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Controlled Site-Selective Reaction of γ,γ-Dialkoxyallylic Zirconium Species with Carbonyl Compounds: A New Method for the Construction of *gem*-Dialkoxycyclopropane Derivatives

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Carbon−carbon bond-forming reactions of allylic organometallics with electrophiles have been recognized as one of the most fundamental means in organic synthesis, and a number of applications for the construction of biologically active molecules have been reported.[1] Normally, allylic organometallics react with electrophiles at the α- or γ-position of a metal center. We have reported the carbon−carbon bond-forming reactions by use of the allylic and related zirconium species as reactive intermediates.[2] These zirconium species can be generated by treating allylic ethers with a zirconocene−butene complex ("Cp_2Zr")[3] through the formation of zirconacyclopropane and the following β-elimination of the alkoxyl group. Very recently, we reported the preparation of the γ,γ-dialkoxyallylic zirconium species **2** and its reaction with aromatic and α,β-unsaturated aldehydes (eq 1).[4] In this reaction, addition of the γ,γ-dialkoxyallylic zirconium species **2** to the carbonyl group occurred in SEi′ mode; thus, **2** behaved as an α,β-unsaturated acyl anion equivalent. This zirconium species **2** possibly has two reactive sites: one is the γ-position of the zirconium atom as an allylic zirconium species as reported previously,[4] and the other is the β-position as a ketene dialkyl acetal.[5] We found that *under Lewis acid promoted conditions, this zirconium species **2** reacts with a variety of carbonyl compounds selectively at the β-position in the first step, followed by the cyclopropanation reaction to afford the gem-dialkoxycyclopropane derivatives **4***[6] (eq 2). Furthermore, by treating the compound **4** with acid (trifluoroacetic acid), the β,γ-unsaturated carboxylic ester **5** was obtained, which is formally derived when the γ,γ-dialkoxyallylic zirconium species **2** reacts at the α-position of the zirconium atom (eq 3); that is, **2** can serve as a homoenolate anion equivalent.[7] We report herein this controlled site-selective reaction of the γ,γ-dialkoxyallylic zirconium species **2** leading to a new preparative method for the *gem*-dialkoxycyclopropane derivatives **4**.

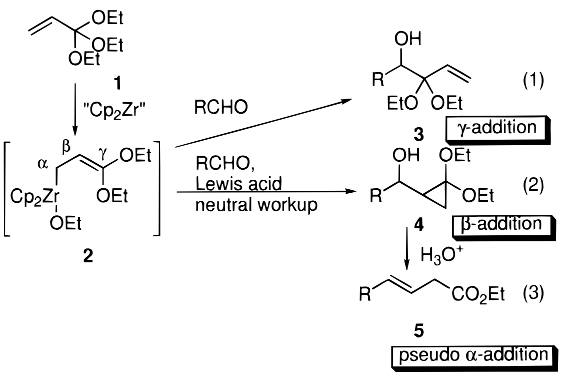
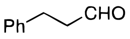
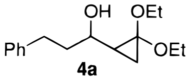
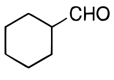
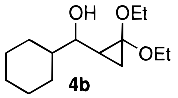
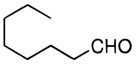
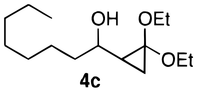
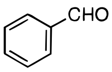
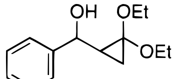
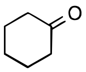
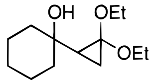
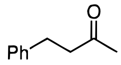
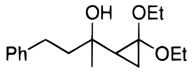


Table 1. Reaction of γ,γ-Dialkoxyallyliczirconium Species with Carbonyl Compound under Lewis Acid Promoted Conditions[a]

entry	carbonyl compound	Lewis acid	product[b]	yield (%)[c]
1		$BF_3{\cdot}OEt_2$	 **4a**	75
2		$TiCl_4$	**4a**	57
3		TMSOTf	**4a**	88
4		TMSOTf	 **4b**	87
5		TMSOTf	 **4c**	75
6		TMSOTf	 **4d**	81
7		TMSOTf	 **4e**	83
8		TMSOTf	 **4f**	76

[a] Reaction conditions: **2** (3 mmol based on the ortho ester),[4] carbonyl compound (3.6 mmol), Lewis acid (3.3 mmol), toluene (26 mL), −78 °C to room temperature, 2 h, then NH_4Cl(aq). [b] Relative stereochemistries were not determined. Diastereomeric ratio was 1:1 to 2:1. [c] Isolated yield after column chromatography (neutral silica gel).

