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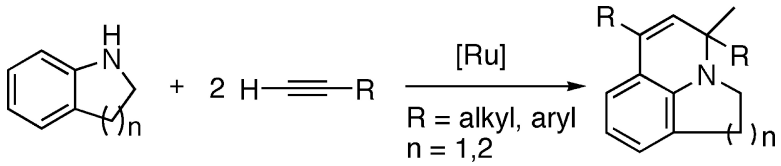

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Catalytic Synthesis of Tricyclic Quinoline Derivatives from the Regioselective Hydroamination and C−H Bond Activation Reaction of Benzocyclic Amines and Alkynes

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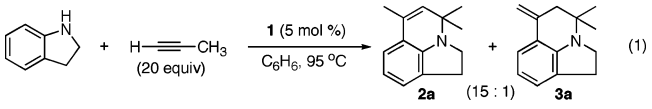
Catalytic C−H bond activation reaction is a highly attractive method in organic synthesis since it can give the products directly from readily available and unreactive starting materials without forming copious amount of byproducts.[1] In particular, considerable efforts have been devoted to the development of effective C−H bond activation methods for forming biologically important quinolines, indoles, and related polycyclic alkaloids.[2−7] Selected recent examples include: Heck-type coupling reaction involving 1,4-metal migration,[3] intramolecular C−H bond oxidative annulation of indoles,[4] combinatorial synthesis of quinoline derivatives from Lewis acid-catalyzed Mannich-like coupling reaction of arylamines, aldehydes, and alkenes,[5] and intramolecular alkylation and carboxylation of alkenylindoles.[6] A remarkably regioselective chelate-directed C−H bond activation methodology has also been developed and subsequently applied to the synthesis of quinoline-containing teleocidin B4 core.[7] A significantly more challenging task is to design an *intermolecular* version of the reaction since most of the reported examples involve *intramolecular* C−H bond activation methods. We recently reported a catalytic intermolecular C−H bond coupling reaction of cyclic amines and alkenes by using a ruthenium−hydride complex $(PCy_3)_2(CO)RuHCl$.[8] Here we report an effective catalytic method for the synthesis of tricyclic quinoline derivatives from the hydroamination and C−H bond activation reaction of benzocyclic amines and alkynes.

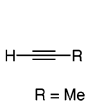
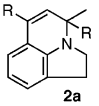
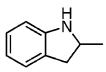
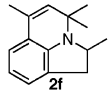
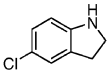
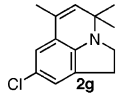
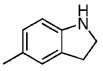
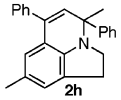
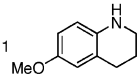
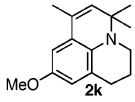
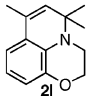
We initially discovered that the cationic ruthenium−hydride complex $[(PCy_3)_2(CO)(CH_3CN)_2RuH]^+BF_4^-$ (**1**)[9] is an effective catalyst for the coupling reaction of benzocyclic amines and terminal alkynes. For example, the treatment of indoline (30 mg, 0.25 mmol) with excess propyne (20 equiv) in the presence of **1** (5 mol %) in benzene at 95 °C for 24 h cleanly produced the tricyclic products **2a** and **3a** (15:1) in 81% combined yield (eq 1). The catalytic reaction produced tricyclic hydroquinoline structure directly from the regioselective coupling reaction of indoline and 2 equiv of propyne.



