Angewandte
International Edition Chemie

Synthetic Methods

DOI: 10.1002/anie.201204286

Baeyer–Villiger Oxidation and Oxidative Cascade Reactions with Aqueous Hydrogen Peroxide Catalyzed by Lipophilic $Li[B(C_6F_5)_4]$ and $Ca[B(C_6F_5)_4]_2$**

*Muhammet Uyanik, Daisuke Nakashima, and Kazuaki Ishihara**

The Baeyer–Villiger (BV) oxidation is one of the most important transformations in organic synthesis, because valuable lactones and esters can be obtained directly from the corresponding ketones.[1] Classically, percarboxylic acids (that is, *meta*-chloroperbenzoic acid (*m*CPBA), peracetic acid, etc.) are used for BV oxidation.[1] However, the use of percarboxylic acids results in the formation of one equivalent of the corresponding carboxylic acid or its salt as waste. Moreover, percarboxylic acids are expensive and/or shock sensitive. Therefore, current research is focused on the replacement of percarboxylic acids with more atom-economic and milder oxidants like aqueous hydrogen peroxide.[1c,2] There have been some successful examples of the BV oxidation of ketones with aqueous hydrogen peroxide promoted by Lewis acids (Pt^{II}, Sn^{IV}, Sc^{III}, etc.),[3] Brønsted acids (TsOH, etc.),[4] tin-containing zeolites,[5] hydrotalcites,[6] selenides,[7] and flavin-based organocatalysts.[8] Despite the considerable progress in this field, the development of a more selective and efficient BV oxidation under mild reaction conditions is still required.[1,9] We envisaged that water- and oxidant-tolerant lipophilic acids might be good candidates as catalysts of the BV oxidation with aqueous hydrogen peroxide.

Fluorinated tetraarylborates such as tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, $[B\{3,5\text{-}(CF_3)_2C_6H_3)_4\}]^-$, and tetrakis(pentafluorophenyl)borate, $[B(C_6F_5)_4]^-$, are usually used as weakly coordinating counter anions for transition metal catalysts to enhance their acidity and/or solubility.[10] However, there have only been a few studies on the use of Group 1 and Group 2 metal salts of these borates.[11] In 2000, Sonoda, Mori and co-workers used dehydrated $Li[B\{3,5\text{-}(CF_3)_2C_6H_3\}_4]$ as a Lewis acid catalyst for the Diels–Alder reaction.[11a] In the same year, Mukaiyama and co-workers reported the use of $Li[B(C_6F_5)_4]$ for the benzylation of aromatic compounds and alcohols.[11b,c] Later, Liu and co-workers used $Na[B\{3,5\text{-}(CF_3)_2C_6H_3\}_4]\cdot 2\,H_2O$ for the polymerization of vinyl ethers,[11d] the Mannich reaction,[11e] Friedel–Crafts addition,[11f] and the hydrolysis of acetals.[11g] However, to the best of our knowledge, these alkali or alkaline earth metal tetraarylborates have never been used for oxidation reactions.

Fluorinated tetraarylborates are highly lipophilic,[10] therefore we envisioned that their alkali or alkaline earth metal salts might exhibit efficient catalytic activity for the BV oxidation with aqueous hydrogen peroxide under biphasic conditions. Thus, we expected these salts to promote both the nucleophilic attack of hydrogen peroxide to the carbonyl group and the subsequent rearrangement of a Criegee intermediate through acid activation of the carbonyl group in the organic phase or at the phase interface. In sharp contrast, conventional hydrophilic Lewis or Brønsted acids serve as catalysts in the aqueous phase or at the phase interface, and consequently lead to not only BV oxidation to give lactones, but also to the subsequent hydrolysis of lactones. Furthermore, when unsaturated ketones were used as starting materials in the presence of conventional acid catalysts, epoxidation competed with the BV oxidation.[3,4] We report herein that Lewis acidic and lipophilic alkali or alkaline earth metal borates, such as $Li[B(C_6F_5)_4]$ or $Ca[B(C_6F_5)_4]_2$, are extremely active catalysts for the selective BV oxidation of various cycloalkanones with 30 wt % aqueous hydrogen peroxide.

