Enantioselective Protonation of Silyl Enol Ethers and Ketene Disilyl Acetals with Lewis Acid-Assisted Chiral Brønsted Acids: Reaction Scope and Mechanistic Insights

Shingo Nakamura,† Masanobu Kaneeda,† Kazuaki Ishihara,‡ and Hisashi Yamamoto*,†

Contribution from the Graduate School of Engineering, CREST, Japan Science and Technology Corporation (JST), and Research Center for Advanced Waste and Emission Management (ResCWE), Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

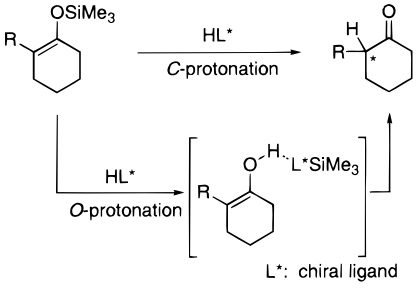
Received April 3, 2000

Abstract: Enantioselective protonation is a potent and efficient way to construct chiral carbons. Here we report details of the reaction using Lewis acid-assisted chiral Brønsted acids (chiral LBAs). The 1:1 coordinate complex of tin tetrachloride and optically active binaphthol ((*R*)- or (*S*)-BINOL) can directly protonate various silyl enol ethers and ketene disilyl acetals to give the corresponding α-aryl ketones and α-arylcarboxylic acids, respectively, with high enantiomeric excesses (up to 98% ee). A catalytic version of enantioselective protonation has also been achieved using stoichiometric amounts of 2,6-dimethylphenol and catalytic amounts of monomethyl ether of optically active BINOL in the presence of tin tetrachloride. This protonation is also effective for producing α-halocarbonyl compounds (up to 91% ee). DFT calculations on the B3LYP/LANL2DZ level show that the conformational structure of the chiral LBA and the orientation of activated proton on (*R*)-BINOLs are important for understanding the absolute stereochemistry of the products.

Introduction

Enantioselective protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds.[1−6] The protonation of metal enolates by chiral proton sources[2] and the hydrolysis of enol esters catalyzed by enzymes[3] or antibodies[4] have been reported. Most of these reactions proceed via enolate anions/enols under basic or neutral conditions. The acid-promoted hydrolysis of enol ethers is an interesting alternative whose enantioselectivity has been little investigated.[5,6] Silyl enol ethers, which are synthetic equivalents of enols or enolates, are more stable than the corresponding metal enolates, and can be isolated. If the protonolysis of silyl enol ethers favors *C*-protonation or initial *O*-protonation with subsequent transfer of the proton under the influence of the ligand, it should be possible to develop an enantioselective protonation of achiral silyl enol ethers using chiral proton donors (Scheme 1).[5,7]

Scheme 1



In general, it is difficult to control the enantioselectivity in the protonation of silyl enol ethers with simple chiral Brønsted

* To whom correspondence should be addressed.

† The Graduate School of Engineering.

‡ ResCWE.

(1) Recent reviews: (a) Hünig, S. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21, p 3851. (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (c) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411.

(2) Recent reports: (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175 and references therein. (b) Yanagisawa, A.; Kuribayashi, T.; Kikuchi, T.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 107. (c) Fuji, K.; Kawabata, T.; Kuroda, A. *J. Org. Chem.* **1995**, *60*, 1914 and references therein. (d) Vedejs, E.; Lee, N. J. *Am. Chem. Soc.* **1995**, *117*, 891. (e) Takahashi, T.; Nakao, N.; Koizumi, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3293 and references therein. (f) Martin, J.; Lansne, M.-C.; Plaquevent, J.-C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *38*, 7181. (g) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857 and references therein. (h) Yanagisawa, A.; Inanami, H.; Yamamoto, H. *Chem. Commun.* **1998**, 1573. (i) Yanagisawa, A.; Kikuchi, T.; Yamamoto, H. *Synlett* **1998**, 174. (j) Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253. (k) Part. L.; Mojovic, L.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2509. (l) Asensio, G.; Cuenca, A.; Gavina, P.; Medio-Simon, M. *Tetrahedron Lett.* **1999**, *40*, 3939 and references therein. (m) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamada, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595 and references therein.

(3) (a) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614. (b) Kume, Y.; Ohta, H. *Tetrahedron Lett.* **1992**, *33*, 6367. (c) Katoh, O.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1935.

(4) Fuji, I.; Lerner, R. A.; Janda, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 8528.

(5) For enantioselective protonation of ketene silyl acetals, see: (a) Cavelier, F.; Gomez, R.; Jacquier, R.; Verducci, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2501. (b) Cavelier, F.; Gomez, S.; Jacquier, R.; Verducci, J. *Tetrahedron Lett.* **1994**, *35*, 2891.

(6) For enantioselective protonation of enol ethers by catalytic antibodies, see: (a) Reymond, J.-L.; Reber, J.-L.; Lerner, R. A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 475. (b) Jahangiri, G. K.; Reymond, J.-L. *J. Am. Chem. Soc.* **1994**, *116*, 11264. (c) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 3653 and references therein.

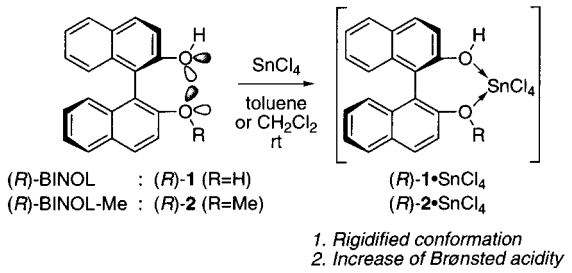
(7) A study of protonolysis of silyl enol ethers carried out by Novice et al. indicated *C*-protonation in the case of *tert*-butyl dimethylsilyl enol ethers, while no conclusion was arrived at for trimethyl silyl enol ethers: Novice, M. H.; Seikaly, H. R.; Seiz, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 5835.

10.1021/ja001164i CCC: $19.00 © 2000 American Chemical Society
Published on Web 08/10/2000

acids. The main reasons are the bonding flexibility between the proton and its chiral counterion, the orientational flexibility of the proton, and the fact that the available proton sources are limited to acidic compounds such as chiral carboxylic acids and sulfonic acids. We speculated that the coordination of Lewis acids with Brønsted acids would restrict the orientation of protons and raise the acidity, and if there is some attractive interaction between the reagents and silyl enol ethers, asymmetric induction from chiral Brønsted acids to these ethers could occur through protonation.

Thus, we developed a 1:1 complex of optically active (*R*)-binaphthol ((*R*)-BINOL or (*R*)-**1**)·$SnCl_4$ that was a highly effective chiral proton donor for enantioselective protonation of prochiral silyl enol ethers and ketene bis(trialkylsilyl) acetals (Scheme 2).[8] The protons in (*R*)-**1** are activated by the

Scheme 2. Chiral LBAs Prepared from (*R*)-BINOL Derivatives and $SnCl_4$



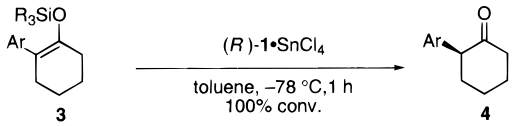
coordination of tin tetrachloride, while the orientation is restricted by that. *The Lewis acid-assisted chiral Brønsted acid such as (R)-1·SnCl4 is abbreviated as (R)-LBA.*[9] The chiral LBA, (*R*)-**1**·$SnCl_4$, is generated in situ from (*R*)-**1** and tin tetrachloride in toluene or dichloromethane at room temperature, and is stable as a coordinate complex in the solvent even at room temperature. This system has excellent practical potential because of the simple and convenient preparation of (*R*)-LBA, the recoverability of optically pure (*R*)-**1** (commercially available) as a chiral proton donor, and the high enantioselectivities which can be realized with a predictable absolute configuration.

We report here research details on the enantioselective protonation of prochiral trialkylsilyl enol ethers and ketene bis(trialkyl)silyl acetals using chiral LBAs prepared from tin tetrachloride and (*R*)-**1** and its derivative (*R*)-**2**. The relationship between the enantioselectivities and substitution effects on (*R*)-BINOL was investigated through several control experiments and model studies of DFT calculations on the B3LYP/LANL2DZ level.

Results and Discussion

Enantioselective Protonation of Silyl Enol Ethers and Ketene Disilyl Acetals Derived from 2-Arylcarbonyl Compounds Using Chiral LBAs. In the first stage, the enantioselective protonation of silyl enol ethers derived from 2-arylcarbonyl compounds using stoichiometric amounts of (*R*)-**1**·$SnCl_4$ as a chiral LBA was described. The representative results are

Table 1. Enantioselective Protonation of **3a**−**f** by (*R*)-**1**·$SnCl_4$[a]



entry	**3** (Ar, R_3Si)[b]	ee (%) of product,[c] (config)-(rotn)
1	**3a** (Ph, Me_3Si)	91 (97), (*S*)-(−)
2	**3b** (Ph, *t*-$BuMe_2Si$)	86 (96), (*S*)-(−)
3	**3b** (Ph, *t*-$BuMe_2Si$)	86 (96), (*R*)-(+)[d]
4	**3c** (*p*-MeC_6H_4, *t*-$BuMe_2Si$)	82 (93), (*S*)-(−)
5	**3d** (*p*-$MeOC_6H_4$, Me_3Si)	96, (*S*)-(−)
6	**3e** (2-naphthyl, Me_3Si)	91, (*S*)-(−), → 99[e]
7	**3f** (2-naphthyl, *t*-Bu_2Me_2Si)	91, (*S*)-(−)

[a] Unless otherwise noted, silyl enol ethers **3a**−**f** were added at −78 °C to a toluene solution of LBA, which was previously prepared from 1.1 equiv of **1** and 1.0 equiv of $SnCl_4$, to give corresponding ketones **4a**−**f** quantitatively within 1 h. [b] Thermodynamic silyl enol ethers **3a** (94% regioisomeric purity), **3b** (90% regioisomeric purity), **3c** (88% regiosomeric purity), and **3d**−**f** (>99% regioisomeric purity) were used. [c] Determined by HPLC analysis; values in parentheses were corrected for the regioisomeric purity of **3**. [d] (*S*)-BINOL **1** was used in place of (*R*)-**1**. [e] Enantiomeric excess of the product after recrystallization from a CH_2Cl_2−hexane mixed system.

summarized in Table 1. Trimethylsilyl enol ether **3a**[10] derived from 2-phenylcyclohexanone (**4a**) was chosen as a model substrate for the enantioselective protonation because **3a** could be prepared as a single isomer (*Z*), and steric and/or attractive interactions between the phenyl group of **3a** and the naphthyl moiety of (*R*)-**1** were expected with the enantioselective protonation. In the presence of a stoichiometric amount of chiral LBA, which was generated from (*R*)-**1** and tin tetrachloride in toluene, the protonation of trimethylsilyl enol ether **3a** proceeded even at −78 °C and afforded the corresponding ketone (*S*)-**4a** with high enantioselectivity (entry 1). The similar enantioselectivity was also observed for the protonation of *tert*-butyldimethylsilyl enol ether **3b** with (*R*)-**1**·$SnCl_4$ (entry 2). Therefore, the enantioselectivity is independent of the *O*-substituent (SiR_3) of **3**.[11] The protonation proceeded more slowly and more enantioselectively in toluene than in dichloromethane. Interestingly, when the protonation was performed in dichloromethane, (*R*)-**1** was converted to a mixture of disilyl and monosilyl ethers of (*R*)-**1**; on the contrary, when the protonation was performed in toluene, it was converted to only the latter product. This observation suggested that the protonation of **3** in dichloromethane partially occurred with the monosilyl ether of (*R*)-**1** activated by tin tetrachloride less enantioselectively, although the side reaction did not proceed at all in toluene.

