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Pd-Catalyzed Decarbonylative Cross-Couplings of Aroyl Chlorides

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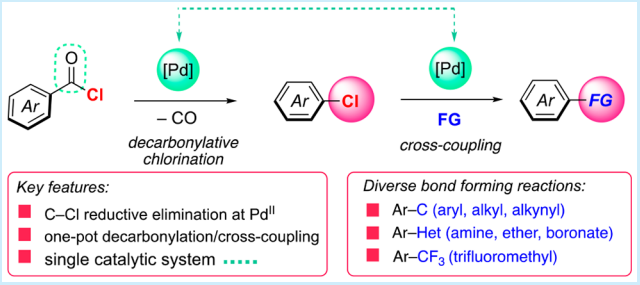
Supporting Information

ABSTRACT: This report describes a method for Pd-catalyzed decarbonylative cross-coupling that enables the conversion of carboxylic acid derivatives to biaryls, aryl amines, aryl ethers, aryl sulfides, aryl boronate esters, and trifluoromethylated arenes. The success of this transformation leverages the Pd^0/Brettphos-catalyzed decarbonylative chlorination of aroyl chlorides, which can then participate in diverse cross-coupling reactions *in situ* using the same Pd catalyst.



Metal-catalyzed cross-coupling reactions are among the most versatile methods for the construction of carbon−carbon and carbon−heteroatom bonds.[1] Traditionally these transformations are performed using aryl halides as electrophiles. However, more recent efforts have focused on the use of carboxylic acid derivatives as the electrophilic coupling partners by leveraging metal-mediated decarboxylation or decarbonylation of these substrates.[2−9] Carboxylic acids and derivatives offer the distinct advantages that they are inexpensive and readily available and are also present in numerous natural products and bioactive molecules. As such, general methods for cross-coupling with these substrates would offer practical and strategic advantages in the context of complex molecule synthesis.[2]

Seminal reports on decarbonylative cross-coupling reactions of carboxylic acid derivatives have demonstrated the viability of this approach for the construction of various types of C−C bonds.[4−6] Examples include the decarbonylative cross-coupling of esters or anhydrides with organoboron and organozinc reagents to form biaryls,[4] with alkenes to form styrene derivatives,[5] and with alkynes to form aryl acetylenes.[6] Recent reports have also demonstrated Ni-, Pd-, or Rh-catalyzed decarbonylative couplings of aryl esters or amides to access arylboron,[7] arylsilane,[8] and aryl ether products.[9] However, despite recent progress in the field, decarbonylative cross-coupling reactions still have several key limitations. First, only a limited set of cross-coupling products can be accessed. For instance, there are no general methods for the decarbonylative conversion of carboxylic acid derivatives to aryl halides, aryl amines, or trifluoromethylated arenes. Second, most existing decarbonylative cross-couplings are specific to one type of C−C or C−X bond-forming reaction. As such, there are no general conditions for accessing diverse C−C and C−X coupled products from a single carboxylic acid derivative. Herein, we address these limitations through the development of a Pd-catalyzed decarbonylative coupling of aroyl chlorides. Notably, aroyl chlorides are valuable starting materials because they can be readily synthesized from a variety of carboxylic acid derivatives.[10] Moreover, they have proven to be effective substrates for Rh[4f,5c,d] and Pd[5b] decarbonylative cross-coupling reactions to form $C(sp^2)-C(sp^2)$ bonds. As shown in Figure 1,

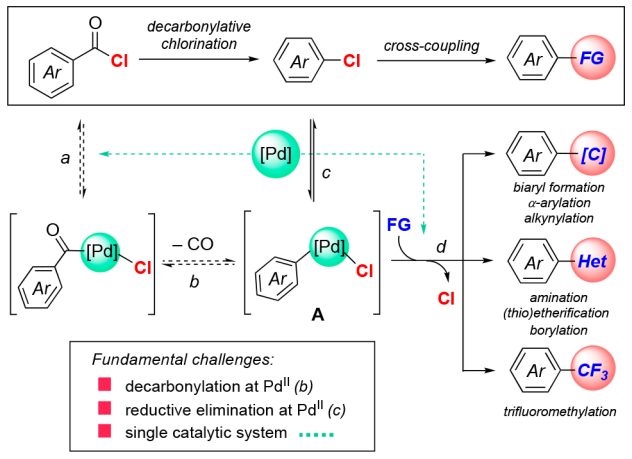


Figure 1. Design of a Pd-catalyzed decarbonylative chlorination and subsequent cross-coupling reaction.

our proposed Pd-catalyzed decarbonylative cross-coupling from aroyl chlorides leverages C−Cl bond-forming reductive elimination from Pd^{II} as a key step.[11−13] The resulting aryl chloride products then engage *in situ* with the same Pd catalyst to form C−C, C−N, C−O, C−S, C−B, and $C-CF_3$ bonds.

