C–H Activation

DOI: 10.1002/anie.201306425

Metalation Dictates Remote Regioselectivity: Ruthenium-Catalyzed Functionalization of *meta* C_{Ar}–H Bonds**

*Francisco Juliá-Hernández, Marco Simonetti, and Igor Larrosa**

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

In the last few decades, methods for the transition-metal-catalyzed functionalization of aromatic C–H bonds have been extensively studied, thus 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 which proceed by a concerted metalation-deprotonation (CMD) pathway.[1a] The most frequently used approach, however, involves the use of directing groups which allow access to *ortho*-functionalized aromatic compounds by a chelation-assisted cyclometalation.[2] In contrast, 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 been the development of two main strategies for *meta* functionalization (Figure 1). Firstly, Hartwig et al.[3] and Smith et al.[4] reported the one-pot iridium-catalyzed borylation and functionalization reactions of 1,3-disubstituted arenes at C5. Regioselectivity was shown to be dictated by a minimization of the steric bulk around the catalyst (Figure 1a). Sterics have also been suggested as the controlling factor in some palladium-mediated processes.[1d] In a second strategy, regiocontrol is achieved through coordination of the transition-metal catalyst to a directing group, thus facilitating the approach of the catalyst to induce functionalization of the *meta* C–H bonds (Figure 1b). This type of functionalization was demonstrated by Yu et al. who designed a removable directing group for palladium-catalyzed olefination reactions of *meta* C–H bonds and proceed through the formation of a macropalladacycle (Figure 1b).[5] Coordination to a copper(III) catalyst and a subsequent Heck-type mechanism has also been invoked to explain the regioselectivity in the copper-catalyzed *meta*-selective arylation of anilides and β-aryl carbonyl compounds reported by Gaunt et al. (Figure 1b),[6] even though the exact mechanism of this reaction remains unclear.[7]

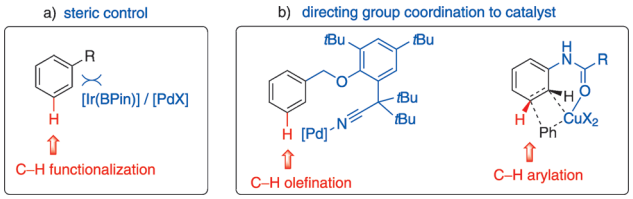
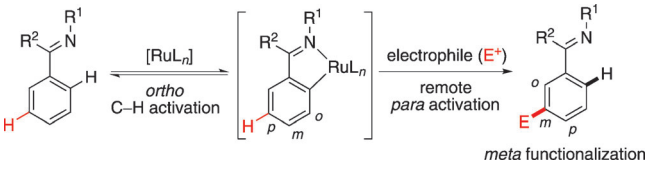


Figure 1. Control of regioselectivity in functionalization of *meta* C–H bonds.

Very recently, a new strategy to tackle the *meta*-selective functionalization challenge has been developed. In this novel approach, a cyclometalated ruthenium intermediate containing a σ-aryl bond is initially formed, and then the ruthenium center itself becomes a directing group, thus directing the electrophilic attack to the position *para* to the ruthenium 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 Hofmann and Ackermann (Scheme 2).[10]

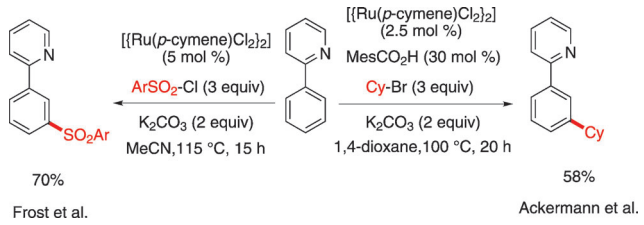


Scheme 1. Ruthenium-catalyzed functionalization of *meta* positions by remote *para* activation.

Pioneering studies by Frost et al. showed that the selective catalytic *meta* sulfonation of 2-phenylpyridine takes place in the presence of [{Ru(*p*-cymene)Cl_2}$_2$] (*p*-cymene = 1-isopropyl-4-methylbenzene) upon reaction with sulfonyl chlorides

[*] Dr. F. Juliá-Hernández, M. Simonetti, Dr. I. Larrosa
School of Biological and Chemical Sciences
Queen Mary University of London
Joseph Priestley Building, Mile End Road, E1 4NS, London (UK)
E-mail: i.larrosa@qmul.ac.uk
Homepage: http://webspace.qmul.ac.uk/ilarrosa/index.html

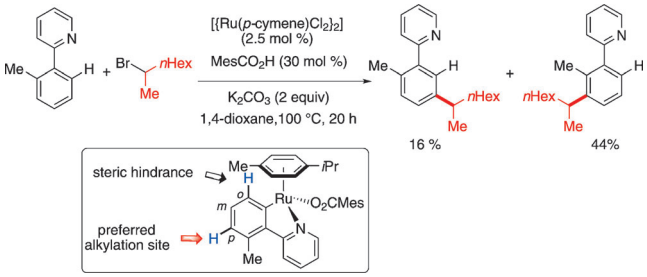
[**] We thank the European Research Council for funding and a Starting Research Grant to I.L.



