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A General and Straightforward Route toward Diarylmethanes. Integrated Cross-Coupling Reactions Using (2-Pyridyl)silylmethylstannane as an Air-Stable, Storable, and Versatile Coupling Platform

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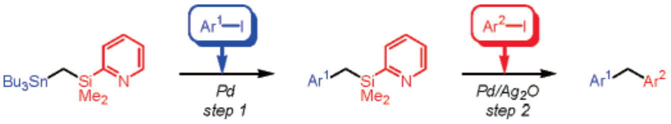
ABSTRACT

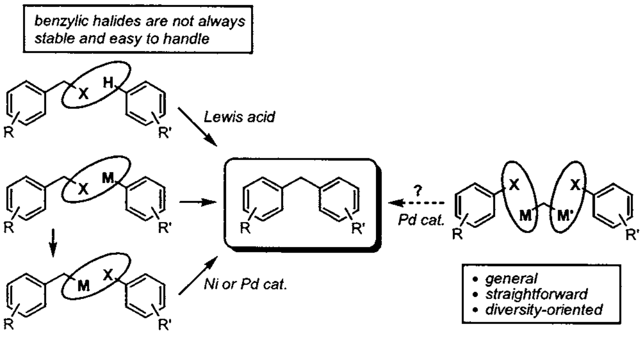


Pharmacologically important diarylmethane structures have been prepared in a straightforward manner through sequentially integrated Pd-catalyzed cross-coupling reactions. (2-Pyridyl)silylmethylstannane was found to be an air-stable, storable, and versatile coupling platform in this synthetic strategy.

Diarylmethanes are ubiquitous structural constituents in pharmacologically important molecules with many interesting actions.[1] They are also frequently used as subunits in supramolecular structures such as macrocycles, catenanes, and rotaxanes.[2] With the advent of high throughput chemistry, a general, straightforward, and diversity-oriented synthetic method toward this class of compounds is in high demand.

Classically, diarylmethanes have been elaborated by the Friedel−Crafts alkylation using aromatic compounds and benzylic halides or by S_N2-type reaction using arylmetals and benzylic halides (Scheme 1). Alternatively, metal-catalyzed cross-coupling reactions of arylmetals and benzylic halides, or aryl halides and benzylic metals (usually prepared from benzylic halides), have been used as a viable synthetic strategy (Scheme 1). However, all these methods are limited

Scheme 1. Synthetic Routes toward Diarylmethanes



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(1) For examples: (a) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321. (b) Wai, J. S.; Egbertson, M. S.; Payne, L. S.; Fisher, T. E.; Embrey, M. W.; Tran, L. O.; Melamed, J. Y.; Langford, H. M.; Guare, J. P., Jr.; Zhuang, L.; Grey, V. E.; Vacca, J. P.; Holloway, M. K.; Naylor-Olsen, A. M.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Gabryelski, L. J.; Young, S. D. *J. Med. Chem.* **2000**, *43*, 4923. (c) Boyd, R. E.; Rasmussen, C. R.; Press, J. B.; Raffa, R. B.; Codd, E. E.; Connelly, C. D.; Li, Q. S.; Martinez, R. P.; Lewis, M. A.; Almond, H. R.; Reitz, A. B. *J. Med. Chem.* **2001**, *44*, 863.

(2) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

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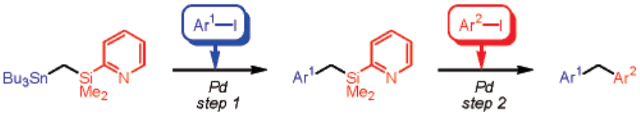
by the availability of benzylic halides, which are not always stable and easy to handle and, hence, not suitable for the production of large numbers of molecules in a combinatorial way.[3]

We envisioned that a mixed gem-dimetalmethane (MCH_2M')[4,5] would be a suitable coupling platform for a general and straightforward synthesis of diarylmethanes if selective arylation at each of the carbon−metal bonds could be realized using Pd-catalyzed cross-coupling chemistry (Scheme 1).[6] However, to our knowledge, such a straightforward strategy has not been reported for the preparation of diarylmethanes.

