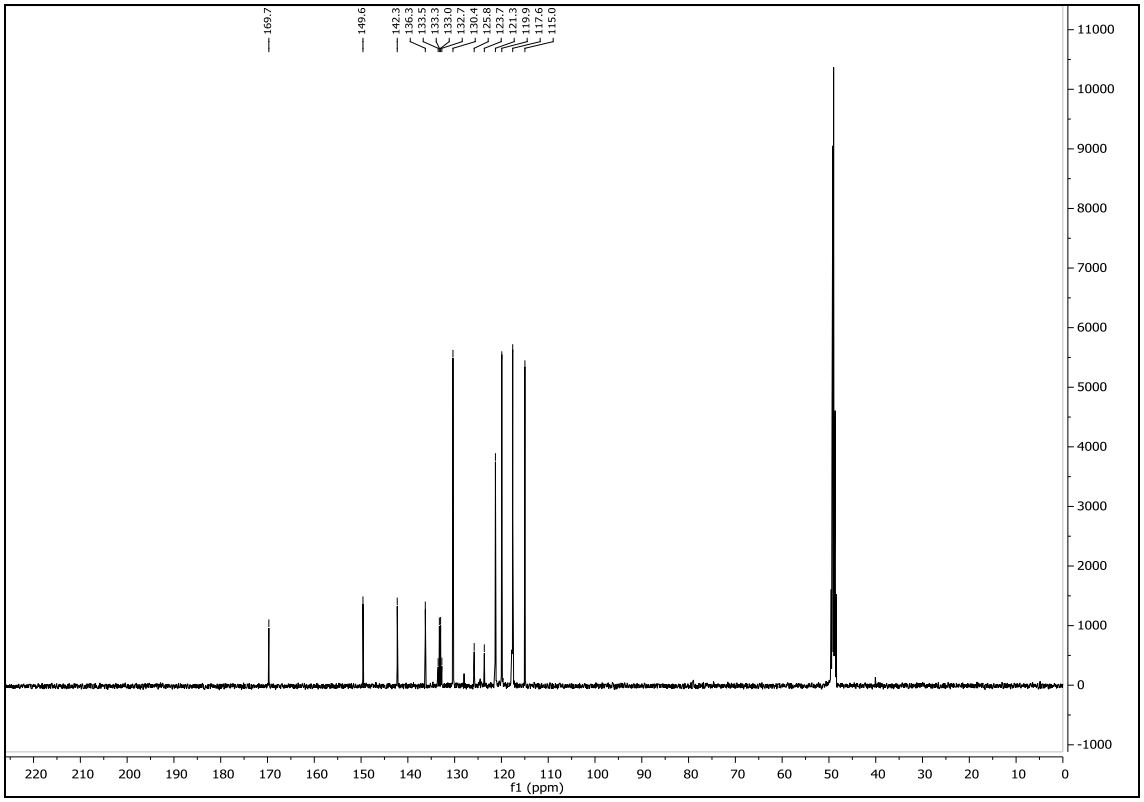
Benzyl (3-((3,5-bis(trifluoromethyl)phenyl)carbamoyl)phenyl)carbamate



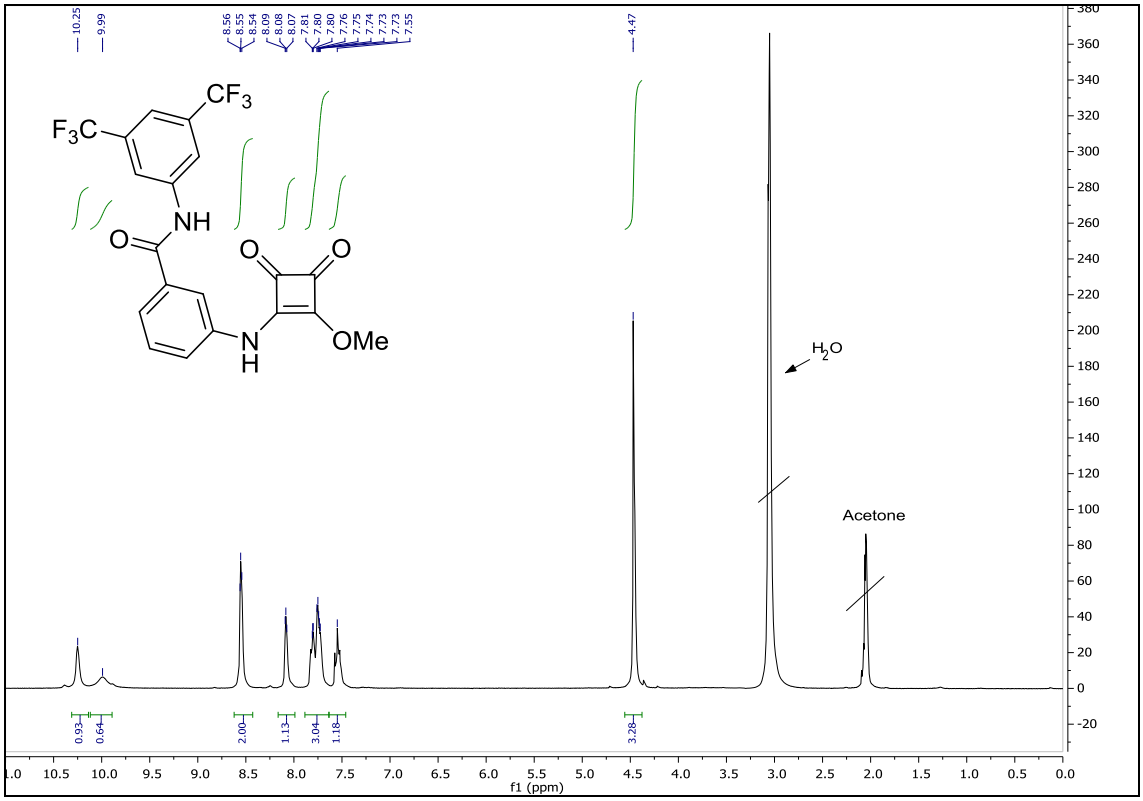


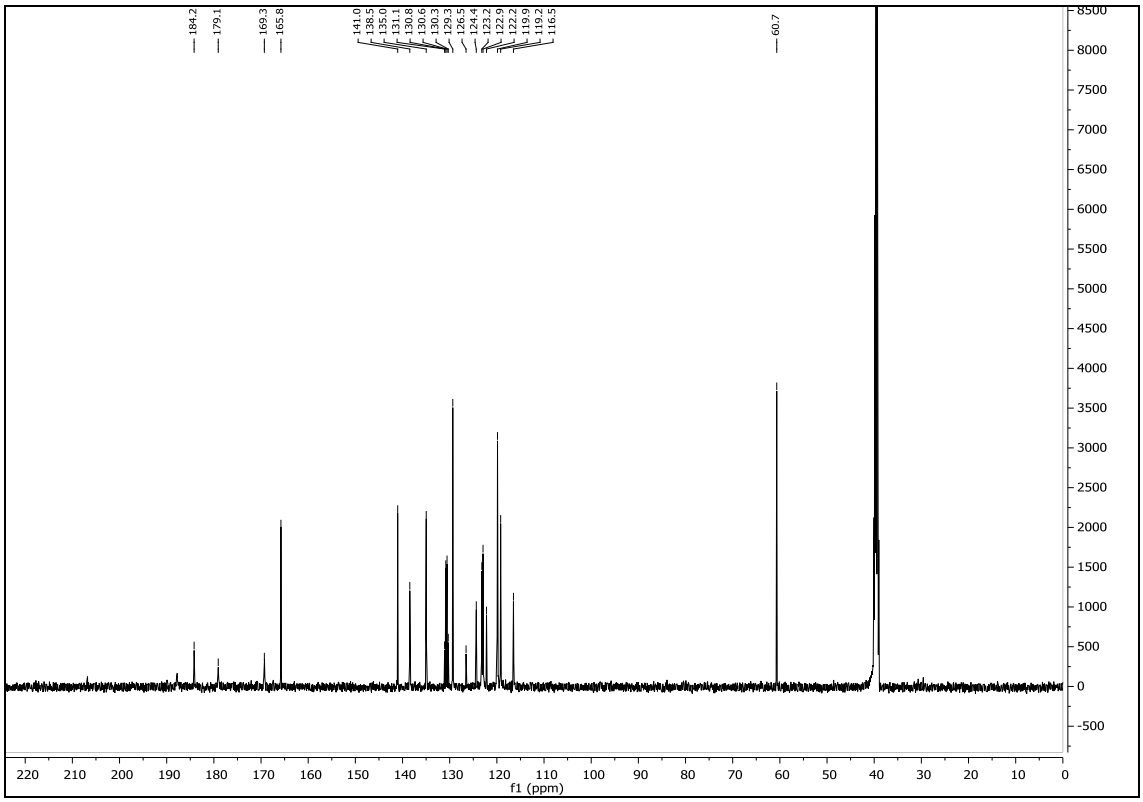
3-Amino-*N*-(3,5-bis(trifluoromethyl)phenyl)benzamide



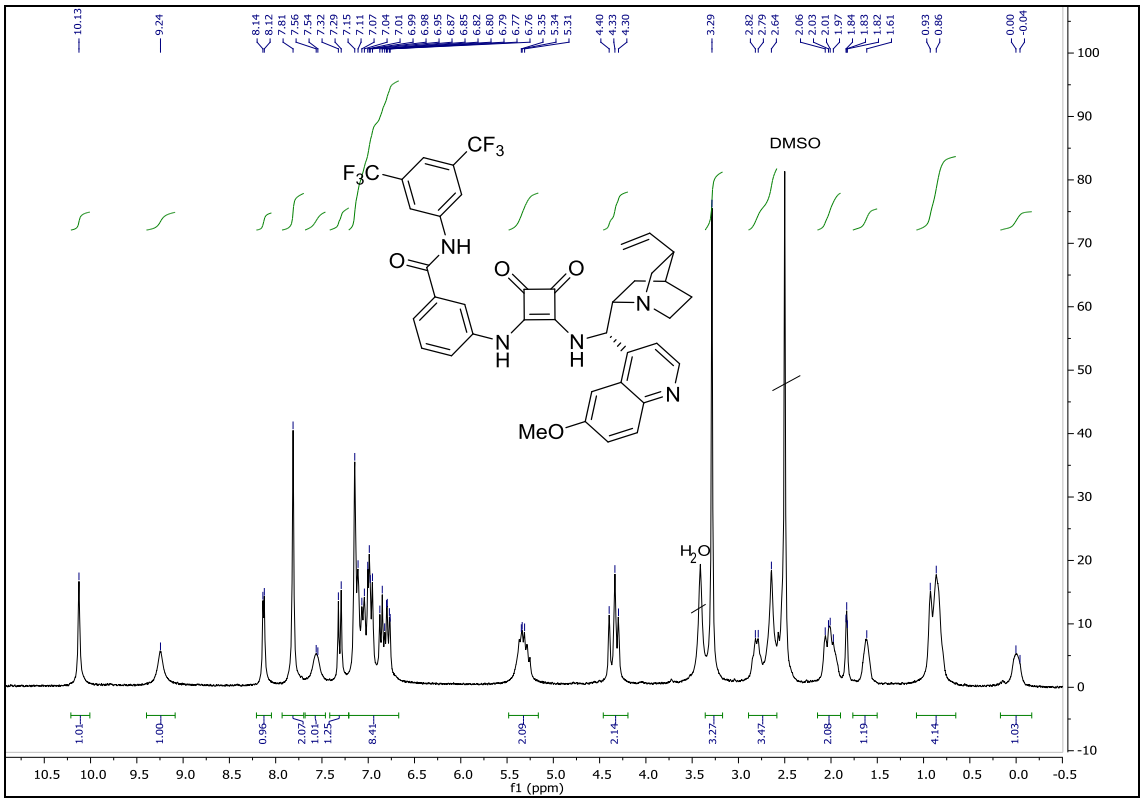


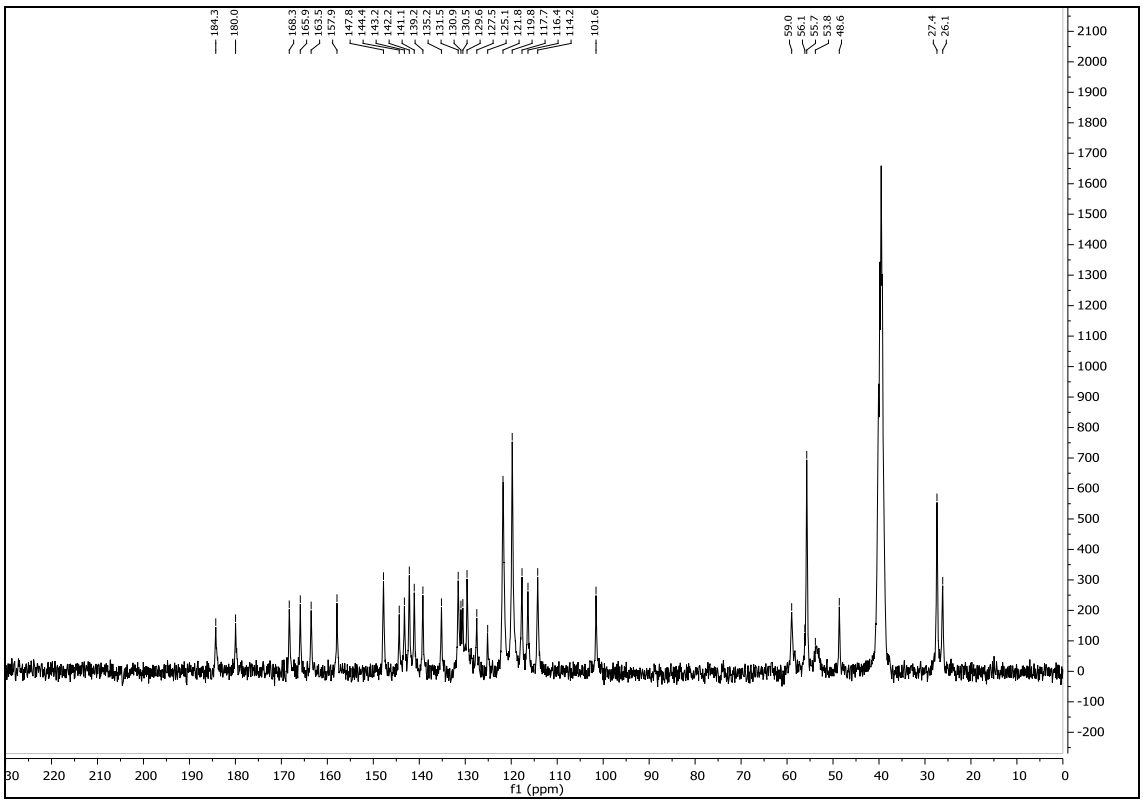
_N_-(3,5-bis(trifluoromethyl)phenyl)-3-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)benzamide





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



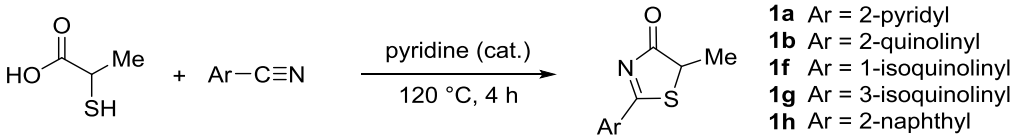


5.3. **Experimental section of chapter 2**

5.3.1. **General procedure for the synthesis of 5*H*-thiazol-4-ones 1a–h**

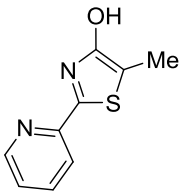
5.3.1.1. **General procedure for the synthesis of 5*H*-thiazol-4-ones**

5.3.1.1.1. General procedure A:[342]



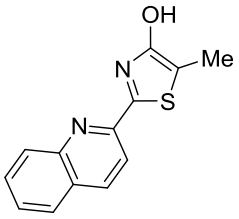
In an inert atmosphere, the corresponding carbonitrile (1 equiv.) was treated with the commercially available 2-mercaptopropanoic acid (1 equiv.) and pyridine (20 mol %). The mixture was stirred for 4 h at 120 °C. During this time, a yellow mass was formed which was collected by filtration and washed with methanol, diethyl ether.[343]

5-Methyl-2-(pyridin-2-yl)thiazol-4-ol (1a)



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

5-Methyl-2-(quinolin-2-yl)thiazol-4-ol (1b)

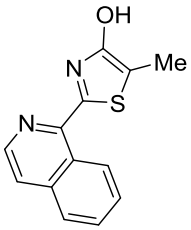


The title compound **1b** was prepared from quinoline-2-carbonitrile (1.5 g, 10 mmol) and 2-mercaptopropanoic acid (1.06 g, 10 mmol) according to the general procedure A. The resulting solid was washed with diethyl ether. Yellow solid; yield: 2.2 g, 9.1 mmol, 91%. m.p. = 232-234 °C. ^{1}H NMR (300 MHz, DMSO), δ: 9.59 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 6.97 (t, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, DMSO), δ:

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

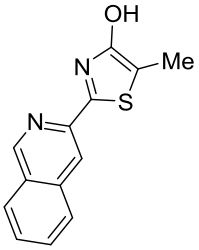
159.3, 158.8, 150.6, 147.1, 137.5, 130.4, 128.5, 128.0, 127.9, 126.9, 116.6, 107.2, 9.4. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0592, found: 243.0597.

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



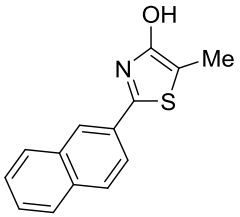
The title compound **1f** was prepared from isoquinoline-1-carbonitrile (1.5 g, 10 mmol) and 2-mercaptopropanoic acid (1.06 g, 10 mmol) according to the general procedure A, the solid was washed with diethyl ether. Yellow solid, yield: 1.50 g, 6.2 mmol, 62%. m.p. = 207– 29 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 – 9.48 (m, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 8.06 – 7.59 (m, 4H), 2.41 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ: 160.43, 152.17, 151.98, 142.67, 135.65, 129.84, 132.72, 128.39, 125.68, 124.34, 115.27, 101.42, 8.98. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0593, found: 243.0598.

2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (1g)



The title compound **1g** was prepared from isoquinoline-3-carbonitrile (1.5 g, 10 mmol) and 2-mercaptopropanoic acid (1.06 g, 10 mmol) according to the general procedure A, the solid was washed with diethyl ether. Yellow solid, yield: 1.77 g, 7.3 mmol, 73%. m.p. = 212– 214 °C. ^{1}H NMR (300 MHz, DMSO) δ: 10.33 (s, 1H), 9.27 (s, 1H), 8.30 (s, 1H), 8.08 (dd, *J* = 14.2, 8.0 Hz, 2H), 7.78 (ddd, *J* = 9.3, 5.9, 1.8 Hz, 1H), 7.70 – 7.61 (m, 1H), 2.25 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ: 159.33, 154.15, 152.63, 144.61, 135.65, 131.32, 130.74, 128.39, 127.88, 127.43, 113.64, 105.35, 9.37. HRMS: $C_{13}H_{10}N_2OS$ $[M+H]^+$ calcd.: 243.0593, found: 243.0592.

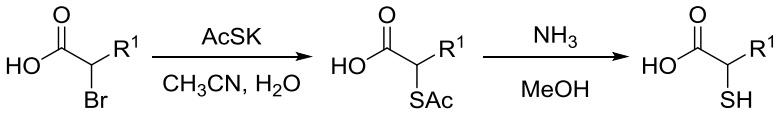
5-Methyl-2-(naphthalen-2-yl)thiazol-4-ol (1h)



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

5.3.1.1.2. General procedure B:[344]

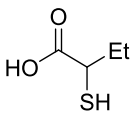
5.3.1.1.2.1. General procedure for the synthesis of α-mercaptocarboxylic acids[345]



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

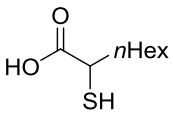
To a solution of the commercially available α-bromocarboxylic acid (25 mmol, 1 equiv.) in 60 mL of anhydrous CH_3CN was added a solution of potassium thioacetate (50 mmol, 2 equiv.) in water (15 mL), and the mixture was stirred for 3 h. The organic solvent was evaporated and the mixture was diluted with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

2-Mercaptobutanoic acid



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

2-Mercaptooctanoic acid

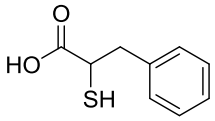


The title compound was prepared from 2-bromooctanoic acid (4.43 mL, 25 mmol) according to the general procedure. Orange oil; yield: 4.92 g,

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

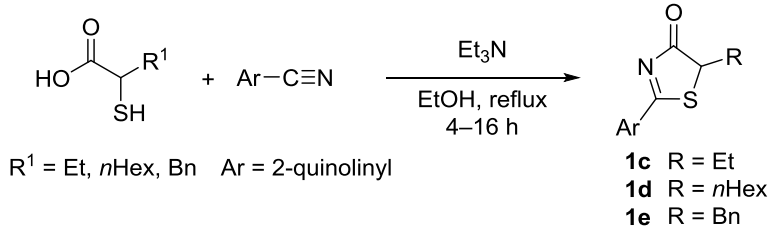
25 mmol, 100%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.35 (dt, *J* = 8.9, 7.4 Hz, 1H), 2.17 (s, 1H), 2.03–1.83 (m, 1H), 1.83–1.63 (m, 1H), 1.54–1.22 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H).

2-Mercapto-3-phenylpropanoic acid



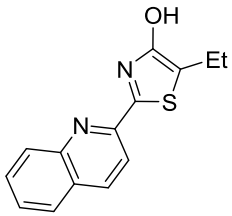
The title compound was prepared from 2-bromo-3-phenylpropanoic acid (5.73 g, 25 mmol) according to the general procedure. Orange oil; yield: 4.49 g, 24.65 mmol, 99%. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.25–7.03 (m, 5H), 3.55 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.21 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.82 (dd, *J*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

*5.3.1.1.2.2. General procedure for the synthesis of 5H-thiazol-4-ones **1c–e**[346]*



The corresponding carbonitrile (1 eq., 10 mmol) was refluxed with the corresponding α-mercaptocarboxylic acid (1 eq., 10 mmol) and triethylamine (5 eq., 50 mmol) in ethanol (20 mL) in an inert atmosphere. The mixture was stirred at 110 °C and the reaction was monitored by TLC. After reaction completion, the reaction mixture was evaporated under reduced pressure and the resulting solid was washed with diisopropyl ether.[347]

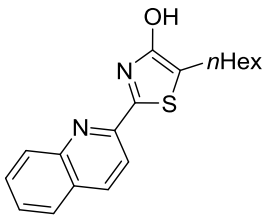
5-Ethyl-2-(quinolin-2-yl)thiazol-4-ol (1c)



The title compound **1c** was prepared from quinoline-2-carbonitrile (0.77 g, 5 mmol) and 2-mercaptobutanoic acid (0.6 g, 5 mmol) according to the general procedure B. The resulting solid was washed with diisopropyl ether. Green solid; yield: 1.1 g, 4.35 mmol, 87%. m.p. = 100–104 °C. ^{1}H NMR (300 MHz, DMSO), δ: 8.44 (d, *J* = 8.6 Hz, 1H), 8.11 (t, *J* = 8.2 Hz, 1H), 8.05–7.86 (m, 2H), 7.79 (dd, *J* = 13.6, 6.5 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO), δ: 158.5, 150.6, 147.1, 138.4, 137.5, 131.5, 130.4, 129.5, 129.1, 128.4, 128.3, 128.0, 127.9, 126.9, 123.8, 116.6, 114.8, 17.7, 15.6. HRMS: $C_{14}H_{13}N_2OS$ $[M+H]^+$ calcd.: 257.0759, found: 257.0749.

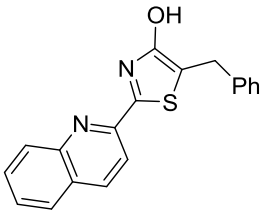
[346] Adapted from: J. E. Shaffer, S. A. Thomson, *US Patent* 5.087.631 Feb 11, **1992**.
[347] Keto-enol-tautomerism can be detected in chloroform by ^{1}H-NMR analysis.

5-Hexyl-2-(quinolin-2-yl)thiazol-4-ol (1d)



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

5-Benzyl-2-(quinolin-2-yl)thiazol-4-ol (1e)



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

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

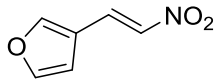
Nitroalkenes **2a**–**e** and **2g**–**i** are commercially available and were purchased from commercial suppliers.

5.3.2.1. General procedure A[349]

To a solution of the corresponding aldehyde (1 equiv., 10 mmol) and nitromethane (1 equiv., 0.5 mL, 10 mmol) in ethanol (2.5 mL) at 0 ºC an aqueous NaOH 1M solution (1 equiv., 1 mL, 10 mmol) was added. After 10 min under vigorous stirring the reaction mixture became yellow. Then acetic acid (1 equiv., 0.6 mL, 10 mmol) was added and the aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent

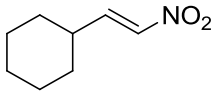
evaporated under reduced pressure to afford the corresponding nitro alcohol, which was dissolved in dichloromethane (10 mL) and cooled at 0 ºC. Then trifluoroacetic acid anhydride (1 equiv., 0.8 mL, 10 mol) and triethylamine (4 equiv., 5.5 mL, 40 mmol) were added dropwise. The reaction mixture was stirred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

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



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

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



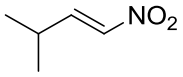
The title compound was prepared from cyclohexanecarboxaldehyde (1 equiv., 1.2 mL, 10 mmol) following the general procedure. Yellow oil, yield: 0.74 g, 4.8 mmol, 48%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.26–7.17 (m, 1H), 6.93 (dd, *J* = 13.5, 1.3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

5.3.2.2. General procedure B[348]

Nitromethane (1 equiv., 1.1 mL, 20 mmol) was added to a stirred solution of the corresponding aldehyde (1 equiv., 20 mmol) in ethanol (35 mL) at 0 ºC, followed by dropwise addition of 10N NaOH solution (1.05 equiv., 201 mL, 21 mmol). The resulting mixture was stirred at 0 ºC for 1 hour and then a mixture of 1:1 HCl 37%: H_2O (12 mL:12 mL) was added. The reaction mixture was stirred at 0 ºC for 1 hour, then extracted with dichloromethane (3 x 50 mL), dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

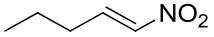
[348] Bourguignon, J.; Le Nard, G.; Queguiner, G. *Can. J. Chem*. **1985**, *63*, 2354–2361.

3-Methyl-1-nitrobut-1-ene 2j[349]



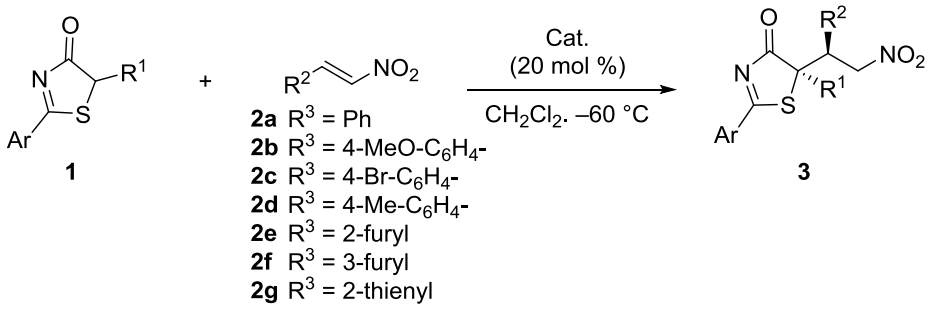
The title compound **2j** was prepared from isobutyraldehyde (1.8 mL, 20 mmol) according to the general procedure A. Yellow oil, yield: 1.0 g, 9.1 mmol, 46%. All data were consistent with those previously reported. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.31–7.18 (m, 1H), 6.94 (dd, *J* = 13.5, 1.4 Hz, 1H),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

1-Nitropent-1-ene 2l[349]



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

5.3.3. General procedure for the asymmetric conjugate addition of 5*H*-thiazol-4-ones to nitroolefins



5.3.3.1. Asymmetric reaction

To a mixture of the corresponding thiazolone (1 equiv., 0.3 mmol) and the nitroolefin (0.6 mmol, 2.0 equiv.), in dichloromethane (0.6 mL) cooled to –60 °C the catalyst was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (monitored by ^{1}H NMR). The reaction mixture was directly purified by flash column chromatography on silica gel without previous workup to afford the expected adducts.

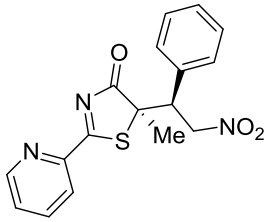
5.3.3.2. Racemic reaction

Racemic compounds were prepared following the above procedure using triethylamine (20 mol %) as the catalyst at –20 °C.

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

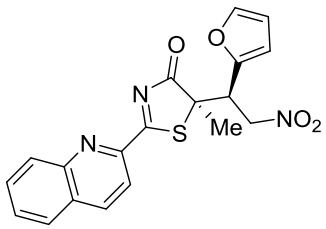
5.3.3.3. **Characterization data for compounds 3a–3g**

(*R*)-5-Methyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(pyridin-2-yl)thiazol-4(5*H*)-one (3aa)



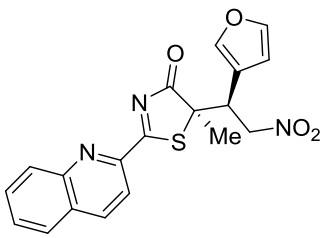
The title compound **3aa** was prepared from 5-methyl-2-(pyridin-2-yl)thiazol-4-ol (**1a**) (57.7 mg, 0.3 mmol) and nitrostyrene (**2a**) (89.4 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 81.9 mg, 0.24 mmol, 80%. $[\alpha]_D^{25}$= -58.2 (*c*= 1.00, 80% *ee*, CH_2Cl_2). m.p. 185–186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.73 (d, *J* = 4.2 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.35–7.28 (m, 2H), 7.28–7.14 (m, 3H), 5.15 (dd, *J* = 13.2, 4.7 Hz, 1H), 4.94 (dd, *J* = 13.2, 10.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 4.7 Hz, 1H), 1.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 195.8, 194.1, 150.0, 148.8, 137.3, 134.2, 129.0, 128.7, 128.7, 128.5, 123.7, 75.9, 65.1, 50.2, 23.9. HRMS: $C_{17}H_{15}N_3O_3S$ $[M+H]^+$ calcd.: 342.0912, found: 342.0909. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 42.8 min (min.) and 47.2 min (major.)).

(*R*)-5-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3be)



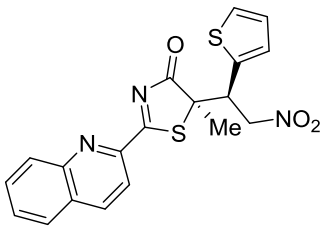
The title compound **3be** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**1b**) (72.7 mg, 0.3 mmol) and 2-(2-nitrovinyl)furan (**2e**) (83 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 110 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= -73.3 (*c*= 0.5, 91% *ee*, CH_2Cl_2). m.p. 89–91 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.33 (s, 2H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.82 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.32 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.38–6.22 (m, 2H), 5.30–5.16 (m, 1H), 4.98 (dd, *J* = 13.4, 10.5 Hz, 1H), 4.33 (dd, *J* = 10.5, 4.1 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.3, 194.8, 149.6, 149.3, 148.3, 143.5, 138.1, 131.3, 131.0, 130.1, 128.4, 120.1, 111.2, 110.5, 74.4, 64.9, 44.9, 23.9. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_4S$ $[M+H]^+$ calcd.: 382.0862, found: 382.0871. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 46.2 min (major.) and 51.2 min (min.)).

(*R*)-5-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3bf)



The title compound **3bf** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**1b**) (72.7 mg, 0.3 mmol) and 3-(2-nitrovinyl)furan (**2f**) (83 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 109 mg, 0.285 mmol, 95%. $[\alpha]_D^{25}$= –161.7 (*c*= 1.00, 89% *ee*, CH_2Cl_2). m.p. 166–169 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.18 (m, 3H), 7.91 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.83 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.41 (s, 1H), 7.24 (t, *J* = 1.6 Hz, 1H), 6.43 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.05 (dd, *J* = 12.7, 4.3 Hz, 1H), 4.76 (dd, *J* = 12.7, 10.8 Hz, 1H), 4.19 (dd, *J* = 10.8, 4.3 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.2, 195.3, 149.4, 148.5, 144.0, 142.4, 138.2, 131.5, 131.1, 130.3, 128.6, 120.3, 119.7, 110.5, 65.6, 43.2, 24.6. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_4S$ $[M+H]^+$ calcd.: 382.0862, found: 382.0866. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 48.7 min (major.) and 56.2 min (min.)).

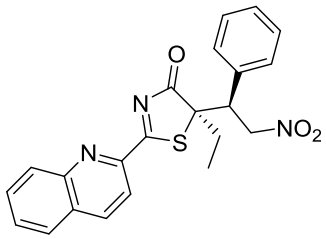
(*R*)-5-Methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3bg)



The title compound **3bg** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**1b**) (72.7 mg, 0.3 mmol) and 2-(2-nitrovinyl)thiophene (**2g**) (93 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 111 mg, 0.28 mmol, 93%. $[\alpha]_D^{25}$= –244.7 (*c*= 1.00, 92% *ee*, CH_2Cl_2). m.p. 173-176 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.36–8.20 (m, 3H), 7.91 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.84 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.75–7.66 (m, 1H), 7.15 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.06 (dt, *J* = 7.1, 3.6 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.24–5.11 (m, 1H), 4.85 (dd, *J* = 12.9, 10.6 Hz, 1H), 4.54 (dt, *J* = 10.6, 5.3 Hz, 1H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.0, 193.8, 148.3, 147.4, 137.1, 135.8, 130.4, 130.1, 129.2, 128.3, 127.4, 126.3, 125.8, 119.2, 64.6, 53.0, 46.2, 23.7. UPLC-DAD-QTOF: $C_{19}H_{16}N_3O_3S_2$ $[M+H]^+$ calcd.: 398.0633, found: 398.0634. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC,

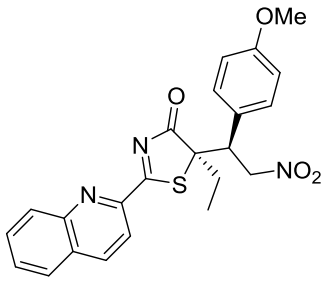
hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 61.6 min (min.) and 75.6 min (major.)).

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3ca)



The title compound **3ca** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**1c**) (77 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 116 mg, 0.285 mmol, 95 %. $[\alpha]_D^{25}$= –221.9 (*c*= 1.00, 97% *ee*, CH_2Cl_2). m.p. 89-92 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.24 (dt, *J* = 14.3, 8.5 Hz, 3H), 7.85 (ddd, *J* = 11.6, 9.8, 4.8 Hz, 2H), 7.71 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.08 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.93 (dd, *J* = 13.1, 11.0 Hz, 1H), 4.21 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.35–2.05 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.8, 194.4, 149.5, 148.7, 138.5, 134.0, 132.6, 131.9, 131.7, 131.4, 130.6, 128.8, 124.0, 120.6, 72.0, 51.2, 30.9, 9.9.UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 406.1225, found: 406.1235. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 32.1 min (min.) and 38.6 min (major.)).

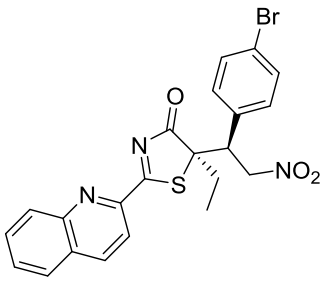
(*R*)-5-Ethyl-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cb)



The title compound **3cb** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**1c**) (77 mg, 0.3 mmol) and 4-methoxy-nitrostyrene (**2b**) (108 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 122 mg, 0.28 mmol, 95%. $[\alpha]_D^{25}$= –270.0 (*c*= 0.6, 97% *ee*, CH_2Cl_2). m.p. 85–87 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.31–8.15 (m, 3H), 7.93–7.79 (m, 2H), 7.69 (ddd, *J* = 13.5, 7.3, 3.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.07 (dd, *J* = 12.9, 4.6 Hz, 1H), 4.93 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.19 (dd, *J* = 10.9, 4.6 Hz, 1H), 3.68 (s, 3H), 2.34–2.03 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.4, 194.4, 160.2, 149.3, 148.4, 138.0, 131.3, 131.0, 130.10, 128.5, 126.5, 120.2, 115.1, 114.5, 72.3, 55.7, 50.8, 30.3, 9.7. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_4S$ $[M+H]^+$ calcd.: 436.1331, found: 436.1327. The enantiomeric purity of the

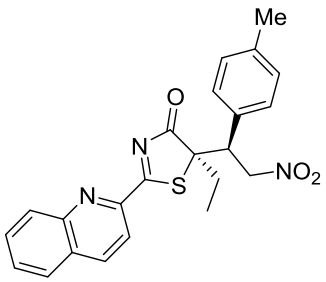
major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 30.3 min (min.) and 33.0 min (major.)).

(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cc)



The title compound **3cc** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**1c**) (77 mg, 0.3 mmol) and 4-bromo-nitrostyrene (**2c**) (137 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 117 mg, 0.24 mmol, 81%. $[\alpha]_D^{25}$= –233.3 (*c*= 1.00, 97% *ee*, CH_2Cl_2). m.p. 91–93 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.24 (dt, *J* = 14.3, 8.5 Hz, 3H), 7.85 (ddd, *J* = 11.6, 9.8, 4.8 Hz, 2H), 7.74–7.57 (m, 1H), 7.29 (dd, *J* = 24.5, 8.6 Hz, 4H), 5.08 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.93 (dd, *J* = 13.1, 11.0 Hz, 1H), 4.21 (dd, *J* = 11.0, 4.6 Hz, 1H), 2.35–2.05 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.8, 194.4, 149.5, 148.7, 138.5, 134.0, 132.6, 131.9, 131.7, 131.4, 130.6, 128.8, 124.0, 120.6, 72.0, 51.2, 30.9, 9.9. UPLC-DAD-QTOF: $C_{22}H_{19}BrN_3O_3S$ $[M+H]^+$ calcd.: 484.0331, found: 484.0341. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 26.6 min (min.) and 29.8 min (major.)).

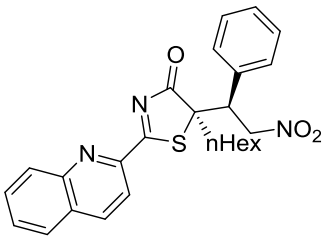
(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cd)



The title compound **3cd** was prepared from 5-ethyl-2-(quinolin-2-yl)thiazol-4-ol (**1c**) (77 mg, 0.3 mmol) and 4-methyl-nitrostyrene (**2d**) (98 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 109 mg, 0.26 mmol, 87%. $[\alpha]_D^{25}$= –251.5 (*c*= 0.35, 94% *ee*, CH_2Cl_2). m.p. 93–95 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.18 (m, 3H), 7.93–7.80 (m, 2H), 7.74–7.66 (m, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.11 (dd, *J* = 13.0, 4.6 Hz, 1H), 5.05–4.90 (m, 1H), 4.19 (dt, *J* = 16.5, 8.2 Hz, 1H), 2.27 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.21 (s, 3H), 2.13 (dd, *J* = 13.8, 7.2 Hz, 1H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.5, 194.4, 149.5, 148.5, 139.2, 138.1, 131.8, 131.4, 131.2, 131.1, 130.5, 130.2, 129.9, 129.9, 128.6, 120.3, 72.3, 51.2, 30.3,

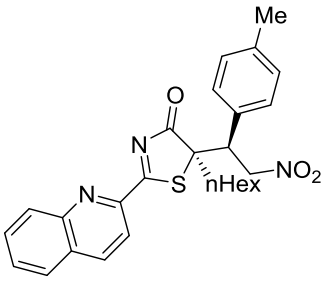
21.8, 9.8. UPLC-DAD-QTOF: $C_{23}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 420.1382, found: 420.1391. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 32.4 min (min.) and 36.4 min (major.)).

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3da)



The title compound **3da** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**1d**) (94 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 133 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= –165.3.0 (*c*= 0.98, 92% *ee*, CH_2Cl_2). m.p. 72–74 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.32–8.13 (m, 3H), 7.95–7.76 (m, 2H), 7.75–7.63 (m, 1H), 7.37 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.19 (dd, *J* = 5.0, 1.8 Hz, 3H), 5.06 (ddd, *J* = 23.9, 13.1, 7.7 Hz, 2H), 4.23 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.12 (ddt, *J* = 16.9, 5.7, 4.0 Hz, 2H), 1.50–1.08 (m, 8H), 0.81 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.5, 194.5, 149.5, 148.5, 138.2, 134.8, 131.5, 131.2, 131.1, 130.3, 130.1, 129.4, 129.2, 128.6, 120.3, 71.5, 51.8, 37.3, 32.2, 29.9, 25.4, 23.2, 14.7. UPLC-DAD-QTOF: $C_{26}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 462.1851, found: 462.1850. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 39.1 min (min.) and 47.4 min (major.)).

