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Triphenylphosphine-Catalyzed Alkylative Iododecarboxylation with Lithium Iodide under Visible Light

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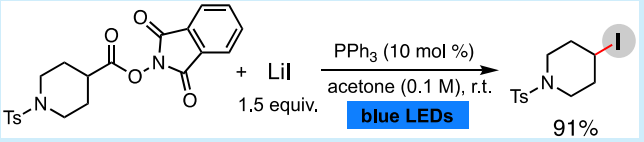
ABSTRACT: Under irradiation of 456 nm blue light-emitting diodes, PPh_3 catalyzes the iododecarboxylation of aliphatic carboxylic acid derived *N*-(acyloxy)phthalimide with lithium iodide as an iodine source. The reaction delivers primary, secondary, and bridgehead tertiary alkyl iodides in acetone solvent, and the alkyl iodide products were easily used to generate C−N, C−O, C−F, and C−S bonds to allow various decarboxylative transformations without using transition-metal or organic-dye-based photocatalysts.



Decarboxylative transformations[1] that convert a carboxylate group into a functionality that is a versatile handle for various further transformations, such as the recent development of alkylative decarboxylative borylation,[2,3] are of great significance in organic synthesis. Alternatively, a low-cost alkylative iododecarboxylation reaction has similarly high merits for use with aliphatic carboxylic acids in organic synthesis. The importance of decarboxylative halogenation of aliphatic carboxylates in organic synthesis is reflected in several named reactions, such as the Hunsdiecker reaction,[4] the Kochi reaction,[5] and Barton halogenative decarboxylation[6] (Figure 1A). Decarboxylative halogenation generates organohalides, which are among the most versatile building blocks in modern organic synthesis.[7] Alkyl iodide represents the most reactive electrophile among the various alkyl halides; thus, efficient iododecarboxylation offers a platform for a variety of decarboxylative transformations.[8] Iododecarboxylation of aromatic carboxylic acids and their derivatives has been extensively reported.[9] Notably, a recent report by Larrosa et al.[10] delineated an efficient transition-metal-free iododecarboxylation of arene carboxylic acid using molecular iodine. Reported examples of iododecarboxylation of aliphatic carboxylic acid derivatives include halogenative decarboxylation of Barton esters with iodoform,[11] oxidative methods using $PhI(OAc)_2/I_2$ or *N*-iodoamides under light,[12] decarboxylation of bridgehead carboxylic acid with *t*-BuOCl and HgI_2,[13] and a recent photoredox method using iridium photoredox catalyst and *N*-iodosuccinimide.[14] The propensity of iodine cations to undergo electrophilic substitution with arenes presents another challenge in chemoselective iododecarboxylation for complex molecules containing electron-rich arene moieties.[15] A method using an alkali iodide salt under mild redox neutral conditions would thus be useful for transformation of complex substrates, but has not been developed.

We posited that photoactivation of transiently assembled chromophores composed of a redox-active ester (RAE), an iodide salt, and a triarylphosphine for alkyl radical generation, providing an expedient method for alkylative iododecarboxylation.[16] The principle of radical generation is based on the photoactivation of an electron donor−acceptor (EDA) encounter complex in an organic solvent cage to generate free-radical ions after diffusion (Figure 1B).[17] Solvation and noncovalent interactions between substrates play crucial roles in determining the productive photoactivation and subsequent diffusion process.[18] This principle of photoactivation can be utilized to design a catalytic cycle for bond formation with a catalyst that facilitates electron transfer from a donor moiety to an acceptor moiety and to suppress undesired back electron transfer to induce further fragmentation of radical ion species[19] (Figure 1B). As depicted in Figure 1C, an iodide salt, PPh_3, and an RAE transiently assemble to form a chromophore that absorbs up to blue visible light in the UV−vis spectrum (see Supporting Information for details). The EDA encounter complex can be a transiently assembled species in a solvent cage that is held through weak, noncovalent interactions,[20,21] and hence is not isolable. Photoactivation of the EDA encounter complex results in an electron transfer process that forms an $[I\text{-}PPh_3]^\bullet$ radical and a phthalimide radical anion, which triggers subsequent decarboxylation to deliver an alkyl radical. It is worth mentioning that, although similar UV−vis absorption spectra were observed in the absence of PPh_3 (see Supporting Information for more details), the presence of PPh_3 is crucial to suppress back electron transfer from the phthalimide radical anion to $^\bullet I$, by forming thermodynamically stable $[I\text{-}PPh_3]^\bullet$, and to prevent formation of I_2, which was found to be detrimental.[16] The alkyl radical reacts with [I-

