Reductive amination and enantioselective amine synthesis by photoredox catalysis

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**Abstract:** Photochemistry usually functions on a one-photon-one-electron basis, leading to unstable radical intermediates that must be intercepted rapidly to allow efficient product formation. This can render multi-electron reductions and enantioselective reactions particularly challenging. In this minireview, we discuss recent advances in the area of photodriven multi-electron transfer with a particular focus on our own work on reductive amination and the enantioselective synthesis of amines via combined photoredox and enzyme catalysis. Polarity-matched hydrogen atom transfer (HAT) between photochemically-generated α-amino alkyl radicals and thiols is a key step in these reactions. A cyclic reaction network comprised of light-driven imine reduction by an Ir-photocatalyst and enantioselective amine oxidation by the enzyme monoamine oxidase (MAO-N-9) was used to obtain enantioenriched amines from imines.

1. Introduction

Reductive amination of carbonyl compounds is one of the most widely used methods for the synthesis of amines. Traditional approaches often rely on hydride sources such as NaBH3CN, which are toxic as well as air and moisture sensitive.[1] There have been significant efforts to use alternative reducing agents including molecular hydrogen,[2] silanes,[3] formates,[4] and Hantzsch esters,[5] but photochemical approaches to reductive amination are yet very scarce. Recently, there has been significant progress in this area, as presented in the first half of this minireview.

Many pharmaceuticals, agrochemicals, and natural products contain chiral amines, and chiral amines may serve as ligands in asymmetric catalysis or as reagents for kinetic resolution in organic synthesis. Accordingly, enantioenriched chiral amines represent very attractive and important synthetic targets. Whilst traditional methods such as for example the asymmetric hydrogenation are very well developed,[6] there are yet comparatively few photochemical approaches. Enantioenriched products are particularly challenging to obtain photochemically,[7] but important progress was achieved recently by using a combination of photoredox and enzyme catalysis in cascade reactions. The second part of this minireview is devoted to such catalytic networks, with particular focus on the synthesis of enantioenriched amines from imines.



**Scheme 1.** (a) Traditional (thermal) reductive amination and its photochemical analogue. (b) Relevant bond dissociation energies (BDEs). (c) Mechanism for interception of α-amino alkyl radicals via polarity-matched HAT.[8]

2. Photochemical reductive amination

The first method for reductive amination by photoredox catalysis was reported only very recently.[8] The photochemical point of attack is the iminium species formed from condensation of the carbonyl and amine substrates in equilibrium (Scheme 1a). Iminium cations have reduction potentials that are readily within striking range of many transition metal-based photocatalysts such as the commonly used [Ru(bpy)3]2+ (bpy = 2,2’-bipyridine) or [Ir(ppy)3] (ppy = 2-(phenyl)pyridine) complexes and their derivatives,[9] hence the light-driven reduction of iminium cations to α-amino alkyl radicals is straightforward. The key challenge is to intercept these unstable intermediates in an efficient manner by hydrogen atom transfer (HAT), to reduce them to the alkylated amine before unproductive reverse or side reactions occur.

Ascorbate quenches photoexcited [Ru(bpy)3]2+ reductively to yield [Ru(bpy)3]+,[10] and the latter is a sufficiently strong electron donor to produce α-amino alkyl radicals from iminium cations. However, whilst ascorbate is a commonly used hydrogen atom donor, its reaction with α-amino alkyl radicals is slow because the latter are electronic rich, nucleophilic species and ascorbate is an anion. Consequently, when merely using ascorbate as reductant and as an H-atom source, the photochemical reductive amination is very inefficient and produces only modest yields, despite the considerable driving-force (ca. 16 kcal/mol) for the relevant HAT step (see pertinent bond dissociation energies (BDEs) in Scheme 1b).[8]

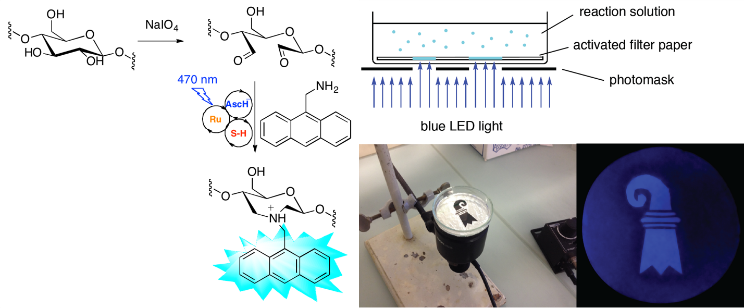


**Scheme 2.** Selection of products accessible via photochemical reductive amination. See ref. [8] for full reaction scope.