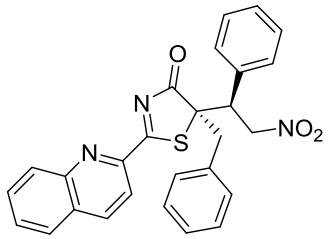
(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3dd)



The title compound **3dd** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**1d**) (94 mg, 0.3 mmol) and 4-methyl-nitrostyrene (**2d**) (98 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 140 mg, 0.29 mmol, 96%. $[\alpha]_D^{25}$= –185.6 (*c*= 0.99, 98% *ee*, CH_2Cl_2). m.p. 75–78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.25 (dt, *J* = 8.5, 6.9 Hz, 3H), 7.95–7.80 (m, 2H), 7.75–7.67 (m, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 5.14 (dd, *J* = 13.0, 4.6 Hz, 1H), 5.00 (dd, *J* = 13.0, 10.9 Hz, 1H), 4.21 (dd, *J* = 10.9, 4.6 Hz, 1H), 2.19 (s, 3H), 2.07 (ddd, *J* = 16.2, 11.9, 5.8 Hz, 1H), 1.47–1.12 (m, 8H), 0.84 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.4, 194.5, 149.4, 148.4, 139.1, 138.0, 131.6, 131.4, 131.1, 131.0, 130.2, 129.9, 129.8, 128.5, 120.3, 71.5, 51.4,

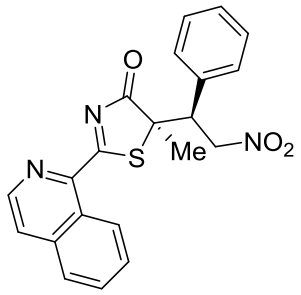
37.2, 32.1, 29.8, 25.2, 23.1, 21.7, 14.6. UPLC-DAD-QTOF: $C_{27}H_{30}N_3O_3S$ $[M+H]^+$ calcd.: 476.2008, found: 476.2013. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 85/15, flow rate= 0.5 mL/min, retention times: 40.7 min (min.) and 47.7 min (major.)).

(*R*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3ea)



The title compound **3ea** was prepared from 5-benzyl-2-(quinolin-2-yl)thiazol-4-ol (**1e**) (95 mg, 0.3 mmol) and nitrostyrene (**2a**) (89 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 126 mg, 0.27 mmol, 90%. $[\alpha]_D^{25}$= -95.5 (*c*= 0.54, 99% *ee*, CH_2Cl_2). m.p. 189–194 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.19 (dd, *J* = 18.4, 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 11.0, 8.4 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.49–7.39 (m, 2H), 7.31–7.06 (m, 8H), 5.25–4.97 (m, 2H), 4.39 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.64–3.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 196.7, 193.8, 149.1, 148.3, 137.8, 134.9, 134.3, 131.4, 131.2, 131.1, 130.9, 130.2, 130.0, 129.8, 129.4, 129.2, 128.9, 128.6, 128.4, 128.2, 120.0, 78.0, 77.8, 77.6, 77.2, 77.2, 71.9, 51.36, 43.4. UPLC-DAD-QTOF: $C_{27}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 468.1382, found: 468.1391. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 24.1 min (major.) and 27.8 min (min.)).

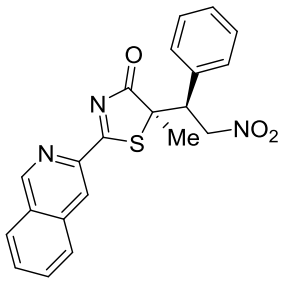
(*R*)-2-(isoquinolin-3-yl)-5-methyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)thiazol-4(5*H*)-one (3fa)



The title compound **3fa** was prepared from 2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (**1f**) (72.7 mg, 0.3 mmol) and 4-methyl-*β*-nitrostyrene (**2a**) (98 mg, 0.6 mmol) according to the general procedure. The title compound was obtained as a 86:14 mixture of isomers. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 112 mg, 0.29 mmol, 95 %. m.p. 106–108 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (s, 1H), 8.69 (s, 1H), 8.11 – 8.04 (m, 1H), 8.00 – 7.92 (m, 2H), 7.85 – 7.76 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.18 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.94 (dt, *J* = 11.0, 8.1 Hz, 1H), 4.18 (dt, *J* = 10.9, 5.6 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.4, 195.1, 153.9, 143.5, 139.5, 136.1, 132.8, 132.3, 132.0, 131.8, 130.9, 130.3, 129.9, 129.0, 123.9, 66.4, 51.0, 22.1. UPLC-DAD-QTOF: $C_{21}H_{18}N_3O_3S$

$[M+H]^+$ calcd.: 392.1069, found: 392.1071. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.7 min (mayor.) and 25.2 min (min.). Processed Channel Descr.: PDA 260.0 nm).

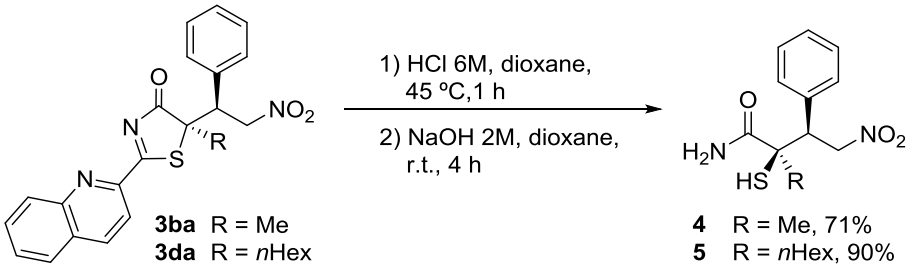
(*R*)-2-(isoquinolin-3-yl)-5-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-5-methylthiazol-4(5H)-one (3ga)



The title compound **3ga** was prepared from 2-(isoquinolin-3-yl)-5-methylthiazol-4-ol (**1g**) (72.7 mg, 0.3 mmol) and nitrostyrene (**2a**) (137 mg, 0.6 mmol) according to the general procedure. The title compound was obtained as a 91:9 mixture of isomers. The crude material was purified by flash column chromatography on silica gel (eluting with dichloromethane) to afford the title compound as a yellow solid. Yield: 106 mg, 0.27 mmol, 90 %. m.p. 101–103 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.29 (d, *J* = 3.4 Hz, 1H), 8.69 (s, 1H), 8.12 – 8.05 (m, 1H), 7.99 (dd, *J* = 8.9, 4.6 Hz, 1H), 7.87 – 7.76 (m, 3H), 7.39 – 7.31 (m, 2H), 7.24 (dt, *J* = 9.0, 2.2 Hz, 2H), 5.14 (dd, *J* = 13.2, 4.5 Hz, 1H), 4.92 (dd, *J* = 13.2, 11.0 Hz, 1H), 4.19 (dd, *J* = 11.0, 4.5 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.6, 195.0, 154.1, 143.4, 136.3, 134.4, 133.1, 133.0, 132.1, 131.9, 130.2, 129.2, 124.4, 124.3, 66.1, 51.0, 25.5. UPLC-DAD-QTOF: $C_{21}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1073. The enantiomeric purity of the major diastereoisomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 36.6 min (mayor.) and 42.3 min (min.). Processed Channel Descr.: PDA 260.0 nm).

5.3.4. **Elaboration of adducts**

5.3.4.1. **Hydrolysis of adducts 3ba and 3da**

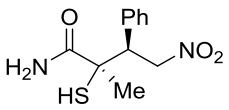


The reaction adduct (1 mmol, 1 equiv.) was dissolved in a mixture of dioxane (5 mL) and HCl 6N (1.84 mL, 11.04 mmol, 12 equiv.). The resulting solution was heated at 45 °C for 1 h. After this period the cooled reaction mixture was treated at 0 °C with

saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane 1/1).

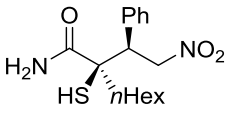
The obtained product was dissolved in 1 mL of dioxane at 0 °C, and a 2 M aqueous solution of NaOH (0.8 mL, 1.60 mmol, 2.5 eq.,) was added dropwise. The resulting mixture was stirred at room temperature for 4 h and afterwards the reaction was quenched with 2 M aq. $NaHSO_4$. The combined organic phases were washed with an aqueous solution of saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the pure product which was used as such in the next step.

(*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide (4)



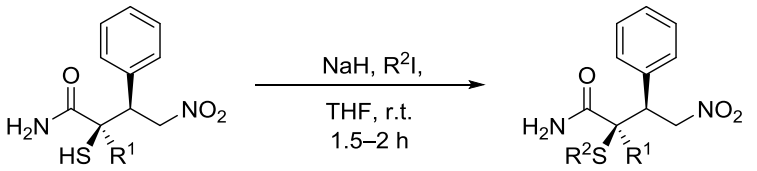
Yield: 335.4 mg, 0.82 mmol, 71%. $[\alpha]_D^{25}$= +2.9 (*c*= 1.00, 93% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.35–7.28 (m, 5H), 6.42–6.31 (m, 1H), 5.52–5.41 (m, 1H), 5.14–5.05 (m, 2H), 4.22 (dd, *J* = 8.8, 6.1 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 175.3, 135.4, 129.1, 128.6, 128.4, 77.0, 54.0, 52.0, 26.9. UPLC-DAD-QTOF: $C_{11}H_{14}N_2O_3S$ $[M+H]^+$ calcd.: 254.0725, found: 254.0721. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak OD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 33.2 min (major.) and 48.6 min (min.)).

(*R*)-2-mercapto-2-((S)-2-nitro-1-phenylethyl)octanamide (5)



Yellow oil; yield: 58.2 mg, 0.22 mmol, 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (dd, *J* = 12.5, 5.2 Hz, 5H), 6.58 (s, 1H), 6.16 (s, 1H), 5.15 – 4.88 (m, 1H), 4.40 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 2.13 (d, *J* = 17.6 Hz, 2H), 1.73 – 1.49 (m, 1H), 1.51 – 1.03 (m, 8H), 1.01 – 0.71 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9, 136.0, 130.2, 129.6, 129.4, 129.2, 129.0, 67.9, 61.1, 51.4, 40.2, 32.3, 30.5, 30.1, 29.8, 26.2, 23.3, 15.0, 14.8.UPLC-DAD-QTOF: $C_{10}H_{12}N_2O_3S$ $[M+H]^+$ calcd.: 240.0569, found: 240.0571.

5.3.4.2. ***S*-Alkylation of α-mercapto carboxylic acid derivatives 4–5**

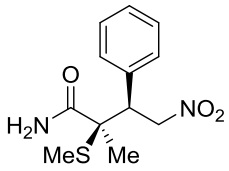


4 R^1 = Me
5 R^1 = *n*Hex

6 R^1 = Me; R^2 = Me
7 R^1 = Me; R^2 = Allyl
8 R^1 = *n*Hex; R^2 = Allyl

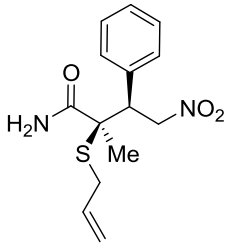
To a solution of the corresponding amide (0.24 mmol, 1 equiv.) in dry THF (1mL) under argon atmosphere was added NaH 60% in mineral oil (11 mg, 0.29 mmol, 1.2 equiv.). The mixture was cooled to 0 ºC and then the corresponding alkyl halide (1.2 equiv) was added. The mixture was stirred at room temperature for 2h and then quenched with 2 M aq. $NaHSO_4$. The organic layer was separated and washed with an aqueous solution of saturated $NaHCO_3$ (25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with ethyl acetate/hexane 1/1).

(*2R,3S*)-2-Methyl-2-(methylthio)-4-nitro-3-phenylbutanamide (6)



The title compound **6** was prepared from (*2R,3S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide (**4**) (61 mg, 0.24 mmol) and MeI (18 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 58.2 mg, 0.22 mmol, 90%. $[\alpha]_D^{25}$= -14.2 (*c*= 1.00, 93% ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.37–7.27 (m, 5H), 6.69–6.49 (m, 1H), 5.56–5.36 (m, 1H), 5.13–5.00 (m, 2H), 3.99 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.10 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 174.4, 134.99, 130.0, 128.5, 127.9, 94.6, 77.0, 55.7, 51.2, 21.4, 12.4. UPLC-DAD-QTOF: $C_{12}H_{17}N_2O_3S$ $[M+H]^+$ calcd.: 269.0882, found: 269.0885.

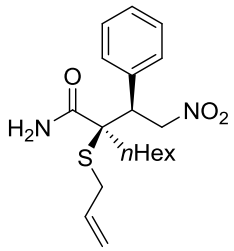
(*2R,3S*)-2-(Allylthio)-2-methyl-4-nitro-3-phenylbutanamide (7)



The title compound **7** was prepared from (*2R,3S*)-2-mercapto-2-methyl-4-nitro-3-phenylbutanamide (**4**) (61 mg, 0.24 mmol) and allyl iodide (27 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 65.7 mg, 0.22 mmol, 93%. $[\alpha]_D^{25}$= -2.2 (*c*= 0.5, 93% ee, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36–7.27 (m, 5H), 6.63–6.48 (m, 1H), 5.56–5.41 (m, 1H), 5.29–4.98 (m, 4H), 3.99 (dd, *J*

= 10.4, 4.6 Hz, 1H), 3.34–3.11 (m, 2H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 174.2, 134.9, 132.8, 129.4, 128.6, 128.6, 119.0, 77.0, 56.6, 51.8, 33.2, 22.4. UPLC-DAD-QTOF: $C_{14}H_{19}N_2O_3S$ $[M+H]^+$ calcd.: 295.1116, found: 295.1118.

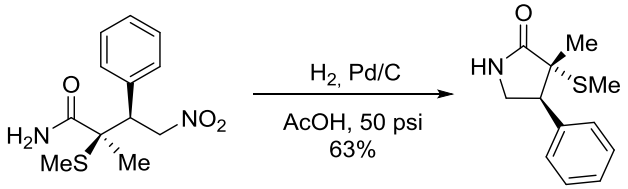
(*R*)-2-(Allylthio)-2-((*S*)-2-nitro-1-phenylethyl)octanamide (8)



The title compound **8** was prepared from (*R*)-2-mercapto-2-((S)-2-nitro-1-phenylethyl)octanamide (**5**) (78 mg, 0.24 mmol) and allyl iodide (27 µL, 0.29 mmol) according to the general procedure. Yellow oil; yield: 80 mg, 0.22 mmol, 91%. $[\alpha]_D^{25}$= –9.1 (*c*= 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.13 (m, 5H), 6.30 (s, 1H), 5.83 (ddt, *J* = 14.2, 10.0, 7.1 Hz, 2H), 5.32 – 4.96 (m, 3H), 3.99 (dt, *J* = 19.6, 9.8 Hz, 1H), 3.27 – 3.04 (m, 2H), 1.79 – 1.44 (m, 4H), 1.27 (d, *J* = 12.0 Hz, 7H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.2, 135.3, 132.6, 129.4, 128.5, 128.4, 118.9, 78.0, 61.0, 49.8, 34.9, 33.2, 31.6, 29.7, 29.4, 24.7, 22.5, 14.0. UPLC-DAD-QTOF: $C_{19}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 365.1899, found: 365.1912.

5.3.4.3. **Reduction of the nitro group in 14: formation of γ-lactam 9**

(*3R,4S*)-3-Methyl-3-(methylthio)-4-phenylpyrrolidin-2-one (9)



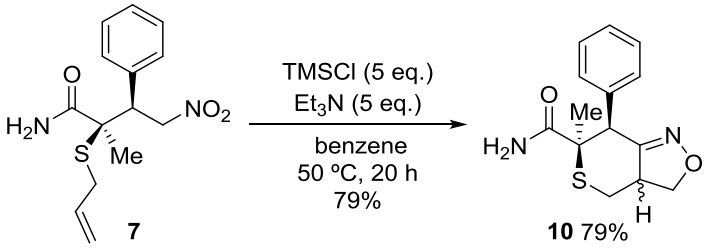
6 **9**

10% Palladium on carbon (15 mg) was added to a solution of (*2R,3S*)-2-methyl-2-(methylthio)-4-nitro-3-phenylbutanamide **6** (32 mg, 0.12 mmol) in acetic acid (5.0 mL). The reaction vessel was evacuated and back-filled with hydrogen (3x) and afterwards the reaction mixture was stirred under hydrogen atmosphere (50 psi) at room temperature overnight. The reaction mixture was filtered over celite, concentrated, and a saturated aqueous sodium carbonate solution was added. The mixture was extracted with dichloromethane (3x 10mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate 80/20 to 50/50) to give the title compound as a colourless oil. Yield: 16 mg, 0.076 mmol, 63%. $[\alpha]_D^{25}$= 0.82 (*c*= 0.50, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.34–7.23 (m, 5H), 6.45 (bs, 1H), 3.89

(m, 1H), 3.56 (m, 1H), 3.42 (s, 1H), 2.22 (s, 3H), 1.04 (s, *3*H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 177.2, 139.0, 129.4, 128.6, 128.3, 127.9, 127.5, 52.0, 50.4, 45.2, 18.4, 12.4. UPLC-DAD-QTOF: $C_{12}H_{16}NOS$ $[M+H]^+$ calcd.: 222.0953, found: 222.0964.

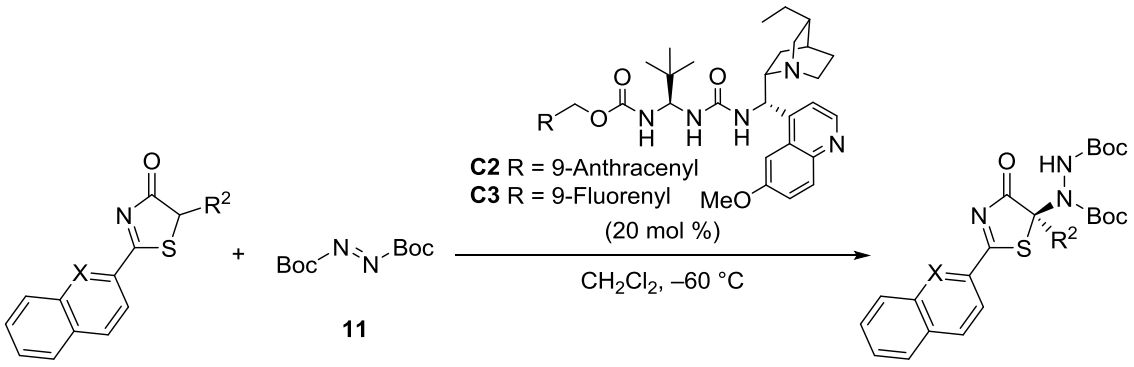
5.3.4.4. **1,3-Dipolar cyloaddition of 7**

(*6R,7S*)-6-Methyl-7-phenyl-3a,4,6,7-tetrahydro-3*H*-thiopyrano[4,3-c]isoxazole-6-carboxamide (10)



To a solution of nitroalkane **7** (1 eq., 70 mg, 0.24 mmol) in 1.5 mL of C_6H_6 under Ar atmosphere were added Et_3N (5 eq., 165 µl, 1.2 mmol) and freshly distilled TMSCl (4 eq., 121 µl, 0.96 mmol). After the addition was complete the mixture was warmed to 50°C and stirred for 20 h. Afterwards, the reaction mixture was cooled to 0ºC and treated with 1.5 mL of HCl 2M. The acidic mixture was stirred for 20 min at room temperature and then was washed with water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate 80/20 to 50/50, Hexane:AcOEt). Yield: 52 mg, 0.19 mmol, 79%. (dr 1.4:1). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.72–7.27 (m, 5H), 5.39 (bs, 2H), 5.23 (bs, 2H), 4.66 (t, *J* = 9.0 Hz, 1H) (Major), 4.44 (t, *J* = 9.0 Hz, 1H) (Minor), 4.35 (s, 1H), 3.96-3.82 (m), 3.64-3.48 (m), 3.04-2.87 (m), 1.82 (s, 3H) (Minor), 1.41 (s, 3H) (Minor). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 173.1 (Major), 173.1 (Minor), 159.6 (Major), 158.2 (Minor), 137.0 (Minor), 134.2 (Major), 130.5, 128.9, 128.4, 128.3, 128.0, 127.5, 73.3 (Major), 73.0 (Minor), 55.9 (Major), 55.1 (Minor), 49.0 (Major), 48.5 (Minor), 44.8 (Minor), 30.8 (Major), 30.2 (Minor), 27.3 (Minor), 22.7 (Major). UPLC-DAD-QTOF: $C_{14}H_{16}N_2O_2S$ $[M+H]^+$ calcd.: 277.1011, found: 277.1013.

5.3.5. **General procedure for the asymmetric conjugate addition of 5*H*-thiazol-4-ones to di-*tert*-butyl azodicarboxylate**



1b X = N, R^2 = Me
1d X = N, R^2 = *n*Hex
1h X = C, R^2 = Me

12 X = N, R^2 = Me
13 X = N, R^2 = *n*Hex
14 X = C, R^2 = Me

5.3.5.1. **Asymmetric reaction**

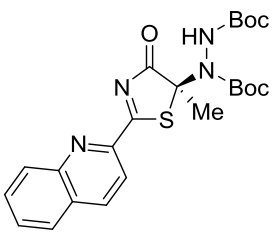
To a mixture of the corresponding thiazolone (0.3 mmol, 1 equiv.) and di-*tert*-butyl azodicarboxylate (0.6 mmol, 2 equiv.) in dichloromethane (0.6 mL) at − 60 °C the catalyst was added. The resulting suspension was stirred at − 60 °C, until the signals of the thiazolone had disappeared (monitored by *1*H NMR). The reaction mixture was purified by flash column chromatography on silica gel without treatment to afford the expected adducts.

5.3.5.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using triethylamine (20 mol %) as the catalyst at –20 °C.

5.3.5.3. **Characterization data for compounds 12–14**

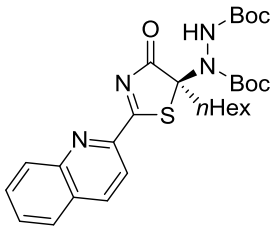
(*S*)-Di-*tert*-butyl 1-(5-methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (12)



The title compound **12** was prepared from 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**1b**) (74 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 113.4 mg, 0.24 mmol, 80%. $[\alpha]_D^{25}$= +72.3 (*c*= 1.00, 96% *ee*, CH_2Cl_2). m.p.

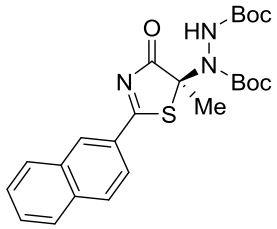
110– 115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 8.3 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.86–7.74 (m, 1H), 7.74–7.58 (m, 1H), 6.70 (s, 1H), 1.82 (s, 3H), 1.53 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 197.2, 155.9, 152.8, 149.9, 147.9, 137.3, 130.7, 130.6, 129.3, 127.9, 119.6, 83.5, 82.4, 79.3, 28.3, 28.1, 25.9. UPLC-DAD-QTOF: $C_{23}H_{29}N_4O_5S$ $[M+H]^+$calcd.: 473.1859, found: 473.1866. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 21.9 min (min.) and 72.3 min (major.)).

(*S*)-Di-*tert*-butyl 1-(5-hexyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (13)



The title compound **13** was prepared from 5-hexyl-2-(quinolin-2-yl)thiazol-4-ol (**1d**) (94 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 138 mg, 0.26 mmol, 85%. $[\alpha]_D^{25}$= +67.8 (*c*= 1.00, 96% *ee*, CH_2Cl_2). m.p. 64– 67 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.41 (s, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 6.68 (s, 1H), 2.09 (s, 2H), 1.52 (s, 9H), 1.45 (s, 8H), 1.35 (s, 9H), 0.79 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$), δ 197.3, 190.8, 155.9, 152.9, 149.9, 147.9, 137.6, 137.2, 130.7, 130.5, 130.1, 129.6, 129.2, 127.8, 119.7, 83.4, 83.2, 82.3, 60.5, 54.0, 37.9, 31.8, 31.5, 29.4, 29.3, 28.3, 28.1, 22.7, 22.6, 14.3, 14.0. UPLC-DAD-QTOF: $C_{28}H_{39}N_4O_5S$ $[M+H]^+$calcd.: 543.2641, found: 543.2642.. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 14.8 min (min.) and 36.0 min (major.)).

(*S*)-Di-*tert*-butyl 1-(5-methyl-2-(naphthalen-2-yl)-4-oxo-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (14)

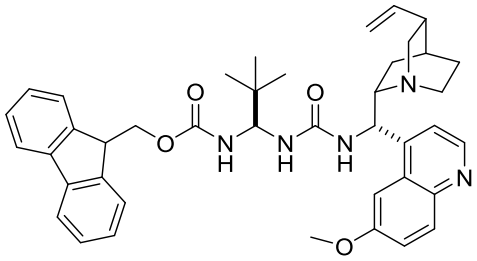


The title compound **14** was prepared from 5-methyl-2-(naphthalen-2-yl)thiazol-4-ol (**1h**) (72 mg, 0.3 mmol) and di-*tert*-butyl azodicarboxylate (138 mg, 0.6 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the title compound as a yellow solid. Yield: 99 mg, 0.21 mmol, 70%. $[\alpha]_D^{25}$= +118.1 (*c*= 1.00, 74% *ee*, CH_2Cl_2). m.p. 120– 124 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.75 (d, *J* = 12.9 Hz, 1H), 8.20 (dd, *J* =

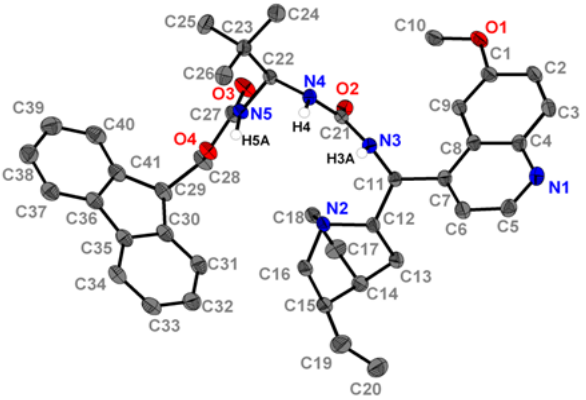
18.8, 8.5 Hz, 1H), 7.95 (dd, *J* = 17.6, 8.2 Hz, 3H), 7.63 (dt, *J* = 14.7, 6.8 Hz, 2H), 6.81 (s, 1H), 1.88 (s, 3H), 1.56 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 194.8, 190.4, 156.0, 152.6, 136.7, 132.6, 130.8, 130.1, 129.9, 129.3, 128.8, 128.0, 127.3, 124.2, 82.5, 80.6, 28.3, 28.0, 26.2. UPLC-DAD-QTOF: $C_{24}H_{30}N_3O_5S$ $[M+H]^+$calcd.: 472.1906, found: 472.1920. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 24.4 min (min.) and 62.0 min (major.)).

5.3.6. **X-Ray Analysis: ORTEP diagrams of compounds C1 and 5bc.**

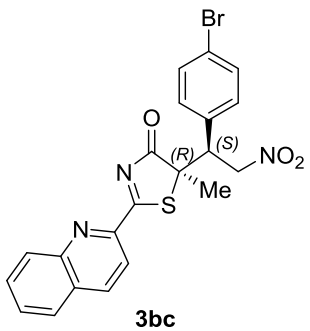
CCDC-930440 contains the supplementary crystallographic data for the structural analysis of **C1**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



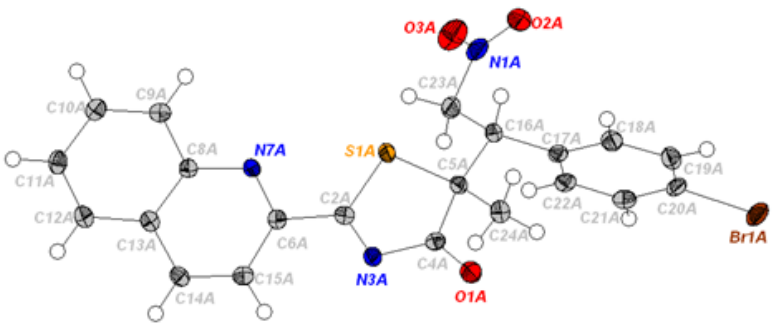
C1



CCDC-947275 contains the supplementary crystallographic data for the structural analysis of **3bc**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



3bc



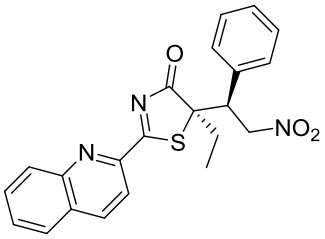
5.3.7. **HPLC chromatograms**

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3ca)

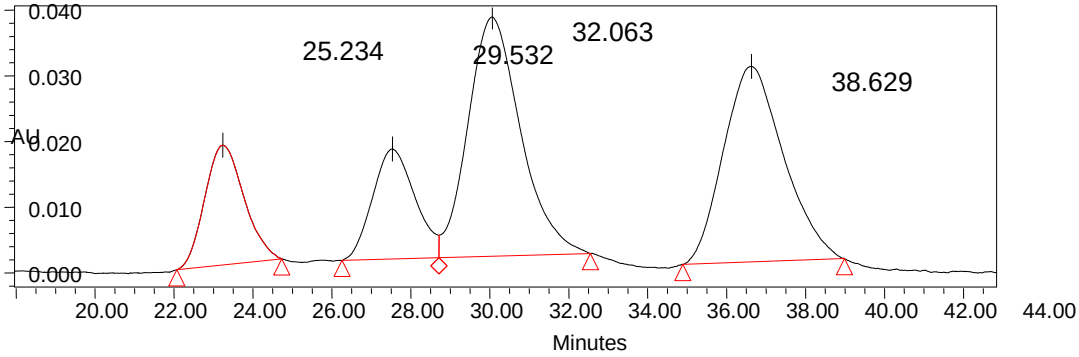
Daicel Chiralpak IA, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

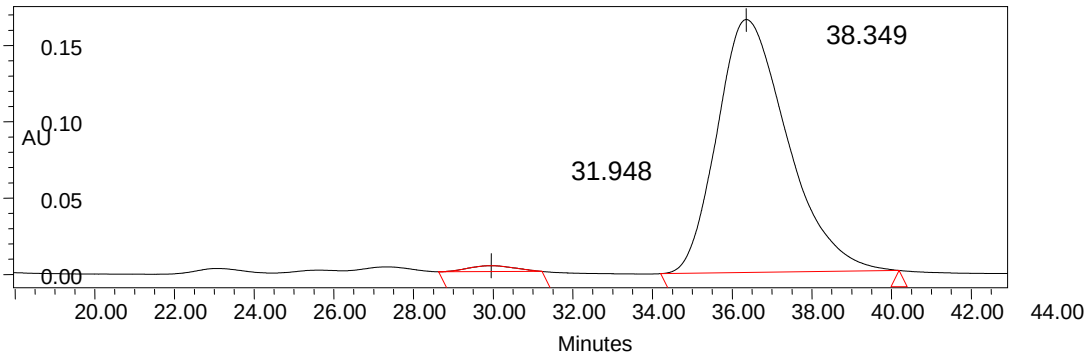


Rac-**3ca**



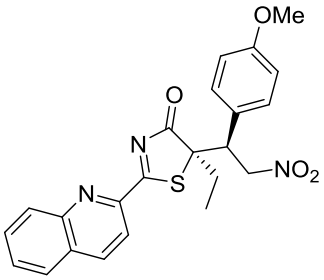
	Retention Time	% Area
1	25.234	13.95
2	29.532	13.85
3	32.063	37.40
4	38.629	34.80

3ca



	Retention Time	% Area
1	31.948	1.52
2	38.349	98.48

(*R*)-5-Ethyl-5-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cb)

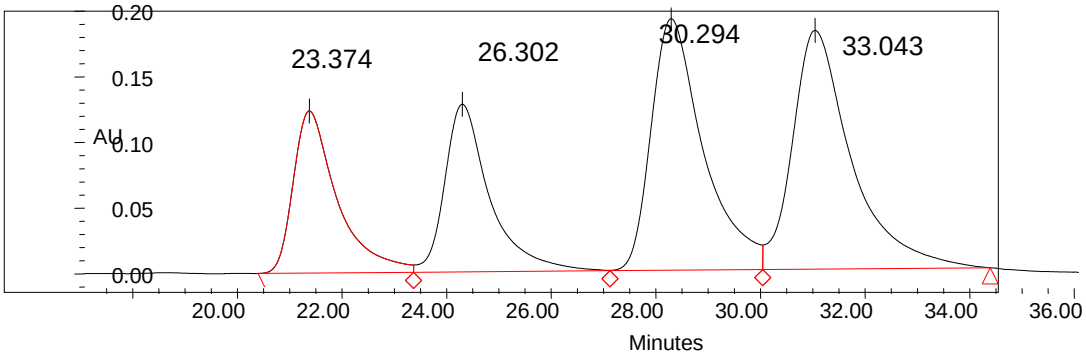


Daicel Chiralpak IA, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

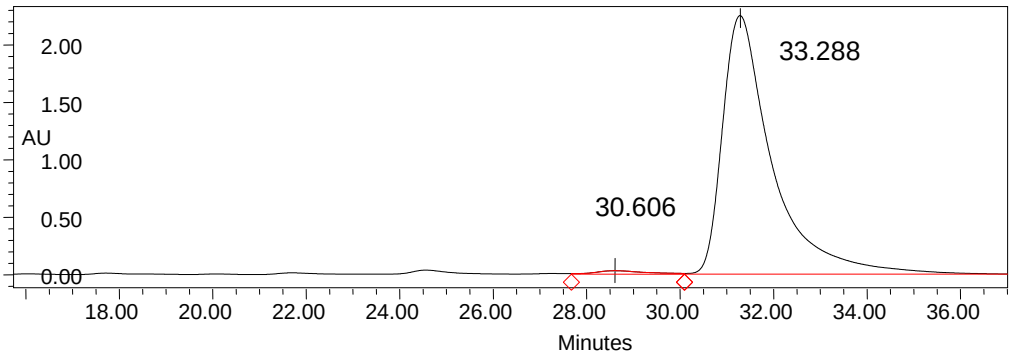
Processed Channel Descr.: PDA 260.0 nm.

Rac-**3cb**



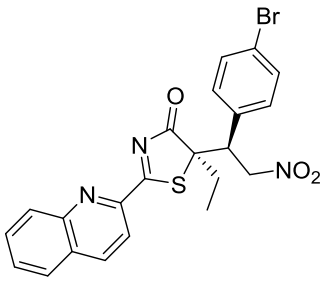
	Retention Time	% Area
1	23.374	17.04
2	26.302	18.02
3	30.294	31.34
4	33.043	33.60

3cb



	Retention Time	% Area
1	30.606	1.34
2	33.288	98.66

(*R*)-5-((*S*)-1-(4-Bromophenyl)-2-nitroethyl)-5-ethyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cc)

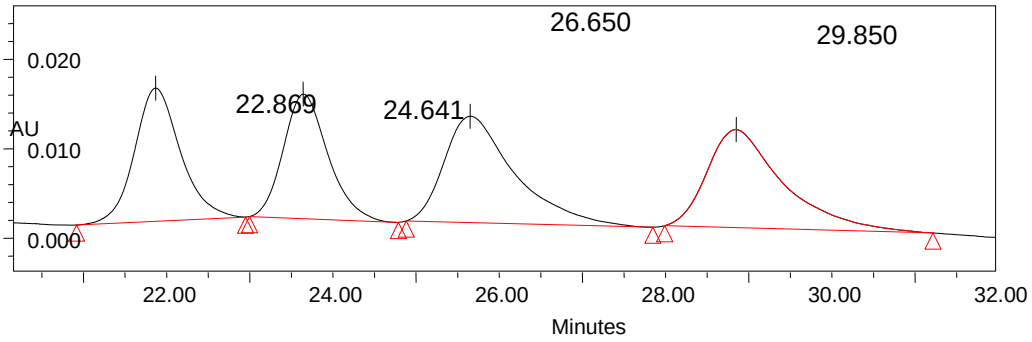


Daicel Chiralpak IB, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

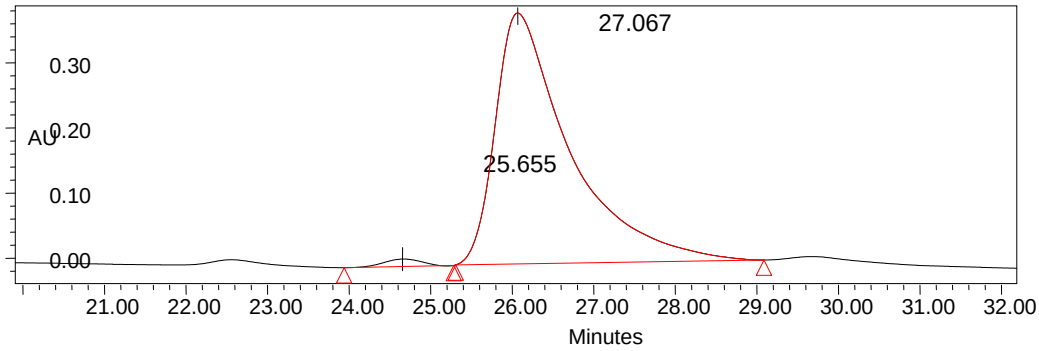
Processed Channel Descr.: PDA 260.0 nm.

Rac-**3cc**



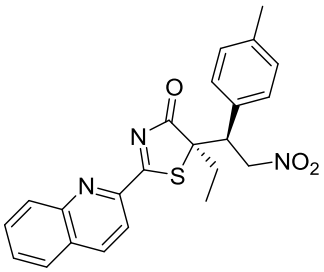
	Retention Time	% Area
1	22.869	23.05
2	24.641	20.90
3	26.650	28.10
4	29.850	27.95

3cc



	Retention Time	% Area
1	25.655	1.46
2	27.067	98.54

(*R*)-5-Ethyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3cd)

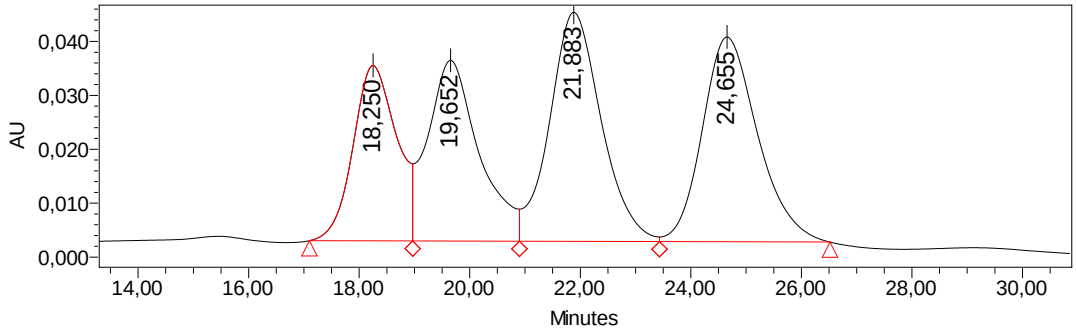


Daicel Chiralpak IA, hexane/isopropanol 75/25

flow rate= 0.5 mL/min,

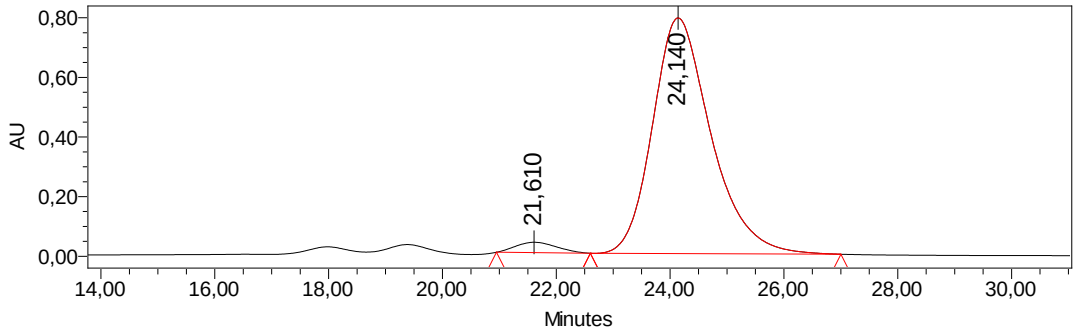
Processed Channel Descr.: PDA 260.0 nm.

