Organic LETTERS

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Rh(III)-Catalyzed Carbocyclization of 3-(Indolin-1-yl)-3-oxopropanenitriles with Alkynes and Alkenes through C−H Activation

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Supporting Information

ABSTRACT: Rh(III)-catalyzed carbocyclization reactions of 3-(indolin-1-yl)-3-oxopropanenitriles with alkynes and alkenes have been developed to form 1,7-fused indolines through C−H activation. These reactions have a broad range of substrates and high yields. Unsymmetrical aryl−alkyl substituted alkynes proceeded smoothly with high regioselectivity. Electron-rich alkynes could undergo further oxidative coupling reaction to form polycyclic compounds. For alkenes, 1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-ones were formed via C(sp^2)−H bond alkenylation and C(sp^2)−H, C(sp^3)−H oxidative coupling reactions.

The 1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one and 4-methylene-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolone skeletons can be found in numerous natural bioactive products, marketed drugs, and other functional molecules (Figure 1).[1] Most

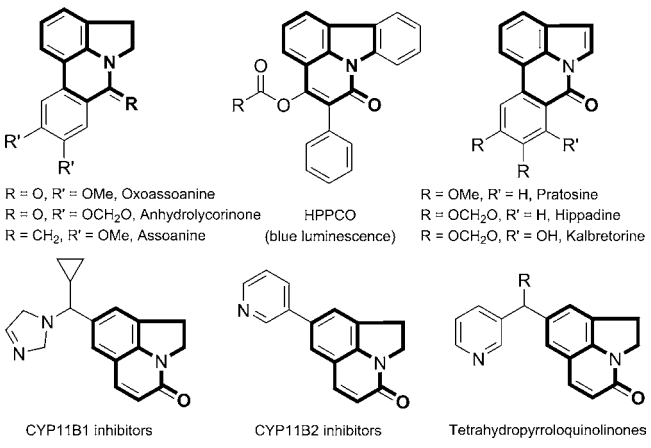
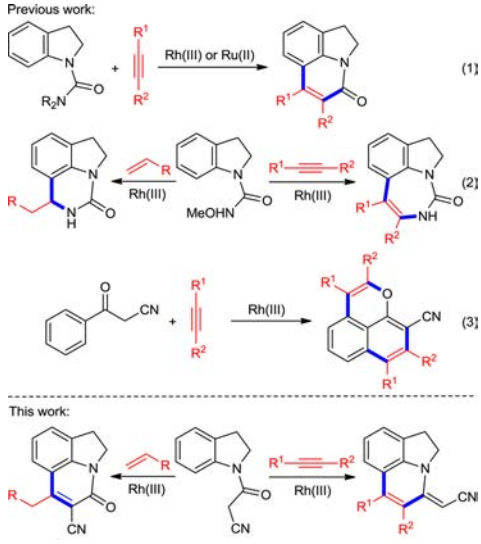


Figure 1. Representative examples contain 1,2-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-4-one or 4-methylene-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolone skeleton.

are synthesized via Fischer indolization,[1a] Pd-catalyzed annulation,[1b] or Friedel−Crafts reaction,[1d] which need multiple steps to synthesize prefunctionationalized precursors. There are limited literatures about building this motif via a direct C−H functionalization strategy (Scheme 1, eqs 1−2).[2] Thus, development of an atom-economical and environmentally friendly method for the rapid assembly of 1,7-fused indolines remains in high demand.

Scheme 1. Rh(III)- and Ru(II)-Catalyzed Annulations with Alkynes or Alkenes



Transition-metal-catalyzed C−H bond functionalization has achieved significant advancements in recent years.[3] Especially, Rh(III)-catalyzed intermolecular annulation reactions with alkynes or alkenes have proven to be a powerful method for the concise synthesis of complex cyclic molecules.[4] Among these examples, most proceed by cleavage of C−H/N−H or C−H/O−H bonds, followed by annulation with alkynes or alkenes.[4,5] In fact, the carbocyclization reactions via nucleophilic addition of

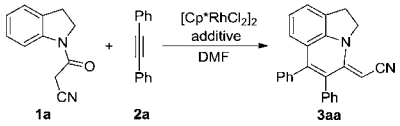
Received: August 23, 2016
Published: September 20, 2016

DOI: 10.1021/acs.orglett.6b02521
Org. Lett. 2016, 18, 5066−5069

alkenyl-metal intermediate to a polar carbonyl are particularly rare.[2a,6] The carbocyclization reactions via a C(sp^2)−H, C(sp^3)−H oxidative coupling are also very limited.[5,7] In 2012, our group reported Rh(III)-catalyzed cascade oxidative annulation reactions of benzoylacetonitriles with alkynes, affording substituted naphtha[1,8-*bc*]pyrans (Scheme 1, eq 3).[7] Herein we report Rh(III)-catalyzed carbocyclization reactions of 3-(indolin-1-yl)-3-oxopropanenitriles with alkynes and alkenes.

