Stereoselective synthesis of unnatural α-amino acid derivatives through photoredox catalysis

Stereoselective synthesis of a wide range of unnatural α-amino acid derivatives was realized under benign conditions in the absence of transition-metal-based catalysts. The introduced α-amino acid side-chains were derived from ubiquitous carboxylic acids, which were transformed into the key C-centered radical intermediates through photoredox-mediated one-electron oxidation and decarboxylation. Stereoselective addition of these radicals to a chiral N-sulfinyl imine delivered a wide scope of unnatural α-amino acid derivatives in generally good yields and with excellent diastereoselectivity.
Stereoselective synthesis of unnatural $\alpha$-amino acid derivatives through photoredox catalysis†

Andrey Shatskiy, Anton Axelsson, Elena V. Stepanova, Jian-Quan Liu, Azamat Z. Temerdashev, Bhushan P. Kore, Björn Blomkvist, James M. Gardner, Peter Dinér and Markus D. Kärkäs*

A protocol for stereoselective C-radical addition to a chiral glyoxylate-derived $N$-sulfinyl imine was developed through visible light-promoted photoredox catalysis, providing a convenient method for the synthesis of unnatural $\alpha$-amino acids. The developed protocol allows the use of ubiquitous carboxylic acids as radical precursors without prior derivatization. The protocol utilizes near-stoichiometric amounts of the imine and the acid radical precursor in combination with a catalytic amount of an organic acridinium-based photocatalyst. Alternative mechanisms for the developed transformation are discussed and corroborated by experimental and computational studies.

Introduction

Unnatural $\alpha$-amino acids constitute an important class of biologically relevant compounds that are widely used in both pharmaceutical industry and for fundamental research within molecular and structural biology. A number of pharmaceuticals based on unnatural $\alpha$-amino acids are currently available, including angiotensin-converting enzyme (ACE) inhibitors for the treatment of cardiovascular and renal diseases, antiviral medicines, and others. Recently, peptidomimetic $\alpha$-ketoamide inhibitors based on unnatural $\alpha$-amino acids have received increased attention as drug candidates for treatment of COVID-19 disease caused by the SARS-CoV-2 coronavirus, highlighting the high demand for such building blocks.

A variety of synthetic strategies to access unnatural amino acid derivatives have been developed over the years, with some notable methods being the catalytic asymmetric Strecker-type reactions, asymmetric hydrogenation of dehydroamino acids, and electrophilic and nucleophilic alkylation of glycine derivatives (Fig. 1A). Among these, functionalization or reduction of $\alpha$-imino esters offers a straightforward route to various enantiomerically enriched $\alpha$-amino acids. Traditionally, these strategies have employed polar retrosynthetic disconnections, which often require the use of (super)stoichiometric amounts of toxic and highly sensitive reagents at low temperatures, thereby limiting the substrate scope and practicality for scale up of these reactions. These limitations have recently been challenged by re-introduction of free-radical reaction manifolds,

Fig. 1. (A) Selected two- and one-electron strategies for synthesis of unnatural $\alpha$-amino acids. (B) Common precursors for radical addition to imines employed in photoredox catalytic systems. (C) Diasteroselective decarboxylative alkylation of $N$-sulfinyl imines with non-activated carboxylic acids.
aided by the developments in base-metal catalysis, electrosynthesis and photoredox catalysis, leading to a vast array of strategies for light-induced modification and synthesis of amino acids and peptides. Among these, radical addition to imines through photoredox catalysis was demonstrated in symmetric and asymmetric fashion (Fig. 1B). In 2017, Aleman and co-workers reported a protocol for asymmetric radical addition to imines mediated by visible light. The developed catalytic system made use of a chiral sulfoxide auxiliary group, commonly employed in the synthesis of chiral amines. Here, the C-centered radical was generated through visible light-mediated reductive cleavage of the N-O bond in a redox-active phthalimide ester, followed by radical addition to the N-sulfanyl imine. The reductive nature of this protocol required the use of a stoichiometric amount of a reducing agent (Hantzsch ester). More recently, a related Ni-based catalytic system was described by Baran and co-workers. This protocol employed a tetrachloro-substituted redox-active ester as the radical precursor, with Zn as a stoichiometric reducing agent and a Ni-based catalyst for mediating the C-C bond formation. Although this protocol displayed an impressive substrate scope, it is associated with moderate atom-economy, limiting its applicability for large-scale synthesis.

