J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Uncovering the Mechanism of the Ag(I)/Persulfate-Catalyzed Cross-Coupling Reaction of Arylboronic Acids and Heteroarenes

Niki R. Patel and Robert A. Flowers, II*

Department of Chemistry, Lehigh University, Bethlehem, Pennsylvania 18015, United States

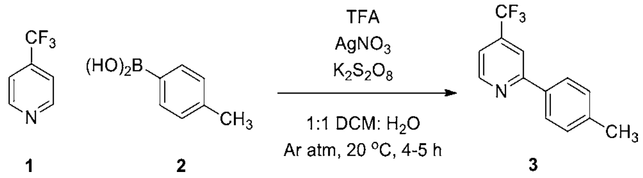
Supporting Information

ABSTRACT: The catalytic cross-coupling of arylboronic acids with pyridines through single-electron oxidation provides efficient access to substituted heterocycles. Despite the importance of this reaction, very little is known about its mechanism, and as a consequence, it is unclear whether the full scope of the transformation has been realized. Here we present kinetic and spectroscopic evidence showing a high degree of complexity in the reaction system. The mechanism derived from these studies shows the activation of Ag(I) for reduction of persulfate and an off-cycle protodeboronation by the pyridine substrate. These results provide key mechanistic insights that enable control of the off-cycle process, thus providing higher efficiency and yield.

Catalytic oxidation via single-electron transfer is becoming one of the most important approaches for the formation of C−C bonds in molecules of pharmaceutical and biological importance.[1] A great deal of recent effort has focused on two general methods: (1) visible-light photoredox catalysis[2] and (2) metal-catalyzed oxidation.[3] In both approaches, the use of a terminal oxidant is often required. In addition, the use of readily available starting materials in these reactions can provide a wide range of related structures, which is important for screening in medicinal chemistry and the construction of building blocks important in materials chemistry. In this vein, the recent work of Baran and co-workers on the Ag(I)/persulfate-catalyzed cross-coupling of arylboronic acids with electron-deficient pyridines is of fundamental importance.[4] Their approach overcomes several of the shortcomings of the traditional Minisci reaction,[5] most importantly the addition of aryl radicals to an aromatic heterocycle. In addition, the method is procedurally elegant and has broad substrate scope. Although the reaction provides access to a variety of substituted heteroarenes, a second addition of Ag catalyst and stoichiometric oxidant are often required. In view of the importance of this bond-forming reaction, it is our supposition that a detailed mechanistic study of the system would facilitate a more efficient approach to reaction design using the Ag(I)/persulfate catalytic system. Herein we present mechanistic data defining the roles of the individual components in the reaction. These data reveal a great degree of mechanistic complexity that, once understood, provides a more effective approach to this catalytic system, thus extending its utility.

To study the system, the reaction of 1 mmol of 4-trifluoromethylpyridine (**1**) and 1.5 mmol of *p*-tolylboronic acid (**2**) in 1:1 dichloromethane (DCM)/water containing 20 mol % $AgNO_3$ (with respect to **1**), 3 mmol of potassium persulfate, and 1 mmol of trifluoroacetic acid (TFA) was examined (Scheme 1). Protonation of pyridine by TFA produces a better radicophile and enhances the selectivity for the 2-position.[6] To maintain controlled reaction conditions, the solvents were degassed and the reaction was carried out under an argon atmosphere. The exclusion of air from the reaction resulted in a 76% isolated yield, compared with the 81% yield reported by Baran and co-workers, which required a second addition of $K_2S_2O_8$ and $AgNO_3$.[4] Additionally, toluene was obtained as a side product in roughly 30% yield (with respect to **2**). The increased yield upon removal of oxygen is consistent with the previously proposed free-radical mechanism.[4] These higher-yielding conditions were suitable for thorough mechanistic studies.

