UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Switching from meta- to ortho-Selectivity by a Cyclometalated Ruthenium Catalyst

Sukowski, V.; Fernández-Ibáñez, M.A.

DOI
10.1016/j.chempr.2020.05.016

Publication date
2020

Document Version
Final published version

Published in
Chemical Science

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/policies/open-access-in-dutch-copyright-law-taverne-amendment)

Link to publication

Citation for published version (APA):
Sukowski, V., & Fernández-Ibáñez, M. A. (2020). Switching from *meta*- to *ortho*-Selectivity by a Cyclometalated Ruthenium Catalyst. *Chemical Science*, *6*(6), 1209-1211. https://doi.org/10.1016/j.chempr.2020.05.016

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.
UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Download date:15 Sept 2026

Switching from *meta*- to *ortho*-Selectivity by a Cyclometalated Ruthenium Catalyst

Verena Sukowski[1] and M. Ángeles Fernández-Ibáñez[1,*]

Catalyst-controlled site selectivity in C–H functionalization reactions is a long-standing challenge. In this issue of *Chem*, Larrosa and co-workers employ a cyclometalated ruthenium catalyst (RuBnN) to reverse the conventional *meta*-selectivity to the unprecedented *ortho*-selectivity in the C(sp^2)–H alkylation of arenes with secondary alkyl halides.

Controlling selectivity is a key issue for the development of efficient transformations in organic synthesis. In the field of metal-catalyzed C–H activation, this is a major challenge given that C–H bonds are ubiquitous in organic molecules. To this end, in the last decades, the control of site selectivity in C–H functionalization reactions has been accomplished mainly with the use of directing groups (DGs). For the functionalization of arenes, the DG enables the formation of the *ortho*-cyclometalated complex, therefore providing the *ortho*-functionalized products.[1] An exception to this general trend is the chemistry related to ruthenium (Ru)-catalyzed C–H alkylation reactions with secondary and tertiary alkyl halides. In this case, the cyclometalation occurs at the *ortho*-position, and depending on the nature of the alkyl halide, *ortho*- or *meta*-alkylated products are obtained. Generally, the *ortho*-cyclometalated Ru complex undergoes oxidative addition of aryl or primary alkyl halides to provide *ortho*-alkylated products, whereas the oxidative addition of secondary or tertiary alkyl halides is more challenging and does not take place under standard reaction conditions. Instead, an alkyl radical that preferentially adds *para* to a Ru(III)–C bond is formed, providing *meta*-alkylated products (Figure 1A, top).[2]

In this issue of *Chem*, Larrosa and coworkers report the use of a cyclometalated Ru catalyst to switch the conventional *meta*-selectivity with secondary alkyl halides to the unprecedented *ortho*-selectivity (Figure 1A, bottom).[3] In 2018, the same authors initiated the design and development of the new cyclometalated RuBnN catalyst I (Figure 1B) with the discovery that the postulated mechanism of Ru-catalyzed *ortho*-C–H arylation of N(sp^2)–chelating substrates with aryl halides had been incorrect for over two decades.[4] In the commonly accepted mechanism, the oxidative addition of

