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Direct Deoxygenative Intramolecular Acylation of Biarylcarboxylic Acids

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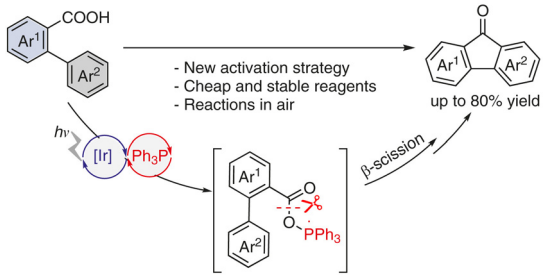

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Abstract A photocatalyzed intramolecular cyclization is developed for the synthesis of fluorenones. In this photoredox reaction, triphenylphosphine is used as an inexpensive and effective deoxygenative reagent for biarylcarboxylic acids to give acyl radicals, which quickly undergo intramolecular radical cyclization. Reactions in the presence of air and continuous flow photoredox technology demonstrate the generality and practicality of this process.

Key words photocatalytic, deoxygenation, triphenylphosphine, radical cyclization, flow chemistry

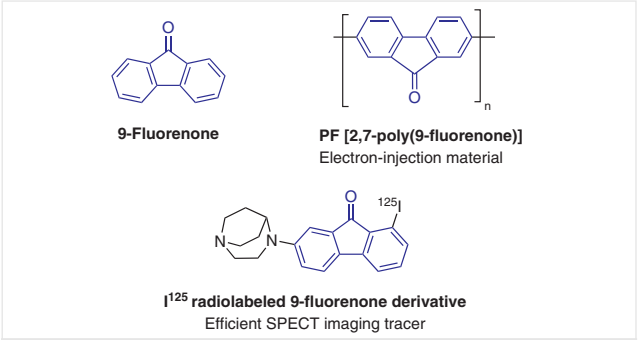

Figure 1 The application of fluorenone derivatives

Fluorenone is a cornerstone in photoelectric materials and biologically active molecules (Figure 1).[1] Recently, fluorenones have been successfully applied as hydrogen atom transfer (HAT) catalysts in organic synthesis.[2] Hence, the construction of the fluorenone skeleton is of significant importance and has gained considerable attention. They are typically prepared via the classical Friedel–Crafts acylation of the corresponding acids,[3] however, the method suffers from the use of strong and excess acids, poor functional group tolerance and incompatibility with electron-rich arenes. Recently, when using strong oxidants as HAT reagents, such as $K_2S_2O_4$ and *t*-BuOOH, aldehydes and α-keto acids have been found to undergo dehydrogenation or decarboxylation to generate nucleophilic acyl radicals, triggering the desired transformation.[4] Alternatively, cycloaddition reactions,[5] oxidation of fluorenones or fluorenes[6] and cyclocarbonylation[7] can also be used to prepare fluorenones. However, high temperatures and the use of excess oxidants are disadvantages of these processes.

Carboxylic acids are abundant in nature and have been successfully used as acyl precursors.[8] In 2014, a rhodium-catalyzed intramolecular acylation of 2-aryl acids was developed to synthesize fluorenones through an acylrhodium species at a temperature of 160 °C (Scheme 1, a).[9] During the last decade, photoredox catalysis has proven to be a valuable and powerful method for the development of new chemical reactions that involve single-electron transfer (SET) processes.[10] Previously, our group developed a photoredox catalytic decarboxylation of anhydrides generated from biarylcarboxylic acids and dimethyl dicarbonate (DMDC).[11] Recently, our group disclosed the first direct and practical deoxygenation of acids (as acyl sources) with triphenylphosphine.[12] This powerful strategy has been applied in direct deoxygenative ketone synthesis, deoxygenative deuter-

