Organocatalysis

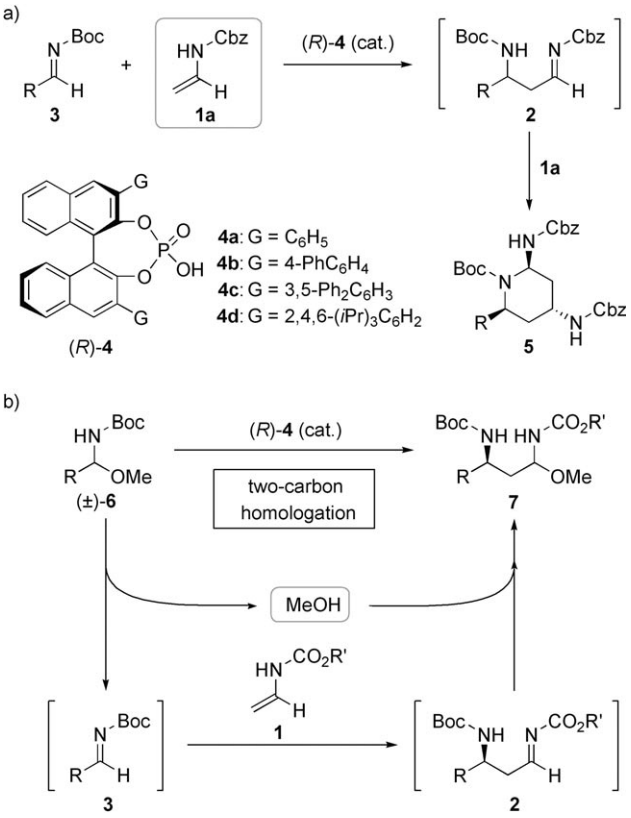
DOI: 10.1002/anie.200805385

Activation of Hemiaminal Ethers by Chiral Brønsted Acids for Facile Access to Enantioselective Two-Carbon Homologation Using Enecarbamates**

Masahiro Terada, Kyoko Machioka, and Keiichi Sorimachi*

The homologation of a carbon unit is an important and fundamental methodology used in the construction of carbon frameworks in synthetic organic chemistry. Much attention has been devoted to the development of two-carbon homologation using acetaldehyde anion equivalents, as these can be directly utilized in further transformations.[1] From a synthetic viewpoint, enecarbamates (**1**)(Scheme 1) are attractive as acetaldehyde anion equivalents for two-carbon homologation[2] because they are readily available and can provide aldimine products, which can be directly derivatized into nitrogen-containing compounds. However, the utilization of enecarbamates (**1**) in two-carbon homologation has rarely been exploited,[2,3] presumably because of the high reactivity of the aldimine products that leads to overreaction. Recently, by taking advantage of the formation of aldimine (**2**) as a reactive intermediate, our research group has developed a cascade reaction, which involves enecarbamate **1a** and imines **3** (Scheme 1a), and is catalyzed by a chiral Brønsted acid.[4] The chiral phosphoric acid (**4b**)[4–8] functions as an efficient stereoselective catalyst for the cascade transformation, which gives rise to piperidine derivatives (**5**) in high enantio- and diastereoselectivity.

In an effort to develop two-carbon homologation using enecarbamates (**1**), we attempted to suppress the formation of piperidine derivatives (**5**). However, all attempts at using imines (**3**) were unsuccessful; the intermediary aldimine (**2**) could not be detected at all despite thorough optimization of the reaction conditions. Even when an excess of the initial imine (**3**) was used, piperidine derivatives (**5**) were exclusively formed. The difficulties associated with the high reactivity of the intermediary aldimine (**2**) prompted us to explore alternative methods to establish an efficient two-carbon homologation protocol. We therefore turned our attention to the use of hemiaminal ethers (**6**), instead of imines (**3**), as the initial substrate (Scheme 1b). In a reaction of hemiaminal ether (**6**) under the influence of an acid catalyst, it might be anticipated that an intermediary aldimine (**2**) is entrapped by methanol,[8] which is generated during the course of imine (**3**) formation. Herein, we report the successful application of the proposed two-carbon homologation using chiral phosphoric acids (**4**) as an enantioselective catalyst. The method enables facile access to highly enantioenriched 1,3-diamine derivatives, which are pharmaceutically and biologically intriguing molecules.



