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Versatile Catalysts for the Suzuki Cross-Coupling of Arylboronic Acids with Aryl and Vinyl Halides and Triflates under Mild Conditions

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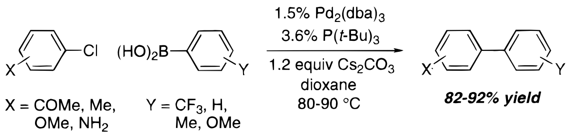
Abstract: Through the use of $Pd_2(dba)_3/P(t\text{-}Bu)_3$ as a catalyst, a wide range of aryl and vinyl halides, including chlorides, undergo Suzuki cross-coupling with arylboronic acids in very good yield, typically at room temperature; through use of $Pd(OAc)_2/PCy_3$, a diverse array of aryl and vinyl triflates react cleanly at room temperature. Together, these two catalyst systems cover a broad spectrum of commonly encountered substrates for Suzuki couplings. Furthermore, they display novel reactivity patterns, such as the selective cross-coupling by $Pd_2(dba)_3/P(t\text{-}Bu)_3$ of an aryl chloride in preference to an aryl triflate, and they can be used at low loading, even for reactions of aryl chlorides. Preliminary mechanistic work indicates that a palladium monophosphine complex is the active catalyst in the cross-coupling of aryl halides.

Introduction

The palladium-catalyzed Suzuki cross-coupling of aryl halides and aryl triflates with arylboronic acids to form biaryls has emerged as an extremely powerful tool in organic synthesis.[1] Compounds that contain a biaryl linkage have a diverse spectrum of applications, ranging from materials science[2] to pharmaceuticals. For example, with respect to pharmaceuticals, the biaryl group is a key feature in the sartan family of drugs for high blood pressure[3,4] and in important natural products, such as the vancomycin antibiotics.[5] Although the Suzuki cross-coupling is most commonly used to synthesize biaryls, reactions of vinyl halides/triflates with arylboronic acids, to generate styrene derivatives, are an important component of the broad utility of the process. The innocuous nature of boronic acids, which are generally nontoxic and thermally, air-, and moisture-stable, is a practical advantage of the Suzuki reaction, relative to many other cross-coupling processes.

There are a large number of parameters in a Suzuki reaction — palladium source, ligand, additive, solvent, temperature, etc. — and there are, correspondingly, a large number of protocols for accomplishing the transformation, the choice of which depends on the structure of the reactants.[1] Clearly, the development of a general protocol that could reliably effect cross-coupling, independent of the structure of the reactants, would be worthwhile.

In 1998, we discovered that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyzes the Suzuki cross-coupling of a wide array of aryl chlorides and arylboronic acids (eq 1).[6] The high reactivity of this system toward typically unreactive aryl chlorides suggested to us that it might serve as a very versatile catalyst, under mild conditions,[7] for Suzuki cross-couplings of other substrates. In this report, we describe significant progress toward substantiating that possibility.



(1)

Results and Discussion

Suzuki Cross-Coupling of Aryl Chlorides. By way of background, at the time that we initiated our studies of palladium chemistry, one of the most important limitations of the Suzuki cross-coupling reaction was the poor reactivity of aryl chlorides, which are perhaps the most attractive family of aryl halide substrates due to their low cost and their ready availability.[8,9] In fact, prior to 1998, reports of efficient palladium-catalyzed Suzuki couplings of aryl chlorides were limited to reactions of

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(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Miyaura, N. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1998; Vol. 6, pp 187−243. (d) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2. (e) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303.

(2) For example, see: *Step Growth Polymers for High-Performance Materials*; Hedrick, J. L., Labadie, J. W., Eds.; ACS Symp. Ser. 624; American Chemical Society: Washington, DC, 1996.

(3) The key step in the synthesis of Losartan is a Suzuki cross-coupling reaction: Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151−8156.

(4) For reviews on sartans and Losartan, see: (a) Birkenhager, W. H.; de Leeuw, P. W. *J. Hypertens.* **1999**, *17*, 873−881. (b) Goa, K. L.; Wagstaff, A. J. *Drugs* **1996**, *51*, 820−845.

(5) For a review, see: Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152.

(6) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388.

(7) "There are few examples of ambient temperature Suzuki-type biaryl couplings": ref 1b.

(8) The low reactivity of aryl chlorides in cross-coupling reactions is generally ascribed to their reluctance to oxidatively add to Pd(0). Aryl halides that bear an electron-withdrawing group oxidatively add to Pd(0) more readily than do the corresponding unsubstituted aryl halides. For discussions, see: Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062.

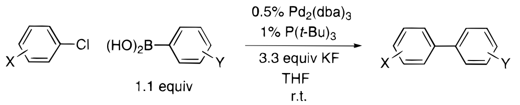
(9) Stürmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307−3308.

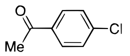
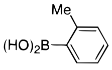
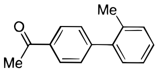
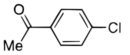
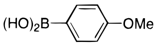
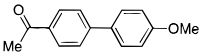
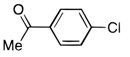
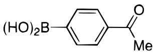
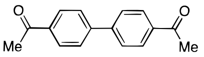
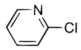
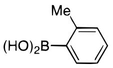
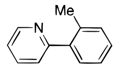
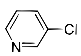
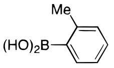
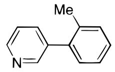
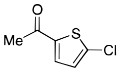
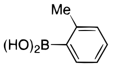
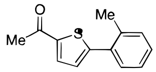
10.1021/ja0002058 CCC: $19.00

activated substrates (i.e., heteroaryl chlorides and aryl chlorides that bear an electron-withdrawing group), which generally only proceeded at high temperature (75−130 °C).[10,11] Since 1998, several research groups have described electron-rich ligands for palladium that overcome this limitation, specifically, aryldialkylphosphines (Buchwald;[12] Bei and Guram[13]), P(t-Bu)$_3$ (Fu[6,14]), and *N*-heterocyclic carbenes (Nolan;[15] Herrmann[16]).[17,18] With respect to Suzuki couplings of aryl chlorides that proceed at room temperature, the only successful catalyst systems reported to date are those of Buchwald (very general) and of Kocovsky (one example).[18]

In our initial communication, we reported a general method for the Suzuki cross-coupling of aryl chlorides and arylboronic acids in the presence of a Pd$_2$(dba)$_3$/P(t-Bu)$_3$ catalyst system, with Cs$_2$CO$_3$ as the base (80−90 °C in dioxane; eq 1);[6,19] toward the end of that study, we discovered that CsF is also a highly effective base.[20,21] We have since investigated the replacement of CsF by less expensive KF,[12b,c] and we have found that Suzuki reactions are even more rapid in the presence of KF. The P(t-Bu)$_3$:Pd is an important parameter: whereas use of a 1:1 ratio furnishes a very active catalyst, use of a 2:1 ratio leads to an extremely slow reaction.[22] Among palladium sources, Pd$_2$(dba)$_3$ is superior to Pd(OAc)$_2$.[23]

Table 1. Suzuki Cross-Couplings of Activated Aryl Chlorides at Room Temperature



Entry	(Hetero)Aryl Chloride	Boronic Acid	Product	Yield[a]
1				99%
2				93%
3				84%
4				97%
5[b]				77%
6				99%

[a] Isolated yield, average of two runs. [b] 1.5% Pd$_2$(dba)$_3$ and 3% P(t-Bu)$_3$ were used.