Typical examples are summarized in Table 1. In the presence of Lewis acid, the γ,γ-diethoxyallylic zirconium species **2**,

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(1) For reviews on preparations and reactions of allylic organometallic reagents, see: (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (d) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.1. (e) Yamamoto, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.2. (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

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(5) For the reaction of ketene dialkylacetal with carbonyl compounds, see: (a) Scheeren, J. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 71. (b) Mattay, J.; Buchkremer, K. *Heterocycles* **1988**, *27*, 2153. (c) Hofstraat, R. G.; Lange, J.; Scheeren, H. W.; Nivard, R. J. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2315. (d) Aben, R. W. M.; Smit, R.; Scheeren, J. W. *J. Org. Chem.* **1987**, *52*, 365. (e) Hofstraat, R. G.; Scheeren, H. W.; Nivard, R. J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 561. (f) Aben, R. W. M.; Scheeren, J. W. *Tetrahedron Lett.* **1983**, *24*, 4613. (g) Aben, R. W. M.; Scheeren, J. W. *Synthesis* **1978**, 400. (h) Scheeren, H. W.; Aben, R. W. M.; Ooms, P. H. J.; Nivard, R. J. F. *J. Org. Chem.* **1977**, *42*, 3128. (i) Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282.

(6) For the preparation and synthetic utility of *gem*-dialkoxycyclopropanes, see: (a) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.14. (b) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792.

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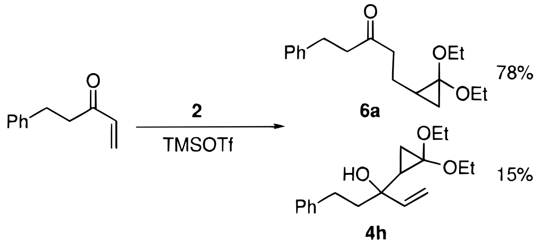
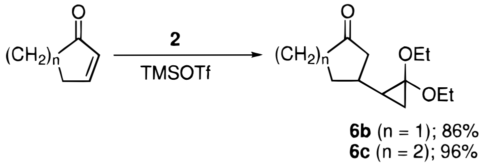


(4)

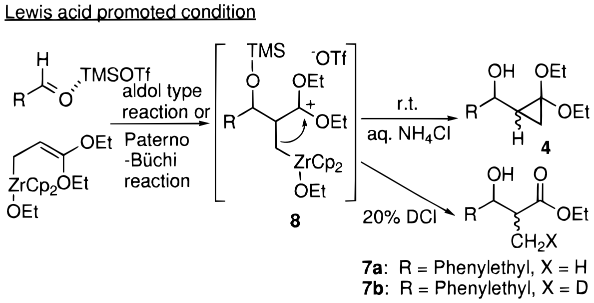


(5)

prepared from triethyl orthoacrylate (**1**) with "Cp_2Zr",[4] smoothly reacted with aldehydes to afford the *gem*-diethoxycyclopropane derivatives **4** as a diastereomeric mixture.[8] The use of Lewis acid brought about a remarkable contrast with respect to not only the reactivity but also the site-selectivity, since **2** itself did not react with aliphatic aldehydes and the normal allylic zirconium reaction (γ-addition) occurred with aromatic or α,β-unsaturated aldehydes.[4] Under the Lewis acid promoted conditions, toluene was more effective solvent as compared with THF. Regarding the Lewis acid, when boron trifluoride diethyl ether complex was employed, the reaction of **2** with 3-phenylpropionaldehyde gave **4a** in 75% yield along with a small amount of uncyclized product **7a** (entry 1). This result may support the following discussion for the mechanism of this reaction (vide infra). Trimethylsilyl trifluoromethanesulfonate (TMSOTf) smoothly promoted the reaction of **2** to afford the compound **4a** in 88% yield without the formation of **7a** (entry 3). Similarly, the zirconium species **2** reacted with not only aliphatic aldehydes but also aromatic aldehyde to give the cyclopropane derivatives (**4b**, **4c**, and **4d**) in good yields (entries 4−6).[9] Ketones also reacted with this reagent to afford the adduct (**4e**, **4f**), while the adduct was relatively unstable due to the facile elimination of the hydroxyl group during the acidic silica gel column chromatography (entries 7 and 8).[10]

