Tetrahedron Letters 54 (2013) 6407–6410

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Osmium (VI) catalyzed chemoselective oxidation of allylic and benzylic alcohols ☆

Shekaraiah Devari [a,b], Ramesh Deshidi [a,b], Manjeet Kumar [b], Arvind Kumar [a,b], Simmi Sharma [b], Masood Rizvi [c], Manoj Kushwaha [d], Ajai Prakash Gupta [d], Bhahwal Ali Shah [a,b,*]

[a] Academy of Scientific and Innovative Research, India
[b] Natural Product Microbes, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-Tawi, J&K 180001, India
[c] Department of Chemistry, University of Kashmir, Hazaratbal, J&K, India
[d] Quality Assurance and Quality Control Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-Tawi, J&K 180001, India

ARTICLE INFO

Article history:
Received 27 July 2013
Revised 4 September 2013
Accepted 11 September 2013
Available online 18 September 2013

Keywords:
Oxidation
$K_2[OsO_2(OH)_4]$
Chloramine-T
Allylic alcohols
Chemoselective

ABSTRACT

A mild and highly chemoselective approach to oxidation of allylic, electron rich/deficient benzylic, and heterocyclic alcohols employing catalytic quantities of $K_2[OsO_2(OH)_4]$ (3 mol %) and chloramine-T (50 mol %) is described. The protocol offers short reaction times (25 min–2 h), controlled oxidation, and tolerance to a variety of substrates. A systematic mechanistic study based on the LC-ESI-MS/MS reveals the presence of imidotriooxoosmium species which further reacts with alcohol to give the oxidized product.

One of the key transformations in organic synthesis is the chemoselective oxidation of alcohols to corresponding carbonyl compounds. Over the years numerous oxidation methods such as TEMPO,[1] Swern,[2] Dess-Martin periodinane,[3] IBX,[4] MnO_2,[5] etc., have been reported. Precious metal catalysts such as Pd,[6] Ru,[7] Au,[8] and Pt[9] have also been employed for the same, which generally involve relatively large amounts of the catalyst and most of the time results in over oxidation. Despite many advances in the oxidation methods, chemoselective oxidation of alcohols particularly allylic and benzylic alcohols still remains challenging. To address this issue several methods like DDQ/$NaNO_2$,[10] DDQ/$(MnOAc)_3$,[11] NBS/thiourea,[12] and vanadium complexes[13] have been developed in recent years. Osmium (VI), used routinely for dihydroxylation of olefins,[14] synthesis of triols from allyl alcohols,[15] and amino hydroxylation with chloramine-T,[16] has also been employed in the oxidation of allylic alcohols by activating it with either quinuclidine and copper salts[17] or DABCO.[18] However, the reactions are not chemoselective for allylic/benzylic alcohols and they use large quantities of ligands and take long time to complete i.e., >24 h. We reasoned that if quinuclidine or DABCO can be used as ligand for oxidation with $K_2[OsO_2(OH)_4]$, a chloramine-T catalyzed process could also be established. In this Letter, we report a highly chemoselective oxidation of allylic and benzylic alcohols catalyzed by Os (VI) and chloramine T at rt in neutral reaction medium and in the presence of air. The simplicity of the protocol, short reaction times (25 min–2 h), tolerance to a variety of substrates specially electron deficient benzyl alcohols, and controlled oxidation are some of the added advantages over the existing methods.

Initial investigation of Os (VI) and chloramine-T catalyzed oxidation was studied using benzyl alcohol as a model substrate to establish the reaction parameters. The reaction of benzyl alcohol in the presence of 10 mol % $K_2[OsO_2(OH)_4]$ and 0.5 equiv chloramine-T in *t*BuOH:H_2O (1:1) for 45 min gave benzaldehyde in 96% yields (Table 1, entry 1). To show the utility of the present reaction system for the oxidation of alcohols we focussed our attention on optimizing the reaction conditions by decreasing the loading of expensive metal catalyst (Table 1). The lowering of catalyst, $K_2[OsO_2(OH)_4]$ from 10 to 3 mol %, did not significantly alter the reaction yields, however, though inconsequential, there was a slight increase in reaction times (Table 1, entries 2 and 3). Nevertheless, further decreasing the amount of catalyst to 1 mol % led to a significant drop in the yields (63%) (Table 1, entry 4) with longer reaction time. Increasing the amount of chloramine-T from 0.5 to 2 equiv showed no significant effect on the yield or time (Table 1, entries 5 and 6). Thus, catalyst loading of 3 mol % with 0.5 equiv of

