

Triphenylphosphine-catalyzed Alkylative Iododecarboxylation with Lithium Iodide under Visible Light

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Article

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Abstract

Photoactivation of an electron donor–acceptor encounter complex in an organic solvent cage, a phenomenon that has been described in Mulliken theory, has been known for decades, but it has not been employed as a photoactivation step in the design of photocatalysis for organic synthesis until recent years. We report herein an iododecarboxylation reaction that applies this concept for photoactivation by using a catalyst to facilitate electron transfer and to suppress back electron transfer in the photoexcited state. Under irradiation of 456 nm blue light-emitting diodes, PPh₃ catalyzes the iododecarboxylation of aliphatic carboxylic acid-derived N-(acyloxy)phthalimide with lithium iodide as 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. This protocol is applicable to redox-active esters derived from various natural products and pharmaceuticals.

Background

Decarboxylative transformations^{1–4} 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^{5,6}, are of great significance in organic synthesis. Alternatively, a low-cost alkylative decarboxylative iodination 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 reaction⁷, the Kochi reaction⁸, and Barton halogenative decarboxylation⁹ (Fig. 1A). Decarboxylative halogenation generates organohalides, which are among the most versatile building-blocks in modern organic synthesis^{10–12}. Alkyl iodide represents the most reactive electrophile among the various alkyl halides; thus, efficient decarboxylative iodination offers a platform for a variety of decarboxylative transformations¹³ from easily available carboxylic acids. Decarboxylative iodination of aromatic carboxylic acids and their derivatives has been extensively reported^{14,15}. Notably, a recent report by Larrosa and co-workers¹⁶ delineated an efficient transition-metal-free decarboxylative iodination of arene carboxylic acid using molecular iodine. However, reports on efficient decarboxylative iodination of aliphatic carboxylic acid derivatives remain relatively rare because alkyl iodides are susceptible to various metal catalysts and nucleophiles. Reported examples of decarboxylative iodination of aliphatic carboxylic acid derivatives include halogenative decarboxylation of Barton esters with iodoform¹⁷, oxidative methods using iodobenzene diacetate and molecular iodine under light¹⁸, decarboxylation of bridgehead carboxylic acid with *t*-BuOCl and HgI₂¹⁹, and a recent photoredox method using iridium photoredox catalyst and N-iodosuccinimide that proceeds with moderate yields²⁰. The propensity of iodine cations to undergo electrophilic substitution with arenes presents another challenge in chemoselective decarboxylative iodination for complex molecules containing electron-rich arene moieties²¹. Decarboxylative iodination

using an iodide salt under mild redox neutral conditions would thus be useful for direct functionalization of complex substrates. We posited that our recently reported strategy of photoactivation of transiently assembled chromophores composed of a redox-active ester (RAE), an iodide salt, and a triarylphosphine for alkyl radical generation, provides an expedient method for alkylative decarboxylative iodination²². 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 diffusion²³ (Fig. 1B). Solvation and noncovalent interactions between substrates play crucial roles in determining the productive photoactivation and subsequent diffusion process^{24–27}. 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^{28,29} (Fig. 1B). Herein, we implement this hypothesis to design a decarboxylative iodination of aliphatic carboxylates.

As depicted in Fig. 1C, an iodide salt, triphenylphosphine, and an RAE transiently assemble to form a chromophore as indicated by the light-yellow appearance of the solution and absorbs up to blue visible light in the UV-Vis spectrum (see Supplementary Information for details). The EDA encounter complex can be a transiently assembled species in a solvent cage that is held through weak, noncovalent interactions^{30–33}, and hence is not isolable. Photoactivation of the EDA encounter complex results in an electron transfer process that forms an $\cdot\text{I}-\text{PPh}_3$ 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 Supplementary Information for more details), the presence of PPh_3 is crucial to suppress back electron transfer from the phthalimide radical anion to $\cdot\text{I}$ by forming thermodynamically stable $\cdot\text{I}-\text{PPh}_3$, and to prevent formation of I_2 , which was found to be detrimental. The alkyl radical reacts with $\cdot\text{I}-\text{PPh}_3$ to produce alkyl iodides and regenerate PPh_3 ; hence, the reaction is catalytic in PPh_3 . We document herein a PPh_3 -catalysed photochemical alkylative decarboxylative iodination of aliphatic carboxylic acid-derived RAEs. The simplicity and low cost of this protocol, taken together with the high electrophilicity of alkyl iodides under either $\text{S}_{\text{N}}2$ or metal-catalysed conditions, provide an expedient pathway for the development of a variety of decarboxylative transformations.

