JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Cyclization Reactions of Anode-Generated Amidyl Radicals

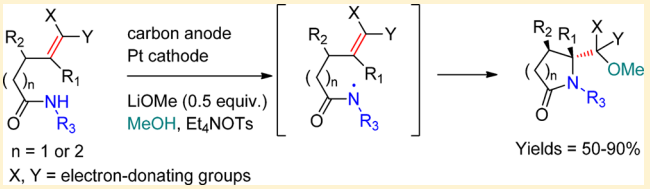
Hai-Chao Xu,[†,§] John M. Campbell,[‡,§] and Kevin D. Moeller*[,‡]

[†]Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China

[‡]Department of Chemistry, Washington University in St. Louis, St. Louis, Missouri 63130, United States

Supporting Information

ABSTRACT: Amidyl radicals have been generated from amides under mild conditions electro-oxidatively. Their reactivity toward electron-rich double bonds to form five- and six-membered rings has been demonstrated experimentally and explored with density functional theory (DFT) calculations (UB3LYP/6-31G(d,p)).

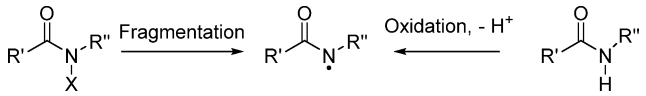


INTRODUCTION

Nitrogen-centered radicals are potentially important reactive intermediates for synthetic organic chemistry.[1] In particular, the cyclization of nitrogen-centered radicals onto carbon−carbon double bonds provides a promising route to biologically important *N*-heterocycles. Among the various kinds of nitrogen-centered radicals, amidyl radicals have attracted attention due to their high reactivity and electrophilic nature.[2]

The generation of amidyl radicals frequently involves the cleavage of an N-halogen,[3] N−N,[4] N−O,[2,5] or N−S[6] bond (Scheme 1). Studer and co-workers have shown that amidyl radicals may be generated by hydrogen atom abstraction from an amide.[7] Many of these approaches involve the use of toxic tin compounds, and the precursors for such fragmentation reactions are often not stable. In addition, the highly electrophilic nature of these amide derivatives can cause undesirable side-reactions.

Scheme 1. Generation of Amidyl Radicals by Fragmentation Reactions and Chemical Oxidation

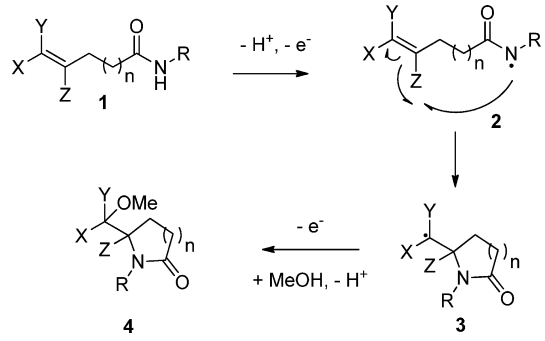


Recently, the generation of amidyl radicals directly from amides through chemical oxidation has been reported.[8,9] These methods avoid the preparation of amide derivatives and have therefore increased the synthetic utility of amidyl radicals. However, the reactions frequently require an excess of the chemical oxidant and high temperatures, a situation that imposes limitations on the synthetic utility of the reactions. Hence, the development of a more general and gentle process for the generation of amidyl radicals is of great importance.

Electrochemistry has been demonstrated as an easily implemented,[10] reagentless, and mild method for the generation of reactive intermediates such as radicals and radical ions.[11,12] For example, we have previously shown that an anodic oxidation reaction can be used to oxidatively couple primary amines[13] and sulfonamides[14] with electron-rich olefins at room temperature to afford *N*-heterocycles. We report here that electrochemical methods can also be applied to generate amidyl radicals directly from amides under mild conditions. Amidyl radicals synthesized in this fashion readily add to olefins to generate lactams.

We envisioned that anodic oxidation of amide **1** would lead to amidyl radical **2** (see Scheme 2).[15] Intramolecular addition of the radical onto an appropriately positioned double bond would give cyclized radical **3**. A second single-electron oxidation followed by solvent (MeOH) trapping of the subsequent cation would afford the final product **4**. Lactams like **4** are pyroglutamate derivates that form the core structure of many biologically active compounds such as (−)-dysibetaine,[16] salinosporamide A,[17] lactasystin,[18] and stephacidin A[19] (Figure 1). The method is intriguing in that it has the potential to readily form the key tetrasubstituted carbon that lies at the center of such structures.

Scheme 2. Proposed Intramolecular Anodic Coupling of Amides and Olefins[a]



[a]X,Y = electron donating groups

Received: November 26, 2013
Published: December 11, 2013

   dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

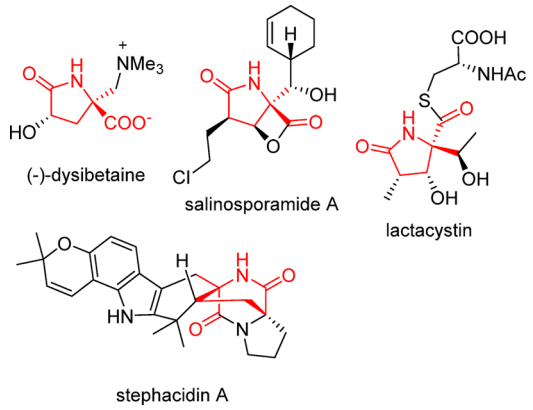
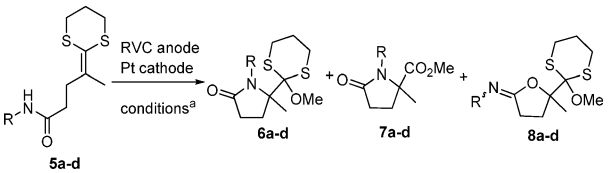


Figure 1. Selected examples of biologically active lactams.

RESULTS AND DISCUSSION

Identification of Suitable Substrates. Our study began with the identification of suitable amides for the cyclization. To this end, a series of amides **5a–d** were prepared and submitted to the electrolysis reaction (Table 1). Initially, a ketene dithioacetal was chosen as the olefinic coupling partner for the reactions because of its excellent reactivity in previously studied anodic cyclizations.[13,14]

Table 1. Identification of Suitable Amides for the Cyclizations



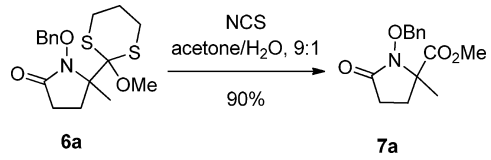
entry	substrate	product, yield (%)		
1	**5a**, R = OBn	**6a**, 80	**7a**, 8	**8a**, ND[b]
2[c]	**5a**, R = OBn	**6a**, 81	**7a**, 3	**8a**, ND
3[d]	**5a**, R = OBn	**6a**, ND	**7a**, ND	**8a**, 88
4	**5b**, R = Ph	**6b**, 87	**7b**, ND	**8b**, ND
5	**5c**, R = H	**6c**, ND	**7c**, ND	**8c**, ND
6	**5d**, R = Me	**6d**, ND	**7d**, ND	**8d**, 75

[a]Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et_4NOTs, 0.5 equiv of LiOMe, 6 mA, 2.0–2.2 F/mol, room temperature. [b]Not detected. [c]A 6-V lantern battery was used as the power source. [d]2,6-Lutidine (6 equiv) was used as base.

Anodic oxidation of *O*-benzyl hydroxamate **5a** was conducted in an undivided cell (a three-necked round-bottomed flask) equipped with a reticulated vitreous carbon (RVC) anode and a platinum wire cathode (see the Supporting Information for more details). The electrolysis was conducted in a methanol solution with the use of Et_4NOTs as the electrolyte and 0.5 equiv of LiOMe as a base. Under these conditions, a constant current of 6 mA was passed through the cell at room temperature to afford the desired product **6a** in 80% yield along with methyl ester **7a** in 8% yield (Table 1, entry 1). The reaction required 2 F/mol of charge. During the electrolysis, acid was produced at the anode, and an equal amount of base (methoxide) was produced at the cathode because of the reduction of methanol solvent. In this way, the reaction remained at the initial basic pH established by the substoichiometric amount of LiOMe added.

The methyl ester **7a** was derived from hydrolysis of **6a**. It is not known whether this hydrolysis reaction occurred with adventitious water in the electrolysis medium or during the workup following the reaction. Compound **6a** can be readily hydrolyzed to the synthetically more relevant methyl ester **7a** in the presence of *N*-chlorosuccinimide (NCS) (Scheme 3).[20]

Scheme 3. Hydrolysis of 6a



Although the electrolysis reactions in this work were carried out using a potentiostat to maintain constant current, simpler power supplies can also be used. For example, oxidation of **5a** with a 6-V lantern battery (see the Supporting Information for more details) as the power source afforded **6a** and **7a** in 81 and 3% yield, respectively (Table 1, entry 2).

Under the same electrolysis conditions used for entry 1, oxidation of *N*-phenyl amide **5b** afforded the desired lactam **6b** in 87% yield (Table 1, entry 4). Cyclizations that employed other substituents on the amidyl nitrogen were not as successful. When unsubstituted amide **5c** was used as a substrate for the reaction, a complex mixture of products that could not be characterized was obtained (Table 1, entry 5). Oxidation of the *N*-methyl amide **5d** gave iminolactone **8d** in 75% yield (entry 6).[15]

The difference between the successful reactions and unsuccessful reactions appears to be related to the pK_a of the starting amide. *O*-Benzyl hydroxamates and *N*-phenyl amides have pK_a's lower than that of methanol.[21] Thus, when exposed to the basic reaction conditions employed for the electrolysis, amides **5a** and **5b** exist as their anionic conjugate bases. The half-wave oxidation potential ($E_{p/2}$) of an *O*-benzyl hydroxamate anion and an *N*-phenyl amide anion were measured by cyclic voltammetry to be 0.52 and 0.80 V, respectively, vs a Ag/AgCl reference electrode. These oxidation potentials are lower than that of the ketene dithioacetal ($E_{p/2}$ = 1.06 V vs Ag/AgCl) and indicate that the initial oxidation of **5a** and **5b** occurs at the amide anion rather than the olefin generating amidyl radical **2** (Scheme 2).

The half-wave oxidation potentials of substrates **5a** and **5b** were measured to be 0.40 and 0.71 V vs Ag/AgCl, respectively. The observation that these compounds exhibit an oxidation potential lower than any of their isolated functional groups is consistent with an oxidation step that is followed by a fast cyclization. The cyclization consumes the oxidized product at the electrode surface and thus lowers the observed potential.[13]

The primary amide in **5c** and the *N*-methyl amide in **5d**, on the other hand, are less acidic than methanol, and their neutral forms are oxidized at higher potentials ($E_{p/2}$ > 1.5 V vs Ag/AgCl) than the ketene dithioacetal. As a result, the electrolysis of these substrates begins with the oxidation of the olefin to a radical cation followed by trapping with the nucleophilic oxygen of the neutral amide to ultimately give the iminolactone **8**.[15]

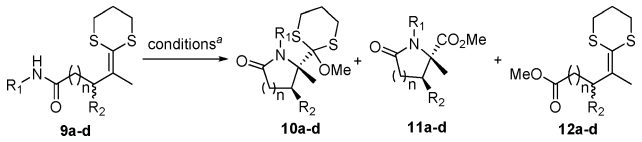
The necessity of deprotonation of the amide prior to the electrolysis was demonstrated by the use of less basic conditions. When lithium methoxide was replaced with 2,6-lutidine as a base, the electrolysis of **5a** did not yield the desired

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379–391

lactam **6a**. Instead, iminolactone **8a** was isolated in an 88% yield (Table 1, entry 3). Under these conditions, the *O*-benzyl hydroxamate remained neutral. Hence, the reaction under the less basic conditions most likely started with the oxidation of the electron-rich olefin instead of the amide.

Exploration of Diastereoselectivity and Ring Size Limitations. Next, questions concerning the diastereoselectivity of the reactions and the size of the rings that could be formed were probed. The diastereoselectivity of the reaction was examined by placing a methyl group on the chain connecting the amide and the electron-rich olefin (Table 2, entry 1). In this case, the reaction led to a 78% yield of **10a**, along with 8% of methyl ester **11a**, both as a single diastereomer. The stereochemistry of the products was assigned in analogy to earlier cyclizations.[13,14] Hence, the oxidative cyclization allows for the generation of the tetrasubstituted carbon with complete control over relative stereochemistry.

