

Copper-Catalyzed Conjugate Addition of a Bis(triorganosilyl) Zinc and a Methyl(triorganosilyl) Magnesium

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Abstract: A practical copper-catalyzed conjugate silylation of α,β -unsaturated carbonyl compounds **4** utilizing bis(triorganosilyl) zinc reagent **3** is described. Moreover, mixed methyl(triorganosilyl) magnesium **7** also transfers its silyl ligand to simple enones **4** under copper catalysis.

Key words: catalysis, cuprates, silicon, zinc, copper

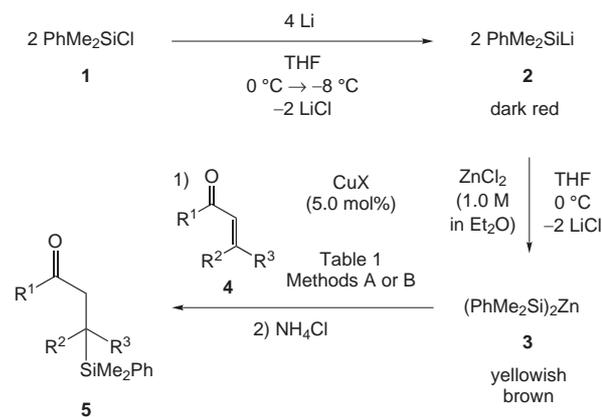
The fundamental discovery of the stereoretentive oxidation of a C–Si into a C–O bond (Tamao–Fleming oxidation)¹ has significantly amplified synthetic interest in C–Si bond forming reactions and suitable reagents.² Notably, silyl cuprates have emerged as exceptionally effective reagents for such transformations.³ Introduction of a silicon group via conjugate addition is usually effected using the $(\text{PhMe}_2\text{Si})_2\text{Cu}(\text{CN})\text{Li}_2$ ⁴ reagent which is conveniently prepared from the corresponding silyl lithium and half-stoichiometric amounts of CuCN .⁵ PhMe_2SiLi (**2**) is employed in these reactions because of the ease of its accessibility⁶ as well as the well-investigated oxidative degradation¹ of the PhMe_2Si group.

However, these synthetically valuable reagents^{2,3} are afflicted with two shortcomings as its use requires stoichiometric amounts of copper with only one of the two silyl groups being transferred. In particular, equimolar quantities of copper salts are detrimental to large-scale reactions. Accordingly, a user-friendly silyl cupration catalytic in copper using stoichiometric amounts of the silyl group is a worthwhile goal.

These issues have been addressed by Nozaki,⁷ Lipshutz,⁸ and Hosomi⁹ and have led to three conceptually different approaches: (i) 1,4-addition of the mixed zincate $\text{PhMe}_2\text{SiZnMe}_2\text{Li}$ in the absence of any copper catalyst,⁷ (ii) $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ -catalyzed (3.0 mol%) silyl cupration employing mixed zincate $\text{PhMe}_2\text{SiZnMe}_2\text{Li}$,⁸ and (iii) copper-catalyzed (5.0 mol%) conjugate silylation utilizing disilane $(\text{PhMe}_2\text{Si})_2$.⁹ In the former processes the silyl ligand is entirely delivered to the α,β -unsaturated acceptor but needs handling of pyrophoric Me_2Zn .^{7a,b,8}

We have discovered that bis(triorganosilyl) zincs¹⁰ undergo smooth conjugate addition in the presence of catalytic amounts (5.0 mol%) of miscellaneous copper salts. Herein, we wish to report a practical reaction protocol for the

1,4-addition of bis(triorganosilyl) zincs applicable to a wide variety of enones. Furthermore, if complete transfer of the silyl ligand is desired, mixed alkyl(triorganosilyl) magnesiums are also potent silyl group sources under copper catalysis.



Scheme 1 Preparation and conjugate addition of $(\text{PhMe}_2\text{Si})_2\text{Zn}$ (**3**)

Bis(triorganosilyl) zincs have remained almost unnoticed in organosilicon chemistry and synthetic applications thereof are scarce.^{10,11} This is particularly surprising since preparation and handling is simple as exemplified by the synthesis of **3** (Scheme 1). Reductive metalation of silyl chloride **1** (**1** \rightarrow **2**) and subsequent admixture of 0.5 equivalents ZnCl_2 (**2** \rightarrow **3**) provides the requisite $(\text{PhMe}_2\text{Si})_2\text{Zn}$ reagent **3**¹¹ in almost quantitative yield.^{12a}

Additionally, silyl zincs are generally less basic and nucleophilic than the corresponding silyl lithiums^{13a} as verified in control experiments. Reagent **3** displayed less reactivity towards ketones and esters which qualifies **3** as a silyl transfer reagent in transition metal-catalyzed processes such as conjugate addition reactions.¹⁴

We were pleased to find this assumption confirmed when **3** cleanly reacted with equimolar amounts of an enone **4** in the presence of various copper salts¹⁵ (**4** \rightarrow **5**, Scheme 1).^{13b} After an initial screening of reaction conditions, we elaborated two protocols which differ in reaction temperature (Method A: 2 h at -78°C ^{12b} or Method B: >6 h at -20°C ^{12c}). Independent of the copper source, these worked equally well for 2-cyclohexenone (**4a**, Table 1, entries 1–4).

