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Synthesis of Biaryls via Decarboxylative Pd-Catalyzed Cross-Coupling Reaction

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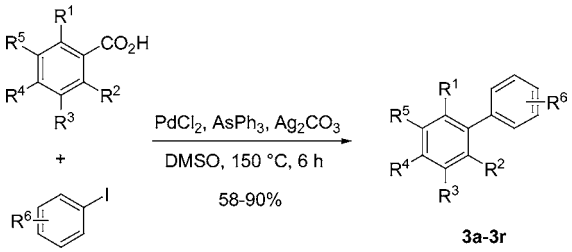
ABSTRACT



A simple and efficient route to biaryls via Pd-catalyzed decarboxylative cross-couplings of arene carboxylic acids and aryl iodides is reported. The $PdCl_2/AsPh_3$ catalytic system in the presence of Ag_2CO_3 in DMSO was found to be particularly efficient to perform this transformation. This reaction can be extended to the synthesis of various biaryls, including sterically hindered biaryls, with yields ranging from 58% to 90%.

A general aim of modern organic synthesis is to develop new ways of formation of carbon−carbon (C−C) bonds. In this respect, Pd-catalyzed cross-coupling reactions offer powerful and versatile synthetic methods for the creation of C−C bonds, in particular, for the preparation of biaryls.[1,2] These compounds are important for the preparations of biologically active molecules[3] and herbicides[4] and also find important applications in the fields of molecular recognition,[5] liquid crystals,[6] organic semiconductors,[7] or metal ligands for catalysis.[8]

The Suzuki−Miyaura Pd-catalyzed cross-coupling reaction of aryl halides and arene boronic acids is the predominant method for the synthesis of biaryls.[1a,9] This reaction requires mild reaction conditions and generally proceeds in high yields. One of its few drawbacks is the high price of many

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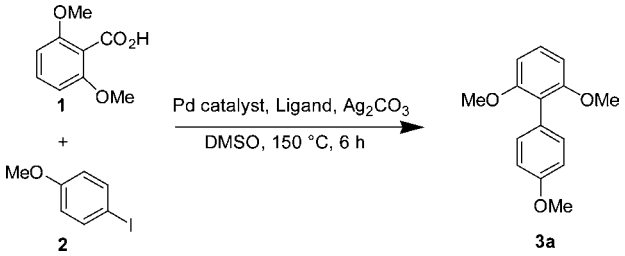
arene boronic acids, which could even, in certain cases, be difficult to prepare. Because carboxylic acids are widely available, they could represent an interesting alternative to the arene boronic acids. Their use for this reaction, which is related to the Suzuki−Miyaura process, has recently been described by two groups.[10−13] This prompts us to disclose herein our own results. Goossen et al. reported the preparation of biaryls via a Pd-catalyzed decarboxylative coupling reaction in the presence of a bimetallic Pd/Cu catalyst.[10] Good yields have been obtained, but mostly for carboxylic acids bearing electron-withdrawing groups. This procedure is somewhat tedious and often has to be adapted to the nature of the arene carboxylic acid. The Boehringer Ingelheim group reported a Pd-catalyzed arylation reaction of heteroaromatic carboxylic acids with aryl halides.[11] Herein, we report a versatile one-step synthesis of biaryls via a Pd-catalyzed cross-coupling reaction of both electron-rich and electron-deficient arene carboxylic acids with various aryl iodides. This method can also be used for the preparation of sterically hindered biaryls.

The determination of the reaction conditions was performed with 2,6-dimethoxybenzoic acid, 4-iodoanisole, and Ag_2CO_3 in DMSO (Table 1).[13b] It turned out that $PdCl_2$ was the most active catalyst, and the desired biaryl **3a** was obtained in 51% yield (entry 1).[14] Apart from $PdCl_2(MeCN)_2$ which gave almost identical results (entry 2), other Pd(II) or Pd(0) catalysts (entries 3−8) or Ni(II) derivatives [$NiCl_2(PPh_3)_2$ or $Ni(acac)_2$] were unsuccessful. Modifications of the nature of the base (Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, AgOAc, or TMSOK) or of the solvent (sulfolane, DMA, DMF, or DMSO/DMF mixtures[13b]), addition of various salts ($LiBF_4$, LiCl, $MgCl_2$, $CaCl_2$, CsCl, $BiCl_3$, or CuI[10]), or decrease of the amount of Ag_2CO_3 afforded only much lower yields of **3a**. Despite the fact that Pd catalysts containing phosphine ligands were less efficient than $PdCl_2$ (see above), we carried out the reaction with $PdCl_2$ in the presence of additional Ph_3P (entry 9) or numerous other phosphines (e.g., PCy_3, DavePhos, xanthphos, or BINAP), and as expected, **3a** was obtained in lower yields. Interestingly, the addition of $AsPh_3$ was much more beneficial, with **3a** being isolated in 71% yield (entry 10) and even in 90% yield if a slight excess (1.3 equiv) of carboxylic acid **1** was used. Surprisingly, only complex mixtures were obtained in the presence of other arsine or stibine ligands such as 1,2-bis(diphenylarsino)ethane (entry 12) and triphenylstibine (entry 13). Using either 0.3 equiv of $PdCl_2$ and 0.1 equiv of $AsPh_3$ or 0.3 equiv of $PdCl_2$ and 0.1 equiv of $AsPh_3$ afforded **3a** in only 50% and 66% yields, respectively. In the presence of $AsPh_3$ (0.6 equiv), attempts to lower the temperature to 100 °C or to decrease the amount of $PdCl_2$ to 0.1 equiv afforded **3a** in much lower yields, whereas replacing 4-iodoanisole by 4-bromoanisole gave no biaryl **3a**. Additionally, use of microwave irradiation (150 °C, 10 min) yielded almost identical results and was therefore not pursued.

