

Lewis Acid Induced Toggle from Ir(II) to Ir(IV) Pathways in Photocatalytic Reactions: Synthesis of Thiomorpholines and Thiazepanes from Aldehydes and SLAP Reagents

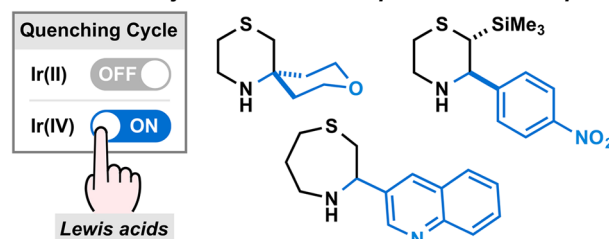
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S Supporting Information

ABSTRACT: Redox neutral photocatalytic transformations often require careful pairing of the substrates and photoredox catalysts in order to achieve a catalytic cycle. This can limit the range of viable transformations, as we recently observed in attempting to extend the scope of the photocatalytic synthesis of N-heterocycles using silicon amine protocol (SLAP) reagents to include starting materials that require higher oxidation potentials. We now report that the inclusion of Lewis acids in photocatalytic reactions of organosilanes allows access to a distinct reaction pathway featuring an Ir(III)*/Ir(IV) couple instead of the previously employed Ir(III)*/Ir(II) pathway, enabling the transformation of aromatic and aliphatic aldehydes to thiomorpholines and thiazepanes. The role of the Lewis acid in accepting an electron—either directly or via coordination to an imine—can be extended to other classes of photocatalysts and transformations, including oxidative cyclizations. The combination of light induced reactions and Lewis acids therefore promises access to new pathways and transformations that are not viable using the photocatalysts alone.

photomediated synthesis of thiomorpholines & thiazepanes



INTRODUCTION

Chiral saturated N-heterocycles are privileged scaffolds for modern drug discovery and are present in an increasing number of newly approved small molecule drugs.^{1,2} To provide access to these structures^{3–6} in a predictable manner from readily available starting materials, our group has developed stannyl amine protocol (SnAP) reagents for the one-step transformation of aldehydes and ketones into a wide variety of N-heterocycles.^{7–14} These reagents and protocols have been widely adopted and have emerged as a leading method for the small scale synthesis of morpholines, piperazines, oxazepanes, diazepanes, and thiomorpholines, including substituted and spirocyclic variants. The SnAP chemistry is characterized by broad substrate scope and versatility under a standard set of reaction conditions, making it ideally suited for preparing libraries of saturated N-heterocycles. The requirement for stoichiometric tin reagents and halogenated solvents, however, renders it unsuited for large-scale reactions and the development of sustainable routes to these important structures.

As part of efforts to develop tin-free alternatives to the SnAP reagents, we recently reported the synthesis of N-Bn piperazines using silicon-based SLAP (silicon amine protocol) reagents under photocatalytic conditions (Scheme 1a).^{15–18} The requisite redox cycle is achieved by the combination of two single-electron transfer events: (1) oxidation of the α -silyl amines ($E_p = +0.65$ V vs SCE for 1-((trimethylsilyl)methyl)piperidine)¹⁹ and (2) reduction of the N-centered radical formed upon radical cyclization ($E_{1/2}^{\text{red}} > -1.5$ V vs SCE for dialkylaminy radicals or radical cations).^{20,21} The relatively

high reduction potential of the second step necessitated the use of a specific photocatalyst Ir^{III}[(ppy)₂dtbbpy]PF₆ (Ir(III), where ppy = 2-phenylpyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine), one of the few promoters that offer both sufficient oxidation and reduction ability ($E_{1/2}^{*\text{III}/\text{II}} = +0.66$ V and $E_{1/2}^{\text{III}/\text{II}} = -1.51$ V vs SCE in MeCN)^{22,23} for N-alkyl and N-aryl piperazine-forming SLAP (SLAP Pip) reagents. Unfortunately, its relatively low oxidation ability was not sufficient for the corresponding SLAP reagents that would form thiomorpholines from α -silyl sulfides ($E_p = +1.1$ – 1.4 V vs SCE in MeCN) or morpholines from α -silyl ethers ($E_p = +1.90$ V vs SCE in MeCN).^{24–27}

