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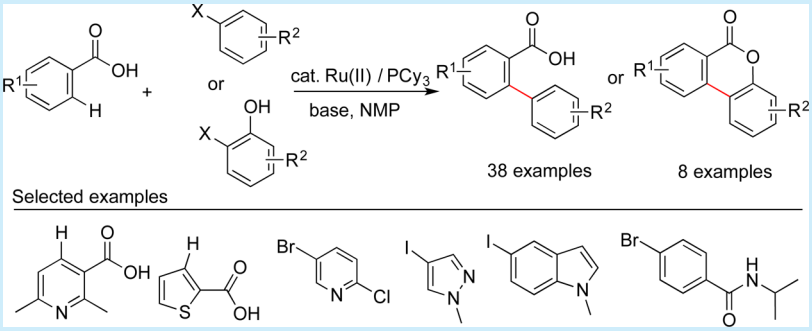
Ruthenium-Catalyzed C−H Arylation of Diverse Aryl Carboxylic Acids with Aryl and Heteroaryl Halides

Liangbin Huang and Daniel J. Weix*

University of Rochester, Rochester, New York 14627-0216, United States

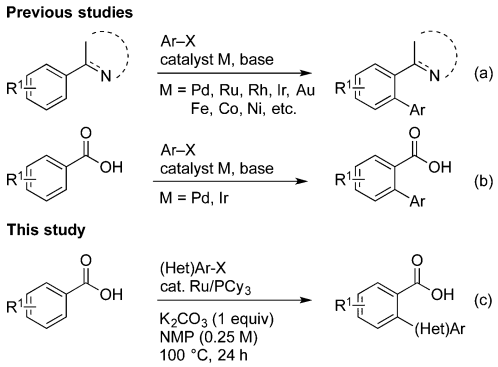
Supporting Information



ABSTRACT: Ruthenium ligated to tricyclohexylphosphine or di-*tert*-butylbipyridine catalyzes the arylation of carboxylic acids with diverse aryl halides (iodide, bromide, and triflate; aryl and heteroaryl). In addition, arylations with 2-iodophenol formed benzochromenones, carboxylate was shown to be a stronger donor than an amide, and the arylation of a pyridine carboxylate was demonstrated. Stoichiometric studies demonstrated that the added ligand is required for reaction with the electrophile but not the C−H bond.

The synthesis of biaryls by directed C−H arylation has become an essential tool in organic synthesis.[1] However, the majority of arylation methods still rely on strongly coordinating donor groups that can be inconvenient to introduce and remove (Scheme 1a).[1,2] A major advance was the finding that certain catalysts are capable of C−H arylation *ortho* to a carboxylic acid directing group, a weak donor[3] that is a versatile intermediate in organic synthesis.[4] C−H arylation with arylboron reagents,[3b,5] arenes,[6] and aryl electrophiles[3a,7] (Scheme 1b) has been demonstrated with a variety of metal catalysts. While powerful, significant challenges remain; for example, nitrogen-containing heteroaryl substrates have not been demonstrated for carboxylate directing groups.[8]

Scheme 1. C−H Arylation with Aryl Electrophiles



Although Ru-catalyzed C−H arylation has been extensively studied[9] and Ru-catalyzed C−H functionalization can be directed by the carboxylic acid group,[10] no examples of carboxylic acid directed C−H arylation have been reported. The notable lack of examples with ruthenium inspired us to initially examine a multimetallic solution[4c,11] of Ru and Ni, but the data eventually led us to an overlooked, relatively simple single-metal system (Scheme 1c).

We initially examined a combination of Ru and Ni catalysis to achieve the transformation (Table 1). Although [Ru(*p*-cymene)Cl_2]$_2$ or (dtbbpy)$NiBr_2$ alone failed to provide any of the C−H arylation product, the combination of the two catalysts formed product **3a** in 45% yield (entries 1−3). To our surprise, however, we found that the ligand on the nickel complex (4,4′-di-*tert*-butyl-2,2′-bipyridine, dtbbpy) was the key, and a reaction run with Ru and dtbbpy provided the same yield as the reaction run with nickel (entry 4). While many reports on ligand-free C−H arylation with strong directing groups exist,[9a] Ackerman has used PCy_3 with ruthemium[9l] for arylation with a triazole directing group, and palladium-catalyzed reactions often use added ligands.[12] We report here that this ruthenium catalyst is a general solution for *ortho* C−H arylation of benzoic acid derivatives and overcomes some limitations of the Pd- and Ir-catalyzed methods.

