

## The Role of Iodotrimethylsilane in the Conjugate Addition of Butylcopper·Lithium Iodide to $\alpha$ -Enones; Silylation of an Intermediate $\pi$ -Complex

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The effect of TMSCl (chlorotrimethylsilane) on the rate as well as the stereochemical outcome of conjugate additions of organocuprates to  $\alpha,\beta$ -unsaturated carbonyl compounds has been studied by several groups.<sup>1</sup> In previous work, we have introduced iodotrimethylsilane<sup>2</sup> (TMSI) as an efficient promoter in conjugate additions of mono-organocopper compounds RCu·LiI to  $\alpha$ -enones and -enoates.<sup>3</sup> In this paper, we focus on the effect of TMSI on the formation of TMS enol ethers in the early stages of the reaction. It is shown by quenching the reactions after short times that TMSI induces direct formation of the TMS enol ether from a presumed mono-organocopper–enone  $\pi$ -complex. We also report the activating effect of pyridine on the conjugate addition of BuCu·LiI in the absence of TMSI.

Conjugate addition of organocopper reagents in the presence of TMSCl and TMSI has received considerable attention in recent years. Besides the rate-accelerating effect generally observed, the presence of TMSCl often leads to formation of TMS enol ethers<sup>1a,b</sup> although exceptions have been noted.<sup>1c</sup> Following the early observations by Normant et al.,<sup>4</sup> Corey and Boaz reported the dramatic effect of TMSCl on the stereochemistry in the conjugate addition of organocuprates to a bicyclic  $\gamma$ -alkoxy enone.<sup>1c</sup> Based on these results, they proposed that TMSCl traps an intermediate  $\pi$ -complex ( $d-\pi^*$ )<sup>5</sup> leading to a silylated Cu(III) intermediate, which undergoes subsequent reductive elimination.

Kuwajima and Nakamura have suggested that TMSCl functions as a Lewis acid toward the  $\alpha$ -enone prior to addition of the copper reagent<sup>6</sup> to explain the stereochemical changes in the conjugate addition of dibutylcuprates to 2- and 5-substituted 2-cyclohexenones in the absence or presence of the additive.

A third possibility involves the interaction between TMSCl and the diorganocuprate prior to reaction with the enone as observed by Lindstedt et al.<sup>7</sup> using <sup>13</sup>C NMR. On the basis of changes in the <sup>7</sup>Li and <sup>35</sup>Cl NMR spectra of organocuprates and organocuprate–TMSCl mixtures, Lipshutz et al.<sup>8</sup> proposed that the Cl of TMSCl coordinates Li<sup>+</sup> in the organocuprate thereby increasing the electrophilic character of the silicon and

**Table 1.** LRPs for the Conjugate Addition of BuCu·LiI to 2-Cyclohexenone (**1**) in the Presence of TMSI<sup>a</sup>

entry	reagent	time <sup>b</sup>	<b>3</b> + <b>4</b> (%)	<b>2</b> (%)	<b>1</b> (%)
1	[BuCu·LiI + TMSI] then <b>1</b>	0.001	27 (>99:1)	5	64
2		0.01	28 (>99:1)	4	59
3		0.1	50 (>99:1)	6	35
4		1.0	55 (98:2)	8	29
5	[BuCu·LiI + <b>1</b> ] then TMSI	0.001	34 (93:7)	2	54
6		0.01	40 (93:7)	3	45
7		0.1	49 (93:7)	3	34
8		1.0	53 (92:8)	9	23
9	BuCu·LiI then [ <b>1</b> +TMSI]	0.001	56 (>99:1)	<1	32
10		0.01	58 (>99:1)	2	30
11		0.1	56 (>99:1)	4	31
12		1.0	60 (>99:1)	7	21

<sup>a</sup> All reactions were run in THF at  $-78$  °C. <sup>b</sup> Given in hours (h): 1.0 h = 60 min, 0.1 h = 6.0 min, 0.01 h = 36 s, 0.001 h = 4 s.

the ability to coordinate to the enone carbonyl oxygen. This model suggested that the conjugate addition and the formation of TMS enol ethers occurred in one step.

A fourth alternative was recently put forward by Bertz et al. who proposed that the Cl of TMSCl attacks copper in the organocuprate–enone  $\pi$ -complex to induce formation of the product enolate via a tetracoordinate square-planar  $\beta$ -cuprio intermediate.<sup>9</sup> They investigated the conjugate addition of Bu<sub>2</sub>CuLi·LiI to 2-cyclohexenone in the presence of excess TMSCl. The important observation was that the TMS enol ether is formed in a subsequent silylation step in Et<sub>2</sub>O as well as in THF.

