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Polyoxometalate Catalysis

Chemo- and Regioselective Direct Hydroxylation of Arenes with Hydrogen Peroxide Catalyzed by a Divanadium-Substituted Phosphotungstate**

*Keigo Kamata, Taiyo Yamaura, and Noritaka Mizuno**

Phenols with one or more functional groups are valuable organic intermediates related to resins, plastics, pharmaceuticals, and agrochemicals in the chemical industry.[1] Most of these phenols are industrially produced by multistep processes. Therefore, the direct catalytic hydroxylation of arenes to phenols with green oxidants, such as H_2O_2,[2] N_2O,[3] and O_2, in combination with reductants[4] has attracted much attention.[5] Whereas the catalytic oxidation of benzene to phenol has been extensively investigated, little is known about the selective direct hydroxylation of substituted derivatives.

Numerous metal catalysts, such as Ti, V, Mn, Fe, Co, Cu, Ru, Pt, and polyoxometalates (POMs), have been developed for the oxidation of arenes with H_2O_2.[2] However, hydroxylation of arenes with functional groups usually leads to a mixture of *ortho*-, *meta*-, and *para*-substituted phenols. Furthermore, most systems for the oxidation of alkylarenes preferentially oxidize the aromatic side-chain sp^3 C–H bonds rather than the aromatic ring sp^2 C–H bonds, because the bond dissociation energies (BDEs) of the $ArCR_2$–H bonds (ca. 375 kJ mol^{-1}) are much lower than those of the Ar–H bonds (ca. 470 kJ mol^{-1}).[5,6] Natural enzymes can chemo- and regioselectively hydroxylate alkylarenes through molecular recognition.[7] However, synthetic catalysts have scarcely achieved highly chemo- and regioselective hydroxylation of alkylarenes, especially with reactive secondary and tertiary aromatic side-chain sp^3 C–H bonds.

Recently, we have reported the formation of non-free-radical and electrophilic oxidants with high steric hindrance, such as $[\gamma\text{-}PW_{10}O_{38}V_2(\mu\text{-}OH)(\mu\text{-}OOH)]^{3-}$ and $[\gamma\text{-}PW_{10}O_{38}V_2(\mu\text{-}O_2)]^{3-}$, by the reaction of a divanadium-substituted phosphotungstate, $[\gamma\text{-}PW_{10}O_{38}V_2(\mu\text{-}OH)_2]^{3-}$ (**I**; Supporting Information, Figure S1) with H_2O_2.[8] Such oxidants can efficiently catalyze various oxidative functional group transformations. Herein, we apply the **I**-catalyzed oxidation system to direct hydroxylation of various structurally diverse arenes to phenols. The present system shows unique chemo- and regioselectivity for the formation of *para*-phenols from monosubstituted benzenes. This study provides the first example of a synthetic catalyst that can chemoselectively hydroxylate alkylarenes with reactive secondary and tertiary aromatic side-chain C–H bonds without significant formation of the corresponding side-chain oxygenated products.

