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Facile Synthesis of Isoindolinones via Rh(III)-Catalyzed One-Pot Reaction of Benzamides, Ketones, and Hydrazines

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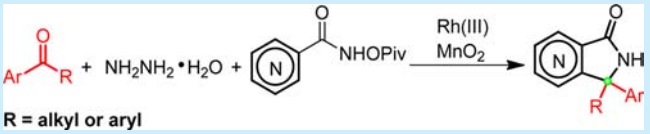
Supporting Information

ABSTRACT: A Rh(III)-catalyzed one-pot reaction of benzamides, ketones, and hydrazines for facile access to isoindolinones is reported. In this method, various ketones are transformed into donor−donor diazo compounds, which sequentially engage in insertion with benzamides under Rh(III) catalysis to generate *N*-substituted quaternary isoindolinones.



Isoindolinones represent an important class of nitrogen-containing heterocycles, which widely exist in natural products and biologically active compounds.[1] Representative examples are depicted in Figure 1. Pestalachloride A was

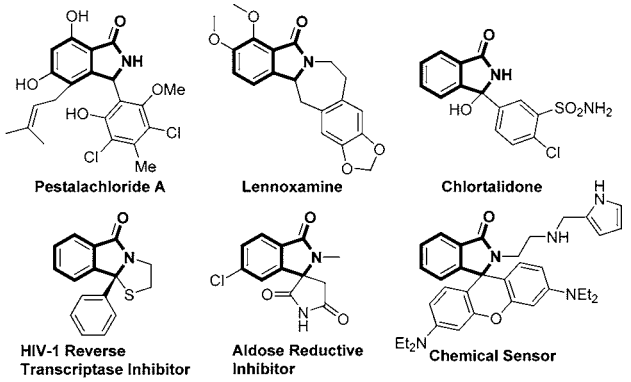
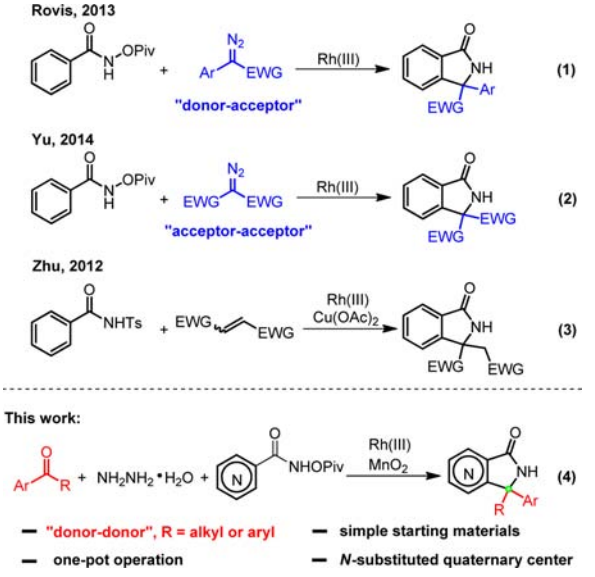


Figure 1. Representative structures involving isoindolinone.

identified as an antifungal metabolite from the plant endophytic fungus *Pestalotiopsis adusta* by Che and co-workers,[2] lennoxamine is also an isoindolinone alkaloid isolated from the Chilean barberries species,[3] and chlortalidoneis a diuretic drug used to treat hypertension.[4] Functionalized isoindolinones have also been investigated as HIV-1 reverse transcriptase inhibitors, aldolase reductive inhibitors, and also chemical sensors.[5] Therefore, the ability to access these types of heterocycles from simple materials is important.

Rh(III)-catalyzed direct functionalization of C−H bonds has become a powerful tool for C−C, C−O, and C−N bond formation, offering a straightforward entry into the synthesis of various valuable heterocycles.[6] In particular, Rh(III)-catalyzed C−H activation/cycloaddition of a benzamide with an alkyne, alkene, allene, and diazo compound have been well developed by Miura, Fagnou, Glorius, Li, Rovis, etc. over the past five years.[7] Mechanistically, these reactions involve rhodacycle formation and subsequent [4 + 2], [4 + 1], and [4 + 3] cyclization.

