

Suzuki–Miyaura Reactions of Arenediazonium Salts Catalyzed by Pd(0)/C. One-Pot Chemoselective Double Cross-Coupling Reactions[†]

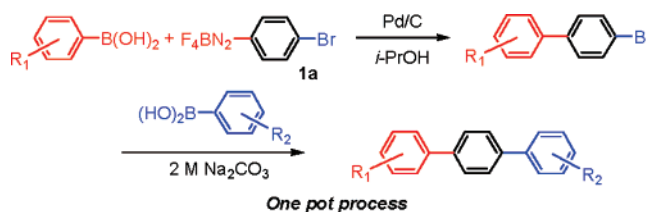
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ABSTRACT



The Suzuki–Miyaura cross-coupling of arenediazonium tetrafluoroborate salts with boronic acid partners catalyzed by Pd(0)/C is described as a practical and efficient alternative to classical homogeneous conditions. Reactions conducted in alcoholic solvents proved to be extremely fast using mild conditions. Additionally, we developed a chemoselective double Suzuki–Miyaura cross-coupling in a single reaction vessel allowing the synthesis of unsymmetrical terphenyls.

Over the years, the Suzuki–Miyaura reaction has become one of the most significant palladium-catalyzed methods for C–C bonds creation. A huge number of studies have been devoted to the development of this cross-coupling since the pioneering work from Suzuki and Miyaura.¹ Both academic and industrial laboratories are interested in this process for many reasons: (1) a wide range of functional groups are tolerated due to mild conditions; (2) boron compounds (especially boronic acids) are readily available, stable, and weakly toxic; and (3) dry solvents are generally not required. Striking results have been recently reported using a homogeneous source of palladium (Pd(OAc)₂, Pd₂dba₃, ...) associated with an appropriate ligand.² Using these newly

reported procedures, aryl or vinyl iodide, bromide, and even chloride can be coupled under mild conditions.

Although extremely efficient, homogeneous catalysis suffers from several drawbacks including the contamination of the product by residual Pd species even after purification and the use of costly, sensitive, and sometimes not commercially available ligands. To solve these issues, heterogeneous catalysis using Pd/C as a practical and inexpensive source of palladium under ligandless conditions proved to be an excellent alternative method³ as exemplified by reported industrial applications.⁴ The vast majority of studies

[†] This paper is dedicated to the memory of Charles Mioskowski, who passed away on June 2, 2007.

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concerning the Suzuki–Miyaura reaction involve the use of halogenated or sulfonated electrophiles (iodide, bromide, chloride, or triflate). However, it has been reported that arenediazonium salts are also effective electrophiles in palladium cross-coupling reactions.⁵ Surprisingly, only a few reports⁶ have described their use for the Suzuki–Miyaura coupling since the pioneering work of the Genet⁷ and Sengupta groups.⁸ From an industrial point of view, diazonium electrophiles, readily prepared from inexpensive anilines, compete favorably with less reactive and more expensive halogenated electrophiles. In connection with our studies related to the chemistry of Pd/C,⁹ we wish to disclose in this paper our investigations concerning the cross-coupling of arenediazonium salts with boronic acid partners under ligandless and heterogeneous conditions.¹⁰

We initiated our optimization studies by selecting diazonium salt **1a** and phenyl boronic acid **2a** as partners for the Suzuki–Miyaura cross-coupling. We screened a variety of technical grade solvents at moderate temperature (50 °C) and with 5 mol % of Pd(0)/C as catalyst. The source of Pd(0)/C used in this study is that commonly used for hydrogenation and hydrogenolysis. The results compiled in Table 1 clearly

Table 1. Optimization Studies

entry	solvent	time (h)	yield ^a (%)
1	DME	12	15
2	DME/H ₂ O	2	47
3	1,4-dioxane	12	3
4	i-PrOH	2	91
5	EtOH	2	84
6	CH ₃ OH	0.5	92

^a Yields are an average of two runs.

highlight the beneficial effect of alcoholic solvents from which methanol seems the most efficient in terms of yield

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Table 2. Cross-Coupling of Arenediazonium Salts

Ar-N ₂ BF ₄		Ar'-B(OH) ₂		Pd(0)/C (5 mol %)		Ar-Ar'	
1.2 equiv		1 equiv		MeOH			
entry	Ar-N ₂ BF ₄	Ar'-B(OH) ₂	product	time (min)	Yield (%) ^a		
1				30	92		
2				30	77		
3				5	73		
4				5	81		
5				20	89		
6				20	78		
7				30	71 ^b		
8				20	61 ^{c,d}		

^a Isolated yields are an average of two runs. ^b 1.7 equiv of diazonium salt and 1 equiv of boronic acid were used. ^c 1 equiv of diazonium salt and 1.7 equiv of boronic acid were used. ^d Compound **3h** decomposes rapidly on standing.

