Metalation Dictates Remote Regioselectivity: Ruthenium-Catalyzed *meta* Arene C–H Functionalization

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Keywords:
arenes · C–H activation · ruthenium · regioselectivity · alkylation

In the last few decades, transition metal-catalyzed aromatic C–H bond functionalization methodologies have been extensively studied, resulting in powerful new tools for synthesis in academia and in industry.[1] Amongst the many challenges, controlling the regioselectivity in the C–H activation step is indispensable for designing efficient functionalization processes. Often, the most acidic C–H bond in an arene can be functionalized preferentially, such as in the functionalization of electron-poor heteroarenes or in direct arylation reactions that proceed via a concerted metalation-deprotonation (CMD) pathway.[1a] The most frequently used approach, however, involves the use of directing groups which allow accessing *ortho*-functionalized aromatic compounds via a chelation-assisted cyclometalation.[2] On the other hand, the development of a general catalytic transformation at the *meta* and *para* position of aromatic compounds with high levels of selectivity remains a challenge. Recent breakthroughs in this area have seen the development of two main strategies for *meta*-functionalization (Figure 1). Firstly, Hartwig *et al*.[3] and Smith *et al*.[4] reported the iridium-catalyzed borylation and further one-pot functionalization reactions of 1,3-disubstituted arenes at C5. Regioselectivity was shown to be dictated by a minimization of the steric hindrance around the catalyst (Figure 1, *a*). Sterics have also been suggested as the controlling factor in some Pd-mediated processes.[1d] In a second strategy, regiocontrol is achieved via coordination of the transition metal catalyst to a directing group, which facilitates the approach of the catalyst to induce *meta* C-H functionalization (Figure 1, *b*). This was demonstrated in a recent feat of engineering by Yu *et al*., with the design of a removable directing group for palladium-catalyzed *meta* C–H olefination reactions that proceed through the formation of a macro-palladacycle (Figure 1, *b*).[5] Coordination to a Cu(III) catalyst followed by a Heck-type mechanism has also been invoked to explain the regioselectivity in the copper-catalyzed *meta*-selective arylation of anilides reported by Gaunt *et al*. (Figure 1, *b*),[6] albeit the exact mechanism of this reaction is still controversial.[7]

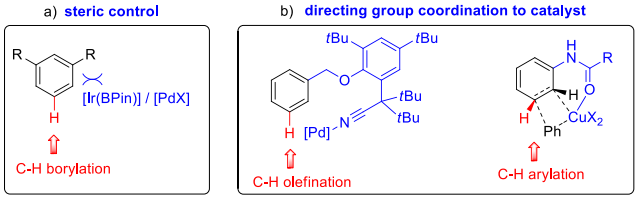
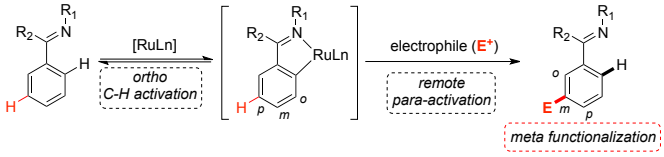


Figure 1. Control of regioselectivity in C–H *meta*-functionalization.

Very recently, a new strategy to tackle the *meta*-selective functionalization challenge has been developed. In this novel approach, after the initial formation of a cyclometalated ruthenium intermediate containing a σ–aryl bond, the ruthenium metal itself becomes a directing group which then steers an electrophilic attack to its *para* position by inductive and mesomeric effects (Scheme 1).[8] After protodemetalation, a *meta* substituted arene is obtained. This concept has been successfully applied to the *meta*-sulfonation and *meta*-alkylation of arenes containing traditional *ortho*-directing groups by Frost *et al*.[9] and Ackermann *et al*. (Scheme 2).[10]



Scheme 1. Ruthenium-catalyzed *meta*-functionalization via remote *para*-activation.

Pioneering studies by Frost's group showed that the selective catalytic *meta*-sulfonation of 2-phenylpyridine takes place in the presence of dichloro(*p*-cymene)Ru(II) dimer (*p*-cymene: 1-isopropyl-4-methylbenzene) upon reaction with sulfonyl chlorides (Scheme 2, left). No reaction occurred in the absence of the catalyst, and no products arising from *ortho* or *para* functionalization was observed. Both electron withdrawing and donating groups are tolerated on the aryl sulfonyl chloride, as well as substituents in C4' on the 2-phenylpyridine. Experimental evidence suggests the initial cyclometalation of the substrate followed by reaction with the sulfonating agent.

