JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

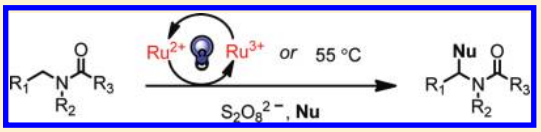
Friedel–Crafts Amidoalkylation via Thermolysis and Oxidative Photocatalysis

Chunhui Dai, Francesco Meschini, Jagan M. R. Narayanam, and Corey R. J. Stephenson*

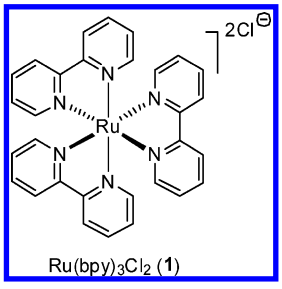
Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

Supporting Information

ABSTRACT: Friedel–Crafts amidoalkylation was achieved by oxidation of dialkylamides using persulfate ($S_2O_8^{2-}$) in the presence of the visible light catalyst, $Ru(bpy)_3Cl_2$, at room temperature, via a reactive *N*-acyliminium intermediate. Alternatively, mild heating of the dialkylamides and persulfate afforded a metal and Lewis acid-free Friedel–Crafts amidoalkylation. Alcohols and electron-rich arenes served as effective nucleophiles, forming new C–O or C–C bonds. In general, photocatalysis provided higher yields and better selectivities.



Photoredox catalysis has emerged as a powerful tool for organic synthesis.[1] Extensive studies demonstrated that photocatalysts, such as $Ru(bpy)_3Cl_2$ (**1**), can initiate single electron transfer (SET) processes under visible light irradiation, providing a new means to selectively activate molecules and promote chemical transformations.[2] For instance, by harnessing the reductive quenching cycle of $Ru(bpy)_3Cl_2$, we have recently demonstrated the oxidative functionalization of *N*-arylamines.[3,4] Key to this process was the mild and efficient visible light promoted generation of iminium ion intermediates, using $Ru(bpy)_3Cl_2$ and $BrCCl_3$ as the terminal oxidant. The amino radical cation was generated through oxidation of *N*-aryltetrahydroisoquinoline by Ru^{2+}* (E_{red} = +0.84 V vs SCE). A subsequent H-atom abstraction, or deprotonation followed by oxidation, provided the electrophilic iminium ion intermediate (Scheme 1, top).



In line with our investigative pursuit into α-amine functionalization via visible light mediated photoredox catalysis, we decided to explore the formation of *N*-acyliminium ions. *N*-Acyliminium ions are known to be more reactive than the simple *N*-alkyliminium or *N*-aryliminium ions and thus open to a broader range of functionalization.[5] The importance of *N*-acyliminium ions in organic synthesis has been well documented, especially in the synthesis of alkaloid natural products.[6] In general, these highly reactive *N*-acyliminium ions historically are generated in situ from α-oxyalkylated amides by Lewis acid- or Brønsted acid-promoted elimination,[7] or through direct anodic oxidation of amides.[8] However, amides have a significantly more positive reduction potential (2.0 V for primary amides, 1.8 V for secondary amides, and 1.2–1.5 V (vs SCE) for tertiary amides)[9] than the corresponding amines, making them far less susceptible to direct oxidation, including photocatalyst-mediated oxidation.

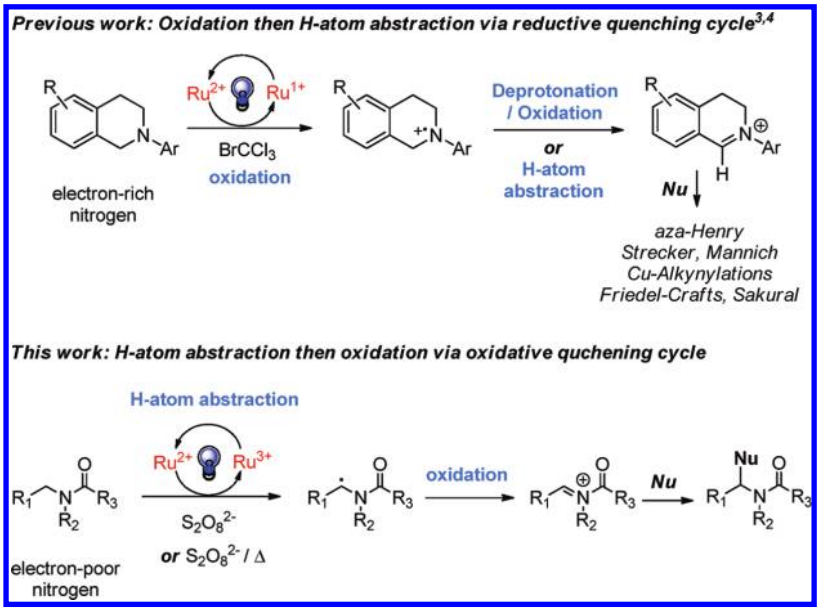
However, this difficulty in oxidation can be circumvented by reordering the steps, that is, C–H abstraction followed by oxidation. The α-amine C–H bond has been shown to be prone to H-atom abstraction under a number of reaction conditions, normally requiring a combination of metal complex catalyst/peroxide and sometimes elevated temperatures are needed.[10,11] The α-amino radical thus generated is strongly reducing, potentially allowing for the generation of *N*-acyliminium ions by a photocatalyzed oxidation (Scheme 1, bottom). Meanwhile, one of the hallmarks of visible light photocatalysis is the mild reaction condition and outstanding functional group tolerance, which would provide some advantages over the current methods. It is well precedented that persulfate ($S_2O_8^{2-}$) is an effective oxidative quencher of $Ru(bpy)_3^{2+}$*,[12] and the generated sulfate radical anion ($SO_4^{\cdot -}$) is a reactive intermediate known to abstract activated hydrogen atoms and also to be a strong oxidant.[13] Herein, we report a visible light enabled Friedel–Crafts amidoalkylation using persulfate at room temperature via the oxidative quenching cycle of $Ru(bpy)_3Cl_2$. In addition, a metal-free thermal decomposition of persulfate was observed upon heating the reaction to 55 °C, leading to the same amide oxidation products albeit with attenuated yields and selectivities.

