Asymmetric Synthesis

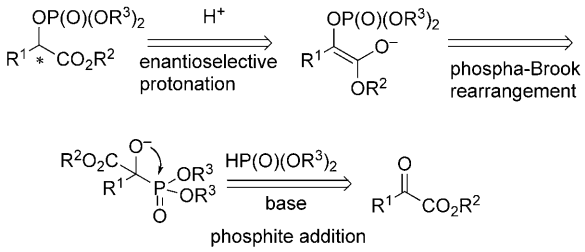
DOI: 10.1002/anie.201007568

Catalytic Enantioselective Protonation of α-Oxygenated Ester Enolates Prepared through Phospha-Brook Rearrangement**

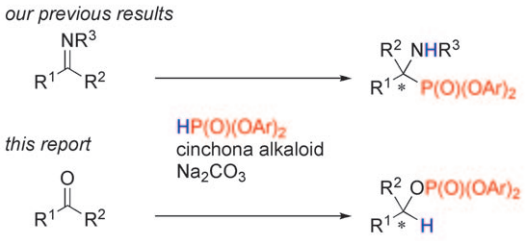
*Masashi Hayashi and Shuichi Nakamura**

The enantioselective protonation of prochiral enolates has been studied extensively as one of the simplest and most straightforward methods of accessing a wide range of optically active α-substituted carbonyl compounds. The most challenging step of this process is the development of a catalytic enantioselective protonation of enolates, for which the substrate scope is relatively limited.[1] While the reaction affords a convenient synthetic method for the preparation of chiral α-oxygenated esters, there are no reports on the catalytic enantioselective protonation of enolates derived from α-oxygenated esters. In particular, the development of an enantioselective synthesis of optically active phosphoric monoesters constructed with chiral secondary alcohols is highly desirable because of the biological activity of such compounds, which are present in DNA, fostriecin,[2] cytostatine,[3] and enigmazole,[4] and for their synthetic importance.[5] Herein, we report a novel synthesis of optically active phosphoric esters through the catalytic enantioselective protonation of α-phosphonyloxy enolates, which were prepared from the nucleophilic addition of phosphites to α-ketoesters and a subsequent phospha-Brook rearrangement (Scheme 1).[6]

Only a few examples of enantioselective reactions of ketones with phosphites have been reported.[7,8] In 2009, Feng and co-workers reported their pioneering work on the enantioselective addition of phosphites to α-ketoesters using 15 mol% of a chiral thiourea catalysts to give α-hydroxy phosphonates as hydrophosphonylation products with up to 91% *ee*.[7a] Feng and co-workers also reported the enantioselective hydrophosphonylation of trifluoromethyl ketones using 10 mol% of chiral aluminum catalysts.[7d] Ooi and co-workers demonstrated the highly enantioselective addition of a phosphite to ynones using 5 mol% of tetraaminophosphonium phosphite as a chiral catalyst.[7c] Despite the impressive progress achieved in the enantioselective reaction of ketones with phosphites, all of these reactions gave chiral α-hydroxy phosphonates. Recently, we have reported the first enantioselective reaction of phosphites with various ketimines catalyzed by cinchona alkaloids and Na_2CO_3 to give chiral α-amino phosphonates as hydrophosphonylation products with high enantioselectivity.[9] We herein report the synthesis of optically active α-phosphonyloxy esters by the reaction of α-ketoesters with phosphites under reaction conditions similar to those used in our first report (Scheme 2).



Scheme 1. Enantioselective protonation of α-phosphonyloxy enolates prepared through a phospha-Brook rearrangement.



Scheme 2. Reaction of ketimines or ketones with phosphites in the presence of cinchona alkaloids and Na_2CO_3.

