Cooperative Carbene Photocatalysis for β-Amino Ester Synthesis

Nao Tanaka, Joshua L. Zhu, Oniya L. Valencia, Cullen R. Schull, Karl A. Scheidt*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208, USA. E-mail: scheidt@northwestern.edu

Photochemistry, N-heterocyclic carbenes, aminocarboxylation, β-amino acids, quaternary centers

ABSTRACT: β-Amino acids are useful building blocks of bioactive molecules, including peptidomimetics and pharmaceutical compounds. The current limited accessibility to $\beta^{2,2}$-type amino acids which bear an α-quaternary center has limited their use in chemical synthesis and biological investigations. Disclosed herein is the development of a new *N*-heterocyclic carbene/photocatalyzed aminocarboxylation of olefins, affording $\beta^{2,2}$-amino esters with high regioselectivity. The generation of nitrogen-centered radicals derived from simple imides via a sequence of deprotonation and single-electron oxidation allows for the subsequent addition to *gem*-disubstituted olefins regioselectively. The intermediate tertiary radicals then cross-couple with a stabilized azolium-based radical generated *in situ* to efficiently construct the quaternary centers. Mechanistic studies including Stern-Volmer fluorescence quenching experiments support the proposed catalytic cycle.

β-Amino acids are privileged chemical moieties found in biologically active molecules and natural products.[1] This class of compounds has attracted synthetic chemists due to their potential as precursors to γ-amino alcohols, β-lactams,[2] and other prevalent motifs in catalysis, synthesis and medicine. In addition to their utility as building blocks in small molecule synthesis, β-amino acid incorporation into peptides has been reported to improve their stability and biological activities.[3] They can be classified based on their substitution patterns: β^3-, β^2-, $\beta^{2,3}$-, $\beta^{3,3}$-, $\beta^{2,2}$-amino acids,[4] with the last type being the most inaccessible due to the quaternary center at the α-position. Whereas efficient methods to access to β^3- and $\beta^{2,3}$-amino acids have enabled thorough investigation of their bioactive applications, further exploration of $\beta^{2,2}$ analogues[5] has been hampered by their synthetic inaccessibility.

Given their broad applicability in chemistry, there are numerous approaches to access β-amino acids,[6] including classical reactions such as the Mannich reaction,[7] conjugate addition of nitrogen-based nucleophiles,[8] hydrogenation of β-amino α,β-unsaturated systems,[7b] and the Arndt-Eistert homologation from activated α-amino acids.[9] Among those methods, the Mannich-type reaction is most thoroughly developed, including recent enantioselective reactions with chiral phosphoric acid catalysis[10] or N-heterocyclic carbene (NHC) catalysts.[11] However, a large majority of these methods afforded β^3-, β^2-, and $\beta^{2,3}$-types, and a general approach to synthesize the $\beta^{2,2}$-type still remains challenging.[12] Consequently, the development of methodologies for accessing $\beta^{2,2}$-amino acids that complement established approaches would be of value to synthetic chemists and chemical biologists.

Photocatalysis has become a powerful strategy in synthetic organic chemistry, featuring mild photoexcitation processes

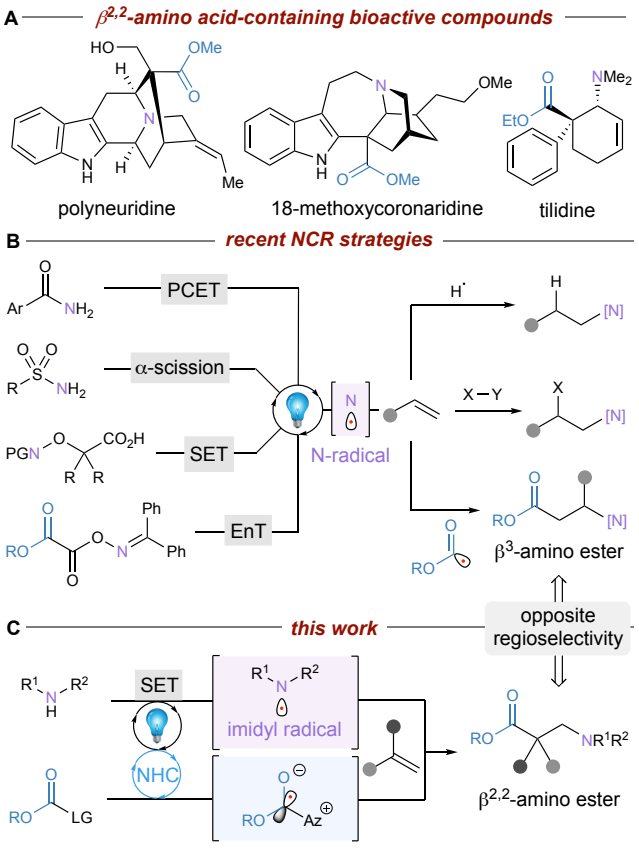


Figure 1. (A) $\beta^{2,2}$-amino ester-containing bioactive compounds[13] (B) Recent reports of NCR generation and intermolecular alkene reactivity (C) This work: dual NHC/photocatalysis for $\beta^{2,2}$-amino ester synthesis.

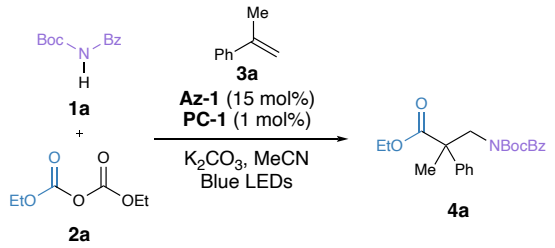
and single-electron redox pathways.[14] Photocatalysis has enabled unique bond disconnections that were previously not attainable by traditional two-electron chemistry. Additionally, recent advances in photochemical approaches to nitrogen-centered radicals (NCRs) have accelerated the development of photocatalytic methodologies that access valuable nitrogenated compounds.[15]

