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Ruthenium-Catalyzed Oxidative C−H Bond Olefination of *N*-Methoxybenzamides Using an Oxidizing Directing Group

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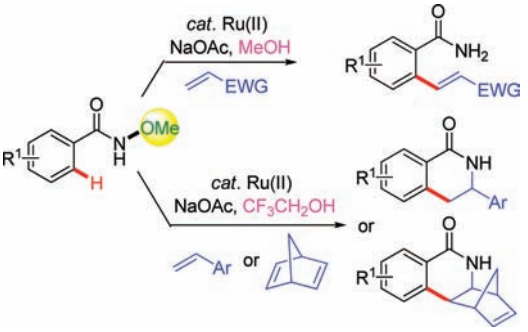
ABSTRACT



Ruthenium-catalyzed oxidative C−H bond olefination of *N*-methoxybenzamides using an oxidizing directing group with a broad substrate scope is reported. The reactions of *N*-methoxybenzamides with acrylates in MeOH and styrene (or norbornadiene) in CF_3CH_2OH afforded two types of products.

Transition-metal-catalyzed direct C−H bond transformations have attracted significant interest, because these approaches allow the use of cheaper and more readily available starting materials.[1] Generally, the use of an external oxidant is required to regenerate the catalyst in the oxidative C−H bond functionalization reaction. Consequently, stoichiometric amounts of the reduced external oxidant are produced as waste, and harsh oxidative reaction conditions are required. In the past two years, the use of an oxidizing directing group that acts as both a directing group and an (internal) oxidant has emerged in this field.[2] This efficient method has been independently developed in palladium- and rhodium-catalyzed C−H bond transformation reactions by the research groups of Cui and Wu,[3] Hartwig,[4] Yu,[5] Guimond and Fagnou,[6] and Glorius.[7] Recently, we first applied this strategy in the synthesis of

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isoquinolones from *N*-methoxybenzamides *via* ruthenium-catalyzed C−H bond activation at room temperature.[8]

The Mizoroki−Heck reaction[9] is one of the most important metal−catalyzed C−C bond-forming processes. As an attractive alternative, the Fujiwara−Moritani reaction[10] is the oxidative olefination of normally unreactive aryl C−H bonds. In recent reports, palladium[11] and rhodium[12] complexes are the most frequently used catalysts in the Fujiwara−Moritani reaction. However, the analogous ruthenium-catalyzed processes[13] were less explored, except the elegant contributions from the research groups of Milstein,[14] Miura and Satoh,[15] and Yi.[16] Very recently, [{$RuCl_2$(*p*-cymene)}$_2$] catalyzed C−H bond activation reactions of aromatic acids and aryl ketones with olefins were reported by the research groups of Ackermann[13c] and Jeganmohan,[13f] respectively. Herein, we disclose our development of a ruthenium-catalyzed oxidative C−H bond olefination using the CONH(OMe) group[6a,17] as an oxidizing directing group. We found that the reaction of *N*-methoxybenzamides with acrylates in MeOH and styrene (or norbornadiene) in CF_3CH_2OH afforded two types of products.

Our success in the ruthenium-catalyzed C−H bond annulations of *N*-methoxybenzamides with alkynes using an oxidizing directing group[8a] prompted us to examine their reactions with alkenes. Initially, the reactions of *N*-methoxybenzamide (**1a**) with activated alkenes were examined. To our delight, treatment of **1a** (1.0 equiv) with *n*-butyl acrylate (**2a**) (1.8 equiv) in the presence of 5.0 mol % of [{$RuCl_2$(*p*-cymene)}$_2$] and 30 mol % of NaOAc in CH_3OH at 60 °C for 4 h gave the Heck-type product **3aa** in 87% yield with excellent *E*-stereoselectivity (Scheme 1). The structure of **3aa** was confirmed by ^{1}H and ^{13}C NMR analysis and mass spectrometry. No desired product was obtained in the absence of a ruthenium catalyst or acetate. The acetate is crucial for the cyclometalation step[1b] and the regeneration of the catalyst.[8a] Other salts, such as K_2CO_3, were unsuitable for the reaction.