Diazo compounds are reactive carbon components in rhodium catalysis, the donor group of diazo compounds stabilizing the electron-deficient metal carbenes and attenuating their reactivity.[8] Recently, Rovis reported a Rh(III)-catalyzed C−H activation/cyclization of benzamides with donor/acceptor diazo compounds as a method for accessing to isoindolinones (eq 1),[9] and more recently, Yu also



independently reported the same reaction using acceptor/acceptor diazo compounds (eq 2).[10] Meanwhile, Zhu and coworkers developed an alternative synthesis of isoindolinones via Rh(III)-catalyzed C−H activation/cyclization of benzamides

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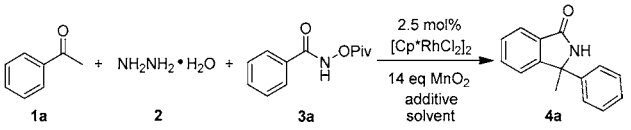
with electron-defficient olefins (eq 3).[11] Despite this, the development of Rh(III)-catalyzed C−H activation of benzamides and the coupling with donor−donor diazo compounds remains a challenge and of importance.

Continuing our interest in Rh(III)-catalyzed C−H activation/cyclization for heterocycles synthesis,[12] herein we report a facile synthesis of isoindolinones with an *N*-substituted quaternary center via a Rh(III)-catalyzed one-pot reaction of benzamides and ketones using MnO_2 as oxidant. The main advantage of the method is that it features simple starting materials, mild reaction conditions, and easy operation (eq 4).

We initially commenced our study by investigating the one-pot reaction of acetophenone **1a**, hydrazine **2**, and *N*-(pivaloyloxy)benzamide **3a** with a catalytic amount of $[Cp^*RhCl_2]_2$ in CH_3CN at room temperature. To our delight, we found that formation of the isoindolinone product **4a** occurred in 45% yield (Table 1, entry 1). Our survey of

Table 1. Optimization of the Reaction Conditions[a]



entry	additive	solvent	yield[b] (%)
1	CsOAc (1 equiv)	CH_3CN	45
2	CsOAc (1 equiv)	MeOH	20
3	CsOAc (1 equiv)	DCM	50
4	CsOAc (1 equiv)	toluene	36
5	CsOAc (1 equiv)	THF	53
6	**HOAc (0.2 equiv)/CsOAc (1 equiv)**	**THF**	**72 (75)[c]**
7[d]	HOAc (0.2 equiv)/CsOAc (1 equiv)	THF	41
8[e]	HOAc (0.2 equiv)/CsOAc (1 equiv)	THF	38
9[f]	HOAc (0.2 equiv)/CsOAc (1 equiv)	THF	0
10[g]	HOAc (0.2 equiv)/CsOAc (1 equiv)	THF	75

[a]Reaction conditions: **1a** (0.34 mmol), **2** (0.4 mmol), solvent (2.0 mL), **3a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), and additive. [b]Yields of isolated products. [c]The value in parenthese refers to 1 mmol scale. [d]Conducted at 50 °C. [e]6.0 equiv of MnO_2. [f]$Pd(OAc)_2$ was used as catalyst. [g]Acetophenone and hydrazine were replaced with acetophenone hydrazone.

solvents (entries 2−5) showed that THF was optimal for furnishing the product in 53% yield (entry 5). Interestingly, the catalytic addition of acetic acid could facilitate this reaction to improve the yield to 72% yield (entry 6), probably because acetic acid could accelerate formation of the hydrazone intermediate, and the yield of the 1 mmol scale could be up to 75%. An attempt to lower MnO_2 loading led to a decreased yield of 41% (entry 7).[13] Further optimization showed that increasing the temperature to 50 °C also resulted in a lower yield (entry 8). Replacing $[Cp^*RhCl_2]_2$ with $Pd(OAc)_2$ completely shut down the reactivity, demonstrating the necessity of the Rh(III) catalyst (entry 9), while the direct use of (1-phenylethylidene) hydrazine would deliver the product in a slightly higher yield (entry 10). The structure of isoindolinone **4a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 2).[14]