[1]Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, the Netherlands

*Correspondence: m.a.fernandezibanez@uva.nl

https://doi.org/10.1016/j.chempr.2020.05.016

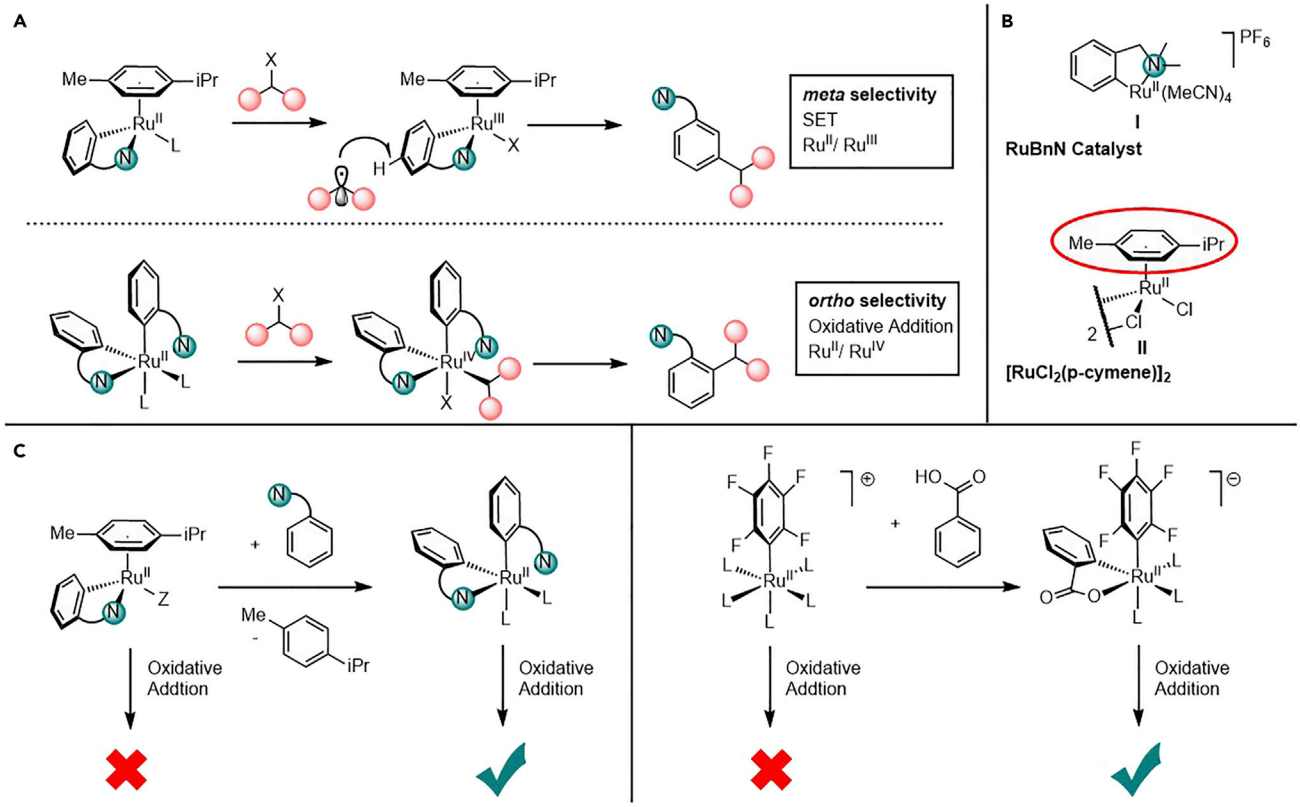

Figure 1. Ru-Catalyzed C–H Functionalization

(A) *Meta*- versus *ortho*-reactivity in Ru-catalyzed alkylation reactions with secondary alkyl halides.

(B) New cyclometalated Ru catalyst **I** and commonly used Ru catalysts **II**.

(C) Ru catalyst that can and cannot undergo oxidative addition with alkyl or aryl halides.

the aryl halide was taking place after the formation of the *ortho*-Ru-cyclometalated complex, and then reductive elimination provided the *ortho*-arylated product. However, the authors' studies revealed that after the formation of the *ortho*-Ru-cyclometalated complex and before the oxidative addition of the aryl halide, another substrate undergoes C–H activation on the same Ru catalyst (Figure 1C, left), leading to a catalyst with two covalently attached aryl groups on the Ru center and making a highly electronically rich Ru complex that is more prone to undergoing oxidative addition. On the basis of this knowledge, Larrosa and co-workers designed a new class of cyclometalated Ru catalysts, **I** (Figure 1B), that allows C–H arylation reactions under mild reaction conditions with high efficiency and excellent functional-group tolerance, as demonstrated by its application in the late-stage arylation of a wide variety of pharmaceuticals.

In addition to this work, in 2018 Larrosa and co-workers unveiled the mechanism of Ru(II)-catalyzed arylation of non-directed fluoroarenes,[5] a methodology that was published for the first time in 2016.[6] The key to the success of this reaction was the presence of a benzoate salt. Similar to previous work, studies revealed that the aryl–Ru(II) species coming from initial C–H activation of the fluoroarene undergoes a second C–H activation of benzoic acid, which is necessary to provide an electronically rich benzoate-cyclometalated Ru catalyst, which then undergoes oxidative addition with aryl halides (Figure 1C, right). Furthermore, both studies showed that the *para*-cymene ligand of the frequently used dichloro(*p*-cymene)Ru(II) dimer **II** (Figure 1B) needs to dissociate to form the active bis-arylated Ru catalyst. With all this knowledge, the authors envisioned the work presented in this issue of *Chem* on the Ru-catalyzed *ortho*-C–H alkylation of arenes with secondary alkyl halides.

