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Preliminary Communication

Enantioselective Protonation of Ketene Bis(trimethylsilyl) Acetals Derived from α-Aryl-α-haloacetic Acids Using LBA*

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

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

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Optically active α-halocarboxylic acids and derivatives are important and versatile building blocks in organic synthesis. Lewis acid assisted chiral Brønsted acid (LBA) was recently prepared *in situ* from tin(IV) tetrachloride and optically pure binaphthol and shown to be an effective reagent for enantioselective protonation of prochiral silyl enol ethers and ketene bis(trialkylsilyl) acetals. In this paper we describe highly enantioselective protonation of ketene bis(trimethylsilyl) acetals prepared from α-aryl-α-haloacetic acids using LBA. This is a new methodology for the enantioselective synthesis of α-aryl-α-haloacetic acid derivatives, and the commercially available chiral binaphthol can be recovered efficiently for reuse.

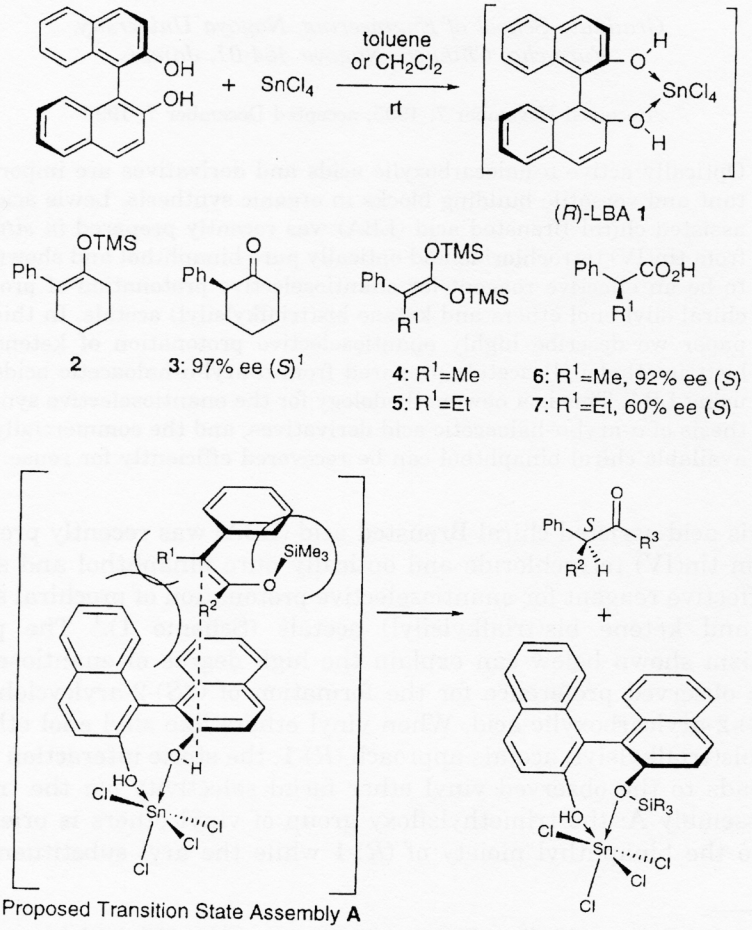
Lewis acid assisted chiral Brønsted acid (LBA) was recently prepared *in situ* from tin(IV) tetrachloride and optically pure binaphthol and shown to be an effective reagent for enantioselective protonation of prochiral silyl enol ethers and ketene bis(trialkylsilyl) acetals (Scheme 1).[1] The proposed mechanism shown below can explain the high degree of enantioselectivity and the observed preference for the formation of (2*S*)-2-arylcyclohexanone and (2*S*)-2-arylcarboxylic acid. When vinyl ethers like silyl enol ethers and ketene bis(trialkylsiyl) acetals approach (*R*)-**1**, the steric interaction between them leads to the observed vinyl ether facial selectivity *via* the transition state assembly **A**: the trimethylsiloxy group of vinyl ethers is oriented opposite to the binaphthyl moiety of (*R*)-**1** while the aryl substituent stacks

* Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.

** Author to whom correspondence should be addressed.

on the naphthalene ring. When R^1 of the vinyl ethers becomes more bulky, enantioselectivity is reduced because of the steric hindrance between another naphthalene ring and R^1: **4** (R^1 = Me) → **6** (92% ee), **5** (R^1 = Et) → **7** (60% ee).

We expected that the chiral protonation reagant **1** would be effective for ketene bis(trimethylsilyl) acetals prepared from α-aryl-α-haloacetic acids. Optically active α-halocarboxylic acids and derivatives are important and versatile building blocks in organic synthesis. For instance, α-chloroalkanoic acids bearing chiral side groups are useful starting materials for the synthesis of chlorohydrins,[2a] alkyloxiranes,[2a] and 1-amino-2-alkanols[2b] of high

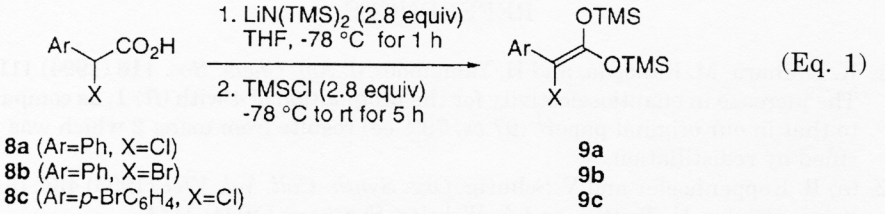


Scheme 1

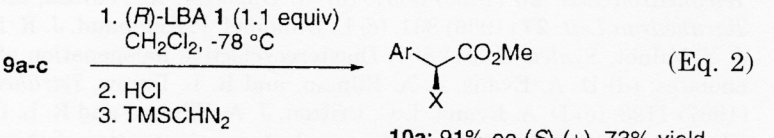
enantiomeric purity. Various methods have been developed for the preparation of optically active α-halocarboxylic acids and derivatives.[3–5] In the case of α-aryl-α-haloacetic acid derivatives, however, some racemization is often observed due to the enhanced stability of carbenium ions in homobenzylic position.[4h] In this paper we describe highly enantioselective protonation of ketene bis(trimethylsilyl) acetals prepared from α-aryl-α-haloacetic acids using LBA **1**.

