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Electrocatalytic Aziridination of Alkenes Mediated by n-Bu_4NI: A Radical Pathway

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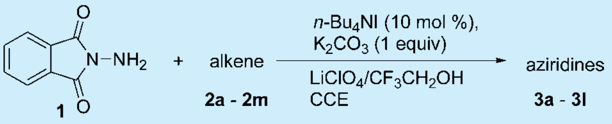
S *Supporting Information*

ABSTRACT: Efficient electrocatalytic aziridination of alkenes has been achieved for the first time. A structurally broad range of aziridines was easily accessed using an undivided cell operated at constant current and mediated by a catalytic quantity of n-Bu_4NI. The electrocatalytic reaction also proceeded in the absence of additional conducting salt. The aziridination is proposed to follow a radical mechanism.



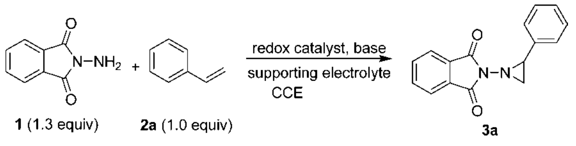
The efficient synthesis of aziridines is of importance as a result of their varied and extensive biological activities as well as their potential as building blocks for the synthesis of other nitrogen-containing compounds.[1] The transition-metal-catalyzed aziridination of an alkene with nitrene precursors is the most popular and commonly used approach to construct an aziridine subunit.[2,3] Of course, environmentally benign, metal-free aziridination reactions are desirable, and consequently, a variety of protocols have been developed. For instance, Komatsu and co-workers reported the first I_2-catalyzed aziridination reaction of alkenes with chloramine-T, wherein chloramine-T serves not only as a nitrene source but also as an oxidant.[4] Later, aqueous HBr/H_2O_2,[5] phenyltrimethylammonium tribromide ($PhNMe_3{}^+Br_3{}^-$),[6] or *tert*-butyl hypoiodite[7] was employed to afford *N*-tosylaziridines. *N*-Aminoheterocycles are also well-known nitrene precursors, and in this context, Che and Yudin[8] independently reported the aziridination of alkenes using *N*-aminophthimide (Pht-NH_2) and hypervalent iodine (e.g., $PhI(OAc)_2$) as an oxidant. Unfortunately, the catalytic version of the reaction failed.[8] Inspired by the excellent work of Ishihara,[9] Zhdankin et al. were able to achieve the catalytic aziridination by using n-Bu_4NI/m-CPBA.[10] Given that the aziridines referred to above were obtained as their *N*-protected derivatives, thereby requiring a subsequent deprotection step, De Vos was inspired to develop a direct catalytic aziridination of styrenes employing molecular iodine or ammonium iodide as a catalyst and sodium hypochlorite as the terminal oxidant in the presence of surfactants.[11]

The electrochemical aziridination of alkenes with Pht-NH_2 has also been reported, and moderate to good yields of aziridines have been obtained via controlled potential electrolysis conducted in a divided cell.[12] Since a potentiostat is typically not available in a traditional organic laboratory, and the use of a divided cell leads to increased cell voltages, we foresaw an opportunity to simplify and possibly improve the methodology. Herein we report our findings.

We are interested in electrochemical C−H oxidative functionalization reactions that are induced by redox catalysts. In this context, we have developed a novel type of redox catalyst based upon the triarylimidazole scaffold and have achieved the oxidative activation of benzylic C−H bonds to afford aldehydes, ketones, and benzoates.[13] Recently, we have also achieved the electrochemical synthesis of benzoxazoles and the electrochemical oxidative amination of benzoxazoles with secondary amines using halide anion redox catalysts.[14] These results reveal that electrochemically generated halide species of one form or another (see below) can serve as efficient reagents that can be employed in place of organic hypervalent iodine or a combination of iodine-containing catalyst and external co-oxidant. Based on our observations and experience, we hypothesized that reactive electrochemically generated halide species might also be applied to the catalytic aziridination of alkenes. Herein, we report an efficient approach using n-Bu_4NI as a redox catalyst and Pht-NH_2 as the source of electrophilic nitrogen. The process is easily carried out at a constant current in an undivided cell. To the best of our knowledge, this work represents the first example of the electrocatalytic aziridination of alkenes and further demonstrates that halide ions are versatile redox mediators capable of promoting a variety of different transformations.

