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Communications to the Editor

Room-Temperature Alkyl−Alkyl Suzuki Cross-Coupling of Alkyl Bromides that Possess β Hydrogens

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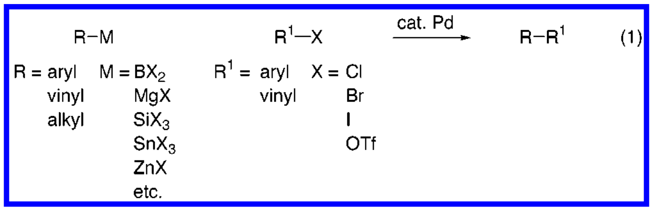
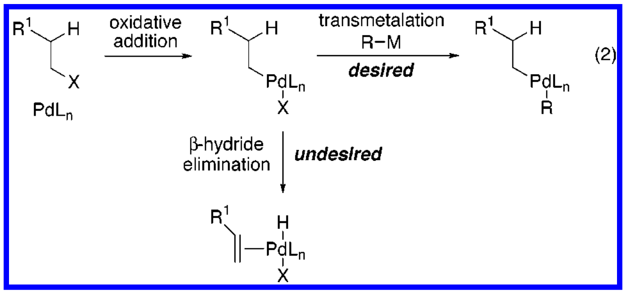
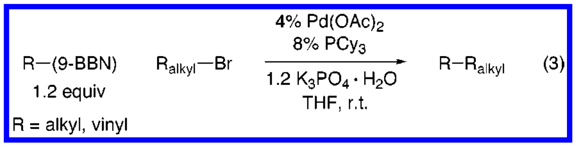
Palladium-catalyzed couplings of organometallic reagents with aryl and vinyl electrophiles (eq 1) have become classic methods for generating carbon−carbon bonds.[1] Not only sp^2-hybridized but also sp^3-hybridized organometallics can be employed. On the other hand, palladium-catalyzed couplings in which the halide/triflate is sp^3-hybridized are rather uncommon.[1−3]



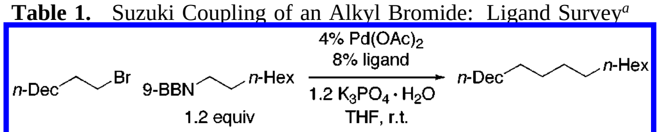
Slow oxidative addition of alkyl halides/triflates to palladium and facile β-hydride elimination (eq 2) are two likely causes for this comparative lack of success. Indeed, to date most palladium-catalyzed couplings of alkyl electrophiles have involved substrates that are activated toward oxidative addition and that lack β hydrogens (e.g., benzyl halides). For the Suzuki reaction in particular, among alkyl halides/triflates, only iodides have been shown to couple with any generality ($Pd(PPh_3)_4$, 60 °C; 45−71% yield).[4,5] On the other hand, to the best of our knowledge, there are no examples of Suzuki reactions of alkyl bromides that possess β hydrogens. In this communication, we describe a method for achieving Suzuki cross-couplings of a variety of alkyl bromides under surprisingly mild conditions (room temperature; eq 3).

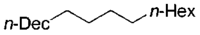




Like alkyl halides/triflates, aryl chlorides were long considered to generally be unsuitable partners in palladium-catalyzed couplings, due in part to a reluctance to undergo oxidative addition.[6] In view of recent reports that the use of bulky, electron-rich phosphines can lead to palladium catalysts effective for reactions of aryl chlorides,[7] we decided to pursue the possibility that such ligands might also be useful in couplings of alkyl halides. As a test reaction, we chose to examine the unprecedented Suzuki cross-coupling of an alkyl bromide that contains β hydrogens (1-bromododecane) with an alkylborane (*B*-*n*-octyl-9-BBN).