Scheme 1. Enecarbamate (**1**) as a two-carbon homologating agent. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

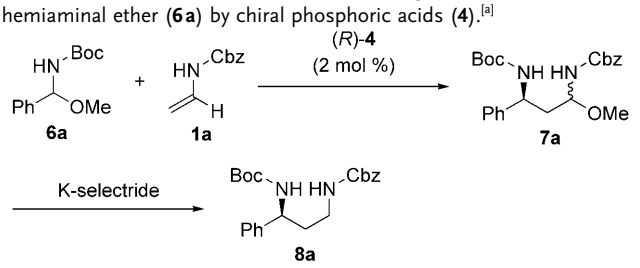
An initial experiment of the proposed homologation was conducted using an enecarbamate (**1a**) and a hemiaminal ether (**6a**) in the presence of the chiral phosphoric acid (*R*)-**4** (Table 1). Pleasingly, the homologation proceeded smoothly and the desired hemiaminal product (**7a**) was obtained in an acceptable yield, albeit as a diastereomeric mixture (Table 1, entry 1). The enantioselectivity at the C3 position of **7a** was determined after reduction of the newly formed hemiaminal

[*] Prof. Dr. M. Terada, K. Machioka, K. Sorimachi
Department of Chemistry
Graduate School of Scienece, Tohoku University
Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
Fax: (+81) 22-795-6602
E-mail: mterada@mail.tains.tohoku.ac.jp
Homepage: http://hanyu.chem.tohoku.ac.jp/~web/lab/index2.html

[**] This work was supported by JSPS with a Grant-in-Aid for Scientific Research (A; grant no. 20245021). We also thank the Japan Society for the Promotion of Sciences for a JSPS Research Fellowship for Young Scientists (K.S.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805385.

Table 1: Enantioselective two-carbon homologation via activation of hemiaminal ether (**6a**) by chiral phosphoric acids (**4**).[a]



Entry	4	Solvent	t [h]	Yield [%][b]	d.r. of 7a[c]	ee [%] of 8a[d]
1	4a	$CDCl_3$	0.5	65	74:26	73
2	4b	$CDCl_3$	0.5	41	68:32	86
3	4c	$CDCl_3$	0.5	87	43:57	89
4	4c	CH_2Cl_2	3	73	42:58	92
5	4c	toluene	3	72	45:55	92
6	4c	CH_3CN	3	83	45:55	89
7	4c	Et_2O	9	61	50:50	94
8	4c	iPr_2O	10	74	50:50	94

[a] All reactions were carried out using (*R*)-**4** (0.004 mmol, 2 mol%), **1a** (0.20 mmol), and **6a** (0.22 mmol, 1.1 equiv) in 2.0 mL of the indicated solvent at room temperature. [b] Combined yield of the diastereomeric mixture of **7**. [c] Relative configuration was not determined. [d] The *ee* value was determined by HPLC on a chiral stationary phase. The absolute configuration of **8a** was proved to have the *S* form; see the Supporting Information for details.

moiety by K-selectride, and the corresponding 1,3-diamine derivative (**8a**) was obtained in an optically active form. Evaluation of several chiral phosphoric acids (**4**) revealed that the 3,5-terphenyl-derived catalyst (**4c**) was optimal (Table 1, entry 3). Although various organic solvents were tolerated (Table 1, entries 4–8), ethereal solvents were found to be the best in terms of enantioselectivity. Diisopropyl ether was employed for the subsequent investigation owing to the higher chemical yield.

Next a series of aromatic hemiaminal ethers (**6b–f**) was investigated in the reaction of **1a** (Table 2). Good to high enantioselectivity was observed with these hemiaminal ethers. The reactivity of the hemiaminal ethers (**6**) was substantially

Table 2: Homologation of various aromatic hemiaminal ethers (**6b–f**) with enecarbamate (**1a**) catalyzed by (*R*)-**4c**.[a]

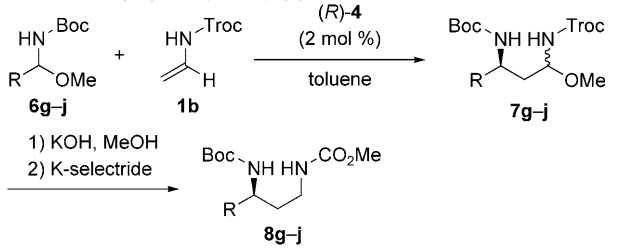
Entry	6 (R)	7	Yield [%][b]	d.r. of 7[c]	8	ee [%][d] of 8
1	6b (2-MeC_6H_4)	7b	74	33:67	8b	91
2	6c (4-MeC_6H_4)	7c	90	59:41	8c	90
3[e]	6d (4-$MeOC_6H_4$)	7d	99	53:47	8d	88
4	6e (4-BrC_6H_4)	7e	88	49:51	8e	95
5[f]	6f (4-NCC_6H_4)	7f	44	54:46	–	84[g]