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

(Scheme 2, left). No reaction occurred in the absence of the catalyst, and no products arising from *ortho* or *para* functionalization were observed. Both electron-withdrawing and electron-donating groups are tolerated on the aryl sulfonyl chloride, as well as substituents at C4′ on the 2-phenylpyridine. Experimental evidence suggests the initial cyclometalation of the substrate and subsequent reaction with the sulfonating agent.

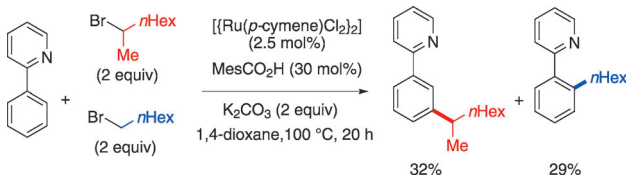
In the report from Hofmann and Ackermann, the authors describe the *meta*-selective C–H bond alkylation of 2-phenylpyridines, azole-substituted arenes, and pyrimidine derivatives with secondary alkyl bromides (Scheme 2, right). Ruthenium(II) carboxylate complexes were essential for promoting the direct alkylation. The catalyst can be generated in situ from $[\{Ru(p\text{-cymene})Cl_2\}_2]$ and a carboxylate, with 2,4,6-trimethylbenzoate ($MesCO_2^-$) proving to be particularly active. Substituents at C3′ and C4′ of the 2-phenylpyridine were well tolerated, thus yielding the functionalized products in moderate to good yields. However, C2′-substituted substrates led to a mixture of the two possible *meta* regioisomers derived from the electrophilic attack at the *ortho* and *para* positions with respect to the metalation site (Scheme 3).



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

It is well known that cyclometallated complexes of late transition metals containing σ-C–M bonds display increased electron density on the aryl ligand at the *ortho* and *para* positions,[8] but as a result of steric factors around the metal center, the electrophilic attack occurs preferentially at the less hindered *para* position.

Interestingly, whereas secondary alkyl bromides afford complete *meta* selectivity, primary substrates lead exclusively to the *ortho*-alkylated product.[11] This selectivity 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 to understand this remarkable switch in selectivity.



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

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, and is suggestive of an electrophilic-aromatic-substitution-type reaction (S_EAr). Also consistent with an S_EAr, the authors report a KIE of 1.0 for the *meta* C–H bond in 2-(3,4,5-trideuterophenyl)pyridine. Although most of the experimental evidence points towards an S_EAr pathway, 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) 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 by a radical pathway in which an aryl radical is induced by oxidation of the metal center 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. Nitration, chlorination, bromination, iodination, sulfonation, acylation, and formylation at the *para* position of organometallic complexes of Ru, Os, Rh, Ir, Pd, and Pt have been achieved under mild reaction conditions, thus suggesting a breadth of possibilities for further catalytic *meta*-functionalization reactions.[8]

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, thus 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 *meta* regioselectivity.

Received: July 23, 2013
Published online: September 12, 2013

[1] a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; b) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; c) O. Daugulis, H. Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; d) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem.* **2012**, *124*, 10382; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; e) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910.

[2] a) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.
[3] a) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864; b) D. W. Robbins, J. F. Hartwig, *Angew. Chem.* **2013**, *125*, 967; *Angew. Chem. Int. Ed.* **2013**, *52*, 933.
[4] J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith, 3rd, *Science* **2002**, *295*, 305.
[5] D. Leow, G. Li, T. S. Mei, J. Q. Yu, *Nature* **2012**, *486*, 518.
[6] a) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593; b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 483; *Angew. Chem. Int. Ed.* **2011**, *50*, 463; c) B. Chen, X. L. Hou, Y. X. Li, Y. D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668.
[7] Arylation in the absence of copper was possible under identical reaction conditions, but at higher temperatures; see Ref. [6b].
[8] M. Gagliardo, D. J. Snelders, P. A. Chase, R. J. Klein Gebbink, G. P. van Klink, G. van Koten, *Angew. Chem.* **2007**, *119*, 8710; *Angew. Chem. Int. Ed.* **2007**, *46*, 8558.
[9] O. Saidi, J. Marafie, A. E. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Kohn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298.
[10] N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877.
[11] L. Ackermann, P. Novak, R. Vicente, N. Hofmann, *Angew. Chem.* **2009**, *121*, 6161; *Angew. Chem. Int. Ed.* **2009**, *48*, 6045.
[12] S. H. Wadman, R. W. Havenith, M. Lutz, A. L. Spek, G. P. van Klink, G. van Koten, *J. Am. Chem. Soc.* **2010**, *132*, 1914.

