Photoredox-Enabled Decarboxylative Synthesis of Unnatural α-Amino Acids
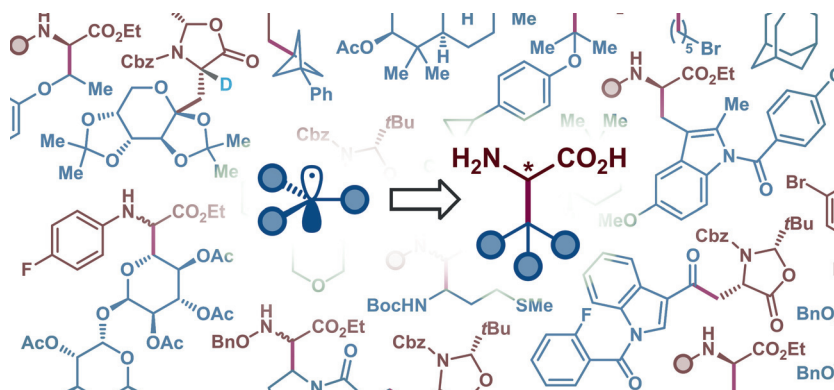
Andrey Shatskiy
Markus D. Kärkäs*

Department of Chemistry, KTH Royal Institute of Technology,
100 44 Stockholm, Sweden
karkas@kth.se

Published as part of the Special Section
EuCheMS Organic Division Young Investigator Workshop

Abstract   Recently, development of general synthetic routes to unnatural α-amino acids has gained significant momentum, driven by the high demand for such building blocks in fundamental research within molecular and structural biology, as well as for development of new pharmaceuticals. Herein, we highlight the recent progress in employing photoredox-mediated synthetic methods for accessing unnatural α-amino acids with a focus on various decarboxylative radical-based strategies.

Key words   amino acids, decarboxylation, photoredox catalysis, radicals
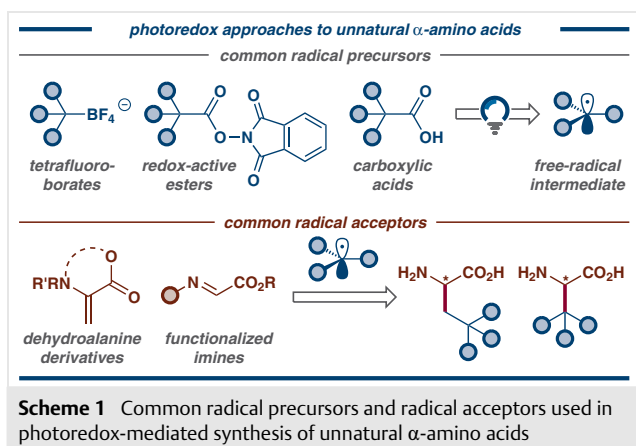
Andrey Shatskiy (left) graduated as an engineer in polymer processing technology from the D. Mendeleev University of Chemical Technology of Russia in 2011. In 2014, he completed a master's program in organic chemistry at Stockholm University and subsequently joined the group of Professor Björn Åkermark at Stockholm University as a PhD student. His graduate studies were focused on the development and mechanistic studies of ruthenium-based water-oxidation catalysts. He received his PhD degree in 2018 and then joined the Kärkäs group as a postdoctoral researcher at KTH Royal Institute of Technology, Stockholm. Currently, his research interests include photoredox catalysis, solar fuels, and organic electrosynthesis.

Markus D. Kärkäs (right) received his undergraduate degree from Stockholm University in 2008. In the same year he began his graduate studies under the direction of Professor Björn Åkermark at Stockholm University. His thesis concerned the development and mechanistic insight of artificial water oxidation catalysts. After receiving his PhD degree in 2013, he joined Professor Corey Stephenson's research group at the University of Michigan as a postdoctoral fellow. His postdoctoral work focused on the development of photochemical methods for valorization of lignin. In late 2016, he returned to the Department of Organic Chemistry at Stockholm University. In August 2018, he joined the Department of Chemistry at KTH Royal Institute of Technology as an assistant professor. His research interests include photoredox catalysis, organic electrosynthesis, and transition-metal catalysis.

Natural α-amino acids represent perhaps the most versatile class of natural products, as assembling a limited set of just about 20 of such building blocks into peptides and proteins makes it possible to control the vast majority of biochemical processes in every living cell.[1] Expanding the set of natural α-amino acids by preparing their analogues through enzymatic[2] and classical chemical synthesis[3] has been recognized as an indispensable tool for studying and engineering the protein functions and development of new pharmaceuticals.[4]

Chemical synthesis of unnatural α-amino acids has been realized mostly through the two-electron reaction manifolds, including Strecker-type reactions,[3a] phase-transfer catalysis,[3b] asymmetric hydrogenation of unsaturated α-amino acid precursors,[3c] and other stereoselective methods.[3d–f] In recent years, reactions proceeding through open-shell free-radical intermediates have also drawn significant attention, allowing both *de novo* synthesis of unnatural α-amino acids and modification of peptides and proteins through noncanonical retrosynthetic strategies (Scheme

