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Catalyst Control in Positional-Selective C−H Alkenylation of Isoxazoles and a Ruthenium-Mediated Assembly of Trisubstituted Pyrroles

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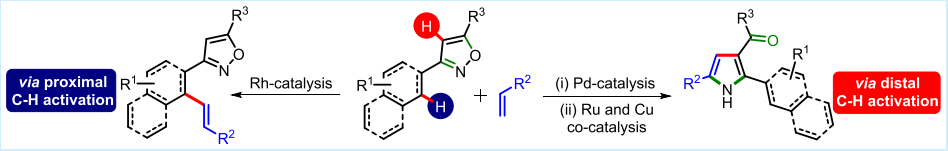
Supporting Information

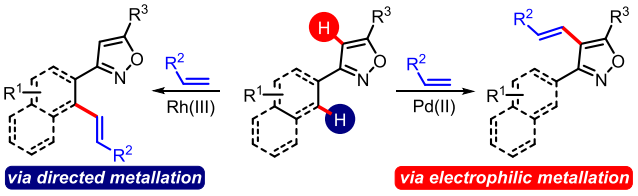


ABSTRACT: High levels of catalyst control are demonstrated in determining the positional selectivity in C−H alkenylation of isoxazoles. A cationic rhodium-mediated, strong-directing group promotes C(sp^2)-H activation at the proximal aryl ring whereas, the palladium-mediated electrophilic metallation leads to the C(sp^2)-H activation at the distal position of the directing group. Synthetic elaboration of this C−H alkenylation product via ruthenium and copper co-catalysis leads to an efficient method for the assembly of densely substituted pyrroles.

Control of positional selectivity within a reacting species is one of the most important aspects of organic chemistry.[1] In recent years, controlling this site or positional selectivity in transition-metal-catalyzed C−H functionalization reactions has become increasingly better understood.[2,3] In addition to the widely employed method of using directing groups to govern site selectivity, steric and electronic effects, solvent, ligand, and catalyst control are increasingly popular techniques for selective C−H bond functionalization.[4]

Isoxazoles are ubiquitous scaffolds that can be found in a variety of life-saving drugs and pharmaceuticals, as well as in biologically active natural products.[5−7] In addition, isoxazoles serve as versatile intermediates[8,9] and have been extensively employed in various catalytic transformations to afford a diverse array of synthetically useful heterocycles, as well as biologically relevant molecules.[10] Therefore, the transition-metal-catalyzed direct C−H functionalization of isoxazoles has emerged as an important aspect in synthetic organic chemistry. In 2008, Wu and co-workers reported the *o*-arylations as well as alkylations of 3,5-diarylisoxazoles using phenyl and alkylboronic acids in the presence of stoichiometric amount of palladium salts.[11] In 2014, Patel and co-workers also reported the palladium-catalyzed *ortho*-aroylations and acetoxylations of 3,5-diarylisoxazoles.[12] In this report, we disclose a catalyst-controlled, positional-selective C−H alkenylation of substituted isoxazoles (Scheme 1). In this work, a cationic rhodium-mediated, strong-directing group promoted C−H activation results in the proximal C−H bond functionalization. In contrast, a covalent Pd catalyst prefers an electrophilic C−H activation pathway to yield the distal C−H bond functionalization. The product of the Pd catalysis was then successfully elaborated to yield densely functionalized pyrroles via a ruthenium and copper co-catalyzed transformation.

Scheme 1. Catalyst Control in Positional-Selective C−H Alkenylations



We began our efforts by screening a variety of reaction conditions (see the Supporting Information (SI) for details) to achieve the proximal C−H bond functionalization. Our attempts to optimize the reaction conditions using ruthenium catalysis resulted primarily in N−O bond cleavage of isoxazole to give keto-amines, along with the formation of a trace amount of the desired *o*-olefinated product (see the SI for details). Under rhodium catalysis, the N−O bond cleavage was not observed and the *o*-olefinated product was obtained in a decent yield. After considerable optimizations, the best conditions were found to be $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2·H_2O$ (2 equiv), and CH_3CO_2H (1 equiv) in tetrahydrofuran (THF) at 100 °C. In order to explore the generality of the present investigations, a variety of substituted isoxazoles were coupled with various activated olefins using the optimized conditions to afford various *o*-olefinated products in moderate to good yield

