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Rhodium(III)-Catalyzed C−H Olefination for the Synthesis of *ortho*-Alkenyl Phenols Using an Oxidizing Directing Group

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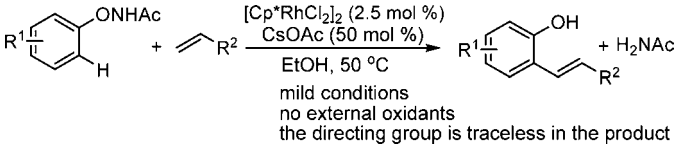
ABSTRACT



By using an oxidizing directing group, a mild, efficient Rh(III) catalyzed C−H olefination reaction between *N*-phenoxyacetamides and alkenes was developed. This reaction provided a straightforward way for the synthesis of *ortho*-alkenyl phenols, and the directing group is traceless in the product.

Transition-metal-catalyzed C−H olefination of arenes using alkenes has emerged as a powerful strategy to directly functionalize arenes.[1,2] This process has an advantage over the traditional Mizoroki−Heck reaction[3] by eliminating the need for preactivation of arenes. For the sake of acquiring high regioselectivity and reactivity, a directing group is usually assembled in the substrate. A variety of directing groups have been developed for this particular reaction, and important advances have been made toward synthetically useful transformations. Despite the tremendous progress, most C−H olefination reactions required stoichiometric amounts of metal oxidants or other additives along with high temperatures. Recently, the use of an oxidizing directing group[4] was introduced in the field of C−H activation, and several external oxidant-free C−H olefinations of arenes (Scheme 1)[5] were reported. In these reactions, an oxygen attached to the nitrogen directing group acts as an internal oxidant to maintain catalytic turnover. It is noteworthy that in all these reactions, the O-linked part functioned as the leaving group, and the nitrogen directing group remained in the product.[6] Our group recently discovered a novel oxidizing directing group for a rhodium(III)-catalyzed C−H functionalization of *N*-phenoxyacetamides with alkynes,

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(2) For some examples, see: (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (b) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728. (c) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (d) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (e) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (f) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (g) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7242.

(3) *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009.

(4) For a review, see: Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977.

(5) (a) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009**, *131*, 13888. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (c) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736. (d) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (e) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504.

(6) For some examples, see: (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (d) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (e) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (f) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (g) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (h) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66.

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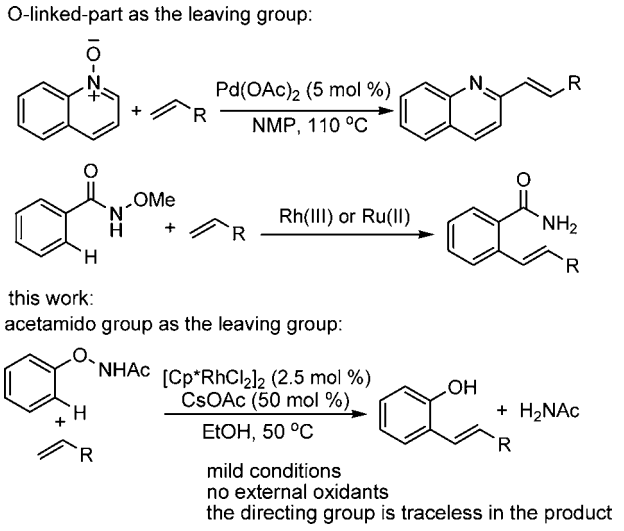
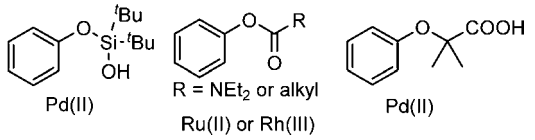
in which the acetamido group could act as the leaving group.[7] This prompted us to explore more transformations starting from *N*-phenoxyacetamides, and the C−H olefination reactions between *N*-phenoxyacetamides and alkenes are reported here.

Scheme 1. Oxidizing Directing Group Directed C−H Olefination of Arenes



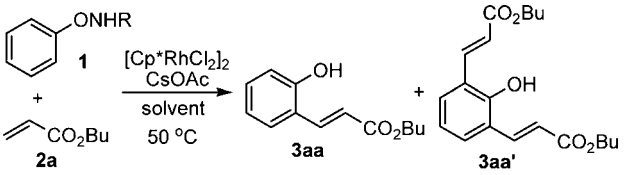
ortho-Alkenyl phenols are important building frameworks in synthetic chemistry,[8] which have attracted broad interest from synthetic chemists. Directed by a silanol group,[9a] carbonyl group,[9b,c] or carboxylic acid,[9d] transition metal catalyzed *ortho* C−H olefination of phenol derivatives provided straightforward and efficient ways to produce diverse *ortho*-alkenyl phenols (Scheme 2).