With this improved method, we can cleanly effect Suzuki cross-couplings of activated aryl chlorides under significantly milder conditions (room temperature) and with lower catalyst loadings (0.5% Pd$_2$(dba)$_3$ and 1% P(t-Bu)$_3$) than we had previously reported (Table 1; cf. eq 1).[24−26] Thus, 4′-chloroacetophenone cross-couples efficiently with sterically hindered, with electron-rich, and with electron-poor arylboronic acids (entries 1−3, Table 1).[27] Chloro-substituted pyridines and thiophenes, which have the potential to bind to palladium through nitrogen or sulfur, are also suitable substrates for room-temperature Suzuki reactions (entries 4−6, Table 1).

More vigorous conditions are typically required to effect Suzuki cross-couplings of electron-rich aryl chlorides (70−100 °C; Table 2). The use of a slightly higher P(t-Bu)$_3$:Pd ratio (1.5:1) at higher reaction temperatures appears to stabilize the catalyst and to decrease the precipitation of palladium metal.[28] Under these conditions, electron-rich aryl chlorides, including 4-chloroaniline, couple efficiently with both aryl- and alkylboronic acids (entries 1−3, Table 2).[29]

Room-Temperature Suzuki Cross-Coupling of Aryl Bromides. There are relatively few examples of Suzuki cross-couplings of aryl bromides that proceed at room temperature.[30]

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[10] (a) Gronowitz, S.; Hörnfeldt, A.-B.; Kristjansson, V.; Musil, T. *Chem. Scr.* **1986**, *26*, 305−309. (b) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052−2055. (c) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273−2276. (d) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743−746. (e) Janietz, D.; Bauer, M. *Synthesis* **1993**, 33−34. (f) Uemura, M.; Nishimura, H.; Kamikawa, K.; Nakayama, K.; Hayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 1909−1912. (g) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849. (h) Zhang, H.; Chan, K. S. *Tetrahedron Lett.* **1996**, *37*, 1043−1044. (i) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 2993−2996. (j) Shen, W. *Tetrahedron Lett.* **1997**, *38*, 5575−5578.

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[12] (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

[13] (a) Bei, X.; Crevier, T.; Guram, A. S.; Jandeleit, B.; Powers, T. S.; Turner, H. W.; Uno, T.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 3855−3858. (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797−6803.

[14] For other applications of P(t-Bu)$_3$ in palladium-catalyzed couplings of aryl chlorides, see: (a) Amination: Nishiyama, M.; Yamamoto, T.; Koie, Y.; *Tetrahedron Lett.* **1998**, *39*, 617−620. Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (b) Heck reaction: Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123-2132. (c) Reaction of ketone enolates: Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (d) Reaction of alkoxides: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840. (e) Amidocarbonylation: Kim, J. S.; Sen, A. *J. Mol. Catal. A* **1999**, *143*, 197−201. (f) Stille reaction: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413.

[15] Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

[16] (a) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96. (b) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **1999**, *585*, 348−352.

[17] See also: Firooznia, F.; Gude, C.; Chan, K.; Satoh, Y. *Tetrahedron Lett.* **1998**, *39*, 3985−3988.

[18] See also: Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714−7715.

[19] For an application of this method, see: Firooznia, F.; Gude, C.; Chan, K.; Marcopulos, N.; Satoh, Y. *Tetrahedron Lett.* **1999**, *40*, 213-216.

[20] See footnote 9 of ref 6.

[21] (a) Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961−964. (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

[22] For an explanation of this observation, see the section that describes mechanistic work on Suzuki cross-couplings of aryl chlorides and aryl bromides (vide infra).

[23] For our original optimization work, see ref 6.

[24] In the absence of P(t-Bu)$_3$, no coupling between 4′-chloroacetophenone and *o*-tolylboronic acid is observed at room temperature (cf. Table 1, entry 1).

[25] Under these nonaqueous conditions, hydrolytic cleavage of the B−C bond is not a concern. For discussions of this issue, see ref 1.

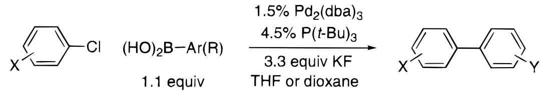
[26] Dioxane is also a suitable solvent.

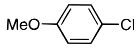
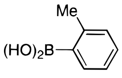
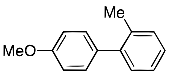
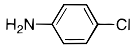
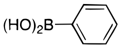
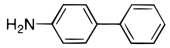
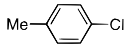
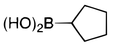
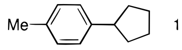
[27] Cross-coupling can also be effected at 0 °C, although the reaction is slower.

[28] However, as we have observed for Suzuki cross-couplings of electron-poor aryl chlorides, reactions of electron-rich aryl chlorides proceed very slowly when a 2:1 ratio of P(t-Bu)$_3$:Pd is employed.

[29] The need for a higher temperature for the reaction of cyclopentylboronic acid may be due to the slower rate of transmetalation by alkylboron compounds, relative to arylboron compounds. For example, see ref 21b.

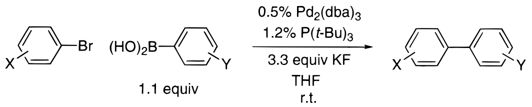
Table 2. Suzuki Cross-Couplings of Unactivated Aryl Chlorides

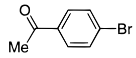
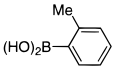
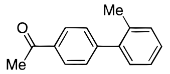
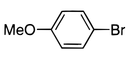
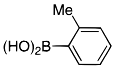
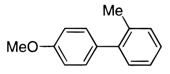
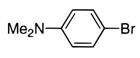
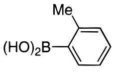
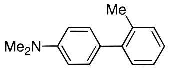
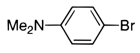
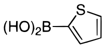
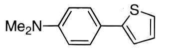
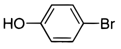
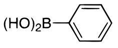
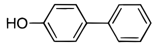
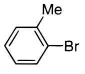
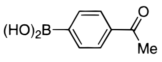
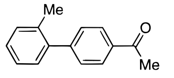
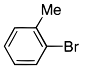
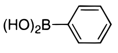
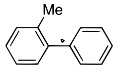
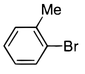
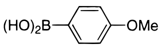
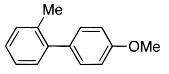


Entry	Aryl Chloride	Boronic Acid	Product	Temp.	Yield[a]
1				70 °C	88%
2				90 °C	82%
3				100 °C	75%

[a] Isolated yield, average of two runs.

Table 3. Suzuki Cross-Couplings of Aryl Bromides at Room Temperature



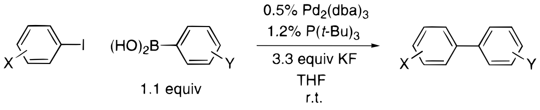
Entry	Aryl Bromide	Boronic Acid	Product	Yield[a]
1				98%
2				95%
3				98%
4				99%
5				97%
6				94%
7				92%
8				98%

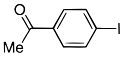
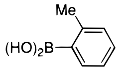
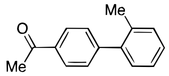
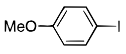
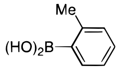
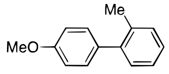
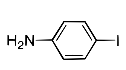
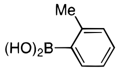
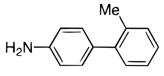
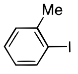
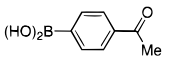
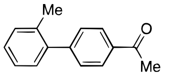
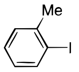
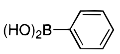
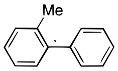
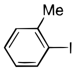
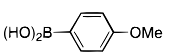
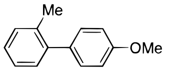
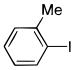
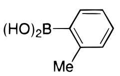
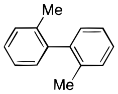
[a] Isolated yield, average of two runs.