The enantioselective protonation of several silyl enol ethers **3** derived from 2-arylcyclohexanones **4** with (*R*)-**1**·$SnCl_4$ under optimum conditions is also summarized in Table 1. The reactions were generally complete within 1 h at −78 °C to give the corresponding 2-arylcyclohexanones **4** with excellent enantioselectivities. Both enantiomers of **4** could be obtained from

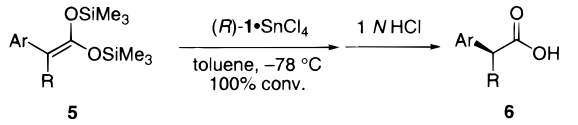
(8) (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *Croat. Chem. Acta* **1996**, *69*, 513. (c) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (d) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 6429.

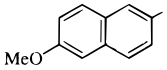
(9) The other LBA-related reports are listed: (a) Ishihara, K.; Ishida, Y.; Nakamura, S.; Yamamoto, H. *Synlett* **1997**, 758. (b) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444. (c) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.

(10) For references on regioselective preparation of thermodynamic silyl enol ethers, see: (a) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: San Diego, 1988; p 100. (b) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345. (c) House, H. O.; Fischer, W. F., Jr.; Mclauglin, T. E.; Peet, N. P. *J. Org. Chem.* **1971**, *36*, 3429. (d) Zembayashi, M.; Tamao. K.; Kumada, M. *Synthesis* **1977**, 422. (e) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643.

(11) Although we had previously reported that the enantioselectivity for the protonation of **3a** with (*R*)-**1**·$SnCl_4$ was 79% ee,[8a] the enantioselectivity was improved to 97% ee according to our retrial using **3a**, which was purified by redistillation. Therefore, our previous report[8a] that the enantioselectivity was incresed by using the sterically bulky trialkylsilyl group such as *tert*-butyldimethylsilyl group is incorrect.

Table 2. Enantioselective Protonation of **5a**−**e** by (*R*)-**1**·$SnCl_4$[a]



entry	**5** (Ar, R)	ee (%) of product,[b] (config)-(rotn)
1	**5a** (Ph, Me)	92, (*S*)-(+)
2	**5a'**	95, (*S*)-(+)[c]
3	**5b** (Ph, Et)	60, (*S*)-(+)
4	**5c** (*p*-(*i*-Bu)C_6H_4, Me)	94, (*S*)-(+)
5	**5d** ( , Me)	92, (*S*)-(+) → 98[d]
6	**5e** (Ph, OMe)	87, (*S*)-(+)

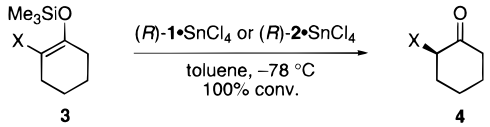
[a] Unless otherwise noted, ketene disilyl acetals **5a**−**e** were added at −78 °C to a toluene solution of LBA, which was previously prepared from 1.1 equiv of **1** and 1.0 equiv of $SnCl_4$, to give corresponding carboxylic acids **6a**−**e** quantitatively within 1 h. [b] Determined by HPLC analysis after methylation using $TMSCH_2N_2$. [c] Et_3Si was used instead of Me_3Si. [d] Enantiomeric excess of the product after recrystallization from a CH_2Cl_2−hexane mixed system.

3 depending on the choice of optically active BINOL: (*S*)- and (*R*)-**4** were obtained using (*R*)- and (*S*)-**1**·$SnCl_4$, respectively (entries 2 and 3). Unfortunately, enantioselectivity was low in the cases of the protonation of silyl enol ethers derived from 2-alkylcyclohexanones (e.g., entry 4 in Table 3, 42% ee (*R*) for **3g**, Ar = X = Me). Attractive interactions between arenes in these reactions were suggested, and the details are discussed in the later part of the present paper.

We applied the chiral LBA to the enantioselective protonation of ketene bis(trialkylsilyl) acetals **5**[10,12] derived from 2-arylcarboxylic acids **6**. Optically active 2-arylcarboxylic acids **6** including the pharmaceutical compounds ibuprofen (**6c**) and naproxen (**6d**) are quite important compounds.[13] Representative results are summarized in Table 2. The crude carboxylic acids **6**, which were formed with excellent enantiomeric excess in most cases, were isolated in quantitative yield. The enantioselectivity, which was determined by HPLC as that on the corresponding methyl esters after methylation quantitatively without racemization, was independent of the steric features of trialkylsilyl substituents (entries 1 and 2). Simple recrystallization of the (*S*)-methyl ester of **6d** could be used to upgrade the optical purity (entry 5). It is noteworthy that the protonation of the ketene silyl acetal, 63:37 diastereomer ratio (*E* and *Z*), derived from the methyl ester of **6d** and chlorotrimethylsilane by (*R*)-**1** gave the (*S*)-methyl ester of **6d** with decreased enantioselectivity (79% ee).

Enantioselective Protonation of Silyl Enol Ethers Bearing a Halogen Atom. Optically active compounds bearing halogens are widely found in nature[14] and play important roles in analytical, industrial, and medicinal chemistries. In particular, optically active α-haloketones are interesting for their spectroscopic and physical properties. However, only limited ways to construct them have been reported[15] because of their instability and the difficulty in the resolution of racemic α-halocarbonyl compounds. In the next stage, we describe the enantioselective protonation of silyl enol ethers and ketene disilyl acetals bearing a halogen atom with chiral LBAs.

Table 3. Enantioselective Protonation of Silyl Enol Ethers **3**[a]



entry	**3** (X)[b]	ee (%), (config)-(rotn)[c] (*R*)-**1**·$SnCl_4$	(*R*)-**2**·$SnCl_4$
1	**3h** (Cl)	83 (84), (*R*)-(−)	87 (88), (*R*)-(−)
2	**3i** (Br)		87 (88), (*R*)-(−)
3	**3a** (Ph)	91 (97), (*S*)-(−)	94 (98), (*S*)-(−)
4	**3g** (Me)	40 (42), (*R*)-(−)	51 (53), (*R*)-(−)

[a] Unless otherwise noted, silyl enol ethers **3a**, **3g**, **3h**, and **3i** were added at −78 °C to a toluene solution of chiral LBA, which was previously prepared from 1.1 equiv of (*R*)-**1** or (*R*)-**2** and 1.0 equiv of $SnCl_4$, to give corresponding ketones **4a**, **4g**, **4h**, and **4i** quantitatively within 1 h. [b] Thermodynamic silyl enol ethers **3h** (98% regioisomeric purity), **3i** (97% regioisomeric purity), **3a** (94% regiosomeric purity), and **3g** (94% regioisomeric purity) were used. [c] Determined by HPLC or GC analysis; values in parentheses were corrected for the regioisomeric purity of silyl enol ethers.

The enantioselective protonation of **3h** with (*R*)-**1**·$SnCl_4$ or (*R*)-**2**·$SnCl_4$ gave (*R*)-(−)-**4h** with high ee values. The results are summarized in Table 3. Interestingly, these ee values are much higher than those of **4g**, and were not almost influenced by the modifications of BINOLs. This tendency was the same as that of **3a** shown in Table 3. The enantioselective protonation of **3i** using (*R*)-**2**·$SnCl_4$ also gave (*R*)-(−)-**4i** with 88% ee. The high level of asymmetric induction may be attributed to halogen−arene attractive interactions.[16,17]

In contrast, high enantioselectivity was not achieved in the protonation of ketene bis(trimethylsilyl) acetals prepared from α-halopropionic acids with (*R*)-**1**·$SnCl_4$, probably because ketene disilyl acetals derived from them exhibited too much reactivity to use the weak attractive interactions efficiently.

Asymmetric synthesis of α-aryl-α-haloacetic acids is also very attractive.[15] Enantioselective protonation of ketene bis(trimethylsilyl) acetals **5f**−**i** by (*R*)-**1**·$SnCl_4$ was performed, and the results are shown in Table 4. Very good results were obtained with the Cl-substituted ketene bis(trimethylsilyl) acetals **5g** and **5i**. The enantioselectivity in the reaction of **5g** (X = Cl) was

(12) (a) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: San Diego, 1988; p 102. (b) Alinaworth, C.; Kuo, Y.-N. J. *Organomet. Chem.* **1972**, *46*, 73. (c) Kuo, Y.-N.; Chen, F.; Ainaworth, C. *J. Chem. Soc., Chem. Commun.* **1971**, 136. (d) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: San Diego, 1988; p 77.

(13) For a recent review of Profen drugs, see: Stahly, G. P.; Starrett, R. M. In *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: Chichester, 1997; pp 17−40.

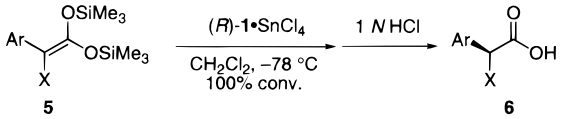
(14) (a) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2085. (b) Murai, A. In *Comprehensive Natural Products Chemistry*; Sir Derek, D., Nakanishi, K., Meth-Cohen, O., Sankawa, U., Eds.; Elsevier Science Ltd.: Oxford, 1999; Vol. 1, p 303.

(15) Recent reports: (a) Angibaud, A.; Caumette, J. L.; Desmurs, J. R.; Duhamel, L.; Plé, G.; Valnot, J. Y.; Duhamel, P. *Tetrahedron; Asymmetry* **1995**, *6*, 1919. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011. (c) Oppolzer, W. *Pure. Appl. Chem.* **1990**, *62*, 1241. (d) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799. (e) Sabiri, M.; Shao, L.; Sakurai, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877. (f) Kalaritis, P.; Regenye, R. W. *Organic Syntheses*; Wiley: New York, Collect. Vol. VIII, 258. (g) Koppenhoefer, B.; Schurig, V. *Organic Syntheses*; Wiley: New York, Collect. Vol. VIII, 119. (h) Fritz-Langhals, E.; Schütz, G. *Tetrahedron Lett.* **1993**, *34*, 293. (i) Giordano, C.; Coppi, L.; Restelli, A. *J. Org. Chem.* **1990**, *55*, 5400.

(16) (a) Hanna, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 285. (b) Hanna, M. W.; Williams, D. E. *J. Am. Chem. Soc.* **1968**, *90*, 5358. (c) Cook, E. G., Jr.; Schug, J. C. *J. Chem. Phys.* **1970**, *53*, 723. (d) Schug, J. C.; Dyson, M. C. *J. Chem. Phys.* **1973**, *58*, 297.

(17) Although silyl enol ethers derived from 2-chlorocycloheptanone and 2-chlorocyclopentanone were also examined for the reaction, their ee values were only moderate.