With the optimized conditions in hand, we evaluated the generality of this reaction. As depicted in Table 2, various benzamides with valuable functional groups like isopropyl, methoxy, chloro, iodo, and nitro reacted smoothly in this one-pot reaction to afford the corresponding isoindolinones **4a−i** in

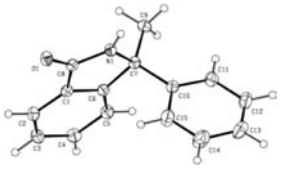
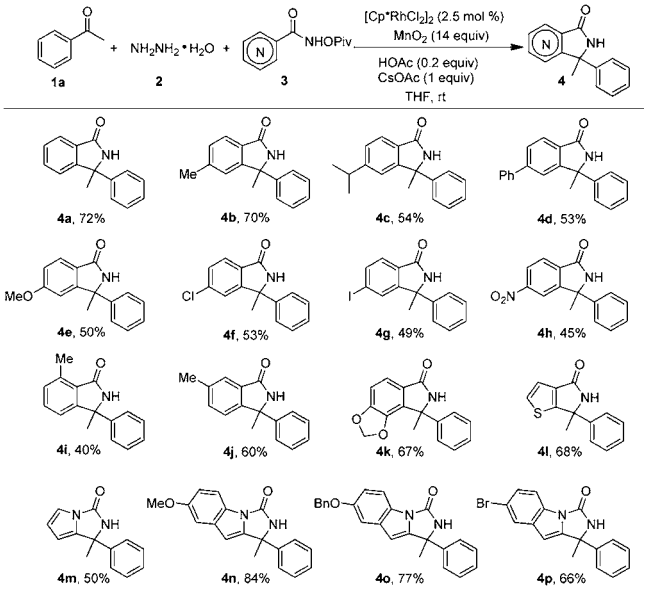


Figure 2. ORTEP representation of the X-ray crystal structure of **4a**.

Table 2. Substrate Scope of Benzamides[a]



[a]Isolated yields are given. Reaction conditions: **1** (0.34 mmol), **2** (0.4 mmol), HOAc (0.04 mmol), THF (2 mL), 2−3 h, 60 °C; then **3** (0.2 mmol), MnO_2 (14 equiv), CsOAc (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), rt, 8−10 h.

moderate to good yields (40%−72%), thus offering ample opportunity for further derivatization. Additionally, when *meta*-substituted benzamides were applied, good regioselectivity favoring activation of the less hindered C−H bond was observed, and a single product (**4j**) was obtained. Moreover, polysubstituted acetophenones were also tolerated in this process affording isoindolinones, and interestingly, when piperonyloyl amide was used, the reaction favored activation of the more hindered C−H bond to deliver the product **4k** in excellent yield. Heterocyclic amides such as thiophene-3-carboxamide were also applicable in this transformation to afford the corresponding fused lactam analogue **4l**. Additionally, *N*-(pivaloyloxy)-1*H*-pyrrole-1-carboxamide and *N*-(pivaloyloxy)-1*H*-indole-1-carboxamides reacted smoothly to deliver the privileged imidazolidinones **4m−p**.

Next, a variety of aryl ketones were utilized to construct diverse isoindolinones (Table 3). Differential substitution on the aromatic ring of acetophenones gave the desired products in good yields (**5a**,**b**). Heterocyclic ketones were tolerated and proceeded well in this process to deliver the products in good yields (**5c**,**d**). Moreover, functionalized ketones were applicable regardless of aryl substitution or alkyl substitution to produce the isoindolinones in good yields (**5e−i**). It should be noted that cyclic ketones such as 9-fluorenone and *N*-methylisatin proceeded well in this one-pot transformation to deliver the fused isoindolinones (**5j−l**). Therefore, this process represents a general and distinct approach toward privileged isoindolinones from simple starting materials.

