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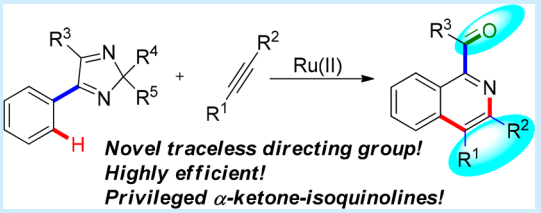
Synthesis of α-Ketone-isoquinoline Derivatives via Tandem Ruthenium(II)-Catalyzed C−H Activation and Annulation

Xiao-Lin Wu and Lin Dong*

Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

Supporting Information

ABSTRACT: A new ruthenium(II)-catalyzed tandem C−H activation/cyclization/hydrolysis cascade process of 2*H*-imidazoles and alkynes for facile and regioselective access to α-ketone-isoquinolines has been successfully developed. 2*H*-Imidazole as the novel traceless directing group has been well applied in this paper. The protocol features mild reaction conditions and easily accessible starting materials, and α-ketone-isoquinolines could be applied to further construct more complex heterocyclic compounds.



Isoquinoline has received much attention due to a wide range of biological activities (Figure 1).[1] Thus, diverse

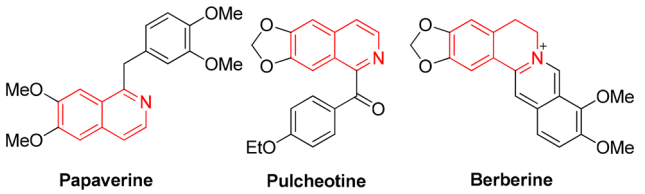
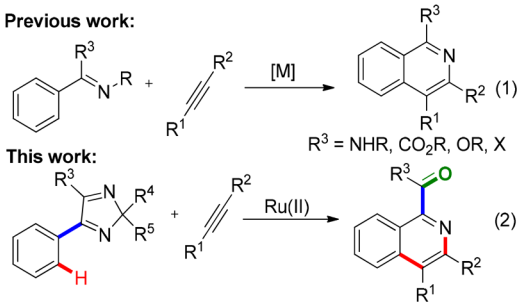


Figure 1. Pharmaceuticals and natural products bearing isoquinolines.

synthetic methods have been developed for constructing isoquinoline derivatives.[2] Furthermore, chemists continued to devise novel synthetic methodologies based on the principles of atom- and step-economy.[3] In 2003, Jun et al. pioneered chelation-assisted C−H activation to synthesize isoquinoline.[4] Since then, different coupling partners such as imines, amines, hydrazones, and azides have also been utilized (Scheme 1, eq 1).[5−7]

Scheme 1. Construction of α-Substituted Isoquinolines via Tandem C−H Activation/Annulation



However, despite that synthesis of isoquinolines has achieved great success via C−H activation, highly functionalized isoquinoline derivatives have rarely been developed, and α-substituted isoquinolines were only limited to amine, ester, ether, α-alkyl, and aryl groups.[8] In addition, 2*H*-imidazole as the directing group has not been studied in C−H activation yet.[9] Therefore, there is increased interest in developing α-ketone isoquinoline derivatives.[10] Herein, we report a less expensive ruthenium(II)-catalyzed cascade reaction to build novel α-ketone-isoquinoline derivatives via C−H activation/cyclization/hydrolysis of imide into the carbonyl group cascade process of 2*H*-imidazoles and alkynes (Scheme 1, eq 2). It is worth mentioning that the 2*H*-imidazoles in this cascade reaction can act as a traceless directing group.

We commenced our investigations by examining the cascade cyclization between 2,2,4-trimethyl-5-phenyl-2*H*-imidazole (**1a**) and 1,2-diphenylethyne (**2a**) under various reaction conditions (Table 1). To our delight, in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), the cyclization product **3aa** can be generated in 40% yield (entry 1) after reacting at 100 °C in DCE for 12 h. Further introduction of $Cu(OTf)_2$ (1 equiv) and CF_3COOAg (1 equiv) as the co-oxidant can improve the yield of **3aa** (entries 2−7). The solvent screening showed that the product yield is very sensitive to the variation of solvent, and TFE is a suitable solvent (entries 8−12). In addition, the addition of acid is beneficial to the reaction, and 1-AdCOOH proved to be the most effective additive (entries 13−16). In addition, substitutions of cyclohexyl and phenyl groups (**1b** and **1c**) at the 2 position on the 2*H*-imidazole ring were also tolerated in the tandem reaction but exhibited slightly less reaction efficiency, probably due to the steric effect (entries 17 and 18). Furthermore, the reactions could be carried out on larger scales, and the yields of **3aa** have declined but still in good yields (entries 19 and 20). However, the data implied that the scale of reactions had a crucial effect on the efficiency of this one-pot reaction.[11]

