Spirocyclizative Remote Arylcarboxylation of Non-Activated Arenes with CO_2 *via* Visible-Light-Induced Reductive Dearomatization

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Abstract

Visible-light-induced reductive dearomatization of non-activated arenes is a very challenging transformation and remains in its infancy. Herein, we report a novel strategy to achieve a visible-light-induced spirocyclizative remote arylcarboxylation of non-activated arenes including naphthalenyl- and phenyl-bearing aromatics with CO_2 under mild conditions through a radical-polar crossover cascade (RPCC). This reductive dearomatization protocol rapidly delivers a broad range of spirocyclic and valuable carboxylic acid derivatives from readily accessible aromatic precursors with generally good regioselectivity and chemoselectivity.

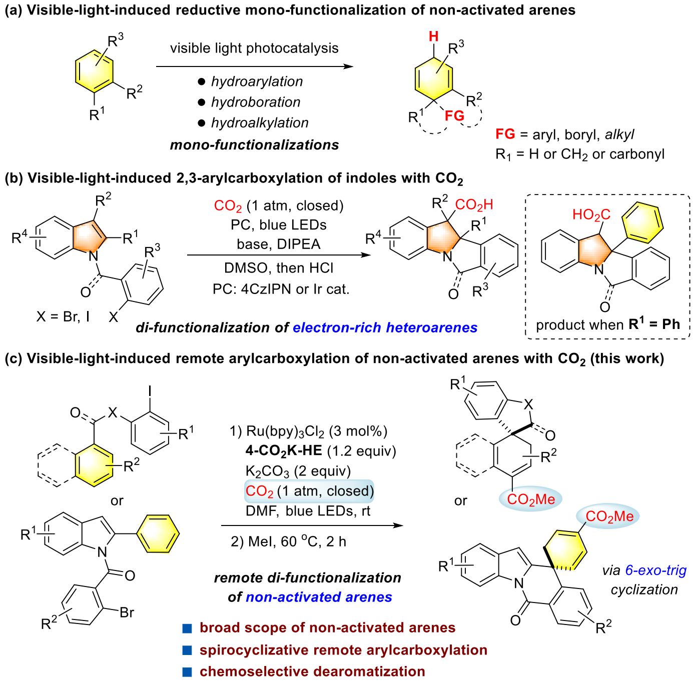
Keywords

carbon dioxide utilization, non-activated arene, dearomatization, photocatalysis, spirocyclization

Introduction

Dearomatization represents a unique synthetic strategy that converts readily available planar arenes into valuable three-dimensional alicyclic molecules.[1-6] Notable methods include the Birch reduction,[7] transition-metal-catalyzed dearomative functionalization,[8,9] oxidative dearomatization of electron-rich (hetero)aromatics,[10] and UV-light promoted photochemical cycloadditions.[11] However, the progress was mainly made in the studies of heteroaromatics such as indoles, and electron-rich arenes such as phenols and naphthols.[1-24] In contrast, only limited important advances have been made in the dearomatization of electronically unbiased aromatics such as naphthalene and benzene derivatives that possess high resonance stabilization energy.[6,25-34] Of particular note, the You group recently reported an elegant highly diastereoselective 1,4-difunctionalization of 1-naphthamides *via* Palladium-catalyzed dearomatization at slightly elevated temperature.[25] Therefore, the dearomatization of non-activated arenes remains challenging, and the development of a mild and complementary protocol for dearomatization of non-activated arenes is highly desirable.

In recent years, visible-light photoredox catalysis[35-44] has emerged as a promising strategy for developing mild protocols for dearomatization,[45-58] including several significant protocols for the dearomatization of non-activated arenes,[59-73] such as dearomative cycloadditions mainly from the groups of Sarlah and Bach,[59-62] and oxidative dearomatization.[63-65] A distinct redox-neutral hydroalkylative dearomatization of naphthalene derivatives was also reported by the group of Zhang, Mei and You.[66] However, there are only a handful of reports on visible-light-induced reductive dearomatization of non-activated arenes.[67-73] Of particular note, the groups of König[67] and Miyake[68] independently reported the challenging photoredox catalyst (PC) promoted Birch-type reduction of arenes. Meanwhile, dearomative mono-functionalizations of arenes including hydroalkylation[69-71] and hydroboration[72] through photoreduction were disclosed by the groups of such as Stephenson,[69] Murakami,[70] and Curran,[72] respectively (Scheme 1a). Notably, the Jui group achieved the only visible-light-induced reductive spirocyclizative hydroarylation of arenes via radical-polar crossover using an amine reductant (Scheme 1a),[73] avoiding the use of toxic reagents such as SmI_2/HMPA (hexamethylphosphoramide)[74] in similar traditional transformations. Despite these significant progresses, di-functionalization of non-activated arenes through visible-light-induced reductive dearomatization remains challenging possibly due to competing protonation and re-aromatization.



