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Facile One-Pot Synthesis of 2,3-Dihydro-1*H*-indolizinium Derivatives by Rhodium(III)-Catalyzed Intramolecular Oxidative Annulation via C–H Activation: Application to Ficuseptine Synthesis

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Abstract. Various substituted indolizidinium, quinolizinium and pyrido[1,2-a]azepinium salts synthesized from benzaldehydes (or α,β-unsaturated aldehydes) and alkyne-amines catalyzed by rhodium complex via C–H activation is demonstrated. The reaction was carried out under mild reaction conditions using $Cu(BF_4)_2{\cdot}6H_2O$ as the oxidant and the anion source and inexpensive oxygen as co-oxidant. A reaction mechanism involving imine formation followed by an *ortho* C–H activation, alkyne isertion and reductive elimination via a 7-membered rhodacycle is proposed. The present method is successfully applied to the synthesis of natural product, ficuseptine.

The indolizidine, quinolizidine and pyrido[1,2-a]azepinium alkaloids are important hetrocycles and are found in many naturally occuring alkaloids.[1] Such as louludinium chloride, ipalbidium, ficuseptine, juliprosine, tylophorine-D, dehydrotylophorine, clathryimine (B and C), and CCR5 antagonist anibamine C (Figure 1).[2] Among these alkaloids, ficuseptine, isolated from *Ficus Septica,* shows interesting antibacterial and antifungal activities and. Bracher and Daab first reported a five-step synthesis of ficuseptine via Suzuki and Sonogashira couplings followed by Sandmeyer iodination reaction.[3] Later, Snider and Neubert reported a one-pot synthesis of ficuseptine by using biomimic intramolecular Chichibabin pyridine synthesis.[4] However, these methods suffered from harsh and tedius reaction conditions.

Transition metal-catalyzed C–H functionalization has been a promising method for the synthesis of various *N*-containing heterocycles,[5] particularly, quaternary ammonium salts,[6] which are important key intermediates found in many natural products and medicinal ingredients.[1] Rh-[7] Ru-[8] and Co-catalyzed[9] intermolecular oxidative annulation of a variety of arylmethan-imines, arylpyridines, diazoarenes, *N*-hetrocyclic carbenes (NHC) and arylpyridinium salts with alkynes to give quarternary ammonium salts via C–H activation were intensively investigated. Recently, rhodium- and ruthenium-catalyzed C–H activation and intramolecular oxidative coupling of alkyne tethers as key steps for synthesis of *N*-hetrocycles was developed by several groups. Park and co-workers discovered a Rh-catalyzed intramolecular annulation of alkyne-tethered hydroxamic esters to afford isoquinolones.[10] Later, Mascarenas and Gulias *et al.* reported a Rh-catalyzed synthesis of tricyclic isoquinolines by intramolecular annulations of alkyne-tethered benzamides.[11] At the same time, Jia and Liu reported a Rh(III)-catalyzed intramolecular amidoarylation of alkynes via C–H activation to give fused tricyclic indole scaffolds.[12] Reddy and co-workers developed a microwave assisted Ru-catalyzed intramolecular annulation of alkyne-tethered benzamides to afford tricyclic isoquinolinones.[13] Very recently, Hua and co-workers revealed a mild Rh(III)-catalyzed inter- and intra-molecular annulations of alkyne-tethered ketones and amines to afford polyhetrocycles via cascade oximation.[14]