When 3-phenyl-1-propanol (**2a**) or 3-(4-methoxyphenyl)-1-propanol (**2b**) was treated with $Ru(bpy)_3Cl_2$ (1.0 mol %), $Na_2S_2O_8$ (5.0 equiv) and 2,6-lutidine (2.0 equiv) in DMF, upon visible light irradiation for 12 h at room temperature, formation of the *N*,*O*-aminal product (**3a** or **3b**), presumably resulting for DMF oxidation followed by nucleophilic trapping, was observed (Scheme 2).[14] Despite complete consumption of

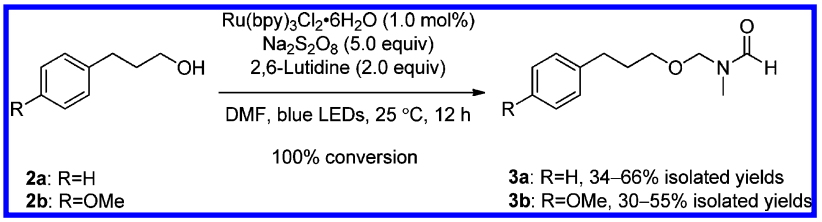
Received: January 24, 2012
Published: March 29, 2012

dx.doi.org/10.1021/jo300162c | J. Org. Chem. 2012, 77, 4425–4431

Scheme 1. α-C−H Functionalization of Amines and Amides via Visible Light-Mediated Photocatalysis



Scheme 2. Formation of *N,O*-Aminals

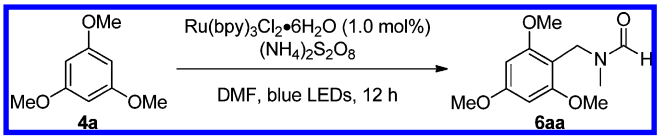


the starting material, the isolated yields were relatively low (30−66%) because of the lability of the *N,O*-aminals during the aqueous workup and chromatographic purification. However, these results demonstrated that *N*-acyliminium ions could be generated via the visible light-mediated reduction of persulfate at room temperature.

We next explored the use of electron-rich aromatics as nucleophiles to form more stable C−C bonds via a Friedel−Crafts reaction. At the onset, 1,3,5-trimethoxybenzene (**4a**) was chosen as the nucleophile in DMF. Full consumption of **4a** was observed when treated with $Ru(bpy)_3Cl_2$, and 5.0 equiv of persulfate after 12 h of visible light irradiation at room temperature (Table 1, entry 1). Little or no conversion was observed in the absence of catalyst or light (Table 1, entries 2−4), and rigorous degassing was required to achieve optimal results, presumably a consequence of undesired and unproductive excited state energy transfer with oxygen. Persulfate was found to be essential for the transformation, requiring 5.0 equiv for optimal results (Table 1, entries 5−6). Interestingly, we discovered that reactivity was observed in the absence of photocatalyst (Table 1, entry 7); however, the reaction required elevated temperature (55 °C). This result verified that Friedel−Crafts amidoalkylation can be achieved in a metal- and Lewis acid-free condition via the thermolysis of persulfate.

With the optimized conditions in hand, we then examined various electron-rich aromatic and heteroaromatic substrates with dialkylamides in the presence of ammonium persulfate, under both photocatalytic and thermolytic conditions (Table 2). Treatment of 1,3,5-trimethoxybenzene (**4a**) with $Ru(bpy)_3Cl_2$ in DMF (**5a**) at room temperature under photocatalytic conditions afforded monosubstituted product **6aa** exclusively, in contrast to thermolytic conditions, which gave both monosubstituted (**6aa**) and disubstituted products (**7aa**, Table 2, entry 1). Switching to DMA (**5b**), both photocatalysis and thermolysis provided monosubstituted (**6ab**) and disubstituted products (**7ab**, Table 2, entry 2) in a 3.9:1 ratio, but better yields were observed under photocatalytic reaction conditions. A differentiated dialkylamide, such as 1-methyl-2-pyrrolidinone (**5c**), afforded a mixture of regioisomeric, monosubstituted products **6ac** and **6ac′** (Table 2, entry 3) under both reaction conditions, but higher selectivities were observed with photocatalysis. Surprisingly, when 1,2,3-trime-