Scheme 2. Substrates for the Synthesis of *ortho*-Alkenyl Phenols via C−H Activation



In these approaches, an additional step is necessary to remove the directing group for the synthesis of *ortho*-alkenyl phenols. We herein disclose a Rh(III)-catalyzed C−H olefination of *N*-phenoxyacetamides affording *ortho*-alkenyl phenols in one step. The nitrogen directing group was traceless in the product (Scheme 1). This reaction was not sensitive to moisture and air and proceeded smoothly under mild conditions without an external oxidant.

Table 1. Reaction Conditions Screening[a]



			yield (%)[b]	
entry	R	solvent	**3aa**	**3aa′**
1	Ac (**1a**)	CH_3CN	64	13
2	Ac (**1a**)	THF	61	7
3	Ac (**1a**)	$ClCH_2CH_2Cl$	49	21
4	Ac (**1a**)	DME	53	8
5	Ac (**1a**)	MeOH	90	<5
6	Ac (**1a**)	EtOH	89	<5
7	Ac (**1a**)	EtOH	84[c]	<5
8	Ac (**1a**)	EtOH	85	6[d]
9	Piv (**1j**)	EtOH	N. R.	
10	Ts (**1k**)	EtOH	62	<5
11	CONHBu (**1l**)	EtOH	<10	

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.28 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), CsOAc (0.5 equiv), solvent (0.05 M), 50 °C, 3−8 h. [b] ^1H NMR yield. [c] Isolated yield. [d] 1.0 mol % of $[RhCp^*Cl_2]_2$ was used as the catalyst; 48 h.

We initiated our study with the coupling of *N*-phenoxyacetamide (1.0 equiv) and butyl acrylate (1.4 equiv). Among the screened catalysts, to our delight, $[Cp^*RhCl_2]_2$ gave the desired *ortho*-alkenyl phenol **3aa** (Table 1). The diolefinated phenol **3aa′** was detected as the main side product (Table 1, entries 1−4), and a 21% NMR yield of **3aa′** was observed when dichloroethane was used as the solvent (Table 1, entry 3). Fortunately, EtOH appeared to be the ideal solvent, affording the desired product in 89% NMR yield, and the side product **3aa′** could finally be suppressed to less than 5% yield (Table 1, entry 6).[10] The catalyst loading can be reduced to 1.0 mol % without significant change in yield, albeit with a prolonged reaction time (Table 1, entry 8). Compared with *N*-phenoxyacetamide, other substrates with different substituents on the nitrogen atom were found to be ineffective or less effective (Table 1, entries 9−11). The optimized conditions were ultimately identified as 2.5 mol % of $[Cp^*RhCl_2]_2$, and 50 mol % of CsOAc in EtOH at 50 °C.

(7) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6033.

(8) (a) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308. (b) Koehler, K.; Gordon, S.; Brandt, P.; Carlsson, B.; Bäcksbro-Saeidi, A.; Apelqvist, T.; Agback, P.; Grover, G. J.; Nelson, W.; Grynfarb, M.; Färnegardh, M.; Rehnmark, S.; Malm, J. *J. Med. Chem.* **2006**, *49*, 6635. (c) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214. (d) Barancelli, D. A.; Salles, A. G., Jr.; Taylor, J. G.; Correia, C. R. D. *Org. Lett.* **2012**, *14*, 6036. (e) Singh, F. V.; Wirth, T. *Synthesis* **2012**, *44*, 1171.

