CHEMISTRY
A EUROPEAN JOURNAL

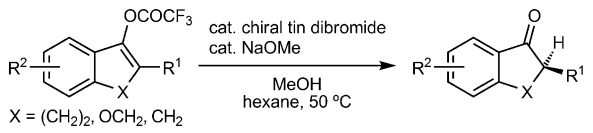
ChemPubSoc
Europe

DOI: 10.1002/chem.201302975

Enantioselective Protonation of Alkenyl Trifluoroacetates Catalyzed by Chiral Tin Methoxide

Akira Yanagisawa,* Takuya Sugita, and Kazuhiro Yoshida[a]

Carbonyl compounds possessing a tertiary carbon atom at their α-position are often encountered in natural products or biologically active molecules. One of the promising ways to acquire such compounds in an enantioselective fashion is the asymmetric protonation of enolates, enols, enol ethers, or enol esters.[1–4] For the transformation, various chiral catalysts, including chiral Brønsted acid catalysts and chiral Lewis acid catalysts, are available. In contrast, examples of transformations employing chiral base catalysts are few. We have previously reported a method for preparing chiral tin methoxide catalysts, which uses sodium methoxide and the corresponding chiral tin dibromides bearing a 3,3′-substituted binaphthyl moiety.[5a] The in situ generated chiral tin methoxides are efficiently transformed into chiral tin enolates in the reaction with alkenyl trichloroacetates. The thus-obtained chiral tin enolates show adequate nucleophilicity toward various electrophiles and undergo asymmetric transformations, including the aldol reaction,[5] the Mannich-type reaction,[6] 1,3-dipolar cycloaddition,[7] γ-lactone synthesis,[8] and the *N*-nitroso aldol reaction.[9] We envisioned that if a prochiral alkenyl ester derived from a ketone containing a tertiary carbon atom at the α-position were used as the substrate for the chiral tin catalysis in the presence of an alcohol, the asymmetric protonation of an in situ generated chiral tin enolate would be possible. We report herein, the enantioselective protonation of cyclic alkenyl trifluoroacetates with methanol by using chiral tin dibromide and sodium methoxide as precatalysts (Scheme 1).

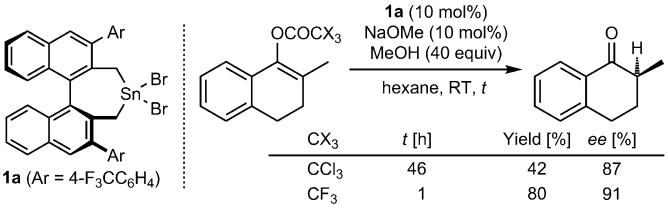


Scheme 1. Enantioselective protonation of cyclic alkenyl trifluoroacetates catalyzed by in situ generated chiral tin methoxide.

[a] Prof. Dr. A. Yanagisawa, T. Sugita, Prof.Dr. K. Yoshida
Department of Chemistry, Graduate School of Science
Chiba University, Inage, Chiba 263-8522 (Japan)
Fax: (+81) 43-290-2789
E-mail: ayanagi@faculty.chiba-u.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302975.

We initially adopted a 2-methyl-1-tetralone-derived alkenyl trichloroacetate as the substrate for the protonation and optimized the reaction conditions. As a result, when the alkenyl trichloroacetate was treated with chiral tin dibromide **1a** (10 mol%) and NaOMe (10 mol%) in the presence of MeOH (40 equiv) in hexane at room temperature for 46 h, (*S*)-enriched 2-methyl-1-tetralone with 87% enantiomeric excess (*ee*) was obtained in 42% yield (Scheme 2). We then



CX_3	*t* [h]	Yield [%]	*ee* [%]
CCl_3	46	42	87
CF_3	1	80	91

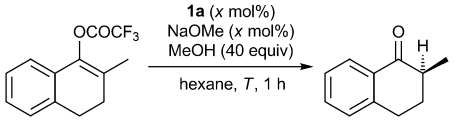
Scheme 2. Optimization of alkenyl esters.

examined the ability of alkenyl trifluoroacetates to generate chiral tin enolates. Alkenyl esters have been shown to be superior substrates for the enantioselective protonation employing a cinchona alkaloid as the chiral catalyst.[3r,10] We attempted the asymmetric protonation of a 2-methyl-1-tetralone-derived alkenyl trifluoroacetate and, as a consequence, obtained the targeted ketone in a satisfactory yield with improved enantiomeric excess in the reaction for 1 h (Scheme 2).