With the optimized conditions in hand, we then investigated the reaction of various substituted benzamides **1** with **2a** (Scheme 1). Both electron-rich and -poor *N*-methoxybenzamides participated well in this reaction and gave the corresponding alkene derivatives **3aa**−**3ma** in moderate to excellent yields. It is noteworthy that many important functional groups on the aromatic ring of benzamides **1**, such as methoxy, fluoro, chloro, bromo, iodo, nitro, ester, and acetyl substituents (**3da**−**3la**), were compatible in the present catalytic reaction. These findings offer the opportunity for further coupling to afford more complicated molecules. Extension of this reaction to heteroaryl carboxamides turned out to be successful. *N*-Methoxy-1-methyl-indolyl-2-carboxamide (**1n**) and *N*-methoxythiophenyl-2-carboxamide (**1o**) reacted with *n*-butyl acrylate to yield **3na** and **3oa** in good yield (Scheme 1). Moreover, various acrylates, such as methyl acrylate (**2b**), ethyl acrylate (**2c**), *tert*-butyl acrylate (**2d**), and benzyl acrylate (**2e**), efficiently reacted with **1a** to produce the corresponding Heck-type products **3ab**−**3ae** in good to excellent yield (Scheme 1). As a result of the use of an oxidizing directing group, the reactions were completely *ortho*- and mono-olefination selective in all cases. This is in contrast to the use of an external oxidant together with a directing group in the established metal-catalyzed olefination methods.[11,12]

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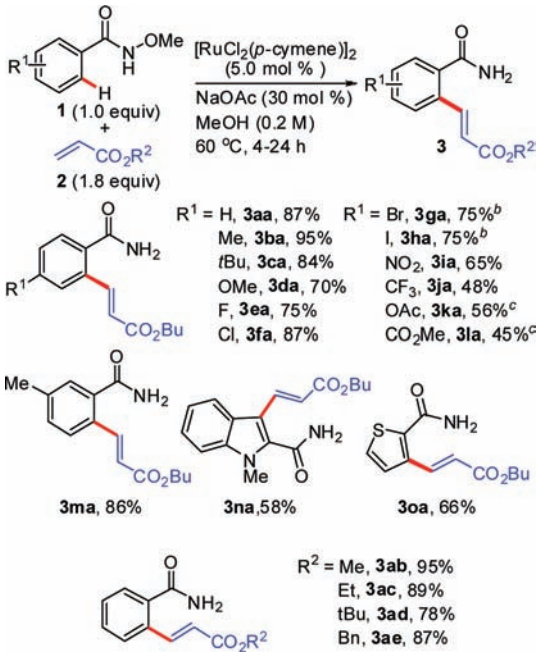
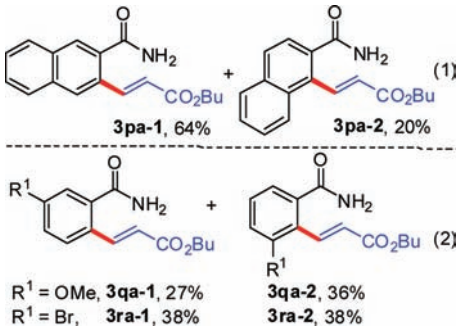
Scheme 1. Results of Ruthenium-Catalyzed Oxidative C−H Olefination with Acrylic Acid Esters[a]



