Additive-Free Palladium-Catalyzed Decarboxylative Cross-Coupling of Aryl Chlorides

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Supporting Information

ABSTRACT: The cross-coupling of sodium (hetero)aryl carboxylates with (hetero)aryl chlorides proceeds with 1 mol % palladium catalyst and does not require inorganic base, silver salts, or copper salts. This coupling uses two low energy partners, and the only stoichiometric byproducts are carbon dioxide and sodium chloride. The substrate scope includes less activated aryl chlorides and carboxylates (>25 examples). The palladium



loading could be reduced to 0.1 mol %, and Buchwald-style precatalysts could be used.

ross-coupling is a widely used reaction manifold that enables the rapid construction of (hetero)biaryl bonds.^{1,2} However, the nucleophilic coupling partner (boronic acid or other arylmetal species) can be unstable, difficult to access, and/or expensive.³⁻⁶ Decarboxylative cross-coupling uses benzoic acids or benzoate salts as potential replacements for more expensive and less stable nucleophilic cross-coupling partners.⁷⁻¹⁶ Benzoic acids are readily available, stable, low cost, and low energy starting materials. However, decarboxylative cross-coupling reactions have been limited by (i) the use of multiple metals, (ii) mechanistic ambiguity, (iii) high reaction temperatures, and (iv) limited substrate scope. Additionally, aryl bromides, iodides, and triflates are the most common electrophiles in decarboxylative cross-couplings because of their increased reactivity toward oxidative addition.¹⁸⁻²⁰ However, these electrophiles are less accessible and generate more toxic byproducts than aryl chlorides.^{18,21} The reaction of aryl chlorides with benzoate salts represents the coupling of two of the most stable, lowest energy, and most readily available coupling partners. As such, developing new cross-coupling reactions between benzoate salts and aryl chlorides is desirable.

In 2008, Goo β en reported the first decarboxylative crosscoupling with aryl chlorides.²² This system used both copper and palladium co-catalysts (Scheme 1a). In 2010, Liu²³ and Forgione^{24,25} published separate reports on the palladiumcatalyzed coupling of benzoate salts or heteroaryl carboxylic acids, respectively. These reactions proceeded with aryl chlorides, bromides, and triflates (Scheme 1b,c).^{23,24} Both reactions were limited in scope. The conditions reported by Liu were only shown to be compatible with polyfluorobenzoates, while the conditions reported by Forgione were only shown to be compatible with 5-membered heteroaromatic carboxylic acids. Additionally, the later conditions used a cesium base and a full equivalent of tetrabutylammonium chloride additive.

Recently, we reported an intermolecular salt-free doubledecarboxylative aryl allylation.²⁶ This reaction was enabled by





judicious choice of $(COD)Pd(CH_2TMS)_2$ (Pd1) as the palladium precatalyst.^{26,27} Other precatalysts were significantly less effective. During that work, low yields were observed for substrates containing an aryl bromide or chloride, which was likely due to competitive oxidative addition into the carbon– halide bond. This observation prompted a re-exploration of the decarboxylative cross-coupling of aryl chlorides. Herein, improved conditions are disclosed that provide efficient access to (hetero)biaryl products. Compared with previous reports, the work described here (i) operates at a lower catalyst loading, (ii) uses the sodium carboxylate, (iii) is additive free, and (iv) is compatible with electron-deficient benzoates,

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electron-rich benzoates, and heteroaryl carboxylates (Scheme 1d).

We began by reinvestigating a substrate that was problematic for Liu (Scheme 1c).²³ A 14% yield was reported for the decarboxylative cross-coupling of potassium 2,4,6-trifluorobenzoate. As reported, in our hands this coupling resulted in less than 20% of the desired biaryl product (Table 1, entry 1).

Table 1. Optimization of Decarboxylative Cross-Coupling

F	F O OM F CI	Me –	X mol % [Pd] (PC) 120 °C, 2 dioxand	$ \begin{array}{c} \frac{6}{7_{3}}, \\ \frac{7_{3}}{4}, \\ e \\ F \\ 3a \end{array} $	F Me
entry ^a	[Pd] 1	l a:2a (equiv)	Μ	$X \pmod{\%}$	yield of $3a^b$ (%)
1 ^{<i>c</i>}	$Pd(OAc)_2$	1.5:1.0	K	4	18
2	$Pd(OAc)_2$	1.0:3.0	Κ	10	8
3	Pd1	1.0:3.0	Κ	10	42
4	Pd1	1.0:3.0	Li	10	nd
5	Pd1	1.0:3.0	Na	10	65
6	$Pd(OAc)_2$	1.0:3.0	Na	10	29
7	Pd ₂ dba ₃	1.0:3.0	Na	5	trace
8	Pd2	1.0:3.0	Na	5	56
9	Pd3	1.0:3.0	Na	5	56
10	Pd4	1.0:3.0	Na	10	62
11	Pd1	1.0:3.0	Na	5	69
12	Pd1	1.0:3.0	Na	1	73
13	Pd1	1.0:3.0	Na	0	n.d.
14	Pd1	1.0:1.5	Na	1	74
15	Pd1	1.5:1.0	Na	1	81
16 ^d	Pd1	1.5:1.0	Na	1	80
17^e	Pd1	1.5:1.0	Na	1	84
	Pd_TM	s CI Pd CI	Ph_ C	Pd Cl Pd Pd Pd Ph	()-g- P->
	Pd1	Pd2		Pd3	Pd4

