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Visible-Light-Induced Decarboxylative Iodination of Aromatic Carboxylic Acids

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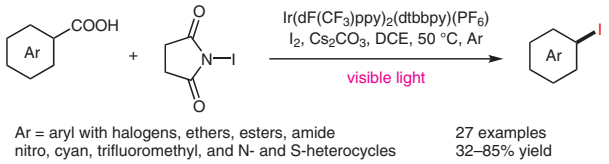

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Abstract A convenient, efficient and practical visible-light-induced decarboxylative iodination of aromatic carboxylic acids has been developed, and the corresponding aryl iodides were obtained in good yields. The method shows some advantages including the use of readily available aromatic carboxylic acids as the starting materials, simple and mild conditions, high efficiency, wide substrate scope and tolerance of various functional groups.

Key words visible-light, photoredox, aromatic carboxylic acids, decarboxylation, iodination

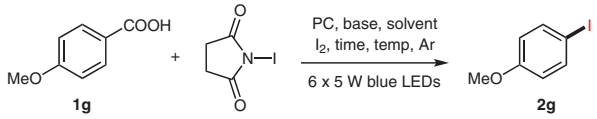
Aromatic compounds are ubiquitous in nature and organic chemicals, and their functions are highly dependent on the functional groups on the aromatic rings.[1] Therefore, functional group transformations on aromatic rings is a key and long-term theme in organic chemistry. In the past several decades, transition-metal-catalyzed transformations of aromatic halides have been powerful protocols in organic synthesis.[2] Aryl and heteroaryl iodides are important building blocks, and they show much higher reactivity than the corresponding bromides and chlorides in coupling reactions, particularly with respect to transition-metal-catalyzed formation of carbon–carbon and carbon–heteroatom bonds.[3] Besides high reactivity of aryl and heteroaryl iodides, they exhibit diverse biological and pharmaceutical activities. For example, they have been used in anticancer therapy,[4] X-ray contrast imaging,[5] and hypothyroidism and myxedema coma treatment.[6] Therefore, it is highly desirable to develop a convenient and efficient approach to aryl and heteroaryl iodides from inexpensive and abundant starting materials. It is well known that direct iodination of arenes with iodine via electrophilic substitution under common conditions is difficult because of the low reactivity of iodine.[7] In previous methods, the synthesis of aryl and heteroaryl iodides were performed by using the following procedures: (a) electrophilic aromatic substitution;[8] (b) directed *ortho*-metalation;[9] (c) use of directing groups;[10] (d) halogen exchange;[11] (e) formation of aryl diazonium salt intermediates.[12]

Aromatic carboxylic acids, which occur widely in natural products and common chemicals, are inexpensive and readily available compounds, so their decarboxylative transformation into aromatic halides is attractive. It is well known that the Hunsdiecker reaction with anhydrous silver carboxylates as substrates affords good reactivity for aliphatic carboxylic acids.[13] However, the range of suitable substrates is very limited for the decarboxylative halogenation of aromatic carboxylic acids.[14] Recently, great efforts have been made to realize this process, but some drawbacks including the use of stoichiometric transition-metal additives,[14,15] poor substrate scope, and/or poor selectivity[16] are unavoidable. For these reasons, a multi-step process from aromatic carboxylic acids to aryl halides is usually required.[17] Recently, Glorius and co-workers developed the visible-light-induced decarboxylative bromination, chlorination, and iodination of aliphatic carboxylic acids.[18] A breakthrough for the decarboxylative iodination of aromatic carboxylic acids with iodine in the presence of K_3PO_4 was reported by Larrosa and co-workers.[19] Unfortunately, low efficiency for aromatic carboxylic acids containing electron-withdrawing groups and the requirement for high temperature for some substrates hampers wide application of this method. Recently, visible-light photoredox catalysis has become a powerful protocol in organic synthesis, and some novel and interesting reactions have been devel-

oped.[20] Very recently, Glorius and co-workers reported decarboxylation of aryl carboxylic acids to provide aryl radicals under mild conditions (55 °C) in the presence of dimethyl 2-bromo-2-methylmalonate as the oxidant, and the reaction was proposed to proceed via benzoyl hypobromite intermediates.[21] As part of our continuing research on visible-light photoredox organic reactions,[22] we report herein a convenient and efficient visible-light-induced decarboxylative iodination of aromatic carboxylic acids that proceeds under mild conditions.

