Organic LETTERS
Letter
pubs.acs.org/OrgLett

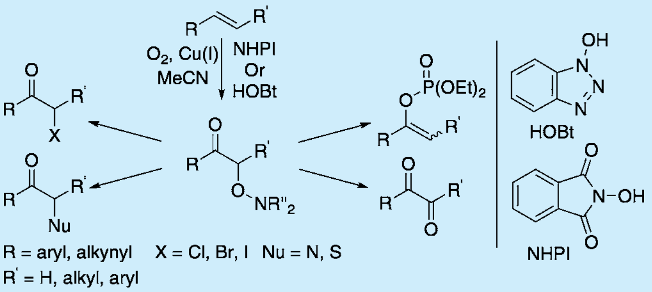
Copper(I)-Catalyzed Oxidation of Alkenes Using Molecular Oxygen and Hydroxylamines: Synthesis and Reactivity of α-Oxygenated Ketones

Alexander A. Andia, Matthew R. Miner, and K. A. Woerpel*

Department of Chemistry, New York University, New York, New York 10003, United States

S Supporting Information

ABSTRACT: The copper(I)-catalyzed oxidation of alkenes with molecular oxygen and *N*-hydroxyphthalimide (NHPI) or *N*-hydroxybenzotriazole (HOBt) provided α-oxygenated ketones. The reaction proceeded under a balloon of O_2 at room temperature to furnish the dioxygenated products in 50−90% yield. These compounds, particularly the HOBt derivatives, can be further functionalized with phosphorus, nitrogen, and sulfur nucleophiles to give synthetically useful products.



Oxidation of alkenes is a valuable tool for the preparation of 1,2-diols,[1] α-hydroxyketones,[2] and 1,2-dicarbonyl compounds.[3] Although many transition-metal-catalyzed reactions afford these compounds,[4,5] molecular oxygen is rarely utilized as the source of oxygen atoms. The development of a method to oxidize alkenes using this abundant and environmentally benign source of oxygen atoms is desirable.[6]

Although significant progress has been made incorporating molecular oxygen into hydrocarbons and alkynes,[7−11] the dioxygenation of alkenes using molecular oxygen remains largely unexplored.[12,13] Current methods suffer from the use of expensive transition metals[14,15] and toxic metals such as osmium or require dialkylperoxides as initiators.[16−19] During the course of our studies, Punniyamurthy and co-workers reported an oxidation of alkenes using air, Cu(II), and *N*-hydroxyphthalimide (NHPI, Figure 1) to provide β-keto-*N*-alkoxyphthalimides.[20] In this Letter, we report our observation that copper(I)-catalyzed oxidations of alkenes with molecular oxygen and hydroxylamine derivatives, particularly *N*-hydroxybenzotriazole (HOBt, Figure 1), form α-oxygenated ketones that can undergo subsequent transformations to provide a variety of synthetically useful products.

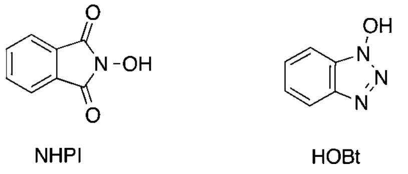
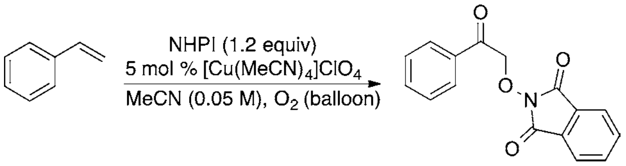


Figure 1. Hydroxylamines used in the oxidations of alkenes.

The copper(I)-catalyzed oxidation of alkenes with molecular oxygen was developed through the addition of NHPI to styrene derivatives. While the use of a variety of metal catalysts, including $Co(OAc)_2$, $Fe(acac)_3$, $Mn(OAc)_2{\cdot}4H_2O$, $VO(acac)_2$, CrO_3, $CuCl_2$, $Cu(acac)_2$, and CuCl could be used in the reaction, we found that styrene, combined with NHPI and 5 mol % $[Cu(MeCN)_4]ClO_4$ under an atmosphere of O_2 (balloon) in MeCN, provided the α-oxygenated ketone **1a** in 86% yield after 12 h (Scheme 1). Leaving the reaction open to air also produced the desired oxidation products, but in lower yield and only after increased reaction time.

