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Bifunctional Guanidine via an Amino Amide Skeleton for Asymmetric Michael Reactions of β-Ketoesters with Nitroolefins: A Concise Synthesis of Bicyclic β-Amino Acids**

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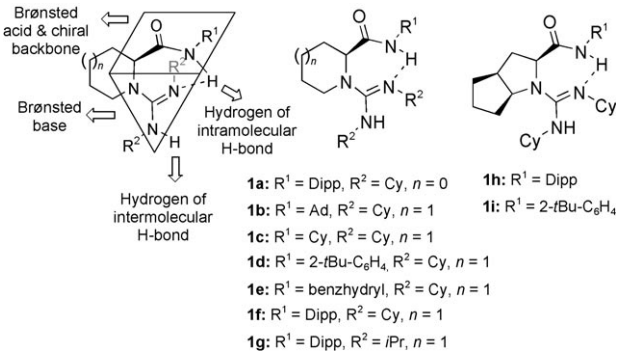
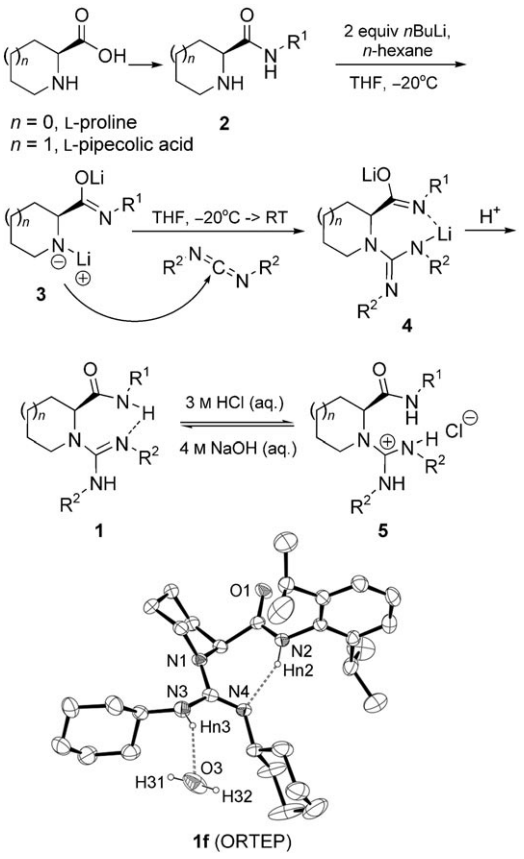
As a result of the significance of and ever-increasing interest in guanidine in chemistry and biology, the development of new synthetic strategies for the efficient construction of such molecules is an important goal of research carried out in both academic and industrial laboratories.[1] Chiral guanidine catalysts share common characteristics, such as high pK_a values and dual hydrogen-bonding modes for the molecular recognition of β-ketoester anions.[2] Michael addition of cyclic β-ketoesters to nitroolefins is an efficient synthetic tool for the construction of nitrogen-containing ketoesters with a quaternary carbon stereocenter.[3,4] Transformation of the corresponding adducts, such as reduction to γ-amino acids or oxidation to δ-lactones, could yield a variety of useful synthetic intermediates.[4] Over the past few years, chiral guanidine catalysts have been attractive targets in asymmetric organocatalysis.[5,6] However, despite the development of several excellent guanidine catalysts,[2,6] α-amino acids, which are naturally abundant, have not been widely employed as a chiral source for bifunctional guanidines,[5d,e,6c] moreover the development of a facile synthetic method for the production of guanidines is a challenge of great potential interest. Therefore, a bifunctional guanidine featuring a chiral amino amide backbone was designed to promote the asymmetric 1,4-addition of β-ketoesters to nitroolefins with dual activation in one molecule (Scheme 1).[3,6]

Rigid cyclic α-amino amides, such as those derived from L-proline, L-pipecolic acid, or L-ramipril acid, are promising candidates as the chiral backbone because they can offer a series of sterically hindered amides simultaneously. Thus, the practical synthesis of guanidine was achieved by addition of the lithium amino amide to the carbodiimide to construct the conjugated trinitrogen carbon plane (Scheme 2).[7] It was discovered with X-ray diffraction analysis of a single crystal of **1f**[8] that the guanidine formed two H-bonds, one intramolecularly and one intermolecularly.