A preliminary examination of the use of commercially available $Li[B(C_6F_5)_4]$ (1 mol %) in the BV oxidation of cyclopentanone (**1a**) with 1.1 equivalents of 30 wt % H_2O_2 in dichloroethane (DCE) at 50 °C afforded δ-valerolactone (**2a**) in 94 % yield (Table 1, entry 1).[12] In contrast, other conventional lithium salts, that is, $LiNTf_2$, $LiBF_4$, and $LiBPh_4$, exhibited very poor catalytic activities under similar reaction conditions (Table 1, entries 2–5). To our delight, the catalyst loading of $Li[B(C_6F_5)_4]$ could be reduced to 0.1 mol % without affecting the chemical yield (Table 1, entry 5). Moreover, the Ca^{II} salt, $Ca[B(C_6F_5)_4]_2$, which was easily prepared by a cation exchange reaction from the corresponding Li^I salt,[13] showed higher catalytic activity (Table 1, entry 6).

It was expected that the hydrated metal complexes, $M[B(C_6F_5)_4]_m\cdot(H_2O)_n$ might act as a Lewis acid assisted Brønsted acid (LBA)[14] catalyst under aqueous reaction conditions. After screening several Brønsted acids as alternative co-catalysts to water, we found that the reaction rate was significantly accelerated with the addition of oxalic acid (Table 1, entry 7).[13] Notably, no reaction occurred in the presence of oxalic acid only (Table 1, entry 8). Therefore, an in situ generated highly reactive LBA species,

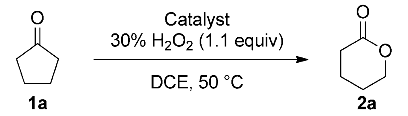
---

[*] Dr. M. Uyanik, D. Nakashima, Prof. Dr. K. Ishihara
Graduate School of Engineering, Nagoya University
Furo-cho, Chikusa-ku, Nagoya 464-8603 (Japan)
E-mail: ishihara@cc.nagoya-u.ac.jp
Homepage: http://www.nubio.nagoya-u.ac.jp/nubio4/index.htm
Prof. Dr. K. Ishihara
Japan Science and Technology Agency (JST), CREST (Japan)

[**] Financial support for this project was provided by JSPS.KAKENHI (20245022, 22750087), NEDO, and the Global COE Program of MEXT. We are grateful to the Tosoh Finechem Corporation for providing $Li[B(C_6F_5)_4]$.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204286.

Table 1: Investigation of the catalytic activities of Li^I or Ca^{II} salts.[a]



Entry	Catalyst (mol%)	t [h]	**2a**, Yield [%][b]
1	$Li[B(C_6F_5)_4]\cdot 2.5\,Et_2O$ (1)	8	94
2	$LiNTf_2$ (1)	24	28
3	$LiBF_4$ (1)	24	10
4	$LiBPh_4$ (1)	24	<1
5[c]	$Li[B(C_6F_5)_4]\cdot 2.5\,Et_2O$ (0.1)	22	98
6[c]	$Ca[B(C_6F_5)_4]_2\cdot 11\,H_2O$ (0.1)	6	97
7[c]	$Ca[B(C_6F_5)_4]_2\cdot 11\,H_2O$ (0.1) + $(CO_2H)_2$ (1)	3	98 (94)[d]
8	$(CO_2H)_2$ (1)	24	<1

[a] Unless otherwise noted, a solution of **1a** (1 mmol) and 30 wt% H_2O_2 in DCE was heated at 50 °C in the presence of catalyst. [b] Determined by ^{1}H NMR analysis. [c] 20 mmol scale. [d] Yield of isolated product. DCE = dichloroethane. Tf = trifluoromethanesulfonate.

