ChemPubSoc Europe

DOI: 10.1002/chem.201304877

CHEMISTRY
A European Journal
Full Paper

Asymmetric Catalysis

Ureidopeptide-Based Brønsted Bases: Design, Synthesis and Application to the Catalytic Enantioselective Synthesis of β-Amino Nitriles from (Arylsulfonyl)acetonitriles

Saioa Diosdado, Rosa López, and Claudio Palomo*[a]

Abstract: The addition of cyanoalkyl moieties to imines is a very attractive method for the preparation of β-amino nitriles. We present a highly efficient organocatalytic methodology for the stereoselective synthesis of β-amino nitriles, in which the key to success is the use of ureidopeptide-based Brønsted base catalysts in combination with (arylsulfonyl)acetonitriles as synthetic equivalents of the acetonitrile anion. The method gives access to a variety of β-amino nitriles with good yields and excellent enantioselectivities, and broadens the stereoselective Mannich-type methodologies available for their synthesis.

Introduction

Current interest in organocatalysis has focused much attention on the development of chiral Brønsted bases (BBs) to catalyse proton-transfer reactions for the production of optically enriched products.[1] In particular, catalysts that combine a site with BB character and another site with hydrogen-bond donor ability have emerged as the most powerful tools to achieve this goal.[2] Remarkable advances in this context have been made since the first chiral thiourea–tertiary amine catalyst **A**, developed by Takemoto[3] (Figure 1). Works by Connon,[4] Dixon[5] and Soós[6] have revealed urea/thiourea-substituted *Cinchona* alkaloids **B** and **C** to be excellent bifunctional BB catalysts for several reactions[7] and, more recently, other bifunctional BB catalysts (sulfinylurea–tertiary amine,[8] squaramides,[9,10] benzimidazole–tertiary amine[11] and quinazolone–tertiary amine)[12] that illustrate the concept of multiple catalyst–substrate interactions have been reported.[13] Despite these significant advances, strong substrate dependence is still quite common and catalyst optimisation is often required. To meet the need of many challenging asymmetric reactions, the design of new, readily accessible BB catalysts to assist with rapid architecture modification is, therefore, desirable. In this context, a significant observation has been made by Schreiner and co-workers,[14] who suggested that the success of thio-(urea) BB catalysts that contain the 3,5-bis(trifluoromethyl)-phenyl group may be attributed to the participation of both N–H bonds of the thiourea unit and the *ortho* C–H bond of the aryl group during substrate activation. On this basis, and given the proved efficacy of synthetic peptides for fine-tuning the reactivity and selectivity of several synthetic transformations,[15] we have recently developed ureidopeptide-based BBs as a new sub-family of organic catalysts (Figure 1).[16] These compounds are distinguished by the presence of an N,N-diacylaminal unit (in place of the bis(trifluoromethyl)phenyl group) and a urea moiety as hydrogen-bond donors, both in close proximity to an additional stereo-directing group. These bifunctional BBs are readily accessible from the corresponding α-amino acid derived isocyanates and amino *Cinchona* alkaloids and have been shown to be very effective catalysts for the conjugate addition reaction of 5*H*-thiazol-4-ones to nitroolefins.

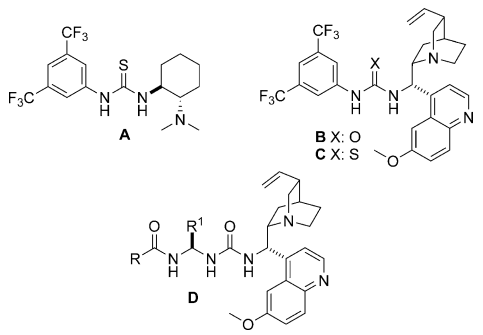


Figure 1. Prototypical (thio)urea–tertiary amine catalysts (**A**–**C**) and ureidopeptide-based Brønsted base catalysts **D**.

Herein, we present further evidence of the potential scope of these BBs and document the Mannich-type reaction of (arylsulfonyl)acetonitriles with *N-tert*-butoxycarbonyl (*N*-Boc) imines to give β-amino nitriles with very high enantioselectivity.