Scheme 1. Designation of the bifunctional catalysts evaluated. Dipp = 2,6-diisopropylphenyl, Ad = 1-adamantyl, Cy = cyclohexyl.



Scheme 2. Practical synthesis of the amino amide based bifunctional guanidines[8] and an ORTEP representation of the structure of **1f**. THF = tetrahydrofuran.

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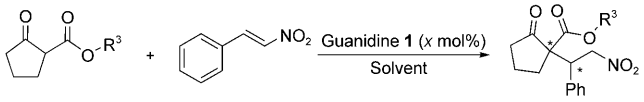
A series of chiral guanidines as organocatalysts were synthesized and evaluated in the Michael addition of β-ketoesters to nitroolefins under mild conditions, a reaction that affords adducts with a chiral quaternary carbon atom. With regard to the amino amide backbones, the L-pipecolic acid derivative **1f** was superior to the L-proline- and L-ramipril-acid-derived catalysts **1a** and **1h**; **1f** gave the desired product **8** in 95:5 d.r. with 87% *ee* (Table 1, entry 6 versus entries 1 and 8). Further examinations were focused on the sterically hindered amide subunit. The results suggested that the amide subunit in the guanidine had a significant impact on the enantioselectivity of the reaction, and the 2,6-diisopropylphenyl amide was the best one (Table 1, entry 6 versus entries 2–5 and 9). The replacement of the Cy group by an isopropyl group in the guanidine moiety provided an equivalent outcome (Table 1, entry 7 versus entry 6); however, catalyst **1g** is hard to synthesize. Thus, we moved on to an evaluation of the β-ketoester by varying the R^3 substituent and found that the *t*Bu group was suitable to improve both the d.r. and *ee* values (Table 1, entry 10 versus entries 12 and 13). Finally, substantial improvement was realized by solvent screening. The reaction was completed at −15 °C in EtOAc in the presence of 2 mol% of **1f** to furnish **8a** quantitatively with a 99:1 *syn*/*anti* ratio and a 95% *ee* value for the major product (Table 1, entry 19 versus entries 14–18).

Table 1: Optimization of the reaction conditions.[a]



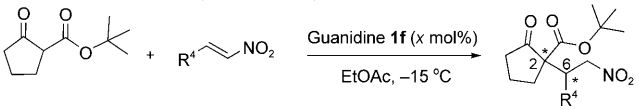
6 7a 8

Enrty	Cat.	*x* [mol%]	R^3	Solvent	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][c]
1	**1a**	5	Et	THF	74	78:22	7
2	**1b**	5	Et	THF	60	87:13	53
3	**1c**	5	Et	THF	95	88:12	60
4	**1d**	5	Et	THF	99	92:8	68
5	**1e**	5	Et	THF	99	91:9	61
6	**1f**	5	Et	THF	98	95:5	87
7	**1g**	5	Et	THF	98	95:5	86
8	**1h**	5	Et	THF	84	92:8	40
9	**1i**	5	Et	THF	91	89:11	50
10	**1f**	5	*t*Bu	THF	97	96:4	90
11	**1g**	5	*t*Bu	THF	80	98:2	92
12	**1f**	5	Cy	THF	96	97:3	90
13	**1f**	5	Ad	THF	94	98:2	93
14	**1f**	5	*t*Bu	Et_2O	67	97:3	93
15	**1f**	5	*t*Bu	PhMe	81	98:2	89
16	**1f**	5	*t*Bu	CH_2Cl_2	58	94:6	73
17	**1f**	5	*t*Bu	EtOAc	92	98:2	91
18[d]	**1f**	2	*t*Bu	EtOAc	96	98:2	94
19[d,e]	**1f**	2	*t*Bu	EtOAc	98	99:1	95

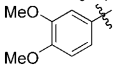
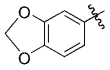
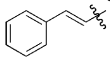
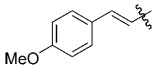
[a] Unless otherwise noted, the reaction was carried out with 0.15 mmol β-ketoester and 0.2 mmol nitroolefin in solvent (1 mL) at 0 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] In 0.5 mL of solvent. [e] Reaction was carried out at −15 °C for 32 h.

