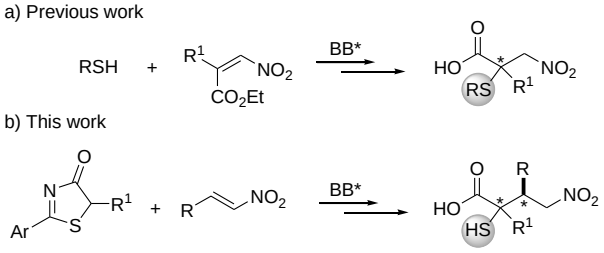
Catalytic Enantioselective Synthesis of Tertiary Thiols From 5H-Thiazol-4-ones and Nitroolefins Mediated By a Bifunctional Ureidopeptide-Based Brønsted Base Catalyst

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

Dedicated to Prof. C.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 analogs as the pronucleophilic reaction partners. 5H-Thiazol-4-ones, on the other hand, have been well known for a long time and have found several applications in pharmaceutical and medicinal chemistry.[3] Although structurally related to 5H-oxazol-4-ones,[4] and 4H-oxazol-5-ones (azlactones)[5], 5H-thiazol-4-ones have, as far as we know, been never explored in asymmetric synthesis in spite of the fact that their may be easily deprotonated[6] and 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 scarcely explored owing to the insufficient catalytic enantioselective methodology for their preparation in optically pure form.[9]

The most general practice for the synthesis of organosulfur compounds involves reaction of a sulfur nucleophile with an electrodeficient π–olefin acceptor.[10] By this way Zhang and coworkers[11] reported an efficient catalytic asymmetric synthesis of tertiary thiols using chiral Brønsted bases and β–substituted β–ethoxycarbonyl nitroalkene acceptors. Inversely, 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 coworkers[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-h] 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



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.

the asymmetric synthesis of tertiary thiols are clearly necessary to help to fill this important gap in organic chemistry. The inherent difficulty associated with the stereoselective construction of quaternary stereogenic centers is probably the reason that justifies this limited number of studies.[16] In connection with our efforts directed towards the asymmetric synthesis of organosulfur compounds, ie. β,β–disubstitued β–mercapto carboxylic acids[17a,b] and thiiranes[17c] we now focused on the enantioselective generation of a quaternary stereogenic center at α– position of α–mercapto carboxylic acids.[18] We report here the first highly diastereo- and enantioselective direct Michael addition of 5H-thiazol-4-ones to nitroolefins, Scheme 1, that 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 nitroolefin **5a** (R: Ph).[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 ºC. In every case product **6a** (R: Ph) was obtained but with disappointing chemical and stereochemical results (12-40% ee's).[21] Next, on the basis of pioneering studies of Takemoto and subsequent seminal works by Jacobsen, Connon, Dixon and Soós on bifunctional (urea)thiourea-tertiary amine catalysts,[22] we examined catalysts **I**, **II** and **III**. However, as the results in Table 1 show catalyst **I** led to almost

[*] S. Diosdado, J. Etxabe, J. Izquierdo, Dr. A. Landa, Dr. A. Mielgo, I. Olaizola, Dr. R. López and Prof. Dr. C. Palomo
Departamento de Química Orgánica I
Facultad de Química
Universidad del País Vasco. Apdo. 1072
20080 San Sebastián (Spain)
Fax: (+34)943-015270
E-mail: claudio.palomo@ehu.es

