

Visible-Light-Mediated Umpolung Reactivity of Imines: Ketimine Reductions with Cy₂NMe and Water

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S Supporting Information

ABSTRACT: A novel carbanionic reactivity of imines mediated by photoredox catalysis is demonstrated. The umpolung imine reactivity is exemplified by proton abstraction from water as a key step in the reduction of benzophenone ketimines to amines (up to 98% yield). Deuterium is introduced into amines efficiently using D₂O as an inexpensive deuterium source (\geq 95% D ratio). The mechanism of this unusual transformation is probed.



ver the past decade, photoredox catalysis has emerged as a powerful tool to conduct radical transformations initiated by light energy.¹ Under photoredox catalysis, imines are reduced via single electron transfer (SET) processes to generate highly reactive radical anion intermediates. Elegant studies by the MacMillan and Molander groups have shown that the imine radical anions undergo radical coupling reactions with other alkyl radical intermediates to afford α -alkylated amines (Scheme 1, eq 1).² With aminomethyl radical species,





the radical coupling reactions with the imine radical anion intermediates afforded ethylenediamine derivatives, as shown by the Ooi and Rueping groups.³ Rueping, Sudo, and their coworkers independently demonstrated the dimerization of these radical anion intermediates (Scheme 1, eq 2).⁴ The teams of Chen and Dixon discovered imine radical anions add to allylic

sulfones, leading to homoallylic amine derivatives (Scheme 1, eq 3).⁵

While imines have traditionally been used as electrophiles in organic transformations, these recent photoredox studies shed light on the potential reactivity of imines via C-centered radicals. Although the reactivity can be envisioned to occur through a carbon-based radical (Scheme 1, eqs 1-3), another resonance form can be drawn with the radical on nitrogen, and the anion on carbon, as illustrated in resonance form B (Scheme 1, eq 4). Indeed, a previous report on electrochemical reductions of imines has indicated that the radical anion intermediates were stabilized by resonance A/B in some cases.⁶ Although **B** might be anticipated to exhibit umpolung reactivity, such behavior has not been previously reported to our knowledge. Herein, we disclose the umpolung reactions' of ketimines under photocatalytic conditions, as demonstrated by their reduction⁸ in the presence of amines and water.

We have recently been interested in the umpolung⁹ and radical reactivity¹⁰ of the azaallyl species derived from aldimines and ketimines. The importance of amine derivatives in medicinal chemistry inspired us to explore the reactivity of imines under photoredox conditions. Unfortunately, our initial experiments with the N-benzyl imine of benzaldehyde and a variety of photoredox catalysts and sacrificial amines failed to yield the desired reduction product 2, probably because of the high energy of the carbanion-based resonance form **B**.⁶

We next turned our attention to ketimines derived from benzophenone to better stabilize the carbanionic resonance form B. Thus, with ketimine 1a, 10 equiv of water, and 2 equiv of triethylamine as the sacrificial electron donor, reaction mixtures were subjected to irradiation with a blue light-emitted diode (LED) at room temperature in the presence of various

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photocatalysts (5 mol %). To our delight, the reduction product **2a** was generated in 41% assay yield (AY, determined by HPLC) with the common photoredox catalyst $[Ru(bpy)_3]$ -Cl₂ (**Ru-1**) (Table 1, entry 1). Similar results were observed

Table 1. Optimization of Umpolung Reduction of Ketimine 1a Mediated by Visible Light a



^{*a*}Reactions conducted with **1a** (0.1 mmol), H₂O (1 mmol), catalyst (0.1–5 mol %) and amine (0.2 mmol) in 1 mL MeCN at room temperature under 20 W blue LED irradiation. ^{*b*}Yields determined by HPLC using mesitylene as internal standard. N.D. = not detected. ^{*c*}Catalyst loading = 5 mol %, reaction time = 40 min. ^{*d*}Catalyst loading = 1 mol %, reaction time = 100 min. ^{*e*}Catalyst loading = 0.5 mol %, reaction time = 4. ^{*b*}. ^{*f*}Catalyst loading = 0.1 mol %, reaction time = 12 h, isolated yield: 98%.

