Facile Formation of β-Hydroxyboronate Esters by a Cu-Catalyzed Diboration/Matteson Homologation Sequence

Cameron M. Moore,[‡] Casey R. Medina,[†,‡] Peter C. Cannamela,[†] Melissa L. McIntosh,[‡] Carl J. Ferber,[†] Andrew J. Roering,[†] and Timothy B. Clark*,[†]

[†]Department of Chemistry and Biochemistry, University of San Diego, 5998 Alcala Park, San Diego, California 92110, United States
[‡]Department of Chemistry, Western Washington University, 516 High Street Bellingham, Washington 98225, United States

Ⓢ *Supporting Information*

ABSTRACT: The copper-catalyzed diboration of aldehydes was used in conjunction with the Matteson homologation, providing the efficient synthesis of β-hydroxyboronate esters. The oxygen-bound boronate ester was found to play a key role in mediating the homologation reaction, which was compared to the α-hydroxyboronate ester (isolated hydrolysis product).

The synthetic utility of the diboration/homologation sequence was demonstrated through the oxidation of one product to provide a 1,2-diol.
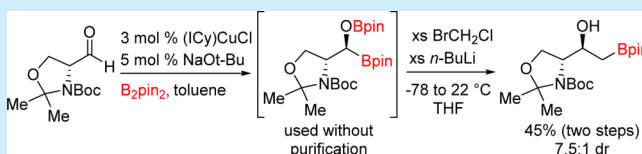
Advances in methods that incorporate boron into organic compounds[1−11] and those which utilize the carbon−boron bond[1,6,7,10−15] for a variety of transformations have resulted in its extensive use as a synthetic handle in target-directed synthesis. Boron has also seen numerous direct applications to health issues, including the first boron-containing pharmaceutical drug Velcade.[16,17] While the traditional methods to incorporate boron into an organic substrate, such as hydroboration of alkenes and alkynes and organolithium addition to a trialkoxyborane, are highly robust, they result in a limited scope of functional group motifs that can be applied to complex synthetic targets. Metal-catalyzed borylation reactions have made significant contributions to this field in recent years and have led to a number of new transformations that incorporate a carbon−boron bond into functional groups that were inaccessible through traditional methods. One such reaction is the diboration of polarized double bonds;[18−21] until recently, this process was limited to select examples for the diboration of imines and thiocarbonyls. In 2006, however, Sadighi and co-workers reported the first example of carbonyl diboration, which was mediated by an *N*-heterocyclic carbene (NHC)−copper catalyst.[22−24] Subsequent studies have utilized these diboration products in the Suzuki−Miyaura coupling of trifluoroborate salts of the resulting α-hydroxyboronate esters[25] and in the formation of trisubstituted vinylboronate esters by acid-catalyzed elimination.[26]

Our group recognized the potential to combine carbonyl diboration with 1,2-metalate rearrangements[7,13,15,27] as a way to access complex β-hydroxyboronate esters from simple starting materials (Scheme 1). Such a transformation would allow one to introduce a boron substituent into an advanced synthetic intermediate through an aldehyde or ketone and utilize the extensive area of homologation chemistry to incorporate a complex side chain into that intermediate. For example, the homologation of protected α-oxoboronate ester **B** with LiCHCl₂ would provide β-oxoboronate ester **C** with the newly installed

Scheme 1. Diboration/Homologation Sequence
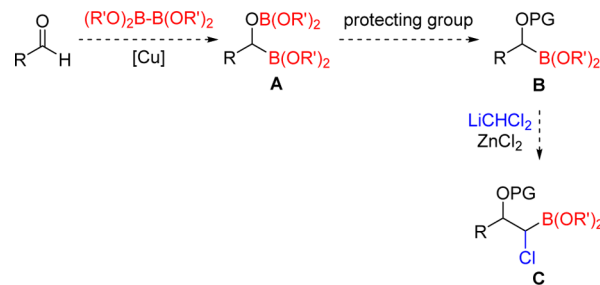
C−Cl bond and the C−B bond still intact for further functionalization. We herein report the direct Matteson homologation of α-oxoboronate esters obtained through the copper-catalyzed diboration of aldehydes.

