

Rh Catalyzed Olefination and Vinylation of Unactivated Acetanilides

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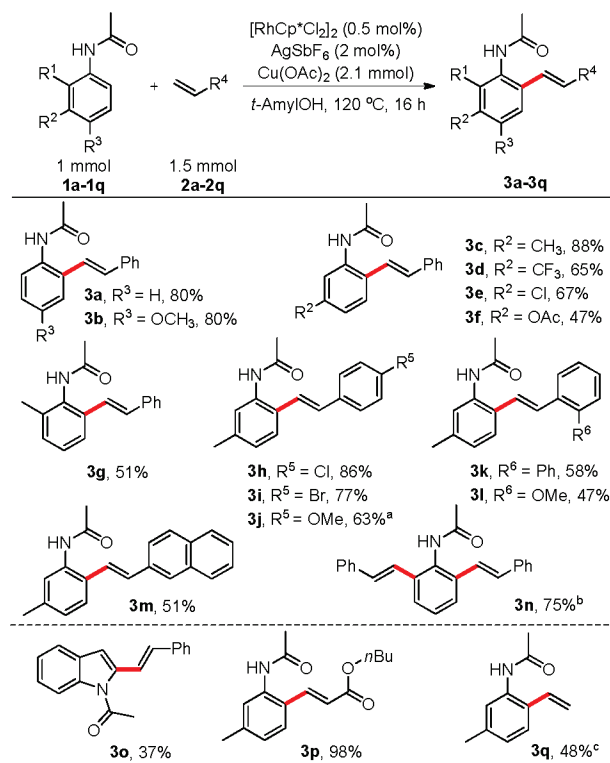
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Abstract: In the catalyzed oxidative olefination of acetanilides (oxidative-Heck coupling), Rh offers great advantages over more common Pd catalysts. Lower catalyst loadings, large functional group tolerance (in particular to halides), and higher reactivity of electron-neutral olefins (styrenes) are some of the attractive features. Most interestingly, even ethylene reacts to yield the corresponding acetanilido-styrene. Moreover, the Cu^{II} oxidant can also be utilized in catalytic amounts with air serving as the terminal oxidant.

Arguably, the Heck reaction is one of the most popular and distinct cross-coupling reactions.¹ The *oxidative* Heck reaction, utilizing a C–H instead of a C–X bond, as pioneered by Fujiwara and Moritani,² obviates the need for prior functionalization steps and is thus even more atom economic and versatile.³ Recently, mostly using Pd catalysts, a number of spectacular advances have been made by Yu et al.⁴ and others.^{5–7} Among these, van Leeuwen et al. showed that acetanilides were very effective in directing Pd catalyzed C–H bond activation and oxidative olefination.⁶ Nevertheless, in these cases the substrate scope is often limited to acrylates as coupling partners, which limits applications of these methods. Miura, Satoh et al. recently reported the Rh catalyzed oxidative mono- and bis-olefination of phenylpyrazoles and pyridines with styrene derivatives.⁷ The application of substrates bearing synthetically more versatile functional groups and their selective coupling with different classes of olefins, especially electron-neutral ones, would be highly desirable. Herein we report the selective Rh catalyzed oxidative olefination of acetanilides⁸ with different classes of olefins, most notably styrenes and ethylene. This represents a general method of broad utility for the *ortho*-olefination of aniline derivatives.

Gratifyingly, the C–H bond activation of acetanilide (**1a**) and subsequent coupling to styrene was found to proceed smoothly at 0.2 M in *tert*-amyl alcohol as solvent employing only 0.5 mol% of [RhCp*Cl₂]₂ catalyst precursor (120 °C, 16 h, Scheme 1).⁹ The resulting *trans* product **3a** was isolated in 80% yield.¹⁰ In contrast, neither the unprotected aniline nor the electronically related phenyl acetate nor nitrobenzene afforded any conversion under these conditions. Using electron-rich *para*-methoxyacetanilide (**1b**) or *meta*-methyl-acetanilide (**1c**) afforded the corresponding stilbene derivatives **3b** and **3c** in high isolated yield.⁹ Furthermore, products **3c–f, h–m, p, q** were all obtained with very high regioselectivities. In these cases, the olefination occurs selectively in *para*-position to the functional group R², whether it is electron-donating (R² = CH₃ or OAc) or electron-withdrawing (R² = CF₃ or Cl). This is consistent with mechanistic experiments of Fagnou et al. on *meta*-substituted acetanilides, demonstrating that, while a reversible hydrorhodation occurs on both positions *ortho* to the directing group, only the less sterically hindered site allows the new C–C bond to form.^{8a} Importantly, halide functional groups were tolerated, both in the acetanilide (**3e**) and in the styrene substrate (**3h, i**). Even valuable brominated products can be formed efficiently, with no proto-debromination or Heck coupling products

Scheme 1. Rh Catalyzed Olefination and Vinylation of Acetanilides, Conditions, and Isolated Yields



^a Reaction temperature: 140 °C. ^b 2.5 mol % of [RhCp*Cl₂]₂ and 9 mmol of styrene. ^c 2.5 mol % of [RhCp*Cl₂]₂ and 2 bar of ethylene in dioxane.

