

### Chiral SEM Ether–Tin Tetrachloride as an Enantioselective Hydroxymethylating Reagent for Silyl Enol Ethers: $\gamma$ -Effect of Silicon

Kazuaki Ishihara,<sup>†</sup> Hiroko Nakamura,<sup>‡</sup> and Hisashi Yamamoto<sup>\*‡</sup>

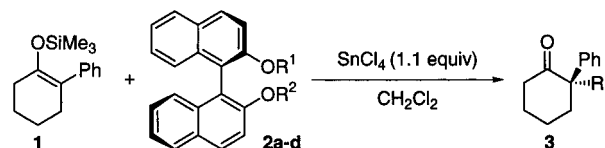
Graduate School of Engineering  
Nagoya University, CREST, JST  
ResCWE, Nagoya University, Furo-cho  
Chikusa, Nagoya 464-8603, Japan

Received May 19, 1999

The asymmetric synthesis of  $\alpha$ -hydroxymethyl carbonyl compounds is currently the subject of considerable interest due to their versatility as dual-function chiral synthons. To our knowledge, there have been no reports of successful enantioselective hydroxymethylations of prochiral metal enolates with formaldehyde because of the instability and small steric size of gaseous formaldehyde.<sup>1</sup> Recently, we developed optically active binaphthol (BINOL) and its derivatives–tin tetrachloride as highly effective chiral proton sources for silyl enol ethers.<sup>2</sup> We envisaged that the enantioselective alkoxylation of silyl enol ethers would be possible by introducing suitable carbon electrophiles in place of the activated protons. We report here the first enantioselective alkoxylation reagents for silyl enol ethers, alkoxylation ethers of chiral BINOL–tin tetrachloride.<sup>3</sup> *The use of BINOL as a chiral leaving group in this process achieved a high level of asymmetric induction.* The absolute stereocontrol using a chiral auxiliary as a leaving group can offer a direct and efficient route to an enantiomer, but very few successful examples have been reported.<sup>4</sup>

Various alkoxylation ethers of (*R*)-BINOL were examined using trimethylsilyl enol ether **1** derived from 2-phenylcyclohexanone in the presence of 1.1 equiv of tin tetrachloride (Table 1).<sup>5</sup> The use of **2a** and **2b** gave (*R*)-**3** in modest yields with moderate enantioselectivities (entries 1 and 2). These reactions proceeded in toluene more slowly than in dichloromethane, and the addition of excess tin tetrachloride or an increase in the reaction temperature promoted the decomposition of **1**. In contrast, the use of the SEM ether **2d** accelerated the alkoxylation, and (*R*)-**3** was obtained in 91% yield with 75% ee (entry 4). This noticeable phenomenon can be explained by the interaction between silicon and a  $\gamma$  positive charge as homohyperconjugation (the  $\gamma$ -effect).<sup>6</sup> Finally, high enantioselectivity (up to 94% ee) was achieved by performing the reaction in 1-chloropropane at  $-125$  °C for long periods (entries 5 and 6). Only one alkoxylation group in **2** was consumed in this reaction. Interestingly, **2c** was somewhat less reactive than **2d** (entry 3). The 2-(trimethylsilyl)ethoxymethylation

Table 1. Enantioselective Alkoxylation of **1**<sup>a</sup>



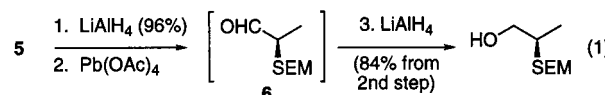
entry	<b>2</b> (R <sup>1</sup> , R <sup>2</sup> ) <sup>b</sup>	temp, time (°C, h)	yield (%)	ee (%), <sup>c</sup> (conf)-(rotn)
1 <sup>d</sup>	<b>2a</b> (MOM, MOM)	−78, 3	56	51, ( <i>R</i> )−(+)
2	<b>2b</b> (BOM, BOM)	−78, 3	55	43, ( <i>R</i> )−(+)
3	<b>2c</b> (SEM, Me)	−78, 2	79	71, ( <i>R</i> )−(+)
4	<b>2d</b> (SEM, SEM)	−78, 1	91	75, ( <i>R</i> )−(+)
5 <sup>e</sup>	<b>2d</b>	−125, 1 to −78, 1	94	81, ( <i>R</i> )−(+)
6 <sup>e</sup>	<b>2d</b>	−125, 47	55	94, ( <i>R</i> )−(+)
7	SEMCl <sup>f</sup>	−78, 0.5	90	