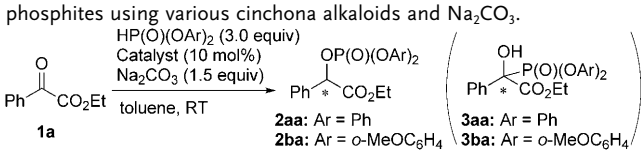
The enantioselective reaction of ethyl phenylglyoxylate **1a** with diphenyl phosphite (3.0 equiv) was carried out in the presence of 10 mol% of cinchona alkaloids and stoichiometric amounts of Na_2CO_3 (1.5 equiv) at room temperature (Table 1). The reaction of **1a** with diphenyl phosphite using quinine and Na_2CO_3 resulted in product **2aa**, which was obtained through nucleophilic addition of the phosphite to **1a** and subsequent phospha-Brook rearrangement. The reaction without Na_2CO_3 proceeded slowly to give **2aa** in low yield together with addition product **3aa** with a 46% yield (Table 1, entries 1 and 2). Optimization studies of the reaction of **1a** with various cinchona alkaloids have shown that quinine and quinidine are efficient organocatalysts in the reaction of **1a** with diphenyl phosphite (Table 1, entries 3–6, see also the Supporting Information). The reaction with diphenyl phosphite (1.3 equiv) and a catalytic amount of Na_2CO_3

[*] M. Hayashi, Prof. S. Nakamura
Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5245
E-mail: snakamur@nitech.ac.jp
Homepage: http://www.ach.nitech.ac.jp/~organic/shibata/shibata.html

[**] This work was supported by the Tatematsu Foundation. We are grateful to Zeon Co. for a gift of cyclopentyl methyl ether.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007568.

Table 1: Enantioselective reaction of ethyl phenylglyoxylate **1a** with diaryl phosphites using various cinchona alkaloids and Na_2CO_3.



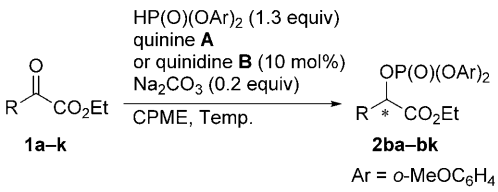
Entry	Catalyst (mol%)	Ar	Yield of **2** [%]	*ee* [%][a]
1[b]	quinine (10)	Ph	17[c]	58 (*S*)
2	quinine (10)	Ph	99	46 (*S*)
3	quinidine (10)	Ph	91	63 (*R*)
4	cinchonine (10)	Ph	98	22 (*R*)
5	cinchonidine (10)	Ph	88	19 (*S*)
6	Ac-quinidine (10)	Ph	97	39 (*S*)
7[d]	quinidine (10)	Ph	93	64 (*R*)
8[d,e]	quinidine (10)	Ph	94	70 (*R*)
9[d,e]	quinidine (10)	*o*-$MeOC_6H_4$	79	74 (*R*)
10[d,e,f]	quinidine (10)	*o*-$MeOC_6H_4$	98	92 (*R*)
11[d,e,f]	quinidine (2)	*o*-$MeOC_6H_4$	94	92 (*R*)
12[d,e,f]	quinine (10)	*o*-$MeOC_6H_4$	97	91 (*S*)
13[d,e,f,g]	quinidine (10)	*o*-$MeOC_6H_4$	98	90 (*R*)

[a] The absolute configuration of **2** is given in parentheses. [b] Reaction carried out without using Na_2CO_3. [c] **3aa** (46%) was obtained. [d] Phosphite (1.3 equiv) and Na_2CO_3 (0.2 equiv) was used. [e] Cyclopentyl methyl ether was used as a solvent. [f] The reaction was carried out at −40°C. [g] Water (10.0 equiv) was added.

(0.2 equiv) also led to good results (Table 1, entry 7). The reaction in cyclopentyl methyl ether (CPME) afforded **2aa** with a higher enantioselectivity than in toluene (Table 1 entry 8). It should be noted that an electron-rich phosphite such as bis(*o*-methoxyphenyl) phosphite enhanced the enantioselectivity of the product (Table 1, entry 9). The reaction at lower temperature (−40°C) resulted in even more rigorous enantiofacial control (Table 1, entry 10). Importantly, decreasing the catalyst loading to 2 mol%, which represents the lowest catalyst loading employed in the asymmetric hydrophosphonylation of ketones, had little effect on enantioselectivity and yield (Table 1, entry 11). The reaction with quinine gave (*S*)-**2ba** with an opposite configuration compared with that obtained in the reaction with quinidine (Table 1, entry 12). Most enantioselective protonations are generally sensitive to moisture and water: however, the reaction observed in the presence of water also afforded the product **2ba** with high enantioselectivity (Table 1, entry 13).

