OL Organic Letters

pubs.acs.org/OrgLett Letter

# Photocatalytic Imidazolium Ester- and Phosphine-Mediated Radical Relay for Access to Structurally Complex Indanone-3-carboxylates

Dongmei Chen, Jianbo Liu, Lala Wang, Huimin Xia,* Yonggui Robin Chi, and Shi-Chao Ren*

Cite This: https://doi.org/10.1021/acs.orglett.6c01511 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information


■ diverse product scaffolds ■ radical relay process ■ mild & efficient strategy ■ antifungal activity

**ABSTRACT:** Indanone-3-carboxylates are key organic synthetic intermediates for a range of bioactive molecules. However, their efficient synthesis, particularly for structurally complex indanone-3-carboxylates, still faces challenges such as cumbersome steps and harsh conditions. Herein, we report a photocatalytic imidazolium ester- and phosphine-mediated dehydroxylative cyclization/acylation of 2-vinylbenzoic acids. This radical relay strategy enables the efficient preparation of structurally diverse indanone-3-carboxylates from readily available 2-vinylbenzoic acids and nitrogen heterocyclic carbene (NHC)-based azolium salts under mild conditions. The reaction exhibits broad substrate scope and, notably, allows facile access to carbon-cycle-fused indanone-3-carboxylate scaffolds that are challenging to obtain using conventional methods. Preliminary bioactivity assays reveal that several products possess good antifungal activity, demonstrating the potential of this method to advance the development of indanone-3-carboxylate-related bioactive molecules.



Indanone-3-carboxylates are a key synthetic intermediate for a range of bioactive molecules such as antitumor,[1] antidiabetic,[2] and antinociception[3] (Figure 1a). Conventionally, its synthesis relies on the Friedel−Crafts acylations of pre-prepared 2-arylsuccinic acid.[4] However, the electronic affinity of Friedel−Crafts acylations significantly limited the product's structural diversity (Figure 1b, top left). Transition metal catalysis has long been used to synthesize indanone-3-carboxylates. For instance, Larock and co-workers reported a straightforward synthetic method via palladium-catalyzed decarbonylative cyclization of unsaturated aryl iodides under 40 atm CO (Figure 1b, bottom left).[5] Li and co-workers reported an elegant rhodium-catalyzed cyclization reaction between $\alpha$-diazo esters and phenacyl ammonium salts to afford the precursor of indanone-3-carboxylates (Figure 1b, top right).[6] Recently, Zhu reported a photocatalytic synthesis of indanones via a novel hydrogen radical-shuttle process, which was successfully extended to preparing indanone-3-carboxylates (Figure 1b, bottom right).[7] A combined Brønsted base-promoted $CO_2$ fixation into benzylic C−H bonds was also used for indanone-3-carboxylates synthesis (Figure 1b, middle right).[8] Despite these advances, the reported strategies suffer from inefficiency and challenges, especially for preparing structurally complex indanone-3-carboxylates due to the requirement of pre-prepared substrates, harsh conditions, limited functional group tolerance, and restriction on the substrate's structure. Therefore, the development of practical and reliable synthetic methods for constructing structurally complex indanone-3-carboxylates is highly desirable and meaningful.

Radical relay reactions have attracted substantial attention due to their capability to construct two or more bonds in one step, enabling a significant increase in molecular complexity.[9] Recently, radical nitrogen heterocyclic carbene (NHC) catalysis has emerged as a mild and powerful radical acylation strategy for ketone or ester synthesis (Figure 1c).[10] Key steps of these reactions involve the radical cross-coupling of the persistent NHC-bound ketyl radical and a transient carbon-centered radical species.[11] The field has achieved significant advancements[12] since the pioneering work of Ohmiya et al. in 2019,[13] including the extension of this strategy for the synthesis of carboxylic esters[14] and in radical relay reactions. On the basis of our experience in radical NHC catalysis,[15] we hypothesize that a radical relay reaction that involves the above cross-coupling process as the acylation step would provide an efficient process for preparing indanone-3-carboxylates. The required acyl radical species for generating the benzylic radical of 1-indanone can be formed from 2-vinylbenzoic acids via a phosphine-mediated dehydroxylation process, which was

Received: April 7, 2026
Revised: May 30, 2026
Accepted: June 4, 2026

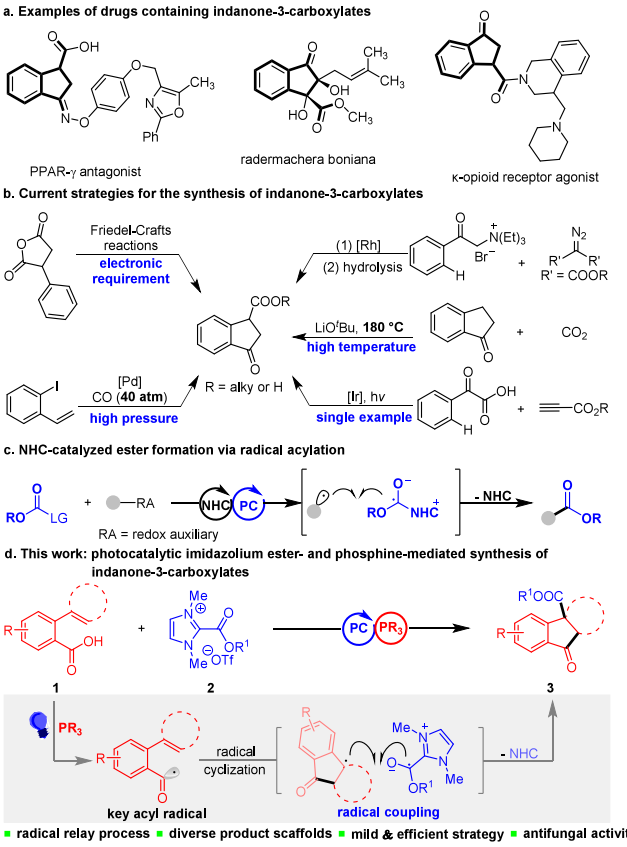


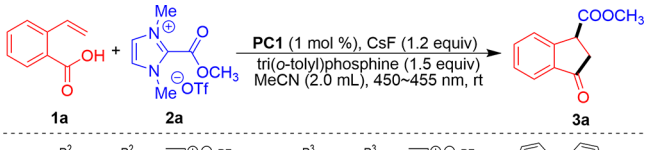

**Figure 1.** Background and design of photocatalytic imidazolium ester- and phosphine-mediated synthesis of indanone-3-carboxylates.

