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COMMUNICATIONS

Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C−H Functionalization

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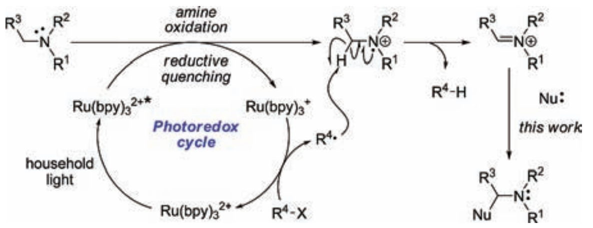
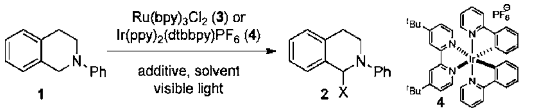
The catalytic oxidation of sp^3 C−H bonds adjacent to nitrogen provides reactive imines or iminium ions and is a powerful method for amine functionalization.[1] Preliminary mechanistic investigations during our recent studies of photoredox catalysis for reductive dehalogenation reactions[2] suggested that iminium ions were likely byproducts in the reaction using tertiary amines as reductants (Scheme 1).[3,4] In light of the mechanism presented in Scheme 1, we anticipated that with an appropriately chosen oxidant (R^4−X functions as an oxidant in this reaction), the generated iminium ion could be trapped by a variety of nucleophiles under photoredox conditions. Indeed, radical cation intermediates generated under electrochemical,[5a] metal-[5b] or electron-transfer-mediated[5c,d] oxidation conditions have been shown to undergo decomposition to give the corresponding imines.[5e] In this communication, we describe the realization of the generation of iminium ions under photoredox conditions in the context of an oxidative aza-Henry reaction.[6]

Scheme 1. Iminium Ion Generation Using Photoredox Catalysis



Our initial studies focused on tetrahydroisoquinoline **1**, a substrate that is known to undergo oxidative C−H functionalization by Ru(III),[7] Cu(I),[8] and, as shown more recently, V(IV)[9] or I(III).[10] Using conditions closely related to those we used for reductive dehalogenation, we subjected **1** to oxidation using diethyl bromomalonate (**5**) as the stoichiometric oxidant.[2] After 2 h, **1** was converted into a more polar compound upon treatment with 2 mol % $Ru(bpy)_3Cl_2$ in *N*,*N*-dimethylformamide (DMF) in the presence of **5** (Table 1, entry 1), providing methoxyaminal **2** (X = OMe) in 73% yield. Use of CH_3OH as the solvent for the reaction also resulted in the complete conversion of **1** to the methoxyaminal (entry 2). We were surprised to find that the latter compound was formed even in the absence of **5**; however, the reaction was significantly slower (entry 3). From this surprising result, a change of solvent to nitromethane provided the oxidative Henry reaction product in 81% isolated yield after 20 h (entry 4). Degassing the reaction slowed the reaction (76% conversion after 20 h; entry 5), indicating that adventitious oxygen in the reaction may play a role in the mechanism but is not explicitly required. The use of a more reactive iridium catalyst,[11] $Ir(ppy)_2(dtbbpy)PF_6$, **4**,[4d,12] significantly accelerated the reaction, and complete conversion was observed after 10 h (92% isolated yield; entry 6). Importantly, no conversion was observed when the reaction was conducted in the dark (entry 7), while a very slow background reaction (83% conversion after ∼7.5 days) was observed in the absence of catalyst (entry 8).

Table 1. Oxidative Iminium Ion Generation and Trapping



entry	conditions[a]	conversion[b] (yield[c])
1	**3** (2 mol %), $(EtO_2C)_2CHBr$ (**5**, 1.5 equiv) DMF, 2 h; X = OCH_3	100 (73)[d]
2	**3** (1 mol %), **5** (1.5 equiv), CH_3OH, 2 h; X = OCH_3	100
3	**3** (1 mol %), ***no additive***, CH_3OH, 16 h; X = OCH_3	100
4	**3** (1 mol %), CH_3NO_2, 20 h; X = CH_2NO_2	100 (81)
5	**3** (1 mol %), CH_3NO_2, 20 h; X = CH_2NO_2; ***reaction was degassed***	76
6	**4** (1 mol %), CH_3NO_2, 10 h; X = CH_2NO_2	100 (92)
7	**4** (1 mol %), ***no light***, CH_3NO_2, 48 h; X = CH_2NO_2	0
8	***no catalyst***, CH_3NO_2, 180 h; X = CH_2NO_2	83

[a] With the exception of entry 5, the reactions were not rigorously degassed. [b] Calculated on the basis of crude ^{1}H NMR analysis. [c] Isolated yield after purification by chromatography on SiO_2. [d] Purified on SiO_2 using CH_3OH as a cosolvent.

A variety of *N*-aryltetrahydroisoquinolines were subjected to the optimized conditions [**4** (1 mol %), RCH_2NO_2, r.t.] and uniformly afforded the desired coupling products in excellent yields (90−96%; Table 2, entries 1−8). Both nitromethane (entries 1, 3, and 5−9) and nitroethane (entries 2 and 4) provided the desired products. The reaction was generally insensitive to electronic effects on the aromatic rings (entries 3−8). Although the process was markedly slower, C−H oxidation of a nonbenzylic amine cleanly afforded the desired coupling product in moderate yield (40% conversion after 72 h; entry 9). These results compare favorably with the known oxidative aza-Henry reaction reported by Li and co-workers using Cu(I) and ^{t}BuOOH.[6b,c] Although the Cu-mediated process is faster, the Ir-mediated process reported herein provides the desired products in higher yields, with the notable exception of the unactivated amine in entry 9.