As a consequence, Buchwald's recent report of a general method for accomplishing this process represents a notable advance.[12]

We have determined that we can effect room-temperature Suzuki cross-couplings of a broad spectrum of aryl bromides and arylboronic acids using the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system that we have described for the coupling of aryl chlorides.[31] As illustrated in Table 3, this catalyst furnishes the desired biaryls in excellent yields (92−99%). Thus, aryl bromides that are electron-poor or electron-rich couple cleanly with sterically hindered *o*-tolylboronic acid (entries 1−3, Table 3). Particularly noteworthy are the reactions of very electron-rich 4-bromo-*N*,*N*-dimethylaniline (entries 3−4, Table 3) and 4-bromophenol (entry 5, Table 3), which proceed to completion in 0.3−5 h.

Table 4. Suzuki Cross-Couplings of Aryl Iodides at Room Temperature



Entry	Aryl Iodide	Boronic Acid	Product	Yield[a]
1				96%
2				97%
3[b]				95%
4[c]				96%
5				97%
6				94%
7				98%

[a] Isolated yield, average of two runs. [b] 2.4% $P(t\text{-}Bu)_3$ was used. [c] 1.1 equiv of $AgBF_4$ was added.

The $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system is also tolerant of electronic variation in the arylboronic acid component. For example, 2-bromotoluene reacts cleanly at room temperature with electron-poor, electron-neutral, and electron-rich boronic acids (entries 6−8, Table 3).[32]

Room-Temperature Suzuki Cross-Coupling of Aryl Iodides. Aryl iodides are usually the most reactive aryl halides in palladium-catalyzed cross-coupling reactions.[33] We have established that, under the conditions that we have developed, a wide array of Suzuki reactions of aryl iodides with arylboronic acids proceed in excellent yield at room temperature (Table 4; 94−98%). Thus, electronically diverse aryl iodides react uniformly cleanly with sterically hindered *o*-tolylboronic acid (entries 1−3, Table 4), and electronically diverse arylboronic acids couple efficiently with 2-iodotoluene (entries 4−6, Table 4).[34] Di-ortho-substituted biaryls are also readily accessible (entry 7, Table 4).

Surprisingly, under these conditions, cross-couplings of aryl iodides are slower than the corresponding reactions of aryl bromides. This observation suggests that, in the case of aryl

---

(30) (a) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (b) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123−15134. (c) Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406−1408. (d) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437−14450. (e) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095−2096. (f) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (g) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744. (h) Bussolari, J. C.; Rehborn, D. C. *Org. Lett.* **1999**, *1*, 965−967.

(31) Room temperature Suzuki cross-couplings of aryl bromides can also be accomplished with $Pd(OAc)_2$ as the palladium source and PCy_3 as the phosphine.

(32) Because these reaction mixtures are heterogeneous, the relative times that are necessary for the cross-couplings to proceed to completion may not reflect the relative intrinsic reactivities of the substrates.

(33) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysis;* Wiley: New York, 1995. (c) Farina, V. In *Comprehensive Organometallic Chemistry 2*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 3.4. (d) Reference 1.

(34) For the Suzuki reaction illustrated in entry 4, cross-coupling was slow in the absence of $AgBF_4$. Use of $(n\text{-}Bu)_4NCl$ or $(n\text{-}Bu)_4NF$ as an additive was also effective.

iodides, oxidative addition may not be the turnover-limiting step of the catalytic cycle.[35]

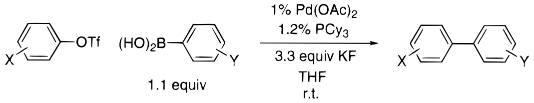
Room-Temperature Suzuki Cross-Coupling of Aryl Triflates. Because they are easily synthesized from readily available phenols, aryl triflates are an important family of substrates for cross-coupling reactions.[36] In the case of Suzuki reactions, aryl triflates are known to be less reactive than the corresponding iodides and bromides,[37] and elevated reaction temperatures have been employed in essentially all of the reactions of aryl triflates that have been reported to date.[38]

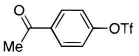
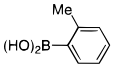
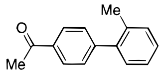
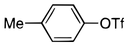
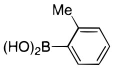
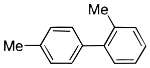
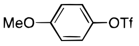
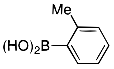
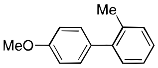
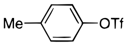
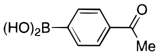
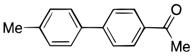
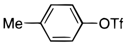
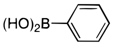
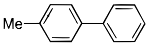
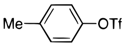
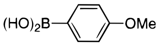
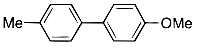
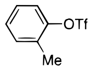
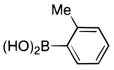
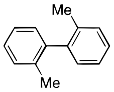
In our initial studies, we attempted to apply the $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ catalyst system to the coupling of 4-methoxyphenyl triflate and *o*-tolylboronic acid. Surprisingly, we observed no appreciable reaction at room temperature or even after 8 h at 60 °C. The addition of KBr[37] or the use of $Pd(OAc)_2$ did not significantly improve the coupling process. We decided to explore other trialkylphosphines as ligands, based on speculation that the larger steric demand of a triflate relative to a halide might require the use of a less bulky, but nevertheless electron-rich, phosphine. We were pleased to discover that when we employ a $Pd(OAc)_2$/PCy_3 catalyst system, the Suzuki reaction of 4-methoxyphenyl triflate and *o*-tolylboronic acid proceeds to completion within 6 h at room temperature (1% $Pd(OAc)_2$, 1.2% PCy_3, 3.3 equiv of KF).[39,40]

Under these conditions, we can efficiently cross-couple a broad spectrum of aryl triflates and arylboronic acids in quite good yield (Table 5). Variation in the electronic nature of the aryl triflate and of the arylboronic acid is well-tolerated (entries 1−6, Table 5), as is the presence of ortho substituents (entry 7, Table 5; 5% $Pd(OAc)_2$).[41]

Suzuki Cross-Coupling of Sterically Hindered Substrates. Although there have been a number of reports of Suzuki reactions of aryl halides that form hindered biaryls (i.e., two or more ortho substituents), couplings of this type can be difficult, requiring vigorous conditions and furnishing modest yields.[1] In particular, Suzuki cross-couplings that efficiently generate biaryls with three ortho substituents are not commonplace, especially with aryl chlorides as substrates.[12c,42]

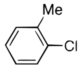
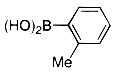
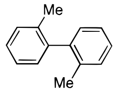
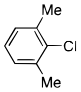
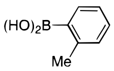
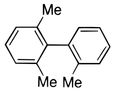
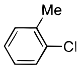
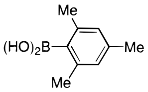
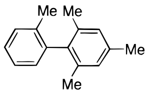
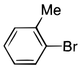
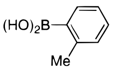
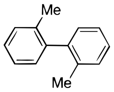
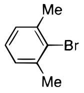
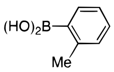
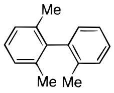
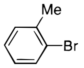
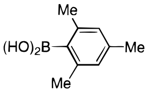
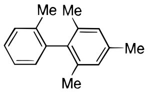
Table 5. Suzuki Cross-Couplings of Aryl Triflates at Room Temperature



Entry	Aryl Triflate	Boronic Acid	Product	Yield[a]
1				96%
2				95%
3				98%
4				97%
5				97%
6				94%
7				82%[b]

[a] Isolated yield, average of two runs. [b] 5% $Pd(OAc)_2$/6% PCy_3 was used.

