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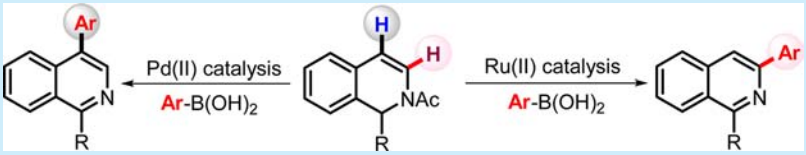
One Substrate, Two Modes of C−H Functionalization: A Metal-Controlled Site-Selectivity Switch in C−H Arylation Reactions

Virendra Kumar Tiwari, Neha Kamal, and Manmohan Kapur*

Department of Chemistry, 330, Academic Building II, Indian Institute of Science Education and Research Bhopal, Bhopal-Bypass Road, Bhauri, Bhopal 462066, Madhya Pradesh, India

Supporting Information



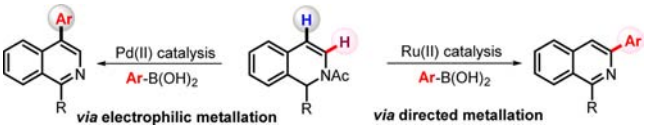
ABSTRACT: A unique site-selectivity switch has been achieved in the ruthenium-catalyzed C−H arylation reaction of *N*-acetyl-1,2-dihydroisoquinolines. This metal-mediated switch is antipodal to the previous report on the palladium-mediated C-4 C−H arylation on the same substrate. Mechanistic details reveal interesting aspects of the reaction pathway, and kinetic studies bring out the difference in the modes of C−H activation adopted by the two catalytic systems.

Selectivity plays a pivotal role in organic synthesis. When multiple outcomes are possible under a single reaction condition, favoring one of them exclusively, via control of chemo-, regio-, or stereoselectivity forms the very basis of synthesis.[1] Controlling site selectivity is a primary concern in C−H activation and subsequent functionalization, simply due to the fact that several C−H bonds exist in the substrate that possess the same bond dissociation energies as well as chemical environment.[2,3] Innate reactivity is often invoked for site selectivity in electronically biased systems.[4] In other substrates, the most preferred route is the deployment of Lewis basic directing groups.[5] The outcome and efficiency of the transformation is dependent on the coordination ability of the directing group. It is quite likely that the two approaches would also differ in the mechanism adopted for C−H activation.[6]

Switching site selectivity within a single substrate requires an efficient demarcation between the two approaches, and this concept has been utilized mostly in heterocyclic substrates such as indoles, pyrroles, and pyrazolopyrimidines.[7] Approaches include changing the electronic/steric nature of the substrate as well as employing reagent controls (solvent or additive).[7a,c] Often, a directing group can guide the transformation to two different neighboring sites depending on the reagents or catalyst systems employed.[8] We report herein a unique ruthenium mediated site-selectivity switch in the C−H arylation of *N*-acetyl-1,2-dihydroquinolines, thus leading to 3-aryl isoquinolines.

This result is completely antipodal to our previous report on palladium catalyzed C−H arylation on the same substrate which led to 4-aryl isoquinolines (Scheme 1).[9] In the previous case we had obtained distal C−H bond functionalization, whereas in the present case we have achieved the proximal C−H bond functionalization and a clear distinction can be made in the two modes of C−H activation.[10] The direct functionalization of π-deficient heterocycles is a challenge, and often regioselectivity is poor, primarily due to the reduced coordination ability and reactivity of these heterocycles. Substrate modification and introduction of directing groups are indirect methods of achieving C−H functionalization at selected positions in these heterocycles.[11,12]

Scheme 1. Metal-Controlled Site-Selectivity Switch



Isoquinolines are among the most prevalent structures in biologically relevant molecules,[13] and 3-substituted isoquinolines and in particular 3-arylisoquinolines have attracted much attention from chemists owing to their prominent biological activities.[14] Isoquinolines exist in various oxidation states as isoquinolines, and dihydro- and tetrahydroisoquinolines exist in numerous natural products and bioactive molecules.[15] In this context, dihydroisoquinolines constitute synthetically strategic molecules since they are precursors to both isoquinolines and tetrahydroisoquinolines.[16]

In our previous studies on palladium catalyzed C-4 C−H arylation of *N*-acetyl-1,2-dihydroquinolines,[9] we had observed varying quantities of the minor regioisomer corresponding to the C-3 arylation in some of the substrates. This led us to wonder whether the reaction conditions could be tweaked to exclusively favor the C-3 arylation. To our delight (after considerable optimization), switching to ruthenium catalysis completely inverted the selectivity to favor the C-3 C−H arylation (see Supporting Information for details). The initial

