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Photoredox Radical/Polar Crossover Enables Construction of Saturated Nitrogen Heterocycles

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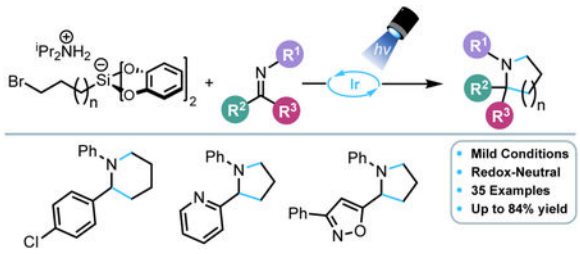
Abstract

Photoredox-mediated radical/polar crossover (RPC) processes offer new avenues for the synthesis of cyclic molecules. This process has been realized for the construction of medium-sized saturated nitrogen heterocycles. Photocatalytically generated alkyl radicals possessing pendant leaving groups engage imines in C–C bond formation, and subsequent reduction of the intermediate nitrogen-centered radical triggers anionic ring closure. With the aid of visible light irradiation, substituted pyrrolidines, piperidines, and azepanes can be prepared under mild, redox-neutral conditions.

Graphical Abstract



Heterocyclic compounds comprise 87% of known small molecule therapeutics.[1] Nitrogen-based heterocycles in particular are among the most common subunit in drug molecules.[2] These structures also serve as the backbone of ligands and appear in numerous natural and designed molecules.[1,2] In the context of drug development, the improved pharmacological

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, details of high-throughput screening, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds. (PDF)

Notes

The authors declare no competing financial interest.

properties of compounds with higher fractions of sp^3-hybridized centers[3] has sparked an increasing interest in incorporating saturated nitrogen-heterocycles in bioactive molecules.[4] Piperidines are the most prominent saturated nitrogen-heterocycles in therapeutic compounds, followed closely by piperazines and pyrrolidines.[2] The popularity and utility of these heterocycles motivates the pursuit of novel synthetic methods to prepare these cyclic systems in a mild and modular fashion.

The most common approach to introduce saturated nitrogen-heterocycles is a C–N bond-forming process through S_NAr chemistry, cross-coupling strategies such as Buchwald-Hartwig amination, or peptide coupling.[1,5] However, many medicinally relevant compounds possess α-substitution (often aryl, Figure 1), which poses challenges to these methods (Figure 2). A classical method for the synthesis of α-arylated nitrogen heterocycles is a lithiation followed by treatment with an electrophile or conversion into a suitable nucleophile (i.e., cuprate or zincate) for cross-coupling.[6] Another class of increasingly popular reactions are single-electron variants of the lithiation approach, initiated either through hydrogen-atom transfer (HAT)[7] or photoredox-induced oxidation of radical precursors (such as a carboxylic acids or trifluoroborates).[8] Although powerful, these strategies are contingent on having a preconstructed saturated *N*-heterocycle that is subsequently functionalized with the group of interest.

A less common approach to α-arylated nitrogen heterocycles is the construction of the ring from acyclic precursors through an annulation process. The most obvious way to accomplish such a process, reductive amination, is notoriously challenging, considering that the cyclic imine intermediate is prone to polymerization/dimerization.[9] Recently, a resurgence in methods based on the Hofmann–Löffler–Freytag (HLF) reaction have yielded elegant approaches to pyrrolidines from amines with distal olefins.[10] Like-wise, PCET has allowed lactams to be prepared from cyclization of an amidyl radical containing a pendant olefin.[11]

Recently, Bode and co-workers have developed a copper-mediated annulation process using “SnAP” reagents.[12] This strategy involves condensation of an organotin-tethered amine with an aldehyde to generate an aldimine. Subsequent oxidative generation of a heteroatom-stabilized primary carbon-centered radical via destannylative fragmentation triggers *6-endo-trig* cyclization. Reduction of the aminyl radical provides the desired nitrogen-heterocycle (e.g., thiomorpholine, oxazepane, 3-alkoxypyrrolidine). A silicon-variant of the annulation paradigm has also been developed using “SLAP” reagents and transitioned to continuous flow.[13]

The identification of various precursors that furnish alkyl radicals under photoredox conditions, such as Bode’s SLAP reagents, has led to the discovery of previously nonviable reactions and allowed new synthetic disconnections to be realized.[14] Visible-light photoredox catalysis provides a means to tap the synthetic potential of radicals in a way not possible when using stoichiometric radical generation techniques, while still retaining the benefits associated with odd-electron reactivity. These hallmarks of photoredox processes have precipitated their rapid uptake in both academia and industry, especially for late-stage functionalization.[15] Visible-light-mediated approaches have revolutionized an array of

different reaction classes, including cross-coupling,[16] cycloaddition,[17] and, recently, radical/polar crossover (RPC)[18] processes.

