C–H Activation

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Ruthenium-Catalyzed *meta*-Selective C–H Bromination

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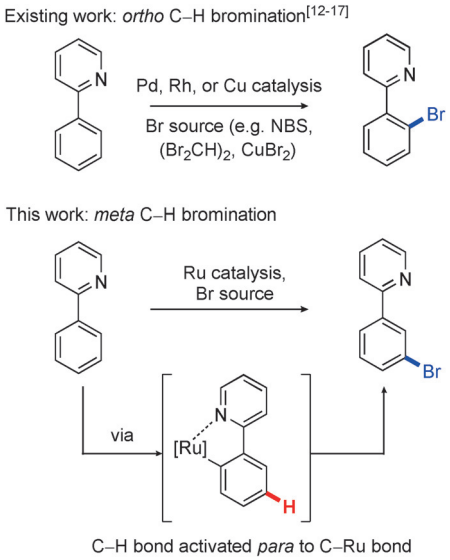
Abstract: *The first example of a transition-metal-catalyzed, meta-selective C–H bromination procedure is reported. In the presence of catalytic [{Ru(p-cymene)Cl$_2$}$_2$], tetrabutylammonium tribromide can be used to functionalize the meta C–H bond of 2-phenylpyridine derivatives, thus affording difficult to access products which are highly predisposed to further derivatization. We demonstrate this utility with one-pot bromination/arylation and bromination/alkenylation procedures to deliver meta-arylated and meta-alkenylated products, respectively, in a single step.*

The field of catalytic C–H bond functionalization has grown significantly in recent years, thus offering new disconnections which can streamline synthetic routes and produce less waste.[1] Several molecular architectures are now established for reliable C–H transformation, with arene C–H functionalization *ortho* to a directing group, by cyclometalation, being a prominent example.[2] By contrast, *meta* functionalization is a more difficult reaction as the analogous cyclometalation processes are not at the chemists' disposal. Given that stepwise *meta* functionalization is often challenging using classical arene chemistry, the development of new catalytic methods that address *meta* C–H functionality is of pressing importance.[3] Several ground-breaking reaction systems have been developed to tackle this problem, principally in the areas of palladium and copper-catalyzed C–C bond formation,[4–8] and iridium-catalyzed borylation.[9] A third way of achieving *meta* functionalization has recently been described by the groups of Frost and Ackermann, where ruthenium catalysis is used for *meta* sulfonylation and alkylation, respectively.[10] These reactions are thought to proceed by *ortho* ruthenation, thus affording an arylruthenium intermediate which exhibits a strong directing effect for functionalization at the C–H position *para* to the C–Ru bond.[11] Addition of a suitable electrophile will thus result in overall *meta* substitution upon protonolysis of the C–Ru bond and completion of the catalytic cycle.

We were interested in exploring this concept in the context of *meta* bromination (Scheme 1). Aryl bromides are supremely versatile functional groups, with methods for C–H *ortho* bromination, and halogenation in general, undergoing extensive development in the C–H activation literature.[12–17] However, *meta* bromination has yet to be described using transition-metal catalysis, and is restricted to very forcing reaction conditions in Friedel–Crafts bromination of electron-poor arenes (e.g., N–Br reagent in neat H_2SO_4 for bromination of nitrobenzene).[18] A one-step *meta*-selective bromination, under mild reaction conditions, would open up a new pathway to valuable 1,3-bromo-functionalized arenes, which are currently prepared by tedious multistep routes. More generally, it would create a catalyst-controlled bromination system, where bromination of the same arene substrate could be directed to either the *ortho*- or *meta*-position depending upon the choice in catalyst.



Scheme 1. Transition-metal-catalyzed C–H bromination.

We began by screening electrophilic bromine sources in the presence of a base, catalytic [{Ru(*p*-cymene)Cl$_2$}$_2$], and 2-phenylpyridine (**1a**), as the substrate. Initial results showed that NBS, bromine, and pyridinium tribromide gave minimal conversion to the desired *meta*-brominated product **2a** (Table 1, entries 1–5). The failure of pyridinium tribromide is notable (entry 5) as this reagent has been successfully used to stoichiometrically brominate organo-ruthenium complexes.[11] Gratifyingly, we observed successful *meta* bromination on switching to tetrabutylammonium tribromide (TBATB) in 1,4-dioxane, with **2a** being formed with excellent conversion (entry 10). Use of a carboxylate additive in ruthenium catalyzed C–H activation chemistry has extensive precedent in work from the group of Ackermann,[19] and acted in the current case to increase yields of the isolated products by 5–10%. The reaction did not occur in the absence of

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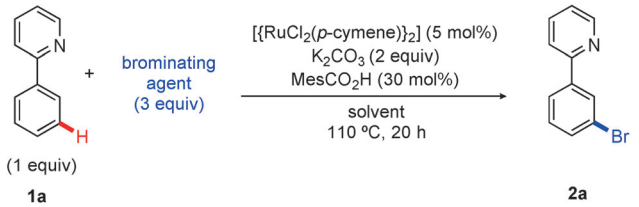
Table 1: Reaction development.