Table 6. Suzuki Cross-Couplings To Form Sterically Hindered Biaryls

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 3.6% $P(t\text{-}Bu)_3$ 60 °C	93%
2				1.5% $Pd_2(dba)_3$ 4.2% PCy_3 60 °C	89%[c]
3				1.5% $Pd_2(dba)_3$ 4.5% PCy_3 90 °C	93%[d]
4				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$ r.t.	96%
5				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$ r.t.	98%
6				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$ r.t.	97%

[a] Standard conditions: 1.0 equiv of aryl halide. 1.1 equiv of boronic acid, 3.3 equiv of KF, THF. [b] Isolated yield, average of two runs. [c] Product contained 4% 2.2′-dimethylbiphenyl. [d] 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, and toluene as solvent; the product from one run contained 5% mesitylene.

We have established that we can synthesize sterically hindered biaryls from a variety of precursors in good yield (Table 6, 89−98%) using the palladium sources ($Pd_2(dba)_3$ or $Pd(OAc)_2$) and the phosphines ($P(t\text{-}Bu)_3$, PCy_3) that we have described above. For example, aryl chlorides serve as excellent substrates for Suzuki cross-couplings that generate disubstituted (entry 1, Table 6) and trisubstituted biaryls (entries 2 and 3, Table 6). The reaction tolerates substrates that bear two substituents ortho to either the chlorine (entry 2, Table 6) or the boronic acid (entry 3, Table 6), and it proceeds under relatively mild conditions and with moderate catalyst loadings. While our standard system for Suzuki reactions of aryl chlorides ($Pd_2(dba)_3$/$P(t\text{-}Bu)_3$) can

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(35) For further discussion, see the section that describes mechanistic work on Suzuki cross-couplings of aryl iodides (vide infra).

(36) For reviews of the chemistry of vinyl and aryl triflates, see: (a) Ritter, K. *Synthesis* **1993**, 735−762. (b) Stang, P. J.; Hanack, M.; Subrmanian, L. R. *Synthesis* **1982**, 85−126.

(37) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

(38) (a) For a report of a room-temperature cross-coupling of phenyl triflate with 9-octyl-9-BBN, see ref 37. (b) For a report of a room-temperature cross-coupling of a vinylboronic acid with an *activated* aryl triflate (bearing a 4-(ethoxycarbonyl) group), see: Torrado, A.; Lopez, S.; Alvarez, R.; de Lera, A. R. *Synthesis* **1995**, 285−293.

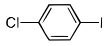
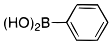
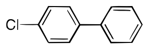
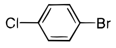
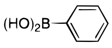
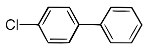
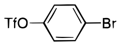
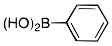
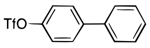
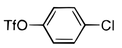
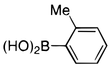
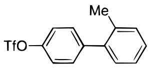
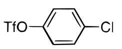
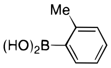
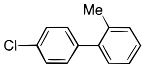
(39) Cone angle of PCy_3: 170°. Cone angle of $P(t\text{-}Bu)_3$: 182°. For an extensive compilation of phosphine cone angles, see: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1−7.

(40) Notes: (1) Use of $Pd_2(dba)_3$/PCy_3 leads to a slower cross-coupling reaction. (2) It is likely that *o*-tolylboronic acid is reducing Pd(II) to catalytically active Pd(0); consistent with this hypothesis, we observe the formation of ~1% of the homocoupled product, 2,2′-dimethylbiphenyl. For a mechanistic study and leading references, see: Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346−2352. (3) No cross-coupling is observed in the absence of PCy_3. (4) Use of 1% $Pd(OAc)_2$/2.4% PCy_3, instead of 1% $Pd(OAc)_2$/1.2% PCy_3, leads to a slower reaction. (5) $Pd(OAc)_2(PCy_3)_2$ and $Pd(PCy_3)_2$ are also effective cross-coupling catalysts.

(41) Under other, more vigorous conditions for Suzuki reactions, hydrolysis of the triflate is sometimes observed. For example, see: (a) Coudret, C.; Mazenc, V. *Tetrahedron Lett.* **1997**, *38*, 5293−5296. (b) Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665−1668.

(42) (a) For the cross-coupling of a heteroaryl chloride, see refs 10d and 10h. (b) For a nickel-catalyzed cross-coupling, see: Galland, J.-C.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323−2326.

Table 7. Chemoselective Suzuki Cross-Couplings

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield[b]
1				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$	98%
2				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$	97%
3				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$	98%
4				1.5% $Pd_2(dba)_3$ 3.0% $P(t\text{-}Bu)_3$	95%
5				3.0% $Pd(OAc)_2$ 6.0% PCy_3	87%

[a] Standard conditions: 1.0 equiv of aryl halide, 1.0 equiv of boronic acid, 3.0 equiv of KF, THF, room temperature. [b] Isolated yield.

also be employed for the synthesis of trisubstituted biaryls (entries 2 and 3, Table 6), we have found the use of less sterically hindered PCy_3 to be advantageous for this particular application.

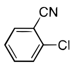
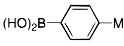
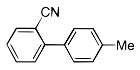
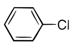
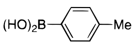
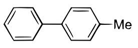
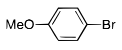
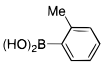
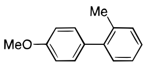
Suzuki cross-couplings of aryl bromides also furnish disubstituted (entry 4, Table 6) and trisubstituted (entries 5 and 6, Table 6) biaryls in excellent yield. These reactions proceed cleanly at room temperature in the presence of 0.5% $Pd_2(dba)_3$/1.2% $P(t\text{-}Bu)_3$. To the best of our knowledge, there are only two examples of room-temperature couplings of unactivated aryl bromides to produce di-ortho-substituted biaryls,[12c,30b] and there is no precedent for room-temperature coupling of an unactivated aryl bromide to produce a tri-ortho-substituted biaryl.[43]

Relative Reactivity of Aryl Chlorides, Bromides, Iodides, and Triflates: Chemoselective Suzuki Cross-Coupling. For substrates that bear more than one halide/triflate, the ability to effect selective monofunctionalization through Suzuki cross-coupling can be a powerful tool.[44] For previously described palladium catalysts, the general order of reactivity is the following: I > Br $\gtrsim$ OTf $\gg$ Cl.[1]

We have established that with the $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ catalyst system it is possible to carry out highly selective monofunctionalizations of difunctionalized arenes (Table 7). Not surprisingly, an iodo and a bromo group react in preference to a chloro group, providing the chlorinated biaryl in excellent yield (entries 1 and 2, Table 7). In the case of 4-bromophenyltriflate, we observe very selective reaction of the bromide in the presence of the triflate (entry 3, Table 7).[45,46]

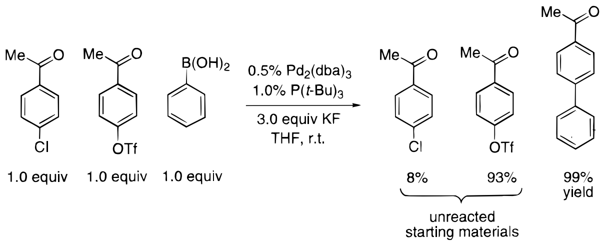
In view of the low reactivity of aryl triflates toward the $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ catalyst system, we speculated that it might even be possible to effect a selective Suzuki coupling of a chloride in the presence of a triflate. To the best of our knowledge, there is no precedent in *any* palladium-catalyzed cross-coupling process for greater reactivity toward an aryl chloride than toward an aryl triflate. As illustrated in entry 4 of Table 7, *$Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ does indeed react with the chloride of 4-chlorophenyltriflate in preference to the triflate, with excellent selectivity*. In contrast, $Pd(OAc)_2$/PCy_3 exhibits the conventional pattern of reactivity (entry 5, Table 7).[47] Thus, simply through appropriate choice of catalyst, one can selectively cross-couple an aryl chloride in the presence of an aryl triflate, or vice versa.

