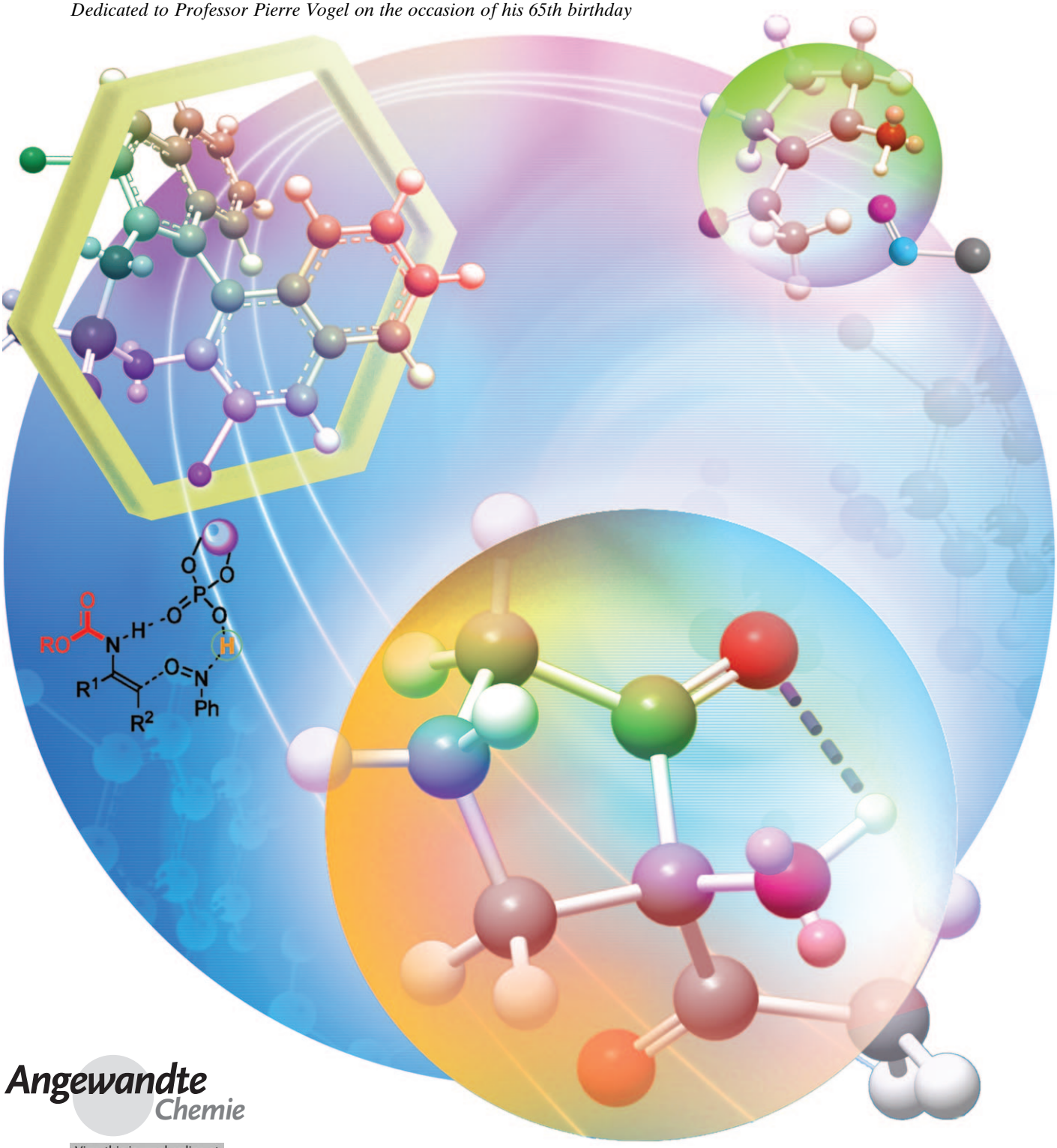
Asymmetric Aminoxylation

DOI: 10.1002/anie.201002640

Chiral Brønsted Acid Catalyzed Enantioselective α-Aminoxylation of Enecarbamates**

