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Rhodium(III)-Catalyzed Cascade Cyclization/Electrophilic Amidation for the Synthesis of 3-Amidoindoles and 3-Amidofurans

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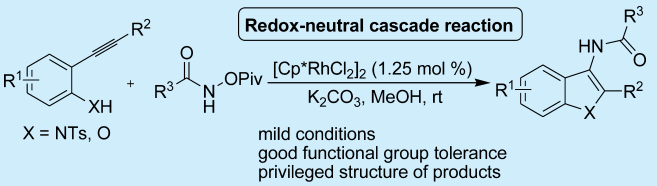
Supporting Information

ABSTRACT: A rhodium(III)-catalyzed cascade cyclization/electrophilic amidation using *N*-pivaloyloxylamides as the electrophilic nitrogen source has been developed. This protocol provides an efficient route for the synthesis of 3-amidoindoles and 3-amidofurans under mild conditions with good functional group tolerance. The synthetic utility of this reaction has been demonstrated through the derivatization of the 3-amidoindoles to several heterocycle-fused indoles.



The employment of electrophilic nitrogen sources (R_2N^+) containing an N−X bond in transition-metal-catalyzed C−N bond formation has received increasing attention.[1] Tremendous methodologies have been developed in this area to construct diverse amines with high efficiency under external oxidant-free conditions, which provide useful complements to conventional C−N bond formation reactions. The most extensively studied electrophilic nitrogen sources include oximes and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines, which introduce an imino or alkylamino group into the product.[1] The expansion of transition-metal-catalyzed electrophilic amination to other kinds of nitrogen sources, such as amido-transfer reagent,[2] has not been well studied. Recently, hydroxyamide derivatives were found to act as the electrophilic nitrogen source in transition-metal-catalyzed C−H functionalization[3] and cross-coupling reactions[4] to give the amide products. Further exploration of hydroxyamide derivatives as the electrophilic amidation reagent in more diverse cascade reactions remains untapped.

Indoles are privileged structures in natural and synthetic biologically active products.[5] Among the various indole derivatives, 3-amino- and 3-amido-substituted indoles are attractive as useful intermediates for synthetic organic chemistry[6] and as promising candidates for drug design.[7] Therefore, the development of efficient synthetic methodology to access these indole derivatives has received much attention,[8] and recently, a few versatile and concise strategies for their preparation have been developed.[9,10] For example, Beller and co-workers developed a direct synthesis of 2-methyl-3-amidoindoles by zinc-promoted hydrohydrazination of *N*-acylpropargylamines.[9] Hirano and Miura reported a copper-catalyzed annulative electrophilic amination approach to 3-(dialkylamino)benzoheteroles starting from *o*-alkynylphenols and -anilines.[10] Based on our interest in the exploration of cascade reactions using electrophilic amination strategy, we disclose herein a rhodium-catalyzed cascade cyclization/electrophilic amidation of *o*-alkynylaniline or *o*-alkynylphenol with *N*-pivaloyloxylamide as the amidation reagent. This protocol provides an efficient method for the synthesis of 3-amidoindoles and 3-amidofurans under mild conditions with good functional group tolerance. Moreover, the obtained 3-amidoindoles could be further transformed to several heterocycle fused indoles, which demonstrates the synthetic value of this transformation.

Our initial experiments were carried out with *o*-alkynylaniline **1a** and 2-phenyl-*N*-(pivaloyloxy)acetamide (**2a**) as the model substrates in the presence of $[Cp^*RhCl_2]_2$ (1.25 mol %) (Table 1). Gratifyingly, when the reaction was treated with K_2CO_3 as a base in CH_3CN at room temperature, the desired 3-amidoindole (**3aa**) was produced in 78% yield along with indole **3aa′** as the main side product (Table 1, entry 1). Screening of solvents suggested MeOH was the ideal choice, which afforded the desired product in 91% yield (Table 1, entries 1−5). Other bases, such as KOAc, NaOAc, DBU, and Na_2CO_3, also afforded the desired product in similar yields (Table 1, entries 6−9). Decreasing the amount of base resulted in a significant drop in yield (70%, entry 10). In addition, this cascade cyclization/amidation did not proceed in the absence of the Rh catalyst or base additive (Table 1, entries 11 and 12).[11]