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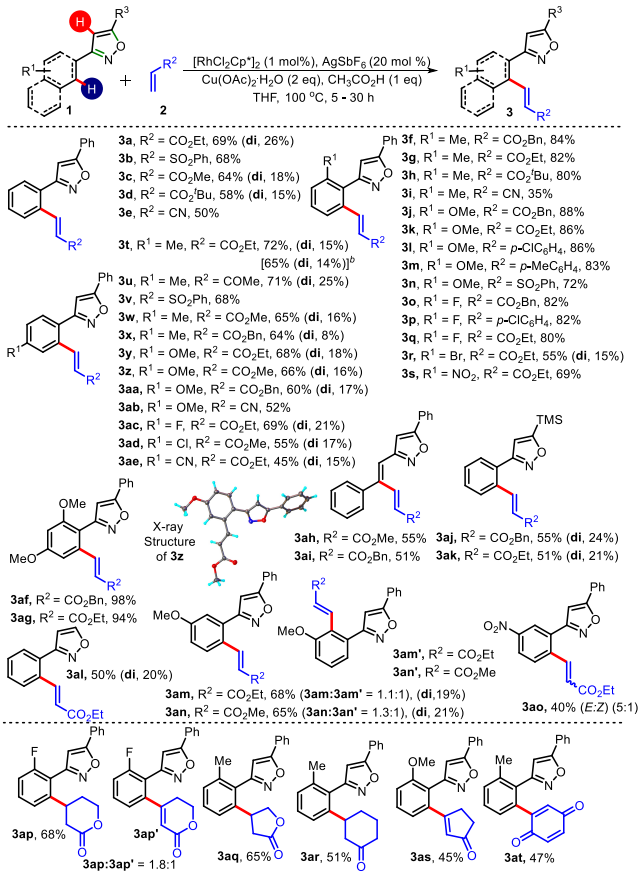
(Scheme 2). In all cases, the site selectivity was exclusive and no C−H olefinations arising out of electrophilic metallation

Scheme 2. Substrate Scope for *ortho*-Alkenylation of 3,5-Diarylisoxazole[a]



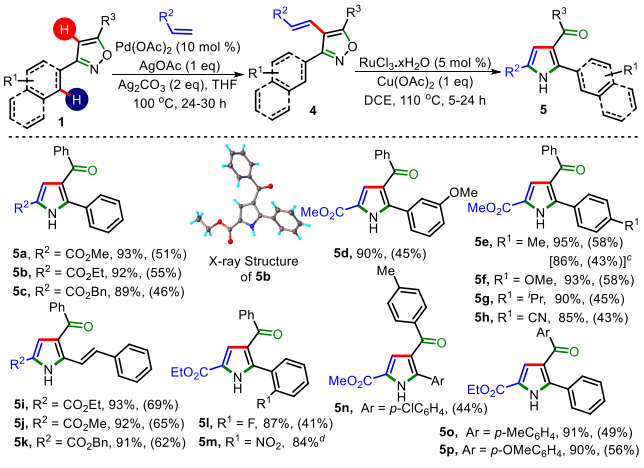
[a]All yields are isolated yields. [b]Yield for the reaction on 1 mmol scale.

were detected at the isoxazole ring. With 3,5-diarylisoxazole, electron-donating substituents on the 3-aryl ring did not hamper the reaction outcome and the corresponding *o*-alkenylated products were obtained in good yields. However, the presence of electron-withdrawing substituents in the 3-aryl ring resulted in a sluggish rate of reaction and the corresponding olefinated product were furnished in slightly reduced yields (Scheme 2). The site selectivity was unambiguously proven by X-ray crystallographic analysis of **3z**.