*Min Lu, Yunpeng Lu, Di Zhu, Xiaofei Zeng, Xinsheng Li, and Guofu Zhong**

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



α-Hydroxy carbonyl compounds are key motifs encountered throughout natural products and pharmacueticals; thus, the preparation of chiral α-hydroxy ketones has been of great interest and has motivated a tremendous wealth of strategies for their synthesis.[1] Catalytic asymmetric α-aminoxylation reactions[2–6] are one of the most facile and conventional synthetic methods towards chiral α-hydroxy ketones. However, despite considerable efforts in the area of α-aminoxylation, so far the substrate scopes have been limited to aldehydes,[4] cyclic ketones,[5] and β-dicarbonyl compounds.[6] The use of linear ketones resulted in significant decrease in both the reactivity and selectivity,[7] while no examples with aromatic ketones have been documented, possibly because of the severe steric hindrance which strongly inhibited the covalent binding of the catalyst.

To address these challenges, enecarbamate **1** was chosen as an activated ketone nucleophile (Figure 1);[8] we envisioned that in the presence of an electron-withdrawing carbamate group (TS), instead of an electron-donating pyrrolidine moiety (used in proline catalysis, TS*), the undesired N-addition pathway might be suppressed. The fact that both the *E* and *Z* isomers of enecarbamates can be conveniently prepared provides additional flexibility for this approach.[9] Meanwhile, chiral Brønsted acids[10,11] would be attractive alternatives for overcoming the limitations of proline catalysis in α-aminoxylation reactions, as selective protonation of the basic nitrogen of nitrosobenzene should be realized by a judicious choice of stronger acid (TS).[12] However, no efficient C–O bond formation of enecarbamates has been reported, despite recent successes in the catalytic asymmetric aza–ene reactions of enecarbamates with aldehydes[13] and imines.[14] In a continuation of our long standing work in aminoxylation chemistry,[15] we recently discovered that highly enantioselective α-hydroxylation of β-dicarbonyl compounds can be achieved through activation of nitroso compounds with binol-derived phosphoric acids.[6] To further explore the extent of this novel activation mode, herein we describe the first chiral-phosphoric-acid-catalyzed α-aminoxylation of ene-carbamates, and its one-pot application leading to direct access of optically pure α-hydroxy ketones, β-amino alcohols, and oxazolidinones.

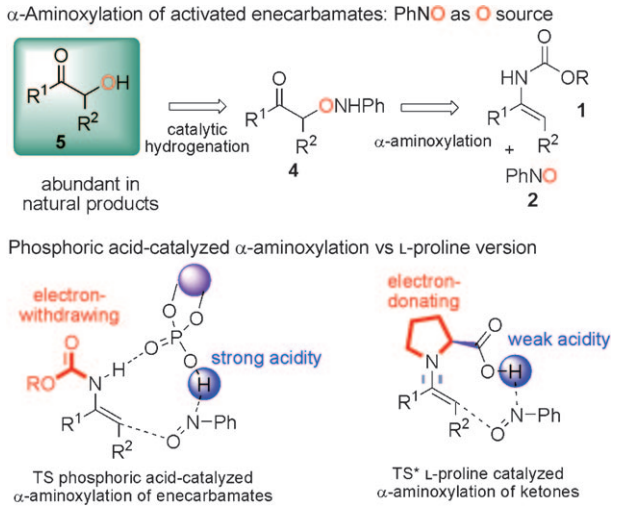


Figure 1. Projected synthesis of chiral α-hydroxy ketones **5**.

On the basis of our initial DFT calculations (Figure 2),[16] it was found that with a stronger Brønsted acid, such as phosphoric acid, as the catalyst, the O-selective pathway (TS-1) would be favored by 2.91 kcal mol^{-1}; we proposed that the utility of this activation mode would rely on the identification of a phosphoric acid **3** with suitable R groups that could induce high levels of enantiocontrol in the C–O bond-forming step. To test this concept, we carried out the reaction using 1.1 equivalents of enecarbamate **1a** and nitrosobenzene **2a** (Table 1).[16] As expected, 5 mol% of phosphoric acid (*R*)-**3a** effectively promoted the reaction in dichloromethane at room temperature within 5 minutes (Table 1, entry 1). The reaction can be monitored easily by observation of its color change from green to orange, and, after hydrolysis, furnished the desired product **4a** in 88% yield with almost complete O-selectivity (O/N > 95:5), accompanied by promising enantioselectivity (90:10 e.r.).

