C–H Activation

DOI: 10.1002/anie.201105755

One-Pot Synthesis of Isoquinolinium Salts by Rhodium-Catalyzed C–H Bond Activation: Application to the Total Synthesis of Oxychelerythrine**

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Highly substituted isoquinolinium salts are valuable and versatile intermediates for synthetic organic chemistry[1] and are widely utilized for the construction of various natural products and bioactive molecules.[2] The traditional methods for the synthesis of isoquinolinium salts from isoquinolines and alkyl halide derivatives is limited by the number of substituted isoquinolines that are readily available. As a result, the development of new versatile methods for the synthesis of isoquinolinium salts has become an important task in metal-catalyzed organic reactions. In this context, Heck and co-workers reported the formation of isoquinolinium salts from the reaction of cyclopalladated benzaldimines and alkynes,[3] but they did not succeed in making the reaction catalytic. Later, Larock and co-workers,[4a–b] and our group[4c] independently reported a palladium- and nickel-catalyzed synthesis of isoquinoline derivatives from *N*-*tert*-butyl *o*-halobenzaldimines and alkynes. Recently, Fagnou et al. developed a rhodium-catalyzed synthesis of isoquinolines from *N*-*tert*-butyl benzaldimines and alkynes through C–H activation and cyclization.[5a] Chiba and co-workers reported a Rh^{III}-catalyzed formation of isoquinolines from aryl ketone O-acyloximes and alkynes.[5b–c] In 2009, Miura et al. reported an efficient synthesis of polysubstituted isoquinoline derivatives by rhodium-catalyzed C–H bond activation of benzophenone imines with alkynes.[5d] Previously, the formation of dihydroisoquinolines through the catalytic electrophilic activation of the alkyne group in *o*-alknylbenzaldimines were described.[6] In all of these reactions, isoquinolinium salts were proposed as the intermediates but were never isolated. In 2009, we reported an efficient regioselective nickel-catalyzed annulation of 2-halobenzaldimines with alkynes to give isoquinolinium salts[7a–b] and the application of the method to the synthesis of isoquinolinone alkaloids.[7b] However, this nickel-catalyzed reaction requires a halide source, 2-halobenzaldimine, as the substrate. To the best of our knowledge, there is no report of the formation of isoquinolinium salts catalytically involving C–H bond activation as a key step. Very recently, Jones et al. reported the formation of isoquinolinium salts from *N*-benzylidenemethylamine, 2-phenylpyridine, and benzo[*h*]quinoline with DMAD (dimethyl acetylenedicarboxylate) through C–H bond activation.[8] The method required a stoichiometric amount of $[\{RhCp^*Cl_2\}_2]$ ($Cp^* = Me_5C_5$), and DMAD was the only alkyne used. Our continued interest in metal-catalyzed C–H activation[9] and the reactions of isoquinolinium salts[7] prompted us to explore the catalytic formation of isoquinolinium salts through C–H activation. Herein, we report an effective [RhCp*]-catalyzed three-component reaction of aryl aldehydes, methylamines, and alkynes to afford isoquinolinium salts regioselectively through C–H activation and annulation. Moreover, the present rhodium-catalyzed C–H activation reaction provides a very convenient and useful method for the synthesis of isoquinolinium salts under halide-free conditions.

The treatment of benzaldehyde (**1a**; 0.36 mmol) with diphenyl acetylene (**2a**; 0.30 mmol) and methylamine **3a** (0.45 mmol in 35% aqueous solution) in the presence of $[\{RhCp^*Cl_2\}_2]$ (2.0 mol%), $AgBF_4$ (1.0 equiv), and $Cu(OAc)_2$ (1.0 equiv) in *tert*-amyl alcohol at 110°C for 3 hours gave the isoquinolinium salt **4a** in 91% yield upon isolation (Table 1, 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 spectra, as well as MS data. The ^{19}F and ^{11}B NMR spectral data of the tetrafluoroborate anion are in agreement with those reported previously.[10] To the best of our knowledge, this is the first report for the synthesis of isoquinolinium salts by catalytic C–H activation.