Treatment of *N*-substituted indoline **1a** (1.2 equiv) with diphenylacetylene **2a** (1.0 equiv) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (0.25 equiv) in DMF (0.5 mL) at 100 °C for 12 h gave the desired product (*Z*)-2-(5,6-diphenyl-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-ylidene)acetonitrile (**3aa**) in 91% yield (Table 1, entry 1). The yield of **3aa** increased to

Table 1. Optimization of Reaction Conditions[a]



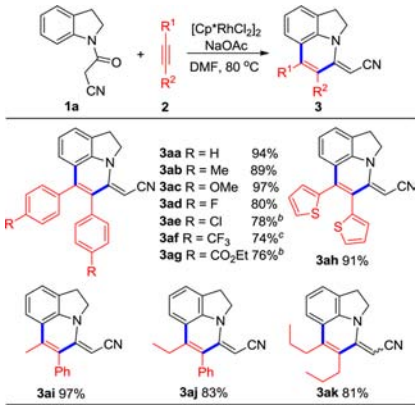
entry	cat. (mol %)	additive (equiv)	temp (°C)	yield[b] (%)
1	$[Cp^*RhCl_2]_2$ (5)	$Cu(OAc)_2{\cdot}H_2O$ (0.25)	100	91
2	$[Cp^*RhCl_2]_2$ (5)	AgOAc (0.5)	100	96
3	$[Cp^*RhCl_2]_2$ (5)	NaOAc (0.5)	100	95
4	$[Cp^*RhCl_2]_2$ (5)	NaOAc (0.5)	80	95
5	**$[Cp^*RhCl_2]_2$ (3)**	**NaOAc (0.5)**	**80**	**94**
6	$[Cp^*RhCl_2]_2$ (2)	NaOAc (0.5)	80	88
7	$[Cp^*RhCl_2]_2$ (3)	NaOAc (0.5)	60	90
8	$[Cp^*RhCl_2]_2$ (5)	none	80	nr
9	none	NaOAc (0.5)	80	nr
10	$[(p\text{-cymene})RuCl_2]_2$ (5)	NaOAc (0.5)	100	21
11	$[Cp^*IrCl_2]_2$ (5)	NaOAc (0.5)	100	trace

[a]Conditions: **1a** (0.24 mmol, 1.2 equiv), **2a** (0.2 mmol, 1.0 equiv), catalyst, additive, and DMF (0.5 mL) at the indicated temperature for 12 h, under Ar. [b]Isolated yield.

96% when 0.5 equiv of AgOAc was used instead of $Cu(OAc)_2{\cdot}H_2O$ (entry 2). Changing the additive to NaOAc afforded **3aa** in 95% yield (entry 3). Then, the effect of the loading of $[Cp^*RhCl_2]_2$ and the temperature were examined (entries 4−7). No product was observed in the absence of $[Cp^*RhCl_2]_2$ or NaOAc (entries 8−9). Some other transition metal catalysts such as $[Cp^*IrCl_2]_2$ and $[(p\text{-cymene})RuCl_2]_2$ were also tested. $[Cp^*IrCl_2]_2$ did not work, and $[(p\text{-cymene})RuCl_2]_2$ gave a low yield under the present reaction conditions (entries 10−11). Changing the CN group of **1a** to CO_2Et or NEt_3Br^- failed to give any product, suggesting that the CN group may not only work as an electron-withdrawing group but also as a codirecting group. Finally, we chose the reaction conditions of entry 5 as the standard conditions after comprehensive consideration (condition A).

