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Palladium-Catalyzed Cross-Coupling of Arenediazonium Salts with Arylboronic Acids

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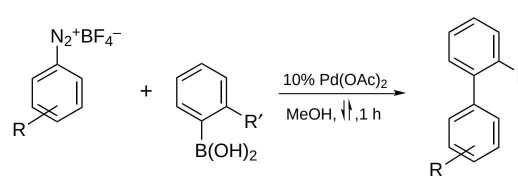
In recent years, the palladium-catalyzed cross-coupling reaction has evolved as a powerful synthetic tool for the construction of unsymmetrical biaryls.[1] The reaction, which is vastly superior to the classical methods of biaryl synthesis (Gomberg−Bachmann and Ullmann synthesis),[2] usually involves an arylmetal species (ArM) acting upon an aryl electrophile (Ar′X) in presence of a Pd^0 catalyst. Numerous versions of this reaction, featuring various arylmetals (Arm, M = MgX,[3] ZnX,[4] SnR_3,[5] $B(OH)_2$,[6] SiF_nR_{3-n}[7]), are known today among which the aryltins[5] and arylboronic acids[6] have found widespread synthetic applications. However, for all practical purposes, the aryl electrophile component (Ar′X) in these reactions has been limited to the conventional use of halides (Br, I) and the newly emerged triflates.[8] In order to broaden the scope of the cross-coupling reaction, we addressed this latter limitation and sought new Ar′X components as alternatives to the above. Although *O*-aryl carbamates,[9a] aryl sulfones,[9b] and aryl mesylates[9c] have recently been promoted as new Ar′X components, cross coupling of the former two are limited to selected Grignard reagents and suffer from harsh reaction conditions and poor functional group tolerence properties, whereas aryl mesylates give good yields in their Ni-catalyzed reactions with arylboronic acids. While pursuing a general program on Pd-catalyzed reactions of arenediazonium salts,[10] we reasoned that these salts armed with an excellent nucleofuge (N_2) would be a superior alternative to all those mentioned above and decided to explore them as aryl electrophile components in cross-coupling reactions. Although arenediazonium salts have been used in Heck reactions, which we have recently extended to aqueous reaction conditions,[10] their use in cross-coupling reactions are virtually unknown except for an isolated report with organostannanes.[11] We have now successfully engaged them in cross-coupling reaction with arylboronic acids and in this Note, disclose our preliminary results.

Scheme 1



1 **2** **3**

a; R = *p*-Cl
b; R = *o*-Me
c; R = *o*-OMe
d; R = *o*-CO_2Me
e; R = *m*-COMe
f; R = *p*-Me
g; R = *p*-OMe
h; R = *p*-CO_2Me
i; R = *p*-Br

a; R′ = H
b; R′ = Me

Initial screening of the reaction conditions with the diazonium salt **1a** and $PhB(OH)_2$ **(2a)** revealed that the usual "Suzuki protocol" (DME, $Pd(PPh_3)_4$, aqueous Na_2CO_3) caused extensive decomposition of the diazonium salt, the main culprit being triphenylphosphine. After much experimentation, the desired cross coupling was ultimately achieved with 10 mol % $Pd(OAc)_2$ in refluxing MeOH or EtOH *in the absence of any added base* to produce the biaryl **3a** in 80% yield (Scheme 1, Table 1). Alcoholic solvents[12] (over DME, DMF, CH_3CN) are absolutely essential for this reaction whereas external bases, thought to be key components in Suzuki-couplings, are not required and in fact, are detrimental to success. Ligandless $Pd(OAc)_2$,[13] or 10% Pd−C[14] (entry 2, Table 1) were found to be the only effective catalysts for this reaction.

The synthetic efficacy of this reaction was studied with a number of arenediazonium salts **(1a−i)** and the boronic acids **2a,b** which produced the unsymmetrical biaryls **3a−k** in fair to excellent yields (Table 1). While all cross-

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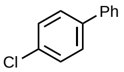
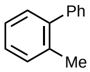
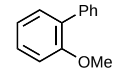
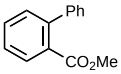
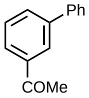
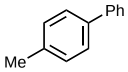
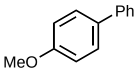
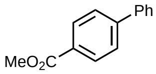
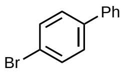
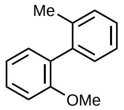
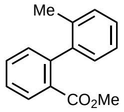
Table 1. Cross-Coupling of Arenediazonium Salts 1 with Arylboronic Acids 2 (Scheme 1)