Scheme 1. Cross-Coupling Reaction of Electron-Deficient Pyridine 1 with Arylboronic Acid 2



Kinetic studies were performed in which either the loss of **1** or the growth of product was followed over time via gas chromatography (GC). A "same excess" experiment using the conditions contained in Table 1 was performed to determine the stability of the catalytic $AgNO_3$ during the course of the reaction.[7] If the total catalyst concentration remains constant during the course of the reaction, the rates of the two reactions should be identical. When the rate profiles of runs 1 and 2 were compared, they did not overlay (Figure 1), consistent with a decrease in $[AgNO_3]$ during the course of the reaction.

Table 1. Conditions for the "Same Excess" Experiment

run	**1** (M)	**2** (M)	excess (M)	$K_2S_2O_8$ (M)	excess (M)	$AgNO_3$ (M)
1 (100%)	0.10	0.15	0.050	0.30	0.20	0.020
2 (50%)	0.050	0.10	0.050	0.25	0.20	0.020

Received: January 21, 2013
Published: March 11, 2013

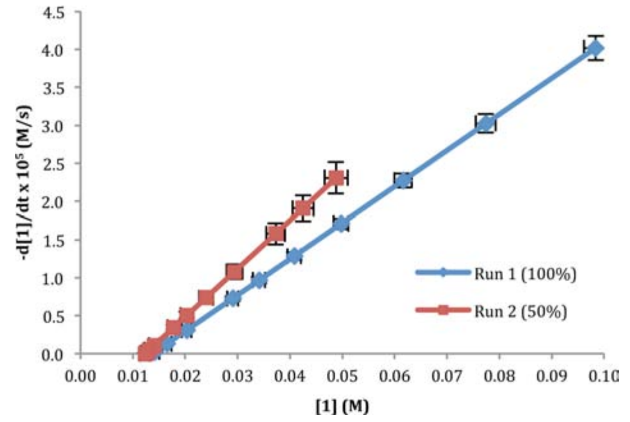


Figure 1. Rate vs [**1**] for the two runs in the "same excess" experiment.

To determine the rate order with respect to each substrate in the reaction, "different excess" experiments were performed. The reaction was found to be approximately first order in **1** and $AgNO_3$. Initial experiments showed the order with respect to $K_2S_2O_8$ to be zero. In view of the low solubility of $K_2S_2O_8$, it was possible that the true order could be masked by phase transfer. To examine this physical process, the more soluble $Na_2S_2O_8$ was employed in the reaction, and an order of approximately 1 was observed. Surprisingly, increasing the initial concentration of **2** resulted in an overall decrease in reaction rate (Figure 2). The order with respect to **2** was determined through normalization of −d[**1**]/dt according to eq 1:

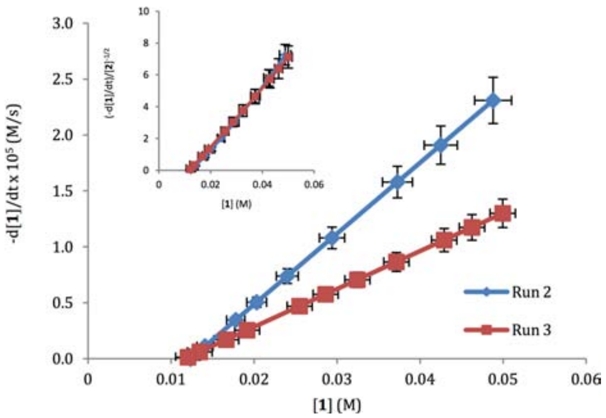


Figure 2. Rate vs [**1**] for the "different excess" experiment for **2**. Run 3 was performed by increasing [**2**] to 0.30 M and keeping the concentrations of all other reactants the same as in run 2 in Table 1.

$$-\frac{(\mathrm{d}[\mathbf{1}]/\mathrm{d}t)}{[\mathbf{2}]^{x}} = k_{\mathrm{obs}}[\mathbf{1}] \tag{1}$$

where x is the order with respect to **2**. Overlay of the two reaction profiles was observed when $x = -0.5$, indicating that the reaction is inverse half order with respect to **2** (Figure 2 inset).

