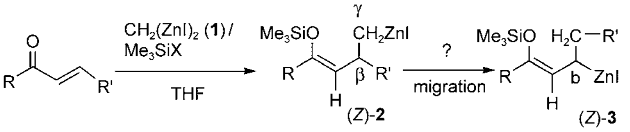
Angewandte
Chemie

Organozinc Reagents

Preparation of Enolate–Homoenolate Species as (Z)-γ-Siloxyallylmetal Equivalents: Sequential 1,4-Addition of Bis(iodozincio)methane to 1,4-Dicarbonylbutenes and Cyclopropanation**

*Takaharu Hirayama, Koichiro Oshima, and Seijiro Matsubara**

gem-Dizinc reagents, which have two nucleophilic sites on a carbon atom, have been used for a variety of molecular transformations based on repetition of C−C bond formation on the same carbon atom.[1] In our series of investigations on their reactivity, we have also found that 1,4-addition of bis(iodozincio)methane (**1**) to *s-cis*-α,β-unsaturated ketones such as chalcone or phenyl 1-propenyl ketone in the presence of chlorotrimethylsilane gives (*Z*)-trimethylsilyl enol ethers of γ-iodozincioketone stereoselectively.[2] If we can force migration of the iodozincio group from the γ position to the β position stereospecifically, (*Z*)-3-siloxyallylmetal species, which are considered to be a useful synthetic tool, will become available (Scheme 1). Various 3-alkoxyallylmetal species have been reported.[3,4] As achiral 3-alkoxyallylmetal reagents which give *vic*-diols diastereoselectively by reaction with aldehyde, derivatives of B,[5] In,[6] Sn,[7] Al,[8] Fe,[9] and Cr[10] have been shown to be valuable. The corresponding optically active reagents based on Al,[11] Sn,[12] Ti,[13] and B[14] have also been applied for the enantioselective synthesis of *vic*-diols. In all cases, some limitation arises from preparation of the stereochemically defined 3-alkoxyallylmetal reagent. Using our method (Scheme 1), we can prepare diastereoselectively (*Z*)-3-alkoxyallylmetal reagents containing an additional functional group R′. Here we describe a novel method



Scheme 1. Preparation of (*Z*)-3-siloxyallylzinc species (*Z*)-**3** by 1,4-addition of bis(iodozincio)methane (**1**) via (*Z*)-**2**.

---

[*] T. Hirayama, Prof. Dr. K. Oshima, Prof. Dr. S. Matsubara
Department of Material Chemistry
Graduate School of Engineering
Kyoto University
Kyoutodaigaku-Katsura, Nishikyo, Kyoto 615-8501 (Japan)
Fax: (+81) 75-383-2438
E-mail: matsubar@orgrxn.mbox.media.kyoto-u.ac.jp

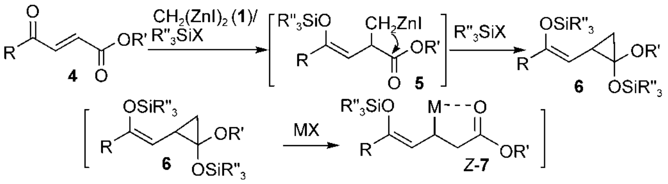
[**] This work was supported financially by the Japanese Ministry of Education, Science, Sports, and Culture. The financial support provided by Chugai Pharmaceutical Co., Ltd. and by the Takahashi Industrial and Economical Research Foundation is acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200500133

to prepare the *Z* isomers of 3-siloxyallylzinc reagents as well as their highly diastereoselective reaction with tosylimines.

