

Organocatalytic Asymmetric α -Aminoxylation/Aza-Michael Reactions for the Synthesis of Functionalized Tetrahydro-1,2-oxazines**

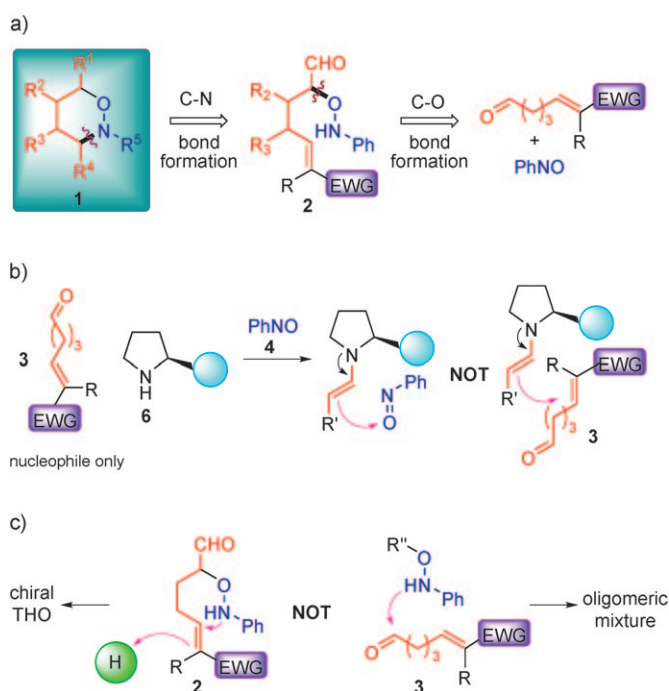
Min Lu, Di Zhu, Yunpeng Lu, Yuxuan Hou, Bin Tan, and Guofu Zhong*

Dedicated to Professor Richard A. Lerner on the occasion of his 70th birthday

Enantiopure 1,2-oxazines are prevalent in complex natural products^[1] and are versatile building blocks for asymmetric synthesis. They are potential scaffolds which can be elaborated into medicinal targets.^[2] Although a number of reports document methodologies devised for the synthesis of 1,2-oxazine derivatives,^[3] only two general routes for tetrahydro-1,2-oxazines (THOs) have been used including the addition of nitrones to activated cyclopropanes, which was developed by Sibi et al.,^[4a] and the sequential nitroso aldol/Michael addition of cyclic enones reported by Yamamoto et al.^[4b,c] However, the substrate scope for these two examples are limited, and the development of a practical, asymmetric synthetic procedure to access enantiopure functionalized THOs from acyclic starting materials is highly desirable.

Recently, the field of asymmetric catalysis has included organocatalysis involving chiral secondary amine catalysts^[5] which is amenable to domino processes.^[6] α -Aminoxylation^[7] directed tandem reactions^[3g,h,8] were first developed by our group,^[8a,b] demonstrating the advantages of a rapid, catalytic, and atom-economical process that yielded enantiomerically pure products. This approach therefore seemed ideal for the asymmetric introduction of an O–N moiety. Our ongoing interest in organocatalytic domino reactions,^[9] combined with the challenge of utilizing the amine component, generated after the first aminoxylation step, in a subsequent step prompted us to investigate the domino α -aminoxylation/aza-Michael reaction for the synthesis of enantiopure functionalized THOs.

The structure of THO **1** can be assembled by using two reactions to form both the C–O and C–N bonds (Scheme 1 a); for example, the α -aminoxylation of alkenal **3** with nitroso-benzene **4** and subsequent nucleophilic attack of the in situ generated amine on Michael acceptor **2**. Initially, we recognized that a number of chemoselectivity issues needed to be addressed: 1) In addition to α -aminoxylation the enamine



Scheme 1. Proposed synthesis of chiral THO **1**. a) Enantioselective organocatalytic THO synthesis by a C–O/C–N sequence. b) Enamine-catalyzed α -aminoxylation versus Michael addition. c) Aza-Michael addition versus nucleophilic attack on the C=O group and subsequent asymmetric protonation. EWG = electron-withdrawing group.