At first, the visible-light-induced decarboxylative iodination of 4-methoxybenzoic acid (**1g**) with *N*-iodosuccinimide (NIS) leading to 1-iodo-4-methoxybenzene (**2g**) was used as the model to optimize the photocatalytic conditions. As shown in Table 1, four Ru and Ir photocatalysts, $[Ru(bpy)_3]Cl_2$ (**A**), [*fac*-Ir(ppy)$_3$] (**B**), $Ir(ppy)_2(dtbbpy)(PF_6)$ (**C**), and $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (**D**), were tested using 5 mol% iodine as additive, Cs_2CO_3 as base and 1,2-dichloroethane (DCE) as solvent under Ar atmosphere and irradiation with six 5 W blue LEDs (λ_{max} = 455 nm) at 50 °C for 24 h (entries 1–4); $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (**D**) gave the highest yield (entry 4), and no product was observed in the absence of photocatalyst (entry 5). Next, four other bases, K_2CO_3, Na_2CO_3, Li_2CO_3, and K_3PO_4, were screened, and Cs_2CO_3 was found to be an optimal base (compare entries 4, 6–9). No iodination occurred in the absence of base (entry 10). Subsequently, other solvents including CCl_4, MeCN, dioxane, and DMF were attempted, and they were inferior to DCE (compare entries 4, 11–14). When the reaction was carried out at 25 or 70 °C, lower yields were afforded (entries 15 and 16). The yield decreased when the amount of iodine as the additive was reduced from 5 to 2 mol% (entry 17), and a similar yield to that in entry 4 was obtained with 10 mol% iodine (compare entries 4 and 18). A 27% yield was obtained in the absence of I_2 (entry 19). The yield decreased when the amount of NIS was changed to 2 equivalents from 3 equivalents (entry 20). Use of 4 equiv of NIS provided a similar yield to that in entry 4 (compare entries 4 and 21). The results above showed that use of 3 equiv of NIS was a good choice. Only a small amount of target product was observed with 1.5 equiv of I_2 in the absence of NIS (entry 22). Shortening of the reaction time from 24 h to 12 h led to a decline of yield (entry 23), and the same yield as that in entry 4 was provided when the reaction time was extended from 24 h to 36 h (compare entries 4 and 24). The reaction did not work without irradiation with visible light (entry 25) or under air (entry 26). In addition, we used *N*-bromosuccinimide (NBS) (3.0 equiv) and Br_2 (20%) instead of NIS and I_2, and 4-boromoanisole was obtained in 13% yield.

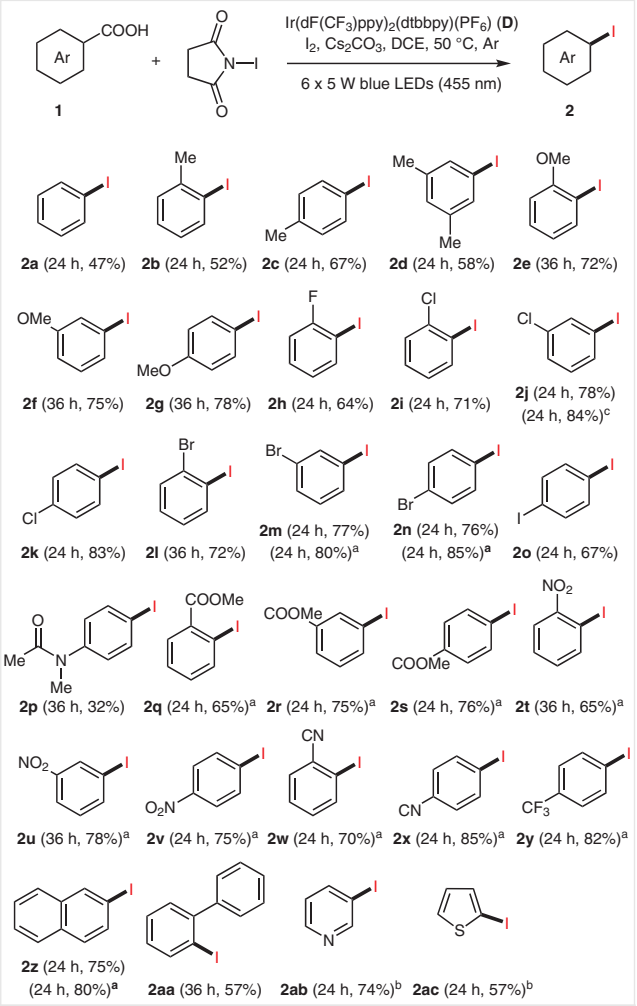
Table 1 Optimization of Conditions for Visible-Light-Induced Decarboxylative Iodination of 4-Methoxybenzoic Acid (**1g**) Leading to 1-Iodo-4-methoxybenzene (**2g**)



