

Employing the simple monosilylcopper reagent, Li[PhMe₂SiCuI], in 1,4-addition reactions†

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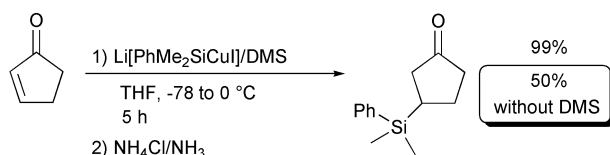
Conjugate addition reactions using the simple Li[PhMe₂SiCuI] reagent to a variety of α,β -unsaturated carbonyl compounds is described; dimethyl sulfide from the purification of CuI plays a key role for very high yields as well as high stereoselectivities in the formation of β -silyl carbonyl compounds.

Carbon–silicon bonds have fundamental roles in organic synthesis, for example as control moieties for stereochemistry in chemical reactions,¹ or as precursors to introduce a hydroxy function.² Among the silyl substituted variants available, the dimethylphenylsilyl group is very useful because it can be removed under oxidative conditions (Tamao–Fleming)^{3,2b} to make alcohols *via* retention of stereochemistry.^{2a} Hence, establishing the carbon–silicon bond configuration in the β -position to a carbonyl group serves as a complementary way of making enantiomerically pure aldol fragments. The most frequent way of introducing a PhMe₂Si group to a β -carbonyl carbon is *via* the conjugate addition of a silylcuprate reagent to an α,β -unsaturated carbonyl compound.^{4b,5}

Much attention has been focused on the silylcyanocuprates, depicted as (PhMe₂Si)₂Cu(CN)Li₂,^{6a} or Li[(PhMe₂Si)₂Cu]–LiCN,^{6b} as PhMe₂Si donors over the last two decades,^{4a} yet it is rather surprising that little consideration has been paid to the simpler Li[PhMe₂SiCuI]⁷ reagent in conjugate addition reactions. We now report that the Li[PhMe₂SiCuI] reagent works extraordinarily well, which counters previous indications.⁸ The monosilylcopper reagent is more useful than expected for 1,4-type additions (Scheme 1).

We have obtained high yields of products in the conjugate addition process employing the simple monosilylcopper reagent even without external additives, such as tributylphosphine,^{8b} HMPA,^{8a} or dialkylzinc.⁹ In THF at –78 °C, Li[PhMe₂SiCuI] was prepared from 1 equiv of LiSiMe₂Ph and 1 equiv¹⁰ of CuI, purified *via* its dimethyl sulfide complex.¹¹ The corresponding α,β -unsaturated substrate was added at –78 °C, and the reaction temperature was increased toward 0 °C over a period of 5–8 h depending on the reactivity of the starting material. Representative results are shown in Table 1.¹²

The Li[PhMe₂SiCuI] reagent seems mild enough to work in the presence of fairly sensitive substrates, and slow enough to prompt diastereoselective additions. Our results obtained with



Scheme 1

† Electronic supplementary information (ESI) available: Typical experimental procedure, ¹H-NMR, ¹³C-NMR, MS and IR spectral data for all β -silyl carbonyl compounds (PDF). See <http://www.rsc.org/suppdata/cc/b2/b210792a/>

the simple monosilylcopper reagent are superior to those from other known silylcopper classes on the same substrates,¹³ not only with respect to chemical yield, but also levels of stereoselectivity. High chemical yields (71–99%) using α,β -unsaturated ketones, aldehydes, and esters, suggests that there is little, if any, oligomerization. We found the monosilylcopper reagent obtained from CuI/DMS undergoes efficient conjugate additions to moderately unreactive α,β -unsaturated substrates with imides as well as esters, where excellent isolated yields (>90%) were obtained (entries 5 and 6). Remarkably, Li[PhMe₂SiCuI] also underwent a conjugate addition with an α,β -unsaturated amide in 60% yield (entry 9), showing that it is possible to conduct a conjugate addition in the presence of fairly acidic protons. A significant advantage in terms of cost and reducing chemical waste is that preparing Li[PhMe₂SiCuI] requires only one equivalent of PhMe₂SiLi, whereas other commonly used silyl copper reagents, *e.g.* Li[(PhMe₂Si)₂Cu]–LiCN, require two equivalents of PhMe₂SiLi per CuCN.

