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Rh(III)-Catalyzed Chemodivergent Annulations between Indoles and Iodonium Carbenes: A Rapid Access to Tricyclic and Tetracyclic *N*-Heterocylces

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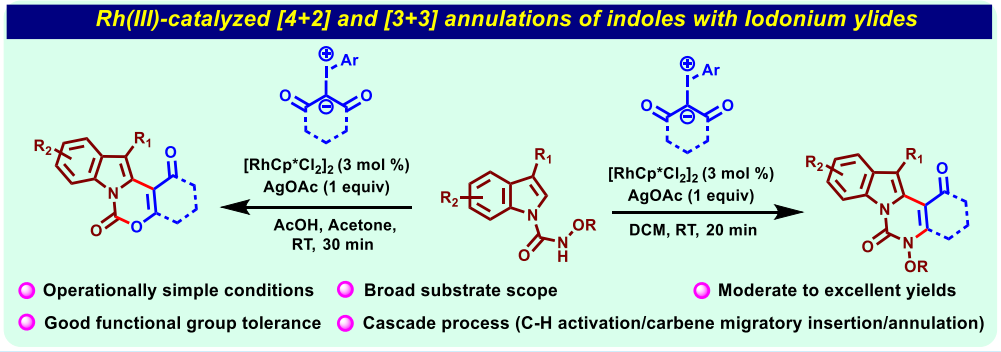

ABSTRACT: Herein, we report an acid-controlled highly tunable selectivity of Rh(III)-catalyzed [4 + 2] and [3 + 3] annulations of *N*-carboxamide indoles with iodonium ylides lead to form synthetically important tricyclic and tetracyclic *N*-heterocycles. Here, iodonium ylide serves as a carbene precursor. The protocol proceeds under operationally simple conditions and provides novel tricyclic and tetracyclic scaffolds such as 3,4-dihydroindolo[1,2-*c*]quinazoline-1,6(2*H*,5*H*)-dione and 1*H*-[1,3]oxazino[3,4-*a*]indol-1-one derivatives with a broad range of functional group tolerance and moderate to excellent yields. Furthermore, the protocol synthetic utility was extended for various chemical transformations and was easily scaled up to a large-scale level.

In nitrogen heterocycles, indole and pyrrole scaffolds are central structural motifs and can be found in a large number of natural products, pharmaceuticals, and manufactured functional molecules.[1] In particular, pyrimido[1,6-*a*]indol-1(2*H*)-ones, pyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones, and 1*H*-[1,3]oxazino[3,4-*a*]indol-1-one scaffolds are an integral part of fluorescent materials and diverse biologically active compounds such as 5-HT3 receptor antagonists, antihypertensive agents, CNS depressants, and others.[2,3] Consequently, the synthesis of these derivatives gained considerable attention in both organic and medicinal chemistry.[4] Although numerous methods have been well-developed to assemble these moieties, most of the methods involve multiple synthetic steps and harsh reaction conditions. Therefore, developing a scope to establish direct approaches with easily available starting materials and mild reaction conditions is highly desirable.

The past decade has witnessed the burgeoning of the directing-group-assisted transition-metal-catalyzed C−H functionalizations with carbene precursors, which are widely applied in alkylations, alkenylations, arylations, and annulations.[5] Note that, for the first time, Yu et al. reported Rh(III)-catalyzed C−H alkylation of arene C−H bonds with carbene precursors.[6] Henceforth, this protocol has emerged as a robust tool for a wide variety of C−H functionalizations with carbenes.[7] However, many reports employed diazo compounds as carbene precursors, which are highly explosive and toxic in nature. To overcome these difficulties, Wang and co-workers,[8] Glorious and co-workers,[9] Aissa and co-workers,[10] Chang and co-workers,[11] and Li and co-workers[12] introduced nondiazo carbene counterparts such as hydrazones, triazoles, sulfoxonium ylides, enynones, and iodonium ylides, which are successfully utilized in various sp^2 and sp^3 C−H functionalizations.[13] The carbene precursors have been shown enormous diversity in the above-mentioned C−H functionalizations; however, regiodivergent and chemodivergent synthetic transformations by the identical catalyst system with operationally simple method remains very limited.

