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Ru(II)-Catalyzed C−H Bond Activation for the Synthesis of Substituted Isoquinolinium Salts from Benzaldehydes, Amines, and Alkynes

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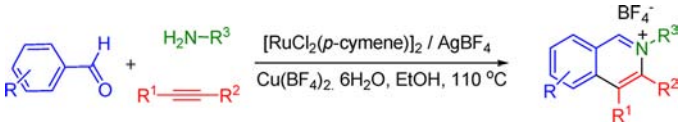
ABSTRACT



An efficient method for the synthesis of substituted isoquinolinium salts from benzaldehydes, amines, and alkynes via ruthenium-catalyzed C−H bond activation and annulation in one pot is described.

Highly substituted isoquinolinium salts are versatile building blocks for a number of naturally occurring products[1a−d] and have attracted much attention due to their unique biological activities.[1e−h] Previously, metal-mediated isoquinolinium salt synthesis has been demonstrated.[2] Later, several metal-catalyzed syntheses of isoquinolines from *N*-*tert*-butyl-*o*-halobenzaldimines,[3a−c] *N*-*tert*-butyl benzaldimines,[3d] aryl ketoximes,[3e−h] and alkynes were reported. In all of these reactions, isoquinolinium salts were proposed as the intermediates but were never isolated. Recently, we reported an efficient regioselective nickel-catalyzed annulation of 2-halobenzaldimines,[4a,b] *ortho*-iodoketimines with alkynes to give isoquinolinium salts.[4c] However, this nickel-catalyzed reaction requires a halide source, 2-halobenzaldimine or ketimine, as the substrate. Recently, the preparation of isoquinolinium salts involving C−H bond activation as a key step was reported. A $[RhCp^*Cl_2]_2$-mediated C−H bond activation/annulation reaction of 2-phenylpyridine and benzo[*h*]quinoline with DMAD (dimethyl acetylenedicarboxylate) to form isoquinolinium salts was shown by Jones et al. in 2008.[5] Very recently, we observed a [RhCp*]-catalyzed one-pot three-component reaction of aryl aldehydes, amines, and alkynes to afford isoquinolinium salts through C−H activation and annulation.[6] However, the methods described above require an expensive rhodium metal complex as the catalyst. The use of cheaper, environmentally benign alternative catalysts is still desirable in metal-catalyzed organic synthesis.

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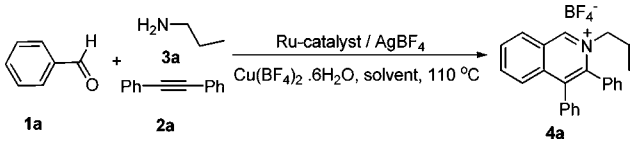
Table 1. Optimization Studies for the Ru(II)-Catalyzed Isoquinolinium Salts from Aryl Aldehyde, Propyl Amine with Alkynes[a]



entry	catalyst	solvent	yield (%)[b]
1	**$[RuCl_2(p\text{-cymene})]_2$**	**EtOH**	**92(90)**
2	$[RuCl_2(benzene)]_2$	EtOH	69
3	$[RuCl_2(COD)]_n$	EtOH	56
4	$RuCl_2(PPh_3)_3$	EtOH	8
5	$RuCl_3 \cdot xH_2O$	EtOH	0
6	$[RuCl_2(p\text{-cymene})]_2$	*t*-amylOH	87
7	$[RuCl_2(p\text{-cymene})]_2$	*t*-BuOH	67
8	$[RuCl_2(p\text{-cymene})]_2$	2-ethoxyethanol	54
9	$[RuCl_2(p\text{-cymene})]_2$	DCE	28
10	$[RuCl_2(p\text{-cymene})]_2$	toluene	16
11		EtOH	0

[a] Unless otherwise mentioned, all reactions were carried out using aryl aldehyde **1** (0.36 mmol), alkyne **2** (0.30 mmol), amine **3** (0.6 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $AgBF_4$ (10.0 mol %), $Cu(BF_4)_2 \cdot 6H_2O$ (0.6 mmol), and EtOH (2.5 mL) at 110 °C for 12 h. [b] Yields were determined by the ^1H NMR integration method.

