ORGANIC LETTERS

2005
Vol. 7, No. 7
1403−1406

Stereoselective Synthesis of α-Silylamines by the Direct Addition of Silyl Anions to Activated Imines

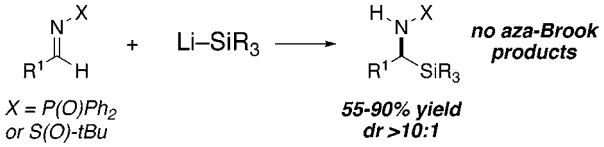
David M. Ballweg, Rebecca C. Miller, Danielle L. Gray, and Karl A. Scheidt*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208

scheidt@northwestern.edu

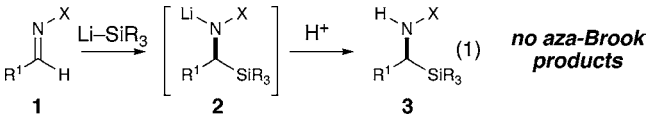
Received February 4, 2005

ABSTRACT



A highly efficient stereoselective synthesis of unusual α-silylamines via a direct silyl anion addition reaction is reported. This approach is convergent and avoids any problematic aza-Brook shifts of the anionic intermediates. The use of enantiopure *tert*-butanesulfinyl imines as the electrophiles affords exceedingly high levels of diastereocontrol for the newly formed stereogenic carbon.

The stereoselective incorporation of silicon into molecules is an important goal in organic synthesis due to the utility of the resulting organosilanes. An unusual class of these molecules is α-silylamines, and the efficient access to these compounds is becoming increasingly significant due to their unique biological[1] and pharmacological properties.[2] Surprisingly, in light of the potential benefits of these chiral compounds, there are relatively few stereoselective syntheses of α-silylamines. In this paper, we report a highly diastereoselective synthesis of protected α-silylamines (**3**) from the addition of silyl anions to activated imines (**1**) by the attenuation of potential aza-Brook processes of the anionic intermediate **2** (eq 1).



Although amines possessing α-silyl groups have been known for over 50 years, the established routes to synthesize these compounds, such as the additions of amines to halomethylsilanes[3] or by reduction of amides,[4] involve circuitous approaches that preclude asymmetric induction. The palladium-catalyzed disilylation of an imine at elevated temperatures has been reported, but this process remains very limited in scope.[5] A recently reported stereoselective approach to α-silylamines utilizing reverse aza-Brook rearrangements can be accomplished with high levels of enantioselectivity in the presence of (−)-sparteine.[6]

In connection with our focus on investigating new methods to incorporate silicon into organic molecules,[7] we reasoned that a convergent and flexible route to construct the desired

(1) (a) Banik, G. M.; Silverman, R. B. *J. Am. Chem. Soc.* **1990**, *112*, 4499−4507. (b) Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pulm, M.; Keim, C.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140−165.

(2) (a) Chen, C. A.; Sieburth, S. M.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. *Chem. Biol.* **2001**, *8*, 1161−1166. (b) Showell, G. A.; Mills, J. S. *Drug Discuss. Today* **2003**, *8*, 551−556. (c) Kim, J.; Glekas, A.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3625−3627. (d) Mutahi, M. W.; Nittoli, T.; Guo, L. X.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363−7375.

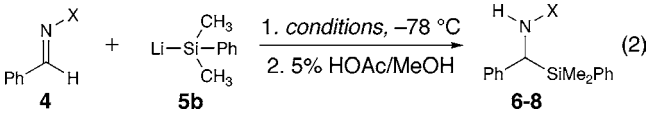
(3) For a seminal example, see: Noll, J. E.; Speier, J. L.; Daubert, B. F. *J. Am. Chem. Soc.* **1951**, 3867−3871. For a representative synthesis, see: Mariano, P. S.; Zhang, X.; Xu, W. *J. Am. Chem. Soc.* **1991**, *113*, 8863−8878.

(4) (a) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191−2194. (b) Kashimura, S.; Ishifune, M.; Muria, Y.; Murase, H.; Shimomura, M.; Shono, T. *Tetrahedron Lett.* **1998**, *39*, 6199−6202. (c) Fleming, I.; Mack, S. R.; Clark, B. P. *Chem. Commun.* **1998**, 713−714.