Excellent yield was also obtained for the sterically more hindered γ,γ -dialkylated substrate **4b** (Table 1, entry 5);

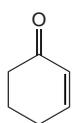
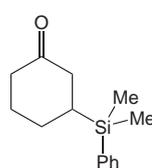
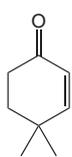
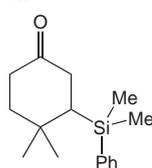
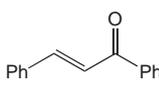
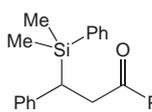
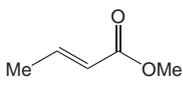
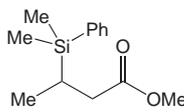
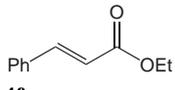
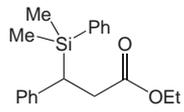
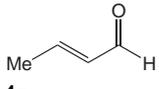
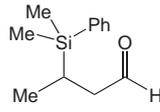
furthermore, β,β -disubstituted isophorone (**4c**) underwent conjugate addition in good yield (Table 1, entry 6). These enones required higher reaction temperatures (Method B) and CuI appeared to be superior to CuCN. However, efforts to accelerate this process by using additives such as Me_3SiCl ¹⁶ (stoichiometric) or $\text{Sc}(\text{OTf})_3$ (catalytic)⁸ did not result in any improvement of reaction rates.

Similarly, chalcone (**4d**) performed poorly applying Method A (Table 1, entry 7) but yields greatly increased at elevated temperature (Table 1, entries 8–10); CuI and $\text{Cu}(\text{OTf})_2$ were more effective than CuCN. Esters **4e** and **4f** provided the β -silylated products **5e** and **5f** in good isolated yields (Table 1, entries 11–15).

Conversely, aldehyde **4g** was not compatible with Method B showing considerable decomposition (Table 1, entry 17). Acceptable yield was seen at lower temperature applying the mild Method A (Table 1, entry 16).

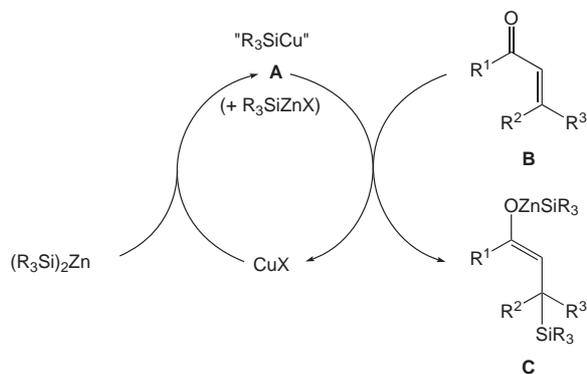
The above-described simple transmetalation step from lithium to zinc (**2** \rightarrow **3**, Scheme 1) overcomes the demand for stoichiometric amounts of copper. This represents an alternative to the elegant methodologies introduced by Lipshutz⁸ and Hosomi.⁹ Nevertheless, hypothetical intermediate **A** generated by ligand exchange of $(\text{R}_3\text{Si})_2\text{Zn}$ and CuX only releases one silyl group to the α,β -unsaturated substrate **B** as illustrated in a simplified catalytic cycle (Scheme 2). The other, non-transferable silyl ligand re-

Table 1 Conjugate Addition of **3** to α,β -Unsaturated Carbonyl Compounds **4**^a

Entry	Enone	Product	Catalyst	Method	Yield (%) ^b
1			CuCN	A	90
2			CuCN	B	80
3			CuI	B	85
4	4a	5a	$\text{Cu}(\text{OTf})_2$	B	85
5			CuI	B	90
6	4c	5c	CuI	B	70
7			CuCN	A	30
8			CuCN	B	70
9			CuI	B	90
10	4d	5d	$\text{Cu}(\text{OTf})_2$	B	90
11			CuCN	A	70
12			CuCN	B	80
13			CuI	B	80
14	4e	5e	$\text{Cu}(\text{OTf})_2$	B	80
15			CuI	B	80
	4f	5f			
16			CuCN	A	55
17	4g	5g	CuI	B	20

^a For Methods A and B see ref.¹².

