DOI: 10.1002/adsc.201700146
Advanced Synthesis & Catalysis

Tunable *Cinchona*-Based Thioureas-Catalysed Asymmetric Epoxidation to Synthetically Important Glycidic Ester Derivatives

Sara Meninno,[a] Luca Zullo,[a] Jacob Overgaard,[b] and Alessandra Lattanzi[a,*]

[a] Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, Via Giovanni Paolo II, 84084 Fisciano, Italy
Fax: (+39)-089-969-603; phone: (+39)-089-969-563; e-mail: lattanzi@unisa.it
[b] Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus, Denmark

Received: February 5, 2017; Revised: February 14, 2017; Published online: ■■ ■■, 0000

Supporting information for this article can be found under http://dx.doi.org/10.1002/adsc.201700146.

Abstract: A novel class of synthetically important glycidic esters has been obtained *via* an asymmetric epoxidation of *trans*-α-cyano-α,β-unsaturated esters catalysed by a multifunctional *Cinchona* alkaloid-derived thiourea/*tert*-butyl hydroperoxide (TBHP) system. The glycidic esters, isolated in excellent yield with complete *trans*-diastereocontrol and high enantioselectivity, proved to be versatile building blocks to access challenging small targets bearing a quaternary stereocenter.

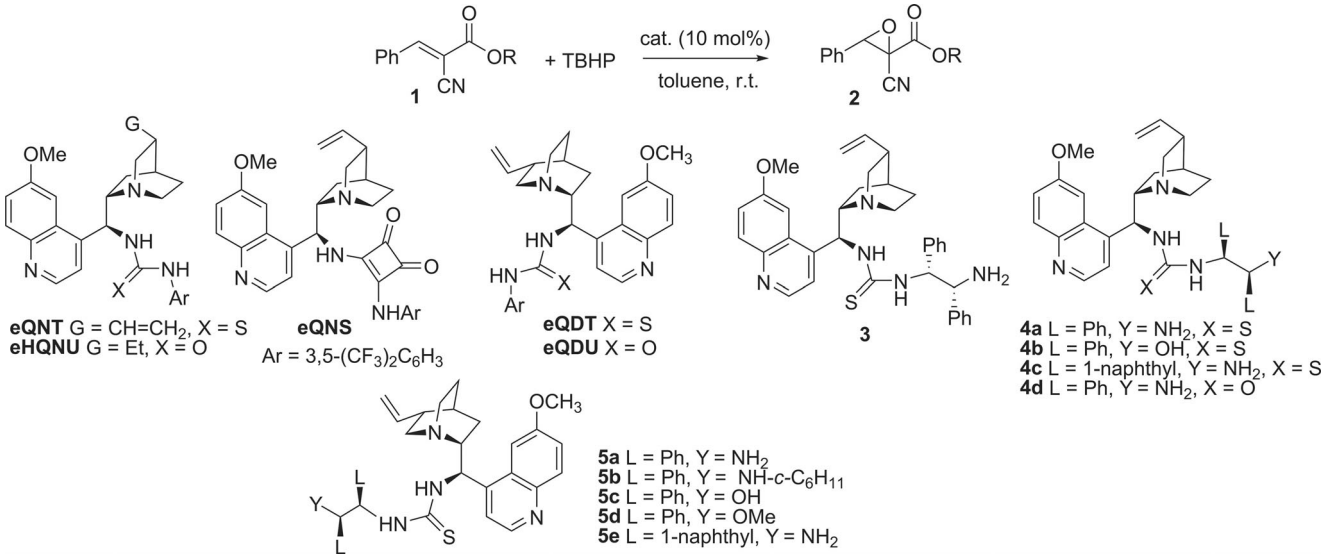
Keywords: amine-thiourea catalysts; asymmetric catalysis; electron-deficient compounds; epoxidation; glycidic esters; organocatalysis

