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Boronic Acids: New Coupling Partners in Room-Temperature Suzuki Reactions of Alkyl Bromides. Crystallographic Characterization of an Oxidative-Addition Adduct Generated under Remarkably Mild Conditions

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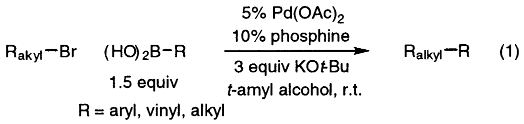
Although tremendous progress has been made in recent years in the development of effective methods for palladium-catalyzed cross-couplings of aryl and vinyl electrophiles,[2] comparable success has not yet been achieved for reactions of alkyl electrophiles, particularly unactivated (e.g., not allylic or benzylic) substrates that possess β hydrogens.[3−6] During the past few years, we have described catalyst systems that can accomplish Suzuki cross-couplings[7] of alkyl bromides, chlorides, and tosylates with alkyl-(9-BBN) derivatives.[4b−d]

While the generally straightforward synthesis of alkyl-(9-BBN) derivatives via the hydroboration of olefins makes them attractive coupling partners, they suffer from the drawback of not being readily handleable in air or commercially available. In contrast, a wide array of boronic acids, which are air-stable, can be purchased.[8] As a consequence of these practical considerations, the ability to employ boronic acids in Suzuki cross-couplings of alkyl electrophiles represents a very important objective.[9] In this Communication we describe the progress that we have made toward realizing this goal; specifically, we report a catalyst system that effects room-temperature cross-couplings of alkyl bromides with a range of aryl-, vinyl-, and alkylboronic acids (eq 1). In addition, we present mechanistic work that establishes that oxidative addition of an alkyl bromide to a Pd(0) complex can occur under remarkably mild conditions (0 °C) to generate a stable adduct that can be characterized by X-ray crystallography.



$$R_{alkyl}{-}Br \quad \underset{\substack{1.5\ equiv \\ R\,=\,aryl,\ vinyl,\ alkyl}}{(HO)_2B{-}R} \quad \xrightarrow[\substack{3\ equiv\ KO\textit{t}\text{-}Bu \\ \textit{t}\text{-}amyl\ alcohol,\ r.t.}]{\substack{5\%\ Pd(OAc)_2 \\ 10\%\ phosphine}} \quad R_{alkyl}{-}R \qquad (1)$$

Unfortunately, the conditions that we had found to be optimal for Suzuki couplings of alkyl bromides with 9-BBN-derived reagents are ineffective for reactions of boronic acids (Table 1, entry 1; <2%). We surveyed a broad spectrum of parameters, and an illustrative subset of our findings is provided in Table 1. For example, we explored the use of a variety of Lewis basic additives, and we determined that KO*t*-Bu is the best among those that we have examined (entries 1−4). The choice of solvent has a significant impact on the efficiency of the cross-coupling; employing either dioxane or *tert*-amyl alcohol, rather than THF, leads to a marked enhancement in yield (entries 5 and 6; ~63%).[10]

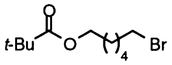
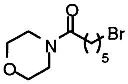
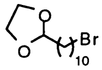
Not surprisingly, the structure of the phosphine plays an important role in determining the outcome of the reaction. The use of PCy_2Et, which is less sterically demanding than PCy_3, leads to a lower yield of the cross-coupling product (entry 6 vs entry 7; 63% → 39%). Although very hindered $P(t\text{-}Bu)_3$ is completely ineffective (entry 8; <2%), less bulky $P(t\text{-}Bu)_2Et$ furnishes a detectible quantity of the target compound (entry 9; 4%). Remarkably, a further decrease in the size of the phosphine—to commercially available $P(t\text{-}Bu)_2Me$[11]—provides a dramatic increase in reactivity (entry 10; 85%).[4d,12]

Table 1. Suzuki Cross-Coupling of *n*-OctBr with $PhB(OH)_2$ (5% $Pd(OAc)_2$, 10% ligand, rt): Effect of Additive, Solvent, and Ligand

entry	additive	solvent	ligand	yield (%)[a]
1[b]	$K_3PO_4{\cdot}H_2O$	THF	PCy_3	<2
2	KF	THF	PCy_3	<2
3	NaOMe	THF	PCy_3	3
4	KO*t*-Bu	THF	PCy_3	11
5	KO*t*-Bu	dioxane	PCy_3	64
6	KO*t*-Bu	*tert*-amyl alcohol	PCy_3	63
7	KO*t*-Bu	*tert*-amyl alcohol	PCy_2Et	39
8	KO*t*-Bu	*tert*-amyl alcohol	$P(t\text{-}Bu)_3$	<2
9	KO*t*-Bu	*tert*-amyl alcohol	$P(t\text{-}Bu)_2Et$	4
10	**KO*t*-Bu**	***tert*-amyl alcohol**	$\mathbf{P(\mathit{t}\text{-}Bu)_2Me}$	**85**

[a] Average of two runs. Determined by GC versus a calibrated internal standard. [b] Conducted according to the procedure in ref 4b.

