Direct Chlorohydrin and Acetoxy Alcohol Synthesis from Olefins Promoted by a Lewis Acid, Bis(trimethylsilyl) Peroxide and (CH₃)₃SiX

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The use of bis(trimethylsilyl) peroxide (BTSP) offers a useful method for selective Baeyer−Villiger oxidations in the presence of C−C double bonds.[1] The reaction proceeds efficiently upon treatment with BTSP, catalytic amounts of $SnCl_4$, and additives such as (±)-*trans*-1,2-(diamino)cyclohexane and (±)-*trans-N,N'*-bis(*p*-toluenesulfonyl)cyclohexane-1,2-diamine, giving the corresponding Baeyer−Villiger product in which the C−C double bond remains unchanged. On the other hand, we have found that olefins are directly functionalized to chlorohydrins and also acetoxy alcohols in one pot by the combination of BTSP, trimethylsilyl (TMS) X (X = Cl, OAc), and a catalytic amount of Lewis acid (Scheme 1). We describe these results, including a possible reaction mechanism, as well as a preliminary application to metal-catalyzed asymmetric direct chlorohydrin formation from olefins, in this contribution.

The reaction using cyclohexene was examined in detail. It was first found that the reaction of cyclohexene with $SnCl_4$ (10 mol %), BTSP (2 mol equiv), and TMSCl (2 mol equiv), in CH_2Cl_2 at −20 °C for 48 h, provided the chlorohydrin **1a** in 69% yield after acidic workup. On the other hand, in the absence of TMSCl, almost quantitative starting material was recovered. The stereochemistry of **1a** was determined by comparison with an authentic sample. The present new method for the direct synthesis of chlorohydrins was successfully applied to a variety of olefins as shown in Scheme 1.[2,3] It is noteworthy that the chlorohydrins **6a** and **7a** can be synthesized in a highly stereocontrolled manner.[4]

To get some insight into the mechanism of this novel chlorohydrin synthesis, the reaction of $SnCl_4$ with BTSP was first examined. It was found that when 1 mol equiv of BTSP (^{13}C: $\delta = -1.27$, ^{29}Si: $\delta = 27.35$) was reacted with $SnCl_4$ in CH_2Cl_2 at −20 °C for 1 h, evolution of Cl_2 gas was observed. This was confirmed by the reaction of *trans*-5-decene to give the corresponding *erythro*-dichloride in 5% yield together with the chlorohydrin **5a** (78%), although in other cases, no dichloride could be isolated. Furthermore, the NMR spectrum showed the quantitative formation of hexamethyldisiloxane (^{13}C: $\delta = 2.01$, ^{29}Si: $\delta = 7.45$). These results suggest that $(Cl_2SnO)_n$ (**8**) is formed as the active catalyst concomitantly with Cl_2 and hexamethyldisiloxane by the reaction of $SnCl_4$ and BTSP (Scheme 2). Actually, ($Cl_2SnO \cdot 1.5$ pyridine complex)$_n$ was successfully obtained by adding pyridine to the mixture, and the structure was confirmed by comparison with an authentic sample (IR).[5,6]

Scheme 1. Direct Chlorohydrin and Acetoxy Alcohol Synthesis from Olefins with BTSP, TMSX, and Lewis Acids[a]

Olefin	Product	X	Conditions	Time (h)	Isolated Yield (%)
		Cl (**1a**)	A	48	69
		Cl (**1a**)	B	24	92
		OAc (**1b**)	C	6.5	78
		Cl (**2a**)	A	72	73
		Cl (**2a**)	B	72	74
		OAc (**2b**)	C	21	71
		Cl (**3a**)	A	48	66
		Cl (**3a**)	B	192	85
		OAc (**3b**)	C	24	73
		Cl (**4a**)	A	72	62
		Cl (**4a**)	B	72	68
		OAc (**4b**)	C	45	58
		Cl (**5a**)	A	72	78
		Cl (**5a**)	B	144	71
		5c	C	23	72[b]
		Cl (**6a**)	A	24	77
		OAc (**6b**)	C	16	80
		Cl (**7a**)	A	72	75
			C	24	67 (**7b + 7d**)

X = OAc (**7b**); 23%   **7d**; 44%

[a] Reactions under conditions A were performed at −20 °C. Reactions under conditions B and C were performed at ambient temperature. [b]4 mol equiv of BTSP was used.