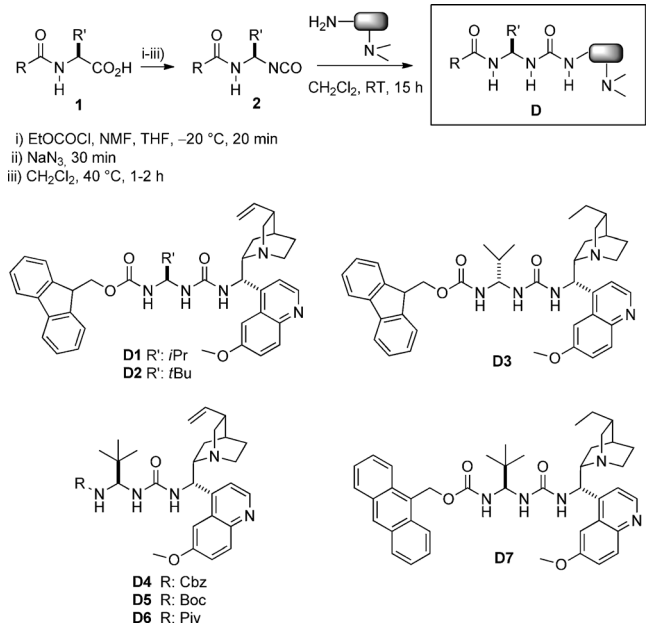
[a] *Dr. S. Diosdado, Dr. R. López, Prof. Dr. C. Palomo*
Departamento de Química Orgánica I
Facultad de Química
Universidad del País Vasco
Apdo. 1072, 20080 San Sebastián (Spain)
E-mail: claudio.palomo@ehu.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201304877.

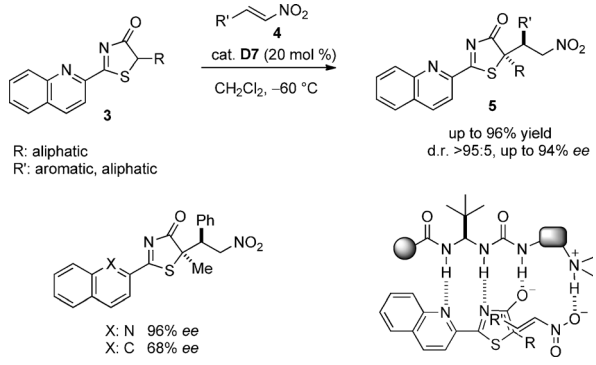
Results and Discussion

Ureidopeptide-based BBs are readily accessible by simple condensation of α-amino acid derived isocyanates **2** and the appropriate 9-epi-9-amino *Cinchona* alkaloids. By this method (Scheme 1), we have easily prepared catalysts **D** from valine and *tert*-leucine derivatives **1**, with good overall yields.

These BBs efficiently catalysed the reaction of thiazolones **3** with nitro-olefins **4** to produce adducts **5** (Scheme 2). This



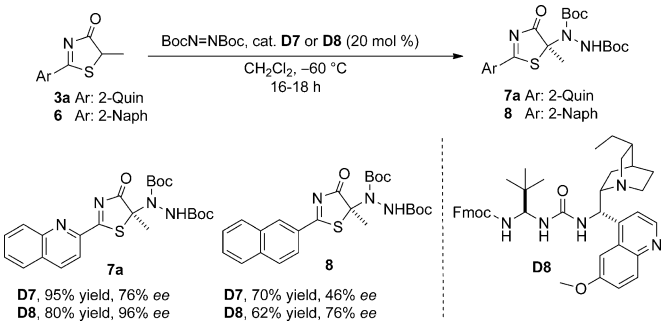
Scheme 1. Preparation of ureidopeptide-based Brønsted bases. NMF = *N*-methylformamide, Cbz = carbobenzyloxy, Piv = pivalolyl.



Scheme 2. Conjugate addition of thiazolone **3** to nitro-olefins **4** promoted by catalyst **D7** and proposed model for the addition.

reaction involves the construction of a tetrasubstituted α-carbon atom and represents the first direct BB-mediated Michael reaction of α-mercapto carboxylate surrogates.[17] The best results were obtained with catalyst **D7**, which tolerates nitro-olefins that bear β-aryl substituents with either electron-donating or electron-withdrawing groups, heteroaromatic β substituents and even the recalcitrant β-alkyl-substituted nitro-olefins. Also, thiazolones with short, large and ramified alkyl chains afford the corresponding adducts **5** with high diastereo- and enantioselectivity, which shows the generality of this asymmetric route to tertiary thiols.[18]

