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Rh(III)-catalyzed synthesis of 1-substituted isoquinolinium salts *via* a C–H bond activation reaction of ketimines with alkynes†

Natarajan Senthilkumar, Parthasarathy Gandeepan, Jayachandran Jayakumar and Chien-Hong Cheng*

An efficient synthesis of highly substituted isoquinolinium salts from ketimines and alkynes *via* a Rh(III)-catalyzed C–H bond activation and annulation reaction is described.

Isoquinolinium cation is an important structural motif found in many naturally occurring compounds, which exhibit numerous important biological activities.[1] They are also known as potential intermediates for the synthesis of many bioactive and heterocyclic compounds.[2] Owing to their broad application, several metal-mediated or catalyzed methods have been known for the synthesis of isoquinolinium salts from *ortho*-halo imines.[3,4] Recently, transition-metal-catalyzed C–H bond activation reactions have played an important role in the formation of carbon–carbon and carbon–heteroatom bonds.[5] In particular, Rh(III)-complexes have revealed great potential in the synthesis of various heterocyclic and carbocyclic compounds through the C–H bond activation reactions.[6] In this context, we have demonstrated the Rh(III) and Ru(II)-catalyzed C–H activation reactions for the synthesis of isoquinolinium salts from aldehydes, amines and alkynes.[7] In addition to isoquinolinium salts, Rh(III)-catalyzed C–H activation reactions have also been applied in the synthesis of pyridoisoquinolinium,[8a,b] cinnolinium[8c,d] and quinolizinium[8e] salts. The known C–H activation reactions to produce isoquinolinium salts all involve aldehyde imines and no example was reported for formation of isoquinolinium salts from ketimines. A key reason is that the reaction of ketones with amines to form the corresponding ketimines and water is in general thermodynamically unfavorable.[7] Thus, the synthesis of ketimines by carefully removing the water produced is required prior to the catalytic reaction with alkynes. In addition, the exclusion of water in the reaction solution to prevent the hydrolysis of ketimines is necessary. It should be noted that the 1-substituted isoquinolinium cation is an important core in natural and pharmaceutical products (Fig. 1).[9] Our continuous interest in the transition-metal-catalyzed C–H bond activation reactions[10] and the reactions for the synthesis of nitrogen containing salts prompts us to tackle this problem. Herein, we report an efficient C–H activation route for the synthesis of 1-substituted isoquinolinium salts from ketimines and alkynes using a Rh(III) catalyst system.

Several types of ketimines were successfully prepared by refluxing an equimolar mixture of the corresponding ketones and amines in toluene using a Dean–Stark apparatus. Fortunately, the reaction of **1a** (0.365 mmol) with diphenylacetylene (**2a**) (0.281 mmol) in the presence of 2.0 mol% of $[RhCp^*Cl_2]_2$, $AgBF_4$ (0.281 mmol) and $Cu(OAc)_2$ (0.281 mmol) in *t*-amylOH (2 mL) at 110 °C for 4 h proceeded smoothly; isoquinolinium salt **3aa** was obtained in 83% isolated yield (Table 1). This C–H activation reaction depends greatly on the choice of solvent. Among the solvents examined, *t*-amylOH gave the highest yield of salt product **3aa** of 83%. Other alcohols like EtOH and MeOH were less effective giving **3aa** in 80 and 55% yields, respectively; the other solvents including DMF, *o*-dichlorobenzene, 1,2-dichloroethane (DCE), toluene and 1,4-dioxane were totally inactive (see ESI† for a detailed optimization study).

Having the optimized reaction conditions in hand, we then examined the reaction of various substituted acetophenone imines (**1b–k**) with diphenylacetylene (Table 1). Thus, 4-bromo, 4-iodo, 4-methoxy and 4-phenyl acetophenone imines **1b–e** afforded the

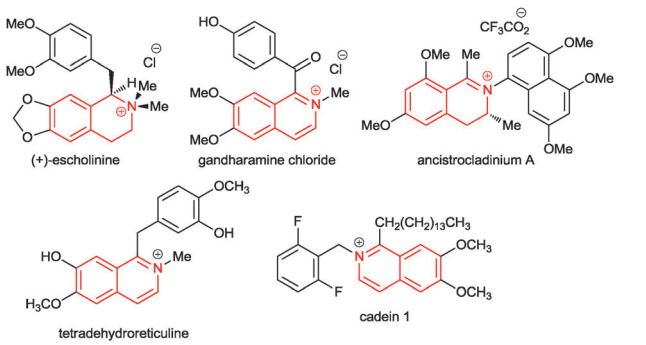
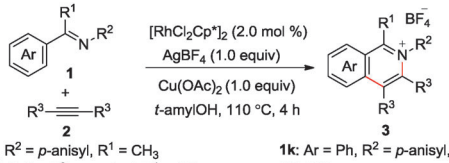


Fig. 1 Examples of natural products and bio-active molecules having a 1-substituted isoquinolinium core structure.

