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Palladium-Catalyzed Decarboxylative Coupling of Quinolinone-3-Carboxylic Acids and Related Heterocyclic Carboxylic Acids with (Hetero)aryl Halides

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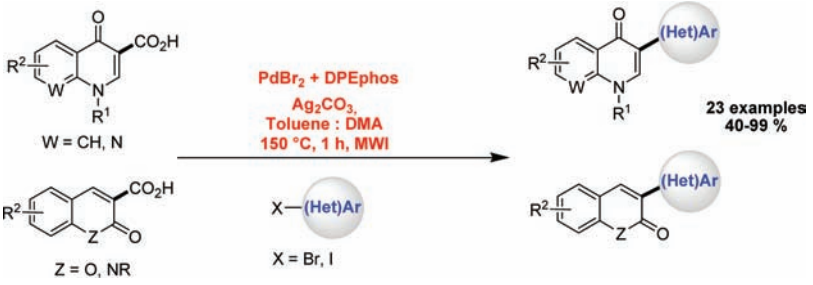
ABSTRACT



An efficient and practical decarboxylative cross-coupling reaction of quinolin-4(1*H*)-one 3-carboxylic acids with (hetero)aryl halides has been established. Under a bimetallic system of $PdBr_2$ and silver carbonate, the protocol proved to be general, and a variety of 3-(hetero)aryl 4-quinolinones and related heterocycles, such as 3-aryl-1,8-naphthyridin-4(1*H*)-ones, 3-arylcoumarins, 3-arylquinolin-2(1*H*)-ones, and 2-arylchromones, can be prepared in good to excellent yields.

The transition metal-catalyzed decarboxylative cross-coupling[1] of aryl carboxylic acids with aryl halides is a useful alternative to traditional methods (e.g., Negishi, Stille, Suzuki−Miyaura) in sp^2 carbon−carbon bond formation. These decarboxylative reactions, employing easily available carboxylic acids as nucleophilic coupling partners, avoid the need for stoichiometric amounts of the organometallic reagent, some of which are toxic or must be prepared through multistep procedures. Typically, the decarboxylation protocol requires the use of a bimetallic system based on a palladium complex to activate the aryl halide together with a copper or silver salt promoting the decarboxylation step to generate an arylmetal species.[2]

In contrast to the much more developed palladium-catalyzed decarboxylative reaction of σ electron poor

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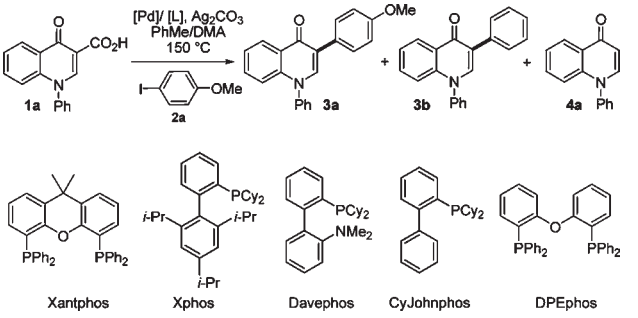
benzoic acids with aryl halides for biaryl synthesis,[3] decarboxylative couplings of heterocyclic carboxylic acids with aryl halides have received much less attention. In these instances, very few heterocycles were studied. Steglich et al.[4] reported a single example of an intramolecular reaction of a pyrrole carboxylic acid with a bromoarene within a total synthesis of lamellarin L. Forgione and Bilodeau[5] reported intermolecular decarboxylative couplings of five-membered heterocyclic carboxylic acid substrates (e.g., pyrrole, furan, oxazole, and thiazole) with aryl bromides under palladium catalysis. Subsequently, other groups have extended this method to substituted azoles, including 2-aryloxazoles,[6] 3,4-dioxypyrrole,[7] and benzothiophene.[8] Outside of these contributions, there have been no focused efforts on heterocyclic carboxylic acid couplings. Given the stability and high availability of heterocyclic carboxylic acids relative to heterocyclic organometallics, the reaction has great potential for the synthesis of multiheteroaryl bioactive compounds.

