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Rhodium-Catalyzed β-Selective Oxidative Heck-Type Coupling of Vinyl Acetate via C−H Activation

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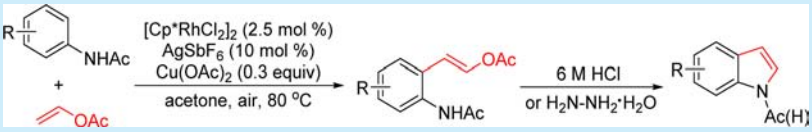
Supporting Information

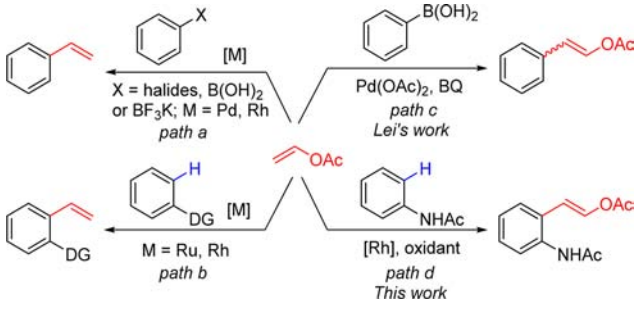


ABSTRACT: An efficient Rh(III)-catalyzed direct *ortho*-C−H olefination of acetanilides with vinyl acetate was developed. This protocol provides a straightforward pathway to a series of (*E*)-2-acetamidostyryl acetates, giving access to indole derivatives following a simple hydrolysis/cyclization process.

Since the pioneering work by Fujiwara and Moritani,[1] transition-metal-catalyzed direct oxidative alkenylations of (hetero)arenes through two-fold C−H bond cleavages have attracted considerable attention from synthetic chemists.[2] Recently, atom- and step-economical pathways based on Pd-, Rh-, and Ru-catalyzed direct olefinations of aromatic C−H bonds with alkenes were developed.[2,3] However, a survey of the pertinent literature reveals that most of the oxidative C−H olefination reactions employed activated alkenes such as acrylates and styrenes. It is only recently that a few examples of oxidative olefination of arenes with "unactivated" aliphatic alkenes were reported.[4,5] Notably, the direct alkenylation of arenes with electron-rich alkenes, such as vinyl esters, enol ethers, and enamides, is still a challenging issue.

Vinyl acetate is frequently used as an easy-to-handle and inexpensive vinyl source. In Pd-catalyzed cross-coupling reactions with aryl halides or organoboron compounds, vinyl acetate is often employed instead of vinyl chloride, bromide, or tosylate as a more convenient vinylic electrophile (path a, Scheme 1).[6,7] Recently, several examples concerning transition-metal-catalyzed directed C−H alkenylation of arenes with vinyl acetate were reported (path b, Scheme 1).[8,9] In 2007, Kakiuchi et al. reported the first ruthenium-catalyzed alkenylation of aromatic C−H bonds in arylpyridines with alkenyl acetates.[8] In all of these examples, the acetoxy group serves as a leaving group of the electrophilic substrates. In 2015, Ellman et al. developed a Rh(III)-catalyzed directed C−H alkenylation of arylpyridines and benzamides with vinyl acetate for the synthesis of a range of styrene derivatives.[9] Normally, β-selective Heck reaction of electron-rich olefins is difficult, owing to the different electronic properties of the two olefin carbons.[10] Recently, Lei and co-workers reported the first Pd-catalyzed oxidative β-arylation of vinyl acetate with various arylboronic acids (path c, Scheme 1).[10] Corresponding direct β-selective Heck-type couplings between aromatic C−H bonds and vinyl acetate were seldom reported.[5g,11] Herein, we report the first Rh(III)-catalyzed regio- and stereoselective alkenylation of acetanilides with vinyl acetate (path d, Scheme 1). Later, the *ortho*-alkenylated acetanilides can be readily cyclized into indole derivatives under mild conditions.

Scheme 1. Alkenylation of Aromatic Compounds with Vinyl Acetate



Continuing with our interest in the exploration of vinyl acetate as acetylene equivalent,[12,13] we envisioned that indole derivatives could be readily synthesized through C−H activation initiated cyclization of acetanilides with vinyl acetates. Therefore, we initially conducted the reaction of 3′-methylacetanilide (**1a**) with vinyl acetate (**2a**) under rhodium catalysis. To our surprise, a β-selective Heck-type coupling product was formed instead of the indole derivative. After screening a range of reaction conditions (see the Supporting Information), we found that the reaction of **1a** with 5 equiv of **2a** in the presence of 2.5 mol % of $[Cp^*RhCl_2]_2$, 10 mol % of $AgSbF_6$, and 1.1 equiv of $Cu(OAc)_2·H_2O$ in acetone at 80 °C for 12 h led to the formation of (*E*)-2-acetamido-4-methylstyryl acetate (**3aa**) in 66% yield (Table 1, entry 1). Higher temperature was found to decrease the yield of **3aa** (56%, entry 2). When the amount of **2a** was increased to 10 equiv, **3aa** was isolated in slightly higher yield (70%, entry 3).

