

Iridium(III)-Catalyzed Intermolecular C(sp³)-H Insertion Reaction of Quinoid Carbene through a Radical Mechanism

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Abstract: Herein is described an Ir(III) porphyrin-catalyzed intermolecular C(sp³)-H insertion reaction of quinoid carbene (QC). The reaction was designed by harnessing the hydrogen atom transfer (HAT) reactivity of metal-QC species with aliphatic substrates followed by a radical rebound process to afford C-H arylation products. This methodology is efficient for the arylation of activated hydrocarbons such as 1,4-cyclohexadienes (down to 40 min reaction time, up to 99% yield, up to 1.0 g scale); it features unique regioselectivity which is mainly governed by steric effect, as the insertion into primary C-H bonds is favored over secondary and/or tertiary C-H bonds in substituted cyclohexene substrates. Mechanistic studies revealed a radical mechanism for the reaction.

Introduction

Transition metal-catalyzed carbene transfer and insertion reactions constitute powerful synthetic tools in modern organic chemistry.^[1] In particular, catalytic carbene C-H insertion reactions with α -diazocarbonyl compounds allow direct functionalization of sp³ and/or sp² C-H bonds (Figure 1a).^[2] Alternatively, metal-carbene intermediates serving as aryl synthons have been demonstrated with quinone diazides as carbene sources;^[3] the thus formed metal-quinoid carbene (QC) species is electrophilic^[4] and termed as “umpoled phenol” by Baran and co-worker.^[5] Although several examples of C(sp²)-H QC insertion reactions into simple arenes and directing group-containing substrates have been reported in the literature,^[6] catalytic activation/functionalization of C(sp³)-H bonds by metal-QC intermediates remains rarely explored.^[7] Very recently we

have demonstrated that, in addition to carbene transfer reactivity, isolated Ru(II)-QC complexes could undergo stoichiometric hydrogen atom transfer (HAT) reactions with activated C(sp³)-H bonds,^[4] thereby displaying their metallaquinone feature;^[8] this has inspired us to develop a stepwise radical-based C(sp³)-H insertion pathway analogous to those involving metal-oxo species.^[2c] Although catalytic carbene C-H insertion reactions are dominated by concerted mechanism,^[2b,c,e] radical pathway has been reported for several intramolecular reactions^[9] which are mostly initiated by open-shell carbene radical species;^[10] great challenge still lies in the development of intermolecular reactions. The closed-shell Ru-QC complexes could undergo intermolecular HAT with aliphatic C-H substrates, yet no subsequent radical rebound process was observed presumably due to reductive quenching of ligand radical by the electron-rich Ru(II) center (Figure 1b);^[4] we envisioned that changing the metal center to a less reducing Ir(III)^[11] might increase the lifetime of the ligand radical and thus facilitate the rebound step. Herein is described a protocol of Ir(III) porphyrin-catalyzed intermolecular QC insertion reactions into C(sp³)-H bonds via a radical mechanism.

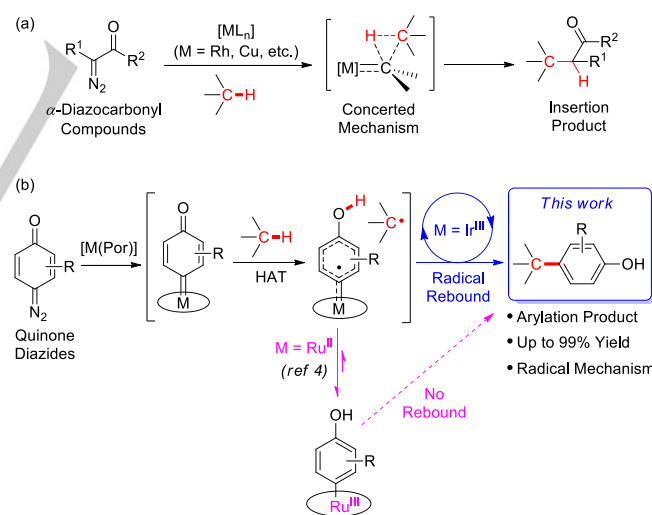


Figure 1. Intermolecular metal-carbene C(sp³)-H insertion catalysis. (a) Conventional approach with α -diazocarbonyl compounds. (b) Ir(III) porphyrin-catalyzed QC insertion reaction (this work) based on the stoichiometric HAT reactivity of Ru(II)-QC complexes reported in ref 4. Por = porphyrinato dianion.

