

Cp*Ir(III)-Catalyzed Mild and Broad C–H Arylation of Arenes and Alkenes with Aryldiazonium Salts Leading to the External Oxidant-Free Approach

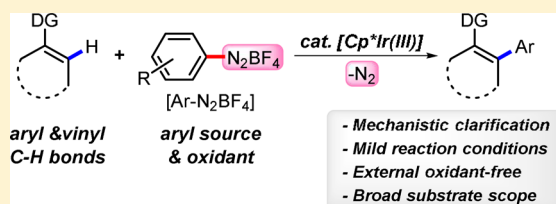
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Supporting Information

ABSTRACT: Reported herein is the development of Cp*Ir(III)-catalyzed direct C–H arylation of arenes and alkenes using aryldiazonium tetrafluoroborates, the use of which as an aryl precursor and also as an oxidant via C–N₂ bond cleavage was a key to success in achieving a mild and external oxidant-free procedure. Mechanistic experiments and DFT calculations revealed the turnover-limiting step to be closely related to the formation of an Ir(V)-aryl intermediate rather than the presupposed C–H cleavage. Under the developed mild arylation conditions, a wide range of benzamides were smoothly arylated. In addition, synthetic utility of the current C–H arylation procedure was also demonstrated successfully for the (*Z*)-selective arylation of enamides and C8-selective reaction of quinoline *N*-oxides.



INTRODUCTION

Since Bergman's seminal study on the alkane C–H activation using an iridium complex,¹ the high reactivity of Ir(III) species toward C–H bond cleavage has attracted the intensive attention of chemists.² As a result, significant advances have been made in the catalytic C–H functionalization, representatively borylation, based on the iridium catalyst system (Scheme 1a, left).³ Together with the ability to mediate facile C–H bond cleavage, a notable feature of iridium(III) species in catalytic borylation is its compatibility with the internal oxidant⁴ of reactants (H–B or B–B bond) enabling an Ir(III)/Ir(V) catalytic cycle.⁵ However, despite this remarkable progress, the development of other types of iridium-catalyzed external oxidant-free C–H functionalization has not been realized until recently.

Continuing our research efforts in the development of novel catalytic C–H functionalization,⁶ we wondered whether the Cp*Ir(III)-catalyst system could be utilized to realize mild and external oxidant-free C–H functionalization of arenes and alkenes, in particular for an oxidative arylation reaction. Since half-sandwich iridium(III) complexes are known to readily activate chelation group-containing hydrocarbons, giving rise to the corresponding cyclometallates in a stoichiometric manner (Scheme 1a, right),⁷ applying suitable reactants with built-in-oxidants was envisaged to result in an efficient redox-active catalytic cycle. Indeed, as a proof-of-concept, we previously developed a series of Ir-catalyzed direct and mild C–N bond forming reactions by employing organic azides⁸ or hydroxylamine derivatives^{9,10} as the amino source, also working as internal oxidants via N–N₂ or N–O bond cleavage, respectively (Scheme 1b).^{8–11} This achievement led us to envision that

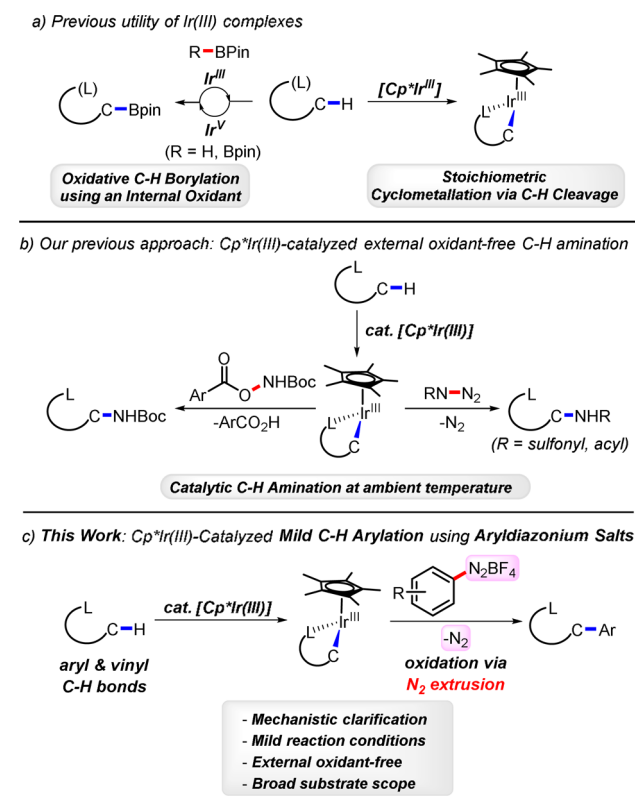
direct C–H arylation might be plausible by optimizing proper aryl precursors which also play a role as an oxidant under the perspective iridium catalytic conditions.

Owing to the prevalence of aryl to aryl or aryl to vinyl scaffolds in diverse organic materials and pharmaceuticals, transition metal-catalyzed direct C–H arylation has been extensively studied as a straightforward route to construct carbon-aryl bonds.^{6,12} Despite the significant advance made in this field, however, the majority of the developed C–H arylation protocols still suffer from harsh conditions such as high reaction temperatures¹³ and the need for excess amounts of external oxidants and/or additives. Therefore, the development of mild and broad C–H arylation methods free from external oxidants and additives is highly desirable. These considerations led us to find the Cp*Ir(III)-catalyzed C–H arylation using aryldiazonium salts as an arylating reagent under external oxidant-free conditions (Scheme 1c). Although aryldiazonium salts have been spotlighted as a convenient arylating reagent,^{14–16} the utilization of these compounds in transition metal-catalyzed direct C–H arylation has not been achieved except one pioneering example of the Pd-catalyzed C–H arylation developed by Sanford and co-workers.¹⁶ They successfully merged high-valent palladium catalysis¹⁷ and photoredox-catalysis using ruthenium photosensitizer¹⁸ to achieve a mild arylation procedure. However, this reaction still requires a large excess of aryldiazonium salts and suffers from narrow substrate scope.

