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Photochemical Dual Radical Coupling of Carboxylates with Alkenes/Heteroarenes via Diradical Equivalents

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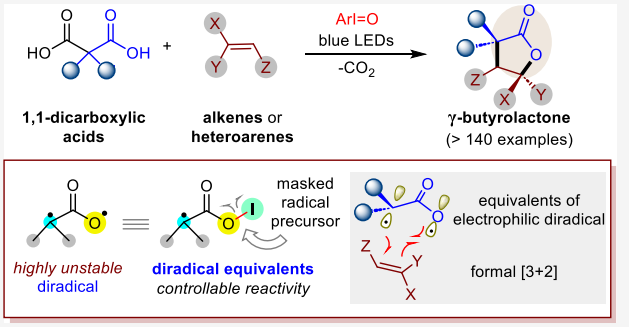
ABSTRACT: Carboxylate diradical intermediates, with α-carbon and carboxylic oxygen acting as reactive radical centers, represent a highly attractive and long-sought species in reaction design and synthesis. However, capturing these intermediates for diradical coupling reactions poses a formidable challenge due to their inherent instability and spontaneous decarboxylation. Here, we addressed this challenge by temporarily masking the carboxylate oxygen radical reactivity via a photocleavable dynamic oxygen−iodine bond. This approach effectively prevents unwanted decarboxylation and enables the controlled utilization of the carboxylate oxygen radical in forming new bonds. Carboxylates and alkenes/heteroarenes, among the most readily available raw materials, can now seamlessly couple via radical pathways to form γ-butyrolactones, which are common motifs found in numerous natural products and bioactive molecules. Ionic reaction pathways via traditional intermediates of carboxylates are ruled out based on experimental studies and density functional theory (DFT) calculations. This strategy overcomes the substrate limitations of traditional methods, significantly expanding the range of applicable alkenes/heteroarenes. Our method allows transforming carboxylates and alkenes via new reaction modes to diverse products and offers new insights into developing di- and multiradical equivalents for unprecedented reactions and synthetic designs.



INTRODUCTION

Carboxylic acids and alkenes/heteroarenes are among the most readily available synthetic building blocks and serve as structural motifs in numerous functional molecules.[1,2] The carboxylic acids and their derivatives are commonly activated via polar intermediates for electron-pair-transfer reactions such as amide synthesis.[3] In another arena, α-carbon centered[4−7] or carboxylic oxygen-centered[8,9] radical intermediates (Figure 1A, **A1** and **A2**) from carboxylic acids and their derivatives can be obtained for single-electron-transfer (SET) reactions. For instance, the exploration of carboxylic oxygen radical intermediates (**A2**) has led to many powerful transformations, including the well-known Hunsdiecker decarboxylation,[10,11] Barton decarboxylation,[12,13] and recently a sizable number of elegant visible light-promoted reactions.[14−23] However, it remains elusive to obtain diradical intermediates (**A3**) from carboxylates, where both the α-carbon and the carboxylic oxygen atom each bear a singly occupied electron. This is because such radical intermediate is highly unstable and can lead to the rapid formation of liable α-lactone in its open-shell singlet state and/or undergo nearly spontaneous decarboxylation in its triplet state,[24,25] with an estimated activation energy (ΔG) of 4.5 kcal mol^{-1} via DFT (see Figure S3). We postulated that the challenges may be overcome if the carboxylic oxygen radical can be temporarily masked (as illustrated by diradical equivalent **A4**). In this manner, a new class of two-carbon one-oxygen three-atom diradical synthons (**A5**) can be obtained for further reactions such as the controlled diradical cycloaddition with alkenes.[26−33]

Here we disclose that 1,1-dicarboxylic acids can react with alkenes and (hetero)arenes to form γ-butyrolactones in the presence of iodosoarenes (ArI=O) under blue LED irradiations (Figure 1B). The reaction starts with in situ reaction of a dicarboxylic acid **B1** with ArI=O to form an oligomeric adduct **B4** with labile O−I bonds. Under mild visible light irradiation, the adduct can reach its excited state, leading to homolytic O−I bond cleavage[34] to form a carboxylic oxygen-centered radical intermediate **B5**. Following a barrierless decarboxylation process, α-carbon centered carboxylate radical intermediate **B6** can be obtained. This electrophilic radical reacts with the sp^2 carbon of an alkene (or

