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Iridium(III)- and rhodium(III)-catalyzed coupling of anilines with α -diazoesters *via* chelation-assisted C–H activation†

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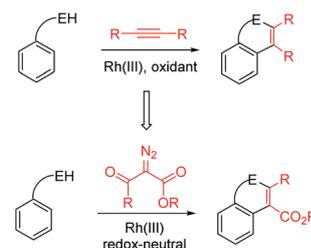
Iridium and rhodium complexes exhibited complementary activity in the coupling of *N*-functionalized anilines with α -diazoesters *via* C–H activation. The coupling with α -diazo β -ketoesters was realized under Ir(III) catalysis to afford ester-functionalized indoles. In contrast, coupling with α -diazomalونات under Rh(III) catalysis afforded alkylation products without any annulation. Mechanistic studies have been performed and an iridacycle has been isolated as an intermediate.

Indoles are important building blocks in synthetic organic chemistry. They are also a key structure motif widely present in natural products and pharmaceuticals that have exhibited important biological activity.¹ Consequently, increasing efforts have been devoted to the synthesis of indoles. Arguably, the Fischer indole synthesis² and the Larock indole synthesis³ are among the most commonly employed methods. However, the Fischer indole synthesis required the usage of a strong acid under harsh conditions, which may pose issues of functional group compatibility. On the other hand, the Larock indole synthesis required the employment of 2-iodonated anilines and generated a stoichiometric amount of inorganic wastes.

In order to achieve high efficiency and high atom-economy, the C–H activation strategy has been increasingly employed in recent years, especially in the synthesis of heterocycles.⁴ This strategy takes advantage of the ubiquitous C–H bond in unactivated arenes as the direct source. In 2008, Fagnou and co-workers reported a highly efficient rhodium(III)⁵-catalyzed oxidative synthesis of indoles starting from readily available acetanilides and alkynes *via* C–H activation.⁶ Inspired by this work, a number of Rh(III)-catalyzed syntheses of nitrogen heterocycles such as indoles and isoquinolines, among others, have been reported.⁷ In addition, the synthesis of indoles has also been extended to catalysis by other transition metals.⁸ To address the limitation of using a stoichiometric amount of an oxidant, Glorius reported in 2013 the employment of arenes

bearing an oxidizing hydrazine directing group⁹ for indole synthesis.¹⁰

Very recently, Yu, Li, Rovis, and others demonstrated that Rh(III) and Ir(III) catalysts can effect the coupling of arenes with (activated) diazoesters *via* C–H activation, leading to alkylation, in which the diazo compounds act as a C1 source (carbene precursor).¹¹ Subsequently, the groups of Glorius, Bolm, Wang, Zeng, and others reported that these diazoesters can function as a C2 source in that the electrophilic carbonyl group in the diazoesters can further participate in cyclization reactions under redox-neutral conditions.¹² In the case of α -diazoacetylacetates, a C=C double bond was incorporated into the newly formed heterocycles. This amounts to the same type of product as was obtained under the oxidative cyclization conditions using alkynes (Scheme 1). Although Rh(III)-catalyzed C–H activation-coupling with α -diazoacetylacetates has been reported, Ir(III) catalysts have been rarely used. In addition, the synthesis of indoles *via* this redox-neutral strategy remains limited.^{11e,13} Thus, it is necessary to explore this type of indole synthesis using readily available *N*-phenyl-2-aminopyridines, although we and others have previously investigated the C–H activation of this substrate in the coupling with unsaturated molecules.¹⁴ We now report the Ir(III)-

Scheme 1 Annulative coupling using alkynes *versus* α -diazoesters.^aDalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China^bLaboratory of Multi Scale Materials and Molecular Catalysis, School of Materials Science and Engineering, Anhui University of Science and Technology, Huainan, 232001, China. E-mail: clpan@aust.edu.cn, xwli@dicp.ac.cn

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Table 1 Optimization of reaction conditions^a

Entry	Solvent	Time	Yield ^b
1	H ₂ O	1 h	75%
2	H ₂ O : EtOH (2 : 1)	1 h	82%
3	H ₂ O : EtOH (2 : 1)	5 h	89%
4	EtOH	5 h	53%
5 ^c	H ₂ O : EtOH (2 : 1)	5 h	N.R.
6 ^d	H ₂ O : EtOH (2 : 1)	5 h	62%
7 ^e	H ₂ O	5 h	N.R.
8 ^f	H ₂ O	5 h	80%