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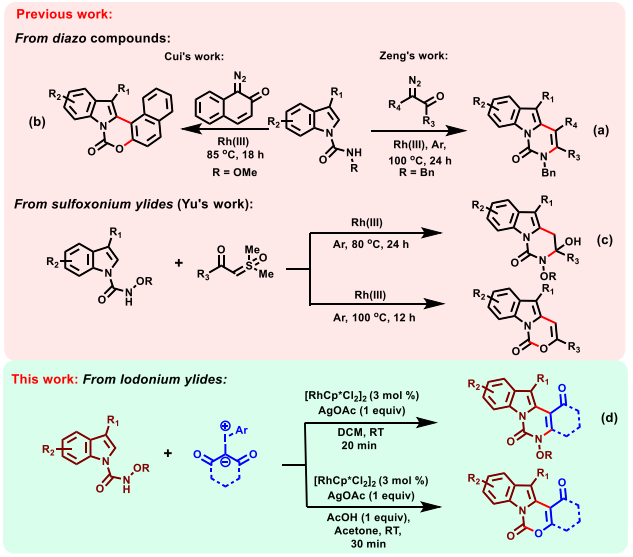
On the other hand, it is great privilege to any catalysis researcher to develop a single catalytic system performing multiple reactions with common substrates via tunable reactivity. The tunable reactivity can alter the reaction pathway and brings the diversity in synthesis/outcome. In this regard, recently, *N*-carboxamide indoles and carbene precursors have been utilized for such tunable selective reactions via transition-metal-catalyzed C−H functionalization, because of their high flexibility and diverse reactivity.[14,15] For example, Zeng and co-workers pioneered in Rh(III)-catalyzed [4 + 2] annulation of *N*-alkylaminocarbonyl indole with α-acyl diazo compounds for rapid assembly of 2*H*-pyrimido[1,6-*a*]indol-1-one derivatives (Scheme 1a).[16] Cui and co-workers developed in Rh(III)-catalyzed [3 + 3] annulation of *N*-carboxamide indoles and diazonaphthalen-2(1*H*)-ones for fused oxazinones synthesis (Scheme 1b).[17] Very recently, Yu group disclosed the synthesis of dihydropyrimidoindolone and tricyclic [1,3]oxazino[3,4-*a*]indol-1-ones derivatives via Rh(III)-catalyzed cascade [4 + 2]/[3 + 3] annulations of *N*-carbamoyl indoles with sulfoxonium ylides (Scheme 1c).[18] Although these reactions provide an attractive route to indole C−H annulation, limited substrate scope, prolonged reaction time and harsh reaction conditions made them less attractive.

To the best of our knowledge, transition-metal-catalyzed chemodivergent annulation of indoles with iodonium ylides has not been reported previously. Herein, we report, for the first time, acid-controlled Rh(III)-catalyzed chemodivergent annulations of *N*-alkoxy-1*H*-indole-1-carboxamides and iodonium ylides. The reaction affords a wide range of 2*H*-pyrimido[1,6-*a*]indol-1-ones and 1*H*-[1,3]oxazino[3,4-*a*]-indol-1-ones with moderate to excellent yields under mild reaction conditions (Scheme 1d). The desired analogues are core structures of many biologically active compounds.[2,3]