Table 4. Enantioselective Protonation of **5f**−**i** by (*R*)-**1**·$SnCl_4$[a]



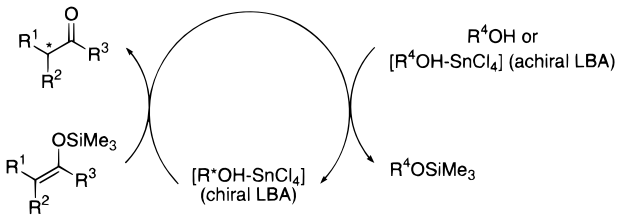
entry	**5** (Ar, X)	ee (%) of product,[b] (config)-(rotn)
1	**5f** (Ph, F)	70, (+)
2	**5g** (Ph, Cl)	91, (*S*)-(+)
3	**5h** (Ph, Br)	83, (*S*)-(+)
4	**5i** (*p*-BrC_6H_4, Cl)	84, (*S*)-(+)

[a] Unless otherwise noted, ketene disilyl acetals **5f**−**i** were added at −78 °C to a toluene solution of LBA, which was previously prepared from 1.1 equiv of **1** and 1.0 equiv of $SnCl_4$, to give corresponding carboxylic acids **6f**−**i** quantitatively within 1 h. [b] Determined by HPLC analysis after methylation using $TMSCH_2N_2$.

higher than that of **5h** (X = Br). These results would be attributable to Cl being sterically smaller than Br. The absolute stereochemistries on the protonation of **5g**−**i** are consistent with those of **5a**−**e**. Unfortunately, although α-fluoro-α-arylpropionic acid is available as a chiral modifier for assay,[18] the enantiomeric excess of the protonation of **5f** (X = F) with the smallest halogen F was moderate, probably due to some undesired interactions between F and the reagent.

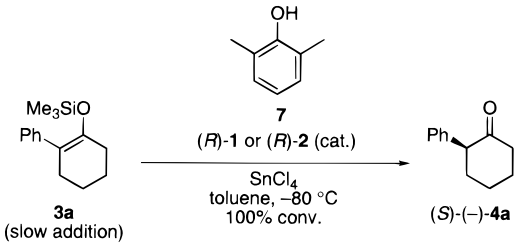
Enantioselective Protonation Using Catalytic Amounts of (*R*)-LBA. In the second stage, we realized the catalytic version of the enantioselective protonation.[9b,19] The rationale for the catalytic cycle for enantioselective protonation using (*R*)-LBA is outlined in Scheme 3. The cycle presupposes the following:

Scheme 3. General Outline of the Catalytic Cycle for Enantioselective Protonation of Silyl Enol Ethers Using Chiral LBA



(1) after protonation of silyl enol ethers with chiral LBA, the chiral proton source must be regenerated by the transfer of a proton from the achiral proton source while that source is transformed to a silyl ether by the transfer of a silyl group from silyl enol ether; (2) tin tetrachloride must be predominantly coordinated to the chiral proton source; (3) the reactivity of achiral LBA generated from the achiral proton source and tin tetrachloride must be much lower than that of the chiral proton source or its chiral LBA.

Table 5. Chiral LBA-catalyzed Enantioselective Protonation of **3a**[a]



entry	(*R*)-**1** or (*R*)-**2** (concn, mol %)	$SnCl_4$ concn (mol %)	time[b] (h)	ee[c] (%)
1[d]	(*R*)-**2** (2)	110	1	82 (90)
2	(*R*)-**2** (5)	110	0.5	83 (91)
3	(*R*)-**1** (5)	110	0.5	73 (80)
4	(*R*)-**2** (2)	50	2	82 (90)
5[e]	(*R*)-**2** (2)	50	2	90
6[d,f]	(*R*)-**2** (20)	16	1	0
7[g]	(*R*)-**1** (100)	100	0.2	88 (97)
8[g]	(*R*)-**2** (100)	100	0.2	89 (98)

[a] Unless otherwise noted, **3a** (91% regioisomeric purity) was slowly added dropwise at −80 °C to a solution of (*R*)-**2**, **7**, and tin tetrachloride in toluene to give **4a** in a quantitative yield. [b] Addition time of **3a**. [c] Determined by HPLC analysis; values in parentheses were corrected for the regioisomeric purity of **3a**. [d] Toluene−CH_2Cl_2 (3:2) was used as solvent. [e] **3a** (>99% regioisomeric purity) was used. [f] The conversion was less than 48%. [g] See Table 1.

On the basis of the above working hypothesis, we realized the chiral LBA-catalyzed enantioselective protonation of **3a**. Representative results are summarized in Table 5. In the presence of stoichiometric amounts of tin tetrachloride and 2,6-dimethylphenol (**7**) as an achiral proton source in toluene, the protonation of **3a** with (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl ((*R*)-BINOL-Me, **2**) (2−5 mol %) proceeded to give ketone **4a** with high enantioselectivity (entries 1 and 2). Although a similar result was observed with the catalytic use of (*R*)-**1**, the resulting enantioselectivity was only moderate (entry 3). The phenol **7** was the most effective achiral proton source among a variety of aromatic alcohols screened, including 2,4,6-trimethylphenol, 2,6-diethylphenol, 2,6-diisopropylphenol, and 4-bromo-2,6-dimethylphenol. While tin tetrachloride efficiently promoted protonation in substoichiometric quantities (entries 4 and 5), its use in less molar quantities than a chiral proton source remarkably lowered the reactivity, and the enantioselectivity was also lost (entry 6). The stoichiometric protonation of **3a** with (*R*)-**2**·$SnCl_4$ as well as (*R*)-**1**·$SnCl_4$ gave **4a** in excellent enantioselectivity (entries 7 and 8).

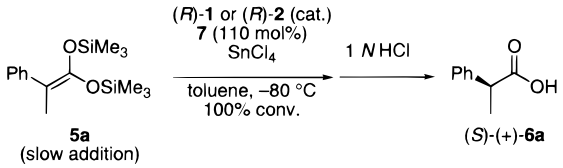
To demonstrate that the scope of this strategy is not limited to **3a**, we applied this catalytic system to ketene bis(trimethylsilyl) acetal **5a**. The results are summarized in Table 6. The protonation of **5a** with (*R*)-**2** (10 mol %) in the presence of stoichiometric amounts of tin tetrachloride and **7** exhibited moderate enantioselectivity (entry 1). A high degree of enantioselectivity was attained using catalytic amounts of (*R*)-**2** (10 mol %) and tin tetrachloride (8 mol %) (entry 2). Tin tetrachloride efficiently promoted the protonation of **5a** with (*R*)-**2** in less molar quantities than a chiral proton source, since **5a** is much more reactive than **3a**. In addition, (*R*)-**2** was far superior to (*R*)-**1** as a chiral proton source in the catalytic protonation of **5a** (entry 3 vs entry 4).

The procedures optimized for the catalytic enantioselective protonations of **3a** and **5a** have been applied to the synthesis of (−)-2-phenylcycloheptanone (**9**), (*S*)-(−)-2-(2-naphthyl)cyclo-

(18) (a) Barrelle, M.; Hamman, S. *J. Chem. Res. (S)* **1995**, 317. (b) Hamman, S.; Barrelle, M.; Tetaz, F.; Beguin, J. *J. Fluorine Chem.* **1987**, *37*, 85.

(19) For recent studies on the catalytic enantioselective protonation, see: (a) Aboulhoda, S. J.; Henin, F.; Muzart, J.; Thorey, C.; Behnen, W.; Martens, J.; Mehler, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1321. (b) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888. (c) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372. (d) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805. (e) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366. (f) Muzart, F.; Hénin, S.; Aboulhoda, J. *Tetrahedron: Asymmetry* **1997**, *8*, 381. (g) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589. (h) Yanagisawa, A.; Watanabe, T.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1997**, 956. (i) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691. (j) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1974**, *39*, 8691, (k) Aboulhoda, S. J.; Reiners, I.; Wilken, J.; Henin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1847. (l) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043.

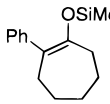
Table 6. Chiral LBA-catalyzed Enantioselective Protonation of **5a**[a]



entry	(*R*)-**1** or (*R*)-**2** (concn, mol %)	$SnCl_4$ concn (mol %)	time[b] (h)	ee[c] (%)
1	(*R*)-**2** (10)	110	1	68
2	(*R*)-**2** (10)	8	1	94
3	(*R*)-**2** (5)	4	2	80
4	(*R*)-**1** (5)	4	2	22

[a] Unless otherwise noted, **5a** was slowly added dropwise at −80 °C to a solution of (*R*)-**2**, **7** and tin tetrachloride in toluene to give **6a** in a quantitative yield. [b] Addition time of **5a**. [c] Determined by esterification with $TMSCH_2N_2$ and HPLC analysis.

Table 7. Chiral LBA-Catalyzed Enantioselective Protonation of Several Substrates[a]

entry	substrate	(*R*)-**2** (mol%)	$SnCl_4$ (mol%)	time[b] (h)	product yield (%)	product ee (%) (config)-(roton)
1	 **8**[c]	5	110	0.5	92	84(97),[d] (–)
2	**3e**[e]	5	50	0.5	84	91(95),[d] (*S*)-(–)
3	**5c**	10	8	1	80	93, (*S*)-(+)[f]

[a] Unless otherwise noted, a substrate was slowly added dropwise at −80 °C to a solution of **2**, **7**, and tin tetrachloride in toluene to give the product in a quantitative yield. [b] Addition time of a substrate. [c] Compound **8** (86% regioisomeric purity) was used. [d] Determined by HPLC analysis; values in parentheses were corrected for the regioisomeric purity of silyl enol ethers. [e] Compound **3e** (96% regioisomeric purity) was used. [f] Determined by esterification with $TMSCH_2N_2$ and HPLC analysis.

hexanone (**4e**), and (*S*)-(+)-ibuprofen (**6c**) as shown in Table 7. To the best of our knowledge, this method is the most simple, easy, and general catalytic way to obtain biologically active 2-arylpropionic acids.

There are two important differences between the protonations of silyl enol ethers and ketene disilyl acetals. One is the amount of tin tetrachloride, and the other is the effect of *O*-protection of **1**. They depend largely on the difference of reactivity between silyl enol ethers and ketene disilyl acetals.

The ^1H NMR spectrum of the reaction mixture of (*R*)-**1**·$SnCl_4$ and **3a** in toluene-d_8 at −80 °C exhibited two singlets for the trimethylsilyl groups of the monosilyl ether of (*R*)-**1** and chlorotrimethylsilane at −0.26 and 0.16 ppm, respectively, at a molar ratio of 85:15.[20] In contrast, *the ^1H NMR spectrum of the reaction mixture of (R)-2·$SnCl_4$ and 3a at −80 °C exhibited only one singlet for chlorotrimethylsilane.* The formation of chlorotrimethylsilane led us to anticipate the possibility of generating tin aryloxide intermediates **10** and **11** (Scheme 4).

The experimental results shown in Table 5 can be reasonably explained by assuming that the tin aryloxide intermediate **11** is reconverted to (*R*)-**2**·$SnCl_4$ by receiving a proton and a chloride from **7** and chlorotrimethylsilane and/or tin tetrachloride,

(20) The disilyl ether of (*R*)-**1** was not observed at all. In fact, the mixture of tin tetrachloride and the monosilyl ether of (*R*)-**1** was less reactive for **3a** (−78 °C, 5 min, <21% conversion). Considering the steric and electronic effects of the trimethylsilyl group, the rigid formation of (*R*)-LBA from the monosilyl ether of (*R*)-**1** and tin tetrachloride should be rather difficult.

