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Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis

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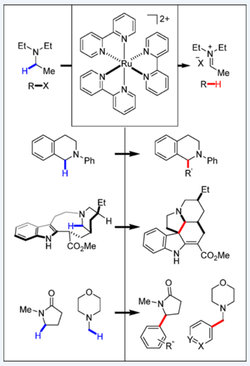

CONSPECTUS: While the use of visible light to drive chemical reactivity is of high importance to the development of environmentally benign chemical transformations, the concomitant use of a stoichiometric electron donor or acceptor is often required to steer the desired redox behavior of these systems. The low-cost and ubiquity of tertiary amine bases has led to their widespread use as reductive additives in photoredox catalysis. Early use of trialkylamines in this context was focused on their role as reductive excited state quenchers of the photocatalyst, which in turn provides a more highly reducing catalytic intermediate.

In this Account, we discuss some of the observations and thought processes that have led from our use of amines as reductive additives to their use as complex substrates and intermediates for natural product synthesis. Early attempts by our group to construct key carbon−carbon bonds via free-radical intermediates led to the observation that some trialkylamines readily behave as efficient hydrogen atom donors under redox-active photochemical conditions. In the wake of in-depth mechanistic studies published in the 1970s, 1980s and 1990s, this understanding has in turn allowed for a systematic approach to the design of a number of photochemical methodologies through rational tuning of the amine component. Minimization of the C−H donicity of the amine additive was found to promote desired C−C bond formation in a number of contexts, and subsequent elucidation of the amine's redox fate has sparked a reevaluation of the amine's role from that of reagent to that of substrate.

The reactivity of tertiary amines in these photochemical systems is complex, and allows for a number of mechanistic possibilities that are not necessarily mutually exclusive. A variety of combinations of single-electron oxidation, C−H abstraction, deprotonation, and β-scission result in the formation of reactive intermediates such as α-amino radicals and iminium ions. These processes have been explored in depth in the photochemical literature and have resulted in a firm mechanistic grasp of the behavior of amine radical cations in fundamental systems. Harnessing the synthetic potential of these transient species represents an ongoing challenge for the controlled functionalization of amine substrates, because these mechanistic possibilities may result in undesired byproduct formation or substrate decomposition. The presence of tertiary amines in numerous alkaloids, pharmaceuticals, and agrochemicals lends credence to the potential utility of this chemistry in natural product synthesis, and herein we will discuss how these transformations might be controlled for synthetic purposes.

INTRODUCTION

Historically, $Ru(bpy)_3^{2+}$ and similar photoactive complexes have been used for water oxidation[1] and CO_2 reduction,[2] with examples of the latter often employing tertiary amines as sacrificial electron donors. Recent photochemical methods using $Ru(bpy)_3Cl_2$[3] reported by MacMillan,[4] Yoon,[5] and our group[6] utilized amines as reductive intermediates or as stoichiometric additives for quenching of the $Ru(bpy)_3^{2+*}$ photoexcited state to initiate fundamentally important organic reactions (Scheme 1).[7] The use of amines as reductants for photocatalysis is ideal, because trialkylamines are inexpensive, ubiquitous, and readily oxidized.[8] As the research field has progressed, further practical understanding of amine reactivity in these systems has allowed for a broadening scope of application in photoredox catalysis.[9] Herein, we will discuss the progression of results that have led to our current implementation of amines, first as additives and later as substrates, in photoredox catalysis and share some of the insights gleaned in this process.

The use of tertiary amines as reductive quenchers is not limited to net-reductive transformations, and there are many examples of redox-neutral transformations that utilize amines as stoichiometric additives.[7a] As evidenced by the redox cycle of $Ru(bpy)_3^{2+}$ (Scheme 1A), the ground state reducing potential of the complex ($E_{1/2}^{II/I} = -1.33$ V vs SCE) is significantly more negative than that of the excited state ($E_{1/2}^{III/II*} = -0.81$ V vs SCE).[10] As a consequence, $Ru(bpy)_3^{2+}$ mediated photoredox reactions that require a strong reduction potential sometimes incorporate stoichiometric reductive quenchers in order to access the more strongly reducing Ru^{1+} species.

While trialkylamines have often been exploited for this purpose, through the years an understanding of further reactivity of the amine radical cation has evolved to the point where the amine can be used as a substrate for controlled photochemical oxidation. Using triethylamine as an example, single-electron

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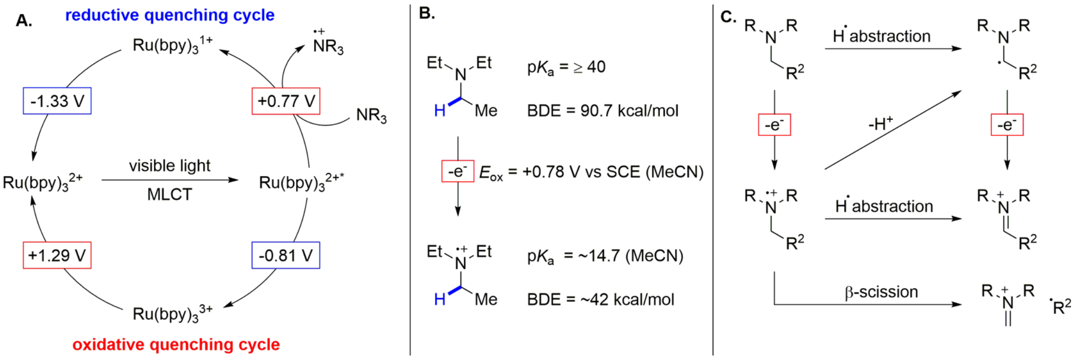
Scheme 1. Redox Cycle of Ru(bpy)$_3^{2+}$ and Further Amine Reactivity