Table 1. Suzuki Coupling of an Alkyl Bromide: Ligand Survey[a]



entry	ligand[a]	% yield after 16 h (by GC) 	 
1	PCy_3	85	<2
2	PPh_3	<2	<2
3	P(2-furyl)$_3$	<2	<2
4	P(*o*-tol)$_3$	<2	14
5	P(2,4,6-trimethoxyphenyl)$_3$	<2	31
6	dppf	<2	12
7	binap	<2	<2
8	$P(OPh)_3$	<2	<2
9	$AsPh_3$	<2	<2
10	P(*t*-Bu)$_3$	<2	21
11	P(*n*-Bu)$_3$	9	27
12	dcpe	<2	21
13	P(*i*-Pr)$_3$	68	6

[a] In the case of bidentate ligands, 4% of the ligand was used.

We were pleased to discover that $Pd(OAc)_2/PCy_3$, in the presence of $K_3PO_4{\cdot}H_2O$, serves as an efficient catalyst for this alkyl−alkyl coupling process (Table 1, entry 1). Among the ligands that we have investigated, PCy_3 is uniquely effective (entries 2−13). Under otherwise identical conditions, we observe no cross-coupling in the presence of triarylphosphines (monodentate: entries 2−5; bidentate: entries 6−7), a phosphite (entry 8), and an arsine (entry 9). Other electron-rich trialkylphosphines are also markedly less useful than PCy_3 (cone angle: 170°).[8] For

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(1) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.

(2) (a) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187−3204. (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018−3020.

(3) Knochel has described a nickel-catalyzed method for effecting sp^3−sp^3 couplings of primary alkyl iodides and organozinc reagents: (a) Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723−2725. (b) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387−2390. (c) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544−3553.

(4) For reviews of the Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2.

(5) (a) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694. Under these conditions, "alkyl bromides [...] never provide the corresponding coupling products." (b) For couplings of iodocyclopropanes, for which β-hydride elimination is precluded, see: Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718−8719. Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809−2812. Martin, S. F.; Dwyer, M. P. *Tetrahedron Lett.* **1998**, *39*, 1521−1524.

(6) (a) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; pp 193−226. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

(7) For leading references, see: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

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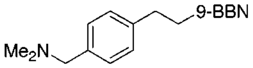
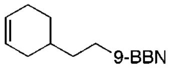
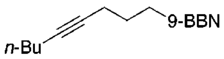
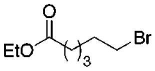
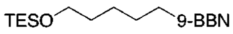
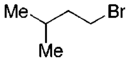
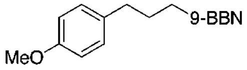
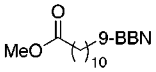
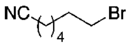
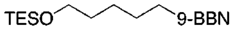
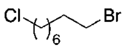
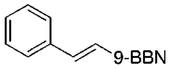
Table 2. Room-Temperature Suzuki Cross-Coupling of Alkyl Bromides (eq 3): Reaction Scope

entry	R–(9-BBN)[a]	R_{alkyl}–Br	yield (%)[b]
1	*n*-Hex–(9-BBN)	*n*-Dodec–Br	93
2		*n*-Dodec–Br	78[c]
3		*n*-Dodec–Br	85
4			58
5			72
6		*n*-Hex–Br	80
7			81
8			81
9		*n*-Dodec–Br	66

[a] Prepared by hydroboration with 9-BBN of the corresponding alkene/alkyne and used without purification. [b] Isolated yield, average of two runs. [c] 1.05 equiv of R-(9-BBN) was used.

example, more hindered P(*t*-Bu)$_3$ (entry 10; cone angle: 182°), less hindered P(*n*-Bu)$_3$ (entry 11; cone angle: 132°), and bidentate dcpe (entry 12) afford little or none of the desired product. In fact, among the other trialkylphosphines that we have examined, only P(*i*-Pr)$_3$ furnishes a significant amount of the target compound (entry 13; cone angle: 160°).

We have established that Pd(OAc)$_2$/PCy$_3$/K$_3$PO$_4$•H$_2$O catalyzes the room-temperature Suzuki cross-coupling of an array of β-hydrogen-bearing alkyl bromides with alkyl- and vinylboranes (Table 2).[9,10] The mildness of these conditions for coupling alkyl bromides contrasts with the higher temperatures employed in Suzuki's reactions of alkyl iodides (60 °C).[5a] As shown in entry 1, Pd(OAc)$_2$/PCy$_3$ cross-couples unfunctionalized partners in excellent yield (93%). The process tolerates a wide range of functional groups, including amines, alkenes, esters, alkynes, ethers, and nitriles (entries 2–7). Furthermore, alkyl bromides can be coupled selectively in the presence of alkyl chlorides (entry 8), and vinylboranes can serve as coupling partners (entry 9).