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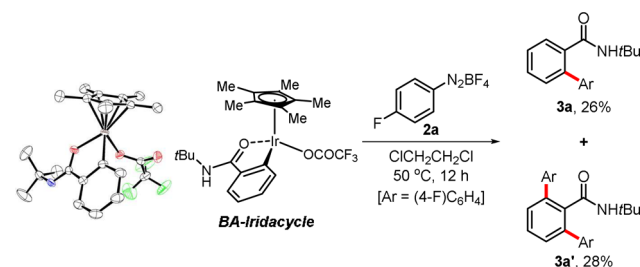
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Scheme 1. Ir(III)-Catalyzed External Oxidant-Free C–H Functionalization



RESULTS AND DISCUSSIONS

Stoichiometric Arylation with Iridacycle Complex. We commenced our study by examining a working hypothesis that Cp*Ir(III)-catalyzed C–H arylation would be plausible with aryldiazonium salt as an arylating reagent also working as an oxidant. First, a metallacyclic species **BA-Iridacycle** was readily prepared in 43% yield (1.33 g) according to our previously reported method¹⁹ in a gram scale reaction of *N*-*tert*-butylbenzamide with [Cp*IrCl₂]₂ (see Supporting Information, SI, for details). Structure of **BA-Iridacycle** was determined by NMR and X-ray crystallographic analysis. When a stoichiometric reaction of **BA-Iridacycle** with a slightly excess amount of 4-fluorophenyldiazonium tetrafluoroborate (**2a**) was conducted, we were pleased to observe that the desired arylation indeed proceeded, affording a mixture of mono- (**3a**) and bis-arylated products (**3a'**) in 26% and 28% yield, respectively (Scheme 2). Although the stoichiometric reaction was not further optimized to control the degree of arylation (mono- vs

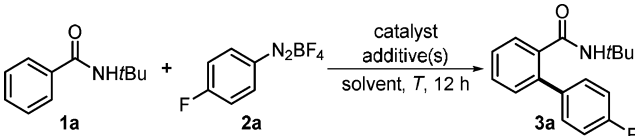
Scheme 2. Stoichiometric Reaction of **BA-Iridacycle** with Aryldiazonium Salt **2a**

bis-), this result was regarded as highly promising, guiding a catalytic version of the above C–H arylation reaction.

Stoichiometric to Catalytic: Optimization of Ir-Catalyzed C–H Arylation. Having observed the reactivity in a stoichiometric arylation reaction, we next endeavored to search for optimal *catalytic conditions* in a model reaction of *N*-*tert*-butylbenzamide (**1a**) with 4-fluorophenyldiazonium tetrafluoroborate (**2a**, Table 1).^{12f–h} Pleasingly, the desired conversion indeed did proceed by applying a catalytic amount of [IrCp*Cl₂]₂ (5 mol %) and AgNTf₂ (20 mol %, entry 1). It was noteworthy that, in contrast to the stoichiometric reaction, the monoarylated product **3a** was obtained almost exclusively, and only a trace amount (<5%) of bis-arylated product **3a'** was formed under the catalytic conditions. The arylation did not occur in the absence of Ir catalyst or Ag additive, implying that the generation of cationic Ir(III) species is crucial in the current transformation (entries 2–3). The efficiency of this catalytic arylation was dependent on solvents employed. While slightly decreased product yield was obtained in dichloromethane (entry 4), no conversion was observed in polar aprotic solvents such as THF, 1,4-dioxane, acetone, DMF, or acetonitrile (entries 5–9). However, the reaction was sluggish in polar protic solvents including methanol or *tert*-amyl alcohol (entries 10–11). This result was reasoned that polar solvents readily coordinate to the vacant site of active iridium species, thus making the diazonium salt unable to bind effectively to the iridium metal center.

On the basis of this assumption, when 2,2,2-trifluoroethanol, which has lower Lewis basicity compared to the conventional alcoholic solvents,²⁰ was employed as a solvent, the product was formed in high yield (70%, entry 12). In addition, the arylation took place in similar yield even at mild temperature (35 °C, entry 13). Screening of silver additives revealed that AgBF₄ was also effective for this arylation, albeit in slightly decreased yield (entry 14) when compared to AgNTf₂. In addition, it was found that a catalytic amount (30 mol %) of acetate additive (NaOAc) induced a notable improvement in yield (entry 15).^{7,21} The arylation did not take place in the absence of Ag additive even under the optimized conditions (entry 16). Slightly decreased product yield was obtained with lower loading of iridium catalyst (entry 17). It should be noted that this arylation afforded a monoarylated product **3a** almost exclusively even when of benzamide **1a** was used as a limiting reagent albeit in lower yield (entry 18). It is noteworthy that the reaction proceeded smoothly even under O₂ atmosphere (1 atm) or in the absence of visible light, thus implying that the present arylation did not proceed via a radical-mediated pathway (entries 19–20).^{16,18}