^{*a*}Reaction conditions: benzoate **1a** (50–75 μ mol), aryl chloride **2a** (50–150 μ mol), [**Pd**] (0.50–5.0 μ mol), PCy₃ (1.0–10 μ mol), dioxane (0.25 M). ^{*b*}Yield determined by calibrated GC–FID analysis using biphenyl as an internal standard. Reactions were run in duplicate or triplicate, and the average yield is reported. ^{*c*}Reaction was conducted at 3 times the scale and at 160 °C. ^{*d*}Reaction was conducted using a new, unused stir bar and vial. ^{*e*}Reaction was conducted at 10 times the scale. nd = not detected.

When the temperature was reduced to 120 °C, less than 10% of the product was obtained even with increased catalyst loading (entry 2). Changing the precatalyst to Pd1 dramatically improved the yield (entry 3), confirming the core hypothesis that precatalyst Pd1 is adventitious for this coupling. Using a sodium benzoate instead of a potassium benzoate improved the yield, while the lithium benzoate was unreactive (Table 1, entries 4 and 5). The use of the sodium benzoate with $Pd(OAc)_2$ was beneficial; but it was still inferior to the reaction with precatalyst Pd1 (entry 5 vs 6). The common precatalyst Pd₂dba₃ was unreactive, which may be due to nanoparticle formation (entry 7).²⁸ Other precatalysts, which are designed to liberate Pd⁰, were comparable to Pd1 (entries 8-10). Reducing the catalyst loading from 10 mol % to 1 mol % did not significantly affect the yield (entries 11-12). No reaction occurred without palladium (entry 13).

Reducing the excess of reagent (entry 14) and changing the aryl chloride to be the limiting reagent (entry 15) improved the yield. An unused vial and stir bar were used to avoid possible contamination from other metals,²⁹ which did not alter the results (entry 16). Lastly, the scale of the reaction could be increased 10-fold without an impact on yield (entry 17).

Changing the aryl chloride from electron-deficient substrate **2a** to electron-rich substrate **2b** substantially decreased the yield (Table 2, entry 1). A dependence on the electrophile was

Table 2. Ligand Optimization with PMPCl

F F 1a	O F Cl 2b	1 mol % Pd1 2 mol % XPhos 140 °C, 72 h dioxane F	F F Sb
entry ^a	ligand	temp (°C)	yield 3b ^b (%)
1	PCy ₃	120	trace
2	PCy ₃	140	15
3 ^c	BrettPhos	140	12
4	BrettPhos	140	34
5	AdBrettPhos	140	26
6	RuPhos	140	26
7	SPhos	140	85
8	XPhos	140	87

^{*a*}Reaction conditions: benzoate 1a (50 μ mol), aryl chloride 2b (75 μ mol), Pd1 (0.50 μ mol), ligand (1.0 μ mol), dioxane (0.10 M). ^{*b*}Yield determined by calibrated GC–FID analysis using biphenyl as an internal standard. Reactions were run in duplicate, and the average yield is reported. ^{*c*}The reaction was conducted with 1 mol % ligand.

unexpected because decarboxylation was calculated to be the rate-determining step in similar reactions, $^{23,30-33}$ although a DFT study by Fang³⁴ showed that the rate-determining step can be highly substrate dependent. These DFT calculations used PMe₃ as a model ligand. 23,34 Therefore, these results may not transfer to catalytic reactions using PCy₃ or another ligand. Furthermore, the room-temperature cross-coupling of aryl chlorides is known, $^{35-37}$ and the calculated barrier for oxidative addition 23,38 indicates that this elementary step should be facile at elevated temperatures. These thoughts prompted a second cycle of optimization. Increasing the temperature from 120 to 140 °C afforded a modest improvement in the yield (entry 2). Use of Buchwald-style ligands, which are competent at difficult oxidative additions, provided higher yields (entries 3-8). 35,39 In particular, both SPhos (entry 7) and XPhos (entry 8) were optimal.