We also examined the reaction of γ,γ-dialkoxyallylic zirconium species **2** with α,β-unsaturated carbonyl compounds. Under TMSOTf-promoted conditions, the 1,4-addition reaction at the β-position of **2** with 5-phenylpent-1-en-3-one predominantly proceeded to afford **6a** in good yield (eq 4).[11] With cycloalkenones, 1,4-adduct **6b** and **6c** were selectively obtained (eq 5).

Scheme 1



A plausible mechanism for the formation of cyclopropane derivatives **4** is shown in Scheme 1. In the presence of Lewis acid, the ketene diethyl acetal character overcomes the allylic zirconium character, and the aldol-type reaction or Paterno−Büchi reaction of γ,γ-dialkoxyallylic zirconium species **2** with the aldehyde first proceeded at the β-position of **2** to afford the intermediate **8**.[12] The in situ generated oxocarbenium intermediate **8** then smoothly reacts intramolecularly with the alkyl zirconium species to form the *gem*-diethoxycyclopropane derivatives **4**.[13] To ascertain the possibility of the existence of the intermediate **8**, we examined the deuterium incorporation at the methyl group in the compound **7**. Thus, after stirring the γ,γ-diethoxyallylic zirconium species **2** with 3-phenylpropionaldehyde in the presence of TMSOTf at −78 °C for 5 min, 20% deuterium chloride in D_2O was added to the reaction mixture. After workup, products **4a** and **7b** were obtained in 44% (diastereomeric ratio, 5:4) and 35% (diastereomeric ratio, 5:3) yield, respectively. Formation of the compound **7b** having a deuterium atom (>85%) at the α-methyl group should support the preexistence of zirconium at this position, thereby the reaction pathway to **4** involves the intermediate **8**.

In summary, we have revealed here the interesting reactivity of the γ,γ-dialkoxyallylic zirconium species **2** in the reaction with carbonyl compounds. This species reacted with the carbonyl compound at the β-position of the zirconium atom in the presence of trimethyl trifluoromethanesulfonate, and the *gem*-dialkoxycyclopropane derivatives could be obtained via the aldol-type or Paterno−Büchi reaction and the following cyclization. It is noteworthy that all three carbons in the allylic moiety of this species can participate in the reaction with the carbonyl compound, and this participation can be controlled by the choice of reaction conditions.

Supporting Information Available: Experimental details and characterization for all new compounds (7 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[8] All new compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, and elemental analysis.

[9] Molecular design of an HMG CoA reductase inhibitor having a *gem*-dihydroxycyclopropyl carbinol moiety was reported: Dowd, P.; Kaufman, C.; Abeles, R. H. *J. Am. Chem. Soc.* **1984**, *106*, 2703.

[10] It would be expected that the ring opening of the compound **4** can be Easily promoted by acidic treatment. Indeed, when the compounds **4a** and **4e** were treated with 50% aqueous trifluoroacetic acid in chloroform at room temperature, the corresponding β,γ-unsaturated esters **5a** (82%, *E*,*Z* mixture) and **5e** (86%) were obtained, respectively.

[11] In the case of (*E*)-2-hexenal, a competitive reaction of 1,2-addition and 1,4-addition was observed in the presence of TMSOTf.

[12] See ref 5a.

[13] For the intramolecular cyclization of homoenolate anion for construction of cyclopropane and related reactions, see: (a) Rühlmann, K. *Synthesis* **1971**, 236. (b) Rousseau, G.; Slougui, N. *J. Am. Chem. Soc.* **1984**, *106*, 7283. (c) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (d) Rieke, R. D.; Sell, M. S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 5429. (e) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (f) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.