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α-Alkyl-α-aminosilanes. 1. Metalation and Alkylation Between Silicon and Nitrogen.

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Abstract: *tert*-Butyl carbamate derivatives of readily available aminomethyltrialkylsilanes have been studied for their ability to undergo metalation between nitrogen and silicon, followed by reaction with an electrophile. Metalation is rapid and reaction with a variety of electrophiles proceeds efficiently. When a benzyl group is attached to nitrogen, benzylic deprotonation competes with deprotonation next to silicon. Copyright © 1996 Elsevier Science Ltd

Alpha-amino silanes have found many uses in organic synthesis, functioning as precursors of α-amino carbanions to initiate Sommelet-Hauser[1] and Stevens rearrangements,[2] in Peterson olefinations[3] leading to enamines,[4] and in photoelectron transfer chemistry.[5] They also function in the Vedejs approach to azomethine ylides for [3+2] cycloadditions.[6] A number of α-aminosilanes have been prepared and tested for biological activity.[7]

Despite these many investigations, almost all of these examples involve amino*methyl*silanes, due to the commercial availability of chloromethylsilanes and the dirth of other α-chloroalkylsilanes (with the exception of 1-chloroethyltrimethylsilane).[8] Four syntheses of aminomethyltrimethylsilane from (chloromethyl)-trimethylsilane have been detailed,[9] and other aminomethylsilanes can be prepared from the commercially available (chloromethyl)dimethylchlorosilane, (chloromethyl)methyldichlorosilane, and (chloromethyl)-trichlorosilane.[10]

The ready availability of aminomethylsilanes suggests their use as a convenient starting point for the synthesis of α-substituted analogs. While this could, in principle, be accomplished through cationic or radical intermediates,[11] the attributes of nitrogen and silicon are ideally suited for carbanion pathways. Such an approach (Figure 1) would rely on the well-known stablization of α-anions by silicon,[12] and the ability of

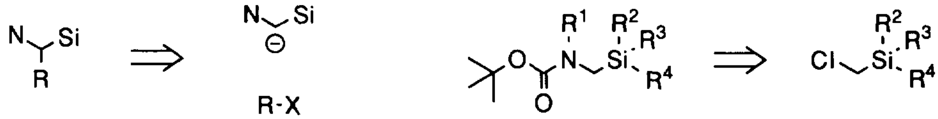
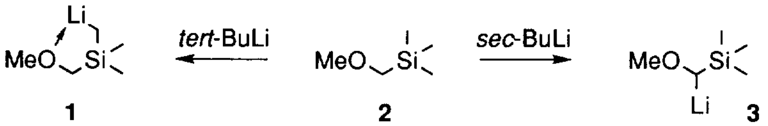


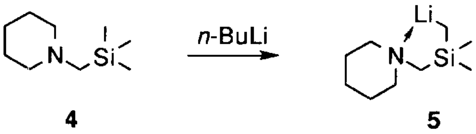
Figure 1. Retrosynthetic approach to α-alkyl-α-aminosilanes from readily available aminomethylsilanes.

nitrogen derivatives to direct proximal metalation.[13] We describe here our initial investigations of this approach to α-substituted-α-aminosilanes employing *tert*-butoxycarbonyl (Boc) derivatives of aminomethyltrimethylsilane and related metalation substrates.

Metalation between silicon and oxygen is well known, a prominent example being methoxymethyltrimethylsilane (**2**). The metalation chemistry of **2** is illustrative of the influence of both inductive electronic effects and proximity directing effects (equation 1). Metalation by *tert*-butyllithium yields the kinetic product **1**, with the ether acting as a metalation directing group.[14] In contrast, the use of *sec*-butyllithium leads to the thermodynamic lithium reagent **3**.[15] Use of *n*-butyllithium reveals yet a third pathway, nucleophilic attack at silicon.[14] In the case of tertiary amine **4**, where the heteroatom alpha to silicon is less electronegative and more Lewis acidic than oxygen, metalation occurs at one of the methyl groups (equation 2).[16-18]

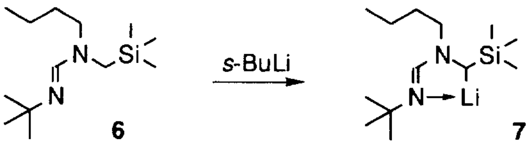


(1)

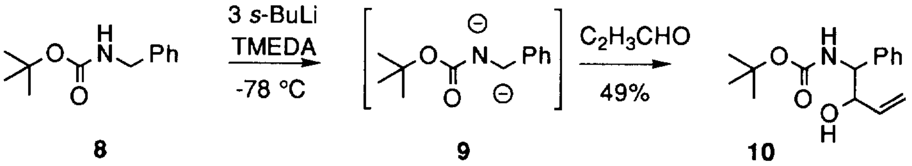


(2)

The use of a nitrogen derivative to direct metalation between nitrogen and silicon was demonstrated by Meyers with formamidine **6**, a useful aldehyde homologating reagent.[4] Additional inspiration for the work described here was found in the work of Greene et al. in which the dianion **9** was generated from benzylamine derivative **8**.[19] The ability of silicon to stabilize an α-anion has been compared to that of phenyl,[20] and so we prepared the trimethylsilyl analog of **8**, compound **13**.