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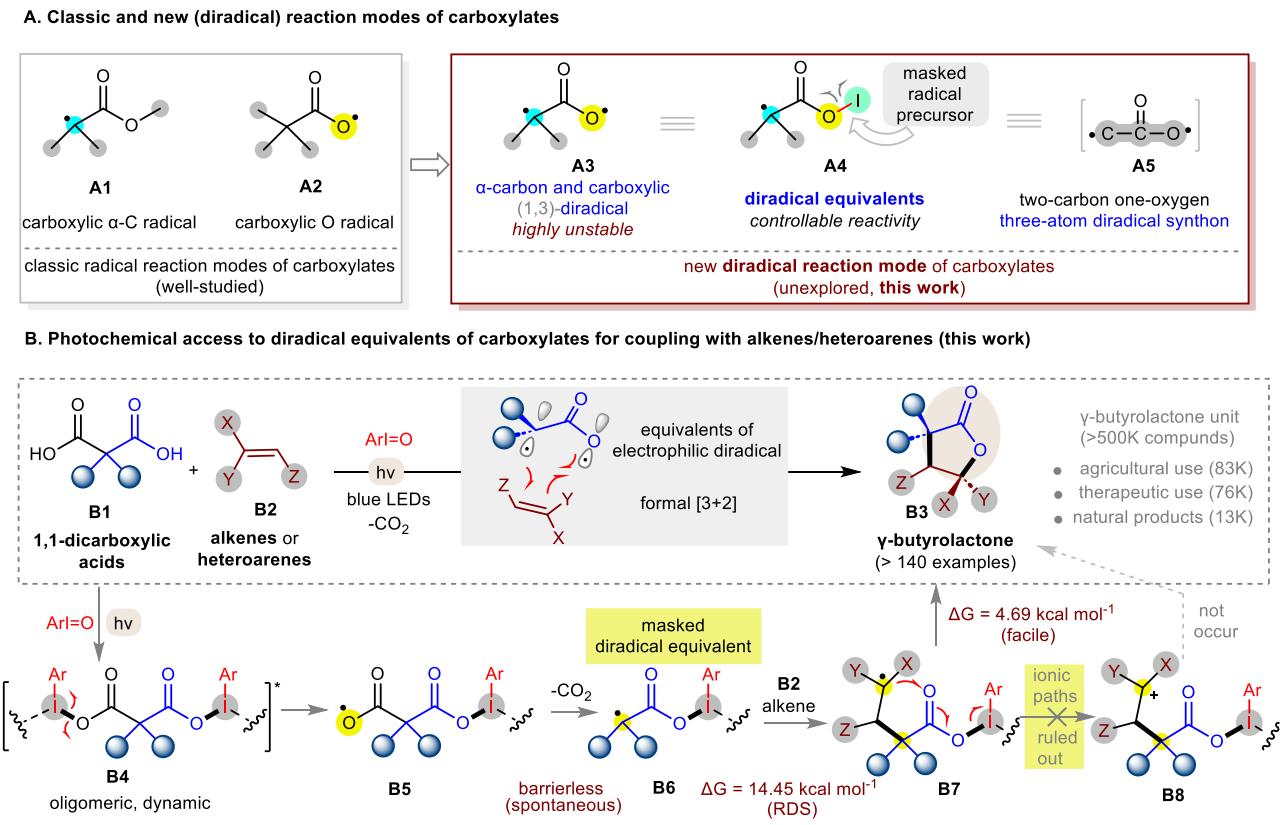

Figure 1. Background and our design of diradical reaction modes of carboxylates. (A) Classic monoradical reaction modes of carboxylic acid derivatives with either the α-carbon or the carboxylic oxygen atom as a radical center, vs our design of diradical equivalent intermediates where both the α-carbon and carboxylic oxygen atom react as radical species. (B) Coupling of 1,1-dicarboxylic acids with alkenes (and heteroarenes) to form γ-butyrolactones, in which the dicarboxylic acids are activated as diradical equivalents intermediate under photoexcitation.

heteroarene), forming a new carbon−carbon bond and transforming into a new carbon radical intermediate **B7**. The subsequent intramolecular radical cyclization process leads to the homolytic cleavage of the O−I bond (demasking of oxygen radical), facilitating the formation of product. DFT calculations reveal that the radical addition of intermediate **B6** to an alkene is the rate-determining step (RDS), with an activation energy of 14.45 kcal mol^{-1}, while the radical cyclization occurs rapidly with a relatively low barrier (ΔG = 4.69 kcal mol^{-1}). The complete reaction energy profile is summarized in Figure S4. Notably, in previous studies using aliphatic carboxyl radical (**A2**) as intermediate, rapid decarboxylation occurs ($k \approx 10^{9}$ s^{-1})[35] to form carbon-centered radical, and it is carbon atom (not the carboxyl oxygen atom) that is used to form the new chemical bond in the product. In this regard, our method offers a new strategy for bringing the carboxylate oxygen atom to the product by masking the highly reactive carboxylic oxygen radicals. From intermediate **B7** to product **B3**, an alternative ionic reaction pathway (via oxidizing the carbon radical **B7** to a carbocation **B8**) is ruled out based on experiments. Such ionic pathways have been previously involved in the synthesis of γ-butyrolactones under different substrate reaction scenarios.[36−40] For example, alternative photochemical methods for the synthesis of γ-butyrolactones from olefins and α-halo carboxylic acids (or their derivatives) are, however, primarily limited to styrenes.[41−43]

γ-Butyrolactone is one of the most common structural units found in over five hundred thousand natural and synthetic molecules, with a wide range of applications in fields such as medicine and agrochemicals (as revealed by a SciFinder search conducted in September 2024). Our strategy via coupling masked carboxylate diradical intermediates with alkenes/heteroarenes drastically expands the availability and structural diversity of such molecules. Compared to previous methods (with ionic pathways as key part the transformations) that require prefunctionalization of substrates and/or matching the redox reactivity between the catalyst and substrate (or reaction intermediates),[36−45] our methodology comprises a set of highly effective radical relay events that bypass ionic pathways, thereby enabling an impressively broad substrate scope of more than 140 examples. The mild reaction conditions, straightforward operation, and ease of scalability render our protocol highly promising for practical applications. Given the extremely broad availability of carboxylic acids and alkenes/heteroarenes, our methods allow for quick access to large molecular libraries of γ-butyrolactones. It also enables late-stage modification of medicines, natural products, and other bioactive molecules bearing unsaturated units. On the fundamental and conceptual side, our study provides an effective strategy for utilizing di- and potentially multiradical intermediates by introducing dynamic shielding functionalities. We hope our study will inspire strategic revisions for the synthesis of organic molecules, where the coupling of di- and multiradical intermediates with other substrates offers significant benefits.

