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Ruthenium-Catalyzed *meta*-Carboxylation

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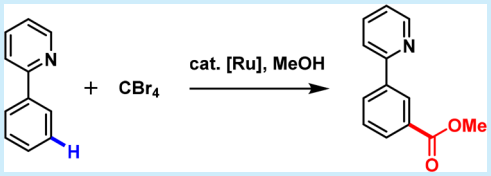
Supporting Information

ABSTRACT: The *meta*-carboxylation of arenes containing pyridine and other azine-directing groups is reported. Using carbon tetrabromide as the C1 source, ruthenium(III) trichloride catalysis enables functionalization of the arene *meta*-C−H position, affording carboxy methyl ester products after *in situ* reaction with methanol.

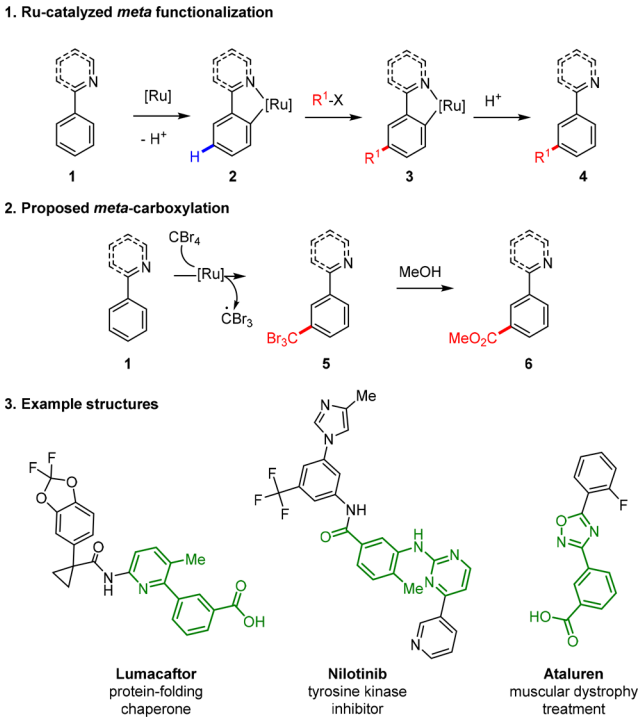


The *meta*-functionalization[1] of arene C−H bonds using ruthenium catalysis is a burgeoning area of research, enabling *meta*-selective arene bond construction in a very direct way.[2] The principle is set out in Scheme 1 and involves the *in situ* formation of ruthenacycle **2** from an arene substrate featuring a strong directing group such as a pyridine and ruthenium catalyst (frequently $[RuCl_2(cymene)]_2$) capable of cycloruthenation. Certain classes of electrophiles are then observed to add *para* to the C−Ru bond, which upon protonolysis of the metal complex reveals 1,3-*meta*-substituted arene product **4**. Initial observations on the reactivity of stoichiometric complexes **2** with strong electrophiles were suggestive of simple S_EAr chemistry.[3] However, subsequent studies on catalytic *meta*-alkylation with secondary and tertiary alkyl halides have identified a radical pathway[4] via postulated electron transfer pathways from Ru(II) species. Successful *meta*-functionalizations to date using the Ru method encompass sulfonylation with sulfonyl chlorides,[5] 2° and 3° alkylation with alkyl halides,[4,6] benzylation using tolyl components,[7] bromination,[8] and nitration.[9] Despite these notable advances, it is clear that several classes of bond formation remain to be established within the Ru-*meta* regime. With this goal in mind, we were interested in exploring a Ru-catalyzed *meta*-carboxylation.

The selective carboxylation of arenes is a fundamental transformation in synthesis frequently used to install a C1 moiety for elaboration into acid, ester, or amide functionalities that are widely represented in functional molecules (Scheme 1). Selective *meta*-carboxylation would introduce a new approach to these motifs, contrasting favorably with both existing stoichiometric lithiation processes and classical Friedel−Crafts acylation chemistry that is not amenable to the 1,3-*meta* substitution pattern. Ru-catalyzed carbonylative and acylative processes are well-established in the *ortho* series with Murai's *ortho*-carbonylative alkylation of 2-phenylpyridine using CO/ethylene being formative work in the field of catalytic C−H activation.[10,11] For *meta*-carboxylation, however, we were interested in exploiting the electron transfer pathways implicated in C−C bond formation with alkyl halides.

Mukminov and co-workers have demonstrated the use of CBr_4 as a masked carboxylation reagent,[12a] introducing the

Scheme 1. Ruthenium-Catalyzed Carboxylation



CO_2Me group to benzofurans using iron catalysis and methanolysis of the incipient tribromomethyl adduct.[13] More recently, Bandini and co-workers used photoredox catalysis to effect a similar transformation using CBr_4 and indoles.[12b] We were therefore interested in exploring the SET behavior of this reagent for *meta*-carboxylation.