---

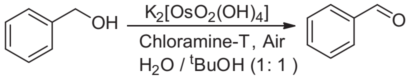
☆ CSIR-IIIM Communication No. **IIIM/1590/2013**.

* Corresponding author. Tel.: +91 (191) 2569000 010; fax: +91 (191) 2569333/2569017.

E-mail addresses: bhahwal@gmail.com, bashah@iiim.ac.in (B.A. Shah).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.036

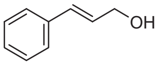
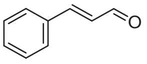
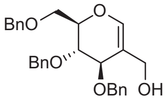
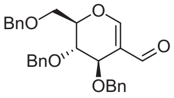
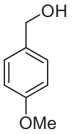
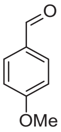
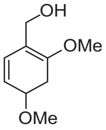
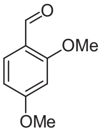
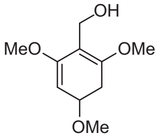
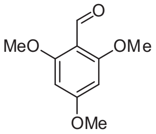
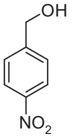
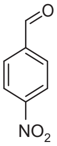
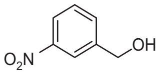
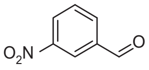
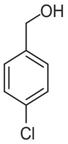
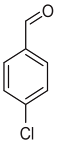
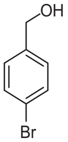
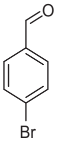
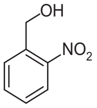
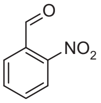
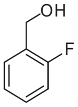
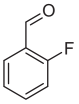
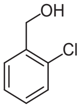
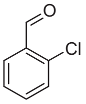
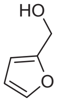
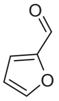
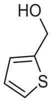
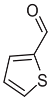
Table 1
Optimization of Os (VI) catalyzed oxidation



Entry	Os (VI)[a] (mol %)	Ch-T[b] (equiv)	Temp (°C)	Time	Yield (%)
1	10	0.5	rt	45 min	96
2	5	0.5	rt	50 min	93
3	3	0.5	rt	1 h	92
4	1	0.5	rt	2 h	63
5	1	1	rt	2 h	67
6	1	2	rt	2 h	66
7	3	1	rt	1 h	94
8	3	0.5	0	12 h	<10
9	3	0.5	50	1.5 h	70
10	3	0.5	100	1 h	65
11	10	0	rt	12 h	NR
12	0	10	rt	12 h	NR

[a] Os (VI) = $K_2[OsO_2(OH)_4]$.
[b] Ch-T = chloramine-T; NR = no reaction.

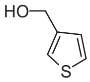
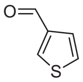
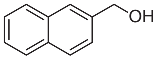
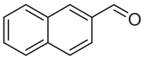
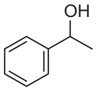
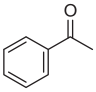
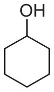
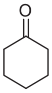
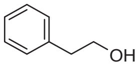
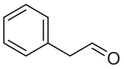
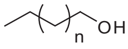
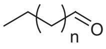
Table 2
Oxidation of allylic/benzylic alcohols catalyzed by $K_2[OsO_2(OH)_4]$ and chloramine-T