Rac-**3cd**



	Retention Time	% Area
1	18,250	19,04
2	19,652	23,22
3	21,883	29,44
4	24,655	28,31

3cd



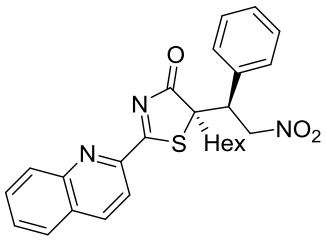
	Retention Time	% Area
1	21,610	3,00
2	24,140	97,00

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3da)

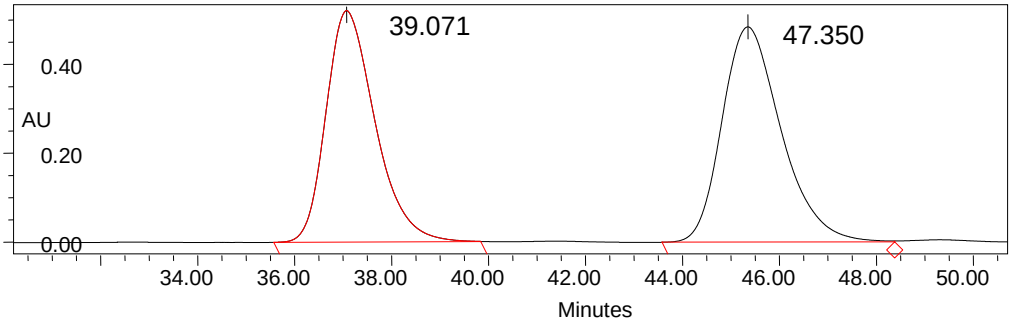
Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

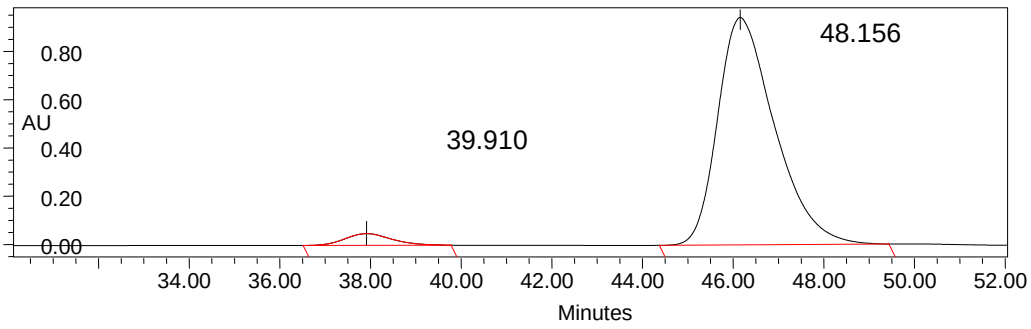


Rac-**3da**



	Retention Time	% Area
1	39.071	47.10
2	47.350	52.90

3da



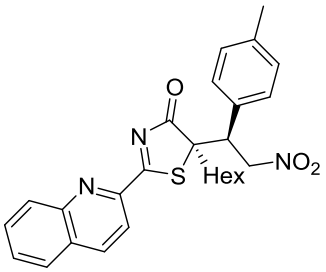
	Retention Time	% Area
1	39.910	4.06
2	48.156	95.94

(*R*)-5-Hexyl-5-((*S*)-2-nitro-1-*p*-tolylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3dd)

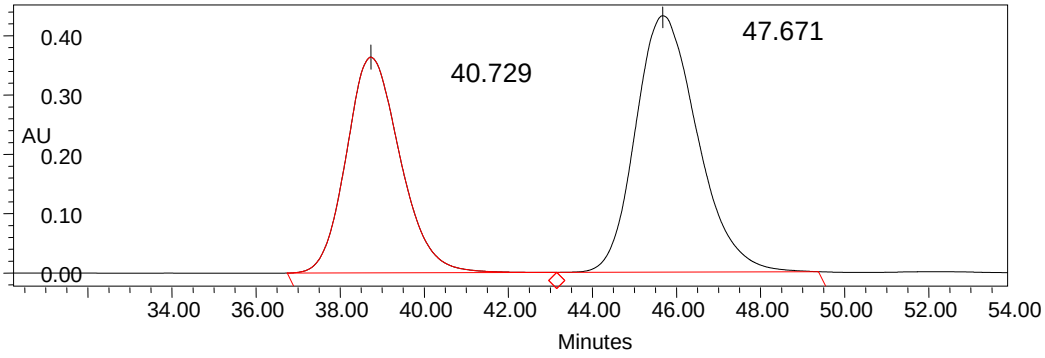
Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

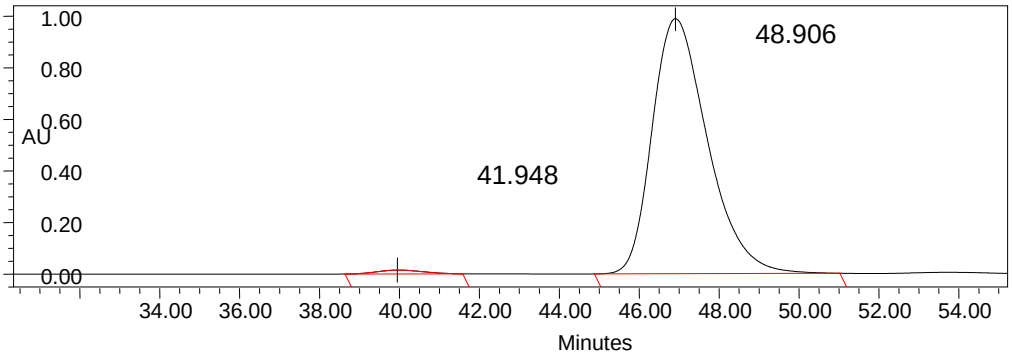


Rac-**3dd**



	Retention Time	% Area
1	40.729	42.32
2	47.671	57.68

10d



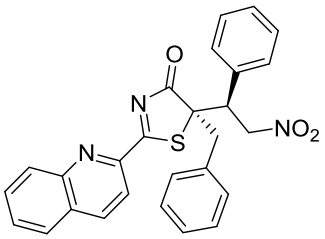
	Retention Time	% Area
1	41.948	1.25
2	48.906	98.75

(*R*)-5-Benzyl-5-((*S*)-2-nitro-1-phenylethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3ea)

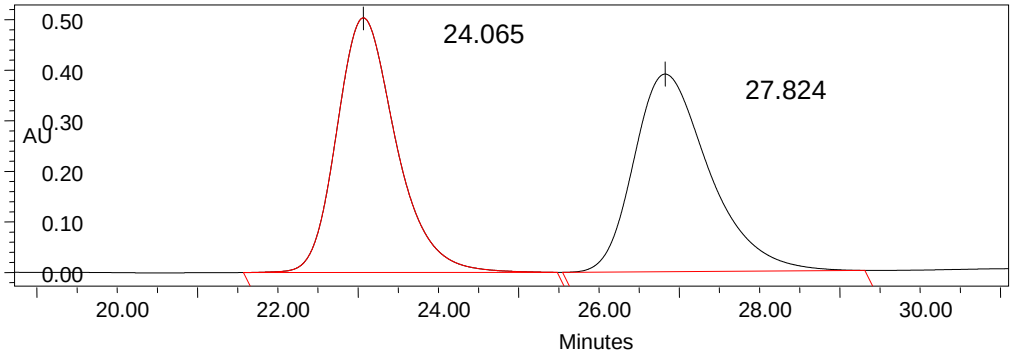
Daicel Chiralpak IC, hexane/isopropanol 50/50

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

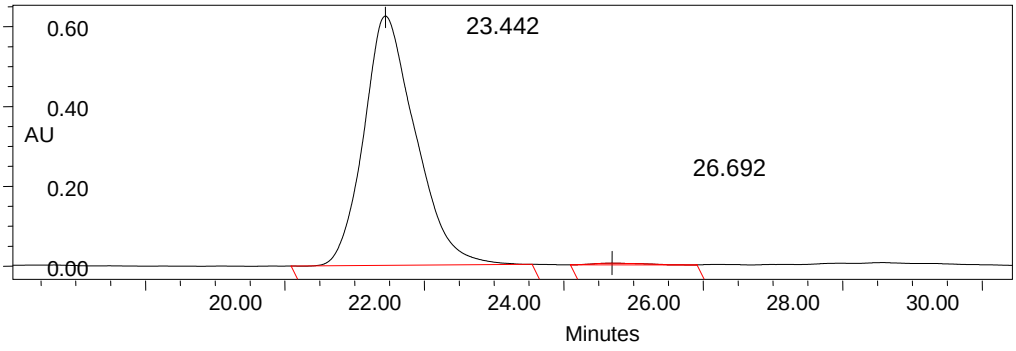


Rac-**3ea**



	Retention Time	% Area
1	24.065	50.45
2	27.824	49.55

3ea



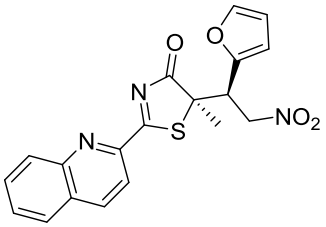
	Retention Time	% Area
1	23.442	99.38
2	26.692	0.62

(*R*)-5-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5H)-one (3be)

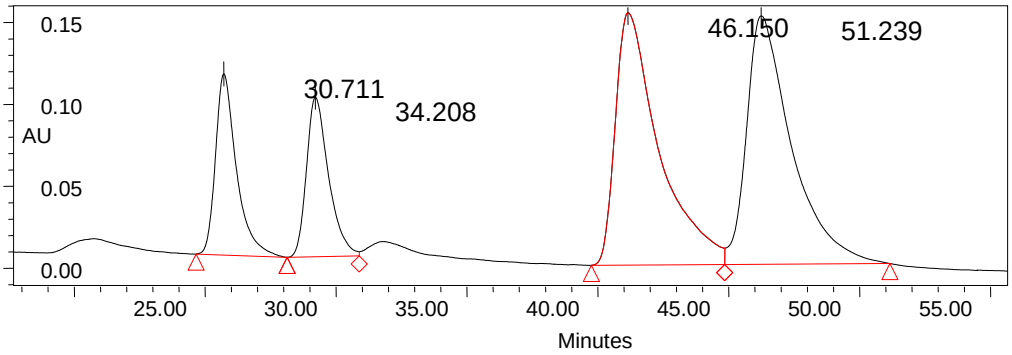
Daicel Chiralpak IB, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

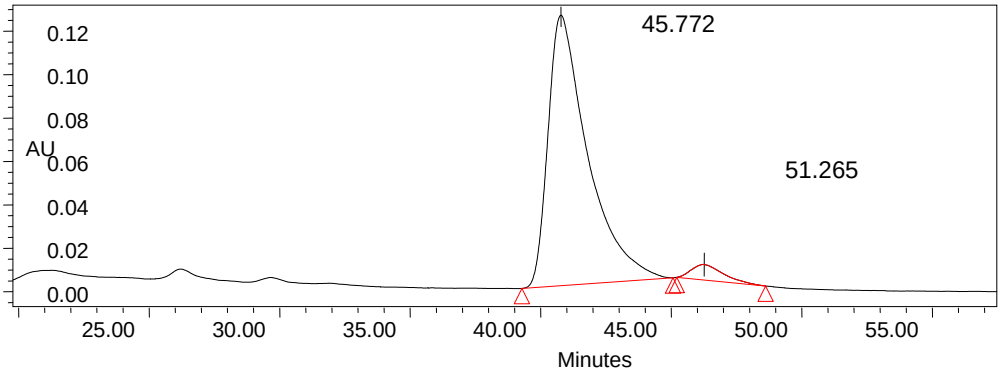


Rac-**3be**



	Retention Time	% Area
1	30.711	12.90
2	34.208	11.97
3	46.150	37.24
4	51.239	37.88

3be



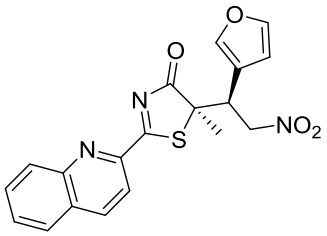
	Retention Time	% Area
1	45.772	95.65
2	51.265	4.35

(*R*)-5-((*S*)-1-(Furan-3-yl)-2-nitroethyl)-5-methyl-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3bf)

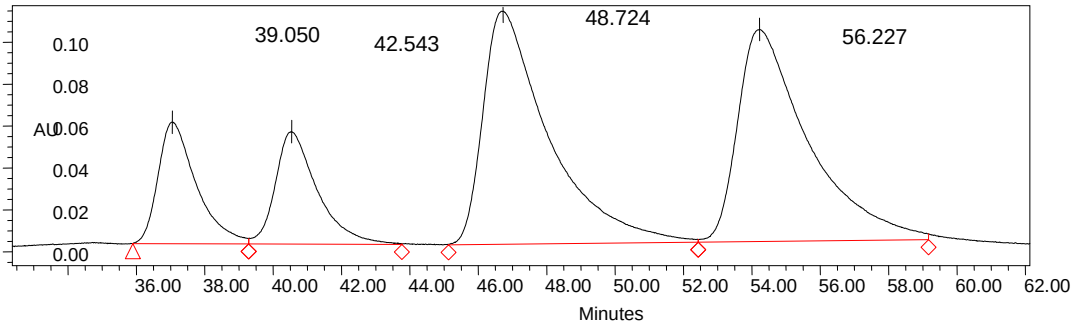
Daicel Chiralpak IB, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 260.0 nm.

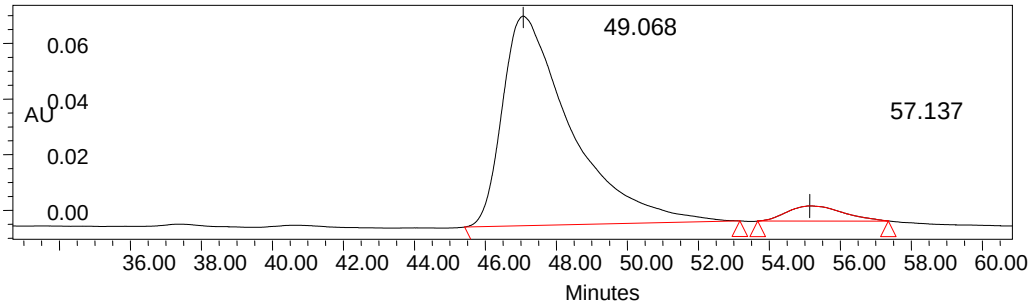


Rac-**3bf**



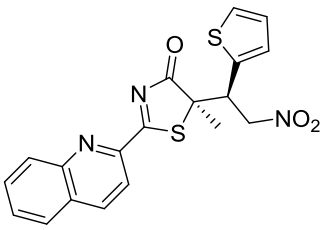
	Retention Time	% Area
1	39.050	11.73
2	42.543	11.87
3	48.724	38.63
4	56.227	37.76

3bf



	Retention Time	% Area
1	49.068	94.44
2	57.137	5.56

(*R*)-5-Methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-(quinolin-2-yl)thiazol-4(5*H*)-one (3bg)

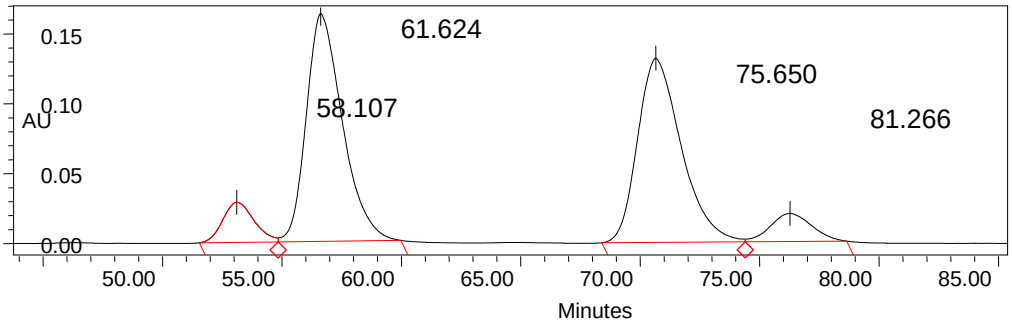


Daicel Chiralpak IC, hexane/isopropanol 85/15

flow rate= 0.5 mL/min,

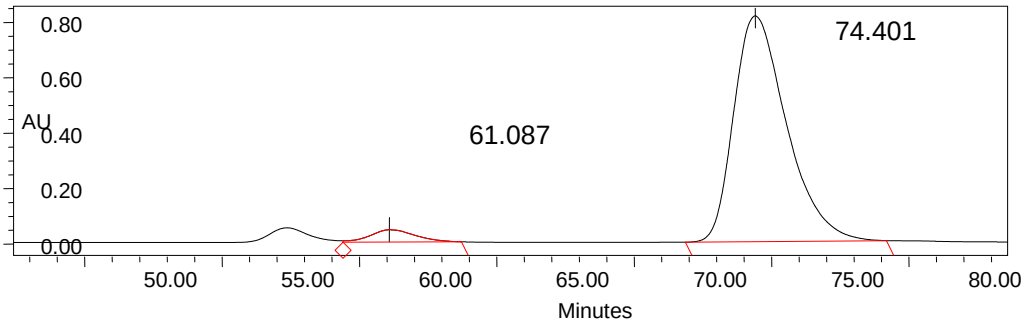
Processed Channel Descr.: PDA 260.0 nm.

Rac-**3bg**



	Retention Time	% Area
1	58.107	6.70
2	61.624	44.06
3	75.650	43.07
4	81.266	6.18

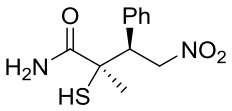
3bg



	Retention Time	% Area
1	61.087	4.36
2	74.401	95.64

(*2R,3S*)-2-Mercapto-2-methyl-4-nitro-3-phenylbutanamide (4)

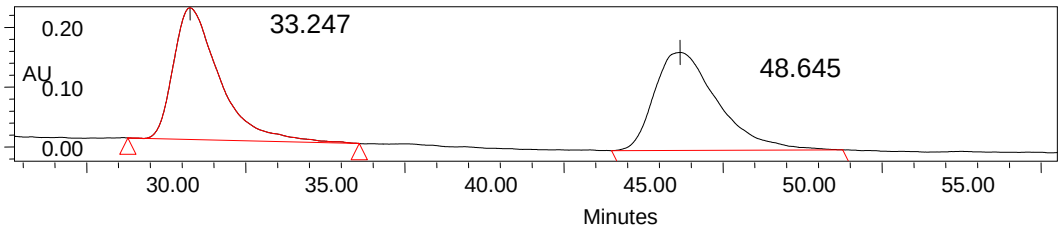
Daicel Chiralpak OD-H, hexane/isopropanol 80/20



flow rate= 0.5 mL/min,

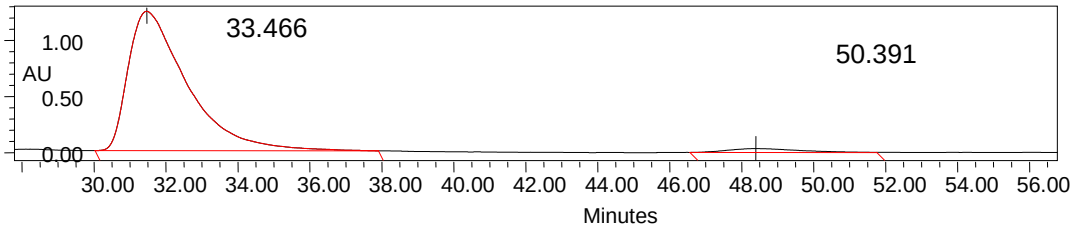
Processed Channel Descr.: PDA 210.0 nm.

Rac-**4**



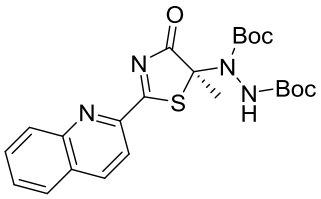
	Retention Time	% Area
1	33.247	49.51
2	48.645	50.49

4



	Retention Time	% Area
1	33.466	96.64
2	50.391	3.36

(*S*)-Di-*tert*-butyl 1-(5-methyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (12)

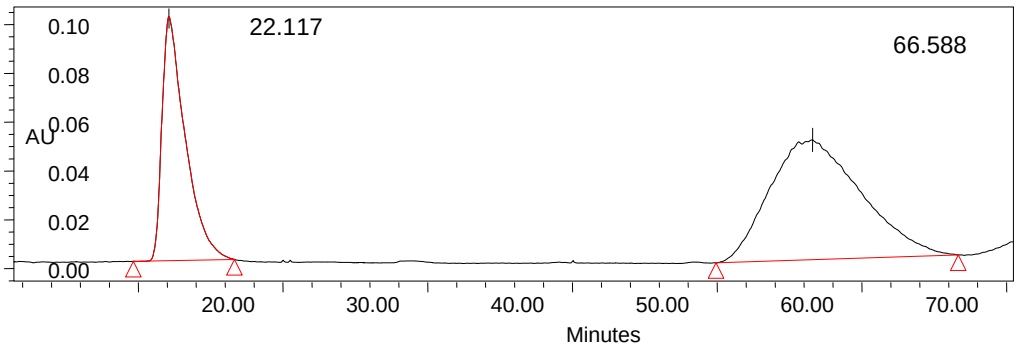


Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

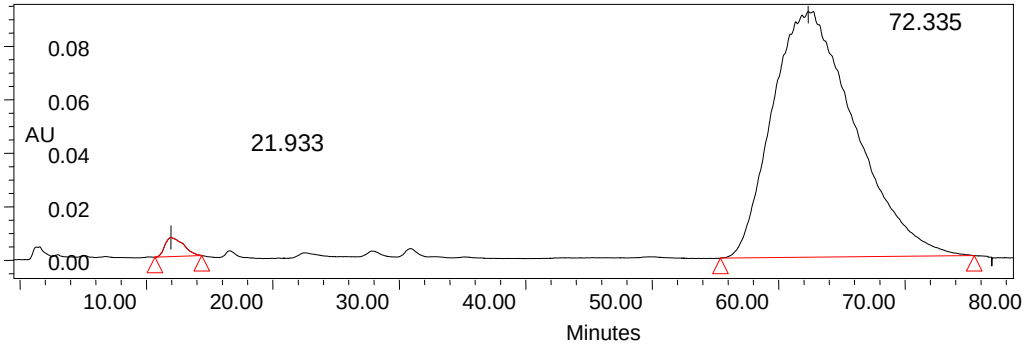
Processed Channel Descr.: PDA 262.0 nm.

Rac-12



	Retention Time	% Area
1	22.117	34.15
2	66.588	65.85

12



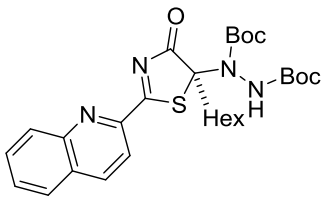
	Retention Time	% Area
1	21.933	1.71
2	72.335	98.29

(*S*)-Di-*tert*-butyl 1-(5-hexyl-4-oxo-2-(quinolin-2-yl)-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (13)

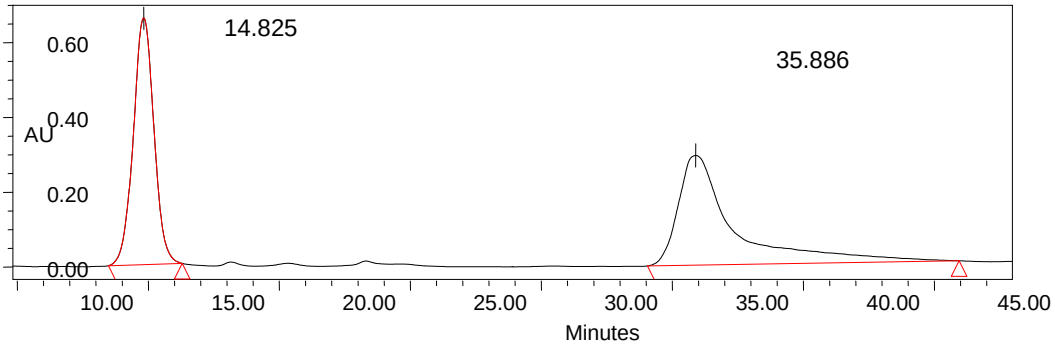
Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 262.0 nm.

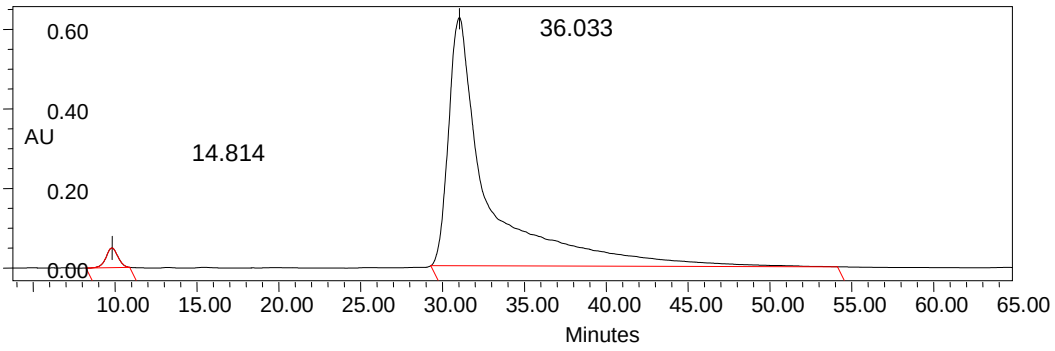


Rac-13



	Retention Time	% Area
1	14.825	45.42
2	35.886	54.58

13



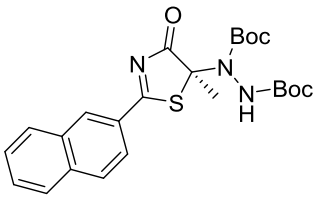
	Retention Time	% Area
1	14.814	2.33
2	36.033	97.67

(*S*)-Di-*tert*-butyl 1-(5-methyl-2-(naphthalen-2-yl)-4-oxo-4,5-dihydrothiazol-5-yl)hydrazine-1,2-dicarboxylate (14)

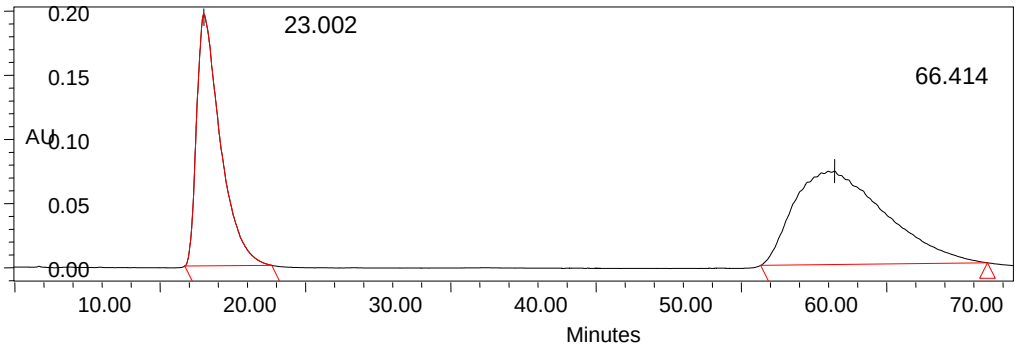
Daicel Chiralpak IC, hexane/isopropanol 80/20

flow rate= 0.5 mL/min,

Processed Channel Descr.: PDA 262.0 nm.

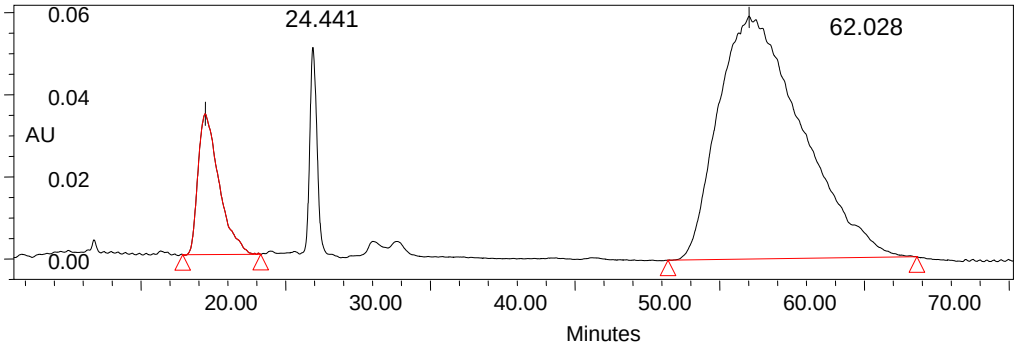


Rac-14



	Retention Time	% Area
1	23.002	41.08
2	66.414	58.92

14



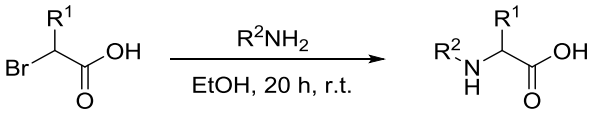
	Retention Time	% Area
1	24.441	12.74
2	62.028	87.26

5.4. **Experimental section of chapter 3**

5.4.1. **General procedure for the synthesis of 1*H*-imidazol-4(5*H*)-ones 16–18.**

5.4.1.1. **Preparation of *N*-substituted amino acids and amino esters.**

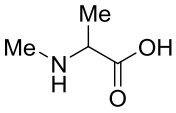
5.4.1.1.1. Procedure for the synthesis of N-methyl amino acids.[350]



R^1 = Me, Bn, *n*Hex, *i*Bu, *i*Pr
R^2 = Me, *i*Bu

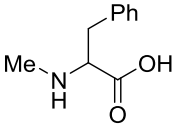
Methylamine (33% wt in EtOH, 20 mL, 160 mmol, 4 equiv.) was added to a stirred solution of the corresponding α-bromocarboxylic acid (40 mmol, 1 equiv.) in ethanol (24 mL) at 0 °C. The cooling bath was removed and the reaction was stirred at room temperature for 48 hours. The reaction mixture was evaporated under reduced pressure and the residue was crushed with acetone. If the acetone was not enough to obtain a proper solid, some drops of methanol were added, in order to solve any excess of the starting materials. Filtration of the suspension afforded the corresponding *N*-methyl α-amino acid as a white solid.

_N_-Methyl alanine



The title compound was prepared from 2-bromopropanoic acid (4.6 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 2.78 g, 27 mmol, 90 %. m.p. = 315–317°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.64 (q, *J* = 7.2 Hz, 1H), 2.72 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H).

_N_-Methyl phenylalanine

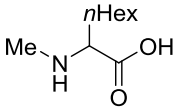


The title compound was prepared from 2-bromo-3-phenylpropanoic acid (9.2 g, 40 mmol) and methylamine (33% wt in EtOH, 20 mL, 160 mmol) according to the general procedure. Yield: 3.93 g, 22 mmol, 55 %. m.p. = 252–254°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.50 – 7.25 (m,

[350] Adapted from: I. J. Collins, J. C. Hannam, T. Harrison, A. Madin, M. P. Ridgill, *GB Patent* 4.728 Oct 31, **2003**.

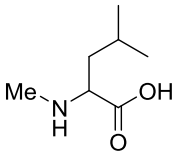
5H), 3.88 (t, *J* = 6.3 Hz, 1H), 3.25 (d, *J* = 6.3 Hz, 2H), 2.70 (s, 3H).

2-(Methylamino)octanoic acid



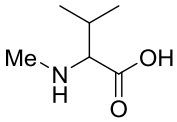
The title compound was prepared from 2-bromooctanoic acid (8.93 g, 40 mmol) and methylamine (33% wt in EtOH, 20 mL, 160 mmol) according to the general procedure. Yield: 5.84 g, 33.7 mmol, 84 %. m.p. = 246– 250°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.59 (t, *J* = 5.8 Hz, 1H), 2.72 (s, 3H), 1.98 – 1.78 (m, 2H), 1.49 – 1.19 (m, 8H), 1.00 – 0.78 (m, 3H).

***N*-Methyl leucine**



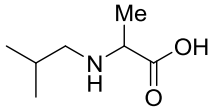
The title compound was prepared from 2-bromo-4-methylpentanoic acid (5.85 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 3.84 g, 26.43 mmol, 88 %. m.p. = 300–305°C. ^{1}H NMR (300 MHz, D_2O) δ: 3.59 (t, *J* = 6.7 Hz, 1H), 2.72 (s, 3H), 1.72 (qd, *J* = 12.9, 10.9, 6.7 Hz, 3H), 0.98 (d, *J* = 4.3 Hz, 6H).

***N*-Methyl valine**



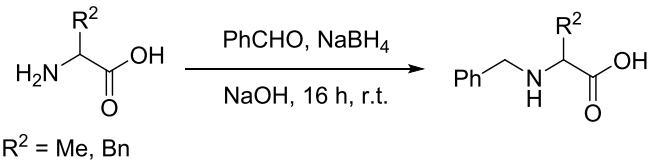
The title compound was prepared from 2-bromo-3-methylbutanoic acid (5.43 g, 30 mmol) and methylamine (33% wt in EtOH, 15 mL, 120 mmol) according to the general procedure. Yield: 2.91 g, 22.2 mmol, 74 %. m.p. = 302–307°C. ^{1}H NMR (300 MHz, D_2O+CF_3CO_2D) δ: 3.59–3.54 (m, 1H), 2.64–2.60 (m, 3H), 2.18–2.14 (m, 1H), 0.96–0.84 (m, 6H).

***N*-Isobutyl alanine**



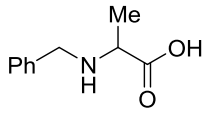
The title compound was prepared from 2-bromopropanoic acid (2.78 ml, 30 mmol) and 2-methylpropan-1-amine (5.96 ml, 60 mmol) according to the general procedure. The crude material was purified by crushing the reaction crude with acetone to afford the title compound as a white solid. Yield: 3.48 g, 24 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.68 (q, *J* = 9, 9 Hz, 1H), 2.96-2.83 (m, 2H), 2.10-1.96 (m, 1H), 1.51 (d, *J* = 6 Hz, 3H), 1.02 (dd, *J* = 3, 3 Hz 1H).

5.4.1.1.2. Procedure for the synthesis of N-benzyl amino acids.[351]



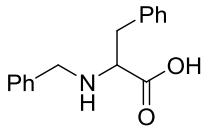
Benzaldehyde (5.09 mL, 50.0 mmol) was added to a vigorously stirred solution of the amino acid (50.0 mmol) in aqueous NaOH (2 M, 25 mL). The emulsion was stirred for 30 min before the mixture was cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The mixture was allowed to warm to room temperature, then stirred for a further hour before a second equivalent of benzaldehyde (5.09 mL, 50.0 mmol) was added. The slurry was stirred vigorously for 30 min, cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The white mixture was stirred for a further 2 h then diluted with H_2O (30 mL) and washed with dichloromethane (2 × 30 mL). Hydrochloric acid (1 M) was added until neutral pH was obtained and the resulting white precipitate was collected by filtration, washed with water (2 × 10 mL) and then acetone (2 × 10 mL) to give the *N*-benzyl amino acid as a white powder.

_N_-Benzyl alanine



The title compound was prepared from alanine (4.45 g, 50 mmol) according to the general procedure. Yield: 4.57 g, 25.4 mmol, 51 %. m.p. = 270–272°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.51 (s, 5H), 4.25 (dd, *J* = 13.0, 4.2 Hz, 2H), 3.73 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H).

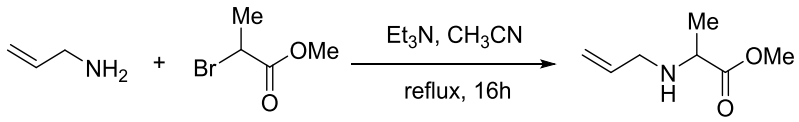
_N_-Benzyl phenylalanine



The title compound was prepared from phenylalanine (8.26 g, 50 mmol) according to the general procedure. Yield: 6.4 g, 25 mmol, 50 %. m.p. = 230–233°C. ^{1}H NMR (300 MHz, D_2O) δ: 7.45–6.99 (m, 10H), 3.58 (dd, *J* = 41.9, 12.6 Hz, 2H), 3.27 (t, *J* = 6.9 Hz, 1H), 2.83 (dd, *J* = 6.7, 2.4 Hz, 2H).

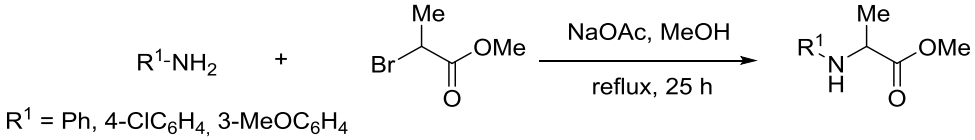
[351] P. Dzygiel, T. B. Reeve, U. Piarulli, M. Krupicka, I. Tvaroska, C. Gennari *Eur. J. Org. Chem.* **2008**, *7*, 1253–1264.

5.4.1.1.3. Synthesis of methyl N-allyl alaninate.[352]



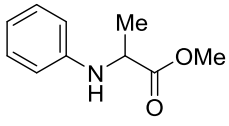
A solution of allylamine (7.7 g, 135 mmol, 1 equiv) and Et_3N (13.6 g, 135 mmol, 1 equiv) in CH_3CN (100 mL) was added to methyl 2-bromopropanoate (26.4 g, 135 mmol) and the mixture was heated under reflux. After 16 h saturated $NaHCO_3$ (100 mL) was added and the mixture was extracted with ethyl acetate (450 mL), dried over $MgSO_4$, filtered and the solvents evaporated under reduced pressure. Purification by silica gel column chromatography, eluting with hexane/ethyl acetate (3:2), gave the aminoester as a colourless oil. Yield: 15.89 g, 111 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.95 – 5.75 (m, 1H), 5.21 – 5.05 (m, 2H), 3.72 (d, *J* = 0.6 Hz, 3H), 3.37 (q, *J* = 7.0 Hz, 1H), 3.30 – 3.08 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H).

5.4.1.1.4. Synthesis of methyl N-aryl alaninate.[353]



A solution of the corresponding aniline (9.2 mL, 100 mmol, 1 equiv.), sodium acetate (8.3 g, 100 mmol, 1 equiv.) and methyl 2-bromopropanoate (11.16 mL, 100 mmol, 1 equiv) in methanol (3 mL) was heated under reflux for 25 h. After being cooled to room temperature, the mixture was diluted with water (40 mL) and extracted with diethyl ether (2 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to afford the aminoester as a yellow oil.

Methyl *N*-phenyl alaninate

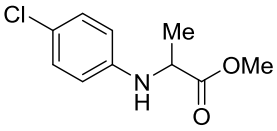


The title compound was prepared from methyl 2-bromopropanoate (11.16 mL, 100 mmol) and aniline (9.2 mL, 100 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 10 g, 56 mmol, 56 %. ^{1}H

[352] Adapted from: I. Coldham, B. C. Dobson, S. R. Fletcher and A. I. Franklin *Eur. J. Org. Chem.* **2007**, *16*, 2676–2686.
[353] Adapted from: D. Kato, K. Miyamoto, H. Ohta *Tetrahedron: Asymmetry* **2004**, *15*, 2965–2973.

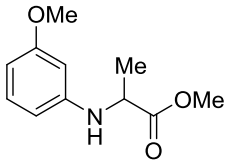
NMR (300 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.82 – 6.72 (m, 1H), 6.62 (dd, *J* = 8.7, 1.1 Hz, 2H), 4.17 (q, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H).

Methyl *N*-(4-chlorophenyl)alaninate



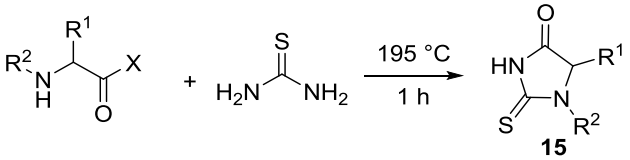
The title compound was prepared from methyl 2-bromopropanoate (3.30 ml, 30 mmol) and 4-chloroaniline (3.84 g, 30 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 5.36 g, 25.2 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.13-7.10 (m, 2H), 6.54-6.51 (m, 2H), 4.13-4.09 (m, 2H), 3.73 (s, 3H), 1.46 (d, *J* = 9 Hz, 3H).

Methyl *N*-(3-methoxyphenyl)alaninate



The title compound was prepared from 2-bromo-3-methylbutanoic acid (5.43 g, 30 mmol) and 3-methoxyaniline (3.37 ml, 30 mmol) according to the general procedure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 5:1) to afford the title compound as a yellow oil. Yield: 4.64 g, 22.2 mmol, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.08 (t, *J* = 8.1 Hz, 1H), 6.31 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 6.22 (ddd, *J* = 8.0, 2.3, 0.9 Hz, 1H), 6.16 (t, *J* = 2.3 Hz, 1H), 4.15 (t, *J* = 4.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H).

5.4.1.2. General procedure for the synthesis of thiohydantoins 15.[354]



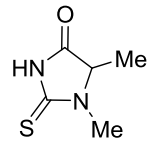
R^1 = Me, Bn, *n*Hex, *i*Bu, *i*Pr
R^2 = Me, Bn, allyl, *i*Bu, Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$
X = OH, OMe

A mixture of the corresponding *N*-substituted amino acid or their methyl ester (1 equiv) and thiourea (3 equiv) was placed in a flask and heated under stirring. When the oil bath temperature reached 180 °C, the mixture started to melt (m.p. of thiourea = 175–178 °C) and about 5 minutes later (when the temperature reached 190 °C) the homogenous liquid started to fume and reflux and the solution turned an amber color. After 10 minutes, the fuming ceased. The reaction mixture was kept at this temperature

[354]Adapted from: Z. D. Wang , S. O. Sheikh and Y. Zhang *Molecules* **2006**, *11*, 739–750.

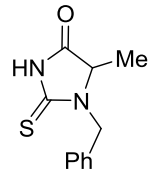
for an additional hour. The flask was then allowed to cool down to room temperature and ethyl acetate was added. A white precipitate formed, which was filtered off. The mother liquid was then evaporated under reduced pressure and the resulting crude was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 70:30) to afford the title compound as a white solid.

1,5-Dimethyl-2-thioxoimidazolidin-4-one



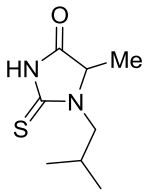
The title compound was prepared from *N*-methyl alanine (1.03 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.29 g, 9 mmol, 90 %. m.p. = 151–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (s, 1H), 4.07 (q, *J* = 7.2 Hz, 1H), 3.25 (s, 3H), 1.52 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 174.7, 61.7, 32.1, 15.3. UPLC-DAD-QTOF: $C_5H_9N_2OS$ $[M+H]^+$ calcd.: 145.0436, found: 145.0430.

1-Benzyl-5-methyl-2-thioxoimidazolidin-4-one



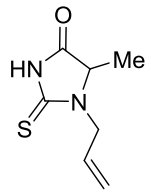
The title compound was prepared from *N*-benzyl alanine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.20 g, 6.5 mmol, 65 %. m.p. = 140–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.97 (s, 1H), 7.49 – 7.21 (m, 4H), 5.03 (dd, *J* = 377.3, 15.1 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 1H), 1.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.0, 134.8, 129.2, 128.6, 128.2, 58.5, 48.0, 15.0. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0751.

