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Expedient Synthesis of Pyrroloquinolinones by Rh-Catalyzed Annulation of *N*-Carbamoyl Indolines with Alkynes through a Directed C−H Functionalization/C−N Cleavage Sequence

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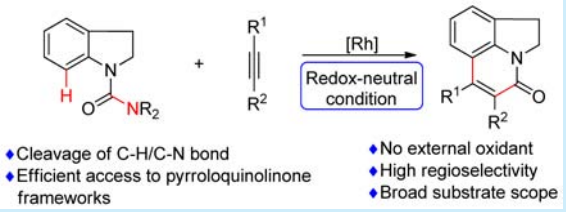
Supporting Information

ABSTRACT: A Rh-catalyzed redox-neutral C−H functionalization of *N*-carbamoyl indolines with various internal alkynes has been developed. The reaction, which involves the sequential cleavage of the C−H bond of the indoline at the C7-position and the C−N bond of the urea motif, provides a divergent protocol to rapidly assemble fused-ring pyrroloquinolinone analogues by using a direct alkenylation/annulation strategy with high efficiency and selectivity.



Indoline alkaloids possessing the pyrroloquinolinone skeleton have garnered considerable interest in the area of synthetic and pharmaceutical chemistry.[1] Reported protocols to access this azatricyclic framework are highly varied and generally focus on Fischer indolization,[1a] intramolecular Pd-catalyzed annulation,[1b] Friedel−Crafts reaction,[1d] etc. Nevertheless, those transformations suffer from major drawbacks such as multiple prefunctionalization steps, harsh reaction conditions, and functional group compatibility. Thus, the development of an atom-economical and straightforward method for the rapid assembly of pyrroloquinolinones remains in high demand, given that the structural motifs serve as building blocks in many natural products and biologically active molecules (Figure 1). Herein, we introduce an attractive alternative via a direct C−H functionalization strategy[2] to address those problematic issues.

Transition-metal-catalyzed intermolecular annulation of arenes with alkynes has proven to be a powerful method for the concise synthesis of complex cyclic molecules,[3,4] wherein

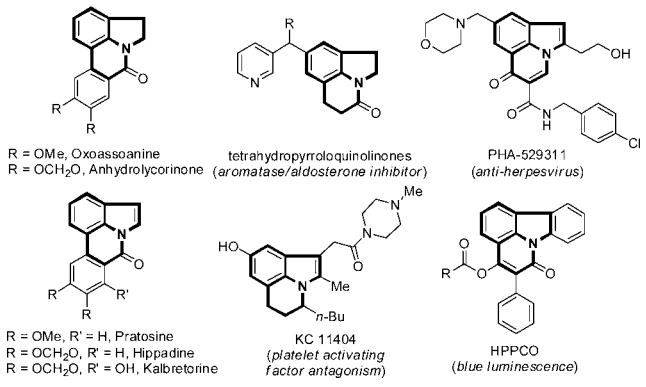


Figure 1. Representative examples of some pyrrolo[3,2,1-*ij*]quinolines.

cleavage of the N−X (X = H, O, N) bond of the directing group is generally associated with aromatic C−H bond cleavage for achieving the formation of two bonds simultaneously. In fact, although the nucleophilic addition of alkenyl-metal intermediate, generated by insertion of alkyne into C−metal bond, to polar carbonyls or imines is well established,[5] its related reaction with a less reactive amide or urea-based directing group involving C−N bond cleavage is more challenging and particularly rare.[6] As known, the urea-based directing group has been extensively utilized in a range of C−H functionalization reactions[7] since the first introduction by the Lloyd-Jones and Booker-Milburn group.[8] Very recently, the research groups of Oestreich,[9] Antonchick,[10] and Shibata[11] independently developed direct C-7 alkenylation of indolines[12] using urea as the directing group (Scheme 1a). Despite a plethora of advancements in the C−H functionalization of indolines, there are very few examples utilizing indoline as a template via a C−H functionalization/annulation cascade to build the pyrroloquinoline framework. The sole synthetic route, to the best of our knowledge, was elegantly reported by Yi through a hydroamination pathway (Scheme 1b).[13] However, the employment of 2 equiv of terminal alkynes synthetically limited the diversity of products. In pursuing our interest in Rh catalysis,[14] herein we report an unprecedented strategy for the convenient construction of valuable functionalized pyrroloquinolinone derivatives by a Rh catalyst. This distinct activation mode allows for a sequential C−H/C−N cleavage with a urea moiety serving as both a directing group and electrophile (Scheme 1c).