Table 1. Optimization and Control Experiments

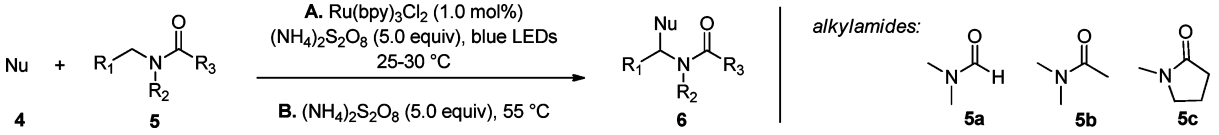


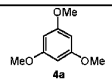
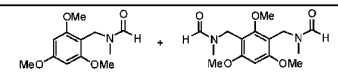
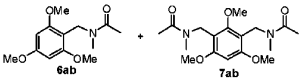
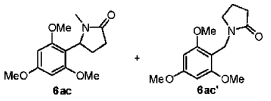
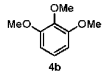
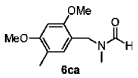
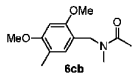
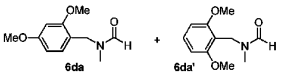
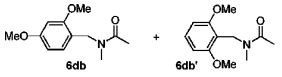
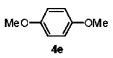
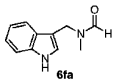
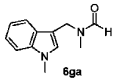
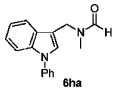
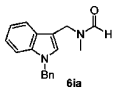
entry	conditions[a]	conversion (%)[b]
1	catalyst, persulfate (5.0 equiv), 25 °C	99
2	**no catalyst**, persulfate (5.0 equiv), 25 °C	<5
3	catalyst, persulfate (5.0 equiv), 25 °C, **no blue LEDs**	0
4	catalyst, persulfate (5.0 equiv), 25 °C, **no degassing**	59
5	catalyst, **no persulfate**, 25 °C	0
6	catalyst, **persulfate (4.0 equiv)**, 25 °C	86
7[c]	**no catalyst**, persulfate (5.0 equiv), **55 °C**	99

[a]Except for entries 4 and 7, the reactions were rigorously degassed. [b]Determined by crude ^{1}H NMR. [c]Reaction was complete in 2 h.

dx.doi.org/10.1021/jo300162c | J. Org. Chem. 2012, 77, 4425−4431

Table 2. Oxidation of Dialkylamides and Coupling with Electron-Rich Aromatics



entry	substrate	alkylamide	product	photocatalysis[a] (A) T (°C)	hour	yield (%)[c]	thermolysis[b] (B) T (°C)	hour	yield (%)[c]
1	 4a	5a	 6aa + 7aa	25	12	89 only 6aa	55	12	75 6aa:7aa=12:1
2	4a	5b	 6ab + 7ab	25	12	72 6ab:7ab=3.9:1	55	12	64 6ab:7ab=3.9:1
3	4a	5c	 6ac + 6ac'	25	12	85 6ac:6ac'=50:1	55	12	86 6ac:6ac'=11:1
4	 4b	5a/5b	NR	25	12	NR	55-85	12	NR
5	 4c	5a	 6ca	30	36	66 (82)[e]	55	36	45 (57)[e]
6	4c	5b	 6cb	30	36	68 (85)[e]	55	36	35 (53)[e]
7	 4d	5a	 6da + 6da'	30	60	44 (67)[e] 6da:6da'=12:1	55	60	42 (66)[e] 6da:6da'=10:1
8	4d	5b	 6db + 6db'	30	60	40 (51)[e] 6db:6db'=9.5:1	55	60	31 (48)[e] 6db:6db'=8.1:1
9	 4e	5a/5b	NR	30	60	NR	55-85	60	NR
10	 4f	5a	 6fa	25	12	10	55	12	8
11	 4g	5a	 6ga	25	2	23	55	2	28
12	 4h	5a	 6ha	25	12	56	55	2	45
13	 4i	5a	 6ia	25	12	52	55	2	44

[a]The reaction was degassed (freeze−pump−thaw) and carried out under argon atmosphere using a nucleophile (**4**, 0.5 mmol) and ammonium persulfate (2.5 mmol) in the presence of $Ru(bpy)_3Cl_2$ (1.0 mol %) in dialkylamides (**5**, 5.0 mL). [b]The reaction was carried out under argon atmosphere using a nucleophile (**4**, 0.5 mmol) and ammonium persulfate (2.5 mmol) in dialkylamides (**5**, 5.0 mL). [c]Isolated yields . [d]Determined by crude ^1H NMR. [e]Yields are based on recovered starting material.

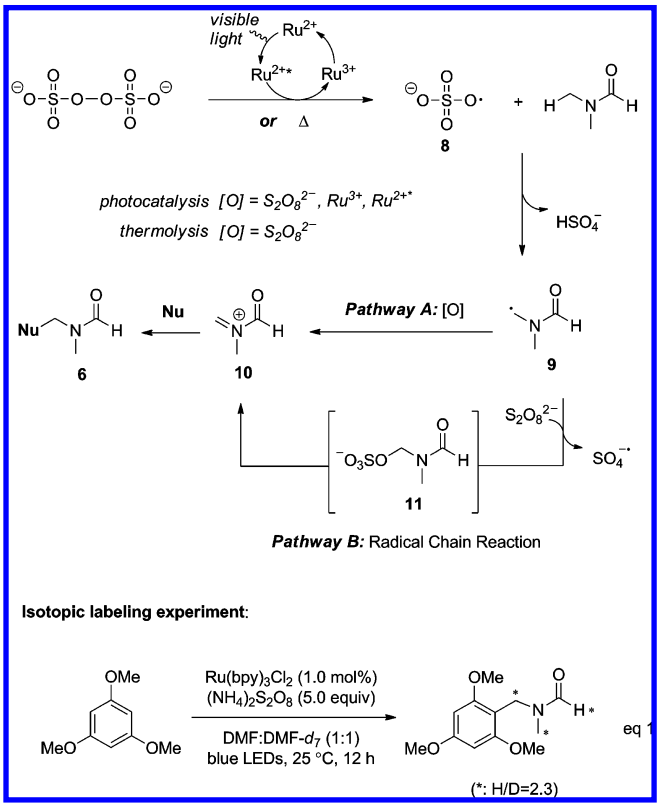
thoxybenzene (**4b**) was treated with the same conditions in the presence of **5a** or **5b**, the reaction failed to provide either of the desired products. Prolonged reaction time or higher temperature did not improve the conversion (Table 2, entry 4). Less nucleophilic substrates, such as **4c** and **4d**, needed higher temperatures and longer reaction times under photocatalytic conditions, although under thermolytic conditions, higher temperatures did not show obvious improvement (Table 2, entries 5−8). Substrates that have multiple nucleophilic sites, such as **4d**, generated mixtures of regioisomers. Furthermore, 1,4-dimethoxybenzene (**4e**) failed to provide the desired products (Table 2, entry 9). Highly reactive substrates, such