Optimization of the reaction conditions was initiated using Pht-NH_2 as a nitrogen source and styrene **2a** as a model substrate (Scheme 1). We initially performed the aziridination reaction in a divided cell using the constant current electrolysis (CCE)

Scheme 1. Initial Optimization of the Indirect Electrochemical Synthesis of Aziridine 3a



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technique, in the presence of 20 mol % of sodium iodide as a redox catalyst; the results are summarized in Table S1 of the Supporting Information. The desired aziridine **3a** was not detected when a Pt anode was used, and the starting *N*-aminophthalimide was recovered intact (Table S1, entry 1). The reaction also did not occur when $Et_3N/HOAc/CF_3CH_2OH$ served as the supporting electrolyte-solvent combination (Table S1, entry 2). Changing the anode from platinum to glassy carbon did lead to the formation of aziridine **3a** albeit in a 32% yield (Table S1, entry 3). It is known that constant current electrolysis in a divided cell leads to higher cell resistance than in an undivided cell, which may cause a decrease of the reaction selectivity and the formation of byproducts. As expected, a simple beaker-type cell worked nicely and **3a** was obtained in a 55% yield (Table S1, entry 4). The observation differs from Yudin and co-workers in that, under their conditions (viz., controlled potential at 1.8 V vs an Ag wire using a Pt anode and cathode) only products from alkene reduction were isolated when an undivided cell was employed.[12]

Our screening of supporting electrolytes revealed that $LiClO_4$ in CF_3CH_2OH gave superior results to others that were examined, affording **3a** in a 67% isolated yield (Table S1, entry 5). In addition, a simple graphite rod proved to be a suitable working electrode (56% isolated yield of **3a**; Table S1, entry 6). These results indicate that the indirect electrochemical aziridination of styrene with Pht-NH_2 occurred most efficiently using a simple carbon electrode (GC or graphite), thereby complementing previously reported results, although the exact reason(s) for the difference is not clear at the present time.[12] It is noteworthy that the electrochemical aziridination could also be achieved in the absence of additional supporting electrolyte (Table S1, entry 7). This observation is significant since the use of large amounts of supporting electrolyte detracts from the notion that electroorganic synthesis is a "green and sustainable" process.[15]

Subsequent redox catalyst screening revealed that both the anion and the cation of the redox catalyst play an important role (Table S1, entries 5−13). For example, of the redox catalysts tested (n-Bu_4NI, Et_4NI, NaI, n-Bu_4NBr, NaBr, n-Bu_4NCl), iodide ion-containing mediators gave moderate to good yields of **3a** (48−67%, Table S1, entries 5, 8, and 9); inferior results were obtained when bromide served as the redox catalyst (27−36%, Table S1, entries 10 and 11), and no reaction occurred in the case of chloride-based mediators (Table S1, entry 12). Of the counterions, n-Bu_4N^+ proved to be preferable to Et_4N^+ and Na^+ (note Table S1, entries 5, 8, and 9), and n-Bu_4NI gave the highest yield in the mediated electrochemical aziridination reaction of styrene. Reducing the amount of n-Bu_4NI from 20 to 10 mol % afforded nearly the same yield of **3a** (Table S1, entries 5 and 13), whereas an inferior yield (46%) was obtained using 5 mol % of n-Bu_4NI (Table S1, entry 14). Thus, our control experiments indicate that n-Bu_4NI is a crucial component of the electrochemical aziridination process, since **3a** is not detected in its absence (Table S1, entry 15).

Further efforts to optimize the reaction conditions showed that the amount and nature of the base is of significance. For example, the use of excess (3 equiv) K_2CO_3 led to decomposition of **3a**, and only 23% was isolated (Table S1, entry 16). Replacing potassium carbonate with 2,6-lutidine also afforded a low yield (21%) (Table S1, entry 17). The aziridination did not occur in the presence of NaOAc (Table S1, entry 18), and only a very low yield of **3a** was obtained in the absence of base (Table S1, entry 19); in its absence, Pht-NH_2 is recovered unchanged.