1).[5] Harnessing the full potential of free-radical intermediates was made possible by the development of new photoredox methods[6] employing the next-generation metal-[7] and organic-based photocatalysts.[8] In classical radical chemistry, achieving the desired transformation typically requires consecutive atom-transfer processes accompanied by a radical chain reaction, in which each step of the cyclic process involves free-radical intermediates.[9] Conversely, in photoredox catalysis, visible light-initiated single-electron transfer (SET) processes are prevalent and can be rationally combined with proton–electron transfer and atom-transfer reactions, while innate radical chain reactions are observed only in a limited number of photocatalytic systems.[10] These factors together with the availability of a large number of bench-stable photocatalysts with finely tunable electrochemical and photophysical properties has allowed applying photoredox catalysis to the synthesis and modification of complex chemotypes, including natural products, inaccessible with classical radical chemistry.[6]

Scheme 1 Common radical precursors and radical acceptors used in photoredox-mediated synthesis of unnatural α-amino acids

Photoredox-mediated synthesis of unnatural α-amino acids has been demonstrated in both symmetric and asymmetric fashion using a variety of synthetic strategies. Among these, addition of photochemically generated free-radical species to unsaturated radical acceptors currently represents the most common synthetic approach. Two notable classes of radical acceptors giving rise to unnatural α-amino acids are dehydroalanine[11] and α-imino ester derivatives,[12] which can be used for assembling complex α-amino acids branched at the γ- and β-positions, respectively. Effective addition of alkyl radicals to chiral cyclic dehydroalanine derivatives was demonstrated early on by Beckwith and co-workers, providing the desired unnatural α-amino acids in moderate yields and moderate to excellent diastereoselectivity.[13] However, the key C-centered free-radical intermediates in these reactions were generated from alkyl iodides either under thermal control or harsh UV-light irradiation with toxic stannanes or mercuric halides as the radical initiators, severely limiting applicability of this synthetic approach.

Realizing such free-radical-mediated reactions in a more sustainable fashion under mild reaction conditions became possible with widespread introduction of photoredox catalysis. In an early photoredox catalytic system demonstrated by Yoshimi, Hatanaka, and co-workers, the radical addition to an α-imino ester derivative (glyoxylic oxime ether) was achieved with phenanthrene (Phen) as the photoredox catalyst and 1,4-dicyanobenzene (DCB) as an electron-transfer mediator (Scheme 2).[14] In this reaction, readily available carboxylic acids were used in place of alkyl halides as precursors to the free-radical species with overall reaction being redox-neutral. Only moderate yields of the desired unnatural α-amino acid products could be obtained, yet this approach paved the road to a number of other photocatalytic decarboxylative strategies for modification of α-amino acids.[15]
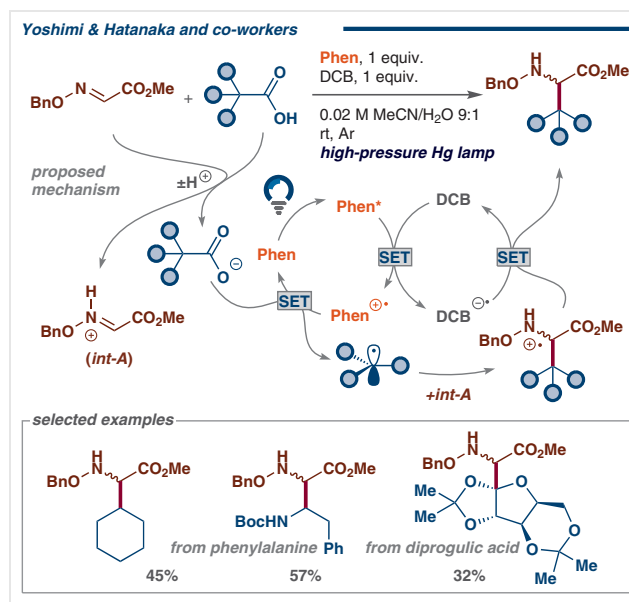

Scheme 2 Photocatalytic approach to unnatural α-amino esters demonstrated by Yoshimi, Hatanaka, and co-workers

More recently, photoredox-mediated decarboxylative reaction manifolds have received renewed attention. A number of more selective decarboxylation methods has been reported, operating via either one-electron reduction of redox-active esters or one-electron oxidation of carboxylate salts.[16] Some examples of light-mediated decarboxylative synthesis of unnatural α-amino acids through radical addition to achiral α-imino ester derivatives were demonstrated with redox-active esters as radical precursors (Scheme 3).[17] Shen and co-workers employed N-hydroxyphthalimide (NHPI) esters as the radical precursors with an N-protected α-imino ester as the radical acceptor.[17a] In this photocatalytic system, [Ru(bpy)₃]²⁺ and the Hantzsch ester (HE) were employed as the photocatalyst and the sacrificial electron donor, respectively. The photocatalytic cycle was

