ACS Catalysis

Perspective

Cite This: ACS Catal. 2020, 10, 2009–2025

pubs.acs.org/acscatalysis

α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives

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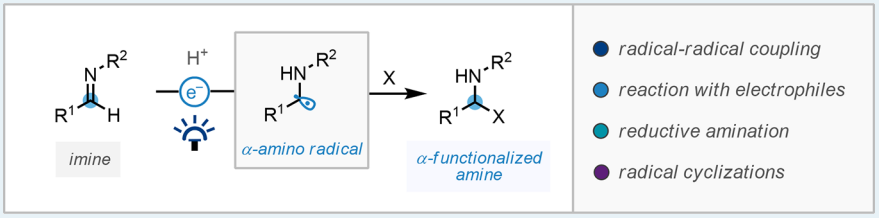


ABSTRACT: The construction and manipulation of amine-containing architectures is of importance to academic and industrial development and discovery programs. The photochemical single-electron reduction of imine derivatives to generate α-amino radical intermediates has emerged as a powerful umpolung strategy for opening up underexplored routes to such amine motifs. Furthermore, these radicals have been shown to engage in a wide variety of chemistry, including radical−radical coupling, addition to electrophiles, and reductive amination chemistry. The concept has also begun to see application to iminium ion intermediates and the extension to enantiocontrolled C−C bond formation. This Perspective covers recent efforts in this synthetic strategy to simple and complex amine structures alike.

KEYWORDS: *photoredox catalysis, amine, imine, radical, reductive*

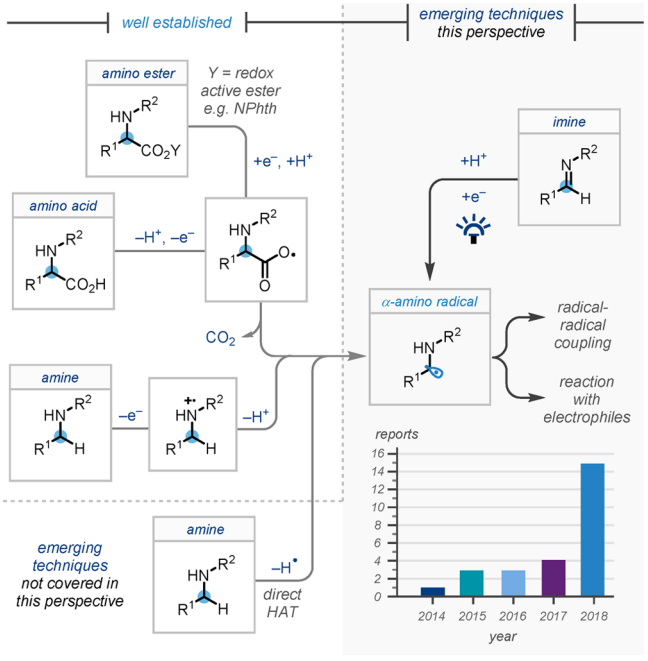
I. INTRODUCTION

Amine-containing chemical architectures are important and sought-after motifs with wide-ranging applications across the pharmaceutical and agrochemical sectors into natural product chemistry and also fine chemical research.[1] In order to satisfy the ever-increasing demand, there has been a persistent need for new synthetic access to, and manipulation of, simple and complex amine structures. For these reasons, some of the most elegant developments in contemporary synthetic methods such as C−H functionalization,[2] organocatalysis,[3] photoredox catalysis,[4] and electrochemical synthesis[5] have placed amines as a key focal point.

One such strategy that has received great interest in recent times is the use of α-amino radicals as reactive open-shell intermediates, which are capable of engaging in a plethora of synthetic transformations (Scheme 1).[6] Classically, α-amino radicals can be derived from three one-electron pathways: single-electron oxidation of a parent amino acid carboxylate (with loss of CO_2),[7] single-electron oxidation and proton loss from an amine substrate,[8] and single-electron reduction and protonation of a redox active amino ester (with loss of CO_2).[9,10] These transformations were traditionally facilitated by organic-/metal-based stoichiometric oxidants/reductants; however, developments in (photo)redox catalysis have advanced these methods into the catalytic domain.[11]

Furthermore, in recent years new techniques for the generation and manipulation of α-amino radicals through the single-electron reduction of imine derivatives have emerged.[12] Historically, while the single-electron reduction of carbonyl derivatives has been well-established since the 1970s utilizing stoichiometric (commonly lanthanide-based) reductants,[13] the

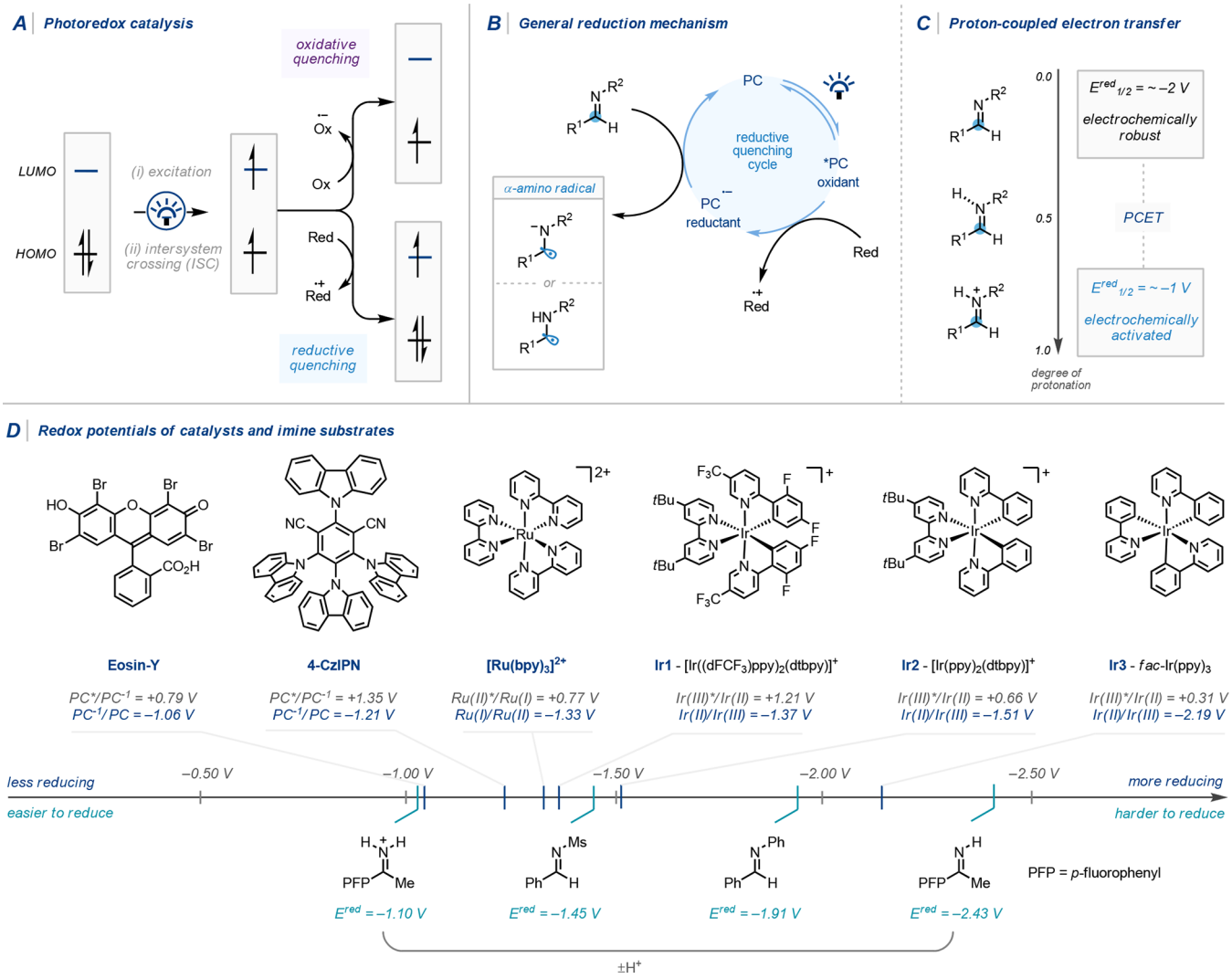
Scheme 1. Synthetic Methods for the Generation of α-Amino Radicals



Received: November 19, 2019
Revised: December 24, 2019
Published: January 21, 2020

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 2. Mechanistic Considerations in the Photocatalytic Single-Electron Reduction of Imine Derivatives: (A) Overview of Photoredox Catalysis; (B) Model Catalytic Cycle; (C) Concept of Proton-Coupled Electron Transfer; (D) Electrochemical Properties of Photocatalysts and Imines Discussed in This Perspective[a]



[a]Reduction potentials are given vs the saturated calomel electrode (SCE).

analogous reduction of imines was not achieved until 1990, when a samarium diiodide mediated aza-pinacol coupling was achieved by Imamoto and co-workers.[14] Subsequent synthetic work using stoichiometric reductants and elegant electrochemical studies established these intermediates as potentially viable synthons in the organic chemist's toolbox.

Although the renaissance of photoredox catalysis began in 2008,[15] it was not until 2014 when the first photocatalytic single-electron reduction of imine derivatives was incorporated into new synthetic methodology.[16] This Perspective covers these seminal reports in the photochemical formation and manipulation of imine-derived α-amino radicals, further applications to radical–radical coupling, addition to electrophiles, reductive amination chemistry, subsequent extension to α-amino radical generation from iminium ions, and explorations in rendering these processes enantioselective.

II. MECHANISTIC CONSIDERATIONS

Before the synthetic methodology harnessed using the single-electron reduction of imines is detailed, it is worth discussing the photo- and electrochemistry of imines and the catalysts and conditions used to activate them.

The concept of photoredox catalysis focuses on the absorbance of a photon, which promotes one electron in the HOMO of a photocatalyst to the corresponding LUMO. Subsequent metal-to-ligand charge transfer (MLCT, in the case of metal-based systems) and intersystem crossing (ISC) give a long-lived triplet state, which does not readily decay to the singlet ground state, as the transition is spin forbidden (Scheme 2A).[4a] This triplet state can then donate an electron to a suitable oxidant (losing the high-energy electron, known as oxidative quenching) or gain an electron from a suitable reductant (pairing the electron located in the lower orbital, known as reductive quenching). The quenching mode in operation is entirely dependent on the reaction conditions, and reductive quenching cycles are operative in the majority of the transformations discussed herein. In a model system for the single-electron reduction of imines (Scheme 2B), a photocatalyst can absorb a photon, promoting it to the photoexcited state. Subsequent quenching by a suitable reductant (Red)

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009–2025

delivers a reduced photocatalytic species and the radical cation of the reductant. The reduced photocatalyst can then deliver an electron to an imine derivative to afford the corresponding α-amino radical. Such an electron transfer event re-forms the ground-state photocatalyst, completing the catalytic cycle.

When the relevant reduction potentials of imine substrates (Scheme 2D) are studied, it is clear that *N*-sulfonyl imines ($E^{red}_{1/2}$ = −1.45 V vs saturated calomel electrode [SCE herein])[17] are more readily reduced to form the α-amino radical anion than *N*-arylimines ($E^{red}_{1/2}$ = −1.91 V vs SCE),[18] and even more so than N−H imines ($E^{red}_{1/2}$ = −2.43 V vs SCE).[19] Interestingly, these numbers fall out of range of a large majority of photocatalysts utilized by research groups in this Perspective (Scheme 2D), suggesting that transfer of an electron from these catalysts to a neutral imine should be thermodynamically unfavored.