Scheme 1. Optimized Reaction Conditions



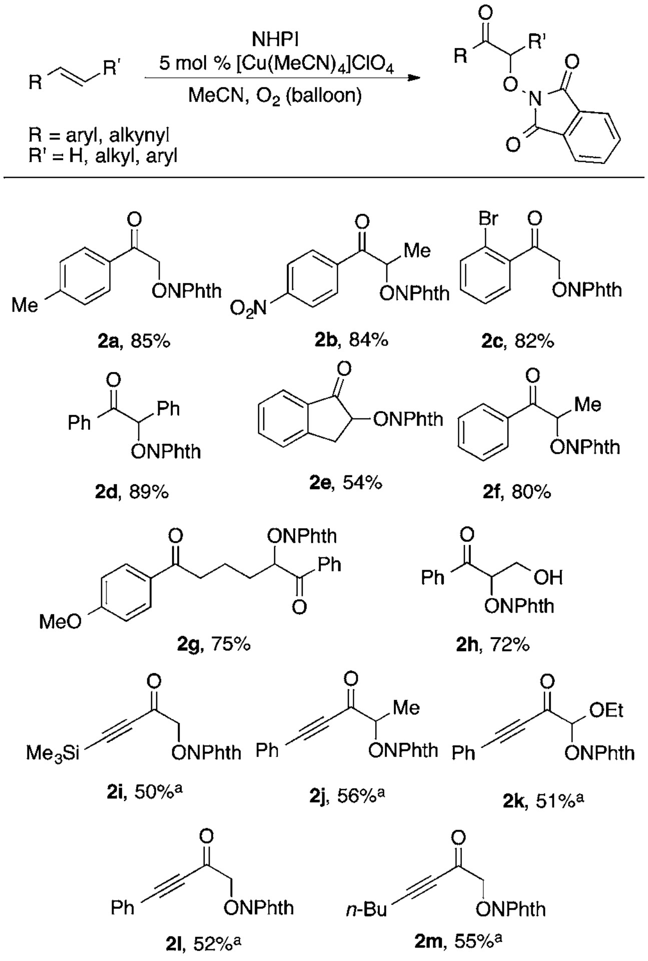
1a, 86%

The reaction likely proceeds according to the mechanism postulated by Punniyamurthy and co-workers.[20] Under an oxygen atmosphere, Cu(I) is likely to be oxidized to Cu(II),[21] which is the active catalyst. Based on their isotopic labeling and radical trapping experiments, they determined that the reaction is initiated by the generation of a nitroxyl radical,[22] which undergoes addition to the alkene to give a stabilized, carbon-centered radical.[23] This radical is then trapped with molecular oxygen, and subsequent decomposition occurs to form the ketone.[24−26] The formation of a stabilized carbon radical is further supported by the substrate scope of the reaction (vide infra).

Received: April 16, 2015
Published: May 8, 2015

DOI: 10.1021/acs.orglett.5b01120
Org. Lett. 2015, 17, 2704−2707

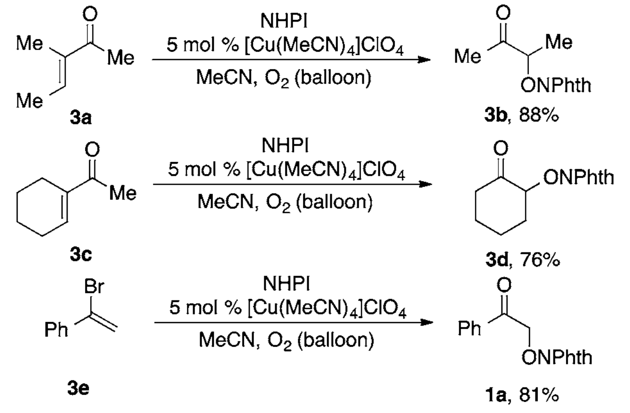
Scheme 2. Oxidation of Styrenes and Enynes



[a]Using 20 mol % [Cu(MeCN)$_4$]ClO$_4$.

