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## **Copper-Free and Copper-Promoted Conjugate Addition Reactions of Bis(triorganosilyl) Zincs and Tris(triorganosilyl) Zincates**

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**Abstract:** In the course of our investigations directed towards an asymmetric copper-catalyzed silyl transfer from bis(triorganosilyl) zincs onto  $\alpha$ , $\beta$ -unsaturated carbonyl compounds, the presence of Lewis acidic lithium cations and the uncatalyzed background reaction were identified as major causes thwarting appreciable enantioselection. The latter finding underlines once more that copper is often not even required in the conjugate addition of bis(triorganosilyl) zincs and tris(triorganosilyl) zincates alike.

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

In synthetic organic chemistry, silicon attached to saturated carbon serves either as a masked hydroxyl group or as a linchpin for carbon–carbon bond-forming reactions.<sup>1</sup> Importantly, both oxidative degradation<sup>2</sup> and palladiumcatalyzed cross-coupling<sup>3</sup> of the carbon–silicon bond proceed with immaculate retention of the configuration at the silicon-bearing carbon, thereby qualifying this functional group for stereoselective synthesis.

Among the numerous methods available today, the conjugate addition of silicon-metal reagents is still one of the main carbon-silicon bond-forming reactions.<sup>4</sup> Classical cuprates such as (R<sub>3</sub>Si)<sub>2</sub>CuLi·LiCN as well as R<sub>3</sub>SiCu·LiCN<sup>5</sup> and, more recently, R<sub>3</sub>SiCu·LiI stabilized by Me<sub>2</sub>S<sup>6</sup> were introduced and utilized with considerable success. Whereas these reagents rely on stoichiometric amounts of copper, several procedures requiring copper as catalyst are also available: cuprate-catalyzed 1,4-addition of mixed zincates<sup>7</sup> [Me<sub>2</sub>CuLi·LiCN (3.0 mol%)/ (R<sub>3</sub>Si)Me<sub>2</sub>ZnLi], copper-catalyzed 1,4-addition of bis(triorganosilyl) zincs8 [CuCN (5.0 mol%)/(R<sub>3</sub>Si)<sub>2</sub>Zn], and formal copper-catalyzed 1,4-addition of disilanes<sup>9</sup> [(CuOTf)<sub>2</sub>·PhH (5.0 mol%)/R<sub>3</sub>SiSiR<sub>3</sub>]. The conjugate silyl transfer from (mixed) zincates proceeds even in the absence of a copper catalyst.<sup>10</sup>

In light of the synthetic relevance of silicon attached to stereogenic carbon (vide supra), stereoselective carbonsilicon bond formation by means of copper-mediated conjugate addition of silicon nucleophiles to  $\alpha$ , $\beta$ -unsaturated carbonyl compounds is a worthwhile objective. For this, some diastereoselective, chiral-auxiliary-based methods were developed.<sup>11</sup> Conversely, catalytic asymmetric variants are still elusive and, to date, an enantioselective, palladium-catalyzed 1,4-bissilylation<sup>12</sup> of  $\alpha,\beta$ -unsaturated ketones remains the sole example.<sup>13</sup> In this paper, we present an attempt to perform our recently reported<sup>8</sup> copper-catalyzed silylzincation of  $\alpha,\beta$ -unsaturated carbonyl compounds enantioselectively. Within this investigation, we learned that bis(triorganosilyl) zincs cleanly react with virtually all standard acceptors in the absence of a copper catalyst. A comparison of the known copper-catalyzed<sup>8</sup> and the novel copper-free process is provided.

We reasoned that our reagent–copper catalyst combination,  $(R_3Si)_2Zn/Cu(OTf)_2$  (5.0 mol%),<sup>8</sup> is comparable to  $R_2Zn/Cu(OTf)_2$  that has been successfully employed in the copper-catalyzed enantioselective conjugate addition of diorganozincs.<sup>14</sup> Consequently, we adopted these established reaction conditions and simply replaced Et<sub>2</sub>Zn by  $(Me_2PhSi)_2Zn$  ( $1 \rightarrow 2$ , Scheme 1).<sup>15</sup> As exemplified by a selected experiment, adduct 2 was invariably formed as a racemic mixture in the presence of phosphoramiditebased ligand L.



Scheme 1 Attempted asymmetric copper-catalyzed conjugate addition

In the mechanism proposed for the copper-catalyzed 1,4addition of  $R_2Zn$ , high  $\pi$ -face selectivity is attributed to a conformationally rigid bimetallic complex of the enone moiety and the zinc reagent–copper catalyst couple with a ligand-to-copper ratio  $L/Cu(I) = 2:1.^{14}$  By analogy, the related desired chelate in our catalysis might be depicted as **A** (Figure 1).