Moreover, we were pleased to find that commercially available $(Sn^{II}O)_n$ could promote chlorohydrin formation (Scheme 1).[3,7] Thus, the active species of the catalyst would be $(Cl_2SnO)_n$. Second, the epoxide was found not to be the intermediate in this reaction. During the reaction, none of the corresponding epoxide was detected by TLC or NMR analysis. Furthermore, when the mixture of cyclohexene oxide and cycloheptene was subjected to the chlorohydrin-forming conditions ($SnCl_4$ (10 mol %), BTSP (1.2 mol equiv), and TMSCl (2 mol equiv)), *trans*-2-chlorocycloheptanol was obtained in 84% yield with cyclohexene oxide remained unchanged. Finally, from the ^{18}O-labeling experiment, it was found that the oxygen atom of the product chlorohydrin was derived from the oxygen atom of $(Cl_2SnO)_n$ species. We

(1) (a) Suzuki, M.; Takada, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902−904. (b) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029−2032. (c) Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971−973.
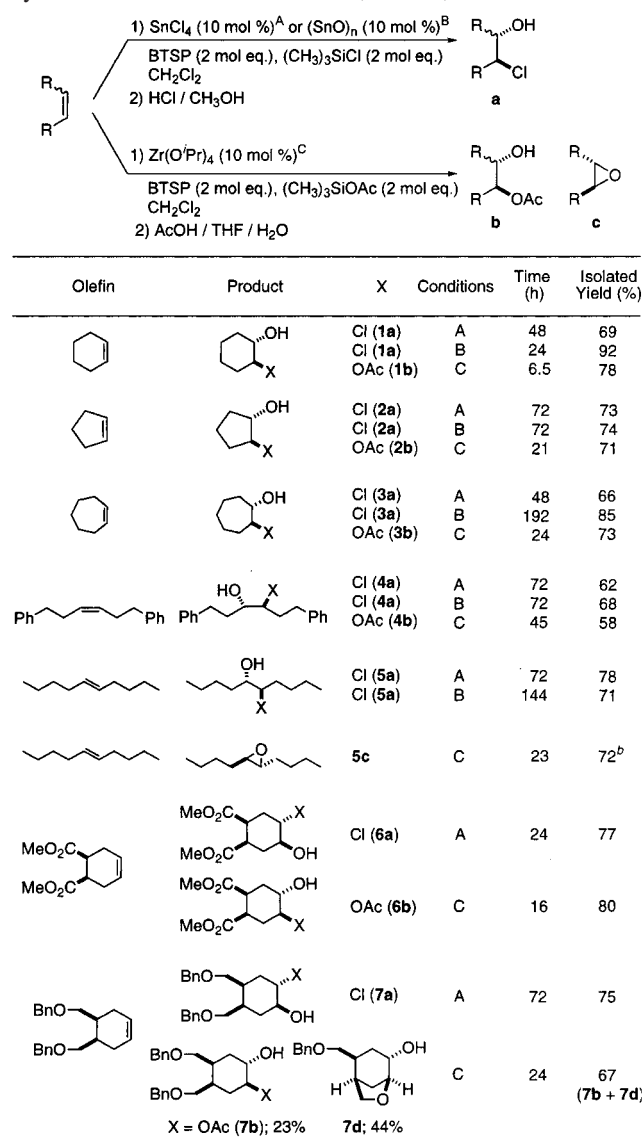
(2) For chlorohydrin synthesis from olefins, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; 325−326.

(3) See Supporting Information for experimental details.

(4) The stereochemistry was unequivocally determined by converting to (1R*,2S*,4R*,5S*)-1,2-bis(*tert*-butyldiphenylsilyloxymethyl)-4,5-epoxycyclohexane, whose structure is known by X-ray analysis. Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783−4784. For the determination of the relative stereochemistry of other compounds, see Supporting Information.

(5) Dehnicke, V. K. *Z. Anorg. Allg. Chem.* **1961**, *308*, 72−78.

(6) For the discussion of oligomeric structure of oxotin complexes, see: Davies, A. G.; Smith, P. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1982; Chapter 11, Vol. 2, p 519.