Under the optimized conditions, various nitroolefin substrates were investigated to afford a wide range of products **8** containing quaternary chiral centers with high *ee* values (83–97% *ee*) and excellent diastereomeric ratios (99:1 d.r. in most cases; Table 2). It is interesting to note that not only the monosubstituted aryl substrates but also condensed-ring and α,β-unsaturated nitroolefins had no obvious effects on the enantioselectivities and reactivities (Table 2, entries 1–6, 9–11, and 14–22). However, the disubstituted aryl substrates slightly influenced the reactivities; this was caused by the electronic or steric properties of the substrates (Table 2, entries 7, 8, 12, 13, and 20). In particular, despite catalyst

Table 2: Substrate scope for the asymmetric Michael reaction.[a]



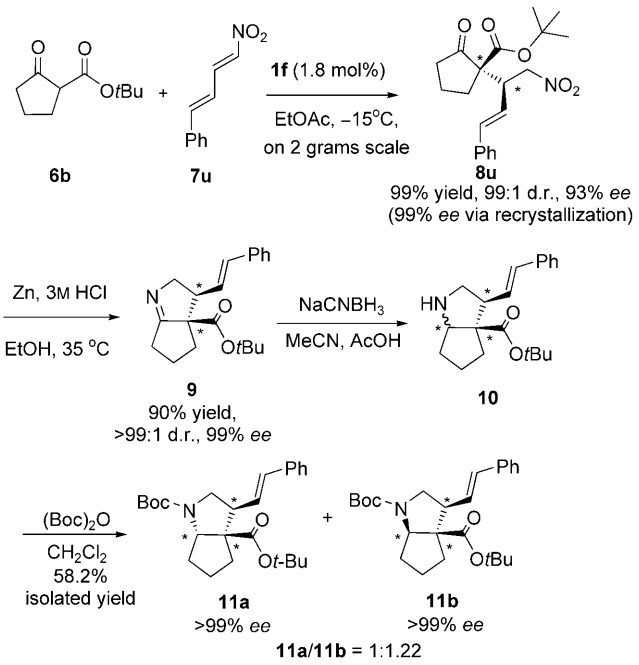
6b 7a–y 8a–y

Entry	R^4	*x* [mol%]	Prod.	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][c]
1	Ph	2	**8a**	98 (79)[d]	99:1	95 (>99)[d]
2	2-MeC_6H_4	3	**8b**	98	89:11	96
3	3-MeC_6H_4	3	**8c**	90	99:1	95
4	4-MeC_6H_4	2	**8d**	99	96:3	92
5	3-$MeOC_6H_4$	2	**8e**	82	>99:1	95
6	4-$MeOC_6H_4$	2	**8f**	80	98:2	94
7		5	**8g**	75[e,f]	>99:1	93
8		5	**8h**	76[e,f]	>99:1	95
9	2-ClC_6H_4	2	**8i**	99	>99:1	95
10	3-ClC_6H_4	2	**8j**	82	>99:1	95
11	4-ClC_6H_4	2	**8k**	95	>99:1	95
12	2,4-$Cl_2C_6H_3$	5	**8l**	99[f,g]	99:1	96
13	2,6-$Cl_2C_6H_3$	5	**8m**	54[f]	88:12	83
14	4-FC_6H_4	2	**8n**	93	99:1	97
15	4-BrC_6H_4	2	**8o**	99 (80)[d]	99:1	95 (>99)[d,h]
16	4-$NO_2C_6H_4$	4	**8p**	94	99:1	92
17	1-naphthyl	2	**8q**	80	>99:1	91
18	2-naphthyl	2	**8r**	99	85:15	96
19	4-PhC_6H_4	2	**8s**	80	99:1	96
20	3-PhO-4-FC_6H_3	2	**8t**	93	>99:1	96
21		2	**8u**	99 (75)[d]	>99:1	93 (>99)[d]
22		2	**8v**	83	99:1	93
23	2-furyl	2	**8w**	99	99:1	90
24	2-thienyl	2	**8x**	99	>99:1	93
25	*c*-hexyl	5	**8y**	70[f]	99:1	92

