RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2018, **8**, 30050

Rh(III)-catalyzed synthesis of tetracyclic isoquinolinium salts *via* C–H activation and [4+2] annulation of 1-phenyl-3,4-dihydroisoquinolines and alkynes in ethanol†

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Received 25th June 2018
Accepted 5th August 2018

DOI: 10.1039/c8ra05443f

rsc.li/rsc-advances

An efficient and convenient method to construct tetracyclic isoquinolinium salts *via* $[Cp^*RhCl_2]_2$ catalyzed C–H activation and [4 + 2] annulation reactions in ethanol is described. This reaction is very fast and highly efficient in the green solvent ethanol. The reaction works with a broad substrate scope affording the products in good to excellent yields in a short time. Moreover, a ratio of S/C up to 10 000 could be achieved with gram scale synthesis.

Introduction

N-Heterocyclic quaternary ammonium salts and their derivatives are versatile heterocyclic compounds found in many natural[1] and synthetic products[2] and are well-known for their potent biological activities[3] (Fig. 1). Therefore, the development of improved methodologies to synthesize new N-heterocyclic quaternary ammonium salts still remains highly desirable.

In recent years, significant advancements have been made in transition-metal-catalyzed C–C bond formation *via* C–H activation, among which rhodium-catalyzed direct C–H bond activations are powerful strategies to synthesize various polycyclic skeletons and N-heterocyclic scaffolds, due to their high efficiency and atom economy.[4] Particularly, using aldehyde imine/ketimine substrates to construct an isoquinoline skeleton *via* C–H annulation has been documented. Earlier, methods for the synthesis of isoquinolinium salts by C–H activation and [4 + 2] annulation of various imines have been studied (Scheme 1, eqn (1) and (2)),[5] such as by Cheng's group[5b,6] and Xu's group.[7] Recently, You's group reported a Rh-catalyzed cascade C–H activation/[4 + 2] annulation of aldoximes with alkynes to synthesize multisubstituted protoberberine skeletons.[8] In the meantime, the synthesis of isoquinoline compounds by the [4 + 2] annulation of open-ring imines has also been reported (Scheme 1, eqn (3)).[9] Fagnou's group used $[Cp^*Rh(MeCN)_3]$ $[SbF_6]_2$ to catalyze the formation of isoquinoline compounds from *N-tert*-butylbenzaldimines and internal alkyne.[9] Similar work has also been reported by Lade,[10] Dong,[11] Chiba,[12] Cheng,[13] Zhao[14] *et al.* In addition, there are some reports about the reaction of Rh, Ir and Ru-catalyzed [3 + 2] annulation using imine as a directing group (Scheme 1, eqn (4)).[15]

A close look at the literature precedents revealed that all the previously elegant examples regarding the isoquinolinium salts syntheses mainly focused on the use of acyclic aldimines or ketimines, while not even a single example, starting from the cyclic imines, such as 3,4-dihydroisoquinoline, has been documented. Inspired by these work, we proposed that it was possible to use the imine group of dihydroisoquinoline as a directing group to furnish C–H activation and [4 + 2] annulation to construct tetracylic isoquinolinium salts. Herein, we report Rh-catalyzed [4 + 2] annulations of cyclic-imine of 1-phenyl-3,4-dihydroisoquinolines to synthesis tetracyclic isoquinolinium salts in ethanol. Notably, ethanol is safer and more environmentally friendly compared with some other organic

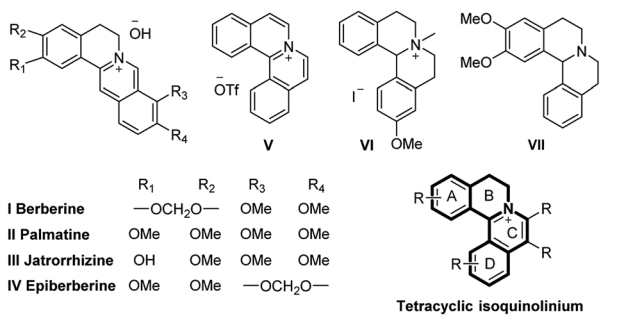

Fig. 1 Representative tetracyclic isoquinolinium salts and their derivatives in medicinal chemistry and natural products.

