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

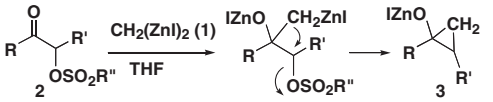
Kenichi Nomura and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoutodaigaku-katsura, Nishikyo-ku, Kyoto 615-8510

(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]

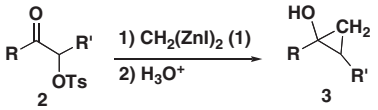
Bis(iodozincio)methane (**1**) had been already shown not to possess enough nucleophilicity to attack a carbonyl group of simple ketone in its Wittig-type methylenation reaction,[7c,7d] but can perform nucleophilic addition into a ketone carrying a coordinative hetero-atom such as methoxy or hydroxy 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/%	
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

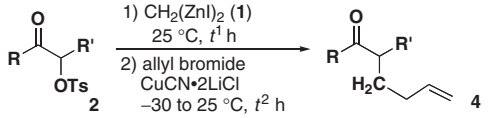
[a]Ketone (1.0 mmol), bis(iodozincio)methane (3.0 mmol, 0.5 M in THF), and THF were used. [b]3-Phenyl-3-propanone was obtained in 43% yield. [c]3-(2-Furyl)-3-propanone was obtained in 50% yield. [d]3-Undecanone was obtained in 59% yield.

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

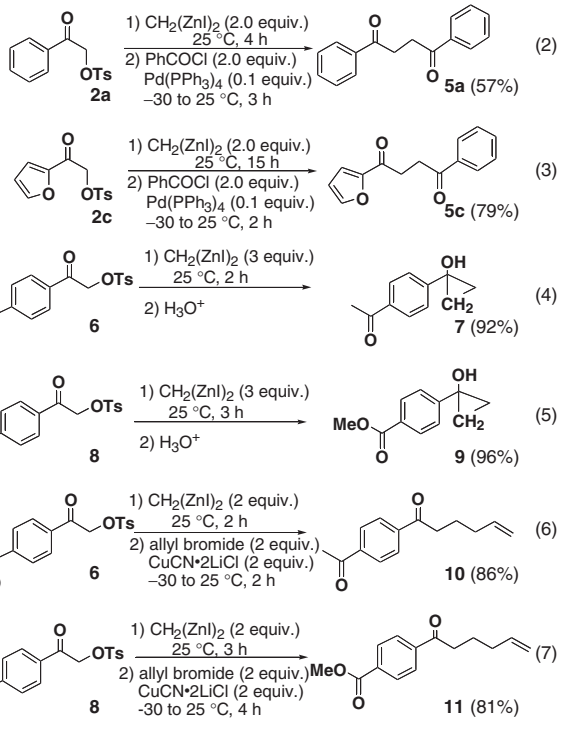
Table 2. Homoallylation of α-tosyloxy ketone **2**[a]



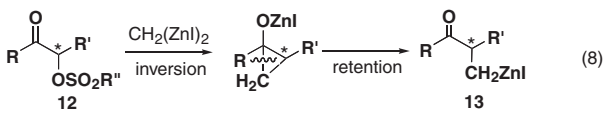
Run	R	R′		t^1/h	t^2/h	Yield/%	
1	Ph	H	**2a**	4	4	85	**4a**
2	Ph	Me	**2b**	4	4	76	**4b**
3	2-Naphthyl	Me	**2c**	18	20	78	**4c**
4	*p*-$MeOC_6H_4$	Me	**2d**	24	12	55	**4d**
5	*p*-$CF_3C_6H_4$	Me	**2e**	3	5	87	**4e**
6	2-Furyl	H	**2f**	15	6	79	**4f**
7	Octyl	H	**2g**	24	3	84	**4g**
8	Me	Heptyl	**2h**	72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

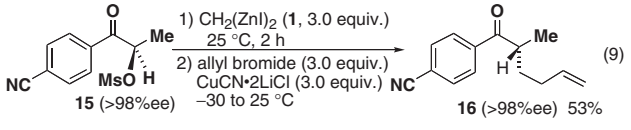
needs the assistance of a titanium salt,[7d] that to α-alkoxy ketone proceeds smoothly without any additive.[10] These observations imply that the cyclopropanol formation from α-tosyloxy ketone may be performed even in the presence of another ketone group in the substrate. As shown in eqs 4 and 5, α-tosyloxy 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**.



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.



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]

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