Table 2. $Pd/P(t\text{-}Bu)_2Me$-Catalyzed Suzuki Cross-Couplings of Alkyl Bromides with Boronic Acids (eq 1)

entry	$R_{alkyl}{-}Br$	R	yield (%)[a]	
			$P(t\text{-}Bu)_2Me$	$[HP(t\text{-}Bu)_2Me]BF_4$
1	*n*-Oct–Br	Ph	87	90
2		4-(MeS)C_6H_4	68	66
3	$BnO{-}(CH_2)_6{-}Br$	4-(MeO)C_6H_4	85	84
4	$TBSO{-}(CH_2)_6{-}Br$	4-(F_3C)C_6H_4	63	67
5		*o*-tolyl	71	76
6		1-naphthyl	97	93
7		mesityl	89	91
8	$NC{-}(CH_2)_6{-}Br$	(*E*)-1-hexenyl	85	87
9	*n*-Dodec−Br	*n*-Hex	66	62

[a] Isolated yield.

These conditions have proved to be useful for coupling a range of alkyl bromides with an array of boronic acids (Table 2). Thus, the catalyst system tolerates a wide variety of functional groups, including esters (entry 2), ethers and thioethers (entries 2−5), amides (entry 5), acetals (entry 6), and nitriles (entry 8). An electronically diverse set of boronic acids can be coupled (entries 2−4),[13] as can hindered substrates (entries 5−7). Aryl- as well as vinyl- (entry 8) and unhindered alkyl- (entry 9) boronic acids are suitable partners in this process.[14]

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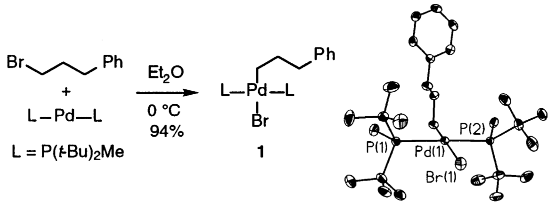
Because, like most trialkylphosphines, P(t-Bu)$_2$Me is susceptible to oxidation and can therefore be inconvenient to handle, we decided to determine if the corresponding phosphonium salt, [HP(t-Bu)$_2$Me]BF$_4$, which is air- and moisture-stable and will soon be commercially available,[15] can be used in place of the phosphine in these cross-couplings.[16] Not surprisingly, on the basis of our prior work, the two reagents are interchangeable, furnishing nearly identical yields of the desired product (Table 2).

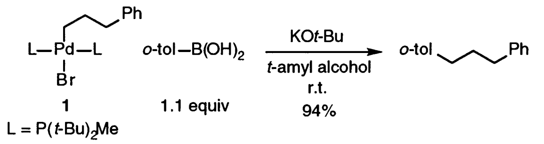
The reluctance of unactivated alkyl halides to oxidatively add to Pd(0) is generally believed to be one of the barriers that impedes the development of efficient methods to cross-couple this class of substrates.[3] In view of the report of Suzuki that Pd(PPh$_3$)$_4$-catalyzed coupling reactions of alkyl iodides require heating to 60 °C,[4a] the ability of Pd(OAc)$_2$/P(t-Bu)$_2$Me to cross-couple more challenging alkyl bromides at room temperature is noteworthy. Indeed, we have discovered that alkyl bromides oxidatively add to Pd(P(t-Bu)$_2$Me)$_2$ at 0 °C (eq 2).[17,18]



(2)

Moreover, adduct **1** is sufficiently stable to be crystallographically characterized (eq 2). Thus, because of the high reactivity of Pd/P(t-Bu)$_2$Me toward oxidative addition, it is possible to generate complex **1** under conditions that are sufficiently mild that β-hydride elimination, which is believed to be the other major impediment to effective cross-coupling of alkyl halides, does not occur.[19]

Finally, we have established that adduct **1** is chemically competent; upon treatment with a boronic acid, cross-coupling occurs to furnish the anticipated product (eq 3).[20]



