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# Alkenyl- and aryl[2-(hydroxymethyl)phenyl]-dimethylsilanes: Tetraorganosilanes for the practical cross-coupling reaction*

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*Abstract*: Readily accessible and highly stable alkenyl- and aryl[2-(hydroxymethyl)-phenyl]dimethylsilanes cross-couple with various aryl and alkenyl halides under mild reaction conditions employing $K_2CO_3$ as a base at 35–80 °C. The reaction tolerates a diverse range of functional groups including silyl protections. The silicon residue, cyclic silyl ether, is readily recovered and reused on a gram-scale synthesis. Intramolecular coordination of a proximal hydroxyl group is considered to efficiently form pentacoordinated silicates having a transferable group at an axial position.

*Keywords*: cross-coupling; homogeneous catalysis; biaryl; palladium; silicon.

## INTRODUCTION

The metal-catalyzed cross-coupling reaction is now an indispensable tool for modern organic synthesis [1]. Among many cross-coupling protocols, a silicon-based methodology is gaining increasing importance and interest in view that silicon reagents are generally highly stable and nontoxic [2]. In 1988, Hiyama and Hatanaka revealed that readily accessible organo(halo)silanes undergo transmetallation to palladium(II), an oxidative adduct of aryl halides to palladium(0), upon treatment with a fluoride activator to form pentacoordinate silicates, achieving the cross-coupling reaction [3]. Since this discovery, in situ formation of pentacoordinated silicates by use of halosilanes or alkoxysilanes in the presence of a fluoride activator has been a standard strategy in the silicon-based cross-coupling protocol [2]. However, halosilanes and alkoxysilanes are sensitive to heat, moisture, base, and/or acid, and thus have not always been reagents of choice for synthetic chemists irrespective of aforementioned attractive properties of organosilicon compounds. A recent breakthrough in this field is the use of silanols as coupling agents initiated independently by Mori/Hiyama [4] and Denmark [5]. Silanols are relatively stable compared with halosilanes and alkoxysilanes and allow the cross-coupling reaction to proceed even at room-temperature, significantly milder reaction conditions ever reported. Furthermore, recent developments in highly stable tetraorganosilicon reagents, so-called "masked silanols", that have a labile silacyclobutyl [6], 2-pyridyl [7], 2-thienyl [8], electron-poor aryl [9], benzyl [10], allyl [11], or even phenyl [12] group have raised the synthetic potential of the silicon-based cross-coupling reaction [13]. They form silanols in situ upon treatment with TBAF or $KOSiMe_3$ to undergo cross-coupling reaction under

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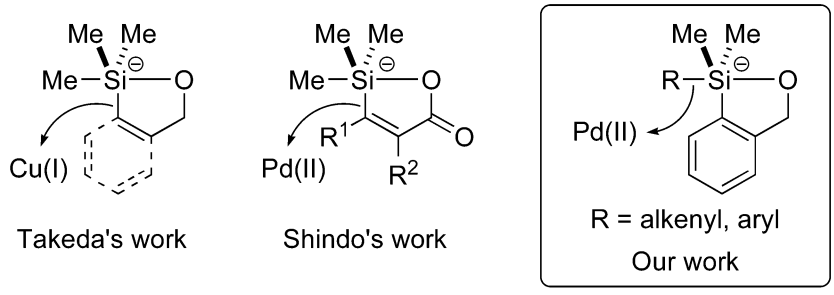
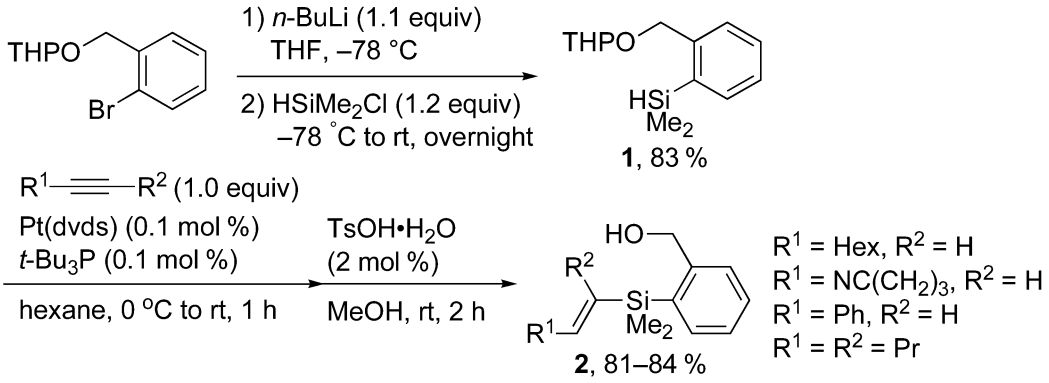
very mild conditions. Thus, the remaining synthetic problem in the silicon-based protocol is the use of relatively expensive fluoride activators, which are incompatible with several functional groups including common silyl protectors. Only a few successful examples of a fluoride-free process are available, which utilize NaOH [14], $KOSiMe_3$ [12,15], $Cs_2CO_3$ [16], or stoichiometric amount of transition-metal promoters [4,17] with halosilanes, alkoxysilanes, silanols, or some specific tetraorganosilanes.