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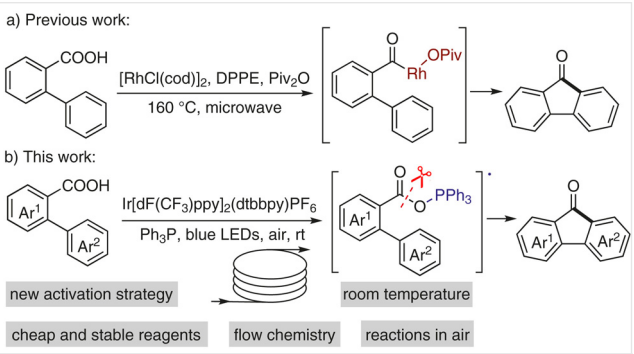
ation and deoxygenative arylation. Similar deoxygenative pathways were also applied in organic transformations by Doyle[13] and others.[14] As ongoing research, we report a photoredox intramolecular cyclization of biarylcarboxylic acids using cheap and stable Ph_3P as a deoxygenation reagent (Scheme 1, b). This study provides a practical and straightforward protocol for the preparation of fluorenone scaffolds under air conditions, and further enhances its utility in synthetic applications utilizing continuous flow synthesis.

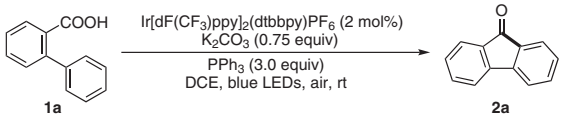


Scheme 1 Recent representative work on the synthesis of fluorenones

We started our investigations on the direct deoxygenative acylation with 2-phenylbenzoic acid (**1a**) as a model substrate. The optimized reaction conditions were determined to be Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2 mol%) as the photocatalyst, PPh_3 (3.0 equiv) as the deoxygenative reagent, together with K_2CO_3 (0.75 equiv) as the inorganic base in DCE under blue LEDs at room temperature (Table 1, entry 1). The target product, 9*H*-fluoren-9-one (**2a**), was obtained in 70% isolated yield. Replacing Ph_3P with Ph_2POMe or $P(OEt)_3$ resulted in none of the desired product being detected (entries 2 and 3). Other inorganic base led to lower yields (entries 4 and 5). A lower oxidation potential photocatalyst, Ir[dF(Me)ppy]$_2$(dtbbpy)PF_6 [$^{1/2}E_{red}$ ($^*Ir^{III}/Ir^{II}$) = +0.97 V vs SCE; τ = 1.2 μs],[15] resulted in a slightly decreased yield (entry 6). Control experiments showed that PPh_3, air, light and the photocatalyst all play a crucial role in the reaction (entries 7–9).

With optimized reaction conditions in hand, the scope of the reaction was investigated. The versatility of this cyclization reaction with different substrates and the generality of the strategy is demonstrated by the examples shown in Figure 2.[16] Acids **1** with substituents on the Ar^2 ring were initially examined in this cyclization reaction and they can afford the desired products (**2a–2o**) in moderate to good yields. Substrates with electron-donating substituents [methyl (**1b**), methoxy (**1c**) and *tert*-butyl (**1d**)] or with an electron-withdrawing trifluoromethyl substituent (**1h**) were found to undergo efficient intramolecular acylation to give the corresponding products **2b–d**,**h**. Biarylcarboxylic acids with halogen substituents (**1e–g**,**n**) also reacted in good yields. Two disubstituted substrates (**1i**,**j**) also showed good activity, whilst acid **1k** with an *ortho*-Cl substituent was also compatible. When a halogen was located at the *meta*-position of the Ar^2 ring (**1n**), the reaction proceeded

Table 1 Optimization of the Reaction Conditions[a]



Entry	Deviation from standard conditions	Yield[b]
1	none	70%
2	Ph_2POMe instead of Ph_3P	nd
3	$P(OEt)_3$ instead of Ph_3P	nd
4	K_2HPO_4 instead of K_2CO_3	40%
5	K_3PO_4 instead of K_2CO_3	45%
6	Ir[dF(Me)ppy]$_2$(dtbbpy)PF_6	55%
7	no Ph_3P	nd
8	under Ar	nd
9	in the dark	nd

[a] *Standard reaction conditions*: **1a** (0.1 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2 mol%), Ph_3P (3.0 equiv), K_2CO_3 (0.75 equiv), DCE (2 mL), 2 blue LEDs (45 W), 24 h, rt, under air.
[b] Isolated yield; nd = not detected.

