Lewis Acid Assisted Chiral Brønsted Acid for Enantioselective Protonation of Silyl Enol Ethers and Ketene Bis(trialkylsilyl) Acetals

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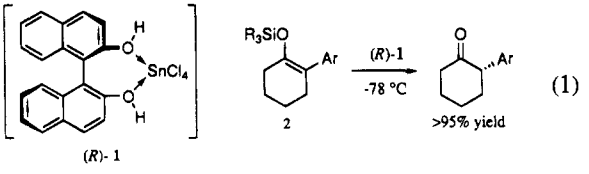
Enantioselective protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds.[1-6] Examples have been reported of protonation of metal enolates by chiral proton sources[2] and hydrolysis of enol esters catalyzed by enzymes[3] or antibodies.[4] All of these reactions involved enolates under basic or neutral conditions. The acid-promoted hydrolysis of enol ethers is an interesting alternative which has been little investigated for enantioselectivity.[5-7] Silyl enol ether, which is a synthetic equivalent of enol or enolate, is more stable than the corresponding metal enolate and can be isolated. Herein we report a new *Lewis acid assisted chiral Brønsted acid* (LBA)[8] for enantioselective protonation of prochiral silyl enol ethers and ketene bis(trialkylsilyl) acetals.

The LBA **1** as a new reagent for protonation was generated *in situ* from optically pure binaphthol and tin tetrachloride in toluene or dichloromethane at −78 °C. The protons in optically active binaphthol are activated by the coordination of tin tetrachloride. Silyl enol ethers **2** (Ar = Ph) derived from 2-phenylcyclohexanone were chosen for initial optimization study because **2** could be prepared as a single isomer (*Z*), and steric interactions between the phenyl group of **2** (Ar = Ph) and the naphthyl moiety of **1** were expected with the enantioselective protonation. Actually, in the presence of a stoichiometric amount of (*R*)-**1** in dichloromethane, the *C*-protonation of the trimethylsilyl enol ether **2** (Ar = Ph, R = Me)[9] proceeded even at −78 °C and was controlled sterically to form (*S*)-2-phenylcyclohexanone with good enantioselectivity (79% ee).



(1)

On the basis of the above observation, we studied the *O*-substituent (SiR_3)-dependent enantioselectivity of **1** (1 equiv), which promoted protonation of **2** (Ar = Ph, 1 equiv) in dichloromethane at −78 °C. The results of these experiments are summarized in Table 1. The enantioselectivity of the reaction was dramatically increased by using sterically bulky *O*-substituents. The protonation of the *tert*-butyldimethylsilyl enol ether **2** (Ar = Ph, SiR_3 = Si*t*-BuMe$_2$) occurred with excellent enantioselectivity (93% ee, entry 5). Further, the best result (96% ee) was achieved by using toluene as solvent (entry 6). In the present reaction, (*R*)-binaphthol was converted to a mixture of 2,2′-disiloxy-1,1′-binaphthyl and 2-siloxy-2′-hydroxy-1,1′-binaphthyl in dichloromethne solution, while it was converted to only the latter product in toluene. It was noted that the enantioselective protonation of **2** proceeded with a catalytic amount (10 mol %) of tin tetrachloride, which is known to be toxic (entry 3).

The enantioselective protonation of a variety of silyl enol ethers **2**,[9] derived from 2-arylcyclohexanones, with (*R*)-**1** under

Table 1. Enantioselective Protonation of **2** by **1** (Eq 1)[a]

entry	silyl enol ether **2**[b] Ar	R_3Si	solvent	time[c] (min)	ee (%) of product,[d] (config)-(rotn)
1	Ph	Me_3Si	CH_2Cl_2	5	79, (*S*)-(−)[e,f]
2[g]			CH_2Cl_2	5	81, (*S*)-(−)[e,f]
3[h]			CH_2Cl_2	23 × 60	77, (*S*)-(−)-[e,f]
4		Et_3Si	CH_2Cl_2	30	91, (*S*)-(−)[e,f]
5		*t*-BuMe_2Si	CH_2Cl_2	30	93, (*S*)-(−)[e,f]
6		*t*-BuMe_2Si	toluene	60	96, (*S*)-(−)[e,f]
7[i]		*t*-BuMe_2Si	toluene	60	96, (*R*)-(+)[e,f]
8	*p*-MeC_6H_4	*t*-BuMe_2Si	toluene	60	93, (−)[j]
9	*p*-$MeOC_6H_4$	*t*-BuMe_2Si	toluene−CH_2Cl_2	60	85, (−)[e]
10	2-naphthyl	Me_3Si	toluene	60	91, (−) → 99[e,k]
11		*t*-BuMe_2Si	toluene	60	91, (−)[e]