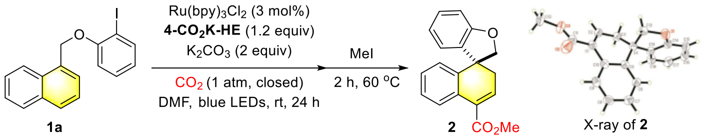
Scheme 1 *Visible-light-induced reductive dearomatization of non-activated arenes.*

More recently, our group reported the reductive arylcarboxylation of styrenes with CO_2 via a radical-polar crossover cascade (RPCC), which was initiated by highly reactive aryl radicals that were generated from the reduction of readily available aryl halides.[75] We wondered whether this RPCC process[75-89] could be applied for dearomative di-functionalization of non-activated arenes with CO_2. Notably, during our investigation, the Yu group reported the 2,3-arylcarboxylation of indoles, a class of well-studied electron-rich heteroarene in dearomatization reactions, *via* 5-exo-trig cyclization (Scheme 1b).[90] Surprisingly, a chemoselective dearomatization of non-activated phenyl ring *via* 6-exo-trig cyclization occurred with 2-phenyl indoles substates under our reaction conditions, leading to products that were distinct from those of Yu's work (Scheme 1c). In line with our continuous interest in catalytic utilization of CO_2,[91,92] which is an abundant, low-cost, sustainable and nontoxic C1 building block, herein, we report a spirocyclizative remote arylcarboxylation of arenes with CO_2 by visible-light-induced reductive dearomatization of aromatics bearing naphthalenyl, phenyl, and quinolinyl groups via RPCC, providing a rapid access to valuable complex three-dimensional frameworks (Scheme 1c). Notably, a novel type of Hantzsch ester reaductant, i.e., 4-potassium carboxylate HE (4-CO_2K-HE), was discovered during our study.

Results and Discussion

To start our investigation, naphthalene derivative **1a** (Table 1) was employed as the model substrate, which was irradiated under 30 W blue LEDs in the presence of a commercially available PC $Ru(bpy)_3Cl_2$ and an atmospheric pressure of CO_2 at ambient temperature. After extensive investigation of the reaction conditions, the spirocyclic 1,4-arylcarboxylation product **2**, which was the methylated product from original carboxylic acid due to its ease of isolation, was obtained in a 83% isolated yield by employing a novel 4-CO_2K-HE reductant[93-95] and K_2CO_3 as the base in DMF (entry 1). The structure of **2** was confirmed by X-ray analysis, representing a formal remote C–H carboxylation with CO_2.[96-98] Control reactions revealed that no product was detected in the absence of either a PC or light, indicating the reaction was induced by light (entries 2 and 3). A significant decrease in the yield was observed when the reaction was carried out under nitrogen atmosphere (entry 4), suggesting that some CO_2 could be produced from the oxidation of 4-CO_2K-HE. Notably, not any product was detected without adding the reductant 4-CO_2K-HE (entry 5), which acted much better than other reductants such as HEH and DIPEA, revealing the critical role of 4-CO_2K-HE for the reaction (entries 6 and 7). Of note, no desired product could be received using HCO_2K, which was in contrast to our previous reductive arylcarboxylation of styrenes with CO_2 (entry 8). The yield decreased dramatically when the reaction was carried out in the absence of K_2CO_3 (entry 9). After screening other PCs such as 4CzIPN (2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile) and iridium complexes, $Ru(bpy)_3Cl_2$ proved to be the most suitable one (entries 10-12). Slight decrease in the yield was observed when the loading of PC was reduced to 2 mol% (entry 13). Moreover, solvents were also evaluated, and DMF was found to be the best out of a variety of solvents such as DMSO, DMA, and CH_3CN (entries 14-16). Finally, no desired product was obtained when the bromide analog of **1a** was employed and most of the starting material was recovered (entry 17).

