Cross-Coupling

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A General Pd-Catalyzed Decarboxylative Cross-Coupling Reaction between Aryl Carboxylic Acids: Synthesis of Biaryl Compounds**

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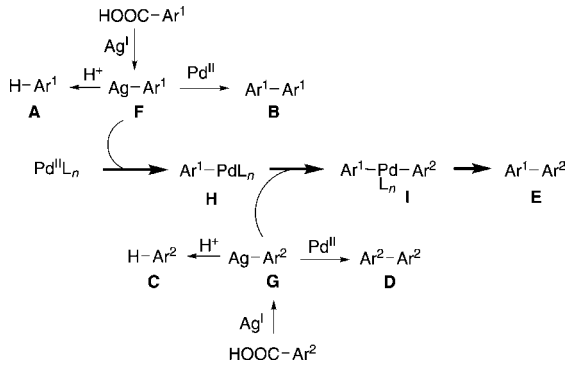
Biaryl compounds have fascinated chemists for over 100 years because of their scientific and commercial value, and they are still a focus of interest to synthetic chemists. Over the past three decades, the persistent efforts of synthetic chemists to develop efficient methods for transition-metal-catalyzed cross-coupling reactions have revolutionized the synthesis of biaryl compounds.[1,2] These methods, in particular palladium-catalyzed cross-coupling reactions between aryl halides and aryl organometallics, are widely used in modern academic and industrial laboratories, but some limitations still remain. Traditional cross-coupling methods require pre-activated coupling partners, such as expensive and/or moisture-sensitive organometallic reagents, and frequently produce unwanted, often toxic, stoichiometric side-products.[1] Demands for a sustainable development of society have provided the impetus for chemists to develop more atom-economical and greener reactions. In this context, significant advances have recently been made in the development of catalytic methods for the direct arylation of aromatic C–H bonds, thus offering a very promising way to generate valuable biaryl compounds from simple starting materials in an atom- and step-economical fashion.[2i,3] Although many elegant studies have demonstrated that high selectivity can be achieved in such direct arylation reactions by tuning directing groups, electronic effects, and steric factors, significant room for improvement remains.[3]

Decarboxylative cross-coupling reactions of aryl carboxylic acids have recently emerged as an attractive and alternative approach to the synthesis of biaryl compounds because a wide range of structurally diverse aryl carboxylic acids are readily available.[4–9] Aryl carboxylic acids are versatile arylating reagents that can be coupled with aryl halides,[6] aryl organometallics,[8r] and even unfunctionalized (hetero)arenes,[7] and release carbon dioxide as a side-product. The aryl metal species generated in situ from the decarboxylation of aryl carboxylic acids determine the regioselectivity of the aryl–aryl coupling in a similar way to the main group metal reagents in conventional cross-coupling reactions. New catalytic methods for efficient decarboxylative cross-coupling are highly desirable. Herein, we report a general method for the Pd-catalyzed decarboxylative cross-coupling of aryl carboxylic acids. This protocol not only allows the cross-coupling of aryl carboxylic acids that are electronically different but also those that are electronically similar; the yields are generally good and a wide range of aryl carboxylic acids serve as suitable substrates.

Our investigation on the decarboxylative cross-coupling of aryl carboxylic acids stemmed from the mechanistic hypothesis that is outlined in Scheme 1. This reaction may occur through a sequence of steps consisting of an Ag-promoted decarboxylation of both carboxylic acid substrates to generate the respective aryl–Ag^I species (**F** and **G**), transmetalation of the respective aryl groups from Ag^I to Pd^{II} to generate a Pd complex bearing two different aryl fragments (**I**), and reductive elimination to give the product **E**.[2k–m] In principle, this mechanism is plausible because each step in the catalytic cycle is known.[7d,h,i] However, the successful development of such a decarboxylative cross-coupling reaction is a great challenge because aryl–Ag^I species (**F** and **G**) tend to undergo protodecarboxylation[9] or decarboxylative homocoupling.[8l] These side reactions become prevalent when the transmetalation of the aryl group from Ag to Pd to generate the Pd complex **I** and the product-generating reductive elimination step are not sufficiently fast, or when one of the two decarboxylation steps is much faster than the other. The optimal reaction conditions should fulfill the following requirements: 1) preferential formation of the Pd complex **I**; 2) fast transmetalation of the aryl groups from



Scheme 1. Proposed mechanism for the decarboxylative cross-coupling reaction of aryl carboxylic acids.