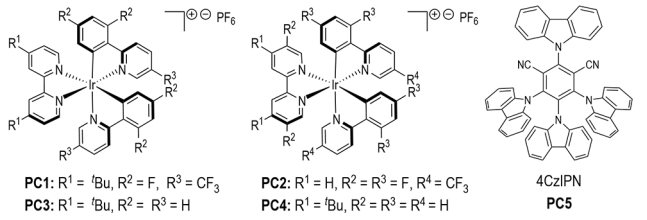
disclosed independently by the groups of Zhu and Doyle in 2018,[16] with substantial applications in the synthesis of valuable molecules.[17] Herein, we report a photocatalytic imidazolium ester- and phosphine-mediated dehydroxylative cyclization/acylation of 2-vinylbenzoic acids. This radical relay reaction enables the efficient preparation of a range of structurally diverse indanone-3-carboxylates from readily available 2-vinylbenzoic acids and imidazolium esters under mild reaction conditions. Notably, the reaction is competent for constructing carbon-cycle-fused indanone-3-carboxylates, which are challenging or impossible to prepare through previously reported strategies. Preliminary bioactivity assessments indicated that some of the products exhibited good antifungal activity, demonstrating the potential utility of our reaction for agrochemical development.

## Reaction Optimization

To pursue our hypothesis, 2-vinylbenzoic acid (**1a**, 0.1 mmol) and imidazolium ester (**2a**, 0.15 mmol) were selected as the model substrates. The optimized reaction conditions involved 1.5 equiv of tri(*o*-tolyl)phosphine (**P1**) as an oxygen-atom transfer reagent, 1 mol % of **PC1** as the photocatalyst, 1.2 equiv of CsF as a base, acetonitrile as the solvent, and irradiation with blue LEDs. In this case, the desired product was obtained in 36% yield (Table 1, entry 1). Replacing the current **PC1** with other photocatalysts resulted in lower yields (entries 2−5). Switching from acetonitrile to other solvents resulted in lower yields as well (entries 6−8). Among the bases tested, 1.5 equiv of $K_2CO_3$ gave the best result (entries 9−13). Replacement of triphenyl phosphine ($PPh_3$) with **P1** decreased the yield, whereas methyldiphenylphsphine ($MePPh_2$) afforded

**Table 1. Optimization of the Reaction Conditions**[a]




| Entry | Variation from the initial conditions | 3a [%][b] |
|---|---|---|
| 1 | none | 36 |
| 2 | **PC2** instead of **PC1** | 30 |
| 3 | **PC3** instead of **PC1** | 15 |
| 4 | **PC4** instead of **PC1** | n.d. |
| 5 | **PC5** instead of **PC1** | 30 |
| 6 | DCM as a solvent | 28 |
| 7 | DMF or DMSO as a solvent | 10 |
| 8 | THF or EA as a solvent | 16, 15 |
| 9 | $NaHCO_3$ as a base | 12 |
| 10 | DMAP as a base | 20 |
| 11 | $Li_3PO_4$ as a base | trace |
| 12 | $K_2CO_3$ as a base | 44 |
| 13 | $K_2CO_3$ (1.5 equiv) as a base | 50 |
| 14 | As entry 13, $PPh_3$ instead of **P1** | 36 |
| 15 | As entry 13, $MePPh_2$ instead of **P1** | 52 |
| 16 | As entry 15, MeCN (5.0 mL) instead | 60 |
| 17 | As entry 16, **1a** (0.12 mmol), **2a** (0.1 mmol) | 72 |
| 18 | As entry 17, extend the reaction time to 17 h | 78 (75[c]) |
| 19 | no **PC** or no light | 0 |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **P1** = tri(*o*-tolyl)phosphine (0.15 mmol), CsF (0.12 mmol), **PC1** (1 mol %), MeCN (2 mL), irradiation with 450−455 nm, rt, 10 h. [b]Yield was determined by NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield.

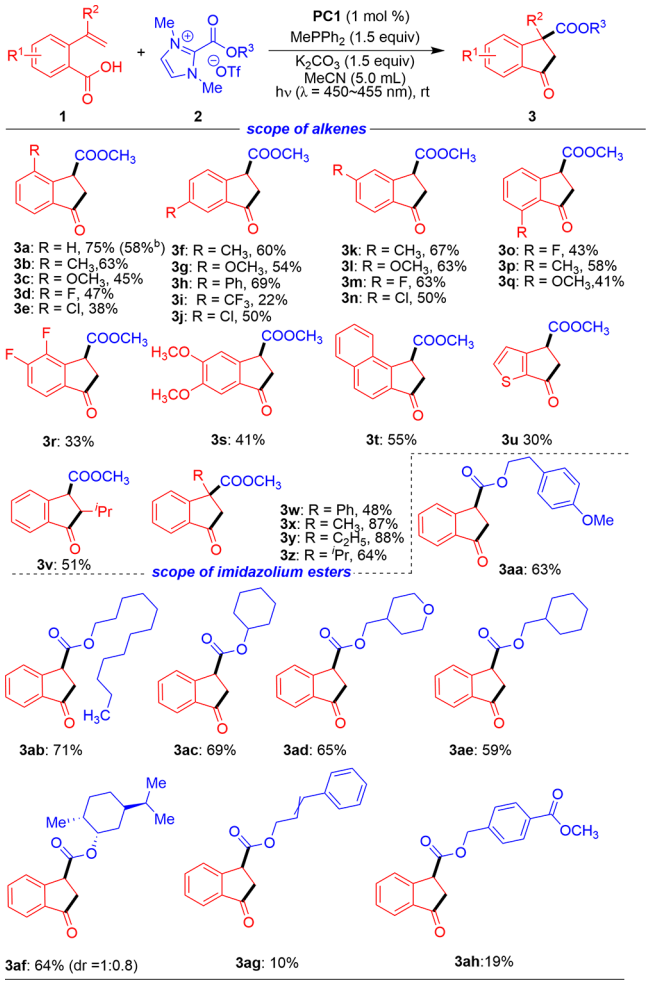
a 52% yield (entries 14−15). Increasing the acetonitrile volume to 5.0 mL further improved the yield (entry 16). The molar ratio of **1a** to **2a** was also investigated, and a 1.2:1 ratio was found to be optimal (entry 17). Extending the reaction time from 10 to 17 h further enhanced the yield to 78% with an isolated yield of 75% (entry 18). Notably, 20% yield of 2,3-dihydro-1*H*-inden-1-one was detected as a side product. Control experiments indicate that both light and the photocatalyst are crucial for a successful dehydroxylative cyclization/acylation (entry 19).