^b Averaged yield (3 runs) of isolated analytically pure material.



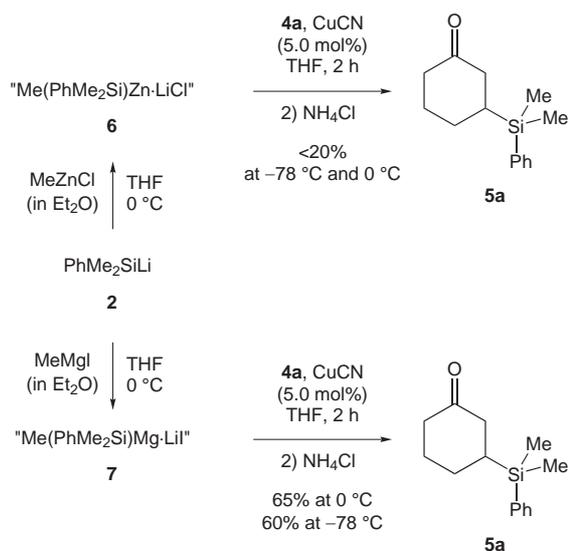
Scheme 2 Simplified catalytic cycle¹⁷

mains in the zinc enolate **C**, which could possibly give stoichiometric amounts of silicon-containing by-products.

These encouraging results prompted us to investigate the copper-catalyzed conjugate addition of mixed alkyl(triorganosilyl) zincs and magnesiums (Scheme 3).¹⁸ This is tempting since it is known from stoichiometric reactions that the silyl ligand in mixed alkyl silyl cuprates is selectively transferred from these reagents.¹⁸

However, mixed methyl(triorganosilyl) zinc **6** performed sluggishly and only minor amounts of product **5a** were formed along with decomposed starting material (**4a** → **5a**, Scheme 3).

To our surprise, the corresponding mixed methyl(triorganosilyl) magnesium **7**¹¹ reacted with **4a** (1.01 equiv) at $-78\text{ }^{\circ}\text{C}$ in the presence of CuCN (5.0 mol%) giving **5a** in moderate yield which improved slightly at higher temperature ($0\text{ }^{\circ}\text{C}$, Scheme 3). This transformation satisfies the two essential requirements of an efficient silyl cupration since it is catalytic in copper and uses only one equivalent of a silyl group. Though, yields are generally not as high as for zinc reagent **3**.



Scheme 3 Conjugate addition of mixed methyl(triorganosilyl) zinc **6** and magnesium **7**

In summary, we have established the first synthetic application of a bis(triorganosilyl) zinc reagent which is prepared from a triorganosilyl lithium by straightforward transmetalation using an etheral solution of ZnCl_2 . The synthetic potential of this organometallic had been underestimated in the past, as we were able to demonstrate its practical value as a silicon source in the copper-catalyzed conjugate silylation of enones. Our facile reaction protocol is a useful alternative to known stoichiometric variants^{3–5} and complements existing procedures which are catalytic in copper.^{8,9} It is noteworthy that, in principle, this catalytic process is applicable to mixed methyl(triorganosilyl) magnesiums which reduces squandering of equimolar amounts of a silyl ligand. The development of a catalytic asymmetric version of this reaction is currently under investigation in our laboratories.

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References

- (1) For comprehensive reviews on the Tamao–Fleming oxidation see: (a) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599. (b) Fleming, I. *Chemtracts, Org. Chem.* **1996**, *9*, 1.
- (2) (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley-Interscience: New York, **2000**. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: Orlando, **1988**.
- (3) (a) Lipshutz, B. H. In *Organometallics in Synthesis. A Manual*; Schlosser, M., Ed.; Wiley-VCH: Weinheim, **2002**, 665. (b) Dieter, R. K. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2002**, 79. (c) Singer, R. D. In *Science of Synthesis*, Vol. 4; Ley, S. V.; Fleming, I., Eds.; Thieme: Stuttgart, **2002**, 231. (d) Fleming, I. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford Academic Press: New York, **1994**, 257. (e) Tamao, K.; Kawachi, A. *Adv. Organomet. Chem.* **1995**, *38*, 1.
- (4) (a) Lipshutz, B. H.; James, B. *J. Org. Chem.* **1994**, *59*, 7585. (b) For $\text{Li}[(\text{PhMe}_2\text{Si})_2\text{Cu}]\text{-LiCN}$ see: Bertz, S. H.; Miao, G.; Eriksson, M. *Chem. Commun.* **1996**, 815.
- (5) (a) Ager, D. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1978**, 177. (b) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520. (c) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527. (d) For $\text{Et}_2\text{NPh}_2\text{SiCu}(\text{CN})\text{Li}$ see: Tamao, K.; Kawachi, A.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 3989. (e) For $\text{Li}[\text{PhMe}_2\text{SiCu}]$ as its dimethylsulfide complex see: Dambacher, J.; Bergdahl, M. *Chem. Commun.* **2003**, 144.
- (6) Gilman, H.; Lichtenwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 608.
- (7) (a) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (b) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701. (c) Vaughan, A.; Singer, R. D. *Tetrahedron Lett.* **1995**, *36*, 5683.