(5) Tanaka, M.; Uchimaru, Y.; Williams, N. A. *J. Chem. Soc., Dalton Trans.* **2003**, 236−243.

10.1021/ol050244u CCC: $30.25
Published on Web 03/05/2005

Table 1. Optimization of Silyl Anion Addition



4 5b 6-8

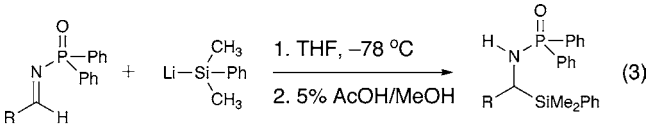
entry	X	solvent	equiv anion[a]	yield[b] (%)	product
1	Ph (**4a**)	THF	3	mixture	
2	Benzyl (**4b**)	THF	3	mixture	
3	SO_2Ph (**4c**)	THF	3	63	**6**
4	$P(O)Ph_2$ (**4d**)	THF	2	52	**7**
5	$P(O)Ph_2$ (**4d**)	toluene	2	39	**7**
6	$P(O)Ph_2$ (**4d**)	THF	3	**88**	**7**
7	$P(O)(OEt)_2$ (**4e**)	THF	3	53	**8**

[a] Relative to imine. [b] Isolated yield after chromatographic purification.

N−C−Si bonding triad of α-silylamines would involve the direct addition of a silyl nucleophile to an appropriately activated C═N system. Astonishingly, this convergent bond-forming strategy has not been disclosed.[8] The advantages of this approach include high modularity with regard to electrophile and nucleophile, potential control of the newly formed stereogenic center, and ease of further synthetic elaboration of the resulting protected amine. The main potential problem with this direct approach is that the resulting anion after silyl nucleophile addition could undergo a 1,2-silyl shift (aza-Brook rearrangement), thereby locating the silyl group on nitrogen and thus generating a carbanion.[9] If this migratory aptitude of silicon can be controlled, then the realization of this strategy is possible.

The exploration of this desired bond forming reaction was initiated by surveying various imine electrophiles (Table 1, eq 2). We anticipated that the nitrogen substituent would play crucial roles of activating the carbon center and subsequent localization of the resulting anion on the nitrogen to avoid any aza-Brook rearrangements. At the outset of our studies, we chose dimethylphenylsilyllithium as the nucleophile due to its stability and ease of preparation.[10] Initially, complex mixtures were generated when the *N*-phenyl- and *N*-benzylimines were employed (entries 1 and 2).[11] We postulated that a stronger electron-withdrawing group was needed to delocalize the nitrogen anion generated in situ, thereby potentially minimizing the aza-Brook pathway. After

Table 2. Dimethylphenylsilyllithium Additions to Imines[a]



5b 8-19

entry	R	yield[b] (%)	product
1	Ph	88	**7**
2	1-naphth	64	**9**
3	2-naphth	61	**10**
4	3-MePh	74	**11**
5	4-MePh	75	**12**
6	2-OMe-Ph	90	**13**
7	4-OMe-Ph	86	**14**
8	4-F-Ph	77	**15**
9	2-Cl-Ph	55	**16**
10	4-Cl-Ph	83	**17**
11	2-furyl	91	**18**
12	$PhCH_2{=}CH_2$	58	**19**

[a] Reaction at 0.2 M and 3 equiv of **5b**. [b] Isolated yields after purification.

surveying various activating substituents on nitrogen, *N*-diphenylphosphinylimines[12] emerged as optimal substrates for the silyl anion additions. Further optimization of the reaction, including nucleophilic equivalents and the use of additives, culminated in a general high-yielding procedure employing 3 equiv of the silyllithium species in THF (entry 6).[13]

With the optimized conditions identified, the scope of the process with regard to electrophile structure has been examined (Table 2, eq 3).[14] The reaction affords good yields of the protected α-silylamines when aryl aldimines are employed.[15] Furthermore, this methodology is relatively insensitive to the position of substituents on the aromatic ring.[16] The use of an α,β−unsaturated imine (entry 12) provides the 1,2-addition product (**19**) in moderate yield (58%). Attempts to expand the scope of the reaction by employing imines with enolizable protons (e.g., derived from ketones and saturated aldehydes) have met with limited success to date.[17]