On the other hand, intramolecular activation is recently disclosed by Takeda and coworkers. What they reported is alkenyl- and aryl(trimethyl)silanes having a proximal hydroxyl group undergo smooth transmetallaton from silicon to copper without fluoride activation [18]. The resulting copper reagents undergo palladium-catalyzed cross-coupling reaction with aryl iodides. Shindo has also disclosed similar effect of a carboxyl group cis to a trimethylsilyl group, achieving fluoride-free cross-coupling reaction [19]. These examples clearly show that intramolecular coordination by a negatively charged oxygen nucleophile accelerates transmetallation from silicon to a late transition metal in a highly efficient manner. However, a critical limitation of these precedents is that a transferable group is always an oxygen-based activating functionality. Accordingly, we have embarked on design of stable tetraorganosilicon reagents having an activating organofunctional group independent of a transferable group, allowing a diversity of introducible organic groups on silicon. We report herein that alkenyl- and aryl[2-(hydroxymethyl)phenyl]dimethylsilanes undergo cross-coupling highly efficiently with aryl and alkenyl iodides under significantly mild conditions in the presence of $K_2CO_3$ as a base [20,21].



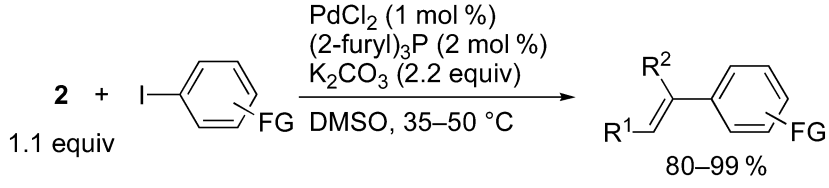

## SYNTHESIS AND CROSS-COUPLING REACTION OF ALKENYL[2-(HYDROXYMETHYL)PHENYL]DIMETHYLSILANES

Aryl(dimethyl)silane **1**, prepared from THP-protected 2-bromobenzyl alcohol, was treated with an alkyne in the presence of a platinum catalyst to give various (*E*)-alkenyl[2-(hydroxymethyl)phenyl]dimethylsilanes **2** in good yields after acidic deprotection (Scheme 1). Quantitative recovery of (*E*)-octenyl[2-(hydroxymethyl)phenyl]dimethylsilane after treatment with an aqueous 1 M HCl or 1 M NaOH solution in THF at 50 °C for 24 h showed the fair stability of the silicon reagents toward an acid or base.




**Scheme 1**

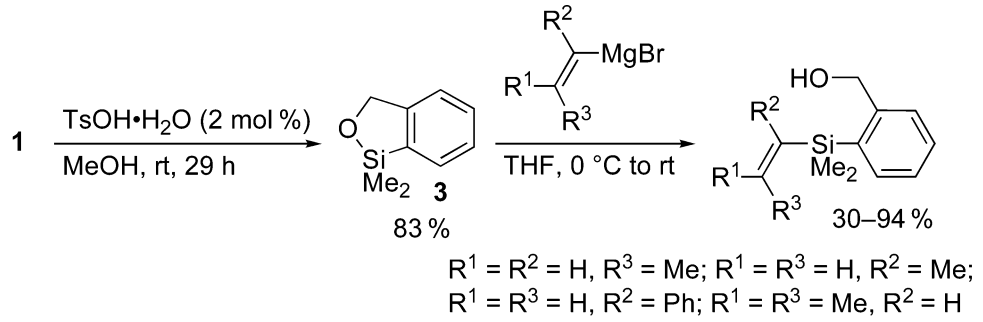
The resulting alkenylsilanes were found to react with various aryl iodides having a functional group such as cyano, ester, keto, formyl, nitro, chloro, methoxy, hydroxyl, or TBDMS-ether. It is worth noting that the reaction proceeds with a readily available $PdCl_2$/(2-furyl)$_3$P catalyst (1 mol %) using $K_2CO_3$ (2.2 equiv) as a mild and inexpensive base in DMSO at 35–50 °C (eq. 1).