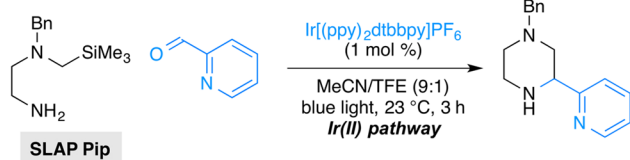
We now report that Lewis acid additives are an unexpectedly simple but effective means of accessing an alternative photocatalytic cycle with the same iridium catalyst, one with distinct oxidation and reduction potentials that allow the formation of thiomorpholines from the corresponding SLAP reagents and light (Scheme 1b). Under these conditions, the commercially available Ir^{III}[(ppy)₂dtbbpy]PF₆ catalyst is effective and can be used to prepare a wide range of thiomorpholine and thiazepane products. Mechanistic studies support reduction of a sacrificial amount of the Lewis acid coordinated imine (2·LA⁺) by the photoexcited *Ir^{III}[(ppy)₂dtbbpy]⁺ (Ir(III)*), inducing a switch of catalytic pathway to an oxidative quenching cycle (Scheme 1c). The resulting Ir^{IV}[(ppy)₂dtbbpy]²⁺ (Ir(IV)) possesses higher oxidation ability ($E_{1/2}^{\text{IV}/\text{III}} = +1.69$ V vs SCE

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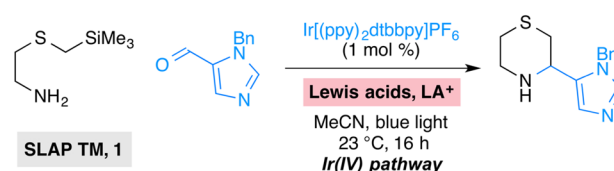
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Scheme 1. Photomediated Synthesis of Saturated N-Heterocycles, Such as (a) Piperazines and (b) Thiomorpholines and Thiazepanes, Using SLAP Reagents. (c) Mechanistic Switch in the Presence of Lewis Acids (LA)

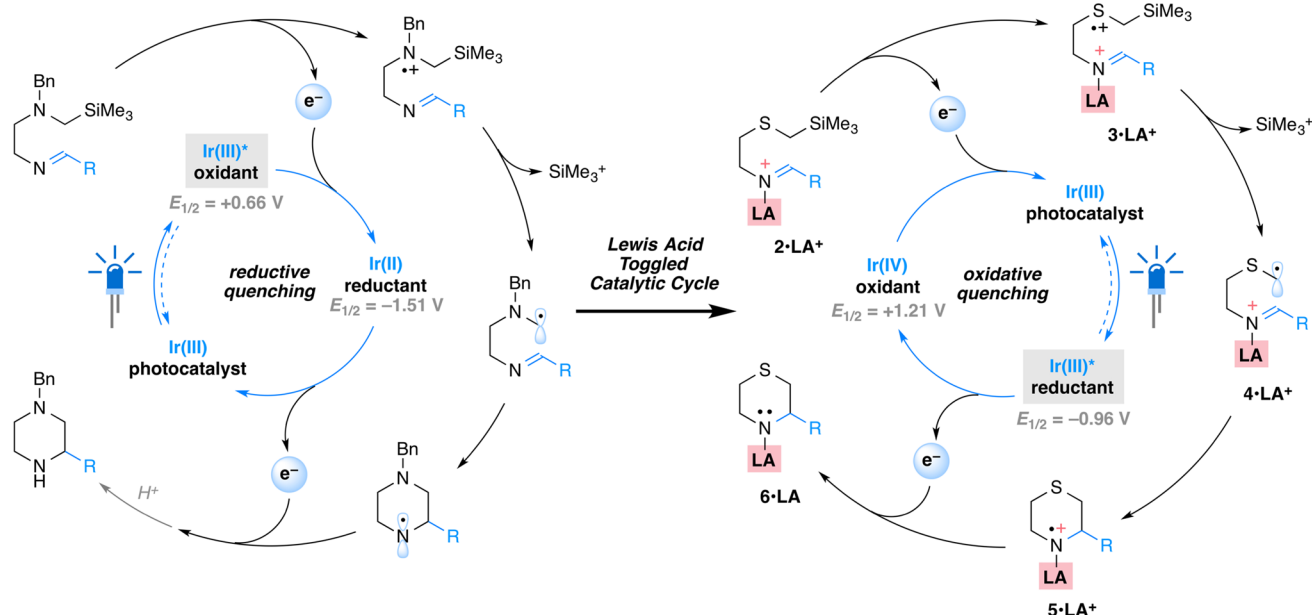
(a) **Previous work:** Photocatalytic piperazine synthesis