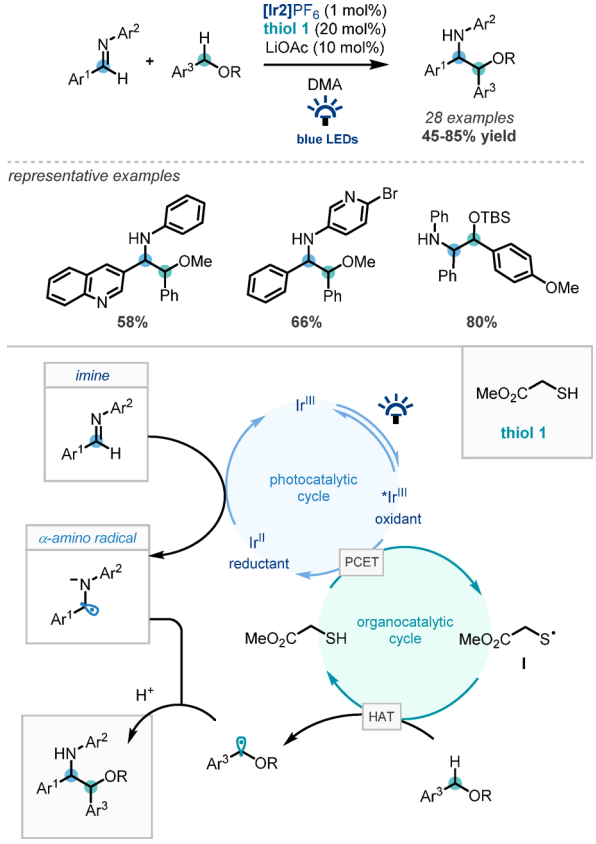
Despite this, a phenomenon commonly referred to as proton-coupled electron transfer (PCET) has shown that coordination of a Brønsted acidic species can increase the reduction potential (become less negative) of Lewis basic functional groups such as imines.[20] It has been reported that PCET events take place along the coordinate (Scheme 2C) between unprotonated and fully protonated basic functional group.[21] An illuminating case of the effect of an acid on reduction potentials is exemplified with the ammonia-derived imine of *p*-fluoroacetophenone, where an increase (less negative) in reduction potential is observed ($E^{red}_{1/2}$ = −2.43 to −1.10 V vs SCE, Scheme 2D).[19] This same photochemical activation of imine substrates has also been achieved with certain Lewis acids.[19] Even if not formally discussed in the original reports, it is likely that these acid−base interactions assist in rendering challenging electron transfer events more energetically feasible.

III. INITIAL PHOTOCATALYTIC STUDIES

In 2014 MacMillan and co-workers were the first to exploit this concept in photocatalytic synthesis. The authors disclosed the redox-neutral coupling of benzylic ethers and *N*-arylimines (Scheme 3).[16] The report was conceptualized by drawing on seminal studies on thiyl radical hydrogen atom transfer chemistry by Roberts.[22] The authors proposed that the photoexcited iridium catalyst (Ir2) is quenched by the thiol organocatalyst (thiol 1, facilitated by the lithium acetate additive) to deliver an iridium(II) species and the thiyl radical (**I**). Despite the mismatched redox potentials, the authors suggested that this reducing iridium species ($E^{\circ}_{1/2}$ = −1.51 V vs SCE) can reduce the *N*-arylimine via single electron transfer ($E^{\circ}_{1/2}$ = −1.98 V vs SCE)—to give the key α-amino radical. Conceivably either the thiol or the lithium salt could facilitate this electron transfer process. Concurrently, the thiyl radical is proposed to take part in an energetically feasible hydrogen atom transfer (HAT) event from the benzyl ether, delivering the α-oxo radical. Finally, radical−radical coupling of the two open-shell intermediates in the catalytic cycle forges the C−C bond, affording the β-amino ether product. The authors demonstrated a broad scope of *N*-arylimines and benzyl ethers, although some limitations arose when heterobenzyl ethers were used.

Following this report, in 2015 the MacMillan group reported a further elegant development, where a second photoredox/organocatalysis synergistic platform enabled the β-Mannich reaction of cyclohexanone derivatives (Scheme 4). Building on their previous studies on analogous ketones (in place of imines),[23] they suggested that a photoexcited iridium complex can undergo reductive quenching by the DABCO additive,

Scheme 3. Photocatalytic Coupling of Imines and Benzyl Ethers



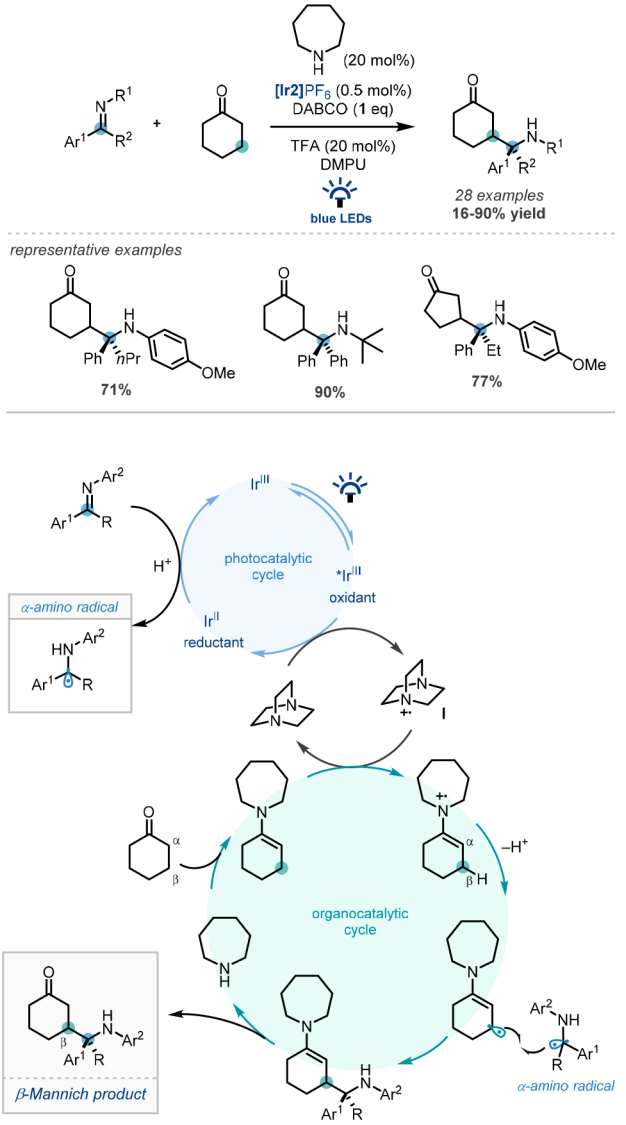
forming the corresponding iridium(II) species and the aminyl radical cation (**I**). The reducing iridium species is suggested to deliver an electron to an imine starting material, with concomitant proton transfer, thus affording the α-amino radical.

The aminyl radical cation (**I**) has been postulated to oxidize the Stork enamine intermediate—produced via condensation of the cyclohexanone with the azepane cocatalyst—regenerating DABCO and producing the enamine radical cation. Deprotonation of this intermediate at the β-position delivers the 5πe$^-$ enaminyl radical. The authors suggest that radical−radical coupling of this intermediate and the α-amino radical forges the C−C bond, with subsequent hydrolysis affording the β-Mannich product and re-forming the azepane cocatalyst. This method was shown to be efficient for the construction of challenging 1,4-aminoketone scaffolds, utilizing both ketimine and aldimine derivatives, and cyclopentanone motifs were also shown to be effective substrates.

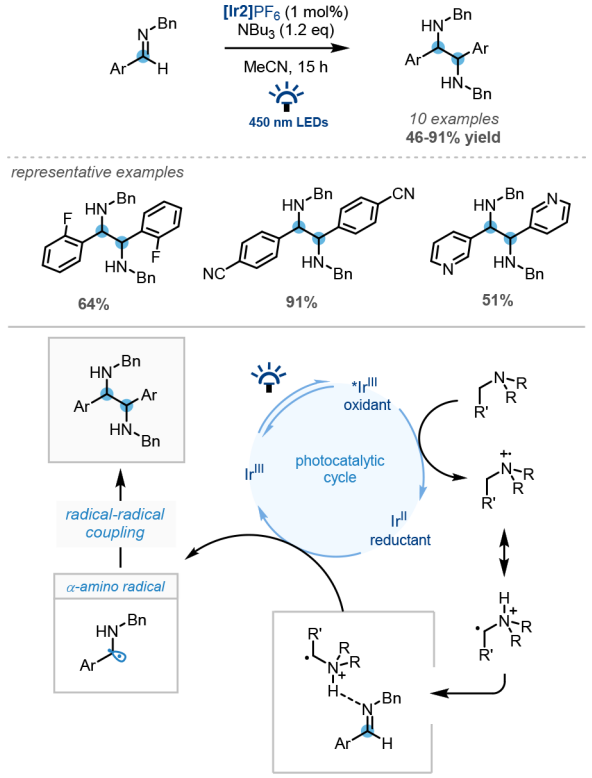
Contemporaneously with this MacMillan report, Rueping and co-workers disclosed the photocatalytic aza-pinacol coupling of carbonyl and imine derivatives (Scheme 5).[24] In this chemistry, they suggest that a photoexcited iridium(III) catalyst is quenched by a tertiary amine reductant (tributylamine) to afford the iridium(II) species and the amine radical cation. The authors then provide two alternative mechanisms for the activation of the carbonyl/imine derivatives to lower the redox potential into an accessible range for the photocatalyst: (1) the radical cation can form a three-center−two-electron interaction with the C═X bond or (2) facile proton transfer from this intermediate delivers the protonated α-amino(oxo) radical, which can activate the carbonyl/imine through PCET.

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 4. Photocatalytic β-Mannich Reaction of Imine and Cyclohexanone Derivatives



Scheme 5. Photocatalytic Reductive Aza-Pinacol Reaction



These methods would produce the α-amino(oxo) radical, which under the conditions was shown to dimerize to the aza-pinacol structure. Studies into additive effects led the authors to suggest that the PCET mechanism is probably at play in creating the 1,2-diamine products.

Later in 2015, Ooi and co-workers reported a major development in this field regarding the photocatalytic enantioselective coupling of imines and amines (Scheme 6).[17] This method operates through two modes of accessing α-amino radicals: the first through single-electron oxidation and subsequent proton loss of a tertiary amine and the second through single-electron reduction of an *N*-sulfonyl imine derivative. The authors propose that a tertiary amine derivative quenches the photoexcited iridium(III) species—in a similar manner to Rueping's report above—with proton loss delivering the α-amino radical. Concurrent reduction of an *N*-mesylimine with the iridium(II) species generated above affords the *N*-mesyl radical anion, which at this time is ion-paired by the positively charged iridium(III) ground state complex. The authors then suggest that this salt engages in a prompt ion exchange with the chiral aminophosphonium ion to create the key chiral radical ion pair. This intermediate is then proposed to engage in a radical−radical coupling mechanism with the previously formed α-amino radical to construct the C−C bond, with enantiocontrol arising from the aminophosphonium counterion.

