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Ruthenium-catalyzed synthesis of indole derivatives from *N*-aryl-2-aminopyridines and alpha-carbonyl sulfoxonium ylides†

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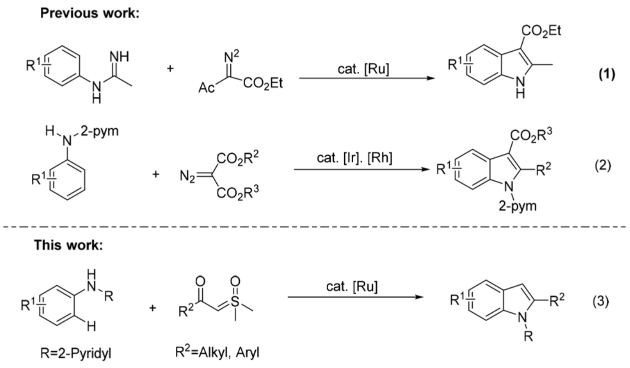
Indole is a ubiquitous structural motif with important applications in many areas of chemistry. Given this, a simple and efficient Ru(II)-catalyzed synthesis of indole *via* intermolecular annulation of *N*-aryl-2-aminopyridines and sulfoxonium ylides was proposed and accomplished. Excellent selectivity and good functional group tolerance of this transformation were observed. This protocol provides easy access to a wide variety of useful indoles in the presence of a commercially available [Ru(*p*-cymene)Cl_2]$_2$ catalyst. A possible mechanism for the reaction pathway was also proposed. More importantly, this reaction will offer a useful method for the construction of enantioenriched indole frameworks.

The skeleton of indole is widely prevalent in biologically active compounds, natural products and materials.[1] Owing to the great structural diversity of biologically active indoles, highly convenient methods for their synthesis have been constantly pursued for a long time and varieties of approaches have been achieved. Among them, the well-established Fischer indole synthesis[2] and Larock indole synthesis[3] have attracted significant attention because of their extensive application prospects. However, these reactions also face some nonignorable drawbacks. For example, the Fischer reaction can be limited in scope due to the stability of the hydrazine component and strong acidic reaction conditions. Moreover, poor selectivity was also observed when it was applied to synthesize 4- or 6-monosubstituted indoles; on the other hand, expensive multi-substituted 2-iodinated anilines are required as starting materials in the Larock indole synthesis. As a result, development of an efficient, atom-economical and environmentally benign synthetic strategy appears to be attractive and highly desirable.

In recent years, researchers have focused on the development of transition-metal-catalyzed C–H bond functionalization for the construction of C–C and C–heteroatom bonds.[4] This strategy takes advantage of the ubiquitous C–H bond in unactivated arenes as the direct source. Various transition metal complexes involving Ru,[5] Rh,[6] Pd,[7] Ir[8] and Co[9] have been effectively applied for the *ortho* C–H functionalization of the pyrimidyl moiety and other directing groups. Moreover, efficient synthesis of indole derivatives using transition metals has also been greatly employed. Among them, transition metal-catalyzed C–H activation/metal–carbenoid insertion provides an effective and atom-economical approach for C–X (X = C, N, O and S, *etc.*) bond construction. Significant work by Li[10] and coworkers has realized efficient synthesis of indoles using the imidamides and diazo compounds as substrates by employing this strategy [Scheme 1, eqn (1)]. Very recently, Li[11] and Mishra[12] reported Ir(III)- and Rh(III)-catalyzed intermolecular indole synthesis which also employed diazo compounds as carbenes [Scheme 1, eqn (2)]. However, diazo substrates face the drawbacks of being potentially unstable explosives (Table 1).



Scheme 1 Transition-metal-catalyzed synthesis of indole derivatives.

