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The Crystallographic Structure of a Lewis Acid-Assisted Chiral Brønsted Acid as an Enantioselective Protonation Reagent for Silyl Enol Ethers

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It is difficult to control the enantioselectivity in the protonation of silyl enol ethers with chiral Brønsted acids, mainly due to bond flexibility between the proton and its chiral counterion, the orientational flexibility of the proton, and the fact that the proton sources available are limited to acidic compounds such as carboxylic acids. To overcome these difficulties, we have developed a Lewis acid-assisted chiral Brønsted acid (LBA) system.[1,2] The coordination of Lewis acids with Brønsted acids restricts the orientation of protons and increases their acidity. Optically active binaphthol (BINOL) derivative·$SnCl_4$ complexes are very effective as enantioselective protonation reagents for silyl enol ethers.[1] However, their exact structures have not yet been determined.[3] We describe here optically active 1,2-diarylethane-1,2-diol derivative·$SnCl_4$ as a new type of LBA for the enantioselective protonation as well as its crystallographic structure.

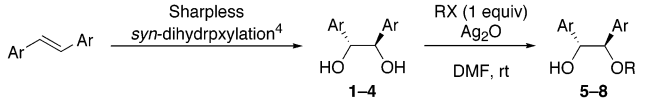
As shown in Scheme 1, (*R*,*R*)-**2**−**4** were prepared in high chemical and optical yields by Sharpless *syn*-dihydroxylation of the corresponding (*E*)-1,2-diarylethenes, which were in turn obtained by McMurry or Wittig reactions.[4] The selective monoetherification[5] of **2**−**4** effectively increased their solubility in organic solvents.

The enantioselective protonation of **9** was examined using (*R*,*R*)-**1**−**4** (1.1 equiv) and $SnCl_4$ (1.1 equiv) (Table 1). The reaction proceeded in CH_2Cl_2 at −78 °C and gave (*S*)-**10** with 96% ee (entry 4). The same enantioselectivity was observed using (*R*,*R*)-**6** (entry 5). (*R*,*R*)-**4** was almost insoluble under the above conditions, while (*R*,*R*)-**6** dissolved in CH_2Cl_2 and toluene even at −78 °C. The enantioselectivity was somewhat diminished in toluene (entry 6). In contrast, in the presence of commercially available (*R*,*R*)-hydrobenzoin (**1**) and $SnCl_4$, protonation did not proceed completely at −78 °C, and the ee value was relatively low (entry 1). (*R*,*R*)-**2** and **3** exhibited good reactivity, but the ee values were low (entries 2 and 3).

Monoalkyl ethers (*R*,*R*)-**6**−**8** were examined for the enantioselective protonation of various silyl enol ethers in the presence of $SnCl_4$. The results are summarized in Table 2. The corresponding ketones and carboxylic acids were isolated in quantitative yield. High enantioselectivities were observed for the protonation of trimethylsilyl enol ethers derived from aromatic ketones and ketene bis(trimethylsilyl)acetals derived from 2-arylalkanoic acids.[6] Although dichloromethane was used for the protonation of silyl enol ethers, toluene was a better solvent for highly reactive ketene bis(trimethylsilyl)acetals, because the protonation proceeded more quickly in a polar solvent. The scope of substrates that are suitable for enantioselective protonation was extended by using the new chiral LBA complexes in place of (*R*)-BINOL derivatives·$SnCl_4$. For example, the enantioselectivities in the protonation of silyl enol ether derived from **11** and ketene disilylacetal derived from **17** were increased from 37 to 83% ee (entry 1) and from 37 to 76% ee (entry 7), respectively. Nonsteroidal antiinflammatory drugs[7] such as naproxen (**12**)[7] and ibuprofen (**13**) were obtained with 86 and 90% ee, respectively (entries 2 and 3). The absolute stereopreference for ketene bis(trimethylsilyl) acetals was similar to that for **9**.

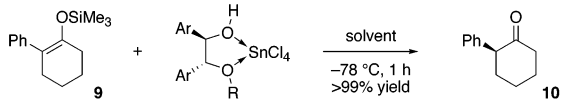
To understand the absolute stereopreference in the protonation, the crystallization of LBA was attempted. In most cases, however, $SnCl_4$-free Brønsted acids were preferentially crystallized in the presence of $SnCl_4$, because Brønsted acid·$SnCl_4$ was less likely to undergo crystallization than was Brønsted acid, and the complexation was reversible.[3] Fortunately, a colorless crystal of (*R*,*R*)-**5**·$SnCl_4$ was obtained from a 1:1 molar mixture of (*R*,*R*)-**5** and $SnCl_4$ in dichloromethane at 0 °C. This result can be explained in terms of the relatively tight complexation between $SnCl_4$ and (*R*,*R*)-**5**, which is less acidic than (*R*,*R*)-**6**−**8** and (*R*)-BINOL derivatives. Single-crystal X-ray diffraction analysis of this LBA revealed the structure shown in Figure 1. Although the activated proton (H_{act}) in (*R*,*R*)-**5**·$SnCl_4$ could not be located exactly, the high electron density was certainly distributed in the pseudoequatorial direction. Interestingly, the apical Sn1−Cl3 bond is ca. 0.05 Å longer than