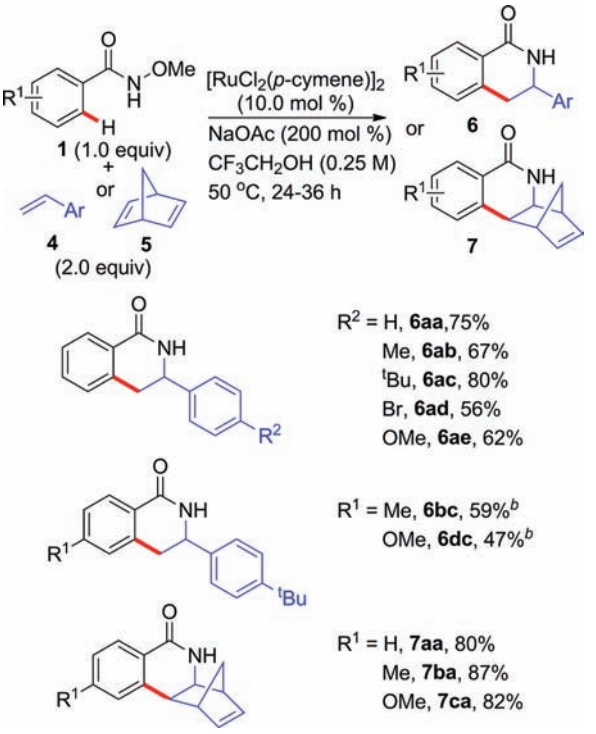
[a] Isolated yield. [b]6 mol %of $[RuCl_2(p\text{-cymene})]_2$ was used. [c]7.5 mol % of $[RuCl_2(p\text{-cymene})]_2$ was used.



We then studied the regioselectivity of this reaction. Examination of the *meta*-substituted benzamide scope revealed that the conversion of *meta*-substituted **1m** and the β-naphthyl derivative **1p** was largely controlled by steric interactions. The former afforded **3ma** as the sole product (Scheme 1), whereas the latter yielded **3pa-1** as a major regioisomer (eq 1). In contrast, when substrates **1q** and **1r** with electronegative heteroatoms in the *meta*-position were applied, significant amounts of regioisomers **3qa-2** and **3ra-2** were produced through C−H bond transformations at the 2-position of the arenes (eq 2). The observed site selectivity of different substrates was in agreement with that found by Ackermann[8b,13g] and us,[8a] which resulted from the C−H bond acidity[1b] or Ru−C bond stability.[18]

Subsequently, we tested the catalytic reaction with styrenes and norbornadiene. No corresponding alkenylated

Scheme 2. Results of Ruthenium-Catalyzed Oxidative C−H Olefination with Phenylethylene and 2,5-Norbornadiene[a]



[a] Isolated yield. [b]70 °C.

product was observed under the optimized reaction conditions described above. The same reaction was examined with other solvents. After some trials, we were surprised to find that the reaction worked smoothly in 2,2,2-trifluoroethanol (TFE) and afforded 3,4-dihydroisoquinolinone derivative **6aa** in 75% isolated yield with a higher catalyst loading (10 mol %) (Scheme 2).[19] However, treatment of **1a** with *n*-butyl acrylate **2a** in TFE still gave the Heck-type product **3aa**. Notably, Glorius has reported that the rhodium-catalyzed reaction of **1a** with acrylates/styrene afforded *ortho*-olefinated products.[7] Replacement of the *N*-methoxy group of **1a** by the *N*-pivalate group led to the formation of 3,4-dihydroisoquinolinone derivatives.[6b,7] Under the reaction conditions in TFE, various substituted styrenes (**4b**−**4e**) with either electron-donating or -withdrawing groups and norbornadiene (**5a**) were good candidates for this reaction and produced **6ab**−**6ae** and **7aa** in moderate to high yield (Scheme 2). 4-Methyl and 4-methoxy substituted benzamides **1b** and **1d** also reacted well with 4-*tert*-butylstyrene (**4c**) and norbornadiene (**5a**) to give 3,4-dihydroisoquinolinone derivatives **6bc**, **6dc**, **7ba**, and **7ca** in 47−87% yield, respectively (Scheme 2). Disappointedly, other strained alkenes, such as norbornene and cyclohexene, were not suitable substrates for this reaction and gave the desired products in very low yield (< 5%) under

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(19) Under otherwise identical conditions, approximately 10% and 40% of **6aa** was obtained in the reaction of **1a** and styrene (**4a**) catalyzed by 5.0 and 7.5 mol % of $[\{RuCl_2(p\text{-cymene})\}_2]$, respectively.

the optimized reaction conditions. The structures of complexes **6ad** and **7ca** were further confirmed by X-ray diffraction analysis (Figure 1).