As is the case for Suzuki reactions of sp^2-hybridized halides/triflates, our cross-couplings of alkyl bromides are not highly moisture-sensitive. In fact, water (from K$_3$PO$_4$•H$_2$O) is an important component of the reaction system—essentially no coupling occurs when anhydrous K$_3$PO$_4$, rather than K$_3$PO$_4$•H$_2$O, is employed. By adding 1 equiv of water to reactions with anhydrous K$_3$PO$_4$, we obtain the reactivity afforded by K$_3$PO$_4$•H$_2$O.[11]

By ^{11}B NMR spectroscopy, we have investigated the role of water in our Suzuki cross-coupling system. When we introduce anhydrous K$_3$PO$_4$ into a THF solution of *B*-*n*-hexyl-9-BBN, the ^{11}B NMR spectrum does not change (δ 78). On the other hand, when we mix *B*-*n*-hexyl-9-BBN with K$_3$PO$_4$•H$_2$O (1:1), the resonance at δ 78 is replaced by a signal at δ 4, which corresponds to the hydroxyl-bound "ate" complex.[12,13] For Suzuki reactions, such four-coordinate boron adducts are believed to play a key role in transmetalation ($R-PdL_n-X + R^1{}_3B(OH)^- \rightarrow R-PdL_n-R^1$).[4,14]

In summary, we have developed the first method for achieving Suzuki cross-couplings of alkyl bromides that contain β hydrogens, under surprisingly mild conditions (room temperature). This work represents a significant expansion in the scope of the Suzuki reaction. We are currently exploring other palladium-catalyzed couplings of alkyl halides and triflates.

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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.

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(8) (a) For a compilation of cone angles, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1–7. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313–348.

(9) General procedure: In air, Pd(OAc)$_2$ (9.0 mg, 0.040 mmol), PCy$_3$ (22.4 mg, 0.080 mmol), and K$_3$PO$_4$•H$_2$O (276 mg, 1.20 mmol) are added to a reaction vessel equipped with a stir bar. The vessel is sealed with a septum and purged with argon for 15 min. The trialkylborane (1.2 mmol; 0.50 M solution in THF) and then the alkyl bromide (1.0 mmol) are added by syringe. The resulting heterogeneous reaction mixture is stirred vigorously at room temperature for 16–24 h. At the conclusion of the reaction, the mixture is diluted with Et$_2$O, filtered through silica gel with copious washings (Et$_2$O), concentrated, and then purified by flash column chromatography.

(10) Notes: (a) Dioxane and DME can also be employed as solvents. (b) Carbonates may be used as the base. (c) A 1:1 ratio of Pd:PCy$_3$ provides comparable results. (d) Pd(OAc)$_2$(PCy$_3$)$_2$ (Neilan, J. P.; Laine, R. M.; Cortese, N.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 3455-3460) and commercially available, air-sensitive Pd(PCy$_3$)$_2$ are comparable in effectiveness to Pd(OAc)$_2$/PCy$_3$. We chose to focus our study on Pd(OAc)$_2$/PCy$_3$ because both components are commercially available and easily handled in air. (e) Under these conditions, boronic acids, secondary alkyl bromides, and secondary alkyl-9-BBN reagents are not suitable coupling partners.

(11) With <1 equiv of water, decreased activity is observed. With 1, 4, 7, and 10 equiv of water, essentially identical results are obtained.

(12) (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470. (b) Köster, R.; Seidel, G.; Wrackmeyer, B. *Chem. Ber.* **1992**, *125*, 617–625.

(13) As expected, we have determined that KOH can be employed as the base in alkyl–alkyl Suzuki cross-coupling reactions (e.g., 1-bromododecane couples with *B*-*n*-hexyl-9-BBN in 92% yield).

(14) According to ^{31}P NMR, during the course of the cross-coupling reaction, Pd(PCy$_3$)$_2$ (δ 40) is the predominant phosphorus-containing species.