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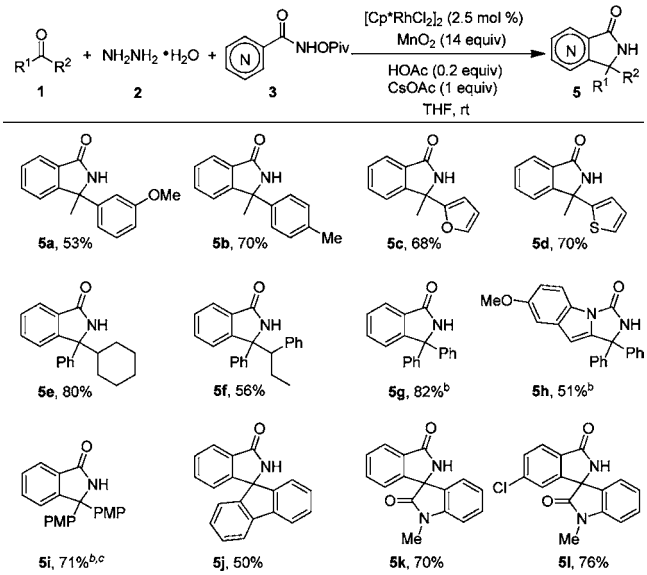
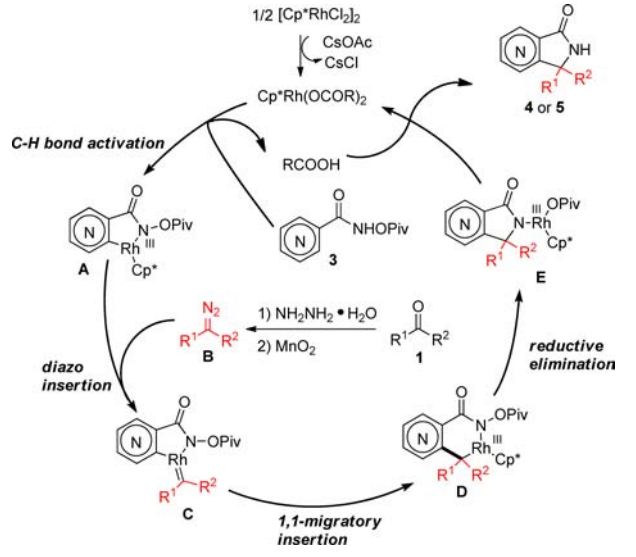
Table 3. Substrate Scope of Aromatic Ketones[a]



[a]Isolated yields are given. Reaction conditions: **1** (0.34 mmol), **2** (0.4 mmol), HOAc (0.04 mmol), THF (2 mL), 2−3 h, 60 °C; then **3** (0.2 mmol), MnO_2 (14 equiv), CsOAc (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), rt, 8−10 h. [b]Corresponding hydrazones were used in this reaction. [c]PMP = *p*-methoxyphenyl.

On the basis of these experiments and literature reports, a plausible mechanism is proposed in Scheme 1. The initial

Scheme 1. Proposed Mechanism



rhodium dicarboxylate is generated from $[Cp^*RhCl_2]_2$ and CsOAc, and a carboxylate-assisted C−H activation of benzamides occurs via a concerted metalation/deprotonation (CMD) pathway to form rhodacycle **A**. Then a diazo insertion occurs between **A** and **B**, which is generated in situ from the ketones, hydrazine, and MnO_2 to form intermediate **C**. The subsequent 1,1-migratory insertion of **C** generates **D**, and the following reductive elimination delivers **E**. The final step is protonation of **E** to furnish the isoindolinone product with concomitant Rh(III) catalysis regeneration. Therefore, the direct utilization of acetophenone hydrazone instead of acetophenone and hydrazine would also lead to the same product.

In summary, we have developed a unique Rh(III)-catalyzed one-pot reaction of benzamides, ketones, and hydrazines for facile access to functionalized isoindolinones. Its main advantage is that it features simple starting materials, mild reaction conditions, and high efficiency.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and compound characterization. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01016.

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1038763 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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