We speculated that thiols or ascorbic acid (AscH$_2$) might produce the desired reductive amination products (Scheme 1). Amines could be intercepted rapidly enough to process.3 Although the possibility of the reverse process in photosensitizer in presence of a suitable sacrificial electron donor,3 however, it was not a priori clear whether the amines.2 These photo-generated aminoalkyl radicals through excitation of a [Ru(bpy)$_3$]$_2^+$ carbonyl compounds, can be reduced rather easily to iminium ions, formed from amines and 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, aminoalkyl radical intermediates received considerable attention, in particular as one-electron photo-oxidation products of amines.2 These photo-generated 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 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 aminoalkyl radical intermediates. We expected that iminium ions, formed from amines and carbonyl compounds, can be reduced rather easily to 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 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

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.

**Abstract:** Excitation of a Ru(II) photosensitizer in presence of ascorbic acid leads to reduction of iminium ions to electron-rich 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 aminoalkyl radicals through excitation of a [Ru(bpy)$_3$]$_2^+$ photosensitizer in presence of a suitable sacrificial electron donor, (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.

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Herein, we report a new method of reductive amination by combining photoinduced electron transfer and polarity-matched HAT. Compared to traditional (thermal) reductive amination methods, 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.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Reducing agent</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CN</td>
<td>MPA, 3 eq.</td>
<td>0</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>p-MePhSH, 3 eq.</td>
<td>0</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>TEA, 1.5 eq.</td>
<td>0</td>
</tr>
<tr>
<td>CH$_3$CN/H$_2$O 3:1 (v/v)</td>
<td>Asch$_2$, 1.5 eq.</td>
<td>39</td>
</tr>
<tr>
<td>CH$_3$CN/H$_2$O 3:1 (v/v)</td>
<td>MPA, 3 eq. + Asch$_2$, 1.5 eq.</td>
<td>74</td>
</tr>
<tr>
<td>CH$_3$CN/H$_2$O 3:1 (v/v)</td>
<td>MPA, 3 eq. + Asch$_2$, 0.2 eq.</td>
<td>67</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>MPA, 3 eq. + Asch$_2$, 0.2 eq.</td>
<td>85</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>MPA, 3 eq. + Asch$_2$, 0.2 eq.</td>
<td>74</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>MPA, 3 eq. + Asch$_2$, 0.2 eq.</td>
<td>0</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>p-MePhSH, 3 eq. + Asch$_2$, 0.2 eq.</td>
<td>23</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>DL-dithiothreitol, 1.5 eq. + Asch$_2$, 0.2 eq.</td>
<td>72</td>
</tr>
</tbody>
</table>

[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.
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 the presence of 1 mol % [Ru(bpy)_3]Cl_2 under irradiation at 470 nm. 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).

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 3(a–d) in good to excellent yields (78–95%). When using ketones instead of aldehydes, the reductive aminations with aniline 2a were essentially quantitative (3(e–h)). The reactions of pivaldehyde with electron-rich and halogen-substituted anilines generated the corresponding products (3(i–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 (3(m and n) (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](image-url)

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).

![Scheme 4](image-url)

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 AscH2 as the only reductant. Interestingly, in presence of both MPA and AscH2, 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 AscH2 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 \( \alpha \)-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 \( \text{Ru(bpy)}_3^* \) to \( \alpha \)-aminoalkyl radical 5. 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. 10^8 s^-1 (see SI page S14). Then, hydrogen atom abstraction from AscH-/AscH2 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 AscH2 are present, HAT from the thiol group to \( \alpha \)-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, 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/AscH2 to \( \alpha \)-aminoalkyl radical 5 is at least as fast as 10^8 M^-1 s^-1, based on our experimental observations (Scheme 5; SI page S14).

The key conclusion from the experiments summarized in Schemes 4 and 5 is that \( \alpha \)-aminoalkyl radicals are indeed very likely intermediates, and MPA undergoes much faster HAT with these radicals than AscH-/AscH2.

H/D kinetic isotope effect (KIE) studies of the reaction between pivaldehyde and 2a corroborate the hypothesis of different HAT pathways with MPA and AscH2 (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 AscH2, photogenerated \( \alpha \)-aminoalkyl radicals react more than one hundred times faster with MPA (\( k_{2,a} \approx 10^7 M^-1 s^-1 \)) than with AscH-/AscH2, i.e., the thiol group of MPA is the primary HAT donor leading to the desired reductive amination products (process HATa in Figure 1a). However, in absence of AscH2 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 \( \alpha \)-aminoalkyl radicals (dashed circular arrows in Figure 1a).

The key role of AscH/AscH2 is to intercept the thiyl radicals formed after HAT between MPA and the \( \alpha \)-aminoalkyl radicals (process HATb in Figure 1), and this is known to occur with rate constants of \( k_{2,b} \approx 10^4 \sim 10^5 M^-1 s^-1 \). This process regenerates thioles from thiyl radicals, and the likely oxidation product is dehydroascorbic acid (DHA). The latter can then be reduced back to AscH/AscH2 by selective two-electron oxidation of thioles (MPA) to disulfides (called polar reaction in Figure 1a; SI page S18), explaining the accumulation of disulfide oxidation product and the need for only sub-stoichiometric amounts of AscH2 (see above).

![Figure 1](image)

**Figure 1.** Polarity-matched hydrogen atom transfer.

This mechanism basically relies on the polarity matching of the HAT process (Figure 1b). The \( \alpha \)-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).\textsuperscript{12} Instead, attack of nucleophilic \( \alpha \)-aminoalkyl radicals at the S-H bond of MPA leads to rapid formation of an electrophilic thyl radical even though this process is associated with much less thermodynamic driving force.\textsuperscript{12} However, the subsequent reaction between electrophilic thyl radicals and nucleophilic ascorbate is much favored and occurs in irreversible fashion, thereby suppressing undesired reverse HAT.

The inherent value of the photocatalytic 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\textsubscript{4} to expose possibility of performing reductive amination with temporal and spatial reaction control under irradiation with visible light.\textsuperscript{12} A collimated LED lamp providing 455 nm light that passed through a handmade 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.).\textsuperscript{13}

In conclusion, we developed the first reductive amination of aldehydes and ketones with amines by photocatalytic catalysis. The reaction has broad scope and provides good to excellent yields, as illustrated by 16 different examples. The combination of MPA and AsCH\textsubscript{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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**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.

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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.

Xingwei Guo*, Oliver S. Wenger*

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