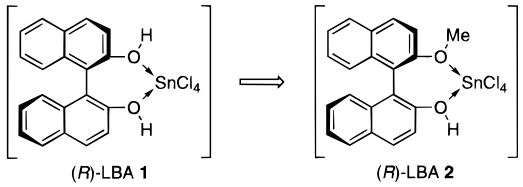
First Example of a Highly Enantioselective Catalytic Protonation of Silyl Enol Ethers Using a Novel Lewis Acid-Assisted Brønsted Acid System

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

Graduate School of Engineering, Nagoya University
Furo-cho, Chikusa, Nagoya 464-01, Japan

Received July 15, 1996

The recent development of the enantioselective protonation of enolates using stoichiometric or catalytic amounts of chiral proton sources has been one of the most useful advances in synthetic chemistry.[1,2] In most of these reactions, metal enolates are used under basic or neutral conditions. We recently reported that an optically active binaphthol (BINOL)−tin tetrachloride complex **1** is a highly effective chiral proton source for enantioselective protonation of a prochiral silyl enol ether, which is an isolable synthetic equivalent of enol or enolate.[3] We refer to this activated proton source as a Lewis acid-assisted Brønsted acid or LBA.[3] We report here catalytic systems for the enantioselective protonation of prochiral trimethylsilyl enol ethers using a novel chiral LBA **2**.[2]



(*R*)-LBA **1** (*R*)-LBA **2**

The rationale for the catalytic cycle for enantioselective protonation using LBA is outlined in Scheme 1. The catalytic cycle presupposes the following: (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 the achiral proton 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 LBA generated from the achiral proton source and tin tetrachloride must be much lower than that of the chiral proton source or its LBA.

On the basis of the above working hypothesis, we realized the LBA-catalyzed enantioselective protonation of trimethylsilyl enol ether **3** derived from racemic 2-phenylcyclohexanone. Representative results are summarized in Table 1. In the presence of stoichiometric amounts of tin tetrachloride as a Lewis acid and 2,6-dimethylphenol (**5**) as an achiral proton source in toluene, the protonation of **3** with (*R*)-2-hydroxy-2′-methoxy-1,1′-binaphthyl (BINOL-Me) (2−5 mol %) was accelerated and controlled sterically to form ketone **4** with high enantioselectivity (entries 1 and 2). Although a similar result was observed with the catalytic use of (*R*)-BINOL, the resulting enantioselectivity was only moderate (entry 3). Compound **5** 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

Scheme 1. The General Outline for the Catalytic Cycle for Enantioselective Protonation of Silyl Enol Ethers Using LBA

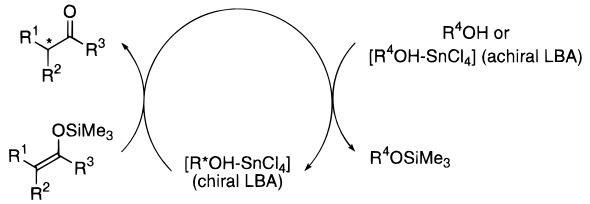
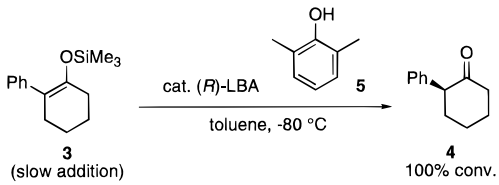


Table 1. Chiral LBA-Catalyzed Enantioselective Protonation of **3**[a]



3 (slow addition) **4** 100% conv.

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

[a] Unless otherwise noted, **3** (91% regioisomeric purity) was slowly added dropwise at −80 °C to a solution of (*R*)-BINOL-Me, **5**, and tin tetrachloride in toluene to give **4** in a quantitative yield. [b] Addition time of **3**. [c] Determined by HPLC analysis; values in parentheses were corrected for the regioisomeric purity of **3**. [d] A 3:2 toluene−CH_2Cl_2 solvent was used. [e] Compound **3** (>99% regioisomeric purity) was used. [f] The conversion was less than 48%. [g] See ref 3a for the procedure for the stoichiometric reaction. [h] See ref 5.

protonation in substoichiometric quantities (entries 4 and 5),[4] its use in less molar quantities than a chiral proton source remarkably lowered the reactivity (entry 6). The stoichiometric protonation of **3** with (*R*)-LBA **2** as well as (*R*)-LBA **1** gave **4** in excellent enantioselectivity (entries 7 and 8).[5]