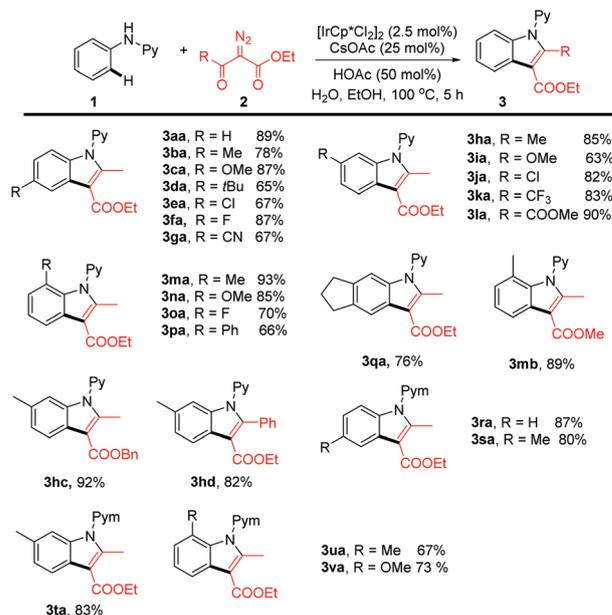
^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), [IrCp*Cl₂]₂ (2.5 mol%), solvent (3 mL), 100 °C, 5 h, under air. ^b Isolated yields based on **1**. ^c No CsOAc was used. ^d No AcOH was used. ^e No catalyst was used. ^f [RhCp*Cl₂]₂ was used as a catalyst.

and Rh(III)-catalyzed coupling between *N*-phenyl-2-aminopyridines and different activated diazoesters.

We embarked on our studies with the optimization of the coupling of *N*-phenyl-2-aminopyridine (**1a**) with ethyl α -diazoacetylacetate (Table 1). The reaction proceeded well when catalyzed by [IrCp*Cl₂]₂ in the presence of CsOAc and HOAc using water as a green solvent even after 1 h (entry 1).

The coupled product **3aa** was identified as an ester-functionalized indole. The yield was further improved to 82% when a mixed solvent of water/EtOH was used (v/v = 2 : 1). Prolonging the reaction time to 5 h led to the isolation of **3aa** in 89% yield (entry 3), and the reaction could be performed under air without loss of the isolated yield of the product. Screening also indicated that using EtOH as the sole solvent only afforded inferior results (entry 4). The catalytic amount of CsOAc proved necessary, and omission of HOAc also gave rise to reduced yield (entry 6). Control experiments also confirmed that the metal catalyst is necessary (entry 7). While a slightly lower yield was obtained using the rhodium congener as a catalyst (entry 8), we stuck to iridium catalysis due to the relatively low cost of iridium and the rarity of iridium(III)-catalyzed C–H activation of arenes.¹⁵

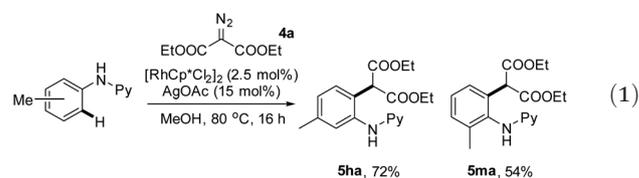
Having established the optimal conditions, we next explored the scope of generality of this coupling system (Scheme 2). *N*-Phenyl-2-aminopyridines bearing electron-donating, -withdrawing, and halogen groups at the *para* position in the benzene ring all coupled smoothly with ethyl α -diazoacetylacetate in consistently high efficiency, and the indole products were isolated in 67–87% yield (**3ba–3ga**). Introduction of different *meta* substituents is also well-tolerated, and in all cases C–H functionalization occurred at the less hindered *ortho* site in high regioselectivity (**3ha–3la** and **3qa**). The reaction also tolerated substrates bearing *ortho* substituents (**3ma–3pa**), indicative of the tolerance of the steric effect caused by these *ortho* substituents. The diazo ester is not limited to ethyl α -diazoacetylacetate, and several other



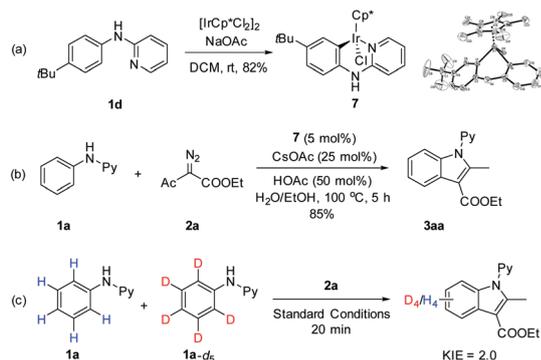
Scheme 2 Substrate scope of Ir-catalyzed annulative synthesis of indoles. Reaction conditions: **1** (0.3 mmol), diazoester (0.45 mmol), [IrCp*Cl₂]₂ (2.5 mol%), CsOAc (25 mol%), HOAc (50 mol%), H₂O (2 mL), EtOH (1 mL), 100 °C, 5 h, under air. Isolated yield after column chromatography.

esters bearing different substituents also reacted in comparable or even higher efficiency (**3mb**, **3bc**, and **3bd**). In addition to the 2-pyridyl directing group, the directing group has also been successfully extended to a 2-pyrimidyl and the reaction proceeded with equally high efficiency regardless of the substitution pattern of the phenyl ring (**3ra–3va**). All these results indicated that the catalytic system has the advantage of high efficiency, high selectivity, and good functional group tolerance.

