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Silyl Cuprate Couplings: Less Silicon, Accelerated, Yet *Catalytic* in Copper

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Among the myriad uses of silicon in organic synthesis,[1] the dimethylphenylsilyl moiety occupies a special niche, perhaps most notably in its service as a hydroxyl group surrogate.[2] Introduction of this moiety is commonly effected via a silyl cuprate reagent, such as that formed from CuCN and 2 equiv of $PhMe_2SiLi$ (i.e., "$(PhMe_2Si)_2Cu(CN)Li_2$").[3] This species, now in its second decade of usage, requires not only 2 equiv of silyllithium but, more importantly, stoichiometric amounts of copper which detract from its appeal, in particular for large-scale reactions. We now report a solution to these issues which allows for consumption of only one silyl group, is applicable to highly hindered substrates, and relies on catalytic amounts of Cu(I). In addition, we disclose the unprecedented use of a rare earth as a new catalyst for accelerating 1,4-additions of an in situ derived silylcuprate.

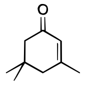
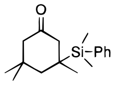
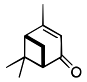
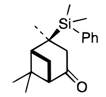
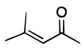
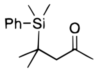
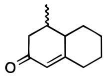
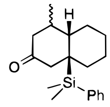
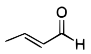
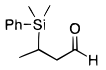
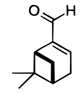
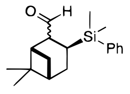
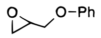
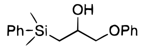
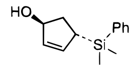
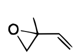
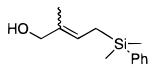
Addition of a toluene solution of Me_2Zn to preformed $PhMe_2SiLi$ in THF at −78 °C generates known $PhMe_2SiZnMe_2Li$.[4] Introduction of 3 mol % of the higher order cyanocuprate $Me_2Cu(CN)Li_2$ to this mixed zincate followed by a substrate leads to high yields of silylated adducts (Figure 1). The presumed reactive species, mixed cuprate $(PhMe_2Si)(Me)Cu(CN)Li_2$ (**1**, Scheme 1), generated in situ via a facile, rapid ligand exchange at low temperatures,[5] selectively releases silicon rather than methyl from copper.[6] Representative examples are illustrated in Table 1. Conjugate additions were studied in highly challenging, β,β-disubstituted enones including isophorone, verbenone, mesityl oxide, and an octalone (entries 1−4), with which excellent yields of β-silylated products were obtained. 1,4-Addition to crotonaldehyde and myrtenal were equally successful (entries 5 and 6). Cuprate alkylations with epoxides also proceeded smoothly to the 1,2- or 1,4-silyl alcohols (entries 7−9). Poor results with the corresponding zincates alone[4,7] clearly indicated the key role being played by copper in this chemistry.

$$PhMe_2Si\text{-}Li \xrightarrow[3.\quad E^+]{1.\quad Me_2Zn \\ 2.\ cat\ Me_2Cu(CN)Li_2} PhMe_2Si\text{-}E$$

[E^+ = enones, enals, enoates, epoxides, and 1-alkynes]

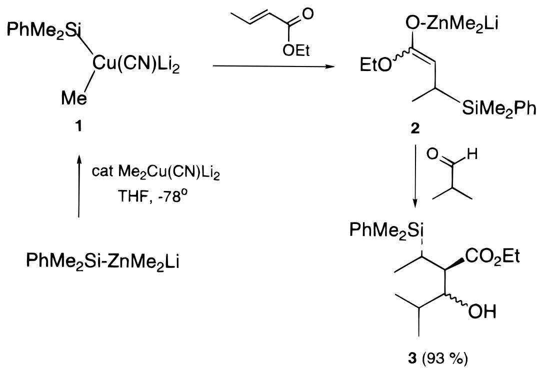
Figure 1.

Table 1. Reactions of $PhMe_2SiZnMe_2Li$ + cat $Me_2Cu(CN)Li_2$

Entry	Substrate	Product[a]	Yield with zincate alone (%)[b]	Yield with zincate + 3% cuprate (%)[c]
1			31[d]	90
2			35	97
3			e	83
4			e	69[f]
5			e	84
6			e	88[g]
7			e	84
8			e	86
9			e	96[h]

[a] Characterized by spectral and HRMS data. [b] Same conditions as used for reactions where 3 mol % cuprate was present. [c] Isolated, chromatographically purified materials. [d] See ref 4. [e] Not attempted. [f] Ratio of isomers is 3:1. [g] Ratio is 4:1. [h] *E*:*Z* ratio is 1:1.