Scheme 4. Tin Aryloxide Intermediates Predicted by ^1H NMR Analyses

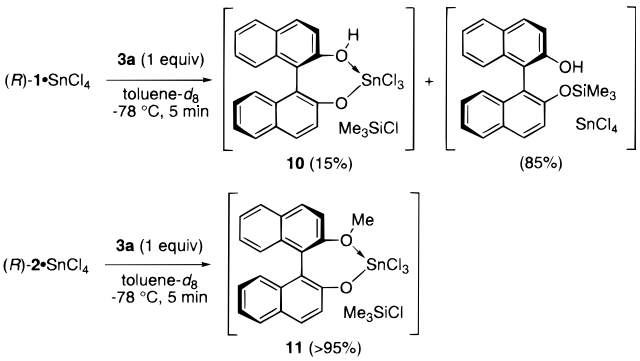


Table 8. Comparison of the Reactivities of LBAs in the Protonation of **3a** to **4a**[a]

LBA	conversion of **3a** to **4a** (%)[b]
(*R*)-**2**·$SnCl_4$	100
7·$SnCl_4$	17
$SnCl_4$[c]	0

[a] The reaction was quenched with pyridine after 5 min since **3a** was added to a solution of a stoichiometric amount of LBA in toluene at −78 °C over 3 min. [b] Determined by ^1H NMR analysis of the crude products. [c] Blank test: the experiment was performed without any proton sources.

respectively. The production of the silyl ether of **7** was ascertained by ^1H NMR analysis of the reaction mixture at −80 °C. The poor results observed with small amounts of tin tetrachloride can be explained by unfavorable weak associations between (*R*)-**2**·$SnCl_4$ and excess **7** to weaken the acidity. Chelation between excess tin tetrachloride per chiral proton source and **7** prevents the deactivation of (*R*)-**2**·$SnCl_4$, and may promote proton transfer from **7** to **11**. Nevertheless, achiral LBA **7**·$SnCl_4$ is not acidic enough to react predominantly with **3a** in the presence of (*R*)-**2**·$SnCl_4$. The reactivity of (*R*)-**2**·$SnCl_4$ is certainly much greater than that with **7**·$SnCl_4$ in toluene (Table 8). The catalytic cycle for the enantioselective protonation of ketene disilyl acetal **5a** catalyzed by (*R*)-**2**·$SnCl_4$ is rather simple, since excess tin tetrachloride per chiral proton source is not added (entry 2 in Table 6). In this case, (*R*)-**2**·$SnCl_4$ should be regenerated from intermediate **11** by acquiring a proton and a chloride from **7** and chlorotrimethylsilane, respectively. Considering the catalytic systems for both **3a** and **5a**, the protonation of **3a** with (*R*)-**2**·$SnCl_4$ is the rate-determining step, at least in the latter system, since the regeneration of chiral LBA proceeds without participation of tin tetrachloride.

To the best of our knowledge, the catalytic protonations described here are the first examples of the highly enantioselective protonation of silyl enol ethers in the presence of a catalytic amount of chiral proton source.

The existence of "kinetic" silyl enol ether included as a minor regioisomer of the substrate was a critical problem in the enantioselective protonation of "thermodynamic" silyl enol ether **3**. Although several protocols are known for the regioselective preparation of thermodynamic silyl enol ethers, there are no general methods for obtaining thermodynamic silyl enol ethers of >99% purity.[10] We solved this problem by selective protonolysis of a kinetic regioisomer using achiral LBA **7**·$SnCl_4$, which is milder than (*R*)-**1**·$SnCl_4$ as a protonation reagent (Scheme 5). For example, a little excess molar amount of **7**·$SnCl_4$ per minor regioisomer included in silyl enol ether **3a** as substrate was used to protodesilylate the kinetic regioisomer, which is more reactive than **3a**. The crude mixture of **3a** and

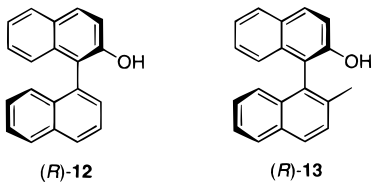


Figure 1. Monodentate BINOL derivatives.

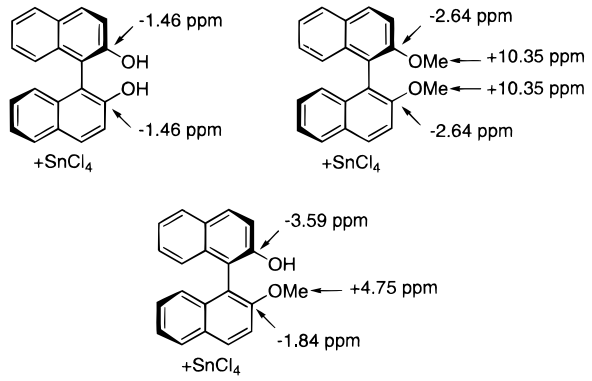
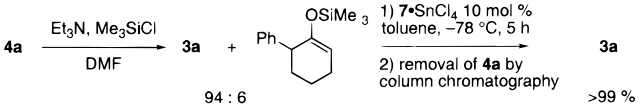


Figure 2. Changes in ^{13}C NMR (75 MHz, in CD_2Cl_2, −78 °C) shifts for BINOL derivatives which were observed upon complexation with $SnCl_4$ [$\Delta\delta = \delta$(chiral LBA) − δ(chiral BINOL derivative) values are given].

4a obtained was easily separated by column chromatography on silica gel.

Scheme 5



Control Experiments and DFT Calculations of the Biphenol·$SnCl_4$ Complex. In control experiments,[21] it was ascertained that the present protonation of **3a** using (*R*)-**1**·$SnCl_4$ did not occur via tin enolate. The chiral LBAs can give their protons to silyl enol ethers directly.

So what is the real structure of chiral LBA? What makes the enantioselectivity of products so high? Actually, we have not yet succeeded in any X-ray diffraction analysis of chiral LBAs. But control experiments using monodentate ligands having a binaphthyl backbone, (*R*)-**12** and (*R*)-**13** shown in Figure 1, with 1 equiv of tin tetrachloride showed no reactivity on the protonation of **3a** even under the same conditions as shown in Table 1. The bidentate coordination of **1** and **2** with tin tetrachloride seems to be crucial for the transition state. Moreover, each ^{13}C NMR analysis for the complexes (*R*)-**1**·$SnCl_4$ and dimethyl ether of (*R*)-**1**·$SnCl_4$ exhibited only one species with a symmetrical structure, and the analysis of (*R*)-**2**·$SnCl_4$ also showed one species (Figure 2). These results appear to indicate at least the existence of an *n*:*n* bidentate complex of the Brønsted acid and the Lewis acid.

Finally, structures of biphenol derivative·$SnCl_4$ complexes were estimated using Becke's three-parameter hybrid method and the Lee-Yang-Parr correlation functional (B3LYP), and all charges shown in this paper were evaluated by the natural population analysis (NPA).[22] On the basis of the assumption that (*R*)-BINOL·$SnCl_4$ complexes are 1:1 complexes, we used the calculation models of biphenol·$SnCl_4$ and monomethyl ether of biphenol(biphenol-Me)·$SnCl_4$ to express (*R*)-**1**·$SnCl_4$ and (*R*)-**2**·$SnCl_4$, respectively. The results are shown in Figures 3 and 4. As for the biphenol·$SnCl_4$ complex (Figure 3), the calculations have predicted that the chelation of the complex occurs at an equatorial−equatorial site on tin, and the length of Sn−O (2.377 Å) was shorter than Sn−Cl_a (2.406 Å) and longer than Sn−Cl_e (2.350 Å). It is noteworthy that acidic protons are likely to be located at pseudoaxial sites parallel to an apical chloride on the tin, and electrostatic interaction between the acidic protons and the chloride is expected. The calculations show that the conformational structure of biphenol-Me·$SnCl_4$ is analogous to that of biphenol·$SnCl_4$ (Figure 4). It was confirmed that Brønsted acidity of phenols is truly enhanced by coordination of tin tetrachloride (charge on the activated proton of biphenol·$SnCl_4$ 0.546, charge on that of biphenol-Me·$SnCl_4$ 0.549) compared to that of a phenol (charge on the proton 0.489).

The high degree of enantioselectivity attained in these reactions and the observed preference for the formation of (*S*)-**4**

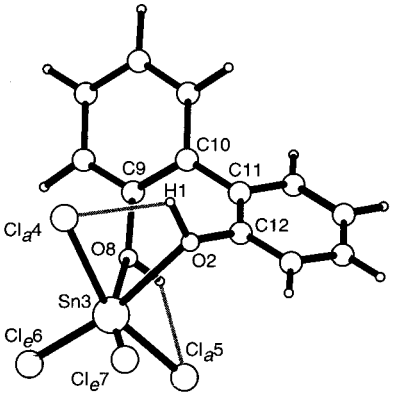


Figure 3. Optimized structures of the biphenol·$SnCl_4$ complex ("*e*" = equatorial, "*a*" = apical). Calculated on the B3LYP/LANL2DZ level (total energy −677.115 600 380 au). Selected distances (Å): H1−O2 = 0.979, H1−Cl_a4 = 2.458, O2−Sn3 = Sn3−O8 = 2.377, Sn3−Cl_a4 = Sn3−Cl_a5 = 2.406, Sn3−Cl_e6 = Sn3−Cl_e7 = 2.350. Torsion angles (deg): H1−O2−Sn3−Cl_a4 = −5.9, C9−C10−C11−C12 = −52.9.

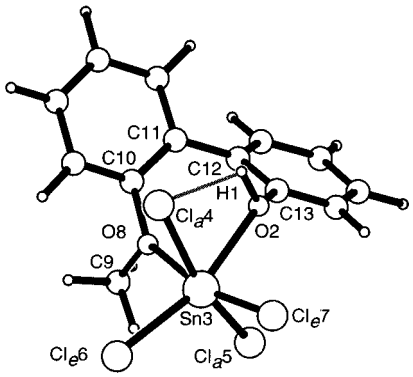
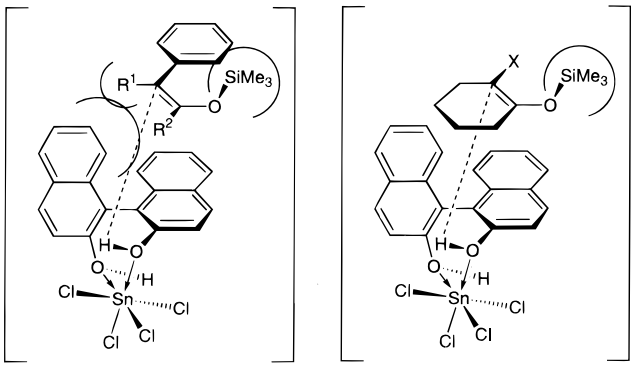


Figure 4. Optimized structures of the biphenol-Me·$SnCl_4$ complex ("*e*" = equatorial, "*a*" = apical). Calculated on the B3LYP/LANL2DZ level (total energy = −716.404 523 766 au). Selected distances (Å): H1−O2 = 0.980, H1−Cl_a4 = 2.462, O2−Sn3 = 2.316, Sn3−Cl_a4 = 2.416, Sn3−Cl_a5 = 2.386, Sn3−Cl_e6 = 2.367, Sn3−Cl_e7 = 2.358, Sn3−O8 = 2.396, O8−C9 = 1.477. Torsion angles (deg): H1−O2−Sn3−Cl_a4 = −2.2, C10−C11−C12−C13 = −53.3.

