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Rh(III)-catalyzed selective C7-H functionalization of indolines with 1,3-enynes enables access to six-membered 1,7-fused indolines

Yunkai Shi [a,b], Chao Chen [b,e], Yaxi Yang [b,c,d], Bing zhou [b,c,d,*]

[a] Institute of Pharmaceutical Research and School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou 450001, China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China
[c] University of Chinese Academy of Sciences, 19 Yuquan Road, Beijing 100049, China
[d] School of Pharmaceutical Science and Technology, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Hangzhou 310024, China
[e] Department of Medicinal Chemistry, School of Pharmacy, Fudan University, 826 Zhangheng Road, Pudong New District, Shanghai 201203, China

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ABSTRACT

We described herein a Rh(III)-catalyzed C7-selective C—H activation/annulation of indolines with 1,3-enynes to efficiently access various privileged 1,7-fused indolines bearing an all-carbon quaternary stereogenic carbon center. Notably, the resulting products can be readily transformed into 1,7-fused indoles, further widening the C-7 derivatization of indoles and highlighting the synthetic utility of this methodology.

Introduction

The indoles and indolines are common fragments in numerous bioactive natural products, pharmaceutically important compounds, other functional molecules and even marketed drugs [1]. Among them, 1,7-fused indolines are particularly noteworthy owing to their great potential in pharmaceuticals and agrochemicals (Fig. 1) [2]. Therefore, the development of catalytic and practical methods to efficiently access various 1,7-fused indolines, is highly desirable and of prime synthetic value.

The transition metal-catalyzed C—H functionalizations have advantages over traditional protocols because substrate preactivation is unnecessary [3,4]. In this regard, it would be highly desirable and attractive if we can take advantage of selective C7-H fuctionalization/annulation of indolines with proper coupling partners to directly access a variety of 1,7-fused indolines. Recently, some elegant examples of transition-metal-catalyzed C7-H functionalization/annulation of indolines with different coupling partners have been disclosed by several groups and us [5], including alkynes, alkenes, allylic alcohols, and carbon monoxide. Despite significant progress, the development of catalytic synthetic methods to expand the range of products and access structurally more complex and diverse 1,7-fused indolines, is still highly desirable.

1,3-Enynes, are important compounds in organic chemistry and have been utilized as a C1, *C*2 or C3 annulation synthon in the transition-metal-catalyzed C—H functionalizations [6]. In this context, given the importance of 1,7-fused indolines and with our continuing interest in the transition-metal-catalyzed C—H functionalization [7], we herein reported a Rh(III)-catalyzed C7-selective C—H activation/annulation of indolines with 1,3-enynes to efficiently access various privileged six-membered 1,7-fused indolines bearing an all-carbon quaternary stereogenic carbon center.

Results and discussion

We commenced our study with the coupling of *N*-methoxycarbamoyl-protected indoline (**1a**) and 1,3-enynes (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %) and various additives (200 mol %) in 1,4-dioxane at 70 ℃ for 48 h (Table 1, entries 1–4). $Cu(OAc)_2$ was identified as the best additive, affording the **3a** in 20% yield (entry 1). Next, a screening of the solvent proved THF to be the optimal choice (entries 5–9), giving **3a** in 37% yield. The prepared Rh (III) precursor $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ led to a higher yield (entry 10). Increasing the reaction temperature to 85℃ further improved the reaction efficiency (entry 11) but a higher reaction temperature (100 ℃) decreased the yield (entry 12). Other catalyst system proved ineffective in this reaction (entries 13–15). This annulation reaction did not occur in the absence of the rhodium catalyst and the oxidant $Cu(OAc)_2$ (entries 16 and 17).

* Corresponding author.
E-mail addresses: zhoubing@simm.ac.cn, zhoubing2012@hotmail.com (B. zhou).