Our continuing interest in metal-catalyzed C−H activation[6,7] and the reactions of isoquinolinium salts[4,6] prompted us to explore the formation of isoquinolinium salts via C−H activation using different metal complexes as the catalysts. Herein, we report an effective Ru(II)-catalyzed three-component reaction of aryl aldehydes, amines, and alkynes to form isoquinolinium salts through C−H activation and annulation. Previously, the most efficient ruthenium(0)-catalyzed chelation-assisted C−H bond activation has been reported by Murai and other research groups.[8] Recently, many $[RuCl_2(p\text{-cymene})]_2$-catalyzed C−H activation reactions have been reported.[9]

Treatment of benzaldehyde **1a** (0.36 mmol) with diphenyl acetylene **2a** (0.30 mmol) and propyl amine **3a** (0.60 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $AgBF_4$ (10 mol %), and $Cu(BF_4)_2 \cdot 6H_2O$ (2.0 equiv) in EtOH at 110 °C for 12 h gave isoquinolinium salt **4a** in 90% isolated yield (Table 2, entry 1). The structure of **4a** containing an isoquinolinium cation and a tetrafluoroborate anion was confirmed by its ^1H, ^{13}C, ^{19}F, and ^{11}B NMR and mass data. The ^{19}F and ^{11}B NMR spectral data of tetrafluoroborate anion are in agreement with those reported previously.[10]

This ruthenium-catalyzed C−H activation and annulation reaction depends greatly on the reaction conditions. To understand the nature of this reaction and to find the optimized reaction conditions, the effects of ruthenium complex and solvent on the yield of **4a** were examined. Ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ is most effective forming isoquinolinium salt product **4a** in 92% yield determined by an NMR integration method (Table 1, entry 1) or 90% isolated yield (Table 2, entry 1). Other ruthenium complexes including $[RuCl_2(benzene)]_2$, $[RuCl_2(COD)]_n$, and $RuCl_2(PPh_3)_3$ were also active, giving **4a** in 69−8% yields (entries 2−4), but $RuCl_3 \cdot xH_2O$ was totally inactive (entry 5). The choice of solvents is also vital to the catalytic reaction. The best solvent is EtOH in which **4a** was obtained in 90% yield. *t*-Amyl alcohol is also effective giving **4a** in 87% yield (entry 6). Other solvents such as *t*-BuOH, 2-ethoxyethanol, DCE, and toluene were less effective for the catalytic reaction giving **4a** in 67, 54, 28 and 16% yield, respectively (entries 7−10). Control experiments revealed that in the absence of a ruthenium catalyst or copper salt, no **4a** was obtained (entry 11). In the absence of silver salt, **4a** was observed in 86% yield. However, longer reaction time (24 h) is necessary (see Supporting Information for detailed studies).

Under similar reaction conditions, various substituted benzaldehydes (**1b**−**g**) reacted with diphenyl acetylene **2a** and propylamine **3a** to give the corresponding isoquinolinium salts in Table 2. Thus, 4-methylbenzaldehyde **1b** afforded **4b** in 89% yield (entry 2). Similarly, 4-methoxy benzaldehyde **1c** gave **4c** in 91% yield (entry 3). It is noteworthy that the structure of compound **4c** was further confirmed by a single-crystal X-ray diffraction. The catalytic reaction is also compatible with halo substituents on the aromatic ring of benzaldehyde **1**. Thus, the reaction of 4-bromo- and 4-chlorobenzaldehydes **1d**−**e** with **2a** and **3a** gave isoquinolinium salts **4d** and **4e** in 72 and 80% yield, respectively (entries 4 and 5). To understand the regioselectivity of *meta*-substituted benzaldehyde with **2a** and **3a**, we chose 3-chlorobenzaldehyde (**1f**) and 3,4-(methylenedioxy)benzaldehyde (**1g**) as the substrates. Thus, **1f** gave regioisomers **4f** and **4f'** in a 70:30 ratio in 78% combined

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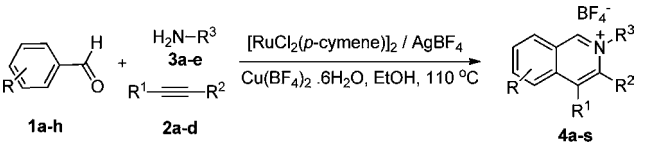
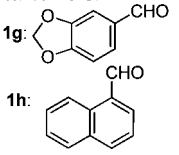
Table 2. Results of Ruthenium-Catalyzed C−H Activation and Annulation of Benzaldehydes, Amines, and Alkynes[a]

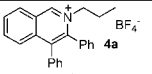
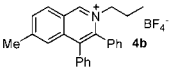
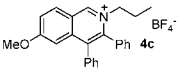
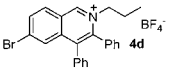
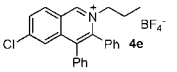
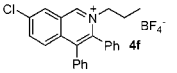
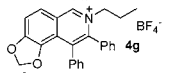
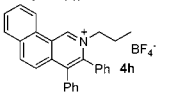
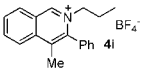
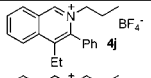
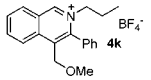
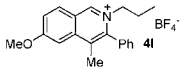
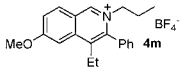
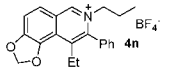
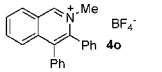
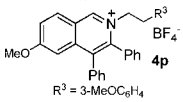
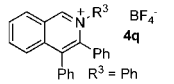
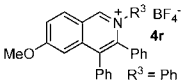
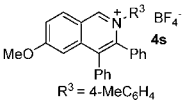


