Organic & Biomolecular Chemistry

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DOI: 10.1039/C5OB01171J

COMMUNICATION

An Efficient Synthesis of Isoquinolines via Rhodium-Catalyzed Direct C-H Functionalization of Arylhydrazines

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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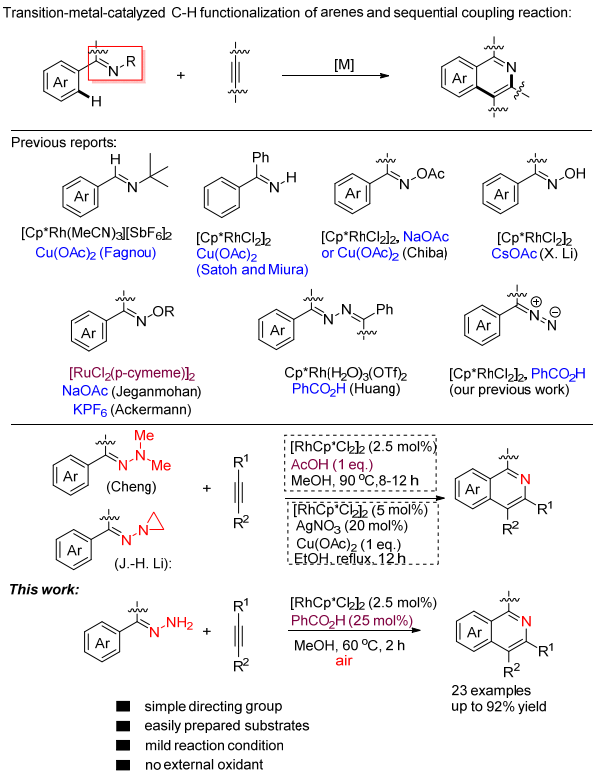
A highly efficient rhodium-catalyzed C-H activation of arylhydrazines and coupling with internal alkynes has been realized under mild conditions. The isoquinolines have been prepared in moderate to excellent yields in high efficiency. This methodology features the use of readily available starting materials, simple hydrazine moiety as directing group, in the absence of an external metal co-oxidant under an air atmosphere. The C-H bond activation, N-N bond cleavage have been successively realized under mild conditions.

Isoquinolines are key motifs found in numerous natural products and pharmaceuticals with diverse biological activities.[1] Thus, various methods have been developed to construct the isoquinoline skeleton over the past decades.[2] Recently, the transition-metal-catalyzed direct C-H bond functionalization of arenes bearing a pre-installment directing groups followed by coupling with internal alkynes, has represented as a powerful tool to rapidly construct the diverse and functional group flexible isoquinolines.[3]

In 2009, Fagnou reported the rhodium-catalyzed oxidative isoquinoline synthesis using N-*t*-Bu aryl aldimines as directing groups and internal nitrogen source.[4] Satoh and Miura developed the use of benzophenone imines in this reaction.[5] However, the use of stoichiometric amount of $Cu(OAc)_2$ as an external oxidant was crucial to complete the catalytic cycle. In 2010, Chiba described a rhodium-catalyzed synthesis of isoquinolines from ketone *O*-acyloximes and internal alkynes with the use of NaOAc as an effective additive and an external co-oxidant was not needed.[7] Later, Li reported the use of oxime as directing group and CsOAc as the additive also leading to the rapid formation of isoquniolines.[7] The oximes have been thought as oxidizing-directing groups during the rhodium-catalyzed procedures. By replacing the rhodium catalysts with ruthenium complexes, Jeganmohan[8] and Ackermann[9] independently realized the synthesis of isoquinolines via C-H bond activation under mild conditions in 2012. Recently, Huang reported an efficient $Cp^*Rh(H_2O)_3(OTf)_2$-catalyzed conversion of azines to



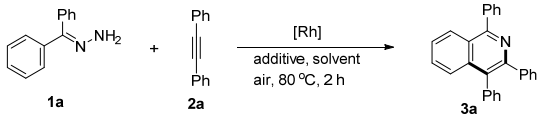
Scheme 1 Synthesis of isoquinolines via transition-metal-catalyzed C-H functionalization.

synthesize isoquinolines.[10] Notably, this reaction was performed under an air atmosphere under room temperature in the presence of 25 mol% of benzoic acid. In 2013, Cheng reported the introduction of hydrazone as oxidizing directing group in isoquinoline synthesis using stoichiometric of acetic acid.[11] Li and co-workers described

the use of aziridinylimines as practical substrates in the presence of $AgNO_3$ and $Cu(OAc)_2$.[12] They also found that the use of free hydrazines resulted in the formation of indenes. Just recently, our group realized the first C-H functionalization of diazo compounds through rhodium relay catalysis to produce isoquinolines in high efficiency.[13] Consistent with our former report, we reported here a highly efficient rhodium-catalyzed isoquinolines synthesis from aryl hydrazines and internal alkynes under mild conditions. This approach has several advantages: the readily available substrates which can be prepared by simple condensation of ketones with cheap hydrazine. An external co-oxidant is not indispensable and benzoic acid is an effective additive to promote the catalytic cycle under air.