We have also investigated the influence of silyl anion structure on the reaction. Fortunately, a variety of silyl anions could be added (Table 3, eq 4). Trimethylsilyllithium was

(6) (a) Sieburth, S. M.; Somers, J. J.; OHare, H. K. *Tetrahedron* **1996**, *52*, 5669−5682. (b) Barberis, C.; Voyer, N. *Tetrahedron Lett.* **1998**, *39*, 6807−6810. (c) Sieburth, S. M.; O'Hare, H. K.; Xu, J.; Chen, Y.; Liu, G. *Org. Lett.* **2003**, *5*, 1859−1861. (d) Sieburth, S. M.; Liu, G. *Org. Lett.* **2003**, *5*, 4677−4679.

(7) (a) Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 84−85. (b) Clark, C. T.; Milgram, B. C.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 3977−3980.

(8) An approach with *N*,*N*′-dialkyliminium ions prepared in situ using 10 equiv of $LiClO_4$ (5 M in Et_2O) has been reported: Saidi, M. R.; Ipaktschi, J.; Mojtahedi, M. M.; Naimi-Jamal, M. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3709−3711. (b) Strohmann, C.; Abele, B. C. In *Organosilicon Chemistry III*; Auner, N., Weis, J., Eds.; VCH: Weinheim, 1997; pp 206−210.

(9) Duff, J. M.; Brook, A. G. *Can. J. Chem.* **1977**, *55*, 2589−2600.

(10) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209−1214. Solutions of **4** in THF can be stored at −30 °C under nitrogen for several months.

(11) Preliminary data suggests that reductive coupling products are the predominant species from these reactions. This intriguing possibility is currently under investigation.

(12) (a) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270−273. (b) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561−5568.

(13) Fewer equivalents of silyl anion result in lower isolated yields.

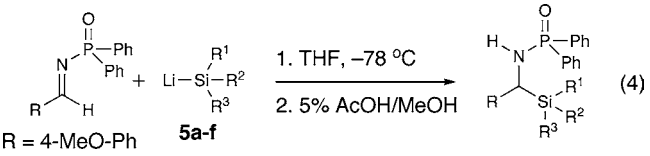
(14) **A Representative Proceedure.** To a 25 mL Schlenk flask was added 1 equiv of imine and THF (0.2 M), and the mixture was cooled to −78 °C. To this solution was added 3 equiv of silyllithium (approximately 1 M in THF). After being stirred at −78 °C for 20 min, the reaction was quenched with 5% acetic acid in methanol (10 mL) at −78 °C. The mixture was diluted with ethyl acetate and then washed with water and brine. After drying, the remaining residue was purified using flash chromatography to yield pure protected α-silylamines.

(15) The structures of these unusual compounds have been confirmed by X-ray crystallography. See the Supporting Information for details.

(16) The use of nitro aromatic imines afforded no products, presumably due to complications resulting from incompatibilities with the silyl anion.

(17) The acetophenone-derived imine afforded only 11% yield of desired product (42% recovered imine). Studies to attenuate of the basicity of the silyl anions to successfully engage this class of imine are currently underway.

Table 3. Survey of Silyl Anion Nucleophile Structure[a]

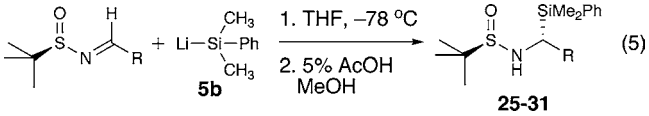


(4)

entry	anion	R^1	R^2	R^3	yield[a] (%)	product
1	**5a**	CH_3	CH_3	CH_3	67	**20**
2	**5b**	CH_3	CH_3	Ph	86	**14**
3	**5c**	CH_3	Ph	Ph	80	**21**
4	**5d**	Ph	Ph	Ph	8	**22**
5	**5e**	CH_3	CH_3	2,4-Me_2Ph	53	**23**
6	**5f**	CH_3	CH_3	5-Me-2-furyl	28	**24**

[a] Reaction at 0.2 M and 3 equiv of **5**. [b] Isolated yields after purification.