Accordingly, we optimized the reaction conditions by using the alkenyl trifluoroacetate. The results are summarized in Table 1. Reducing the amounts of the pre-catalysts to 2 mol% did not cause a significant deceleration of the reaction (compare entries 2 and 1, Table 1). To obtain a product with a higher enantiomeric ratio, we elevated the reaction temperature. The reaction at 50 °C increased the enantioselectivity to 93% *ee* (entry 5).

We further examined the effects of substituents at 3,3′-positions of chiral tin precatalyst **1**. When Ph-substituted chiral tin dibromide **1c** was used, the protonation proceeded and both yield and enantiomeric excess were higher than those obtained by using chiral tin dibromide **1a**, which has 4-$F_3CC_6H_4$ groups at its 3,3′-positions (Table 2, compare entries 3 and 1). Because the employment of 3,3′-unsubstituted chiral tin precatalyst **1e** (Ar=H) resulted in a low enantiomeric excess (entry 4), bulky substituents at the 3,3′-posi-

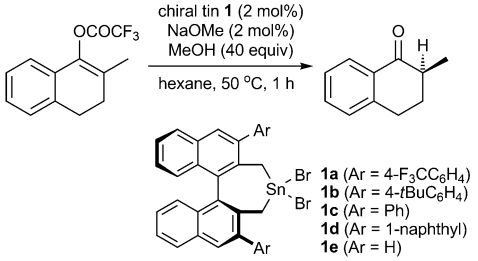
Table 1. Optimization of reaction conditions.[a]



Entry	x [mol%]	T [°C]	Yield [%][b]	*ee* [%][c]
1	10	RT	80	91
2	2	RT	77	91
3	2	30	87	90
4	2	40	82	92
5	2	50	82	93

[a] Unless otherwise specified, the reaction was carried out by using chiral tin dibromide **1a** (x mol%), sodium methoxide (x mol%), alkenyl trifluoroacetate (1 equiv), and methanol (40 equiv) in hexane. [b] Isolated yield. [c] Determined by HPLC analysis.

Table 2. Asymmetric protonation by using various chiral tin catalysts.[a]



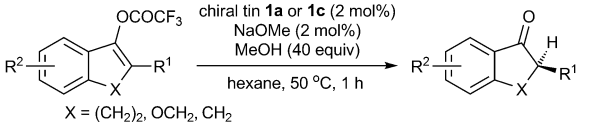
Entry	Chiral tin	Yield [%][b]	*ee* [%][c]
1	**1a**	82	93
2	**1b**	>99	88
3	**1c**	94	94
4	**1d**	80	92
5	**1e**	98	65

[a] Unless otherwise specified, the reaction was carried out by using chiral tin dibromide **1** (2 mol%), sodium methoxide (2 mol%), alkenyl trifluoroacetate (1 equiv), and methanol (40 equiv) in hexane at 50°C for 1 h. [b] Isolated yield. [c] Determined by HPLC analysis.

tions were found to be effective in attaining a high level of asymmetric induction in the protonation.