Compared to carbon-centered radicals, methods to access NCRs are still limited, despite an extensive history of their use in organic synthesis. Most of the photochemical methodologies utilize pre-oxidized N–X type NCR precursors,[16] where a photocatalyst facilitates the N–X bond cleavage via single-electron transfer (SET) or triplet energy transfer (EnT). More recently, several methodologies have demonstrated access to a variety of NCR species from non-pre-oxidized nitrogen sources.[17] Those include proton-coupled electron transfer (PCET) chemistry[18] by the Knowles group,[19] an intriguing α-scission strategy using a phosphine catalyst by the Doyle group,[20] decarboxylative/decarbonylative SET models by the Studer[21] and Leonori groups,[22] and the Glorius group's EnT protocol,[23] which features a decarboxylative radical fragmentation triggered by triplet EnT to release alkoxycarbonyl and iminyl radicals (**Figure 1B**). The alkoxycarbonyl radical species can add to olefins and the resultant carbon-centered radical intermediates can be trapped by the iminyl radical counterpart to afford β^3-amino ester products. These methods typically require either prefunctionalization or the use of specific types of activating reagents. Qin and co-workers reported the use of *N*-benzoyl alkylsulfinamide as an NCR precursor, wherein a relatively common base K_2HPO_4 deprotonated the imide, enabling photocatalytic oxidation of the imidyl anion.[24] Nevertheless, in their work, the intermediate NCR rapidly fragments to afford even primary carbon-centered radicals, driven by the formation of *N*-sulfinylbenzamide. To the best of our knowledge, there is no report for both NCR generation from a simple imide using a common inorganic base and its use to prepare nitrogenous products.

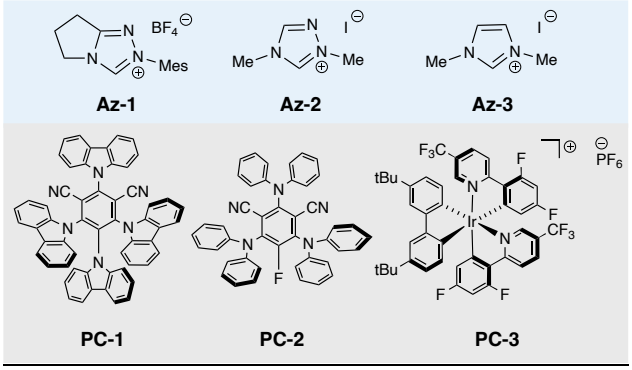
Besides NCR methods, the field of photocatalysis has also experienced a significant increase in C–C bond formation methodologies over the past decade. In particular, NHC-based radical intermediates have been demonstrated to effectively promote radical cross-coupling to construct new C–C bonds.[25] Ohmiya achieved single-electron oxidation of Breslow intermediates using *N*-hydroxyphthalimide esters, leading to radical-radical coupling of the generated ketyl and tertiary radicals to prepare ketones with α-quaternary centers.[26] In a different approach, our group reported the first example of the radical coupling of catalytically generated acyl azoliums using photocatalysis, wherein Hantzsch ester-derived benzylic or alkyl radicals coupled with the NHC-derived ketyl radical, affording ketone products.[27] Following this initial report, similar types of transformations using different radical coupling partners were achieved by our group,[28] Studer,[29] Chi,[30] and other groups.[31] While these examples include three component reactions, the use of geminal disubstituted olefins to construct α-quaternary carbonyl products remains underexplored. More importantly, this azolium-based chemistry has focused on aryl and alkyl *ketone* products, not esters. Lastly, there are few examples of using heteroatom-centered radicals to form C–X and C–C bonds, affording β-heteroatom-substituted ketones.[32]

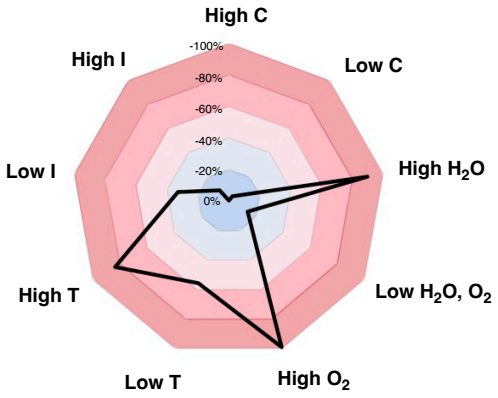
We envisioned that combination of NHC/photocatalysis to incorporate esters[33] instead of ketones, and a novel protocol to generate NCRs would lead to a new platform for $\beta^{2,2}$-amino

Table 1. Optimization of Reaction Conditions and Control Experiments



entry	deviation from standard	Yield (%)[a,b]
1	none	99 (85)
2	**Az-2** instead of **Az-1**	0
3	**Az-3** instead of **Az-1**	0
4	**PC-2** instead of **PC-1**	81
5	**PC-3** instead of **PC-1**	47
6	Cs_2CO_3 instead of K_2CO_3	99
7	DBU instead of K_2CO_3	0
8	DMF instead of MeCN	32
9	THF instead of MeCN	0
10	5 mol% **Az-1**, 0.05 M	70
11	no NHC catalyst	0
12	no photocatalyst	0
13	no light	0
14	no base	0





[a] Reaction conditions unless otherwise indicated: **1a** (0.1 mmol), **2a** (0.25 mmol), **3a** (0.15 mmol), **Az** (0.015 mmol), base (0.15 mmol; DBU = 1,8-Diazabicyclo(5.4.0)undec-7-ene), **PC** (1 μmol), and solvent (0.02 M; DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran) irradiated for 18 h. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard. Isolated yield given in parenthesis.