Results And Discussion

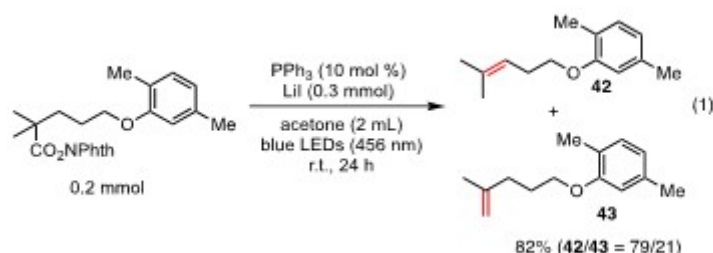
The optimized reaction conditions are shown at the top of Fig. 2. In a transparent Schlenk tube, a mixture of RAE (**1**) (0.2 mmol), lithium iodide (0.3 mmol), and a catalytic amount of PPh_3 (10 mol%) in degassed acetone solvent (0.1 M) was irradiated under blue LEDs at room temperature for 24 h. The desired iodination product **2** was obtained in 91% yield and only a trace amount of decarboxylative protonation by-product **3** was detected by ^1H NMR analysis. Key controlling parameters are shown in Fig. 2. The results of testing various alkali iodides, shown in the first row of Fig. 2, showed that as the cation radius of the alkali metal increases (from Li to Cs), the yield of **2** gradually decreases. Protonation by-product **3**

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 $n\text{-Bu}_4\text{NI}$ as 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. Solvation heavily influences the extent to which a transiently assembled EDA encounter complex¹⁸ can affect the reaction outcome (second row of Fig. 2). Amide solvents such as DMF and DMA primarily resulted in the formation of decarboxylative protonation 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 reduced yield. In sharp contrast, the use of nonan-5-one or 3-methylbutan-2-one as the solvent resulted in no decarboxylative transformation.

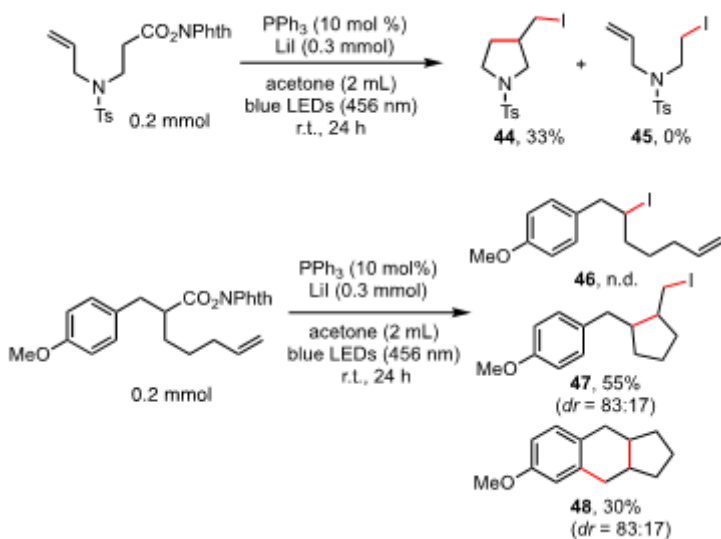
The scope of the reaction is summarized in Fig. 3. A broad range of alkyl carboxylates with various functionalities was readily converted into the corresponding primary, secondary, and bridgehead tertiary alkyl iodides. Functional groups, such as ether (**4**, **14**), imide (**5**), aryl bromide (**6**), 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 by-product 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**).

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 Fig. 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 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.

