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# Conjugate Addition of Dimethylphenylsilyllithium to α,β-Unsaturated Carbonyl Compounds *Mediated* by Sub-stoichiometric Quantities of Dimethylzinc

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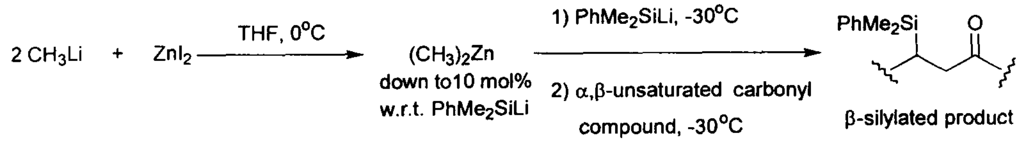
**Abstract:** Dimethylphenylsilyllithium undergoes conjugate addition to a variety of α,β-unsaturated enones in the presence of sub-stoichiometric amounts of dimethylzinc. Down to 10 mol % of $Me_2Zn$ facilitates these reactions to afford good to excellent yields of β-silylated products. This catalytic behavior is displayed when the $Me_2Zn$ used is generated *in situ* from the addition of methyllithium to zinc (II) iodide or when used directly from a commercial source. This methodology in which sub-stoichiometric quantities of the reactive organometallic reagent are present at a given time may provide a route for catalytic enantioselective conjugate addition of trialkylsilyl moieties to enones.

Recently we reported the conjugate addition of lithium dimethylphenylsilyl(dialkyl)zincate reagents to a variety of α,β-unsaturated carbonyl compounds to afford β-silylated products in good to excellent yields.[1] This study described the use of lithium dimethylphenylsilyl(dialkyl)zincate reagents prepared from the addition dimethylphenylsilyllithium to dimethylzinc that was generated *in situ* from the addition of two equivalents of methyllithium to zinc(II) halide salts (e.g. $ZnCl_2$ or $ZnI_2$).[2] This method was seen as a safer complementary method to that described by Fleming *et al.* in which pyrophoric $Me_2Zn$ or $Et_2Zn$ was used directly from a commercial source.[3]

Clearly if the ligands used to prepare the mixed lithium dimethylphenylsilyl(dialkyl)zincate reagents contained chirality it may be possible to induce asymmetry in these addition reactions. The value of these reagents to the synthetic chemist as asymmetric reagents would be further enhanced if the metal atom being used could be present in catalytic amounts; in essence affording a chiral catalyst. With this ultimate goal in mind we decided to vary the relative amounts of $PhMe_2SiLi$ and $Me_2Zn$ combined in these reactions. Hence, we report herein the conjugate addition of dimethylphenylsilyllithium, $PhMe_2SiLi$, to a variety of α,β-unsaturated carbonyl compounds *mediated* by $Me_2Zn$. These reactions, in which sub-stoichiometric quantities of $Me_2Zn$ are used, afford synthetically useful amounts of β-silylated products. It has been demonstrated that the $Me_2Zn$ used in these reactions can be added to the reaction mixtures directly as obtained from commercial sources or can be generated *in situ* from the addition of two equivalents of methyllithium to one equivalent of $ZnI_2$ (Equation 1).[4]



(1)

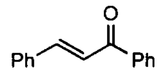
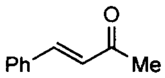
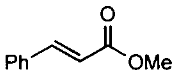
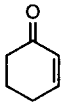
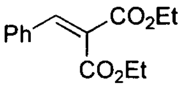
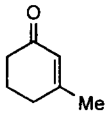
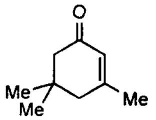
In agreement with earlier studies good to excellent yields of β-silylated adducts can be obtained when dimethylphenylsilyllithium and dimethylzinc are reacted in equimolar quantities followed by addition of enone substrate (Table 1). [1,3] Interestingly, we found that these reactions continued to afford good to excellent yields of β-silylated products even when sub-stoichiometric amounts of dimethylzinc, prepared *in situ* or used directly from a commercial source, were added to the reaction mixture. When the amount of $Me_2Zn$ present was one half the amount of $PhMe_2SiLi$ added, good to excellent yields of the β-silylated products were obtained while no 1-dimethylphenylsilyl alcohol, the 1,2-addition products resulting from the addition of excess $PhMe_2SiLi$ to the carbonyl carbon atom, was observed in any case.[5] It was demonstrated that quantities down to 20 mol % or 10 mol % of $Me_2Zn$, with respect to the amount of dimethylphenylsilyllithium, (i.e. ~ 5 :1 to ~ 10:1 ratio of $PhMe_2SiLi$ : $Me_2Zn$), efficiently mediate the conjugate addition of $PhMe_2SiLi$ to α,β-unsaturated cyclic and acyclic ketones, esters, and diesters. Once again no 1,2-addition products from the addition of excess $PhMe_2SiLi$ were observed in any case. When 5 mol % of $Me_2Zn$ (i.e. ~ 20:1 ratio of $PhMe_2SiLi$ : $Me_2Zn$) is utilized in these reactions we found a dramatic decrease in the isolated yield of silylated products. This could be due to inadvertent quenching of the small amount of active organometallic reagent present in solution by adventitious moisture that had crept into the reaction flask. At all proportions of $Me_2Zn$, poor yields of the β-silylated product were obtained when using the branched enone, isophorone, (Entry 7, Table1) as a substrate.

