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Rh(III)-Catalyzed Oxidative Annulation Leading to Substituted Indolizines by Cleavage of C(sp^2)−H/C(sp^3)−H Bonds

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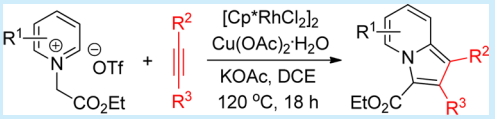
Supporting Information

ABSTRACT: Rhodium(III)-catalyzed oxidative annulation reactions of pyridinium trifluoromethanesulfonate salts with alkynes leading to substituted indolizines by cleavage of C(sp^2)−H/C(sp^3)−H bonds are developed. The starting materials are readily available, and the reactions have a broad substrate scope. This reaction overcomes some drawbacks of the previous indolizine synthetic methods and provides a new efficient route to indolizine derivatives.



Indolizines, as a vital class of N-heterocycles with a 10 π-delocalized electrons, have received much attention because of their molecular structure and important biological activities.[1] Indolizine derivatives have many pharmaceutical applications, including antituberculosis agents, antibacterial agents, anticancer agents, anti inflammatory agents, antihistaminic agents, phosphatase inhibitors, aromatase inhibitors, etc. (Figure 1).[1d] Thus, direct and valuable strategies for synthesis of indolizine derivatives are highly desired.

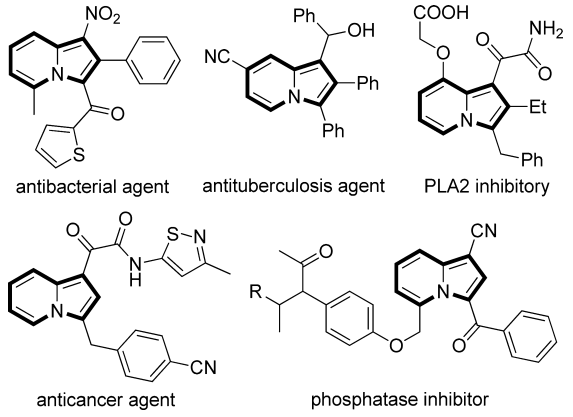


Figure 1. Examples of biologically active indolizine derivatives.

Diverse synthetic methods to access these molecules have been reported, including the traditional reactions of 2-alkylpyridine or their derivatives with acid anhydrides,[2] 1,3-dipolar cycloadditions of pyridiniums with electron-deficient alkenes[3] and alkynes,[4] and transition-metal-catalyzed intramolecular nucleophilic attack reaction of alkynylpyridines.[5] In addition, multicomponent approaches for the synthesis of indolizines,[6] copper-catalyzed [3 + 2] cyclization of pyridines toward alkenyldiazoacetates,[7] and photocatalysis to indolizines[8] were also reported recently. The main disadvantage of these reactions are their limited substrate availability. Thus, efficient methods from simple and readily available starting materials to indolizine derivatives are still valuable.

In the past decade, the transition-metal-catalyzed directed C−H bond activation as a versatile approach in organic synthesis has attracted much attention.[9] In particular, Rh(III)-catalyzed functionalization of the C(sp^2)−H bond and annulation have been used widely because of their high efficiency and broad substrate scopes.[10] In comparison to C(sp^2)−H bond activation and annulation, similar reactions via C(sp^3)−H bond activation are still relatively rare.[11] Following our continuous interest in Rh(III)-catalyzed C−H bond activation and heterocycle building,[11b,c,12] herein we report an efficient Rh(III)-catalyzed oxidative annulation reaction of pyridinium trifluoromethanesulfonate salts with alkynes leading to substituted indolizines by cleavage of C(sp^2)−H/C(sp^3)−H bonds.

In an initial attempt, the reaction of pyridinium trifluoromethanesulfonate salt (**1a**) with diphenylacetylene (**2a**) was explored to screen the reaction conditions (Table 1). Pyridinium trifluoromethanesulfonate salt (**1a**) (0.4 mmol) was treated with diphenylacetylene (**2a**) (0.2 mmol) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), KOAc (0.4 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol) in DCE at 100 °C for 18 h under Ar atomosphere. The desired product **3aa** was obtained in 90% yield (Table 1, entry 1). The structure of compound **3aa** was confirmed by its ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS). The presence of base was crucial for the reaction. KOAc was proven to be the best base (entries 1−6), and **3aa** was not formed without base (entry 7). Subsequently, other different oxidant copper salts were tested (entries 8−10), but they did not show positive

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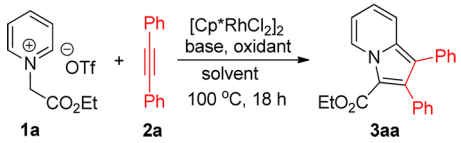
Table 1. Optimization of Reaction Conditions[a]



