ACS Catalysis

pubs.acs.org/acscatalysis

Research Article

Energy-Transfer-Enabled Regioconvergent Alkylation of Azlactones via Photocatalytic Radical−Radical Coupling

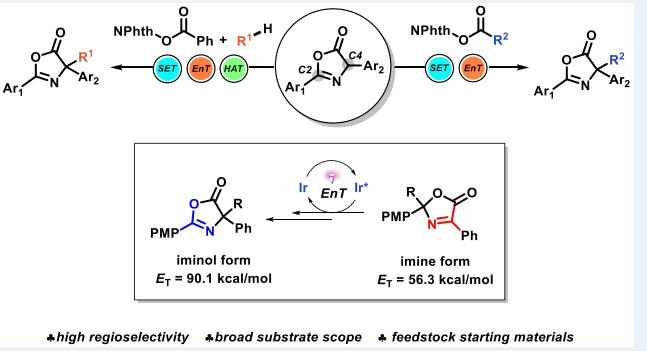
Kun Zhu, Yunhan Ma, Zugen Wu, Jie Wu,* and Yixin Lu*

Cite This: *ACS Catal.* 2023, 13, 4894−4902

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: C-4-selective functionalization of azlactones provides access to α,α-disubstituted unnatural α-amino acids, which has been extensively investigated in the past decades. However, a vast majority of such transformations are two-electron transfer reactions. Herein, leveraging on the persistent radical effect, we develop photocatalytic energy transfer-enabled regioconvergent alkylation of azlactones with redox-active esters via radical−radical couplings. This strategy is extended to the utilization of simple alkanes as the radical precursors, whereby the aryl redox-active esters play a dual role of an oxidant and a hydrogen-atom-transfer agent. Notably, the excited state Ir(III) photocatalyst enables selective activation of the unwanted imine products through triplet energy transfer, delivering C-4-functionalized azlactones with high regioselectivity. Both experimental investigations and density functional theory calculations on the reaction mechanism were performed, supporting EnT-enabled regioconvergent photocatalytic radical−radical coupling reaction pathways.



KEYWORDS: *α,α-disubstituted α amino acid, azlactone, persistent radical effect, energy transfer, hydrogen atom transfer*

Unnatural α,α-disubstituted α-amino acids are key structures in natural products and bioactive molecules.[1] In biological sciences, the conformational stability induced by the two side chains makes α,α-disubstituted unnatural amino acids highly stable toward proteolysis; thus, they are invaluable tools in peptide SAR studies, building up peptidomimetic libraries, and uncovering therapeutic agents. Not surprisingly, development of efficient synthetic approaches to access such structural motifs has continued to be an active research area.[2,3]

The chemistry of azlactones has been extensively studied for the past decades, due to their importance in the synthesis of amino acid derivatives. In the most common mode of transformations,[4] an azlactone would serve as a nucleophilic reaction partner, often through deprotonation of its acidic proton, to react with a range of electrophiles (Figure 1A). In an interesting approach, Curto and Kozlowski disclosed a palladium-catalyzed chemoselective arene sp^3 C−H activation. Mechanistically, it is believed that the azlactone dimer plays an important role in the observed C−H activation (Figure 1B).[5] Subsequently, Ohshima and co-workers reported an iron-catalyzed cross-coupling of azlactones via a transient homocoupling dimer strategy.[6] Despite all the marvelous progress of azlactone chemistry accomplished to date which is largely based on two-electron transfer reactions, it would still be highly desirable to develop novel approaches to functionalize azlactones in a mechanistically novel manner, allowing the use of a broad range of reaction partners that are complementary to those in the existing methods. It was with

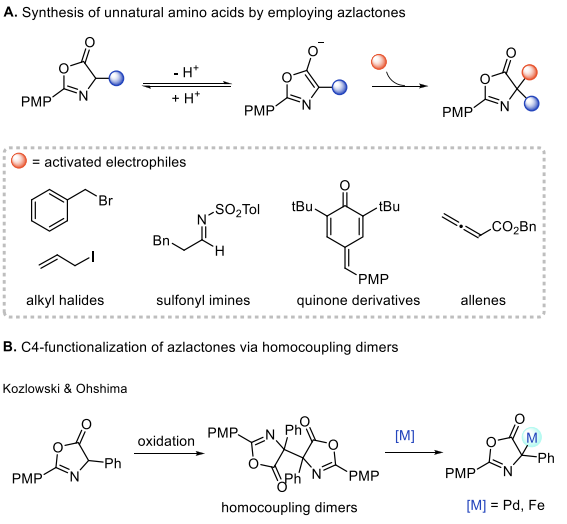


Figure 1. Synthesis of unnatural amino acids employing azlactones. PMP = *p*-methoxyphenyl.

Received: November 20, 2022
Revised: March 14, 2023

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

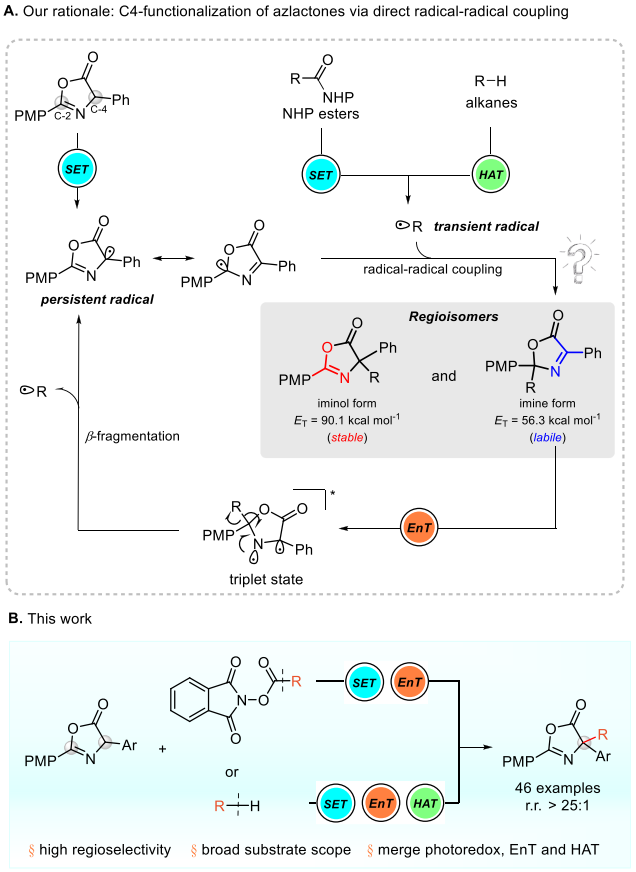


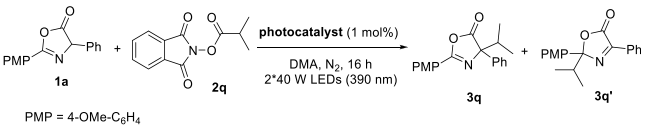
Figure 2. Functionalization of azlactones via photocatalytic radical coupling. NHP = *N*-hydroxyphthalimide.

this goal in mind that we started our investigation described in this report.

