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Multicomponent Synthesis of Isoindolinones by Rh^{III} Relay Catalysis: Synthesis of Pagoclone and Pazinaclone from Benzaldehyde

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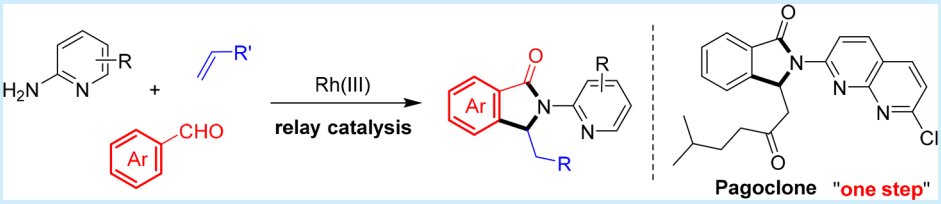
Supporting Information



ABSTRACT: A practical one-pot isoindolinone synthesis enabled by Rh^{III} catalysis was developed. The advantage of this protocol is that it does not require pre-preparation of amide substrates, because Rh^{III} participates in two reactions independently. This mild, operationally multicomponent process transforms a wide variety of commercially available aldehydes into the corresponding γ-lactams in good yields, thereby demonstrating that *N*-pyridin-2-yl benzamide is an effective directing group. Notably, the anxiolytic drugs pagoclone and pazinaclone can be directly prepared by this methodology.

Nitrogen-containing organic compounds are ubiquitous in nature and are essential to life. They are also important intermediates and products of the chemical and pharmaceutical industries. Among these, isoindolinones represent a significant class of heterocycles that are widely found in natural products and biologically active compounds.[1] Some representative examples of these compounds are depicted in Figure 1.

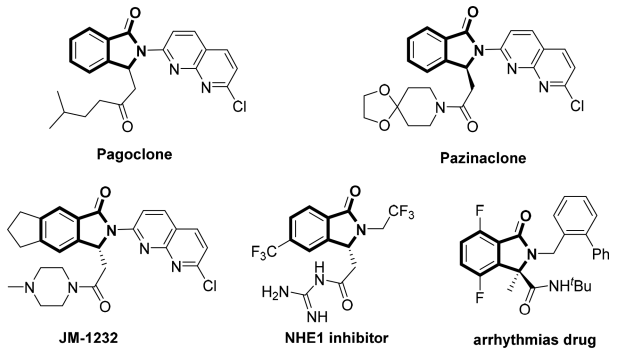
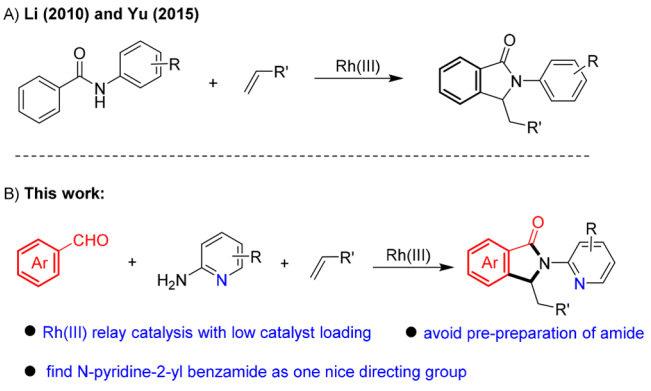


Figure 1. Representative biologically active molecules including isoindolinone.

Pagoclone is an anxiolytic drug from the cyclopyrrolone family that is known to bind to the benzodiazepine receptor site of the GABA-A receptor.[2] In addition, pazinaclone and JM-1232 also have been reported to be benzodiazepine receptor agonists for the treatment of anxiety.[3] The last two compounds have been studied as an NHE1 inhibitor and a potential drug for the treatment of cardiac arrhythmias, respectively.[4]