Initial efforts to develop the method outlined in Scheme 1 focused on the formation and isolation of α-hydroxyboronate esters. The diboration was achieved using a previously reported,[23] modified version of Sadighi's original conditions.[22] [1,3-Dicyclohexylimidazol-2-ylidene]copper(I) chloride (ICy-CuCl) (3 mol %) was used as the precatalyst in the presence of 5 mol % of sodium *tert*-butoxide and a slight excess of bis(pinacolato)diboron (B₂pin₂) at ambient temperature (Scheme 2). Under these conditions, the diboration is complete in 1−7 h. Purification by silica gel chromatography also cleaves the oxygen−boron bond and provides the corresponding α-hydroxyboronate esters **1−4** in variable yield.[23] Sterically congested boronate esters **1−3** were isolated in good yields, but products derived from primary aldehydes were prone to decomposition on silica gel chromatography, providing a low yield of **4**.

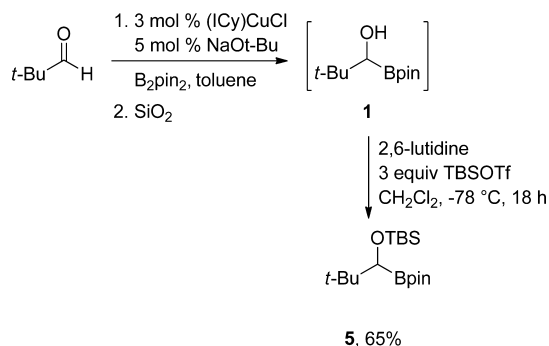## Scheme 2. Cu-Catalyzed Diboration/Hydrolysis Sequence

## Scheme 3. Cu-Catalyzed Diboration/Protection Sequence
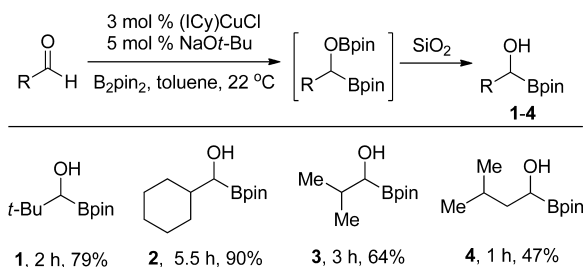
To avoid the challenges associated with isolating sensitive α-hydroxyboronate esters by chromatography the direct protection of unpurified α-oxoboronate esters was examined. To liberate the alcohol without causing partial decomposition, the crude reaction mixture was passed through a silica plug to obtain desired alcohol **1** (Scheme 3). The unpurified material was then treated with excess TBSOTf and 2,6-lutidine in dicholormethane to provide the protected alcohol in good yield.

With protected α-oxoboronate ester **5** in hand, a Matteson homologation reaction was examined with LiCH$_2$Cl,[28] providing β-oxoboronate ester **6** in moderate yield (Scheme 4). While the

Scheme 4. Matteson Homologation of Boronate Ester 5
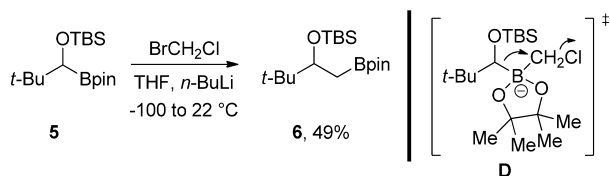
formation of **6** was promising, several attempts to optimize the reaction were unsuccessful. Use of alternative protecting groups in place of *tert*-butyldimethylsilyl resulted in poor yields of the corresponding α-oxoboronate esters and were not viable options for the synthetic sequence.

In an attempt to further bypass the complications associated with protecting the α-hydroxyboronate ester, a direct Matteson homologation of the diboration intermediate was examined. The crude diboration product was filtered through Celite to remove the copper catalyst,[29] and the homologation was optimized with 3 equiv of BrCH$_2$Cl/*n*-BuLi, which was added in excess to account for the presence of the O—Bpin bond which would likely consume 1 equiv of *n*-BuLi/LiCH$_2$Cl (Scheme 5). Under these conditions, the diboration/direct homologation of pivaldehyde provided β-hydroxyboronate ester **7** in moderate yield over the

Scheme 5. Diboration/Direct Homologation of Pivaldehyde
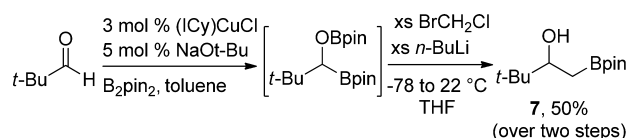
two-step sequence. Notably, this sequence avoids the isolation of the sensitive α-hydroxyboronate ester intermediate and delays purification to the more robust β-hydroxyboronate esters.[30] The resulting β-heteroatom-substituted boronate esters are generally challenging functional group motifs to access due to the propensity of these substrates to result in elimination of the X—B bond to provide the corresponding alkene, which is not observed under these reaction conditions.[31,32]