Our studies commenced by evaluating the feasibility of the annulation reactions of *N*-substituted indolines **1** with diphenylacetylene **2a** in the presence of active cationic Rh[III]

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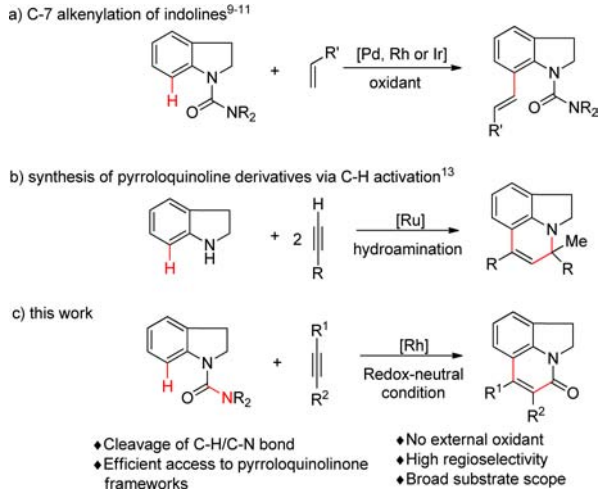
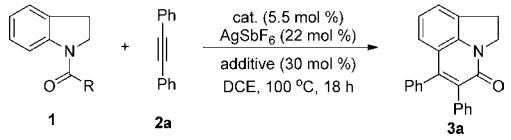
Scheme 1. Direct C-7 Alkenylation of Indolines via C−H Activation



species. Unsurprisingly, the carboxylate group, which has been recognized as a weakly coordinating directing group,[15] failed to generate the desired product (Table 1, entry 1). The *N*,*N*-dimethylcarbamoyl group was subsequently tested and afforded the expected pyrroloquinolinone **3a**, albeit with a low yield (entry 2). After screening a series of additives, we were pleased to find that $Cu(OAc)_2$ could slightly enhance the catalytic activity (entries 3−6). Replacing $Cu(OAc)_2$ with $Cu(OTf)_2$ led to considerable improvement of the yield to 42% (entry 7). Encouraged by this intriguing observation, a number of Lewis acids bearing a triflate moiety were then screened. Gratifyingly, we found that the use of $Zn(OTf)_2$ could afford the product in 70% yield (entries 8−11). Although the exact mechanism of action of $Zn(OTf)_2$ is unclear, it may play a critical role in promoting the catalytic efficiency by coordination with the triple bond to activate the alkyne substrate as well as increasing the electrophilicity of the urea motif.[16] Adjusting the stoichiometry of $Zn(OTf)_2$ led to a slight decrease in yields (entries 12−13). Additionally, we also found that a related cationic Rh^{III} catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ alone was totally ineffective for this catalytic reaction (entry 14). Likewise $[Ru(p\text{-cymene})Cl_2]_2$ failed to mediate the reaction (entry 15). To probe the impact of the directing group on the reaction efficiency, we screened several carbamoyl groups and finally determined that the morpholine motif was the best directing group at this stage (entries 16−18).

Having obtained the optimal reaction conditions, we proceeded to investigate the scope and limitation of the reaction with different internal alkynes (Scheme 2). Symmetrical diaryl-substituted alkynes incorporating electron-donating or -withdrawing substituents could be efficiently converted into the corresponding desired products in good yields (**3b−d**). In addition, with unsymmetrical aryl-alkyl substituted alkynes, the reaction proceeded smoothly with high regioselectivity, providing the annulation products in which the aryl group is proximal to the carbonyl group. The methyl and other functional groups (F, Cl) on the aryl moiety were all well tolerated (**3f−h**). Increasing the carbon length of alkyl groups (Me, Et, Pr) would lower the

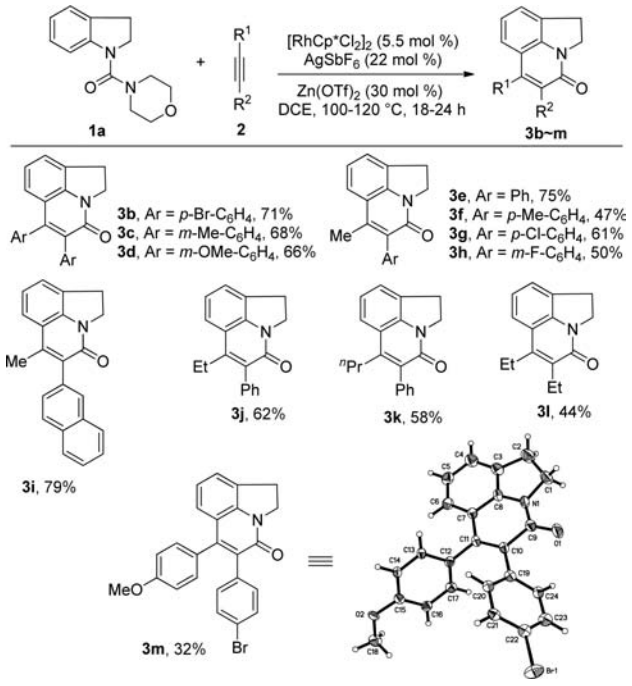
Table 1. Reaction Condition Optimization[a]