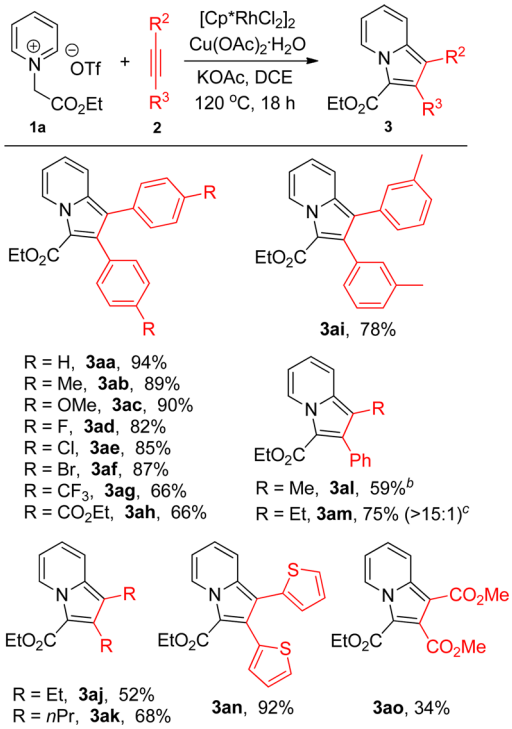
entry	base	oxidant	solvent	yield[b] (%)
1	KOAc	$Cu(OAc)_2·H_2O$	DCE	90
2	NaOAc	$Cu(OAc)_2·H_2O$	DCE	73
3	CsOAc	$Cu(OAc)_2·H_2O$	DCE	89
4	K_2CO_3	$Cu(OAc)_2·H_2O$	DCE	89
5	K_3PO_4	$Cu(OAc)_2·H_2O$	DCE	89
6	Cs_2CO_3	$Cu(OAc)_2·H_2O$	DCE	53
7		$Cu(OAc)_2·H_2O$	DCE	trace
8	KOAc	$Cu(CF_3CO_2)_2$	DCE	trace
9	KOAc	$Cu(OTf)_2$	DCE	trace
10	KOAc	Cu(II) 2-ethylhexanoate	DCE	39
11	KOAc		DCE	38
12	KOAc	$Cu(OAc)_2·H_2O$	toluene	23
13	KOAc	$Cu(OAc)_2·H_2O$	dioxane	17
14	KOAc	$Cu(OAc)_2·H_2O$	MeCN	15
15	KOAc	$Cu(OAc)_2·H_2O$	*t*-AmOH	15
16[c]	KOAc	$Cu(OAc)_2·H_2O$	DCE	20
17[d]	KOAc	$Cu(OAc)_2·H_2O$	DCE	29
18[e]	**KOAc**	**$Cu(OAc)_2·H_2O$**	**DCE**	**94**
19[f]	KOAc	$Cu(OAc)_2·H_2O$	DCE	19
20[g]	KOAc	$Cu(OAc)_2·H_2O$	DCE	14
21[h]	KOAc	$Cu(OAc)_2·H_2O$	DCE	79
22[i]	KOAc	$Cu(OAc)_2·H_2O$	DCE	80

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), base (0.4 mmol), oxidant (0.2 mmol), solvent (2.5 mL), 100 °C, 18 h, under Ar atmosphere. [b]Isolated yield. [c]Without $[Cp^*RhCl_2]_2$. [d]80 °C. [e]120 °C. [f]Switched the anion of **1a** to chloride. [g]Switched the anion of **1a** to bromide. [h]Switched the anion of **1a** to SbF_6^-. [i]Switched the anion of **1a** to PF_6^-.

effects on the reaction. In the absence of oxidant, **3aa** was also obtained in 38% yield (entry 11). When DCE was switched to other solvents, the yields of the reaction decreased significantly to 15−23% (entries 12−15). In the absence of Rh(III) catalyst, the yield of the reaction was only 20% (entry 16). Examination of the temperature showed that 120 °C proved to be the best, affording **3aa** in 94% isolated yield (entries 17 and 18). Finally, when the anion of substrate **1a** was switched to chloride, bromide, SbF_6^-, and PF_6^- (entries 19−22), **3aa** was obtained in 19%, 14%, 79%, and 80% yields, respectively. This indicated that the coordination ability of the anion has notable influence on the reaction and the weakly coordinated anions gave better results. Thus, we determined our best conditions as shown in entry 18.

