DOI: 10.1002/adsc.201600452
Advanced Synthesis & Catalysis

Rhodium-Catalyzed Regioselective Synthesis of Isoindolium Salts from 2-Arylpyridines and Alkenes in Aqueous Medium under Oxygen

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Received: April 28, 2016; Revised: August 31, 2016; Published online: ■■ ■■, 0000

Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600452.

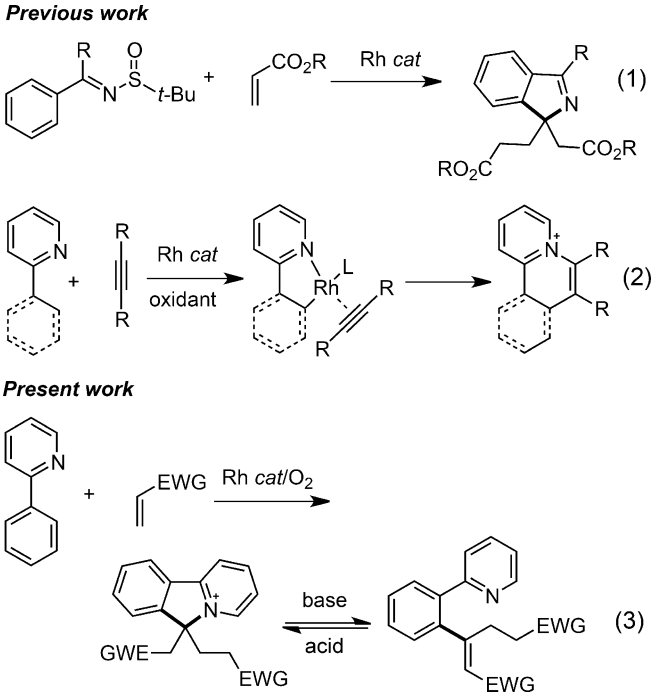
Abstract: A highly regioselective synthesis of pyrido[2,1-*a*]isoindolium salts from 2-arylpyridines and two equivalents of electron-deficient alkenes catalyzed by rhodium is demonstrated. The reaction was carried out in aqueous medium at 110 °C using inexpensive oxygen as oxidant. Reverse aza-Michael addition of the isoindolium salt occurs when the salt was treated with base to give a β-disubstituted alkene product. A reaction mechanism involving an *ortho* C–H olefination of 2-arylpyridine by alkene, intramolecular aza-Michael addition, deprotonation at the β-carbon of the alkene fragment followed by another Michael addition to give the final product is proposed.

Keywords: alkenes; C–H activation; isoindolium salts; Michael addition; rhodium catalysis

Transition metal-catalyzed C–H functionalization has been extensively investigated and become a powerful tool for organic synthesis.[1] The transformations do not require pre-functionalization and can provide atom- and step-economical methods for the synthesis of highly substituted products.[2] However, in many cases, the C–H functionalization required a stoichiometric amount of expensive oxidant such as copper and silver salts and toxic organic solvents. A typical example is the directing group (DG) assisted *ortho* olefination of arenes. Several metals such as palladium,[3] rhodium,[4] ruthenium[5] cobalt and nickel are known to catalyze the reactions in the presence of a stoichiometric amount of oxidant.[6] Thus the development of *ortho* olefination and related reactions using cheap oxidants and environmentally benign green solvents is still greatly sought after. Transition metal-catalyzed C–H bond functionalization using oxygen as the oxidant is known.[3,5,9,11] Furthermore, there are a few C–H functionalization reactions known to be carried out in aqueous medium.[7] However, to the best of our knowledge, there are no reports on the C–H functionalization catalyzed by transition metal complexes using both oxygen or air as the oxidant and water as the solvent.

Two traditional approaches were reported for the synthesis of isoindolium salts, by cycloaddition and photocyclization reactions requiring *ortho*-ester arylpyridines and *N*-(2-halobenzyl)pyridinium bromide, respectively.[8] Very recently, Sanford and co-workers developed a Pd-catalyzed synthesis of cyclic pyridinium salts *via* the pyridine-directed olefination of the C(sp^3)–H bond followed by intramolecular Michael addition.[9] Very recently, Li and co-workers reported a Rh-catalyzed synthesis of 1*H*-isoindole *via* *N*-sulfinylketoimines directed C–H coupling with di-alkenes under redox neutral conditions [Scheme 1, Eq. (1)].[10] Inspired by these previous works and our experience in metal-catalyzed synthesis of various isoquinolinium and pyridinium, salts *via* C–H activation [Eq. (2)],[11] we herein report a Rh-catalyzed regioselective synthesis of pyridoisoindolium salts from arylpyridines and alkenes *via* C–H olefination/cyclization in aqueous medium under 1 atm of O_2 gas [Eq. (3)]. Isoindolium salts and the derivatives belong to a new type of azafluorenes that have attracted significant attention due to their bioactivities.[12]