Initially, hydrazine (**1a**) and alkyne (**2a**) were employed as model substrates to screen the reaction parameters (Table 1). First, using 2.5 mol% of rhodium complexes in methanol at 80 °C in the presence of 0.25 eq. of benzoic acid revealed that $[Cp^*RhCl_2]_2$ gave the best result and afforded **3a** in 88% isolated yield in 2 hours (entry 2), whereas $Rh_2(OAc)_4$, $Rh_2(esp)_2$ and $[RhCl(cod)]_2$ were totally inert in this reaction (entries 3 to 5). Also, in the absence of benzoic acid, no **3a** was detected (entry 1). This phenomenon indicated that to accomplish the catalytic cycle, the acid is indispensable to facilitate the molecular oxygen to oxidize Rh^I to regenerate the active Rh^{III} species.[10,14] When *p*-toluenesulfonic acid and pivalic acid were used as additive, **3a** was isolated in low to moderate yield (entries 6 and 7). Next, several solvents were also examined. The use of DMF and toluene led to quite low yields (entries 8 and 9). Other alcohols such as *n*-butanol and ethanol gave lower yields (entries 10 and 11). Moreover, both increasing and reducing the amount of benzoic acid were detrimental to the reaction (entries 12 and 13). Furthermore, the reaction was sluggish at room temperature (entry 14). Lower catalyst loading (1 mol%) gave a slightly lower yield with longer reaction time (entry 15).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Additive (equiv.)	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	-	MeOH	<5
2	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	MeOH	88
3	$Rh_2(OAc)_4$	$PhCO_2H$ (0.25)	MeOH	0
4	$Rh_2(esp)_2$	$PhCO_2H$ (0.25)	MeOH	0
5	$[RhCl(cod)]_2$	$PhCO_2H$ (0.25)	MeOH	0
6	$[Cp^*RhCl_2]_2$	TsOH (0.25)	MeOH	36
7	$[Cp^*RhCl_2]_2$	PivOH (0.25)	MeOH	55
8	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	DMF	12
9	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	toluene	<5
10	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	*n*-BuOH	24
11	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	EtOH	52
12	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.5)	MeOH	76
13	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.1)	MeOH	63
14[c]	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	MeOH	31
15[d]	$[Cp^*RhCl_2]_2$	$PhCO_2H$ (0.25)	MeOH	82

Reaction conditions: [a]All reactions were carried out with **1a** (1 mmol), **2a** (1.2 mmol), catalyst (0.025 mmol), solvent (3 mL) under air at 80 °C for 2 hours unless otherwise noted. [b]Isolated yields. [c]The reaction was performed at room temperature. [d] 1 mol% of $[Cp^*RhCl_2]_2$ was used and the reaction time was 8 hours.

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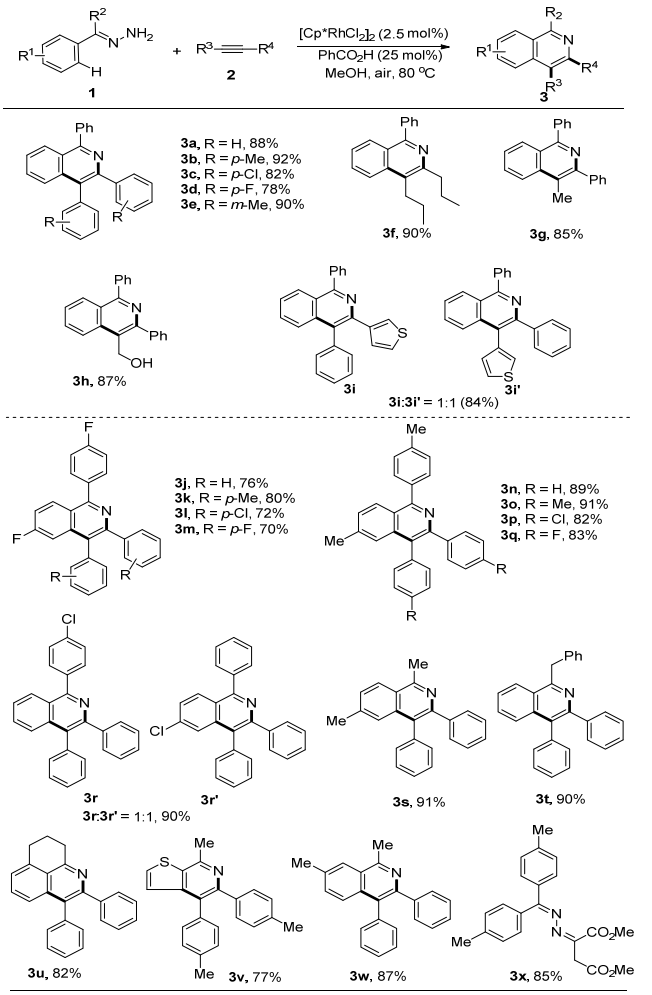
Under the optimal reaction condition, the substrate scope of hydrazines and alkynes were investigated (Table 2). Generally, all of the reactions proceeded smoothly to afford isoquinolines **3** in moderate to excellent yields. The reaction of **1a** with various alkynes was firstly carried out to examine the reactivity of alkynes in this reaction. For the symmetric diaryl alkynes, the phenyl moiety bearing electron-donating substituents displayed better reactivity and gave the corresponding products in higher yield than the electron-withdrawing substituents (**3b** to **3e**). The alkyl alkyne and alkyl phenyl were also tolerated in this reaction and the desired products were obtained in high yields (**3f** and **3g**). The hydroxyl substituted alkyne gave the isoquinoline **3h** in 87% yield. However, when un-symmetric diaryl alkyne was used, two regio-isomers were detected in almost 1:1 ratio (**3i**/**3i'**).