However, most of the above methods have not been applied to the synthesis of natural product. Recently, we reported a mild Rh-catalyzed intramolecular alkyne tethered imines providing a direct access to protoberberine alkaloids.[15a] We also developed various methods for the synthesis of isoquinolinium, cinnolinium, quinolizinium, and pyridinium salts via metal-catalyzed C–H activation.[15] Our continued interest in the application of metal-catalyzed C–H activation to natural product synthesis prompts us to investigate the synthesis of 2,3-dihydro-1*H*-indolizinium salts from the reaction of benzaldehydes and α,β-unsaturated aldehydes with alkyne-amines using Rh(III) species as the catalyst. Herein, we report the results of this study and the application of this methodology to the synthesis of 2,3-dihydro-1*H*-indolizinium alkaloid, ficuseptine.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, compound characterization, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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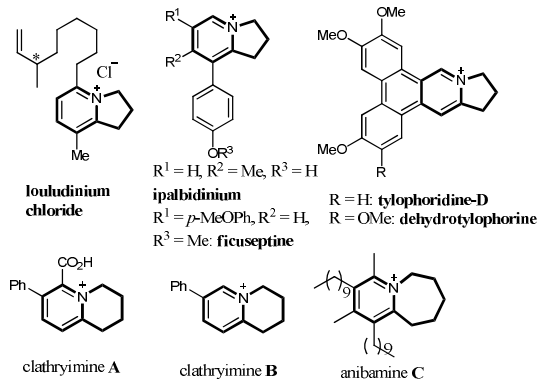
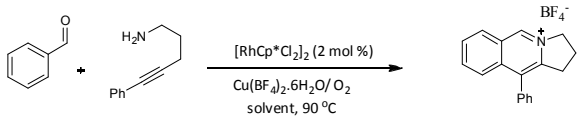


Figure 1. Representative naturally occurring and synthetic quaternary indolizinium, quinolizinium and pyrido[1,2-a]azepinium alkaloids.

To find the optimized conditions for the reaction of benzaldehyde **1a** with alkyne-amine **2a** to give 2,3-dihydro-1*H*-indolizinium salt **3aa**, we examined the effect of catalyst, and solvent used (see Table 1) on the yield of **3aa**. Treatment of **1a** (0.36 mmol), **2a** (0.30 mmol) and $Cu(BF_4)_2{\cdot}6H_2O$ (0.30 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2 mol %) in *t*-amylOH (2.0 mL) under O_2 (1 atm) for 6 h gave indolizinium salt **3aa** consisting of BF_4^- as the anion in 76% isolated yield (Table 1, entry 1). The presence of BF_4^- anion and the structure of **3aa** were confirmed by its ^1H, ^{13}C, ^{19}F and ^{11}B NMR spectra and HRMS data. The other solvents including *t*-butanol, *i*-propanol, TFE, methanol, DME, THF and DCE were also tested to give the expected product **3aa** in moderate to excellent yields (entries 2-8). Among these solvents *t*-butanol was found to be the best solvent for the reaction affording **3aa** in 95% yield (entry 2), while methanol also gave **3aa** in 81% yield (entry 5). To find the most suitable catalyst for the reaction, we investigated several metal catalysts in which $[Cp^*Rh(MeCN)_3][BF_4]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ affords **3aa** in 86 and 45% yields, respectively. In contrast, $Pd(OAc)_2$, $[RhCl(PPh_3)]$ and $Co(OAc)_2{\cdot}2H_2O$ gave only a trace or no **3aa** (entries 11-13). Notably, when the reaction was carried out without catalyst, no product **3aa** was formed (entry 14). When the reaction was performed in air, **3aa** was obtained in 70% yield (entry-15). Alkyne-amines **2** was prepared from commercially available 5-chloropent-1-yne in three steps in 60–75 yields (see Supporting Information).[16]

Table 1. Optimization studies for the reaction of benzaldehyde **1a** with alkyne-amine **2a**.[a]



1a 2a 3aa

Entry	Catalyst	Solvent	Yield [%][b]
1	$[RhCp^*Cl_2]_2$	*t*-amylOH	76
2	**$[RhCp^*Cl_2]_2$**	***t*-butanol**	**95**
3	$[RhCp^*Cl_2]_2$	*i*-propanol	46
4	$[RhCp^*Cl_2]_2$	TFE	70
5	$[RhCp^*Cl_2]_2$	methanol	81
6	$[RhCp^*Cl_2]_2$	DME	65
7	$[RhCp^*Cl_2]_2$	THF	70
8	$[RhCp^*Cl_2]_2$	DCE	66
9	$[Cp^*Rh(MeCN)_3][BF_4]_2$	*t*-butanol	86
10	$[Ru(p\text{-cymene})Cl_2]_2$	*t*-butanol	45
11	$Pd(OAc)_2$	*t*-butanol	NR
12	$[RhCl(PPh_3)]$	*t*-butanol	NR
13	$Co(OAc)_2.2H_2O$	*t*-butanol	Trace
14	-	*t*-butanol	NR
15	$[RhCp^*Cl_2]_2$	*t*-butanol	70[c]