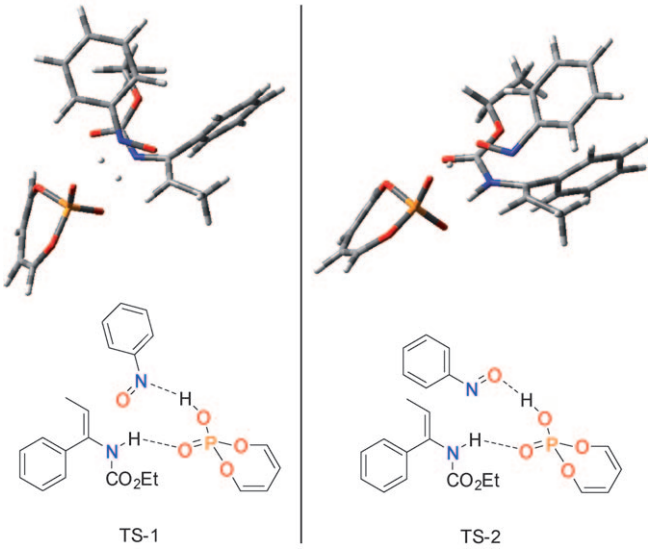


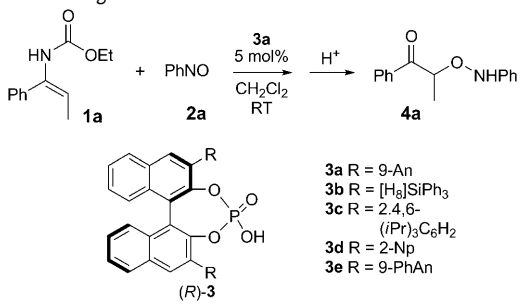
Figure 2. DFT-calculated lowest-energy transition state for the O-selective (TS-1) and N-selective (TS-2) pathways.[16]

[*] M. Lu, Dr. Y. Lu, D. Zhu, X. Zeng, Dr. X. Li, 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

[**] Research support from the Ministry of Education in Singapore (ARC12/07, no. T206B3225) and Nanyang Technological University (URC, RG53/07 and SEP, RG140/06) is gratefully acknowledged. Y.L. thanks the Division of Chemistry and Biological Chemistry at Nanyang Technological University for providing the computational resources.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002640.

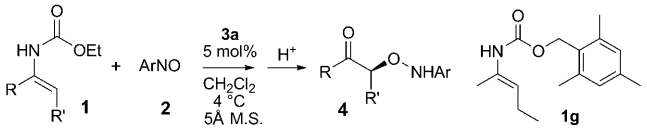
Table 1: Screening of reaction conditions.[a]



Entry	Solvent	t [h]	O/N[b]	Yield [%][c]	e.r.[d]
1	CH_2Cl_2	0.1	>95:5	88	90:10
2	toluene	0.1	94:6	85	88:12
3	THF	12	<5:95	-	–
4[e]	CH_2Cl_2	0.2	>95:5	90	92:8
5[f]	CH_2Cl_2	0.5	>95:5	85	90:10
6[e,g]	CH_2Cl_2	0.2	>95:5	95	97:3
7[e,g,h]	CH_2Cl_2	0.5	>95:5	90	96:4
8[e,g,i]	CH_2Cl_2	0.1	<5:95	-	–

[a] For screening details, see the Supporting Information. [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction conducted at 4 °C. [f] Reaction conducted at −20 °C. [g] 5 Å M.S. were added. [h] 2 mol% of **3a** was used. [i] (*Z*)-**1a** was used instead of (*E*)-**1a**. An = anthryl, Np = naphthyl, THF = tetrahydrofuran.

