Visible-light photosensitized aryl and alkyl decarboxylative carbon-heteroatom and carbon-carbon bond formations

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Abstract

Despite significant progress in aliphatic decarboxylation, an efficient and general protocol for radical aromatic decarboxylation has lagged far behind. Herein, we describe a general strategy for rapid access to both aryl and alkyl radicals by photosensitized decarboxylation of the corresponding carboxylic acids esters followed by their successive use in divergent carbon-heteroatom and carbon-carbon bond forming reactions. Identification of a suitable activator for carboxylic acids is the key to bypass a competing single electron transfer mechanism and "switch on" an energy transfer mediated homolysis of unsymmetrical *σ*-bonds for a concerted fragmentation/decarboxylation process.

Introduction

Harnessing the reactivity of ubiquitous functional groups by means of functional group interconversion plays an important role in synthetic chemistry and many biological processes.[1] Inspired by the intriguing efficiency of enzymatic decarboxylation,[2] recent years have seen an upsurge in developing new decarboxylative functionalization strategies to utilize the cheap, stable and highly prevalent carboxylic acids as versatile building blocks.[3] Elegant work by the groups of Okada,[4] Baran,[5] Aggarwal,[6] Hu[7] and others[8] have identified *N*-hydroxyphthalimide-derived redox active esters (RAE) as an efficient activating group for aliphatic carboxylic acids in divergent decarboxylative functionalization reactions via single electron transfer (SET) pathways (Fig. 1A). However, adoption of similar strategy for aromatic decarboxylation has been limited to borylation so far.[9] To date, aromatic decarboxylation has been realized mainly by concerted decarboxylative metalation/ functionalization processes as pioneered by Goossen[10], Larrosa[11] and Su.[12] These processes are often limited by substrate bias and requirement for harsh reaction conditions to facilitate the unfavorable direct decarboxylation. Alternatively, SET mediated reductive[13] or oxidative decarboxylation processes[14] have also been developed for specific cases. However, necessity of stoichiometric oxidant or reductant along with the prerequisite for redox properties match in each electron transfer step can limit the catalyst turnover and the choice of coupling partner.[15] Thus, a general protocol for mild aromatic decarboxylation remains elusive.

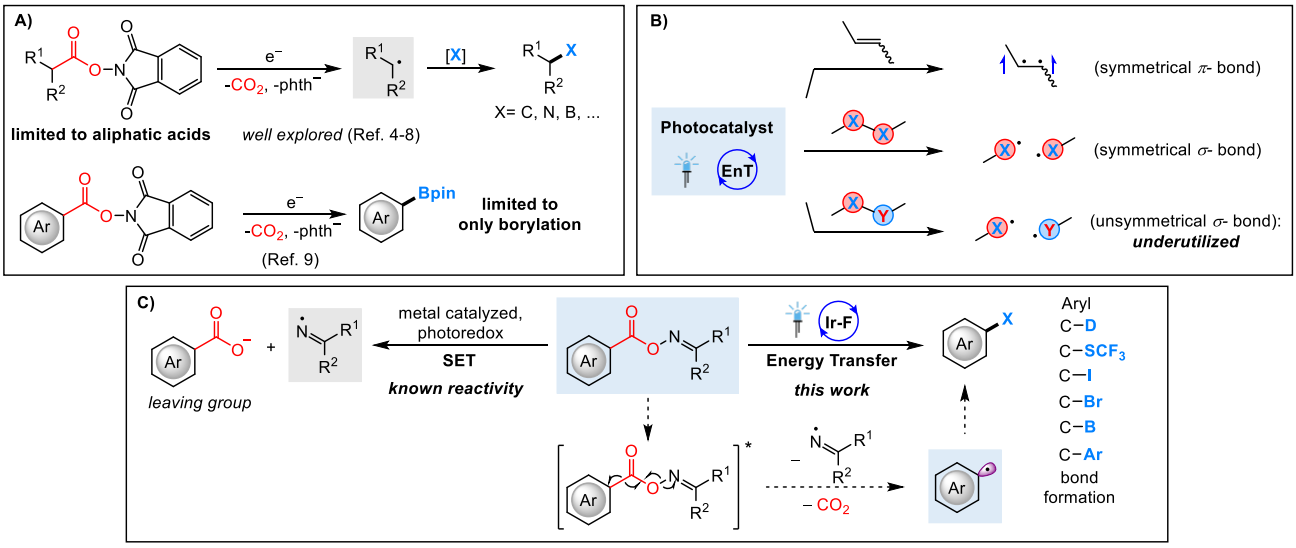


Figure 1. A) Current status of radical decarboxylative functionalization. B) Current status of visible-light induced energy transfer processes. C) Development of aryl decarboxylative functionalization strategy by switching the mechanism from SET to EnT pathway.