[a] Unless otherwise noted all reactions were carried out using (*R*)-**4c** (0.004 mmol, 2 mol%), **1a** (0.20 mmol), and **6** (0.22 mmol, 1.1 equiv) in 2.0 mL of diisopropyl ether at room temperature for 10 h. [b] Combined yield of the diastereomeric mixture of **7**. [c] Relative configuration is not determined. [d] The *ee* value was determined by HPLC on a chiral stationary phase. [e] Reaction time was 3.5 h. [f] In toluene at 50°C for 3.5 h. [g] Averaged value was determined from a diastereomeric mixture of **7**.

depended on the electronic properties of the substituents on the aromatic ring. In general, hemiaminal ethers with electron-donating groups displayed higher reactivity, thus affording the desired products in high yield (Table 2, entries 2 and 3). The higher yield is likely to result from the electron-donating groups which promote the generation of imines (**3**).

We further applied the present homologation to aliphatic hemiaminal ethers (**6g–j**). However, the reaction of **6g** (R = Et) with **1a** afforded the desired hemiaminal product (**7**) in less than 30% yield, and was accompanied by a significant amount of by-products that included a trimer of **1a** (a piperidine derivative) [4]—which would be delivered via protonation of **1a** at the double bond to generate an imine which can undergo additional transformation (Scheme 1a)[6g,i] To prevent the protonation of the enecarbamate (**1**) by the acid catalyst (**4**), we introduced the more electron-withdrawing trichloroethoxycarbonyl (Troc) group to the enecarbamate (**1b**) (Table 3). As a result, the chemical yield was

Table 3: Homologation of aliphatic hemiaminal ether (**6g–j**) with enecarbamate (**1b**) catalyzed by (*R*)-**4**.[a]

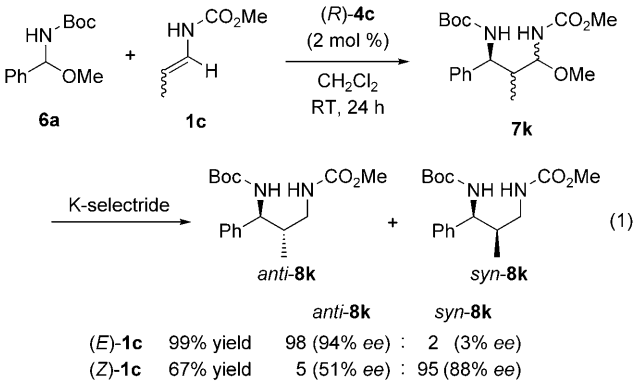


Entry	4	6 (R)	7	Yield [%][b]	d.r. of 7[c]	8	ee [%][d] of 8
1[e]	4c	6g (Et)	7g	62	46:54	8g	79
2[e]	4d	6g (Et)	7g	38	41:51	8g	91
3	4d	6g (Et)	7g	83	69:31	8g	96
4	4d	6h (Me)	7h	79	47:53	8h	86
5[f]	4d	6i (*i*Pr)	7i	56	50:50	8i	98
6	4d	6j (*i*Bu)	7j	84	46:54	8j	97

[a] Unless otherwise noted all reactions were carried out using (*R*)-**4** (0.004 mmol, 2 mol%), **1b** (0.20 mmol), and **6** (0.22 mmol, 1.1 equiv) in toluene (0.6 mL, 0.33 M) at room temperature for 10 h. [b] Combined yield of the diastereomeric mixture of **7**. [c] Relative configuration was not determined. [d] The *ee* value was determined by HPLC on a chiral stationary phase. The absolute configuration of **8a** was proved to have the *R* form; see the Supporting Information for details. [e] In toluene (2.0 mL, 0.10 M) of for 16 h. [f] Reaction time was 72 h.