Thiols are electrophilic H-atom donors, and should therefore react more rapidly with nucleophilic α-amino alkyl radicals. However, there is essentially no driving-force for HAT from a thiol such as mercaptopropionic acid (MPA) to α-amino alkyl radicals (compare relevant S-H and C-H BDEs in Scheme 1b), making this a reversible process. Consequently, no product accumulates when using MPA as the sole reductant and H-atom source along with [Ru(bpy)3]2+.

However, the combination of ascorbate and MPA is successful, because both effects described above can be exploited (Scheme 1c): Initial HAT between the thiol donor and the α-amino alkyl radicals is fast because it is polarity-matched. The thiyl radicals formed in this process react with ascorbate in another polarity-matched HAT before they undergo the undesired reverse reaction (dashed arrows in Scheme 1c) with the alkylated amine product. Experiments with a radical clock-type substrate support the mechanism in Scheme 1c by demonstrating that the polarity-matched HAT to α-amino alkyl radicals from MPA is considerably faster than non-matched HAT from ascorbate.[8] The concept of polarity-matched HAT has long been known,[11] and has also been exploited in other recent photoredox studies.[12] Interestingly, the terminal oxidation product of the MPA / ascorbate combo is the disulfide form of MPA, and it seems plausible that initially formed dehydroascorbate oxidation product is reduced back to ascorbate by MPA under formation of the respective disulfide (not shown in Scheme 1c). This leads to a situation in which ascorbate can be used in sub-stoichiometric quantities for the photochemical reductive amination.

The typical reaction conditions therefore involved equimolar quantities of carbonyl compound and amine substrate, 3 equivalents of MPA, 20 mol % of ascorbate, and 1 mol % of [Ru(bpy)3]Cl2 in methanol at room temperature.[8] Continuous irradiation of such mixtures at 470 nm with an LED (ca. 14 W) over 1 to 20 hours led to very good yields for most of the explored substrates (a few examples are given in Scheme 2). The reaction scope includes both aldehyde and ketone substrates combined with aromatic and aliphatic amines.[8] Most of the reactions were performed on a 0.5 mmol scale, but the gram-scale amination of pivaldehyde with L-tryptophan methyl ester was readily possible with extended irradiation time (30 hours) and occurred under complete retention of enantiopurity.



**Scheme 3.** Photopatterning on activated cellulose support (filter paper) by reductive amination with a fluorescent anthracene marker.[8]

The photochemical reductive amination can be performed on activated cellulose supports, prepared via treatment of commercial filter paper with NaIO4.[8] Exposed carbonyl groups of the cellulose support were reductively aminated with a fluorescent marker to display the possibility of spatial reaction control. For this purpose the filter paper was set into a Petri dish, layered with a reaction mixture containing 9-(aminomethyl)-anthracene, ascorbate, MPA, and [Ru(bpy)3]Cl2. Irradiation with blue light from the bottom through a photomask (made from aluminum foil) permitted spatial reaction control. After washing the reaction mixture off, the anthracene-labeling of the filter paper became readily detectable under UV light (Scheme 3).

More recently, yet another method for photochemical reductive amination was reported.[13] In this case, Ir photocatalysts were employed to access α-amino alkyl radicals via oxidation of an aminal species formed in a pre-equilibrium condensation reaction (Scheme 4a). For some substrates, the α-amino alkyl radical intermediate could be converted to a benzylic anion by the one-electron reduced Ir photocatalyst, but those radicals with too negative reduction potentials had to be intercepted by HAT with an aromatic thiol H-atom donor. B2O3 was used as additive, which likely acts as a Lewis acid and desiccant. The reaction scope included both electron-rich and electron-deficient aromatic aldehydes. Suitable amine reaction partners included morpholine, thiomorpholine, piperidines, Boc-protected piperazine, and pyrrolidines. Acyclic amines were unsuitable.