[a] Unless otherwise mentioned, all reactions were carried out using benzaldehyde **1a** (0.36 mmol), alkyne-amine **2a** (0.30 mmol), $[Cp^*RhCl_2]_2$ (2.0 mol %), $Cu(BF_4)_2{\cdot}6H_2O$ (0.30 mmol), O_2 (1 atm, ca 1.5 L) and solvent (2.0 mL) at 90 ºC for 6 h. [b] Yields were measured by ^1H NMR, using mesitylene as an internal standard. [c] Air was used instead of O_2.[NR = No Reaction]

To evaluate the scope of the present reaction, first, we examined the reactions of *para*-substituted benzaldehydes **1a–1f** with alkyne-amine **2a** under the optimized reaction conditions (entry 6, Table 1). Thus, **2a** reacted with *p*-bromo **1b**, phenyl **1c,** ethyl **1d,** methoxy **1e** and nitro benzaldehydes **1f** to afford the expected indolizinium salts **3ba–3fa** in 81-91% yields. The substituents, either electron-donating or -withdrawing, at the para position of **1** all appear to give excellent product yield. The structure of **3aa** was further confirmed by the results of single-crystal X-ray diffraction.[17] We also tested the reactivity of *ortho*-substitued benzaldehydes with **2a**. Both 2-methyl- **1g** and 2-nitrobenzaldeyhydes **1h** reacted with **2a** nicely under the standard conditions to provide salts **3ga** and **3ha** in 78 and 75% yields, respectively. Further, it is interesting to know that the regioselectivity of *m*-substituted and *m,p*-disubstituted benzaldehydes were investigated. Thus, 3-methoxybenzaldehyde **1i** reacted with alkyne **2a** efficiently to afford regioisomeric products **3ia** and **3ia'** in a 50:50 ratio in 84% yield. These results suggest that the C-H bond activation and annulation reaction occurred nearly equally at both the *ortho* positions of benzaldehyde groups. However, the reaction of 3-bromo-4-methoxybenzaldehyde **1j** and 3,4-dimethoxybenzaldehyde **1k** with **2a** proceeded at C-6 position to afford **3ja**, and **3ka** in high regioisomeric ratios of 98:2 and 90:10 in 82 and 85% combined yields, respectively. The C-H bond activation and annulation reaction occurred more favorably at the 6-position of the *m,p*-dimethoxy group. In contrast, the reaction of benzo[*d*][1,3]dioxole-5-carbaldehyde **1l** with **2a** proceeded favorably at C-2 position to afford regioisomers **3la** in a 90:10 ratio in 78% combined yield.[15a] The regioselectivity of the major product is opposite to most of the *m,p-di*substituted benzaldehydes. Furan-2-carbaldehyde **1m** and thiophene-2-carbaldehyde **1n** also underwent C-H bond activation and annulation with alkyne-amine **2a** to afford the corresponding indolizinium salts **3ma** and **3na** in 75 and 84% yields, respectively.