Entry	Substrate	Product	Time	Yields (%)
1			100 min	92
2			120 min	89
3			45 min	90
4			30 min	96
5			25 min	99
6			120 min	79
7			120 min	82
8			120 min	88
9			90 min	86
10			120 min	55
11			120 min	58
12			90 min	61
13			120 min	78
14			120 min	80

chloramine-T was found to be the condition of choice. The effect of temperature variation on reaction was also monitored; both the increase and decrease in the reaction temperature lead to the loss of yields (Table 1, entries 8–10). To confirm the necessity of both the components for reaction, we carried out the reaction of benzyl alcohol alone in the presence of Os (VI) catalyst as well as chloramine-T, which resulted in no product formation (Table 1, entries 11 and 12). Even increasing their loading and increasing reaction times resulted in no product formation, thereby implying that both the components are necessary for reaction to take place.

Using the optimized reaction conditions, the substrate scope of the oxidation reaction was then examined (Table 2). The reaction of cinnamyl alcohol and carbohydrate precursor, tri-*O*-benzyl-d-glucal-3-ylmethanol gave the corresponding aldehydes in 92% and 89% yields, respectively (Table 2 entries 1 and 2) without formation of amino or di-hydroxylated side products. Next we focused our attention toward oxidation of various substituted/unsubstituted benzylic alcohols. The reaction of electron rich alcohols like 4-methoxy, 2,4-dimethoxy, and 2,4,6-trimethoxy benzyl alcohols gave corresponding aldehydes in excellent yields and less reaction times (Table 2, entries 3–5), as electron donating substituents are known to activate the benzyl alcohols. Despite the fact that electron withdrawing substituents are considered to be deactivating groups in oxidation reaction, the reaction of *p*-nitro and *m*-nitro benzyl alcohols to the corresponding aldehydes (Table 2, entries 6, and 7) proceeded efficiently giving products in 79% and 82% yields, respectively. It would be pertinent to mention that electron deficient benzyl alcohols having nitro substituents have been found inert to oxidation in some cases.[24] The reaction of *p*-chloro and *p*-bromo benzyl alcohols also gave corresponding aldehydes in good quantities (Table 2 entries 8 and 9). Ortho substituted benzyl alcohols (Table 2 entries 10–12) oxidized slowly and gave lower yields as compared to meta and para substituted compounds, which may be possibly due to enhanced deactivation of ring system at ortho position. The oxidation of heterocyclic alcohols like 2-furfuryl methanol, 2-thiophenyl methanol, and 3-thiophenyl methanol also proceeded smoothly to give corresponding products in quantitative yields (Table 2 entries 13–15). The reaction can also be conveniently extended to bicyclic system such as β-naphthyl alcohol (Table 2, entry 16) and secondary benzyl alcohol like 1-phenyl ethanol (Table 2, entry 17) to give corresponding products in good yields. Non-allylic alcohols

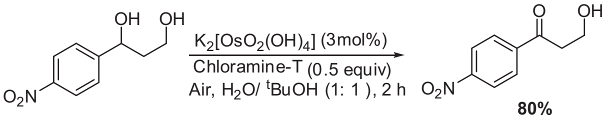
Table 2 (*continued*)

Entry	Substrate	Product	Time	Yields (%)
15			120 min	73
16			60 min	83
17			120 min	91
18			24 h	0
19			24 h	0
20	 n = 5,6,8	 n = 5,6,8	24 h	0

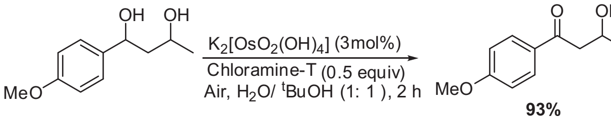
(Table 2 entries 18–20) were found inert to oxidation even up to 24 h, reinforcing the fact that the reaction is highly selective for benzylic and allylic alcohols.