Table 4. Stereoselective Silyl Anion Additions



(5)

entry	R	yield[b] (%)	selectivity (dr)[a]	product
1	Ph	73	95:5	**25**
2	4-Me-Ph	72	95:5	**26**
3	4-MeO-Ph	75	95:5	**27**
4	1-naphthyl	60	90:10	**28**
5	2-naphthyl	90	95:5	**29**
6	$PhCH_2$=CH_2	70	95:5	**30**
7	*t*-Bu	72	95:5	**31**

[a] Determined by 500 MHz ^{1}H NMR. [b] Isolated yields after purification.

added in moderate yield (67%, entry 1), but we turned our attention to silyl nucleophiles possessing aryl groups since arylsilanes have the potential to undergo further synthetic manipulations.[18] The silyl anion can accommodate up to two phenyl substituents in these additions (entries 2 and 3), but the triphenylsilyllithium anion is presumably too hindered to undergo nucleophilic addition and thus affords a low yield of the desired amide **22**. The 2,4-dimethylphenyl-dimethylsilyl anion and the furyl silyl anion undergo smooth addition (entries 5 and 6), although the yields in these cases are only moderate at best. It is well documented that the structure of the aryl component of these anions greatly impacts their stability and utility in synthesis as nucleophiles.[19]

With the above information in hand, we turned our attention to developing a stereoselective variant of our direct silyl group installation. Although the development of chiral versions of *N*-diphenylphosphinyl imines was initially pursued, we rapidly discovered that the exposure of *tert*-butanesulfinyl imines[20] to silyl anions (such as **5b**) provides good yields and excellent levels of diastereoselection (>90:10) for the α-silylamine products (Table 4, eq 5).[21] The reaction provides uniformly high selectivities for sulfinyl imines derived from aromatic aldehydes, but like the *N*-diphenylphosphinylimines, saturated imines are not viable substrates for this reaction, presumably due to the presence of enolizable protons.

To determine the absolute configuration of the newly formed stereocenter in this process, single crystals of **31** were grown and subjected to X-ray diffraction (Figure 1).[22] Interestingly, the highly unusual S−N−C−Si bonding arrangement shows no interaction between the Lewis basic sulfinyl oxygen and silicon atom in the solid state.[23] The sizable substituents around the central C11 carbon promote significantly large bond distortions from ideal sp^3 bond angles. To our surprise, the C11 (*R*)-diastereomer favored in this process (with the (*R*)-sulfinyl imine) is the opposite isomer than the one predicted via the closed transition-state model suggested by Ellman for the majority of organometallic additions.[24,25] Although unusual, it has been observed previously that the selectivity for nucleophilic additions to these *N*-butanesulfinylimines is highly dependent on the organometallic species and reaction conditions.[26]

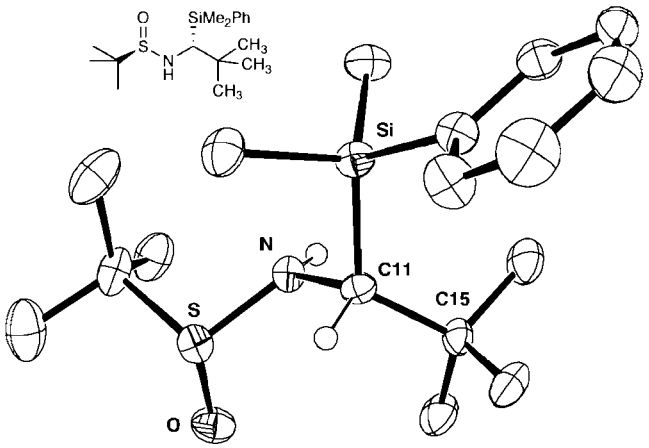


Figure 1. ORTEP structure of **31** at 50% ellipsoid probability. Selected bond distances (Å) and angles (deg): N−S, 1.63; Si−C11, 1.91; N−C11, 1.49; N−C11−Si, 102.8; S−N−C11, 117.9; Si−C11−C15, 121.0.