Using this methodology, the authors created a library of 1,2-diamine products with enantiomeric excess of up to 97% on a range of *N*-mesylimines and tertiary amines. Ooi and co-workers further expanded this chemistry in 2016, utilizing α-silylamines as precursors for the formation of α-amino radicals, which then engaged in the same catalytic cycle as above.[25]

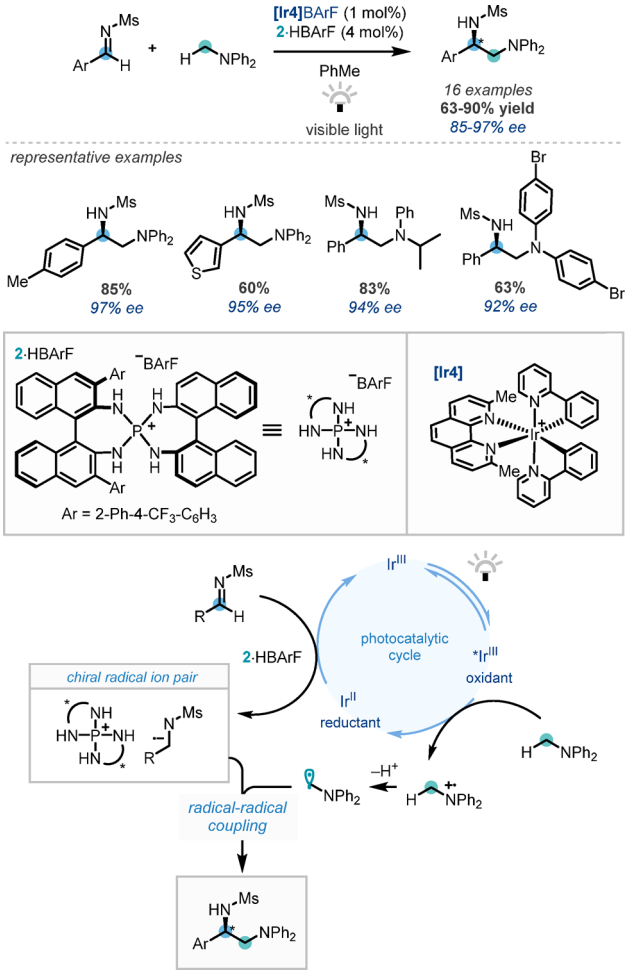
In 2016, Rueping and co-workers also reported their investigation into the coupling of two α-amino radicals generated via complementary activation modes (Scheme 7A).[26] Using finely tuned reaction conditions, they were able to use less easily reduced *N*-arylimines ($E^{\circ}_{1/2}$ = −1.91 V vs SCE) (cf. *N*-sulfonylimines in Ooi's work ($E^{\circ}_{1/2}$ = −1.45 V vs SCE)). The authors described the beneficial use of a Li_2CO_3 additive to enable efficient reactivity, and a variety of benzaldehyde- and glyoxylate-derived imines were well-tolerated, although in the latter case, longer reaction times were required. Furthermore, they also demonstrated the use of *N*-alkylsilanes and amino acids as α-amino radical precursors (Scheme 7B), giving rise to similar 1,2-diamine structures in good yields, thus demonstrating further access points to these compounds.

IV. REACTION WITH ELECTROPHILES

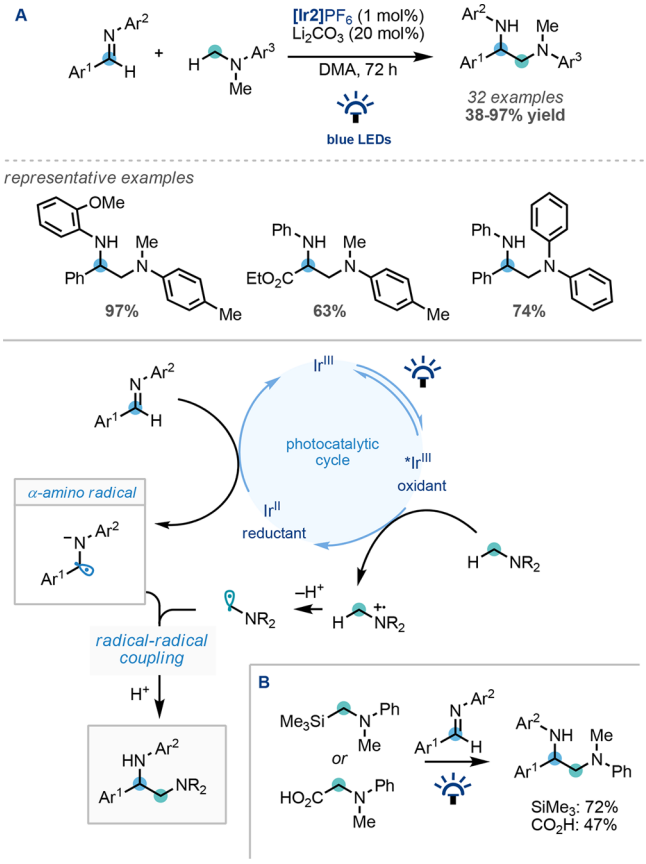
Following these seminal reports on the use of photocatalytic techniques for the generation of α-amino radicals from imine derivatives, the stage was set for new applications of these open-shell intermediates. Until this point, the α-amino radicals have delivered C−C bond formation through radical−radical coupling mechanisms. Despite this, there has been a long-

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 6. Photocatalytic Enantioselective Redox-Neutral Coupling of *N*-Sulfonylimines and Tertiary Amines



Scheme 7. Photocatalytic Coupling of *N*-Arylimines and Tertiary Amines



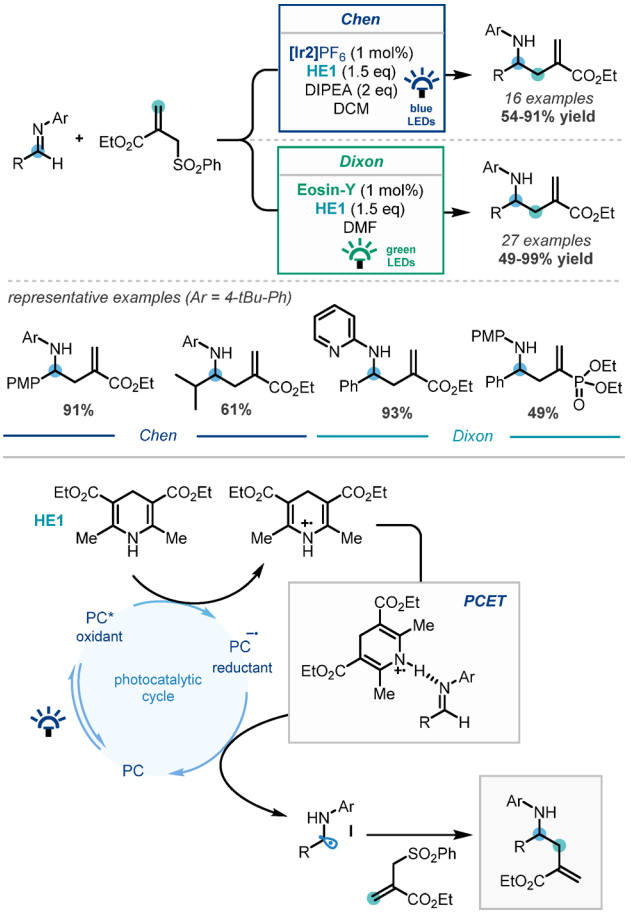
standing interest in the reaction of radical intermediates with electrophilic Michael acceptors in so-called Giese-type reactivity.[27] Within this concept, the α-amino radical can behave as a nucleophilic entity, in the generation of Michael adducts, inaccessible through traditional two-electron chemistry.

Reducing this concept to practice, in late 2016, two reports in close succession—the first from Chen[28] and the second from Dixon[29]—disclosed the reverse polarity allylation of imine derivatives, via the addition of an α-amino radical to an electrophilic Michael acceptor (Scheme 8). These reports demonstrated that the Hantzsch ester (HE1) played a crucial role as an electron and proton donor in the activation of imines (and also aldehydes in Chen's report). Both publications propose that the Hantzsch ester serves to quench a photoexcited iridium(III) species to deliver the Hantzsch ester radical cation and the activated and reducing iridium(II) species. The newly formed, weakly acidic Hantzsch radical cation is able to activate an imine substrate via a proton-coupled electron transfer (PCET) mechanism, generating the α-amino radical (**I**) and the ground-state iridium(III). The resulting α-amino radical can then add to the α,β-unsaturated system, forging the C−C bond and producing the γ-amino radical intermediate. In the case of the allyl sulfone coupling partners, elimination of the sulfinate leaving group to give the allylated product could take place through either one-electron elimination via β-scission or further single-electron reduction and subsequent two-electron E1$_{cb}$ elimination. Both reports demonstrate a wide variety of functional group tolerance, and in Chen's work, even more difficult-to-reduce alkylimine derivatives were effective in the transformation. Dixon's report also demonstrated the beneficial use of the readily available organic dye Eosin-Y as the photocatalyst.

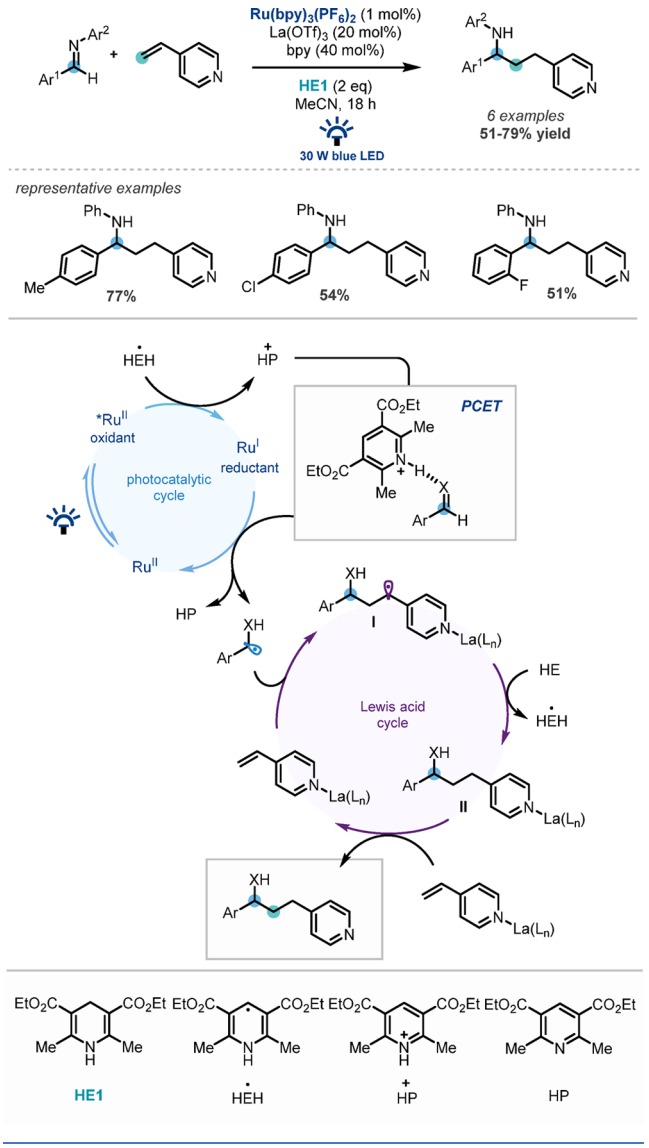
In 2017, Ngai and co-workers reported the photocatalytic reductive coupling of aldehyde and imine derivatives with vinylpyridines (Scheme 9).[30] The authors disclosed a key addition of a lanthanide Lewis acid additive as vital for reaction efficiency. Interestingly, luminescence quenching studies suggested that the aldehyde/imine, the vinylpyridine, or the commercial Hantzsch ester did not quench the photoexcited ruthenium(II) species. For this reason, it was suggested that a downstream Hantzsch intermediate (HEH$^{\bullet}$) was responsible for quenching the photocatalyst to form the reducing ruthenium(I) species and the protonated Hantzsch pyridine (HP^{+}), poised to activate the aldehyde/imine substrate in a PCET mechanism to deliver the α-heteroatom radical. The α-oxo/amino radical then adds to a lanthanum(III)-coordinated/activated vinylpyridine substrate, resulting in the formation of **I**. It is proposed that HAT from the Hantzsch ester (HE) to this intermediate delivers the C−C coupled product (**II**) and the HEH$^{\bullet}$ necessary to complete the catalytic cycle. While the report focused primarily on aldehyde substrates, they also achieved good yields with a modest scope of *N*-arylimines.