In an ongoing medicinal chemistry program directed toward hsp90,[9] an exciting new target in cancer drug discovery,[10] we required the synthesis of 3-(hetero)aryl-4-quinolinones **3**. Traditional strategies to prepare such molecules involve the construction of the heterocycle rings by nontrivial multistep reaction sequences.[11] Alternative routes consist of the one pot tandem condensation–cyclization of anilines with 3-(2-bromophenyl)-3-oxopropanal derivatives,[12] or palladium-catalyzed Suzuki cross-coupling of 3-halo-4-quinolinones with boronic acids.[13] As part of our continuing effort at the functionalization of heterocycles via transition-metal-catalyzed reactions,[14] we decided to explore the ability of the 4-quinolinone 3-carboxylic acids **1** to participate in metal-catalyzed decarboxylative cross-coupling reactions with various (hetero)-aryl halides. From a synthetic viewpoint, this coupling should be the shortest and most efficient route to

Table 1. Optimization of the Pd-Catalyzed Decarboxylative Coupling of Quinolinone-3-carboxylic Acid **1a** with 4-Iodoanisole **2a**[a]



entry	[Pd]	ligand	ratio[b] **1a/3a/3b/4a**	yield (%)[c]
1	$PdCl_2$	PPh_3	7/56/29/8	42
2	$PdBr_2$	PPh_3	0/64/32/5	52
3	PdI_2	PPh_3	20/47/22/11	39
4	$Pd(OAc)_2$	PPh_3	40/42/15/2	–
5	$PdBr_2$	P(*o*-tolyl)$_3$	0/17/0/83	–
6	$PdBr_2$	P(*c*-hexyl)$_3$	12/20/68	–
7	$PdBr_2$	Xantphos	2/51/43/4	49
8	$PdBr_2$	Xphos	0/36/0/64	–
9	$PdBr_2$	Davephos	1/40/0/59	–
10	$PdBr_2$	CyJohnphos	1/15/0/84	–
11	$PdBr_2$	DPEphos	0/82/13/5	77
12	**$PdBr_2$**	**DPEphos**	**0/85/10/5**	**81**[d,e]
13	$PdBr_2$	DPEphos	7/72/16/5	60

[a] **1a** (1 equiv), 4-iodoanisole (2 equiv), [Pd] (5 mol %), [L] (10 mol %), Ag_2CO_3 (1 equiv), toluene/DMA (3.6/0.4 mL, 0.05M), 8 h at 150 °C. [b] Ratio was determined by ^{1}H NMR in the crude reaction mixture based on the chemical shift of the proton signal (ppm) at the 2-position (**1a**: δ = 8.79, **3a**: δ = 7.79, **3b**: δ = 7.83). [c] Isolated yields of **3a**. [d] Heating the reaction under microwave irradiation (MWI) for 1 h at 150 °C. [e] No reaction occurred in the absence of $PdBr_2$ or ligand and in the absence of $PdBr_2$ and ligand.

