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COMMUNICATION

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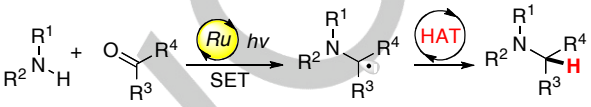
Reductive Amination by Photoredox Catalysis via Polarity-Matched Hydrogen Atom Transfer

Xingwei Guo* and Oliver S. Wenger*

Abstract: Excitation of a Ru(II) photosensitizer in presence of ascorbic acid leads to reduction of iminium ions to electron-rich α-aminoalkyl radical intermediates that are rapidly converted to reductive amination products via thiol-mediated hydrogen atom transfer (HAT). As a result, reductive amination of carbonyl compounds with amines via photoredox catalysis proceeds in good to excellent yields and with broad substrate scope, as illustrated by 17 different examples including detailed mechanistic studies. The three key novelties of this work are: (i) the rapid interception of electron-rich radical intermediates by polarity-matched HAT in a photoredox reaction, (ii) the method of reductive amination by photoredox catalysis itself, and (iii) the application of this new method for temporally and spatially controlled reactions on a solid support, as demonstrated by attachment of a fluorescent dye on an activated cellulose support via photoredox-catalyzed reductive amination.

Photoinduced electron transfer usually leads to unstable radicals that can react along multiple pathways, and it is often very challenging to intercept these radicals in controlled fashion to obtain desirable two-electron reduction products in good yields. Understanding the reactivity of radical intermediates is therefore essential for successful photoredox catalysis.[1] Recently, α-aminoalkyl radical intermediates received considerable attention, in particular as one-electron photo-oxidation products of amines.[2] These photo-generated α-aminoalkyl radicals were then used for C-C bond-forming and C-H bond breaking processes.[3] Although the possibility of the reverse process in which a substrate is photo-reduced to an α-aminoalkyl intermediate followed by its further reduction to a stable two-electron reduction product was explicitly pointed out in an early study by Giannotti and Whitten in 1980,[4] there exist currently no photoredox catalysis methods for overall two-electron reductions via α-aminoalkyl radical intermediates.

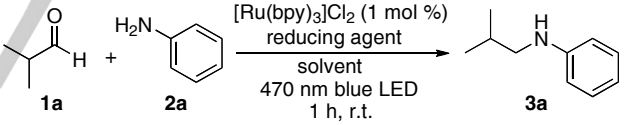
We expected that iminium ions, formed from amines and carbonyl compounds, can be reduced rather easily to α-aminoalkyl radicals through excitation of a $[Ru(bpy)_3]^{2+}$ photosensitizer in presence of a suitable sacrificial electron donor.[3] However, it was not a priori clear whether the α-aminoalkyl intermediates could be intercepted rapidly enough to produce the desired reductive amination products (Scheme 1). We speculated that thiols or ascorbic acid ($AscH_2$) might be suitable reaction partners for hydrogen atom transfer (HAT), particularly in view of the recently reported hydroamination of unactivated olefins via photoredox catalysis with thiol HAT co-catalysts.[5]



Scheme 1. Photoredox strategy for reductive amination.

Herein, we report a new method of reductive amination by combining photoinduced electron transfer and polarity-matched HAT.[6] Compared to traditional (thermal) reductive amination methods,[7] our photoredox catalysis procedure offers the advantage of spatial and temporal reaction control, as demonstrated with the photo-patterning of a cellulose surface via light-driven reductive amination using an anthracene fluorophore. The concept of polarity-matched HAT applied in our study should be transferrable to other types of photoredox reactions in which reduction of electron-rich radical intermediates is required.

Table 1. Identification of suitable reaction conditions. [a], [b]



1a 2a 3a

entry	solvent	reducing agent	yield / %
1	CH_3CN	MPA, 3 eq.	0
2	CH_3CN	*p*-MePhSH, 3 eq.	0
3	CH_3CN	TEA, 1.5 eq.	0
4	CH_3CN/H_2O 3:1 (v:v)	$AscH_2$, 1.5 eq.	39
5	CH_3CN/H_2O 3:1 (v:v)	MPA, 3 eq. + $AscH_2$, 1.5 eq.	74
6	CH_3CN/H_2O 3:1 (v:v)	MPA, 3 eq. + $AscH_2$, 0.2 eq.	67
7	CH_3OH	MPA, 3 eq. + $AscH_2$, 0.2 eq.	85
8	CH_3OH	MPA, 3 eq. + $AscH_2$, 0.2 eq.	74[c]
9	CH_3OH	MPA, 3 eq. + $AscH_2$, 0.2 eq.	0[d]
10	CH_3OH	*p*-MePhSH, 3 eq. + $AscH_2$, 0.2 eq.	23
11	CH_3OH	DL-dithiothreitol, 1.5 eq. + $AscH_2$, 0.2 eq.	72

