ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

Cite this: *Org. Chem. Front.*, 2025, **12**, 6480

Palladium/photoredox catalysis for a decarboxylative radical C(sp^3)–C(sp^3) cross-coupling reaction of γ-methylidene-δ-valerolactones with alkyl carboxylic acids

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Received 9th July 2025,
Accepted 13th August 2025

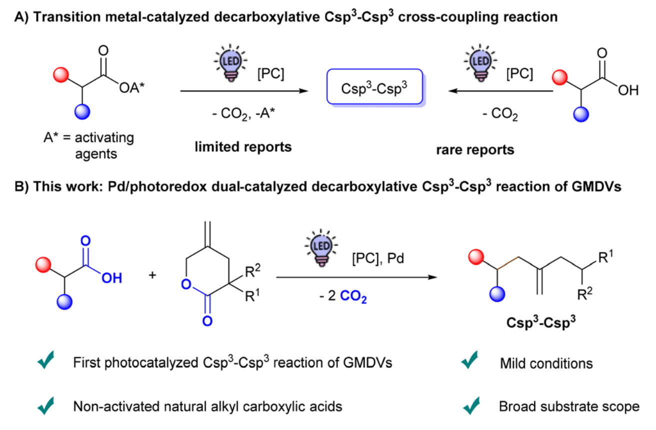
DOI: 10.1039/d5qo01005e

rsc.li/frontiers-organic

Developing applicable methods to forge linkages between sp^3- and sp^3-hybridized carbons is of great significance in drug discovery. Here, a radical decarboxylative C(sp^3)–C(sp^3) cross-coupling of γ-methylidene-δ-valerolactones (GMDVs) and alkyl carboxylic acids was developed by combining photocatalysis and palladium catalysis, providing the target products in good to excellent yields (up to 97% yield). The reaction exhibited a broad substrate scope and wide functional group compatibility.

Transition metal-catalyzed decarboxylative cross-coupling has emerged as a strategically significant methodology in modern organic synthesis, which features inherent atom economy through liberation of CO_2 as the sole byproduct, aligning with green chemistry principles.[1] Parallel advancements in photoredox catalysis and synergistic transition metal/photoredox dual catalytic systems have revolutionized radical-mediated C–C bond formation, enabling mild, energy-efficient protocols that circumvent traditional harsh reaction conditions.[2] The integration of decarboxylative strategies with photoredox catalysis presents a compelling synergy, combining operational simplicity with environmental benignity.[3] However, current methodologies predominantly require preactivation of carboxylic acids into reactive intermediates such as *N*-hydroxyphthalimide esters or hypervalent iodine(III) species.[4] This activation barrier has rendered direct utilization of naturally occurring alkyl carboxylic acids in photoredox-mediated Csp^3–Csp^3 cross-coupling reactions exceptionally rare,[5] despite their theoretical potential as ideal coupling partners (Scheme 1A). The development of such underdeveloped yet fundamentally important transformations therefore represents a significant frontier in catalytic methodology, offering opportunities to streamline synthetic sequences while accessing structurally diverse molecular architectures through operationally simple, sustainable protocols.

γ-Methylidene-δ-valerolactones (GMDVs), first established as versatile C4-synthons through Shintani and Hayashi's seminal [4 + *n*] cycloaddition chemistry in 2007,[6,7] have remained underexplored as coupling partners compared to conventional organometallic reagents. Our prior investigations revealed the unique reactivity profile of these cyclic systems, demonstrating their capacity as *O*-allylation reagents for phenolic substrates through Csp^3–O bond formation under mild conditions.[8a] Very recent advances in our group further expanded this paradigm through the development of a Pd^0/Cu^{II}/VB_2-catalyzed *N*-allylation protocol with aniline derivatives under blue LED irradiation, achieving efficient construction of allylamine architectures.[8b] Despite these advances, the direct engagement of GMDVs in Csp^3–Csp^3 bond-forming processes



Scheme 1 Strategies for the decarboxylative Csp^3–Csp^3 cross-coupling reaction.

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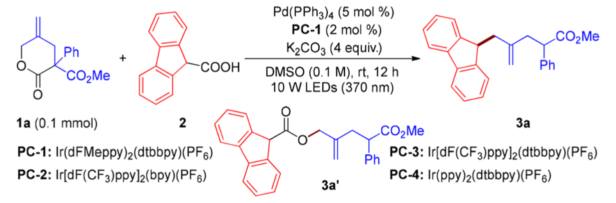
has remained conspicuously absent from the synthetic toolbox. To address this gap, we herein disclose a pioneering dual decarboxylative strategy that synergistically combines GMDVs with alkyl carboxylic acids under palladium/photoredox dual catalysis (Scheme 1B).