The development of new stereoselective methodologies for the epoxidation of alkenes is at the forefront of asymmetric catalysis.[1] The importance of epoxides is widely recognised in the realm of natural products and as versatile intermediates in several total syntheses of biologically active compounds. Given the feasibility of stereocontrolled ring-opening reactions, several small building blocks such as 1,2-functionalised products can be attained.[2] Since the pivotal discoveries in the 1980s, intensive investigations have focused on the development of efficient systems for the epoxidation of functionalised alkenes, namely allylic and homoallylic alcohols and unfunctionalised alkenes by metal-catalysed[3] and organocatalytic systems.[4] In the case of epoxides deriving from electron-poor alkenes, additional transformations are possible *via* manipulation of the electron-withdrawing group.[5] A multitude of methods exists to effect the asymmetric epoxidation of *trans*-acyclic enones,[6] far less are available for aliphatic and cyclic enones[4f–h] and differently substituted enals[4a,i,7] and only a few have been reported for mono- and disubstituted α,β-unsaturated esters. This is not surprising since these alkenes are "borderline substrates" in terms of reactivity, being challenging for either an electrophilic or nucleophilic oxidative system. Chiral ketone-derived dioxiranes, Mn(III)-salen/NaOCl and yttrium-chiral biphenyldiol/Ph_3AsO/TBHP systems developed, respectively, by Shi's,[8] Jacobsen's[9] and Shibasaki's[10] groups afforded glycidic esters in generally good yield and good to excellent enantioselectivity. A few indirect oxidative methods were also reported.[11] The value of optically active glycidic esters, has been demonstrated in the asymmetric synthesis of important pharmaceuticals, namely the blood pressure lowering agent Diltiazem,[12] the phenylisoserine Taxol side-chain,[12] the antibiotic Chloramphenicol A[13] and natural products.[14]

We recently disclosed the ability of *Cinchona* alkaloid-derived thioureas to catalyse a highly enantioselective epoxidation of α-aroyl acrylamides with TBHP to afford terminal epoxides.[15] Prompted by our interest in developing asymmetric epoxidation reactions[16] and with the knowledge that *Cinchona* alkaloid-derived thioureas behave as effective bifunctional catalysts in nucleophilic epoxidations, we chose α-cyano-α,β-unsaturated esters as our playground. At the outset of this work an asymmetric version for this class of alkenes was still unknown, likewise the synthetic potential of this class of epoxides.[17] Herein, we report the first asymmetric epoxidation of *trans*-α-cyano-α,β-unsaturated esters, which proceeded with complete diastereocontrol, high conversion and enantioselectivity when using multifunctional *Cinchona* alkaloid-derived thioureas. Moreover, further elaborations of the enantioenriched epoxides showed that these epoxides can be valuable intermediates to access small chiral targets that are difficult to prepare by alternative methods.

Initial studies focused on the screening of different bifunctional organocatalysts in the epoxidation of the model *trans*-α,β-unsaturated ester **1a** using TBHP in

Table 1. Catalyst screening.[a]



Entry	R	Cat. [mol%]	Time [h]	Yield [%][b]	*er*[c]
1	Et	**QN**	25	**2a**, 54	63:37
2	Et	**eQNT**	60	**2a**, 59	24:76
3	Et	**eHQNU**	17	**2a**, 60	23:77
4	Et	**eQDT**	24	**2a**, 22	61:39
5	Et	**eQDU**	24	**2a**, 53	51:49
6[d]	Et	**eQNS**	64	**2a**, 6	45:55
7	Et	**3**	41	**2a**, 52	75:25
8	Et	**4a**	20	**2a**, 30	35:65
9	Et	**4b**	40	**2a**, 30	45:55
10	Et	**4c**	23	**2a**, 76	13:87
11	Et	**4d**	70	**2a**, 8	nd
12	Et	**5a**	17	**2a**, 81	84:16
13	Et	**5b**	19	**2a**, 60	67:33
14	Et	**5c**	41	**2a**, 13	60:40
15	Et	**5d**	110	**2a**, <5	nd
16	Et	**5e**	17	**2a**, 88	89:11
17	Bn	**5e**	23	**2b**, 70	89:11
18	*t*-Bu	**5e**	46	**2c**, 60	83:17
19	Me	**5e**	23	**2d**, 96	89.5:10.5

[a] *Reaction consitions*: 0.05 mmol scale of **1** (*C* 0.2 M) using TBHP (1.2 equiv.) at room temperature.
[b] Determined by ^{1}H NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as an internal standard.
[c] Determined by chiral HPLC analysis.
[d] Reaction performed with 5 mol% of catalyst in $CHCl_3$ as solvent.