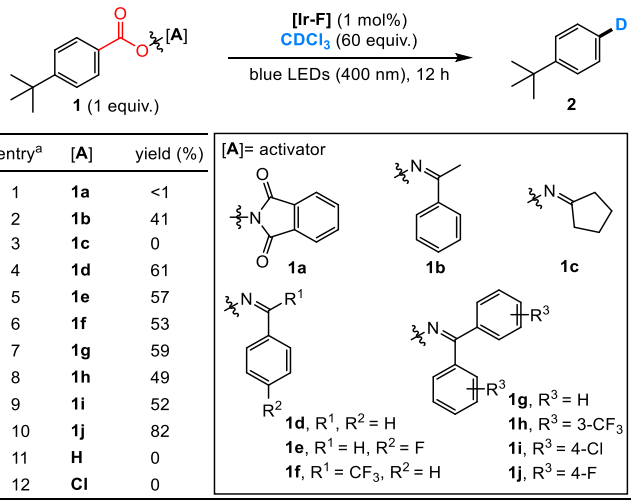
One major challenge for aromatic decarboxylation is the stability of the aryl carboxyl radical against decarboxylation (10^4-10^5 s^{-1} compared to ~10^9 s^{-1} for alkyl carboxyl radical).[16] To circumvent this challenge, we hypothesized that a concerted fragmentation/decarboxylation sequence from a preformed carboxylic acid ester could lead to the desired aryl radical. Previously, use of Barton ester for aryl decarboxylation was mainly restricted by the requirement of high reaction temperature, low substrate stability and uncontrolled side reactions.[16] In this regard, our approach was inspired by the pioneering studies of Hasebe and Tsuchiya, who used hydroxylamine-derived active esters for radical decarboxylation under UV irradiation.[17] However, harsh reaction conditions, use of large excess of the trapping reagents to compete with different side reactions and the requirement for specialized reaction setup have prevented their widespread use in recent years. Building on our recent studies on the photosensitized homolytic cleavage of S–S bonds,[18] we envisioned that visible-light-mediated energy transfer for homolytic cleavage of N–O bond could represent a promising approach to this problem.

Within the last decade, visible-light photocatalysis has been utilized to achieve several impressive reactivities mainly through SET processes.[19] Conversely, the other distinct reactivity mode of photocatalyst excited states, namely the energy transfer (EnT) pathway, has remained relatively underdeveloped.[20] So far, the use of visible-light mediated energy transfer process has been limited to sensitize weak π-bonds (in cycloaddition reactions,[21] *E*/*Z* isomerization[22] and deracemization[23]), symmetrical σ-bonds[18] and transition-metal complexes.[24] To date, visible light induced energy transfer from excited photocatalysts has not been exploited to sensitize and cleave unsymmetrical σ-bonds (Fig. 1B). This is largely due to the inherent electronegativity bias of the unsymmetrical σ-bonds that generally promotes facile SET process (either reductive or oxidative) to outcompete EnT reactivity in presence of a photocatalyst.[25] Indeed, a series of transformations were achieved by exploiting the *N*-centered radical generated from the bond polarity driven SET reduction of the N–O bond of hydroxylamine-derived activated esters yielding a stabilized benzoate species as the leaving group (Fig. 1C).[26] In contrary, bypassing the SET pathway by an EnT pathway could lead to concerted fragmentation/decarboxylation process to generate the desired aryl radical. Importantly, in absence of any redox event, such decarboxylation strategy should be independent of the intrinsic regeneration/turnover of the catalyst. In this context, herein we report an effective visible light sensitization of unsymmetrical N–O σ-bonds to trigger a unique radical decarboxylation of aryl carboxylic acid esters and its application in divergent decarboxylative functionalization to form a series of key C–X and C–C bonds (Fig. 1C). Further, this strategy was successfully extended to alkyl carboxylic acids eventually providing a general decarboxylative functionalization strategy.