Catalytic radical reactions have been extensively investigated in the past few decades,[7] and the key feature of which is the involvement of highly reactive radical intermediates, as opposed to polar species in a myriad of polar chemical reactions. We reasoned that the C-4 functionalization of azlactones via radical pathways may significantly broaden the scope of the reaction, if only a radical activation of inert partners can be achieved. In fact, studies of azlactones in radical processes date back to the 1980s,[8] which were mainly focused on the oxidative coupling of azlactones. These earlier studies suggest that the C-4 radical species of azlactones could be considered as a persistent radical due to the captodative and steric effects.[9] Nevertheless, the employment of azlactones in radical reactions is rather limited, due to their propensity for dimerization and tendency to undergo photolysis which extrudes a molecule of carbon dioxide or carbon monoxide to yield the corresponding nitrile ylide or acetamide.[8a,g] Furthermore, the difficulty in differentiating the C-2 and C-4 radical resonance forms of azlactones makes the regioselective cross-coupling reactions challenging. At the outset, there was no report on the direct cross-coupling of azlactone radicals with other transient radical species.[10] We therefore aimed to develop such a radical process in a regioselective manner and engage readily available feedstock chemicals as the cross-coupling partners.

In recent years, photocatalysis has become a powerful strategy for the activation of feedstock molecules in organic chemistry.[11] Selective excitation of light-harvesting catalysts can promote single-electron transfer (SET), energy transfer (EnT), or hydrogen-atom-transfer (HAT) processes to access reactive radicals from a wide range of available radical precursors, enabling nonclassical C−C bond formations.[12−14] To develop azlactone radical chemistry, we envisioned that the photomediated SET process facilitates the generation of azlactone persistent radical species. Leveraging on the persistent radical effect, subsequent cross-coupling reactions with other in situ generated transient radicals are highly feasible. We carried out density functional theory (DFT) calculations to determine the triplet energies of C-2 and C-4-substituted regioisomers, which are 56.3 and 90.1 kcal/mol, respectively. With such a triplet energy difference, we believe that a regioconvergent functionalization of azlactones enabled by EnT is highly feasible; EnT activates the more labile C-2

Table 1. Evaluation of Photocatalysts[a]



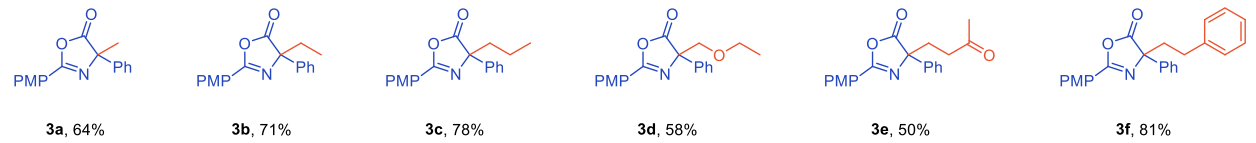
entry	photocatalyst	E_T (kcal/mol)[b]	yield (%) (**3q**:**3q′**)[c]
1	none	\	41 (76:24)
2	$[Ir(ppy)_2dtbbpy]PF_6$	49.2	56 (79:21)
3	fac-$Ir(ppy)_3$	55.2	45 (76:24)
4	fac-$Ir(4\text{-}CF_3ppy)_3$	56.4	58 (77:23)
5	fac-$Ir(dFppy)_3$	60.1	47 (>25:1)
6	$[Ir(dFCF_3ppy)_2dtbbpy]PF_6$	60.1	56 (>25:1)
7	$[Ir(dF(Me)ppy)_2dtbbpy]PF_6$	60.2	53 (>25:1)
8	$[Ir(dFCF_3ppy)_2bpy]PF_6$	60.4	56 (>25:1)
9[d]	$[Ir(dFCF_3ppy)_2dtbbpy]PF_6$	60.1	69(64) (>25:1)

[a]Reaction conditions: **1a** (0.1 mmol), **2q** (0.2 mmol), and the photocatalyst (0.001 mmol) in DMA (1 mL), room temperature, 2 × 40 W LEDs (390 nm), 16 h under N_2. [b]Values from the literature.[17] [c]Yields determined by analysis of the crude ^{1}H NMR spectra using mesitylene as an internal standard. Ratio of **3q**/**3q′** determined by high-performance liquid chromatography analysis of the mixed regioisomers. [d]The optimal conditions: **1a** (0.1 mmol), **2q** (0.3 mmol) and Hantzsch ester (0.1 mmol) in MeCN/DMA = 9/1 (1 mL), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (0.001 mmol), 60 °C, 2 × 40 W LEDs (390 nm), 16 h under N_2. Yield in the bracket refers to the isolated yield. LED, light-emitting diode; DMA, dimethylacetamide.

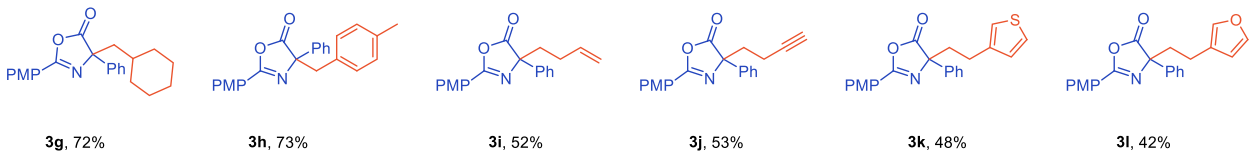
https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

Scheme 1. Scope of Couplings of Azlactones with Redox Esters[a]

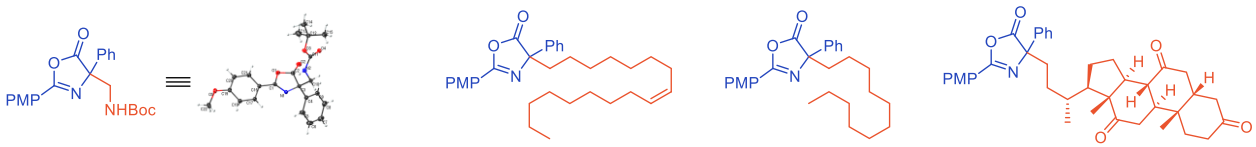
from primary acids:



3a, 64% **3b**, 71% **3c**, 78% **3d**, 58% **3e**, 50% **3f**, 81%

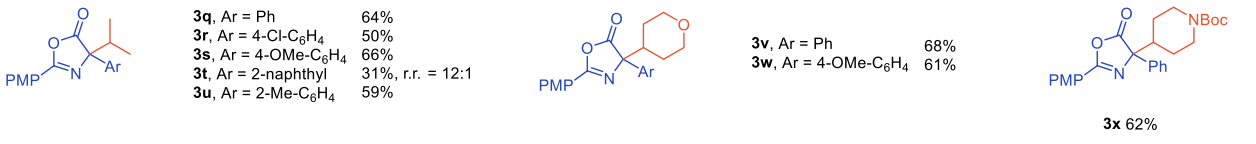


3g, 72% **3h**, 73% **3i**, 52% **3j**, 53% **3k**, 48% **3l**, 42%

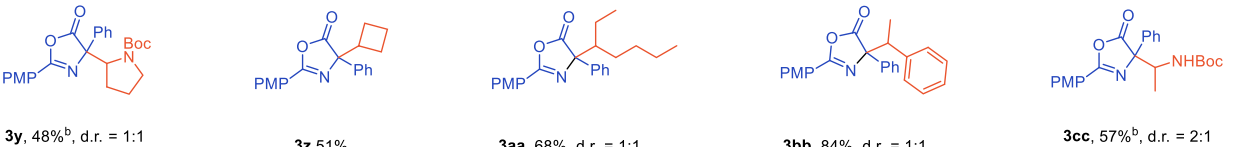


3m, 67%[b] from Boc-glycine — crystal structure of **3m** (CCDC:2212036) — **3n**, 66% from oleic acid — **3o**, 71% from lauric acid — **3p**, 62%, d.r. = 1:1 from dehydrocholic acid