Results and Discussion

We initiated our trial with 1,4-cyclohexadiene (CHD) as the aliphatic C-H substrate (5 equiv) and [Ir(TTP)Me] (2 mol%) as the catalyst, and the C(sp³)-H arylated product **1a** was obtained in

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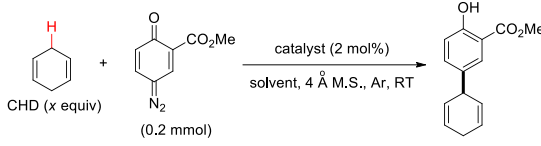
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48% yield (Table 1, entry 1). The reaction was significantly retarded by a bulkier porphyrin ligand such as TMP or TDCPP (entry 2–3), and gratifyingly, by using OEP ligand that is free of porphyrin *meso*-substituents, an increase in yield of **1a** to 62% was observed (entry 4); these findings suggest that spatial environment of the catalyst might play an important role in this reaction. Other common catalysts for carbene transfer reactions showed no to low activity under the reaction conditions (entry 5–7; see also Table S1). The product yield was subsequently improved to 88% by adding 10 equiv of CHD (entry 8).

Table 1. Optimization of reaction conditions.^[a]



[Ir(TTP)Me]: Ar = *p*-tolyl;
[Ir(TMP)Me]: Ar = mesityl;
[Ir(TDCPP)Me]: Ar = 2,6-Cl₂C₆H₃

[Ir(OEP)Me]

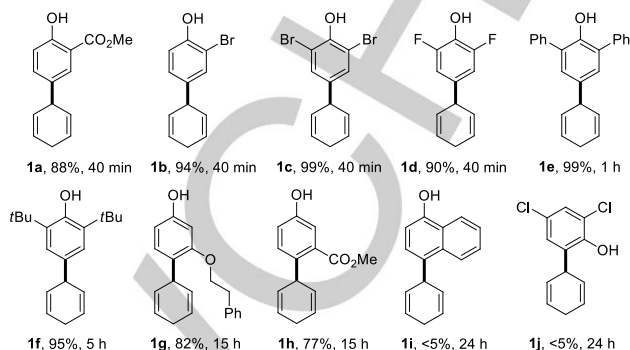
Entry	Catalyst	x (equiv of CHD)	Yield of 1a [%] ^[b]
1	[Ir(TTP)Me]	5	48
2	[Ir(TMP)Me]	5	14
3	[Ir(TDCPP)Me]	5	9
4	[Ir(OEP)Me]	5	62
5	[Rh ₂ (esp) ₂] ^[c]	5	5
6	[Cu(CH ₃ CN) ₄ (BF ₄)]	5	<1
7	[Co(TTP)]	5	<1
8	[Ir(OEP)Me]	10	88

[a] Reaction condition: quinone diazide (0.2 mmol), catalyst (0.004 mmol), CHD (*x* equiv), and 4 Å molecular sieves (M.S., 60 mg) in dichloromethane (DCM, 1 mL) at RT. [b] Yields were determined by ¹H NMR with PhTMS (phenyltrimethylsilane) as internal standard. [c] H₂esp = $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid.

