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Rh(III)-Catalyzed Directed C−H Olefination Using an Oxidizing Directing Group: Mild, Efficient, and Versatile

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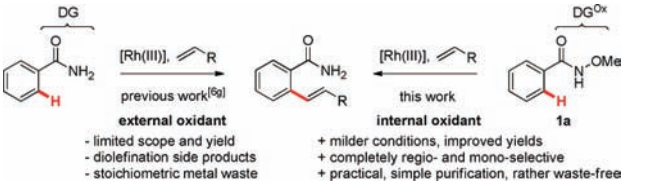
Supporting Information

ABSTRACT: An efficient Rh(III)-catalyzed oxidative olefination by directed C−H bond activation of *N*-methoxybenzamides is reported. In this mild, practical, selective, and high-yielding process, the N−O bond acts as an internal oxidant. In addition, simply changing the substituent of the directing/oxidizing group results in the selective formation of valuable tetrahydroisoquinolinone products.

Over the past decades, the Mizoroki−Heck reaction[1] has become one of the most important and distinct metal-catalyzed C−C bond-forming processes. However, the activation of normally unreactive C−H bonds allows access to new products, the use of cheaper, more readily available starting materials, and, thus, increased sustainability.[2] Consequently, an attractive alternative to the Heck reaction is the oxidative coupling of unactivated aryl C−H bonds with olefins, the Fujiwara−Moritani reaction.[3] One of the most popular strategies to obtain a selective C−H activation is the use of a neighboring directing group (DG) that precomplexes the metal and directs it to the desired position.[4−6] Mostly Pd-[4] and Rh-catalyzed[6] directed olefinations of aromatic C−H bonds have been reported. Generally, the use of external oxidants requires rather harsh oxidative reaction conditions and high reaction temperatures and provides stoichiometric amounts of the reduced external oxidant as waste. In addition, the scope and yield of these transformations are limited. For example, in the only reported olefination using primary benzamides as DGs, the reaction conditions are quite harsh, resulting in limited substrate scope and yields and, depending on the substitution pattern, the formation of diolefination side products (Scheme 1).[6g] Thus, application of innovative DGs with improved directing qualities, representing useful functional groups, that are tunable and show increased levels of reactivity and selectivity should be beneficial.

One emerging strategy in the area of C−H activation chemistry is the use of entities that at the same time act as both DG and (internal) oxidant (DG^{Ox}).[7] Recently, the groups of Cui and Wu,[8] Hartwig,[9] and Yu[10] applied DGs bearing an N−O bond as oxidant in different Pd-catalyzed C−H activation reactions. Very recently, Fagnou et al. reported on the Rh(III)-catalyzed isoquinoline synthesis by using the N−O bond of *N*-methoxybenzamides **1** as oxidant and coupling it with internal alkynes.[11] The only olefination reaction among these, the olefination of quinoline-*N*-oxides by Cui and Wu,[8] still requires a high reaction temperature (110 °C) and, like most Pd-catalyzed oxidative olefinations, is largely limited to acrylates as coupling partner.

Scheme 1. Improving Oxidative C−H Olefination Reactions by Using Internal Oxidants



Herein we report a uniquely efficient Rh(III)-catalyzed C−H olefination reaction of *N*-methoxybenzamides **1**, enabled by the use of CONH(OMe) as DG as well as internal oxidant (DG^{Ox}, Scheme 1). This results in numerous advantages: the reaction proceeds under mild conditions, is very practical and completely regio- and monoselective, and, most importantly, results in improved yields and substrate scope. Moreover, a slight structural variation of this DG^{Ox} group allowed the switching of the reaction to yield valuable cyclized lactam products, providing mechanistic insight into these processes.

Benzoic acid derivatives are of great importance; thus, for maximum relevance of our study, we selected a valuable carboxylic acid derivative as DG^{Ox}. We commenced our study with the coupling of *N*-methoxybenzamide (**1a**) and styrene (**2a**, Table 1). The use of $[Cp^*RhCl_2]_2$ (1.0 mol %) as catalyst together with CsOAc (30 mol %) as additive[11] at 60 °C in MeOH resulted in the formation of the desired *trans*-olefinated benzamide **3aa**. Spectroscopically pure product was obtained in 90% yield by simply washing the crude reaction mixture with chilled MeOH.[12] Diolefinated or *cis*-olefin side products were not observed by GC-MS nor by ^{1}H NMR of the crude reaction mixture.[13]