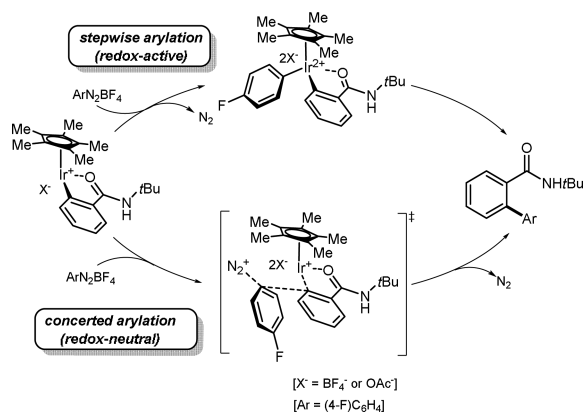
Mechanistic Investigations: DFT Calculations. Given the observed reactivity of the current Ir-mediated arylation allowing for mild conditions, we embarked on the mechanistic studies to delineate the working mode of this catalysis. We initially hypothesized that the current C–H arylation might be operated mainly in two stages: (i) generation of a cationic iridacyclic species via the concerted metalation-deprotonation (CMD) pathway,²² and (ii) coordination of aryldiazonium salt to the metal center of iridacycle and then carbon-aryl bond formation. We envisaged that the carbon-aryl bond formation may proceed via either stepwise or concerted route (Scheme 3).^{23a} In a stepwise pathway, the coordination of aryldiazonium salt to an iridacyclic species would lead to an Ir(V)-aryl intermediate^{5,11,24,25} by releasing N₂ molecule, and subsequent reductive elimination will afford the desired arylated product

Table 1. Optimization for Ir-Catalyzed C–H Arylation Reaction^a


entry	catalyst (mol %)	additive(s) (mol %)	solvent	T (°C)	yield (3a) ^b
1	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	1,2-DCE	50	55
2	[IrCp*Cl ₂] ₂ (5)		1,2-DCE	50	N.R.
3		AgNTf ₂ (20)	1,2-DCE	50	N.R.
4	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	CH ₂ Cl ₂	50	40
5	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	THF	50	N.R.
6	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	1,4-dioxane	50	N.R.
7	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	acetone	50	N.R.
8	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	DMF	50	N.R.
9	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	CH ₃ CN	50	N.R.
10	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	MeOH	50	N.R.
11	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	<i>t</i> AmylOH	50	12
12	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	CF ₃ CH ₂ OH	50	70
13	[IrCp*Cl ₂] ₂ (5)	AgNTf ₂ (20)	CF ₃ CH ₂ OH	35	68
14	[IrCp*Cl ₂] ₂ (5)	AgBF ₄ (20)	CF ₃ CH ₂ OH	35	56
15 ^c	[IrCp*Cl ₂] ₂ (5)	AgBF ₄ (20)/NaOAc (30)	CF ₃ CH ₂ OH	35	83 (78)
16 ^c	[IrCp*Cl ₂] ₂ (5)	NaOAc (30)	CF ₃ CH ₂ OH	35	N.R.
17 ^c	[IrCp*Cl ₂] ₂ (2.5)	AgBF ₄ (10)/NaOAc (15)	CF ₃ CH ₂ OH	35	73
18 ^d	[IrCp*Cl ₂] ₂ (5)	AgBF ₄ (20)/NaOAc (30)	CF ₃ CH ₂ OH	35	60 ^e
19 ^{e,f}	[IrCp*Cl ₂] ₂ (5)	AgBF ₄ (20)/NaOAc (30)	CF ₃ CH ₂ OH	35	81
20 ^{e,g}	[IrCp*Cl ₂] ₂ (5)	AgBF ₄ (20)/NaOAc (30)	CF ₃ CH ₂ OH	35	79

^aConditions: **1a** (0.15 mmol), **2a** (0.1 mmol), catalyst, additive(s), and solvent (0.5 mL) at the indicated temperature for 12 h under argon atmosphere. Unless otherwise mentioned, **3a** was obtained in major and only trace (<5%) amount of **3a'** was produced. ^bNMR yields (%) are given and isolated yields are shown in parentheses. ^c**1a** (0.3 mmol), **2a** (0.2 mmol), and solvent (1.0 mL). ^d**1a** (0.2 mmol), **2a** (0.3 mmol), and solvent (1.0 mL). ^e7% of **3a'** was produced. ^fReaction under O₂ (1 atm.). ^gReaction under dark.

Scheme 3. Plausible Carbon-Aryl Bond Forming Pathways in the Ir-Catalyzed C–H Arylation



(redox-active). However, in a concerted arylation process (redox-neutral), the carbon-aryl bond formation will be coincided with N₂ extrusion without forming an Ir(V)-aryl intermediate.⁶¹