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 8. Photocatalytic Synthesis of α-Allylated Amines via PCET Reduction of Imine Derivatives



Scheme 9. Photocatalytic Reductive Coupling of *N*-Arylimines and Vinylpyridines



V. APPLICATION TO C–C BOND FORMATION

Molander and co-workers pioneered the development of hypervalent silicates as radical precursors in photoredox catalysis[31] and in 2017 applied these substrates in the alkylation of imine derivatives (Scheme 10).[32] This simple, metal-free, and scalable protocol utilized alkyl bis(catecholato)silicates, where photocatalytic single-electron transfer (SET) oxidation generated primary and secondary alkyl radicals (**I**). From this point the authors present two viable mechanisms. In the first instance, radical addition into the imine substrate would generate the *N*-centered radical **II**, and reduction to close the catalytic cycle would deliver alkylated imine (path A). Alternatively, single-electron reduction of the *N*-sulfonyl imine to radical anion **III** (path B) and subsequent radical–radical coupling would deliver the C–C coupled product. This redox-neutral synthetic method was shown to be applicable to *N*-sulfonyl as well as *N*-(hetero)aryl aldimines with a remarkably wide range of alkylsilicates. Additionally, chemoselective alkylation of sulfonyl aldimines over aldehydes was also demonstrated.

As a further extension of their report on the reductive arylation of carbonyl derivatives under visible-light photoredox catalysis, Xia and co-workers also achieved reductive coupling between aryl imines and 1,4-dicyanobenzene (1,4-DCB), furnishing α-arylated amines in moderate to good yields (Scheme 11).[33]

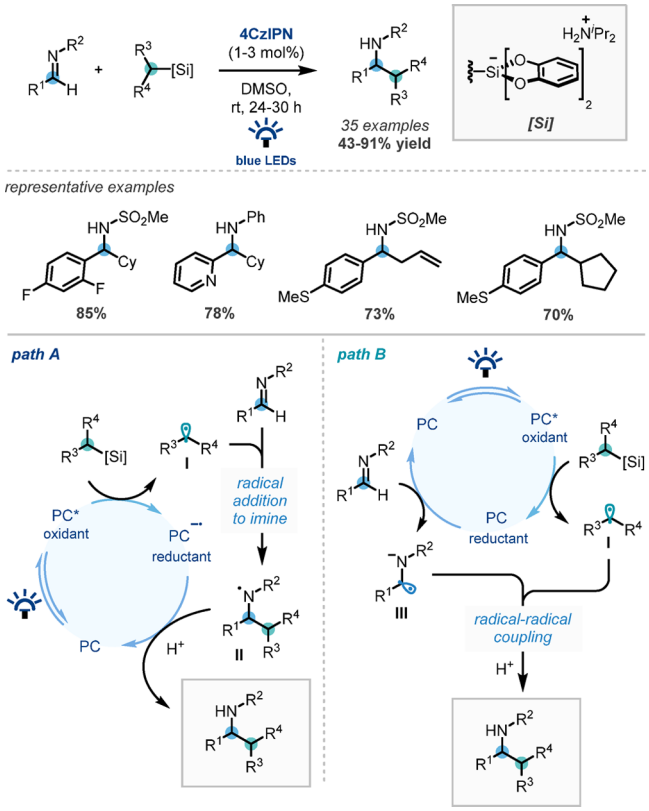
Notably, this methodology was successfully applied to the generation of an α-tertiary amine derivative via reductive coupling of the corresponding ketimine. Mechanistically, this radical–radical cross-coupling is proposed to involve two photocatalytic cycles, with triethylamine playing a pivotal role as both reductant and proton donor.

In the context of imine alkylation, the Yu group disclosed a photocatalytic/Brønsted acid cocatalytic system for efficient C–C coupling (Scheme 12).[34] Alkyl radicals are generated from 4-alkyl-1,4-dihydropyridines (Hantzsch ester derivatives) by single-electron oxidation. These reactive radical intermediates then follow a mechanistic pathway similar to that proposed in Molander's study, whereby the authors suggest either a radical addition or a radical–radical coupling pathway to product formation. Two conditions were reported, one for aldimine derivatives (conditions A) and the other for cyclic isatin-derived imine structures (conditions B). Broad functional group tolerance (including heterocycles) was demonstrated, and importantly the method was also amenable to ketimine alkylation, creating quaternary centers.

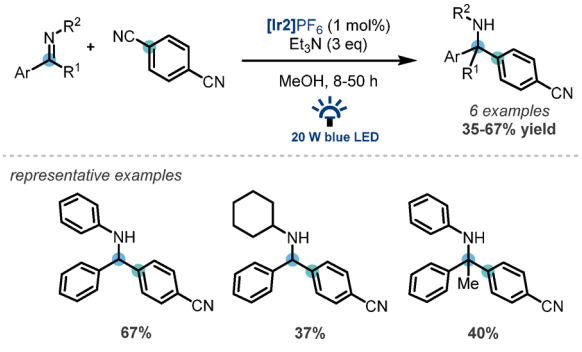
As part of a photocatalytic coupling strategy between *N*-arylamines and aldehydes/ketones, Wang and co-workers also applied these Brønsted acid activated conditions to a small

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009–2025

Scheme 10. Photocatalytic Coupling of Alkyl Silicates and *N*-Sulfonylimine Derivatives



Scheme 11. Photocatalytic Coupling of Imine Derivatives and Dicyanobenzenes

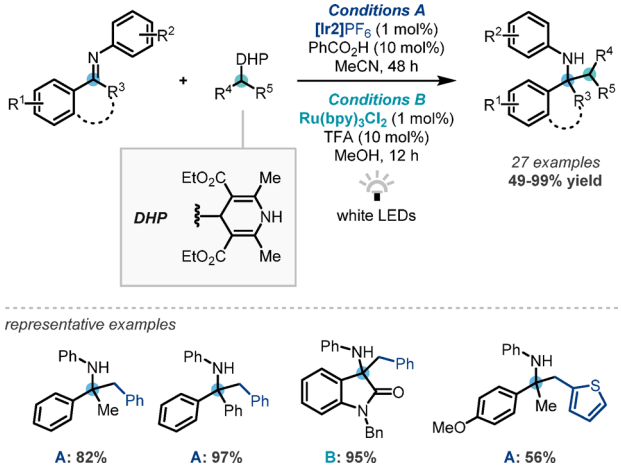


subset of aldimine substrates for the synthesis of vicinal diamines.[35]

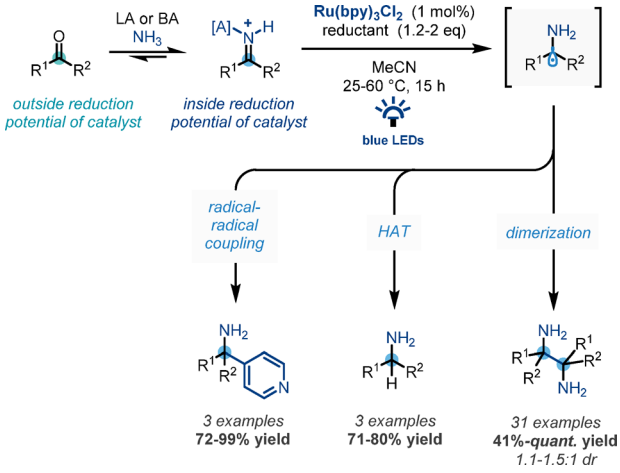
In 2018, Gilmore and co-workers disclosed the formation of α-amino radicals from in situ generated unprotected imines (Scheme 13).[19] This method relies on chemoselective activation of aldehydes/ketones by a Lewis or Brønsted acid in the presence of ammonia (either aqueous or gaseous depending on the subsequent reactivity of the α-amino radical) that are efficiently reduced under photocatalytic conditions to generate key underexplored primary amine α-amino radicals. This novel intermediate was shown to engage in dimerization to generate unprotected vicinal diamines and radical−radical coupling with 4-cyanopyridine and undergo HAT to construct primary amines.

Recently, Dixon and co-workers reported a visible-light-mediated reverse polarity Povarov reaction protocol for the

Scheme 12. Photocatalytic Coupling of Hantzsch Ester Derivatives and *N*-Arylimines



Scheme 13. Using Ammonia in the Photocatalytic Reductive Coupling of Imines

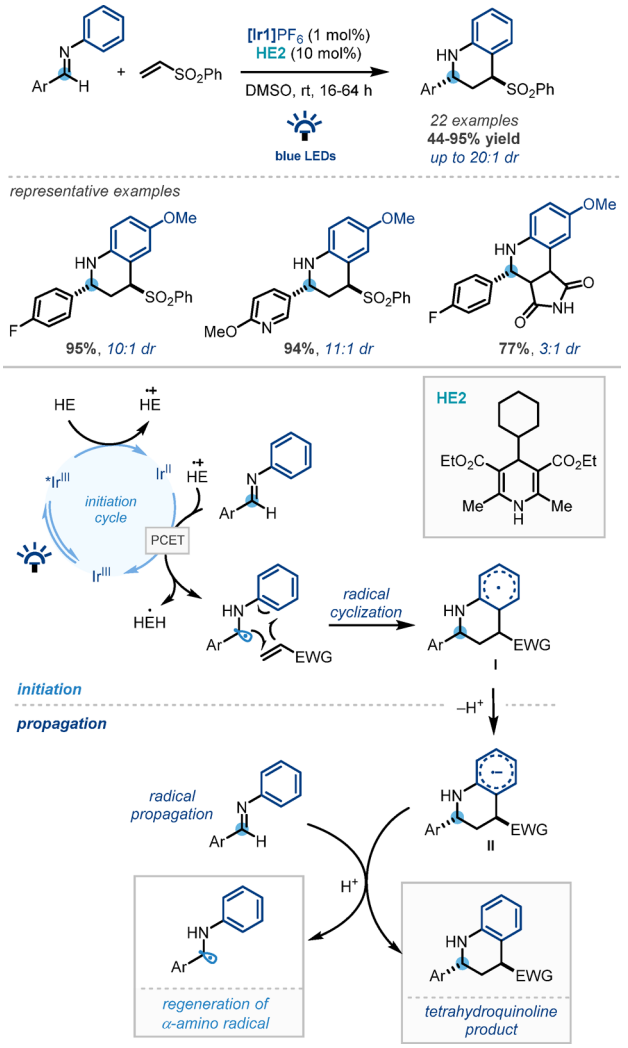


construction of complex tetrahydroquinoline scaffolds from readily available aryl imines and electron-deficient alkenes (Scheme 14).[36] The postulated mechanism involves a photocatalytic initiation cycle with a substoichiometric amount of a Hantzsch ester derivative (HE2) to generate the key nucleophilic α-amino radical via a proton-coupled electron transfer (PCET) process. A radical cyclization cascade of this key α-amino radical with the alkene moiety gives rise to a stabilized radical Povarov intermediate (**I**), with a predominant trans configuration. A radical chain process was proposed (supported by quantum yield calculations),[37] with subsequent facile deprotonation of **I** affording a radical anion intermediate (**II**) capable of reducing the next molecule of the *N*-arylimine, thus delivering the desired product with concomitant regeneration of the α-amino radical. A good scope with a variety of imine derivatives was reported, and reactivity with both vinyl sulfone and maleimide coupling partners was established.

