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# Efficient Synthesis of α-Tertiary α-Silylamines from Aryl Sulfonylimidates via One-Pot, Sequential C–Si/C–C Bond Formations

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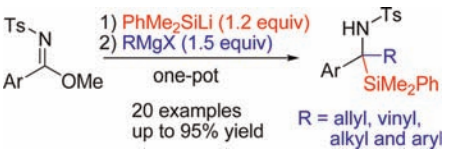
## ABSTRACT




**An efficient and flexible route for the synthesis of α-tertiary (α,α-dibranched) α-silylamines via sequential reactions of sulfonylimidates using readily available phenyldimethylsilyllithium and Grignard reagents is described. The procedure allows successive formation of C–Si/C–C bonds in a single flask.**

α-Silylamines, also called silylmethylamines (SMAs), and their derivatives have attracted considerable attention due to their biological activities and their applications in synthetic transformations[1] ever since they were first described in 1951.[2] Although numerous SMAs have been characterized and used in various applications, few reports exist of α-tertiary amines containing α-silyl groups ($R_2$SMA), in part because they cannot be prepared efficiently by current methods.

To access such hindered α-silylamines, conventional methods for the synthesis of typical tertiary amines[3] cannot be easily applied. This strategy involves the addition of carbanions to ketimines, but the equivalent addition of silyl nucleophiles to ketimines has not given satisfactory yields.[4] In 2011, the Oestreich group achieved CuCN-catalyzed addition of $Me_2PhSi–Bpin$ (pin = pinacolate) to ketimines (Scheme 1, path 1).[5] However, the need for toxic copper(I) cyanide and the somewhat tedious procedures to prepare the nucleophilic silyl reagent, $Me_2PhSi–Bpin$,[6] make this approach less practical. An alternative approach to producing α-tertiary α-silylamines would be to couple carbanions with imines derived from acylsilanes (*C*-silylimines) or their functional equivalents

(1) For a review of the chemistry and biological activities of silylmethylamines and their derivatives, see: Picard, J.-P. *Adv. Organomet. Chem.* **2005**, *52*, 175.

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(4) For examples of low-yield reactions, see: (a) The addition of dimethylphenylsilyllithium to acetophenone-derived imine to afford the desired silylmethylamine in 11% yield: Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403. (b) The addition of diphenylmethylsilyllithium to acetone-derived imine gives a 31% yield: Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035.

(5) Vyas, D. J.; Fröhlich, R.; Oestreich, M. *Org. Lett.* **2011**, *13*, 2094.

(6) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **2000**, *19*, 4647.

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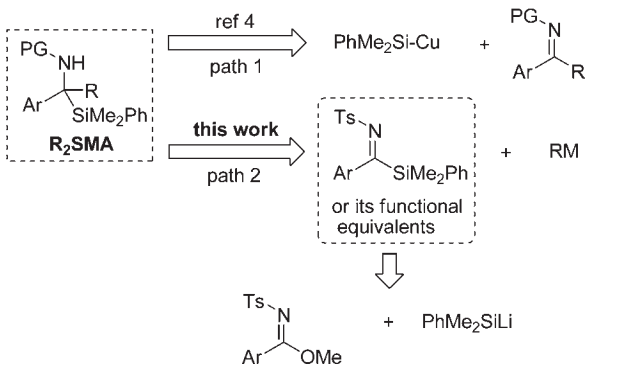
(Scheme 1, path 2). However, a common method of synthesizing ketimines, i.e., condensation of amines with all-carbon ketones, is inappropriate when acylsilanes are used as substrates. In this case, the reaction does not afford the desired silyl azomethines; instead, it usually results in the loss of silyl groups due to silyl migration (1,2-Brook rearrangement).[7,8]

Our interest in the chemistry of sulfonylimidates and silicon-containing compounds[9] led us to speculate that addition of a silyl nucleophile to the azomethine of sulfonylimidates could furnish *N*-sulfonyl-*C*-silylimines or their functional equivalents,[3h,10] which would then combine with carbanions to afford the desired α-tertiary α-silylamines (Scheme 1, path 2, RM = organometallic reagents).[11−13] Here we report an efficient and flexible method for the synthesis of α-tertiary α-silylamines in which silyllithium reagents and Grignard reagents are sequentially added to sulfonylimidates in one pot.