With a direct method for the stereoselective synthesis of these unusual polyatomic molecules in hand, we are currently exploring their synthetic potential. The phosphorus- and sulfur-based activating groups for these reactions can be removed easily in good yield by exposure to acidic conditions (Scheme 1). Furthermore, the resulting primary amines can be further elaborated to the carbamate (**32**), notably without

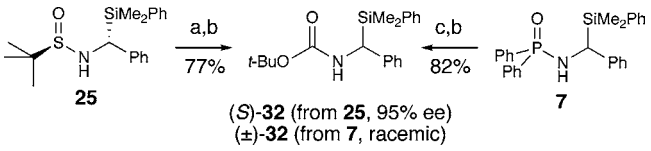
(18) For selected examples of transformations of arylsilanes, see: (a) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A.; Varchi, G. *J. Org. Chem.* **1999**, *64*, 8008−8013. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541. (c) Ichikawa, J.; Ishibashi, Y.; Fukui, H. *Tetrahedron Lett.* **2003**, *44*, 707−710.

(19) Corey, E. J.; Lee, T. W. *Org. Lett.* **2001**, *3*, 3337−3339 and references therein.

(20) For reviews of sulfinyl imines in synthesis, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003−8030. (b) Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995.

(21) For a related approach utilizing trialkylstannane nucleophiles, see: Kells, K. W.; Chong, J. M. *Org. Lett.* **2003**, *5*, 4215−4218.

Scheme 1. Synthetic Transformations of α-Silyl Compounds **7** and **25**[a]



[a] Key: (a) 4 N HCl in dioxane; (b) $(t\text{-BuOCO})_2O$, THF; (c) concd HCl.

loss of the silyl group and in the case of **25**, without epimerization of the newly formed stereogenic center.

In conclusion, the addition of silyl nucleophiles to activated imines is a direct and highly stereoselective route to the synthesis of chiral α-silylamines. The use of *N*-diphenylphosphinyl and *N*-*tert*-butanesulfinyl functional groups attenuates potentially competing aza-Brook rearrangements and therefore facilitates high yields of α-silylamines. The overall process currently accommodates nonenolizable imines and various silyl anion structures. Further investigations to delineate the synthetic utility of these unique compounds are underway in our laboratory and will be reported in due course.

Acknowledgment. Financial support for this work has been provided by Northwestern University and the NSF (CHE-0348979). We thank Amgen for unrestricted support in the form of a New Investigator Award and R.C.M. thanks NU for a Summer Undergraduate Research Fellowship. We acknowledge Dr. Joern Winterfeld (Wacker Chemical Corp.) for providing organosilanes used in this work.

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

OL050244U

(22) Information regarding the X-ray analysis of **31** is as follows: crystal system: orthorhombic, space group *P*212121, unit cell dimensions 6.4 × 16.6 × 18.3 Å. Data were collected on a Bruker Smart 1000 CCD with Mo Kα radiation. CCDC 257698 (**ent-25**), CCDC 257699 (**31**), and CCDC 257700 (**11**) contain the supplementary crystallographic data for these structures. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax (+44) 1223-336-033; deposit@cdc.cam.ac.uk). For an X-ray structure of a related α-silylamine, see: Bolm, C.; Kasyan, A.; Drauz, K.; Gunther, K.; Raabe, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2288−2290.

(23) For an example of Si−O interactions in the solid state, see: Dixon, D. A.; Hertler, W. R.; Chase, D. B.; Farnham, W. B.; Davidson, F. *Inorg. Chem.* **1988**, *27*, 4012−4018 and references therein. For a review of hypervalent silicon, see: Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371−1448.

(24) Liu, G. C.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914.

(25) The X-ray crystallographic structure of **ent-25** also displays a high preference for this unusual diastereomeric pattern. In contrast, the opposite diastereoselectivity is observed with seemingly related tralkylstannyl anion additions, see ref 19.

(26) (a) Cogan, D. A.; Liu, G. C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883−8904. (b) For an example of diastereoselective phosphite additions to enantiopure sulfinylimines, see: Lefebvre, I. M.; Evans, S. A., Jr. *J. Org. Chem.* **1997**, *62*, 7532−7533.