dx.doi.org/10.1021/jo300162c | J. Org. Chem. 2012, 77, 4425−4431

as indole (**4f**, Table 2, entry 10) and *N*-methylindole (**4g**, Table 2, entry 11), performed poorly for this oxidative coupling reaction. We speculate that the low yield was due to the oxidative decomposition of the highly electron-rich substrate itself or the loss of the product **4fa** and **4ga** by oxidation at the methylene carbon adjacent to the amide nitrogen.[15] When switching to indoles known to be less prone to oxidation, such as *N*-phenyl indole (**4h**, Table 2, entry 12) and *N*-benzyl indole (**4i**, Table 2, entry 13), the reactions gave moderate yields of the desired products. In all cases, substitution at the C-2 position of the indoles was not observed. As a general observation, photocatalysis provided higher yields and better selectivities than thermolysis.

Plausible mechanisms for the oxidation of dialkylamides, using DMF as an example, are shown in Scheme 3. Under the photocatalytic conditions, persulfate[16] is reduced by Ru(bpy)$_3^{2+*}$ to give sulfate and sulfate radical anion **8**. Alternatively, under thermal conditions, persulfate may decompose to generate 2 equiv of **8**. The alkyl amide (DMF in this case) can then undergo H-atom abstraction by **8** to give α-amido radical **9**. Direct oxidation of **9** by Ru^{3+} (+1.27 V vs SCE)[17] or via electron-transfer of persulfate can lead to *N*-acyliminium ion **10** (pathway A), which can also be achieved via a radical chain process (pathway B) to give oxyalkylamide **11** followed by elimination of sulfate. Either way, the generated acyliminium ion **10** is susceptible to nucleophilic trapping by various electron-rich arenes to afford the desired product **6**. Intermolecular H-atom abstraction was supported by an isotopic labeling experiment using 1:1 mixture of DMF/DMF-d_7 as solvent with **4a**, which provided the product with a H/D ratio of 2.3:1. Surprisingly, a very small amount (7%) of deuterium incorporation on the aromatic ring of the product also occurred. This might be the result of a reversible oxidation of trimethoxybenzene during the course of the reaction (Scheme 3, eq 1).

Scheme 3. Plausible Reaction Mechanism



In conclusion, utilizing the oxidative quenching cycle of Ru(bpy)$_3$Cl$_2$ and a mechanistically distinct reaction design compared to previous studies in photoredox catalysis, we have developed a protocol for the oxidative functionalization of dialkyl amides. Persulfate was found to be an inexpensive and efficient reagent for this transformation and is operative under either thermal or photochemical reaction conditions. Electron-rich species, such as alcohols and arenes, served as suitable nucleophiles. In most cases, photocatalysis provided higher yields and better selectivities for the Friedel–Crafts reactions compared with the thermolytic reaction conditions. This method is highlighted by its operational simplicity and mild reaction conditions. Further studies on substrate expansion are now in progress.

EXPERIMENTAL SECTION

General Remarks. Glassware was dried in a 170 °C oven or flame-dried under vacuum and cooled under inert atmosphere before use. Chemicals were either used as received or purified according to the procedures outlined in *Purification of Common Laboratory Chemicals*. All reactions were performed using common dry, inert atmosphere techniques. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300, Varian Unity Plus 400, or Varian 500 spectrometers, using an internal deuterium lock.

General Procedure for the Oxidation of Alkylamides Using Ru(bpy)$_3$Cl$_2$ Catalyst (Table 2). A flame-dried 10 mL Schlenk flask with a rubber septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (5.0 μmol), the corresponding substrate (0.5 mmol), and ammonium persulfate (2.5 mmol). Then, 5.0 mL of dry dimethylformamide (DMF), dimethylacetamide (DMA), or 1-methyl-2-pyrrolidinone (DMP) was added via syringe. The mixture was degassed by the freeze–pump–thaw procedure (3×), and placed in a 250 mL beaker with blue LEDs wrapped inside. The reaction mixture was stirred at room temperature (or 30 °C using a 100 mL beaker) under argon atmosphere for the time specified in Table 2. Then, the mixture was poured into a separatory funnel containing 100 mL of ethyl acetate and 50 mL of saturated NaHCO$_3$ solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with H$_2$O (2 × 50 mL) and brine and dried over Na$_2$SO$_4$. Solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel to afford the desired product.