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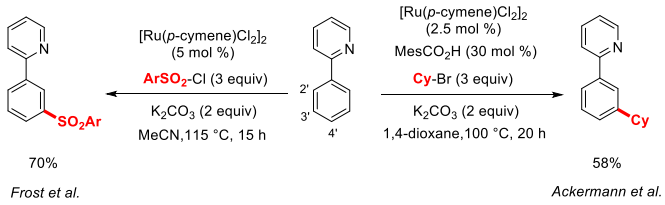
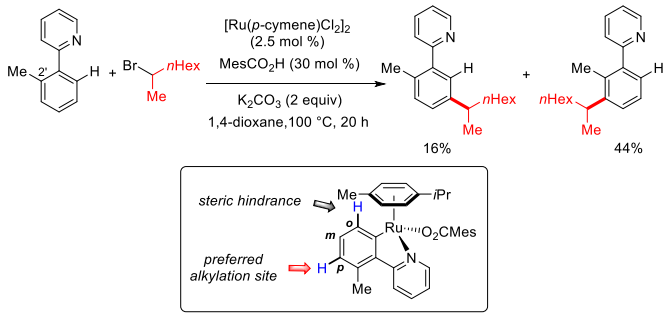
[**] We thank the European Research Council for funding and a Starting Research Grant to I.L.



Scheme 2. Ruthenium-catalyzed *meta*-selective sulfonation and alkylation.

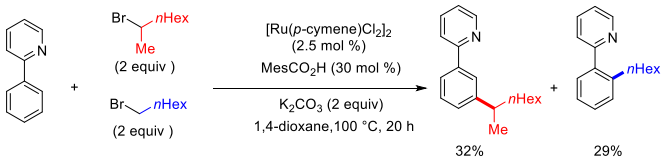
In Ackermann's recent paper, the authors report the *meta*-selective C-H bond alkylation of 2-phenylpyridines, azole-substituted arenes and pyrimidine derivatives with secondary alkyl bromides (Scheme 2, right). Ruthenium(II) carboxylate complexes were essential for promoting the direct alkylation. The catalyst can be generated *in situ* from dichloro(*p*-cymene)Ru(II) dimer and a carboxylate; 2,4,6-trimethylbenzoate ($MesCO_2^-$) proving particularly active. Substituents in C3' and C4' of the 2-phenylpyridine were well tolerated, yielding the functionalized products in moderate to good yields. However, C2' substituted substrates led to a mixture of the two possible *meta*-regioisomers, deriving from the electrophilic attack in *ortho* and *para* in respect to the metalation site (Scheme 3). It is well known that cyclometalated complexes of late transition metals containing σ–C-M bonds display increased electron density on the aryl ligand at *ortho* and *para*,[8] but due to steric factors around the metal centre, the electrophilic attack occurs preferentially at the less hindered *para* position.



Scheme 3. Regioselectivity of alkylation on 2'-substituted 2-phenylpyridines.

Interestingly, whereas secondary alkyl bromides afford complete *meta* selectivity, primary substrates lead exclusively to the *ortho*-alkylated product.[11] This was further demonstrated by reaction of 2-phenylpyridine with an equimolecular mixture of secondary and primary alkyl bromides, which showed complete chemoselectivity (Scheme 4). Further mechanistic investigations will be needed in order to understand this remarkable switch in selectivity.

Intermolecular competition experiments for the *meta*-alkylation of 4'-methoxy-2-phenylpyridine and 4'-fluoro-2-phenylpyridine with 2-bromooctane showed the former to react 2.6 times faster, suggestive of an electrophilic aromatic substitution-type reaction. Also consistent with an S_EAr, the authors report a KIE of 1.0 for the *meta*-C-H in 2-(3,4,5-trideuterophenyl)pyridine. Although most of the experimental evidence points towards an S_EAr pathway, TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) is reported to negatively affect the alkylation reaction. Thus, a radical mechanism cannot be completely ruled out. Indeed, in related studies ligand dimerization reactions of cycloruthenated complexes have been shown to occur *via* a radical pathway in which an aryl radical is induced by oxidation of the metal centre to Ru(III).[12] In addition to dimerization reactions, intriguing reactivity on the aryl ligands in late transition metal cyclometalated complexes has been previously described in stoichiometric processes. *Para* nitration, chlorination, bromination, iodination, sulfonation, acylation and formylation of organometallic complexes of Ru, Os, Rh, Ir, Pd and Pt have been achieved under mild conditions suggesting a breadth of possibilities for further catalytic *meta*-functionalization reactions.[8]



Scheme 4. Competition experiment between primary and secondary alkyl bromides.

In conclusion, a novel and alternative approach to selectively sulfonate and alkylate a C-H bond *meta* to a directing group has been successfully demonstrated. Contrary to previous strategies, the transition metal catalyst is not directly involved in the C-H functionalization step, but instead acts as a secondary directing group, which alters the reactivity of the starting molecule, promoting reactions with electrophiles. Future mechanistic studies along with the already reported stoichiometric examples could potentially lead to a general method for introducing a wide variety of functional groups with high levels of difficult to achieve *meta*-regioselectivity.

Received: ((will be filled in by the editorial staff))
Published online on ((will be filled in by the editorial staff))

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