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Intramolecular cascade annulation triggered by C—H activation via rhodium hydride intermediate

Liangliang Song[a], Xiaoyong Zhang[b], Guilong Tian[a,*], Koen Robeyns[c], Luc Van Meervelt[d], Jeremy N. Harvey[b,*], Erik V. Van der Eycken[a,e,*]

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven Celestijnenlaan 200F, 3001, Leuven, Belgium
[b] Department of Chemistry, KU Leuven Celestijnenlaan 200F, 3001, Leuven, Belgium
[c] IMCN, Molecules Solids and Reactivity division (MOST), Université catholique de Louvain, Place Pasteur 1, 1348 Louvain-la-Neuve, Belgium
[d] Biomolecular Architecture, Department of Chemistry, KU Leuven Celestijnenlaan 200F, 3001, Leuven, Belgium
[e] Peoples' Friendship University of Russia (RUDN University), 6 Miklukho-Maklaya Street, Moscow, 117198, Russia

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ABSTRACT

A novel intramolecular cascade annulation of *O*-substituted *N*-hydroxybenzamides for the synthesis of indolizinones triggered by rhodium(III)-catalyzed sequential C(sp^2)-H activation and C(sp^3)-H amination is developed. This method features air as the oxidant, a broad substrate scope and excellent functional-group tolerance, including various heterocyclic substrates. The applicaton of indolizinone products with aminal functionality is demonstrated by further derivatization. Mechanistic studies and DFT calculations indicate that two pathways are involved in the formation of indolizinones via rhodium hydride intermediate.

1. Introduction

Transition-metal-catalyzed C—H activation and functionalization has played a prominent role in synthetic organic chemistry in the last decade [[1]]. Especially rhodium(III)-catalyzed C—H activation followed by annulation with 2π components (such as alkenes, alkynes) has received significant interest for constructing N-heterocycles and carbocycles because of its high efficiency, selectivity and functional-group tolerance [[2]]. For intermolecular annulation reactions, most of them result in the formation of a single ring, suffering from uncontrolled regioselectivity, which inevitably leads to mixtures of positional isomers, especially when unsymmetrical alkynes are employed [1e,2i,2j,3]. When sequential twofold C–H activation and couplings or combination of C—H activation/coupling and further interactions with a proximal group is accessed, polycycles can be built, providing an efficient strategy for the construction of important complicated scaffolds [4]. However, intramolecular annulations can make it much easier to achieve high regioselectivity and to form the polycycles common in complex molecules [5].

Heterocycles are widely included in potential medicine candidates because of their ability to improve aqueous solubility, reduce lipophilicity and form hydrogen bonds with biomolecules [6]. Nevertheless, for medicinally important heterocyclic substrates, C—H activation and functionalization has limited applications as heterocycles usually coordinate strongly to metal catalysts, leading to either poisoning or undesired selectivity [7]. Although several approaches have been established to provide

significant improvements in C—H activation and functionalization of heterocycles, they are mainly limited to specific transformations and narrow substrate scope [7c,8].

Tetracyclic scaffolds exist widely in natural products, e.g. in pharmacologically relevant rosettacin [5b,[9]], oxypalmatine [10], lycorine [11], norketoyobyrine [12], mappicine [13] and camptothecin [9d,14] (Fig. 1), which have noteworthy potent antitumor, antiviral and anticholinesterase activities. Although several methods for the construction of these scaffolds have been accomplished [10–14], most of them need many steps or harsh conditions. Therefore it is necessary to develop novel synthetic methodologies for the synthesis of tetracyclic scaffolds.

Moreover, using air as oxidant is better than pure oxygen, because it is costless, easier to handle and much safer [15]. Based on our previous studies on the construction of polycycles through Rh^{III}-catalyzed C(sp^2)-H activation [16], we set out to investigate whether a Rh^{III}-catalyzed sequential C(sp^2)-H activation and C(sp^3)-H amination of hydroxamic esters would constitute a route for the synthesis of indolizinones under air (Scheme 1). An irreversible C–H bond cleavage of substrate **1** to produce a five-membered rhodacycle followed by coordination with the alkyne affords intermediate **Int-A**. This could then undergo insertion

* Corresponding authors.
E-mail addresses: guilongtian6@gmail.com (G. Tian), jeremy.harvey@kuleuven.be (J.N. Harvey), erik.vandereycken@kuleuven.be (E.V. Van der Eycken).

