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Preview

Iron-catalyzed direct decarboxylative azidation

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In this issue, West and co-workers report a photocatalytic direct decarboxylative azidation of carboxylic acids that is enabled by a merger of iron-catalyzed ligand-to-metal charge transfer (LMCT) and radical–ligand transfer (RLT), rendered catalytic by the multifaceted reactivity of iron nitrate.

Organoazides have recently emerged as centrally important and versatile synthetic intermediates. They have been used extensively for the construction of triazoles via a cycloaddition with alkynes in the context of click chemistry.[1] Organoazides are also widely used as nitrene precursors and in a plethora of other synthetic methods.[2]

Due to the reactivity of the azido group, its installation is best accomplished in the later stages of a multistep synthesis. Such late-stage azidation, however, is difficult to achieve as there are few means of installing the azide moiety selectively in the presence of existing functional groups. Typical azidation methods include nucleophilic substitution reactions of reactive alkyl halides[2] and late-stage metal-catalyzed C–H azidations;[3] however, these approaches have limitations in the substrate scope and availability or require specialized azidation reagents.

Aliphatic carboxylic acids are inexpensive commodity chemicals featuring a wide range of structural diversity that have seen increasing use as precursors to reactive alkyl radicals via decarboxylation.[4] The decarboxylation of carboxylic acids typically requires preactivation to affect homolysis, for example by preparation of reductively activatable derivatives.[5] However, recent advances in photocatalysis have provided simplified routes to alkyl radicals from carboxylic acids by enabling direct, light-induced decarboxylation (Figure 1A). For example, decarboxylation of *in situ*-produced carboxylate anions by an outer-sphere single electron transfer (SET) process can produce alkyl radicals directly from carboxylic acids.[6] Another emergent approach entails acridine photocatalysis that affects a direct decarboxylation of carboxylic acids in the absence of an additional base via proton-coupled electron transfer (PCET).[7]

Photoinduced ligand-to-metal charge transfer (LMCT) processes offer a mechanistically distinct route to radical intermediates as an alternative to outer-sphere SET processes and PCET. In this approach, earth-abundant 3d transition metals, such as iron and copper, form metal-substrate complexes in the electronic ground state. Upon photoexcitation, the metal-substrate bond undergoes homolysis via an inner-sphere $\pi \rightarrow d$ redox process resulting in a reduced metal center and a dissociated radical intermediate. As with acridine photocatalysis, the advantage of the LMCT approach is that the oxidation is proximity controlled and thus highly chemoselective, occurring only at the metal-bound ligand and allowing this approach to be utilized in the presence of oxidizable functional groups.[8] This approach is exemplified by a recently described direct decarboxylative alkylation of nitrogen-centered heteronucleophiles.[9] Following base-mediated formation of a copper(II)-carboxylate complex, light-induced LMCT results in formation of a carboxylate radical that undergoes decomposition to furnish a carbon-centered radical (Figure 1A). The resulting alkyl radical is further oxidized to a carbocation by excess copper(II) salt in a radical–polar crossover (RPC). Subsequent reaction with a nitrogen-centered nucleophile furnishes the C–N coupling products. Whereas a merger of radical and polar pathways in RPC combines the mildness and functional group tolerance of photoredox catalysis with the facility of reactions between polar intermediates, formation of discrete carbocations may limit the scope to carboxylic acids that can form stable carbocations and lead to competitive elimination pathways.

In this issue, West and co-workers report a photocatalytic decarboxylative azidation of carboxylic acids that provides a conceptually different approach to merging photoinduced LMCT with the downstream C–N bond formation and catalyst regeneration (Figure 1B).[10] Here, the C–N bond-forming reaction is proposed to proceed via formation of an iron(III) carboxylate complex that, upon photoexcitation, undergoes LMCT to generate a carbon-centered radical after decarboxylation of the intermediate carboxylate radical. Importantly, instead of relying on the oxidation of the alkyl radical to the carbocation via RPC, West and co-workers devised a catalytic system that affects azidation by a radical–ligand transfer (RLT) process from an *in situ*-formed iron azide complex. This approach enables formation of C–N bonds using

