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Rh(III)-Catalyzed Cascade Annulations To Access Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones via C−H Activation: Synthesis of Rosettacin

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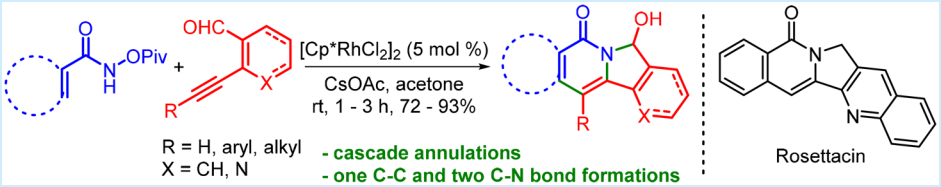
Supporting Information



ABSTRACT: An efficient protocol for the synthesis of diversely substituted 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones from the reaction of *N*-(pivaloyloxy)benzamides with 2-alkynyl aldehydes has been developed, which proceeds through sequential alkyne insertion followed by addition of the amide nitrogen on to the aldehyde. This method provided the products with aminal functionality as a handle for further diversification. The synthetic utility of this strategy was successfully illustrated by the concise, two-step synthesis of an alkaloid, rosettacin, and a topoisomerase I inhibitor.

Indolizin-5(3*H*)-ones fused with aromatic or heteroaromatic units are key structural frameworks embedded in various natural products (Figure 1) such as camptothecin, rosettacin,

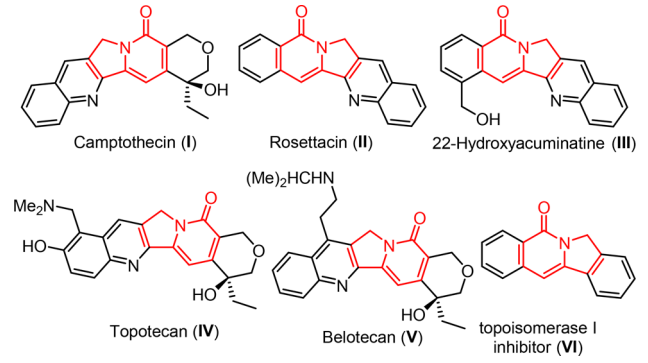


Figure 1. Representative compounds with an indolizin-5(3*H*)-one structural motif.

22-hydroxyacuminatine, and synthetic compounds (camptothecin analogues, e.g., topotecan, belotecan) that exhibit a wide range of interesting biological and medicinal properties.[1−3] Consequently, several strategies have been developed to synthesize these important scaffolds[4,5] including a recently developed flexible strategy to various natural products by Gao and co-workers.[4a] Nonetheless, conceptually different synthetic approaches that provide an access to diversification are still of great interest.

Transition-metal-catalyzed annulation reactions via C−H activation have gained importance as a powerful step- and atom-economical method for the construction of complex molecules.[6] In particular, [Cp*Rh^{III}]-catalyzed direct aryl C−H functionalization toward the insertion of alkyne into aromatic substances holding different directing groups is one of the widely explored reactions, leading to diverse heterocyclic compounds.[7] Fagnou and co-workers discovered that the *N*-pivaloyloxy group can act as a directing group as well as an internal oxidant through N−O bond cleavage during the synthesis of isoquinolones (Figure 2a).[8] Later, this directing group was extensively used in [Cp*Rh^{III}]-catalyzed coupling reactions with alkynes to access isoquinolone derivatives.[9] In 2014, Lin and co-workers identified a novel cascade reaction of O-substituted *N*-hydroxybenzamides with cyclohexadienone-

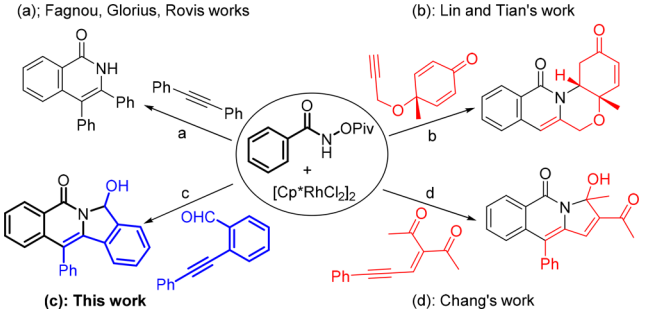


Figure 2. Rh(III)-catalyzed annulations of *N*-(pivaloyloxy)benzamide with alkynes.

