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Synthesis of 2-Substituted Indoles by Iridium (III)-Catalyzed C-H Functionalization of *N*-phenylpyridin-2-amines

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ABSTRACT

A highly regioselective synthesis of 2-substituted indoles was realized through Ir(III)-catalyzed C–H functionalization of *N*-phenylpyridin-2-amines followed by the reaction with sulfoxonium ylides and intramolecular cyclization under mild conditions. The reaction completed with broad range of substrate scopes and gave various 2-substituted indoles in up to 98% yields.

Introduction

Indole is a privileged scaffold with numerous applications in both life sciences and material sciences [1]. In particular, 2-arylindoles [2] and 2-aliphatic substituted indoles [3] are intriguing structural motifs owing to their presence in a series of marketed drugs (Figure 1). Consequently, tremendous efforts have been devoted to constructing 2-substituted indole scaffolds. Recently, Rh- [4], Pd- [5], Ru- [6], Ni- [7] and other transition metals [8] catalyzed C−H functionalization provided a fundamental step for the preparation of various 2-substituted indoles.

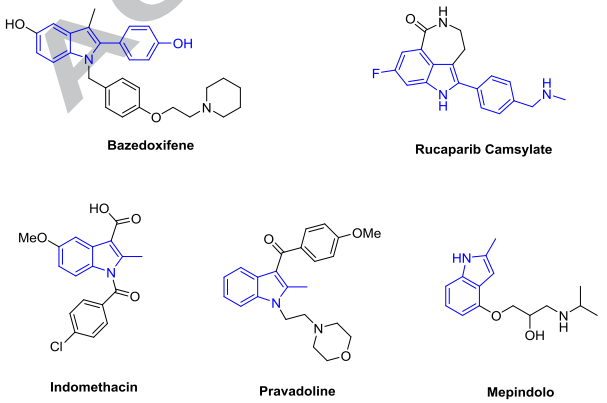
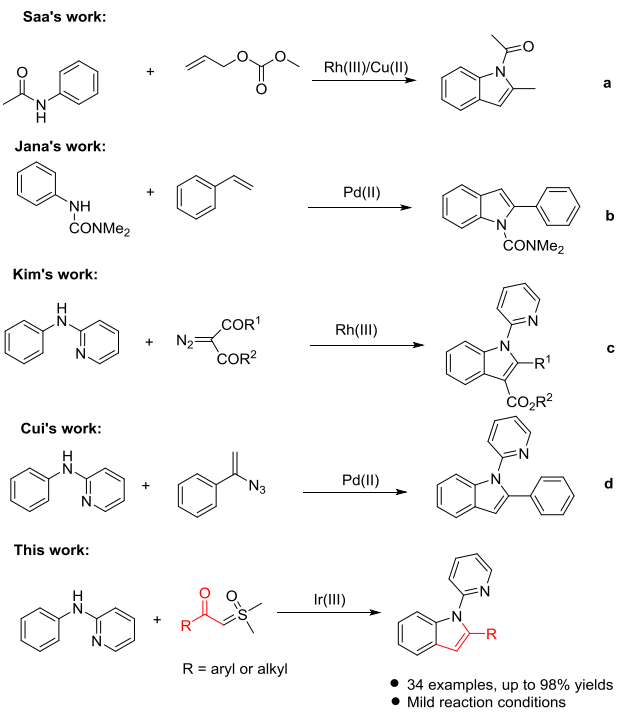


Fig.1 Selected drugs containing 2-substituted indoles

In 2013, Saá's group [9] reported a Rh(III)-catalyzed synthesis of 2-methylindoles with stoichiometric copper(II) as oxidant (Scheme 1a). Shortly after, Jana's group [10] developed a palladium-catalyzed synthesis of 2-arylindole



Scheme 1 Synthesis of 2-substituted indoles via annulative C–H activation.

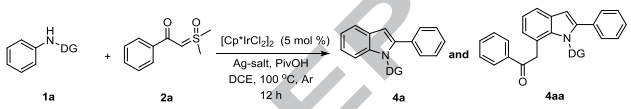
(Scheme 1b). More recently, Kim and Cui applied diazo compounds and vinyl azides to synthesize 2-substituted indoles (Scheme 1c and 1d) [11]. Despite the significant advance made in this field, the previous methods still suffer from limited

substrate scopes or the need for potential dangerous diazo compounds. Therefore, the development of a versatile and safe method is highly desirable. Li [12] and others [13] found that sulfoxonium ylides could worked as a safer carbene precursors in various C−H activation catalyzed by Rh(III) [14], Ru(II) [15], and Co(III) [16]. Based on our previous work [17], herein, we wish to report an Ir(III)-catalyzed synthesis of 2-substituted indoles from *N*-phenylpyridin-2-amines and sulfoxonium ylides via C−H functionalization and cyclization.