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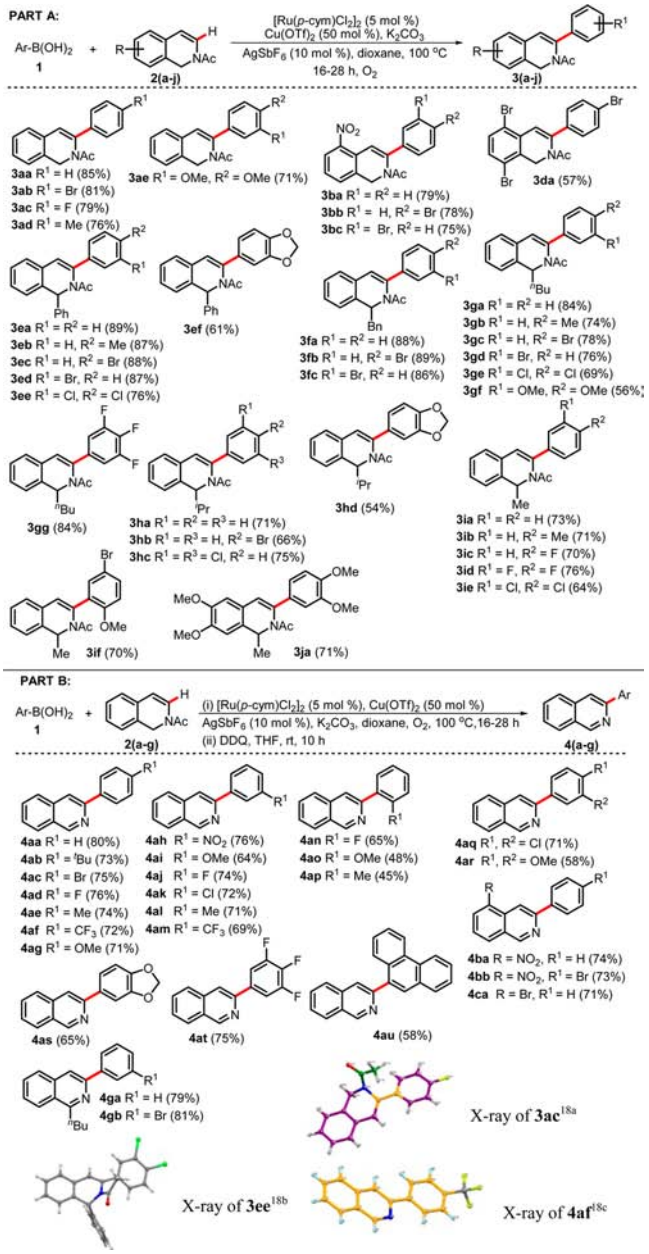
screening studies were carried out using the simple *N*-acetyl-1,2-dihydroisoquinoline as the substrate. Phenylboronic acid was chosen as the model aryl coupling partner. In one of our previous works on C−H arylation, we had optimized the reaction for the heteroatom-directed C-2 arylation of indole;[17] we attempted the same optimized catalytic combination with a model substrate, but the reaction did not yield the desired results. However, when we used an additive (1-Ad)-CO_2H with the previously optimized conditions, this resulted in desired 3-aryldihydroisoquinoline (59% yield), but this (1-Ad)-CO_2H additive did not work with electron-rich boronic acids. Among all the additives scanned, $AgSbF_6$ had the best performance. We extensively scanned the bases, in which Ag_2O worked better than AcONa, K_3PO_4, and Cs_2CO_3, and among all, K_2CO_3 gave the best results. The use of solvents other than dioxane led to a considerable decrease in yield, and in the case of isopropyl alcohol, the reaction did not work. $Cu(OTf)_2$ (50 mol %) was found to be crucial for the transformation. The utilization of other oxidants such as $Cu(OAc)_2{\cdot}H_2O$, BQ, AgOAc, and Ag_2CO_3 resulted in poor transformations. A 5 mol % catalyst loading was found to be optimum for the transformation, although in most cases 3 mol % was sufficient for a good transformation. The reaction did not work without the ruthenium catalyst, as the starting material was recovered, proving that the ruthenium catalyst is necessary for the transformation. We also investigated the significance of $Cu(OTf)_2$ and additive $AgSbF_6$, and both were found to be necessary for the reaction. We found $[RuCl_2(p\text{-cym})]_2$/$Cu(OTf)_2$/K_2CO_3/$AgSbF_6$/O_2 in Dioxane as the best performing combination. The optimized conditions worked very efficiently for most of the substrates and boronic acids examined (Scheme 2, Part A). The reaction worked well with arylboronic acids carrying electron-neutral and electron-withdrawing substituents (these were more reactive) and gave an excellent yield with exclusive regioselectivity. A variety of electron-rich arylboronic acids were investigated, and these provided moderate to excellent yields of the corresponding products. When the disubstituted electron-rich aryl boronic acids were exposed to the optimized conditions, the expected 3-arylisoquinoline products were obtained in moderate yield. The total reaction time for the electron-rich arylboronic acids was found to be slighly prolonged as compared to others. Polysubstituted arylboronic acids also worked well with the optimized reaction conditions. Substituents at *ortho*-position to the arylboronic acid were tolerated and provide 3-arylisoquinoline in moderate to good yield. We then proceeded to investigate the steric and electronic influence around the isoquinolines. The substrates bearing an electron-withdrawing substituent are more reactive than the unsubstituted ones. The substrates bearing an electron-rich substituent also worked under the optimized reaction conditions, and products were obtained in moderate yields. In addition, we tested the steric influence at C-1 of the *N*-acetyl-1,2-dihydroisoquinolines and found that the reaction worked quite well with exclusive regioselectivity in all cases. Aryl boronic acids bearing reactive motifs such as halogens exhibited excellent chemoselectivity. This is an added advantage of this methodology that these halogroups can be further functionalized to yield densely functionalized products. As a second illustration of this strategy, we demonstrated the synthetic utility of the synthesized 3-aryl-1,2-dihydroisoquinolines compounds by converting these to the corresponding 3-arylisoquinoline in the same pot by using DDQ (Scheme 2, Part B). We successfully synthesized a small