We began our studies using 2-phenylpyridine **1a** as the starting material and limiting reagent with 3 equiv of CBr_4 and 5 mol % of $[Ru(p\text{-cymene})Cl_2]_2$ in a solvent mixture of methanol/1,4-dioxane using potassium acetate as a base (Table 1). Pleasingly, under these conditions we achieved a 42%

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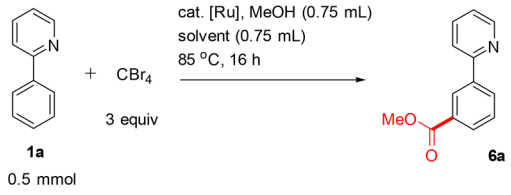
Table 1. Reaction Development[a]



entry	catalyst	additive	cosolvent	yield[b]
1	$[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %)	KOAc (2 equiv)	1,4-dioxane	42
2	$[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %)		1,4-dioxane	50
3	$Ru_3(CO)_{12}$ (5 mol %)		1,4-dioxane	0
4	$RuCl_3{\cdot}xH_2O$ (5 mol %)		1,4-dioxane	50
5[c]	$RuCl_3{\cdot}xH_2O$ (5 mol %)		1,4-dioxane	49
6	$RuCl_3{\cdot}xH_2O$ (5 mol %)		DMA	37
7	$RuCl_3{\cdot}xH_2O$ (5 mol %)		MeCN	15
8	$RuCl_3{\cdot}xH_2O$ (5 mol %)		none	39
9	$RuCl_3{\cdot}xH_2O$ (5 mol %)	$MesCO_2H$ (30 mol %)	1,4-dioxane	45
10	$RuCl_3{\cdot}xH_2O$ (5 mol %)	PPh_3 (10 mol %)	1,4-dioxane	52
11	$RuCl_3{\cdot}xH_2O$ (10 mol %)		1,4-dioxane	59[d]

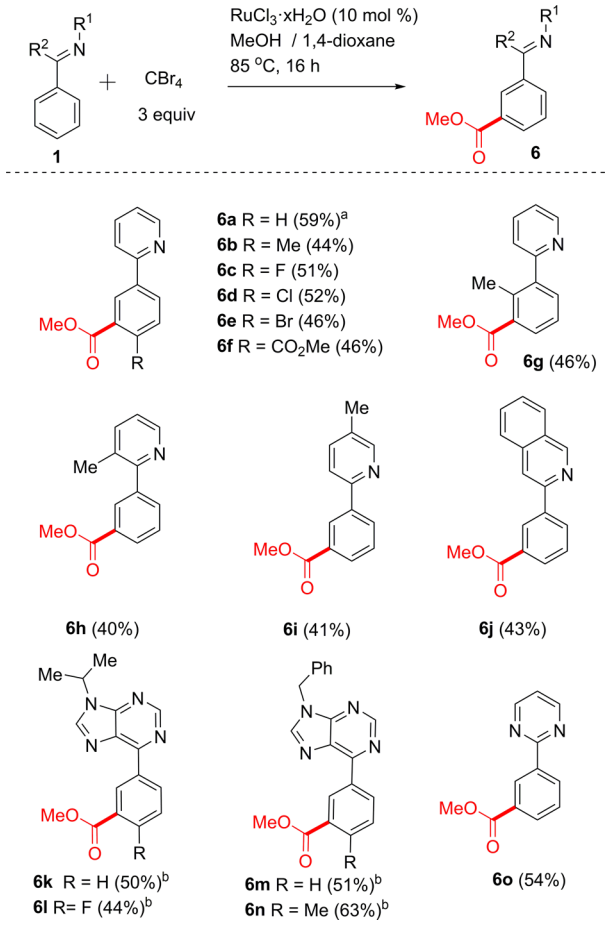
[a]Reaction conditions: 2-phenylpyridine (0.50 mmol, 1.0 equiv), CBr_4 (1.50 mmol, 3.0 equiv), catalyst (as specified), methanol (0.75 mL), and solvent (0.75 mL) under a nitrogen atmosphere at 85 °C for 16 h in a 5 mL microwave vial. [b]NMR yield using 1,3,5-trimethoxybenzene as the internal standard. [c]Reaction completed under air atmosphere. [d]Isolated yield.

conversion of the desired *meta*-carboxylated product (entry 1), and removal of the base increased this to 50% (entry 2).