(3)

In summary, we have described the first palladium- or nickel-catalyzed method for coupling a diverse set of boronic acids and unactivated alkyl electrophiles (bromides) that possess β hydrogens. In view of the well-established utility of the Suzuki reaction and the important advantages of boronic acids over other coupling partners, we anticipate that this work may lead to new strategies for applying Suzuki cross-couplings in organic synthesis. On the mechanistic side, we have determined that Pd(P(t-Bu)$_2$Me)$_2$ undergoes oxidative addition under surprisingly mild conditions; the resulting adduct is sufficiently stable toward β-hydride elimination that it can be structurally characterized, and it is a chemically competent intermediate in the cross-coupling process, reacting with a boronic acid to generate the expected product. Ongoing studies are directed toward enhancing our understanding of the origin of the unusual reactivity of this catalyst, as well as expanding the scope of these coupling reactions.[21]

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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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(1) Correspondence concerning the X-ray crystal structure should be directed to I.D.H.
(2) (a) *Topics in Current Chemistry*, Vol. 219; Miyaura, N., Ed.; Springer-Verlag: New York, 2002. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
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(4) Palladium-catalyzed Suzuki couplings. (a) Alkyl iodides: Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691−694. (b) Alkyl bromides: Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (c) Alkyl chlorides: Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945−1947. (d) Alkyl tosylates: Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.*, in press.
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(7) For reviews of the Suzuki reaction, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2.
(8) For example, Frontier Scientific and Aldrich each sell more than 100 boronic acids.
(9) We are aware of only one report of a Suzuki cross-coupling of a boronic acid with an alkyl electrophile that bears β hydrogens: Yang, G.-S.; Xie, X.-j.; Zhao, G.; Ding, Y. *J. Fluorine Chem.* **1999**, *98*, 159−161 (reactions of fluorinated alkyl iodides).
(10) We decided to focus on *tert*-amyl alcohol, because the reaction components are more soluble in this solvent.
(11) Strem Chemicals: catalog #15−1020.
(12) Notes. (a) Other ligands that are ineffective: P(o-tol)$_3$, AsPh$_3$, P(t-Bu)$_2$-OH, and 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene). (b) Pd$_2$(dba)$_3$, [(π-allyl)PdCl]$_2$, and PdCl$_2$(cod) are as effective as Pd(OAc)$_2$.
(13) In preliminary studies, heteroarylboronic acids, as well as certain electron-deficient arylboronic acids, have not proved to be suitable coupling partners.
(14) Notes. (a) In the presence of 1 equiv of H$_2$O, the cross-coupling proceeds in comparable yield. (b) We have not attempted to individually maximize the turnover number (TON) for these cross-coupling reactions. However, for the coupling of 1-bromooctane with phenylboronic acid, we have determined that use of 0.5% Pd(OAc)$_2$ and 1.0% of P(t-Bu)$_2$Me or [HP(t-Bu)$_2$Me]BF$_4$ furnishes an 81−84% yield of the desired product, corresponding to a TON of ~160. (c) We generally observe lower yields for reactions of more hindered substrates. To date, we have not achieved couplings of secondary alkyl bromides or secondary alkylboronic acids.
(15) Strem Chemicals: catalog #15−1023.
(16) For examples of the interchangeability of trialkylphosphines and their corresponding phosphonium salts in an array of processes, see: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295−4298.
(17) Notes: (a) Pd(P(t-Bu)$_2$Me)$_2$ catalyzes the room-temperature coupling of alkyl bromides with boronic acids. (b) Consistent with the results in Table 1 (entries 9 vs 10), whereas Pd(P(t-Bu)$_2$Me)$_2$ reacts quickly (100% conversion within 30 min at room temperature) with Br(CH$_2$)$_3$Ph to predominantly form the oxidative-addition adduct, Pd(P(t-Bu)$_2$Et)$_2$ reacts much more slowly (20% conversion after 20 h at room temperature) to exclusively generate the product of β-hydride elimination.
(18) For a recent study of the oxidative addition of an *aryl* bromide to a Pd(0) complex at 25−70 °C, see: Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346−9347.
(19) Upon warming to 50 °C, complex **1** undergoes β-hydride elimination.
(20) Adduct **1** also serves as a *catalyst* for the coupling of alkyl bromides with boronic acids at room temperature.
(21) The conditions described in eq 1 are not suitable for Suzuki cross-couplings of boronic acids with alkyl chlorides.

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