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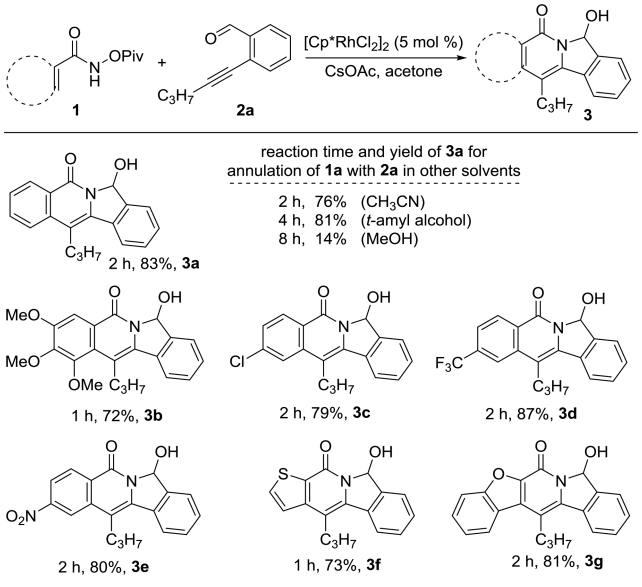
containing 1,6-enynes to obtain *N*-substituted isoquinolones through alkyne insertion followed by aza-Michael addition reaction (Figure 2b).[10] Encouraged by these findings, we envisioned a new cascade annulation of *N*-(pivaloyloxy)-benzamides with 2-alkynyl aldehydes involving sequential isoquinolone formation/addition of NH on to aldehyde (to give the aminal). The successful development of this annulation would lead to an unprecedented facile synthesis of 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones (Figure 2c), which could be readily transformed into polycyclic indolizin-5(3*H*)-ones and their analogues. In continuation of our work on alkyne-assisted annulations,[11] herein we report the results of the above proposed reaction and the total synthesis of rosettacin via rhodium(III)-catalyzed C−H activation cascade annulations. As far as we are aware, such a strategy comprising alkyne insertion followed by the addition of NH on to aldehyde (aminal formation) had not been reported. Very recently, however, while our work was in progress, Chang's research group reported the annulation of *N*-pivaloyloxy benzamide with conjugated enynones to access the tricyclic isoquinolinones (Figure 2d).[12] Nevertheless, there are sufficient differences between the two methods to warrant a further communique on the new work undertaken.

We commenced our studies with the reaction between *N*-(pivaloyloxy)benzamide (**1a**) and 2-(pent-1-yn-1-yl)-benzaldehyde (**2a**). It was observed that the reaction proceeded smoothly in the presence of [$(Cp^*RhCl_2)_2$] (5 mol %) and CsOAc (2 equiv) in acetone at room temperature to give 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-one **3a** in 83% yield in 2 h (Scheme 1). A similar result was observed in other solvents like CH_3CN (2 h, 76%) as well as in *tert*-amyl alcohol (4 h, 81%), while in MeOH a low yield (14%) of the product **3a** was isolated along with starting materials. Having identified the optimized conditions, the scope of this cascade annulation approach was investigated, through the coupling of various *N*-(pivaloyloxy)amides with alkynyl aldehyde **2a** (Scheme 1). Hydroxamic acids containing both electron-donating (3,4,5-trimethoxy, **1b**) as well as electron-withdrawing groups such as 4-chloro (**1c**), 4-trifluoromethyl (**1d**) and 4-nitro (**1e**) smoothly participated in the double annulation without any substantial effect on the outcome of the reaction to furnish the corresponding 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **3b−e** in 72−87% yield. It is noteworthy that the present cascade process was not limited to *N*-(pivaloyloxy)benzamides, but it could also be extended to *N*-(pivaloyloxy)heteroaryl carboxamides. This was successfully tested by the reactions of *N*-(pivaloyloxy)thiophene-2-carboxamide (**1f**) and benzofuran-2-carboxamide (**1g**) with **2a** to obtain the annulated products **3f** (73%) and **3g** (81%), respectively.

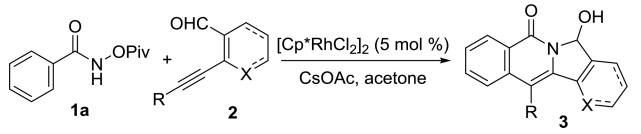
We also evaluated the scope of the reaction with respect to 2-alkynyl aldehyde substrates (Table 1). The annulation reactions of (2-alkynyl) benzaldehydes bearing *n*-butyl (**2b**), cyclopropyl (**2c**), cyclohexyl (**2d**), 2-hydroxyethyl (**2e**), and phenyl (**2f**) with **1a** afforded the corresponding 12-substituted 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **3h−l** in good yields, indicating that neither the alkyl nor aryl group on the alkyne functionality influenced the reaction outcome. Note in

