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Rh(III)-Catalyzed C−H Activation of Benzamides and Chemodivergent Annulation with Benzoxazinanones: Substrate Controlled Selectivity

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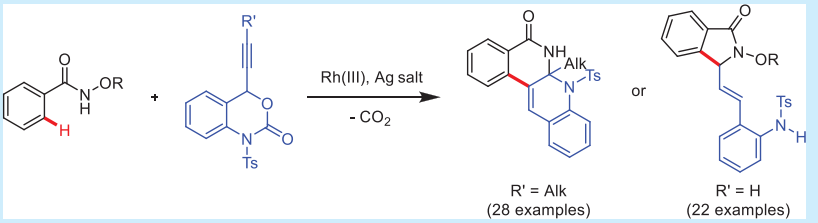
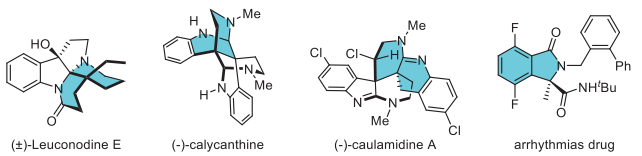


ABSTRACT: Decarboxylative annulation of propargyl carbamates with benzamides has been realized via rhodium-catalyzed C−H bond activation under mild conditions, delivering two distinct classes of heterocycles in high efficiency and selectivity under substrate control. This protocol provides a direct synthetic method for the preparation of functionalized 1,8-naphthyridines and isoindolinones.

N-heterocycles are important structural skeletons in the fields of pharmaceuticals, agrochemicals, organic synthesis, and materials science.[1] The development of novel methods for the synthesis of functionalized *N*-heterocycles has attracted significant attention. Despite the conspicuously potential of *N*-heterocycles, efficient methods for their synthesis, especially routes to access fused, complex *N*-heterocycles, are still underdeveloped. Naphthyridines[2] and isoindolinones[3] are among those important hectocycles that have been widely encountered in diverse natural products and bioactive molecules, and representative natural products possessing these core motifs are known to exhibit notable biological activities (Scheme 1). The significance of these heterocycles has called for the development of novel synthetic methods.

Scheme 1. Selected Natural Products with 1,8-Naphthyridines and Isoindolinones Frameworks



Metal-allenylidene species are highly reactive intermediates that have been employed toward construction of synthetically significant *N*-heterocycles,[4] and both propargylic esters and carbamates have been utilized as representative reagents to generate metal-allenylidene intermediates. Metal-allenylidenes have been extensively studies in diverse [4 + 1],[5] [4 + 2],[6] [4 + 3],[7] and [3 + 3][8] cycloaddition reactions. In 2016, Xiao and Lu group reported seminal examples of formal [4 + 1] cycloaddition of copper-allenylidene intermediates with sulfur ylides.[5] An asymmetric decarboxylative [4 + 2] annulation system of propargyl carbamates and carboxylic acids was established via cooperating copper and organocatalysts by the Gong and Wu group in 2017.[6a,b] Subsequently, various unsaturated reagents have been applied to deliver heterocycles in intermolecular annulation, including aldehydes, 2-silyloxyfurans derivatives, hexahydro-1,3,5-triazines, and others.[6c−g] Metal-allenylidene species can also readily undergo intramolecular annulation to give functional indole skeletons.[6e,9] In 2016, the Xiao group reported a copper-catalyzed decarboxylative amination/hydroamination of propargylic carbamates for expedient synthesis of two types of indoles.[9a] Later, Cu-catalyzed coupling of propargylic carbamates and 3-substituted indoles was achieved, thereby furnishing polycyclic indolines in high efficiency and selectivity.[9c] Very recently, pioneering report by Xiao and Lu group revealed a Cu-catalyzed dearomatization-rearomatization strategy via functionalization of copper-allenylidene with aza-sulfur ylides to afford benzimidazolines,[10] and a related system was also presented by Sun and co-workers (Scheme 2a).[11]