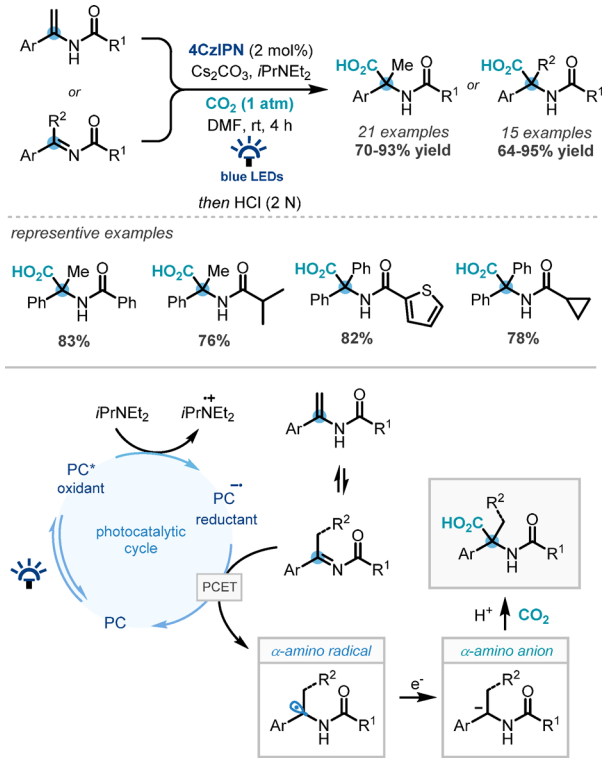
The ability to capture CO_2 as a molecular building block has become an important field in synthetic chemistry in recent years.[38] In the context of photocatalytic imine reduction, a 2018 report from Yu and co-workers disclosed the coupling of imines and CO_2 to afford the valuable α,α-disubstituted α-amino acid scaffold (Scheme 15).[39] This metal-free method is proposed to

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 14. Photocatalytic Reverse Polarity Redox-Neutral Povarov Reaction



Scheme 15. CO_2 Fixation Using Photocatalytic Reductive Imine Chemistry



proceed through two sequential reductive photocatalytic cycles. The first cycle involves reduction of the imine/enamine to give an α-amino radical. In a second cycle, the latter would be fully reduced to a nucleophilic α-amino anion, which traps CO_2 (1 atm) to generate the corresponding α-amino acid after acidic workup. The synthetic utility of this method was demonstrated by derivatization toward pharmaceutically relevant heterocycles such as hydantoins and oxazol-5(4*H*)-ones.

Later in 2018, Fan and Walsh also reported a visible-light-mediated method to synthesize diaryl α-amino acids via umpolung hydrocarboxylation of ketimines (Scheme 16A).[40] Despite the similarity of the reagents and conditions to those described above, the authors proposed an alternative mechanism involving the radical anion intermediates **I** and **II**. Their presented mechanism involved the quenching of the photoexcited iridium(III) species by Cy_2NMe, generating the reducing iridium(II) and the trialkylamine radical cation. C-centered radical anion **I** is then formed via the single-electron reduction of the corresponding ketimine, and its resonance form (*N*-centered radical anion **II**) engages with the amine radical cation in a HAT process to give the key carbanion intermediate **III**. It is believed that this anion reacts with CO_2 to form the carboxylate, which is isolated either as the α-amino ester derivative (following an esterification step) or as the dicyclohexylamine salt. The latter of these methods highlights the utility of this simple protocol in generating important building blocks, without the need for chromatographic purification techniques.

Following on from this report, in late 2018, Fan and Walsh also disclosed the successful trapping of this putative anionic intermediate with aldehydes to create 1,2-amino alcohol structures (Scheme 16B).[41] This transformation was amenable to a variety of imine substrates including heterocyclic and aliphatic examples.

As discussed previously, photocatalytic decarboxylation via the single-electron oxidation of carboxylate salts is an efficient means of producing C-centered radicals.[7] Recently, Lu and co-workers have applied this concept to the formation of benzylated *N*-arylamines (Scheme 17).[42] The key benzyl radical is obtained after SET between the carboxylate anion and the photoexcited iridium(III) species, generating an iridium(II) species capable of reducing aldimine to the corresponding C-centered radical anion. The desired alkylated product is generated via radical−radical coupling followed by a protonation step. The authors ruled out a possible radical-addition pathway into the imine due to the observation of reduced imine and imine dimer byproducts. This simple protocol grants access to a variety of β-arylethylamines from readily available starting materials. Importantly, primary, secondary, and tertiary arylacetic acids were successfully implemented, but the method would not extend to ketimines and alkyl aldimine substrates.

The modification of amino acid structures has important applications in drug discovery and biomolecule synthesis.[43] In late 2018, Dixon and co-workers reported an efficient one-pot photocatalytic umpolung synthesis of valuable 1,3-diamine motifs from aldehyde, aniline, and dehydroalanine derivatives

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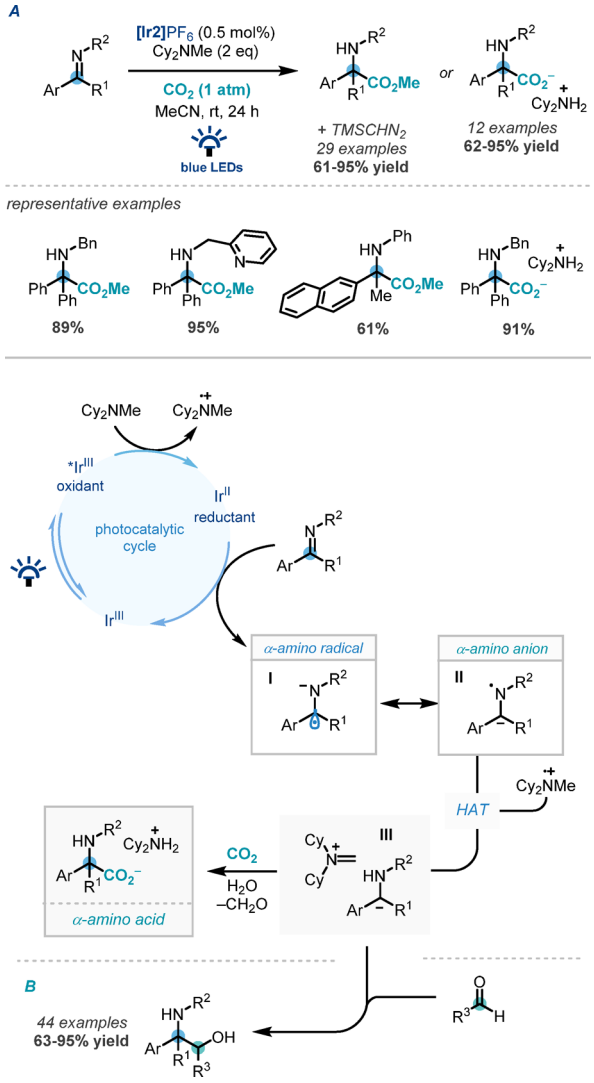
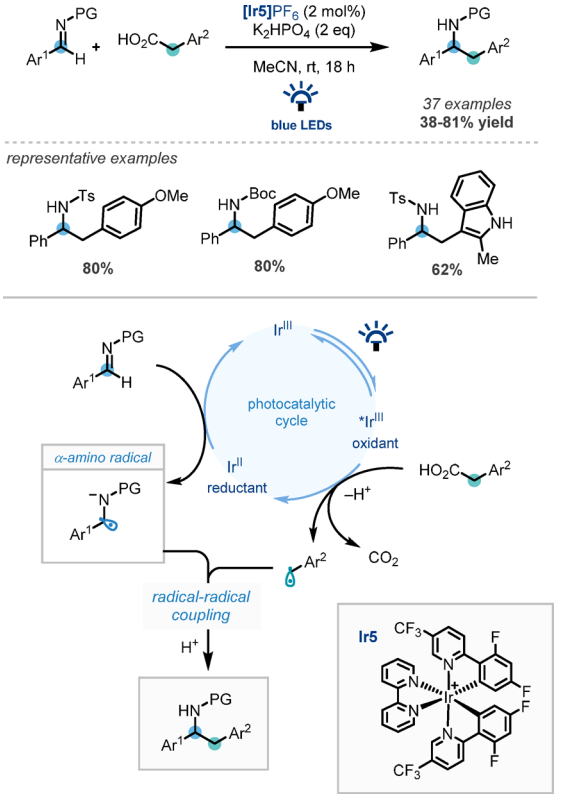
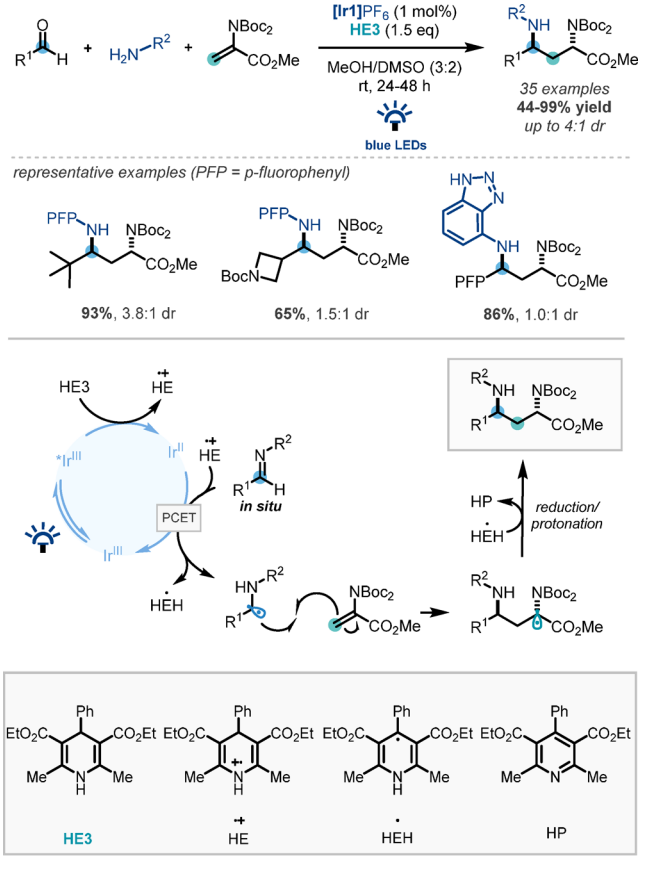
Scheme 16. CO_2 Fixation and Amino Acid Synthesis Using Single-Electron Reduction of Imines



Scheme 17. Decarboxylative Photocatalytic Coupling of Carboxylic Acids and Imine Derivatives



Scheme 18. Three-Component Photocatalytic Construction of 1,3-Diamines



(Scheme 18).[44] This three-component coupling reaction was proposed to take place by reduction of in situ formed imine derivatives to generate the nucleophilic α-amino radical, which are able to engage in Giese-type radical addition reactions with a protected dehydroalanine (DHA) derivative to form 1,3-diamine constructs in moderate to high yields and moderate to good diastereoselectivity. This methodology was shown to be tolerant of a wide range of functionalities with respect to both the aldehyde and the amine coupling partners and demonstrated remarkable efficiency with *N*-containing heterocycles and imines derived from aliphatic aldehydes.

Furthermore, Dixon and co-workers incorporated this same concept of reductive functionalization of imine derivatives, utilizing Hantzsch esters as essential reductants, into their primary amine C−H functionalization platform.[45] The report describes the initial condensation of an α-branched primary amine with a 3,5-di-*tert*-butylquinone derivative, which afforded a key ketimine intermediate (Scheme 19, I).