proposed to proceed through reductive quenching of the photocatalyst by HE, furnishing the reduced form of the photocatalyst that is responsible for one-electron reduction of the NHPI ester, onsetting its decomposition to a C-centered radical. The thus-formed C-centered radical then undergoes addition to the α-imino ester followed by hydrogen atom transfer (HAT) from the HE-derived species, furnishing the desired N-protected α-amino ester product. Interestingly, addition of an inorganic base (K₂CO₃) to the reaction mixture resulted in significant improvement of selectivity, presumably, by preventing formation of umpolung products from reductive dimerization of the aldimine radical acceptor. Based on the computational studies, the base was proposed to modulate the reactivity of one-electron oxidized HE, improving the efficiency of the last HAT step. This photocatalytic system was applied for synthesis of a range of unnatural α-amino esters derived from primary, secondary, and tertiary C-radicals, including α-heteroatom radicals derived from carbamate-protected natural α-amino acids. The majority of the products were isolated in high yields (>80%) and the protocol tolerated such sensitive functional groups as terminal alkene and alkyl bromide.

A related photochemical synthetic strategy was demonstrated by Mariano, Wang, and co-workers (Scheme 3).[17b] Here, N-aryl-protected α-imino esters were employed as radical acceptors with N-hydroxytetrachlorophthalimide (TCNHPI) esters of protected uronic acids as radical precursors. Employing an electron-poor TCNHIP redox-active group ($E_{pc} \approx -0.81$ V vs SCE, saturated calomel electrode; $E_{pc} \approx$ ca. -1.2 V vs SCE for the NHIP esters) allowed conducting the reaction in the absence of any photocatalyst, as the excited state of HE was sufficiently reducing to trigger generation of the C-centered radicals from the TCNHIP ester radical precursors. The reaction was completely prohibited in the absence of iPr₂NEt·HBF₄ as a stoichiometric additive, implying that protonation of the N-aryl-substituted imine radical acceptor is required for effective addition of a nucleophilic C-centered radical intermediate. As expected, the α-amino ester products were obtained with no stereoselectivity at the α-position, yet excellent α-stereoselectivity for the anomeric position of the carbohydrate substrates, guided by the steric and stereoelectronic factors. High isolated yields (generally >80%) of the desired α-amino ester products were obtained for a range of hexose and pentose sub-
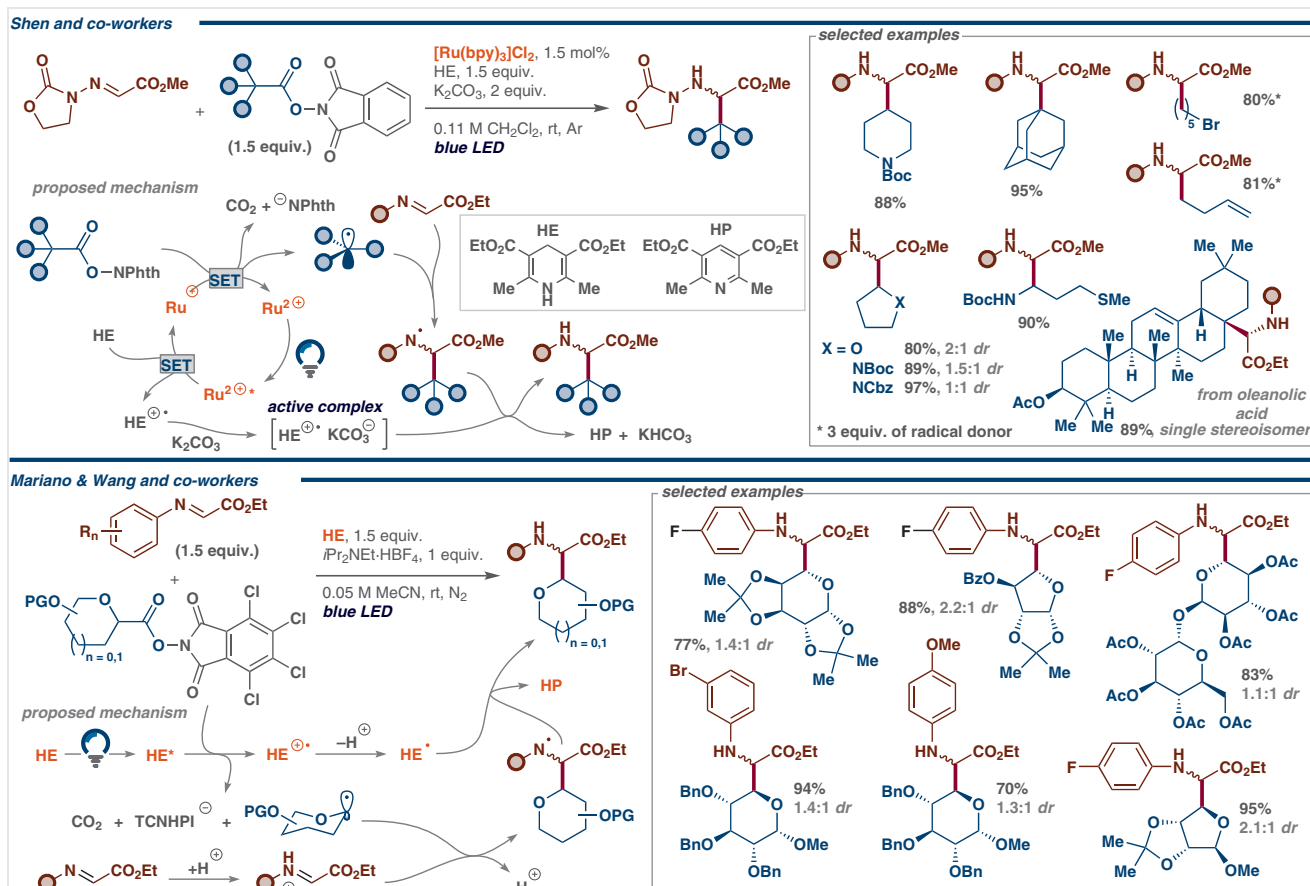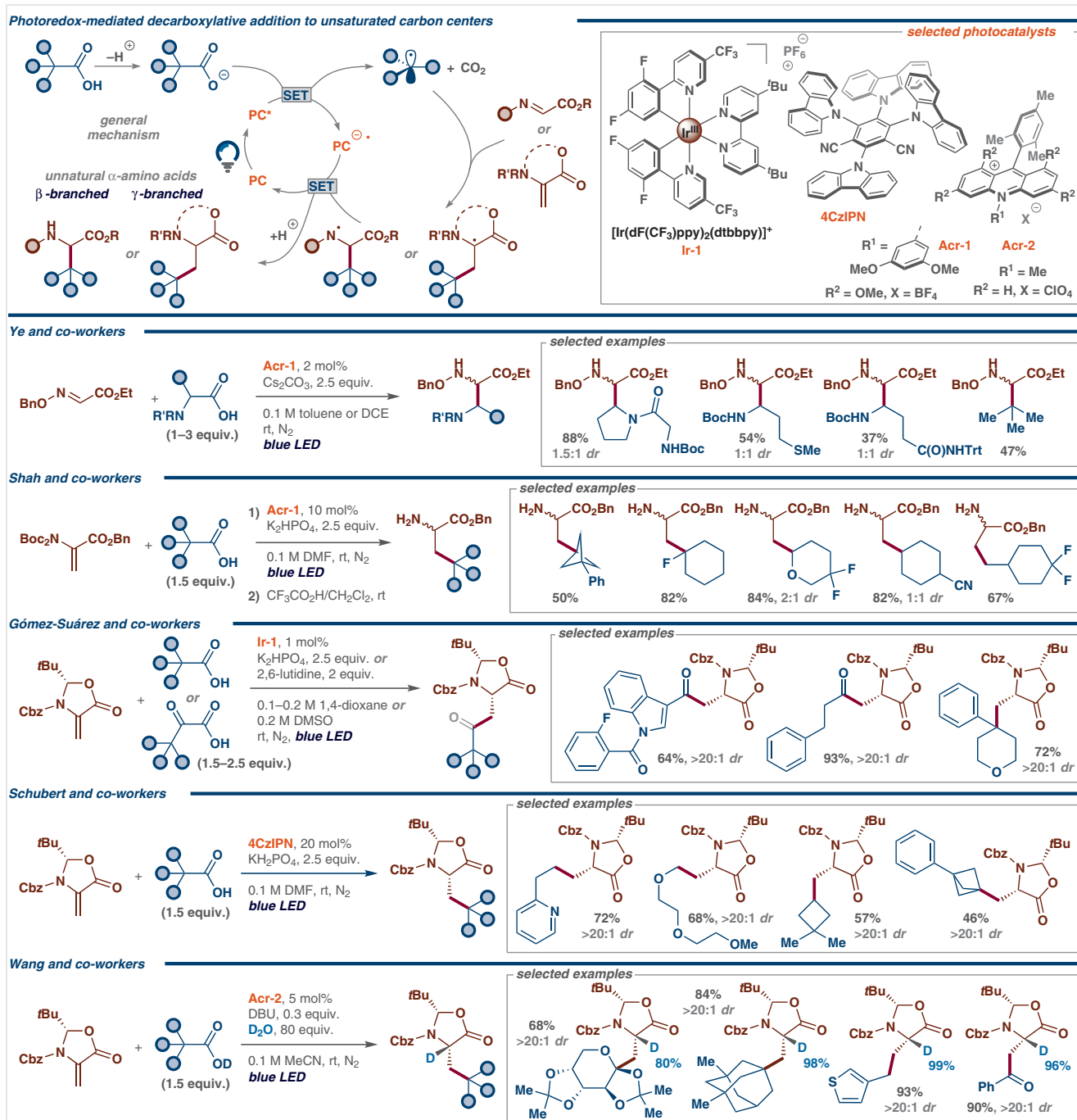

Scheme 3 Photoredox-mediated synthesis of unnatural α-amino esters with redox-active esters as radical precursors

strates bearing the common for carbohydrate chemistry O-protecting groups.

