Organocatalysis

DOI: 10.1002/ange.201305644

Catalytic Enantioselective Synthesis of Tertiary Thiols From 5*H*-Thiazol-4-ones and Nitroolefins: Bifunctional Ureidopeptide-Based Brønsted Base Catalysis**

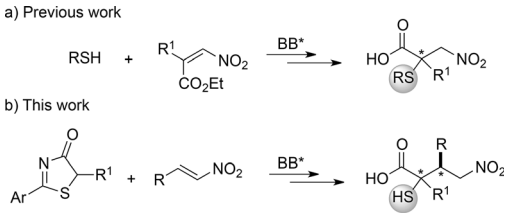
*Saioa Diosdado, Julen Etxabe, Joseba Izquierdo, Aitor Landa, Antonia Mielgo, Iurre Olaizola, Rosa López, and Claudio Palomo**

Dedicated to Professor Carmen Nájera

The direct catalytic reaction between an enolizable carbonyl compound and an electrophile under proton-transfer conditions has emerged as a challenging versatile transformation in organic synthesis.[1] Over the last years several chiral Brønsted bases have been developed to promote this transformation diastereo- and enantioselectively.[2] However, successful examples are mostly limited to 1,3-dicarbonyl compounds and acidic carbon analogues as the pronucleophilic reaction partners. 5*H*-Thiazol-4-ones, in contrast, have been well known for a long time and have found several applications in pharmaceutical and medicinal chemistry.[3] Although structurally related to 5*H*-oxazol-4-ones[4] and 4*H*-oxazol-5-ones (azlactones),[5] 5*H*-thiazol-4-ones have, as far as we know, been never been used in asymmetric synthesis in spite of the fact that they may be easily deprotonated[6] and in spite of the importance of thiols and organosulfur compounds in organic synthesis[7] and chemical biology.[8] In this context, whilst chiral secondary thiol derivatives have been the subject of most investigations, tertiary thiols have remained mostly unexplored owing to the insufficient catalytic enantioselective methodology for their preparation in optically pure form.[9]

The most general synthesis of organosulfur compounds involves reaction of a sulfur nucleophile with an electron-deficient π-olefin acceptor.[10] By using this approach Zhang and co-workers[11] reported an efficient catalytic asymmetric synthesis of tertiary thiols using chiral Brønsted bases and β-substituted β-ethoxycarbonyl nitroalkene acceptors. Conversely, tertiary thiols may be produced through conjugate additions of sulfur-based carbon pronucleophiles.[12] For instance, using rhodanines as carbon pronucleophiles and iminium catalysis, Ye and co-workers[13] have recently reported the conjugate addition and the Diels–Alder reaction to α,β-unsaturated ketones and 2,4-dienals, respectively. Tertiary thiols have also been accessed through enantioselective α-sulfenylation of aldehydes,[14a] 1,3-dicarbonyl compounds,[14b] β-keto phosphonates,[14c] and 3-substituted oxindoles.[14d–g] Other methods include thiofunctionalization of unactivated alkenes,[15a] amination of 3-thiooxindoles,[15b] and the aldol[15c] and Mannich[15d] reactions of α-sulfanyl lactones. Accordingly, whilst many methodologies for the enantioselective synthesis of secondary thiols exist, approaches for the asymmetric synthesis of tertiary thiols are clearly necessary to help fill this important gap in organic chemistry. The inherent difficulty associated with the stereoselective construction of quaternary stereogenic centers is probably the reason for the limited number of studies.[16] In connection with our efforts directed towards the asymmetric synthesis of organosulfur compounds, that is, β,β-disubstituted β-mercapto carboxylic acids[17a,b] and thiiranes,[17c] we focused on the enantioselective generation of a tetrasubstituted carbon atom at the α position of α-mercapto carboxylic acids.[18] We report herein the first highly diastereo- and enantioselective direct Michael addition of 5*H*-thiazol-4-ones to nitroolefins (Scheme 1) and it provides a quick entry to functionalized tertiary thiols. To this end, design and synthesis of ureidopeptide-based Brønsted bases, a novel subfamily of organic catalysts, are also documented for the first time.

We began our study by evaluating several Brønsted bases for the reaction of the readily available thiazolone **1**[19] with the nitroolefin **5a** (R = Ph; Scheme 2).[20] Initially, the reaction was explored using several representative cinchona alkaloids such as quinine, 9-epi-quinine, quinidine, and $(DHQ)_2PYR$ in CH_2Cl_2 at −60 °C. In every case the product