Scheme 2. Scope of Ruthenium-Catalyzed Synthesis of 3-Aryl-1,2-dihydroisoquinolines[a]



[a]All yields are isolated yields.

library of biologically significant 3-arylisoquinolines with structural variations at a variety of positions. This amounted to an indirect conversion of the parent isoquinoline to 3-arylisoquinoline, a transformation that is very difficult to achieve by traditional methods.

The outcome of this transformation was very intriguing especially since we had obtained a regioselective transformation at C-4 when using palladium catalysis.[9] In that transformation we had proposed a heteroatom-guided (electrophilic) palladation pathway.[19] In the present case we were sure that the electrophilic metalation would not be followed and that the reaction was following a heteroatom-directed pathway, assisted by the *N*-acyl group (Scheme 3). We then carried out control reactions to negate the possibility of a 1,2-migration of the metal to the neighboring position (Scheme 4). In both cases,

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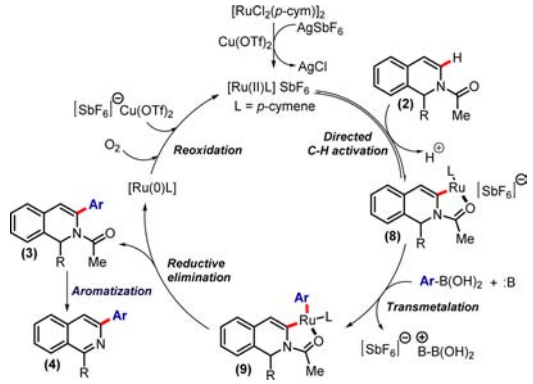
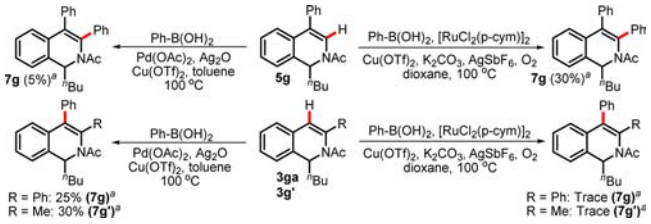
Scheme 3. Plausible Mechanism for the Transformation