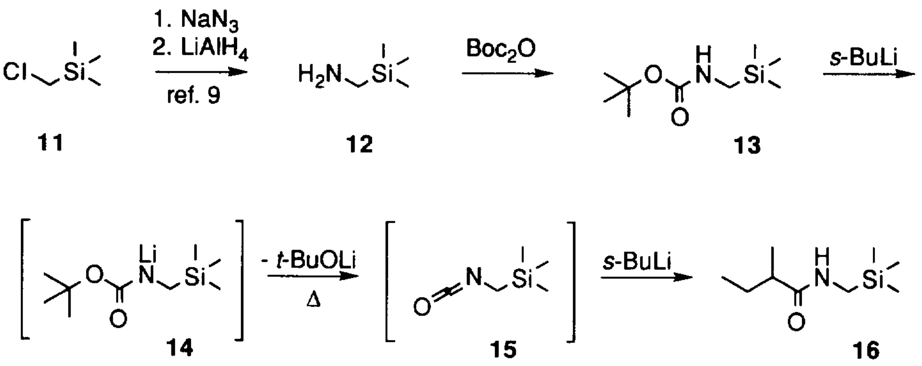
(3)



(4)

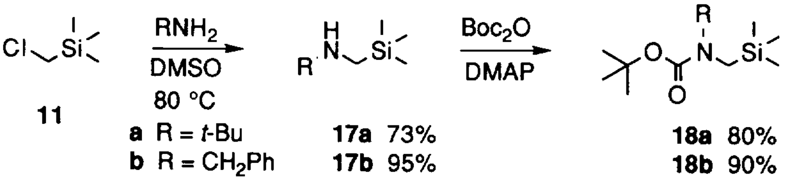
RESULTS AND DISCUSSION

Silane **13** was prepared from the amine **12**[9] on treatment with di-*tert*-butyldicarbonate. This could be accomplished, starting with chloromethylsilane **11**, without purification of intermediates. Attempts to generate a dianion of **13** with excess *sec*-butyllithium or *tert*-butyllithium at temperatures below 0 °C, and trap with an aldehyde, resulted solely in recovery of starting **13**. An attempt to force a metalation by raising the temperature to 35 °C gave amide **16**, presumably formed by loss of *tert*-butoxide from anion **14** and subsequent trapping of the resulting isocyanate with *sec*-butyllithium.



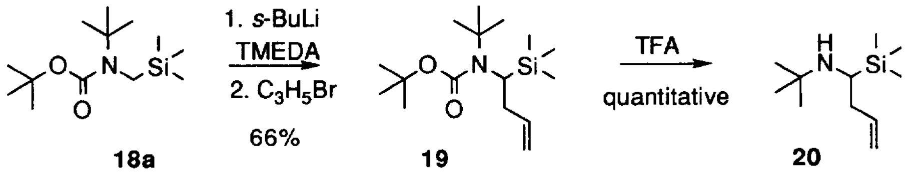
Scheme 1. Attempted metalation of **13**.

Dianions **9** and related compounds[21] benefit from delocalization of both negative charges. In the case of **14**, deprotonation between nitrogen and silicon would generate a localized, albeit silicon stabilized, anion next to the urethane anion. The proximity of these two charges may account for the difficulty encountered in its generation. We therefore prepared the two *N*-alkyl derivatives **18a** and **18b** by reaction of chloromethyltrimethylsilane **11** with *tert*-butylamine[22] and benzylamine, respectively, followed by treatment with di-*tert*-butyldicarbonate.



Scheme 2. Synthesis of *tert*-butyl *N*-alkyl-*N*-trimethylsilylmethylcarbamate **18**.

Metalation of **18a** proved to be straightforward and, on addition of allyl bromide, product **19** was isolated in good yield. Treatment of **19** with trifluoroacetic acid smoothly removed the Boc group to give **20** quantitatively. Removal of the *tert*-butyl group in **20** however, proved to be difficult. Heating **20** to reflux in trifluoroacetic acid, formic acid, acetic acid, or propionic acid returned only unchanged **20**, while heating to

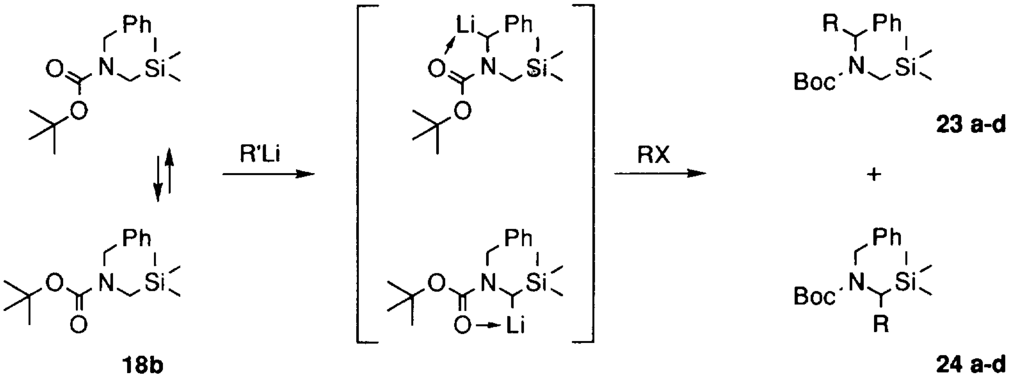


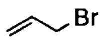
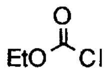
Scheme 3. Metalation and alkylation of *N*,*O*-di-*tert*-butyl-*N*-trimethylsilylmethyl carbamate.

reflux in concentrated hydrochloric or hydrobromic acid resulted in decomposition.[23,24] Metalation between silicon and nitrogen with a Boc-protected amine had been effectively demonstrated with this substrate, nevertheless a more readily removable nitrogen substituent was desired and the use of **18a** was abandoned.

N-Benzyl derivative **18b** also proved amenable to metalation, however metalation of the α-phenyl position occurred competitively with deprotonation alpha to silicon.[25] The metalation at both positions may

Table 1. Metalation of **18b** and reaction with electrophiles.