1-Isobutyl-5-methyl-2-thioxoimidazolidin-4-one



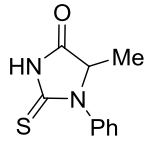
The title compound was prepared from *N*-isobutyl alanine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. (Column chromatography on silica gel eluting with hexane/ethyl acetate, 80:20) Yield: 1.47 g, 7.9 mmol, 79 %. m.p. = 84–87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 4.13 (q, *J* = 6Hz, 1H), 4.05-3.97 (m, 1H), 3.05 (dd, *J* = 6Hz, 1H), 2.09-1.99 (m, 1H), 1.44 (d, *J* = 9 Hz, 2H), 0.95 (d, *J* = 6 Hz, 3H), 0.88 (d, *J* = 9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.8, 59.2, 51.0, 27.1, 20.3, 19.8, 14.8. UPLC-DAD-QTOF: $C_8H_{15}N_2OS$ $[M+H]^+$ calcd.: 187.0905, found: 187.0893.

1-Allyl-5-methyl-2-thioxoimidazolidin-4-one



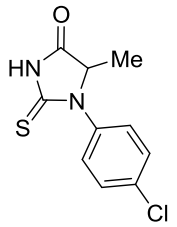
The title compound was prepared from methyl *N*-allyl alaninate (1.43 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.31 g, 7.7 mmol, 77 %. m.p. = 109–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 5.90 – 5.68 (m, 1H), 5.41 – 5.19 (m, 2H), 4.83 (dd, *J* = 15.5, 4.9 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 3.99 – 3.83 (m, 1H), 1.47 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 174.8, 131.1, 120.3, 59.5, 47.5, 15.5. UPLC-DAD-QTOF: $C_7H_{11}N_2OS$ $[M+H]^+$ calcd.: 171.0592, found: 171.0597

5-Methyl-1-phenyl-2-thioxoimidazolidin-4-one



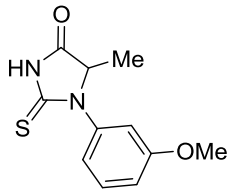
The title compound was prepared from methyl *N*-phenyl alaninate (1.79 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.73 g, 8.4 mmol, 84 %. m.p. = 188–191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 7.53 – 7.33 (m, 5H), 4.60 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.4, 174.1, 136.7, 130.0, 129.1, 127.3, 122.7, 63.0, 16.1. UPLC-DAD-QTOF: $C_{10}H_{11}N_2OS$ $[M+H]^+$ calcd.: 207.0592, found: 207.0593.

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



The title compound was prepared from methyl (4-chlorophenyl)alaninate (2.13 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 2.05 g, 8.5 mmol, 85 %. m.p. = 170–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.01 (s, 1H), 7.47-7.35 (m, 4H), 4.57 (q, *J* = 6, 9 Hz, 1H), 1.43 (d, *J* = 9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.0, 173.1, 134.7, 134.4, 129.9, 128.2, 62.4, 15.7. UPLC-DAD-QTOF: $C_{10}H_{10}ClN_2OS$ $[M+H]^+$ calcd.: 241.0202, found: 241.0193.

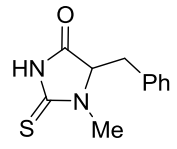
1-(3-Methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from methyl (3-methoxyphenyl)alaninate (2.09 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. (Column chromatography on silica gel eluting with hexane/ethyl acetate, 2:1) Yield: 1.89 g, 8 mmol, 80 %. m.p. = 145–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.87 (s, 1H), 7.41-7.35 (t, J = 9 Hz, 1H), 7.01-6.91 (m, 3H), 4.57 (q, J = 9 Hz, 1H), 3.83 (s, 3H), 1.44 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.7, 173.2, 160.4, 137.7,

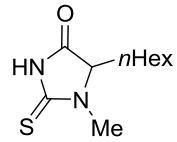
130.4, 118.7, 114.2, 113.6, 62.6, 56.7, 15.7. UPLC-DAD-QTOF: $C_{11}H_{13}N_2O_2S$ $[M+H]^+$ calcd.: 237.0698, found: 237.0684.

5-Benzyl-1-methyl-2-thioxoimidazolidin-4-one



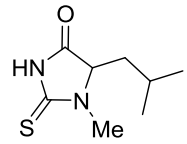
The title compound was prepared from *N*-methyl phenylalanine (1.79 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.85 g, 8.4 mmol, 84 %. m.p. = 130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.39 – 7.07 (m, 6H), 4.31 (t, *J* = 4.8 Hz, 1H), 3.41 – 3.16 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.7, 172.4, 133.8, 129.4, 129.3, 129.2, 129.1, 127.9, 66.6, 63.0, 35.7. UPLC-DAD-QTOF: $C_{11}H_{13}N_2OS$ $[M+H]^+$ calcd.: 221.0749, found: 221.0751.

5-Hexyl-1-methyl-2-thioxoimidazolidin-4-one



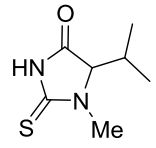
The title compound was prepared from 2-(methylamino)octanoic acid (1.73 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.73 g, 8.1 mmol, 81 %. m.p. = 79–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.40 (s, 1H), 4.08 (dd, *J* = 5.7, 3.6 Hz, 1H), 3.20 (s, 3H), 1.91 (ddd, *J* = 27.8, 7.8, 2.7 Hz, 2H), 1.25 (d, *J* = 5.4 Hz, 8H), 0.91 – 0.71 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.13, 174.28, 65.74, 32.12, 31.89, 29.34, 29.27, 23.44, 22.94, 14.45. UPLC-DAD-QTOF: $C_{10}H_{19}N_2OS$ $[M+H]^+$ calcd.: 215.1213, found: 215.1209.

5-Isobutyl-1-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from *N*-methyl leucine (1.45 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.47 g, 7.9 mmol, 79 %. m.p. = 125–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.76 (s, 1H), 4.05 (t, *J* = 5.9 Hz, 1H), 3.24 (s, 3H), 1.99 – 1.85 (m, 1H), 1.84 – 1.74 (m, 1H), 0.98 (d, *J* = 0.7 Hz, 1H), 0.96 (d, *J* = 6.5 Hz, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 173.8, 64.1, 38.1, 32.2, 24.2, 23.1, 22.6. UPLC-DAD-QTOF: $C_8H_{15}N_2OS$ $[M+H]^+$ calcd.: 187.0905, found: 187.0908.

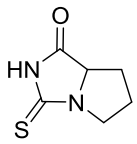
5-isoPropyl-1-methyl-2-thioxoimidazolidin-4-one



The title compound was prepared from *N*-methyl valine (1.31 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 1.20 g, 7 mmol, 70 %. m.p. = 137–140 °C. ^{1}H NMR (300 MHz,$CDCl_3$) δ: 8.87 (s, 1H), 3.91 (dd, *J* = 3.4, 0.7 Hz, 1H), 3.24 (s, 3H), 2.32 (ddt, *J* =

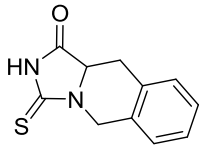
10.4, 7.0, 3.4 Hz, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.2, 173.0, 70.4, 32.8, 30.0, 17.5, 16.8. UPLC-DAD-QTOF: $C_7H_{13}N_2OS$ $[M+H]^+$ calcd.: 173.0749, found: 173.0750.

3-Thioxohexahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one



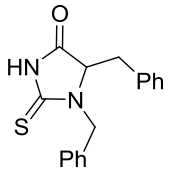
The title compound was prepared from proline (1.15 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 968 mg, 6.2 mmol, 62 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.54 (s, 1H), 4.28 (dd, *J* = 10.4, 6.7 Hz, 1H), 3.94 (dt, *J* = 11.6, 8.1 Hz, 1H), 3.52 (ddd, *J* = 12.0, 8.7, 3.5 Hz, 1H), 2.42 – 2.05 (m, 3H), 1.79 (dd, *J* = 11.4, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 186.9, 175.6, 67.4, 48.4, 27.6, 27.0. UPLC-DAD-QTOF: $C_6H_9N_2OS$ $[M+H]^+$ calcd.: 157.0436, found: 157.0434.

3-Thioxo-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5*H*)-one



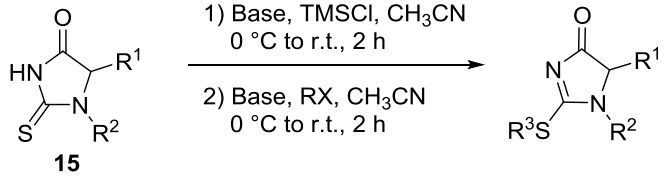
The title compound was prepared from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1.77 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. The crude product was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, from 70:30 to 50:50). Yellow solid. Yield: 1.62 g, 7.4 mmol, 74 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.44 – 7.11 (m, 4H), 5.42 (d, *J* = 17.2 Hz, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 4.26 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.32 (dd, *J* = 15.6, 4.7 Hz, 1H), 3.12 – 2.90 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.5, 173.7, 131.2, 130.6, 129.9, 128.2, 128.0, 127.3, 59.5, 46.1, 31.2. UPLC-DAD-QTOF: $C_{11}H_{11}N_2OS$ $[M+H]^+$ calcd.: 219.0592, found: 219.0595.

1,5-Dibenzyl-2-thioxoimidazolidin-4-one

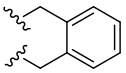


The title compound was prepared from *N*-benzyl phenylalanine (2.55 g, 10 mmol) and thiourea (2.18 g, 30 mmol) according to the general procedure. Yield: 2.63 g, 8.9 mmol, 89 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.22 (s, 1H), 7.50 – 6.93 (m, 10H), 5.79 (d, *J* = 15.0 Hz, 1H), 4.26 – 4.05 (m, 2H), 3.19 (ddd, *J* = 27.7, 14.5, 4.7 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.0, 173.3, 134.4, 133.92, 129.0, 128.7, 128.6, 128.1, 128.1, 127.4, 62.8, 47.9, 35.1.. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1056, found: 297.1062.

5.4.1.3. **General procedure for the synthesis of 1*H*-imidazol-4(5*H*)-ones 16–18**



	R^1	R^2
16a	Me	Me
16b	Me	Bn
16c	Me	*i*Bu
16d	Me	Allyl
16e	Me	Ph
16f	Me	4-ClC_6H_4
16g	Me	3-$MeOC_6H_4$

	R^1	R^2
16h	Bn	Me
16i	*n*Hex	Me
16j	*i*Bu	Me
16k	*i*Pr	Me
16l	-$CH_2CH_2CH_2$-	
16m		
16n	Bn	Bn

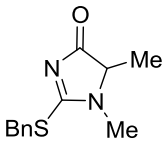
16 R^3 = Bn
17a R^1, R^2, R^3 = Me
18a R^1, R^2 = Me; R^3 = Et

METHOD A: A solution of the corresponding thiohydantoin **15** (5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with freshly distilled triethylamine (0.84 mL, 6 mmol, 1.2 equiv.) and, after 5 min at 0 °C, freshly distilled TMSCl (0.99 mL, 6 mmol, 1.2 equiv.) was added. A white precipitate formed instantaneously. The reaction mixture was warmed up to room temperature and stirred for 2 hours. The solution was cooled to 0 °C and freshly distilled triethylamine (2.8 mL, 20 mmol, 4 equiv.) and benzyl bromide (1.19 mL, 10 mmol, 2 equiv.) were added. The mixture was then warmed up to room temperature and monitored by TLC (hexane/ethyl acetate, 1:2). After reaction completion (2-3 h), the reaction mixture was diluted with CH_2Cl_2 and washed with water. The clear yellow solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography.

METHOD B: A solution of the corresponding thiohydantoin (453 mg, 5 mmol, 1 equiv.) in freshly distilled anhydrous CH_3CN (2 mL/mmol) at 0 °C was treated with DIPEA (distilled, 1.05 mL, 6 mmol, 1.2 equiv.) and, after 5 min at 0 °C, freshly distilled TMSCl (0.99 mL, 6 mmol, 1.2 equiv.) was added. The reaction mixture was warmed up to room temperature and stirred for 2 hours. The solution was cooled to 0 °C and DIPEA (distilled, 3.48 mL, 24 mmol, 4 equiv.) and the corresponding alkyl iodide (10 mmol, 2 equiv) were added. The mixture was then warmed up to room temperature and monitored by TLC (hexane/ethyl acetate, 1:2). After reaction completion (2–3 h), the reaction mixture was diluted with CH_2Cl_2 and washed with water. The clear yellow solution was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting yellow oil was purified by silica gel flash column chromatography.

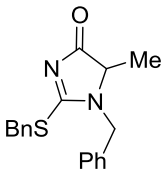
(**Note:** Imidazolones **16**–**18** decompose over time and should be stored in a refrigerator under argon atmosphere (at –30 °C they are stable for at least 1 month)).

2-(Benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (16a)



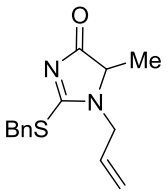
The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 576 mg, 2.46 mmol, 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.13 (m, 5H), 4.49 (s, 2H), 3.82 (q, *J* = 7.3 Hz, 1H), 2.98 (s, 3H), 1.37 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.3, 183.3, 135.5, 128.9, 128.4, 127.6, 62.6, 36.3, 30.6, 14.5. UPLC-DAD-QTOF: $C_{12}H_{15}N_2OS$ $[M+H]^+$ calcd.: 235.0905, found: 235.0910.

1-Benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (16b)



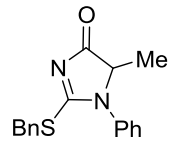
The title compound was prepared from 1-benzyl-5-methyl-2-thioxoimidazolidin-4-one (1.10 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Yellow oil. Yield: 1.3 g, 4.2 mmol, 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.10 (m, 15H), 4.75 (d, *J* = 15.9 Hz, 1H), 4.68 (d, *J* = 1.5 Hz, 1H), 4.61 (s, 2H), 4.54 (d, *J* = 4.7 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.39 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.8, 183.9, 135.7, 134.5, 129.4, 128.8, 128.1, 127.6, 60.9, 48.7, 37.2, 15.2. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1231.

1-Allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (16d)



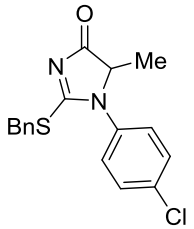
The title compound was prepared from 1-allyl-5-methyl-2-thioxoimidazolidin-4-one (851 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 859 mg, 3.30 mmol, 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 – 6.88 (m, 5H), 5.63 – 5.38 (m, 1H), 5.14 – 4.83 (m, 2H), 4.33 (s, 2H), 4.00 – 3.58 (m, 3H), 1.18 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 184.1, 136.0, 131.1, 129.6, 129.2, 128.4, 119.8, 61.5, 47.6, 37.3, 15.6. UPLC-DAD-QTOF: $C_{14}H_{17}N_2OS$ $[M+H]^+$ calcd.: 261.,1056, found: 261.1053.

2-(Benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (16e)



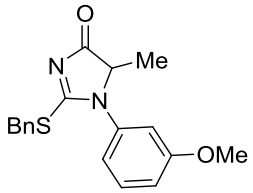
The title compound was prepared from 5-methyl-1-phenyl-2-thioxoimidazolidin-4-one (1.03 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.01 g, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56 – 7.14 (m, 10H), 4.57 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 1H), 1.43 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, MeOD) δ: 190.7, 184.9, 137.1, 136.5, 130.9, 130.2, 130.1, 130.0, 129.7, 128.9, 127.7, 65.3, 37.5, 15.6. UPLC-DAD-QTOF: $C_{17}H_{17}N_2OS$ $[M+H]^+$ calcd.: 297.1062, found: 297.1064.

2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (16f)



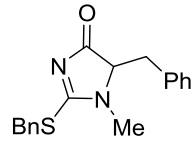
The title compound was prepared from 1-(4-chlorophenyl)-5-methyl-2-thioxoimidazolidin-4-one (1.20 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. White solid. Yield: 1.36 g, 4.15 mmol, 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.17 (m, 9H), 4.53 (s, 2H), 4.35 (q, *J* = 6 Hz, 1H), 1.40 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.8, 183.4, 135.4, 134.7, 134.1, 130.2, 129.3, 128.9, 128.1, 127.8, 63.9, 37.3, 15.6. UPLC-DAD-QTOF: $C_{17}H_{16}ClN_2OS$ $[M+H]^+$ calcd.: 331.0672, found: 331.0675.

2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (16g)



The title compound was prepared from 1-(3-methoxyphenyl)-5-methyl-2-thioxoimidazolidin-4-one (1.17 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 1.38 g, 4.25 mmol, 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.23 (m, 6H), 6.94-6.75 (m, 3H), 4.53 (s, 2H), 4.37 (q, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 1.41 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.6, 182.8, 160.1, 136.1, 135.3, 130.2, 128.9, 128.3, 127.5, 117.8, 113.6, 111.8, 63.4, 55.2, 36.7, 15.1.

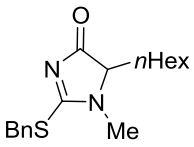
5-Benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (16h)



The title compound was prepared from 5-benzyl-1-methyl-2-thioxoimidazolidin-4-one (1.10 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 25:75. Yellow oil. Yield: 1.15 g, 3.7 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 6.85 (m, 10H), 4.39 (dd, *J* = 13.1 Hz, 2H), 4.09 (t, *J* = 5.2 Hz, 1H), 3.15 (dd, *J* = 28.0,

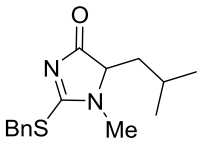
5.2 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.8, 184.0, 135.4, 134.7, 128.5, 128.0, 127.2, 126.6, 67.7, 35.9, 35.4, 31.4. UPLC-DAD-QTOF: $C_{18}H_{19}N_2OS$ $[M+H]^+$ calcd.: 311.1218, found: 311.1226.

2-(Benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (16i)



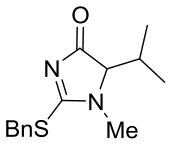
The title compound was prepared from 5-hexyl-1-methyl-2-thioxoimidazolidin-4-one (1.07 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.03 g, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.04 (m, 5H), 4.47 (s, 2H), 3.82 (dd, *J* = 5.5, 3.9 Hz, 1H), 2.96 (s, 3H), 1.96 – 1.66 (m, 2H), 1.36 – 0.98 (m, 8H), 0.90 – 0.69 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.1, 184.3, 136.2, 129.5, 129.1, 128.2, 67.4, 37.0, 31.8, 31.4, 29.3, 29.2, 23.6, 22.8, 14.3. UPLC-DAD-QTOF: $C_{17}H_{25}N_2OS$ $[M+H]^+$ calcd.: 305.1682, found: 305.1684.

2-(Benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (16j)



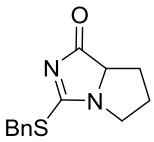
The title compound was prepared from 5-isobutyl-1-methyl-2-thioxoimidazolidin-4-one (0.93 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 25:75. Colourless oil. Yield: 661 mg, 3.55 mmol, 71%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.17 (m, 5H), 4.66 – 4.43 (m, 2H), 3.01 (s, 3H), 2.00 – 1.65 (m, 2H), 1.52 – 1.34 (m, 1H), 0.85 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.0, 185.6, 135.8, 129.9, 129.4, 128.6, 90.5, 43.7, 36.8, 28.7, 24.2, 24.1, 23.9. UPLC-DAD-QTOF: $C_{15}H_{21}N_2OS$ $[M+H]^+$ calcd.: 277.1369, found: 277.1371.

2-(Benzylthio)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (16k)



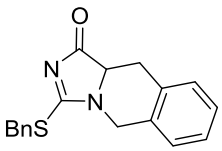
The title compound was prepared from 5-isopropyl-1-methyl-2-thioxoimidazolidin-4-one (861 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil. Yield: 892 mg, 3.4 mmol, 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 – 7.01 (m, 5H), 4.54 (s, 2H), 3.74 (d, *J* = 3.2 Hz, 1H), 3.05 (s, 3H), 2.28 (td, *J* = 7.0, 3.2 Hz, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.4, 184.8, 136.4, 129.7, 129.4, 128.5, 72.4, 37.4, 32.3, 29.9, 17.8, 17.3. UPLC-DAD-QTOF: $C_{14}H_{19}N_2OS$ $[M+H]^+$ calcd.: 263.1218, found: 263.1225.

3-(Benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (16l)



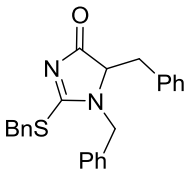
The title compound was prepared from 3-thioxohexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (781 mg, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30. Colourless oil. Yield: 1.07 g, 4.35 mmol, 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 7.11 (m, 5H), 4.62 – 4.38 (m, 2H), 4.15 (t, *J* = 8.3 Hz, 1H), 3.54 – 3.19 (m, 2H), 2.30 – 1.95 (m, 3H), 1.68 (ddd, *J* = 12.2, 9.9, 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.7, 188.2, 135.2, 128.4, 128.1, 127.2, 68.2, 53.2, 47.4, 35.9, 27.5, 25.4. UPLC-DAD-QTOF: $C_{13}H_{15}N_2OS$ $[M+H]^+$ calcd.: 247.0905, found: 247.0909.

3-(Benzylthio)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (16m)



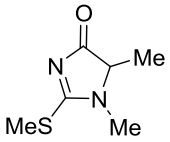
The title compound was prepared from 3-thioxo-2,3,10,10a-tetrahydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (1.09 g, 5 mmol) according to procedure A. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Yellow oil. Yield: 1.2 g, 3.9 mmol, 78%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.00 (m, 9H), 4.72 (s, 2H), 4.66 (dd, *J* = 144.9, 16.4 Hz, 1H), 4.55 (s, 2H), 3.27 (d, *J* = 16.4 Hz, 1H), 2.98 (d, *J* = 16.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.7, 183.8, 135.5, 130.8, 130.6, 129.9, 129.9, 129.4, 128.6, 128.2, 127.7, 126.9, 126.6, 85.5, 44.7, 37.0, 36.9. UPLC-DAD-QTOF: $C_{18}H_{17}N_2OS$ $[M+H]^+$ calcd.: 309.1062, found: 309.1060.

1,5-Dibenzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (16n)



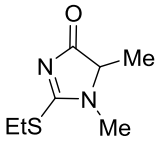
The title compound was prepared from 1,5-dibenzyl-2-thioxoimidazolidin-4-one (1.48 g, 5 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Yellow oil. Yield: 1.53 g, 3.95 mmol, 79%. (10% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 6.75 (m, 15H), 4.66 (d, *J* = 15.9 Hz, 1H), 4.60 – 4.37 (m, 2H), 4.17 (d, *J* = 15.9 Hz, 1H), 4.05 (dd, *J* = 6.2, 4.5 Hz, 1H), 3.15 (dd, *J* = 42.0, 5.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 184.5, 135.6, 135.2, 133.9, 128.9, 128.5, 127.6, 127.2, 65.1, 48.9, 36.6, 36.1. UPLC-DAD-QTOF: $C_{24}H_{23}N_2OS$ $[M+H]^+$ calcd.: 387.1526, found: 387.1521.

1,5-Dimethyl-2-(methylthio)-1*H*-imidazol-4(5*H*)-one (17a)



The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) and iodomethane (0.62 mL, 10 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil, stored at –30 °C. Yield: 498 mg, 3.15 mmol, 63%. (13% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (q, *J* = 7.2 Hz, 1H), 3.07 (s, 3H), 2.66 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H). UPLC-DAD-QTOF: $C_6H_{11}N_2OS$ $[M+H]^+$ calcd.: 159.0592, found: 159.0589.

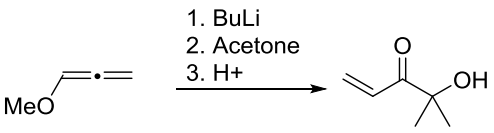
2-(Ethylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (18a)



The title compound was prepared from 1,5-dimethyl-2-thioxoimidazolidin-4-one (453 mg, 5 mmol) and iodoethane (0.80 mL, 10 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 70:30 to 0:100. Colourless oil, stored at –30 °C. Yield: 577 mg, 3.35 mmol, 67%. (15% of the corresponding *O*-benzylated adduct is obtained). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.80 (q, *J* = 7.2 Hz, 1H), 3.28 – 3.14 (m, 2H), 3.01 (s, 3H), 1.45 – 1.29 (m, 5H). UPLC-DAD-QTOF: $C_7H_{13}N_2OS$ $[M+H]^+$ calcd.: 173.0749, found: 173.0747.

5.4.2. General procedure for the synthesis of α'-silyloxy enone 39.

5.4.2.1. General procedure for the synthesis of α'-hydroxy enone 38.[355]

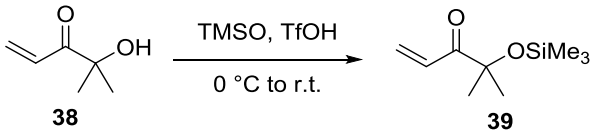


To a solution of methoxypropadiene (3.50 g, 50 mmol) in dry Et_2O (100 mL) at − 40 °C, *n*BuLi (2.5 M in hexanes, 22 mL, 55 mmol) was added under nitrogen and the reaction was stirred at − 40 °C for 10 min. Then, acetone (4.04 mL, 55 mmol) in dry Et_2O (55 mL) was added within 5 min. The reaction was stirred at the same temperature for 0.5 h and quenched with H_2O (100 mL). The resulting mixture was allowed to warm to room temperature and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford 2-methyl-3-methoxy-3,4-pentadien-2-ol as a yellow liquid (5.65 g) (82%) that was employed in the next step without further purification.

[355] C. Palomo, M. Oiarbide, J. García, A. González, E. Arceo *J. Am. Chem. Soc.* **2003**, *125*, 13942–13943.

The material from previous step (2-methyl-3-methoxy-3,4-pentadien-2-ol, 5.65 g, 44 mmol) was added dropwise to 5% aq. H_2SO_4 (110 mL) at 0 °C and the mixture was stirred for 1.5 h. After this time the reaction was allowed to warm to room temperature and the solution was saturated with solid NaCl. The mixture was extracted with Et_2O (5 × 60 mL) and the combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give a yellow oil which upon distillation afforded the enone as a colorless liquid (4.42 g) (88%). ^{1}H NMR ($CDCl_3$) δ: 6.73 (dd, 1H, CH, J= 9.5 Hz, J'= 16.8 Hz), 6.50 (dd, 1H, HCH, J= 2.2 Hz, J'= 16.8 Hz), 5.82 (dd, 1H, HCH, J= 2.2 Hz, J'= 10.3 Hz), 1.38 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ: 202.3, 131.1, 128.8, 75.4, 26.1. IR (neat, cm^{-1}) 3445 (OH), 1693 (C=O).

5.4.2.2. **General procedure for the synthesis of α'-silyloxienone 39.** [356]

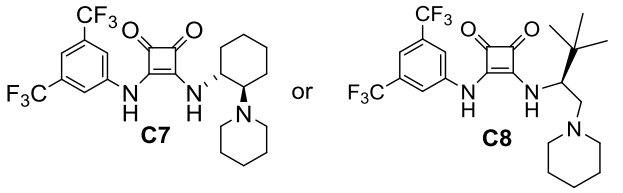


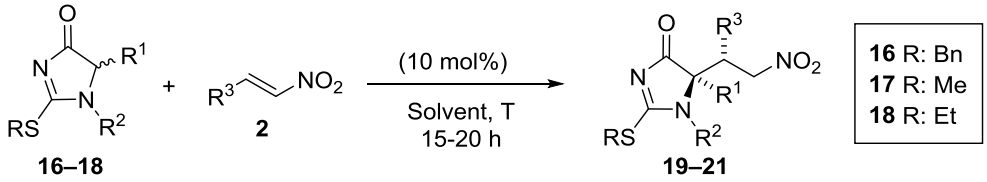
38 **39**

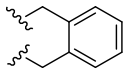
3-(Trimethylsilyl)-2-oxazolidinone (TMSO) (3.4 mL, 22.5 mmol, 1.5 equiv) and 3 drops of trifluoromethanesulfonic acid were added to 4-hydroxy-4-methylpent-1-en-3-one (1.68 g, 15 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 2 h. The resulting brown suspension was diluted with pentane (20 mL) and subsequently washed with water (20 mL) and $NaHCO_3$ sat. (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (eluent pentane/Et_2O, 98:2) to afford the title compound (**79**) as a colorless oil. Yield: 2.6 g, 14.0 mmol, 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.03 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.38 (dd, *J* = 17.3, 2.1 Hz, 1H), 5.72 (dd, *J* = 10.4, 2.1 Hz, 1H), 1.37 (s, 6H), 0.14 (s, 9H).

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

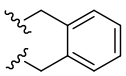
5.4.3. **General procedure for the asymmetric conjugate addition of 1*H*-imidazol-4(5*H*)-ones to nitroolefins**





	R^1	R^2
16a	Me	Me
16b	Me	Bn
16c	Me	*i*Bu
16d	Me	Allyl
16e	Me	Ph
16f	Me	4-ClC_6H_4
16g	Me	3-$MeOC_6H_4$
16h	Bn	Me
16i	*n*Hex	Me
16j	*i*Bu	Me
16k	*i*Pr	Me
16l	-$CH_2CH_2CH_2$-	
16m		

2a	R^3 = Ph
2b	R^3 = 3-MeC_6H_4
2c	R^3 = 4-BrC_6H_4
2d	R^3 = 4-MeC_6H_4
2e	R^3 = 2-furyl
2g	R^3 = 2-thienyl
2h	R^3 = 3-MeC_6H_4
2i	R^3 = 3-$MeOC_6H_4$
2j	R^3 = *i*Pr
2k	R^3 = Cy
2l	R^3 = *n*Pr

	R^1	R^2	
19a	Me	Me	
19b	Me	Bn	
19c	Me	*i*Bu	
19d	Me	Allyl	
19e	Me	Ph	
19f	Me	4-ClC_6H_4	
19g	Me	3-$MeOC_6H_4$	
19h	Bn	Me	
19i	*n*Hex	Me	
19j	*i*Bu	Me	
19k	*i*Pr	Me	
19l	-$CH_2CH_2CH_2$-		
19m			
20a	Me	Me	R: Me
21a	Me	Me	R: Et

5.4.3.1. **Asymmetric reaction**

For aromatic nitroalkenes: To a solution of the corresponding imidazolone (0.3 mmol, 1 equiv) and the corresponding aromatic nitroalkene (0.6 mmol, 2.0 equiv) in dichloromethane (0.75 mL) at -20 °C the catalyst (0.03 mmol, 10 mol %) was added. The resulting solution was stirred at the same temperature until consumption of the imidazolone (monitored by ^{1}H NMR). The reaction mixture was then directly purified by flash column chromatography (eluting with hexane/ethyl acetate, 70:30) to afford the title compound as a colourless oil.

For aliphatic nitroalkenes: A solution of the corresponding imidazolone (0.3 mmol, 1 equiv), the corresponding aliphatic nitroalkene (0.9 mmol, 3 equiv) and the catalyst (0.06 mmol, 20 mol %) in 1,2-dichloroethane (0.5 mL) was heated up to 50 °C. The solution was stirred at the same temperature until consumption of the imidazolone (monitored by ^{1}H NMR). The reaction mixture was then directly purified by flash column

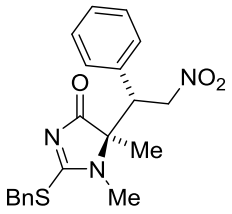
chromatography (eluting with hexane/ethyl acetate) to afford the title compound as a colourless oil.

5.4.3.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using **C4** (20 mol %) as catalyst at –20 °C.

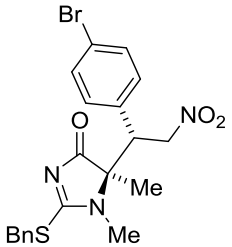
5.4.3.3. **Characterization data for compounds 19–21**

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19aa)



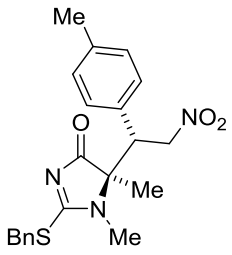
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**16a**) (70.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 111 mg, 0.29 mmol, 97 %. (diastereomeric mixture 93:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.08 (m, 10H), 5.20 (dd, *J* = 13.7, 10.3 Hz, 1H), 5.03 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.46 (d, *J* = 13.4 Hz, 1H), 4.28 (d, *J* = 13.4 Hz, 1H), 3.81 (dd, *J* = 10.3, 4.3 Hz, 1H), 2.92 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.5, 183.5, 135.4, 128.6, 128.4, 128.3, 128.2, 127.4, 127.4, 74.9, 70.7, 48.7, 35.7, 28.7, 20.0. UPLC-DAD-QTOF: $C_{20}H_{21}N_3O_3S$ $[M+H]^+$ calcd.: 384.1382, found: 384.1385.

(*R*)-2-(Benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (19ac)



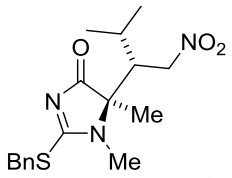
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**16a**) (70.5 mg, 0.3 mmol) and (*E*)-1-bromo-4-(2-nitrovinyl)benzene (**2c**) (136.8 mg, 0.6 mmol) according to procedure A. Yield: 114 mg, 0.24 mmol, 82 %. (diastereomeric mixture 94:6). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.14 (m, 7H), 7.07 – 7.00 (m, 2H), 5.25 – 4.89 (m, 2H), 4.38 (dd, *J* = 59.5, 13.5 Hz, 2H), 3.77 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.92 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 184.8, 136.0, 133.7, 132.6, 131.8, 129.9, 129.5, 129.4, 128.6, 123.4, 75.7, 71.2, 49.4, 37.0, 29.5, 21.1. UPLC-DAD-QTOF: $C_{20}H_{21}BrN_3O_3S$ $[M+H]^+$ calcd.: 462.0487, found: 462.0487.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19ad)



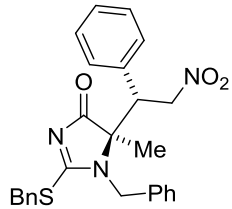
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**16a**) (70.5 mg, 0.3 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2d**) (97.5 mg, 0.6 mmol) according to procedure A. Yield: 108 mg, 0.27 mmol, 91 %. (diastereomeric mixture 90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 – 7.10 (m, 5H), 7.03 (d, *J* = 0.9 Hz, 4H), 5.21 – 4.88 (m, 2H), 4.37 (dd, *J* = 56.9, 13.3 Hz, 2H), 3.76 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.89 (s, 3H), 2.26 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.4, 184.4, 138.9, 136.2, 131.4, 130.0, 129.5, 129.2, 128.4, 128.0, 76.1, 71.4, 49.7, 36.8, 29.5, 21.6, 21.1.UPLC-DAD-QTOF: $C_{21}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 398.1538, found: 398.1537.

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-3-methyl-1-nitrobutan-2-yl)-1*H*-imidazol-4(5*H*)-one (19aj)



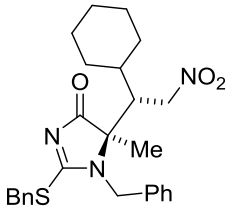
The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**16a**) (70.5 mg, 0.3 mmol) and (*E*)-3-methyl-1-nitrobut-1-ene (**2j**) (103.5 mg, 0.9 mmol) according to procedure B. Yield: 60.8 mg, 0.17 mmol, 58 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.14 (m, 5H), 5.29 (dd, *J* = 15.0, 5.9 Hz, 1H), 4.67 – 4.47 (m, 2H), 4.39 (dd, *J* = 15.0, 4.1 Hz, 1H), 2.97 (s, 3H), 2.69 (ddd, *J* = 6.0, 4.1, 2.1 Hz, 1H), 1.63 – 1.49 (m, 1H), 1.38 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.1, 183.9, 129.7, 129.4, 128.6, 71.3, 47.7, 37.2, 29.0, 27.2, 23.2, 21.7, 17.5. UPLC-DAD-QTOF: $C_{17}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 350.1538, found: 350.1548.

(*R*)-1-Benzyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ba)



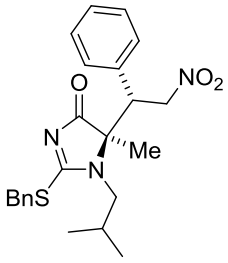
The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16b**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 117 mg, 0.26 mmol, 85 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.05 (m, 15H), 5.19 (dd, *J* = 13.7, 10.2 Hz, 1H), 5.02 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.50 (s, 2H), 4.46 (d, *J* = 13.4 Hz, 1H), 4.24 (d, *J* = 13.4 Hz, 1H), 3.94 (dd, *J* = 10.2, 4.3 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.2, 185.3, 135.9, 135.2, 134.4, 129.5, 129.5, 129.4, 129.2, 129.2, 128.9, 128.4, 127.7, 76.1, 72.3, 50.1, 48.2, 37.3, 22.4. UPLC-DAD-QTOF: $C_{26}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 460.1695, found: 460.1711.

(*R*)-1-Benzyl-2-(benzylthio)-5-((*R*)-1-cyclohexyl-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (19bk)



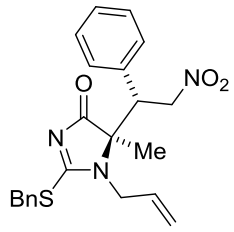
The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16b**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)cyclohexane (**2k**) (139.5 mg, 0.9 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 90:10. Yield: 55.9 mg, 0.12 mmol, 40 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.21 (m, 10H), 5.21 (dd, *J* = 15.0, 6.7 Hz, 1H), 4.77 (d, *J* = 13.3 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 2H), 4.51 (d, *J* = 13.3 Hz, 1H), 4.29 (dd, *J* = 15.0, 3.7 Hz, 1H), 2.57 (dq, *J* = 5.5, 2.4, 1.9 Hz, 1H), 1.79 – 1.48 (m, 5H), 1.32 (s, 3H), 1.09 – 0.82 (m, 4H), 0.69 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 190.3, 184.6, 136.3, 135.2, 129.8, 129.7, 129.7, 129.6, 129.4, 129.4, 129.2, 129.2, 129.0, 128.9, 128.6, 127.9, 72.1, 70.8, 48.5, 48.2, 37.6, 37.5, 33.0, 28.4, 27.3, 27.0, 26.4, 22.3. UPLC-DAD-QTOF: $C_{26}H_{32}N_3O_3S$ $[M+H]^+$ calcd.: 466.2164, found: 466.2170.

(*R*)-2-(Benzylthio)-1-isobutyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ca)



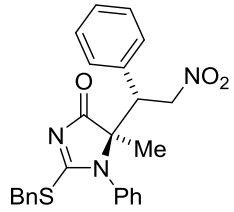
The title compound was prepared from 2-(benzylthio)-1-isobutyl-5-methyl-1*H*-imidazol-4(5*H*)-one (**16c**) (82.7 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Yield: 99 mg, 0.23 mmol, 78 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.14 (m, 10 H), 5.21– 5.00 (m, 2H), 4.34 (dd, J = 12 Hz, 1H), 4.24 (dd, J = 12 Hz, 1H), 3.85 (dd, J = 6, 3 Hz, 1H), 3.13 (dd, *J* = 6Hz, 1H), 2.99 (dd, *J* = 9 Hz, 1H), 2.13-2.02 (m, 1H), 1.62 (s, 3H), 0.90 (dd, J = 3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.5, 185.0, 135.3, 133.8, 129.1, 128.7, 128.0, 127.9, 75.7, 72.0, 52.0, 49.5, 37.0, 28.5, 22.1, 20.6. UPLC-DAD-QTOF: $C_{23}H_{27}N_3O_3S$ $[M+H]^+$ calcd.: 426.1851, found: 426.1866.

(*R*)-1-Allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19da)



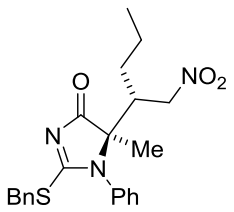
The title compound was prepared from 1-allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16d**) (78 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 94.6 mg, 0.23 mmol, 77 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.04 (m, 10H), 5.66 (dd, *J* = 16.6, 10.7 Hz, 1H), 5.33 – 5.11 (m, 3H), 5.03 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.43 (d, *J* = 13.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.01 – 3.72 (m, 3H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.1, 184.8, 136.0, 134.5, 131.6, 129.5, 129.3, 129.2, 128.4, 128.3, 120.3, 76.0, 72.2, 49.9, 46.8, 37.1, 22.2. UPLC-DAD-QTOF: $C_{22}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 410.1538, found: 410.1558.

(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (19ea)



The title compound was prepared from 2-(benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (**16e**) (88.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 86.9 mg, 0.195 mmol, 65 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 – 6.81 (m, 15H), 5.21 – 4.85 (m, 2H), 4.52 (d, *J* = 13.3 Hz, 1H), 4.29 (d, *J* = 13.2 Hz, 1H), 3.66 (dd, *J* = 10.4, 4.2 Hz, 1H), 1.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.0, 185.6, 135.6, 134.7, 134.1, 130.0, 129.7, 129.2, 129.0, 128.9, 128.8, 128.8, 128.8, 128.0, 72.3, 50.5, 44.2, 37.0, 24.2. UPLC-DAD-QTOF: $C_{25}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 446.1538, found: 446.1553.