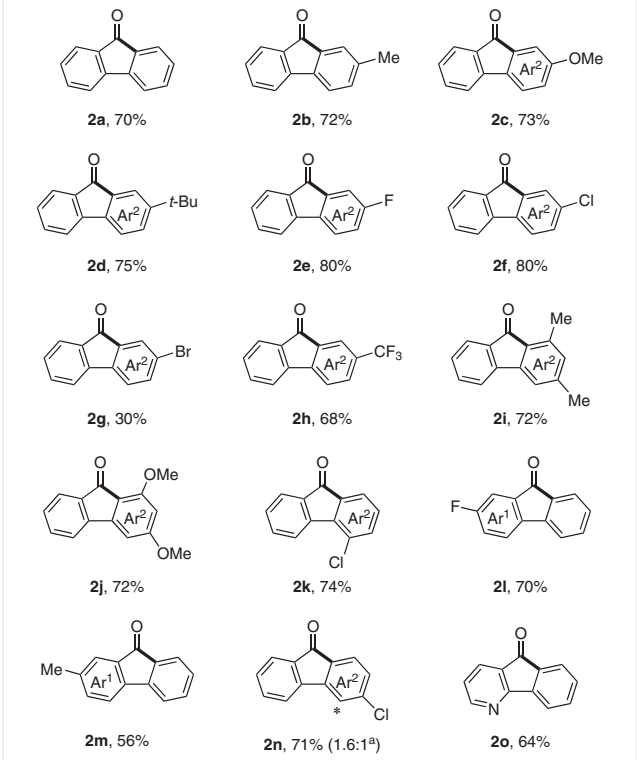
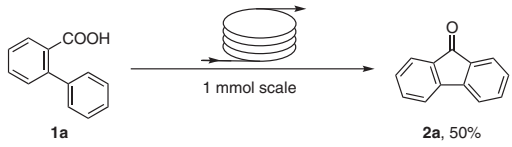


Figure 2 Substrate scope. [a] Regioselectivity determined by GC.

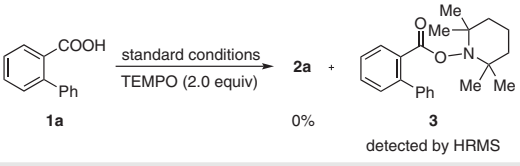
smoothly with good regioselectivity to afford product **2n**. In addition, an acid with an electron-withdrawing group (**1l**) on the Ar^1 ring gave a higher yield of the corresponding product **2l** compared with an acid possessing an electron-donating group (**1m**) on the same aryl ring. Heteroaromatic acid **1o** was converted into the desired fluorenone **2o** in an acceptable 64% yield.

Continuous flow technology has attracted more and more attention in recent years,[17] and shows some significant advantages over conventional batch reactions, including the in situ formation and direct use of reaction intermediates, convenience of temperature control, increased reaction contact area, and ease of amplification. Hence, the model reactant **1a** was used to study this intramolecular cyclization reaction under continuous flow conditions. The direct deoxygenative intramolecular acylation can be scaled up to 1 mmol with lower loading of the photocatalyst by the use of continuous micro-tubing reactors,[18] which leads to enhanced utility in synthetic applications (Scheme 2).



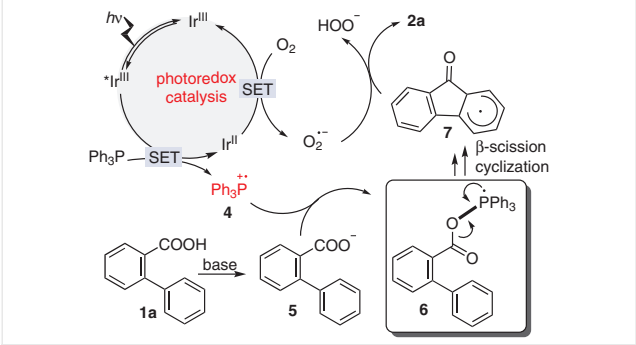
Scheme 2 Continuous flow transformations. *Conditions*: **1a** (1.0 equiv, 1.0 mmol), PPh_3 (3.0 equiv, 3.0 mmol), K_2CO_3 (0.5 equiv, 0.5 mmol, 120 mesh), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%, 0.01 mmol), DCE (30 mL), 2 blue LEDs (45 W), rt, under air.