Table 8. Suzuki Cross-Couplings with Low Catalyst Loadings

Entry	Aryl Halide	Boronic Acid	Product	Conditions[a]	Yield[b]
1				0.05% $Pd_2(dba)_3$ 0.1% $P(t\text{-}Bu)_3$ r.t., 24 h	99%
2				0.005% $Pd_2(dba)_3$ 0.01% $P(t\text{-}Bu)_3$ 90 °C, 25 h	97%
3				0.05% $Pd_2(dba)_3$ 0.12% $P(t\text{-}Bu)_3$ 100 °C, 43 h	92%
4				0.005% $Pd_2(dba)_3$ 0.012% $P(t\text{-}Bu)_3$ r.t., 48 h	98%

[a] Standard conditions: 1.0 equiv of aryl halide, 1.1 equiv of boronic acid, 3.3 equiv of KF, dioxane or THF. [b] Isolated yield, average of two runs.

The competition experiment illustrated in eq 2 provides further evidence for the remarkable selectivity of $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ for chlorides over triflates. These data indicate that k_{Ar-Cl}/k_{Ar-OTf} exceeds 20 for this reaction.[48,49]



(2)

Suzuki Cross-Coupling with Low Catalyst Loadings. We developed the Suzuki cross-coupling methods reported above (Tables 1−5) with the goal of providing general and reliable procedures that should work on the first try for a large majority of the substrates that one might encounter; we therefore did not attempt to optimize reaction conditions for each substrate pair. Of course, in an industrial setting, cost considerations provide a strong impetus for optimizing a particular process, especially with respect to minimizing the amount of catalyst that is used. To provide a sense for the turnover numbers that are achievable with $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$, we have examined Suzuki cross-couplings of several substrates with low catalyst loadings (Table 8).

We chose to explore the Suzuki reaction of 2-chlorobenzonitrile with *p*-tolylboronic acid, due to the fact that the product, 2-cyano-4′-methylbiphenyl, is a key intermediate in the synthesis of angiotensin II receptor antagonists that are used for the treatment of hypertension.[50] At room temperature this cross-coupling proceeds in 99% yield with a 0.1% loading of palladium (0.05% $Pd_2(dba)_3$), corresponding to ∼1000 turnovers (entry 1, Table 8). An even higher turnover number can be

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(43) Thus far, our attempts to efficiently produce biaryls that bear four ortho substituents have been unsuccessful.

(44) For example, see: (a) Kawada, K.; Arimura, A.; Tsuri, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 973−975. (b) Hird, M.; Gray, G. W.; Toyne, K. J. *Mol. Cryst. Liq. Cryst.* **1991**, *206*, 187−204.

(45) The $Pd(OAc)_2$/PCy_3 catalyst system also reacts with the bromide of 4-bromophenyltriflate with very high selectivity. For conditions under which $Pd(PPh_3)_4$ furnishes high selectivity, see ref 37 (in contrast with ref 41b).

(46) A competition experiment between 4-ethylbromobenzene (1 equiv) and 4-methylphenyltriflate (1 equiv) for reaction with phenylboronic acid (1 equiv) using $Pd(OAc)_2$/PCy_3 as the catalyst resulted in exclusive coupling with the aryl bromide; in contrast, only modest selectivity for the bromide was reported for a Suzuki reaction catalyzed by $Pd(PPh_3)_4$ (ref 37).

(47) In the presence of 3.0% $Pd(OAc)_2$/3.6% PCy_3, low selectivity is observed.

(48) The phosphine, not the palladium source, controls chloride/triflate selectivity. A competition experiment conducted with $Pd(OAc)_2$/$P(t\text{-}Bu)_3$ yielded results similar to the experiment conducted with $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$.

(49) Use of 1% $Pd(OAc)_2$/1.2% PCy_3 leads to predominant Suzuki cross-coupling of the aryl triflate, rather than the aryl chloride.

(50) For leading references, see: Goubet, D.; Meric, P.; Dormoy, J.-R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516−4518.

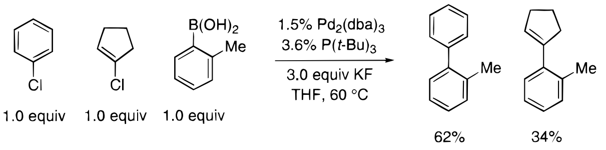
achieved at higher temperature; thus, at 90 °C, the Suzuki reaction goes to completion with just 0.01% Pd, corresponding to nearly 10,000 turnovers (entry 2, Table 8; 97% yield). This is the highest turnover number that we are aware of for a Suzuki cross-coupling of an aryl chloride.[51,52]

We can also achieve high turnover with other substrates. For example, we observe a turnover number of ~900 at 100 °C for the Suzuki reaction of chlorobenzene and *p*-tolylboronic acid (entry 3, Table 8). With respect to aryl bromides, we can cross-couple electron-rich, deactivated *p*-bromoanisole with *o*-tolylboronic acid at room temperature in 98% yield with 0.01% Pd, corresponding to a turnover number of ~10,000 (entry 4, Table 8).[53]

Suzuki Cross-Coupling of Vinyl Halides and Vinyl Triflates. Vinyl halides/triflates are another important family of cross-coupling partners in the Suzuki reaction;[1] couplings of this class of compounds have played a key role in the synthesis of a diverse array of natural products, including palytoxin,[54] rutamycin,[55] and epothilone.[56] In light of our success in developing general and mild catalyst systems for coupling aryl halides/triflates, we decided to pursue the application of these methods to Suzuki reactions of the corresponding vinyl compounds. As shown in Table 9, we have found that it is indeed possible to efficiently cross-couple vinyl halides/triflates with boronic acids, under conditions very similar to those employed for the corresponding aryl compounds.

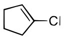
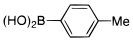
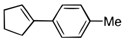
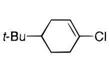
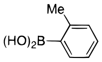
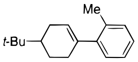
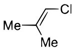
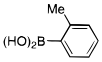
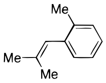
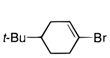
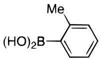
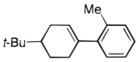
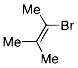
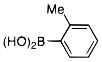
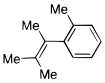
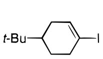
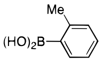
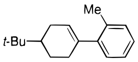
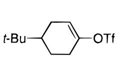
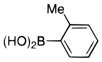
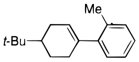
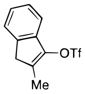
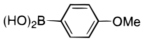
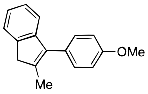
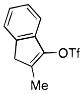
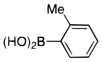
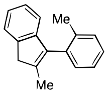
For vinyl chlorides, $Pd_2(dba)_3/P(t\text{-}Bu)_3$ has proved to be an excellent catalyst, furnishing the desired coupling products in good yield at 50−60 °C. Thus, as illustrated in entries 1 and 2 of Table 9, olefins that bear a substituent geminal to the chloro group react cleanly under these conditions. The cross-coupling of 1-chloro-2-methylbutene establishes that the reaction also tolerates a substituent cis to the chloride (entry 3). To the best of our knowledge, these data represent the first examples of Suzuki couplings of unactivated vinyl chlorides: previous reports have been limited to activated substrates wherein the vinyl chloride is conjugated to an electron-withdrawing group.[57]

In other palladium-catalyzed cross-coupling processes, vinyl chlorides have proved to be significantly more reactive than aryl chlorides.[33] To investigate the relative reactivity of aryl and vinyl chlorides in Suzuki reactions catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3$, we conducted a competition experiment between chlorobenzene and 1-chlorocyclopentene for *o*-tolylboronic acid (eq 3). Interestingly, we observed that $Pd_2(dba)_3/P(t\text{-}Bu)_3$ reacts preferentially with chlorobenzene. As far as we know, this is the first palladium-based cross-coupling catalyst that reacts more readily with an aryl chloride than with a vinyl chloride.