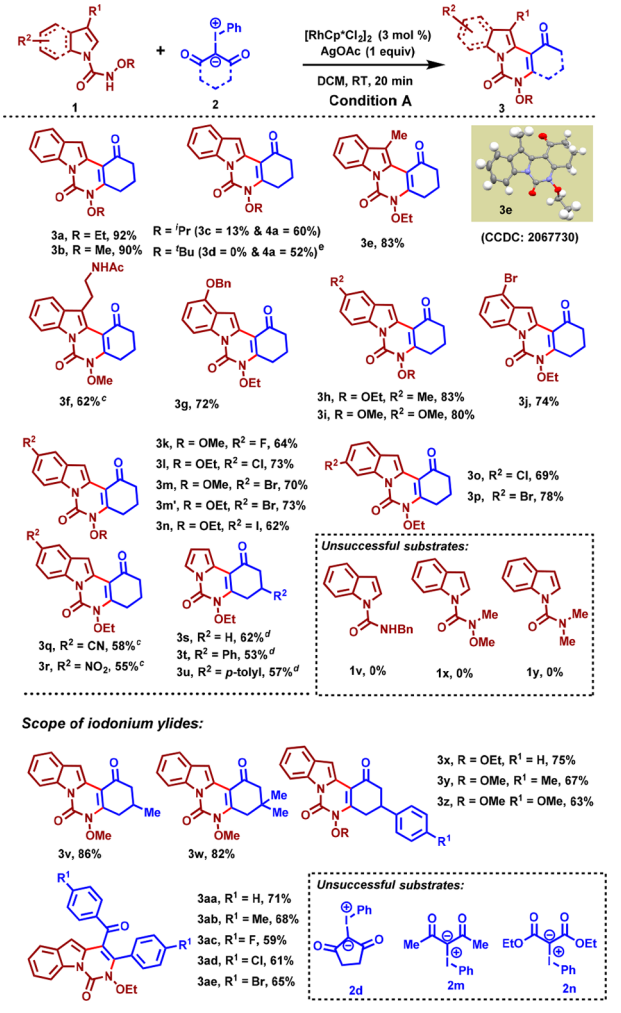
To test the tunable selectivity, we commenced our investigation by using *N*-ethoxy-1*H*-indole-1-carboxamide (**1a**) and 2-(phenyl-λ^3-iodaneylidene)cyclohexane-1,3-dione (**2a**) as the model substrates. Initial experiments revealed that a combination of $[RhCp^*Cl_2]_2$ and AgOAc is beneficial for the reaction (see the Supporting Information for a detailed optimization). Based on that, we were delighted to observe that the formation of the [4 + 2] annulation product **3a** and [3 + 3] annulation product **4a** in yields of 10% and 25% (see the SI for details). After detail optimization studies, to our delight, the catalytic system comprising $[RhCp^*Cl_2]_2$, AgOAc and DCM as solvent delivered the desired [4 + 2] annulation product **3a** in 92% yield. After that, a complete selectivity switch was observed by using a catalytic system comprising $[RhCp^*Cl_2]_2$, AgOAc, AcOH, and acetone as the solvent, and it delivered the [3 + 3] annulation product **4a** in 85% yield (see the SI for a detailed optimization). We hypothesized that the additive with acid combination might facilitate the formation of [3 + 3] annulation product by activating the amide carbonyl group toward the oxygen attack for the formation of **4a**.[15d]

Having identified suitable reaction conditions, turning our attention to the substrate scope, we initially probed variations for the [4 + 2] annulation (Scheme 2). Indole having *N*-methoxyamide and *N*-ethoxyamide substituents reacted smoothly and furnished the corresponding desired products in excellent yields (**3a** and **3b**). However, sterically hindered *N*-alkoxy carbamoyl indoles such as *N*-isopropoxy and *N*-*tert* butoxy substituents deliver the [3 + 3] annulation product

Scheme 1. Overview of the Work



Scheme 2. Scope of [4 + 2] Annulation[a,b]



[a]Conditions:**1** (0.1 mmol), **2a** (0.11 mmol), DCM (2.0 mL). [b]Isolated yield. [c]The reaction was run for 6 h. [d]HFIP (1.0 mL), 80 °C, 10 h.[e]The reaction was run for 2 h.

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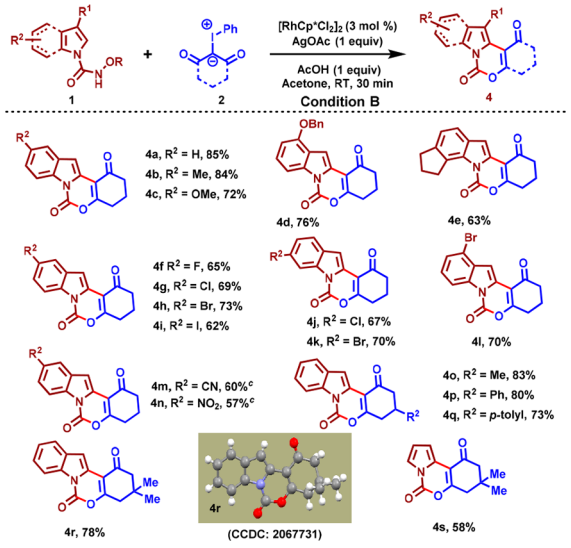
(**4a**) instead of [4 + 2] annulation (**3c** and **3d**). We assumed that, because of the bulkiness of the corresponding products (**3c** and **3d**) may encourage the nucleophilic attack by the enol oxygen followed by the elimination of hindered byproduct NH_2OR, leading to favors the formation of **4** instead of **3**. 3-Alkyl-substituted indoles were also well-tolerated and delivered the targeted products in good to excellent yields (**3e** and **3f**). The structure of **3e** was confirmed by X-ray crystallography. Gratifyingly, indole having either electron-donating or electron-withdrawing substituents (OBn, Me, OMe, F, Cl, Br, and I) reacted with iodonium ylide (**2a**) to generate the desired products **3** in good to excellent yields (**3g**−**3p**). Notably, when π-electron withdrawing groups (CN and NO_2) were subjected to the described optimized conditions, the annulated product was formed in moderate levels of yield (**3q** and **3r**). We reasoned that the substituents might be creating the poor electron density at indole C2-position. To our delight, pyrrole-substituted *N*-carboxyamides also performed well and produced the corresponding products in moderate to good yields (**3s**−**3u**). In contrast, alkyl-derived *N*-carbamoyl indoles (**1v**, **1x**, and **1y**) failed to provide the desired annulated product, presumably because of the inability to participate in the oxidative addition step.

