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Ir(III)-Catalyzed Oxidative Coupling of NH Isoquinolones with Benzoquinone

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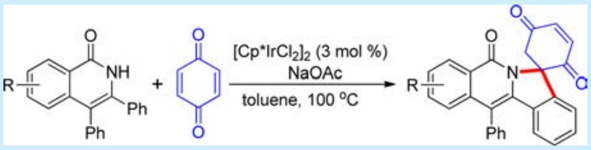
Supporting Information

ABSTRACT: The oxidative coupling reactions of NH isoquinolones with 1,4-benzoquinone proceeded efficiently to form spiro compounds in the presence of an Ir(III) catalyst through C−H activation. The reactions have a broad range of substrates, with nearly quantitative yields, without the use of external oxidants. For 1,4-naphthoquinone and other substituted 1,4-benzoquinone substrates the reactions also gave high yields with $Cu(OAc)_2{\cdot}H_2O$ as an external oxidant. A catalytically competent five-membered iridacycle has been isolated and structurally characterized, thus revealing a key intermediate in the catalytic cycle.



In the past decade, transition-metal-catalyzed C−H bond functionalization has achieved significant advances.[1] Among them the Ir-catalyzed C−H bond activation and related reactions have attracted increasing attention.[2−5] Many groups, such as Satoh and Miura, Ison, Chang, Shibata, Yang and Zhou, Li, Zhu et al., continuously disclose Cp*Ir(III)-catalyzed direct C−H transformations.[3−5] However, in comparison with the extensive applications of Cp*Rh(III)[6] and Ir(I)[2] catalysts, the Cp*Ir(III)-catalyzed C−H bond activation reactions are still limited. Since Cp*Ir(III) complexes have been among the most effective in stoichiometric C−H activation reactions,[7] they should still have tremendous potential in catalytic C−H activation reactions.

The 1-azaspiro[4.5]decane1-azasipro[4.5]decane motif can be found in some natural products (Figure 1).[8] The quinone moiety possesses electron and proton transfer properties that are essential to nearly every living organism.[9] However, several common methods for C−C bond formation on *α*,*β*-unsaturated carbonyl compounds (such as the addition of organometallics and Heck coupling) failed on quinones due to their unique electronic properties.[10] There is little literature about C−H bond functionalization reactions using benzoquinone as a substrate.[3b,4g,10b,11] Ison[3b] and Xu[11a] reported the Cp*Ir(III)- and Cp*Rh(III)-catalyzed reactions of benzoic acid or *N*-methoxybenzamide with benzoquinone (or hydroquinone) to give 2-hydroxy-6*H*-benzo[*c*]chromen-6-ones (Scheme 1, eqs 1−2).

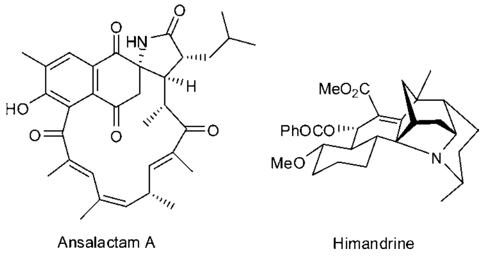
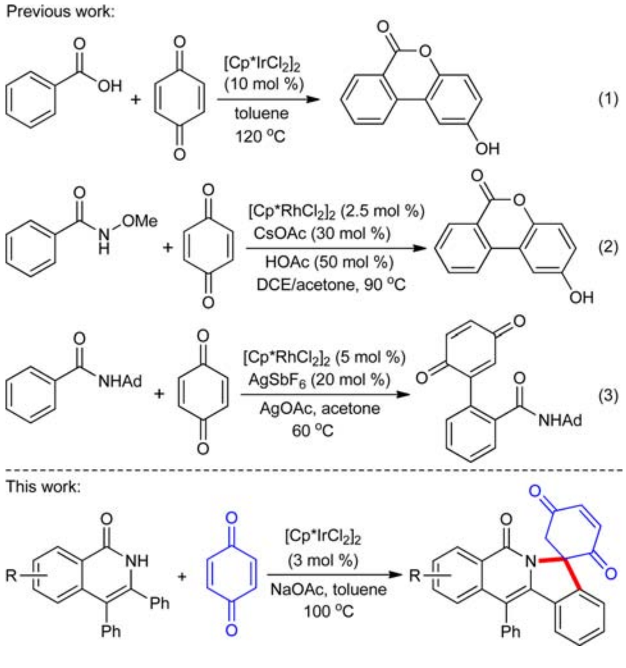