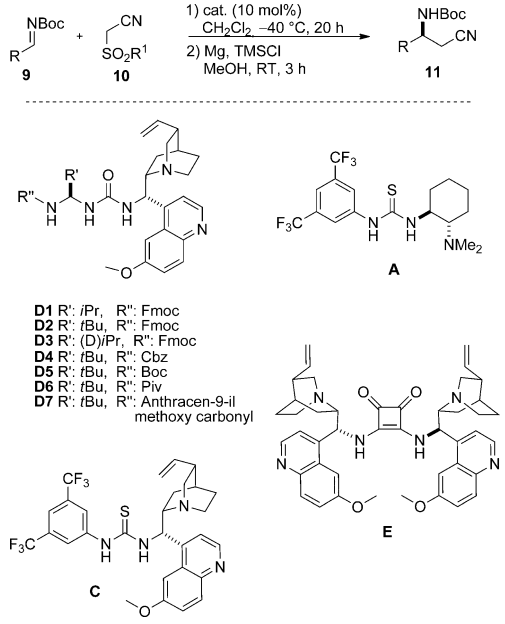
During this study, it was observed that replacement of the 2-quinoline substituent in the thiazolone framework by a naphthyl moiety caused a loss of stereoselectivity. A representative example of this observation is shown in Scheme 2. This result was attributed to the additional basic centre of the substrate donor, which could interact with one of the three accessible N–H protons of the catalyst, most likely from the aminal moiety, as shown in the model depicted in Scheme 2. A similar trend was observed in the α-amination reaction of thiazolones **3a** and **6** with *tert*-butylazodicarboxylate (to give **7a** and **8**, respectively), regardless of the catalyst employed (Scheme 3).



Scheme 3. Catalytic enantioselective α-amination of thiazolones **3a** and **6**.

Given these observations and with the aim to test the potential scope of this sub-family of catalysts within the context of organocatalytic carbon–carbon bond formation,[19] we decided to evaluate the Mannich reaction between *N*-Boc imines **9** with substrate donors that lacked additional Lewis basic sites, such as (arylsulfonyl)acetonitriles **10**[20] (Scheme 4). This reaction, after desulfonylation of the intermediate adducts, provides β-amino nitriles, which are useful intermediates for the preparation of β-amino acids and 1,3-diamines.[21] Whereas several catalytic asymmetric direct Mannich reactions that involve β-dicarbonyl compounds,[22] malonic acid derivatives[23] and β-(arylsulfonyl) carbonyl compounds[24] have been developed, very few direct Mannich methodologies for the production of α-unsubstituted β-amino nitriles in a highly enantioselective fashion are available.[25,26]

We were gratified to observe that, amongst the catalysts tested, the ureidopeptide-based BBs were the most effective for the reaction of (phenylsulfonyl)acetonitrile (**10a**) with *N*-Boc imine **9a** (R = Ph; Table 1). After 20 h of stirring at −40 °C, catalysts **D1**–**D7** promoted nearly complete conversion. The stereochemical outcome of the reaction was uniform and the *R* configuration was observed for adduct **11a**, regardless of the catalyst employed.[27] The results presented in Table 1 show that the bulk of the R' substituent in the catalyst has a great impact on enantioselectivity; catalyst **D2**, which bears a *tert*-butyl group, produced **11a** with 85% *ee* (compare Table 1, entries 1 and 2). Additionally, the combination L-α-amino acid/



Scheme 4. Mannich addition of sulfonyl acetonitriles **10** to *N*-Boc imines **9** promoted by chiral Brønsted bases.

Table 1. Catalyst screening for the Mannich reaction of **9a** (R = Ph) to produce **11a**.

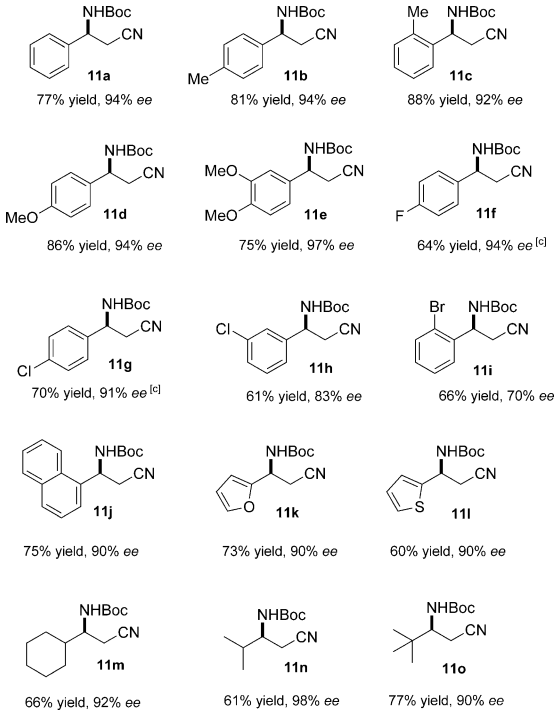
Entry	Cat.	R^1, sulfone	Conv. [%][b]	*ee* [%][c]
1	**D1**	Ph, **10a**	>95	65
2	**D2**	Ph, **10a**	>95	85
3	**D3**	Ph, **10a**	85	54
4	**D4**	Ph, **10a**	>95	75
5	**D5**	Ph, **10a**	>95	70
6	**D6**	Ph, **10a**	>95	65
7	**D7**	Ph, **10a**	82	83
8	**D2**	2-naphthyl, **10b**	>95	94 (93)[d]
9	**D2**	2-naphthyl, **10b**	>95[e]	90[e]
10	**D2**	1-naphthyl, **10c**	>95	70
11	**A**	Ph, **10a**	75	40
12	**A**	2-naphthyl, **10b**	70	40
13	**C**	Ph, **10a**	>95	15
14	**C**	2-naphthyl, **10b**	90	50
15	**E**	2-naphthyl, **10b**	88	45