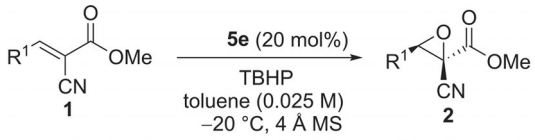
toluene at room temperature (Table 1). The quinine (QN)-mediated epoxidation proceeded with complete diastereocontrol to *trans*-epoxide **2a**, which was isolated in acceptable yield, albeit in low enantioselectivity (entry 1). Among the classical *Cinchona* alkaloid-derived bifunctional organocatalysts, eQNT and eHQNU enabled the formation of the opposite enantiomer of **2a** in satisfactory yield and comparable enantiocontrol (entries 2 and 3). eQDT and eQDU were less efficient catalysts, with eQDU affording an almost racemic product (entries 4 and 5). The quinine-derived squaramide was totally uneffective, showing that the nature of the H-bonding donor group played a major role in the catalysis (entry 6).

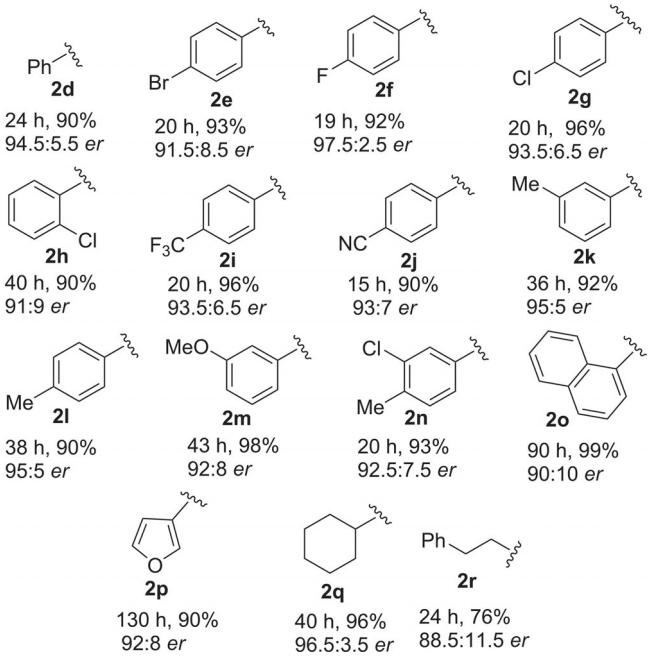
The presence of additional chiral moieties, bearing Brønsted acid groups, in proline or *Cinchona* alkaloid-derived thiourea catalysts improved their activity and enantiocontrol, by virtue of supplementary H-bonding and matching effects established in the catalyst-reagent reactive complex.[18] Inspired by these findings, we checked *Cinchona* alkaloid-derived thioureas incorporating 1,2-diarylethylenediamine or 1,2-diphenylethyleneamino alcohol groups. The (*R*,*R*)-1,2-diphenylethylenediamine unit in catalyst **3**