To demonstrate that the scope of this strategy is not limited to silyl enol ethers derived from 2-arylcyclohexanones, we applied this catalytic system to ketene bis(trimethylsilyl) acetal **6** derived from racemic 2-phenylpropanoic acid (**7**). The results are summarized in Table 2. The protonation of **6** with (*R*)-BINOL-Me (10 mol %) in the presence of stoichiometric amounts of tin tetrachloride and **5** exhibited moderate enantioselectivity (entry 1). A high degree of enantioselectivity was attained using catalytic amounts of (*R*)-BINOL-Me (10 mol %) and tin tetrachloride (8 mol %) (entry 2).[6] Tin tetrachloride

(1) For reviews of enantioselective protonations, see: (a) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, II-421. (b) Waldmann, H. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 413.

(2) For recent studies on the catalytic enantioselective protonation of enolates under basic conditions, see: (a) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1044. (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.

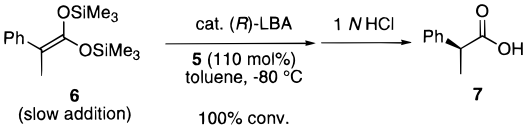
(3) (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. (b) Ishihara, K.; Nakamura, S.; Yamamoto, H. *Croat. Chem. Acta* **1996**, *69*, 513.

(4) Representative procedure for the enantioselective protonation of **3** catalyzed by (*R*)-**2** (Table 1, entry 5): Under an argon atmosphere, to a solution of **5** (41 mg, 0.33 mmol) in toluene (5 mL) were added a solution of (*R*)-BINOL-Me (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** (0.9 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 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 hexane−ethyl acetate) gave the pure product **4** (47 mg, 89% yield) as a white solid. The enantiomeric excess was determined to be 90% by HPLC analysis using a Daicel Chiral OD-H column, 200:1 hexane−*i*-PrOH with detection at 210 nm (elution times (1.0 mL/min flow) for the enantiomers of 22.7 (major, *S*) and 26.5 min (minor, *R*)).

(5) The increase in enantioselectivity for the protonation of **3** with (*R*)-**1** compared to that in our original paper[3a] is due to the use of **3** (purified by redistillation).

S0002-7863(96)02414-6 CCC: $12.00

Table 2. Chiral LBA-Catalyzed Enantioselective Protonation of **6**[a]

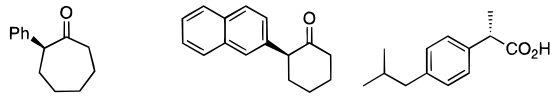


entry	chiral proton source, mol %	$SnCl_4$ (mol %)	time (h)[b]	ee (%)[c]
1	(*R*)-BINOL-Me, 10	110	1	68
2	(*R*)-BINOL-Me, 10	8	1	94
3	(*R*)-BINOL-Me, 5	4	2	80
4	(*R*)-BINOL, 5	4	2	22

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

efficiently promotes the protonation of **6** with (*R*)-BINOL-Me in less molar quantities than a chiral proton source, since **6** is much more reactive than **3**. In addition, (*R*)-BINOL-Me is far superior to (*R*)-BINOL as a chiral proton source in the catalytic protonation of **6** (entry 3 vs 4).

The procedures optimized for the catalytic enantioselective protonations of **3** and **6** have been applied to the synthesis of (−)-2-phenylcycloheptanone (**8**), (−)-2-(2-naphthyl)cyclohexanone (**9**),[3a] and (*S*)-(+)-ibuprofen (**10**).[3a]



(−)-**8** 84(97)% ee, 92% yield[7,8] (−)-**9** 91(95)% ee, 84% yield[8,9] *S*-(+)-**10** 93% ee, 80% yield[10]

The present study was prompted by our previous finding that a small amount of (*R*)-BINOL, together with the corresponding monosilyl ether, was observed by TLC, although the stoichiometric reaction of **3** with (*R*)-LBA **1** in toluene gave **4** in a quantitative yield.[11] The ^{1}H NMR spectrum of the reaction mixture in toluene-d_8 at −80 °C exhibited two singlets for the trimethylsilyl groups of the monosilyl ether of (*R*)-BINOL and chlorotrimethylsilane at −0.26 and 0.16 ppm, respectively, at a molar ratio of 85:15. *On the other hand, the ^{1}H NMR spectrum of the reaction mixture of **3** and (R)-LBA **2** at −80 °C exhibited only one singlet for chlorotrimethylsilane.* The formation of chlorotrimethylsilane lead us to anticipate the possibility of generating tin aryloxide intermediates **11** and **12** (Scheme 2).