(b) **This work:** Photomediated thiomorpholine/thiazepane synthesis



(c) Proposed mechanistic switch from reductive quenching to oxidative quenching



in MeCN)^{22,23} than the photoexcited Ir(III)* ($E_{1/2}^{*III/II} = +0.66$ V) as an oxidant. It is therefore able to effectively promote single electron oxidation on the sulfur of α -silyl sulfides ($2\cdot LA^+$), desilylation to give $3\cdot LA^+$, and generation of the C-centered radical $4\cdot LA^+$. After cyclization, the Lewis acid coordinated N-centered radical ($5\cdot LA^+$) has a lower reduction potential than its uncoordinated counterpart,^{20,21} allowing the cycle to be completed by reduction with Ir(III)*. In preliminary studies, the combination of Lewis acids and photoredox catalysts^{28–35} enables transformations not possible with photocatalysts alone and is poised to become a general strategy for expanding the scope of photocatalytic reactions.

REACTION DESIGN

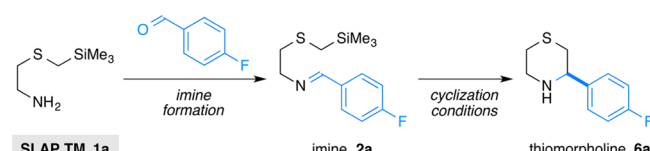
At the outset of our studies with thiomorpholine-forming SLAP (SLAP TM) reagents, we examined photoredox catalysts that provide higher oxidation potentials in their photoexcited states. For example, the excited state species of photocatalyst Ir^{III}[dF(CF₃)ppy]₂(dtbbpy)PF₆ ($E_{1/2}^{*III/II} = +1.21$ V vs SCE in MeCN; where dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine)^{22,23} should be able to oxidize the α -silyl sulfides of SLAP TM reagents. However, attempted cyclizations with these catalysts led to no desired products, likely due to insufficient ability ($E_{1/2}^{III/II} = -1.37$ V vs SCE in MeCN)^{22,23} to reduce the N-centered radical and complete the catalytic cycle.^{36–38} We therefore questioned in the other case of using Ir^{III}[(ppy)₂dtbbpy]PF₆ whether it would be possible to access an alternative catalytic cycle: if its photoexcited species Ir(III)* could serve as a reductant, would the resulting Ir(IV)

species ($E_{1/2}^{IV/III} = +1.21$ V vs SCE in MeCN)^{22,23} be able to oxidize the SLAP TM reagents? More importantly, as the reduction ability of *Ir^{III}[(ppy)₂dtbbpy]⁺ ($E_{1/2}^{*III/IV} = -0.96$ V vs SCE in MeCN)^{22,23} seems too low for reducing the uncoordinated N-centered radical, will such radicals be easier to reduce in the presence of suitable additives?

RESULTS AND DISCUSSION

Our standard conditions for SnAP chemistry^{7–14} (Table 1, entry 1) and the previously reported photocatalytic system for SLAP Pip reagents¹⁵ (entry 2) were not effective, and no formation of thiomorpholine **6a** from imine **2a** was observed. We therefore surveyed additives that would allow the photocatalyst Ir^{III}[(ppy)₂dtbbpy]PF₆ to access the oxidative quenching cycle, in which the photoexcited Ir(III)* species functions as a reducing agent. Several potential oxidants,³⁹ including I₂, triphenylcarbenium tetrafluoroborate (Ph₃C⁺BF₄⁻), and benzoquinone in the presence of Ir(III) under blue light irradiation, were tested (entry 3). However, the reactions resulted in a mixture of unidentified products and hydrolysis; no desired product was observed.

We therefore considered activation of the imine with Lewis acids to induce reduction by Ir(III)* and selected trimethylsilyl trifluoromethanesulfonate (TMSOTf) for initial studies. Substoichiometric amounts or a single equivalent of TMSOTf was not effective (entry 4), but the addition of 2 equiv led to the formation of the desired product in 36% yield, as judged by ¹H NMR; no significant side products were observed (entry 5). Control experiments confirmed the requirement for TMSOTf,