Results and Discussion

We initiated our studies with *N*-phenylpyridin-2-amine **1a** and sulfoxonium ylide **2a** as model substrates in the presence of $[IrCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %) and PivOH (1 eq) in DCE under Ar at 100 °C for 12 h. We were delighted to obtain the desired product **4a** in 44% yield and byproduct **4aa** in 33% yield, which was formed by the reaction of **4a** and the second sulfoxonium ylide (Table 1, entry 1). It was found that silver salts had a significant influence on the reaction. To our delight, AgOAc gave the best result and increased the yield of **4a** to 75% (entries 2−5). Screening of solvents revealed that DCE is the preferred solvent in this transformation (entries 5-8). Moreover, acetic acid was a better additive than PivOH, afforded the product **4a** in 81% yield (entry 9). Increasing the amount of **2a** could not improve the yield due to the increased amount of byproduct **4aa** (entry 10). Control experiments confirmed that poor yields of **4a** were obtained when additive was omitted (entry 11). Furthermore, when the directing group replaced by –COMe or $–CONMe_2$ the reaction was complicated (entry 12 and 13). Therefore, the optimal reaction conditions were established as **1a** (0.4 mmol), **2a** (0.48 mmol, 1.2 equiv), $[IrCp^*Cl_2]_2$ (5 mol %), AgOAc (20 mol %), and HOAc (0.4 mmol, 1 eq) in DCE (3 mL) stirred at 100 °C for 12 h under Ar protection.

Table 1
Optimization of reaction conditions[a]

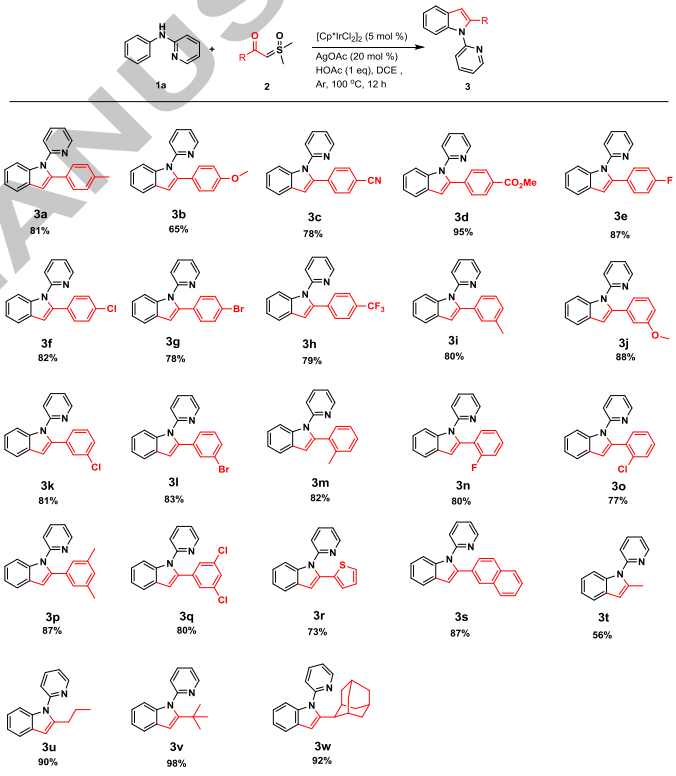


Entry	[Ag]	solvent	yield of **4a**(%)[b]	yield of **4aa** (%)[b]
1	$AgSbF_6$	DCE	44	33
2	AgOTf	DCE	44	9
3	$AgBF_4$	DCE	44	37
4	$AgNTf_2$	DCE	19	38
5	AgOAc	DCE	75	10
6	AgOAc	toluene	66	-
7	AgOAc	TFE	33	38
8	AgOAc	THF	31	9
9[c]	**AgOAc**	**DCE**	**81**	-
10[d]	$AgSbF_6$	DCE	34	65
11[e]	AgOAc	DCE	45	-
12[f]	AgOAc	DCE	-	-
13[g]	AgOAc	DCE	-	-

[a] Reaction Conditions: **1a** (0.4 mmol), **2a** (0.48 mmol, 1.2 eq), $[Cp^*IrCl_2]_2$: (5 mol %), [Ag]: (20 mol %), PivOH: (1 eq), 12 h, 100 °C, Ar. DCE = 1,2-dichloroethane, PivOH = pivalic acid, TFE = 2,2,2-trifluoroethanol, DG = 2-pyridinyl.
[b] Isolated yield.
[c] HOAc as an additive.
[d] **2a** (0.88 mmol, 2.2 eq).
[e] No additive
[f] DG = -COMe
[g] DG = $-CONMe_2$