Furthermore, we explored the scope of this transformation by modulating the carbene precursors (see Scheme 2). To our delight, the reaction occurred in good to excellent yields with a variety of substituents at the C5 position of cyclohexane-1,3-dione-derived ylides. The substitutions Me, diMe, Ph, *p*-tolyl, and anisole were well-tolerated and afforded the desired products (**3v**−**3z**). In contrast, we were pleased to find that 1,3-diphenylpropane-1,3-dione-derived iodonium ylides are well-facilitated for the [4 + 2] annulation, thus resulting in the corresponding tricyclic products in good to excellent yields (**3aa**−**3ae**). Note that, for the first time, these ylides were utilized in direct C−H functionalization reactions. However, cyclopentane-1,3-dione-derived iodonium ylide (**2d**) and aliphatic iodonium ylides (**2m** and **2n**) did not proceed under standard conditions, it demonstrated that the transformation is sensitive to the size and nature of the dione compounds.

Furthermore, we investigated the substrate scope for the formation of [1,3]oxazino[3,4-*a*]indol-1-one derivatives **4** under the optimized reaction conditions (Scheme 3). Various substitutions on indole such as H, Me, OMe, OBn, and tetracyclopentanes were well-tolerated and afforded the corresponding cyclized products in high yields (**4a**−**4e**). To our delight, diverse halogen-substituted indoles also underwent the [3 + 3] cyclization to afford the desired products in good to excellent yields (**4f**−**4l**), which are suitable substrates for various cross-coupling reactions. Notably, the π-electron-withdrawing groups at indole caused slow reactivity, resulting in diminished yields of corresponding annulated product (**4m**−**4n**). Interestingly, diverse iodonium precursors participated efficiently in the [3 + 3] annulation, thus offering the respective products in excellent yields (**4o**−**4r**). The structure of **4r** was confirmed by X-ray crystallography. Notably, the reaction was efficient with pyrrole substituted *N*-carboxyamide and produced **4s** in decent yield.

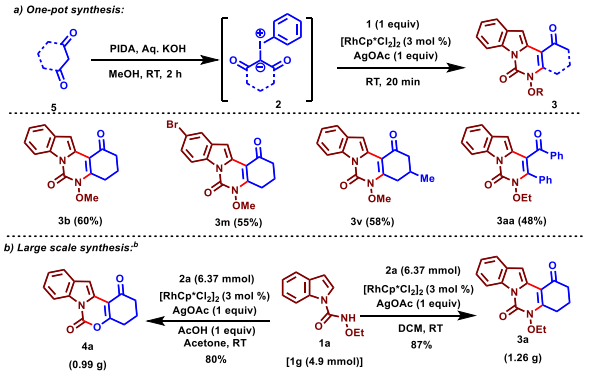
To our curiosity on step economy process, we have developed a one-pot protocol for the synthesis of tri- and tetracyclic derivatives by combining *in situ* formation of iodonium ylide from the 1,3-dicarbonyl compound followed by Rh(III)-catalyzed C−H annulation (Scheme 4a). Satisfyingly,

Scheme 3. Scope of [3 + 3] Annulations[a,b]



[a]Conditions:**1** (0.1 mmol), **2a** (0.11 mmol), Acetone (2.0 mL). [b]Isolated yield. [c]The reaction was run for 3 h.