Table 1. Screening and Optimization of Reaction Conditions with Imine^{a,b}


entry	cyclization condition	result ^c
1	SnAP conditions: Cu(OTf) ₂ (1.0 equiv), 2,6-lutidine (1.0 equiv), CH ₂ Cl ₂ /HFIP (4:1)	imine recovered
2	SLAP N-Bn conditions: Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	imine recovered
3	oxidants (I ₂ , Ph ₃ C ⁺ ·BF ₄ ⁻ , or benzoquinone, 2.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	unidentified byproducts
4	TMSOTf (1.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	mostly imine recovered
5	TMSOTf (2.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 34%
6	TMSOTf (2.0 equiv), MeCN, 60 °C	mostly imine recovered
7	BF ₃ ·MeCN (2.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 36%
8	Bi(OTf) ₃ (2.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 56%
9	Cu(OTf) ₂ (2.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 42%
10	Bi(OTf) ₃ (1.0 equiv), Cu(OTf) ₂ (1.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 47%
11	Bi(OTf) ₃ (0.5 equiv), Cu(OTf) ₂ (1.0 equiv), Ir[(ppy) ₂ dtbbpy]PF ₆ (1 mol %), MeCN, BL	6a, 46%

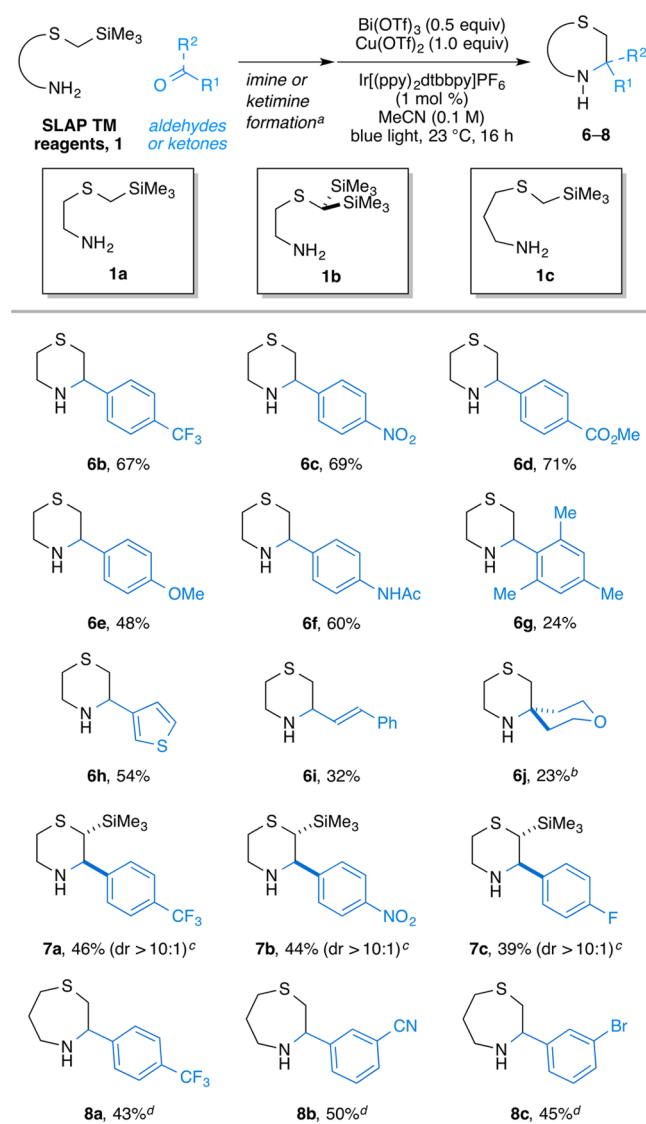
^aReactions were conducted at 23 °C for 16 h, unless stated otherwise.

^bEach reaction was performed on a 0.10 mmol scale in 0.1 M concentration. ^cCalculated yield from ¹H NMR measurement of unpurified reaction mixture with 1,3,5-trimethoxybenzene as an additional internal standard. BL = blue light; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

Ir^{III}[(ppy)₂dtbbpy]PF₆, and blue light for product formation; TMSOTf alone was not effective in the absence of light or the photocatalyst (entry 6). Various Lewis acids including BF₃·MeCN (entry 7), Bi(OTf)₃ (entry 8), Cu(OTf)₂ (entry 9), and many others (e.g., BiCl₃, BiBr₃, In(OTf)₃, Sc(OTf)₃) were found to promote the cyclization. Interestingly, the use of BF₃·Et₂O did not afford the cyclized product. We also observed that the presence of certain cosolvents including THF and alcohols (e.g., MeOH and HFIP) suppressed the reaction.