Table 2 Substrate scope[a,b]

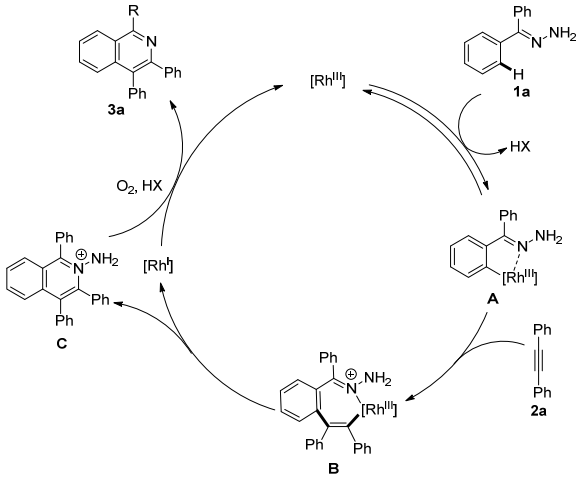


[a]All reactions were carried out with **1** (1 mmol), **2** (1.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $PhCO_2H$ (0.25 mmol), in MeOH (3 mL) under air at 80 °C for 2 hours. [b]Isolated yields.

Next, the reaction of different hydrazines with alkynes was further examined (Table 2). The symmetric *para*-fluoro substituted

diphenylmethylene hydrazine afforded the corresponding isoquinolines in lower yields than none-substituted and *para*-methyl substituted hydrazines (**3j** to **3m** compared with **3a** to **3e** and **3n** to **3q**). The un-symmetric aryl hydrazine gave two regio isomers in 1:1 ratio (**3r** vs **3r'**). The phenylalkylidene hydrazines were also evaluated as ideal substrates in this reaction and led to the corresponding isoquinolines in high yields (**3s** to **3u**). The use of thiophene substituted hydrazine also produced the isoquinoline in 77% yield (**3v**). Moreover, the *meta*-methyl substituted phenyl hydrazine delivered **3w** as single isomer in 87% yield. Notably, the use of propiolates in this reaction only provided **3x** as the final product and the corresponding isoquinoline was not detected. Moreover, the terminal alkyne was totally inert in this reation.

Based on the above experiments, a possible reaction mechanism was proposed in Scheme 2. In the presence of $[Cp^*RhCl_2]_2$, the *ortho*-C-H activation of **1a** occurs under the assistance of the nitrogen atom of the hydrazine, which generates the active intermediate **A**. Then **A** undergoes insertion to alkyne **2a** to give formation of seven-membered intermediate **B**. Then reductive elimination of this iminium cation would lead to the formation of isoquinolinium cation **C** and $[Rh^I]$ species, which would provide isoquinoline **3a** and regeneration of the $[Rh^{III}]$ species under a redox process in the presence of air and benzoic acid.



Scheme 2 Proposed reaction mechanism

In summary, we have demonstrated here a highly efficient rhodium-catalyzed approach to prepare isoquinolines. This methodology featured the use of readily available hydrazine as the directing group, in the presence of simple benzoic acid and in the absence of an external metal co-oxidant under mild reaction conditions. Moreover, the C-H bond activation and N-N bond cleavage have been realized under an air atmosphere.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (No. 21172023), A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110) for their financial supports. S. Zhang thanks for an internship from Changzhou University.

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DOI: 10.1039/C5OB01171J

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Electronic Supplementary Information (ESI) available: [details of experiment procedures, and spectra datas]. See DOI: 10.1039/c000000x/

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