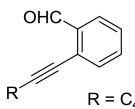
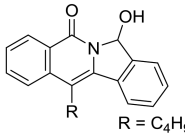
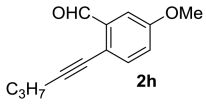
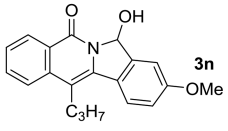
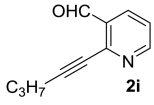
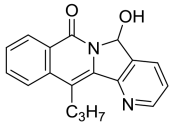
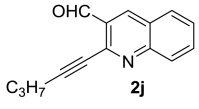
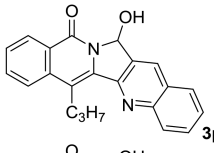
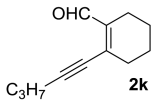
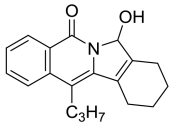
Scheme 1. Optimization and Sope of *N*-(Pivaloyloxy)amides[a,b]



[a]Unless otherwise specified, **1** (1.5 equiv), **2a** (0.29 mmol), [Cp^*RhCl_2]$_2$ (5 mol %), and CsOAc (0.58 mmol) in acetone (2 mL) was stirred for the given time at rt. [b]Isolated yields.

Table 1. Reaction of 1a with Various 2-Alkynyl Aldehydes[a]



entry	alkynyl aldehyde	time (h)	product	yield (%)[b]
1	 R = C_4H_9, **2b**	1	 R = C_4H_9, **3h**	85
2	R = cyclopropyl, **2c**	2	R = cyclopropyl, **3i**	93
3	R = cyclohexyl, **2d**	2	R = cyclohexyl, **3j**	91
4	R = CH_2CH_2OH, **2e**	1.5	R = CH_2CH_2OH, **3k**	90
5	R = Ph, **2f**	1	R = Ph, **3l**	81
6	R = H, **2g**	1	R = H, **3m**	72
7	 **2h**	3	 **3n**	93
8	 **2i**	2.5	 **3o**	82
9	 **2j**	2	 **3p**	85
10	 **2k**	2	 **3q**	78

[a]Unless otherwise specified, **1a** (0.3 mmol), **2** (0.2 mmol), [Cp^*RhCl_2]$_2$ (5 mol %), and CsOAc (0.4 mmol) in acetone (2 mL) was stirred for the given time at rt. [b]Isolated yield.

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particular that 2-ethynylbenzaldehyde (**2g**) participated in this rhodium-catalyzed C−H activation and cascade annulation reaction with **1a** under the optimal conditions to afford **3m** in 72% yield, which suggests that a terminal alkyne group is well tolerated. 2-(Pent-1-yn-1-yl)benzaldehyde containing OMe substitution on the phenyl ring **2h** successfully underwent the reaction to give **3n** in 93% yield. Additionally, when the phenyl group was replaced by a heteroaromatic ring, the corresponding products were still obtained in high yield. For instance, 2-(pent-1-yn-1-yl)nicotinaldehyde (**2i**) and 2-(pent-1-yn-1-yl)-quinoline-3-carbaldehyde (**2j**) furnished the corresponding annulated products **3o** (82%) and **3p** (85%), respectively. To our delight, a cyclohexene ring (**2k**) could be used instead of the benzene ring in the alkynyl aldehyde, leading to the corresponding isoquinolin-5(7*H*)-one **3q** in 78% yield. Based on the results obtained, we believe that the reaction proceeds (Figure 3) via alkyne insertion into the five-membered

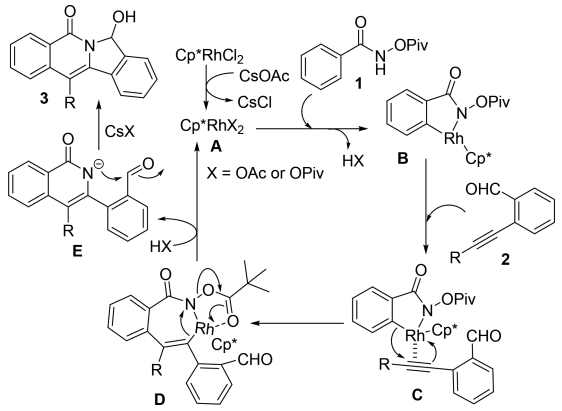
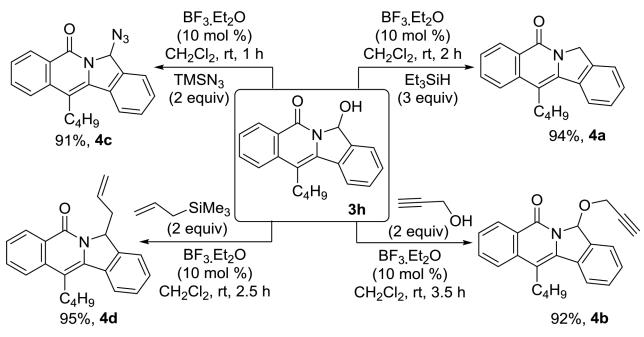


Figure 3. Plausible reaction pathway.

rhodacycle **B**, C−N bond reductive elimination with N−O bond cleavage (**C** and **D**) and base-mediated addition of amide NH on to aldehyde (**E**), similar to the cascade reactions reported by Lin et al. and Chang et al.[10,12] They have extensively studied various experiments to understand and support their proposed reaction pathway.