We first sought to identify a Pd-catalyst for the conversion of aroyl chlorides to aryl chlorides. As shown in Figure 1, a plausible catalytic cycle for this transformation could involve (a) oxidative addition of the acyl C−Cl bond at Pd^0;[14] (b) decarbonylation;[14,15] and (c) C−Cl bond-forming reductive elimination.[12,13] To date, the only reported example of this

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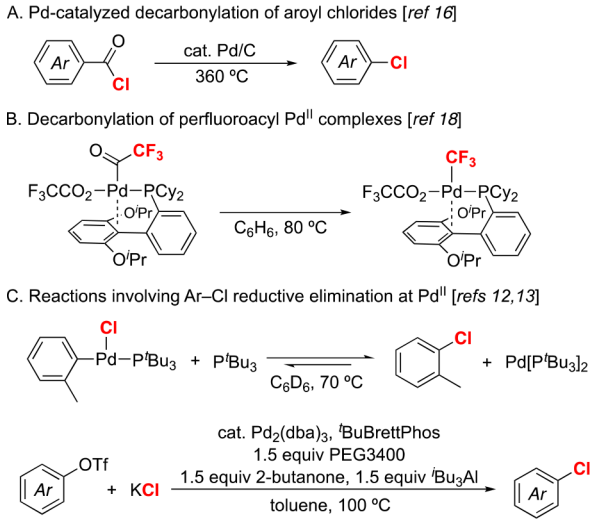
reaction catalyzed by Pd involves the use of Pd/C at 360 °C (Scheme 1A).[16,17] The requirement for extremely high temperatures likely reflects kinetic challenges associated with the decarbonylation[14] and/or C−Cl coupling steps of the cycle.[11−13]

Scheme 1. Decarbonylation Reactions and Reductive Elimination of Aryl Chloride at Pd(II)



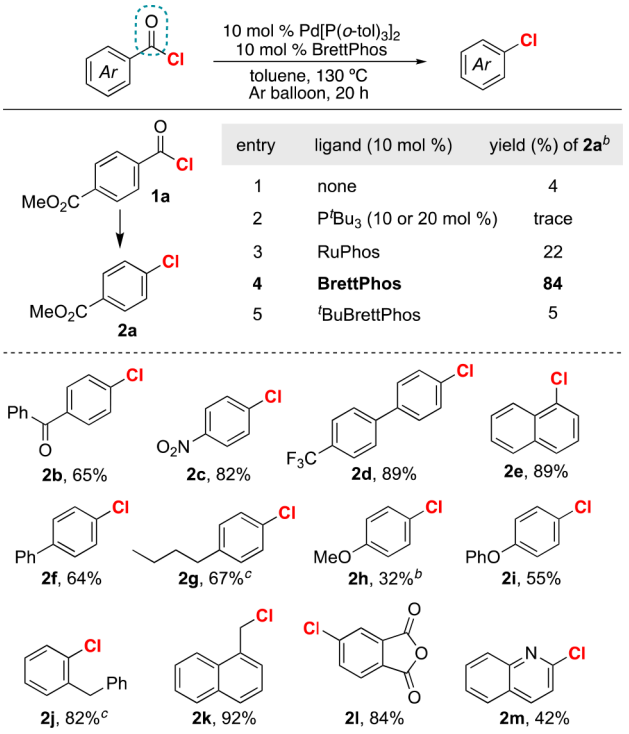
We have previously reported that perfluoroacylpalladium complexes undergo decarbonylation at 80 °C in benzene (Scheme 1B).[18] In this system, decarbonylation was fastest with the electron-rich and sterically bulky monophosphine ligand RuPhos. Other groups have reported that related monophosphines, including P^tBu_3[12] and ^{t}BuBrettPhos,[13] promote both stoichiometric and catalytic aryl−Cl coupling at Pd^{II} (Scheme 1C). As such, we reasoned that these three ligands would serve as an attractive starting point for developing the proposed decarbonylative chlorination of aroyl chlorides.