Table 2. Electrolysis of 9a−d



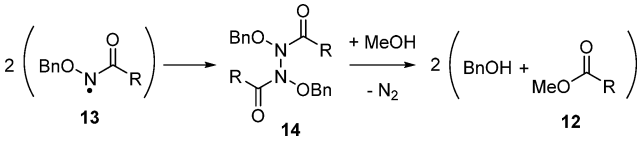
entry	substrate	product, yield (%)		
1	**9a**, n = 1, R_1 = OBn, R_2 = Me	**10a**, 78	**11a**, 8	**12a**, ND
2	**9b**, n = 2, R_1 = OBn, R_2 = H	**10b**, 73	**11b**, 10	**12b**, ND
3	**9c**, n = 3, R_1 = OBn, R_2 = H	**10c**, ND	**11c**, ND	**12c**, 74 (85)[b]
4	**9d**, n = 2, R_1 = Ph, R_2 = H	**10d**, ND	**11d**, ND	**12d**, ND

[a]Reticulated vitreous carbon anode, platinum wire cathode, MeOH, 0.1 M Et_4NOTs, 0.5 equiv of LiOMe, 6 mA, 2.0−2.2 F/mol. [b]The reaction was conducted at 65 °C.

Cyclization to form the more challenging six-membered ring product with concomitant formation of a tetrasubstituted carbon was also successful with the use of the *O*-benzyl hydroxamate. The oxidation of **9b** provided **10b** and **11b** in 73 and 10% yield, respectively (Table 2, entry 2). The oxidation potential of **9b** was measured under the reaction conditions to be 0.41 V ($E_{p/2}$ vs Ag/AgCl), similar to that of substrate **5a** ($E_{p/2}$ = 0.40 V vs Ag/AgCl). This observation suggests that the six-membered ring cyclization is still very fast.

Attempts to form a seven-membered ring product from the oxidation of substrate **9c** failed (Table 2, entry 3). Instead, methyl ester **12c** was isolated in 74% yield. Running the reaction at higher temperature did not improve the cyclization. The formation of **12c** could be explained by the known dimerization of the *N*-alkoxyamidyl radical **13** to give a hydrazide **14** (Scheme 4).[8e,22] Decomposition of **14** under the reaction conditions led to the methyl ester **12c** and benzyl alcohol. Benzyl alcohol was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Scheme 4. Proposed Pathway for the Conversion of an Amidyl Radical to a Methyl Ester



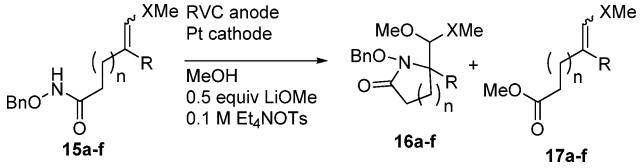
The oxidation potential of **9c** ($E_{p/2}$ = 0.52 V vs Ag/AgCl) is the same as that of an isolated *O*-benzyl hydroxamate and much higher than the potentials measured for **5a** ($E_{p/2}$ = 0.40 V vs Ag/AgCl) and **9a** ($E_{p/2}$ = 0.41 V vs Ag/AgCl). These observations indicate that the seven-membered ring cyclization is much slower than the five- and six-membered ring cyclizations and too slow to compete with the dimerization reaction.

While the *O*-benzyl hydroxamate cyclized nicely to form six-membered ring products, oxidation of the *N*-phenyl amide **9d** afforded a complex mixture of products (Table 2, entry 4). Neither the desired δ-lactam nor the methyl ester was detected.

Extension to Other Electron-Rich Olefins. With the initial success of the reactions in hand, attention was turned to the nature of the olefin used for the cyclization. In this regard, it is important to note that the desired cyclization reactions are two electron oxidation processes. In such reactions, the removal of a second electron from the cyclic product is critical (Scheme 2, oxidation of radical **3**). This second oxidation is best facilitated by electron-donating substituents on the olefin. When this requirement is not satisfied sufficiently, the cyclizations are less successful.[23]

For the current study, coupling reactions with both vinyl sulfides and enol ethers were explored (Table 3). These olefins exhibit oxidation potentials higher than ketene dithioacetals, and so do not interfere with the oxidation of the amide anion. Both have proven to be successful coupling partners for past anodic cyclizations.[12] The electrolysis of vinyl sulfide substrate **15a** at room temperature led to the desired lactam product **16a** in a 60% isolated yield (entry 1). The yield improved to 88% by carrying out the electrolysis at higher temperature (entry 2).

Table 3. Cyclizations with Vinyl Sulfides and Enol Ethers



entry	substrate	n, X, R	T (°C)	product, yield (%)	
1	**15a**	1, S, Me	25	**16a**, 60[a]	**17a**, ND[b]
2	**15a**	1, S, Me	65	**16a**, 88	**17a**, ND
3	**15b**	1, O, Me	25[d]	**16b**, 41[c]	**17b**, ND
4	**15c**	2, S, Me	25[d]	**16c**, ND	**17c**, 68
5	**15d**	2, O, Me	25[d]	**16d**, ND	**17d**, 51
6	**15e**	2, S, H	25[d]	**16e**, 55	**17e**, 3
7	**15f**	2, O, H	25[d]	**16f**, 8	**17f**, 17

[a]An 11% yield of the product hydrolyzed to an aldehyde was obtained. [b]Not detected. [c]A trace amount of the product hydrolyzed to an aldehyde was obtained. [d]Heating the reaction did not improve the yield of the cyclized product.

Anodic oxidation of enol ether **15b** was less successful. In this case, the anodic cyclization gave rise to a 41% yield of lactam **16b** at room temperature. A small amount of aldehyde and benzyl alcohol was also observed in the ^{1}H NMR spectrum of the crude reaction mixture. The formation of benzyl alcohol suggested that the dimerization reaction was competing with the cyclization. In this case, running the reaction at higher temperature (65 °C) did not improve the cyclization.

Attempts to form six-membered rings with either the vinyl sulfide **15c** or the enol ether **15d** were not successful (Table 3,

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

entries 4 and 5). In both cases, only methyl esters **17c** or **17d** were obtained from the reaction, indicating that the radical−radical dimerization was the dominant pathway.

Electrolysis of the less hindered substrates **15e** and **15f** did lead to the cyclized products **16e** and **16f** in 55 and 8% yield, respectively (Table 3, entries 6 and 7). Methyl esters **17e** and **17f** were also obtained suggesting that the radical−radical dimerization pathway was still competing with the cyclization.

Computational Results.[24] To better understand the synthetic observations made, we turned to computational methods to probe the reactivity and limitations of amidyl radicals. Density functional theory has been utilized to successfully investigate the structure and energetics of open-shell molecules,[25] although it does carry with it some significant limitations.[26] We have endeavored to maintain a close link between our computational findings and the experimental results.

We first set out to corroborate our mechanistic understanding of the cyclizations. Transition structures for the cyclization of *O*-benzyl hydroxamate radicals and *N*-phenyl amidyl radicals were located at the DFT level of theory (UB3LYP/6-31G(d,p)).[27] The intrinsic reaction coordinates (IRC) before and after the transition structures were computed (Figures 2 and 3). Analysis of the unpaired spin density

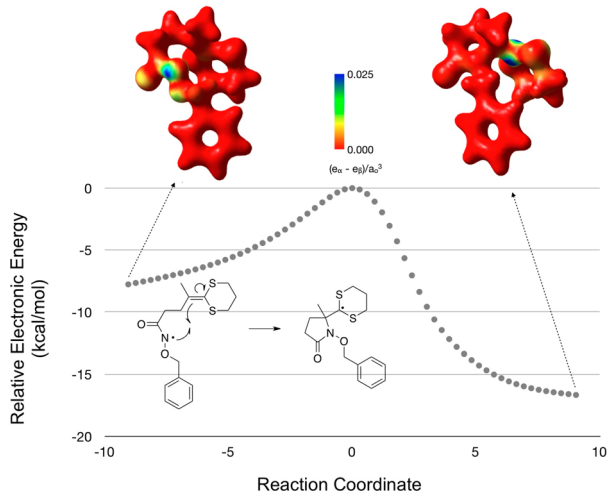


Figure 2. Intrinsic reaction coordinate around the transition structure for the addition of an *O*-benzyl hydroxamate amidyl radical to a ketene dithioacetal. The color maps represent the unpaired electron spin density, expressed in units of unpaired electrons per cubic bohr ($(e_\alpha - e_\beta)/a_o^3$), mapped onto the total electron density surface.

distribution in the structures in the IRC curves showed that the radical was localized primarily at the nitrogen in all structures leading to the transition structure. These calculations along with the cyclic voltammetry studies suggested that the cyclizations followed a radical type mechanism, as depicted in Scheme 2.

Next, we computationally explored the energetics of the cyclizations presented in Figures 2 and 3 (Table 4). After optimization of the product and reactant radical species and incorporation of the thermal energy contributions, the coupling of an *N*-phenyl amidyl radical to a ketene dithioacetal to form a five-membered ring was found to have an activation energy of 10.7 kcal/mol and was exergonic by −6.1 kcal/mol (Table 4, entry 1). The analogous coupling of an *O*-benzyl hydroxamate radical to a ketene dithioacetal was found to have a higher

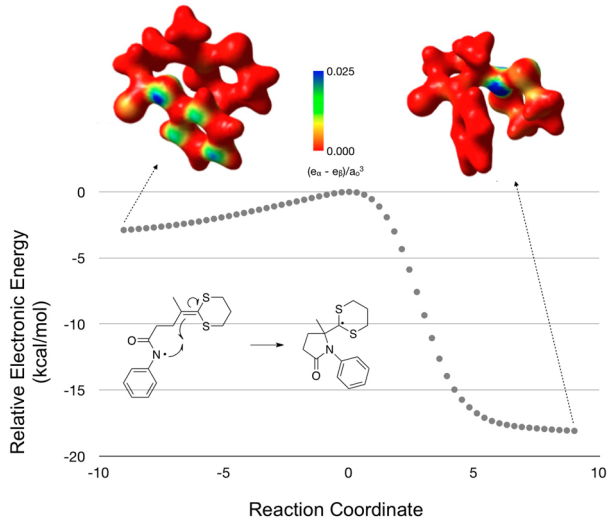
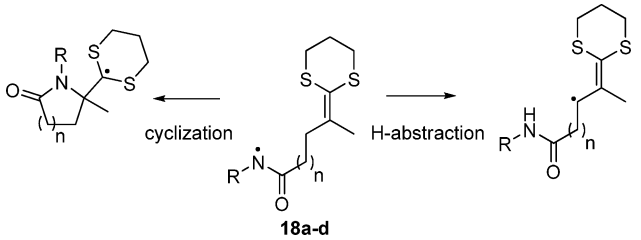


Figure 3. Intrinsic reaction coordinate around the transition structure for the addition of *N*-phenyl amidyl radical to a ketene dithioacetal. The color maps represent the unpaired electron spin density, expressed in units of unpaired electrons per cubic bohr ($(e_\alpha - e_\beta)/a_o^3$), mapped onto the total electron density surface.

Table 4. Calculated Reaction Energetics for Amidyl Radical Cylizations with Ketene Dithioacetal



		cyclization (kcal/mol)		H abstraction (kcal/mol)	
entry	radical	$\Delta G^{\ddagger}$	ΔG	$\Delta G^{\ddagger}$	ΔG
1	**18a**, n = 1, R = Ph	10.7	−6.1	NA	NA[a]
2	**18b**, n = 1, R = OBn	15.8	−1.6	NA	NA
3	**18c**, n = 2, R = Ph	15.0	0.1	13.4	−13.2
4	**18d**, n = 2, R = OBn	16.8	1.3	18.5	−2.7

[a]Not applied.

activation energy ($\Delta G^{\ddagger}$ = 15.8 kcal/mol) and was less exergonic (ΔG = −1.6 kcal/mol). Both of these cyclizations were experimentally successful and led to a good yield of the cyclized product.

When six-membered ring cyclizations were attempted, couplings involving *N*-phenyl amidyl radicals were not experimentally successful, while couplings involving *O*-benzyl hydroxamate radicals were. We suspected that this was due to a competing 1,5-H abstraction, which is a known reaction pathway for amidyl radicals.[6c,28] Our calculations seemed to indicate that 1,5-H abstraction was indeed the problem with *N*-phenyl amidyl radical reactions (entry 3). 1,5-H abstraction was found to have an activation energy lower than cyclization for the *N*-phenyl amidyl radical **18c**. These results probably explain why the electrolysis of **9d** gave no cyclized product (Table 2, entry 4). For the analogous reaction involving the *O*-benzyl hydroxamate radical **18d** (entry 4), the cyclization had a lower activation energy than 1,5-H abstraction, which would allow for a successful cyclization. These results are consistent with the

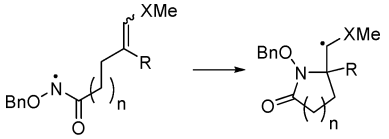
dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

experimental observation that the electrolysis **9b** afforded good yield of the cyclized product (Table 2, entry 2).