(1)

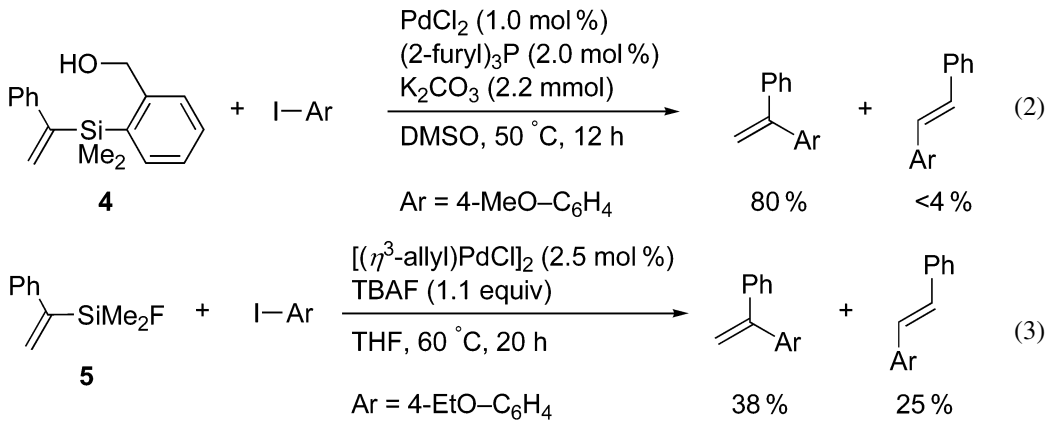
FG = CN, $CO_2$Et, C(O)Me, CHO, $NO_2$, Cl, MeO, $CH_2OH$, $CH_2OSiMe_2$*t*-Bu

Alkenylsilanes can also be prepared by the reactions of cyclic silyl ether **3**, which is available by treatment of **1** with an acid catalyst in MeOH, with the corresponding Grignard reagents (Scheme 2).

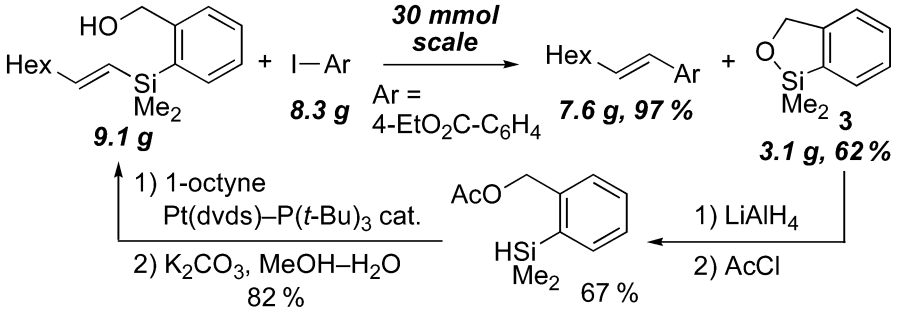



**Scheme 2**

The resulting alkenylsilanes also cross-coupled with aryl iodides in stereo- and regiospecific manners. Especially, it is worth noting that α-phenylvinylsilane **4** reacts with 4-iodoanisole exclusively at the *ipso*-position, whereas the corresponding fluorosilane **5** is recorded to undergo *cine*-substitution to some extent (eq. 2 vs. eq. 3) [22].



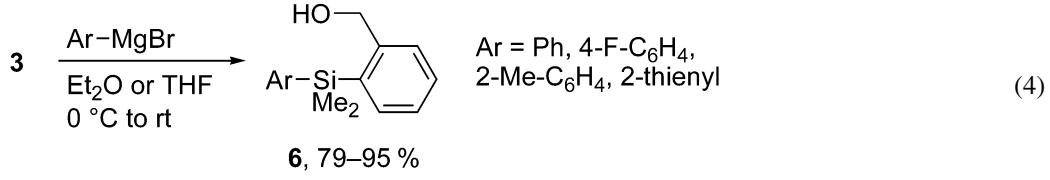

A gram-scale synthesis is successfully carried out under the identical conditions (Scheme 3). Hereby, cyclic silyl ether **3**, a silicon residue of the present protocol, can be recovered by distillation (62 % yield) and reused to synthesize the starting alkenylsilane through reduction followed by hydrosilylation across 1-octyne.



