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Authors: Jingjing Shi, Mingliang Liu, Wanchun Gong, Erli You, Haizhen Zhang, Lei Shi, and Weiguo Cao

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Synthesis of Isoquinolines via Ir(III)-catalyzed C–H Activation/Annulation from Benzimidates with Hydroxylisopropylalkynes

Mingliang Liu[a,b], Wanchun Gong[b], Erli You[b], Haizhen Zhang[b], Lei Shi[b], Weiguo Cao[a,c]*, Jingjing Shi[b]*

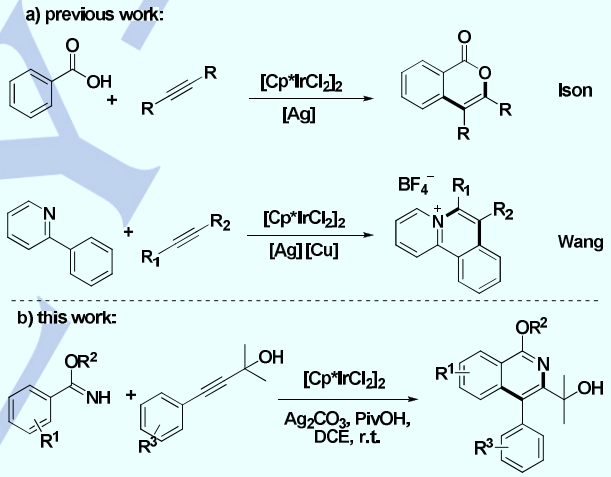
Dedication ((optional))

Abstract: Ir(III)-catalyzed cascade C–H activation/annulation of benzimidates with hydroxylisopropylalkynes has been reported. A broad range of isoquinolines have been prepared in one step with good functional group tolerance, and high efficiency.

Introduction

Isoquinolines, like some other heterocyclic skeletonsare widely existed in countless synthetic compounds that display various biological activity, includinganalgesic, antitumor, anti-inflammatory, and antipsychotic.[1] As aresult, many efforts have been made to achieve an efficient synthesis of these skeletons. C–H activation/annulation is currently a topic attracting significant interest. With the advent of transition metal-catalyzed C–H activation reactions, several synthetic methodologies toward isoquinolines based on straightforward oxidative C–H annulations were elegantly developed. The majority of these methods take the advantage of the kinds of transition metals, such as rhodium, cobalt, manganese, iridium.[2] Although these methods are effective, It is still necessary to develop new catalytic system, directing groups and coupling partners because of their interesting biological properties.

Cp*Ir(III) is powerful to catalyze aromatic C–H functionalization to construct C–C bond using diazo compounds, terminal alkynes, terminal alkenes, diaryliodonium salts, construct C–N bond using organic azides, dioxazolones, intramolecular amino group, and construct C–X (X = Cl, Br, I) bond using N-halosuccinimides.[3] Many C–H activation/annulations reactions were developed in the manners of redox neutrality, however, oxidative C–H functionalization/annulation reactions catalyzed by Cp*Ir(III) have been reported rarely (Scheme 1a).[4] One of the reasons may be the weaker oxidation capacity of Cp*Ir(III).[5] We hypothesized that suitable directing groups and coupling partners were necessary for the purpose of constructing heterocycles. Imidates as a directing group with higher electron density of the N-atom was reported by Glorius in the Rh-catalyzed oxidative cascade reaction of C−H amidation and N−N bond formation, subsequently Ru or Co -catalyzed imidates directing oxidative cascade reaction involving C−H activation/annulations was expanded.[6] Oxidative annulation of the arene C–H bond with alkyne has been widely reported for the construction of six-membered heteroarenes, and catalyzed by Rh(III),[7] Ru(II),[8] Co(III),[9] Pd(II),[10] Fe(III).[11] Herein, we describe an efficient way to prepare diverse isoquinoline derivatives with readily available benzimidates and hydroxylisopropylalkynes under oxidative conditions(Scheme 1b).