[a] Reactions were carried out at 0.5 mmol scale by using **10** (1.5 equiv) in CH_2Cl_2 (3 mL) at −40 °C. [b] Conversion for the organocatalysed addition determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] $CHCl_3$ used as solvent. [e] Reaction performed at −20 °C.

9-epi-9-amino quinine seemed to reinforce the asymmetric induction exerted by the catalyst (compare Table 1, entries 1 and 3). Parameters such as sulfone substitution and reaction conditions were evaluated by using catalyst **D2**. The nature of the R^1 group in the sulfone moiety remarkably affected the asymmetric induction (Table 1, entries 8–10). The best result was produced from (2-naphthylsulfonyl)acetonitrile **10b** (Table 1, entry 8) which led to the β-amino nitrile **11a** with 94% *ee*. Among the solvents, methylene chloride and chloroform gave the best results. Low or non-existent *ee* values were obtained in toluene and THF, respectively, and in diethyl ether no appreciable transformation was detected after 48 h. Reaction temperatures below −40 °C produced partial catalyst precipitation, whereas at −20 °C the reaction between *N*-Boc imine **9a** and **10b** afforded the corresponding β-amino nitrile **11a** in a diminished 90% *ee* (Table 1, entry 9). In sharp contrast, catalysts such as the thiourea–tertiary amine **A**, the *Cinchona*-based thiourea **C** and the *Cinchona*-based squaramide **E** provided the product **11a** with poor enantioselectivity regardless of the (arylsulfonyl) acetonitrile employed (Table 1, entries 11–15).

Next, we explored the generality of the optimised procedure in the preparation of several representative chiral β-amino nitriles. Catalyst **D2** promoted the addition reaction of **10b** to a variety of *N*-Boc-protected imines within 15–24 h at −40 °C to afford the corresponding enantio-enriched β-amino nitriles in good yields over two steps (addition and desulfonylation). The data presented in Table 2 shows that the *ee* values were high for aryl *N*-Boc imines with electron-donating groups, irrespective of the position or quantity of such groups. For example, the reaction with imines **9b–e** led to the corresponding products **11b–e** with 92–97% *ee*. Aryl *N*-Boc imines with electron-withdrawing groups produced enantio-enriched β-amino nitriles with slightly reduced yields and enantioselectivities that, in some instances, could be increased up to 94% *ee* by reduction of the reaction temperature to −60 °C, although prolonged reactions times were required for reaction completion

Table 2. *N*-Boc imine scope for the Mannich reaction with sulfonyl acetonitrile **10b** promoted by catalyst **D2**.



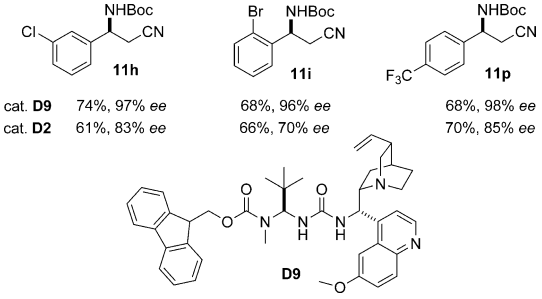
[a] Reactions were carried out at 0.5 mmol scale by using imine (1 equiv), **10b** (1.3 equiv) and catalyst (0.1 equiv) in CH_2Cl_2 (3 mL) at −40 °C for 15–24 h. [b] The *ee* values were determined by HPLC analysis on a chiral stationary phase. [c] Reaction carried out at −60 °C for 36–40 h.

(**11 f** and **11 g**). The method also worked well for imines with bulkier groups (**11 j**) and heteroaromatic azomethines, such as **9 k** and **9 l**, to afford adducts **11 j**–**l** in 90% *ee*. The procedure was even applicable to stable α-branched alkyl-substituted *N*-Boc imines to give the desired β-amino nitriles **11 m**–**o** in good yields and enantioselectivities up to 98% *ee*.