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $[Ru(bpy)_3]Cl_2$ (0.005 mmol), reducing agent (0.75 or 1.5 mmol), in 1.0 mL deaerated solvent at 25 °C with 470 nm LED (14 W) irradiation. [b] Yields were determined by ^1H NMR analysis. [c] With 0.1 mol % $[Ru(bpy)_3]Cl_2$. [d] Reaction in the dark.

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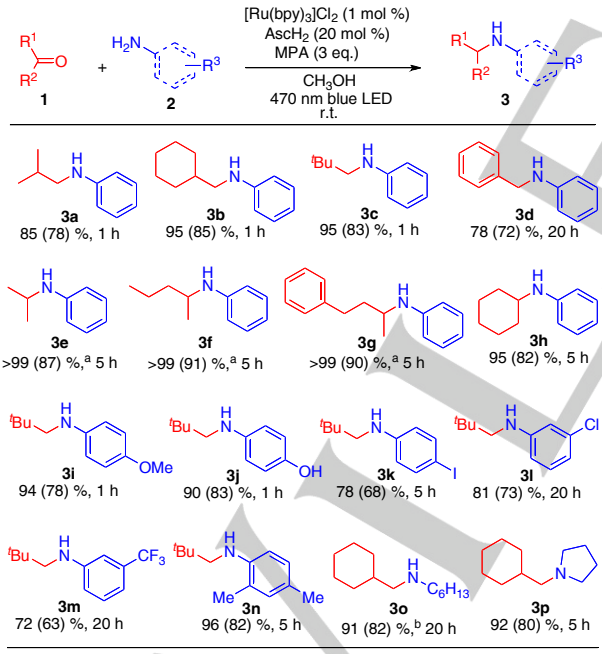
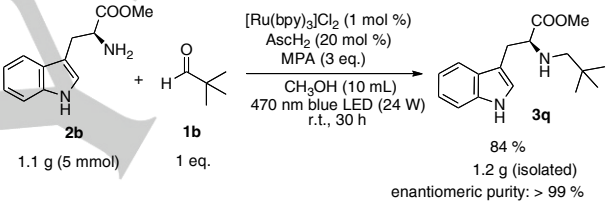
We started our investigations with the reaction between isobutyraldehyde **1a** and aniline **2a** as model substrates. Aliphatic (3-mercaptopropionic acid, MPA) and aromatic thiols (*para*-thiocresol) alone (Table 1, entries 1 & 2) failed to promote reductive amination in presence of 1 mol % $[Ru(bpy)_3]Cl_2$ under irradiation at 470 nm. The frequently used sacrificial donor triethylamine (TEA) led to no product either (entry 3). However, ascorbic acid enabled the desired reaction between **1a** and **2a** to product **3a** in 39% yield after 1 hour in deaerated 3:1 (v:v) CH_3CN/H_2O at 25 °C (entry 4). The product yield was improved to 74% by using a combination of MPA (3 eq.) and ascorbic acid (1.5 eq.) (entry 5). Interestingly, the ascorbic acid was not consumed in the course of the reaction, but instead MPA served as a terminal reductant, leading to the accumulation of disulfide oxidation product. Thus, when reducing the amount of ascorbic acid to sub-stoichiometric quantities (20 mol%), the product **3a** was still obtained in 67% yield (entry 6). As a further optimization, we changed to methanol solvent giving the desired product **3a** in 85% yield (entry 7). Reduced catalyst loading (0.1 mol% $[Ru(bpy)_3]Cl_2$) resulted in only slightly decreased yield (74%, entry 8). A control experiment performed in the dark led to no product at all (entry 9). Other thiols than MPA were also examined under optimized conditions. *Para*-thiocresol only resulted in 23% yield (entry 10), but DL-dithiothreitol promoted the desired reaction in 72% yield (entry 11).