Although, the majority of the report discloses the trapping of the ketimine intermediate with a range of nucleophiles, it was also shown to be amenable to reverse polarity functionalization. This was achieved through the single-electron reduction of the

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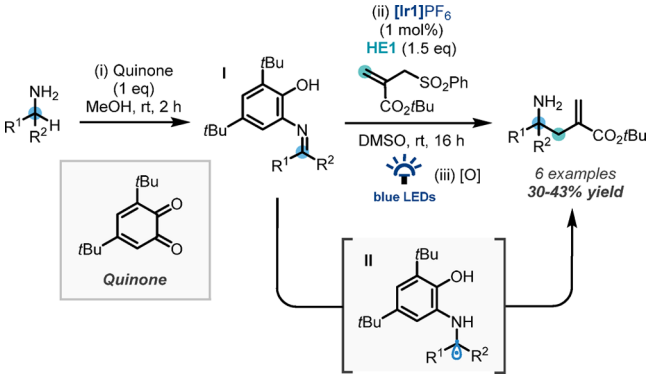
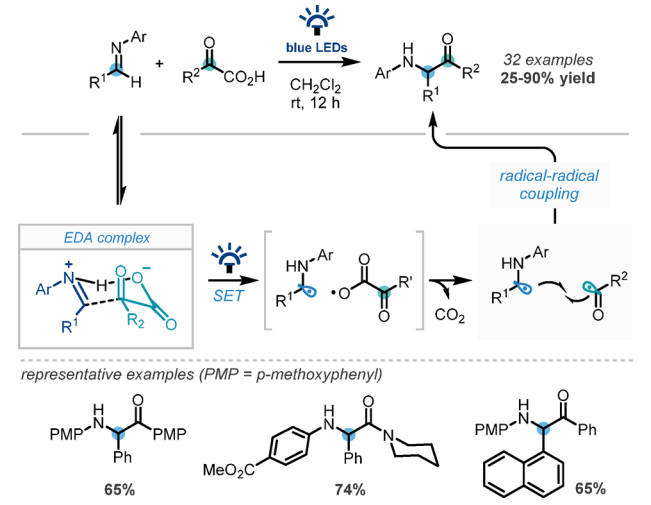
Scheme 19. Synthesis of Primary α-Tertiary Amines via Photocatalytic Reverse Polarity Imine Reduction



Scheme 20. Catalyst-Free Decarboxylative Coupling of α-Keto Acids and *N*-Arylimines via an EDA Complex

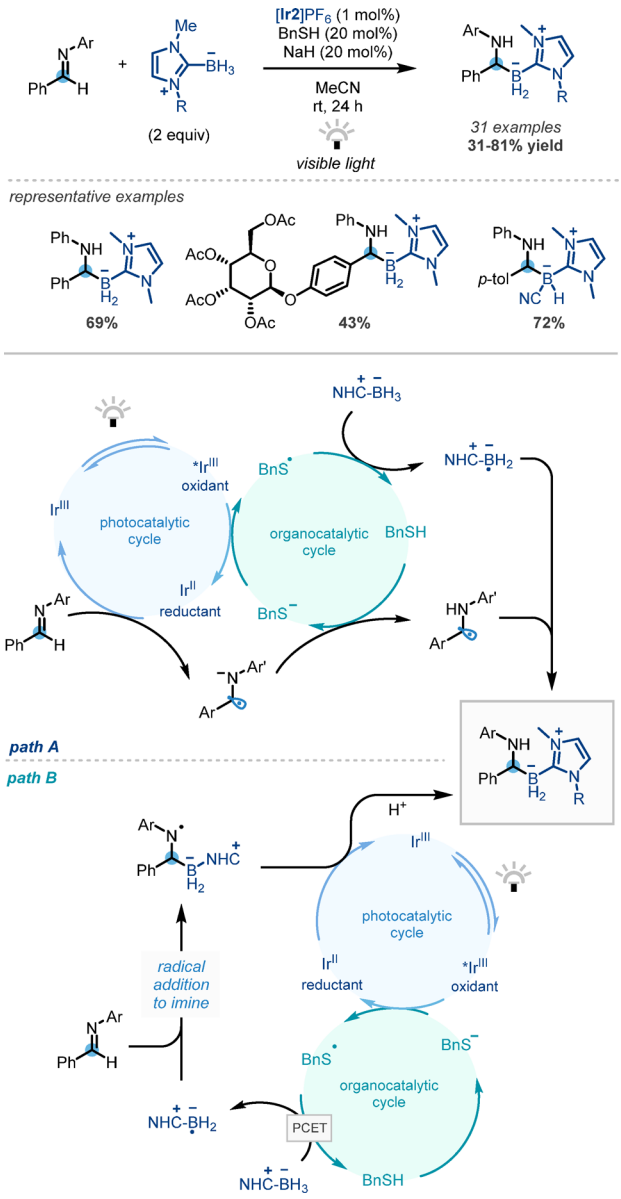


ketimine derivative to the corresponding α-amino radical and subsequent reaction with electrophilic coupling partners. The three-step one-pot protocol allowed for successful α-allylation of α-branched primary amines in modest yields.

All of the investigations discussed up until this point have required the use of a photoredox catalyst to facilitate electron transfer. Conversely, Yu and co-workers have developed an elegant photocatalyst-free procedure for the synthesis of α-amino ketones (Scheme 20).[46] This transformation is proposed to occur via an electron-donor-acceptor (EDA) complex between an aldimine and an α-keto acid. Following absorption of visible light, the EDA complex dissociates into two radical species via single-electron transfer. Decarboxylation of the resulting α-keto carboxy radical generates an acyl radical, and upon radical−radical coupling with the α-amino radical, the desired α-amino ketone was afforded. High functional group tolerance was demonstrated for this mild radical-based acylation protocol, and extension to α-keto amides was also reported. Moreover, a successful one-pot three-component gram-scale protocol was also achieved.

All of the work discussed in this section has centered on the formation of C−C bonds using the single-electron reduction of imine derivatives as the key activation mode. Recent work by Xie and Zhu showcased the application of photoredox catalysis toward inverse hydroboration of imines, through formation of C−B bonds (Scheme 21).[47] Bench stable N-heterocyclic

Scheme 21. Photocatalytic Inverse Hydroboration of Imine Derivatives



carbene (NHC) boranes were used as coupling partners for the transformation, with benzyl mercaptan added as an organic cocatalyst. The thiol is believed to play a crucial role in the reaction, acting as a reductive quencher in the photocatalytic cycle, as well as participating in a PCET event with the imine substrate to generate the α-amino radical intermediate. Moreover, it activates the NHC-borane, which can undergo a radical−radical C−B cross coupling with the α-amino radical to give the final product (path A, Scheme 21). Otherwise, the boron-centered radical can add directly to the imine, with the resulting intermediate further reduced by the iridium(II) species to give the same result (path B, Scheme 21). This strategy was successfully applied to the late-stage borylation of biologically relevant compounds such as estrone and several derivatives of glucose. Although other boranes were found to be incompatible with the reaction system, Xie and Zhu demonstrated that the hydroboration products could be easily converted into α-amino boronates upon hydrolysis. These compounds, in turn, represent an underexplored class of

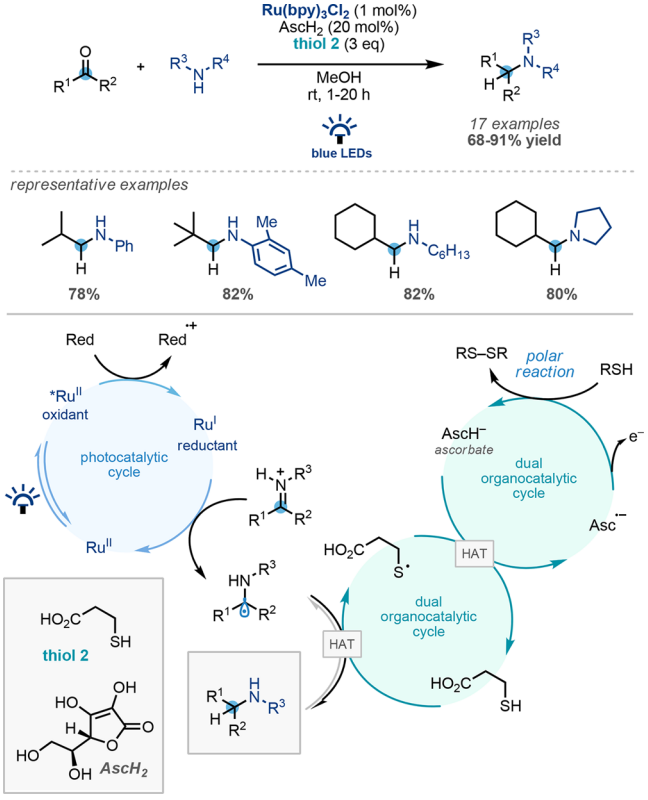
DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

potentially bioactive compounds and can provide further access to medicinally relevant molecules.

VI. APPLICATION TO PHOTOCATALYTIC REDUCTIVE AMINATION

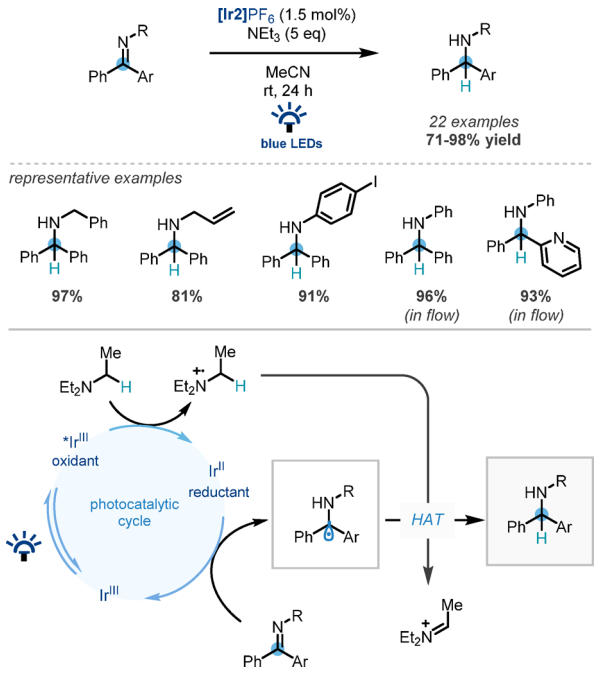
One of the most widely used amine-generating transformations is the reductive amination of carbonyl derivatives. Often the methods deployed necessitate the use of stoichiometric nucleophilic hydride sources, and issues of chemoselectivity can arise.[48] There are obvious benefits in carrying out this ubiquitous chemical manipulation using milder conditions, and recently photocatalytic techniques have begun to emerge.