Table 1 *Optimization of the Reaction Conditions*[a]



Entry	Deviation from standard conditions	yield (%)[b]
1	none	87 (83)[c]
2	without $Ru(bpy)_3Cl_2$	N.D.
3	in the dark	N.D.
4	under a nitrogen atmosphere	37
5	without 4-CO_2K-HE	N.D.
6	HEH (2.0 equiv) as reductant	61
7	DIPEA (2.0 equiv) as reductant	18
8	HCO_2K (2.0 equiv) as reductant	ND
9	without K_2CO_3	41
10	4CzIPN as PC	45
11	$[Ir(ppy)_2(dtbbpy)]PF_6$ as PC	N.D.
12	*fac*-$Ir(bpy)_3$ as PC	N.D.
13	$Ru(bpy)_3Cl_2$ (2 mol%)	73
14	DMSO instead of DMF	60
15	DMA instead of DMF	74
16	CH_3CN instead of DMF	N.D.
17	Br instead of I in **1a**	N.D.

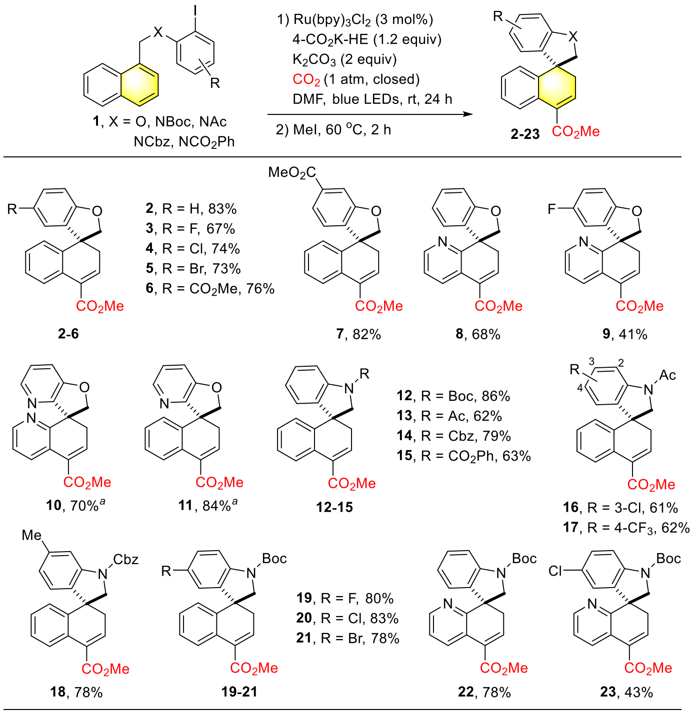
[a] Reaction conditions: **1a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (3 mol%), 4-CO_2K-HE (0.12 mmol, 1.2 equiv), K_2CO_3 (0.2 mmol, 2.0 equiv), DMF (1 mL), 1 atm CO_2, 30 W blue LEDs, rt, 24 h; then MeI (0.5 mmol), 60 °C, 2 h.

[b] Yield was determined by ^{1}H NMR with CH_2Br_2 as internal standard.

[c] Yield of isolated product in parentheses on 0.2 mmol scale.

N.D. = desired product not detected. 4-CO_2K-HE: potassium 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridine-4-carboxylate (4-potassium carboxylate HEH); HEH: Hantzsch ester; bpy: 2,2'-bipyridine; ppy: 2-phenylpyridine; dtbbpy: 4,4-di-*tert*-butyl-2,2'-bipyridine.