The direct homologation procedure was examined with a variety of aldehydes to examine the scope of the transformation. Both branched and linear aldehydes provided the corresponding β-hydroxyboronate ester in moderate to good yield (Scheme 6,

## Scheme 6. Diboration/Direct Homologation of Various Aldehydes
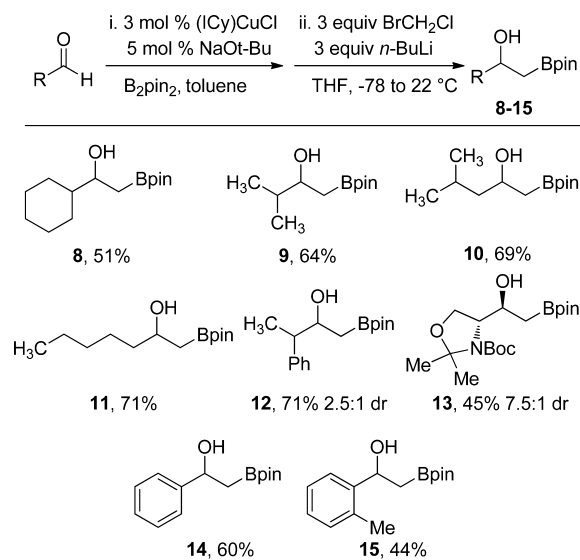
8−13).[33] The diboration/homologation of 2-phenylpropionaldehyde provided **12** in a 2.5:1 mixture of diastereomers. (*S*)-(−)-3-Boc-2,2-dimethyloxazolidine-4-carboxaldehyde also tolerated the reaction conditions, providing **13** as a 7.5:1 mixture of diastereomers. The selectivity of each substrate is slightly lower than a diboration/trifluoroborate formation sequence reported by Molander for these aldehydes (4:1 dr; >20:1 dr, respectively).[25] The difference in selectivity likely results from a modification of the diboration reaction conditions by Molander which includes methanol as a proton source. Benzaldehyde derivatives were also found to tolerate the reaction conditions, providing **14** in 60% and sterically congested **15** in 44% yield. The formation of **14** and **15** is noteworthy since benzaldehyde- and acetophenone-derived α-hydroxyboronate esters[22,23] readily decompose in the presence of air or moisture but tolerate the conditions required for homologation.

The ability to perform a direct homologation of the diboration product raises some questions about the homologation mechanism. The role of the oxygen-bound boronate ester was of particular interest based on the significant influence it would
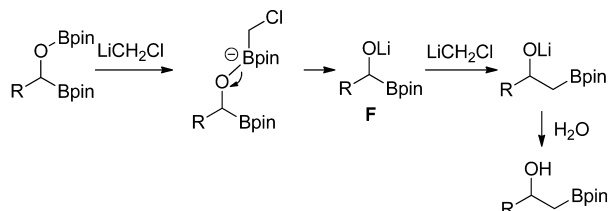
have on the electronics of the substrate during the 1,2-migration step. Three likely mechanisms that distinguish the role of the oxygen-bound boronate ester are shown in Scheme 7. In

Scheme 7. Possible Mechanisms for Direct Homologation of Diboration Products
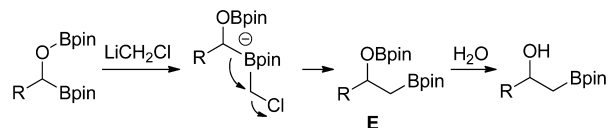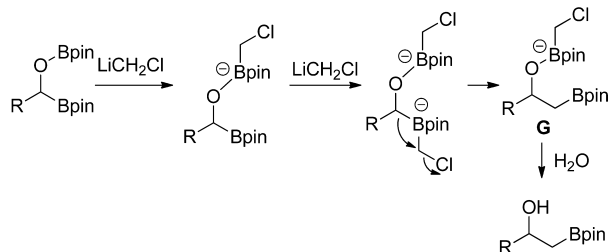

mechanism 1, the oxygen-bound boronate ester does not interact with the LiCH$_2$Cl or n-BuLi, and the homologation takes place at the carbon-bound boronate ester. This mechanism is inconsistent with the need for excess BrCH$_2$Cl/n-BuLi but could be accounted for by adventitious water and/or the presence of other impurities that are not removed upon filtration of the crude reaction mixture. The oxygen-bound boronate ester, however, should be less Lewis acidic than the carbon-bound boronate ester with the added electron donation from oxygen.[34−36]

In mechanism 2, the oxygen−boron bond is cleaved prior to homologation, leaving an alkoxide present during the homologation step. Although the oxygen-bound boronate ester is less Lewis acidic, the oxygen−boron bond is known to be kinetically labile, and the rate of displacement of the boronate ester may be significantly faster than the homologation step. Finally, mechanism 3 involves the coordination of the LiCH$_2$Cl to the oxygen-bound boronate ester without breaking the oxygen−boron bond. It is not clear how the boronate would influence the homologation reaction on the adjacent boron.