Hydroxylation of anisole (**1a**) was carried out under various reaction conditions using an excess of **1a** with respect to H_2O_2 (**1a**/H_2O_2 = 10:1; Table S1). In the presence of **I**, hydroxylation of **1a** in CH_3CN/*t*BuOH (1:1, v/v) efficiently proceeded to give the corresponding methoxyphenols (**2a**) in 70% yield based on H_2O_2. The formation of phenol by the oxidative demethylation of **1a** was not observed. Notably, the *para*-hydroxylation of **1a** preferentially proceeded, and the *ortho*-/*meta*-/*para*-**2a** ratio was 3: < 1:96. The present regioselectivity (96%) for *para*-**2a** was much higher than those reported for stoichiometric reagents, such as peroxytrifluoroacetic acid (21%)[9a] and hydroxyl radical (10%),[9b] or H_2O_2 based catalytic systems, such as sterically hindered metalloporphyrins (23–90%),[2c,10a] TS-1 (a titanium silicate zeolite; 71–75%),[2a] $[Fe(tpaa)(ClO_4)_2]$ (tpaa = tris-[*N*-(2-pyridylmethyl)-2-aminoethyl]amine; 51%),[10b] $[(dppe)Pt(CF_3)(CH_3)(CH_2Cl_2)](ClO_4)$ (dppe = 1,2-bis(diphenylphosphino)ethane; 15%),[2h] and $K_7NiV_{13}O_{38}\cdot 16H_2O$ (0%; Table S2).[2i] Hydroxylation efficiently proceeded even at 298 K without significant changes in catalytic performance. Furthermore, the yield and regioselectivity for hydroxylation of **1a** under air were almost the same as those under argon, showing that the possibility of participation by molecular oxygen in air can be excluded. Compound **I** was much more active than $[\gamma\text{-}SiW_{10}O_{38}V_2(\mu\text{-}OH)_2]^{4-}$.[8] Mono- and trivanadium-substituted phosphotungstates, $[\alpha\text{-}PVW_{11}O_{40}]^{4-}$ and $[\alpha\text{-}H_2PV_3W_9O_{40}]^{4-}$, and monoprotonated $[\gamma\text{-}HPV_2W_{10}O_{40}]^{4-}$ (which has an {OV-(μ-O)(μ-OH)-VO} core) were inactive, suggesting that the active sites are not the V–O–W and V=O sites, but rather the bis-μ-hydroxo site of {OV-$(\mu\text{-}OH)_2$-VO} in **I**. In the presence of tungstates and $HClO_4$, hydroxylation did not proceed.[11] Simple vanadium compounds, including $[VO(O_2)(pic)(H_2O)_2]$ (pic = picolinate) and TBA$[VO_3]$/PCA (TBA = $[(n\text{-}C_4H_9)_4N]^+$, PCA = pyrazine-2-carboxylic acid), which have been reported to be active for the hydroxylation of arenes with H_2O_2,[12] hardly catalyzed hydroxylation under the present reaction conditions.[13]

Hydroxylation of **1a** efficiently proceeded, even when using **I** at a loading of 0.16 mol%, to give **2a** in 67% yield based on H_2O_2 [Eq. (1)]. The regioselectivity was not affected

[*] Dr. K. Kamata, T. Yamaura, Prof. Dr. N. Mizuno
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp
Homepage: http://park.itc.u-tokyo.ac.jp/mizuno/

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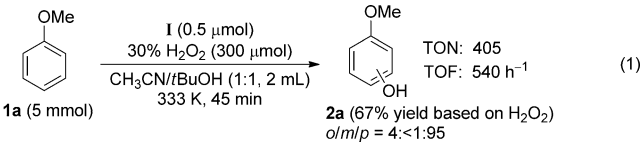


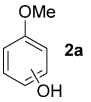
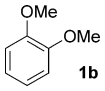
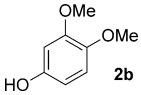
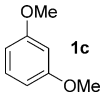
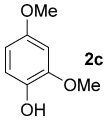
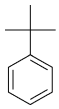
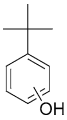
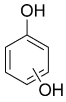
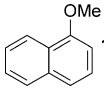
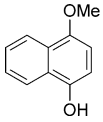
(1)

by reduction of the catalyst loading. In this case, the turnover number (TON) reached up to 405 and the turnover frequency (TOF) was 540 h^{-1}. These values were much larger than those reported for the catalytic systems based on H_2O_2 (TON = < 1–80, TOF = < 1–53 h^{-1}; Table S2).[2,10,13]

Hydroxylation of various arenes was carried out with an excess of substrate relative to H_2O_2 (Table 1). Reactivities of monosubstituted benzenes were dependent on the electronic effects of the substituents on the aromatic rings. Benzenes with electron-donating substituents (**1a**, **1d**, and **1e**) were efficiently hydroxylated to the corresponding phenols in 56–86% yield based on H_2O_2 (Table 1, entries 1, 10, and 11), whereas hydroxylation of bromobenzene gave bromophenols in 7% yield based on H_2O_2 under the same reaction conditions. These reactivities indicate the formation of active electrophilic oxygen species. After the hydroxylation of **1a** was complete (Table 1, entry 2), 30% aqueous H_2O_2 (100 μmol) was added to the resulting reaction solution. Hydroxylation again proceeded with almost the same yield based on H_2O_2 (93%) and regioselectivity for *para*-**2a** (97%) as those observed for the first run (92% yield based on H_2O_2 and 97% regioselectivity for *para*-**2a**; Table 1, entries 2 and 3). Thus, **I** is intrinsically recyclable.[14] Regioselectivities for the hydroxylation of various arenes with H_2O_2 were then investigated. As monosubstituted benzenes with electron-donating groups show predominantly *ortho*/*para* orientation for electrophilic hydroxylation, organometallic complexes without bulky ligands and stoichiometric oxidants give a mixture of *ortho*- and *para*-substituted phenols.[2,9,10] On the other hand, the C–H bonds at the *para* position of monosubstituted benzenes were regioselectively hydroxylated, with 74–95% of *para*-phenol versus total phenol produced (Table 1). The high regioselectivity for *para*-phenol formation is likely due to the *ortho*-hydroxylation being suppressed by the steric crowding between the POM framework and the substituents. Similarly, the high stereospecificity and diastereo- and regioselectivities for **I**-catalyzed epoxidation are explained by the steric constraints of the active site.[8,15,16] Not only monosubstituted benzenes, but also disubstituted ones (**1b** and **1c**) were regioselectively hydroxylated, and **1c** gave the less sterically hindered 2,4-dimethoxyphenol (**2c**) with > 99% selectivity (Table 1, entries 5–8). The substrate 1-methoxynaphthalene (**1f**) was also regioselectively hydroxylated to give 4-methoxy-1-naphthol (**2f**; Table 1, entry 13). Hydroxylation of **1a**, **1c**, and **1e** with relatively low substrate/H_2O_2 ratios (4:1) was also carried out. Yields based on substrate could be increased to 14–18% without significant changes in regioselectivity (Table 1, entries 4, 9, and 12).[17]