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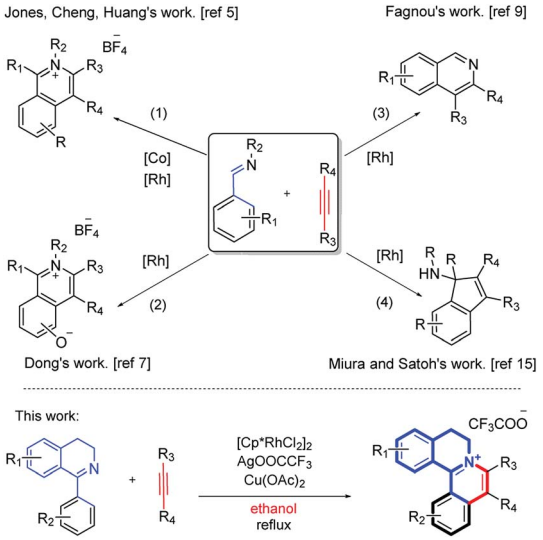
† Electronic supplementary information (ESI) available. CCDC 1828400. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra05443f



Scheme 1 Imine-directed C–H activation.

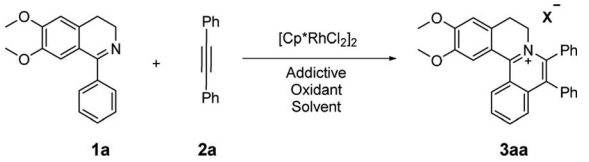
solvents, especially poisonous DCE. Noteworthily, this reaction proceeds with excellent efficiency. What's more, the ratio of S/C could achieve up to 10 000.

Results and discussion

At the outset of our study, $[Cp^*RhCl_2]_2$ was used to catalyze 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline **1a** with diphenylacetylene **2a** to investigate the catalytic performance of additives, solvents, and oxidants (Table 1). When $[Cp^*RhCl_2]_2$ was used as a catalyst, without any additives, **3aa** was barely formed in dioxane (entry 1). Then we explored various silver salts, among which $AgOOCCF_3$ performed most remarkably, and provided 68% yield in 4 h (entry 3). Other silver salts showed little poor performance (entries 2, 4). Meanwhile, the effects of different solvents were investigated (entries 5–10). It is noteworthy that the reaction could get almost quantitative yield in ethanol, with 99% yield in 4 h (entry 10). Meanwhile, we compared the effects of additives, such as copper salts, $K_2S_2O_8$, $C_6H_5I(O_2CCH_3)_2$ and 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) (entries 11–16). Among these additives, $Cu(OAc)_2$ gave the best yield of 99% for **3aa** in 10 minutes (entry 12). However, the reaction could not proceed when only $AgOOCCF_3$ and $Cu(OAc)_2$ were used without Rh catalyst. (entry 17). What is noteworthy is that even when the S/C ratio was 1000, the reaction could finish completely in 10 minutes with 99% isolated yield (entry 18).

With the optimized conditions in hand, a range of electronically and sterically diverse of 3,4-dihydroisoquinoline derivatives were employed using **2a** as a coupling partner to test the substrate tolerance of the Rh(III)-catalyzed tandem [4 + 2] annulation. And the corresponding tetracyclic isoquinolinium salts were constructed in Table 2. A series of 1-aryl-substituted 3,4-dihydroisoquinoline (**1a–g**) could be effectively worked with **2a** in the catalytic reaction with excellent yields (99–95%). However, when the ortho-position of benzene ring was

Table 1 Optimization of the reaction conditions[a]