PC = $[Ru(bpy)_3]Cl_2$ (**A**) $Ir(ppy)_2(dtbbpy)(PF_6)$ (**C**)
[*fac*-Ir(ppy)$_3$] (**B**) $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (**D**)

Entry	PC	Base	Solvent	Temp (°C)	Yield (%)[b]
1	**A**	Cs_2CO_3	DCE	50	NR
2	**B**	Cs_2CO_3	DCE	50	NR
3	**C**	Cs_2CO_3	DCE	50	41
4	**D**	Cs_2CO_3	DCE	50	78
5	–	Cs_2CO_3	DCE	50	NR
6	**D**	K_2CO_3	DCE	50	trace
7	**D**	Na_2CO_3	DCE	50	trace
8	**D**	Li_2CO_3	DCE	50	trace
9	**D**	K_3PO_4	DCE	50	43
10	**D**	–	DCE	50	NR
11	**D**	Cs_2CO_3	CCl_4	50	44
12	**D**	Cs_2CO_3	MeCN	50	27
13	**D**	Cs_2CO_3	dioxane	50	NR
14	**D**	Cs_2CO_3	DMF	50	NR
15	**D**	Cs_2CO_3	DCE	25	9
16	**D**	Cs_2CO_3	DCE	70	54
17[c]	**D**	Cs_2CO_3	DCE	50	46
18[d]	**D**	Cs_2CO_3	DCE	50	79
19[e]	**D**	Cs_2CO_3	DCE	50	27
20[f]	**D**	Cs_2CO_3	DCE	50	64
21[g]	**D**	Cs_2CO_3	DCE	50	77
22[h]	**D**	Cs_2CO_3	DCE	50	8
23[i]	**D**	Cs_2CO_3	DCE	50	52
24[j]	**D**	Cs_2CO_3	DCE	50	78
25[k]	**D**	Cs_2CO_3	DCE	50	NR
26[l]	**D**	Cs_2CO_3	DCE	50	NR

[a] *Reagents and conditions*: argon atmosphere and irradiation with six 5 W blue LEDs (λ_{max} = 455 nm), 4-methoxybenzoic acid (**1f**) (0.3 mmol), *N*-iodosuccinimide (NIS) (0.9 mmol), photocatalyst (PC) (6 μmol), base (0.6 mmol), solvent (3 mL), I_2 (15 μmol, 5 mol%), temperature (25–70 °C), time (24 h) in a 25-mL sealed glass tube. PC = photocatalyst. DCE = 1,2-dichloroethane. NR = no reaction.
[b] Isolated yield.
[c] I_2 (0.6 μmol, 2 mol%).
[d] I_2 (3.0 μmol, 10 mol%).
[e] In the absence of I_2.
[f] 2 equiv of NIS was used.
[g] 4 equiv of NIS was used.
[h] 1.5 equiv of I_2 was used without NIS.
[i] Time: 12 h.
[j] Time: 36 h.
[k] No light.
[l] Under air.