With the optimal reaction conditions in hand, various substituted internal alkynes (**2a**−**k**) were treated with **1a** (Scheme 2). Most reactions proceeded smoothly to afford the corresponding products in good yields. The structures of **3aa** and **3ai** were confirmed by single-crystal X-ray diffraction analysis. Symmetrical diaryl-substituted alkynes with electron-donating groups such as methyl and methoxy groups reacted with **1a** affording the corresponding products **3ab**−**ac** in high yields. Slightly lower yields were obtained with symmetrical diaryl-substituted alkynes bearing electron-withdrawing groups with

Scheme 2. Substrate Scope of Internal Alkynes[a]

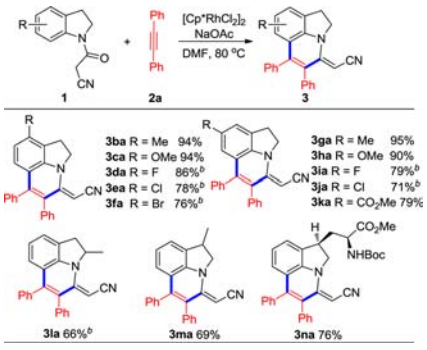


[a]Condition A: **1a** (0.24 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), NaOAc (50 mol %), DMF (0.5 mL), 80 °C, 12 h, under Ar; isolated yields are shown. [b]Condition B: **1a** (0.24 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), NaOAc (50 mol %), DMF (0.5 mL), 100 °C, 12 h, under Ar. [c]Condition C: **1a** (0.24 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (200 mol %), DMF (0.5 mL), 100 °C, 12 h, under Ar.

some conditions changing (**3ad**−**ag**). The 1,2-di(thiophen-2-yl)acetylene also gave a high yield (**3ah**). Unsymmetrical aryl-alkyl substituted alkynes were also employed. To our delight, the reaction proceeded smoothly with high regioselectivity. The regioselectivity of insertion is probably dictated primarily by the electronic effect, providing the annulation products in which the aryl group is proximal to the carbonyl group (**3ai**−**aj**). A mixture of two *Z*,*E*-isomers, which could not be separated, was obtained in 81% yield when dialkyl-substituted oct-4-yne **2k** was used. Other alkynes such as phenylacetylene and dimethyl but-2-ynedioate were also tested. Unfortunately, no desired product was isolated.

In addition to **1a**, different *N*-substituted indolines were examined for the present reaction (Scheme 3). Good to excellent

Scheme 3. Substrate Scope of Indolines[a]



[a]Condition A: **1** (0.24 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), NaOAc (50 mol %), DMF (0.5 mL), 80 °C, 12 h, under Ar; isolated yields are shown. [b]Condition B: **1** (0.24 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), NaOAc (50 mol %), DMF (0.5 mL), 100 °C, 12 h, under Ar.

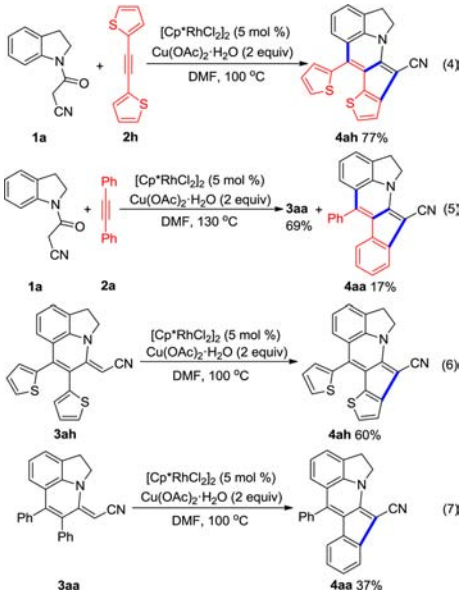
yields were obtained with 3-(indolin-1-yl)-3-oxopropanenitriles bearing methyl, methoxy, bromo, chloro, fluoro, and ester substitution at different positions (**3ba**−**ma**). *N*-Substituted indolines bearing electron-donating substituents afforded the corresponding products in slightly higher yields. It should be noted that the substituted 3-(indolin-1-yl)-3-oxopropanenitrile

DOI: 10.1021/acs.orglett.6b02521
Org. Lett. 2016, 18, 5066−5069

1n derived from L-tryptophan still worked well (**3na**), offering the opportunity for transformation of L-tryptophan in biochemistry research.[8]