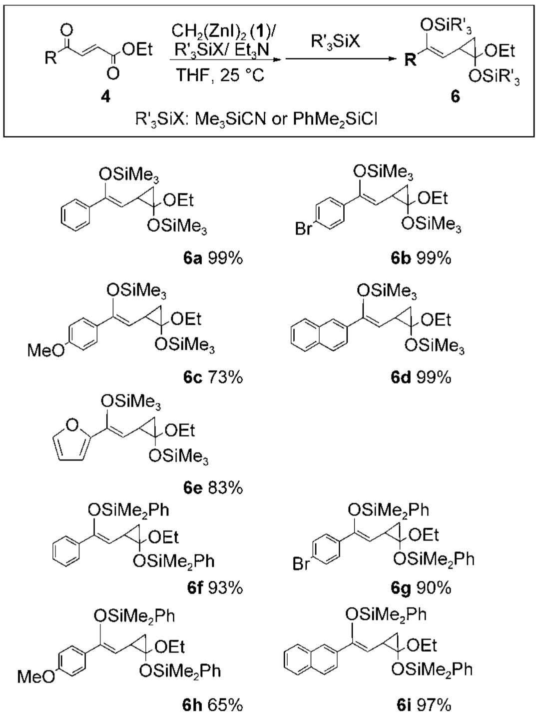
To promote migration of the iodozincio group from the γ- to the β-position (i.e., (*Z*)-**2**→(*Z*)-**3** in Scheme 1), we planned to use ring opening of a cyclopropanol. As shown in Scheme 2, our approach was to prepare enolate–homoenolate derivative **6**[15] by 1,4-addition of **1** to β-carboalkoxy α,β-unsaturated ketone **4**. The 1,4-addition of **1** to **4** in the presence of trimethylsilyl cyanide would afford the (*Z*)-trimethylsilyl enol ether of γ-iodozincio ketone **5** in situ, as shown in Scheme 2. Intramolecular nucleophilic attack on the ester group would give cyclopropane derivative **6**. This is an equivalent of enolate–homoenolate derivative (*Z*)-**7**, since 1-alkoxy-1-trialkylsiloxycyclopropane undergoes a ring-opening reaction in the presence of Lewis acid as a mediator to give a homoenolate, as reported by Nakamura.[16]



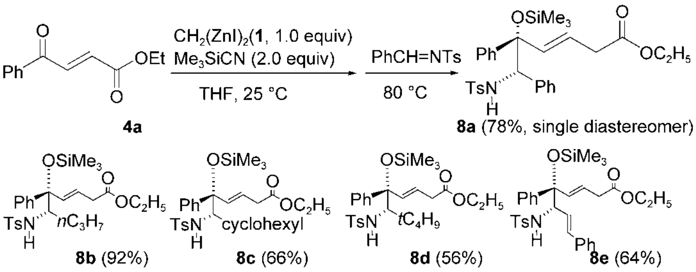
Scheme 2. Reaction concept for preparation of enolate–homoenolate equivalent **6**.

A mixture of ketoester **4a** (R = Ph, R′ = Et; 1.0 mmol), triethylamine (2.5 mmol), and trimethylsilyl cyanide (1.1 mmol) in THF was treated with **1** (1.2 mmol) at 25 °C for 5 min. Some additional trimethylsilyl cyanide (1.1 mmol) was added and the mixture was stirred for 10 min at room temperature. Triethylamine was added to prevent hydrolysis of silyl enol ether during aqueous workup. After aqueous workup, enolate–homoenolate equivalent **6a** (R = Ph, R′ = Et) was obtained in 99% yield. In the same way, enolate–homoenolate equivalents **6b–e** in Scheme 3 were obtained in good yields. When chlorodimethylphenylsilane was used as silylating reagent instead of trimethylsilyl cyanide, the corresponding phenyldimethylsilyl ether derivatives **6f–i** were obtained (Scheme 3). Products **6a–i** in Scheme 3 were obtained as equimolar mixtures of two diastereomers. Although the C=C bonds of these enol ethers were exclusively in the *Z* configuration,[17] formation of the cyclopropane ring (**5**→**6** in Scheme 2) did not proceed diastereoselectively.

