Heterocycles

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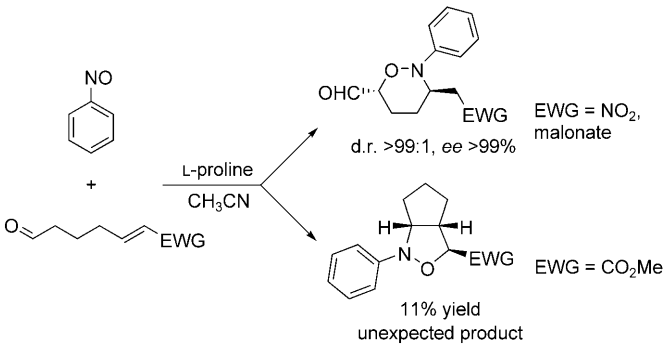
Highly Stereoselective One-Pot Synthesis of Bicyclic Isoxazolidines with Five Stereogenic Centers by an Organocatalytic Process**

*Di Zhu, Min Lu, Lu Dai, and Guofu Zhong**

Dedicated to Professor Pierre Vogel on the occasion of his 65th birthday

Intramolecular nitrone/alkene cycloadditions have received a great deal of attention as a useful methodology for the formation of the intriguing frameworks found in natural products and biologically interesting compounds.[1] The key feature of this approach is the suitable elaboration of the primary cycloadducts, which has proven to be a practical strategy for making different heterocyclic systems.[2] Owing to the labile nature of the N–O bond under mild reducing conditions, the isoxazolidines provide easy access to a variety of 1,3-difunctional amino alcohols.[3] Particularly, if the intramolecular cycloaddition of nitrone is linked to olefin moiety by a tether of appropriate length, the regio- and diastereoselectivities can be dramatically improved. Most importantly, the introduction of a stereogenic center at the α position of the nitrone can result in asymmetric induction, leading to the generation of new stereocenters having defined configurations.[4] However, multistep synthetic routes were required to synthesize molecules bearing stereocenters at the α position of the nitrone and the olefin moiety from optical sources, such as amino acids and sugars. Although several organocatalytic asymmetric nitrone [3+2] cycloadditions have been documented,[5] the enantioselective intramolecular version remains a challenge. Herein, we disclose an organocatalytic one-pot asymmetric synthesis of bicyclic isoxazolidines through a domino process involving a Michael addition/in situ condensation/intramolecular nitrone [3+2] cycloaddition sequence.

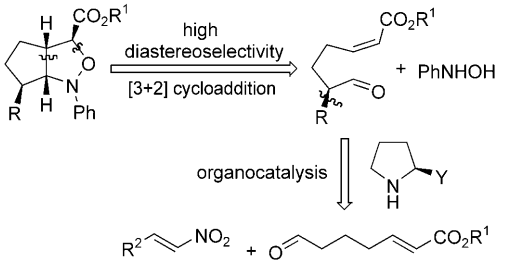
In 2003, our group first described the α-aminoxylation of aldehydes with excellent enantioselectivity.[6a,b] Recently, we also reported highly stereoselective syntheses of tetrahydro-1,2-oxazines by tandem α-aminoxylation and aza-Michael addition.[6] Surprisingly, when we changed the electron-withdrawing group in an aldehyde from a nitro or a malonate group to an ester group, an unexpected bicyclic isoxazolidine product was obtained in 11% yield with high regioselectivity, *endo*/*exo* selectivity, and diastereoselectivity (Scheme 1), by an intramolecular nitrone [3+2] cycloaddition. This finding led us to investigate whether enantiopure bicyclicisoxazolidine products could be obtained if we introduced a stereogenic center at the α position of the aldehyde by asymmetric



Scheme 1. Unexpected bicyclic isoxazolidine product from intramolecular nitrone [3+2] cycloaddition. EWG = electron-withdrawing group.

organocatalysis, which would then undergo subsequent in situ condensation and intramolecular nitrone [3+2] cycloaddition.

Recently, asymmetric organocatalytic domino reactions have provided efficient ways to construct complex molecules, and have become a powerful tool in organic chemistry.[7] Among the organocatalytic reactions explored, extensive efforts have been devoted to the Michael addition of aldehydes to nitroolefins.[8] We rationalized that by introducing a stereocenter at the α position of the aldehyde through an asymmetric Michael addition and then subsequent in situ condensation and intramolecular cycloaddition, a novel approach to furnish enantiopure bicyclic isoxazolidines could be achieved (Scheme 2).