In the context of the latter, our group has initiated a program to apply various radical precursors in RPC processes that lead to annulation reactions, including the cyclopropanation of alkenes (Figure 3).[19] Inspired by the successes of these annulation processes and the SLAP/SnAP paradigm,[13,14] a novel approach to the synthesis of saturated nitrogen-based heterocycles from acyclic species was considered. The crux of this approach is the radical alkylation of an imine using an oxidizable, bifunctional radical precursor. Subsequent reduction of the resulting nitrogen-centered radical would furnish an amide anion that could engage a distal leaving group in an intramolecular displacement. A series of annulation processes (5-, 6-, or even *7-exo-tet* ring closures) can be envisioned using this improved radical/polar crossover approach. Indeed, typical methods to accomplish this type of process require a combination of stoichiometric $Mn_2(CO)_{10}$, $InCl_3$, and UV irradiation.[20]

The proposed annulation makes use of a small set of easily accessible bis(catecholato)silicate radical precursors.[21] These reagents have previously been effective for the radical alkylation of imines[22] and the cyclopropanation of olefins[19a] (Figure 3). Motivated by these previous successes, a preliminary screen was conducted wherein imine **1** was irradiated with a series of 3-halopropylsilicates (Cl, Br, I) in the presence of a photocatalyst [$Ru(bpy)_3(PF_6)_2$] in DMF (Table 1 entries 1-3). Although annulation was observed in all cases, the reaction generally proceeded slowly and gave poor conversion to the desired pyrrolidine **2**. Interestingly, of this series, the 3-bromopropylsilicate proved best. Speculatively, the 3-bromopropyl radical provides a good compromise of stability (3-iodopropyl radical is prone to S_H2 3-*exo-tet* cydization[23]) and reactivity (some addition without cyclization was observed when using 3-chloropropylsilicate). Reducing the loading of the 3-bromopropylsilicate and extending the reaction time led to more than doubling the yield of **2** (entry 4). High throughput experimentation (HTE) techniques revealed that using a twofold excess of the imine reagent provided a higher yield (See Supporting Information). However, excess imine could be recovered upon chromatographic purification in cases where the imine is valuable (such as late-stage derivatization scenarios). Scale up of these conditions gave identical yield in a much shorter period (entry 5). Evaluation of alternative photocatalysts revealed that $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ was superior (entries 6-7). Using this photocatalyst and a more powerful light source, the reaction time was reduced to a mere 30 min (entry 9). Various additives were screened, but gave either similar or diminished yields (see Supporting Information for details). Control studies confirmed irradiation was necessary for reactivity (entry 10), but the reaction could proceed (albeit in poor yield) in the absence of a photocatalyst (entry 11). Given that alkylsilicates are known to fragment when irradiated with UV-A/UV-B light, an electron donor–acceptor complex[24] between the highly conjugated imine and the bis(catecholato) moiety may form, facilitating light-mediated radical generation.

With suitable conditions established, the scope of the annulation process was examined (Scheme 1). In general, when using 3-bromopropylsilicate, a variety of *N*-phenyl aldimines were amenable to the RPC cyclization process to provide the corresponding pyrrolidines. In some cases, extending the reaction time to 16 h was necessary to give improved yield. The