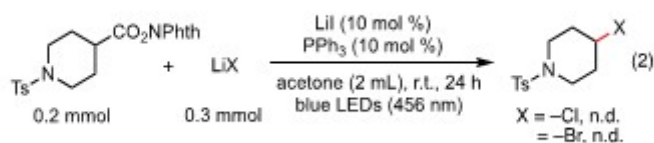
The reaction did not work well for obtaining ordinary tertiary iodide, probably because of the low bond-dissociation energy of the tertiary alkyl–I bond and because of its tendency to generate a tertiary carbon cation³⁴. Testing RAE derived from gemfibrozil resulted in the formation of a mixture of alkene regioisomers (equation 1) with no product of decarboxylative iodination detected.



Radical cyclization experiments unequivocally proved that the reactions proceed through a process involving free alkyl radicals (Scheme 1). Reactions using 1.5 equivalent of LiCl or LiBr in the presence of 10 mol% of Lil did not produce any decarboxylative chlorination or bromination product (equation 2), suggesting that a carbon cation is not oxidatively generated with $^{\bullet}\text{I}-\text{PPh}_3$.



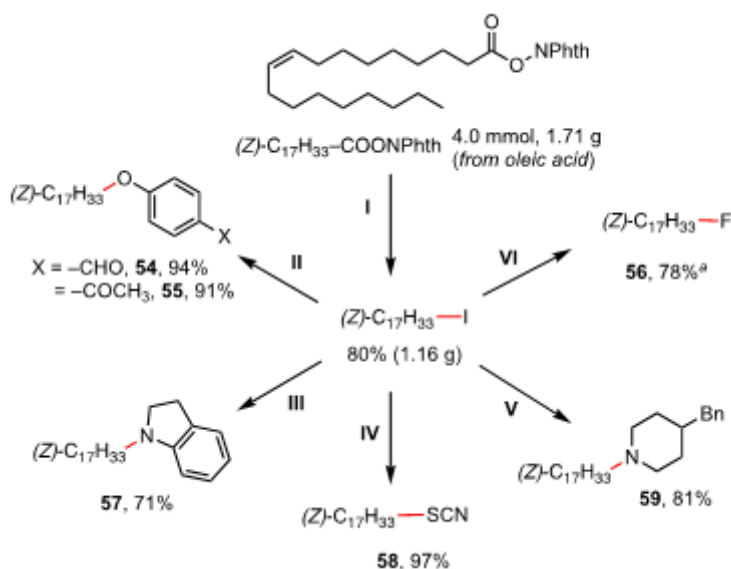
Scheme 1 Radical cyclization experiments.



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 (Fig. 5, **49–53**). Decarboxylative elimination of these carboxylic acids was recently reported using either photoredox/synergistic

catalysis^{35,36} or palladium catalysis under light³⁷. Facile access to alkenes expands the synthetic utility of this low-cost and mild decarboxylative iodination protocol.

The products of decarboxylative iodination can be further used to construct C–O, C–N, C–F, and C–SCN bonds, allowing their subsequent use without requiring the expensive transition metals^{38–41}. As exemplified by the reaction of oleic acid, shown in Scheme 2, a gram-scale decarboxylative iodination reaction produced the corresponding iodide in 80% yield. The primary iodide underwent S_N2-type reaction with oxygen, fluorine, nitrogen, and sulfur nucleophiles to generate ethers (**54**, **55**), fluoride (**56**), amine (**57**, **59**), and thiocyanate (**58**). Subsequent formation of C–N and C–SCN bonds can also be achieved in one pot in good yields without isolation of alkyl iodides (Scheme 3). The procedures thus provide alternative methods for decarboxylative oxygenation, amination, fluorination, and thiocyanation. These additional examples highlight the synthetic utility of the new photodecarboxylative iodination protocol and underline its wide applicability to various synthetic tasks.



Scheme 2 Further transformations for decarboxylative construction of C–O, C–N, C–F, and C–SCN

bonds. ^aThe yield was determined by ¹H NMR spectroscopic analysis using diphenylmethane as internal standard.



Scheme 3 One-pot decarboxylative thiocyanation and amination.