To validate our hypothesis, we commenced the investigation by employing GMDVs **1a** and 9*H*-fluorene-9-carboxylic acid **2** as model substrates in a palladium-catalyzed system (Table 1). The initial reaction utilizing $Pd(PPh_3)_4$ (5 mol%), $Ir(dFMeppy)_2(dtbbpy)(PF_6)$ (**PC-1**, 2 mol%) as a photocatalyst, and K_2CO_3 (4 equiv.) in DMSO under 370 nm UV irradiation (10 W LED) at ambient temperature under a nitrogen atmosphere afforded the Csp^3–Csp^3 coupling product **3a** in 82% isolated yield (entry 1). Control experiments revealed critical dependencies: partial suppression of **3a** formation occurred in the absence of a photocatalyst (entry 2), while exclusive generation of the Csp^3–O byproduct **3a′** was observed under dark conditions (entry 3). Subsequent systematic optimization identified DMA as the superior solvent (96% yield, entry 7 *vs.* entries 1, 5 and 6), outperforming DMF (78%) and maintaining solvent superiority over DMSO (82%). The reaction demonstrated strict base dependence, with Cs_2CO_3 (64%), Na_2CO_3 (78%), KH_2PO_4 (34%), NaH_2PO_4 (39%), KOAc (60%) and NaOAc (60%) proving inferior to K_2CO_3 (entry 1 *vs.* Table S1, entries 2–7). Notably, stoichiometric analysis revealed the necessity of excess **2** (4 equiv.) and K_2CO_3 (4 equiv.), as reduced equivalents diminished yields (entry 9), while substitution of K_2CO_3 and **2** with potassium carboxylate K[**2**] completely abolished reactivity (entry 8), strongly implicating *in situ*-generated H_2O or free carboxylic acid as crucial proton donors. Photocatalyst screening confirmed **PC-1**'s superiority over alternative photocatalysts (entry 7 *vs.* entries 10–12), with 370 nm UV irradiation proving optimal among the tested wavelengths (entry 7 *vs.* entries 13–15). Temporal analysis revealed exceptional reaction efficiency, achieving 94% yield within 2 hours (entry 16), though incomplete conversion (76%) resulted from premature termination at 1 hour (entry 17).

With the optimized conditions in hand, we next investigated the substrate scope of the decarboxylative radical $C(sp^3)$–$C(sp^3)$ cross-coupling reaction between GMDVs **1** and alkyl carboxylic acid **2.** At first, we varied the GMDVs **1** and the results are summarized in Table 2. We were delighted to find that a wide variety of structurally diverse GMDVs bearing either electron-donating groups (Me and OMe), electron-withdrawing groups (Cl and Br) or electron-neutral groups (H) at various positions of the aryl ring smoothly reacted with 9*H*-fluorene-9-carboxylic acid **2**, affording the corresponding cross-coupling products **3a–j** in moderate to excellent yields (entries 1–10). Aliphatic GMDV **3k** did not work well (entry 11), but heteroaromatic 3-thiophene was also tolerated in the reaction, affording the target product **3l** in good yield (entry 12). Gratifyingly, ethyl ester and cyano substrates were also well tolerated, affording the target product **3m** in 91% yield and product **3n** in 97% yield (entries 13 and 14), respectively. Unfortunately,

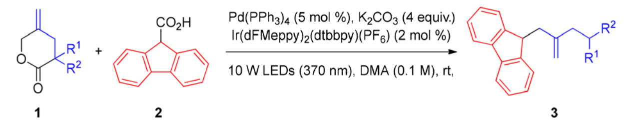
Table 1 Screening of reaction conditions



Entry[a]	Variation from standard conditions	Yield[b] (%)
1	None	82
2	No photocatalyst	32
3	In the dark	np[c]
4	Other bases instead of K_2CO_3	34–78
5	DMF instead of DMSO	62
6	THF	52
7	DMA	96
8	K[**2**] instead of **2**/K_2CO_3	nr
9[d]	**2**/K_2CO_3 (1 : 1, 3.0 equiv.)	64
10[d]	**PC-2** instead of **PC-1**	62
11[d]	**PC-3**	78
12[d]	**PC-4**	38
13[d]	390 nm instead of 370 nm	93
14[d]	427 nm	75
15[d]	456 nm	54
16[d]	2 h	94
17[d]	1 h	76

[a] Standard reaction conditions: under a nitrogen atmosphere, **1a** (0.1 mmol), **2** (0.4 mmol), $Pd(PPh_3)_4$ (5 mol%), $Ir(dFMeppy)_2(dtbbpy)(PF_6)$ (2 mol%), and K_2CO_3 (0.4 mmol) in DMSO (1.0 mL), 370 nm (10 W) at room temperature under N_2 for 12 h. [b] Isolated yield. [c] np = no product; by-product **3a′** was obtained in 7% yield. [d] DMA (1.0 mL) as solvent. nr = no reaction.