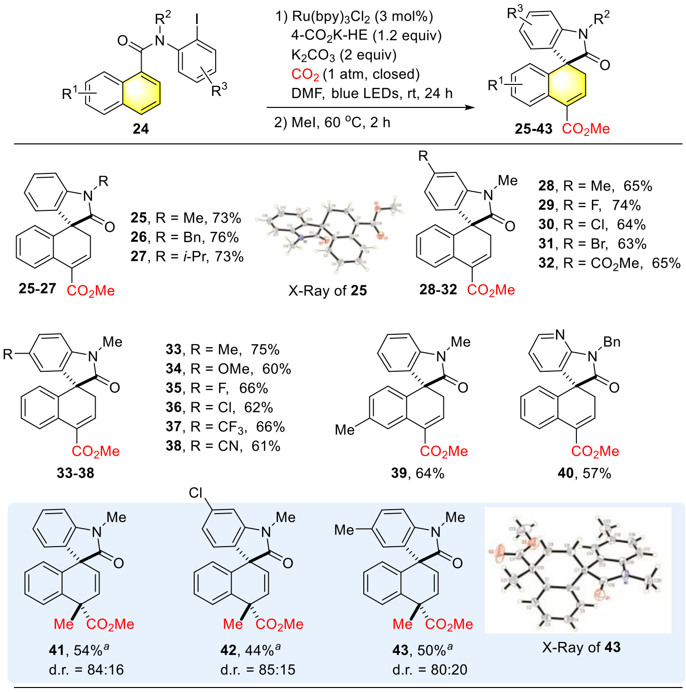
The optimized reaction conditions for **1a** were then tested with a series of naphthalene and quinoline derivatives to investigate the generality of this spirocyclizative arylcarboxylation. As shown in Scheme 2, naphthalene derivatives with a phenol ether linker bearing various functional groups, such as halide (F, Cl and Br) and CO_2Me, afforded the corresponding dearomatized products in good yields (**2**-**7**). Substrates possessing a quinolinyl or/and pyridyl group were also compatible with the protocol to produce structurally diverse heterocycles (**8**-**11**). In addition, *N*-protected aniline linkers with different protecting groups (such as Boc, Ac, Cbz and CO_2Ph) were also tolerated (**12**-**15**). Moreover, several substitution patterns on the aniline ring were allowed with the reaction to give desired products in satisfied yields (**16**-**21**). Finally, spiroindolines could be delivered with quinolinyl substrates with the aniline linkers (**22** and **23**). Of note, only trace amount of side product from competitive hydroarylation reaction could be observed for most of the substrates, except less than 5% of hydroarylation side products were detected with products **9** and **23**.



Scheme 2 *Scope of spirocyclizative arylcarboxylation of naphthalenes and quinolines with CO_2. Reaction conditions:* ***1*** *(0.2 mmol), $Ru(bpy)_3Cl_2$ (3 mol%), 4-CO_2K-HE (0.24 mmol, 1.2 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), DMF (2 mL), 1 atm CO_2, 30 W blue LEDs, rt, 24 h; then MeI (1.0 mmol), 60 °C, 2 h. Isolated yields.* [a]*Methylation conditions: $SOCl_2$ (0.4 mL), MeOH (4 mL), 100 °C, 6 h.*

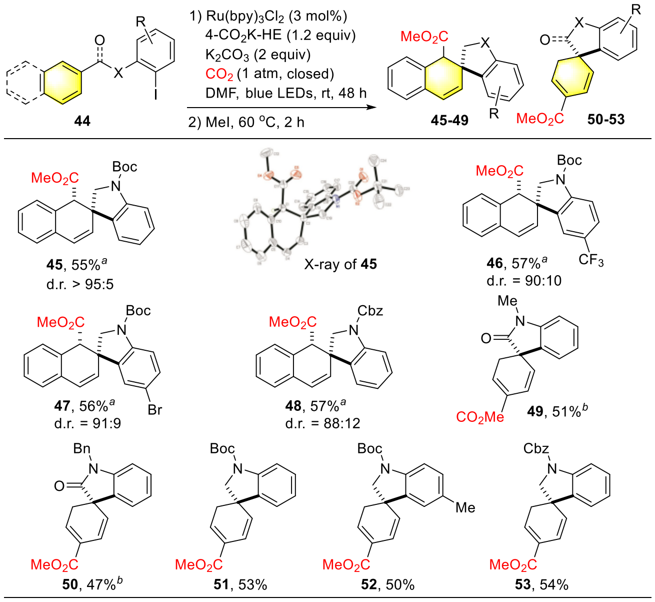
Subsequently, the versatility of the spiro-dearomative arylcarboxylation process was studied with 1-naphthamides (Scheme 3).[25] Pleasingly, using our protocol several *N*-alkyl groups (such as methyl, benzyl and isopropyl) were compatible with the reaction, delivering desired products **25**-**27** in good yields (73–76%).