General Procedure for the Oxidation of Alkylamides Under Thermolysis (Table 2). To a solution of substrate (0.5 mmol) in 5.0 mL of dimethylformamide (DMF), dimethylacetamide (DMA), or 1-methyl-2-pyrrolidinone (DMP) in a 10 mL round-bottom flask was added ammonium persulfate (2.5 mmol). The mixture was then heated to 55 °C and stirred at that temperature for the time specified in Table 2. Then, the reaction mixture was poured into a separatory funnel containing 100 mL of ethyl acetate and 50 mL of saturated NaHCO$_3$ solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed with H$_2$O (2 × 50 mL) and brine and dried over Na$_2$SO$_4$. Solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel to afford the desired product.

***N*-Methyl-*N*-((3-phenylpropoxy)methyl)formamide (3a).** A colorless oil: observed as two rotamers of 82/18 ratio in ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15/8.15 (s, 1 H), 7.31–7.27 (m, 2 H), 7.21–7.16 (m, 2 H), 4.82/4.66 (s, 2 H), 3.45/3.34 (t, J = 6.4 Hz, 2 H), 2.98/2.93 (s, 3 H), 2.71–2.66 (m, 2 H), 1.94–1.87 (m, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.4, 162.8, 141.7, 141.3, 128.4 (two overlapping signals 128.41, 128.37), 128.3, 126.0, 125.8, 80.3, 73.6, 67.7, 66.6, 33.0, 32.3, 32.2, 31.1, 30.9, 29.0; HRMS (ESI) m/z calcd for C$_{12}$H$_{18}$NO$_2$ [M + H]$^+$ 208.1338, found 208.1345.

dx.doi.org/10.1021/jo300162c | J. Org. Chem. 2012, 77, 4425–4431

***N*-((3-(4-Methoxyphenyl)propoxy)methyl)-*N*-methylformamide (3b).** A colorless oil: observed as two rotamers of 81/19 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16/8.16 (s, 1 H), 7.10−7.06 (m, 2 H), 6.85−6.81 (m, 2 H), 4.82/4.65 (s, 2 H), 3.79/3.79 (s, 3 H), 3.44/3.33 (t, J = 6.4 Hz, 2 H), 2.98/2.93 (s, 3 H), 2.65−2.59 (m, 2 H), 1.90−1.83 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 162.7, 157.8 (two overlapping signals 157.85, 157.76), 133.7, 133.4, 129.2, 113.8, 113.7, 80.3, 73.6, 67.7, 66.5, 55.2, 33.0, 31.3 (two overlapping signals 31.32, 31.29), 31.2, 31.1, 28.9; HRMS (ESI) m/z calcd for $C_{13}H_{20}NO_3$ $[M + H]^+$ 238.1443, found 238.1453.

***N*-Methyl-*N*-(2,4,6-trimethoxybenzyl)formamide (6aa).** A colorless solid: observed as two rotamers of 92/8 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25/8.03 (s, 1 H), 6.11/6.11 (s, 2 H), 4.56/4.35 (s, 2 H), 3.81/3.81 (s, 3 H), 3.80/3.80 (s, 6 H), 2.72/2.66 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 162.0, 161.3, 161.1, 160.0, 159.6, 104.4, 103.8, 90.3, 90.2, 55.6, 55.5, 55.3, 41.3, 35.3, 33.0, 28.7; HRMS (ESI) m/z calcd for $C_{12}H_{17}NO_4Na$ $[M + Na]^+$ 262.1055, found 262.1055.

***N*,*N*′-((2,4,6-Trimethoxy-1,3-phenylene)bis(methylene))bis(*N*-methylformamide) (7aa).** A colorless solid. Each component was observed as a set of 2−4 peaks due to existence of three rotamers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25/8.06 (s, 2 H), 6.28/6.28 (s, 1 H), 4.60/4.36 (s, 4 H), 3.84/3.84 (s, 6 H), 3.72/3.71 (s, 3 H), 2.70/2.69/2.67/2.66 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 163.3, 162.3, 160.3, 160.1, 159.9, 159.8, 159.7, 109.4, 109.2, 108.9, 91.5, 91.2, 63.2, 62.8, 55.8, 55.7, 55.6, 42.2 (two overlapping signals 42.22, 42.20), 36.0, 33.1, 28.8, 28.7; HRMS (ESI) m/z calcd for $C_{15}H_{22}N_2O_5Na$ $[M + Na]^+$ 333.1426, found 333.1439.

***N*-Methyl-*N*-(2,4,6-trimethoxybenzyl)acetamide (6ab).** A colorless solid: observed as two rotamers of 80/20 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12/6.12 (s, 2 H), 4.62/4.45 (s, 2 H), 3.82/3.82 (s, 3 H), 3.80/3.79 (s, 6 H), 2.71/2.71 (s, 3 H), 2.28/2.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.0, 161.1, 160.8, 160.0, 159.6, 105.2, 104.8, 90.2, 90.1, 55.6, 55.4, 55.2 (two overlapping signals 55.25, 55.23), 42.1, 37.9, 33.7, 31.1, 22.1, 21.4; HRMS (ESI) m/z calcd for $C_{13}H_{19}NO_4Na$ $[M + Na]^+$ 276.1212, found 276.1208.