intermediate may undergo conjugate addition with another molecule of the alkenal (Scheme 1 b), which is known from previous studies. 2) The aza-Michael addition step may be competing with the undesired inter- or intramolecular nucleophilic attack of the in situ generated amine to the aldehyde (Scheme 1 c).^[10] 3) Central to the utility of this new domino process is the mechanistic requirement that a chiral environment is established to control the aza-Michael addition and the final asymmetric protonation (when R is not a hydrogen atom). This control would ensure high levels of diastereoselectivity for the overall process, which is challenging because of the flexibility of the acyclic substrate. To circumvent the first two problems, a suitable electron-withdrawing group should be used on the Michael acceptor for the C–N bond-forming step while remaining effectively inert during the C–O bond-forming step. In terms of enantiocontrol, we also envisioned that the aza-Michael addition and protonation

[*] M. Lu, D. Zhu, Dr. Y. Lu, Y. Hou, B. Tan, 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

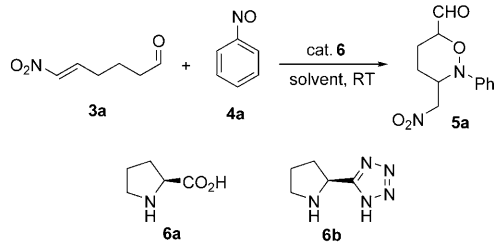
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would take place in a concerted manner by a preferred transition state (see below).

Nitroalkenes are among the most reactive Michael acceptors,^[11] so we started our investigation by using **3a** under the previously established conditions^[7a] (nitroalkenal **3a** (1.5 equiv), nitrosobenzene (1.0 equiv), and L-proline (20 mol %) in DMSO). To our delight, the proposed domino strategy was facile at room temperature and was complete within 30 minutes (Table 1). The course of the reaction was

Table 1: Organocatalytic domino α -aminoxylation/aza-Michael reactions: screening reaction conditions.^[a]



Entry	6 (mol %)	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	d.r. ^[d]
1	6a (20)	DMSO	0.5	46	99	> 99:1
2	6a (20)	DMF	0.5	44	99	> 99:1
3	6a (20)	CH ₃ CN	0.5	55	99	> 99:1
4	6a (20)	CHCl ₃	0.5	53	98	> 99:1
5	6a (20)	THF	24	< 20	n.d.	n.d.
6	6a (20)	H ₂ O	48	< 5	n.d.	n.d.
7	6b (20)	CH ₃ CN	0.5	49	99	> 99:1
8 ^[e]	6a (20)	CH ₃ CN	0.5	59	99	> 99:1
9 ^[e,f]	6a (20)	CH ₃ CN	1	63	> 99	> 99:1
10 ^[e,g]	6a (20)	CH ₃ CN	2	67	> 99	> 99:1
11 ^[e,g]	6a (20)	CH ₃ CN	24 ^[h]	73	> 99	> 99:1
12 ^[e,g]	6a (20) ^[i]	CH ₃ CN	14 ^[h]	90	> 99	> 99:1
13 ^[e,g]	6a (5) ^[i]	CH ₃ CN	24 ^[h]	90	> 99	> 99:1
14 ^[e,g]	6a (0.5) ^[i]	CH ₃ CN	72 ^[h]	77	> 99	> 99:1
15 ^[e,g]	6a (20) ^[i]	CH ₃ CN	8 ^[h]	88 ^[j]	> 99	90:10

[a] Reaction conditions: **4a** (1.0 equiv ; 1 M), **3a** (1.5 equiv), and catalyst **6** at room temperature (23 °C) in the indicated solvent. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Determined by ¹H NMR methods. [e] Used 3 equiv of **3a**. [f] Reaction was conducted at 0 °C. [g] Reaction was conducted at –20 °C. [h] 0.1 M of **4a**. [i] Added 1.0 equiv of TEAB. [j] In situ reduction was performed using NaBH₄ to provide the corresponding alcohol. n.d. = not determined.