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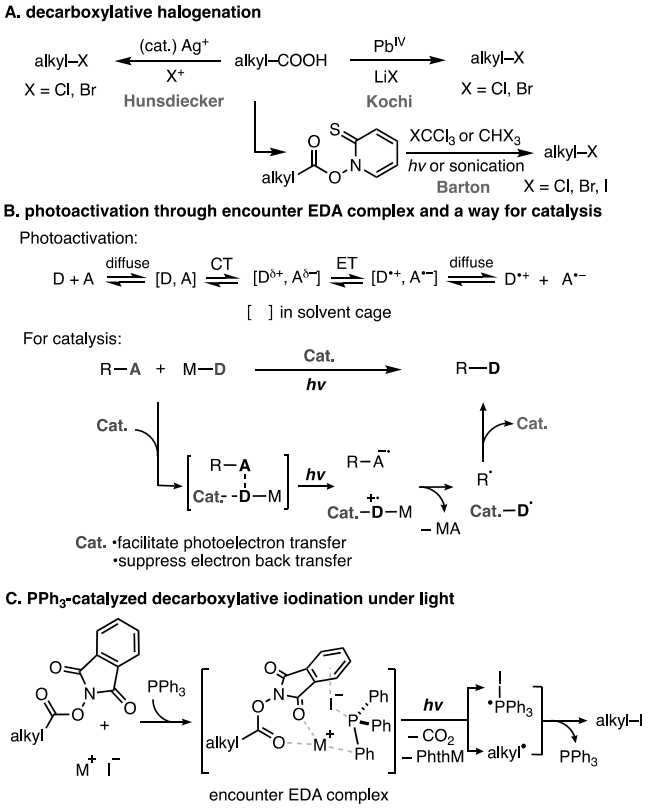

Figure 1. Iododecarboxylation using PPh_3 and MI. (A) traditional decarboxylative halogenation reactions. (B) Concept of photoactivation of encounter electron-donor−acceptor complex in solvent cage for radical generation and a way to design photocatalysis. D = electron donor substrate, A = electron acceptor substrate, CT = charge transfer, ET = electron transfer. (C) Working hypothesis of triphenyl phosphine catalyzed decarboxylative iodination.

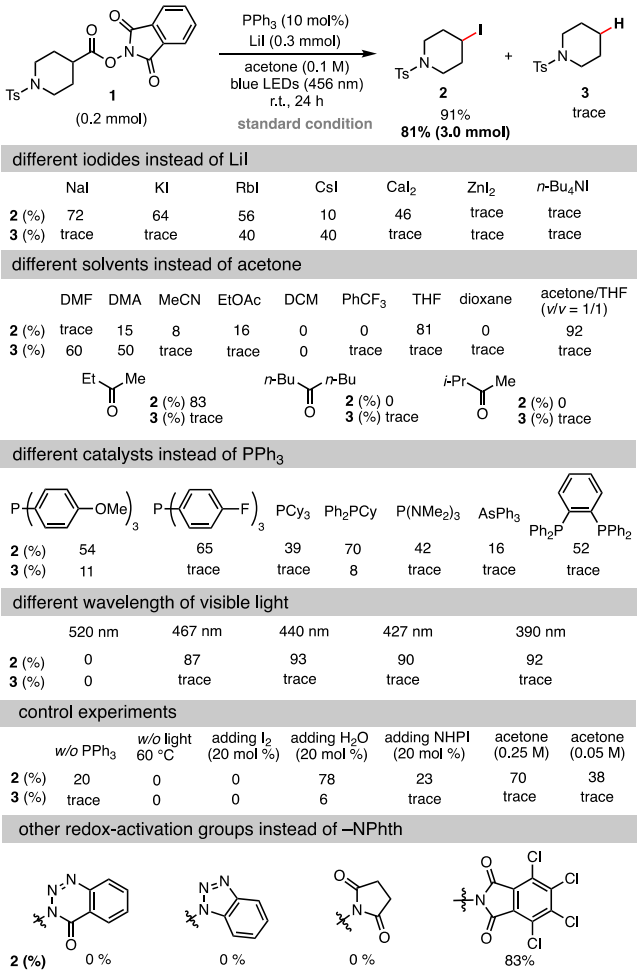

Figure 2. Key reaction-controlling parameters of decarboxylative iodination. The yield was determined by ^1H NMR using diphenylmethane as internal standard. NHPI, *N*-hydroxyphthalimide

$PPh_3]^\bullet$ to produce alkyl iodides and regenerate PPh_3; hence, the reaction is catalytic in PPh_3. The simplicity and low cost of this protocol, taken together with the high electrophilicity of alkyl iodides under either S_N2 or metal-catalyzed conditions, provide an expedient pathway for a variety of decarboxylative transformations.