***N*,*N*′-((2,4,6-Trimethoxy-1,3-phenylene)bis(methylene))bis(*N*-methylacetamide) (7ab).** A colorless solid. Each component was observed as a set of 2−4 peaks due to existence of three rotamers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29/6.28 (s, 1 H), 4.67/4.65/4.47/4.46 (s, 4 H), 3.84/3.83 (s, 6 H), 3.67/3.65 (s, 3 H), 2.71/2.69 (s, 6 H), 2.28/2.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 170.2, 170.1, 160.6, 160.2, 159.8, 159.7, 159.6, 159.5, 159.3, 110.3, 110.2, 109.9, 109.7, 91.4, 91.2, 63.0, 62.5, 62.1, 55.7, 55.6, 55.5, 55.4, 42.9, 38.5, 38.4, 33.7, 33.6, 31.1, 22.0 (two overlapping signals 21.99, 21.96), 21.4; HRMS (ESI) m/z calcd for $C_{17}H_{26}N_2O_5Na$ $[M + Na]^+$ 361.1739, found 361.1729.

1-Methyl-5-(2,4,6-trimethoxyphenyl)pyrrolidin-2-one (6ac). A colorless solid. This product could not be isolated in a pure form, being contaminated with **6ac′** (**6ac**:**6ac′** = 94:6): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 2 H), 5.23 (dd, J = 9.6, 4.6 Hz, 1 H), 3.81 (s, 3 H), 3.77 (s, 6 H), 2.63−2.53 (m, 1 H), 2.53 (s, 3 H), 2.47−2.38 (m, 1 H), 2.36−2.25 (m, 1 H), 2.06−1.97 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 160.8, 159.8 (broad), 108.4, 90.5 (broad), 55.7, 55.2, 53.9, 31.1, 27.3, 23.6; HRMS (ESI) m/z calcd for $C_{14}H_{20}NO_4$ $[M + H]^+$ 266.1392, found 266.1392.

Key peaks for compound **6ac′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 2 H), 3.13 (t, J = 7.0 Hz, 2 H), 1.90−1.82 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 161.0, 159.8, 104.6, 90.2, 55.7, 55.2, 46.0, 34.4, 31.2, 17.6.

***N*-(2,4-Dimethoxy-5-methylbenzyl)-*N*-methylformamide (6ca).** A colorless oil: observed as two rotamers of 75/25 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26/8.11 (s, 1 H), 6.97/6.87 (s, 1 H), 6.42/6.42 (s, 1 H), 4.48/4.28 (s, 2 H), 3.84/3.84/3.83/3.82 (s, 6 H), 2.82/2.74 (s, 3 H), 2.13/2.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 162.5, 158.3, 157.9, 156.8, 156.7, 131.8, 131.5, 118.3, 117.8, 115.3, 114.7, 94.8, 94.7, 55.6, 55.4, 48.4, 41.3, 34.1, 28.9, 15.1; HRMS (ESI) m/z calcd for $C_{12}H_{17}NO_3Na$ $[M + Na]^+$ 246.1106, found 246.1104.

***N*-(2,4-Dimethoxy-5-methylbenzyl)-*N*-methylacetamide (6cb).** A colorless oil: observed as two rotamers of 62/38 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98/6.79 (s, 1 H), 6.43/6.41 (s, 1 H), 4.53/4.40 (s, 2 H), 3.84/3.83/3.82 (s, 6 H), 2.91/2.88 (s, 3 H), 2.16/2.13/2.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.5, 157.8, 157.6, 156.5, 156.1, 131.5, 129.4, 118.2, 117.9, 116.7, 115.4, 94.8, 94.7, 55.6, 55.4 (two overlapping signals 55.44, 55.37), 55.3, 49.2, 44.1, 35.5, 33.1, 21.8, 21.2, 15.2, 15.1; HRMS (ESI) m/z calcd for $C_{13}H_{19}NO_3Na$ $[M + Na]^+$ 260.1263, found 260.1251.

***N*-(2,4-Dimethoxybenzyl)-*N*-methylformamide (6da).** A colorless solid: observed as two rotamers of 75/25 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24/8.10 (s, 1 H), 7.13/7.03 (d, J = 8.8 Hz, 1 H), 6.46−6.43 (m, 2 H), 4.48/4.29 (s, 2 H), 3.80/3.79 (s, 6 H), 2.83/2.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 162.6, 161.0, 160.4, 158.8, 158.6, 130.7, 130.4, 116.6, 116.1, 104.2, 103.8, 98.7, 98.4, 55.4, 55.3 (two overlapping signals 55.35, 55.29), 48.6, 41.7, 34.2, 29.0; HRMS (ESI) m/z calcd for $C_{11}H_{16}NO_3$ $[M + H]^+$ 210.1130, found 210.1138.

***N*-(2,6-Dimethoxybenzyl)-*N*-methylformamide (6da′).** A colorless solid. This product could not be isolated in a pure form, being contaminated with **6da**. The following data were obtained from a pure form by an alternative synthetic route, which resemble the spectra of the mixture: observed as two rotamers of 91/9 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29/8.05 (s, 1 H), 7.25 (t, J = 8.4 Hz, 1 H), 6.55/6.55 (d, J = 8.4 Hz, 2 H), 4.65/4.43 (s, 2 H), 3.82/3.81 (s, 6 H), 2.74/2.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 162.1, 159.3, 158.9, 129.6, 129.3, 111.7, 111.2, 103.5, 55.7, 55.6, 41.4, 35.5, 33.1, 28.8; HRMS (ESI) m/z calcd for $C_{11}H_{15}NO_3Na$ $[M + Na]^+$ 232.0950, found 232.0943.

