

Biaryl Synthesis via Decarboxylative Pd-Catalyzed Reactions of Arenecarboxylic Acids and Diaryliodonium Triflates

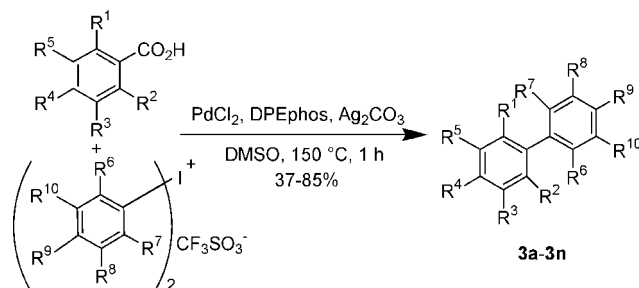
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ABSTRACT



A novel simple and efficient synthesis of biaryls via a Pd-catalyzed decarboxylative cross-coupling reaction of arenecarboxylic acids and diaryliodonium triflates is described. The PdCl₂/DPEphos catalytic system in the presence of Ag₂CO₃ in DMSO was found to be the most efficient. Various biaryls, including sterically hindered biaryls, were synthesized with yields ranging from 37 to 85%.

The importance of biaryls is easily shown by the broad applications of these compounds¹ as key building blocks for the syntheses of pharmaceutically active molecules,² herbicides,³ liquid crystals,⁴ organic semiconductors,⁵ or metal

ligands for catalysis.⁶ The Suzuki–Miyaura Pd-catalyzed reaction of aryl halides and areneboronic acids is the most powerful method for the formation of aryl–aryl bonds.^{7,8} This reaction proceeds under mild conditions and generally affords the biaryls in high yields. One of its few drawbacks is often the high price or the difficulty to prepare the areneboronic acids. Arenecarboxylic acids represent a prom-

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ising alternative to areneboronic acids due to their wide availability and low price.^{9,10} The group of Goossen has described an efficient preparation of biaryls via a Pd-catalyzed decarboxylative coupling of arenecarboxylic acids and aryl halides in the presence of a bimetallic Pd/Cu catalyst.¹¹ The Boehringer Ingelheim group has reported a Pd-catalyzed arylation of heteroaromatic carboxylic acids,¹² while our group has presented a simple and efficient route to biaryls via a Pd-catalyzed coupling of arenecarboxylic acids and aryl iodides.^{13,14} We decided then to investigate the coupling of arenecarboxylic acids with diaryliodonium salts instead of aryl iodides.

Hypervalent iodine reagents have received a large amount of attention in organic synthesis since they are nontoxic, moisture-, and air-stable reagents.¹⁵ In particular, the reactivity of diaryliodonium salts is of current interest. These compounds are now easily obtained from simple arenes via an easy one-step procedure recently reported by the group of Olofsson.¹⁶ Due to their electron-deficient nature and hyperleaving group ability, diaryliodonium salts find some applications for carbon–carbon bond-forming reactions: α -arylations of carbonyl compounds,¹⁷ Cu-catalyzed reactions with organostannanes or organoboranes,¹⁸ and Pd-catalyzed cross-couplings¹⁹ with arenes²⁰ or areneboronic acids.²¹ Herein, we will describe new synthetic potentialities

achieved for aryl–aryl bond formation from diaryliodonium salts and arenecarboxylic acids.

Inspired by our previous work,¹³ we started the optimization of the reaction conditions by heating a mixture of 2,6-dimethoxybenzoic acid, Ag₂CO₃, PdCl₂, and various diphenyliodonium salts at 120 °C in DMSO (Table 1).²² We found

Table 1. Determination of the Reaction Conditions

entry	X [−]	Pd catalyst (equiv)	ligand	temp (°C)	yield (%) ^a
1 ^b	PF ₆ [−]	PdCl ₂	—	120	65
2 ^b	CF ₃ SO ₃ [−]	PdCl ₂	—	120	64
3 ^b	NO ₃ [−]	PdCl ₂	—	120	62
4 ^b	Cl [−]	PdCl ₂	—	120	35
5 ^b	PF ₆ [−]	Pd(OAc) ₂	—	120	44
6 ^b	PF ₆ [−]	Pd(O ₂ CCF ₃) ₂	—	120	56
7 ^b	PF ₆ [−]	PdCl ₂ (MeCN) ₂	—	120	59
8 ^b	PF ₆ [−]	PdCl ₂ (PCy ₃) ₂	—	120	45
9 ^b	PF ₆ [−]	PdCl ₂ (PPh ₃) ₂	—	120	68
10 ^b	PF ₆ [−]	Pd(PPh ₃) ₄	—	120	59
11 ^b	PF ₆ [−]	Pd ₂ dmba ₃	—	120	38
12 ^{b,c}	PF ₆ [−]	PdCl ₂	P(o-tolyl) ₃	120	57
13 ^{b,c}	PF ₆ [−]	PdCl ₂	cy johnphos	120	55
14 ^{b,c}	PF ₆ [−]	PdCl ₂	davephos	120	53
15 ^{b,c}	PF ₆ [−]	PdCl ₂	xphos	120	52
16 ^{b,c}	PF ₆ [−]	PdCl ₂	<i>tert</i> -Bu xphos	120	67
17 ^{b,d}	PF ₆ [−]	PdCl ₂	dppe	120	61
18 ^{b,d}	PF ₆ [−]	PdCl ₂	DPEphos	120	72
19 ^{b,d}	PF ₆ [−]	PdCl ₂	DPEphos	150	76 (85) ^e
20 ^{e,f}	PF ₆ [−]	PdCl ₂	DPEphos	150	80 ^e