To further define the scope of α -diazo esters, diethyl α -diazomalonate (**4a**) has been applied as a coupling partner. However, essentially no desired coupling occurred under the iridium-catalyzed conditions. We next resorted to rhodium(III)-catalysis. By following the conditions that we previously reported,^{11c} the coupling of *N*-phenyl-2-aminopyridines with diethyl α -diazomalonate afforded the *ortho* alkylation product in good yield without any cyclization (eqn (1)).

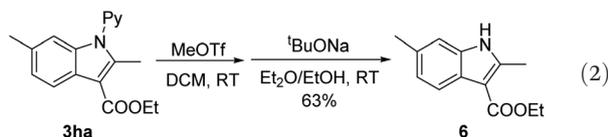


To demonstrate the removability of the directing group, derivatization of a coupled product (**3ha**) has been performed. Treatment of **3ha** with MeOTf led to *N*-methylation. Subsequent base-treatment in the presence of EtOH afforded the corresponding unprotected NH indole **6** in 63% overall yield



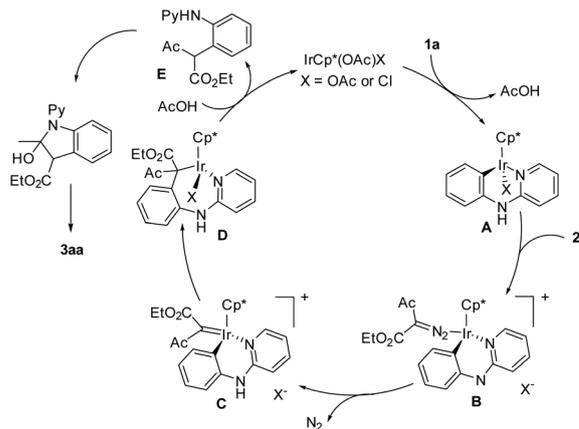
Scheme 3 Mechanistic studies.

(eqn (2)). This result indicates the synthetic utility of our coupling method, and synthesis of **6** using other methods is not trivial.¹⁶



Mechanistic studies have been performed on the coupling of *N*-phenyl-2-aminopyridines with α -diazooacetylacetate (Scheme 3). To explore the relevancy of C–H activation and the interactions between the arene substrate and the iridium catalyst, a stoichiometric reaction has been performed between **1d** and $[\text{IrCp}^*\text{Cl}_2]_2$ in the presence of a base.¹⁷ An iridacycle **7** was isolated in 82% yield and was fully characterized by X-ray crystallography. When **7** was used as a catalyst for the coupling of **1a** and **2a** under otherwise the same conditions, the product **3aa** was isolated in 85% yield, a yield closely comparable to that obtained under the original conditions using $[\text{IrCp}^*\text{Cl}_2]_2$. These results pointed to a conclusion that the reaction occurred *via* a C–H activation pathway and **7** is a likely intermediate or a direct precursor. To further understand the C–H activation process, the kinetic isotope effect (KIE) has been measured. The KIE result obtained *via* intermolecular competition using an equimolar mixture of **1a** and **1a-d₅** under low conversion gave $k_{\text{H}}/k_{\text{D}} = 2.0$. This suggests that C–H activation is probably involved in the turnover-limiting step.

On the basis of these preliminary results and literature precedents, a plausible mechanism is proposed (Scheme 4). Starting from a $\text{IrCp}^*(\text{OAc})\text{X}$ ($\text{X} = \text{OAc}$ or Cl) catalyst, coordination of the pyridyl nitrogen and subsequent cyclometalation afforded iridacycle **A**. The incoming diazoester **2a** undergoes coordination to afford **B**. Notably, the coordination of **2a** requires dissociation of the X ligand because of the coordination saturation of **A**. This accounts for the role of a highly polar solvent (water and EtOH), which assists the dissociation of the X ligand and stabilizes the separated charges. In addition, the coordination and C–H activation of **1a** may also require the dissociation of the X ligand if a concerted metalation–deprotonation mechanism is followed. Intermediate **B** is proposed to undergo denitrogenation to afford



Scheme 4 Proposed mechanism.

a carbene intermediate **C**. Migratory insertion of the Rh–C bond into the carbene gives an iridium alkyl species **D**, and protonolysis of the Ir–C bond generates an alkylated intermediate **E** and returns the active catalyst. Intermediate **E** is proposed to undergo nucleophilic cyclization followed by dehydration to eventually furnish the indole product **3aa**. In contrast to the high reactivity of diazoacetylacetates, the reaction stopped at the alkylation stage when a diazomalonnate was used.

Conclusions

In summary, we have achieved highly efficient couplings between *N*-phenyl-2-aminopyridines and activated diazoesters. The reactions proceeded *via* a C–H activation pathway, and iridium and rhodium catalysts offered complementary activity. The coupling with α -diazo β -ketoesters proceeded under iridium catalysis to give indole products as a result of C–H activation, subsequent alkylation, and eventual nucleophilic cyclization. In contrast, the coupling with α -diazomalonnates only afforded the alkylation product and high efficiency was realized only with a rhodium(III) catalyst. The pyridyl directing group can be readily removed. This operationally simple method offers direct access to functionalized indoles starting from simple and readily available arenes and may find applications in the synthesis of complex structures.

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