Figure 1. Some natural products contain a 1-azaspiro[4.5]decane1-azasipro[4.5]decane motif.

Scheme 1. Cp*Rh(III)- and Cp*Ir(III)-Catalyzed C−H/C−C Coupling and Annulations with Benzoquinone



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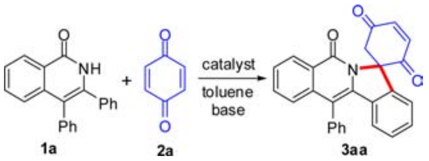
Li[11b] and Hong[11c] also reported the Cp*Rh(III)-catalyzed reactions of *N*-adamantyl benzamide with benzoquinone to give the C−C coupling product (Scheme 1, eq 3). Herein we report the Cp*Ir(III)-catalyzed oxidative coupling of NH isoquinolones with benzoquinone involving C−C and C−N bond formation giving spiro compounds. As known to all, benzoquinone is usually a compatible oxidant with $Pd(OAc)_2$.[12] In this work, benzoquinone works as both an electron-withdrawing alkene and a compatible external oxidant.

By treating isoquinolone (**1a**) with benzoquinone (**2a**) (2 equiv) in the presence of $[Cp^*IrCl_2]_2$ (5 mol %), NaOAc (2 equiv), and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv) in toluene (1 mL) at 100 °C for 12 h, the desired product 2′-phenyl-5′-*H*-spiro[cyclohex[3]ene-1,7′-isoindolo[2,1-*b*]isoquinoline]-2,5,5′-trione (**3aa**) was obtained in 88% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]