We also investigated the energetics of the dimerization pathway of the *O*-benzyl hydroxamate radical (conversion of **13** to **14**, Scheme 4). This reaction was calculated to be highly exothermic (ΔG = −15.2 kcal/mol). However, no transition structure could be located, probably because of the very small barrier associated with radical−radical combination reactions.[29]

A computational analysis of the coupling of *O*-benzyl hydroxamate radicals with enol ethers and vinyl sulfides also gave some helpful insights into the cyclization reactions (Table 5). The coupling of either an enol ether or a vinyl sulfide to an

Table 5. Calculated Energetics for Cyclizations with Vinyl Sulfides and Enol Ethers



19a-f **20a-f**

entry	radical	$\Delta G^{\ddagger}$ (kcal/mol)	ΔG (kcal/mol)
1	**19a**, *n* = 1, X = S, R = Me	14.9	−1.1
2	**19b**, *n* = 1, X = O, R = Me	14.3	0.8
3	**19c**, *n* = 2, X = S, R = Me	16.4	4.2
4	**19d**, *n* = 2, X = S, R = H	14.0	−1.0
5	**19e**, *n* = 2, X = O, R = Me	15.3	5.1
6	**19f**, *n* = 2, X = O, R = H	13.1	1.3

O-benzyl hydroxamate to form six-membered rings was not successful when the olefin was trisubstituted. However, when the olefin was only disubstituted, some of the desired cyclized product was obtained. The calculations indicate that the experimental observations are perhaps best explained by the exothermicity of the cyclization reaction. When the cyclization is endergonic (entries 3 and 5), the reaction leads to the formation of the unwanted methyl ester (see experimental results in Table 3). When the cyclization is exergonic (entry 4), the reaction leads to the formation of the cyclized product.

In an exergonic cyclization, cyclized radical **3** (Scheme 2) will be present in a higher concentration than the noncyclized radical **2**. The increased concentration of **3** facilitates its oxidation, which is critical to the electrolysis reaction.[23] An increased energetic preference for **3** also avoids unwanted side-reactions arising from **2** such as dimerization.

In the case of entry 6, calculations predicted that the cyclic radical was slightly higher in energy that the acyclic amidyl radical ($\Delta G_{cyclization}$ = 1.3 kcal/mol). In this case, only a small amount of cyclized product was obtained experimentally (Table 3, entry 7). This observation cannot be generally applied, however.

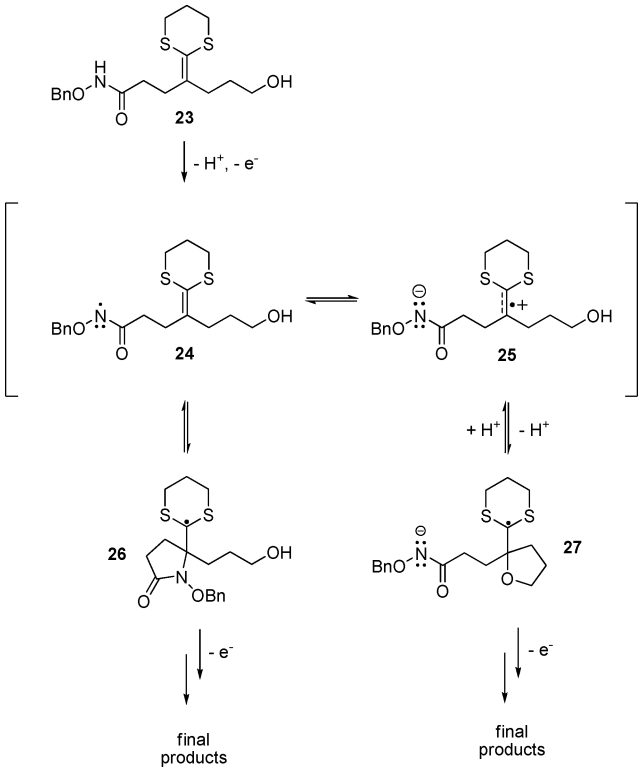
Computational analysis also suggests that the energy difference between the acyclic amidyl radical and the cyclized radical is small for reactions that originate from the coupling of a ketene dithioacetal to an *O*-benzyl hydroxamate to form a six-membered ring. For example, the cyclization originating from **18d** was calculated to be endergonic by 1.3 kcal/mol (Table, entry 4). In this case, the cyclization leads to a good yield of the desired product (Table 2, entry 2). Assuming that the computational results are reliable, we suspect that for **18d** the ease with which the cyclic radical is oxidized plays a large role in the success of the cyclization. The efficient oxidation of the dithiane radical will drain the equilibrium between the cyclic and acyclic radicals toward the desired product.

Our computational findings, along with the experimental results, indicate that the exothermicity of the radical cyclization is a significant consideration. We propose that the best way to ensure a successful cyclization is to design the reaction such that the cyclized radical intermediate is close to or lower in energy than the uncyclized amidyl radical. This can be achieved by appropriately substituting the olefin in a way that best stabilizes the cyclized radical, or alternatively by relieving the steric strain of the cyclized radical.

Competition Experiments. Unlike the sulfonamide anion ($E_{p/2}$ = 0.90 V vs Ag/AgCl) studied previously,[14] the *O*-benzyl hydroxamate anion ($E_{p/2}$ = 0.52 V vs Ag/AgCl) in this work is oxidized at a significantly lower potential than the ketene dithioacetal ($E_{p/2}$ = 1.06 V vs Ag/AgCl). In the case of the sulfonamide anion, competition studies were used to demonstrate that the *N*-localized radical underwent a reversible intramolecular electron transfer to generate a radical cation localized at the ketene dithioacetal.[14c] We wanted to see if this equilibrium still played a role in amidyl radical reactions.

To this end, competition substrate **23** was synthesized (Scheme 5). The electrolysis of **23** may lead to two mechanistic

Scheme 5. Competition Experiment Design



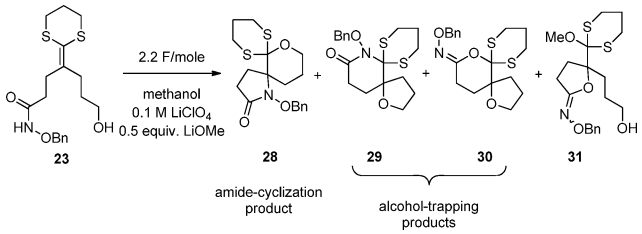
pathways. First, amidyl radical **24** may couple to the olefin to give intermediate **26** with no intramolecular electron transfer. Alternatively, an intramolecular single electron transfer from the closely positioned olefin to the amidyl radical may occur to form **25**. In this case, trapping of the radical cation by the alcohol would afford intermediate **27**. Both intermediates **26** and **27** undergo a second single electron oxidation at the anode, which ultimately leads to the formation of the final product(s) from each pathway. Once the final products are formed, the reaction is over as the final products cannot convert back to the

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

open-shell intermediates. The outcome of the reaction is determined by the equilibrium between open-shell intermediates **24**, **25**, **26**, and **27**.

The experimental results for the electrolysis of **23** are shown in Table 6. We chose lithium perchlorate as the electrolyte for this electrolysis reaction. As demonstrated in our previous competition experiments, this change permits the alcohol-trapping pathway to be more competitive.[14c] Results obtained using the standard conditions presented throughout this paper (constant current of 6 mA, room temperature) are shown in entry 2. Product **28**, arising from the amide-cyclization pathway, was obtained in a 58% yield. A small amount of the undesired amide-trapping product **31** was also obtained. It was found that the yield of the amide-cyclization products could be improved marginally by heating the reaction (entry 1).

Table 6. Competition Experiment Results



				yield (%)			
entry	current (mA)	temp. (°C)	base	**28**	**29**	**30**	**31**
1	6	45	LiOMe	65	0	0	3
2	6	25	LiOMe	58	0	0	2
3	6	0	LiOMe	52	2	5	2
4	40	0	LiOMe	25	24	6	0
5	6	25	2,6-lutidine	1	38	12	0

Alcohol-trapping products **29** and **30** were not detected until the reaction was run at 0 °C (entry 3). Increasing the current (that is, the rate of oxidation) also led to higher yields of alcohol-trapping products. At a current of 40 mA and a temperature of 0 °C, alcohol-trapping products **29** and **30** become the most abundant products, with a combined yield of 30% (entry 4). Under these conditions, amide-cyclization was reduced to a 25% yield.

These results indicate that amidyl radicals behave similarly to the previously studied sulfonamide radicals.[14c] The formation of both radicals in the presence of the electron-rich olefin allows for an intramolecular electron transfer reaction and the reversible formation of a radical cation intermediate. The alcohol-trapping pathway for the radical cation is the kinetically favored pathway and may be selected for through the use of low temperature and high current conditions. The higher current helps intermediate **27** to be oxidized quickly before the cyclization can reverse to regenerate intermediate **25**. The amidyl radical cyclization pathway appears to be thermodynamically favored, and may be selected for through the use of high temperature and low current conditions. These conditions facilitate equilibration to the thermodynamically favored intermediate **26** prior to oxidation to the final product.

Alcohol-trapping products were most effectively obtained through the use of less basic conditions (Table 6, entry 5). When 2,6-lutidine was substituted for lithium methoxide, the reaction led to almost no amide cyclization products and a combined 50% yield of alcohol-trapping products. Under these conditions, the amide oxidizes at higher potential than the ketene dithioacetal and the first single electron oxidation took place at the electron-rich olefin.

CONCLUSION

Amidyl radicals can be generated anodically from *O*-benzyl hydroxamates and *N*-phenyl amides under mild conditions. These amidyl radicals undergo cyclization reactions with electron-rich olefins to form both γ- and δ-lactam structures found in a number of biologically active natural products. The radical nature of the cyclizations was supported by cyclic voltammetry data and DFT calculations. The success of these reactions depends on controlling the energetics of the cyclization relative to the competing pathways of radical–radical dimerization and H-abstraction. The relative energetics of these reaction pathways can be modulated to favor cyclization through the appropriate selection of the amide and olefin substituents. In general, ketene dithioacetal groups were found to be the most effective coupling partners for the reactions.

EXPERIMENTAL SECTION

Electrolysis Procedure. A methanol or methanol/tetrahydrofuran solution containing the electrolysis substrate (80–120 mg, 0.03 M) and electrolyte (lithium perchlorate or tetraethylammonium tosylate, 0.1 M) was prepared in a three-necked round-bottom flask under argon atmosphere. If desired for the reaction conditions, lithium methoxide (0.5 equiv, 1 M in methanol) was added to the solution. A reticulated vitreous carbon anode and a platinum cathode were inserted into the solution, and the flask was sonicated for 30 s. Electrolysis was performed with stirring at a constant current of 6.0 mA until 2.2 F/mol of electric charge had been passed through the solution, unless otherwise noted. Thin layer chromatography was used to monitor reaction progress. If the electrolysis reaction was carried out at a higher current, a room-temperature water bath was used to keep the reaction from heating. See the Supporting Information for more details of the electrolysis setup.

If lithium perchlorate was used as the electrolyte, water and ether were added to the reaction upon completion. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated under reduced pressure.

If tetraethylammonium tosylate was used as the electrolyte, the reaction solvent was removed under reduced pressure without performing an extraction.

The crude residue was purified via column chromatography through silica gel with hexanes and ethyl acetate. Compounds containing a ketene dithioacetal moiety were stable to chromatography. However, electrolysis products containing a dithioacetal were not. For these compounds, packing the column with triethylamine (1% by wt) prevented decomposition.

Cyclic Voltammetry. A solution of methanol containing the substrate (0.025 M) and electrolyte (tetraethylammonium tosylate, 0.1 M) was prepared. Lithium methoxide (0.6 equiv, 1 M solution in methanol) was added, if desired. Cyclic voltammetry was performed on a BAS Cell Stand (model C1B-120) using a glassy carbon working electrode (3 mm diameter), a platinum counter electrode, and a Ag/AgCl reference electrode. The potential sweep was performed at a rate of 25 mV/s, with the sweep beginning in the positive direction. This produced an irreversible oxidation wave, and the half-wave oxidation potential ($E_{p/2}$) was reported as the oxidation potential of the substrate.

General Methods. Unless otherwise noted, reactions described herein were performed in flame-died glassware under a dry argon atmosphere. Tetrahydrofuran was distilled from benzophenone and sodium prior to use. Triethylamine was distilled from calcium hydride. Dichloromethane was distilled from calcium hydride. All other

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379–391

solvents, reagents, and starting materials were purchased commercially and used without further purification.

Compounds reported in this work were characterized by NMR, FT-IR, and ESI-MS. ^{1}H and ^{13}C NMR spectra were collected on either a 300 or 600 MHz spectrometer, with chemical shifts reported in ppm as referenced to an internal TMS standard (δ = 0.00 ppm for both ^{1}H and ^{13}C NMR).

Characterization of Electrolysis Products. *1-(Benzyloxy)-5-(2-methoxy-1,3-dithian-2-yl)-5-methyl-2-pyrrolidinone (**6a**).* Isolated as a white, crystalline solid (mp 104−109 °C): IR (neat, cm^{-1}) 1713, 1375, 1066, 754, 699; ^{1}H NMR (300 MHz, CDCl3) δ 7.49−7.26 (m, 5H), 5.21 (d, J = 9.6 Hz, 1H, A of AB pattern), 5.05 (d, J = 9.6 Hz, 1H, B of AB pattern), 3.56 (s, 3H), 2.98−2.78 (m, 4H), 2.67−2.59 (m, 1H), 2.54−2.41 (m, 1H), 2.28−2.19 (m, 1H), 1.99−1.74 (m, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 135.8, 129.4, 128.6, 128.5, 101.4, 77.6, 72.7, 72.7, 53.1, 28.5, 27.1, 22.5, 22.0; HRMS (ESI-FTIRC) m/z (M + H)$^+$ calcd for $C_{17}H_{24}NO_3S_2$ 354.1192, found 354.1189.