Self-aggregation is an intrinsic problem of bifunctional organocatalysts, especially when substrates do not have functional groups able to bind strongly with the catalyst. It has been shown that urea- and thiourea-based bifunctional organocatalysts can form hydrogen-bond aggregates in the solid state[28] and, more recently, NMR spectroscopic studies have corroborated this behaviour, even in solution.[29] Due to this phenomena, the enantioselectivity obtained for a particular transformation can be strongly dependent on concentration and temperature. When the formation of aggregates negatively affects selectivity, the *ee* usually decreases with an increase in the catalyst concentration or decrease in reaction temperature. To gain some insight into the behaviour of the ureidopeptide-based BB catalysts, we performed the Mannich reaction between the *N*-Boc imine **9 e** and **10 b** at various concentrations and catalyst loadings. The data in Figure 2 shows that neither the reaction concentration (based on *N*-Boc imine **9 e**) nor the catalyst loading affect the asymmetric induction promoted by catalyst **D2**. Taking these experimental results into account, it might be argued that, under the conditions of the Mannich reaction, the ureidopeptide-based BB catalysts would exist as monomeric species in solution and only one molecule of catalyst would be involved in the rate-limiting step.

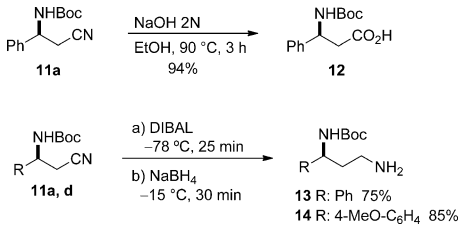
On the other hand, during the optimisation of the methodology, we observed some uneven stereochemical results by alteration of the reaction temperature. For instance, as expected, *ee* values for adducts **11 f** and **11 g** were raised to 94 and 91%, respectively, when the temperature was lowered to −60 °C (89 and 86% *ee*, respectively, were obtained at −40 °C). Nevertheless, the best results for adducts **11 h** and **11 i** were attained at −40 °C and no improvement was observed when the temperature was lowered to −60 °C. Furthermore, under these conditions, conversion was lower due to the fact that catalyst **D2** and *N*-Boc imines **9 h** and **9 i** are partially insoluble below −40 °C.

The high degree of modularity in the catalyst architecture quickly allowed us to establish the benefits of a bulky group in the geminal position of the N,N-diacyl aminal, along with the presence of aromatic groups at the nitrogen atom of the α-amino acid unit. Thus, replacement of the terminal FmocNH moiety by the bulkier FmocN(Me) group (catalyst **D9**) was beneficial; enantioselectivity was improved, particularly in the reaction of aryl imines with electron-withdrawing groups. Reaction of **10 b** with *N*-Boc imines **9 h**, **9 i** and **9 p** carried out at −40 °C in the presence of catalyst **D9** provided the corresponding adducts with excellent *ee* values relative to those obtained with catalyst **D2** (Scheme 5).



Scheme 5. Enantiomeric excesses obtained for β-amino nitriles **11 h**, **11 i** and **11 p** with catalysts **D9** and **D2**.

Finally, the absolute configuration of the adducts was further confirmed by transformation of adduct **11 a** into the known β-amino acid **12**, and by assuming an uniform reaction mechanism. In addition, adducts **11** could be easily manipulated to produce enantio-enriched 1,3-diamines which are common structural motifs in naturally occurring and synthetic molecules (Scheme 6).



Scheme 6. Elaboration of adducts to β-amino acids and 1,3-diamines. DIBAL = diisobutylaluminium hydride.

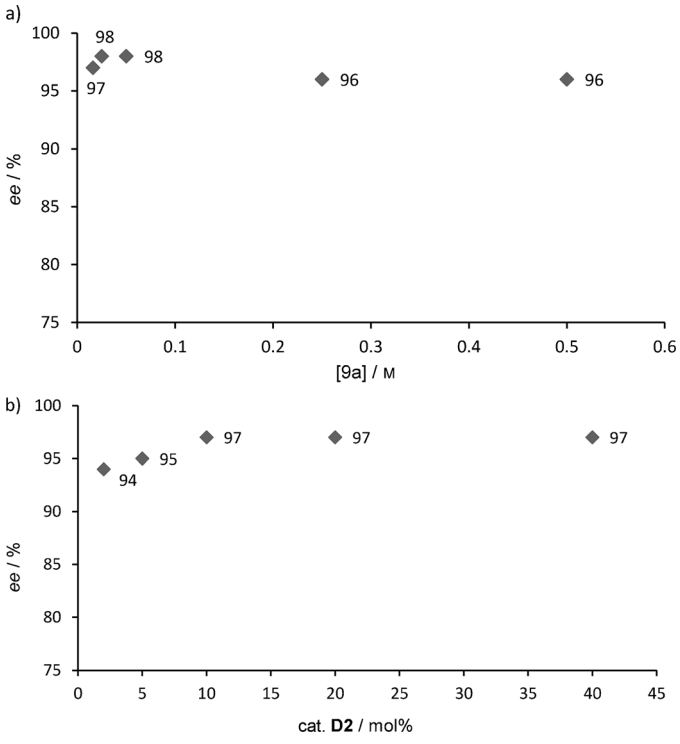


Figure 2. Effect on enantioselectivity of a) reaction concentration and b) catalyst loading.