Using the optimized conditions, we explored the scope of the cascade cyclization/electrophilic amidation for the synthesis of 3-amidoindoles (Scheme 1). *o*-Alkynylanilines with different functional groups in the phenyl ring reacted smoothly with **2a** with excellent yields (**3ba**−**ha**, 88−99%). Both electron-rich

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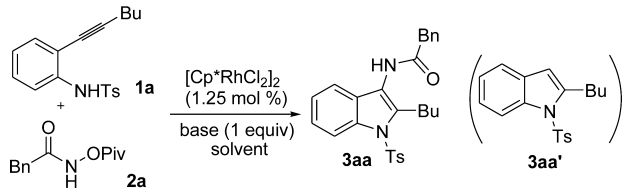
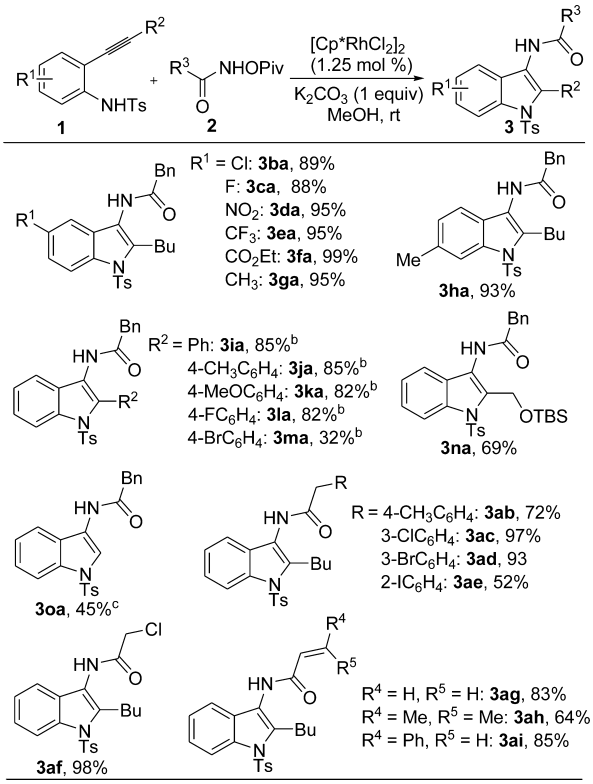
Table 1. Reaction Optimizations for the Synthesis of 3-Amidoindoles[a]



entry	base	solvent	yield[b] (%) 3aa	3aa′
1	K_2CO_3	CH_3CN	78	14
2	K_2CO_3	DCE	15	41
3	K_2CO_3	THF	ND	ND
4	K_2CO_3	DMF	5	75
5	K_2CO_3	MeOH	91	35
6	Na_2CO_3	MeOH	85	41
7	NaOAc	MeOH	91	41
8	KOAc	MeOH	85	33
9	DBU	MeOH	85	14
10[c]	K_2CO_3	MeOH	70	19
11		MeOH	ND	ND
12[d]	K_2CO_3	MeOH	ND	90

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), $[Cp^*RhCl_2]_2$ (1.25 mol %), and base (0.1 mmol) in solvent (0.5 mL) at room temperature for 12 h. [b]Isolated yield. [c]0.5 equiv of K_2CO_3 was used. [d]Without catalyst.

Scheme 1. Substrates Scope for the Coupling of *o*-Alkynylanilines 1 with *N*-Pivaloyloxylamide 2[a]