*1-(Benzyloxy)-5-(2-methoxy-1,3-dithian-2-yl)-5-methyl-2-pyrrolidinone (**6b**).* Isolated as a yellow, crystalline solid (mp 123−140 °C): IR (neat, cm^{-1}) 1697, 1362, 1086, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 3.34 (s, 3H), 3.00−2.68 (m, 6H), 2.50−2.40 (m, 1H), 2.06−1.75 (m, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 138.6, 128.5, 127.8, 103.0, 52.0, 31.4, 30.7, 29.1, 28.6, 25.1, 21.7; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for 324.1086, found 324.1100.

*Methyl 1-(benzyloxy)-2-methyl-5-oxo-2-pyrrolidinecarboxylate (**7a**).* IR (neat, cm^{-1}) 1740, 1718, 1454, 756, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.30 (m, 5H), 5.12, (d, J = 10.2 Hz, 1H, A of AB pattern), 5.06 (d, J = 10.2 Hz, 1H, B of AB pattern), 3.77 (s, 3H), 2.58−2.35 (m, 2H), 2.30−2.21 (m, 1H), 2.00−1.89 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 173.0, 135.4, 129.9, 129.0, 128.7, 78.6, 66.0, 53.1, 29.1, 26.7; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for 286.1055, found 286.1051.

*(Benzyloxy)[5-(2-methoxy-1,3-dithian-2-yl)-5-methyl-4,5-dihydro-3H-fur-2-ylidene]amine (**8a**).* Isolated as a 4:1 mixture of isomers: IR (neat, cm^{-1}) 1674, 1453, 1052, 732, 698; ^{1}H NMR (300 MHz, CDCl3) δ 7.43−7.22 (m, 5H), 4.97 (s, major, 1.6H), 4.93 (s, minor, 0.4H), 3.54 (s, major, 2.4H), 3.52 (s, minor, 0.6H), 3.02−2.56 (m, 7H), 1.97−1.76 (m, 3H), 1.57 (s, major, 2.4H), 1.50 (s, minor, 0.6H); ^{13}C NMR (75 MHz, $CDCl_3$, only data for major isomer are given) δ 159.2, 138.8, 128.5, 128.0, 127.6, 100.6, 96.9, 75.9, 53.1, 31.9, 28.0, 27.7, 26.7, 23.0, 22.9; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{17}H_{24}NO_3S_2$ 354.1192, found 354.1192.

*N-Methyl[5-(2-methoxy-1,3-dithian-2-yl)-5-methyl-4,5-dihydro-3H-fur-2-ylidene]amine (**8d**).* Isolated as a clear, yellow oil. Isolated as a single isomer: IR (neat, cm^{-1}) 1714, 1126, 1062; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 3H), 3.19−2.71 (m, 4H), 2.89 (s, 3H), 2.63−2.50 (m, 3H), 2.02−1.77 (m, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 163.4, 100.0, 93.4, 53.7, 34.7, 32.2, 28.8, 27.4, 27.0, 23.8, 22.6; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{11}H_{20}NO_2S_2$ 262.0930, found 262.0936.

*1-(Benzyloxy)-5-(2-methoxy-1,3-dithian-2-yl)-4,5-dimethyl-2-pyrrolidinone (**10a**).* Isolated as a single diastereomer: IR (neat, cm^{-1}) 1706, 1376, 1080; ^{1}H NMR (300 MHz, CDCl3) δ 7.50−7.47 (m, 2H), 7.37−7.33 (m, 3H), 5.25 (d, J = 9.6 Hz, 1H, A of AB pattern), 5.05 (d, J = 9.6 Hz, 1H, B of AB pattern), 3.58 (s, 3H), 2.94−2.71 (m, 6H), 2.01−1.76 (m, 3H), 1.44 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 135.7, 129.4, 128.6, 128.5, 102.7, 77.4, 75.3, 53.0, 36.5, 30.7, 28.4, 28.1, 22.4, 19.3, 16.1; HRMS (ESI-FTICR) m/z (M + H)$^+$ calcd for $C_{18}H_{26}NO_3S_2$ 368.1349, found 368.1344.

*1-(Benzyloxy)-6-(2-methoxy-1,3-dithian-2-yl)-6-methyl-2-piperidinone (**10b**).* Isolated as a clear, colorless gum: IR (neat, cm^{-1}) 1671, 1332, 1085, 734, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.34−7.26 (m, 3H), 5.20 (d, J = 9.6 Hz, 1H, A of AB pattern), 4.83 (d, J = 9.6 Hz, 1H, B of AB pattern), 3.54 (s, 3H), 2.91−2.80 (m, 4H), 2.49−2.40 (m, 3H), 1.96−1.78 (m, 4H), 1.62 (m, appears as a singlet, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 136.1, 129.2, 128.4, 128.3, 102.9, 73.7, 53.0, 35.5, 34.2, 28.4, 28.1, 22.4, 22.2, 18.2; HRMS (ESI-FTICR) m/z (M + H)$^+$ calcd for $C_{18}H_{26}NO_3S_2$ 368.1349, found 368.1348.

*Methyl 1-(benzyloxy)-2,3-dimethyl-5-oxo-2-pyrrolidinecarboxylate (**11a**).* Isolated as a single diastereomer in the form of a white, crystalline solid (mp 77−81 °C): IR (neat, cm^{-1}) 1737, 1727, 754, 701; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.33 (m, 5H), 5.17 (d, J = 9.9 Hz, 1H, A of AB pattern), 5.08 (d, J = 9.9 Hz, 1H, B of AB pattern), 3.76 (s, 3H), 2.62 (dd, J = 16.8, 8.7 Hz, 1H), 2.50−2.42 (m, 1H), 1.97 (dd, J = 16.8, 6.6, 1H), 1.31 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.2, 135.5, 129.7, 128.9, 128.6, 78.4, 69.5, 53.0, 35.1, 32.9, 15.7, 15.0; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{15}H_{20}NO_4$ 278.1387, found 278.1386.

*Methyl 1-(benzyloxy)-2-methyl-6-oxo-2-piperidinecarboxylate (**11b**).* IR (neat, cm^{-1}) 1739, 1678, 756, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.28 (m, 5H), 5.10 (d, J = 9.6 Hz, 1H, A of AB pattern), 4.88 (d, J = 9.6 Hz, 1H, B of AB pattern), 3.74 (s, 3H), 2.57−2.51 (m, 2H), 2.22−2.15 (m, 1H), 1.99−1.89 (m, 1H), 1.79−1.70 (m, 2H), 1.59 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.1, 135.6, 129.6, 128.7, 128.6, 128.6, 69.1, 53.0, 36.2, 33.5, 23.0, 18.3; HRMS (ESI-TOF) m/z (M + Na)$^+$ cald for $C_{14}H_{17}NO_4Na$ 286.1055, found 286.1051.

*Methyl 6-(1,3-dithian-2-ylidene)heptanoate (**12c**).* Isolated as a clear, green-yellow oil: IR (neat, cm^{-1}) 1737, 1434, 1192; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.82−2.76 (m, 4H), 2.33−2.25 (m, 4H), 2.09−2.03 (m, 2H), 1.83 (s, 3H), 1.62−1.51 (m, 2H), 1.41−1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.2, 119.8, 51.6, 35.5, 34.1, 30.4, 30.3, 27.5, 25.2, 24.7, 20.3; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{12}H_{20}O_2S_2Na$ 283.0802, found 283.0797.

*1-(Benzyloxy)-5-[methoxy(methylthio)methyl]-5-methyl-2-pyrrolidinone (**16a**).* Isolated as a 5:1 mixture if diastereomers in the form of a yellow, crystalline solid (mp 83−90 °C): IR (neat, cm^{-1}) 1714, 1453, 1092, 755, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.28 (m, 5H), 5.22 and 5.13 (minor and major, respectively; d, J = 9.9 Hz, 1H, A of AB pattern), 4.96 and 4.93 (major and minor, respectively; d, J = 9.9 Hz, 1H, B of AB pattern), 4.33 (major, s, 1H), 4.28 (minor, s, 1H), 3.45 (minor, s, 3H), 3.41 (major, s, 3H), 2.60−2.33 (m, 1H), 2.27−2.20 (m, 2H), 2.18 (major, s, 3H), 2.14 (minor, s, 3H), 1.71−1.60 (m, 1H), 1.35 (minor, s, 3H), 1.31 (major, s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 135.7, 129.6, 128.9, 128.6, 94.0, 78.4, 67.5, 58.3, 27.3, 25.5, 23.5, 15.5; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{15}H_{21}NO_3SNa$ 318.1140, found 318.1136.

*1-(Benzyloxy)-5-(dimethoxymethyl)-5-methyl-2-pyrrolidinone (**16b**).* IR (neat, cm^{-1}) 1712, 1076, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (m, 5H), 5.19 (d, J = 9.9 Hz, 1H, A of AB pattern), 4.91 (d, J = 9.9 Hz, 1H, B of AB pattern), 4.22 (s, 1H), 4.38 (s, 3H), 4.35 (s, 3H), 3.46−2.17 (m, 3H), 1.58−1.47 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 135.7, 129.6, 128.9, 128.6, 108.6, 78.5, 65.6, 59.1, 57.6, 27.5, 23.9, 21.9; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{15}H_{21}NO_4Na$ 302.1368, found 302. 1375.

1-(Benzyloxy)-2-methyl-5-oxo-2-pyrrolidinecarbaldehyde. Isolated as a clear, yellow oil: IR (neat, cm^{-1}) 1707, 1065, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.43−7.34 (m, 5H), 5.00 (s, 2H), 2.41 (t, J = 7.8 Hz, 2H), 2.16−2.07 (m, 1H), 1.82−1.72 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 172.7, 135.0, 129.9, 129.3, 128.9, 78.7, 69.4, 26.1, 25.1, 17.3; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{13}H_{16}NO_3$ 234.1125, found 234.1126.

*1-(Benzyloxy)-6-[methoxy(methylthio)methyl]-2-piperidinone (**16e**).* Isolated as a 5:1 mixture of diastereomers in the form of a yellow, crystalline solid (mp 68−76 °C): IR (neat, cm^{-1}) 3467, 2923, 1700; ^{1}H NMR (300 MHz, CDCl3) δ 7.48−7.33 (m, 5H), 5.01 (d, J = 10.8 Hz, 1H, A of AB pattern), 4.93 (d, J = 10.8 Hz, 1H, B of AB pattern), 4.75 (d, J = 2.6 Hz, 0.83H), 4.72 (d, J = 3.9 Hz, 0.17H), 3.74 (dt, J (d) = 3.9 Hz, J (t) = 6.9 Hz, 0.17H), 3.56 (dt, J (d) = 2.5 Hz, J (t) = 6.0 Hz, 0.83H), 3.44 (s, 3H), 2.54−2.40 (m, 2H), 2.16 (s, 0.5H), 2.15 (s, 2.5H), 2.05−1.8 (m, 3H), 1.62−1.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 135.5, 129.5, 128.8, 128.5, 88.8, 76.1, 64.6, 58.0, 33.5, 23.6, 19.0, 15.1; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{15}H_{21}NO_3SNa$ 296.1315, found 296.1316.

*1-(Benzyloxy)-6-(dimethoxymethyl)-2-piperidinone (**16f**).* Isolated as a white, crystalline solid (mp 80−90 °C): IR (neat, cm^{-1}) 3468,

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

2918, 2848, 1723, 1700; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46−7.42 (m, 2H), 7.40−7.33 (m, 3H), 5.00 (d, J = 10.8 Hz, 1H, A of AB pattern), 4.96 (d, J = 10.8 Hz, ^{1}H, B of AB pattern), 4.59 (d, J = 3 Hz, 1H), 3.47 (s, 3H), 4.46−3.42 (m, 1H), 3.41 (s, 3H), 2.44 (t, J = 7.2 Hz, 2H), 2.04−1.97 (m, 1H), 1.97−1.89 (m, 1H), 1.77−1.69 (m, 1H), 1.56−1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 135.5, 129.5, 128.7, 128.5, 104.5, 75.9, 61.7, 58.0, 56.6, 33.4, 22.3, 18.8; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{15}H_{21}NO_4Na$ 280.1543, found 280.1553.

*Methyl 5-methyl-6-(methylthio)-5-hexenoate (**17c**).* Isolated as a 3:2 mixture of isomers in the form of a clear, colorless oil: IR (neat, cm^{-1}) 2950, 2920, 1738, 1624, 1436; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (s, 0.4H), 5.61 (s, 0.6H), 3.67 (s, 3H), 2.33 (t, J = 7.8 Hz, 0.8H), 2.29 (t, J = 7.5 Hz, 1.2H), 2.25 (s, 1.8H), 2.22 (s, 1.2H), 2.19 (t, J = 8.1 Hz, 0.8H), 2.09 (t, J = 7.5 Hz, 1.2), 1.82−1.67 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 135.7, 134.9, 121.5, 121.2, 51.5, 38.4, 33.4, 33.5, 33.3, 32.8, 22.9, 22.7, 22.5, 17.6, 17.3, 17.2; HRMS (ESI-FTIRC) m/z (M + H)$^+$ calcd for $C_9H_{17}O_2S$ 189.0943, found 189.0944.

