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Ruthenium(II)-Catalyzed Oxidant-Free Coupling/Cyclization of Benzimidates and Sulfoxonium Ylides to Form Substituted Isoquinolines

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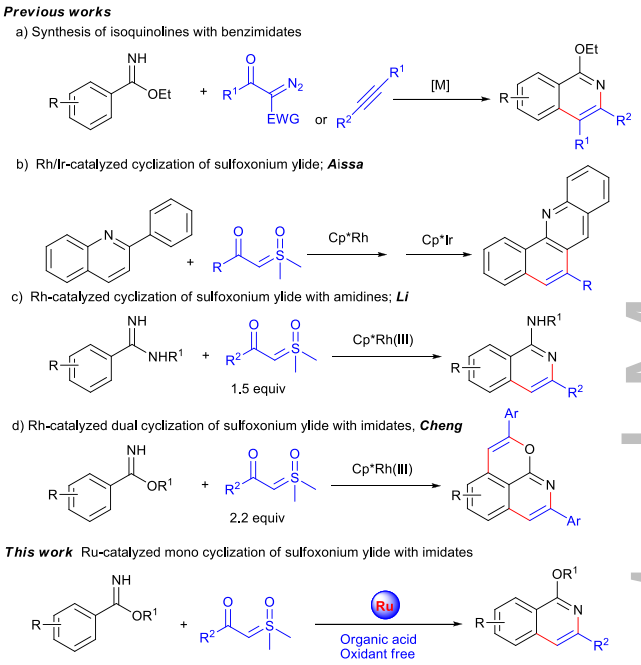
Abstract: A ruthenium-catalyzed direct mono-C–H functionalization/annulation cascade reaction of benzimidates and sulfoxonium ylides has been developed. The reaction proceeds smoothly with a broad range of substrates, giving access to a variety of isoquinoline derivatives in moderate to good yields using an organic acid additive under oxidant free conditions.

Keywords: Benzimidate; Isoquinoline; Oxidant-free; Ruthenium catalyst; Sulfoxonium ylide

Isoquinoline is a basic core structure in various biological active natural products,[1] organic materials[2] and pharmaceuticals.[3] Traditional methods for the synthesis of isoquinolines include the Pictet–Spengler and Bischler–Napieralski reactions, which require harsh conditions and activated starting materials.[4] Therefore, flexible methods for the highly efficient synthesis of isoquinolines and their derivatives have attracted much research attention. Among these efforts, the direct C–H functionalization/cyclization of arenes remains a commonly used protocol. The transition-metal-catalyzed C–H activation/annulation of substituted imidates (Scheme 1a),[5] oximes,[6] amidines,[7] oxadiazoles,[8] and hydrazines[9] is the most efficient method for the construction of isoquinoline skeleton. However, in most cases, a stoichiometric amount of oxidants and expensive metal additives are required. Therefore, the development of an efficient and operationally simple process for preparing isoquinolines remains challenging and in high demand.

Sulfoxonium ylides,[10] which can produce metal carbenes through rhodium and iridium catalysis,[11] are used as carbene-transfer reagents. Compared with diazo compounds, sulfoxonium ylides have the advantages of simple handling and good stability, and have been applied to the



Scheme 1. Previous design and this work: synthesis of quinolines and isoquinolines.

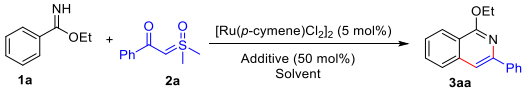
synthesis of carbocycles, *N*-heterocycles, and fused heteroarenes using NH-sulfoximines, ketoximes or aryl imidates through rhodium-catalyzed annulation.[12] More recently, Aïssa and coworkers reported an efficient rhodium-catalyzed cross-coupling of carbonyl oxosulfonium ylides to form aryl ketones, followed by treatment with a catalytic amount of iridium complex to afford annulated benz[c]acridines in good yields (Scheme 1b).[12a] Li and coworkers have reported a rhodium-catalyzed mono C–H functionalization/annulation reaction of amidines and sulfoxonium ylides to prepare substituted isoquinolines in good to excellent yields (Scheme 1c).[12g] Cheng disclosed