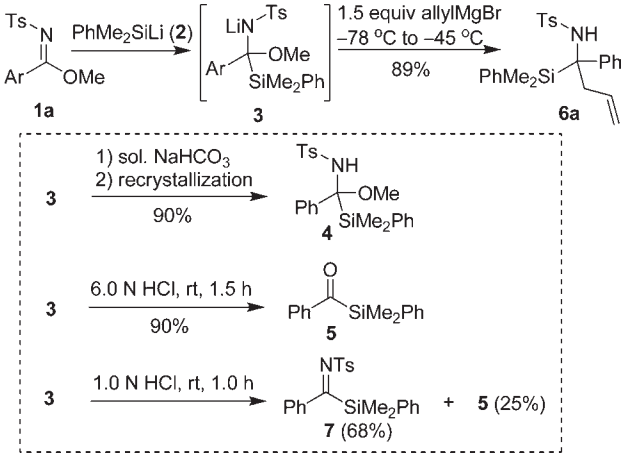
To test the reactivity of sulfonylimidates, we chose $PhMe_2SiLi$,[14] which is the most commonly used silyllithium reagent due to its easy preparation and handling. To our delight, the addition of silyllithium **2** to methyl *N*-Ts-phenylimidate **1a** proceeded smoothly at −78 °C to give the silyl *N*,*O*-aminal product **4** in 90% yield after

**Scheme 1.** Strategies to Synthesize $R_2SMA$




quenching with aqueous $NaHCO_3$ (Scheme 2), while phenyl acylsilane **5** was obtained in 85% yield under strongly acidic quenching conditions (6 N aqueous HCl).[15] Interestingly, quenching the reaction with 1.0 N aqueous HCl gave acylsilane-derived imine **7** in moderate yield (68%), as well as **5** in 20% yield. No double addition was observed even when excess silyllithium was used. Adding 1.5 equiv of allylmagnesium bromide directly to the reaction mixture and warming it to −45 °C over 2.5 h gave the α,α-

**Scheme 2.** Preliminary Results for the Reaction of Sulfonylimidate **1a**, $PhMe_2SiLi$, and AllylMgBr




disubstituted α-silylamine **6a** in 89% yield. Notably, no silyl group migration (aza-Brook rearrangement)[16] occurred in this one-pot, streamlined synthesis of α-tertiary α-silylamines. Addition of 1.0 equiv of allylmagnesium bromide to the solution of **1a** prior to introduction of the silyllithium **2** resulted in the formation of a substantial amount of Ph-$(allyl)_2C$−NHTs, formed by double addition of a Grignard reagent to **1a**, in addition to the desired product **6a**. Moreover, $PhMe_2Si$−Bpin was inert toward sulfonylimidate when the reaction conditions described previously were

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(8) Brook, A. G.; Golino, C.; Matern, E. *Can. J. Chem.* **1978**, *56*, 2286.

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(10) Adams, R.; Reifschneider, W. *J. Am. Chem. Soc.* **1956**, *78*, 3825.

(11) Selected examples of sequential introduction of two different or identical nucleophiles to ketones, thioamides, amides, or lactim ethers are described below. Some of the reactions must be facilitated by preactivating transformations, oxophilic metal derivatives, or Lewis acids. For ketones, see: (a) Reetz, M. T.; Westermann, J. *J. Org. Chem.* **1983**, *48*, 254. For thioamides, see: (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (c) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780. (d) Agosti, A.; Britto, S.; Renaud, P. *Org. Lett.* **2008**, *10*, 1417. (e) Murai, T.; Ui, K.; Narengerile *J. Org. Chem.* **2009**, *74*, 5703. For amides, see: (f) Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501. (g) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037. (h) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369. (I) Seebach, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 96 and references therein. (j) Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem., Int. Ed.* **2011**, *49*, 3037.

(12) For coupling of two identical nucleophiles to lactim ethers (cyclic imidates), see: (a) Cervinka, O. *Collect. Czech. Chem. Commun.* **1959**, *24*, 1146. (b) Lukes, R.; Cerny, M. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2886. (c) Sernmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507. (d) Zezza, C. A.; Smith, M. B.; Ross, B. A.; Arhin, A.; Cronin, P. L. E. *J. Org. Chem.* **1984**, *49*, 4397.