Despite the better outcome with Bi(OTf)₃ among the Lewis acids in Table 1, our evaluation of the substrate scope (vide infra) revealed that imines from electron-donating aldehydes usually gave superior results with Cu(OTf)₂. In the case of thiazepane formation, the use of Bi(OTf)₃ was nearly always superior to Cu(OTf)₂. Other Lewis acids, including TMSOTf and BF₃·MeCN, were almost as effective but gave, in general, slightly lower yields. As a compromise, we combined the two Lewis acids (Bi(OTf)₃ (0.5 equiv) and Cu(OTf)₂ (1.0 equiv)) to provide a “first-try” general protocol applicable to most substrates (Table 1, entry 11). Substrate specific optimization by changing the Lewis acid can improve the outcome in many examples.

With the optimal reaction conditions in hand, the substrate scope of thiomorpholine and thiazepane formation from a variety of aliphatic and aromatic aldehydes and ketones was examined (Scheme 2). The cyclization tolerated a broad spectrum of different substituents and functional groups.

Scheme 2. Substrate Scope of SLAP TM Reagents with Nonheterocyclic Aldehydes and Ketones^a


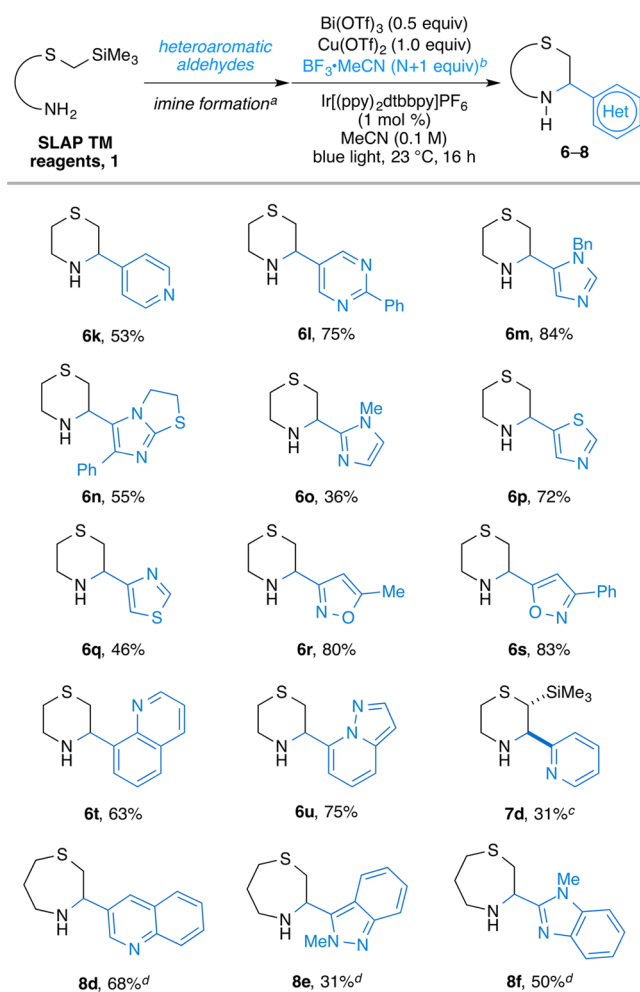
^a(a) See the Supporting Information for the details. (b) Additional BF₃·MeCN (2.0 equiv) and extended reaction time (48 h) were applied. (c) The diastereomeric ratios were determined by ¹H NMR measurement of unpurified reaction mixture. (d) Reaction time was 48 h.

Aliphatic and hindered aldehydes also provided the desired cyclized products, albeit in reduced yields. Interestingly, in the cyclization from the bistrimethylsilyl SLAP reagent **1b**, only monodesilylated, 2,3-disubstituted products **7** were generated, always as the *trans* diastereomers; fully desilylated products were not detected in the unpurified reaction mixture. This observation can be attributed to the lower oxidation potentials of α-bistrimethylsilyl sulfides than the α-monotrimethylsilyl counterparts.²⁴ In addition, these cyclization conditions also allowed for the synthesis of thiazepanes **8**, albeit with longer reaction times. This is an important finding, as our attempts at forming thiazepanes with SnAP reagents were plagued by low yield and poor conversion under our standard conditions.

In early evaluations, imines derived from heteroaromatic aldehydes were challenging, likely because the basic nitrogen atoms could bind to the Lewis acids, hampering access to the photocatalytic cycle. By “protecting” the heteroaromatic

moieties *in situ* with $\text{BF}_3 \cdot \text{MeCN}$, followed by a simple basic workup to remove the Lewis acids after the cyclization, we could easily expand the substrate scope to include these important substrates. A series of imines containing different types of heteroaromatic substituents (e.g., pyridine, pyrimidine, isoxazole, thiazole, and imidazole) were examined and found to give the cyclization product in good yields (Scheme 3).

