

Catalytic Asymmetric Hydroxymethylation of Silicon Enolates Using an Aqueous Solution of Formaldehyde with a Chiral Scandium Complex

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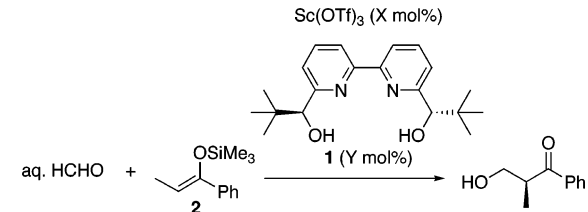
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Formaldehyde is one of the most important C1 electrophiles in organic synthesis. Although hydroxymethylation of enolates with formaldehyde provides an efficient method to introduce a C1 functional group at the α -position of carbonyl groups, there have been few successful examples of catalytic asymmetric hydroxymethylation that satisfy synthetic utility in terms of both yield and selectivity for a wide range of substrates.¹ To achieve such reactions, Lewis acid-catalyzed hydroxymethylation of silicon enolates² is promising. The reactions proceed regioselectively, and excellent substrate generality and synthetic efficiency can be expected.³ As for the source of formaldehyde, use of a commercial aqueous solution of formaldehyde is the most convenient, because tedious and harmful procedures to generate formaldehyde monomer from formaldehyde oligomers such as paraformaldehyde and trioxane can be avoided.⁴ Although we have previously reported the use of an aqueous solution of formaldehyde for hydroxymethylation of silicon enolates,⁵ it is still difficult to realize catalytic asymmetric versions of this reaction. Quite recently, the catalytic asymmetric hydroxymethylation of silicon enolates in aqueous solvents was first achieved by our group⁶ and Yamamoto et al.⁷ However, in both cases, the enantioselectivities were moderate, and there still remained several issues to be resolved. To achieve a higher level of yields and selectivity in this reaction, development of a new catalytic system is required. We report here that a novel chiral scandium complex has realized highly enantioselective, catalytic hydroxymethylation of silicon enolates with a formaldehyde aqueous solution.

First, we screened various chiral ligands in scandium triflate ($\text{Sc}(\text{OTf})_3$)-catalyzed asymmetric hydroxymethylation using a commercial aqueous solution (35%) of formaldehyde, because $\text{Sc}(\text{OTf})_3$ is one of the strongest Lewis acids that can be used for aldol reactions in aqueous solvents.⁸ It was found that **1**⁹ was an effective ligand and afforded high selectivity in the reaction of silicon enolate **2** in $\text{H}_2\text{O}/\text{EtOH}$ (Table 1, entry 1). To increase the yield and selectivity, we investigated the reaction conditions further (Table 1). When alcoholic cosolvents were used, lower yields were obtained because rapid hydrolysis of the silicon enolate occurred (entries 2–4). On the other hand, water-soluble aprotic cosolvents such as THF, 1,2-dimethoxyethane (DME), 1,4-dioxane, and acetonitrile afforded high yields (entries 5–8). When water without organic cosolvents was used, the reaction proceeded sluggishly (entry 9). Under higher concentration and at lower temperature in $\text{H}_2\text{O}/\text{DME}$, the reaction proceeded in high yield with high selectivity even using 10 mol % of the catalyst (entry 11). Five mol % of the catalyst also worked well (entry 12).

Under the optimized conditions as shown in Table 1, entry 11, we next examined other substrates and were delighted to find that various substrates could be successfully employed (Table 2). Silicon enolates having an ethyl or a siloxy group on the α -position of the carbonyl groups gave the products with high selectivity (entries 2 and 3). Moreover, it is noted that asymmetric quaternary carbons