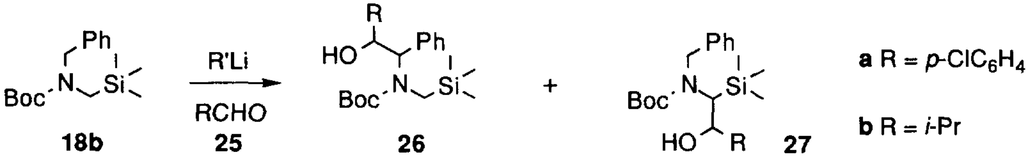
Entry	R–X	Conditions*	Isolated Yield (%)	23 : 24
a	D–OCH_3	**A**	97	0.9 : 1
b		**B**	59	0.7 : 1
c	 EtO–C(=O)–Cl	**B**	76	1 : 1
d	Me_3Si–Cl	**A**	50	1 : 0

* A: *sec*-butyllithium (3 eq) and TMEDA (3 eq) in diethyl ether at -78 °C, 5 min.
Entry **a**: 30 eq of methanol-*d*. Entry **d**: warm to 0 °C, add 5 eq of silane.
B: *tert*-butyllithium (1.3 eq) and TMEDA (1. 3 eq) in ether at -78 °C.
Entry **b**: after 15 min add allyl bromide and then warm to 10 °C.
Entry **c**: after 1 h add chloroformate.

reflect an equilibrium between the two amide conformations of **18b** (Table 1). Treatment with either *sec*-butyllithium or *tert*-butyllithium at -78 °C generated a bright yellow anion that decolorized on addition of an electrophile. Deuteration was found to be high (Table 1, entry **a**, 100% deuterium incorporation by mass spectroscopy), and by ^2H NMR the deuterium was found to be distributed at the two positions, slightly favoring the position alpha to silicon (**24a**). Allyl bromide and ethyl chloroformate produced similar results. With trimethylchlorosilane however, only reaction of the benzyl anion was observed.

Mixtures of α-phenyl and α-silyl products were also found when an aldehyde was used as the electrophile. Both an aromatic (**25a**) and an aliphatic aldehyde (**25b**) reacted at -78 °C to give **26** and **27**, with both products expected to form as a mixture of diastereomers. Generally, a 1:1 mixture of diastereomers **26** was found, whereas the α-silyl alkylation product **27** was produced, in some cases, as largely one diastereomer.

Table 2. Metalation of **18b** and reaction with aldehydes.



Entry	RCHO	Metalation Conditions*	Isolated Yield (%)	26 (ratio)‡	:	27 (ratio)‡
1	25a	A	90	1 (1.7 : 1)	:	1.4 (7.6 : 1)
2	25a	B	90	1 (1 : 1)	:	1.1 (1 : 1)
3	25a	C	nd	1 (1.3 : 1)	:	0
4	25b	D	83	1 (1 : 1)	:	1.4 (2.7 : 1)

* A: *sec*-butyllithium (1.3 eq) and TMEDA (1.3 eq) in diethyl ether at -78 °C.
B: *sec*-butyllithium (1.3 eq) in THF at -78 °C 1 h.
C: *sec*-butyllithium (0.8 eq) and TMEDA (0.8 eq) in diethyl ether at -78 °C 1 h, rt 1h, -78 °C.
D: *sec*-butyllithium (3 eq) and TMEDA (3 eq) in diethyl ether at -78 °C, 20 °C 1 h, -78 °C.
‡ identity of the major diastereomer not determined.

The somewhat variable ratio of products derived from anions **21** and **22**, and in particular the results with chlorotrimethylsilane (Table 1), could result simply from differences in the reactivity of the electrophile with each anion or the two anions **21** and **22** could equilibrate competitively with reaction of the electrophile (Figure 2). Deuteration experiments with less than a full equivalent of *sec*-butyllithium confirm that **21** and **22** will equilibrate to give the thermodynamically favored α-phenyl anion **21**. These experiments are described in the accompanying paper. Similarly, under equilibrating conditions (Table 2, entry 3) only alkylation next to the phenyl group was found.

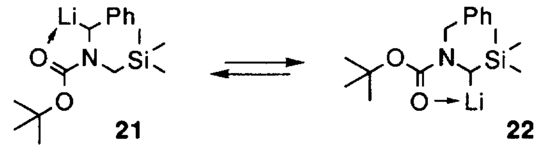
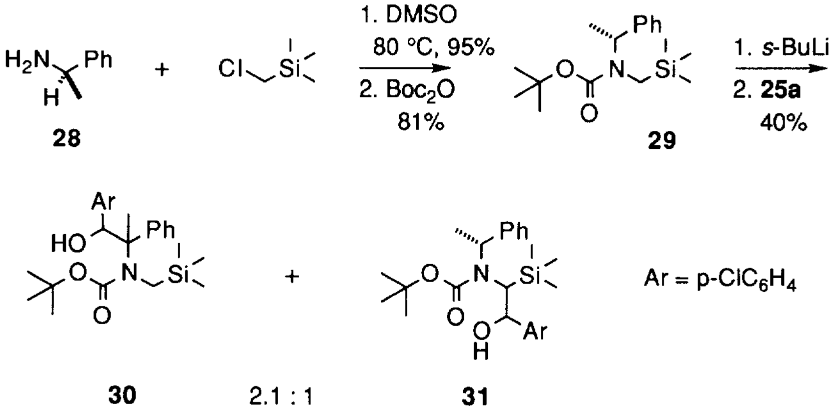


Figure 2. The products of the metalation of **18b** can equilibrate.

The success with **18a** and **18b** in the metalation–alkylation sequence led to a third-generation metalation substrate **29**. The kinetic nature of the metalation process suggests that simply increasing the steric bulk at the benzylic position would direct the metalation to the desired alpha-silyl position. A number of studies competing primary vs. secondary sites[26] and secondary vs. tertiary sites[27] alpha to nitrogen have found a strong preference for metalation at the less hindered position. To test this idea, (*R*)-α-methylbenzylamine **28** was used to prepare substrate **29**. We anticipated that the chiral center might influence the metalation–alkylation step and lead not only to increased site selectivity (e.g., an increase in alpha-silyl metalation) but also to a degree of diastereoselectivity. Despite adequate precedence, both of these expectations proved flawed.

Metalation of **29**, followed by addition of *p*-chlorobenzaldehyde, gave a 40% yield of adducts **30** and **31**. Surprisingly, the presence of the methyl group alpha to the phenyl group served to *increase* the amount of benzyl metalation at the expense of alpha-silyl metalation. The reasons for this unexpected selectivity, perhaps a result of a conformational bias for **29**, remain unclear.