The optimized reaction conditions are shown at the top of Figure 2. In a transparent Schlenk tube, a mixture of RAE (**1**) (0.2 mmol), lithium iodide (0.3 mmol), and a catalytic amount of PPh_3 (10 mol %) in degassed acetone solvent (0.1 M) was irradiated under blue LEDs at room temperature for 24 h. The desired iodination product **2** was obtained in 91% yield, and only a trace amount of decarboxylative hydrogen atom transfer (HAT) byproduct **3** was detected by ^1H NMR analysis. LiI was observed to be not fully soluble under the optimal conditions. Key controlling parameters are shown in Figure 2. The results of testing various alkali iodides, shown in the first row of Figure 2, showed that as the cation radius of the alkali metal increases (from Li to Cs), the yield of **2** gradually decreases. Reduction byproduct **3** through the HAT process from solvent was detected in significant amounts when RbI or CsI was used. The conversion of **1** dramatically decreased when CaI_2 was used, resulting in a low yield (46%) of **2**. The use of either ZnI_2 or n-Bu_4NI as the iodine source was entirely ineffective. These results revealed a significant cation effect and suggest that the cations affect assembly of the chromophore in a solvent cage, and hence affect the rate of electron transfer and subsequent radical decarboxylation. Following our previous assumption,[16] a cation−π interaction is critical to associate the LiI/RAEs chromophore with PPh_3, which is essential to suppress undesired back electron transfer in the excitation state. As the strength of the cation−π interaction is largely predicted by electrostatics, large alkali cations (K, Rb, Cs) have relatively weaker cation−π interaction compared to small cations of higher charge density. Solvation heavily affects the reaction outcome by influencing formation of a transiently assembled EDA encounter complex[18] and iodine abstraction of generated radical (second row of Figure 2). Amide solvents such as DMF and DMA primarily resulted in the formation of decarboxylative HAT products. Acetonitrile (MeCN), ethyl acetate (EtOAc), dichloromethane (DCM), and trifluorotoluene ($PhCF_3$) were all unsuitable solvents. Tetrahydrofuran (THF) was a suitable solvent, whereas the use of dioxane as solvent gave no product. A mixed THF/acetone solvent system appeared to be optimal. The remarkable and subtle solvent effect was also demonstrated by testing ketone derivatives as solvent. Acetone is an optimal solvent, and using butan-2-one gave a reduced yield. In sharp contrast, the use of nonan-5-one or 3-methylbutan-2-one as the solvent resulted in no decarboxylative transformation.

Examination of a series of phosphines with different sterics and electronic natures (third row in Figure 2; see the

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Supporting Information for more details) showed that the simplest PPh_3 appeared to be the best. Addition of 10 mol % O=PPh_3 to the reaction mixture had no effect on the outcome, whereas the addition of 20 mol % I_2 entirely killed the reaction. The reaction was not sensitive to the catalytic amount (20 mol %) of water, but addition of 20 mol % of NHPI was detrimental. Irradiation with blue LED was essential. The application of green light of 520 nm was totally ineffective, whereas light of wavelengths 467, 440, 427, or 390 nm was comparably effective, a phenomenon that correlates with the UV−vis absorption spectrum (fourth row of Figure 2). Besides light and PPh_3, the concentration is also crucial. A concentration of 0.1 M in acetone was optimal. Further concentrated solution (0.25 M) resulted in poor solubility of substrates and low yield. Dilution was unfavorable for chromophore assembly and significantly reduced the reaction efficiency. Tetrachloro-*N*-hydroxyphthalimide-derived RAE gave a slightly lower yield compared with *N*-hydroxyphthalimide, whereas other activation groups, such as 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one, 1-hydroxybenzotriazole, and *N*-hydroxysuccinimide were ineffective. *N*-Hydroxyphthalimide ester of arene carboxylic acid was not reactive under the optimal conditions. The quantum yield of this reaction was measured to be 0.69 (see the Supporting Information for details), which is consistent with a closed redox cycle involving a radical quenching step (Figure 1C).