Scheme 1 Substrate scope for visible-light-induced decarboxylative iodination of aromatic carboxylic acids (**1**). *Reagents and conditions*: Argon atmosphere and irradiation with six 5 W blue LEDs (λ_{max} = 455 nm), aromatic carboxylic acid (**1**) (0.3 mmol), *N*-iodosuccinimide (NIS) (0.9 mmol), Ir(dF(CF_3)ppy)$_2$(dtbbpy)(PF_6) (**D**) (6 μmol), Cs_2CO_3 (0.6 mmol), DCE (3 mL), I_2 (15 μmol, 5 mol%), temperature (50 °C), 24 or 36 h in a 25-mL sealed glass tube. Isolated yield. [a] *N*-Iodosuccinimide (NIS) (1.5 mmol), I_2 (60 μmol, 20 mol%). [b] *N*-Iodosuccinimide (NIS) (1.5 mmol), I_2 (60 μmol, 20 mol%), and CH_3CN (3 mL) replaced DCE as the solvent.

After developing the optimal photocatalytic conditions, the substrate scope of the reaction with respect to aromatic carboxylic acids was investigated (Scheme 1). First, benzoic acids containing electron-donating groups, including methyl and methoxy groups were tested, and the corresponding iodinated products were obtained in moderate to good yields (see **2a–g**); the methoxybenzoic acids gave higher yields than the corresponding methylbenzoic acids, and *p*-methoxybenzoic acid showed higher reactivity than *o*-, *m*-methoxybenzoic acids, but a longer time was required. When benzoic acids containing weak electron-withdrawing groups, including F, Cl, Br and I, were used as the substrates, their reactivity was satisfactory (see **2h–o**). We attempted to increase amounts of NIS and I_2, and the corresponding yields were promoted (see **2j**, **2m** and **2n**). Unfortunately, 4-(*N*-methylacetamido)benzoic acid was not a good substrate (see **2p**). Next, benzoic acids containing strong electron-withdrawing groups, including ester, nitro, cyano, and trifluoromethyl, were surveyed, and their reactivity remained robust (see **2q–y**). However, substrates containing strong electron-withdrawing groups exhibited weak reactivity in Larrosa's protocol,[19] so our method is a valuable supplement for the iodination of aromatic carboxylic acids. 2-Naphthoic acid was a good substrate (see **2z**), and iodination of 2-biphenylcarboxylic acid afforded the corresponding product in 57% yield (see **2aa**). Two heteroaryl carboxylic acids, nicotinic acid and 2-thienylcarboxylic acid, were also effective substrates when the solvent was changed to MeCN from DCE (see **2ab** and **2ac**). The present method can tolerate a number of functional groups, including C–F, C–Cl, C–Br and C–I bonds, ether, ester, nitro, cyan and trifluoromethyl groups, as well as *N*- and *S*-heterocycles.

To reveal the mechanism of the visible-light-induced decarboxylative iodination of aromatic carboxylic acids, Stern–Volmer fluorescence quenching experiments were performed. As shown in Figure 1A, 484 nm fluorescence induced by photocatalyst Ir(dF(CF_3)ppy)$_2$(dtbbpy)(PF_6) (**D**) in DCE was observed when it was excited at 435 nm, and the fluorescence intensity dramatically decreased when the cesium salt of 4-methoxybenzonic acid (**1g**) was added in the presence of tetrabutylammonium iodide. The addition of NIS with different concentrations did not cause a change of the fluorescence emission spectra in the absence of the cesium salt of 4-methoxybenzoic acid (**1g**) in DCE (see Figure 1B) (see Supporting Information for details). The results above indicate that a single-electron transfer occurred from 4-methoxybenzoic acid cesium salt to photocatalyst Ir(dF(CF_3)ppy)$_2$(dtbbpy)(PF_6) (**D**), which is coincident with the result reported by Glorius and co-workers.[21,23]

Next, two radical trapping experiments were performed under the standard conditions. As shown in Scheme 2A, reaction of 2-benzoylbenzoic acid (**1ad**) with NIS provided an iodinated product, (2-iodophenyl)(phenyl)methanone (**2ad**), and a cyclic product, 9*H*-fluoren-9-one (**3**), in 34% and 41% yields, respectively. The result showed the occurrence of an aromatic radical during the reaction. When 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) as a radical trapping agent was added to the reaction system of **1g** and NIS, only a trace amount of **2g** was observed (Scheme 2B), which also indicated the occurrence of a radical process. When benzoyl hypoiodite (**5**) from reaction of 4-methoxyl benzonic acid and *t*-butyl hypoiodite (**4**) was used as the substrate under the standard conditions, product **2g** was obtained in 47% yield (Scheme 2C). The result showed that the reaction in Scheme 1 could involve benzoyl hypoiodite intermediates.