reaction tolerated imines derived from both electron-rich and electron-poor benzaldehydes, including a free phenol (**5**). The cyclization of benzothiophene, isoxazole, and pyridine-containing imines successfully provided pyrrolidines **10**-**12**. Substituents with a variety of steric and electronic characteristics were tolerated on either of the aryl rings on the imine substrate. In particular, replacement of the *N*-phenyl group with a *p*-methoxyphenyl (PMP) group gave comparable yield of pyrrolidine product (**2** vs. **19**). Given the ability to oxidatively cleave PMP groups, these species would be suitable for further derivatization. Additionally, other cleavable groups were compatible with the RPC annulation process. Both *p*-toluenesulfonyl and *N,N*-dimethylsulfamidyl aldimines underwent the cyclization process to provide **22** and **23**, respectively, but in diminished yields. Unfortunately, the process could not be extended to unprotected (NH) imines, *N*-Boc-imines, or hydrazones. Using a 4-bromobutylsilicate and identical reaction conditions, piperidines were accessible from aldimines in comparable yields (**24**-**27**). Attempts using either a 5-bromopentylsilicate or 5-iodopentylsilicate reagent did provide azepane **28**, although in low yield. The major product observed was the uncyclized alkyl halide. In these cases, the rate of protonation by the acidic ammonium counterion of the alkylsilicate likely exceeds the rate of 7-*exo*-*tet* cyclization. Smaller rings could not be obtained through this method; only traces of the corresponding aziridine were observed. The inability to access the requisite 2-bromoethylsilicate (likely because of facile β-silyl elimination) prevented any attempts at preparing azetidines.

Ketimines were also amenable to the reaction, allowing pyrrolidines with α-quaternary centers to be assembled rapidly. In general, ketimines derived from benzophenones fared best. Various aryl ring substituents had minimal effect on yield (**29**-**32**), an observation consistent with aldimines. Mixed aryl-alkyl ketimines could be used, albeit with diminished yields. Subjecting a ketimine derived from an α-CF_3 ketone enabled synthesis of α-CF_3-substituted pyrrolidine **33**. Similarly, an acetophenone-derived ketimine was competent in the annulation process (**34**). Ketimines also provide opportunities for bicyclic ring construction, as demonstrated by the preparation of benzopyrrolizidine **35**. This bicyclic structure bears resemblance to the core of recently reported anticancer candidates.[25] Piperidines bearing α-quaternary centers are also accessible using this RPC approach. Aryl ketiminoacetates and ketimidates, however, were not amenable to this process. The formation of piperidines from ketimines using the analogous 4-bromobutylsilicate reagent was not as effective as piperidine formation, and in some cases unexpected side products were observed.

Based on the prior art[18-21] and our own observations during the course of this study, the following sequence of events constitute a plausible mechanistic path for the annulation process: (1) Visible light-mediated photoexcitation of **I** to its excited state **II**; (2) Reductive quenching of **II** ($E_{1/2}$ [P*/P]: 1.35 V vs SCE) by the bifunctional alkylsilicate ($E_{1/2}$ = +0.4–0.7 vs SCE for most alkylsilicates); (3) Homolytic fragmentation of oxidized **IV** to furnish alkyl radical **V**, which readily adds to imine **VI**, giving the *N*-centered radical **VII**; (4) SET reduction of**VII** by the reduced state of **III** to provide amide anion **VIII**; (5) C-N bond formation and ring closure by way of anionic cyclization, giving **IX** (Fig. 4).

The radical/polar annulation process described herein enables the rapid construction of saturated nitrogen heterocycles from acyclic precursors. This RPC reaction accommodates

numerous functional groups, occurs under mild conditions, and can be completed in as little as 30 minutes. Furthermore, its modular nature allows various medium-sized rings to be assembled from a single imine by adjusting the alkylsilicate used, and it also permits quaternary centers to be established α to nitrogen with ease. The inherent flexibility and benign conditions of this strategy make it ideal for the late-stage introduction of saturated *N*-containing heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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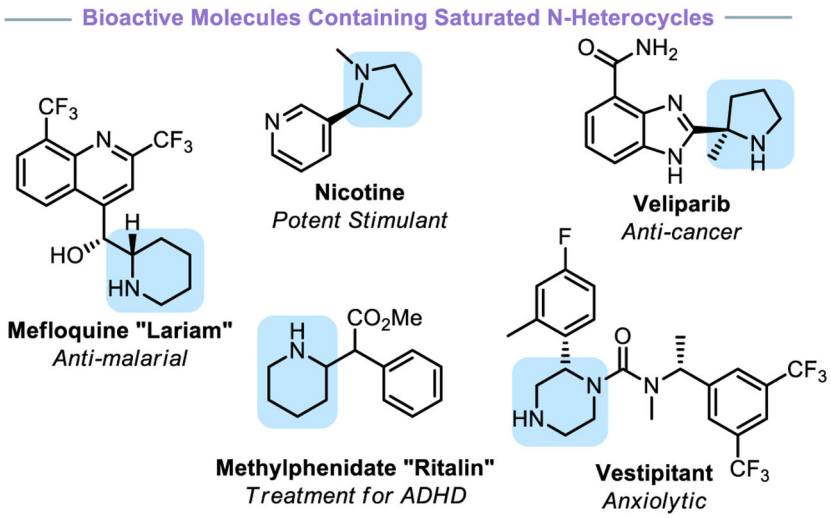