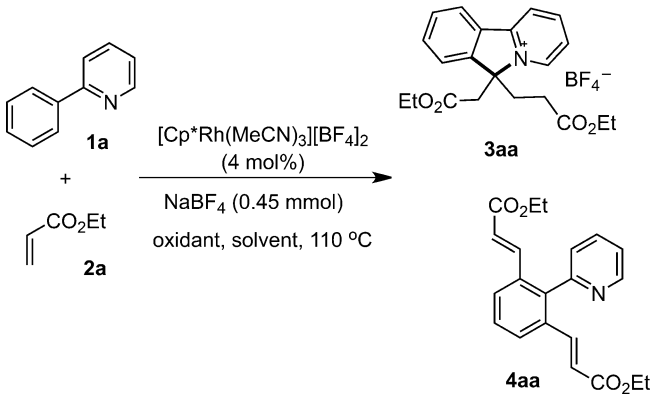
To find the optimized conditions for the reaction of 2-phenylpyridine **1a** with ethyl acrylate **2a** to give pyridoisoindolium salt **3aa**, we examined the effect of oxidant, and solvent used (see Table 1) on the yield of



Scheme 1. Ketoimine and pyridine directed *ortho*-C–H activation/cyclization by Rh catalyst.

3aa. We began with the reaction conditions consisting of **1a** (0.4 mmol), **2a** (1.00 mmol), and $NaBF_4$ (0.45 mmol) in the presence of $[Cp^*Rh(MeCN)_3][BF_4]_2$ (4 mol%) in *t*-amyl alcohol (2.5 mL) under O_2 (1 atm). The reaction solution was heated at 110 °C for 16 h to provide salt product **3aa** in 76% yield (Table 1, entry 1). The structure of **3aa**, containing an isoindolium cation and a tetrafluoroborate anion, was confirmed by its ^1H, ^{13}C, ^{19}F, and ^{11}B NMR spectra and MS data. The other solvents including *t*-butyl alcohol, toluene, DMF, and methanol were also tested to give product **3aa** but in lower 72–22% yields (entries 2–5). Unexpectedly, water was found to be the most effective solvent for the reaction affording **3aa** in 92% yield (Table 1, entry 6). In this pyridoisoindolium salt formation reaction, an oxidant is required. To find a suitable oxidant for the reaction, we investigated the oxidation activities of O_2, air, $Cu(OAc)_2$, CuO, $CuCl_2$, BQ and $K_2S_2O_8$ (entries 7–12). Again, to our surprise, O_2 gave the highest product yield, while $Cu(OAc)_2$ and CuO are also active affording **3aa** in 66 and 82% yields, respectively. In contrast, $CuCl_2$, BQ and $K_2S_2O_8$ gave only a trace or no **3aa** (entries 10–12). Notably, when the reaction was carried out without a solvent, product **3aa** was formed in 5% yield (entry 13). In the absence of $NaBF_4$, the reaction also gave salt **3aa** in 65% yield based on the ^1H NMR measurement. In this case, the counter anion is expected to be OH^- (entry 14). Under the reaction conditions, we believe that water acts both as the proton and hydroxide sources. More detailed optimization studies for the reaction of **1a** with **2a** are presented in the Supporting Information. Notably, we did not observe any *ortho* divinylated products (**4aa**) under these reaction conditions.