It is noteworthy that in the reaction, if substrates **1a** and **3a** were replaced by the corresponding pre-synthesized imine, the reactions also proceeded but with much lower yield (19%). In the absence of $AgBF_4$ **4a** is formed, but in the absence of $Cu(OAc)_2$ **4a** was observed in 53% yield. Thus, we think that $AgBF_4$ (1.0 equiv) provides an inert anion necessary for the isolation of isoquinolinium salt and removes the chloride on the rhodium complex to facilitate the catalytic reaction. In addition, Ag^+ also serves as an oxidant for the reaction. Since the reaction requires two equivalents of the oxidant, we added $Cu(OAc)_2$ (1.0 equiv) to the reaction as the second oxidant. In fact, if we used two equivalents of $AgBF_4$ without any $Cu(OAc)_2$, the catalytic reaction proceeded smoothly to afford 92% of **4a** (for detailed studies see the Supporting Information).

The choice of silver salt is crucial for the success of the present catalytic reaction. Various silver salts were examined for the reaction of **1a** with **2a** and **3a**. Among them, $AgBF_4$ gave the best results, thus affording **4a** in 91% yield. $AgSbF_6$ was also effective in giving **4a** in 67% yield. Other silver salts

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[**] We thank the National Science Council of Republic of China (NSC-99-2811M-007-089) for support of this research.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105755.

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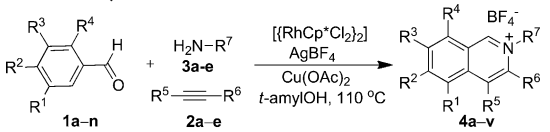
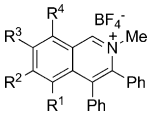
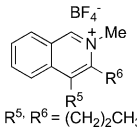
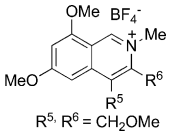
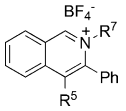
Table 1: Results of rhodium-catalyzed C–H activation and annulation of benzaldehydes, amines, and alkynes.[a]



1a: R^1, R^2, R^3, R^4 = H
1b: R^2 = Et
1c: R^2 = OMe
1d: R^2 = OMe, R^4 = OMe
1e: R^1, R^2, R^3 = OMe
1f: R^1 = Br, R^3, R^4 = OMe
1g: R^2 = F
1h: R^2 = Cl
1i: R^2 = Br
1j: R^2 = Ph
1k: R^2 = CO_2Me
1l: R^2 = NO_2
1m: R^3 = Cl
1n: R^3 = Br
1b–n: H substituents are omitted

2a: R^5, R^6 = Ph
2b: R^5, R^6 = $(CH_2)_2CH_3$
2c: R^5, R^6 = CH_2OMe
2d: R^5 = Me, R^6 = Ph
2e: R^5 = CH_2OMe, R^6 = Ph

3a: R^7 = Me
3b: R^7 = $(CH_2)_2CH_3$
3c: R^7 = CH_2Ph
3d: R^7 = Ph
3e: R^7 = 4-$OMeC_6H_4$

Entry	1	2	3	Product 4[b]		Yield [%][c]
1	1a	2a	3a		**4a**: R^1, R^2, R^3, R^4 = H	91
2	1b	2a	3a		**4b**: R^2 = Et	84
3	1c	2a	3a		**4c**: R^2 = OMe	92
4	1d	2a	3a		**4d**: R^2, R^4 = OMe	96
5	1e	2a	3a		**4e**: R^1, R^2, R^3 = OMe	78
6	1f	2a	3a		**4f**: R^1 = Br, R^3, R^4 = OMe	83
7	1g	2a	3a		**4g**: R^2 = F	82
8	1h	2a	3a		**4h**: R^2 = Cl	78
9	1i	2a	3a		**4i**: R^2 = Br	71
10	1j	2a	3a		**4j**: R^2 = Ph	83
11	1k	2a	3a		**4k:** R^2 = CO_2Me	58
12	1l	2a	3a		**4l**: R^2 = NO_2	–
13	1m	2a	3a		**4m**: R^3 = Cl **4m'**: R^1 = Cl	78 (92:8)
14	1n	2a	3a		**4n**: R^3 = Br **4n'**: R^1 = Br	81 (92:8)
15	1a	2b	3a	 $R^{5,}$ R^6 = $(CH_2)_2CH_3$	**4o**	88
16	1d	2c	3a	 $R^{5,}$ R^6 = CH_2OMe	**4p**	70
17	1a	2d	3a		**4q**: R^5, R^7 = Me	85
18	1a	2e	3a		**4r**: R^5 = CH_2OMe, R^7 = Me	79
19	1a	2a	3b		**4s**: R^5 = Ph, R^7 = $(CH_2)_2CH_3$	83
20	1a	2a	3c		**4t**: R^5 = Ph, R^7 = CH_2Ph	87
21	1a	2a	3d		**4u**: $R^{5,}$ R^7 = Ph	76
22	1a	2a	3e		**4v**: R^5 = Ph, R^7 = 4-$OMeC_6H_4$	80