	1	**2**	biaryl **3**		yield,[a] %
1	**1a**	**2a**		**3a**	80
2	**1a**	**2a**	**3a**		73[b]
3	**1b**	**2a**		**3b**	90
4	**1c**	**2a**		**3c**	75
5	**1d**	**2a**		**3d**	70[c]
6	**1e**	**2a**		**3e**	65
7	**1f**	**2a**		**3f**	86
8	**1g**	**2a**		**3g**	82
9	**1h**	**2a**		**3h**	75
10	**1i**	**2a**		**3i**	80
11	**1c**	**2b**		**3j**	40
12	**1d**	**2b**		**3k**	45[c]

[a] Isolated yield. [b] 10% Pd−C used as catalyst. [c] At 25 °C.

couplings studied are extremely rapid (1 h) in refluxing methanol, some can be equally facile at room temperature especially when highly activated diazonium salts are used (entries 5 and 12). Cross-couplings with $PhB(OH)_2$ are not affected by *ortho* substituents on the diazonium component. Thus, yields in the *para* series (entries 7−9) are only a shade better than the corresponding *ortho* isomers (entries 3−5). Only in the cases of *ortho,ortho′*-disubstituted biaryls **(3j,k)**, do steric effects come into play causing lowering of yields (entries 11, 12). In sharp contrast to Suzuki couplings with aryl halides,[6a] the present reaction shows only marginal electronic effects. For a given substitution pattern, diazonium salts having strongly electron-withdrawing substituents (e.g., CO_2Me) produced slightly lower yields than those having electron-donating groups (e.g. Me or OMe) (cf. entries 3−5 and 7−9). These results suggest that oxidative addition of PdL_n to the diazonium salts may not be the rate-limiting step for these reactions.[15]

Since the present cross-coupling reactions do not require an external base which, on the contrary, is essential for Suzuki couplings with aryl bromides, the (*p*-bromophenyl)diazonium salts **(1i)** can be selectively cross-coupled at the diazonium end to give *p*-bromobiphenyl **(3i)** in high yield (entry 10). This opens up new synthetic options toward differential cross-coupling reactions employing two different arylboronic acids. As expected of boronic acid couplings, the reaction shows good functional group tolerance properties and successful cross-couplings to sterically hindered *ortho,ortho′*-biaryls **3j,k** can also be achieved, albeit in moderate yields (entries 11 and 12). Nitro-substituted diazonium salts, however, failed to participate in this reaction probably due to their relatively high redox-potentials and a preference for homolytic dediazonization pathways.[10a]

In summary, we have introduced a new cross-coupling reaction using arenediazonium salts as the aryl electrophile component. The reaction holds several advantages over the existing cross-coupling repertoire: it is operationally simple, *uses alcoholic reaction conditions*, and starts with anilines which in many cases are more readily available than the halides and phenols. These, together with the option for selective cross-coupling in bromo-substituted arenediazonium salts, promises wide application of this new regime in unsymmetrical biaryl synthesis.[16]

Experimental Section

General Procedure for Cross-Coupling of Arenediazonium Salts with Arylboronic Acids. A solution of arylboronic acid (2.0 mmol), arenediazonium salt (2.2 mmol), and $Pd(OAc)_2$ (0.2 mmol) in methanol (5 mL) was heated under reflux for 1 h. After being cooled to room temperature, it was filtered through Celite, and the filtrate was diluted with water and extracted with ether (3 × 10 mL). Removal of ether followed by silica gel chromatography (0−10% EtOAc in petroleum ether) gave the respective biaryls **3a**−**c**,**e**−**j**. For **3d** and **3k**, the same procedure was followed except that the diazonium salt **1d** was added last to the mixture of arylboronic acid and $Pd(OAc)_2$ in MeOH and stirred at 25 °C for 8 h.

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Supporting Information Available: General experimental procedure and spectral data for **3a**−**k** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(15) Oxidative addition of PdL_n to aryl iodides has been proposed as the rate-limiting step in Suzuki couplings: see ref 12c.

(16) While this manuscript was under the reviewing process, a similar work appeared in the literature: Darses, S.; Jeffery, T.; Genet, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3857.