- (8) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021.
- (9) (a) Ito, H.; Ishizuka, T.; Tateiwa, J.-i.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196. (b) See also: Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 85. (c) For other catalyst systems see: Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5579. (d) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598.
- (10) Hameon, I.; Singer, R. D. In *Science of Synthesis*, Vol. 4; Ley, S. V.; Fleming, I., Eds.; Thieme: Stuttgart, **2002**, 225.
- (11) For a single report on the preparation of **3** and an application in a silyl metalation reaction see: Morizawa, Y.; Oda, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1163; this seminal publication also includes the magnesium reagent **7**.
- (12) (a) **Preparation of Zinc Reagent 3**: Phenyl dimethylsilyl chloride (**1**, 0.828 mL, 854 mg, 5.00 mmol, 2.50 equiv) was maintained with freshly cut lithium (large excess) in THF (10 mL) at $-8\text{ }^{\circ}\text{C}$ under argon atmosphere for 18 h. In order to separate **2** (4.00 mmol, ca. 80% conversion; for a titration procedure see ref.^{3d}) from unreacted lithium metal, the resulting dark red solution was transferred to another flask via a double-ended cannula. At $0\text{ }^{\circ}\text{C}$, ZnCl_2 (2.00 mL, 2.00 mmol, 1.00 equiv, 1 M in Et_2O) was added accompanied by a color change from red to yellowish brown. The reaction mixture was maintained at this temperature for further 15 min and was ready to use. (b) **Method A**: A suspension of CuX (5.0 mol%) and THF (5 mL) was pre-cooled to $-78\text{ }^{\circ}\text{C}$ and treated with **3** (2.00 mmol, 1.00 equiv) via syringe. The auburn reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$ and maintained at this temperature for 20 min. Addition of enone **4** (2.02 mmol, 1.01 equiv) to the re-cooled ($-78\text{ }^{\circ}\text{C}$) reaction mixture was followed by stirring for 2 h at $-78\text{ }^{\circ}\text{C}$. Upon completion of the reaction, the reaction mixture was poured into sat. aq. NH_4Cl (25 mL) and the flask was rinsed with MTBE (25 mL). The aqueous phase was separated and extracted with MTBE ($3 \times 25\text{ mL}$). The combined organic phases were extracted with H_2O (25 mL) and brine (25 mL). After drying (Na_2SO_4), the solvents were evaporated under reduced pressure and the resulting crude product **5** was purified by flash chromatography on silica gel using cyclohexane–MTBE solvent mixtures. (c) **Method B**: A mixture of enone **4** (2.02 mmol, 1.01 equiv), CuX (5.0 mol%), and toluene (5 mL) was cooled to $-20\text{ }^{\circ}\text{C}$. To this mixture was then added **3** (2.00 mmol, 1.00 equiv) via syringe. The reaction mixture was maintained at $-20\text{ }^{\circ}\text{C}$ for $>6\text{ h}$ and poured into sat. aq. NH_4Cl (25 mL). Work-up and purification of **5** as described for Method A.
- (13) (a) This also applies to triorganosilyl zinc chlorides (R_3SiZnCl) prepared from R_3SiLi and equimolar amounts of ZnCl_2 . (b) Only traces of conjugate addition products **5** were seen with R_3SiZnCl under copper catalysis.
- (14) (a) It should be noted that Me_3SiLi undergoes rapid 1,4-addition to β -monosubstituted ketones in the absence of any copper catalyst. See: Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063. (b) Conversely, we have isolated substantial amounts of the 1,2-adduct when treating enone **4a** with PhMe_2SiLi (**2**).
- (15) $\text{Cu}(\text{OTf})_2$ is believed to be reduced in situ as described for the conjugate addition of dialkylzincs: Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2002**, 224.
- (16) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (c) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087. (d) Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345.
- (17) The generation of **3** from **1** produces a fourfold excess of LiCl , which might function as a Lewis acid.
- (18) (a) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 770. (b) Singer, R. D.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 3510.