Scheme 2. Retrosynthetic analysis for the enantioselective synthesis of bicyclic isoxazolidine derivatives.

[*] D. Zhu, M. Lu, L. Dai, Prof. Dr. G. Zhong
Division of Chemistry and Biological Chemistry
School of Physical and Mathematical Sciences
Nanyang Technological University
21 Nanyang Link, Singapore 637371 (Singapore)
Fax: (+65) 6791-1961
E-mail: guofu@ntu.edu.sg

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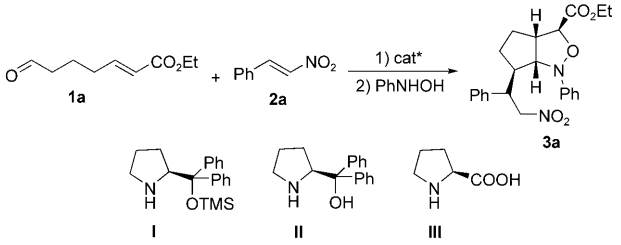
We started our experiments by combining 10 mol% Jørgensen's catalyst **I**, 0.1 mmol of 7-oxohept-2-enoate (**1a**), and 0.12 mmol of nitroolefin **2a** in 0.5 mL of hexanes, and then stirred the mixture at room temperature. After the Michael addition step was complete, 0.15 mmol of *N*-hydroxylbenzenamine was added to the reaction mixture, which was then stirred for another hour. To our delight, after workup the desired product **3a** was isolated in 65% yield with a 85:15 diastereomeric ratio (d.r.) and excellent enantioselectivity (>99% *ee*; Table 1, entry 1).

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



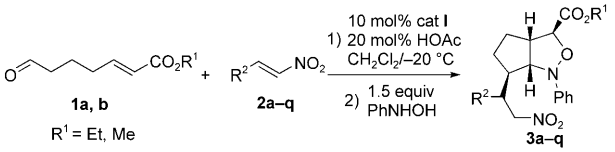
Entry	Solvent	*T* [°C]	*t* [h][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	hexane	23	1	65	85:15	99
2[f]	hexane	23	24	<20	n.d.	n.d.
3[g]	DMSO	23	1	<20	n.d.	n.d.
4	toluene	23	1	56	68:32	94
5	CH_2Cl_2	23	3	75	88:12	99
6	$CHCl_3$	23	3	71	85:15	99
7	CH_3CN	23	3	72	86:14	99
8	H_2O	23	4	67	88:12	99
9[h]	CH_2Cl_2	23	2	79	92:8	99
10[i]	CH_2Cl_2	23	2	65	92:8	99
11[j]	CH_2Cl_2	23	2	81	93:7	99
12[j]	CH_2Cl_2	0	8	83	94:6	99
13[j]	CH_2Cl_2	−20	24	84	97:3	99
14[k]	CH_2Cl_2	−20	36	79	97:3	99

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), and catalyst **I** (10 mol%) in solvent (0.5 mL). After the aldehyde was consumed, *N*-hydroxybenzenamine (0.15 mmol) was added. [b] Reaction time of Michael step. [c] Yield of isolated product. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Determined by HPLC methods using a Chiralcel AD-H column. [f] Used 10 mol% of catalyst **II**. [g] Used 10 mol% of catalyst **III**. [h] Added 10 mol% HOAc. [i] Added 10 mol% of benzoic acid. [j] Added 20 mol% of HOAc. [k] Added 5 mol% catalyst **I** and 10 mol% HOAc. DMSO = dimethyl sulfoxide, n.d. = not determined, TMS = trimethylsilyl.