The above methods proved efficient for the synthesis of a wide range of unnatural α-amino acids; however, employing the phthalimide redox-active esters renders the overall transformation as reductive and requires superstoichiometric amounts of an HE reducing agent, significantly decreas-

ing the atom economy of the process. This factor can be effectively overcome by direct oxidation of readily available unactivated carboxylic acids as radical precursors, which renders the overall transformation redox-neutral. Yet, activation of free carboxylic acids through oxidative SET is generally more challenging and is associated with lower chemoselectivity of the process.

Scheme 4 Photoredox-mediated synthesis of unnatural α-amino esters/acids with unactivated carboxylic acids as radical precursors

A. Shatskiy, M. D. Kärkäs   THIEME OPEN ACCESS   **Synpacts**

Photoredox-mediated synthesis of unnatural α,β-diamino acids was demonstrated by Ye and co-workers, employing *N*-Boc-protected α-amino acids as radical precursors and glyoxylic oxime ether as the radical acceptor.[18] An organic acridinium-based photocatalyst **Acr-1** with a moderately oxidizing excited state ($E^* \approx +1.65$ V vs SCE) was observed to be efficiently quenched by the deprotonated carboxylic acid substrates, furnishing the key C-centered radical intermediates upon extrusion of CO_2 from the carboxylate radical (Scheme 4). Moderate to high yields of the desired α,β-diamino ester products were observed; however, the method was less efficient (47% yield) when using pivalic acid as the radical precursor, highlighting that radicals that are not stabilized by α-heteroatom are more challenging to incorporate in this type of photocatalytic system.

More recently, several methods for photoredox-mediated decarboxylative radical addition reactions featuring a more diverse set of unactivated carboxylic acids as radical precursors were employed for the synthesis of γ-branched unnatural α-amino acids.[19] For these catalytic systems, acyclic and cyclic dehydroalanine derivatives were used as radical acceptors. Shah and co-workers demonstrated efficient addition of functionalized primary, secondary, and tertiary radicals to an *N,N*-di-Boc-protected dehydroalanine benzyl ester,[19a] using the same acridinium-based photocatalyst (**Acr-1**) as in the catalytic system developed by Ye.[18] Diastereoselective variants of such radical addition manifolds were demonstrated with the use of a chiral *N*-Cbz-protected methyleneoxazolidinone derived from dehydroalanine by the groups of Gómez-Suárez,[19b] Schubert,[19c] and Wang[19d] (Scheme 4). Curiously, although these photocatalytic systems are expected to operate through a related mechanism, the identified optimal reaction conditions included three different photocatalysts and solvents – iridium-, carbazole-, and acridinium-based photocatalysts with 1,4-dioxane or DMSO, DMF, and MeCN as solvents for the three photocatalytic systems, respectively. In all cases, excellent diastereo-

selectivity was observed for the radical addition reactions. For the photocatalytic system described by Wang,[19d] conducting the reaction in the presence of D_2O also allowed selective deuterium labeling of the resulting amino acids at the α-position. Notably, the photocatalytic system by Gómez-Suárez[19b] was applied to a diverse set of aromatic and aliphatic α-keto acid radical precursors, although with generally lower yields of the desired products.

Photoredox-mediated radical addition to dehydroalanine and α-imino ester derivatives has also been recently demonstrated with other radical precursors, including electron-deficient alkyl bromides,[17c] heteroaryl bromides,[20a] alkyl bis(catecholato)silicates,[20b] silyl hemiaminals obtained *in situ* from tertiary amides,[20c] hydrosilanes,[20d] alkyl trifluoroborates,[20e,f] alkyl enol ethers,[20g] ketals,[20h] and *in situ* formed iminium ion.[20i] Furthermore, related transformations were achieved via C–H activation in amines,[20j] aldehydes,[20k] and adamantanes.[20l]

Concurrently with the recently surfaced decarboxylative strategies for photoredox-mediated synthesis of unnatural α-amino acids, our group aimed at realizing this approach with a chiral glyoxylate-derived *N*-sulfinyl imine as the radical acceptor.[21]