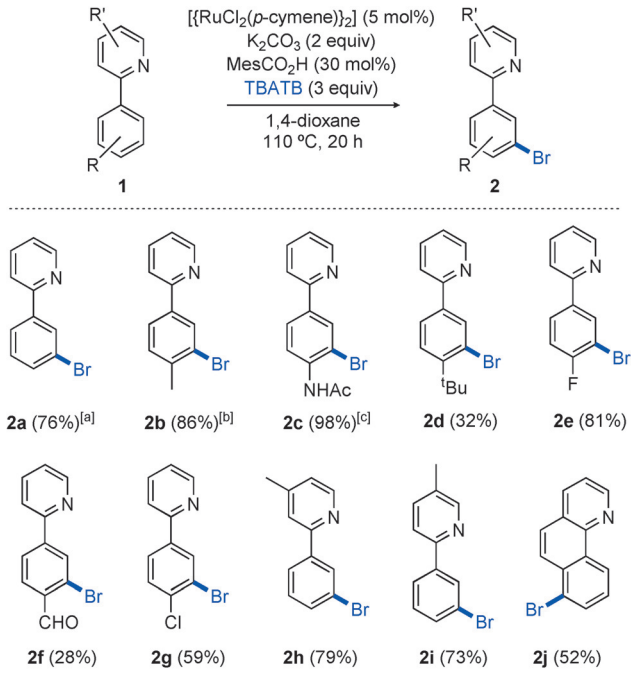


Entry	Brominating agent	Solvent	**1a**/**2a**[a]
1	NBS	acetonitrile	>99:1
2	NBS	1,4-dioxane	>95:5
3	Br_2	acetonitrile	>99:1
4	Br_2	1,4-dioxane	>99:1
5	pyridinium tribromide	1,4-dioxane	>99:1
6	TBATB	acetonitrile	>99:1
7	TBATB	water	>99:1
8[b]	TBATB	1,4-dioxane	10:90
9[c]	TBATB	1,4-dioxane	>99:1
10	TBATB	1,4-dioxane	5:95

[a] Ratio of **1a**/**2a** is based on ^{1}H NMR analysis of crude reaction mixtures after work-up. [b] Reaction carried out without $MesCO_2H$ additive. [c] Experiment carried out without ruthenium catalyst.

ruthenium catalyst (entry 9) and in solvents other than 1,4-dioxane, no product was observed. Finally, the reaction was observed to be air-sensitive. In cases where the reaction was set up without rigorous removal of air, conversions were inconsistent but generally much lower.

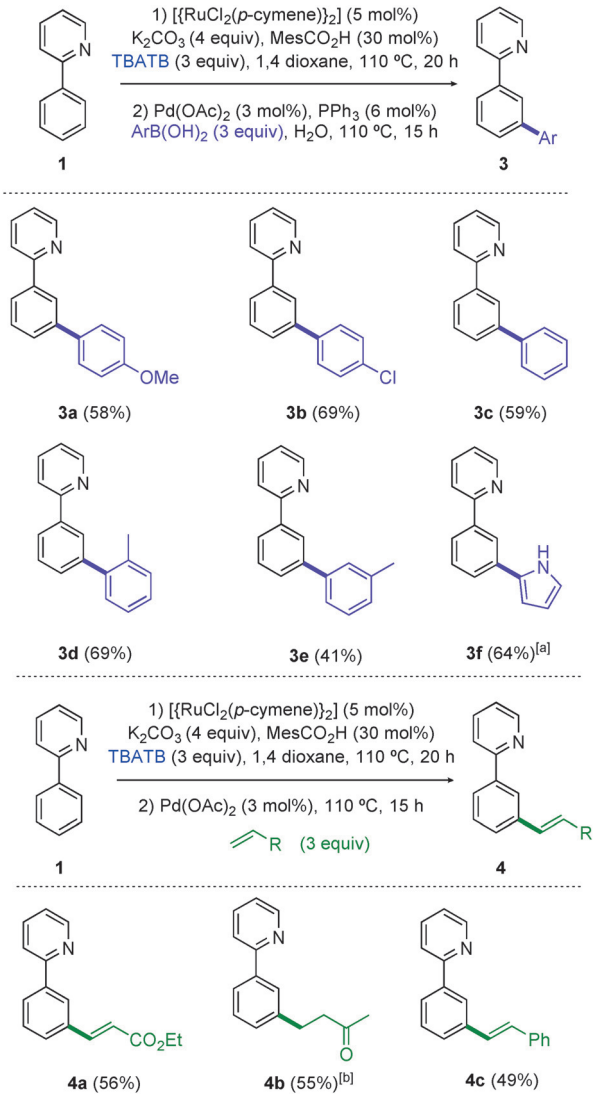
With the optimized reaction conditions in hand, we sought to explore the substrate scope (Scheme 2). We were pleased to find that both electron-donating (**2b–d**) and electron-withdrawing groups (**2e–g**) in the *para*-position of the aromatic ring were well tolerated, producing good to excellent yields of the bromide. In cases where the *para*-substituent possesses significant steric bulk the reaction still proceeds, but at a slower rate, thus resulting in a low yield after 20 hours (**2d**). It should be noted that in low-yielding cases, the majority of the remaining material can be accounted for as starting the 2-phenylpyridine substrate. The reaction is remarkably selective for the monobrominated, rather than the dibrominated, product, despite using an excess of brominating agent. Over-bromination has been problematic in some previous examples of metal-catalyzed *ortho* bromination.[13b,15a] The selectivity obtained in the *meta* bromination relative to other transition-metal-catalyzed bromination methods is exemplified by the reaction of benzo[h]quinoline to give the 7-brominated compound **2j**. This product could not be obtained selectively by using existing bromination methods,[20] and it contains a new C–Br bond at a useful site for further modification. Functionalized benzoquinolines are used extensively as ligands in areas such as photoredox catalysis, metallo-supramolecular chemistry, and organic electronics, where methods for modifying the ligand structure are essential to fine-tune electronic properties.