Using XPhos, the aryl chloride scope was broad. The two model compounds were isolated in the expected yields (Scheme 2, 3a,b). When the scale was increased to 1 mmol, the yield was not affected (3b). Electronically neutral electrophiles gave a high yield of the biaryl product (3c-e). Electrophiles with an electron-withdrawing group in the *para* position were competent coupling partners (3f-h). A substrate with an *ortho*-electron-donating group (3i) or an *ortho*electron-withdrawing group (3j) provided a good yield. Reactive functional groups such as an ester (3k) or an aldehyde (3l) were tolerated. Heterocycles were competent coupling partners for the decarboxylation (3m,n), and a double-decarboxylative coupling was possible (3o).

A screen of additives was conducted to test the robustness of the reaction (see the Supporting Information).^{40,41} Reactive

Scheme 2. Substrate Scope of Aryl Chlorides



^{*a*}Reactions were run in duplicate or triplicate, and the average isolated yield is reported. ^{*b*}Reaction was conducted with PCy₃ at 120 °C. ^{*c*}Reaction was conducted on a 1 mmol scale. ^{*d*}Reaction time was 48 h. ^{*e*}Reaction was conducted at 160 °C. ^{*f*}Reaction was conducted with 0.3 mmol **20**, with 3 equiv of benzoate using 2 mol % of **Pd1**, at 160 °C.

groups such as an alkene, nitrile, ketone, alcohol, aniline, phenol, furan, indole, or acetal did not inhibit the reaction. Decyne was fully consumed, but its presence had only a minimal impact on the yield. The presence of 2,4-dimethoxypyridine inhibited the reaction, but the presence of 3,5-dimethylpyridine did not affect the yield. Additionally, the yield was not diminished when the free carboxylic acid was used in conjunction with 1.1 equiv of Na_2CO_3 (see the Supporting Information).

The scope of sodium carboxylates that participate in this decarboxylative coupling was explored. Other 2,6-difluoroarenes were tolerated (Scheme 3, 4a-c). Sodium pentafluorobenzoate coupled efficiently (4d) as did other polyfluoroarenes (4e-g). Substrates with one or both *o*-fluorine atoms substituted for a trifluoromethyl (4h) or methoxy group (4i,j) afforded acceptable yields of the biaryl. Heterocyclic carboxylates were competent coupling partners (4k-n). The benzoate scope for decarboxylative cross-coupling has limitations, but the scope is complementary to the Suzuki– Miyaura cross-coupling. In particular, polyfluoroboronic acids

Scheme 3. Substrate Scope of (Hetero)aryl Carboxylates



^{*a*}Reactions run in duplicate, and the average isolated yield is reported. ^{*b*}Reaction time was 48 h at 0.12 M dioxane. ^{*c*}Reaction conducted at 120 °C for 48 h. ^{*d*}Reactions conducted at 160 °C for 72 h. ^{*e*}Reaction conducted at 180 °C for 72 h at 0.1 M dioxane. ^{*f*}Reactions conducted at 180 °C for 72 h. ^{*g*}Reactions conducted at 180 °C. ^{*h*}Isolated as an inseparable mixture along with an *N*-arylation byproduct.

and heteroaryl boronic acids are prone to protodeborylation under Suzuki–Miyaura conditions. $^{4-6}$

Ideally, cross-coupling would be promoted with only a trace loading of palladium.⁴² The catalyst loading was stressed to determine the lowest operable loading (Table 3). A high yield and conversion were observed using 0.5 mol % of Pd1 (entry 1). Using a 0.1 mol % or 0.05 mol % catalyst loading decreased the yield due to incomplete conversion (entries 2 and 3). This demonstrates that up to 800 turnovers are possible with this system.

Precatalyst **Pd1** is not ideal for general use due to its relatively high cost and sensitivity. Fortunately, the Buchwald lab recently described air-stable and commercially available precatalysts with XPhos or SPhos ligands.^{43,44} These precatalysts performed on par with precatalyst **Pd1** in this system. Using SPhos-G3 or XPhos-G2 at 1 mol % catalyst loading resulted in complete conversion and a high yield (entries 4 and 5). Further reducing the loading to 0.1 mol % afforded similar results to complex **Pd1** across a range of precatalysts (entries 6–9).

In conclusion, we report a palladium-catalyzed crosscoupling between sodium carboxylates and aryl chlorides. This coupling uses a low catalyst loading and two of the lowest energy coupling partners. Therefore, this process represents one of the most efficient approaches to cross-coupling, with

Table 3. Reduced Catalyst Loading and Buchwald Complexes



^{*a*}Reaction conditions: benzoate **1a** (0.3 mmol), aryl chloride **2b** (0.2 mmol), [**Pd**] (2.0–0.1 μ mol), dioxane (0.2 M). ^{*b*}Yield determined by calibrated GC–FID analysis using biphenyl as an internal standard. Reactions were run in duplicate or triplicate, and the average yield is reported.

only CO_2 and NaCl as stoichiometric byproducts. Further developments will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01620.

Experimental procedures and data (PDF)

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The authors declare no competing financial interest.

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