The orders with respect to the reaction components are shown in Table 2. The orders with respect to persulfate and $AgNO_3$ are consistent with a process in which catalytic Ag(I) is oxidized by persulfate. The orders obtained for **1** and **2** are surprising. If the reaction is indeed proceeding through initial oxidation of **2** followed by addition to **1**, the first order observed for **1** compared to the inverse half order for **2** suggests a more complicated process.

Table 2. Observed Rate Orders in the Cross-Coupling Reaction of 1 and 2

component	**1**	**2**	$K_2S_2O_8$	$AgNO_3$
order	1	−0.5	0^a	1

[a] Due to the low solubility of $K_2S_2O_8$ (4.72 g/100 mL at 20 °C);[10] when $Na_2S_2O_8$ (54.6 g/100 mL) was used, the order was found to be approximately 1.

The formation of silver−pyridine complexes is well-established in the literature.[8] In addition, there is literature precedent describing the activation of Ag(I) by amines toward oxidation by persulfate.[9] Bonchev and Aleksiev showed that the addition of a suitable nitrogen-containing neutral ligand such as phenanthroline, ethylenediamine, or pyridine to Ag(I)/persulfate reactions resulted in acceleration of the oxidation of Ag(I) to Ag(II).[9] This activating effect was attributed to a lowering of the potential of the Ag(II)/Ag(I) couple.

To investigate the possible interaction between **1** and $AgNO_3$, ^1H NMR studies were carried out in D_2O to mimic the reaction conditions (Figure 3). Downfield shifts of the resonances for the aromatic protons of **1** were observed upon addition of TFA (Figure 3b) or $AgNO_3$ (Figure 3d) to **1** in D_2O. Upon addition of TFA and $AgNO_3$ (Figure 3c), a slight upfield shift of the aromatic proton resonances relative to the mixture of **1** and TFA (Figure 3b) was observed. The lack of overlay of the spectra is consistent with equilibrium complexation between **1** and Ag(I) under the reaction conditions.

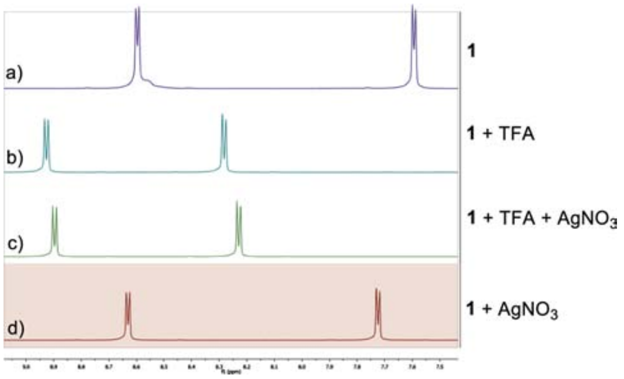


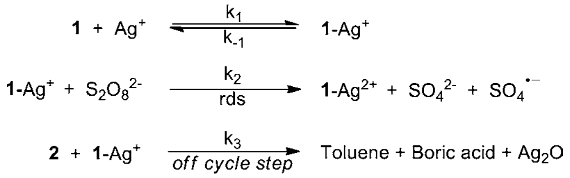
Figure 3. ^1H NMR spectra of **1** with additives.

With some insight into the possible role of **1**, we next focused on the mechanistic role of **2**. An inverse order is typically indicative of one of two possible scenarios: (1) the presence of the reaction component shifts the equilibrium, decreasing the concentration of the intermediate prior to the rate-determining step, or (2) the component behaves as an antagonist acting outside the desired pathway that leads to the product. In view of the long history of the Ag(I)/persulfate oxidation system, it was instructive to examine the literature carefully for possible precedents to explain the unusual observations obtained from the kinetic studies. Investigations of the interaction between $AgNO_3$ and boronic acids in ammoniacal solution date back to the 1880s.[11] These early studies showed that while alkylboronic acids reduce Ag(I) through a Ag−alkyl intermediate, aromatic boronic acids form an insoluble salt. Heating of this salt leads to hydrolytic cleavage, producing an arene, boric acid, and Ag_2O.[11]

