Organic LETTERS

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Rhodium(III) Catalyzed Carboamination of Alkenes Triggered by C−H Activation of *N*-Phenoxyacetamides under Redox-Neutral Conditions

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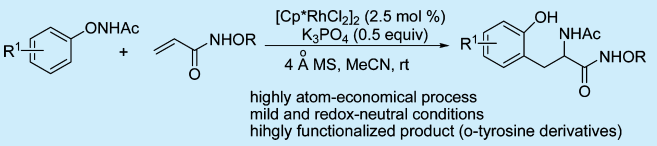
Supporting Information

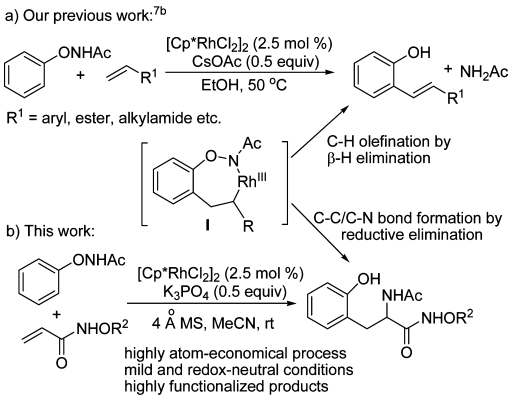
ABSTRACT: *N*-Alkoxyacrylamides are coupled with *N*-phenoxyacetamides by Rh^{III} catalysis through C−H functionalization and amido group transfer under external oxidant-free conditions, which affords acyclic alkene carboamination products in an atom-economical way. Mechanistic insight into this transformation indicates the amide group in *N*-alkoxyacrylamide plays a critical role in this C−C/C−N bond formation reaction. This methodology provides a highly efficient way to construct *o*-tyrosine derivatives under mild conditions.



Tranisition metal catalyzed C−H functionalization constitutes an economical and straightforward approach for site-selective formation of carbon−carbon and carbon−heteroatom bonds.[1] Intensive research efforts in this field have led to a variety of useful synthetic applications. One example is carboamination of alkenes using an unactivated arene or alkene as the carbon functionality source.[2,3] The C−H bond to be involved in carboamination usually presents intramolecularly with the nitrogen functionality source.[2] In some rare cases, inexpensive unactivated arenes could react intermolecuarly with alkenes bearing pendant amines to give a carboamination product.[3] Although these transformations are synthetically useful for the construction of a broad array of nitrogen heterocycles, stoichiometric amounts of oxidant, mostly a metallic oxidant, are normally used to regenerate the catalyst or produce high oxidant state metal species. To obviate this limitation, an attractive redox-neutral strategy employing an oxidizing N−O directing group[4] has been applied in this field, which furnishes nitrogen heterocycles as the carboamination product and liberates a small molecule (ROH) as the result of the N−O bond cleavage.[5] Therefore, it is of great value to develop new alkene carboaminations that can construct the acyclic product in an atom-economical and efficient way. During the preparation of this manuscript, Rovis and co-workers reported a rhodium(III)-catalyzed intermolecular *syn*-carboamination of alkenes from enoxyphthalimides, which reaches this goal.[6]

In our previous work, we disclosed a rhodium(III)-catalyzed C−H olefination of *N*-phenoxyacetamide[7] affording *ortho*-alkenyl phenols as the product and acetamide as the waste (Scheme 1a).[7b] One of the potential intermediates proposed in that work is the seven-membered rhodacycle **I**, which undergoes facile *β*-H elimination to give the olefination product. In fact, the inhibition of *β*-hydride elimination is a challenge in making the reaction of $C(sp^3)$−M species more diversified and the coordinative saturation of metal center is a frequently used strategy to overcome this difficulty.[8,5a] Thus, we reasoned that introducing a coordinating functional group in the substrates may enable the metal center in intermediate **I** to be coordinatively saturated, which might divert the reaction from the C−H olefination toward the alkene carboamination. Here, we validate this design by the employment of *N*-alkoxyacrylamide as the coupling partner in the Rh^{III}-catalyzed C−H functionalization of *N*-phenoxyacetamide to produce 2-hydroxyphenylalanine (*o*-tyrosine) derivatives.[9] In this reaction, the amido group is formally transferred from the oxidizing directing group to the alkene. While the synthesis of the *o*-tyrosine backbone in literature was mainly achieved via

Scheme 1. Diversified Reactions between *N*-Phenoxyacetamides and Alkenes



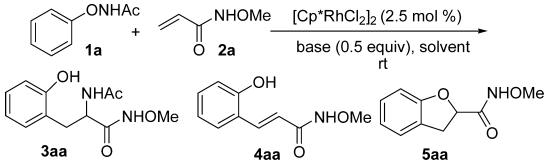
Received: March 9, 2016

DOI: 10.1021/acs.orglett.6b00616
Org. Lett. XXXX, XXX, XXX−XXX

multistep processes,[9d−f] our protocol represents an efficient way to construct this useful structure unit under very mild conditions.

