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# Palladium-Catalyzed Suzuki–Miyaura Cross-Couplings of Sulfonyl Chlorides and Boronic Acids

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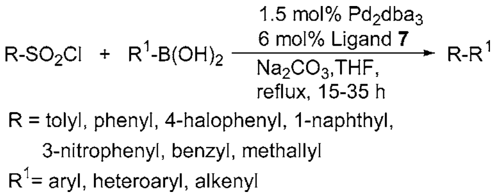
## ABSTRACT



$$\text{R-SO}_2\text{Cl} + \text{R}^1\text{-B(OH)}_2 \xrightarrow[\text{Na}_2\text{CO}_3\text{,THF, reflux, 15-35 h}]{\text{1.5 mol\% Pd}_2\text{dba}_3\text{, 6 mol\% Ligand }\mathbf{7}} \text{R-R}^1$$

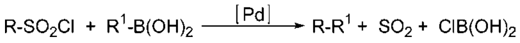
R = tolyl, phenyl, 4-halophenyl, 1-naphthyl, 3-nitrophenyl, benzyl, methallyl

$R^1$= aryl, heteroaryl, alkenyl

**Arene-, arylmethane, and alk-2-ene-1-sulfonyl chlorides undergo Suzuki–Miyaura cross-coupling with arene-, heteroarene-, and alkeneboronic acids in THF at reflux. The reactivity order is ArI > ArSO$_2$Cl > ArBr ≫ ArCl.**

The palladium-catalyzed Suzuki−Miyaura reaction has emerged as an extremely powerful method for the cross-coupling of aryl bromides, iodides, and triflates with boronic acids.[1] Coupling between electron-rich or electron-neutral aryl chlorides and arene boronic acids is also possible by using palladium complexes with sterically hindered, electron-rich, or carbene ligands such as those developed by Buchwald,[2] Fu,[3] and Herrmann,[4] respectively. Aryl arenesulfonates can cross-couple with arylboronic acids.[5] Vinylation,[6] carbonylation[7] and homocoupling[8] of arenesulfonyl chlorides have already been described. Recently, we have disclosed the palladium-catalyzed Stille cross-coupling of sulfonyl chlorides and organostannanes.[9] We are reporting here that arene-, phenylmethane-, and 2-methylprop-2-enesulfonyl chlorides can be condensed with arene-, heteroarene-, and alkeneboronic acids in the presence of a palladium catalyst (Scheme 1).

**Scheme 1.** Cross-Coupling of Sulfonyl Chlorides with Boronic Acids



$$\text{R-SO}_2\text{Cl} + \text{R}^1\text{-B(OH)}_2 \xrightarrow{[\text{Pd}]} \text{R-R}^1 + \text{SO}_2 + \text{ClB(OH)}_2$$

In our first search for optimal reaction conditions, we explored the condensation of *p*-toluenesulfonyl chloride

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[1] For reviews, see for example: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (e) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875−1916.

[2] (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550−9561.

[3] (a) For a recent review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388.

[4] (a) For recent review, see: Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309. (b) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee H. M.; Yang, C.; Nolan S. P. *J. Organomet. Chem.* **2002**, *653*, 69−82. (c) Herrmann, W. A.; Reisiner, C. P.; Spieger, M. *J. Organomet. Chem.* **1998**, *557*, 93−96. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805.

[5] (a) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060−1065. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818−11819.

[6] (a) Kasahara, A.; Izumi, T.; Kudou, N.; Azami, H.; Yamamato, S. *Chem. Ind. (London)* **1988**, 51−52. (b) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, *30*, 975−976. (c) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin. Trans. 1* **1990**, *8*, 2207−2211.

[7] Miura, M.; Itoh, K.; Nomura, M. *Chem. Lett.* **1989**, 77−78.

[8] Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Chem. Lett.* **1990**, 459−460.

[9] Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* In press.

