

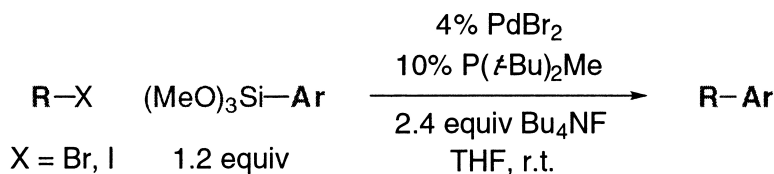
Communication

**Room-Temperature Hiyama Cross-Couplings
of Arylsilanes with Alkyl Bromides and Iodides**

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Room-Temperature Hiyama Cross-Couplings of Arylsilanes with Alkyl Bromides and Iodides

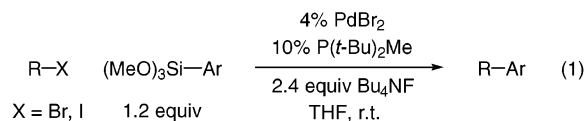
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The palladium-catalyzed Hiyama coupling of organosilicon compounds with organic halides and sulfonates is an important method for producing carbon–carbon bonds.^{1,2} Relative to some of the other organometallic reagents that are employed in cross-coupling processes, organosilicon compounds can be attractive due to their ease of handling and/or low toxicity. To date, nearly all studies of the Hiyama reaction have focused on couplings of C_{sp}²–X electrophiles (e.g., aryl and vinyl halides and triflates). In contrast, we are unaware of examples of palladium-catalyzed Hiyama cross-couplings of unactivated C_{sp}³–X electrophiles.³

During the past two years, we have reported that Pd/PR₃-based (PR₃ = a bulky trialkylphosphine, such as P(*t*-Bu)₂Me or PCy₃) catalyst systems can effect Suzuki reactions of alkyl bromides, chlorides, and tosylates.⁴ Building on our initial observations, Beller established that Pd/PR₃ can achieve Kumada–Murahashi couplings of alkyl chlorides,⁵ and we determined that Pd/PR₃ can catalyze Stille reactions of alkyl bromides.⁶ In this Communication, we describe the development of a method for accomplishing room-temperature Hiyama cross-couplings of alkyl bromides and iodides (eq 1), thereby expanding the scope of this important process and providing further evidence of the versatility of Pd/PR₃-based catalysts.



Perhaps not surprisingly, under the conditions that we have reported for achieving Suzuki reactions of alkyl bromides,^{4a,d} we observe essentially no cross-coupling of dodecyl bromide with (MeO)₃SiPh (Table 1, entries 1 and 2). Fluoride is a common activating agent for Hiyama couplings, presumably through formation of a more reactive hypervalent silicate intermediate. We have exploited Me₄NF as an activator for Pd/P(*t*-Bu)₂Me-catalyzed Stille reactions of alkyl bromides;⁶ unfortunately, these conditions were ineffective for the desired Hiyama cross-coupling (entry 3). However, after an extensive investigation of reaction parameters, we discovered that PdBr₂/P(*t*-Bu)₂Me/Bu₄NF efficiently couples the bromide with the organosilane at room temperature (entry 4).

Under otherwise identical conditions in the absence of PdBr₂ or P(*t*-Bu)₂Me, none of the Hiyama product is generated (Table 1, entries 5 and 6, respectively). Furthermore, PPh₃ is an ineffective ligand (entry 7). As we have observed for other cross-coupling reactions of C_{sp}³–X electrophiles,^{4,6} the efficiency of carbon–carbon bond formation is very dependent on the bulk of the trialkylphosphine. Thus, either increasing (P(*t*-Bu)₂Me → P(*t*-Bu)₃; entry 4 vs entry 8) or decreasing (P(*t*-Bu)₂Me → P(*i*-Pr)₂Me; entry 4 vs entry 9) the steric demand of the phosphine leads to a substantial drop in the yield of the coupling product. Interestingly, we have determined that a carbene ligand, IMes, can furnish a modestly effective catalyst (entry 10).