Following the procedure for preparation of **6a** in Scheme 3 without addition of triethylamine, we added the tosylimine of benzaldehyde before aqueous workup and then raised the reaction temperature to 80 °C. As shown in Scheme 4, β-siloxylamine derivative **8a** was obtained as a single diastereomer after 4 h. The structure was also determined by X-ray analysis (Figure 1). The enolate–homoenolate equivalent **6a** reacted as (*Z*)-3-trimethylsiloxyallylmetal (*Z*)-**7**, since the 1-trimethylsiloxy-1-ethoxycyclopropane group in **6a** was converted to the homoenolate by the mediation of divalent zinc salts such as zinc(II) iodide and cyanide that were present in the reaction mixture. Examples



Scheme 3. Synthesis of trialkylsilyl enolate–homoenolates **6**.



Scheme 4. Reaction of enolate–homoenolate prepared from **4a** with various imines.

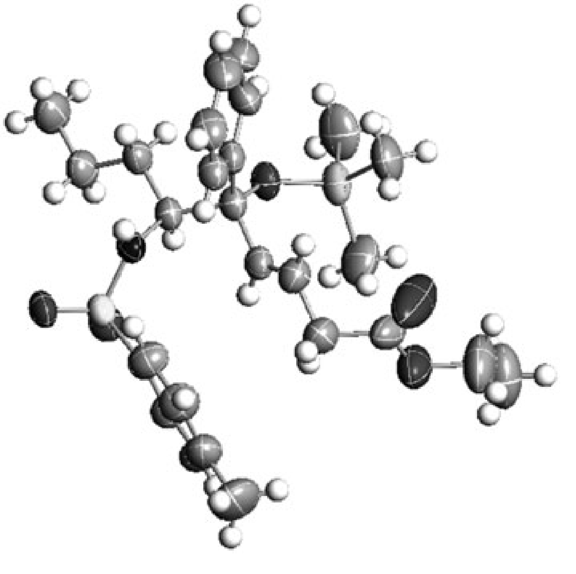


Figure 1. X-ray structure of **8a**.

of the reaction of **6a** with other tosylimines are also shown in Scheme 4. In all cases, the *threo*-β-siloxylamines were obtained with high diasteroselectivity.[18]

The reason for these extraordinarily high diastereoselectivities in the reaction of **6a** with imines in Scheme 4 is not clear. One possible explanation is that **6a** transforms into the β-zincioester (*Z*)-**7a**, which may have a fixed conformation due to coordination (Figure 2). If β-zincioester (*Z*)-**7a** reacts with (*E*)-tosylimine with activation by Lewis acid, as in **9**, the *threo* isomer **8a** will be a major product.

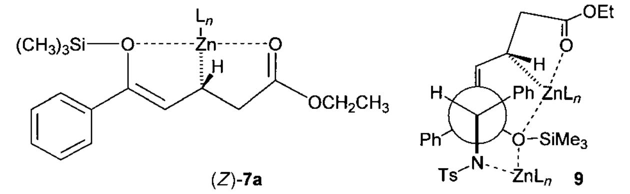
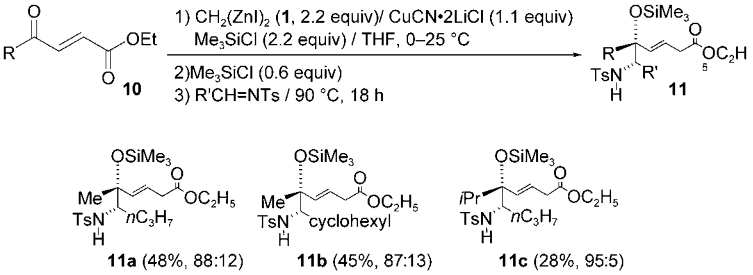


Figure 2. Proposed conformation of (*Z*)-**7a** and the transition state **9**.

Mediation with copper salt was required for reaction of *gem*-dizinc reagent **1** with aliphatic derivatives of **4** (Scheme 5; **10**, R = alkyl). Treatment of **1** with copper salt in THF at −50 °C gave a copper reagent, which adds to aliphatic enone as we reported previously.[2] Treatment of **10** with the copper reagent from **1** in the presence of silylating agent gave enolate–homoenolate in situ, which added to tosylimines at 80 °C. The diastereoselectivities were inferior to those obtained with the aromatic substrates shown in Scheme 4 but were sill good.