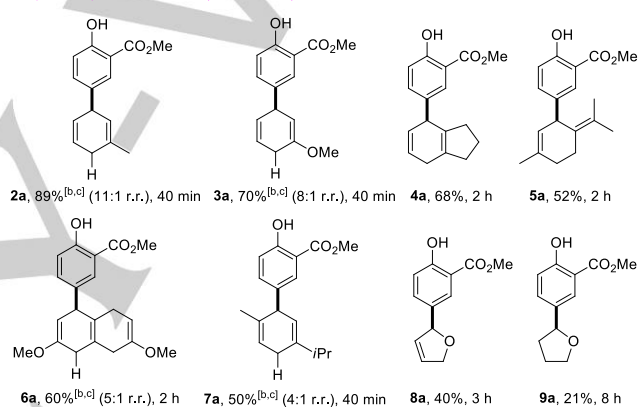
With the optimized catalyst and reaction conditions (condition A) in hand, we next investigated the substrate scope of this methodology. Various *p*-quinone diazides, including those with electron-withdrawing ester and halogen groups (**1a–d,h**) as well as electron-donating alkyl and alkoxy groups (**1f,g**), could be converted to the corresponding substituted phenol products in high to quantitative yields with CHD as substrate (Scheme 1). Steric encumbrance around the carbonyl oxygen atoms of the QC moieties (**1a–f**) showed minor influence on the reaction outcomes; on the other hand, installation of substituents *ortho* to the carbene carbon (**1g,h**) led to much longer reaction time and slightly decreased product yields. Arylation products derived from benzo-fused *p*-quinone diazide or *o*-quinone diazide could hardly be detected (**1i,j**).



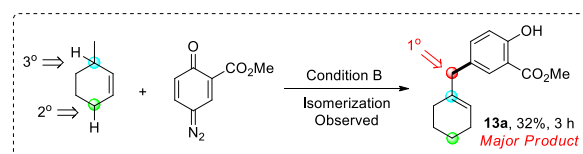
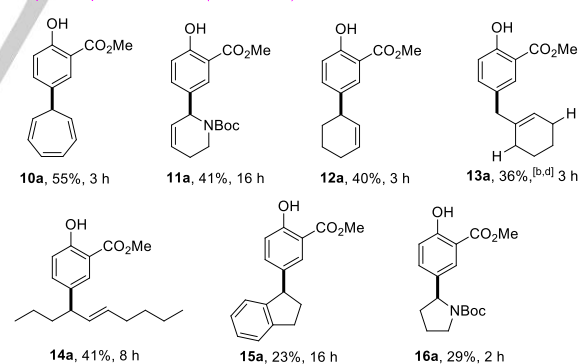
Scope of diazo compound (Condition A)



Scope of aliphatic substrate (Condition A)



Scope of aliphatic substrate (Condition B)

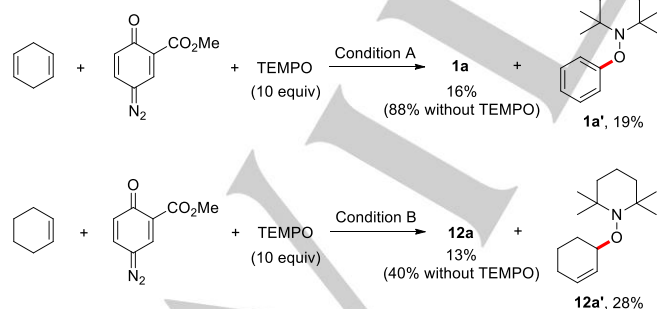


Scheme 1. Substrate scope. Isolated yields are reported. [a] Condition A: quinone diazide (0.2 mmol), [Ir(OEP)Me] (0.004 mmol), aliphatic substrate (2 mmol), and 4 Å M.S. (60 mg) in DCM (1 mL) at RT. Condition B: quinone diazide (0.2 mmol), [Ir(OEP)Me] (0.004 mmol), aliphatic substrate (1 mL), and 4 Å M.S. (60 mg) at 50 °C. [b] Major regioisomer is shown. [c] Overall yield of all regioisomers. Yields and regioselectivity were determined by ¹H NMR. [d] 1-Methylcyclohexene as substrate. Inset: Primary C(sp³)-H insertion product (**13a**) as major product with 3-methylcyclohexene as substrate.

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Scope of the aliphatic substrates was then studied. Arylation was readily achieved onto substituted CHDs, terpinolene, and 2,5-dihydrofuran, all of which contain doubly activated C(sp³)–H bonds (allylic and/or α to oxygen), with moderate to high product yields under condition A (Scheme 1, **2–8a**); less activated substrate such as tetrahydrofuran (THF) resulted in markedly lower yield (**9a**). Under a harsher condition (condition B), our methodology was further extended to substrates bearing C–H bonds that are allylic, benzylic, and/or α to nitrogen (**10–16a**), including those which could not be activated by Ru-QC species (e.g., cyclohexenes).^[4] Compared to the oxygen-containing heterocycles (**8–9a**), the nitrogen analogues (**11a**, **16a**) exhibited lower reactivity, which is likely due to the bulkiness of the *N*-Boc (Boc = *tert*-butyloxycarbonyl) groups. Except for indane (**15a**), QC transfer onto benzylic C–H bonds was unsuccessful, which is attributable to the steric hindrance exerted by the phenyl rings. The unactivated aliphatic hydrocarbons (*n*-hexane, cyclooctane) were not activated by the Ir-QC intermediate.