The transformation worked well with almost all the activated olefins that were screened, including acrylates, acrylonitriles, styrenes, vinyl sulfones, as well as enones (Scheme 2). The reaction worked well with α,β-unsaturated lactones, as well as cyclic enones. In some cases, the β-hydride elimination product was not observed; instead, the hydroarylation product, arising out of protodemetallation of the intermediate obtained after the migratory insertion, was observed.[13] In the case of 6-membered α,β-unsaturated lactones with 2-fluoro isoxazole mixture of product (hydroarylation and alkenylation) was obtained (**3ap** and **3ap'**; see Scheme 2). The reaction worked decently with monosubstituted (**3al**, Scheme 2) as well as a silyl-substituted isoxazole (**3aj** and **3ak**; see Scheme 2). Interestingly, the reaction worked quite well for the C(sp^2)-H olefination with a C5-vinyl substituent, thereby generating a very interesting diene system (**3ah** and **3ai**; see Scheme 2).

In 2011, Wheeler and co-workers had reported the direct alkenylation of the isoxazole ring,[14] whereas the direct arylations of isoxazoles using aryl iodides was reported by Nakamura and co-workers.[15] The coupling of alkenes and alkynes with 3,5-dimethyl-4-iodoisoxazole, 3-ethoxy-4-iodo-5-methylisoxazole has also been reported.[16] Based on our previous experience of C−H functionalization at distal positions within heterocycles,[17] we successfully switched the selectivity of the C−H olefination from the proximal arene ring C−H to the isoxazole C(4)−H by employing electrophilic metallation. Upon screening a variety of catalyst systems in different solvents to explore the selective olefination at the isoxazole ring, we found that $Pd(OAc)_2$, along with AgOAc (1 equiv) and Ag_2CO_3 (2 equiv) in THF at 110 °C, was the optimum condition (Scheme 3). The absence of silver acetate

Scheme 3. Substrate Scope for C(4)−H Alkenylation of 3,5-Diarylisoxazole and Subsequent Transformation to Pyrroles[a]



[a]All yields are isolated yields. [b]Values in parentheses indicate yield over two steps. [c]Yield for reaction on 1 mmol scale. [d]Directly synthesized from corresponding crude alkenylated product.

led to sluggish rate of reaction whereas oxidants other than silver carbonate led to the formation of *o*-olefinated product. With this optimized condition the scope of the present alkenylation reaction was further extended to various substituted activated alkenes and the reaction was found to be quite general (Scheme 3).

The utility of direct C-4 alkenylations of isoxazole was examined in the synthesis of pyrroles. When we subjected our synthesized C-4 olefinated isoxazoles under conditions such as $FeCl_2{\cdot}4H_2O$ (10 mol %) in acetonitrile,[18] we unfortunately could not get the desired pyrrole product. After considerable optimization (see the SI for further details) and we found that the cooperative catalysis involving $RuCl_3{\cdot}xH_2O$ (5 mol %), $Cu(OAc)_2$ (1 equiv) in DCE at 110 °C gave the desired pyrrole (Scheme 3) in very decent yield. The reaction worked well with all the substrates and we were able to synthesize a variety of trisubstituted pyrroles with moderate to good yields. The outcome of the cyclization was directly dependent on the initial palladium-mediated C(4)−H olefination of the isoxazole moiety. The palladium-mediated C−H olefination reaction seemed to work well with activated olefins such as acrylates but did not work with styrenes. The ruthenium catalyst was found to be necessary for the transformation to pyrroles; the reaction