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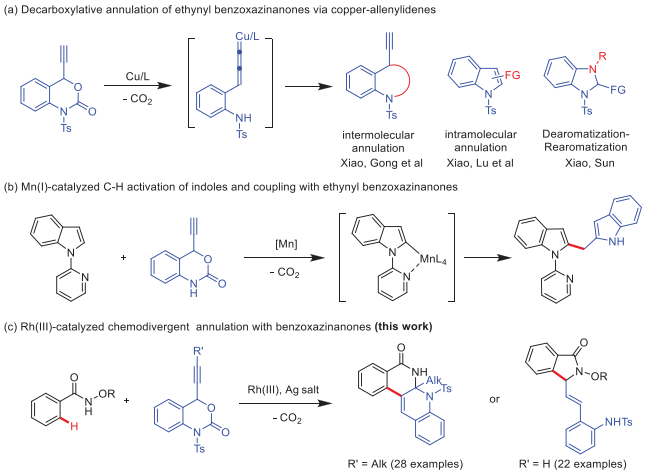
Scheme 2. Rh(III)-Catalyzed Decarboxylative Cyclization of Benzoxazinanones

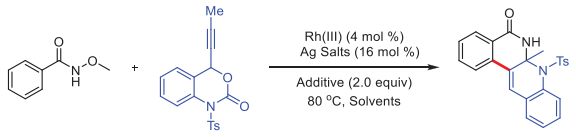


Catalytic C−H activation has emerged as a powerful and efficient strategy toward synthesis of value-added heterocycles.[12] The Glorius group applied cyclic propargyl carbamates as interesting coupling reagents in Mn-catalyzed C−H activation, where organomanganese species is involved as a key intermediate rather than a Mn-allenylidene that reacts with the propargyl carbamates via an aromatization cascade (Scheme 2b).[13] Over the past few decades, rhodium(III)-catalyzed C−H activation has garnered great attention to achieve annulation reactions via C−H activation of aryl amides bearing different directing groups.[14] Despite the potential rich chemistry by integration of C−H bond activation and annulation with propargyl carbonates,[15] only very limited examples had been documented so far, possibly due to the limited compatibility and limited availability of propargyl carbonates. We reasoned that bifunctional arenes bearing a proximal nucleophilic group should allow a sequence of C−H activation, C−C coupling, and cyclization with the electrophilic and bifunctional propargyl carbamates. We now report efficient decarboxylative annulations of benzamides and cyclic propargyl carbamates for the synthesis of two distinct panels of heterocycles under substrate control (Scheme 2c).

We commenced our studies by optimization of the reaction of *N*-methoxybenzamide (**1a**) and a methyl-substituted benzoxazinanone (**2a**, Table 1). $[Cp^*RhCl_2]_2$ was found to be an efficient catalyst (entries 1−2). Detailed screening of the Ag salts revealed that $AgSbF_6$ was the best one, affording **3aa** in 75% yield (entry 1). Among the several solvents examined, dichloromethane effectively promoted this reaction (entry 6), whereas the use of MeOH inhibited this reaction (entry 8). Next, a panel of additives were examined. Benzoic acid was identified as the best choice, furnishing the annulation product **3aa** in 85% yield (entry 11). Furthermore, lowering the reaction temperature to 60 °C provided an adverse effect on the chemical yield (entries 12). However, when the reaction was conducted at 100 °C, the yield of **3aa** was slightly decreased to 81% (entry 13).

We next explored the scope of benzamides (Scheme 3). A series of *N*-alkoxybenzamides were explored in the coupling with **2a**, and they all react with good to high efficiency regardless of the leaving group. The structure of **3aa** was characterized by X-ray diffraction (CCDC 2268962). We found that benzamides equipped with an electron-rich group at different positions of aryl ring tend to react with relatively higher yields than those with an electron-withdrawing group (**3ab**−**3ad** vs **3ae**−**3ai**, **3aj** vs **3ak**, **3am** vs **3an**), delivering the target molecules in moderate to high yield (71−91%). Besides, *meta*-substituted *N*-methoybenzamides reacted exclusively at the less hindered *ortho* site (**3aj**-**3al**). It is worth mentioning that the *ortho* substituted benzamides were also amenable to the reaction conditions despite the steric effect (**3am** and **3an**). The heterocycle derived amides, such as 1-benzothiophene, thiophene, and 9-fluorenone were also applicable (**3ao**−**3aq**). Additionally, the natural product estrone derivative also proved