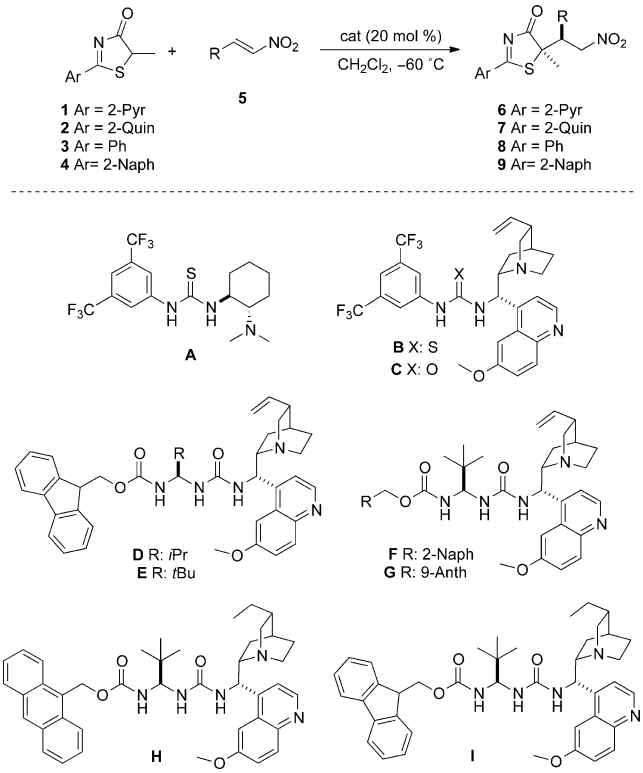


Scheme 1. Organocatalytic Michael approaches to α,α-disubstituted α-mercapto carboxylic acids mediated by chiral Brønsted bases (BB*). a) Asymmetric construction of C–S bond. b) Asymmetric construction of C–C bond.

[*] S. Diosdado, J. Etxabe, J. Izquierdo, Dr. A. Landa, Dr. A. Mielgo, I. Olaizola, Dr. R. López, Prof. Dr. C. Palomo
Departamento de Química Orgánica I, Facultad de Química
Universidad del País Vasco
Apdo. 1072, 20080 San Sebastián (Spain)
E-mail: claudio.palomo@ehu.es

[**] Support has been provided by the University of the Basque Country UPV/EHU (UFI QOSYC 11/22), Basque Government (GV grant No IT-291-07 and SAIOTEK 2012), and Ministerio de Ciencia e Innovación (MICINN, Grant CTQ2010-21263-C02), Spain. S.D., J.E., and I.O. thank MEC. We also thank SGIker (UPV/EHU) for providing NMR, HRMS, X-ray, and computational resources. We also thank S. Vera and M. Zalacain for their help with catalyst preparation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201305644.



Scheme 2. Conjugate addition of 5-methyl 5*H*-thiazol-4-ones to nitro olefins promoted by chiral Brønsted bases.

6a (R = Ph) was obtained but with disappointing chemical and stereochemical results (12–40% *ee*).[21] Next, on the basis of the pioneering studies of Takemoto and co-workers, and subsequent seminal works by the groups of Jacobsen, Connon, Dixon, and Soós on bifunctional (urea)thiourea-tertiary amine catalysts,[22] we examined the catalysts **A**–**C**. However, as the results in Table 1 show **A** led to almost racemic **6a** (entry 1), whilst no improvement was essentially observed with either **B** or **C** (entries 2 and 3).

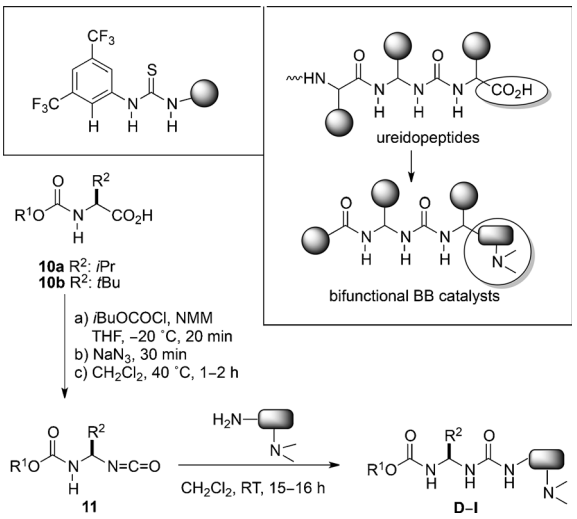
At this stage and in view of these results we focused on catalyst design. Like the catalysts **A**–**C**, most thiourea (urea)

Table 1: Catalyst screening for the 1,4-addition of 5*H*-thiazol-4-ones **1**–**4** to nitrostyrene **5a** (R = Ph).[a]

Entry	Comp.	Cat.	Prod. (R=Ph)	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1**	**A**	**6a**	48	53	83:17	20
2	**1**	**B**	**6a**	20	53	60:40	35
3	**1**	**C**	**6a**	20	48	54:46	40
4	**1**	**D**	**6a**	20	88	91:9	40
5	**1**	**E**	**6a**	20	92	95:5	66
6	**1**	**F**	**6a**	20	90	94:6	70
7	**1**	**G**	**6a**	20	86	90:10	78
8	**1**	**H**	**6a**	20	80	93:7	80
9	**2**	**H**	**7a**	20	93	95:5	96
10	**3**	**H**	**8a**	20	65	85:15	55
11	**4**	**H**	**9a**	20	55	75:25	68