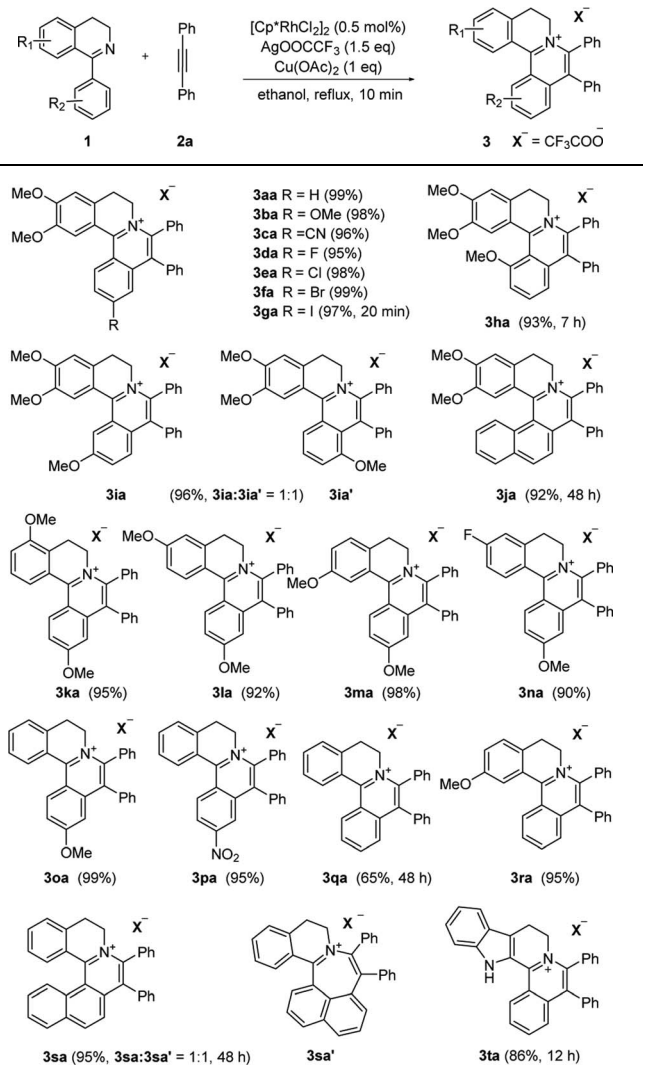
Entry	Oxidant	Additive	Solvent	Time	**3aa** (%)[b]
1	—	—	Dioxane	4 h	ND
2	AgOTf	—	Dioxane	4 h	40
3	$AgOOCCF_3$	—	Dioxane	4 h	68
4	AgOAc	—	Dioxane	4 h	Trace
5	$AgOOCCF_3$	—	DCE	4 h	70
6	$AgOOCCF_3$	—	Toluene	4 h	95
7	$AgOOCCF_3$	—	DCM	4 h	25
8[c]	$AgOOCCF_3$	—	DMF	4 h	70
9[c]	$AgOOCCF_3$	—	DMSO	4 h	45
10	$AgOOCCF_3$	—	EtOH	4 h	99
11[d]	$AgOOCCF_3$	$CuCl_2 \cdot 2H_2O$	EtOH	10 min	25
12[d]	$AgOOCCF_3$	$Cu(OAc)_2$	EtOH	10 min	99
13[d]	$AgOOCCF_3$	$Cu(CF_3COO)_2$	EtOH	10 min	92
14[d]	$AgOOCCF_3$	$K_2S_2O_8$	EtOH	10 min	81
15[d]	$AgOOCCF_3$	$C_6H_5I(O_2CCH_3)_2$	EtOH	10 min	90
16[d]	$AgOOCCF_3$	DDQ	EtOH	10 min	Trace
17[d,e]	$AgOOCCF_3$	$Cu(OAc)_2$	EtOH	10 min	ND
18[f]	$AgOOCCF_3$	$Cu(OAc)_2$	EtOH	10 min	99

[a] Reaction conditions unless otherwise specified: **1a** (0.32 mmol), **2a** (1 eq.), 0.5 mol% of $[Cp^*RhCl_2]_2$, 1.0 eq. of oxidants, 3 mL of solvent, reflux, ND = Not Detected. [b] Isolated yield. [c] 120 °C. [d] 1 eq. of additives. [e] No $[Cp^*RhCl_2]_2$ was added. [f] S/C = 1000, **1a** (1.6 mmol), **2a** (1 eq.), 1.5 eq. of oxidants, 1 eq. of $Cu(OAc)_2$.