Previously, Baran and co-workers demonstrated a highly versatile stereoselective radical-based approach to unnatural α-amino acids with the same radical acceptor.[22] In this catalytic system, the free-radical intermediates were generated by one-electron reduction of TCNHPI esters with Zn as the stoichiometric reducing agent (3 equiv.) and a Ni-based promoter (25 mol%). Aiming at improving the atom economy of this process and excluding the use of toxic transition-metal reagents, our group attempted the radical-addition reaction under photoredox conditions in a redox-neutral fashion, using unactivated carboxylic acids as the radical precursors. Similar to the previous observations by Maestro, Alemán, and co-workers,[23] high sensitivity of the *N*-sulfinyl imine substrate to the typical decarboxylation
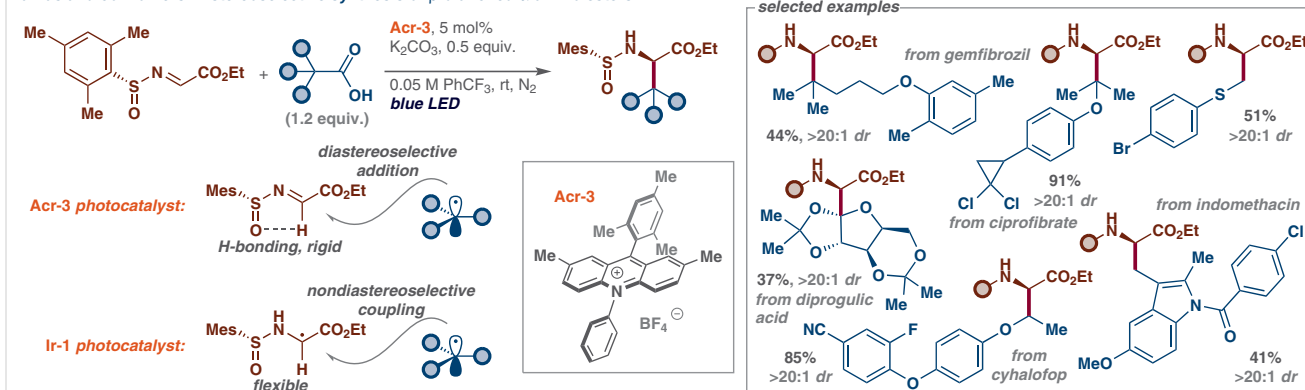
Scheme 5 Diastereoselective photoredox-mediated synthesis of unnatural α-amino esters with unactivated carboxylic acids as radical precursors demonstrated by Kärkäs and co-workers

conditions was observed, completely prohibiting the desired reaction. Gratifyingly, careful optimization of the reaction conditions revealed that employing the highly oxidizing acridinium-based photocatalyst **Acr-3** ($E^* \approx$ ca. 2.09 V vs SCE)[8f] with α,α,α-trifluorotoluene (PhCF$_3$) as the solvent furnished the model pivalic acid derived product in high yield (91%) and excellent diastereoselectivity (> 95:5 *dr*), while using near-stoichiometric amounts of the radical precursor and acceptor (Scheme 5). The optimized reaction conditions were then applied to a diverse set of carboxylic acid substrates.

In general, the highest yields of the desired chiral α-amino esters were obtained with tertiary and α-heteroatom-stabilized radicals, while secondary and primary radicals appeared to be less efficient. Notably, the reaction tolerated a magnitude of molecular functionalities, including aliphatic and aromatic ethers and ketones; fluoro-, chloro-, and bromo-substituted aromatic substrates; aliphatic substrates containing CF$_2$, CF$_3$, and CCl$_2$ functionalities; aryl cyanide- and alkyl aryl thioether-containing substrates. A few pharmaceutically relevant compounds were efficiently employed as the radical precursors, including gemfibrozil, cyhalofop, nateglinide, ciprofibrate, indomethacin, and diprogulic, fenofibric and clofibric acids. In all cases, excellent diastereoselectivity was observed at the α-position of the product, while several compounds also displayed slight diastereoselectivity at the β-position. Selective removal of the *N*-sulfinyl amide chiral auxiliary group was demonstrated under mild acidic conditions in near-quantitative yields for complex α-amino ester products derived from indomethacin, cyhalofop, and nateglinide, highlighting the practicality of the devised reaction.

The mechanism of the developed transformation was proposed based on the literature precedents and the results of electrochemical, spectroscopic, and computational mechanistic studies. In the proposed catalytic cycle, the excited-state acridinium photocatalyst is quenched by the carboxylate anion via an SET process, furnishing the carboxylate radical that quickly fragments to the key C-centered radical intermediate. This intermediate undergoes addition to the chiral glyoxylate-derived *N*-sulfinyl imine substrate in the stereodetermining step of the reaction, furnishing a transient N-centered radical. The latter is transformed into the desired product upon SET from the reduced photocatalyst and protonation, concurrently closing the photocatalytic cycle. A detailed computational study of the stereodetermining radical-addition step highlighted the key role exerted by the intramolecular hydrogen bonding in the *N*-sulfinyl imine substrate for the stereoselective outcome of the reaction. Interestingly, no intramolecular hydrogen bonding was observed for the one-electron-reduced form of the substrate (α-amino radical), explaining the poor diastereoselectivity when the reaction is conducted with a more reducing Ir-based photocatalyst, as was observed during optimization of the reaction conditions.

The described decarboxylative strategies for synthesis of β- and γ-branched unnatural α-amino acids cover vast chemical space, making a significant contribution to the previously explored synthetic strategies. In particular, employing ubiquitous carboxylic acids with electron-deficient radical acceptors allows accessing unnatural α-amino acids in a redox-neutral fashion, eliminating the need for stoichiometric oxidation/reduction agents and additional synthetic steps for introduction of the redox-active groups. The photoredox-mediated radical-based reaction manifolds allows conducting the synthesis under mild conditions and in the presence of various functional groups that would be intolerable under typical nucleophilic addition or transition metal catalysis conditions. Yet, a major remaining challenge is to realize such radical manifolds in a stereoselective fashion without chiral auxiliaries – the challenge persistent to all radical chemistry with no general solution.[24]