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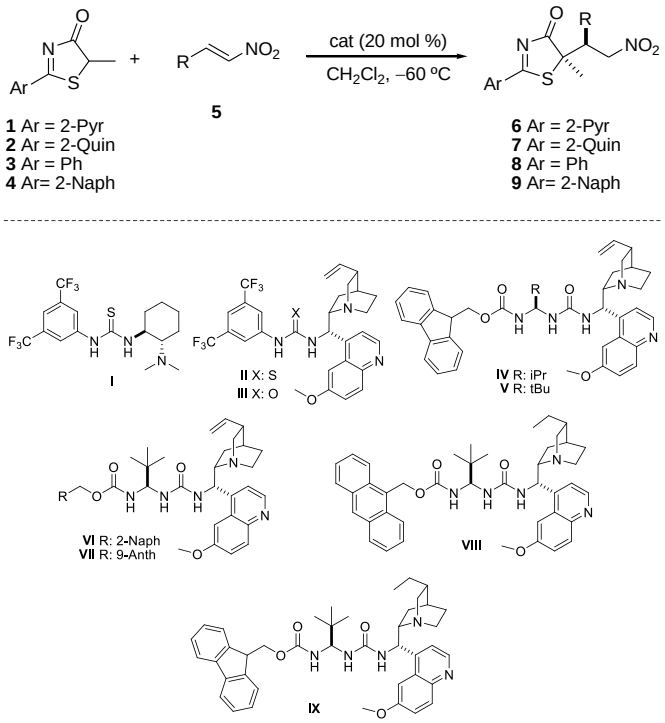
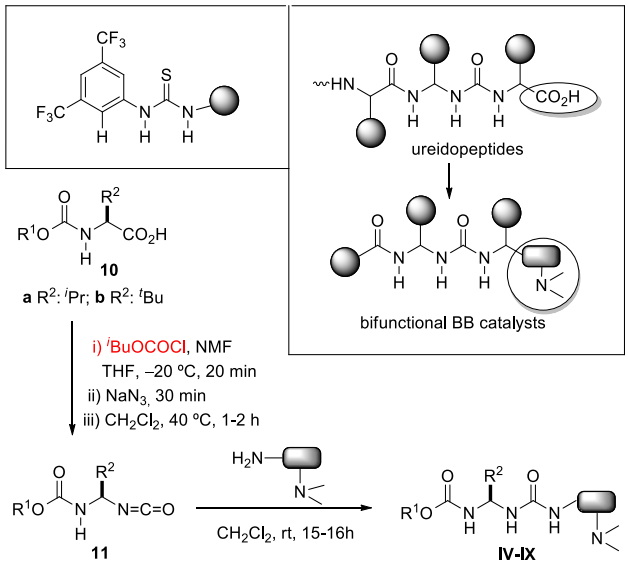


Scheme 2. Conjugate addition of 5-methyl 5H-thiazol-4-ones to nitro olefins promoted by chiral Brønsted bases.

racemic **6a** (entry 1), whilst no improvement was essentially observed either with catalyst **II** or with catalyst **III** (entries 2,3).

At this stage and in view of these results focus was then turned on catalyst design. Like catalysts **I, II**, and **III** most thiourea (urea) based Brønsted bases, known to date, display the 3,5-(bis(trifluoromethyl)phenyl group, a structural motif that was introduced first by Schreiner and Wittkopp in 2002 for hydrogen bond catalysis.[23] Recently, Schreiner and co-workers have also 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*-CH 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



Scheme 3. Ureidopeptide-based Brønsted bases: Catalysts preparation.

whether the urea derivatives **IV-IX** might be more appropriate catalysts for promoting the above reaction. These products display as new features the presence of a N,N´-diacyl aminal unit, in place of the bis(trifluoromethyl)phenyl group, and an urea moiety as hydrogen bond donors and both in close proximity to an additional stereodirecting group. This type of structures closely resembles to ureidopeptides, Scheme 3, which 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.

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

Entry	Comp.	Cat.	Prod. (R: Ph)	t, h	Yield (%)[b]	dr[c]	ee[d]
1	**1**	**I**	**6a**	48	53	83:17	20
2		**II**		20	53	60:40	35
3		**III**		20	48	54:46	40
4		**IV**		20	88	91:9	40
5		**V**		20	92	95:5	66
6		**VI**		20	90	94:6	70
7		**VII**		20	86	90:10	78
8		**VIII**		20	80	93:7	80
9	**2**	**VIII**	**7a**	20	93	95:5	96
10	**3**	**VIII**	**8a**	20	65	85:15	55
11	**4**	**VIII**	**9a**	20	55	75:25	68

[a] Reactions conducted at –60 ºC on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitro olefin/thiazolone/catalyst 2:1:0.2). [b] Yield of the isolated major isomer. [c] Determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] Determined by chiral HPLC.