when using $[Ru(bpy)_3](PF_6)_2$, indicating that the anion of the catalyst does not affect its reactivity (Table 1, entry 2). However, the other ruthenium catalysts $[Ru(bpz)_3]Cl_2$ and $[Ru(bpz)_3](PF_6)_2$ were not effective in this transformation (Table 1, entries 3 and 4). Catalyst *fac*-Ir(ppy)_3 (Ir-1) and its derivatives (Ir-2 and Ir-3) were also tested, but they did not exhibit activity (Table 1, entries 5–7). However, when the catalyst $[Ir(2',4'-F_2-5-CF_3-ppy)_2(bpy)]PF_6$ (Ir-4) was used, 73% AY was obtained, suggesting higher activity of $[Ir(ppy)_2(bpy)]PF_6$ type catalysts (Table 1, entry 8). Slightly improved AY was obtained when using related iridium catalysts with either fewer fluorines on the phenyl-pyridine ligand (Ir-5, Ir-5, Ir 87% AY) (Table 1, entry 9) or bulky tBu substituents on the bipyridine ligand (Ir-6, 75% AY) (Table 1, entry 10). These results suggest that catalysts with more electron-rich ligands might exhibit greater activity. Therefore, we next examined catalysts with fewer fluorines, while maintaining the tBu substituents on the ligands. We were pleased to find that excellent results were obtained with catalysts Ir-7, Ir-8, and Ir-9 (\geq 94% AY) (Table 1, entries 11–13).

Sacrificial electron donors were screened next. Among the five amines tested [TEA, NMe₃, TMEDA, $EtN(iPr)_2$ and Cy_2NMe], all gave excellent results (\geq 94% AY) (Table 1, entries 13–17). It is noteworthy that quantitative yield was observed with Cy_2NMe after 40 min (Table 1, entry 17). With the optimized catalyst and electron donor in hand, we next focused on decreasing the catalyst loading. Although longer reaction times were needed at lower loadings of Ir-9 (Table 1, entries 18–20), excellent yields were maintained with catalyst loadings as low as 0.1 mol % (98% isolated yield) (Table 1, entry 20).

Encouraged by the efficiency of this catalytic reduction of imines, we next aimed to explore the scope. The results are summarized in Scheme 2. Substrates with benzyl groups bearing *ortho-, meta-,* or *para-*chloro substituents worked smoothly under the standard conditions (2b-2d) (82–93%). Other halogens, e.g., 4-F (2e) (98%) or 4-Br (2f) (97%), also gave very high yields. The substrate bearing a 4-CF₃-substituted

Scheme 2. Visible-Light-Mediated Umpolung Transformation of Ketimines^a



^aReaction was conducted with 1 (0.1 mmol), H_2O (1 mmol), catalyst (0.1 mol %) and Cy_2NMe (0.2 mmol) in 1 mL MeCN at room temperature under 20 W blue LED irradiation. Isolated yield.

benzyl exhibited slightly decreased reactivity (2g) (84%). The reductions were efficient when substrates with electrondonating groups, such as 4-Me, 4-*t*-Bu or 4-OMe, were employed, which provided the amine products in 90–94% yields (2h-2j).

Heterocycles are important in medicinal chemistry. With this in mind, we examined substrates with heteroatom-substituted benzyl groups. The 2- and 3-pyridyl derivatives afforded products in 65% and 73% yields (2k and 2l, respectively). Substrates bearing 2-thiophenyl and 2-furanyl groups furnished products 2m and 2n in \geq 97% yield. The N-phenyl imine provided the reduction product 20 in 84% yield. The reaction remained efficient when electron-withdrawing 2-F (2p) (94%) or electron-donating 4-OMe substituents (2q) (93%) were introduced into the N-aryl group. A heterocyclic substrate bearing a N-(3-pyrridyl) imine was reduced in 86% yield (2r).

N-Alkyl imines were examined next. N-Methyl and n-butyl imines afforded the products 2s and 2t in 95% and 92% yields, respectively. Reaction with N-allyl imine led to 2u in excellent yield (95%), indicating selectivity for reduction of the N=C bond over the C=C bond. The use of benzophenone derivatives with halogen 2-F, 2-Cl, or 4-Cl, or electron-donating 4-Me or 4-OMe groups did not affect the reactivity (83–96%) (2v-2z). The 9-fluorenyl imine was also tested, affording the amine product 2aa in 87% yield. Finally, when reduction of the 2-thiophenyl substrate was performed under the standard conditions, the desired product 2ab was obtained in 84% yield. It is noteworthy that the radical coupling adducts between ketimines and Cy₂NMe were not detected with these substrates, indicating a different mechanism for the current transformation, compared to previously reported radical processes.^{3,4}