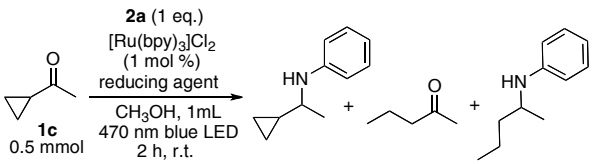
Scheme 2. Reactions of carbonyl compounds **1** and amines **2**. ^1H NMR and isolated yields (in parentheses) are indicated below the reductive amination products. Reaction conditions: carbonyl compound (0.5 mmol), amine (0.5 mmol), $[Ru(bpy)_3]Cl_2$ (1 mol%), ascorbic acid (20 mol%), MPA (1.5 mmol) in 1 ml MeOH with 470 nm LED (14 W) irradiation. [a] using 2 eq. of ketone. [b] using 2 eq. of amine.

With the fundamental discovery that the combination of MPA and $AscH_2$ permits reductive amination via photoredox catalysis at hand, and after having optimized conditions, we next turned to investigate the reaction scope (Scheme 2). Different aliphatic and aromatic aldehydes reacted with aniline **2a** to the desired products (**3a**-**d**) in good to excellent yields (78-95%). When using ketones instead of aldehydes, the reductive aminations with aniline **2a** were essentially quantitative (**3e**-**h**). The reactions of pivaldehyde with electron-rich and halogen-substituted anilines generated the corresponding products (**3i**-**l**) in good yields (78-90%), and the presence of a phenol group was unproblematic (**3j**). Meta-trifluoromethyl substituted anilines and 2,4-dimethyl substituted anilines were also transformed smoothly to the desired products (**3m** and **3n**) (72% and 96%, respectively). Beyond anilines, aliphatic amines were also examined. Both primary and secondary amines reacted efficiently with cyclohexanecarboxaldehyde to give the desired products **3o** and **3p** in 91% and 92% yield, respectively. In summary, our photoredox method of reductive amination is efficient and broadly applicable, including aliphatic and aromatic aldehydes, ketones, anilines, as well as primary and secondary aliphatic amines as possible reaction partners.



Scheme 3. Photoredox-catalyzed reductive amination performed on a gram scale.

Importantly, this reaction could also be performed on a gram scale with comparable efficiency (84% yield of isolated product) and complete retention of enantiopurity (> 99%) as demonstrated by the reaction of L-tryptophan methyl ester (**2b**) with pivaldehyde **1b** (Scheme 3, SI page S7).



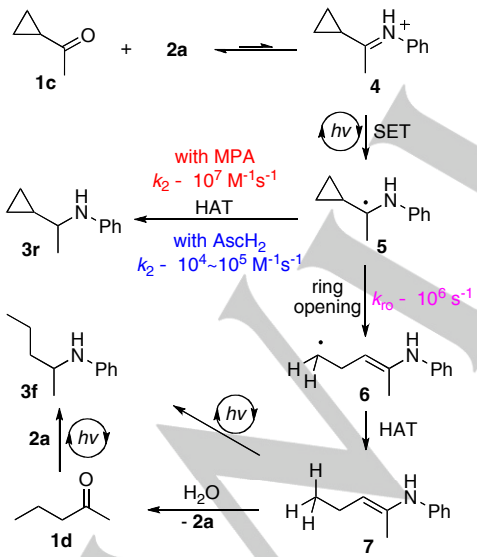
reducing agent	3r	1d	3f
$AscH_2$ (20 mol %), MPA (3 eq.)	41(25)%	~1%	3%
$AscH_2$ (1.5 eq.)	< 1%	16%	~1%

Scheme 4. Radical clock experiments with and without MPA. See SI page S9 for details.

Our mechanistic studies began with radical clock reactions (Scheme 4) between methyl cyclopropyl ketone **1c** and aniline **2a** under standard MPA/$AscH_2$ reaction conditions on the one

hand (as in Scheme 2 or in entry 7 of Table 1), as well as under conditions without MPA using $AscH_2$ as the only reductant. Interestingly, in presence of both MPA and $AscH_2$, mainly the ring retention reductive amination product **3r** was formed (41%), whereas only trace amounts of the simple ring opening product 2-pentanone **1d** (1%) and its corresponding reductive amination product **3f** (3%) were detected. Conversely, when using $AscH_2$ as the only reducing agent, 2-pentanone **1d** is the main product (16%) while the ring retention reductive amination product **3r** remains unobservable and only traces of **3f** (1%) are formed.