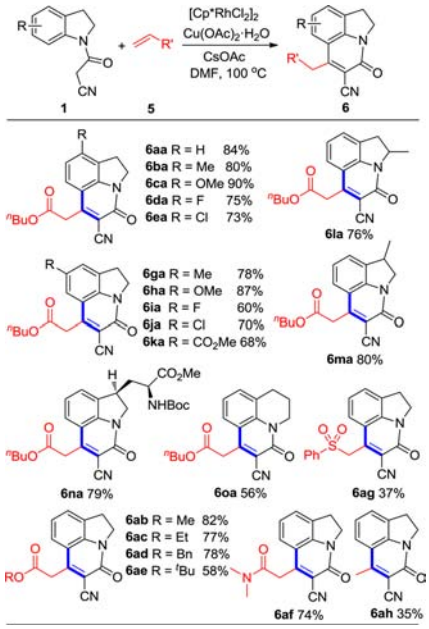
Interestingly, when the reaction of **1a** with **2h** was carried out in the presence of 2 equiv of $Cu(OAc)_2·H_2O$ instead of NaOAc, a new coupling product **4ah** was isolated in 77% yield (Scheme 4, eq 4). A mixture of **4aa** (17%) and **3aa** (69%) was obtained when **1a** reacted with **2a** in the presence of $Cu(OAc)_2·H_2O$ and $[Cp^*RhCl_2]_2$, even though the temperature was increased to 130 °C (Scheme 4, eq 5). No **4ah** was detected when **3ah** reacted with only 2 equiv of $Cu(OAc)_2·H_2O$, but a 60% yield was obtained in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2·H_2O$ (Scheme 4, eq 6), which may prove **4ah** was formed via Rh(III) catalyzed C−H/C−H oxidative coupling of **3ah**. Similarly, **4aa** was obtained in 37% yield when **3aa** reacted with $Cu(OAc)_2·H_2O$ and $[Cp^*RhCl_2]_2$ (Scheme 4, eq 7). The structure of **4aa** was confirmed by single-crystal X-ray diffraction analysis. From comparison of **2a**, **2f** (no oxidative coupling product, Scheme 2), and **2h**, the oxidative coupling reaction is thought to possibly favor the electron-rich arenes.

Scheme 4. Coupling Reaction of 3ah and 3aa



The coupling reaction of 3-(indolin-1-yl)-3-oxopropanenitrile (**1a**) with acrylate was also investigated. By treating the *N*-substituted indoline **1a** (1.0 equiv) with butyl acrylate **5a** (2.0 equiv) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2·H_2O$ (2.5 equiv), and CsOAc (0.5 equiv) in DMF (0.5 mL) at 100 °C for 12 h, the six-membered annulation product **6aa** was obtained in 84% yield (for detailed optimization studies, see Table S1 in the Supporting Information). The structure of **6ba** was confirmed by its ^1H and ^{13}C NMR spectra, mass spectrometry data, and single-crystal X-ray diffraction analysis. Having obtained the optimal reaction conditions, we proceeded to investigate the scope and limitation of the reaction with different 3-(indolin-1-yl)-3-oxopropanenitriles (Scheme 5). In general, *N*-substituted indolines bearing methyl and methoxy at different positions proved to be very compatible with the current system (**6ba**−**ca**, **6ga**−**ha**). 3-(Indolin-1-yl)-3-oxopropanenitrile with electron-withdrawing functional groups such as halogen and ester were also tolerated (**6da**−**ea**, **6ia**−**ka**). To our delight, the substituted 3-(indolin-1-yl)-3-oxopropanenitrile **1n** derived from L-tryptophan gave the corresponding product **6na** in 79% yield. When 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-oxopropanenitrile **1o** was used the corresponding product **6oa** was obtained in 56% yield. The scope of the alkenes was also explored (Scheme 5). Satisfyingly, various acrylates such as butyl (**5a**), methyl (**5b**), ethyl (**5c**), and benzyl (**5d**) afforded the corresponding 1,7-fused indolines (**6aa**−**ad**) in good yields. *tert*-Butyl acrylate (**5e**) gave a lower yield (58%) probably due to the steric effect of the substrate. *N*,*N*-Dimethylacrylamide and (vinylsulfonyl)benzene were also tolerated and gave the desired product in 74% and 37% yield (**6af**, **6ag**), respectively. In addition, a decarboxylation product was obtained in 35% yield when acrylic acid was used (**6ah**). No obvious desired products were detected when some other alkenes such as acrylonitrile, *N*-methylmaleimide, and styrene were used.