Table 2 Substrate scope for GMDVs **1**[a]



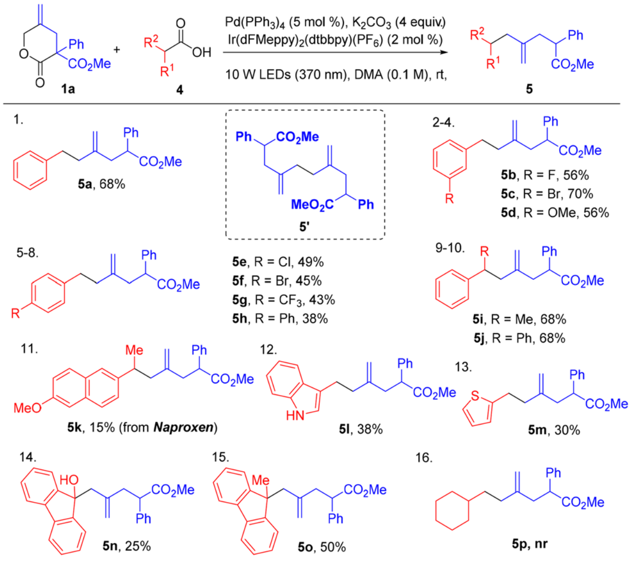
Entry[a]	R^1	R^2	3	Yield[b] (%)
1	Ph	CO_2Me	**3a**	94
2	2-ClC_6H_4	CO_2Me	**3b**	86
3	2-BrC_6H_4	CO_2Me	**3c**	40
4	2-MeC_6H_4	CO_2Me	**3d**	81
5	2-MeOC_6H_4	CO_2Me	**3e**	85
6	4-MeC_6H_4	CO_2Me	**3f**	75
7	4-MeOC_6H_4	CO_2Me	**3g**	78
8	$3,4\text{-Me}_2C_6H_3$	CO_2Me	**3h**	72
9	$3,4\text{-(MeO)}_2C_6H_3$	CO_2Me	**3i**	89
10	$3,4\text{-(OCH}_2\text{O)C}_6H_3$	CO_2Me	**3j**	70
11	Bn	CO_2Me	**3k**	25
12	3-Thiophene	CO_2Me	**3l**	90
13	Ph	CO_2Et	**3m**	91
14	Ph	CN	**3n**	97
15	Ph	Ph	**3o**	nd[c]

[a] Standard reaction conditions: under a nitrogen atmosphere, **1** (0.1 mmol), **2** (0.4 mmol, 4.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), $Ir(dFMeppy)_2(dtbbpy)(PF_6)$ (2 mol%), and K_2CO_3 (0.4 mmol, 4.0 equiv.) in DMA (1.0 mL), blue LEDs (370 nm, 10 W) at room temperature for 2 h. [b] Isolated yield. [c] nd = not determined.

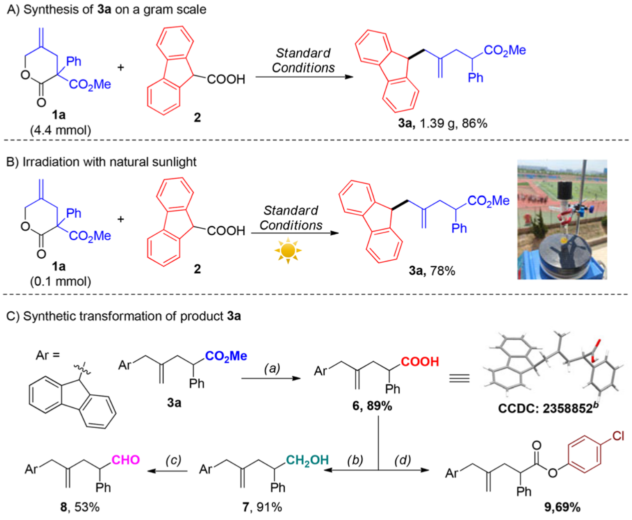
no desired product was observed when di-phenyl-substituted GMDV was introduced into the reaction (entry 15).