Steric effect was found to play an essential role in dictating the regioselectivity. Installation of a simple methyl or methoxy group α to the reactive methylene position of CHD could induce a relatively high regioselectivity ratio (r.r., 8:1 to 11:1) in the product mixture (**2–3a**, Scheme 1). For substituted cyclohexenes, the steric factor was found to override the stability order of alkyl radicals: (i) for 1-methylcyclohexene, primary C–H insertion reaction to give **13a** dominated over insertion into secondary C–H bonds (Scheme 1); (ii) for 3-methylcyclohexene, **13a** was again the major product with other regioisomers only detected in trace amount (inset of Scheme 1). We propose the HAT-initiated radical isomerization^[12] of 3-methylcyclohexene to 1-methylcyclohexene (Scheme S1) to follow a mechanism similar to that proposed by Norton and coworkers in related studies; the 1-methylcyclohexene then acts as a substrate for the Ir catalysis to afford **13a**, as has been investigated in Scheme 1. These findings infer that the radical rebound process is relatively slow and sterically demanding, which is accountable for the fact that less hindered porphyrin ligands and substrates generally gave better reaction outcomes (vide supra).

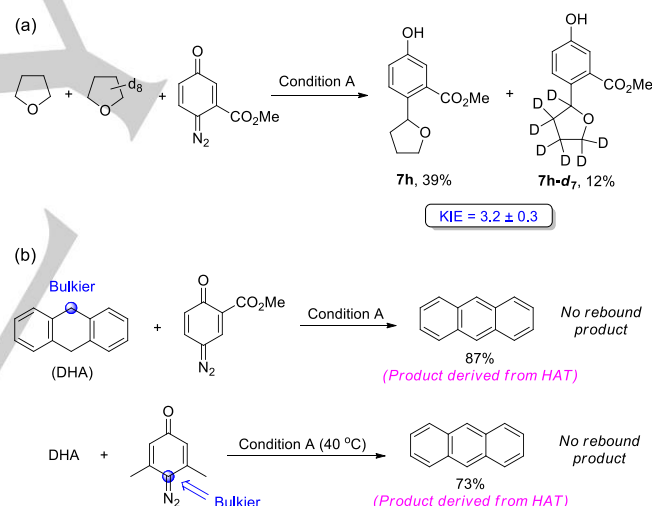


Scheme 2. Radical trapping experiments.

The proposed radical mechanism of this methodology is substantiated by trapping experiments (Scheme 2). With CHD (condition A) and cyclohexene (condition B) as substrates, addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) resulted

in markedly lower yields of **1a** and **12a**, together with the formation of TEMPO-trapped products **1a'** and **12a'**, respectively (**1a'** is likely derived from oxidation of the initially trapped product); this serves as a strong proof for the intermediacy of alkyl radical in the catalytic cycle. The low overall yields of C–H arylation product (**1a/12a**) and TEMPO-trapped product (**1a'/12a'**) are attributable to the formation of side products and some insoluble black precipitate (see the Supporting Information for details).

Further investigations were conducted on the HAT step (Scheme 3). A KIE (kinetic isotope effect) value of 3.2 ± 0.3 was obtained with THF/THF-*d*₈ as substrates (Scheme 3a). Although the quinoid oxygen atom of the Ir-QC intermediate is likely responsible for the HAT step,^[4] it has been suggested computationally that electrophilic carbene carbon might also mediate such a process.^[13] Steric control experiments were designed to address this issue (Scheme 3b): for 9,10-dihydroanthracene (DHA) substrate, HAT reactivity of Ir-QC maintained yet the rebound step was not observed; even by shielding the carbene carbon with two *ortho* substituents, the HAT reaction could still take place. These results indicate that changing the steric environment around the carbene carbon has little effect on the HAT step which is in disfavor of the HAT mechanism occurring at the carbene carbon.