(entry 7) remarkably affected the sense of asymmetric induction displayed by the eQNT scaffold (entry 2), leading to the opposite enantiomer. A decreased activity and moderate mismatching effect were also observed when the (*S*,*S*)-enantiomer was incorporated into catalyst **4a** (entry 8) and with catalyst **4b**, bearing the (*S*,*S*)-amino alcohol portion (entry 9), attesting the importance of the polar group. However, a matching effect was observed with catalyst **4c**, bearing a sterically demanding (*S*,*S*)-1,2-di-1-naphthylethylenediamine unit, with the product being recovered in better yield and up to 87:13 *er* (entry 10). A comparison of the activity of catalysts **4a** and **4d** (entries 8 and 11), showed the urea analogue **4d** to be almost unreactive even after a prolonged reaction time.[19] Hence, we chose the thiourea-based catalysts for further investigations. We next explored the "pseudoenantiomeric" series based on the eQD scaffold. Interestingly, the presence of the (*R*,*R*)-diamine unit in catalyst **5a** assured a significant matching effect (entry 12) when compared to the modest performance observed with eQDT (entry 4). Replacing the primary amine with a secondary amine, a hydroxy or a methoxy group, respectively in catalysts **5b–d**, dramatically depressed the efficiency and enantiocontrol through to a complete loss of activity (entries 13–15). These findings confirmed the essential role played by the polar groups in the catalysis and they could be interpreted in view of a better ability of the primary amine to be engaged in an H-bonding network with the reagents.[20] The most hindered catalyst **5e** afforded the best result in terms of yield and enantioselectivity (entry 16). The nature of the ester group in the starting alkenes was next investigated. Alkenes bearing more sterically demanding groups were more slowly converted into the corresponding epoxides which showed slightly lower *ee* values (entries 17 and 18). The α,β-unsaturated methyl ester was converted into the epoxide **2d** best, in terms conversion and level of enantiocontrol (entry 19). Further optimisation of the hydroperoxide nature and reaction conditions led to a significant improvement in the epoxidation of *trans*-methyl 2-cyano-3-phenylacrylate, whose epoxide **2d** was obtained with 94.5:5.5 *er*, when working at a 20 mol% loading of **5e**, with TBHP as the oxidant at −20 °C in the presence of molecular sieves.[21] With the optimised conditions in hand, we next examined the applicability of the epoxidation (Table 2).

Pleasingly, a broad range of differently substituted α-cyanocinnamates with electron-poor or electron-rich substituents was converted into the *trans*-epoxides with excellent yield (76–99%) and high enantiocontrol (up to 97.5:2.5 *er*). The *ortho*-substituted epoxides (**2h** and **2o**) were formed with somewhat lower, but fairly good levels of enantioselectivity. Alkenes bearing double aryl substitution and heteroaromatic residues gave good results (epoxides **2n** and **2p**). Interestingly, the epoxidation could be applied with success to less reactive β-alkyl-substituted α-cyano-α,β-unsaturated esters. Indeed, the corresponding epoxides **2q** and **2r** were obtained in 96% and 77% yields, 96.5:3.5 *er* and 88.5:11.5 *er*, respectively.

Table 2. Scope of the asymmetric epoxidation of alkenes **1**.[a,b,c]





[a] *Reaction conditions*: 0.1 mmol scale of **1** (*c* 0.025 M) using TBHP (1.2 equiv.) and 20 mol% of **5e** at −20 °C.
[b] Product isolated after flash chromatography.
[c] Determined by chiral HPLC analysis. Absolute configuration determined by X-ray crystallography.

The absolute configuration of epoxide **2e** was unambiguously determined to be (2*S*,3*R*) by X-ray crystallographic analysis, and the configurations of the other epoxides were assigned by analogy (Figure 1).[22]

To assess the synthetic potential of this new class of optically active epoxides, we envisaged some useful transformations to prepare products of great interest,