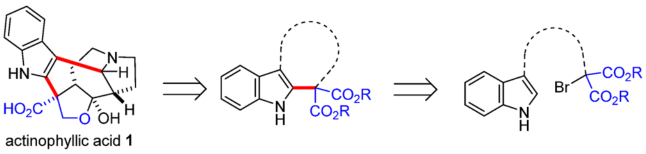
oxidation to the radical cation results in a dramatic estimated acidification of the α-amino C−H bond (Scheme 1B).[8,11,12] The α-C−H bond of the aminium ion is also significantly weakened to an estimated ∼42 kcal/mol.[13] Detailed studies by Lewis,[14] Mariano,[15] and Saveant,[16] to name a few,[17] have elucidated many mechanistic aspects of amine radical cation α-C−H functionalization in terms of electronics, sterics, and regiochemical outcome. This remarkable activation through the removal of a single electron allows for a number of subsequent mechanistic pathways leading to useful reactive synthetic intermediates (Scheme 1C). We have found a number of instances in which these modes of reactivity can be controlled and will delineate some of the guiding design features of these reactions below.

NATURAL PRODUCTS AS INSPIRATION FOR REACTION DEVELOPMENT

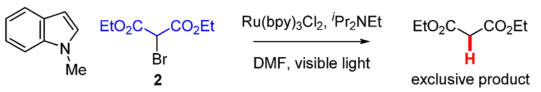
Our initial interest in the reactivity afforded by photoredox catalysis arose from strategic bond disconnections in the context of complex molecule synthesis. At the start of our research program, the natural product actinophyllic acid **1** served as inspiration for novel bond disconnections in the context of photoredox catalysis (Scheme 2A).[18] Specifically, the ability to directly functionalize the 2-position of indoles with a malonate equivalent was envisioned to allow for the desired bond disconnections en route to the natural product. Using Ru(bpy)$_3$Cl$_2$ as the photocatalyst and ^{i}Pr$_2$NEt as the reductive quencher, the initial attempt to perform the light-mediated intermolecular functionalization of *N*-methylindole with diethyl bromomalonate **2** resulted in complete hydrodehalogenation of the bromomalonate reactant (Scheme 2B), giving diethyl malonate as the exclusive product.

Scheme 2. Actinophyllic Acid as Inspiration for Radical Indole Malonation

A. Actinophyllic acid as inspiration for intra- or intermolecular indole functionalization chemistry



B. Initial attempt for intermolecular indole malonation using photoredox catalysis



Further experimentation related to indole functionalization was motivated by another natural product of interest, (+)-gliocladin C, **3** (Scheme 3A). We were curious whether we could access tertiary radical intermediates such as **4** through the photochemical single-electron reduction of related bromopyrroloindoline scaffolds.[19] Again using ^{i}Pr$_2$NEt as the reductive quencher, initial attempts to couple the Boc-protected bromopyrroloindoline substrate **5** with indole resulted in the isolation of the hydrodehalogenated product **6** in 75% yield (Scheme 3B). While the lack of desired intermolecular reactivity represented a setback in terms of our goals of natural product synthesis, we realized that the general efficiency that we observed for the reductive hydrodehalogenation reactivity may be leveraged into a more generalized methodology.[20]

Initial investigations into the reaction conditions were performed using substrate **7**, which could be dehalogenated in high yield using 10 equiv of the formate salt of Hunig's base in DMF in only 4 h (Table 1, entry 1).[6] It was found that substitution of diisopropylethylamine with triethylamine resulted in incomplete conversion (only 25%) after a significantly increased reaction time of 24 h (entry 2). Further experimentation revealed that Hantzsch ester **8** could be used in place of formic acid to significantly decrease the equivalents of additive used (entry 3). The scope of the reaction was found to encompass a number of activated alkyl halides, but unactivated vinyl and aryl halides were unaffected under the reaction conditions.

Mechanistically, it is expected that this reaction proceeds through reductive quenching of the Ru(bpy)$_3^{2+*}$ excited state. As a result of this quenching process, the trialkylammonium formate radical cation is thought to perform the role of the major H atom source in the reaction. The observed difference in reactivity between the triethyl- and diispropylethylamine additives was valuable information, which we were next able to use as a design principle to minimize hydrodehalogenation byproduct formation; we eagerly applied this knowledge toward our previous goals of indole functionalization. With the hypothesis that the rate of an intramolecular indole functionalization reaction may be sufficient to outcompete intermolecular C−H abstraction from a poor H-atom donor, we began to investigate this chemistry using tethered malonates such as **9** (Scheme 4).[21] As supported by previous observations, the use of Hunig's base as a reductive quencher in an intramolecular radical addition to indole resulted in a significant amount of hydrodehalogenation byproduct **10** (Scheme 4A). Triethylamine was again found to be less promoting of hydrodehalogenation (*vide supra*) and as a result was selected for the more generalized conditions (Scheme 4B).

