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Synthesis of Cyclopropanols via Cyclopropanation of Zinc Enolates

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Abstract: The reaction of α-iodoketones with diethylzinc afforded zinc enolates which were converted into the corresponding cyclopropanols in good yields upon treatment with CH_2I_2 and Et_2Zn. The use of α-iodoketone having a carbon-carbon double bond as a substrate proved that cyclopropanation of the enolate moiety proceeded chemoselectively. Cyclopropanation of the zinc enolates derived from α,β-unsaturated ketones via 1,4-addition of organozinc species was also achieved.

There are numerous cyclopropane-mediated reactions in organic synthesis and, therefore, cyclopropanol has been regarded as a versatile synthetic intermediate.[1] Some effective methods to prepare cyclopropanol have been reported.[2,3] There are only a few examples, however, that provide cyclopropanols directly from metal enolates except silyl enolates.[4, 5] We have already reported that treatment of α-iodoketones with various kinds of organometallic reagents such as butyllithium, Grignard reagents, Et_2Zn, Me_3Al, and Et_3B effectively afforded the corresponding metal enolates.[6] It then occurred to us that, if the Simmons-Smith type reaction[7] of these resulting metal enolates proceeded satisfactorily, this and the metal enolate formation procedure would combine to provide an expeditious route to cyclopropanols. We have indeed found that cyclopropanation of zinc enolates by zinc carbenoid proceeded effectively.

Treatment of 3-iodo-2-undecanone (**1a**, 1.0 mmol) with two equivalents of diethylzinc (1.0 *M* hexane solution, 2.0 mmol) in ether (5 ml) at 0 °C afforded a zinc enolate quantitatively. Diiodomethane (1.5 mmol) was added at 0 °C to the resulting mixture of zinc enolate and residual one equivalent of Et_2Zn. After 3 h of stirring, the resulting mixture was cooled to −78 °C and was quenched with methanol to afford a cyclopropanol **2a** in 82% yield (Scheme 1).[8] Quenching at low temperature such as −78 °C was critical to obtain **2** in good yield. An addition of 1*M* HCl at 0 °C provided only a trace amount of the cyclopropanol and two isomeric ketones, 2-dodecanone and 3-methylundecanone (8:2), were obtained as the main product in 60% combined yield.[9] The use of hexane as a solvent gave a similar result (83%, *c*/*t* = 90/10), while the loss of stereoselectivity was observed in THF (88%, *c*/*t* = 72/28). In dichloromethane, the yield of cyclopropanol decreased though the stereoselectivity was somewhat improved (63%, *c*/*t* = 94/6).

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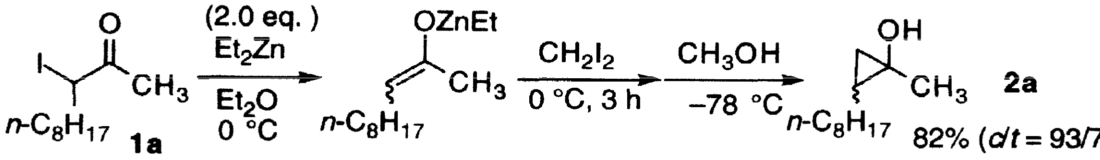
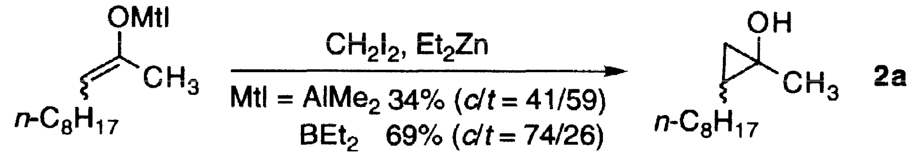
Scheme 1



We also examined the reaction of zinc carbenoid with other metal enolates which were derived from 3-iodo-2-undecanone and Me_3Al or Et_3B. The cyclopropanation of the corresponding diethylborane or dimethylaluminum enolate gave disappointing results from the viewpoint of the yields and stereoselectivities (Scheme 2).