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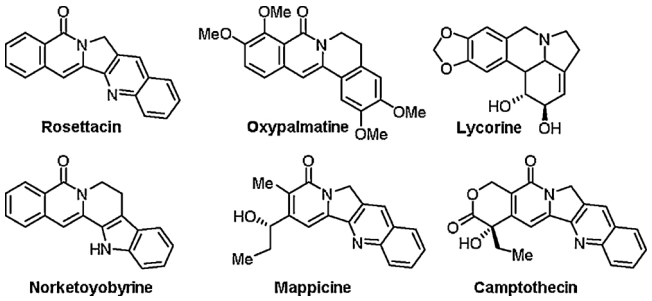
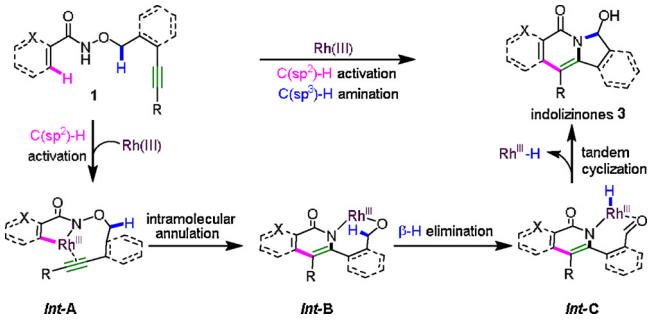


Fig. 1. Selected examples of natural products with a tetracyclic scaffold.



Scheme 1. Our Design.

into the Rh-C bond, reductive elimination and oxidative addition into the N–O bond to give intermediate **Int-B**, which could undergo β-H elimination to form rhodium hydride intermediate **Int-C**. Tandem cyclization would then afford the desired indolizinones **3**, with regeneration of the catalyst *via* oxidation of the rhodium hydride species. However, due to the involvement of a rhodium hydride species, and the need to form two C−N bonds and one C−C bond selectively in a one-pot cascade, the proposed process is clearly highly challenging. While our work was ongoing, Reddy reported a Rh^{III}-catalyzed intermolecular annulation for the synthesis of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones [4 m]. However, their substrate scope was limited to terminal or alkyl substituted alkynes.

2. Experimental

2.1. Materials and methods

Substrates **1p** and **1s-v** were synthesized from reported literature [5b]. Commercially available reagents were used without additional purification. Column chromatography was performed with silica gel (70-230 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM (300 or 400 or 600 MHz) spectrometer at ambient temperature using $CDCl_3$ or DMSO-d_6 as solvent. HRMS (ESI) spectrometry data were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer [Synapt G2 high definition mass spectrometer (HDMS), Waters, Milford, MA]. Samples were infused at 3 μL min^{-1}, and spectra were obtained in the positive ionization mode with a resolution of 15,000 [full width at half maximum (FWHM)] with leucine encephalin as lock mass. Melting points were recorded on a Reichert Thermovar apparatus and are uncorrected. For ^{13}C spectra, compounds with some symmetry have less number of signals than the corresponding number of signals of molecular formula. In some cases, some signals are overlapped.

2.2. Preparation of substrates *1a-n, 1q and 1w-c'*

To a 100 mL round-bottom flask [5b], under N_2, was added 2-((2-ethynylbenzyl)oxy)isoindoline-1,3-dione (5.0 mmol), $PdCl_2(PPh_3)_2$ (0.25 mmol), CuI (0.25 mmol) and anhydrous TEA (20 mL). The mixture was stirred at room temperature for 1 min and then PhI (6.0 mmol) was added. The flask was placed in a preheated oil bath (60 °C). The reaction was stirred overnight and then cooled to room temperature and checked by TLC. The reaction was filtered over celite, washing with dichloromethane. The solvent was removed and the residue purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 6:1 to 1:1) to afford 2-((2-(phenylethynyl)benzyl)oxy)isoindoline-1,3-dione.

In a 100 mL round-bottom flask was charged 2-((2-(phenylethynyl) benzyl)oxy)isoindoline-1,3-dione (3.0 mmol) [5b], solvent 15 mL [MeOH/DCM (1:2)], and then slowly added hydrazine monohydrate (3.3 mmol), then stirred at room temperature for 4 h. Upon completion (indicated by TLC), the solvent was then removed under reduce pressure. The residue was washed with DCM and filtered, collected the DCM part and removed the solvent to give the crude *O*-alkoxylamine, which was used in next step without further purification.

The crude *O*-alkoxylamine which was obtained in the previous step was added to a biphasic mixture of K_2CO_3 (3.6 mmol) in solvent 15 mL [EA/H_2O (2:1)] [5b]. The resulting solution was cooled to 0 °C followed by dropwise addition of the acid chloride (3.3 mmol) dissolved in a minimum amount of EtOAc. The reaction was allowed to stir at same temperature for 6 h. Upon completion (indicated by TLC), the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 4:1 to 1:1) to give the product **1a-n**, **1q** and **1w-c'**.