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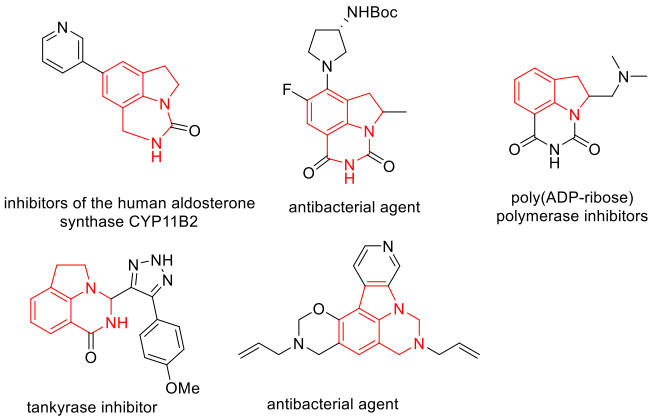
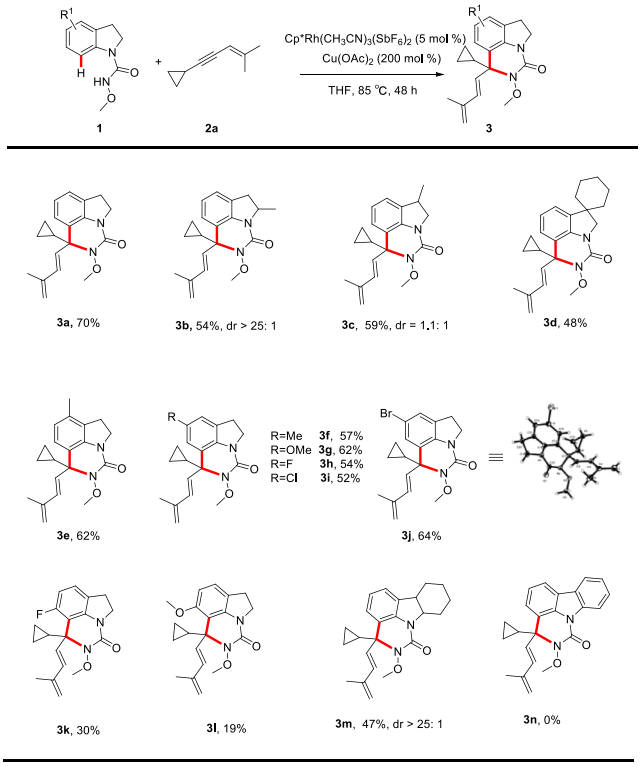


Fig. 1. Representative bioactive 1,7-fused indolines.

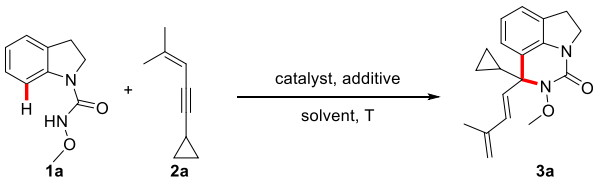
With the optimized reaction conditions in hand, the substrate scope of indolines was investigated. As shown in Scheme 1, indolines containing both electron-donating(**3b** – **g**) and withdrawing (**3h** – **j**) groups proceeded smoothly in this transformation to give the corresponding six-membered 1,7-fused indolines in moderate to good yields. Moreover, substitutions at the *C*2– (**3b**), C3– (**3c**, **d**), C4- (**3e**), C5- (**3f** – **j**) and even C6- (**3k** and **3l**) position were tolerated. The structure of **3j** was unambiguously conformed by an X-ray crystallographic analysis (CCDC 2067486). Of special importance, indolines bearing chloro (**3i**) and bromo (**3j**) functional groups were also compatible with this catalytic system, thus offering the opportunity for further transformations, for example, the metal-catalyzed cross-coupling reactions. To our delighted, tricyclic hexahydrocarbazole (**3m**) were also fully applicable to this catalytic system. Notably, the *C*2-substitution gave an excellent diastereomeric selectivity (**3b** and **3m**). Carbazole failed to deliver the desired product **3n**.

The scope of enynes was also explored (Scheme 2). 1,3-enynes with various alkyl, cycloalkyl and aryl groups coupled smoothly with **1a**, furnishing the desired products **4b-i** in moderate to good yield, although the reaction efficiency decreased with a bulky substituent (**4h** and **4i**).