[a] Unless otherwise mentioned, all reactions were carried out using aryl aldehyde **1** (0.36 mmol), alkyne **2** (0.30 mmol), amine **3** (0.45 mmol in 35% aqueous solution), [{RhCp*Cl_2}$_2$] (2.0 mol%), $AgBF_4$ (0.3 mmol), $Cu(OAc)_2$ (0.3 mmol), and *tert*-amyl alcohol (2.5 mL) at 110°C for 3 h. [b] For **4b–n**, H substituents are omitted. [c] Yield of isolated product.

including AgOAc, Ag_2CO_3, and Ag_2O did not give the expected isoquinolinium product. Various oxidants were also tested for the reaction. Among these $Cu(OAc)_2$ was found to be most effective, thus giving **4a** in 91% yield. Other oxidants including $Cu(OTf)_2$ and oxygen are also effective delivering **4a** in 88 and 73% yield, respectively. Of the solvents tested for the catalytic reaction, *tert*-amyl alcohol afforded the highest product yield of 91%. Others such as EtOH, *t*BuOH, 1,2-dichloroethane, CH_3CO_2H and MeOH gave **4a** in 90, 72, 64, 59, and 58% yield, respectively.

Under similar reaction conditions, various substituted benzaldehydes (**1b–j**) reacted with diphenyl acetylene (**2a**) and methylamine (**3a**) to give the corresponding isoquinolinium salts. Thus, 4-ethylbenzaldehyde (**1b**) afforded **4b** in 84% yield (Table 1, entry 2). Benzaldehydes **1c–f** with electron-rich groups reacted nicely with **2a** and **3a** to give **4c–f** in good yield (entries 3–6). The catalytic reaction is also compatible with halo substituents on the aromatic ring of benzaldehyde **1**. Thus, the reaction of various halo-substituted benzaldehydes (**1g–i**) with **2a** and **3a** gave isoquinolinium salts **4g–i** in good yield (entries 7–9). In addition, 4-phenylbenzaldehyde (**1j**) reacted with **2a** and **3a** to provide **4j** in 83% yield (entry 10). The reaction of 4-methylesterbenzaldehyde (**1k**) with gave **4k** in 58% yield (entry 11), but the reaction of 4-nitrobenzaldehyde did not give the expected isoquinolinium salt (entry 12). To understand the regioselectivity of the *meta*-substituted benzaldehyde with **2a** and **3a**, we chose 3-chloro- (**1m**) and 3-bromobenzaldehyde (**1n**) as the substrates. Thus, **1m** gave the regioisomers **4m** and **4m′** in a 92:8 ratio in 78% combined yield (entry 13), and **1n** afforded the regioisomers **4n** and **4n′** in a 92:8 ratio and 81% combined yield (entry 14).

In addition to **2a**, symmetrical aliphatic alkynes including oct-4-yne (**2b**) and 1,4-dimethoxy-2-butyne (**2c**) reacted with **1a** and **1d**, respectively, in the presence of **3a** to give the corresponding products **4o** and **4p** (entries 15 and 16). 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 (**2d**) and the propargylic ether **2e** gave **4q** and **4r**, respectively (entries 17 and 18). No other regioisomeric product was detected in these two reactions. The regiochemistry of products **4q** and **4r** was confirmed by NOE experiments.

The scope of the amine used in the present catalytic reaction was also tested. In addition to methylamine, propyl- and benzylamine (**3b**,**c**) reacted smoothly to afford **4s** and **4t**, respectively (entries 19 and 20). Similarly, aromatic amines including aniline (**3d**) and *p*-anisidine (**3e**) reacted nicely to give **4u** and **4v**, respectively (entries 21 and 22).