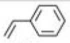
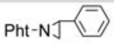
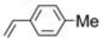
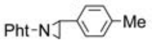
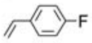
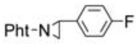
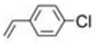
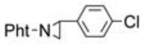
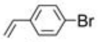
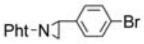
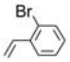
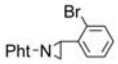
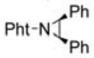
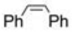
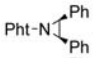
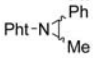
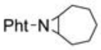
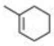
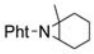
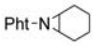
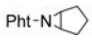
Finally, the effect of current density was also examined. A current density of 4 mA/cm^2 proved optimal (Table S1, entries 5, 20, and 21). No obvious influence of charge was observed, and good yields of **3a** were obtained when 2.5−3.5 F/mol was used (Table S1, entries 22 and 23).

From the results described above, we conclude that the optimal reaction conditions call for using a constant current electrolysis at a current density of 4 mA/cm^2, an undivided cell equipped with a GC anode and an iron plate cathode, 0.1 equiv of n-Bu_4NI to serve as the redox catalyst, and CF_3CH_2OH as the solvent.

With the optimized conditions in hand, we investigated the scope and generality of the reaction (Table 1). All styrene derivatives **2a−f** proved to be useful substrates and led to good yields of the corresponding aziridines **3a−f**. For example, styrene and *p*-methylstyrene afforded aziridines **3a** and **3b** in 65% and 71% yields, respectively (entries 1 and 2). The reaction of Pht-NH_2 and styrenes bearing inductively electron withdrawing groups, such as fluoro, chloro, and bromo groups appended at the *para*-position, also gave good yields of **3c−e** (entries 3−5), whereas a lower yield (57%) of **3f** was obtained when bromine was located at the *ortho* position (entry 6). The conditions also tolerate disubstituted aromatic alkenes (entries 7−9). Notably, the *cis*-geometry of product **3g** was the sole stereoisomer formed when either *trans*- or *cis*-stilbene **2g** and **2h** was subjected to the electrolysis (entries 7 and 8). A density functional calculation (B3LYP/6-31G(d)) reveals *cis*-**3g** to be more stable than its *trans*

Table 1. Scope of Electrocatalytic Aziridination Mediated by *n*-Bu_4NI under Standard Conditions[a]

$$\underset{\mathbf{1}}{\text{Pht-NH}_2} + \underset{\mathbf{2a - 2m}}{\text{alkene}} \xrightarrow[\text{LiClO}_4\ /\ \text{CF}_3\text{CH}_2\text{OH}\ \ \text{CCE}]{\text{Bu}_4\text{NI (10 mol \%), K}_2\text{CO}_3\text{ (1 equiv)}} \underset{\mathbf{3a - 3l}}{\text{aziridines}}$$

entry	alkene		aziridine		yield (%)
1		**2a**		**3a**	65
2		**2b**		**3b**	71
3		**2c**		**3c**	63
4		**2d**		**3d**	65
5		**2e**		**3e**	68
6		**2f**		**3f**	57
7		**2g**		**3g**	68
8		**2h**		**3g**	65
9		**2i**		**3h**	62[b]
10		**2j**		**3i**	23(48)[c]
11		**2k**		**3j**	27(51)[c]
12		**2l**		**3k**	(24)[c]
13		**2m**		**3l**	(29)[c]