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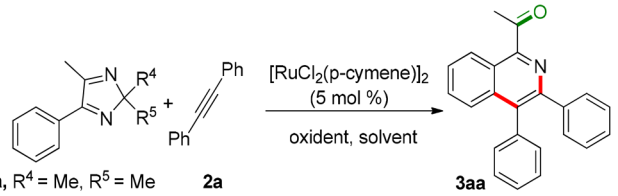
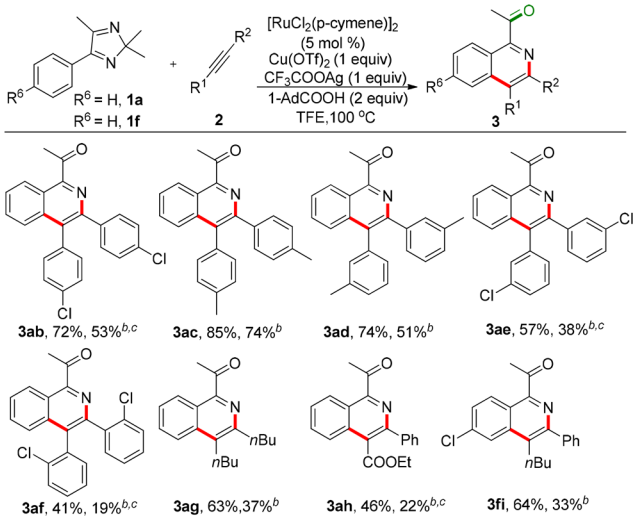
Table 1. Reaction Optimization[a]



entry	oxidant/equiv	additive	solvent	yield of **3aa** (%)[b]
1	$Cu(OAc)_2·H_2O$/2	--	DCE	40%
2	$Cu(acac)_2$/2	--	DCE	32%
3	$Cu(OTf)_2$/2	--	DCE	43%
4	CF_3COOAg/2	--	DCE	21%
5	AgOAc/2	--	DCE	33%
6	$Cu(OTf)_2$/1 + CF_3COOAg/1	--	DCE	58%
7	$Cu(OTf)_2$/1 + AgOAc/1	--	DCE	32%
8	$Cu(OTf)_2$/1 + CF_3COOAg/1	--	TFE	65%
9	$Cu(OTf)_2$/1 + CF_3COOAg/1	--	PhCl	33%
10	$Cu(OTf)_2$/1 + CF_3COOAg/1	--	dioxane	25%
11	$Cu(OTf)_2$/1 + CF_3COOAg/1	--	MeCN	N.R.
12	$Cu(OTf)_2$/1+ CF_3COOAg/1	--	MeOH	48%
13	$Cu(OTf)_2$/1 + CF_3COOAg/1	PivOH	TFE	70%
14	$Cu(OTf)_2$/1 + CF_3COOAg/1	1-AdCOOH	TFE	77%
15	$Cu(OTf)_2$/1 + CF_3COOAg/1	$PhOCH_2COOH$	TFE	65%
16	$Cu(OTf)_2$/1 + CF_3COOAg/1	AcOH	TFE	62%
17[c]	$Cu(OTf)_2$/1 + CF_3COOAg/1	1-AdCOOH	TFE	51%
18[d]	$Cu(OTf)_2$/1 + CF_3COOAg/1	1-AdCOOH	TFE	32%
19[e]	$Cu(OTf)_2$/1 + CF_3COOAg/1	1-AdCOOH	TFE	69%
20[f]	$Cu(OTf)_2$/1 + CF_3COOAg/1	1-AdCOOH	TFE	51%

[a]Reaction conditions: **1a** (0.05 mmol, 1 equiv), **2a** (1.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (2 equiv), solvent (0.5 mL) at 100 °C for 12 h under air. [b]Isolated yield. [c]**1b**, R^4 = R^5 = cyclohexyl. [d]**1c**, R^4 = Me, R^5 = Ph. [e]**1a** (0.3 mmol). [f]**1a** (2 mmol).