a Rh-catalyzed dual functionalization/cyclization reaction of imidates and sulfoxonium ylides, with the desired C–H functionalized and dual cyclized fused pyrano[4,3,2-ij]isoquinolines afforded in good yields (Scheme 1d).[12h] When a 1:1 molar ratio of starting materials was used, a mono-C–H coupling/cyclization occurred, however, the yield was low. Although notable advances have been made in such transformations, most of them involve expensive catalysts, such as Ir and Rh complexes and additives (silver salts). Owing to its high catalytic activity and low cost, ruthenium has become another attractive metal catalyst for C–H bond activation, and has been applied as a catalyst in the synthesis of *N*-heterocyclic compounds, including isoquinolines.[13,14] To our knowledge, no effective protocols for the ruthenium-catalyzed transformation of sulfoxonium ylides have been reported.[15] As a continuation of our interest in unactivated C–H bond functionalization and carbenoid chemistry,[16] we herein report a ruthenium-catalyzed C–H coupling/annulation of sulfoxonium ylides and benzimidates for the synthesis of isoquinoline derivatives using only an inexpensive organic acid additive under oxidant-free, base-free, and salt-free conditions.

Initially, benzimidate **1a** and sulfoxonium ylide **2a** were chosen as model substrates. To our delight, a 1:1.5 ratio mixture of **1a** and **2a** with 5 mol% $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst afforded desired annulation product **3aa** in 35% yield after reacting in EtOH at 100 °C for 12 h (Table 1, entry 1). When 20 mol% $AgSbF_6$ was added, **3aa** was isolated in a slightly decreased yield (32%). To further improve the yield, various organic acids were investigated. Several common organic acids were tested, including acetic acid (AcOH), pivalic acid (Piv-OH), 1-adamantaneacetic acid (Adm-1-COOH), and benzoic acid (PhCOOH) and its derivatives, with 3,5-Me_2PhCOOH (mesitylenic acid) giving the best result (entries 3–7). Next, different solvents were screened, with the results indicating that EtOH/2,2,2-trifluoroethanol (TFE) mixed solvent was the best choice (entry 11). Other sterically bulky acids gave similar results to that of mesitylenic acid (entries 13–15). A lower yield of **3aa** (56%) was achieved when the reaction was performed at a lower temperature of 80 °C compared with that at 100 °C (entries 17 and 18). Therefore, the best result (74% yield) was achieved using $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) and mesitylenic acid (50 mol%) in EtOH/TFE at 100 °C. It is also worth mentioning that only trace amount of bis C-H activation product could be observed under the standard conditions.[17]

With the optimized conditions in hand, we then investigated the generality of this mono-C–H functionalization/annulation process. Initially, a

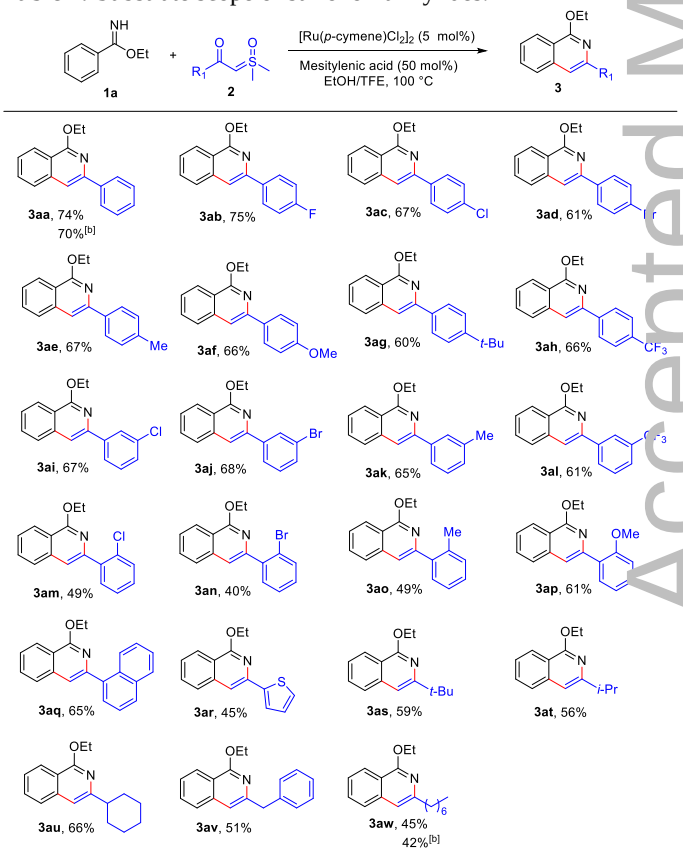
Table 1. Optimization of the reaction conditions.[a]