Results and discussion

Inspired by the use of *N*-hydroxyphthalimide based RAE in aliphatic decarboxylation, we rationalized that such *N*-hydroxy esters could be a good starting point for the proposed EnT mediated cleavage of the N–O bond. This is supported by the reported N–O bond dissociation energy of ~45 kcal mol^{-1},[27] which can be attained under suitable photosensitized conditions. Consequently, [Ir(dF(CF_3)ppy)$_2$(dtbbpy)](PF_6) (**[Ir-F]**, dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5- trifluoromethylpyridine,

Table 1. Effect of different activators



entry[a]	[A]	yield (%)
1	**1a**	<1
2	**1b**	41
3	**1c**	0
4	**1d**	61
5	**1e**	57
6	**1f**	53
7	**1g**	59
8	**1h**	49
9	**1i**	52
10	**1j**	82
11	**H**	0
12	**Cl**	0

[a]All reaction were carried out on a 0.10 mmol scale and yields were measured by gas chromatography using anisole as an internal standard.

dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) was selected as the preferred photocatalyst due to its long excited state lifetime (τ = 2.3 μs) and high triplet energy of 60.8 kcal mol^{-1}.[28] We chose decarboxylative deuteration as the model reaction for initial assessment and optimization studies since deuterium-labeled compounds are important diagnostic tools in drug discovery research and pharmaceutical industry.[29] Moreover, with the beneficial generation of more reactive aryl radicals under our proposed reaction design, deuterium atom abstraction from most common and inexpensive deuterium source such as $CDCl_3$ should be thermodynamically favored ($BDE_{C–H}$ ($CHCl_3$) = 93.8 kcal mol^{-1} [30] versus $BDE_{C–H}$ (benzene) = 113.5 kcal mol^{-1} [31]). This would eliminate the need for the synthesis of the expensive deuterated analogues of benchmark H-donors like tributyltin hydride, thiol or silanes.[30] Accordingly, RAE **1a** was investigated in the decarboxylative deuteration using $CDCl_3$ as the deuterium source and **[Ir-F]** as the photosensitizer. Only a trace amount of 4-(*tert*-butyl)benzoic acid was observed without the desired deuterated product (Table 1, entry 1). A probable SET reduction of RAE **1a** is only possible either by the excited photocatalyst **[Ir-F]*** in oxidative quenching (in Ir(III)*/Ir(IV) step) or by the reduced photocatalyst in a reductive quenching cycle (in Ir(II)/Ir(III) step). Though the SET reduction by **[Ir-F]*** is not viable ($E_{1/2}^{III*/IV}$ = -0.89 V vs SCE), but the thermodynamic feasibility of an undesired electron transfer process between **[Ir-F]** ($E_{1/2}^{II/III}$ = +1.37 V vs SCE) and **1a** ($E_{1/2}^{red}$ = -1.4 V vs SCE)[9a] prompted us to search for more suitable *N*-hydroxy esters with even lower reduction potentials to ensure only an energy transfer mechanism can be operative. In this regard, we focused our attention on different oxime esters, owing to their higher redox stability.[25] Promisingly, when acetophenone derived **1b** was employed under identical condition, 41% yield of the desired decarboxylated product **2** was observed (Table 1, entry 2). Encouraged by this finding, we evaluated a series of aldoxime and ketoxime esters as activating groups (see Table 1). Aliphatic ketoxime **1c** did not undergo decarboxylation (entry 3),[25] but aromatic aldoximes (**1d**, **1e**) and ketoximes (**1f**-**1i**) were found effective with varying levels of success (entries 4-9). Finally, an ideal balance between redox stability, ease of sensitization and practicality was observed with 4,4'-difluorobenzophenone oxime ester **1j** which

provided 82% yield of the desired deuterated product **2** (entry 10). Such oxime esters can be easily synthesized in two steps from 4,4'-difluorobenzophenone on a multigram scale and mostly without chromatographic purification.[32] As a control, simple 4-(*tert*-butyl)benzoic acid or its acid chloride were employed under identical condition and no deuterated product was observed (entries 11,12). Although small amounts of water did not hamper the desired reactivity, expectedly the presence of oxygen was found detrimental.

