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Iridium(III) Catalysts with an Amide-pendant Cyclopentadienyl Ligand: Double Aromatic Homologation Reactions of Benzamides via Fourfold C–H Activation.

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Dedicated to Professor Shunichi Hashimoto on the occasion of his 70th birthday.

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Abstract: The synthesis, characterization, and catalytic performance of iridium(III) catalysts that bear an amide-pendant cyclopentadienyl ligand ([$Cp^AIrI_2]_2$) is reported. These [$Cp^AIrI_2]_2$ catalysts were obtained from the complexation of a Cp^A ligand precursor with [Ir(cod)OAc]$_2$ followed by oxidation. Double aromatic homologation reactions of benzamides with alkynes via fourfold C–H activation proceeded in good to high yield by using [$Cp^AIrI_2]_2$ catalysts, demonstrating their high catalytic performance for this challenging transformation.

Group 9 metal complexes with a pentamethylcyclopentadienyl ligand (Cp^*M^{III}; M = Co, Rh, Ir) have been widely used for catalytic C–H functionalization reactions and enabled a variety of atom- and step-economical organic transformations (Figure 1a).[1] While Cp^*Rh^{III} catalysts are the most general and frequently used among the triad, Cp^*Co^{III} and Cp^*Ir^{III} often exhibit reactivity and selectivity that are different from those of Cp^*Rh^{III} and may thus be a complementary option when examining unprecedent C–H functionalization reactions.[1d,e] On the other hand, as electronic and steric effects of ancillary ligands are also important factors in metal-catalyzed transformations, several research groups have developed modified Cp ligands to achieve high and/or unique reactivity and selectivity.[2-9] Besides steric modifications that forge a steric bias around the piano-stool structure of CpM^{III} complexes,[2] including chiral Cp^x ligands for enantioselective reactions,[3] the introduction of electron-withdrawing groups on the Cp ligands to render the metal catalysts electron-deficient is the most successful approach (Figure 1b).[2,4,5,6a,b,7,8] Rovis and co-workers have developed a series of Rh^{III} catalysts that bear electronically-tuned Cp ligands and examined their catalytic properties,[2,5] revealing that $Cp^{*CF3}Rh^{III}$ catalysts exhibit higher reactivity in [4+2] annulation reactions of oxime derivatives to provide (dihydro)pyridines via olefinic C–H activation.[5a,b] Some of the authors of this manuscript (Y.S. and K.T.) have developed a bis-(ethoxycarbonyl)-substituted cyclopentadienyl rhodium (Cp^ERh^{III}) catalyst and an amide-pendant cyclopentadienyl rhodium (Cp^ARh^{III}) catalyst (Figure 1b), which exhibited high reactivity in several C–H functionalization reactions.[7,8] Both of these electron-deficient rhodium(III) catalysts are synthesized by direct complexation of $RhCl_3$ with the corresponding fulvene precursors, which in turn can be prepared by rhodium(I)-catalyzed [2+2+1] cycloaddition reactions.

Despite such progress in the development of electron-deficient Cp ligands, surprisingly little attention has been focused on their applications to other group 9 metal catalysis.[9,10] This dearth could possibly, at least in part, be attributed to the decreased stability of electron-deficient CpM^{III} complexes and the corresponding difficulties associated with their synthesis. Rovis and co-workers have synthesized several monoaryl- or diaryl-substituted cyclopentadienyl iridium catalysts and revealed that a moderately electron-deficient $Cp^{*((CF3)Ar)2}Ir^{III}$ catalyst (Figure 1c) exhibits improved or unique chemoselectivity, regioselectivity, and reactivity in olefin functionalization and non-directed C–H functionalization reactions.[9] These pioneering studies as well as the success of electron-deficient Cp ligands in rhodium(III) catalysis suggest that further development of electron-deficient CpM^{III} catalysts could lead to a significant expansion of catalytic C–H functionalization reactions.

Herein, we report the synthesis of moderately electron-deficient cyclopentadienyl iridium(III) catalysts with a pendant amide moiety ([$Cp^AIrI_2]_2$) and their high catalytic activity in aromatic homologation reactions of benzamides and four alkynes via fourfold C–H activation to provide highly substituted anthracene derivatives (Scheme 1c: This work).[11-13] A stepwise synthetic route to the [$Cp^AIrI_2]_2$ catalysts involves the complexation of [Ir(cod)OAc]$_2$ and Cp^AH precursors that can be obtained from the reduction of the corresponding fulvenes.[14] The fourfold C–H activation/functionalization reactions of benzamides proceeded in good to excellent yield only when the [$Cp^AIrI_2]_2$ catalysts were employed.