A variety of aromatic alkenes and enynes were suitable substrates for the oxidation (Scheme 2). Styrenes with electron-donating and electron-withdrawing substituents on the aromatic ring were tolerated under the reaction conditions, furnishing oxidized products **2a** and **2b** in 85% and 84% yield, respectively. The cyclic alkene indene was also a viable substrate, providing the α-oxygenated ketone **2e** in 54% yield. Styrenes containing a carbonyl group were also oxidized to give the corresponding α-oxygenated ketone product **2g** in 75% yield. Free hydroxyl groups were tolerated, as evidenced by the formation of ketone **2h** in 72% yield with no indication of oxidation of the hydroxyl group. The oxidation of enynes required an increase in catalyst loading (20 mol %) to provide the α-oxygenated ketones in appreciable yields. The use of 5 mol % [Cu(MeCN)$_4$]ClO$_4$ resulted in low yields and long reaction times. Enynes bearing alkyl, phenyl, and silyl substituents were oxidized to give the corresponding ketones **2i**–**2m** in 50–56% yield.

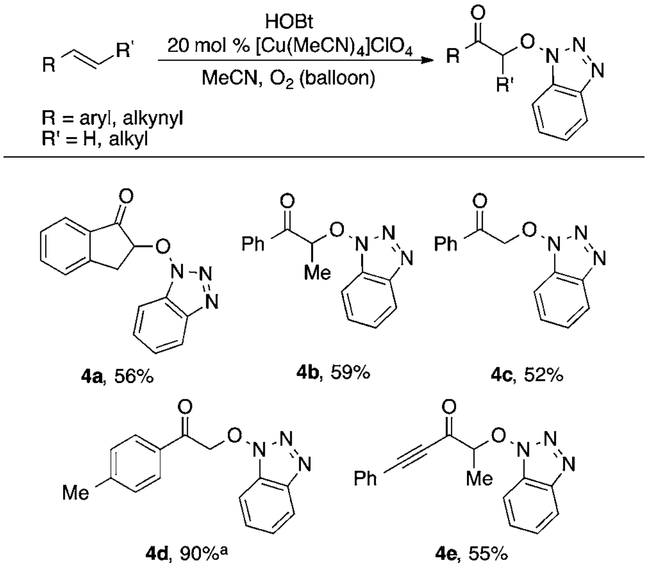
Scheme 3. Oxidation of Enones and α-Bromostyrene



In addition to styrenes and enynes, enones were found to give oxidized products under the optimized conditions (Scheme 3). The oxidation of enone **3a** led to the deacetylated ketone **3b** in 88% yield. Similarly, the cyclic enone **3c** was also deacetylated under the reaction conditions to afford the ketone **3d** in 76% yield. Deacetylation likely proceeds through a mechanism resembling the copper-catalyzed oxidative cleavage of β-ketoesters.[27,28] Ketone **1a** can also be obtained in 81% yield through the oxidation of α-bromostyrene, likely formed by hydrolysis of a mixed peroxyacetal intermediate.[29]

With the role of NHPI established in the oxidation, we sought to explore other hydroxylamines that would effect similar oxidations. The oxidation of styrenes using HOBt also produced α-oxygenated ketones. Treatment of styrenes with 20 mol % [Cu(MeCN)$_4$]ClO$_4$ under an oxygen atmosphere gave the desired ketones **4a**–**4d** in 52–90% yield (Scheme 4).

Scheme 4. Oxidations with HOBt



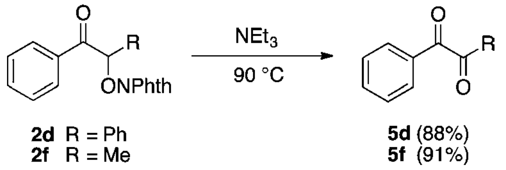
[a]Yield determined by ^{1}H NMR spectroscopic analysis with DMF as an internal standard.