1a: R = H
1b: R = 4-Me
1c: R = 4-OMe
1d: R = 4-Br
1e: R = 4-Cl
1f: R = 3-Cl



2a: R^1, R^2 = Ph
2b: R^1 = Me, R^2 = Ph
2c: R^1 = Et, R^2 = Ph
2d: R^1 = CH_2OMe, R^2 = Ph

3a: R^3 = $(CH_2)_2CH_3$
3b: R^3 = Me
3c: R^3 = $(CH_2)_2$-3-$MeOC_6H_4$
3d: R^3 = Ph
3e: R^3 = 4-MeC_6H_4

entry	1	2	3	product 4	yield (%)[b]
1	**1a**	**2a**	**3a**	 **4a**	90
2	**1b**	**2a**	**3a**	 **4b**	89
3	**1c**	**2a**	**3a**	 **4c**	91
4	**1d**	**2a**	**3a**	 **4d**	72
5	**1e**	**2a**	**3a**	 **4e**	80
6	**1f**	**2a**	**3a**	 **4f**	78 (70:30)[c]
7	**1g**	**2a**	**3a**	 **4g**	65
8	**1h**	**2a**	**3a**	 **4h**	90
9	**1a**	**2b**	**3a**	 **4i**	77
10	**1a**	**2c**	**3a**	 **4j**	74
11	**1a**	**2d**	**3a**	 **4k**	69
12	**1c**	**2b**	**3a**	 **4l**	79
13	**1c**	**2c**	**3a**	 **4m**	76
14	**1g**	**2c**	**3a**	 **4n**	56
15	**1a**	**2a**	**3b**	 **4o**	94[d]
16	**1c**	**2a**	**3c**	 **4p** R^3 = 3-$MeOC_6H_4$	67
17	**1a**	**2a**	**3d**	 **4q** R^3 = Ph	67
18	**1c**	**2a**	**3d**	 **4r** R^3 = Ph	70
19	**1c**	**2a**	**3e**	 **4s** R^3 = 4-MeC_6H_4	75

[a] Unless otherwise mentioned, all reactions were carried out using aryl aldehyde **1** (0.36 mmol), alkyne **2** (0.30 mmol), amine **3** (0.60 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $AgBF_4$ (10.0 mol %), $Cu(BF_4)_2 \cdot 6H_2O$ (0.6 mmol), and EtOH (2.5 mL) at 110 °C for 12 h. [b] Isolated yields. [c] Regioisomeric ratio; the structure of the major isomer is shown in the table. [d] Methylamine (35% aqueous solution).

yield (entry 6). For **1g**, the reaction with **2a** and **3a** proceeded in a regioselective manner to give **4g** in 65% yield (entry 7). In this reaction, there are two possible C−H bond activation sites at C2 and C6 of **1g**, but the activation occurs at steric-hindered C6. In addition, the reaction of 1-napthaldehyde **1f** with **2a** and **3a** gave isoquinolinium salts **4h** in 90% yield (entry 8).

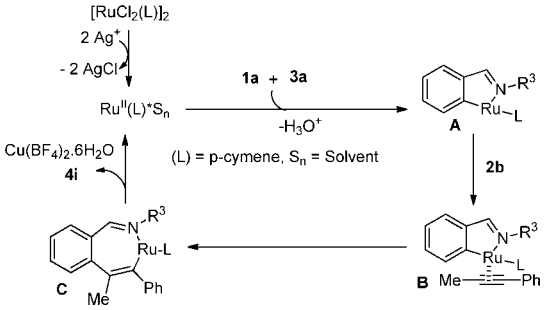
To understand the regioselectivity of the present reaction, unsymmetrical alkynes were employed as the substrates for the reaction with **1a** and **3a**. Thus, 1-phenyl-1-propyne (**2b**) gave **4i** in 77% yield (entry 9). No other regioisomeric product was detected in the reaction. The regiochemistry of product **4i** was confirmed by NOE experiments. In a similar fashion, phenyl-1-butyne (**2c**) and propargylic ether **2d** also reacted with **1a** and **3a** in a highly regioselective manner, providing isoquinolinium salt derivatives **4j** and **4k** in 74 and 69% yield, respectively (entries 10 and 11). In a similar manner, the reaction of phenyl-1-propyne (**2b**) and phenyl-1-butyne (**2c**) with **1c** and **3a** gave isoquinolinium salts **4l** and **4m** in 79 and 76% yield, respectively

(entries 12 and 13). The regioselectivity of unsymmetrical alkynes is similar to those observed previously.[2c,4] On the other hand, 3,4-(methylenedioxy)benzaldehyde (**1g**) reacted with **2c** and **2a**, affording **4n** in 56% yield along with trace of C6 C−H bond activation product (entry 14). The result indicates that the C−H activation occurs mainly at the sterically more hindered C2 instead of C6 position.