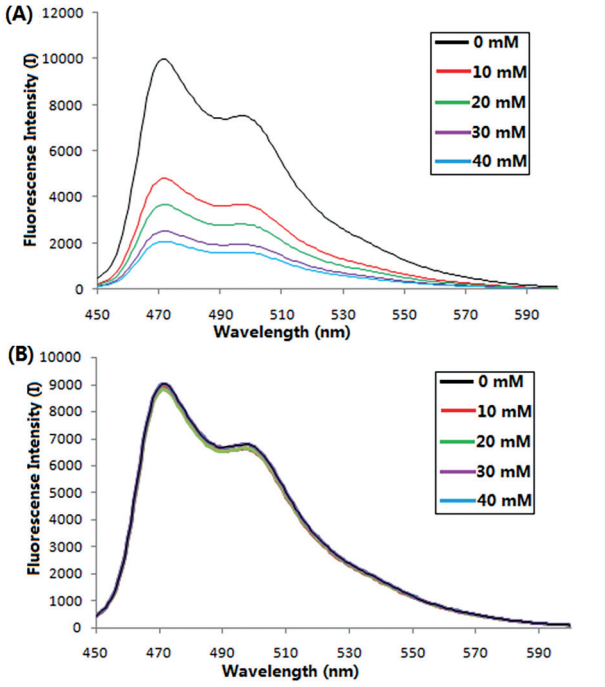
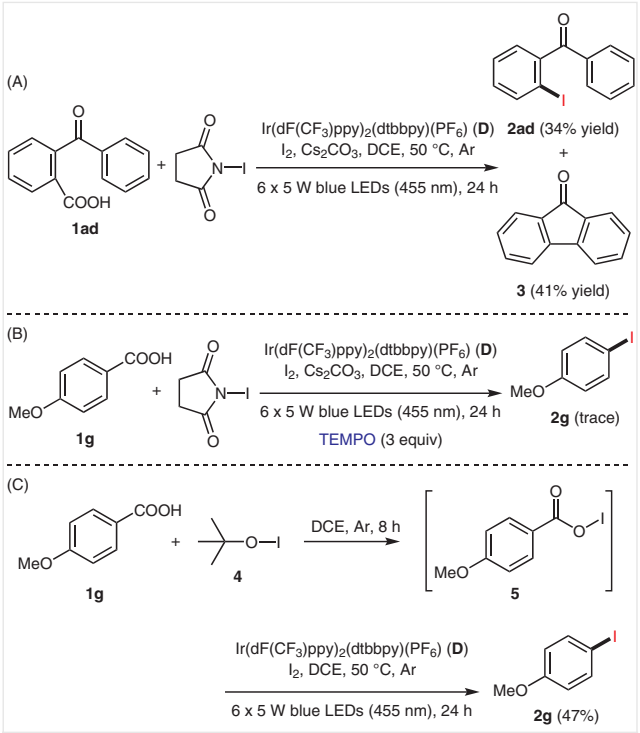
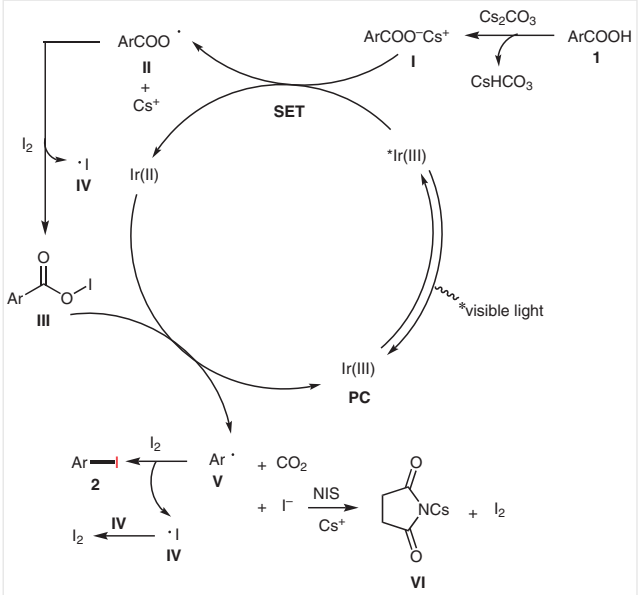