2.3. Preparation of substrate *1o*

To a 100 mL round-bottom flask, under N_2 [5b], was added 2-((2-bromobenzyl)oxy)isoindoline-1,3-dione (5.0 mmol), $PdCl_2(PPh_3)_2$ (0.25 mmol), CuI (0.25 mmol) and anhydrous TEA (20 mL). The mixture was stirred at room temperature for 1 min and then alkyne (6.0 mmol) was added. The flask was placed in a pre-heated oil bath (60 °C). The reaction was stirred overnight and then cooled to room temperature and checked by TLC. The reaction was filtered over celite, washing with dichloromethane. The solvent was removed and the residue purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 6:1 to 1:1) to afford 2-((2-(4-phenylbut-1-yn-1-yl)benzyl)oxy)isoindoline-1,3-dione.

In a 100 mL round-bottom flask was charged 2-((2-(4-phenylbut-1-yn-1-yl)benzyl)oxy)isoindoline-1,3-dione (3.0 mmol), solvent 15 mL [MeOH/DCM (1:2)] [5b], and then slowly added hydrazine monohydrate (3.3 mmol), then stirred at room temperature for 4 h. Upon completion (indicated by TLC), the solvent was then removed under reduce pressure. The residue was washed with DCM and filtered, collected the DCM part and removed the solvent to give the crude *O*-alkoxylamine, which was used in next step without further purification.

The crude *O*-alkoxylamine which was obtained in the previous step was added to a biphasic mixture of K_2CO_3 (3.6 mmol) in solvent 15 mL [EA/H_2O (2:1)] [5b]. The resulting solution was cooled to 0 °C followed by dropwise addition of the acid chloride (3.3 mmol) dissolved in a minimum amount of EtOAc. The reaction was allowed to stir at same temperature for 6 h. Upon completion (indicated by TLC), the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 4:1 to 1:1) to give the product **1o**.

2.4. Preparation of substrate *1r*

To a 100 mL round-bottom flask [5b], under N_2, was added 2-chloro-3-quinolinecarboxaldehyde (5.0 mmol), $PdCl_2(PPh_3)_2$

(0.25 mmol), CuI (0.25 mmol) and anhydrous TEA (20 mL). The mixture was stirred at room temperature for 1 min and then (tert-butyldimethylsilyl)acetylene (6.0 mmol) was added. The flask was placed in a preheated oil bath (60 °C). The reaction was stirred overnight and then cooled to room temperature and checked by TLC. The reaction was filtered over celite, washing with dichloromethane. The solvent was removed and the residue purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 10:1 to 4:1) to afford 2-((tert-butyldimethylsilyl)ethynyl)quinoline-3-carbaldehyde.

A solution of 2-((tert-butyldimethylsilyl)ethynyl)quinoline-3-carbaldehyde (4.0 mmol) in THF (10 mL) and water (1 mL) was cooled to 0 °C, $NaBH_4$ (4.8 mmol) was then added [5b]. After stirring for a further period of 1 h, the reaction was completed as indicated by TLC. The reaction mixture was extracted twice with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure, affording the crude product, which was used in next step without further purification.

To a stirring solution of CBr_4 (7.2 mmol) in DCM (12 mL), a solution of crude product from the previous step in DCM was added to the resulting mixture at 0 °C [17]. After stirring for another 5 min, a solution of PPh_3 (8.0 mmol) in DCM was added dropwise at 0 °C. The reaction media was then stirred at 0 °C for 1 h (judging by TLC analysis). The solution was concentrated in *vacuo*. The obtained crude product was purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 20:1 to 10:1) to give the desired product 3-(bromomethyl)-2-((tert-butyldimethylsilyl)ethynyl)quinoline.

To a stirred mixture of *N*-hydroxyphthalimide (3.0 mmol) and 3-(bromomethyl)-2-((tert-butyldimethylsilyl)ethynyl)quinoline (3.3 mmol) in DMF (6 mL) was added DBU (3.6 mmol) slowly at ambient temperature [18]. After completion of the addition, water (20 mL) was added, and the precipitate was filtered off and washed with water to afford 2-((2-((tert-butyldimethylsilyl)ethynyl)quinolin-3-yl)methoxy)isoindoline-1,3-dione used in next step without further purification.

In a 100 mL round-bottom flask was charged 2-((2-((tert-butyldimethylsilyl)ethynyl)quinolin-3-yl)methoxy)isoindoline-1,3-dione (3.0 mmol) [5b], solvent 15 mL [MeOH/DCM (1:2)], and then slowly added hydrazine monohydrate (3.3 mmol), then stirred at room temperature for 4 h. Upon completion (indicated by TLC), the solvent was then removed under reduce pressure. The residue was washed with DCM and filtered, collected the DCM part and removed the solvent to give the crude *O*-alkoxylamine, which was used in next step without further purification.