[a] Reactions conducted at −60 °C on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2). [b] Yield of the isolated major isomer. [c] Determined by ^{1}H NMR (300 MHz) spectroscopy analysis on the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase.

based Brønsted bases known to date display the 3,5-bis(trifluoromethyl)phenyl group, a structural motif which was introduced first by Schreiner and Wittkopp in 2002 for hydrogen-bond catalysis.[23] Recently, Schreiner and co-workers suggested that the success of these catalysts may be attributed in part to the participation of both N–H bonds of the thiourea unit and the *ortho* C–H bond of the aryl group during the substrate activation event.[24] Based on this observation and given the proved efficacy of synthetic peptides for fine-tuning of reactivity and selectivity of several significant synthetic transformations[25] we wondered whether the urea derivatives **D**–**I** might be more appropriate catalysts for promoting the above reaction. These products display, as new features, the presence of an N,N′-diacyl aminal unit in place of the bis(trifluoromethyl)phenyl group, and an urea moiety as hydrogen-bond donors, and both are in close proximity to an additional stereodirecting group. This type of structure closely resembles ureidopeptides (Scheme 3), which



Scheme 3. Ureidopeptide-based Brønsted bases: Catalyst preparation. NMM = *N*-methylmorpholine, THF = tetrahydrofuran.

have been recognized for their ability to develop hydrogen-bond interactions.[26] It was expected that the replacement of the α-amino acid terminus by an amino cinchona moiety in ureidopeptides should result in new bifunctional Brønsted base catalysts with several sites amenable for structural modification.

Although, several different classes of ureidopeptide-based catalysts may be made readily accessible from the available pools of both α-amino acids (or peptides) and primary-tertiary diamines, we intended first to take advantage of the tunable aminal moiety for catalyst optimization. To the best of our knowledge this family of ureidopeptide-based Brønsted base catalysts have not been previously reported. Thus, starting from valine and the *tert*-leucine derivatives **10a** and **10b**, the catalysts **D**–**I** were easily prepared by reaction of the respective intermediate isocyanates **11**[26b] with 9-epi-9-amino-9-deoxyquinine or 9-epi-9-amino-9-deoxyhydroquinine in yields within the 70–80% range for the latter step (Scheme 3). A single-crystal X-ray analysis of **E** (Figure 1)

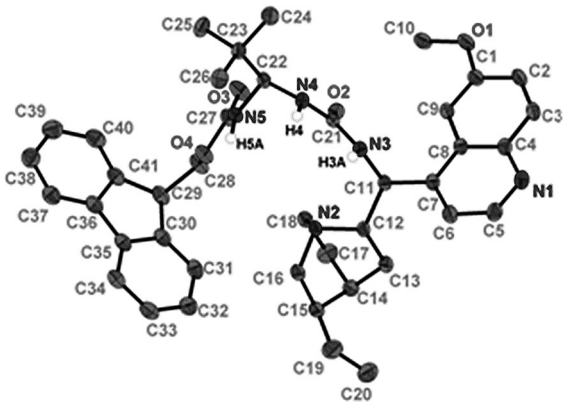


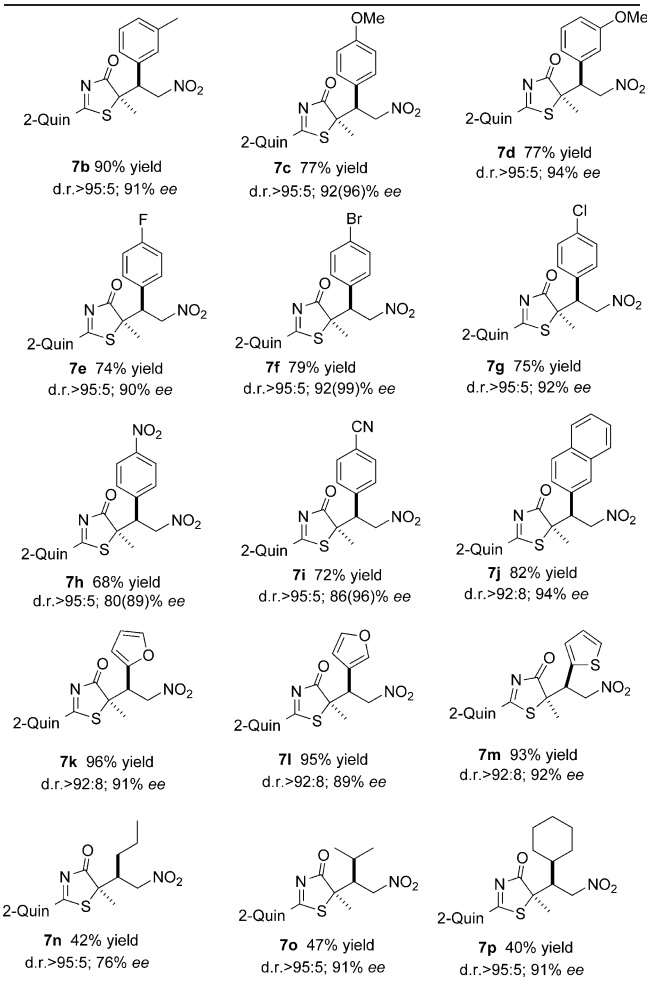
Figure 1. ORTEP representation for **E**. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

shows that N-H groups, in the N,N′-diacyl aminal and the urea moiety, are oriented in the same direction and that neither of them display any apparent tendency to develop intramolecular hydrogen bonds.[21]

