Pergamon

Tetrahedron Letters, Vol. 38, No. 15, pp. 2709-2712, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00435-8

SmI_2-Mediated Reductive Enolization of α-Hetero-Substituted Ketones and Enantioselective Protonation

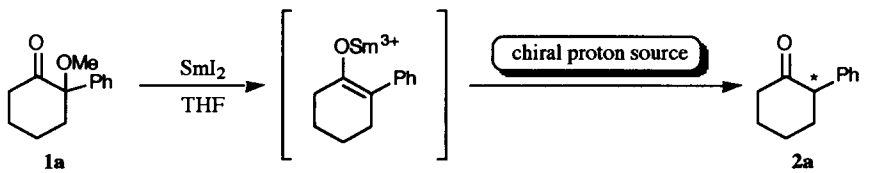
Yutaka Nakamura, Seiji Takeuchi,* and Yoshiaki Ohgo
Niigata College of Pharmacy†, 5-13-2 Kamishin'ei cho, Niigata 950-21, Japan

Makoto Yamaoka, Akihiro Yoshida, and Koichi Mikami*
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

Abstract: *High enantioselectivity (up to 94% ee) has been achieved in the protonation of samarium enolates which were generated by SmI_2-mediated reduction of 2-aryl-2-methoxycyclohexanones using a C_2-symmetric chiral diol as a proton source.* © 1997 Elsevier Science Ltd.

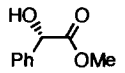
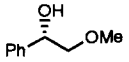
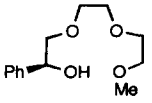
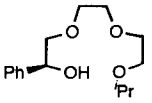
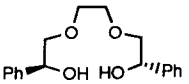
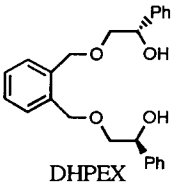
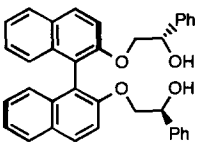
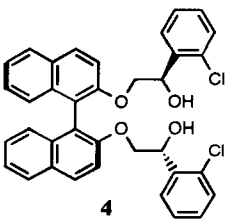
Enantioselective protonations of vinylic acetate with an enzyme and of metal enolates with chiral proton sources such as alcohols, phenols and metal complexes thereof are useful methods to prepare chiral carbonyl compounds or carboxylic acid derivatives bearing a stereogenic center at the α-position.[1] The reactions are attractive from the practical point of view since some of these reactions were successfully converted to the catalytic processes in high enantioselectivities.[2] The NCP† group has already reported the enantioselective protonation (up to 97% ee) of samarium enolates which are generated by a SmI_2-mediated reaction between unsymmetrical dialkylketene and allyl halides, with the use of a C_2-symmetric chiral diol, DHPEX (α,α'-di[(*S*)-2-hydroxy-2-phenylethyl]-*o*-xylenedioxide), as a proton source,[3] and also the catalytic version of the reaction (93% ee).[4]

Molander *et al.* have reported that a wide range of α-hetero-substituted carbonyl compounds are rapidly reduced under mild conditions by SmI_2[5] in the presence of an achiral proton source such as methanol.[6] The reaction has been applied extensively to the syntheses of natural polyhydroxy ketones such as taxol derivatives[7] and carbohydrate-containing macrolide antibiotics.[8] However, no enantioselective version of Molander's reaction had been reported. Thus, we examined the reaction using the α-methoxy substrate (**1a**)[9] bearing an α-phenyl substituent and various chiral hydroxy ethers as chiral proton sources.[10] The results are summarized in Table 1.



1a **2a**

Table 1. Enantioselective protonation of samarium enolate prepared from 2-methoxy-2-phenylcyclohexanone.[a]

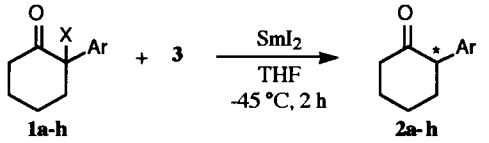
Entry	Chiral proton source	Reaction temp. (°C)	% Yield	% ee [b]	Config. [c]
1		r.t.[d]	89	38	*R*
2		r.t.	85	39	*R*
3		r.t.	85	48	*R*
4		r.t.	92	37	*R*
5		r.t.	83	58	*R*
6	 DHPEX	r.t.	65	54	*R*
7	DHPEX	r.t.	89	58	*R*
8	 **3**	r.t.	88	65	*R*
9	 **4**	r.t.	63	65	*S*
10	**3**	-45	70	87	*R*

[a] The reactions were carried out using 1.1 mol *equiv.* (entry 1-6) or 2.0 mol *equiv.* (entry 7-10) of the chiral proton source and 2.4 mol *equiv.* of SmI_2 for 0.5 h (entry 1-9) or 2 h (entry 10). [b] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H. [c] Configuration of **2a** was determined by specific rotation. See Ref. 12. [d] Room temperature.