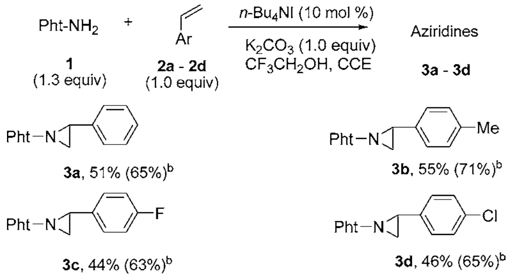
[a] Conditions: Pht-NH_2 (1.3 mmol), alkene (1 mmol) and n-Bu_4NI (0.1 mmol) in 10 mL of CF_3CH_2OH containing $LiClO_4$ (0.1 mol/L), undivided cell, GC anode and iron plate cathode, current density of 4 mA/cm^2, room temperature. [b] Cis/trans ratio is 2:1 based on ^1H NMR. [c] The yield in parentheses was afforded at 0 °C.

counterpart by 2.33 kcal/mol (for detailed geometry of *trans*- and *cis*-**3g**, see the Supporting Information). These results strongly suggest that the aziridination reaction proceeds via a stepwise process. The stepwise pathway is further implicated from the aziridination reaction of *trans*-1-phenylpropene, **2i**, where a *cis*/*trans* mixture of **3i** was formed in a 62% total yield and a 2:1 ratio of *cis*-/*trans*-isomer (entry 9).

The standard reaction conditions also proved to be applicable to the aziridination of aliphatic cycloalkenes, although the yield was not satisfactory. As shown in Table 1, the reactions of cycloheptene and 1-methylcyclohexene gave the corresponding aziridine **3g** and **3h** in only 23% and 27% yields, respectively (entries 10 and 11). Given the poor yields, further condition optimization was performed, and we were pleased to discover that the yields of **3g** and **3h** could be increased to 48% and 51%, respectively, when the electrochemical aziridination reaction was performed at 0 °C (see data in parentheses, entries 10 and 11). Despite much effort, the reaction of cyclohexene and cyclopentene still afforded inferior results, and less than 30% yields of **3i** and **3j** were obtained (entries 12 and 13). It is noteworthy that two byproducts were also isolated from the aziridination of each aliphatic cycloalkene, but their structures have not yet been determined on the basis of examination of their NMR and HRMS spectral data.

As mentioned above, the electrochemical aziridination of styrene proceeded smoothly in the absence of $LiClO_4$, although with some sacrifice in yield (51% vs 65%; note entry 7 of Table S1). Inspired by this observation and being cognizant of the fact that the presence of large quantities of electrolyte leads to separation problems and the production of unwanted waste materials, we further investigated the electrocatalytic aziridination of alkenes without employing additional supporting electrolyte. As shown in Scheme 2, all styrenes bearing electron-rich or electron-poor substituents gave moderate yields of the corresponding aziridines, although in a slightly lower yield than in the presence of electrolyte (Scheme 2).

Scheme 2. Electrocatalytic Aziridination in the Absence of Additional Supporting Electrolyte[a]

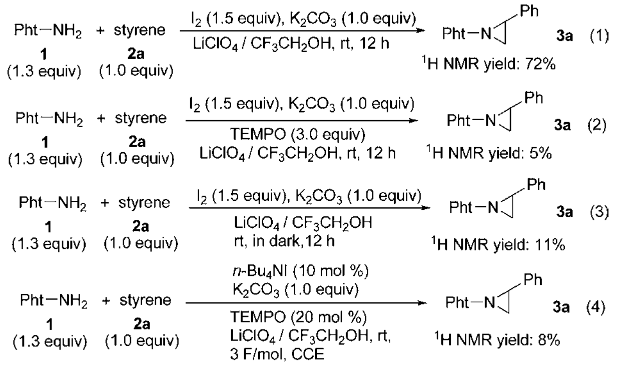


[a] Conditions: Pht-NH_2 (1.3 mmol), alkene (1 mmol), and n-Bu_4NI (0.1 mmol) in 10 mL of CF_3CH_2OH, undivided cell, GC anode and iron plate cathode, current density of 4 mA/cm^2, room temperature. [b] The yield in parentheses is obtained in the presence of supporting electrolyte.