Although, from this design 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 *tert*-leucine derivatives **10a** and **10b**, catalysts **IV-IX** 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 isolated yields within the range of 70-80% for the latter step. A single crystal X-ray analysis of **V** 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, Figure 1.[21]

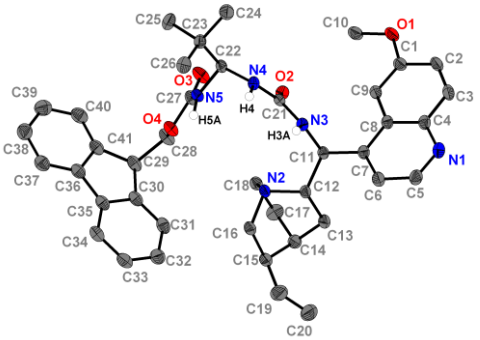
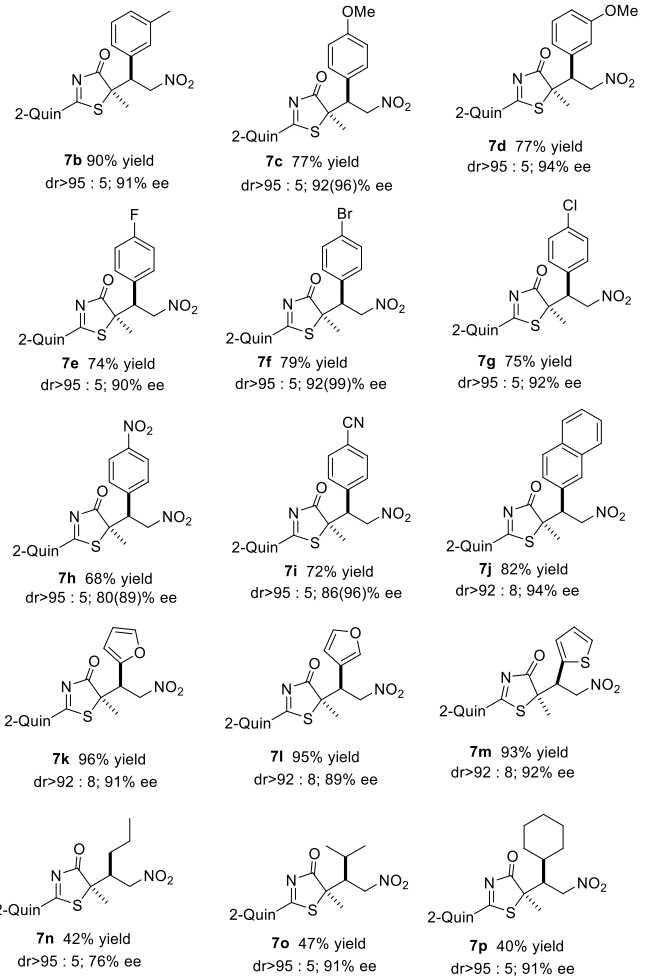


Figure 1. ORTEP representation for **V** depicted at 50% probability. Hydrogen atoms (except H3A, H4 and H5A) omitted for clarity.

Experiments with these catalysts revealed an improvement in diastereoselectivity. Also, by increasing the size of the aminal substituent from isopropyl to *tert*-butyl, catalysts **IV** and **V**, enantioselectivity raised up to 66%, but still insufficient (Table 1, entries 4, 5). Further improvements in the reaction selectivity were

observed with catalyst **VI** and **VII** (entries 6,7) and the best result was produced with catalyst **VIII** that provided product **6a** in 80% yield and 80% ee (entry 8). In subsequent experiments it was found that using quinoline-derived thiazolone **2** and catalyst **VIII** the corresponding product **7a** (entry 9) was produced in 93% yield as a 95:5 mixture of diastereomers and with 96% ee for the major isomer. On the other hand, using thiazolones **3** and **4** the corresponding