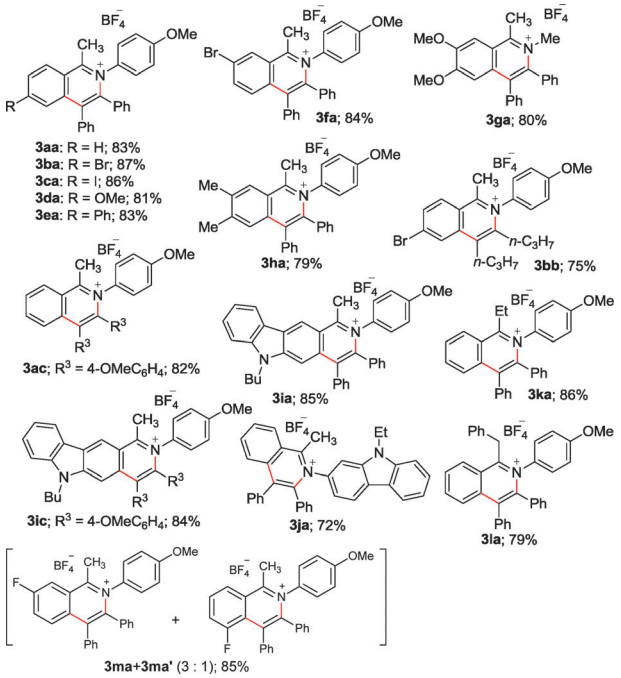
Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan. E-mail: chcheng@mx.nthu.edu.tw; Fax: +886-3-5724698; Tel: +886-3-5721454

† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c3cc49467e

Table 1 Results of Rh(III)-catalyzed annulation of acetophenone imines with internal alkynes[a,b]



1a: Ar = Ph, R^2 = *p*-anisyl, R^1 = CH_3
1b: Ar = 4-BrC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
1c: Ar = 4-IC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
1d: Ar = 4-OMeC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
1e: Ar = 4-PhC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
1f: Ar = 3-BrC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
1g: Ar = 3,4-diOMeC_6H_3, R^2 = Me, R^1 = CH_3
1h: Ar = 3,4-diMeC_6H_3, R^2 = *p*-anisyl, R^1 = CH_3
1i: Ar = *N*-butylcarbazol-3-yl, R^2 = *p*-anisyl, R^1 = CH_3
1j: Ar = Ph, R^2 = *N*-ethylcarbazol-3-yl, R^1 = CH_3
1k: Ar = Ph, R^2 = *p*-anisyl, R^1 = CH_2CH_3
1l: Ar = Ph, R^2 = *p*-anisyl, R^1 = CH_2Ph
1m: Ar = 3-FC_6H_4, R^2 = *p*-anisyl, R^1 = CH_3
2a: R^3 = Ph
2b: R^3 = *n*-C_3H_7
2c: R^3 = *p*-anisyl

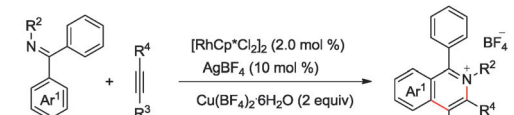


[a] Unless otherwise mentioned, all reactions were carried out using acetophenone imine **1** (0.365 mmol), alkyne **2** (0.281 mmol), $[RhCp^*Cl_2]_2$ (3.4 mg, 0.00562 mmol), $AgBF_4$ (54 mg, 0.281 mmol) $Cu(OAc)_2$ (51 mg, 0.281 mmol) in *t*-amyl alcohol (2.0 mL) at 110 °C for 4 h. [b] Isolated yields based on **2**.