Table 1. Optimization of Reaction Conditions[a]



entry	Rh (III)	Ag salt	additive	solvent	yield (%)
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	PivOH	DCE	75
2	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	-	PivOH	DCE	64
3	$[Cp^*RhCl_2]_2$	AgOTf	PivOH	DCE	73
4	$[Cp^*RhCl_2]_2$	$AgNTf_2$	PivOH	DCE	62
5	$[Cp^*RhCl_2]_2$	$AgPF_6$	PivOH	DCE	68
6	$[Cp^*RhCl_2]_2$	$AgSbF_6$	PivOH	DCM	82
7	$[Cp^*RhCl_2]_2$	$AgSbF_6$	PivOH	THF	79
8	$[Cp^*RhCl_2]_2$	$AgSbF_6$	PivOH	MeOH	N.R.
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$	CH_3CO_2H	DCM	76
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$MesCO_2H$	DCM	74
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$PhCO_2H$	DCM	85
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$PhCO_2H$	DCM	77[b]
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$PhCO_2H$	DCM	81[c]

[a]The reactions were carried out with **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), and Ag salt (16 mol %) in DCM (2.0 mL) at 80 °C for 24 h under N_2. Isolated yields. [b]60 °C. [c]100 °C.

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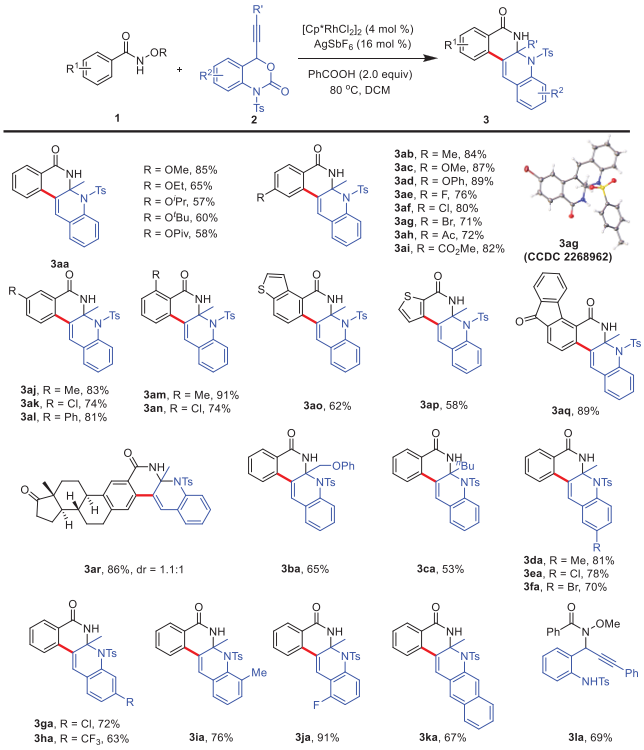
Scheme 3. Substrate Scope for Formal [4 + 2] Cycloaddition[a]



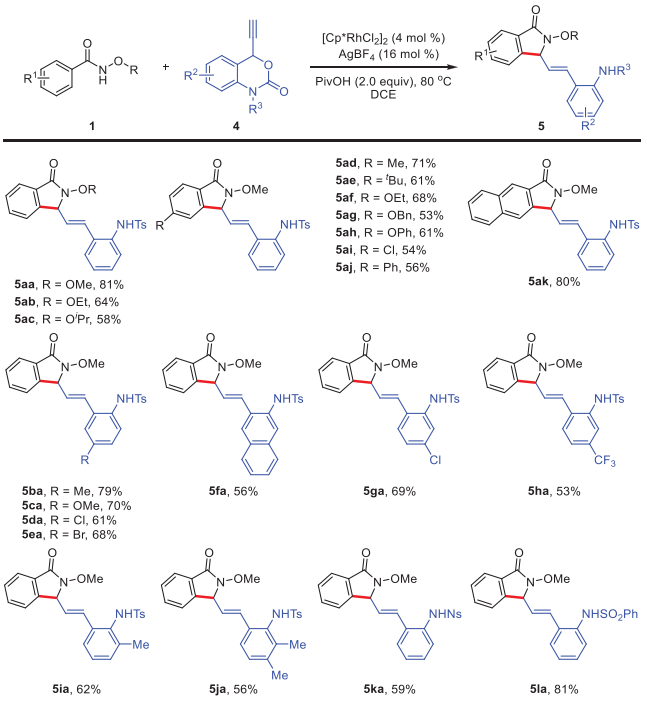
[a]All reactions were performed with **1** (0.1 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), and PhCOOH (2.0 equiv) in DCM (2.0 mL) at 80 °C for 24 h under N_2. Isolated yields.

amenable to the reaction (**3ar**, dr = 1.1:1), demonstrating the potential of further poststage functionalization.