In the past decade, explosive progress has been made in the development of Cp*Rh-catalyzed C−H activation that offers powerful support to the design and synthesis of various skeletons such as lactams,[5] pyridines,[6] and others.[7] In particular, rhodium-catalyzed C−H olefination of benzamide with terminal olefins followed by annulation to form γ-lactam is one of the most classic of such syntheses (Scheme 1A). Li[8] first reported Rh^{III}-catalyzed oxidative-coupling reactions between benzamides and olefins, followed by intramolecular Michael reactions to form γ-lactam. On the basis of the competitive reaction, it was concluded that transformation is favored for benzamides with electron-poor *N*-phenyl groups. Thus, Sun and Yu[9] later reported an elegant improved synthesis and showed that the

Scheme 1. Rh(III)-Catalyzed C−H Olefination toward Isoindolinones



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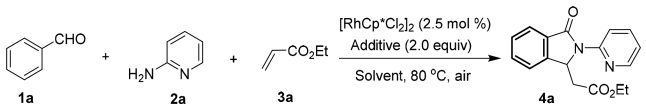
use of an *N*-pentafluorophenyl benzamide directing group is crucial for this transformation.

On the other hand, multicomponent reactions (MCRs), defined as the processes that combine at least three reactants in the same pot to generate a product containing most of the atoms of the starting materials,[10] have been heavily exploited to prepare small molecules with atom/step economy, efficiency, and structural diversity. Therefore, the development of MCRs for the construction of biologically interesting molecules always exhibits opportunities and challenges due to the simple experimental procedures and one-pot ecofriendly synthesis method. In light of our ongoing interest in heterocycles synthesis,[11] herein we designed the one-pot multicomponent isoindolinone synthesis enabled by relay catalysis of rhodium(III), starting from commercially available aldehydes, 2-pyridinamine, and olefins (Scheme 1B). However, to achieve the expected reaction, the following two challenges must be overcome: (1) amide rather than iminium should be generated in situ from benzaldehydes and aromatic amine and (2) the catalytic amount of $[Cp^*RhCl_2]_2$ must act as the relay catalyst for both oxidative amidation and olefination.

To our delight, we overcame these challenges and obtained the target product. Unlike the many previously reported studies where the formed iminium acted as the directing group,[12] we selectively realized amidation in our catalytic system, similar to that previously reported for copper and other metal catalysts.[13] We began our investigation with the coupling among benzaldehyde **1a**, pyridin-2-amine **2a**, and ethyl acrylate **3a**. Selected results are shown in Table 1. The use of $[Cp^*RhCl_2]_2$ as the single catalyst and $Cu(OAc)_2$ as the oxidant in MeCN yielded lactam **4a** in 70% yield (Table 1, entry 1). Encouraged by this preliminary observation, we attempted to improve the reaction efficiency by screening various solvents and oxidant (entries 2−7). It was found that $Cu(OAc)_2$ was the best oxidant. Among the screened solvents, MeCN afforded the best yield. Lowering of the temperature to 60 °C resulted in a lower yield (entry 8). An attempt to lower the loading of $Cu(OAc)_2$ also failed, because a smaller yield was obtained (entry 10). On the other hand, it was found that conducting the reaction under nitrogen atmosphere facilitated this one-pot transformation, improving the yield to 91% yield (entry 9).

Table 1. Optimization of the Reaction Conditions[a]