With the optimized reaction conditions in hands, we investigated the reaction of various sulfoxonium ylides (Table 2). The reaction proceeded smoothly to afford indoles in good yields with excellent functional group compatibility. Sulfoxonium ylides bearing electron-donating or withdrawing groups at *para*-position of the aromatic ring displayed high reactivity, providing the desired products **3a–3h** in 65–95% yields. Similarly, *meta*- and *ortho*- substituted sulfoxonium ylides with methyl, methoxy, chloro, bromo, and flouro groups could also afforded desired products **3i-3o** in 77-88% yields. Moreover, disubstituted benzoyl sulfoxonium ylides were well tolerated in this transformation, providing the corresponding products **3p** and **3q** in 87% and 80% yields. Furthermore, this reaction was not limited to phenyl substrates, sulfoxonium ylides containing a thiophene ring or naphthalene gave **3r** and **3s** in 73% and 87% yields respectively. Comparably, sulfoxonium ylides with alkyl substituents showed better reactivity to deliver the corresponding products **3t-3w** in 56%-98% yields.

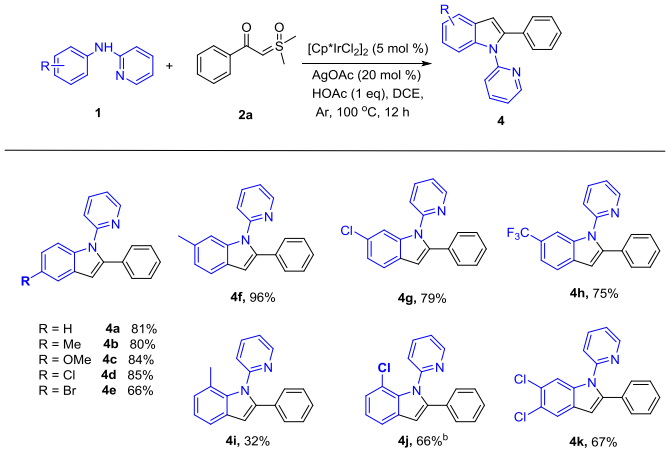
Table 2
Scope of substituted sulfoxonium ylides[a].



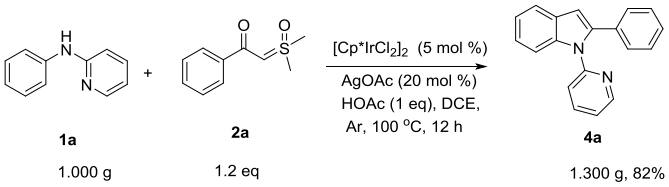
[a] Reaction Conditions: **1a** (0.4 mmol), **2** (0.48 mmol, 1.2 eq), $[Cp^*IrCl_2]_2$ (5 mol %), AgOAc (20 mol %), HOAc (1 eq), 12 h, 100 °C, Ar.

After exploration of sulfoxonium ylides, we investigated the scope and limitation of *N*-phenylpyridin-2-amines (Table 3). *N*-Phenyl-2-aminopyridines bearing electron-donating and withdrawing groups at *para* position of benzene ring all reacted smoothly with sulfoxonium ylides with high efficiency and gave corresponding 2-arylindoles **4b-4e** in 66–85% yields. Accordingly, good to high isolated yields obtained for *meta*-substituted substrates **4f–4h** indicated full tolerance of various substituents. In sharp contrast, *ortho*-methylaniline were ineffective substrates in this reaction, giving **4i** and **4j** in 32% and 22% yields. Luckily, the yield of **4j** could improved to 66% by prolonging the reaction time to 24 h. Moreover, disubstituted aniline also well tolerated and gave coupling product **4k** in 67% yield. To demonstrate the synthetic utility of this protocol, a scale-up reaction of *N*-phenylpyridin-2-amine **1a** and **2a** was carried out under the optimized conditions, giving corresponding product **4a** in 82% yield (Scheme 2).

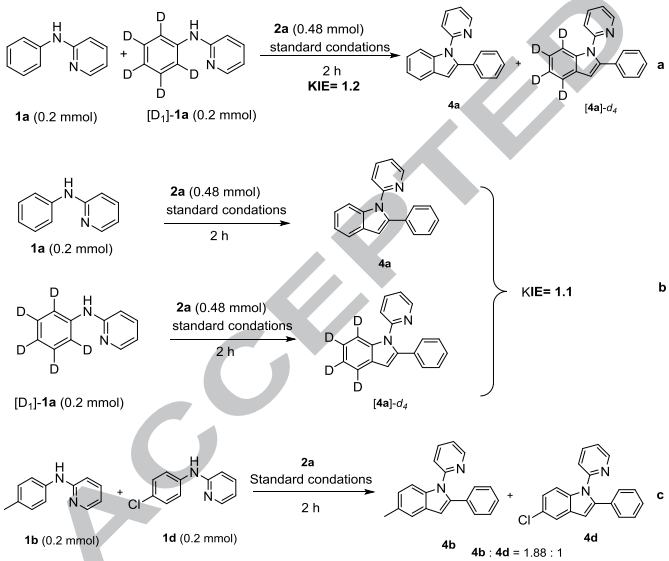
Table 3
Scopes of substituted *N*-phenylpyridin-2-amines[a]



[a] Reaction Conditions: **1** (0.4 mmol), **2a** (0.48 mmol, 1.2 eq), $[Cp^*IrCl_2]_2$ (5 mol %), AgOAc (20 mol %), HOAc (1 eq), 12 h, 100 °C, Ar. [b] 24 h.