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Scheme 3. Gliocladin C as Inspiration for Methodology Development

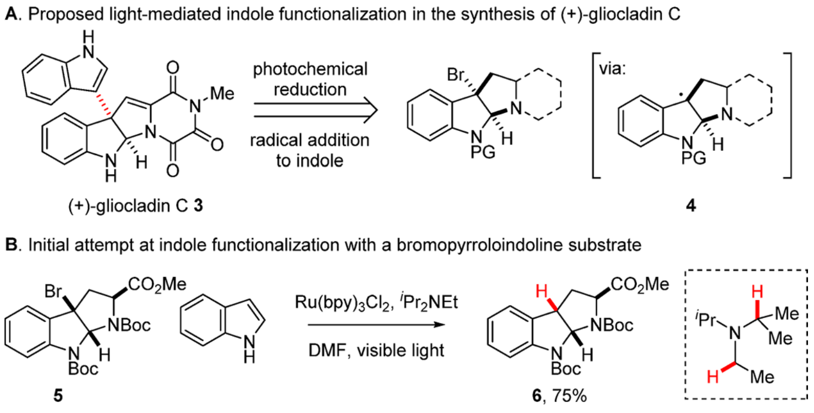
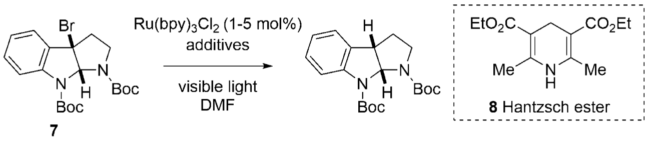


Table 1. Optimization of the Reductive Dehalogenation Reaction



entry	additives	time (h)	yield (%)
1	^{i}Pr$_2$NEt (10 equiv), HCOOH (10 equiv)	4	90
2	Et$_3$N (10 equiv), HCOOH (10 equiv)	24	20
3	^{i}Pr$_2$NEt (2 equiv), **8** (1.1 equiv)	4	95

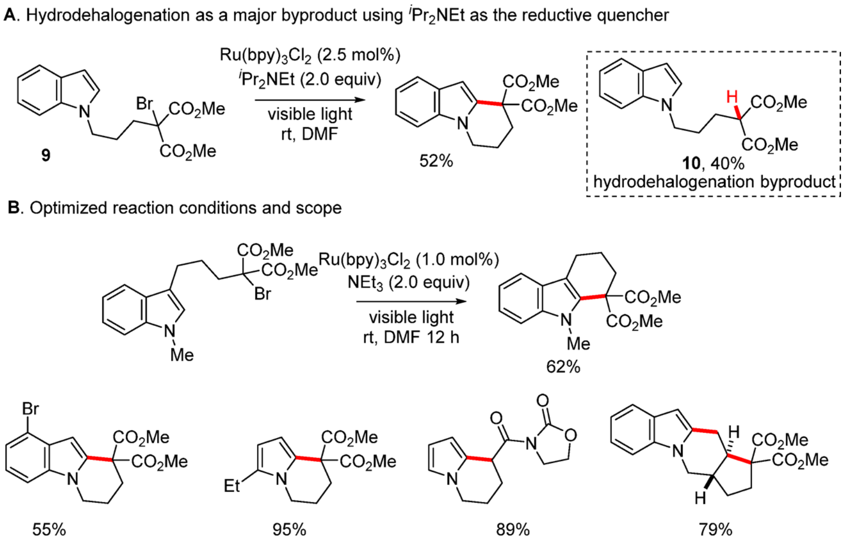
While hydrodehalogenation was minimized by using triethylamine, a number of additional insights were uncovered during the investigation of this reaction. Most notably, when substrate **11** was subjected to the standard conditions, a mixture of three products was produced, with acetaldehyde incorporated product **12** present in 20% yield (Scheme 5A).[22] The genesis of this material can be rationalized through iminium formation from the triethylamminium radical cation, either through direct C−H abstraction or a sequential deprotonation−oxidation process (Scheme 5B). Tautomerization of the iminium ion provides an enamine equivalent, which is electronically paired with the electron-poor malonyl radical to produce the undesired aldehyde product **12** after radical addition, oxidation, and hydrolysis of the product iminium ion. The isolation of this material was further evidence of our mechanistic hypotheses involving α-amino C−H chemistry and provided further confidence in our understanding of the observed reactivity going forward.

■ TERTIARY AMINES AS SUBSTRATES

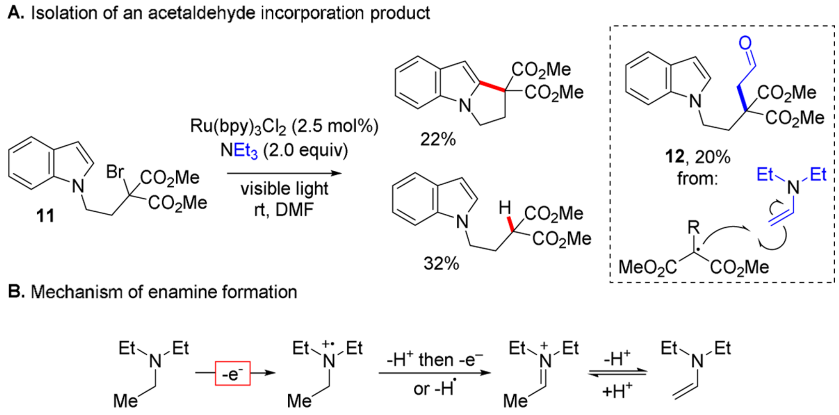
With this insight into the fate of the amine component, the possibility of applying this chemistry to the α-functionalization of tertiary amine-containing substrates became more appealing to us.[23] The issue of regioselectivity in α-amino functionalization was vital, because factors determining which C−H bond would react were expected to be governed chiefly by substrate characteristics.[14] With this in mind, efforts to functionalize *N*-aryl tetrahydroisoquinolines were undertaken.[24] In our initial design, we anticipated that we could leverage our prior observations in Scheme 5 to selectively form iminium ions; we expected a dual role for the bromomalonate, where it first would behave as the terminal oxidant before subsequent enlistment as a nucleophile (Scheme 6A).

An early experiment along these lines utilized *N*-phenyl tetrahydroisoquinoline **13** as the substrate (Scheme 6B). Using the photocatalyst Ru(bpy)$_3$Cl$_2$ and diethyl bromomalonate **2** in DMF, the reaction was run with an aim to produce malonate functionalization at the benzylic position of the substrate.