entry	R	cat.	additive	yield (%)[b]
1	OEt	$[RhCp^*Cl_2]_2$	-	0
2	NMe_2	$[RhCp^*Cl_2]_2$	-	10
3	NMe_2	$[RhCp^*Cl_2]_2$	PivOH[c]	trace[f]
4	NMe_2	$[RhCp^*Cl_2]_2$	MeOH[c]	trace[f]
5[d]	NMe_2	$[RhCp^*Cl_2]_2$	-	0
6	NMe_2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$[e]	17
7	NMe_2	$[RhCp^*Cl_2]_2$	$Cu(OTf)_2$	42
8	NMe_2	$[RhCp^*Cl_2]_2$	$Mg(OTf)_2$	39
9	NMe_2	$[RhCp^*Cl_2]_2$	$Sc(OTf)_3$	trace[f]
10	NMe_2	$[RhCp^*Cl_2]_2$	AgOTf	62
11	NMe_2	$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$	70
12	NMe_2	$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$[g]	65
13	NMe_2	$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$[h]	59
14[d]	NMe_2	$[RhCp^*(MeCN)_3](SbF_6)_2$	$Cu(OTf)_2$	trace[f]
15	NMe_2	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OTf)_2$	0
16	NEt_2	$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$	38
17		$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$	54
18		$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$	73

[a]Typical reaction conditions: **1** (1.5 equiv), **2a** (1.0 equiv), catalyst (5.5 mol %), $AgSbF_6$ (22 mol %), and additive (30 mol %) in 1,2-dichloroethane (1.0 mL) at 100 °C for 18 h. [b]Yields of isolated products. [c]1.2 equiv was used. [d]No $AgSbF_6$. [e]50 mol % was used. [f]Trace if any. [g]11 mol % was used. [h]60 mol % was used.

Scheme 2. Scope with Respect to Internal Alkyne[a]



[a]For **3a−d** and **3m**, the reactions were run at 100 °C for 18 h. For **3e−l**, the reactions were run at 120 °C for 24 h.

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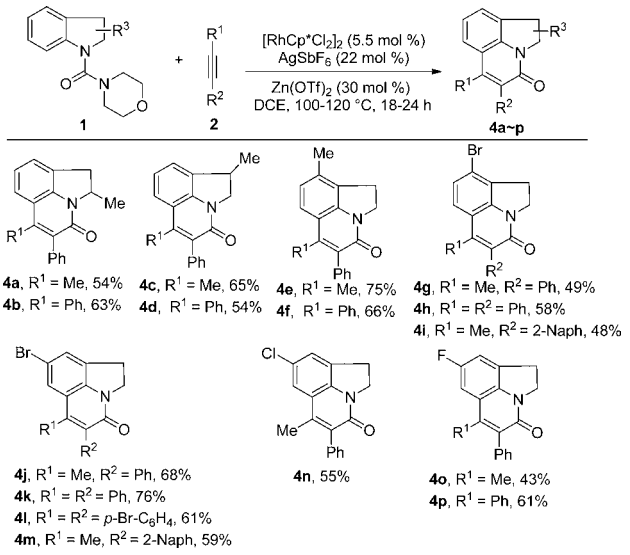
reactivity gradually while moderate yields were obtained (**3j** and **3k**). It is significant to note that a dialkyl-substituted alkyne, exemplified with 3-hexyne, is also compatible with this protocol in an acceptable yield (**3l**). Notably, the use of an electronically differentiated diaryl-substituted alkyne gave **3m** in a highly regioselective manner.[17] Unfortunately, a TMS-substituted alkyne failed to react which is probably attributed to its instability under the standard conditions.