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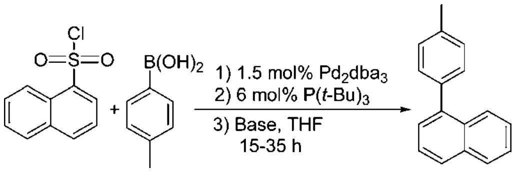
(TsCl) with 3-nitrobenzeneboronic acid in the presence of various catalysts such as $Pd(PPh_3)_4$, $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$ + $P(t\text{-}Bu)_3$, $Pd_2(dba)_3$ + tri-2-furylphosphine, and $Pd_2(dba)_3$ + 2-(di-*tert*-butylphosphino)biphenyl in boiling DME, DMF, THF, or dioxane.[10] Cross-coupling occurred only in the presence of a base such as $K_2CO_3$, $Cs_2CO_3$, $K_3PO_4$, or $Et_3N$. The best yield (60%) was obtained using 8 mol % $Pd(PPh_3)_4$ and 2.0−3.0 equiv of $K_2CO_3$.

Then, we searched to optimize the proportion of palladium employed, screening different sterically hindered, electron-rich, or carbene ligands,[11] as well as bases and solvents (Table 1 and Figure 1) for 1-naphthalenesulfonyl chloride reacting with 4-methylbenzeneboronic acid.

**Table 1.** Screening of Bases for Suzuki−Miyaura Cross-Coupling of Sulfonyl Chloride and Boronic Acid



| entry | base | yield[a] |
|---|---|---|
| 1 | $Et_3N$ | 10 |
| 2 | NaOAc | 5 |
| 3 | $Cs_2CO_3$ | 0 |
| 4 | $K_3PO_4$ | 19 |
| 5 | $K_2CO_3$ | 41 |
| 6 | $Na_2CO_3$ | 60 |
| 7 | $Li_2CO_3$ | 28 |

[a] Yields of cross-coupling products determined after flash chromatography.

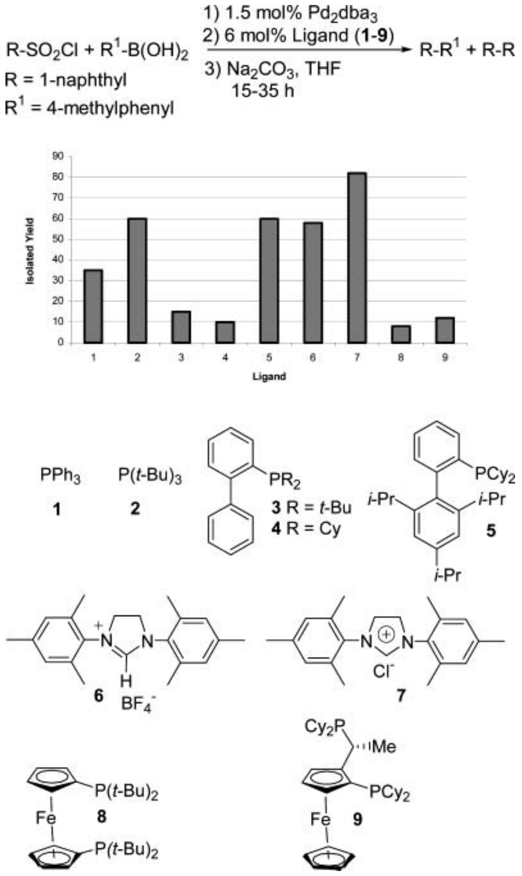


**Figure 1.** Screening of ligands for Suzuki−Miyaura cross-coupling of sulfonyl chloride and boronic acid.

We found that $Na_2CO_3$ is a better activator for the boronic acid (without destroying the sulfonyl chloride) compared to other bases such as $Et_3N$, $Cs_2CO_3$, NaOAc, $K_3PO_4$, $K_2CO_3$, or $Li_2CO_3$. When using $Cs_2CO_3$ as a base, the formation of the cross-coupling product was not observed, but all the starting sulfonyl chloride was consumed. When NaOAc was used as a base, the cross-coupling product was isolated in low yield (6%). Under these conditions, starting sulfonyl chloride was consumed in ca. 5 h. This is explained by the fact that the sulfonyl chloride is converted into the corresponding sulfonate, which retards the reaction.