## Substrate Scope

With the optimized reaction conditions (Table 1, entry 18) in hand, we next investigated the scope of variously substituted 2-vinylbenzoic acid substrates (**1**) using the imidazolium esters **2a** (Table 2) as the model reaction partner. In general, both electron-donating and electron-withdrawing functional groups at the 3-, 4-, 5-, or 6-position of the 2-vinylbenzoic acid were compatible (**3a**−**3q**). Notably, this strategy enabled the synthesis of compound **3i**, as traditional Friedel−Crafts acylation is typically infeasible when the benzene ring contains a deactivating group (trifluoromethyl). Disubstituted 2-vinylbenzoic acids, such as 3,4-difluoro- and 4,5-dimethoxybenzoic acid, smoothly afforded the corresponding esters **3r** and **3s** in


https://doi.org/10.1021/acs.orglett.6c01511
Org. Lett. XXXX, XXX, XXX−XXX

**Table 2. Substrate Scope**[a]




[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), **PC1** (1 mol %), $MePPh_2$ (0.15 mmol), irradiation with a blue LED, rt, and 17 h. [b]1.0 mmol scale experiment.

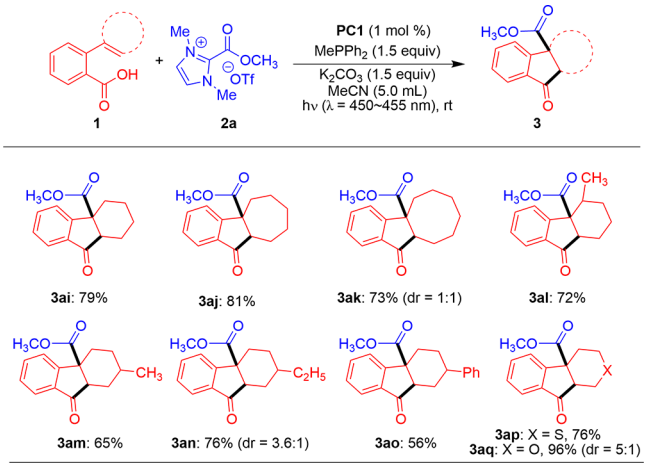
slightly lower yields. Gratifyingly, this reaction was also tolerant of fused-ring aromatic carboxylic acids, such as naphthalene, affording the product **3t** in a moderate yield. Besides aromatic ring substrates, heteroaromatic ring substrates also underwent this transformation smoothly to afford **3u**, albeit in a lower yield. In addition, a series of $\alpha$- or $\beta$-substituted 2-vinylbenzoic acids, bearing either aryl or alkyl groups, afforded compounds **3v**−**3z** in moderate to excellent yields.

Having demonstrated the success of our strategy for the synthesis of indanone-3-carboxylates, we next examined the current reaction for 2-vinylbenzoic acid (**1a**) with various imidazolium esters (**2**). A variety of esters derived from primary and secondary alcohols were obtained (**3aa**−**3af**) in moderate to good yields. Imidazolium esters bearing functionalities such as alkene and ester groups are competent substrates for the current reactions, albeit with remarkably low yields (**3ag**−**3ah**). It is worth noting that, when starting with an enantiopure imidazolium ester, the product was obtained with complete retention of stereochemistry (**3af**).

## Applications

To further demonstrate the power of the current method, we applied it in the synthesis of polycyclic indanone-3-carboxylates (Table 3), which are challenging or impossible to obtain via previously reported methods. Pleasingly, a diverse

**Table 3. Application in Polycyclic Compounds**[a]




[a]Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), **PC1** (1 mol %), $MePPh_2$ (0.15 mmol), irradiation with a blue LED, rt, 17 h.

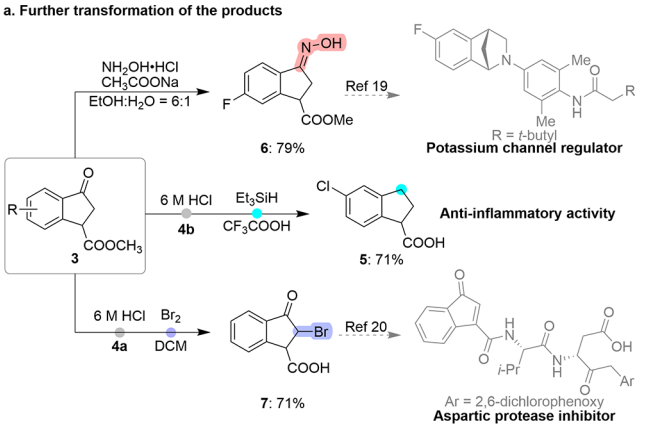
range of endocyclic alkenes was successfully converted to carbon ring-fused products. For example, carbocyclic substrates, including six-, seven-, and eight-membered carbocycles, were well tolerated in this transformation, affording the desired products (**3ai**−**3ak**) in good yields. Additionally, six-membered rings bearing alkyl or aryl substituents proceeded smoothly to give polycyclic compounds (**3al**−**3ao**) in moderate to good yields. More importantly, six-membered heterocycles containing oxygen or sulfur atoms were also compatible, delivering the target compounds **3ap** and **3aq** in excellent yields (Table 3). These examples highlight this protocol for the practical synthesis of polycyclic indanone-3-carboxylates.