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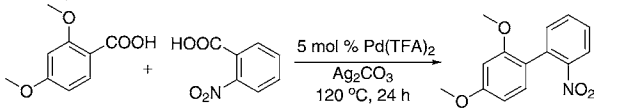
Ag to Pd; 3) fast reductive elimination of the cross-coupling product from the Pd complex **I**; 4) achieving a balance in the rates of the two decarboxylation steps. One of our strategies was to identify a suitable ligand to modify the electron density and steric environment on palladium, so that the formation of the Pd intermediate bearing two different aryl groups would be favored,[10] and both the transmetalation from Ag to Pd and the reductive elimination of the cross-coupling product would be accelerated.[11] The other strategy was to control the factors affecting the rate of decarboxylation to establish a balance between two different decarboxylation steps.[7d,h,i,9b,c]

Guided by the above requirements, we screened solvents, phosphine ligands, and palladium sources for the reaction of 2,4-dimethoxybenzoic acid (**1a**) with 2-nitrobenzoic acid (**2a**) (Table 1). The choice of solvent is known to control the decarboxylation rate,[7d,h,i,9b,c] and the choice of phosphine ligand is known to have a profound effect on the formation of the key Pd intermediate, as well as on the transmetalation and

Table 1: A selection of results from the optimization studies on the decarboxylative cross-coupling reaction of 2-nitrobenzoic acid with 2,4-dimethoxybenzoic acid.[a]



1a **2a** **3a**

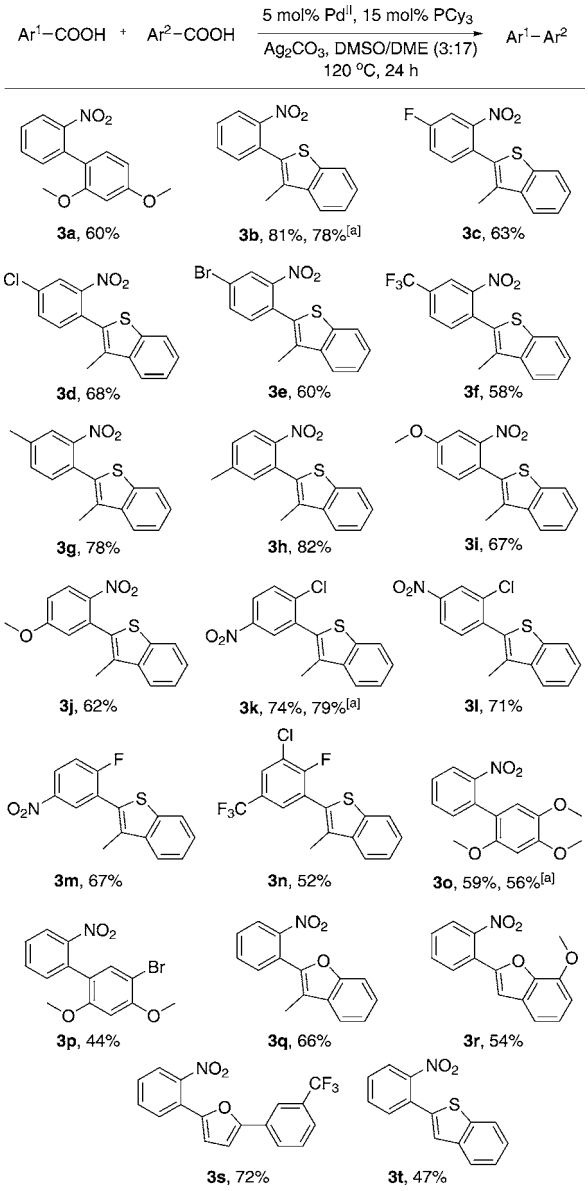
Entry	Ligand	Solvent(v:v)	Yield [%][b]
1	–	NMP	trace
2	–	DMSO/DMF(1:20)	trace
3	PCy_3	DMSO/DMF(1:20)	30
4	PCy_3	DMSO/dioxane(1:20)	39
5	PCy_3	DMSO/dioxane(3:17)	46
6	PCy_3	DMSO/dioxane(4:16)	33
7	PCy_3	DMSO/DME(2:18)	48
8	PCy_3	DMSO/DME(3:17)	60
9	PCy_3	DMSO/DME(4:16)	52
10	PPh_3	DMSO/DME(3:17)	trace
11	$tBu_3P{\cdot}HBF_4$	DMSO/DME(3:17)	trace
12	$PCp_3{\cdot}HBF_4$	DMSO/DME(3:17)	24
13	$iPr_3P{\cdot}HBF_4$	DMSO/DME(3:17)	36
14	S-Phos	DMSO/DME(3:17)	8
15	DavePhos	DMSO/DME(3:17)	8
16	*tert*-Butyl XPhos	DMSO/DME(3:17)	7
17	XPhos	DMSO/DME(3:17)	5
18[c]	PCy_3	DMSO/DME(3:17)	54
19[d]	PCy_3	DMSO/DME(3:17)	35
20[e]	PCy_3	DMSO/DME(3:17)	57
21[f]	PCy_3	DMSO/DME(3:17)	50