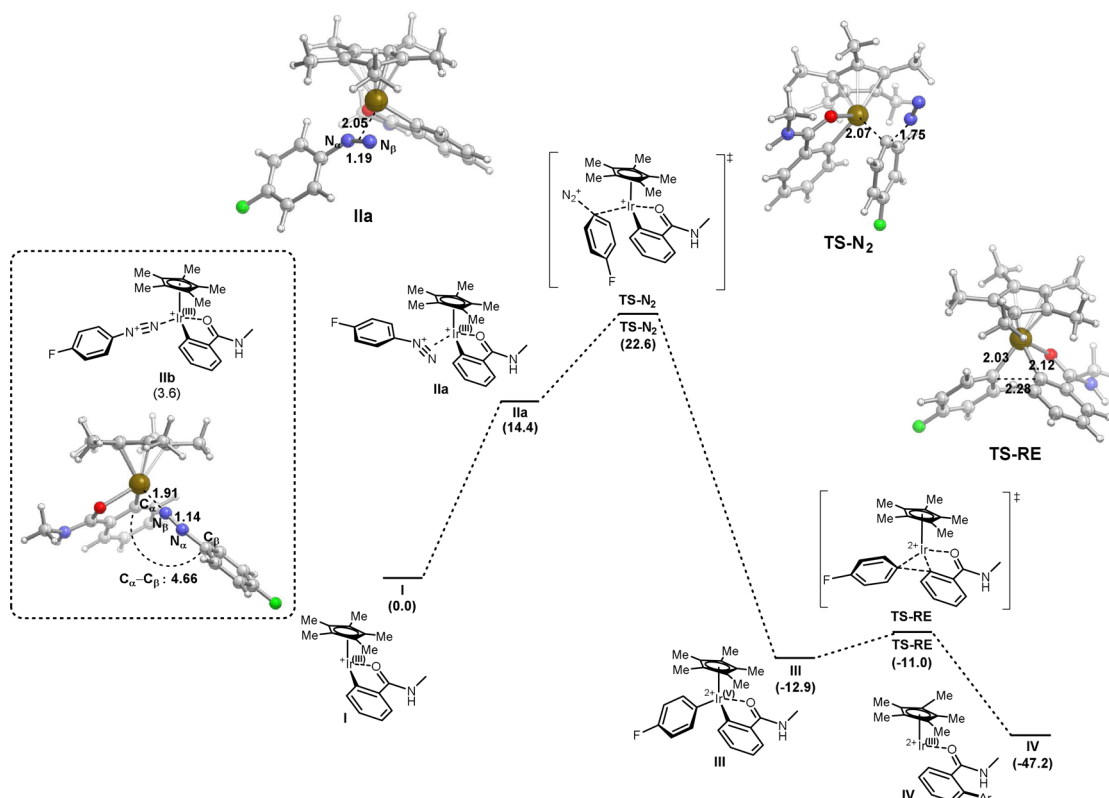
For a better understanding of the interplay between aryldiazonium salt and cationic iridacyclic species eventually leading to the aryl–aryl bond formation, density functional theory (DFT) calculations were carried out (Scheme 4). *N*-Methylbenzamide and 4-fluorophenyldiazonium tetrafluoroborate were selected as model substrate and aryl source, respectively, for the theoretical study.²³

As the initial step, a diazonium salt coordinates to a cationic iridacyclic species **I** to form an Ir-aryldiazonium adduct.²⁶ Side-

on binding of an aryldiazonium ion to the iridium metal center would afford a complex **IIa**, and this process was calculated to be endergonic by 14.4 kcal/mol. The bond length between N_α and N_β of the bound aryldiazonium moiety in **IIa** was shown to be 1.19 Å, which is within a range of a triple bond character (the nitrogen–nitrogen bond of unbound 4-fluorophenyldiazonium ion was calculated to be 1.12 Å). This result strongly suggests that the formation of an iridium–aryldiazene complex does not occur when aryldiazonium ion interacts with the metal center of iridacycle **I**, which is in a stark contrast to the previously reported reactivity of diazonium salts in reaction with various metal complexes.^{14,26} In addition, the calculated bond elongation between N_α and N_β of diazonium ion of an iridium complex **IIa** implies that the occupied pi-bonding orbital of the N_α–N_β triple bond coordinates to the iridium metal center.

Subsequent DFT calculations revealed that the diazonium iridacycle complex **IIa** undergoes the carbon-aryl bond forming process through a stepwise pathway, involving an iridium(V)-aryl intermediate **III**. The activation energy for this redox-active pathway was calculated to be 22.6 kcal/mol from a cationic iridacycle **I** via a transition state **TS-N₂**, leading to the formation of a high-valent iridium-aryl intermediate **III** via the oxidative N₂ extrusion. Complex **III** then undergoes a reductive elimination with a very low energy barrier (1.9 kcal/mol), passing through a transition state **TS-RE** to lead to the formation of the desired arylated product coordinated to a cationic iridium(III) species (**IV**). Although the end-on binding of a diazonium species to the metal center leads to the formation of iridacyclic complex **IIb** (Scheme 4, left) and the

Scheme 4. Potential Energy Surface for the Formation of Carbon-Aryl Bond from an Iridacyclic Intermediate I with 3D Structures of Selected Computed Intermediates

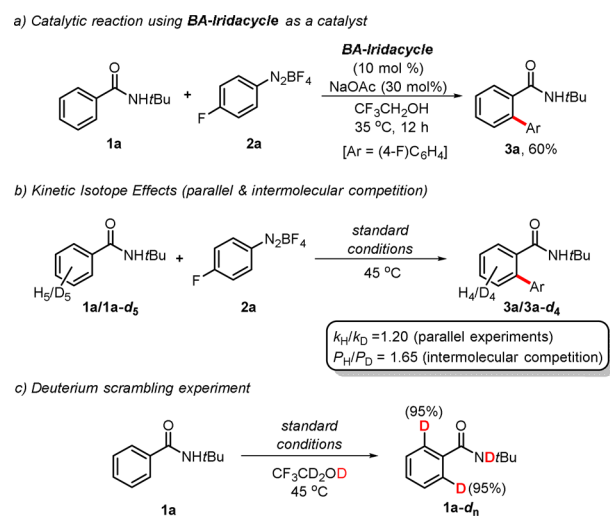


formation of this complex is energetically more favorable over **IIa** by 10.8 kcal/mol, it was found that **IIb** is unable to undergo subsequent carbon-aryl bond formation. To verify the possibility of **IIb** to undergo a redox-active arylation pathway, the corresponding iridium-aryldiazenide complex, which could be generated via the oxidation of the iridium metal center by the aryldiazonium moiety, was selected as the initial structure for the geometry optimization. However, all trials were converged to the original structure **IIb**, thus strongly implying that this iridacyclic intermediate is oxidatively inert (see SI for details). In addition, owing to the quite long distance (4.66 Å) between C_{α} and C_{β} in **IIb**, the proposed concerted (redox-neutral) arylation mechanism also cannot be operative.