Table 1. Optimization studies for the reaction of 2-phenylpyridine with ethyl acrylate.[a]



Entry	Solvent	Oxidant	Yield [%][b] of **3aa**
1	*t*-amyl alcohol	O_2	76
2	*tert-butyl* alcohol	O_2	72
3	toluene	O_2	22
4	DMF	O_2	55
5	methanol	O_2	41
6	**H_2O**	**O_2**	**92**
7	H_2O	air	60
8	H_2O	$Cu(OAc)_2$	66
9	H_2O	CuO	82
10	H_2O	$CuCl_2$	trace
11	H_2O	BQ	0
12	H_2O	$K_2S_2O_8$	0
13	–	O_2	5
14	H_2O	O_2	65[c]

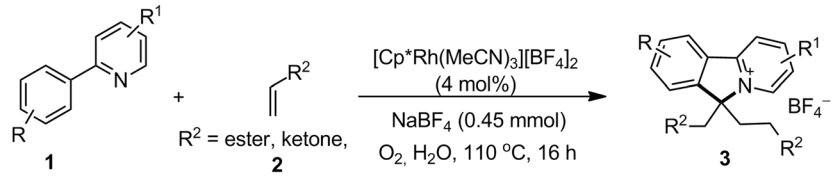
[a] Unless otherwise mentioned, all reactions were carried out using 2-phenylpyridine **1a** (0.4 mmol), ethyl acrylate **2a** (1.0 mmol), $[Cp^*Rh(MeCN)_3][BF_4]_2$ (4.0 mol%), $NaBF_4$ (0.45 mmol), oxidant·(0.8 mmol) or O_2 (1 atm, *ca* 1.5 L) and solvent (2.5 mL) at 110 °C for 16 h.

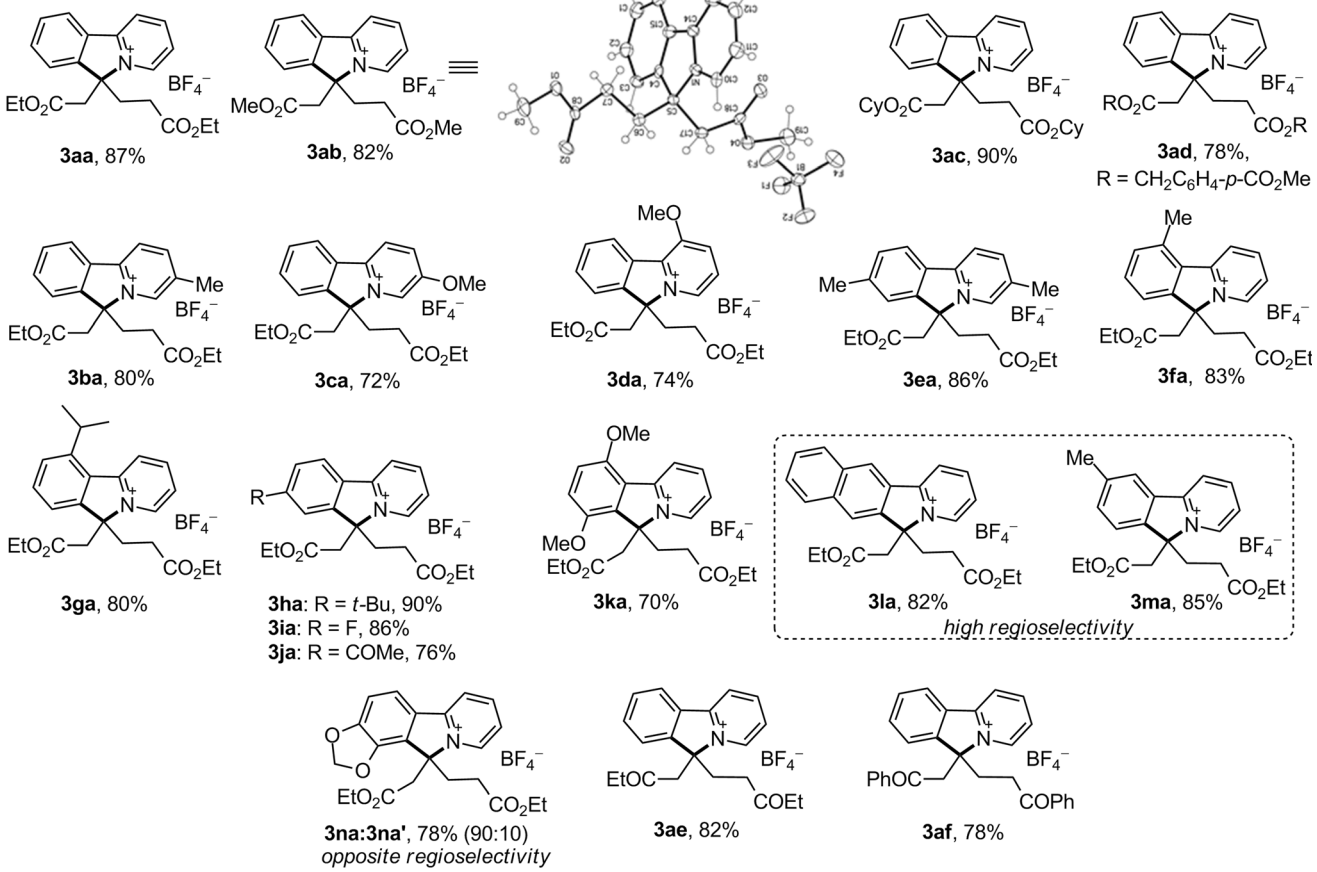
[b] Yields were measured by ^1H NMR, using mesitylene as an internal standard.