Scheme 3. Substrate Scope of SLAP TM Reagents with Heterocyclic Aldehydes^a



^a(a) See the Supporting Information for the details. (b) N = the number of heteroatoms on the heterocyclic ring. (c) The diastereomeric ratios were determined by ^1H NMR measurement of unpurified reaction mixture. (d) Reaction time was 48 h.

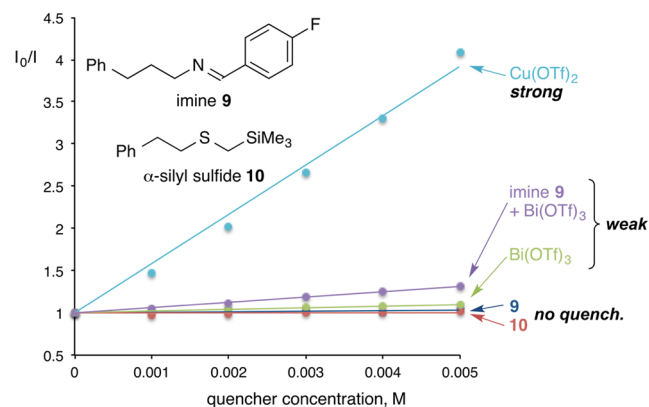
MECHANISTIC CONSIDERATIONS

We initially considered several possible explanations for the beneficial effect of Lewis acids on the photocyclization to afford thiomorpholines. In one hypothesis, the Lewis acid could coordinate to the sulfur atom of the SLAP TM reagents, thereby modulating their oxidation potentials and allowing the reagents to be oxidized by the $\text{Ir}(\text{III})^*$. This hypothesis, however, was both counterintuitive—as coordination should raise, rather than lower, the oxidation potential—and was discounted by electrochemical studies that showed almost no change to the oxidation potential of a model substrate in the presence of Lewis acids.⁴⁰

Our favored mechanism features a role for the Lewis acid or the corresponding coordinated imine as an electron acceptor

from the photoexcited $\text{Ir}(\text{III})^*$ species to form the $\text{Ir}(\text{IV})$ oxidant. The resulting $\text{Ir}(\text{IV})$ species ($E_{1/2}^{\text{IV/III}} = +1.21$ V)^{22,23} should be able to oxidize the α -silyl sulfide ($E_p = +1.1$ – 1.4 V)^{24–27} to form the C-centered radical that would deliver the N-centered radical followed by cyclization. This stabilized, N-centered radical cation (shown as $5 \cdot \text{LA}^+$, Scheme 1c) is regarded as having a lower reduction potential than the uncoordinated N-centered radical,^{20,21} and can likely be reduced by $\text{Ir}(\text{III})^*$ to give the Lewis acid coordinated product ($6 \cdot \text{LA}$) and complete the catalytic cycle (Scheme 1c). To support this conjecture, we performed Stern–Volmer fluorescence quenching experiments of the current photocatalyst $\text{Ir}[(\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ with different reaction components (Figure 1).

(a) Stern–Volmer measurements of $\text{Ir}(\text{III})$ with different reaction components



(b) proposed initiation of photocatalytic cycle

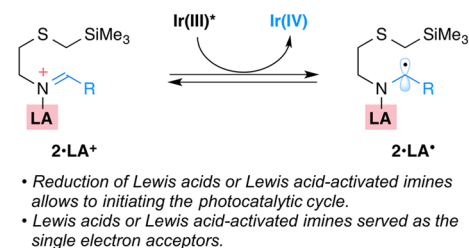


Figure 1. (a) Stern–Volmer quenching experiments of $\text{Ir}[(\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ (100 μM in MeCN) with different reaction components. (b) Proposed reduction of Lewis acid activated imine.