Notably, substrates bearing electron-donating groups (Me and OMe), or electron-withdrawing groups (halides, CO_2Me, CF_3 and CN) at the *meta* or *para* position of the phenyl ring were all tolerated with this reaction without much difference in reactivity, affording the desired products in generally good yields (28-38, 60–75%). Substrate bearing a methyl at the C6 position gave the desired product **39** in 64% yield. In addition, substrate with a pyridyl group was also viable in this transformation, providing the target product **40** in an acceptable yield. Of note, substrates bearing a methyl at the C4 position of the naphthalenyl were tolerated, producing the 4-carboxylated products (**41**-**43**) in reasonable yields, though about 10% of hydroarylation side product was also observed for these examples.



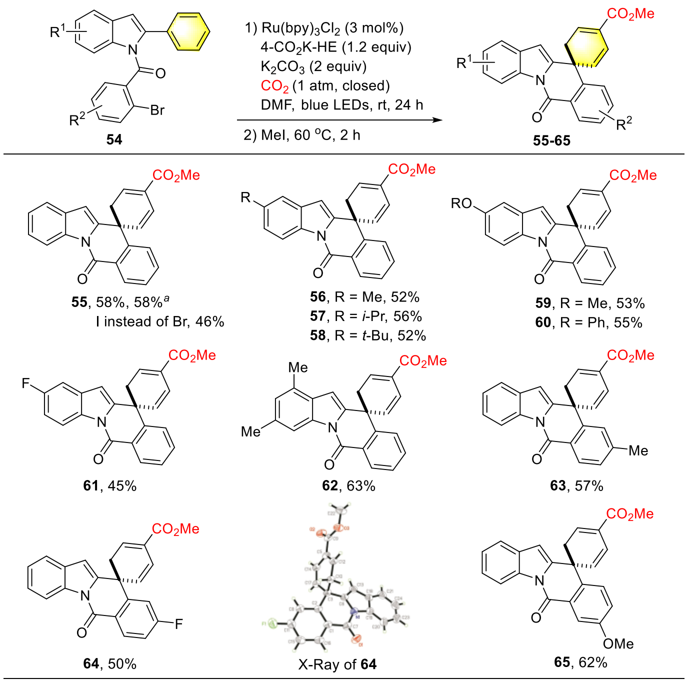
Scheme 3 *Scope of spirocyclizative arylcarboxylation of 1-naphthamides with CO_2. Reaction conditions:* ***24*** *(0.2 mmol), $Ru(bpy)_3Cl_2$ (3 mol%), 4-CO_2K-HE (0.24 mmol, 1.2 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), DMF (2 mL), 1 atm CO_2, 30 W blue LEDs, rt, 24 h; then MeI (1.0 mmol), 60 °C, 2 h. Isolated yields. [a]Yield of major diastereomer, minor diastereomer not isolated.*

Furthermore, the reaction was explored with 2-tethered naphthalenes and phenyl aromatics (Scheme 4). Pleasingly, after subjected to our reaction conditions, 2-tethered naphthalenes led to 1,2-arylcarboxylation dearomatized products (**45**-**48**) whose structures were different from abovementioned remote 1,4-arylcarboxylation of 1-tethered naphthalenes, albeit in moderate yields. Of note, some 1,2-hydroarylation side product (10-20%) was also generated with these substrates. Importantly, this approach could be applied to dearomatize challenging benzamide and non-activated phenyl rings (**49**-**53**), though the scope is limited for this type of substrate and a phenanthridin-6-one side product (10-20%) was observed with products **49** and **50** and some minor unknown side products were also produced with products **51**-**53**.