Ketone **4e** was produced from the corresponding enyne in 55% yield. This reaction indicates that the oxidation of enynes under these reaction conditions may also be general. These results show that the oxygen-centered radical derived from HOBt exhibits much of the same reactivity as the nitroxyl radical of NHPI.

The α-oxygenated ketone products formed in Schemes 2 and 4 can serve as precursors to other synthetically useful compounds. Treatment of α-alkyl substituted ketones, such as **2d** and **2f**, with NEt$_3$ at 90 °C led to the formation of 1,2-diketones **5d** and **5f** in high yield (Scheme 5).[30] Punniyamurthy and co-workers have demonstrated that ketones **2a** and **2d** undergo Baeyer–Villiger reactions and that the phthalimide

DOI: 10.1021/acs.orglett.5b01120
Org. Lett. 2015, 17, 2704–2707

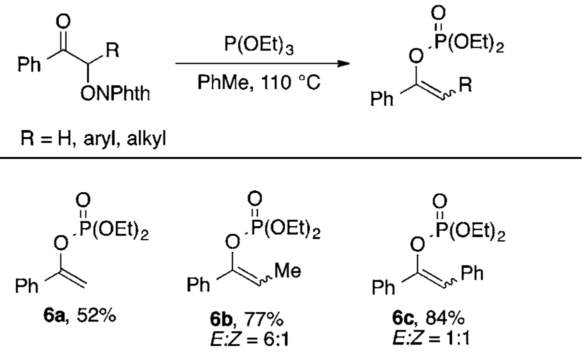
Scheme 5. Formation of 1,2-Diketones



group can be removed upon treatment with hydrazine to yield alkoxyamines.[20]

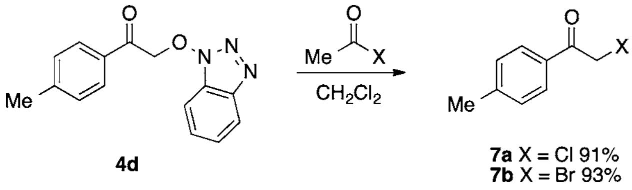
The α-oxygenated ketones also serve as precursors to vinyl phosphates, which are useful substrates for a variety of metal-catalyzed cross-coupling reactions.[31] The treatment of α-oxygenated ketone **1a** with triethyl phosphite in toluene at 110 °C formed the vinyl phosphate **6a** in 52% yield (Scheme 6).[32,33] Under the same conditions, oxidized ketones **2f** and **2d** gave vinyl phosphates **6b** and **6c** as mixtures of alkene isomers in 77% and 84% yields, respectively. These results led us to believe that the phthalimide moiety could be treated as a pseudohalide. Numerous nucleophilic substitutions were attempted, but all were unsuccessful in displacing the phthalimide moiety, however.

Scheme 6. Formation of Vinyl Phosphates



By contrast, the hydroxybenzotriazole moiety engaged smoothly in nucleophilic displacement reactions (Scheme 7).

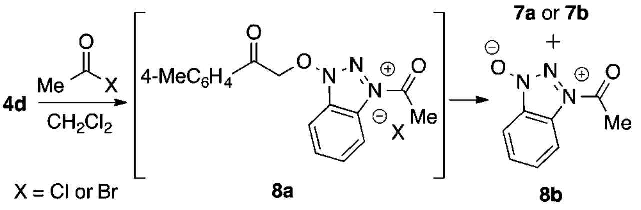
Scheme 7. Formation of α-Bromo and α-Chloro Ketones



