C–H Activation

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Rhodium-Catalyzed Oxidative Olefination of C–H Bonds in Acetophenones and Benzamides**

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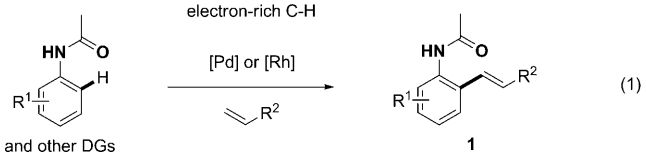
In memory of Keith Fagnou

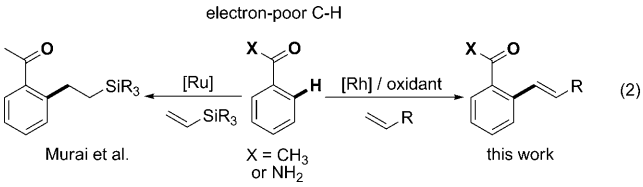
The oxidative Heck-type reaction, as pioneered by Fujiwara and Moritani,[1] has emerged as an attractive method for the coupling of arenes and olefins, because in contrast to the traditional Heck reaction,[2] it obviates prior activation of either reaction partner. For this transformation, palladium is the established catalyst,[3–5] for example in the C–H oxidative olefination of acetanilides with acrylate derivatives reported by van Leeuwen et al.[4] and in the use of remote carboxylic acids as efficient directing groups described by Yu et al.[5] Miura and Satoh et al.,[6] we,[7] and others have looked at other transition metals for these C–H activation processes, specifically rhodium, which often allows lower catalytic loadings, higher selectivities, and broader olefin scope.

Recently we have had some success with the rhodium-catalyzed coupling of unactivated acetanilides (electron-rich arenes) with styrenes and even ethylene [Eq. (1); the atoms in bold are part of the directing group (DG), the bond in bold is the coupling site].[7a] In contrast, the C–H activation process-



(1)

es of many difficult-to-activate, electron-poor substrates such as common carbonylated arenes remain underdeveloped.[8] Acetophenones, for example, were found by Murai et al. to undergo *ortho* C–H activation with ruthenium catalysts but reacted with only a limited scope of very electron-rich, generally silylated olefins [Eq. (2)].[8d] Furthermore, the process is not oxidative, rendering stilbene derivatives out of reach. Herein we report on the oxidative olefination of acetophenones and electronically related benzamides[9] with a broad range of olefins.



(2)

Understanding and utilizing the characteristics of these commonly occurring directing groups, on their own, or in concert, should have a strong impact on synthetic organic chemistry. For some time, we believed that the electron-richness of the C–H-activated arenes was critical to the high conversions in the rhodium-catalyzed oxidative olefination,[10] as the most electron-rich acetanilide substrates afforded the highest yields in couplings with electron-neutral styrenes.[7a] We were therefore surprised to find that the significantly less nucleophilic ketone moiety of acetophenones is also a suitable directing group for this rhodium-catalyzed oxidative Heck-type reaction.[11] Acetophenone coupled with styrene selectively to furnish stilbene **2a** in 57% yield (Scheme 1).[12] In contrast to acetanilides and benzamides (see below), electron-poor 3-trifluoromethylacetophenone did not react. In reactions of activated *n*-butyl acrylate, lower catalyst loadings could be used (0.5 mol% of Rh dimer), affording slightly higher yields with both substituted and unsubstituted acetophenones (**2e** and **2f**, Scheme 1). Interestingly, the coupling of a polycyclic 2-acetophenone derivative with styrene furnished the corresponding product **2h** in an improved yield of 72% and required only 0.5 mol% catalyst precursor. The polycyclic character of the substrate seems to be beneficial for the efficiency of the C–H functionalization, an effect that we speculate could be attributed to the extended aromatic conjugation. Interestingly, even challenging 2-vinyl-5-trifluoromethylacetanilide (**1a**), which itself was prepared from ethylene and the corresponding acetanilide in 65% yield by rhodium catalysis under standard conditions [Eq. (1)],[13] could be coupled with a polycyclic 2-acetophenone derivative with high selectivity although in moderate yield and only under harsher conditions (2.5 mol% rhodium precursor, 140°C, product **2i**, 44% yield; Scheme 1). This reactivity trend was confirmed when acetyl indole substrates