Conclusions

In summary, a PPh_3 -catalyzed iododecarboxylation protocol for use with aliphatic carboxylates and lithium iodide under irradiation with blue light has been developed. The reaction uses lithium iodide as 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.

Methods

General procedure for iododecarboxylation. Redox-active esters (1.0 equiv., 0.2 mmol) (if solid), LiI (1.5 equiv., 0.3 mmol), and PPh_3 (10 mol%) were added to a 10 mL transparent Schlenk tube equipped with a stirring bar. The tube was evacuated and filled with argon (three cycles). To these solids, redox-active esters (1.0 equiv., 0.2 mmol) (if liquid) and acetone (2.0 mL) were added under argon atmosphere. The reaction mixture was stirred under irradiation with blue LEDs (Kessil, PR160–456 nm) maintained at approximately room temperature. After 24 h, the mixture was transferred to a round-bottom flask and concentrated with a rotary evaporator. The product was purified by flash column chromatography on silica gel.

Declarations

Author contributions

R.S. conceived the concept, guided the project, and wrote the manuscript; M.-C.F. and J.-X.W. performed the experiments; and M.-C.F., and R.S. analyzed the data and participated in the preparation of the manuscript.

Competing financial interests.

The authors declare no competing financial interests.

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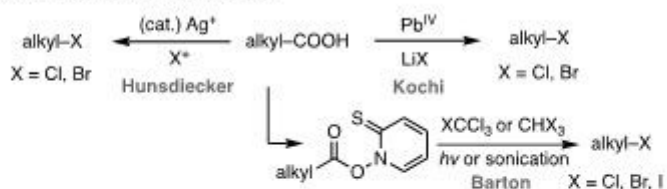
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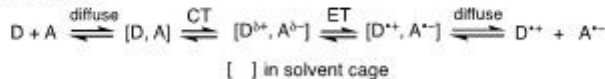
Figures

A. decarboxylative halogenation

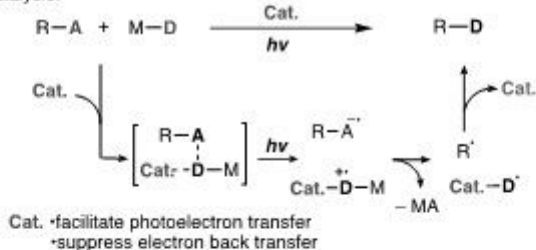


B. photoactivation through encounter EDA complex and a way for catalysis

Photoactivation:



For catalysis:



C. PPh₃-catalyzed decarboxylative iodination under light

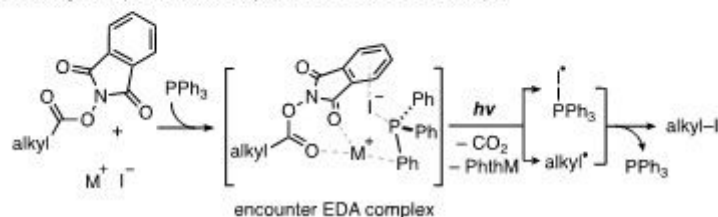
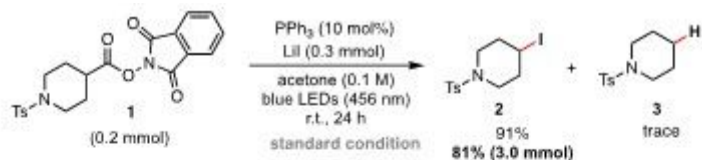


Figure 1

Iododecarboxylation using PPh₃ and MI. A, Traditional decarboxylative halogenation reactions. B, Concept of the photoactivation of an electron donor–acceptor encounter complex in a solvent cage for radical generation that can be used in the design of photocatalysis systems. D, electron donor substrate or moiety; A, electron acceptor substrate or moiety; CT, charge transfer; ET, electron transfer. C, Working hypothesis for triphenylphosphine-catalysed decarboxylative iodination.