In principle, several mechanisms can be envisaged for this metal-free aziridination reaction. For example, it is believed that a nitrene is generated in situ when $PhI(OAc)_2$) is used as an oxidant in the aziridination reaction of alkenes with Pht-NH_2,[8] as is the case for the direct electrochemical synthesis of aziridines.[12] Alternatively, the n-Bu_4NI/m-CPBA[10] (or HBr/H_2O_2[5])-mediated aziridination of alkenes has been shown to proceed via the in situ generation of hypoiodite. Recently, Minakata proposed that iodine radical ($I^\bullet$) and its radical anion ($I_2^{\bullet -}$) induced the aziridination of styrenes with PhI=NTs when catalyzed by a combination of iodine and n-Bu_4NI.[16]

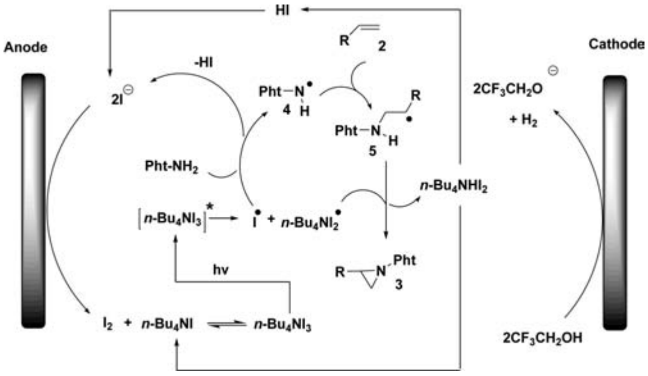
To gain insight into the mechanism of our n-Bu_4NI-catalyzed electrochemical aziridination, control experiments were carried out. As shown in Scheme 3, the oxidative aziridination of styrene proceeded smoothly to afford a 72% yield of **3a** (by ^1H NMR) when 1.5 equiv of molecular iodine was used as an oxidant, under otherwise identical conditions (eq 1), but without passing electricity. The experiment shows that the active iodine species in our case is not hypoiodite since it cannot form without the assistance of another oxidant. When the I_2-mediated aziridination reaction was performed in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), a radical scavenger, less than 5% yield of **3a** was obtained (eq 2). Furthermore, when the reaction was run in the dark, aziridination was also suppressed (eq 3). Since triiodide (I_3^-) is known to be in equilibrium with I_2 and I^-, and triiodide can be photoexcited by visible light to generate iodine radical ($I^\bullet$) and iodine radical anion ($I_2^{-\bullet}$),[17] our results suggest that the reaction involves these two reactive intermediates, $I^\bullet$ and $I_2^{-\bullet}$, and that it is promoted by ambient laboratory light. To further demonstrate the viability of a radical pathway, the reaction was repeated under the standard electrochemical conditions but in the presence of TEMPO. Under these conditions, <8% of **3a** formed (eq 4). Since the oxidation potential of iodide is less than that of TEMPO (0.30 V for iodide compared with 0.58 V for TEMPO (vs Ag/0.5 M $AgNO_3$ in CH_3CN)), TEMPO will be available to serve as a trapping agent. The outcome implies that the active species is iodine radical and that when it is trapped by TEMPO the yield of **3a** is greatly diminished. In addition, a mechanism involving the formation of a nitrene is ruled out because the aziridination of an alkene via a singlet nitrene occurs stereoselectively, while we observe the loss of alkene stereochemistry (note Table 1, entries 7–9).

Scheme 3. Control Experiments



On the basis of the observations described above and Minakata's results,[16] we propose the mechanism shown in Scheme 4 for the iodide-mediated electrochemical aziridination. Initially, the anodic oxidation of iodide generates molecular iodine, which then reacts with n-Bu_4NI to generate ammonium triiodide (n-Bu_4NI_3) in equilibrium with I_2 and n-Bu_4NI. Upon excitation by visible light, $I^\bullet$ and $I_2^{\bullet -}$ are formed. Hydrogen atom abstraction from Pht-NH_2 by $I^\bullet$ forms the aminyl radical **4**, which is trapped by the alkene **2** to form radical **5**. The homolytic cleavage of the N–H bond of **5** is assisted by $I_2^{\bullet -}$ via the abstraction of an H atom, and is followed by intramolecular cyclization to furnish the aziridine products **3**. Simultaneously,

Scheme 4. Proposed Mechanism for the Iodide-Mediated Electrochemical Synthesis of Aziridines



iodide is regenerated and re-enters the catalytic cycle. Since it is easier to form an iodine radical by oxidation of iodide than it is to form a bromine radical via oxidation of bromide, better results are anticipated when iodide ion containing mediators are used.