Scheme 22. Photocatalytic Reductive Amination Utilizing Thiols as the Hydrogen Source

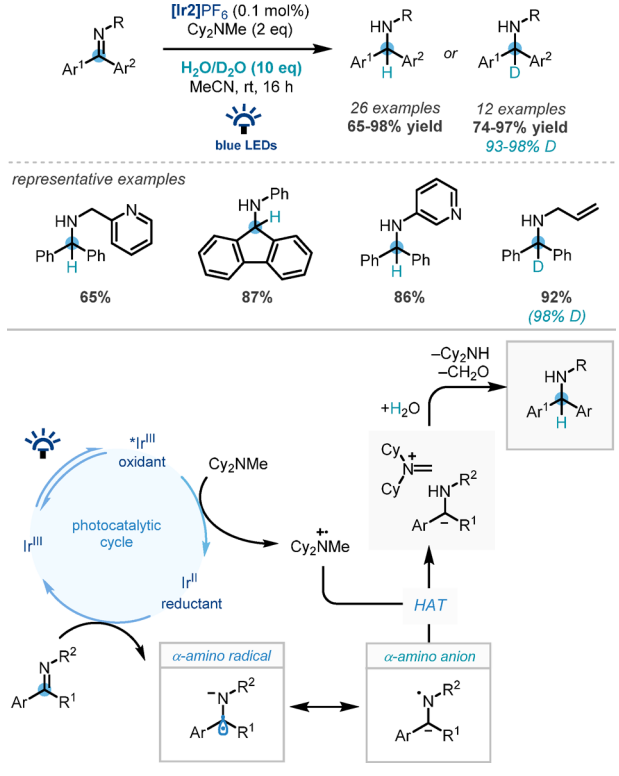


In early 2018, Wenger and co-workers reported the reductive amination of a broad range of aldehydes and ketones, utilizing a polarity-matched hydrogen atom transfer reaction to deliver the reduced amine product from a photocatalytically generated α-amino radical (Scheme 22).[49] Notably, the authors disclose the formation of a tertiary amine product, derived from the corresponding dialkyliminium ion. This observation constitutes the first reported example of the photocatalytic single-electron reduction of iminium ions to the corresponding α-amino radical. Preliminary studies found that the addition of traditionally used sacrificial donors such as thiols, tertiary amines, and ascorbic acid did not yield the desired product. However, the combination of an excess of 3-mercaptopropionic acid (MPA, thiol 2) with catalytic amounts of ascorbic acid (20 mol%) led to formation of the desired secondary amine in good yields. Interestingly, ascorbic acid was not consumed during the course of the reaction. Given this experimental observation, Wenger proposed a dual organocatalytic cycle operating in tandem with the photoredox step.

Scheme 23. Photocatalytic Reduction of Imine Derivatives Using Triethylamine



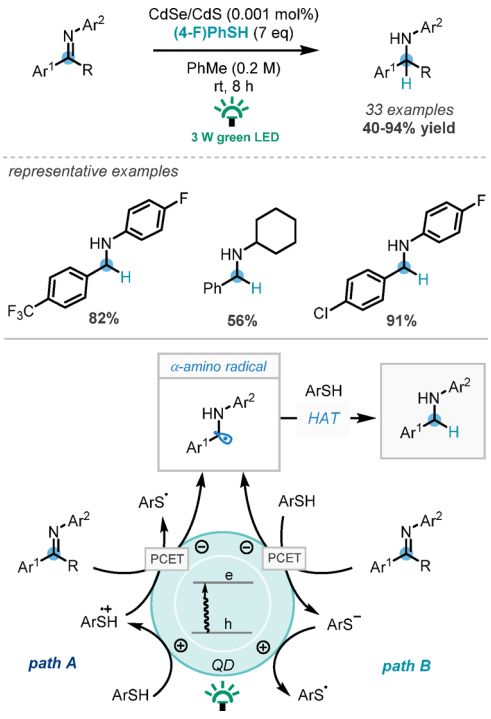
Scheme 24. Photocatalytic Reduction of Imines Using Cy_2NMe and Water



Following the reduction of a protonated iminium species (formed in situ, most likely facilitated by the 3-mercaptopropionic acid) by the Ru(I) species, the resulting α-amino radical intermediate then abstracts a hydrogen from the thiol to give the final product. The authors suggest that the thiol is re-formed through an HAT event with ascorbate. Subsequent oxidation of the ascorbate radical anion and polar reaction with an

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

Scheme 25. Photocatalytic Reduction of Imines via Transfer Hydrogenation Using Quantum Dots as Catalysts



additional 1 equiv of MPA leads to full recovery of the ascorbate anion and consumption of the thiol. Although the entity responsible for activating the ruthenium photocatalyst was not specified, control experiments suggest that MPA is a poor reductive quencher of the photoexcited ruthenium(II) intermediate. Hence, ascorbic acid, and its corresponding intermediates, are important for the proper functioning of both the photo- and organocatalytic cycles. The utility of this transformation was also exemplified by applications in photopatterning of cellulose-derived materials.

Contemporaneously with this report, Polyzos and co-workers reported a similarly elegant reductive amination, wherein a simple tertiary amine functions as both a photocatalytic quencher and a hydrogen source (Scheme 23).[50] The study revealed that numerous amine donors, such as triethylamine, DIPEA, and tributylamine, were amenable to the reaction conditions. Furthermore, the diarylamine substrate scope tolerated a wide range of electron-rich and electron-deficient functionalities to give the desired products in excellent yield. The authors were able to demonstrate potential large-scale applications of their methodology by performing the reaction on a gram scale in a flow reactor. For all 10 examples, no loss in yield or reaction efficiency was observed in their flow system.

Later in 2018, Fan and Walsh reported their reductive amination protocol enabled by tertiary amines and water (Scheme 24).[51] The authors also demonstrated the application to the synthesis of α-deuteroamine structures when D_2O was used in the reaction mixture. In comparison to previous alternatives that use expensive metal-based deuterides, this is an attractive feature of this chemistry. Similarly to Polyzos's reported conditions, Fan and Walsh employed a tertiary amine (Cy_2NMe in this case) as a reductive quencher for the photocatalytic cycle. It was suggested that the reduced photocatalyst then delivers an electron to an imine substrate in a single-electron-transfer process to deliver the α-amino radical anion. They then propose a mechanism similar to that discussed in their CO_2 fixation work above.[40] Here, in the final step, water is proposed to deliver the proton at the α-position.

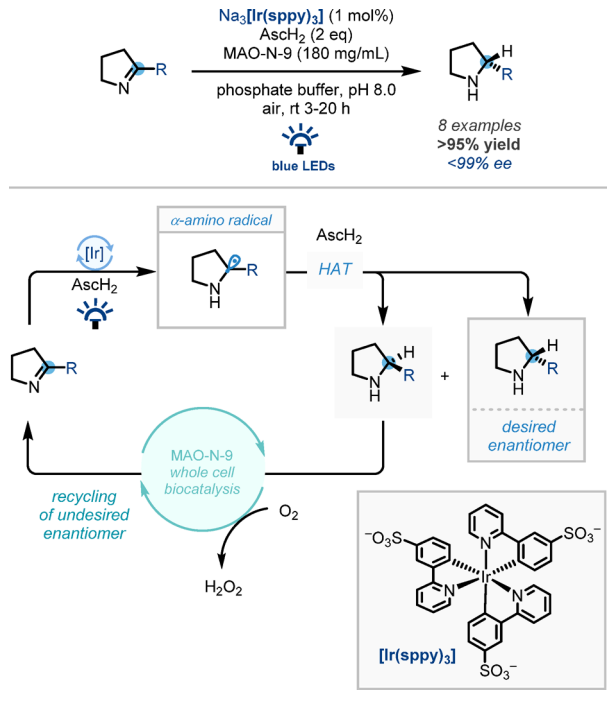
Given their ideal physicochemical properties, quantum dots (QD) have recently emerged as a new class of photocatalysts that have increasingly been applied to synthetic organic transformations.[52]

In one such example, Pu and Shen have demonstrated that CdSe/CdS core/shell QDs could successfully catalyze the photochemical reduction of *N*-arylimines with efficacy comparable to that of commonplace transition-metal-based photocatalysts (Scheme 25).[53] Upon irradiation with green light, electrons are excited to the conduction band of the QD, where they can reduce the imine substrate in a PCET event assisted by 4-fluorothiophenol (path B, Scheme 25) or its thiyl radical derivative (path A, Scheme 25). The resulting α-amino radical intermediate performs a HAT from a second equivalent of thiol to give the final secondary amine product. As well as acting as a proton source for the overall transformation, the thiol acts as a reductant, pumping electrons back into the system, thereby closing the cationic hole created upon imine reduction and regenerating the QD photocatalyst in the process. The broad scope and tolerance of both electron-donating and electron-withdrawing functionalities on both sections of the imine substrates by the QD-based photocatalytic cycle showcases the viability of using these colloidal nanocrystals in the exploration of visible-light-driven synthetic transformations.

VII. EXPLORATION IN ENANTIOSELECTIVITY

Achieving stereocontrol in photochemical methodology has been an area of extensive exploration in recent literature reports.[9b,54] Following Ooi's landmark report on the highly enantioselective coupling of imines and amines (Scheme 6),[17] in 2018, Ward, Wenger, and co-workers presented a novel

Scheme 26. Photoredox/Enzymatic Dual Catalytic System for Enantioselective Reduction of Imine Derivatives



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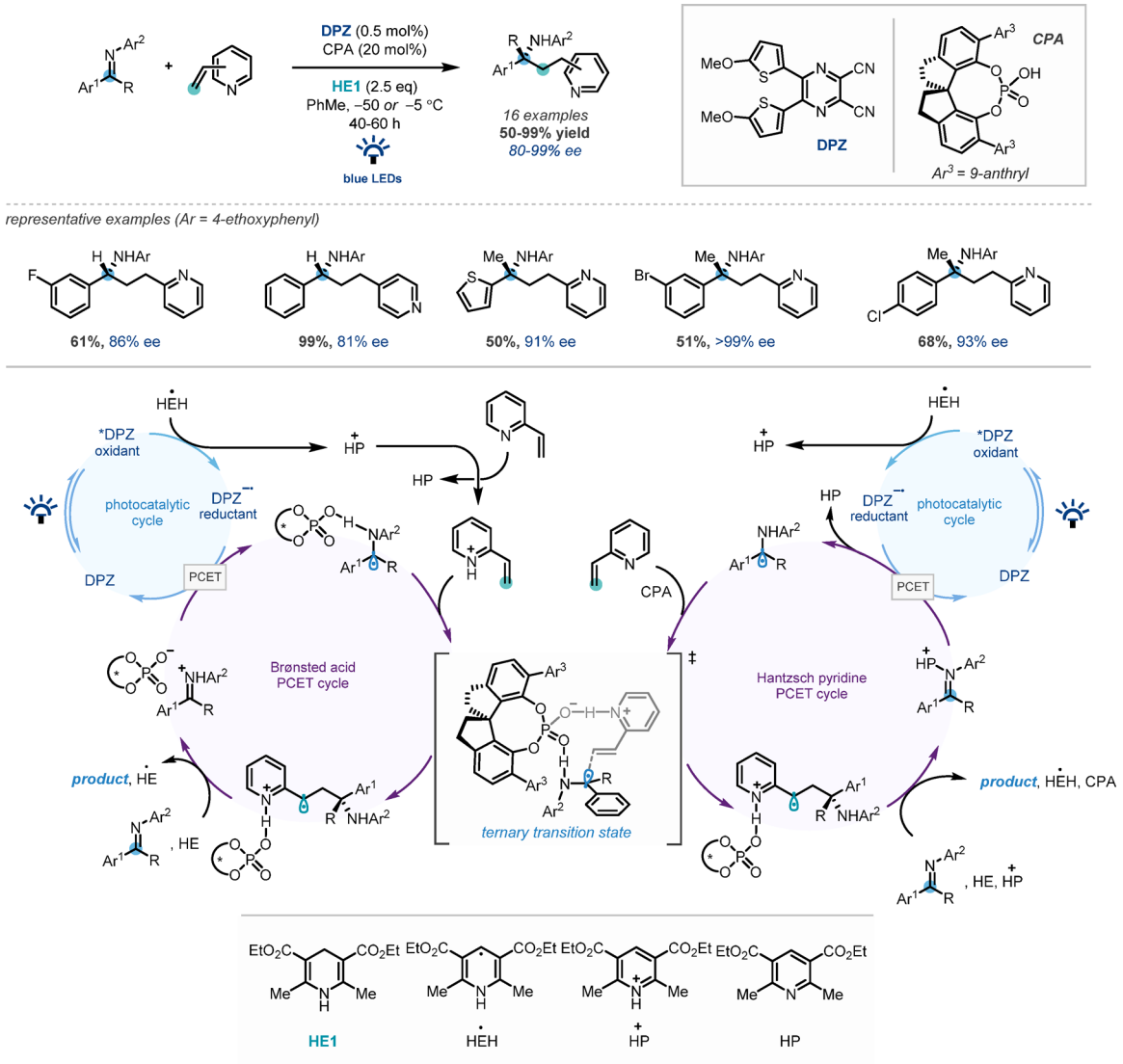
Scheme 27. Enantioselective Reductive Coupling of Prochiral Imine-Derived α-Amino Radicals and Vinylpyridines



approach that combined photoredox and enzymatic catalysis in one pot to synthesize chiral amines (Scheme 26).[55] The authors proposed an unprecedented cyclic reaction network in an aqueous environment to achieve the overall goal of enantioselective imine reduction.