Figure 1 (A) The fluorescence emission spectra of $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (**D**) (4 mM) with different concentrations of 4-methoxybenzoic acid cesium salt excited at 435 nm in DCE. (B) The fluorescence emission spectra of $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (**D**) (4 mM) with different concentrations of NIS excited at 435 nm in the absence of 4-methoxybenzoic acid cesium salt in DCE.



Scheme 2 Radical trapping experiments under the standard conditions: (A) Decarboxylative reaction 2-benzoylbenzoic acid (**1ad**). (B) Treatment of 4-methoxybenzonic acid (**1g**) with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). (C) Reaction of benzoyl hypoiodite.



Scheme 3 A possible mechanism for the visible-light-induced decarboxylative iodination of aromatic carboxylic acids

According to the results above, and the experiments on variation of reactant and product with time and the electron paramagnetic resonance (EPR) studies (see Figures S4 and S5 in Supporting Information), a possible mechanism for the visible-light-induced decarboxylative iodination of aromatic carboxylic acids is proposed in Scheme 3. First, treatment of aromatic carboxylic acid **1** with Cs_2CO_3 leads to the corresponding cesium salt **I**. Ir(III) photocatalyst transforms into its excited state *Ir(III) under irradiation of visible light, and reduction of *Ir(III) by **I** through a single-electron transfer (SET) provides Ir(II) and radical **II** (see Figure S5-b in the Supporting Information). Reaction of radical **II** with iodine gives benzoyl hypoiodite **III** and iodine radical **IV**. Reduction by Ir(II) and decarboxylation of benzoyl hypoiodite **III** affords aromatic radical **V** and I^-,[21] and treatment of **V** with I_2 yields the target product **2**, leaving iodine radical **IV**. Meanwhile, reaction of I^- with NIS in the presence of Cs^+ provides I_2 and **VI**, and the complex of iodine radical **IV** also gives I_2.

In summary, we have developed a convenient, efficient and practical visible-light-induced decarboxylative iodination of aromatic carboxylic acids. The corresponding aryl iodides were obtained in good yields.[24] Especially, aromatic

carboxylic acids containing strong electron-withdrawing groups were also good substrates in the decarboxylative iodination. The present method shows some advantages including readily available starting materials, simple and mild conditions, high efficiency, wide substrate scope, and tolerance of various functional groups. We believe that the method will find wide application in the functional group transformation of aromatic compounds.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610188.

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(24) **General procedures for the iodination of aromatic carboxylic acidsGeneral procedure A:** To a 15 mL test tube with septum, Cs_2CO_3 (0.6 mmol, 195 mg), aromatic carboxylic acid (**1**; 0.3 mmol), [Ir(dF(CF$_3$)ppy)$_2$dtbbpy]PF$_6$ (**D**; 6 μmmol, 6.7 mg), *N*-iodosuccinimide (NIS; 0.9 mmol, 202.5 mg), and I_2 (15 μmol, 5 mol%) were added. The tube was evacuated and backfilled with argon three times, and then 3 mL of anhydrous 1,2-dichloroethane (DCE) was added through a syringe under argon. The tube was sealed with Parafilm M® and placed in an oil bath with a contact thermometer, and the reaction was carried out at 50 °C under irradiation with 6 × 5 W blue LEDs (λ_{max} = 455 nm). After 24 or 36 h, the resulting mixture was filtered through a 2 cm thick pad of silica, and the silica was washed with dichloromethane (50 mL). The filtrate was collected and the solvent was removed in vacuo. The crude residue was purified by silica gel flash column chromatography to provide the target product **2** (Note: The reaction was very sensitive to moisture, and the yields sharply decreased to less than 5% when 0.01 equivalent of H_2O was added to the reaction system).