Table 2: Substrate scope of the chiral phosphoric acid catalyzed α-aminoxylation of enecarbamates.[a]



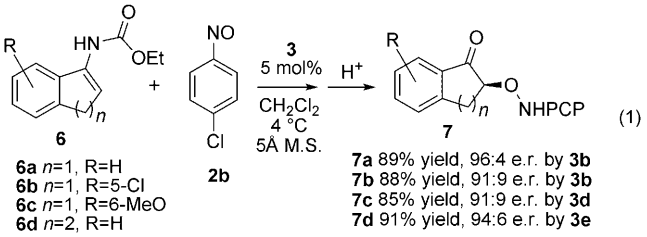
1a–f R' = Me
1h R' = Et

Entry	R	Ar	Yield [%][b]	e.r.[c]
1	Ph (**1a**)	Ph (**2a**)	95 (**4a**)	97:3
2	Ph (**1a**)	*p*-ClC_6H_4 (**2b**)	95 (**4b**)	98:2
3	Ph (**1a**)	*p*-BrC_6H_4 (**2c**)	93 (**4c**)	98:2
4	Ph (**1a**)	*p*-Tol (**2d**)	44 (**5**)	97:3
5	Ph (**1a**)	*m*-ClC_6H_4 (**2e**)	91 (**4d**)	98:2
6	Ph (**1a**)	*o*-ClC_6H_4 (**2f**)	89 (**4e**)	96:4
7	Ph (**1a**)	*p*-$CO_2MeC_6H_4$ (**2g**)	98 (**4f**)	97:3
8	*p*-ClC_6H_4 (**1b**)	*p*-ClC_6H_4 (**2b**)	96 (**4g**)	98.5:1.5
9	*p*-$MeOC_6H_4$ (**1c**)	*p*-ClC_6H_4 (**2b**)	93 (**4h**)	96.5:3.5
10	*p*-Tol (**1d**)	*p*-ClC_6H_4 (**2b**)	95 (**4i**)	97:3
11	*m*-Tol (**1e**)	*p*-ClC_6H_4 (**2b**)	90 (**4j**)	96:4
12	*o*-Tol (**1f**)	*p*-ClC_6H_4 (**2b**)	89 (**4k**)	96:4
13[d]	Me (**1g**)	*p*-ClC_6H_4 (**2b**)	90 (**4l**)	90:10
14	Ph (**1h**)	*p*-ClC_6H_4 (**2b**)	92 (**4m**)	98:2

[a] For detailed reaction conditions, see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC or GC analysis on a chiral stationary phase. [d] 10 mol% of **3c** was used.

Aromatic solvents delivered similar results (Table 1, entry 2); however, when ethereal solvents were used, N-addition was favored (Table 1, entry 3, O/N < 5:95). Notably, although a prolonged reaction time was required at 4 °C, an efficient catalytic performance with higher e.r. was observed (Table 1, entry 4, e.r. 92:8); further lowering the temperature to −20 °C gave rise to diminished enantiocontrol (Table 1, entry 5). Remarkably, both the yields and optical purity were improved in the presence of 5 Å molecular sieves (Table 1, entry 6; 95% yield, e.r. 97:3). Catalyst loadings as low as 2 mol% could be utilized without compromising the reactivity and selectivity (Table 1, entry 7). It is also noteworthy that when changing the enecarbamate geometry from *E* to *Z*, a dramatic inversion in O/N selectivity was observed (Table 1, entry 8).[17]

Experiments that probed the scope of this novel transformation under optimized conditions are summarized in Table 2. A broad spectrum of nitrosoarenes could be employed in the reaction to afford the desired products in excellent yields and high enantioselectivities (Table 2, entries 1–7), with the exception of 4-nitrosotoluene (Table 2, entry 4) in which N–O bond heterolysis was observed after the initial aminoxylation.[6] Enecarbamates derived from aromatic ketones that have substituents with various electronic and steric properties were also found to efficiently react with 4-chloronitrosobenzene (**2b**), and the products were obtained in high enantioselectivities (Table 2, entries 8–12). For aliphatic-ketone-derived enecarbamate, the use of an ethyl carbamate group resulted in poor enantioselectivity (70:30 e.r.); nevertheless, following systematic modification of the carbamate group as well as fine tuning of the catalyst,[16] wer found that the mesitylmethyl group was able to provide enough steric bulkiness when subjected to the chiral environment created by catalyst **3c**, and the product **4l** was isolated in 90% yield with 90:10 e.r. (Table 2, entry 13). Furthermore, the more-challenging enecarbamates derived from indanones and tetralones could also successfully undergo α-aminoxylation to give α-oxygenated products in good yields and *ee* values [Eq. (1)], although specific catalyst was needed for