Along with the investigations for the redox-active arylation pathway, the feasibility of the redox-neutral pathway was extensively examined. Unfortunately, however, all attempts to locate a plausible transition state in the proposed concerted pathway were not successful. Although several transition state candidates were obtained, intrinsic reaction coordinate (IRC) calculations revealed that such geometries are not the proper transition states between intermediate **IIa** and **IV**. Instead, it was observed that all candidate structures were eventually connected to iridium(V)-aryl intermediate **III** in IRC calculations rather than **IV**, thus suggesting that the redox-active process is more feasible than the alternative pathway.

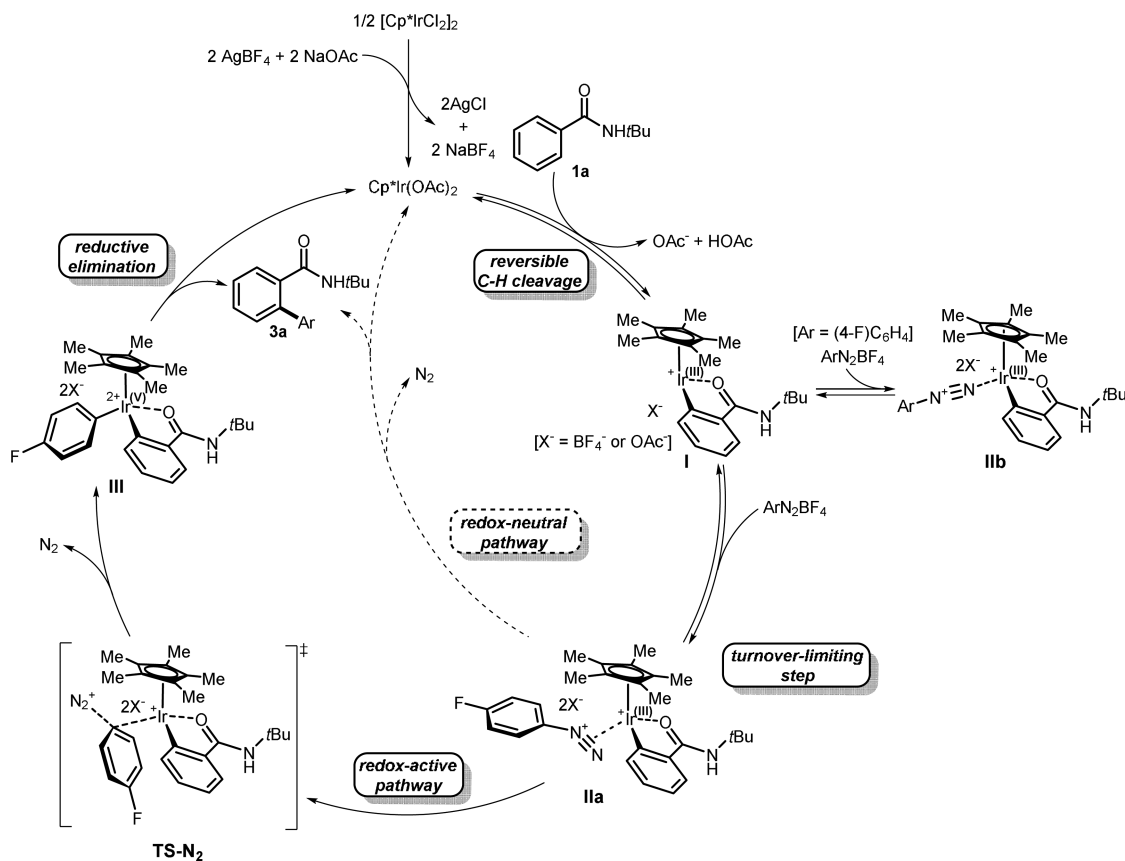
Mechanistic Experimental Studies. A series of experiments were also performed to shed light on the mechanistic aspects of the present C–H activation process. The fact that **BA-Iridacycle**, a fully characterized metallacyclic species as shown in Scheme 2, can catalyze the arylation reaction (Scheme 5a) together with the observed reactivity of the iridacyclic species toward a stoichiometric arylation (Scheme 2) suggests

Scheme 5. Preliminary Mechanistic Studies on the C–H Activation Step of the Arylation Reaction



that this cationic iridacyclic intermediate should be involved in the catalytic cycle. When kinetic isotope effect (KIE) studies were performed, only small values of KIE were obtained from either parallel experiments ($k_{\text{H}}/k_{\text{D}} = 1.20$) or intermolecular competition ($P_{\text{H}}/P_{\text{D}} = 1.65$, Scheme 5b). In addition, significant deuterium incorporation (95%) was observed at the ortho-position of recovered benzamide (**1a**) when the reaction was carried out in deuterated alcohol solvent (Scheme 5c), implying that the C–H bond cleavage is reversible and less related to the turnover-limiting stage. These experimental results in combination with the above DFT calculations led us

Scheme 6. Proposed Catalytic Cycle



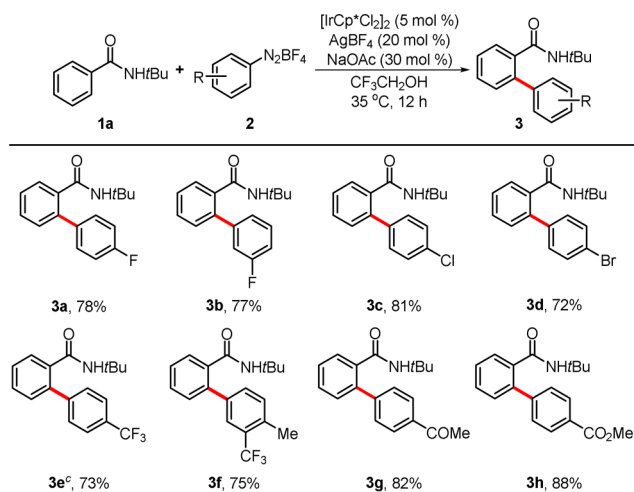
to assume that the generation of a high-valent iridium(V)-aryl intermediate would be the slowest in the proposed catalytic cycle (for the energy profile of the overall catalytic cycle, see SI).²⁷