*Methyl 6-methoxy-5-methyl-5-hexenoate (**17d**).* Isolated as a 3:2 mixture of isomers: IR (neat, cm^{-1}) 2950, 2934, 1739, 1684, 1455, 1437; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 3.67 (s, 3H), 3.54 (s, 1.8H), 3.50 (1.2H), 2.29 (q, J = 7.5 Hz, 2H), 2.09 (t, J = 7.2 Hz, 0.8H), 1.90 (t, J = 7.2 Hz, 1.2H), 1.71 (quintet, J = 7.2 Hz, 2H), 1.58 (s, 1.8H), 1.52 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 174.2, 142.5, 142.4, 112.9, 112.6, 59.3, 59.2, 51.5, 51.4, 33.5, 33.3, 33.2, 28.1, 23.1, 22.5, 17.0, 12.5; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_9H_{16}O_3Na$ 195.0992, found 195.1000.

*Methyl 6-(methylthio)-5-hexenoate (**17e**).* Tentatively assigned on the basis of ^{1}H NMR data. Isolated as a 3:2 mixture of trans:cis isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, J = 15 Hz, 0.6H, major isomer), 5.93 (d, J = 9.6 Hz, 0.4H, minor isomer), 5.56−5.20 (m, 1H), 3.67 (s, 3H), 2.33 (q, J = 7.5 Hz, 2H), 2.27 (s, 1.2H, minor isomer), 2.23 (s, 1.8H, major isomer), 2.15 (quintet, J = 7.2 Hz, 2H), 1.74 (quintet, J = 7.2 Hz, 0.8H, minor isomer), 1.72 (quintet, J = 7.2 Hz, 1.2H, major isomer).

*Methyl 6-methoxy-5-hexenoate (**17f**).* Isolated as a 2:1 mixture of isomers in the form of an unstable, clear, colorless oil: IR (neat, cm^{-1}) 3033, 2998, 2950, 1738, 1655, 1453, 1437; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, J = 12.6 Hz, 0,67H), 5.90 (d, J = 6.3 Hz, 0.33H), 4.68 (dt, J (d) = 12.6 Hz, J (d) = 7.5 Hz, 0.67H), 4.31 (dt, J (d) = 6.3 Hz, J (t) = 7.2 Hz, 0.33H), 3.67 (s, 3H), 3.57 (s, 1H), 3.50 (s, 2H), 2.32 (t, J = 7.5 Hz, 0.67H), 2.31 (t, J = 7.5 Hz, 1.33H), 2.10 (q, J = 7.5 Hz, 0.67H), 1.97 (q, J = 7.5 Hz, 1.33H), 1.68 (quintet, J = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 174.2, 147.8, 146.9, 105.5, 101.7, 59.5, 55.9, 51.5, 51.4, 33.5, 33.2, 27.1, 25.8, 25.0, 23.3; HRMS (ESI-FTIRC) m/z (M + H)$^+$ calcd for $C_8H_{15}O_3$ 159.1016, found 159.1012.

*(Electrolysis Product **28**).* Isolated as a clear, amorphous gum: IR (neat, cm^{-1}) 2955, 2930, 1710, 1497, 1454, 1423, 1411; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 2H), 7.40−7.27 (m, 3H), 5.54 (d, J = 9.3 Hz, 1H, A of AB pattern), 5.23 (d, J = 9.3 Hz, 1H, B of AB pattern), 4.01 (t, J = 5.4 Hz, 2H), 3.29−3.06 (m, 2H), 2.78−2.50 (m, 4H), 2.35−2.20 (m, 2H), 2.20−2.02 (m, 2H), 1.95 (t, J = 13.2 Hz, 1H), 1.88−1.69 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 135.7, 129.5, 128.31, 128.28, 96.6, 76.8, 67.0, 62.5, 30.3, 27.8, 26.6, 26.1, 26.0, 24.8, 21.9; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{18}H_{23}NO_3S_2Na$ 388.1017, found 388.1012.

*(Electrolysis Product **29**).* Isolated as a clear, colorless oil: IR (neat, cm^{-1}) 2952, 2926, 2874, 1672; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.50 (m, 2H), 7.41−7.29 (m, 3H), 5.26 (d, J = 9.2 Hz, A of AB pattern, 1H), 5.14 (d, J = 9.2 Hz, B of AB pattern, 1H), 4.13 (dt, J (d) = 6.6 Hz, J (t) = 8.1 Hz, 1H), 4.07−3.98 (m, 1H), 3.4−3.18 (m, 2H), 2.97−2.62 (m, 4H), 2.47−1.69 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 135.7, 129.4, 128.4 (two overlapping peaks), 87.9, 80.7, 77.6, 70.4, 36.0, 29.21, 29.18, 28.8, 28.6, 26.0, 23.2; HRMS (ESI- FTIRC) m/z (M + H)$^+$ calcd for $C_{18}H_{24}NO_3S_2$ 366.1192, found 366.1192.

*(Electrolysis Product **30**).* Isolated as a white, crystalline solid (mp 126−132 °C): IR (neat, cm^{-1}) 2952, 2918, 2867, 1672; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.18 (m, 5H), 5.02 (s, 2H), 4.08−3.88 (m, 2H), 3.36−3.20 (m, 1H), 3.12−2.98 (m, 1H), 2.81−2.56 (m, 4H), 2.23−1.73 (m, 6H), 1.63 (s, 1H), 1.57 (dt, J (d) = 13.2 Hz, J (t) = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.1, 128.1, 127.6, 127.2, 95.6, 89.9, 75.4, 62.8, 31.5, 30.8, 26.2, 26.1, 25.6, 24.8, 21.8; HRMS (ESI-FTICR) m/z (M + H)$^+$ calcd for 366.1192, found 366.1191.

*(Electrolysis Product **31**).* Isolated as a clear, colorless oil: IR (neat, cm^{-1}) 3422, 2932, 1701, 1695, 1690; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.65−7.30 (m, 5H), 5.09 (d, J = 9.6 Hz, A of AB pattern, 1H), 5.02 (d, J = 9.6 Hz, B of AB pattern, 1H), 4.46 (t, J = 5.2 Hz, not present after addition of D_2O, 1H), 3.58 (s, 3H), 3.41−3.32 (2H), 3.10−2.98 (m, 2H), 2.96−2.88 (m, 2H), 2.56−2.51 (m, 1H), 2.37−2.25 (m, 2H), 2.22−2.14 (m, 1H), 2.11−2.02 (m, 1H), 2.00−1.92 (m, 1H), 1.80−1.68 (m, 2H), 1.43−1.33 (m, 1H), 1.27−1.15 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0, 135.5, 128.5, 128.2, 128.1, 99.9, 75.6, 74.6, 60.6, 52.7, 28.3 (two overlapping signals), 28.0, 26.6, 26.0, 24.8 (broad), 21.9; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{19}H_{27}NO_4S_2Na$ 420.1277, found 420.1274.

Synthesis of Electrolysis Substrates. *Ethyl 4-(1,3-dithian-2-ylidene)valerate.* For the synthesis of the title compound from ethyl levulinate, see ref 15.

*1-(O-Benzyloxyamino)-4-(1,3-dithian-2-ylidene)-1-pentanone (**5a**).* To a suspension of *O*-benzylhydroxylamine hydrochloride (0.72g, 4.5 mmol) in tetrahydrofuran (15 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 15 mL, 15 mmol) at −78 °C. The resulting mixture was stirred at 0 °C until a clear solution was obtained. The reaction was cooled down to −78 °C, and ethyl 4-(1,3-dithian-2-ylidene)valerate (0.74 g, 3.0 mmol) in tetrahydrofuran (3 mL) was added. The reaction was stirred at the same temperature for 5 h. Water and ether were added. The organic phase was separated, and the aqueous phase was extracted with ether twice. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with a 3:1 mixture of ether:hexane to give the title compound as a white, crystalline solid (0.69 g, 71% yield, mp 87−90 °C): IR (neat, cm^{-1}) 3187, 1655, 749, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 and 8.33 (2s, 1H), 7.34−7.26 (m, 5H), 4.84 (s, 2H), 2.82−2.75 (m, 4H), 2.60 (t, J = 7.8 Hz, 2H), 2.36−2.00 (m, 4H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 137.7, 135.7, 129.5, 128.8, 121.6, 78.3, 31.7, 30.3, 30.1, 24.9, 20.3; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{16}H_{21}NO_2S_2Na$ 346.0905, found 346.0911.

*1-Anilino-4-(1,3-dithian-2-ylidene)-1-pentanone (**5b**).* To a solution of ethyl 4-(1,3-dithian-2-ylidene)valerate in tetrahydrofuran and water (3:1 ratio) was added lithium hydroxide monohydrate. The reaction mixture was stirred overnight and then treated with 1 M aqueous HCl until to adjust the pH to 1. The reaction mixture was extracted three times with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under a vacuum.

To a solution of the residue (assumed to be 4-(1,3-dithian-2-ylidene)valeric acid, 0.57g, 2.6 mmol), aniline (0.48 g, 5.2 mmol) and 4-dimethylaminopyridine (0.032 g, 0.26 mmol) in dichloromethane was added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 0.75 g, 3.9 mmol) at room temperature. The reaction was stirred overnight. Ether and 1 M hydrochloric acid were added. The organic phase was separated and washed with 1 M hydrochloric acid twice. The combined aqueous phase was extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel to afford the desired product as a white, crystalline solid (0.65 g, 85% yield, mp 101−106 °C): IR (neat, cm^{-1}) 3297, 1659, 1599, 1544, 1498, 1442, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (br, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.30−7.25 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 2.87−2.72 (m, 6H), 2.46−2.41 (m, 2H), 2.11−2.03 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.3, 137.7, 129.1, 124.4, 121.7, 120.3, 36.0, 31.9, 30.3, 30.1, 24.9, 20.3; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{15}H_{19}NOS_2$ 294.0981, found 294.0989.

*4-(1,3-Dithian-2-ylidene)valeramide (**5c**).* To a solution of ethyl 4-(1,3-dithian-2-ylidene)valerate in tetrahydrofuran and water (3:1 ratio) was added lithium hydroxide monohydrate. The reaction mixture was

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

stirred overnight and then treated with 1 M aqueous HCl until to adjust the pH to 1. The reaction mixture was extracted three times with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under a vacuum.

To a solution of the residue (assumed to be 4-(1,3-dithian-2-ylidene)valeric acid, 0.44 g, 2.0 mmol) in tetrahydrofuran (5 mL) was added triethylamine (0.29 mL, 2.1 mmol). The solution was cooled to 0 °C, and ethyl choroformate (0.20 mL, 2.1 mmol) was added. The reaction was stirred at the same temperature for 0.5 h. Ammonium hydroxide (28−30% in water, 2.5 mL) was added. The resulting reaction mixture was stirred overnight. Dichloromethane and water were added. The organic phase was separated and washed with 1 N sodium hydroxide, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed in vacuo to give the desired product as a colorless solid (0.35 g, 82%): IR (neat, cm^{-1}) 3345, 3185, 1667, 1643, 909; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (br, 1H), 5.89 (br, 1H), 2.90−2.85 (m, 4H), 2.67 (t, J = 8.1 Hz, 2H), 2.31 (t, J = 8.1 Hz, 2H), 2.16−2.08 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 138.0, 121.3, 34.3, 31.9, 30.3, 30.1, 24.9, 20.2; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_9H_{16}NOS_2$ 218.0668, found 218.0671.

*4-(1,3-Dithian-2-ylidene)-1-(methylamino)-1-pentanone (**5d**).* To a solution of ethyl 4-(1,3-dithian-2-ylidene)valerate in tetrahydrofuran and water (3:1 ratio) was added lithium hydroxide monohydrate. The reaction mixture was stirred overnight and then treated with 1 M aqueous HCl until to adjust the pH to 1. The reaction mixture was extracted three times with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under a vacuum.

To a solution of the residue (assumed to be 4-(1,3-dithian-2-ylidene)valeric acid, 0.287 g, 1.32 mmol) in dichloromethane were added triethylamine (0.20 mL, 1.45 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 0.274 g, 1.45 mmol), 4-dimethylaminopyridine (0.016 g, 0.13 mmol), and methylamine hydrochloride (0.096 g, 1.4 mmol). The reaction was stirred overnight and quenched with 1 N hydrochloric acid. The organic phase was separated, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed through silica gel to afford the desired compound as a white, crystalline solid (0.219 g, 72%, mp 97−102 °C): IR (neat, cm^{-1}) 3305, 1642, 1557; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (br, 1H), 2.90−2.84 (m, 4H), 2.81 (s, 1.5 H), 2.79 (s, 1.5 H), 2.69−2.64 (m, 2H), 2.29−2.24 (m, 2H), 2.16−2.08 (m, 2H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.3, 121.2, 34.9, 32.2, 30.3, 30.2, 26.6, 24.9, 20.2; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_{10}H_{18}NOS_2$ 232.0824, found 232.0826.