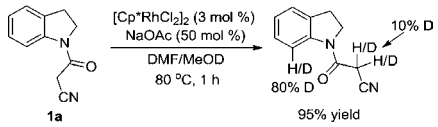
Scheme 5. Substrate Scope of Alkenes and Indolines[a]



[a]Condition D: **1** (0.2 mmol), **5** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2·H_2O$ (200 mol %), CsOAc (50 mol %), DMF (0.5 mL), 100 °C, 12 h, under Ar. Isolated yields are shown.

To gain mechanistic insight, a hydrogen−deuterium exchange experiment using MeOD was performed. The result indicated that the cleavage of the C−H bond at the indoline C7-position was a reversible process (Scheme 6).

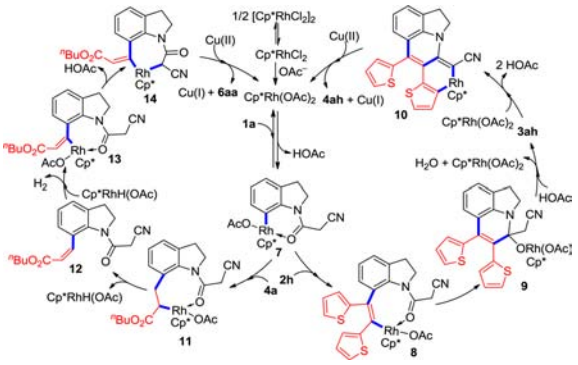
Scheme 6. H/D Exchange Experiment



Based on the above experimental results, the known transition-metal-catalyzed C−H bond functionalization reactions and our group's previous research, a plausible mechanism was proposed for the present catalytic reaction (Scheme 7). The first step is likely to be a C-7 C(sp^2)−H activation process affording a six-membered rhodacycle intermediate **7**, which would subsequently be involved in coordination and insertion of an alkyne leading to the alkenyl−Rh intermediate **8**. An intramolecular nucleophilic addition of the C(sp^2)−Rh bond into the carbamoyl group leads to the intermediate **9**. After protonation with HOAc and

DOI: 10.1021/acs.orglett.6b02521
Org. Lett. 2016, 18, 5066−5069

Scheme 7. Plausible Catalytic Cycle



elimination of H_2O, **3ah** was obtained in the absence of $Cu(OAc)_2 \cdot H_2O$. The double $C(sp^2)$−H activation of **3ah** delivers intermediate **10** when $Cu(OAc)_2 \cdot H_2O$ was used, which undergoes a reductive elimination to afford the final coupling product **4ah** and Cp*Rh(I). Cp*Rh(I) is oxidized by $Cu(OAc)_2 \cdot H_2O$ to $Cp^*Rh(OAc)_2$ for the next catalytic cycle. Similarly, insertion of olefin to the C−Rh bond of **7** affords the eight-membered rhodacycle **11**. This rhodacycle might undergo a β-hydrogen elimination to provide the intermediate **12**, which undergoes a $C(sp^2)$−H activation and a $C(sp^3)$−H activation to deliver intermediates **13** and **14**. After a C−C reductive elimination and a double bond shift, the final product **6aa** and Cp*Rh(I) are formed. Cp*Rh(I) is oxidized by $Cu(OAc)_2 \cdot H_2O$ to $Cp^*Rh(OAc)_2$ for the next catalytic cycle.

In summary, we have developed Rh(III)-catalyzed carbocyclization reactions of 3-(indolin-1-yl)-3-oxopropanenitriles with alkynes and alkenes to form 1,7-fused indolines through C−H activation. The reactions proceeded with a broad range of substrates. For alkynes, almost all products are highly regio- and stereoselective. Electron-rich alkynes could undergo oxidative coupling to form a polycyclic compound. For alkenes, the Rh(III)-catalyzed carbocyclization is through $C(sp^2)$−H, $C(sp^3)$−H oxidative coupling. A plausible mechanism has been proposed, and more details of the mechanism are being explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02521.

Full experimental procedures, optimization of reaction conditions, characterization and ^1H, ^{13}C, and ^{19}F NMR spectra of products (PDF)

Crystallographic data for **3aa**, **3ai**, **4aa**, and **6ba** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21372122, 21672108, and 21421062) and Natural Science Foundation of Tianjin (16JCZDJC31700) for financial support.

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DOI: 10.1021/acs.orglett.6b02521
Org. Lett. 2016, 18, 5066−5069