While the reaction conditions preclude a number of experiments that would distinguish between these mechanisms without advanced instrumentation,[37] the identity of the starting α-oxoboronate ester could be used to rule out one of the mechanisms. Performing the homologation reaction with either the diboration intermediate, which could be isolated by filtering through Celite under an inert atmosphere, or with an α-hydroxyboronate ester (such as **1−4**, obtained as shown in Scheme 2) was envisioned to distinguish between the two reaction pathways. If the alkoxide was formed under the reaction conditions (mechanism 2, intermediate **F**), both starting materials should lead to the formation of **F** directly and should result in similar conversion to the β-hydroxyboronate ester. If the

reaction was proceeding through mechanism 1 or 3 the two substrates should diverge in product formation.

Isobutyraldehyde was used as the source of the two α-oxoboronate esters **16** and **3**, which were subjected to the homologation conditions individually (Scheme 8). While

**Scheme 8. Matteson Homologation of α-Oxoboronate Esters 16 and 3**
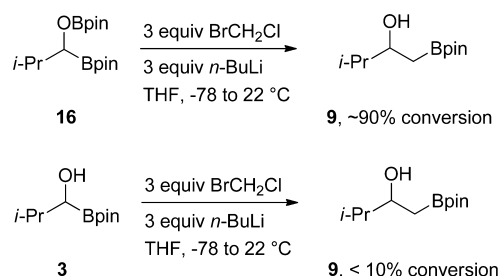
diboronate **16** resulted in ca. 90% conversion to **9**, α-hydroxyboronate ester **3** resulted in <10% conversion to **9**, providing primarily unreacted **3** as the major component. This experiment suggests that **3** is not competent in the homologation reaction. Since alkoxide **F** (Scheme 7, mechanism 2) would readily form under the reaction conditions with alcohol **3**, these results are inconsistent with mechanism 2.

To distinguish between mechanism 1 and 3, a ^{11}B NMR spectrum of the reaction mixture was obtained prior to an aqueous workup of the reaction. Under mechanism 1, diboronated product **E** is expected (Scheme 7). Alternatively, mechanism 3 would result in intermediate **G**. These reaction intermediates are readily distinguishable by ^{11}B NMR spectroscopy. Upon examination of the reaction mixture by ^{11}B NMR spectroscopy, three major peaks were observed at δ 33.6, 22.3, and 6.8 ppm (see the Supporting Information for the spectrum). The peak at 33.6 ppm has a chemical shift similar to that of the C-bound boron of **9** (Scheme 8) and is consistent with either mechanism. The peak at 22.3 ppm is consistent with the oxygen-bound boron of **E** by analogy to the ^{11}B NMR of **16** and related compounds.[22] Although the peak at 22.3 ppm is consistent with intermediate **E**, it is also consistent with unreacted diboronate **16**, and the broad nature of ^{11}B NMR spectroscopy precludes the distinction of these compounds, which have similar chemical shifts. More importantly, this peak is much smaller than the peak at 6.8 ppm and is unlikely to be the major component of the reaction mixture.

Finally, the peak at 6.8 ppm is consistent with a tetra-coordinated trialkoxyboroalkane, as proposed by intermediate **G** (Scheme 7). Several compounds that contain tetra-coordinated boron, derived from pinacolboronate esters, have been reported in the literature [both pinB(OR)R′ and pinB(OR)H], resulting in ^{11}B NMR chemical shifts of 6−10 ppm.[38−40] On the basis of these comparisons, the major component of the reaction mixture is assigned as intermediate **G**; therefore, the experimental data are most consistent with mechanism 3.

To demonstrate the efficiency of the reaction and the potential utility of the β-hydroxyboronate ester products, unpurified boronate ester **8** was oxidized and protected as acetonide **17** (Scheme 9). The four-step reaction sequence required only a single purification step, providing 62% overall yield. The overall yield is higher than the yield of **8**, suggesting that the β-hydroxyboronate esters do not result in complete recovery upon

Scheme 9. Four-Step Synthetic Sequence via Boronate Ester 8
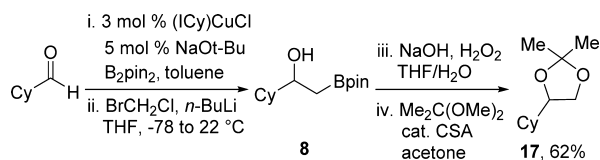
purification. Alternative reactions that functionalize the C−B bond should also allow for increased yields.