(1)

The complex **1** was found to be less effective for electron-deficient terminal alkynes; for example, the analogous reaction of indoline with phenylacetylene predominantly gave a simple hydroamination product. The search for a more effective ruthenium catalyst was ensued, and $Ru_3(CO)_{12}/NH_4PF_6$ (1:3 molar ratio) was found to be the most effective catalyst among the selected ruthenium complexes.[10] Thus, 1 mol % of $Ru_3(CO)_{12}/NH_4PF_6$ gave a quantitative yield of **2a** and **3a** (20:1, 99%) in less than 12 h for the reaction described in eq 1. Previously, the catalytic system $Ru_3(CO)_{12}/NH_4PF_6$ has been utilized for hydroamination and C−C bond activation reactions.[11]

Table 1. Coupling Reaction of Benzocyclic Amines and Terminal Alkynes[a]

entry	amine	alkyne	product	[Ru] (mol %)	t (h)	yd (%)[b]
						
1		R = Me	**2a**	1	12	99
2		R = Et	**2b**	1	12	92
3		R = Ph	**2c**	3	16	83
4		R = *p*-Tol	**2d**	3	16	85
5		R = CH_2OMe	**2e**	3	16	42
6			 **2f**	3	16	78
7			 **2g**	1	16	95
8			 **2h**	5	24	88
						
9		R = Me	**2i**	3	16	93
10		R = Ph	**2j**	5	20	68
11			 **2k**	1	16	93
12			 **2l**	10	24	90

[a] Reaction conditions: amine (1.5 mmol), alkyne (10−20 mmol), [Ru] = $Ru_3(CO)_3/NH_4PF_6$ (1:3), benzene (2−5 mL), 95 °C. [b] Isolated yields.

The scope of the coupling reaction was explored by using the $Ru_3(CO)_{12}/NH_4PF_6$ catalytic system (Table 1). Both five- and six-membered benzocyclic amines were found to readily undergo the regioselective coupling reaction with terminal alkynes to give the cyclized products **2** and trace amounts of the isomerization products **3** (<5%). No coupling product was formed with sterically demanding terminal alkynes such as with 3-methyl-1-butyne and internal alkynes. Analytically pure organic products were isolated after a simple column chromatography on silica gel, and their structure was completely established by spectroscopic methods.

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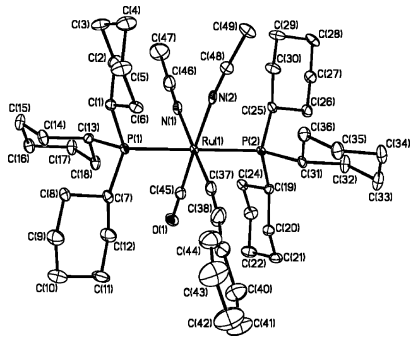
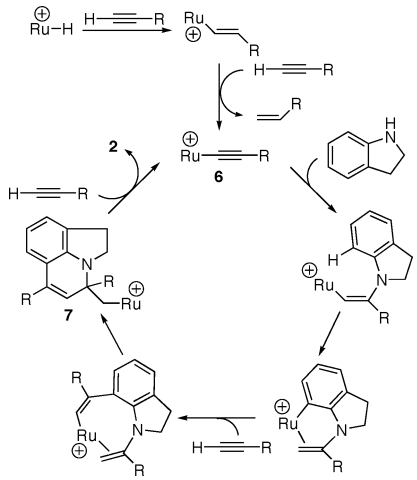


Figure 1. Molecular structure of the cation part of **5**.

Scheme 1



In an effort to gain insights on the nature of intermediate species, the reaction mixture of **1** (30 mg, 34 μmol) and HC≡CPh (10 mg, 0.1 mmol) in C_6D_6 was monitored by NMR. After heating the reaction tube at 60 °C for 10 min, a set of new peaks due to the cationic ruthenium−vinyl complex $[(PCy_3)_2(CO)(CH_3CN)_2RuCH{=}CHPh]^+BF_4^-$ (**4**) appeared as indicated by the characteristic vinyl resonances at δ 8.03 and 6.38 (d, J = 18.3 Hz) by ^{1}H NMR and the new phosphorus signal at δ 24.3 by ^{31}P NMR.[12] Upon further heating of the reaction mixture for 10 min at 80 °C, the peaks due to the cationic ruthenium−acetylide complex **5** appeared at the expense of the vinyl complex **4**. In particular, the complex **5** exhibited two alkynyl carbon signals at δ 111.4 and 103.7 (t, J_{PC} = 17.3 Hz), of which only the latter peak was coupled with the phosphorus atoms. The formation of styrene was also observed in the crude reaction mixture.