substituted by methoxy group (**1h**), the reaction speed went down apparently. The product **3ia** and **3ia′** was successfully obtained in 96% yield with the regioselectivity of 1 : 1. In addition, using naphthalene-substituted **1j**, the reaction proceed slower than **1a**, which indicated that steric effect could influence the reaction process. Then, we investigated the effect of steric and electronic influences on the isoquinoline core (**1k–o**). Notably, the substrates bearing both electron-withdrawing and electron-donating substituted at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring (**1b**, **1k–o**) reacted fast to provide excellent yields. However, the reaction significantly weakened to 65% yield even in 48 hours when **1q** was used as a substrate. For naphthalene-substituted substrates, **1s** gave mixture product **3sa** and **3sa′**. Interestingly, **1j** only afforded pure product **3ja**. It indicated that electronic influences on the isoquinoline core played an important role on the regioselectivity of the reaction process. Notably, the **1t** could be converted to corresponding quaternary ammonium salt **3ta** in good yield, whose reduction product bears the key hetero-tetracyclic scaffolds of reserpine.[16] The structure of the final product **3ba** was characterized by X-ray crystallography (Fig. 2).

The examination of the scope of various alkynes **2** was shown in Table 3. The result revealed that wide substrate tolerance with both internal aryl and alkyl alkynes. For alkynes, both electron-donating and -withdrawing substituents on the phenyl ring proceeded smoothly with **1a** to furnish **3ab–e** with good

Table 2 Substrate Scope of dihydroisoquinolines[a,b]



[a] Reaction conditions unless otherwise specified: 0.32 mmol of **1**, 0.32 mmol of **2a**, 0.5 mol% of $[Cp^*RhCl_2]_2$, 1.5 eq. of $AgOOCCF_3$, 1 eq. of $Cu(OAc)_2$, 3 mL of ethanol, 10 min. [b] Isolated yield.

yields, though need a longer time than disubstituent alkynes **2a**. To our delight, alkyl-substituted alkyne **2f** exhibited the similar excellent reactivity as that of aryl-substituted alkyne. Especially, different with other's work,[5c,6a,6c,7,8] unsymmetrical alkynes **2g**

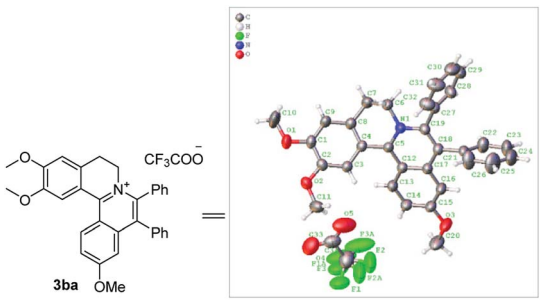
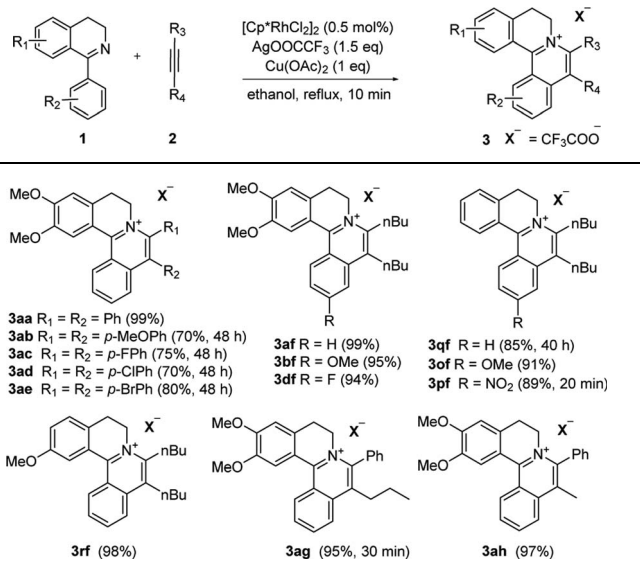


Fig. 2 X-ray crystal structure of **3ba**.