Table 1. Optimization of Reaction Conditions^a



entry	solvent	X	Y	time (h)	yield ^b (%)	ee ^c (%)
1	$\text{H}_2\text{O}/\text{EtOH} = 1/9$	20	24	1.5	32	87
2	$\text{H}_2\text{O}/\text{MeOH} = 1/9$	20	24	1	14	81
3	$\text{H}_2\text{O}/\text{PrOH} = 1/9$	20	24	2	35	62
4	$\text{H}_2\text{O}/\text{PrOH} = 1/9$	20	24	11	53	80
5	$\text{H}_2\text{O}/\text{THF} = 1/9$	20	24	2	78	73
6	$\text{H}_2\text{O}/\text{DME} = 1/9$	20	24	6	81	83
7	$\text{H}_2\text{O}/1,4\text{-dioxane} = 1/9$	20	24	15	86	84
8	$\text{H}_2\text{O}/\text{CH}_3\text{CN} = 1/9$	20	24	15	87	80
9	H_2O	20	24	67	5	66
10	$\text{H}_2\text{O}/\text{DME} = 1/9$	20	24	21	82	90
11	$\text{H}_2\text{O}/\text{DME} = 1/9$	10	12	24	80	90
12	$\text{H}_2\text{O}/\text{DME} = 1/9$	5	6	24	67	86

^a Reaction was performed at 0 °C (entries 1–9) or –20 °C (entries 10–12). The amounts of formaldehyde were 10 equiv (entries 1–10) or 5 equiv (entries 11 and 12). The reaction was performed in 0.18 M (entries 1–10) or 0.36 M (entries 11 and 12) concentrations. ^b Isolated yield after silica gel chromatography. ^c Ee was determined by chiral HPLC analysis.

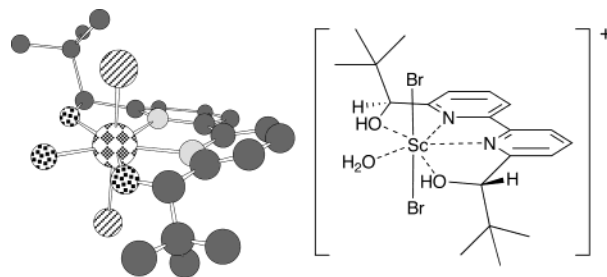


Figure 1. $[\mathbf{1}\cdot\text{ScBr}_2\cdot\text{H}_2\text{O}]^+$ moiety in the X-ray structure of $[\mathbf{1}\cdot\text{ScBr}_2\cdot\text{H}_2\text{O}]\cdot\text{Br}\cdot\text{H}_2\text{O}$. Hydrogen atoms are omitted for clarity.

were constructed with high selectivities (entries 6–11 and 13–15). Unfortunately, in the cases where rapid hydrolysis of silicon enolates occurred, the reactions resulted in low yields (entries 12, 16). In some cases, addition of 2,6-di-*tert*-butylpyridine slightly improved the yield (entry 3).^{10,11}

To obtain some information on the chiral Sc complex, X-ray crystal structural analysis was performed. Single crystals that were suitable for X-ray analysis were obtained from a **1**– ScBr_3 complex (Figure 1).¹² The complex adopts a pentagonal bipyramidal structure¹³ in which the hydroxy groups of **1** coordinate to Sc^{3+} in a tetradentate manner. Formation of this type of structure may be a key for obtaining high enantioselectivity. In addition, on considering the absolute configurations of some of the hydroxymethylated

Table 2. Catalytic Asymmetric Hydroxymethylation of Silicon Enolates^a

entry	silicon enolate	time (h)	yield ^b (%)	ee ^c (%)
1		24	80	90
2		30	66	88
3		32 (53)	39 53	78 80) ^d
4		26	74	87 ^e
5		65	73	92 ^f
6		14	90	90
7		20	80	94
8		50	84	94 ^f
9		10	50	85 ^g
10		20	68	91 ^g (R)
11		2	62	90 ^g
12 ^h		34	26	78 ^g (R)
13		21	63	60
14		19	77	67
15		31	59	80 ^f
16		47	24	94 (S)

^a Reaction was performed in 0.36 M concentration. ^b Isolated yield after silica gel chromatography. ^c Ee was determined by chiral HPLC analysis. Absolute configuration is shown in parentheses. ^d 2,6-Di-*tert*-butylpyridine (100 mol %) was added. ^e *T* = -30 °C. ^f *T* = -40 °C. ^g Ee was determined by chiral HPLC analysis of its benzoate. ^h Reaction was performed in H₂O/CH₃CN.

products^{6,14} shown in Tables 1 and 2, it is clear that formaldehyde tends to react with the same face of the silicon enolates in no relation to the substituents at the α -position.