Scheme 1. Preparation of (*R*,*R*′)-1,2-Diarylethane-1,2-diol Derivatives[a]



[a] **1** (Ar = Ph), >99% ee; **2** (Ar = 3,4,5-$F_3C_6H_2$), ee was not determined; **3** (Ar = C_6F_5), 82% ee → 94% ee after recrystallization; **4** (Ar = 3,5-$(CF_3)_2C_6H_3$), >99% ee; **5** (Ar = Ph, R = Me), >99% ee; **6** (Ar = 3,5-$(CF_3)_2C_6H_3$, R = Bn), >99% ee; **7** (Ar = 3,5-$(CF_3)_2C_6H_3$, R = *o*-$FC_6H_4CH_2$), >99% ee; **8** (Ar = 3,5-$(CF_3)_2C_6H_3$, R = Me), >99% ee.

Table 1. Enantioselective Protonation of **9** with (*R*,*R*)-LBAs[a]



entry	chiral Brønsted acid[b]	solvent	ee (%) [config.][c]
1[d]	**1**	toluene−CH_2Cl_2 (1:1 (v/v))	66 [*S*]
2	**2**[e]	CH_2Cl_2	51 [*S*]
3	**3**[f]	CH_2Cl_2	35 [*R*]
4	**4**	CH_2Cl_2	96 [*S*]
5	**6**	CH_2Cl_2	96 [*S*]
6	**6**	toluene	91 [*S*]

[a] A 0.2 M solution of **9** (0.1 mmol) was added dropwise to a solution of chiral Brønsted acid (0.11 mmol) and $SnCl_4$ (0.11 mmol) over a 5 min period at −78 °C. [b] Unless otherwise noted, >99% ee of chiral Bronsted acids was used. [c] The ee value of **10**. [d] The reaction was carried out at −78 °C for 1.5 h, but some **9** remained. [e] The ee value of **2** ($[\alpha]^{26.6}_D$ = −54.0 (*c* 0.36, $CHCl_3$)) was unknown. [f] 94% ee of **3** was used.

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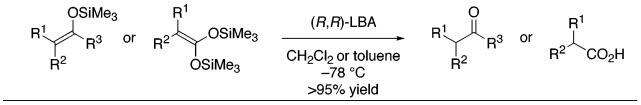
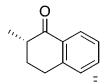
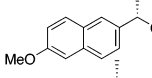
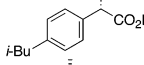
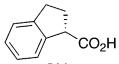
Table 2. Enantioselective Protonation of Silyl Enol Ethers or Ketene Disilyl Acetals with (*R*,*R*)-LBAs



entry	LBA	solvent	product		ee (%) [config.][a]
1	(*R*,*R*)-**6**•$SnCl_4$	CH_2Cl_2		**11**	83 [*S*] *cf.* 37 [*S*][b]
2	(*R*,*R*)-**7**•$SnCl_4$	toluene		**12**	86 [*S*]→98 [*S*][c]
3	(*R*,*R*)-**7**•$SnCl_4$	toluene		**13**	90 [*S*]
4	(*R*,*R*)-**8**•$SnCl_4$	toluene		**14**	90 [*S*]
5	(*R*,*R*)-**7**•$SnCl_4$	toluene		**15**	85 [*S*]
6	(*R*,*R*)-**7**•$SnCl_4$	toluene		**16**	85 [*S*]
7	(*R*,*R*)-**6**•$SnCl_4$	toluene		**17**	76 [*S*] *cf.* 37 [*R*][b]

[a] The ee values were determined by HPLC or GC analysis of ketones or methyl esters derived from carboxylic acids (cat. $HfCl_4$•$(THF)_2$ in MeOH).[8] [b] The ee values are indicated when (*R*)-BINOL derivatives•$SnCl_4$ were used in toluene. [c] The ee value after recrystallization from a CH_2Cl_2−hexane bilayer system.