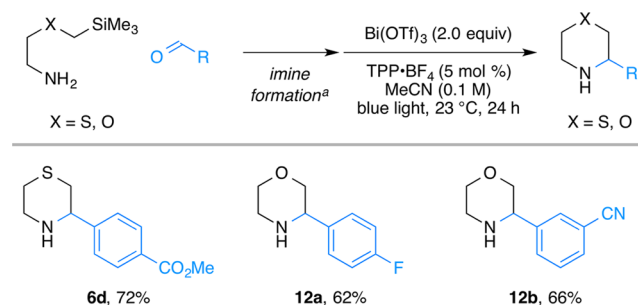
Neither imine 9 nor α -silyl sulfide 10 alone showed a linear relationship in the Stern–Volmer quenching experiments with $\text{Ir}^{\text{III}}[(\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ (Figure 1a), which supported the unproductive result from the initial screening of reaction conditions (Table 1, entry 2). Interestingly, further investigations showed that the fluorescence was quenched in the presence of $\text{Cu}(\text{OTf})_2$ and $\text{Bi}(\text{OTf})_3$ respectively, consistent with favored reduction of $\text{Cu}(\text{OTf})_2$ ($E^0 = +0.8$ V vs SCE)³⁹ and $\text{Bi}(\text{OTf})_3$ (E^0 ca. -0.1 V vs SCE)⁴¹ by the excited species $^*\text{Ir}^{\text{III}}[(\text{ppy})_2\text{dtbbpy}]^+$ ($E_{1/2}^{*\text{III/IV}} = -0.96$ V vs SCE in MeCN).^{22,23} The cyclic voltammetry experiment also supported that the reduction of $\text{BF}_3 \cdot \text{MeCN}$ ($E_p = -0.28$ V vs SCE in MeCN) and TMSOTf ($E_p = -0.18$ V vs SCE in MeCN) be favored by the $\text{Ir}(\text{III})^*$ species.⁴⁰ On the other hand, the fluorescence of $\text{Ir}(\text{III})^*$ was quenched by the Lewis acid activated imines (Figure 1a, the purple line), suggesting that the proposed reduction can also be applied to other Lewis acid–imine complexes, such as those imine complexes with

TMSOTf, Bi(OTf)₃, and BF₃·MeCN. Collectively, these Lewis acids—or more likely their coordinated counterparts—serve as electron acceptors and react with the photoexcited species Ir(III)* to generate Ir(IV) (Figure 1b), which initiates the photocatalytic cycle.^{42,43} It is worth noting that the product from the final reduction step is the Lewis acid coordinated thiomorpholine (6-LA, Scheme 1c), which is consistent with the need for a superstoichiometric amount of Lewis acid for successful cyclizations.

Equally important to the success of the overall reaction is reduction of the N-centered radical by a photoexcited state Ir(III)* species. Although the Ir(III)* reductant ($E_{1/2}^{*III/IV} = -0.96$ V)^{22,23} has a lower reduction potential than the Ir(II) species ($E_{1/2}^{III/II} = -1.51$ V) formed in the alternative system, we found it to be sufficient to reduce the Lewis acid coordinated N-centered radical (5-LA⁺). In the case of Cu(II) this is not surprising since the reduced Cu(OTf)–imine complex can be regarded as the same as the Cu(I) species–imine (radical anion) thought to be involved in copper catalyzed SNAP chemistry.^{7–14}

As the Lewis acid–N-centered radical cation complexes are easier to reduce than their uncoordinated variants, this conjecture suggests that photocatalysts with stronger oxidizing abilities (which usually have poorer reducing power) could be used to broaden the substrate scope of the SLAP chemistry. For the synthesis of substituted morpholines, the oxidation of α -silyl ethers ($E_p = +1.90$ V vs SCE in MeCN)^{24–27} is challenging, since the current photocatalyst Ir^{III}[(ppy)₂dtbbpy]PF₆—even in its Ir(IV) state—is not suited to perform the oxidation. We therefore examined cyclizations with the organic photocatalyst, 2,4,6-triphenylpyrylium tetrafluoroborate (TPP·BF₄), selected for its high oxidation ability ($E(S^*/S^{*-}) = +2.02$ V).^{44–47} While the reduced catalyst has rather low reduction potential ($E(S/S^{*-}) = -0.32$ V), this was sufficient to reduce the Lewis acid coordinated imine. With this system, both thiomorpholines and morpholines can be prepared using TPP·BF₄ as the photocatalyst (Scheme 4).