With these optimized conditions, the reaction of a series of ketones and bis(*o*-methoxyphenyl) phosphite using quinine or quinidine was examined (Table 2). The reaction of α-ketoesters bearing electron-donating groups such as methyl or methoxy groups with quinine gave the corresponding products **2bb–be** in high yields (73–99%) and high enantioselectivities (83–90% *ee*), although α-ketoesters with sterically demanding groups such as an *o*-methyl gave product **2bc** in lower yield compared with the reaction of **1a** (Table 2, entries 2–5). The reaction of electron-deficient α-ketoesters bearing fluoro, chloro, or bromo groups in the *para* position of the benzene ring gave products **2bf–bh** with 88–89% *ee* (Table 2, entries 6–8). The α-ketoester with a 2-naphthyl group also gave the product **2bi** with 99% yield and 85% *ee*

Table 2: Enantioselective reaction with various ketones **1a–k** using quinine or quinidine.

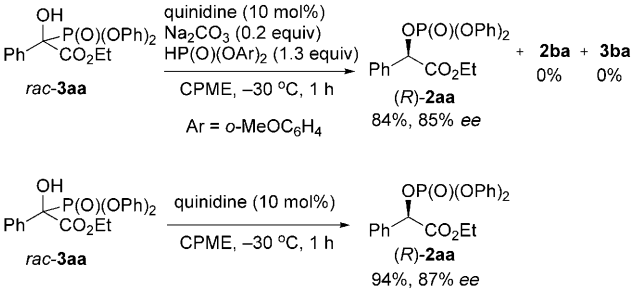


Entry	**1**: R	Cat.	*T* [°C]	*t* [h]	Yield [%]	*ee* [%][a]
1	**1a**: Ph	**A**	−40	72	92	91 (*S*)
2	**1b**: *p*-MeC_6H_4	**A**	−30	48	84	89 (*S*)
3[b]	**1c**: *o*-MeC_6H_4	**A**	−30 to 0	96	73	84 (*S*)
4	**1d**: *m*-MeC_6H_4	**A**	−30	48	99	90 (*S*)
5	**1e**: *p*-$MeOC_6H_4$	**A**	−30	60	83	83 (*S*)
6	**1f**: *p*-FC_6H_4	**A**	−30	24	99	89 (*S*)
7	**1g**: *p*-ClC_6H_4	**A**	−30	24	94	88 (*S*)
8	**1h**: *p*-BrC_6H_4	**A**	−30	18	98	88 (*S*)
9	**1i**: 2-naphthyl	**A**	−30	48	99	85 (*S*)
10	**1j**: $PhCH_2CH_2$	**A**	−30 to 0	48	97	79 (*S*)
11[b]	**1k**: cyclohexyl	**A**	−30 to 23	48	91	87 (*S*)
12	**1a**: Ph	**B**	−40	96	98	92 (*R*)
13	**1b**: *p*-MeC_6H_4	**B**	−30	48	90	91 (*R*)
14[b]	**1c**: *o*-MeC_6H_4	**B**	−30 to 0	96	79	87 (*R*)
15	**1d**: *m*-MeC_6H_4	**B**	−30	48	99	90 (*R*)
16	**1e**: *p*-$MeOC_6H_4$	**B**	−30	60	90	87 (*R*)
17	**1f**: *p*-FC_6H_4	**B**	−30	18	99	91 (*R*)
18	**1g**: *p*-ClC_6H_4	**B**	−30	24	92	90 (*R*)
19	**1h**: *p*-BrC_6H_4	**B**	−30	18	99	90 (*R*)
20	**1i**: 2-naphthyl	**B**	−30	48	99	88 (*R*)
21	**1j**: $PhCH_2CH_2$	**B**	−30 to 0	48	99	85 (*R*)
22[b]	**1k**: cyclohexyl	**B**	−30 to 0	72	92	90 (*R*)

[a] The absolute configuration of **2a** is given in parentheses. [b] Na_2CO_3 (1.0 equiv) was used.