The scope of the amine used in the present catalytic reaction was also tested. In addition to propylamine, methyl- and 2-(3-methoxyphenyl)ethylamine (**3b**,**c**) reacted smoothly with **1a** and **1c** to afford **4o** and **4p** in 94 and 67% yield, respectively (entries 15 and 16). Similarly, aromatic amines also worked for this reaction. Thus, aniline **3d** reacted nicely with **1a** and **1c** with **2a** to give **4q** and **4r**, respectively, in good yield (entries 17 and 18). In a similar fashion, *p*-toluidine (**3e**) reacted nicely with **1c** and **2a** to give **4s** in 75% yield (entry 19).

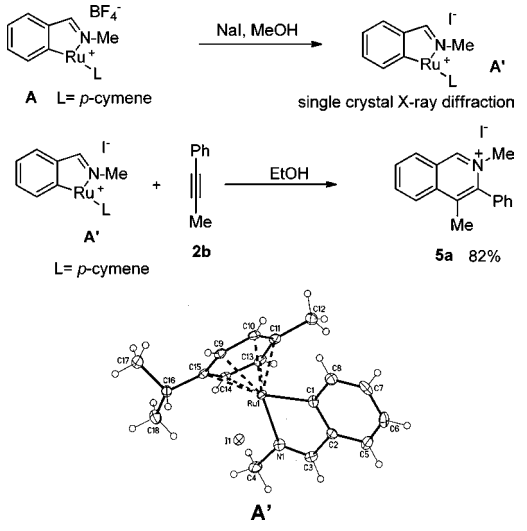
On the basis of the chemistry of known metal-catalyzed C−H bond activation/annulation reactions,[6−9,11] a possible mechanism to account for the present catalytic reaction is proposed (Scheme 1). The catalytic cycle is likely initiated by the removal of chloride by Ag^+ in $[RuCl_2(p\text{-cymene})]_2$ followed by coordination of imine nitrogen (in situ generation of imine from **1a** and **3a**) to the ruthenium species and subsequent *ortho*-C−H bond activation to form a five-membered ruthenacycle **A**. Regioselective insertion of alkyne **2b** into the ruthenium−carbon bond of intermediate **B** gives the seven-membered ruthenacycle **C**. Reductive elimination of **C** affords the final isoquinolinium salt **4i** and Ru(I). The ruthenium species is reoxidized by $Cu(BF_4)_2$ to regenerate the active Ru(II) species for the next cycle.

Scheme 1. Proposed Mechanism for the Formation of Isoquinolinium Salt



To support the proposed mechanism, we tried to isolate the key intermediate **A** (Scheme 1). Thus, heating **1a** and **3a** in the presence of 0.10 equiv of $[RuCl_2(p\text{-cymene})]_2$ and 0.40 equiv of $AgBF_4$ in EtOH (or) *t*-amyl alcohol at 110 °C for 6 h led to the isolation of five-membered ruthenacycle **A** in 75% yield. The five-membered ruthenacycle is a salt with BF_4^- as the counteranion and is characterized by its ^1H, ^{13}C NMR, and IR data. However, attempt to crystallize intermediate **A** by various solvents under different conditions failed. Fortunately, when intermediate **A** was treated with NaI in MeOH at room temperature for 0.15 h, **A**′ with iodide as the counteranion was isolated in 70% yield (Scheme 2). Single crystals of **A**′ were readily obtained from a methanol solution, and the structure was determined by X-ray diffraction. As shown in Scheme 2, the ruthenium complex is a 16-electron system containing a cyclometalated benzaldehyde imine and *p*-cymene ligand only. The iodide is not coordinated to the ruthenium(II) center. As expected, the reaction of **A**′ with 1-phenyl-1-propyne (**2b**) in EtOH at 80 °C for 2 h gave regioselective isoquinolinium salt **5a** in 82% yield (Scheme 2).

Scheme 2. Structure and Reactivity of Intermediate **A**



In conclusion, we have successfully developed a new highly regioselective ruthenium-catalyzed synthesis of substituted isoquinolinium salts from the reaction of benzaldehydes, amines, and alkynes via C−H bond activation and annulation. The proposed mechanism is strongly supported by the isolation of a five-membered ruthenacycle and an intermediate organic compound. Further application of this methodology in natural product synthesis and investigation of the detailed mechanism are in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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