During our recent program using a dimethyl(2-pyridyl)silyl (2-PyMe$_2$Si) group as a removable directing group,[7−9] we developed several 2-PyMe$_2$Si-based mixed gem-dimetalmethanes such as silylmethyllithium,[10] silylmethylmagnesium,[11] and silylmethylstannane.[12] We envisaged that 2-PyMe$_2$SiCH$_2$SnBu$_3$ (**1**) should be particularly suitable as a platform for diarylmethane synthesis because of its practical advantages: (i) stable to air and moisture,[13] (ii) storable, and (iii) easy to prepare (two steps from 2-bromopyridine) in a large scale (>10 g).[12] In this communication, we report the use of **1** as an excellent mixed gem-dimetalmethane for the preparation of diarylmethanes through sequentially integrated Pd-catalyzed cross-coupling reactions with aryl iodides (Scheme 2). Advantageous features of our strategy are that (i) because of the reactivity difference of two carbon−metal bonds (C−Sn vs C−Si), selective and stepwise arylations should be possible, and (ii) because both of the aryl groups of diarylmethane structure stem from readily available aryl iodides (more than 20 000 aryl iodides are commercially available), the synthesis becomes sufficiently diversity-oriented (Scheme 2).[14]

Scheme 2. Synthetic Strategy toward Diarylmethanes through Sequential Pd-Catalyzed Cross-Coupling Reactions



Although it has been well-known that silylmethylstannanes are unreactive[15] toward cross-coupling reaction (Migita−Kosugi−Stille coupling),[16] we have established that a (2-pyridyl)silylmethylstannane such as **1** undergoes Pd-catalyzed cross-coupling reaction with aryl iodide **2** (step 1 in Scheme 2) presumably due to the pyridyl-to-palladium coordination effect in the transmetalation step.[12] Therefore, the second cross-coupling reaction (Hiyama coupling, step 2 in Scheme 2)[17] is the initial focal point of our campaign toward diarylmethane synthesis.

Although we have already reported that the cross-coupling reactions of *alkenyl*(2-pyridyl)silanes with aryl iodides are efficiently catalyzed by PdCl$_2$(PhCN)$_2$/TBAF[18] system,[7b] we had several concerns in our mind prior to the investigation described herein. (i) If we are conducting the second cross-coupling (cross-coupling using *benzylic* silanes) under the mechanism similar to that used for alkenyl(2-pyridyl)silanes (cross-coupling proceeds through the intermediacy of silanol with quantitative removal of pyridyl group from silicon), the protonation of benzylic group must be slower than the transmetalation and the protonation of pyridyl group. Otherwise, it will end up in exclusive protodesilylation. (ii) Judging from the paucity in the literature, a benzylic group might be more difficult to transfer from silicon to palladium (and then to coupling product) than other common transfer groups such as aryl, alkenyl, alkynyl, and allyl groups.[19] (iii) If the above-mentioned concerns were found to be the case, alternative activation of the ArCH$_2$−SiMe$_2$Py bond must be developed.

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[3] For an excellent approach toward a diarylmethane library: Vanier, C.; Lorgé, F.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1679.

[4] For excellent reviews on gem-dimetalmethane: (a) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241. (b) Normant, J. F. *Acc. Chem. Res.* **2001**, *34*, 640.

[5] For selected examples: (a) Knochel, P. *J. Am. Chem. Soc.* **1990**, *112*, 7431. (b) Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 486. (c) Nakamura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. *Org. Lett.* **2001**, *3*, 3137. (d) Matsubara, S.; Oshima, K.; Utimoto, K. *J. Organomet. Chem.* **2001**, *617−618*, 39. (e) Shimizu, M.; Kurahashi, T.; Hiyama, T. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1062.

[6] *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

[7] (a) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (b) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (c) Itami, K.; Koike, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 6957. (d) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (e) Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J. *J. Organomet. Chem.* **2002**, *653*, 105. (f) Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.*, in press.

[8] 2-PyMe$_2$Si group can also be used as a phase tag for acid/base extraction. Yoshida, J.; Itami, K. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1086.

[9] For the use of a removable directing group in metal-catalyzed reactions, see: (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (b) Breit, B. *Eur. J. Org. Chem.* **1998**, 1123. (c) Jun, C. H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (d) Buezo, N. D.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890. (e) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750.

[10] (a) Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J. *J. Org. Chem.* **2001**, *66*, 3970. (b) Itami, K.; Nokami, T.; Yoshida, J. *Tetrahedron* **2001**, *57*, 5045.