To exemplify the practical applicability of this protocol, a gram-scale reaction under the standard conditions was conducted to obtain **3h** in 85% yield. Various transformations of this 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-one were also explored (Scheme 2). For example, the reaction of **3h** with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ (10 mol %) in CH_2Cl_2 underwent the reduction of hemiaminal to give isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (a commonly found structural motif

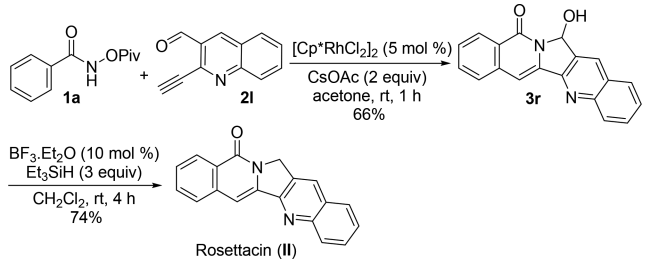
Scheme 2. Diversification of Aminal 3h[a]



in several bioactive natural products) **4a** in 94% yield. Likewise, the treatment of **3h** with other nucleophiles such as propargylic alcohol, TMS-N_3 and allyltrimethyl silane under $BF_3.Et_2O$ (10 mol %)/CH_2Cl_2 conditions offered the functionalized isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones **4b** (92%), **4c** (91%), and **4d** (95%) via C−O, C−N, and C−C bond formations, respectively.

In order to showcase the synthetic value of this Rh(III)-catalyzed cascade reaction, we decided to carry out the total synthesis of rosettacin (**II**). Rosettacin, one of the aromathecin alkaloids, is used as camptothecin/luotonin A hybrid for binding to the topo-I/DNA covalent binary complex.[2e,f] To date, the total synthesis of rosettacin has been accomplished by nine research groups.[4,13] For instance, the groups of Glorius[13a] and Park[13b] have independently reported the synthesis of **II** in more than five steps employing an intramolecular annulation as the key reaction. We have accomplished the synthesis of rosettacin via the present intermolecular annulation between *N*-(pivaloyloxy)benzamide (**1a**) and 2-ethynylquinoline-3-carbaldehyde (**2l**) in two steps (Scheme 3). The reaction of **1a** with

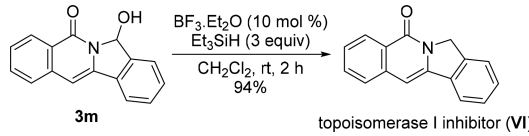
Scheme 3. Total Synthesis of Rosettacin



2l, under the developed conditions, provided the corresponding diannulated product **3r** in 66% yield. The reduction of aminal of **3r** in the presence of $BF_3{\cdot}Et_2O$ (10 mol %)/Et_3SiH in CH_2Cl_2 afforded the rosettacin (**II**) in 74% yield (Scheme 3). This approach was amenable to the synthesis of various analogues of rosettacin through the acid-catalyzed substitution reactions of the annulated product **3r** with different nucleophiles.

Additionally, the isoquinolin-5(7*H*)-one **3m** was transformed into the topoisomerase I inhibitor, isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one **VI**, in 94% yield (Scheme 4). It is important to mention that there are four synthetic approaches known for the synthesis of **VI** to date, each involving harsh conditions or multistep reaction sequence.[2c,4b,14]

Scheme 4. Synthesis of Topoisomerase I Inhibitor



In conclusion, we have developed a one-pot efficient method for the synthesis of 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones from *N*-(pivaloyloxy)amides and 2-alkynyl aldehydes by Rh(III)-catalyzed C−H functionalization. Both aryl and heteroaryl substrates having different substituents were found to be effective coupling partners. Moreover, the present reactions are first examples of cascade Rh(III)-catalyzed alkyne insertion/intramolecular amide nitrogen addition to aldehydes.

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The significance of the products having aminal functionality was shown by further diversification through substitutions in the five-membered ring. Additionally, the application of this method in a short synthesis of rosettacin and topoisomerase I inhibitor was also demonstrated. The flexibility and the extensive scope of this cascade annulation approach should find applications in the synthesis bioactive natural product-like molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03509.

Experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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