With the optimized conditions in hand, we further explored the reaction of **1a** with a variety of alkynes (Scheme 1). All of the reactions proceeded smoothly to afford the desired products **3** in moderate to excellent yields. For the diarylalkynes bearing an electron-donating group such as a methyl and methoxyl groups at the *para*-position of the phenyl ring afforded the desired products in higher yields (**3ab** 89%, **3ac** 92%). The halide (F, Cl, Br)-substituted diarylalkynes were well tolerated, affording the corresponding products in 82−87% yields (**3ad**−**af**). In contrast, the diarylalkynes with electron-withdrawing groups (CF_3, CO_2Et) at *para*-position of the phenyl ring gave lower yields (**3ag**, **3ah**) than those with

Scheme 1. Substrate Scope of Alkynes[a]



[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2·H_2O$ (0.2 mmol), KOAc (0.4 mmol), DCE (2.5 mL), 120 °C, 18 h, under Ar atmosphere; isolated yields are shown. [b]Single product was obtained. [c]Major isomer is shown.

electron-donating groups. Also, *m*-methyl-substituted diarylalkyne (**3ai**) gave 78% yield. Beside diarylalkynes, the aliphatic alkynes were also tolerated, affording the expected products in moderate yields (**3aj**, **3ak**). Apart from the symmetrical alkynes, the unsymmetrical alkynes were also tested for the present reaction. The reaction gave the regioselective products (**3al**, **3am**) with the aryl group proximal to the carboxylate group. The regioselectivity is from the regioselective insertion of an alkyne into the Rh−C bond.[12a] To our delight, the di(2-thienyl)acetylene also reacted smoothly with **1a** to give the desired product **3am** in 92% yield. However, using the electron-deficient alkyne, dimethyl acetylenedicarboxylate, the desired product **3ao** was obtained only in 34% yield.

Various substituted pyridinium trifluoromethanesulfonate salts under the optimized reaction conditions were also examined, and the results are shown in Scheme 2. Pyridinium salts bearing either an electron-donating or electron-withdrawing group at the *para*-position of pyridine ring were able to undergo this transformation to afford the corresponding indolizines in moderate to good yields (**3ba**−**ha**). As the yields show, the substrates with electron-withdrawing groups at the pyridine ring gave better results, while the substrate with the strongly electron-donating *N*,*N*-dimethylamino group at the pyridine ring only gave 24% yield (**3ia**). For pyridinium salts with *meta*-substituted groups, mixtures of two regioisomers with ratios of ∼7:1 (**3ja**) and 6:1 (**3ka**) were obtained in good yields. It was not possible to separate the two isomers by column chromatography to give the pure isomers. The pyridinium salts with *ortho*-substituted groups gave moderate yields (**3la**, **3ma**) because of steric effects. Aside from pyridinium salts, the quinolinium and isoquinolinium salts

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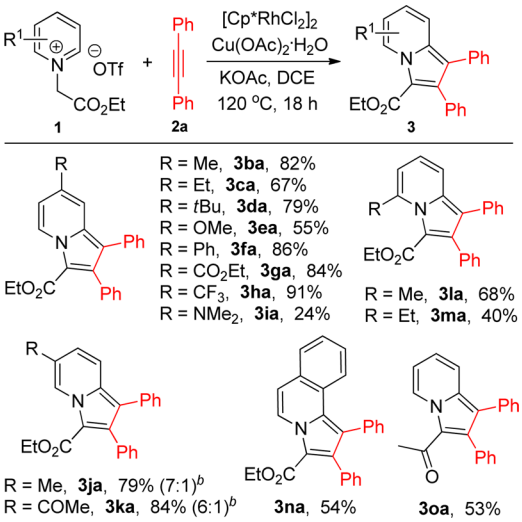
Scheme 2. Substrate Scope of Pyridinium Salts[a]

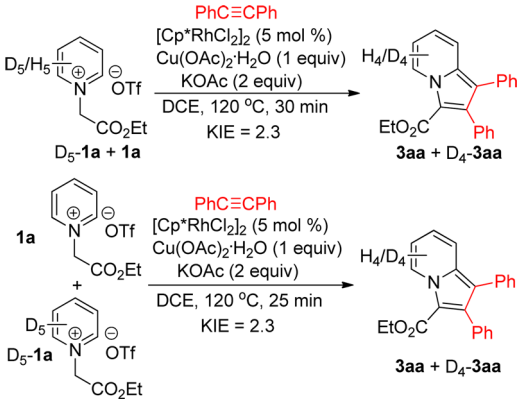


[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.2 mmol), KOAc (0.4 mmol), DCE (2.5 mL), 120 °C, 18 h, under Ar atmosphere; isolated yields are shown. [b]Major isomer is shown.

were also tested. The isoquinolinium salt afforded the desired product (**3na**) in 54% yield, while the quinolinium salt only gave a trace amount of product, probably due to the steric hindrance. Aside from 1-(2-ethoxy-2-oxoethyl)pyridinium derivatives, other typological pyridinium salts such as 1-methylpyridinium, 1-(cyanomethyl)pyridinium, 1-benzylpyridinium, 1-(pyridine-2-ylmethyl)pyridinium, and 1-(2-(dimethylamino)-2-oxoethyl)pyridinium were also tested. However, none of them could afford the desired product. Gratifyingly, when 1-(2-oxopropyl)pyridinium trifluoromethanesulfonate salt was used, the expected product (**3oa**) was obtained in 53% yield.

