Preparation of Zinc–Homoenolate from α-Sulfonyloxy Ketone and Bis(iodozincio)methane

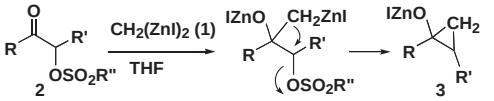
Kenichi Nomura and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoutodaigaku-katsura, Nishikyo-ku, Kyoto 615-8510

(Received October 16, 2006; CL-061217; E-mail: matsubar@orgrxn.mbox.media.kyoto-u.ac.jp)

Treatment of α-sulfonyloxy ketone with bis(iodozincio)-methane gives a zinc cyclopropoxide which is formed via a nucleophilic addition of the reagent to carbonyl group followed by an intramolecular substitution reaction.

Preparation of cyclopropanol has been well investigated,[1] since Cottle reported the first example of cyclopropanol formation from epichlorohydrin in 1942.[2] Various types of cyclopropanol preparations have been reported: for example, cyclopropanation of enols by carbenoid,[3] treatment of ester derivatives with Sm–CH_2I_2,[4] chromium-mediated cyclization of α,β-unsaturated enal,[5] and Kulinkovich reaction of organotitanium reagent.[6] Although these existing methods offer us a variety of methods for preparation of cyclopropanols, we tried to add a direct method to prepare cyclopropanol using a reaction of methylene dianion with a carbonyl compound carrying a leaving group at α-position. We have studied the reaction of bis(iodozincio)-methane (**1**),[7] which is easily prepared from zinc, diiodomethane, and a catalytic amount of lead.[8] We examined how to utilize the reagent for a reaction with α-sulfonyloxy ketone as a substrate including the enantiomerically pure material. Zinc–cyclopropoxide, which will be formed in situ, also possesses high potential for organic synthesis as a metal–homoenolate equivalent.[9]

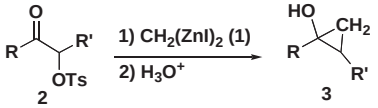
Bis(iodozincio)methane (**1**) had been already shown not to possess enough nucleophilicity to attack a carbonyl group of simple ketone in its Wittig-type methylenation reaction,[7c,7d] but can perform nucleophilic addition into a ketone carrying a coordinative hetero-atom such as methoxy or hydroxy group at α-position by an acceleration effect for nucleophilic attack of an organometallic reagent through chelation.[10,11] Along this line, it is expected that treatment of α-sulfonyloxy ketone **2** with bis(iodozincio)methane (**1**) affords zinc–cyclopropoxide **3** via a nucleophilic attack of **1** and an intramolecular substitution reaction as shown in eq 1.[12,13] In other words, a sulfonyloxy group will act not only as an accelerator of nucleophilic attack of **1** but also a good leaving group for the cyclopropanation reaction. The formed zinc–cyclopropoxide can react as zinc–homoenolate.



(1)

As shown in Table 1, α-tosyloxy ketone **2** (1.0 mmol) in THF (4 mL) was treated with bis(iodozincio)methane (**1**, 3.0 mmol, 0.5 M in THF) at 25 °C. After being stirred for the period shown in Table 1, the mixture was treated with saturated aqueous NH_4Cl. The difficulty of isolation of cyclopropanol was also observed in Runs 1, 6, and 7 (R′ = H). Purification by short silica-gel column chromatography gave the corresponding cyclopropanol. Substrates having a stereogenic center afforded the cyclopropanol as a diastereomeric mixture.