Experiments with these catalysts revealed an improvement in diastereoselectivity. Also, by increasing the size of the aminal substituent from isopropyl to *tert*-butyl (catalysts **D** and **E**), enantioselectivity increased up to 66%, but was still insufficient (Table 1, entries 4 and 5). Further improvements in the reaction selectivity were observed with the catalysts **F** and **G** (entries 6 and 7) and the best result was produced with the catalyst **H**, which provided the product **6a** in 80% yield and 80% *ee* (entry 8). In subsequent experiments it was found that by using the quinoline-derived thiazolone **2** and catalyst **H** the corresponding product **7a** (entry 9) was produced in 93% yield as a 95:5 mixture of diastereomers with 96% *ee* for the major isomer. In contrast, using the thiazolones **3** and **4**, the corresponding addition products **8a** and **9a** (entries 10 and 11) were formed in lower diastereomeric ratios and *ee* values, results which seem to indicate that the pyridine and quinoline nitrogen atoms of the thiazolones **1** and **2** play a significant role in reaction stereocontrol. A representative selection of nitroolefins was evaluated to establish the generality of this asymmetric route to tertiary thiols. As the data in Table 2 shows, nitroolefins bearing β-aryl substituents with either electron-donating or electron-withdrawing groups are almost equally tolerated, thus giving the corresponding adducts with good diastereomeric ratios, typically greater than 95:5 and *ee* values of up to 96%. For example, performing the reaction with the substrates **5b, 5c**, and **5d**, led to the corresponding products **7b, 7c**, and **7d** as single diastereomers with *ee* values within the 91–94% range. The nitroolefins **5e**, **5f**, and **5g** with inductively electron-withdrawing fluoro, bromo, and chloro substituents, respectively, also provided excellent chemical and stereochemical results, whereas the nitrostyrenes **5h** and **5i** bearing mesomeric electron-withdrawing substituents gave the corresponding **7h** and **7i** with slightly reduced enantioselectivities. The method also works with nitroolefins having heteroaromatic β-substituents such as for **5k, 5l**, and **5m** to afford adducts **7k, 7l**, and **7m**, respectively, with good yields and stereoselectivities. Even the recalcitrant β-alkyl-substituted nitroolefins participate in this reaction to give the desired adducts essentially as single diastereomers, albeit in modest chemical yield (typically 40%). The unbranched aliphatic nitroolefin **5n** led to the product **7n** with a modest 76% *ee*, whereas the branched aliphatic substrates **5o** and **5p** provided **7o** and **7p**, respectively, in 91% *ee*. In this study we have employed 20 mol% of catalyst but it is worth mentioning that reactions using 10 mol% of the catalyst proceeded equally well without compromising either selectivity or chemical yield (Table 2 and see the Experimental Section).

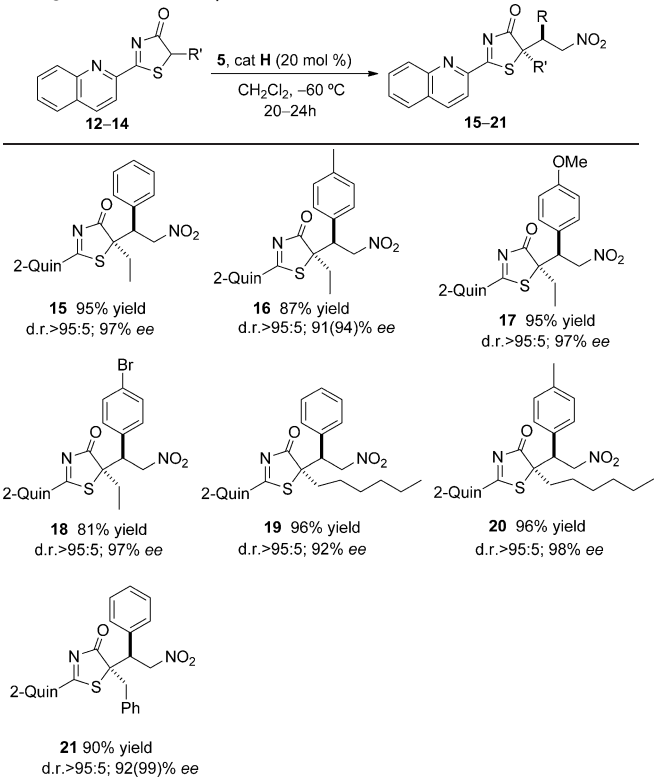
Thiazolones with short, large, and branched alkyl chains, also participate in this reaction (Table 3), and in all cases good to excellent yields were observed and the products were obtained with high enantioselectivity. The 5-ethylthiazolone **12**, for example, afforded the products **15**–**18**, essentially as