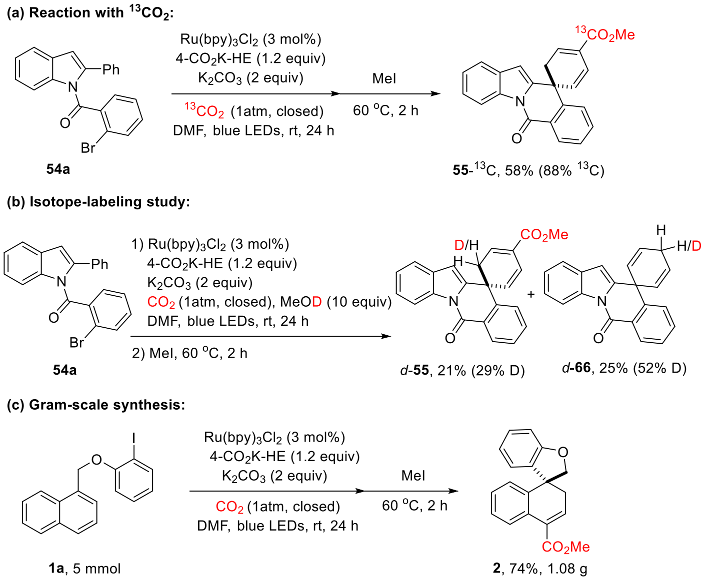
Scheme 4 *Scope of spirocyclizative arylcarboxylation of 2-tethered naphthalenes and phenyl aromatics with* CO_2*. Reaction conditions:* ***44*** *(0.2 mmol),* $Ru(bpy)_3Cl_2$ *(3 mol%), 4-*CO_2K*-HE (0.24 mmol, 1.2 equiv),* K_2CO_3 *(0.4 mmol, 2.0 equiv), DMF (2 mL), 1 atm* CO_2*, 30 W blue LEDs, rt, 48 h; then MeI (1.0 mmol), 60 °C, 2 h. Isolated yields.* [a]*Structure of major diastereomer displayed; 10-20% of hydroarylation side product observed.* [b]*24 h.*

During the study, we also obtained surprisingly unexpected reactivity with 2-phenyl indoles (Scheme 5). Interestingly, dearomatization occurred predominantly at non-activated phenyl ring via 6-*exo*-trig cyclization rather than at the activated indole ring's C2–C3 double bond via 5-*exo*-trig in previous study with the same substrate,[90] leading to spirocyclic product **55** with a formal remote C–H carboxylation.[96-98] The rationale for this chemoselectivity is not clear at present. Initially, the iodide substrate was also employed, but it was less effective than its bromide analog (**55**). It should be mentioned that the original carboxylic acid product was isolated in a lower yield than its methyl ester product **55**. We suspected the product might be labile, resulting in a relatively lower yield. Gratifyingly, substrates bearing a series of substituents on the indole ring or the aryl bromide ring could be converted into the corresponding products in moderate yields (56-65). It should be mentioned, generally about 5% of arylcarboxylation of indole's C2–C3 double bond and/or about 5% of direct debromination side products were also observed.



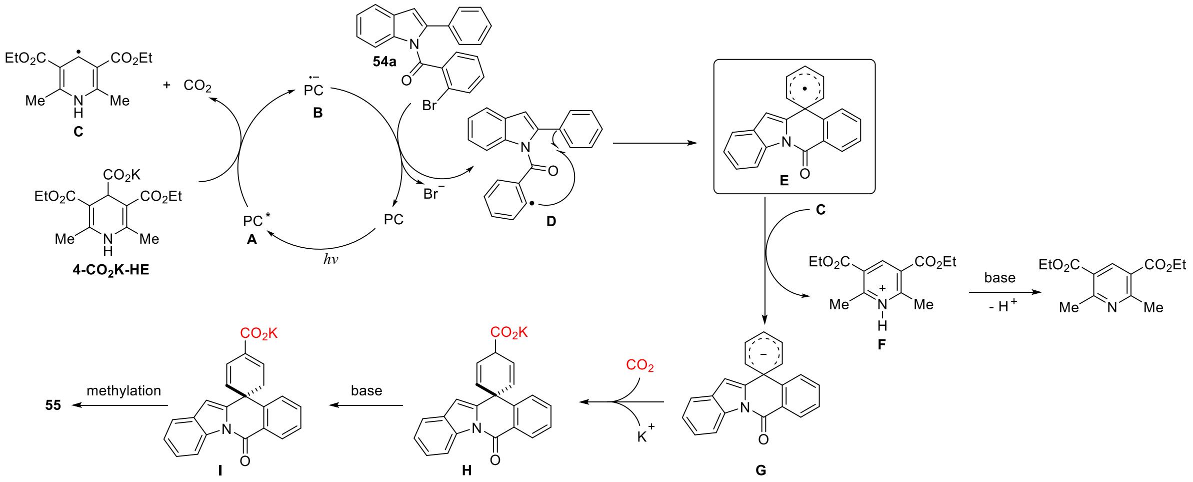
Scheme 5 *Scope of spirocyclizative arylcarboxylation of 2-phenyl indoles with CO_2. Reaction conditions:* ***54*** *(0.2 mmol), $Ru(bpy)_3Cl_2$ (3 mol%), 4-CO_2K-HE (0.24 mmol, 1.2 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), DMF (2 mL), 1 atm CO_2, 30 W blue LEDs, rt, 24 h; then MeI (1.0 mmol), 60 °C, 2 h. Isolated yields; about 5% of arylcarboxylation of indole's C2–C3 double bond and/or about 5% of debromination side products were observed. ^{a}2 mmol scale.*