Table 1. Preparation of cyclopropanol **3**[a]



Run	R	R′		Time/h	Yield/%		Ratio
1	Ph	H	**2a**	2	56[b]	**3a**	—
2	Ph	Me	**2b**	10	86	**3b**	76/24
3	2-Naphthyl	Me	**2c**	15	99	**3c**	67/33
4	*p*-$MeOC_6H_4$	Me	**2d**	20	81	**3d**	67/33
5	*p*-$CF_3C_6H_4$	Me	**2e**	4	88	**3e**	72/28
6	2-Furyl	H	**2f**	15	38[c]	**3f**	—
7	Octyl	H	**2g**	15	31[d]	**3g**	—
8	Me	Heptyl	**2h**	20	48	**3h**	95/5

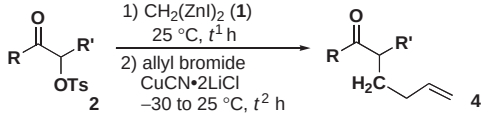
[a]Ketone (1.0 mmol), bis(iodozincio)methane (3.0 mmol, 0.5 M in THF), and THF were used. [b]3-Phenyl-3-propanone was obtained in 43% yield. [c]3-(2-Furyl)-3-propanone was obtained in 50% yield. [d]3-Undecanone was obtained in 59% yield.

Without isolating cyclopropanol, we examined a direct copper-mediated allylation where zinc–cylopropoxide acts as a homoenolate equivalent.[9] The reaction mixture obtained from the ketone **2** (1.0 mmol) and the reagent **1** (2.0 mmol, 0.5 M in THF) was treated with CuCN·2LiCl (2.0 mmol) at −30 °C. Allyl bromide was added to the resulting mixture. As shown in Table 2, allylated ketones **4** were obtained in good yields.

As shown in eqs 2 and 3, acylation of homoenolate was also examined. Treatment of zinc–cyclopropoxides obtained from **2a** and **2c** with benzoyl chloride in the presence of Pd-catalyst gave 1,4-diketones **5a** and **5c**.

While the nucleophilic addition of **1** to a simple ketone

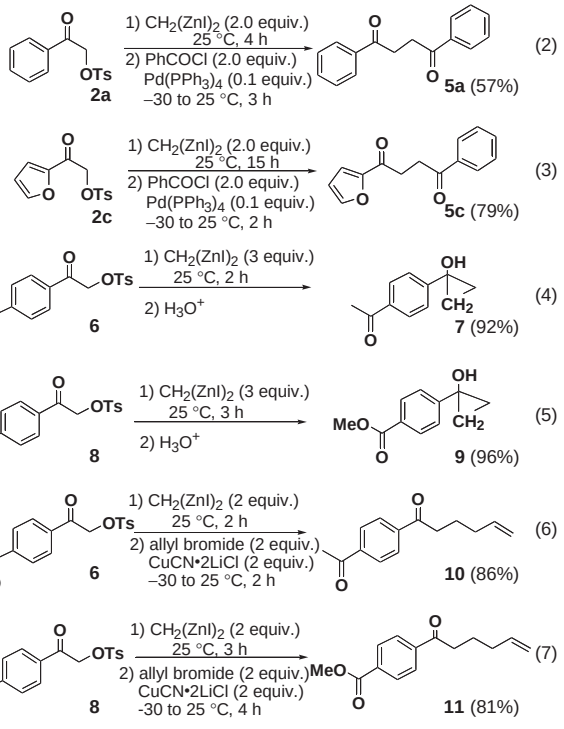
Table 2. Homoallylation of α-tosyloxy ketone **2**[a]



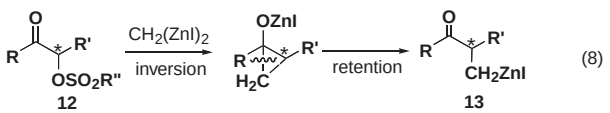
Run	R	R′		t^1/h	t^2/h	Yield/%	
1	Ph	H	**2a**	4	4	85	**4a**
2	Ph	Me	**2b**	4	4	76	**4b**
3	2-Naphthyl	Me	**2c**	18	20	78	**4c**
4	*p*-$MeOC_6H_4$	Me	**2d**	24	12	55	**4d**
5	*p*-$CF_3C_6H_4$	Me	**2e**	3	5	87	**4e**
6	2-Furyl	H	**2f**	15	6	79	**4f**
7	Octyl	H	**2g**	24	3	84	**4g**
8	Me	Heptyl	**2h**	72	6	53	**4h**