To demonstrate the utility of this method, product derivatization was performed (Scheme 1a). Hydrolysis and reduction of product **3j** afforded indane-1-carboxylic acid **5**, which possesses anti-inflammatory activity.[18] The ketone moiety of compound **3m** underwent condensation with hydroxylamine hydrochloride to give oxime **6** in a 79% yield. Compound **6** serves as an important intermediate in the synthesis of a novel regulator.[19] Product **3a** underwent hydrolysis (dilute HCl) and subsequent selective halogenation with $Br_2$ at room temperature to afford compound **7** in an acceptable yield. Compound **7** is a vital precursor for the synthesis of aspartic protein inhibitors.[20]

As part of our continuous interest in the design and preparation of structurally innovative small molecules with biological activity in agricultural applications, we evaluated the antifungal activity of the synthesized products against *Ralstonias solanacearum* (*R.s.*) and *Phomopsis sp* (*P.s.*). The commercial bactericide azoxystrobin was used as a positive control. As shown in Scheme 1b, several compounds exhibited excellent inhibitory activity against *R.s.* and *P.s.* at 50 $\mu$g/mL, outperforming the commercial fungicide azoxystrobin. This result highlights the potential of this synthetic methodology in agrochemical development.


https://doi.org/10.1021/acs.orglett.6c01511
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 1. Synthetic Applications and Antifungal Activity Investigation**[a]




[a]All data were obtained as the average of three replicates; the commercial bactericide azoxystrobin was selected as the positive control.

## Mechanistic Investigations

To gain insight into the reaction mechanism, several experimental studies were conducted (Figure 2). First, a radical trapping experiment was performed under standard reaction conditions, and traces of **3a** were detected in the presence of 3.0 equiv of TEMPO, indicating that a radical process might be involved (Figure 2a). Next, a 2-(1-cyclopropylvinyl)benzoic acid **1ar** was synthesized and employed in a radical clock reaction under standard conditions (Figure 2b). Interestingly, product **3ar** was obtained rather than ring-opening product **3ar′**. This may be attributed to the stability of the benzylic radical intermediate and a faster radical−radical coupling process than the ring-opening process.[21] Although the ring-opening product was not obtained, the acyl and alkoxycarbonyl radicals were both trapped by TEMPO, and the corresponding adducts were detected by ESI-HRMS (Figure 2a). These results indicate that an acyl radical pathway could be possible.[22] Next, the Stern−Volmer fluorescence quenching experiments were performed with the $MePPh_2$ and the photocatalyst (Figure 2c, left). The results showed that the photoexcited **PC1*** could be quenched efficiently by $MePPh_2$, exhibiting a linear relationship (Figure 2c, right). At last, light on−off experiments revealed that the product accumulates only during the illumination period (Supplementary Figure 3). In addition, the quantum yield was measured ($\phi$ = 0.011) and clearly indicated that the successful progression of the reaction requires continuous light irradiation. Nonetheless, these results can not exclude the contribution of short radical chain propagation processes to product formation.[23]

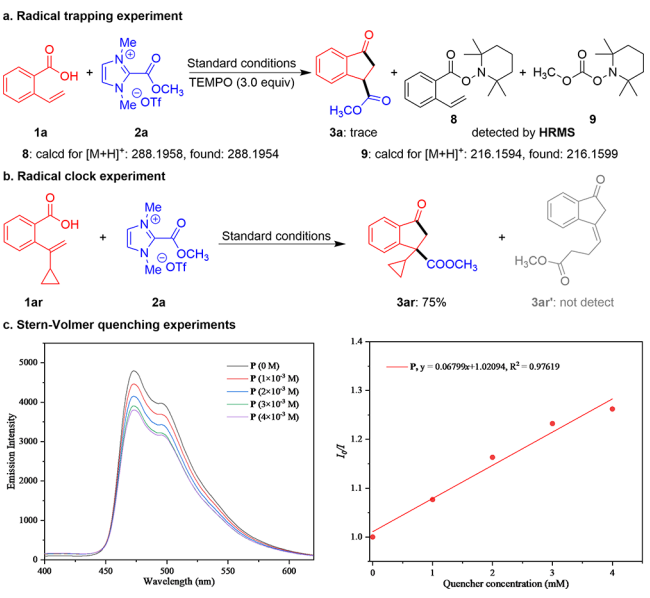
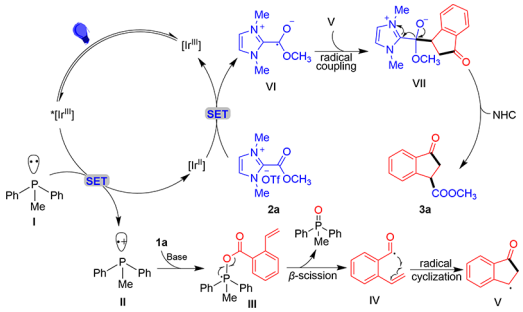



**Figure 2.** Mechanistic studies.

Based on the results of the mechanistic studies and previously reported literature, we proposed a possible reaction pathway for the current reactions (Scheme 2). The photo-

**Scheme 2. Possible Reaction Pathway**




excited[24] *Ir(dF($CF_3$)ppy)$_2$(dtbbpy)$PF_6$ can undergo single-electron transfer (SET) oxidation with $MePPh_2$ (**I**) to form the phosphine radical cation (**II**), which could trigger the proposed radical deoxygenation.[25] This radical cation (**II**) then reacts with the carboxylate anion to generate the phosphoryl radical (**III**), followed by $\beta$-selective C(acyl)−O bond cleavage, driven by the thermodynamic impetus for the formation of diphenylmethylphosphine oxide. This process releases the acyl radical (**IV**), which undergoes a 5-*endo*-trig radical cyclization[26] to afford the benzyl radical intermediate (**V**). Meanwhile, the reduction of **2a** by the reduced $Ir^{II}$ species generates the stabilized alkoxycarbonyl radical[14h] (**VI**). Radical−radical coupling between the benzylic radical (**V**) and alkoxycarbonyl radical (**VI**) delivers the tetrahedral intermediate (**VII**). Finally, elimination of the carbene from fragmentation **VII** results in the desired product (**3a**).

