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Letter

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Carbon–Silicon Bond Formation in the Synthesis of Benzylic Silanes

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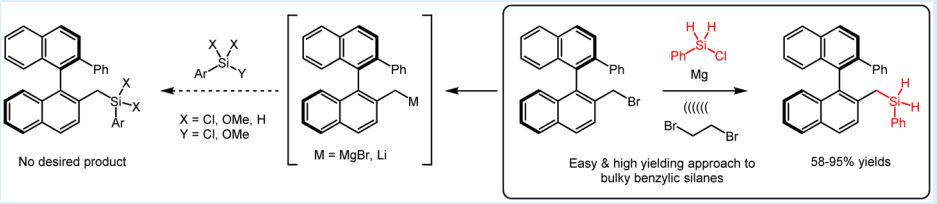
Supporting Information

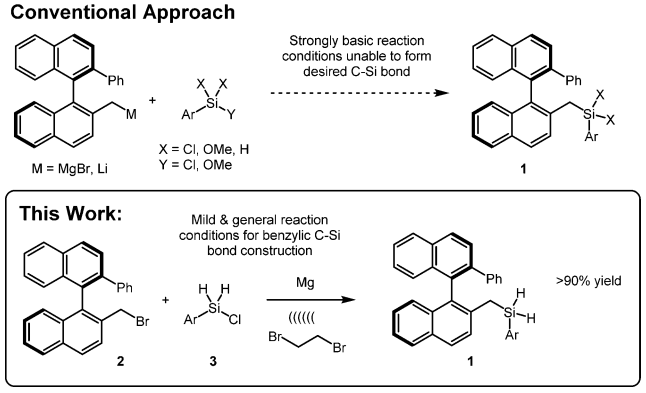


ABSTRACT: Sterically encumbered organosilanes can be difficult to synthesize with conventional, strongly basic reagents; the harsh reaction conditions are often low yielding and not suitable for many functional groups. As an alternative to the typical anionic strategies to construct silanes, the coupling of benzylic halides and arylhalosilanes with sonication has been identified as a high yielding and general strategy to access bulky and functionalized benzylic silanes. This new methodology provides a solution for the synthesis of families of bulky benzylic silanes for study in catalysis and other areas of chemical synthesis.

Organosilanes[1] are valuable products of chemical synthesis that offer interesting platforms for study in drug discovery,[2] catalysis,[3,4] and sensing.[5] Yet, despite recent progress, difficulties in carbon–silicon bond construction can hamper the development of organosilanes and their associated applications. The limitations of the available methods became strikingly apparent to us when we sought to synthesize somewhat complex organosilanes to study in the context of catalysis.

In connection with our ongoing research program focused on metal-free catalyst[3a,b,4] design, we met the challenge of constructing enantiopure benzylic silanediols (e.g., **1**, X = OH, Scheme 1), organosilanes with two OH groups on silicon ($R_2Si(OH)_2$). Benzylic carbon–silicon bonds are frequently constructed under strongly basic reaction conditions (i.e., organolithiums or Grignards, Scheme 1). The conventional strongly basic reaction conditions presented at least two obstacles that hindered progress in several of our silanediol catalyst syntheses: (1) they were plagued with exceedingly low yields and (2) they were not functional group tolerant enough to enable access to families of silanediols for structure–activity relationship studies. In an attempt to overcome these challenges associated with the available methods, we explored more general approaches to synthesize benzylic organosilanes (**1**) that could easily be converted into organosilanols. This letter details our findings of benzylic C(sp^3)–Si bond formation via the Barbier-type coupling of suitable silicon reagents (**3**) and benzylic halides (**2**).

Scheme 1. Barbier-Type Benzylic C–Si Bond Formation



We routinely take advantage of lithiation followed by silylation in the construction of BINOL-based silanediol catalysts.[4] For example, cyclic BINOL-based silanediol **4** was isolated in a useful synthetic yield after a three-step one-flask lithiation and silacyclization sequence (eq 1, Scheme 2). To our surprise, this approach did not translate to similar acyclic variants. Several attempts at lithiation under a variety of conditions followed by reaction with a number of different electrophilic silyl reagents (e.g., $SiCl_4$, $Si(OMe)_4$, $PhSiH_2Cl$) failed to form the desired C–Si bond (Scheme 2a). The formation of the benzylic Grignard reagent followed by treatment with a silylating agent did not provide the desired product regardless of our efforts at optimizing various reaction parameters, such as solvent, reaction temperature, and benzylic halide (Scheme 2b). Briefly, success was encountered with the desired C–Si bond formation after swapping the polarity of the reaction partners (i.e., nucleophilic silicon and electrophilic carbon): the addition of phenylsilyllithium to benzylic bromide **2** gave rise to the desired silane **1a** in 52% yield (Scheme 2c).

