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Complex Induced Proximity Effect Enhancement in α-Silyl Carbanion Generation. A General Conversion of 2-Silyl Benzamides into 2-Fluorosilylacetophenones

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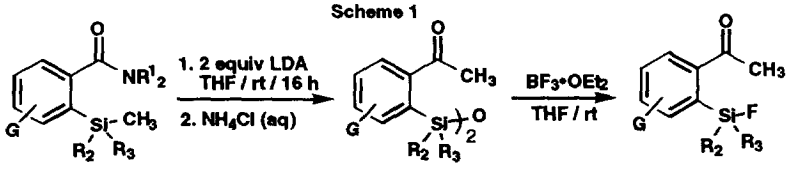
Abstract: LDA treatment of 2-silylated benzamides **1** affords 2-fluorosilylated acetophenones **3** in a general process likely driven by CIPE-facilitated α-silyl carbanion formation and rearrangement (**Scheme 3**); oxidation (H_2O_2) of the products gives 2-hydroxyacetophenones and catechols (**Scheme 4**). Copyright © 1996 Elsevier Science Ltd

The salient obervation by Peterson almost thirty years ago[1] that tetramethylsilane and n-butyltrimethylsilane undergo metalation (t-BuLi/TMEDA) provided the first experimental verification of the enhanced acidity of α-hydrogens of organosilanes relative to those of the corresponding hydrocarbons.[2] Subsequently, such unactivated α-silyl carbanion formation has been sporadically reported, often as competitive and minor paths of desired metalation processes.[3] In many of these cases, the presence of strongly coordinating groups implies the operation of a complex induced proximity effect (CIPE)[4] in the α-silyl deprotonation step. Low yields have precluded the widespread synthetic application of this variation of α-heteroatom metalation.[5] Herein, we report the LDA-mediated conversion of ortho-silylated benzamides **1** into ortho-fluorosilylated acetophenones **3** (**Scheme 1**) thus demonstrating, for the first time, an efficient and general α-silyl metalation process. We also show that the resulting products (**3**) are readily transformed into ortho-hydroxyacetophenones (**10**) and catechols (**12**). The overall results offer new, potentially synthetically valuable, carbanionic organosilicon chemistry.

Scheme 1

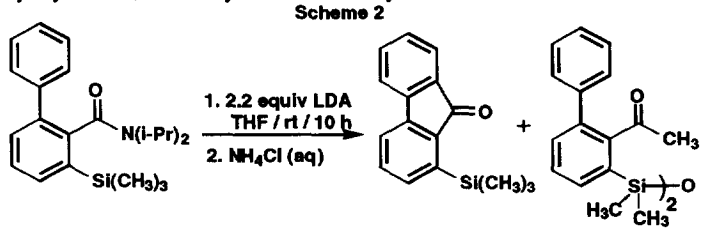


1 **2** **3**

R^1 = Et, i-Pr$_2$; R^2 = R^3 = Me; R^2 = Me, R^3 = Ph; R^2 = R^3 = Ph; if Si(CH$_3$)R^2R^3 = SiEt$_3$, SiPh$_3$ → N.R.

In the course of studies on the directed remote metalation of biaryl amides and O-carbamates,[6] we observed that LDA treatment of the ortho-silylated **4** followed by standard aqueous workup afforded, in addition to the expected product of Directed remote Metalation (DreM) (**5**),[6a] the disiloxane **6** as the major product (**Scheme 2**). We therefore investigated the generality of **1**→**2**, in which the DreM process is precluded (G ≠ o-Ph); in the course of these studies, the disiloxanes **2** proved difficult to characterize and hence were transformed into the stable, mostly crystalline, fluorosilyl derivatives **3** by treatment with boron trifluoride etherate.[7]