The crude *O*-alkoxylamine which was obtained in the previous step was added to a biphasic mixture of K_2CO_3 (3.6 mmol) in solvent 15 mL [EA/H_2O (2:1)] [5b]. The resulting solution was cooled to 0 °C followed by dropwise addition of the acid chloride (3.3 mmol) dissolved in a minimum amount of EtOAc. The reaction was allowed to stir at same temperature for 6 h. Upon completion (indicated by TLC), the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-heptane/ethyl acetate from 4:1 to 1:1) to give the product **1r**.

2.5. Preparation of products *3a-c'* and *2a*

To a Schlenk flask equipped with a stir bar were added **1a-c'** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol) and 1,4-dioxane (3.0 mL) under air. The reaction was stirred for 8 h at 60 °C, cooled to room temperature. The solvent was removed in *vacuo* and the remaining residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 4:1 to 1:2) to afford the product **3a-c'** and **2a**.

2.6. Preparation of compounds *4a-d*

To the solution of **3a** (0.2 mmol) in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [16b]. To the resulting solution, Et_3SiH (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 4:1 to 1:1) to afford **4a**.

To the solution of **3a** (0.2 mmol) in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [16b]. To the resulting solution, propargyl alcohol (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 10:1 to 2:1) to afford **4b**.

To a suspension of **3a** (0.2 mmol) in DCE (1 mL) at room temperature was added naphthalene (2 mmol) and stirred for 10 min [19]. To this suspension, TFA (2.2 mmol) was added. The reaction mixture was heated to 75 °C and maintained for 16 h (monitored by TLC). It was then cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 10:1 to 4:1) to afford **4c**.

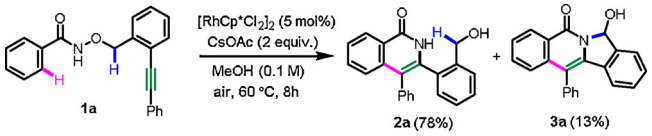
To a suspension of **3a** (0.2 mmol) in DCE (1 mL) at room temperature was added propionitrile (2.5 mmol) and stirred for 10 min [19]. To this suspension, TFA (2.2 mmol) was added. The reaction mixture was heated to 75 °C and maintained for 16 h (monitored by TLC). It was then cooled to room temperature, diluted with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 4:1 to 1:1) to afford **4d**.

2.7. Preparation of compound *5*

A 25 mL round-bottomed flask equipped with a stirring bar is charged with **3p** (0.2 mmol), *tetra-n*-butylammonium fluoride (TBAF, 1 M in THF, 0.4 mL, 0.4 mmol) and 2 mL of anhydrous THF [5b]. Then allowed to stir at room temperature for 12 h. The solvent was removed and the residue was used in next step without further purification. To the solution of above residue in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [16b]. To the resulting solution, Et_3SiH (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 4:1 to 1:1) to afford **5**.

2.8. Preparation of compound *6*

A 25 mL round-bottomed flask equipped with a stirring bar is charged with **3 r** (0.2 mmol), *tetra-n*-butylammonium fluoride (TBAF, 1 M in THF, 0.4 mL, 0.4 mmol) and 2 mL of anhydrous THF [5b]. Then allowed to stir at room temperature for 12 h. The solvent was removed and the residue was used in next step without further purification. To



Scheme 2. Initial Attempt to Synthesize Indolizinone.

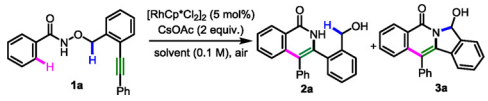
the solution of above residue in DCM (2 mL) was added $BF_3{\cdot}Et_2O$ (0.2 mmol) at 0 °C and stirred for 5 min [16b]. To the resulting solution, Et_3SiH (0.6 mmol) dissolved in DCM (1 mL) was added dropwise for 5 min at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The residue was purified by a silica gel column chromatography (*n*-heptane/ethyl acetate from 2:1 to 1:2) to afford **6**.

3. Results and discussion

Our initial attempt began with the reaction of hydroxamic ester **1a** using 5 mol% $[RhCp^*Cl_2]_2$ as the catalyst and CsOAc (2 equiv.) as the base. When the reaction was conducted in MeOH at 60 °C for 8 h, the envisaged indolizinone **3a** was obtained in 13% yield, and structurally characterized by X-ray crystallography. Isoquinolone **2a** was also observed in 78% yield (Scheme 2).