Table 2. Substrate Scope of Aminocarboxylation and Synthetic Application of the Products

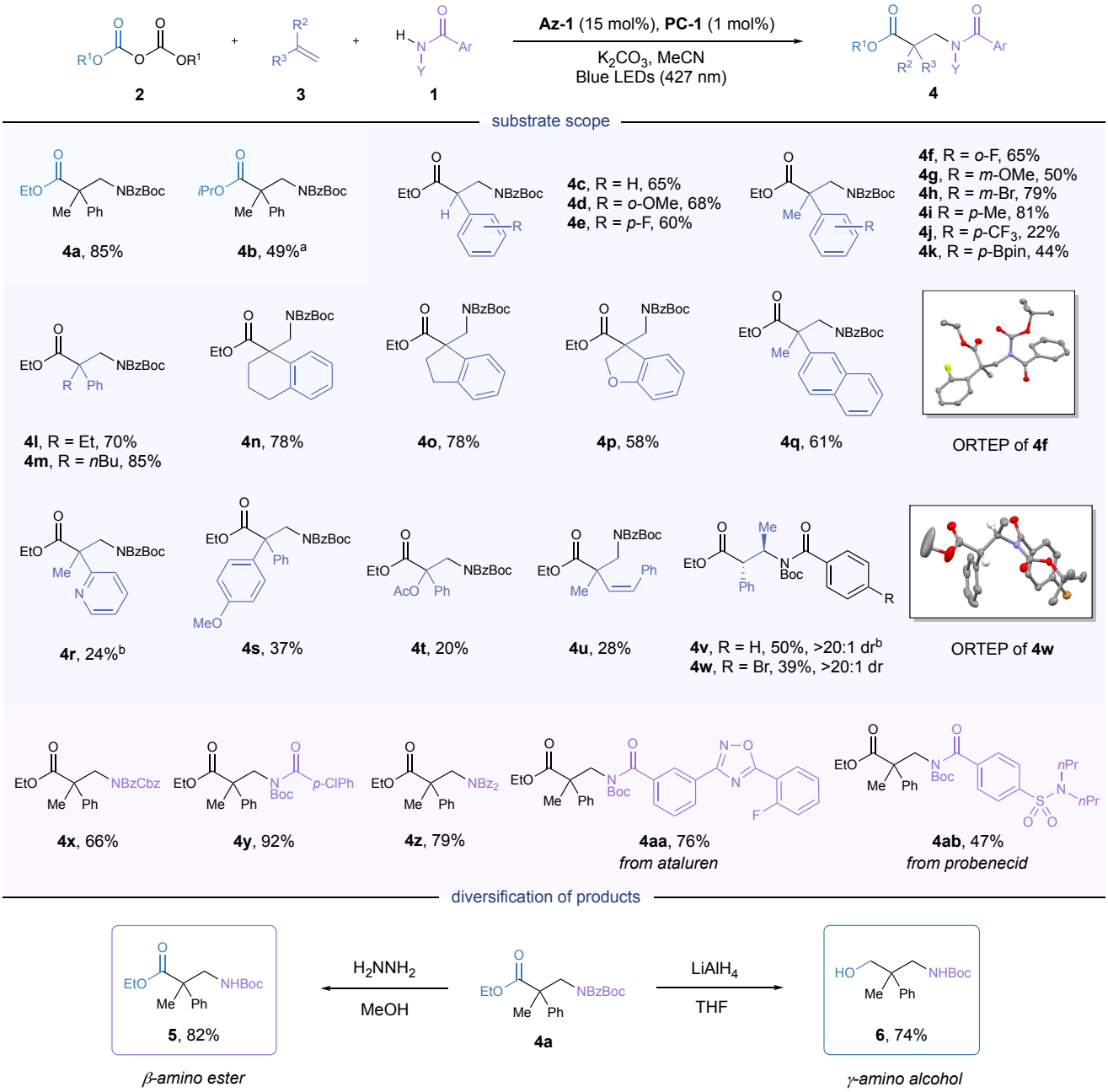


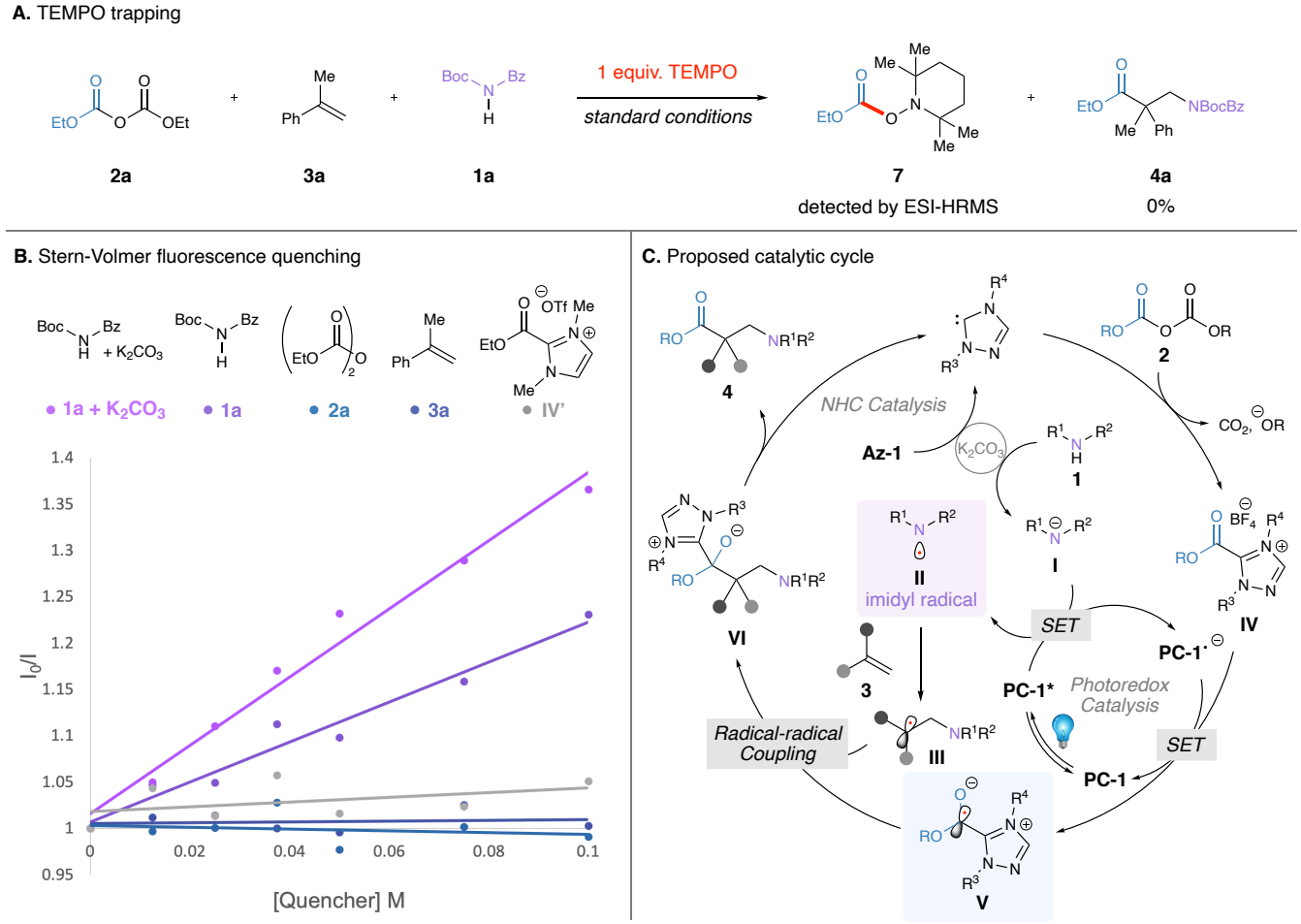
Table 2. Reaction conditions unless otherwise indicated: imide (0.2 mmol), pyrocarbonate (0.5 mmol), styrene (0.3 mmol), **Az-1** (0.03 mmol), K_2CO_3 (0.3 mmol), **PC-1** (2 μmol), and solvent (MeCN, 0.02 M) irradiated with 427 nm LEDs for 18h. [a] pyrocarbonate (0.6 mmol). [b] styrene (0.4 mmol), 40 h.