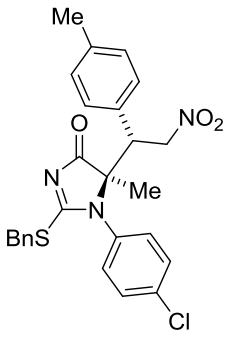
(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-1-nitropentan-2-yl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (19el)



The title compound was prepared from 2-(benzylthio)-5-methyl-1-phenyl-1*H*-imidazol-4(5*H*)-one (**19e**) (88.5 mg, 0.3 mmol) and (*E*)-1-nitropent-1-ene (**2l**) (139.5 mg, 0.6 mmol) according to procedure B. Flash chromatography: hexane/ethyl acetate, 80:20. Yield: 63 mg, 0.15 mmol, 51 %. (diastereomeric mixture 80:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 – 7.09 (m, 10H), 5.19 (dd, *J* = 14.7, 6.6 Hz, 1H), 4.61 – 4.41 (m, 2H), 4.35 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.58 – 2.47 (m, 1H), 1.69 – 1.57 (m, 1H), 1.44 (s, 3H), 1.34 – 1.19 (m, 3H), 0.94 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl^3$) δ: 188.9, 185.2, 135.4, 133.9, 130.5, 130.4, 130.3, 129.3, 129.3, 128.9, 128.1, 128.1, 74.3, 72.5,

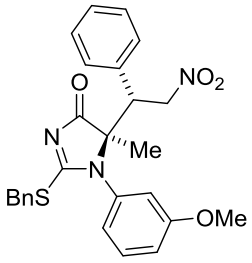
41.8, 37.1, 30.1, 21.1, 20.3, 14.2. UPLC-DAD-QTOF: $C_{22}H_{26}N_3O_3S$ $[M+H]^+$ calcd.: 412.1695, found: 412.1709.

(*R*)-2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19fd)



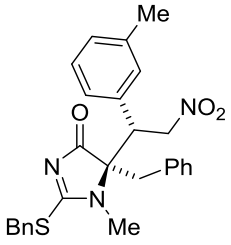
The title compound was prepared from 2-(benzylthio)-1-(4-chlorophenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16f**) (99 mg, 0.3 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2d**) (97.5 mg, 0.6 mmol) according to procedure A. Yield: 123 mg, 0.24 mmol, 83 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.32 (m, 2H), 7.30-7.21 (m, 5H), 7.07– 7.05 (m, 2H), 6.98-6.93 (m, 2H), 6.83-6.78 (m, 2H), 5.11-4.94 (m, 2H), 4.53 (dd, *J* = 12 Hz, 1H), 4.30 (d, *J* = 15 Hz, 1H), 3.57 (dd, J = 3, 6 Hz, 1H), 2.33 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.8, 185.5, 138.9, 136.2, 135.6, 132.5, 131.5, 130.3, 130.0 129.7, 129.2, 128.9, 128.5, 128.1, 72.3, 50.3, 37.0. 24.3, 21.3 UPLC-DAD-QTOF: $C_{26}H_{24}ClN_3O_3S$ $[M+H]^+$ calcd.: 494.1305, found: 494.1309.

(*R*)-2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ga)



The title compound was prepared from 2-(benzylthio)-1-(3-methoxyphenyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16g**) (97.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Yield: 122 mg, 0.23 mmol, 85 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.22 (m, 9 H), 7.16– 7.12 (m, 2H), 6.99-6.95 (m, 1H), 6.56-6.52 (m, 1H), 6.37-6.35 (m, 1H), 5.18-4.99 (m, 2H), 4.53 (d, *J* = 15 Hz, 1H), 4.32 (d, J = 12 Hz, 1H), 3.75 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 185.5, 160.2, 135.6, 160.2, 135.6, 135.0, 134.8, 130.4, 129.2, 128.9, 128.8, 127.9, 120.6, 115.4, 114.7, 77.2, 72.3, 55.5, 50.5, 37.0, 24.2. UPLC-DAD-QTOF: $C_{26}H_{25}N_3O_4S$ $[M+H]^+$ calcd.: 476.1644, found: 476.1649.

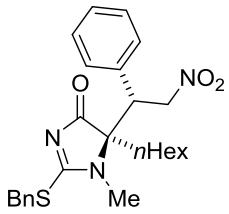
(*R*)-5-Benzyl-2-(benzylthio)-1-methyl-5-((*R*)-2-nitro-1-(*m*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19hb)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (**16h**) (93 mg, 0.3 mmol) and (*E*)-1-methyl-3-(2-nitrovinyl)benzene (**2b**) (97.9 mg, 0.6 mmol) according

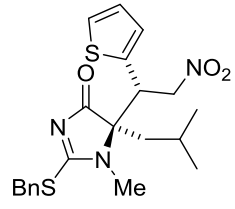
to procedure A. Yield: 117 mg, 0.24 mmol, 82 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 – 6.95 (m, 14H), 5.31 – 5.13 (m, 2H), 4.19 (s, 2H), 3.93 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 3.04 (d, *J* = 13.7 Hz, 1H), 2.82 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.1, 184.9, 138.6, 135.9, 134.3, 133.2, 129.6, 129.4, 128.9, 128.9, 128.7, 128.7, 127.8, 127.7, 125.0, 76.2, 76.1, 49.7, 40.8, 36.1, 30.3, 21.5. UPLC-DAD-QTOF: $C_{27}H_{28}N_3O_3S$ $[M+H]^+$ calcd.: 474.1851, found: 474.1856.

(*R*)-2-(Benzylthio)-5-hexyl-1-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ia)



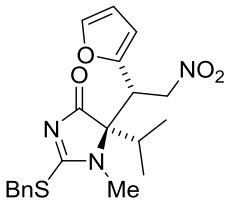
The title compound was prepared from 2-(benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**16i**) (91.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 90:10. Yield: 110.1 mg, 0.24 mmol, 81 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37-7.15 (m, 10H), 5.23-5.03 (m, 2H), 4.37 (dd, *J* = 12, 15 Hz, 2H), 3.78 (dd, *J* = 3,6 Hz, 1H), 2.86 (s, 3H), 2.16-2.03 (m, 1H), 1.82-1.72 (m, 1H), 1.29-1.22 (m, 8H), 0.90-0.85 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.3, 184.5, 135.9, 134.3, 129.0, 128.9, 128.7, 127.9, 127.9, 75.7, 75.1, 49.1, 36.3, 34.0, 31.5, 29.0, 3.5, 22.5, 14.1. UPLC-DAD-QTOF: $C_{25}H_{32}N_3O_3S$ $[M+H]^+$ calcd.: 454.2164, found: 454.2161.

(*R*)-2-(Benzylthio)-5-isobutyl-1-methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-imidazol-4(5*H*)-one (19jg)



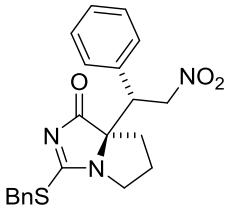
The title compound was prepared from 2-(benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**16j**) (82.9 mg, 0.3 mmol) and (*E*)-2-(2-nitrovinyl)thiophene (**2g**) (93 mg, 0.6 mmol) according to procedure A. Yield: 109 mg, 0.25 mmol, 84 %. (diastereomeric mixture 92:8)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.18 (m, 5H), 7.12 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 3.8, 1.2 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.24 – 4.92 (m, 2H), 4.40 (dd, *J* = 23.8, 13.6 Hz, 2H), 4.03 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.95 (s, 3H), 1.98 (dd, *J* = 14.2, 7.6 Hz, 1H), 1.74 (dd, *J* = 14.2, 4.6 Hz, 1H), 1.40 (ddd, *J* = 6.6, 3.9, 1.5 Hz, 1H), 0.95 – 0.73 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.6, 185.2, 136.4, 135.7, 129.6, 129.2, 128.4, 127.8, 126.9, 125.7, 76.6, 75.1, 45.0, 42.6, 36.8, 30.1, 25.4, 24.5, 23.6. UPLC-DAD-QTOF: $C_{21}H_{26}N_3O_3S_2$ $[M+H]^+$ calcd.: 432.1416, found: 432.1426.

(*R*)-2-(Benzylthio)-5-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (19ke)



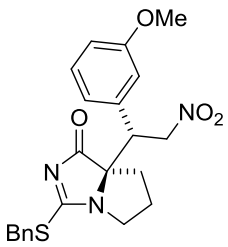
The title compound was prepared from 2-(benzylthio)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**16k**) (78.7 mg, 0.3 mmol) and (*E*)-2-(2-nitrovinyl)furan (**2e**) (85.5 mg, 0.6 mmol) according to procedure A. Yield: 90 mg, 0.23 mmol, 75 %. (diastereomeric mixture 93:7)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.16 (m, 6H), 6.34 – 6.20 (m, 2H), 5.07 (dd, *J* = 13.6, 11.6 Hz, 1H), 4.63 (dd, *J* = 13.6, 3.4 Hz, 1H), 4.46 (dd, *J* = 15.2, 13.6 Hz, 2H), 4.33 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.98 (s, 3H), 2.25 – 2.11 (m, 1H), 1.04 (dd, *J* = 6.9, 6.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.0, 185.8, 148.6, 143.2, 136.2, 129.7, 129.3, 128.6, 111.4, 110.0, 74.1, 40.3, 37.3, 32.5, 31.6, 17.1, 17.0. UPLC-DAD-QTOF: $C_{20}H_{24}N_3O_4S$ $[M+H]^+$ calcd.: 402.1488, found: 402.1497.

(*R*)-3-(benzylthio)-7a-((*R*)-2-nitro-1-phenylethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (19la)



The title compound was prepared from 3-(benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**16l**) (73.5 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 99 mg, 0.23 mmol, 83 %. (diastereomeric mixture 90:10)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 – 7.12 (m, 9H), 5.09 (dd, *J* = 13.5, 11.4 Hz, 1H), 4.78 (dd, *J* = 13.5, 3.9 Hz, 1H), 4.42 (dd, *J* = 13.2, 8.9 Hz, 2H), 3.87 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.63 – 3.44 (m, 1H), 3.17 – 2.99 (m, 1H), 2.10 – 1.93 (m, 2H), 1.89 – 1.52 (m, 2H).^{13}C NMR (75 MHz, CDCl3) δ:194.2, 190.5, 135.8, 134.8, 129.5, 129.4, 129.4, 129.3, 129.2, 129.1, 128.6, 79.1, 75.9, 50.2, 49.7, 37.5, 30.8, 27.1. UPLC-DAD-QTOF: $C_{21}H_{22}N_3O_3S$ $[M+H]^+$ calcd.: 396.1382, found: 396.1395.

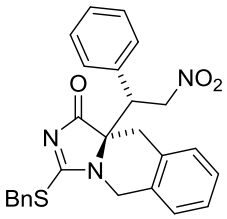
(*R*)-3-(Benzylthio)-7a-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (19li)



The title compound was prepared from 3-(benzylthio)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (**16l**) (73.5 mg, 0.3 mmol) and (*E*)-1-methoxy-3-(2-nitrovinyl) benzene (**2i**) (108 mg, 0.6 mmol) according to procedure A. Yield: 99.6 mg, 0.23 mmol, 78 %. (diastereomeric mixture 87:13). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33– 7.21 (m, 6H), 6.87-6.79 (m, 3H), 5.08-4.99 (m, 1H), 4.76 (dd, *J* = 6, 9 Hz, 1H), 4.45 (q, *J* = 12, 15 Hz, 2H), 3.78 (s, 3H), 3.59-3.51 (m, 1H), 3.16-3.07 (m, 1H), 2.09-1.58 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.0, 190.1, 159.8,

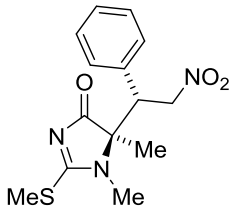
136.0, 130.0, 129.2, 128.2, 115.1, 113.8, 78.7, 75.6, 55.4, 50.0, 49.3, 37.2, 30.4, 26.6. UPLC-DAD-QTOF: $C_{22}H_{23}N_3O_4S$ $[M+H]^+$ calcd.: 426.1488, found: 426.1491.

(*R*)-3-(Benzylthio)-10a-((*R*)-2-nitro-1-phenylethyl)-10,10a-dihydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one (19ma)



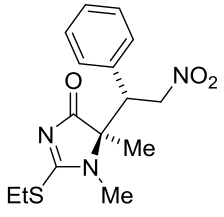
The title compound was prepared from 3-(benzylthio)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (**16m**) (93 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 85 mg, 0.19 mmol, 62 %. (diastereomeric mixture 98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 – 6.97 (m, 14H), 5.30 – 5.09 (m, 2H), 4.68 (d, *J* = 16.6 Hz, 1H), 4.50 (d, *J* = 13.4 Hz, 1H), 4.39 (s, 1H), 4.35 (d, *J* = 13.3 Hz, 1H), 3.77 – 3.63 (m, 1H), 3.27 (d, *J* = 16.5 Hz, 1H), 3.09 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 189.3, 184.0, 135.9, 135.0, 130.7, 129.9, 129.6, 129.4, 129.3, 129.2, 129.1, 128.8, 128.4, 128.4, 128.0, 126.7, 76.1, 68.6, 46.8, 45.4, 36.8, 35.0, 30.1. UPLC-DAD-QTOF: $C_{26}H_{24}N_3O_3S$ $[M+H]^+$ calcd.: 458.1538, found: 458.1541.

(*R*)-1,5-Dimethyl-2-(methylthio)-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (20aa)



The title compound was prepared from 1,5-dimethyl-2-(methylthio)-1*H*-imidazol-4(5*H*)-one (**17a**) (48 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.4 mmol) according to procedure A. Yield: 66.3 mg, 0.21 mmol, 72 %. (diastereomeric mixture 92:8). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29-7.15 (m, 5H), 5.23-5.15 (m, 1H), 5.04-4.98 (m, 1H), 3.80 (dd, J = 3, 3 Hz, 1H), 2.48 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 188.9, 185.0, 134.3, 129.7, 129.0, 128.9, 127.9, 75.6, 71.0, 49.7, 29.2, 20.8, 14.7. UPLC-DAD-QTOF: $C_{14}H_{18}N_3O_3S$ $[M+H]^+$ calcd.: 308.1069, found: 308.1072.

(*R*)-2-(Ethylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (21aa)

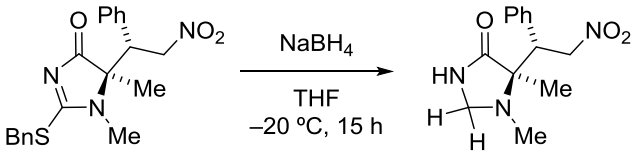


The title compound was prepared from 2-(ethylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**18a**) (51 mg, 0.3 mmol) and (*E*)-(2-nitrovinyl)benzene (**2a**) (90 mg, 0.6 mmol) according to procedure A. Yield: 59.8 mg, 0.19 mmol, 62 %. (diastereomeric mixture 90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.10 (m, 5H), 5.20 (dd, *J* = 13.7, 10.3 Hz, 1H), 5.01 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.79 (dd, *J* = 10.3, 4.3 Hz,

1H), 3.24 – 3.06 (m, 1H), 3.06 – 2.90 (m, 1H), 2.92 (s, 3H), 1.54 (s, 3H), 1.17 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.1, 184.5, 134.2, 129.7, 129.0, 128.9, 128.8, 128.8, 127.8, 75.5, 70.6, 49.6, 29.1, 26.9, 20.6, 15.1. UPLC-DAD-QTOF: $C_{15}H_{20}N_3O_3S$ $[M+H]^+$ calcd.: 322.1225, found: 322.1223.

5.4.4. **Elaboration of adducts 19aa, 19ac, 19da.**

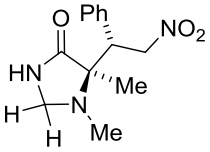
5.4.4.1. **Synthesis of imidazolidinone 22.**



19aa **22**

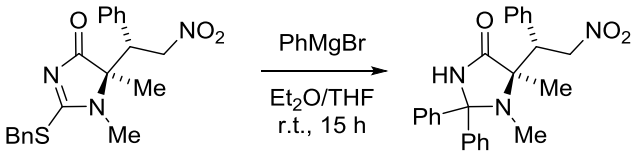
To a solution of **19aa** (52 mg, 0.14 mmol, 1 equiv.) in THF (0.7 mL) at –20 °C under inert atmosphere was added sodium borohydride (11 mg, 0.28 mmol, 2 equiv.). The reaction mixture was stirred for 15 h at the same temperature and afterwards quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 50:50).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidin-4-one (22)



Yield: 35 mg, 0.13 mmol, 94 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 – 7.17 (m, 6H), 5.21 (dd, *J* = 13.4, 11.1 Hz, 1H), 4.71 (dd, *J* = 13.4, 4.3 Hz, 1H), 4.26 (dd, *J* = 4.5, 0.9 Hz, 1H), 3.86 – 3.70 (m, 2H), 2.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.2, 136.2, 130.1, 128.9, 65.8, 65.3, 50.6, 35.7, 16.5. UPLC-DAD-QTOF: $C_{13}H_{18}N_3O_3$ $[M+H]^+$ calcd.: 264.1348, found: 264.1350.

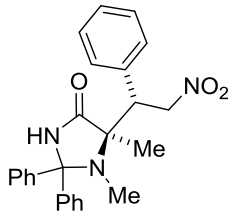
5.4.4.2. **Synthesis of *gem*-diarylated adduct 23.**



19aa **23**

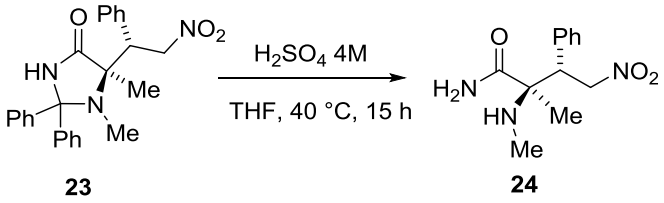
To a solution of **19aa** (76 mg, 0.2 mmol, 1 equiv.) in THF (1 mL) at 0 °C under inert atmosphere was added phenylmagnesium bromide (1M in Et_2O, 0.6 mL, 1 mmol, 5 equiv.). The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 50:50).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2,2-diphenylimidazolidin-4-one (23)



Yield: 66 mg, 0.16 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (s, 1H), 7.49 – 6.57 (m, 17H), 5.25 (dd, *J* = 13.5, 11.3 Hz, 1H), 4.71 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.76 (dd, *J* = 11.3, 3.6 Hz, 1H), 2.05 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.4, 142.4, 140.9, 137.5, 129.8, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 126.9, 120.7, 115.5, 82.8, 77.2, 66.8, 52.1, 29.7, 20.0. UPLC-DAD-QTOF: $C_{25}H_{26}N_3O_3$ $[M+H]^+$ calcd.: 416.1974, found: 416.1974.

5.4.4.3. **Synthesis of *N*-methyl amino amide 24.**[357]

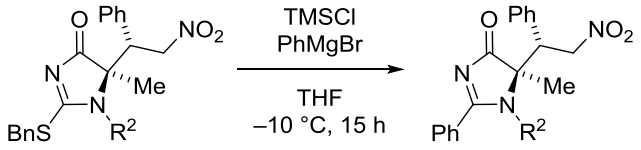


23 **24**

To a solution of 1-methyl-2,2-diphenylimidazolidin-4-one **23** (41.5 mg, 0.10 mmol) in 0.5 mL THF at 0 °C was added dropwise an aqueous solution of H_2SO_4 4M (0.5 mL). The resulting mixture was stirred at 40 °C 16 h and afterwards the reaction was quenched with an aqueous solution of NaOH 1M (2.0 mL). The mixture was diluted with saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2 × 15mL). The combined extracts were washed with brine (20 mL) and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluent: hexane:ethyl acetate 7:1 to ethyl acetate). Yield: 22.6 mg, 0.09 mmol, 90 %. $[\alpha]_D^{25}$= +14.0 (*c*= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 – 7.25 (m, 5H), 6.96 (s, 1H), 5.34 (dd, *J* = 13.6, 11.1 Hz, 2H), 4.98 (dd, *J* = 13.6, 3.5 Hz, 1H), 3.79 (dd, *J* = 11.1, 3.5 Hz, 1H), 2.37 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 136.1, 129.2, 129.1, 128.5, 78.2, 64.1, 50.1, 29.1, 21.3. UPLC-DAD-QTOF: $C_{12}H_{18}N_3O_3$ $[M+H]^+$ calcd.: 252.1348, found: 252.1350.

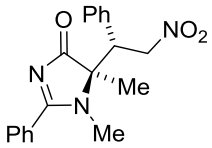
[357] M. Pangerl, C. C. Hughes and D. Trauner *Tetrahedron* **2010**, *66*, 6626–6631.

5.4.4.4. **Synthesis of monoarilated adduct 25.**



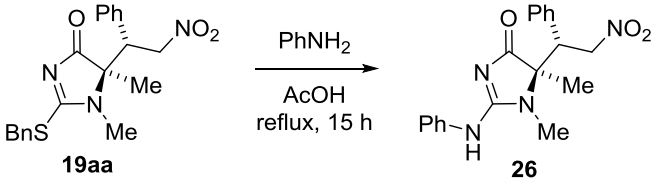
To a solution of **19aa** (0.2 mmol, 1 equiv.) in THF (1 mL) at –10 °C under inert atmosphere was added TMSCl (24 µL, 0.1 mmol, 1 equiv.) and phenylmagnesium bromide (1M in THF, 0.6 mL, 0.6 mmol, 3 equiv.). The reaction mixture was stirred for 15 h at –10 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 0:100).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-phenyl-1*H*-imidazol-4(5*H*)-one (25)



Yield: 57.3 mg, 0.17 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54 – 7.00 (m, 10H), 5.33 – 5.03 (m, 2H), 3.91 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.08 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 192.0, 180.0, 134.4, 132.1, 129.1, 129.1, 128.7, 128.5, 127.8, 118.3, 75.5, 69.3, 50.0, 30.5, 20.8. UPLC-DAD-QTOF: $C_{19}H_{20}N_3O_3$ $[M+H]^+$ calcd.: 338.1505, found: 338.1510.

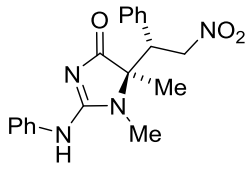
5.4.4.5. **Synthesis of *N*-methyl aminohydantoin 26.**[358]



To a solution of **19aa** (38 mg, 0.1 mmol, 1 equiv.) in glacial acetic acid (0.5 mL) under inert atmosphere was added aniline (0.10 mL, 0.11 mmol, 1.1 equiv.). The reaction mixture was stirred under reflux for 16 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with water and extracted with ethyl acetate (2 × 5 mL). The organic layer was dried over $MgSO_4$ and solvents were evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20 to 0:100).

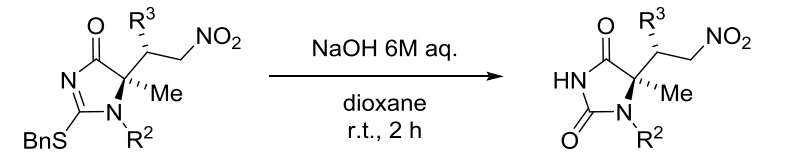
[358] Adapted from: Godlewskim, M. et al. PCT Int. Appl. (WO9823595), June 4, 1998.

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-2-(phenylamino)-1*H*-imidazol-4(5*H*)-one (26)



Yield: 24 mg, 0.07 mmol, 68 %. ^{1}H NMR (300 MHz, CD_3OD) δ: 7.40 – 7.00 (m, 10H), 5.28 (dd, *J* = 13.5, 11.2 Hz, 1H), 5.10 (dd, *J* = 13.5, 4.3 Hz, 1H), 3.96 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.04 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ: 191.4, 168.0, 136.6, 130.5, 129.7, 129.5, 129.4, 126.5, 124.7, 76.5, 70.7, 50.4, 27.7, 20.5. UPLC-DAD-QTOF: $C_{19}H_{21}N_4O_3$ $[M+H]^+$ calcd.: 353.1614, found: 353.1610.

5.4.4.6. **Synthesis of hydantoins 27, 28 and 29.**

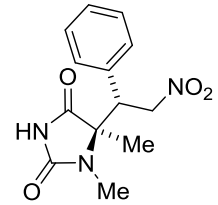


19aa R^2: Me R^3: Ph
19ac R^2: Me R^3: 4-BrC_6H_4
19da R^2: Allyl R^3: Ph

27 R^2: Me R^3: Ph
28 R^2: Me R^3: 4-BrC_6H_4
29 R^2: Allyl R^3: Ph

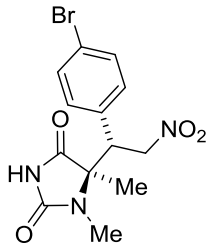
The corresponding adduct **19aa**, **19ac**, **19da** (1 equiv.) was dissolved dioxane (5 mL) and cooled to 0 °C. NaOH 6M (11 equiv.) was added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After this period the solution was treated at 0 °C with a saturated aqueous solution of NH_4Cl. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with ethyl acetate/hexane, from 70:30 to 50:50).

(*R*)-1,5-Dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (27)



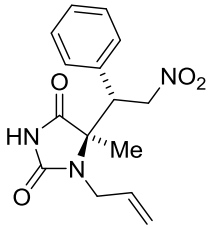
The title compound was prepared from (*R*)-2-(benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (**19aa**) (410 mg, 1.07 mmol) according to the general procedure. White foam. Yield: 211 mg, 0.76 mmol, 71 %. $[\alpha]_D^{25}$= +26.8 (*c*= 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.34 – 7.25 (m, 3H), 7.18 – 7.10 (m, 2H), 5.16 (dd, *J* = 13.7, 10.2 Hz, 1H), 4.97 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.87 (dd, *J* = 10.2, 4.7 Hz, 1H), 2.86 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 154.9, 134.3, 129.7, 129.6, 128.3, 76.1, 67.6, 49.3, 25.4, 20.9. UPLC-DAD-QTOF: $C_{13}H_{16}N_3O_4$ $[M+H]^+$ calcd.: 278.1141, found: 278.1143.

(*R*)-5-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)-1,5-dimethylimidazolidine-2,4-dione (28)



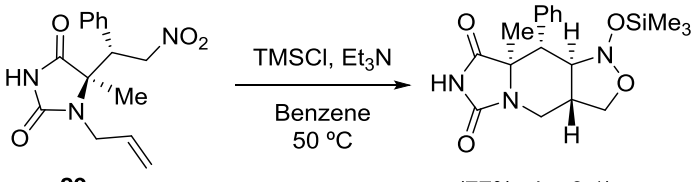
The title compound was prepared from (*R*)-2-(benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**19ac**) (197 mg, 0.43 mmol) according to the general procedure. White solid. Yield: 112 mg, 0.31 mmol, 73 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (s, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.14 (dd, *J* = 13.8, 10.4 Hz, 1H), 4.93 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.84 (dd, *J* = 10.4, 4.6 Hz, 1H), 2.87 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 179.6, 175.4, 133.0, 132.8, 129.9, 123.7, 75.1, 70.4, 48.7, 29.9, 20.4. UPLC-DAD-QTOF: $C_{13}H_{13}BrN_3O_4$ $[M+H]^+$ calcd.: 354.0089, found: 354.0087.

(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (29)



The title compound was prepared from (*R*)-1-allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (**19da**) (54 mg, 0.13 mmol) according to the general procedure. White foam. Yield: 24 mg, 0.08 mmol, 61 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.37 – 7.04 (m, 5H), 5.94 – 5.71 (m, 1H), 5.32 – 5.07 (m, 3H), 4.96 (dd, *J* = 13.7, 4.7 Hz, 1H), 4.10 (dd, *J* = 16.0, 5.3 Hz, 1H), 3.90 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.65 (dd, *J* = 16.0, 6.9 Hz, 1H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 155.1, 134.2, 133.4, 129.6, 129.6, 128.5, 119.1, 76.1, 68.4, 49.5, 43.3, 22.3. UPLC-DAD-QTOF: $C_{15}H_{18}N_3O_4$ $[M+H]^+$ calcd.: 304.1297, found: 304.1306.

5.4.4.7. **Intramolecular silyl nitronate olefin cycloaddition (ISOC) of 29.**

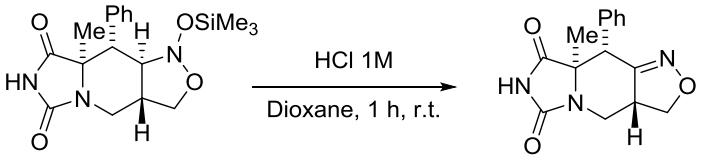


29 (77%, dr= 9:1)

To a solution of hydantoin **29** (101 mg, 0.33 mmol, 1 equiv.) in benzene (2.5 mL) under inert atmosphere were added freshly distilled Et_3N (280 µL, 2 mmol, 6 equiv.) and freshly distilled TMSCl (213 µL, 1.67 mmol, 5 equiv.). After addition was complete the mixture was warmed to 50 °C and stirred for 48 h. Afterwards, the reaction mixture was cooled to 0 °C, quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate 80:20 to 50:50) to yield the corresponding *N*-trimethylsilyloxyisoxazoline. Yield: 95 mg, 0.25 mmol, 77%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.64 (s, 1H), 7.33-7.16 (m, 5H), 4.64-

4.60 (m, 1H), 4.35-4.30 (m, 1H), 3.73-3.53 (m , 2H), 3.17 (d, *J* = 12 Hz, 1H), 2.96-2.87 (m, 2H), 1.34 (s, 3H), -0.29 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.2, 154.6, 134.1, 130.4, 12.2, 127.9, 73.4, 70.4, 64.4, 49.8, 42.2, 39.6, 16.7, -1.0. UPLC-DAD-QTOF: $C_{18}H_{26}N_3O_4Si$ $[M+H]^+$ calcd.: 376.1693, found: 376.1689.

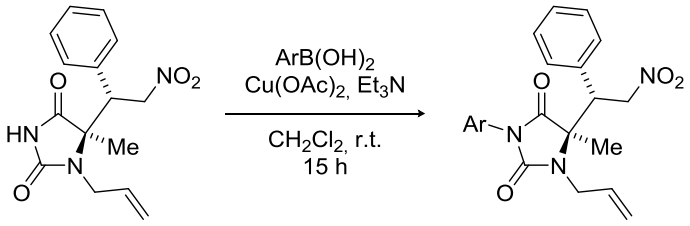
5.4.4.8. **Synthesis of isoxazoline 30.**



(*dr* = 9:1) **30** (83 %, *dr* = 9:1)

A solution of the *N*-trimethylsilyloxyisoxazoline (95 mg, 0.25 mmol, 1 equiv.) in dioxane (1 mL) was cooled to 0 °C and then treated with 10% aqueous HCl. The reaction mixture was stirred for 1 h at rt and afterwards poured into water and extracted with ether. The ether extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by short plug of silica gel (eluent: 80:20 to 0:100, hexane/ethyl acetate). Yield: 59 mg, 0.21 mmol, 83%. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 9.70 (s, 1H), 7.57 – 7.11 (m, 5H), 4.63 – 4.46 (m, 2H), 4.16 (d, *J* = 1.3 Hz, 1H), 3.99 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.58 (ddd, *J* = 10.6, 7.4, 1.3 Hz, 1H), 3.11 (dd, *J* = 13.3, 10.9 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 174.5, 157.3, 154.2, 132.7, 128.5, 128.0, 72.0, 65.4, 51.0, 48.4, 40.7, 16.9. UPLC-DAD-QTOF: $C_{15}H_{16}N_3O_3$ $[M+H]^+$ calcd.: 286.1189, found: 286.1192.

5.4.4.9. ***N*-Arylation of hydantoin 29.**[359]



29 (*dr* = 9:1)

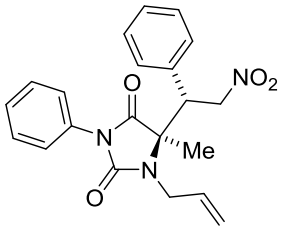
31 Ar = Ph
32 Ar = 3,5-$Me_2C_6H_3$

A slurry of (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**29** from big scale reaction *dr* 9:1, Table 50 page 140 compound **19da**) (30 mg, 0.1 mmol, 1 equiv.), arylboronic acid (0.2 mmol, 2 equiv.), $Cu(OAc)_2$ (18 mg, 0.1 mmol, 1 equiv.) in CH_2Cl_2 (0.5 mL) was stirred at room temperature for 15 h. The progress of the reaction was monitored by TLC. The products were isolated from the crude reaction

[359] D. M. T. Chan, K. L. Monaco, R.-P. Wang, M. P. Winters *Tetrahedron Letters* **1998**, *39*, 2933-2936.

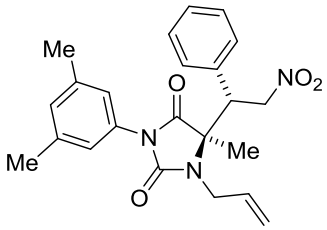
mixture by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20).

(*R*)-1-Allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-3-phenylimidazolidine-2,4-dione (31)



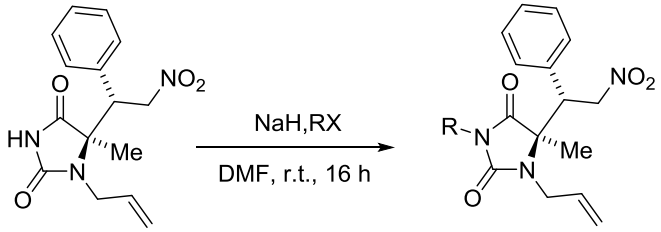
The title compound was prepared from (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**29**) (30 mg, 0.1 mmol) and phenyl boronic acid (24 mg, 0.2 mmol, 2 equiv) according to the general procedure. Yellow oil. Yield: 29 mg, 0.08 mmol, 76 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 – 7.27 (m, 7H), 7.19 – 7.13 (m, 2H), 7.03 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.99 – 5.83 (m, 1H), 5.40 – 5.16 (m, 3H), 5.03 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.28 (dd, *J* = 15.8, 5.4 Hz, 1H), 4.01 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.87 – 3.76 (m, 1H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.2, 153.8, 133.1, 129.2, 129.2, 129.2, 129.1, 129.0, 128.5, 128.2, 126.0, 118.9, 75.5, 66.5, 49.0, 43.2, 21.6. UPLC-DAD-QTOF: $C_{21}H_{22}N_3O_4$ $[M+H]^+$ calcd.: 380.1610, found: 380.1612.

(*R*)-1-Allyl-3-(3,5-dimethylphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (32)



The title compound was prepared from (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**29**) (30 mg, 0.1 mmol) and 3,5-dimethylphenyl boronic acid (30 mg, 0.2 mmol, 2 equiv) according to the general procedure. Yellow oil. Yield: 32.6 mg, 0.08 mmol, 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.29 (m, 3H), 7.20 – 7.13 (m, 2H), 6.97 (s, 1H), 6.58 (s, 2H), 6.00 – 5.84 (m, 1H), 5.40 – 5.15 (m, 3H), 5.03 (dd, *J* = 13.8, 4.9 Hz, 1H), 4.34 – 4.22 (m, 1H), 4.00 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.81 (dd, *J* = 15.8, 7.0 Hz, 1H), 2.29 (s, 6H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8, 154.5, 139.4, 133.6, 130.9, 129.6, 129.6, 128.7, 124.4, 119.3, 76.0, 66.9, 49.4, 43.7, 22.1, 21.7. UPLC-DAD-QTOF: $C_{23}H_{26}N_3O_4$ $[M+H]^+$ calcd.: 408.1923, found: 408.1921.

5.4.4.10. *N*-Alkylation of hydantoin 29.[360]

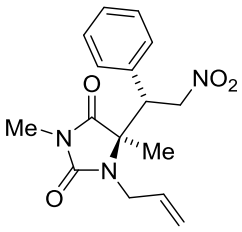


29 (*dr* = 9:1)

33 R = Me
34 R = Bn

Sodium hydride (60% dispersion in mineral oil, 38.4 mg, 1 mmol, 1 equiv.) was added to a solution of (*R*)-1-allyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (**29** from big scale reaction *dr* 9:1, Table 50 page 140 compound **19da**) (303 mg, 1.0 mmol, 1 equiv.) in DMF (4 mL) at 0 ^{o}C. The mixture was stirred for 30 min, then the corresponding alkyl halide (1.2 mmol, 1.2 equiv.) was added dropwise. The cooling bath was removed and the reaction was stirred at room temperature for 16 h. The mixture was added to water (20 mL) and extracted with Et_2O. The organic layer was dried with anhyd. $MgSO_4$, evaporated and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 80:20).

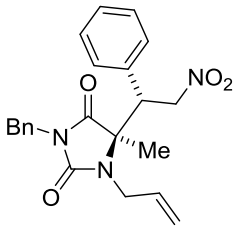
(*R*)-1-Allyl-3,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (33)



The title compound was prepared adding iodomethane (74.1 µL, 1.2 mmol, 1.2 equiv.) according to the general procedure. Colourless oil. Yield: 259 mg, 0.82 mmol, 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.27 (m, 3H), 7.09-7.06 (m, 2H), 5.89-5.77 (m, 1H), 5.33-5.13 (m, 3H), 5.01-4.95 (m, 1H), 4.21-4.13 (m, 1H), 3.93-3.88 (m, 1H), 3.76-3.67 (m, 1H), 2.79 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.3, 154.8, 133.8, 133.2, 129.4, 128.9, 128.8, 128.6, 127.8, 118.2, 75.4, 66.6, 48.8, 42.7, 24.4, 21.1. UPLC-DAD-QTOF: $C_{16}H_{20}N_3O_4$ $[M+H]^+$ calcd.: 318.1454, found: 318.1451.

[360] Adapted from Owen, David Alan et al From U. S., 6566384, 20 May 2003

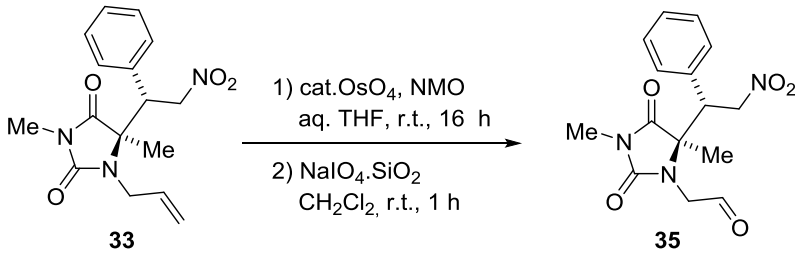
(*R*)-1-Allyl-3-benzyl-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)imidazolidine-2,4-dione (34)



The title compound was prepared adding benzyl bromide (142.8 µL, 1.2 mmol, 1.2 equiv.) according to the general procedure. Yellow oil. Yield: 330 mg, 0.84 mmol, 84 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 7.16-7.10 (m, 1H), 6.99-6.87 (m, 4H), 5.91-5.78 (m, 1H), 5.33-5.21 (m, 2H), 5.11 (dd, *J* = 9, 12 Hz, 1H), 4.97 (dd, *J* = 3, 6 Hz, 1H), 4.50 (d, 2H), 4.16-4.08 (m, 1H), 3.88 (dd, *J* = 6,3 Hz, 1H), 3.68-3.65 (m, 1H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 154.8, 135.3, 133.6, 133.3, 129.6, 129.2, 129.0, 128.8, 128.5, 128.1, 127.8, 118.6, 76.0, 66.3, 49.2, 43.1, 42.7, 22.2. UPLC-DAD-QTOF: $C_{22}H_{24}N_3O_4$ $[M+H]^+$ calcd.: 394.1767, found: 394.1762.

5.4.4.11. Intramolecular Henry reaction.

5.4.4.11.1. Synthesis of aldehyde.[361]



33 **35**

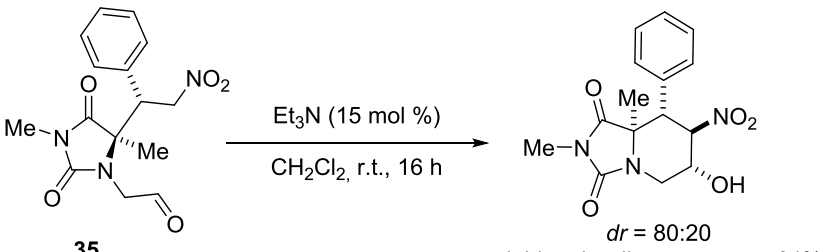
Step 1-Synthesis of the diol: OsO_4 (2.5 wt% in 2-methyl-2-propanol, 175.7 mg , 0.0164 mmol, 0.02 equiv.) and 4-methylmorpholine *N*-oxide (125 mg, 1.1 mmol, 1.3 equiv.) were added to a solution of hydantoin **33** (0.82 mmol, 1 equiv.) in THF (6 mL) and H_2O (2 mL) at room temperature. The mixture was stirred for 16 h, then a solution of $NaHSO_3$ in H_2O 40% w/v (2.3 mL, 9 mmol, 11 equiv.) was added and the resulting mixture was stirred for 10 min. The mixture was diluted with 20 mL of brine and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50 to 0:100) to afford the diol as white foam (Yield: 0.7 mmol, 86 %).

Step 2-Synthesis of the aldehyde: $NaIO_4$ supported on silica gel (1.5 g, 1.4 mmol, 2.0 equiv.) was added to a solution of previously prepared diol (1 equiv., 0.7 mmol) in DCM

[361] Adapted from: R. L. Danheiser et al. *J. Org. Chem.* **2013**, *78*, 9396-9414.

