

# (2-Methoxyphenyl)dimethylsilyl Lithium and Cuprate Reagents Offer Unique Advantages in Multistep Synthesis<sup>†</sup>

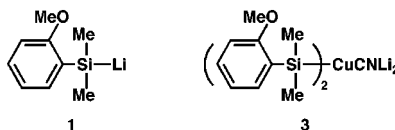
Thomas W. Lee and E. J. Corey\*

Department of Chemistry and Chemical Biology, Harvard University,  
12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received August 14, 2001

## ABSTRACT



The new silyllithium reagent **1** and the corresponding cyanocuprate **3** are readily generated under optimal conditions and are useful for the formation of C–Si bonds. Tamao–Fleming oxidation of such C–Si bonds can be effected under very mild conditions.

Trialkyl/arylsilyllithium reagents now play a valuable role in the synthesis of complex organic molecules because they provide a unique avenue for the attachment of silyl groups to carbon for use as control elements<sup>1,2</sup> or as equivalents of the hydroxyl function (via Tamao–Fleming oxidation<sup>3</sup>). The most commonly used silyllithium reagent is PhMe<sub>2</sub>SiLi, which is readily generated by reaction of PhMe<sub>2</sub>SiCl with lithium metal.<sup>2b,c</sup> Surprisingly, this method of formation often fails even for closely related silyl groups. In fact, Fleming has published a paper describing the “failure in several attempts to prepare arylsilyl-lithium reagents.”<sup>4</sup> The most striking example in that paper involved the simple replacement of phenyl by *p*-tolyl, in which case the reaction afforded only the corresponding disilane with no further conversion to silyllithium reagent. It is generally agreed that at least

one phenyl group on silicon is necessary for the formation of silyllithium reagent. The only exceptions to this rule are tri-*o*-tolylsilyllithium, mesityldimethylsilyllithium, and hydrido-dimesitylsilyllithium.<sup>2c,5</sup> In each of these cases, silyllithium reagent was probably generated directly from chlorosilane without the intervention of disilane as a result of steric shielding about the silicon center. The inaccessibility of many silyllithium compounds is perhaps the reason PhMe<sub>2</sub>SiLi is by far the most widely used reagent even though the Tamao–Fleming oxidation of the PhMe<sub>2</sub>SiC subunit may fail in the presence of sensitive functional groups.<sup>3</sup>

We recently reported an enantioselective total synthesis of the marine natural product eunicenone A in which a silyl group attached to carbon played a key role both in controlling the position- and stereoselectivity of a catalytic enantioselective Diels–Alder reaction (Scheme 1) and as a precursor of another functionality.<sup>6</sup> During this research we examined several new alternatives to the PhMe<sub>2</sub>Si group since this structural subunit was marginal with regard to stereocontrol and caused problems in a Tamao–Fleming oxidation.<sup>6</sup> These studies led to the discovery of (2-methoxyphenyl)dimethylsilyllithium (**1**) as a superior alternative to PhMe<sub>2</sub>SiLi, with regard to both the electron-donating properties of the silyl

<sup>†</sup> Dedicated to Professor Ian Fleming.

(1) (a) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; Wiley: New York, 2000. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988. (c) Webber, W. P. *Silicon Reagents in Organic Synthesis*; Springer: Berlin, 1983. (d) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981. (e) Fleming, I.; Barbero, A.; Walker, D. *Chem. Rev.* **1997**, *97*, 2063.

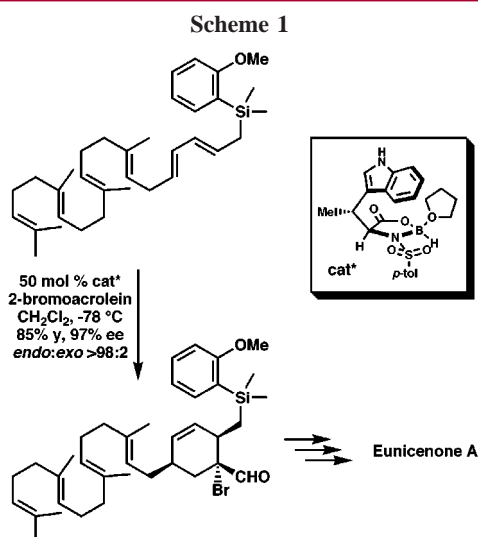
(2) (a) Lickiss, P. D.; Smith, C. M. *Coord. Chem. Rev.* **1995**, *95*, 75. (b) Fleming, I. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 257–292. (c) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403.