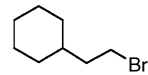
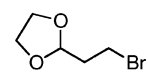
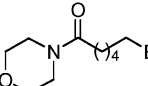
With PdBr₂/P(*t*-Bu)₂Me/Bu₄NF, we can achieve an array of Hiyama reactions of alkyl bromides in fairly good yield (65–81%;

Table 1. Effect of Reaction Parameters on the Hiyama Cross-Coupling of an Alkyl Bromide

entry	conditions	yield (%) ^a
1	4% Pd(OAc) ₂ , 8% PCy ₃ , K ₃ PO ₄ ·H ₂ O	0
2	5% Pd(OAc) ₂ , 10% P(<i>t</i> -Bu) ₂ Me, KO <i>t</i> -Bu	0
3	2.5% [(<i>π</i> -allyl)PdCl] ₂ , 15% P(<i>t</i> -Bu) ₂ Me, Me ₄ NF, 3 Å molec. sieves	0
4	4% PdBr₂, 10% P(<i>t</i>-Bu)₂Me, 2.4 equiv of Bu₄NF	81
5	10% P(<i>t</i> -Bu) ₂ Me, 2.4 equiv of Bu ₄ NF	0
6	4% PdBr ₂ , 2.4 equiv of Bu ₄ NF	0
7	4% PdBr ₂ , 10% PPh ₃ , 2.4 equiv of Bu ₄ NF	8
8	4% PdBr ₂ , 10% P(<i>t</i> -Bu) ₃ , 2.4 equiv of Bu ₄ NF	0
9	4% PdBr ₂ , 10% P(<i>i</i> -Pr) ₂ Me, 2.4 equiv of Bu ₄ NF	23
10	4% PdBr ₂ , 10% IMesHCl, 2.4 equiv of Bu ₄ NF ^b	36

^a Determined by GC versus a calibrated internal standard (average of two runs). ^b IMesHCl: 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride.

Table 2. Palladium-Catalyzed Hiyama Cross-Couplings of Alkyl Bromides at Room Temperature

entry	R-Br	yield (%) ^a	[HP(<i>t</i> -Bu) ₂ Me]BF ₄
1	C ₁₁ H ₂₃ Br	75	88
2		81	85
3	BnOCH ₂ CH ₂ CH ₂ CH ₂ Br	68	46
4		71	69
5	NC(CH ₂) ₃ Br	70	47
6	AcO(CH ₂) ₃ Br	65	42
7	EtO-C(=O)-(CH ₂) ₄ -Br	79	66
8		73	66

^a Isolated yield, average of two runs.

Table 2). As illustrated in the table, a spectrum of functional groups, including ethers, acetals, nitriles, esters, and amides, are compatible with the cross-coupling conditions.⁷

Because of the oxygen sensitivity of many trialkylphosphines, which can make their handling inconvenient, we have advocated the use of the corresponding air- and moisture-stable phosphonium

Table 3. Room-Temperature Hiyama Cross-Couplings of Alkyl Bromides with Arylsilanes

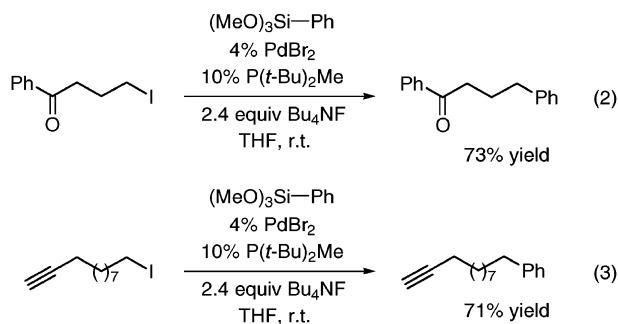
entry	R-Br	Ar	yield (%) ^a
1		<i>p</i> -anisyl	66
2		<i>p</i> -fluorophenyl	55
3		<i>o</i> -tolyl	59
4		2-naphthyl	67
5		<i>p</i> -anisyl	69
6		<i>p</i> -fluorophenyl	36
7		<i>o</i> -tolyl	76
8		2-naphthyl	70
9		<i>p</i> -anisyl	82
10		<i>p</i> -fluorophenyl	50
11		<i>o</i> -tolyl	72
12		2-naphthyl	84