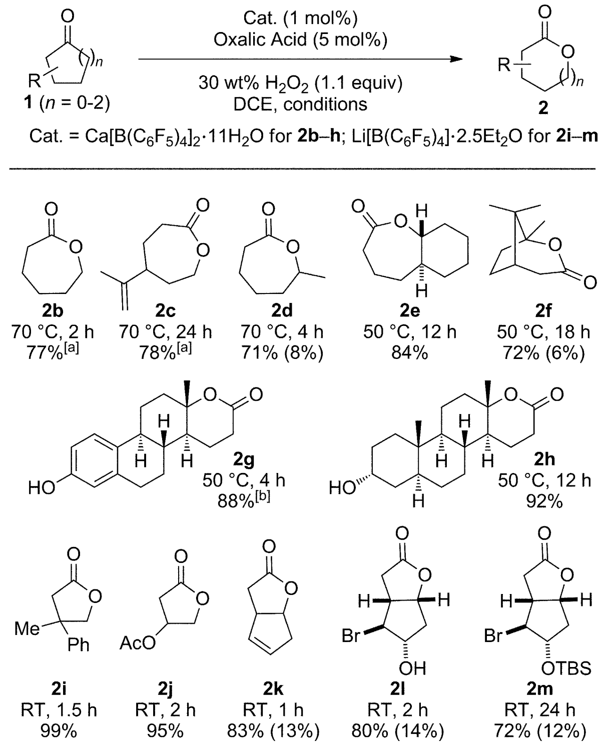
$M[B(C_6F_5)_4]_m\cdot[(CO_2H)_2]_n$, might be the active catalyst when oxalic acid is used as a co-catalyst.[13]

Importantly, lactone **2a** was obtained in high yields when less-polar solvents such as toluene, benzene, and dichloroethane (DCE) were used, and the latter gave the best results. In sharp contrast, the use of water-miscible organic solvents such as acetonitrile, dimethyl formamide, ethanol, etc. led to rather low conversion. Thus, these results suggest that the biphasic system is essential for the efficiency of the present BV oxidation.

We next examined the substrate scope for the present BV oxidation system under the optimized reaction conditions (Scheme 1). Four-, five- and six-membered cycloalkanones (**1**) were smoothly oxidized to the corresponding lactones (**2**) in high yields. Notably, both $Ca[B(C_6F_5)_4]_2$ and $Li[B(C_6F_5)_4]$ could be used as catalysts in most cases. However, the Ca^{II} salt gave slightly better results than the Li^I salt, particularly, for the oxidation of five- and six-membered cycloalkanones.

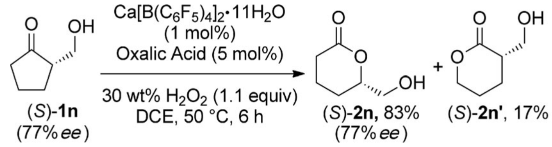
Although the oxidation rate was accelerated in the presence of oxalic acid, hydrolysis of the lactone products was also promoted in some cases (**2b** and **2c**). The BV oxidation of unsymmetrical cycloalkanones gave the corresponding lactones with normal regioselectivities (**2d**–**h**, and **2k**–**m**).

Several functional groups such as terminal and internal alkenyl (**1c** and **1k**), hydroxy (**1g**, **1h**, and **1l**), acetoxy (**1j**), silyloxy (**1m**), and halo (**1l** and **1m**) groups were tolerated under the present reaction conditions. In fact, these BV oxidations gave the corresponding lactones **2** in high yields, chemoselectively. Notably, the oxidation of hydroxysteroidal ketones **1g** and **1h** gave the corresponding lactones **2g** and **2h**, respectively, in high yields as single regioisomers without any other oxidation products. In contrast, the use of *m*CPBA in place of H_2O_2 gave phenol or alcohol oxidation by-products.[13] In addition, the oxidation of **1c** and **1k** with *m*CPBA under standard reaction conditions gave the epoxides as the major product.[13] The use of TsOH[4a–c] as a catalyst for the BV oxidation of **1c** and **1k** with hydrogen peroxide gave a complex reaction mixture or very low conversions.[13]



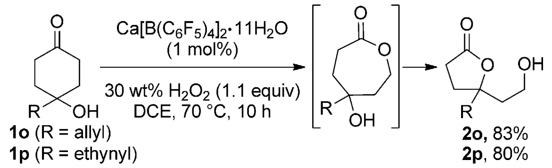
Scheme 1. BV Oxidation of various cycloalkanones **1**. Reaction conditions and yields of isolated lactones **2** are shown. Yields of the minor regioisomers **2′** are shown in parentheses. For details, see the Supporting Information. [a] Reaction was performed in the absence of oxalic acid. [b] Ca^{II} salt (2 mol%), oxalic acid (10 mol%), and 30 wt% H_2O_2 (2 equiv) were used. Ac = Acetyl. TBS = *tert*-butyldimethylsilyl.