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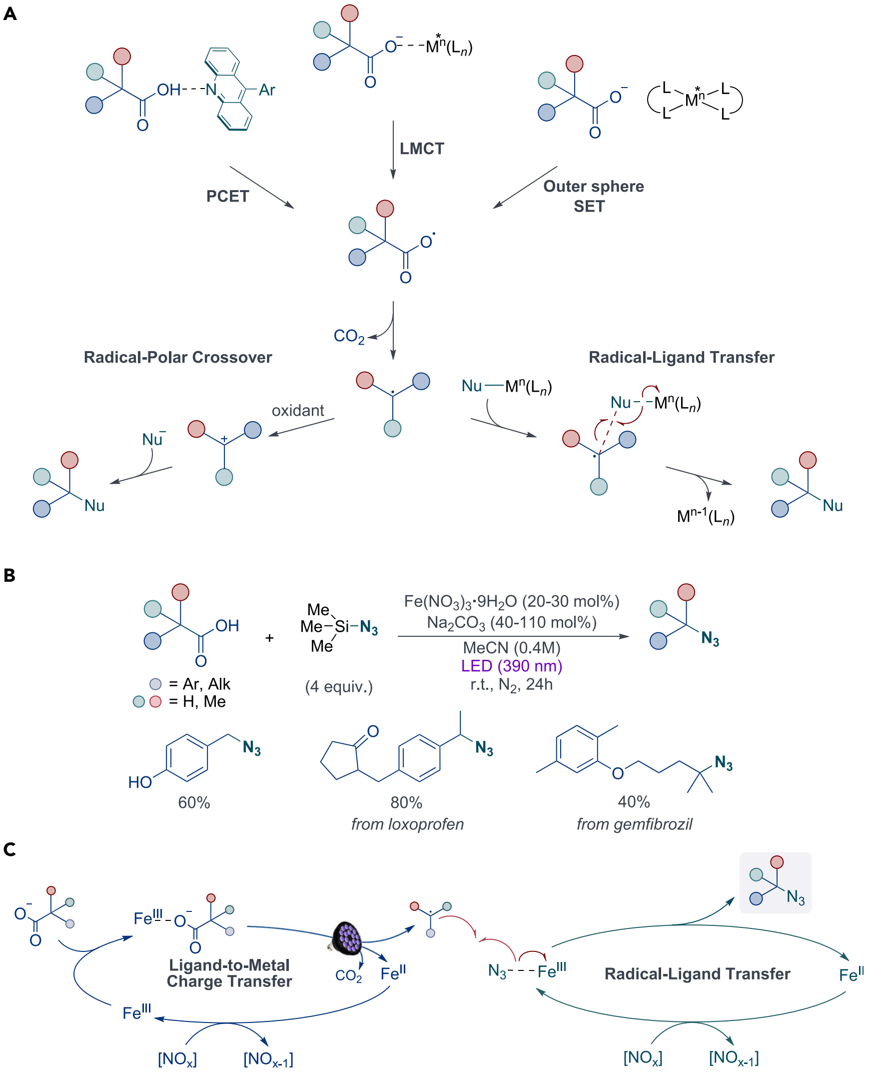

Figure 1. Iron nitrate-catalyzed direct decarboxylative azidation

(A) Modes of photocatalytic direct decarboxylation and downstream RPC and RLT processes.

(B) Reaction conditions and representative products of the iron nitrate-catalyzed decarboxylative azidation.

(C) Proposed mechanism.

an array of carboxylic acids, taking advantage of the RLT that does not rely on the formation of stable carbocation intermediates.

Several features of the new catalytic system are worthy of further discussion. The photoinduced decarboxylative azidation reaction is rendered catalytic without the addition of an external terminal oxidant or the use of superstoichiometric quantities of the metal salt to serve as an oxidant. The judicious selection of inexpensive iron(III) nitrate as the iron catalyst also provides nitrate anions, which were found to selectively oxidize the iron(II) species following RLT, allowing for regeneration of the catalytically active iron(III) species and thus employing a single reagent as both catalyst source and oxidant while using substoichiometric quantities of the metal.

A principal challenge in developing the photocatalytic decarboxylative azidation reaction based on an LMCT/RLT system was identifying a chemoselective oxidant for the regeneration of the iron catalyst, as an effective oxidant would need to chemoselectively reform Fe(III) without interfering with either of the critical LMCT or RLT steps. Among a variety of iron(III) salts evaluated, iron(III) nitrate was uniquely capable of providing the azidation product under catalytic conditions, suggesting that nitrate was a competent terminal oxidant (Figure 1C). The role of the nitrate counteranion as a terminal oxidant was supported by mechanistic studies that included enabling catalytic activity of otherwise inefficient iron(III) and iron(II) chlorides by adding sodium nitrate, thus demonstrating that the nitrate anion was capable of regenerating the catalytically active iron(III) species. Notably, an RPC-based mechanism was ruled out when no carbocation-mediated rearrangement products were observed with substrates that could produce rearrangement-prone carbocations if RPC were operational.

Importantly, the LMCT/RLT-based azidation reaction was found to proceed smoothly with unprotected phenol and anilines that could otherwise be susceptible to alkylation in the presence of carbocation intermediates. Furthermore, the applicability of the reaction for late-stage azidation, which is of particular value owing to the synthetic challenges associated with producing azido group-containing substrates, was demonstrated by the azidation of commercially available active pharmaceutical ingredients.

In summary, the work reported by West and co-workers is an important milestone in the development of C–N bond-forming methodologies under mild, functional-group tolerant conditions. The use of iron(III) nitrate as both iron and oxidant source in this photocatalytic reaction enables a practical and efficient azidation reaction by merging iron-catalyzed LMCT and RLT processes. Additionally, the use of nitrate as a chemoselective terminal oxidant is noteworthy as it allows for a successful catalyst turnover with sub-stoichiometric quantities of metal salts.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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