ester synthesis (**Figure 1C**). In this work, we deploy simple pyrocarbonates and imides as a carboxyl group source and a nitrogen source, respectively. In our reaction design, a sterically and electronically tuned imide could be deprotonated by exposure to mild base and then undergo single-electron oxidation *preferentially* over direct transamidation with the pyrocarbonates. We hypothesized that in this manner NHC/photo-mediated generation of the key radical species would facilitate the key radical relay with geminal disubstituted olefins, thereby leveraging the stability of the intermediate tertiary radicals to efficiently construct the α-quaternary centers, along with regioselective N–C and C–C bond-formation.

Based on this plan, we selected *N*-Boc benzamide (**1a**) as an imide starting material, diethylpyrocarbonate (**2a**) as a carboxyl source, and α-methyl styrene (**3a**) as a model alkene substrate. After extensive screening of the reaction conditions, the desired α-methyl-α-phenyl-β-imidyl ethyl ester **4a** was isolated in 85% yield (99% NMR yield) when using *N*-mesityl pyrrolotriazolium (**Az-1**), 4CzIPN (**PC-1**), and K_2CO_3 under irradiation of blue LEDs (427 nm) in MeCN (**Table 1**, entry 1). In contrast to **Az-1,** neither triazolium **Az-2** nor imidazolium **Az-3** provided the desired reactivity (entries 2, 3). While 3DPAFIPN (**PC-2**) afforded a comparable reaction efficiency (entry 4), a significant decrease in

yield was observed when replaced with iridium photocatalyst **PC-3** (entry 5).

Scheme 1. Mechanistic Studies and Proposed Catalytic Cycle



A brief survey of bases showed that cesium carbonate was a viable alternative for this reaction system (entry 6) whereas organic base DBU did not afford any of the desired product (entry 7). Switching the solvent to DMF or THF, which are also commonly used in similar photochemical reactions, provided lower yields of product **4a** (entries 8, 9). A good yield of 70% was obtained when the loading amount of **Az-1** was reduced to 5 mol% along with an increase of the concentration (entry 10). Control experiments afforded no product, indicating that this reaction is dependent on both NHC and photocatalyst (entries 11-14).

A robustness analysis of the optimized conditions was performed to demonstrate the practical nature of this protocol (Table 1, bottom; see the Supporting Information for details)[34]. Only a slight reduction in yield was observed for changes in concentration, but a significant decrease in yields was observed when the reaction was run in the presence of water (1% v/v) or under air. However, a good yield was maintained by using non-degassed acetonitrile without additional drying under inert atmosphere (i.e., low oxygen and low water). While the reaction at low temperature proceeded at a reduced rate, high temperature conditions led to unidentified side reactions and a lower overall yield. A lower yield was obtained when increasing the distance from the light source, suggesting that photon flux is also crucial to this reaction.

With the optimal reaction conditions in hand, the substrate scope was explored (**Table 2**). Firstly, replacement of **2a** with diisopropylpyrocarbonate or isopropyl chloroformate furnished **4b**, albeit with a lower yield than the ethyl version presumably due to the steric hindrance. Styrene, which bears no α-substituent, provided access to β^2-amino ester product **4c** in a good yield. An *ortho*-substituted aryl group was also successfully tolerated at α-position of the product (**4d**). Fluorine at the *para*-position was also tolerated (**4e**). A variety of functional groups including both electron-donating and electron-withdrawing groups at different positions of the aryl side of the α-methylstyrenes were tolerated, providing several products in moderate to good yields (**4f-j**) including pinacol boronic ester-containing product **4k**. In addition to successful introduction of longer carbon chains at the α-position (**4l,m**), bicyclic styrene-derived products were obtained (**4n-p**), which would be difficult to access through other synthetic means. Products bearing naphthyl (**4q**) or pyridyl (**4r**) groups instead of the phenyl group were prepared, and an α,α-diaryl product was also obtained (**4s**). A vinyl acetate-type substrate was employed in the reaction to afford an α-*O*-substituted product (**4t**), albeit with a reduced yield. A diene-containing substrate successfully furnished the α-methyl-α-cinnamyl product along with *E*/*Z* isomerization of the cinnamyl moiety (**4u**). When β-methyl styrene was employed, the corresponding $\beta^{2,3}$-amino ester product (**4v,w**) was obtained in a moderate yield with excellent

diastereoselectivity (>20:1). We also explored the scope of compatible imide-type coupling partners. Alternate carbamate (**4x**) and benzoyl (**4y**) substitution was tolerated, providing the corresponding products in good to excellent yields. *N*-benzoyl benzamide also delivered the desired ester in a good yield as well (**4z**). Finally, $\beta^{2,2}$-amino esters derived from commercial drugs ataluren (**4aa**) and probenecid (**4ab**) were prepared and isolated in 76% and 47%, respectively.