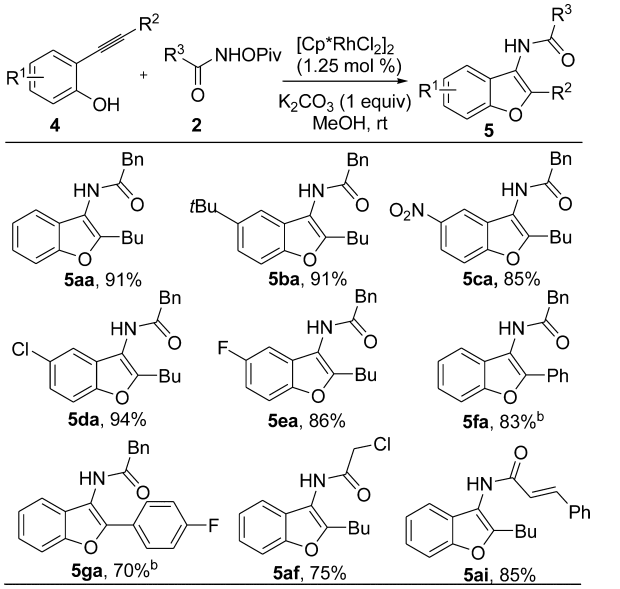


[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (1.25 mol %), and K_2CO_3 (0.1 mmol) in MeOH (0.5 mL) at room temperature for 12 h; isolated yield was reported. [b]$[Cp^*RhCl_2]_2$ (2.5 mol %) was used. [c]**1o** (0.1 mmol) and **2a** (0.14 mmol) were used.

and electron-deficient aryl substituents at the alkyne terminus were tolerated, producing the desired 3-amidoindoles in moderate to good yields (**3ia**−**ma**, 32−85%).[12] In addition to alkyl- or aryl-substituted alkynes, terminal alkyne **1o** was suitable substrate as well (**3oa**, 45%). Furthermore, various *N*-pivaloyloxylamides were also explored, wherein both alkyl- and alkenyl-derived substrates could participate in the reaction with **1a**. The use of 2-chloroacetamide derivative led to an excellent yield of the corresponding product **3af**, leaving the sp^3 C−Cl bond intact. When α,β-unsaturated hydroxamic acid derivatives **2g**−**i** were employed, the reactions proceeded readily to afford the desired products in good yields (**3ag**−**ai**, 64−85%) without any 1,4-addition byproducts. The good functional group tolerance makes this transformation be useful for further structural manipulations. Of note, *N*-pivaloyloxyl benzamide is not an effective coupling partner.

Inspired by the above success, we turned our attention to *o*-alkynylphenols for the synthesis of 3-amidobenzofurans. Under the standard conditions, a series of 3-amidobenzofurans were synthesized in good yields (Scheme 2). A variety of functional

Scheme 2. Substrates Scope for the Coupling of *o*-Alkynylphenols 4 with *N*-pivaloyloxylamide 2[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (1.25 mol %) and K_2CO_3 (0.1 mmol) in MeOH (0.5 mL) at room temperature for 12 h; isolated yield was reported. [b]$[Cp^*RhCl_2]_2$ (2.5 mol %) was used.

groups on o-alkynylphenol were compatible with the reaction conditions, and *N*-pivaloyloxylamides possessing alkyl or vinyl substituents exhibited good reactivity.

To highlight the synthetic value of the new reaction, several transformations were conducted (Scheme 3). Deprotection of TBS ether in **3na** could easily give the alcohol **6** in excellent yield (Scheme 3a). The one-step cyclization of **6** with Lawesson's reagent in toluene proceeded smoothly to produce the 4,5-dihydro-1,3-thiazino[5,4-*b*]indoles **7**,[13a] which is known as a latent inhibitor of human leukocyte elastase and α-chymotrysin. In another example, removal of the tosyl group in **3ia** was carried out with excess Mg in methanol to produce compound **8** (Scheme 3b). The cyclization of **8** with the aid of P_2O_5 furnished 11*H*-indolo[3,2-*c*]isoquinoline **9** in 39%