^a Isolated yield, average of two runs.

salts as a convenient alternative.^{8,9} In the studies that we have previously reported, the phosphine and the salt generally furnish comparable reaction yields. As illustrated in Table 2, for our Hiyama cross-coupling protocol, replacement of P(*t*-Bu)₂Me with [HP(*t*-Bu)₂Me]BF₄ still leads to formation of the desired products, although in more modest yields for reactions of functionalized alkyl bromides (e.g., entries 3, 5, and 6).

In addition to exploring the scope of this coupling method with respect to the alkyl bromide (Table 2), we have also examined the effect of variations in the structure of the arylsilane. As illustrated in Table 3, an electronically and sterically diverse array of organosilanes undergo cross-coupling in the presence of PdBr₂/P(*t*-Bu)₂Me/Bu₄NF. Among the substrates shown, electron-poor arylsilanes are the least suitable reaction partners (entries 2, 6, and 10).

We have established that this method is not limited to Hiyama cross-couplings of alkyl bromides; the same protocol is also effective for reactions of iodides. Thus, PdBr₂/P(*t*-Bu)₂Me/Bu₄NF catalyzes the coupling of functionalized alkyl iodides in good isolated yield at room temperature (eqs 2 and 3).



In summary, we have developed the first method for achieving Hiyama couplings of unactivated alkyl bromides and iodides. The desired carbon-carbon bond formation proceeds under mild conditions (room temperature) with good functional-group tolerance. Our current efforts are directed at further expanding the scope of palladium-catalyzed couplings of C_{sp}³-X electrophiles.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For a review of the Hiyama reaction, see: Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 10. See also: Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58–61.
- (2) For some recent developments in Hiyama cross-coupling chemistry, see: (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835–846. (b) Itami, K.; Nokami, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 5600–5601 and references therein.
- (3) For an overview of the difficulty of achieving coupling reactions of C_{sp}³-X electrophiles, see: Cardenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387. See also: Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187–3204.
- (4) (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100. (b) Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947. (c) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912. (d) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.
- (5) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059.
- (6) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718–3719.
- (7) (a) Air-stable PdBr₂(P(*t*-Bu)₂Me)₂ is equally effective. (b) The reaction does not appear to be sensitive to the presence of small amounts of water, but it is sensitive to the Pd:P(*t*-Bu)₂Me ratio. (c) During the course of the reaction, Pd(P(*t*-Bu)₂Me)₂ is the predominant phosphorus-containing species. (d) These conditions are not effective for the coupling of the following: more hindered alkyl bromides and iodides with PhSi(OMe)₃ (<2% yield for the reaction of cyclohexyl bromide or cyclohexyl iodide); (allyl)Si(OMe)₃ or (vinyl)Si(OMe)₃ with *n*-dodecyl bromide (<2% yield); alkyl chlorides or alkyl tosylates with PhSi(OMe)₃ (5% and 15% yield for *n*-dodecyl chloride and *n*-dodecyl tosylate, respectively). (e) Under these conditions, other arylsilicon compounds (e.g., PhSiCl₃ and PhSiMe₂-Cl) do not cross-couple with *n*-dodecyl bromide (<2% yield).
- (8) For examples in which phosphines and their corresponding phosphonium salts can be used interchangeably in palladium-catalyzed coupling processes, see: (a) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298. (b) References 4d and 6.
- (9) Strem Chemicals catalog numbers: P(*t*-Bu)₂Me (#15-1020); [HP(*t*-Bu)₂Me]BF₄ (#15-1023).

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