[a] Reaction conditions: 5 mol% of $Pd(TFA)_2$, 15 mol% of phosphine ligand, 0.2 mmol of **1a**, 1.2 equiv of **2a**, 3 equiv of Ag_2CO_3, 2 mL solvent, 120°C, 24 h. [b] Yield of isolated product. [c] $PdCl_2$ was used in place of $Pd(TFA)_2$. [d] $PdBr_2$ was used in place of $Pd(TFA)_2$. [e] $[PdCl_2(MeCN)_2]$ was used in place of $Pd(TFA)_2$. [f] $[PdCl_2(PhCN)_2]$ was used in place of $Pd(TFA)_2$. Cy = cyclohexyl, DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, DMF = dimethylformamide, DME = 1,2-dimethoxylethane, DMSO = dimethylsulfoxide, NMP = *N*-methylpyrrolidone, $PCp_3{\cdot}HBF_4$ = tricyclopentylphosphine tetrafluoroborate, TFA = trifluoroacetate, S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, *tert*-Butyl XPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisoproylbiphenyl, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

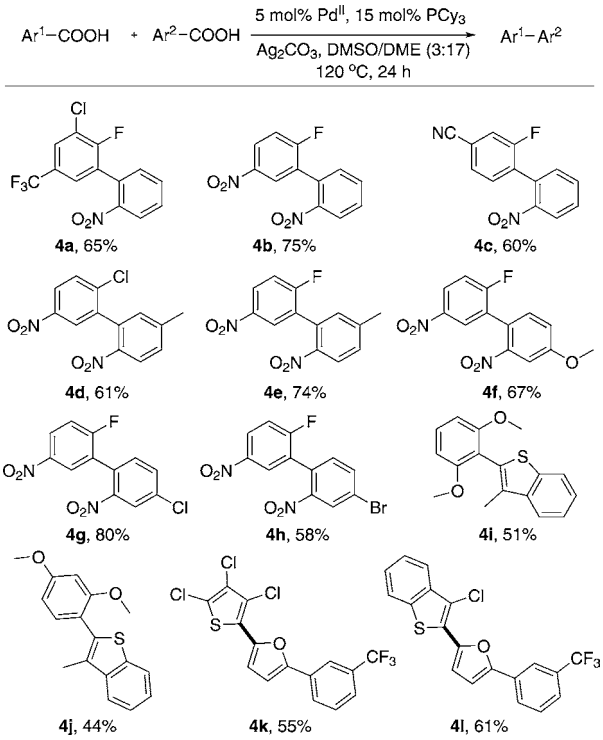
reductive elimination steps.[10,11] Initially, we observed that polar solvents such as NMP and DMSO/DMF (1:20), which are usually used for decarboxylative cross-coupling reactions, gave only a trace amount of the desired product **3a** together with significant amounts of side-products derived from protodecarboxylation (entries 1 and 2).[13] The addition of the phosphine ligand PCy_3 (15 mol%) to the reaction system resulted in an increase of the yield of product **3a** to 30% (entry 3), thus illustrating the beneficial effect of the phosphine ligand. When DMSO/dioxane (1:20) was used as a solvent in place of DMSO/DMF (1:20), a higher yield was obtained (entry 4). Additionally, it was observed that varying the ratio of DMSO to dioxane also had an effect on the yield of **3a** (entries 4–6). Further optimization of the solvent revealed that DMSO/DME (3:17) was the best solvent system (entry 8). The identity of the phosphine ligand used also had an effect on the yield of **3a** (entries 8 and 10–17). Among the ligands tested, PCy_3 afforded the best result (entry 8). While varying the phosphine it was found that in the cases in which a poor yield of **3a** was obtained, the yields of side-products arising from protodecarboxylation and/or homocoupling increased significantly (entries 10–12, 14–17); it was further noted that whereas electron-deficient aryl carboxylic acid **2a** underwent both homocoupling and protodecarboxylation side reactions, the electron-rich substrate **1a** underwent predominant protodecarboxylation. In the case where iPr_3P was used, the low yield of **3a** was associated with incomplete conversion of the aryl carboxylic acids rather than the above side reactions (entry 13).[13] Other palladium sources were also tested (entries 8 and 18–21) and $[PdCl_2(MeCN)_2]$ was shown to be nearly as efficient as $Pd(TFA)_2$ (entry 20), whereas the others were found to be inferior (entries 18, 19, and 21).