RESULTS AND DISCUSSION

Reaction Development and Mechanistic Investigations. We selected commercially available cyclobutane-1,1-dicarboxylic acid **C1** and alkene **D1** as model substrates, with

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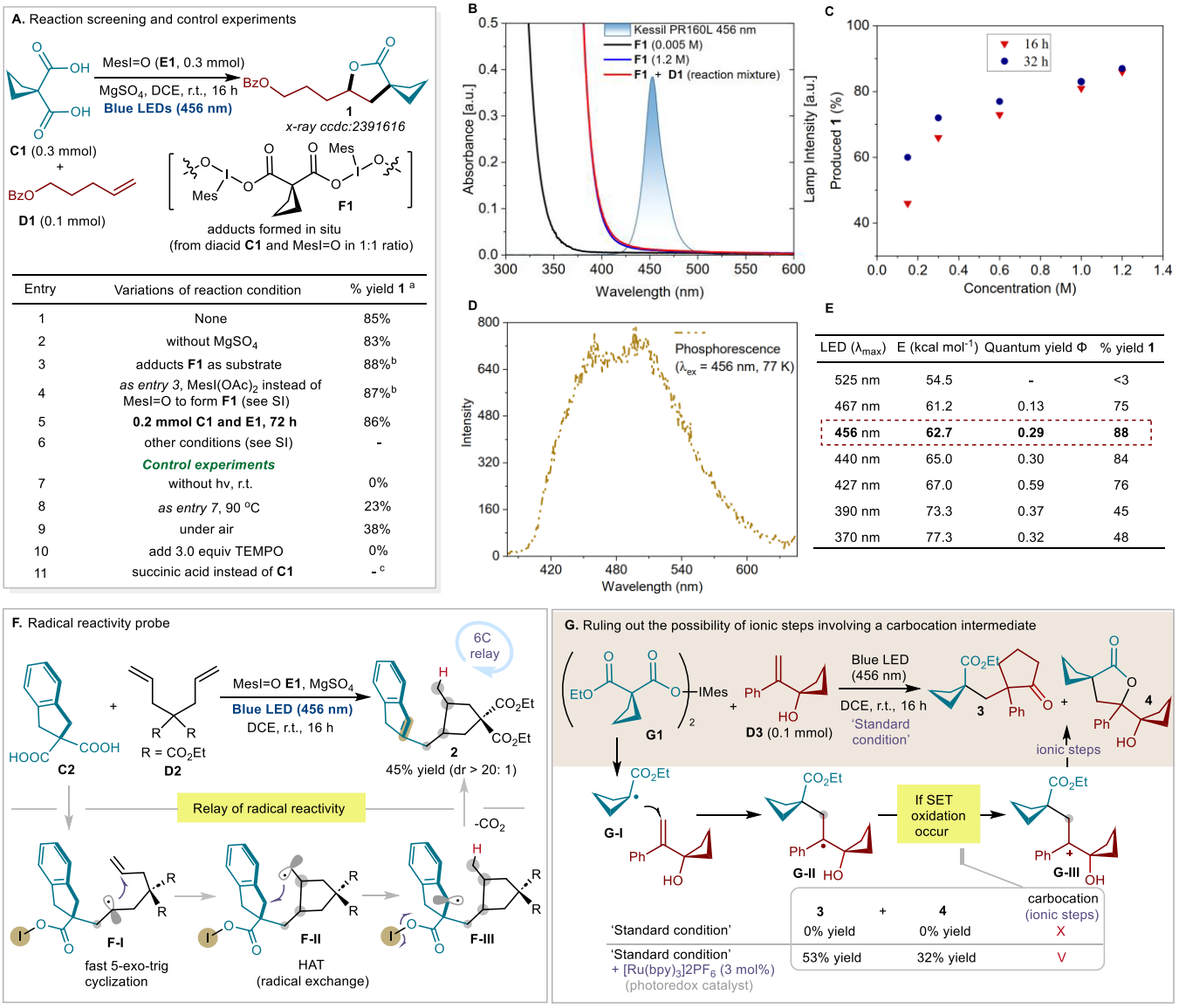

Entry	Variations of reaction condition	% yield **1** [a]
1	None	85%
2	without $MgSO_4$	83%
3	adducts **F1** as substrate	88%[b]
4	*as entry 3*, $MesI(OAc)_2$ instead of MesI=O to form **F1** (see SI)	87%[b]
5	**0.2 mmol C1 and E1, 72 h**	86%
6	other conditions (see SI)	-
	Control experiments	
7	without hv, r.t.	0%
8	*as entry 7*, 90 °C	23%
9	under air	38%
10	add 3.0 equiv TEMPO	0%
11	succinic acid instead of **C1**	-[c]

LED (λ_{max})	E (kcal mol^{-1})	Quantum yield Φ	% yield **1**
525 nm	54.5	-	<3
467 nm	61.2	0.13	75
456 nm	**62.7**	**0.29**	**88**
440 nm	65.0	0.30	84
427 nm	67.0	0.59	76
390 nm	73.3	0.37	45
370 nm	77.3	0.32	48