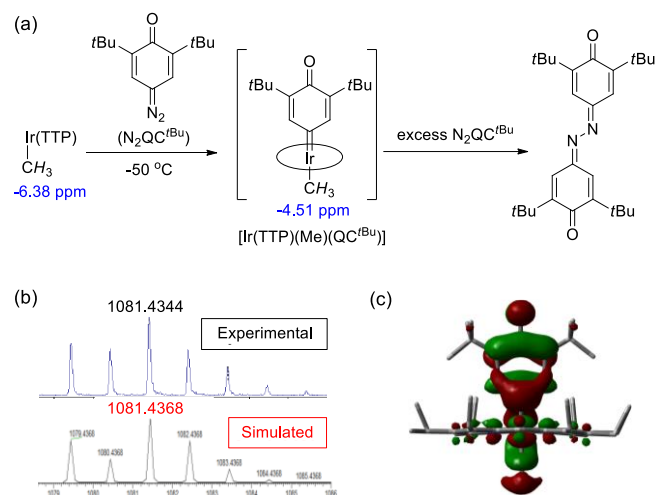


Scheme 3. Mechanistic studies on the HAT step. (a) Kinetic isotope effect. (b) Control experiments.

Detection of Ir-QC intermediate was subsequently carried out. Addition of N₂QC^{tBu} into a CDCl₃ solution of [Ir(TTP)Me] at –50 °C led to the formation of a new species with a downfield shift of Ir–CH₃ at –4.51 ppm (Scheme 4a and Figure S1), which is comparable to that observed for [Ir(TTP)(Me)(C(Ph)CO₂Me)] (–4.80 ppm)^[14] and is tentatively assigned to [Ir(TTP)(Me)(QC^{tBu})]; however, it could only be formed in ~10% yield, and further addition of diazo precursor caused its decomposition to the azine product (Scheme 4a).^[15] This intermediate was also detected by MALDI-HRMS (matrix-assisted laser desorption/ionization-high resolution mass spectrometry) in which both the experimental *m/z* values and isotopic pattern are consistent with its formulation

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(Scheme 4b). We envision that the HAT reactivity of the diamagnetic Ir-QC intermediate^[16] is similar to those of organic quinones^[17] and Ru-QC complexes.^[4] Density functional theory (DFT) calculations on $[\text{Ir}(\text{OEP})(\text{Me})(\text{QC}^{\text{tBu}})]$ revealed that its LUMO (lowest unoccupied molecular orbital) is mainly QC π^* in character (Scheme 4c), which is similar to Ru-QC complexes.^[4]



Scheme 4. Detection of Ir-QC intermediate $[\text{Ir}(\text{TTP})(\text{Me})(\text{QC}^{\text{tBu}})]$ by ^1H NMR (a) and MALDI-HRMS (b), and calculated QC^{tBu} π^* orbital (LUMO) for $[\text{Ir}(\text{OEP})(\text{Me})(\text{QC}^{\text{tBu}})]$ (c).