(21) It was ascertained that the present protonation of **3a** using (*R*)-**1**·$SnCl_4$ did not occur via tin enolate by the following control experiment: **3a** was stable in the presence of tin tetrachloride (1 equiv) at −78 °C over 2.5 h. Kuwajima et al. reported the formation of α-trichlorostannyl ketones in the reaction of tin tetrachloride with silyl enol ethers at 35 °C. Nakamura, E.; Kuwajima, I. *Chem. Lett.* **1983**, 59.

(22) NBO 4.0: Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F., Theoretical Chemistry Institute, University of Wisconsin, Madison, 1996.



14 **15**

Figure 5. Proposed transition-state assemblies. R^1 = alkyl groups or halogen atoms. R^2 = alkyl groups or $OSiMe_3$. X = halogen atoms.

and (*S*)-**6** merit comment. If the protonolysis of silyl enol ethers with LBA favors *C*-protonation,[7] the proposed transition state shown in Figure 5 can explain this preference. Silyl enol ethers **3** or ketene disilyl acetals **5** enantioface-selectively approach (*R*)-**1** via the transition-state assembly **14** due to the stereoelectronic effects between them: the trimethylsiloxy group of **3** or **5** orients opposite to the binaphthyl moiety of (*R*)-**1**, while the aryl substituent stacks on the naphthalene ring, possibly due to $\pi-\pi$ electronic attractive interaction. The asymmetric induction of α-aryl-α-haloacetic acids **6f**−**i** was also controlled by the $\pi-\pi$ attractive interaction (Table 4). If R (or X) of ketene disilyl acetals **5** were bulky, enantioselectivity would be reduced because of steric hindrance between another naphthalene ring and R^1 (entry 1 vs entry 3 in Table 2, entry 2 vs entry 3 in Table 4).

For silyl enol ethers **3h** and **3i** bearing a halogen atom in place of an aryl group, the absolute stereochemistry of the protonation of them was the same as that of **3a**. This result suggests some $n-\pi^*$ attractive interaction[16,17] between a halogen atom of the silyl enol ethers and a naphthalene ring of chiral LBAs may occur in the transition-state assembly **15** (Figure 5).

Conclusions

Acidic protons in optically active binaphthol, which is commercially available in either enantiomeric form, are activated by coordination of tin tetrachloride to form chiral LBA, and can be used as chiral proton sources for the protonation of silyl enol ethers and ketene bis(trialkylsilyl) acetals with unprecedented enantioselectivity, in quantitative yield and with predictable absolute configuration. The chiral LBA system is also effective for the catalytic version: Three different "acids", **2**, **7**, and tin tetrachloride, which coexist in a reaction flask, function as chiral proton reagent, achiral proton source, and their activator, respectively. DFT calculations on the B3LYP/LANL2DZ level clarified the orientation of the activated protons, and indicated the possibility of designing new chiral LBAs using theoretical computer calculations.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded on a Shimadzu FT-IR 8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-200, Gemini-300, or VXR 500 spectrometer. Tetramethylsilane was used as internal standard for ^{1}H NMR (δ 0.00 ppm), $CDCl_3$ for ^{13}C NMR (δ 77.00 ppm), and $CF_3C_6H_5$ for ^{19}F NMR (δ −63.90 ppm). High-performance liquid chromatography (HPLC) was done with Shimadzu 10A instruments using 4.6 mm × 25 cm Daicel CHIRALCEL OD-H, OJ, and AS. GC analysis was done with a Shimadzu 17A instrument using γ-TA (0.25 mm × 20 m), β-TA (0.25 mm × 20 m), and PEG (0.25 mm × 25 m). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry argon. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF^{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck 9385. FAB mass spectral analyses were accomplished at the Graduate School of Engineering, Nagoya University. In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co., Inc. as "anhydrous" and stored over 4A molecular sieves. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Tin tetrachloride was distilled under argon. (*R*)-BINOL **1** was purchased from Kankyo Kagaku Center Co., Ltd. (*R*)-BINOL-Me **2** was prepared by use of the Mitsunobu reaction.[23]

Preparation of Racemic 2-Arylcycloalkanones 4a−f. The arylation of cyclohexanone (10 mmol) with a solution of aryllithium [generated from aryl bromide (11 mmol) and *tert*-butyllithium (11 mmol) in THF (30 mL) at −78 °C] at −78 °C for 0.5 h afforded 1-arylcyclohexanol, which was treated with a mixture of concentrated sulfuric acid (1.7 mL) and acetic acid (6.6 mL) at 0 °C for 0.5 h and purified by column chromatography on silica gel to give 1-arylcyclohexene in 80−90% overall yield. Hydroboration of 1-arylcyclohexene (8 mmol) with a solution of BH_3 (8 mmol) in THF at 0 °C for 1 h and at 25 °C for 1 h and the subsequent treatment by water (2 mL), 3N NaOH (8 mL), and 30% hydrogen peroxide (8 mL) gave 2-arylcyclohexanol (ca. 80% yield), which was oxidized by PCC (16 mmol) in dichloromethane at 25 °C for 8 h and purified by column chromatography on silica gel to give the desired 2-arylcyclohexanone as a white solid in a quantitative yield.

The physical properties and analytical data of the ketones thus obtained are listed below.

2-Phenylcyclohexanone (4a or 4b): Obtained from Aldrich Chemical Co., Inc.

2-(4-Methylphenyl)cyclohexanone (4c):[24] IR (KBr) 2938, 1705 (C=O), 1518, 1445, 1308, 1192, 1123, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75−2.60 (m, 8H, O=C$(CH_2)_4$), 2.35 (s, 3H, CH_3), 3.59 (dd, J = 5.5, 11.9 Hz, 1H, O=CCH), 7.05 (d, J = 8.0 Hz, 2H, ArH), 7.17 (d, J = 8.0 Hz, 2H, ArH).

2-(4-Methoxyphenyl)cyclohexanone (4d):[25] IR (KBr) 2926, 1703 (C=O), 1615, 1516, 1449, 1253, 1179, 1125, 1032, 828, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75−2.32 (m, 6H, O=$CCH_2(CH_2)_3$), 2.38−2.58 (m, 2H, O=CCH_2), 3.57 (dd, J = 6.0, 13.5 Hz, 1H, O=CCH), 3.80 (s, 3H, OCH_3), 6.89 (d, J = 8.6 Hz, 2H, ArH), 7.07 (d, J = 8.6 Hz, 2H, ArH).

2-(2-Naphthyl)cyclohexanone (4e or 4f):[26] IR (KBr) 2938, 2863, 1709 (C=O), 1447, 1125, 822, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75−2.62 (m, 8H, O=C$(CH_2)_4$), 3.78 (dd, J = 5.5, 12.0 Hz, 1H, O=CCH), 7.28 (dd, J = 1.8, 8.5 Hz, 1H, ArH), 7.40−7.48 (m, 2H, ArH), 7.59 (s, 1H, ArH), 7.76−7.82 (m, 1H, ArH), 7.81 (d, J = 8.5 Hz, 2H, ArH).

2-Methylcyclohexanone (4g): Obtained from Aldrich Chemical Co., Inc.

2-Phenylcycloheptanone (9):[27] Obtained from Aldrich Chemical Co., Inc.

Preparation of 2-Halocycloalkanones 4h and 4i. 2-Bromocyclohexanone (**4i**) was produced from 1-(trimethylsiloxy)cyclohex-1-ene with a simple method reported reported previously.[10d] 2-Chlorocyclohexanone (**4h**) was purchased from Aldrich Chemical Co., Inc.

Preparation of 2-Aryl-1-(trialkylsilyloxy)cyclohex-1-enes 3a−f and 2-Phenyl-1-(trimethylsiloxy)cyclohept-1-ene (8).[8a,c,10a] To a solution of 2-arylcycloalkanone (12.5 mmol) and triethylamine (30 mmol) in DMF (25 mL) was added trialkylsilyl chloride (15 mmol) dropwise with stirring. The mixture was heated in an oil bath at 130 °C for 90

(23) Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3125.
(24) Hussey, A. S.; Herr, R. R. *J. Org. Chem.* **1959**, *24*, 843.
(25) Mueller, G. P.; May, R. *J. Am. Chem. Soc.* **1949**, *71*, 3313.
(26) Caubere, P.; Mourad, M. S. *Bull. Soc. Chim. Fr.* **1974**, *7*−*8*, 1415.
(27) Rathke, M. W.; Vogiazolou, D. *J. Org. Chem.* **1987**, *52*, 3697.

h. On cooling, it was diluted with ether (20 mL),, and washed with ice-cold sodium hydrogen carbonate solution (20 mL). The aqueous phase was re-extracted with ether (3 × 20 mL). After drying over $MgSO_4$ and concentration in vacuo, distillation of the residue gave the thermodynamic silyl enol ether (ca. 80% yield), in an enriched regioisomeric ratio (>99:1 to 90:10).

The physical properties and analytical data of the silyl enol ethers thus obtained are listed below.

2-Phenyl-1-(trimethylsilyloxy)cyclohex-1-ene (3a):[28] IR (film) 2932, 1650 (C=C), 1493, 1443, 1356, 1252, 1196, 909, 862, 758, 698 cm^{-1}, ^1H NMR ($CDCl_3$, 500 MHz) δ −0.05 (s, 9H, $Si(CH_3)_3$), 1.62−1.85 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.13−2.24 (m, 2H, $CH_2(CH_2)_2CH_2$), 2.32−3.43 (m, 2H, $CH_2(CH_2)_2CH_2$), 7.10−7.41 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.46, 23.28, 23.44, 29.43, 31.06, 116.33, 125.45, 127.58, 128.52, 141.38, 145.62; LR FAB^+-MS *m/z* 246 ($[M]^+$, $C_{15}H_{22}OSi$ requires 246.4). Six percent of 6-phenyl-1-(trimethylsilyloxy)cyclohex-1-ene (^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 9H, $Si(CH_3)_3$) was included.

Preparation of 3a (>99% Regioisomeric Purity). To a solution of 2,6-dimethylphenol (281 mg, 2.3 mmol) in toluene (10 mL) was added a 1 M solution of tin tetrachloride in dichloromethane (2.3 mL, 2.3 mmol) at room temperature to generate achiral LBA in little excess compared to the kinetic isomer. After the achiral LBA solution was cooled to −78 °C, a solution of **3a** (5.67 g, 23 mmol, 92% regioisomeric purity) which was prepared as above was added dropwise. After being stirred for 1 h at −78 °C, the reaction mixture was poured into ice−aqueous $NaHCO_3$, extracted with ether twice, dried over magnesium sulfate, and concentrated in vacuo. The crude oil was purified by column chromatography on silica gel 60 silanized (eluent, hexane alone) and distillation (3.5 Torr, 106 °C) to afford **3a** (5.08 g, 21 mmol, >99% regioisomeric purity).

2-Phenyl-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (3b): GC (PEG, 100 kPa, column temperature 150 °C) t_R = 18.6 min; IR (film) 2930, 1663 (C=C), 1362, 1254, 1198, 1130, 905, 830, 780, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ −0.17 (s, 6H, $Si(CH_3)_2$), 0.73 (s, 9H, *t*-Bu), 1.60−1.82 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.12−2.21 (m, 2H, $CH_2(CH_2)_2CH_2$), 2.29−2.38 (m, 2H, $CH_2(CH_2)_2CH_2$), 7.10−7.34 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.26, 17.97, 23.29, 23.49, 25.62, 29.95, 31.07, 116.51, 125.54, 127.62, 128.93, 141.60, 145.43; LR FAB^+-MS *m/z* 288 ($[M]^+$, $C_{18}H_{28}OSi$ requires 288.5). Ten percent of 6-phenyl-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (GC (PEG, 100 kPa, column temperature 150 °C) t_R = 14.8 min) was included.