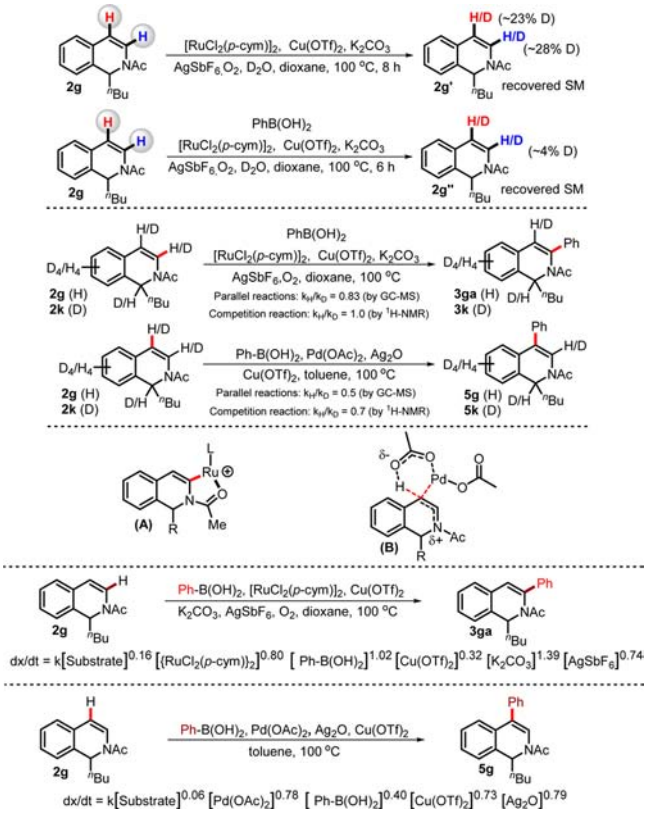
blocking either the C-4 or C-3 position resulted in arylations that were particular only to a specific site and catalyst system.

Scheme 4. Control Reactions To Prove Site Selectivity[a]



[a]The remaining material was aromatized starting material.

Scheme 5. Reversibility of Metalation and Kinetic Studies



This clearly ruled out a pathway involving a 1,2 migration of the metal, either from C-3 to C-4 or from C-4 to C-3. Monitoring the reaction by NMR clearly proved the point (see Figure S27 in the Supporting Information), and in the ruthenium catalysis only the peak corresponding to C3−H was affected indicating the formation of a ruthenacycle at C-3.

Studies carried out to investigate the reversibility of the metalation indicated that the C−H activation step was reversible, and these also indicated that the steps following the C−H activation were faster than the reverse reaction. This was evident from the lower deuterium content in the recovered starting material when the reaction was carried out in the presence of the arylboronic acid (Scheme 5). Kinetic isotope effect studies brought out interesting aspects of the reaction. In the case of the ruthenium catalyzed reaction, a KIE was not observed, indicating that the rate limiting step did not involve the C-3 C−H bond cleavage.[20] Interestingly, in the palladium catalyzed transformation we obtained a value far lower than 1. This indirectly supported our proposed electrophilic palladation mechanism in which there was a change in hybridization of C-4 (sp^2 to sp^3), and in such cases the KIE value can be far lower than 1.[21] It is also possible that the transition state for the palladium-catalyzed C-4 C−H activation step is a combination of electrophilic activation as well as an acetate assisted CMD pathway, with the former dominating the latter ((B), Scheme 5). These observations clearly indicate completely different modes of C−H activation operating in the two catalytic cycles, the distal C−H being activated via electrophilic metalation whereas the proximal C−H is activated via heteroatom-directed metalation. In view of these interesting outcomes, we were curious to see which of the reactants were involved in the rate-limiting steps. We then proceeded to study the order of the two reactions, and in the ruthenium catalyzed reaction, the transformation was first-order with respect to the catalyst, base, and the boronic acid whereas, in the case of the palladium catalyzed reaction, the transformation was not first-order with respect to the boronic acid but was first-order regarding the catalyst, base, and additive.[22] This, in a way, indicated the involvement of the transmetalation step as a rate-limiting factor in the ruthenium-catalyzed transformation. To determine whether the boronic acid would exhibit a Hammett dependency with respect to substituents, we carried out studies in this direction (see Figure S28, Supporting Information). The Hammett plot resulted in a low value for the reaction constant (ρ^+ = 0.322), indicating the absence of a substituent effect on the transmetalation step or indicating that the mesomeric effect on the developing negative charge on the boronic acid was only nominal.[22]

To conclude, in the metal-controlled site-selectivity switch, a clear distinction has been made in the two modes of C−H arylation: the proximal C−H is activated via the ruthenium catalysis whereas the distal C−H is activated via the palladium catalysis. The mechanistic studies and kinetic data point to electrophilic C−H activation via palladium catalysis whereas chelation-controlled C−H activation occurs in ruthenium catalysis. The site-selectivity control makes it possible to access both 3- and 4-arylisoquinolines from a single starting material. The newly developed ruthenium-catalyzed transformation provides access to a wide spectrum of structurally diverse 3-arylisoquinolines, with high yields and exclusive regioselectivity. Chemoselectivity observed with the halo-substituted arylboronic acids is an added advantage of the method.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03558.

Experimental details and spectral characterization of all new compounds (PDF)
Crystal structure of **3ac** (CIF)
Crystal structure of **3ee** (CIF)
Crystal structure of **4af** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mk@iiserb.ac.in.

ORCID

Manmohan Kapur: 0000-0003-2592-6726

Notes

The authors declare no competing financial interest.

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