^a Yields determined by ¹H NMR of the crude reaction mixtures, calculated versus the starting acid. ^b Reagents and reaction conditions: 2,6-dimethoxybenzoic acid (1.0 equiv), diphenyliodonium salt (1.0 equiv), Ag₂CO₃ (3.0 equiv), and Pd catalyst (0.3 equiv) were added successively to DMSO and heated at the indicated temperature for 1 h. ^c Reactions performed in the presence of a monodentate ligand (0.6 equiv). ^d Reactions performed in the presence of a bidentate ligand (0.3 equiv). ^e Reaction performed with an excess of diphenyliodonium hexafluorophosphate (1.25 equiv). Reagents were added in two portions (for further details see Supporting Information). ^f Reaction carried out in the presence of PdCl₂ (0.2 equiv) and DPEphos (0.2 equiv).

that the hexafluorophosphate and triflate gave the best results and afforded, respectively, the desired biaryl **3a** in 65 and 64% yields (entries 1 and 2). A slightly lower 62% yield was obtained with diphenyliodonium nitrate (entry 3), whereas diphenyliodonium chloride afforded **3a** in a much lower 35% yield (entry 4). A screening of Pd catalysts was then performed using diphenyliodonium hexafluorophosphate

(22) (a) The diphenyliodonium salts were obtained from commercial sources. (b) No diphenyliodonium salt was recovered. In addition to **3a**, starting material **1** and 1,3-dimethoxybenzene were present.

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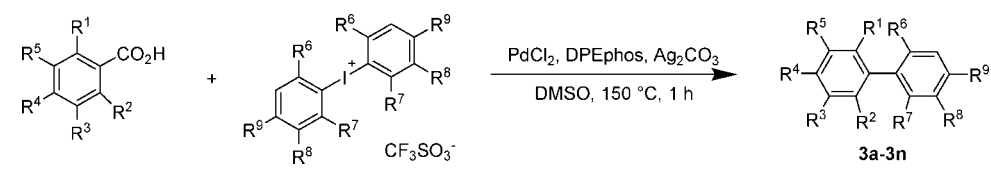
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Table 2. Synthesis of Biaryls



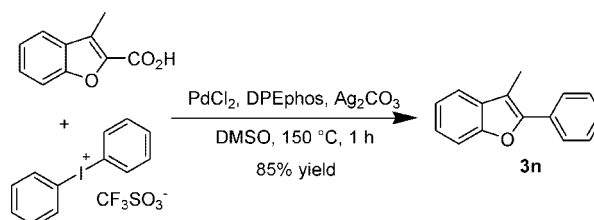
entry ^a	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	product	yield (%) ^b
1	OMe	OMe	H	H	H	H	H	H	H	3a	75
2	OMe	OMe	H	OMe	H	H	H	H	H	3b	80
3	OMe	OMe	Br	H	H	H	H	H	H	3c	67
4	OiPr	OiPr	H	H	H	H	H	H	H	3d	72
5	NO ₂	H	OMe	OMe	H	H	H	H	H	3e	85
6	NO ₂	H	H	H	H	H	H	H	H	3f	81
7	NHPiv	F	H	H	H	H	H	H	H	3g	83
8	F	F	F	F	F	H	H	H	H	3h	80
9	OMe	OMe	H	H	H	H	H	H	F	3i	73
10	OMe	OMe	H	H	H	H	H	H	Br	3j	63
11	OMe	OMe	H	H	H	H	H	H	<i>t</i> -Bu	3k	76
12	OMe	OMe	H	H	H	Me	H	Me	H	3l	57
13	OMe	OMe	H	H	H	Me	Me	H	Me	3m	37

^a Reagents and reaction conditions: arenecarboxylic acid (1.0 equiv), diaryliodonium triflate (1.25 equiv), Ag₂CO₃ (3.0 equiv), DPEphos (0.2 equiv), and PdCl₂ (0.2 equiv). ^b Isolated yields after flash chromatography of the crude reaction mixture on silica gel.