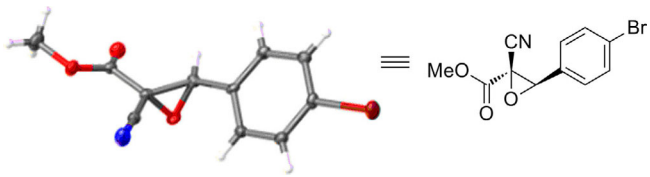
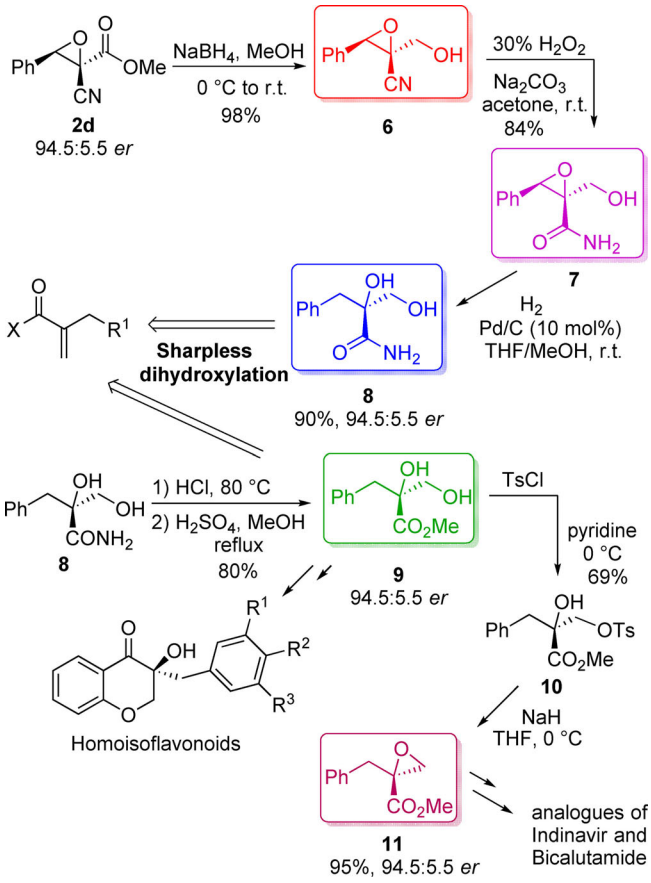


Figure 1. X-ray crystal structure of (2*S*,3*R*)-**2e**, thermal ellipsoids drawn at 50% probability.



Scheme 1. Synthetic elaborations of glycidic esters **2**.

starting from model epoxide **2d**, *via* chemo- and regioselective reactions at the functional groups (Scheme 1).

Treatment of enantioenriched epoxide **2d** with $NaBH_4$ affected selective reduction of the ester group in almost quantitative yield to give the cyano epoxy alcohol **6**.[23] The previously reported stoichiometric Sharpless Ti/tartrate-mediated asymmetric epoxidation of poorly reactive 2-cyanoallylic alcohols leading to compounds **6**,[24] suffered from modest conversions. Epoxide **6** was hydrolysed to the corresponding *cis*-α-amido epoxide **7** in 84% yield. The following regioselective ring-opening reaction, performed under catalytic hydrogenation conditions, gave the α,β-dihydroxy amide **8**, bearing a tetrasubstituted carbon, in 90% yield. This compound was also readily transformed into methyl ester **9**. Products of the types **8** and **9** can be accessed by Sharpless asymmetric dihydroxylation of the corresponding 2-substituted acrylates or acrylamides.

However, the asymmetric induction appears to be highly dependent on the nature of the α-substituent and ester groups.[25] In the case of α-substituted acrylamides, only Weinreb amides afforded high enantioselectivity.[26] Esters of type **9** have been used as starting material to synthesise Eucomols, a subclass of homoisoflavonoids, compounds endowed with a broad range of biological activities.[25b] Tosylation of diol **9** followed by base-promoted ring-closure led to challenging terminal epoxy methyl ester **11** in 65% two-step overall yield and 94.5:5.5 *er*, attesting that no racemisation occurred over the entire sequence. (*S*)-Epoxide **11** is a particularly attractive and versatile compound, used as building block for the synthesis of a new class of HIV-1 protease inhibitors, analogues of Indinavir.[27] Moreover, (*S*)-epoxide **11** can be employed as a key intermediate for the synthesis of Bicalutamide-like molecules, which displayed very promising activity toward prostate cancer cell lines.[28]

To rationalise the stereoselectivity of the reaction, we propose a tentative transition state model for the oxa-Michael addition step, which should be the rate- and stereoselectivity-determining step of the process (Figure 2). A fast ring closure to the epoxide would

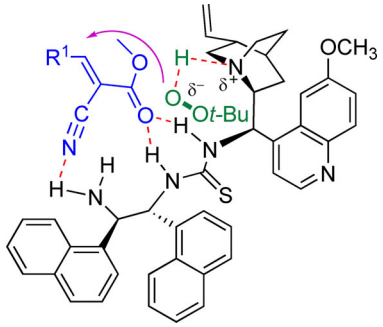


Figure 2. Proposed stereochemical model.