Furthermore, different alkyl carboxylic acids were examined. As depicted in Scheme 2, the reaction proceeded well when primary carboxylic acids bearing electron-withdrawing groups (F, Cl, Br, and CF_3), electron-donating groups (OMe and Ph) or electron-neutral groups (H) were applied, affording the desired products **5a–h** in moderate yield and a byproduct **5′** was observed. Moreover, substrates bearing various heterocycles, such as indole **4l** or thiophene **4m**, could also work, affording the target products **5l and m** in slightly lower yields. In addition, secondary benzylic-type carboxylic acids **4i and j** also exhibited good reactivity. To our delight, commercially available and commonly-used anti-inflammatory drugs, such as naproxen **4k**, were tolerated in this radical cross-coupling to afford the corresponding products. Finally, tertiary carboxylic acids were also investigated. To our satisfaction, the reactions could work well when flurenol **4n** and 9-methylfluorene-9-carboxylic acid **4o** were used as substrates, and the target products could be obtained in up to 50% yield. Unfortunately, the reaction did not work with inactivated aliphatic carboxylic acid **3p**.

Under the standard conditions, the developed decarboxylative cross-coupling reaction of GMDVs **1a** (1.08 g, 4.4 mmol) could be performed on a gram scale, affording the product **3a** in 86% yield (Scheme 3A). In addition, a sunlight-accelerated experiment was carried out, affording the desired product **3a** in 78% yield (Scheme 3B). To further confirm the structures of products **3** and **5**, compound **3a** was hydrolyzed with LiOH in a mixture of methanol and water to obtain carboxylic acid **6** in 89% yield. The solid structure of compound **6** (CCDC 2358852) was unambiguously assigned by X-ray crystallography (Scheme 3C-*a*).[10]



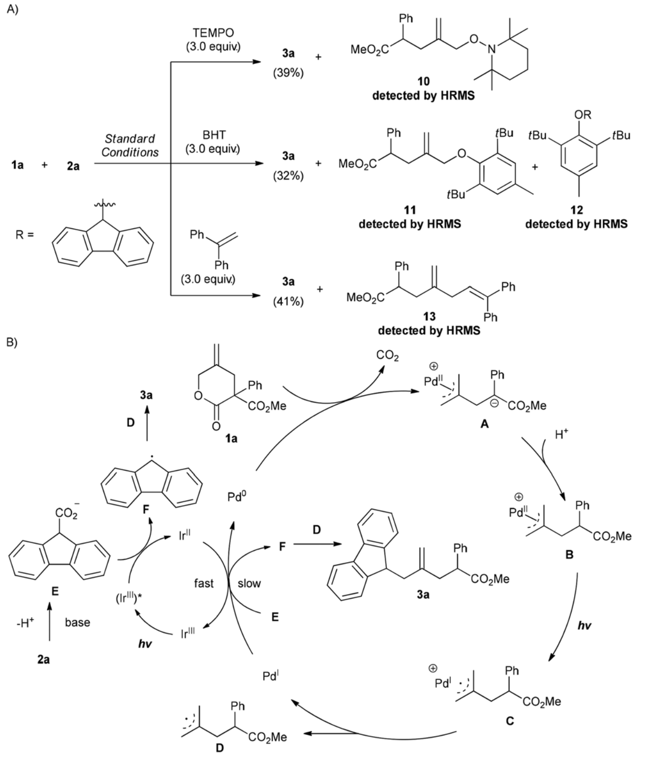
Scheme 2 Substrate scope for alkyl carboxylic acids **4**.[a] [a] Standard reaction conditions: under a nitrogen atmosphere, **1a** (0.1 mmol), **4** (0.4 mmol, 4.0 equiv), $Pd(PPh_3)_4$ (5 mol%), $Ir(dFMeppy)_2(dtbbpy)(PF_6)$ (2 mol%), K_2CO_3 (0.4 mmol, 4.0 equiv.) in DMA (1.0 mL), blue LEDs (370 nm, 10 W) at room temperature for 2 h, Isolated product yield.



Scheme 3 Gram-scale reaction and synthetic transformation of **3a**.[a] [a] Reaction conditions: (a) $LiOH·H_2O$ (2.0 equiv.), $MeOH/H_2O$ (10 : 1, 2.2 mL), rt, and 12 h. (b) DIBAL-H (1.0 mL), THF (0.1 M), rt, and 12 min. (c) PCC (1.5 equiv.), NaOAc (1.5 equiv.), DCM (0.1 M), rt, and 12 h. (d) 4-ClC_6H_4OH (0.8 equiv.), DMAP (10 mol%), DCC (0.8 equiv.), DCM (0.5 mL), N_2, rt, and 15 h. [b] ORTEP drawing at 30% ellipsoid probability.