Table 3 Substrate Scope of the alkynes[a,b]

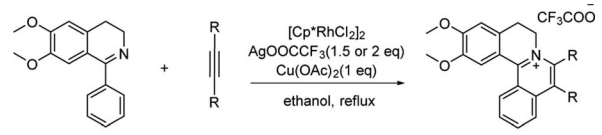


[a] Reaction conditions unless otherwise specified: 0.32 mmol of **1**, **2** (1 eq.), 0.5 mol% of $[Cp^*RhCl_2]_2$, 1.5 eq. of $AgOOCCF_3$, 1 eq. of $Cu(OAc)_2$, 3 mL of ethanol, 10 min. [b] Isolated yield.

and **2h** reacted very fast with **1a** to give pure products instead of regioisomers with excellent yields in 10 minutes. The structure of **3ag** and **3ah** were determined by the NOESY analysis. It needs to point out that the present conditions are specific and highly efficient for the synthesis of tetracylic isoquinolinium salts.

Considering, metal alkenyl intermediates may undergo [3 + 2] annulation to imine group for non-cyclicimines, we have also investigated the scope of non-cyclicimine substrates in Table S2.† Interestingly, we found non-cyclicimines gave N-heterocyclic quaternary ammonium salts of [4 + 2] annulation of imines not of [3 + 2] annulation. Generally, the results of Table 2 and S2† suggested that the dihydroisoquinoline

Table 4 Gram-scale synthesis of **3aa** and **3af**[a,b]



Entry	S/C	3/g	Time	Yield%
1	1000	**3aa**/0.451	10 min	99
2[c]	5000	**3aa**/2.252	24 h	99
3[d]	5000	**3aa**/2.253	2.5 h	99
4[e]	10 000	**3aa**/4.505	22 h	99
5[f]	5000	**3af**/2.090	48 h	99

[a] Reaction conditions unless otherwise specified: **1a** (0.8091 mmol), 1.5 eq. of $AgOOCCF_3$, 15 mL of ethanol. [b] Isolated yield. [c] **1a** (4.0453 mmol). [d] **1a** (4.0453 mmol), 2 eq. of $AgOOCCF_3$. [e] **1a** (8.0906 mmol), 2 eq. of $AgOOCCF_3$. [f] **1a** (4.0453 mmol), 2 eq. of $AgOOCCF_3$, 15 mL of ethanol.

showed much higher activity than non-cyclicimines in the $[Cp^*RhCl_2]_2/AgOOCCF_3/Cu(OAc)_2$ catalyst system.

To assess the scalability of this Rh(III)-catalyzed C–H bond activation and annulation process, gram-scale reaction of **1a** with **2a** and **2f** were performed (Table 4). Firstly, 99% yield of **3aa** was obtained in 10 minutes while the S/C = 1000 (entry 1). Then the S/C was gradually increased to 10 000, and 4.505 g of **3aa** was obtained in 99% yield in 22 h (entry 4). What's more, the alkynes **2f** could conduct well with **1a** at 5000 of S/C ratio and 2.09 g of **3af** was obtained in 99% yield (entry 5). These results showed the catalytic system has fairly good catalytic capability and practicality.

Conclusions

In summary, we have developed a simple and efficient catalytic method for transforming the imine substrates especially the dihydroisoquinoline compounds to quaternary ammonium salts with the utilization of rhodium catalyzed C–H activation and [4 + 2] annulation in ethanol in a very short time and with remarkable yield under mild reaction conditions. Additionally, with the aid of $AgOOCCF_3$ and $Cu(OAc)_2$, the reaction time and catalytic performance can be greatly enhanced, so that a ratio of S/C up to 10 000 could be achieved with gram scale substrate. It provides an efficient strategy to synthesise tetracyclic isoquinolinium salts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was co-supported by the research project of the Fund of Science and Technology Agency of Chengdu (2015-HM01-00311-SF), the Administration of Traditional Chinese Medicine of Sichuan (2016Q037), the fund of Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, Chengdu University (ARRLKF17-10) and the Fundamental Research Funds for the Central Universities (2682017CX091).

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