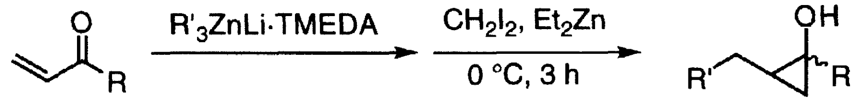
Scheme 2



Therefore, we focused on the synthesis of cyclopropanols through a Simmons-Smith type reaction of zinc enolates derived from various α-iodoketones or α-iodoaldehydes. The representative results are summarized in Table 1. The aliphatic α-iodoketones (**1a**, **1b**, and **1c**) were converted into the corresponding cyclopropanols in good yields (Entries 1–3). In these cases, high *cis* stereoselectivities were observed. Cyclopropanation of zinc enolate from α-iodopropiophenone (**1d**) gave an inferior result (Entry 4). It is notable that chemoselective cyclopropanation of the enolate moiety of the zinc enolate was observed in the reaction of **1e** which has a terminal C-C double bond (Entry 5). Treatment of tertiary α-iodoaldehydes (**1f** and **1g**) with diethylzinc afforded the corresponding zinc enolates which were further converted into the corresponding secondary cyclopropanols (**2f** and **2g**) (Entries 6 and 7). The use of 2-iodododecanal (**1h**) gave a complex mixture because the corresponding zinc enolate could not be obtained upon treatment with diethylzinc (Entry 8).

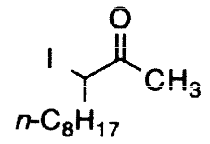
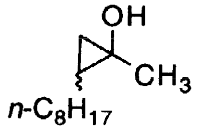
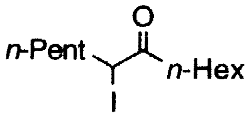
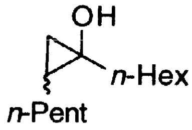
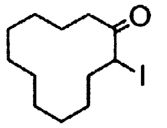
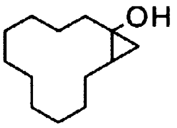
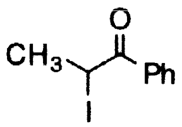
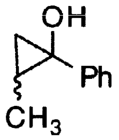
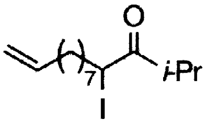
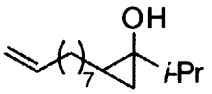
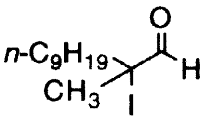
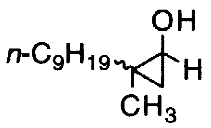
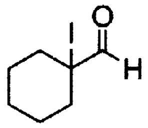
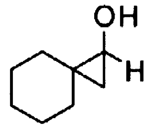
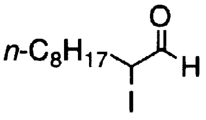
Then, we turned our attention to three-component synthesis of cyclopropanols from α,β-unsaturated ketones, alkylzinc, and diiodomethane in one-pot. It was reported that an addition of trialkylzincate, prepared from three equivalents of alkyllithium and $ZnCl_2$·TMEDA, to vinyl ketones afforded the corresponding zinc enolates effectively.[10] It was expected that treatment of these zinc enolates with zinc carbenoid might provide cyclopropanols. In fact, this proved to be the case and the corresponding cyclopropanols were obtained in good yields, starting from vinyl ketones (Scheme 3).