## Conclusion

In summary, we established a photocatalytic imidazolium ester- and phosphine-mediated dehydroxylative cyclization/acylation of 2-vinylbenzoic acids and imidazolium esters. This transformation proceeds via a radical relay involving the deoxygenation of carboxylic acid, intramolecular radical cyclization, and radical−radical coupling. This protocol enables


https://doi.org/10.1021/acs.orglett.6c01511
Org. Lett. XXXX, XXX, XXX−XXX

the efficient and facile synthesis of diverse carbocycle-fused indanone-3-carboxylates, which are challenging to access with previous methods. Moreover, this reaction features mild reaction conditions, a broad substrate scope, and excellent functional group tolerance. We believe that the current strategy will bring new ideas for the design of functionalized indanone-3-carboxylate derivatives.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.6c01511.

Experiment procedures and characterization of the products (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Huimin Xia** − *School of Pharmaceutical Science, Guizhou University, Guiyang 550025, China*; Email: hmxia@gzu.edu.cn

**Shi-Chao Ren** − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*; orcid.org/0000-0003-4248-6021; Email: scren@gzu.edu.cn

### Authors

**Dongmei Chen** − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*

**Jianbo Liu** − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*

**Lala Wang** − *State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*

**Yonggui Robin Chi** − *School of Chemistry, Chemical Engineering, and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore; State Key Laboratory of Green Pesticide, Guizhou University, Guiyang 550025, China*; orcid.org/0000-0003-0573-257X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.6c01511


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (22371058); the Science and Technology Department of Guizhou Province (Qiankehejichu-ZK[2024]Key009, Qiankehejichu-ZD[2026]011).

## ■ REFERENCES


(1) (a) Yuen, L. H.; Dana, S.; Liu, Y.; Bloom, S. I.; Thorsell, A.-G.; Neri, D.; Donato, A. J.; Kireev, D.; Schüler, H.; Franzini, R. M. A Focused DNA-Encoded Chemical Library for the Discovery of Inhibitors of NAD+-Dependent Enzymes. *J. Am. Chem. Soc.* **2019**, *141*, 5169−5181. (b) Wang, M.-Z.; Xie, W.-J.; Guan, Y.-F.; Song, X.; Hung, N. V.; Cuong, N. M.; Santarsiero, B. D.; Fong, H. H. S.; Soejarto, D. D.; Zhang, H.-J. Bioactive Constituents from Radermachera boniana. *ChemistrySelect* **2016**, *1*, 1575−1579.

(2) Imoto, H.; Sugiyama, Y.; Kimura, H.; Momose, Y. Studies on Non-Thiazolidinedione Antidiabetic Agents. 2. Novel Oxyiminoalkanoic Acid Derivatives as Potent Glucose and Lipid Lowering Agents. *Chem. Pharm. Bull.* **2003**, *51*, 138−151.

(3) Zhang, L.-s.; Wang, J.; Chen, J.-c.; Tao, Y.-m.; Wang, Y.-h.; Xu, X.-j.; Chen, J.; Xu, Y.-g.; Xi, T.; Hu, X.-w.; Wang, Y.-j.; Liu, J.-g. Novel κ-opioid receptor agonist MB-1C-OH produces potent analgesia with less depression and sedation. *Acta Pharmacol. Sin.* **2015**, *36*, 565−571.

(4) (a) Gan, Z.-J.; Wang, Y.-H.; Xu, Y.-G.; Guo, T.; Wang, J.; Song, Q.; Xu, X.-J.; Hu, S.-Y.; Wang, Y.-J.; Wang, D.-C.; Sun, D.-Z.; Zhang, D.; Xi, T.; Li, H.-D.; Zhang, H.-B.; Hang, T.-J.; Lu, H.-G.; Liu, J.-G. Discovery, stereospecific characterization and peripheral modification of 1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]−1,2,3,4-tetrahydroisoquinolines as novel selective κ opioid receptor agonists. *Org. Biomol Chem.* **2015**, *13*, 5656−5673. (b) Ju, T.; Zhou, Y.-Q.; Cao, K.-G.; Fu, Q.; Ye, J.-H.; Sun, G.-Q.; Liu, X.-F.; Chen, L.; Liao, L.-L.; Yu, D.-G. Dicarboxylation of alkenes, allenes and (hetero)arenes with $CO_2$ via visible-light photoredox catalysis. *Nat. Catal.* **2021**, *4*, 304−311. (c) Li, J.; Zhang, Y.; Zhu, S.; Chu, L. Photocatalyzed Dicyanation of Alkenes Enabled by Phosphorus Radical Cation Addition. *Chem.—Eur. J.* **2025**, *31*, No. e202501154. (d) Zhou, X.; Yang, H.; Zhao, Z.; Ning, H.; Shan, Y.; Cheng, M.; Zhang, P.; Li, F.; Sun, L.; Li, F. Photoelectrochemical dicarboxylation of styrene with $CO_2$ to phenylsuccinic acid on a Ni-decorated silicon photocathode. *Green Chem.* **2025**, *27*, 13041−13050.

(5) Gagnier, S. V.; Larock, R. C. Palladium-Catalyzed Carbonylative Cyclization of Unsaturated Aryl Iodides and Dienyl Triflates, Iodides, and Bromides to Indanones and 2-Cyclopentenones. *J. Am. Chem. Soc.* **2003**, *125*, 4804−4807.

(6) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. Rhodium-Catalyzed C−H Activation of Phenacyl Ammonium Salts Assisted by an Oxidizing C−N Bond: A Combination of Experimental and Theoretical Studies. *J. Am. Chem. Soc.* **2015**, *137*, 1623−1631.

(7) Yang, B.; Li, S.-J.; Wang, Y.; Lan, Y.; Zhu, S. Hydrogen radical-shuttle (HRS)-enabled photoredox synthesis of indanones via decarboxylative annulation. *Nat. Commun.* **2021**, *12*, 5257.

(8) Shigeno, M.; Tohara, I.; Sasaki, K.; Nozawa-Kumada, K.; Kondo, Y. Combined Brønsted Base-Promoted $CO_2$ Fixation into Benzylic C−H Bonds of Alkylarenes. *Org. Lett.* **2022**, *24*, 4825−4830.

(9) Huang, H.-M.; Garduño-Castro, M. H.; Morrill, C.; Procter, D. J. Catalytic cascade reactions by radical relay. *Chem. Soc. Rev.* **2019**, *48*, 4626−4638.