**Scheme 4.** (a) Photoredox-catalyzed reductive amination via oxidation of *in situ* formed aminal species.[13] (b) Sequence of photoinduced PCET and thermal HAT converting imines to amines with CdSe/CdS core-shell quantum dots as photocatalysts.[14]

A recent study reported on the photocatalytic reduction of imines to amines using CdSe/CdS core-shell quantum dots at loadings of 0.001 mol % as photocatalysts (Scheme 4b).[14] A broad range of aldimines and ketimines were easily reduced under photoirradiation in presence of thiophenols. Imine reduction by the photoexcited quantum dots is thermodynamically unfavorable by ca. 0.8 eV, and therefore the authors speculated that the photoinduced electron transfer from the quantum dots to the imine substrate is proton-coupled with thiophenol serving as proton source. This mechanistic proposal seems plausible given other recent studies, which found that proton-coupled electron transfer (PCET) with photoexcited CdS enabled the reduction of nitrobenzene to aniline.[15] The presumed PCET products here are α-amino alkyl radicals, which are then converted to amines by HAT from thiophenol (Scheme 4b),[14] in analogy to the reductive amination methods discussed above.[8, 13]

Motivated by the prospect of performing chemoselective imine reduction in the presence of functional groups typically susceptible to reduction under traditional hydrogenation conditions, Polyzos and coworkers developed a photocatalytic transfer hydrogenation method for diarylimines.[16] Interestingly, this reaction relies on triethylamine as both a single-electron donor and H-atom donor (Scheme 5a) without the need for thiols. HAT to the carbon-centered radical intermediate occurs from the aminium radical cation (Et3N·+) which results from the initial reductive excited-state quenching step with the photocatalyst. Et3N·+ has a very low N-H BDE (ca. 42 kcal/mol), and deuterium-labeling studies with Et3N-d15 confirmed that this reductant also acts as H-atom source. The [Ir(ppy)2(dtbpy))]+ complex (ppy = 2-(phenyl)pyridine, dtbpy = 4,4’-di-*tert*-butyl-2,2’-bipyridine) was the most efficient photocatalyst, allowing the efficient synthesis of a range of benzhydrylamines that are key structural motifs in opioid receptor agonists, dopamine transporter ligands, and histamine H1 antagonists. Importantly, the anticipated chemoselectivity for imine reduction was indeed observed in the presence of ketone, ester, and nitrile groups, which would typically undergo reduction when subjected to transfer hydrogenation or hydrosilylation conditions. A flow chemistry approach permitted effective scale-up and significantly shorter reaction times.



**Scheme 5.** (a) Hydrogenation of diarylamines using Et3N as combined SET and H-atom donor; PC = photocatalyst.[16] (b) Photoredox-mediated access to primary amine α-amino radicals leading to reductive dimerization or reductive amination in the presence of Lewis (LA) or Brönsted acids (BA).[17] (c) Visible-light driven ketimine reductions with proton abstraction from water as a key step.[18]

Whilst the abovementioned photoredox methods for reductive amination gave access to secondary and tertiary amines,[8, 13] Gilmore and coworkers recently developed a chemoselective photoredox synthesis of unprotected primary amines (Scheme 5b).[17] Toward this end, N-H imines were generated in situ from ammonia and aldehydes or ketones. A key challenge in this respect was the fact that ammonia is less nucleophilic than primary amines, resulting in a slow equilibrating condensation. This can cause problems because typical carbonyl substrates are more readily reduced the then N-H ketamines, leading to ketyl radical anions (and subsequently functionalized alcohols) rather than the desired α-amino carbon radicals. This was successfully counteracted by using Lewis or Brönsted acids, making the N-H imine more energetically favorable to reduce than the respective ketone. Using [Ru(bpy)3]2+, *i*Pr2NEt, Sc(OTf)3 and NH3 in MeOH/MeCN, a broad range of (hetero)aromatic aldehydes were efficiently reduced to primary 1,2-diamines in a formal dimerization reaction (Scheme 5b, downward arrow). Aliphatic aldehydes, by contrast, were not suitable substrates, presumably because the respective α-amino carbon radicals are not sufficiently stable. For similar reasons, the reductive dimerization proceeded better with aryl and alkyl ketones than with aromatic aldehydes. Adapting the conditions to include thiophenol as an H-atom donor permits reductive amination (Scheme 5b, far right). For this purpose, Hantzsch ester instead of *i*Pr2NEt was used, and TFA was employed instead of Sc(OTf)3.