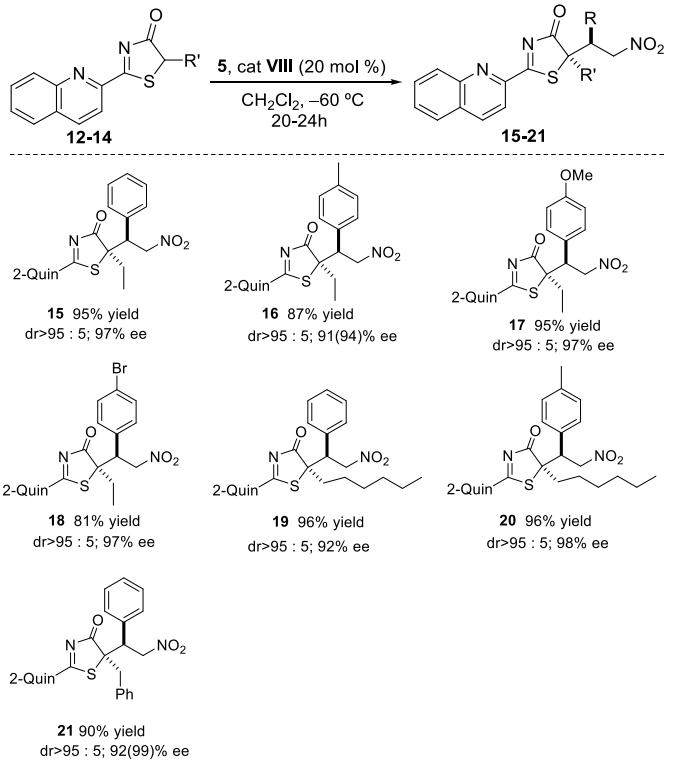
Table 2. Conjugate addition of thiazolone **2** to nitro olefins **5** promoted by catalyst **VIII**.[a-d]



[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitro olefin/thiazolone/catalyst 2:1:0.2) at -60ºC for 20-24h. [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. Data in parentheses were obtained after crystallization from diethyl ether or diisopropyl ether. Using 10 mol% of catalyst loading essentially same results for **7c**, **7f** and **7o** were attained.

addition products **8a** and **9a** (entries 10,11) were formed in lower diastereomeric ratios and ee's, results that seem to indicate that the pyridine and quinoline nitrogen atoms of thiazolones **1** and **2** play a significant role on reaction stereocontrol. A representative selection of nitroolefins was evaluated in order to establish the generality of this asymmetric route to tertiary thiols. As the survey collected in Table 2 shows, nitroolefins bearing β-aryl substituents with either electron-donating or electron-withdrawing groups are almost equally tolerated giving the corresponding adducts with good diastereomeric ratios, typically greater than 95:5 and ee´s up to 96%. For example, performing the reaction with substrates **5b, 5c,** and **5d,** products **7b, 7c** and **7d** were essentially produced as single diastereomers and with ee´s within the range 91-94%. Nitroolefins **5e**, **5f** and **5g** with inductively electron-withdrawing fluoro, bromo, and chloro substituents also provided excellent chemical and stereochemical results whereas nitrostyrenes **5h** and **5i** bearing mesomeric electron-withdrawing substituents gave the corresponding **7h** and **7i** with slighthly reduced enantioselectivities. The method also works with nitroolefins with heteroaromatic β–substituents such as **5k, 5l** and **5m** to afford adducts **7k, 7l** and **7m** 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 yields, typically 40%. Unbranched aliphatic nitroolefin **5n** led to the product **7n** with modest 76% ee whereas branched aliphatic substrates **5o** and **5p** provided **7o** and **7p** in 91% ee. In this study we have employed 20 mol% of catalyst but it is mention to note that using 10 mol% of catalyst loading the reactions proceeded equally well without compromising either selectivity or chemical yield (Table 2 and experimental section).