***N*-(2,4-Dimethoxybenzyl)-*N*-methylacetamide (6db).** A colorless solid: observed as two rotamers of 62/38 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14/6.96 (d, J = 8.8 Hz, 1 H), 6.47−6.43 (m, 2 H), 4.54/4.42 (s, 2 H), 3.81/3.80/3.79 (s, 6 H), 2.93/2.89 (s, 3 H), 2.15/2.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.8, 160.5, 160.1, 158.5, 158.2, 130.4, 128.2, 117.9, 116.8, 104.2, 103.8, 98.6, 98.3, 55.4, 55.3 (two overlapping signals 55.33, 55.30), 55.2, 49.5, 44.7, 35.8, 33.3, 21.8, 21.2; HRMS (ESI) m/z calcd for $C_{12}H_{17}NO_3Na$ $[M + Na]^+$ 246.1106, found 246.1113.

***N*-(2,6-Dimethoxybenzyl)-*N*-methylacetamide (6db′).** A colorless solid. This product could not be isolated in a pure form, being contaminated with **6db**. The following data were obtained from a pure form by an alternative synthetic route, which resemble the spectra of the mixture: observed as two rotamers of 80/20 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25/7.23 (t, J = 8.0 Hz, 1 H), 6.56/6.55 (d, J = 8.0 Hz, 2 H), 4.71/4.53 (s, 2 H), 3.82/3.81 (s, 6 H), 2.73/2.73 (s, 3 H), 2.31/2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.1, 159.3, 158.9, 129.4, 129.0, 112.7, 112.2, 103.5 (two overlapping signals 103.54, 103.51), 55.7, 55.5, 42.3, 38.2, 33.8, 31.2, 22.0, 21.3; HRMS (ESI) m/z calcd for $C_{12}H_{17}NO_3Na$ $[M + Na]^+$ 246.1106, found 246.1099.

***N*-((1*H*-Indol-3-yl)methyl)-*N*-methylformamide (6fa).** A yellow oil: observed as two rotamers of 54:46 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42/8.12 (s, 1 H), 8.30−8.17 (br s, 1 H), 7.71/7.54 (d, J = 7.6 Hz, 1 H), 7.39 (t, J = 9.0 Hz, 1 H), 7.24−7.17 (m, 3 H), 4.71/4.59 (s, 2 H), 2.83/2.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 162.3, 136.6, 136.3, 126.6, 126.3, 124.2, 123.6, 122.5, 122.3, 120.0, 119.8, 119.1, 118.3, 111.5, 111.2, 110.5, 110.1, 45.4, 38.8, 33.9, 29.2; HRMS (ESI) m/z calcd for $C_{22}H_{25}N_4O_2$ $[2M + H]^+$ 377.1978, found377.1965.

***N*-Methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)formamide (6ga).** A yellow oil: observed as two rotamers of 54:46 ratio in ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41/8.10 (s, 1 H), 7.69/7.52 (d, J = 8.0 Hz, 1 H), 7.35−7.22 (m, 2 H), 7.17−7.11 (m, 1 H), 7.05/7.00 (s, 1 H), 4.68/4.57 (s, 2 H), 3.79/3.77 (s, 3 H), 2.83/2.81 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 162.0, 137.1, 136.9, 128.6, 128.0, 127.1, 126.7, 122.0, 121.8, 119.5, 119.3, 119.2, 118.4, 109.4, 109.1 (two overlapping signals 109.13, 109.08), 108.7, 45.1, 38.4, 33.7, 32.6, 32.5, 29.0; HRMS (ESI) m/z calcd for $C_{12}H_{14}N_2ONa$ $[M + Na]^+$ 225.1004, found 225.1006.

dx.doi.org/10.1021/jo300162c | *J. Org. Chem.* 2012, 77, 4425−4431

***N*-Methyl-*N*-((1-phenyl-1*H*-indol-3-yl)methyl)formamide (6ha).** A yellow oil: observed as two rotamers of 54:46 ratio in ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48/8.11 (s, 1 H), 7.73−7.53 (m, 7 H), 7.43−7.38 (m, 1 H), 7.25−7.11 (m, 2 H), 4.66/4.63 (s, 2 H), 2.84/2.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 162.2, 139.4, 139.2, 136.5, 136.2, 129.7, 129.6, 128.0, 127.7, 127.6, 127.0, 126.8, 126.5, 124.3, 124.2, 123.0, 122.9, 120.7, 120.5, 119.7, 118.8, 111.9, 111.5, 110.9, 110.5, 45.2, 38.6, 33.9, 29.3; HRMS (ESI) m/z calcd for $C_{17}H_{16}N_2ONa$ $[M + Na]^+$ 287.1160, found 287.1165.