With the optimal reaction conditions in hand, we studied the catalytic enantioselective protonation of numerous alkenyl trifluoroacetates. The results obtained with 2-methyl-1-tetralone and related cyclic ketone derivatives are shown in Table 3. Both the 2-ethyl and the 2-allyl derivatives provided high optical purities identical with that of 2-methyl-1-tetralone (entries 1–3, Table 3). In contrast, the reaction of the 2-benzyl derivative led to an unsatisfactory chemical yield and enantiomeric excess, probably due to the steric bulkiness of the substituent. However, use of more Lewis acidic chiral tin precatalyst **1a** in place of **1c** with the same alkenyl trifluoroacetate gave an isolated yield and an enantiomeric excess of more than 90% (entries 4 and 5). The existence of an electron-donating group on the aromatic ring did not have a significant influence on the reactivity of the substrates (entries 6–8). Alkenyl trifluoroacetates of 2-alkyl-1-indanones were also preferable substrates for the present asymmetric protonation; they exhibited sufficient reactivity

Table 3. Asymmetric protonation of various alkenyl trifluoroacetates.[a]



Entry	X	R^1	R^2	Chiral tin	Yield [%][b]	*ee* [%][c]
1	$(CH_2)_2$	Me	H	**1c**	94	94
2	$(CH_2)_2$	Et	H	**1c**	86	94
3	$(CH_2)_2$	Allyl	H	**1c**	92	94
4	$(CH_2)_2$	Bn	H	**1c**	43	69
5	$(CH_2)_2$	Bn	H	**1a**	91	92
6	$(CH_2)_2$	Me	6-MeO	**1c**	88	93
7	$(CH_2)_2$	Me	6-MeO	**1a**	90	83
8[d]	$(CH_2)_2$	Me	7-MeO	**1c**	97	93
9	CH_2	Me	H	**1c**	82	80
10	CH_2	Me	H	**1a**	92	70
11	CH_2	Et	H	**1c**	71	79
12	CH_2	Et	H	**1a**	85	85
13[e]	CH_2	nC_8H_{17}	H	**1c**	93	63
14[e]	CH_2	nC_8H_{17}	H	**1a**	>99	64
15[f]	OCH_2	Me	H	**1c**	83	81
16[f]	OCH_2	Bn	H	**1c**	94	69

[a] Unless otherwise specified, the reaction was carried out by using chiral tin dibromide **1a** or **1c** (2 mol%), sodium methoxide (2 mol%), alkenyl trifluoroacetate (1 equiv), and methanol (40 equiv) in hexane at 50°C for 1 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was performed for 2 h. [e] The reaction was performed at 60°C. [f] The reaction was performed for 3 h.

toward a chiral tin methoxide under conventional reaction conditions, although their asymmetric induction was moderate (entries 9–14). In general, chiral tin dibromide **1a** was a more suitable precatalyst than **1c** for the substrates to acquire high chemical yields (compare entries 10, 12, and 14 with entries 9, 11, and 13). 4-Chromanone derivatives could be also applied to this asymmetric protonation and in fact, nonracemic 3-alkyl-4-chromanones were efficiently obtained by this method (entries 15 and 16).

To derive useful information about the structure of an in situ generated chiral tin bromide methoxide in solution, we investigated the nonlinear effect of the asymmetric protonation. We prepared chiral tin dibromide **1c** containing various optical purities (100, 80, 50, 20, and 0% *ee*) and carried out the reaction of 6-methoxy-2-methyl-1-tetralone-derived alkenyl trifluoroacetate by using **1c** of diverse enantiomeric excesses in hexane at 50°C for 1 h. As a result, a positive nonlinear effect between the enantiomeric excess of **1c** and that of the product was clearly observed (Figure 1). In particular, in the case of the catalyst possessing 20% *ee*, a 2.5-fold amplification of the enantiomeric excess was observed.

Judging from the above-mentioned results on the nonlinear effect, chiral tin bromide methoxide catalysts are considered to exist in equilibrium among homochiral dimers ((*S*,*S*)- and (*R*,*R*)-dimer), monomers ((*S*)- and (*R*)-monomer), and a heterochiral dimer ((*S*,*R*)-dimer). An example of a chiral tin bromide methoxide derived from **1c** (Ar = Ph) is shown in Figure 2. To realize the positive nonlinear relationship between the enantiomeric excess of **1c** and that of the product, the (*S*)- and (*R*)-monomer should be the