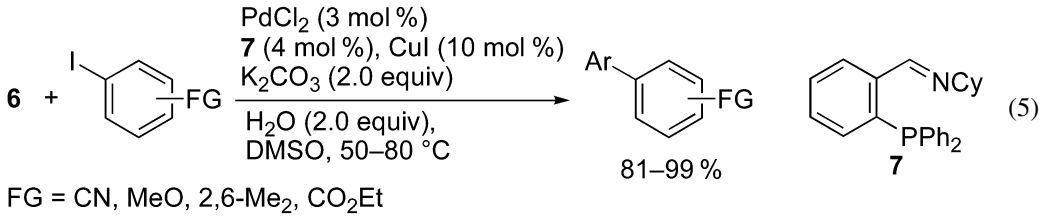

**Scheme 3**

## SYNTHESIS AND CROSS-COUPLING REACTION OF ARYL[2-(HYDROXYMETHYL)PHENYL]DIMETHYLSILANES

Aryl[2-(hydroxymethyl)phenyl]dimethylsilanes **6** were similarly prepared by the ring-opening reaction of **3** with aryl Grignard reagents (eq. 4).




Selective transfer of the desired aryl group differentiating from 2-(hydroxymethyl)phenyl in **6** is a definitely challenging problem. Indeed, we have observed that a catalyst system employing $PdCl_2$ (3 mol %), iminophosphine ligand **7** (4 mol %), CuI (10 mol %) in the presence of $H_2O$ and $K_2CO_3$ in DMSO at 50–80 °C successfully induce the cross-coupling reaction of **6** with ethyl 4-iodobenzoate (eq. 5). A pentacoordinated silicate intermediate having a rather electron-withdrawing aryl group at an axial position (vide supra) apparently accounts for the selective aryl transfer.




## CONCLUSION

A new silicon-based cross-coupling protocol using alkenyl- and aryl[2-(hydroxymethyl)phenyl]dimethylsilanes under mild conditions employing $K_2CO_3$ as a base has been described. Fine-tuning of the reagent structures may be necessary to expand the scope of the present cross-coupling chemistry as a general synthetic tool. This subject will be addressed by flexible functionalization of 2-(hydroxymethyl)phenyl group as well as alkyl groups on a silicon atom. Development of a more atom-economical preparation of the arylsilane reagents, which do not rely on the use of the aryl Grignard reagents, is also be an important issue. Recent reports on the preparation of arylsilanes by the palladium- or rhodium-catalyzed cross-coupling of aryl halides with triorgano- or trialkoxysilanes may be a clue to solve the problem [23]. In addition, direct silylation of aromatic compounds with disilane is certainly a potent strategy for arylsilane synthesis [24]. In any case, highly chemoselective transformations using the highly stable silicon reagents presented herein would find a widespread use by synthetic chemists in a diverse range of fields. Current efforts are also directed to other metal-catalyzed reactions using these reagents.