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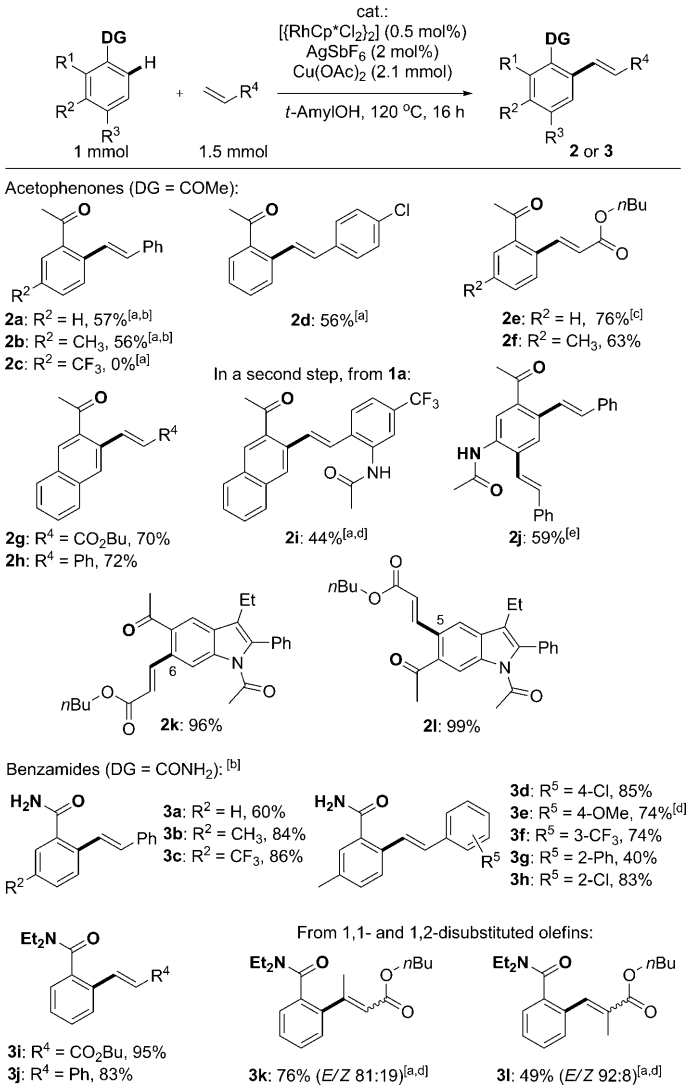


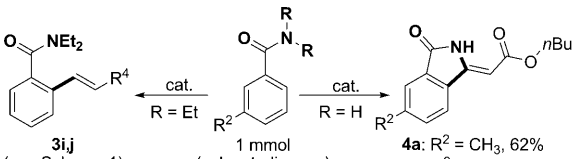
Scheme 1. Rhodium-catalyzed C–H oxidative Heck-type reaction of acetophenones and benzamides: Reaction conditions and yields of isolated products. [a] 2.5 mol% [{RhCp*Cl_2}$_2$]. [b] Reaction in 1,4-dioxane. [c] Difficult separation, 76% yield by NMR analysis. [d] Reaction at 140 °C. [e] 4.2 equiv $Cu(OAc)_2$, 3 equiv styrene, and 2.5 mol% [{RhCp*Cl_2}$_2$]. Cp* = η^5-C_5Me_5.

were engaged in the reaction, and the corresponding products were obtained with outstanding selectivity (**2k**, 96%, **2l**, 99%).[14] In these cases, the heterocyclic character of the substrate is not only tolerated, but seems to facilitate the C–H functionalization process. The indole core, a most important structural motif in nature, presents six different aromatic C–H positions (2-H to 7-H). Accessing each of them selectively through C–H functionalization processes is certainly a great challenge, which we have been able to partly address with our methodology. The functionalization of positions 2-H and 3-H is arguably more trivial as their reactivities are usually very distinct from those of the other C–H positions.[15,16] With the sequential combination of Fagnou's rhodium-catalyzed indole synthesis, a C–H activation of acetanilides followed by coupling to alkynes,[10a,17,18] and our oxidative olefination method, we were able to selectively address positions 5-H (**2l**), 6-H (**2k**), and 7-H (**1b**,**c**).[16–18]