The Li[PhMe₂SiCuI] reagent was scrutinized in asymmetric conjugate additions to some optically active α,β -unsaturated

Table 1 Reactions of Li[PhMe₂SiCuI]

Entry	Substrate	Product ^a	Yield (%) ^b
1			82 ^c
2			71 ^c
3			95 ^c
4			91 ^c
5			99 ^c
6			92 ^c
7			63 ^c
8			76 ^e
9			60 ^c

^a Characterized by NMR (¹H and ¹³C), IR and MS. ^b Isolated and purified. ^c Reactions were conducted using a CuI·0.75DMS complex. ^d Ratio of diastereomers. ^e 99.999% reagent purity CuI (Aldrich). ^f 0.75 equivalents of DMS vs. CuI.

substrates, (entries 5–8). In entry 5,¹⁴ not only is the chemical yield almost quantitative but also de is 94% for the conjugate addition of the monosilylcopper reagent. This result is somewhat surprising since tributylphosphine was reported ‘imperative’ for the Li[PhMe₂SiCuI] reagent to undergo a conjugate addition to an imide, even at 0 °C.^{8b} Likewise, the Li[(PhMe₂Si)₂Cu]LiCN reagent typically gives 50% de to the same substrate. Moreover, Koga’s glutamic acid based auxiliary^{15,16} is a very efficient chiral director for asymmetric conjugate addition of Li[PhMe₂SiCuI] (entry 6). As a final point, the present Li[PhMe₂SiCuI] system is more attractive than the introduced silylzincate, PhMe₂SiZnEt₂Li,^{9b} because yields are comparable, levels of diastereomeric excess are higher, and the monosilylcopper reagent is easier to make.

As for the copper source, CuI purified via its dimethyl sulfide (DMS) complex is crucial for the Li[PhMe₂SiCuI] reagent to undergo a smooth 1,4-addition reaction. Applying one equivalent of the Aldrich 99.999% grade CuI, versus one equivalent of LiSiMe₂Ph in THF, without the presence of DMS, provided only 50% of the β-silylated product (Scheme 1). The presence of DMS has dramatic effects on the rate, stability and selectivity of BuCu/LiI, as reported by Bertz.¹⁷ DMS remaining from the purification process of CuI seems likely a component responsible for the higher yield, possibly due to a more soluble silylcopper reagent. Additionally, the presence of DMS plays a fundamental role in favoring the formation of one major diastereomer in the conjugate addition. Thus, employing Koga’s 2-pyrrolidinone (entry 7) and the Li[PhMe₂SiCuI] reagent made from the 99.999% grade CuI, in the absence of DMS, not only lowered the yield from 92% to 63%, it also reduced the diastereomeric ratio of the conjugate addition product from 92% to 0% de! When DMS was combined with the 99.999% grade CuI, the yield and the diastereomeric ratio of the β-silylated product increased significantly (entry 8).

The CuI·DMS complex initially formed in the purification process of CuI has been reported to be unstable and loses DMS rapidly to form the more stable CuI·0.75DMS stoichiometry.¹¹ At that point, the DMS concentration remains essentially constant.¹⁸ A four month old sample of CuI·0.75DMS taken from a light-protected bottle, gave identical yields and stereoselectivities in the conjugate addition reactions as a freshly prepared sample of CuI·0.75DMS.

This paper shows that excellent results in diastereoselective conjugate additions can be obtained employing the monosilylcopper reagent, Li[PhMe₂SiCuI]. It is suggested that the CuI should be purified via its DMS complex prior to making the monosilylcopper reagent. We have also demonstrated that external additives such as tributylphosphine, HMPA, or dialkylzinc are unnecessary, even though only one equivalent, not two, of silyl lithium reagent is used. Employing the simple Li[PhMe₂SiCuI] reagent obtained from CuI, could be an attractive alternative to the use of CuCN, which (although it provides catalytic activity)^{5a} is used in conjunction with stoichiometric quantities of the R₂Zn reagents. In summary, the Li[PhMe₂SiCuI] system is expected to be a very useful reagent, for the chemo- and diastereoselective formation of silicon–carbon bonds in organic synthesis.

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