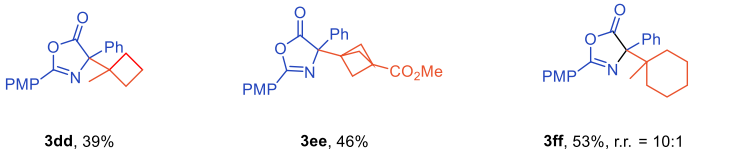
from scondary and tertiary acids:



3x 62%



3y, 48%[b], d.r. = 1:1 from Boc-proline — **3z** 51% — **3aa**, 68%, d.r. = 1:1 — **3bb**, 84%, d.r. = 1:1 — **3cc**, 57%[b], d.r. = 2:1 from Boc-alanine



3dd, 39% — **3ee**, 46% — **3ff**, 53%, r.r. = 10:1

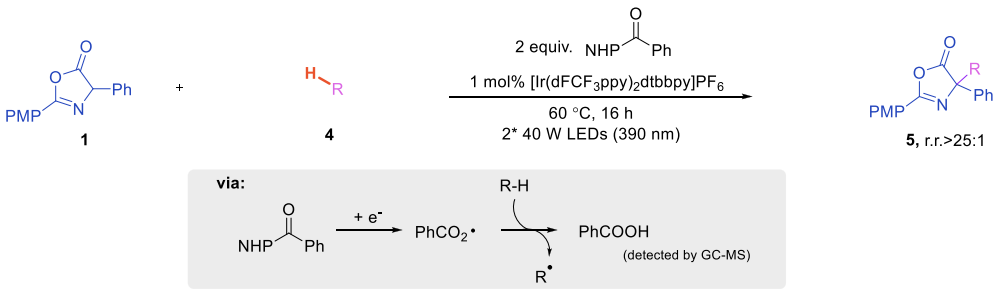
[a] **1** (0.1 mmol), **2** (0.3 mmol) and Hantzsch ester (0.1 mmol) in 1 mL MeCN/DMA (9:1), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (0.001 mmol), 60 °C, 2 × 40 W LEDs (390 nm), N_2, 16 h. [b] **1** (0.1 mmol), **2** (0.3 mmol) and Hantzsch ester (0.1 mmol) in 1 mL DMA, r.t., 2 × 40 W LEDs (390 nm), N_2, 16 h. Boc = *tert*-butyloxycarbonyl.

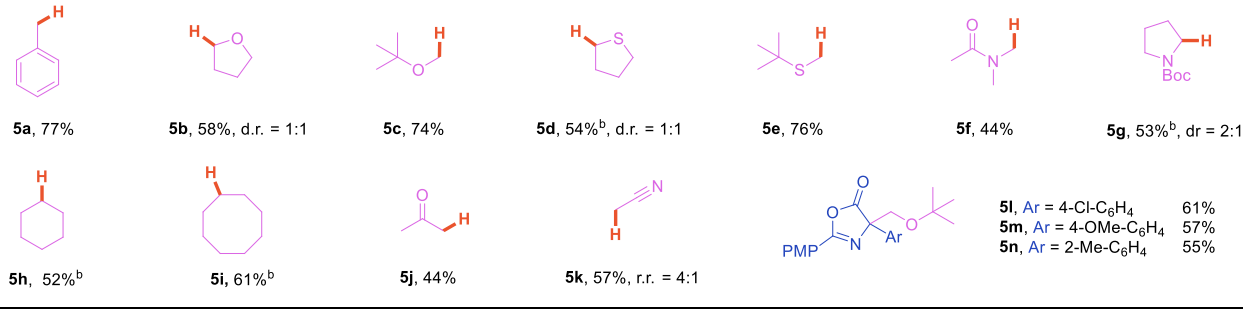
regioisomer, which undergoes β-fragmentation to regenerate the active azlactone radical (Figure 2A). Herein, we report an unprecedented EnT-enabled regioconvergent alkylation of azlactones with redox-active esters via a photocatalytic radical−radical coupling process. Furthermore, this strategy is extended to include simple alkanes as the cross-coupling partners, whereby aryl redox-active esters function as both an oxidant and a HAT agent (Figure 2B). The experimental investigations and DFT calculations were performed to gain insight into the reaction mechanism. It is noteworthy that most of the existing strategies for the activation of unsaturated substrates via a photoenergy-transfer process are focused on double-bond photoisomerization[15] and cyclization reactions.[16] Our study provides a highly regioselective azlactone functionalization enabled by an EnT process.

We started our investigation by choosing azlactone **1a** and redox-active ester **2q** as the model substrates and evaluated the catalytic effects of various photocatalysts, and the results are summarized in Table 1. The cross-coupling reaction took place under 390 nm light irradiation in the absence of a photocatalyst, with poor regioselectivity (entry 1). Screening of various photocatalysts revealed that around 4:1 ratio of C-4/

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

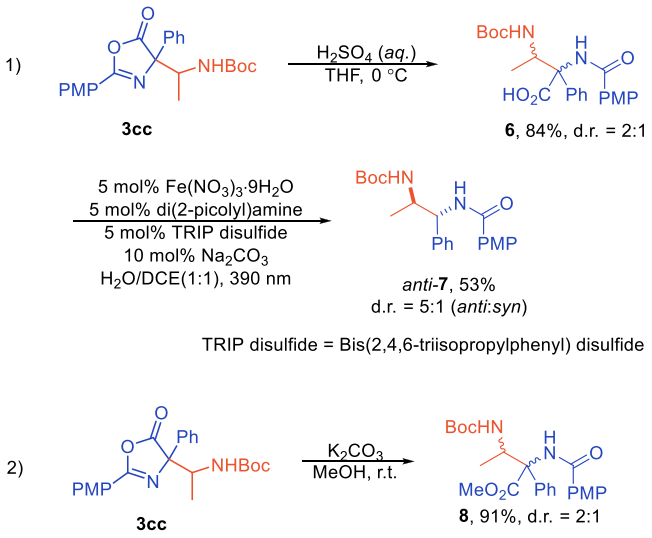
Scheme 2. Scope of Couplings of Azlactones with Alkanes[a]





[a]**1** (0.1 mmol), **4** (1 mL), $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (0.001 mmol), phenyl redox-active ester (0.1 mmol), 60 °C, 2 × 40 W LEDs (390 nm), N_2, 16 h. [b]**1** (0.1 mmol), **4** (0.2 mL) in 0.8 mL $PhCF_3$, $[Ir(dFCF_3ppy)_2dtbbpy]PF_6$ (0.001 mmol), phenyl redox-active ester (0.1 mmol), 60 °C, 2 × 40 W LEDs (390 nm), N_2, 16 h.