Scheme 1



1 **2** **3** (93 %)
[2:1 ratio of isomers]

Initial cuprate couplings with α,β-unsaturated carbonyl substrates, which are catalytic in copper, implicate an intermediate zinc enolate (e.g., **2**, Scheme 1),[8] which is potentially subject to further C−C bond constructions. Thus, trapping **2**, derived from

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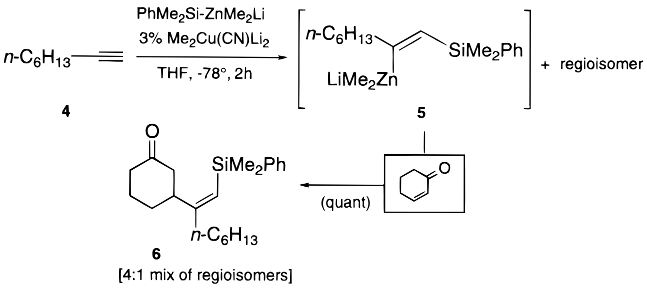
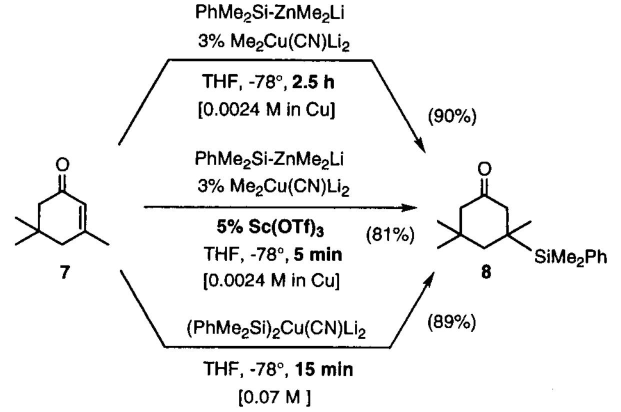
Scheme 2

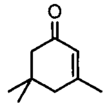
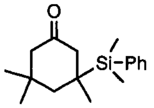
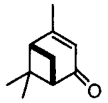
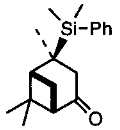
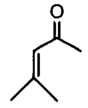
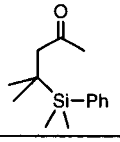


Scheme 3



ethyl crotonate, with an aldehyde prior to an aqueous workup afforded the α-alkylated, β-silylated product **3** in good overall yield. Likewise, copper-catalyzed silylcupration of terminal alkyne **4** leads to presumed intermediate vinylzincate[9] **5** (Scheme 2). Subsequent exposure of **5** to cyclohexenone, given the continuing presence of Cu(I), induces a second-stage Michael addition ultimately affording the 3-component coupling product **6**.

Table 2. Effect of Additives on Rates of 1,4-Addition Reactions of Enones with Silylzincate/3% Cuprate

Substrate	Additive	Yield	Time	Product
	Sc(OTf)$_3$[a]	81%	5 min	
	Yb(OTf)$_3$[a]	82%	15 min	
	TMSCl[b]	63%[c]	5 min	
	BF$_3$•OEt$_2$[b]	22%[d]	1 min	
	Sc(OTf)$_3$[a]	90%	5 min	
	Sc(OTf)$_3$[a]	79%	5 min	

[a] 5 mol % was used. [b] 1.2 equiv were used. [c] The remaining mass was starting material. [d] 1,2-Adduct was the major product.

Due to the catalytic nature of this process, as well as the requirement for only 1 equiv of silyl ligand, reaction rates can be slowed considerably relative to those expected with stoichiometric silyl cuprate **1**. That is, several bimolecular events must occur for a successful catalytic cycle (i.e., cuprate−zincate transmetalation, 1,4-addition, copper/lithium enolate−zincate transmetalation). Thus, for example, while disilylcuprate **1** (at 0.07 M) reacts with isophorone **7** in 15 min, this highly diluted (0.0024 M in cuprate) copper-catalyzed zincate coupling requires 2.5 h under otherwise identical conditions (−78 °C, THF; Scheme 3). In an effort to accelerate this process, we considered the usual additives Me$_3$SiCl[10] and BF$_3$·OEt$_2$.[11] Unfortunately, there are some unattractive features associated with these: both are used in excess, the former generates a silyl enol ether requiring subsequent hydrolysis, and the latter is limiting in its functional group tolerance. To our knowledge, no other additive of any generality is known in copper chemistry which increases rates of Michael additions *and gives the carbonyl product directly*. We have found that Yb(OTf)$_3$ and, especially, Sc(OTf)$_3$[12] significantly enhance 1,4-additions of silyl cuprates and do so in a catalytic fashion. Hence, for the case of isophorone (Scheme 3), in the presence of only 5 mol % Sc(OTf)$_3$, along with 3 mol % cuprate and the silylzincate, adduct **8** is obtained in 5 min. Similarly, treatment of both verbenone and mesityl oxide under the influence of this rare earth derivative reduced reaction times from hours to 5 min (Table 2). Thus, these couplings, which are *catalytic in both* copper and Sc(OTf)$_3$, are at least three times faster than the corresponding reactions done stoichiometrically in cuprate![13]

In summary, valuable silylated derivatives can now be realized using a silylzincate/cyanocuprate transmetalation scheme. Most notably, the process minimizes the amount of silyl ligand involved and requires the presence of only small percentages of transition metal, Cu(I). While efficiencies are high, rates of couplings with Michael acceptors are slowed. This observation has led to the unprecedented use of catalytic amounts of Sc(OTf)$_3$ as an additive for accelerating 1,4-additions of a silyl group via organocopper reagents. Other uses of rare earth derivatives in cuprate chemistry are now under active investigation.

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Supporting Information Available: Experimental details and ^{1}H NMR spectra for all new compounds (20 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(13) Thus, the Sc(OTf)$_3$ more than makes up for the fact that the cuprate is ca. 30 times less concentrated when used catalytically in these couplings (i.e., compare concentrations of Cu(I) in Scheme 3, last two reactions).