[11] Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2337.

[12] Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 8773.

[13] No detectable decomposition of **1** has been observed after extended (>1 month) exposure to air.

[14] Schreiber, S. L. *Science* **2000**, *287*, 1964.

[15] Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. For an exception: Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

[16] Mitchell, T. N. in ref 6, Chapter 4.

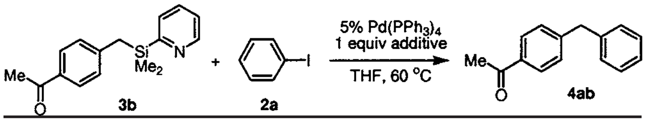
[17] For early works: (a) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542. (b) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (c) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. For reviews: (d) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (e) Hiyama, T. in ref 6, Chapter 10. (f) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 61. For selected recent examples: (g) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821. (h) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (i) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (j) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (k) ref 7b. (l) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439. (m) Hosoi, K.; Nozaki, K.; Hiyama, T. *Chem. Lett.* **2002**, 138. (n) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

[18] Abbreviations: TBAF = tetrabutylammonium fluoride. TASF = tris(diethylamino)sulfonium difluorotrimethylsilicate.

[19] In the literature, there is only one specific example of benzylic group transfer from silicon in a cross-coupling reaction. Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

Thus, we searched for the conditions of a second cross-coupling by using benzylic silane **3b** and iodobenzene (**2a**) as model substrates and $Pd(PPh_3)_4$ as a catalyst (Table 1).

Table 1. Effect of Additive on Pd-Catalyzed Cross-Coupling Reaction of **3b** with **2a**[a]



entry	additive	result
1	none	no reaction
2	KF	protodesilylation
3	TBAF	protodesilylation
4	TASF	protodesilylation
5	Ag_2O	**4ab** (55%) + **5** (27%)
6	AgO	**4ab** (52%) + **5** (12%)
7	AgOAc	**4ab** (40%) + **5** (16%)
8	$AgBF_4$	protodesilylation
9	AgF	protodesilylation
10	Ag_2S	no reaction
11	CuO	no reaction
12	Cu_2O	no reaction
13	Au_2O_3	no reaction

[a] Reaction conditions: **3b** (0.30 mmol), **2a** (0.36 mmol), $Pd(PPh_3)_4$ (5 mol %), additive (0.30 mmol), THF (2 mL), 60 °C, 8−48 h.

First we subjected several fluorides (KF, TBAF, and TASF[18]) to accelerate the rate-determining transmetalation step (entries 2−4). However, the addition of fluoride resulted in quantitative protodesilylation of **3b** in all cases. These results clearly implicate that the transmetalation of benzylic silane is much slower than the protodesilylation.

The obvious need for an alternative activation method of the $ArCH_2-SiMe_2Py$ bond led us to further investigations. After many scouting experiments, we found that the addition of Ag_2O[20] promoted the benzylic group transfer from **3b** to afford the corresponding diarylmethane **4ab** in 55% yield along with (2-pyridyl)benzene **5** (27%) (entry 5). It was found that the addition of AgO also promoted the desired cross-coupling reaction (entry 6). However, with the required reaction time (8 h for Ag_2O; 45 h for AgO) taken into account, Ag_2O may be the additive of choice for this cross-coupling reaction. The addition of AgOAc was found to be less effective than that of Ag_2O (entry 7). Other silver salts such as $AgBF_4$, AgF, and Ag_2S did not promote the reaction (entries 8−10). Interestingly, the addition of similar metal oxides such as CuO, Cu_2O, and Au_2O_3 did not exhibit any promoting effect (entries 11−13). From these results, it is obvious that silver salts that possess a relatively strong Ag−O bond are effective for the activation. Although it is clear that more experimental data must be accumulated to settle the mechanism of this activation, a plausible explanation is shown in Figure 1.

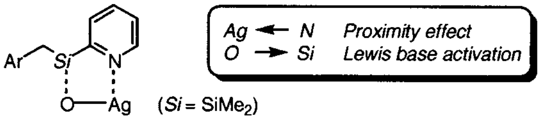
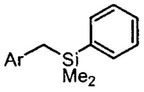


Figure 1. A plausible explanation for the activation of **3** with silver salts having a relatively strong Ag−O bond.