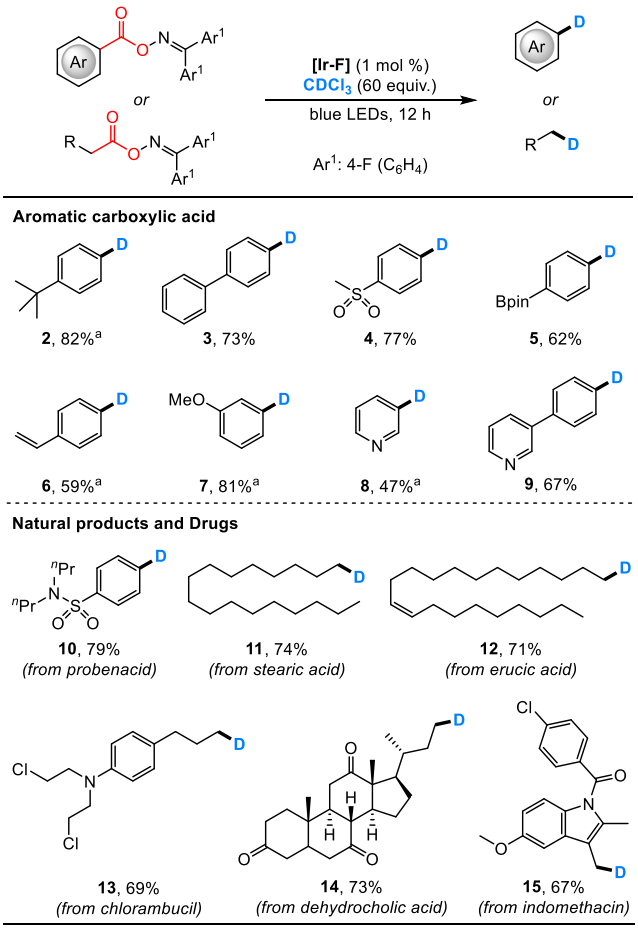
Having determined the optimal reaction conditions, we first sought to explore the generality of this process with respect to different aryl carboxylic acids (Table 2). A range of electron-donating as well as electron-withdrawing benzoic acids with a variety of functional groups including sulfone, pinacolatoborane, olefin and alkoxy, sulfonamide were well tolerated under this decarboxylation protocol (Table 2, entries **2**-**7**, **10**). Notably, tolerance towards highly diversifying pinacolatoborane and labile styrene functional groups highlights the mildness of this method (Table 2, entries **5**, **6**). Different nitrogen containing heterocycles were employed successfully (Table 2, entries **8**, **9**). In all these cases, effective deuteration (>97% D-incorporation) occurred exclusively at the *ipso*-position to the carboxylic acid group. Generally, For the substrates with moderate yields the parent carboxylic acids were detected as the major side products while full consumption of the starting esters was observed. However, sterically demanding *ortho*-substituted acid were found mostly unreacted with lower yields, potentially due to the inefficient energy transfer from the excited photocatalyst to the substrate.

Impressively, this decarboxylation strategy was not only limited to aryl carboxylic acids but could also be successfully extended to alkyl carboxylic acids. Despite significant progress in aliphatic decarboxylation, decarboxylative deuteration remained challenging owing to the requirement of specialized tin hydride or thiol based D-atom donor source.[15] Encouraged by this finding, we applied this strategy to different natural products and drug molecules containing carboxylic acid functionality. Probenecid, an aromatic carboxylic acid derivative as well as aliphatic carboxylic acids such as stearic acid, erucic acid, chlorambucil, dehydrocholic acid and indomethacin were converted to the desired deuterated products in good yields (Table 2, entries **10**-**15**).

Next, we proceeded to survey an array of other trapping reagents which might be suitable for the functionalization of the weakly nucleophilic aryl radical. For all these studies, ethyl acetate or acetonitrile were identified as preferred solvents, since trapping of the aryl radical by a stoichiometric amount of electrophile was faster than hydrogen atom abstraction (HAA) from these solvents. To date, the high energy barrier associated with aromatic decarboxylation has prevented the discovery of a decarboxylative trifluoromethylthiolation (SCF_3) protocol. Our exploration of different electrophilic -SCF_3 sources led us to identify very simple conditions for aromatic decarboxylative trifluoromethylthiolation (Supplementary Table 2.3.2). As representative examples, three aromatic carboxylic acids (Table 3, entries **16**-**18**), two pyridine and quinoline based heterocyclic carboxylic acids (entries **19**, **20)** and one biorelevant aliphatic carboxylic acid (entry **21**) were tested and all of them delivered the desired trifluoromethylthiolated products under the optimized reaction conditions.