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

References

(1) Petsko, G. A.; Ringe, D. *Protein Structure and Function*; Primers, in. Biology., Ed.; Oxford University Press: London, **2009**.
(2) (a) Xue, Y.-P.; Cao, C.-H.; Zheng, Y.-G. *Chem. Soc. Rev.* **2018**, *47*, 1516. (b) Almhjell, P. J.; Boville, C. E.; Arnold, F. H. *Chem. Soc. Rev.* **2018**, *47*, 8980. (c) Hedges, J. B.; Ryan, K. S. *Chem. Rev.* **2020**, *120*, 3161.
(3) (a) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728. (d) Michaux, J.; Niel, G.; Campagne, J.-M. *Chem. Soc. Rev.* **2009**, *38*, 2093. (e) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (f) Ma, J.-A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4290.
(4) (a) Neumann-Staubitz, P.; Neumann, H. *Curr. Opin. Struct. Biol.* **2016**, *38*, 119. (b) Ravikumar, Y.; Nadarajan, S. P.; Hyeon Yoo, T.; Lee, C.; Yun, H. *Trends Biotechnol.* **2015**, *33*, 462. (c) Meister, D.; Taimoory, S. M.; Trant, J. F. *Pept. Sci.* **2019**, *111*, e24058. (d) Zhang, W. H.; Otting, G.; Jackson, C. J. *Curr. Opin. Struct. Biol.* **2013**, *23*, 581. (e) Kim, C. H.; Axup, J. Y.; Schultz, P. G. *Curr. Opin. Chem. Biol.* **2013**, *17*, 412. (f) Grauer, A.; König, B. *Eur. J. Org. Chem.* **2009**, 5099. (g) Blaskovich, M. A. T. *J. Med. Chem.* **2016**, *59*, 10807.
(5) (a) Liu, J.-Q.; Shatskiy, A.; Matsuura, B. S.; Kärkäs, M. D. *Synthesis* **2019**, *51*, 2759. (b) Rahman, M.; Mukherjee, A.; Kovalev, I. S.; Kopchuk, D. S.; Zyryanov, G. V.; Tsurkan, M. V.; Majee, A.; Ranu, B. C.; Charushin, V. N.; Chupakhin, O. N.; Santra, S. *Adv. Synth.*

Catal. **2019**, *361*, 2161. (c) Larionov, V. A.; Stoletova, N. V.; Maleev, V. I. *Adv. Synth. Catal.* **2020**, *362*, 4325. (d) Aguila Troyano, F. J.; Merkens, K.; Anwar, K.; Gómez-Suárez, A. *Angew. Chem. Int. Ed.* **2021**, *60*, 1098. (e) Bottecchia, C.; Noël, T. *Chem. Eur. J.* **2019**, *25*, 26. (f) Raynal, L.; Rose, N. C.; Donald, J. R.; Spicer, C. D. *Chem. Eur. J.* **2021**, *27*, 69. (g) King, T. A.; Mandrup Kandemir, J.; Walsh, S. J.; Spring, D. R. *Chem. Soc. Rev.* **2021**, *50*, 39. (h) Bogart, J. W.; Bowers, A. A. *Org. Biomol. Chem.* **2019**, *17*, 3653. (i) Malins, L. R. *Pept. Sci.* **2018**, *110*, e24049.

(6) (a) Kärkäs, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683. (b) Cannalire, R.; Pelliccia, S.; Sancineto, L.; Novellino, E.; Tron, G. C.; Giustiniano, M. *Chem. Soc. Rev.* **2021**, *50*, 766. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898.

(7) (a) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. *Org. Process Res. Dev.* **2016**, *20*, 1156. (b) Hockin, B. M.; Li, C.; Robertson, N.; Zysman-Colman, E. *Catal. Sci. Technol.* **2019**, *9*, 889. (c) Glaser, F.; Wenger, O. S. *Coord. Chem. Rev.* **2020**, *405*, 213129.

(8) (a) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C. *ACS Omega* **2016**, *1*, 66. (b) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244. (c) Vega-Peñaloza, A.; Mateos, J.; Companyó, X.; Escudero-Casao, M.; Dell'Amico, L. *Angew. Chem. Int. Ed.* **2021**, *60*, 1082. (d) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (e) Zilate, B.; Fischer, C.; Sparr, C. *Chem. Commun.* **2020**, *56*, 1767. (f) Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059.

(9) Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 58.

(10) (a) Shatskiy, A.; Liu, J.-Q.; Kärkäs, M. D. *Chem* **2021**, *7*, 283. (b) Kärkäs, M. D.; Matsuura, B. S.; Stephenson, C. R. J. *Science* **2015**, *349*, 1285. (c) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426. (d) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2019**, *58*, 3730.

(11) Bogart, J. W.; Bowers, A. A. *Org. Biomol. Chem.* **2019**, *17*, 3653.

(12) Eftekhari-Sis, B.; Zirak, M. *Chem. Rev.* **2017**, *117*, 8326.

(13) (a) Axon, J. R.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1995**, 549. (b) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem. Commun.* **1990**, 1087.

(14) Yoshimi, Y.; Kobayashi, K.; Kamakura, H.; Nishikawa, K.; Haga, Y.; Maeda, K.; Morita, T.; Itou, T.; Okada, Y.; Hatanaka, M. *Tetrahedron Lett.* **2010**, *51*, 2332.