Figure 2. Reaction development and mechanistic investigations. (A) Reaction screening and control experiments. Standard reaction condition: alkenes **D1** (0.1 mmol, 1.0 equiv), cyclobutane-1,1-dicarboxylic acid **C1** (0.3 mmol,3.0 equiv), MesI=O **E1** (0.3 mmol, 3.0 equiv), $MgSO_4$ (50 mg), DCE (0.25 mL), the reaction was irradiated with one blue LED (λ_{max} = 456 nm) at r.t. for 16 h. [a] Isolation yields are given. [b] Adduct **F1** was used as substrate in place of the addition of acid **C1**, MesI=O **E1**, and $MgSO_4$.[c] No lactone product was observed. (B) UV−visible absorption spectra of adduct **F1** (black, 0.005 M; blue, 1.2 M) and the combined reaction mixture (red, **F1** 1.2 M, **D1** 0.4 M). Emission spectra of Kessil PR160L 456 nm Blue LEDs (gradient blue). (C) The correlation between the concentration of the adduct **F1** and the yield of product **1**. The yields at different reaction times were recorded separately (red, 16 h; blue, 32 h). (D) Phosphorescence emission spectra of adduct **F1** obtained through excitation at 456 nm at 77 K. (E) Quantum yields and reaction yields under irradiation with LEDs of varying emission spectra; see Tables S4 and S7. (F) Radical reactivity probe experiment. Reaction conditions as Figure 2A, entry 1. (G) Control experiments to rule out ionic steps involving carbocation intermediate.

iodosomesitylene **E1** (MesI=O) employed as the activating agent and anhydrous $MgSO_4$ used as a dehydration agent. At room temperature, after 16 h of irradiation with blue LEDs (Kessil PR160L lamp, λ_{max} = 456 nm) in 1,2-dichloroethane (DCE), alkene **D1** was fully consumed, and the desired product **1** was obtained with an 85% isolation yield (Figure 2A, entry 1). The stoichiometric water produced during the reaction has a minimal impact on the yield (entry 2). An alternative strategy with similar efficacy involves directly using the iodine(III) carboxylate adduct **F1**, rapidly formed by mixing equimolar amounts of acid **C1** with iodosomesitylene **E1** or commercially available $MesI(OAc)_2$ (entries 3 and 4). Although hypervalent iodines are environmentally friendly chemical reagents and can be regenerated from monovalent iodine,[46] we aim to reduce its usage for practical applications. Encouragingly, by extending the reaction time to 72 h, the amount of hypervalent iodine can be reduced to an acceptable 2.0 equiv. without compromising the yield (entry 5). Next, we conducted a series of control experiments to identify the key mechanistic features of the reaction. In the absence of blue LEDs, the reaction did not proceed at room temperature (entry 7). When heated to 90 °C, only 23% yield was obtained (entry 8), while further increases in temperature resulted in nonproductive decomposition of the starting materials. Conducting the reaction under atmospheric conditions resulted in a marked decline in yield, possibly due to

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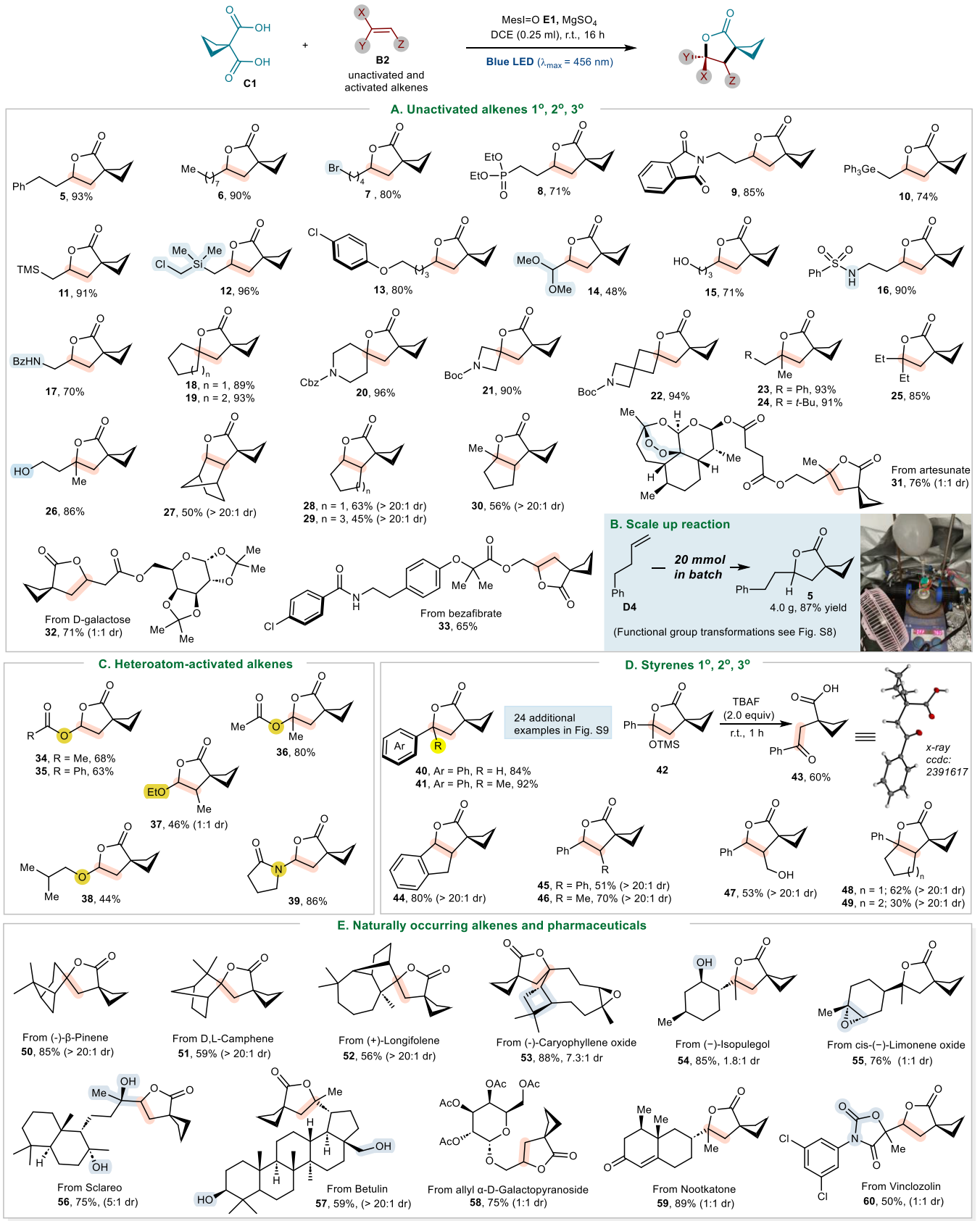