The BV oxidation of (*S*)-2-(hydroxymethyl)cyclopentanone (**1n**) gave (*S*)-**2n**[15] without any racemization [Eq. (1)].



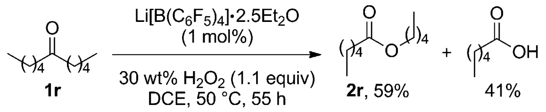
(1)

Interestingly, the BV oxidation of 4-hydroxycyclohexanones **1o** and **1p** gave the more-stable five-membered hydroxylactones **2o** and **2p** through successive intramolecular transesterification [Eq. (2)].

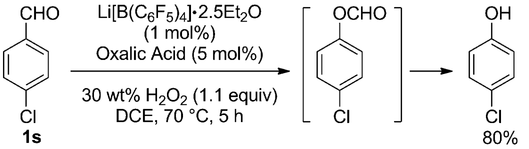


(2)

When linear ketones or aldehydes were oxidized, the ester products were also hydrolyzed simultaneously; the oxidation of **1r** gave the corresponding ester **2r** (59% yield) together with hexanoic acid (41% yield) [Eq. (3)]. Additionally, the oxidation of 4-chlorobenzaldehyde (**1s**) gave the 4-chlorophenol in 80% yield after hydrolysis of the corresponding formate [Eq. (4)].

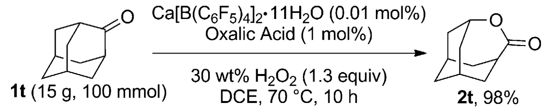


(3)



(4)

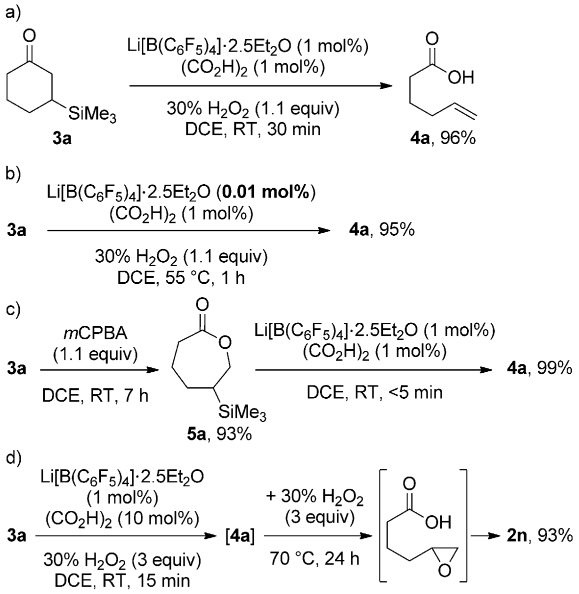
To demonstrate the practicality of the present BV catalysis, we examined the oxidation of 2-adamantanone (**1t**) on a 100 mmol (15 g) scale with only 0.01 mol% of Ca^{II} salt catalyst [Eq. (5)]. The desired lactone **2t** was obtained in 98% yield upon isolation (TON up to 9800). Notably, **2t** is used industrially as a starting material for the production of polymers, drugs, etc.[16]



(5)