[a]Ketone (1.0 mmol), bis(iodozincio)methane (2.0 mmol, 0.5 M in THF), CuCN·2LiCl (2.0 mmol), allyl bromide (2.0 mmol), and THF were used.

needs the assistance of a titanium salt,[7d] that to α-alkoxy ketone proceeds smoothly without any additive.[10] These observations imply that the cyclopropanol formation from α-tosyloxy ketone may be performed even in the presence of another ketone group in the substrate. As shown in eqs 4 and 5, α-tosyloxy ketone with an additional functional group was examined for the cyclopropanol formation. In the presence of a ketone **6** or an ester **8**, the nucleophilic cyclopropanation was observed at α-tosyloxy ketone (**7** and **9**) group without affecting any other carbonyl group. Allylation of copper-mediated zinc–cyclopropoxide also worked well (eqs 6 and 7).

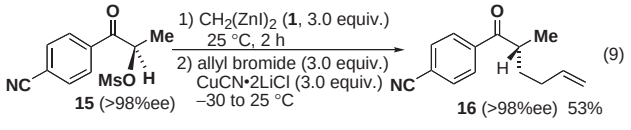


As described in Table 1 (Runs 2–5 and 8), treatment of chiral α-tosyloxy ketones with **1** gave cyclopropanols as a mixture of diastereomers. The ratio reflects the diastereofacial selectivity of **1** in the nucleophilic attack to the carbonyl group of **2**. The following cyclopropane ring formation is a stereospecific S_N2 reaction. As shown in eq 8, use of an optically active α-sulfonyloxy ketone **12** is expected to afford an optically active zinc–homoenolate **13**. As the stereogenic center at oxygen atom-substituted carbon of zinc–cyclopropoxide will be converted into a carbonyl group accompanying C–C bond fission, the homoenolate **13** will be formed with reflecting the optical purity of **12**.



(8)

As shown in eq 9, optically active mesylate **15** was treated with **1** to form zinc–cyclopropoxide. The cyclopropoxide was treated with allyl bromide in the presence of copper salt. The product **16** was obtained without loss of optical purity.



(9)

Thus, the specific reaction of bis(iodozincio)methane with α-sulfonyloxy ketone gives zinc–cyclopropoxide with high chemoselectivity. As zinc–cyclopropoxide is an equivalent of zinc–homoenolate, the further C–C bond-forming reaction can be performed. The reaction of optically active α-sulfonyloxy ketone[14] with **1** in eq 9 has not been well optimized, but the C–C bond-forming reaction with inversion of stereochemistry using intramolecular cyclopropanation gives a convenient method to synthesize an optically active ketone.[15]

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology. The financial support provided by Chugai Pharmaceutical Co., Ltd.