<sup>a</sup> For details, see Supporting Information. <sup>b</sup> 1.1 equiv of **2** was used. MOM = MeOCH<sub>2</sub>; BOM = BnOCH<sub>2</sub>; SEM = Me<sub>3</sub>SiCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> Toluene was used. <sup>e</sup> 1-Chloropropane was used. <sup>f</sup> SEMCl was used in place of **2**.

also proceeded with SEMCl in the presence of tin tetrachloride (entry 7).<sup>3,7,8</sup>

The generality and scope of the tin tetrachloride-mediated SEM addition were explored using several trimethylsilyl enol ethers (Table 2). Good enantioselectivities were observed in the reaction of aromatic silyl enol ethers (R<sup>3</sup> = aryl; entries 1–4) and aliphatic silyl enol ethers (R<sup>1</sup> = *tert*-alkyl, R<sup>3</sup> = small alkyl; entries 5–7). Unfortunately, low enantioselectivity was observed in the reaction of silyl enol ethers derived from 2-phenylcyclohexanone and 2-alkylcyclohexanones (R<sup>3</sup> = Me, *i*-Pr). Interestingly, the absolute stereochemical course in the case of **4** is opposite that in the case of **1**. The 2-(trimethylsilyl)ethyl group was easily removed in quantitative yield without racemization by treatment with hydrogen fluoride–pyridine at room temperature.

To demonstrate the effectiveness of the present reaction, optically active ketone **5** obtained in the reaction of Heathcock's silyl enol ether **4**<sup>9</sup> (entry 7) was converted to synthetically more useful aldehyde **6** in high yield according to their protocol<sup>9</sup> (eq 1).



The regioselective cleavage of acetals in these reactions indicates that tin tetrachloride predominantly coordinates with the oxygen atom of the OAr group. In addition, a <sup>13</sup>C NMR study established that the addition of 1 equiv of tin tetrachloride to **2a** gave rise to a symmetrical complex **A** (Figure 1).<sup>10</sup> Furthermore, the optimized geometry **B** of a 2,2'-di(methoxymethoxy)-1,1'-biphenyl-tin tetrachloride was obtained from a partial PM3 calculation of the MOM units on the basis of a B3LYP/LANL2DZ<sup>11</sup>-optimized

(7) Lithium enolates/SEMCl: (a) Crich, D.; Davies, J. W. *J. Chem. Soc., Chem. Commun.* **1989**, 1418. (b) Crich, D.; Lim, L. B. L. *Synlett* **1990**, 117. (c) Paquette, L. A.; Ra, C. S.; Silvestri, T. W. *Tetrahedron* **1989**, *45*, 3099. Lithium enolates/BOMCl: (d) Wagner, J.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1634. Trialkylsilyl enol ethers/MOMCl/B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>: (e) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1993**, 577.

(8) Trialkylsilyl enol ethers/R<sub>3</sub>SCH<sub>2</sub>Cl/TiCl<sub>4</sub> or ZnBr<sub>2</sub>: Paterson, I. *Tetrahedron* **1988**, *44*, 4207 and references therein.

(9) Mori, I.; Ishihara, K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 1114.

(10) The possibility of an unsymmetrical structure, in which two oxygen atoms in a single MOM group of **2a** are coordinated to the tin atom, was clearly denied. Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1996; Chapter 4.

(11) (a) Dunning, T. H., Jr. *J. Chem. Phys.* **1970**, *53*, 2823. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284.