Figure 1 Mechanistic model

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We believe that in our case an intermediate of type **A** might not be formed since  $(Me_2PhSi)_2Zn$  is contaminated with a four-fold excess of lithium chloride  $[(Me_2PhSi)_2Zn = (Me_2PhSi)_2Zn \cdot 4LiCl]$ , which is inevitably introduced in the synthesis of the zinc reagent via reductive lithiation<sup>16</sup> and transmetallation (top, Scheme 2). Lewis acidic lithium cations will compete with any zinc species for coordination at the Lewis basic carbonyl oxygen. The less rigid complex **B** might then be the predominant intermediate, in which facial selectivity of the coordinated chiral monosilylcopper species<sup>17</sup> is markedly diminished (Figure 1).



Scheme 2 Contamination with lithium or potassium chloride

In order to verify this hypothesis, we exchanged lithium for less Lewis acidic potassium chloride by using the potassium–graphite intercalation compound KC<sub>8</sub> in the reductive metallation step<sup>18</sup> (bottom, Scheme 2). We were pleased to find that this modification, for the first time, resulted in a distinct enantiomeric excess<sup>19</sup> in a copper-catalyzed conjugate silyl transfer ( $\mathbf{1} \rightarrow \mathbf{2}$ , Scheme 3).<sup>20</sup> Variation of the copper source (CuI or CuCN) brought no further improvement of enantioselectivity.



Scheme 3 Influence of the Lewis acidity of the counter cation

In the initial phase of the elaboration of a reliable reaction protocol for the copper-catalyzed conjugate addition of bis(triorganosilyl) zincs, we had already detected that in some cases (Me<sub>2</sub>PhSi)<sub>2</sub>Zn would undergo the 1,4-addition even without a copper catalyst.<sup>21</sup> If this background reaction is as fast as the copper-catalyzed reaction pathway, asymmetric induction would always be marginal. We, therefore, returned to a careful analysis of the copper-free reaction of  $\alpha$ , $\beta$ -unsaturated carbonyl compounds with (Me<sub>2</sub>PhSi)<sub>2</sub>Zn (Method B, Table 1). For comparison, yields obtained for (Me<sub>2</sub>PhSi)<sub>2</sub>Zn in the presence of catalytic amounts of CuCN (Method A, Table 1)<sup>8</sup> and for the previously reported tris(triorganosilyl) zincate (Me<sub>2</sub>PhSi)<sub>3</sub>ZnLi<sup>22</sup> (Method C, Table 1) are listed. Independent of the reaction conditions, 2-cyclohexenone (1) cleanly underwent 1,4-addition in excellent yields  $(1 \rightarrow 2,$ Table 1, entry 1). In contrast, increased steric hindrance in  $\gamma,\gamma$ -disubstituted derivative **3** prevented the conjugate silyl transfer from  $(Me_2PhSi)_2Zn$  and  $(Me_2PhSi)_3ZnLi$ , respectively at low temperature  $(\mathbf{3} \rightarrow \mathbf{4}, \text{ Table 1}, \text{ entry 2})$ . This substrate was later used in a reactivity study (vide infra). Isophorone (**5**) with two substituents in the  $\beta$ -position emerged as completely inert towards the zinc reagents without a copper catalyst even at higher temperatures (**5**  $\rightarrow$  **6**, Table 1, entry 3). In the end, **5** was the only enone requiring a copper catalyst. Reaction of lactone **7** gave **8** in good yield with CuCN and moderate yield without CuCN (**7**  $\rightarrow$  **8**, Table 1, entry 4). Chalcone (**9**) (**9**  $\rightarrow$  **10**, Table 1, entry 5) and acyclic esters **11** and **13** (**11**/**13**  $\rightarrow$ **12**/**14**, Table 1, entries 6 and 7) performed equally well on applying Methods A, B, and C.

Since  $\gamma,\gamma$ -disubstituted **3** was less reactive than its parent compound **1**, we tested the effect of copper on the reaction rate using **3** (Table 2). While **3** was completely unreactive at -78 °C, it was cleanly converted into **4** within minutes in the presence of CuCN (5.0 mol%) at -20 °C (Table 2, entry 1). At the same temperature and in the absence of CuCN, conversion was substantially slower, yet afforded **4** in reasonable yield (Table 2, entries 1–4). Hence, a copper catalyst is not necessary for a successful conjugate silylation of a variety of  $\alpha,\beta$ -unsaturated carbonyl compounds; it merely accelerates or promotes this process.

In summary, we have demonstrated that a catalytic asymmetric variant of our copper-catalyzed 1,4-addition of bis(triorganosilyl) zincs is complicated by: 1) the presence of an excess of Lewis acidic lithium chloride and 2) the facile uncatalyzed silyl transfer. This copper-free conjugate addition is general (six examples) except for  $\beta$ , $\beta$ -disubstituted  $\alpha$ , $\beta$ -unsaturated carbonyl compounds (one example). Whereas in most conjugate addition reactions and some silylzincations of alkynes<sup>17</sup> copper is not needed, it is essential in the related allylic substitution reaction.<sup>23</sup>

Reagents obtained from commercial suppliers were used without further purification unless otherwise noted. All reactions were performed in flame-dried glassware under a static pressure of argon. Liquids and solutions were transferred with syringes or double-ended needles. Solvents were dried prior to use following standard procedures (tetrahydrofuran, diethyl ether, and toluene). Technical grade solvents for extraction or chromatography (cyclohexane and *tert*-butyl methyl ether) were distilled before use. Analytical TLC was performed on silica gel SIL G-25 glass plates by Macherey– Nagel (Germany) and flash chromatography on silica gel 60 (40–63  $\mu$ m, 230–400 mesh, ASTM) by Merck (Germany) using the indicated solvents. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub> on a Bruker DRX 500 instrument. All compounds gave satisfactory elemental analyses.