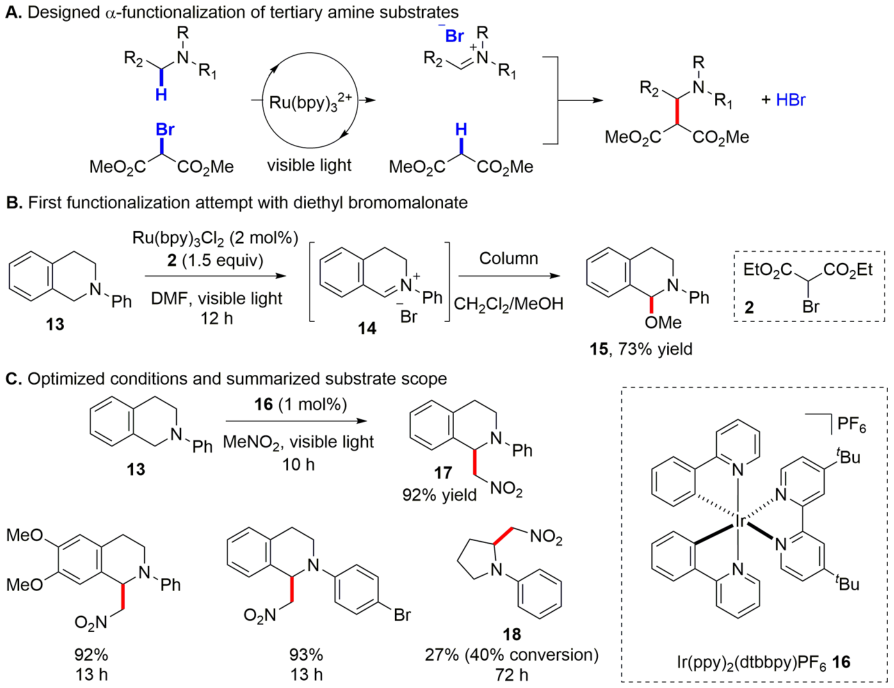
Scheme 4. Intramolecular Radical Malonation of Heterocycles



Scheme 5. Understanding the Fate of the Amine Reductive Quencher



Scheme 6. Oxidative Functionalization of *N*-Aryl Tetrahydroisoquinolines



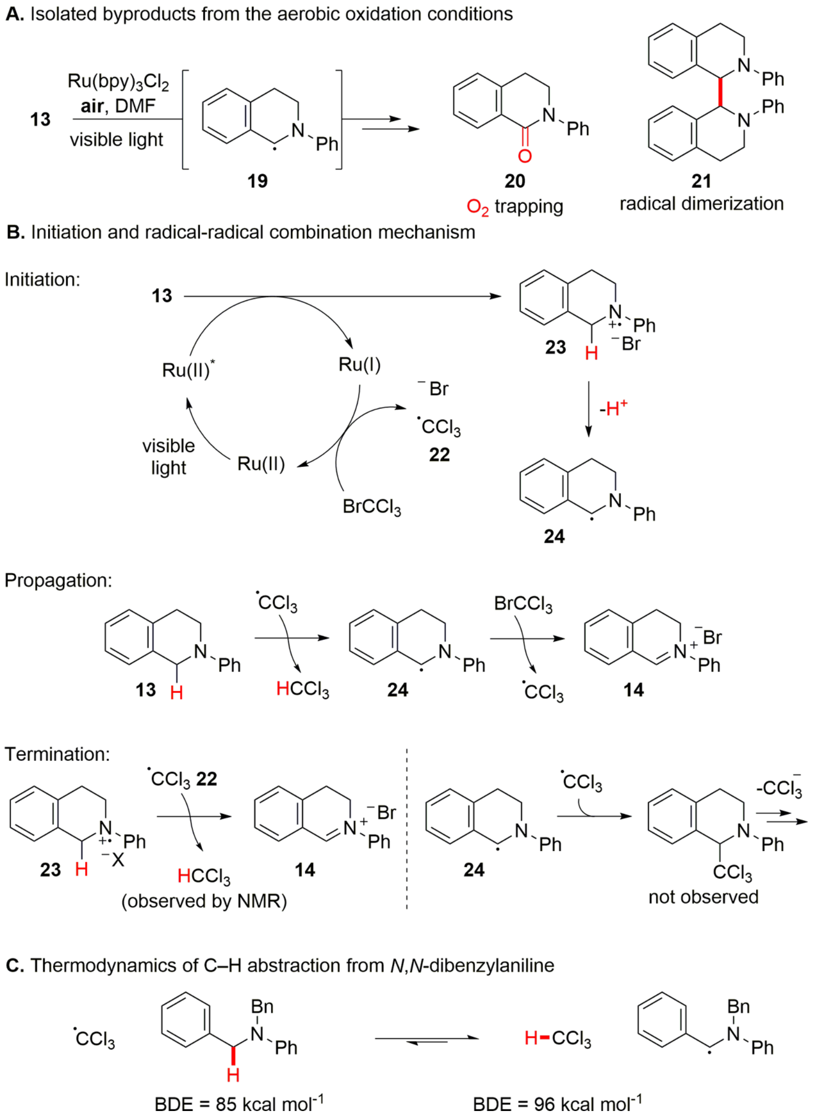
Curiously, the starting material was consumed in an overnight reaction, but none of the desired product was observed. Instead, after careful analysis of the reaction, **15** was isolated as the sole product, resulting from methanol trapping of iminium **14** during column chromatography.