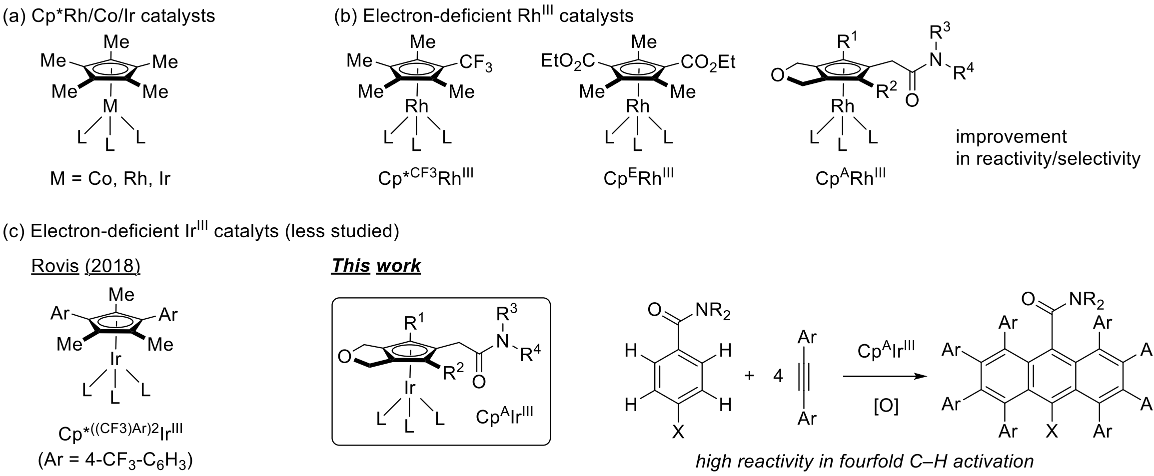
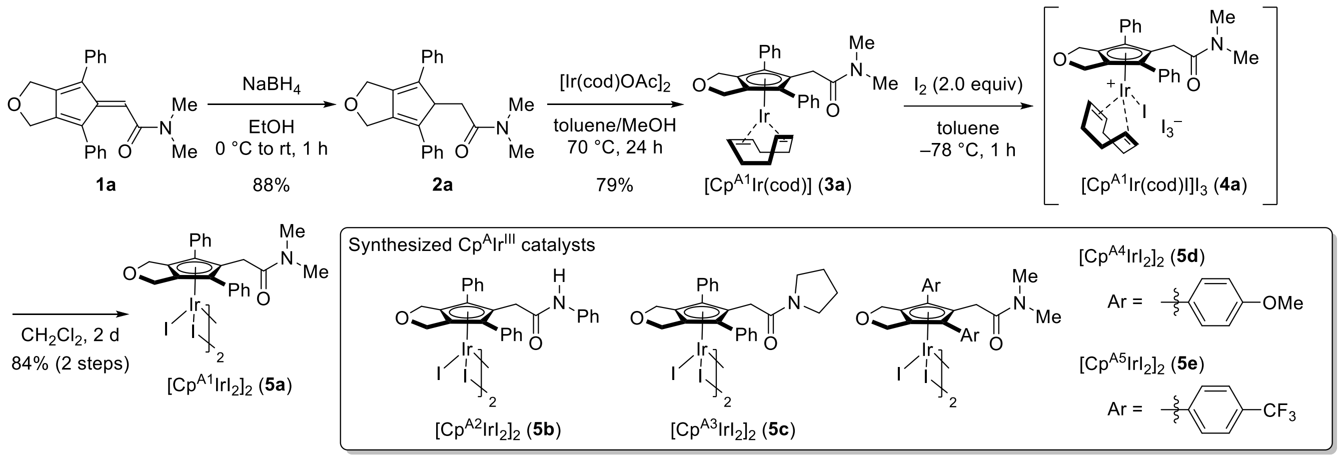


Figure 1. Cp*M^{III} (M = Co, Rh, Ir) catalysts and representative examples of their electron-deficient analogues.