(Table 2, entry 9). On the other hand, the reaction with quinidine instead of quinine gave the opposite enantiomer of products **2ba–bk** with high enantioselectivity (Table 2, entries 12–22).

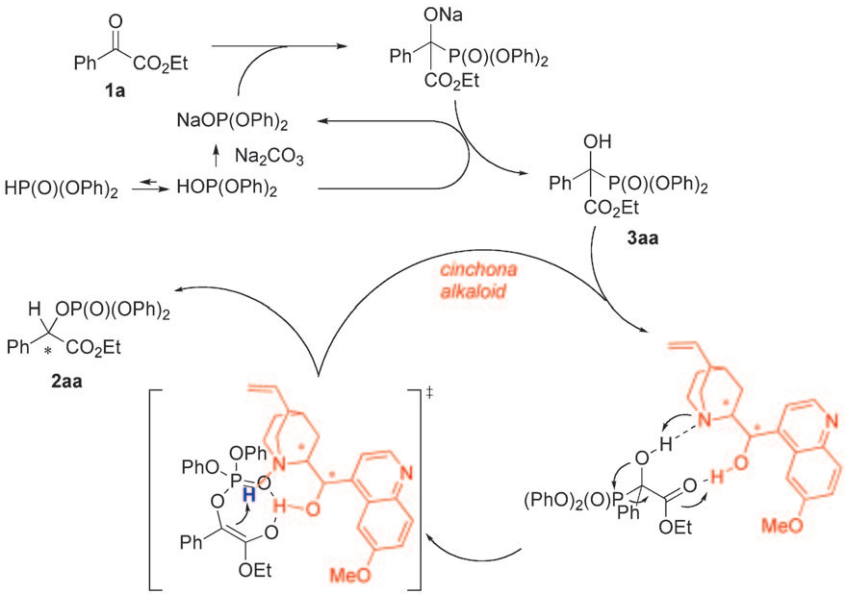
In order to clarify the reaction pathway of the enantioselective reaction, we tried some reactions using racemic α-hydroxy phosphonate *rac*-**3aa** (Scheme 3). The reaction of *rac*-**3aa** with bis(*o*-methoxyphenyl) phosphite in the presence of quinidine and Na_2CO_3 afforded the phospha-Brook rearrangement product **2aa** in high yield and with high enantioselectivity. In this reaction, product **2ba** or **3ba** from the cross-hydrophosphonylation with bis(*o*-methoxyphenyl)



Scheme 3. Control experiments for the phospha-Brook rearrangement from *rac*-**3aa**.

phosphite could not be observed, therefore, retro-hydrophosphonylation of *rac*-**3aa** could be ruled out. The enantioselectivity of the reaction of α-ketoesters with phosphite results from the enantioselective protonation of prochiral enolates in the kinetic process. On the other hand, the reaction of *rac*-**3aa** with only quinidine also promptly proceeded to give **2aa** with high enantioselectivity. This result implies that Na_2CO_3 activates only the addition of phosphites to **1a**.

The catalytic cycle for the addition of phosphite, the phospha-Brook rearrangement, and the enantioselective protonation is shown in Scheme 4. The most acidic compound in the reaction is diphenyl phosphite. Therefore, Na_2CO_3 reacts with diphenyl phosphite to give the sodium salt of phosphite, which reacts with **1a** to give the addition product



Scheme 4. Catalytic cycle for the addition of phosphites, the phospha-Brook rearrangement, and the enantioselective protonation.

3aa. The nitrogen atom of the cinchona alkaloids would activate the nucleophilicity of the hydroxy group in **3aa** to give α-phosphonyloxy enolates by phospha-Brook rearrangement. On the other hand, protection of the hydroxy group in quinidine did not give a good result (Table 1, entry 6). This result implies that the hydrogen bonding between the hydroxy groups of the cinchona alkaloids and α-phosphonyloxy enolates plays a key role in exerting enantioselectivity. Then, the generated α-phosphonyloxy enolates was protonated by the protonated cinchona alkaloids to give product **2aa** with high enantioselectivity together with the regeneration of cinchona alkaloids. Therefore, cinchona alkaloids also act as proton transfer reagents.