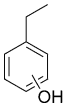
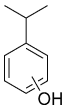
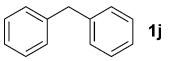
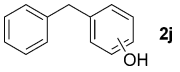
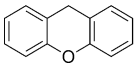
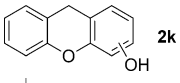
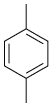
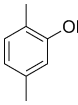
This system could also be applied to the chemoselective oxidation of various kinds of alkylarenes to phenols (Table 2). Toluene (**1g**) was chemoselectively oxidized to cresols (**2g**) without significant formation of side-chain oxygenated products, such as benzyl alcohol, benzaldehyde, and benzoic acid (Table 2, entry 1). The ring/chain ratio (ring-oxygenated products/side-chain-oxygenated products) was 98:2, and the value was quite different from those of vanadium complexes such as $[V_2O_3(sha)_3(H_2O)_3]$ (sha = *N*-Salicyl hydroxamate), [V(O)(Cl) $(pbha)_2$] (pbha = *N*-phenyl benzohydroxamate), and $[VO(acac)_2]$ (acac = acetylacetonate) (0:100–25:75; Table S3).[2b,18] Ethylbenzene (**1h**), cumene (**1i**), and diphenylmethane (**1j**), which all possess more reactive secondary

Table 1: Regioselective hydroxylation of arenes with H_2O_2 catalyzed by **I**.[a]

Entry	Substrate	Y_S [%][b]	Y_O [%][c]	Product	(Selectivity [%])[d]
1	 **1a**	2	85	 **2a**	(>99) *o*/*m*/*p* = 5:<1:95
2[e]	**1a**	2	92	**2a**	(99) *o*/*m*/*p* = 3:<1:97
3[e,f]	**1a**	2	93	**2a**	(99) *o*/*m*/*p* = 3:<1:97
4[g]	**1a**	14	56	**2a**	(91) *o*/*m*/*p* = 1:<1:99
5[h]	 **1b**	5	50	 **2b**	(>99)
6	**1b**	2	78	**2b**	(>99)
7[h]	 **1c**	8	80	 **2c**	(>99)
8	**1c**	2	93	**2c**	(>99)
9[g]	**1c**	16	64	**2c**	(>99)
10	 **1d**	1	56	 **2d**	(99) *o*/*m*/*p* = <1:25:74
11[h,i]	 **1e**	2	86	 **2e**	(85) *o*/*m*/*p* = 5:<1:95
12[g,j]	**1e**	18	85	**2e**	(81) *o*/*m*/*p* = <1:<1:99
13[h]	 **1f**	6	63	 **2f**	(>99)