different iodides instead of LiI							
	Nal	KI	RbI	CsI	CaI ₂	ZnI ₂	<i>n</i> -Bu ₄ NI
2 (%)	72	64	56	10	46	trace	trace
3 (%)	trace	trace	40	40	trace	trace	trace

different solvents instead of acetone									
	DMF	DMA	MeCN	EtOAc	DCM	PhCF ₃	THF	dioxane	acetone/THF (w/v = 1/1)
2 (%)	trace	15	8	16	0	0	81	0	92
3 (%)	60	50	trace	trace	0	trace	trace	trace	trace

Et-C(=O)-Me	<i>n</i> -Bu-C(=O)- <i>n</i> -Bu	<i>i</i> -Pr-C(=O)-Me
2 (%) 83	2 (%) 0	2 (%) 0
3 (%) trace	3 (%) trace	3 (%) trace

different catalysts instead of PPh ₃							
	P(<i>p</i> -OMe-C ₆ H ₄) ₃	P(<i>p</i> -F-C ₆ H ₄) ₃	PCy ₃	Ph ₂ PCy	P(NMe ₂) ₃	AsPh ₃	Ph ₂ P(Ph)PPh ₂
2 (%)	54	65	39	70	42	16	52
3 (%)	11	trace	trace	8	trace	trace	trace

different wavelength of visible light					
	520 nm	467 nm	440 nm	427 nm	390 nm
2 (%)	0	87	93	90	92
3 (%)	0	trace	trace	trace	trace

control experiments					
	w/o PPh ₃	w/o light, 60 °C	addition of I ₂ (20 mol %)	acetone (0.25 M)	acetone (0.05 M)
2 (%)	20	0	0	70	38
3 (%)	trace	0	0	trace	trace

other redox-activation groups instead of -NPhth			
2 (%) 0 %	0 %	0 %	83 %

Figure 2

Key reaction-controlling parameters for decarboxylative iodination. The yield was determined by ¹H NMR spectroscopic analysis using diphenylmethane as internal standard.