Conclusions

We have realized an effective organocatalytic Mannich-type reaction of *N*-Boc imines and sulfonyl acetonitriles, which allows the production of α-unsubstituted β-amino nitriles in a highly enantioselective fashion. The method demonstrates the efficacy of the ureidopeptide-based BB catalysts to perform the organocatalytic reaction and (2-naphthylsulfonyl)acetonitrile to act as a synthetic equivalent of the acetonitrile anion. The process offers a simple and efficient route for the catalytic enantioselective synthesis of β-amino nitriles and also provides experimental evidence for the potential scope of this family of BB catalysts.

Experimental Section

Typical procedure for the Mannich reaction of *N*-Boc imine 9a and sulfonyl acetonitrile 10b (11a)

Sulfonyl acetonitrile **10b** (0.150 g, 0.65 mmol, 1.3 equiv) was added to a mixture of **9a** (0.5 0mmol, 1 equiv) and catalyst **D2** (0.034 g, 0.05 mmol, 0.10 equiv) in dry CH_2Cl_2 (3 mL) at $-40\,^{\circ}C$ under a nitrogen atmosphere. The reaction mixture was stirred for 15 h, then quenched with HCl (5 mL, 0.1 N) and extracted with CH_2Cl_2 (3× 3 mL). The combined organic layers were washed with HCl (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2/MeOH (1:1, 3 mL) and Mg (0.24 g, 10 mmol, 20 equiv), 1,2-dibromoethane (0.01 mL) and TMSCl (0.01 mL) were added at 0 °C. The reaction mixture was stirred for 3–5 h at rt. The mixture was quenched with a saturated solution of NH_4Cl (5 mL) and filtered over Celite. The filtrate was diluted with EtOAc (20 mL) and washed with brine (3×10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography on silica gel (90:10 hexane/Et_2O) to produce pure **11a** (0.095 g, 77%) as a white solid. M.p. 109–113 °C; $[\alpha]_D^{25} = -5.6$ ($c = 0.6$, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$ (m, 5H), 5.17–4.92 (m, 2H), 3.11–2.85 (m, 2H), 1.50 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.8$, 138.5, 129.2, 128.7, 126.2, 116.9, 80.6, 51.3, 28.2, 25.2 ppm; chiral HPLC (Chiralpak IA; hexane/*i*PrOH 95:5; 0.5 mL min^{-1}, 210 nm): retention time (t_R) minor = 27.8 min, t_R (major) = 31.8 min; 94% *ee*; HRMS (TOF, MS, CI): *m/z* calcd for $C_{10}H_{11}N_2O$: 174.0793 [*M* H–C_4H_9O]$^+$; found:174.0793.

Acknowledgements

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. thanks MEC for a grant. We also thank S. Vera and A. Puente for their help with some transformations.

Keywords: Brønsted bases · nitriles · organocatalysis · peptides · 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.

[3] a) T Okino, 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; see also: c) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–9965.

[4] H. McCooey, S. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.

[5] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483.

[6] B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.

[7] For recent reviews on (thio)urea-tertiary amines, see: a) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; b) W. Y. Siau, J. Wang, *J. Catal. Sci. Technol.* **2011**, *1*, 1298–1310; c) H. B. Jang, J. S. Oh, C. E. Sogn, in *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics, Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 119–168; d) T. Inokuma, Y. Takemoto, in *Asymmetric Organocatalysis 2, Brønsted Base and Acid Catalysis, and Additional Topics, Science of Synthesis* (Ed.: K. Maruoka), Thieme, Stuttgart, **2012**, pp. 437–497.

[8] a) M. T. Robak, M. Trincado, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 15110–15111; b) K. L. Kimmel, M. T. Robak, J. A. Ellman, *J. Am. Chem. Soc.* **2009**, *131*, 8754–8755; c) K. L. Kimmel, J. D. Weaver, *Chem. Sci.* **2012**, *3*, 121–125.

[9] a) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417; b) Y. Zhu, J. P. Malerich, V. H. Rawal, *Angew. Chem.* **2010**, *122*, 157–160; *Angew. Chem. Int. Ed.* **2010**, *49*, 153–156.

[10] For reviews on squaramides, see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; b) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346.

[11] a) D. Almasi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163–6168; b) L. Zhang, M. Lee, S. Lee, J. Lee, M. Cheng, B. Jeong, H. Park, S. Jew, *Adv. Synth. Catal.* **2009**, *351*, 3063–3066.