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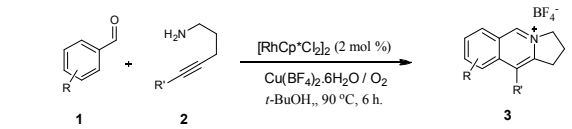
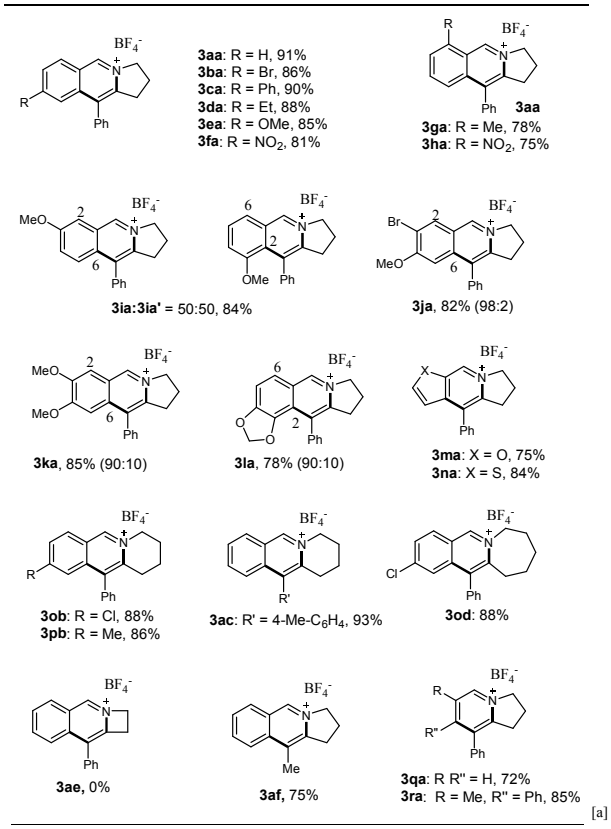
Table 2. Results of Rh-catalyzed reaction of aldehydes and amino-alkynes.[a,b]

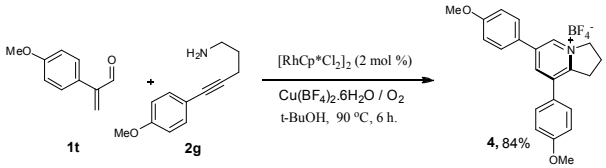




[a]Unless otherwise mentioned, all reactions were carried out using alkyne-amines **2** (0.40 mmol), aldehydes **1** (0.48 mmol), $[Cp^*RhCl_2]_2$ (2.0 mol %), $Cu(BF_4)_2{\cdot}6H_2O$ (0.45 mmol), O_2 (1 atm, ca 1.5 L) and *t*-butanol (2.5 mL) at 90 °C for 6 h. [b] Isolated yields.

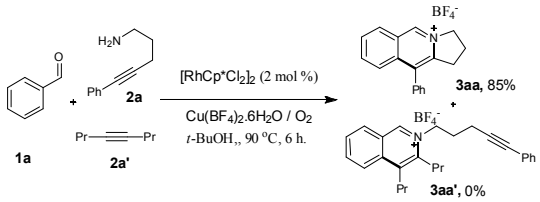
Next, we examined the reactions of benzaldehydes with $ArC{\equiv}C(CH_2)_nNH_2$ (**2**) by varying the alkyl chain length under standard reaction conditions. Thus, **2b** (n = 4) reacted with 4-chloro benzaldehyde **1o** and 4-methylbenzaldehyde **1p** smoothly to afford 1,2,3,4-tetrahydro-pyrido-isoquinolinium salts **3mb** and **3nb** in 88 and 86% yields, respectively. Similarly, alkyne-amine **2c** where Ar is *p*-tolyl, reacted with benzaldehyde **1a** smoothly to afford the corresponding tetrahydro-pyrido-isoquinolinium salts **3ac** in 93% yield. In a similar manner, 4-chloro benzaldehyde **1o** also reacted with 7-phenylhept-6-yn-1-amine **2d** efficiently to afford salt product **3od** containing a fused azacycloheptane ring in 88% yield. In contrast, the reaction of 4-phenylbut-3-yn-1-amine **2e** with benzaldehyde **1a** did not give the expected 4-membered ring salt product, due to the large ring strain of the expected product. Similarly, we examined the reactions of benzaldehydes **1a** with $MeC{\equiv}C(CH_2)_3NH_2$ **2g** under the standard reaction conditions to aford the expected salt product **3af** in 75% yield. In addition, the present Rh-catalyzed C–H activation reaction also can be applied to α,β-unsaturated aldehydes. Thus, the reaction of acrylaldehyde **1q** and (*E*)-2-methyl-3-phenylacrylaldehyde **1r** with akyne-amine **2a** afforded the corresponding dihydroindolizinium salts **3qa** and **3ra** in 72 and 85% yields, respectively. These results stimulate us to find and design a novel synthesis of natural product.