With these promising results in hand, we began to optimize the reaction conditions (Table 1). Solvent screening with 1,4-dioxane, DMF, toluene, DCE, THF, CH_3CN and acetone, identified 1,4-dioxane as the preferred medium for reaction, giving **3a** in 52% yield, together with **2a** in 35% yield (Table 1, entries 2–8). The alternative catalyst [Ru(*p*-cymene)$Cl_2]_2$, gave a very poor conversion of **3a** (Table 1, entry 9). Increased or decreased temperature did not improve the yield of **3a** (Table 1, entries 10–11). The employment of a longer reaction time gave **3a** in 49% yield (Table 1, entry 12). Increasing the catalyst loading to 10 mol%, delivered **3a** in 55% yield (Table 1, entry 13). Decreasing the catalyst loading to 2.5 mol%, afforded **3a** in 31% yield (Table 1, entry 14). Without CsOAc, the reaction worked very slowly (Table 1, entry 15). Further, when the reaction was performed for only 30 min under optimized conditions, the products **3a** and **2a** were obtained in 12% and 16% yields, respectively (Table 1, entry 16). This indicated that **3a** was formed from the beginning.

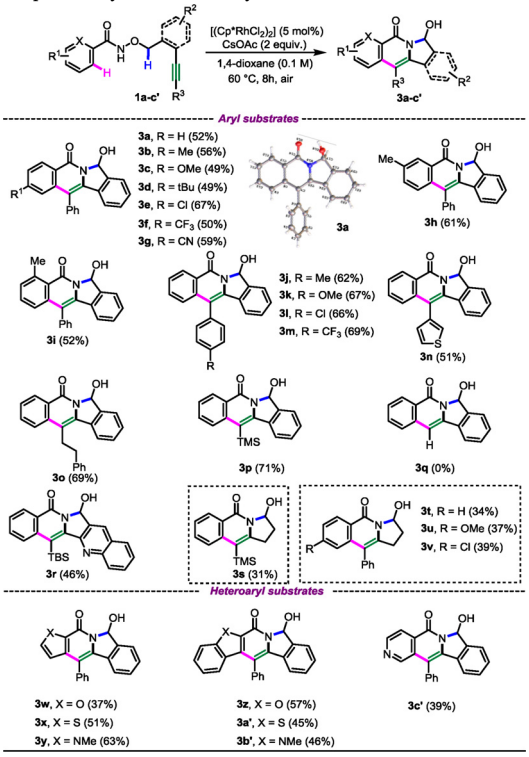
Table 1
Optimization of the Reaction Conditions.[a].



Entry	Solvent	T (°C)	T (h)	Yield(3a, 2a)[b]
1	MeOH	60	8	(13%, 78%)
2	**1,4-Dioxane**	**60**	**8**	**(52%, 35%)**
3	DMF	60	8	(10%, 46%)
4	Toluene	60	8	(21%, 51%)
5	DCE	60	8	(15%, 62%)
6	THF	60	8	(41%, 45%)
7	CH_3CN	60	8	(26%, 58%)
8	Acetone	60	8	(31%, 47%)
9[c]	1,4-Dioxane	60	8	(< 5%, 62%)
10	1,4-Dioxane	40	8	(42%, 37%)
11	1,4-Dioxane	80	8	(41%, 51%)
12	1,4-Dioxane	60	16	(49%, 32%)
13[d]	1,4-Dioxane	60	8	(55%, 28%)
14[e]	1,4-Dioxane	60	8	(31%, 51%)
15[f]	1,4-Dioxane	60	8	(9%, 21%)
16	1,4-Dioxane	60	0.5	(12%, 16%)

[a] Conditions: **1a** (0.3 mmol), catalyst (0.015 mmol), CsOAc (0.6 mmol), solvent (3.0 mL).
[b] Isolated yield.
[c] [Ru(*p*-cymene)$Cl_2]_2$ (5 mol%) was used instead of $[RhCp^*Cl_2]_2$.
[d] $[RhCp^*Cl_2]_2$ (10 mol%) was used.
[e] $[RhCp^*Cl_2]_2$ (2.5 mol%) was used.
[f] Without CsOAc.

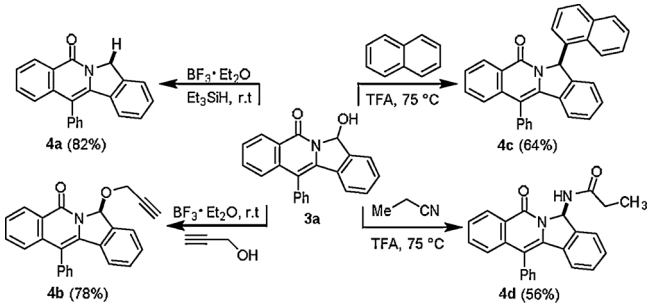
Table 2
Scope for Aryl and Heteroaryl Substrates.[a,b].