Entry	Additive	Solvent	Yield (%)[b]
1	none	EtOH	35
2[c]	$AgSbF_6$	EtOH	32
3	AcOH	EtOH	54
4	Piv-OH	EtOH	49
5	Adm-1-COOH	EtOH	52
6	PhCOOH	EtOH	51
7	3,5-Me_2PhCOOH	EtOH	60
8	3,5-Me_2PhCOOH	TFE	48
9	3,5-Me_2PhCOOH	HFIP	48
10	3,5-Me_2PhCOOH	DCE	21
11	**3,5-Me_2PhCOOH**	**EtOH/TFE(1:1)**	**74**
12	3,5-Me_2PhCOOH	EtOH/HFIP(1:1)	62
13	N-Ac-Ile-OH	EtOH/TFE (1:1)	68
14	2,4-Me_2PhCOOH	EtOH/TFE (1:1)	70
15	3,5-*t*Bu_2PhCOOH	EtOH/TFE (1:1)	69
16	AcOH	EtOH/TFE (1:1)	65
17[d]	3,5-Me_2PhCOOH	EtOH/TFE (1:1)	56
18[e]	3,5-Me_2PhCOOH	EtOH/TFE (1:1)	74

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol), additive (0.5 equiv), and $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) in solvent (2.0 mL) stirred at 100 °C for 12 h.
[b] Isolated yields.
[c] 0.2 equiv of $AgSbF_6$ was used.
[d] Performed at 80 °C.
[e] Performed at 120 °C.

Table 2. Substrate scope of sulfoxonium ylides.[a]



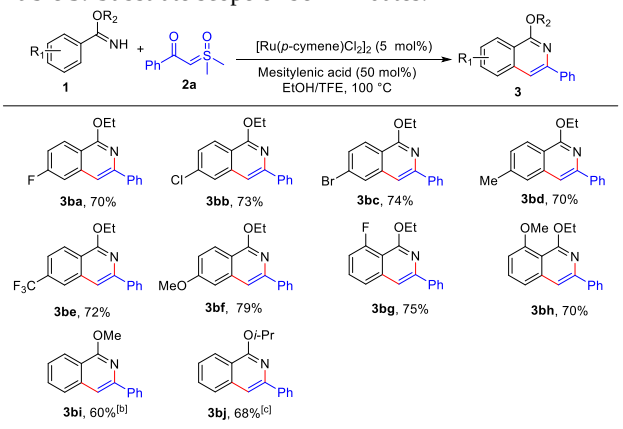
[a] Reaction conditions: **1a** (0.2 mmol), sulfoxonium ylide **2** (0.3 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), mesitylenic

acid (0.5 equiv.), TFE/EtOH (2 mL, 1:1 (v/v)) at 100 °C for 12 h; isolated yield.
[b] Using 1 gram of **1a**.

series of substituted sulfoxonium ylides were subjected to this transformation, with the reaction proceeded smoothly to yield the corresponding isoquinolines in moderate to good yields (Table 2). Firstly, sulfoxonium ylides containing F, Cl, Br, CH_3, or CF_3 substituents at the *para* or *meta* positions of the aryl ring were investigated. These reactions proceeded well, affording yields of 60%–75%. Ylides substituted with OCH_3 or *t*-Bu groups at the *para* position reacted well with **1a**, giving corresponding products **3af** and **3ag** in 66% and 60% yields, respectively. However, ylides with Cl, Br, or CH_3 *ortho*-substituents gave the desired isoquinolines in dramatically decreased yields of around 40%. Naphthalene and heteroaromatic derivatives derived from sulfoxonium ylides were well tolerated under the present conditions, affording 3-aryl isoquinolines **3aq** and **3ar** in 65% and 45% yields, respectively. Furthermore, alkyl sulfoxonium ylides bearing *t*-Bu, *i*-Pr, and cyclohexyl groups reacted smoothly with **1a** to give products **3as**–**3au** in good yields. Furthermore, two unbranched alkyl sulfoxonium ylides were subjected to the optimal reaction conditions, with the corresponding products **3av** and **3aw** obtained in 51% and 45% yields, respectively. Finally, ylide **1a** was also reacted with two representative sulfoxonium ylides on a gram-scale under optimal conditions, affording the corresponding products **3aa** and **3aw** in slightly reduced yields of 70% and 42%, respectively.