To examine the Ag(I)-initiated hydrolysis under the reaction conditions, stoichiometric quantities of **2** and $AgNO_3$ were stirred in 1:1 DCM/H_2O. After approximately 5 min, the formation of a gray/silver-colored precipitate was observed, consistent with silver oxide as described in previous studies. The formation of toluene as a byproduct of this reaction was confirmed by gas chromatography−mass spectrometry (GC−MS). To probe the system further, two reactions were carried out. The first involved the reaction of 1.5 mmol of **2** with 1.0 mmol of $AgNO_3$ in 1:1 DCM/H_2O. A second reaction was run under the same conditions with 1.0 mmol of **1**. Approximately 0.84 mmol of toluene was formed when **1** was included in the reaction mixture, compared with 0.23 mmol when **1** was excluded, a finding consistent with inhibition of $AgNO_3$ and consumption of **2** outside the desired reaction pathway. The increase in toluene formation in the presence of **1** is also consistent with interaction between **1** and $AgNO_3$ and the classic studies on the reaction of $AgNO_3$ and boronic acids in ammoniacal solutions.[8,11]

On the basis of the observed kinetic and spectroscopic data, the proposed reaction mechanism (Scheme 2) involves (i) a pre-equilibrium step in which **1** and Ag(I) form a complex; (ii) reduction of $S_2O_8^{2-}$ by the Ag(I)−**1** complex, which is the rate-determining step; and (iii) an off-cycle step involving protodeboronation of **2** accelerated by the Ag(I)−**1** complex. As shown in the Supporting Information (SI), applying the steady-state approximation to the Ag(I)−**1** complex and accounting for all of the states of Ag(I) affords the following expression for the reaction rate:

Scheme 2. Mechanism of Ag(I)/Persulfate Catalysis in Coupling of Arylboronic Acids and Electron-Deficient Pyridines



$$-\frac{d[\mathbf{1}]}{dt} = k_1k_2[\mathbf{1}][S_2O_8^{2-}][Ag^I]_{tot}\left(\frac{k_{-1} + k_2[S_2O_8^{2-}] + k_3[\mathbf{2}]}{k_{-1}^2 + 2k_{-1}k_3[\mathbf{2}] + k_3^2[\mathbf{2}]^2}\right) \tag{2}$$

The derived rate law can be compared to the empirical rate law (eq 3), in which **1**, $S_2O_8^{2-}$, and Ag(I) are first order and **2** is inverse half order:

$$-\frac{d[\mathbf{1}]}{dt} \approx k_{obs}\frac{[\mathbf{1}][S_2O_8^{2-}][Ag^I]_{tot}}{[\mathbf{2}]^{0.5}} \tag{3}$$

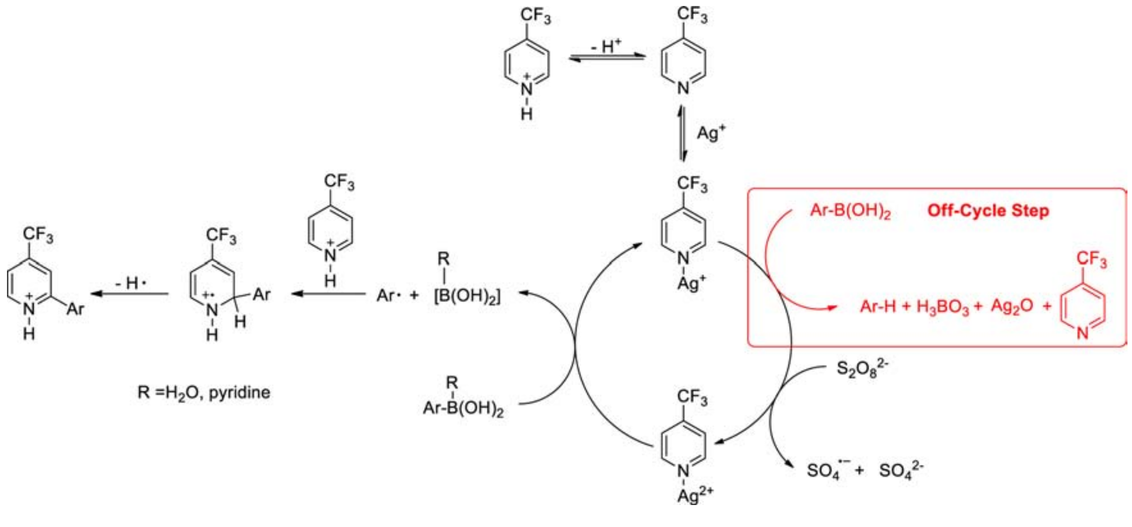
The orders in the empirical rate law can be equated to the orders of 1 with respect to **1** and Ag(I), the positive additive order with respect to $S_2O_8^{2-}$, and the overall inverse fractional order with respect to **2** shown in the derived rate law.