Scheme 4. Despite the additional steric hinderance, metalation of **29** yields largely the benzylic anion.

Metalation between nitrogen and silicon in aminomethyltrimethylsilanes, utilizing a *tert*-butoxycarbonyl directing group, requires the nitrogen to be fully substituted. When the second substituent on nitrogen is a benzyl group, competition of metalation next to silicon and metalation next to phenyl results in a mixture of products. Nevertheless, this approach to α-substituted aminomethylsilanes is an effective procedure for introducing electrophiles into readily available aminomethylsilanes. Further investigations directed toward the efficient elaboration of primary amines of this type will be reported in due course.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on a GE QE-300, a Brüker AC-250, or a Brüker AM-300 spectrometer. NMR data are reported in ppm as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and b describes a broad peak), coupling constant, and interpretation. In some cases, the NMR spectra of the urethanes exhibited a doubling of absorbances due to rotational isomers, and these are noted in listing of spectral data. High-resolution mass spectra were obtained on a VG 7070 or an HP 5989A GC/MS using ammonia or methane as the carrier gas. FAB mass spectra were obtained on a VG ZAB spectrometer.

Elemental analyses were performed by Atlantic Microlabs (Norcross, GA) or Galbraith Laboratories, Inc. (Knoxville, TN). Mass spectra were performed by the Mass Spectrometry Facility at the University of California at Riverside.

***N*-Boc-(aminomethyl)trimethylsilane (13).** To a solution of chloromethyltrimethylsilane **11** (12.3 g, 0.10 mol) in DMF (80 mL) was added NaN_3 (7.80 g, 0.12 mol) and the solution was then stirred at 80 °C for 48 h.[28] The resulting golden-yellow solution was diluted with water (50 mL) and extracted with ether (3 x 50 mL). The combined extracts were washed with water (2 x 50 mL), 10% LiCl solution (2 x 50 mL), and saturated NaCl (1 x 50 mL), dried over Na_2SO_4, and carefully concentrated *in vacuo* gave 7.96 g (ca. 62%) of crude (azidomethyl)trimethylsilane. The product was taken up in ether (50 mL) and added dropwise to a 0 °C stirred suspension of $LiAlH_4$ (4.17 g, 0.11 mol) in 200 mL of ether, keeping the temperature between 5-8 °C.[9c] Cautious addition of 1% NH_4OH (10 mL), filtration of the salts and distillation of the ether gave a colorless oil. IR analysis indicated an absence of azide. The amine (ca. 60 mmol) was taken up in methylene chloride (200 mL) and triethylamine (20 mL) and di-*tert*-butyldicarbonate (26.19 g, 0.12 mol) was added in portions. After 18 h the solution was washed with 10% HCl and then water. The combined aqueous phases were extracted with ether and the combined organics were dried over Na_2SO_4. Concentration gave an orange oil that was taken up in hexane. Cooling gave urethane **13** as a colorless solid: mp = 72-73.5 °C; ^1H NMR ($CDCl_3$) δ 4.26 (bs, 1H), 2.55 (d, J=6.0, 2H), 1.40 (d, 9H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.9, 78.9, 30.3, 28.4, -2.8.

***N*-Phenylmethyl-(aminomethyl)trimethylsilane (17b).** Chloromethyltrimethylsilane (5.0 g, 41 mmol) and benzylamine (9.23 g, 86 mmol) were dissolved in 80 mL of DMSO and heated to reflux overnight. After cooling, the reaction was poured into 400 mL of water, extracted with ether (3 x 80 mL) and the combined ether extracts were washed with 1% Na_2CO_3 solution, dried over $MgSO_4$, and concentrated to give a yellow oil. The crude material was passed through a plug of silica gel with 15:85 ethyl acetate/hexanes and concentrated to give 7.5 g of **17b** (95%). ^1H NMR ($CDCl_3$) δ 0.01 (s, 9H), 2.0 (s, 2H), 3.7 (s, 2H), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 140.6, 128.2, 128.1, 126.7, 58.1, 39.5, -2.6; IR (neat) 3321, 3084-3026, 2953-2780, 1945, 1871, 1805, 1248, 861 cm^{-1}; MS 194 (100, MH^+), 178 (70), 102 (38), 91 (20); HRMS calcd. for $C_{11}H_{20}NSi$ 194.1377, found 194.1365. Anal. Calcd. for $C_{11}H_{19}NSi$: C, 68.33; H, 9.90; N, 7.24. Found: C, 68.21; H, 9.93; N, 7.15.

***N,O*-di-*tert*-butyl-*N*-trimethylsilylmethyl urethane (18a).** To a solution of *N-tert*-butyl-(aminomethyl)trimethylsilane **17a**[22] (3.91 g, 24.6 mmol) and of triethylamine (5.14 mL, 36.8 mmol) in methylene chloride (40 mL) at rt was added 4-dimethylaminopyridine (0.09 g, 0.03 mmol), and di-*tert*-butyldicarbonate (6.77 g, 29.5 mmol). The reaction mixture was stirred for 48 hours. After evaporation of the solvent, the mixture was dissolved in a mixture of methanol (10 mL) and NH_4OH (2 mL) and stirred for 2 h. After dilution with water (100 mL) and extraction twice with ether, the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (1:9 ethyl acetate/hexane) gave the product as a clear oil that was distilled under reduced pressure (55 °C, 0.4 mm Hg) to afford 5.1 g of **17b** (80%). ^{1}H NMR ($CDCl_3$) δ 2.79 (s, 2H), 1.46 (s, 9H), 1.36 (s, 9H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 78.8, 55.1, 35.4, 29.6, 28.6, 27.8, -1.14; IR (neat) 2990, 1688 cm^{-1}; MS 260 (27, MH$^+$), 188 (16), 160 (100), 102 (17); HRMS calcd. for $C_{13}H_{30}NO_2Si$ 260.2054, found 260.2046; Anal. Calcd for $C_{13}H_{29}NO_2Si$; C, 60.18; H, 11.27; N, 5.40. Found C, 60.04; H, 11.27; N, 5.33.