Scheme 2

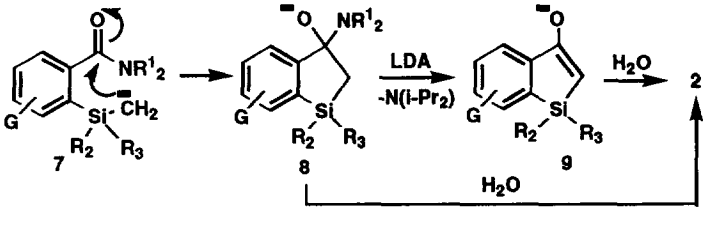


4 **5 (12%)** **6 (28%)**

The Table, depicting the scope and limitations of the preliminary study, deserves commentary. The use of 2 equiv of LDA provides optimum yields, less (1.5 equiv) resulting in isolation of variable amounts of starting benzamide **1**. Employing LiTMP (2 equiv) led to comparable results while LHMDS did not effect the conversion presumably owing to basicity differences.[8] In general, moderate to high yields of conversion **1**→**3** may be achieved. Steric effects due to $CONEt_2$ vs $CON(i\text{-}Pr)_2$ appear not to play an important role (entries 1, 3, 5) but this is not the case for crowded silicon environment (entries 4, 6). Competitive p-tolyl anion generation[9] may compromise the result in entry 2 for the diethyl amide (44%) which is expected to undergo intermolecular self-condensation more readily than the more encumbered corresponding diisopropyl amide. Although evidence was not obtained, the low yield in entry 7 may be due to benzyne formation. While the bisilylated benzamide (entry 10) behaved as expected, the corresponding phthalamide (entry 8) gave a mono- rather than a di-acetyl derivative, even under forcing and excess LDA conditions. Replacement of up to two methyls by phenyls (entries 11, 12) does not greatly discourage the reaction;[10] however, the corresponding o-$SiPh_3$[11] and o-$SiEt_3$[12] systems showed no evidence for α-silyl carbanion chemistry based on product analysis.

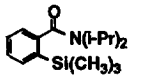
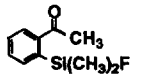
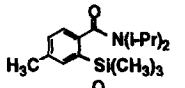
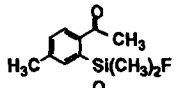
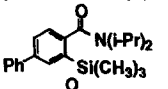
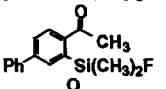
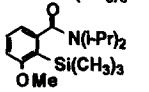
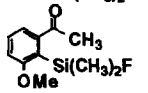
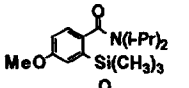
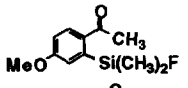
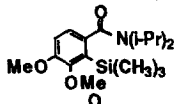
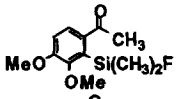
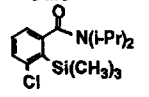
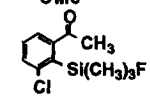
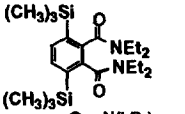
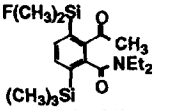
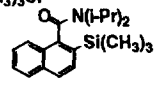
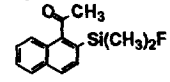
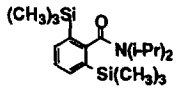
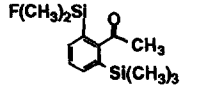
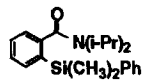
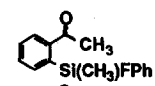
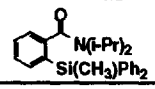
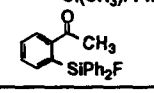
A plausible mechanism for the reaction (**Scheme 3**) involves deprotonation of **1** leading to **7** which undergoes cyclization to the tetrahedral intermediate **8** which, in turn, either *via* silaindenol **9**, by loss of diisopropyl amide anion or directly, by hydrolysis upon workup, affords product **2**. While the CIPE-assisted ortho (and ortho') deprotonation of tertiary benzamides under *in situ* LiTMP/TMSCl conditions has been demonstrated by the formation of 2,6-disilylated products in high yields,[13] the generation of **7** appears to be the thermodynamically more favorable process. Attempts to obtain evidence for anionic species **7** and **9** (D_2O, silyl and alkyl halide quenches) have been inconclusive to date.[14]