We then moved on to survey the scope of cyclic propargylic carbamates under optimal condition. As shown in Scheme 3, various functionalized internal alkynes of benzoxazinanones could be transformed into the aminal products (**3ba**−**3ka**) in good to excellent yields, including a phenoxymethyl and a long alkyl chain on the alkyne terminus (**3ba** and **3ca**). Additionally, the variation of the substituent to electron-withdrawing and -donating groups at the different positions of the aryl ring all gave the corresponding products in a good overall yield (**3da**−**3ka**). Substrates with chloro, bromo, and methyl at the 6-positions also reacted smoothly to yield the products in comparable yields (**3da**−**3fa**, 70−81% yields). Besides, chloro and trifluoromethyl groups at the 7-positions were isolated in 72% and 63% yields, respectively (**3ga** and **3ha**). Surprisingly, no formation of the cyclization product was observed when a phenyl-substituted alkyne was used, and the acyclic product **3la** was obtained *via* N−H propargylation without C−H activation.

To further investigate the generality of substrates of cyclic propargylic carbamates, we next focused on studying the corresponding terminal alkynes in this transformation (Scheme 4). To our surprise, ethynyl benzoxazinanone **4a** coupled to afford a skeletally different five-membered cyclization products **5aa** with a trans-configured C=C bond in high yield with retention of the *N*-OMe group in the product. An array of benzamides containing different *N*-substituents were then examined, where the *N*-OMe-substituted benzamide **4a** still exhibited higher reactivity. We then explored benzamides

Scheme 4. Substrate Scope of Formal [4 + 1] Cycloaddition[a]

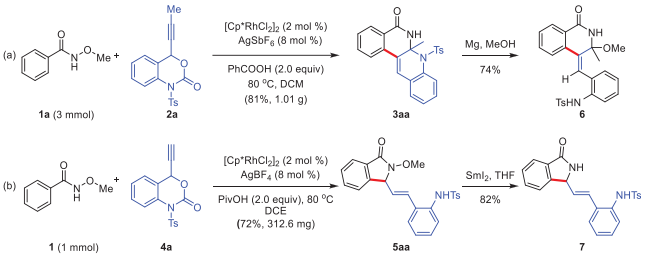


[a]Reaction conditions: **1a** (0.1 mmol), **4a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgBF_4$ (16 mol %), and PivOH (2.0 equiv) in DCE (2.0 mL) at 80 °C for 24 h under N_2. Isolated yields.

bearing diverse electron-donating, halogen, and naphthyl groups at the *para* positions, and the products were isolated in moderate to high yields (56−80%, **5ad**−**5ak**). Meanwhile, a series of propargylic carbamates, including diverse substituents in the arene ring, were also capable (**5ba**−**5la**). With respect to an electron-deficient Ns group on the nitrogen, the yield of the annulation product was still acceptable (**5ka**, 59% yield).

Synthetic utility of this methodology was determined for representative products (Scheme 5). The efficiency of this

Scheme 5. Derivatization Reactions



method on a larger scale was investigated. The six-/five-membered annulated products **3aa** and **5aa** were readily scaled up to 3 and 1 mmol, respectively, with good yields (Scheme 5a and b). It was observed that compound **3aa** could be transformed to a hemiaminal product **6** in high efficiency in the presence of a methanol solvent (Scheme 5a). Treatment of **3aa** with SmI_2 led to cleavage of the N−O bond, affording product **7** in excellent yield (Scheme 5b).