***N*-Boc-*N*-benzyl-(aminomethyl)trimethylsilane (18b).** Using a procedure identical to that described for **18a**, **18b** was isolated as a colorless oil in 90% yield after bulb-to-bulb distillation (95 °C, 0.05 mm Hg). ^{1}H NMR ($CDCl_3$) δ 7.2-7.4 (m, 5H), 4.42 and 4.45 (2s, 2H), 2.69 and 2.73 (2s, 2H), 1.46 and 1.52 (2s, 9H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.9, 155.4, 138.3, 128.3, 127.6, 127.2, 127.0, 84.9, 52.7, 51.6, 37.8, 37.2, 28.4, 27.3, -1.6; IR (neat) 3086-3084, 2974, 1689, 1247, 1171, 852 cm^{-1}; MS 294 (35, MH$^+$), 238 (100), 222 (59), 194 (59), 91 (39); HRMS calcd. for $C_{16}H_{28}NO_2Si$ 294.1889, found 294.1890; Anal. Calcd. for $C_{16}H_{27}NO_2Si$: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.13; H, 9.19; N, 4.97.

(*N*-Boc-*N*-*tert*-butyl)-1-amino-1-trimethylsilyl-3-butene (19). To **18a** (0.224 g, 0.86 mmol) and TMEDA (0.40 mL, 2.6 mmol) in 10 mL of ether at -78 °C was added dropwise *sec*-butyllithium (2.54 mL of a 1.02 M soln in cyclohexane, 2.6 mmol). The resulting yellow solution was warmed to -20 °C for 1 hr, cooled to -78 °C, and allylbromide (0.25 mL, 2.8 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 1 h at which time most of the yellow color had disappeared. After addition of 50 mL of saturated NH_4Cl solution and extraction with ether (2 x 35 mL), the combined organic extracts were washed with 20 mL of saturated NaCl and dried over $MgSO_4$. Flash chromatography (5:95 ethyl acetate/hexane) afforded 0.170 g of **19** (66%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.78 (m, 1H), 5.02 (d, J=15.5 Hz, 1H), 4.99 (d, J=8.3 Hz, 1H), 2.83 (d, J=7.5 Hz, 1H), 2.81 (d, J=7.7 Hz, 1H), 2.44 (m, 2H), 1.47 (s, 9H), 1.35 (s, 9H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.5, 138.1, 116.1, 78.5, 35.4, 30.6, 28.8, -0.42; MS 300 (21, MH$^+$), 244 (21), 202 (13), 172 (18); HRMS calcd. for $C_{16}H_{34}NO_2Si$: 300.2354, found 300.2359; Anal. Calcd for $C_{16}H_{33}NO_2Si$: C, 64.16; H 11.10; N, 4.68. Found C, 64.17; H, 11.14; N, 4.74.

1-*tert*-Butylamino-1-trimethylsilyl-3-butene (20). Urethane **19** (60 mg, 0.20 mmol) was dissolved in trifluoroacetic acid (4 mL) and stirred for 1 hour. After concentration on a rotary evaporator, the residue was taken up in 10 mL of a 15% NaOH solution and extracted with ether (2x 20 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated to afford 40 mg (100%) of **20** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.00 (d, J=15.5 Hz, 1H), 4.96 (d, J=8.3 Hz, 1H), 2.32 (m, 2H), 2.17 (m, 1H), 1.05 (s, 9H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 137.4, 115.9, 41.1, 39.2, 38.5, 29.7, -2.3, -3.7; MS 200 (100, MH$^+$), 158 (18), 144 (18), 126 (21), 102 (16); HRMS calcd. for $C_{11}H_{26}NSi$: 200.1835, found 200.1833.

***N*-Boc-*N*-α-deuterobenzyl-(aminomethyl)trimethylsilane (23a)** and ***N*-Boc-*N*-benzyl-(α-deutero-aminomethyl)trimethylsilane (24a).** To a mixture of *sec*-butyllithium (1.67 mL of a 1.3M solution in hexane, 2.2 mmol) and TMEDA (0.33 mL, 2.2 mmol) in ether (1 mL) at -78 °C was added a solution of **18b** (212 mg, 0.72 mmol) in ether (1 mL) over a period of 5 min after which time the reaction mixture was quenched by rapid addition of methanol-d_1 (0.88 mL, 30 eq). The resulting solution was poured into sat NH_4Cl solution (25 mL), extracted with ether (5 x 10 mL), the combined extracts were washed with sat' NaCl solution, dried over $MgSO_4$, and concentrated to give 206 mg (97%) of **23a** and **24a** (100% D_1 by mass spectroscopy): ^{2}H NMR (5% $CDCl_3$ in $CHCl_3$) δ 4.38 (s), 2.68 (s). MS 295 (100, MH^+), 239 (50), 195 (57).

***N*-Boc-(*N*-trimethylsilylmethyl)-1-amino-1-phenyl-3-butene (23b)** and **(*N*-Boc-*N*-Benzyl)-1-amino-1-trimethylsilyl-3-butene (24b).** To a solution of **18b** (620 mg, 2.1 mmol) and TMEDA (1.3 eq., 2.7 mmol) in ether (6 mL) at -78 °C was added dropwise *tert*-butyllithium (1.95 mL of a 1.4M solution in hexane, 2.7 mmol). After 15 min, allyl bromide (0.9 mL, 10.5 mmol) was added dropwise and the reaction mixture was allowed to warm slowly to 10 °C over 8 h. The mixture was poured into sat NH_4Cl solution and extracted with ether (5 x 10mL). The combined extracts were washed with sat NaCl solution, dried over $MgSO_4$, and concentrated. Flash chromatography (3:97 ethyl acetate/hexane) gave 176 mg of **23b** (25%) and 240 mg of **24b** (34%) as colorless oils.