References and Notes

1 For general reviews, see: a) O. G. Kulinkovich, *Chem. Rev.* **2003**, *103*, 2597. b) D. H Gibson, C. H. DePuy, *Chem. Rev.* **1974**, *74*, 605. c) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165. d) J. Salaün, *Chem. Rev.* **1989**, *89*, 1247.
2 a) J. K. Magrane, Jr., D. L. Cottle, *J. Am. Chem. Soc.* **1942**, *64*, 484. b) G. W. Stahl, D. L. Cottle, *J. Am. Chem. Soc.* **1943**, *65*, 1782.
3 a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323. b) A. B. Charette, J. F. Marcoux, F. Bélanger-Gariépy, *J. Am. Chem. Soc.* **1996**, *118*, 6792. c) J. M. Denis, J. M. Conia, *Tetrahedron Lett.* **1972**, *13*, 4593. d) G. M. Rubottom, M. I. Lopez, *J. Org. Chem.* **1973**, *38*, 2097. e) H. H. Wasserman, D. C. Clagett, *Tetrahedron Lett.* **1964**, 341. f) E. Wenkert, *Acc. Chem. Res.* **1980**, *13*, 27. g) S. Murai, T. Aya, N. Sonoda, *J. Org. Chem.* **1973**, *38*, 4354.
4 a) T. Imamoto, Y. Kamiya, T. Hatajima, H. Takahashi, *Tetrahedron Lett.* **1989**, *30*, 5149. b) T. Imamoto, N. Takiyama, *Tetrahedron Lett.* **1987**, *28*, 1307. c) T. Imamoto, T. Hatajima, N. Takiyama, T. Takeyama, Y. Kamiya, T. Yoshizawa, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127. d) S. Fukuzawa, H. Furuya, T. Tsuchimoto, *Tetrahedron* **1996**, *52*, 1953.
5 C. Toratsu, T. Fujii, T. Suzuki, K. Takai, *Angew. Chem., Int. Ed.* **2000**, *39*, 2725.
6 a) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Prityts kaya, *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 2027. b) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, *Synthesis* **1991**, 234. c) O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789. d) F. Sato, H. Urabe, S. Okamoto, *Chem. Rev.* **2000**, *100*, 2835.
7 a) S. Matsubara, K. Oshima, K. Utimoto, *J. Organomet. Chem.* **2001**, *617–618*, 39. b) S. Matsubara, K. Oshima, *Proc. Jpn. Acad.* **2003**, *79*, 71. c) S. Matsubara, K. Oshima, in *Modern Carbonyl Olefination*, ed. by T. Takeda, Wiley-VCH, Weinheim, **2004**, Chap. 5, pp. 200–222. d) S. Matsubara, T. Mizuno, T. Otake, M. Kobata, K. Utimoto, K. Takai, *Synlett* **1998**, 1369. e) S. Matsubara, K. Oshima, H. Matsuoka, K. Matsumoto, K. Ishikawa, E. Matsubara, *Chem. Lett.* **2005**, *34*, 952.
8 a) K. Takai, T. Kakiuchi, Y. Kataoka, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 2668. b) K. Takai, T. Kakiuchi, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 2671.
9 a) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1977**, *99*, 7360. b) S. Murai, I. Ryu, N. Sonoda, *J. Organomet. Chem.* **1983**, *250*, 121. c) I. Kuwajima, E. Nakamura, *Top. Curr. Chem.* **1990**, *133*, 3. d) J. H. Youn, J. Lee, J. K. Cha, *Org. Lett.* **2001**, *3*, 2935.
10 K. Ukai, D. Arioka, H. Yoshino, H. Fushimi, K. Oshima, K. Utimoto, S. Matsubara, *Synlett* **2001**, 513.
11 a) X. Chen, E. R. Hortelano, E. L. Eliel, S. V. Frye, *J. Am. Chem. Soc.* **1992**, *114*, 1778. b) K. Utimoto, A. Nakamura, S. Matsubara, *J. Am. Chem. Soc.* **1990**, *112*, 8189.
12 a) T. Hirayama, K. Oshima, S. Matsubara, *Angew. Chem., Int. Ed.* **2005**, *44*, 3293. b) K. Ukai, K. Oshima, S. Matsubara, *J. Am. Chem. Soc.* **2000**, *122*, 12047. c) K. Nomura, K. Oshima, S. Matsubara, *Tetrahedron Lett.* **2004**, *45*, 5957. d) K. Nomura, K. Oshima, S. Matsubara, *Angew. Chem., Int. Ed.* **2005**, *44*, 5860.
13 T. Sato, M. Watanabe, T. Watanabe, Y. Onoda, E. Murayama, *J. Org. Chem.* **1988**, *53*, 1894.
14 Obtained from optically active α-hydroxy ketone which was prepared from silyl enol ether and AD-mix-α: T. Hashiyama, K. Morikawa, K. B. Sharpless, *J. Org. Chem.* **1992**, *57*, 5067.
15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) December 16, 2006; doi:10.1246/cl.2007.164