being detectable, showing one advantage of this Rh catalyzed transformation compared to many Pd catalyzed ones. These latter products allow further functionalization through other cross-coupling reactions.^{1b} Interestingly, 2-methyl-acetanilide **1g** led to product **3g** in only 51% isolated yield, quite below our expectation, considering that the electronically analogous product **3c** was obtained in high yield (88%). We attribute this decrease to the steric hindrance between the amide directing group and the CH₃ in the *ortho*-position, thus disturbing the planarity of the substrate. Similarly, when *N*-methyl-acetanilide was engaged as a substrate in the reaction, only 13% conversion to the expected product was observed (**3r**, conversion determined by ¹H NMR).¹¹ This *ortho*-steric effect may also account for the fact that the transformation virtually stops at the mono-olefination stage. In other words, the second C–H activation is disfavored compared to the first one due to the loss of planarity induced by steric hindrance with the stilbene functional group on the other *ortho* position. Thus, a planar conformation of the acetanilide seems important for effective direction of the metal and successive C–H bond activation. Interestingly, it was found possible to achieve further olefination to the bis-olefinated product by increasing the catalyst loading (2.5 mol%) and the styrene

concentration (cosolvent). The bis-olefinated product (**3n**) was obtained in 75% isolated yield (Scheme 1).

Additionally, this method was found applicable to the olefination of biologically relevant acetyl-indole, bearing a tertiary amide directing group, resulting in the selective coupling at the 2-position, although in modest yield under standard conditions (Scheme 1, **3o**).¹²

Our preliminary investigation indicates that the initial rate of the reaction is high but tends to decrease dramatically. Indeed, product **3a** is already obtained in 77% conversion after only 3 h (80% after 16 h, Scheme 1). Furthermore, our investigation shows that in all cases it is difficult to reach full conversion. This indicates that the product is a strong competitor for coordination to the active sites of the catalyst due to bidentate binding through the acetyl and the olefin functionalities.¹³ Thus, the product seems to be a poison to its own formation. In the case of activated olefins such as butyl-acrylate, however, a quantitative yield of the coupling product could be obtained (**3p**, 98%, Scheme 1). In this case the reaction is so fast that 90% conversion (¹H NMR) is obtained after only 5 min.⁹ Thus, the average TOF is ~1080 h⁻¹, a high value for C–C bond formation catalysis.¹⁴ Moreover, preliminary experiments show that air can serve as an oxidant in this reaction when using a catalytic amount of Cu(OAc)₂ (10 mol %). This afforded **3c** and **3p** in 61% and 97% isolated yields, respectively (no reaction was obtained without Cu salt).⁹ While Liu, Guo et al. reported the use of O₂ as an oxidant in a related Pd catalyzed C–H activation,^{6b} arguably, the use of air or O₂ as terminal oxidants in homogeneous rhodium catalysis is less common.

Importantly, submitting the catalytic system to a mild pressure of ethylene (2 bar) selectively yielded styrene **3q** in 48% yield, although a higher catalytic loading is required in this case to achieve a satisfactory conversion (2.5 mol%, Scheme 1).^{9,15} Neither diolefination nor multiple step coupling products were observed. The preparation of styrenes by direct catalytic oxidative-Heck coupling with ethylene is usually acknowledged to be difficult, poorly selective, and only feasible under harsh conditions.¹⁶ The implications of this discovery are therefore tremendous due to the synthetic versatility of the vinyl group.¹⁷ Furthermore, the high tolerance of this transformation (e.g., halides, esters) leads to the assumption that this reaction could be incorporated in late stage total synthesis.

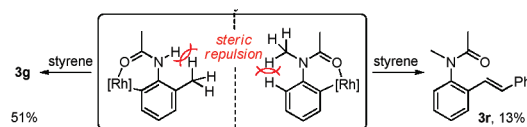
In conclusion, we have developed a novel methodology to achieve the direct *ortho* olefination and vinylation of acetanilides. This methodology is attractive since the catalytic loadings are very low and since acetanilides are easily prepared and hydrolyzed to the corresponding anilines. It also allows electron-withdrawing (R² = CF₃, **3d**) as well as -donating groups (R³ = OMe, **3b**) and provides the products in yields of up to 98% (**3p**). Furthermore this method affords the direct and selective vinylation of acetanilides from ethylene (product **3q**), a powerful method for the preparation of styrenes. The versatility of the produced olefins, the general attractiveness of the method, and the high levels of regio- and chemoselectivity obtained should lead to many applications, especially in natural product total synthesis.

Acknowledgment. We thank the Alexander von Humboldt Foundation (F.P.) and AstraZeneca for generous support as well as Souvik Rakshit (**1o**) and Dr. Tatiana Besset (**2j**, **2l**) for discussions and substrate preparation. The research of F.G. has been supported by the Alfred Krupp Prize for Young University Teachers of the Alfred Krupp von Bohlen und Halbach Foundation.

Supporting Information Available: Experimental and characterization details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) See Supporting Information for further information.
- (10) The transformation is highly selective for the formation of the *trans*-olefin product. The *cis*-isomer was not detected, neither by GC-MS nor by ¹H NMR of the crude products.
- (11) Steric congestion near the acetanilide directing group slows down the reaction and deteriorates the yield:



- (12) Increasing the temperature or the catalytic loading did not significantly improve the yield in this case. However, no side products were observed.
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JA103834B