To check the chemoselectivity of our reaction system we studied the competitive oxidation of two different alcohols. First, the oxidation of diols such as 1-(*p*-nitrophenyl)-propane-1,3-diol[19] (Eq. 1) containing a terminal primary hydroxyl group and 1-(4-methoxyphenyl)butane-1,3-diol[19] (Eq. 2) that resulted in the selective oxidation of secondary benzylic alcohol. Next we explored the chemoselective oxidation of a mixture of benzyl alcohol and cyclohexanol (Eq. 3) and 1-phenyl ethanol and 2-phenyl ethanol (Eq. 4) resulting in complete oxidation of benzyl alcohol and 1-phenyl ethanol, with no product formation from cyclohexanol and 2-phenyl ethanol. A similar trend was observed with cinnamyl alcohol and 1-undecanol (Eq. 5) and glucal derivative and cyclohexanol (Eq. 6), where both the cinnamyl alcohol and glucal derivative gave the corresponding aldehydes, whereas 1-undecanol and cyclohexanol remained unoxidized.

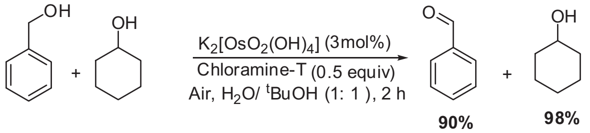
In an attempt to go through mechanistic insight, necessity of each component was investigated by LC-ESI-MS/MS monitoring of oxidation reaction of benzyl alcohol (Fig. 1). Initially, $K_2[OsO_2(OH)_4]$ was added to *t*-BuOH:H_2O (Table 1, entries 11 and 12), and stirred for two minutes followed by addition of chloramine-T (m/z 203.9 $[M-Na]^-$ at t_R10.18 min) and benzyl alcohol. After stirring for ten minutes LC-ESI-MS/MS analysis was performed. The reaction revealed the formation of imidotriooxoosmium (VIII) (I) species indicated by m/z 408.70 $[M+H]^+$ at t_R 11.84 min and also confirmed by daughter ion peak of detosylated Os (VIII) complex at m/z 276.40 $[M+Na]^+$ at t_R 6.86 min (Fig. 2). In the next step, benzyl alcohol undergoes nucleophilic addition on osmium (VIII) center followed by intramolecular proton transfer from the hydroxyl group to nitrogen confirmed by m/z 518.70 $[M+H]^+$ at t_R 4.52 min (II) and detosylated daughter ion peak at m/z 362.70 $[M+Na]^+$ at t_R 7.41 min (Fig. 2). The rearrangement is followed by the exclusion of benzaldehyde and regeneration of active catalyst. Benzaldehyde formed as final product was identified as *N*-benzyl anisidine (m/z 214.0 $[M+H]^+$ at t_R 4.28 min) by adding *p*-anisidine followed by reduction with $NaBH_4$.



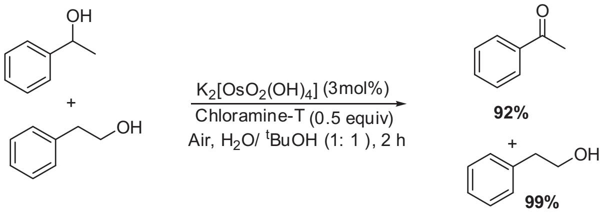
(1)



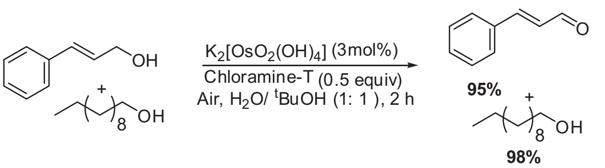
(2)



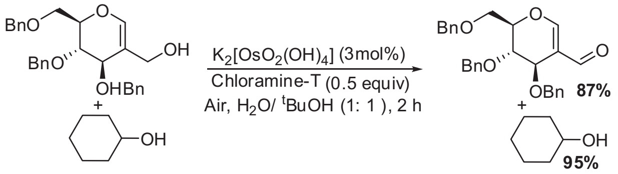
(3)



(4)



(5)



(6)