We first investigated the direct complexation of $IrCl_3$ with a Cp^A ligand (Scheme S1 in the Supporting Information). The reductive complexation of fulvene **1a**, which effectively afforded $[Cp^ARhCl_2]_2$ catalysts in a previous study,[8a] failed to furnish the desired iridium(III) complex. We also attempted a standard synthetic procedure for $[CpIrCl_2]_2$ complexes using diene **2a** obtained from the reduction of **1a** using $NaBH_4$, which was again ineffective. Only the Cp^A precursor (**1a** or **2a**) was recovered along with some decomposed material in both cases.

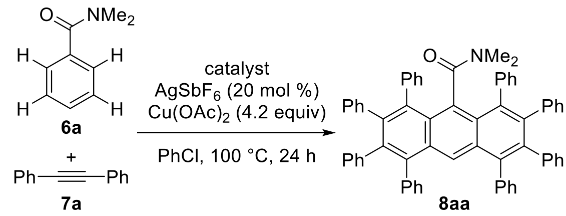
In contrast, the mild preparation protocol for Cp^xRh^I and Cp^xIr^I complexes developed by Cramer and co-workers[14] was successful, even when using electron-deficient Cp^A ligands (Scheme 1). Namely, when the reduced Cp^A precursor **2a** was treated with $[Ir(cod)OAc]_2$ in toluene and MeOH, the corresponding iridium(I) complex bearing a cod ligand (**3a**) was obtained in 79% yield. The structure of **3a** was unambiguously determined by a single-crystal X-ray diffraction analysis. Subsequently, we examined the oxidation of this intermediate to form a catalytically active iridium(III) species. While the treatment of **3a** with I_2 at ambient temperature resulted in a complex mixture containing a dissociated Cp^A ligand, lowering the reaction temperature to –78 °C and using two equivalents of I_2 led to a clean and complete conversion. The ^1H NMR spectrum of the resulting compound, however, indicated the unexpected presence of a coordinating cod ligand. Based on a report by Kudinov and co-workers,[15] we speculated that cationic intermediate **4a** was generated under these conditions. Gratifyingly, intermediate **4a** gradually converts in CH_2Cl_2 into the desired complex **5a** without a cod ligand. The X-ray diffraction analysis of a single crystal obtained from a solution of **5a** in CH_2Cl_2 confirmed its dimeric structure in the solid state (for details, see the Supporting Information). On the other hand, the ^1H NMR spectrum of **5a** in $CDCl_3$ exhibited a 5.6:1 mixture of two different species. As the addition of DMSO to the solution resulted in a single DMSO adduct, **5a** can be expected to exist as an equilibrium mixture with different coordination structures in solution. The established stepwise synthetic protocol was applied to other Cp^A precursors, providing several $[Cp^AIrI_2]_2$ catalysts (**5b**-**5e**; for details, see the Supporting Information). It should be noted that a moderately acidic NH moiety did not interfere with the catalyst synthesis (**5b**). The protocol also allowed the preparation of both more electron-rich (**5d**) and electron-deficient (**5e**) catalysts.