# Copper-Free 1,4-Addition of Bis(triorganosilyl) Zinc; General Procedure

A freshly prepared  $Et_2O$  solution of  $(Me_2PhSi)_2Zn^8$  (2.00 mmol, 1.00 equiv) was cooled to the indicated temperature and treated with the  $\alpha$ , $\beta$ -unsaturated carbonyl compound (2.00 mmol, 1.00 equiv) via a syringe. The resulting reaction mixture was maintained at this temperature for 5 h and then poured into sat. aq NH<sub>4</sub>Cl (25 mL). The aqueous phase was separated and extracted with *tert*-butyl methyl

O vvvv	Methods A-C		Method $A^8$ (Oestreich et al.): CuCN (5.0 mol%) (Me <sub>2</sub> PhSi) <sub>2</sub> Zn (1.0 equiv) THF-Et <sub>2</sub> O-PhMe = 10:2:5 -20 °C	Method B (this work): (Me <sub>2</sub> PhSi) <sub>2</sub> Zn (1.0 equiv) THF-Et <sub>2</sub> O = 5:1 -78 °C or 0 °C		Method C (this work): (Me <sub>2</sub> PhSi) <sub>3</sub> ZnLi (1.0 equiv) THF-Et <sub>2</sub> O = 5:1 -78 °C or 0 °C
Entry	Substrate	Product	Yield (%) for Method A	Temp (°C)	Yield (%) for Method B	Yield (%) for Method C
1	0 1	Me Si-Me Ph	90	-78	85	95
2	Me Me	2 Me Me Me Ph	90	-78	0 (see Table 2)	0
3	3 Me Me 5	4 Me Me Me Me Ph	70	0	0	0
4	7	6 O Me Sí-Me Ph	70	0	40	-
5	Ph Ph 9	8 Ph Ph Si <sup>-Me</sup> Ph	70	-78	75	55
6	MeO MeO Me	Neo Meo Me Si-Me Ph	80	-78	70	70
7	Eto Ph	$ \begin{array}{c}                                     $	80	-78	80	70

 $\begin{array}{lll} \textbf{Table 1} & Comparative Investigation of the Copper-Catalyzed Conjugate Addition of Bis(triorganosilyl) Zincs and the Copper-Free Conjugate Addition of Bis(triorganosilyl) Zincs [(Me_2PhSi)_2Zn] as well as Tris(triorganosilyl) Zincates [(Me_2PhSi)_3ZnLi] \\ \end{array}$ 

Table 2 Copper-Promoted Conjugate Addition



ether (3  $\times$  25 mL). The combined organic layers were back-extracted with H<sub>2</sub>O (25 mL) and brine (25 mL). After drying (Na<sub>2</sub>SO<sub>4</sub>), the solvents were evaporated under reduced pressure and the resulting crude product was purified by flash chromatography on silica gel using cyclohexane–*tert*-butyl methyl ether solvent mixtures.

### 3-Dimethylphenylsilyl-4,4-dimethylcyclohexanone (4)

 $R_f = 0.67$  (cyclohexane–*tert*-butyl methyl ether, 2:1).

IR (film): 1713 (s) (C=O) cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 0.34$  (s, 3 H), 0.37 (s, 3 H), 0.96 (s, 3 H), 1.08 (s, 3 H), 1.37 (dd, J = 3.8, 14.0 Hz, 1 H), 1.65 (ddd, J = 4.4, 6.6, 13.4 Hz, 1 H), 1.69 (ddd, J = 4.6, 13.5, 13.5 Hz, 1 H), 2.22 (ddd, J = 2.0, 3.8, 15.3 Hz, 1 H), 2.26 (dddd, J = 2.0, 4.5, 4.5, 14.9 Hz, 1 H), 2.35 (ddd, J = 1.0, 14.0, 14.9 Hz, 1 H), 2.45 (ddd, J = 0.8, 5.7, 14.2 Hz, 1 H), 7.30–7.36 (m, 3 H), 7.44–7.50 (m, 2 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = -2.2, -1.3, 23.7, 31.6, 33.3, 37.1, 38.2, 39.3, 44.2, 128.0, 129.2, 133.9, 138.6, 213.1.

LRMS (CI, NH<sub>3</sub>):  $m/z = 278 [M + NH_4]^+$ .

Anal. Calcd for  $C_{16}H_{24}OSi$  (260.45): C, 73.79; H, 9.29. Found: C, 73.61; H, 9.18.

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