Results and discussion

Inspired by the catalytic systems developed by the Aleman and Baran groups, we sought to realize a protocol for diastereoselective decarboxylative radical addition to chiral N-sulfanyl imines that would utilize ubiquitous non-activated carboxylic acids as radical precursors. A related direct decarboxylative addition process was attempted by the Aleman group for a benzaldehyde-derived N-sulfanyl imine under reaction conditions reported by MacMillan; however, no formation of the desired product was observed (see the ESI for ref. 13a). Similarly, we observed no desired product with pivalic acid 2a as the radical precursor and N-sulfanyl imine 1 as the radical acceptor when the reaction was conducted in DMSO with [Ir(dF(CF3)ppy)2(dtbbppy)]PF6 as photocatalyst (Table 1, entry 1), presumably due to fast decomposition of N-sulfanyl imine 1. Gratifyingly, changing the solvent to CH2Cl2, trifluorotoluene (PhCF3) furnished the desired product 3a in fairly good yield of 65%, although with poor diastereoselectivity (Table 1, entry 2). Using other bases in place of Cs2CO3 completely prohibited the reaction (for details on the optimization studies, see the ESI). Further optimization of the reaction conditions for the primary acids 2o and 2p did not result in improved yields (Tables S2 and S3), illustrating the intrinsic instability of the respective radical intermediates and/or the photocatalyst under the employed conditions. Benzyl-type radicals were generally inefficient (see Fig. 2, unsuccessful substrates); however, a cyclopropyl-substituted benzylic radical and an indole-derived benzylic-type radical provided the expected products 3f and 3q, respectively, in satisfactory yields.

The carboxylic acid radical precursors that furnish stabilized α-heteroatom α-C radicals generally provide the addition products in good to excellent yields. Gratifyingly, N-Boc-protected α-amino acid radical precursors based on piperolic acid, proline, valine, and phenylalanine furnished the expected amino acid derivatives 3r-u in generally excellent yields, exemplifying a prominent synthetic route to biologically active α,β-diamino acids. The α-O-substituted radicals derived from dialkyl (3v, 3w) and alkyl aryl ethers (3g-i, 3x) provided the expected products in moderate and excellent yields, respectively. To our delight, a primary α-S-substituted radical containing an aryl bromide functionality afforded the expected product 3y in satisfactory yield despite combining several structural features that can be deleterious under free-radical conditions. The sterically-demanding carbohydrate-based radical derived from diprogulic acid 2j delivered the monosaccharide-amino acid conjugate product 3j in satisfactory yield and excellent diastereoselectivity at both the α- and β-stereocenters (>95 : 5 α/β dr).

The developed transformation was successfully applied for late-stage derivatization of a number of complex biologically-active compounds, including gemfibrozil (2b), ciprofibrate...
Table 1  Optimization of the reaction conditions for the decarboxylative radical addition to a glyoxylate-derived N-sulfonyl imine\(^a\)

| Entry | Photocatalyst | Base | Time | Yield\(^b\) | dr\(^b\) |
|-------|---------------|------|------|-------------|--------|
| 1\(^a\) | [Ir(dF(CF3)ppy)2(dtbbpy)]\(^+\)PF\(_6\)\(^-\), 1 mol% | Cs2CO3, 0.2 equiv. | 20 min | — | — |
| 2 | [Ir(dF(CF3)ppy)2(dtbbpy)]\(^+\)PF\(_6\)\(^-\), 1 mol% | Cs2CO3, 0.2 equiv. | 20 min | 65% | 4 : 1 |
| 3 | 4CzIPN, 1 mol% | Cs2CO3, 0.2 equiv. | 20 min | — | — |
| 4 | [Mes-Acr-Ph](BF\(_4\)), 1 mol% | Cs2CO3, 0.2 equiv. | 20 min | 27% | >95 : 5 |
| 5 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | Cs2CO3, 0.2 equiv. | 20 min | 48% | >95 : 5 |
| 6 | [Mes-Acr-Ph](BF\(_4\)), 5 mol% | Cs2CO3, 0.2 equiv. | 60 min | 66% | >95 : 5 |
| 7 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | Cs2CO3, 0.2 equiv. | 60 min | 73% | >95 : 5 |
| 8 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | Cs2CO3, 0.2 equiv. | 60 min | 78% | >95 : 5 |
| 9 | [Mes-Acr-Ph](BF\(_4\)), 5 mol% | K2PO4, 0.2 equiv. | 60 min | 80% | >95 : 5 |
| 10 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | K2CO3, 0.2 equiv. | 60 min | 84% | >95 : 5 |
| 11 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | K2CO3, 0.05 equiv. | 60 min | <5% | — |
| 12 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | K2CO3, 0.5 equiv. | 60 min | 85% | >95 : 5 |
| 13 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | K2CO3, 0.5 equiv. | 60 min | 77% | >95 : 5 |
| 14 | [Mes-Acr-Me](BF\(_4\)), 5 mol% | K2CO3, 0.5 equiv. | 60 min | 91% | >95 : 5 |
| 15 | As entry 13, but with tBu-sulfonyl imine 4 | — | — | — | — |
| 16 | As entry 13, but with p-Tol-sulfonyl imine 5 | — | — | 50% | 7 : 1 |