<sup>†</sup> Research Center for Advanced Waste and Emission Management.

<sup>‡</sup> Graduate School of Engineering.

(1) While far from efficient, there is nevertheless a report on the enantioselective hydroxymethylation. Fujii, M.; Sato, Y.; Aida, T.; Yoshihara, M. *Chem. Express* **1992**, *7*, 309.

(2) (a) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411 and references therein. (b) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 6429. (c) Ishihara, K.; Ishida, Y.; Nakamura, S.; Yamamoto, H. *Synlett* **1997**, 758. (d) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444. (e) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906.

(3) For the diastereoselective aldol-type reactions of chiral enolates with SEMCl, see: Suzuki, S.; Narita, H.; Harada, K. *J. Chem. Soc., Chem. Commun.* **1979**, 29.

(4) Yanagisawa, A.; Nomura, N.; Yamada, Y.; Hibino, H.; Yamamoto, H. *Synlett* **1995**, 841 and references therein.

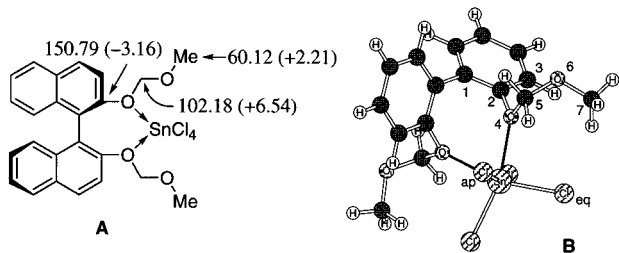
(5) Although the reaction of **1** with *p*-methoxybenzyl ether of (*R*)-BINOL–tin tetrachloride at  $-40$  °C for 5 h gave the desired  $\alpha$ -benzyl ketone in 58% yield, no asymmetric induction was observed.

(6) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677.

**Table 2.** Enantioselective 2-(Trimethylsilyl)ethoxymethylation<sup>a</sup>

entry	silyl enol ether	temp., time (°C, h) <sup>b</sup>	product <sup>b</sup>	yield (%), ee (%), <sup>c</sup> (conf)-(rotn)
1 <sup>d</sup>		-125, 1 to -78, 1		91, 82, (+)
2 <sup>d</sup>		-125, 1 to -78, 1		76, 77, (+)
3 <sup>d</sup>		-125, 108		57, 86, (+)
4 <sup>e</sup>		-78, 17		75, 64, (+)
5 <sup>e</sup>		-97, 3		78, 71, (+)
6 <sup>e</sup>		-97, 6		87, 74, (+)
7 <sup>e</sup>		-97, 6		80, 79, (R)-(+)

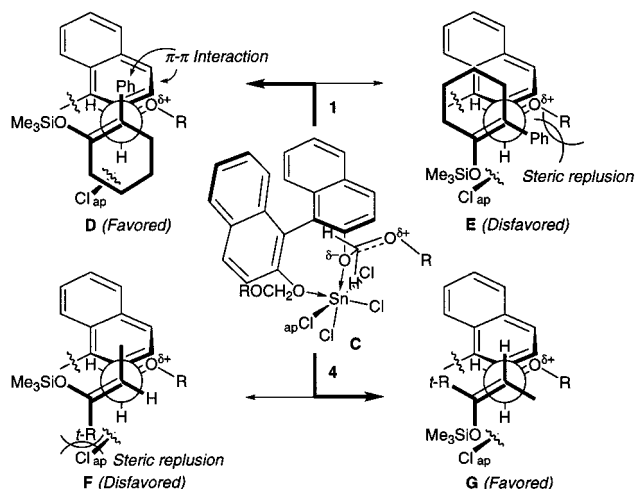
<sup>a</sup> For details, see Supporting Information. <sup>b</sup> Indicated for 2-(tri-methylsilyl)ethoxymethylation. <sup>c</sup> Determined by HPLC or GC analysis. <sup>d</sup> 1-Chloropropane was used. <sup>e</sup> Dichloromethane was used. <sup>f</sup> *E:Z* = 17:83.