We have previously reported the isolation of TMS enol ethers in high yields from conjugate additions of RCu·LiI compounds to  $\alpha$ -enones in the presence of TMSI,<sup>10</sup> and we recently extended the scope of this protocol to include conjugate addition of copper acetylides.<sup>11</sup> However, so far we have made no special attempts to determine if the TMS enol ether is the initial product from the conjugate addition at low temperature or if it is formed in a subsequent silylation step. To address this problem, we have studied the reaction between BuCu·LiI, TMSI and 2-cyclohexenone (**1**) in dilute (0.05 M) THF solution.<sup>12</sup>

By quenching the reactions at low temperature after increasing time intervals, it is possible to monitor the buildup of product, either as the conjugate adduct 3-butylcyclohexanone (**2**) or the TMS enol ether 3-butyl-1-((trimethylsilyloxy)cyclohexene (**3**), as well as the disappearance of the starting material. Using the concept of logarithmic reactivity profiles (LRPs), recently introduced in organocopper chemistry by Bertz et al.,<sup>9,13</sup> we have performed three different sets of reactions in the presence of TMSI. They differ in the order of addition of **1** and TMSI to BuCu·LiI. These results are summarized in Table 1.

When **1** was added to a mixture of BuCu·LiI and TMSI at  $-78$  °C, a considerable amount of TMS enol ether **3** was formed already after 0.001 h, and it gradually increased with time (entries 1–4). Traces of the regioisomeric TMS enol ether 5-butyl-1-((trimethylsilyloxy)cyclohexene (**4**) were also observed. However, one reaction mixture was stirred for 10 h at  $-78$  °C before the reaction was quenched to give a 75% yield of **3** and **4** with an isomer ratio of 85:15. Apparently, TMSI can promote some isomerization of the TMS enol ethers over an extended time even at  $-78$  °C.

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In the second LRP, TMSI was added to a mixture of BuCu·LiI and **1** at  $-78\text{ }^{\circ}\text{C}$  (entries 5–8). The ratio (ca. 93:7) of the TMS enol ethers **3** and **4** is similar for all reaction times, which may suggest some isomerization under the reaction conditions. Addition of a mixture of TMSI and **1** to BuCu·LiI (entries 9–12) led to the immediate formation of the TMS enol ether **3** in good yield<sup>14</sup> together with minor amounts of **2**. It appears as the premixing of TMSI and **1** before addition to BuCu·LiI gives the highest yields of **3** after 0.001 and 0.01 h at  $-78\text{ }^{\circ}\text{C}$ .

For control purposes and as a blank experiment, BuCu·LiI was reacted with **1** in the absence of TMSI. Addition of **1** to BuCu·LiI in THF at  $-78\text{ }^{\circ}\text{C}$  immediately gave greenish-yellow suspensions<sup>15</sup> which indicates formation of a  $\pi$ -complex.<sup>16,15</sup> Quenching these reactions with aqueous sodium hydrogen carbonate after 0.001, 0.01, or 0.1 h returned the starting enone,<sup>15</sup> whereas the 1.0 h reaction gave 4% of **2** along with recovered **1**. In strong contrast, quenching a 0.1 h reaction only 0.001 h after addition of 3 equiv of pyridine gave 20% of **2**. This shows that pyridine can have an activating effect also on the conjugate addition of BuCu·LiI as has been recently shown for organocuprates.<sup>13</sup> When triethylamine was used instead of pyridine, only 3% of **2** was observed.

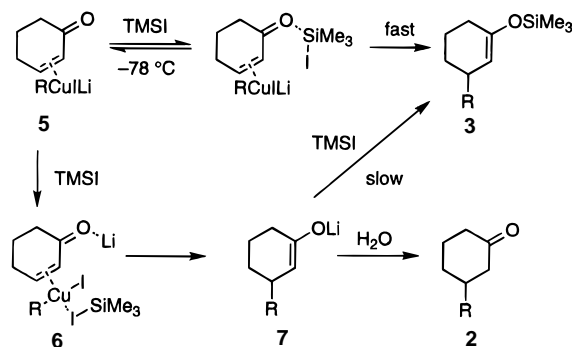
All reactions that contained TMSI were quenched at  $-78\text{ }^{\circ}\text{C}$  by addition of 3 equiv of Et<sub>3</sub>N followed by 6 mL of aqueous saturated sodium hydrogen carbonate after 0.001 h. In addition to **3**, a minor amount of **2** was observed in almost all reactions involving TMSI, and it also seemed to increase slightly with time.<sup>17</sup> Control experiments where pure **3** in THF was subjected to the quench conditions gave 85% of recovered TMS enol ether and 4% of **2** formed from hydrolysis of **3**, presumably by HI from hydrolyzed TMSI. The conjugate adduct 3-butylcyclohexanone (**2**) was stable under the quench conditions.