Deviations from the conditions in entry 13

- Under air (60 min) 12% >95 : 5
- No photocatalyst (60 min) — —
- No light (60 min) — —

\(^a\) The reactions were performed on 0.1 mmol scale: stock solutions of pivalic acid 2 and the photocatalyst (each in 1 mL of the solvent) were mixed with N-sulfonyl imine 1 and the base under anhydrous conditions, and stirred under irradiation with 440 nm blue LED light at room temperature (for details, see the ESI). \(^b\) Determined by \(^1\)H NMR of crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard.
is excited by visible light ($\lambda_{\text{max}} = 425$ nm) to a highly oxidizing excited state $\text{Acr}^+$ ($E(\text{Acr}^+/\text{Acr}) = 2.09$ V vs. SCE).\(^{25}\) In this state, the photocatalyst can abstract an electron from the deprotonated carboxylic acid via a single-electron transfer (SET) event to generate a carboxylate radical while being reduced to the acridinium radical $\text{Acr}^-$. The steady-state and time-resolved fluorescence quenching measurements for tetrabutylammonium pivalate as the model radical precursor demonstrated efficient quenching of the excited acridinium photocatalyst with Stern–Volmer quenching constant $K_{SV} = 237.5$ M$^{-1}$ and bimolecular quenching constant $k_q = 6.8 \times 10^{9}$ M$^{-1}$ s$^{-1}$, while no quenching was observed for the free pivalic acid (Fig. 3B, S3 and S4†). The carboxyl radical formed via SET then extrudes CO$_2$ to yield a C-centered radical, which undergoes addition to the N-sulfynyl imine 1 in the key step of the reaction, forming an $\alpha$-alkylated N-centered radical. Finally, the N-centered radical is
reduced by acridinium radical Acr, closing the photocatalytic cycle and furnishing the desired product 3 upon protonation (Fig. 3A).

In order to gain better understanding of the stereo-determining C–C bond forming step in the proposed mechanism, DFT calculations were performed on the M062X-D3/6-311+G(d,p) level of theory (for details, see the ESI†). First, the structure of the N-sulfinyl imine radical acceptor 1 was evaluated. Previously, Alemán and co-workers tentatively suggested an s-cis conformation around the N–S bond as being more stable in such compounds due to the hydrogen bonding between the imine proton and the sulfoxide oxygen. Such a conformational preference would then lead to the a-(R) product when the S(R)-sulfinyl imine is employed as the radical acceptor. This stereochemical outcome was indeed observed for both Alemán’s and our catalytic system. The calculations confirmed that the s-cis conformer is more stable compared to the s-trans-1 conformer by 3.8 kcal mol⁻¹, corresponding to >99.8 : 0.2 ratio between the conformers from the Boltzmann distribution at room temperature (Fig. 3C). In the s-cis conformer, the hydrogen bonding between the imine hydrogen and the sulfoxide oxygen could be observed from the non-covalent interaction (NCI) plots, while no hydrogen bonding was present in the s-trans-1 conformer (for a detailed discussion, see the ESI†).

Subsequently, the radical addition step was evaluated for the tert-butyl radical donor and the N-sulfinyl imine radical acceptor 1. The computed Gibbs free energy and enthalpy diagrams for tert-butyl radical addition to 1, and calculated structures for the re-TS and si-TS transition states.