Preliminary mechanistic studies were conducted to explore the reaction mechanism (Scheme 6). First, considerable H/D exchange at the *ortho* positions was accessed by treatment of

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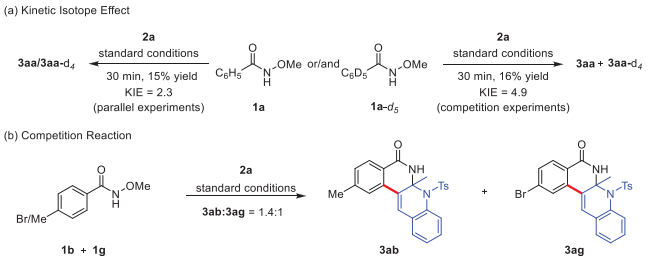
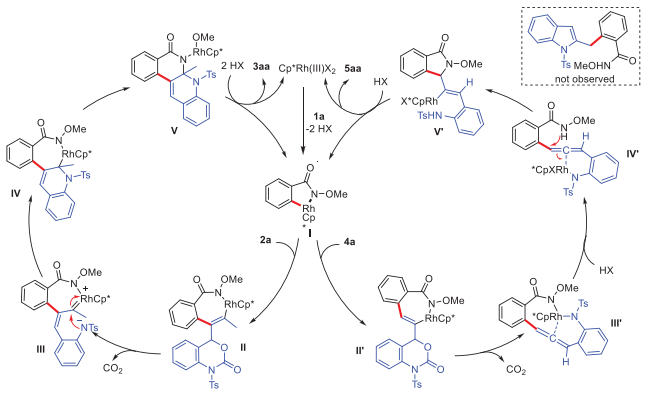
Scheme 6. Mechanistic Studies



the pentadeuterated benzamide **1a**-d_5 in the absence of **2a** under the standard condition, thus suggesting that the C−H activation step was reversible in this reaction (see the Supporting Information for more details). Moreover, the parallel (KIE = 2.3) and competition (KIE = 4.9) reactions both gave a rather large kinetic isotope effect for the synthesis of the six-membered heterocycles, suggesting that C−H cleavage might be involved in the turnover-determining step (Scheme 6a). Competitive reactions of benzamide with different electrical properties have been evaluated, and it was found that the more electron-rich benzamide **1b** (*para* Me) tends to exhibit a slightly higher reactivity (Scheme 6b).

We then proposed a substrate-dependent reaction mechanism (Scheme 7). Initially, the highly reactive rhodium(III)

Scheme 7. Proposed Mechanism for the Chemodivergent Annulations



species is generated from the Rh precatalyst $[Cp^*RhCl_2]_2$ in the presence of a Ag salt. The reaction likely commences with chelation-assisted C−H activation, leading to a five-membered rhodiumcycle **I** upon cyclometalation.[16] In the case of the internal alkyne (Scheme 7 left), insertion of the propargyl carbamate **2a** is proposed to give intermediate **II**. Subsequently, this alkenyl intermediate likely undergoes elimination-decarboxylation to generate rhodium carbene species **III** with a pendent NTs nucleophile. Afterward, intramolecular nucleophilic addition of the NTs group to the carbene results in the formation of a rhodium alkyl **IV**. Finally, the desired product **3aa** was furnished after a reductive elimination/N−O bond oxidative addition sequence,[17] thereby regenerating the active Rh(III) complex. For a terminal alkyne such as ethynyl benzoxazinanone **4a** (Scheme 7 right), β-oxygen elimination-decarboxylation of the related alkenyl intermediate **II′** then produces an allene intermediate **III′**.[13] A subsequent intramolecular nucleophilic cyclization of the benzamide further gives rise to alkenyl intermediate **V′**, and protonolysis eventually affords the isoindolin-1-one product and completes the catalytic cycle. In this system, the indole product resulting from nucleophilic addition of the NTs group was not detected, possibly due to the steric and electronic effects of the nitrogen nucleophile, which stays contrast to Glorius report in Mn-catalysis.[13] On the basis of the structure of the products, we rationalized that the chemodivergence originates from the regioselectivity of the alkyne insertion. In the case of the terminal alkyne, the rhodium is proximal to the oxygen leaving group to allow for β-elimination.

In summary, we have developed substrate-dependent annulation systems for efficient synthesis of two classes of functionalized *N*-heterocycles by Rh(III) catalyzed C−H activation of benzamides. The coupling of benzoxazinanone with an internal alkyne unit afforded 1,8-naphthyridines. In contrast, isoindolin-1-ones skeletons were accessed from benzoxazinanone with a terminal alkynyl group. The chemodivergence likely originates from the different regioselectivity of the alkyne insertion. These new transformations may garner significant attention from the synthetic community for their good compatibility of functional groups. Moreover, the asymmetric synthesis of other *N*-heterocycles containing chiral centers will be further explored in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02371.

Experimental details, characterization data (PDF)

Accession Codes

CCDC 2268962 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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