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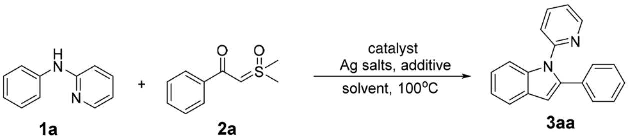
Table 1 Optimization studies on the synthesis of indoles[a]



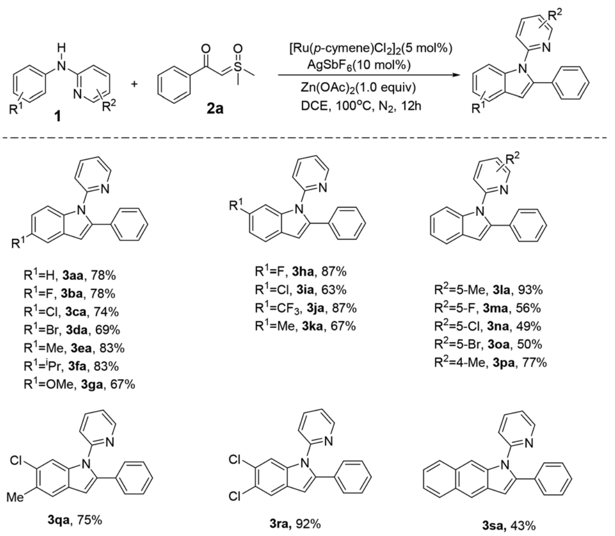
Entry	Catalyst	Ag salts	Additive	Solvent	Yield[b]
1	$[IrCp^*Cl_2]_2$	—	$Zn(OAc)_2$	DCE	18
2	$[RhCp^*Cl_2]_2$	—	$Zn(OAc)_2$	DCE	11
3	$Cp^*Co(CO)I_2$	—	$Zn(OAc)_2$	DCE	0
4	$[Ru(p\text{-cymene})Cl_2]_2$	—	$Zn(OAc)_2$	DCE	48
5	$[Ru(p\text{-cymene})Cl_2]_2$	—	HOAc	DCE	29
6	$[Ru(p\text{-cymene})Cl_2]_2$	—	$Cu(OAc)_2$	DCE	0
7	$[Ru(p\text{-cymene})Cl_2]_2$	—	CsOAc	DCE	15
8	$[Ru(p\text{-cymene})Cl_2]_2$	—	PivOH	DCE	37
9	$[Ru(p\text{-cymene})Cl_2]_2$	—	NaOAc	DCE	15
10	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DCE	63
11	$[Ru(p\text{-cymene})Cl_2]_2$	$AgBF_4$	$Zn(OAc)_2$	DCE	53
12	$[Ru(p\text{-cymene})Cl_2]_2$	$AgNTf_2$	$Zn(OAc)_2$	DCE	53
13	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	CH_3CN	40
14	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	TFE	14
15	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	$PhCF_3$	13
16	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	THF	53
17	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DMSO	0
18	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DCE	55[c],59[d]
19	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	$Zn(OAc)_2$	DCE	78[e]
20	—	$AgSbF_6$	$Zn(OAc)_2$	DCE	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol%), Ag salts (10 mol%), additive (1 equiv.) and a solvent (2.5 mL) at 100 °C for 12 h. [b] Isolated yields after column chromatography. [c] At 90 °C. [d] At 110 °C. [e] Under a N_2 atmosphere.

Sulfur ylides have been known as potentially safe precursors of metal carbenes.[13] They are safe to synthesize and provide crystalline, bench-stable compounds. They are widely used as important building blocks in annulation reactions with nucleophilic directing groups. For example, in 2018, Fan[14] presented a highly regioselective synthesis of diversely substituted benzo[*a*]carbazoles and indolo[2,1-*a*]-isoquinolines using 2-arylindoles with sulfoxonium ylides. In the same year, Zeng[15] developed an alternative synthetic approach toward 1,2-benzothiazines through Ru(II)-catalyzed coupling-cyclization of sulfoximines with alpha-carbonyl sulfoxonium ylides. Sulfoxonium ylides used as methylene synthons are also widely applied in other organic syntheses, including metal-free catalytic systems.[13b] Encouraged by these eminent studies, herein a simple Ru-catalyzed synthesis of indole was developed by introducing *N*-aryl-2-aminopyridines with alpha-carbonyl sulfoxonium ylides as substrates [Scheme 1, eqn (3)].