[a] Unless otherwise noted, the reaction was carried out with 0.15 mmol β-ketoester and 0.2 mmol nitroolefin in EtOAc (0.5 mL) at −15 °C for 32 h. [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy and chiral HPLC. Results are in accordance with literature data.[3b] [d] Data in parentheses were obtained after a single recrystallization. [e] In 1.0 mL EtOAc/THF (1:1). [f] Reaction was carried out for 48 h. [g] In 1.0 mL of EtOAc. [h] The absolute configuration was determined to be (2*R*,6*S*) by X-ray diffraction analysis.[14]

loadings of 5 mol%, electron-donating disubstituted aromatic substrates suffered lower reactivities (Table 2, entries 7 and 8). It is noteworthy that excellent *ee* and d.r. values have been achieved in the asymmetric Michael addition of heteroaromatic and aliphatic nitroolefins (up to 93% ee; Table 2, entries 23–25) because the corresponding adducts have great potential in natural product synthesis.

On account of the high efficiency in the guanidine organocatalysis approach and the synthetic potential of the Michael adducts, the reaction was carried out on a 7 mmol scale in the presence of **1f** (1.8 mol%) with the cinnamonic substrate **7u** and gave the desired product in 99% yield and with 99:1 d.r. and 93% *ee* (Table 2, entry 21; Scheme 3). The



Scheme 3. Large-scale synthesis of **8u** and the ramipril analogues. Boc = *tert*-butoxycarbonyl.

optically pure (99% *ee* after a single recrystallization) product **8u** was successfully converted exclusively into the corresponding aza-bicyclocarboxylate **9** in good yield by zinc-mediated reduction[9] followed by an intramolecular aza-cyclization without any loss of stereoselectivity.[10] Further reductive addition of the imine with $NaCNBH_3$ under weak-acid conditions afforded a ramipril analogue, amino acid ester **10**, which was then N-protected by using $(Boc)_2O$. The *N*-Boc-β-ramipril-type amino acid ester **11**, featuring a chiral functional group with an adjacent quaternary carbon stereocenter, possesses great potential in pharmaceutical synthesis.

To gain insight into the dual-activation mode, comparative experiments were carried out with the N–Me derivative of the amide catalyst.[11] Under optimal conditions, it gave 54% yield, a *syn*/*anti* ratio of 93:7, and 71% *ee* for the major product. These results indicate that the NH proton of the amide moiety is vital for the high activity and stereoselectivity. Direct evidence was observed by NMR spectroscopy analyses and deduced from experimental observations. The NH proton of the amide in **1f** showed a strong deshielding effect, with a broad peak shape at $\delta = 11.43$ ppm due to the characteristic strong intramolecular hydrogen bonding,[12] which implies that the N–H moiety of the amide in catalyst **1f** might act as a Brønsted acid.[13] Based on the X-ray diffraction analysis of both the guanidine and the adducts, a preliminary mechanism for this direct nitro-Michael reaction of cyclic β-ketoesters has been proposed to illustrate the dual-activation mode. As depicted in Figure 1, the intramolecular