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(15) Similarly, methyl *N*-Tf-phenylimidate underwent the addition reaction and gave phenyl acylsilane **5** in 84% yield. This method for synthesizing aryl acylsilanes can be considered complementary to Scheidt's protocol. Scheidt's protocol is efficient for preparing alkyl acylsilanes using silyllithium species; however, it offers limited possibilities for aryl acylsilanes due to the undesired Brook rearrangement and subsequent transformations. See: Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977.

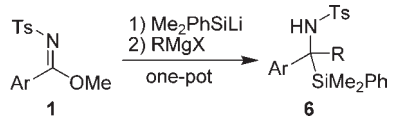
(16) (a) Brook, A. G.; Duff, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 4692. (b) Duff, J. M.; Brook, A. G. *Can. J. Chem.* **1977**, *55*, 2589.

used,[5] and no C−Si bond formation occurred. Control experiments indicated that both *N*,*O*-aminal **4** and acylsilane-derived imine **7** are extremely reactive to Grignard reagents. For example, compounds **4** and **7** reacted with 3 equiv of MeMgBr to give the α-tertiary α-silylamine PhMe(PhMe$_2$Si)C−NHTs in yields of 90% and 95%, respectively.

The scope and limitations of this three-component coupling protocol were investigated in the reactions of a series of aryl tosylimidates and Grignard reagents with PhMe$_2$SiLi (Table 1). When allylmagnesium bromide was used, aryl *N*-Ts-imidates bearing electron-withdrawing (**1b** and **1c**) or electron-donating substituents (**1d** and **1e**) on the phenyl groups were viable participants in the coupling reaction, providing α,α-disubstituted α-silylamine **4b**−**e** in yields of 88−93% (entries 2−5), while moderate to low yields were obtained in the cases of 1-naphthyl sulfonylimidate **1f** and heteroaromatic sulfonylimidates **1g** and **1h** (entries 6−8). A 1-g scale preparation of **6a** gave an even higher yield than the microscale reaction (entry 1, 95% vs 89%). In addition to allylMgBr, alkyl and aryl Grignard reagents proved effective in the three-component couplings, allowing efficient access to diverse products (entries 10−16). Freshly prepared vinylmagnesium bromide was also a suitable coupling partner and showed good reactivity, giving the desired product **6i** in 60% yield (entry 9). Vinyl silylamines are precursors for silicon-containing α-amino acids[17] that have important functions in peptidomimetic strategies.[18] It should be noted that the quality of Grignard reagents is crucial to successful coupling. When the reaction was set up using 3.0 equiv of commercially available vinylmagnesium bromide[19] from a freshly opened bottle and incubated at −78 °C for 3 h, no desired product was obtained. Instead, the reaction exclusively gave the *N*-sulfonyl-*C*-silyl-phenylimine **7** due to the decomposition of a tetrahedral intermediate (Scheme 2).[20] The failure of the commercial vinylmagnesium bromide may be at least partially due to the reagent's degradation.

Not unexpectedly, using bulky Grignard reagents possessing a *β*-hydrogen atom in the reactions reduced the yields of α,α-disubstituted α-silylamines; these Grignard reagents can also act as reducing agents in combination with sterically hindered electrophiles.[21] Thus, using isopropylmagnesium chloride or cyclohexylmagnesium bromide (entries 16 and 17) gave the side product, α-branched α-silylamines (RSMA) **6r** (Ar = Ph and R = H), due to hydride transfer from the Grignard reagents along with moderate to low yields of the desired products **6p** and **6q**.