(3) (a) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(4) Rahman, N. A.; Fleming, I.; Zwicky, A. B. *J. Chem. Res., Miniprint* **1992**, 2401.

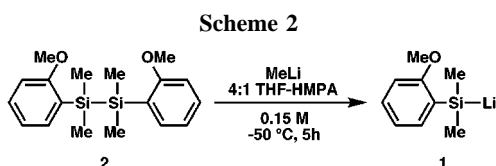
(5) (a) Müller, H.; Weinzierl, U.; Seidel, W. *Z. Anorg. Allg. Chem.* **1991**, *603*, 15. (b) Weidenbruch, M.; Kramer, K. *Z. Naturforsch., B: Chem. Sci.* **1985**, *40B*, 601.

(6) Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 1872.



group and Tamao–Fleming oxidation of sensitive substrates. This paper reports on the generation of **1** and its use in synthesis and also on some related new reagents which, although not suited for the synthesis outlined in Scheme 1, are probably useful for other applications.

The generation of **1** was carried out from the disilane **2**, which was synthesized by the reaction of 2-methoxyphenyllithium with commercially available *sym*-dichlorotetra-methyldisilane (Scheme 2).<sup>7</sup> The conditions for the formation

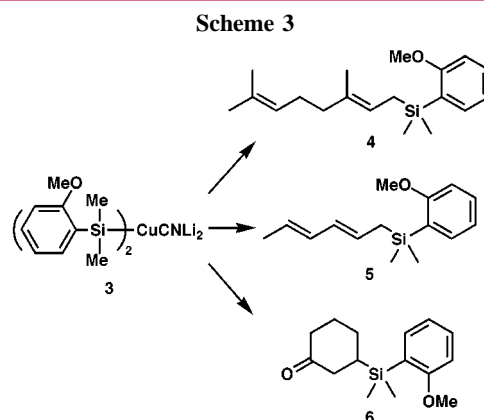


of **1** from **2** were found to be critical. Methyl lithium was superior to *n*-BuLi for the reaction, and the optimum temperature was found experimentally to be  $-50\text{ }^{\circ}\text{C}$  with 4:1 THF/hexamethylphosphoric triamide (HMPA)<sup>8</sup> as solvent. The appreciable instability of solutions of **1** at  $-30\text{ }^{\circ}\text{C}$  precludes the use of this or higher temperature for its generation from **2**. Solutions of **1**, which are dark red in color, produce (2-methoxyphenyl)dimethylsilane upon treatment with methanol. Reaction of **1** with 0.5 equiv of CuCN at

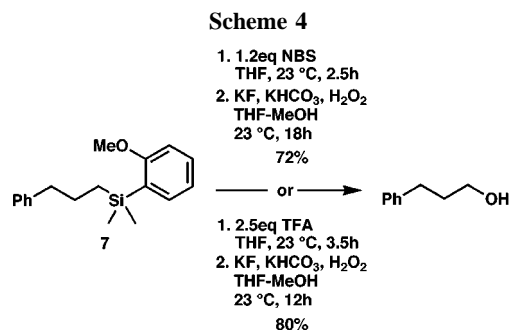
(7) The conditions described herein were arrived at after extensive experimentation. Many methods previously used for preparing PhMe<sub>2</sub>SiLi failed to afford the desired silyllithium reagent **1**. Attempts to generate **1** from (2-methoxyphenyldimethyl)silyl chloride with lithium metal in THF were unsuccessful (see also ref 4). Attempts to prepare **1** or its potassium analogue from (2-methoxyphenyl)dimethylsilane by deprotonation with LDA or KHMDS in THF or KH in DME were unpromising. The reaction of ArMe<sub>2</sub>SiH with *n*-BuLi or *t*-BuLi led to displacement of H by *n*-Bu or Me by *t*-Bu, respectively.