(10) (a) Chen, K.-Q.; Sheng, H.; Liu, Q.; Shao, P.-L.; Chen, X.-Y. N-heterocyclic carbene-catalyzed radical reactions. *Sci. China Chem.* **2021**, *64*, 7−16. (b) Dai, L.; Ye, S. Recent advances in N-heterocyclic carbene-catalyzed radical reactions. *Chin. Chem. Lett.* **2021**, *32*, 660−667. (c) Ishii, T.; Nagao, K.; Ohmiya, H. Recent advances in N-heterocyclic carbene-based radical catalysis. *Chem. Sci.* **2020**, *11*, 5630−5636. (d) Ling, D.; Ran, Y.; Yang, F.; Yang, X.; Wu, X.; Ren, S.-C.; Jin, Z. Advances in N-heterocyclic carbene organocatalysis from 2015 to 2024. *Chem. Soc. Rev.* **2025**, *54*, 8725−8808. (e) Liu, K.; Schwenzer, M.; Studer, A. Radical NHC Catalysis. *ACS Catal.* **2022**, *12*, 11984−11999.

(11) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74−108.

(12) (a) Bay, A. V.; Fitzpatrick, K. P.; Betori, R. C.; Scheidt, K. A. Combined Photoredox and Carbene Catalysis for the Synthesis of Ketones from Carboxylic Acids. *Angew. Chem., Int. Ed.* **2020**, *59*, 9143−9148. (b) Goto, Y.; Sano, M.; Sumida, Y.; Ohmiya, H. N-heterocyclic carbene- and organic photoredox-catalysed meta-selective acylation of electron-rich arenes. *Nat. Synth.* **2023**, *2*, 1037−1045. (c) Li, C.-B.; Li, X.-N.; Li, Z.-C.; Li, J.; Wang, Z.-X.; Gao, Z.-H.; Ye, S. Enantioselective Acylation of Benzylic C($sp^3$)−H Bond Enabled by a Cooperative Photoredox and N-Heterocyclic Carbene Catalysis. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202421151. (d) Li, J.-L.; Liu, Y.-Q.; Zou, W.-L.; Zeng, R.; Zhang, X.; Liu, Y.; Han, B.; He, Y.; Leng, H.-J.; Li, Q.-Z. Radical Acylfluoroalkylation of Olefins through N-Heterocyclic Carbene Organocatalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1863−1870. (e) Li, M.; Wu, Y.; Song, X.; Sun, J.; Zhang, Z.;

Zheng, G.; Zhang, Q. Visible light-mediated organocatalyzed 1,3-aminoacylation of cyclopropane employing N-benzoyl saccharin as bifunctional reagent. *Nat. Commun.* **2024**, *15*, 8930. (f) Li, Q.-Z.; Zou, W.-L.; Yu, Z.-Y.; Kou, X.-X.; Liu, Y.-Q.; Zhang, X.; He, Y.; Li, J.-L. Remote site-selective arene C−H functionalization enabled by N-heterocyclic carbene organocatalysis. *Nat. Catal.* **2024**, *7*, 900−911. (g) Liu, C.; Zhang, Z.; Zhao, L.-L.; Bertrand, G.; Yan, X. Mesoionic Carbene-Catalyzed Formyl Alkylation of Aldehydes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202303478. (h) Liu, W.-D.; Lee, W.; Shu, H.; Xiao, C.; Xu, H.; Chen, X.; Houk, K. N.; Zhao, J. Diastereoselective Radical Aminoacylation of Olefins through N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 22767−22777. (i) Meng, Q.-Y.; Döben, N.; Studer, A. Cooperative NHC and Photoredox Catalysis for the Synthesis of $\beta$-Trifluoromethylated Alkyl Aryl Ketones. *Angew. Chem., Int. Ed.* **2020**, *59*, 19956−19960. (j) Wang, H.-Y.; Wang, X.-H.; Zhou, B.-A.; Zhang, C.-L.; Ye, S. Ketones from aldehydes via alkyl C(sp3)−H functionalization under photoredox cooperative NHC/palladium catalysis. *Nat. Commun.* **2023**, *14*, 4044. (k) Wang, L.; Ma, R.; Sun, J.; Zheng, G.; Zhang, Q. NHC and visible light-mediated photoredox co-catalyzed 1,4-sulfonylacylation of 1,3-enynes for tetrasubstituted allenyl ketones. *Chem. Sci.* **2022**, *13*, 3169−3175. (l) Wang, X.; Yang, R.; Zhu, B.; Liu, Y.; Song, H.; Dong, J.; Wang, Q. Direct allylic acylation via cross-coupling involving cooperative N-heterocyclic carbene, hydrogen atom transfer, and photoredox catalysis. *Nat. Commun.* **2023**, *14*, 2951. (m) Yin, Y.; Feng, J.; Wang, L.; Zhang, H.; Du, D. Regioselective Radical 1,4-Difunctionalization of 1,3-Cyclohexadiene via NHC Catalysis. *Org. Lett.* **2025**, *27*, 13055−13060.

(13) Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854−3858.

(14) (a) Tanaka, N.; Zhu, J. L.; Valencia, O. L.; Schull, C. R.; Scheidt, K. A. Cooperative Carbene Photocatalysis for $\beta$-Amino Ester Synthesis. *J. Am. Chem. Soc.* **2023**, *145*, 24486−24492. (b) Schull, C. R.; Cao, J.; Mitton-Fry, S. R.; Mrksich, M.; Scheidt, K. A. C($sp^3$)−H Carboxylation via Carbene/Photoredox Cooperative Catalysis. *ACS Catal.* **2025**, *15*, 1287−1293. (c) Ji, D.-S.; Zhou, C.; Zhang, X.; Ye, Y.; Bao, X.; Yuan, Y.; Huo, C. Photoredox/NHC Dual Catalysis Enabled de Novo Synthesis of $\alpha$-Amino Acids Derivatives. *Org. Lett.* **2024**, *26*, 8435−8440. (d) Cao, J.; Schull, C. R.; Scheidt, K. A. Deconstructive Radical−Radical Coupling for Programmable Remote Acylation. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202507542. (e) McGill, M. J.; Wayment, A. X.; Schull, C. R.; Scheidt, K. A. Dual NHC/HAT-Promoted Esterification to Access $\alpha$-Aryl Glycines. *Adv. Synth. Catal.* **2025**, *367*, No. e202401207. (f) Wayment, A. X.; Scheidt, K. A. Three-Component Synthesis of $\gamma$-Amino Esters with $\alpha$-Quaternary Carbon Centers via NHC/Photoredox Dual Catalysis. *Adv. Synth. Catal.* **2025**, *367*, No. e70013. (g) Liu, Y.; Ji, S.; Wang, J. Light-Driven Organocatalytic Enantioselective Radical $\alpha$-Carbamoylation of Amines. *CCS Chem.* **2026**, *8*, 1284−1294. (h) Zhu, J. L.; Scheidt, K. A. Photocatalytic acyl azolium-promoted alkoxycarbonylation of trifluoroborates. *Tetrahedron* **2021**, *92*, No. 132288.