These observations can be explained by the competition between ring opening of the α-aminoalkyl radical intermediate **5** (Scheme 5) and direct hydrogen atom transfer to **5**, as discussed in the following. The reactants **1c** and **2a** are in equilibrium to form iminium cation **4**. The latter can be reduced easily by photogenerated $Ru(bpy)_3^+$ to α-aminoalkyl radical **5**.[3] In absence of MPA, intermediate **5** undergoes fast and irreversible ring opening to generate the primary radical **6**. The rate constant for this process is estimated to be ca. 10^6 s^{-1} (see SI page S14).[8] Then, hydrogen atom abstraction from $AscH^-/AscH_2$ leads to enamine **7**, and subsequent hydrolysis forms **1d**, the main product in absence of MPA (Scheme 4). Reductive amination of **1d** with **2a** then leads to the small observable amount of **3f**. Under the more relevant conditions when both MPA and $AscH_2$ are present, HAT from the thiol group to α-aminoalkyl radical **5** is evidently faster than the intramolecular ring opening process, explaining the formation of aminated cyclopropyl compound **3r** as the main product. Based on the product ratio of [**3r**] : [**1d**]+[**3f**] and the known rate constants for ring opening of closely related carbon-centered radical clocks,[9] we estimate that the reaction rate of HAT from MPA is ca. 10^7 M^{-1} s^{-1} (see SI page S14 for details). The reaction rate of HAT from $AscH^-/AscH_2$ to α-aminoalkyl radical **5** is estimated to be at least one hundred times slower, i. e., ca. 10^4 ~ 10^5 M^{-1} s^{-1}, based on our experimental observations (Scheme 5; SI page S14).



Scheme 5. Radical mechanism and HAT kinetics revealed by radical clock experiments.

The key conclusion from the experiments summarized in Schemes 4 and 5 is that α-aminoalkyl radicals are indeed very likely intermediates, and MPA undergoes much faster HAT with these radicals than $AscH^-/AscH_2$.

H/D kinetic isotope effect (KIE) studies of the reaction between pivaldehyde and **2a** corroborate the hypothesis of different HAT pathways with MPA and $AscH_2$ (SI page S12).

The complete mechanistic proposal that emerges from all these investigations is illustrated in Figure 1a. Under the optimized conditions with 3 eq. of MPA and 0.2 eq. of $AscH_2$, photogenerated α-aminoalkyl radicals react more than one hundred times faster with MPA ($k_{2,a} \approx 10^7$ M^{-1} s^{-1}) than with $AscH^-/AscH_2$, i. e., the thiol group of MPA is the primary HAT donor leading to the desired reductive amination products (process HAT_a in Figure 1a). However, in absence of $AscH_2$ there is no product formation at all (Table 1, entry 1), and this can be explained by the reversible nature of HAT between MPA and α-aminoalkyl radicals (dashed circular arrows in Figure 1a). The key role of $AscH^-/AscH_2$ is to intercept the thiyl radicals formed after HAT between MPA and the α-aminoalkyl radicals (process HAT_b in Figure 1), and this is known to occur with rate constants of $k_{2,b} \approx 10^8$~10^9 M^{-1} s^{-1}.[10] This process regenerates thiols from thiyl radicals, and the likely oxidation product is dehydroascorbic acid (DHA). The latter can then be reduced back to $AscH^-/AscH_2$ by selective two-electron oxidation of thiols (MPA) to disulfides (called polar reaction in Figure 1a; SI page S18),[11] explaining the accumulation of disulfide oxidation product and the need for only sub-stoichiometric amounts of $AscH_2$ (see above).

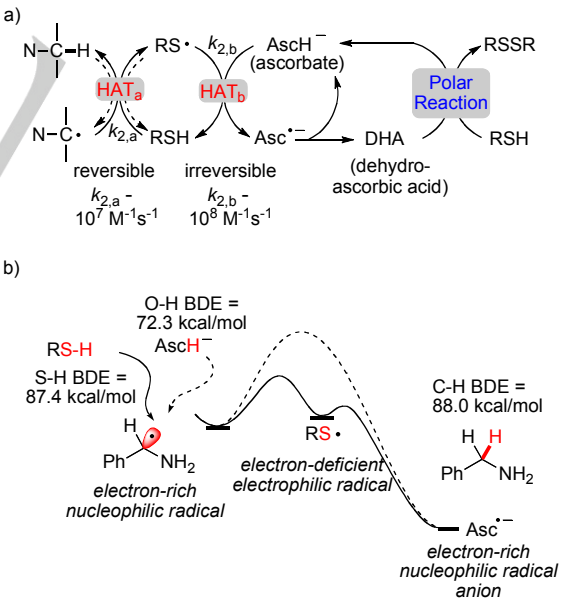


Figure 1. Polarity-matched hydrogen atom transfer.