The acetylide complex **5** was subsequently isolated in 81% yield from a preparatory scale reaction of **1** with phenylacetylene in THF, and its structure was established by X-ray crystallography (Figure 1). The molecular structure of **5** showed an octahedral geometry with two trans PCy_3 ligands and cis arrangement between the acetylide and CO ligands. The bond distances of the acetylide ligand, Ru−C(37) = 2.008(5) Å and C(37)−C(38) = 1.188(7) Å, are comparable to the previously reported ruthenium−acetylide complexes.[13] The catalytic activity of isolated complex **5** was found to be identical to that of **1** for the coupling reaction of indoline and propyne.

A possible mechanism of the catalytic reaction is shown in Scheme 1. The successful isolation of the catalytically active complex **5** implicates a cationic ruthenium−acetylide species as the key species for the catalytic reaction. The acetylide complex **6** is initially generated from the reaction of a ruthenium−hydride complex with 2 equiv of a terminal alkyne, as indicated by the observation of ruthenium−vinyl complex **4** along with the formation of styrene. The hydroamination reaction of the acetylide species **6** via an initial N−H bond activation and intramolecular migratory insertion of the amine substrate would form the cationic vinyl species.[14] The subsequent *ortho*-C−H arene bond activation, the second alkyne insertion, and the regioselective migratory insertion/cyclization sequences would yield the cationic alkyl species **7**. Since **7** does not have any β-hydrogens, either oxidative addition/reductive elimination or σ-bond metathesis of the terminal alkyne must be invoked for the formation of **2** and the regeneration of the acetylide species **6**.

The following preliminary results provided supporting evidence for the reaction mechanism. The reaction of indoline with excess DC≡CPh (10 equiv) and $Ru_3(CO)_{12}/NH_4PF_6$ (3%) yielded the product **2c** with extensive deuterium incorporation on both vinyl (85% D) and methyl (81% D) positions as well as on the arene hydrogen para to the amine group (∼50%) as measured by both ^{1}H and ^{2}H NMR. Conversely, ca. 25% of the methyl group and 30% of the vinyl hydrogen of **2c** were found to contain the deuterium when N-deuterated indoline was reacted with 10 equiv of HC≡CPh. These results indicate that both C−H and N−H bond activation steps are reversible.

In summary, an efficient catalytic C−H bond activation/hydroamination protocol has been developed for the synthesis for tricyclic quinoline derivatives. A catalytically active cationic ruthenium−acetylide complex **5** has been isolated and characterized. Efforts to establish a detailed mechanism as well as the role of ruthenium−acetylide species in amination reactions are currently underway.

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Supporting Information Available: Experimental procedure, characterization data, and crystallographic data of **5** (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Yi, C. S.; Liu, N.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *Organometallics* **1997**, *16*, 3729 and references therein.
(14) The treatment of **5** with *p*-MeO−C_6H_4C≡CH (5 equiv) in THF for 3 h at 80 °C produced a ∼1:1 mixture of **5** and the alkyne-exchanged complex $[(PCy_3)_2(CO)(CH_3CN)_2RuC{\equiv}CC_6H_4$-*p*-$OMe]^+BF_4^-$. A negligible isotope effect of $k_{NH}/k_{ND} = 1.1 \pm 0.1$ was measured from the reaction of indoline and N-deuterated indoline with propyne (THF, 95 °C). Also, the catalytic reaction by **1** was found to be inhibited by PCy_3.[10] While these results are most consistent with an intramolecular insertion mechanism, we still cannot rigorously rule out a nucleophilic addition mechanism.

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