With several such $[Cp^AIrI_2]_2$ catalysts with different functionalities in hand, we turned our attention to their applications in catalytic C–H functionalization reactions. Aromatic homologation via sequential C–H activations has been extensively studied as a powerful strategy to rapidly access extended aromatic π-conjugated organic materials since the seminal report by Satoh, Miura, and co-workers in 2008.[12a] To evaluate the potential of the newly developed $[Cp^AIrI_2]_2$ catalysts, we selected *N*,*N*-dimethylbenzamide **6a** as the model substrate and investigated its homologation reaction with diphenylacetylene **7a**. Eventually, we found that the reaction of **6a** and four equivalents of alkyne **7a** using $[Cp^{A1}IrI_2]_2$ **5a**/$AgSbF_6$ as the catalyst and $Cu(OAc)_2$ as the terminal oxidant in PhCl afforded polyphenylated anthracene derivative **8aa** in almost quantitative yield (Table 1, entry 1). The structure of **8aa** was determined by a single-crystal X-ray diffraction analysis (for details, see the Supporting Information). It is noteworthy that one-pot double aromatic homologation reactions via fourfold C–H activation have scarcely been reported to date. Although Satoh, Sato, Miura, and co-workers, as well as Li and co-workers have reported this type of reactions using a Cp*Rh^{III} catalyst, the applicable substrates were limited to those bearing a strongly coordinating azole-type directing group.[12a,d,e] With this background in mind, we examined different $[Cp^AIrI_2]_2$ catalysts as well as other CpM^{III} catalysts under the optimized reaction conditions (Table 1, entries 2-9). While $[Cp^{A3}IrI_2]_2$ **5c** and $[Cp^{A4}IrI_2]_2$ **5d** exhibited similarly high reactivity, $[Cp^{A2}IrI_2]_2$ **5b** and $[Cp^{A5}IrI_2]_2$ **5e** afforded lower yields (entries 2-5). We speculate that the poor reactivity of **5b** might be due to its poor solubility, and the more electron-deficient nature of **5e** might lead to low stability. When a standard $[Cp^*IrCl_2]_2$ was used as the catalyst, only a naphthalene derivative **9** was observed in moderate yield (<50%), indicating the inferior activity of the $[Cp^*IrCl_2]_2$ catalyst especially in the second aromatic homologation (entry 6). On the other hand, Cp*$Co(CO)I_2$ and $[Cp^*RhCl_2]_2$ did not afford any aromatic homologation products (entries 7 and 8) and $[Cp^{A1}RhCl_2]_2$ resulted in the formation of a complex mixture (entry 9) probably due to their lower or different chemoselectivity compared to the $[Cp^AIrI_2]_2$ catalysts. All these



Scheme 1. Established synthetic route to and the structures of Cp^{A}Ir^{III} catalysts.

Table 1. Aromatic double homologation reactions of benzamide **6a** with alkyne **7a** via fourfold C–H activation: Optimized conditions and control experiments.[a]



Entry	Catalyst	% Yield[b]
1	[Cp^{A1}IrI$_2$]$_2$ **5a** (5 mol %)	>95
2	[Cp^{A2}IrI$_2$]$_2$ **5b** (5 mol %)	9
3	[Cp^{A3}IrI$_2$]$_2$ **5c** (5 mol %)	>95
4	[Cp^{A4}IrI$_2$]$_2$ **5d** (5 mol %)	>95
5	[Cp^{A5}IrI$_2$]$_2$ **5e** (5 mol %)	65
6	[Cp*IrCl$_2$]$_2$ (5 mol %)	<5
7	[Cp*RhCl$_2$]$_2$ (5 mol %)	0
8	Cp*Co(CO)I$_2$ (10 mol %)	0
9	[Cp^{A1}RhCl$_2$]$_2$ (5 mol %)	<5

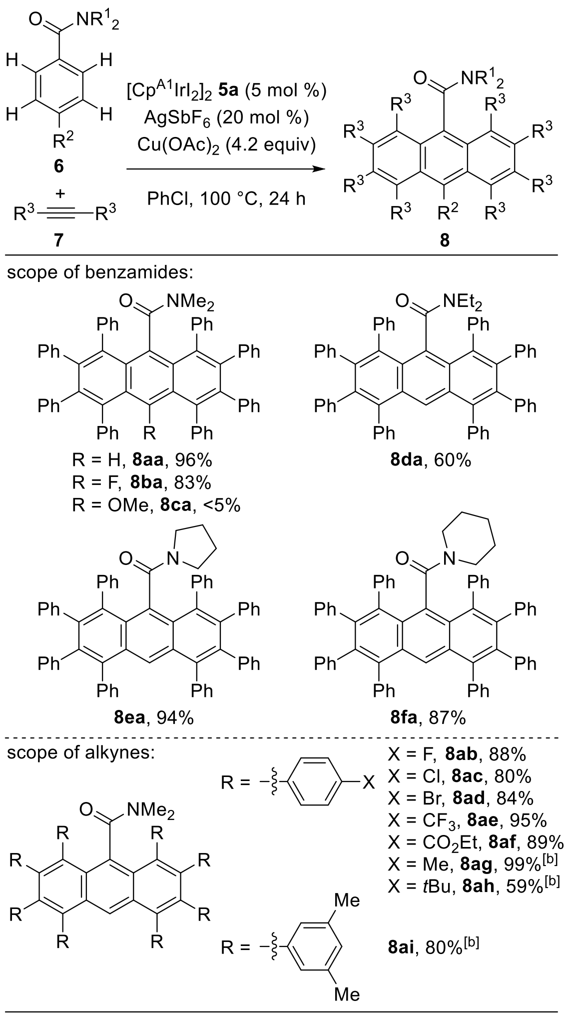
[a] Reaction conditions: **6a** (0.025 mmol), **7a** (0.113 mmol), [Cp^{A1}IrI$_2$]$_2$ **5a** (0.00125 mmol), AgSbF$_6$ (0.005 mmol), and Cu(OAc)$_2$ (0.105 mmol) in PhCl (0.25 mL) at 100 °C for 24 h under an argon atmosphere. [b] Yields were determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard.