Table 2: Conjugate addition of the thiazolone **2** to nitroolefins **5** promoted by catalyst **H**.[a–d]

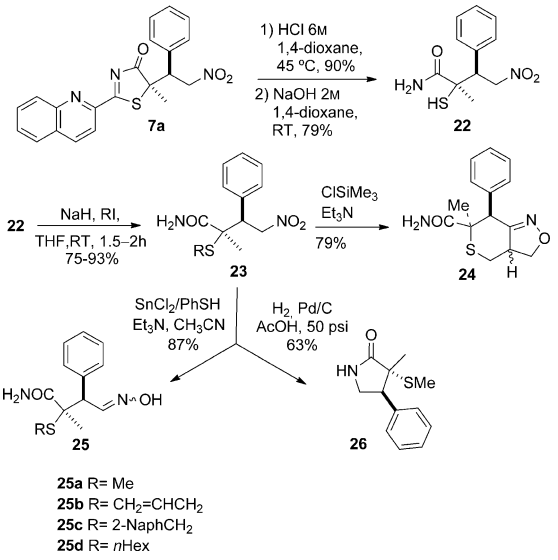


[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroolefin/thiazolone/catalyst 2:1:0.2) at −60°C for 20-24 h. [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^{1}H NMR (300 MHz) spectroscopy on the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. Data within parentheses were obtained after crystallization from diethyl ether or diisopropyl ether. By using a 10 mol% catalyst loading, essentially the same results for **7c**, **7f**, and **7o** were attained.

Table 3: Thiazolone scope.[a–d]



[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroalkene/thiazolone/catalyst 2:1:0.2). [b] Yields refer to the isolated major isomer. [c] The d.r. values were determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase.



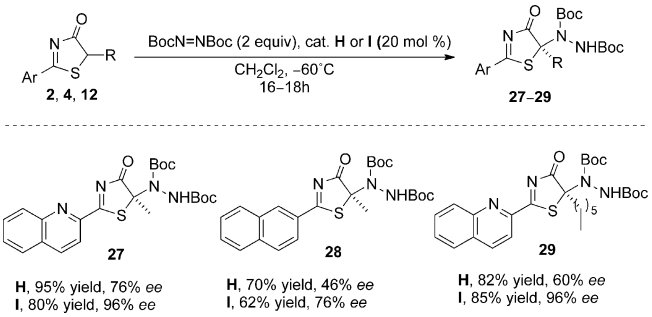
Scheme 4. Elaboration of adducts to α,α-disubstituted α-mercapto carboxylic acid derivatives.

sole diastereomers with excellent yields and 91–97% *ee*. Similarly, the hexyl (**13**) and benzyl (**14**) thiazolones, provided adducts **19, 20**, and **21** in very good yields, and diastereo- and enantioselectivities.

A practical aspect of the present methodology is the general crystallinity of the starting susbtrates, the thiazolones **2** and **12**–**14** and nitroolefin **5**, a property which is readily transformed into the resulting products **7** and **15**–**21**. Thus, a single crystallization, generally from diethyl ether or diisopropyl ether, provided products with increased enantiomeric purity. The absolute configuration of the adducts was established by a single-crystal X-ray analysis of **7 f**[21] and by assuming a uniform reaction mechanism.

Transformation of the adduct **7a** into the α,α-disubstituted α-mercapto carboxylic acid derivative **22**, by simple ring opening under mild acid conditions and subsequent saponification of the resulting thioester intermediate, illustrates the utility of the method. Thus, unlike the majority of procedures for the preparation of organosulfur compounds which generally give aryl or alkyl thioethers,[9–15] our method provides a quick entry to mercapto compounds with the thiol group in its free form (Scheme 4). Therefore, the question that we examined next was to establish whether these adducts could be S alkylated without affecting the nitro group. Besides steric constraints, there is the fact that upon exposure to benzyl halides and base, nitro compounds are cleanly reduced to oximes.[27] Gratifyingly, treatment of the adduct **22** with a series of halides in the presence of sodium hydride furnished the corresponding S-alkylated adducts **23** in 75–93% yields. Therefore, our approach also provides rapid access to a variety of thioether derivatives from a single common intermediate, a practical aspect that facilitates access to more elaborated products as exemplified in the formation of the tetrahydrothiopyran-fused isoxazoline **24** from **23 b**. In contrast, oximes such as **25 c**, may also be obtained in good yields by treatment of the respective thioether adduct with a $SnCl_2$/PhSH/Et_3N system,[28] whilst exposure to H_2 over Pd on charcoal under 50 psi enabled reduction of the nitro group to the amino function, thus leading to γ lactams.