Interestingly, the reaction was found to proceed with 100% conversion in methanol without the use of diethylbromomalonate; however, later experiments revealed that the reaction slowed significantly in the absence of oxygen, pointing toward oxygen's role as the terminal oxidant.[25] With nitromethane as the solvent, high yields of the aza-Henry product **17** could be obtained (Scheme 6C). We also experimented with the use of the cyclometalated heteroleptic iridium-based catalyst $Ir(ppy)_2(dtbbpy)PF_6$,[26] **16**, which we found to accelerate the aerobic aza-Henry reaction significantly and provide the product in higher yield. A slow background reaction was observed, providing 83% conversion of the starting material after 5 days when no catalyst was present. An unexpected challenge associated with this chemistry was encountered upon evaluation of the substrate scope. A wide range of *N*-aryl tetrahydroisoquinolines provided >90% yield in 18 h or less; however, *N*-phenyl pyrrolidine provided 27% yield of the aza-Henry product **18** in only 40% conversion after a 72 h reaction time.

The aerobic oxidation reactions were somewhat slow (10−18 h) compared with reaction rates with terminal organic oxidants such as diethylbromomalonate (2 h). Additionally, byproducts were often isolated from the reactions, including the endocyclic amide **20** and dimer **21**, both presumably arising from an *α*-amino radical intermediate (Scheme 7A).[27] We postulated that anaerobic oxidation of the substrate using a suitable oxidant such as bromochloroform may result in direct iminium formation through C−H abstraction from **13** by the resulting trichloromethyl radical **22** (Scheme 7B).

While the anaerobic use of $BrCCl_3$ was empirically effective in eliminating the observed byproducts, the profound increase in observed reactivity is likely attributable to an efficient chain propagation mechanism (Scheme 7B). Propagation of the free-radical intermediates through sequential atom-transfer reactions may explain how the reaction is able to proceed with such efficiency. Direct C−H abstraction from the closed shell

Scheme 7. Mechanistic Possibilities for Substrate Oxidation with $BrCCl_3$


A. Isolated byproducts from the aerobic oxidation conditions

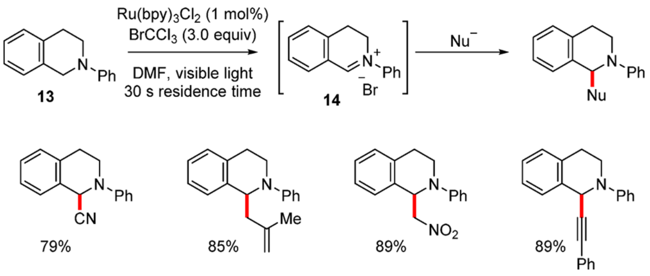
B. Initiation and radical-radical combination mechanism

C. Thermodynamics of C–H abstraction from *N*,*N*-dibenzylaniline

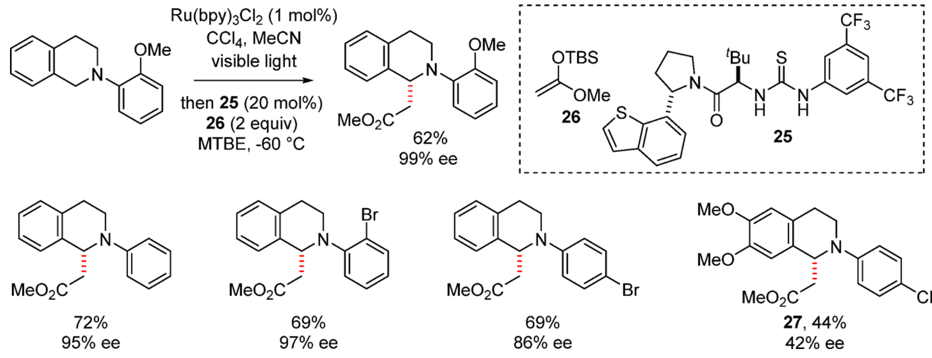
substrate **13** would form the α-amino radical **24**, which then can be further oxidized by another equivalent of $BrCCl_3$ to form the iminium ion **14** while reforming an additional equivalent of trichloromethyl radical. The radical–radical disproportionation between **22** and **23** is a statistically disfavored termination step, since presumably the individual concentrations of the two free-radical intermediates are low. The propagation mechanism is also statistically favored, because the $BrCCl_3$ is used in stoichiometric excess (3 equiv). Furthermore, the bond dissociation energies (BDE) of this propagation are estimated to align with a thermodynamically favored process, since the experimental C–H BDE of chloroform is 96 kcal/mol[28] while the BDE of a methylene C–H bond of *N*,*N*-dibenzylaniline is measured at 85 kcal/mol (Scheme 7C).[29] More recent work from our group has provided evidence for a propagation mechanism in a light-mediated atom transfer reaction.[30] One of the benefits of these types of mechanisms is that in the event of a chain termination, reactive intermediates can be continuously produced by the catalyst.

While the use of $BrCCl_3$ decreased reaction times to 3 h, we have been able to shorten reaction time even further by applying the optimized oxidative conditions in a flow reactor.[31] For example, the oxidation of *N*-phenyl tetrahydroisoquinoline **13** to the iminium ion **14** proceeds with a residence time[32] of only 0.5 min (Scheme 8), which corresponds to material throughput of 5.75 mmol h^{-1}, a roughly 70-fold increase in comparison to batch reaction material throughput. The flow reaction can be eluted into a stirred solution of nucleophile for facile structural diversification, with cyanation, allylation, and alkynylations all proceeding in good yields.