23b: ^{1}H NMR ($CDCl_3$) δ 7.24-7.16 (m, 5H), 5.72 (m, 1H), 5.21 and 5.46 (bs, 1H), 5.06 (d, J=17.5, 1H), 4.98 (d, J=10.0, 1H), 2.61 (m, 2H), 2.36 (bs, 1H), 2.13 (bs, 1H), 1.42 (s, 9H), -0.26 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.3, 140.4, 135.2, 128.3, 127.9, 127.4, 117.2, 79.3, 57.6 and 58.7, 34.9, 33.1, 28.6, -0.98; MS 334 (21, MH^+), 278 (32), 262 (100), 192 (8), 91 (1); HRMS calcd for $C_{19}H_{32}NO_2Si$ 334.2202, found 334.2191; Anal. Calcd. for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.46; H, 9.32; N, 4.14.

24b: ^{1}H NMR ($CDCl_3$) δ 7.21-7.26 (m, 5H), 5.68(m, 1H), 4.96 (d, J=17.5, 1H), 4.88(d, J=12.5, 1H), 4.58 (d, J=15.0, 1H), 3.98 and 4.13 (2d, J=15.0, 1H), 2.75 (m, 1H), 2.45 (m, 1H), 2.24 (m, 1H), 1.48 and 1.59 (2s, 9H), -0.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.4, 138.9 and 139.1, 137.1 and 137.4, 128.8, 128.2, 127.1, 116.2, 79.1, 53.4, 49.5 and 50.3, 34.0 and 34.6, 28.4 and 28.8, -1.3 and -1.5; MS 334 (11, MH^+), 278 (32), 262 (100), 234 (8), 192 (6), 91 (4); HRMS calcd for $C_{19}H_{32}NO_2Si$ 334.2202, found 334.2199; Anal. Calcd. for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.51; H, 9.32; N, 4.12.

Ethyl [2-*N*-Boc-trimethylsilylmethylamino]-2-phenylacetate (23c) and **ethyl [2-(*N*-Boc-*N*-benzylamino)-2-trimethylsilyl]acetate (24c).** To a solution of **18b** (116 mg, 0.40 mmol) in ether (1 mL) and TMEDA (0.08 mL, 0.5 mmol) at -78 °C was added dropwise *tert*-butyllithium (0.40 mL of a 1.30M solution in hexane, 0.52 mmol). After 1 h, ethyl chloroformate (0.2 mL, 2 mmol) was added rapidly. The mixture solidified and was removed from the cooling bath and warmed until stirring could be resumed. The mixture was then poured into sat NH_4Cl solution and extracted with ether (5 x 5 mL). The combined extracts were washed with sat NaCl and dried over $MgSO_4$, filtered and concentrated. Flash chromatography (6:94 ethyl acetate/hexane) afforded 111 mg (76%) of **23c** and **24c** as an inseparable mixture. The following data are selected from the ^{1}H and ^{13}C NMR spectra: ^{1}H NMR ($CDCl_3$) δ ~5.60-5.76 (2 bs, α-carbonyl proton for **23c**), 4.84 and 3.96 (2d, J=15.0, diastereotopic benzyl protons), ~4.0-4.4 (2m, ester ethylene protons), 3.36 (s, α-carbonyl proton for **24c**), 2.78 and ~2.40 (2bs, diastereotopic α-silyl protons), 1.46 and 1.48 (2s, Boc), 0.08 and -0.14 (1s, 1bs, trimethylsilyl); ^{13}C NMR ($CDCl_3$) δ 172.0 and 170.6 (ester carbonyls), 138.2 and 135.6

(quaternary phenyl), 80.2 and 79.8 (Boc carbonyl), 28.4 and 28.3 (Boc), 14.2 and 14.1 (ester methyls), -0.62 and -1.5 (Si-Me$_3$); HRMS calcd. for $C_{19}H_{32}NO_4Si$ 366.2100, found 366.2110. Anal. Calcd. for $C_{19}H_{31}NO_4Si$: C, 62.43; H, 8.55; N, 3.83. Found: C, 62.38; H, 8.51; N, 3.75.

***N*-Boc-*N,N*-bis((trimethylsilyl)methyl)benzylamine (23d).** A -78 °C solution of **18b** (105 mg, 0.36 mmol) in ether (1 mL) and TMEDA (0.16 mL, 1.07 mmol) was transferred via cannula to a -78 °C solution of *sec*-butyllithium (0.83 mL of a 1.3M solution in hexane, 1.07 mmol) in ether (3 mL). The resulting bright yellow solution was warmed to 0 °C and chlorotrimethylsilane (0.24 mL, 1.79 mmol) was added dropwise. After 80 min at at 0 °C the solution had lost most of its yellow color. The reaction mixture was poured into 20 mL of a sat NH_4Cl solution and extracted with ether (2 x 35 mL). The combined organic extracts were washed with 20 mL saturated NaCl, dried over $MgSO_4$, filtered and concentrated to yield a clear oil. Flash chromatography (9:1 hexane/ethyl acetate) afforded 42 mg (40%) of recovered **18b** and 63 mg (50%) of **23d** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.11 (m, 5H), 3.32 (s, 1H), 3.03 (d, *J*=15Hz, 2H), 2.31 (d, *J*=15Hz, 2H), 1.50 (s, 9H), -0.37 (s, 18H); ^{13}C NMR (CDC13) 128.1, 127.3, 28.5, -0.1, -1.6; IR (neat) 3583, 2920, 2850, 1713, 1364, 1222 cm^{-1}. MS 366 (38, MH$^+$), 310 (38), 294 (100), 278 (26); HRMS calcd. for $C_{19}H_{36}NO_2Si_2$ 366.2285, found 366.2296.