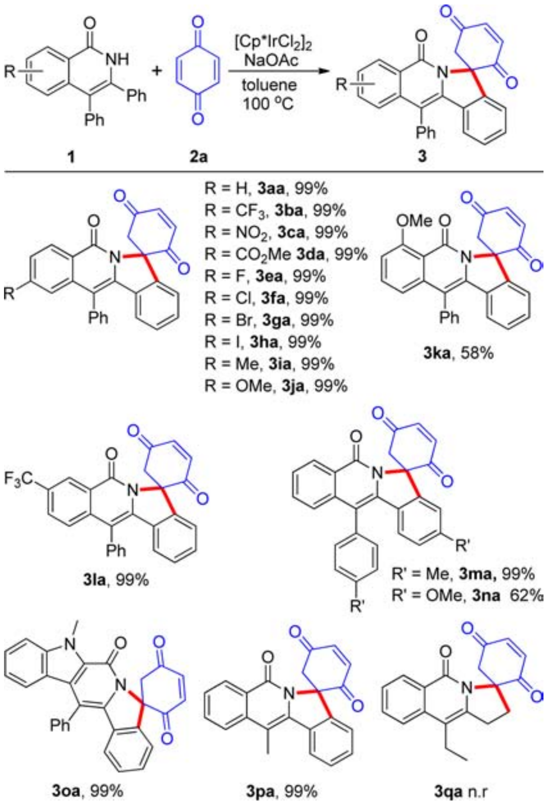


entry	cat. (mol %)	base (equiv)	temp (°C)	yield (%)[b]
1[c]	$[Cp^*IrCl_2]_2$ (5)	NaOAc (2)	100	88
2	$[Cp^*IrCl_2]_2$ (5)	NaOAc (2)	100	99
3	$[Cp^*IrCl_2]_2$ (5)	none	100	n.r.
4	none	NaOAc (2)	100	n.r.
5[d]	$[Cp^*IrCl_2]_2$ (5)	NaOAc (2)	100	23
6	$[Cp^*IrCl_2]_2$ (3)	NaOAc (2)	100	99
7	**$[Cp^*IrCl_2]_2$ (3)**	**NaOAc (0.5)**	**100**	**99**
8	$[Cp^*IrCl_2]_2$ (3)	NaOAc (0.5)	80	38
9	$[Cp^*RhCl_2]_2$ (3)	NaOAc (0.5)	100	41
10	$[(p\text{-cymene})RuCl_2]_2$ (3)	NaOAc (0.5)	100	26

[a] Conditions: **1a** (0.2 mmol), **2a** (0.44 mmol, 2.2 equiv), catalyst, base, and toluene (1 mL) at the indicated temperature for 12 h, under Ar. [b] Isolated yield. [c] **2a** (0.4 mmol, 2 equiv); $Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol) was added. [d] **2a** (0.2 mmol, 1 equiv).

The yield of **3aa** increased to 99% while 2.2 equiv of benzoquinone were used instead of $Cu(OAc)_2{\cdot}H_2O$ (entry 2). The yield was significantly decreased when using 1 equiv of benzoquinone (entry 5), which indicated that benzoquinone may also act as an oxidant in this reaction. No product was observed in the absence of $[Cp^*IrCl_2]_2$ or NaOAc (entries 3−4). To our delight, decreasing the loading of $[Cp^*IrCl_2]_2$ to 3.0 mol % and the loading of NaOAc to 50 mol % had no obvious influence on the reaction (entries 6−7). Decreasing the temperature led to a much lower yield (entry 8). It should be noted that other transition metal catalysts such as $[Cp^*RhCl_2]_2$ and $[(p\text{-cymene})RuCl_2]_2$ gave low yields under the present reaction conditions (entries 9−10). Finally, we chose the reaction conditions of entry 7 as the standard conditions (condition A).

Scheme 2. Substrate Scope of Isoquinolones[a]

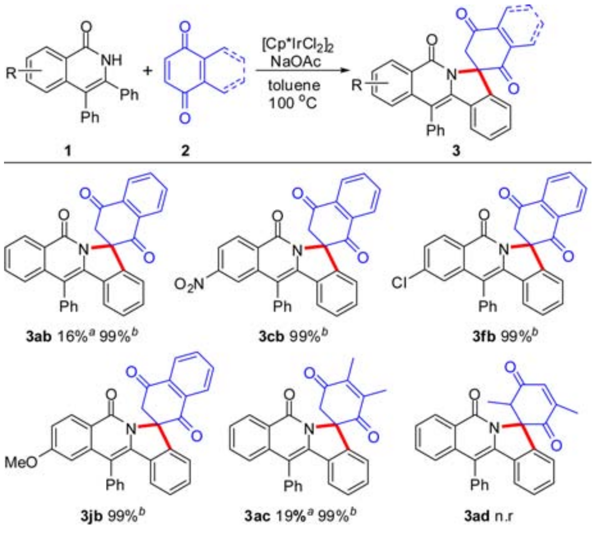


[a] Condition A: **1** (0.2 mmol), **2a** (0.44 mmol), $[Cp^*IrCI_2]_2$ (3 mol %), NaOAc (50 mol %), toluene (1.0 mL), 100 °C, 12 h, under Ar. Isolated yields are shown.