Scheme 3. Elaboration of C-4-Alkylated Products



C-2 regioisomers (**3q**/**3q′**) was obtained when photocatalysts possessing a triplet state energy (E_T) below 60 kcal mol^{-1} were utilized (entries 2−4). With the employment of photocatalysts having E_T > 60 kcal mol^{-1}, the cross-coupling product **3** was obtained in moderate yield and with excellent regioselectivity (entries 5−8). Subsequently, we extensively investigated reaction conditions (see the Supporting Information, Table S1 for details). When the reaction was performed in mixed solvents (CH_3CN/DMA = 9:1), with Hantzsch ester as a sacrificial donor, and at an elevated temperature (60 °C), the desired C4-regioisomer of the cross-coupling product **3q** was obtained in 64% yield (entry 9).

With the optimized reaction conditions in hand, we proceeded to examine the reaction scope, focusing on different redox-active esters derived from readily available carboxylic acids (Scheme 1). Simple linear primary aliphatic acids of various chain lengths (**3a**−**3c**), as well as alkyl substituents bearing an ether (**3d**), a ketone (**3e**), an aryl (**3f**), or a cyclohexyl (**3g**) moiety at the terminal position were all found to be compatible with the reaction conditions, leading to the formation of the corresponding azlactone derivatives in good yields with excellent regioselectivities. The reaction was also applicable to functionalized primary acids containing a benzylic (**3h**), a terminal alkenyl (**3i**), an alkynyl (**3j**), or a heterocyclic moiety (**3k**, **3l**). Moreover, the good functional group tolerance of this method enables the synthesis of complex azlactone derivatives through late-stage functionalization of biologically active molecules, including Boc-glycine (**3m**), oleic acid (**3n**), lauric acid (**3o**), and dehydrocholic acid (**3p**). For azlactone C-4 aryl substituents, arenes containing both electron-donating and electron-withdrawing groups at the *para*- or *ortho*- position are well-tolerated, and the corresponding azlactone derivatives were obtained in modest to good yields (**3q**−**3u**). Remarkably, secondary carboxylic acid-derived redox-active esters underwent the alkylation with excellent regioselectivity. Tetrahydropyranyl (**3v**, **3w**), N-Boc-piperidinyl (**3x**), N-Boc-pyrrolidinyl (**3y**), cyclobutyl (**3z**), and alkyl chain substituents (**3aa**−**3cc**) could all be readily incorporated into C-4-functionalized azlactones. Redox-active esters from hindered tertiary carboxylic acids also delivered the coupling products with high regioselectivity, albeit with slightly decreased yields (**3dd**−**3ff**).

We next considered to include simple alkanes as a reaction partner for the functionalization of azlactones (Scheme 2). For the direct C−H activation of simple alkane substrates, the benzoyloxy radical (PhCOO˙) derived from the redox-active ester may serve as a HAT agent.[18] Specifically, the phenyl redox-active ester is anticipated to play a dual role as an oxidizing agent and a precursor of HAT agent. After reduction

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

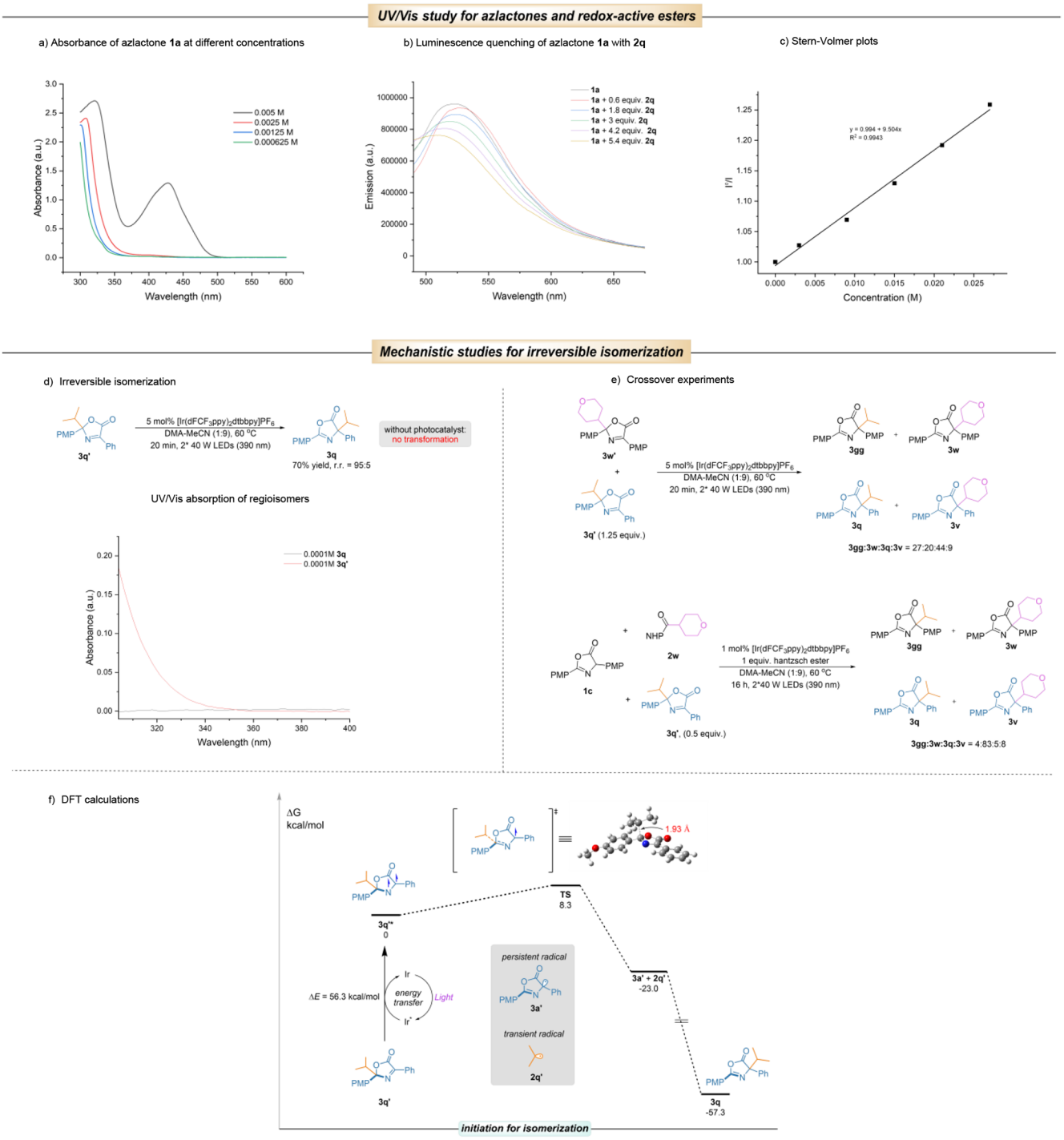


Figure 3. Mechanistic studies.

of the redox-active ester via a SET process, the in situ generated benzoyloxy radical (BDE = 111 kcal/mol) quickly abstracts the hydrogen atom from the C(sp^3)−H bonds of alkane substrates, and the resulting C(sp^3) radicals couple with the persistent azlactone radicals. Activated alkanes such as toluene (**5a**) and several hydridic C(sp^3)−H bonds adjacent to heteroatoms such as the oxygen, nitrogen, or sulfur atom gave highly regioselective coupling products in modest to good yields (**5b**−**5g**). Interestingly, the reaction worked very well for the unactivated alkanes such as cyclohexane (**5h**) and cyclooctane(**5i**). Moreover, substrates bearing an acidic α-proton, e.g., acetone (**5j**) and acetonitrile (**5k**), could also be employed. Finally, the variation of the aromatic substituent of azlactones was evaluated, regardless of the electronic nature and substitution patterns of the aryl moiety, the coupling reaction proceeded smoothly and furnished the desired cross-coupling products in decent yields (**5l**−**5n**).