On the basis of the above theoretical and experimental considerations, a catalytic cycle is proposed in Scheme 6. First, $\text{Cp}^*\text{Ir}(\text{OAc})_2$, generated in situ from $[\text{Cp}^*\text{IrCl}_2]_2$ precursor by the action of silver and acetate additives, would induce a reversible C–H bond cleavage of benzamide via a concerted metalation and deprotonation (CMD) pathway to give a cationic cyclometalated iridium(III) intermediate **I**. The coordination of an aryldiazonium ion to the iridium metal center of **I** will lead to the formation of aryldiazonium iridacycle adduct (**IIa** or **IIb**). On the basis of the computational studies, it is now clear that only **IIa**, formed by the side-on binding of an arylating reagent to the metal center, undergoes the subsequent catalytic cycle, whereas **IIb** will be inert toward the remaining arylation processes. Theoretical studies revealed that the iridacycle complex **IIa** will give rise to the formation of an Ir(V)-aryl intermediate **III** via oxidative N_2 extrusion, passing through a TS-N_2 transition state. Finally, the highly facile (almost barrierless) reductive elimination of the high-valent iridium-aryl complex **III** will result in the desired arylated product with the regeneration of a catalytically active Ir(III) species. Both kinetic isotope studies and DFT calculations strongly indicate that the formation of an iridium(V)-aryl intermediate **III** from an iridacycle **I** and aryldiazonium salt is a turnover-limiting step in an overall catalytic cycle. It should be noted, however, that although the above mechanistic proposal is based on the calculated redox-active arylation pathway, an

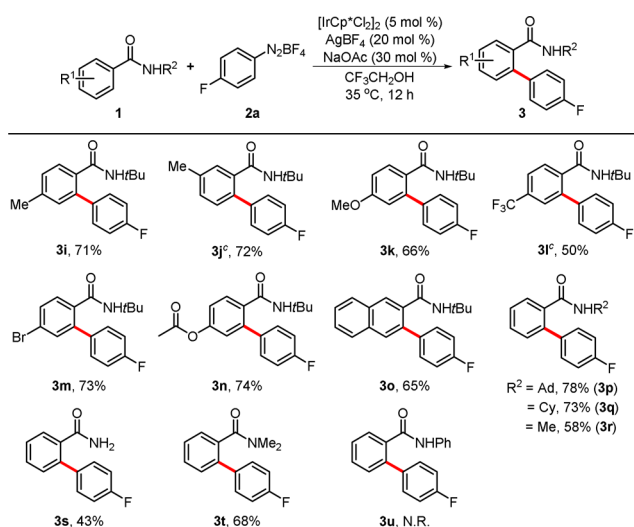
alternative pathway (concerted redox-neutral) cannot be completely ruled out at the present stage.

Synthetic Scope: Aryldiazonium Salts and Benzamides. With the optimized reaction conditions in hand, we next investigated the scope of the current arylation by examining various aryldiazonium salts (**2**) in reaction with *N*-tert-butylbenzamide (**1a**, Table 2). Phenyldiazonium salts bearing fluoro at the para- (**2a**) or meta-position (**2b**) participated in the arylation without difficulty, leading to the corresponding arylated products in high yields. In addition, phenyldiazonium salts substituted with other halogens such as bromo (**2d**) or chloro (**2c**) at the para-position readily reacted in good yields. The current C–H arylation proceeded also efficiently with electron-withdrawing arylating reactant (**2e**). Although the reaction of aryldiazonium salts substituted with electron-donating or neutral groups was less effective, an arylating reagent having both an electron-donating and a withdrawing group (**2f**) was facile under the present conditions. Phenyldiazonium salts having ketone (**2g**) or ester groups (**2h**) afforded the corresponding functionalized arylation products in excellent yields, thus showcasing high functional group tolerance of this arylation procedure.

The scope of benzamides (**1**) was next investigated in reaction with 4-fluorophenyldiazonium tetrafluoroborate (**2a**, Table 3). Benzamides having methyl group at the para- (**1i**) or meta-position (**1j**) underwent the arylation in good yields. It should be mentioned that the arylation took place at the sterically less demanding C–H bond highly selectively (**3j**). The reaction efficiency was almost maintained irrespective of the electronic variation at the arene part of benzamides (**1k–1l**), although the use of benzamide bearing a strongly electron-

Table 2. Substrate Scope of Aryldiazonium Salts^{a,b}

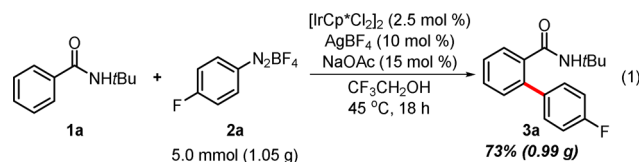
^a**1a** (0.3 mmol), **2** (0.2 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (5 mol %), AgBF_4 (20 mol %), and NaOAc (30 mol %) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.0 mL) at 35 °C for 12 h; isolated yields. ^bIn all cases, only trace (<5%) amount of bis-arylated product was observed. ^cThe reaction was conducted without using NaOAc .