Treatment of compound **6** with DIBAL-H in THF at room temperature led to the reduction of the carboxyl group, providing alcohol **7** in 91% yield (Scheme 3C-*b*), which could be further oxidized with PCC in DCM to afford aldehyde **8** in 53% yield (Scheme 3C-*c*). Moreover, compound **3a** could also react with 4-ClC_6H_4OH to afford product **9** in 69% yield (Scheme 3C-*d*).

To investigate the mechanism of this transformation, several control experiments were performed. Initially, three radical trapping experiments were conducted. Under the standard conditions, the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), 2,6-di-tertbutyl-4-methylphenol (BHT) and 1,1-diphenylethylene to the reaction solution significantly suppressed these transformations, and the radical trapping intermediates **10–13** were detected by HRMS, respectively (Scheme 4A). These results, as well as the formation of byproduct **5′**, indicated the presence of allyl and benzyl radicals in this reaction. Stern–Volmer quenching experiments indicate that a combination of K_2CO_3 and **2** quenches the photocatalyst (Fig. S8). Interestingly, when the combination of K_2CO_3 and **2** was replaced by fluorene-9-carboxylic acid **2** or its potassium salt, this reaction did not work, suggesting that K_2CO_3 should be used as a proton shuttle between **2** and Pd(II)-1,4-zwitterionic complexes. In addition, it was found that this reaction also worked in the absence of a photosensitizer, albeit in lower yield. This result indicates that in addition to Ir(III) photooxidants, Pd(I) species could also oxidize the carboxylate of **2** to generate benzyl radicals but with lower reactivity. Finally, we performed an on–off experiment. The reaction progressed smoothly upon irradiation with light (Fig. S9), while the reaction paused during the “light-off” periods. These results, as well as the quantum yield (1.73%), suggest that the present transformation was not a radical-chain process.



Scheme 4 (A) Control experiment and (B) proposed mechanism.

Based on the above mechanistic studies and previous reports,[9] a mechanism for this decarboxylative cross-coupling is proposed (Scheme 4B). This transformation starts with the palladium-catalyzed decarboxylation of GMDVs to generate Pd(II)-1,4-zwitterionic complexes **A**, which are easily protonated to form intermediate **B** by the combination of K_2CO_3 and **2**. The allyl Pd(II) intermediate **B** undergoes homolysis to form hybrid allyl Pd(I) radical **C** by utilizing light energy,[10] followed by the generation of free allyl radical **D** and Pd(I). On the one hand, the generated Pd(I) complex slowly reacted with carboxylate **E** from fluorene-9-carboxylic acid **2** to regenerate the Pd(0) catalyst and benzyl radical **F**. On the other hand, a single electron transfer (SET) between carboxylate **E** and excited Ir(III) released radical **F**, along with the generation of Ir(II), which much faster reacted with Pd(I) to regenerate the Pd(0) catalyst and Ir(III) photosensitizer. Finally, the generated allyl radical **D** coupled with benzyl radical **F** to form the desired product **3a**.

Conclusions

In summary, here, we have successfully demonstrated a mild and efficient decarboxylative radical $C(sp^3)$–$C(sp^3)$ cross-coupling reaction of γ-methylidene-δ-valerolactones with various alkyl carboxylic acids by combining photocatalysis and palladium catalysis. Primary, secondary and tertiary carboxylic acids can all be well tolerated to afford the target products in moderate to excellent yields. Meanwhile, GMDVs were first employed in the photoredox-catalyzed procedure and exhibited a broad substrate scope and outstanding functional group tolerance, which provides an alternative approach for $C(sp^3)$–$C(sp^3)$ bond formation.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI. The SI contains: general experimental information, optimization of reaction conditions, experimental procedure, characterization data for target products, mechanistic studies, X-ray crystallography data and copies of NMR spectra of compounds. See DOI: **https://doi.org/10.1039/d5qo01005e**.

CCDC 2358852 contains the supplementary crystallographic data for this paper.[11]

Acknowledgements

We thank the Natural Science Foundation of Shandong Province for Distinguished Young Scholars (ZR2020JQ07), the Natural Science Foundation of Shandong Province, China (No. ZR2019PB020), and Qingdao University of Science and Technology for financial support.

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