In conclusion, we have achieved successful catalytic asymmetric hydroxymethylation of silicon enolates using a **1**-Sc(OTf)₃ complex as the catalyst. In this reaction, a commercial aqueous solution of formaldehyde can be used, and as a result, this process can be conducted very easily and safely. This new catalytic system will provide not only a useful method to synthesize optically active α -hydroxymethylated carbonyl compounds but also a guide to various kinds of catalytic asymmetric C–C bond-forming reactions in aqueous media.¹⁵

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Supporting Information Available: Experimental procedures, spectral data, and crystallographic data (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Catalytic asymmetric hydroxymethylation without using silicon enolates: (a) Fujii, M.; Sato, Y.; Aida, T.; Yoshihara, M. *Chem. Express* **1992**, *7*, 309. (b) Kuwano, R.; Miyazaki, H.; Ito, Y. *Chem. Commun.* **1998**, *71*. (c) Torii, H.; Nakada, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.
- (2) For a review on silicon enolates, see: Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformation*; Bellus, D., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, I., Thomas, E. J., Trost, B. M., Eds.; Georg Thieme Verlag: Stuttgart, 2002; Vol. 4, p 317.
- (3) For reviews on asymmetric aldol reactions, see: (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (b) Carreira, E. M. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998. (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.
- (4) Trioxane was used as a formaldehyde surrogate: Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
- (5) (a) Kobayashi, S. *Chem. Lett.* **1991**, 2187. For hydroxymethylation of a silicon enolate in aqueous media without any catalysts, see: (b) Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065.
- (6) Manabe, K.; Ishikawa, S.; Hamada, T.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 10439.
- (7) Ozawa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* **2003**, 2219.
- (8) (a) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227.
- (9) (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
- (10) 2,6-Di-*tert*-butylpyridine was used as an additive for Lewis acid-catalyzed aldol reactions. For example: (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4275. (b) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989.
- (11) It is also noteworthy that water is essential in this reaction. To see the effects of water in this catalytic system, we performed an asymmetric aldol reaction of benzaldehyde where anhydrous conditions were easy to access. While the reaction of benzaldehyde with **2** in H₂O/DME (1:9) at -20 °C for 21 h proceeded smoothly with good yield (76%) and modest selectivity (syn/anti = 78/22, 59% ee (syn)) using 10 mol % of the chiral Sc catalyst, the reaction in DME without water did not proceed at all (-20 °C, 24 h). This result indicates that water plays an important role for the catalytic activity in this system. For effects of water in rare earth metal triflate-catalyzed aldol reactions, see: Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. Also see: ref 10b.
- (12) We performed the hydroxymethylation of **2** using 20 mol % Sc³⁺ source and 24 mol % **1** in H₂O/1,4-dioxane at 0 °C. As a result, Sc(OTf)₃ and ScBr₃ afforded almost the same results (Sc(OTf)₃: 15 h, 86% yield, 84% ee; ScBr₃: 22 h, 75% yield, 83% ee).
- (13) Pentagonal bipyramidal structures have also been reported for Sc(OTf)₃-complexes with chiral ligands: (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.
- (14) (a) Baliri, P. L.; Catelani, G.; Giori, R.; Mastroianni, E. *Enantiomer* **1998**, *3*, 357. (b) Miyaoka, H.; Kajiwara, Y.; Hara, M.; Suma, A.; Yamada, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 3189.
- (15) For reviews on catalytic asymmetric carbon–carbon bond-forming reactions in aqueous media, see: (a) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4094.

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