On the basis of the chemistry of known metal-catalyzed C–H bond activation/annulation reactions,[7–9,11] 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 from [{RhCp*Cl_2}$_2$] by Ag^+, coordination of the imine nitrogen atom (in situ

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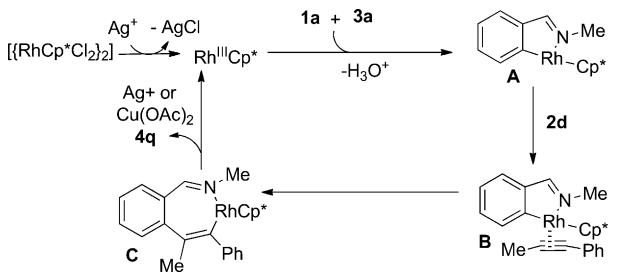
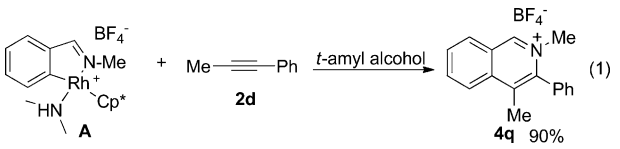


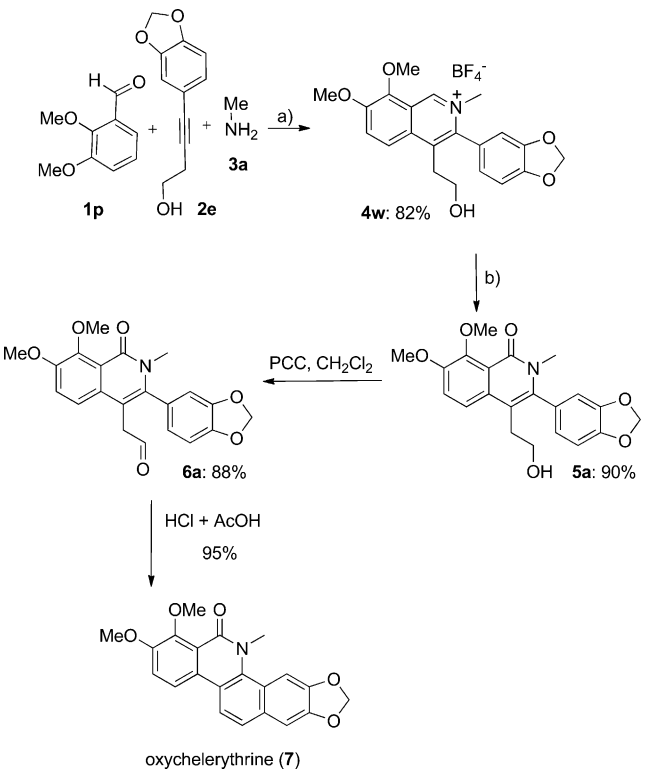
Scheme 1. Proposed mechanistic pathway for the formation of isoquinolinium salt.

generation of imine from **1a** and **3a**) to the rhodium species, and subsequent *ortho* C–H bond activation to form the five-membered rhodacycle **A**. Regioselective insertion of the alkyne **2d** into the rhodium–carbon bond of intermediate **B** gives the seven-membered rhodacycle **C**. Reductive elimination of **C** affords the final isoquinolinium salt **4q** and Rh^{I}. The rhodium species is reoxidized by $Cu(OAc)_2$ or Ag^+ to regenerate the active Rh^{III} species for the next cycle.

To support the proposed mechanism, we tried to isolate the intermediate **A** shown in Scheme 1. Thus, heating **1a** and **3a** in the presence of 0.1 equivalents of $[\{RhCp^*Cl_2\}_2]$ and 1 equivalent of $AgBF_4$ in *tert*-amyl alcohol at 110 °C for 1 hour led to the isolation of the five-membered rhodacycle **A** in 86 % yield. This complex was characterized by its ^1H and ^{13}C NMR spectra, as well as IR data. In addition, the structure was determined by single-crystal X-ray diffraction (see the Supporting Information). Surprisingly, the amine coordinated to the rhodium center in **A** is dimethylamine, not the original methylamine. This is likely to be a result of a partial conversion of methylamine into dimethylamine under the reaction conditions. A similar conversion was reported and such a mechanism has been proposed before.[12] The reaction of **A** with 1-phenyl-1-propyne (**2d**) in *tert*-amyl alcohol at 110 °C for 0.15 hours regioselectively gave the isoquinolinium salt **4q** in 90 % yield [Eq. (1)].