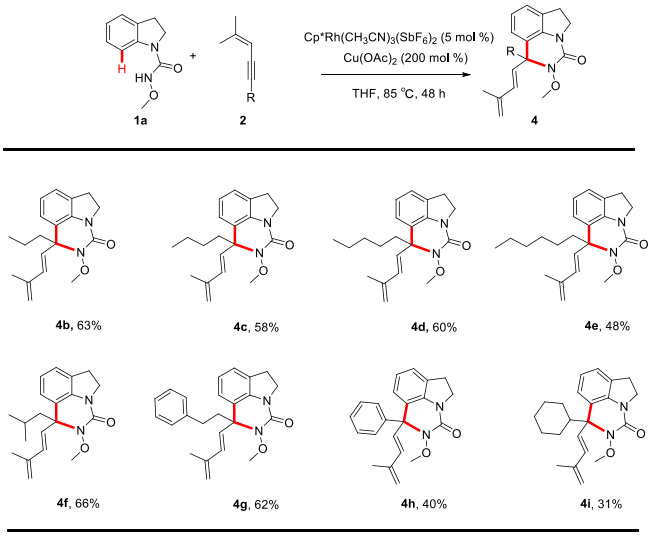
Scheme 1. Substrate scope of indolines[a] [a] Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2 (0.3 mmol, 1.5 equiv), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol %) and $Cu(OAc)_2$ (200 mol %) in THF (2.0 mL) for 48 h at 85 °C; yield isolated by column chromatography.

Table 1
Reaction optimization[a].



Entry	catalyst	additive	T[℃]	solvent	yield of **3a** (%)
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	1,4-dioxane	20
2	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	70	1,4-dioxane	11
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	70	1,4-dioxane	0
4	$[Cp^*RhCl_2]_2$	AgF_2	70	1,4-dioxane	9
5	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	THF	37
6	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	DCE	0
7	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	EtOH	12
8	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	DMSO	0
9	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	70	DMF	0
10	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2$	70	THF	52
11	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2$	85	THF	70
12	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	$Cu(OAc)_2$	100	THF	46
13	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OAc)_2$	70	THF	0
14	$[Rh(COD)Cl]_2$	$Cu(OAc)_2$	70	THF	0
15	$[Cp^*IrCl_2]_2$	$Cu(OAc)_2$	70	THF	0
16	–	$Cu(OAc)_2$	70	THF	0
17	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$	–	70	THF	0

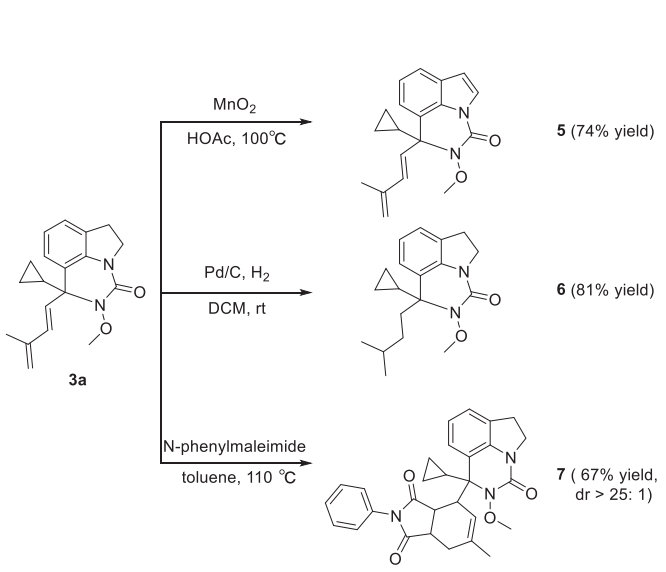
[a] Conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (5 mol %) and additive (200 mol %) in Solvent (1 mL) for 48 h. Yield isolated by column chromatography.