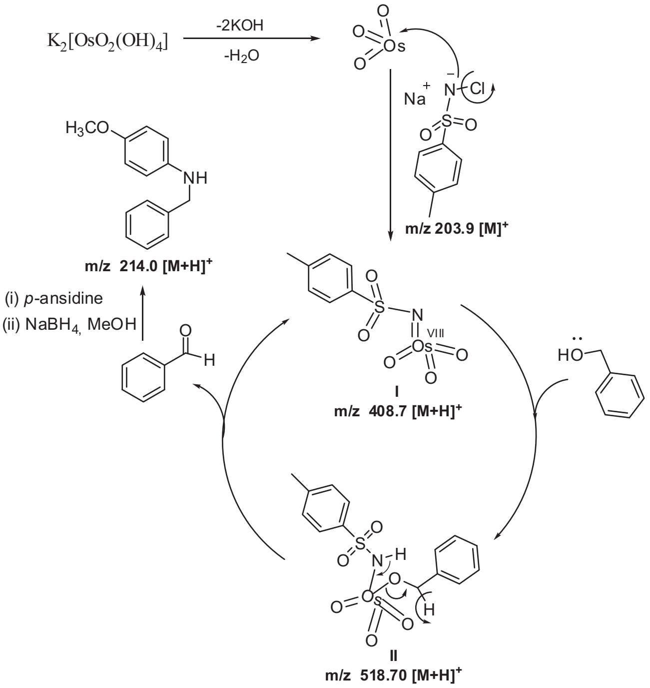


Figure 1. Plausible mechanism of Os (VI) and chloramine-T catalyzed oxidation.

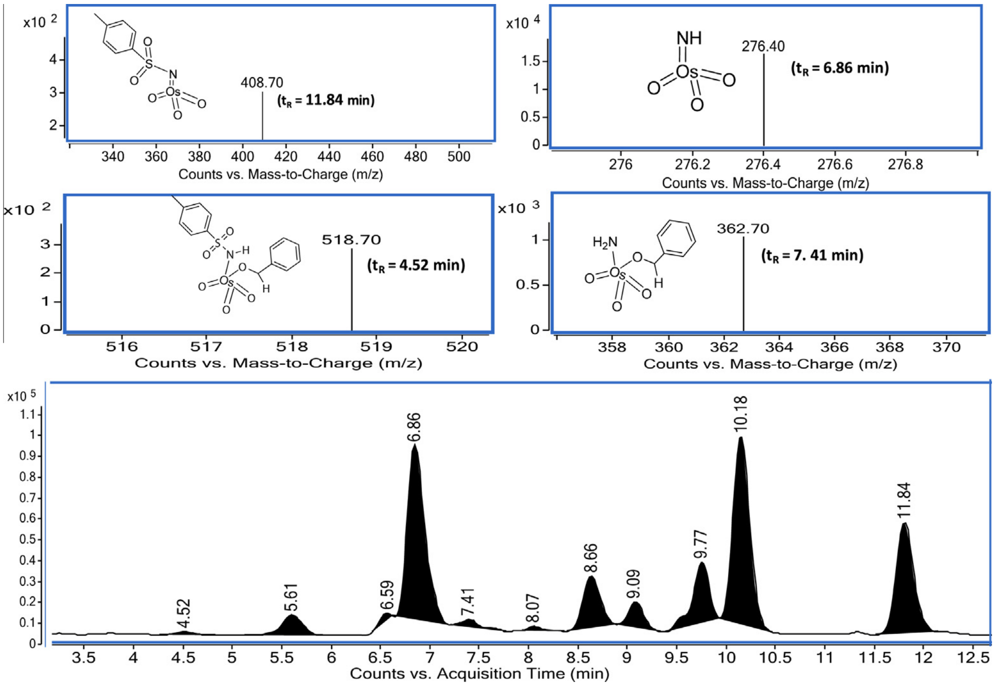


Figure 2. LC-ESI-MS/MS analysis to investigate mechanism of oxidation of benzyl alcohol with $K_2[OsO_2(OH)_4]$ and chloramine-T after 10 min; LC spectra of active species (**I**) in reaction mixture along with MS spectra for peak at t_R 11.84 min and daughter ion peak at t_R 6.86 min; active species (**II**) (formation of **II** from **I**) including MS spectra for peak at t_R 4.52 min and daughter ion peak at t_R 7.41 min.