Scheme 5. Reaction of enolate–homoenolate prepared from aliphatic enone **10** with various imines.

Thus, the results allow us to propose a novel method to prepare stereochemically defined γ-siloxyallyl zinc species using 1,4-addition reactions of a *gem*-dizinc reagent. In addition, these zinc reagents add to tosylimines with high diastereoselectivity.

Experimental Section

1: A mixture of Zn (25 mmol), diiodomethane (1.0 mmol), and $PbCl_2$ (0.005 mmol) in THF (2.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. Diiodomethane (10 mmol) in THF (20 mL) was added dropwise to the mixture over 15 min at 10 °C with vigorous stirring. The mixture was stirred for 2 h at 25 °C. After the stirring was stopped, the reaction vessel was allowed to stand undisturbed for several hours. Excess zinc was separated by sedimentation. The ^1H NMR spectra of the obtained supernatant showed a broad singlet at −1.2 ppm at 0 °C corresponding to the methylene proton of **1**. The concentration was determined by ^1H NMR spectroscopy with 2,2,3,3-tetramethylbutane as an internal standard. The supernatant was used for further reaction as a solution of **1** in THF (0.4–0.5 M). In a sealed vessel, a solution of **1** can be stored at room temperature at least for two months.

6a (general procedure for **6**): A solution of **1** (0.4 M, 3.0 mL, 1.2 mmol) in THF was added dropwise to a solution of **4a** (0.2 g, 1.0 mmol), triethylamine (0.35 mL, 2.5 mmol), and trimethylsilyl cyanide (0.14 mL, 1.1 mmol) in THF (2.0 mL) at 25 °C. After the mixture had been stirred for 5 min, some additional trimethylsilyl cyanide (0.14 mL, 1.1 mmol) was added and stirring was continued for 10 min at 25 °C. Water (0.5 mL) was added to the reaction mixture at 0 °C. The mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After chromatography on a short silica-gel column with hexane/ether/triethylamine as eluent, **6a** was obtained in 97 % yield as a mixture of two diastereomers (55:45). These diastereomers arised from the configuration of the cyclopropane ring. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.42$–7.48 (m, 2 H), 7.26–7.31 (m, 2 H), 7.19–7.24 (m, 1 H), 5.08 (d, $J = 9.6$ Hz, 0.55 H), 5.07 (d, $J = 9.6$ Hz, 0.45 H), 3.60–3.76 (m, 2 H), 2.18 (ddd, $J = 6.5$, 10.0, 10.0 Hz, 0.55 H), 2.16 (ddd, $J = 6.0$, 9.6, 10.5 Hz, 0.45 H), 1.39 (dd, $J = 5.5$, 10.5 Hz, 0.55 H), 1.28 (dd, $J = 5.5$, 10.5 Hz, 0.45 H), 1.21 (t, $J = 9.0$ Hz, 1.35 H), 1.20 (t, $J = 9.0$ Hz, 1.65 H), 0.88 (dd, $J = 5.5$, 6.0 Hz, 0.45 H), 0.76 (dd, $J = 5.5$, 6.0 Hz, 0.55 H), 0.22 (s, 5 H), 0.20 ppm (s, 4 H), 0.16 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): minor product $\delta = 149.6$, 139.0. 128.2, 127.4, 125.2, 109.7, 89.5, 62.1, 25.4, 23.7, 22.2, 15.5, 0.94, 0.83 ppm; major product $\delta = 149.5$, 139.0. 128.2, 127.4, 125.2, 110.0, 89.9, 61.9, 25.4, 23.7, 22.6, 15.5, 0.94, 0.83 ppm; MS (ESI): m/z: 387 $[M^+(C_{19}H_{32}O_3Si_2)+Na^+]$.