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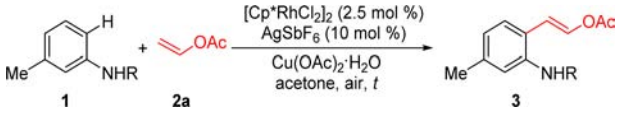
Table 1. Optimization of the Reaction Conditions[a]



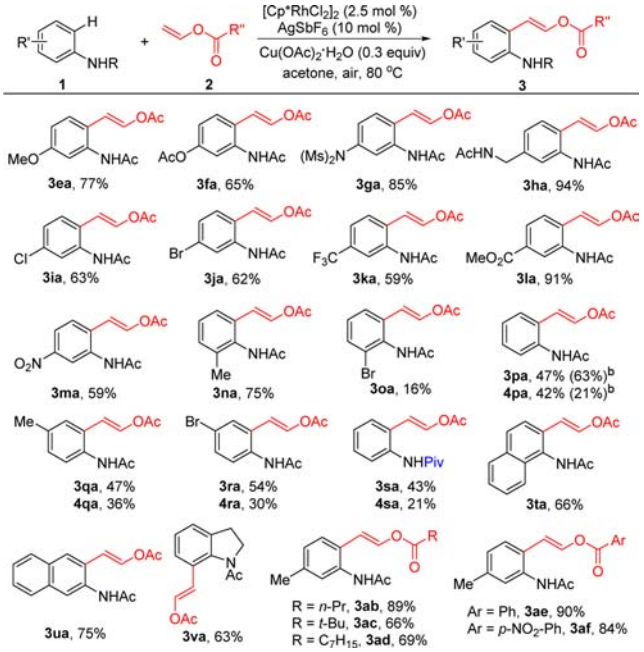
entry	R	$Cu(OAc)_2·H_2O$ (equiv)	acetone (mL)	yield (%)[b]
1	Ac (**1a**)	1.1	1.5	66
2[c]	Ac (**1a**)	1.1	1.5	56
3[d]	Ac (**1a**)	1.1	1.5	70
4[d]	Ac (**1a**)	1.1	0.8	73
5[d]	Ac (**1a**)	0.3	0.8	85 (68)[e]
6[d]	Ac (**1a**)		0.8	52
7[d]	Piv (**1b**)	1.1	1.5	54
8[d]	Piv (**1b**)	0.3	0.8	70
9[d]	$COCF_3$ (**1c**)	1.1	1.5	0
10[d]	$CONMe_2$ (**1d**)	1.1	1.5	trace

[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2·H_2O$, acetone, 80 °C, in air for 12 h. [b]Isolated yield. [c]100 °C. [d]10 equiv of vinyl acetate. [e]Yield of 7.00 mmol scale reactions (1.10 g of **3aa**).

Carrying out the reaction in a smaller volume of acetone afforded 73% yield of **3aa** (entry 4). Gratifyingly, performing the reaction in the presence of only 0.3 equiv of $Cu(OAc)_2·H_2O$ gave the desired product in 85% yield (entry 5). Then, the 7.00 mmol scale synthesis of **3aa** in 68% yield proved the scalability of this transformation. Notably, the reaction also worked without $Cu(OAc)_2·H_2O$, affording **3aa** in 52% yield (entry 6). Subsequently, pivaloyl-protected aniline *N*-(*m*-tolyl)pivalamide (**1b**) was also employed as the substrate, which afforded the corresponding product **3ba** in relatively lower yields (entries 7 and 8). However, no significant amount of alkenylation products could be isolated for the reactions of 2,2,2-trifluoro-*N*-(*m*-tolyl)acetamide (**1c**) and 1,1-dimethyl-3-(*m*-tolyl)urea (**1d**) with **2a**, respectively (entries 9 and 10).

With the optimized conditions in hand, we explored the scope of the catalytic reaction with various substituted acetanilides and vinyl esters (Scheme 2). Treatment of a series of *meta*-substituted acetanilides (**1e**−**m**) with vinyl acetate **2a** provided the corresponding alkenylated products **3ea**−**ma** in good yields (59−94%). Both electron-donating (−Me, −OMe, −OAc, $-NMs_2$, $-CH_2NHAc$) and electron-withdrawing (Cl, Br, $-CF_3$, CO_2Me, NO_2) substituents on the phenyl ring are well-tolerated. Although several functional groups, such as CH_2NHAc and CO_2Me, on the phenyl ring also have weak coordinating ability, the alkenylation takes place selectively at the *ortho* position of the acetylamino group. Sterically hindered 2-methylacetanilide **1n** and 2-bromoacetanilide **1o** reacted with vinyl acetate **2a** to give the corresponding alkenylated products **3na** and **3oa** in 75 and 16% yields, respectively. It suggested that the catalytic *ortho*-C−H olefination was affected by the steric congestion between the bulkier *o*-bromo-substituent and the amide directing group, which induced the loss of planarity of the substrate.[3c] Furthermore, acetanilide **1p** and 4-substituted acetanilides **1q,r** reacted nicely with **2a**, affording mixtures of mono- and dialkenylated products (**3pa**−**ra**, 47−63%; **4pa**−**ra**, 21−42%). *N*-(*m*-Tolyl)pivalamide (**1s**) with a bigger directing group also reacted with **2a** to give a mixture of mono- and dialkenylated products (**3sa**, 43%; **4sa**, 21%). *N*-(Naphthalen-1-yl)acetamide **1t**, *N*-(naphthalen-2-yl)acetamide **1u**, and 1-(indolin-1-yl)ethan-1-one **1v** also efficiently partici-