We postulate that the catalytic cycle for ketimine reduction starts with catalyst excitation by visible-light irradiation to give $[Ir]^{3+*}$, which then abstracts one electron from Cy_2NMe to produce $[Ir]^{2+}$ and the amine radical cation. Subsequent single electron transfer from $[Ir]^{2+}$ to the ketimine regenerates $[Ir]^{3+}$ and reduces imine 1 to the radical anion, which is stabilized by resonance forms $A^{3c,4a,5a}$ and $B.^6$ Since the *N*-radical in resonance form B is highly reactive, it would be quickly quenched by the Cy_2NMe radical cation to give iminium intermediate C. Subsequent deprotonation of H_2O by the ketiminyl anion forms a C–H bond, affording the final reduced product 2 (see Scheme 3).

Scheme 3. Postulated Reaction Pathway



Another possible pathway to afford **2** entails a carbon-based radical of either **A** or protonated **A** from a PCET process (proton-coupled electron transfer),¹¹ which abstracts a hydrogen atom from $[Cy_2NMe]^+$ or Cy_2NMe . To differentiate these pathways from carbanion-based deprotonation of water, we performed the reaction using D₂O under the same conditions and monitored the reaction using ¹H NMR spectroscopy in MeCN-*d*₃. Integration of the resulting reaction mixture indicated 93% deuterium incorporation at the benzylic *C*-*H* in the product, clearly showing that water supplies the proton in the C–H bond-forming step (Scheme 4, eq 1).





To further examine the role of water, we performed the reaction in the absence of added water in MeCN- d_3 and followed the reaction by ¹H NMR spectroscopy (Scheme 4, eq 2). After 12 h of reaction, ¹H NMR indicated a complex mixture with 22% of starting material **1a**, 44% of reduced product **2a** and 34% of unidentified side products, indicating that water is essential for the completion of the umpolung reduction. When the reaction was performed in the absence of catalyst¹² or Cy₂NMe or was conducted in darkness, no reduction product was observed, indicating each component is essential for the reaction (see Scheme S1 in the Supporting Information).

Conventionally, the introduction of a deuterium atom into an imine requires expensive deuterated reducing agents, e.g., NaBD₄. Our method offers an efficient way to make α deuterated amines using D₂O, which is arguably the most ideal deuterium source, because of its safety and low cost. Therefore, several representative substrates were chosen to react with D₂O under the standard conditions. Excellent deuterium ratios were obtained in all cases (\geq 95% D, 74–97% yield) (2k–2ab in Scheme 5). The advantage of using D₂O instead of other expensive deuterated reducing agents was further exemplified with large-scale reactions. Reaction of 1 mmol of 10 with D₂O was performed, furnishing the deuterated amine 2o(D) in 93% yield with 97% D incorporation. The reaction scale was further extended to 2 g of 1t (8.5 mmol), affording the α -deuterated product 2t(D) in 95% yield and 98% D ratio.

In summary, photoredox catalysis has engendered new transformations of imines, mainly via exploiting the carbonbased radical reactivity of the radical anion intermediate **A**. Herein, we advance a novel polarity-inverted reactivity of imine radical anions. At this early stage of our work, we proposed that the observed reactivity via the carbanionic resonance structure **B** is favored, because of stabilization of the negative charge by delocalization over the two aryl groups. Based on this reactivity, we have developed an extremely efficient catalytic system for a visible-light-mediated umpolung reduction of imines. Excellent yields with a broad range of ketimine substrates have been obtained. Our method is safer and more environmentally friendly by harvesting light energy, compared to the traditional Scheme 5. Synthesis of α -Deuterated Amines using D_2O^{α}



^aReactions conducted with 1 (0.1 mmol), D_2O (1 mmol), catalyst (0.1 mol %) and Cy₂NMe (0.2 mmol) in 1 mL MeCN at room temperature under 20 W blue LED irradiation. Isolated yield. Large-scale reactions were performed at 1 mmol scale for **20** and 8.5 mmol scale for **2t**.

imine reductions using hydride¹³ or other reducing agents.¹⁴ Furthermore, deuterium can be introduced into imines effectively using D_2O , instead of expensive deuterated reducing agents. Other transformations harnessing the reactivity of the carbanionic resonance form **B** are currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00778.

Procedures, characterization data, and spectra for all new compounds (PDF)

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Letter

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