To demonstrate the synthetic utility of these products, the benzoyl group of **4a** was removed selectively using hydrazine hydrate to provide β-amino ester **5** in 82% yield. Ester **4a** was also exposed to lithium aluminum hydride, undergoing a tandem reduction-deprotection and affording γ-amino alcohol **6** in 74% yield. Hydrolysis of the ethyl ester moiety or removal of the Boc group of **5** would provide complementary β-peptide building blocks. Furthermore, β-carbamate esters like **5** have been previously reported to be directly converted into the corresponding β-lactam products.[35] These transformations showcase the broad variety of β-amino acid scaffolds accessible in a few steps from simple starting materials.

We also investigated the mechanism of this transformation, starting with preliminary control experiments (**Table 1**, entries 11-14). The omission of NHC catalyst, photocatalyst, irradiation, or base from the standard reaction conditions led to no conversion to the desired product. Furthermore, addition of three equivalents of TEMPO to the standard reaction conditions also suppressed product formation (**Scheme 1A**), suggesting a radical mechanism. From the TEMPO-trapping reaction mixture, adduct **7** was detected by ESI-HRMS, supporting the intermediacy of an NHC-stabilized alkoxycarbonyl radical. Finally, a Stern-Volmer fluorescence quenching analysis was performed with the photocatalyst and the various reaction components (**Scheme 1B**). Pyrocarbonate **2a** and styrene **3a** both showed no photocatalyst quenching at concentrations up to 0.1M. Isolated ester azolium **IV'** provided a minor amount of photocatalytic quenching at 0.1M, but *N*-Boc benzamide **1a** demonstrated a higher rate of photocatalyst quenching at identical concentrations. Furthermore, analysis of equimolar mixtures of **1a** and potassium carbonate, despite the limited solubility of the latter in acetonitrile, yielded the highest rates of quenching among the components studied, supporting a reductive quenching pathway to generate the NCR. Nevertheless, due to the small amount of quenching observed due to azolium **IV'**, we cannot fully rule out an oxidative quenching pathway. From these experiments we propose the following as the predominant mechanism (**Scheme 1C**). Following excitation, photocatalyst **PC-1*** can generate key imidyl radical intermediate **II** either through oxidation of imidyl anion **I** or direct PCET of imide **1a**. In either case, NCR **II** is rapidly trapped by styrene **3** to afford benzylic radical **III**. In the NHC catalytic cycle, the active carbene catalyst is formed by deprotonation of precatalyst **Az-1**. Nucleophilic addition to pyrocarbonate **2** yields ester azolium **IV** *in situ*, which can be reduced by **PC-1** radical anion to form stabilized radical **V** and turn over **PC-1**. In comparison with chloroformates, the employment of pyrocarbonates led to the generation of alkoxide ions, which maintained the basic conditions, providing higher reaction efficiency. Radical cross-coupling between **III** and **V** provides alkoxide **VI**, which rapidly collapses to afford $\beta^{2,2}$-amino ester **4** and the free carbene catalyst. We investigated the possibility of photocatalytic reduction of radical **III** to a benzylic anion followed by nucleophilic addition to **2** to form product **4**, but the lack of reactivity observed in the absence of **Az-1** (**Table 1**, entry 11) suggests that this pathway is not operative.

In summary, we have developed a dual NHC/photocatalyzed synthesis of β-amino esters. This mild and modular transformation combines styrenes, imides, and pyrocarbonates to yield a variety of sterically-congested $\beta^{2,2}$-amino esters in moderate to excellent yields. Mechanistic studies support the generation of both a transient imidyl radical which is rapidly trapped by styrenes as well as a stabilized alkoxycarbonyl radical from an *in-situ* generated ester azolium. Notably, in comparison to the large variety of NHC/photocatalysis ketone syntheses, this is the first use of this platform to install a synthetically versatile carboxy group and harness an intermolecular NCR relay process.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General information, experimental procedures, characterization of compounds, Stern-Volmer experiments, and XRD data. (PDF).

Crystallographic files (CIF).

AUTHOR INFORMATION

Corresponding Author

* Karl A. Scheidt – Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States; orcid.org/0000-0003-4856-3569; Email: scheidt@northwestern.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The authors thank Northwestern University, the National Institute of General Medical Sciences (R35 GM136440) and the NSF (CHE-2154820) for support of this work. We thank Charlotte Stern (NU) and Christos Malliakas (NU) for assistance with X-ray crystallography.

ABBREVIATIONS

NHC, *N*-heterocyclic carbene; NCR, *N*-centered radical; SET, single electron transfer; EnT, triplet energy transfer; PCET, proton-coupled electron transfer; DMF, dimethylformamide; THF, tetrahydrofuran; NMR, nuclear magnetic resonance; TEMPO, (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl; ESI-HRMS, electrospray ionization high resolution mass spectrometry; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene.

REFERENCES

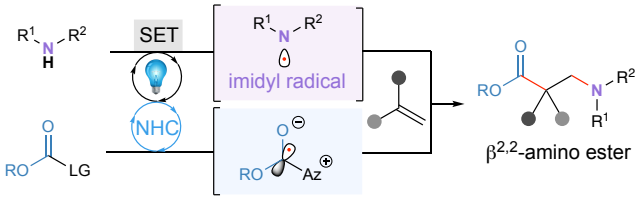
(1) (a) von Nussbaum, F.; Spiteller, P. β - Amino Acids in Nature. In *Highlights in Bioorganic Chemistry*; 2004; pp 63-89; (b) Spiteller, P. β - Amino Acid Biosynthesis. In *Amino Acids, Peptides and Proteins in Organic Chemistry*; 2009; pp 119-161; (c) Kudo, F.; Miyanaga, A.; Eguchi, T. Biosynthesis of natural products containing beta-amino acids. *Nat. Prod. Rep.* **2014**, *31*, 1056-1073.