To test the proposed strategy, a brief survey of alkenes was conducted and *N*-methoxyacrylamide (**2a**) was found to give encouraging results. Under the reaction conditions that were developed for C−H olefination, the reaction between *N*-phenoxyacetamide (**1a**) and **2a** delivered the desired product **3aa** in 33% yield along with C−H olefination product **4aa** and dihydrobenzofuran **5aa** (Table 1, entry 1). This result

Table 1. Selected Optimization Studies[a]



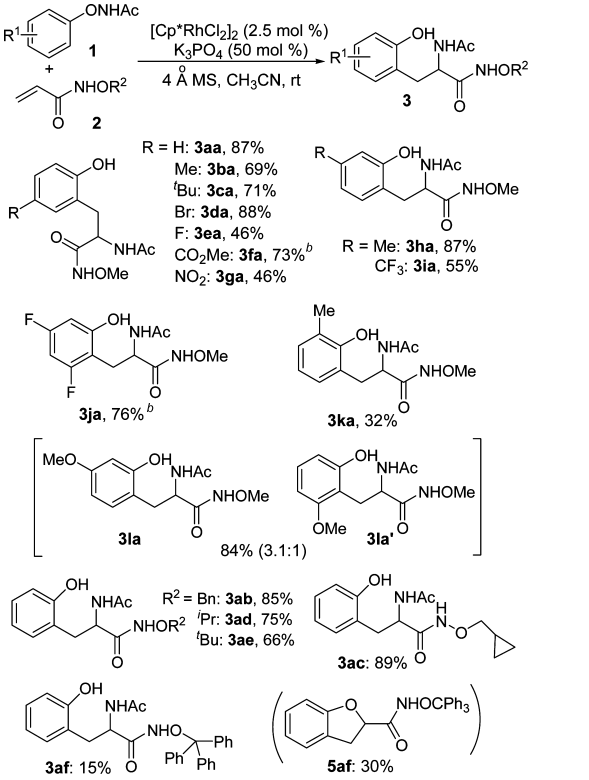
				yield (%)[b]		
entry	solvent	base	time (h)	3aa	4aa	5aa
1[c]	ethanol	CsOAc	24	36	26	26
2	CH_3CN	CsOAc	14	69	10	23
3	CH_3CN	Cs_2CO_3	90	50	3	ND
4	CH_3CN	K_2CO_3	92	52	2	ND
5	CH_3CN	KOAc	22	57	5	15
6	CH_3CN	K_3PO_4	48	78	ND	ND
7[d]	CH_3CN	K_3PO_4	20	93	ND	ND

[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), and base (0.5 equiv) in solvent at rt. [b]^{1}H NMR yield. [c]Run at 50 °C. [d]4 Å MS (50 mg) were added.

prompted us to improve the yield of **3aa**, and the selected optimization studies were shown in Table 1. Solvent effects were dramatic, and a significantly improved yield (69%) was observed with CH_3CN as the solvent (entry 2). Screening of several bases revealed K_3PO_4 as the optimal choice giving **3aa** in 78% yield (entries 3−6). The addition of molecular sieves was found to increase the reaction rate as well as the yield of **3aa** (entry 7). Under the optimized conditions, the rhodium catalyzed coupling of *N*-phenoxyactamide and *N*-methoxyacrylamide afforded **3aa** in 87% isolated yield without any olefination product or dihydrobenzofuran.