We then investigated the use of alternative ruthenium catalysts to the commonly employed $[Ru(p\text{-cymene})Cl_2]_2$. $Ru_3(CO)_{12}$ had been successful in *meta*-nitration as reported by Zhang;[9] however it resulted in no product formation in our reaction (entry 3). Conversely, the use of ruthenium trichloride was more successful giving a comparable conversion to $[Ru(p\text{-cymene})Cl_2]_2$ (entry 4). As ruthenium trichloride is a cheaper catalyst; all subsequent reactions were completed using this basic ruthenium source. The reaction did not display sensitivity to air (entry 5) and proceeded with alternative solvents such as DMA, MeCN, and pure methanol but with lower efficiencies (entries 6–8). Carboxylate additives, common in Ru-catalyzed C–H activation, had little impact (entry 9), as did the use of triphenylphosphine, recently demonstrated to great effect in *meta*-difluoroalkylation (entry 10).[6c,d] An isolated yield of 59% was recorded upon increasing the catalyst loading to 10 mol % (entry 11), and control experiments established that no product formation took place in the absence of ruthenium trichloride.

With the optimized reaction conditions in hand, we sought to explore the substrate scope (Scheme 2). The reaction conditions tolerated both electron-donating (**6b**) and electron-withdrawing groups (**6c–f**) in the *para* position. Halogen substituents worked well (**6c–e**), providing the opportunity for further functionalization via cross coupling reactions. *ortho*-Substituents on the phenyl ring were tolerated as demonstrated by **6g** in contrast to our previous work on *meta*-bromination.[8a] However, *meta*-substituents were not tolerated, giving no conversion. This is in-line with general reactivity trends in Ru *meta*-C–H functionalization, where *meta*-substituents block one 3-position and sterically hinder the adjacent *ortho*-2 position preventing effective ruthenacycle formation that would activate the 5-position. The directing group was restricted to azine-type nitrogens but was successful for isoquinolines (**6j**), purines (**6k–n**), and pyrimidines (**6o**). None of the *ortho*-carboxy products were detected in this study, in line with the emerging picture of more sterically encumbered

Scheme 2. Substrate Scope for *meta*-Carboxylation



[a]Scale up to 2.5 mmol gave 53% yield after 24 h. [b]MeOH (1.5 mL) and 1,4-dioxane (1.5 mL) used as solvent.

carbon-centered radicals preferring the *meta* mode of addition.[6g] The tribromomethyl intermediate (**5** in Scheme

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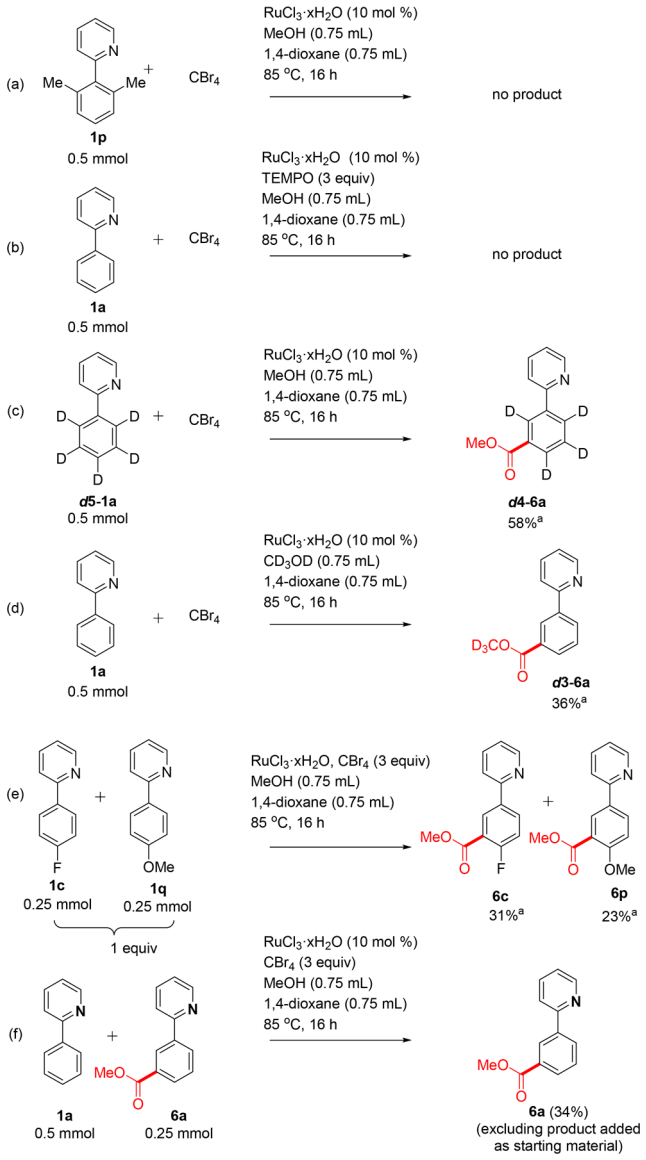
1) was never detected, as it is known to undergo rapid methanolysis at elevated temperatures.[13] Alternative alcohol or C1 components generally gave poor conversions under the reaction conditions; for example, ethanol furnished the ethyl ester product in a very low 18% yield. Formylation with $CHCl_3$ under conventional Ru-*meta* conditions of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), K_2CO_3, and Piv-Val-OH (30 mol %) in 1,4-dioxane did proceed to the analogous aldehyde but only in 22% yield.

