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Rhodium(III)-Catalyzed Annulation of Pyridinones with Alkynes via Double C−H Activation: A Route to Functionalized Quinolizinones

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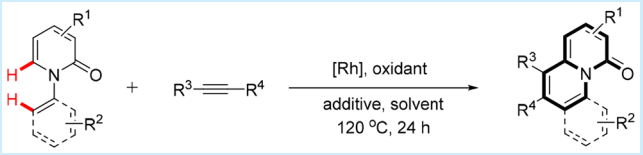
Supporting Information

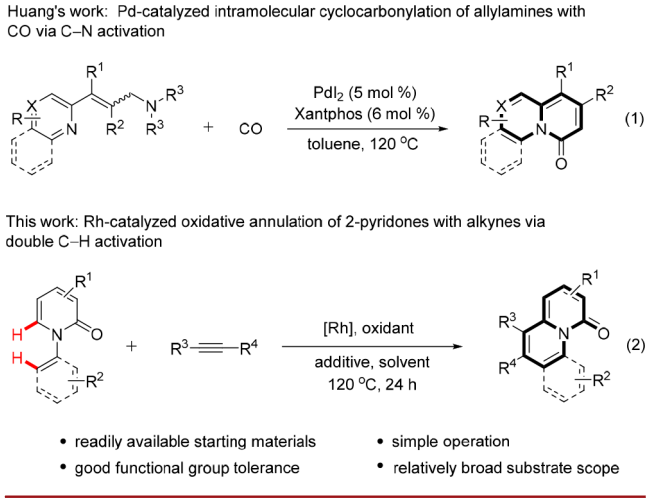
ABSTRACT: A Rh(III)-catalyzed oxidative annulation of pyridin-2(1*H*)-ones with alkynes via double C−H activation to produce highly functionalized 4*H*-quinolizin-4-ones is disclosed. This reaction features easily available starting materials, simple manipulation, a relatively wide substrate scope, and good functional group tolerance. The application of this protocol is demonstrated by the synthesis of a known fluorescent quinolizino[3,4,5,6-*ija*]quinolinium salt.



N-Heteroaryl scaffolds are frequently found in a large number of natural products, pharmaceuticals, agrochemicals, and organic materials.[1] Owing to their broad application, numerous methods have been developed for the synthesis of *N*-heteroaromatics, especially π-extended *N*-heteroarenes.[2] Quinolizinones are a kind of *N*-heterocycles that have received much attention with broad applications as treatments for Alzheimer's disease, HIV, Type 2 diabetes, and Mg^{2+} selective fluorescent probes.[3] However, facile approaches to 4*H*-quinolizin-4-ones are extremely rare. The known routes to 4*H*-quinolizin-4-ones include condensation of ylidenemalonodinitriles with quinoline 1-oxides, tandem condensation of α-substituted picolines with β,β-dichloropropenals and cyclization, thermal cyclization of α-butenynyl substituted pyridine *N*-oxides, intramolecular vinylketene cyclization, addition of malonic esters to alkynylpyridines, sequential multicomponent reaction/allylation/Heck reaction, tandem Horner−Wadsworth−Emmons olefination/cyclization of β-ketopyridines with phosphonoacetate, sequential *N*-alkylation of 6-halo-2-pyridones/Stille cross-coupling/ring-closing metathesis/palladium-catalyzed dehydrogenation reaction, and thermal intramolecular cyclization of (η^4-vinyketene)-$Fe(CO)_3$ complexes.[4] Recently, Huang revealed a highly efficient palladium-catalyzed intramolecular cyclocarbonylation of allylamines with CO by C−N bond activation to construct diverse substituted 4*H*-quinolizin-4-ones (Scheme 1, eq 1).[5] Despite significant progress, these reported methods typically suffer from narrow substrate scope, tedious synthetic procedure, and uneasily available or complex substrates. Thus, the development of a straightforward and efficient approach to quinolizinones is still in high demand.

Transition-metal-catalyzed C−H activation/cyclization with alkynes has proved to be a powerful tool to construct a variety of heterocycles and carbocycles.[6] In particular, Rh(III)-catalyzed oxidative annulation of arenes or alkenes with alkynes has been regarded as an effective strategy to synthesize a variety of highly functionalized cyclic compounds owing to high atom and step economy, a broad substrate scope, and good functional group tolerance.[7] Herein we describe a facile Rh(III)-catalyzed oxidative cyclization of pyridin-2(1*H*)-one derivatives with alkynes for the synthesis of 4*H*-quinolizin-4-ones, including π-extended 4*H*-quinolizin-4-ones (Scheme 1, eq 2).