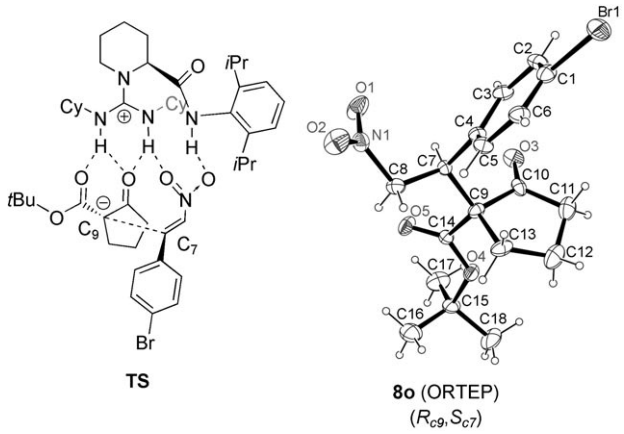


Figure 1. The dual-activation mode of guanidine **1f** (**TS**) and the ORTEP representation of product **8o** (R_{C9},S_{C7}) from the X-ray analysis.[14]

H-bond of catalyst **1f** was released and transformed to activate the two substrates simultaneously. The most favorable transition state (**TS**) shows the guanidine unit to be a Brønsted base, on which strong zwitterionic hydrogen bonds with the Michael donor can be built,[5,6f,i] while the NH moiety of the amide acts as a Brønsted acid to activate the Michael acceptor.[2d,6] This plausible **TS** leads to mostly *syn* products, in accordance with the substrate generality.

In conclusion, we have presented an example of the introduction of amino amides into the guanidine framework to create organocatalysts for the asymmetric Michael addition of β-ketoesters to nitroolefins. Catalyst **1f** demonstrated high stereoselectivities (up to > 99:1 d.r. and 97% *ee*) and yields (up to 99%) for a wide range of substrates. The reaction could be easily scaled up under mild conditions to facilitate a concise synthesis of a bicyclic β-amino acid. The comparative experiments and X-ray diffraction analysis of the catalyst structures revealed both the guanidine group and the NH proton of the amide are important for the dual-activation mode.

Experimental Section

β-Ketoester **6b** (27.6 mg, 0.15 mmol) was added to a stirred solution of nitroolefin (1.33 equiv, 0.2 mmol) and guanidine **1f** (2 mol%, 1.5 mg, 0.005 mmol) in EtOAc (0.50 mL, analytical-reagent grade) at −15 °C. After being stirred for 32 h, the reaction mixture was

concentrated in vacuum. The residue was purified by column chromatography on silica gel to afford the desired product.

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Keywords: amino acids · asymmetric synthesis · guanidines · Michael addition · organocatalysis

[1] a) R. G. S. Berlinck, A. C. B. Burtoloso, M. H. Kossuga, *Nat. Prod. Rep.* **2008**, *25*, 919 – 954; b) T. Ishikawa, T. Kumamoto, *Synthesis* **2006**, 737 – 752.

[2] For reviews, see: a) Y. Yamamoto, S. Kojima in *The Chemistry of Amidines and Imidates*, *Vol. 2* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1991**, pp. 485 – 526; b) K. A. Schug, W. Lindner, *Chem. Rev.* **2005**, *105*, 67 – 114; c) P. Blondeau, M. Segura, R. Pérez-Fernández, J. de Mendoza, *Chem. Soc. Rev.* **2007**, *36*, 198 – 210; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; e) T. Ishikawa, T. Isobe, *Chem. Eur. J.* **2002**, *8*, 552 – 557; f) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488 – 507.

[3] a) *Asymmetric Organocatalysis* (Eds.: H. Berkessel, H. Gröger), Wiley-VCH, Weinheim, **2005**; b) S. Shirakawa, S. Kobayashi, *Synlett* **2006**, 1410 – 1412; c) Z. H. Zhang, X. Q. Dong, D. Chen, C. J. Wang, *Chem. Eur. J.* **2008**, *14*, 8780 – 8783; d) H. M. Li, Y. Wang, L. Tang, F. H. Wu, X. F. Liu, C. Y. Guo, B. M. Foxman, L. Deng, **2005**, *117*, 107 – 110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105 – 108.

[4] For recent reviews of asymmetric Michael additions, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; b) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726 – 1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688 – 1690; c) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365.