To gain further insight into the cyclization, a radical-trapping experiment was conducted (Scheme 3). In the presence of the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the reaction was completely inhibited and none of the desired product **2a** was observed. Moreover, the corresponding acyl radical was trapped by TEMPO, which indicates that this transformation may involve radical intermediates.



Scheme 3 Radical-trapping experiment

Based on previous work[4c,f,12a] and the radical-trapping experiment with TEMPO, a plausible reaction mechanism is proposed (Scheme 4). Under irradiation, the photoexcited catalyst $^*Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ [$E_{1/2}^{red}$ ($^*Ir^{III}/Ir^{II}$) = +1.21 V vs SCE)] goes through a single-electron transfer (SET) process with PPh_3 to give the radical cation **4**, which quickly reacts with carboxylate anion **5** to produce the phosphoryl radical **6**. Next, β-selective C(acyl)–O bond cleavage results in triphenylphosphine oxide being released. Subsequent cyclization then leads to the formation of intermediate **7**. Under air, O_2 can oxidize [Ir^{II}] to its ground state and close the photocatalytic cycle. The resulting $O_2^{\bullet-}$ species would then oxidize **7** to give the final product **2a**.



Scheme 4 The proposed mechanism

In summary, a green, mild and simple method to access fluorenone derivatives is described. A number of substituted fluorenones[17] have been synthesized via this process, which may have potential as luminescent materials. Continuous flow chemistry[18] was successfully applied in this deoxygenative intramolecular acylation, showing the potential for scale-up and possible industrialization of the process. Further studies on the cyclization of aliphatic carboxylic acids are underway in our laboratory.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707246.

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(16) **Fluorenones 2a–o; General Procedure**
Biarylcarboxylic acid **1** (0.1 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.3 mg, 0.02 mmol), Ph_3P (78.6 mg, 0.3 mmol), K_2CO_3 (10.4 mg, 0.075 mmol) and DCE (2 mL) were added to a 10 mL Schlenk tube equipped with a magnetic stir bar. The tube was placed at a distance of ~5 cm from 2 blue LEDs (45 W) under air, and the resulting solution was stirred for 24 h. After the reaction was complete (monitored by TLC), the mixture was concentrated under vacuum to remove DCE and the residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 5:1) to afford the product **2**.
9*H*-Fluoren-9-one (2a)
Compound **2a** (12.6 mg, 70%) was synthesized using the general procedure and isolated as a yellow solid; mp 81–82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.3 Hz, 2 H), 7.53–7.47 (m, 4 H), 7.29 (td, *J* = 7.3, 1.2 Hz, 2 H). MS (EI): *m*/*z* (%) = 180.0 (100) [M$^+$].
2-Methyl-9*H*-fluoren-9-one (2b)
Compound **2b** (14 mg, 72%) was synthesized using the general procedure and isolated as a yellow solid; mp 90–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.3 Hz, 1 H), 7.47–7.44 (m, 3 H), 7.39 (d, *J* = 7.5 Hz, 1 H), 7.29–7.23 (m, 2 H), 2.37 (s, 3 H). MS (EI): *m*/*z* (%) = 194.1 (100) [M$^+$].
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(18) **Flow Chemistry; General Procedure**
Biarylcarboxylic acid **1a** (198 mg, 1 mmol), PPh_3 (786 mg, 3 mmol), K_2CO_3 (69 mg, 0.5 mmol, 120 mesh), and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (11.7 mg, 0.01 mmol) were placed in a round-bottom flask (100 mL). DCE (30 mL) was added under air and the mixture was pumped at a rate of 82 mL min^{-1} using a peristaltic pump under irradiation with 2 blue LEDs (45 W). After 8.5 h, the reaction was complete. The mixture was concentrated under vacuum to remove DCE and the residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 5:1) to afford the product **2a**.