Ketene bis(trimethylsilyl) acetal **9** was synthesized in the following manner (Eq. 1). α-Aryl-α-haloacetic acid **8** was treated with 2.8 equiv. of lithium hexamethyldisilazide in THF at –78 °C for 1 h to generate the corresponding dianion, and then 2.8 equiv. of TMSCl was added and the solution was allowed to come to ambient temperature in 5 h. Concentration of the mixture and distillation gave **9** as a colourless oil.[6]

(*R*)-**1** was prepared *in situ* by adding 1.0 equiv. of tin(IV) tetrachloride to a solution of 1.1 equiv. of (*R*)-binaphthol in dry CH_2Cl_2 at ambient temperature. After stirring for 10 min, the solution of (*R*)-**1** was cooled to –78 °C and a solution of **9** (1 equiv.) in CH_2Cl_2 was added dropwise at the same temperature. The protonation proceeded rapidly. After stirring for 10 min, the reaction was quenched with a 1:1 mixture of aqueous 1 N HCl and THF at –78 °C. Then the resulting solution was poured into aqueous $NaHCO_3$ and washed with ether. The aqueous layer was acidified with 4 N HCl and extracted with ether twice, dried over $MgSO_4$, and concentrated *in vacuo*. The crude products were quantitatively esterified with $TMSCHN_2$ in methanol. Concentration *in vacuo* and flash chromatography on silica gel provided **10** as a colourless oil in good yield (Eq. 2). Racemization of **10** was not ob-



(Eq. 1)



(Eq. 2)

served by this method. Enantiomeric excess was established by HPLC analysis using a chiral column.[7] Absolute configurations of the adducts **10a** and **10b** from (*R*)-**1** were determined by comparison with those of authentic samples prepared from methyl mandelate by the known procedure.[4a]

Of great interest to us were the steric and electronic effects of halogen substituent in enantioselective protonation of ketene bis(trimethylsilyl) acetals **9** by LBA **1**. Very good results were obtained with Cl-substituted ketene bis(trimethylsilyl) acetals such as **8a** and **8c**. The enantioselectivity in the reaction of **8a** (X = Cl) was higher than that of **8b** (X = Br). These results could be attributable to Cl being sterically smaller than Br. It is noted that similar enantioselectivity with **8a** has been obtained in the protonation of **4** (R^1 = Me).

In conclusion, this paper describes a new methodology for the enantioselective synthesis of α-aryl-α-haloacetic acid derivatives. Protons in optically active binaphthol, which is available in either enantiomeric form, is activated by coordination of tin(IV) tetrachloride and can be used as a chiral proton source for the protonation of ketene bis(trimethylsilyl) acetals to α-aryl-α- haloacetic acids with unprecedented enantioselectivity, in good yield and with predictable absolute configuration. In addition, the commercially available chiral binaphthol can be recovered efficiently for reuse. We believe that the methodology described herein will prove to have many applications and that further improvements are likely.

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7. HPLC (hexane/*i*-PrOH = 20 : 1, flow rate = 1.0 mL/min, Daicel OD-H column), t_R = 5.5 min for (*R*)-(–)-**10a**, t_R = 5.8 min for (*S*)-(+)-**10a**. HPLC (hexane/*i*-PrOH = 20 : 1, flow rate = 1.0 mL/min, Daicel OD-H column), t_R = 5.4 min for (*R*)-(–)-**10b**, t_R = 6.1 min for (*S*)-(+)-**10b**. HPLC (hexane/*i*-PrOH = 20 : 1, flow rate = 1.0 mL/min, Daicel OJ column), t_R = 14.7 min for minor enantiomer of **10c**, t_R = 15.7 min for major enantiomer of **10c**.

SAŽETAK

Enantioselektivna protonacija keten-bis(trimetilsilil)-acetala izvedenih od α-aril-α-haloacetil kiselina upotrebom LBA

Kazuaki Ishihara, Shingo Nakamura i Hisashi Yamamoto

Optički aktivne α-halogenkarboksilne kiseline i njihovi derivati važni su i široko primjenjivani gradbeni blokovi u organskoj sintezi. Lewisovim kiselinama pomognuta Brønstedova kiselina (LBA) nedavno je *in situ* pripravljena iz kositrova(IV) tetraklorida i optički čistog binaftola, i pokazala se efikasnim reagensom u enantioselektivnoj protonaciji prokiralnih silil-enoletera i keten-bis(trialkilsilil)-acetala. U ovom se radu opisuje visoko enantioselektivna protonacija keten-bis(trimetilsilil)-acetala pripravljenih iz α-aril-α-halogenoctene kiseline uz upotrebu LBA. To je nova metoda enantioselektivne sinteze derivata α-aril-α-halogenoctene kiseline, pri čemu se komercijalno vrijedni kiralni binaftol može efikasno regenerirati i ponovo koristiti.