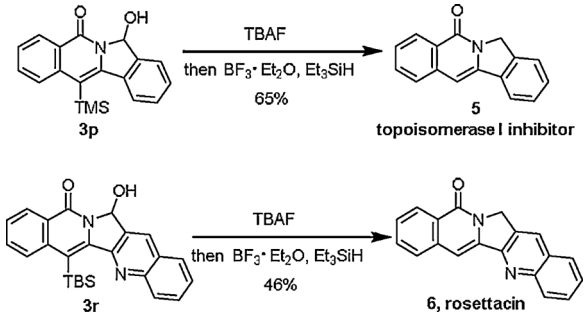
[a] Conditions: **1** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), CsOAc (0.6 mmol), 1,4-dioxane (3.0 mL).
[b] Isolated yield.

Next, various substrates were studied to evaluate the scope of the protocol under the optimized reaction conditions (Table 2). The reaction was applicable to hydroxamic esters with various electron-donating or electron-withdrawing groups at the *para* position of the benzamide moiety. The corresponding products **3b-g** were obtained in 49–67% yield. Reaction with *ortho* or *meta*-methyl benzamide also smoothly proceeded to give the corresponding indolizinone in the yields of 52% (**3i**) and 61% (**3 h**) respectively. The electronic nature of the phenyl substituent of the alkyne appeared to have limited effects on the reaction outcome, and the corresponding products **3j-m** were observed in 62–69% yield. Additionally, the phenyl group could be replaced by a heteroaryl, an aliphatic group or a TMS group without a significant impact on the results for the corresponding indolizinones **3n-p**. However, the terminal alkyne substrate could not yield the corresponding product **3q**. 2-Ethynylquinoline substrate worked well, yielding the corresponding indolizinone **3r** (46%). Furthermore, substrates with flexible tethers bearing different substituents were well tolerated, leading to the corresponding indolizinones **3s-v** in 31–39% yield. Considering the fact that heterocycles are widespread in natural products and medicines, we extended the reaction scope to heteroaryl carboxamides, such as furan, thiophene, pyrrole, benzofuran, benzothiophene and indole. They all smoothly furnished the corresponding products **3w-b'** in 37–63% yield. Even isonicotinamide substrate could deliver the corresponding indolizinone **3c'** in 39% yield.

Next various transformations of **3a** were employed (Scheme 3). Under the conditions of $BF_3{\cdot}Et_2O/Et_3SiH$, **3a** was reduced to give **4a** in 82% yield. This scaffold is involved in many natural products and



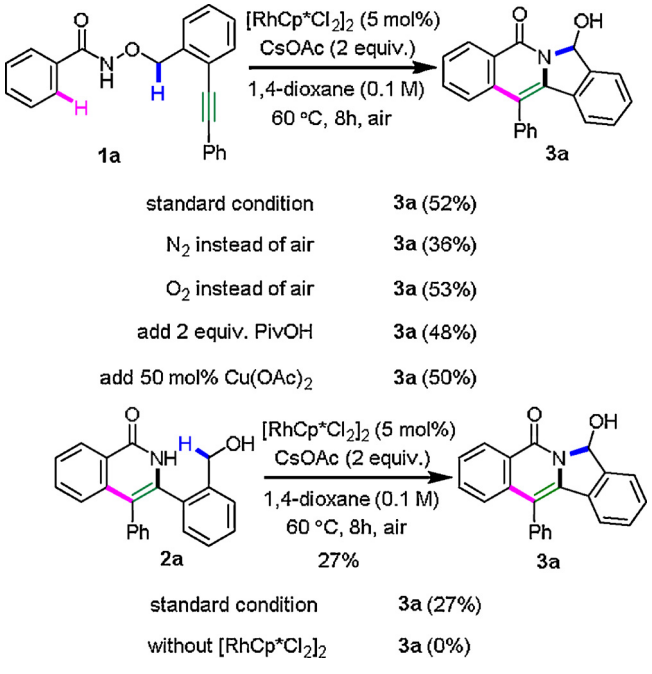
Scheme 3. Transformations of Indolizinone **3a**.