Figure 3. Scope of alkenes. Standard reaction condition as Figure 2A, entry1: alkenes **B2** (0.1 mmol, 1.0 equiv), cyclobutane-1,1-dicarboxylic acid **C1** (0.3 mmol, 3.0 equiv), MesI = O **E1** (0.3 mmol, 3.0 equiv), $MgSO_4$ (50 mg), DCE (0.25 mL), the reaction was irradiated with one blue LED (λ_{max} = 456 nm) at r.t. for 16 h. (A) Scope of unactivated alkenes. The ratio of diastereoisomers (dr) was determined by NMR analysis. (B) Scale-up reaction of alkene **D4**. The image displays the corresponding reaction apparatus. (C) Scope of heteroatom-activated alkenes. (D) Scope of styrenes. (E) Late-stage modifications of naturally occurring alkenes and pharmaceuticals.

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quenching of the excited state by oxygen (entry 9). Additionally, the reaction can be completely inhibited by the addition of radical scavengers, such as TEMPO (2,2,6,6-tetramethylpiperidinyloxy) (entry 10). All these observations support the intermediacy of light triggered radical species. Notably, succinic acid failed to produce the lactone product, possibly due to the polarity mismatch between the generated nucleophilic carbon radical and the unactivated alkenes,[47−49] highlighting the unique reactivity of electrophilic diradical equivalents derived from 1,1-dicarboxylic acids under our protocol (entry 11). Maleic and phthalic acids are also ineffective substrates.

Next, specific mechanism details were further interrogated. Analysis of the UV−vis spectra revealed that no ground-state aggregation of the substrates occurred (such as electron donor−acceptor complexes), as evidenced by the nearly coincident absorption profiles of adduct **F1** (blue) and the reaction mixture (red) (Figure 2B). UV−vis analysis of **F1** shows a concentration dependent absorption in the visible light region at 1.2 M (blue), which correlates with the higher yields observed at increasing substrate concentrations, as illustrated in Figure 2C. Adduct **F1** exhibits weak absorption within the emission range of the 456 nm LED, yet this LED irradiation results in high reaction efficiency. This phenomenon is likely to arise from spin-forbidden transitions (S_0-T_n),[50,51] which typically occur in compounds containing heavy atoms, such as iodine-containing reagents.[50,52−54] Phosphorescence was observed by irradiation at 456 nm (Figure 2D), indicating that the excitation of adduct **F1** to its triplet state occurred under our reaction conditions. We subsequently evaluated the quantum yields and reaction yields under irradiation with LEDs of varying emission spectra (Figure 2E). The observed quantum yields ($\Phi < 1$), together with light on/off experiments (Figure S5), indicate that continuous irradiation is essential to excite the iodine(III) carboxylate adduct and initiate reactive radical formation, although limited radical-chain propagation may also contribute to product generation. Irradiation with the Kessil 456 nm LED did not result in the highest quantum yield but provided the optimal reaction yield. This suggests that the weakly absorbing transition within the emission region of the 456 nm LED is more favorable for the productive reaction pathway.

We subsequently performed a radical reactivity probe experiment using nonconjugated diene **D2** as the substrate, obtaining cyclic product **2** with a 45% yield (Figure 2F). The formation of **2** involves a series of logical radical events, including the initial radical addition of masked diradical species, rapid 5-*exo*-trig radical cyclization, hydrogen atom transfer (HAT), and subsequent double bond formation facilitated by CO_2 elimination. This reaction showcases a highly efficient radical relay process across six carbon atoms, providing strong support for our mechanism proposal. Next, we utilized a photoredox catalysis promoted semipinacol rearrangement reaction[55] as a probe to rule out the possible ionic steps (Figure 2G). When using monocarboxylic acid-derived carboxylate **G1** as the substrate in a reaction with alkene **D3**, it can be postulated that if the oxidation of radical **G-I** to carbocation intermediate **G-II** occurs, the resulting products would include the semipinacol rearrangement product **3** and lactone **4**, which arises from the interception of the carbocation by water.[36] Nonetheless, these two products were not detected under our reaction conditions. When the photoredox catalyst $[Ru(bpy)_3]2PF_6$ (which can oxidize **G-I** to **G-II**) was added to the reaction, the results changed, affording product **3** with a 53% yield and lactone **4** with a 32% yield. These results indicate that iodine(III) carboxylates and their excited species are not capable of oxidizing even benzyl carbon radicals in our conditions (additional control experiments, see Figure S7), thereby ruling out polar steps that include carbocation intermediates.