Figure 1.
Bioactive nitrogen-containing heterocycles.

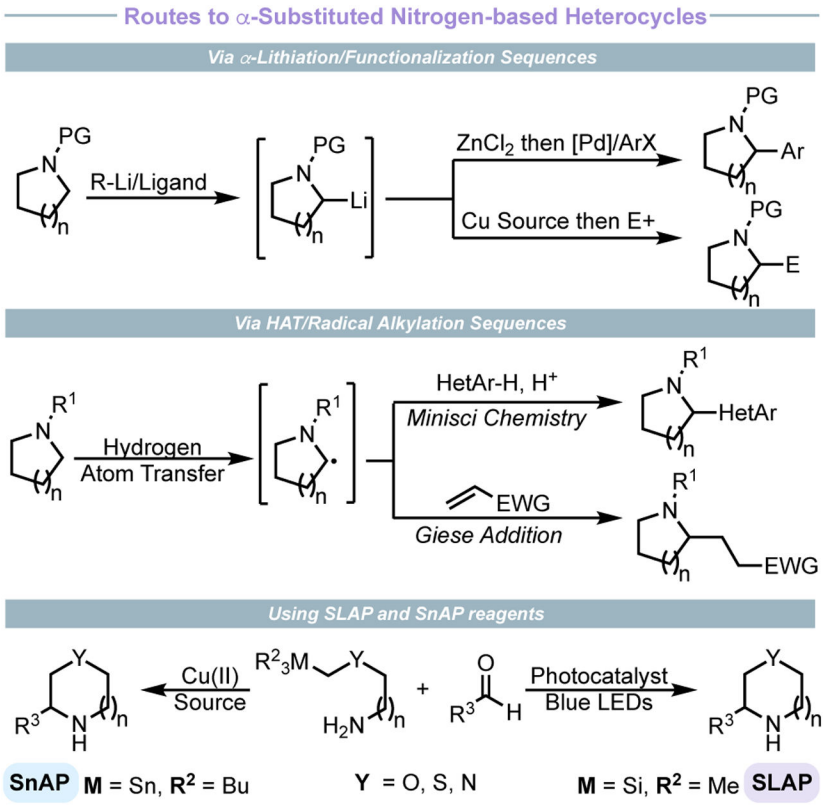


Figure 2.
Typical approaches to saturated nitrogen heterocycles.

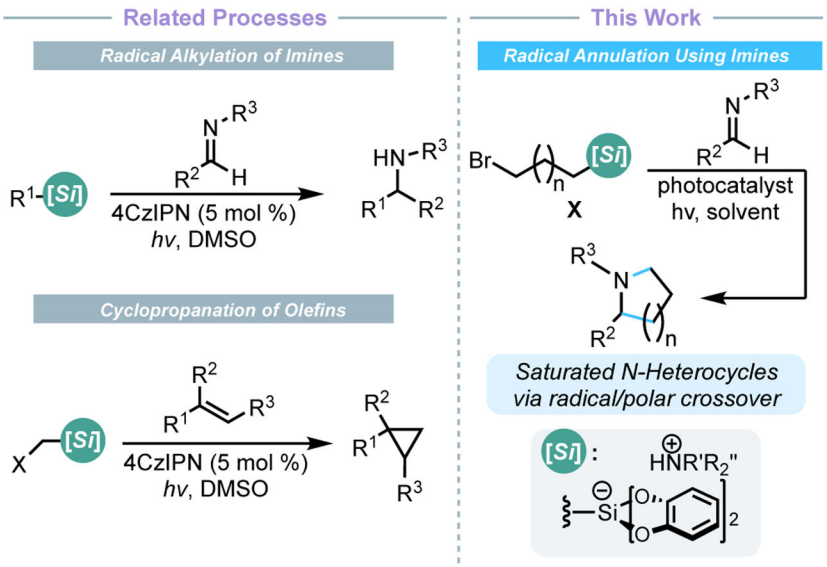


Figure 3.
Comparison of related developments to this work.