(3)

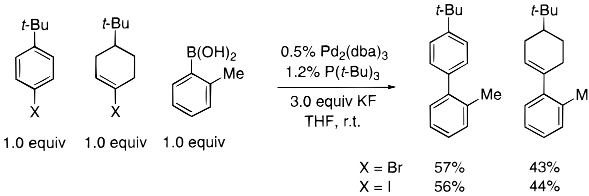
Table 9. Suzuki Cross-Couplings of Vinyl Halides and Vinyl Triflates

Entry	Vinyl Halide/Triflate	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 3.6% $P(t\text{-}Bu)_3$ 50 °C	87%
2				1.5% $Pd_2(dba)_3$ 3.6% $P(t\text{-}Bu)_3$ 60 °C	91%
3				1.5% $Pd_2(dba)_3$ 3.6% $P(t\text{-}Bu)_3$ 50 °C	76%
4				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$ r.t.	98%
5				0.5% $Pd_2(dba)_3$ 1.2% $P(t\text{-}Bu)_3$ r.t.	95%
6				2.5% $Pd_2(dba)_3$ 6.0% $P(t\text{-}Bu)_3$ r.t.	91%
7				1.0% $Pd(OAc)_2$ 1.2% PCy_3 r.t.	96%
8				1.0% $Pd(OAc)_2$ 1.2% PCy_3 r.t.	96%
9				4.0% $Pd(OAc)_2$ 4.8% PCy_3 r.t.	69%

[a] Standard conditions: 1.0 equiv of vinyl halide/triflate, 1.1 equiv of boronic acid, 3.3 equiv of KF, THF. [b] Isolated yield, average of two runs.

Just as $Pd_2(dba)_3/P(t\text{-}Bu)_3$ can couple aryl bromides or iodides in very good yield at room temperature (Tables 3 and 4), under identical conditions it can also couple vinyl bromides or iodides, including sterically hindered 2-bromo-3-methylbutene (entries 4−6, Table 9). It is important to note that there have been several other examples of room-temperature Suzuki reactions of unactivated (albeit less bulky) vinyl bromides.[58]

We have conducted competition experiments between aryl bromides/iodides and their vinyl counterparts. As with chlorides (eq 3), we have found that aryl bromides/iodides react more rapidly than do vinyl bromides/iodides (eq 4), by a small margin. To the best of our knowledge, this reactivity pattern is unique to the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system.[1]



(4)

Vinyl triflates are a particularly useful class of cross-coupling substrates because of their ready synthesis from carbonyl compounds.[1,36] Due to the potential lability of vinyl triflates, the availability of mild reaction conditions can be critical for efficient coupling of sensitive substrates. We have established

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(51) (a) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849. (b) References 12b and 12c.

(52) This corresponds to producing 5.7 g of 2-cyano-4′-methylbiphenyl with 1.4 mg of $Pd_2(dba)_3$.

(53) To the best of our knowledge, 950 is the highest turnover number that has been reported for a room-temperature Suzuki coupling of an aryl bromide (with an activated aryl bromide, 4-bromoacetophenone; ref 30e).

(54) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-i.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525−7530.

(55) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459.

(56) Su, K.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757−759.

(57) (a) Satoh, N.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3471−3473. (b) Boland, G. M.; Donnelly, D. M. X.; Finet, J.-P.; Rea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2591−2597.

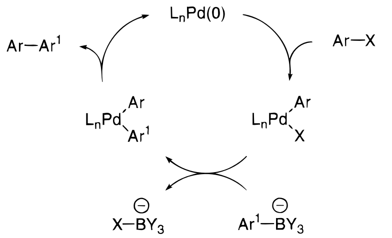
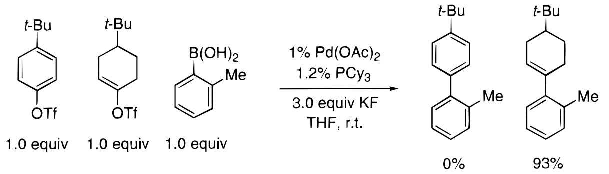


Figure 1. Outline of the catalytic cycle for the Suzuki cross-coupling reaction.

that, as with aryl triflates, the combination of $Pd(OAc)_2$ and PCy_3 furnishes good yields for room-temperature Suzuki reactions of vinyl triflates (entries 7−9, Table 9).[59] Even extremely hindered substrates cross-couple under these conditions,[60] although the reaction requires a higher catalyst loading and proceeds in somewhat lower yield if the boronic acid is also bulky (entries 8 and 9, Table 9). As far as we know, there are only scattered examples of Suzuki couplings of vinyl triflates that occur at room temperature.[61]

In a $Pd(OAc)_2/PCy_3$-catalyzed competition experiment between an aryl triflate and a vinyl triflate for reaction with *o*-tolylboronic acid, we observe the "typical" pattern of aryl vs vinyl reactivity: greater reactivity of the vinyl compound (eq 5; >100:1 selectivity).[62] This result further highlights the unusual reactivity of $Pd_2(dba)_3/P(t\text{-}Bu)_3$ toward aryl halides.



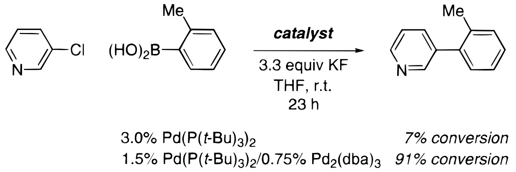
(5)

Mechanistic Study of the Suzuki Cross-Coupling of Aryl Chlorides and Aryl Bromides. An outline of the commonly accepted mechanism for the Suzuki cross-coupling reaction is illustrated in Figure 1.[1] To gain some insight into the $Pd_2(dba)_3/P(t\text{-}Bu)_3$ catalyst system, we have pursued a series of NMR and reactivity studies.