Both light and catalyst are required for efficient conversion to the aza-Henry products (Table 1, entries 7 and 8). In addition, the exclusion of oxygen from the reaction results in a lower rate (Table 1, entry 5). Since nitrobenzene is a known oxidative quencher of $Ru(bpy)_3^{2+*}$,[13] we could not immediately rule out possible mechanisms involving this pathway. Accordingly, we conducted a series of fluorescence quenching experiments in which the fluorescence emission of a solution of **4** in CH_3NO_2 was found to be decreased by **1** in a concentration-dependent fashion, implicating the amine as a reductive quencher of the excited-state iridium complex.[14] On the basis of this information, we propose the following mechanism for the C−H oxidation/aza-Henry reaction under photoredox catalysis (Scheme 2). Radical cation **7** is formed by reductive quenching of the excited state of **4** by **6**, forming the powerful reducing agent Ir^{2+} [Ir(III)/Ir(II) −1.51 V vs SCE]. Catalyst turnover may be accomplished by the reduction of nitromethane to its radical anion and/or adventitious

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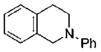
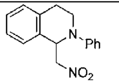
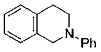
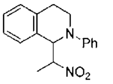
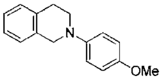
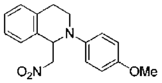
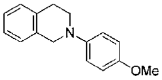
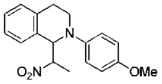
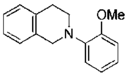
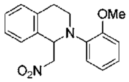
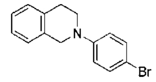
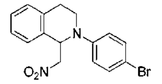
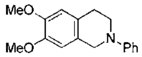
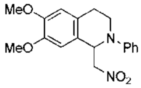
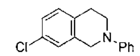
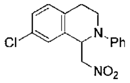
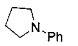
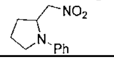
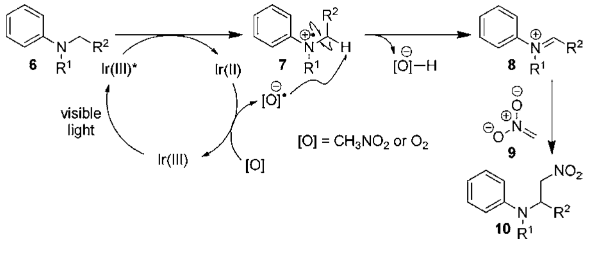
Table 2. Oxidative Aza-Henry Reaction

entry	substrate[f]	product	time (h)	yield (%)[a]
1			10	92[b]
2			16	96[b,c]
3			18	96[b]
4			18	92[b,d]
5			16	90[b]
6			13	93[b]
7			13	92[b]
8			18	95[b]
9			72	27[b,e]

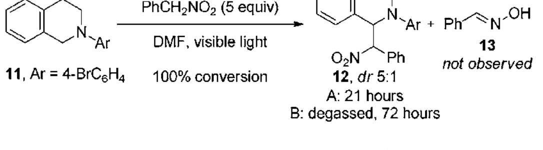
[a] Isolated yield after purification on SiO_2. [b] Conditions: **4** (1.0 mol %), visible light, CH_3NO_2, rt. [c] dr = 2:1. [d] dr = 2.3:1. [e] Conversion = 40% as determined by crude ^1H NMR analysis. [f] See ref 15.

Scheme 2. Plausible Mechanism



oxygen.[16] This radical anion may abstract a hydrogen atom from the trialkylammonium radical cation to form the desired iminium ion, **8**.[2] Addition of **9** to the iminium forms the observed product.

The product of nitromethane reduction is presumably nitrosomethane (or the oxime tautomer), neither of which were we able to observe in our reactions. We reasoned that the use of a less volatile nitro compound could provide evidence in favor of our proposed mechanism. Treatment of **11** with $PhCH_2NO_2$ (5 equiv) in DMF in the presence of $Ir(dtbbpy)(ppy)_2PF_6$ (1 mol %) and visible light resulted in full conversion to the desired oxidative coupling product **12** (5:1 dr) (eq 1):[17]



(1)

We did not observe the presence of **13** by ^1H NMR analysis of the crude reaction mixture, indicating that catalyst turnover may proceed via reaction with oxygen. However, rigorous degassing of the reaction in eq 1 also resulted in clean formation of **12**, albeit with an attenuated rate, suggesting that the nitroalkane may also play a role in catalyst turnover. Importantly, these experiments demonstrate that the reaction of nitro compounds other than those conveniently used as the solvent also cleanly provide the desired product using DMF as solvent.

In summary, we have reported an operationally simple method for the oxidative coupling of nitroalkanes with tertiary *N*-arylamines using visible-light photoredox catalysis. Importantly, the reaction proceeds in high chemical yield using only 1 mol % Ir(III) catalyst and visible light without the need for an external oxidant. Further studies expanding upon the scope of this transformation as well as further mechanistic investigations are currently underway.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Full conversion of **11** to **12** was observed by crude ^1H NMR analysis, but **12** was not stable under purification by chromatography.

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