With the optimized reaction conditions in hand, the scope of this system for the synthesis of *o*-tyrosine derivatives was investigated (Scheme 2). We were pleased to find that this new transformation was productive for a variety of substituted *N*-phenoxyacetamides in the coupling with *N*-methoxyacrylamide (**2a**). Several important functional groups such as halogens (F, Br), trifluoromethyl, ester, methoxy, and nitro group were well tolerated. Notably, the substrates with a strong electron-withdrawing group (**3fa** and **3ga**) or electron-donating group (**3la** and **3la′**) participated well under standard reaction conditions furnishing the desired product with moderate to good yields. It was noted that *orth*-CH_3 substituted *N*-phenoxyacetamide gave a relatively low yield (**3ka**, 32%) compared with the *para*- and *meta*- substituted analogues (**3ba** and **3ha**, 69% and 87%, respectively). When substrates with a *meta*-CF_3 and *meta*-CH_3 group were employed, C−H functionalization took place at a less hindered position selectively (**3ha** and **3ia**). In contrast, the *meta*-OMe substituted substrate produced two isomers in the ratio 3.1:1 (**3la**:**3la′**).

Scheme 2. Reaction Scope for the Synthesis of *o*-Tyrosine Derivatives[a]



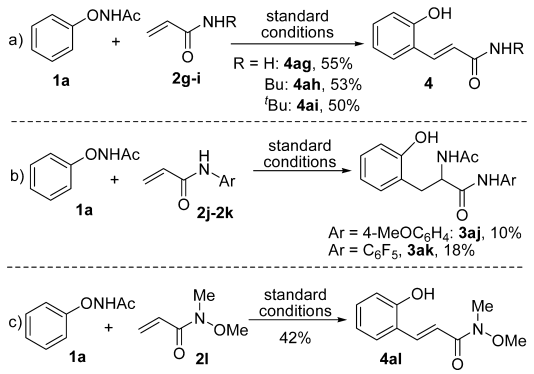
[a]Reaction conditions: substrate **1** (0.24 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), K_3PO_4 (0.1 mmol), and 4 Å MS (100 mg) in CH_3CN (0.5 mL) at rt under N_2; isolated yields were given. [b]After 20 h, a second batch of $[Cp^*RhCl_2]_2$ (2.5 mol %) was added, and the reaction proceeded for another 20 h.

Various *N*-alkoxyacrylamides were then subjected to the reaction with *N*-phenoxyacetamide (**1a**) under standard conditions. With the *N*-alkoxyl substituent as the methoxy, benzyloxy, and cyclopropylmethoxy group (**2a**−**2c**), the reaction proceeded smoothly affording good yields of the desired products (**3aa**−**3ac**, 85%−89%).[10] Alkenes with a more hindered alkoxy group (^{i}PrO, ^{t}BuO, and Ph_3CO) resulted in decreased yields (**3ad**−**3af**, 15%−75%). Especially, the reaction of *N*-triphenylmethoxyacrylamide (**2f**) with **1a** led to a low yield of the desired product (**3af**, 15%). While no C−H olefination product was detected in this reaction, the main side product was dihydrobenzofuran **5af**. These results indicated the steric property of the alkoxy group in the alkenes influenced the outcome of the C−C/C−N formation reaction.

To better understand the role of the *N*-alkoxy group in the alkenes,[11] different substituted acrylamides were applied to this reaction. Under standard conditions, the reaction of **1a** with acrylamides **2g**−**i** afforded the C−H olefinatin product exclusively (Scheme 3a). While C−C/C−N formation was influenced by the steric property of the alkoxy group in *N*-alkoxyacrylamides, no steric effect was observed for C−H olefination when different acrylamides **2g**−**i** were employed. The employment of aryl substituted acrylamides (**2j** and **2k**) could furnish a low yield of carboamination products along with C−H olefination products (Scheme 3b). Modification of the electronic properties of the aryl group in *N*-aryl acrylamides did not alter the yield of the carboamination product significantly. In addition, the C−H olefinatin product was produced

DOI: 10.1021/acs.orglett.6b00616
Org. Lett. XXXX, XXX, XXX−XXX

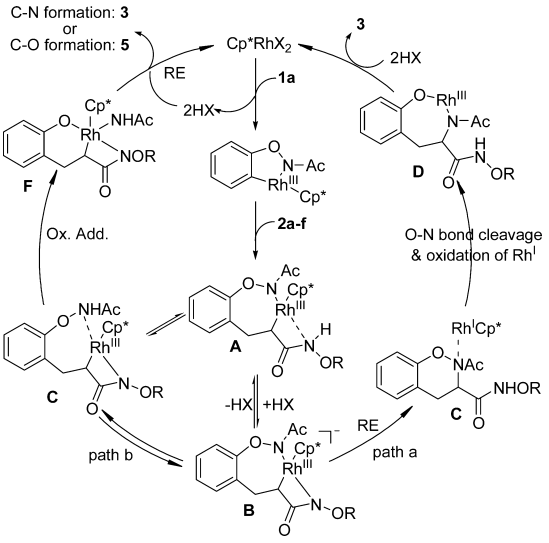
Scheme 3. Test of Different Substituted Acrylamides



exclusively with *N*-methoxy-*N*-methylacrylamide **2l** as the alkene substrate (Scheme 3c). Overall, these results demonstrate that the *N*-substituent in acrylamide influences the reaction outcome by modulating the character of the amide group, and the N−H bond rather than the *N*-alkoxy group in acrylamide is indispensible for the carboamination.