Table 3. Substrate Scope of Benzamides^{a,b}

^a**1** (0.3 mmol), **2a** (0.2 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (5 mol %), AgBF_4 (20 mol %), and NaOAc (30 mol %) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.0 mL) at 35 °C for 12 h; isolated yields. ^bIn all cases, only trace (<5%) amount of bis-arylated product was observed. ^c $[\text{IrCp}^*\text{Cl}_2]_2$ (5 mol %), AgNTf_2 (20 mol %) were used at 45 °C.

withdrawing group led to a slightly decreased yield (**3l**). In addition, functional groups such as halide and acetate groups were well tolerated (**3m–3n**) to prove the mild reaction conditions of the current arylation procedure. 2-Naphthamide (**1o**) was readily arylated at the sterically more accessible position to afford the desired product in a synthetically acceptable yield. The arylation efficiency was revealed to be little affected by the variation at the *N*-alkyl moiety of benzamides (**1p–1r**). It is worthwhile to note that not only secondary benzamides, but also primary (**1s**) and tertiary (**1t**) benzamides underwent the arylation in moderate to good yields, thus highlighting the broad substrate scope of the present arylation protocol. However, *N*-phenylbenzamide was not effective (**3u**).

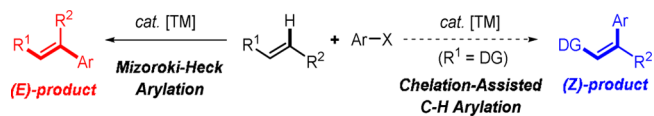
To demonstrate the synthetic utility of the present arylation protocol, a reaction of benzamide **1a** and aryldiazonium salt **2a** was performed on a 5 mmol scale of aryldiazonium salt (eq 1).



Gratifyingly, the arylation efficiency was found to be maintained at a high level in this large scale even with the lower catalyst loading (2.5 mol %) to give the desired product **3a** in 73% (0.99 g) yield.

Direct C–H Arylation of Challenging Substrates: (Z)-Selective Arylation of Olefins. Transition metal-catalyzed Mizoroki–Heck type reaction of olefins with various types of arylating reagents has been regarded as one of the most important carbon–carbon bond forming methods to find a wide utility in organic synthesis.²⁸ While early examples of the Heck-olefination were shown to employ electronically biased alkenes to guarantee satisfactory regio- and stereoselectivity, extensive efforts have subsequently been made in expanding the scope to include electronically nonbiased olefins.^{15a,b,29} However, these improved procedures afford mainly (*E*)-styrenyl products (Scheme 7, left), whereas the formation of

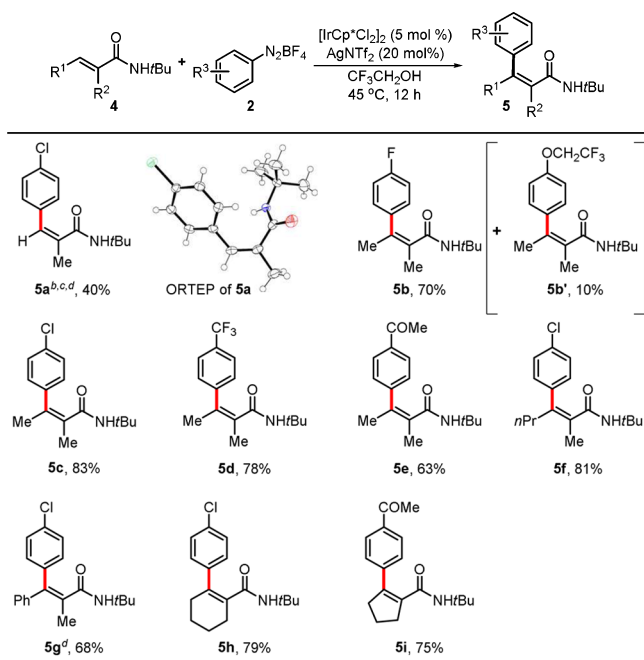
Scheme 7. Two Approaches in the Aryl Olefination



(*Z*)-isomers in major is difficult to achieve. In this aspect, a handful of chelation-assisted C–H arylation approaches have been developed to facilitate the selective (*Z*)-styrenyl arylation (Scheme 7, right).³⁰ However, they still suffer from narrow substrate scope and harsh reaction conditions, thus demanding milder and more general new catalyst systems to develop.

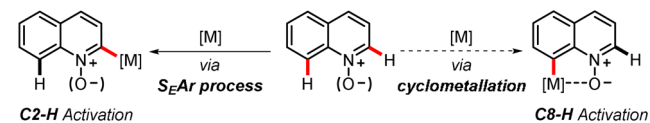
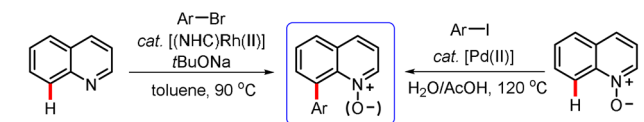
With the above considerations in mind, we examined the arylation of *N*-*tert*-butylmethacrylamide (**4a**) with 4-chlorophenyldiazonium tetrafluoroborate (**2c**) under slightly modified conditions (Table 4). Gratifyingly, **4a** underwent the arylation smoothly at 55 °C to afford the desired product (**5a**) with exclusive (*Z*)-selectivity, albeit in moderate yield, thus proving the excellent regio- and stereoselectivity of the current arylation protocol. Stereochemistry of product **5a** was unambiguously confirmed by NMR and X-ray crystallographic analyses. Product yields were significantly improved even at 45 °C when trisubstituted vinylamides were employed as substrates. For example, tiglamide was smoothly reacted with aryldiazonium salts bearing halogens (**5b–5c**),³¹ trifluoromethyl (**5d**), and ketone (**5e**) groups to afford the corresponding arylated products in high yields with perfect (*Z*)-selectivity. Efficiency was maintained high when β -substituents such as propyl (**5f**) and phenyl (**5g**) groups were present. In addition, cyclic enamides were readily arylated in high yields (**5h–5i**).