We tested a number of other nitrogen and phosphorus ligands, but only 4,4′-di-*tert*-butyl-2,2′-bipyridine (48%), 4,4′-

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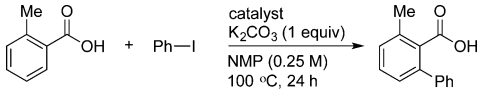
Table 1. C−H Arylation Catalyst Optimization[a]



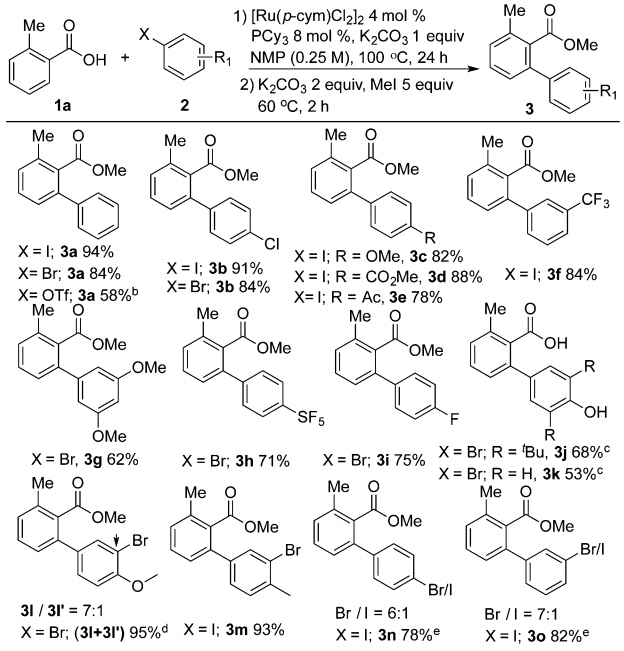
entry	catalyst	3a[b] (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %)	nd
2	$NiBr_2$·diglme/dtbbpy (4 mol %)	nd
3	$[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %) and $NiBr_2$·diglme/dtbbpy (4 mol %)	45
4	$[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %) and dtbbpy (4 mol %)	48
5	$[Ru(p\text{-cymene})Cl_2]_2$ (4 mol %) and PCy_3 (8 mol %)	91 (94[c])
6	$RuCl_3{\cdot}3H_2O$ (8 mol %) and PCy_3 (8 mol %)	68

[a]Reactions run with 2-methylbenzoic acid **1a** (0.25 mmol) and **2a** (1.5 equiv). [b]GC yield of methyl ester, uncorrected. [c]Isolated yield of methyl ester. Dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

dimethoxy-2,2′-bipyridine (58%), 6,6′-dimethyl-2,2′-bipyridine (67%), triphenylphosphine (51%), 1,4-bis(diphenylphosphino)butane (44%), and tricyclohexylphosphine (94%) gave a promising yield of product. The presence of a cymene ligand is not essential, and a simple $RuCl_3$ hydrate performed nearly as well (entry 6). See the Supporting Information for details on the other ligands examined and further optimization data.

Under the optimal conditions, ArI and ArBr are both suitable for these transformations. Various functional groups are tolerated including Cl, OMe, CO_2Me, Ac, CF_3, SF_5, F, and OH groups (Scheme 2, **3a−k**). In addition, the dihalide arenes could undergo selective C−H arylation at less sterically hindered or more activated positions (Scheme 2, **3l−o**). Finally, while chlorobenzene did not couple in high yield (data not shown), phenyl triflate coupled in a promising yield. In

Scheme 2. Substrate Scope of Aryl Electrophile.[a]

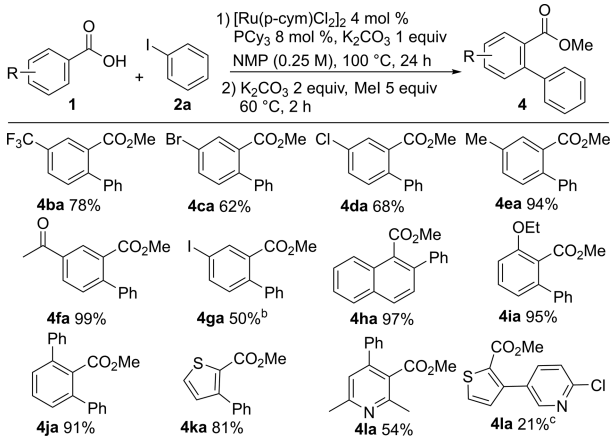


[a]Reactions run with **1a** (0.25 mmol) and **2** (1.5 equiv). [b]Five mol % dtbbpy as ligand at 80 °C. [c]Methylation step was not run. Product isolated as free acid. [d]The depicted product was isolated along with the product of substitution at the bromide *ortho* to the methoxy group (**3l′**). [e]**2** (3 equiv) at 80 °C.

cases where lower yields were observed, the reactions were usually incomplete, with unreacted starting materials remaining.