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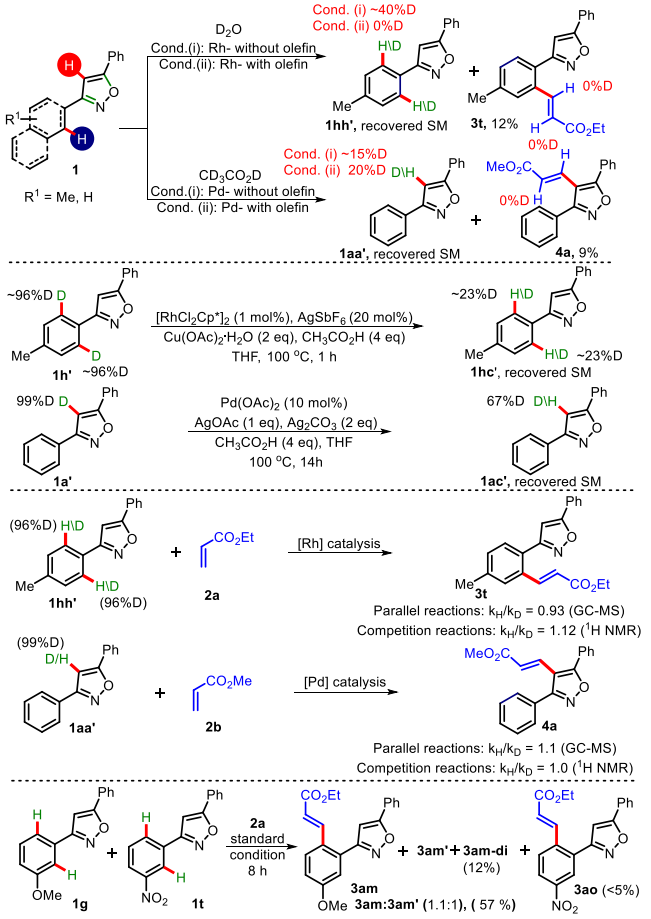
did not work without it. This indirectly indicated that the transformation was not just a copper-mediated one.

Experiments were conducted to gain more insights into the plausible pathways of the transformations (Scheme 4). To check the reversibility of the C−H metallation, the reactions were performed in the presence of D_2O or CD_3CO_2D. Although the reaction was slightly sluggish in the presence of D_2O, considerable deuteration was found at the relevant sites of the recovered starting material in both the rhodium- as well as palladium-catalyzed reactions (Scheme 4).