This mechanism basically relies on the polarity matching of the HAT process (Figure 1b). The α-aminoalkyl intermediates are electron-rich nucleophilic radicals, and consequently direct HAT from an electron-rich H-atom donor such as ascorbate is not

favored, even if a fairly large driving force of ~16 kcal/mol can be estimated for that process based on the relevant bond dissociation energies (BDEs) (Figure 1b).[12] Instead, attack of nucleophilic α-aminoalkyl radicals at the S-H bond of MPA leads to rapid formation of an electrophilic thiyl radical even though this process is associated with much less thermodynamic driving force.[12] However, the subsequent reaction between electrophilic thiyl radicals and nucleophilic ascorbate is much favored and occurs in irreversible fashion, thereby suppressing undesired reverse HAT.

The inherent value of the photoredox-catalyzed reductive amination is further demonstrated by a photo-patterning reaction on activated cellulose support, illustrating the so far unique possibility of performing reductive amination with temporal and spatial control. A filter paper was treated with $NaIO_4$ to expose aldehyde groups (Figure 2), and then it was layered with a methanol solution of 9-(aminomethyl)-anthracene (1 mM), $[Ru(bpy)_3]Cl_2$ (1 mM), ascorbic acid (20 mM), and MPA (100 mM). A collimated LED lamp providing 455 nm light that passed through a hand-made mask was employed for photo-irradiation during 1 hour (SI page S16). The mask ensured illumination of only selected parts of the activated filter paper. After removing the filter paper from the solution and washing it with brine and hydroxylamine hydrochloride solution, the anthracene-labeled zones of the filter paper can easily be seen under UV irradiation (Figure 2, bottom left) due to anthracene fluorescence. We believe this new methodology of substrate immobilization enabled by visible light with both temporal and spatial control could be useful for a variety of applications, for example in biochemical contexts (biochips, biosensors, etc).[13]

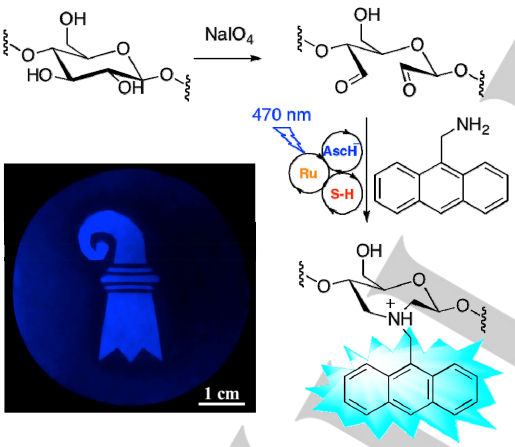


Figure 2. Photo-patterning of a cellulose support (filter paper) with visible light, using photoredox catalyzed reductive amination (SI page S16). The immobilization of fluorescent anthracene labels was made visible afterwards under UV irradiation (bottom left). The image shows the official emblem of the Swiss canton Basel-Stadt.

In conclusion, we developed the first reductive amination of aldehydes and ketones with amines by photoredox catalysis. The reaction has broad scope and provides good to excellent yields, as illustrated by 16 different examples. The combination of MPA and $AscH_2$ enables polarity-matched HAT to intercept electron-rich reactive radical intermediates in an efficient, irreversible manner, and this concept should be broadly applicable to other photoredox and radical processes. The inherent value of reductive amination by photoredox catalysis compared to traditional (thermal) methods was demonstrated by labeling an activated cellulose surface with fluorescent anthracene markers, showing that our method permits temporal and spatial reaction control under irradiation with visible light.

Acknowledgements

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Keywords: photocatalysis • photochemistry • amination • hydrogen transfer • immobilization

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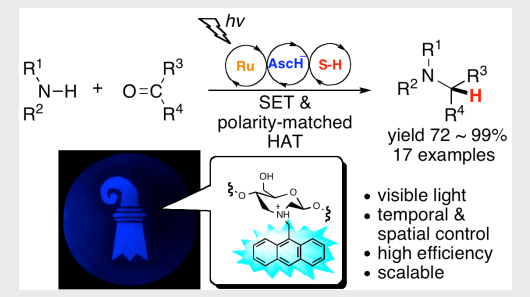
Entry for the Table of Contents

Layout 1:

COMMUNICATION

The first photoredox method for reductive amination is reported. Substrate scope studies are accompanied by in-depth mechanistic investigations. This new method allows temporal and spatial control of reductive amination reactions, for example on solid supports.



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