A variety of benzoic acid derivatives were also arylated in high yield (Scheme 3). Both electron-rich and electron-poor

Scheme 3. Scope of Aryl Carboxylic Acid.[a]

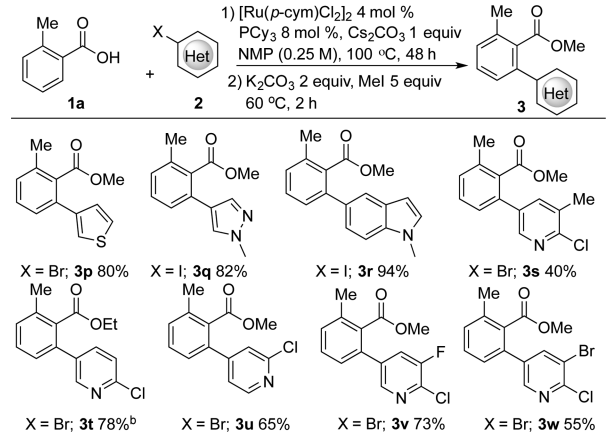


[a]Reactions run as in Scheme 2. [b]**2a** (3 equiv). [c]5-Bromo-2-chloropyridine 1.5 equiv.

aromatic acids are equally tolerated (**4ba** vs **4ia**), and halogens on the benzoic acids were also tolerated. The latter presents a convenient handle for further elaboration. Impressively, thiophene and pyridine carboxylic acids also coupled in promising yields. While less hindered pyridine carboxylic acids failed to couple,[13] this is the first example of a directed C−H functionalization on a free pyridine carboxylic acid.[8,14]

A general advantage of this Ru-catalyzed C−H arylation method over the previously reported Ir- and Pd-catalyzed methods is the tolerance of heteroaryl substrates, especially electrophiles (Scheme 4). For these substrates, the dimerization

Scheme 4. C−H Arylation with Heteroaryl Electrophiles[a]



[a]Reactions run with **1a** (0.25 mmol), **2** (1.5 equiv). [b]Esterification with EtI instead of MeI, isolated yield of ethyl ester.

of the benzoic acid was a major side reaction (up to 20%). Switching from K_2CO_3 to Cs_2CO_3 as the base suppressed this side reaction (10% or less).[6e] 4-Iodo-1*H*-pyrazole and 5-iodo-1-methyl-1*H*-indole were also transformed into the corresponding arylheteroaryl biarenes (Scheme 4, **3q−r**). Multifunctional pyridyl bromides were also transformed into the corresponding

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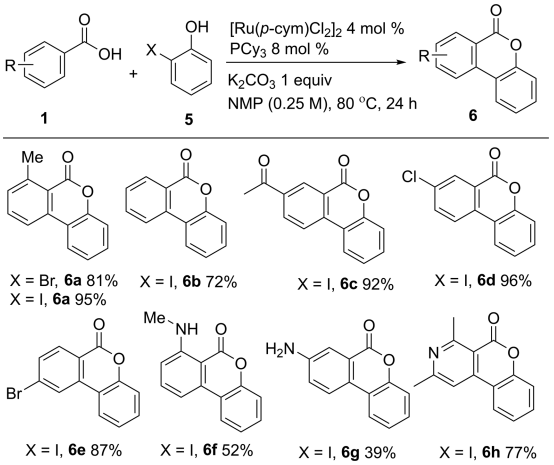
products in moderate to good yields (Scheme 4, **3s**–**w**). The C–H arylation also selectively occurred at the less sterically hindered position (Scheme 4, **3w**). Finally, in contrast to cross-dehydrogenative coupling, which can only couple at the 2-position of thiophene,[6a,d] this method allows access to 3-position of thiophene (Scheme 4, **3p**).