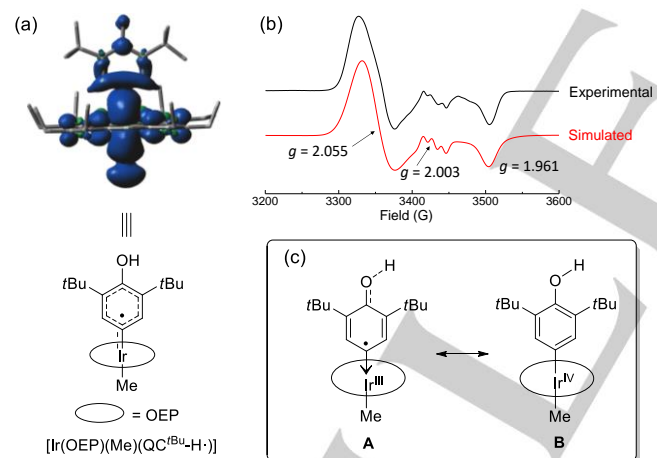
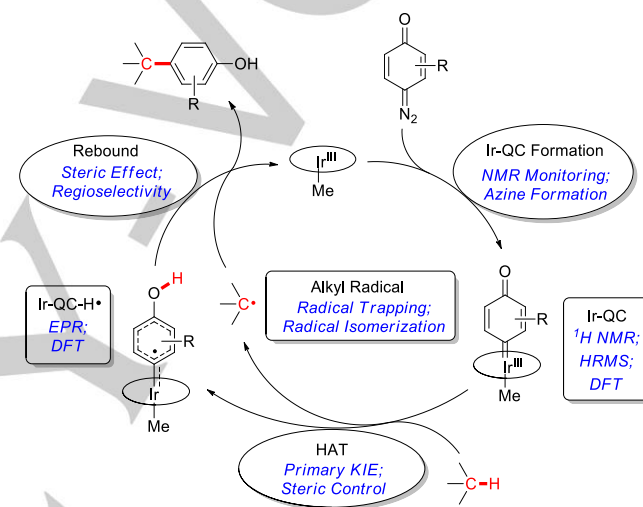


Figure 2. Calculated spin density (a) and EPR study (b) for Ir-QC-H intermediate $[\text{Ir}(\text{OEP})(\text{Me})(\text{QC}^{\text{tBu-H}})]$. In the EPR spectrum, signals at $g = 2.003$ are attributable to alkyl radical and/or ligand radical. (c) Proposed resonance forms (A and B) for Ir-QC-H intermediate.

We further performed DFT calculations on the Ir-QC-H intermediate $[\text{Ir}(\text{OEP})(\text{Me})(\text{QC}^{\text{tBu-H}})]$. The QC ligand was found to be more aromatized in the Ir-QC-H intermediate (Figure S4). The spin density is mainly distributed on the QC moiety (40%) and lesser on the Ir ion (20%, Figure 2a), which supports our proposal that an Ir(III) center could help preserve the radical character of the QC ligand (Scheme 5). For the QC moiety, the spin density

was calculated to be mainly localized around the carbene unit (75% out of the whole QC moiety), consistent with the reaction outcome that radical rebound takes place at the carbene carbon. X-band EPR (electron paramagnetic resonance) spectrum (100 K) of the reaction mixture containing $[\text{Ir}(\text{OEP})\text{Me}]$, $\text{N}_2\text{QC}^{\text{tBu}}$, and DHA revealed signals with $g_x = 2.055$ and $g_y = 1.961$ (Figure 2b). Although the EPR pattern and g_x , g_y values could be suggestive of an Ir(IV)^[18] formulation (B in Figure 2c),^[19] the EPR signals are much sharper (Figure S3) and the g_z value is significantly deviated from those obtained for the geometrically similar Ir(IV) salen complexes (g_x , $g_y = 2.10$ – 2.17 and $g_z = 1.51$ – 1.55).^[18c] We suggest that the proposed ligand-centered radical form (A in Figure 2c) to have significant contribution to the electronic structure of the Ir-QC-H intermediate.



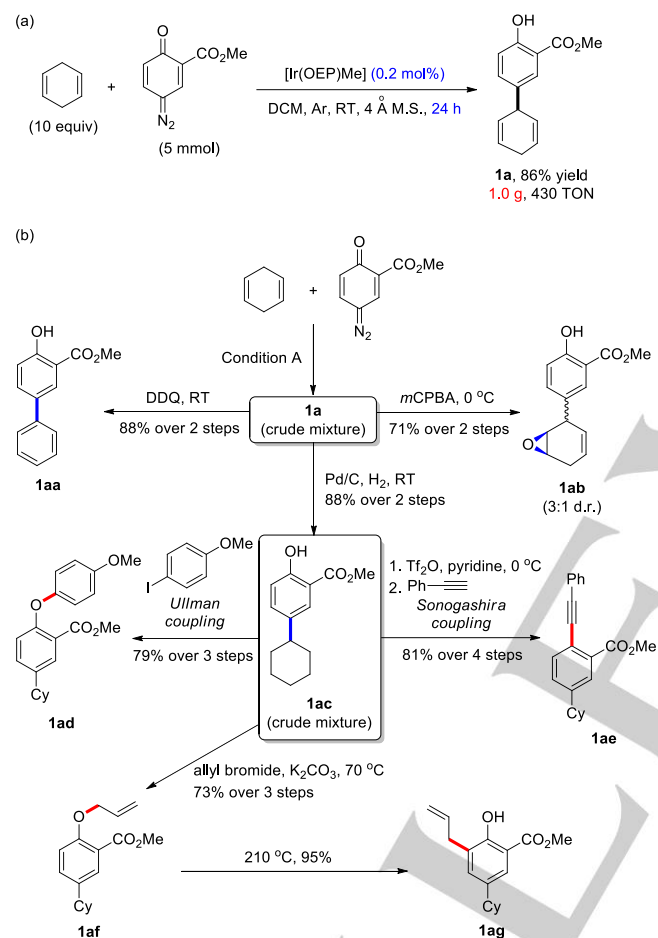
Scheme 5. Summary of mechanistic studies for the proposed catalytic cycle.