The experimental results shown in Table 1 can be reasonably explained by supposing that the tin aryloxide intermediate **12** is reconverted to (*R*)-LBA **2** by receiving a proton and a chloride from **5** and chlorotrimethylsilane and/or tin tetrachloride,

Scheme 2. Tin Aryloxide Intermediates Predicted by ^{1}H NMR Analyses

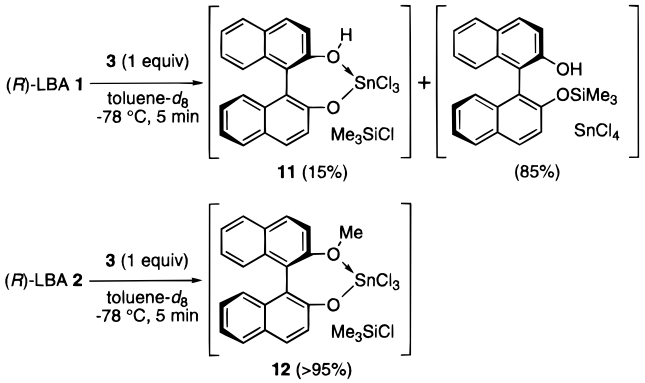


Table 3. Comparison of the Reactivities of LBAs in the Protonation of **3** to **4** at −78 °C

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

[a] A reaction time of 5 min was employed. The reaction was quenched with pyridine after 5 min since **3** was added to a solution of a stoichiometric amount of LBA in toluene at −78 °C over 3 min. [b] Determined by ^{1}H 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 **5** was ascertained by ^{1}H 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 **2** and excess **5**. Chelation between excess tin tetrachloride per chiral proton source and **5** prevents the deactivation of **2** and may promote proton transfer from **5** to **12**. Nevertheless, **5**−tin tetrachloride is not acidic enough to react predominantly with **3** in the presence of (*R*)-LBA **2**. The reactivity of **2** is certainly much greater than that with **5**−tin tetrachloride in toluene (Table 3).

The catalytic cycle for the enantioselective protonation of **6** catalyzed by (*R*)-LBA **2** is rather simple, since excess tin tetrachloride per chiral proton source is not added. In this case, **2** should be regenerated from intermediate **12** by acquiring a proton and a chloride from **5** and chlorotrimethylsilane, respectively. Considering the catalytic systems for both **3** and **6**, the protonation of **3** with LBA **2** 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 proposed catalytic cycles are supported by ^{1}H NMR analytical data, which strongly suggest the generation of chlorotrimethylsilane and tin aryloxide intermediates **11** and **12** *in situ*. These and other possible mechanisms are under further investigation, especially with regard to the design of more highly enantioselective catalytic systems.

Acknowledgment. This study was supported in part by a Grant-in-Aid for Scientific Study from the Ministry of Education, Science, and Culture of the Japanese Government.

Supporting Information Available: Experimental procedures and analytical data for all compounds (4 pages). See any current masthead page for ordering and Internet access instructions.

JA962414R

(6) Representative procedure for the enantioselective protonation of **6** catalyzed by (*R*)-**2** (Table 2, entry 2). The reaction was carried out similar to that described in ref 4. 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 hexane−ethyl acetate and then ethyl acetate alone) provided the pure product **7** (42 mg, 93% yield) as a white solid. The enantiomeric excess was determined to be 94% by esterification with $TMSCH_2N_2$ in methanol and HPLC analysis using a Daicel Chiral OJ column, 9:1 hexane−*i*-PrOH with detection at 210 nm (elution times (1.0 mL/min flow) for the enantiomers: 10.7 (major, *S*) and 12.7 min (minor, *R*)).

(7) The same reaction conditions with entry 2 in Table 1 were used.

(8) Values in parentheses were corrected for the regioisomeric purities of silyl enol ethers.

(9) The same reaction conditions with entry 2 in Table 1 were used except that tin tetrachloride concentration was reduced to 50 mol %.

(10) The same reaction conditions with entry 2 in Table 2 were used.

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