(10 mL). The suspension was stirred at room temperature for 1 h. The reaction mixture was filtrated through a sintered glass funnel and the filtrate was concentrated to afford the aldehyde **35** as white foam used in the next step without purification (Yield: 0.5 mmol, 71 %).

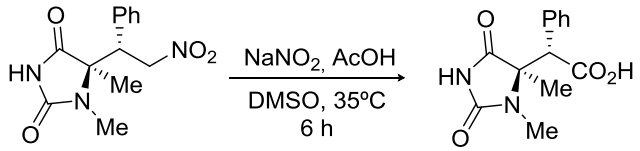
5.4.4.11.2. Intramolecular cyclization.



35 **36**

To a solution of aldehyde **35** (97 mg, 0.3 mmol, 1 equiv.) in 1.5 mL of DCM was added Et_3N (6.3 µL, 0.045 mmol, 0.15 equiv.). The reaction mixture was stirred for 16 h at room temperature and white precipitate was generated. Then, the organic layer was concentrated under reduced pressure and the crude product was purified by silica flash chromatography (eluting with hexane/ethyl acetate: 70:30 to 50:50,) to afford the desired product as white solid. Yield: 61 mg, 0.19 mmol, 64 % (major. diasteroisomer) $[\alpha]_D^{25}$= +1.71 (*c*= 2, Acetone, major. diastereomer). ^{1}H NMR (300 MHz, Acetone-d_6) δ: 7.31-7.30 (m, 5H), 5.47 (dd, *J* = 6, 6 Hz, 1H), 4.36 (dd, J = 3, 3 Hz, 1H), 4.19-4.13 (m, 1H), 3.65 (d, *J* = 6Hz, 1H), 3.07 (dd, J = 6, 6 Hz, 1H), 2.95 (s, 3H), 2.83 (s, 1H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 174.1, 155.6, 134.2, 129.4, 129.0, 92.1, 70.7, 63.2, 52.1, 41.9, 25.5, 16.8. UPLC-DAD-QTOF: $C_{15}H_{18}N_3O_5$ $[M+H]^+$ calcd.: 320.1246, found: 320.1245.

5.4.4.12. **Synthesis of carboxylic acid 37.**[362]



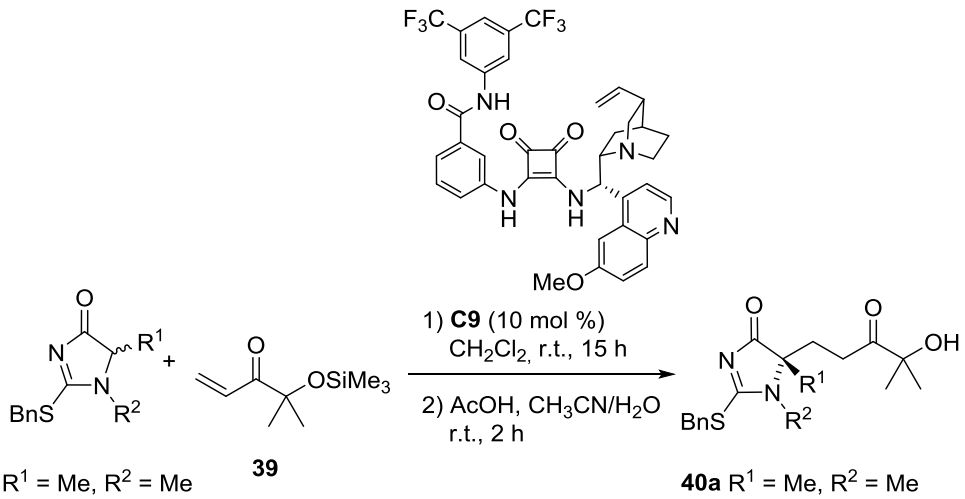
27 **37**

A solution of the nitroalkane N (0.19 mmol, 51mg), sodium nitrite (3 equiv., 0.55 mmol, 34 mg) and acetic acid (10 equiv., 1.9 mmol, 120 µL) in DMSO (0.5 mL) was stirred at 35ºc for 6h. After this period the reaction mixture was treated with HCl 1N (5 mL) and the product was extracted from the aq. phase with Et_2O (4 x 5mL). The

[362] Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529–1532.

combined organic phases were dried with anhyd. $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was washed with Et_2O giving the pure product *S*-((2*R*,3*S*)-1-amino-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl) **37** as white solid. Yield 43 mg, 0.164 mmol (86 %). $[\alpha]_D^{25}$= +15.8 (*c*= 0.50, MeOH). m.p. 230–232 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.34 (m, 5H), 4.09 (s, 1H), 2.56 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.9, 173.2, 158.9, 134.8, 131.3, 129.5, 129.3, 68.0, 57.2, 26.9, 20.8. UPLC-DAD-QTOF: $C_{13}H_{14}N_2O_4$ $[M+H]^+$ calcd.: 263.1032, found: 263.1034.

5.4.5. **General procedure for the asymmetric conjugate addition of 1*H*-imidazol-4(5*H*)-ones to α'-silyloxyenone 39.**



39

16a R^1 = Me, R^2 = Me
16b R^1 = Me, R^2 = Bn
16d R^1 = Me, R^2 = Allyl
16h R^1 = Bn, R^2 = Me
16i R^1 = *n*Hex, R^2 = Me
16j R^1 = *i*Bu, R^2 = Me
16n R^1 = Bn, R^2 = Bn

40a R^1 = Me, R^2 = Me
40b R^1 = Bn, R^2 = Me
40d R^1 = *n*Hex, R^2 = Me
40h R^1 = *i*Bu, R^2 = Me
40i R^1 = Me, R^2 = Bn
40j R^1 = Me, R^2 = Allyl
40n R^1 = Bn, R^2 = Bn

5.4.5.1. **Asymmetric reaction**

To a solution of the corresponding imidazolone (0.2 mmol, 1 equiv.) and the 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one **39** (0.6 mmol, 3 equiv.) in dichloromethane (0.5 mL) at room temperature catalyst **C9** (10 mol %) was added. The resulting solution was stirred at the same temperature until consumption of the imidazolone (monitored by ^{1}H NMR). The reaction mixture was then quenched with an aqueous solution of HCl (0.1 M) and extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The reaction crude was then solved in an acetonitrile/water 2:1 mixture (1.5 mL) and acetic acid (0.3 mL, 5 mmol, 25 equiv.) was added to the solution. Desilylation was monitored by TLC. After

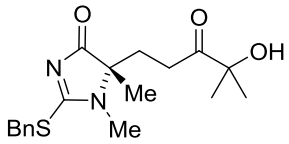
reaction termination, the solution was treated with saturated aqueous solution of $NaHCO_3$ until neutralization. The product was extracted from the aq. phase with dichloromethane and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with hexane/ethyl acetate, 70:30).

5.4.5.2. **Racemic reaction**

Racemic compounds were prepared following the above procedure using **C4** (20 mol %) as the catalyst at room temperature.

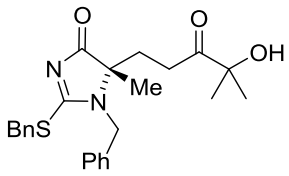
5.4.5.3. **Characterization data for compounds 40**

(*S*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (40a)



The title compound was prepared from 2-(benzylthio)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**16a**) (47 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 56 mg, 0.16 mmol, 82 %. $[\alpha]_D^{25}$= +9.0 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.20 (m, 5H), 4.55 (dd, *J* = 3.5 Hz, 2H), 2.93 (s, 3H), 2.57 – 2.40 (m, 1H), 2.36 – 2.22 (m, 1H), 2.20 – 1.92 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.9, 189.7, 183.2, 135.4, 129.0, 128.6, 127.8, 69.6, 36.3, 29.6, 29.4, 28.4, 28.4, 26.2, 21.2. UPLC-DAD-QTOF: $C_{18}H_{25}N_2O_3S$ $[M+H]^+$ calcd.: 349.1586, found: 349.1582.

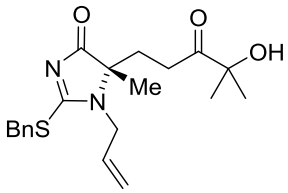
(*S*)-1-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (40b)



The title compound was prepared from 1-benzyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16b**) (62.1 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 66.2 mg, 0.16 mmol, 78 %. $[\alpha]_D^{25}$= –4.2 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 6.98 (m, 10H), 4.34 (dd, *J* = 13.3 Hz, 2H), 3.24 (d, *J* = 14.1 Hz, 1H), 2.93 (s, 3H), 2.88 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.49 (m, 1H), 2.36 – 2.11 (m, 3H), 1.29 (d, *J* = 13.3 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 189.24, 184.5, 136.2, 134.2, 129.6, 129.3, 129.1, 128.8, 128.7, 128.2, 127.7, 75.5,

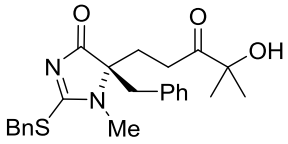
42.0, 36.5, 30.3, 29.3, 28.7, 26.8, 26.8. UPLC-DAD-QTOF: $C_{24}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 425.1899, found: 425.1899.

(*S*)-1-Allyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (40d)



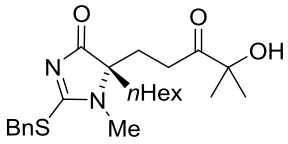
The title compound was prepared from 1-allyl-2-(benzylthio)-5-methyl-1*H*-imidazol-4(5*H*)-one (**16d**) (52.1 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 57.7 mg, 0.15 mmol, 77 %. $[\alpha]_D^{25}$= +10.5 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 – 7.19 (m, 5H), 5.84 – 5.62 (m, 1H), 5.34 – 5.18 (m, 2H), 4.56 (dd, *J* = 13.2, 9.4 Hz, 2H), 3.99 – 3.88 (m, 2H), 3.51 (s, 1H), 2.49 (ddd, *J* = 18.2, 8.9, 6.2 Hz, 1H), 2.35 – 1.91 (m, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.3, 189.9, 183.6, 135.7, 131.5, 129.4, 129.0, 128.2, 120.1, 116.6, 70.5, 42.6, 37.0, 29.8, 29.5, 26.7, 22.6. UPLC-DAD-QTOF: $C_{20}H_{27}N_2O_3S$ $[M+H]^+$ calcd.: 375.1742, found: 375.1753.

(*R*)-5-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (40h)



The title compound was prepared from 5-benzyl-2-(benzylthio)-1-methyl-1*H*-imidazol-4(5*H*)-one (**16h**) (62 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Yellow solid. Yield: 64 mg, 0.15 mmol, 75 %. $[\alpha]_D^{25}$= +20.2 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 6.95 (m, 10H), 4.48 – 4.15 (m, 2H), 3.23 (d, *J* = 14.0 Hz, 1H), 2.93 (s, 3H), 2.88 (d, *J* = 14.1 Hz, 1H), 2.67 – 2.50 (m, 1H), 2.36 – 2.09 (m, 3H), 1.29 (d, *J* = 13.0 Hz, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 189.0, 184.3, 135.9, 134.0, 129.7, 129.3, 129.1, 127.9, 127.4, 127.4, 75.2, 41.7, 36.3, 30.0, 29.5, 28.45, 26.6, 26.5. UPLC-DAD-QTOF: $C_{24}H_{29}N_2O_3S$ $[M+H]^+$ calcd.: 425.1899, found: 425.1899.

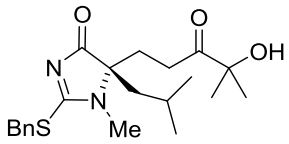
(*S*)-2-(Benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (40i)



The title compound was prepared from 2-(benzylthio)-5-hexyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**16i**) (60.9 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 67.8 mg, 0.16 mmol, 81 %. $[\alpha]_D^{25}$= +3.1 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR

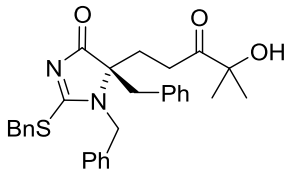
(300 MHz, $CDCl_3$) δ: 7.46 – 7.16 (m, 5H), 4.55 (s, 2H), 2.89 (s, 3H), 2.58 – 2.40 (m, 1H), 2.32 – 2.17 (m, 1H), 2.13 – 1.92 (m, 2H), 1.93 – 1.76 (m, 1H), 1.69 – 1.53 (m, 1H), 1.32 – 1.07 (m, 15H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.8, 190.0, 184.4, 136.4, 129.7, 129.4, 128.6, 74.5, 37.1, 35.8, 32.1, 30.3, 29.5, 29.3, 28.9, 27.0, 23.7, 23.0, 14.6. UPLC-DAD-QTOF: $C_{23}H_{35}N_2O_3S$ $[M+H]^+$ calcd.: 419.2363, found: 419.2361.

(*R*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (40j)



The title compound was prepared from 2-(benzylthio)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (**16j**) (55.3 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 55.5 mg, 0.14 mmol, 71 %. $[\alpha]_D^{25}$= +12.3 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.17 (m, 5H), 4.55 (s, 2H), 2.89 (s, 3H), 2.45 (dd, *J* = 8.5, 6.3 Hz, 1H), 2.33 – 2.13 (m, 1H), 2.00 (ddd, *J* = 12.9, 8.5, 5.5 Hz, 2H), 1.81 (dd, *J* = 14.7, 7.2 Hz, 1H), 1.59 (dd, *J* = 14.7, 5.3 Hz, 1H), 1.48 – 1.35 (m, 1H), 1.27 (d, *J* = 14.3 Hz, 6H), 0.82 (dd, *J* = 9.8, 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.5, 189.7, 183.8, 136.1, 129.3, 128.9, 128.1, 73.4, 43.7, 36.6, 29.8, 29.5, 29.1, 26.6, 24.6, 23.8, 23.5. UPLC-DAD-QTOF: $C_{21}H_{31}N_2O_3S$ $[M+H]^+$ calcd.: 391.2055, found: 391.2060.

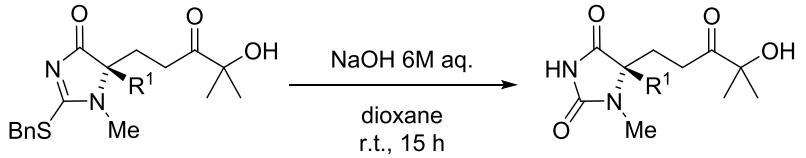
(*R*)-1,5-Dibenzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1*H*-imidazol-4(5*H*)-one (40n)



The title compound was prepared from 1,5-dibenzyl-2-(benzylthio)-1*H*-imidazol-4(5*H*)-one (**16n**) (77.3 mg, 0.2 mmol) and 4-methyl-4-((trimethylsilyl)oxy)pent-1-en-3-one (**39**) (112 mg, 0.6 mmol) according to the general procedure. Colourless oil. Yield: 83.1 mg, 0.17 mmol, 83 %. $[\alpha]_D^{25}$= +1.28 (*c*= 1.00, 92 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 – 6.92 (m, 15H), 4.55 (dd, *J* = 15.9 Hz, 2H), 4.39 (dd, *J* = 13.3 Hz, 2H), 3.19 (dd, *J* = 14.9 Hz, 2H), 2.45 – 2.29 (m, 1H), 2.13 – 1.95 (m, 2H), 1.90 – 1.74 (m, 1H), 1.19 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.2, 189.1, 185.3, 135.8, 129.9, 129.7, 129.6, 129.3, 129.2, 129.0, 129.0, 128.4, 128.0, 49.0, 42.8, 37.5, 30.0, 29.8, 27.3, 27.0. UPLC-DAD-QTOF: $C_{30}H_{33}N_2O_3S$ $[M+H]^+$ calcd.: 501.2206, found: 501.2210.

5.4.6. **Elaboration of adducts 40.**

5.4.6.1. **Synthesis of hydantoins 41–43.**

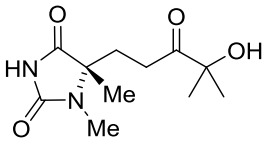


40a R^1 = Me
40h R^1 = Bn
40i R^1 = *n*Hex

41 R^1 = Me, 60%
42 R^1 = Bn, 87%
43 R^1 = *n*Hex, 72%

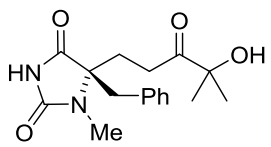
The corresponding adduct **40** (361.1 mg, 0.92 mmol, 1 equiv.) was dissolved in dioxane (5 mL) and cooled to 0 °C. NaOH 6M (1.84 mL, 11.04 mmol, 12 equiv.) was added at 0°C and the reaction mixture was stirred at room temperature for 15 h. After this period the solution was treated at 0 °C with a saturated aqueous solution of NH_4Cl. The product was extracted from the aq. phase with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (eluting with hexane/ethyl acetate, from 70:30 to 0:100).

(*S*)-5-(4-Hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylimidazolidine-2,4-dione (41)



The title compound was prepared from (*S*)-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (**40a**) (172 mg, 0.5 mmol) according to the general procedure. Colourless oil. Yield: 73.1 mg, 0.3 mmol, 60 %. $[\alpha]_D^{25}$= –6.46 (*c*= 1.00, 99 % *ee*, MeOH). ^{1}H NMR (300 MHz, MeOD) δ: 2.84 (s, 3H), 2.68 – 2.48 (m, 2H), 2.20 – 1.89 (m, 2H), 1.45 (s, 3H), 1.30 (s, 6H). ^{13}C NMR (75 MHz, MeOD) δ: 215.4, 179.1, 157.8, 77.8, 66.7, 31.3, 29.5, 26.7, 24.6, 21.7. UPLC-DAD-QTOF: $C_{11}H_{19}N_2O_4$ $[M+H]^+$ calcd.: 243.1339, found: 243.1343.

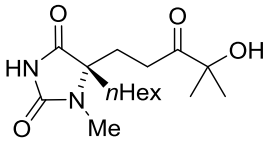
(*R*)-5-Benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (42)



The title compound was prepared from (*R*)-5-benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (**40h**) (352.0 mg, 0.7 mmol) according to the general procedure. White foam. Yield: 193 mg, 0.61 mmol, 87%. $[\alpha]_D^{25}$= +0.6 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.15 (s, 1H), 7.26 – 6.90 (m, 5H), 4.04 (s, 1H), 2.94 (dd, *J* = 33.7, 14.3 Hz, 2H), 2.78 (s, 3H), 2.63 –

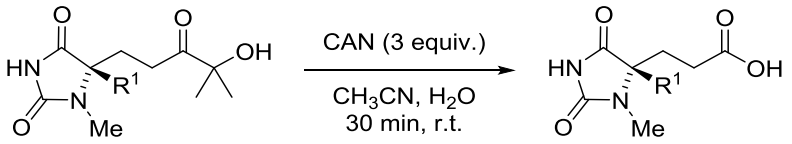
2.31 (m, 2H), 2.14 – 2.02 (m, 2H), 1.23 (d, *J* = 2.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.7, 175.5, 156.2, 133.8, 129.6, 128.7, 127.7, 77.2, 70.3, 40.7, 29.9, 28.2, 26.5, 25.1. UPLC-DAD-QTOF: $C_{17}H_{23}N_2O_4$ $[M+H]^+$ calcd.: 319.1658, found: 319.1666.

(*S*)-5-Hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (43)



The title compound was prepared from (*S*)-2-(benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (**40i**) (418.6 mg, 1 mmol) according to the general procedure. Flash chromatography: hexane/ethyl acetate, 70:30. White foam. Yield: 225 mg, 0.72 mmol, 72%. $[\alpha]_D^{25}$= +4.4 (*c*= 1.00, 94 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 3.63 (s, 1H), 2.76 (s, 3H), 2.58 – 2.37 (m, 1H), 2.13 – 1.95 (m, 1H), 1.92 – 1.75 (m, 1H), 1.63 (s, 1H), 1.43 – 1.00 (m, 16H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 213.6, 176.2, 156.6, 69.5, 35.2, 32.0, 30.1, 29.4, 28.9, 27.1, 27.0, 24.9, 23.6, 23.0, 14.5. UPLC-DAD-QTOF: $C_{16}H_{29}N_2O_4$ $[M+H]^+$ calcd.: 313.2122, found: 313.2127.

5.4.6.2. **Synthesis of carboxylic acids 44–45.**[363]



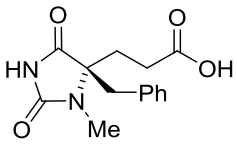
42 R^1 = Bn
43 R^1 = *n*Hex

44 R^1 = Bn, 65%
45 R^1 = *n*Hex, 74%

To a solution of the corresponding α'-hydroxy ketone **42**–**43** (1 mmol) in acetonitrile (12 mL) at 0 °C was added dropwise a solution of cerium(IV)ammonium nitrate (CAN) (1.64 g, 3 mmol, 3 equiv.) in water (6 mL) and the mixture was stirred at the same temperature for 30 minutes. Then water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were washed with water (20 mL), dried over $MgSO_4$, filtered and the solvent evaporated to afford the corresponding carboxylic acid. The crude material was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate, 50:50) to afford the title compound as a white solid.

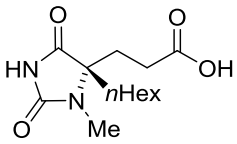
[363] Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155.

(*R*)-3-(4-Benzyl-3-methyl-2,5-dioxoimidazolidin-4-yl)propanoic acid (44)



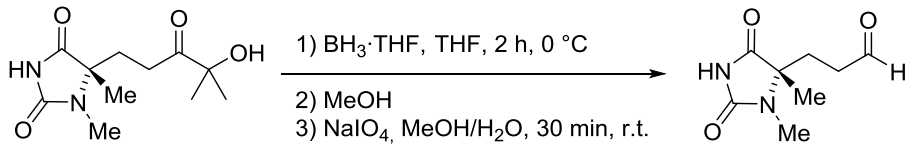
The title compound was prepared from (*R*)-5-benzyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (**42**) (107.0 mg, 0.34 mmol) according to the general procedure. White solid. Yield: 61 mg, 0.22 mmol, 65%. $[\alpha]_D^{25}$= +0.6 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.36 – 7.01 (m, 5H), 3.04 (dd, *J* = 47.9, 13.3 Hz, 2H), 2.92 (s, 3H), 2.42 – 2.16 (m, 4H). ^{13}C NMR (75 MHz, MeOD) δ: 177.5, 175.5, 158.0, 135.6, 130.7, 129.4, 128.3, 71.8, 41.2, 30.5, 29.3, 25.4. UPLC-DAD-QTOF: $C_{14}H_{17}N_2O_4$ $[M+H]^+$ calcd.: 277.1188, found: 277.1185.

(*S*)-3-(4-Hexyl-3-methyl-2,5-dioxoimidazolidin-4-yl)propanoic acid (45)



The title compound was prepared from (*S*)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methylimidazolidine-2,4-dione (**43**) (62.0 mg, 0.2 mmol) according to the general procedure. White solid.Yield: 40.5 mg, 0.15 mmol, 74%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (s, 1H), 2.79 (s, 3H), 2.46 – 1.97 (m, 2H), 1.84 (d, *J* = 2.5 Hz, 1H), 1.75 – 1.51 (m, 1H), 1.28 (d, *J* = 14.7 Hz, 10H), 1.01 – 0.76 (m, 3H).^{13}C NMR (75 MHz, MeOD) δ: 176.4, 175.9, 156.8, 69.5, 35.0, 31.8, 30.0, 29.3, 28.7, 24.8, 23.4, 22.9, 14.4. UPLC-DAD-QTOF: $C_{13}H_{23}N_2O_4$ $[M+H]^+$ calcd.: 271.1652, found: 271.1658.

5.4.6.3. **Synthesis of aldehyde 46.**

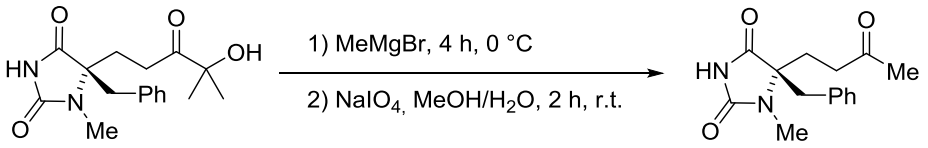


41 **46**

BH_3·THF complex (1M in THF, 0.6 mL, 0.6 mmol, 2 equiv.) was added to a solution of (*S*)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethylimidazolidine-2,4-dione (**41**) (74 mg, 0.3 mmol, 1 equiv.) in dry THF (2 mL) at 0 °C and the resulting solution was stirred at the same temperature for 2 h. The reaction was monitored by TLC (hexane/ethyl acetate, 1:1). After reaction completion, MeOH (1 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were evaporated under reduced pressure and the residue thus obtained was solved in MeOH (2 mL) again. A suspension of sodium periodate $NaIO_4$ (320 mg, 1.5 mmol, 5 equiv.) in water (1 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 30 min and solvents were evaporated under reduced pressure. Water (6 mL) was added to the crude product and the resulting mixture was

extracted with ethyl acetate (3 × 6 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel flash column chromatography (hexane/ethyl acetate, 80:20 to 0:100) affording title product **46** as a white solid. Yield: 48 mg, 0.26 mmol, 87%. $[\alpha]_D^{25}$= –1.83 (*c*= 1.00, 99 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.75 (s, 1H), 8.40 (s, 1H), 2.82 (s, 3H), 2.51 – 2.25 (m, 2H), 2.18 – 1.95 (m, 2H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.7, 175.9, 155.2, 65.2, 38.1, 27.0, 24.5, 21.5. UPLC-DAD-QTOF: $C_8H_{13}N_2O_3$ $[M+H]^+$ calcd.: 185.0921, found: 185.0919.

5.4.6.4. **Synthesis of ketone 47.**



MeMgBr (3M in Et_2O, 0.5 mmol, 5 equiv.) was added to a solution of α-hydroxy ketone **41** (107 mg, 0.34 mmol, 1 equiv.) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at the same temperature until the reaction was finished (monitored by TLC). Then a saturated aqueous solution of NH_4Cl (9 mL) was added at 0 °C and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The solvents were evaporated under reduced pressure and the residue thus obtained was solved in MeOH (1.8 mL). A suspension of sodium periodate $NaIO_4$ (321 mg, 1.5 mmol, 5 equiv.) in water (0.9 mL) was added to the solution at room temperature. The reaction mixture was stirred at the same temperature for 30 min and solvents were evaporated under reduced pressure. Water (9 mL) was added to the crude product and the resulting mixture was extracted with ethyl acetate (3 × 9 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, affording directly the pure product **47** without the need for further purification. Yield: 74 mg, 0.27 mmol, 79%. $[\alpha]_D^{25}$= +23.1 (*c*= 1.00, 96 % *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.31 – 7.00 (m, 5H), 3.04 (dd, *J* = 44.6, 14.3 Hz, 2H), 2.91 (s, 3H), 2.52 – 2.27 (m, 1H), 2.26 – 2.19 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.3, 174.8, 155.4, 133.7, 129.6, 128.8, 127.7, 70.2, 40.7, 37.3, 30.3, 28.1, 25.1.UPLC-DAD-QTOF: $C_{15}H_{19}N_2O_3$ $[M+H]^+$ calcd.: 275.1390, found: 275.1396.

5.4.7. ^{1}H NMR studies.

5.4.7.1. Catalyst–substrate interactions

^{1}H NMR spectra of each of the following compounds in $CDCl_3$ at –10 °C (0.02 M) were recorded: (i) nitrostyrene **2a**, (ii) 1*H*-imidazol-4(5*H*)-one **16a** and (iii) catalyst **C7**. Sub-sequently, ^{1}H NMR spectra of the following mixtures were recorded under the same conditions (0.02 M in $CDCl_3$ at –10 °C): (iv) **C7**/**16a** (1:1 mixture), (v) **C7**/**2a** (1:1 mixture), and (vi) **C7**/**2a** (1:1 mixture) + 1 equivalent **16a**. The aromatic portion of the spectra (i) to (vi) are depicted below. Note the downfield shift of proton H_A of catalyst **C7** upon addition of imidazolone **16a**, regardless of the presence (vi) or absence (iv) of nitrostyrene.

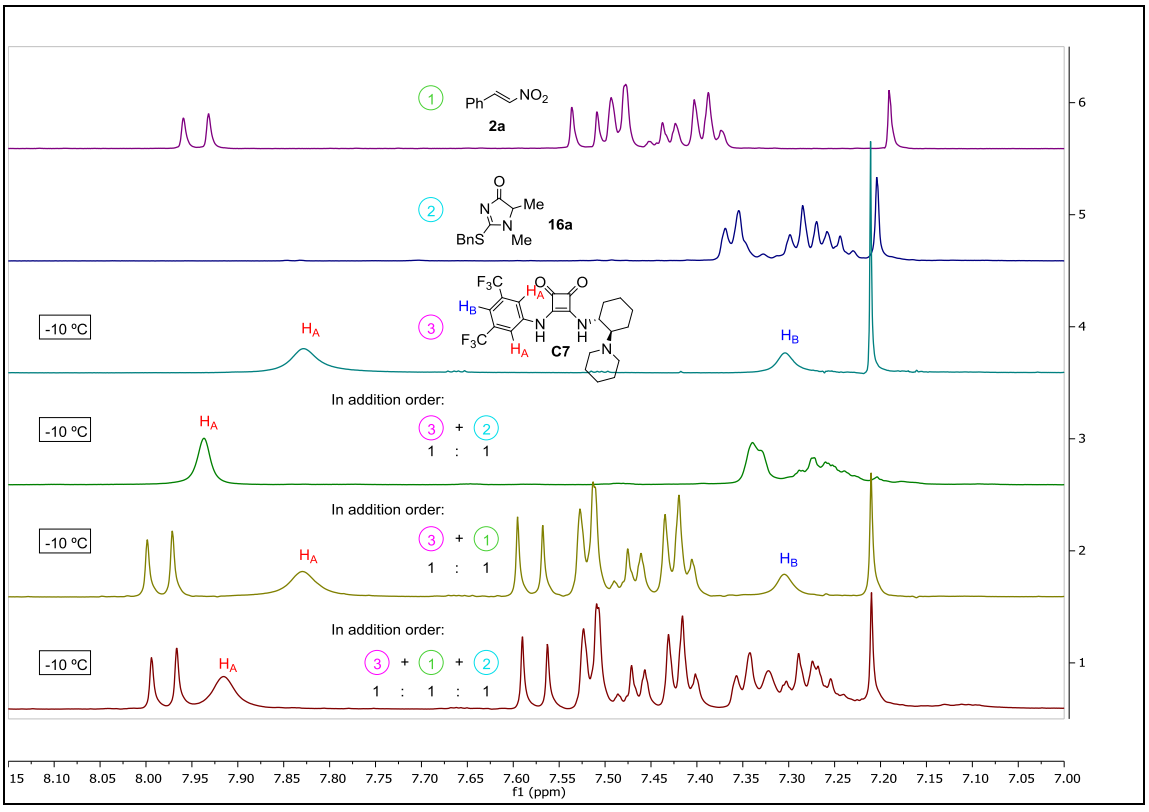
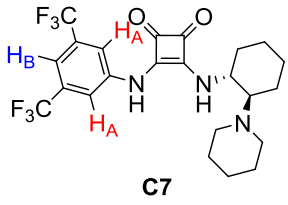


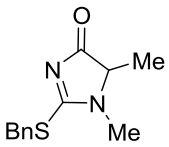
Figure 44. 1H NMR spectra (aromatic portion) of pure samples of compounds **C7**, **16a** and **2a** (0.02 M in CDCl3 at –10 °C) and some of their mixtures.

5.4.7.2. **Catalyst saturation**

In an independent study, the ^{1}H NMR spectra of catalyst **C7** (0.02 M in $CDCl_3$ at –10 °C) were recorded in the presence of increasing amounts of 1*H*-imidazol-4(5*H*)-one **16a** (increments of 0.25 equivalent until saturation), and the chemical shift of the aromatic ortho protons H_A was monitored.



C7



16a

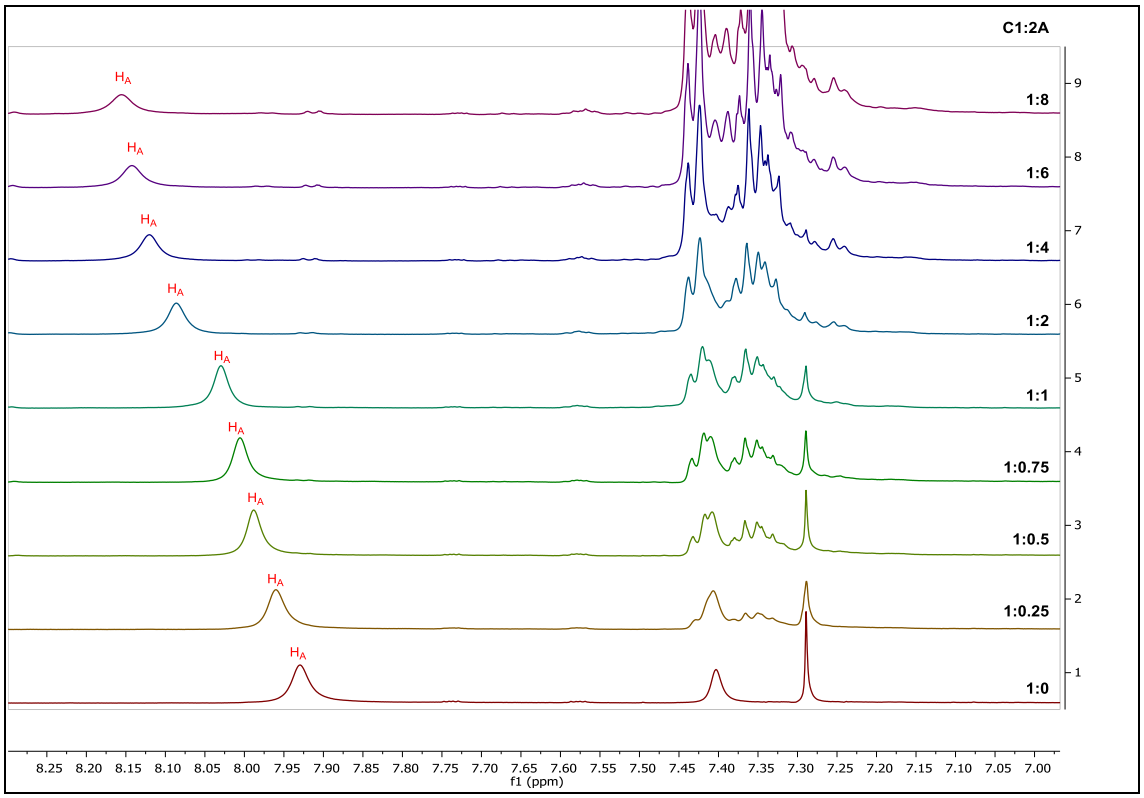
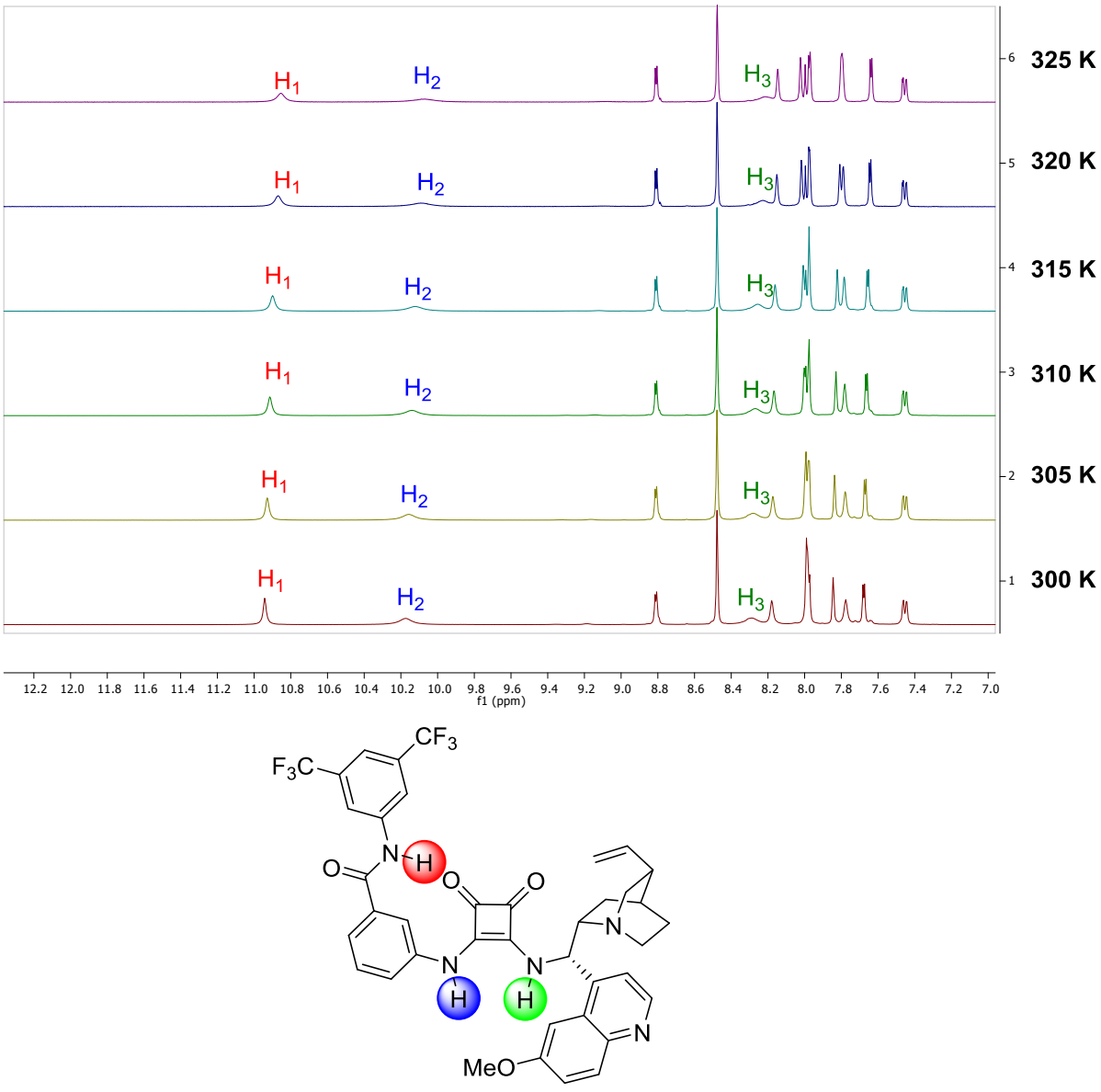


Figure 45. ^{1}H NMR spectra (aromatic portion) of **C7** (0.02 M) in the presence of vari-able amounts (from none to 8 equivalents) of **16a** (recorded in $CDCl_3$ at –10 °C).

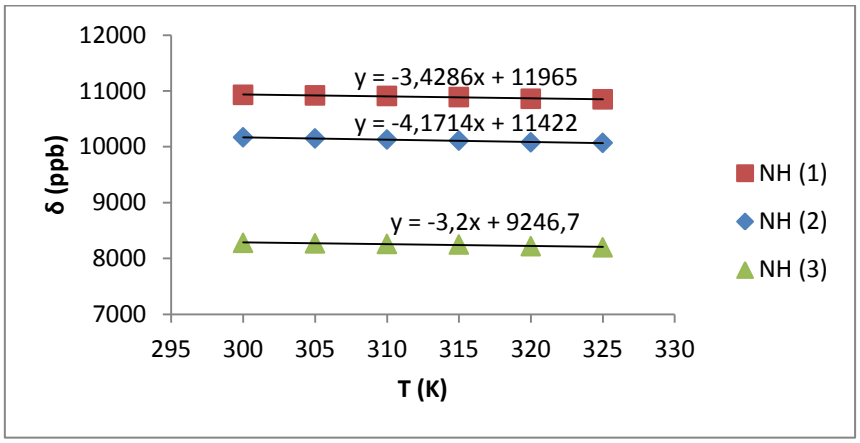
5.4.7.3. **Conformational analysis of C9 through *H*-bond thermal gradient study**

A study was performed measuring the temperature gradient of the *NH* protons of catalyst **C9** (0.02 M in $CDCl_3$) Measurement were made from 300 to 325 K, calculating their thermal coefficient in 5 K intervals. Values closer to $\Delta\delta/\Delta T(H_N) = -2.0$ are indicative of intramolecular *H*-bond. Values above $\Delta\delta/\Delta T(H_N) = -4.0$ indicate that no *H*-bond is occurring.[364] The values obtained for **C9** ($\Delta\delta/\Delta T(H_1) = -3.4$; $\Delta\delta/\Delta T(H_2) = -4.2$; $\Delta\delta/\Delta T(H_3) = -3.2$) indicate that H_1 and H_3 have a weak *H*-bond interaction, although the values are not high enough to confirm an intramolecular *H*-bond.