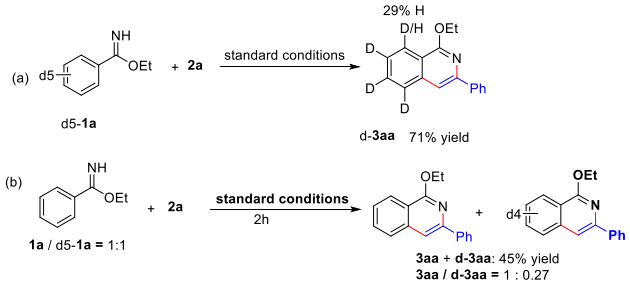
Next, the substrate scope of benzimidate derivatives was investigated (Table 3). Unsurprisingly, a variety of benzimidates bearing election-withdrawing or electron-donating groups at the 2- or 4-position of the aryl ring reacted smoothly, affording expected products **3ba**–**3bj** in good yields, as shown in Table 3. Notably, when isopropyl-

Table 3. Substrate scope of benzimidates.[a]



[a]Reaction conditions: benzimidate **1** (0.2 mmol), sulfoxonium ylide **2a** (0.3 mmol), [Ru(*p*-Cymene)Cl_2]$_2$ (5 mol %), mesitylenic acid (0.5 equiv) in TFE/EtOH (1/1, 2 mL) at 100 °C for 12 h, isolated yield.
[b] MeOH was used instead of EtOH.
[c] *i*-PrOH was used instead of EtOH.

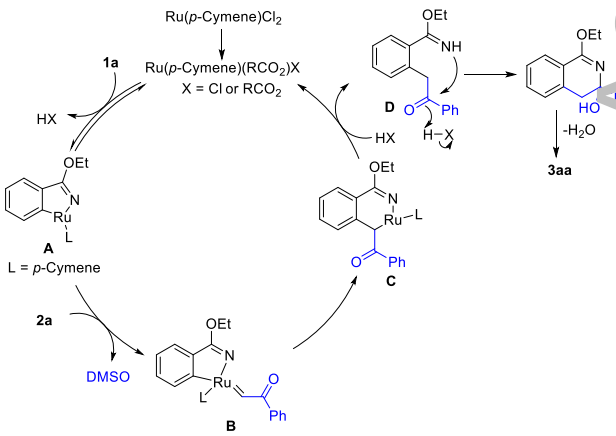
substituted benzimidate was reacted under the optimized conditions, mixed products **3aa** and **3bj** were obtained in 55% yield. When corresponding alcohols other than ethanol were used as the solvent, desired isoquinolines **3bi** and **3bj** were afforded in 60% and 68% yields, respectively.



Scheme 2. Control experiments

To better understand the mechanism of this transformation, control experiments were designed and conducted (Scheme 2). First, when benzimidate d5-**1a** was used instead of **1a** under the optimized conditions, desired deuterated product d-**3aa** was obtained in 71% yield with 29% hydrogen incorporation at the C-8 position of the product, indicating a reversible C–H activation process. [14i, 15] Next, the reaction of a 1:1 mixture of **1a** and d5-**1a** produced both **3aa** and d-**3aa** in 45% yield. As a D/H exchange process on d-**3aa** was involved in the catalytic sequence, the exact KIE could not be determined. However, the ratio of products **3aa** and d-**3aa** indicated a KIE above 3, which suggested that cleavage of the aromatic C–H bond was the rate-determining step.

Based on the experimental results above and previous reports,[18] a plausible reaction pathway was proposed, starting from the Ru(*p*-cymene)(RCO_2)X (X = RCO_2 or Cl) species, as shown in Scheme 3. First, C–H metalation of **1a** occurs, producing five-membered cyclic ruthenacycle intermediate **A**. Carbene formation then occurs through the reaction of **A** with a sulfoxonium ylide, generating carbene intermediate **B** through the elimination of DMSO. [15] Next, migratory insertion of the carbene into the Ru–C bond affords six-membered ruthenacycle



Scheme 3. Proposed mechanism of annulative coupling.

intermediate **C**. [11-12, 16] Protonolysis of **C** with acid might then occur, producing acylmethylated intermediate **D**, which undergoes successive addition/dehydrating steps under the acidic conditions to afford product **3aa**. [5, 12g, 12h, 15]

In summary, we have developed an inexpensive ruthenium-catalyzed mono *ortho*-C–H functionalization and annulation reaction of benzimidates and sulfoxonium ylides. A variety of substrates were used to access biologically interesting isoquinolines in good yields. The reaction was conducted using a readily available organic acid as additive under oxidant-free, base-free, and salt-free conditions, which are attractive features of this new method.

Experimental Section

To a 10-mL reaction tube with a screw-cap and a magnetic stir-bar under an argon atmosphere were added benzimidate (0.2 mmol), sulfoxonium ylide (1.5 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5.0 mol%), 3,5-dimethylbenzoic acid (0.5 equiv.), dry ethanol (1.0 mL), and TFE (1.0 mL). The reaction mixture was stirred at 100 °C until the starting material disappeared (as monitored by TLC). The solvent was then evaporated under vacuum and the residue purified by silica gel column chromatography using petroleum ether as the eluent to afford the desired product.

Acknowledgements

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