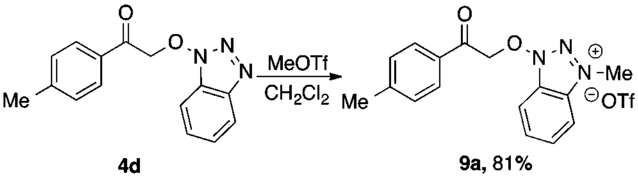
The reactions of ketone **4d** with acetyl chloride or acetyl bromide provided the α-haloketones **7a** and **7b** in high yield. We hypothesized that the acetyl halide reacted with the nucleophilic N3 nitrogen of the benzotriazole group,[34] forming species **8a** (Scheme 8). The liberated halide anion then displaced the benzotriazolyl moiety, resulting in the formation of **7a** or **7b** and the zwitterionic species **8b**. This hypothesis was further supported by the lack of reactivity of **4d** upon treatment with sodium iodide. With this initial success, we explored other means of activating the benzotriazole group.

Activation of the benzotriazole moiety with methyl triflate provided an isolable, reactive substrate that underwent a variety of nucleophilic displacement reactions. Treatment of ketone **4d** with 1.2 equiv of methyl triflate provided the triflate salt **9a** in 81% yield in 1 h (Scheme 9). The salt **9a** could be used in nucleophilic displacement reactions without further purification. Subjecting the salt **9a** to Finkelstein reaction conditions[35,36] furnished the α-iodo ketone **10a** in 93% yield (Scheme 10). Nitrogen and sulfur nucleophiles were also successful in displacing the methylated benzotriazole moiety (Scheme 11). Using sodium azide as the nucleophile led to the α-azido ketone **11a** in 89% yield. Potassium ethyl xanthate could be used to provide the xanthate ester **11b** in 86% yield. While much is known about the ability of the benzotriazole group to act as a leaving group in a variety of reactions,[37,38] its *N*-hydroxy derivative remains unexplored as a leaving group. These data (vide supra) suggest that HOBt derivatives such as

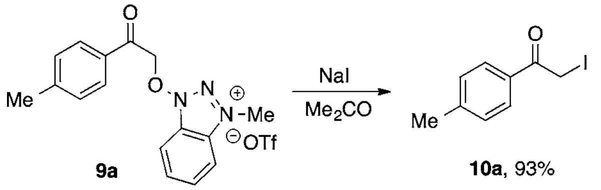
Scheme 8. Formation of Zwitterionic Leaving Group



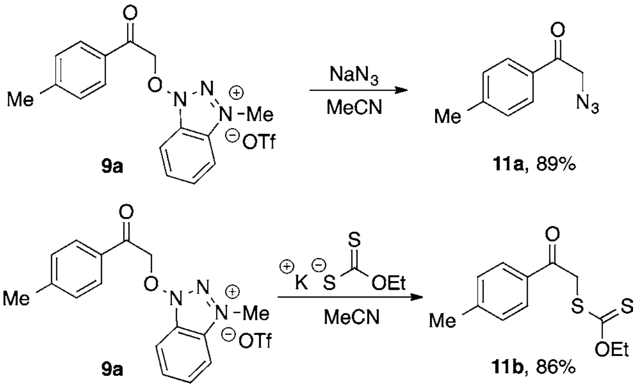
Scheme 9. Activation of HOBt with MeOTf



Scheme 10. Finkelstein Reaction of Activated HOBt Derivative



Scheme 11. Displacement of Activated HOBt Derivatives with Nitrogen and Sulfur Nucleophiles



4d, upon activation, may display some of the same characteristics as benzotriazole derivatives.

In conclusion, we have demonstrated the copper(I)-catalyzed oxidation of alkenes using molecular oxygen and the hydroxylamines NHPI or HOBt. The oxidation likely proceeds through a radical process in which molecular oxygen is incorporated into the resulting ketone. The reaction is general for both styrenes and enynes. The resulting oxidized products serve as precursors to a variety of synthetically useful compounds, such as 1,2-diketones, vinyl phosphates, and α-haloketones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01120.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kwoerpel@nyu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the National Science Foundation (CHE-0848121). M.R.M. acknowledges a Margaret Strauss Kramer Fellowship from the NYU Department of Chemistry. The Bruker Avance-400 MHz Spectrometer was acquired through the support of the National Science Foundation (CHE-01162222). We thank Dr. Chin Lin (NYU) for assistance with NMR spectroscopy and mass spectrometry.