[c] In the absence of $NaBF_4$.

To evaluate the scope of the present reaction, we examined the reactions of various acrylates (**2a–2d**) with **1a** under the optimized reaction conditions (entry 6, Table 1). Thus, **1a** reacted with methyl acrylate **2b**, cyclohexyl acrylate **2c** and benzyl acrylate **2d** to afford the corresponding isoindolium salts **3ab–3ad** in 85, 82 and 90% yields, respectively (Table 2). The structure of **3ab** was further confirmed by the results of a single-crystal X-ray diffraction study.[13] Next, we tested the effect of substituents of the arylpyridines on the reaction with **2a**. Substrates **1** bearing as substituents 5-methyl (**1b**), 5-methoxy (**1c**) and 3-methoxy (**1d**) on the pyridine ring reacted with **2a** effectively under the standard conditions to provide salts

Table 2. Results of Rh-catalyzed reaction of arylpyridines and alkenes.[a,b]





[a] Unless otherwise mentioned, all reactions were carried out using arylpyridines **1** (0.4 mmol), alkenes **2** (1.0 mmol), $[RhCp^*(CH_3CN)_3](BF_4)_2$ (4.0 mol%), $NaBF_4$ (0.45 mmol), O_2 (1 atm, *ca* 1.5 L) and water (2.5 mL) at 110 °C for 16 h.
[b] Isolated yields.