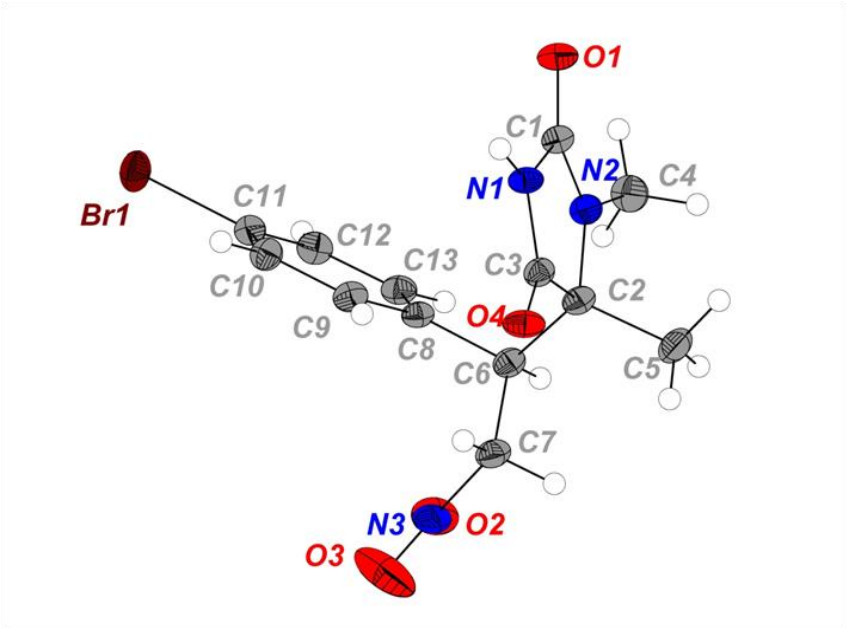
[364] Kessler, H. *Angew. Chem. Int. Ed.* **1982**, *21*, 512–523.

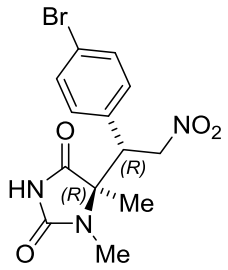
	δ (ppb)		
T (K)	***NH* (1)**	***NH* (2)**	***NH* (3)**
300	10930	10170	8280
305	10920	10150	8270
310	10910	10130	8260
315	10890	10110	8250
320	10860	10080	8220
325	10850	10070	8200



5.4.8. **X-Ray Analysis: ORTEP diagrams of compounds 28 and 44.**

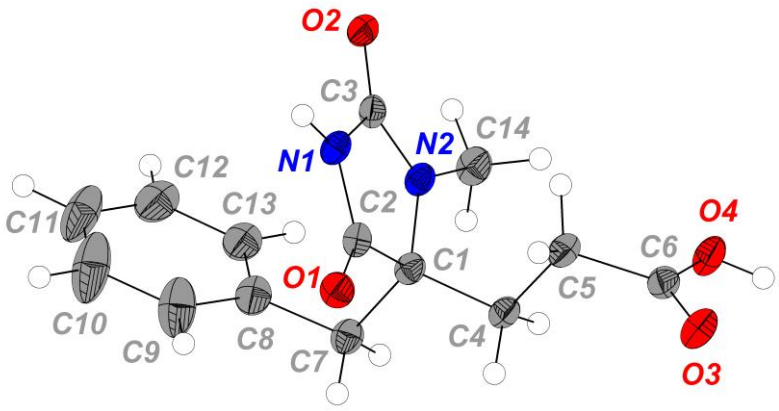
CCDC-1044978 contains the supplementary crystallographic data for the structural analysis of **28**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

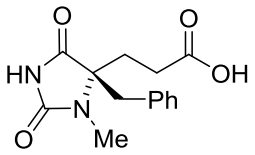




28

CCDC-1044937 contains the supplementary crystallographic data for the structural analysis of **44**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

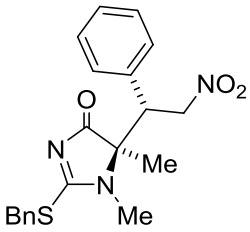




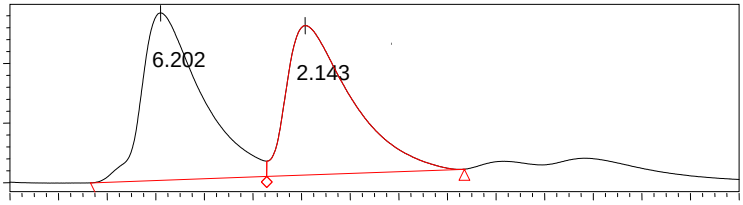
44

5.4.9. **HPLC chromatograms**

(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19aa)

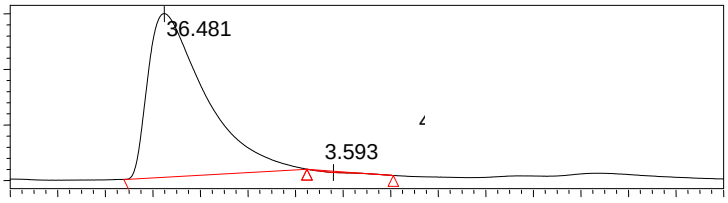


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 36.5 min (major.) and 45.6 min (min.). Processed Channel Descr.: PDA 239.0 nm).



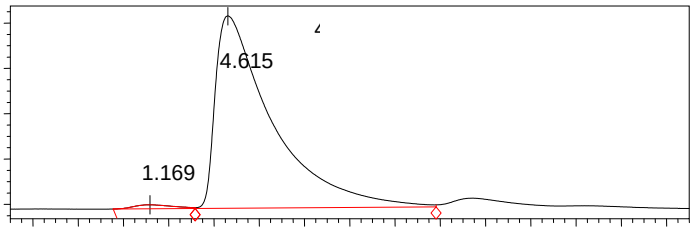
	Retention Time	% Area
1	36.202	50.99
2	42.143	49.01

Using Cat. C7



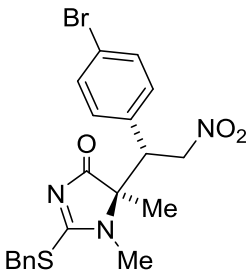
	Retention Time	% Area
1	36.481	99.57
2	43.593	0.43

Using Cat. C8

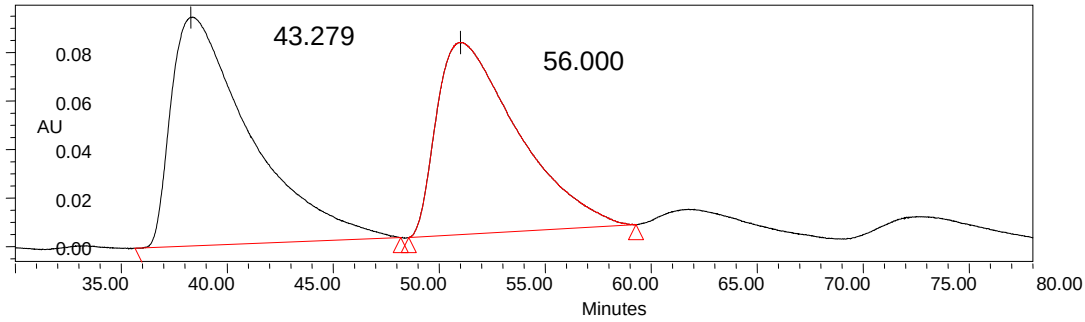


	Retention Time	% Area
1	41.169	1.39
2	44.615	98.61

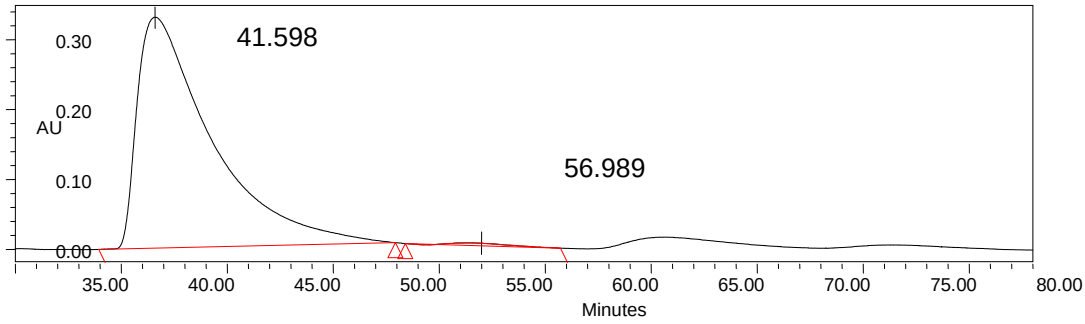
(*R*)-2-(Benzylthio)-5-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-1,5-dimethyl-1*H*-imidazol-4(5*H*)-one (19ac)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 41.6 min (major.) and 57.0 min (min.). Processed Channel Descr.: PDA 210.0 nm).

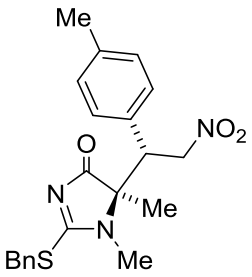


	Retention Time	% Area
1	43.279	53.71
2	56.000	46.29

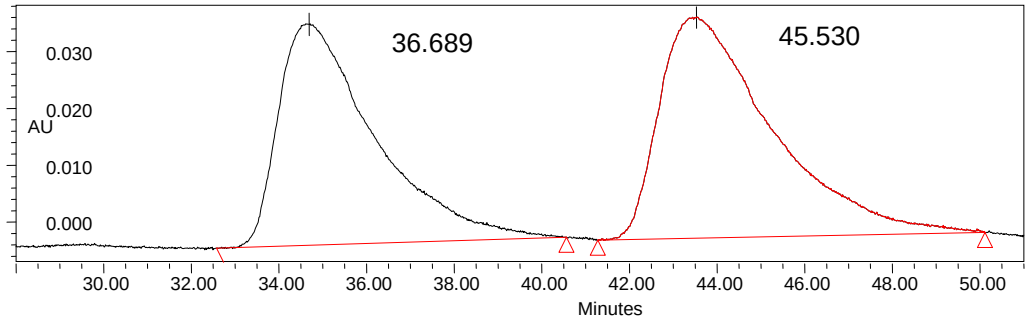


	Retention Time	% Area
1	41.598	99.12
2	56.989	0.88

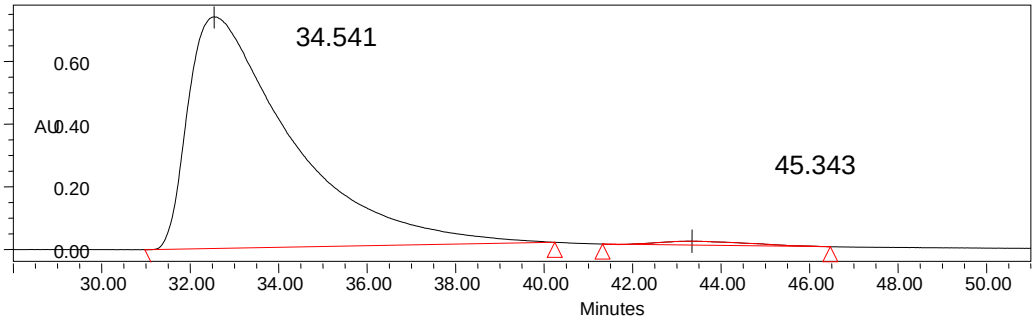
(*R*)-2-(Benzylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19ad)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 34.5 min (major.) and 45.3 min (min.). Processed Channel Descr.: PDA 239.0 nm).

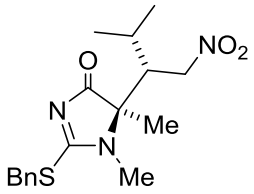


	Retention Time	% Area
1	36.689	46.17
2	45.530	53.83

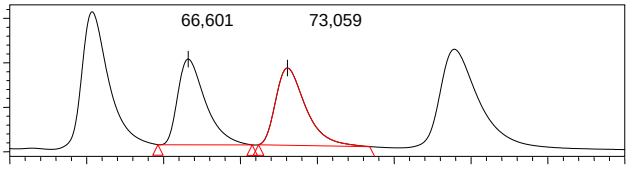


	Retention Time	% Area
1	34.541	98.55
2	45.343	1.45

(S)-2-(Benzylthio)-1,5-dimethyl-5-((*S*)-3-methyl-1-nitrobutan-2-yl)-1*H*-imidazol-4(5*H*)-one (19aj)

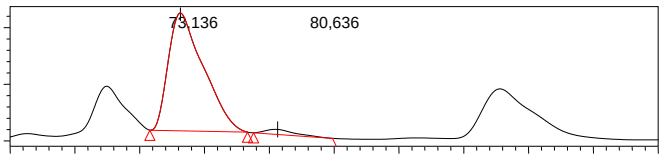


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 68.9 min (min.) and 75.3 min (major.). Processed Channel Descr.: PDA 254.0 nm).



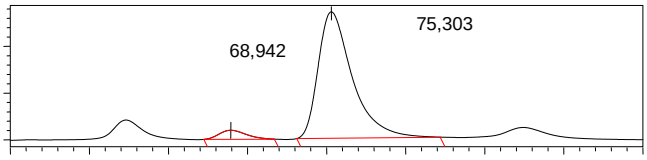
	Retention Time	% Area
1	66.601	50.49
2	73.059	49.51

Using Cat. C7



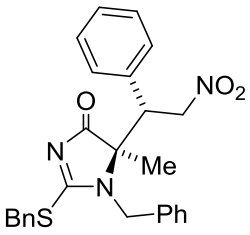
	Retention Time	% Area
1	73.136	96.56
2	80.636	3.44

Using Cat. C8

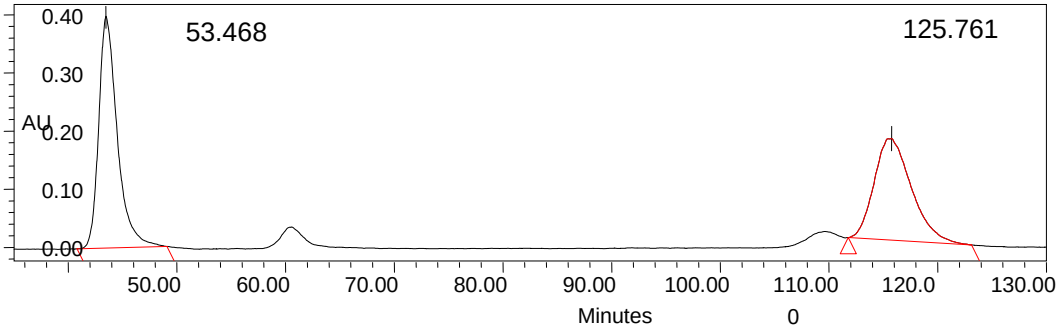


	Retention Time	% Area
1	68.942	5.36
2	75.303	94.64

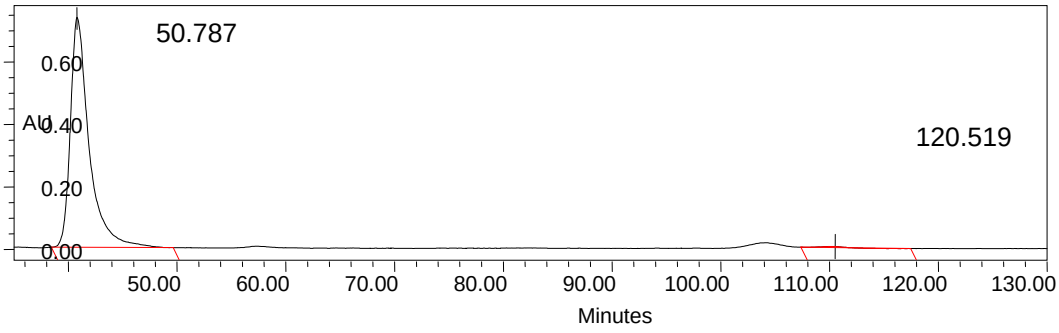
(*R*)-1-Benzyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ba)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 50.8 min (major.) and 120.5 min (min.). Processed Channel Descr.: PDA 210.0 nm).

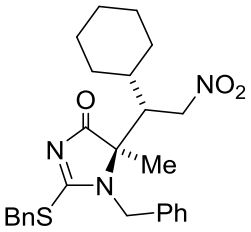


	Retention Time	% Area
1	53.468	53.05
2	125.761	46.95

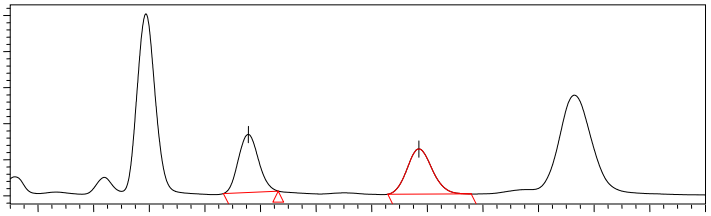


	Retention Time	% Area
1	50.787	99.72
2	125.362	0.28

(*S*)-1-Benzyl-2-(benzylthio)-5-((*S*)-1-cyclohexyl-2-nitroethyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (19bk)

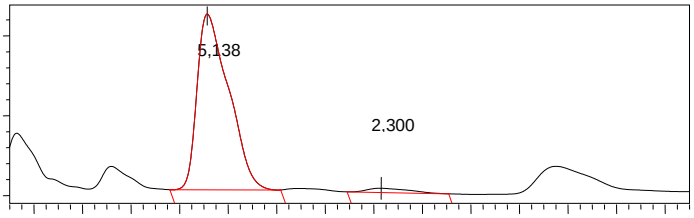


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.5 min (min.) and 29.7 min (major.). Processed Channel Descr.: PDA 254.0 nm).



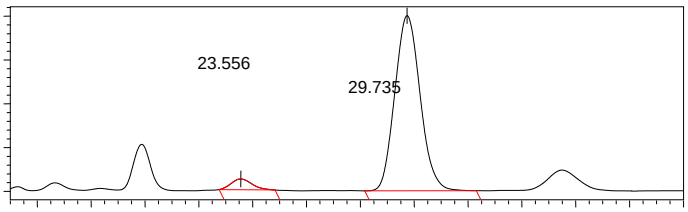
	Retention Time	% Area
1	23.563	50.52
2	29.693	49.48

Using Cat. C7



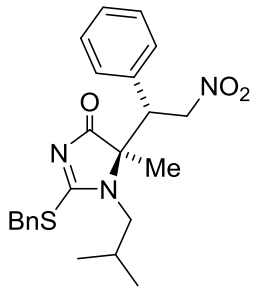
	Retention Time	% Area
1	25.138	96.89
2	32.300	3.11

Using Cat. C8

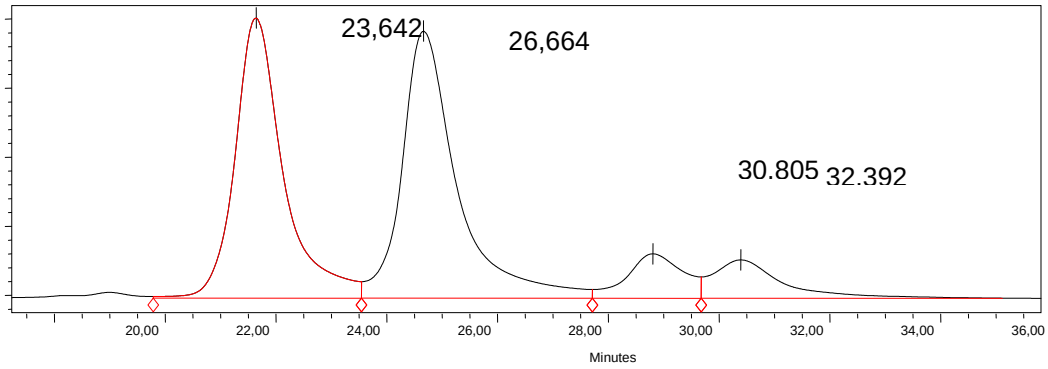


	Retention Time	% Area
1	23.556	4.80
2	29.735	95.20

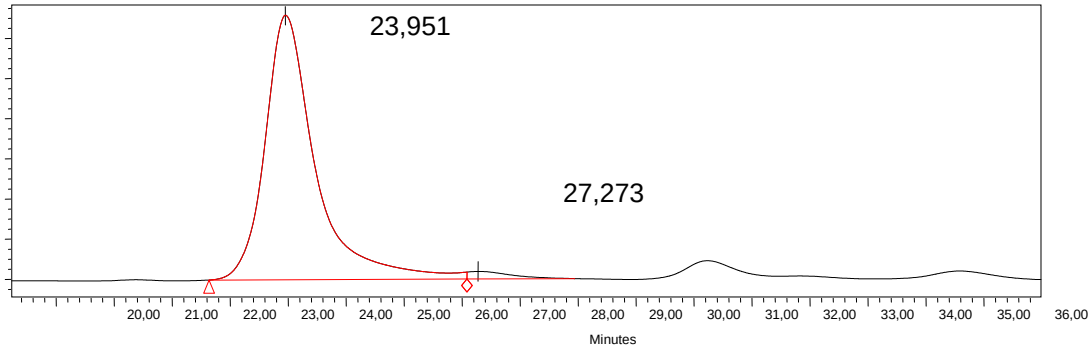
(R)-2-(benzylthio)-1-isobutyl-5-methyl-5-((R)-2-nitro-1-phenylethyl)- 1*H*-imidazol-4(5*H*)-one (19ca)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol/ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 24.0 min (major.) and 27.3 min (min.). Processed Channel Descr.: PDA 209.8 nm).

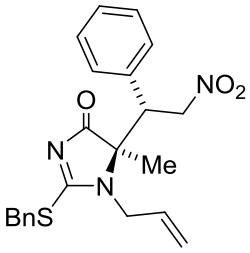


	Retention Time	% Area
1	23.642	41.15
2	26.664	44.04

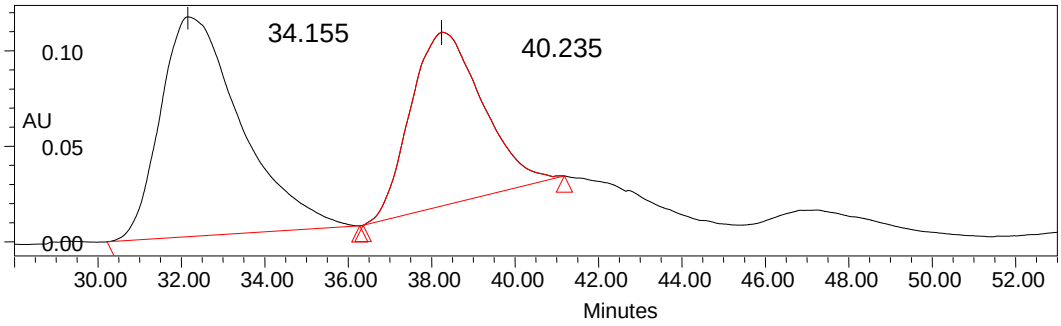


	Retention Time	% Area
1	23.956	96.26
2	27.295	3.74

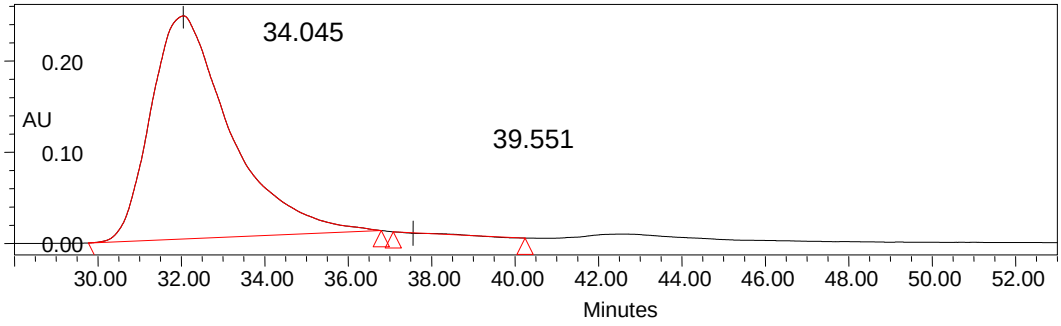
(*R*)-1-Allyl-2-(benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19da)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 34.0 min (major.) and 39.6 min (min.). Processed Channel Descr.: PDA 242.0 nm).

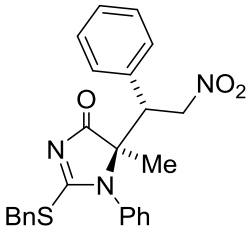


	Retention Time	% Area
1	34.155	58.62
2	40.235	41.38

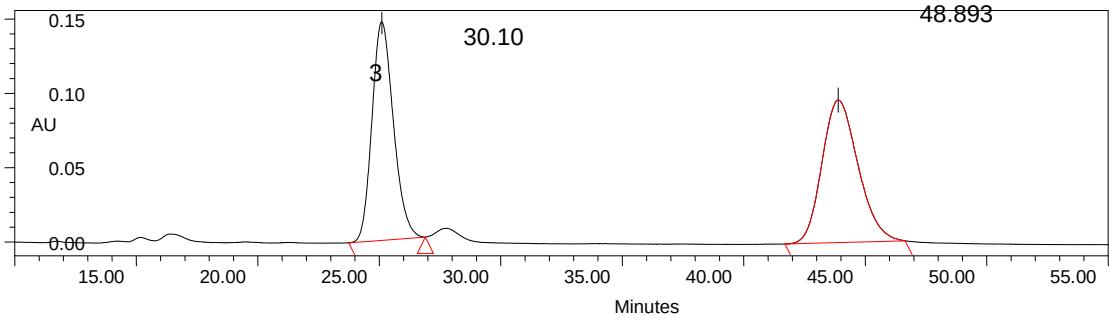


	Retention Time	% Area
1	34.045	99.84
2	39.551	0.16

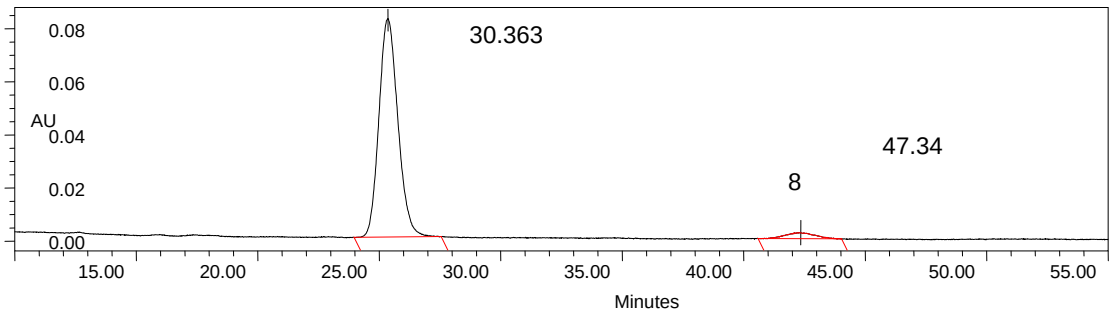
(*R*)-2-(Benzylthio)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-imidazol-4(5*H*)-one (19ea)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 30.4 min (major.) and 47.3 min (min.). Processed Channel Descr.: PDA 250.0 nm).

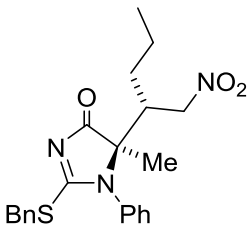


	Retention Time	% Area
1	30.103	47.67
2	48.893	52.33

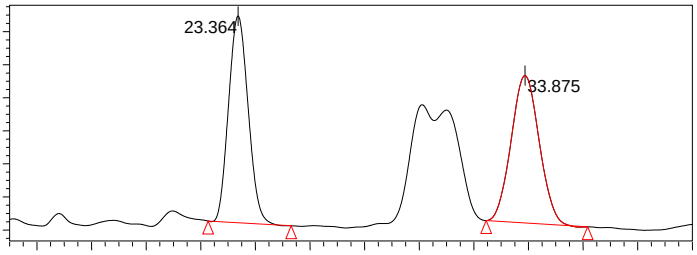


	Retention Time	% Area
1	30.363	95.89
2	47.348	4.11

(*S*)-2-(Benzylthio)-5-methyl-5-((*S*)-1-nitropentan-2-yl)-1-phenyl-1H-imidazol-4(5H)-one (19el)

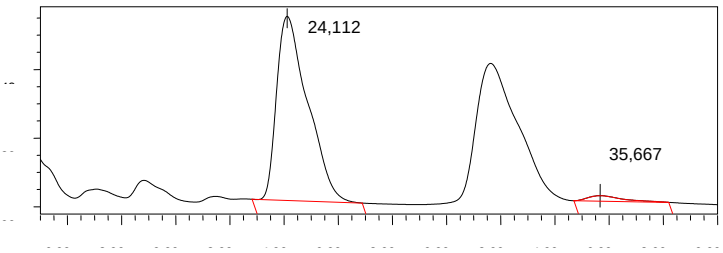


The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 23.2 min (min.) and 33.6 min (major.). Processed Channel Descr.: PDA 247.0 nm).



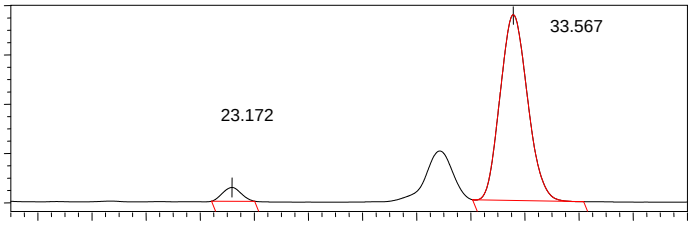
	Retention Time	% Area
1	23.364	49.49
2	33.875	50.51

Using Cat. C7



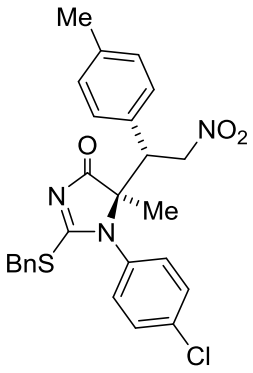
	Retention Time	% Area
1	24.112	96.79
2	35.667	3.21

Using Cat. C8

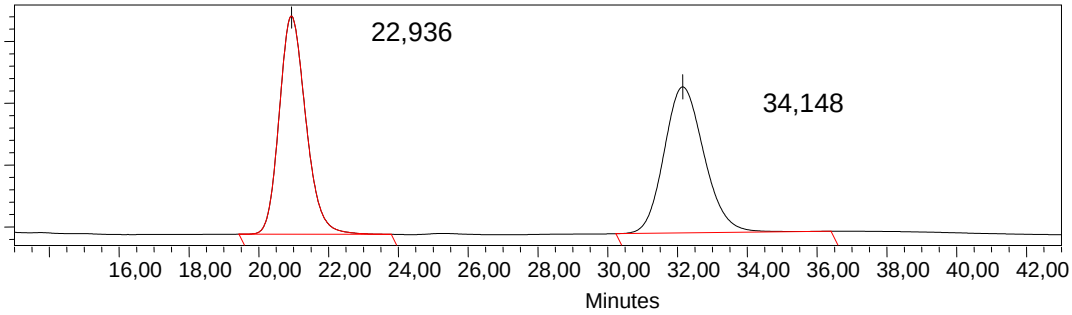


	Retention Time	% Area
1	23.172	4.71
2	33.567	95.29

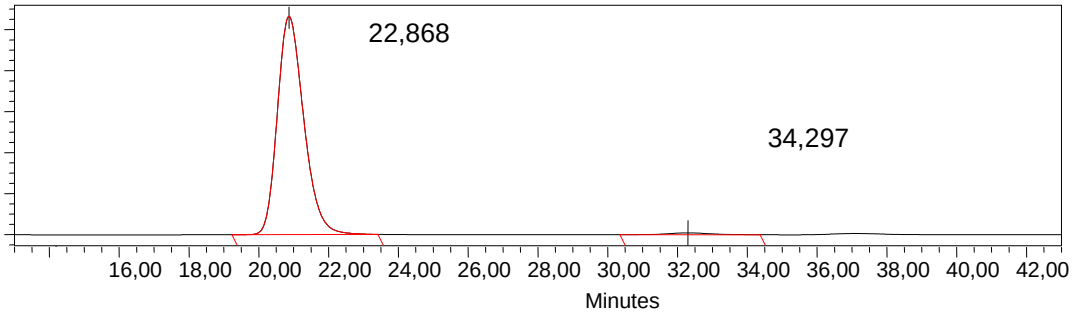
(*R*)-2-(Benzylthio)-1-(4-chlorophenyl)-5-methyl-5-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19fd)



The denantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 22.9 min (major.) and 34.3 min (min.). Processed Channel Descr.: PDA 255.2 nm).

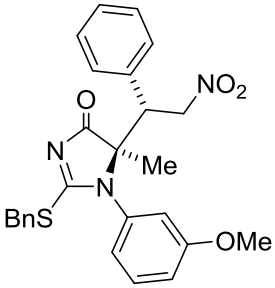


	Retention Time	% Area
1	22.936	49.96
2	34.148	50.04

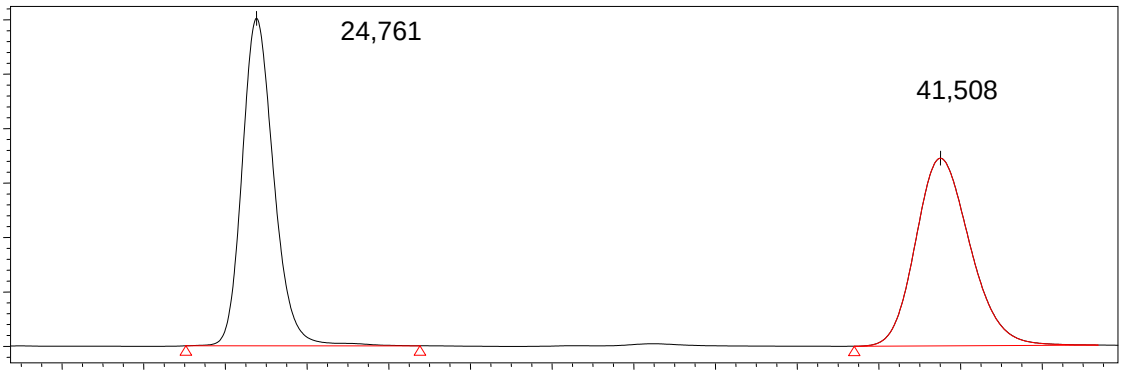


	Retention Time	% Area
1	22.868	98.70
2	34.297	1.30

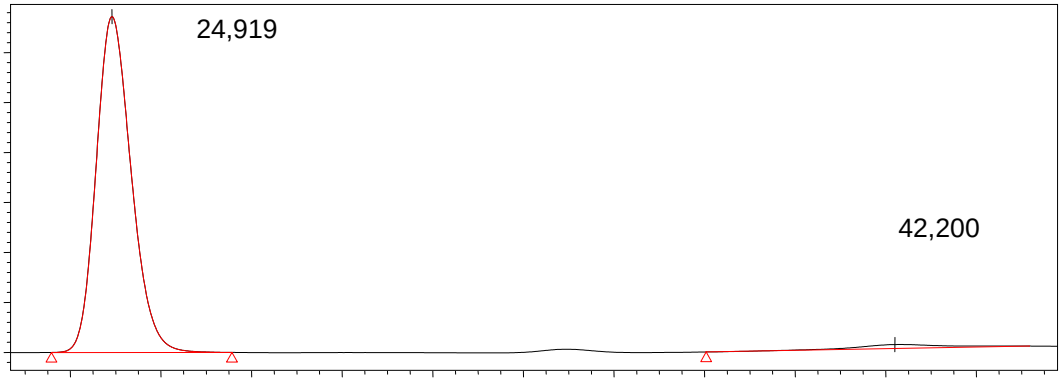
(*R*)-2-(Benzylthio)-1-(3-methoxyphenyl)-5-methyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (19ga)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 25.0 min (major.) and 35.0 min (min.). Processed Channel Descr.: PDA 255.2 nm).

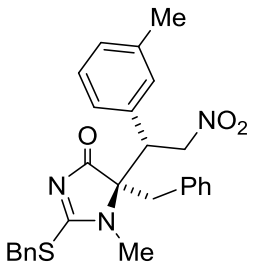


	Retention Time	% Area
1	24.761	50.34
2	41.508	49.66

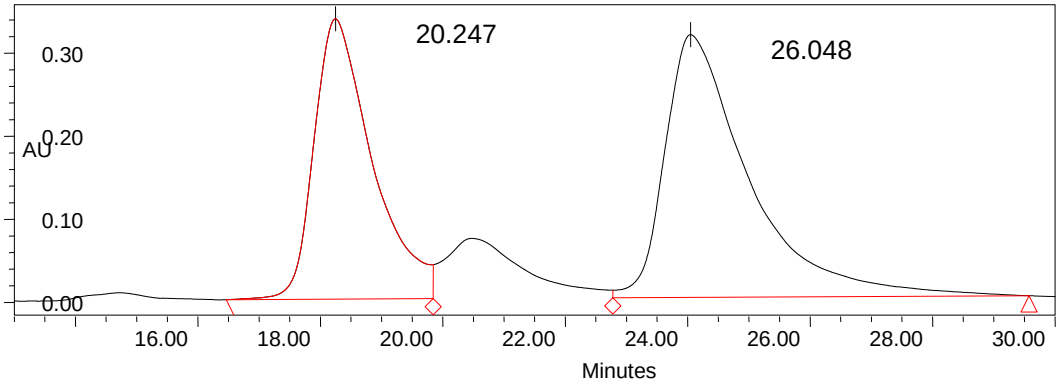


	Retention Time	% Area
1	24.919	97.63
2	42.200	2.37

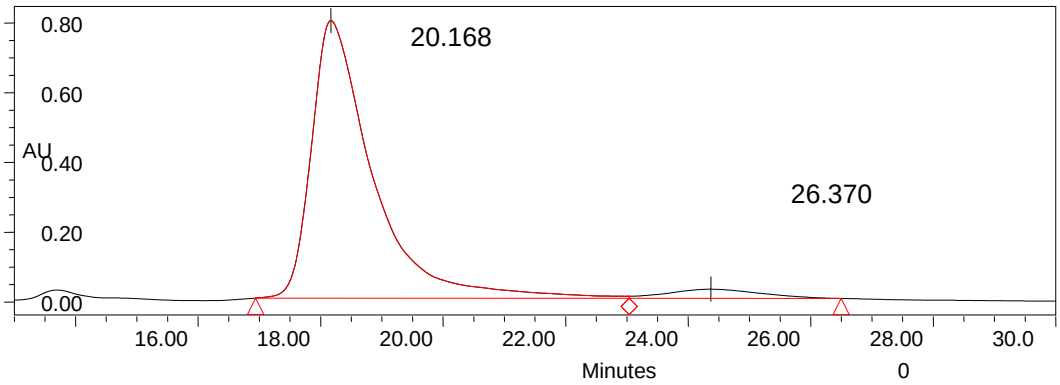
(*R*)-5-Benzyl-2-(benzylthio)-1-methyl-5-((*R*)-2-nitro-1-(*m*-tolyl)ethyl)-1*H*-imidazol-4(5*H*)-one (19hb)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 20.2 min (major.) and 26.4 min (min.). Processed Channel Descr.: PDA 242.0 nm).

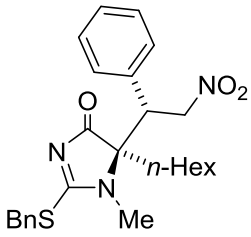


	Retention Time	% Area
1	20.247	42.50
2	26.048	57.50

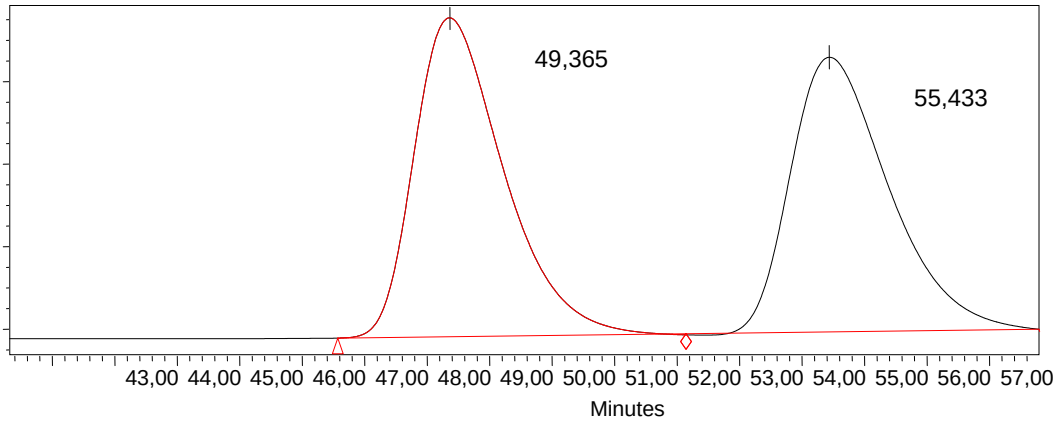


	Retention Time	% Area
1	20.168	95.25
2	26.370	4.75

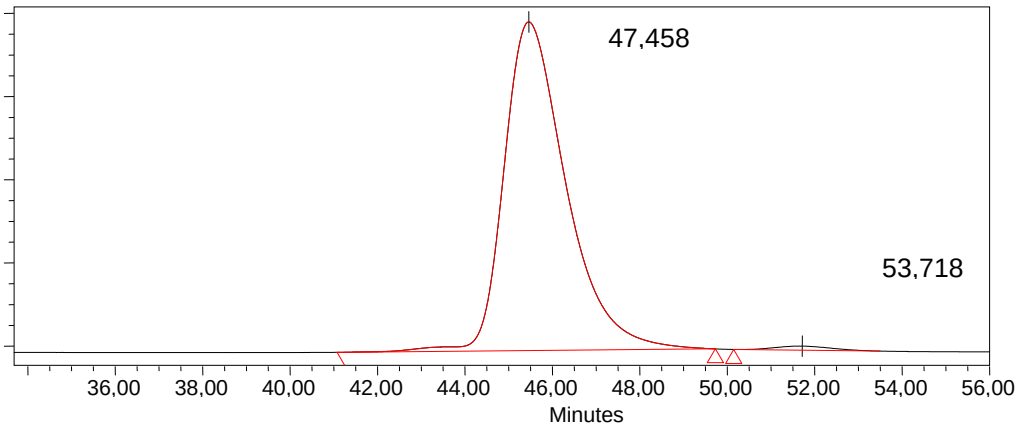
(*R*)-2-(benzylthio)-5-hexyl-1-methyl-5-((*R*)-2-nitro-1-phenylethyl)- 1*H*-imidazol-4(5*H*)-one (19ia)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 47.5 min (major.) and 53.7 min (min.). Processed Channel Descr.: PDA 254 nm).