be in agreement with the observed complete control of the diastereoselectivity. The crucial importance of the NH_2 and thiourea groups in tuning the enantioselectivity might be ascribed to cooperative H-bonding engagement with the cyano and ester groups of the alkene.[29] The NH_2 unit of the sterically encumbered C_2-symmetrical diamine portion would act as a conformationally rigid H-bonding handle, fixing the orientation of the alkene toward a preferential attack of the alkene *Re*-face by the alkyl hydroperoxide.[30,31]

In conclusion, we have developed the first asymmetric epoxidation of α-cyano-α,β-unsaturated esters by using a multifunctional *Cinchona* alkaloid-derived thiourea, bearing a 1,2-diamine chiral unit. The epoxides were obtained in excellent yield, complete diastereoselectivity and very good to high enantiocontrol. Importantly, optically active α-cyano glycidic esters are useful building blocks to prepare small targets of high synthetic value. Finally, it is interesting to point out that this study has wider implications in non-covalent organocatalysis. Up to now, bi- and multifunctional organocatalysts, bearing primary amines, have been extensively used almost exclusively in covalent organocatalysis,[32] the so-called aminocatalysis, ex-

ploiting the iminium-enamine activation of carbonyl compounds. A primary amine, which can be readily installed in multifunctional organocatalysts, can also provide helpful donor-acceptor H-bonding interactions, still rarely explored in the non-covalent activation strategy.[20]

Experimental Section

General Procedure for the Asymmetric Synthesis of Glycidic Esters 2

A sample vial was charged with the (*E*)-2-cyano acrylate **1** (0.10 mmol) and catalyst **5e** (13.6 mg, 0.02 mmol) in anhydrous toluene (4 mL). Then activated molecular sieves (≈40 mg) and finally TBHP (≈5.5 M in decane, 22 μL, 0.12 mmol) were added. The mixture was stirred at −20 °C until completion, as monitored by TLC. Purification of the crude mixture by flash chromatography (eluting in gradient from PE/diethyl ether 98/2 to 70/30) gave enantioenriched epoxides **2d–r**.

Acknowledgements

We thank MIUR, University of Salerno, POR Regione Campania FESR 2007-2013-O.O. 2.1 (FarmaBioNet) and the Danish National Research Foundation (DNRF-93) for financial support. We thank Dr. P. Iannece (University of Salerno) for assistance with mass spectra and elemental analyses.

References

[1] For recent reviews, see: a) *Modern Oxidation Methods*, (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, **2010**; b) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.* **2014**, *114*, 8199–8256; c) C. Wang, H. Yamamoto, *Chem. Asian J.* **2015**, *10*, 2056–2068; d) O. Cussó, X. Ribas, M. Costas, *Chem. Commun.* **2015**, *51*, 14285–14298; e) K. K. Krishnan, A. M. Thomas, K. S. Sindhu, G. Anilkumar, *Tetrahedron* **2016**, *72*, 1–16.

[2] For reviews, see: a) *Aziridines and Epoxides in Organic Synthesis*, (Ed.: A. Yudin), Wiley-VCH, Weinheim, **2006**; b) N. Bala, S. S. Chimni, *Tetrahedron: Asymmetry* **2010**, *21*, 2879–2898.

[3] For selected examples, see: a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) R. A. Johnson, K. B. Sharpless, in: *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, chapter 6A, pp 231–280; c) S. Bhadra, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2015**, *137*, 15612–15615; d) S. Kondo, K. Saruhasi, S. Kenichi, K. Matsubara, K. Miyaji, T. Kubo, K. Matsumoto, T. Katsuki, *Angew. Chem.* **2008**, *120*, 10349–10352; *Angew. Chem. Int. Ed.* **2008**, *47*, 10195–10198; e) J. L. Olivares-Romero, Z. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2013**, *135*, 3411–3413; f) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286–287.