Next, we applied our new catalytic conditions to the oxidation of β-silyl cyclohexanones. According to Hudrlik et al.,[17] the BV oxidation of β-silyl ketones with *m*CPBA is directed by the silyl group to selectively give esters of β-hydroxysilanes, which are useful for the synthesis of unsaturated esters or acids. Interestingly and unexpectedly, the oxidation of β-trimethylsilyl cyclohexanone (**3a**) with 1.1 equivalents of 30 wt% H_2O_2 in the presence of $Li[B(C_6F_5)_4]$ (1 mol%) and oxalic acid (1 mol%) at room temperature afforded 5-hexenoic acid (**4a**) in 96% yield as the sole product (Scheme 2a). The expected lactone **5a**, which was obtained by oxidation with *m*CPBA (Scheme 2c), was not detected. Notably, the oxidation rate was significantly accelerated in the presence of a β-silyl group; hence the reaction quickly occurred even at room temperature (Scheme 2a versus Scheme 1, **2b**). Moreover, the catalyst loading of Li^{I} salt could be reduced to 0.01 mol% without affecting the chemical yield (Scheme 2b). In contrast, the oxidation rate was not affected by the presence of a β-silyl substituent when *m*CPBA was used.[17a] We believe unsaturated acid **4a** is generated through the BV oxidation of **3a** and the subsequent fast β-elimination of silyl lactone intermediate **5a**. In fact, treatment of **5a** under similar reaction conditions in the absence of oxidant gave **4a** quantitatively within a few minutes (Scheme 2c). In sharp contrast, treatment with acid (excess $BF_3{\cdot}Et_2O$) or base (KOH, KH, etc.) under harsh reaction conditions was needed for the β-elimination of silyl lactones to give the corresponding unsaturated carboxylic acids.[17] Thus, we have developed the first oxidative cascade reaction of β-silyl cyclohexanones.

Our catalytic system could also be used for the oxidative cyclization of unsaturated acids.[18] After the conversion of ketone **3a** into unsaturated acid **4a**, three additional equivalents of H_2O_2 were added to the same flask to give hydroxylactone **2n** in 93% yield through epoxidation/cyclization reactions (Scheme 2d). Notably, a higher loading of oxalic acid (10 mol%) and a high temperature (70°C) were needed for the oxylactonization step. To the best of our knowledge, this is the first example of the transition-metal-free catalytic oxylactonization of unsaturated carboxylic acids using hydrogen peroxide.

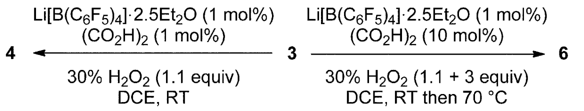


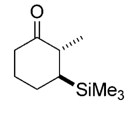
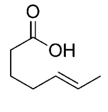
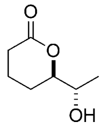
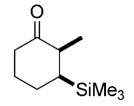
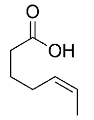
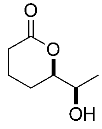
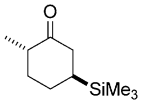
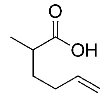
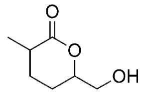
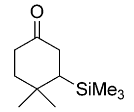
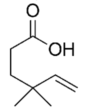
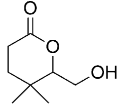
Scheme 2. a) Transformation of β-trimethylsilyl cyclohexanone **3a** to **4a** through a BV oxidation/β-elimination reaction sequence. b) Oxidation with low catalyst loading (0.01 mol%). c) Control experiments: Oxidation of **3a** with *m*CPBA gave silyl lactone, which was easily converted into **4a** by β-elimination under our reaction conditions. d) Cascade oxidative transformation of **3a** into hydroxylactone **2n** through BV oxidation/β-elimination and subsequent epoxidation/cyclization reaction sequences.

Under these optimized reaction conditions either unsaturated acids **4** or hydroxylactones **6** could be obtained from the corresponding β-silyl cyclohexanones **3**, depending on the amounts of hydrogen peroxide and oxalic acid used (Table 2). Notably, the oxidation of 2-substituted β-silyl ketones **3** gave either the corresponding unsaturated acids **4** or hydroxylactones **6** as sole products in a stereospecific manner (Table 2, entries 1 and 2). However, the oxidation of **3d** gave **6d** as a diastereomeric mixture (Table 2, entry 3).

In summary, we have developed highly efficient and selective $Li[B(C_6F_5)_4]$ or $Ca[B(C_6F_5)_4]_2$ catalyzed BV oxidations of various cycloalkanones with 30 wt% aqueous hydrogen peroxide to give the corresponding lactones in high yield. Additionally, we have found that the reaction rate is accelerated with the use of oxalic acid as a co-catalyst. Moreover, β-silyl cyclohexanones can be oxidized to either the corresponding unsaturated carboxylic acids or hydroxylactones in high yields through BV oxidation/β-elimination reaction sequences and subsequent epoxidation/cyclization reaction sequences, by controlling the amounts of H_2O_2 and oxalic acid. These reactions proceed under mild conditions and tolerate various functional groups.