The C-4 functionalized azlactones are known as powerful precursors for α,α-disubstituted α-amino acid derivatives.[4i] Thus, the synthetic utility of our protocol was demonstrated by further transformations (Scheme 3). Treated with aqueous H_2SO_4 in THF, **3cc** was fully converted to the corresponding

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

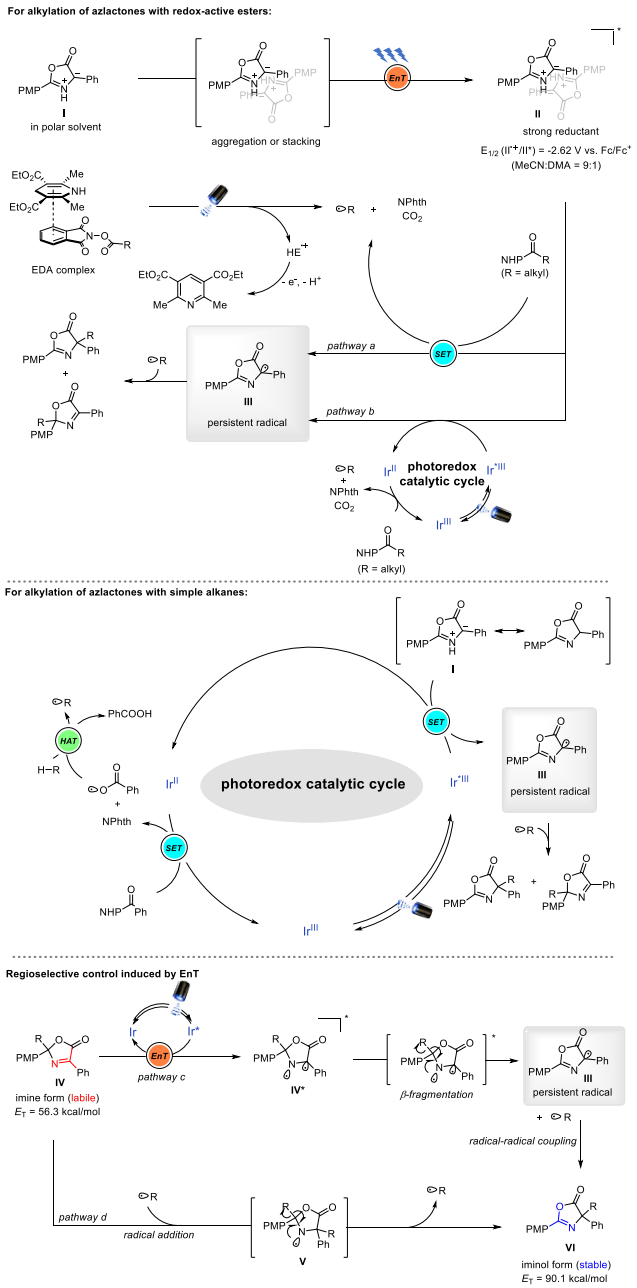


Figure 4. Proposed plausible mechanisms. NPhth = phthalimide.

carboxylic acid **6**. Subsequent decarboxylative protonation of **6** afforded 1,2-damine *anti*-**7** bearing different protecting groups.[19,20] In addition, ring opening of azlactone **3cc** under mild basic conditions led to the formation of the α-,α-disubstituted α-amino acid derivative **8** in an excellent yield.

To gain insights into the mechanistic pathways leading to this radical−radical coupling, a series of control experiments were conducted. With the increase of the concentration of azlactone **1**, a new band (350−500 nm) appeared in its absorption spectrum. We believe that such a new absorption band may be attributed to the aggregation or stacking effect of azlactones in a mesoionic form[21] (Figure 3a). The Stern−Volmer quenching experiments showed that photoexcited azlactone **1a** could be effectively quenched by redox-active ester **2q** (Figure 3b,c). The redox potential of **1a** at the excited state ($E_{1/2}$ (I^{+}/I*) = −2.62 V vs Fc/Fc^{+}) was estimated by the combination of the UV/vis absorption spectrum and the corresponding cyclic voltammetry (CV) measurement (Figures S1 and S5). Furthermore, no obvious red-shift was observed when azlactone **1a** was mixed with redox-active ester **2q** under basic conditions, which excludes the possibility of an electron donor−acceptor (EDA) complex formation (Figure S2). A few extra experiments were performed to understand EnT-enabled regioselectivity. With the treatment of Ir-photocatalyst, C-2-substituted isomer **3q′** irreversibly isomerized to C-4-substituted **3q** with an isomeric ratio of 95:5 (**3q**:**3q′**). However, no isomerization was observed in the absence of the Ir-photocatalyst. The quantum yield (φ (10%) = 76.1) indicated that a radical chain process might be involved (see the Supporting Information for details). Compared with C-4-substituted **3q**, C-2-substituted **3q′** has a much stronger absorption in the region of 300−360 nm (Figure 3d). The phenomenon of irreversible isomerization between different regioisomers was further confirmed by the crossover experiments (Figure 3e). When two C-2-substituted regioisomers **3w′** and **3q′** bearing distinguishable groups were treated with the Ir-photocatalyst under light irradiation, crossover products with a ratio of 27:20:44:9 (**3gg**:**3w**:**3q**:**3v**) were obtained. In another experiment, when azlactone **1c** was mixed with redox-active ester **2w** and C-2-substituted **3q′** under the standard reaction conditions, a mixture of four crossover products was formed. DFT calculations using UB3LYP were also performed (Figure 3f). The triplet energy of **3q′** was computed to be 56.3 kcal/mol, which is sufficient to undergo triplet-triplet energy transfer (TTEnT) with excited [Ir(dFCF_3ppy)$_2$dtbbpy]PF_6 (E_T = 60.1 kcal/mol). The excited **3q′*** smoothly undergoes β-fragmentation with a barrier of 8.3 kcal/mol, leading to the formation of isopropyl radical **2q′** and azlactone radical **3a′**.[22] A subsequent radical−radical cross-coupling reaction between **2q′** and **3a′** delivers the desired product **3q**.