Our initial studies focused on the decarbonylative chlorination of **1a** using $Pd[P(o\text{-tol})_3]_2$ as a Pd^0 source.[19] Without added ligand, the yield of aryl chloride **2a** was 4% (Scheme 2, entry 1). The addition of P^tBu_3 did not improve this transformation (entry 2). However, the use of 10 mol % of RuPhos resulted in a 22% yield of **2a** (entry 3). BrettPhos proved to be the optimal ligand, providing **2a** in 84% yield (entry 4).

The Pd/Brettphos-catalyzed decarbonylative chlorination was next applied to a series of acid chloride substrates (Scheme 2). Electronically diverse aroyl chlorides reacted under the optimal conditions to afford aryl chlorides **2a−j** in moderate to high isolated yields. Esters, ketones, nitro, and anhydride groups were well-tolerated. Relatively hindered *ortho*-substituted aroyl chlorides reacted to afford **2e** and **2j** in high yields. This method also enabled the formation of the $C(sp^3)$−Cl bond in benzylic chloride **2k** in 92% yield.

Aryl chlorides are valuable synthetic intermediates because they can be used as electrophiles for Pd-catalyzed cross-coupling reactions.[1] Furthermore, the combination of Pd^0 and Brettphos is one of the most general catalyst systems for aryl chloride cross-coupling.[20,21] As such, we next sought to leverage this decarbonylative chlorination system to access diverse cross-coupled products in a single pot. Using **1a** and **1e** as substrates, we carried out decarbonylative chlorination and then directly

Scheme 2. Scope of Decarbonylative Chlorination[a]



entry	ligand (10 mol %)	yield (%) of **2a**[b]
1	none	4
2	P^tBu_3 (10 or 20 mol %)	trace
3	RuPhos	22
4	**BrettPhos**	**84**
5	^{t}BuBrettPhos	5

[a]General conditions: acid chloride (0.5 mmol, 1 equiv), $Pd[P(o\text{-tol})_3]_2$ (0.1 equiv), BrettPhos (0.1 equiv), toluene (1.5 mL), 130 °C under Ar balloon, 20 h. Isolated yields. [b]GC yield. [c]$Pd(dba)_2$ in dioxane.

added a nucleophilic coupling partner and heated for an additional 20 h (Scheme 3). This two-step, one-catalyst procedure enabled C−C coupling to generate Suzuki−Miyaura biaryl products **3** and **6**, α-arylation product **7**, and alkynylation product **8** in good to excellent yields. Aryl amines (**4**, **9**, **10**), ethers (**5**, **11**), thioethers (**12**), and boronate esters (**13**) were also formed in good yields. Notably, these transformations were all conducted under a single set of reaction conditions without the need for optimization.

Fluoroalkylated arenes are prevalent in both pharmaceutical and agrochemicals.[22] We noted that Pd^0/Brettphos is a uniquely effective Pd catalyst for the cross-coupling of aryl chlorides with perfluoroalkyl nucleophiles.[21d] As such, we next pursued a two-step, one-catalyst process for converting aroyl chlorides to trifluoromethylated arenes. As shown in Scheme 3B, 1-trifluoromethyl naphthalene **14** was obtained in 72% yield via sequential $Pd(dba)_2$/Brettphos-catalyzed decarbonylative chlorination of **1e** followed by the addition of $TESCF_3$ and KF. Other aroyl chlorides were also transformed to their corresponding trifluoromethyl arenes **15−19**.

The reactions in Scheme 3 would be even more attractive if they did not require sequential addition of the aroyl chloride and then nucleophile. With most nucleophiles, this procedure leads to either decomposition of the aroyl chloride or direct coupling with the nucleophile prior to decarbonylation. However, we hypothesized that, for trifluoromethylation with $TESCF_3$, the low solubility of the KF activator in dioxane might slow transmetalation sufficiently to enable decarbonylation to proceed. Indeed, as shown in Scheme 4, the combination of substrates **1e** or **1j**, Pd catalyst, $TESCF_3$, and KF afforded the decarbonylative trifluoromethylation products **14** and **17** in 81% and 52% yield, respectively.