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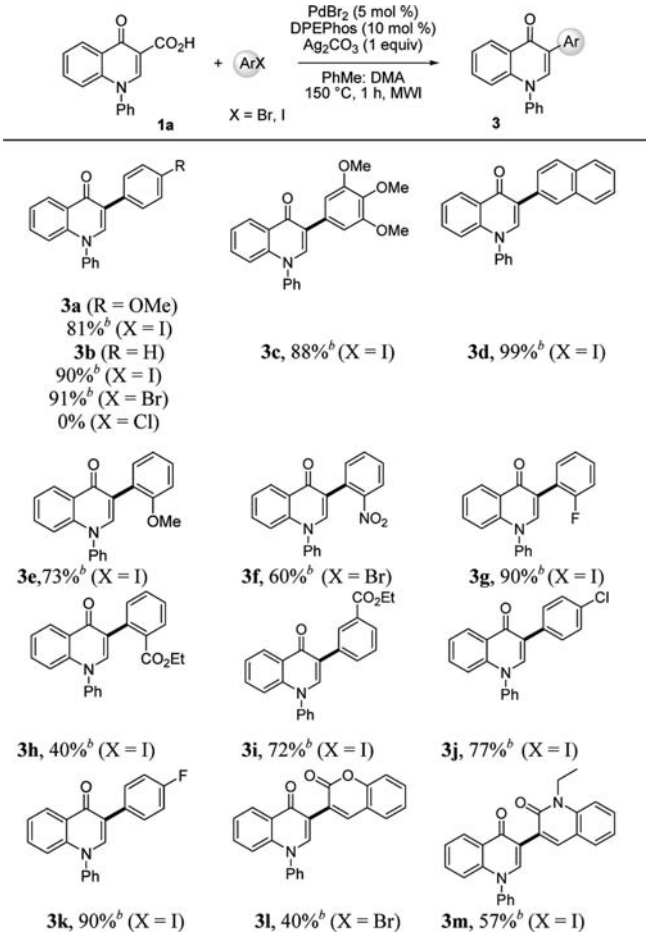
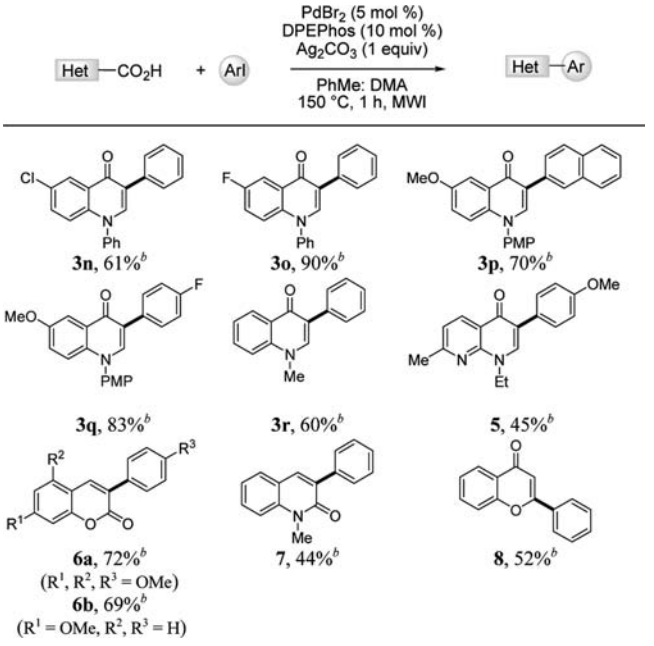
Scheme 1. Pd-Catalyzed Decarboxylative Coupling of **1a** with Various (Hetero)aryl Halides[a]



[a] Reactions of **1** (1 equiv) with ArX (2 equiv) were performed under MWI in a sealed Schlenk tube at 150 °C in toluene/DMA (3.6/0.4 mL, 0.05 M) by using $PdBr_2$ (5 mol %), DPEPhos (10 mol %), and Ag_2CO_3 (1 equiv). [b]Isolated yields.

Scheme 2. Pd-Catalyzed Decarboxylative Coupling of Heterocyclic Carboxylic Acid Derivatives with Various Aryl Iodides[a]



[a] Reactions of heterocyclic carboxylic acid (1 equiv) with ArI (2 equiv) were performed under MWI in a sealed Schlenk tube at 150 °C in toluene/DMA (3.6/0.4 mL, 0.05 M) by using $PdBr_2$ (5 mol %), DPEPhos (10 mol %), and Ag_2CO_3 (1 equiv). [b]Isolated yields.

3-(hetero)arylquinolin-4(1*H*)-ones **3** for the purpose of medicinal chemistry screening programs. To the best of our knowledge, there is no report describing the formation of **3** and related heterocycles using this idea. Herein we report our success on the development of such a protocol.

In our initial study, 4-quinolinone 3-carboxylic acid **1a** and 4-iodoanisole **2a** were chosen as model substrates for the decarboxylative coupling process. The reaction was first investigated under previously reported conditions for decarboxylative couplings of azole carboxylic acid substrates,[6] using $PdCl_2$ (5 mol %)/PPh_3 (10 mol %) as the catalyst system and Ag_2CO_3 (1 equiv) as the base in toluene/DMA at 150 °C for 8 h. However, this transformation was inefficient and resulted in concomitant formation of the expected 3-arylquinolinone derivative **3a**, together with **3b**, and byproduct **4a** derived from protodecarboxylation of **1a**. After a tedious separation, **3a** was isolated in a low 42% yield (Table 1, entry 1). Of note, compound **3b** arises from the aryl migration between the metal center and coordinated phosphine in the Pd(II) complex. This reactivity is quite rare but has nevertheless already been reported.[15] To circumvent the formation of byproducts **3b** and **4a**, an extensive screening of various reaction parameters (palladium, ligand, solvent, base, and temperature) was conducted (for more details, see Supporting Information). As shown in Table 1, PdI_2 and $Pd(OAc)_2$ were less effective (entries 3 and 4), whereas $PdBr_2$ gave a slightly better yield as compared to that of $PdCl_2$ (52%, entry 2). Evaluation of other ligands revealed that the nature of phosphine has an important influence on the reaction selectivity (entries 2, 5−11). Thus, we were delighted to find that the use of the bidentate phosphine DPEphos (entry 11) in combination with $PdBr_2$ in toluene/DMA at 150 °C for 8 h is superior to all other choices (compare entries 2 and 5−11). Having determined optimal conditions for the formation of **3a** using classical heating, we attempted to use microwave activation to enhance the reaction rate and possibly to reduce the reaction time as well as to increase the yield. We were pleased to find that the coupling of **1a** with **2a** under microwave irradiation using similar conditions as those of entry 11 provided **3a** in an 81% isolated yield after only 1 h (entry 12). It should be noted that carrying out the reaction using traditional oil bath heating (150 °C, 1 h, sealed tube) induced a lowering of the conversion rate and provided **3a** in only 60% yield (entry 13). This result clearly demonstrated the benefit of using microwave irradiation. In summary, the best