Based on all the above experimental and theoretical studies, a plausible mechanism is proposed (Figure 4). In polar solvents, azlactones exist predominantly in mesoionic form **I**. Under 390 nm light irradiation, direct excitation of concentrated **I** leads to its excited state **II** ($E_{1/2}$ ($\mathbf{II}^{+}$/**II***) = −2.62 V vs Fc/Fc^{+}), which then reduces either redox-active ester or the photoexcited Ir catalyst. Both pathways result in the formation of azlactone radical **III** and the corresponding alkyl radical species. Moreover, the alkyl radical can also be generated through the EDA complex of Hantzsch ester (HE) and redox-active ester.[23] Finally, the radical−radical cross-coupling reaction forms the desired product. For the alkylation reaction employing simple alkanes, a HAT process is involved. The azlactone radical **III** is generated upon oxidative quenching of excited Ir-photocatalyst. Subsequently, oxidation of the reduced Ir-photocatalyst by phenyl redox-active ester then forms a benzoyloxy radical (PhCOO$^{\cdot}$), which abstracts the hydrogen atom from the C(sp^3)−H bond of alkanes, yielding the corresponding alkyl radical species. Finally, the radical−radical coupling delivers the desired coupling product. To account for the EnT-induced regioselectivity, we propose that the EnT from the excited Ir-photocatalyst to the ground-state C2-substituted regioisomer **IV** (E_T = 56.3 kcal/mol) furnishes the triplet state **IV***, which undergoes a facile β-fragmentation to regenerate azlactone radical **III** and alkyl radical, and the same radical−radical coupling completes the reaction. An alternative radical addition pathway cannot be ruled out; the addition of alkyl radical to **IV** gives rise to

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

intermediate **V**, which undergoes a β-fragmentation, forming product **VI** and regenerating alkyl radical.[24]

In summary, we have developed an efficient alkylation of azlactones with redox-active esters or simple alkanes via a photocatalytic radical−radical cross-coupling reaction. The reported reactions are highly regioselective, enabled by an EnT process. The strategy introduced herein is mechanistically intriguing, entailing synergistic interplays of photoredox SET, HAT, and EnT processes. The reaction protocols are mild, with good functional group tolerance, and applicable to a broad range of substrates. It is noteworthy that persistent radicals are readily generated through single-electron oxidation of azlactones, key for the subsequent radical−radical cross-coupling reaction. An unprecedented photo EnT-enabled regioselectivity is discovered, through selective activation and transformation of unwanted regioisomers. Moreover, the phenyl redox-active ester represents a rare example of oxidative HAT reagent, where most reported HAT reagents in the literature are reductive by nature.[25] We are currently working toward the discovery of novel photochemical reactions, leveraging on the conceptual advancement presented in this report.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c05698.

Experimental procedure, optimization tables, and characterization data for all the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jie Wu − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore;* orcid.org/0000-0002-9865-180X; Email: chmjie@nus.edu.sg

Yixin Lu − *Joint School of National University of Singapore and Tianjin University, International Campus of Tianjin University, Fuzhou, Fujian 350207, China; Department of Chemistry, National University of Singapore, Singapore 117543, Singapore;* orcid.org/0000-0002-5730-166X; Email: chmlyx@nus.edu.sg

Authors

Kun Zhu − *Joint School of National University of Singapore and Tianjin University, International Campus of Tianjin University, Fuzhou, Fujian 350207, China; Department of Chemistry, National University of Singapore, Singapore 117543, Singapore*

Yunhan Ma − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore*

Zugen Wu − *Department of Chemistry, National University of Singapore, Singapore 117543, Singapore*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.2c05698

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Y.L. thanks the Singapore National Research Foundation, Prime Minister's Office for the NRF Investigatorship Award (A-0004067-00-02). Financial support from the Ministry of Education of Singapore (A-0008481-00-00) is also acknowledged.

■ REFERENCES

(1) For selected reports, see: (a) Toniolo, C.; Bonora, G. M.; Bavoso, A.; Benedetti, E.; di Blasio, B.; Pavone, V.; Pedone, C. Preferred Conformations of Peptides Containing α,α-Disubstituted α-Amino Acids. *Biopolymers* **1983**, *22*, 205−215. (b) Toniolo, C.; Benedetti, E. Structures of Polypeptides from α-Amino Acids Disubstituted at the α-Carbon. *Macromolecules* **1991**, *24*, 4004−4009. (c) Cornish, V. W.; Mendel, D.; Schultz, P. G. Probing Protein Structure and Function with an Expanded Genetic Code. *Angew. Chem., Int. Ed.* **1995**, *34*, 621−633. (d) Gibson, S. E.; Guillo, N.; Tozer, M. J. Towards Control of χ-Space: Conformationally Constrained Analogues of Phe, Tyr, Trp and His. *Tetrahedron* **1999**, *55*, 585−615. (e) England, P. M. Biochemical and Biophysical Studies of Heme Transport Proteins: HtaA, HtaB, and ChtB from the Corynebacterium Diphtheriae. *Biochemistry* **2004**, *43*, 11623−11629. (f) Tanaka, M. Design and Synthesis of Chiral α,α-Disubstituted Amino Acids and Conformational Study of Their Oligopeptides. *Chem. Pharm. Bull.* **2007**, *55*, 349−358. (g) Beaulieu, P. L.; Bos, M.; Cordingley, M. G.; Chabot, C.; Fazal, G.; Garneau, M.; Gillard, J. R.; Jolicoeur, E.; LaPlante, S.; McKercher, G.; Poirier, M.; Poupart, M. A.; Tsantrizos, Y. S.; Duan, J.; Kukolj, G. Discovery of the First Thumb Pocket 1 NS5B Polymerase Inhibitor (BILB 1941) with Demonstrated Antiviral Activity in Patients Chronically Infected with Genotype 1 Hepatitis C Virus (HCV). *J. Med. Chem.* **2012**, *55*, 7650−7666. (h) Monn, J. A.; Valli, M. J.; Massey, S. M.; Hao, J.; Reinhard, M. R.; Bures, M. G.; Heinz, B. A.; Wang, X.; Carter, J. H.; Getman, B. G.; Stephenson, G. A.; Herin, M.; Catlow, J. T.; Swanson, S.; Johnson, B. G.; McKinzie, D. L.; Henry, S. S. Synthesis and Pharmacological Characterization of 4-Substituted-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates: Identification of New Potent and Selective Metabotropic Glutamate 2/3 Receptor Agonists. *J. Med. Chem.* **2013**, *56*, 4442−4455. (i) Blaskovich, M. A. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.* **2016**, *59*, 10807−10836.

(2) (a) Vogt, H.; Bräse, S. Recent Approaches towards the Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids. *Org. Biomol. Chem.* **2007**, *5*, 406−430. (b) Soloshonok, V.; Sorochinsky, A. Practical Methods for the Synthesis of Symmetrically α,α-Disubstituted α-Amino Acids. *Synthesis* **2010**, *2010*, 2319−2344.

(3) (a) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. The Synthesis of Amino Acids by Phase-Transfer Reactions. *Tetrahedron Lett.* **1978**, *19*, 2641−2644. (b) O'Donnell, M. J. The Enantioselective Synthesis of α-Amino Acids by Phase-Transfer Catalysis with Achiral Schiff Base Esters. *Acc. Chem. Res.* **2004**, *37*, 506−517.