The significance of this Rh-catalyzed intra-molecular C–H activation/annulation reaction is further demonstrated by its application to the direct synthesis of a indolizinium alkaloid ficuseptine (Scheme 1). Thus, the reaction of 5-(4-methoxyphenyl)pent-4-yn-1-amine **2g** (0.40 mmol) with 2-(4-methoxyphenyl)acrylaldehyde[18] **1t** (0.48 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2.0 mol %) and $Cu(BF_4)_2{\cdot}6H_2O$ (0.45 mmol) in *t*-butanol under 1 atm of O_2 at 90 °C for 6 h afforded ficuseptine **4** with BF_4^- as the counter anion in 84% isolated yield.[4]



Scheme 1. One-pot synthesis of ficuseptine by Rh-catalyzed C–H activation/ annulation reaction.

To compare the reactivity of alkyne-amine **2** with an alkyne which cannot directly link to the aldehyde group of **1**, equal molar amounts of benzaldehyde **1a**, alkyne-amine **2a**, and 4-octyne **2a'** were dissolved in *t*-butanol and allowed to react under the standard reaction conditions. Interestingly, the reaction gave only the intramolecular annulation product **3aa**. The intermolecular annulation product **3aa'** was not formed. These results suggest that the intramolular annulation is much faster than the intermolecular reaction (Scheme 2).



Scheme 2. Inter- and intra-molecular Rh-catalyzed annulation reaction.[a] Standard reaction conditions.

Based on the known transition-metal catalyzed directing group-assisted inter- and intra-molecular C–H activation/annulation reactions,[5–15] a possible reaction mechanism is proposed for this catalytic reaction (Scheme 3). The catalytic cycle is probably initiated by the coordination of the imine nitrogen generated in situ from **1a** and **2a** to Rh(III), and is followed by the *ortho* C–H bond activation to form five-membered rhodacycle **I** and the release of H_3O^+. Next, the coordination of the intramolecular alkynyl group in **I** to the Rh center affords intermediate **II**. Further insertion of the alkynyl group into the Rh–C bond gives a bicyclic six- and seven-membered rhodacycle **III**. Reductive elimination of **III** affords the final salt, **3aa**, and Rh(I). The Rh(I) species is reoxidized by Cu(II) or O_2 to regenerate the active Rh(III) species for the next catalytic cycle.

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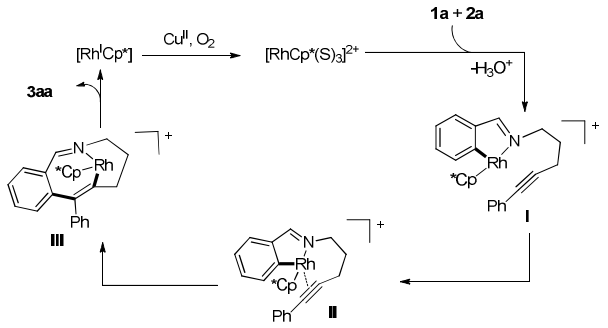

Scheme 3. Proposed catalytic cycle.

Conclusions

In summary, we have successfully developed an efficient Rh(III)/Cu/O_2 system for the one-pot synthesis of *bi- tri-* and *hetro*-cyclic fused quaternary ammonium salts from substituted benzaldehydes or α,β-unsaturated aldehydes and alkyne-amines via C–H activation. This protocol is succuessfully applied to the synthesis of natural product ficuseptine **4** in excellent yields. Notably, the present method is suitable for the convenient synthesis of a variety of indolizidinium, quinolizinium and pyrido[1,2-a]azepinium functionalized alkaloids. Application of the present method to other natural product synthesis is underway.

Acknowledgement

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