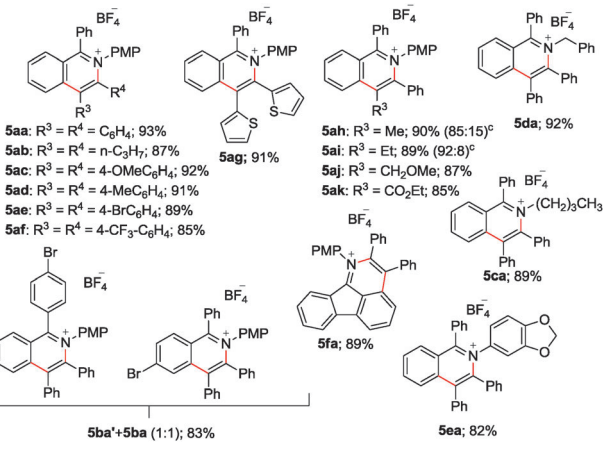
corresponding isoquinolinium salts **3ba–ea** in 81–87% yields. The catalytic reaction is compatible nicely with *meta* substitution on the phenyl ring of acetophenone imines. As a result, 3-bromo-, 3,4-dimethyl- and 3,4-dimethoxy substituted substrates **1f–h** afforded the corresponding isoquinolinium salts **3fa**, **3ga** and **3ha** in 84, 80 and 79% yields, respectively. These *meta*-substituted substrates **1f–h** possess two possible C–H activation sites and are selectively functionalized only at the less hindered site. In products **3ba**, **3ca** and **3fa**, the halo substituents remain intact and can be used for further transformations. Dialkylalkyne 4-octyne (**2b**) also reacted smoothly with **1b** to give isoquinolinium salt **3bb** in 75% yield. Furthermore, the reaction of indoloacetophenone imine **1i** with alkynes **2a** and **2c** gave salt products **3ia** and **3ic** in 85 and 84% yields, respectively. As expected, *N*-carbazolyl acetophenone imine **1j** also reacted with **2a** effectively to provide isoquinolinium salt **3ja** in 72% yield. The reaction of propiophenone imine **1k** with **2a** gave isoquinolinium salt **3ka** in 86% yield. Benzyl phenyl ketoimine **1l** reacted smoothly with **2a** to form 1-benzyl substituted isoquinolinium salt **3la** in 79% yield. Finally, 3-fluoro acetophenone imine **1m** underwent a reaction with **2a** to give two regio isomeric products **3ma** + **3ma′** in a 3 : 1 ratio in 85% combined yield.

Having achieved the synthesis of isoquinolinium salts from substituted acetophenone imines, we tested the reaction of benzophenone imine with various alkynes. Under similar reaction conditions, *N*-4-methoxyphenyl benzophenone imine **4a** reacted with diphenylacetylene **2a** to give isoquinolinium salt **5aa** in 97% isolated yield. To avoid excess amount of expensive Ag salt, we re-optimized the reaction conditions (see ESI†) and found that the reaction of **4a** (0.365 mmol) and diphenyl acetylene **2a** (0.281 mmol) in the presence of $[RhCp^*Cl_2]_2$ (2.0 mol%), $AgBF_4$ (0.0281 mmol) and $Cu(BF_4)_2{\cdot}H_2O$ (0.562 mmol) in *t*-amylOH (2 mL) at 110 °C for 4 h gave **5aa** in 93% isolated yield (Table 2). With these modified reaction conditions, we examined various electron rich and electron deficient symmetrical alkynes **2b–g** with **4a** to produce isoquinolinium salts. Thus, the reaction of 4-OMe, 4-Me, 4-Br and 4-CF_3 substituted diphenylacetylenes

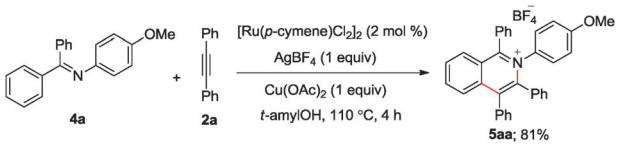
Table 2 Results of Rh(III)-catalyzed annulation of benzophenone imines with internal alkynes[a,b]