Scheme 1. Cp*Ir(III)-catalyzed oxidative annulation

Results and Discussion

We commenced our investigation using ethyl benzimidate **1a**, and hydroxylisopropylalkyne **2a** as model substrates, in the presence of $[Cp^*IrCl_2]_2$ (10 mol%) and AgOAc (1.2 equiv) in MeOH at room temperature for 12 h. Fortunately, the cascade reaction proceeded smoothly to afford the desired product **3aa** (Table 1, entry 1) in 40% yield. The isolated yield of **3aa** dramatically increased to 68% yield when Ag_2CO_3 was used as the additive (entry 2). Further screening revealed that DCE was a desirable solvent to achieve this transformation in higher yield (78%, entry 5). Interestingly, continuing to add PivOH further improved the yield (87%, entry 7). The yield was nearly unaffected when lower the catalyst loading to 5% (entry 8).

Table 1. Optimization of the Reaction Conditions.[a]

[a] School of Environmental and Chemical Engineering, Shanghai University
99 Shangda Road, Shanghai 200444, P. R. China
http://www.chem.shu.edu.cn/Default.aspx?tabid=12790
E-mail: wgcao@staff.shu.edu.cn
[b] Shanghai Institute of Materia Medica, Chinese Academy of Sciences
501 Haike Road, Shanghai 201203, P. R. China
http://www.simm.cas.cn
E-mail: shijingjing@simm.ac.cn
[c] Department of Chemistry, Innovative Drug Research Center, Shanghai University
99 Shangda Road, Shanghai 200444, P. R. China

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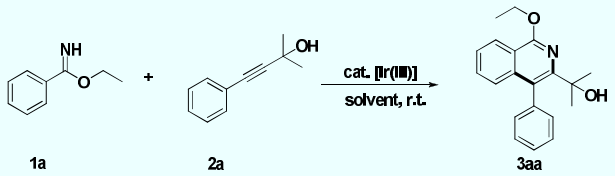
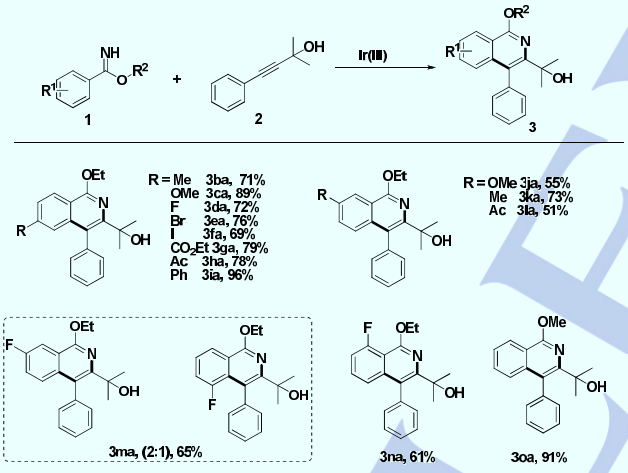


1a 2a 3aa

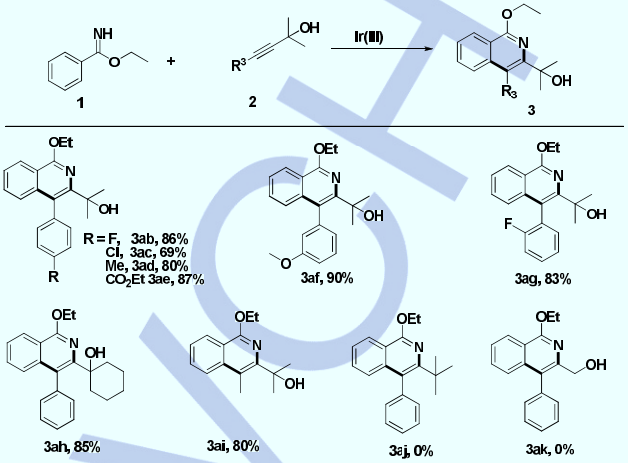
Entry	Catalyst (mol%)	Additive	Solvent	Yield (%)[b]
1	$[Cp^*IrCl_2]_2$ (10)	AgOAc	MeOH	40
2	$[Cp^*IrCl_2]_2$ (10)	Ag_2CO_3	MeOH	68
3	$[Cp^*IrCl_2]_2$ (10)	$Cu(OAc)_2$	MeOH	50
4	$[Cp^*RhCl_2]_2$ (10)	Ag_2CO_3	MeOH	36
5	$[Cp^*IrCl_2]_2$ (10)	Ag_2CO_3	DCE	78
6	$[Cp^*IrCl_2]_2$ (10)	Ag_2CO_3	1,4-dioxane	51
7[c]	$[Cp^*IrCl_2]_2$ (10)	Ag_2CO_3	DCE	87
8[c]	**$[Cp^*IrCl_2]_2$ (5)**	**Ag_2CO_3**	**DCE**	**86**
9[c]	$[Cp^*IrCl_2]_2$ (2.5)	Ag_2CO_3	DCE	67