[12] T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470–10477.

[13] For related thiourea–*Cinchona* based catalysts that illustrate this concept, see: a) T. Marcelli, R. N. S. van der Hases, J. H. Van der Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931; b) C. Palacio, S. J. Connon, *Org. Lett.* **2011**, *13*, 1298–1301; for selected examples of Brønsted base catalysts with multi-functional hydrogen-bond donors, see: c) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756; d) C.-J. Wang, X.-A. Dong, Z. H. Zhong, Z. Y. Xue, H.-L. Teng, *J. Am. Chem. Soc.* **2008**, *130*, 8606–8607; e) N. Li, W. Wu, F. Yu, H. Huang, X. Liang, J. Ye, *Org. Biomol. Chem.* **2011**, *9*, 2505–2511; f) M.-Y. Zhao, W. H. Tang, M. Y. Chen, D.-K. Wei, T.-L. Dai, M. Shi, *Eur. J. Org. Chem.* **2011**, 6078–6084; g) B. Liu, X. Han, Z. Dong, H. Lv, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2013**, *24*, 1276–1280.

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

[15] 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.

[16] S. Diosdado, J. Etxabe, J. Izquierdo, A. Landa, A. Mielgo, I. Olaizola, R. López, C. Palomo, *Angew. Chem.* **2013**, *125*, 12062–12067; *Angew. Chem. Int. Ed.* **2013**, *52*, 11846–11851.

[17] For recent direct methods to produce α,α-disubstituted mercapto carboxylic acid derivatives, see: enamine-mediated Michael reaction of rhodanines: a) F. Yu, H. Hu, X. Gu, J. Ye, *Org. Lett.* **2012**, *14*, 2038–2041; Mannich reaction of α-sulfonyl lactones: b) S. Takechi, N. Kumagai, M. Shibasaki, *Org. Lett.* **2013**, *15*, 2632–2635; thio Diels–Alder reaction: c) H. Jiang, D. C. Cruz, Y. Li, V. H. Lauridsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 5200–5207; electrophilic α-amination of 3-thiooxindoles: d) F. Zhou, X.-P. Zang, C. Wang, X.-L. Zhau, J. Zhou, *Chem. Commun.* **2013**, *49*, 2022–2024; after submission of this work, a paper that dealt with the enantioselective allylation of thiazolones was published: e) W. Chen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 377–382.

[18] For a review of tertiary thiols, see: J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582–595.

[19] a) U. Scheffler, R. Mahrwald, *Chem. Eur. J.* **2013**, *19*, 14346–14396; b) *Comprehensive Enantioselective Organocatalysis: Catalysis, Reactions, and Applications, Vols. 1–3* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.

[20] a) P. B. González, R. López, C. Palomo, *J. Org. Chem.* **2010**, *75*, 3920 – 3922; for a related reaction, see: b) K. Ohmatsu, A. Goto, T. Ooi, *Chem. Commun.* **2012**, *48*, 7913 – 7915; for selected reviews on Mannich reactions, see: c) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940 – 1948; d) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797 – 5815; e) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Chem. Rev.* **2008**, *37*, 29 – 41; f) D. Enders, E. Jafari, *Synthesis* **2013**, *45*, 2769 – 2812; g) see Ref. [19b], Vol. 3, Chapter 28, p. 793 and Chapter 29, p. 841.

[21] For β-amino acids, see: a) *Enantioselective Synthesis of β-Amino Acids* (Eds.: E. Juaristi, V. A. Soloshonok), Wiley-VCH, Weinheim, **2005**; b) E. F. Kleinmann, in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, Chapter 4.1; c) R. Caputo, E. Cassano, L. Logobardo, G. Palumbo, *Tetrahedron* **1995**, *51*, 12337 – 12350; d) T. Hintermann, D. Seebach, *Chimia* **1997**, *51*, 244 – 247; e) U. Koert, *Angew. Chem.* **1997**, *109*, 1922 – 1923; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1836 – 1837; f) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173 – 180; for chiral diamines, see: g) *Chiral Amine Synthesis* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**; h) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753 – 819.