General procedure B: To a 15 mL test tube with septum, Cs_2CO_3 (0.6 mmol, 195 mg), aromatic carboxylic acid (**1**; 0.3 mmol), [Ir(dF(CF$_3$)ppy)$_2$dtbbpy]PF$_6$ (**D**; 6 μmol, 6.7 mg), NIS (1.5 mmol, 337.5 mg) and I_2 (60 μmol, 20 mol%) were added. The tube was evacuated and backfilled with argon three times, and then 3 mL of anhydrous DCE was added through a syringe under argon. The tube was sealed with Parafilm M® and placed in an oil bath with a contact thermometer, and the reaction was carried out at 50 °C under irradiation with 6 × 5 W blue LEDs (λ_{max} = 455 nm). After 24 h or 36 h, the resulting mixture was filtered through a 2 cm thick pad of silica, and the silica was washed with CH_2Cl_2 (50 mL). The filtrate was collected and the solvent was removed in vacuo. The crude residue was purified by silica gel flash column chromatography to provide the target product **2** (Note: The reaction was very sensitive to moisture, and the yields sharply decreased to less than 5% when 0.01 equivalent of H_2O was added to the reaction system).

General procedure C: To a 15 mL test tube with septum, Cs_2CO_3 (0.6 mmol, 195 mg), aromatic carboxylic acid (**1**; 0.3 mmol), [Ir(dF(CF$_3$)ppy)$_2$dtbbpy]PF$_6$ (**D**; 6 μmol, 6.7 mg), NIS (1.5 mmol, 337.5 mg) and I_2 (60 μmol, 20 mol%) were added. The tube was evacuated and backfilled with argon for times, and then 3 mL of anhydrous CH_3CN was added through a syringe under argon. The tube was sealed with Parafilm M® and placed in an oil bath with a contact thermometer, and the reaction was carried out at 50 °C under irradiation with 6 × 5 W blue LEDs (λ_{max} = 455 nm). After 24 h, the resulting mixture was filtered through a 2 cm thick pad of silica, and the silica was washed with CH_2Cl_2 (50 mL). The filtrate was collected and the solvent was removed in vacuo. The crude residue was purified by silica gel flash column chromatography to provide the target product **2** (Note: The reaction was very sensitive to moisture, and the yields sharply decreased to less than 5% when 0.01 equivalent of H_2O was added to the reaction system).Three representative examples are shown as follows:

1-Iodo-3-methoxybenzene (**2f**)[25]

Eluent: pentane/diethyl ether 50:1, the solvent was removed under reduced pressure. Yield: 52.7 mg (75%) by following general procedure A. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29 (d, *J* = 8.24 Hz, 1 H), 7.26 (s, 1 H), 7.0 (t, *J* = 8.24 Hz, 1 H), 6.87 (d, *J* = 8.70 Hz, 1 H), 3.78 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.2, 130.9, 129.9, 123.1, 113.8, 94.5, 55.5. EI-MS: M^+ *m*/*z* 234.

Methyl 4-iodobenzoate (**2s**)[25]

Eluent: pentane/diethyl ether 50:1, the solvent was removed under reduced pressure. Yield: 59.7 mg (76%) by following general procedure B. White solid; mp 113–115 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, *J* = 8.24 Hz, 2 H), 7.64 (d, *J* = 8.24 Hz, 2 H), 3.95 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.0, 137.2, 130.6, 129.2, 100.4, 52.2. EI-MS: *m*/*z* = 262 [M^+].

3-Iodopyridine (**2ab**)[26]

Eluent: pentane/diethyl ether 5:1, the solvent was removed at 0 °C under reduced pressure. Yield: 45.5 mg (65%) by following general procedure C. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.86 (s, 1 H), 8.79 (d, *J* = 5.04 Hz, 1 H), 7.94 (d, *J* = 8.24 Hz, 1 H), 7.42 (t, *J* = 6.87 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.7, 144.3, 139.6, 130.2, 129.4, 128.9, 128.2, 120.1, 127.7, 98.8. EI-MS: *m*/*z* = 205 [M^+]

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