To see if the pyridyl group on silicon is necessary in this cross-coupling reaction, we subsequently subjected other related benzylic silanes. $PhMe_2SiCH_2Ar$ (**6**) and $(MeO)Me_2SiCH_2Ar$ (**7**) did not undergo cross-coupling with the aid of the $Pd(PPh_3)_4/Ag_2O$ catalyst, which indicates that the pyridyl group is also crucial for this cross-coupling reaction.[21] Moreover, the hydrochloride of $2\text{-}PyMe_2SiCH_2Ar$ (**8**) also failed to cross-couple with aryl iodide. Thus, it may be reasonable to assume that the beneficial effect of the pyridyl group is attributed to the coordinating (directing) ability of this group (proximity effect shown in Figure 1).



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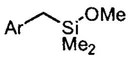

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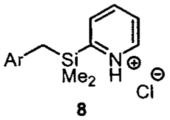

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Having established the conditions for the second cross-coupling reaction, we commenced our sequential cross-coupling reactions toward diarylmethanes (Scheme 3). Gratifyingly, **1** underwent efficient and selective integrated cross-coupling reactions with a wide array of electronically and structurally diverse aryl iodides in good yields (Scheme 3). As can be seen in the syntheses of **4ab** and **4ba**, the same diarylmethane could be prepared by interchanging the order of the addition of aryl iodides. The advantage is apparent as we can choose a high-yielding route by simply changing the addition order from the same set of reagents. The successful synthesis of diarylmethanes containing ketone and ester functionalities may be the advantage of our methods since

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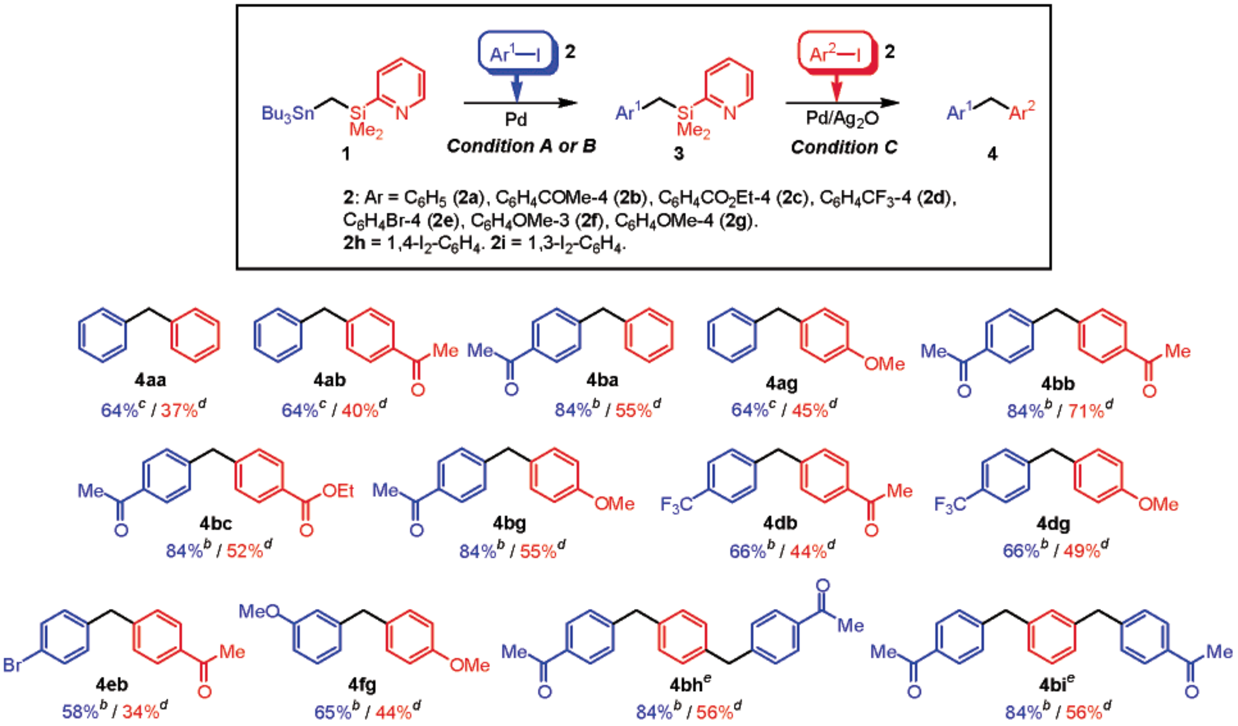
(20) For the use of Ag_2O in Pd-catalyzed cross-coupling reactions: (a) Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756. (b) Malm, J.; Björk, P.; Gronowitz, S.; Hörnfeldt, A. B. *Tetrahedron Lett.* **1992**, *33*, 2199. (c) Gutierrez, A. J.; Terhorst, T. J.; Matteucci, M. D.; Froehler, B. C. *J. Am. Chem. Soc.* **1994**, *116*, 5540. (d) Gilmann, T.; Weeber, T. *Synlett* **1994**, 649. (e) Chen, H. C.; Deng, M. Z. *J. Org. Chem.* **2000**, *65*, 4444. (f) ref 17i. (g) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213. (h) Mori, A.; Kondo, T.; Kato, T.; Nishihara, Y. *Chem. Lett.* **2001**, 286.