Concerning the mechanism of these reactions,[29] we believe that the quinoline nitrogen atom of these thiazolone substrates could interact through a hydrogen bond with one of the three accessible N-H protons of the catalyst, likely with one of the aminal moieties, thereby providing a well-ordered transition state during the reaction. This assumption nicely accounts for the better behavior of quinolyl thiazolone substrates versus the 2-naphthyl thiazolone **4**. Further support for this assumption was provided from the amination reaction of the thiazolones **2**, **4**, and **12** with *tert*-butylazodicarboxylate (Scheme 5). Whilst in this case enantiocontrol proceeded better with **I** rather than with **H**, thiazolones bearing the quinoline moiety (**2** and **12**) furnished once again a better stereochemical outcome than the 2-naphthyl thiazolone **4**. Despite these observations, however, the actual activation model of these bifunctional Brønsted bases at this stage of our investigation[30] remains to be clarified. Whereas the above assumption appears reasonable for enolate ions having additional Lewis basic functionality, there is evidence from this laboratory that this structural element in the pronucleophile is not a prerequisite for catalyst efficiency and that these bifunctional ureidopeptide-based Brønsted bases are advantageous for a variety of transformations which are currently under study.[31]



Scheme 5. Catalytic enantioselective α-amination of thiazolones. Boc = *tert*-butoxycarbonyl.

In summary, we have realized the first direct catalytic Michael reaction of α-mercapto carboxylate surrogates with nitroolefins involving the construction of a fully substituted α-carbon atom. The method demonstrates the efficacy of 5*H*-thiazol-4-ones as a new class of S-carrying pronucleophiles providing α,α-disubstituted α-mercapto carboxylic acid derivatives with good yields and high diastereo- and enantioselectivities and, consequently, the method contributes to broadening the currently limited methodology available for the catalytic enantioselective synthesis of tertiary thiols. From an intuitive design we have introduced for the first time a new family of Brønsted base catalysts whose architecture can be easily modified by simply choosing the appropriate α-amino-acid-derived (or peptide) isocyanate and a survey of naturally or synthetically primary/tertiary diamines. Since strong substrate dependence is quite common in reactions promoted by Brønsted bases we believe these new catalysts may help to address this challenging issue.

Experimental Section

The catalyst **H** (67.6 mg, 0.1 mmol, 10 mol %) was added to a mixture of 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**2**) (242.3 mg, 1.0 mmol, 1 equiv) and nitrostyrene **5a** (298.3 mg, 2.0 mmol, 2 equiv) in dichloromethane (2.0 mL) cooled to −60 °C. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (16 h; monitored by ^{1}H NMR spectroscopy wherein there was disappearance of the methyl signal at $\delta = 1.46$ ppm). The crude reaction mixture was directly purified by flash column chromatography on silica gel (eluting with dichloromethane) to give adduct **7a** as a yellow solid. Yield: 364 mg, 93 %.

7a: $[\alpha]_D^{25} = -100.5$ ($c = 1.00$, 96 % *ee*, CH_2Cl_2). m.p. 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.16 (m, 3H), 7.95–7.78 (m, 2H), 7.76–7.64 (m, 1H), 7.43–7.32 (m, 2H), 7.31–7.12 (m, 3H), 5.19 (dd, $J = 13.2$, 4.6 Hz, 1H), 5.00 (dd, $J = 13.2$, 10.7 Hz, 1H), 4.22 (dd, $J = 10.7$, 4.6 Hz, 1H), 1.85 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.9$, 194.2, 148.7, 147.7, 137.4, 134.2, 134.2, 130.7, 130.4, 130.4, 129.5, 129.0, 128.7, 128.5, 127.8, 76.0, 65.1, 50.3, 24.0 ppm. UPLC-DAD-QTOF: $C_{21}H_{17}N_3O_3S$ $[M+H]^+$ calcd.: 392.1069, found: 392.1065. The enantiomeric purity of the major diastereomer was found to be 96 % (98 % *ee* after crystallization from diethyl ether) and was determined by HPLC analysis [Daicel Chiralpak AD-H, *n*-hexane/isopropanol/ethanol 85:14:1, flow rate = 0.5 mL min^{-1}, retention times: 45.5 min (minor) and 57.2 min (major)].

Received: July 1, 2013
Published online: September 17, 2013

Keywords: Brønsted bases · organocatalysis · peptides · sulfur heterocycles · synthetic methods