Further, the aryl radicals were trapped with stoichiometric amount of chloroiodomethane (CH_2ClI) to promote decarboxylative iodination. Tolerance towards a series of important functionalities including both electron donating

Table 2. Scope for decarboxylative deuteration



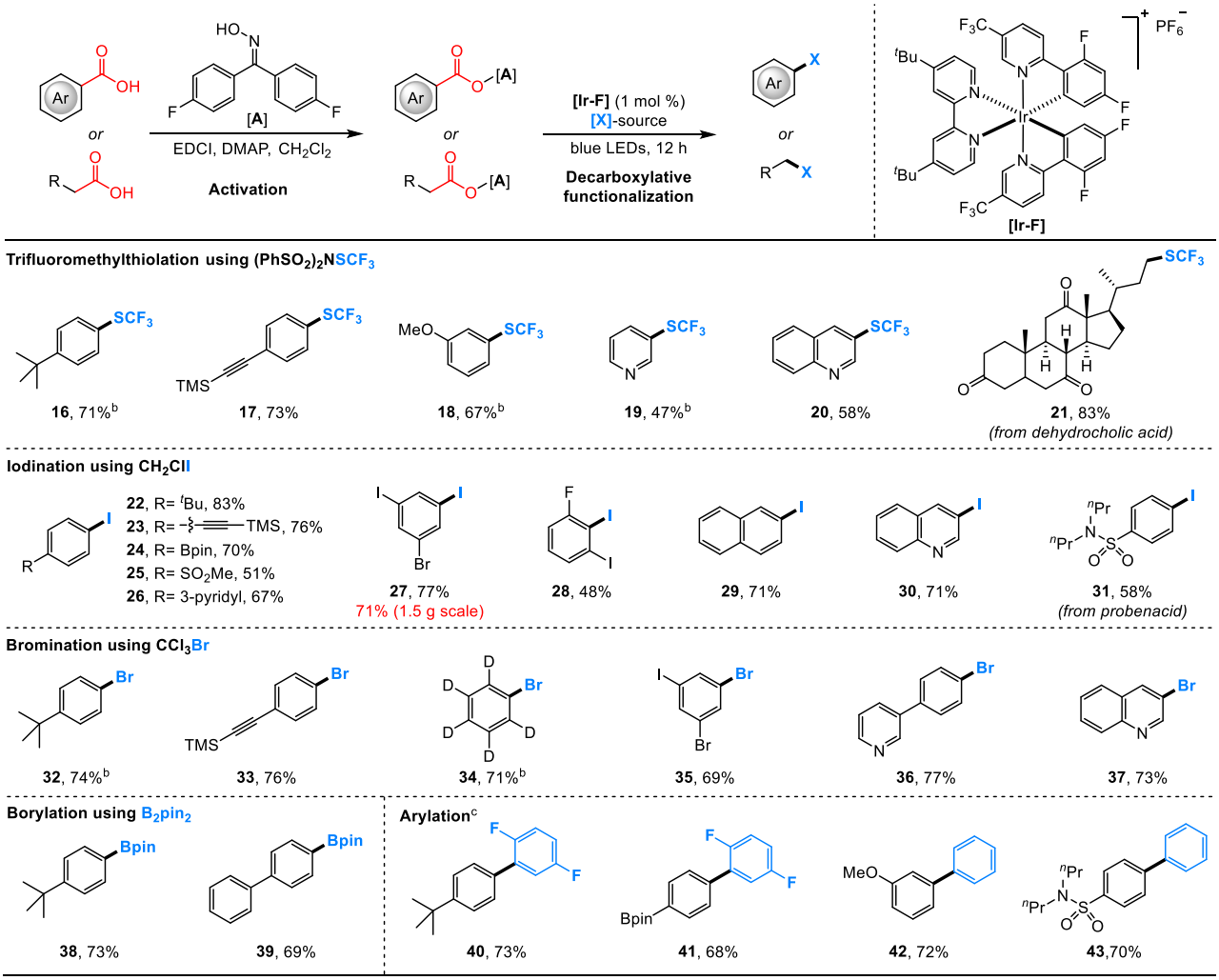
All reactions were carried out on a 0.30 mmol scale and the yields refer to isolated products. [a]Yield determined by gas chromatography.

and withdrawing groups were observed (Table 3, entries **22**-**28**, **31**). Both *para*- and *meta*-substituted aryl carboxylic acids performed well in this reaction (entries **22**-**27**); however, *ortho* substitution led to diminished yield of the desired product (entry **28**). Different nitrogen-based heterocycles (entries **26**, **30**) and the probenecid derivative **31** further proved the generality of this decarboxylation approach. Importantly, a scale up study showed that **27** could be prepared on gram scale with only a slight decrease in product yield.