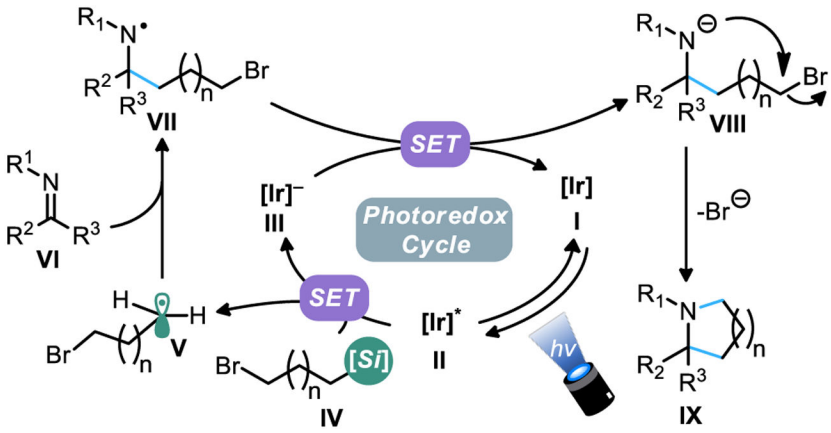
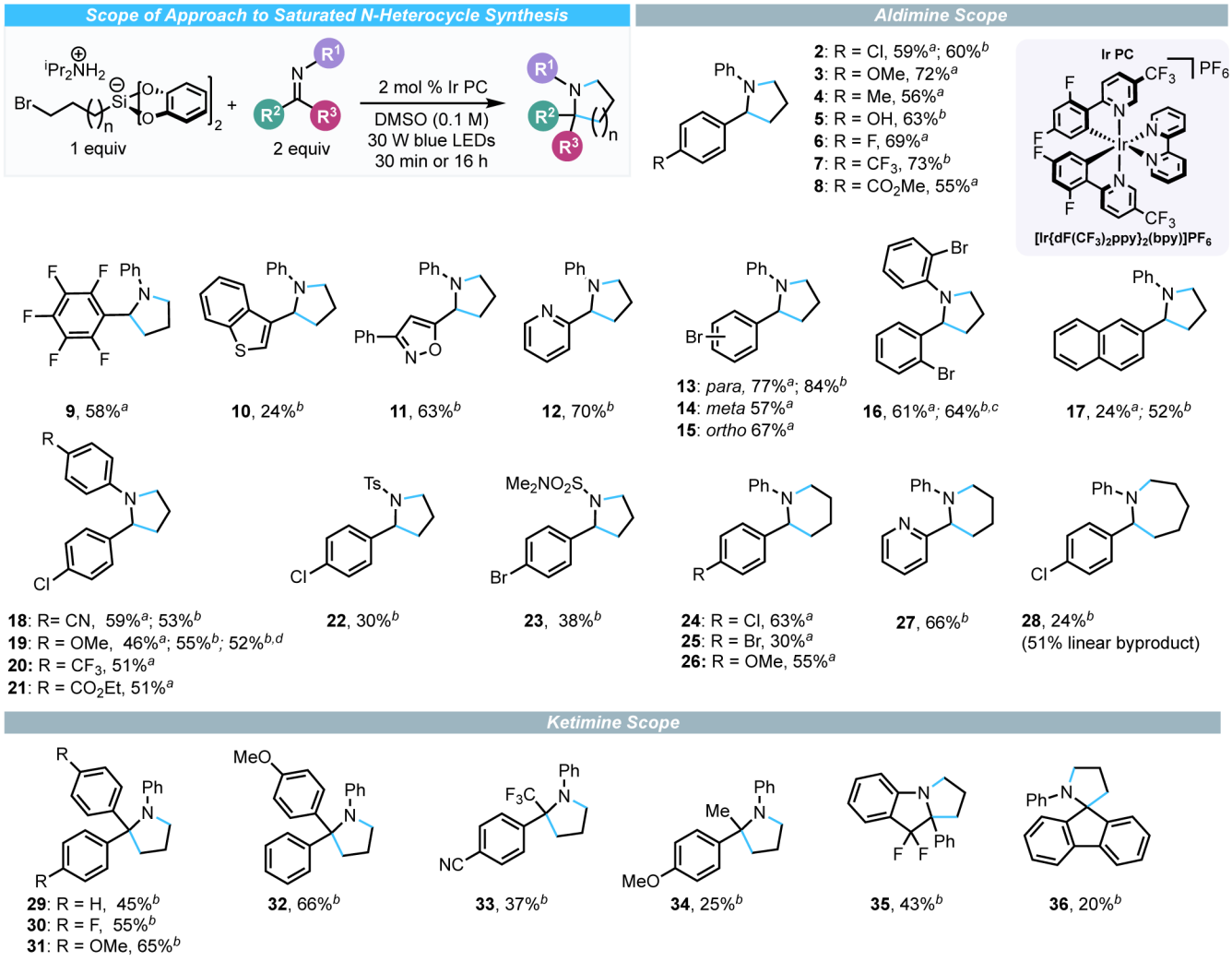