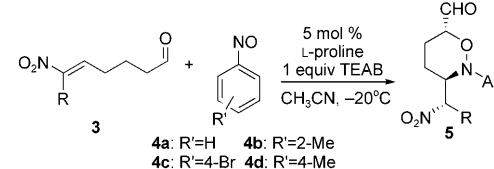
easily monitored by observing the change in the color of the solution from green to orange. After the workup, pure THO **5a** was isolated in 46% yield with 99% enantiomeric excess (*ee*) and a diastereomeric ratio (d.r.) greater than 99:1 (Table 1, entry 1). This reaction led to the first successful isolation of a stable aldehyde after the α -aminoxylation, and the rare case of an inactivated amine undergoing a conjugate addition with an aliphatic nitroalkene with high stereoselectivity.^[12] A preliminary screening indicated that the catalytic activity and the asymmetric induction were dependent on the solvent. Excellent enantio- and diastereoselectivities were obtained in polar, protophilic solvents, such as DMSO and DMF (Table 1, entries 1 and 2). A halogenated solvent possessing a lower polarity was also tolerated (Table 1, entry 4), whereas an ethereal solvent (THF) and water had deleterious effects on the reactivity (Table 1, entries 5 and 6).

Among the solvents tested, polar, protophobic acetonitrile was found to be best with respect to the chemical yield and optical purity (Table 1, entry 3). It is also noteworthy that although **6a** proved to be an excellent catalyst in the α -aminoxylation, pyrrolidine-based tetrazole **6b**^[13] induced reaction with lower conversion (Table 1, entry 7). Performing the reaction with a larger excess of **3a** led to complete conversion, and **5a** was isolated in 59% yield (Table 1, entry 8). Having identified the optimal reaction medium, we examined the temperature effect on the transformation. Notably, considerable side reactions can be detected at 0 °C (Table 1, entry 9), but suppression of the homodimerization was accomplished at –20 °C (Table 1, entry 10). To avoid making intractable byproducts, the reaction mixture was diluted (Table 1, entry 11).

Next, the effect of the catalyst loading was evaluated. Remarkably, in the presence of tetraethylammonium bromide (TEAB) (Table 1, entry 12)^[14] a catalyst loading as low as 0.5 mol % could be used without any loss in the *ee* values or the d.r. numbers (Table 1, entry 14). For operational convenience 5 mol % L-proline, under otherwise identical reaction times, ensured high levels of reaction efficiency and enantioselectivity (Table 1, entry 13). Notably, after the in situ reduction, the d.r. of the corresponding alcohol significantly dropped to 90:10 (Table 1, entry 15), albeit the *ee* value was not affected. This result implied that L-proline played an important role in diastereocontrol.

We then explored the scope of these transformations by using the optimized reaction conditions. The method was applied to a variety of nitroalkenal substrates, and as shown in

Table 2: Organocatalytic domino α -aminoxylation/aza-Michael reactions: substrate scope.^[a]



Entry	R	ArNO	Yield [%] ^[b]	<i>ee</i> [%] ^[c]	d.r. ^[d]
1	H (3a)	4a	90 (5a)	> 99	> 99:1
2	H (3a)	4b	79 (5b)	97	> 99:1
3	H (3a)	4c	88 (5c)	> 99	> 99:1
4	Me (3b)	4a	75 (5d)	99	> 99:1
5	Me (3b)	4c	73 (5e)	99	> 99:1
6	Et (3c)	4a	68 (5f)	> 99	> 99:1
7	Et (3c)	4c	60 (5g)	> 99	> 99:1
8	Ph (3d)	4a	73 (5h)	> 99	> 99:1
9	Bn (3e)	4a	50 (5i)	> 99	> 99:1
10	Bn (3e)	4c	66 (5j)	99	> 99:1
11	<i>p</i> MeC ₆ H ₄ CH ₂ (3f)	4a	47 (5k)	> 99	> 99:1
12	<i>p</i> MeC ₆ H ₄ CH ₂ (3f)	4c	45 (5l)	> 99	> 99:1
13	<i>p</i> ClC ₆ H ₄ CH ₂ (3g)	4a	78 (5m)	> 99	> 99:1
14	<i>p</i> ClC ₆ H ₄ CH ₂ (3g)	4c	78 (5n)	> 99	> 99:1
15	<i>p</i> BrC ₆ H ₄ CH ₂ (3h)	4a	75 (5o)	> 99	> 99:1
16	<i>p</i> BrC ₆ H ₄ CH ₂ (3h)	4c	70 (5p)	99	> 99:1
17	H (3a)	4d	90 (5q)	> 99	> 99:1

[a] Reaction conditions: **4a** (1.0 equiv ; 0.1 M), **3a** (3.0 equiv), TEAB (1.0 equiv), and **6a** (5 mol %) at –20 °C in CH₃CN. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Determined by ¹H NMR methods.