2-[*N*-Boc-trimethylsilylmethylamino]-2-phenyl-1-(*p*-chlorophenyl)ethanol (26a) and **2-(*N*-Boc-*N*-benzylamino)-2-trimethylsilyl-1-(*p*-chlorophenyl)ethanol (27a).** To a -78 °C solution of **18b** (121 mg, 0.41 mmol) in ether (1 mL) and TMEDA (0.08 mL, 0.53 mmol) was added dropwise *sec*-butyllithium (0.42 mL of a 1.26M soln in cyclohexane, 0.53 mmol). After 1 h a solution of *p*-chlorobenzaldehyde (87 mg, 0.63 mmol) in ether (2 mL) was added dropwise to the bright yellow reaction mixture. After an additional 1 h the mixture was poured into 25 mL of sat NH_4Cl solution. The aqueous phase was extracted with ether (5 x 5 mL), and the combined extracts were washed with 25 mL of saturated NaCl, dried over $MgSO_4$, and concentrated to give 205 mg crude product. Flash chromatography using a gradient of 5%-7%-9% ethyl acetate/hexanes gave 67 mg of **26a** (38%) as a 1.7:1 mixture of diastereomers by NMR and 92 mg of **27a** (52%) as a 7.6:1 mixture of diastereomers by NMR. Analytically pure samples of each diastereomer were prepared by preparative TLC and by recrystallization from hexanes.

26a, major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.18-7.39 (m, 9H), 5.37 (bs, 1H), 4.55 and 4.77 (2bs, 1H), 2.72 (d, *J*=15.6, 1H), 2.46 (d, *J*=15.6, 1H), 1.53 (s, 9H), -0.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 157.5, 140.5, 137.9, 133.2, 128.6, 128.5, 128.4, 128.3, 127.8, 80.6, 75.1, 71.4, 39.9, 28.5, -1.5; MS 434 (4, MH$^+$), 378 (7), 236 (34), 192 (71), 91 (32), 77 (22), 73 (100), 57 (99); HRMS calcd for $C_{23}H_{33}NO_3SiCl$ 434.1918, found 434.1928; Anal. Calcd. for $C_{23}H_{32}NO_3SiCl$: C, 63.64; H, 7.43; N, 3.23. Found: C, 63.70; H, 7.48; N, 3.21.

26a, minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.19-7.31 (m, 9H), 5.35 (bs, 1H), 4.03 and 4.77 (2bs, 1H), 2.64 (bs, 1H), 2.33 (d, *J*=15.0, 1H), 1.33 (s, 9H), -0.3 (bs, 9H); ^{13}C NMR ($CDCl_3$) δ 140.1, 137.2, 133.6, 129.3, 128.5, 128.4, 128.3, 128.1, 79.9, 72.7, ~68.0(broad), ~39.0(broad), 28.3, -1.4; IR (KBr) 3442, 3064-3027, 2976, 1678, 1443, 1387, 1244, 1157, 1010, 1097, 856 cm^{-1}; MS 434 (46, MH$^+$), 375 (57), 192 (100); HRMS calcd for $C_{23}H_{33}NO_3SiCl$ 434.1918, found 434.1913;

27a, major diastereomer: m.p. 110-111 °C; ^{1}H NMR ($CDCl_3$) δ 7.06-7.42 (m, 9H), 5.10 (d, *J*~4, 1H), 4.75 (bs, 1H), 4.28 (d, *J*=14.7, 1H), 4.16 (d, *J*=14.7, 1H), 2.60 (s, 1H), 1.60 (s, 9H), -0.12 (s, 9H); ^{13}C NMR

($CDCl_3$) δ 157.8, 141.9, 137.6, 132.6, 128.8, 128.6, 128.1, 127.8, 127.3, 80.7, 76.0, 59.9, 54.7, 28.5, 0.14; IR (KBr) 3462, 3008-3087, 2980-2905, 1668, 1244, 1166, 1119, 836 cm^{-1}; MS 434 (37, MH$^+$), 416 (7), 378 (12), 360 (100), 244 (42), 192 (79); HRMS calcd. for $C_{23}H_{33}NO_3SiCl$ 434.1918, found 434.1911; Anal. Calcd. for $C_{23}H_{32}NO_3SiCl$: C, 63.64; H, 7.43; N, 3.23. Found: C, 63.71; H, 7.42; N, 3.30.

27a, minor diastereomer: m.p. 118 °C; ^{1}H NMR ($CDCl_3$) δ 6.93-7.32 (m, 9H), 4.98 (s, 1H), 4.28 (d, *J*=15.0, 1H), 3.10 (d, *J*=15.0, 1H), 2.73 (s, 1H), 1.51 (s, 9H), -0.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 158.7, 143.0, 137.3, 132.5, 128.7, 128.4, 128.3, 127.6, 127.3, 81.0, 74.8, 59.5, 54.8, 28.4, -0.6; IR (KBr) 3460, 3063, 3026, 2977, 1666, 1476, 1436, 1246, 1164, 845 cm^{-1}; MS 434 (23, MH$^+$), 416 (7), 378 (4), 360 (100), 244 (28), 192 (62); HRMS calcd. for $C_{23}H_{33}NO_3SiCl$ 434.1918, found 434.1909; Anal. Calcd. for $C_{23}H_{32}NO_3SiCl$: C, 63.64; H, 7.43; N, 3.23. Found: C, 63.79; H, 7.48; N, 3.32.

1-(*N*-Boc-*N*-benzylamino)-1-trimethylsilyl-3-methylbutanol (26b) and **1-(*N*-Boc-trimethylsilylmethylamino)-1-phenyl-3-methylbutanol (27b)**. To a solution of **18b** (0.500 g, 1.70 mmol) and TMEDA (0.77 mL, 5.1 mmol) in ether (10 mL) at -78 °C was added dropwise *sec*-butyllithium (5.0 mL of a 1.02M soln in cyclohexane, 5.1 mmol). The resulting yellow solution was stirred at -78 °C for 1 h, and *i*-butyraldehyde (0.51 mL, 5.6 mmol) was added dropwise. The reaction was left to stir at -78 °C for 1 h at which time most of the yellow color had disappeared. The reaction mixture was poured into 50 mL of sat NH_4Cl, and extracted with ether (2 x 35 mL). The combined organic extracts were washed with 20 mL of saturated NaCl and dried over $MgSO_4$. Flash chromatography (9:1 hexane/ethyl acetate) gave 218 mg of **26b** (35%) as a 1:1 mixture of diastereomers and 299 mg of **27b** (48%) as a 2.7:1 mixture of diastereomers.