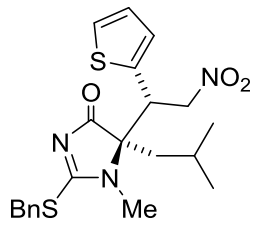


	Retention Time	% Area
1	49.365	50.33
2	55.433	49.67

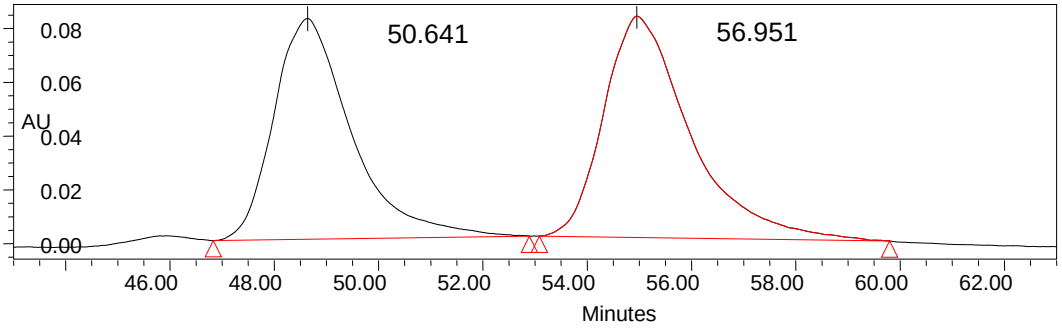


	Retention Time	% Area
1	47.458	98.27
2	53.718	1.73

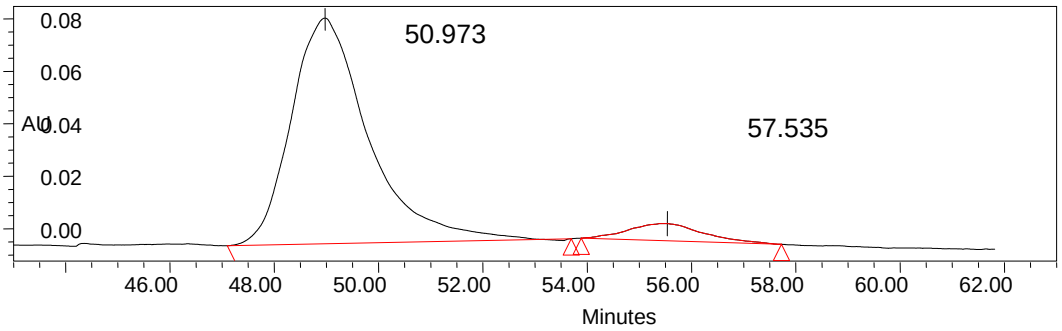
(*R*)-2-(Benzylthio)-5-isobutyl-1-methyl-5-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-1*H*-imidazol-4(5*H*)-one (19jg)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 50.9 min (major.) and 57.5 min (min.). Processed Channel Descr.: PDA 239.0 nm).

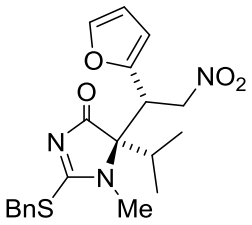


	Retention Time	% Area
1	50.641	47.28
2	56.951	52.72

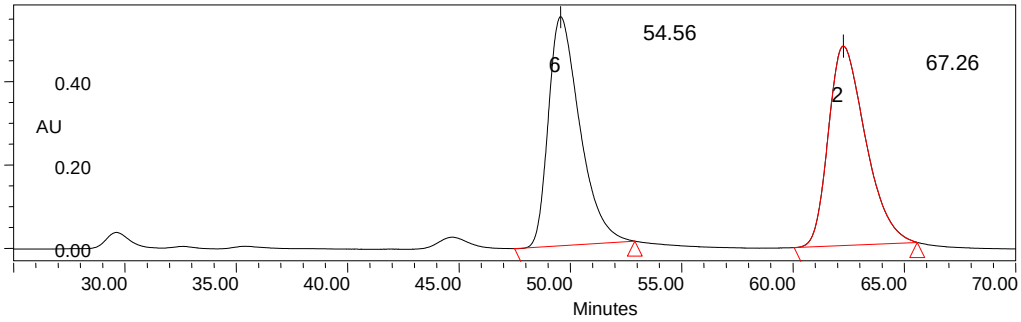


	Retention Time	% Area
1	50.973	93.16
2	57.535	6.84

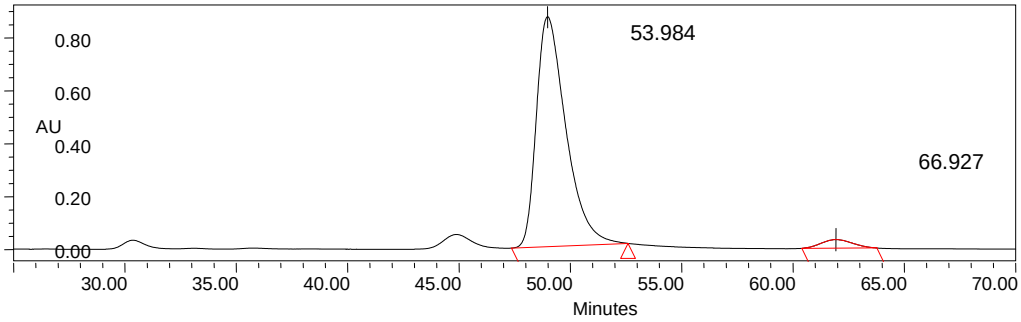
(*R*)-2-(Benzylthio)-5-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-isopropyl-1-methyl-1*H*-imidazol-4(5*H*)-one (19ke)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 59.0 min (major.) and 66.9 min (min.). Processed Channel Descr.: PDA 249.0 nm).

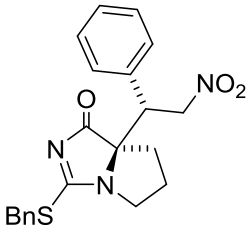


	Retention Time	% Area
1	54.566	49.29
2	67.262	50.71

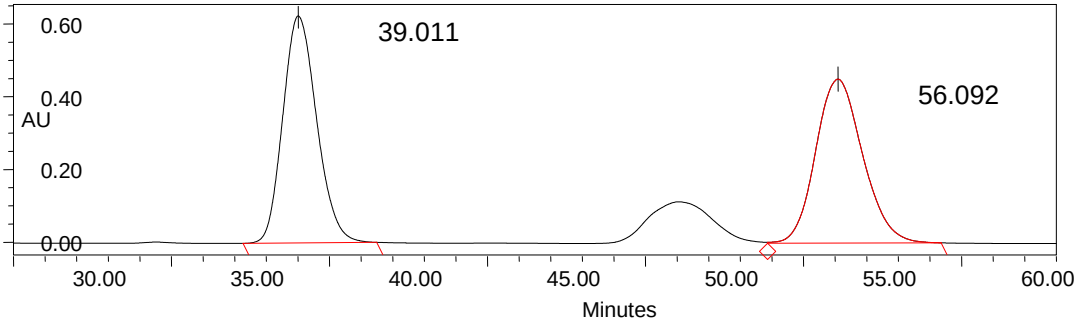


	Retention Time	% Area
1	53.984	96.22
2	66.927	3.78

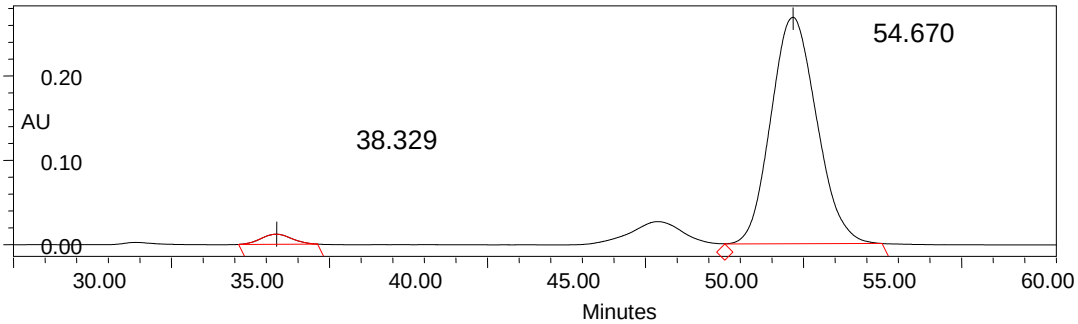
(*R*)-3-(benzylthio)-7a-((*R*)-2-nitro-1-phenylethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-one (19la)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 38.3 min (min.) and 54.7 min (major.). Processed Channel Descr.: PDA 242.0 nm).

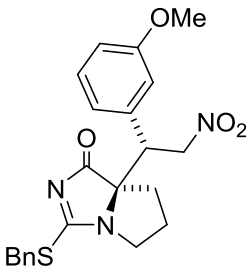


	Retention Time	% Area
1	39.011	49.95
2	56.092	50.05

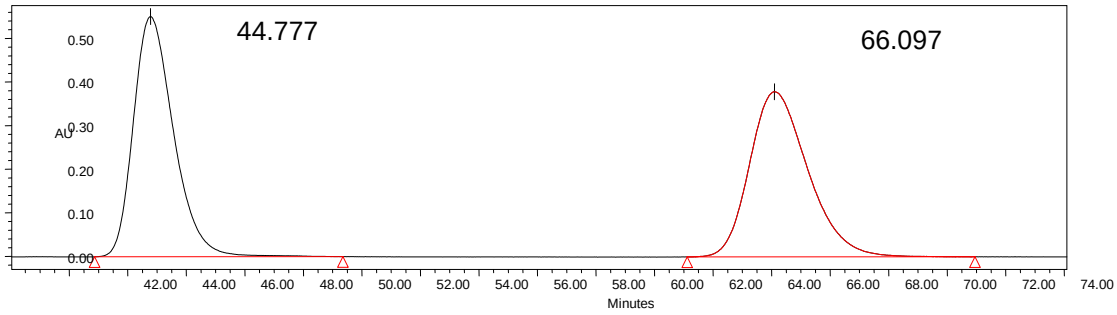


	Retention Time	% Area
1	38.329	2.91
2	54.670	97.09

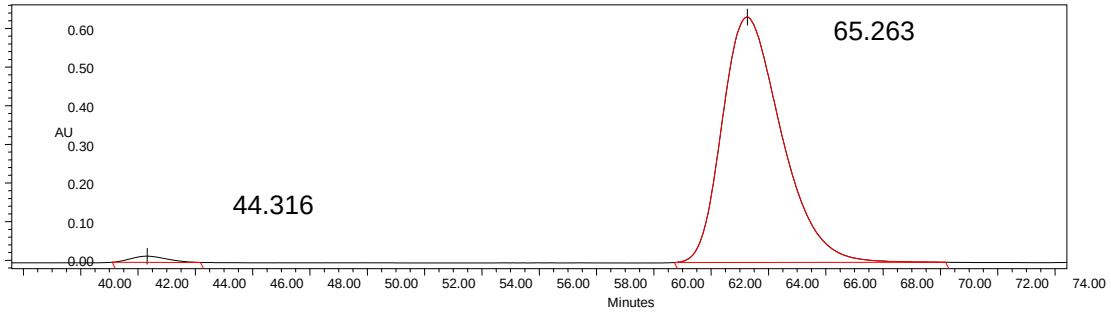
(*R*)-3-(Benzylthio)-7a-((*R*)-1-(3-methoxyphenyl)-2-nitroethyl)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[1,2-c]imidazol-1-one (19li)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 50/50, flow rate= 0.5 mL/min, retention times: 44.3 min (minor.) and 65.3 min (major.). Processed Channel Descr.: PDA 255.2 nm).

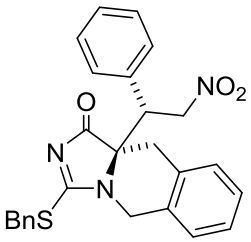


	Retention Time	% Area
1	44.777	50.10
2	66.097	49.90

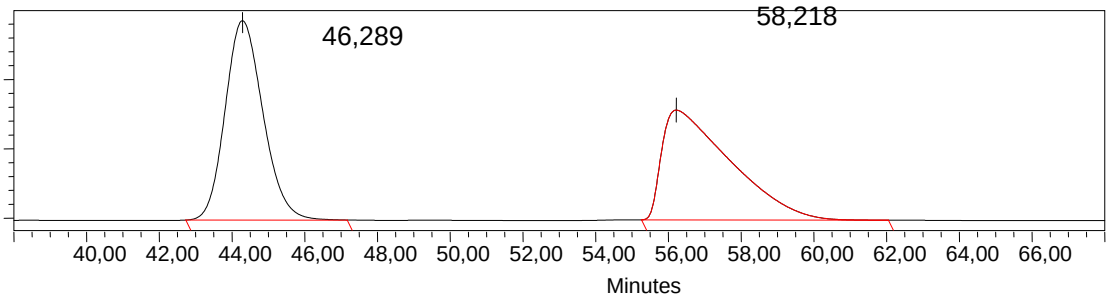


	Retention Time	% Area
1	44.316	1.48
2	65.263	98.52

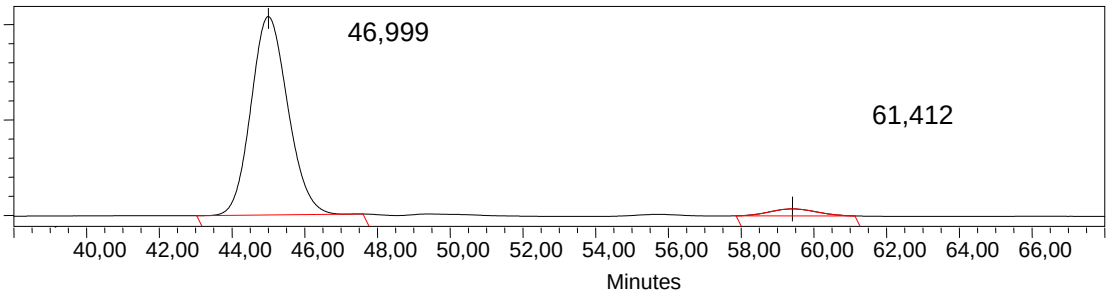
(*R*)-3-(Benzylthio)-10a-((*R*)-2-nitro-1-phenylethyl)-10,10a-dihydroimidazo[1,5-b]isoquinolin-1(5*H*)-one (19ma)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 47.0 min (major.) and 61.4 min (min.). Processed Channel Descr.: PDA 255.2 nm).

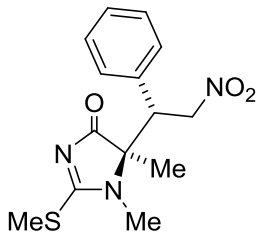


	Retention Time	% Area
1	46.289	50.09
2	58.218	49.91

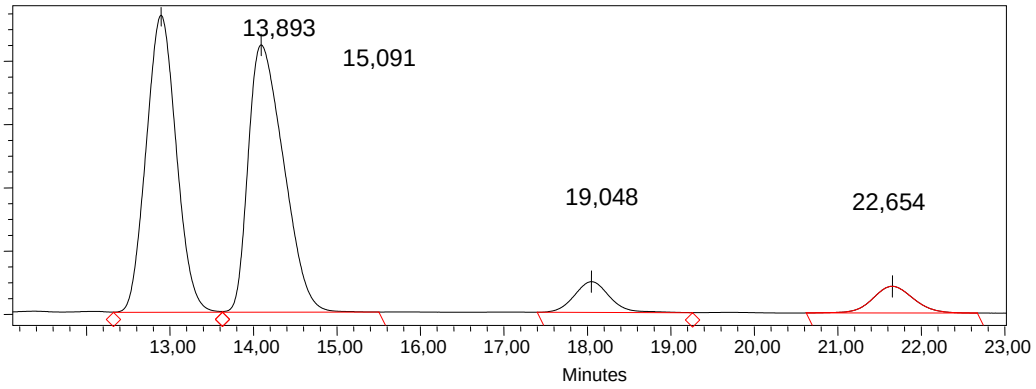


	Retention Time	% Area
1	46.999	95.71
2	61.412	4.29

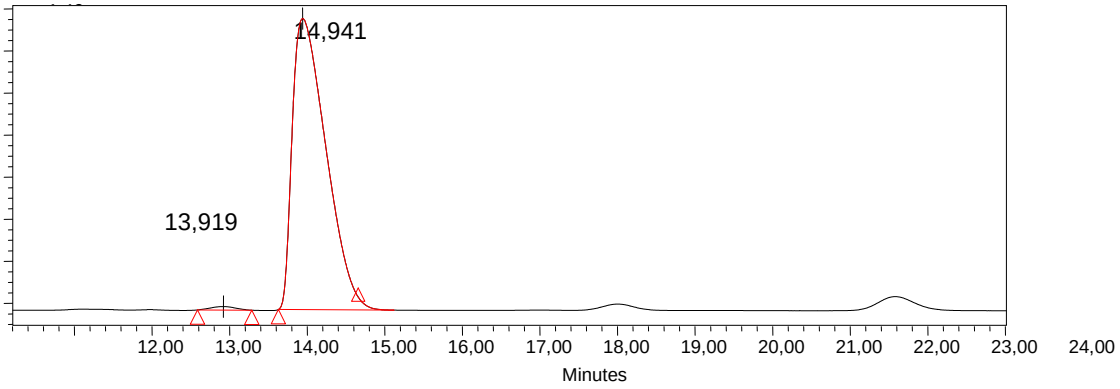
(*R*)-1,5-dimethyl-2-(methylthio)-5-((R)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (20)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/isopropanol 70/30, flow rate= 0.5 mL/min, retention times: 13.9 min (min.) and 14.9 min (major.). Processed Channel Descr.: PDA 254 nm).

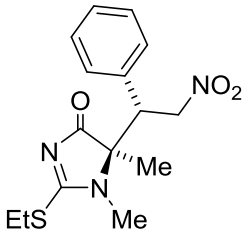


	Retention Time	% Area
1	13.893	48.70
2	15.091	51.30

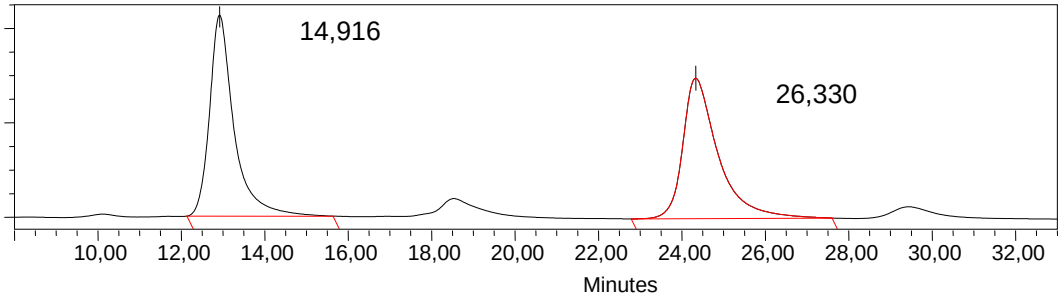


	Retention Time	% Area
1	13.919	0.77
2	14.941	99.23

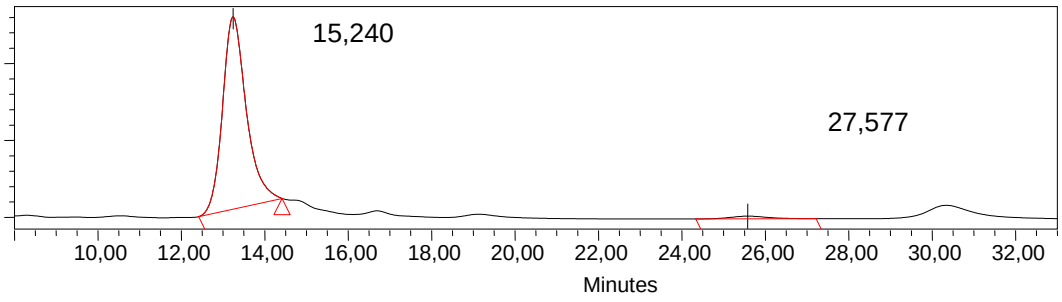
(*R*)-2-(Ethylthio)-1,5-dimethyl-5-((*R*)-2-nitro-1-phenylethyl)-1*H*-imidazol-4(5*H*)-one (21)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 75/25, flow rate= 0.5 mL/min, retention times: 15.2 min (major.) and 27.6 min (min.). Processed Channel Descr.: PDA 254 nm).

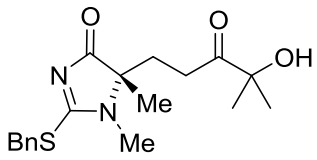


	Retention Time	% Area
1	14.916	49.79
2	26.330	50.21

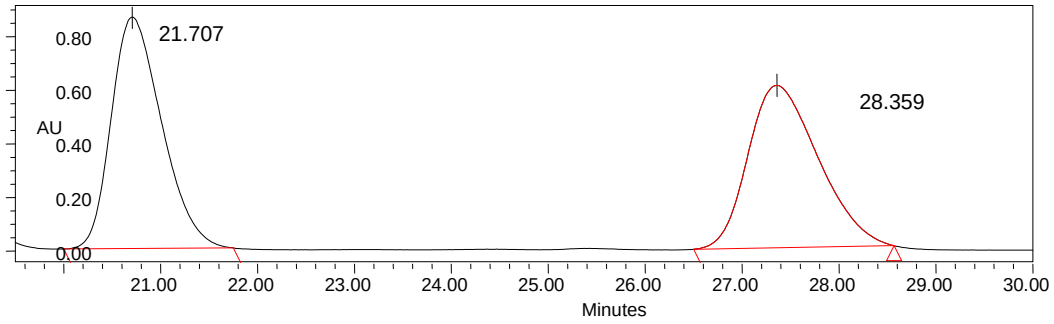


	Retention Time	% Area
1	15.240	97.82
2	27.577	2.18

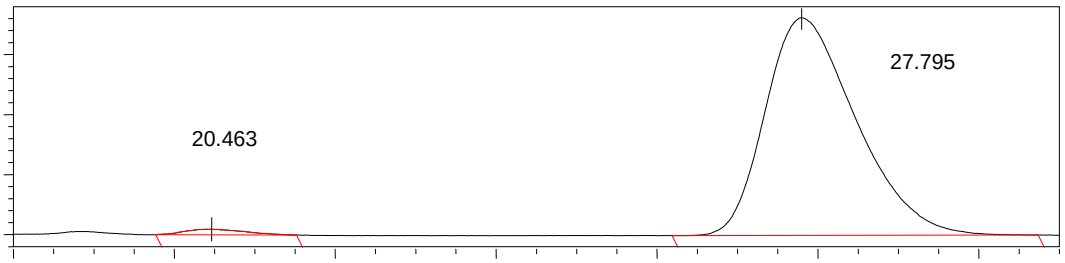
(*S*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1,5-dimethyl-1H-imidazol-4(5*H*)-one (40a)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 40/60, flow rate= 0.5 mL/min, retention times: 20.5 min (min.) and 27.8 min (major.). Processed Channel Descr.: PDA 238.0 nm).

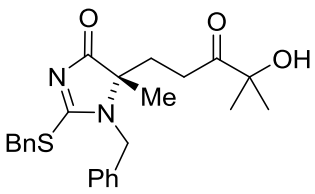


	Retention Time	% Area
1	21.707	50.65
2	28.359	49.35

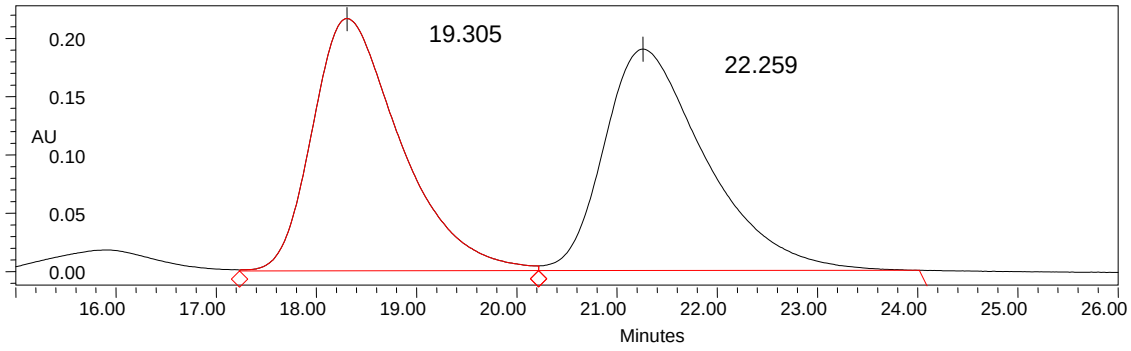


	Retention Time	% Area
1	20.463	1.68
2	27.795	98.32

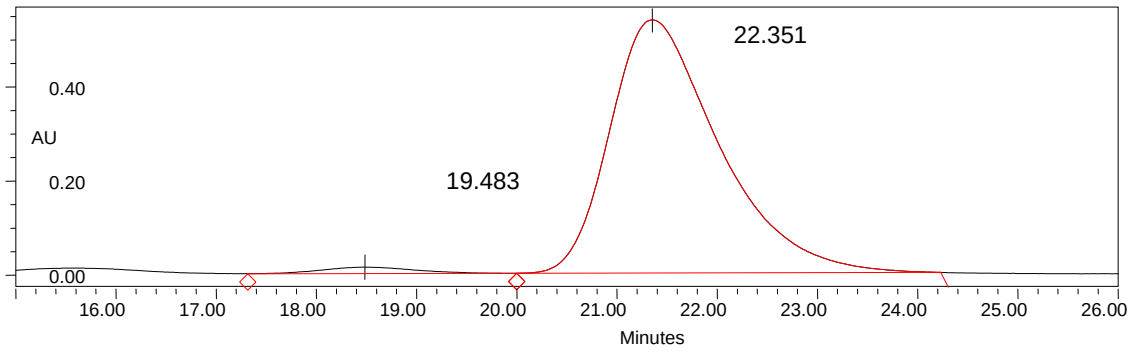
(*S*)-1-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (40b)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 19.5 min (min.) and 22.4 min (major.). Processed Channel Descr.: PDA 240.0 nm).

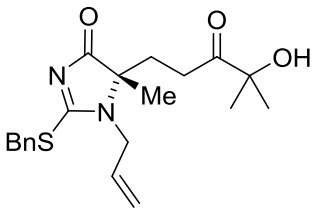


	Retention Time	% Area
1	19.305	49.76
2	22.259	50.24

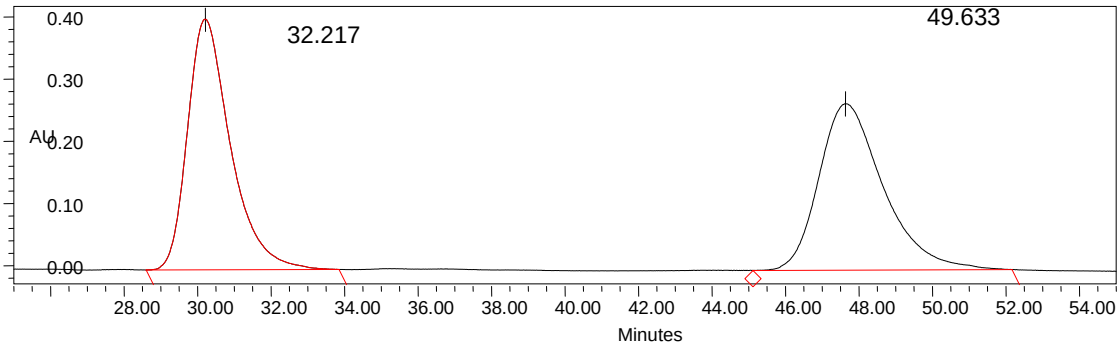


	Retention Time	% Area
1	19.483	2.15
2	22.351	97.85

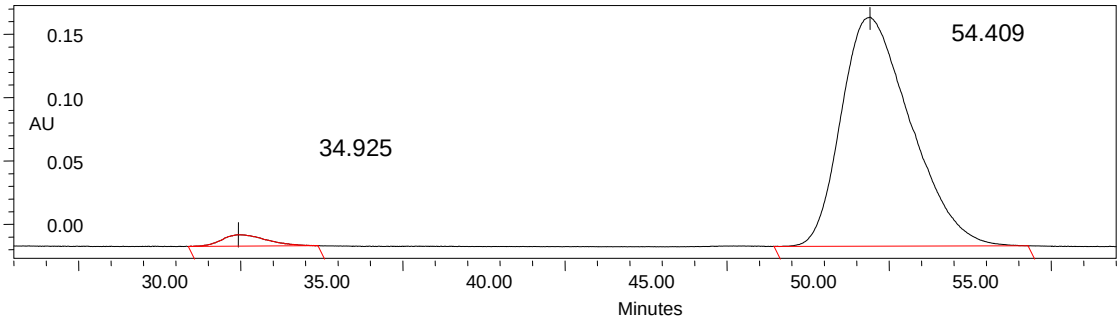
(*S*)-1-Allyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-methyl-1*H*-imidazol-4(5*H*)-one (40d)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 34.9 min (min.) and 54.4 min (major.). Processed Channel Descr.: PDA 239.0 nm).

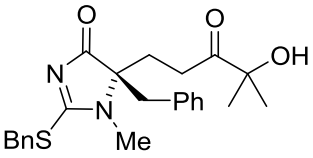


	Retention Time	% Area
1	32.217	50.17
2	49.633	49.83

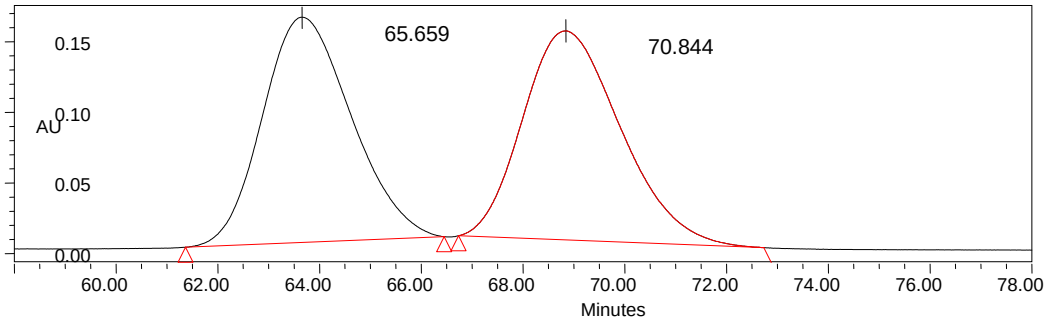


	Retention Time	% Area
1	34.925	3.07
2	54.409	96.93

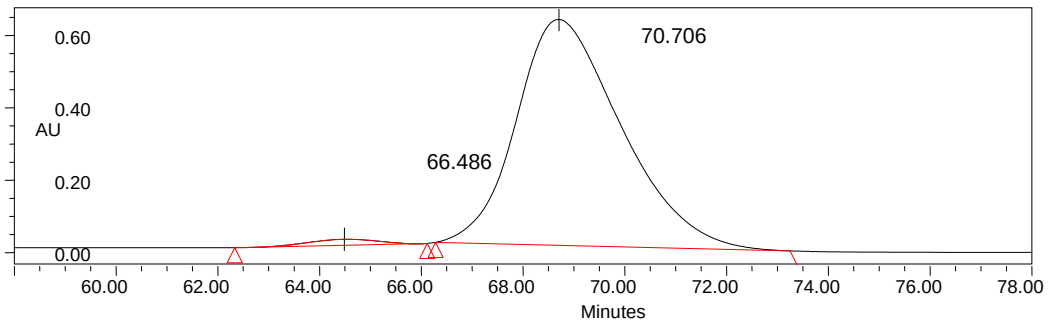
(*R*)-5-Benzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (40h)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 66.5 min (min.) and 70.7 min (major.). Processed Channel Descr.: PDA 239.0 nm).

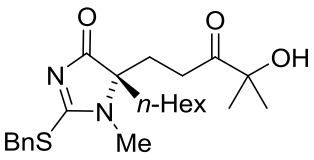


	Retention Time	% Area
1	65.659	49.44
2	70.844	50.56

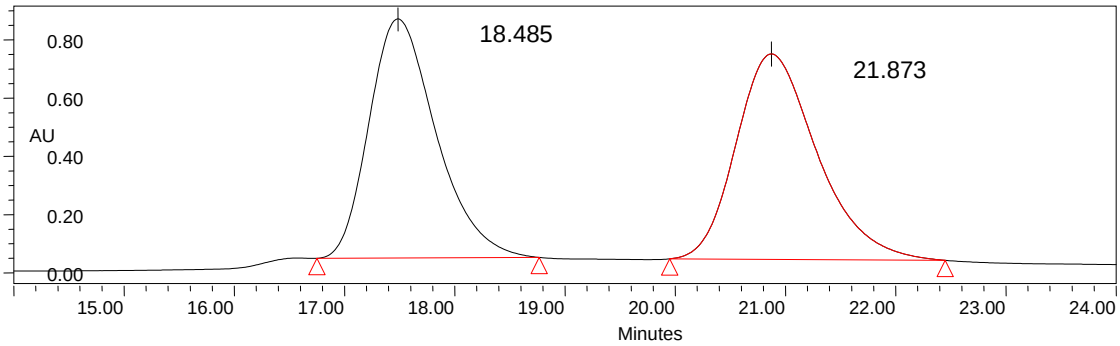


	Retention Time	% Area
1	66.486	1.69
2	70.706	98.31

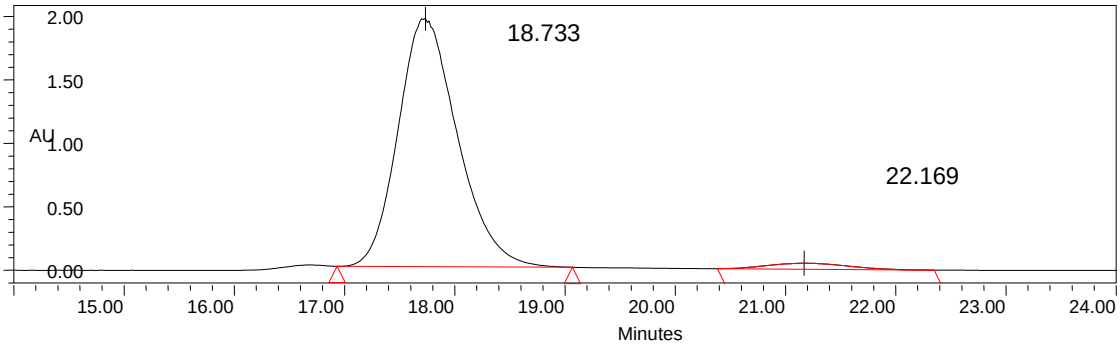
(*S*)-2-(Benzylthio)-5-hexyl-5-(4-hydroxy-4-methyl-3-oxopentyl)-1-methyl-1*H*-imidazol-4(5*H*)-one (40i)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 18.8 min (major.) and 22.2 min (min.). Processed Channel Descr.: PDA 238.0 nm).

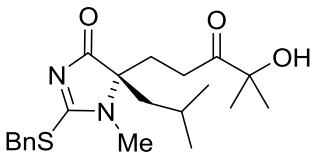


	Retention Time	% Area
1	18.485	49.04
2	21.873	50.96

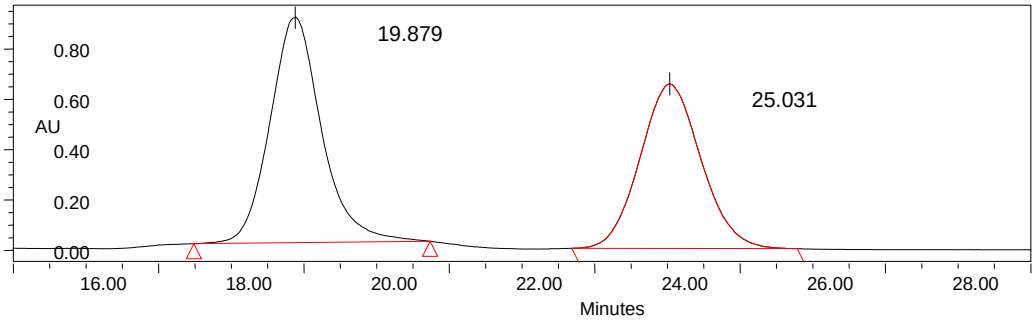


	Retention Time	% Area
1	18.733	96.81
2	22.169	3.19

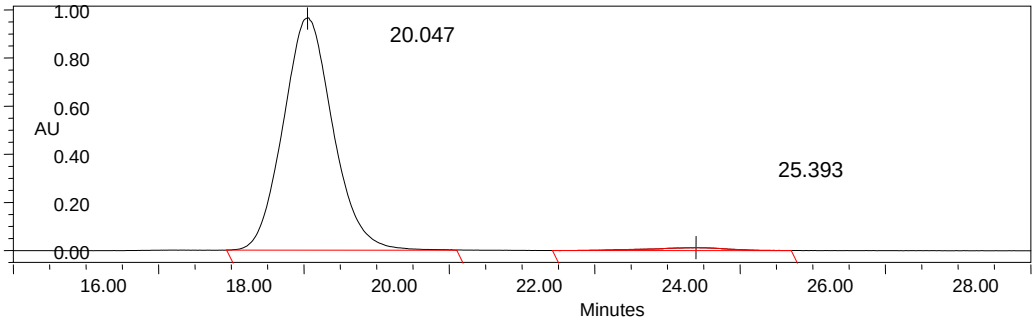
(*R*)-2-(Benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)-5-isobutyl-1-methyl-1*H*-imidazol-4(5*H*)-one (40j)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IC, hexane/isopropanol 60/40, flow rate= 0.5 mL/min, retention times: 20.0 min (major.) and 25.4 min (min.). Processed Channel Descr.: PDA 236.0 nm).

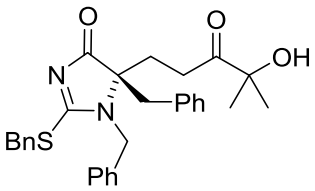


	Retention Time	% Area
1	19.879	53.69
2	25.031	46.31

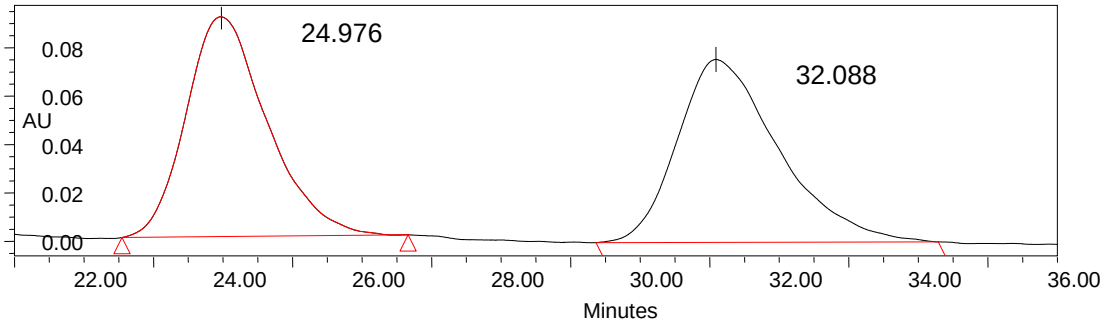


	Retention Time	% Area
1	20.047	98.06
2	25.393	1.94

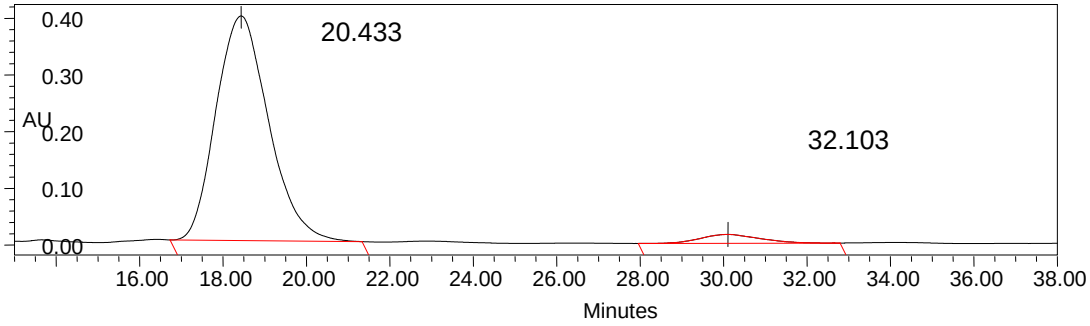
(*R*)-1,5-Dibenzyl-2-(benzylthio)-5-(4-hydroxy-4-methyl-3-oxopentyl)- 1*H*-imidazol-4(5*H*)-one (40n)



The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 80/20, flow rate= 0.5 mL/min, retention times: 20.4 min (major.) and 32.1 min (min.). Processed Channel Descr.: PDA 210.0 nm).



	Retention Time	% Area
1	24.976	49.16
2	32.088	50.84



	Retention Time	% Area
1	20.433	95.80
2	32.103	4.20

PUBLICATIONS