Direct C–H Arylation of Challenging Substrates: C8-Arylation of Quinoline *N*-Oxides. Quinoline derivatives are an important class of nitrogen-containing heterocycles widely utilized in synthetic, medicinal, and materials chemistry.³² As a result, transition metal-catalyzed direct C–H functionalization

Table 4. Substrate Scope of Enamides^a

^a**4** (0.3 mmol), **2** (0.2 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (5 mol %), and AgNTf_2 (20 mol %) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.0 mL) at $45\text{ }^\circ\text{C}$ for 12 h; isolated yields. ^bSubstrate (0.2 mmol) and aryldiazonium salt (0.36 mmol). ^cSubstrate decomposition occurred. ^dAt $55\text{ }^\circ\text{C}$.

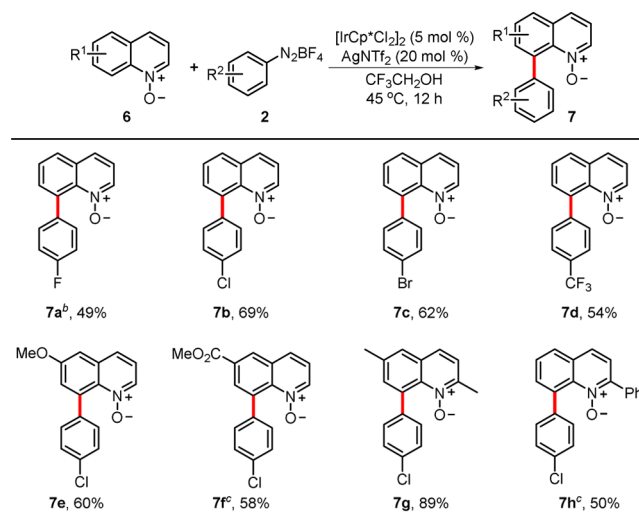
of quinolines or their *N*-oxides has been actively investigated. While a number of examples have appeared for the C2-functionalization of quinolines (*N*-oxides) by taking advantage of the intrinsic acidity of the C2–H bond adjacent to the pyridyl nitrogen (Scheme 8a, left),^{33,34} direct C8-functionaliza-

Scheme 8. C–H Functionalization of Quinoline (*N*-oxides)a) Mode of C–H activation of Quinolines (*N*-oxides)b) Previously reported direct C–H arylation of Quinolines (*N*-oxides)

tion of quinolines (*N*-oxides) has rarely been achieved.³⁵ In this context, notable breakthroughs have been made in recent years including our own to achieve the C-8 regioselectivity using *N*-oxide as a directing group (Scheme 8a, right).^{8d,36} These results led us to investigate the feasibility of direct C8-arylation of quinoline *N*-oxides via our current C–H arylation protocol. It should be mentioned that although two examples of C8-selective C–H arylation of quinolines (our own work)^{35a} and quinoline *N*-oxides^{36d} were reported, these methods suffer from harsh reaction conditions and narrow substrate scope (Scheme 8b).

To test the viability of the remote arylation of quinolines, a reaction of quinoline *N*-oxide with aryldiazonium salt **2a** was examined in the presence of AgNTf_2 . We were delighted to see

that the desired arylation indeed take place leading to a C8-arylated product albeit in moderate yield (**7a**, Table 5).

Table 5. Substrate Scope of Quinoline *N*-Oxides^a

^a**6** (0.2 mmol), **2** (0.3 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (5 mol %), AgNTf_2 (20 mol %) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.0 mL) at $45\text{ }^\circ\text{C}$ for 12 h; isolated yields. ^bRun for 8 h. ^cRun at $55\text{ }^\circ\text{C}$.

Arylating reagents bearing electron-withdrawing groups such as bromo, chloro, or trifluoromethyl participated in the arylation with quinoline *N*-oxide to afford the desired products in acceptable yields (**7b–7d**). Subsequent investigation on the substrate scope of quinoline *N*-oxides revealed that electronic variation of substituents in quinoline *N*-oxides did not deteriorate the reaction efficiency (**7e–7f**). A substrate having a methyl group at the C2-position smoothly underwent the arylation to afford product **7g** in excellent yield. It is worthwhile to note that the regioselectivity of the current arylation was maintained even in the presence of an additional phenyl group that is also a potential reacting site (**7h**). While it remains unclear which properties of 2,2,2-trifluoroethanol make this solvent most suitable for the present arylation, its reduced Lewis basicity and high polarity are assumed to allow for mild reaction conditions by facilitating the complete dissolution of aryldiazonium salts.²⁰ In addition, the high ionizing power of this solvent may also contribute to the stabilization of high-valent cationic iridacyclic intermediates.

CONCLUSIONS

We have reported herein the development of a mild and external oxidant-free $\text{Cp}^*\text{Ir}(\text{III})$ -catalyzed direct C–H arylation of arenes and alkenes using aryldiazonium tetrafluoroborates as a convenient aryl group donor, also working as an oxidant via C–N₂ bond cleavage. On the basis of the experimental and theoretical (DFT) studies, a catalytic pathway involving the formation of an Ir(V)-aryl intermediate via oxidative N₂ extrusion is proposed. In addition, the mechanistic investigations showed that the turnover-limiting step is more closely related to the generation of the high-valent iridium intermediate rather than the C–H bond cleavage. The reaction conditions are mild over a broad range of substrates and arylating reagents. In fact, while benzamides underwent the arylation with high efficiency, direct arylation of enamides was readily achieved with excellent regio- and stereoselectivity

leading to (*Z*)-styrenyl products. In addition, C8-selective C–H arylation of quinoline *N*-oxides was also proven to be facile. We believe that the present arylation protocol will offer a powerful synthetic tool for the facile construction of arylated compounds of high utility in various research areas.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedures and characterization of new compounds, Cartesian coordinates of computed structures, and X-ray analyses. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04043.

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Notes

The authors declare no competing financial interest.

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