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), catalyst (mol%) and additive (0.36 mmol.) in a solvent (2 mL) for 12 h. [b] Isolated yield; [c] PivOH (0.3 mmol) was added.

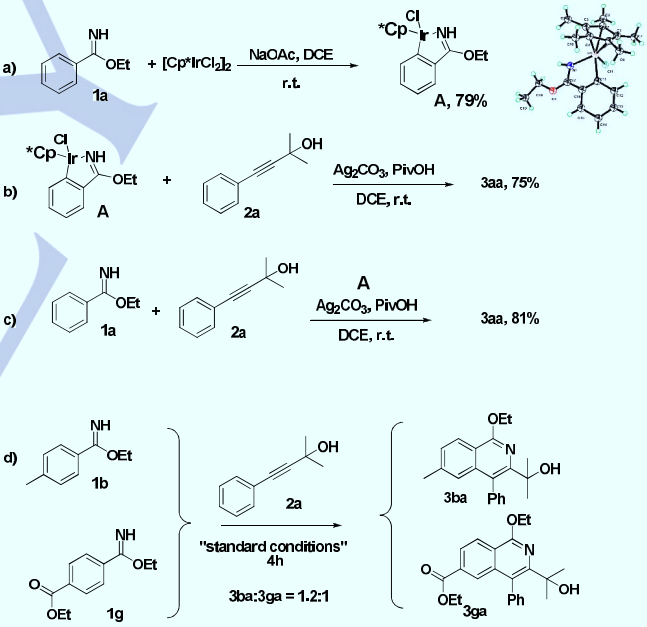


Scheme 2. Substrate scope of benzimidates. Reaction Condition: **1** (0.3 mmol), **2** (0.45 mmol), $[Cp^*IrCl_2]_2$ (5% mol), Ag_2CO_3 (0.36 mmol), PivOH (0.3mmol), DCE (2 mL), r.t. for 12 h. Yield of the isolated product.

With the optimized conditions in hand (Table 1, entry 8), we further explored the scope of substituted benzimidates (Scheme 2). The ethyl benzimidates substituted with electron-donating or -withdrawing groups at the *para*-, *meta*-, or *ortho*- position underwent C–H activation/cyclization cascade proceed smoothly to afford corresponding substituted isoquinolines **3ba**-**na** in moderate to excellent yields (51-96%). Moreover, this reaction showed good compatibility with a wide range of valuable functional groups including fluoro (**3da**, **3ma**), bromo (**3ea**), iodo (**3fa**), ester (**3ga**), and acetyl (**3ha**, **3la**) substituents which can be used for further functional group manipulations. It is noteworthy that m-fluorobenzimidate afforded a pair of regioisomers (2:1), which was confirmed by H^1 NMR and LCMS with a total yield of 65%.



Scheme 3. Substrate scope of propargyl alcohols. Reaction Condition: **1** (0.3 mmol), **2** (0.45 mmol), $[Cp^*IrCl_2]_2$ (5% mol), Ag_2CO_3 (0.36 mmol), PivOH (0.3 mmol), DCE (2 mL), r.t. for 12 h. Yield of the isolated product.



