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Reductive Lithiation of Methyl Substituted Diarylmethylsilanes: Application to Silanediol Peptide Precursors

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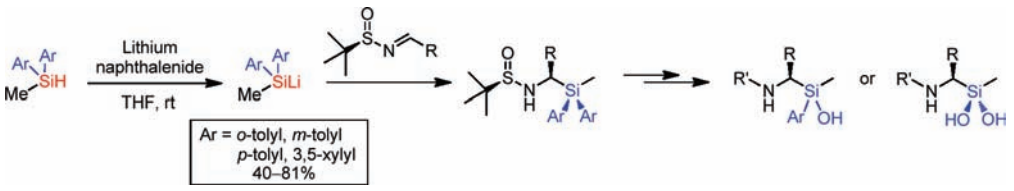
ABSTRACT



Reductive lithiation of methyl-substituted diarylmethylsilanes using lithium naphthalenide represents a practical method for the preparation of the corresponding silyl lithium reagents. Their addition to chiral sulfinimines affords versatile precursors to silanols and silanediols. The replacement of the currently used diphenylsilane motif by a more labile diarylsilane moiety allows the selective hydrolysis of one or two aryl groups by treatment with TFA.

Lithiosilanes play a valuable role as silicon transfer reagents in organic and organometallic chemistry.[1] In organic synthesis, they have been used principally for the nucleophilic introduction of protecting groups[2] and also to attach silyl groups to carbon as control elements for the regio- and stereoselectivity in the synthesis of complex molecules.[3] The discovery of biologically active silicon-containing structures in the quest for drug development has increased the use of silylllithium reagents for the incorporation of silicon in organic compounds.[4]

One of the most recent and notable examples of silicon in bioactive molecules is the silanediol group, introduced by Sieburth and co-workers in 1998,[5] as a new mimic of the tetrahedral intermediate in peptide hydrolysis (Scheme 1). The same group demonstrated that a range of these silanediol isosteres displayed high inhibitory activities against both aspartic and metalloproteases.[5b,d,f]

In previous work,[6] we have reported an efficient approach to silanediol peptide mimics, which involves the

(1) (a) Tamao, K; Kawachi, A. *Adv. Organomet. Chem.* **1995**, *38*, 1. (b) Lickiss, P. D.; Smith, C. M. *Coord. Chem. Rev.* **1995**, *145*, 75. (c) Sekiguchi, A.; Lee, V. Y.; Nanjo, M. *Coord. Chem. Rev.* **2000**, *210*, 11. (d) Uhlig, W. *J. Organomet. Chem.* **2003**, *685*, 70.

(2) (a) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(3) (a) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403. (b) Fleming, I.; Barbero, A.; Walker, D. *Chem. Rev.* **1997**, *97*, 2063. (c) Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 1872.

(4) (a) Organ, M. G.; Buon, C.; Decicco, C. P.; Combs, A. P. *Org. Lett.* **2002**, *4*, 2683. (b) Ballweg, D. M.; Miller, R. C.; Gray, D. L.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 1403.

(5) (a) Sieburth, S. M.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812. (b) 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. (c) Mutahi, M. W.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (d) Kim, J.; Glekas, A.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3625. (e) Kim, J.; Sieburth, S. M. *J. Org. Chem.* **2004**, *69*, 3008. (f) Kim, J.; Sieburth, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2853. (g) Kim, J.; Hewitt, G.; Carroll, P.; Sieburth, S. M. *J. Org. Chem.* **2005**, *70*, 5781. (h) Juers, D. H.; Kim, J.; Matthews, B. W.; Sieburth, S. M. *Biochemistry* **2005**, *44*, 16524. (i) Sieburth, S. M.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311.