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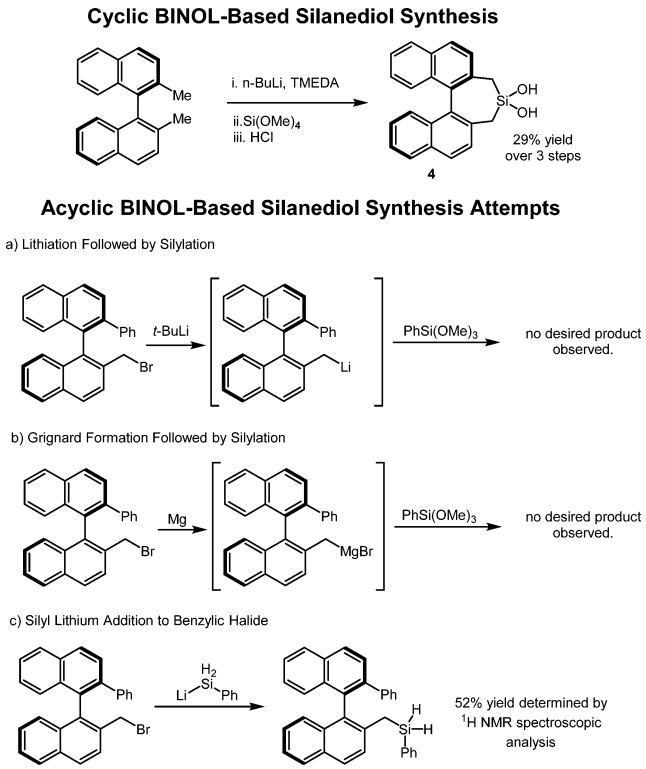
Scheme 2. Benzylic C−Si Bond Forming Strategies Attempted

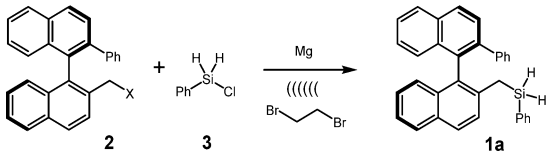


Unfortunately, the silyl lithium approach was not a general solution, as the phenyl ring on the silyl species could not be altered even slightly: electron-donating or -withdrawing groups on the phenyl ring were not acceptable. Not even naphthyl rings were tolerated on the silyl lithium species.

The limits of our early attempts toward benzylic silanediol synthesis prompted us to explore more uncommon benzylic C(sp^3)−Si bond forming reaction conditions that may afford us higher yields and/or be more tolerant of the functional groups on both of the reaction partners. The results of our own experimentation, working in combination with Lee and co-workers' demonstration of the power of sonication in aryl−silicon bond formation,[6] encouraged us to pursue Barbier-type reaction conditions to establish the desired C−Si bond. We were delighted to find that Barbier-type coupling of benzylic bromide **2** (X = Br) and phenylchlorosilane **3** gave rise to desired silane **1a** in 94% yield (Table 1).

We determined that equivalents of silyl chloride from 5 to 1.5 equiv did not affect the yield, all giving >90% yield of **1a** (entries 1−3). The nature of the benzylic halide had a slight influence on the yield. The benzylic bromide was the highest yielding under optimized conditions (entry 3), while both the chloride and iodide gave rise to lower, but still excellent yields of product (entries 4 and 5). With straightforward and high yielding reaction conditions identified for the formation of benzylic C−Si bonds, we set out to test the limits of the benzylic halide and chlorosilane reaction partners (Table 2). Phenylchlorosilane afforded 94% of the desired benzylic silane product (**1a**). Both electron-rich and electron-poor aryl silanes were well tolerated in the process. For example, the more electron-rich 4-methoxy phenylchlorosilane yielded 88% of benzyl silane **1b** while electron-poor 4-fluoro phenylchlorosilane resulted in a 90% yield of **1c**. We were pleased to see

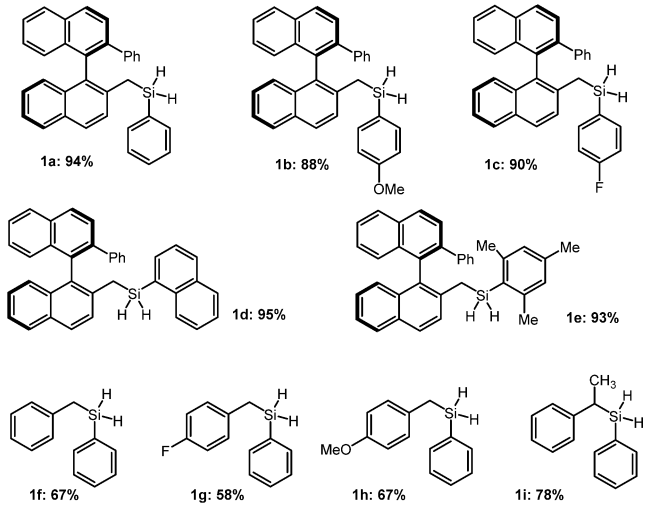
Table 1. Optimization of Barbier-Type Coupling for BINOL-Based Silanediol Synthesis[a]



entry	X	equiv **3**	yield (%)
1	Br	5	95[b]
2	Br	3	92[b]
3	Br	1.5	94[c]
4	Cl	1.5	81[c]
5	I	1.5	90[c]

[a]Reactions conducted in THF (0.2 M) for 30 min at 23 °C. See Supporting Information for details. [b]Yield determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields after flash column chromatography on silica gel.