4-(1,3-Dithian-2-ylidene)-3-methylvaleric acid. To a solution of 2-trimethylsilyl-1,3-dithiane (3.84 g, 20 mmol) in tetrahydrofuran (40 mL) was added *n*-butyllithium (1.6 M in hexanes, 12.5 mL, 20 mmol) at −78 °C under argon atmosphere. The solution was stirred at the same temperature for 0.5 h and then 0 °C for 0.5 h. 3-Methyl-4-oxopentanoic acid (1.30 g, 10 mmol) in tetrahydrofuran (5 mL) was added at −78 C. The reaction was allowed to warm to room temperature gradually and stirred overnight. Water and ether were added. The aqueous phase was separated and acidified by 1 N hydrochloric acid to pH 2. The solution was exacted with ether twice. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (eluting with ether:hexane = 1:2) to give the desired product (0.40 g, 17%): IR (neat, cm^{-1}) 1705, 1297, 911; ^1H NMR (300 MHz, $CDCl_3$) δ 3.74−3.61 (m, 1H), 2.83−2.77 (m, 4H), 2.37−2.23 (m, 2H), 2.08−2.94 (m, 2H), 1.73 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 140.4, 121.6, 39.5, 34.5, 30.4, 30.1, 25.1, 18.5, 15.1; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_{10}H_{16}O_2S_2$ 233.0664, found 233.0665.

*1-(O-Benzyloxyamino)-4-(1,3-dithian-2-ylidene)-3-methyl-1-pentanone (**9a**).* To a solution of 4-(1,3-dithian-2-ylidene)-3-methylvaleric acid (320 mg, 1.38 mmol) in dichloromethane (3 mL) were added triethylamine (0.20 mL, 1.44 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 291 mg, 1.52 mmol), and *O*-benzylhydroxylamine hydrochloride (253 mg, 1.58 mmol) at room temperature under argon atmosphere. The reaction was stirred overnight. Ether and 1 N hydrochloric acid were added. The organic phase was separated, and aqueous phase was extracted with dichloromethane. The combined organic solution was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (silica gel, eluting with ether/hexane, 3/1) to provide the title compound as a clear, colorless oil (395 mg, 85%): IR (neat, cm^{-1}) 3183, 1654, 745, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (br, 1H), 7.37−7.35 (m, 5H), 4.93−4.83 (m, 2H), 3.66−3.63 (m, 1H), 2.87−2.76 (m, 4H), 2.13−2.04 (m, 4H), 1.75 (s, 3H), 0.99 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 140.7, 135.7, 129.4, 128.7, 121.4, 78.3, 53.8, 38.6, 34.7, 30.3, 30.0, 25.1, 18.5, 15.1; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_{17}H_{24}NO_2S_2$ 338.1243, found 338.1245.

Ethyl 5-(1,3-dithian-2-ylidene)hexanoate. The title compound was prepared from ethyl 5-oxohexanoate by following literature procedure used for the synthesis of ethyl 4-(1,3-dithian-2-ylidene)-valerate and was obtained in a 75% yield: IR (neat, cm^{-1}) 1732, 1244, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 6.9 Hz, 2H), 2.88−2.81 (m, 4H), 2.38 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.14−2.06 (m, 2H), 1.89 (s, 3H), 1.78−1.67 (m, 2H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 139.0, 120.7, 60.3, 31.2, 33.9, 30.4, 30.2, 25.1, 23.2, 20.2, 14.4; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_{12}H_{21}O_2S_2$ 261.0977, found 261.0978.

*1-(O-Benzyloxyamino)-5-(1,3-dithian-2-ylidene)-1-hexanone (**9b**).* The title compound was obtained in a 67% yield (0.52 g) from ethyl 5-(1,3-dithian-2-ylidene)hexanoate (0.78 g, 3.0 mmol) by following the procedure employed for the synthesis of **6a**. Isolated as a clear, yellow oil: IR (neat, cm^{-1}) 3186, 1655, 748, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.39 (s, 5H), 4.92 (s, 2H), 2.88−2.78 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 2.13−2.02 (m, 4H), 1.88 (s, 3H), 1.80−1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 139.3, 135.7, 129.4, 128.8, 120.5, 78.3, 35.3, 32.8, 30.4, 30.3, 25.0, 23.7, 20.2; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_{17}H_{23}NO_2S_2Na$ 360.1072, found 360.1068.

Methyl 6-(1,3-dithian-2-ylidene)heptanoate. The title compound was prepared from methyl 6-oxoheptanoate by following literature procedure used for the synthesis of ethyl 4-(1,3-dithian-2-ylidene)-valerate and was isolated in 64% yield. For characterization and spectral data, see electrolysis product **12c**.

*1-(O-Benzyloxyamino)-6-(1,3-dithian-2-ylidene)-1-heptanone (**9c**).* The title compound was prepared from methyl 6-(1,3-dithian-2-ylidene)heptanoate using the same procedure for the synthesis of **6a**. Hence, starting with 3.0 mmol of methyl 6-(1,3-dithian-2-ylidene)-heptanoate, the desired product was obtained as a white, crystalline solid (0.69 g, 65% yield, mp 110−114 °C): IR (neat, cm^{-1}) 3194, 3062, 3029, 1658, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (br, 1H), 7.36 (s, 5H), 4.87 (s, 2H), 2.85−2.77 (m, 4H), 2.32 (t, J = 7.8 Hz, 2H), 2.11−2.03 (m, 4H), 1.86 (s, 3H), 1.61−1.54 (m, 2H), 1.42−1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 140.3, 135.6, 129.4, 128.8, 119.7, 78.4, 48.7, 35.5, 33.9, 33.3, 30.5, 30.3, 27.4, 25.2, 20.3; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_{18}H_{25}NO_2S_2$ 374.1224, found 374.1221.

*1-Anilino-5-(1,3-dithian-2-ylidene)-1-hexanone (**9d**).* To a solution of ethyl 5-(1,3-dithian-2-ylidene)hexanoate (0.47g, 1.8 mmol) in tetrahydrofuran (6 mL) and water (2 mL) was added lithium hydroxide monohydrate (0.38 g, 9.0 mmol). The reaction mixture was stirred overnight. 1 N hydrochloric acid was added to adjust the pH of the aqueous solution to 1. Ether was then added, and organic phase was separated. The aqueous phase was exacted with ether twice. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under a vacuum to give a white solid.

This white solid (assumed to be 5-(1,3-dithian-2-ylidene)hexanoic acid) was dissolved in dichloromethane (5 mL). Aniline (0.33 g, 3.6 mol), 4-dimethylaminopyridine (22 mg, 0.18 mmol), and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 0.52 g, 2.7 mmol) were added. The resulting mixture was stirred overnight. 1 N hydrochloric acid was added. The organic phase was separated and washed with 1 N hydrochloric acid twice. The combined aqueous phase was extracted with dichloromethane. The

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

organic phases were combined, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with ether/hexane, 1:1) to provide the title compound as a yellow, crystalline solid (0.39 g, 70%, mp 75−78 °C): IR (neat, cm^{-1}) 3297, 1659, 1599, 1543, 1498, 1442, 755; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.33 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 2.91−2.84 (m, 4H), 2.47 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.17−2.07 (m, 2H), 1.94 (s, 3H), 1.92−1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 139.5, 138.3, 129.1, 124.3, 120.5, 120.2, 37.1, 35.3, 30.5, 30.3, 25.1, 23.8, 20.3; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_{16}H_{21}NOS_2Na$ 330.0957, found 330.0959.

Ethyl 4-methyl-5-(methylthio)-4-pentenoate. To a suspension of (methylthiomethyl)triphenylphosphonium chloride (10.7 g, 30 mmol) in tetrahydrofuran (100 mL) was added a *n*-butyllithium solution (1.6 M in hexanes, 18.7 mL, 30 mmol) at 0 °C under argon atmosphere. After the addition was complete, the clear solution was stirred at 0 °C for 30 min and then treated with ethyl levulinate (S-47, 4.2 mL, 30 mmol). The reaction was warmed to room temperature and then stirred overnight. The reaction was cooled to 0 °C, and brine and ether were added. The organic phase was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated. Chromatography on silica gel gave the title compound as a colorless oil (2.5 g, 45%): IR (neat, cm^{-1}) 1732, 1372, 1157; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (s, 1H), 4.09 (q, J = 7.2 Hz, 2H), 2.44−2.32 (m, 4H), 2.21 (s, 3H), 1.69 (m, 3H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 134.1, 121.8, 60.5, 34.4, 33.2, 17.8, 17.3, 14.4; HRMS (ESI-TOF) m/z $(M + H)^+$ calcd for $C_9H_{17}O_2S$ 189.0944, found 189.0944.

*1-(O-Benzyloxyamino)-4-methyl-5-(methylthio)-4-penten-1-one (**15a**).* The title compound was synthesized from ethyl 4-methyl-5-(methylthio)-4-pentenoate using the same procedure for the synthesis of **6a**. Hence, starting with 1.7 mmol of ethyl 4-methyl-5-(methylthio)-4-pentenoate, the title compound was obtained as a white solid with a melting point close to room temperature (0.41 g, 91% yield, mp ≤ 35 °C): IR (neat, cm^{-1}) 3185, 1654, 750, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 9.21, 8.99, 8.25 (3s, br, 1H), 7.34 (s, 5H), 5.61 (s, 1H), 4.84 (s, 2H), 2.42−2.11 (m, 7H), 1.70, 1.66 (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 135.6, 133.8, 129.4, 128.8, 122.3, 78.3, 34.7, 31.9, 23.0, 17.8, 17.3; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_{14}H_{19}NO_2SNa$ 288.1034, found 288.1036.

Ethyl 5-methoxy-4-methyl-4-pentenoate. To a suspension of methoxymethyltriphenylphosphonium chloride (2.16 g, 15.0 mmol) in tetrahydrofuran (50 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 15.0 mL, 15.0 mmol) at 0 °C. The dark red solution was stirred at the same temperature for 0.5 h and then treated with ethyl levulinate. The reaction was allowed to warm to room temperature slowly and stirred overnight. Brine was added, followed by ether. The organic layer was separated and aqueous layer extracted twice with ether. The combined organic layers were dried with anhydrous magnesium sulfate and concentrated in vacuo. Chromatography through silica gel gave the title compound as a mixture of isomers (1.60 g, 62%): IR (neat, cm^{-1}) 1735, 1685, 1207, 1129; ^1H NMR (300 MHz, $CDCl_3$, isolates as a 2.7:1 mixture of two isomers) δ 5.81, 5.75 (2s with fine couplings, 1H), 4.11 (q, J = 6.9 Hz, 2H), 3.53, 3.51 (2s, 3H), 2.39−2.17 (m, 4H), 1.58, 1.53 (2s with fine couplings, 3H), 1.24 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 173.4, 142.8, 142.7, 112.3, 112.1, 60.3, 59.4, 33.6, 32.7, 29.6, 24.8, 17.2, 14.4, 12.6; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_9H_{16}O_3Na$ 195.0992, found 195.0985.

*1-(O-Benzyloxyamino)-5-methoxy-4-methyl-4-penten-1-one (**15b**).* The title compound was prepared from ethyl 5-methoxy-4-methyl-4-pentenoate by following the procedure employed for the synthesis of **6a**. Starting with 3.2 mmol of ethyl 5-methoxy-4-methyl-4-pentenoate, the desired product was isolated as a white oil (0.52 g, 65% yield): IR (neat, cm^{-1}) 3187, 1656, 1207, 1129, 750, 698; ^1H NMR (300 MHz, $CDCl_3$, isolated as a 2:1 mixture of isomers) δ 9.13 (major) and 9.08 (minor) (2s, br, 1H), 7.34 (s, 5H), 5.77 (major) and 5.65 (minor) (2s, 1H), 4.84 (s, 2H), 3.47 (major) and 3.38 (minor) (2s, 3H), 2.28−2.12 (m, 4H), 1.53 (major) and 1.47 (minor) (2s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 170.6, 143.1, 142.6, 135.8, 129.4, 129.4, 128.7, 78.3, 59.4, 32.3, 31.9, 29.9, 24.5, 17.2, 12.7; HRMS (ESI-TOF) m/z $(M + Na)^+$ calcd for $C_{14}H_{19}NO_3Na$ 272.1263, found 272.1261.