(15) (a) Ren, S.-C.; Lv, W.-X.; Yang, X.; Yan, J.-L.; Xu, J.; Wang, F.-X.; Hao, L.; Chai, H.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Alkylation of Carboxylic Esters *via* Direct Photoexcitation of Acyl Azolium Intermediates. *ACS Catal.* **2021**, *11*, 2925−2934. (b) Ren, S.-C.; Yang, X.; Mondal, B.; Mou, C.; Tian, W.; Jin, Z.; Chi, Y. R. Carbene and photocatalyst-catalyzed decarboxylative radical coupling of carboxylic acids and acyl imidazoles to form ketones. *Nat. Commun.* **2022**, *13*, 2846−2855. (c) Nie, G.; Tu, T.; Liao, T.; Liu, D.; Ye, W.; Ren, S.-C. *N*-heterocyclic carbene and photocatalyst-catalyzed rapid access to indole ketones via radical C($sp^3$)-H acylation. *Green Chem.* **2024**, *26*, 5397−5408. (d) Zhang, T.; Wang, L.; Peng, X.; Liao, T.; Chen, D.; Tu, T.; Liu, D.; Cheng, Z.; Huang, S.; Ren, S.-C.; Zhang, X.; Chi, Y. R. NHC-mediated photocatalytic para-selective C-H acylation of aryl alcohols: regioselectivity control *via* remote radical spiro cyclization. *Sci. China. Chem.* **2025**, *68*, 3611−3621. (e) Liao, T.; Zhao, X.; Yang, F.; Xu, G.; Chen, D.; Tu, T.; Huang, S.; Ren, S.-C.; Chi, Y. R. Carbene-Catalyzed Nitrogen to Carbon Aryl Migration via a Radical-Neutral Crossover Process. *ACS Catal.* **2025**, *15*, 16356−16368. (f) Ye, W.; Wang, L.; Cheng, Z.; Zhao, X.; Liu, J.; Chen, D.; Xia, H.; Ren, S.-C. NHC-Catalyzed Single-Electron Oxidation and Alkylation of Imines: Alkene Difunctionalization and Dehydrogenative Coupling. *ACS Catal.* **2026**, *16*, 4902−4913.

(16) (a) Stache, E. E.; Ertel, A. B.; Rovis, T.; Doyle, A. G. Generation of Phosphoranyl Radicals via Photoredox Catalysis Enables Voltage−Independent Activation of Strong C−O Bonds. *ACS Catal.* **2018**, *8*, 11134−11139. (b) Zhang, M.; Xie, J.; Zhu, C. A general deoxygenation approach for synthesis of ketones from aromatic carboxylic acids and alkenes. *Nat. Commun.* **2018**, *9*, 3517.

(17) (a) Guo, H.-M.; Wu, X. Selective deoxygenative alkylation of alcohols via photocatalytic domino radical fragmentations. *Nat. Commun.* **2021**, *12*, 5365. (b) Guo, Y.-Q.; Wang, R.; Song, H.; Liu, Y.; Wang, Q. Visible-Light-Induced Deoxygenation/Defluorination Protocol for Synthesis of $\gamma,\gamma$-Difluoroallylic Ketones. *Org. Lett.* **2020**, *22*, 709−713. (c) Jiang, H.; Mao, G.; Wu, H.; An, Q.; Zuo, M.; Guo, W.; Xu, C.; Sun, Z.; Chu, W. Synthesis of dibenzocycloketones by acyl radical cyclization from aromatic carboxylic acids using methylene blue as a photocatalyst. *Green Chem.* **2019**, *21*, 5368−5373. (d) Li, S.; Shu, H.; Wang, S.; Yang, W.; Tang, F.; Li, X.-X.; Fan, S.; Feng, Y.-S. Cooperative NHC and Photoredox Catalysis for the Synthesis of 1,4-Dicarbonyl Compounds via Diacylation of Alkenes. *Org. Lett.* **2022**, *24*, 5710−5714. (e) Li, Y.; Shao, Q.; He, H.; Zhu, C.; Xue, X.-S.; Xie, J. Highly selective synthesis of all-carbon tetrasubstituted alkenes by deoxygenative alkenylation of carboxylic acids. *Nat. Commun.* **2022**, *13*, 10. (f) Ling, B.; Yao, S.; Ouyang, S.; Bai, H.; Zhai, X.; Zhu, C.; Li, W.; Xie, J. Nickel-Catalyzed Highly Selective Radical C−C Coupling from Carboxylic Acids with Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202405866. (g) Martinez Alvarado, J. I.; Ertel, A. B.; Stegner, A.; Stache, E. E.; Doyle, A. G. Direct Use of Carboxylic Acids in the Photocatalytic Hydroacylation of Styrenes To Generate Dialkyl Ketones. *Org. Lett.* **2019**, *21*, 9940−9944. (h) Ning, Y.; Wang, S.; Li, M.; Han, J.; Zhu, C.; Xie, J. Site-specific Umpolung amidation of carboxylic acids via triplet synergistic catalysis. *Nat. Commun.* **2021**, *12*, 4637. (i) Ruzi, R.; Liu, K.; Zhu, C.; Xie, J. Upgrading ketone synthesis direct from carboxylic acids and organohalides. *Nat. Commun.* **2020**, *11*, 3312. (j) Su, J.; Mo, J.-N.; Chen, X.; Umanzor, A.; Zhang, Z.; Houk, K. N.; Zhao, J. Generation of Oxyphosphonium Ions by Photoredox/Cobaloxime Catalysis for Scalable Amide and Peptide Synthesis in Batch and Continuous-Flow. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202112668. (k) Wang, H.; Liu, Z.; Das, A.; Bellotti, P.; Megow, S.; Temps, F.; Qi, X.; Glorius, F. Radical thioesterification via nickel-catalysed sensitized electron transfer. *Nat. Synth.* **2023**, *2*, 1116−1126. (l) Xia, P.-J.; Ye, Z.-P.; Hu, Y.-Z.; Song, D.; Xiang, H.-Y.; Chen, X.-Q.; Yang, H. Photocatalytic, Phosphoranyl Radical-Mediated N−O Cleavage of Strained Cycloketone Oximes. *Org. Lett.* **2019**, *21*, 2658−2662. (m) Xie, Z.-Z.; Chen, P.; Huang, C.; Xiang, M.; Gao, J.; Zheng, Y.; Chen, X.-Q.; Chen, K.; Yang, H. Photoredox-Driven Deoxygenative Cross-Coupling of Alcohols with Carbonyl Compounds. *ACS Catal.* **2025**, *15*, 20843−20852. (n) Zhang, M.; Yuan, X.-A.; Zhu, C.; Xie, J. Deoxygenative Deuteration of Carboxylic Acids with $D_2O$. *Angew. Chem., Int. Ed.* **2019**, *58*, 312−316. (o) Zhou, C.; Shatskiy, A.; Temerdashev, A. Z.; Kärkäs, M. D.; Dinér, P. Highly congested spiro-compounds via photoredox-mediated dearomative annulation cascade. *Commun. Chem.* **2022**, *5*, 92.