This high level of reactivity allows an impressively low reaction temperature and, as a consequence, high yields and a remarkably broad substrate scope (Table 1). The reaction does not require an inert atmosphere and can conveniently be run on a 10 mmol scale.[13] Many important functional groups like iodides, bromides, methoxy, nitro, ester, and acetyl were well tolerated.[14,15] In addition, alkenes bearing organometallic (**2l**) and heterocyclic groups (**2m**) also reacted well. Moreover, acrylates smoothly react to the Heck-type product at even lower temperature (40 °C), largely avoiding the overreaction to a five-membered lactam.[16]

Naturally, in all cases the reactions were completely *ortho*-selective. Moreover, as a direct consequence of the use of an internal oxidant, in each case the reactions nicely stopped after

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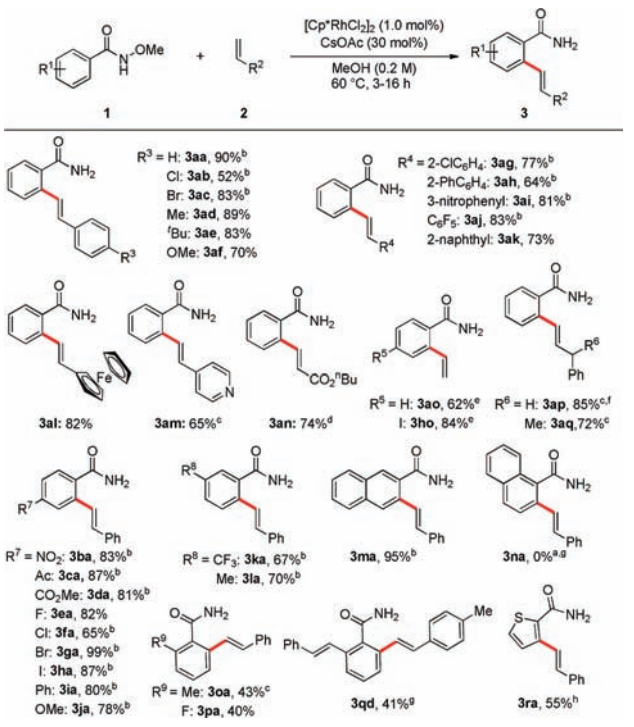
Table 1. Scope on the Rhodium-Catalyzed Olefination[a]



[a] Reaction conditions: 1a (1.0 mmol), alkenes 2 (1.5 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol %), CsOAc (30 mol %), dry MeOH (0.2 M), 60 °C, 3−16 h, Ar atmosphere. Isolated yields are given. Unless otherwise mentioned, product was purified by column chromatography. [b] Product was purified by simply washing with MeOH.[14] [c] Reaction run at 80 °C. [d] Reaction run at 40 °C for 0.7 h. [e] Run under 5 bar of ethylene. [f] Ratio of olefin regioisomers = 10:1. [g] Reaction run at 110 °C. [h] Reaction run at 80 °C for 60 h, then 8 h at 100 °C.

mono-olefination. This is in contrast to the common use of DGs together with an external oxidant in Rh-catalyzed olefinations.[6] In these latter reactions, double olefination can only be suppressed by steric shielding expressed by a carefully chosen substitution pattern. Thus, the mono-olefination selectivity of our oxidizing DG presents a distinct and important advantage over established methods.

Intriguingly,[17] using gaseous ethylene (5 bar) as an alkene coupling partner, under standard reaction conditions, we were pleased to get the terminal olefin (**3ao**, **3ho**) in good—and compared to the use of benzamide as the DG,[6g] dramatically improved—yield of up to 84%. No further arylation of the terminal olefin of these products was observed.

It should be noted that some other terminal alkenes (1-octene, 1,4-hexadiene) gave only trace amounts of product under standard conditions. However, allylbenzene (**2p**) and 3-phenyl-1-butene (**2q**) can also be smoothly transformed to the desired product (**3ap** and **3aq**, respectively) in good yield, presumably due to π-interaction of the phenyl group with the metal. When the *meta*-substituted **1k** and **1l** or the β-naphthyl derivative **1m** was used, *ortho*-rhodation took place regioselectively at the less hindered site, providing **3ka** and **3la**.[11] Interestingly, α-naphthyl derivative **1n** did not provide any of the desired product at 60 °C nor at 110 °C. However, it is important to note that many olefin substrates successfully employed in this study fail to provide good amounts of the desired coupling product when benzamides or related substrates are employed (Scheme 1, left; for example, 3-nitrostyrene (**2i**), vinylferrocene (**2l**), 4-vinylpyridine (**2m**), ethylene (**2o**), and allylbenzene (**2p**)).