(7) The use of $(Bu_2SnO)_n$ and $Sn^{IV}O_2$ gave less satisfactoy results in terms of reaction rate.

**Scheme 2.** Possible Mechanism of Chlorohydrin Formation from Olefins
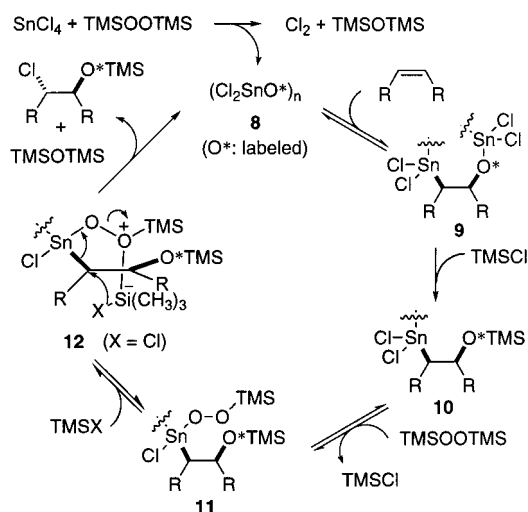
prepared ^{18}O-labeled $(Cl_2SnO)_n$ by the reaction of $SnCl_4$ and ^{18}O-labeled BTSP.[3] The reaction using this pregenerated $(Cl_2Sn^{18}O)_n$ (1 mol equiv), ^{16}O-BTSP (2 mol equiv) and TMSCl (2 mol equiv) afforded ^{18}O-labeled product **6a** in 44% yield. The incorporation of ^{18}O atom was detected by mass spectroscopy after conversion to the corresponding epoxide. From this evidence, a possible reaction mechanism for chlorohydrin formation is postulated in Scheme 2. The first step may be an insertion of an olefin to a Sn−O bond to give **9**.[8] Maybe this step is an equilibrium process, in which starting **8** and the olefin are in a thermodynamically more favored state.[9] As a result, no reaction could proceed in the absence of TMSCl. Reaction of **9** with TMSCl followed by the attack of BTSP could give **11**. Furthermore, the reaction of **11** with TMSCl possibly via the transition state **12** could give the TMS-protected chlorohydrin and hexamethyldisiloxane with the regeneration of the catalyst **8**. This model also explains the stereochemistry of **6a** and **7a**, in which the hydroxyl group exists *cis* to the ester or ether group that can function as directing groups for $(Cl_2SnO)_n$ by coordination.[10]

Next, we extended this novel reaction to the formation of more synthetically useful diol derivatives. Development of one-step *trans*-diol derivative formation from olefin is quite challenging.[11] We expected that if we used TMSOAc, instead of TMSCl, *trans*-β-acetoxy alcohols could be obtained via the hypothetical transition state **12** (X = OAc). In fact, the $SnCl_4$-catalyzed reaction of TMSOAc afforded a 5 (61%):1 (12%) mixture of acetoxy alcohol **1b** and chlorohydrin **1a**. Having obtained this exciting result, we optimized the reaction conditions and found that Zr-$(O^iPr)_4$ was the best Lewis acid for the acetoxy alcohol formation.[12] Thus, in the presence of $Zr(O^iPr)_4$ (10 mol %), BTSP (2 mol equiv), and TMSOAc (2 mol equiv), *trans*-β-acetoxy alcohols were obtained in good yields (Scheme 1).[3] Interestingly, the Zr-catalyzed reaction proceeds, contrasting with the Sn-catalyzed

reaction, via an epoxide intermediate,[13] which was confirmed by ^{1}H NMR of the reaction mixture, as well as by the fact that the epoxide reacted smoothly to give the acetoxy alcohol.[3] Moreover, in the case of *trans*-5-decene, the epoxide (**5c**) was the major product, and only a trace amount of the acetoxy alcohol was obtained. Judging from the stereochemistry of **6b** and **7b**,[14] the epoxide formation was found to take place from the opposite side of the ester and ether groups. Importantly, of $Zr(O^iPr)_4$, BTSP, and TMSOAc, each is essential for generating the active species. Thus, in the absence of TMSOAc, even epoxidation did not take place. Furthermore, the epoxide did not afford the acetoxy alcohol in the absence of BTSP. Although the structure of the catalytic species is not clear at this point, it appears that the actual catalytic species may be an oxozirconium complex.[15]