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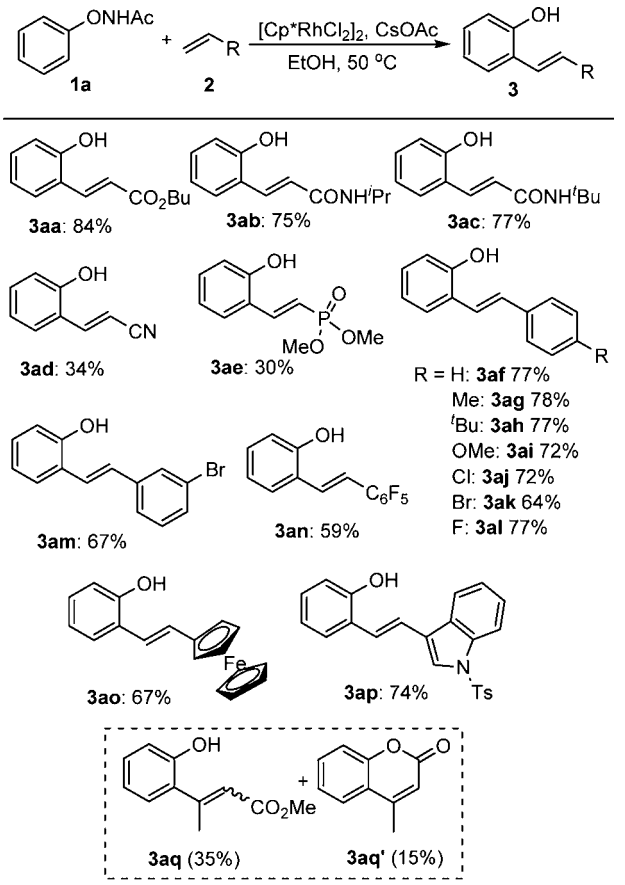
(10) The reason for the formation of the diolefination product **3aa′** is unclear. Control experiments demonstrated that **3aa** cannot be transformed to **3aa′** under reaction conditions. The addition of some external oxidants such as $Cu(OAc)_2$ or AgOAc could not increase the yield of **3aa′**.

Scheme 3. Olefin Scope for C−H Olefination of *N*-Phenoxyacetamide[a]

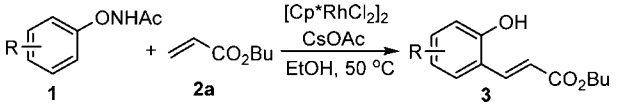


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.28 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), CsOAc (0.5 equiv), EtOH (0.05 M), 50 °C, 3−16 h; isolated yield was reported.

With the optimized conditions in hand, various olefins were successfully employed for the novel transformation (Scheme 3). All the cases were totally *ortho*-selective. Good to excellent yields were observed with acrylic derivatives as the substrates (**3aa**−**3ac**). Acrylonitrile resulted in a moderate conversion despite its high inclination to polymerization (**3ad**). Noteworthily, vinylphosphonate was also a good reactant for this transformation (**3ae**). Styrene and its derivatives readily participated in this olefination reaction. Moreover, the ferrocenyl group (**3ao**) and heterocycle (**3ap**) were well tolerated to give good yields of the desired products. Delightfully, β,β-disubstituted alkenes also reacted smoothly, affording a mixture of *ortho*-alkenyl phenol and chromen-2-one (**3aq** and **3aq′**). However, terminal alkyl alkenes such as 1-octene gave poor results.

The effect of the substituents on *N*-phenoxyacetamide was then tested (Table 2). The C−H bond olefination proceeded smoothly with different substituted *N*-phenoxyacetamides. Notably, the substrate with a strong electron-withdrawing nitro group also gave the desired product with a moderate yield (Table 2, entry 8). When meta-substituted *N*-phenoxyacetamide was employed, olefination took place at the less hindered C−H bond selectively (Table 2, entries 3 and 6).

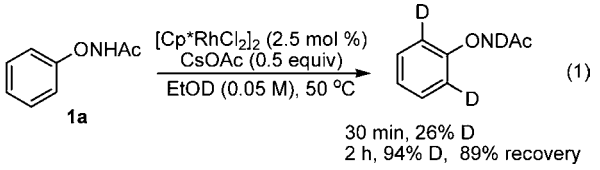
Table 2. Reaction Scope for Substituted *N*-Phenoxyacetamides[a]



entry	substrate	product	yield (%)
1	**1a**: R = H	**3aa**	84
2	**1b**: R = 2-Me	**3ba**	81
3	**1c**: R = 3-Me	**3ca**	77
4	**1d**: R = 4-Me	**3da**	85
5	**1e**: R = 4-Ph	**3ea**	77
6	**1f**: R = 3-CF_3	**3fa**	69
7	**1g**: R = 4-F	**3ga**	61
8	**1h**: R = 4-NO_2	**3ha**	45[b]
9	**1i**: R = 3,5-difluoro	**3ia**	70

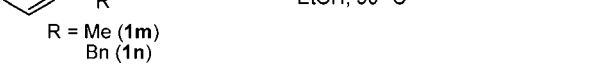
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.28 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), CsOAc (0.5 equiv), EtOH (0.05 M), 50 °C, 3−8 h; Isolated yield was reported. [b] ^1H NMR yield.