(2) Magriotis, P. A. Recent Progress in the Enantioselective Synthesis of beta-Lactams: Development of the First Catalytic Approaches. *Angew. Chem. Int. Ed.* **2001**, *40*, 4377-4379.

(3) (a) Seebach, D.; Gardiner, J. β-Peptidic Peptidomimetics. *Acc. Chem. Res.* **2008**, *41*, 1366-1375; (b) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, L. Peptides containing beta-amino acid patterns:

challenges and successes in medicinal chemistry. *J. Med. Chem.* **2014**, *57*, 9718-9739.
(4) Seebach, D.; Beck, A.; Capone, S.; Deniau, G.; Grošelj, U.; Zass, E. Enantioselective Preparation of β^2-Amino Acid Derivatives for β-Peptide Synthesis. *Synthesis* **2008**, *2009*, 1-32.
(5) Seebach, D.; Abele, S.; Sifferlen, T.; Hänggi, M.; Gruner, S.; Seiler, P. Preparation and Structure ofβ-Peptides Consisting of Geminally Disubstitutedβ2,2- andβ3,3-Amino Acids: A Turn Motif forβ-Peptides. *Helv. Chim. Acta* **1998**, *81*, 2218-2243.
(6) Juaristi, E.; Soloshonok, V. A. *Enantioselective Synthesis of β-Amino Acids*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2005.
(7) (a) Arend, M.; Westermann, B.; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044-1070; (b) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. Recent advances in the catalytic asymmetric synthesis of beta-amino acids. *Chem. Soc. Rev.* **2010**, *39*, 1656-1691.
(8) (a) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. Organocatalytic Synthesis of N-Phenylisoxazolidin-5-ones and a One-Pot Synthesis of β-Amino Acid Esters. *Org. Lett.* **2008**, *10*, 953-956; (b) Qian, B.; Chen, S.; Wang, T.; Zhang, X.; Bao, H. Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted β-Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 13076-13082.
(9) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. β-Peptides: Synthesis by Arndt-Eistert homologation with concomitant peptide coupling. Structure determination by NMR and CD spectroscopy and by X-ray crystallography. Helical secondary structure of a β-hexapeptide in solution and its stability towards pe. *Helv. Chim. Acta* **1996**, *79*, 913-941.
(10) Wang, K.; Yu, J.; Shao, Y.; Tang, S.; Sun, J. Forming All-Carbon Quaternary Stereocenters by Organocatalytic Aminomethylation: Concise Access to beta(2,2) -Amino Acids. *Angew. Chem. Int. Ed.* **2020**, *59*, 23516-23520.
(11) (a) Kawanaka, Y.; Phillips, E. M.; Scheidt, K. A. N-Heterocyclic Carbene-Catalyzed Enantioselective Mannich Reactions with α-Aryloxyacetaldehydes. *J. Am. Chem. Soc.* **2009**, *131*, 18028-18029; (b) Xu, J.; Chen, X.; Wang, M.; Zheng, P.; Song, B. A.; Chi, Y. R. Aminomethylation of enals through carbene and acid cooperative catalysis: concise access to beta(2)-amino acids. *Angew. Chem. Int. Ed.* **2015**, *54*, 5161-5165.
(12) (a) Abele, S.; Seebach, D. Preparation of Achiral and of Enantiopure Geminally Disubstituted β-Amino Acids for β-Peptide Synthesis. *Eur. J. Org. Chem.* **2000**, *2000*, 1-15; (b) Yu, J.-S.; Noda, H.; Shibasaki, M. Quaternary β2,2-Amino Acids: Catalytic Asymmetric Synthesis and Incorporation into Peptides by Fmoc-Based Solid-Phase Peptide Synthesis. *Angew. Chem. Int. Ed.* **2018**, *57*, 818-822; (c) Nascimento de Oliveira, M.; Arseniyadis, S.; Cossy, J. Palladium-Catalyzed Asymmetric Allylic Alkylation of 4-Substituted Isoxazolidin-5-ones: Straightforward Access to β2,2-Amino Acids. *Chem. Eur. J.* **2018**, *24*, 4810-4814; (d) Noda, H.; Shibasaki, M. Recent Advances in the Catalytic Asymmetric Synthesis of β 2 - and β 2,2 - Amino Acids. *Eur. J. Org. Chem.* **2019**, *2020*, 2350-2361; (e) Cunillera, A.; Ruiz, A.; Godard, C. Synthesis of β 2,2-Amino Esters via Rh-Catalysed Regioselective Hydroaminomethylation. *Adv. Synth. Catal.* **2019**, *361*, 4201-4207.
(13) (a) Antonaccio, L. D.; Pereira, N. A.; Gilbert, B.; Vorbrueggen, H.; Budzikiewicz, H.; Wilson, J. M.; Durham, L. J.; Djerassi, C. Alkaloid Studies. XXXIII.1 Mass Spectrometry in Structural and Stereochemical Problems. VI.2 Polyneuridine, A New Alkaloid from Aspidosperma polyneuron and Some Observations on Mass Spectra of Indole Alkaloids3. *J. Am. Chem. Soc.* **1962**, *84*, 2161-2169; (b) Bromm, B.; Meier, E.; Scharein, E. Antagonism between tilidine and naloxone on cerebral potentials and pain ratings in man. *Eur. J. Pharmacol.* **1983**, *87*, 431-439; (c) Glick, S. D.; Kuehne, M. E.; Maisonneuve, I. M.; Bandarage, U. K.; Molinari, H. H. 18-Methoxycoronaridine, a non-toxic iboga alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats. *Brain Res.* **1996**, *719*, 29-35.