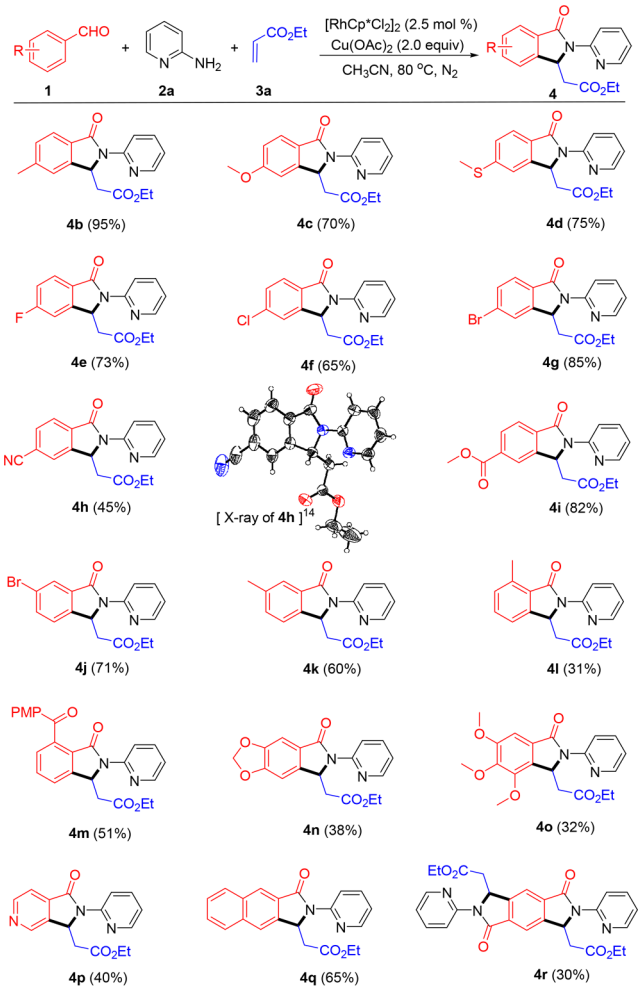


entry	additive	solvent	yield (%)[b]
1	$Cu(OAc)_2$	MeCN	70
2	$Cu(OAc)_2$	THF	10
3	$Cu(OAc)_2$	MeOH	trace
4	$Cu(OAc)_2$	TFIP	trace
5	AgOAc	MeCN	trace
6	$Mn(OAc)_3$	MeCN	trace
7	$CuSO_4$	MeCN	trace
8[c]	$Cu(OAc)_2$	MeCN	40
9[d]	$Cu(OAc)_2$	MeCN	91
10[e]	$Cu(OAc)_2$	MeCN	76

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), additive (0.4 mmol), solvent (2 mL), 80 °C, 8 h. [b]Yields of isolated products. [c]Reaction at 60 °C. [d]Under N_2 atmosphere. [e]$Cu(OAc)_2$ 2.0 equiv. TFIP = hexafluoroisopropanol.

With the optimized reaction conditions in hand (Table 1, entry 9), we first investigated the scope of the substituted benzaldehydes (Scheme 2). Various benzaldehydes with valuable functional groups such as methoxy, methylthio, bromo, cyano, ester, and acyl reacted smoothly with **2a** and **3a** to afford the corresponding isoindolinones (**4b**−**4i**) in moderate to excellent yields (45−95%), thus offering a broad range of opportunities for further derivation. In addition, the structure of **4h** was further confirmed by single-crystal X-ray analysis. These results show that the reactions of the benzaldehydes bearing electron-donating and -withdrawing groups at the *para* position had no obvious effect on this transformation. Additionally, when meta-substituted benzaldehydes were applied, good regioselectivity favoring the activation of the less hindered C−H bond was observed, and the sole product was obtained in good yields (**4j** and **4k**). However, for the ortho- and polysubstituted benzaldehydes, the yields of the desired products were lower (**4l**−**4o**). Heteroaryl and naphthyl substituents were also compatible, and the expected products were found in moderate

Scheme 2. Scope of Benzaldehyde Substrate[a]



[a]Isolated yields are given. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (0.4 mmol), MeCN (2 mL), under N_2 atmosphere, 80 °C, 8 h. PMP = *para*-methoxyphenyl.