At the outset of this study, we first performed a reaction between *N*-aryl-2-pyridinamine (**1a**, 0.20 mmol) and sulfoxonium ylide (**2a**, 0.30 mmol) using $[IrCp^*Cl_2]_2$ (5 mol%) as a catalyst in dichloroethane (2.5 mL) at 100 °C under an enclosed atmosphere for 12 h. The desired product **3aa** was obtained in 18% yield (entry 1). Other catalysts such as $[RhCp^*Cl_2]_2$ and $Cp^*Co(CO)I_2$ gave inferior results (entries 2 and 3). To our delight, the isolated yield of **3aa** dramatically increased to 48% when $[Ru(p\text{-cymene})Cl_2]_2$ was used as a catalyst (entry 4). Encouraged by this result, we investigated other additives and found that the yield could not be further improved compared to the $Zn(OAc)_2$ additive (entries 4–9). Further optimization studies indicated that the addition of a cationic generator *i.e.* silver hexafluoroantimonate ($AgSbF_6$), could further improve the yield, indicating that $AgSbF_6$ was the most effective cationic generator. Subsequently, screening of solvents revealed that 1,2-dichloroethene was the optimal choice (entries 13–17). Temperature also significantly influenced this reaction, as **1a** showed low reactivity at 90 °C or 110 °C (entry 18). Surprisingly, when the reaction was carried out under a N_2 atmosphere, a dramatic increase in the reaction yield (78%) was observed (entry 19). Control experiments revealed that no reaction occurred when the catalyst $[Ru(p\text{-cymene})Cl_2]_2$ was absent, which indicated that the metal catalyst was essential for this transformation (entry 20).

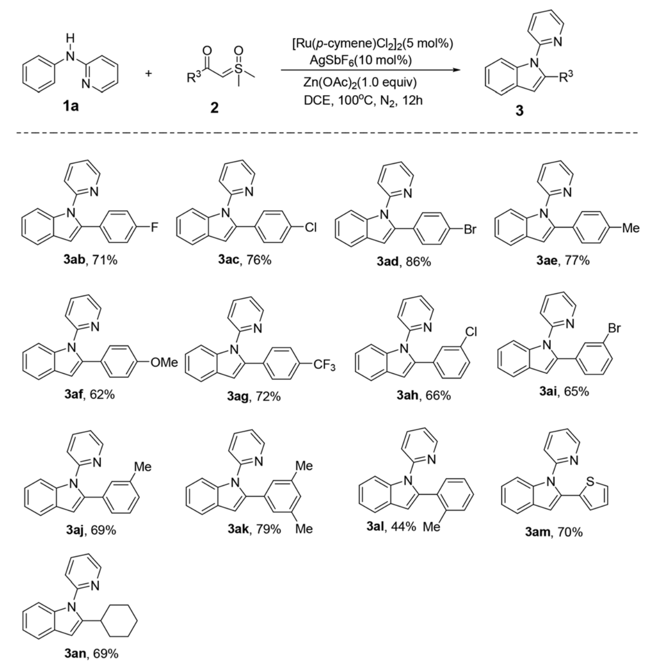
With an optimized catalytic system in hand, we examined the scope of *N*-phenylpyrimidin-2-amines (Scheme 2). *N*-(Substituted phenyl)-2-pyridin-amines bearing halide substituents (4-F, 4-Cl, and 4-Br) and other electron-donating groups (4-Me, 4-iPr, 4-OMe) were well tolerated and gave the corresponding products (**3ba–3ga**, 69–83%) in moderate to good yields. *N*-Phenyl-pyridin-2-amine bearing an electron-withdrawing group (**1j**), halide groups (**1h**, **1i**) or an alkyl group (**1k**) at the *meta* position all coupled smoothly with **2a** to furnish the corresponding indoles in good yields (**3ha–3ka**). The substituent on the pyridine ring of *N*-(substituted phenyl)-2-pyridin-amines showed obvious electronic effects on the reaction activity, affording the products **3la–3pa** in moderate to good yields (49–93%). When disubstituted substrates (**1t**, **1u**) were used, the substituted indole derivatives **3qa** and **3ra** were obtained with 75% and 92% yields, respectively. The large *N*-(naphthalene-2-yl)pyridine-2-amine also readily participated in the coupling reaction to provide product **3sa** in 43% yield.



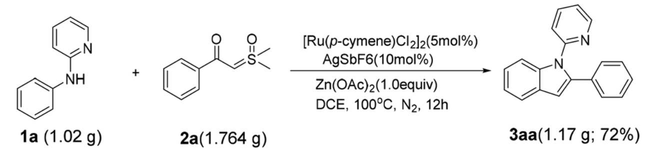
Scheme 2 Scope of anilines in the synthesis of indoles. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $AgSbF_6$ (10 mol%), $Zn(OAc)_2$ (1 equiv.) and DCE (2.5 mL) at 100 °C for 12 h. Isolated yields after column chromatography.