1-(Benzyloxy)-6-hydroxy-6-methyl-2-piperidinone. 4-Acetylbutyric acid (1 mL, 8.124 mmol, 1 equiv) and *N*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl, 1.868 g, 9.749 mmol, 1.2 equiv) were combined in a flask under an argon atmosphere, suspended in dichloromethane (17 mL), and cooled to 0 °C. The suspension was then treated with triethylamine (2.19 mL, 16.25 mmol, 2 equiv), stirred at room temperature for 30 min, and cooled back to 0 °C. *O*-Benzylhydroxylamine hydrochloride (1.310 g, 8.124 mmol, 1 equiv) was added, and the reaction was warmed to room temperature and stirred overnight. The following morning, hydrochloric acid (3 M) was added until a pH of 4 was reached, and the reaction was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed through silica gel with a mixture of hexanes and ethyl acetate to give the desired product as a white, crystalline solid (0.8031 g, 42%, mp 97−100 °C): IR (neat, cm^{-1}) 3317, 2946, 2886, 1707, 1685, 1654, 1637, 1630, 1454; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.45 (m, 2H), 7.43−7.34 (m, 3H), 5.13 (d, J = 9.6 Hz, 1H, A of AB pattern), 4.87 (d, J = 9.6 Hz, 1H, B of AB pattern), 2.91−2.84 (m, 0.7H), 2.60−2.39 (m, 2H), 2.13−1.86 (m, 3H), 1.76−1.64 (m, 1H), 1.61 (s, 3H), 1.57−1.53 (m, 0.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 135.3, 129.5, 128.7, 128.5, 88.7, 78.2, 37.2, 33.8, 27.2, 17.0; HRMS (ESI-FTIRC) m/z $(M + Na)^+$ calcd for $C_{13}H_{17}NO_3Na$ 236.1281, found 236.1280.

*1-(O-Benzyloxyamino)-5-methyl-6-(methylthio)-5-hexen-1-one (**15c**).* (Methylthiomethyl)triphenylphosphonium chloride (0.7324 g, 3.113 mmol, 1 equiv), was suspended in 8 mL of tetrahydrofuran under an argon atmosphere, cooled to 0 °C, and treated with *n*-butyllithium. After stirring for 30 min at 0 °C, 1-(benzyloxy)-6-hydroxy-6-methyl-2-piperidinone was added to the reaction as a solution in 10 mL of tetrahydrofuran. The reaction was warmed to room temperature and stirred for 41 h. Saturated aqueous ammonium chloride was added to quench the reaction. The reaction was extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed with a 1:1 mixture of hexanes:ethyl acetate to give the desired product as a colorless oil (0.7480 g, 86%): IR (neat, cm^{-1}) 3186, 3064, 3030, 2957, 2920, 2872, 1654, 1507; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20−7.64 (2 bs, 1H), 7.39 (s, 5H), 5.66−5.51 (m, 1H), 4.98−4.74 (bs, 2H), 2.46−1.89 (m, 7H), 1.86−1.64 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.6, 135.5, 134.9, 129.0, 128.4, 121.3, 121.0, 77.9, 38.3, 32.8, 32.5, 32.3, 23.5, 23.0, 22.6, 17.6, 17.2, 17.0; HRMS (ESI-FTIRC) m/z $(M + H)^+$ calcd for $C_{15}H_{22}NO_2S$ 280.1355, found 280.1366.

*1-(O-Benzyloxyamino)-6-methoxy-5-methyl-5-hexen-1-one (**15d**).* Methoxymethyltriphenylphosphonium chloride (3.238 g, 9.735 mmol, 3 equiv) was suspended in tetrahydrofuran (5 mL) under an argon atmosphere, cooled to 0 °C, and treated with lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 9.74 mL, 9.735 mmol, 3 equiv). The reaction mixture was stirred at 0 °C for 30 min and treated with 1-(benzyloxy)-6-hydroxy-6-methyl-2-piperidinone (0.7636 g, 3.245 mmol, 1 equiv) as a solution in tetrahydrofuran (20 mL) and warmed to room temperature. After stirring overnight, the reaction was quenched with saturated aqueous ammonium chloride and extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed with a 1:1 mixture of hexanes and ethyl acetate to give the desired product as a yellow oil and a 3:2 mixture of isomers (0.7007 g, 82%): IR (neat, cm^{-1}) 3190, 2933, 2837, 1681, 1655, 1508, 1497, 1455; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78−7.54 (2 bs, 1H), 7.39 (s, 5H), 5.82−5.64 (m, 1H), 4.97−4.69 (bs, 2H), 3.52 (s, 1.8H), 3.35 (s, 1.2H), 2.51−1.79 (m, 4H), 1.79−1.61 (m, 2H), 1.55 (s, 1.8H), 1.49 (s, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 171.1, 142.3, 142.2, 135.7, 129.2, 128.5, 113.2, 112.7, 77.9, 59.14, 59.07, 33.2, 32.3, 27.8, 23.6, 23.0, 16.9, 12.5;

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

HRMS (ESI-FTIRC) m/z (M + Na)$^+$ calcd for $C_{15}H_{21}NO_3Na$ 286.1418, found 286.1414.

Glutaraldehydic acid. 5-Hexenoic acid (2.074 g, 18.17 mmol) was dissolved in dichloromethane to a concentration of 0.2 M and cooled to −78 °C. Ozone was blown over the surface of the solution until a dark blue color was obtained after approximately 30 min. Solution was then purged with oxygen until excess ozone had dissipated and blue color had diminished. Dimethyl sulfide (10 equiv) was added, and the reaction was allowed to slowly warm from −78 °C to room temperature over the course of several hours. After 10 h, the solvent was removed in a vacuum, and the residue was chromatographed through a short column of silica gel with hexanes and ethyl acetate to give the desired product as a colorless oil (1.999 g, 95% yield): IR (neat, cm^{-1}) 3418, 3184, 2949, 2740, 17.6, 1410; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 2.57 (t, J = 7.2, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.97 (q, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 179.0, 42.7, 32.9, 17.0; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_5H_8O_3Na$ 139.0366, found 139.0361.

6-(Methylthio)-5-hexenoic acid. (Methylthiomethyl)-triphenylphosphonium chloride (6.799 g, 18.95 mmol, 2.2 equiv) was suspended in tetrahydrofuran (30 mL) under an argon atmosphere, cooled to 0 °C, and treated with sodium bis-(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 18.95 mL, 18.95 mmol, 2.2 equiv). The resulting solution was stirred for 30 min at 0 °C and treated with glutaraldehydic acid (1.000 g, 8.614 mmol, 1 equiv). The reaction was allowed to warm to room temperature and stirred for 6 h. Water and diethyl ether were added. The layers were separated, and the aqueous layer washed twice with diethyl ether. The aqueous layer was then acidified with hydrochloric acid (3 N) to pH 4 and extracted three times with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was chromatographed through a short silica gel column with a 2:1 ratio of hexanes to ethyl acetate to give the desired compound as a clear, colorless oil and a 3:2 ratio of isomers (1.063 g, 77%): IR (neat, cm^{-1}) 3012, 2921, 2668, 1708, 1610, 1435, 1413; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.75 (bs, 1H), 6.01 (d, J = 15.0 Hz, 0.6H), 5.93 (d, J = 9.3 Hz, 0.4H), 5.43 (m, 1H), 2.37 (q, J = 6.9 Hz, 2H), 2.27 (s, 1.2H), 2.23 (s, 1.8H), 2.21−2.11 (m, 2H), 1.81−1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 128.2, 127.1, 125.4, 125.2, 33.4, 33.3, 28.3, 24.4, 23.9; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_7H_{13}O_2S$ 161.0631, found 161.0633.

*1-(O-Benzyloxyamino)-6-(methylthio)-5-hexen-1-one (**15e**).* The title compound was prepared according to the procedure for the synthesis of **15f**. The starting material was totally consumed in the reaction, and so no bicarbonate wash was performed. However, two acid washes (hydrochloric acid, pH 2) of the crude mixture were required to remove other impurities. Thus, beginning with 0.7125 g of 6-(methylthio)-5-hexenoic acid, 0.9837 g of the desired product was obtained as a colorless oil and a 3:2 mixture of isomers (83%): IR (neat, cm^{-1}) 3189, 3090, 3063, 2982, 2921, 2868, 1656, 1514, 1497, 1454, 1437; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26−7.61 (bs, 1H), 7.39 (s, 5H), 5.95 (d, J = 14.1 Hz, 0.4H), 5.91 (d, J = 9.3 Hz, 0.6H), 5.93−5.66 (m, 1H), 5.01−4.72 (bs, 2H), 2.51−2.30 (bm, 0.4H), 2.25 (s, 1.2H), 2.22 (s, 1.8H), 2.19−1.97 (m, 3.6H), 1.81−1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.4, 128.9, 128.4, 128.3, 128.3, 127.7, 127.2, 125.6, 124.6; HRMS (ESI-TOF) m/z (M + Na)$^+$ calcd for $C_{14}H_{19}NO_2SNa$ 266.1209, found 266.1210.

6-Methoxy-5-hexenoic acid. Methoxymethyltriphenylphosphonium chloride (4.077 g, 11.54 mmol, 2.2 equiv) was suspended in tetrahydrofuran (10 mL) under an argon atmosphere, cooled to 0 °C, and treated with sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 11.5 mL, 11.54 mmol, 2.2 equiv). The resulting solution was stirred at 0 °C for 30 min and then treated with glutaraldehydic acid (0.6089 g, 5.244 mmol, 1 equiv) as a solution in 3 mL of tetrahydrofuran. The reaction was stirred at room temperature for 6 h, and then water and diethyl ether were added. The layers were separated, and the aqueous layer was washed twice with diethyl ether. The aqueous layer was then acidified with 3 N hydrochloric acid to pH 3, whereupon it was extracted three times with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude residue was chromatographed through silica gel with a 3:1 mixture of hexanes:ethyl acetate to give the title compound as a 1:1 mixture of isomers in the form of a clear, colorless oil (0.7560 g, 65%): IR (neat, cm^{-1}) 3036, 3001, 2937, 2667, 1708, 1656, 1455, 1442, 1412; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.33 (bs, 1H), 6.30 (d, J = 12.6, 0.5H), 5.91 (d, J = 6.3 Hz, 0.5H), 4.68 (dt, J (d) = 12.6 Hz, J (t) = 7.2 Hz, 0.5H), 4.31 (dt, J (d) = 6.9 Hz, J (t) = 7.5 Hz, 0.5H), 3.58 (s, 1.5H), 3.51 (s, 1.5H), 2.37 (t, J = 7.5 Hz, 0.5H), 2.36 (t, J = 7.5 Hz, 0.5H), 2.12 (q, J = 7.2 Hz, 0.5H), 2.00 (q, J = 7.2 Hz, 0.5H), 1.69 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 180.4, 147.9, 147.1, 105.3, 101.6, 59.4, 55.8, 33.5, 33.2, 27.1, 25.6, 24.6, 23.2; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_7H_{13}O_3$ 145.0859, found 145.0860.

*1-(O-Benzyloxyamino)-6-methoxy-5-hexen-1-one (**15f**).* 6-Methoxy-5-hexenoic acid (0.3102 g, 2.152 mmol, 1 equiv), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.6187 g, 3.228 mmol, 1.5 equiv), and *O*-benzylhydroxylamine hydrochloride (0.5152 g, 3.228 mmol, 1.5 equiv) were added to the same flask and suspended in dichloromethane under an argon atmosphere. The suspension was cooled to 0 °C and treated with triethylamine (0.45 mL, 3.228 mmol, 1.5 equiv). After the reaction mixture was stirred for 30 min, another 0.45 mL of triethylamine was added. The reaction mixture was warmed to room temperature and stirred overnight. The next morning, 3 N hydrochloric acid was added until the reaction reached pH 4. The aqueous layer was extracted three times with dichloromethane. The organic extracts were combined, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was dissolved in diethyl ether and washed with aqueous sodium bicarbonate until unreacted starting material was removed from organic layer. The organic layer was then separated, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting residue was chromatographed through a short silica gel column with a 1:2 ratio of hexanes:ethyl acetate to give the desired compound as a colorless oil (0.3595 g, 67%): IR (neat, cm^{-1}) 3192, 3091, 3061, 3032, 2995, 2935, 2959, 1656; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45−7.72 (2 bs, 1H), 7.39 (s, 5H), 6.25 (d, J = 12.9 Hz, 0.67H), 5.90 (d, J = 6.3 Hz, 0.33H), 4.99−4.86 (bs, 2H), 4.72−4.56 (m, 0.67H), 4.29 (q, J = 7.2 Hz, 0.33H), 3.49 (bs, 3H), 2.35 (t, J = 7.8 Hz, 0.67H), 2.13−2.06 (m, 2H), 1.95 (q, J = 7.2 Hz, 1.33H), 1.68 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 171.0, 147.7, 146.9, 135.5, 129.2, 128.6, 105.7, 101.8, 78.1, 59.4, 55.9, 32.4, 32.3, 27.1, 26.2, 25.4, 23.0; HRMS (ESI-TOF) m/z (M + H)$^+$ calcd for $C_{14}H_{20}NO_3$ 250.1438, found 250.1437.