Further experiments were carried out to obtain better insight into the reaction mechanism. No reaction happened in the absence of cesium acetate and the reaction proceeded smoothly with $Cp^*Rh(OAc)_2$ as the catalyst, which suggested that the acetate anion was crucial and $Cp^*Rh(OAc)_2$ may be the active catalyst. When **1a** was treated with a catalytic amount of $[RhCp^*Cl_2]_2$ and CsOAc in deuterated ethanol at 50 °C, the N−O bond remained intact, and deuterium was incorporated exclusively at the *ortho* position of the directing group (eq 1). In contrast, no deuterium incorporation was found in the absence of CsOAc. A competition olefination experiment between electronically different *N*-phenoxyacetamide derivatives, **1g** and **1d**, indicated that electron-deficient **1g** was more reactive. Taken together, these results implied that concerted metalation−deprotonation (CMD)[11] might be responsible for the C−H activation.



(1)

N-Alkyl-substituted phenoxyacetamides (**1m** and **1n**) did not give any desired product under standard conditions, indicating the N−H bond in the substrate was indispensable for the C−H bond olefination (eq 2).

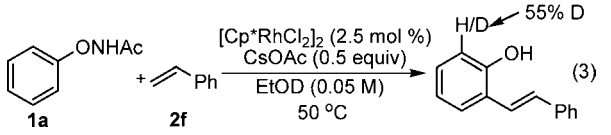


(2)

When the reaction between **1a** and styrene (**2f**) was performed in deuterated ethanol, the desired product had 55% deuterium incorporation (eq 3), which illustrated the

(11) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

C−H activation is reversible in the presence of alkene. Furthermore, the electron-deficient alkene was found to insert into the C−Rh bond more quickly than the electron-abundant one. Also, a primary KIE value of 2.4 was observed,[12] so the C−H bond cleavage may be the rate-determining step.



Taking the above experiments and the mechanism studies of precedent literature[13] into consideration, we put forward the plausible catalytic cycle in Scheme 4. After the generation of an active catalyst by anion exchange with cesium acetate, a facile arene rhodation afforded intermediate **A**, which was followed by alkene insertion, giving seven-membered rhodacycle intermediate **B**. Subsequently, β-H elimination and reductive elimination took place, giving intermediate **D**.[14,15] Since the stoichiometric experiments have demonstrated that the N−O bond could be cleaved by Rh(I) complexes,[7,16] it is reasonable to propose that Rh(I) in intermediate **D** could be oxidized by the intramolecular N−O bond, forming the desired product **3**, acetamide,[17] and Rh(III) to complete the catalytic cycle.

(12) The reported KIE value is the relative ratio of the initial rates measured separately using **1a** or **1a-*d5*** as the substrate under standard reaction conditions.

(13) (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (b) Liu, B.; Fan, Y.; Gao, Y.; Sun, C.; Xu, C.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 468. (c) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.* **2012**, *77*, 3017.

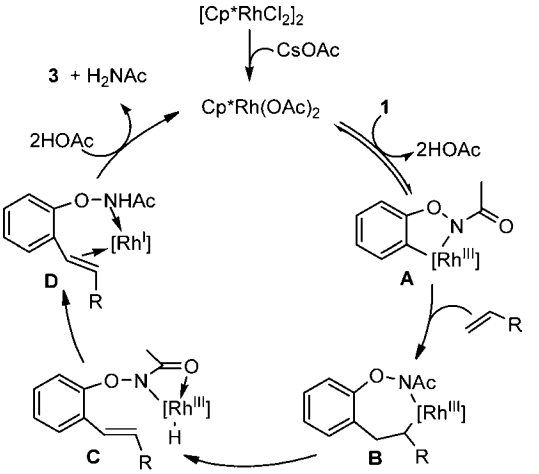
(14) Rh(I) can bind effectively with olefin ligands: Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

(15) Intermediate **B** might undergo oxidative addition before β-H elimination to form a rhodium(V) species, followed by reductive elimination. This possibility cannot be ruled out at present.

(16) Das, A.; Basuli, F.; Peng, S.-M.; Bhattacharya, S. *Inorg. Chem.* **2001**, *41*, 440.

(17) For the reaction between **1a** and **2a** under standard conditions, acetamide was distinguished in crude ^{1}H NMR and isolated by flash chromatogaraphy after the reaction completed.

Scheme 4. Proposed Catalytic Cycle



In summary, by using an oxidizing directing group, a mild, efficient Rh(III) catalyzed C−H olefination reaction between *N*-phenoxyacetamides and alkenes was developed. This reaction provided a straightforward method for the synthesis of *ortho*-alkenyl phenols, and the directing group was traceless in the product. More detailed mechanism studies on the O−N bond cleavage and further properties of the novel directing group are being explored in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.