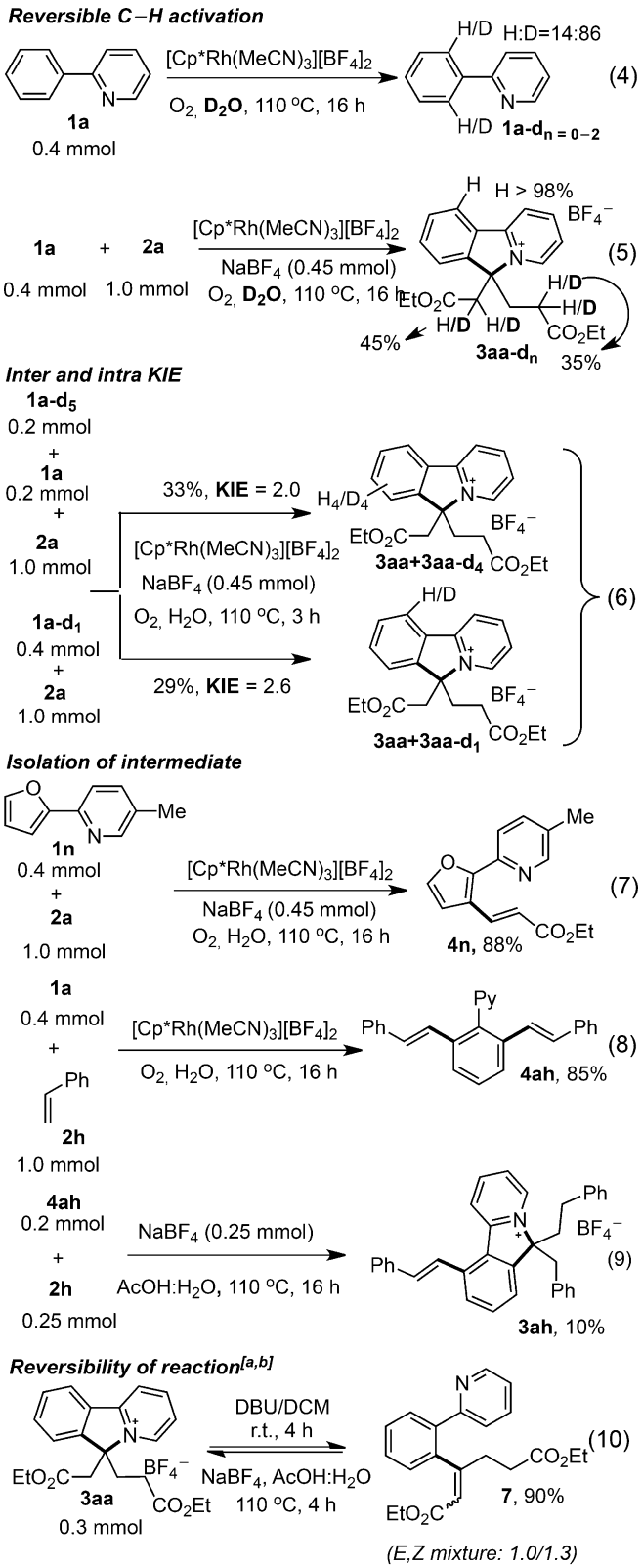
(**3ba–3da**) in 74–80% yields. (3-Methylphenyl)-5-methylpyridine **1e** also reacted smoothly with **2a** to give product **3ea** in 86% yield. Similarly, substrates **1** with various substituents on the phenyl ring (**1f–j**) also reacted smoothly with **2a** to afford the corresponding products (**3fa–3ja**) in 76–90% yields. The results show that products **3** were formed in good to excellent yields with either electron-rich or electron-poor substituents on the phenyl ring of **1**. The reaction of 2-(2,5-dimethoxyphenyl)pyridine **1k** with **2a** also proceeded nicely affording the expected product **3ka** in 70% yield. To understand the regioselectivity of this reaction, *m,p*-disubstituted and *m*-substituted phenylpyridines were investigated. Thus, 2-napthyl-2-pyridine **1l** and 2-(*m*-tolyl)pyridine **1m** reacted with **2a** efficiently to afford **3la** and **3ma** in 82 and 85% yields, respectively. The C–H bond activation and annulation reaction occurred only at the 3-position of the naphthyl and *m*-tolyl groups. In contrast, the reaction of 2-(benzo[*d*][1,3]dioxol-5-yl)pyridine (**1n**) with **2a** proceeded at the C-2 position to afford the regioisomers **3na** and **3na′** in a 90:10 ratio in 78% combined yield.[4m,11f] The regioselectivity of this product is opposite to that of most of the *m*-substituted phenylpyridines. In addition to acrylate, ethyl vinyl ketone (**2e**), and phenyl vinyl ketone (**2f**) also underwent reaction with **1a** to afford the corresponding isoindolium salts **3ae** and **3af** in 78–82% yields.

To understand the present catalytic reaction mechanism, several experiments were performed as shown

in Scheme 2. To see whether *ortho* H/D exchange of **1a** occurs, we heated the substrate in D_2O at 110 °C in the absence of **2a** [Scheme 2, Eq. (4)]. The ^1H NMR spectrum of **1a** after reaction revealed 86% deuteration at both *ortho* positions of the phenyl ring of **1a**, indicative of reversible C–H activation in the absence of acrylate. In contrast, when the reaction of **1a** with **2a** was performed in D_2O, no deuterium was incorporated into the benzene ring [Eq. (5)]. The results suggest that alkene insertion is much faster than the reverse step of C–H activation. Additionally, H/D exchange was observed at both α-methylene positions of product **3aa** [Eq. (5)]. We carried out a competition experiment between equimolar amounts of deuterio-**1a**-$\mathbf{d_5}$ and **1a** with **2a** for 3 h. The experiment gave an intermolecular kinetic isotope effect (k_H/k_D) of 2.0 measured by ^1H NMR integration [Eq. (6)]. Similarly, the intramolecular H/D competition gave an intramolecular kinetic isotope effect (k_H/k_D) of 2.6 [Eq. (6)]. This result suggests that the C–H bond cleavage is likely involved in the rate-limiting step.[14] The catalytic reaction of **1a** with **2a** in the absence of $NaBF_4$ still proceeded to give salt **3aa** in 60% yield (see Table 1, entry 14).