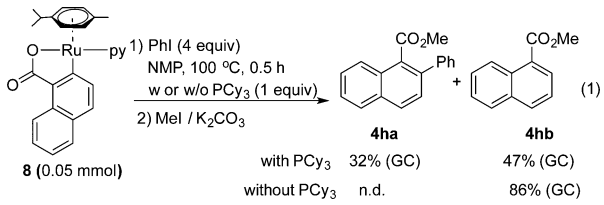
The tolerance of these reaction conditions to unprotected phenols prompted us to examine the synthesis of 6*H*-benzo[*c*]chromen-6-ones through the C–H arylation of aryl carboxylic acids with 2-iodophenol (Scheme 5). Chromenones of this type have extensive biological activity[15] and have never been assembled by this route before.

Scheme 5. Construction of 6*H*-benzo[*c*]chromen-6-ones[a]



[a]Reactions run with **1** (0.25 mmol) and **5** (1.5 equiv).

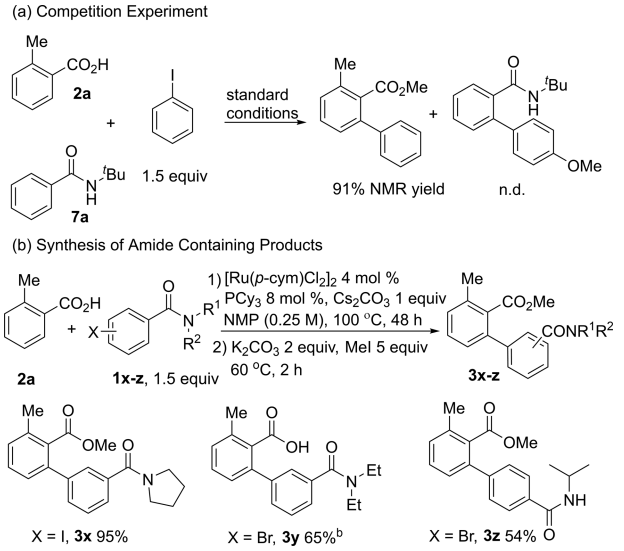
Given that no product was observed in reactions without added ligand, we briefly examined the role of the ligand in stoichiometric C–H arylation. C–H arylations with ruthenium directed by strong donors are proposed to proceed by initial cyclometalation followed by oxidative addition of the electrophile.[9f,j,16] Therefore, we reacted (*p*-cymene)Ru(κ^2-*O*,*C*-naphthenoate) (py) (**8**) with iodobenzene both with and without ligand (eq 1).[10b] Product forms only in the presence of PCy_3.



While we do not know why the yield of **4ha** from **8** is lower than expected, **8** is an excellent catalyst for this transformation and is kinetically competent (see the Supporting Information). These studies are consistent with PCy_3 reaction with **8** to form a new intermediate that is capable of reacting with iodobenzene to form product **4ha**, but other mechanisms remain possible.[16]

This "turn-on" of reactivity with carboxylic acids by the addition of PCy_3 prompted us to compare carboxylic acids to a stronger amide directing group (Scheme 6). *While nitrogen directing groups are generally considered stronger directors in a variety of transformations,*[9g,k,17] *under these conditions carboxylic acids override amides* (Scheme 6b, products **3x**–**z**). This opens up opportunities for sequential, orthogonal functionalization

Scheme 6. Carboxylic Acid vs Amide as a Directing Group[a]



[a]Reactions run with **2a** (0.25 mmol), **1x**–**z** (1.5 equiv). [b]Methylation step was not run. Product isolated yield as acid.

since the amide group is a powerful directing group in combination with various metal catalysts.[2,9g,k]

We anticipate that the ruthenium-catalyzed, carboxylate-directed C–H arylation of aromatic and heteroaromatic carboxylic acids with aryl and heteroaryl halides will find widespread use in organic synthesis. In addition to having a different substrate and reactivity profile than the better studied palladium catalysts, ruthenium is also more abundant and of lower cost. The ability to utilize heteroaromatic carboxylic acids as substrates could be of particular utility in the synthesis of active pharmaceutical ingredients.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02862.

Additional tables of experimental data, mechanistic experiments, experimental details, and product characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: daniel.weix@rochester.edu.

Notes

The authors declare no competing financial interest.

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(13) Two other less-hindered pyridine carboxylic acids failed to couple (nicotinic acid and picolinic acid). This result, along with the results in Scheme 4 and Figures S3 and S4, suggest that unhindered pyridines act as ligands and inhibit catalysis.

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