(14) (a) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075-10166; (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898-6926.
(15) (a) Zard, S. Z. Recent progress in the generation and use of nitrogen-centred radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603-1618; (b) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999-5022; (c) Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. Hydroxylamine Derivatives as Nitrogen-Radical Precursors in Visible-Light Photochemistry. *Chem. Eur. J.* **2018**, *24*, 12154-12163; (d) Jiang, H.; Studer, A. Chemistry With N-Centered Radicals Generated by Single-Electron Transfer-Oxidation Using Photoredox Catalysis. *CCS Chemistry* **2019**, 38-49; (e) Pratley, C.; Fenner, S.; Murphy, J. A. Nitrogen-Centered Radicals in Functionalization of sp(2) Systems: Generation, Reactivity, and Applications in Synthesis. *Chem. Rev.* **2022**, *122*, 8181-8260; (f) Kwon, K.; Simons, R. T.; Nandakumar, M.; Roizen, J. L. Strategies to Generate Nitrogen-centered Radicals That May Rely on Photoredox Catalysis: Development in Reaction Methodology and Applications in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 2353-2428.
(16) (a) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. Enantioselective Direct α-Amination of Aldehydes via a Photoredox Mechanism: A Strategy for Asymmetric Amine Fragment Coupling. *J. Am. Chem. Soc.* **2013**, *135*, 11521-11524; (b) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. N-Acyloxyphthalimides as Nitrogen Radical Precursors in the Visible Light Photocatalyzed Room Temperature C–H Amination of Arenes and Heteroarenes. *J. Am. Chem. Soc.* **2014**, *136*, 5607-5610; (c) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. Nitrogen-centered radical-mediated C–H imidation of arenes and heteroarenes via visible light induced photocatalysis. *Chem. Commun.* **2014**, *50*, 9273-9276; (d) Song, L.; Zhang, L.; Luo, S.; Cheng, J.-P. Visible-Light Promoted Catalyst-Free Imidation of Arenes and Heteroarenes. *Chem. Eur. J.* **2014**, *20*, 14231-14234; (e) Davies, J.; Svejstrup, T. D.; Fernandez Reina, D.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and N-Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 8092-8095; (f) An, X.-D.; Yu, S. Photoredox-Catalyzed Radical Relay Reaction Toward Functionalized Vicinal Diamines. *Synthesis* **2018**, *50*, 3387-3394.
(17) (a) Chu, J. C. K.; Rovis, T. Amide-directed photoredox-catalysed C–C bond formation at unactivated sp3 C–H bonds. *Nature* **2016**, *539*, 272-275; (b) Stateman, L. M.; Wappes, E. A.; Nakafuku, K. M.; Edwards, K. M.; Nagib, D. A. Catalytic β C–H amination via an imidate radical relay. *Chem. Sci.* **2019**, *10*, 2693-2699.
(18) Murray, P. R. D.; Cox, J. H.; Chiappini, N. D.; Roos, C. B.; McLoughlin, E. A.; Hejna, B. G.; Nguyen, S. T.; Ripberger, H. H.; Ganley, J. M.; Tsui, E.; Shin, N. Y.; Koronkiewicz, B.; Qiu, G.; Knowles, R. R. Photochemical and Electrochemical Applications of Proton-Coupled Electron Transfer in Organic Synthesis. *Chem. Rev.* **2022**, *122*, 2017-2291.
(19) (a) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic alkylation of remote C–H bonds enabled by proton-coupled electron transfer. *Nature* **2016**, *539*, 268-271; (b) Zhu, Q.; Graff, D. E.; Knowles, R. R. Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 741-747; (c) Nguyen, S. T.; Zhu, Q.; Knowles, R. R. PCET-Enabled Olefin Hydroamidation Reactions with N-Alkyl Amides. *ACS Catal.* **2019**, *9*, 4502-4507.
(20) Chinn, A. J.; Sedillo, K.; Doyle, A. G. Phosphine/Photoredox Catalyzed Anti-Markovnikov Hydroamination of Olefins with Primary Sulfonamides via alpha-Scission from Phosphoranyl Radicals. *J. Am. Chem. Soc.* **2021**, *143*, 18331-18338.