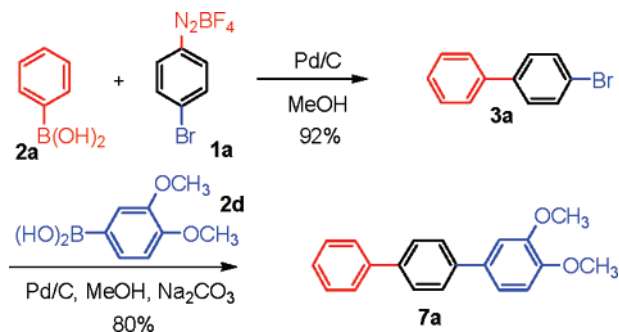
and rate for the cross-coupling. Interestingly, while 1,4-dioxane has been used successfully with homogeneous catalysts,⁷ it gives only a sluggish reaction with Pd(0)/C. It should be noted that the conditions developed do not require the use of a base, resulting in a high chemoselectivity at the

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Scheme 1. Synthesis of Terphenyl

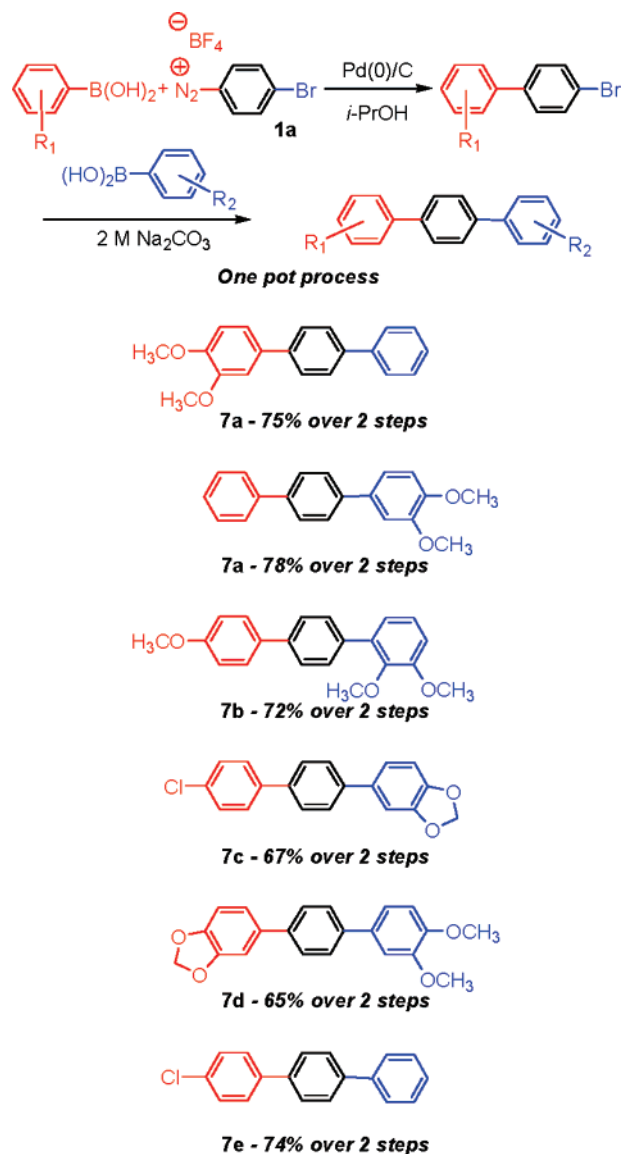


diazonium group. Indeed, no evidence for a competing electrophilic reactivity of the bromine atom was observed in this case. Next, the cross-coupling of a variety of arene-diazonium salts and boronic acids was examined using optimized conditions; the results are shown in Table 2. All arene-diazonium tetrafluoroborate salts were easily accessed by reaction of the corresponding anilines with sodium nitrite and tetrafluoroboric acid.¹¹ Importantly, the prepared arene-diazonium tetrafluoroborate salts showed excellent stability over 2 years when stored at -20°C .