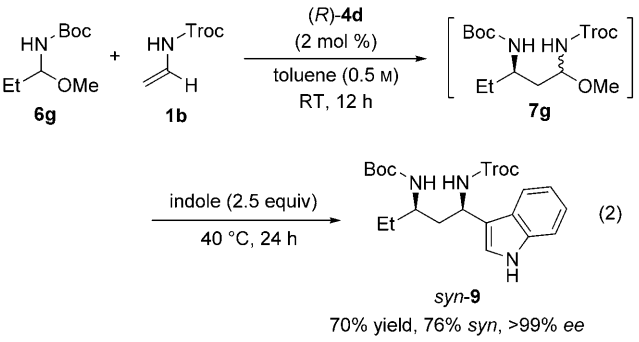
improved to an acceptable level using catalyst **4c** in toluene (Table 3, entry 1). Further screening of catalysts and reaction conditions led to the formation of the corresponding product (**7g**) in good yield along with high enantioselectivity under optimal reaction conditions in which the catalyst **4d** was used at high concentration (Table 3, entry 3). The present protocol is applicable to other aliphatic hemiaminal ethers (**6h–j**) while maintaining a high level of enantioselectivity; albeit with a slight decrease in enantioselectivity for the less bulky **6h** (R = Me; Table 3, entry 4).

The present homologation method can be applied to a substituted enecarbamate (**1c**) [Eq. (1)]. Either *anti*- or *syn*-



8k were obtained in a highly diastereoselective manner from the respective geometric isomers of **1c**, and each of the major diastereomers exhibited good to high enantioselectivity.

Finally, we attempted a sequential transformation involving a homologation/Friedel–Crafts reaction in one-pot [Eq. (2)]. The sequential process was carried out using **6g**



and **1b** in the presence of catalyst **4d**, followed by introduction of indole (into the same reaction flask) directly after completion of the homologation of **6g** with **1b**. The catalyst **4d** also accelerated the Friedel–Crafts reaction[6b,h] of **7g** with indole and afforded the desired product (**9**) in good yield in nearly optically pure form; albeit with moderate *syn* diastereoselectivity. The extremely high enantioselectivity observed for *syn*-**9** could be attributed to double asymmetric induction[9] arising from an ideal matching between the respective chiralities of the optically active hemiaminal product (**7g**) and the catalyst (*R*)-**4d**. The absolute configuration of the major isomer of **9** was determined to be 1*R*,3*R* (*syn*) by X-ray crystallographic analysis.[10]

In conclusion, we have developed an enantioselective two-carbon homologation method using enecarbamate derivatives as an acetaldehyde anion equivalent through the activation of hemiaminal ethers by a chiral phosphoric acid catalyst. The present method is applicable to not only aromatic hemiaminal ethers but also to aliphatic hemiaminal ethers to give the corresponding product in good to high enantioselectivity. The method provides practical access to enantioenriched 1,3-diamine derivatives, which are potentially useful synthetic intermediates of biologically interesting molecules. Further investigation of enecarbamate derivatives as two-carbon sources is in progress and aims to develop efficient enantioselective organic transformations.

Experimental Section

Chiral phosphoric acid ((*R*)-**4c**, 2 mol%, 3.2 mg, 0.004 mmol) and hemiaminal ether (**6a**, 52.2 mg, 0.22 mmol) were added to a dried test tube and the atmosphere was replaced by nitrogen. Once diisopropyl ether (2.0 mL) was added and (*R*)-**4c** and **6a** were dissolved, enecarbamate (**1a**, 35.4 mg, 0.20 mmol) was introduced at room temperature. The reaction mixture was stirred for 10 h before the reaction was quenched by the addition of saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4. After the solvents were evaporated, the crude material (**7a**) was used for further transformation without purification. The hemiaminal derivative (**7a**) was dissolved into toluene (2.0 mL), and K-selectride (1.0 M, 0.62 mL) was added to the solution at −78 °C. The reaction mixture was stirred until it reached 10 °C before the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4. After the solvents were evaporated, the crude material was purified by chromatography (eluent: *n*-hexane/AcOEt = 8:1–1:1) to give **8a** in 64% yield (over 2 steps) as a white solid. The *ee* value of **8a** was determined to be 94% by HPLC methods on a chiral stationary phase. **8a**: $R_f = 0.35$ (*n*-hexane/AcOEt = 2:1); HPLC on a chiral stationary phase using a Chiralpak IA column (*n*-hexane/*i*PrOH = 90:10, 1.0 mL min^{-1}, 254 nm, 10 °C) $t_R = 13.6$ min (minor), $t_R = 15.7$ min (major) (94% *ee*); optical rotation: $[\alpha]_D^{23} = -62.3$ g cm^{-3} ($c = 1.01$ g cm^{-3}, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.42$ (9H, s), 1.85–1.92 (1H, m), 2.01 (1H, brs), 3.09 (1H, brs), 3.45 (1H, brs), 4.74 (1H, brs), 4.83 (1H, brs), 5.06–5.12 (2H, m), 5.43 (1H, brs), 7.25–7.36 ppm (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 28.3$, 36.8, 37.9, 52.1, 66.6, 79.8, 126.3, 127.5, 128.0, 128.1, 128.5, 128.8, 136.6, 141.9, 155.7, 156.4 ppm; IR (neat; attenuated total reflection mode): 3329, 3032, 2976, 1687, 1518 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}NaN_2O_4$ ($[M+Na]^+$): 407.1941, found: 407.1942.