(6) (a) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035. (b) Nielsen, L.; Skrydstrup, T. *J. Am. Chem. Soc.* **2008**, *130*, 13145. (c) Hernández, D.; Lindsay, K. B.; Nielsen, L.; Mittag, T.; Bjerglund, K.; Friis, S.; Mose, R.; Skrydstrup, T. *J. Org. Chem.* **2010**, *75*, 3283. (d) Hernández, D.; Nielsen, L.; Lindsay, K. B.; López-García, M. A.; Bjerglund, K.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 3528.

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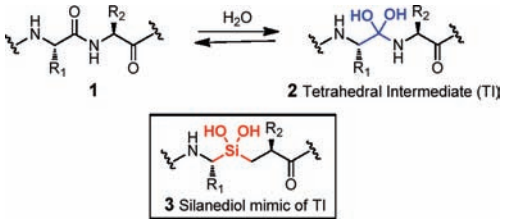
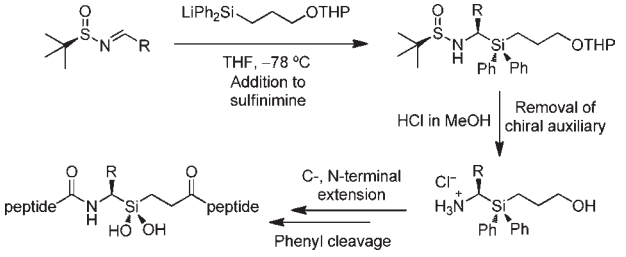
Scheme 1. Silanediols Mimic the Tetrahedral Intermediate in Peptide Hydrolysis



addition of alkyldiphenylsilyl lithium reagents to Ellman's sulfinimines as the key step (Scheme 2). This stereoselective synthesis allows for both N- and C-terminus peptide extension. Nevertheless, an important limitation of this strategy is the final removal of the two phenyl groups to unmask the silanediol. The diphenylsilyl motif has the advantage of being stable toward a broad range of chemical transformations; however, its transformation to the diol requires the initial use of a strong acid, usually TfOH, not compatible with sensitive funcionalities present in complex systems. We therefore set out to search for modified precursors of silanediols to facilitate C−Si bond cleavage with a milder acid thereby extending the scope of the synthesis to other silanediol peptide mimics.

Scheme 2

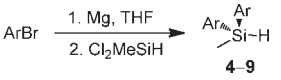


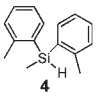
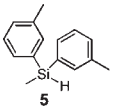
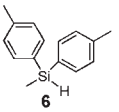
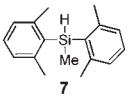
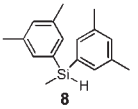
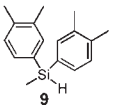
Herein, we report our results examining methyl substituted diarylmethylsilanes as alternative precursors to silanediols. We have found that their lithiation using lithium naphthalenide affords the corresponding diarylsilyl lithium reagents that can successfully replace the currently used diphenylsilyl lithium. The introduction of a more acid labile diarylsilane moiety in peptide precursors facilitates the deprotection of silanediols in acid conditions.

The desired methyl substituted diarylsilanes were easily prepared in good to excellent yields by the addition of the appropriate Grignard reagent to dichloro(methyl)silane (Table 1). The diarylsilanes **4**[7]−**9** were then subjected to lithiation using the standard protocol with Li metal in THF.[6b] All reactions were quenched with TMSCl, which allowed us to isolate and purify the corresponding disilanes. Under

(7) Weickgenannt, A.; Mewald, M.; Muesmann, T. W. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2223.

Table 1. Preparation of Diarylmethylsilanes[a]



entry	Ar	diarylsilane (%)	yield (%)[b]
1	*o*-tolyl	 **4**	87
2	*m*-tolyl	 **5**	77
3	*p*-tolyl	 **6**	93
4	2,6-xylyl	 **7**	64
5	3,5-xylyl	 **8**	91
6	3,4-xylyl	 **9**	81

[a] ArMgX (2.1 equiv), THF, 0 °C, 18 h. [b] Isolated yields after column chromatography on silica gel using pentane as solvent.

these conditions diphenyl(methyl)silane afforded the disilane **17** in 80% yield (Table 2, entry 7). However, the majority of the substituted diarylsilanes showed no reactivity (**5**,[7] **6**,[7] **8**,[7] and **9**), and only in the case of the di(*o*-tolyl)silane could the disilane be isolated in a 25% yield. Diarylsilane **7** decomposed under the reaction conditions.