Whatever the electronic and steric nature of the partners, the cross-coupling proceeded extremely fast since the coupling could be performed in minutes. Close inspection of crude reaction mixtures showed variable amounts of reduction at the diazonium group. This side reaction preferentially occurred with ortho-substituted boronic acids (entry 7), giving lower yield of cross-coupled product. However, this issue has been addressed by the use of a slight excess of diazonium salts (1.7 equiv vs 1.2 equiv). It is possible to assume that the oxidative addition of Pd over activated arene-diazonium salts is so fast (a few minutes as indicated by nitrogen evolution) that the reduction of diazonium occurred concurrently with the transmetalation step. The introduction of heteroaromatic substituents, which are of great importance in the pharmaceutical industry drug discovery processes, is also achievable although less effective (entry 8). Actually, the modest yield obtained for **3h** can likely be attributed to the instability of the benzofuranboronic acid **2g** under our conditions. As a consequence, in contrast with other entries, we used an excess of boronic acid **2g**. At the end of the reaction, a simple filtration to remove the catalyst is required for the workup, highlighting the practicability of the method. Reaction monitoring by nitrogen evolution proved to be extremely useful from a practical point of view since TLC analysis was not required.

Having successfully demonstrated the effectiveness of Pd(0)/C for the coupling of arene-diazonium tetrafluoroborate salts with boronic acids in the absence of base and under ligandless conditions, we envisaged to take advantage of the high chemoselectivity for the diazonium group.

Scheme 2. One-Pot Synthesis of Terphenyls



Indeed, we anticipated that a sequential cross-coupling reaction with two different boronic acids and the bifunctional 4-bromobenzenediazonium tetrafluoroborate salt **1a** could be performed by adjusting experimental conditions to make unsymmetrical terphenyls.

Recently, terphenyls have attracted attention due to a wide range of significant biological activities including potent immunosuppressant, neuroprotective, antithrombotic, anti-coagulant, specific 5-lipoxygenase inhibitory, and cytotoxic activities.¹² In addition, terphenyl and polyphenyl systems are also important structural elements in liquid crystals¹³ and fluorescent compounds.¹⁴

Reasoning that a base would be required for the cross-coupling at the bromide, we first optimized conditions for

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each cross-coupling. We found that the second Suzuki–Miyaura reaction proceeds smoothly on **3a** in the presence of aqueous Na₂CO₃ (Scheme 1).

Multiple transformations performed in a one-pot process are economically advantageous considering the outlays for the catalyst, solvent, purification materials, and time. Given that the synthesis of unsymmetrical terphenyls could be even more interesting when realized in a single reaction vessel, we studied the viability of such a double chemoselective cross-coupling reaction. A literature survey showed that studies devoted to the polycoupling of halogenated electrophiles with different boronic acids in the same pot is quite uncommon.¹⁵ The question was whether the Pd(0)/C, without any additive, was active enough to catalyze two different cross-couplings. Gratifyingly, after some optimizations, we observed that Pd(0)/C was an efficient catalyst to create, in the same reaction vessel, two carbon–carbon bonds. We also found that 2-propanol consistently gave more reproducible results than methanol for the *one-pot* process. As a consequence, the first cross-coupling (e.g., at the diazonium group) proved to be slightly longer, but the second step worked with higher yield. As highlighted in Scheme 2, the protocol developed revealed to be extremely efficient and practical. It is important to note that the synthesis of **7a** proved to be equally efficient in the *one-pot*, two-step Suzuki–Miyaura reaction than in a sequential cross-coupling. The order of introduction of boronic acids has no dramatic influence on the yields (compound **7a**). We particularly focused on the introduction of electron-rich boronic acids since natural

terphenyls are poly-oxygenated. However, the process worked equally well with other boronic acids (compound **7e**).

In summary, we have developed a new application of the Pd/C-catalyzed Suzuki–Miyaura reaction using arene diazonium tetrafluoroborate salts as electrophiles. The catalytic system allowed extremely fast reactions (few minutes) under mild conditions. Taking advantage of the greater reactivity of the diazonium function compared to the bromide, we developed an extremely efficient synthesis of unsymmetrical terphenyls via a double chemoselective cross-coupling in the same reaction vessel. This work extends the scope of Pd/C for C–C bond formation of biaryls and terphenyls. The optimum conditions feature inexpensive reagents and solvents with low toxicity, rendering the method environmentally benign, very practicable, and scalable. Application of this method to the total synthesis of terphenyls is currently being pursued in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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