As shown in Entry 8 and 9 of Table 1, (*R*)-2,2'-di[(*S*)-2-hydroxy-2-phenylethoxy]-1,1'-binaphthyl (DHPEB) (**3**) and (*S*)-2,2'-di[(*R*)-2-(*o*-chlorophenyl)-2-hydroxyethoxy]-1,1'-binaphthyl (**4**)[11] gave 65% ee at room temperature. When DHPEB was added to a solution of the samarium enolate at -45 ℃, the enantiomeric excess of the product was lower than that obtained at room temperature. However, the enantioselectivity was dramatically improved to give the product in 87% ee as shown in Entry 10, when DHPEB was added to the reaction mixture prior to the preparation of the samarium enolate as follows. A SmI_2 solution (0.1 mol·dm^{-3}, 6.3 ml, 0.63 mmol) was added to a solution of **1a** (54.0 mg, 0.264 mmol) and DHPEB (278 mg, 0.529 mmol) in THF (5 ml) with stirring under argon at -45 ℃. After stirring for 2 h at the temperature, the reaction mixture was quenched with 0.1 N hydrochloric acid (4 ml) and extracted with ether (15 ml×3). The organic extract was washed with brine (15 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by preparative TLC to give **2a** (32.2 mg, 70% yield) in 87% ee.

Next, the reaction with several kinds of 2-aryl-2-hetero-substituted cyclohexanone was examined under the same reaction conditions. The results are summarized in Table 2. Among 2-phenylcyclohexanones substituted by chloro, acetoxy, and methoxy groups at the α-position, the enantioselectivity was highest in the case of the methoxy substrate (**1a**). Generally, high enantioselectivities were obtained except for 2-methoxy-2-(1-naphthyl)cyclohexanone (**1g**). 2-Methoxy-2-(*p*-tolyl)cyclohexanone (**1e**) gave the best result (94% ee). The large difference between **1g** and **1h** may be ascribable to the different steric demand of the naphthyl groups of the substrates with the chiral binaphthyl group of DHPEB, although the transition state of the protonation step has not yet been elucidated.

Table 2. Enantioselective protonation of the samarium enolates prepared from 2-aryl-2-hetero-substituted cyclohexanones by DHPEB.[a]



1a-h **2a-h**

Entry	Substrate No.	Ar	X	% Yield	% ee[b]	Config. (Rotn.)[c]
1	**1a**	Ph	OMe	70	87	*R*(+)
2	**1b**	Ph	Cl	79	82	*R*(+)
3	**1c**	Ph	OAc	83	83	*R*(+)
4	**1d**	*p*-$MeOC_6H_4$-	OMe	79	87	(+)
5	**1e**	*p*-MeC_6H_4-	OMe	75	94	(+)
6	**1f**	*p*-ClC_6H_4-	OMe	78	83	(+)
7	**1g**	1-Naphthyl	OMe	81	16	(-)
8	**1h**	2-Naphthyl	OMe	86	90	(+)

[a] The reactions were carried out using 2.0 mol *equiv.* of **3** and 2.4 mol *equiv.* of SmI_2. [b] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H (entry 1-5 and 8) and OJ (entry 6 and 7). [c] Specific rotation was measured in benzene.

Work is now in progress to obtain higher enantioselectivities in more general substrates and to clarify the mechanism of the enantioselective protonation.

Acknowledgment: The authors wish to express their thanks to Nitto Kakagu Kogyo Co., Ltd., for the generous gift of (*R*)-*o*-chloromandelic acid and (*R*)-styrene oxide.

References and Notes:

1. Reviews: (a) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566-2587. (b) Hünig, *S. Houben-Weyl, Methods of Organic Chemistry, Vol. E21d* ; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. Eds.; Thieme: Stuttgart, **1995**; pp. 3851-3911. (c) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, II-421-430.
2. (a) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1042-1044; **1993**, *32*, 1044-1046. (b) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372-374.
3. Takeuchi, S.; Ohira, A.; Miyoshi, N.; Mashio, H.; Ohgo, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1763-1780.
4. Nakamura Y.; Takeuchi, S.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805-2808.
5. Reviews: (a) Inanaga, J. *J. Synth. Org. Chem., Jpn.* **1989**, *47*, 200-211. (b) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453-460. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338.
6. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135-1138.
7. Georg, G. I.; Cheruvallath, Z. S. *J. Org. Chem.* **1994**, *59*, 4015-4018.
8. Yang, B. V.; Massa, M. A. *J. Org. Chem.* **1996**, *61*, 5149-5152.
9. Mikami, K.; Yamaoka, M.; Yoshida, A. *The 70th Annual Meeting of the Chemical Society of Japan*, Tokyo, March 1996, Abstr. II 3H315.
10. 2-Bromo-2-methyl-1-tetralone gave a moderate enantioselectivity (52% ee) using quinidine as a chiral proton source: Takeuchi, S.; Nakamura Y.; Ogura, K.; Tsukamoto, M.; Tashiro, Y.; Ohgo, Y. *The 28th Annual Symposium of the Kanto Branch of the Synthetic Organic Chemical Society of Japan*, Niigata, November 1994, Abstr. p 82.
11. **3** and **4** were synthesized by the reaction of (*R*)- and (*S*)-1,1'-bi-2-naphthol with (*S*)-1-phenyl-2-[(*p*-toluenesulfonyl)oxy]-1-(tetrahydropyranyloxy)ethane and (*R*)-1-(*o*-chlorophenyl)-2-[(*p*-toluenesulfonyl)-oxy]-1-(tetrahydropyranyloxy)ethane which were prepared from (*S*)-mandelic acid and (*R*)-*o*-chloromandelic acid, respectively. Full experimental details will be published elsewhere.
12. Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. (C)* **1971**, 3371-3375.

(*Received in Japan* 24 *January* 1997; *revised* 24 *February* 1997; *accepted* 28 *February* 1997)