[a] Reaction conditions: $TBA_4[\gamma\text{-}HPW_{10}V_2O_{40}]$ (2.5 μmol), $HClO_4$ (2.5 μmol), substrate (5 mmol), CH_3CN/*t*BuOH (1:1, 2 mL), aqueous H_2O_2 (30%, 0.1 mmol), 333 K, 60 min, under Ar (1 atm). Yields and selectivities were determined by GC analysis. [b] Y_S (%) = [products (mol)/initial substrate (mol)] × 100. [c] Y_O (%) = [products (mol)/initial H_2O_2 (mol)] × 100. [d] Selectivity for formation of hydroxylated products. [e] 298 K. [f] Recycling experiment (see the Supporting Information). [g] Reaction conditions: $TBA_4[\gamma\text{-}HPW_{10}V_2O_{40}]$ (2.5 μmol), $HClO_4$ (2.5 μmol), substrate (0.4 mmol), CH_3CN/*t*BuOH (1:1, 2 mL), aqueous H_2O_2 (30%, 0.1 mmol), 298 K, 240 min, under Ar (1 atm). [h] Substrate (1 mmol). [i] 1,4-Benzoquinone (8% selectivity), muconaldehyde (2% selectivity). [j] 1,4-Benzoquinone (18% selectivity), muconaldehyde (1% selectivity).

Table 2: Chemoselective hydroxylation of alkylarenes with H_2O_2 catalyzed by **I**.[a]

Entry	Substrate	Y_S [%][b]	Y_O [%][c] (R/C)	Product	(Selectivity [%])[d]
1[e]	 **1g**	1	60 (98:2)	 **2g**	(86) *o*/*m*/*p* = 7:16:77
2[f]	 **1h**	1	66 (86:14)	 **2h**	(77) *o*/*m*/*p* = 5:20:75
3[g]	 **1i**	1	55 (93:7)	 **2i**	(88) *o*/*m*/*p* = 2:20:77
4[h]	 **1j**	1	47 (97:3)	 **2j**	(97) *o*/*m*/*p* = 9:20:71
5[i]	 **1k**	4	43 (87:13)	 **2k**	(87)
6[j]	 **1l**	1	61 (98:2)	 **2l**	(98) 2,3/3,4 = 5:95
7[k]	 **1m**	1	71 (96:4)	 **2m**	(96) 2,4/3,5/2,6 = 90:9:<1
8[l]	 **1n**	2	98 (88:12)	 **2n**	(45)

[a] Reaction conditions: $TBA_4[\gamma\text{-}HPW_{10}V_2O_{40}]$ (2.5 μmol), $HClO_4$ (2.5 μmol), substrate (5 mmol), CH_3CN/*t*BuOH (1:1, 2 mL), 30% aqueous H_2O_2 (0.1 mmol), 333 K, 60 min, under Ar (1 atm). Yields and selectivities were determined by GC. [b] Y_S (%) = [products (mol)/initial substrate (mol)] × 100. [c] Y_O (%) = [products (mol)/initial H_2O_2 (mol)] × 100. R/C = ring/chain ratio = [(phenols (mol) + quinones (mol)]/side-chain oxygenated products (mol). [d] Selectivity for formation of hydroxylated products. [e] Benzyl alcohol (2% selectivity), 2-Methyl-1,4-benzoquinone (12% selectivity). [f] 1-Phenylethanol (13% selectivity), 2-ethyl-1,4-benzoquinone (9% selectivity). [g] 2-Phenyl-2-propanol (7% selectivity), 2-isopropyl-1,4-benzoquinone (5% selectivity). [h] Benzhydrol (2% selectivity), benzophenone (1% selectivity). [i] **1k** (1 mmol). Xanthydrol (2% selectivity), xanthone (11% selectivity). [j] 2-Methylbenzyl alcohol (2% selectivity). [k] 3-Methylbenzyl alcohol (4% selectivity). [l] 3-Methylbenzyl alcohol (8% selectivity), 4-methylbenzaldehyde (4% selectivity), 2,5-dimethyl-1,4-benzoquinone (43% selectivity).

and tertiary C–H bonds in the side-chain, were also chemoselectively oxidized to the corresponding phenols (**2h**–**2j**; Table 2, entries 2–4). Such high chemoselectivities have scarcely been reported owing to significant side-chain oxygenation and/or isomerization of substrates (Tables S4 and S5). For oxidation of **1h**, the ring/chain ratio was 86:14, and this value is the largest among those reported for catalytic systems based on H_2O_2 (0:100–69:31).[2] Furthermore, *para*-hydroxylation of **1g**–**1j** preferentially proceeded with 71–77% regioselectivities for *para*-**2g**–**2j**, whereas mixtures of regioisomers are typically formed.[19,20] Notably, xanthene (**1k**) with very weak aromatic side-chain sp^3 C–H bonds (BDE = 326 kJ mol^{-1}) was selectively hydroxylated to xanthen-2-ol (**2k**).[6] To the best of our knowledge, this is the first example of chemo- and regioselective hydroxylation of **1i**–**1k** by a synthetic catalyst. Xylenes (**1l**–**1n**) were also chemoselectively oxidized to the corresponding phenols (Table 2, entries 6–8).