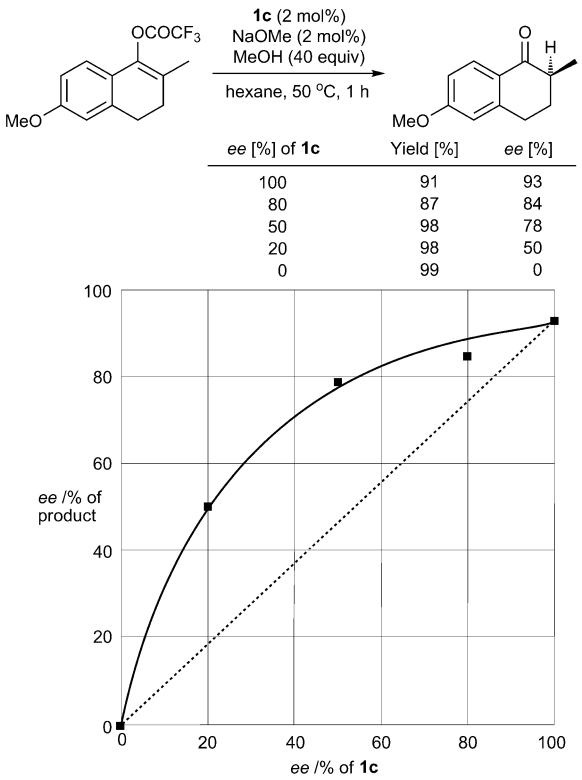


Figure 1. Positive nonlinear effect of the asymmetric protonation.

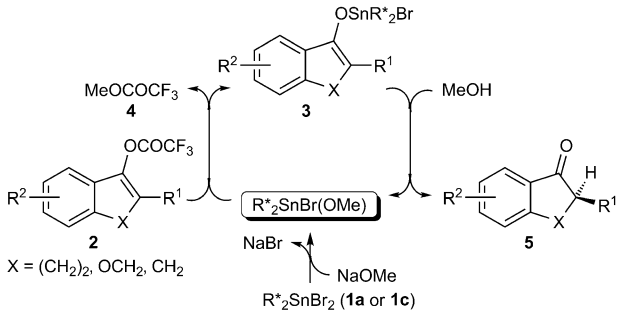


Figure 3. Plausible catalytic cycle for the asymmetric protonation.

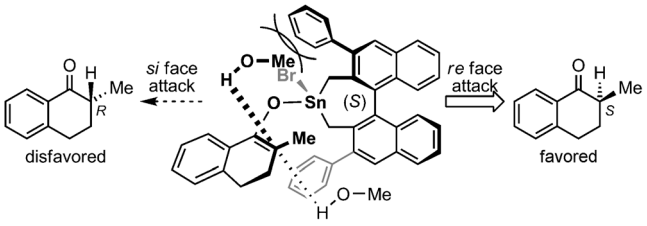


Figure 4. A hypothesis for enantioface discrimination between a chiral tin enolate and methanol.

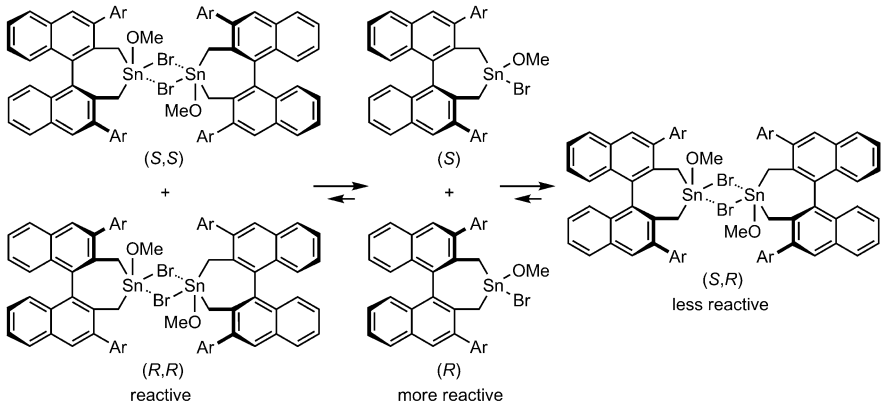


Figure 2. Equilibrium among homochiral dimers, monomers, and a heterochiral dimer (Ar = Ph).

most reactive and the (*S*,*R*)-dimer should be the least reactive in the equilibration.