(21) Recently, Mori has discovered the beneficial effect of Ag_2O as an additive in cross-coupling reaction using silanols.[17i] One could conceive that the cross-coupling using benzylic (2-pyridyl)silane catalyzed by a $Pd(PPh_3)_4/Ag_2O$ system might also proceed through the intermediacy of benzylic silanol as in the case of alkenyl(2-pyridyl)silane as mentioned before.[7b] However, this idea seems unlikely because the pyridyl group is also transferred into the product (**5**). Moreover, we also found that (i) the yields and ratio of **4** and **5** were affected by the substituents on the pyridine ring of **3** and (ii) the cross-coupling reaction of $2\text{-}PySiMe_3$ does not take place with $Pd(PPh_3)_4/Ag_2O$ catalyst. From this presumptive evidence, we are currently assuming that (i) the pyridyl group is retained on silicon and promoting the benzylic group transfer as in Figure 1 and (ii) the transfer of the pyridyl group occurs from the $2\text{-}PyMe_2Si\text{-}X$ species generated after the benzylic group transfer from **3**. However, it is clear that more experimental data must be accumulated to elucidate the mechanism.

Scheme 3. Synthesis of Diarylmethane **4** by Sequentially Integrated Cross-Coupling Reactions of **1** with **2**[a]



[a] Percentage on the left (blue) refers to isolated yield of **3** obtained by the first cross-coupling reaction. Percentage on the right (red) refers to isolated yield of **4** obtained by the second cross-coupling reaction. [b]Condition A: **1** (0.5 mmol), **2** (0.55 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), $P(C_6F_5)_3$ (10 mol %), THF (2 mL), 50 °C, 24−48 h. [c]Condition B: **1** (0.5 mmol), **2** (0.55 mmol), $PdCl_2(CH_3CN)_2$ (5 mol %), $P(C_6H_4CF_3-4)_3$ (10 mol %), THF (2 mL), 70 °C, 24 h. [d]Condition C: **3** (0.30 mmol), **2** (0.36 mmol), $Pd(PPh_3)_4$ (5 mol %), Ag_2O (0.30 mmol), THF (2 mL), 60 °C, 24−48 h. [e]Compounds **2** (0.30 mmol) and **3** (0.46 mmol) were employed.

their incorporation is obviously difficult with the previously reported methods. Moreover, the selective arylation at the Ar−I functionality over the Ar−Br functionality is also feasible (**4eb**), and the resultant opportunity for further functionalization (cross-coupling reaction for example) should be useful for gaining more diversity. When diiodobenzenes (**2h** and **2i**) were employed, dibenzylbenzene derivatives (**4bh** and **4bi**) could indeed be obtained in good yields, which clearly indicates the further possibility of our strategy toward a diverse range of diarylmethane structures. Such simultaneous two-directional synthesis[22] should be useful for the construction of oligo-diarylmethane structures.

In conclusion, we have established a general, straightforward, and diversity-oriented synthesis of pharmacologically important diarylmethane structures through the sequentially integrated cross-coupling reactions using 2-$PyMe_2SiCH_2$-$SnBu_3$ (**1**) as an air-stable, storable, and versatile coupling platform. Since our strategy is not limited by the availability of reagents, the production and screening of a large number of diarylmethanes against the target of interest should be possible.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

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

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(22) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.