results suggest that both the iridium metal center and the Cp^{A} ligand are essential for this challenging double aromatic homologation reaction.

We next examined the scope of the double aromatic homologation reactions (Scheme 3). Both acyclic (**8aa**, **8da**) and cyclic amides (**8ea**, **8fa**) effectively work as the directing groups, providing the desired anthracene products in 60–96% isolated yields. While *p*-fluorobenzamide **6b** furnished the desired fully substituted anthracene (**8ba**) in 83% yield, *p*-methoxybenzamide **6c** did not afford the double aromatic homologation product. Diarylalkynes that bear an electron-withdrawing group exhibited good reactivity and the corresponding products were obtained in high yield (**8ab**-**8af**). Potentially reactive functional groups for further derivatization, such as an aryl bromide and ester, were also compatible (**8ad**, **8af**). The use of DCE as the solvent was required for **8af** due to the poor solubility of the naphthalene intermediate in PhCl. Although relatively electron-rich alkynes are somewhat less reactive, the corresponding products were obtained in moderate to high yield upon increasing the catalyst loading and changing the solvent to 1,4-dioxane (**8ag**-**8ai**). Disappointingly, neither aliphatic alkynes nor terminal alkynes afforded the desired homologation products.

We envisioned that successive first and second aromatic homologation reactions using different alkynes could provide unsymmetrically substituted anthracene derivatives, which would rapidly expand the easily accessible chemical space (Scheme 4). After several preliminary examinations, we found that the single aromatic homologation reaction of benzamide **6a** using two equivalents of alkyne **7a** afforded naphthalene **9** in 88% yield in the presence of 1 mol % of catalyst **5a**. The second homologation reactions also smoothly proceeded with both electron-rich and electron-deficient alkynes to provide densely and unsymmetrically substituted anthracenes (**10a**-**10e**).

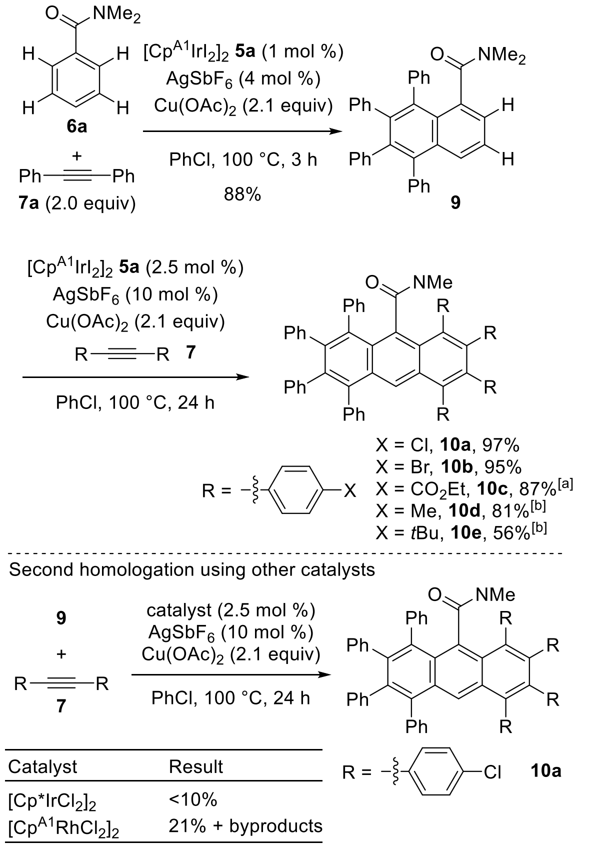
As the standard [Cp*IrCl$_2$]$_2$ catalyst promoted the first homologation step under the conditions in Table 1 to afford naphthalene **9** in moderate yield, we wondered whether it could promote the second homologation when isolated **9** was used as the starting material. When **9** and alkyne **7c** were subjected to the same conditions for the second homologation except for using the [Cp*IrCl$_2$]$_2$ as the catalyst, only trace amounts of anthracene **10a** were observed. The C–H activation of naphthalene **9** directed by the amide moiety would cause severe steric repulsion between the N-Me groups and the peripheral phenyl group, and thus the second homologation from **9** would be much more difficult than the first homologation. Thus, the high reactivity of the [Cp^{A}IrI$_2$]$_2$ catalysts would be crucial for the second step. Moreover, a [Cp^{A1}RhCl$_2$]$_2$ catalyst afforded significantly lower yield than **5a** together with other byproducts, which indicates that its selectivity is insufficient. Although we assume that the higher reactivity of the [Cp^{A}IrI$_2$]$_2$ catalysts could