In conclusion, we have successfully developed a mild, efficient, and highly chemoselective method for oxidation of allylic and benzylic alcohols using a mixture of Os (VI) and chloramine-T in catalytic amount. Thus, owing to its high selectivity, short reaction times and, tolerability to a wide range of substrates, the method should serve as a useful protocol for chemoselective oxidation in a myriad multistep organic synthesis.

Acknowledgements

We thank DST, New Delhi for financial assistance. Also S.D., D.R. and M.K. thank UGC and CSIR, New Delhi for the award of Junior Research Fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.036.

References and notes

1. (a) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499–3548; (b) Miller, R. A.; Hoerrner, R. S. *Org. Lett.* **2003**, *5*, 285–287; (c) Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2006**, *71*, 7087–7090; (d) Mase, N.; Mizumori, T.; Tatemoto, Y. *Chem. Commun.* **2011**, *47*, 2086–2088; (e) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910.
2. (a) Bisai, A.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 8355–8357; (b) Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634–9635.
3. (a) Burkhart, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1988**, *29*, 3433–3436; (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552; (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Venkat Narsaiah, A. *Tetrahedron* **2004**, *60*, 2131–2135; (d) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524–1552.
4. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185; (b) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.
5. (a) Lou, J.-D.; Xu, Z.-N. *Tetrahedron Lett.* **2002**, *43*, 6149–6150; (b) Kamimura, A.; Nozaki, Y.; Ishikawa, S.; Inoue, R.; Nakayama, M. *Tetrahedron Lett.* **2011**, *52*, 538–540.
6. (a) Dijksman, A.; Marino-Gonzalez, A.; Mairata, I. P. A.; Arends, I. W.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826–6833; (b) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034–3035; (c) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810–3813; (d) Muzart, J. *Tetrahedron* **2003**, *59*, 5789–5816; (e) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355.
7. Matsushita, T.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **1999**, 265–266.
8. (a) Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004–18005; (b) Davis, S. E.; Ide, M. S.; Davis, R. J. *Green Chem.* **2013**, *15*, 17–45; (c) Mikami, Y.; Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. Catal *Sci. Technol.* **2013**, *3*, 58–69.
9. (a) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302–8303; (b) Chibani, S.; Michel, C.; Delbecq, F.; Pinel, C.; Besson, M. Catal *Sci. Technol.* **2013**, *3*, 339–350.
10. Wang, L.; Li, J.; Yang, H.; Lv, Y.; Gao, S. *J. Org. Chem.* **2012**, *77*, 790–794.
11. Cosner, C. C.; Cabrera, P. J.; Byrd, K. M.; Thomas, A. M.; Helquist, P. *Org. Lett.* **2011**, *13*, 2071–2073.
12. Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592–1598.
13. Hanson, S. K.; Wu, R.; Silks, L. A. *Org. Lett.* **2011**, *13*, 1908–1911.
14. (a) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187–213; (b) Dobler, C.; Mehltretter, G.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3026–3028; (c) Mehltretter, G. M.; Döbler, C.; Sundermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083–8087; (d) Davis, A. S.; Ritthiwigrom, T.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 4868–4879.
15. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (b) Batt, F.; Piva, O.; Fache, F. *Tetrahedron Lett.* **2008**, *49*, 566–568.
16. (a) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177–179; (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451–454; (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810–2813; (d) Harris, L.; Mee, S. P.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. *J. Org. Chem.* **2011**, *76*, 358–372.
17. Muldoon, J.; Brown, S. N. *Org. Lett.* **2002**, *4*, 1043–1045.
18. Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Eckert, M.; Militzer, H.-C.; Beller, M. *Tetrahedron Lett.* **2001**, *42*, 8447–8449.
19. Kumar, M.; Shah, B. A.; Taneja, S. C. *Adv. Synth. Catal.* **2011**, *353*, 1207–1212.