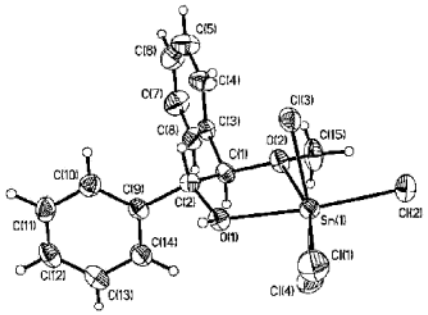


Figure 1. ORTEP drawing of (*R*,*R*)-**5**•$SnCl_4$ (the O1−H_{act} bond distance shown here is not certain, but its direction could be determined). Selected distances (Å): O1−H_{act} = 0.72(3), Sn1−Cl3 = 2.40185(5), Sn1−Cl4 = 2.3522(6), intermolecular H_{act}···C13 = 2.402. Torsion angles (deg): Cl3−Sn1−O1−H_{act} = −64, Cl1−Sn1−O1−H_{act} = 30. Bond angles (deg): Sn1−O1−H_{act} = 119(2), C2−O1−H_{act} = −64(2), intermolecular O1−H_{act}···Cl3 = 171.11.

the apical Sn1−Cl4 bond due to the intermolecular hydrogen bonding interaction between H_{act} and Cl3. The protonation of **9** using crystalline (*R*,*R*)-**5**•$SnCl_4$ in dichloromethane at −78 °C gave (*S*)-**10** with 58% ee (cf. entry 1 in Table 1: (*S*)-**10** with 66% ee). This result supports the idea that the X-ray structure for (*R*,*R*)-**5**•$SnCl_4$ is a real species of the protonation reagent.

The driving force in the enantioselective protonation is the OH/π interaction between its π-bond orbital (HOMO) and the activated proton (LUMO). It has been known that a linear O−H···π bonding interaction has the most preferable direction along with a hydrogen bonding interaction.[9] Therefore, the prochiral face of silyl enol ether would approach the activated proton of LBA perpendicular to its H−O bond.

The direction of the H−O bond in (*R*,*R*)-**8** can be fixed by chelation with $SnCl_4$. On the basis of the X-ray diffraction analysis of LBA and a linear OH/π interaction, the absolute stereopreference in the enantioselective protonation of ketene disilylacetal derived

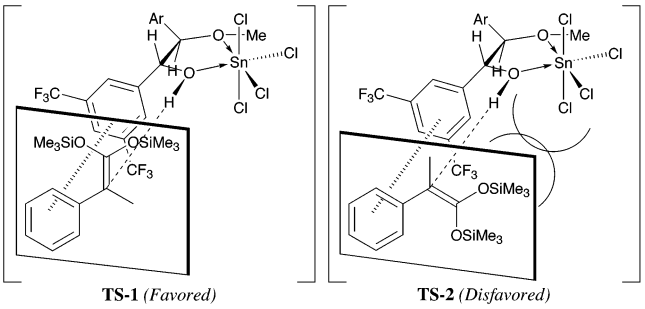


Figure 2. Proposed tranition-state assemblies.

from **14** with (*R*,*R*)-**8**•$SnCl_4$ can be understood in terms of two proposed transition-state assemblies, **TS-1** and **TS-2**, shown in Figure 2. The ketene disilyl acetal should approach (*R*,*R*)-**8**•$SnCl_4$ from the *re*-face via the favored **TS-1** due to the $\pi-\pi$ electronic attractive interaction between a Ph group of the substrate and a 3,5-$(CF_3)_2C_6H_3$ group closer to the H_{act}, while the approach from the *si*-face via **TS-2** would not be favorable due to steric repulsion between Me_3SiO groups and an $SnCl_4$ or CF_3 group.[6] This model can be adopted for all cases shown in Tables 1 and 2.[10]

The most significant finding is that we were able to specify the conformational direction of the H−O bond of LBA, which has some asymmetric inductivity, by X-ray diffraction analysis. The stereochemical course in the enantioselective protonation would be controlled by a linear OH/π interaction with an initial step. The absolute stereopreference in enantioselective reactions using BINOL•$SnCl_4$ can also be explained in terms of this uniformly mechanistic interpretation.[1,2]

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Supporting Information Available: Experimental procedures, spectral data for all new compounds (PDF), and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) Only $SnCl_4$-free BINOL derivatives crystallized from a 1:1 mixture of BINOL derivatives and $SnCl_4$.

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(10) The opposite absolute stereopreference observed in entry 3, Table 1 is probably due to some unexpected interactions between *o*-F and H_{act}, Sn(IV), or Si(IV).

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