A catalytic cycle is postulated for the asymmetric protonation (Figure 3). First, chiral tin dibromide **1a** or **1c** reacts with an equimolar amount of sodium methoxide to afford the corresponding chiral tin bromide methoxide, which is the real catalyst in the present transformation. Subsequently, the generated chiral tin bromide methoxide attacks alkenyl trifluoroacetate **2** to form chiral tin enolate **3** and methyl trifluoroacetate (**4**). The following protonation with methanol gives optically active ketone **5** with regeneration of the chiral tin bromide methoxide. The rate of methanolysis of tin enolate **3** plays an important role in the catalytic cycle.

A hypothesis for the enantioface discrimination between a chiral tin enolate and methanol in the present enantioselective protonation catalyzed by a chiral tin bromide methoxide is shown in Figure 4. Methanol approaches the α-carbon atom of a chiral tin enolate to escape from steric hindrance caused by phenyl groups at the 3,3′-positions of the binaphthyl framework. Consequently, protonation occurs selectively at the *Re* face of the tin enolate to furnish the (*S*)-ketone.

In conclusion, we have developed a novel catalytic asymmetric protonation. The employment of in situ generated chiral tin bromide methoxide as the chiral catalyst and MeOH as the proton source allows the synthesis of various optically active ketones containing a tertiary stereogenic center at the α-position, with an enantioselectivity of up to 94% *ee*. Further studies of the application of the catalytic asymmetric protonation to other substrates are underway.

Experimental Section

General experimental procedure for catalytic asymmetric protonation of alkenyl trifluoroacetates (Tables 2 and 3): NaOMe (1 M) in MeOH (10 μL, 0.01 mmol) and MeOH (0.8 mL) were added to a suspension of

chiral tin dibromide **1** (0.01 mmol) in hexane (3 mL) under an argon atmosphere, and then the resulting mixture was stirred at room temperature for 30 min. Subsequently, alkenyl trifluoroacetate (0.5 mmol) was added to the mixture at this temperature. After the mixture had been stirred for 1 h at 50 °C, the reaction mixture was treated with brine (2 mL) and solid KF (ca. 1 g) at ambient temperature for 3 min. The resulting precipitate was filtered off and the filtrate was extracted with ether (15 mL) three times. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give the corresponding ketone. The enantioselectivity was determined by HPLC analysis by using a chiral column.

Acknowledgements

We gratefully acknowledge the financial support from the Iodine Research Project in Chiba University led by Prof. H. Togo and the COE Start-up Program in Chiba University led by Prof. Takayoshi Arai.

Keywords: alkenyl esters · asymmetric catalysis · ketones · protonation · tin

[1] Reviews: a) S. Hünig in *Houben-Weyl: Methods of Organic Chemistry, Vol. E 21* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Georg Thieme Verlag, Stuttgart, **1995**, p. 3851; b) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566; c) A. Yanagisawa, H. Yamamoto in *Comprehensive Asymmetric Catalysis III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, p. 1295; d) J. Eames, N. Weerasooriya, *Tetrahedron: Asymmetry* **2001**, *12*, 1; e) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; f) A. Yanagisawa in *Comprehensive Asymmetric Catalysis, Supplement 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **2004**, p. 125; g) L. Duhamel, P. Duhamel, J.-C. Plaquevent, *Tetrahedron: Asymmetry* **2004**, *15*, 3653; h) J. T. Mohr, A. Y. Hong, B. M. Stoltz, *Nat. Chem.* **2009**, *1*, 359; i) A. Claraz, S. Oudeyer, V. Levacher, *Curr. Org. Chem.* **2012**, *16*, 2192.