In light of our mechanistic studies[12] and the known literature, the mechanism hypotheses are shown in Scheme 4.

Scheme 4. Proposed Mechanism



The reaction might be initiated by an irreversible C−H activation to give a five-membered rhodacycle, followed by alkene insertion to furnish the key intermediate **A**. Our previous work[7b,c] had shown that the N−H bond in *N*-phenoxyacetamide is crucial for C−H activation, which indicates the deprotonation of *N*-phenoxyacetamide may promote the C−H activation.[13] Having a similar structure with the directing group −ONHAc, the amide group in *N*-alkoxy acrylamide might coordinate with Rh in a similar way. Thus, the amide group in the alkene **2a−f** might act as an anion ligand after deprotonation leading to the anionic Rh complex **B**,[14] which might be in equilibrium with intermediate **A** and **C**. In these C(sp^3)−Rh species, the metal center is coordinatively saturated. As a result, *β*-H elimination was suppressed and no C−H olefination product was observed. In contrast, the amide group in acrylamides (**2g−i**) might not be acidic enough[15] to act as the anionic ligand to the Rh center, thus leading to the C−H olefination product exclusively (Scheme 3a). According to the literature,[14] anionic Rh^{III} complexes could undergo reductive elimination generating Rh^{I} species. We suspect that reductive elimination followed by protonolysis of the anionic amido ligand might take place from the anionic Rh complex **B** affording intermediate **C** and Rh^{I} (path a). Subsequently, Rh^{III} was regenerated by the cleavage of the N−O bond in the oxidizing directing group to form intermediate **D**, which upon protonolysis will produce the desired product **3**.[16] Alternately, the Rh^{III} center in species **C** might be oxidized by the N−O internal oxidant giving the high oxidant state Rh^{V} species **F** (path b),[17] which undergoes reductive elimination to form a C−N or C−O bond and subsequent protonolysis to furnish carboamination product **3** or dihydrobenzofuran product **5**, respectively. The use of a sterically hindered *N*-alkoxy group such as a triphenylmethoxy group (**2f**) may lead to a hindered metal center in intermediate **F**, which might facilitate the dissociation of the acetamido ligand and favor the reductive elimination of the C−O bond to form the product **5**.[18] The current experimental evidence remains insufficient, and further studies to understand the reaction pathway are ongoing in our laboratory.[19]

In conclusion, we have developed a Rh^{III}-catalyzed coupling of *N*-phenoxyacetamide with *N*-alkoxyacrylamide under redox-neutral and mild conditions. This carboamination of alkenes provides an efficient and highly atom-economical way to construct 2-hydroxyphenyl-alanine (*o*-tyrosine) derivatives. Further studies to explore new transformation properties of the directing group based on −ONHAc are in progress in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00616.

Experimental procedures, compounds characterization data, and copies of NMR spectra (PDF)

Crystallographic data for compound **3ab** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (2015CB856600), the National Natural Science Foundation of China (21202184, 21232006, 21572255), and the Chinese Academy of Sciences for financial support.

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DOI: 10.1021/acs.orglett.6b00616
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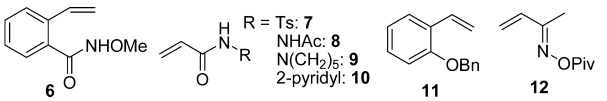
(10) For the crystallographic data for **3ab**, refer to CCDC number 1418659 and the CIF Supporting Information.
(11) A series of alkenes which bear potentially coordinating groups were attempted in the C−H functionalization of **1a** under standard conditions (see below), but no desired alkene carboamination product was observed. While alkenes **6**−**10** were unreactive, alkenes **11** and **12** led to complicated results producing a small amount of C−H olefination products along with other unidentified byproducts.



(12) For deuterium-labeling experiments, see the Supporting Information.
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DOI: 10.1021/acs.orglett.6b00616
Org. Lett. XXXX, XXX, XXX−XXX