Aside from providing insight into the reaction mechanism, these results provide a means to optimize reaction conditions and increase the yield of the reaction. The fact that the reaction is inverse half order with respect to **2** indicates that increasing its concentration is deleterious to the reaction progress. Furthermore, the addition of a reagent capable of preventing the formation of catalytically inactive Ag(I) should be beneficial to the reaction progress (see the SI). To test this supposition, a reaction was initiated using 0.5 M HNO_3 to prevent the formation of catalytically inactive Ag(I).[11c] Employing these modified conditions enabled the catalyst and oxidant loadings to be reduced to 10 mol % $AgNO_3$ and 2 equiv of persulfate, respectively, in 1:1 DCM/water under Ar overnight, leading to an isolated yield of 90%. Additionally, formation of the toluene side product was reduced to 9% (with respect to **2**).

Equipped with a rate expression for the system, the question that still remains unanswered is which species [Ag(II) or $SO_4^{\bullet-}$] oxidizes the boronic acid? The classic work of Anderson and Kochi showed that metastable Ag(II) is responsible for decarboxylation of carboxylic acids to produce radicals by Ag(I)/persulfate.[12] This work was applied by Minisci and co-workers to form substituted heterocycles via a reaction in which an alkyl radical generated from decarboxylation of an acid adds to a heteroarene.[5] In the present reaction, Baran proposed that addition of persulfate radical anion to the arylboronic acid is responsible for intermediate aryl radical formation.[4]

To answer the question posed above, we first examined the use of potassium *p*-tolyltrifluoroborate (**4**) in place of **2**. The

Scheme 3. Proposed Mechanism of the Ag(I)/Persulfate-Catalyzed Arylation of Electron-Deficient Pyridines



reaction was performed under the unoptimized conditions shown in Scheme 1 and provided a 60% isolated yield of **3**. Aryltrifluoroborates are known to hydrolyze under basic conditions.[13] The stability of **4** under the reaction conditions was examined in aqueous acidic media by monitoring the ^{11}B NMR spectrum. A small amount of hydrolysis of **4** to **2** was observed. Next, the reaction with **2** was carried out in the presence of allyl acetate, a well-known radical trap for $SO_4^{\bullet -}$.[14] If $SO_4^{\bullet -}$ acts as the oxidizing agent in the reaction, the addition of allyl acetate would be deleterious to the reaction progress. Interestingly, the addition of 6 equiv of allyl acetate had no impact on the yield, and the reaction rate increased slightly. This observation suggests that decreasing the concentration of $SO_4^{\bullet -}$ through capture by allyl acetate drives the reaction forward toward the formation of product, presumably through the reduction of $S_2O_8^{2-}$ by Ag(I) to form Ag(II). These additional experiments showed that a small amount of **4** was hydrolyzed under the reaction conditions and that reactions with **2** proceeded even when $SO_4^{\bullet -}$ was sequestered by allyl acetate. As a consequence, these experiments are consistent with a process involving Ag(II)-mediated oxidation. Since quaternized boron is more susceptible to single-electron oxidation,[15] we propose that water (solvent) or pyridine interacts with the arylboronic acid to facilitate oxidation by Ag(II).