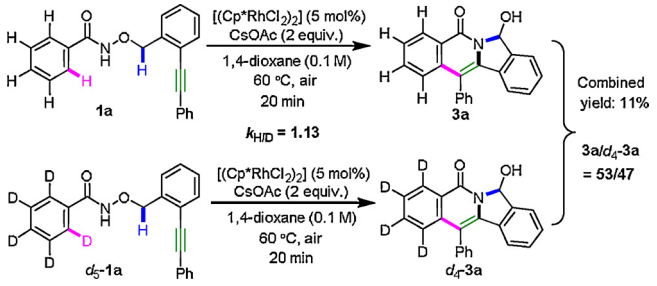
Scheme 4. Synthesis of Topoisomerase I Inhibitor and Rosettacin.

medicines. Similarly, **4b** was obtained in 78% yield through C—O bond formation from the reaction between **3a** and propargyl alcohol. Moreover, the reaction of **3a** with naphthalene in the presence of TFA was performed to afford **4c** in 64% yield *via* C—C bond formation. Likewise, **4d** was given in 56% yield through C–N bond formation by the reaction of **3a** with propionitrile. Additionally, the indolizinone **3p** could be transformed into the topoisomerase I inhibitor (**5**) in 65% yield by one pot. Similarly, indolizinone **3r** could deliver rosettacin (**6**) in 46% yield by one pot (Scheme 4) [9b,20].

To explore the mechanism of this annulation reaction, a series of experiments were performed (Scheme 5). When the reaction of **1a** was conducted under N_2, **3a** was obtained in a lower yield (36%). Using O_2



Scheme 5. Control Experiments.

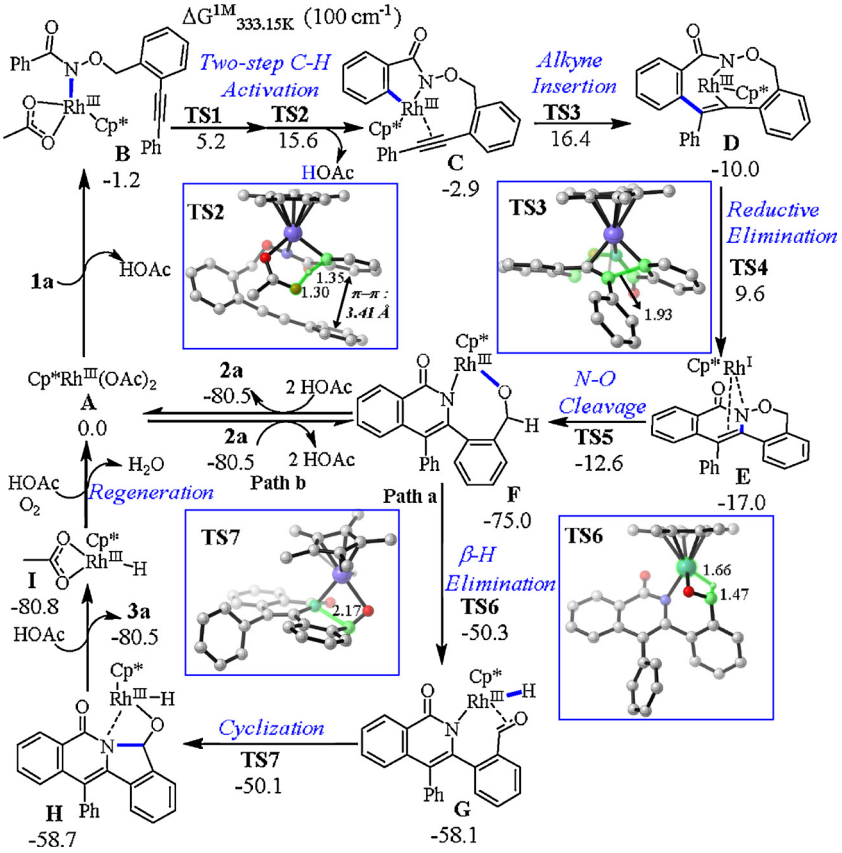


Scheme 6. Study of the Kinetic Isotope Effect.

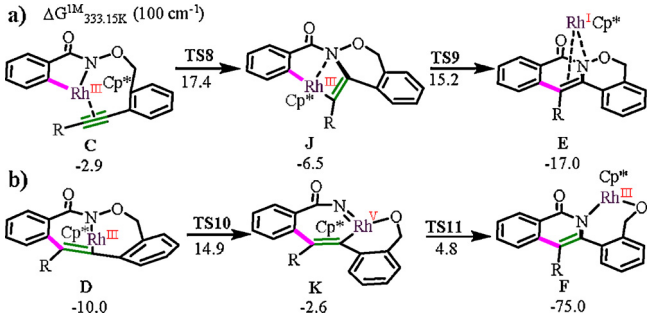
instead of air, the yield of **3a** was improved a little. These results suggest that O_2 is not essential for the reaction and air is enough to accelerate the formation of **3a**. When $Cu(OAc)_2$ as oxidant was added under N_2, no significant change was observed. With PivOH under air, the yield of **3a** decreased. Moreover, under standard conditions, **3a** could be formed from **2a** in 27% yield (just almost half of 52% yield), there was no **3a** formed from **2a** without adding $[RhCp^*Cl_2]_2$. This suggests that two pathways are involved in the construction of **3a** and **2a** is only an intermediate of minor pathway, the main pathway is leading directly to **3a** from **1a**, consistent with the above result (Table 1, entry 12). In addition, a modest kinetic isotope effect (KIE) of $k_H/k_D = 1.13$ was observed using a 1:1 ratio of **1a**/d_5-**1a** in two parallel reactions, indicating that the C–H bond cleavage process is likely not involved in the rate-limiting step (Scheme 6).