(18) (a) Zhanabaeva, M.; Kovalevsky, R. A.; Kucherenko, A. S.; Korlyukov, A. A.; Zlotin, S. G. Tandem process of asymmetric organocatalysis and selective post-functionalization: enantiodivergent synthesis of bioactive Indane-1-carboxylic acid derivatives. *Org. Biomol. Chem.* **2025**, *23*, 5611−5615. (b) Das, S.; Yasmin, H.; Mehedi Masud, M.; Roy, S. C.; Nahar, L.; Mukhlesur Rahman, M.; Gibbons, S.; Bachar, S. C.; Sarker, S. D. Total synthesis and analgesic activity of 6-fluoroindan-1-carboxylic acid. *Tetrahedron* **2008**, *64*, 8642−8645.

(19) Chen, H.; Bo, L.; Zhao, Z.; Cao, W.; Xu, W.; Li, Q.; Wang, J.; Zhang, P.; Jiang, Z.; Zhang, G.; Gao, H.; Gong, H.; Zuo, G.



https://doi.org/10.1021/acs.orglett.6c01511
*Org. Lett.* XXXX, XXX, XXX−XXX

Compound as potassium channel modulator. W.O. Patent WO2014048165A1, 2014.
(20) Wang, D.; Ni, H.; Cao, Y.; Xu, Y.; Gan, Z.; Zhao, J.; Feng, T. Method for preparing 1H-indene-1-ketone-3-methanoic acid compound. C.N. Patent CN102603520A, 2017.
(21) (a) Newcomb, M. Radical Kinetics and Clocks. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley-VCH: Weinheim, 2014; Vol. *1*, Chapter 5, pp 107−124; DOI: 10.1002/9781119953678.rad007. (b) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. Mechanistic Studies in Photocatalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 3730−3747. (c) Halgren, T. A.; Roberts, J. D.; Horner, J. H.; Martinez, F. N.; Tronche, C.; Newcomb, M. Kinetics and Equilibrium Constants for Reactions of α-Phenyl-Substituted Cyclopropylcarbinyl Radicals. *J. Am. Chem. Soc.* **2000**, *122*, 2988−2994.
(22) (a) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. Visible-Light-Mediated Decarboxylation/Oxidative Amidation of α-Keto Acids with Amines under Mild Reaction Conditions Using $O_2$. *Angew. Chem., Int. Ed.* **2014**, *53*, 502−506. (b) Mukherjee, S.; Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Glorius, F. Alkynylation of C (O)−H Bonds Enabled by Photoredox-Mediated Hydrogen-Atom Transfer. *Angew. Chem., Int. Ed.* **2017**, *56*, 14723−14726. (c) Jia, K.; Pan, Y.; Chen, Y. Selective Carbonyl−C($sp^3$) Bond Cleavage To Construct Ynamides, Ynoates, and Ynones by Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 2478−2481. (d) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C−H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 11353−11356.
(23) Cismesia, M. A.; Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci.* **2015**, *6*, 5426−5434.
(24) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363.
(25) (a) Schiavon, G.; Zecchin, S.; Cogoni, G.; Bontempelli, G. Anodic oxidation of triphenylphosphine at a platinum electrode in acetonitrile medium. *J. Electroanal. Chem.* **1973**, *48*, 425−431. (b) Pandey, G.; Pooranchand, D.; Bhalerao, U. T. Photoinduced single electron transfer activation of organophosphines: Nucleophilic trapping of phosphine radical cation. *Tetrahedron* **1991**, *47*, 1745−1752.
(26) (a) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. 5-Endo-trig Radical Cyclizations: Disfavored or Favored Processes? *J. Am. Chem. Soc.* **2002**, *124*, 10765−10772. (b) Dash, R.; Thombare, K. R.; Das, A.; Murarka, S. Visible-light-driven cascade cyclization: a modular approach to functionalized 4-pyrrolin-2-ones. *Chem. Commun.* **2025**, *61*, 17368−17371. (c) Das, A.; Kloene, L.; Chandra, S.; Koenigs, R. M.; Murarka, S. Visible-Light Palladium Catalysis for Alkylated and Difluoroalkylated Pyrazolones. *Chem. Commun.* **2026**, DOI: 10.1039/D6CC01889K.


https://doi.org/10.1021/acs.orglett.6c01511
*Org. Lett.* XXXX, XXX, XXX−XXX