Typically, Ru-catalyzed C–H alkylation with alkyl and benzyl halides provides *ortho*-functionalized products, whereas reaction with secondary alkyl halides exclusively furnishes *meta*-alkylated products. The explanation for the observed switch of site selectivity lies in the different behavior between primary and secondary alkyl halides toward the oxidative addition step. The oxidative addition of secondary alkyl

halides is more challenging than the oxidative addition of primary alkyl halides for both electronic and steric reasons. As a consequence, the majority of the reported C(sp^2)–H alkylation reactions with different transition metals use primary alkyl halides, and those using secondary alkyl halides require harsh reaction conditions and are generally not broadly applicable.[7] The origin of the *meta*-selectivity observed in the reaction with secondary alkyl halides has been explained by the formation of a radical, through a single-electron transfer process, that adds *para* to a Ru(III)–C bond. This observed reactivity is a consequence of the inability of the Ru catalyst to undergo oxidation addition with secondary alkyl halides.[7] Ingeniously, the authors anticipated, on the basis of the previous knowledge gained on the mechanism of Ru-catalyzed *ortho*-C–H arylation reactions, that the use of a cyclometalated Ru complex can enable the oxidative addition of secondary alkyl halides, affording the desired *ortho*-alkylated products. Indeed, stoichiometric experiments using the cyclometalated Ru complex Ru(*o*Me-ppy) showed exclusively the formation of the *ortho*-product and no *meta*-alkylated product, reinforcing their hypothesis that cyclometalated Ru complexes are more prone to undergoing oxidative addition.

Conveniently, C–H alkylation using secondary alkyl bromides and the Ru-cyclometalated complex **I** takes place at low temperature (50°C) and shows excellent functional-group tolerance. First, the methodology has been developed with pyridine as the DG, showing a broad substrate scope with arenes bearing both electron-rich and electron-poor substituents at different positions. Furthermore, the methodology has been applied in late-stage diversification of a variety of relevant medicinal chemistry compounds. Next to the pyridine DG, ketones have been used as DGs in the form of ketimines, and even though the substrate scope is limited to electron-rich arenes, this DG approach is valuable because ketimines can be transformed into amines, ketones, alcohols, and carboxylic acids, as Ackermann and co-workers showed in 2017.[8] For now, the range of DGs is limited, but the reported methodology provides a starting point for further research in this area to expand the methodology to other arenes with or without DGs. Furthermore, the oxidative addition step has been investigated and revealed an S_N2-type mechanism, which offers additional space to enhance the value of the methodology because of the possibility to perform enantioselective reactions.

The methodology presented by the Larrosa group is an excellent example of the importance of understanding the reaction mechanism and how this understanding can lead to the design of more active catalysts. Moreover, in this specific case, the designed new catalyst is capable of switching the site selectivity by altering the mechanism of the reaction, bringing researchers closer to fulfilling the dream of controlling site selectivity in C–H functionalization reactions.

1. Lyons, T.W., and Sanford, M.S. (2010). Palladium-catalyzed ligand-directed C-H functionalization reactions. Chem. Rev. *110*, 1147–1169.

2. Leitch, J.A., and Frost, C.G. (2017). Ruthenium-catalysed σ-activation for remote *meta*-selective C-H functionalisation. Chem. Soc. Rev. *46*, 7145–7153.

3. Wang, G.-W., Wheatley, M., Simonetti, M., Cannas, D.M., and Larrosa, I. (2020). Overcoming ruthenium meta-selectivity: cyclometalated ruthenium-catalyst enables ortho-selective C–H alkylation with secondary alkyl bromides. Chem *6*, this issue, 1369–1378.

4. Simonetti, M., Cannas, D.M., Just-Baringo, X., Vitorica-Yrezabal, I.J., and Larrosa, I. (2018). Cyclometallated ruthenium catalyst enables late-stage directed arylation of pharmaceuticals. Nat. Chem. *10*, 724–731.

5. Simonetti, M., Kuniyil, R., Macgregor, S.A., and Larrosa, I. (2018). Benzoate cyclometalation enables oxidative addition of haloarenes at a Ru(II) center. J. Am. Chem. Soc. *140*, 11836–11847.

6. Simonetti, M., Perry, G.J.P., Cambeiro, X.C., Juliá-Hernández, F., Arokianathar, J.N., and Larrosa, I. (2016). Ru-catalyzed C-H arylation of fluoroarenes with aryl halides. J. Am. Chem. Soc. *138*, 3596–3606.

7. Singh, K.S. (2019). Recent advances in C–H bond functionalization with ruthenium-based catalysts. Catalysts *9*, 173.

8. Li, J., Korvorapun, K., De Sarkar, S., Rogge, T., Burns, D.J., Warratz, S., and Ackermann, L. (2017). Ruthenium(II)-catalysed remote C-H alkylations as a versatile platform to *meta*-decorated arenes. Nat. Commun. *8*, 15430.