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-hydroxy-4-heptanone. (CAS No. 1218900-86-7). *tert*-Butyl(3-iodoopropoxy)-dimethylsilane (1.425 g, 4.746 mmol, 1 equiv) was dissolved in diethyl ether (6 mL) under an argon atmosphere, cooled to −78 °C, and treated with *tert*-butyllithium (1.7 M in hexanes, 5.9 mL, 10.0 mmol, 2.1 equiv). The solution was stirred at −78 °C for 30 min and then at room temperature for 45 min. In a separate flask, δ-butyrolactone was dissolved in tetrahydrofuran (6 mL) under an argon atmosphere, cooled to −78 °C, and treated with the prepared lithium reagent. The reaction was stirred at −78 °C for 15 min and then poured into water (25 mL). The mixture was extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed through silica gel with a mixture of 1:1 hexanes:ethyl acetate to give the desired compound as a colorless oil (0.7886 g, 64%). Spectral data for the title compound have been previously reported.[30]

1-(Benzyloxy)-5-hydroxy-5-[3-[[(1,1-dimethyl)dimethylsilyl]oxy]-propyl]-2-pyrrolidinone. 1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-7-hydroxy-4-heptanone (CAS No. 1218900-86-7, 0.4152 g, 1.594 mmol) was dissolved in acetonitrile (6 mL) under argon. *N*-Methylmorpholine *N*-oxide (1.540 g, 12.73 mmol), water (0.14 mL, 7.96 mmol), and tetrapropylammonium perruthenate (0.0577 g, 0.1591 mmol) were added to the flask, and the reaction was stirred at room temperature for 5 h. Isopropyl alcohol (1.2 mL, 15.91 mmol) was added, and the reaction was stirred for 30 min to quench the reaction. The solvent

dx.doi.org/10.1021/jo402623r | J. Org. Chem. 2014, 79, 379−391

was removed under reduced pressure, and the resulting residue was filtered through silica gel (packed with 1 wt % acetic acid) with ethyl acetate. The filtered solution was concentrated under reduced pressure; ^{13}C NMR analysis showed no aldehyde present in the crude residue, and the crude residue was dried under a vacuum overnight. The following day, the residue was dissolved in dichloromethane (6.1 mL) under argon. *N*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl, 0.3056 g, 1.594 mmol) and *O*-benzylhydroxylamine hydrochloride (0.2544 g, 1.594 mmol) were added to the flask. The suspension was cooled to 0 °C and treated with triethylamine (0.21 mL, 1.59 mmol). The reaction was stirred at room temperature for 30 min and then cooled back to 0 °C and treated with more triethylamine (0.42 mL, 3.19 mmol). The reaction was allowed to stir overnight (approximately 16 h), and then water was added. The aqueous layer was adjusted to pH = 6−7 with 3 N aqueous hydrochloric acid. The layers were separated without vigorous mixing. The aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was chromatographed through silica with hexanes and ethyl acetate (successive ratios of 2:1, 1:1, and then 1:2, hexanes:ethyl acetate) to give the desired product as an amorphous, yellow, waxy solid (0.2299 g, 38%, two steps): IR (neat, cm^{-1}) 3345, 2954, 2928, 2884, 2856, 1690; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53−7.44 (m, 2H), 7.42−7.31 (m, 3H), 5.15 (d, J = 9.9 Hz, 1H, A of AB pattern), 5.08 (d, J = 9.9 Hz, 1H), 4.14 (s, 1H), 3.76−3.52 (m, 2H), 2.61−2.42 (m, 1H), 2.37−2.21 (m, 1H), 2.14−1.95 (m, 3H), 1.84−1.63 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 135.2, 129.4, 128.6, 128.4, 90.8, 78.8, 63.2, 35.1, 29.6, 26.5, 26.1, 25.9, 18.3, −5.4; HRMS (ESI-FTIRC) m/z $(M + Na)^+$ calcd for $C_{20}H_{33}NO_4SiNa$ 402.2071, found 402.2069.

*1-(O-Benzyloxyamino)-4-(1,3-dithian-2-ylidene)-7-hydroxy-1-heptanone (Electrolysis Substrate **23**).* 2-Trimethylsilyl-1,3-dithiane (0.5 mL, 2.6 mmol) was dissolved in tetrahydrofuran (3 mL) under argon, cooled to −78 °C, and treated with *n*-butyllithium (1.6 M in hexanes, 1.6 mL, 2.6 mmol). The resulting solution was stirred at −78 °C for 30 min and then at room temperature for 20 min. The solution was cooled back to −78 °C and treated with 1-(benzyloxy)-5-hydroxy-5-[3-[[(1,1-dimethyl)dimethylsilyl]oxy]propyl]-2-pyrrolidinone (0.4744 g, 1.250 mmol, transferred as a solution in approximately 3 mL of tetrahydrofuran) at room temperature, allowing heat to evolve upon addition. The reaction was stirred overnight (approximately 18 h), quenched with water, and then extracted three times with ethyl acetate. The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was chromatographed through silica gel eluting with hexanes and ethyl acetate (starting with a ratio of 2:1, then 1:1, then 1:2). This protocol yielded 1-(*O*-benzyloxyamino)-4-(1,3-dithian-2-ylidene)-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-heptanone (the TBS-protected title compound) in a 43% yield, along with 47% of the unreacted starting material. The intermediate product was not fully characterized but was carried on to the next step. The intermediate product was placed in a flask and treated with tetrabutylammonium floride (1 M in tetrahydrofuran, 2.7 mL, 2.7 mmol) at room temperature. After stirring for 2 h, water and ethyl ether were added. The mixture was extracted three times with ethyl ether. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting organic residue was chromatographed through silica with ethyl acetate to give the desired product as a clear, yellow, viscous oil (0.4594 g, 100%, or 43% over two steps): IR (neat, cm^{-1}) 3202, 2933, 2871, 1660, 1517, 1497, 1453, 1422; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17−7.60 (2 bs, 1H, exchanges with D2O), 7.39 (s, 5H), 4.99−4.75 (bs, 2H), 3.64−3.59 (m, 2H, becomes t after addition of D_2O, J = 5.9 Hz), 2.93−2.82 (m, 4H), 2.64 (t, J = 7.8 Hz, 2H), 2.54−2.44 (bm, 0.5H), 2.39 (t, J = 7.2 Hz, 2H), 2.23−2.07 (m, 3.5H), 1.80−1.72 (bs, 1H, exchanges with D_2O), 1.66 (quintet, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 141.3, 135.4, 129.3, 128.6 (two overlapping peaks), 122.8, 78.1, 61.9, 31.8, 30.7, 30.1 (two overlapping peaks), 29.7, 29.3, 24.6; HRMS (ESI-FTIRC) m/z $(M + Na)^+$ calcd for $C_{18}H_{25}NO_3S_2Na$ 390.1168, found 390.1160.

■ ASSOCIATED CONTENT

Supporting Information

A general procedure for electrolysis reactions, NMR spectra of new compounds, and detailed computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: moeller@wuchem.edu.

Author Contributions

§H.-C. Xu and J. M. Campbell contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the National Science Foundation, Grant CHE 1151121. Calculations were performed at Yale University using the Gaussian 09 suite of programs licensed to the research group of Jonathan A. Ellman.

■ REFERENCES

(1) For reviews, see: (a) Baralle, A.; Baroudi, A.; Daniel, M.; Fensterbank, L.; Goddard, J.-P.; Lacote, E.; Larraufie, M.-H.; Maestri, G.; Malacria, M.; Ollivier, C. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Chichester, U.K., 2012; pp 767−816. (b) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (c) Stella, L. In *Radicals in Organic Synthesis*, Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 407−426. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (e) Zard, S. Z. *Synlett* **1996**, *7*, 1148. (f) Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. *58*, pp 1−45. (g) Sella, L. *Angew. Chem., Int. Ed.* **1983**, *22*, 337. (h) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241. (i) Neale, R. S. *Synthesis* **1971**, *1*, 1.

(2) (a) Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738. (b) Martinez, E.; Newcomb, M. *J. Org. Chem.* **2006**, *71*, 557.

(3) (a) Mackiewicz, P.; Furstoss, R.; Waegell, B.; cote, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746. (b) Lessard, J.; cote, R.; Mackiewicz, P.; Furstoss, R.; Waegell, B. *J. Org. Chem.* **1978**, *43*, 3750. (c) Göttlich, R. *Synthesis* **2000**, 1561. (d) Heuger, G.; Kalso, S.; Göttlich, R. *Eur, J. Org. Chem.* **2002**, 1848. (e) Schulte-Wülwer, I. A.; Helaja, J.; Göttlich, R. *Synthesis* **2003**, 1886. (f) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229.

(4) (a) Chow, Y. L.; Perry, R. A. *Can. J. Chem.* **1985**, *63*, 2203. (b) (c) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125. (c) Klügge, J.; Herdtweck, E.; Bach, T. *Synlett* **2004**, 1199. (d) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 5983. (e) Danielec, H.; Klügge, J.; Schlummer, B.; Bach, T. *Synthesis* **2006**, 551. (f) Guin, J.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 779. (g) Biechy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1436.

(5) (a) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035. (b) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1992**, *33*, 5913. (c) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933. (d) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1994**, *59*, 2779. (e) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333. (f) Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783. (g) Artman, G. D., III; Waldman, J. H.; Weinreb, S. M. *Synlett* **2002**, 2057. (h) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831.

(6) (a) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877. (b) Gaudreault, P.; Drouin, C.; Lessard, J. *Can. J. Chem.* **2005**, *83*, 543. (c) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625.

(d) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (e) Moutrille, C.; Zard, S. Z. *Chem. Commun.* **2004**, *16*, 1848.
(7) Kemper, J.; Studer, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4914.
(8) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625. (c) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202. (d) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Baluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233. (e) Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991.
(9) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640.
(10) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.
(11) For reviews of organic electrochemistry, see: (a) Lund, H.; Hammerich, O. *Organic Electrochemistry*, 4th ed.; Marcel Dekker, Inc.: New York, 2001. (b) Bard, A. J.; Stratman, M.; Scafer, H. J. *Encyclopedia of Electrochemistry*; Wiley-VCH: Weinheim, Germany, 2004; Vol. 8, Organic Electrochemistry. (c) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605. (d) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265. (e) Bohn, M. A.; Paul, A.; Hilt, G. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Chichester, U.K., 2012; pp 1175−1216.
(12) For a recent account of our research, see: Moeller, K. D. *Synlett* **2009**, 1208.
(13) Xu, H.-C.; Moeller, K. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8004.
(14) (a) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008**, *130*, 13542. (b) Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2010**, *132*, 2839. (c) Campbell, J. M.; Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 18338.
(15) For an example involving the use of saturated amides in anodic coupling reactions, which proceed through an iminolactone intermediate, see: Liu, B.; Duan, s.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101.
(16) (a) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941. (b) Sakai, R.; Suzuki, K.; Shimamoto, K.; Kamiya, H. *J. Org. Chem.* **2004**, *69*, 1180. (c) For recent of synthesis of dysibetaine, see: Isaacson, J.; Loo, M.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1461 and references therein.
(17) (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (b) For recent synthesis of Salinosporamide A, see: Satoh, N.; Yokoshima, S.; Fukuda, T. *Org. Lett.* **2010**, *13*, 3028 and references therein.
(18) (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117. (c) For recent synthesis, see: Gu, W.; Silverman, R. *J. Org. Chem.* **2011**, *76*, 8287 and references therein.
(19) (a) Qian-Cutrone, J.; Huang, S.; Shu, Y.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556. (b) For recent synthesis, see: Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678 and references therein.
(20) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868.
(21) Rajendra, G.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 5385.
(22) Cooley, J. J.; Mosher, M. W.; Khan, M. A. *J. Am. Chem. Soc.* **1968**, *90*, 1867.
(23) (a) Smith, J. A.; Moeller, K. D. *Org. Lett.* **2013**, *22*, 5818. (b) Perkins, R. J.; Xu, H.-C.; Campbell, J. M.; Moeller, K. D. *Beilstein J. Org. Chem.* **2013**, *9*, 1630. (c) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7372.
(24) Density functional theory (DFT) was used to perform all calculations using the unrestricted B3LYP functional, a 6-31G(d,p) basis set, and the SMD methanol solvation model. All calculations were carried out using the Gaussian 09 suite of programs: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.
(25) Bally, T.; Borden, W. T. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; John Wiley and Sons, Inc.: New York, 1999; Vol. *13*, pp 1−97.
(26) For a brief discussion of the considerations involved in applying DFT to open-shell compounds, see our discussion of the computational methodology in reference 14c and the references therein.
(27) We chose the B3LYP functional because of its history of successful application to radical cation systems and also to be consistent with other calculations performed by our research group. The M06 family of functionals has been developed more recently and has enjoyed very successful application to radical cation systems. For more information on M06 functionals, see: (a) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101. (b) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2006**, *110*, 13126. (c) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (d) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
(28) Kuhn, L. P.; Kleinspehn, G. G.; Duckworth, A. C. *J. Am. Chem. Soc.* **1967**, *89*, 3858.
(29) (a) Georgievskii, Y.; Miller, J. A.; Klippenstein, S. J. *Phys. Chem. Chem. Phys.* **2007**, *9*, 4259. (b) Klippenstein, S. J.; Georgievskii, Y.; Harding, L. B. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1133.
(30) Xu, H.-C.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 1720.