Table 1. Determination of the Reaction Conditions



entry	Pd catalyst	ligand	yield (%)[a]
1[b]	$PdCl_2$	–	51
2[b]	$PdCl_2(MeCN)_2$	–	49
3[b]	$Pd(O_2CCF_3)_2$	–	<40
4[b]	$Pd(CN)_2$	–	<40
5[b]	$Pd(OAc)_2$	–	<40
6[b]	$Pd(dppf)_2Cl_2(CH_2Cl_2)_2$	–	<40
7[b]	$Pd(PPh_3)_4$	–	–[c]
8[b]	$Pd_2(dba)_3$	–	–[c]
9[b]	$PdCl_2$	PPh_3	37
10[b]	$PdCl_2$	$AsPh_3$	71 (90)[d]
11[e]	$PdCl_2$	$AsPh_3$	<60
12[b]	$PdCl_2$	$Ph_2As-(CH_2)_2-AsPh_2$	–[c]
13[b]	$PdCl_2$	$SbPh_3$	–[c]

[a] Isolated yields after flash chromatography of the crude reaction mixture on silica gel. [b] Reagents and reaction conditions: 4-iodoanisole (1.0 equiv), 2,6-dimethoxybenzoic acid (1.1 equiv), Ag_2CO_3 (3.0 equiv), ligand (0.6 equiv), and Pd catalyst (0.3 equiv). [c] Complex reaction mixtures were obtained. [d] The reaction was performed using 1.3 equiv of 2,6-dimethoxybenzoic acid. [e] The reaction was performed using 0.1 equiv of $PdCl_2$.

With these reaction conditions in hand, we evaluated the scope and limitation of the reaction using various arene carboxylic acids and aryl iodides (Table 2).[15] The use of the electron-rich 2,6-dimethoxybenzoic acid, 2,4,6-trimethoxybenzoic acid, or 3-bromo-2,6-dimethoxybenzoic acid gave the desired biaryls in good yields (entries 1−3). Interestingly, the sterically more hindered 2,6-diisopropoxybenzoic acid[16]

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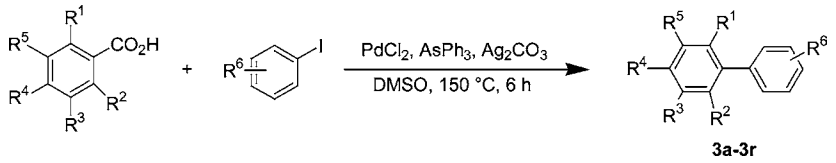
(14) No starting material **1** or **2** was recovered. In addition to **3a**, 1,3-dimethoxybenzene, anisole, and 4,4′-dimethoxybiphenyl were isolated.

(15) Typical experimental procedure: DMSO (6 mL) was added to a mixture of the aryl iodide (0.50 mmol, 1.0 equiv), the arene carboxylic acid (0.65 mmol, 1.3 equiv), Ag_2CO_3 (1.50 mmol, 414 mg, 3.0 equiv), $AsPh_3$ (0.30 mmol, 91.9 mg, 0.6 equiv), and $PdCl_2$ (0.15 mmol, 26.6 mg, 0.3 equiv). The reaction mixture was degased twice with argon and directly heated at 150 °C for 6 h. After cooling to rt, the reaction mixture was filtered with Celite and AcOEt (100 mL) was added to the filtrate. The organic phase was washed with saturated NH_4Cl (70 mL), dried with $MgSO_4$, filtered, and concentrated under a vacuum. The residue was purified by flash chromatography on silica gel to afford pure biaryls after drying under a vacuum (0.1 mbar).