The cyclic imine precursor is reduced (via an α-amino radical and a HAT event) using the water-soluble $Na_3[Ir(sppy)_3]$ photocatalyst ($E^{\circ}_{1/2}$ = −1.89 V vs SCE) to give a racemic mixture of substituted pyrrolidine products. However, the monoamine oxidase (MAO-N-9) enzyme then selectively reoxidizes the (*S*)-amine enantiomer back to the imine, which passes through the photocatalytic cycle once again. This technique allowed for the effective build-up of the *R* enantiomer in solution. Since the enzyme was contained within the cytoplasm of an *E. coli* cell, a spatial separation of the photoredox and biocatalytic processes eliminated any concerns of mutual catalyst inactivation. Although high yields and enantioselectivity were largely limited to alkyl-substituted pyrrolidine examples, this report highlights the value of the dual photoenzymatic concept in the future exploration of such asymmetric catalytic systems.

A further technique to access enantioenriched products via this reductive imine manifold was achieved in 2019 by Jiang and co-workers (Scheme 27). In this report of an enantioselective α-amino radical Giese-type addition,[56] Jiang drew on Ngai's previously mentioned addition to vinylpyridines, which required Lewis acid activation (Scheme 9).[29] Employing a similar mode of activation, Jiang used a chiral phosphoric acid as an activator to lower the LUMO of the vinylpyridine, affording chiral γ-aminopyridines in good to excellent enantioselectivity. Interestingly, Jiang's mechanistic studies revealed two possible PCET mechanisms: the first with the chiral phosphoric acid enabling the PCET and the second with the Hantzsch pyridine cation (HP^+), corresponding to mechanisms posited by Knowles[57] and Ngai,[30] respectively. Regardless, both mechanistic pathways arrive at the same computationally elucidated enantiodetermining transition state, in which the chiral phosphoric acid is bound to the two nitrogen atoms on the pyridine and the protonated α-amino radical by hydrogen-bonding interactions.

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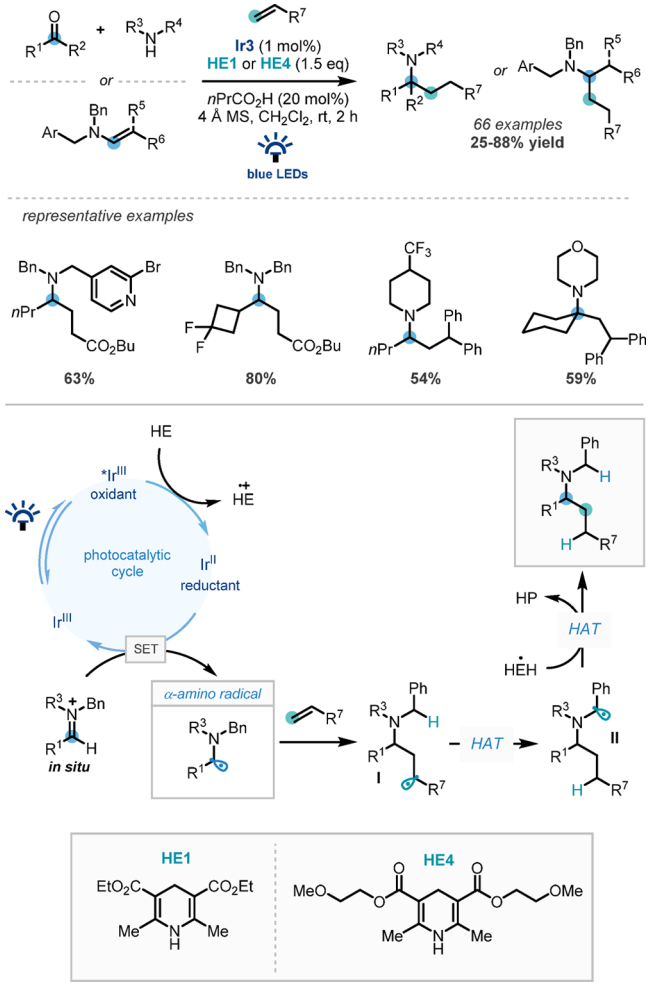
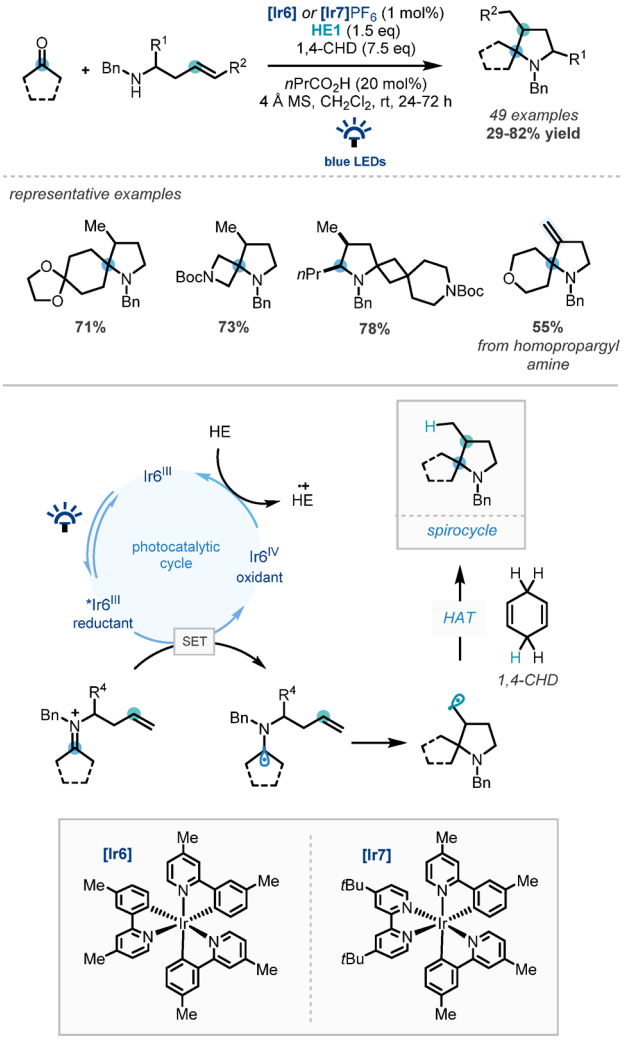
Scheme 28. Photocatalytic Reductive Coupling of Iminium Ions and Alkenes



Scheme 29. Photocatalytic Synthesis of Spirocyclic Amines via the Single-Electron Reduction of Iminium Ion Derivatives



VIII. EXTENSION TO IMINIUM IONS

The majority of the previous examples have focused on the formation of α-amino radical species derived from imines, formed primarily by the condensation of primary amines and anilines with aldehydes or ketones, thereby resulting in secondary amine reaction products. However, iminium ion derived α-amino radicals could also be used to form complex tertiary amine architectures (for a previous standalone example, see Scheme 22).

In 2018, Gaunt and co-workers presented an array of iminium- and enamine-derived α-amino radical additions to conjugated alkenes (Scheme 28).[58] In line with prior reports, the authors suggest that a photoexcited iridium(III) catalyst is initially quenched by a Hantzsch ester reductant (either HE1 or HE4 depending on the isolation procedures) to deliver the Hantzsch radical cation and a highly reducing iridium(II) species ($E^{\circ}_{1/2}$ = −2.19 V vs SCE). The authors propose that this catalytic species can reduce an iminium ion (generated through in situ formation or from protonation of the corresponding enamine) to the nucleophilic α-amino radical via a SET process. These species then efficiently engage in Giese-type additions to conjugated olefins to form a variety of α-branched tertiary amines.

Importantly, control experiments, deuterium incorporation studies, and analysis of byproducts elucidated that the addition adduct (**I**) undergoes a 1,5-HAT event to give the α-amino radical (**II**), which is subsequently quenched by the HEH$^{\bullet}$ intermediate in a further HAT event to give the product. A second route to the product via oxidation of **II** to give a secondary iminium intermediate which can then be reduced via one- or two-electron pathways was also postulated. The authors disclosed a substantial scope of imine substrates and coupling partners, including acrylates, vinyl sulfones, di(hetero)-arylethylene, dehydro-amino acid derivatives, and alkyne structures.

Building on this work, Gaunt and co-workers subsequently reported that the alkene acceptor motif can be tethered to the dialkyl amine, thereby allowing the formation of interesting and topical *N*-heterospirocyclic products via intramolecular cyclization (Scheme 29).[59] Whereas the previous study used conjugated alkenes as Giese-type acceptors, this work describes the use of unactivated alkenes, and high yields of the spirocyclic products were obtained when a more reducing iridium photocatalyst and a sacrificial HAT donor (1,4-cyclohexadiene, 1,4-CHD) were used.

Quenching studies on Ir6 revealed that this catalyst system proceeded via an oxidative quenching cycle. A photoexcited iridium(III) ($E^{\circ}_{1/2}$ = −1.86 V vs SCE) species performs an SET

DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025

reduction on the iminium ion to deliver the α-amino radical and a resulting iridium(IV) species, which is subsequently reduced back to the ground state by the Hantzsch ester. This α-amino radical then undergoes a 5-*exo*-*trig* cyclization to afford the primary radical, which is converted to the methyl group on hydrogen abstraction from 1,4-cyclohexadiene. Altogether, this transformation was successful in constructing diverse and challenging heterocyclic architectures, and interestingly, the use of tethered alkynes delivered the exocyclic alkene product.

IX. CONCLUSION

The single-electron reduction of imine derivatives has been demonstrated to be an emerging and potentially powerful tool in the creation of α-amino radicals, which can be manipulated into complex amine-containing architectures. These α-amino radicals have been demonstrated to partake in radical−radical coupling, reaction with electrophilic acceptors, fixation of CO_2, and hydrogen abstraction, enabling reductive amination chemistry. Furthermore, this concept has been expanded to include enantioselective synthesis and utilized in iminium ion reduction for the synthesis of decorated tertiary amines and spirocycles. A substantial increase in method development in this field has been witnessed over the last five years, and the stage is set for further exploration into more challenging acceptors, generalization of enantioselective variants, and the construction of complex ring structures through radical cascades.[60] These new directions promise to allow the photochemical single-electron reduction of imines to productive α-amino radicals to become a routine umpolung disconnection in small-molecule and natural product syntheses alike.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

J.A.L. thanks the Leverhulme Trust (RPG-2017-069) for a research fellowship. T.Rossolini wishes to thank Astex Pharmaceuticals, Ltd., for generous financial support. T.Rogova is supported by the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB, and Vertex. T.Rogova also thanks the Royal Commission of 1851 Industrial Fellowship and NSERC PGS-D. J.A.P.M. wishes to thank AstraZeneca for a studentship.

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DOI: 10.1021/acscatal.9b05011
ACS Catal. 2020, 10, 2009−2025