



S0040-4039(96)00434-0

Catalytic Enantioselective Protonation of Samarium Enolates by a C₂-Symmetric Chiral Diol

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Abstracts: Relatively high enantioselectivity (up to 93% ee) has been achieved in the catalytic protonation of samarium enolates by the use of a C₂-symmetric homochiral diol as the catalyst and trityl alcohol as an achiral proton source for regeneration of the catalyst.

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Catalytic enantioselective protonation¹ of metal enolates with chiral proton sources is a promising method for the preparation of carbonyl compounds or carboxylic acid derivatives bearing a stereogenic carbon at the α -position. Fehr and coworkers have found that the protonation of a lithium enolate of a thiol ester proceeds with 99% ee, by using *N*-isopropylphedrine as a homochiral proton source. Furthermore, they succeeded in extending the reaction to a catalytic version (90% ee).² However, the method is not generally applicable, because the thiol is employed as the proton source to regenerate the catalyst and the reagent for generation of the enol derivative.

Yanagisawa and Yamamoto have reported the catalytic enantioselective protonation of lithium enolates. By the use of a homochiral imide catalyst, a chiral ketone was obtained in 90% ee. They used imides, phenols and active methylene compounds as achiral proton sources for regeneration of the chiral imide catalyst in the reaction mixture.³ Since the proton sources are used only for regeneration of the catalyst, the method can be applied generally for extending a stoichiometric enantioselective protonation to a catalytic process.

We have investigated the enantioselective protonation of samarium enolates which are formed by the SmI₂-mediated reaction between unsymmetrical dialkylketene and allyl halides, using a C₂-symmetric homochiral diol, DHPEX (α,α' -di[(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide), as a proton source. Since the enantiomeric excess of the products (up to 97% ee) correlated with the *E/Z* ratios of the enolates, the enantioselectivity of the protonation step seemed to be almost 100%.⁴ The chiral proton source, DHPEX, was recovered quantitatively. Thus, we thought that it should be possible to carry out the enantioselective protonation by using a catalytic amount of DHPEX, if a chiral conjugate base of DHPEX is protonated by an achiral proton source in the reaction mixture without protonation of the samarium enolate.

In the stoichiometric reaction (more than 1.0 mol equiv. of DHPEX was used), the reaction temperature was raised from -78 °C to room temperature, but a constant reaction temperature was required for the catalytic reaction. Thus, we investigated the lowest reaction temperature at which the protonation actually occurs to give the highest enantiomeric excess in the stoichiometric reaction and found that -45 °C was the best reaction temperature. The product was obtained in 95% ee when methyl(1-methyl-1-phenylethyl)ketene (1) was used as substrate.

We next carried out the stoichiometric protonation of the samarium enolate by DHPEX (1.0 mol equiv.) in co-existence with 2/3 mol equiv. of an achiral proton source such as *t*-butanol, trityl alcohol, or 2,6-di-*t*-butyl-*p*-cresol at -45 °C. Surprisingly, the same enantiomeric excesses were achieved as in the absence of the achiral proton source. The results demonstrated that DHPEX has much higher protonating ability to the samarium enolate than these sterically congested achiral proton sources at this temperature.

Therefore, we attempted to carry out the catalytic reaction by adding the achiral proton source to the reaction