(4) For selected reports, see: (a) Glemi, M. L.; Pocar, D.; Rossi, L. M. A Convenient Procedure for the 4-Alkylation of 2, 4-Diphenyl-2-oxazolin-5-one under Phase Transfer Conditions. *Synthesis* **1984**, *1984*, 763−765. (b) Trost, B. M.; Ariza, X. Catalytic Asymmetric Alkylation of Nucleophiles: Asymmetric Synthesis of α-Alkylated Amino Acids. *Angew. Chem., Int. Ed.* **1997**, *36*, 2635−2637. (c) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. The Diverse Chemistry of Oxazol-5-(4*H*)-ones. *Chem. Soc. Rev.* **2007**, *36*, 1432−1440. (d) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. Organocatalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids and Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 12031−12037. (e) Uraguchi, D.; Ueki, Y.; Ooi, T. Chiral Tetraaminophosphonium Carboxylate-Catalyzed Direct Mannich-Type Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 14088−14089. (f) Czabaniuk, L. C.; Trost, B. M. Benzylic Phosphates as Electrophiles in the Palladium-Catalyzed Asymmetric Benzylation of Azlactones. *J. Am. Chem. Soc.* **2012**, *134*, 5778−5781. (g) Chen, W.; Hartwig, J. F. Control of Diastereoselectivity for Iridium-Catalyzed Allylation of a Prochiral Nucleophile with a Phosphate Counterion. *J. Am. Chem. Soc.* **2013**, *135*, 2068−2071. (h) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. Azlactone Reaction Developments. *Chem. − Eur. J.* **2016**, *22*, 10294−10318. (i) Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.;

Lu, Y. Regiodivergent Enantioselective γ-Additions of Oxazolones to 2,3-Butadienoates Catalyzed by Phosphines: Synthesis of α,α-Disubstituted α-Amino Acids and N,O-Acetal Derivatives. *J. Am. Chem. Soc.* **2016**, *138*, 265−271. (j) Li, W.; Xu, X.; Liu, Y.; Gao, H.; Cheng, Y.; Li, P. Enantioselective Organocatalytic 1,6-Addition of Azlactones to *para*-Quinone Methides: An Access to α,α-Disubstituted and β,β-Diaryl-α-amino Acid Esters. *Org. Lett.* **2018**, *20*, 1142−1145. (k) Ruan, S.; Lin, X.; Xie, L.; Lin, L.; Feng, X.; Liu, X. Asymmetric Synthesis of 3-Aminodihydrocoumarins via the Chiral Guanidine Catalyzed Cascade Reaction of Azlactones. *Org. Chem. Front.* **2018**, *5*, 32−35. (l) Marra, I. F. S.; de Castro, P. P.; Amarante, G. W. Recent Advances in Azlactone Transformations. *Eur. J. Org. Chem.* **2019**, *2019*, 5830−5855. (m) Xie, L.; Dong, S.; Zhang, Q.; Feng, X.; Liu, X. Asymmetric Construction of Dihydrobenzofuran-2,5-dione Derivatives via Desymmetrization of *p*-Quinols with Azlactones. *Chem. Commun.* **2019**, *55*, 87−90.

(5) Curto, J. M.; Kozlowski, M. C. Chemoselective Activation of sp^3 vs sp^2 C−H Bonds with Pd(II). *J. Am. Chem. Soc.* **2015**, *137*, 18−21.

(6) (a) Tanaka, T.; Tanaka, T.; Tsuji, T.; Yazaki, R.; Ohshima, T. Strategy for Catalytic Chemoselective Cross-Enolate Coupling Reaction via a Transient Homocoupling Dimer. *Org. Lett.* **2018**, *20*, 3541−3544. (b) Tsuji, T.; Tanaka, T.; Tanaka, T.; Yazaki, R.; Ohshima, T. Catalytic Aerobic Cross-Dehydrogenative Coupling of Azlactones en Route to α,α-Disubstituted α-amino Acids. *Org. Lett.* **2020**, *22*, 4164−4170. (c) Matsumoto, Y.; Sawamura, J.; Murata, Y.; Nishikata, T.; Yazaki, R.; Ohshima, T. Amino Acid Schiff Base Bearing Benzophenone Imine As a Platform for Highly Congested Unnatural α-Amino Acid Synthesis. *J. Am. Chem. Soc.* **2020**, *142*, 8498−8505.

(7) (a) Easton, C. J. Free-Radical Reactions in the Synthesis of α-Amino Acids and Derivatives. *Chem. Rev.* **1997**, *97*, 53−82. (b) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem., Int. Ed.* **2016**, *55*, 58−102. (c) Lekkala, R.; Lekkala, R.; Moku, B.; Rakesh, K. P.; Qin, H.-L. Recent Developments in Radical-Mediated Transformations of Organohalides. *Eur. J. Org. Chem.* **2019**, *2019*, 2769−2806. (d) Wu, X.; Zhu, C. Radical-Mediated Remote Functional Group Migration. *Acc. Chem. Res.* **2020**, *53*, 1620−1636.

(8) (a) Dixit, V. M.; Bhat, V.; Trozzolo, A. M.; George, M. V. Sensitized Photooxygenations of Δ^2-Oxazolin-5-ones and Related Studies. *J. Org. Chem.* **1979**, *44*, 4169−4173. (b) Kato, H.; Tani, K.; Kurumisawa, H.; Tamura, Y. Photooxidation of Some Mesoionic and Related Systems. *Chem. Lett.* **1980**, *9*, 717−720. (c) Marquez, A.; Chuaqui, C. A.; Rodriguez, H.; Zagal, L. Generation and Fate of Free Radicals of Δ^2-Oxazolin-5-ones. *Tetrahedron* **1985**, *41*, 2341−2346. (d) Muneer, M.; Tikare, R. K.; Kamat, P. V.; George, M. V. Electron Transfer Reactions. Reaction of Δ^2-Oxazoline-5-ones and Related Substrates with Potassium. *Can. J. Chem.* **1987**, *65*, 1624−1630. (e) Rodriguez, H.; Marquez, A.; Chuaqui, C. A.; Gomez, B. Oxidation of Mesoionic Oxazolones by Oxygen. *Tetrahedron* **1991**, *47*, 5681−5688. (f) Andersen, K. K.; Gloster, D. F.; Bray, D. D.; Shoja, M.; Kjær, A. J. Synthesis of Symmetrical 2,2′,4,4′-Tetrasubstituted[4,4′-bioxazole]-5,5′(4*H*,4′*H*)-diones and Their Reactions with Some Nucleophiles. *Heterocycl. Chem.* **1998**, *35*, 317−324. (g) Escolano, C.; Vázquez, S. *Comprehensive Organic Functional Group Transformations II*; Elsevier: Oxford, U.K., 2005.

(9) (a) Griller, D.; Ingold, K. U. Persistent Carbon-Centered Radicals. *Acc. Chem. Res.* **1976**, *9*, 13−19. (b) Hicks, R. G. What's New in Stable Radical Chemistry? *Org. Biomol. Chem.* **2007**, *5*, 1321−1338. (c) Leifert, D.; Studer, A. The Persistent Radical Effect in Organic Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 74−108.

(10) During the preparation of this manuscript, a paper detailing similar transformations of azlactones with *N*-hydroxyphthalimide esters appeared, see: Li, Y.; Yang, J.; Geng, X.; Tao, P.; Shen, Y.; Su, Z.; Zheng, K. Modular Construction of Unnatural α-Tertiary Amino Acid Derivatives by Multicomponent Radical Cross-Couplings. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202210755.

(11) (a) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102−113. (b) Xuan, J.; Xiao, W. Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828−6838. (c) 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. (d) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166. (e) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926.

(12) Pitre, S. P.; Overman, L. E. Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis. *Chem. Rev.* **2022**, *122*, 1717−1751.