Figure 4.
Plausible mechanism for the annulation process.

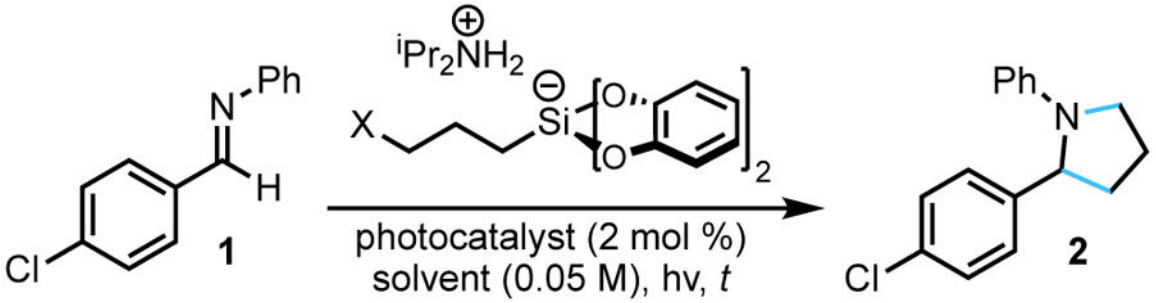


Scheme 1.

Scope of the Radical Alkylation/Cyclization Processes with Imines.[a b]

Table 1.

Optimization of the annulation process.[a]



entry [a]	X	photocat.[b]	solvent	time (h)	yield (%)[c]
1	Cl	[Ru]	DMF	16	8
2	Br	[Ru]	DMF	16	20
3	I	[Ru]	DMF	16	10
4[d]	Br	[Ru]	DMF	48	46
5[e]	Br	[Ru]	DMSO	16	46
6[e]	Br	[Ir]	DMSO	16	54
7[e]	Br	4CzIPN	DMSO	16	35
8[f]	Br	[Ir]	DMSO	16	60
9[f]	**Br**	[Ir]	**DMSO**	**0.5**	**59**
10[f,g]	Br	[Ir]	DMSO	16	–
11[f]	Br	–	DMSO	16	17[h]

[a]Conditions unless otherwise noted: silicate (5 equiv, 1.5 mmol), imine (1.0 equiv, 0.3 mmol), photocatalyst (2 mol %), DMSO (0.1 M), irradiating with 21 W CFL.

[b]Photocatalyst: [Ru] = $[Ru(bpy)_3](PF_6)_2$ and [Ir] = $[Ir\{dF(CF_3)_2ppy\}_2(bpy)]PF_6$.

[c]Isolated yield after purification.

[d]2 equiv of silicate used.

[e]A 1:2 silicate/imine ratio used along with 4 W blue LEDs.

[f]A 1:2 silicate/imine ratio used along with 30 W blue LEDs.

[g]Reaction conducted in the dark.

[h]NMR yield of crude reaction mixture.