Table 2 different substituents were well-tolerated at the α position to the nitro group. The R group of component **3** ranges from simple to sterically demanding groups, as well as valuable functional groups. Good yields were observed although there was some fluctuation depending on the substituents. The variation of the steric effects (Table 2, entries 4–8) or the electronic effects (Table 2, entries 9–16) had only a small impact on the introduction of the third chiral center, which was evidenced by the uniformly high *ee* and d.r. values. Furthermore, this method was applicable to various aromatic nitroso compounds; for example, 2-methyl-, 4-methyl- and 4-bromo-nitrosobenzene (Table 2, entries 2, 3, and 17). The fact that the R and R' groups of precursors **3** and **4**, respectively, can be varied demonstrates the versatility of our approach.

This domino reaction generates up to three stereogenic centers and forms only one out of eight possible stereoisomers. The origin of the high stereoselectivity derives from the α -aminoxylation reaction, which is known to proceed with high enantioselectivity.^[15] This selectivity is maintained in the second step by going through a sterically favored transition state (see below). The relative and absolute configurations of THO **5d** were determined by ¹H NMR nuclear Overhauser effect (NOE) experiments and X-ray crystallography (Figure 1) and compared with respective related α -aminoxylations.^[15,16]

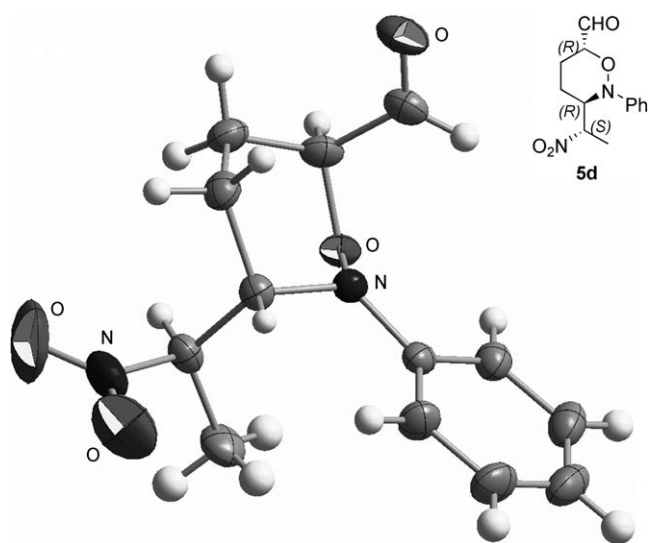


Figure 1. X-ray crystal structure of **5d**.^[16]

Since the aldehyde group and the α -methylnitro group are *trans* and pointing away from each other in the crystal structure of **5d**, it is unlikely that L-proline participates in the reaction by covalent bond catalysis in the transition state of the aza-Michael addition/protonation step. To get some mechanistic insight into this domino reaction, a series of control experiments were carried out (Table 3).

We chose *O*-(*tert*-butyldimethylsilyl)-*N*-phenylhydroxylamine (**7**) and (*E*)-(4-nitrobut-3-enyl)benzene (**8**) as mimics of the in situ generated amine substrate and the nitroalkenyl reactant, respectively. In the absence of any catalyst, the

Table 3: Preliminary mechanistic investigations: catalysis of the aza-Michael addition step.

Entry	Cat. (mol %)	T [°C]	t [h]	Conversion ^[b]
1	none	−20	48	n.r.
2	none	RT	48	n.r.
3	TEA (100)	RT	48	31
4	quinine (20)	RT	18	> 95

[a] Reaction conditions: **7** (1.0 equiv, 0.1 M), **8** (1.0 equiv), and the corresponding catalyst at room temperature in CH₃CN. [b] Determined by ¹H NMR methods. TBS = *tert*-butyldimethylsilyl; n.r. = no reaction.