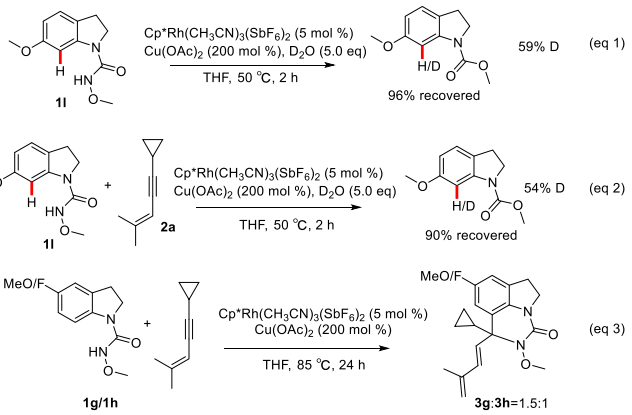
Scheme 2. Substrate scope of various enynes [a] [a] Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2 (0.3 mmol, 1.5 equiv), $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ (5 mol %), and $Cu(OAc)_2$ (200 mol %) in THF (2.0 mL) for 48 h at 85 °C; yield isolated by column chromatography.

The synthetic utility of this method was further highlighted by its successful conversion of 1,7-fused indoline **3a** into 1,7-fused indole **5** (Scheme 3). Moreover, reduction of **3a** with 10% Pd/C under H_2 afforded product **6** in 81% yield. In addition, a Diels–Alder reaction of **3a** with *N*-phenylmaleimide proceeded smoothly to give product **7** in 67% yield.

For a preliminary mechanistic study, H/D exchange experiments were performed. A significant H/D scrambling was observed at the C7-position of indoline when **1l** was reacted with $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ catalyst in THF and D_2O (eq 1). Moreover, in the presence of **2a**, a similar H/D scrambling was observed in the re-isolated **1l** (eq 2). Together, these results indicated the reversibility of the C—H activation. Next, competition experiments using an equimolar mixture of electronically differentiated indolines revealed that C—H activation was slightly kinetically favored for electron-rich indolines (eq 3).



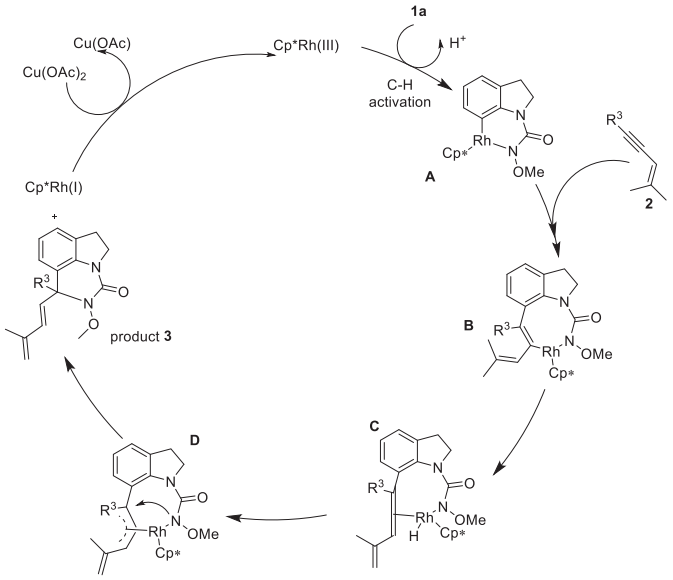
Scheme 3. Synthetic applications of annulation products.



A preliminary mechanistic pathway is postulated for the Rh(III)-catalyzed of indoline C-7 C – H activation/annulation with enynes (Scheme 4)[6f]. First, a Rh(III)-catalyzed reversible C-7 C–H cleavage occurs to give rhodacycle **A** upon proton abstraction. Insertion of enynes to the carbon – rhodium bond of **A** affords the eight-membered rhodacycle **B**. Then, the Rh(III) alkenyl intermediate undergoes δ-hydrogen elimination to produce the Rh(III) enallene hydride intermediate **C**. Subsequent hydride insertion into the allene middle carbon gives the η^3 allyl **D**. Nucleophilic attack of the π–allylrhodium moiety of **D** delivers the product **3** and the Rh(I) species, which can be reoxidized to Rh(III) by $Cu(OAc)_2$.

Conclusions

In summary, we have developed a Rh(III)-catalyzed selective C-7 C – H activation/annulation of indolines with 1,3-enynes. This robust transformation proceeds with a broad functional group tolerance under mild reaction conditions, affording a variety of privileged 1,7-fused indolines bearing an all-carbon quaternary stereogenic carbon center.



Scheme 4. Proposed Mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153065.

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