Scheme 1. Transition-Metal-Catalyzed Synthesis of Quinolizinones via C−N Activation or C−H Activation



Our investigation began with the annulation of (*E*)-1-styrylpyridin-2(1*H*)-one (**1a**) with diphenylacetylene (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2$ (1.0 equiv), and PivOH (20 equiv) in *N*,*N*-dimethylacetamide (DMAc) at 120 °C for 24 h under N_2 (Scheme 2; Table S1). To our delight, the annulated product 7,8,9-triphenyl-4*H*-quinolizin-4-one **3a** was obtained in 63% yield (Table S1, entry 1). Only a trace amount of **3a** was detected in the absence of $Cu(OAc)_2$ (Table S1, entry 3). Switching the solvent to DMF

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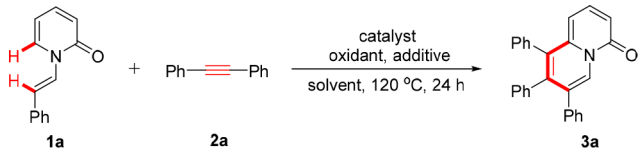
Scheme 2. Optimization of the Reaction Conditions

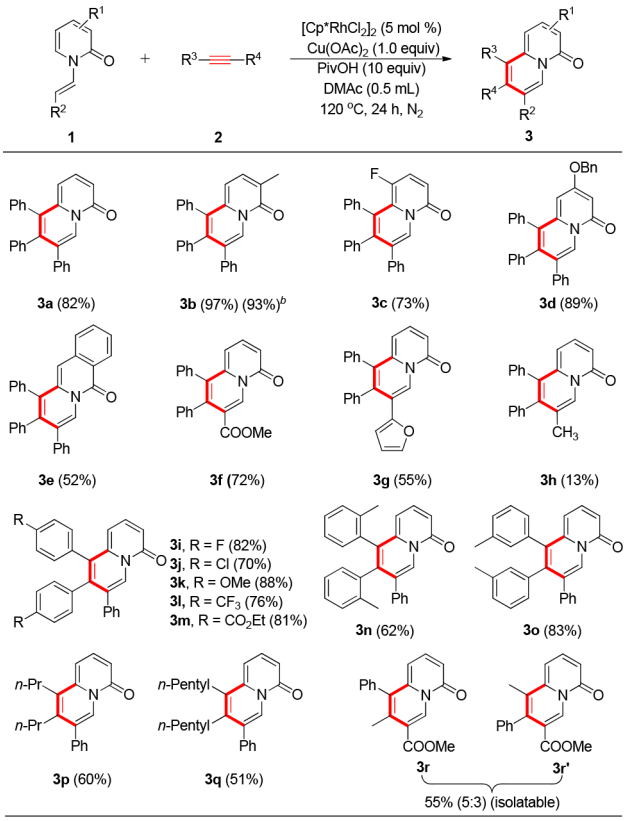


resulted in a similar yield, while other solvents such as DMSO, DCE, dioxane, toluene, and MeOH proved to be much less effective (Table S1, entries 4−10). PivOH often works as a proton shuttle to facilitate the deprotonation process in C−H activation. The amount of PivOH showed a significant influence on the yield of this transformation (Table S1, entries 1 and 11−15). The addition of 10 equiv of PivOH proved to be the best, affording **3a** in 82% yield (Table S1, entry 15). AcOH was less effective (Table S1, entry 16), and almost no desired product was observed when TFA and $TsOH·H_2O$ were attempted (Table S1, entries 17 and 18). The reaction did not proceed in the absence of the Rh(III) catalyst (Table S1, entry 19). Finally, the optimal reaction conditions consisted of $[Cp^*RhCl_2]_2$ (5.0 mol %), $Cu(OAc)_2$ (1.0 equiv), and PivOH (10 equiv) in DMAc (0.5 mL) at 120 °C under N_2 for 24 h (Table S1, entry 15).