reaction did not proceed after 2 days at −20°C (Table 3, entry 1). Elevating the temperature to room temperature provided similar results (Table 3, entry 2), and when 1 equivalent of TEA was used as a Lewis base in the reaction it proceeded sluggishly with a 31 % conversion. This experiment revealed that the tertiary amine itself was not sufficient to enhance the reactivity of **7** (Table 3, entry 3). The introduction of a hydrogen-bond donor,^[17] 20 mol % of quinine, resulted in full conversion within 18 hours. These observations indicate that the aza-Michael addition step is catalyzed by hydrogen-bonding interactions. Combined with the fact that intermediates cannot be detected in the ¹H NMR spectra recorded during the course of the reaction or upon product isolation, a concerted mechanism is proposed. After the α -aminoxylation step, the aza-Michael addition/protonation^[18] proceeds in a synergistic way and is assisted by a molecule of water which participates in two hydrogen bonds; the hydrogen bonds are formed between the water molecule and both the in situ generated amine moiety and the nitro group (Figure 2). DFT calculations^[19] of the lowest energy transition state also confirm this assumption.

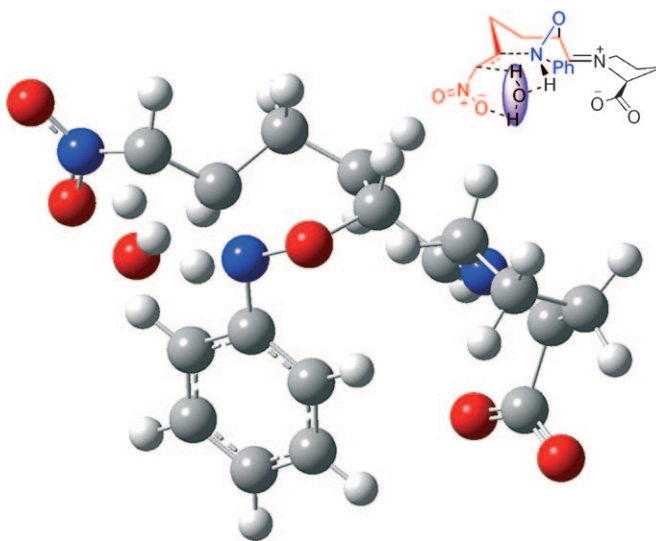


Figure 2. DFT-calculated lowest energy transition state for the aza-Michael addition/protonation in CH₃CN.^[19]

In summary, we have developed a novel, practical, and enantio- and diastereoselective domino reaction for the synthesis of functionalized THOs by using a simple amine catalyst. The results disclosed herein demonstrate the ability to control the regio- and stereochemistry of the reaction for the synthesis of THOs from acyclic substrates. We anticipate that α -aminoxylation directed domino reactions will have great potential in the field of organocatalysis. The reaction, which is easy to perform, proceeds cleanly with complete stereocontrol and does not require a change in the reaction conditions or adding reagents. This discovery is likely to be used in synthetic applications, especially since the α -aminoxylation reaction can be combined with existing domino methods. Applications of this methodology to total syntheses and detailed mechanistic studies will be described in due course.