A small library of ligands was tested, and it was found that the carbene derived by HCl α-elimination from **7** generates, with palladium, the best catalyst (Figure 1).

A wide range of electronically and structurally diverse sulfonyl chlorides and boronic acids can be cross-coupled efficiently under these conditions.[12] Thus, with respect to the electron-rich, electron-neutral, and electron-poor arenesulfonyl chlorides, they react with the boronic acids to provide the corresponding biaryl products in good yields in most cases (Table 2). Self-coupling of boronic acids was observed in some cases as a concurrent reaction.[13] The proportion of the latter was lower in boiling THF than in boiling dioxane, acetonitrile, 1,2-dimethoxyethane, or *p*-xylene. When $Pd(PPh_3)_4$ was used as a catalyst, traces of diarylsulfide were frequently observed. For instance, treatment of *p*-toluenesulfonyl chloride with 4-methoxybenzeneboronic acid in the presence of $Pd(PPh_3)_4$ and $K_2CO_3$ (3 equiv) led to Tol-S-Ar (Ar = 4-methoxyphenyl) that was isolated in 8% yield. This byproduct results probably from the reduction of the sulfonyl chloride into the corresponding sulfenyl chloride,[9,14] which is then coupled with the boronic acid following the Suzuki−Miyaura catalytic cycle (Figure

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(10) See Supporting Information for screening of catalysts and solvents.

(11) All ligands were bought from Strem Chemicals, Inc.

(12) **Typical Experimental Procedure for Catalyst B (Table 3).** A round-bottom flask was dried under vacuum, and to the flask were added the corresponding sulfonyl chloride (1.00 mmol), $Pd_2dba_3$ (0.015 mmol), ligand **7** (0.06 mmol), $Na_2CO_3$ (3 mmol), and the boronic acid (2 mmol) (were weighed in a glovebox) under a nitrogen atmosphere. Then, the flask was connected to a vacuum line and then filled with argon (three times), and THF (5 mL) was added under argon. The reaction mixture was stirred at reflux for 15−35 h. After cooling to room temperature, the mixture was diluted with ether and washed with water. The aqueous layer was extracted again with ether (three times). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure (solvents were removed under reflux on cooling to −20 °C in the cases of compounds with low boiling points or low molecular masses). The residue was purified by FC.

(13) Mañas, M. M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346−2351.

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**Table 2.** Palladium-Catalyzed Suzuki−Miyaura Cross-Couplings of Sulfonyl Chlorides and Boronic Acids

$$\underset{1.0\ \text{equiv}}{\text{R-SO}_2\text{Cl}} + \underset{2.0\ \text{equiv}}{\text{R}^1\text{-B(OH)}_2} \xrightarrow[\text{Base (3 equiv)}\ \text{THF, reflux, 15-35 h}]{\text{Palladium Catalyst}} \text{R-R}^1$$