[2] For notable examples of enantioselective protonation using a stoichiometic amount of chiral proton source: a) K. Ishihara, D. Nakashima, Y. Hiraiwa, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 24; b) G. Asensio, A. Cuenca, N. Rodriguez, M. Medio-Simón, *Tetrahedron: Asymmetry* **2003**, *14*, 3851; c) D. R. Carbery, T. J. Donohoe, *Chem. Commun.* **2004**, 722; d) B. M. Kim, H. Kim, W. Kim, K. Y. Im, J. K. Park, *J. Org. Chem.* **2004**, *69*, 5104; e) T. J. Donohoe, G. C. Freestone, C. E. Headley, C. L. Rigby, R. P. C. Cousins, G. Bhalay, *Org. Lett.* **2004**, *6*, 3055; f) E. Boyd, G. S. Coumbarides, J. Eames, A. Hay, R. V. H. Jones, R. A. Stenson, M. J. Suggate, *Tetrahedron Lett.* **2004**, *45*, 9465; g) G. S. Coumbarides, J. Eames, S. Ghilagaber, M. J. Suggate, *Tetrahedron Lett.* **2004**, *45*, 9469; h) G. S. Coumbarides, J. Eames, J. E. W. Scheuermann, K. F. Sibbons, M. J. Suggate, M. Watkinson, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 906; i) D. Nakashima, H. Yamamoto, *Synlett* **2006**, 150; j) J. Martin, J.-C. Plaquevent, J. Maddaluno, J. Rouden, M.-C. Lasne, *Eur. J. Org. Chem.* **2009**, 5414.

[3] For notable examples of enantioselective protonation using a catalytic amount of a chiral proton source: a) G. Liang, D. Trauner, *J. Am. Chem. Soc.* **2004**, *126*, 9544; b) A. Yanagisawa, T. Touge, T. Arai, *Angew. Chem.* **2005**, *117*, 1570; *Angew. Chem. Int. Ed.* **2005**, *44*, 1546; c) S. L. Wiskur, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 6176; d) C. Schaefer, G. C. Fu, *Angew. Chem.* **2005**, *117*, 4682; *Angew. Chem. Int. Ed.* **2005**, *44*, 4606; e) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406; f) K. Mitsuhashi, R. Ito, T. Arai, A. Yanagisawa, *Org. Lett.* **2006**, *8*, 1721; g) T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer, V. Levacher, *Angew. Chem.* **2007**, *119*, 7220; *Angew. Chem. Int. Ed.* **2007**, *46*, 7090; h) P. Kukula, V. Matoušek, T. Mallat, A. Baiker, *Chem. Eur. J.* **2008**, *14*, 2699; i) C. Fehr, H. Randall, *Chem. Biodiversity* **2008**, *5*, 942; j) C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246; k) T. Poisson, S. Oudeyer, V. Dalla, F. Marsais, V. Levacher, *Synlett* **2008**, 2447; l) M. Morita, L. Drouin, R. Motoki, Y. Kimura, I. Fujimori, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3858; m) D. Uraguchi, N. Kinoshita, T. Ooi, *J. Am. Chem. Soc.* **2010**, *132*, 12240; n) C. H. Cheon, T. Imahori, H. Yamamoto, *Synlett* **2010**, 6980; o) T. Poisson, V. Gembus, V. Dalla, S. Oudeyer, V. Levacher, *J. Org. Chem.* **2010**, *75*, 7704; p) M. Hayashi, S. Nakamura, *Angew. Chem.* **2011**, *123*, 2297; *Angew. Chem. Int. Ed.* **2011**, *50*, 2249; q) C. H. Cheon, O. Kanno, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 13248; r) A. Claraz, J. Leroy, S. Oudeyer, V. Levacher, *J. Org. Chem.* **2011**, *76*, 6457; s) E. M. Beck, A. M. Hyde, E. N. Jacobsen, *Org. Lett.* **2011**, *13*, 4260; t) J.-W. Lee, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 18245; u) E. Yamamoto, D. Gokuden, A. Nagai, T. Kamachi, K. Yoshizawa, A. Hamasaki, T. Ishida, M. Tokunaga, *Org. Lett.* **2012**, *14*, 6178; v) J. Guin, G. Varseev, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 2100.