Table 2. Examples of Silanes Prepared via Barbier-Type Coupling[a]



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

that our Barbier-type coupling was also tolerant of a variety of sterically hindered arylchlorosilane reaction partners. For instance, 1-naphthylchlorosilane gave rise to the highest yield in this Barbier-type coupling at 95% (**1d**). We were delighted to find that the very sterically hindered mesitylchlorosilane yielded 93% of the benzylic silane product **1e**.

Curiosity then prompted us to explore our methodology in coupling reactions of arylchlorosilanes with less complex benzyl bromides. Subjecting benzyl bromide and phenylchlorosilane to the standard reaction conditions yielded 67% of the desired product **1f**. The tolerance of the reaction to benzylic bromides with electron-poor and electron-rich substituents was put to the test. Pleasingly, 4-fluorobenzyl bromide resulted in the desired silane **1g** in 58% yield, while the 4-methoxybenzyl bromide gave rise to 67% of **1h**. We were also happy to observe the coupling of a secondary benzyl bromide afforded the silane product **1i** in 78% yield.

The silane products of our Barbier-type coupling were briefly explored in further reactions of interest to the synthetic community (Scheme 3). Inspired by our own intent to explore benzylic silanediols in catalysis, we found that **1a** was easily oxidized to the silanediol **5** in 60% yield upon treatment with

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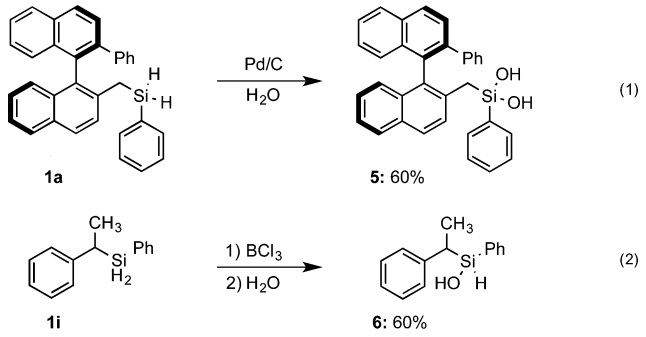
Scheme 3. Uses of Benzylic Silanes



Pd/C and H_2O (eq 1).[7] The conversion of **1i** to the chlorosilane, a species now ready for further functionalization, was achieved with BCl_3 and then treated with H_2O to yield silanol **6** in 60% yield (eq 2).[8]

To conclude, Barbier-type coupling conditions have been identified as a general strategy for the synthesis of benzylic silanes. The reaction conditions benefit from being (1) operationally simple, (2) high yielding, and (3) tolerant of a broad range of functional groups and sterically encumbered reaction partners. This new methodology may present a useful synthetic tactic to enable the construction of more complex silanes for study as catalysts and reagents, among other things.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01223.

General methods, synthetic details, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on organosilanols, see: (a) Chandrasekhar, B.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847−5910. (b) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147−262.

(2) For reviews on organosilanols in drug discovery, see: (a) Sieburth, S. McN.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, *2006*, 311−322. (b) Sieburth, S. McN. *Advances in Silicon Science*; Zelisko, P. M., Ed.; Springer: Dordrecht, 2014, 103−123. (c) Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388−405.

(3) For examples of proposed silanediol hydrogen bond donor catalysis, see: (a) Schafer, A. G.; Wieting, J. M.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 5228−5231. (b) Hardman-Baldwin, A. M.; Mattson, A. E. *ChemSusChem* **2014**, *7*, 3275−3278. (c) Tran, N. T.; Min, T.; Franz, A. K. *Chem. - Eur. J.* **2011**, *17*, 9897−9900.

(4) For examples of proposed silanediol anion-binding catalysis, see: (a) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 11321−11324. (b) Wieting, J. M.; Fisher, T. J.; Schafer, A. G.; Visco, M. D.; Gallucci, J. C.; Mattson, A. E. *Eur. J. Org. Chem.* **2015**, *2015*, 525−533.

(5) Kondo, S.; Bie, Y.; Yamamura, M. *Org. Lett.* **2013**, *15*, 520−523.

(6) Lee, A. S.-Y.; Chang, Y.-T.; Chu, S.-F.; Tsao, K.-W. *Tetrahedron Lett.* **2006**, *47*, 7085−7087.

(7) Nakamura, M.; Matsumoto, Y.; Toyama, M.; Baba, M.; Hashimoto, Y. *Chem. Pharm. Bull.* **2013**, *61*, 237−241.

(8) Sodner, M.; Sandor, M.; Schier, A.; Schmidbauer, H. *Chem. Ber.* **1997**, *130*, 1671−1676.

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