Next, a series of substituted indoline derivatives were then subjected to the annulation reaction with different alkynes (Scheme 3). In general, *N*-carbamoyl indolines bearing methyl,

Scheme 3. Scope of Annulation Reactions of Indolines with Alkynes[a]

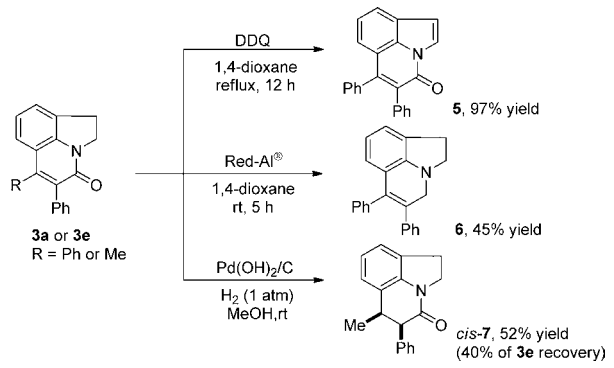


[a]For **4b**, **4d**, **4f**, **4h**, **4k**, **4l**, and **4p**, the reactions were run at 100 °C for 18 h. For others, the reactions were run at 120 °C for 24 h.

bromo, chloro, fluoro substitution at different positions proved to be very compatible with the current system, thereby delivering the highly functionalized pyrroloquinolinones in moderate to good yields (**4a**–**p**).

Further transformations of the annulation adducts have been performed to demonstrate the synthetic utility of this protocol (Scheme 4). Treatment of **3a** with DDQ easily gave the aromatized product **5** in almost quantitative yield. Selective reduction with Red-Al furnished the dihydropyrroloquinoline **6** in 45% isolated yield at full conversion.[18] Instead, $Pd(OH)_2/C$-

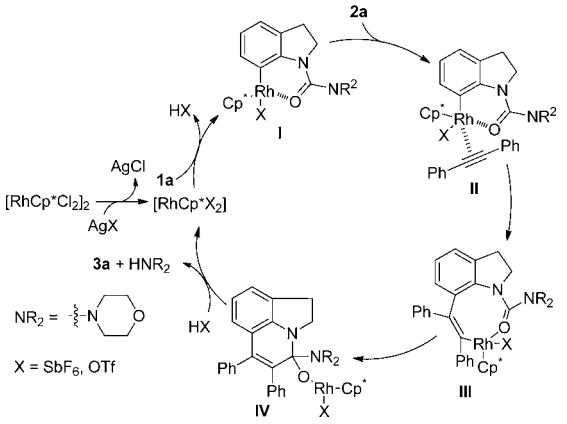
Scheme 4. Synthetic Transformations of Pyrroloquinolinones



mediated hydrogenation of **3e** provided **7** with the double bond being reduced exclusively.

Although the mechanistic details are yet to be ascertained, we propose a plausible catalytic cycle for the pyrroloquinolinone formation (Scheme 5). After generation of active cationic Rh

Scheme 5. Mechanistic Proposal



species, regioselective C–H activation at the 7-position of indoline by coordinating with the carbamoyl group occurs to afford the six-membered rhodacycle **I** which would subsequently be involved in an alkyne insertion leading to the alkenyl–Rh intermediate **III**. It is worth mentioning that the regioselectivity of insertion is dictated primarily by the electronic effect according to the observed results of unsymmetrical alkynes. An intramolecular nucleophilic addition of the C(sp^2)–Rh bond into the carbamoyl group produces the intermediate **IV**, which finally undergoes proto-demetalation to produce the annulation product **3a** by the release of morpholine and regenerating the catalytically active Rh complex.

In conclusion, we have developed a Rh-catalyzed C–H alkenylation/annulation of *N*-carbamoyl indolines with alkynes to afford pyrroloquinolinone derivatives. The balance between the directing ability and the electrophilicity of the carbamoyl group enables the annulation to proceed successfully. As the reaction is redox neutral, no external oxidant is required. Moreover, when unsymmetrical internal alkynes were employed, the annulation adducts were obtained with high regioselectivity. Considering the usefulness of pyrroloquinolinones, we assume that this efficient approach for assembly of the azatricyclic frameworks will be exploited in more applications of biologically active molecule syntheses.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of new compounds, and transformation of pyrroloquinolinone. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) CCDC 1042776 (**3a**), 1042775 (**3e**), and 1042777 (**3m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For **3m**, only the main component atoms of the disordered molecule are displayed.

(18) Although TLC showed the reaction proceeded efficiently, a moderate yield was obtained because compound **6** was unstable under the chromatographic purification procedure.

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