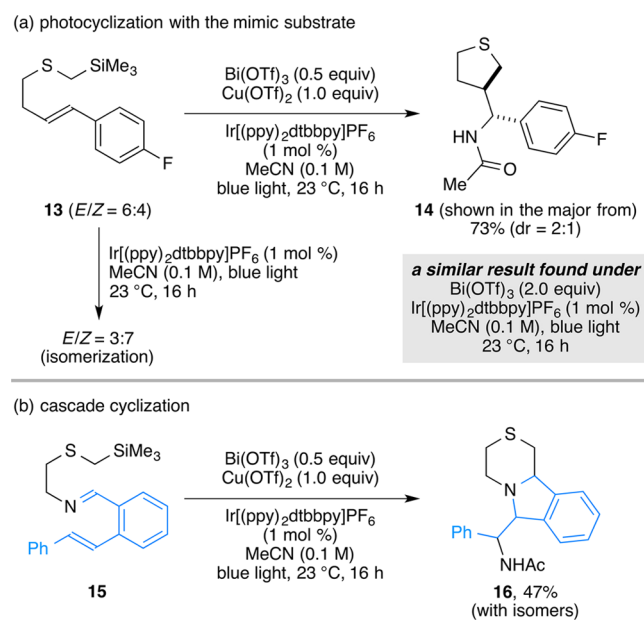
Scheme 4. Application to the Synthesis of Substituted Morpholines and Thiomorpholines^a



^a(a) See the Supporting Information for the details.

In further studies, we found that the combination of Lewis acids and photocatalytic conditions can lead to processes not typically thought to be viable. For example, alkene **13** gives only alkene isomerization in the presence of Ir[(ppy)₂dtbbpy]PF₆ with exposure to blue light, but gives cyclic product **14** when sufficient Cu(OTf)₂ or Bi(OTf)₃ are included in the reaction (Scheme 5). This product is formally a two-electron oxidation, likely via a radical cyclization to form the benzylic radical, which is further oxidized, and the resulting carbocation is trapped with one molecule of acetonitrile.^{48,49} This implies that 2 equiv

Scheme 5. Application to (a) the Cyclization of Mimic Substrate Alkene **13** and (b) Cascade Cyclization with Imine **15**



of the Lewis acid are reduced in the process. A similar observation was made with imine **15**, designed as a probe to capture the formation of the N-centered radical. These studies strongly suggest that the combination of Lewis acids or other electron acceptors can expand the range of accessible transformations available under photomediated conditions.

In summary, we have established that the inclusion of Lewis acids in photomediated reactions can induce an alternative photocatalytic cycle from the same Ir[(ppy)₂dtbbpy]PF₆ catalyst, thereby enabling transformations not available with previous systems. Taking advantage of this phenomenon, we expanded our recently developed SLAP reagents to more challenging thiomorpholine formation. The role of Lewis acids in modulating the reduction potential of the key intermediates can be further extended to other systems, including those mediated by organic photocatalysts. Mechanistic studies also point to a role for Lewis acids as single electron acceptors, resulting in transformations that are formally oxidations. These findings should make possible the development of general conditions for the formation of N-heterocycles from SLAP reagents and enable new photocatalytic transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00334.

Synthetic procedures and characterizations, Stern–Volmer fluorescence quenching experiments, cyclic voltammograms with Lewis acids, and crystallographic data (PDF)

X-ray crystallographic data for **14a** (CIF)

X-ray crystallographic data for **14b** (CIF)

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Notes

The authors declare no competing financial interest.

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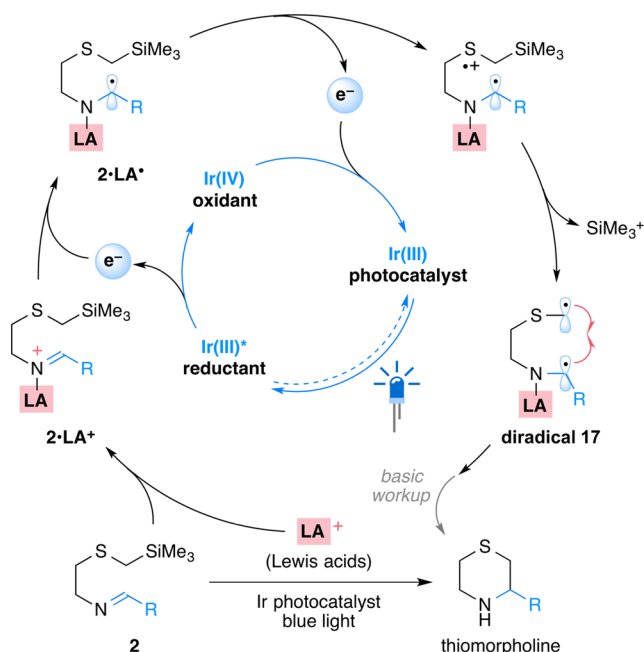
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