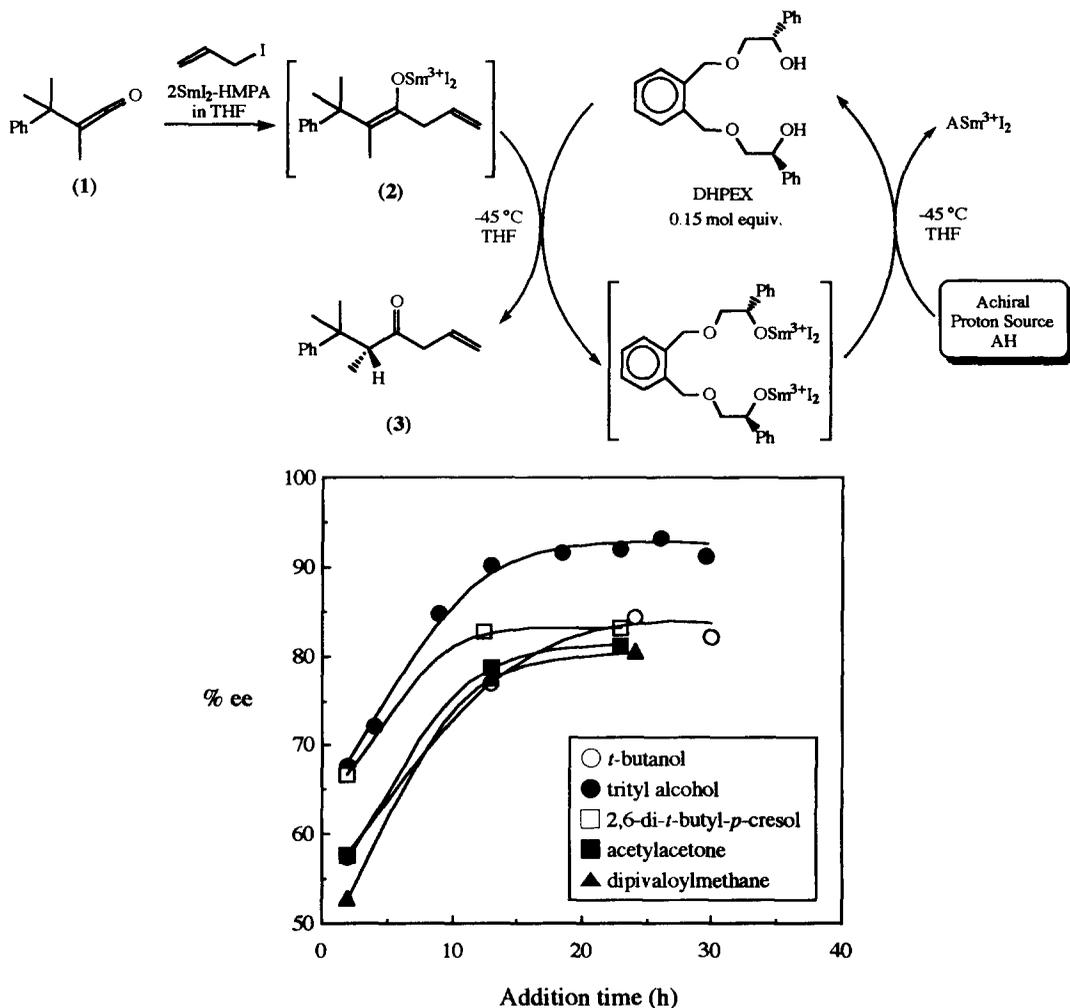
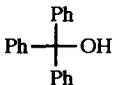
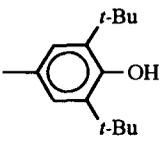
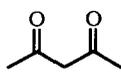
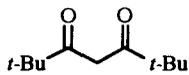


Fig. 1. Correlation between the enantioselectivity of the allyl ketone (3) and the addition time of several achiral proton sources in the catalytic enantioselective protonation.

mixture slowly enough to maintain the ratio of the achiral proton source to DHPEX at least lower than 0.7. In Fig. 1, the correlation is shown between the enantioselectivity and the addition time of several achiral proton sources such as alcohols, phenol, and active methylene compounds. The enantiomeric excess increased and then reached maximum values with longer reaction time in all cases. Table 1 summarizes the results of the experiments. As seen from Fig. 1 and Table 1, trityl alcohol gave the best results and the enantiomeric excess reached 93% when it was added to the reaction mixture over a period of 26 h: the procedure was as follows. A SmI_2 solution (0.1 mol/dm³, 10.0 ml, 1.00 mmol) was added to a solution of (1) (75.6 mg, 0.434 mmol), allyl iodide (311 mg, 1.85 mmol), and HMPA (144 mg, 0.806 mmol) in THF (2 ml) with stirring under argon at room temperature. After 3 min, the reaction mixture was cooled to -45°C and to the reaction mixture a solution of DHPEX (24.6 mg, 0.065 mmol) in THF (4 ml) was added. After 20 min, addition of trityl alcohol (113 mg, 0.434 mmol) in THF (4 ml)

was started by the use of a syringe with a microfeeder. The reaction mixture was treated by usual work-up followed by PTLC to give the allyl adduct (**3**) (51.7 mg, 55% yield) with 93% ee.⁴

Table 1. Catalytic enantioselective protonation of the samarium enolate (**2**) with DHPEX at -45 °C using several achiral proton sources.