Walsh, Fan, and coworkers reported on visible-light driven ketimine reductions that were claimed to involve a novel carbanionic reactivity of imines (Scheme 5c).[18] After initial reductive quenching of photoexcited Ir complexes by Cy2NMe (Cy = cyclohexyl), electron transfer from the reduced photocatalyst to the imine substrate produces an imine radical anion for which two resonance forms can be drawn. Prior photoredox studies involved primarily the resonance form A with the C-centered radical (leading to formal dimerization products) whereas here the authors specifically sought to exploit the carbanionic resonance form B. For this purpose, the focus was set to benzophenone ketimines to better stabilize that carbanionic form by delocalization of the negative charge over two aryl groups. Photocatalyst loadings as low as 0.1 mol % were sufficient for efficient reduction of various benzophenone-based ketimines to amines. Two mechanistic options were considered, including the reaction of resonance form A (or its protonated analogue resulting from PCET) with [Cy2NMe]·+ as an H-atom donor to the carbon-centered radical. However, experiments in D2O showed that water supplies the H/D-atom in the C-H/D bond-forming step. It was therefore concluded that the N-radical carbanionic resonance form B reacts with [Cy2NMe]·+ via H-atom transfer to the N-atom, followed by proton abstraction from water by the ketiminyl radical anion, forming the C-H bond in the last step.

3. Combined enzyme and photoredox catalysis in cascade reactions

The combination of photocatalysis and enzyme catalysis frequently focused on the photochemical generation of redox equivalents for a redox enzyme.[19] For example, with cheap sacrificial electron donors a cofactor such as NAD+ can be photochemically reduced to NADH, and a reductase can subsequently perform an enzymatic reaction using the NADH. Linear cascades, in which a photochemical step forms an intermediate serving as substrate for a biochemical step (or vice versa) are considerably rarer but are beginning to attract increasing attention.[20] The fact that photochemical reactions can easily occur at (or near) room temperature is particularly advantageous for the combination with enzyme catalysis.

In a pioneering study, enantiomerically pure 1,3-mercaptoalkanols were directly accessible from α,β-unsaturated ketones in a one-pot cascade involving an initial photocatalytic thio-Michael addition followed by enantioselective reduction with ketoreductase enzymes (Scheme 6a).[21] NAD(P)H served as a cofactor in this reaction and isopropanol was used as cofactor-recycling agent. The overall reaction was performed in aqueous buffer at pH 7 containing 5% (v/v) DMSO as co-solvent and [Ru(bpy)3]Cl2 as photocatalyst.



**Scheme 6.** (a) One-pot cascade including a photochemical addition of thiols to enones to form ketones, followed by enantioselective reduction of the ketones to mercaptoalkanols by ketoreductase (KRED) enzymes.[21] (b) Cyclic reaction network comprised of photochemical imine to amine reduction and enantioselective recycling of one amine enantiomer back to the imine starting material using the enzyme monoamine oxidase (MAO-N-9).[22]

Recently, we discovered that enantioenriched amines are accessible from imines in a cyclic reaction network comprised of a photochemical reduction and an enzymatic oxidation step.[22] The photochemical imine reduction produced the corresponding racemic amine, and the enzyme oxidized one of the two amine enantiomers back to the imine starting material (Scheme 6b). Over time, such selective recycling leads to the enrichment of the enantiomer which is not recognized by the enzyme.[23] Specifically, this method relied on a water-soluble analogue of the well-known [Ir(ppy)3] photocatalyst and monoamine oxidase (MAO-N-9) in aqueous phosphate buffer at pH 8. Ascorbate was used as reducing agent, and the overall one-pot reaction was performed under air at room temperature. Initial experiments with cell lysates highlighted that the photocatalyst and MAO-N-9 mutually deactivate each other, but this very commonly encountered challenge in the field of combined chemo- and biocatalysis[24] was solved by using whole E. coli cells in which MAO-N-9 had been expressed. Presumably, the anionic nature of the water-soluble (sulfonated) Ir photocatalyst (combined with its high molecular weight) impedes its diffusion through the cell membrane, thus warranting compartmentalization of photochemical and biochemical reaction steps.