Furthermore, the chiral secondary amine catalysts **II** and **III** were tested. Unfortunately, both of them showed deleterious effects on reactivity (Table 1, entries 2–3). The screening of solvents revealed that dichloromethane (CH_2Cl_2) is the most ideal as it gave the best result (Table 1, entry 5). Toluene gave the worst result with 56% yield and 68:32 d.r. The halogenated solvent $CHCl_3$, moderately polar solvent CH_3CN, and the polar solvent H_2O, gave relatively lower yields and diastereoselectivities (Table 1, entries 6–8). Since it had been observed that the addition of some Brønsted acids could promote the formation of the enamine, thereby accelerating amine-catalyzed reactions, we next screened additives by conducting the reaction in the presence of an acid.[9] When acetic acid (10 mol%) was added, the reaction was greatly accelerated and both the yield and diastereoselectivity were improved without any loss in the enantioselectivity (Table 1, entry 9). The addition of 10 mol% benzoic acid also enhanced the diastereoselectivity, but the yield was not satisfactory (Table 1, entry 10). Interestingly, the yield and diastereoselectivity were additionally improved when 20 mol% acetic acid was used (Table 1, entry 11). Having screened the additives, we next investigated the effect of the temperature. Both the yield and diastereoselectivity were improved without any loss in enantioselectivity when the reaction temperature was decreased from room temperature (23°C) to either 0°C or −20°C (Table 1, entries 12 and 13). When the catalyst loading was reduced to 5 mol%, high diastereo- and enantioselectivities of 97:3 d.r. and 99% *ee*, respectively, were achieved, even though the yield fell slightly and the reaction time was prolonged to 36 hours (Table 1, entry 14).

With the optimized conditions in hand, the scope of the organocatalytic one-pot asymmetric domino reaction was explored. A wide range of nitroalkenes **2a–q** was tested under the optimized reaction conditions (10 mol% Jørgensen's catalyst and 20 mol% HOAc in 1 mL of CH_2Cl_2 at −20°C; after the aldehyde was consumed, 1.5 equivalents of *N*-hydroxylbenzenamine was added) and the results are summarized in Table 2. A series of bicyclic isoxazolidines **3a–q** were obtained in good to excellent yields with excellent

Table 2: The scope of the reaction.[a]

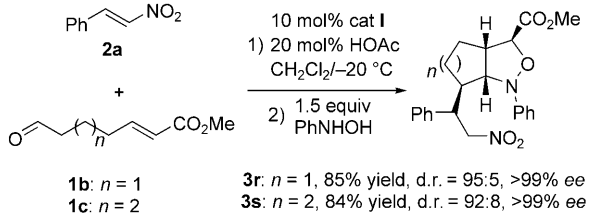


Entry	R^2	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	**3a**	84	97:3	>99
2	2-MeC_6H_4	**3b**	75	94:6	>99
3	3-MeC_6H_4	**3c**	78	92:8	>99
4	4-MeC_6H_4	**3d**	81	95:5	>99
5	4-ClC_6H_4	**3e**	83	95:5	>99
6	4-BrC_6H_4	**3f**	89	95:5	>98
7	4-FC_6H_4	**3g**	84	95:5	>99
8	4-$NO_2C_6H_4$	**3h**	92	95:5	>99
9	4-$OMeC_6H_4$	**3i**	82	95:5	>99
10	3-$OMeC_6H_4$	**3j**	79	94:6	>99
11	2-$NO_2C_6H_4$	**3k**	73	94:6	>99
12	2-ClC_6H_4	**3l**	74	94:6	>99
13	2-BrC_6H_4	**3m**	72	94:6	>99
14	2-furanyl	**3n**	81	95:5	>98
15	2-naphthyl	**3o**	83	94:6	>98
16[e]	*n*Pr	**3p**	62	89:11	>99
17[e]	*i*Pr	**3q**	51	96:4	>99

[a] Reaction conditions: Catalyst **I** (0.02 mmol) and AcOH (0.04 mmol) were added to a solution of nitroolefin (0.24 mmol) and **1a** (0.2 mmol) in CH_2Cl_2 (1 mL) at −20°C; after the aldehyde had been consumed, *N*-hydroxybenzenamine (0.3 mmol) was added, and the mixture stirred for another 2–3 h. [b] Yields of isolated products. [c] d.r. values determined by ^{1}H NMR analysis of the crude reaction mixture. [d] *ee* values determined by HPLC methods employing a Daicel Chiracel AD-H column (see the Supporting Information). [e] Used 3 equiv of **1b**.