2-(4-Methylphenyl)-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (3c): GC (PEG, 100 kPa, column temperature 160 °C) t_R = 16.2 min; IR (film) 2930, 1661 (C=C), 1514, 1472, 1360, 1254, 1196, 912, 833, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.14 (s, 6H, $Si(CH_3)_2$), 0.75 (s, 9H, $SiC(CH_3)_3$), 1.71 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.17 (m, 2H, $CH_2C{=}CCH_2$), 2.31 (s, 3H, $CH_3C_6H_4$), 2.32 (m, 2H, $CH_2C{=}CCH_2$), 7.08 (d, *J* = 7.5 Hz, 2H, ArH), 7.23 (d, *J* = 7.5 Hz, 2H, ArH); LR FAB^+-MS *m/z* 302 ($[M]^+$, $C_{19}H_{30}OSi$ requires 302.5). Twelve percent of 6-(4-methylphenyl)-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (GC (PEG, 100 kPa, column temperature 160 °C) t_R = 13.9 min) was included.

2-(4-Methoxyphenyl)-1-(trimethylsilyloxy)cyclohex-1-ene (3d): IR (film) 2932, 1657, 1609, 1512, 1356, 1262, 1194, 1181, 912, 864, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 9H, $Si(CH_3)_3$), 1.62−1.79 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.12−2.19 (m, 2H, $CH_2C{=}CCH_2$), 2.30−2.38 (m, 2H, $CH_2C{=}CCH_2$), 3.80 (s, 3H, $ArOCH_3$), 6.84 (d, *J* = 9.0 Hz, 2H, ArH), 7.30 (d, *J* = 9.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.53, 23.31, 23.47, 29.50, 31.08, 55.19, 112.98, 113.54, 129.47, 133.82, 145.06, 157.38; LR FAB^+-MS *m/z* 276 ($[M]^+$, $C_{16}H_{24}O_2Si$ requires 276.5). No 6-(4-Methoxyphenyl)-1-(trimethylsilyloxy)cyclohex-1-ene was formed in a detectable amount.

2-Naphthyl-1-(trimethylsilyloxy)cyclohex-1-ene (3e):[12d] IR (film) 2932, 1650 (C=C), 1507, 1358, 1252, 1202, 1184, 918, 845, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.56 (s, 9H, $Si(CH_3)_3$), 1.69−1.82 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.20−2.26 (m, 2H, $CH_2C{=}CCH_2$), 2.44−2.50 (m, 2H, $CH_2C{=}CCH_2$), 7.36−7.85 (m, 7H, ArH).; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.53, 23.28, 23.40, 29.36, 31.16, 116.00, 124.97, 125.45, 126.47, 126.67, 127.37, 127.60, 127.71, 138.86, 146.26; LR FAB^+-MS *m/z* 296 ($[M]^+$, $C_{19}H_{24}OSi$ requires 296.5). Zero or 4% of 6-naphthyl-1-(trimethylsilyloxy)cyclohex-1-ene (^1H NMR ($CDCl_3$, 300 MHz) δ 0.039 (s, 9H, $Si(CH_3)_3$) was contaminated.

2-Naphthyl-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene (3f): IR (film) 2930, 2859, 1655 (C=C), 1253, 1202, 1181, 916, 837, 779, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.18 (s, 6H, $Si(CH_3)_2$), 0.72 (s, 9H, $SiC(CH_3)_3$), 1.70−1.83 (m, 4H, $CH_2(CH_2)_2CH_2$), 2.20−2.26 (m, 2H, $CH_2C{=}CCH_2$), 2.42−2.48 (m, 2H, $CH_2C{=}CCH_2$), 7.35−7.55 (m, 3H, ArH), 7.71−7.79 (m, 4H, ArH). No 6-naphthyl-1-(*tert*-butyldimethylsilyloxy)cyclohex-1-ene was formed in a detectable amount.

2-Phenyl-1-(trimethylsilyloxy)cyclohept-1-ene (8): IR (film) 2923, 1646, 1493, 1443, 1252, 1188, 1111, 889, 843, 792, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.09 (s, 9H, $SiMe_3$), 1.58−1.71 (m, 4H), 1.73−1.84 (m, 2H, CH_2), 2.39−2.48 (m, 4H, $CH_2C{=}CCH_2$), 7.08−7.15 (m, 1H, ArH), 7.22−7.33 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.54, 25.22, 27.57, 32.10, 33.03, 36.17, 121.45, 125.18, 127.48, 128.60, 143.02, 150.89; LR FAB^+-MS *m/z* 260 ($[M]^+$, $C_{16}H_{24}OSi$ requires 260.5). Fourteen percent of 7-phenyl-1-(trimethylsilyloxy)cyclohept-1-ene (^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 9H, $SiMe_3$), 3.52−3.60 (m, 1H, C*H*Ph), 5.14−5.22 (m, 1H, CH=C)) was contaminated.

Preparation of 2-Methyl-1-(trimethylsilyloxy)cyclohex-1-ene (3g).[10b] To a stirred solution of *N*,*N*-diisopropylamine (0.7 mL, 5 mmol) in ether (65 mL) was added dropwise a solution of MeMgI in ether (3.06 mL, 4.9 mmol, 1.6 M) at room temperature. After being stirred overninght, the reaction mixture was cooled to −78 °C. Then 2-methylcyclohexanone (**4g**) (0.448 g, 4 mmol), trimethylsilyl chloride (1.6 mL, 12 mmol), triethylamine (1.8 mL, 13 mmol), and HMPA (0.35 mL, 2 mmol) were added in this order. After being stirred overnight, the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted twice with ether (2 × 20 mL). The aqueous phase was re-extracted with ether (3 × 20 mL). After drying over $MgSO_4$ and concentration in vacuo, distillation of the residue gave the thermodynamic silyl enol ether (ca. 80% yield) in 94% regioisomeric purity: IR (film) 2930, 1686 (C=C), 1252, 1186, 945, 920, 843, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.16 (s, 9H), 1.48−1.68 (m, 4H), 1.54 (s, 3H), 1.90−2.04 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.69, 16.34, 23.04, 23.80, 30.12, 30.28, 111.80, 142.88.; LR FAB^+-MS *m/z* 182 ($[M]^+$, $C_{10}H_{20}OSi$ requires 184.4). Six percent of 6-methyl-1-(trimethylsilyloxy)cyclohex-1-ene (^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 9H, $Si(CH_3)_3$) was included.

Preparation of 2-Halo-1-(trimethylsilyloxy)cyclohex-1-enes 3h and 3i.[10c] To a suspension of 1,4-diazabicyclo[2,2,2]octane (2.40 g, 21.4 mmol) in DMF (6 mL) were added trimethylsilyl chloride (2.0 mL, 15.8 mmol) and 2-halocyclohexanone **3** (9.6 mmol) in this order at room temperature under argon. After being stirred overnight, the mixture was washed with saturated aqueous $NaHCO_3$ solution and extracted twice with ether. The combined etheral phases were dried and concentrated. The crude product was purified by short column chromatography on silica gel and distillation in vacuo to give the corresponding thermodynamic silyl enol ether (ca. 80% yield), in an enriched regioisomeric ratio (>97:3).

2-Chloro-1-(trimethylsilyloxy)cyclohex-1-ene (3h):[10c] GC (PEG, 100 kPa, column temperature 90 °C) t_R = 3.61 min; IR (film) 2942, 1673, 1341, 1254, 1225, 1150, 1011, 914, 845, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.22 (s, 9H), 1.59−1.80 (m, 4H), 2.02−2.21 (m, 2H), 2.25−2.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.66, 22.91, 23.76, 31.13, 32.05, 111.45, 144.85; LR FAB^+-MS *m/z* 204 ($[M]^+$, $C_9H_{17}OSiCl$ requires 204.8). Two percent of 6-chloro-1-(trimethylsilyloxy)cyclohex-1-ene (GC (PEG, 100 kPa, column temperature 90 °C) t_R = 4.32 min) was included.

2-Bromo-1-(trimethylsilyloxy)cyclohex-1-ene (3i):[10d,e] GC (PEG, 100 kPa, column temperature 90 °C) t_R = 5.48 min; IR (film) 2940, 1669, 1354, 1267, 1252, 1221, 1144, 1073, 994, 902, 845, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.24 (s, 9H), 1.59−1.75 (m, 4H), 2.07−2.19 (m, 2H), 2.42−2.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.74, 22.96, 24.48, 31.48, 34.13, 102.54, 146.56; LR FAB^+-MS *m/z* 249 ($[M]^+$, $C_9H_{17}OSiBr$ requires 249.3). Three percent of 6-bromo-1-(trimethylsilyloxy)cyclohex-1-ene (GC (PEG, 100 kPa, column temperature 90 °C) t_R = 6.70 min) was included.

(28) Rubottom, G. M.; Mott, R. C.; Krueger, D. S. *Synth. Commun.* **1977**, *7*, 327.

Preparation of α-Arylcarboxylic Acids 6a−i. 2-Chloro-2-(4-bromophenyl)acetic acid (**6i**) was produced with a simple method reported previously.[29] Other 2-arylcarboxylic acids **6a−h** were purchased.

Preparation of Ketene Bis(trialkylsilyl) Acetals 5a−e.[12a−c] To a solution of LDA (20 mmol) in THF (15 mL) was added a solution of the carboxylic acid (10 mmol) in THF (50 mL) dropwise with stirring at 0 °C, which was continued at 0 °C for a further 0.5 h. Excess trialkylsilyl chloride (50 mmol) was added dropwise over 5 min, and the reaction mixture was allowed to come to ambient temperature over 2 h with stirring. It was then filtered by suction through a pad of Celite, and concentrated using a rotary evaporator. The residue was taken up in ether (5 mL), and filtration and concentration were repeated. Distillation in vacuo of the residue gave the ketene bis(trialkylsilyl) acetals, ca. 90%.

The physical properties and analytical data of the ketene disilyl acetals thus obtained are listed below.

1,1-Bis(trimethylsilyloxy)-2-phenylpropene (5a):[12b] IR (film) 2961, 1655 (C=C) 1254, 1213, 1140, 1069, 963, 851, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.05 (s, 9H, $Si(CH_3)_3$), 0.27 (s, 9H, $Si(CH_3)_3$), 1.90 (s, 3H, $C{=}CCH_3$), 7.07 (tt, J = 2.6, 7.2 Hz, 1H, ArH), 7.20−7.38 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.05, 0.42, 16.51, 94.48, 124.73, 127.53, 128.57, 141.62, 147.28; LR FAB^+-MS m/z 294 ($[M]^+$, $C_{15}H_{26}O_2Si_2$ requires 294.5).

1,1-Bis(triethylsilyloxy)-2-phenylpropene (5a): IR (film) 2957, 2878, 1655 (C=C), 1458, 1414, 1208, 1140, 1005, 816, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.39 (q, J = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$), 0.77 (q, J = 7.8 Hz, 6H, $Si(CH_2CH_3)_3$), 0.80 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 1.04 (t, J = 7.8 Hz, 9H, $Si(CH_2CH_3)_3$), 1.90 (s, 3H, $CH_3C{=}C$), 7.04−7.35 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.69, 5.17, 6.44, 6.65, 16.73, 93.89, 124.66, 127.50, 128.72, 141.88, 147.72; LR FAB^+-MS m/z 342 ($[M]^+$, $C_{18}H_{38}O_2Si_2$ requires 342.7).