The kinetic isotope effect (k_H/k_D) was determined by the **I**-catalyzed competitive hydroxylation of **1g** and [D_8]toluene (**1g**-d_8) with H_2O_2. The intramolecular k_H/k_D value for aromatic ring hydroxylation was 1.0, indicating that the C–H bond cleavage is not included in the rate-determining step for this hydroxylation. The value is smaller than that of hydroxyl radical (1.7)[21] and comparable to those of $[VO(O_2)(pic)(H_2O)_2]$ (0.95–1.05), peroxytrifluoroacetic acid (ca. 1), and cytochrome P450 enzymes (0.95–1.27).[12a,22–24] The addition of a radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol (5 equiv vs. **I**), did not affect the reaction rate, selectivity, or total yield for the hydroxylation of **1a**. No formation of coupling products, such as biphenyls, was observed. Furthermore, the reactivity order for the hydroxylation of a series of monosubstituted benzenes (OH ≈ OMe > Me > Br) decreased in the opposite order of that of the hydroxyl radical system.[21] All these results, including chemo- and regioselectivities, suggest that non-free-radical, electrophilic, metal-based oxidants play an important role in the present hydroxylation method.

In summary, divanadium-substituted phosphotungstate **I** showed high catalytic activity and unique chemo- and regioselectivities for the direct hydroxylation of various arenes with aqueous H_2O_2.

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[1] a) For phenol derivatives, see: H. Fiege, H.-W. Voges, T. Hamamoto, S. Umemura, T. Iwata, H. Miki, Y. Fujita, H.-J. Buysch, D. Garbe, W. Paulus, *Ullmann's Encyclopedia of Industrial Chemistry*, Electronic Release, Wiley-VCH, Weinheim, **2000**; b) for alkylphenols, see: J. F. Lorenc, G. Lambeth, W. Scheffer: *Kirk-Othmer Encyclopedia of Chemical Technology*, Electronic Release, Wiley-VCH, Weinheim, **2003**.

[2] a) D. Bianchi, R. D'Aloisio, R. Bortolo, M. Ricci, *Appl. Catal. A* **2007**, *327*, 295–299; b) X. Wang, J. Wu, M. Zhao, Y. Lv, G. Li, C. Hu, *J. Phys. Chem. C* **2009**, *113*, 14270–14278; c) J.-F. Bartoli, V. Mouries-Mansuy, K. L. Barch-Ozette, M. Palacio, P. Battioni, D. Mansuy, *Chem. Commun.* **2000**, 827–828; d) K. Mori, K. Kagohara, H. Yamashita, *J. Phys. Chem. C* **2008**, *112*, 2593–2600; e) R. Raja, J. M. Thomas, V. Dreyer, *Catal. Lett.* **2006**, *110*, 179–183; f) P. Roy, K. Dhara, M. Manassero, P. Banerjee, *Eur. J. Inorg. Chem.* **2008**, 4404–4412; g) P. K. Tandon, R. Baboo, A. K. Singh, G. Purwar, M. Purwar, *Appl. Organomet. Chem.* **2005**, *19*, 1079–1082; h) A. Marsella, S. Agapakis, F. Pinna, G. Strukul, *Organometallics* **1992**, *11*, 3578–3587; i) F. Gao, R. Hua, *Appl. Catal. A* **2004**, *270*, 223–226.

[3] a) L. V. Pirutko, V. S. Chernyavsky, A. K. Uriarte, G. I. Panov, *Appl. Catal. A* **2002**, *227*, 143 – 157; b) A. Costine, T. O'Sullivan, B. K. Hodnett, *Catal. Today* **2005**, *99*, 199 – 208.

[4] a) S. Niwa, M. Eswaramoorthy, J. Nair, A. Raj, N. Itoh, H. Shoji, T. Namba, F. Mizukami, *Science* **2002**, *295*, 105 – 107; b) M. Tani, T. Sakamoto, S. Mita, S. Sakaguchi, Y. Ishii, *Angew. Chem.* **2005**, *117*, 2642 – 2644; *Angew. Chem. Int. Ed.* **2005**, *44*, 2586 – 2588; c) W. Laufer, W. F. Hoelderich, *Chem. Commun.* **2002**, 1684 – 1685; d) T. Tatsumi, K. Yuasa, H. Tominaga, *J. Chem. Soc. Chem. Commun.* **1992**, 1446 – 1447.