(21) Jiang, H.; Seidler, G.; Studer, A. Carboamination of Unactivated Alkenes through Three-Component Radical Conjugate Addition. *Angew. Chem. Int. Ed.* **2019**, *58*, 16528-16532.
(22) Davies, J.; Sheikh, N. S.; Leonori, D. Photoredox Imino Functionalizations of Olefins. *Angew. Chem. Int. Ed.* **2017**, *56*, 13361-13365.
(23) (a) Patra, T.; Das, M.; Daniliuc, C. G.; Glorius, F. Metal-free photosensitized oxyimination of unactivated alkenes with bifunctional oxime carbonates. *Nat. Catal.* **2021**, *4*, 54-61; (b) Tan, G.; Das, M.; Keum, H.; Bellotti, P.; Daniliuc, C.; Glorius, F. Photochemical single-step synthesis of beta-amino acid derivatives from alkenes and (hetero)arenes. *Nat. Chem.* **2022**, *14*, 1174-1184; (c) Tan, G.; Das, M.; Kleinmans, R.; Katzenburg, F.; Daniliuc, C.; Glorius, F. Energy transfer-enabled unsymmetrical diamination using bifunctional nitrogen-radical precursors. *Nat. Catal.* **2022**, *5*, 1120-1130.
(24) Xue, F.; Wang, F.; Liu, J.; Di, J.; Liao, Q.; Lu, H.; Zhu, M.; He, L.; He, H.; Zhang, D.; Song, H.; Liu, X. Y.; Qin, Y. A Desulfurative Strategy for the Generation of Alkyl Radicals Enabled by Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2018**, *57*, 6667-6671.
(25) (a) Mavroskoufis, A.; Rajes, K.; Golz, P.; Agrawal, A.; Ruß, V.; Götze, J. P.; Hopkinson, M. N. N-Heterocyclic Carbene Catalyzed Photoenolization/Diels–Alder Reaction of Acid Fluorides. *Angew. Chem. Int. Ed.* **2020**, *59*, 3190-3194; (b) Bay, A. V.; Scheidt, K. A. Single-electron carbene catalysis in redox processes. *Trends Chem.* **2022**, *4*, 277-290; (c) Liu, K.; Schwenzer, M.; Studer, A. Radical NHC Catalysis. *ACS Catal.* **2022**, *12*, 11984-11999; (d) 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**; (e) Li, J.; Liang, Z.; Ren, Y.; Gao, J.; Du, D. Facile access to gem-difluorocyclopropanes via an N-heterocyclic carbene-catalyzed radical relay/cyclization strategy. *Org. Chem. Front.* **2023**, *10*, 1669-1674; (f) Liu, C.; Zhang, Z.; Zhao, L.-L.; Bertrand, G.; Yan, X. Mesoionic Carbene-Catalyzed Formyl Alkylation of Aldehydes. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303478; (g) Reimler, J.; Yu, X.-Y.; Spreckelmeyer, N.; Daniliuc, C. G.; Studer, A. Regiodivergent C−H Acylation of Arenes by Switching from Ionic- to Radical-Type Chemistry Using NHC Catalysis. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303222; (h) Su, F.; Zou, J.; Lv, X.; Lu, F.; Long, Y.; Tang, K.; Li, B.; Chai, H.; Wu, X.; Chi, Y. R. Carbene-Catalyzed Intermolecular Dehydrogenative Coupling of Aldehydes with C(sp3)–H Bonds. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303388.
(26) (a) Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 14073-14077; (b) Kakeno, Y.; Kusakabe, M.; Nagao, K.; Ohmiya, H. Direct Synthesis of Dialkyl Ketones from Aliphatic Aldehydes through Radical N-Heterocyclic Carbene Catalysis. *ACS Catal.* **2020**, *10*, 8524-8529; (c) Matsuki, Y.; Ohnishi, N.; Kakeno, Y.; Takemoto, S.; Ishii, T.; Nagao, K.; Ohmiya, H. Aryl radical-mediated N-heterocyclic carbene catalysis. *Nat. Commun.* **2021**, *12*, 3848.
(27) 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.
(28) (a) Bay, A. V.; Fitzpatrick, K. P.; Gonzalez-Montiel, G. A.; Farah, A. O.; Cheong, P. H.; Scheidt, K. A. Light-Driven Carbene Catalysis for the Synthesis of Aliphatic and alpha-Amino Ketones. *Angew. Chem. Int. Ed.* **2021**, *60*, 17925-17931; (b) Bay, A. V.; Farnam, E. J.; Scheidt, K. A. Synthesis of Cyclohexanones by a Tandem Photocatalyzed Annulation. *J. Am. Chem. Soc.* **2022**, *144*, 7030-7037; (c) Wang, P.; Fitzpatrick, K. P.; Scheidt, K. A. Combined Photoredox and Carbene Catalysis for the Synthesis of gamma-Aryloxy Ketones. *Adv. Synth. Catal.* **2022**, *364*, 518-524.
(29) (a) Meng, Q. Y.; Doben, 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; (b) Liu, K.; Studer, A. Direct alpha-Acylation of Alkenes via N-Heterocyclic Carbene, Sulfinate, and Photoredox Cooperative Triple Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 4903-4909; (c) Meng, Q. Y.; Lezius, L.; Studer, A. Benzylic C-H acylation by cooperative NHC and photoredox catalysis. *Nat. Commun.* **2021**, *12*, 2068; (d) Zuo, Z.; Daniliuc, C. G.; Studer, A. Cooperative NHC/Photoredox Catalyzed Ring-Opening of Aryl Cyclopropanes to 1-Aroyloxylated-3-Acylated Alkanes. *Angew. Chem. Int. Ed.* **2021**, *60*, 25252-25257; (e) Döben, N.; Reimler, J.; Studer, A. Cooperative NHC/Photoredox Catalysis: Three Component Radical Coupling of Aroyl Fluorides, Styrenes and Alcohols. *Adv. Synth. Catal.* **2022**, *364*, 3348-3353.
(30) (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.
(31) (a) Sato, Y.; Goto, Y.; Nakamura, K.; Miyamoto, Y.; Sumida, Y.; Ohmiya, H. Light-Driven N-Heterocyclic Carbene Catalysis Using Alkylborates. *ACS Catal.* **2021**, *11*, 12886-12892; (b) Tao, X.; Wang, Q.; Kong, L.; Ni, S.; Pan, Y.; Wang, Y. Branched-Selective Hydroacylation of Alkenes via Photoredox Cobalt and N-Heterocyclic Carbene Cooperative Triple Catalysis. *ACS Catal.* **2022**, *12*, 15241-15248; (c) 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; (d) Dong, Y. X.; Zhang, C. L.; Gao, Z. H.; Ye, S. Iminoacylation of Alkenes via Photoredox N-Heterocyclic Carbene Catalysis. *Org. Lett.* **2023**, *25*, 855-860; (e) Tan, C. Y.; Kim, M.; Hong, S. Photoinduced Electron Transfer from Xanthates to Acyl Azoliums: Divergent Ketone Synthesis via N-Heterocyclic Carbene Catalysis. *Angew. Chem. Int. Ed.* **2023**, *62*, e202306191; (f) 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.
(32) (a) Du, H. W.; Liu, M. S.; Shu, W. Synthesis of beta-Thiolated-alpha-arylated Ketones Enabled by Photoredox and N-Heterocyclic Carbene-Catalyzed Radical Relay of Alkenes with Disulfides and Aldehydes. *Org. Lett.* **2022**, *24*, 5519-5524; (b) Takemura, N.; Sumida, Y.; Ohmiya, H. Organic Photoredox-Catalyzed Silyl Radical Generation from Silylboronate. *ACS Catal.* **2022**, *12*, 7804-7810.
(33) Zhu, J. L.; Scheidt, K. A. Photocatalytic acyl azolium-promoted alkoxycarbonylation of trifluoroborates. *Tetrahedron* **2021**, *92*, 132288.
(34) Pitzer, L.; Schäfers, F.; Glorius, F. Rapid Assessment of the Reaction-Condition-Based Sensitivity of Chemical Transformations. *Angew. Chem. Int. Ed.* **2019**, *58*, 8572-8576.
(35) Badrian, A.; Mamaghani, M. An easy conversion of carbamates of beta-amino esters into the beta-lactams. *Indian J Chem B* **2017**, *56*, 724-731.



intermolecular aminocarboxylation · quaternary center