Table 3.Thiazolone scope.[a-d]



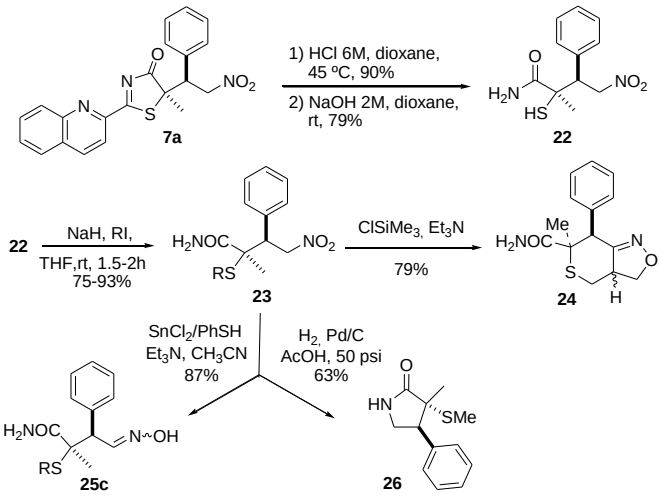
[a] Reactions conducted on a 0.3 mmol scale in 0.6 mL of CH_2Cl_2 (mol ratio nitroalkene/thiazolone/catalyst 2:1:0.2). [b] Yields refer to the isolated major isomer. [c] dr´s determined by ^{1}H NMR (300 MHz) analysis on the crude product. [d] ee´s determined by chiral HPLC.

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 products **15-18**, essentially as sole diastereomers with excellent yields, and 91-97% ee's. Similarly, the hexyl and benzyl thazolones, **13** and **14**, 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, thiazolones **2**, **12-14** and nitroolefin **5**, a property that is readily translated to the resulting products **7, 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 **7f**[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

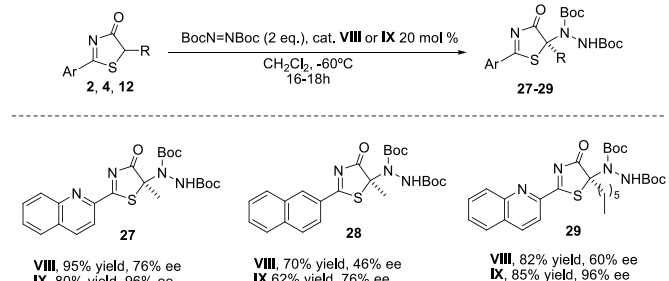
organosulfur compounds that generally give aryl or alkyl thioethers,[9-15] our method provides a quick entry to mercapto compounds with the thiol group in its free form, Scheme 4. Therefore, the question that we examined next was to establish whether these adducts could be S-alkylated without affecting 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 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, in its turn, facilitates access to more elaborated products as exemplified in the formation of the tetrahydrothiopyran fused isoxazoline **24** from **23b**. On the other hand, oximes such as **25c**, may also be obtained in good yields by treatment of the respective thioether adduct with $SnCl_2$ /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 leading to γ-lactams.



a R= Me **b** R= CH_2=$CHCH_2$ **c** R= 2-NaphCH_2 **d** R= n-Hex

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

Concerning the mechanism of these reactions,[29] we believe that the quinoline nitrogen atom of these thiazolone substrates could interact through hydrogen bond with one of the three accessible N-H protons of the catalyst, likely with one of the aminal moiety thereby providing a well ordered transition state during reaction.This assumption nicely accounts for the best behavior of quinolyl thiazolone substrates *versus* 2-naphthyl thiazolone **4**. Further support for this assumption was provided from the amination reaction of thiazolones **2, 4** and **12** with *tert*-butylazodicarboxylate, Scheme 5. Whilst in this case enantiocontrol proceeded better with catalyst **IX** rather than with catalyst **VIII**, thiazolones bearing the quinoline moiety, **2** and **12**, furnished once again 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 that are currently under study. [31]



Scheme 5. Catalytic enantioselective α-amination of thiazolones.

In summary, we have realized the first direct catalytic Michael reaction of α-mercapto carboxylate surrogates with nitroolefins involving a fully substituted α-carbon atom construction. The method demonstrates the efficacy of 5H-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 enantioselectivity and, consequently, the method contributes to broaden the currently limited methodology available for the catalytic enantioselective synthesis of tertiary thiols. From an intuitive design we have also 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 (or peptide) derived 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 be a good help to address this challenging issue.