4a: Ar^1 = Ph, R^2 = 4-OMeC_6H_4
4b: Ar^1 = *p*-BrPh, R^2 = 4-OMeC_6H_4
4c: Ar^1 = Ph, R^2 = butyl
4d: Ar^1 = Ph, R^2 = benzyl
4e: Ar^1 = Ph, R^2 = 3,4-methylene-dioxyphenyl
4f:
2a: R^3 = R^4 = C_6H_5
2b: R^3 = R^4 = *n*-C_3H_7
2c: R^3 = R^4 = 4-OMeC_6H_4
2d: R^3 = R^4 = 4-MeC_6H_4
2e: R^3 = R^4 = 4-BrC_6H_4
2f: R^3 = R^4 = 4-$CF_3C_6H_4$
2g: R^3 = R^4 = thien-2-yl
2h: R^3 = Me, R^4 = Ph
2i: R^3 = Et, R^4 = Ph
2j: R^3 = CH_2OMe, R^4 = Ph
2k: R^3 = CO_2Et, R^4 = Ph



[a] Unless otherwise mentioned, all reactions were carried out using benzophenone imine **4** (0.365 mmol), alkyne **2** (0.281 mmol), $[RhCp^*Cl_2]_2$ (3.4 mg, 0.00562 mmol), $AgBF_4$ (0.0054 g, 0.0281 mmol) $Cu(BF_4)_2{\cdot}6H_2O$ (0.194 g, 0.562 mmol) in *t*-amylOH (2 mL) at 110 °C for 4 h. [b] Isolated yields based on **2**. [c] Ratio of regioisomers (major isomer is shown). PMP = *p*-methoxyphenyl.



Scheme 1 Formation of Ru(II)-catalyzed isoquinolinium salt.

with **4a** afforded the respective isoquinolinium salts in excellent yields. Similarly, oct-4-yne **2b** and 1,2-di(thiophen-2-yl)ethyne **2g** nicely reacted with **4a** to afford products **5ab** and **5ag** in 87 and 91% yields respectively. Unsymmetrical alkynes **2h–k** reacted efficiently with **4a** to give respective isoquinolinium products **5ah–ak** in excellent yields and regioselectivity. Benzophenone imines **4c–e** with *N*-*n*-butyl, -benzyl and -3,4-substituent reacted with **2a** to give corresponding isoquinolinium salts **5ca–5ea** in 89, 92 and 82% yields, respectively. Similarly, the reaction of fluorenone imine **4f** with **2a** gave the desired isoquinolinium salt **5fa** in 89% yield. To understand the regio-selectivity of benzophenone imine with different substituents on the phenyl rings in this catalytic reaction, we chose imine derived from 4-bromobenzophenone **4b** as the substrate for the reaction with **2a**. The ^{1}H NMR spectrum of the product mixture showed that C–H activation occurred equally in both substituted and unsubstituted phenyl rings to give a mixture of **5ba** and **5ba′** in a 1 : 1 ratio in 83% combined yield (Table 2).

In addition to the use of $[RhCp^*Cl_2]_2$ as the catalyst, we also tested the catalytic activity of ruthenium complexes. Gratifyingly, the reaction of benzophenone imine **4a** with **2a** in the presence of 2 mol% of $[Ru(p\text{-cymene})Cl_2]_2$, $AgBF_4$ (1 equiv.) and $Cu(OAc)_2$ (1 equiv.) in *t*-amylOH at 110 °C for 4 h gave **5aa** in 81% isolated yield (Scheme 1). The result indicates that ruthenium complexes can also be employed in the present catalytic reaction.[11]

Based on our experimental results and the known metal-catalyzed directing group-assisted C–H bond activation reactions,[6,7] a plausible mechanism for the present rhodium(III)-catalyzed reaction likely involves the removal of chloride by Ag^+ in $[RhCp^*Cl_2]_2$ to generate a more catalytically active rhodium di-cation.[8a] Then the coordination of the imine substrate to the rhodium(III) center, followed by *ortho* C–H bond activation form a 5-membered rhodacycle. Alkyne coordination and subsequent insertion provides a 7-membered rhodacycle. Finally, reductive elimination gives the isoquinolinium salt product.

In conclusion, we have successfully developed a new method for the synthesis of various 1-substituted isoquinolinium salts from ketimines and alkynes *via* rhodium(III)-catalyzed C–H bond activation. Various substituted acetophenone and benzophenone imines derived from different aliphatic and aromatic amines were successfully employed in this C–H bond activation and annulation reaction. Further applications of this methodology to natural products synthesis are currently under study in our laboratory.

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