In our initial investigation, we focused on determining what forms upon mixing $P(t\text{-}Bu)_3$ with $Pd_2(dba)_3$. We found through ^{31}P and ^1H NMR studies that, for $P(t\text{-}Bu)_3$:Pd ratios between 0.5 and 1.5:1, $Pd(P(t\text{-}Bu)_3)_2$[63] is the only identifiable phosphine-containing species that is present (^{31}P: δ 85.6; THF-d_8).[64] Furthermore, in the presence of excess phosphine ($P(t\text{-}Bu)_3$:Pd = 2−4:1), only $Pd(P(t\text{-}Bu)_3)_2$ and free $P(t\text{-}Bu)_3$ are detected. Thus, the bisphosphine adduct is favored over the monophosphine and the trisphosphine across a wide range of $P(t\text{-}Bu)_3$:Pd ratios.[65]

When we monitor the Suzuki cross-coupling of 3-chloropyridine and *o*-tolylboronic acid by ^{31}P NMR (2.5% $Pd_2(dba)_3$/5% $P(t\text{-}Bu)_3$; THF-d_8), essentially the only species that we observe during the course of the reaction is $Pd(P(t\text{-}Bu)_3)_2$.[66] Since the overall $P(t\text{-}Bu)_3$:Pd ratio is 1:1, this suggests that one-half of the palladium is in the form of $Pd(P(t\text{-}Bu)_3)_2$ and the other half of the palladium is in the form of a phosphine-free complex.

$Pd(P(t\text{-}Bu)_3)_2$ does not appear to be the active catalyst in our Suzuki cross-coupling process. Thus, the reaction of 3-chloropyridine with *o*-tolylboronic acid in the presence of 3% $Pd(P(t\text{-}Bu)_3)_2$ proceeds sluggishly at room temperature (eq 6).[67] However, the addition of phosphine-free $Pd_2(dba)_3$ to the $Pd(P(t\text{-}Bu)_3)_2$ produces a marked increase in the rate of cross-coupling (eq 6).[68,69]



(6)

These observations suggest that a palladium monophosphine adduct may be the active catalyst in these Suzuki couplings[70,71] and that phosphine-free palladium complexes that are present in the reaction mixture may serve an important role by increasing the concentration of the active catalyst. The unusual cross-coupling activity furnished by $P(t\text{-}Bu)_3$ may therefore be attributable both to its size and to its electron-richness: the steric demand favors dissociation (relative to less bulky phosphines) to a monophosphine complex that, due to the donating ability of $P(t\text{-}Bu)_3$, readily undergoes oxidative addition.

For Suzuki reactions of aryl bromides, we observe behavior similar to that of aryl chlorides. Thus, when the cross-coupling of 1-bromo-4-ethylbenzene with phenylboronic acid is monitored by ^{31}P NMR (0.5% $Pd_2(dba)_3$/1.2% $P(t\text{-}Bu)_3$, 3.3 equiv of KF), $Pd(P(t\text{-}Bu)_3)_2$ is the only species that we detect. In a

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(58) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509−6512. Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502−7512. (b) Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551−9554. (c) Johnson, C. R.; Johns, B. A. *Tetrahedron Lett.* **1997**, *38*, 7977−7980. Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856−4865. (d) Koch, F.; Heitz, W. *Macromol. Chem. Phys.* **1997**, *198*, 1531−1544. (e) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965−8975.

(59) $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ are less effective catalyst components.

(60) The vinyl triflate in entries 8 and 9 has proved to be a challenging substrate in other cross-coupling processes. For example, see: Busacca, C. A.; Eriksson, M. C.; Fiaschi, R. *Tetrahedron Lett.* **1999**, *40*, 3101−3104.

(61) (a) Unactivated vinyl triflates: Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030. Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700−709. Reference 30g. (b) Activated vinyl triflates: Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211−3214. Fu, J.-m.; Chen, Y.; Catelhano, A. L. *Synlett* **1998**, 1408−1410.

(62) Farina has shown that vinyl triflates oxidatively add to $Pd(PPh_3)_4$ more rapidly than do aryl triflates: Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434−5444.

(63) (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858. (b) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134−2140.

(64) (a) In the ^1H NMR spectrum, there is a small doublet at δ 1.27, which we have not been able to identify. (b) Through ^{31}P and ^1H NMR experiments, we have established that dba is not coordinated to $Pd(P(t\text{-}Bu)_3)_2$.

(65) (a) For a closely related study, see: Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030−3039. (b) The behavior of $P(t\text{-}Bu)_3$ stands in contrast to that of PPh_3: Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168−3178.

(66) A very small singlet at δ 90.7 is observed at the beginning of the reaction, but it disappears as the reaction progresses.

(67) This is consistent with our observation that the cross-coupling of aryl chlorides is very slow when a $P(t\text{-}Bu)_3$:Pd ratio of 2:1 is employed.

(68) In the absence of $P(t\text{-}Bu)_3$, $Pd_2(dba)_3$ is not an effective catalyst for the cross-coupling of aryl chlorides.

(69) For those concerned about the oxygen sensitivity of $P(t\text{-}Bu)_3$, the 0.5% $Pd(P(t\text{-}Bu)_3)_2$/0.25% $Pd_2(dba)_3$ catalyst system provides a practical alternative to 0.5% $Pd_2(dba)_3$/1% $P(t\text{-}Bu)_3$, since $Pd(P(t\text{-}Bu)_3)_2$ and $Pd_2(dba)_3$ are both air-stable solids. Also, $P(t\text{-}Bu)_3$ is available as a solution in a Sure-Seal bottle from Strem Chemicals.

(70) (a) For a related conclusion regarding a different catalyst for the Suzuki cross-coupling of aryl chlorides, see ref 13b. (b) In contrast, for Suzuki reactions with PPh_3-based catalysts, a palladium bisphosphine adduct is usually invoked (ref 1).

(71) For a study of palladium complexes that contain one $P(t\text{-}Bu)_3$ ligand, see: Krause, J.; Cestaric, G.; Haack, K.-J.; Seevogel, K.; Storm, W.; Pörschke, K.-R. *J. Am. Chem. Soc.* **1999**, *121*, 9807−9823.

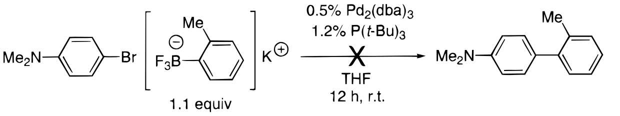
separate experiment, we have established that $Pd(P(t\text{-}Bu)_3)_2$ is a relatively ineffective catalyst for the cross-coupling of aryl bromides.[72]

Mechanistic Study of the Suzuki Cross-Coupling of Aryl Iodides. For $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Suzuki reactions of aryl iodides, $Pd(P(t\text{-}Bu)_3)_2$ is *not* the resting-state palladium−phosphine complex, in contrast to aryl chlorides and aryl bromides. During the cross-coupling of 4-iodotoluene with phenylboronic acid (0.5% $Pd_2(dba)_3$/1.2% $P(t\text{-}Bu)_3$, 3.3 equiv of KF), we observe two resonances by ^{31}P NMR, one at δ 63.4 (free $P(t\text{-}Bu)_3$) and one at δ 58.5;[73] we have tentatively assigned the resonance at δ 58.5 to an oxidative addition adduct.[74] If this assignment is correct, then it appears that, with this catalyst system, the turnover-limiting step for the coupling of aryl iodides occurs after oxidative addition.