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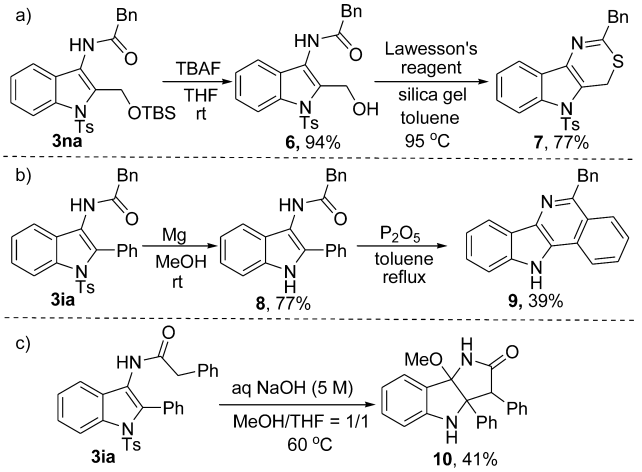
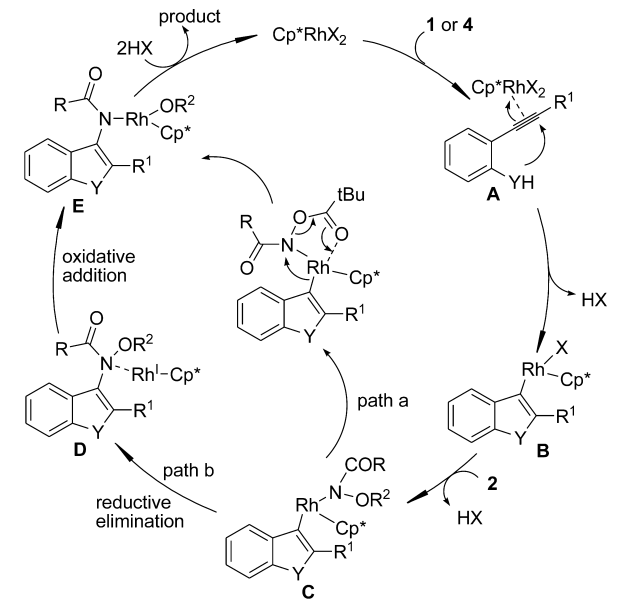
Scheme 3. Derivatizations of 3-Amidoindoles



yield.[13b] Surprisingly, upon reaction with aqueous NaOH in the solution of MeOH and THF, indole **3ia** was transformed to tricyclic indole **10**, which was possibly caused by a radical process with the oxygen in air as the oxidant (Scheme 3c).[14]

On the basis of the experimental results and the precedent literature, the mechanism hypotheses are proposed (Scheme 4).

Scheme 4. Proposed Reaction Mechanism



Initially, the coordination of the triple bond in substrate **1** or **4** to rhodium(III) species enhances the electrophilicity of the triple bond.[15] The subsequent nucleophilic attack of the tethered oxygen or nitrogen on the triple bond generates benzoheterocyclic rhodium(III) species **B**. The intermediate **B** then reacts with the amidation reagent **2** to furnish the expected 3-amido heterocycles and regenerates rhodium(III) species. While the detailed mechanism of this electrophilic amidation step remains to be elucidated, possible reaction pathways can be postulated based on previous studies.[16] Under basic conditions, deprotonation of *N*-pivaloyloxylamides and ligand exchange on intermediate **B** leads to the formation of intermediate **C**. In pathway a, C−N bond formation occurs in concert with N−O bond cleavage, and rhodium remains at the +3 oxidation state.[4,16c] Pathway b features a reductive eliminatioin/oxidative addition sequence involving $Rh^{III}/Rh^{I}/Rh^{III}$ cycle.[16] Both pathways could afford intermediate **E**, which upon protonolysis provides the expected 3-amidobenzoheterocycle and regenerates Rh^{III} to complete the catalytic cycle.[17]

In conclusion, we have developed a novel and efficient method to construct 3-amidoindoles and 3-amidobenzofurans via rhodium(III)-catalyzed nucleophilic attack/umpolung amidation cascade process. This process employed *N*-pivaloyloxylamide as the umpolung amidating reagent, which might find further application in more diverse cascade reactions. The synthetic value of this reaction was highlighted by its utility in the synthesis of heterocycle fused indoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00689.

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

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

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Notes

The authors declare no competing financial interest.

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(11) The reaction of indole **3aa′** with **2a** under optimized conditions cannot afford the desired product 3-amidoindole **3aa**.

(12) For the crystallographic data of **3ma**, see the Supporting Information.

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(17) The possibility of oxidative addition before reductive elimination involving Rh^{V} species cannot be ruled out at present.

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