(15) Yoshimi, Y. *J. Photochem. Photobiol., A* **2017**, *342*, 116.

(16) (a) Patra, T.; Maiti, D. *Chem. Eur. J.* **2017**, *23*, 7382. (b) Jin, Y.; Fu, H. *Asian J. Org. Chem.* **2017**, *6*, 368. (c) Schwarz, J.; König, B. *Green Chem.* **2018**, *20*, 323. (d) Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735. (e) Parida, S. K.; Mandal, T.; Das, S.; Hota, S. K.; De Sarkar, S.; Murarka, S. *ACS Catal.* **2021**, *11*, 1640.

(17) (a) Wang, J.; Shao, Z.; Tan, K.; Tang, R.; Zhou, Q.; Xu, M.; Li, Y.-M.; Shen, Y. *J. Org. Chem.* **2020**, *85*, 9944. (b) Ji, P.; Zhang, Y.; Wei, Y.; Huang, H.; Hu, W.; Mariano, P. A.; Wang, W. *Org. Lett.* **2019**, *21*, 3086. (c) Brandhofer, T.; Mancheño, O. G. *ChemCatChem* **2019**, *11*, 3797.

(18) Wu, G.; Wang, J.; Liu, C.; Sun, M.; Zhang, L.; Ma, Y.; Cheng, R.; Ye, J. *Org. Chem. Front.* **2019**, *6*, 2245.

(19) (a) Shah, A. A.; Kelly, M. J.; Perkins, J. J. *Org. Lett.* **2020**, *22*, 2196. (b) Merkens, K.; Troyano, F. J. A.; Djossou, J.; Gómez-Suárez, A. *Adv. Synth. Catal.* **2020**, *362*, 2354. (c) Zhang, O.; Schubert, J. W. *J. Org. Chem.* **2020**, *85*, 6225. (d) Ji, P.; Zhang, Y.; Dong, Y.; Huang, H.; Wei, Y.; Wang, W. *Org. Lett.* **2020**, *22*, 1557.

(20) (a) Aycock, R. A.; Vogt, D. B.; Jui, N. T. *Chem. Sci.* **2017**, *8*, 7998. (b) Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. *ACS Catal.* **2017**, *7*, 1766. (c) Rogova, T.; Gabriel, P.; Zavitsanou, S.; Leitch, J. A.; Duarte, F.; Dixon, D. J. *ACS Catal.* **2020**, *10*, 11438. (d) Wan, Y.; Zhu, J.; Yuan, Q.; Wang, W.; Zhang, Y. *Org. Lett.* **2021**, *23*, 1406. (e) Sim, J.; Campbell, M. W.; Molander, G. A. *ACS Catal.* **2019**, *9*, 1558. (f) Li, Y.; Zhou, K.; Wen, Z.; Cao, S.; Shen, X.; Lei, M.; Gong, L. *J. Am. Chem. Soc.* **2018**, *140*, 15850. (g) Leitch, J. A.; Rossolini, T.; Rogova, T.; Dixon, D. J. *ACS Catal.* **2020**, *10*, 11430. (h) Rossolini, T.; Ferko, B.; Dixon, D. J. *Org. Lett.* **2019**, *21*, 6668. (i) Reich, D.; Trowbridge, A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2020**, *59*, 2256. (j) Aycock, R. A.; Pratt, C. J.; Jui, N. T. *ACS Catal.* **2018**, *8*, 9115. (k) Wang, X.; Chen, Y.; Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2021**, *23*, 2199. (l) Weigel, W. K.; Dang, H. T.; Yang, H.-B.; Martin, D. B. C. *Chem. Commun.* **2020**, *56*, 9699.

(21) Shatskiy, A.; Axelsson, A.; Stepanova, E. V.; Liu, J.-Q.; Temerdashev, A. Z.; Kore, B. P.; Blomkvist, B.; Gardner, J. M.; Dinér, P.; Kärkäs, M. D. *Chem. Sci.* **2021**, *12*, 5430.

(22) Ni, S.; Garrido-Castro, A. F.; Merchant, R. R.; de Gruyter, J. N.; Schmitt, D. C.; Mousseau, J. J.; Gallego, G. M.; Yang, S.; Collins, M. R.; Qiao, J. X.; Yeung, K.-S.; Langley, D. R.; Poss, M. A.; Scola, P. M.; Qin, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 14560.

(23) Garrido-Castro, A. F.; Choubane, H.; Daaou, M.; Maestro, M. C.; Alemán, J. *Chem. Commun.* **2017**, *53*, 7764.

(24) (a) Saha, D. *Chem. Asian J.* **2020**, *15*, 2129. (b) Prentice, C.; Morrisson, J.; Smith, A. D.; Zysman-Colman, E. *Beilstein J. Org. Chem.* **2020**, *16*, 2363. (c) Silvi, M.; Melchiorre, P. *Nature* **2018**, *554*, 41. (d) Jiang, C.; Chen, W.; Zheng, W.-H.; Lu, H. *Org. Biomol. Chem.* **2019**, *17*, 8673.