**Table 1.** Synthesis of α-Tertiary α-Silylamines (ArRSMA) via Three-Component Coupling[a]




1 6

| entry | imidates (Ar) | Grignard reagents | products | yield (%)[b] |
|---|---|---|---|---|
| 1 | Ph (**1a**) | allylMgBr | **6a** | 89 (95[c]) |
| 2 | 4-MeC$_6$H$_4$ (**1b**) | allylMgBr | **6b** | 91 |
| 3 | 4-MeOC$_6$H$_4$ (**1c**) | allylMgBr | **6c** | 88 |
| 4 | 4-FC$_6$H$_4$ (**1d**) | allylMgBr | **6d** | 93 |
| 5 | 4-ClC$_6$H$_4$ (**1e**) | allylMgBr | **6e** | 90 |
| 6 | 1-naphthyl (**1f**) | allylMgBr | **6f** | 60 |
| 7 | 2-furyl (**1g**) | allylMgBr | **6g** | 54 |
| 8 | 2-thienyl (**1h**) | allylMgBr | **6h** | 35 |
| 9[d] | Ph (**1a**) | vinylMgBr | **6i** | 60 |
| 11 | Ph (**1a**) | MeMgBr | **6j** | 86 |
| 12 | Ph (**1a**) | EtMgBr | **6k** | 88 |
| 13 | Ph (**1a**) | BnMgBr | **6l** | 71 |
| 14 | Ph (**1a**) | Ph-MgBr | **6m** | 66 |
| 15[e] | Ph (**1a**) | 4-FC$_6$H$_4$-MgBr | **6n** | 54 |
| 16[e] | Ph (**1a**) | 4-MeOC$_6$H$_4$-MgBr | **6o** | 58 |
| 17 | Ph (**1a**) | *iso*-propylMgCl | **6p** + **6r** | 54 + 38 |
| 18[f] | Ph (**1a**) | cyclohexylMgBr | **6q** + **6r** | 26 + 57 |
| 19[e] | Ph (**1a**) | $^t$BuMgCl | **6r** | 84 |
| 20[g] | Ph (**1a**) | allylMgBr | **8** | 88 |

[a] All reactions were carried out in THF with 1.2 equiv of phenyldimethylsilyllithium and 1.5 equiv of Grignard reagents unless otherwise noted; see the Supporting Information for details. [b] Isolated yield after silica gel chromatography. [c] 1-g scale reaction. [d] 3.0 equiv of freshly prepared vinylmagnesium bromide were used. [e] 10.0 equiv of Grignard reagent were used. [f] The desired product **6q** was obtained in 55% yield when 10 mol % zinc(II) chloride was used. [g] Ph$_2$MeSiLi was used instead of PhMe$_2$SiLi.

When used in conjunction with 10 mol % zinc chloride,[21a,22] cyclohexylmagnesium bromide tended to transfer the cyclohexyl group rather than the *β*-hydride, increasing the yield of three-component coupling product **6q** to 55%. When the bulkier *tert*-butylmagnesium chloride was used, the reductive pathway predominated, giving the α-secondary α-silylamine **6r** as the sole product in 84% yield.

We further examined this protocol using other silyllithium reagents and sulfonylimidates. Diphenylmethylsilyllithium (Ph$_2$MeSiLi)[23] underwent a similar reaction as PhMe$_2$SiLi to afford coupling product **8** in 88% yield. We also observed the very efficient three-component coupling of **1a**, PhLi, and allylMgBr, affording α,α-disubstituted amine Ph$_2$(allyl)C−NHTs (**9**) in nearly quantitative yield (97%). However, trimethylsilyllithium (Me$_3$SiLi) was not compatible with this coupling protocol.[24] Similarly, enolizable alkyl sulfonylimidates possessing an α-proton were

(17) For oxidative cleavage of amino alkenes to amino acids, see: (a) Yoshida, K.; Yamaguchi, K.; Sone, T.; Unno, Y.; Asai, A.; Yokosawa, H.; Matsuda, A.; Arisawa, M.; Shuto, S. *Org. Lett.* **2008**, *10*, 3571. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron* **2009**, *50*, 4188.

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not suitable candidates for this transformation, presumably due to the potential Neber-type rearrangement initiated by the deprotonation of alkyl sulfonylimidates by silyllithium.[25]

In summary, an efficient method for the synthesis of α-tertiary α-silylamines has been developed. The three-component coupling of aryl tosylimidates, silyllithium, and Grignard reagents in a single flask enables the rapid construction of diverse bulky α-silylamine derivatives.

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**Supporting Information Available.** Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.