To better understand the Rh-catalyzed intramolecular annulation reaction and explore the transformation from **1a** to **3a**, the underlying mechanistic profile was constructed based on density functional theory calculation (B3LYP-D3) results focusing on **1a** as the substrate (Scheme 7). A plausible mechanism for formation of **2a** was identified, involving fairly standard C—H bond activation [21] followed by the hypothesized Rh^{III}-Rh^{I}-Rh^{III} tandem reductive elimination and N—O oxidative addition to yield intermediate **F**, which can undergo ready acetolysis to reversibly form **2a**. Direct formation of **3a** from **1a** (path a) and subsequent transformation from **2a** to **3a** (path b) were also identified. The proposed mechanism starts with substrate coordination to Cp*Rh $(OAc)_2$, which itself is known to be readily obtained from $[Cp^*RhCl_2]_2$ in presence of acetate [22]. Then, C–H activation takes place through an AMLA (ambiphilic metal-ligand assistance)/CMD (concerted metalation–deprotonation) [21] process to yield **C**. Alkyne insertion into the Rh-C bond *via* **TS3** (16.4 kcal/mol) provides intermediate **D**, which can undergo a reductive elimination over the quite demanding **TS4** (19.6 kcal/mol above **D**). The Rh^{I} intermediate **E** is able to insert into the N—O bond in a low-barrier step that is notably exothermic and should thus be irreversible. Two successive and facile protonation steps from **F** then lead to product **2a** and regeneration of catalyst. Two alternative mechanisms for the key bond formation and breaking steps were explored (Scheme 8). Insertion of the alkyne into the Rh-N bond is less facile than into the Rh-C bond, while N—O bond cleavage prior to C—N bond formation requires a Rh^{V}-nitrene intermediate **K** and was also found to be less favorable.

Additional reaction steps (β-H elimination, tandem cyclization and regeneration of catalyst) from intermediate **F** are required to form **3a**. Both β-H elimination to **G** and tandem cyclization to **H** were calculated to be energetically demanding. The tandem cyclization (**TS7**) is predicted to be overall rate-limiting, consistent with the very small kinetic isotope effect (Scheme 6), though **TS6** has a very similar calculated free energy. **TS7** lies 24.9 kcal/mol above intermediate **F** and 30.4 kcal/mol above **2a**. While this barrier may seem high, kinetic modelling (see SI) shows that it is fully consistent with the observed reactivity. After the formation and dissociation of **3a**, the resulting Rh-H intermediate **I** can be easily transformed to the catalyst *via* AcOH assisted H_2-formation pathway (see SI) or AcOH-O_2 assisted H_2O-formation pathway.



Scheme 7. Plausible Pathway of Rh^{III}-Catalyzed Annulation to Afford **2a** and **3a**.



Scheme 8. Energetic Profile (kcal/mol) of a) Pathway Involving Alkyne Insertion into the Rh-N Bond Followed by Reductive Elimination, and b) Pathway Comprised of the N—O Cleavage Prior to the C—N Bond Formation.

4. Conclusions

In conclusion, we have developed a novel intramolecular cascade annulation of *O*-substituted *N*-hydroxybenzamides for the synthesis of indolizinones *via* rhodium(III)-catalyzed sequential C(sp^2)-H activation and C(sp^3)-H amination. This method uses air as the oxidant, shows broad substrate scope and excellent functional-group tolerance, including annulation of various heterocyclic substrates, such as furan, thiophene, pyrrole, benzofuran, benzothiophene, indole and isonicotinamide. The synthetic utility of this strategy is successfully illustrated by the further derivatization of indolizinone products with aminal functionality. This method also provides an efficient approach for the total synthesis of a topoisomerase I inhibitor and rosettacin. Mechanistic studies and DFT calculations suggest that C—H bond cleavage is likely not involved in the rate-limiting step and tandem cyclization is probably the rate-limiting step in the formation of indolizinones, in which two pathways are involved through a rhodium hydride intermediate.

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