Furthermore, we conducted a series of experiments to probe the reaction mechanism. Fagnou et al. showed that the *ortho*-rhodation step in their alkynylation of **1a** is reversible under their reaction conditions.[11] When our reaction was conducted in MeOH for **1a** and in CD_3OD for D_5-**1a** under standard reaction conditions for 5 min in parallel, 32% of the desired product was observed (by ^1H NMR) in both cases.[13] This observation of an intermolecular kinetic isotope effect (k_H/k_D) of 1.0 supports that the *ortho*-rhodation (C−H activation) step is fast relative to the other steps of the catalytic cycle. A competition experiment carried out by coupling the electronically different *para*-substituted benzhydroxamic acid derivatives **1c** and **1j** (equimolar amounts) with styrene (**2a**) for 7 min showed that the rate of the reaction increased ~3.1 times in the order **1j** (4-OMe) < **1c** (4-Ac). The substituents on the aromatic ring influence the DG properties, thus indicating that the electronic nature of the DG plays a prominent role in the rate-determining step.[18] The fact that *N*-methyl-*N*-methoxybenzamide (**1a′**) did not give any product implies that the N−H bond is essential for this reaction. In order to elucidate the role of the *N*-OMe group, two separate reactions of *N*-unsubstituted and *N*-methoxy-substituted benzamides using stoichiometric amounts of $[Cp^*RhCl_2]_2$ were run at 60 °C. Under these conditions, *N*-methoxybenzamide (**1a**) provided around 90% of the desired product **3aa**, together with a small amount of the diolefination product, whereas benzamide largely remained unreacted, and only less than 10% of the mono-olefination product formed.[13] This clearly shows that the *N*-methoxy amide group not only acts as an internal oxidant but also is a better DG than the *N*-unsubstituted primary amide.

To learn about the subsequent steps of the catalytic cycle, we carried out competition experiments between equimolar amounts of electron-rich *p*-methoxystyrene (**2f**) and electron-deficient pentafluorostyrene (**2j**) with **1a** as coupling partner, affording 2 times more **3af** than **3aj** at the initial stage of the reaction. This seems to render the insertion of alkene into the Rh−C_{ar} bond a likely rate-limiting step.[19]

No olefinated product was observed when **1a** and **2a** were treated with catalytic amounts of Rh(I) under reaction conditions. Instead, a considerable amount of demethoxylated benzamide and starting material was obtained.[13] To further examine whether the alkenylated **1** oxidizes the Rh catalyst by an *intra*-molecular redox reaction, another insightful competition experiment was performed (Scheme 2). Equimolar amounts of **1i** and **1q** were added to 5 equiv of **2d** under the standard reaction conditions. The observed 93% recovery of **1q** suggested that the N−OMe bond of alkenylated **1l** acts as a *truly internal* oxidant to convert Rh(I) into Rh(III), completing the catalytic cycle.[20] However, at present, the exact timing and mode of action of the N−O bond cleavage and oxidation of the metal are unclear.[21]

The potential intermediacy of the seven-membered rhodacycle **A** led us to explore the possibility of a different pathway, namely a reductive elimination of **A**, leading to the formation of lactam **5aa** after oxidation of the Rh catalyst (Figure 1). The successful execution would not only represent a synthetically exciting and efficient entry to these compounds but also be an indication for the intermediacy of **A**. The coordinative saturation of the metal center represents one established strategy to suppress β-hydride elimination.[22] Thus, key to success was the use of an *O*-pivaloyl group on the benzamide N, which can potentially chelate the Rh.[23] In addition, small amounts of pivalic

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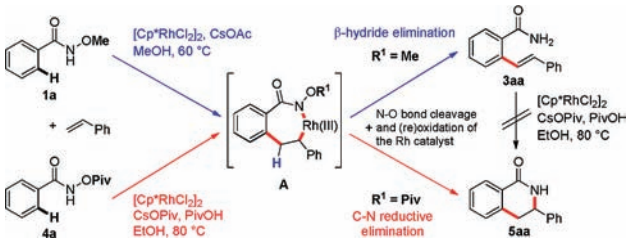


Figure 1. Switching the reaction pathway by choice of different N−OR[1] groups.