1,1-Bis(trimethylsilyloxy)-2-phenylbutene (5b): IR (film) 2961, 1655 (C=C), 1254, 1211, 1138, 994, 849, 758, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.09 (s, 9H, $Si(CH_3)_3$), 0.29 (s, 9H, $Si(CH_3)_3$), 0.92 (t, J = 7.5 Hz, 3H, CH_3CH_2), 2.37 (q, J = 7.5 Hz, 2H, CH_3CH_2), 7.08−7.33 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.03, 0.37, 13.50, 23.62, 101.49, 124.89, 127.54, 129.40, 140.40, 146.79; LR FAB^+-MS m/z 308 ($[M]^+$, $C_{16}H_{28}O_2Si_2$ requires 308.6).

1,1-Bis(trimethylsilyloxy)-2-(4-isobutylphenyl)propene (5c): IR (film) 2957, 1654 (C=C), 1254, 1213, 1140, 1067, 961, 849, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.05 (s, 9H, $Si(CH_3)_3$), 0.28 (s, 9H, $Si(CH_3)_3$), 0.90 (d, J = 6.6 Hz, 6H, $(CH_3)_2CH$), 1.85 (m, 1H, $(CH_3)_2CH$), 1.90 (s, 3H, $CH_3C{=}C$), 2.43 (d, J = 7.1 Hz, 2H, $(CH_3)_2CHCH_2$), 7.02 (d, J = 8.2 Hz, 2H, ArH), 7.28 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.05, 0.41, 16.55, 22.35, 30.32, 45.15, 94.40, 128.27, 128.30, 138.03, 138.85, 147.01; LR FAB^+-MS m/z 350 ($[M]^+$, $C_{19}H_{34}O_2Si_2$ requires 350.7).

1,1-Bis(trimethylsilyloxy)-2-(6′-methoxy-2′-naphthyl)propene (5d): IR (CCl_4) 1655, 1605, 1480, 1254, 1200, 1134, 916, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.04 (s, 9H, $Si(CH_3)_3$), 0.02 (s, 9H, $Si(CH_3)_3$), 1.99 (s, 3H, $CH_3C{=}C$), 3.91 (s, 3H, OCH_3), 7.00−7.10 (m, 2H, ArH), 7.58−7.71 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.07, 0.41, 16.53, 55.08, 94.36, 105.43, 118.24, 125.54, 126.15, 128.23, 128.93, 129.04, 132.27, 136.88, 147.45, 156.96; LR FAB^+-MS m/z 374 ($[M]^+$, $C_{20}H_{30}O_3Si_2$ requires 374.6).

1,1-Bis(triethylsilyloxy)-2-methoxy-2-phenylethene (5e): IR (film) 2957, 1650 (C=C), 1597, 1458, 1414, 1262, 1138, 1026, 799, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.69 (q, J = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$), 0.82 (q, J = 7.8 Hz, 6H, $Si(CH_2CH_3)_3$), 0.95 (t, J = 7.9 Hz, 9H, $Si(CH_2CH_3)_3$), 1.03 (t, J = 7.8 Hz, 9H, $Si(CH_2CH_3)_3$), 3.48 (s, 3H, OCH_3), 7.07−7.58 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 5.08, 5.12, 6.54, 6.72, 58.62, 123.04, 124.71, 125.92, 127.73, 135.26, 146.10; LR FAB^+-MS m/z 394 ($[M]^+$, $C_{21}H_{38}O_3Si_2$ requires 394.7).

Preparation of Ketene Bis(trimethylsilyl) Acetals 5f−i.[12d] To a solution of LiHMDS (28 mmol) in THF (15 mL) was added a solution of the carboxylic acid (10 mmol) in THF (50 mL) dropwise with stirring at −78 °C, which was continued at −78 °C for a further 1 h. Excess trimethylsilyl chloride (28 mmol) was added dropwise over 5 min, and the reaction mixture was allowed to come to ambient temperature over 5 h with stirring. It was then filtered by suction through a pad of Celite, and concentrated using a rotary evaporator. The residue was taken up in ether (5 mL), and filtration and concentration were repeated. Distillation in vacuo (0.4 Torr) of the residue gave the ketene bis(trimethylsilyl) acetals, ca. 90%.

1,1-Bis(trimethylsilyloxy)-2-fluoro-2-phenylethene (5f): IR (film) 2961, 1676, 1283, 1256, 1136, 1042, 922, 847, 758, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.27 (s, 9H, $Si(CH_3)_3$), 0.30 (d, J = 1.8 Hz, 9H, $Si(CH_3)_3$), 7.12 (t, J = 7.5 Hz, 1H, ArH), 7.31 (t, J = 7.5 Hz, 2H, ArH), 7.54 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.47, 0.57 (d, J = 3.8 Hz), 30.47 (d, J = 113.3 Hz), 89.63 (d, J = 186.1 Hz), 122.86 (d, J = 7.7 Hz), 124.99, 127.97 (d, J = 2.6 Hz), 142.98 (d, J = 41.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −171.61 (s).

1,1-Bis(trimethylsilyloxy)-2-chloro-2-phenylethene (5g): IR (film) 2961, 1644, 1254, 1051, 920, 945, 847, 758, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 9H, $Si(CH_3)_3$), 0.34 (s, 9H, $Si(CH_3)_3$), 7.15 (t, J = 7.5 Hz, 1H, ArH), 7.28 (t, J = 7.5 Hz, 2H, ArH), 7.56 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.06, 0.54, 96.71, 126.12, 127.60, 128.44, 136.87, 148.43.

1,1-Bis(trimethylsilyloxy)-2-bromo-2-phenylethene (5h): IR (film) 2961, 1640, 1266, 1254, 1049, 1028, 928, 847, 756, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 9H, $Si(CH_3)_3$), 0.37 (s, 9H, $Si(CH_3)_3$), 7.15 (t, J = 7.5 Hz, 1H, ArH), 7.27 (t, J = 7.5 Hz, 2H, ArH), 7.51 (d, J = 7.5 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.07, 0.46, 86.19, 126.43, 127.62, 129.86, 138.12, 158.87.

1,1-Bis(trimethylsilyloxy)-2-chloro-2-(4-bromophenyl)ethene (5i): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9H, $Si(CH_3)_3$), 0.33 (s, 9H, $Si(CH_3)_3$), 7.39 (d, J = 9.0 Hz, 2H, ArH), 7.46 (d, J = 9.0 Hz, 2H, ArH).

Representative Procedure for the Enantioselective Protonation of Silyl Enol Ethers 3 with Stoichiometric Amounts of (*R*)-1·$SnCl_4$. A heat-gun-dried 25 mL Schlenk flask containing (*R*)-**1** (0.094 g, 0.33 mmol) was charged with dry toluene (6.6 mL, distilled from CaH_2). A solution of tin tetrachloride (0.3 mL, 0.3 mmol, 1.0 M) in dichloromethane (or hexane) was added dropwise at room temperature. After being stirred for 5 min at that temperature, the mixture was cooled to −78 °C. Then starting material **3** (0.3 mmol) was added dropwise. After being stirred for several hours at −78 °C, the mixture was poured into saturated ammonium chloride, extracted with ether twice, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (eluent, 10:1 to 5:1 hexanes−ethyl acetate) gave the pure product **4** as a white solid. The enantiomeric excess of ketones was determined by HPLC analysis.

Representative Procedure for the Enantioselective Protonation of Silyl Enol Ethers 3 with Catalytic Amounts of (*R*)-2·$SnCl_4$. Under an argon atmosphere, to a solution of **7** (0.041 g, 0.33 mmol) in toluene (5 mL) were added a solution of (*R*)-BINOL-Me **2** (1 mL, 0.006 mmol, 6 mM) in toluene and a solution of tin tetrachloride (0.15 mL, 0.15 mmol, 1 M) in dichloromethane. The mixture was stirred at ambient temperature for 0.5 h. The solution was then cooled to −80 °C, and a solution of **3** (0.3 mmol) in toluene (0.9 mL) was added dropwise along the wall of the flask over a period of 2 h. After being stirred for a further 5 min, the mixture was poured into saturated ammonium chloride, extracted with ether twice, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (eluent, 10:1 to 5:1 hexanes−ethyl acetate) gave the pure corresponding ketone **4** as a white solid. The enantiomeric excess was determined by HPLC analysis.

Determination of Enantiomeric Excesses and Absolute Configurations of 2-Arylcycloalkanones Produced by Enantioselective Protonation of 2-Aryl-1-(trialkylsilyloxy)cyclohex-1-enes Using (*R*)-1·$SnCl_4$ or (*R*)-2·$SnCl_4$ (Tables 1, 3, and 7). Enantiomeric ratios were determined by analytical HPLC or chiral GC of the ketones. The absolute configurations were determined by comparison of optical rotation values with literature data.

(*S*)-(−)-2-Phenylcyclohexanone (4a) (entry 1 in Table 1):[2m,30a] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 200:1, flow rate 1 mL/

(29) Gotthardt, H.; Weisshuhn, M. C.; Christl, B. *Chem. Ber.* **1976**, *109*, 9 (2), 740.

(30) (a) Berti, G.; Macchia, B.; Macchia, F.; Menti, L. *J. Chem. Soc. C* **1971**, 3371. (b) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

min) t_R = 17.4 ((*S*)-(−)-enantiomer), 20.2 ((*R*)-(+)-enantiomer) min; $[\alpha]^{29}_D = -93.0°$ (*c* = 1.01, $CHCl_3$) for 91% ee of the product.

(*S*)-(−)-2-(4-Methylphenyl)cyclohexanone (4c) (entry 3 in Table 1):[2m] HPLC (Daicel As column, hexane:*i*-PrOH = 19:1, flow rate 0.5 mL/min) t_R = 13.9 ((*R*)-(+)-enantiomer), 16.4 ((*S*)-(−)-enantiomer) min; $[\alpha]^{27}_D = -65.6°$ (*c* = 0.75, $CHCl_3$) for 82% ee of the product.

(*S*)-(−)-2-(4-Methoxyphenyl)cyclohexanone (4d) (entry 4 in Table 1):[2m] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 19:1, flow rate 1.0 mL/min) t_R = 9.1 ((*S*)-(−)-enantiomer), 11.0 ((*R*)-(+)-enantiomer) min; $[\alpha]^{29}_D = -83.0°$ (*c* = 1.00, $CHCl_3$) for 96% ee of the recrystallized product.

(*S*)-(−)-2-(2-Naphthyl)cyclohexanone (4e) (entry 5 in Table 1):[2m,26] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 19:1, flow rate 0.5 mL/min) t_R = 18.4 ((*S*)-(−)-enantiomer), 21.5 ((*R*)-(+)-enantiomer) min; $[\alpha]^{26}_D = -97.9°$ (*c* = 0.64, $CHCl_3$) for the recrystallized product (99% ee).

(*R*)-(−)-2-Methylcyclohexanone (4g) (entry 4 in Table 3):[31] GC (γ-TA, 100 kPa, column temperature 60 °C) t_R = 10.80 ((*S*)-(+) enantiomer), 12.02 ((*R*)-(−)-enantiomer) min; $[\alpha]^{29}_D = -8.13°$ (*c* = 0.70, $CHCl_3$) for 51% ee of the product.