[4] For notable examples of tandem 1,4-addition/enantioselective protonation by using a catalytic amount of a chiral proton source: a) Y. Ohtsuka, T. Ikeno, T. Yamada, *Tetrahedron: Asymmetry* **2003**, *14*, 967; b) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; c) Y. Hamashima, H. Somei, Y. Shimura, T. Tamura, M. Sodeoka, *Org. Lett.* **2004**, *6*, 1861; d) R. J. Moss, K. J. Wadsworth, C. J. Chapman, C. G. Frost, *Chem. Commun.* **2004**, 1984; e) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571; f) C. G. Frost, S. D. Penrose, K. Lambshead, P. R. Raithby, J. E. Warren, R. Cleave, *Org. Lett.* **2007**, *9*, 2119; g) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159; h) D. Leow, S. Lin, S. K. Chittimalla, X. Fu, C.-H. Tan, *Angew. Chem.* **2008**, *120*, 5723; *Angew. Chem. Int. Ed.* **2008**, *47*, 5641; i) M. P. Sibi, J. Coulomb, L. M. Stanley, *Angew. Chem.* **2008**, *120*, 10061; *Angew. Chem. Int. Ed.* **2008**, *47*, 9913; j) Y. Hamashima, T. Tamura, S. Suzuki, M. Sodeoka, *Synlett* **2009**, 1631; k) S. Lin, D. Leow, K.-W. Huang, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 1741; l) T. Yajima, T. Tonoi, H. Nagano, Y. Tomita, K. Mikami, *Eur. J. Org. Chem.* **2010**, 2461; m) T. Poisson, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7890; n) Y. Hamashima, S. Suzuki, T. Tamura, H. Somei, M. Sodeoka, *Chem. Asian J.* **2011**, *6*, 658; o) N. Fu, L. Zhang, J. Li, S. Luo, J.-P. Cheng, *Angew. Chem.* **2011**, *123*, 11653; *Angew. Chem. Int. Ed.* **2011**, *50*, 11451; p) L. Dai, H. Yang, J. Niu, F.-E. Chen, *Synlett* **2012**, *23*, 314; q) M. E. Kieffer, L. M. Repka, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 5131; r) N. K. Rana, V. K. Singh, *Org. Lett.* **2011**, *13*, 6520; s) K. L. Kimmel, J. D. Weaver, M. Lee, J. A. Ellman, *J. Am. Chem. Soc.* **2012**, *134*, 9058; t) T. Kitanosono, M. Sakai, M. Ueno, S. Kobayashi, *Org. Biomol. Chem.* **2012**, *10*, 7134; u) R. A. Unhale, N. K. Rana, V. K. Singh, *Tetrahedron Lett.* **2013**, *54*, 1911.

[5] a) A. Yanagisawa, T. Satou, A. Izumiseki, Y. Tanaka, M. Miyagi, T. Arai, K. Yoshida, *Chem. Eur. J.* **2009**, *15*, 11450; b) A. Yanagisawa, N. Kushihara, T. Sugita, K. Yoshida, *Synlett* **2012**, *23*, 1783–1788.

[6] A. Izumiseki, K. Yoshida, A. Yanagisawa, *Org. Lett.* **2009**, *11*, 5310.

[7] A. Yanagisawa, A. Izumiseki, T. Sugita, N. Kushihara, K. Yoshida, *Synlett* **2012**, *23*, 107.

[8] A. Yanagisawa, N. Kushihara, K. Yoshida, *Org. Lett.* **2011**, *13*, 1576.

[9] A. Yanagisawa, T. Fujinami, Y. Oyokawa, T. Sugita, K. Yoshida, *Org. Lett.* **2012**, *14*, 2434.

[10] J. Gil, M. Medio-Simon, G. Mancha, G. Asensio, *Eur. J. Org. Chem.* **2005**, 1561.

Received: July 29, 2013
Published online: October 31, 2013