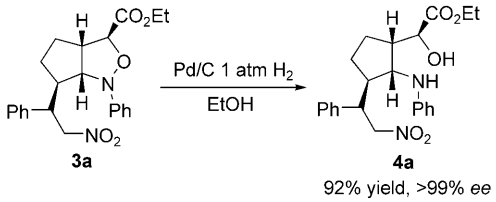
diastereo- and enantioselectivities (up to 97:3 d.r. and up to >99% *ee*). For almost all the nitroalkenes tested, the *ee* values were higher than 98%, but the yields and diastereoselectivities varied with the substitutents on the nitroolefins. Though the nitroalkenes having *ortho*-substituted aryl rings gave slightly lower yields and diastereoselectivities, their enantioselectivities were not affected (Table 2, entries 2 and 11–13). Such a phenomenon could be attributed to the unfavored steric hindrance between the *ortho*-substituted group and the aldehyde in the presence of catalyst **I**. The electronic nature of the substitutents in the aromatic ring has little effect on the yield, diastereo- and enantioselectivity (Table 2, entries 4–9). Nitroalkenes bearing furanyl and naphthyl groups were also successfully used in this reaction with 95:5 d.r. and greater than 98% *ee*, and 94:6 d.r. and greater than 98% *ee*, respectively (Table 2, entries 14 and 15). Furthermore, the aliphatic nitroolefins **2p** and **2q** were also successfully applied in this domino reaction to afford bicyclic products **3p** and **3q**, respectively, with moderate yields, good to excellent diastereoselectivities, and excellent enantioselectivities even though three equivalents of the aldehyde **1b** was required (Table 2, entries 16 and 17).

To study the ring size effect on the diastereo- and enantioselectivity, 5- and 6-alkenylaldehydes (**1b** and **1c**) were applied in this organocatalytic one-pot asymmetric tandem reaction to afford bicyclic [3,3,0]- and [4,3,0]-isoxazolidine derivatives **3r** and **3s**, respectively, with similar results (Scheme 3). Notably, only the *exo* product was



Scheme 3. Study of ring size and its effect on diastereo- and enantioselectivity.

observed when **1c** was used. This result could possibly derive from the presence of the ester group next to the olefin moiety. Furthermore, the bicyclic isoxazolidine **3a** was transformed into an α-hydroxy-γ-amino acid derivative **4a** with 92% yield and greater than 99% *ee*, which may have potential applications in synthetic chemistry and the pharmaceutical industry (Scheme 4).



Scheme 4. Synthesis of α-hydroxy-γ-amino acid derivative.

To determine the configuration of the bicyclic isoxazolidines, the relative configuration of the structure was determined by X-ray crystallograhic analysis of the compound **3g.** The configuration of the stereogenic centers, created by spontaneous formation of C–C bonds and C–O bonds in the intramolecular nitrone [3+2] cycloaddition, were assigned to be C7*S*, C11*S*, C15*R* with reference to the configuration in a previous report (Figure 1).[8c]

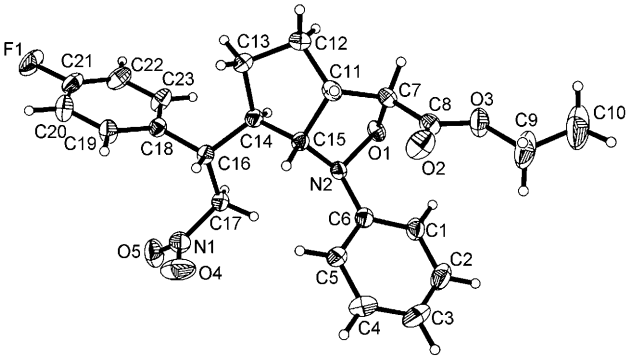


Figure 1. X-ray crystal structure of **3g**.[10] Thermal ellipsoids shown at 50% probability.

In summary, we developed a novel, facile organocatalytic one-pot asymmetric synthesis of bicyclic isoxazolidines with the control of five stereogenic centers by a domino process involving a Michael addition/in situ condensation/intramolecular nitrone [3+2] cycloaddition sequence, and its straight forward application to the synthesis of α-hydroxy-γ-amino acid derivatives. Additional applications to other synthetically useful transformations are underway.

Experimental Section

General procedure: Jørgensen's catalyst **I** (6.5 mg, 0.02 mmol) and HOAc (2.4 mg, 0.04 mmol) were added to a solution of (*E*)-ethyl 7-oxohept-2-enoate (**1a**, 34 mg, 0.2 mmol) and nitroolefin (**2a**, 36 mg, 0.24 mmol) in 1 mL of CH_2Cl_2 at −20 °C. The reaction progress was monitored by TLC methods. After the aldehyde had been consumed, *N*-hydroxybenzenamine (33 mg, 0.3 mmol) was added to the reaction mixture, which was then stirred for another 2 h and charged to a silica gel column directly and purified by flash column chromatography (eluent: EtOAc/hexanes = 10:90→15:85) to afford a white solid (69 mg, 84% yield, d.r. = 97:3 (by ^{1}H NMR analysis of the crude reaction mixture), *ee* > 99% [by HPLC on a chiral phase: chiralcel AD-H column, $\lambda = 254$ nm, *i*PrOH/hexanes = 10:90, 1.0 mL min^{-1}; $t_1 = 12.9$ min (major), $t_2 = 27.7$ min (minor)]. $[\alpha]_D^{23} = -91.1$ deg (c = 10 mg cm^{-3}, $CHCl_3$).