Entry	Achiral Proton Source	Reaction Time (h)	Yield (%)	% ee ^a
1		30	63	82
2		26	55	93
3		23	60	83
4		23	62	81
5		24	65	81

^a Determined by HPLC analysis using Daicel Chiralcel OD on the hydrogenated sample of the reaction product.

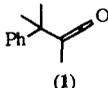
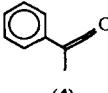
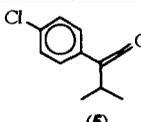
2,6-Di-*t*-butyl-*p*-cresol was the best achiral proton source in the Yanagisawa and Yamamoto reaction system to regenerate the chiral imide catalyst (reaction time was 2 h), but in our system trityl alcohol gave the best results. These results show that both large steric hindrance and adequate acidity of the achiral proton source are required for highly selective protonation of the conjugate base of DHPEX in the presence of the samarium enolate.⁵

Next, the reaction on two other ketenes was examined under the same conditions as above and the results are summarized in Table 2 together with that of (**1**) and the stoichiometric reaction results. The enantioselectivities were similar to those in the stoichiometric reaction in the cases of the two ketenes except methylphenylketene (**4**). In the case of (**4**) the enantioselectivity was disappointingly low and it was not appreciably improved even by the addition of a large amount of HMPA.⁶

Work is now in progress to obtain higher enantioselectivities in more general ketenes in shorter reaction time and to clarify the mechanism of the enantioselective protonation.

Acknowledgement: The present work was supported by a Grant-in-Aid for Encouragement of Young Scientists No. 07740510 to Y. Nakamura from the Ministry of Education, Science and Culture, Japan. The authors wish their thanks to IHARA CHEMICAL KHOGYO Co. Ltd. for the generous gift of samples.

Table 2. Catalytic enantioselective protonation of samarium enolates with DHPEX using trityl alcohol as an achiral proton source at -45 °C.

Ketene	Reaction Time (h)	HMPA (eq.)	Yield (%)	% ee ^a	Config.
 (1)	26	1.9	55	93	R
	2 (Stoichiometric Reaction)	2.0	55	95	R
 (4)	4.5	1.9	61	25	R
	13	6.1	55	49	R
	40 min (Stoichiometric Reaction)	1.9	64	92	R
 (5)	12.5	1.9	72	71	S
	40 min (Stoichiometric Reaction)	2.0	64	76	S

^a Determined by HPLC analysis using Daicel Chiralcel OD for (1) and Chiralcel OB¹ for (4) or ¹H NMR analysis in the presence of Eu(hfc)₃ for (5).

References and Notes

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- a) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1042-1044. b) Fehr, C.; Stempf, I.; Galindo, J. *ibid.* **1993**, *32*, 1044-1046.
- Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372-374.
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- The difference between the Yanagisawa and Yamamoto system and our reaction conditions to give the maximum enantiomeric excesses may come from stronger co-ordination of the oxygen anion to the samarium ion than to the lithium ion. Thus, higher reaction temperature is required for the protonation of the conjugate base of DHPEX and the samarium enolate, which results in more severe reaction conditions for the selective protonation of the conjugate base. Therefore, longer reaction time and weaker acidity are desired for our reaction system compared to the Yanagisawa and Yamamoto system.
- The most noticeable difference between the two kinds of ketene is the configurational structure of the samarium enolates (*Z:E*=96:4 in (4), *Z:E*>99:1 in (1), and *Z:E*=12:88 in *p*-chlorophenylisopropylketene (5)). In the case of (4) the lower enantioselectivity may be brought about by a conformational change of the benzene ring *cis* to the *O*-Sm³⁺ group owing to a change of the co-ordination sphere of the samarium enolate. In the catalytic reaction, trityl alcoholoxide anion is formed during the reaction, and it may disturb the co-ordination sphere of the samarium enolate. See Ref. 4b), details will be reported elsewhere.