8b (general procedure for **8**): A solution of **1** in THF (0.4 M, 3.0 mL, 1.2 mmol) was added dropwise to a solution of **4a** (0.2 g, 1.0 mmol) and trimethylsilyl cyanide (0.14 mL, 1.1 mmol) in THF (2.0 mL) at 25 °C. After the mixture had been stirred for 5 min, trimethylsilyl cyanide (0.14 mL, 1.1 mmol) was added, and stirring was continued for 10 min at 25 °C. A solution of the *N*-tosylimine of butanal (0.27 g, 1.2 mmol) in THF (1.5 mL) was added to the mixture at 25 °C, and the mixture was warmed to 80 °C and stirred at this temperature for 5 h. The resulting mixture was cooled to 0 °C. After addition of water, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide **8b** as a single diastereomer in 92 % yield. Single-crystal X-ray analysis determined the stereochemistry of the product. ^1H NMR ($CDCl_3$): $\delta = 7.69$ (d, $J = 6.5$ Hz, 2 H), 7.33 (d, $J = 6.5$ Hz, 2 H), 7.2–7.3 (m, 5 H), 5.99 (d, $J = 15.5$ Hz, 1 H), 5.76 (dt, $J = 7.0$, 15.5 Hz, 1 H), 4.55 (d, $J = 9.0$ Hz, 1 H), 4.14 (q, $J = 7.5$ Hz, 2 H), 3.76 (ddd, $J = 2.5$, 9.0, 9.0 Hz, 1 H), 3.08 (d, $J = 7.0$ Hz, 2 H), 2.39 (s, 3 H), 1.20–1.42 (m, 2 H), 1.27 (t, $J = 7.5$ Hz, 3 H), 1.06–1.19 (m, 1 H), 0.85–0.95 (m, 1 H), 0.71(t, J=7.0 Hz, 3 H), 0.16 ppm (s, 9 H); ^{13}C NMR (125 Hz, $CDCl_3$): $\delta = 171.5$, 142.7, 142.3, 139.8, 135.8, 129.6, 128.2. 127.9, 127.8, 127.1, 126.8, 81.5, 63.7, 61.1, 38.1, 34.6, 21.7, 19.9, 14.4, 14.1, 2.2 ppm; m.p. 80.0 °C (recrystallized from CH_3CN); HRMS (FAB): m/z: calcd for $C_{27}H_{40}NO_5SiS$: 518.2396 $[(M+1)^+]$; found: 518.2405. Crystal structure data: Triclinic, $a = 10.842(10)$, $b = 12.134(11)$, $c = 13.608(13)$ Å, $\beta = 110.316(15)°$, $V = 1489(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.154$ Mg m^{-3}, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $T = 296$ K, $\theta_{max} = 54.0°$, $R = 0.051$ for 6267 reflections ($I > 2\sigma(I)$).

Received: January 13, 2005

Keywords: allylic compounds · amino alcohols · cyclization · diastereoselectivity · zinc

---

[1] a) P. Knochel, J.-F. Normant, *Tetrahedron Lett.* **1986**, *27*, 4427; P. Knochel, J.-F. Normant, *Tetrahedron Lett.* **1986**, *27*, 4431; b) I. Marek, J.-F. Normant, *Chem. Rev.* **1996**, *96*, 3241; c) S. Matsubara, K. Oshima, *Proc. Jpn. Acad. Ser. B* **2003**, *79*, 71; S. Matsubara, K. Oshima, K. Utimoto, *J. Organomet. Chem.* **2001**, *617–618*, 39; S. Matsubara, *J. Synth. Org. Soc. Jpn.* **2000**, *58*, 118; d) P. Knochel in *Handbook of Grignard Reagents* (Eds.: G. S. Silverman, P. E. Rakita), Marcel Dekker, New York, **1996**, chap. 30; e) F. Berttini, P. Gasselli, G. Zubiani, G. Cainelli, *Tetrahedron* **1970**, *26*, 1281; f) B. J. J. van de Heisteeg, M. A. Schat, G. Tinga, O. S. Akkerman, F. Bickelhaupt, *Tetrahedron Lett.* **1986**, *27*, 6123; g) E. Nakamura, K. Kubota, G. Sakata, *J. Am. Chem. Soc.* **1997**, *119*, 5457; h) A. Hirai, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 11791.