Scheme 8. Flow Functionalization of *N*-Phenyl Tetrahydroisoquinoline

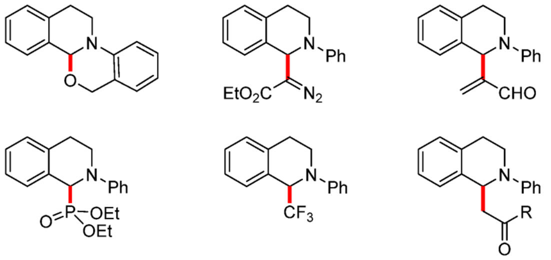


Scheme 9. Asymmetric Nucleophilic Addition Using Anion Binding Catalysis

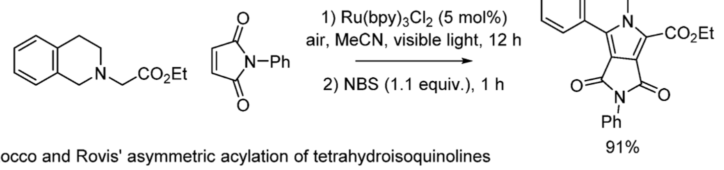


Scheme 10. Selected Reactivity Compatible with Photochemical Amine Oxidation

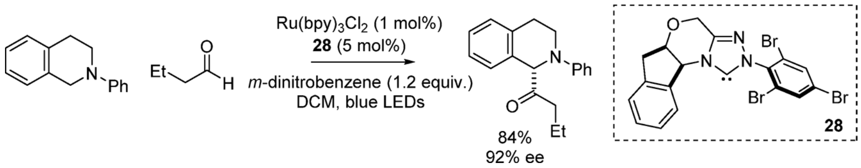
A. Select examples of diverse nucleophile trapping (ref. 34)



B. Xiao's oxidative [3+2] cycloaddition



C. DiRocco and Rovis' asymmetric acylation of tetrahydroisoquinolines



Further work in our lab to elaborate the chemistry of photochemical amine oxidation has involved the asymmetric alkylation of iminium ions of type **14** through the use of chiral anion-binding catalysis in collaboration with Jacobsen and co-workers (Scheme 9).[33] Because the reductive dehalogenation of $BrCCl_3$ or CCl_4 results in the formation of halide counterions associated with the oxidized substrate, it was postulated that the use of thiourea catalysis would enable stereoselective nucleophilic addition.

Initial reactions focused on the use of silyl ketene acetal **26** for nucleophilic addition to the iminium intermediate. Unfortunately, the photocatalyst $Ru(bpy)_3Cl_2$ was found to be entirely insoluble in methyl *tert*-butyl ether (MTBE) as well as other nonpolar solvents known for providing high enantioselectivities in concert with thiourea catalysis. Unsurprisingly, high yields of racemic products were isolated from reactions performed in DMF, CH_2Cl_2, and MeCN. As a solution to the orthogonal polarity requirements for each mode of catalysis a solvent switch was required; The MeCN was removed upon complete photochemical oxidation of the substrate, and the reaction was reconstituted in MTBE for the nucleophilic addition step.

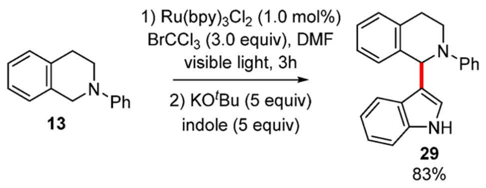
Since our initial report,[23] oxidative amine photoredox catalysis has become more widely adopted, and many additional examples of nucleophilic additions to tetrahydroisoquinolines have been published (Scheme 10A).[34] The versatility of these systems is impressive, and there have been many creative additions to the literature in this context. Xiao and co-workers have demonstrated the compatibility of the photochemical tetrahydroisoquinoline oxidation with dipolar [3 + 2] cycloaddition chemistry (Scheme 10B), performing a final oxidation with *N*-bromosuccinimide (NBS) to provide penta-substituted pyrrole products.[35] Additionally, the oxidative conditions are fully compatible with N-heterocyclic carbene cocatalysis, which DiRocco and Rovis have demonstrated elegantly (Scheme 10C).[36] These extensions of the amine oxidation highlight the versatility and robust nature of the photochemical tetrahydroisoquinoline oxidation.

■ *α*-AMINO C–H AND C–C FUNCTIONALIZATION OF TERTIARY ALIPHATIC AMINES

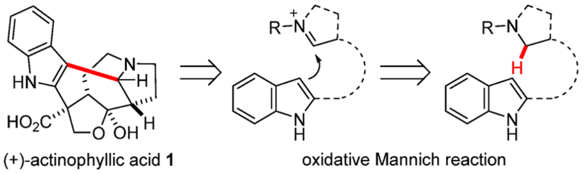
Experimentation with *N*-phenyltetrahydroisoquinoline **13** revealed efficient intermolecular Mannich reactivity with indole to provide **29** in 83% yield (Scheme 11A). These developments toward an efficient *α*-amino functionalization reaction represented additional opportunity for us in alkaloid synthesis, particularly in the context of an oxidative Mannich reaction en

Scheme 11. Alkaloids as Further Inspiration for Reaction Development

A. Intermolecular oxidative Mannich reaction with a tetrahydroisoquinoline substrate



B. Oxidative Mannich reaction as a key bond disconnection



(+)-actinophyllic acid **1**

route to actinophyllic acid **1** (Scheme 11B). With a working knowledge of the α-amino functionalization of tetrahydroisoquinolines and how these processes can be accelerated with flow chemistry, we began developing ways to apply these concepts in a more complex setting. A key challenge was the lack of general substrate scope for the oxidative iminium forming reaction, because early experimentation had shown that even simple dialkyl anilines such as *N*-phenylpyrrolidine were recalcitrant to product formation (*vide supra*).