[5] a) A. Echavarren, A. Galán, J. M. Lehn, J. de Mendoza, *J. Am. Chem. Soc.* **1989**, *111*, 4994 – 4995; b) H. Kurzmeier, F. P. Schmidtchen, *J. Org. Chem.* **1990**, *55*, 3749 – 3755; c) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723 – 5727; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641 – 5645; d) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.* **2005**, *347*, 1643 – 1648; e) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150 – 1160; f) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157 – 160; g) K. Takada, K. Nagasawa, *Adv. Synth. Catal.* **2009**, *351*, 345 – 347; h) C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 9228 – 9229; i) T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem.* **2002**, *114*, 2956 – 2958; *Angew. Chem. Int. Ed.* **2002**, *41*, 2832 – 2834; j) K. Takada, N. Takemura, K. Cho, Y. Sohtome, K. Nagasawa, *Tetrahedron Lett.* **2008**, *49*, 1623 – 1626; k) X. Fu, Z. Jiang, C.-H. Tan, *Chem. Commun.* **2007**, 5058 – 5060; l) M. Terada, T. Ikehara, H. Ube, *J. Am. Chem. Soc.* **2007**, *129*, 14112 – 14113; m) J. Shen, C.-H. Tan, *Org. Biomol. Chem.* **2008**, *6*, 4096 – 4098.

[6] For relevant publications on Michael reactions catalyzed by guanidine-based catalysts, see: a) S. B. Tsogoeva, S. B. Jagtap, Z. A. Ardemasova, V. N. Kalikhevich, *Eur. J. Org. Chem.* **2004**, 4014 – 4019; b) Z. Jiang, Y. Yang, Y. Pan, Y. Zhao, H. Liu, C.-H. Tan, *Chem. Eur. J.* **2009**, 15, 4925 – 4930; c) Q. B. Pan, D. W. Ma, *Chin. J. Chem.* **2003**, *21*, 793 – 796; d) T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, T. Isobe, *Chem. Commun.* **2001**, 245 – 246; e) A. Ryoda, N. Yajima, T. Haga, T. Kumamoto, W. Nakanishi, M. Kawahata, K. Yamaguchi, T. Ishikawa, *J. Org. Chem.* **2008**, *73*, 133 – 141; f) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454 – 1455; g) J. Shen, T. T. Nguyen, Y.-P. Goh, W. Ye, X. Fu, J. Xu, C.-H. Tan, *J. Am. Chem. Soc.* **2006**, *128*, 13692 – 13693; h) Z. Jiang, W. Ye, Y. Yang, C.-H. Tan, *Adv. Synth. Catal.* **2008**, *350*, 2345 – 2351; i) W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454 – 2458; j) M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044 – 16045; k) N. Saito, A. Ryoda, W. Nakanishi, T. Kumamoto, T. Ishikawa, *Eur. J. Org. Chem.* **2008**, 2759 – 2766.

[7] a) W. X. Zhang, M. Nishiura, Z. M. Hou, *Chem. Eur. J.* **2007**, *13*, 4037 – 4051; b) L. Gomez, F. Gellibert, A. Wagner, C. Mioskowski, *Chem. Eur. J.* **2000**, *6*, 4016 – 4020, and references therein.

[8] CCDC 722587 (**1 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] a) C. Tan, X. H. Liu, L. W. Wang, J. Wang, X. M. Feng, *Org. Lett.* **2008**, *10*, 5305 – 5308; b) P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.* **2008**, *10*, 1389 – 1391.

[10] The stereoselectivity of product **9** was determined to be *cis*/*trans* > 99:1, with 99% *ee*. For detailed information, see the Supporting Information.

[11] The catalysis was carried out by using the N–Me derivative of **1 f** for comparison with the N–H catalyst **1 f**. For detailed information, see the Supporting Information.

[12] For detailed information, see the Supporting Information.

[13] B. Qin, X. H. Liu, J. Shi, K. Zheng, H. T. Zhao, X. M. Feng, *J. Org. Chem.* **2007**, *72*, 2374 – 2378.

[14] CCDC 722586 (**8 o**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