In contrast, the reaction of 2-(furan-2-yl)-5-methylpyridine with **2a** provided only the alkenylated product **4n**, the expected salt **3na** was not formed probably owing to the ring strain of this compound which would contain two fused 5-membered rings [Eq. (7)]. We then focused on the reaction of electron richer olefins like styrene **2h** with **1a** under similar reaction conditions; the reaction gave divinylated product **4ah** in 85% isolated yield [Eq. (8)].[4b] Further treatment of **4ah** with **2h** under acidic conditions to afford the corresponding salt **3ah** albeit in only 10% yield [Eq. (9)]. This observation indicates that *ortho*-olefinated 2-phenylpyridine is an intermediate for the final salts. Then, we studied the reversibility of the present isoindolium salts under basic and acid conditions. Treatment of **3aa** with DBU in CH_2Cl_2 led to the C–N cleavage to afford a mixture of β-substituted alkene **7** in 90% yield [Eq. (10)].[9] However, under acidic conditions, **7** cyclized and reversed back to **3aa** (see the Supporting Information). In addition, a competitive reaction was performed using an equimolar amount of ethyl acrylate **2a**, methyl acrylate **2b**, and 2-phenyl pyridine **1a** under the standard reaction conditions (see the Supporting Information). The reaction gave a mixture of isoindolium salt products as expected from the mechanism proposed in Scheme 3.

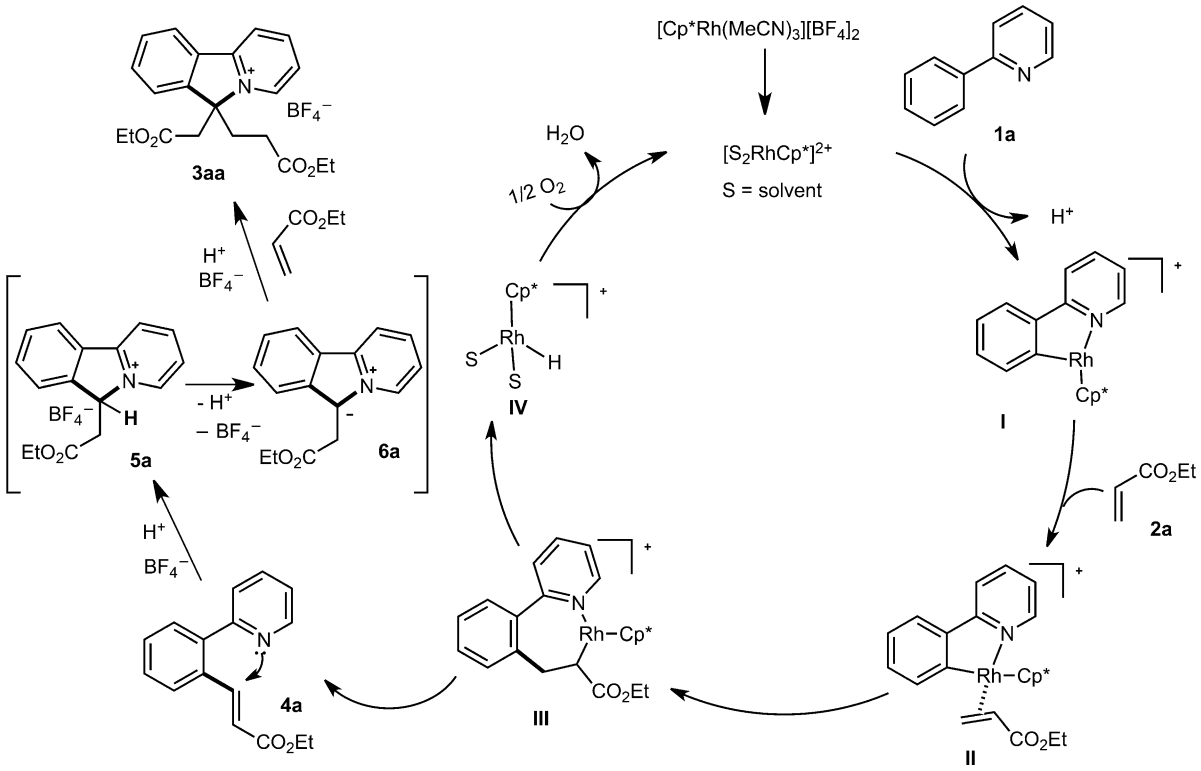
Based on the earlier transition metal-catalyzed directing group-assisted C–H bond olefination/annulation reactions,[1–7,9–11] a reasonable mechanism for the present reaction is proposed and illustrated in (Scheme 3). The catalytic cycle is likely initiated by the coordination of pyridine to rhodium species followed by an *ortho* C–H olefination to form a five-



[a] **3aa** (0.3 mmol), DBU (0.6 mmol) in CH_2Cl_2 (2.5 mL) at room temperature for 2 h.