The commercially available natural product (+)-catharanthine **30** was selected as a starting material for our initial investigations in this area (Scheme 12). A series of reports on the total synthesis of (+)-vinblastine and related natural products by Boger and coworkers detailed the reactivity of **30** upon oxidation by FeCl$_3$.[37] Bolstered by the possibility of promoting carbon−carbon bond fragmentation through reductive quenching of a photocatalyst excited state,[38] we began to investigate the reactivity of catharanthine under photocatalytic conditions.[39]

It was found that light exposure of a solution of catharanthine, Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (2.5 mol %), and trimethylsilylcyanide (TMSCN, 2.0 equiv) in methanol provided the cyanated ring-opened product **31** in 93% yield after 3 h.[40] Application of these exact conditions in a flow reactor resulted in the scalable application of this procedure to 2 g of material in 88% yield. Reliable access to significant amounts of this complex material allowed us to investigate further photochemical reactivity in this context.

In an effort to synthesize the natural product (−)-pseudovincadifformine, **33** (Table 2), from the fragmented and cyanated catharanthine, we subjected the material to a short synthetic route involving hydrogenation of the C15−C20 double bond (catharanthine numbering) followed by quenching of the reaction with sodium borohydride to remove the α-aminonitrile functionality (Scheme 12). The advanced intermediate **32** was obtained through this reduction procedure and served as an ideal substrate for testing further applications of oxidative photoredox catalysis on a complex tertiary aliphatic amine substrate. Specifically, to synthesize **33** from **32**, we recognized the need for selective C−H functionalization on C3 in preference to the two alternative α-amino methylenes on C5 and C21. While attempts at aerobic photochemical oxidation of **32** resulted in a complex mixture of decomposition products (Table 2, entry 1), we were excited to find that the use of BrCCl$_3$ resulted in the formation of the natural product in 22% yield (entry 2). Further evaluation of oxidants revealed that diethyl bromomalonate and diethyl 2-bromo-2-methylmalonate resulted in successively improved yields of the desired product (entries 3−4). No products of C21 oxidation were observed in the reaction mixtures. Subjection of the reaction to a flow protocol at 50 °C with a 5 min residence time resulted in the highest yields of the product, yielding **32** in 58% yield and an 8:1 diastereomeric ratio in favor of the desired ethyl epimer (entry 5).

There are a number of possibilities that may account for the origin of the observed regioselectivity in this oxidative cyclization process. Iminium formation is thought to be limited to C3 and C21, because geometric constraints prevent favorable overlap of the nitrogen lone pair with the C5−H bond. Additionally, while on first approximation C21 may appear to be less sterically encumbered, a three-dimensional analysis of structure **32** reveals that C3 may be equally if not more accessible to either intermolecular deprotonation or H atom abstraction. The possibilities of iminium or amino-radical isomerization cannot be ruled out, because transannular cyclization could be expected to serve as a thermodynamic trap for such equilibria. A further alternative is that as the yield trends upward with the steric bulk of the oxidant, there may be a matching effect in which the more bulky oxidant provides higher regioselectivity in a possible C−H abstraction step. It is worthy of note that this C−H oxidation exhibits rare efficiency for a photochemical aliphatic amine oxidation. Preliminary experimentation in our group has suggested that the transannular nature of the cyclization is responsible for reaction success; similar cyclization attempts on structures without the ethylene tether between the indole and the nitrogen have resulted in decomposition of the starting material, possibly through enamine intermediates.

In an attempt to accomplish a more generally applicable α-functionalization of tertiary aliphatic amines, we have further evaluated this chemistry from a pharmaceutical synthesis standpoint.[41] A collaboration with Lilly Research Laboratories brought our attention to the selective JAK2 inhibitor LY2784544, **35** (Scheme 13A). The industrial synthesis of **35**, which was used to produce over one metric ton of the advanced pharmaceutical intermediate **36**, relied upon a vanadium-mediated addition of *N*-methylmorpholine *N*-oxide to the core imidazopyridazine scaffold.[42] While the exact mechanistic course of this reaction has yet to be elucidated, it may proceed through an exocyclic α-amino radical; consequently, other methods for

Scheme 12. Photochemical Fragmentation of Catharanthine

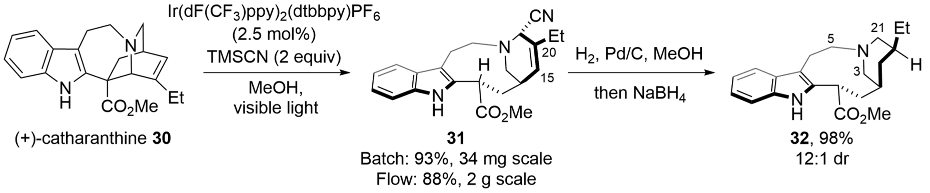
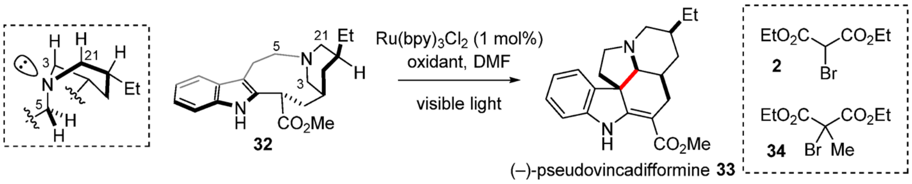