Scheme 2. Test for the Nature of the Oxidant: Internal vs External

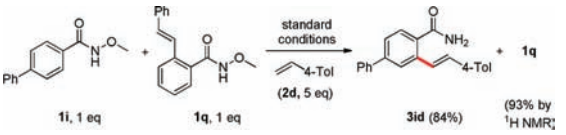
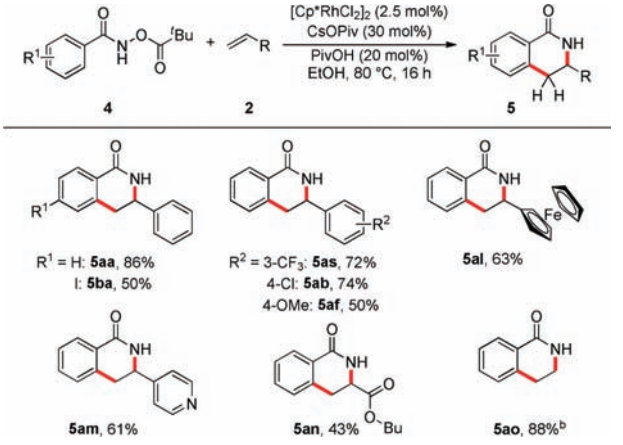


Table 2. Tetrahydroisoquinolinone Synthesis[a]



[a] Reaction conditions: 4 (1.0 mmol), alkenes 2 (1.5 mmol), [Cp*RhCl$_2$]$_2$ (2.5 mol %), CsOPiv (30 mol %), PivOH (20 mol %), dry EtOH (0.2 M), 80 °C, 16 h, Ar atmosphere. Isolated yields are given. [b] Run at 60 °C under 5 bar of ethylene pressure.

acid were found to be beneficial, resulting in the selective formation of **5aa** from **4a** (Table 2).[13] Interestingly, under the same reaction conditions, substrate **1a** leads exclusively to the formation of the olefinated product **3aa**. In addition, when olefination product **3aa** was subjected to these modified reaction conditions, the starting material remained unchanged after 16 h (Figure 1). This clearly rules out the intermediacy of **3aa** in the formation of **5aa** and might be seen as an additional indication for the existence of an intermediate **A** (R^1 = Piv).

Finally, we examined the scope of this interesting reaction by varying both coupling partners (Table 2). The selectivity and substrate scope for this reaction are good for acrylates and styrenes. Interestingly, even in the case of acrylate, the six-membered product **5an** formed. Impressively, treatment of **4a** with 5 bar of ethylene gave the desired product (**5ao**) in excellent yield.

In conclusion, we have developed a novel, regio- and stereoselective, synthetically efficient, mild, and broad substrate scope tolerable olefination reaction by C−H activation. Avoiding external oxidants also results in a clean and rather waste-free process. Excitingly, we have discovered the effect of substituents on the directing group that allows us to obtain either olefinated benzamides or cyclized tetrahydroisoquinolones as products. Arguably, this would be an exciting example of a C(sp^3)−N reductive elimination of a Rh(III) intermediate.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For a recent minireview, see: Patureau, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, 10.1002/anie.201007241. It is interesting to note that, whereas the term "external oxidant" seems to be unambiguous, the term "internal oxidant" can either mean simply that one of the substrates acts as an oxidation equivalent or, in a more limited usage, that the catalyst gets oxidized *internally* before, at, or after the reaction event. For example, the halide group of aryl halides represents a truly internal oxidant in reactions like the Heck reaction.

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(12) Interestingly, using *N*-hydroxybenzamide as substrate, 72% of product **3aa** was obtained.

(13) See Supporting Information for further details.

(14) No dehalogenation or demethoxylation was observed.

(15) In the case of **3ca**, **3da**, and **3ha**, no side product was observed (^{1}H NMR).

(16) In Pd(II)-catalyzed oxidative Heck reactions, the amide group is known for this kind of attack: Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. Indeed, under our standard reaction conditions, we have also observed the five-membered lactam side product.

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(20) Rh(I) can bind effectively with olefin ligands: Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *122*, 1161.

(21) Starting from intermediate **A**, a β-hydride elimination−reductive elimination (to give a Rh^I species)−oxidative addition sequence might seem reasonable. Alternatively, a different order of these steps involving the formation of a Rh^V species could be invoked.

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(23) Other groups on nitrogen gave lower selectivities for the formation of **5aa**: OPiv (9:1 = **5aa**:**3aa**) > O(CO)Tol (2:1) > OAc (1:1) > OH = OMe (only **3aa**); values based on either ^{1}H NMR or GC-MS of the crude reaction mixture. See Supporting Information for further details.

■ NOTE ADDED AFTER ASAP PUBLICATION

After this paper was published ASAP January 28, 2011, new citations were added to ref 11. The corrected version was published February 2, 2011.