It appears as though $Me_2Zn$ is involved in a catalytic cycle in which an amount of lithium dimethylphenylsilyl(dimethyl)zincate equal to the amount of $Me_2Zn$ initially added is formed. This zincate can then react in a conjugate fashion with the enone substrate with concomitant regeneration of $Me_2Zn$ while the silyl moiety is transferred. The regenerated $Me_2Zn$ can then react further with the excess $PhMe_2SiLi$ present and perform repeated conjugate additions until the enone substrate is totally consumed or the organometallic species is "killed" or "poisoned" by some adventitious electrophilic source in the reaction mixture.

It is noteworthy that the dimethylzinc used in these reactions can be used directly as obtained from a commercial source (Aldrich Chemical Company, 2.0 M in toluene) or can be generated *in situ* by the addition of two equivalents of methyllithium to one equivalent of zinc (II) iodide in THF solution. Not only is the *in situ* generation of the dialkylzinc less hazardous using this method but this method enables the potential incorporation of a wide variety of ligands onto the reactive organozincate species present in these solutions. We are presently investigating the scope of ligands, both achiral and chiral, that can be incorporated onto the zinc atom in these reactions.

**Acknowledgments.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, the Natural Sciences and Engineering Research Council of Canada, and Saint Mary's University for support of this research.

**Table 1.** Conjugate Addition of $PhMe_2SiLi$ to α,β-Unsaturated Carbonyl Compounds in the Presence of $Me_2Zn$.

| Entry | **α,β-unsaturated carbonyl compound** | **Ratio of $PhMe_2SiLi : Me_2Zn$** | **% Yield[a,5,6] (Method A)[4]** | **% Yield[b,5,6] (Method B)[4]** |
|---|---|---|---|---|
| 1 |  | 1 : 1 | 91% | 77% |
| | | 2 : 1 | 68% | 86% |
| | | 5 : 1 | 78% | 62% |
| | | 10 : 1 | 38% | 39% |
| | | 20 : 1 | 15% | 29% |
| 2 |  | 1 : 1 | 92% | 67% |
| | | 2 : 1 | 67% | 85% |
| | | 5 : 1 | 71% | 68% |
| | | 10 : 1 | 64% | 38% |
| | | 20 : 1 | 32% | 30% |
| 3 |  | 1 : 1 | 98% | 82% |
| | | 2 : 1 | 60% | 69% |
| | | 5 : 1 | 50% | 67% |
| | | 10 : 1 | 30% | 32% |
| | | 20 : 1 | 32% | 23% |
| 4 |  | 1 : 1 | 95% | 78% |
| | | 2 : 1 | 63% | 61% |
| | | 5 : 1 | 67% | 79% |
| | | 10 : 1 | 68% | 69% |
| | | 20 : 1 | 18% | 75% |
| 5 |  | 1 : 1 | 78% | 71% |
| | | 2 : 1 | 88% | 95% |
| | | 5 : 1 | 65% | 47% |
| | | 10 : 1 | 66% | 51% |
| | | 20 : 1 | 43% | 44% |
| 6 |  | 1 : 1 | 53% | 36% |
| | | 2 : 1 | 47% | 61% |
| | | 5 : 1 | 19% | 47% |
| | | 10 : 1 | 12% | 18% |
| | | 20 : 1 | 12% | 12% |
| 7 |  | 1 : 1 | 14% | 27% |
| | | 2 : 1 | 28% | 43% |
| | | 5 : 1 | 8% | 18% |
| | | 10 : 1 | 3% | 15% |
| | | 20 : 1 | 3% | 4% |

a. Isolated yield obtained when $Me_2Zn$ used directly from commercial source.

b. Isolated yield obtained when $Me_2Zn$ prepared in situ from the addition of 2 $CH_3Li$ + $ZnI_2$ in THF.