Scheme 3



7 **8** **9**

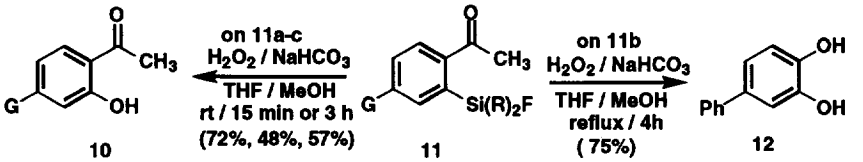
Table. Transformation of o-Silylated Benzamides **1** into o-Fluorosilylacetophenones **3**

Entry	Amide 1	Acetophenone 3	yld,[a] %
1			85 (80)
2			83 (44)
3			83 (81)
4			46 (28)
5			85 (83)
6			34
7			17
8			50
9			71
10			66
11			61
12			73

[a] Yields shown are of chromatoraphically pure and / or recrystallized materials. All compounds show analytical and spectral data consistant with the depicted structures. Yields in parenthesis refer to those derived from the corresponding diethyl amides.

Tamao oxidation[15] of o-fluorosilyl acetophenones **11a-c** (**Scheme 4**) afforded the o-hydroxy derivatives **10a-c** respectively. More vigorous conditions on **11b** resulted also in a Baeyer-Villager rearrangement to furnish the catechol **12** in good yield.

Scheme 4



To conclude, a general and reasonably efficient transformation of o-silylated benzamides **1** into o-fluorosilylated acetophenones **3** has been achieved. While the mechanism of this process, perhaps a further demonstration of CIPE acidity enhancement,[4] remains to be elucidated, its utility, whether for reasons of direct inaccessibility of **3** or their conversion into o-hydroxyacetophenones **11** and catechols **12**, may find synthetic application.[16,17]

References and Notes

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10. In both cases, the silanols corresponding to **2** were isolated and characterized.
11. For anionic cyclization of diarylsulfones to thioxanthen-9-ones where, admittedly, ortho-acidity is higher, see Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 6508.
12. This unreactivity was used to demonstrate the DreM process **4**→**5** ($SiMe_3$ = $SiEt_3$, 63% yield): Zhao, B.-p. Ph.D. Thesis, University of Waterloo, **1994**.
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14. The ketone or enol corresponding to **9** is unknown.
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16. *Typical Experimental Procedure:* To a stirred solution of LDA (8 mmol), freshly prepared from HN(i-Pr)2 (1.1 mL, 8 mmol) and n-BuLi (1.6 M, 8 mmol) in anhyd THF (20 mL) at 0 °C under nitrogen, was added a solution of *N,N*-diisopropyl-4-methoxy-2-trimethylsilylbenzamide (1.22 g, 4.0 mmol) in anhyd THF (10 mL) *via* a double-tipped needle. The reaction mixture was allowed to reach ambient temperature over 15 h, quenched with satd aq NH_4Cl (5 mL), and most of the THF was removed *in vacuo*. The residue was partitioned between H_2O (25 mL) and CH_2Cl_2 (50 mL), the organic phase was separated and the aqueous phase extracted further with CH_2Cl_2 (25 mL). The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oil was dissolved in anhyd THF (10 mL) under nitrogen, boron trifluoride etherate (1.0 mL, 8.1 mmol) was added dropwise, and the reaction mixture was allowed to stand for 18 h. Workup and purification as above (except for the inclusion of a satd aq NaCl wash prior to drying) gave the product (760 mg, 85%) as a colorless solid, which was recrystallized from acetone-water.

17. We are grateful to NSERC Canada for support by way of Research Grant and NSERC/Monsanto Industrial Research Chair programs.

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