The rate of silylation of an enolate in Et<sub>2</sub>O and THF/Et<sub>2</sub>O by TMSI was investigated. Conjugate addition of BuCu·LiI to **1** in pure THF at  $-78\text{ }^{\circ}\text{C}$  was slow<sup>18</sup> and gave rise to complex reaction mixtures already at  $-50\text{ }^{\circ}\text{C}$ . We therefore prepared the enolate in Et<sub>2</sub>O at 0.2 M<sup>19</sup> and diluted the mixture with THF to 0.05 M. Addition of TMSI to such an enolate at  $-78\text{ }^{\circ}\text{C}$  followed by the usual quench with Et<sub>3</sub>N and NaHCO<sub>3</sub> after 0.001 h and 0.01 h gave 6 and 24% of **3**, respectively. The corresponding experiments in pure diethyl ether gave <1% of **3**. Consequently, most of the **3** observed in THF using BuCu·LiI in the presence of TMSI is formed directly from the conjugate addition and not as a result of a subsequent silylation of an intermediate enolate.

For comparison with BuCu·LiI/TMSI, we investigated the conjugate addition of Bu<sub>2</sub>CuLi·LiI/TMSI to 2-cyclohexenone at 0.05 M in THF. Addition of TMSI to a mixture of Bu<sub>2</sub>CuLi·LiI and **1** gave 80 and 79% of **3** after 0.001 and 0.01 h, respectively. In contrast, quenching a 0.001 h reaction without TMSI with NaHCO<sub>3</sub> gave only 9% of **2** which clearly demonstrates the activating effect of TMSI. More importantly, also in the Bu<sub>2</sub>CuLi·LiI case is the silylation of an enolate at  $-78\text{ }^{\circ}\text{C}$  by TMSI too slow to account for the amount of **3** observed.

The predominant formation of **3** from Bu<sub>2</sub>CuLi·LiI/TMSI and **1** in THF differs from the results of Bertz et al.<sup>9</sup> for the Bu<sub>2</sub>CuLi·LiI/6TMSCl system in THF which gave mainly nonsily-

### Scheme 1



lated product.<sup>20</sup> However, we found that Bu<sub>2</sub>CuLi·LiI/TMSI as well as Bu<sub>2</sub>CuLi·LiI/6TMSCl and **1** in Et<sub>2</sub>O did afford mainly nonsilylated product (**2**), in consonance with their results. In two recent studies, it is proposed that nucleophilic attack of TMSCl<sup>9</sup> or solvent (Me<sub>2</sub>O)<sup>21</sup> on an organocuprate–olefin  $\pi$ -complex gives a tetracoordinated square planar  $\beta$ -cuprio intermediate with a low energy barrier toward reductive elimination to product. A corresponding scenario may explain the activating effect of pyridine on the BuCu·LiI reactions in the absence of TMSI but cannot (i.e., via **6**) explain the large amounts of **3** formed at short reaction times in the BuCu·LiI/TMSI or the Bu<sub>2</sub>CuLi·LiI/TMSI system.

What then, is the role of TMSI in the BuCu·LiI reactions? As depicted in Scheme 1, two pathways to the TMS enol ether **3** are conceivable: (i) a process where TMSI silylates a  $\pi$ -complex leading to direct formation of the TMS enol ether or (ii) silylation of an intermediate enolate from conjugate addition of RCu·LiI.

We propose that the powerful silylating agent TMSI<sup>22</sup> can directly silylate an intermediate  $\pi$ -complex **5** to give **3** and that this is the major pathway in THF (Scheme 1). The results are thus consistent with a mechanism analogous to the one proposed by Corey and Boaz for organocuprates and TMSCl.<sup>1c</sup> They stated, “It is likely that the trapping occurs at the  $\pi$ -complex stage since its steady-state concentration is doubtless much greater than that of the copper(III)  $\beta$ -adduct”. The ratios of **3** to **2** from Table 1 suggest that the amount of **3** formed by the proposed mechanism varies from ca 80% (entry 1) up to almost quantitative (entry 9).

In conclusion, we have shown that iodotrimethylsilane in combination with BuCu·LiI or Bu<sub>2</sub>CuLi·LiI in THF leads to direct formation of TMS enol ethers from a presumed organocuprate–enone  $\pi$ -complex. The present results thus appear to rule out significant amounts of an enolate **7** as a viable intermediate on the reaction pathway. On the other hand, they do not allow the discrimination between an  $\alpha$ -cuprio ketone<sup>3c,11</sup> or a silylated  $\beta$ -cuprio intermediate.<sup>1c,21</sup>

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**Supporting Information Available:** General experimental procedures (2 pages). See any current masthead page for ordering and Internet access instructions.

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