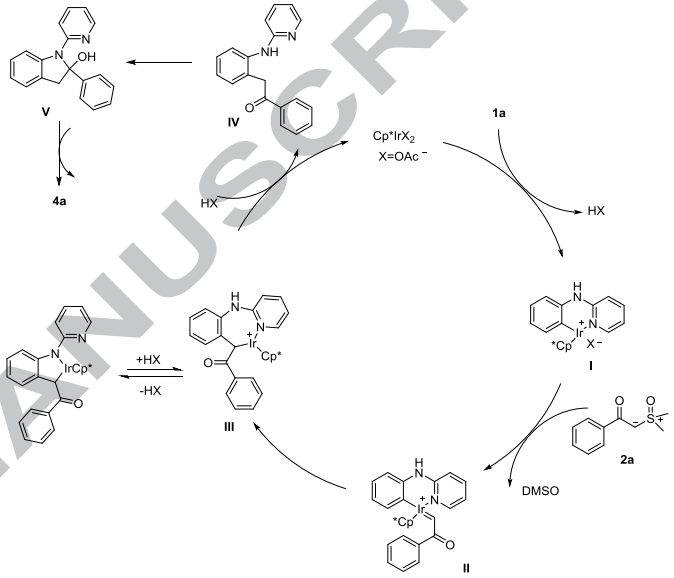
Scheme 2 Gram-scale reaction.



Scheme 3 Mechanistic studies.

For gaining insight into the reaction mechanism, the kinetic isotope effect (KIE) has been measured [18]. The KIE value of intermolecular competition (k_H/k_D = 1.2) and parallel reactions (k_H/k_D = 1.1) indicated that C–H activation is possibly not the rate-determine step in this transformation (scheme 3a and 3b). Moreover, a competition experiment has been performed using substrates bearing different electronic properties [15d]. The reaction of **1b**/**1d** afforded the corresponding products **4b**/**4d** in 1.88:1 ratio based on HPLC analysis, indicating that an electron-donating group tended to favor the reaction (Scheme 3c).

Based on the precedent literature reports [19], a plausible mechanistic pathway was given in Scheme 4. Initially, a pyridinyl directing group on **1a** coordinated to a Ir(III) catalyst, subsequent C–H cleavage generated a six-membered iridacycle intermediate **I**. Then the coordination of the sulfoxonium ylide **2a** reacted with **I** and followed by the elimination of DMSO to produce a metal-carbenoid intermediate **II**. The iridium (III) intermediate **III** was generated by migratory insertion of the Ir-aryl bond into the activated carbine, which then underwent protonation to generate intermediate **IV** and Cp*Ir(III) species for the next catalytic cycle. Finally, intermediate **IV** underwent intramolecular nucleophilic cyclization and dehydration to furnish the final product indole **4a**.



Scheme 4. Proposed Reaction Mechanism

In conclusion, we disclosed a Cp*Ir(III)-catalyzed highly efficient coupling reaction of anilines with sulfoxonium ylides by using pyridinyl as a directing group. The reaction provides a concise synthetic strategy to 2-substituted indoles with good to excellent yields under mild conditions. The further investigations on its synthetic applications are currently underway in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://

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1. Ir(III)-catalyzed C–H activation synthesize 2-substituted indoles efficiently.
2. Various functional groups tolerated and gave 2-substituted indoles in good yields.
3. KIE experiments were conducted to probe the possible mechanism.

Graphical Abstract

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Synthesis of 2-Substituted Indoles by Iridium(III)-Catalyzed C-H Functionalization of *N*-phenylpyridin-2-amines

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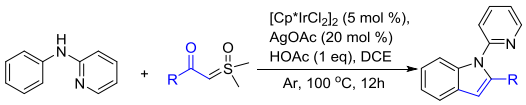
Lei Zhang, Junyu Chen, Jinkang Chen, Licheng Jin, Xiangyun Zheng, Xinpeng Jiang*, and Chuanming Yu*



- 34 examples, up to 98% yields
- Mild reaction conditions

An efficient Ir(III)-catalyzed C–H functionalization for the synthesis of 2-substituted indoles from *N*-phenylpyridin-2-amines and sulfoxonium ylides have been developed. The reaction accomplished with broad range of substrate scopes and gave various 2-substituted indoles in up to 98% yields.