With the optimized conditions in hand, we next investigated the substrate scope of this reaction. As summarized in Scheme 3, a variety of *N*-vinylpyridin-2(1*H*)-ones could smoothly undergo the cyclization reaction to give the desired products in moderate to excellent yields. The 2-pyridinone derivatives with electronically differentiated groups at different positions of the pyridinone skeleton were compatible with the standard reaction conditions (Scheme 3, **3b**−**3e**). The tolerance of functional groups at the terminal position of the alkene was also studied, exemplified by the ester and 2-furanyl substituted substrates (Scheme 3, **3f** and **3g**). However, the attempt with an alkyl substituted substrate ($R^2 = CH_3$) under the standard conditions only gave a low yield of the desired product (Scheme 3, **3h**). This reaction also showed a relatively broad scope of alkynes. Diphenylacetylenes bearing both the electron-donating and -withdrawing groups were successfully engaged in this transformation (Scheme 3, **3i**−**3o**). Functional groups such as methyl, methoxy, fluoro, chloro, trifluoromethyl, and ester were tolerated under the standard reaction conditions. In addition, dialkyl alkynes were also competent substrates in this reaction, giving 4*H*-quinolizin-4-ones in acceptable yields (Scheme 3, **3p** and **3q**). A reaction with alkyl aryl alkyne was carried out, delivering two regioisomers **3r** and **3r′** in a total yield of 55% with a ratio of 5:3.

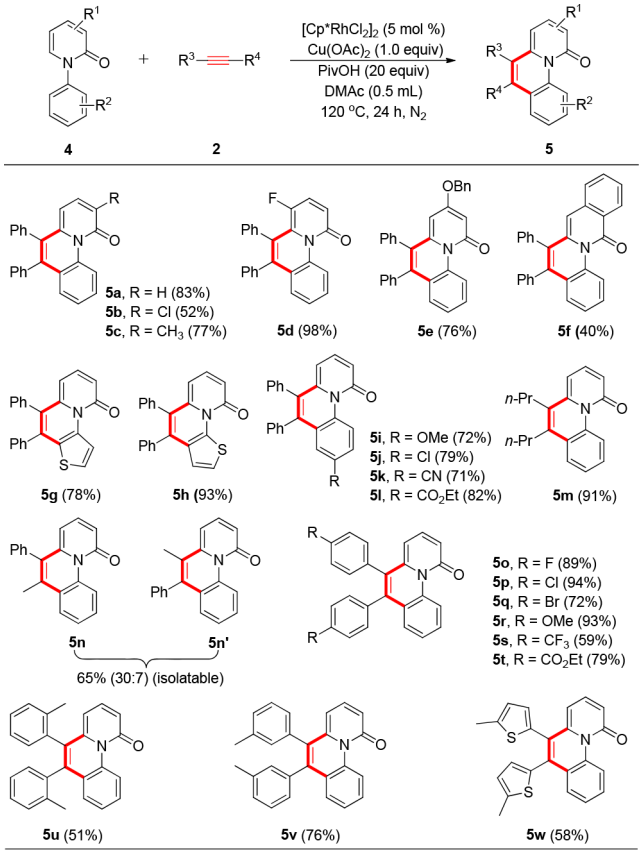
This strategy was successfully extended to the annulation of *N*-arylpyridin-2(1*H*)-ones with alkynes, in which the activation of an aromatic C−H bond instead of an olefinic C−H bond occurred (Scheme 4). For these reactions, 20 equiv of PivOH were employed to provide the best results. Likewise, this

Scheme 3. Annulation of *N*-Vinylpyridin-2(1*H*)-ones with Alkynes[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.30 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (0.01 mmol), $Cu(OAc)_2$ (0.20 mmol), and PivOH (2.0 mmol) were stirred in DMAc (0.5 mL) at 120 °C for 24 h under N_2. [b]1 mmol scale.

Scheme 4. Annulation of *N*-Arylpyridin-2(1*H*)-ones with Alkynes[a]



[a]Reaction conditions: **4** (0.20 mmol), **2** (0.30 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (0.01 mmol), $Cu(OAc)_2$ (0.20 mmol), and PivOH (4.0 mmol) were stirred in DMAc (0.5 mL) at 120 °C for 24 h under N_2.