In addition to anilines, the scope of the reaction with sulfoxonium ylides was also explored (Scheme 3). In general, the coupling reaction of substrate **1a** and various benzoyl-substituted sulfoxonium ylides afforded the annulated products in good yields. The corresponding products were obtained in good yields with electron-withdrawing groups (F, Cl, Br and CF$_3$) or electron-donating groups (Me and MeO–) attached to the *para*-position and *meta*-position of the benzoyl ring of sulfoxonium ylides (**3ab**–**3aj**). When the disubstituted sulfoxonium ylide (**2k**) was explored, the reaction afforded the desired product (**3ak**) in good yield. Moreover, introduction of a methyl group to the *ortho*-position of benzoyl was also tolerated (**3al**), despite the fact that it provided a lower yield. To our delight, this catalytic system could be further extended to α-2-thienoyl sulfoxonium ylide, which could also react with **1a** to give **3am** in 74% yield. The versatility of this robust catalytic system was further mirrored by successfully using alkyl substituted sulfoxonium ylides, which provided the corresponding product (**3an**) in good yield.

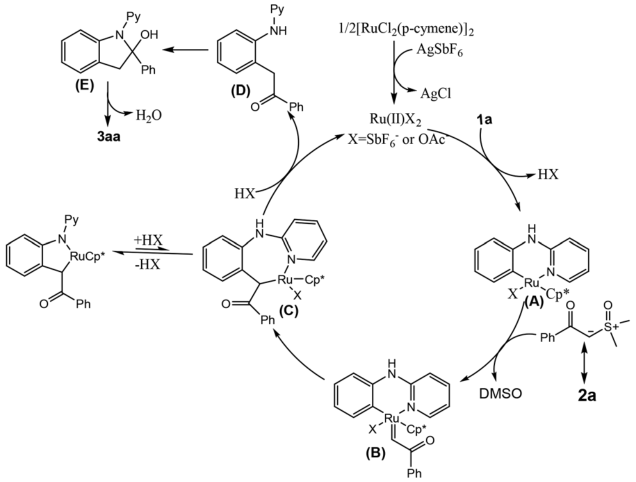
To demonstrate the synthetic utility of this catalytic reaction, a 6 mmol scale synthesis of **3aa** was carried out, and a good yield of 72% was still obtained (Scheme 4). We attempted to remove the pyridyl group in the product, but unfortunately failed by following various typical conditions.



Scheme 3 Scope of sulfoxonium ylides in the synthesis of indoles. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Ru(p-cymene)Cl$_2$]$_2$ (5 mol%), AgSbF$_6$ (10 mol%), Zn(OAc)$_2$ (1 equiv.) and DCE (2.5 mL) at 100 °C for 12 h. Isolated yields after column chromatography.



Scheme 4 Gram-scale synthesis.



Scheme 5 Proposed mechanism for the formation of indoles.

Based on literature reports,[8b,16,17] a plausible mechanism for the annulation of **1a** with **2a** was proposed as depicted in Scheme 5. Initially, the dimeric precursor [Ru(p-cymene)Cl$_2$]$_2$ is converted into [Ru(II)X$_2$] as an active catalyst through the anion exchange. Next, nitrogen coordination of **1a** is followed by cyclometalation to deliver a six-membered ruthenacycle intermediate **A**. Coordination of sulfur ylide **2a** and subsequent elimination of DMSO generate Ru(II) carbene **B**, which then undergoes migratory insertion of the Ru–aryl bond into the activated carbene to afford a seven-membered ruthenacycle intermediate **C**. Protonolysis of the Ru–C bond by HX gives the corresponding intermediate **D**, together with the regeneration of the Cp*Ru(II) catalyst. Intramolecular nucleophilic attack of the imine on the carbonyl group produces **D**, which undergoes dehydration, furnishing **3aa**.

Conclusions

We reported a ruthenium-catalyzed direct C–H functionalization and cross-annulation between *N*-phenylpyrimidin-2-amines and α-aroyl sulfur ylides toward a series of functionalized indoles in good to moderate yields. This catalytic system features mild conditions and a wide range of substrates with excellent functional group tolerance, with DMSO and H$_2$O being the only byproducts.

Conflicts of interest

There are no conflicts to declare.

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