These results were not surprising. It has previously been reported that substitution of the aromatic ring is not well tolerated in lithiations of silyl chlorides, even though the exact role of the phenyl substituents is not understood. It has been proposed that they stabilize the negative charge on silicon through π polarization,[8] but this appears not to be the only effect. Silanes containing a *p*-tolyl, *p*-biphenyl, or *p*-methoxyphenyl group render the symmetric diaryltetramethyldisilane noncleavable by lithium,[9] whereas *p*-methoxyphenylchlorodimethylsilane does not react with Li to form the disilane.[8] Tri-*o*-tolylsilyl lithium[10] and mesityldimethylsilyl lithium[11] are two exceptions to this reactivity because the steric hindrance of these silanes

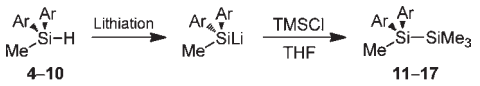
(8) (a) Lambert, J. B.; Schulz, W. J., Jr. Trivalent silyl ions. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: 1989; Vol. 1, Chapter 16, p 1007. (b) Tamao, K.; Kawachi, A. *Adv. Organomet. Chem.* **1995**, *38*, 1.

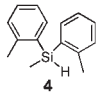
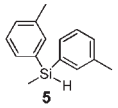
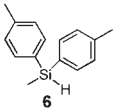
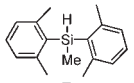
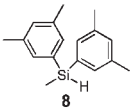
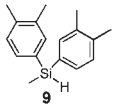
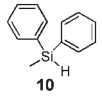
(9) Rahman, N. A.; Fleming, I.; Zwicky, A. B. *J. Chem. Res. (S)* **1992**, 292.

(10) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403.

(11) Müller, H.; Weinzierl, U.; Seidel, W. *Z. Anorg. Allg. Chem.* **1991**, *603*, 15.

Table 2. Lithiation of Diarylmethylsilanes



entry	silane	lithiation conditions	
		Li (% disilane)[a]	Li/naphthalenide (% disilane)[b]
1	 4	**11** (25)	**11** (40)[c]
2	 5	**12** (0)[d]	**12** (82)
3	 6	**13** (0)[d]	**13** (81)
4	 7	**14** (0)[e]	**14** (0)[e]
5	 8	**15** (0)[d]	**15** (77)
6	 9	**16** (0)[d]	**16** (0)[d]
7	 10	**17**[13] (80)	–

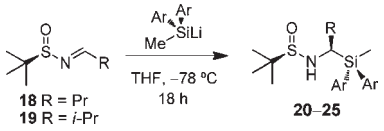
[a] Li (10 equiv), THF, rt, 4−24 h. [b] Li (10 equiv), naphthalene (1 equiv), THF, rt, 1 h; then the diarylsilane was added, and the mixture stirred for 3−4 h. [c] Entry performed at −20 °C. [d] Starting material recovered. [e] Decomposition of starting material.

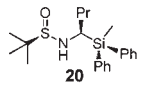
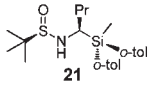
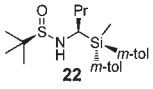
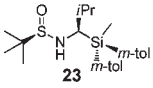
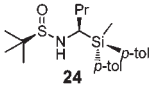
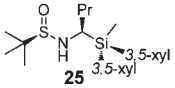
prevents disilane formation. Cleavage of aryl-substituted disilanes to form the corresponding silyl lithium has been achieved, but only by using methyl lithium in conjunction with the HMPA as an additive.[12]

The mechanism for the generation of the silyl lithium reagents from silanes using Li metal involves an initial electron transfer to the aryl group.[14] The presence of electron donating substituents will, however, decrease their propensity for reduction by Li. We therefore tested the possibility of using a soluble reducing agent, such as lithium naphthalenide (LiNp) or lithium 1-(dimethyl-amino)naphthalenide (LDMAN) previously exploited by Kawachi and Tamao,[15] to lithiate a number of phenylsilylchlorides.