Likewise, radical decarboxylative bromination was accomplished for six representative aryl carboxylic acids in synthetically useful yields by using trichlorobromomethane (CCl_3Br) as the bromine source (Table 3, entries **32**-**37**). Remarkably, decarboxylative borylation was also observed for **38** and **39** in presence of bis(pinacolato)diboron (B_2pin_2) and **[Ir-F]** as the photosensitizer. Finally, decarboxylative arylation[33] was achieved by trapping the aryl radical with different arenes to provide the arylated products **40**-**43**. All these transformations further proved the generality and versatility of our current decarboxylation strategy mediated by EnT pathway.

We next turned our attention to the mechanism of this decarboxylation process. First, interaction between the excited photocatalyst **[Ir-F]*** and **1j** was confirmed by phosphorescence quenching of **[Ir-F]*** by **1j** (Supplementary

Table 3. Scope of the energy transfer enabled decarboxylative functionalization[a]



[a]Standard conditions: **[Ir-F]** (1 mol%), trapping reagent (3 equiv.), EtOAc (0.1 M), blue LEDs (λ_{max} = 400 nm), 12 h, isolated yield on a 0.3 mmol scale. [b]GC yield reported, [c]Corresponding arene (1.5 mL) was used as the trapping reagent.

Fig. 3). Subsequently, we investigated the feasibility of an EnT pathway under our reaction conditions. A reaction proceeding from the triplet state should also be possible by direct excitation which distinguishes it from a SET mechanism. Indeed, the same decarboxylation product **2** was observed upon direct photoirradiation with 365 nm LED source, albeit in reduced yield (Fig. 2A). Furthermore, an EnT pathway should also generate a *N*-centered iminyl radical **49** along with the aryl radical under our reaction condition. Iminyl radical **49** derived byproducts **52** and **53** were always observed during our optimization and scope studies. Formation of iminyl radical was further confirmed through intramolecular trapping to produce **44** in comparative yield along with the decarboxylated product **2** (Fig. 2B). Additionally, to determine the feasibility of a SET process, we studied the electrochemical properties of **1j**. An irreversible reduction potential of -2.0 V (*vs* SCE) for **1j** precluded the possibility of SET reduction from either $\mathbf{Ir^{III*}}$ or $\mathbf{Ir^{II}}$ (Supplementary Fig. 4). Conversely, comparison of the calculated triplet energy data of **1j** with the triplet energy of **[Ir-F]*** further validates the thermodynamic feasibility of triplet-triplet energy transfer from **[Ir-F]*** to **1j** (Fig. 2C).[28]

In accordance with all these findings, a detailed description of the proposed mechanism is outlined in Fig. 2D. First, **[Ir-F]** absorbs visible light to generate its triplet excited state **[Ir-F]*** which engages in a TTEnT process with **45** to produce the excited triplet state **45*** and regenerate **[Ir-F]**. At this stage, **45*** can undergo concerted fragmentation through the homolysis of N–O bond to generate the iminyl radical **49** and aryl radical **50** with the release of CO_2. The nucleophilic aryl radical **50** participates in different C–X bond forming process in the presence of suitable trapping reagents to give the corresponding product **51**.[34] On the other hand, sufficiently stable iminyl radical **49** can either undergo hydrogen atom abstraction (HAA) from solvent to generate **52** or dimerize to **53**. Intermolecular trapping of transient aryl radical **50** by long lived iminyl radical **49** was not observed. In an alternate pathway, **45*** could undergo only homolysis of N–O bond to form the aroyloxy radical **48**. However, a direct decarboxylation of **48** is unlikely due to the extensive resonance stabilization of the carboxyl radical with arene-π-system. **48** is known to participate in rapid hydrogen atom Abstraction (HAA) process in a faster rate compared to decarboxylation.[35]