[1] N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4856 – 4868; *Angew. Chem. Int. Ed.* **2011**, *50*, 4760 – 4772.
[2] a) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2010**, *291*, 145 – 200; b) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632 – 653; c) "Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics": *Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**.
[3] a) N. A. Khalil, E. M. Ahmed, H. B. El-Nassan, *Med. Chem. Res.* **2013**, *22*, 1021 – 1027; b) U. V. Grummt, D. Weiss, E. Birckner, R. Beckert, *J. Phys. Chem. A* **2007**, *111*, 1104 – 1110; c) M. M. Véniant, C. Hale, R. W. Hungate, K. Gahm, M. G. Emery, J. Jona, S. Joseph, J. Adams, A. Hague, G. Moniz et al., *J. Med. Chem.* **2010**, *53*, 4481 – 4487.
[4] 5*H*-oxazol-4-ones for the synthesis of α,α-branched α-hydroxy acids. Metal catalysis: a) B. M. Trost, K. Dogra, M. Franzin, *J. Am. Chem. Soc.* **2004**, *126*, 1944 – 1945; b) D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem.* **2012**, *124*, 7641 – 7645; *Angew. Chem. Int. Ed.* **2012**, *51*, 7523 – 7527; c) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin, X. Feng, *Angew. Chem.* **2012**, *124*, 2830 – 2833; *Angew. Chem. Int. Ed.* **2012**, *51*, 2776 – 2779; d) B. M. Trost, K. Hirano, *Angew. Chem.* **2012**, *124*, 6586 – 6589; *Angew. Chem. Int. Ed.* **2012**, *51*, 6480 – 6483; organocatalysis: e) T. Misaki, G. Takimotoa, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286 – 6287; f) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695 – 5697; g) B. Quiau, Y. An, Q. Liu, W. Yang, H. Liu, J. Shen, L. Yan, Z. Jiang, *Org. Lett.* **2013**, *15*, 2358 – 2361; h) H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461 – 463; i) Z. Han, W. Yang, C.-H. Tan, Z. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 1505 – 1511.
[5] Reviews: a) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720 – 734; b) R. A. Mosey, J. S. Fisk, J. T. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755 – 2762; for the sulfur analogs of azlactones, see: c) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, *46*, 300 – 302; d) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, *12*, 876 – 879; e) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, *13*, 1494 – 1497; f) X. Liu, H. Song, Q. Chen, W. Li, W. Yin, M. Kai, R. Wang, *Eur. J. Org. Chem.* **2012**, 6647 – 6655.
[6] E. Täuscher, D. Weib, R. Beckert, J. Fabian, A. Assumpçao, H. Görls, *Tetrahedron Lett.* **2011**, *52*, 2292 – 2294.
[7] a) P. Metzner, A. Thuillier, *Sulfur Reagents in Organic Synthesis* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. S. Rees), Academic Press, **1995**; b) *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**.
[8] L. K. Moran, J. M. Gutteridge, G. J. Quinlan, *Curr. Med. Chem.* **2011**, *18*, 763 – 772.
[9] Review: J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582 – 595.
[10] Review of sulfa-Michael reaction: D. E. Enders, K. Lüttgen, A. A. Narine, *Synthesis* **2007**, 959 – 980.
[11] H. H. Lu, F. G. Zhang, X. G. Meng, S. W. Duan, W. J. Xiao, *Org. Lett.* **2009**, *11*, 3946 – 3949.
[12] Diastereoselective methods: a) B. Strijtveen, R. M. Kellogg, *Tetrahedron* **1987**, *43*, 5039 – 5054; b) J. M. McFadden, G.-L. Frehynot, C. A. Townsend, *Org. Lett.* **2002**, *4*, 3859 – 3862; c) R. Alibés, P. Bayón, P. De March, M. Figueredo, J. Font, G. Marjanet, *Org. Lett.* **2006**, *8*, 1617 – 1620; d) E. A. Tiong, J. L. Gleason, *Org. Lett.* **2009**, *11*, 1725 – 1728.
[13] a) F. Yu, H. Hu, X. Gu, J. Ye, *Org. Lett.* **2012**, *14*, 2038 – 2041; b) K. Zhu, H. Huang, W. Wu, Y. Wei, J. Ye, *Chem. Commun.* **2013**, *49*, 2157 – 2159.

[14] a) M. Marigo, T. C. Wabnitz, D. Filenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804 – 807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797; b) S. Sobhani, D. Fielenbach, M. Marigo, T. C. Wabnitz, K. A. Jørgensen, *Chem. Eur. J.* **2005**, *11*, 5689 – 5694; c) A. Ling, L. Fang, X. Zhu, C. Zhu, Y. Chen, *Adv. Synth. Catal.* **2011**, *353*, 545 – 549; d) Y. Cai, J. Li, W. Chen, M. Xie, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2012**, *14*, 2726 – 2729; e) X. Li, C. Liu, X.-S. Xua, J.-P. Cheng, *Org. Lett.* **2012**, *14*, 4374 – 4377; f) Z. Hang, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan, Z. Jiang, *Org. Lett.* **2012**, *14*, 4670 – 4673; g) C. Wang, X. Yang, C. C. J. Loh, G. Raabe, D. Enders, *Chem. Eur. J.* **2012**, *18*, 11531 – 11535.

[15] a) S. E. Denmark, D. J. P. Kornfilt, T. Vogler, *J. Am. Chem. Soc.* **2011**, *133*, 15308 – 15311; b) F. Zhou, X. P. Zeng, C. Wang, X. L. Zhao, J. Zhou, *Chem. Commun.* **2013**, *49*, 2022 – 2024; c) S. Takechi, S. Yasuda, N. Kunagai, M. Shibasaki, *Angew. Chem.* **2012**, *124*, 4294 – 4298; *Angew. Chem. Int. Ed.* **2012**, *51*, 4218 – 4222; d) S. Takechi, N. Kumagai, M. Shibasaki, *Org. Lett.* **2013**, *15*, 2632 – 2635.