**Figure 1.** <sup>13</sup>C NMR (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>, -78 °C) assignments [ $\delta$  (ppm)] for a **2a**-SnCl<sub>4</sub> complex **A** [ $\Delta\delta = \delta(\mathbf{A}) - \delta(\mathbf{2a})$  are given in parentheses] and the optimized geometry **B** of a 2,2'-di(methoxymethoxy)-1,1'-biphenyl-SnCl<sub>4</sub> complex. Selected bond distances (Å), bond angles (deg), and dihedral angles (deg): O4-C5 = 1.456, C5-O6 = 1.386, Sn-Cl<sub>ap</sub> = 2.397, Sn-Cl<sub>eq</sub> = 2.376, O4-Sn = 2.328, C2-O4-C5 = 111.4, Sn-O4-C5 = 122.1, C5-O6-C7 = 116.4, C1-C2-O4-C5 = -85.7, C3-C2-O4-C5 = 92.4, Cl<sub>ap</sub>-Sn-O4-C5 = 33.0, Cl<sub>eq</sub>-Sn-O4-C5 = -61.5, C2-O4-C5-O6 = -64.0, O4-C5-O6-C7 = -90.6.

geometry for a 2,2'-dimethoxy-1,1'-biphenyl-tin tetrachloride complex (Figure 1).<sup>12</sup> These calculations predicted that the chelation of the di(MOM) ether with tin tetrachloride occurs at an equatorial-equatorial site on tin. It is noteworthy that the C5-O4 bond is almost perpendicular to the C1-C3 axis, presumably

(12) Frisch, M. J. et al. Gaussian 94 (Revision D.6), Gaussian, Inc.: Pittsburgh, PA, 1995.



**Figure 2.** The proposed extended transition states (R = CH<sub>2</sub>CH<sub>2</sub>SiMe<sub>3</sub>).

due to the steric repulsive interactions with apical and equatorial chlorines. Also of interest is the observation that the C5-O6 bond is shorter than the O4-C5 bond that is perpendicular to the C5-O6-C7 plane. This indicates the C5-O6 bond has a partial double-bond character due to the stereoelectronic effect.<sup>13</sup> If the conformation of MOM units in **A** is similar to that in **B**, its most stable conformer would be the reactive oxonium intermediate **C** (R = Me), in which steric repulsion is minimized (Figure 2).

The observed absolute stereochemistries are best explained in terms of the acyclic extended transition-state (TS) mechanism that Noyori et al. postulated in the TMSOTf-catalyzed aldol reactions of dimethyl acetals (Figure 2).<sup>14</sup> In the reaction of **1**, TS **D**, which is stabilized by  $\pi$ - $\pi$  attractive interaction between phenyl and naphthyl groups, is favored over the alternative TS **E**, which is destabilized due to steric repulsion between 2-(trimethylsilyl)ethyl and phenyl groups. On the other hand, in the reaction of **4**, TS **G** is preferable to TS **F**, which is destabilized due to steric repulsion between the *tert*-alkyl group and an apical chlorine. Thus, the stereoselection observed for other silyl enol ethers can also be understood in a similar fashion.

In conclusion, we have demonstrated that **2d**-tin tetrachloride is the first chiral hydroxymethylation reagent for silyl enol ethers, and acetal cleavage is promoted by tin tetrachloride and the  $\gamma$ -effect of silicon. *The present protocol is highly effective for the asymmetric construction of not only tertiary but also quaternary carbon stereocenters.* Studies aimed at developing an improved mechanistic understanding and at further optimizing the enantioselectivity of this reaction are underway.

**Acknowledgment.** We thank Mr. Shingo Nakamura for his helpful discussions on the calculations.

**Supporting Information Available:** Experimental details and optimized geometry in Z-matrix form (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA9916613

(13) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

(14) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.