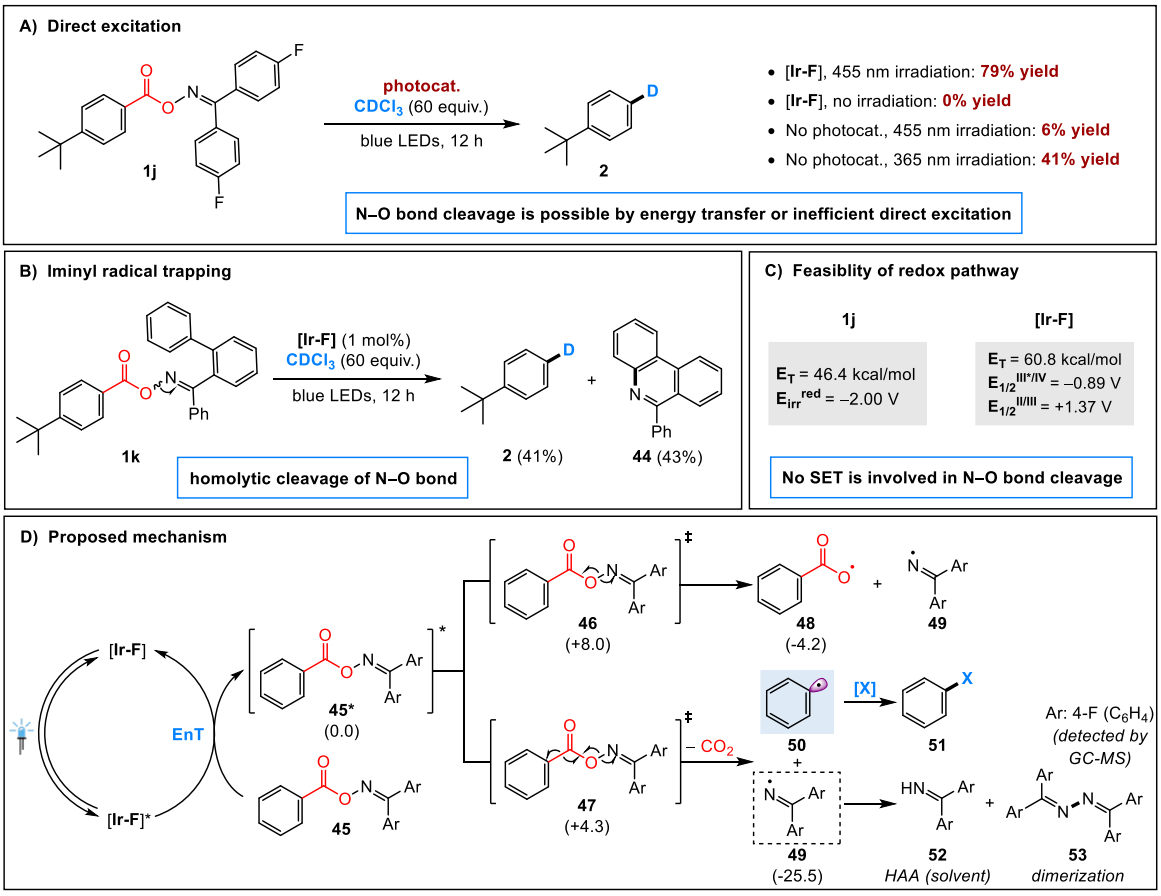


Figure 2. Proposed mechanism supported by experimental and computational studies. Calculated free enthalpies (CAM-B3LYP/def2-TZVPP/CPCM($CHCl_3$)) are given in kcal mol^{-1} and indicated in parentheses. For details see SI.

The absence of this alternative pathway is supported by DFT calculations. Computation of the energy profile of both pathways reveals that a concerted fragmentation/decarboxylation transition state is favoured by 3.7 kcal mol^{-1} over the respective fragmentation transition state (Supplementary Fig. 5). This is in sound agreement with the experimentally observed selectivity for decarboxylation over carboxylic acid formation.

Conclusion

Rationalizing the reactivity differences between aromatic and aliphatic carboxylic acid, we have established a general decarboxylative functionalization strategy valid for both aromatic and aliphatic carboxylic acids. Importantly, independence between the decarboxylation and the functionalization steps provides the flexibility for a diverse set of C–X and C–C bond forming reactions. Comprehensive mechanistic understanding suggests that a triplet-triplet energy transfer mediated concerted homolytic fragmentation/decarboxylation sequence validates the generality for aromatic and aliphatic decarboxylation. All these findings can be potentially applicable towards new strategic C–C bond formation and transition metal catalysis, which are the subject of our current investigation.

Supporting Information

Experimental and computational details, compound characterization data, and spectra (PDF)

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