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[1] a) T. Kano, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 11926–11927; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863–909; c) J. N. Martin, R. C. F. Jones in

Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products (Eds.: A. Padwa, W. H. Pearson), Wiley, Hoboken, NJ, **2003**, chap. 1, pp. 1 – 81; d) K. V. Gothelf in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, chap. 6, pp. 211 – 247; e) S. Kanemasa in *Cycloaddition Reactions in Organic Synthesis*; (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, chap. 7, pp. 249 – 300; f) O. Tamura, N. Mita, T. Okabe, T. Yamaguchi, C. Fukushima, M. Yamashita, Y. Morita, N. Morita, H. Ishibashi, M. Sakamoto, *J. Org. Chem.* **2001**, *66*, 2602 – 2610.

[2] a) A. Hassner in *Heterocycles in Bio-Organic Chemistry* (Eds: J. Pergamon), Royal Society of Chemistry, Cambridge, **1991**; b) U. Chiacchio, A. Rescifina, G. Romeo in *Targets in Heterocyclic Systems. Chemistry and Properties*, *Vol. 1* (Eds.: O. A. Attanasi, D. Spinelli), Italian Society of Chemistry, Italy, **1997**, pp. 225 – 276.

[3] a) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. Desarlo, *Tetrahedron Lett.* **1990**, *31*, 3351 – 3354; b) N. A. LeBel, N. Balasubramanian, *J. Am. Chem. Soc.* **1989**, *111*, 3363 – 3368.

[4] a) R. Romeo, D. Iannazzo, A. Piperno, M. Chiacchio, A. Corsaro, A. Rescifina, *Eur. J. Org. Chem.* **2005**, 2368 – 2373; b) U. Chiacchio, F. Casuscelli, A. Corsaro, V. Librando, A. Rescifina, R. Romeo, G. Romeo, *Tetrahedron* **1995**, *51*, 5689 – 5700.

[5] a) P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 2445 – 2447; *Angew. Chem. Int. Ed.* **2008**, *47*, 2411 – 2413; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874 – 9875; c) W. Du, Y. Liu, L. Yue, Y. Chen, *Synlett* **2008**, 2997 – 3000; d) S. Chow, M. Nevalainen, C. Evans, C. W. Johannes, *Tetrahedron Lett.* **2006**, *48*, 277 – 280.

[6] a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379 – 4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247 – 4250; b) P. J. Chua, B. Tan, G. Zhong, *Green Chem.* **2009**, *11*, 543 – 547; c) G. Zhong, *Chem. Commun.* **2004**, 606 – 607; d) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637 – 1639; e) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **2008**, *10*, 4585 – 4588; f) M. Lu, D. Zhu, Y. Hou, Y. Lu, B. Tan, G. Zhong, *Angew. Chem.* **2008**, *120*, 10341 – 10345; *Angew. Chem. Int. Ed.* **2008**, *47*, 10187 – 10191.

[7] For examples of recent asymmetric domino reactions, see: a) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649 – 7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539 – 7542; b) B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2008**, *10*, 3489 – 3492; c) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425 – 3428; d) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437 – 2440; e) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590 – 1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570 – 1581; f) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119 – 1122; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101 – 1104; g) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986 – 14991; h) M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475 – 5479; i) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710 – 15711; j) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292 – 1297; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272 – 1277.

[8] For selective papers on the asymmetric Michael addition of aldehydes to nitroolefins, see: a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737 – 3740; b) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527 – 2530; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215; d) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393 – 1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369 – 1371; e) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165 – 3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093 – 3097; f) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966 – 4967; g) S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559 – 2562; h) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471 – 473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467 – 469; i) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555 – 558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545 – 548; For recent reviews, see: j) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 – 1716; k) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065 – 2092; l) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365.

[9] a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2527 – 2530; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260 – 5267; c) M. Nakadai, S. Saito, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167 – 8177; d) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474 – 2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420 – 2423; e) Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460 – 462; f) P. Dinér, M. Nielsen, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 2029 – 2033; *Angew. Chem. Int. Ed.* **2007**, *46*, 1983 – 1987.

[10] CCDC 722753 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.