In conclusion, we have developed an efficient electrochemical strategy for the catalytic aziridination of alkenes. The electrochemical synthesis was performed under constant current conditions in a simple undivided cell using a catalytic amount of n-Bu$_4$NI as a redox catalyst and CF_3CH_2OH as the solvent. Additional supporting electrolyte is not required. A wide range of functional groups proved to be compatible with the catalytic system. Control experiments revealed that the electrocatalytic aziridination most likely proceeds via a radical mechanism, rather than through the intermediacy of a nitrene. The results further demonstrate that electrochemically generated reactive halide species constitute versatile reagents in organic synthesis. The application of this chemistry to other chemical transformations is underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Conditions optimization, experimental details, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Aziridines and epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006. (b) Minakata, S. *Acc. Chem. Res.* **2009**, *42*, 1172. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (d) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(2) Minakata, S.; Takeda, Y.; Kiyokawa, K. In *Methods and Applications of Cycloaddition Reaction in Organic Syntheses*; Nishiwaki, N., Ed.; Wiley-VCH: Weinheim, Chapter 2.

(3) For reviews and highlights, see: (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (b) Jung, N.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5538.

(4) (a) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485. (b) Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161.

(5) Jain, S. L.; Sharma, B. B.; Sain, B. *Tetrahedron Lett.* **2004**, *45*, 8731.

(6) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(7) (a) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2006**, 3337. (b) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2007**, 3279.

(8) (a) Li, J. Y.; Liang, J. L.; Chan, P. W. H.; Che, C. M. *Tetrahedron Lett.* **2004**, *45*, 2685. (b) Li, J. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2005**, *7*, 5801. (c) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *ARKIVOC* **2005**, *(iv)*, 26. (d) Krasova, L. B.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 2011. (e) Richardson, R. D.; Desaize, M.; Wirth, T. *Chem.—Eur. J.* **2007**, *13*, 6745.

(9) (a) Uyanik, M.; Okamoto, T.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331.

(10) Yoshimura, A.; Middleton, K. R.; Zhu, C. J.; Nemykin, V. N.; Zhdankin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 8059.

(11) Varszegi, C.; Ernst, M.; van Laar, F.; Sels, B. F.; Schwab, E.; De Vos, D. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1477.

(12) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530. (b) Siu, T.; Picard, C. J.; Yudin, A. K. *J. Org. Chem.* **2005**, *70*, 932.

(13) (a) Zhang, N. T.; Zeng, C. C.; Lam, C. M.; Grur, R. K.; Little, R. D. *J. Org. Chem.* **2013**, *78*, 2104. (b) Zeng, C. C.; Zhang, N. T.; Lam, C. M.; Little, R. D. *Org. Lett.* **2012**, *14*, 1314. (c) Francke, R.; Little, R. D. *J. Am. Chem. Soc.* **2014**, *136*, 427.

(14) (a) Li, W. C.; Zeng, C. C.; Hu, L. M.; Tian, H. Y.; Little, R. D. *Adv. Synth. Catal.* **2013**, *355*, 2884. (b) Gao, W. J.; Li, W. C.; Zeng, C. C.; Tian, H. Y.; Hu, L. M.; Little, R. D. *J. Org. Chem.* **2015**, *80*, 781.

(15) Yoo, S. J.; Li, L. J.; Zeng, C. C.; Little, R. D. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201410207.

(16) Kiyokawa, K.; Kosaka, T.; Minakata, S. *Org. Lett.* **2013**, *15*, 4858.

(17) (a) Gardner, J. M.; Abrahamsson, M.; Farnum, B. H.; Meyer, G. J. *J. Am. Chem. Soc.* **2009**, *131*, 16206. (b) Boschloo, G.; Hagfeldt, A. *Acc. Chem. Res.* **2009**, *42*, 1819.