A proposed mechanism for the reaction is shown in Scheme 3. Under the conditions of the reaction, pyridine coordination to Ag(I) is followed by persulfate oxidation in the rate-limiting step. The resulting Ag(II)−pyridine complex oxidizes the arylboronic acid, producing an aryl radical, which can then add to the pyridinium ion, leading to product. An off-cycle step is also involved outside of the desired pathway, in which the arylboronic acid is protodeboronated, leading to unwanted side products.

The mechanistic experiments described herein show an unexpected degree of complexity in the Ag(I)/persulfate-catalyzed cross-coupling of arylboronic acids and pyridines, information that could not otherwise have been extracted from the use of simple empirical models or studies based on product distributions. The mechanism derived from the spectroscopic and kinetic studies shows that Ag(I) is activated by the pyridine for reduction of persulfate but also contains an off-cycle protodeboronation by the pyridine. These results provide the key mechanistic insight that enables control of the off-cycle process, thus providing higher efficiency and yield. In addition, literature precedent and evidence provided herein demonstrate that Ag(II) is the likely oxidant responsible for the formation of aryl radicals from arylboronic acids. While the studies presented clarify several mechanistic details of the Ag(I)/persulfate-catalyzed cross-coupling of arylboronic acids and pyridines, the results may impact the design and refinement of other radical-based additions proceeding through catalytic oxidations mediated by Ag(I)/persulfate.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, kinetic data, and spectral data, and derivation of eq 2. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

rof2@lehigh.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.A.F. is grateful to the National Institutes of Health (GM075960-03) for support of this work. We thank Dr. James Devery and Dr. Lawrence Courtney for useful discussions and aid in the elucidation of the reaction mechanism and Dr. Brian Casey for initial work on this project

■ REFERENCES

(1) (a) Jahn, U. *Top. Curr. Chem.* **2012**, *320*, 121. (b) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193.

(2) (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

(3) (a) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (d) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M. *J. Am. Chem. Soc.* **2011**, *133*, 3292.

(4) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

(5) Minisci, F.; Bernardi, R.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3575.

(6) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1986**, *51*, 4411.

(7) (a) Mathew, J. S.; Klussman, M.; Iwamura, H.; Valera, F.; Futran, A.; Emanuelsson, E. A. C.; Blackmond, D. G. *J. Org. Chem.* **2006**, *71*, 4711. (b) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302. (c) Devery, J. J., III; Conrad, J. C.; MacMillan, D. W. C.; Flowers, R. A., II. *Angew. Chem., Int. Ed.* **2010**, *49*, 6106. (d) Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2011**, *133*, 10655.

(8) (a) Bruehlman, R. J.; Verhoek, F. H. *J. Am. Chem. Soc.* **1948**, *70*, 1401. (b) Bjerrum, J. *Acta Chem. Scand.* **1972**, *26*, 2734. (c) Vosburgh, W. C.; Cogswell, S. A. *J. Am. Chem. Soc.* **1943**, *65*, 2412.

(9) (a) Alexiev, A.; Bontchev, P. R. *Mikrochim. Acta* **1970**, 13. (b) Bonchev, P. R.; Aleksiev, A. A. *Theor. Exp. Chem.* **1975**, *9*, 144.

(10) Apelblat, A.; Korin, E.; Manzurola, E. *J. Chem. Thermodyn.* **2001**, *33*, 61.

(11) (a) Michaelis, A.; Becker, P. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 180. (b) Johnson, J. R.; Van Campen, M. G.; Grummitt, O. *J. Am. Chem. Soc.* **1938**, *60*, 111. (c) Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711.

(12) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651. (b) Anderson, J. M.; Kochi, J. K. *J. Org. Chem.* **1970**, *35*, 986.

(13) (a) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156. (b) Lennox, A. J. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 7431−7441.

(14) Kalb, A. J.; Allen, T. L. *J. Am. Chem. Soc.* **1964**, *86*, 5107.

(15) Shundrin, L. A.; Bardin, V. V.; Frohn, H.-J. *Z. Anorg. Allg. Chem.* **2004**, *630*, 1253.