Scheme 3. Scope of double aromatic homologation reactions of benzamides with alkynes. Reaction conditions: **6** (0.20 mmol), **7** (0.90 mmol), $[\mathrm{Cp^{A1}IrI_2}]_2$ **5a** (0.01 mmol), $\mathrm{AgSbF_6}$ (0.04 mmol), and $\mathrm{Cu(OAc)_2}$ (0.84 mmol) in PhCl (2 mL) at 100 °C for 24 h under an argon atmosphere. Isolated yields after silica gel column chromatography are given. [a] DCE was used as the solvent instead of PhCl. [b] **6** (0.10 mmol), **7** (0.45 mmol), $[\mathrm{Cp^{A1}IrI_2}]_2$ **5a** (0.01 mmol), $\mathrm{AgSbF_6}$ (0.02 mmol), and $\mathrm{Cu(OAc)_2}$ (0.42 mmol) in 1,4-dioxane (1 mL) at 100 °C for 24 h under an argon atmosphere.

possibly be attributed to their higher electrophilicity, further studies on their properties and reactivity are necessary.

In summary, we have synthesized iridium(III) catalysts that contain an amide-pendant cyclopentadienyl ligand ($[\mathrm{Cp^AIrI_2}]_2$) and examined their catalytic activity for double aromatic homologation reactions of benzamides with alkynes. Densely substituted anthracene derivatives were obtained in high yield only when $[\mathrm{Cp^AIrI_2}]_2$ catalysts were employed as the catalyst, demonstrating their higher catalytic performance for this challenging transformation via fourfold C–H activation than those of other related cobalt, rhodium, and iridium catalysts. Our results may facilitate further development of iridium-catalyzed C–H functionalization reactions to efficiently provide valuable functional molecules as well as the development of newly designed functionalized cyclopentadienyl iridium catalysts.



Catalyst	Result
$[\mathrm{Cp^*IrCl_2}]_2$	<10%
$[\mathrm{Cp^{A1}RhCl_2}]_2$	21% + byproducts

Scheme 4. Successive aromatic homologation reactions for the synthesis of unsymmetrical anthracenes. [a] DCE was used as the solvent instead of PhCl. [b] $[\mathrm{Cp^{A1}IrI_2}]_2$ **5a** (5 mol %) and $\mathrm{AgSbF_6}$ (20 mol %) were used.

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Keywords: iridium • cyclopentadienyl ligand • C–H activation • aromatic homologation • anthracene

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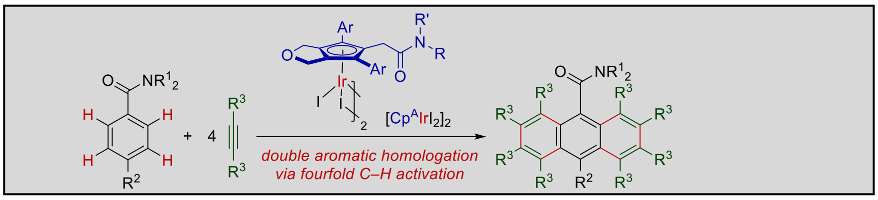

Moderately electron-deficient cyclopentadienyl iridium(III) catalysts bearing a pendant-amide group ([Cp^{A}IrI$_2$]$_2$) were developed. These new iridium catalysts efficiently promoted double aromatic homologation reactions of benzamides with alkynes via fourfold C–H activation, for which standard rhodium, cobalt, and iridium catalysts were ineffective.

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