Reaction Scope. We next systematically investigated the scope generality of this photochemical dual radical coupling protocol via diradical equivalents. As shown in Figure 3A, we first examined the compatibility toward various unactivated alkenes. Simple aliphatic alkenes (**5**, **6**) and a wide range of terminal alkenes that bearing functional groups (**7**−**14**) underwent this reaction smoothly to produce the corresponding γ-butyrolactones in excellent yield. In these reactions, reactive functionalities such as halides (**7**), phosphates (**8**), N-phthalimides (**9**), triphenylgermanium (**10**), alkylsilanes (**11**, **12**), ethers (**13**), and even acid-labile acetals (**14**) remain untouched, providing versatile synthetic handles for further functionalization of these products. Particularly impressive was the tolerance of unprotected nucleophilic reactive sites, such as hydroxyl (**15**), sulfonamide (**16**) and benzamide (**17**) which are problematic in reactions involving cationic intermediates. Reactions of 1,1-disubstituted alkenes give equally excellent results (**18**−**26**). Subsequent studies revealed that cyclic 1,2-disubstituted alkenes (**27**−**29**) and trisubstituted alkenes (**30**) were also suitable substrates, affording products with acceptable yields. Drugs and bioactive molecules, including antimalarial drug artesunate (**31**), which contains a highly sensitive peroxide bond, monosaccharides (**32**), and the lipid-lowering drug bezafibrate (**33**) demonstrate good compatibility with our conditions. Importantly, the reaction can be easily scaled up to a 20 mmol scale in a simple batch setup, affording product **5** with an isolated yield of 87% (4.0 g in 24 h) (Figure 3B). γ-Butyrolactones are valuable intermediates in synthetic chemistry due to their ease of functional group transformations. Some synthetic derivatizations of compound **5** are illustrated in Figure S3. In addition to ubiquitous unactivated alkenes, various electron-rich alkenes conjugated to a heteroatom were identified as suitable substrates, giving the desired products with satisfactory yield (**34**−**39**) (Figure 3C). Finally, we subjected a series of styrenes to the standard photochemical lactonization reaction (Figure 3D). Substituents on the benzene ring, varying in position, steric hindrance, and electronic nature, are well-tolerated with the reaction conditions (**40** and **41**, more examples see Figure S4). Interestingly, TMS-protected enols can be smoothly converted into product **42**. Upon removal of trimethylsilyl (TMS) group, compound **43** can be isolated with a yield of 60%, preserving the tethered carboxylic acid functionalities. Moreover, 1,2-disubstituted styrenes (**44**−**47**), and even trisubstituted styrenes with high steric hindrance (**48**, **49**) could react under our conditions. In these (un)symmetrical alkenes, excellent regioselectivities were achieved, guided by the stability of the radical intermediate. Next, we conducted late-stage modifications of naturally occurring alkenes and pharmaceuticals using our photochemical lactonization protocol. As shown in Figure 3E, the C═C bonds present in various stereochemically complex natural products (**50**−**58**) and drugs (**59**, **60**) were efficiently transformed into the corresponding γ-butyrolactones motifs. The introduction of versatile lactone functionalities significantly expands the range of chemical