Silanes **4**−**9** were therefore subjected to the lithiation procedure using LiNp (Table 2). (*m*-Tolyl)$_2$MeSiLi, (*p*-tolyl)$_2$MeSiLi, and (3,5-xylyl)$_2$MeSiLi were successfully prepared, obtaining the corresponding disilanes **12**, **13**, and **15** in good yields. The formation of (*o*-tolyl)$_2$MeSiLi was more problematic. During the lithiation step, the cleavage of a tolyl−Si bond is produced to generate (*o*-tolyl) MeHSiTMS after quenching with TMSCl. To avoid this side reaction the temperature was lowered to −20 °C affording **11** in 40% yield. The silanes **7** and **9** showed the same reactivity observed using Li metal. The use of catalytic amounts of LiNp was also attempted, but it required longer reaction times giving the silyl lithium reagents in lower yields.

Table 3. Addition of the Silyl Lithium Reagents to Sulfinimines



entry	sulfinimine	Ar	product	yield (dr)[a]
1	**18**	Ph	 **20**	69 (>95:5)
2	**18**	*o*-tolyl	 **21**	38 (>95:5)
3	**18**	*m*-tolyl	 **22**	57 (>95:5)
4	**19**	*m*-tolyl	 **23**	53 (>95:5)
5	**18**	*p*-tolyl	 **24**	58 (>95:5)
6	**18**	3,5-xylyl	 **25**	50 (>95:5)

[a] Isolated yields after column chromatography on silica gel.

These silyl lithium reagents were then examined for their capacity to add to the chiral sulfinimines **18** and **19** following a standard procedure (Table 3).[6a] The corresponding sulfinamides (entries 2−6) were obtained with excellent diastereoselectivity in yields comparable with the addition of diphenyl(methyl)silyl lithium (entry 1).[6a] (*o*-Tolyl)$_2$methylsilyl lithium gave the lowest yield due to steric effects from the *o*-substituent on the aromatic ring (entry 2). Treatment of sulfinimine **19** with (*m*-Tol)$_2$MeSiLi provided **23** in a similar yield (entry 4).

Sulfinimides **22**, **24**, and **25**, the most promising as alternative precursors of silanediols, were then converted to the acetamides **26**−**28** by removal of the chiral auxiliary via treatment with anhydrous methanolic HCl followed by protection of the amine with acetic anhydride and pyridine (Scheme 3).

Acetamides **26**−**28** were used to study the susceptibility of the different methyl substituted diarylsilanes to acid hydrolysis. Both triflic and trifluoroacetic acid were

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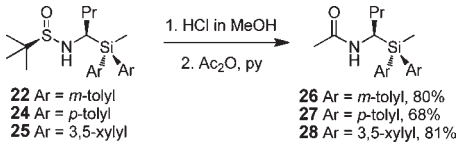
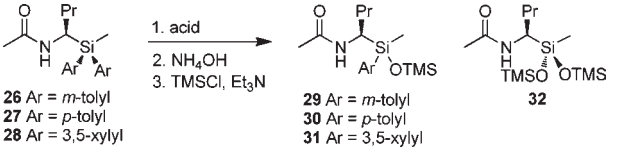
(13) Gilman, H.; Atwell, W. H.; Schwebke, G. L. *J. Organomet. Chem.* **1964**, *2*, 369.
(14) Oestreich, M.; Auer, G.; Keller, M. *Eur. J. Org. Chem.* **2005**, 184.
(15) Kawachi, A.; Tamao, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 945.