***N*-((1-Benzyl-1*H*-indol-3-yl)methyl)-*N*-methylformamide (6ia).** A yellow oil: observed as two rotamers of 55:45 ratio in ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42/8.07 (s, 1 H), 7.59−7.53 (m, 1 H), 7.54/7.50 (s, 1 H), 7.45−7.40 (m, 1 H), 7.30−7.17 (m, 5 H), 7.14−7.08 (m, 1 H), 7.06−6.98 (m, 1 H), 5.40/5.39 (s, 2 H), 4.60/4.57 (s, 2 H), 2.77/2.64 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.0, 138.2, 138.1, 136.3, 136.2, 128.9, 128.7, 128.5 (two overlapping signals 128.53, 128.51), 127.3 (two overlapping signals 127.32, 127.30), 127.0, 126.9, 121.6, 121.5, 119.2, 119.1, 119.0, 118.6, 110.4, 110.2, 109.4 (two overlapping signals 109.41, 109.39), 49.0 (two overlapping signals 48.98, 48.94), 43.8, 37.7, 33.1, 28.4; HRMS (ESI) m/z calcd for $C_{18}H_{18}N_2ONa$ $[M + Na]^+$ 301.1317, found 301.1316.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: crjsteph@bu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research from the NIH-NIGMS (R01-GM096129), NSF (CHE-1056568), the Alfred P. Sloan Foundation, Amgen, Boehringer Ingelheim, and Boston University is gratefully acknowledged. C.D. thanks AstraZeneca for a graduate fellowship. J.M.R.N. thanks the Swiss National Science Foundation for a postdoctoral fellowship. NMR (CHE-0619339) and MS (CHE-0443618) facilities at BU are supported by the NSF.

■ REFERENCES

(1) For recent reviews on photoredox catalysis, see: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102−113. (b) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859−917. (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617−1622.

(2) For selected recent examples of photoredox catalysis in organic synthesis, see: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77−80. (b) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886−12887. (c) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756−8757. (d) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600−13603. (e) Andrews, S. R.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274−7276. (f) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572−8574. (g) Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951−954. (h) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162−1164. (i) C. Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2011**, *3*, 140−145. (j) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160−4163. (k) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655−9659.

(3) (a) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94−97. (b) For a previous study using $Ir(ppy)_2(dtbbpy)PF_6$ as a catalyst, see: Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464−1465.

(4) For selected recent examples of the oxidative functionalization of tertiary amines using photoredox catalysis, see: (a) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360−2362. (b) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852−3855. (c) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171−7175.

(5) For selected recent examples of the applications of *N*-acyliminium ions, see: (a) Sun, H.; Martin, C.; Kesselring, D.; Keller, R.; Moeller, K. D. *J. Am. Chem. Soc.* **2006**, *128*, 13761−13771. (b) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2007**, *129*, 1902−1903. (c) Pilling, A. W.; Boehmer, J.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5428−5430. (d) Othman, R. B.; Affani, R.; Tranchant, M.-J.; Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776−780.

(6) de Koning, H.; Speckamp, W. N. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Verlag: Stuttgart, 1995; Vol. *E 21b*, pp 1953−2009.

(7) For reviews on the generation of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311−2352.

(8) For reviews on the electrochemical oxidation of amides, see: (a) Shono, T. *Tetrahedron* **1984**, *40*, 811−850. (b) Utley, J. *Chem. Soc. Rev.* **1997**, *26*, 157−167. (c) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527−9554.

(9) Steckhan, E. In *Organic Electrochemistry*, 4th ed.; Henning, L., Baizer, M., Eds.; Marcel Dekker Inc: New York, 2001; pp 570 and references therein.

(10) For an example of amide oxidation using Co, Mn with *tert*-butyl hydroperoxide or peracetic acid, see: Doumaux, A. R.; McKeon, J. E.; Trecker, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3992−3993. For a review on Ru catalyzed oxidation of amides, see: Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490−1501. For a review on Cu catalyzed oxidation of amides, see: Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1−28. For a recent example of Fe catalyzed Friedel-Crafts aminoalkylation via oxidation of alkylamides, see: ref 15. For an example of oxidation of amides using persulfate, see: Needles, H. L.; Whitfield, R. E. *J. Org. Chem.* **1966**, *31*, 341−342.

(11) For selected recent examples of α-amino C−H activation using metals and peroxides, see: (a) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169−3171. (b) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005−11012. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672−3673.

(12) (a) White, H. S.; Bard, A. J. *J. Am. Chem. Soc.* **1982**, *104*, 6891−6895. (b) Nickel, U.; Chen, Y.-H.; Schneider, S.; Silva, M. I.; Burrows, H. D.; Formosinho, S. J. *J. Phys. Chem.* **1994**, *98*, 2883−2888. (c) Fancy, D. A.; Kodadek, T. *Proc. Nat. Acad. Sci. U. S. A.* **1999**, *96*, 6020−6024.

(13) For applications of sulfate radical as a strong oxidant, see: (a) Bolletta, F.; Giano, M.; Balzani, V.; Serpone, N. *Inorg. Chim. Acta* **1982**, *62*, 207−213. (b) Minisci, F.; Citterio, A; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27−32. (c) Fürholz, U.; Haim, A. *Inorg. Chem.* **1987**, *26*, 3243−3248.

(14) For a recent example of the synthetic utility of *N*,*O*-aminals, see: Graham, T. J. A.; Shields, J. D.; Doyle, A. G. *Chem. Sci.* **2011**, *2*, 980−984.

(15) Shirakawa, E.; Uchiyama, N.; Hayashi, T. *J. Org. Chem.* **2011**, *76*, 25−34.

(16) The overall two-electron reduction potential of persulfate is 1.75 V vs saturated calomel electrode [SCE]. However, the potential for the

first step in aqueous solution was measured as $\lesssim$0.35 V vs SCE. See: Memming, R. *J. Electrochem. Soc.* **1969**, *116*, 785−790.
(17) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159−244.

dx.doi.org/10.1021/jo300162c | *J. Org. Chem.* 2012, 77, 4425−4431