In summary, an efficient diboration/homologation sequence was developed, avoiding the isolation or protection of the intermediate α-hydroxyboronate esters. The oxygen-bound boronate ester, from aldehyde diboration, was found to serve as a suitable protecting group during the homologation, suggesting that the boronate ester remains bound to the oxygen during the homologation step. Looking forward, aldehyde diboration products will be examined in additional homologations, providing products with increased molecular complexity.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

All experimental procedures and spectral data of products and copies of the ^{1}H, ^{13}C, and ^{11}B NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: clarkt@sandiego.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; Vol. *1*.
(2) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179.
(3) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671.
(4) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1.
(5) Fu, G. C.; Evans, D. A.; Muci, A. R. *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI: Greenwich, CT, 1995; Vol. *1*, p 95.
(6) Brown, H. C.; Zaidlewicz, M. *Organic Syntheses via Boranes-Recent Developments*; Aldrich Chemical Co.: Milwaukee, 2001; Vol. *2*.
(7) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695.
(8) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717.
(9) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
(10) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011; Vol. *1*.
(11) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011; Vol. *2*.
(12) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(13) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.
(14) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
(15) Scott, H. K.; Aggarwal, V. K. *Chem.—Eur. J.* **2011**, *17*, 13124.
(16) Adams, J.; Behnke, M.; Chen, S.; Cruickshank, A. A.; Dick, L. R.; Grenier, L.; Klunder, J. M.; Ma, Y.-T.; Plamondon, L.; Stein, R. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 333.
(17) Matteson, D. S. *Med. Res. Rev.* **2008**, *28*, 233.
(18) Carter, C. A. G.; Vogels, C. M.; Harrison, D. J.; Gagnon, M. K. J.; Norman, D. W.; Langler, R. F.; Baker, R. T.; Westcott, S. A. *Organometallics* **2001**, *20*, 2130.
(19) Mann, G.; John, K. D.; Baker, R. T. *Org. Lett.* **2000**, *2*, 2105.
(20) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910.
(21) Buesking, A. W.; Bacauanu, V.; Cai, I.; Ellman, J. A. *J. Org. Chem.* **2014**, *79*, 3671.
(22) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036.
(23) McIntosh, M. L.; Moore, C. M.; Clark, T. B. *Org. Lett.* **2010**, *12*, 1996.
(24) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586.
(25) Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856.
(26) Guan, W.; Michael, A. K.; McIntosh, M. L.; Koren-Selfridge, L.; Scott, J. P.; Clark, T. B. *J. Org. Chem.* **2014**, *79*, 7199.
(27) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.
(28) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704.
(29) Removal of the remaining copper catalyst was required to obtain the observed conversions; significant decreases in conversion were observed if the filtration was not completed.
(30) α-Hydroxyboronate esters are prone to slow decomposition in air. The rate of decomposition depends on the steric congestion of the substituent. α-Hydroxyboronate ester **1** is stable in air for multiple days, but decomposition products of **4** were observed within a day if left exposed to atmospheric conditions. Benzaldehyde-derived α-hydroxyboronate esters are prone to rapid decomposition, resulting in some decomposition products upon exposure to moisture. β-Hydroxyboronate esters are generally stable when exposed to air or moisture and have been stored for extended periods of time without significant decomposition.
(31) Matteson, D. S.; Liedtke, J. D. *J. Org. Chem.* **1963**, *28*, 1924.
(32) Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 10399.
(33) The inclusion of additives, such as $ZnCl_2$, during the homologation reaction had minimal impact on the reaction yield.
(34) Ashby, M. T.; Sheshtawy, N. A. *Organometallics* **1994**, *13*, 236.
(35) Finocchiaro, P.; Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 7029.
(36) Britovsek, G. J. P.; Ugolotti, J.; White, A. J. P. *Organometallics* **2005**, *24*, 1685.
(37) Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130.
(38) Baslé, O.; Porcel, S.; Ladeira, S.; Bouhadir, G.; Bourissou, D. *Chem. Commun.* **2012**, *48*, 4495.
(39) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314.
(40) Query, I. P.; Squier, P. A.; Larson, E. M.; Isley, N. A.; Clark, T. B. *J. Org. Chem.* **2011**, *76*, 6452.