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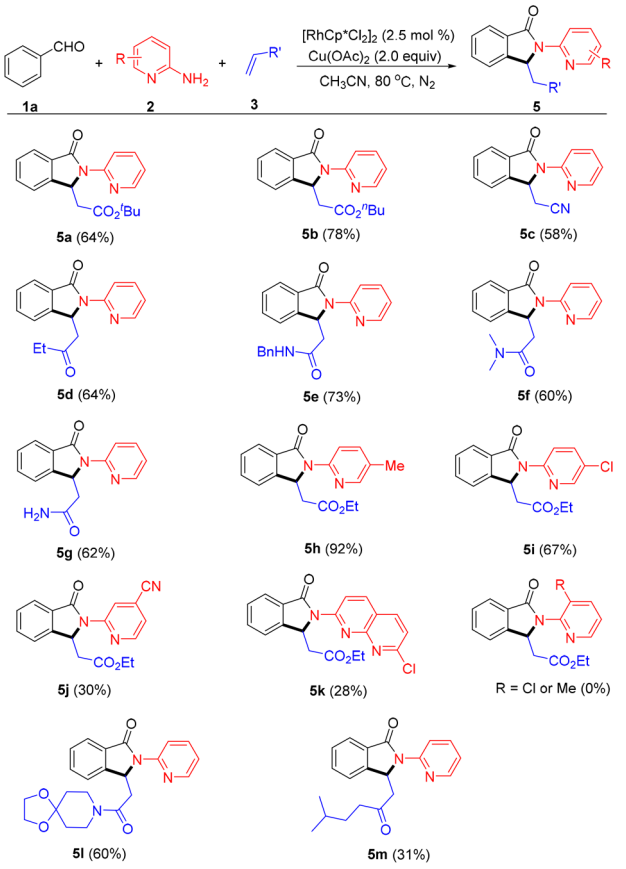
yields (**4p** and **4q**). Interestingly, using 1,4-benzenedicarboxaldehyde as the substrate, the expected symmetrical product **4r** was isolated.

We then investigated the scope of the olefin-coupling partner in this transformation. As shown in Scheme 3, electron-deficient

Scheme 3. Scope of Olefin- and Aniline-Coupling Partners[a]

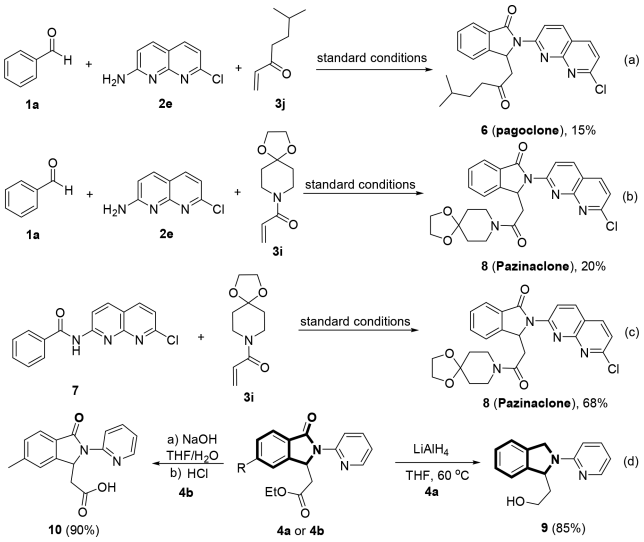


[a]Isolated yields are given. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), **3** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (0.4 mmol), MeCN (2 mL), under N_2 atmosphere, 80 °C, 8 h.

olefins including acrylate, ethyl vinyl ketone, acrylonitrile, and acrylamide can be coupled in good yield to provide lactam products (**5a**−**5g**). Meanwhile, different types of substituents at different positions on the aniline had distinct impacts on the reaction (**5h**−**5k**). It should be noted that analogues of the anxiolytic drugs pagoclone and pazinaclone can be directly prepared by this method (**5l** and **5m**). We also tested the reaction using an electron-deficient aniline (**2f**, see SI) instead of a pyridine-2-amine, but it is not effective. Clearly, this strategy opens a new avenue to the synthesis of these biologically interesting scaffolds with readily available starting materials.