[b] Compound **7** (0.27 mmol), $NaBF_4$ (0.4 mmol) in AcOH:water (2.5:0.5 mL) at 110 °C for 4 h.

Scheme 2. Mechanistic studies.



Scheme 3. A proposed catalytic cycle.

membered rhodacycle **I** and the release of H^+. Coordinative insertion of alkene **2a** to the Rh–C bond of intermediate **II** gives the seven-membered rhodacycle **III** which undergoes β-hydride elimination to afford the *ortho*-alkenylated intermediate **4a** and a Rh–H species **IV**, which is readily oxidized by molecular oxygen to regenerate the active Rh(III) species for the next cycle. Intermediate **4a** undergoes reversible intramolecular Michael addition to the olefin group providing an azafluorene salt **5a** in which the hydrogen attached to the center carbon C-9 is acidic and can be easily deprotonated to form a nitrogen ylide (**6a**).[8d] Then, Michael addition to ethyl acrylate occurs to afford the final product **3aa**. It is noteworthy that the steps from **4a** to the final product in Scheme 3 seem not to require further Rh-assisted C–H activation (see the observation shown in Eq. (9), Scheme 2 and a very recent related report.[15] However, we cannot completely rule out that the second olefination may also be catalyzed by the rhodium complex similar to the mechanism proposed by Li and his co-workers,[10] because we were unable to isolate any mono-olefinated 2-arylpyridine, such as **4a**, to test the current catalytic mechanism.

In summary, we have successfully developed a new, mild but efficient Rh(III)/O_2/H_2O system for the one-pot synthesis of isoindolium salts from substituted 2-phenylpyridines and electron-withdrawing alkenes in aqueous medium. The two alkene moieties in the isoindolium cation are unusually connected to each other *via* a tail to tail manner. The facile formation of nitrogen ylide (**6a**) during the catalytic reaction likely accounts for the formation the carbon-carbon bond in the present isoindolium salt. A mechanistic study strongly shows that the isoindolium salts are in equilibrium with β-substituted alkene **7** under acid or base conditions. The present method is suitable for the synthesis of a library of functionalized azafluorenes.

Experimental Section

General Procedure for the Synthesis of Isoindolium Salts 3

A sealed tube (20 mL) containing 2-phenylpyrine **1** (0.40 mmol), acrylate **2** (1.00 mmol), [Cp*Rh(MeCN)$_3$][BF$_4$]$_2$ (4.0 mol%), and $NaBF_4$ (0.45 mmol) was evacuated and filled with oxygen (O_2, 1 atm, *ca* 1.5 L).[16] Then H_2O (2.5 mL) was added to the system *via* syringe and the reaction mixture was allowed to stir at 110 °C for 16 h. Then, the mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL), filtered through an $MgSO_4$/Celite pad and the pad was further washed with dichloromethane. The combined filtrate was concentrated under vacuum and the residue was purified on a silica gel column using DCM/MeOH (95:5) as eluent to afford the desired pure product **3**.

Acknowledgements

We thank the Ministry of Science and Technology of the Republic of China (MOST 104-2633-M-007-001) for support of this research.

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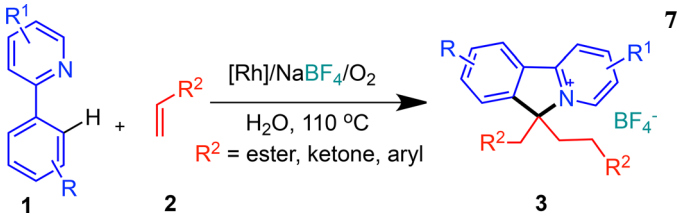
[15] While preparing the manuscript, a related work was reported by Jun et al.: Y. Yi, H. Lee, C.-H. Jun, *Chem. Commun.* **2016**, *52*, 10171–10174.

[16] We conducted the reaction of **1a** and **2a** using a round-bottom flask (25 mL) instead of a sealed tube at lower temperature (100 °C) and at ambient pressure under standard reaction conditions, isoindolium salt **3aa** was obtained in 88% yield with a reaction time of 24 h.



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