[4] For selected examples, see: a) M. Marigo, G. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965; b) H. Kawai, S. Okusu, Z. Yuan, E. Tokunaga, A. Yamano, M. Shiro, N. Shibata, *Angew. Chem.* **2013**, *125*, 2277–2281; *Angew. Chem. Int. Ed.* **2013**, *52*, 2221–2225; c) D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1996**, *118*, 491–492; d) Y. Zhu, K. J. Manske, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 4080–4081; e) X. Feng, L. Shu, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 11002–11003; f) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071; g) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135; h) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232–8235; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112–8115; i) O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227–10229; j) Y. Kobayashi, S. Li, Y. Takemoto, *Asian J. Org. Chem.* **2014**, *3*, 403–407; k) D. Limnios, C. G. Kokotos, *J. Org. Chem.* **2014**, *79*, 4270–4276; l) O. Cusso, M. Cianfanelli, X. Ribas, R. J. M. Klein Gebbink, M. Costas, *J. Am. Chem. Soc.* **2016**, *138*, 2732–2738.

[5] For a review, see: C. Lauret, *Tetrahedron: Asymmetry* **2001**, *12*, 2359–2383.

[6] For recent reviews, see: a) A. Lattanzi, *Curr. Org. Synth.* **2008**, *5*, 117–133; b) S. Colonna, D. Perdicchia, in: *Stereoselective Synthesis 1*, (Eds.: J. G. de Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**, pp 123–153; c) K. M. Weiss, S. B. Tsogoeva, *Chem. Rec.* **2011**, *11*, 18–39.

[7] For selected examples, see: a) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111–3114; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; b) S. Lee, D. W. C. MacMillan, *Tetrahedron* **2006**, *62*, 11413–11424; c) O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Fares, I. Polyak, G. Gopakumar, W. Thiel, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 6677–6693.

[8] a) X.-Y. Wu, X. She, Y. Shi, *J. Am. Chem. Soc.* **2002**, *124*, 8792–8793; b) B. Wang, X.-Y. Wu, O. A. Wong, B. Nettles, M.-X. Zhao, D. Chen, Y. Shi, *J. Org. Chem.* **2009**, *74*, 3986–3989.

[9] a) E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martinez, *Tetrahedron* **1994**, *50*, 4323–4334. For a recent iron-catalysed methodology, see: b) L. Luo, H. Yamamoto, *Eur. J. Org. Chem.* **2014**, 7803–7805.

[10] H. Kakei, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 8962–8963.

[11] a) B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 5434–5437; b) Y.-N. Xuan, H.-S. Lin, M. Yan, *Org. Biomol. Chem.* **2013**, *11*, 1815–1817.

[12] B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3501–3507.

[13] J. Boruwa, J. C. Borah, S. Gogoi, N. C. Barua, *Tetrahedron Lett.* **2005**, *46*, 1743–1746.

[14] a) J. R. Flisak, K. J. Gombatz, M. M. Holmes, A. A. Jarmas, I. Lantos, W. L. Mendelson, V. J. Novack, J. J. Remich, L. Snyder, *J. Org. Chem.* **1993**, *58*, 6247–6254; b) I. López, S. Rodríguez, J. Izquierdo, F. V. González, *J. Org. Chem.* **2007**, *72*, 6614–6617.