[2] a) S. Matsubara, D. Arioka, K. Utimoto, *Synlett* **1999**, 1253; b) S. Matsubara, H. Yamamoto, D. Arioka, K. Utimoto, K. Oshima, *Synlett* **2000**, 1202.

[3] A. R. Katritzky, M. Piffl, H. Lang, E. Anders, *Chem. Rev.* **1999**, *99*, 665.

[4] M. Lombardo, S. Licciulli, C. Trombini, *Pure Appl. Chem.* **2004**, *76*, 657.

[5] a) R. W. Hoffmann, J. Krüger, D. Brückner, *New J. Chem.* **2001**, *25*, 102; b) R. W. Hoffmann, B. Kemper, *Tetrahedron Lett.* **1981**, *22*, 5263; c) R. W. Hoffmann, R. Metternich, *Liebigs Ann. Chem.* **1985**, 2390; d) T. Moriya, A. Suzuki, N. Miyaura, *Tetrahedron Lett.* **1995**, *36*, 1887; e) W. R. Roush, M. R. Michaelides, D. F. Tai, B. M. Laser, W. K. M. Chong, D. J. Harris, *J. Am. Chem. Soc.* **1989**, *111*, 2984.

[6] T. Hirashita, T. Kamei, T. Horie, H. Yamamura, M. Kaway, S. Araki, *J. Org. Chem.* **1999**, *64*, 172.

[7] a) S. Waterlot-Bourdea, J.-L. Parrain, J.-P. Quintard, *J. Org. Chem.* **1999**, *64*, 172; b) G. C. Micalizio, A. N. Pinchuck, W. R. Roush, *J. Org. Chem.* **2000**, *65*, 8730; c) G. E. Keck, D. E. Abbott, M. R. Wiley, *Tetrahedron Lett.* **1987**, *28*, 139.

[8] Y. Yamamoto, K. Komatsu, K. Maruyama, *J. Organomet. Chem.* **1985**, *285*, 31.

[9] S. Jiang, G. E. Agoston, T. Chen, M. P. Cabal, E. Turos, *Organometallics* **1995**, *14*, 4697.

[10] a) K. Takai, K. Nitta, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 5263; b) W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonowski, K. A. Scheidt, *J. Org. Chem.* **2002**, *67*, 4275.

[11] J.-I. Chika, H. Takei, *Tetrahedron Lett.* **1998**, *39*, 605.

[12] a) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31; b) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1996**, *61*, 105; c) W. R. Roush, M. S. Van Nieuwenhze, *J. Am. Chem. Soc.* **1994**, *116*, 8536; d) G. E. Keck, K. A. Savi, E. N. Cressman, D. E. Abbott, *J. Org. Chem.* **1994**, *59*, 7889; e) I. Kadota, K. Kobayashi, H. Okano, N. Asao, Y. Yamamoto, *Bull. Soc. Chim. Fr.* **1995**, *132*, 615.

[13] J. Cossy, C. Willis, V. Bellosta, L. Saint-Jalmes, *Synthesis* **2002**, 951.

[14] a) H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535; b) J. A. Hunt, W. R. Roush, *J. Org. Chem.* **1997**, *62*, 1112.

[15] α,β-Dilithium salts of ketones: I. Ryu, H. Nakahira, M. Ikebe, N. Sonoda, S. Yamamoto, M. Komatsu, *J. Am. Chem. Soc.* **2000**, *122*, 1219.

[16] E. Nakamura, S. Aoki, K. Sekiya, H. Oshino, I. Kuwajima, *J. Am. Chem. Soc.* **1987**, *109*, 8056.

[17] A conjugated addition of bis(iodozincio)methane to 4-phenyl-4-oxo-2-butene in the presence of chlorotrimethylsilane gave (*Z*)-trimethylsilylenol ether diastereoselectively.[2a] An NOE experiment also supported *Z* configuration of **6a**.

[18] For X-ray diffraction, a crystal was mounted on a glass fiber coated with epoxy resin. Measurements were made on a Rigaku Mercury charge-coupled device (CCD) system with graphite monochromated $\mathrm{Mo}_{K\alpha}$ radiation.