From the above consideration, Figure 1 shows a proposed transition state for the enantioselective protonation using quinidine.[10] The diphenylphosphonyl group in α-phosphonyloxy enolates is placed at the opposite position, thus avoiding the steric repulsion with the quinuclidine ring in

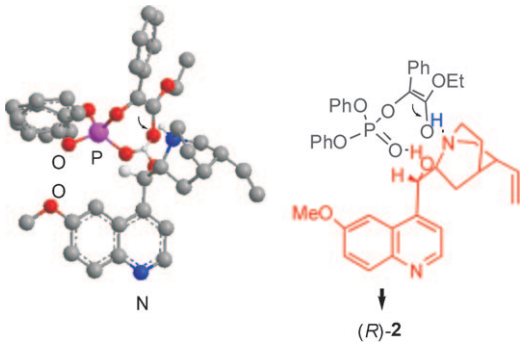
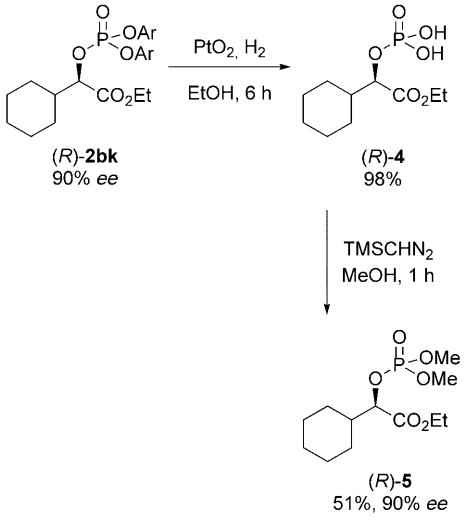


Figure 1. Suggested transition state for the protonation of α-phosphonyloxy enolate using quinidine and diphenyl phosphite.

quinidine. Through this transition state, the protonated quinuclidine ring approaches the *Si* face of the enolate.

We also examined the synthesis of an optically active phosphoric acid monoester from an α-phosphonyloxy ester. The *o*-methoxyphenyl group in **2bk** was removed through reductive cleavage with PtO_2 and hydrogen in EtOH to give the optically active phosphoric acid monoester **4** with 98% yield without loss of enantioselectivity (Scheme 5).[5a] The enantiopurity was determined by HPLC analysis after conversion into the methyl ester derivative **5**.

In conclusion, a novel system for enantioselective protonation reactions through a phospha-Brook rearrangement has been developed. This approach is the first example of catalytic enantioselective protonation of α-oxygenated ester enolates. More significantly, it gives direct access to both enantiomers of the optically



Scheme 5. Synthesis of the optically active phosphoric acid monoester **4**. TMS = trimethylsilyl.

active phosphoric esters having secondary alcohols with satisfactory yields and enantioselectivity using commercially available cinchona alkaloids. Furthermore, although most enolates used for enantioselective protonations are prepared from silyl enol ether or silyl ketene acetal, this is the first report of an enantioselective protonation of ester enolates prepared through the phospha-Brook rearrangement. This method is an attractive alternative for the catalytic in situ formation of enolates. Further studies to investigate the potential of these catalytic systems in other processes are under way.

Experimental Section

General procedure: Ethyl phenylglyoxylate **1a** (0.1 mmol) was added to a solution of quinidine (0.1 mmol), Na_2CO_3 (0.02 mmol), and bis(*o*-methoxyphenyl) phosphite (0.13 mmol) in CPME (2.0 mL) at −40 °C, and the solution was stirred for 72 h. After warming to room temperature, water was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel to give (*R*)-phosphate. (*S*)-Phosphate was obtained by using quinine instead of quinidine.

Received: December 2, 2010
Published online: January 31, 2011

Keywords: enantioselectivity · enolates · organocatalysis · phospha-Brook rearrangement · protonation

[1] For reviews on enantioselective protonation, see: a) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726 – 2748; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566 – 2587; b) A. Yanagisawa, K. Ishihara, H. Yamamoto, *Synlett* **1997**, 411 – 420; c) J. Eames, N. Weerasooriya, *Tetrahedron: Asymmetry* **2001**, *12*, 1 – 24; d) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653 – 3691; e) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359 – 369.