[a] Unless otherwise noted, the reactions were carried out using 1.1 equiv of (*R*)-binaphthol and 1.0 equiv of $SnCl_4$ at −78 °C. [b] The thermodynamic silyl enol ether **2** in an enriched regioisomeric ratio (>99:1 to about 90:10) was used. [c] Reaction times which were expanded on complete conversion were indicated (>95% isolated yield). [d] Enantioselectivity was determined by HPLC analysis of the ketone produced, and ee of product was corrected for the regioisomeric purity of **2**. [e] Daicel Chiral OD-H column. [f] Reference 10. [g] The reaction temperature was −100 °C. [h] 0.1 equiv of $SnCl_4$ was used. [i] (*S*)-Binaphthol was used. [j] Daicel Chiral As column. [k] Enantiomeric excess of the product after recrystallization from a dichloromethane−hexane mixed system.

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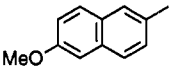
Table 2. Enantioselective Protonation and Ketene Bis(trialkylsilyl) Acetals by (*R*)-**1**[a]

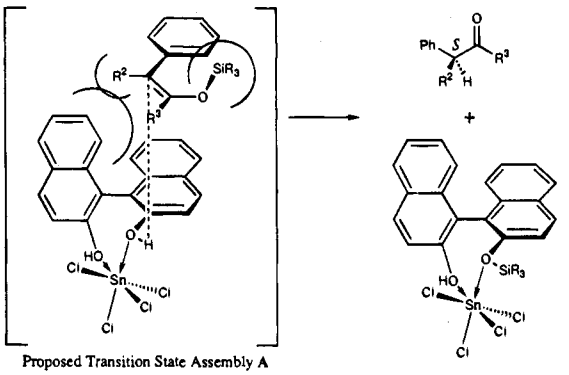
entry	ketene bis(trialkylsilyl) acetal $R^1R^2C{=}C(OSiR_3)_2$ R^1	R^2	SiR_3	ee (%) of methyl ester, (config)-(rotn)
1	Ph	Me	$SiMe_3$	92, (*S*)-(+)[b,c]
2	Ph	Me	$SiEt_3$	95, (*S*)-(+)[b,c]
3	Ph	Et	$SiMe_3$	60, (*S*)-(+)[d,e]
4	*p*-(*i*-Bu)C_6H_4	Me	$SiMe_3$	94, (*S*)-(+)[d,f]
5		Me	$SiMe_3$	92, (*S*)-(+) → 98[g,h,i]
6	Ph	OMe	$SiEt_3$	87, (*S*)-(+)[b,j]

[a] The reactions were carried out in freshly distilled toluene using 1.1 equiv of optically active binaphthol and 1.0 equiv of $SnCl_4$ at −78 °C. All of ketene bis(trialkylsilyl) acetals were completely converted to corresponding silyl esters within 0.5 h and isolated as methyl esters by esterification (>95% yield). [b] Enantioselectivity was determined by HPLC analysis (Daicel Chiral OJ column). [c] Reference 13. [d] Enantioselectivity was determined by HPLC analysis (Daicel Chiral AS column). [e] Reference 14. [f] Reference 15. [g] Enantioselectivity was determined by HPLC analysis (Daicel Chiral OD-H column). [h] Reference 16. [i] Enantiomeric excess of the product after recrystallization from a dichloromethane−hexane mixed system. [j] Reference 17.

optimum conditions[11] is summarized in entries 6−11 (Table 1). The reactions were generally complete after 1 h at −78 °C. Excellent enantioselectivity was achieved in the reactions of the silyl enol ethers of 2-arylcyclohexanones, and both enantiomers could be obtained from racemic 2-arylcyclohexanones depending on the choice of optically active binaphthol (entries 6 and 7): (*S*)- and (*R*)-arylcyclohexanones are obtained using (*R*)- and (*S*)-**1**, respectively. Unfortunately, enantioselectivity was low in the cases of the protonation of silyl enol ethers derived from 2-alkylcycloalkanones (e.g., 42% ee (*R*) for **2**, Ar = Me, R = Me).