Experimental Section

To a mixture of 5-methyl-2-(quinolin-2-yl)thiazol-4-ol (**2**) (242.3 mg, 1.0 mmol, 1 eq.) and nitrostyrene **5a** (298.3 mg, 2.0 mmol, 2 eq.) in dichloromethane (2.0 mL) cooled to -60 ºC catalyst **VIII** (67.6 mg, 0.1 mmol, 10 mol%) was added. The resulting suspension was stirred at the same temperature, until consumption of the thiazolone (16h) (monitored by ^{1}H-NMR by disappearance of the methyl signal at 1.46 ppm). After this time the crude material 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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 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 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 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. 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, hexane/ isopropanol / ethanol 85/14/1, flow rate= 0.5 mL/min, retention times: 45.5 min (min.) and 57.2 min (major.)).

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[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) Science of Synthesis, Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics (Ed.: K. Maruoka), Thieme Verlag, Stuttgart, **2012**.

[3] a) N. A. Khalid, E. M. Ahmed, H. B. El-Nassan, *Med. Chem. Res.* **2012**, 1021-1027. b) U. -V. Grumnt, 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] 5H-oxazol-4-ones for the synthesis of α,α-branched α-hydroxy acids, see: 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*, 6585-6589; *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. Comm. 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. Katrizky; O. Methcohn; C. S. Ree's), 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**, *8*, 763-772.

[9] Review: J. Clayden, P. MacLellan, *Belstein J. Org. Chem.* **2011**, *7*, 582-595.

[10] Review on 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. MacFadden, 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. g) Z. Hang, W. Chen, S. Dong, C. Yang, H. Liu, Y. Pan, L. Yan, Z. Jiang, *Org. Lett.* **2012**, *14*, 4670-4673. h) 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. Tachemi, S. Yasuda, N. Kunagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 4218-4222. d) S. Takechi, N. Kumagai, M. Shibasaki, *Org. Lett.* **2013**, *11*, 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, D. *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. Almasi, 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* (Ed.: 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] 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**, *35*, 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, J. *Catal. Sci. Technol.* **2011**, *1*, 1298-1310. i) H. B. Jang, J. S. Oh, C. E. Song in ref 2, pp. 119-168. j) T. Inokuma, Y. Takemoto in ref.[2], 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*, P. M. Pihko Ed., 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*, 5758-5812. 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]

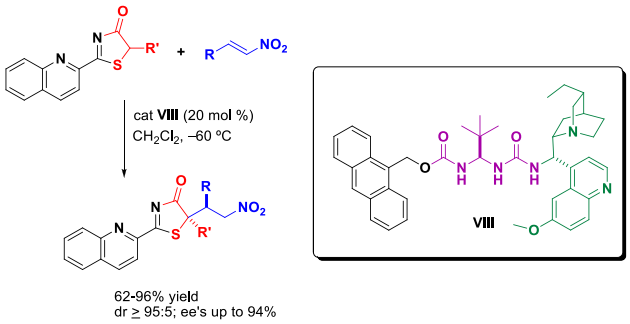
[30] At present not conclusive results are attained from computational studies. The flexibility of the rather large catalyst **VIII** requires an extensive number of reaction modes to be examined. For related work, see: E. Gómez-Bengoa, A. Linden, R. López, I. Mugica-Mendiola, M. Oiarbide, C. Palomo, *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 that is promoted by catalyst **V** in good chemical yields and ee's 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 supplementary material.

From ureidopeptides to bifunctional Brønsted base organocatalysts

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

Catalytic Enantioselective Synthesis of Tertiary Thiols From 5H-Thiazol-4-ones and Nitroolefins Mediated By a Bifunctional Ureidopeptide-Based Brønsted Base Catalyst



62-96% yield
dr ≥ 95:5; ee's up to 94%

An ureidopeptide-based bifunctional Brønsted base efficiently promotes the first direct catalytic Michael reaction of α-mercapto carboxylate surrogates with nitroolefins involving a fully substituded α-carbon atom construction.