Scheme 3



R = CH_3	R' = *n*-Bu	61% (*c*/*t* = 67/33)
R = CH_3	R' = *s*-Bu	86% (*c*/*t* = 77/23)
R = *n*-C_5H_{11}	R' = *n*-Bu	61% (*c*/*t* = 62/38)

Table 1. Synthesis of cyclopropanols from α-iodoketones and α-iodoaldehydes[a)]

Entry	α-Iodocarbonyl compound		Cyclopropanol		Yield(%)	*cis* : *trans*
1		**1a**		**2a**	82	93 : 7
2		**1b**		**2b**	93	87 : 13
3		**1c**		**2c**	58	>99 : <1
4		**1d**		**2d**	34	n. d.
5		**1e**		**2e**	65	51 : 49
6		**1f**		**2f**	92	57 : 43
7		**1g**		**2g**	38	
8		**1h**	complex mixture			

a) α-iodocarbonyl compound (1.0 mmol), and Et_2Zn (2.0mmol) and CH_2I_2 (1.5 mmol) were employed.

Experimental procedure for the three-component synthesis is as follows. To a solution of $ZnCl_2$·TMEDA (265 mg, 1.1 mmol) in THF (3 ml) was added butyllithium (1.65 *M* hexane solution, 2.0 ml, 3.3 mmol) at 0 °C. After being stirred for 10 min, a solution of methyl vinyl ketone (70 mg, 1.0 mmol) in THF (2 ml) was added at –78 °C and the mixture was stirred for 45 min at that temperature. The mixture was warmed to 0 °C and Et_2Zn (1.1 ml, 1.0 *M* hexane solution, 1.1 mmol) followed by a solution of diiodomethane (402 mg, 1.5

mmol) in ether (2 ml) was added and the whole was stirred for 3 h at 0 °C. Then the mixture was cooled to −78 °C and MeOH (1.0 ml) was added to quench the reaction. The whole mixture was poured into a buffer solution (pH = 7.4, 20 ml) and extracted with ethyl acetate (20 ml × 3). Concentration followed by silica gel column purification gave 1-methyl-2-pentyl-1-cyclopropanol (87 mg, 0.61 mmol, *cis*:*trans* = 67:33) in 61% yield.

References and Notes

1. Wong, H. N. C.; Hon, M. -Y.; Tse, C. -W.; Yip, Y. -C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165-198; *The Chemistry of the Cyclopropyl Group*; Patai, S.; Rappoport, Z. Eds; Wiley: New York, 1987.
2. Titanium-mediated synthesis of cyclopropanol. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244-2245; Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Pritytskaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294-298; Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.*Synthesis* **1991**, 234; Kulinkovich, O. G.; Vasilevskii, D. A.; Savchenko, A. I.; Sviridov, S. V. *Zh. Org. Khim.* **1991**, *27*, 1428-1430; Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345-9346; Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919-9920; Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291-292; Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *117*, 4198-4199; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079-6082; Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849-1852.
3. From cyclopropyl metallic compounds. Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986-4988; Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605-609; Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 997-979; Hirabayashi, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 461-464;
4. Cyclopropanation of silyl enolates into cyclopropyl silyl ethers. Murai, S.; Aya, T.; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354-4356; LeGoaller, R.; Pierre, J. -L. *Bull. Soc. Chim. Fr.* **1973**, 1531-1532; Rubottom, G. H.; Lopez, M. I. *J. Org. Chem.* **1973**, *38*, 2097-2099; Girad, C.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3327-3328.
5. Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243-3246; Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* **1987**, *28*, 1307-1308. Very recently, conversion of β-keto esters to γ-keto esters involving cyclopropanation of zinc enolate. Brogan, J. B.; Zercher, C. K. *J. Org. Chem.* **1997**, *62*, 6444-6446.
6. Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463-464.
7. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1-131; Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53-58.
8. The zinc enolate from **1a** and Et$_2$Zn in ether revealed to be an isomeric mixture (*E*/*Z* or *Z*/*E* = 3/7) from ^{1}H NMR experiment. Thus, the reason for the stereoselective formation of *cis*-cyclopropanol **2a** (*c*/*t* = 93/7) is not clear at this stage.
9. Acid catalyzed opening of cyclopropanols, see. Whitlock, Jr., H. W.; Overman, L. E. *J. Org. Chem.* **1962**, *34*, 1962-1963; DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347-3354.
10. 1,4-Addition of trialkylzincate, see. Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679-682; Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437-1440; Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993-3996; Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581-1593.