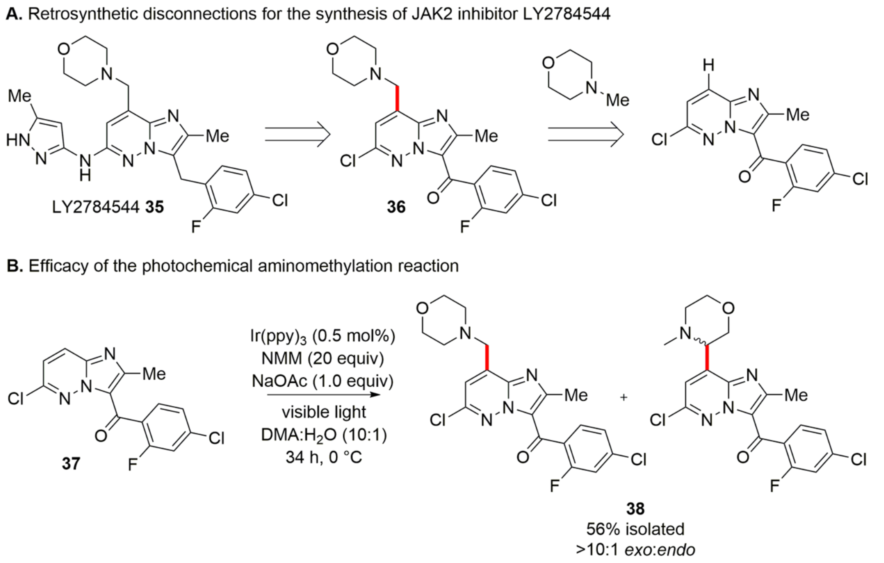
Table 2. Photochemical Oxidative Cyclization To Form (−)-Pseudovincadifformine



entry	oxidant	yield (%)
1	air	0
2	$BrCCl_3$ (3 equiv)	22
3	**2** (3 equiv)	34
4	**34** (3 equiv)	39
5[a]	**34** (3 equiv)	58

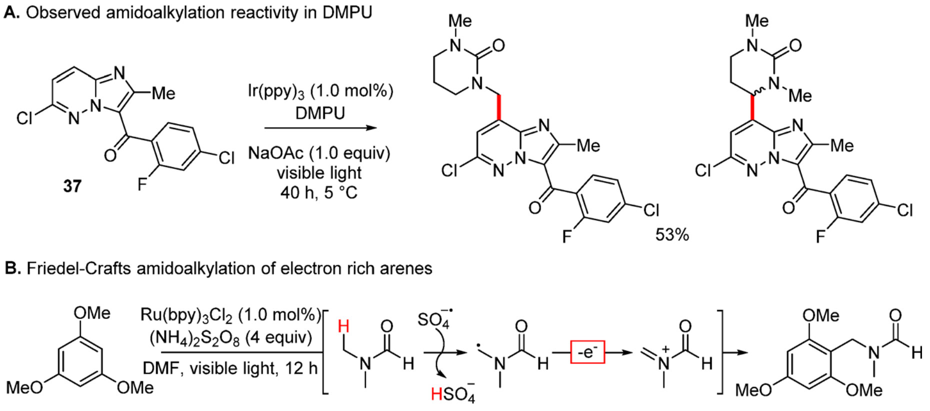
[a] Flow reactor, t_R = 5 min.

Scheme 13. Aliphatic Amine Functionalization for API Synthesis


A. Retrosynthetic disconnections for the synthesis of JAK2 inhibitor LY2784544

B. Efficacy of the photochemical aminomethylation reaction

Scheme 14. Photochemical Amidoalkylation of Heterocycles and Arenes


A. Observed amidoalkylation reactivity in DMPU

B. Friedel-Crafts amidoalkylation of electron rich arenes

the formation of this radical, including photoredox catalysis, were examined.

Initial experiments revealed that in addition to the desired α-amino functionalization reaction, several side products were observed in the reaction mixture, including products of double addition, reductive dechlorination, methylation, and a solvent incorporation adduct. Following extensive optimization, by-product formation was minimized and the product **38** was produced in 56% isolated yield (10:1 *exo*/*endo*, Scheme 13B). The observed reactivity proved challenging to control, resulting in a reactant scope that was broad for the amine component but limited for the heterocyclic coupling partners.

Of note in the discussion of possible mechanistic pathways for this transformation is the observation of amidoalkylation products arising from solvent reactivity. When the reaction was performed in *N*,*N*′-dimethylpropylene urea (DMPU) in the absence of *N*-methyl-morpholine, a mixture of *endo* and *exo* adducts were observed in a 5:1 ratio and combined 53% isolated yield (Scheme 14A). Previous research efforts in our group have revealed that α-amido C−H functionalization in this manner can be accomplished through an initial C−H abstraction from the amide solvent, followed by oxidation to the *N*-acyliminium ion, which is a potent Friedel−Crafts electrophile (Scheme 14B).[43] While the electronic nature of substrate **37** strongly suggests that radical addition is the operative mechanism of heterocycle addition, the analogous reactivity of these two systems suggests that amidoalkylation of these electron-poor substrates is precipitated by direct C−H abstraction.

■ CONCLUSION

This Account has summarized some of our contributions in relation to amine reactivity in light-mediated redox catalysis. Photoredox catalysis has allowed for an environmentally benign approach to the study of amine reactivity; however, significant questions remain to be addressed. The use of aliphatic tertiary amines as substrates is a particularly underexplored area, because previous synthetic work has focused mainly on the use of aniline and tetrahydroisoquinoline substrates. Due to the ubiquity of amine functionality in natural products and commodity chemicals, the ability to controllably oxidize these substrates to access radical and electrophilic functionality is an important goal. There is significant opportunity for this type of C−H oxidation, particularly in complex molecule synthesis, because the efficient formation of α-amino C−C bonds would provide increased retrosynthetic flexibility. Further study in this regard would be beneficial, because the observed differences in reaction efficiency between aryl and aliphatic amines remain to be elucidated experimentally.

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Notes

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