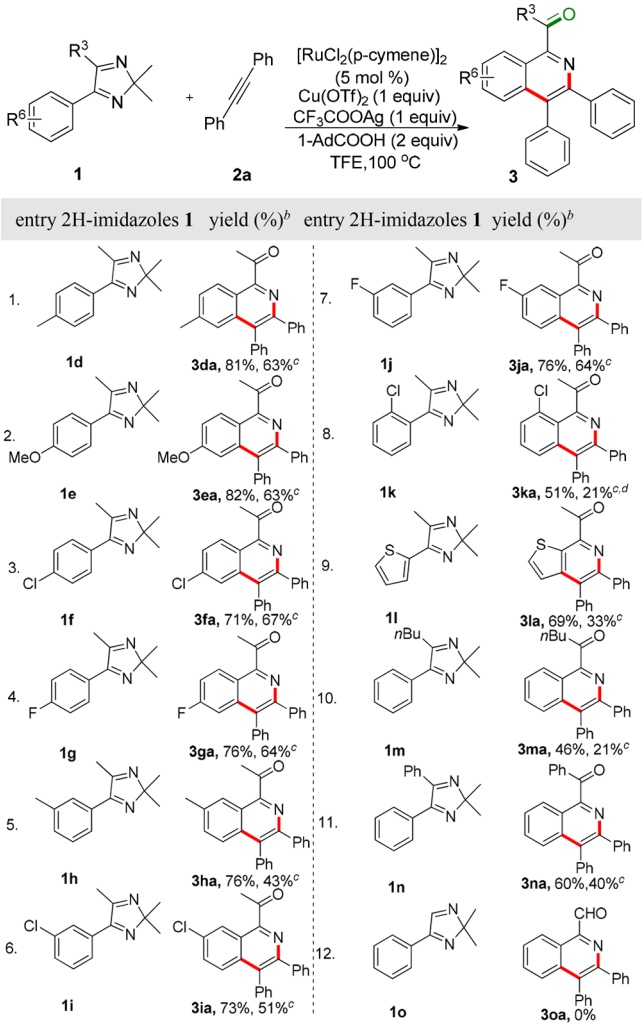
Scheme 2. Substrate Scope of Alkynes[a]



[a]Reaction conditions: unless otherwise specified, **1** (0.05 mmol, 1 equiv), **2** (1.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OTf)_2$ (1 equiv), CF_3COOAg (1 equiv), 1-AdCOOH (2 equiv), and TFE (0.5 mL) at 100 °C for 6−18 h, under air. Isolated yield. [b]**2** (0.3 mmol). [c]PivOH (2 equiv).

Equipped with a set of optimized conditions (Table 1, entry 14), we explored the scope of the cross-coupling reaction by investigating the reaction between 2,2,4-trimethyl-5-phenyl-2*H*-imidazole (**1a**) and various alkynes (Scheme 2). Various diphenylethynes with valuable functional groups on the aromatic ring, either electron-donating or -withdrawing groups, could react smoothly with **1a** to afford the corresponding products (**3ab**−**3ae**) in moderate to good yields (57%−85%). The substituent at the *ortho*-position of the phenyl ring was tolerated in the reaction system but provided the corresponding product **3af** in low yield, which may be influenced by steric effects. It is noteworthy that dialkyl-substituted alkyne **1g** reacted smoothly affording **3ag** in 63% yield. Moreover, single isomers **3ah** and **3fi** were isolated by using nonsymmetrical alkynes as coupling partners. However, terminal alkynes could not react under the standard reaction conditions.

Table 2. Substrate Scope of 2*H*-Imidazoles[a]



[a]Reaction conditions: unless otherwise specified, **1** (0.05 mmol, 1 equiv), **2a** (1.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OTf)_2$ (1 equiv), CF_3COOAg (1 equiv), 1-AdCOOH (2 equiv), and TFE (0.5 mL) at 100 °C for 6−18 h, under air. [b]Isolated yield. [c]**1** (0.3 mmol). [d]PivOH (2 equiv).