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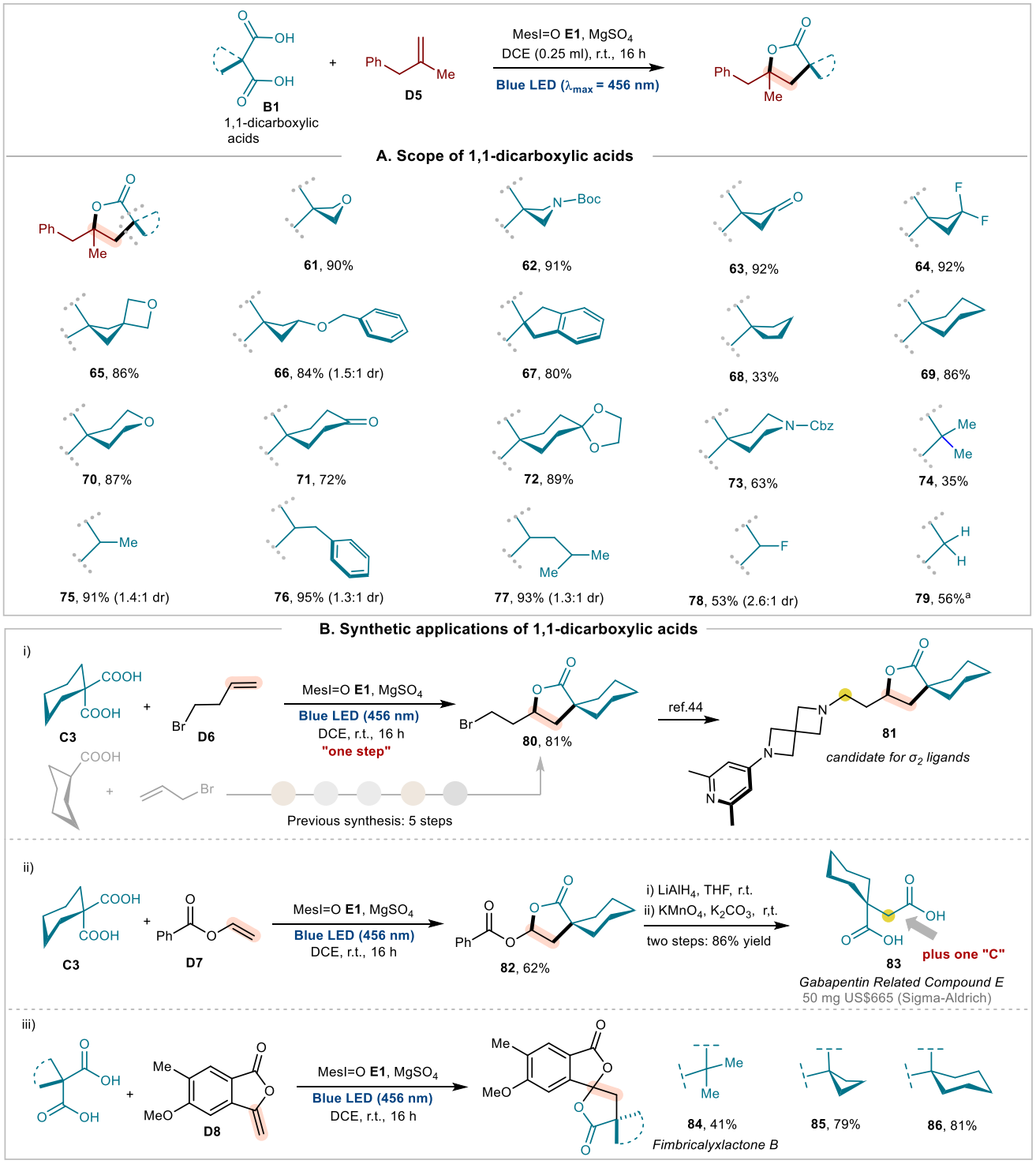

Figure 4. Reaction of 1,1-dicarbonyl acids. (A) Scope of 1,1-dicarboxylic acids. Standard reaction condition as Figure 2A, entry1: alkene **D5** (0.1 mmol, 1.0 equiv), 1,1-dicarboxylic acid **B1** (0.3 mmol, 3.0 equiv), MesI=O **E1** (0.3 mmol, 3.0 equiv), $MgSO_4$ (50 mg), DCE (0.25 mL), the reaction was irradiated with one blue LED (λ_{max} = 456 nm) at r.t. for 16 h. The ratio of diastereoisomers (dr) was determined by NMR analysis. [a] 1,4-Dioxane was used as the solvent instead of DCE. (B) Synthetic application of 1,1-dicarboxylic acids.

transformations applicable to these valuable bioactive molecules.

Subsequently, we continued to investigate the compatibility of this reaction with various 1,1-dicarboxylic acids (Figure 4A). These diacid liners can be categorized by ring size into four (**61**−**66**), five (**67**, **68**), and six-membered (**69**−**73**) rings. Acyclic substrates such as dimethylmalonic acid (**74**), monosubstituted malonic acids (**75**−**78**), and the simplest malonic acid (**79**) can also participate in the reaction smoothly. The success of these 1,1-dicarboxylic acid substrates has unprecedentedly expanded the structural diversity of γ-butyrolactones. It is evident that the easily tunable nature of these core molecular motifs is highly attractive for the optimization of biologically relevant structures. By reacting