Scheme 4. One-Pot Reaction and Large-Scale Synthesis[a]



[a]Conditions: Isolated yield. [b]The reaction was run for 5 h.

the yield of one-pot fashion was comparable with the stepwise pathway. Furthermore, a large scale reaction was performed and reacting 4.9 mmol of indole carboxyamide **1a** with 6.37 mmol of iodonium ylide **2a** under aforementioned reaction conditions, yielding the desired products **3a** in 87% yield (1.26 g) and **4a** in 80% yield (0.99 g) (Scheme 4b). Next, selected transformations of **3** and **4** were carried out to exhibit the synthetic potential of these approaches (see the details in the SI).[19]

In order to gain more insights on the reaction mechanism, a series of control experiments were performed (Scheme 5). A deuterium incorporation experiment was performed by treating **1b** with MeOH-d_4 under standard reaction conditions, and the results showed that 57% and 48% of deuteration at C2 position of indole, which demonstrated that the C−H bond cleavage is reversible in both synthetic transformations (Scheme 5a). The intermolecular competition reactions and parallel reactions gave low KIE values (KIE < 1), indicated that the C−H cleavage did not participate in the rate-limiting step (see Schemes 5b and 5c).

On the basis of literature precedents and our preliminary mechanistic results,[12,15d,18] a possible catalytic cycle was proposed, which is shown in Scheme 6. A five membered

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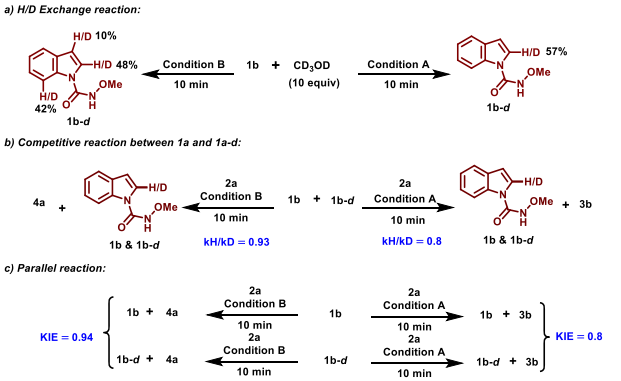
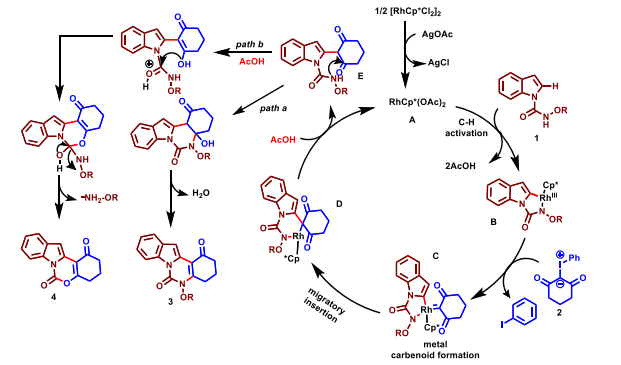
Scheme 5. Mechanistic Studies



Scheme 6. Proposed Mechanism



rhodium species such as **B** is formed by the C−H bond cleavage of *N*-alkoxycarbamoyl indoles (**1**) at C2 position with active rhodium catalyst A. The coordination of iodonium ylide (**2**) to the metal center in **B** followed by loss of iodobenzene, affords the metal carbene species **C**. The subsequent migratory insertion gives intermediate **D**, which undergoes protonation to deliver the intermediate **E** and regenerate the active catalyst species **A**. The intermediate **E** followed two different annulation pathways. In **path a**, the ketone carbonyl is then nucleophilically attacked by the amide NH group, followed by dehydration, to yield the [4 + 2] annulation product **3**. On the other hand, in **path b**, the acid activates the amide group toward nucleophilic attack by the enol oxygen, leading to favors the formation of [3 + 3] annulation product **4**, by the elimination of NH_2OR. We hypothesized that the acid additive stimulates the elimination process through protonation.

In summary, we have described an acid controlled Rh(III)-catalyzed chemodivergent annulations of *N*-alkoxycarbamoyl indoles and iodonium ylides, which provided a synthetically important tri- and tetracyclic *N*-heterocycles under operationally simple conditions. This protocol features broad substrate scope, good tolerance of functional groups, moderate to high yields. The efficiency of this methodology, further demonstrated by a large-scale and one-pot synthesis of desired products. In addition, the annulated products successfully transformed to diverse synthetic analogues. The biological applications of this strategy are in progress in our laboratory, and we anticipate that these privileged motifs will show wide applications in pharmaceutical field.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic analysis (CIF files for compound **3e** (CCDC no. 2067730) and **4r** (2067731) and spectroscopic data for synthesized compounds. . The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01167.

Additional experimental procedures (PDF)

Accession Codes

CCDC 2067730−2067731 contain 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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■ DEDICATION

Dedicated to Dr. Shashi Bala Singh on the occasion of her 63rd birthday.

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