The scope of the reaction is summarized in Figure 3. A broad range of alkyl carboxylates with various functionalities was readily converted into the corresponding primary, secondary, and bridgehead tertiary alkyl iodides. Functional groups such as ether (**4**, **14**), imide (**5**), aryl bromide (**6**), aryl aldehyde (**7**), aryl pinacol boronate (**8**), alkene (**9**), ester (**10**, **26**, **27**), amide (**15**, **16**), trifluoromethyl (**12**), aryl chloride (**13**), aryl iodide (**20**), ketone (**24**), and hydroxy (**25**) were compatible. Iodination of the electron-rich arene moiety (**4**, **6**, **10**) was not observed. N-Protected piperidine iodides, such as *N*-*tert*-butoxycarbonyl (**16**), benzyloxycarbonyl (**17**, **19**), and benzoyl (**18**, **20**), were obtained in good yields. Both cyclic and acyclic secondary carboxylic acid derived RAEs reacted well (**14**−**22**). For the reaction leading to **21**, the byproduct of intramolecular radical cyclization on the *ortho*-C−H of phenyl was detected. Heteroarene moieties, such as thiophene (**11**) and furan (**15**), were tolerated without undergoing electrophilic C−H iodination. RAEs derived from bridgehead carboxylic acids gave bridgehead tertiary iodides in good to excellent yields (**23**−**27**). Decarboxylative iodination at the benzylic position did not proceed probably due to the stability of the benzylic radical. Katritzky salt derived from cyclohexyl amine failed to react under the optimal conditions for RAEs.

The mild redox-neutral conditions of the protocol encouraged us to test synthetic modifications of a series of RAEs derived from natural products and pharmaceuticals. As shown in Figure 4, RAEs derived from linoleic acid (**28**), oleic acid (**29**), erucic acid (**30**), and undecenoic acid (**31**) smoothly underwent decarboxylative iodination with the stereochemical integrity of the alkene moieties remaining intact. RAEs derived from medicinal compounds and complex natural products, such as pregabalin (**32**, **33**), mycophenolic acid (**34**), gabapentin (**35**, **36**), dehydrocholic acid (**37**), chloroambucil (**38**), baclofen (**39**), estrone (**40**), and lithocolic acid (**41**), also reacted smoothly to deliver the corresponding iodides. The relatively low yield of chloroambucil (**38**) could be partially explained by a competitive

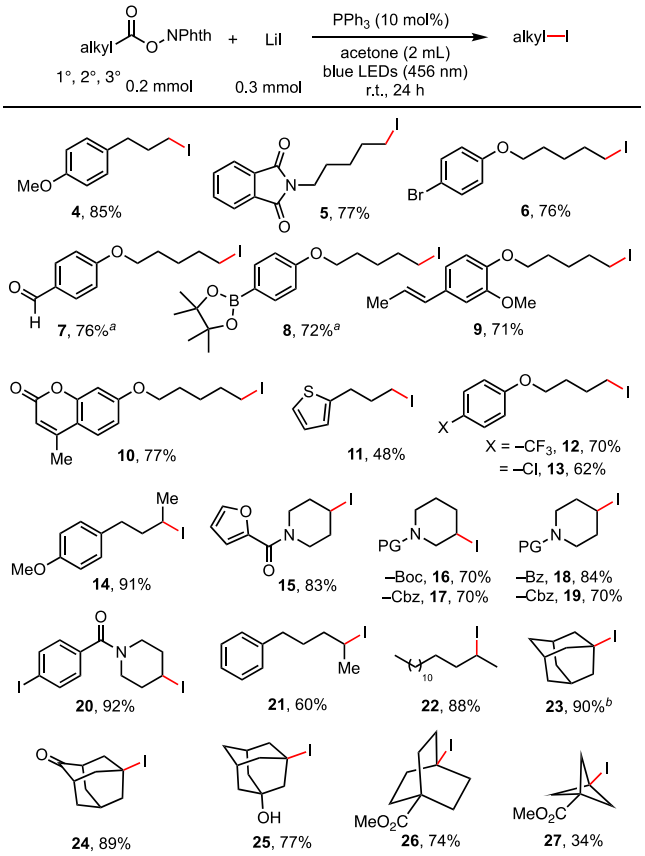
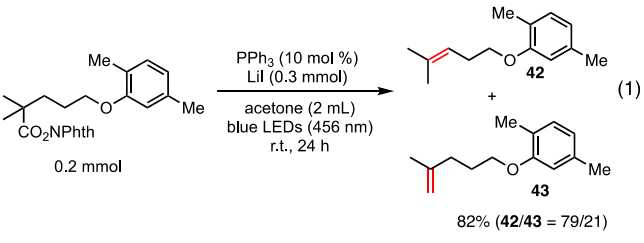