6a *n*=1, R=H
6b *n*=1, R=5-Cl
6c *n*=1, R=6-MeO
6d *n*=2, R=H

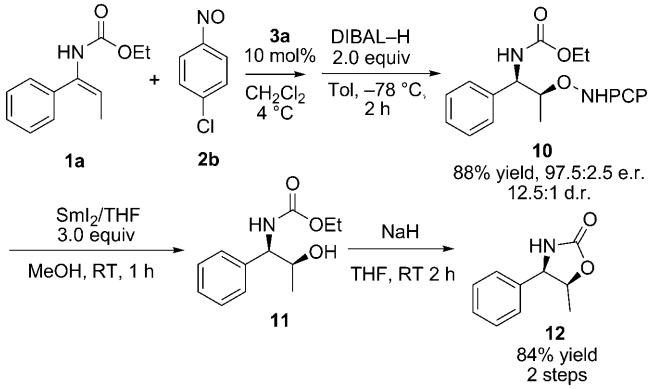
7a 89% yield, 96:4 e.r. by **3b**
7b 88% yield, 91:9 e.r. by **3b**
7c 85% yield, 91:9 e.r. by **3d**
7d 91% yield, 94:6 e.r. by **3e**

(1)

each substrate. The absolute configuration of **4a**, **7a**, and **7d** were determined to be *S* after catalytic hydrogenation to convert them to the corresponding α-hydroxy ketones[16] and comparing the optical rotation with literature.[18] The stereochemistry of other products was tentatively assumed by analogy.

To highlight the synthetic utility of this procedure, we present preliminary results for the one-pot synthesis of orthogonally protected β-amino alcohols and a straightforward access to *cis*-oxazolidinones. The β-amino alcohol moiety is found in a wide range of biologically active natural products,[19] and is also well-recognized in asymmetric synthesis, as many chiral auxiliaries and ligands contain this

substructure.[20] Specifically, after the α-aminoxylation of **1a** had been completed, reduction of the crude product with DIBAL (diisobutylaluminium hydride) at −78 °C efficiently furnished the protected β-amino alcohol **10** in 88 % yield and 12.5:1 d.r. (Scheme 1). After a SmI_2-promoted N−O bond heterolysis, *cis*-oxazolidinone was obtained using a reported procedure.[21]



Scheme 1. Synthesis of β-amino alcohol and cis-oxazolidinone.

In conclusion, we have reported a facile, practically appealing, highly enantioselective Brønsted acid-catalyzed α-aminoxylation of enecarbamates. This procedure considerably extend the substrate scope for the α-aminoxylation reaction to linear and aromatic ketones, allowing convergent and stereoselective access to valuable α-hydroxy ketones, β-amino alcohols, and *cis*-oxazolidinones in their enantiopure form. This discovery also provides mechanistic insights into the N/O selectivity of α-aminoxylation. Further applications of this activation mode to other enantioselective reactions are currently underway.

Received: May 2, 2010
Published online: July 26, 2010

Keywords: α-hydroxy ketones · aminoxylation · asymmetric catalysis · Brønsted acid catalysis · nitroso compounds

[1] For reviews, see: a) F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919; b) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292.

[2] For general reviews, see: a) P. Merino, T. Tejero, *Angew. Chem.* **2004**, *116*, 3055; *Angew. Chem. Int. Ed.* **2004**, *43*, 2995; b) H. Yamamoto, N. Momiyama, *Chem. Commun.* **2005**, 3514.

[3] For Lewis acid catalyzed nitrosol aldol reactions, see: a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038; b) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360; c) M. Kawasaki, P. Li, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 3855; *Angew. Chem. Int. Ed.* **2008**, *47*, 3795.

[4] For organocatalytic α-aminoxylation of aldehydes, see: a) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; c) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293; d) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374; e) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235; f) P. J. Chua, B. Tan, G. Zhong, *Green Chem.* **2009**, *11*, 543.

[5] For organocatalytic α-aminoxylation of ketones, see: a) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; b) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112; For α-aminoxylation of other compounds, see: c) A. Yanagisawa, S. Takeshita, Y. Izumi, K. Yoshida, *J. Am. Chem. Soc.* **2010**, *132*, 5328; d) T. Bui, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2010**, *132*, 5574.