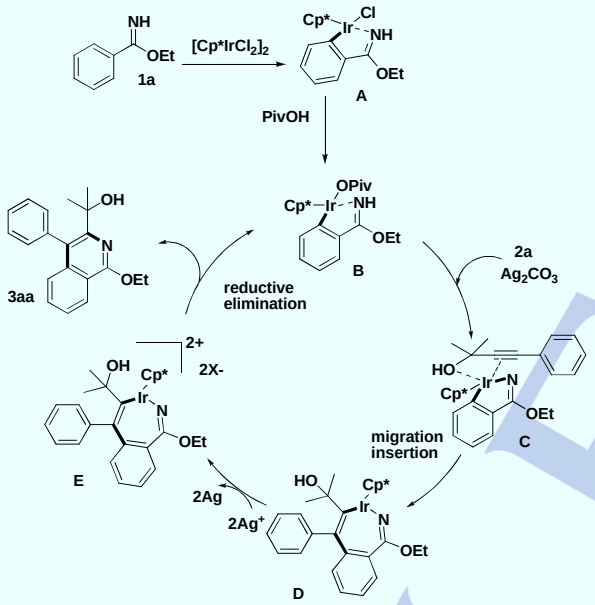
Scheme 4. Mechanistic studies.

Subsequently, we explored the scope of aryl ring of hydroxylisopropylalkyne **2** (Scheme 3). Substrates of the aryl ring all are tolerated in this reaction to give good to excellent yields (69-90%). Substituted in *para*- (**3ab**-**3ae**), *meta*- (**3af**), or *ortho*- (**3ag**) position were all well tolerated in the system. Also, we turned our attention to probe the effects of different the substitutions on the propargyl group, **3ah** was given in 85% yield under the standard conditions, while **3aj** and **3ak** were not detected in the reaction.

To obtain insights into this reaction, preliminary mechanistic studies have been performed. We isolated an Iridacyclic imidate complex **A** from the stoichiometric C–H activation of **1a** (Scheme 4a). The structure of **A** was confirmed by NMR and single-

crystal X–ray diffraction analysis (CCDC 1590341). The reaction of **A**, **2a**, Ag_2CO_3 and PivOH was performed to rapidly afford **3aa** (75% yield, Scheme 4b). Scheme 4c showed that complex **A** was an active catalyst for the coupling/annulation of **1a** and **2a**. In addition, a competition experiment has been performed using an equimolar mixture of **1b**, **1g** and **2a** under the standard conditions, from which **3ba** and **3ga** were obtained in 1.2:1 ratio on the basis of ^{1}H NMR analysis (Scheme 4d), indicating that an electron-donating groups (EDG) tends to kinetically favor the reaction.

On the basis of the known Ir-catalyzed C–H bond activation/ cyclization,[12] a plausible reaction mechanism is shown in Scheme 5. Firstly, **1a** and $[Cp^*IrCl_2]_2$ form the Iridium intermediate **A**, which is easily converted into the active Iridium intermediate **B**. The coordination of alkyne **2a** with complex **B** gives intermediate **C**, and subsequently migratory insertion of alkyne into the phenylimidate **C** (sp^2)–Ir bond gives seven-membered intermediate **D**. Subsequent,the Ir(III) species **D** may be oxidized by Ag(I) to generate the Ir(V) species **E**. Finally, reductive elimination gives product **3aa** and regenerates the active species **B**, closing the catalytic cycle.



Scheme 5. Proposed Reaction Mechanism

Conclusions

In summary, we have developed an efficient strategy for the one-step synthesis of isoquinoline derivatives via a Ir(III)-catalyzed cascade C–H activation/annulation. The reactions can occur under mild conditions with broad functional group tolerance. This protocol employed readily available aromatic imidates and hydroxylisopropylalkynes as starting materials, providing a straightforward and economic strategy to access biologically important isoquinolines.

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Keywords: isoqunoline; benzimidate; hydroxylisopropylalkynes; C–H activation; Iridium

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Layout 2:

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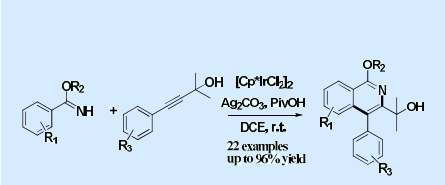

Ir(III)-catalyzed cascade C–H activation/annulation of benzimidates with hydroxylisopropylalkynes has been reported. A broad range of isoquinolines have been prepared in one step with good functional group tolerance, and high efficiency

Ir(III)-catalyzed，C–H Activation

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