**References and Notes.**

1. A. Vaughan and Robert D. Singer *Tetrahedron Lett.* **1995**, *36*, 5683.
2. (a) W. Tückmantel, K. Oshima, and H. Nozaki *Chem. Ber.* **1986**, *119*, 1581.
   (b)Y. Okuda, K. Wakamatsu, W. Tückmantel, K. Oshima, and H. Nozaki *Tetrahedron Lett.* **1985**, *26*, 4629.
3. R. A. N. C. Crump, I Fleming, and C. J. Urch *J. Chem. Soc., Perkin Trans I* **1994**, 701.
4. $Me_2Zn$ obtained from Aldrich Chemical Company, 2.0 M in toluene, is a hazardous pyrophoric starting material whereas $Me_2Zn$ prepared *in situ* from 2 MeLi + $ZnI_2$ in THF is a much safer alternative.
   Typical Procedure: *Preparation of 3-dimethylphenylsilyl-1,3-diphenylpropanone (Entry 1, Table 1)* **Method A**: To a round bottomed flask at -30°C containing 5 mL of freshly distilled THF was added 5.0 mL of $PhMe_2SiLi$ (1.0 M in THF, 5.0 mmol) *via* syringe under inert atmosphere. 0.50 mL of $Me_2Zn$ (2.0 M in toluene, 1.0 mmol) was added to the resulting solution ($PhMe_2SiLi$ :$Me_2Zn$ = 5:1) and allowed to stir at -30°C for 30 min. 0.52 g of chalcone (208.26 g/mol, 2.5 mmol) dissolved in 3 mL of THF were then added dropwise *via* syringe to the reaction mixture and allowed to stir an additional 3 h at -30°C. The reaction was then quenched with 10 mL of water and products extracted with diethyl ether. The combined extracts were concentrated *in vacuo* and purified by silica gel flash chromatography (hexane/ethyl acetate 10:1) affording 0.67 g (78%) of 3-dimethylphenylsilyl-1,3-diphenylpropanone. **Method B**: To a round bottomed flask containing 0.319 g of dry $ZnI_2$ (319.19 g/mol, 1.0 mmol) under inert atmosphere was added 5 mL of freshly distilled THF. 1.33 mL MeLi (1.5 M in ether, 2.0 mmol) was then added dropwise *via* syringe upon cooling to 0°C and the reaction stirred for 30 min. The solution was then cooled to -30°C, 5.0 mL of $PhMe_2SiLi$ (1.0 M in THF, 5.0 mmol) added dropwise *via* syringe, and allowed to stir for another 30 min. 0.52 g of chalcone (208.26 g/mol, 2.5 mmol) dissolved in 3 mL of THF were then added dropwise *via* syringe to the reaction mixture and allowed to stir an additional 3 h at -30°C. The reaction was then quenched with 10 mL of water and products extracted with diethyl ether. The combined extracts were concentrated *in vacuo* and purified by silica gel flash chromatography (hexane/ethyl acetate 10:1) affording 0.53 g (62%) of 3-dimethylphenylsilyl-1,3-diphenylpropanone. Melting Point: 66-68°C $^1H$ NMR ($CDCl_3$): $\delta$ 7.9-6.8 (m, 15H) 3.5 (dd, 1H, $C\underline{H_2}$) 3.2 (dd, 1J, $C\underline{H_2}$) 3.1 (dd, 1H, $C\underline{H}$) 0.29 (s, 3H, Si-$C\underline{H_3}$) 0.23 (s, 3H, Si-$C\underline{H_3}$); $^{13}C$ NMR ($CDCl_3$): $\delta$ 199.0, 142.3, 137.1, 136.8, 134.1, 132.6, 129.2, , 128.9, 128.5, 127.9, 127.7, 127.6, 124.7 , 38.9, 31.0, -3.9, -5.2. IR (KBr): $\nu$ ($cm^{-1}$) 3066.1 and 3024.1, 2955.6, 2895.1, 1956.5, 1882.8, 1815.6, 1800, 1687.0, 747.7, 699.5.
5. When the ratio of $PhMe_2SiLi$ : $Me_2Zn$ : enone was 5:1:1 (i.e. large excess of $PhMe_2SiLi$) we found that the 1,4-addition products were obtained in 41 - 99 % isolated yields. Isophorone (3,5,5- trimethylcyclohex-2-en-1-one) reacted poorly (6% of 1,4-adduct) under these conditions likely due to steric reasons. No 1-dimethylphenylsilyl alcohols resulting from 1,2-addition of $PhMe_2SiLi$ to the carbonyl carbon atom were detected under these conditions in any case.
6. The IR, EI-MS, $^1H$ NMR(400 MHz) and $^{13}C$ NMR (100 MHz) spectral properties of each of the 3-dimethylphenylsilyl substituted products were consistent with those reported in the literature for the assigned structures.

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