Interestingly, as noted in the section on Suzuki reactions of aryl iodides, we have found that cross-couplings of aryl bromides catalyzed by $Pd_2(dba)_3/P(t\text{-}Bu)_3$ proceed more rapidly than do the corresponding reactions of aryl iodides. However, when we conduct a competition experiment between 1-bromo-4-ethylbenzene and 4-iodotoluene for phenylboronic acid (1 equiv of each of the three components) using 0.5% $Pd_2(dba)_3$/1.2% $P(t\text{-}Bu)_3$ as the catalyst, we find that essentially only the aryl iodide is coupled. A possible explanation for these observations is that aryl iodides undergo oxidative addition more rapidly than do aryl bromides (and irreversibly), but that rate-limiting transmetalation of the resulting $Pd(P(t\text{-}Bu)_3)(Ar)(I)$ is less rapid than is transmetalation of $Pd(P(t\text{-}Bu)_3)(Ar)(Br)$.[75]

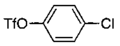
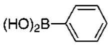
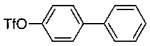
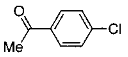
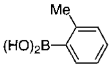
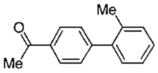
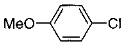
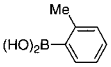
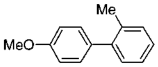
Mechanistic Study of the Role of KF. In Suzuki cross-coupling reactions, it is generally believed that Lewis-base additives facilitate the process by binding to the organoboron reagent, forming a more reactive four-coordinate "ate" complex that transfers the organic group to palladium (Figure 1).[1] In the Wright report that describes the usefulness of fluoride salts in Suzuki reactions, it was suggested that treatment of arylboronic acids with excess fluoride might produce $[Ar{-}BF_3]^-$, and that this might be the species that transfers the aryl group to palladium.[21b]

However, when we treat 4-bromo-*N*,*N*-dimethyaniline with $K[o\text{-tolyl-}BF_3]$[76] and $Pd_2(dba)_3/P(t\text{-}Bu)_3$, we observe no biaryl product after 12 h at room temperature (eq 7), a period of time during which the cross-coupling of 4-bromo-*N*,*N*-dimethyaniline and *o*-tolylboronic acid proceeds to completion in the presence of 3.3 equiv of KF. It therefore seems unlikely in our catalyst system that $K[o\text{-tolyl-}BF_3]$ is responsible for transferring the aryl group to palladium.[77]



(7)

Table 10. Suzuki Cross-Couplings Using a Low Loading of $P(t\text{-}Bu)_3$

Entry	Aryl Chloride	Boronic Acid	Product	Conditions[a]	Yield[b]
1				1.5% $Pd_2(dba)_3$ 1.5% $P(t\text{-}Bu)_3$ 24 h, r.t.	97%
2				1.5% $Pd_2(dba)_3$ 0.6% $P(t\text{-}Bu)_3$ 32 h, r.t.	93%
3				0.5% $Pd_2(dba)_3$ 0.2% $P(t\text{-}Bu)_3$ 8 h, r.t.	99%
4				1.5% $Pd_2(dba)_3$ 1.5% $P(t\text{-}Bu)_3$ 10 h, 70 °C	75%

[a] Standard conditions: 1.0 equiv of aryl chloride, 1.0−1.1 equiv of boronic acid, 3.0−3.3 equiv of KF, THF. [b] Isolated yield.

Suzuki Cross-Couplings with a Low Loading of $P(t\text{-}Bu)_3$. The mechanistic studies described above suggest that a palladium monophosphine complex is the active species in the $Pd_2(dba)_3/P(t\text{-}Bu)_3$-catalyzed Suzuki cross-coupling of aryl chlorides and aryl bromides. Unfortunately, during the course of the reaction, nearly all of the palladium is in the form of $Pd(P(t\text{-}Bu)_3)_2$ and phosphine-free palladium, rather than the catalytically active monophosphine complex. One way to obtain a larger proportion of this complex, relative to $Pd(P(t\text{-}Bu)_3)_2$, is to use a lower ratio of phosphine to palladium.

We have found that use of a ratio of phosphine to palladium lower than 1:1 can indeed lead to an active catalyst system for Suzuki reactions of aryl chlorides (Table 10). Thus, in the presence of 1.5% $P(t\text{-}Bu)_3$/1.5% $Pd_2(dba)_3$ ($\Rightarrow$ 1.5:3.0 $P(t\text{-}Bu)_3$:Pd), 4-chlorophenyltriflate cross-couples with phenylboronic acid in 24 h at room temperature (entry 1, Table 10; 97%). This result is comparable to that obtained under otherwise identical conditions with twice the amount of $P(t\text{-}Bu)_3$. We have discovered that it is even possible to cleanly effect cross-coupling with a 1:5 ratio of phosphine to palladium (entries 2 and 3, Table 10).[78]

It is important to note that low-phosphine conditions cannot be applied universally: for example, less activated aryl chlorides such as 4-chloroanisole couple in lower yield (entry 4, Table 10; 75%) than under the general reaction conditions (entry 1, Table 2; 88%).[79] On the basis of first-try dependability, we therefore recommend use of the general protocol, although for large-scale applications it may be worthwhile to explore low-phosphine conditions.

Conclusions

We have developed general and high-yielding methods for accomplishing Suzuki coupling reactions of arylboronic acids with aryl and vinyl halides ($Pd_2(dba)_3/P(t\text{-}Bu)_3$) and triflates ($Pd(OAc)_2/PCy_3$) (eqs 8 and 9). With these versatile catalyst systems, electronically and sterically diverse reactants can be efficiently cross-coupled, without the need for substrate-specific optimization of reaction conditions. Noteworthy capabilities of these catalysts include the following: cross-coupling of typically unreactive aryl chlorides, including electron-rich aryl chlorides such as 4-chloroaniline; room-temperature cross-coupling of aryl bromides, iodides, and triflates; synthesis of hindered di- and tri-ortho-substituted biaryls; for $Pd_2(dba)_3/P(t\text{-}Bu)_3$, very high

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(72) As with aryl chlorides (ref 69), $Pd(P(t\text{-}Bu)_3)_2/Pd_2(dba)_3$ is an effective catalyst and may be used in place of $Pd_2(dba)_3/P(t\text{-}Bu)_3$.

(73) We also detect the resonance at δ 58.5 when we treat 4-iodotoluene with $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ in the absence of phenylboronic acid and KF.

(74) The resonance disappears at the end of the reaction, at which time a resonance for $Pd(P(t\text{-}Bu)_3)_2$ appears at δ 85.6.

(75) For related conclusions regarding Suzuki reactions catalyzed by PPh_3-based palladium complexes, see: Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151−8156.

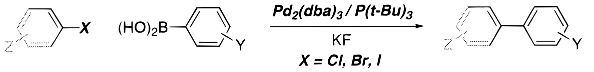
(76) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027.

(77) $KArBF_3$ has been shown to serve as an arylating agent in palladium-catalyzed cross-couplings with arenediazonium salts: Darses, S.; Genet, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393−4396. Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875−1883.

(78) Hartwig has noted that an effective catalyst for palladium-catalyzed C−O bond formation can be formed from a 1:2 mixture of phosphine and palladium: Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225.

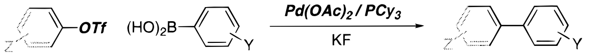
(79) Under low-phosphine conditions above room temperature, there appears to be a greater tendency to form insoluble Pd(0).

For aryl and vinyl halides:



(8)

For aryl and vinyl triflates:



(9)

selectivity for the following order of reactivity, I > Br > Cl, with chlorides being much more reactive than triflates; cross-coupling at low catalyst loading (e.g., 9700 turnovers for the reaction of an aryl chloride); cross-coupling of normally unreactive vinyl chlorides; and room-temperature cross-coupling of vinyl bromides, iodides, and triflates.

In terms of both scope and mildness of conditions, these catalysts for the Suzuki reaction fare well when compared with other catalysts that have been described, and in a number of instances they display reactivity that has no precedent. Preliminary mechanistic work suggests that a palladium monophosphine complex may be the active catalyst, and it is likely that the steric bulk and the electron-richness of the phosphine are the key to the activity of these systems. Ongoing studies are directed at additional mechanistic investigations and at the development of other applications of P(*t*-Bu)$_3$ in palladium-catalyzed cross-coupling processes.

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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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