Scheme 3. Removal of the Chiral Auxiliary



examined, and the resulting silanols and silanediol were protected with TMSCl and Et_3N to obtain the trisiloxanes as more stable precursors (Table 4). As was expected, the aryl−silicon bonds in the three acetamides were cleaved in the presence of TfOH leading to the protected silanediol **32** in good yields (entries 1a, 2a, and 3a). Different concentrations of TFA in CH_2Cl_2 were then tested. The substrates **26** and **28**, containing the *m*-tolyl or the 3,5-xylyl ring as substituents, afforded the silanols **29** and **31** in all cases. However, treatment of acetamide **27** with a 1:1 mixture of TFA/CH_2Cl_2 followed by silylation with TMSCl provided the protected silanediol **32**. The reaction was stirred at rt for 36 h to yield the desired compound in 80%.

Table 4. Hydrolysis of Diarylsilanes

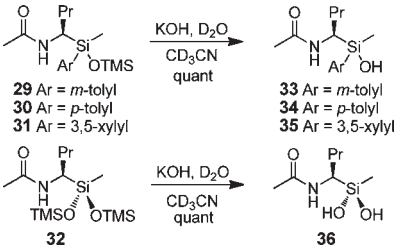


entry	substrate	acid[a]	product (%)[b]
1	**26**	(a) TfOH/CH_2Cl_2 (10 mL, 0.1 M)	**32** (71)
		(b) TFA/CH_2Cl_2 (2 mL, 0.5 M)	SM
		(c) TFA/CH_2Cl_2 (1 mL, 2.6 M)	**29** (80)
		(d) TFA/CH_2Cl_2 (1 mL, 6.5 M)	**29** (77)
2	**27**	(a) TfOH/CH_2Cl_2 (10 mL, 0.1 M)	**32** (70)
		(b) TFA/CH_2Cl_2 (2 mL, 0.5 M)	**30** (79)
		(c) TFA/CH_2Cl_2 (1 mL, 2.6 M)	**30** (66), **32** (10)
		(d) TFA/CH_2Cl_2 (1 mL, 6.5 M)	**32** (80)
3	**28**	(a) TfOH/CH_2Cl_2 (10 mL, 0.1 M)	**32** (72)
		(b) TFA/CH_2Cl_2 (2 mL, 0.5 M)	**31** (80)
		(c) TFA/CH_2Cl_2 (1 mL, 2.6 M)	**31** (78)
		(d) TFA/CH_2Cl_2 (1 mL, 6.5 M)	**31** (70), **32** (5)

[a] See Supporting Information for more details. [b] Isolated yields after column chromatography on silica gel.

Trisiloxanes **29**−**32** displayed sufficient stability for column chromatography, and their hydrolysis with potassium hydroxide in a mixture of deuterium oxide and d_3-acetonitrile afforded silanols **33**−**35** and silanediol **36** in quantitative yields (Scheme 4).

Scheme 4. Deprotection of Silanols and the Silanediol



In conclusion, we have reported a new approach for the preparation of methyl substituted diarylsilyl lithium reagents and their utility in the synthesis of silanol and silanediol peptide precursors. The new diarylmethylsilane moieties fulfill all the requirements to replace the currently used diphenylsilane: tolerance by the lithiation reaction, diastereoselectivity during the sulfinimine addition, sufficient acid stability to allow sulfinamide deprotection, and lability by treatment with TFA. The di(*p*-tolyl)methylsilane motif also emerges as a promising precursor for the selective cleavage of one or both of the aryl−silane bonds. It is intended that these results will be extended to the synthesis of more funtionalized silanol and silanediol containing peptide mimics with potentially interesting biological activity. These results will be reported in due course.

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Supporting Information Available. Experimental methods for the preparation of compounds **4**−**9**, **11**−**16**, **21**−**36** and their characterization. Copies of ^1H and ^{13}C NMR spectra of the new compounds (**7**, **9**, **11**−**16**, **21**−**36**). This material is available free of charge via the Internet at http://pubs.acs.org.