Five-membered cyclic imines worked best for this specific photocatalyst / MAO-N-9 combo, yielding essentially quantitative photochemical conversion and highly enantioenriched product for selected substrates (Scheme 7).[22] The enantioselectivity of the overall reaction depends on whether the amine is a good substrate for the MAO-N-9 enzyme. For instance, an *n*-butyl substituted imine yielded the essentially enantiopure product (Scheme 7a), whilst a benzyl-substituted substrate only led to an enantiomeric excess of 8 % (Scheme 7b). In principle, the substrate scope should be extendable through genetic engineering of the MAO enzyme,[25] but our study focused on providing a proof-of-concept.



**Scheme 7.** Substrate scope of the combined photoredox / enzyme catalysis.[22]

Aside from the imine to secondary amine reduction, the conversion of an iminium cation to an enantiopure tertiary amine was readily possible (Scheme 7c). The reduction of aromatic imines, highlighted by the 1-methyl-3,4-dihydroisoquinoline as substrate, proved considerably more challenging (Scheme 7d). This was attributed to the significant stabilization of the carbon-centered radical intermediate formed upon reduction of the aromatic substrate, making HAT from ascorbate much less favorable than in the case of aliphatic substrates. Addition of thiols allowed to overcome this challenge and the photochemical reaction alone gave essentially quantitative yields. However, the achievable enantiomeric excess remained modest (35%), although the respective (*S*)-amine is a well-accepted substrate by MAO-N-9. It seems plausible that a relatively low oxygen concentration caused by the photocatalyst and the direct aerobic oxidation of thiols is responsible for that. All reactions were performed on small scales (typically 10 mM substrate in 1 ml solutions).

More recently, dynamic kinetic resolution of amines by combined photoredox and enzyme catalysis was reported.[26] Traditional enzymatic kinetic resolution of racemic amines is limited to a maximum yield of 50%, but by combining the kinetic resolution process with in situ photochemical racemization (Scheme 8), significantly higher yields were achieved. Novozym 435 from Candida antarctica lipase B performed enzymatic resolution via acylation, using methyl β-methoxypropionate as the acyl donor. With an Ir photocatalyst (2 %) and 1-octanethiol (50 %) in presence of 4 Å molecular sieves, photoredox-mediated racemization of mono- and 1,4-diamines became possible. Presumably, the photoexcited Ir sensitizer generates electrophilic thiyl radicals that undergo HAT with the electron-rich α C-H bond of the amine substrates to form 1-octanethiol and an α-amino alkyl radical. Reverse HAT then leads back to the thiyl and the amine, accompanied by racemization. The resulting dynamic kinetic resolution in one-pot reactions including all components was applicable to a broad range of primary amines.



**Scheme 8.** Photochemical amine racemization via α-amino alkyl radical intermediates coupled to enantioselective enzymatic acylation for the dynamic kinetic resolution of amines.[26]

4. Conclusions

Photochemical reductive amination as well as the light-driven imine to amine reduction both involve α-amino alkyl radicals as key intermediates that must be intercepted rapidly by HAT. This is readily possible with thiols owing to polarity-matching, making the overall two-electron reduction efficient. The sequence of a photochemically induced single electron transfer (SET) and a thermal HAT step seems to be considerably more straightforward to perform than two consecutive photoinduced electron transfers.[27] Several fundamentally different photochemical methods for reductive amination have been reported recently,[8, 13, 16-17] applicable to a broad range of substrates.

Combined enzyme and photoredox catalysis allowed the enantioselective synthesis of amines from imines in a cyclic reaction network.[22] One key challenge here was the compatibility of an Ir photocatalyst and a monoamine oxidase, which was addressed by a whole cell approach that minimized mutual deactivation of these two catalysts. Photo-biocatalysis is a particularly promising concept for asymmetric cascade reactions for the future, but currently only few examples are known yet.[19-20] After publication of the abovementioned method for the synthesis of enantiomerically pure 1,3-mercaptoalkanols [21] and our own demonstration of enantioselective amine synthesis,[22] two conceptually related studies were reported later in 2018, including one on the stereo-convergent reduction of E/Z mixtures of alkenes,[28] and one focusing on asymmetric C-H bond activation.[29]

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**Keywords:** photocatalysis • photochemistry • electron transfer • enzyme catalysis • asymmetric synthesis

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