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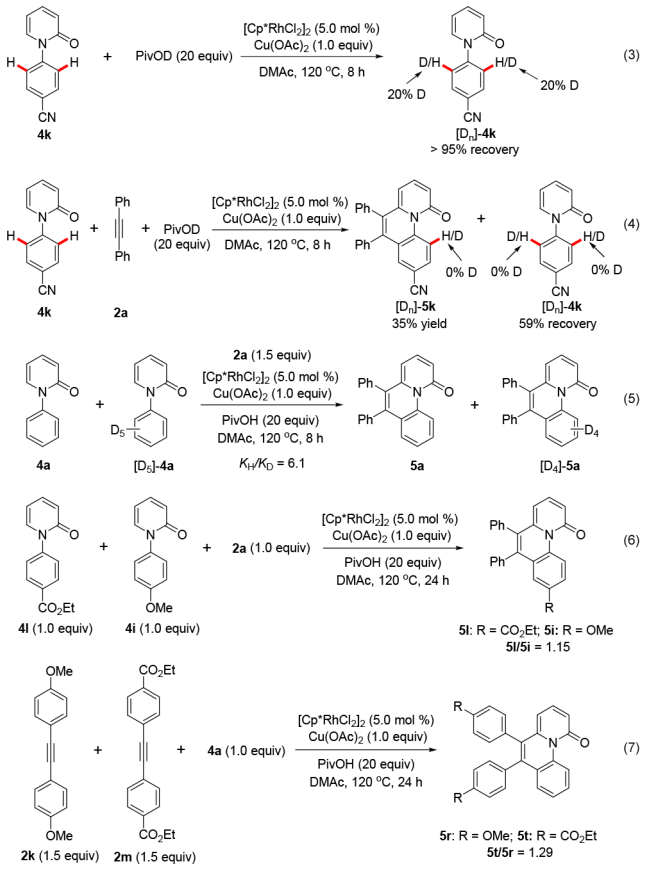
catalytic system exhibited a relatively broad substrate scope for both *N*-arylpyridin-2(1*H*)-ones and alkynes, giving a variety of 4*H*-benzoquinolizin-4-ones in moderate to excellent yields. Notably, the heteroarene-containing substrates such as 1-(thiophen-3-yl)pyridin-2(1*H*)-one, 1-(thiophen-2-yl)pyridin-2(1*H*)-one, and 1,2-bis(5-methylthiophen-2-yl)ethyne worked well under the standard conditions (Scheme 4, **5g**, **5h**, and **5w**). An attempt with 1-phenyl-1-propyne led to two isolatable regioisomers **5n** and **5n′** in a total yield of 65% with a 30:7 ratio.

To shed light on the reaction mechanism, a series of control experiments were conducted (Scheme 5). Treatment of **4k** with

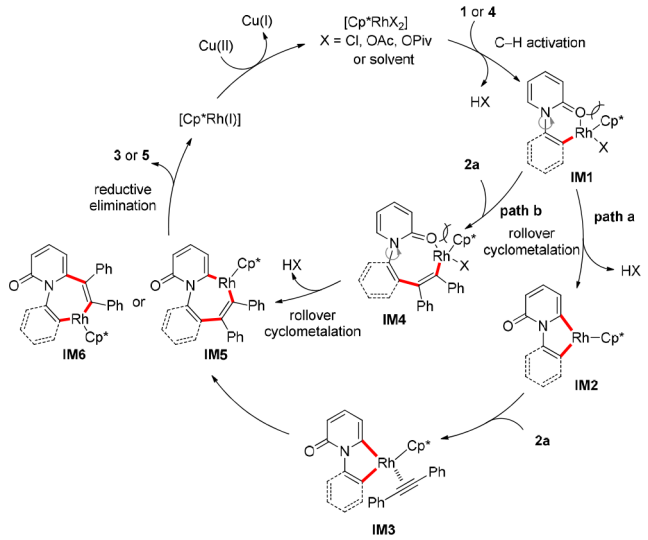
Scheme 5. Mechanism Study



PivOD in the absence of an alkyne under the standard conditions led to 20% deuterium incorporation at the two *ortho*-positions of the phenyl moiety (Scheme 5, eq 3). This result indicated a reversible C−H activation was probably involved in this transformation. However, no H/D exchange was observed in both the isolated product and recovered starting material when the same reaction was performed in the presence of **2a**, implying an irreversible alkyne insertion was likely involved (Scheme 5, eq 4).[8] A large kinetic isotope effect (KIE) value of 6.1 was obtained in the annulation of an equimolar mixture of **4a** and [D_5]-**4a** with diphenylacetylene **2a** under the standard conditions, suggesting that C−H bond cleavage is likely involved in the rate-determining step (Scheme 5, eq 5). Then the intermolecular competition experiment between electronically differentiated **4l** and **4i** was conducted. A small molar ratio of 1.15:1 between the products **5l** and **5i** was obtained, implying an electrophilic aromatic substitution process is less likely involved in the initial C−H activation (Scheme 5, eq 6). Additionally, treatment of **4a** with **2k** with the electron-donating 4-OMe substituent and **2m** with the electron-drawing 4-CO_2Et substituent gave rise to a slightly preferential formation of **5t**, probably because the electron-poor alkyne could more easily undergo coordination and carbometalation (Scheme 5, eq 7).[9]

On the basis of the above observations and the previous literature,[10] a plausible mechanism is proposed in Scheme 6.