Furthermore, the kinetic effect (KIE) experiments were investigated. As shown in Scheme 3, the k_H/k_D values were 2.3

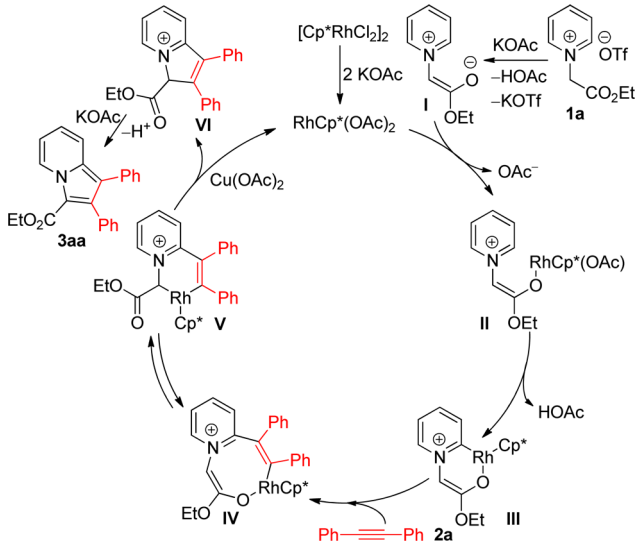
Scheme 3. KIE Experiments



for both of the competitive and parallel reactions, respectively. It indicated that the cleavage of the C−H bond of pyridine ring may have been involved in the rate-determining step.

In the absence of Rh or oxidant, the product **3aa** could be formed in low yields. This suggested that the reaction could follow the nucleophilic [3 + 2] cyclization pathway. The electron-deficient alkyne **2o**, which is more active for the typical [3 + 2] cyclization reaction, was reacted to give the product **3aa** in 34% and 39% yields in the presence and absence of Rh catalyst, respectively. This indicated that our conditions may not be suitable for the typical [3 + 2] cyclization, and the typical [3 + 2] cyclization process may be restrained in the presence of Rh catalyst. On the basis of the above experimental results and the previous reports,[13] a plausible mechanism for this reaction is proposed in Scheme 4, although the typical [3 + 2] cyclization mechanism cannot be fully excluded. The catalytic cycle begins with $Cp^*Rh(OAc)_2$, which comes from the ligand exchange between the acetate salt and rhodium dimer. In the presence of KOAc as base, the pyridinium salt is transferred to the intermediate **I**, which reacts with $Cp^*Rh(OAc)_2$ to form the intermediate **II**. Subsequently, the intermediate **II** undergoes C−H bond activation to generate a six-membered rhodacyclic intermediate **III** with the liberation of an acetic acid molecule. An alkyne coordination and migratory insertion into the Rh−C bond of **III** affords a rather strained eight-membered rhodacycle **IV**. There might exist an equilibrium between intermediate **IV** and the six-membered rhodacycle **V**. Afterward, the intermediate **V** undergoes reductive elimination to give the intermediate **VI** with the liberation of the Rh(I) species, which is concomitantly oxidized by oxidant $Cu(OAc)_2$ to the active Rh(III) catalyst for the next catalytic cycle. Finally, under the effect of base, the intermediate **VI** is transferred to the desired product **3aa** with the loss of a proton. The carboxylate group acts as a directed group in the reaction. The electron-withdrawing effect of the carboxylate group may also increase the acidity of the methylene protons of the pyridinium salt and promote the transformations of **1a** to **I** and **VI** to **3aa**.

Scheme 4. Proposed Reaction Pathway



In summary, we have successfully developed Rh(III)-catalyzed oxidative annulation reactions of pyridinium trifluoromethanesulfonate salts with alkynes leading to substituted indolizines by cleavage of $C(sp^2)$−H/$C(sp^3)$−H bonds. The starting materials are readily available, and the reactions have a broad substrate scope. This reaction overcomes some drawbacks of the previous indolizine synthetic methods and provides a new, efficient route to indolizine derivatives.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01181.

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

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Notes

The authors declare no competing financial interest.

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