We next focused our attention to the scope of the 2*H*-imidazoles (Table 2). Pleasingly, a variety of 2*H*-imidazoles reacted smoothly with **2a**. The substituents at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring were all tolerated in the cascade reaction, providing corresponding products (**3da**−**3ka**) in good to moderate yields. Furthermore, the reaction of thiophene-functionalized 2*H*-imidazole exhibited good efficiency

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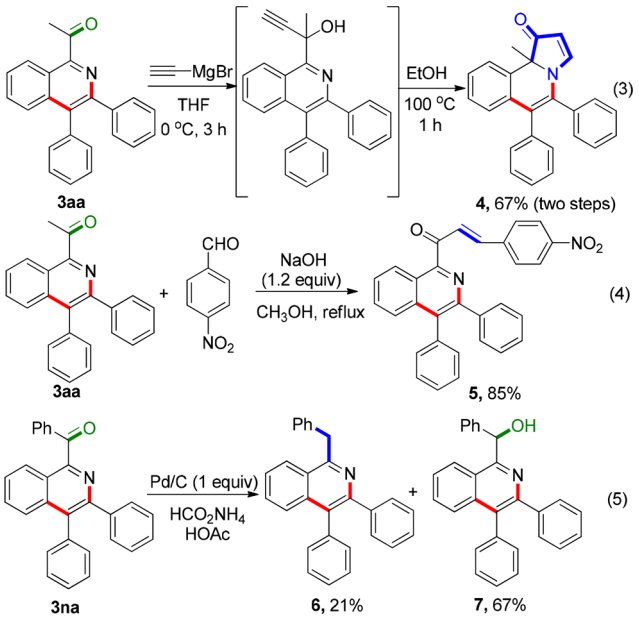
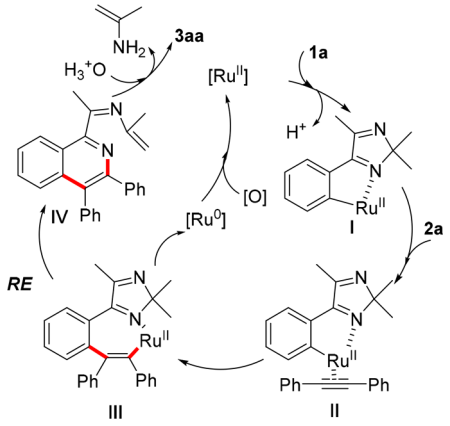
for coupling with **1a**, producing **3la** in 69% yield. The substrates with *n*-butyl or phenyl groups on the 2*H*-imidazole ring also showed good reactivity, delivering various α-ketone-isoquinolines (**3ma** and **3na**) in moderate yields. Depressingly, no corresponding aldehyde product **3oa** was obtained when 2,2-diethyl-4-phenyl-2*H*-imidazole (**1o**) was used.

In order to better illustrate of the α-substituted carbonyl isoquinolines, further transformations of the units were conducted in Scheme 3.[11] Surprisingly, the versatile **3aa**

Scheme 3. Synthetic Applications of the Corresponding Products



Scheme 4. Plausible Reaction Mechanism



could work smoothly to form the novel fused polycyclic product **4** in 67% yield (Scheme 3, eq 3). In addition, **3aa** could be treated with *p*-nitrobenzaldehyde to give the compound **5** in 85% yield (Scheme 3, eq 4). Moreover, **3na** could be reduced by Pd/C to give the compound **6** in 21% yield and **7** in 67% yield (Scheme 3, eq 5).

A relay formalism has been proposed herein for the descriptive mechanism (Scheme 4).[12] First, a coordination of nitrogen by ruthenium and first C−H bond activation occur to generate ruthenium(II) complex intermediate **I**. Subsequent coordination of **2a** is followed by insertion of the C−Ru bond to give complex **III**, which undergoes reductive elimination to generate intermediate **IV**.[12a,11] Then, the reduced Ru is reoxidized to regenerate active species Ru(II) participating in the next catalytic cycle. Finally, the C−N bond cleavage and imide hydrolysis process occurs to afford the annulation product **3aa**.

In summary, we have developed a new ruthenium(II)-catalyzed cascade reaction of 2*H*-imidazoles with alkynes, which involves direct C−H activation/cyclization/hydrolysis of imide into the carbonyl group cascade process by using 2*H*-imidazole as a traceless directing group. Furthermore, a broad scope of α-substituted carbonyl isoquinoline derivatives have been synthesized which could be applied to the concise synthesis of related complex molecules. Further studies of synthetic applications are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02759.

Experimental procedures, structural proofs, and NMR spectra of the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dongl@scu.edu.cn.

ORCID

Lin Dong: 0000-0002-8004-821X

Notes

The authors declare no competing financial interest.

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