Figure 3. Scope for iododecarboxylation of aliphatic RAEs. Reaction conditions: redox-active esters (1.0 equiv, 0.2 mmol), LiI (1.5 equiv, 0.3 mmol), PPh_3 (10 mol %), acetone (2 mL), blue LEDs (456 nm), rt, 24 h. Isolated yield. [a]Mixed solvent of THF (1 mL) and acetone (1 mL) was used. [b]The yield was determined by ^1H NMR using diphenylmethane as internal standard.

Finkelstein reaction. It is worth noting that the unprotected phenolic hydroxyl in mycophenolic acid (**34**) is compatible. For estrone analogue **40**, the electron-rich phenyl ring, which is susceptible to electrophilic halogenation, remained unaffected. The alkyl iodides derived from these natural products and pharmaceuticals are suitable for introduction into bioactive structure motifs to construct complex molecules or for further diversification.

The reaction did not work well for obtaining ordinary tertiary iodide, probably because of the low bond-dissociation energy of the tertiary alkyl−I bond and its tendency to generate a tertiary carbon cation.[22] Testing RAE derived from gemfibrozil resulted in the formation of a mixture of alkene regioisomers (eq 1) with no product of iododecarboxylation detected.



Iododecarboxylation of 4-alkylcyclohexane-1-carboxylate showed little diastereoselectivity (eq 2). RAEs possessing 4-

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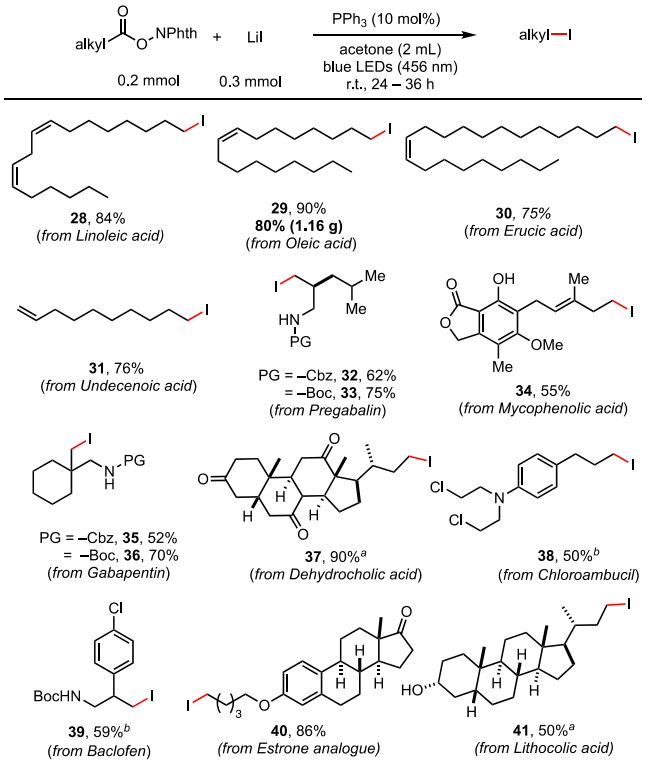
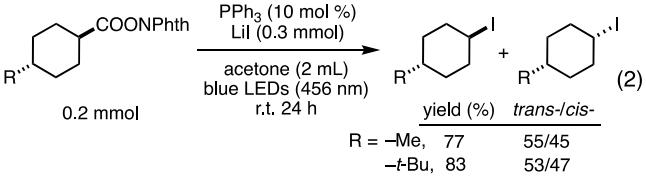
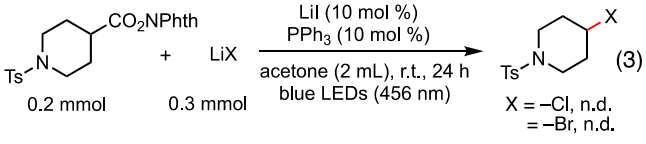


Figure 4. Iododecarboxylation of natural products and pharmaceuticals. Reaction conditions: redox-active esters (1.0 equiv, 0.2 mmol), LiI (1.5 equiv, 0.3 mmol), PPh_3 (10 mol %), acetone (2 mL), blue LEDs (456 nm), rt, 24 h. Yields of isolated products. [a]Mixed solvent of THF (1 mL) and acetone (1 mL) was used. [b]PPh_3 (20 mol %).