[2] K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, T. Imanishi, *J. Am. Chem. Soc.* **2003**, *125*, 8238 – 8243, and references therein.

[3] W.-H. Jung, S. Guyenne, C. Riesco-Fagundo, J. Mancuso, S. Nakamura, D. P. Curran, *Angew. Chem.* **2008**, *120*, 1146 – 1149; *Angew. Chem. Int. Ed.* **2008**, *47*, 1130 – 1133, and references therein.

[4] N. Oku, K. Takada, R. W. Fuller, J. A. Wilson, M. L. Peach, L. K. Pannell, J. B. McMahon, K. R. Gustafson, *J. Am. Chem. Soc.* **2010**, *132*, 10278 – 10285, and references therein.

[5] a) M. Graupner, R. H. White, *Biochemistry* **2001**, *40*, 10859 – 10872; b) A. Sakakura, M. Katsukawa, K. Ishihara, *Angew. Chem.* **2007**, *119*, 1445 – 1448; *Angew. Chem. Int. Ed.* **2007**, *46*, 1423 – 1426; c) T. Murai, T. Takenaka, S. Inaji, Y. Tonomura, *Chem. Lett.* **2008**, *37*, 1198 – 1199; d) H. Ohmiya, U. Yokobori, Y. Makida, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 2895 – 2897, and references therein.

[6] For racemic phospha-Brook rearrangement of ketones with phosphites, see: a) M. Kuroboshi, T. Ishihara, T. Ando, *J. Fluorine Chem.* **1988**, *39*, 293 – 298; b) L. El Kaïm, L. Gaultier, L. Grimaud, A. D. Santos, *Synlett* **2005**, 2335 – 2336, and references therein.

[7] For enantioselective hydrophosphonylation to ketones, see: a) F. Wang, X. Liu, X. Cui, Y. Xiong, X. Zhou, X. Feng, *Chem. Eur. J.* **2009**, *15*, 589 – 592; b) X. Zhou, Y. Liu, L. Chang, J. Zhao, D. Shang, X. Liu, L. Lin, X. Feng, *Adv. Synth. Catal.* **2009**, *351*, 2567 – 2572; c) D. Uraguchi, T. Ito, S. Nakamura, T. Ooi, *Chem. Sci.* **2010**, *1*, 488 – 490; d) X. Zhou, Q. Zhang, Y. Hui, W. Chen, J. Jiang, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, *12*, 4296 – 4299.

[8] For review on enantioselective hydrophosphonylation of aldehydes, see: a) H. Gröger, B. Hammer, *Chem. Eur. J.* **2000**, *6*, 943 – 948; b) P. Merino, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2008**, *350*, 1195 – 1208, and references therein.

[9] S. Nakamura, M. Hayashi, Y. Hiramatsu, N. Shibata, Y. Funahashi, T. Toru, *J. Am. Chem. Soc.* **2009**, *131*, 18240 – 18241. We also reported the enantioselective reaction of *N*-sulfonylimines with phosphite using cinchona alkaloids catalysts, see: S. Nakamura, H. Nakashima, A. Yamamura, N. Shibata, T. Toru, *Adv. Synth. Catal.* **2008**, *350*, 1209 – 1212.

[10] For catalytic enantioselective protonation using cinchona alkaloid derivatives, see: a) H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* **2000**, 2119 – 2133; b) T. Seitz, J. Baudoux, H. Bekolo, D. Cahard, J.-C. Plaquevent, M.-C. Lasne, J. Rouden, *Tetrahedron* **2006**, *62*, 6155 – 6165; c) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem.* **2007**, *119*, 7220 – 7223; *Angew. Chem. Int. Ed.* **2007**, *46*, 7090 – 7093; For catalytic enantioselective protonation using organocatalysts, see: d) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246 – 9247; e) D. Uraguchi, N. Kinoshita, T. Ooi, *J. Am. Chem. Soc.* **2010**, *132*, 12240 – 12242; f) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641.