Scheme 4. Reversibility of Metalation and Kinetic Studies

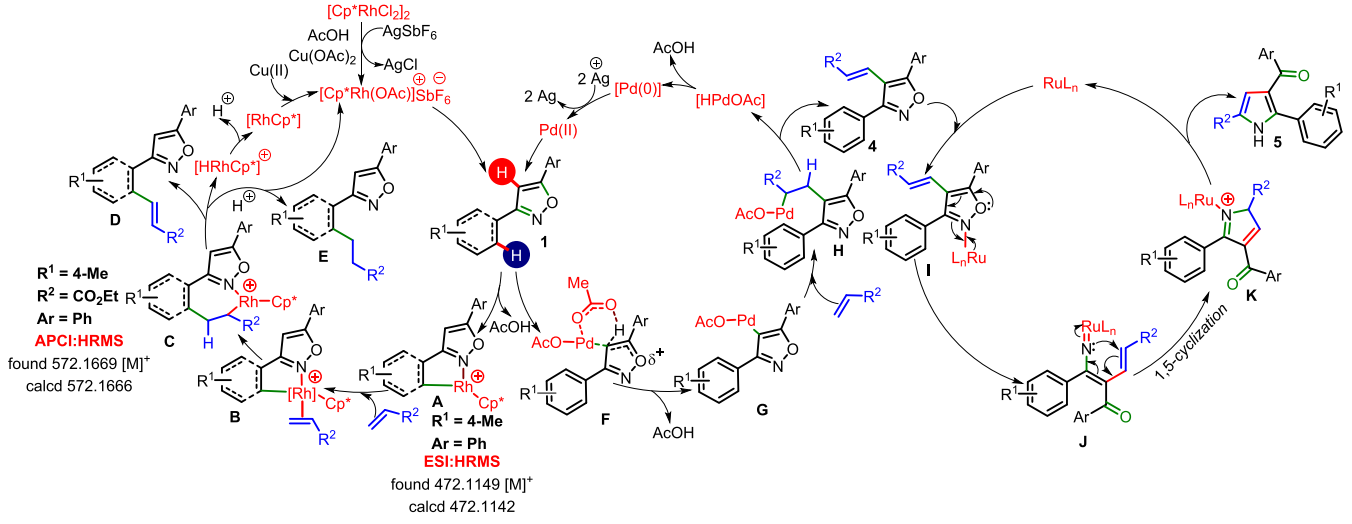


Interestingly, in the case of the rhodium catalysis, the reaction in the presence of the coupling partner did not yield any deuteration at the aryl ring, indicating that the further steps were faster than the demetallation. In the case of palladium catalysis, the reaction in the presence of coupling partner yielded a significant amount of deuteration in recovered starting materials with no deuterium incorporation in the product (Scheme 4). Kinetic isotope effect studies performed via parallel reactions as well as competitive reactions indicated an absence of primary kinetic isotope effect for both the rhodium- as well as the palladium-catalyzed transformations. This proved that the C−H activation is not the rate-limiting step for both the transformations. It is quite possible that either the carbometallation or the β-hydride elimination could be the rate-limiting step in these reactions. Based on these observations and literature reports,[18−20] plausible mechanisms for the transformations are depicted in Scheme 5.

In the case of the rhodium-catalyzed transformation, generation of the cationic catalyst is followed by a directed C−H activation, most probably via a base-assisted internal electrophilic substitution (BIES) reaction.[21a] The site selectivity is governed by the preference of the rhodium catalyst for the strongly coordinating isoxazole nitrogen. The protic medium may play a role in facilitating this step. The fact that substrate **1g** reacted faster than **1t** (Scheme 4) indicated that a BIES mechanism could be operative instead of the concerted metallation−deprotonation (CMD) pathway.[21b] This is followed by coordination of the olefin to the cyclometalated intermediate, followed by carborhodation and subsequent β-hydride elimination to yield the proximal C−H functionalization product. The rhodacycles **A** as well as **C** were detected in HRMS (Scheme 5). In the palladium-catalyzed transformation, it is possible that, because of the considerable covalency of $Pd(OAc)_2$, the preference for the softer mode of activation (electropalladation) is higher, thereby leading to metallation at the isoxazole ring.

After the formation of the C4-palladated intermediate, the subsequent steps are similar to the rhodium-catalyzed transformation. Our hypothesis is also supported by the fact

Scheme 5. Plausible Pathway for the Positional-Selective Transformations and the Ru-Mediated Pyrrole Synthesis



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that the reaction in the combination of $Pd(OAc)_2$ and $Cu(OTf)_2$ also resulted in C−H olefination at the proximal C3-aryl ring, similar to the rhodium-catalyzed transformation (see the SI for details). This clearly indicates that the cationic nature of the catalyst (hard) prefers coordination to the (hard) nitrogen directing group. At this moment, the role of copper in the conversion of **4** to **5** is not very clear. As mentioned earlier, Khlebnikov and co-workers had reported an Fe(II)-mediated transformation of 4-vinylisoxazoles to pyrroles, where an iron-carbene pathway was proposed. In our case, the Fe(II)-mediated pathway did not work and the reaction did not work with just stoichiometric amounts of Cu(II). Thus, Ru was necessary for this transformation. Although the reaction worked well with a Ru(II) catalyst ($[RuCl_2(p\text{-cym})]_2$ (5 mol %) and $Cu(OAc)_2$ (1 equiv), it performed much better with $RuCl_3$ (5 mol %) and $Cu(OAc)_2$ (1 equiv). As shown in Scheme 5, it is possible that a ruthenium-carbene intermediate may be involved in the pathway, which is followed by a 1,5-cyclization to yield the pyrrole product. This Ru- and Cu-mediated cooperative catalysis to yield a pyrrole product did not work with the olefination products arising out of the Rh-catalyzed reaction, since the molecular framework for the cyclization is unavailable in that case.

To conclude, we have demonstrated a catalyst-controlled, positional-selective C−H olefination of substituted isoxazoles. The proximal site selectivity in the rhodium-catalyzed transformation is governed by the cationic nature of the catalyst and the strong coordination to the nitrogen of the isoxazole, whereas the distal site selectivity in the palladium-catalyzed transformation is governed by the more covalent nature of the catalyst. The synthetic elaboration of the palladium-mediated C−H olefination product is demonstrated by a ruthenium- and copper-mediated cooperative catalysis in the synthesis of densely substituted pyrroles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00446.

Experimental details and spectral characterization of all new compounds (PDF)

Accession Codes

CCDC 1884277 and 1884314 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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