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- [1] a) H. Terano, S. Takase, J. Hosoda, M. Kohsaka, *J. Antibiot.* **1989**, *42*, 145–148; b) I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda, Y. Morimoto, *J. Am. Chem. Soc.* **1987**, *109*, 4108–4109; c) M. Iwami, S. Kiyoto, H. Terano, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, *40*, 589–593; d) S. Kiyoto, T. Shibata, M. Yamashita, T. Komori, M. Okuhara, H. Terano, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1987**, *40*, 594–599; e) K. Shimomura, O. Hirai, T. Mizota, S. Matsumoto, J. Mori, F. Shibayama, H. Kikuchi, *J. Antibiot.* **1987**, *40*, 600–606; f) O. Hirai, K. Shimomura, T. Mizota, S. Matsumoto, J. Mori, H. Kikuchi, *J. Antibiot.* **1987**, *40*, 607–611.
- [2] P. G. Tsoungas, *Heterocycles* **2002**, *57*, 915–953.
- [3] a) P. F. Vogt, M. J. Miller, *Tetrahedron* **1998**, *54*, 1317–1348; b) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–165; c) X. Ding, Y. Ukaji, S. Fujinami, K. Inomata, *Chem. Lett.* **2003**, *32*, 582–583; d) K. Koide, J. M. Finkelstein, Z. Ball, G. L. Verdine, *J. Am. Chem. Soc.* **2001**, *123*, 398–408; e) I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett.* **2005**, *7*, 953–955; f) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131–3134; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023–3026; g) S. Kumarn, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Lett.* **2005**, *7*, 4189–4191; h) S. Kumarn, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2006**, 3211–3213.
- [4] a) M. P. Sibi, Z. H. Ma, C. P. Jasperse, *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765; b) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962–5963; c) N. Momiyama, Y. Yamamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 1190–1195.
- [5] For selected reviews on organocatalysis, see: a) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; c) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; d) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; e) D. W. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; f) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
- [6] For reviews on domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttel, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; b) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292–7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; c) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136. For selected examples, see: e) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365–4369; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233–4237; f) J. Casas, M. Engqvist, I. Ibrahim, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367–1369; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345; g) J. W. Yang, M. T. H. Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037; h) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053; i) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986–14991; j) D. Enders, M. R. M. Hüttel, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; k) Y. Hayashi, T. Okano, S. Aratake, D. Hazeldar, *Angew. Chem.* **2007**, *119*, 5010–5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925; l) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894; m) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362–9365; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202–9205; n) C. E. Aroyan, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 256–257; o) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768–769.
- [7] For α -aminoxylation of aldehydes, see: a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379–4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293–8296; d) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374–5378; e) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235–7238; For α -aminoxylation of ketones, see: f) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129–1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109–1112; g) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132–1135; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1115; For reviews, see: h) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514–3525; i) P. Merino, T. Tejero, *Angew. Chem.* **2004**, *116*, 3055–3058; *Angew. Chem. Int. Ed.* **2004**, *43*, 2995–2997.
- [8] a) G. Zhong, *Chem. Commun.* **2004**, 606–607; b) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637–1639; c) D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1577–1580; d) S. Kumarn, A. J. Oelke, D. M. Shaw, D. A. Longbottom, S. V. Ley, *Org. Biomol. Chem.* **2007**, *5*, 2678–2689.
- [9] a) B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett.* **2008**, *10*, 2437–2440; b) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425–3428; c) B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2008**, *10*, 3489–3492.
- [10] Products of the α -aminoxylation of ketones are stable and can be isolated in pure form. However, in the case of the aldehydes, there are reactions that occur between the aldehyde and the amino groups in the products (existing in the form of oligomers), therefore in situ reduction of the aldehydes to the corresponding alcohols is necessary to obtain pure products. For an example, see: Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, *J. Org. Chem.* **2004**, *69*, 5966–5973.
- [11] For a review, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
- [12] For selected examples of diastereoselective aza-Michael additions to nitroalkenes, see: a) P. L. Southwick, J. E. Anderson, *J. Am. Chem. Soc.* **1957**, *79*, 6222–6229; b) A. Kamimura, A. Kadowaki, Y. Nagata, H. Uno, *Tetrahedron Lett.* **2006**, *47*, 2471–2473; c) D. Enders, J. Wiedemann, *Synthesis* **1996**, 1443–1450; d) D. Lucent, P. Heyse, A. Gissot, T. Le Gall, C. Mioskowski, *Eur. J. Org. Chem.* **2000**, 3575–3579.

- [13] a) See ref. [7d]; b) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; c) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.
- [14] The addition of a phase transfer catalyst (PTC) such as TEAB greatly enhanced the solubility of L-proline, which helped to make a homogeneous solution; this increase in the catalyst concentration resulted in a positive effect on reactivity of the substrates.
- [15] For mechanistic studies, see: a) S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem.* **2004**, *116*, 3379–3383; *Angew. Chem. Int. Ed.* **2004**, *43*, 3317–3321; b) P. H.-Y. Cheong, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913; c) H. Iwamura, D. H. Wells, Jr., S. P. Mathew, M. Klussmann, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312–16313.
- [16] CCDC 670447 (**5d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. The X-ray crystal structure of **5d** showed the relative configuration. The absolute configuration was assigned for the α -aminoxy carbon center as *R* based on previous reports and mechanism studies. For reports, see references [7 and 8].
- [17] For selected recent reviews on hydrogen-bonding catalysis, see: a) A. D. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; b) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; c) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110–2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; d) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; e) C. Bolm, T. Rantanen, I. Schiffrers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788–1793; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758–1763; f) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; g) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; h) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013–4016; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; i) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658–7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504.
- [18] For timely examples on organocatalytic asymmetric protonation, see: a) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247; b) 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.
- [19] For computational details, please see the Supporting Information.