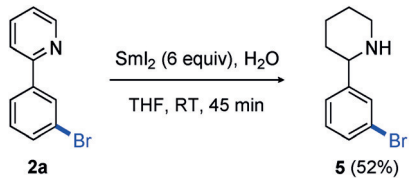
Scheme 2. Substrate scope for *meta* bromination. Yields are those of isolated products. [a] Average of three runs. [b] Average of two runs. [c] Yield without ruthenium catalyst is 10%. NBS = *N*-bromosuccinimide.

As with the sulfonylation system reported by Frost and coworkers,[10a] *meta* substitution on the phenyl ring is not tolerated. Ruthenation is presumably directed to the most sterically accessible *ortho* position, meaning that the pre-existing *meta* substituent is now blocking the site of bromination. Likewise, *ortho* substitution was not tolerated in phenylpyridine substrates. It is likely that this additional steric encumbrance prevents co-planarity of the phenyl–pyridine biaryl, thus disrupting the directed metalation and ensuing bromination. However, with substitution at other positions on the pyridine directing group, the reaction proceeds in excellent yield (**2h**,**i**). Pleasingly, we were able to scale-up the reaction to a 5 mmol scale. By running the reaction for 65 hours, but with half the catalyst loading (2.5 mol%), the yield of isolated **2a** remained at 76%, with 4% of the *ortho*-brominated product also isolated.

To demonstrate the versatility of this methodology, we developed simple one-pot processes to further manipulate the newly installed bromide group in C–C bond-forming reactions (Scheme 3).[21] We could *meta*-arylate by a one-pot bromination/Suzuki–Miyaura coupling: additional base was used in the first step, and after running the bromination for 20 hours, water, $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), and either a boronic acid or ester (3 equiv) were added and the reaction run for a further 15 hours. This one-pot *meta*-arylation procedure worked well for *ortho*-, *meta*-, and *para*-substituted boronic acids, and both electron-withdrawing and electron-donating substituents were tolerated (**3a–e**). The reaction was extended to heteroaromatic boronic esters, with the use of *N*-Boc-pyrrole-2-boronic acid MIDA ester proving effective for the synthesis of **3f** in 64% yield. A *meta*-alkenylation process was also possible: by simply adding $Pd(OAc)_2$ (3 mol%) and three equivalents of a suitable alkene, post-bromination, and heating the reaction to 110°C a one-pot bromination/Heck reaction proceeded. Yields of the alkenylated product over the two steps were good (**4a** and



Scheme 3. Substrate scope for one-pot transformations. Yields are those of isolated products. [a] *N*-Boc-pyrrole-2-boronic acid MIDA ester used as boronic acid starting material. [b] But-3-en-2-ol used as olefin starting material. MIDA = *N*-methyliminodiacetic acid.



Scheme 4. Reduction of pyridine directing group using SmI_2. THF = tetrahydrofuran.

4c), and the use of but-3-en-2-ol gave the alkylated ketone product **4b** in 55% yield.

Finally, we could successfully convert the pyridine directing group into the saturated heterocycle **5** (Scheme 4). Pyridine reduction is a versatile entry point into functionalized piperidines, which are heavily exploited scaffolds in medicinal chemistry. Here, treatment of **2a** with SmI_2/H_2O rapidly reduced the heteroarene,[22] thus leaving the aryl bromide group intact for further manipulation.

To conclude, we report the first example of transition-metal-catalyzed *meta*-selective bromination. The orthogonal selectivity exhibited by ruthenium relative to copper, palladium, and rhodium catalysis offers a catalyst-controlled route to compounds which may have been previously difficult to synthesize. Further, the reaction system is amenable to one-pot, telescoped processes which enable *meta* arylation and *meta* alkenylation. Further investigations into the scope of this chemistry are currently underway in our laboratory.

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