[6] For aminoxylation/O−N bond heterolysis processes, see: a) D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 1577; b) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu, G. Zhong, *J. Am. Chem. Soc.* **2009**, *131*, 4562.

[7] There are scarce examples of linear ketones with almost no N/O selectivity, see: a) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji, *J. Org. Chem.* **2004**, *69*, 5966; b) See Ref. [4d].

[8] For an excellent review, see: R. Matsubara, S. Kobayashi, *Acc. Chem. Res.* **2008**, *41*, 292.

[9] a) R. Matsubara, P. Vital, Y. Nakamura, H. Kiyohara, S. Kobayashi, *Tetrahedron* **2004**, *60*, 9769; b) R. Matsubara, N. Kawai, S. Kobayashi, *Angew. Chem.* **2006**, *118*, 3898; *Angew. Chem. Int. Ed.* **2006**, *45*, 3814; c) R. Matsubara, S. Kobayashi, *Angew. Chem.* **2006**, *118*, 8161; *Angew. Chem. Int. Ed.* **2006**, *45*, 7993.

[10] For reviews, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) M. Terada, *Chem. Commun.* **2008**, 4097; c) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31; d) A. D. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; e) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; f) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; g) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; h) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190.

[11] For selected examples of the phosphoric acid catalyzed reactions, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; e) H. Liu, L.-F. Cun, A.-Q. Mi, Y. Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 6023; f) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617; g) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; h) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484; i) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* **2007**, *9*, 2609; j) M. J. Wanner, R. N. S. Haas, K. R. Cuba, J. H. Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485; k) Y.-X. Jia, J. Zhong, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565; l) S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem.* **2008**, *120*, 2882; *Angew. Chem. Int. Ed.* **2008**, *47*, 2840; m) D. S. Giera, M. Sickert, C. Schneider, *Org. Lett.* **2008**, *10*, 4259; n) C. Baudequin, A. Zamfir, S. B. Tsogoeva, *Chem. Commun.* **2008**, 4637; o) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J.-P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598; p) N. Momiyama, H. Tabuse, M. Terada, *J. Am. Chem. Soc.* **2009**, *131*, 12282; q) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; r) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P.-M. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572; s) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056.

[12] For a seminal work on Brønsted acid catalyzed aminoxylation of cyclic ketone-derived enamines, see: N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080.
[13] M. Terada, K. Soga, N. Momiyama, *Angew. Chem.* **2008**, *120*, 4190; *Angew. Chem. Int. Ed.* **2008**, *47*, 4122.
[14] a) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; b) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336.
[15] a) G. Zhong, *Chem. Commun.* **2004**, 606; b) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637; c) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan, G. Zhong, *Angew. Chem.* **2008**, *120*, 10341; *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; d) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang, G. Zhong, *Org. Lett.* **2008**, *10*, 4585.
[16] For details, see the Supporting Information.
[17] In all cases, the N-addition products were racemic. For calculation studies, see: a) P. H.-Y. Cheong, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 13912; For mechanism studies, see: b) S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem.* **2004**, *116*, 3379; *Angew. Chem. Int. Ed.* **2004**, *43*, 3317; c) H. Iwamura, D. H. Wells, Jr., S. P. Mathew, M. Klussmann, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 16312; For an excellent report on organocatalytic oxyamination, see: d) T. Kano, M. Ueda, J. Takai, K. Maruoka, *J. Am. Chem. Soc.* **2006**, *128*, 6046.
[18] a) W. Adam, R. T. Fell, V. R. Stegmann, C. R. Saha-Möller, *J. Am. Chem. Soc.* **1998**, *120*, 708; b) H. Kajiro, S. Mitamura, A. Mori, T. Hiyama, *Synlett* **1998**, 51; c) K. Naemura, T. Wakebe, K. Hirose, Y. Tobe, *Tetrahedron: Asymmetry* **1997**, *8*, 2585.
[19] a) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431; b) P. Castejon, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron* **1996**, *52*, 7063.
[20] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835.
[21] The relative configuration was determined by NOE effects as well as by comparison with literature data; see: E.-S. Lee, H.-S. Yeom, J.-H. Hwang, S. Shin, *Eur. J. Org. Chem.* **2007**, 3503.