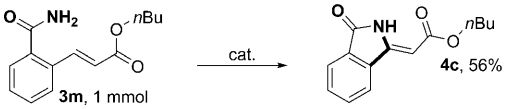
Benzamides are also excellent substrates in this reaction (Scheme 1).[19] Interestingly, whether the benzamide substrate carries electron-withdrawing ($R^2 = CF_3$) or electron-donating groups ($R^2 = CH_3$) does not seem to affect the reaction, as the corresponding coupling products with styrene were isolated in comparably high yields (compare **3b** (84%) and **3c** (86%); Scheme 1). Likewise, both electron-rich (**3e**, 74%) and electron-poor styrenes (**3f**, 74%) are well tolerated (Scheme 1). Again, halide functional groups were also well tolerated (e.g. **3d** and **3h**, 85% and 83%, respectively). Neither proto-dehalogenation nor other cross-coupling side products were observed in these reactions—a clear advantage over analogous palladium-catalyzed oxidative Heck reactions.

Interestingly, coupling a tertiary benzamide (*N*,*N*-diethylbenzamide) with the highly activated *n*-butyl acrylate afforded the desired product of the oxidative Heck reaction in outstandingly high yield and selectivity (**3i**, 95%; Scheme 1). Furthermore, when tertiary *N*,*N*-diethylbenzamide reacted with styrene, the monofunctionalized product of the oxidative Heck coupling formed selectively; indeed, this product was obtained in significantly higher yield than the analogous product from the reaction of the primary benzamide (compare **3a** (60%) and **3j** (83%); Scheme 1). The *N*,*N*-diethylbenzamide directing group is so efficient that even reputedly difficult 1,1- and 1,2-disubstituted olefins (butyl methacrylate and (*E*)-butyl but-2-enoate, respectively) yield the corresponding trisubstituted olefins **3l** and **3k** with moderate to good diastereoselectivity. For comparison, a previously reported palladium-catalyzed oxidative olefination using a similar 1,2-disubstituted olefin proceeded in only 16% yield.[5a]

In contrast, when primary benzamides were coupled to highly activated *n*-butyl acrylate, the major isolated products were found to be *exo*-cyclized γ-butyrolactams,[20] [products **4a–c**, Eqs. (3) and(4)]. Spectroscopic evidence clearly shows that exclusively products with a *Z*-configured exocyclic C=C bond are formed.[13] Engaging substrate **3m** under the standard reaction conditions led to the intramolecular cyclization product **4c** (56% yield), indicating that the product of an oxidative Heck coupling is a probable intermediate in this transformation.[21] In contrast, control substrate **3n** [corresponding saturated lactam, see

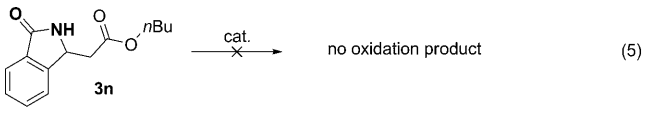


(3)



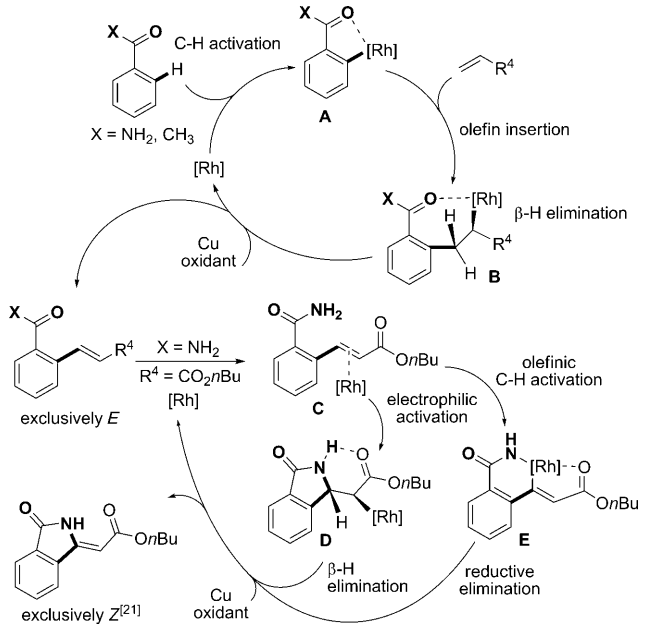
(4)