(entries 5–11). Apart from PdCl₂(PPh₃)₂ (entry 9) which gave **3a** in a slightly better 68% yield, other Pd(II) (entries 5–8) or Pd(0) catalysts (entries 10–11) afforded only lower yields. Several attempts were then carried out to optimize the reaction in conditions derived from them for entry 1: replacing the Pd(II) catalyst with a Ni(II) catalyst (Ni(acac)₂, NiCl₂(PPh₃)₂, NiCl₂(PMe₃)₂), addition of AsPh₃ (0.6 equiv) changing the nature of the base (Li₂CO₃, Na₂CO₃, K₂CO₃, Cs₂CO₃, AgOAc, AgF, Ag₃PO₄, or AgOTf) of the solvent (sulfolane, DMF, DMAc, NMP, dioxane, or DMSO/DMF mixtures), addition of various salts (LiCl, LiBr, LiBF₄, LiOAc, MgCl₂, CaCl₂, SnCl₂, BiCl₃, Fe(acac)₃, or NBu₄Cl). Unfortunately, none of these attempts brought any improvement. The reaction was then carried out in the presence of various phosphines (entries 12–20). It turned out that with DPEphos a 72% yield of **3a** was obtained (entry 18). Using either 0.3 equiv of PdCl₂ and 0.15 equiv of DPEphos or 0.3 equiv of PdCl₂ and 0.6 equiv of DPEphos afforded **3a** in only lower yields. The yield can further be increased to 76% when heating the reaction mixture at 150 °C. Upon reoptimization of the reaction conditions, a 85% yield in **3a** was even achieved when adding the reagents in two portions in the presence of an excess of diphenyliodonium hexafluorophosphate (entry 19). In these conditions, the amount of PdCl₂ could be lowered to 0.2 equiv without decreasing significantly the yield (entry 20).²³ Finally, identical results were obtained in the presence of diphenyliodonium triflate instead of the hexafluorophosphate.

The scope and limitations of the reaction were evaluated using various arenecarboxylic acids and diaryliodonium triflates (Table 2).²⁴ The use of electron-rich 2,6-dimethoxy-

benzoic acid, 2,4,6-trimethoxybenzoic acid, and 3-bromo-2,6-dimethoxybenzoic acid gave the biaryls in good isolated yields (entries 1–3). The sterically hindered 2,6-diisopropoxybenzoic acid afforded the biaryl in still 72% yield (entry 4). An 85% yield was observed with 4,5-dimethoxy-2-nitrobenzoic acid (entry 5). Remarkably, the electron-deficient 2-nitrobenzoic acid gave the expected biaryl in a high 81% yield (entry 6). The reaction of diphenyliodonium triflate with *N*-pivaloyl-protected 2-amino-6-fluorobenzoic acid (entry 7), pentafluorobenzoic acid (entry 8), or 3-methylbenzofuran-2-carboxylic acid (Scheme 1) afforded the

Scheme 1. Synthesis of Biaryl **3n**


expected biaryls in 83%, 80%, and 85% yields, respectively. Unfortunately, a low 27% yield was observed using 2,4-dimethoxybenzoic acid, whereas only traces of biaryls were obtained with benzoic acid. Finally, we reacted successfully various symmetrical diaryliodonium triflates with 2,6-dimethoxybenzoic acid in 57–76% yields (entries 9–12).

(23) **3a** was obtained in <60% yield using 0.1 equiv of PdCl₂ or only 1.5 equiv of Ag₂CO₃.

(24) The diaryliodonium triflates were prepared according to ref 16a.

Noteworthy, a sterically hindered 2,2',6,6'-tetrasubstituted biaryl can be obtained in 37% yield (entry 13).²⁵

In conclusion, we have reported an efficient synthesis of biaryls via a decarboxylative Pd-catalyzed cross-coupling reaction which opens a new and simple route for the formation of aryl–aryl bonds from arenecarboxylic acids. Further investigations are currently in progress in our group

(25) The cross-coupling reaction was also performed with unsymmetrical diaryliodonium triflates. It turned out that (4-methoxyphenyl)(phenyl)iodonium, (phenyl)(2,4,6-trimethylphenyl)iodonium, and (phenyl)(2-thienyl)iodonium triflates afforded mixtures of biaryls. Interestingly, (4-nitrophenyl)(phenyl)iodonium triflate afforded 2,6-dimethoxy-4'-nitrobiphenyl in 60% isolated yield.

to develop the use of iodonium salts for various C–C bond-forming reactions.

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Supporting Information Available: General procedure, ¹H and ¹³C 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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