[15] A. Russo, G. Galdi, G. Croce, A. Lattanzi, *Chem. Eur. J.* **2012**, *18*, 6152–6157.
[16] For selected examples, see: a) A. Lattanzi, P. Iannece, A. Vicinanza, A. Scettri, *Chem. Commun.* **2003**, 1440–1441; b) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579–2582; c) A. Russo, A. Lattanzi, *Org. Biomol. Chem.* **2010**, *8*, 2633–2638.
[17] For a racemic epoxidation of alkenes of type **1**, see: A. Foucaud, M. Bakouetila, *Synthesis* **1987**, 854–856.
[18] For reviews, see: a) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678–20685; b) X. Liu, L. Lin, X. Feng, *Chem. Commun.* **2009**, 6145–6158; c) X. Fang, C.-J. Wang, *Chem. Commun.* **2015**, *51*, 1185–1197. For selected examples on covalent organocatalysis, see: d) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; e) S. Fotaras, C. G. Kokotos, G. Kokotos, *Org. Biomol. Chem.* **2012**, *10*, 5613–5619; f) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433; g) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756; h) J. Luo, H. Wang, F. Zhong, J. Kwiatkowski, L.-W. Xu, Y. Lu, *Chem. Commun.* **2013**, *49*, 5775–5777.
[19] The difference in activity between thiourea and urea catalysts might be ascribed to aggregation effects, demonstrated to be significantly stronger in ureas and possibly influenced by the presence of further polar groups, see: a) M. Obrzud, M. Rospenk, A. Koll, *Phys. Chem. Chem. Phys.* **2014**, *16*, 3209–3219; b) H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Bae, C. E. Song, *Org. Biomol. Chem.* **2010**, *8*, 3918–3922.
[20] For employment of primary amine-thioureas in non-covalent organocatalysis, see: a) A. K. Basak, N. Shimada, W. F. Bow, D. A. Vicic, M. A. Tius, *J. Am. Chem. Soc.* **2010**, *132*, 8266–8267; b) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473–477; c) M. Retini, G. Bergonzini, P. Melchiorre, *Chem. Commun.* **2012**, *48*, 3336–3338.
[21] See the Supporting Information for more details.
[22] CCDC 1523834 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[23] J. Mauger, A. Robert, *Tetrahedron* **1988**, *44*, 2493–2502.
[24] M. Aiai, A. Robert, M. Baudy-Floc'h, P. Le Grel, *Tetrahedron: Asymmetry* **1995**, *6*, 2249–2252.
[25] a) Z.-M. Wang, K. B. Sharpless, *Synlett* **1993**, 603–604; b) S.-s. Jew, H.-a. Kim, J.-h. Kim, H.-g. Park, *Heterocycles* **1997**, *46*, 65–70.
[26] a) A. Avenoza, C. Cativiela, F. Corzana, J. M. Peregrina, D. Sucunza, M. M. Zurbano, *Tetrahedron: Asymmetry* **2001**, *12*, 949–957; b) F. Weber, R. Brückner, *Eur. J. Org. Chem.* **2015**, 2428–2449.
[27] a) J. K. Ekegren, T. Unge, M. Z. Safa, H. Wallberg, B. Samuelsson, A. Hallberg, *J. Med. Chem.* **2005**, *48*, 8098–8102. For a review, see: b) H. V. Motwani, M. De Rosa, L. R. Odell, A. Hallberg, M. Larhed, *Eur. J. Med. Chem.* **2015**, *90*, 462–490.
[28] A. Guerrini, A. Tesei, C. Ferroni, G. Paganelli, A. Zamagni, S. Carloni, M. Di Donato, G. Castoria, C. Leonetti, M. Porru, M. De Cesare, N. Zaffaroni, G. L. Beretta, A. Del Rio, G. Varchi, *J. Med. Chem.* **2014**, *57*, 7263–7279.
[29] For H-bonding interactions of organic nitriles with amines, see: a) J. Masnovi, R. J. Baker, R. L. R. Towns, Z. Chen, *J. Org. Chem.* **1991**, *56*, 176–179; b) N. Ziao, J. Graton, C. Laurence, J.-Y. Le Questel, *Acta Crystallogr. Sect. B* **2001**, *B57*, 850–858.
[30] The key role played by the rigid chiral binding pocket, provided by C_2-symmetrical thiourea-primary amines, has been recently assessed by a DFT study: A. H. Asari, Y. Lam, M. A. Tius, K. N. Houk, *J. Am. Chem. Soc.* **2015**, *137*, 13191–13199.
[31] The significant improvement of the asymmetric induction observed in the model reaction provided by catalyst **5e** *versus* **5a** (Table 1 entries 16 and 12) might be ascribed to a better ability of a larger 1-naphthyl group to shield the approach of the oxidant toward the *Si*-face of the alkene in the hypothetical ternary complex.
[32] For recent reviews, see: a) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051–7071; b) M. Tsakos, C. G. Kokotos, *Tetrahedron* **2013**, *69*, 10199–10222.