26b: As a mixture of isomers: ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.01 (bs, 1H), 4.10 (m, 1H), 2.75 (m, 2H), 2.42 (m, 1H), 1.83 (m, 1H), 1.49 (s, 9H), 1.05 & 1.0 & 0.95 & 0.81 (4 d, *J*=7.2 Hz, 6H), -0.17 & -0.21 (2 s, 9H).

27b: Mixture **27b** was chromatographed (95:5 hexane/ethyl acetate) to give an analytically pure sample of the major diastereomer as a colorless solid: mp 70 °C ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 4.35 (q, 2H), 3.48 (dd, 1H), 2.73 (bs, 1H), 1.62 (m, 1H), 1.50 (s, 9H), 0.93 (d, 3H), 0.63 (d, 3H), 0.03 (s, 9H). MS 366 (35, MH$^+$), 310 (41), 292 (36), 266 (11), 248 (18), 192 (14), 175 (65), 160 (60), 91 (100); HRMS calcd. for $C_{20}H_{36}NO_3Si$ 366.2465, found 366.2452. Anal. Calcd for $C_{20}H_{35}NO_3Si$, C, 65.71; H, 9.65; N, 3.83; Found, C 65.71; H, 9.68; N, 3.79.

***N*-Boc-*N*-[(trimethylsilyl)methyl]-α-(*S*)-methyl benzylamine (29)**. A solution of (*R*)-α-methylbenzylamine (10.8 mL, 84 mmol) and chloromethyltrimethylsilane (4.53 g, 37 mmol) in DMSO (20 mL) was heated to 90 °C for 18 h. After cooling and dilution with 50 mL of water, the mixture was extracted twice with ether, dried over $MgSO_4$ and purified by kugelrohr distillation (54 °C, 3.8 mm Hg) to give 7.32 g (95%) of ((*R*)-α-methylbenzylaminomethyl)trimethylsilane as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.1-7.3 (m, 5H), 3.6 (q, *J*=7.5 Hz, 1H), 1.9 (d, *J*=12.5 Hz, 1H), 1.8 (d, *J*=12.5 Hz, 1H), 1.2 (d, *J*=7.5 Hz, 3H), 1.02 (bs, 1H), -0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 128.2, 126.7, 126.6, 62.1, 37.9, 24.4, -2.7; IR (neat) 3082, 3062, 3024, 1248, 839 cm^{-1}; Anal. Calcd for $C_{12}H_{21}NSi$, C, 69.50; H, 10.21; N, 6.75; Found, C, 69.62; H, 10.16; N, 6.67.

This amine (1.0 g, 4.2 mmol) was taken up methylene chloride (10 mL) and triethylamine (0.87 mL, 6.2 mmol). Di-*t*-butyl dicarbonate (1.1 g, 5.0 mmol) was added in portions and the resulting solution stirred at rt for 25 h. The resulting mixture was diluted with methanol (4 mL) and NH_4OH (0.7 mL) was added. After stirring for 18 h, water was added and the aqueous phase extracted twice with ether. After drying over $MgSO_4$ and concentration, the product was purified by Flash Chromatography (1:9 ethyl acetate/hexane) to give 1.04 g (81%) of **29** as a colorless solid: mp 30-31 °C; ^{1}H NMR (C_6D_6) δ 7.1-7.3 (m, 5H), 5.41 (bs, 1H), 2.32 (s, 2H), 1.46 (s, 9H), 1.27 (d, *J*=10Hz, 3H), 0.06 (bs, 9H) ; ^{13}C NMR (C_6D_6,) 127.6, 127.3, 28.6, 17.0, -0.66; IR (neat) 3030, 2975, 1685, 1245, 1154, 851, 698 cm^{-1}; MS 308 (100, MH$^+$), 252 (79), 236 (47), 208 (65), 105 (37), 73 (24); HRMS calcd. for $C_{17}H_{30}NO_2Si$ 308.2040 found 308.2046; Anal. Calcd for $C_{17}H_{29}NO_2Si$: C, 66.40; H, 9.50; N, 4.55; Found C, 66.15; H, 9.27; N, 4.43.

2-[*N*-Boc-trimethylsilylmethylamino]-2-phenyl-1-(*p*-chlorophenyl)propanol (30) and **2-(*N*-Boc-*N*-α-methylbenzylamino)-2-trimethylsilyl-1-(*p*-chlorophenyl)ethanol (31).** To a -78 °C solution of **29** (118 mg, 0.38 mmol) in ether (1 mL) and TMEDA (0.07 mL, 0.49 mmol) was added dropwise *sec*-butyllithium (0.40 mL of a 1.24M soln in cyclohexane, 0.49 mmol). After 1 h a solution of *p*-chlorobenzaldehyde (80 mg, 0.57 mmol) in ether (1.5 mL) was added dropwise. After an additional 1 h the mixture was poured into 25 mL of sat NH_4Cl solution. The aqueous phase was extracted with ether and the combined organic extracts were washed with sat NaCl, dried over $MgSO_4$, and concentrated to give 161 mg of crude product. Flash chromatography (3:97 ethyl acetate/hexane) gave **30** (46 mg, 27%) and **31** (22 mg, 13%), both as single diastereomers.

30: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 7.07 (d, *J*=9 Hz, 2H), 6.82 (d, *J*=9Hz, 2H), 6.12 (bs, 1H), 5.61 (m, 1H), 2.20 (dd, *J*=18 Hz, 3H), 1.45 (s, 9H), 0.004 (s, 9H).

31: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 7.07 (d, *J*=9 Hz, 2H), 6.75 (d, *J*=9 Hz, 2H), 5.69 (bs, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 2.57 (d, *J*=~7 Hz, 3H), 2.35 (m, 1H), 1.43 (s, 9H), -0.08 (s, 9H).

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