Scheme 6. Plausible Mechanism



Initially, cyclometalation of pyridin-2(1*H*)-one **1** or **4** delivers a six-membered rhodacycle **IM1**. Then a rollover cyclometalation takes place to give a five-membered rhodacyclic intermediate **IM2** possibly owing to the steric hindrance of Cp* and/or the coordination of the solvent.[11] The following alkyne coordination and migratory insertion produce a seven-membered rhodacycle **IM5** or **IM6** (path a). Finally, reductive elimination of **IM5** or **IM6** gives the desired product **3** or **5** and releases the Rh(I) species, which is then reoxidized by $Cu(OAc)_2$ to regenerate the reactive Rh(III) catalyst. Alternatively, in path b, an alkyne insertion followed by rollover cyclorhodation is possibly involved, affording a seven-membered rhodacycle intermediate **IM5**.

Recently, azonia aromatic heterocycles have attracted much attention owing to their great potential applications in organic functional materials.[12] To further demonstrate the utility of this reaction, quinolizino[3,4,5,6-*ija*]quinolinium salt **6**, which was reported as a fluorescent molecule,[13] was synthesized by treatment of **5a** with either a Cp*Co(III) or Cp*Rh(III) catalytic system (Scheme 7, eqs 8 and 9). However, the annulations of compound **3** with diphenylacetylene under otherwise identical conditions failed (Scheme 7, eq 10). Based on the previous reports,[14] a plausible mechanism is proposed (see the Supporting Information). Initially, a carbonyl oxygen-directed C−H activation of compound **5a** delivers a six-membered organometallic intermediate **IM7**, which could further undergo alkyne insertion and nucleophilic addition to the C═O bond to give the intermediate **IM9**. In the presence of $BF_3{\cdot}OEt_2$, a deoxygenation process might take place to give the desired product quinolinium salt **6** along with the release of the metal catalyst.

In conclusion, we have developed a Rh(III)-catalyzed oxidative annulation of pyridin-2(1*H*)-one derivatives with

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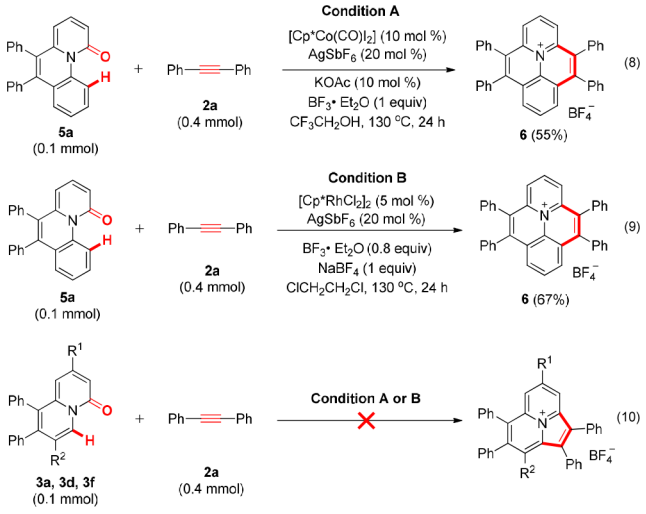
Scheme 7. Synthesis of Quinolizinium Salts



alkynes for the construction of 4*H*-quinolizin-4-ones and 4*H*-benzoquinolizin-4-ones via double C−H activation. This reaction features easily available starting materials, simple manipulation, a relatively wide substrate scope, and good functional group tolerance. Further utilization of this protocol is elucidated by the synthesis of fluorescent quinolizino[3,4,5,6-*ija*]quinolinium salt. Further applications of this catalytic reaction are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01159.

Detailed experimental procedures, characterization data, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of key substrates and final products. (PDF)

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Notes

The authors declare no competing financial interest.

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