The significance of this rhodium-catalyzed C–H activation/annulation reaction is additionally demonstrated by its application to the total synthesis of the isoquinolinone alkaloid oxychelerythrine (**7**). The synthesis of this natural product using the present methodology is shown in Scheme 2. First, the reaction of the aldehyde **1p**, alkyne **2e**, and **3a** in the presence of $[\{RhCp^*Cl_2\}_2]$, $AgBF_4$, and $Cu(OAc)_2$ in *tert*-amyl alcohol at 110 °C for 3 hours gave the isoquinolinium salt **4w** in 82 % yield (isolated) in a highly regioselective manner. No other regioisomer was detected in this catalytic reaction. The regiochemistry was confirmed by the NOE experiments. This isoquinolinium salt was eventually converted into **7** by



Scheme 2. Total synthesis of oxychelerythrine. a) $[\{RhCp^*Cl_2\}_2]$ (2.0 mol %), $AgBF_4$ (1.0 mmol), $Cu(OAc)_2$ (1.0 mmol) and *tert*-amyl alcohol (5.0 mL) at 110 °C for 3 h; b) $K_3[Fe(CN)_6]$ (2.0 mmol), CsOH (1.2 mmol) and $MeOH/H_2O$ (1:1; 10mL) at 80 °C for 12 h.

following the procedure we employed before.[7b] First, **4w** was treated with $K_3[Fe(CN)_6]$ and CsOH[13a] in a mixture of H_2O and MeOH (1:1) to give the isoquinolone **5a** in 90 % yield. Compound **5a** was then transformed into the corresponding aldehyde derivative **6a** in 88 % yield by PCC (pyridinium chlorochromate) oxidation.[13b] After a successful acid-catalyzed ring-closing and a dehydration reaction, **7**[14] was obtained in 95 % yield. The overall yield of **7** from **1p**, **2e**, and **3a** was 62 %, which is much higher than those reported earlier.[14b–c] The alkyne **2e** can be easily prepared from the Sonogashira reaction of commercially available 5-bromobenzo[*d*][1,3]dioxole and 3-butyn-1-ol.[7] It is interesting to note that **7** has exhibited antitumor properties,[15a] and the ability to stimulate GSH transport[15b] and inhibit the BclXL function.[15c] There are a large number of isoquinolinone alkaloids existing in the nature that have a core structure similar to that of oxychelerythrine (**7**). As a result, the methodology shown in Scheme 2 should be very useful for the synthesis of these alkaloids.

In conclusion, we have successfully developed a new highly regioselective rhodium-catalyzed synthesis of substituted isoquinolinium salts from the reaction of benzaldehydes, amines, and alkynes through C–H bond activation and annulation. The protocol was successfully applied to the total synthesis of oxychelerythrine (**7**) with excellent yield. The proposed mechanism is strongly supported by the isolation of a five-membered rhodacycle and an intermediate organic

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compound. Additional applications of this methodology to natural product syntheses and investigations into the detailed mechanism are in progress.

Experimental Section

General procedure for the rhodium-catalyzed synthesis of isoquinolinium salt: A sealed tube containing $[\{RhCp^*Cl_2\}_2]$ (2.0 mol%), $AgBF_4$ (0.30 mmol), and $Cu(OAc)_2$ (0.30 mmol) was evacuated and purged with nitrogen gas three times. Then, *t*-amyl alcohol (2.5 mL), aryl aldehyde **1** (0.36 mmol), alkyne **2** (0.30 mmol), and methylamine **3** (0.45 mmol in 35% aqueous solution) were sequentially added to the mixture via syringe under a nitrogen atmosphere, and the reaction mixture was stirred at 110°C for 3 h. The mixture was cooled to RT and diluted with CH_2Cl_2 (10 mL). The mixture was then filtered through a Celite pad and the Celite pad was washed with CH_2Cl_2 (50 mL). The combined filtrate fractions were concentrated under vacuum and the residue was carefully washed with ethyl acetate and *n*-hexane to afford the desired pure product **4**.

Received: August 15, 2011
Revised: September 29, 2011
Published online: November 15, 2011

Keywords: alkynes · annulation · C—H activation · heterocycles · rhodium

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