[22] For malonates and β-keto esters, see: a) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191 – 1193; for malonates, see: b) F. Fini, L. Bernardi, R. P. Herrera, D. Petersen, A. Ricci, V. Sgarzani, *Adv. Synth. Catal.* **2006**, *348*, 2043 – 2046; c) K. Takada, S. Tanaka, K. Nagasawa, *Synlett* **2009**, 1643 – 1646; d) Y. Sohtome, S. Tanaka, K. Takada, T. Yamaguchi, K. Nagasawa, *Angew. Chem.* **2010**, *122*, 9440 – 9443; *Angew. Chem. Int. Ed.* **2010**, *49*, 9254 – 9257; e) W. Li, B. Song, P. S. Bhadury, L. Li, Z. Wang, X. Zhang, D. Hu, Z. Chen, Y. Zhang, S. Bai, J. Wu, S. Yang, *Chirality* **2012**, *24*, 223 – 231; f) N. Probst, A. Madarász, A. Valkonen, I. Papai, K. Rissanen, A. Neuvonen, P. M. Pihko, *Angew. Chem.* **2012**, *124*, 8623 – 8627; *Angew. Chem. Int. Ed.* **2012**, *51*, 8495 – 8499; g) B. Karimi, E. Jafari, D. Enders, *Chem. Eur. J.* **2013**, *19*, 10142 – 10145; h) T. Kano, T. Yurino, K. Maruoka, *Angew. Chem.* **2013**, *125*, 11723 – 11726; *Angew. Chem. Int. Ed.* **2013**, *52*, 11509 – 11512; for 1,3-diketones and β-keto esters, see: i) M. Hatano, T. Maki, K. Moriyama, M. Arinobe, K. Ishihara, *J. Am. Chem. Soc.* **2008**, *130*, 16858 – 16860.

[23] Malonic half esters: a) H.-N. Yuan, S. Li, J. Nie, Y. Zheng, J.-A. Ma, *Chem. Eur. J.* **2013**, *19*, 15856 – 15860; malonic half thioesters: b) Y. Pan, C. W. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C. H. Tan, *Chem. Eur. J.* **2011**, *17*, 8363 – 8370; β-keto carboxylic acids: c) M. Böhm, K. Proksch, R. Mahrwald, *Eur. J. Org. Chem.* **2013**, 1046 – 1049; d) C. Jiang, F. Zhong, Y. Lu, *Beilstein J. Org. Chem.* **2012**, *8*, 1279 – 1283.

[24] a) C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem.* **2009**, *121*, 5804 – 5807; *Angew. Chem. Int. Ed.* **2009**, *48*, 5694 – 5697; b) C. B. Jacobsen, L. Lykke, D. Monge, M. Nielsen, L. K. Ransborg, K. A. Jørgensen, *Chem. Commun.* **2009**, 6554 – 6556.

[25] For organocatalytic Mannich reactions that involve α-cyanoacetates, see: a) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956 – 2959; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896 – 2899; b) S. Santoro, T. B. Poulsen, K. A. Jørgensen, *Chem. Commun.* **2007**, 5155 – 5157; for α-cyanoketones, see: c) A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 5630 – 5631; d) A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3779 – 3784; for a metal-catalyzed enantioselective decarboxylative cyanoalkylation, see: e) K. Hyodo, M. Kondo, Y. Funahashi, S. Nakamura, *Chem. Eur. J.* **2013**, *19*, 4128 – 4134; for direct methods that involve benzyl nitriles, see: f) J. Aydin, C. S. Conrad, K. J. Szabó, *Org. Lett.* **2008**, *10*, 5175 – 5178; g) L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9610 – 9611; h) K. Hyodo, S. Nakamura, K. Tsuji, T. Ogawa, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 3385 – 3390; aminonitriles: i) Y. Yamashita, M. Matsumoto, Y.-J. Chen, S. Kobayashi, *Tetrahedron* **2012**, *68*, 7558 – 7563; acrylonitriles: j) K. Hyodo, S. Nakamura, N. Shibata, *Angew. Chem.* **2012**, *124*, 10483 – 10487; *Angew. Chem. Int. Ed.* **2012**, *51*, 10337 – 10341; for a Mannich reaction of silyl ketene imines, see: k) J. Zhao, Y. Liu, W. Luo, M. Xie, L. Lin, X. Feng, *Angew. Chem.* **2013**, *125*, 3557 – 3561; *Angew. Chem. Int. Ed.* **2013**, *52*, 3473 – 3477.

[26] For direct catalytic addition of acetonitrile, see: Y. Kawato, N. Kumagai, M. Shibasaki, *Chem. Commun.* **2013**, *49*, 11227 – 11229.

[27] Absolute configuration was determined by comparison with published data. See the Supporting Information.

[28] a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119 – 125; b) A. Berkessel, S. Mukherjee, F. Cleeman, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898 – 1900; c) A. Berkessel, F. Cleeman, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817 – 821; *Angew. Chem. Int. Ed.* **2005**, *44*, 807 – 811.

[29] a) G. Tárkányi, P. Király, S. Varga, B. Vayulka, T. Soos, *Chem. Eur. J.* **2008**, *14*, 6078 – 6086; b) Hyeong. 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.

Received: December 13, 2013
Revised: February 19, 2014
Published online on April 15, 2014