Eq. (5)] did not oxidize to product **4c** under the reaction conditions, indicating that the reaction does not involve a hydroamination step, but proceeds through direct intramolecular oxidative amination. Based on these observations, we propose that the oxidative cyclization reaction proceeds through electrophilic activation of the olefin (see also the cyclization mechanism proposed by Yu et al.;[20] intermediate



(5)

C, Scheme 2), followed by C–N bond formation (intermediate **D**) and subsequent β-hydride elimination. Intermediate **D** is supported by an intramolecular hydrogen bond that forms a six-membered ring, which orientates directs the β-hydride elimination towards the *Z*-configured product,[21] thus explaining the observed outstanding selectivity. Another credible pathway would be the rhodium-catalyzed olefinic C–H activation directed simultaneously by the benzamide and ester moieties (intermediate **E**). This is supported by the fact that only butyl acrylate leads to the cyclized product, and thus the ester functional group must play a pivotal directing role in its formation.



Scheme 2. Plausible catalytic mechanism of the oxidative Heck reaction and the intramolecular oxidative amination.

In conclusion, we have demonstrated that acetophenones and benzamides, both important motifs in nature and in the chemical laboratory, are suitable substrates for the selective rhodium(III)-catalyzed oxidative *ortho*-olefination reaction under the same optimized conditions. Furthermore, both electron-poor and electron-rich styrenes are well tolerated, as are many functional groups such as halides. Benzamides, in particular, have proven to be very reactive substrates, even in couplings with challenging 1,1- and 1,2-disubstituted olefins. Even acetophenones provide acceptable to good yields in this transformation (product **2l**, 99%) with a catalyst loading of only 0.5 mol%. Our observations have shown that the disposition of the aromatic system is a critical factor for achieving high yields and high selectivities, especially when the substrate contains more than one DG (products **2j**, **2k**, **2l**). Finally we have illustrated the relevance and generality of our method by addressing three different C–H positions of the biologically important indole moiety with excellent levels of selectivity and reactivity. We anticipate that this methodology will find applications in the synthesis of complex molecules, for example in the selective diversification of aromatic and heterocyclic cores.

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[11] In contrast, benzaldehydes do not react under these conditions.

[12] Small amounts of di-olefination products are generally observed, together with significant amounts of unreacted starting material.

[13] See the Supporting Information.

[14] The acetyl indole substrates furnishing products **2k** and **2l** were prepared from simple *N*-(4-acetylphenyl)acetamide and *N*-(3-acetylphenyl)acetamide, respectively, through the rhodium-catalyzed indole synthesis originally reported by Fagnou et al.[10a,13]

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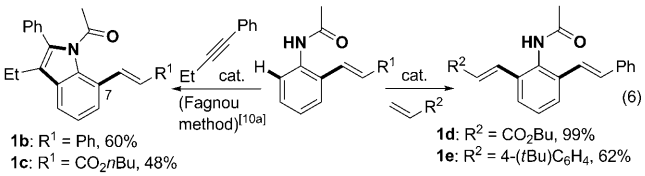
[17] The strategic use of the rhodium-catalyzed functionalization of acetanilides can be further illustrated by Equation (6).



[18] The rhodium-catalyzed synthesis of indoles from acetanilides and internal disubstituted alkynes was originally reported by Fagnou et al. using 2.5 mol% rhodium catalyst.[10a] Indole products **1b** and **1c**, however, have been prepared by us with only 0.5 mol% of the rhodium catalyst precursor.

[19] In contrast, benzoic esters do not seem to be well suited for this transformation. The coupling of ethyl benzoate with styrene provided the desired product in only 33% yield (determined by ^{1}H NMR analysis; reaction conditions: 2.5 mol% [{RhCp*Cl$_2$}$_2$], dioxane, 140 °C, 16 h).

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[21] Utilization of the secondary amide *N*-Me-**3m** under standard conditions resulted in the formation of the corresponding product *N*-Me-**4c** in 38% yield with a reversed *E*/*Z* ratio of 7:1.