The catalytic reaction affording **1a** could be scaled up to 1.0 g with negligible influence on the product yield by using only 0.2 mol% of catalyst; a total turnover number (TON) of 430 could be calculated accordingly (Scheme 6a). These arylated 1,4-cyclohexadiene products, such as **1a**, could be readily functionalized to more complex and useful structures; the crude mixture of **1a** was directly subjected to the following reactions thanks to the high purity. The cyclohexadienyl moiety could be aromatized (**1aa**), epoxidized (**1ab**), and hydrogenated (**1ac**) in 71–88% overall yields starting from the quinone diazide (Scheme 6b). Functionalization of the phenol group could also be performed with **1ac** as a model substrate (also using its crude mixture). Ullman coupling and Sonogashira coupling to afford **1ad** and **1ae** were realized in 79 and 81% overall yields, respectively; alkylation to give **1af** and subsequent Claisen rearrangement to give **1ag** were also achieved in high yields.

Conclusion

In summary, we have developed a direct $\text{C}(\text{sp}^3)\text{-H}$ arylation protocol based on Ir(III) porphyrin-catalyzed quinoid carbene

(QC) insertion reaction. This method tolerates various substituents on the carbene precursors, affording functionalized phenol moieties anchored onto 1,4-cyclohexadienes; several other types of C(sp³)-H bonds (allylic, benzylic, and/or α to heteroatoms) can also be activated and arylated. This methodology is enabled by the HAT reactivity of metal-QC intermediate, which represents a rare example of radical mechanism in intermolecular carbene C-H insertion catalysis. Such a reaction pathway, together with the steric demand of porphyrin ligand, also gives rise to the unique regioselectivity of this reaction.



Scheme 6. (a) Gram-scale synthesis of **1a** and determination of TON. (b) Product transformation of **1a** using crude reaction mixture. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; mCPBA = 3-chloroperbenzoic acid; d.r. = diastereomeric ratio; Tf = triflate; Cy = cyclohexyl.

Acknowledgements

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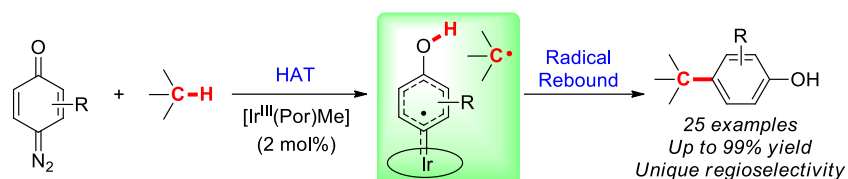
Keywords: carbenes • diazo compounds • homogeneous catalysis • iridium • radical reactions

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Direct intermolecular C(sp³)-H arylation is achieved by an Ir(III) porphyrin-catalyzed formal quinoid carbene (QC) insertion reaction through a stepwise radical mechanism. This reaction is enabled by the hydrogen atom transfer (HAT) reactivity of metal-QC intermediate, and the subsequent radical rebound step is facilitated by an electrophilic Ir(III) center that preserves the radical character of the QC ligand.

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Iridium(III)-Catalyzed Intermolecular C(sp³)-H Insertion Reaction of Quinoid Carbene through a Radical Mechanism