Fig. 3 (A) Outline of the proposed mechanisms with the acridinium- (left) and Ir-based (right) photocatalysts. (B) Steady-state fluorescent quenching and electrochemical measurements. (C) Calculated structures with selected bond distances (Å) for the s-cis and s-trans-1 conformers of N-sulfinyl imine 1. (D) Gibbs free energy and enthalpy diagrams for tert-butyl radical addition to 1, and calculated structures for the re-TS and si-TS transition states.
reactions originated almost exclusively from the enthalpic terms \(\Delta \Delta G^\ddagger = 3.8 \text{ kcal mol}^{-1}\), \(\Delta \Delta H^\ddagger = 3.4 \text{ kcal mol}^{-1}\). The better stabilization of the re-TS is in part due to the stronger hydrogen bonding between the imine hydrogen and the sulfone oxygen for this transition state, as evident from the calculated bond distances and the NCI plots (Fig. 3D and S7†). Additionally, significant steric crowding occurs in the st-TS, where the incoming tert-butyl radical requires the mesityl group to become almost completely coplanar to the sulfoxide S=O bond. In contrast, the mesityl group and the S=O bond in the re-TS are out of plane by 50° while the incoming tert-butyl radical experiences no steric crowding.

An alternative mechanism for a related radical addition to imine derivatives was proposed by Ooi and co-workers. In this mechanism, the key C–C bond-forming step was found to proceed through radical–radical coupling between a C-centered radical and an \(\alpha\)-amino radical formed by one-electron one-proton reduction of an imine substrate. However, under our conditions such a mechanistic pathway seems unlikely due to weak reducing ability of the one-electron reduced form of the photocatalyst (Table 1, entry 2). Indeed, this photocatalysts \((\text{Ir}^{III}/\text{Ir}^{II})\) would not be favored. However, a contribution from the radical–radical coupling pathway would explain the low diastereoselectivity (4 : 1 dr) during formation of product 3a when the reaction was conducted with the \[[\text{Ir}(\text{dpf})_{2}(	ext{bpy})]^{2+} \text{PF}_6^{-}\text{photocatalyst (Table 1, entry 2). Indeed, this photocatalyst displayed relatively low reduction potential (}E_{1/2}(\text{Ir}^{III}/\text{Ir}^{II}) = –1.5 \text{ V vs. SCE, Fig. 3B} \langle \rangle\text{ should not be favored. However, a contribution from the radical–radical coupling pathway would explain the low diastereoselectivity (4 : 1 dr) during formation of product 3a when the reaction was conducted with the [Ir(dpf)(CF$_3$ppy)$_2$(dttbppy)]PF$_6$ photocatalyst (Table 1, entry 2). Indeed, this photocatalyst displayed relatively low reduction potential (}E_{1/2}(\text{Ir}^{III}/\text{Ir}^{II}) = –1.10 \text{ V vs. SCE, Fig. 3B} \rangle\text{, sufficient to reduce the N-sulfinyl imine substrate 1 to the corresponding \(\alpha\)-amino radical. The conformation analysis of this radical then revealed nearly free rotation around the N–S bond with a barrier of ca. 2.5 kcal mol$^{-1}$, while N-sulfinyl imine 1 displayed a significantly higher rotation barrier of ca. 8.0 kcal mol$^{-1}$ and only one dominant conformer. Addition of the tert-butyl radical to the \(\alpha\) amino radical would therefore be expected to proceed with low, if any, diastereoselectivity. The low diastereoselectivity could also be explained by product epimerization during the reaction; however, no epimerization was observed when product 3a was subjected to the comparable reaction conditions with the Ir-based photocatalyst.

Conclusions
In conclusion, a practical protocol for stereoselective synthesis of various \(\alpha\)-amino acids has been developed, employing ubiquitous carboxylic acids as radical precursors and an organic photocatalyst under visible light irradiation. This protocol allows for synthesis of highly functionalized \(\alpha\)-amino acids, which are challenging to prepare through traditional two-electron reaction manifolds. The protocol utilizes near-stoichiometric amounts of reagents and does not produce large quantities of waste, which is an intrinsic disadvantage of the previously described systems utilizing redox-active esters as radical precursors.

Author contributions
A. S. performed optimization studies, major part of substrate scope investigation, electrochemical and spectroscopic studies, and wrote the manuscript. A. A. performed the computational studies and part of the substrate scope investigation. E. V. S., J.-Q. L., and B. B. performed part of the substrate scope investigation. A. Z. T. performed part of the analytic measurements. B. P. K. and J. M. G. assisted during data acquisition and analysis of the spectroscopical studies. M. D. K. conceived and directed the project. P. D. and M. D. K. supervised the project. All authors discussed the results and approved the final version of the manuscript.

Conflicts of interest
There are no conflicts to declare.

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