(13) (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α-Amino C−H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114−1117. (b) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of N-Arylaminomethanes with Aldimines. *J. Am. Chem. Soc.* **2015**, *137*, 13768−13771. (c) Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals. *Angew. Chem., Int. Ed.* **2016**, *55*, 6776−6779. (d) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. Asymmetric Radical−Radical Cross-Coupling through Visible-Light-Activated Iridium Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 685−688. (e) Li, Y.; Han, C.; Wang, Y.; Huang, X.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Asymmetric Reductive Azaarylation of Olefins via Enantioselective Radical Coupling. *J. Am. Chem. Soc.* **2022**, *144*, 7805−7814. (f) Majhi, J.; Dhungana, R. K.; Renteria-Gomez, A.; Sharique, M.; Li, L.; Dong, W.; Gutierrez, O.; Molander, G. A. Metal-Free Photochemical Imino-Alkylation of Alkenes with Bifunctional Oxime Esters. *J. Am. Chem. Soc.* **2022**, *144*, 15871−15878. (g) Tan, G.; Das, M.; Keum, H.; Bellotti, P.; Daniliuc, C.; Glorius, F. Photochemical Single-Step Synthesis of β-Amino Acid Derivatives from Alkenes and (hetero)Arenes. *Nat. Chem.* **2022**, *14*, 1174−1184.

(14) (a) Xie, J.; Jin, H.; Hashmi, A. S. K. The Recent Achievements of Redox-Neutral Radical C−C Cross-Coupling Enabled by Visible-Light. *Chem. Soc. Rev.* **2017**, *46*, 5193−5203. (b) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C−H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016−9085.

(15) (a) Singh, K.; Staig, S. J.; Weaver, J. D. Facile Synthesis of *Z*-Alkenes via Uphill Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 5275−5278. (b) Metternich, J. B.; Gilmour, R. A Bio-Inspired, Catalytic $E \rightarrow Z$ Isomerization of Activated Olefins. *J. Am. Chem. Soc.* **2015**, *137*, 11254−11257. (c) Zhu, C.; Yue, H.; Maity, B.; Atodiresei, I.; Cavallo, L.; Rueping, M. A Multicomponent Synthesis of Stereodefined Olefins via Nickel Catalysis and Single Electron/Triplet Energy Transfer. *Nat. Catal.* **2019**, *2*, 678−687.

(16) (a) Brimioulle, R.; Bach, T. Enantioselective Lewis Acid Catalysis of Intramolecular Enone [2+2] Photocycloaddition Reactions. *Science* **2013**, *342*, 840−843. (b) Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. Enantioselective Photochemistry through Lewis Acid−Catalyzed Triplet Energy Transfer. *Science* **2016**, *354*, 1391−1395. (c) Zhao, J.; Brosmer, J. L.; Tang, Q.; Yang, Z.; Houk, K. N.; Diaconescu, P. L.; Kwon, O. Intramolecular Crossed [2+2] Photocycloaddition through Visible Light-Induced Energy Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 9807−9810. (d) Becker, M. R.; Wearing, E. R.; Schindler, C. S. Synthesis of Azetidines via Visible-Light-Mediated Intermolecular [2+2] Photocycloadditions. *Nat. Chem.* **2020**, *12*, 898−905. (e) Guo, R.; Adak, S.; Bellotti, P.; Gao, X.; Smith, W. W.; Le, S. N.; Ma, J.; Houk, K. N.; Glorius, F.; Chen, S.; Brown, M. K. Photochemical Dearomative Cycloadditions of Quinolines and Alkenes: Scope and Mechanism Studies. *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

(17) (a) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. Advances in Photocatalysis: A Microreview of Visible Light Mediated Ruthenium and Iridium Catalyzed Organic Transformations. *Org. Process Res. Dev.* **2016**, *20*, 1156−1163. (b) Singh, A.; Teegardin, K.; Kelly, M.; Prasad,

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902

K. S.; Krishnan, S.; Weaver, J. D. Facile Synthesis and Complete Characterization of Homoleptic and Heteroleptic Cyclometalated Iridium(III) Complexes for Photocatalysis. *J. Organomet. Chem.* **2015**, *776*, 51−59.
(18) (a) Chateauneuf, J.; Lusztyk, J.; Ingold, K. U. Spectroscopic and Kinetic Characteristics of Aroyloxyl Radicals. 2. Benzoyloxyl and Ring-Substituted Aroyloxyl Radicals. *J. Am. Chem. Soc.* **1988**, *110*, 2886−2893. (b) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. Visible-Light-Promoted Activation of Unactivated C(sp^3)−H Bonds and Their Selective Trifluoromethylthiolation. *J. Am. Chem. Soc.* **2016**, *138*, 16200−16203.
(19) Lu, Y.; West, J. G. Chemoselective Decarboxylative Protonation Enabled by Cooperative Earth-Abundant Element Catalysis. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202213055.
(20) Lucet, D.; Gall, T. L.; Mioskowski, C. The Chemistry of Vicinal Diamines. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627.
(21) (a) Gotthardt, H.; Huisgen, R.; Bayer, H. O. 1,3-Dipolar Cycloaddition Reactions. LIII. Question of the 1,3-Dipolar Nature of Δ^2-Oxazolin-5-ones. *J. Am. Chem. Soc.* **1970**, *92*, 4340−4344. (b) Qin, A.; Lam, J. W. Y.; Tang, B. Z. Luminogenic Polymers with Aggregation-Induced Emission Characteristics. *Prog. Polym. Sci.* **2012**, *37*, 182−209. (c) Olutas, M.; Sagırlı, A. Solvatochromic and Solid-State Emissive Azlactone-Based AIEE-Active Organic Dye: Synthesis, Photophysical Properties and Color-Conversion LED Application. *J. Mol. Liq.* **2020**, *313*, No. 113482.
(22) (a) Dong, Z.; MacMillan, D. W. C. Metallaphotoredox-Enabled Deoxygenative Arylation of Alcohols. *Nature* **2021**, *598*, 451−456. (b) Li, X.; Shui, Y.; Shen, P.; Wang, Y.; Zhang, C.; Feng, C. A Novel Type of Radical-Addition-Induced β-Fragmentation and Ensuing Remote Functionalization. *Chem* **2022**, *8*, 2245−2259.
(23) (a) Wang, P.; Chen, J.; Xiao, W. Hantzsch Esters: an Emerging Versatile Class of Reagents in Photoredox Catalyzed Organic Synthesis. *Org. Biomol. Chem.* **2019**, *17*, 6936−6951. (b) Kammer, L. M.; Badir, S. O.; Hu, R.; Molander, G. A. Photoactive Electron Donor−Acceptor Complex Platform for Ni-mediated C(sp^3)−C(sp^2) Bond Formation. *Chem. Sci.* **2021**, *12*, 5450−5457.
(24) Blackwell, J. H.; Kumar, R.; Gaunt, M. J. Visible-Light-Mediated Carbonyl Alkylative Amination to All-Alkyl α-Tertiary Amino Acid Derivatives. *J. Am. Chem. Soc.* **2021**, *143*, 1598−1609.
(25) (a) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056−2071. (b) Cao, H.; Tang, X.; Tang, H.; Yuan, Y.; Wu, J. Photoinduced Intermolecular Hydrogen Atom Transfer Reactions in Organic Synthesis. *Chem. Catal.* **2021**, *1*, 523−598. (c) Capaldo, L.; Ravelli, D.; Fagnoni, M. Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C−H Bonds Elaboration. *Chem. Rev.* **2022**, *122*, 1875−1924.

https://doi.org/10.1021/acscatal.2c05698
ACS Catal. 2023, 13, 4894−4902