## REFERENCES

1. A. de Meijer and F. Diederich (Eds.). *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim (2004).
2. (a) T. Hiyama and E. Shirakawa. *Top. Curr. Chem.* **219**, 61–85 (2002); (b) S. E. Denmark and R. F. Sweis. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., A. de Meijer and F. Diederich (Eds.), pp. 163–216, Wiley-VCH, Weinheim (2004); (c) J. Tsuji. *Palladium Reagents and Catalysts*, pp. 338–351, John Wiley, Chichester (2004).
3. Y. Hatanaka and T. Hiyama. *J. Org. Chem.* **53**, 918–920 (1988).
4. K. Hirabayashi, J. Kawashima, Y. Nishihara, A. Mori, T. Hiyama. *Org. Lett.* **1**, 299–302 (1999).
5. S. E. Denmark and D. Wehrli. *Org. Lett.* **2**, 565–568 (2000).
6. S. E. Denmark and J. Y. Choi. *J. Am. Chem. Soc.* **121**, 5821–5822 (1999).
7. K. Itami, T. Nokami, J.-i. Yoshida. *J. Am. Chem. Soc.* **123**, 5600–5601 (2001).
8. K. Hosoi, K. Nozaki, T. Hiyama. *Proc. Jpn. Acad.* **78B**, 154–160 (2002).
9. H. Katayama, K. Taniguchi, M. Kobayashi, T. Sagawa, T. Minami, F. Ozawa. *J. Organomet. Chem.* **645**, 192–200 (2002).
10. B. M. Trost, M. R. Machacek, Z. T. Ball. *Org. Lett.* **5**, 1895–1898 (2003).
11. A. K. Sahoo, T. Oda, Y. Nakao, T. Hiyama. *Adv. Synth. Catal.* **346**, 1715–1727 (2004).
12. J. C. Anderson and R. H. Munday. *J. Org. Chem.* **69**, 8971–8974 (2005).
13. (a) H. Katayama, M. Nagao, R. Moriguchi, F. Ozawa. *J. Organomet. Chem.* **676**, 49–54 (2003); (b) B. M. Trost, M. U. Frederiksen, J. P. N. Papillon, P. E. Harrington, S. Shin, B. T. Shireman. *J. Am. Chem. Soc.* **127**, 3666–3667 (2005); (c) S. E. Denmark and S. A. Tymonko. *J. Am. Chem. Soc.* **127**, 8004–8005 (2005); (d) S. E. Denmark and S. Fujimori. *J. Am. Chem. Soc.* **127**, 8971–8973 (2005).

14. (a) E. Hagiwara, K.-i. Gouda, Y. Hatanaka, T. Hiyama. *Tetrahedron Lett.* **38**, 439–442 (1997); (b) M. Shindo, K. Matsumoto, K. Shishido. *Angew. Chem. Int. Ed.* **43**, 104–106 (2004); (c) C. Wolf and R. Lerebours. *Org. Lett.* **6**, 1147–1150 (2004).
15. S. E. Denmark and R. F. Sweis. *J. Am. Chem. Soc.* **123**, 6439–6440 (2001).
16. S. E. Denmark and J. D. Baird. *Org. Lett.* **6**, 3649–3652 (2004).
17. (a) H. Ito, H. Sensui, K. Arimoto, K. Miura, A. Hosomi. *Chem. Lett.* 639–640 (1997); (b) K. Itami, M. Mineno, T. Kamei, J.-i. Yoshida. *Org. Lett.* **4**, 3635–3638 (2002); (c) P. Pierrat, P. Gros, Y. Fort. *Org. Lett.* **7**, 697–700 (2005).
18. (a) H. Taguchi, K. Ghoroku, M. Tadaki, A. Tsubouchi, T. Takeda. *J. Org. Chem.* **67**, 8450–8456 (2002); (b) H. Taguchi, K. Takami, A. Tsubouchi, T. Takeda. *Tetrahedron Lett.* **45**, 429–432 (2004).
19. M. Shindo, K. Matsumoto, K. Shishido. *Synlett* 176–179 (2005).
20. Y. Nakao, H. Imanaka, A. K. Sahoo, A. Yada, T. Hiyama. *J. Am. Chem. Soc*. **127**, 6952–6953 (2005).
21. For allyl- or benzyl[2-(hydroxymethyl)dimethylsilanes, see (a) P. F. Hudrlik, Y. M. Abdallah, A. M. Hudrlik. *Tetrahedron Lett.* **33**, 6747–6750 (1992); (b) P. F. Hudrlik, J. O. Arango, Y. M. Hijji, C. O. Okoro, A. M. Hudrlik. *Can. J. Chem.* **78**, 1421–1427 (2000).
22. Y. Hatanaka, K.-i. Goda, T. Hiyama. *J. Organomet. Chem.* **465**, 97–100 (1994).
23. (a) M. Murata, K. Suzuki, S. Watanabe, Y. Masuda. *J. Org. Chem.* **62**, 8569–8571 (1997); (b) A. S. Manoso and P. DeShong. *J. Org. Chem*. **66**, 7449–7455 (2001); (c) M. Murata, M. Ishikura, M. Nagata, S. Watanabe, Y. Masuda. *Org. Lett*. **4**, 1843–1845 (2002); (d) Y. Yamanoi. *J. Org. Chem.* **70**, 9607–9609 (2005).
24. T. Ishiyama, K. Sato, Y. Nishio, N. Miyaura. *Angew. Chem., Int. Ed*. **42**, 5346–5348 (2003).