(8) (a) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063. (b) Hudrlik, P. F.; Waugh, M. A.; Hudrlik, A. M. *J. Organomet. Chem.* **1984**, *271*, 69. (c) The HMPA/THF ratio and reactant concentration were optimized to ensure a reasonable reaction rate and a homogeneous mixture at  $-50\text{ }^{\circ}\text{C}$ .

$-50\text{ }^{\circ}\text{C}$  initially and then at  $0\text{ }^{\circ}\text{C}$  for 1.5 h affords a cuprate (**3**) reagent of the type (ArMe<sub>2</sub>Si)<sub>2</sub>CuCNLi<sub>2</sub>, which undergoes smooth coupling at  $-50\text{ }^{\circ}\text{C}$  with (*E*)-geranyl benzoate to form **4** (80%) and with (*E,E*)-sorbyl benzoate to form **5** (72%). Reaction of this cuprate with 2-cyclohexenone provided the conjugate adduct **6** (80%) (Scheme 3).

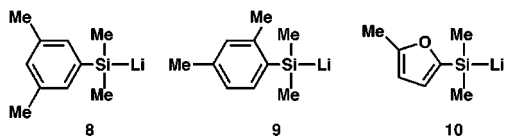


The (2-methoxyphenyl)dimethylsilyl group offers some advantages over the parent phenyldimethylsilyl group because it can be converted oxidatively to an alcohol moiety under much milder conditions and is effectively a more potent  $\sigma \rightarrow \pi$  electron donor.<sup>6</sup> We found that the 2-methoxyphenyl group in **7** undergoes facile Ar–Si cleavage by the action of *N*-bromosuccinimide or trifluoroacetic acid, as shown in Scheme 4. The resulting succinimido- or trifluoro-



roacetoxysilane can then be oxidized under very mild conditions to provide 3-phenylpropanol in good yield.

We have also prepared a series of reagents analogous to **1** but differing in the aryl part using the same method of generation, i.e., reaction of (ArMe<sub>2</sub>Si)<sub>2</sub> with MeLi in 4:1 THF/HMPA at  $-50\text{ }^{\circ}\text{C}$ . In this way we obtained the lithium reagents **8–10** and by further reaction with CuCN also the cuprates (ArMe<sub>2</sub>Si)<sub>2</sub>CuCNLi<sub>2</sub>. The cuprates from **8–10** underwent smooth coupling with (*E*)-geranyl and (*E,E*)-sorbyl benzoate and conjugate addition with 2-cyclohexenone to form the corresponding organosilicon products,<sup>9</sup> the results being very similar to those obtained with cuprate **3** (seven examples, 81–96% yield, see Supporting Information for details).



In summary, the studies reported herein have led to the discovery of the new organosilyllithium reagent **1**, which has considerable potential in multistep synthesis. Very mild conditions for effecting the hydroxy desilylation reactions of the (2-methoxyphenyl)dimethylsilyl group are described.

(9) Various furylsilyl reagents have previously been applied in synthesis; see: (a) Norley, M. C.; Kocienski, P. J.; Faller, A. *Synlett* **1994**, 77. (b) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, 36, 501. (c) Stork, G. *Pure Appl. Chem.* **1989**, 61, 439.

In addition, the chemistry reported above is applicable to the preparation of other silyllithium reagents such as, but not limited to, **8–10**.

**Acknowledgment.** We are grateful to the National Science Foundation and Boehringer Ingelheim Co. for graduate fellowships to T.W.L.

**Supporting Information Available:** Full procedures for the generation of organosilyllithium reagents **1** and **8–10** and the corresponding cyanocuprates, along with examples of their use, and oxidative desilylation of **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0165746