With the optimal reaction conditions in hand, various substituted isoquinolones (**1a−q**) were treated with benzoquinone (**2a**) (Scheme 2). Most reactions proceeded smoothly to afford the corresponding products in nearly quantitative yields, especially for the 6-substituted isoquinolones. Various functional groups commonly encountered in organic synthesis such as CF_3, NO_2, CO_2Me, halide, and methoxy groups (**3ba−ja**) were tolerated very well, ignoring electron-withdrawing or -donating groups. The molecular structure of **3ca** was confirmed by its ^1H and ^{13}C NMR spectra, high-resolution mass spectrometry, and single-crystal X-ray diffraction analysis (see Supporting Information). The *m*-CF_3 substrate (**1l**) still worked very well (99%) while the *o*-OMe substrate (**1k**) gave a moderate yield (58%). Using the isoquinolones synthesized from other symmetrically substituted alkynes as substrates also gave the desired products in good yields (**3ma** and **3na**). Moreover, isoquinolone **1o** derived from *N*-methoxy-1- methyl-1*H*-indole-3-carboxamide and diphenylacetylene and **1p** derived from an unsymmetrical substituted alkyne reacted smoothly with benzoquinone to give **3oa** and **3pa** in excellent yield (99%). No product was detected when the isoquinolone (**1q**) derived from 3-hexyne was used.[13]

In addition to **2a**, different benzoquinones were also examined for the present reaction (Scheme 3). The reaction of 1,4-naphthoquinone (**2b**) with **1a** afforded the desired product in a low yield (16%) with most of the unreacted **2b** being recovered. However, the yield reached 99% when the reaction was undertaken at 120 °C with addition of 2 equiv of $Cu(OAc)_2{\cdot}H_2O$ as the oxidant (condition B). This is probably due to the poor oxidation ability of 1,4-naphthoquinone. 6-Nitro, 6-chloro, and 6-methoxy group substituted isoquinolones also gave excellent yields (99%) under this set of conditions. 2,3-Dimethylbenzoquinone (**2c**) gave a low yield (19%) with condition A but an excellent yield (99%) with condition B. Unfortunately, no product was detected when 2,5-dimethyl benzoquinone was used, probably due to the steric effect of the substrate. Single substituted benzoquinone such as 2-methylbenzoquinone and 2-methoxybenzoquinone

Scheme 3. Substrate Scope of Benzoquinone[a]

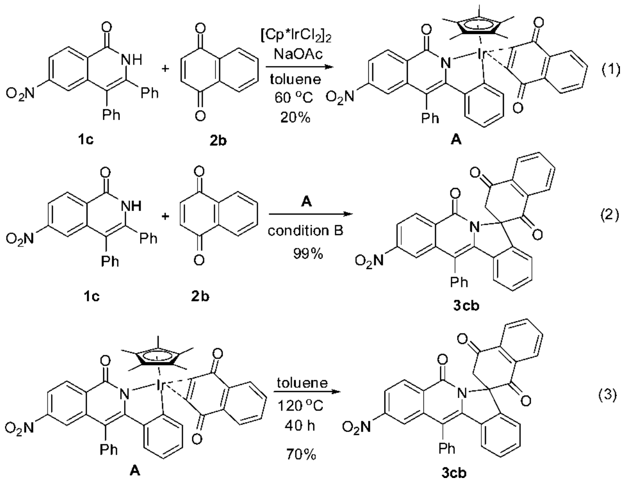


[a]Condition A: **1** (0.2 mmol), **2** (0.44 mmol), $[Cp^*IrCl_2]_2$ (3 mol %), NaOAc (50 mol %), toluene (1.0 mL), 100 °C, 12 h, under Ar. [b]Condition B: **1** (0.2 mmol), **2** (0.24 mmol), $[Cp^*IrCl_2]_2$ (3 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), toluene (1.0 mL), 120 °C, 12 h, under Ar.

were also tested, but all of them gave mixtures of two isomers caused by poor regioselectivity which would not allow separation.