■ REFERENCES

(1) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(2) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287.
(3) Chen, S.; Liu, Z.; Shi, E.; Chen, L.; Wei, W.; Li, H.; Cheng, Y.; Wan, X. *Org. Lett.* **2011**, *13*, 2274.
(4) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329.
(5) Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134.
(6) Hill, C. L. *Nature* **1999**, *401*, 436.
(7) Chung, A.; Miner, M. R.; Richert, K. J.; Rieder, C. J.; Woerpel, K. A. *J. Org. Chem.* **2015**, *80*, 266.
(8) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.
(9) Hwang, Y. H.; Cheng, C. P. *J. Chem. Soc., Chem. Commun.* **1992**, 317.
(10) Tan, K. J.; Wille, U. *Chem. Commun.* **2008**, 6239.
(11) Hwang, Y. H.; Cheng, C. P. *J. Chem. Soc., Chem. Commun.* **1992**, 317.
(12) Ozaki, S.; Hamaguchi, T.; Tsuchida, K.; Kimata, Y.; Masui, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 951.
(13) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736.
(14) Wang, A.; Jiang, H.; Li, X. *J. Org. Chem.* **2011**, *76*, 6958.
(15) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284.
(16) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 13320.
(17) Schmidt, V. A.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4491.
(18) Schmidt, V. A.; Alexanian, E. J. *Chem. Sci.* **2012**, *3*, 1672.
(19) Döbler, C.; Mehltretter, G.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3026.
(20) Bag, R.; Sar, D.; Punniyamurthy, T. *Org. Lett.* **2015**, *17*, 2010.
(21) Karlin, K. D.; Gultneh, Y. Binding and Activation of Molecular Oxygen by Copper Complexes. In *Progress In Inorganic Chemistry*; Lippard, S. J., Eds.; Wiley: Hoboken, NJ, 1987; Vol. 35, p 219.
(22) Coseri, S. *Catal. Rev.* **2009**, *51*, 218.
(23) Hioe, J.; Zipse, H. Radical Stability-Thermochemical Aspects. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Hoboken, NJ, 2012; Vol. 1, p 449.
(24) Hiatt, R.; Irwin, K. C.; Gould, C. W. *J. Org. Chem.* **1968**, *33*, 1430.
(25) Hiatt, R.; Mill, T.; Irwin, K. C.; Castleman, J. K. *J. Org. Chem.* **1968**, *33*, 1428.
(26) Sakaguchi, S.; Kato, S.; Iwahama, T.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1237.
(27) Cossy, J.; Belotti, D.; Bellosta, V.; Brocca, D. *Tetrahedron Lett.* **1994**, *35*, 6089.
(28) Steward, K. M.; Johnson, J. S. *Org. Lett.* **2011**, *13*, 2426.
(29) Hurlocker, B.; Miner, M. R.; Woerpel, K. A. *Org. Lett.* **2014**, *16*, 4280.
(30) Consonni, P.; Favara, D.; Omodei-Salé, A.; Bartolini, G.; Ricci, A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 967.
(31) Sellars, J. D.; Steel, P. G. *Chem. Soc. Rev.* **2011**, *40*, 5170.
(32) Perkow, W.; Ullerich, K.; Meyer, F. *Naturwissenschaften* **1952**, *39*, 113.
(33) Borowitz, I. J.; Firstenberg, S.; Borowitz, G. B.; Schuessler, D. *J. Am. Chem. Soc.* **1972**, *94*, 1623.
(34) Sohn, C. H.; Lee, J. E.; Sweredoski, M. J.; Graham, R. L. J.; Smith, G. T.; Hess, S.; Czerwieniec, G.; Loo, J. A.; Deshaies, R. J.; Beauchamp, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 2672.
(35) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528.
(36) Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645.
(37) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.
(38) Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564.