With the optimized reaction conditions established, we next evaluated the substrate scope of the cross-coupling reaction between electronically different aryl carboxylic acids. As shown in Scheme 2, reactions using a variety of combinations of electron-deficient aryl carboxylic acids with electron-rich aryl carboxylic acids having an array of substituents such as nitro, methoxy, trifluoromethyl, fluoro, chloro, and even bromo, afforded the corresponding cross-coupling products in good yields. Heteroaryl carboxylic acids proved to be good substrates for this reaction and the particular substitution pattern of the phenyl ring of such carboxylic acids did not affect the yield (**3g** versus **3h**, **3i** versus **3j**, and **3k** versus **3l**).

Pleasingly, the decarboxylative cross-coupling reaction between electronically similar aryl carboxylic acids was possible using the optimized reaction conditions (Scheme 3). Both electron-deficient and electron-rich aryl carboxylic acids underwent a cross-coupling reaction with electronically similar partners to give the products in synthetically useful yields. Notably, the biaryl products arising from the decarboxylative cross-coupling reaction of electron-deficient aryl carboxylic acids were isolated in good yield (**4a**–**4h**); these products are not readily accessible using conventional cross-coupling methods because the required organometallic reagents are difficult to synthesize or are of low reactivity. Electron-rich heteroaryl and electron-rich aryl carboxylic



Scheme 2. The decarboxylative cross-coupling reaction between electronically different aryl carboxylic acids. Reaction conditions: 5 mol% of $Pd(TFA)_2$ or $[PdCl_2(MeCN)_2]$, 15 mol% of PCy_3, 1–2 equiv of aryl carboxylic acid, 3 equiv of Ag_2CO_3, 2 mL DMSO/DME (3:17), 120°C, 24 h. [a] Yield of isolated product in reaction run on a 1 mmol scale.



Scheme 3. The decarboxylative cross-coupling reaction between electronically similar aryl carboxylic acids. Reaction conditions: 5 mol% of $Pd(TFA)_2$ or $[PdCl_2(MeCN)_2]$, 15 mol% of PCy_3, 1–2 equiv of aryl carboxylic acid, 3 equiv of Ag_2CO_3, 2 mL DMSO/DME (3:17), 120°C, 24 h.

acids, or combinations thereof, also underwent the expected cross-coupling reaction (**4i**–**4l**), the conjugated products of which are interesting because they are often bioactive[12a] and can be used for the preparation of organic semiconducting materials.[12b] The variety of aryl substituents tolerated in these cross-coupling reactions, such as fluoro, chloro, bromo, trifluoromethyl, methoxyl, cyano, and nitro, provide opportunities for further synthetic elaboration. For example, the nitro-containing biaryl products can be easily converted, through selective reduction, into amino-substituted biaryl compounds, which are common substructures in bioactive compounds.[12c]

In conclusion, we have herein presented a strategy, involving a decarboxylative cross-coupling reaction of aryl carboxylic acids, for the synthesis of asymmetrical biaryl compounds. This protocol not only effects the decarboxylative cross-coupling reaction between electronically different aryl carboxylic acids but also that of electronically similar aryl carboxylic acids; these reactions proceed in good yields and have a broad substrate scope. The choice of solvent and phosphine ligand was found to be crucial for achieving a selective cross-coupling reaction.[14]

Experimental Section

In a glove box, a 25 mL tube equipped with a stir bar was charged with $Pd(TFA)_2$ (0.01 mmol), PCy_3 (0.03 mmol), 2,4-dimethoxybenzoic acid (0.2 mmol), 2-nitrobenzoic acid (0.24 mmol), Ag_2CO_3 (0.6 mmol), DMSO (0.3 mL), and DME (1.7 mL). The tube was fitted with a Teflon screwcap and removed from the glove box. The reaction mixture was stirred at 120°C for 24 h. After cooling to RT, the reaction mixture was diluted with diethyl ether (10 mL) and filtered through a pad of silica gel; the pad of silica gel was then washed with diethyl ether (20–50 mL). The filtrate was washed with a saturated aqueous solution of NaCl (30 mL). The organic phase was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (3% diethyl ether/petroleum ether as eluent) to provide the corresponding product **3a** in 60% yield.

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[13] See the Supporting Information for details.

[14] After publication of this article in EarlyView, the authors were made aware of a related report: K. Xie, S. Wang, Z. Yang, J. Liu, A. Wang, X. Li, Z. Tan, C.-C. Guo, W. Deng, *Eur. J. Org. Chem.* **2011**, 5787 – 5790. The method reported in that paper is however limited to the cross-coupling of 2-nitro benzoic acid or its derivatives with dimethoxy benzoic acids or three fluoro-substituted benzoic acids.