These new reactions prompted us to investigate their applicability to catalytic asymmetric reactions.[16,17] A preliminary result using diisopropyl L-tartrate (L-DIPT) as a chiral ligand is shown in Scheme 3.[3,18−20]

Scheme 3. Catalytic Asymmetric Synthesis of Chlorohydrins from Olefins

1a: n = 2, yield 76%, 56% ee (X = 10; 48 h)
2a: n = 1, yield 86%, 58% ee (X = 20; 72 h)
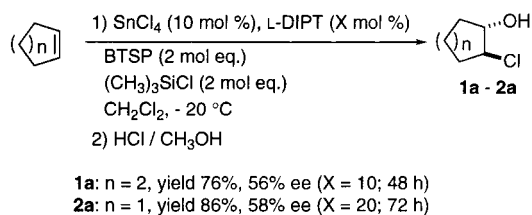
In conclusion, we have developed a conceptually new method for the direct synthesis of chlorohydrins and acetoxy alcohols from olefins. These reactions are potentially extended to catalytic asymmetric processes. Further studies for improvement of enantioselectivities by designing new chiral ligands, are currently under investigation.

Supporting Information Available: Experimental procedures and characterization of the products; details for ^{18}O-labeling experiments. NMR studies for Zr catalytic species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(8) For the reactivity of a Sn−O bond, see ref 6.

(9) **9** was not detected by NMR.

(10) One of the reviewers suggested an interesting alternative mechanism as follows. Reaction of the unstable tin species containing a chlorine with olefin gives the chloronium ion with an oxo(chloro)tin cluster as counterion. Collapse of this ion pair proceeds with carbon−oxygen bond formation. However, the above mechanism can be denied by the following experimental results. Treatment of cyclohexene with $SnCl_4$, BTSP, and TMSOAc gave **1b** (61%) and **1a** (12%). Moreover, reaction of cyclohexene with $SnCl_4$, BTSP, and $TMSN_3$ gave the *trans*-azidohydrin (48%) and **1a** (17%).

(11) Wilson, C. V. In *Organic Reactions*; Adams, R., Ed.; John Willey & Sons Inc. New York, 1957; Chapter 6, Vol. 9, p 350.

(12) The use of other Lewis acids such as $Zr(O^tBu)_4$, $Ti(O^iPr)_4$, and $(Sn^{II}O)_n$ gave less satisfactory results.

(13) Metal-catalyzed epoxidation of olefins by BTSP: Irie, R.; Hosoya, N.; Katsuki, T. *Synlett* **1994**, 255−256. Yudin, A. K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 11536−11537.

(14) **6b** and **7b** were found to be kinetic products: see Supporting Information.

(15) Reaction of cyclohexene with $(AcO)_2Zr=O$, BTSP, and TMSOAc gave the epoxide (26%) and **1b** (3%) for 48 h, and **1b** (73%) and the epoxide (20%) for 498 h.

(16) For a catalytic asymmetric synthesis of chlorohydrins from olefins, see: (a) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790−2791. (b) Hamed, O.; Henry, P. M. *Organometallics* **1998**, *17*, 5184−5189.

(17) For a catalytic asymmetric synthesis of halohydrins from epoxides, see: (a) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428−2429. (b) Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139−7140.

(18) The absolute configuration of 1*S*,2*S*-**1a** was determined by the comparison of the optical rotation; Fukazawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron Asymmetry* **1996**, *7*, 1649−1658. The absolute configuration of 1*S*,2*S*-**2a** was determined by the Mosher method; Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(19) The following results for **1a** were obtained using other tartaric acid derivatives. dimethyl L-tartrate (64% yield, 45% ee); diethyl L-tartrate (58% yield, 51% ee); di-*tert*-butyl L-tartrate (24% yield, 18% ee); *N,N,N′,N′*-tetramethyl-L-tartaramide (12% yield, 2% ee).

(20) Addition of a catalytic amount (30 mol %) of H_2O, thus generating HCl in situ, afforded a positive effect on enantioselectivity. The ee values of **1a** and **2a** increased to 66% from 56% and 63% from 58%, respectively, in the presence of H_2O (both in 70% yields).