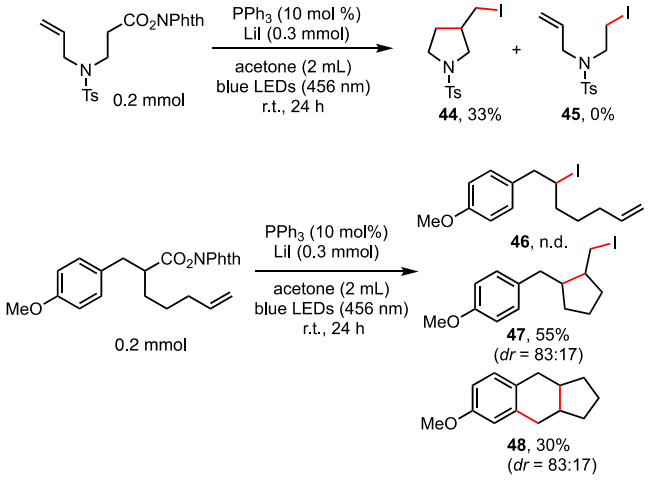


methyl and 4-*tert*-butyl as substituents produced iodination products of similar yields with similar trans-/cis- ratios, revealing that iodine abstraction of alkyl radical from $[I\text{-}PPh_3]^\bullet$ is less sensitive to steric effect. Radical cyclization experiments proved that the reactions proceed through a process involving free alkyl radicals (Scheme 1). Reactions using 1.5 equiv of LiCl or LiBr in the presence of 10 mol % of LiI did not produce any decarboxylative chlorination or bromination product (eq 3), suggesting that a carbon cation is not oxidatively generated with $[I\text{-}PPh_3]^\bullet$.



Simply treating the obtained cyclic secondary alkyl iodides with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 60 °C in one pot generated the alkene products in high yields (Figure 5, **49**–**53**). Decarboxylative elimination of these carboxylic acid was recently reported using either photoredox/transition-metal synergistic catalysis[23] or palladium catalysis under light.[24]

Scheme 1. Radical Cyclization Experiments



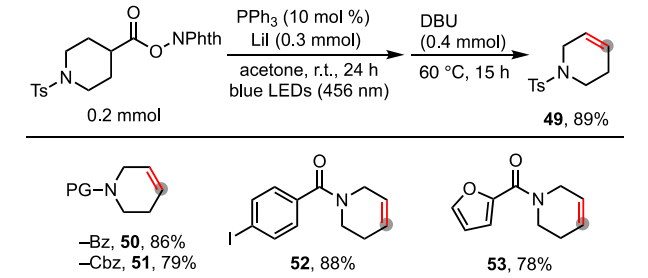


Figure 5. Decarboxylative elimination.

Facile access to alkenes expands the synthetic utility of this low-cost and mild protocol.

The products of iododecarboxylation can be further used to construct C–O, C–N, C–F, and C–SCN bonds (see Supporting Information p S32 for more details), allowing their subsequent use without requiring the expensive catalysts.[25−27] Subsequent formation of C–N and C–SCN bonds can also be achieved in one pot in good yields without isolation of alkyl iodides (see Supporting Information p S35). The procedures thus provide alternative methods for decarboxylative oxygenation, amination, fluorination, and thiocyanation, underlining its wide applicability to various synthetic tasks.

In summary, a PPh_3-catalyzed iododecarboxylation protocol for use with aliphatic carboxylates and lithium iodide under irradiation with blue light has been developed.[28] The reaction uses lithium iodide as the iodine source, proceeds under mild, redox-neutral conditions, and hence is suitable for modification of complex natural products and pharmaceuticals. The activation principle of this protocol is based on the photoactivation of an EDA encounter complex in a solvent cage, and a catalyst for this process facilitates electron transfer and suppresses back electron transfer. The protocol has the advantages of low cost and simplicity and allows versatile follow-up transformations to be applied, thereby expanding the use of aliphatic carboxylic acids in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03173.

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Experimental procedures, reaction parameters, mechanistic investigation, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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