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conditions were found to require **1a** (1 equiv), **2a** (2 equiv), $PdBr_2$ (5 mol %), DPEPhos (10 mol %), and Ag_2CO_3 (1 mmol), in toluene/DMA (9:1) in a sealed Schlenk tube at 150 °C for 1 h under microwave irradiation. A control experiment revealed that the Pd-catalyst and silver carbonate were necessary for the coupling to occur. No product could be formed in the absence of $PdBr_2$, or when Ag_2CO_3 was replaced by other bases (for more details, see Supporting Information).

Prompted by these results, we subsequently investigated the substrate scope for the Pd-catalyzed decarboxylative coupling of **1a** with various (hetero)aryl halides possessing different steric and electronic properties. As illustrated in Scheme 1, both aryl iodide and bromide reacted well providing the desired compound **3b** in excellent yields, whereas no reaction occurred when aryl chloride was used as a coupling partner. Electron-rich and -deficient, meta and para substituted aryl iodides and bromides all efficiently underwent decarboxylative coupling with **1a** in good yields (products **3a**–**d** and **3i**–**k**). In addition, the sterically demanding ortho substitution pattern was tolerated toward the coupling reaction of **1a**, leading to 3-arylquinolin-4(1*H*)-ones **3e**–**h** in yields ranging from 40 to 90%, regardless of the electronic nature of the substituents. Interestingly, this coupling reaction also proceeded successfully in the case of heterocyclic halides such as 3-bromocoumarin[16] and 3-bromoquinolin-2(1*H*)-one, leading to **3l** and **3m** in 40 and 57% yields, respectively.

To expand the scope of our method further, a range of quinolin-4(1*H*)-one 3-carboxylic acids as well as related heterocyclic carboxylic acids were subjected to the coupling protocol with aryl iodides (Scheme 2). We were pleased to observe that *N*-alkyl- and *N*-arylquinolin-4(1*H*)-one 3-carboxylic acids having electron-donating or -withdrawing groups on the aromatic nucleus led to the formation of the corresponding **3n**–**r** in good yields. Interestingly, product **3n** revealed excellent chemical selectivity preserving the C–Cl bond, which could undergo further metal catalyzed functionalization processes.[17] Next, we used this new catalytic system in decarboxylative coupling of other heterocyclic carboxylic acids. Overall, we were pleased with the generality of our protocol. The reaction proceeded in satisfactory yields with 1,8-naphthyridin-4(1*H*)-one, coumarin, quinolin-2(1*H*)-one 3-carboxylic acids, and chromone 2-carboxylic acids to afford the coresponding arylated heterocycles **5**–**8** in moderate to good yields.

In conclusion, we developed an efficient and practical $PdBr_2$/DPEphos catalyzed system for decarboxylative coupling of various quinolin-4(1*H*)-one 3-carboxylic acids with (hetero)aryl halides. The protocol exhibited a broad substrate scope with respect to both the heterocyclic carboxylic acids and (hetero)aryl halides, thus providing an attractive alternative to the existing methods for the synthesis of 3-(hetero)aryl-quinolin-4(1*H*)-ones **3** and related heterecycles **5**–**8** of biological interest.

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Supporting Information Available. Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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