As the next step, we applied **1** to enantioselective protonation of ketene bis(trialkylsilyl) acetals[12] derived from 2-arylcarboxylic acids.[11] Representative results are summarized in Table 2. The crude carboxylic acids, which were formed with excellent enantiomeric excess in every case except for entry 3, were isolated as the corresponding methyl esters in a quantitative yield. The enantioselectivity was independent of the steric features of trialkylsilyl substituents (entries 1 and 2). Simple recrystallization of the (*S*)-methyl ester of naproxen could be used to upgrade the optical purity (entry 5). It is noteworthy that the protonation of the ketene silyl acetal, diastereomer ratio (*E* and *Z*) = 63:37, derived from methyl 6-methoxy-α-methyl-2-naphthaleneacetate and trimethylsilyl chloride by (*R*)-**1** gave the (*S*)-methyl ester of naproxen with decreased enantioselectivity (79% ee).

Scheme 1. Proposed Mechanism for the Enantioselective Protonation by (*R*)-**1**



The high degree of enantioselectivity attained in these reactions and the observed preference for the formation of (2*S*)-2-arylcyclohexanone and (2*S*)-2-arylcarboxylic acid merit comment. The proposed mechanism shown in Scheme 1 can explain this preference. When vinyl ethers like silyl enol ethers and ketene bis(trialkylsilyl) acetals approach (*R*)-**1**, the steric interaction between them leads to the observed vinyl ether facial selectivity via the transition state assembly **A**: the trialkylsiloxy group of vinyl ethers orients opposite to the binaphthyl moiety of (*R*)-**1** while the aryl substituent stacks on the naphthalene ring. If R^2 of the vinyl ethers is bulky, enantioselectivity would be reduced because of steric hindrance between another naphthalene ring and R^2 (entry 3, Table 2). Taking into consideration the experimental results that the protonation of ketene silyl acetals (*E*−*Z* isomeric mixture) derived from esters by **1** provides decreased enantioselectivity, the trialkylsilyl group syn to 2-aryl substituent is likely transferred to the binaphthol side in the protonation of ketene bis(trialkylsilyl) acetals as well as silyl enol ethers derived from 2-arylcyclohexanone.[18]

In conclusion, this paper describes a new simple methodology for the enantioselective protonation of silyl enol ethers and ketene bis(trialkylsilyl) acetals. The chiral LBA **1**, which is available in either enantiomeric form, can be used to promote the formation of ketones and carboxylic acids with unprecedented enantioselectivity, in quantitative yield, and with predictable absolute configuration. In addition, the commercially available chiral binaphthol can be efficiently recovered for reuse. We believe that the methodology described herein will prove to have many applications and that further improvements are likely.

Supplementary Material Available: Full experimental details and listing of spectral data for 2-arylcyclohexanones, silyl enol ethers, and ketene bis(trialkylsilyl) acetals (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Representative procedure for enantioselective protonation by (*R*)-**1**. A solution of (*R*)-binaphthol (94 mg, 0.33 mmol) in dry toluene (6.6 mL, distilled from CaH_2) was cooled to −78 °C in a dry ice−methanol bath, and a solution of tin tetrachloride (0.3 mmol, 1.0 M) in dichloromethane was added dropwise. After 5 min at −78 °C, a solution of freshly prepared vinyl ether (0.3 mmol) in dry toluene (1 mL) was added dropwise along the wall of the flask over 10 min. After the solution was stirred for 1 h at −78 °C, the reaction of silyl enol ethers was quenched with ice water, warmed to room temperature, extracted with ether or ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to afford the crude product. On the other hand, the reaction mixture of ketene bis (trialkylsilyl) acetals was warmed to ambient temperature after being stirred for 30 min at −78 °C and concentrated *in vacuo*. The residue was diluted with methanol (2.5 mL) and converted to methyl ester in the presence of trimethylsilyl chloride (100 μL) under reflux condition. Purifications of the crude ketone and the methyl ester by silica gel chromatography (hexane−ethyl acetate) provided the corresponding pure products (>95% yield), respectively.

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(18) It was ascertained that the present protonation of **2** using **1** did not occur via tin enoltae by the follow control experiment: **2** (Ar = Ph, SiR_3 = $SiMe_3$ or Si-*t*-$BuMe_2$) was stable in the presence of $SnCl_4$ (1 equiv) at −78 °C over 2.5 h. Kuwajima et al. reported the formation of α-trichlorostannyl ketones in the reaction of $SnCl_4$ with silyl enol ethers at 35 °C. Nakamura, E.; Kuwajima, I. *Chem. Lett.* **1983**, 59.