| entry | R | $R^1$ | yield* cat. A[a] | yield* cat. B[b] |
|---|---|---|---|---|
| 1 | 4-methylphenyl | phenyl | 55 | |
| 2 | 4-methylphenyl | 4-methylphenyl | 70 | 92 |
| 3 | 4-methylphenyl | 3-nitrophenyl | 60 | |
| 4 | 4-methylphenyl | 3-formylphenyl | 55 | |
| 5 | 4-methylphenyl | 4-methoxyphenyl | 50 | 65 |
| 6 | 4-methylphenyl | fur-2-yl | 40 | |
| 7 | 4-methylphenyl | (*E*)-2-phenylvinyl | 35 | 48 |
| 8 | 4-methylphenyl | 4-chlorophenyl | 60 | 78 |
| 9 | 4-methylphenyl | 1-naphthyl | 64 | 76 |
| 10 | 4-chlorophenyl | 3-nitrophenyl | 65 | |
| 11 | 4-chlorophenyl | 4-methylphenyl | 62 | 80 |
| 12 | 1-naphthyl | 3-formylphenyl | 55 | 72 |
| 13 | 1-naphthyl | 3-nitrophenyl | 61 | |
| 14 | 1-naphthyl | 4-methylphenyl | 55 | 82 |
| 15 | 1-naphthyl | 4-methylphenyl | 58[c] | 14[d] |
| 16 | 1-naphthyl | 4-methylphenyl | trace[e] | |
| 17 | 1-naphthyl | 4-methylphenyl | 42[f] | |
| 18 | 3-nitrophenyl | 3-nitrophenyl | 78 | |
| 19 | 3-nitrophenyl | 4-methylphenyl | 70 | |
| 20 | 4-nitrophenyl | 4-methylphenyl | 64 | |
| 21 | benzyl | 4-methylphenyl | 30 | |
| 22 | benzyl | 3-nitrophenyl | 35 | 52 |
| 23 | methallyl | 3-nitrophenyl | 35 | 50 |

* Catalyst A: 8−10 mol % $Pd(PPh_3)_4$ and 2−3 equiv of $K_2CO_3$. Catalyst B: 1.5 mol % $Pd_2dba_3$, 6 mol % ligand **7**, and 3 equiv of $Na_2CO_3$. [a] R−S−R was isolated as a side product. [b] R−R was isolated as a side product. [c] Catalyst A and activated charcoal. [d] Catalyst B with 1.0 equiv of TBAB. [e] Performed with 1.5 mol % $Pd(OH)_2/C$ and $Na_2CO_3$ as a base. [f] Performed with 5 mol % $Pd(OAc)_2$, 10 mol % $PPh_3$, and $K_2CO_3$ as a base.

2). In contrast, when using carbene, sterically hindered, or electron-rich ligands, the arylpalladium chloride intermediates can give the corresponding homocoupled product[15] (Figure 2).

After screening the different ligands (**1**−**9**) (Figure 1), we have found that catalyst B (although not tested for all the reactions described here) was more efficient than the classical catalyst A (Table 2).