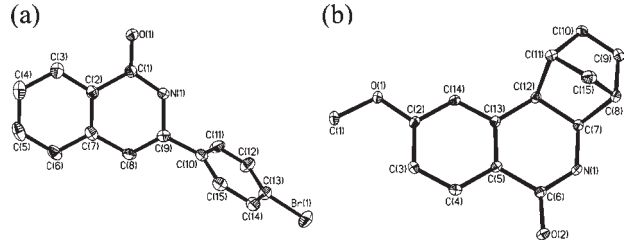
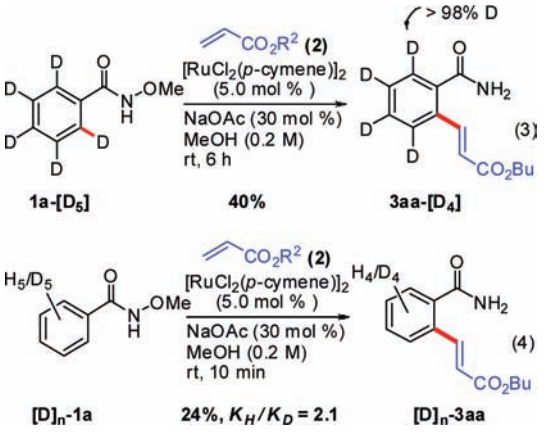


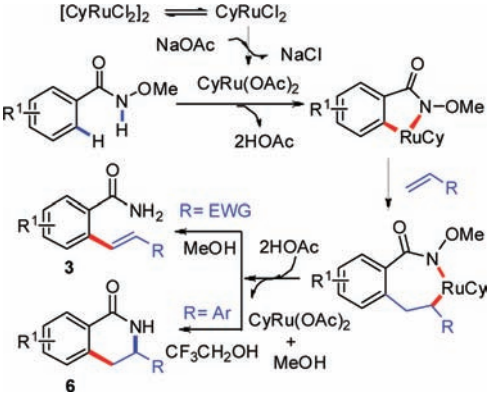
Figure 1. X-ray diffraction analysis of complexes **6ad** (a) and **7ca** (b). Thermal ellipsoids are shown at the 30% level. Hydrogen atoms have been omitted for clarity.

Finally, we conducted experiments with isotopically labeled substrates to probe the working mode of the reaction. Reaction with deuterated starting material **1a-[D_5]** was examined, and no H/D exchange was detected (eq 3). Furthermore, a kinetic isotope effect (KIE) of $k_H/k_D \approx 2.1$ was observed in the intermolecular isotopic study (eq 4). It is suggested that, under the reaction conditions, the C−H bond metalation step is probably irreversible and involved in the rate-determining step.[13c] On the basis of the above data, we proposed the reaction proceeds by an initial intermolecular carboruthenation of alkene *via* rate-determining C−H bond ruthenation and subsequently reductive elimination for product formation (Scheme 3).



In summary, we have developed the first ruthenium-catalyzed oxidative C−H bond olefination of *N*-methoxybenzamides using an oxidizing directing group with a broad substrate scope. The catalytic reaction is exclusively *ortho*- and mono-olefination selective. The use of an internal oxidant results in a mild reaction condition and a clean process. Intriguingly, the reactions with acrylate esters in MeOH afford olefinated benzamides, whereas with styrenes or norbornadiene in TFE provide 3,4-dihydroisoquinolinone derivatives as products. Moreover, the present reaction adds to the rapidly expanding repertoire of internal oxidant directed C−H bond activation reactions.[2−8] Mechanistic studies of the reaction were indicative of an irreversible C−H bond metalation step *via* acetate assistance. Further studies to explore ruthenium-catalyzed oxidative C−H bond transformations and clearly understand the reaction pathway are in progress and will be reported in due course.

Scheme 3. Proposed Mechanism (Cy = *p*-Cymene)



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Supporting Information Available. General experimental procedures, full spectroscopic data for all new compounds, and CIF files giving X-ray structural information for **6ad** and **7ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.