To gain more insight into the mechanism of the present reaction, preliminary mechanistic experiments were carried out. An iridacycle intermediate **A** was isolated by the reaction of 6-nitrobenzoquinone with $[Cp^*IrCl_2]_2$ and 1,4-naphthoquinone (Scheme 4, eq 1). Its structure was fully characterized by ^1H and ^{13}C NMR spectra, high-resolution mass spectrometry, and single-crystal X-ray diffraction analysis (Figure 2). When intermediate **A** was used as the catalyst instead of $[Cp^*IrCl_2]_2$ with condition B, the desired product was obtained in 99% yield (Scheme 4, eq 2). When intermediate **A** was heated in toluene, the final product was obtained in 70% yield (Scheme 4, eq 3). These results supported the idea that the reaction may engage a cyclometalation step and intermediate **A** probably was an active species in this reaction.

Scheme 4. Synthesis and Reactions of Intermediate A



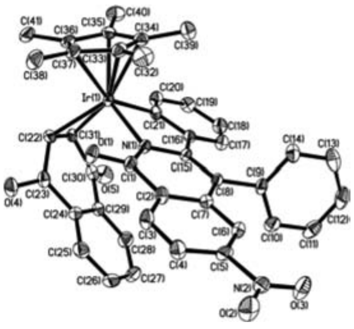
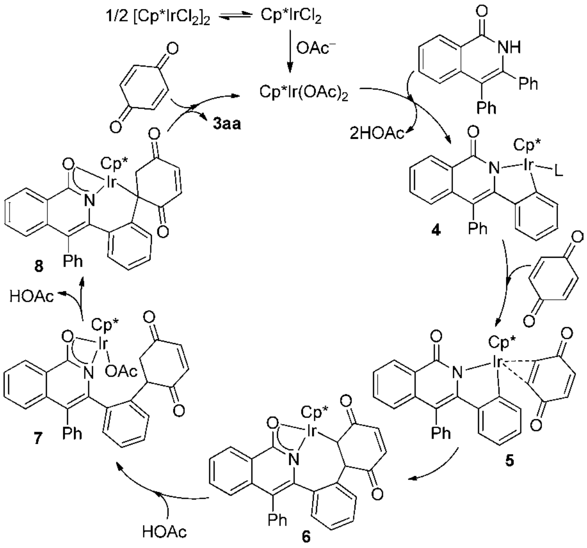


Figure 2. Molecular structure of intermediate **A**.

Based on the above experimental results, the known transition-metal-catalyzed C–H bond functionalization reactions, and our group's research before,[14] a possible mechanism is proposed for the present catalytic reaction (Scheme 5). The first step is likely to be a C(sp^2)–H activation process affording a five-membered iridacycle intermediate **4**. The coordination of benzoquinone to **4** delivers intermediate **5**. The migration insertion of the coordinated benzoquinone into the Ir–C bond leads to intermediate **6**. After protonation with HOAc intermediate **7** is formed.[11a] Subsequent iridation occurs at the α-position to afford iridacycle **8**, which undergoes a C–N reductive elimination to afford the final product and Cp*Ir(I). Cp*Ir(I) is oxidized by benzoquinone in the presence of HOAc to $Cp^*Ir(OAc)_2$ for the next catalytic cycle.

Scheme 5. Plausible Catalytic Cycle



In summary, we have developed an Ir(III)-catalyzed oxidative coupling reaction of NH isoquinolones with benzoquinone to form spiro compounds through C–H activation. The reactions proceeded with a broad range of substrates and nearly quantitative yields, without external oxidants. For 1,4-naphthoquinone and other substituted benzoquinone substrates, the reactions also gave high yields with $Cu(OAc)_2{\cdot}H_2O$ as the oxidant. A catalytically competent five-membered iridacycle has been isolated and structurally characterized, thus revealing a key intermediate in the catalytic cycle. Further efforts to expand the scope of Ir(III)-catalyzed oxidative coupling reactions with benzoquinone and applications of this method in the synthesis of other targets are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01974.

Full experimental procedures, characterization and ^{1}H, ^{13}C, and ^{19}F NMR spectra of products (PDF)

Crystallographic data for **3ca** and intermediate **A** (CIF)

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Notes

The authors declare no competing financial interest.

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