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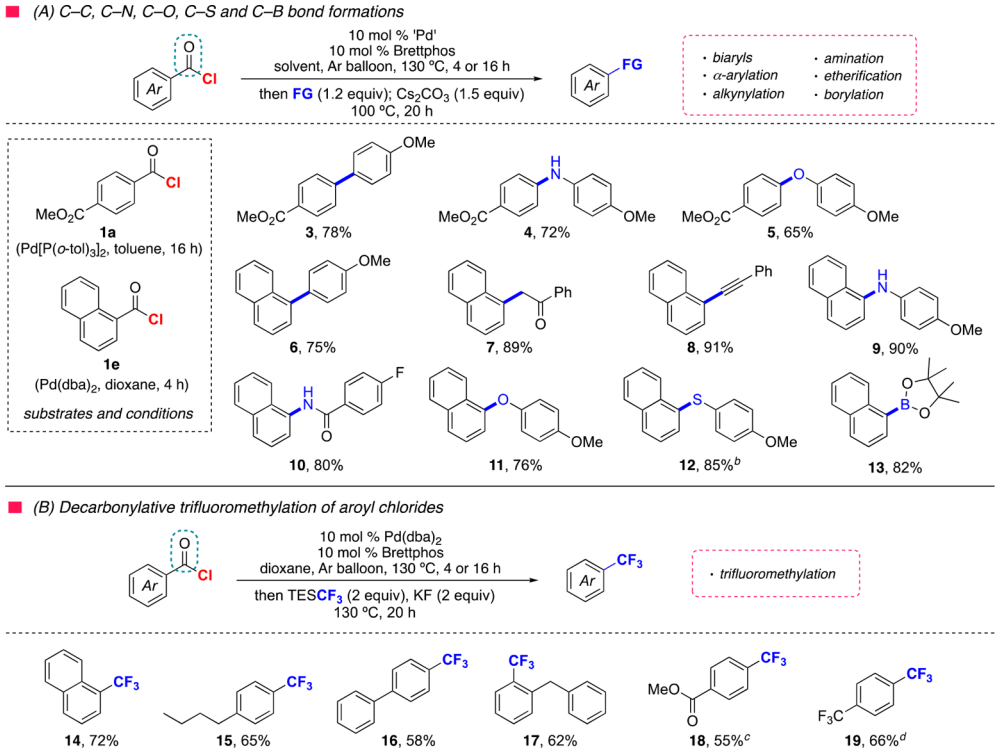
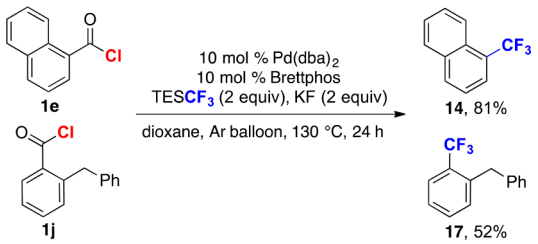
Scheme 3. Scope of Pd-Catalyzed Cross-Coupling Reactions via Decarbonylative Chlorination[a]



[a]General conditions: aroyl chloride (0.5 mmol, 1 equiv), $Pd(dba)_2$ (0.1 equiv), BrettPhos (0.1 equiv), solvent (1.5 mL), 130 °C under Ar balloon, 4 or 16 h; then coupling partner (1.2−2 equiv), base (1.5−2 equiv), 100−130 °C, 20 h. Isolated yields. Coupling partner (product): 4-methoxyphenylboronic acid (**3**, **6**), *p*-anisidine (**4**, **9**), 4-fluorobenzamide (**10**), 4-methoxyphenol (**5**, **11**), acetophenone (**7**), phenylacetylene (**8**), B_2pin_2 (**13**), 4-methoxythiophenol (**12**). Base (product): NaO*t*Bu (**7**), KO*t*Bu (**12**), and KOAc (**13**). [b]An aliquot of $Pd(dba)_2$/dppf (0.01 equiv) in dioxane (0.3 mL) was added in thiolation step. [c]$Pd[P(o\text{-}tol)_3]_2$ as catalyst. [d]^{19}F NMR yield.

Scheme 4. Decarbonylative Trifluoromethylation Does Not Require Sequential Addition of Coupling Partner[a]



[a]Conditions: aroyl chloride (0.5 mmol, 1 equiv), $Pd(dba)_2$ (0.1 equiv), BrettPhos (0.1 equiv), $TESCF_3$ (2 equiv), KF (2 equiv), dioxane (1.5 mL), 130 °C, Ar balloon, 24 h. Isolated yields.

In summary, this letter describes a Pd-catalyzed decarbonylative chlorination of aroyl chlorides. Brettphos is used as a ligand to promote both the decarbonylation and the challenging C−Cl bond-forming reductive elimination. The subsequent addition of a nucleophile/base enables the one-pot conversion of these carboxylic acid derivatives to form C−C, C−N, C−O, C−S, C−B, and C−CF_3 bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02024.

Experimental details, characterization, and NMR data for isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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