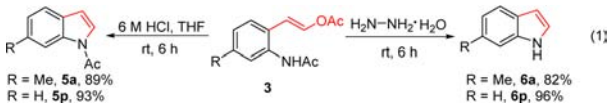
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (2.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2·H_2O$ (0.3 equiv), acetone (0.8 mL), 80 °C, in air for 24 h. Isolated yields are shown. [b]5 equiv of vinyl acetate.

pated in the reaction, providing the corresponding products **3ta**−**va** in 66, 75, and 63% yields, respectively. The reactions of 3′-methylacetanilide **1a** with a range of vinyl esters (**2b**−**2f**) were performed, and the corresponding alkenylation products (**3ab**−**af**) were formed in high yields (66−90%). Subsequently, the catalytic reaction was also examined with prop-1-en-2-yl acetate and 1-phenylvinyl acetate. However, no expected alkenylation products were observed.

Later, we found that the coupling products **3aa** and **3pa** could be successfully converted into *N*-acylindole derivatives **5a** and **5p** or free (NH)-indoles **6a** and **6p** in high yields under hydrolytic conditions (eq 1). Subsequently, the sequential one-



pot processes involving the alkenylation of several acetanilides **1** with vinyl acetate followed by hydrolysis and cyclization were achieved, affording the corresponding *N*-acylindoles in good yields (Scheme 3).

Based on previous research and our results, a plausible mechanism for this *β*-selective Heck-type coupling is proposed in Scheme 4. First, the coordination of a directing amide group with a Cp*Rh(III) center followed by cyclometalation gives a six-membered rhodium intermediate **I**. Thereafter, regioselective insertion of vinyl acetate **2a** into the Rh−C bond affords a rhodacycle **II**, which may undergo *β*-hydrogen elimination to give intermediate **III**.[9a] The rhodium catalyst could be regenerated through the oxidation of the Rh−H intermediate by O_2 and $Cu(OAc)_2$. Notably, during our study, no styrene products derived from reinsertion of the Rh−H bond followed by elimination of acetate were observed.[9]

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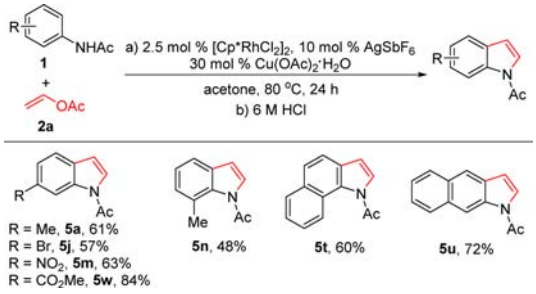
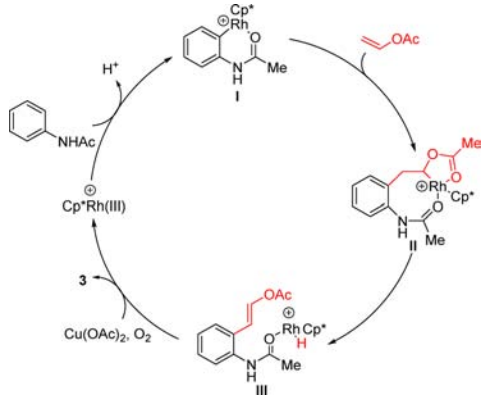
Scheme 3. One-Pot Synthesis of *N*-Acylindoles Starting from Acetanilides and Vinyl Acetate[a]



[a]Reaction conditions: (a) **1** (0.2 mmol), **2a** (2.0 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.3 equiv), acetone (0.8 mL), 80 °C, in air for 24 h, then acetone was removed under vacuum; (b) THF and 6 M HCl were added, and the reaction mixture was stirred at rt for 6 h. Isolated yields are shown.

Scheme 4. Proposed Mechanism



In conclusion, we have developed a Rh(III)-catalyzed highly regio- and stereoselective alkenylation of acetanilides with vinyl acetate. The coupling products were perfectly suited for the next hydrolysis/cyclization, providing an efficient pathway toward indole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03244.

Tables giving optimization details, experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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