Table 2: Oxidative cascade reactions of β-silyl cyclohexanones **3**.



Entry	**3**	**4**, Yield [%]	**6**,[a] Yield [%]
1	 **3b**	 **4b**, 93	 **6b**, 92
2	 **3c**	 **4c**, 92	 **6c**, 85
3	 **3d**	 **4d**, 92	 **6d**, 81 (≈1.4:1 d.r.)
4	 **3e**	 **4e**, 90	 **6e**, 80[b]

[a] **3** was treated with 1.1 equiv of H_2O_2 at room temperature until full conversion, then the reaction mixture was heated at 70 °C in the presence of an additional 3 equiv of H_2O_2. [b] After **3e** was consumed, 8 equiv of H_2O_2 were additionally added.

Received: June 2, 2012

Keywords: alkali metals · alkaline earth metals · borates · lactones · oxidation

---

[1] Selected reviews: a) G. R. Krow, *Org. React.* **1993**, *43*, 251; b) G. Strukul, *Angew. Chem.* **1998**, *110*, 1256; *Angew. Chem. Int. Ed.* **1998**, *37*, 1198; c) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.* **2004**, *104*, 4105.

[2] *Catalytic Oxidations With Hydrogen Peroxide As Oxidant* (Ed.: G. Strukul), Kluwer, Dordrecht, **1992**.

[3] Selected examples: a) M. Del Todesco Frisone, F. Pinna, G. Strukul, *Organometallics* **1993**, *12*, 148; b) A. M. F. Phillips, C. Romao, *Eur. J. Org. Chem.* **1999**, 1767; c) X. Hao, O. Yamazaki, A. Yoshida, J. Nishikido, *Tetrahedron Lett.* **2003**, *44*, 4977; d) K. Mikami, M. N. Islam, M. Yamanaka, Y. Itoh, M. Shinoda, K. Kubo, *Tetrahedron Lett.* **2004**, *45*, 3681; e) R. A. Michelin, P. Sgarbossa, A. Scarso, G. Strukul, *Coord. Chem. Rev.* **2010**, *254*, 646.

[4] Selected examples: a) K. Neimann, R. Neumann, *Org. Lett.* **2000**, *2*, 5629; b) A. Berkessel, M. R. M. Andreae, *Tetrahedron Lett.* **2001**, *42*, 2293; c) A. Berkessel, M. R. M. Andreae, H. Schmickler, J. Lex, *Angew. Chem.* **2002**, *114*, 4661; *Angew. Chem. Int. Ed.* **2002**, *41*, 4481; d) C. G. Piscopo, S. Loebbecke, R. Maggi, G. Sartori, *Adv. Synth. Catal.* **2010**, *352*, 1625; e) G. Peris, S. J. Miller, *Org. Lett.* **2008**, *10*, 3049; f) S. M. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem.* **2008**, *120*, 2882; *Angew. Chem. Int. Ed.* **2008**, *47*, 2840.

[5] A. Corma, L. T. Nemeth, M. Renz, S. Valencia, *Nature* **2001**, *412*, 423.

[6] Selected examples: a) U. R. Pillai, E. Sahle-Demessie, *J. Mol. Catal. A* **2003**, *191*, 93; b) R. Llamas, C. Jiménez-Sanchidrián, J. R. Ruiz, *Tetrahedron* **2007**, *63*, 1435; c) R. Llamas, C. Jiménez-Sanchidrián, J. R. Ruiz, *Appl. Catal. B* **2007**, *72*, 18.

[7] a) G.-J. ten Brink, J.-M. Vis, I. W. C. E. Arends, R. A. Sheldon, *J. Org. Chem.* **2001**, *66*, 2429; b) H. Ichikawa, Y. Usami, M. Arimoto, *Tetrahedron Lett.* **2005**, *46*, 8665.

[8] Selected examples: a) C. Mazzini, J. Lebreton, R. Furstoss, *J. Org. Chem.* **1996**, *61*, 8; b) S. Murahashi, S. Ono, Y. Imada, *Angew. Chem.* **2002**, *114*, 2472; *Angew. Chem. Int. Ed.* **2002**, *41*, 2366; c) P. Ménová, F. Kafka, H. Dvoráková, S. Gunnoo, M. Sanda, R. Cibulka, *Adv. Synth. Catal.* **2011**, *353*, 865.