Received: November 4, 2008
Revised: February 4, 2008
Published online: March 5, 2009

Keywords: asymmetric catalysis · Brønsted acids · hemiaminal ethers · homologation · organocatalysis

[1] For recent selected examples, see: a) S. E. Denmark, T. Bui, *J. Org. Chem.* **2005**, *70*, 10190–10193; b) M. B. Boxer, H. Yamamoto, *Nat. Protoc.* **2006**, *1*, 2434–2438; c) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48–49; d) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 2762–2763; e) Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112–2114; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082–2084; f) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453–455; g) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800–4802; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722–4724; also see: h) S. E. Denmark, S. K. Ghosh, *Angew. Chem.* **2001**, *113*, 4895–4898; *Angew. Chem. Int. Ed.* **2001**, *40*, 4759–4762; i) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; j) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1755.

[2] a) C. Gaulon, P. Gizecki, R. Dhal, G. Dujardin, *Synlett* **2002**, 952–956; b) M. Prashad, Y. Lu, O. Repič, *J. Org. Chem.* **2004**, *69*, 584–586; c) R. Matsubara, N. Kawai, S. Kobayashi, *Angew.*

Chem. **2006**, *118*, 3898 – 3900; *Angew. Chem. Int. Ed.* **2006**, *45*, 3814 – 3816.

[3] For enantioselective aza-ene-type reactions catalyzed by chiral copper complexes, see: a) R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem.* **2004**, *116*, 1711 – 1713; *Angew. Chem. Int. Ed.* **2004**, *43*, 1679 – 1681; b) R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem.* **2004**, *116*, 3320 – 3322; *Angew. Chem. Int. Ed.* **2004**, *43*, 3258 – 3260; c) R. Matsubara, P. Vital, Y. Nakamura, H. Kiyohara, S. Kobayashi, *Tetrahedron* **2004**, *60*, 9769 – 9784.

[4] M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 10336 – 10337.

[5] For recent reviews on chiral Brønsted acid catalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744 – 5758; c) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516 – 532; d) M. Terada, *Chem. Commun.* **2008**, 4097 – 4112.

[6] a) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356 – 5357; b) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804 – 11805; c) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360 – 9361; d) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312 – 2315; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254 – 2257; e) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 133 – 136; f) I. D. Gridnev, M. Kouchi, K. Sorimachi, M. Terada, *Tetrahedron Lett.* **2007**, *48*, 497 – 500; g) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292 – 293; h) M. Terada, S. Yokoyama, K. Sorimachi, D. Uraguchi, *Adv. Synth. Catal.* **2007**, *349*, 1863 – 1867; i) M. Terada, H. Tanaka, K. Sorimachi, *Synlett* **2008**, 1661 – 1664; j) M. Terada, K. Soga, N. Momiyama, *Angew. Chem.* **2008**, *120*, 4190 – 4193; *Angew. Chem. Int. Ed.* **2008**, *47*, 4122 – 4125.

[7] For selected examples, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592 – 1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566 – 1568; b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590 – 7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424 – 7427; c) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696 – 15697; d) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84 – 86; e) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086 – 1087; f) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679 – 2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617 – 2619; g) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765 – 3768; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683 – 3686; h) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2006**, *118*, 4914 – 4916; *Angew. Chem. Int. Ed.* **2006**, *45*, 4796 – 4798; i) D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627; j) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070 – 13071; k) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802 – 14803; and see the Supporting Information for further references.

[8] For enantioselective synthesis of hemiaminal ethers, see: G. Li, F. R. Fronczek, J. C. Antilla, *J. Am. Chem. Soc.* **2008**, *130*, 12216 – 12217.

[9] S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1 – 31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1 – 30.

[10] CCDC 707496 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. See the Supporting Information for a full list of atomic coordinates, bond lengths, and bond angles.