Table 2. Synthesis of Biaryls



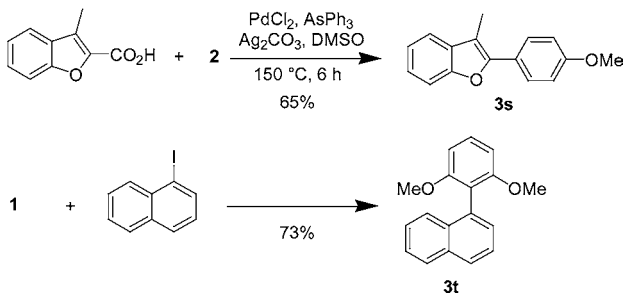
3a-3r

entry[a]	R^1	R^2	R^3	R^4	R^5	R^6	product	yield (%)[b]
1	OMe	OMe	H	H	H	4-OMe	**3a**	90
2	OMe	OMe	H	OMe	H	4-OMe	**3b**	75
3	OMe	OMe	Br	H	H	4-OMe	**3c**	65
4	O^{i}Pr	O^{i}Pr	H	H	H	4-OMe	**3d**	62
5	NO_2	H	OMe	OMe	H	4-OMe	**3e**	79
6	NO_2	H	H	H	H	4-OMe	**3f**	63
7	F	F	F	F	F	4-OMe	**3g**	92
8	F	Cl	H	H	H	4-OMe	**3h**	82
9	OMe	OMe	H	H	H	3-OMe	**3i**	89
10	OMe	OMe	H	H	H	2-OMe	**3j**	62
11	OMe	OMe	H	H	H	4-Me	**3k**	76
12	OMe	OMe	H	H	H	4-Cl	**3l**	78
13	OMe	OMe	H	H	H	2-Br	**3m**	58
14	OMe	OMe	H	H	H	H	**3n**	84
15	OMe	OMe	H	H	H	3-CF_3	**3o**	77
16	OMe	OMe	H	H	H	4-Ac	**3p**	70
17	OMe	OMe	H	H	H	2-NO_2	**3q**	71
18	OMe	OMe	H	H	H	2-CO_2Et	**3r**	59

[a] Reagents and reaction conditions: aryl iodide (1.0 equiv), arene carboxylic acid (1.3 equiv), $PdCl_2$ (0.3 equiv), $AsPh_3$ (0.6 equiv), Ag_2CO_3 (3.0 equiv). [b] Isolated yields after flash chromatography of the crude reaction mixture on silica gel.

gave **3d** in 62% yield (entry 4). Very good results were also obtained by reacting 3,4-dimethoxy-2-nitrobenzoic acid with 4-iodoanisole, and the corresponding biaryl was obtained in 79% yield (entry 5). Remarkably, the electron-deficient 2-nitrobenzoic acid also gave the expected biaryl in 63% yield (entry 6). The cross-coupling reaction of 4-iodoanisole with pentafluorobenzoic acid (entry 7), 2-chloro-6-fluorobenzoic acid (entry 8), and 3-methylbenzofuran-2-carboxylic acid (Scheme 1) afforded 92%, 82%, and 65% yields, respectively. The reaction of *N*-pivaloyl or *N*-acetyl-protected 2-amino-6-fluorobenzoic acid with 4-iodoanisole proceeds only with moderate yields (ca. 25%), whereas benzoic, 2,4-dimethoxybenzoic, 2,4,6-trimethylbenzoic, and *N*-pivaloyl-protected anthranilic acids gave no coupling reaction with 4-iodoanisole and were recovered unchanged. The coupling reaction was also performed between carboxylic acid **1** and many electron-rich or electron-deficient iodobenzenes with yields ranging from 58% to 89% (entries 9−18) and with 1-iodonaphthalene with 73% yield (Scheme 1). Noteworthily, 2,2′,6-substituted hindered biaryls could be obtained in good yields using this procedure (entries 10, 13, 17, and 18).

Scheme 1. Syntheses of Two Other Biaryls



In summary, we have reported a simple and efficient Pd-catalyzed cross-coupling reaction of arene carboxylic acids and aryl iodides. Despite some remaining limitations (high amount of Pd and lack of generality for the carboxylic acids), these preliminary results open a practical and versatile route for the formation of aryl−aryl bonds from arene carboxylic acids. Further investigations are currently in progress in our groups.

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Supporting Information Available: General procedure, ^{1}H and ^{13}C NMR data, and copies of spectra for all biaryls. This material is available free of charge via the Internet at http://pubs.acs.org.

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