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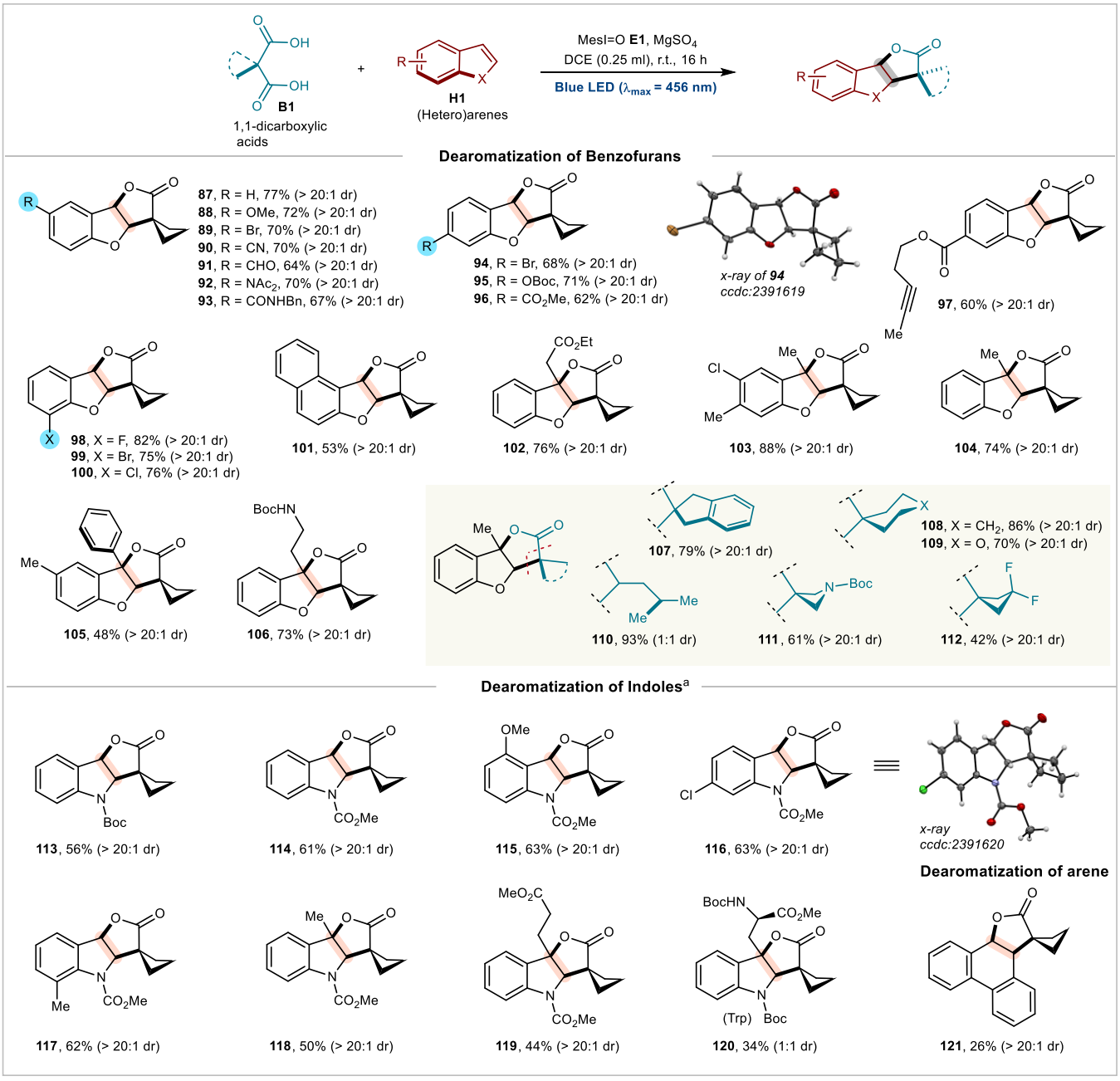

Figure 5. Dearomative γ-butyrolactonization of (hetero)arenes. Standard reaction condition as Figure 2A, entry1: heteroarenes **H1** (0.1 mmol, 1.0 equiv), 1,1-dicarboxylic acid **B1** (0.3 mmol, 3.0 equiv), MesI=O **E1** (0.3 mmol, 3.0 equiv), $MgSO_4$ (50 mg), DCE (0.25 mL), the reaction was irradiated with one blue LED (λ_{max} = 456 nm) at r.t. for 16 h. The ratio of diastereoisomers (dr) was determined by NMR analysis. [a] The reaction time for dearomative γ-butyrolactonization of indoles (**113**−**120**) was 36 h.

diacid **C3** with olefin **D6**, the chemical intermediate **80**, used to synthesize the σ2 protein ligand (**81**), can be obtained with an 80% yield, demonstrating significantly improved synthetic efficiency compared to the 5-step process reported in the literature.[56] Next, reacting **C3** with olefin **D7** produces γ-butyrolactone **82**. Upon sequential reduction and oxidation, it can be converted into the value-added gabapentin-related compound E **83**. We present an effective method for converting 1,1-dicarboxylic acids into succinic acid derivatives through the addition of one carbon atom. Finally, using our photochemical protocol, we successfully achieved the direct synthesis of the natural product fimbricalyxlactone B (**84**)[57] and its derivatives (**85**, **86**) from the corresponding 1,1-dicarboxylic acids and alkene **D8**.

Encouraged by the excellent compatibility of this reaction with alkenes, we next engendered to explore more challenging (hetero)arenes as reaction receptors with the aim of expanding the application repertoire of this photochemical method for modular lactone construction. Dearomatic transformation of (hetero)arenes to rapidly access intricate three-dimensional architectures has attracted continued research interest.[58] However, to the best of our knowledge, dearomatic lactonization reaction remain unexplored. As shown in Figure 5, benzofurans and indoles bearing various functional groups underwent this reaction smoothly, affording the dearomatized

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lactonization products with good yields and excellent diastereoselectivity (**87**−**120**). An especially interesting example was the successful late stage lactonization modification of tryptophan, although the inherent chiral center resulted in an equimolar ratio of diastereomers (**120**). Moreover, even phenanthrene can also undergo this protocol, yielding the dearomatized product (**121**). The excellent stereoselectivity observed in these cases may be attributed to radical events occurring on the same side, which minimize steric hindrance during cyclization. It is important to highlight that these dearomatic products obtained were previously inaccessible.

CONCLUSIONS

In conclusion, we have developed an unprecedented approach to harness otherwise unstable and hardly accessible carboxylate diradical intermediates, where both the α-carbon and carboxylic oxygen act as reactive radical centers. The consecutive dual radical coupling of carboxylates with alkenes and heteroarenes enables efficient synthesis of γ-butyrolactones, key structural motifs found in a wide range of functional molecules, including pharmaceuticals. Our study opens new avenues for reaction development and molecular synthesis by designing di- and potentially multiradical intermediates and their equivalents.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c00835.

X-ray data for compounds **1**, **43**, **45**, **94**, and **116** are freely available at the Cambridge Crystallographic Data Centre under deposition numbers 2391616−2391620. Full experimental details for the preparation of all new compounds, and their spectroscopic and chromatographic data (PDF)

Accession Codes

Deposition Numbers 2391616−2391620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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