Various experiments were conducted to probe the mechanism of the reaction (Scheme 3). Blocking both *ortho* positions

Scheme 3. Mechanistic Probes

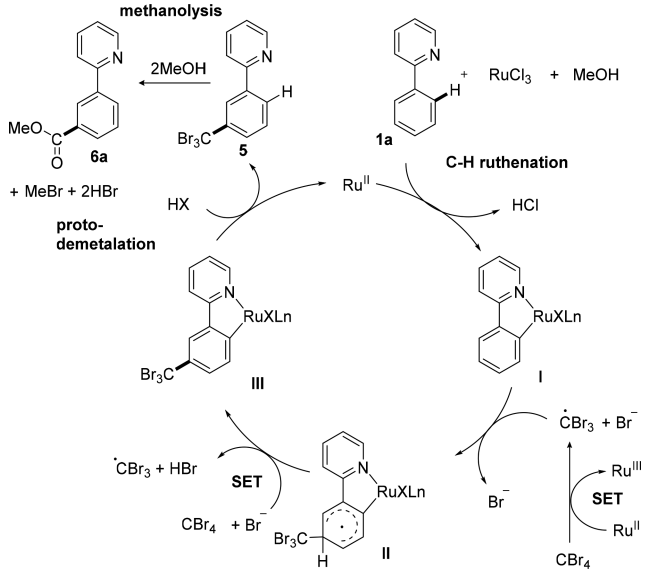


[a]^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

with methyl groups (**1p**) shut down the reaction, establishing that *ortho*-ruthenation is essential and that no background tribromomethylation takes place without it. The reaction was also suppressed by the addition of the radical trap TEMPO consistent with the SET mechanism observed in related systems. Subjecting 2-(phenyl-d_5)pyridine **d_5-1a** to the reaction conditions afforded **d_4-2a** exclusively, indicating that no H/D exchange takes place during the reaction (Scheme 3c); an analogous finding was reported by Huang and Ackermann in their *meta*-bromination systems, both of which proceed in the absence of base.[8b,c] The use of deuterated methanol gave a singular product **d_3-6a**, indicating that the methoxy group results from the methanol present (Scheme 3d). An intermolecular competition between 2-(4-fluorophenyl)-pyridine and 2-(4-methoxyphenyl)pyridine, revealed that the more electron poor substrate was more reactive. This verifies the supposition that an electrophilic substitution mechanism is not operative with CBr_4 in line with Frost and Ackermann's observations on alkyl halide reactivity.[4] Finally, addition of 0.5 equiv of product **6a** to the reaction leads to reduced conversions (Scheme 3f), suggesting that product inhibition may be significant in the reaction due to the creation of an additional ligation site for ruthenium in **6a**. Frost has recently observed esters acting as effective ancillary coordinating groups for ruthenium-catalyzed σ-activation of *N*-pyridyl indoles in this regard.[6f]

A plausible mechanistic pathway is outlined in Scheme 4 based on these observations and previous studies of Ru-*meta*

Scheme 4. Mechanistic Pathway



processes in the literature.[4−9] As Ru(III)-cyclometalated complexes are rare in the literature, it is likely that the $RuCl_3$ is a precatalyst to the cyclometalate **I** familiar to Ru(II) C−H activation chemistry with *in situ* reduction taking place with methanol.[14] SET reduction of CBr_4 by ruthenium will then generate the CBr_3 radical for S_HAr addition. Although the nature of the Ru species involved in this step remains to be elucidated, we note that one electron reduction of carbon tri- and tetrahalides by Ru salts is very well-precedented as the initiation step in Kharasch-type atom transfer radical addition chemistry.[15] The CBr_3 radical then adds *para* to the Ru−C bond to give species **II**. One electron oxidation (in principle by the Ru(III) but more likely by the CBr_4 reagent, which is present in excess) and proton loss rearomatizes the phenyl-pyridine to give **III**. This is followed by a protodemetalation and methanolysis of **5** to give the product.

In summary, we have developed a new *meta*-C−H functionalization reaction that introduces the carboxy group. The reaction exploits the electron transfer character of Ru σ-activation by using CBr_4 as a masked carboxylate moiety,

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proceeds with pyridyl, pyrimidyl, and nucleobase directing groups, and introduces a C1 unit of fundamental synthetic utility. Further studies on this transformation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03387.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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