[16] Recent reviews: a) M. Bella, T. Casperi, *Synthesis* **2009**, 1583 – 1614; b) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295 – 7306; c) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[17] a) C. Palomo, M. Oiarbide, F. Dias, R. López, A. Linden, *Angew. Chem.* **2004**, *116*, 3369 – 3372; *Angew. Chem. Int. Ed.* **2004**, *43*, 3307 – 3310; b) C. Palomo, M. Oiarbide, R. López, P. B. González, E. Gómez-Bengoa, J. M. Saá, A. Linden, *J. Am. Chem. Soc.* **2006**, *128*, 15236 – 15247; c) I. Cano, E. Gómez-Bengoa, A. Landa, M. Maestro, A. Mielgo, I. Olaizola, M. Oiarbide, C. Palomo, *Angew. Chem.* **2012**, *124*, 11014 – 11018; *Angew. Chem. Int. Ed.* **2012**, *51*, 10856 – 10860.

[18] Interest in α-mercapto carboxylic acids also stems from their general use as precursors of 4-thiazolidinones and 2,4-thiazolidinediones, which are key scaffolds for drug design and pharmaceutical agents, see: a) M. Abhinit, M. Ghodke, N. A. Pratima, *Int. J. Pharm. Pharm. Sci.* **2009**, *1*, 47 – 64; b) A. Verma, S. K. Saraf, *Eur. J. Med. Chem.* **2008**, *43*, 897 – 905; c) S. P. Singh, S. S. Parmar, K. R. Raman, V. I. Stenberg, *Chem. Rev.* **1981**, *81*, 175 – 203.

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

[20] For a review on conjugate additions to nitroolefins, see: a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877 – 1894; for reviews on organocatalytic asymmetric conjugate additions, see: b) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561 – 2601; c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; d) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365; e) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065 – 2092; f) *Organocatalytic Enantioselective Conjugate Addition Reactions* (Eds.: J. L. Vicario, D. Badía, L. Carrillo, E. Reyes), RSC, Cambridge, **2010**; g) *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, Weinheim, **2010**.

[21] CCDC 947275 (**E**) and 930440 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

[22] a) O. Tomotaka, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 – 12673; b) H. Miyabe, T. Takemoto, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785 – 795; c) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964 – 8965; d) S. H. McCooey, S. Connon, *Angew. Chem.* **2005**, *117*, 6525 – 6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367 – 6370; e) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481 – 4483; f) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967 – 1969; for recent reviews on (thio)urea-tertiary amines, see: g) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418 – 5427; h) W. Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298 – 1310; i) H. B. Jang, J. S. Oh, C. E. Song in Ref. [2c], pp. 119–168; j) T. Inokuma, Y. Takemoto in Ref. [2c], pp. 437–497.

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

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

[25] a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759 – 5812; b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036 – 12041.

[26] a) V. Semetey, D. Rognan, C. Hemmerlin, R. Graff, J. P. Briand, M. Marraud, G. Guichard, *Angew. Chem.* **2002**, *114*, 1973 – 1975; *Angew. Chem. Int. Ed.* **2002**, *41*, 1893 – 1895; b) V. V. Sureshbabu, B. S. Patil, R. Venkataramanarao, *J. Org. Chem.* **2006**, *71*, 7697 – 7705; c) A. C. Myers, J. A. Kowalski, M. A. Lipton, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5219 – 5222; d) V. Semetey, C. Hemmerlin, C. Didierjean, A. P. Schaffner, A. G. Giner, A. Aubry, J. P. Briand, M. Marraud, G. Guichard, *Org. Lett.* **2001**, *3*, 3843 – 3846.

[27] C. Czekelius, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 618 – 621; *Angew. Chem. Int. Ed.* **2005**, *44*, 612 – 615, and references therein.

[28] a) M. Bartra, P. Romea, F. Urpí, J. Vilarrasa, *Tetrahedron* **1990**, *46*, 587 – 594; b) C. C. Hughes, D. Trauner, *Angew. Chem.* **2002**, *114*, 4738 – 4741; *Angew. Chem. Int. Ed.* **2002**, *41*, 4556 – 4559.

[29] For mechanistic details on Michael reactions with nitroolefins and thiourea-tertiary amine catalysts, see: a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151 – 13160; b) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682 – 2685. Also, see Ref. [22a,b].

[30] At present no conclusive results are attained from computational studies. The flexibility of the rather large catalyst **H** requires an extensive number of reaction modes to be examined. For related work, see: E. Gómez-Bengoa, A. Linden, R. López, I. Mugica-Mendiola, M. Oiarbide, C. Palomo, *J. Am. Chem. Soc.* **2008**, *130*, 7955 – 7966.

[31] An illustrative example is the Mannich reaction of 2-naphthalenesulphonyl acetonitrile with N-Boc imines to afford β-amino nitriles, a reaction which is promoted by catalyst **E** in good chemical yields and *ee* values up to 94%. Full details of this reaction as well as the application of these Brønsted bases to other transformations will be published soon. For some further information see the Supporting Information.