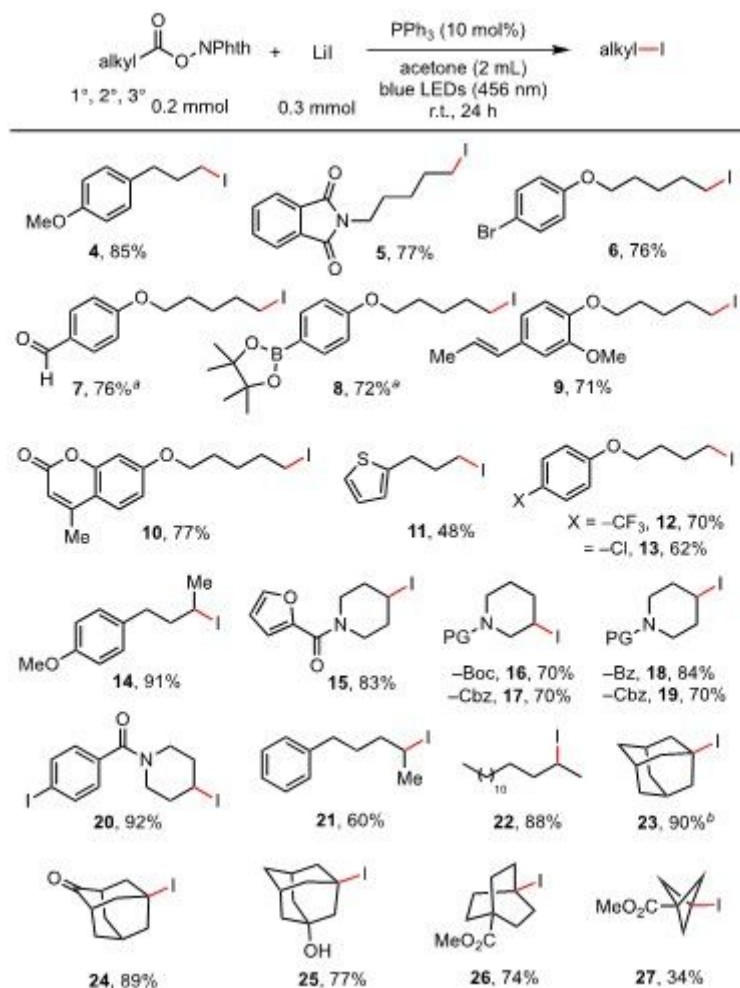


Figure 3

Scope for iododecarboxylation of aliphatic RAEs. Reaction conditions: redox-active esters (1.0 equiv., 0.2 mmol), Lil (1.5 equiv., 0.3 mmol), PPh₃ (10 mol%), acetone (2 mL), blue LEDs (456 nm), r.t., 24 h. Yields of isolated products. a Mixed solvent of THF (1 mL) and acetone (1 mL) was used. b The yield was determined by ¹H NMR spectroscopic analysis using diphenylmethane as internal standard.

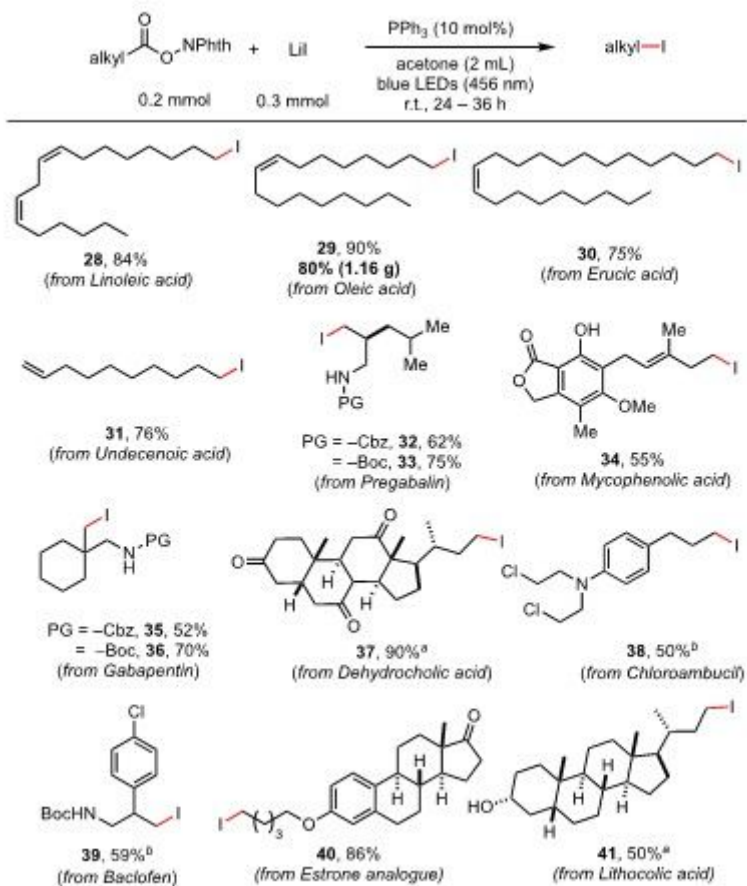


Figure 4

Iododecarboxylation of natural products and pharmaceuticals. Reaction conditions: redox-active esters (1.0 equiv., 0.2 mmol), LiI (1.5 equiv., 0.3 mmol), PPh₃ (10 mol%), acetone (2 mL), blue LEDs (456 nm), r.t., 24 h. Yields of isolated products. a Mixed solvent of THF (1 mL) and acetone (1 mL) was used. b PPh₃ (20 mol%).

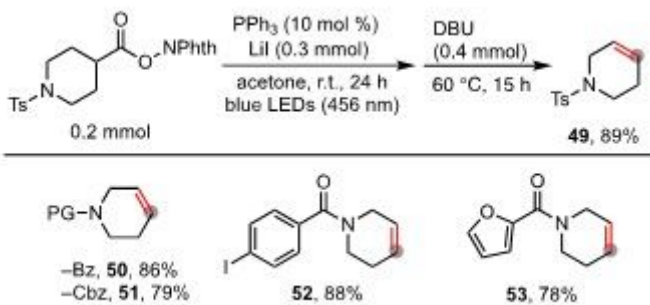


Figure 5

Decarboxylative elimination.

Supplementary Files

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- [SIFMC20200716.docx](#)