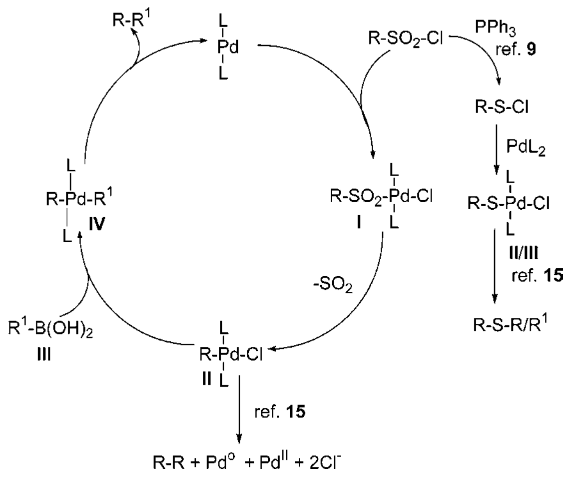


**Figure 2.** Probable catalytic cycle for Suzuki−Miyaura cross-coupling of sulfonyl chlorides and boronic acids.

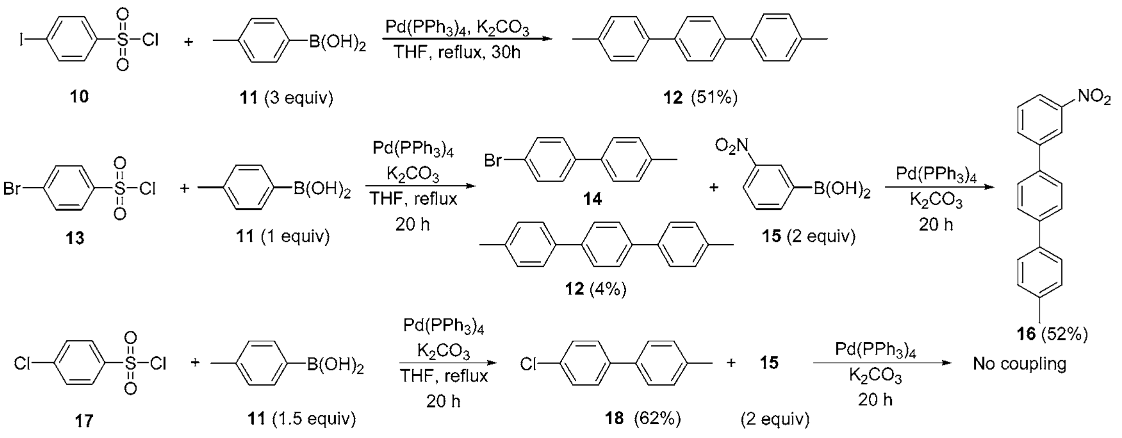
Under nonbasic conditions, the cross-coupling reaction was more efficient in the presence of CuCl (3 equiv) than with $CuBr{\cdot}Me_2S$. With 3 equiv of CuI, no reaction was observed.[10]

With *p*-halogenobenzenesulfonyl chlorides **10**, **13**, and **17**, we have observed that the sulfonyl chloride group is more reactive than the bromo- and chloroarene moieties (Scheme 2).[16] However, iodoarenes are more reactive than arenesulfonyl chlorides.

Recently, Leadbeater and Marco have reported transition-metal-free Suzuki-type coupling reactions using tetrabutylammonium bromide (TBAB) as a phase transfer reagent.[17] We have applied these conditions to our sulfonyl chlorides, but without success.[18] When the reaction is performed in the presence of a palladium catalyst and TBAB, the corresponding cross-coupling product is obtained in a lower yield than in the absence of TBAB (Table 2, entry 15).

When TsCl was mixed with 1 equiv of $PdCl_2(PhCN)_2$ in THF-$d_8$, a signal ($\delta_c$ 145.2 ppm) typical of the C−Pd bond[19]

**Scheme 2.** Reactivity Order for Suzuki−Miyaura Cross-Coupling Is ArI > $ArSO_2Cl$ > ArBr ≫ ArCl



appeared in the $^{13}$C NMR spectra after 10 min at 45 °C. At least two mechanisms can be envisaged for this observation: (1) the metal inserts into the $SO_2-Cl$ bond first with rapid subsequent elimination of $SO_2$ (Figure 2), or (2) the oxidative addition of the palladium occurs first onto the C−S bond, with subsequent elimination of $SO_2$.

We also examined nickel-catalyzed Suzuki−Miyaura cross-coupling reactions between various sulfonyl chlorides and areneboronic acids in the presence of a base, but none of our assays have been met with success.[20]

In summary, a palladium-catalyzed cross-coupling reaction between arene-, phenylmethane-, 2-methylprop-2-enesufonyl chlorides, and arene-, heteroarene-, and alkeneboronic acids is possible. The reaction provides a useful complement to our recently described work of Stille cross-couplings of sulfonyl chlorides and organostannanes[9] and should open new possibilities for medicinal chemistry and material science.

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**Supporting Information Available:** Experimental procedures, characterization of unknown compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For more details, see also ref 9.

(17) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660.

(18) Acetonitrile was used as a solvent instead of water, and $K_2CO_3$ was used as a base.

(19) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc*. **2000**, *122*, 9058−9064.

(20) See Supporting Information for reaction details.