[9] a) S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943; b) R. W. Dugger, J. A. Ragan, D. H. B. Ripin, *Org. Process Res. Dev.* **2005**, *9*, 253.

[10] I. Krossing, I. Raabe, *Angew. Chem.* **2004**, *116*, 2116; *Angew. Chem. Int. Ed.* **2004**, *43*, 2066.

[11] a) K. Fujiki, S. Ikeda, H. Kobayashi, A. Mori, A. Nagira, J. Nie, T. Sonoda, Y. Yagupolskii, *Chem. Lett.* **2000**, 62; b) T. Mukaiyama, M. Nakao, W. Kikuchi, J. Matsuo, *Chem. Lett.* **2000**, 1010; c) M. Nakano, J. Matsuo, T. Mukaiyama, *Chem. Lett.* **2000**, 1352; d) C.-T. Chang, C.-L. Chen, Y.-H. Liu, S.-M. Peng, P.-T. Chou, S.-T. Liu, *Inorg. Chem.* **2006**, *45*, 7590; e) C.-T. Chang, B.-S. Liao, S.-T. Liu, *Tetrahedron Lett.* **2006**, *47*, 9257; f) B.-S. Liao, J.-T. Chen, S.-T. Liu, *Synthesis* **2007**, 3125; g) C.-C. Chang, B.-S. Liao, S.-T. Liu, *Synlett* **2007**, 283.

[12] We initially examined $M[B\{3,5\text{-}(CF_3)_2C_6H_3\}_4]_n$ (M = Li, Na, Ca, Sr) salts as catalysts for the BV oxidation under our reaction conditions. Although they showed high catalytic activities initially, the decomposition of the borate anion was observed during oxidation reaction. In contrast, we confirmed that $M[B(C_6F_5)_4]_n$ (M = Li, Ca) salts were extremely stable under our oxidation conditions. For the comparison of the stability of $[B\{3,5\text{-}(CF_3)_2C_6H_3\}_4]^-$ and $[B(C_6F_5)_4]^-$ borate anions under acidic conditions, see: M. Isshiki, H. Kobayashi, T. Sonoda, *Rep. Inst. Adv. Mater. Study Kyushu Univ.* **1995**, *9*, 47.

[13] For details, see the Supporting Information.

[14] a) K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179; b) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; c) A. Aguado, N. Takenaka, *Synlett* **2011**, 1259.

[15] N. Mase, A. Inoue, M. Nishio, K. Takabe, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3955.

[16] Selected patents: a) J. Yao, J. W. F. Whitehead, N. Tsuno, K. Fuchino, PCT Int. Appl. WO2010010458, Jan 28, **2010**; b) K. Tsutsumi, K. Inoue, K. Funaki, T. Nakano, A. Horai, Jpn. Kokai Tokkyo Koho JP2002338627, Nov 27, **2002**; c) A. P. S. Narula, C. E. J. Beck, M. R. Hanna, U. S. Patent, US4985403, Jan 15, **1991**.

[17] a) P. F. Hudrlik, A. M. Hudrlik, G. Nagendrappa, T. Yimenu, E. T. Zeller, E. Chin, *J. Am. Chem. Soc.* **1980**, *102*, 6894; b) P. F. Hudrlik, A. M. Hudrlik, T. Yimenu, M. A. Waugh, G. Nagendrappa, *Tetrahedron* **1988**, *44*, 3791; c) Y. Inokoishi, N. Sasakura, K. Nakano, Y. Ichikawa, H. Kotsuki, *Org. Lett.* **2010**, *12*, 1616.

[18] For previous methods using Re, W, or Fe, see: a) H. Tan, J. H. Espenson, *J. Mol. Catal. A* **1999**, *142*, 333; b) Y. M. A. Yamada, H. Guo, Y. Uozumi, *Org. Lett.* **2007**, *9*, 1501; c) H. Hamamoto, Y. Suzuki, H. Takahashi, S. Ikegami, *Adv. Synth. Catal.* **2007**, *349*, 2685; d) M. A. Bigi, S. A. Reed, M. C. White, *Nat. Chem.* **2011**, *3*, 216.