(*R*)-(−)-2-Chlorocyclohexanone (4h) (entry 1 in Table 3):[32] GC (γ-TA, 100 kPa, column temperature 75 °C) t_R = 24.5 ((*S*)-(+) enantiomer), 28.5 ((*R*)-(−)-enantiomer) min; $[\alpha]^{30.3}_D = -39.7°$ (*c* = 0.235, $CHCl_3$) for 87% ee of the product.

(*R*)-(−)-2-Bromocyclohexanone (4i) (entry 2 in Table 3):[33] GC (γ-TA, 100 kPa, column temperature 80 °C for 5 min and then warm to 140 °C (+1.0 °C/min)) t_R = 18.0 ((*S*)-(+) enantiomer), 21.0 ((*R*)-(−)-enantiomer) min; $[\alpha]^{28.3}_D = -176.7°$ (*c* = 1.00, CCl_4) for 88% ee of the product.

(−)-2-Phenylcycloheptanone (9) (entry 1 in Table 7):[27] HPLC (Daicel AS column (210 nm), hexane:*i*-PrOH = 20:1, flow rate 1 mL/min) t_R = 8.1 ((+)-enantiomer), 10.5 ((−)-enantiomer) min; $[\alpha]^{24}_D = -100.6°$ (*c* = 1.00, $CHCl_3$) for 84% ee of the product.

Representative Procedure for the Enantioselective Protonation of Ketene Disilyl Acetals 5 with Stoichiometric Amounts of (*R*)-1·$SnCl_4$. A heat-gun-dried 25 mL Schlenk flask containing (*R*)-**1** (0.094 g, 0.33 mmol) was charged with dry toluene or CH_2Cl_2 (6.6 mL, distilled from CaH_2). A solution of tin tetrachloride (0.3 mL, 0.3 mmol, 1.0 M) in dichloromethane (or hexane) was added dropwise at room temperature. After being stirred for 5 min at that temperature, the mixture was cooled to −78 °C. Then starting material **5** (0.3 mmol) was added dropwise. After being stirred for several hours at −78 °C, the reaction mixture was poured into 1 N HCl and extracted with ethyl acetate twice, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (eluent, 10:1 to 5:1 hexanes−ethyl acetate and then ethyl acetate alone) provided the pure carboxylic acid **6** as a white solid. The enantiomeric excess was determined by esterification with $TMSCH_2N_2$ in methanol and HPLC analysis.

Representative Procedure for the Enantioselective Protonation of Ketene Disilyl Acetals 5 with Catalytic Amounts of (*R*)-2·$SnCl_4$. Under an argon atmosphere, to a solution of **7** (0.041 g, 0.33 mmol) in toluene (5 mL) were added a solution of (*R*)-BINOL-Me **2** (1 mL, 0.01 mmol, 10 mM) in toluene and a solution of tin tetrachloride (0.08 mL, 0.008 mmol, 0.1 M) in dichloromethane. The mixture was stirred at ambient temperature for 0.5 h. The solution was then cooled to −80 °C, and a solution of **5** (0.9 mL, 0.3 mmol, 0.33 M) in toluene was added dropwise along the wall of the flask over a period of 2 h. After being stirred for a further 5 min, the reaction mixture was poured into 1 N HCl and extracted with ethyl acetate twice, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (eluent, 10:1 to 5:1 hexanes−ethyl acetate and then ethyl acetate alone) provided the pure carboxylic acid **6** as a white solid. The enantiomeric excess was determined by esterification with $TMSCH_2N_2$ in methanol and HPLC analysis.

Determination of Enantiomeric Excesses and Absolute Configurations of 2-Arylcarboxylic Acids Produced by Enantioselective Protonation of Ketene Bis(trialkylsilyl) Acetals Using (*R*)-1·$SnCl_4$ (Tables 2 and 4). Enantiomeric ratios were determined by analytical HPLC of the methyl 2-arylcarboxylates. The absolute configurations of the methyl esters were determined by comparison of optical rotation values with literature data.

(*S*)-(+)-Methyl 2-Phenylpropanoate (entry 1 in Table 2):[34] HPLC (Daicel OJ column, hexane:*i*-PrOH = 9:1, flow rate 1.0 mL/min) t_R = 9.6 ((*S*)-(+)-enantiomer), 11.0 ((*R*)-(−)-enantiomer) min; $[\alpha]^{29}_D = 86.2°$ (*c* = 1.01, $CHCl_3$) for 92% ee of the methyl ester.

(*S*)-(+)-Methyl 2-Phenylbutanoate (entry 3 in Table 2):[34b,35] HPLC (Daicel AS column, hexane:*i*-PrOH = 400:1, flow rate 0.5 mL/min) t_R = 11.3 ((*S*)-(+)-enantiomer), 12.3 ((*R*)-(−)-enantiomer) min; $[\alpha]^{31}_D = 57.8°$ (*c* = 1.45, $CHCl_3$) for 60% ee of the methyl ester.

(*S*)-(+)-Methyl 2-(4-isobutylphenyl)propionate (methyl ester of ibuprofen) (entry 4 in Table 2):[34b,36] HPLC (Daicel AS column, hexane:*i*-PrOH = 400:1, flow rate 0.5 mL/min) t_R = 9.5 ((*S*)-(+)-enantiomer), 10.1 ((*R*)-(−)-enantiomer) min; $[\alpha]^{29}_D = 59.5°$ (*c* = 1.05, $CHCl_3$) for 94% ee of the methyl etser.

(*S*)-(+)-Methyl 2-(6′-methoxy-2′-naphthyl)propionate (methyl ester of naproxen) (entry 5 in Table 2):[34b,37] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 19:1, flow rate 0.5 mL/min) t_R = 10.5 ((*R*)-(−)-enantiomer), 11.5 ((*S*)-(+)-enantiomer) min; $[\alpha]^{29}_D = 84.1°$ (*c* = 1.00, $CHCl_3$) for 92% ee of the methyl ester.

(*S*)-(+)-Methyl 2-methoxy-2-phenylacetate (entry 6 in Table 2):[38] HPLC (Daicel OJ column, hexane:*i*-PrOH = 9:1, flow rate 1 mL/min) t_R = 6.9 ((*R*)-(−)-enantiomer), 17.2 ((*S*)-(+)-enantiomer) min; $[\alpha]^{23}_D = 77.5°$ (*c* = 1.01, acetone) for 87% ee of the methyl ester.

(+)-Methyl 2-fluoro-2-phenyacetate (entry 1 in Table 4):[18] ^{19}F NMR ($CDCl_3$, 282 MHz) δ −180.52 (d, *J* = 48.8 Hz); HPLC (Daicel OD-H column, hexane:*i*-PrOH = 20:1, flow rate 1.0 mL/min,), t_R = 6.06 ((−)-enantiomer), 6.83 ((+)-enantiomer) min; $[\alpha]^{25}_D = 74.2°$ (*c* = 1.01, acetone) for 70% ee of the methyl ester.

(*S*)-(+)-Methyl 2-chloro-2-phenyacetate (entry 2 in Table 4):[39] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 20:1, flow rate 1.0 mL/min,), t_R = 5.5 ((*R*)-(−)-enantiomer), 5.8 ((*S*)-(+)-enantiomer) min; $[\alpha]^{25}_D = 94.0°$ (*c* = 1.01, acetone) for 91% ee of the methyl ester.

(*S*)-(+)-Methyl 2-bromo-2-phenyacetate (entry 3 in Table 4):[39] HPLC (Daicel OD-H column, hexane:*i*-PrOH = 20:1, flow rate 1.0 mL/min), t_R = 5.4 ((*R*)-(−)-enantiomer), 6.1 ((*S*)-(+)-enantiomer) min; $[\alpha]^{25}_D = 94.2°$ (*c* = 1.00, acetone) for 83% ee of the methyl ester.

(*S*)-(+)-Methyl 2-chloro-2-(*p*-bromo)phenyacetate (entry 4 in Table 4):[39] HPLC (Daicel OJ column, hexane:*i*-PrOH = 20:1, flow rate 1.0 mL/min), t_R = 14.7 ((*R*)-(−)-enantiomer), 15.7 ((*S*)-(+)-enantiomer) min; $[\alpha]^{25}_D = 93.2°$ (*c* = 1.00, acetone) for 84% ee of the methyl ester.

Computational Methods

The geometries of all the structures have been optimized using the hybrid B3LYP as implemented in the Gaussian98[40] package of ab initio programs on Indigo2 R10000. All optimized structures were verified by vibrational frequency calculations. Previous ab initio calculations[41] of the compounds including Sn were made using a 6-31G or LANL2MB basis set; however, we used a LANL2DZ[42] basis set for our studies because heavy metal atoms are well expressed using the ECP-type basis sets. Diffuse functions and polarization functions on O and Cl ($\alpha_{O,diffuse}$ = 0.0483, $\alpha_{O,polarization}$ = 0.85, $\alpha_{Cl,diffuse}$ = 0.0845, $\alpha_{Cl,polarization}$ = 0.60)

(31) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.
(32) Crumbie, R.; Ridley, D. D.; Simpson, G. W. *J. Chem. Soc., Chem. Commun.* **1977**, 315.
(33) (a) Dauphin, G.; Kergomard, A.; Scarset, A. *Bull. Soc. Chim. Fr.* **1976**, 862. (b) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 54.
(34) (a) Yamashita, T.; Yasuda, H.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2165. (b) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.
(35) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1992**, *57*, 2166.
(36) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.
(37) Piccolo, O.; Spreafico, F.; Visentin, G.; Valoti, E. *J. Org. Chem.* **1987**, *52*, 10.
(38) Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.
(39) Absolute configurations were confirmed by comparison with authentic samples derived from natural chiral mandelic acid derivatives. See ref 15a.

and polarization functions on Sn ($\alpha_{O,polarization} = 0.183$) were used.[43] Calculations of the biphenol·$SnCl_4$ complex at the RHF/LANL2DZ level in our previous report on enantioselective ene cyclization[9c] showed Hatree−Fock instability; the DFT calculations exhibited the difference between biphenol·$SnCl_4$ and biphenol·$TiCl_4$, which was inefficient for the enantioselective protonation mentioned above. Taking all into consideration, the B3LYP/LANL2DZ level is much more suitable to study these reagents. All charges were calculated using the NBO program.[22]

Acknowledgment. We thank Drs. Hiroaki Wasada and Yuko Wasada for helpful discussion on the DFT calculations.

Supporting Information Available: **Z**-matrixes of the optimized structures shown in Figures 3 and 4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001164I

(40) Gaussian 98 (Revision A.6): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA, 1998.

(41) (a) Vincent, M. A.; Hillier, I. H.; Hall, R. J.; Thomas, E. J. *J. Org. Chem.* **1999**, *64*, 4680. (b) Yamazaki, S.; Kumagai, H.; Yamada, S.; Yamamoto, K. *J. Org. Chem.* **1998**, *63*, 3371. (c) Yamazaki, S.; Takada, T.; Imanishi, T.; Moriguchi, Y.; Yamabe, S. *J. Org. Chem.* **1998**, *63*, 5919.

(42) (a) Dunning, T. H., Jr. *J. Chem. Phys.* **1970**, *53*, 2823. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 270.

(43) (a) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (b) Huzinaga, S.; Andzelm, J.; Klobukowski, M.; Radzio-Andzelm, E.; Sakai, Y.; Tatewaki, H. *Physical Sciences Data 16: Gaussian Basis Sets for Molecular Calculations*; Elsevier: Amsterdam, 1984; 23.