We moved on to conduct preliminary mechanistic studies to obtain some insight into the reaction mechanism. First, the Stern-Volmer luminescence experiments showed the light-activated Ru catalyst (PC*) was quenched effectively by 4-CO_2K-HE rather than substrate **54a** [See Supporting Information (SI) for details]. To determine the carboxyl source of the product, $^{13}CO_2$ (99% ^{13}C) gas was employed, and 88% ^{13}C incorporation was found in the carboxyl of the product (Scheme 6a). Moreover, the isotope-labeling study that produced the diene product *d*-**66** suggested the possible presence of an anion intermediate (Scheme 6b).[a] Finally, the reaction could be scaled up to 5 mmol without significant decrease in the yield of **2** (Scheme 6c).



Scheme 6 *Mechanistic studies and scale-up reaction.*

A tentative mechanism was proposed based on the above mechanistic studies (Scheme 7). Upon blue light irradiation, the excited PC* (**A**) is produced and subsequently quenched reductively by 4-CO_2K-HE (E = –0.90 V vs. SCE in DMF, see SI) to give reduced PC (**B**) ($E_{1/2}$ [Ru^{II}*/Ru^{I}] = +0.77 V vs. SCE in MeCN)[99] and corresponding dihydropyridine radical (**C**) with the release of CO_2. Reduction of aryl bromide **54a** by **B** ($E_{1/2}$ [Ru^{I}/Ru^{II}] = –1.33 V vs. SCE in MeCN)[99] produces aryl radical **D** which undergoes dearomatization via the 6-*exo*-trig cyclization to afford the spirocyclic radical **E**. Single-electron transfer from the dihydropyridine radical **C** to **E** generates anionic intermediate **G**, which undergoes nucleophilic addition to CO_2 to produce the carboxylate **H**. Finally, base-promoted double bond rearrangement followed by methylation affords methyl ester **55**.



Scheme 7 *Proposed catalytic cycle.*

Conclusion

In conclusion, we have developed a novel strategy of visible-light-induced spirocyclizative remote arylcarboxylation of a series of non-activated arenes including naphthalenes, 2-phenyl indoles and *N*-benzylanilines with CO_2 under mild conditions through RPCC. An interesting unusual chemoselective dearomatization of 2-phenyl indoles via 6-*exo*-trig cyclization was presented. This reductive dearomatization/arylcarboxylation protocol efficiently delivers valuable three-dimensional carboxylic acid derivatives from readily accessible aromatic precursors, providing a distinct method for complex molecule construction.

Footnote

[a] The work leading to dienes as the target products will be submitted to publish elsewhere.

Supporting Information

Supporting Information is available including general experimental procedures, and characterization spectra.

Conflict of Interest

The authors declare no competing financial interest.

Acknowledgements

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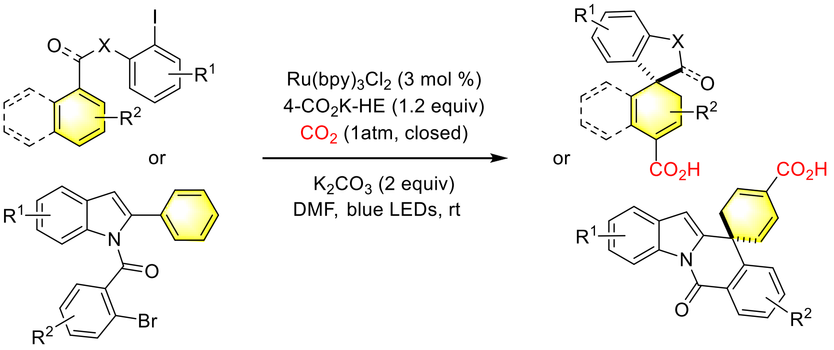
Table of Contents Graphic (required)



■ **non-activated arene dearomatization** ■ **spirocycle formation** ■ **broad scope**

■ **chemoselective cyclization** ■ **remote arylcarboxylation** ■ **photocatalytic CO_2 utilization**