We were particularly interested in applying this strategy to drug synthesis and accessing other compounds with natural-product-like cores. **6** (Pagoclone) and **8** (pazinaclone) can be directly prepared in a single step from benzaldehyde **1a**, albeit with low yields (Scheme 4a,b). We were able to obtain **8** (pazinaclone) with good yield under the standard reactions using amide **7** as the starting material (Scheme 4c), suggesting that formation of amide **7** may not proceed well in this catalytic system. Furthermore, compounds **9** and **10** were obtained in

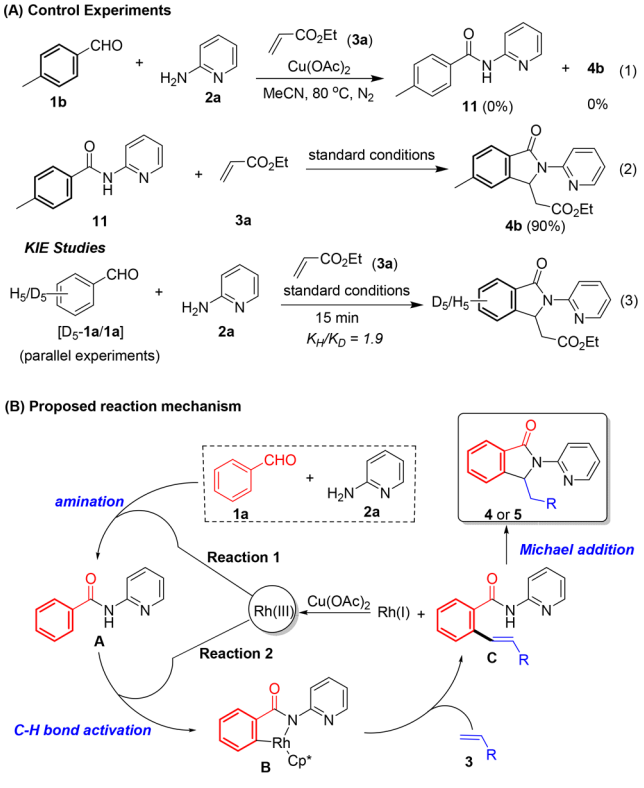
Scheme 4. Synthetic Application and Diversification



good yields by reduction and hydrolysis from **4**, respectively (Scheme 4d).

To obtain insight into the reaction mechanism proposed in Scheme 5B, several control experiments were performed. First,

Scheme 5. Proposed Mechanism



reaction among benzaldehyde **1b**, pyridin-2-amine **2a**, and ethyl acrylate **3a** with 2 equiv of $Cu(OAc)_2$ gave no amide **11** and product **4b** (Scheme 5A, eq (1)). Second, the reaction of amide **11** with olefin **3a** at the standard conditions was evaluated, showing that the expected product **4b** could be isolated in 90% yield (Scheme 5A, eq (2)). We can also get evidence suggesting that the pyridine moiety plays an important role in the direction group (see SI). Next, considering that this Rh(III)-catalyzed

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cascade synthesis includes a C−H activation step, a kinetic isotope effect (KIE) study was conducted (Scheme 5A, eq (3)). A primary KIE (1.9) was obtained, suggesting that C−H bond cleavage occurs during the rate-determining step.[14]

On the basis of these experiments and precedents reported in the literature,[15] a plausible mechanism for this multicomponent synthesis was proposed (Scheme 5B). Catalytic amination between aldehydes **1a** and amine **2a** produces the amide intermediate **A** in the presence of the Rh(III) catalyst. **A** serves as the reagent in the next reaction step, forming rhodacycle **B** via a concerted metalation/deprotonation (CMD) pathway.[16] Then, coordination to the olefin-coupling partner and 1,2-migratory insertion provide the uncyclized intermediate **C**. Reoxidation of the Rh(I) to Rh(III) by $Cu(OAc)_2$ completes the catalytic cycle. **C** subsequently undergoes an in situ Michael addition to give γ-lactam products **4** or **5**.

In summary, we have successfully developed a highly efficient Rh(III) relay catalysis protocol for the synthesis of isoindolinone from simple starting materials in a single operation. Antianxiety and anticonvulsant drugs pagoclone and pazinaclone can be prepared in one step, showing the usefulness of this novel, one-pot, three-component reaction. Furthermore, this convenient methodology demonstrates that *N*-pyridin-2-yl benzamide can act as an effective directing group, which may find broader application in Rh(III) catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04026.

Detailed experimental procedures and characterization data for new compounds **4** and **5** (PDF)

Accession Codes

CCDC 1835723 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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