[5] R. Sheldon, I. W. C. E. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.

[6] a) S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255 – 263; b) J. J. Warren, T. A. Tronic, J. M. Mayer, *Chem. Rev.* **2010**, *110*, 6961 – 7001.

[7] R. Ullrich, M. Hofrichter, *Cell. Mol. Life Sci.* **2007**, *64*, 271 – 293.

[8] a) K. Kamata, K. Yonehara, Y. Nakagawa, K. Uehara, N. Mizuno, *Nat. Chem.* **2010**, *2*, 478 – 483; b) K. Yonehara, K. Kamata, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2011**, *47*, 1692 – 1694; c) K. Kamata, K. Sugahara, K. Yonehara, R. Ishimoto, N. Mizuno, *Chem. Eur. J.* **2011**, *17*, 7549 – 7559; d) T. Yamaura, K. Kamata, K. Yamaguchi, N. Mizuno, *Catal. Today* **2012**, DOI: 10.1016/j.cattod.2012.01.026.

[9] a) J. D. McClure, P. H. Williams, *J. Org. Chem.* **1962**, *27*, 627 – 628; b) S. Tamagaki, K. Suzuki, W. Tagaki, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 148 – 152.

[10] a) J.-F. Bartoli, K. L. Barch, M. Palacio, P. Battioni, D. Mansuy, *Chem. Commun.* **2001**, 1718 – 1719; b) J.-F. Bartoli, F. Lambert, I. Morgenstern-Badarau, P. Battioni, D. Mansuy, *C. R. Chim.* **2002**, *5*, 263 – 266.

[11] a) K. Kamata, K. Yonehara, Y. Sumida, K. Yamaguchi, S. Hikichi, N. Mizuno, *Science* **2003**, *300*, 964 – 966; b) K. Kamata, T. Hirano, S. Kuzuya, N. Mizuno, *J. Am. Chem. Soc.* **2009**, *131*, 6997 – 7004.

[12] a) H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer, R. Weiss, *J. Am. Chem. Soc.* **1983**, *105*, 3101 – 3110; b) G. B. Shul'pin, D. Attanasio, L. Suber, *J. Catal.* **1993**, *142*, 147 – 152; c) M. Bonchio, V. Conte, F. Di Furia, G. Modena, *J. Org. Chem.* **1989**, *54*, 4368 – 4371.

[13] Although the TON (405) of **I** was smaller than that of $K_7NiV_{13}O_{38}\cdot 16H_2O$ (942), the TOF of **I** (540 h^{-1}) was much larger than that of $K_7NiV_{13}O_{38}\cdot 16H_2O$ (135 h^{-1}).[2i] Furthermore, the $K_7NiV_{13}O_{38}\cdot 16H_2O/H_2O_2$ system is not applicable to the chemoselective hydroxylation of toluene because of the significant formation of benzaldehyde and benzoic acid.

[14] The ^{51}V NMR spectrum of **I** after hydroxylation showed a strong −580 ppm signal for **I**, as well as a −671 ppm signal for $VO(OtBu)_3$ (integrated signal intensity; 1% with respect to **I**). These facts show that **I** is stable under the catalytic conditions and that the vanadium species hardly leach into the reaction solution.

[15] A manganese-containing sandwich POM, $[WZnMn_2(ZnW_9O_{34})_2]^{12-}$, shows steric effects for epoxidation of alkenes and unique regioselectivity for epoxidation of (*R*)-(+)-limonene is observed.[16] The more accessible, but less nucleophilic double bond in (*R*)-(+)-limonene is more regioselectively epoxidized in the presence of **I**[8c] and the value of [less substituted epoxide]/[total epoxides] (≥ 0.99) is larger than that of $[WZnMn_2(ZnW_9O_{34})_2]^{12-}$ (0.50), showing the stronger steric effect of **I**.

[16] a) R. Neumann, M. Gara, *J. Am. Chem. Soc.* **1995**, *117*, 5066 – 5074; b) R. Neumann, D. Juwiler, *Tetrahedron* **1996**, *52*, 8781 – 8788.

[17] The industrial hydroxylation of phenol with TS-1 was carried out with a **2e**/H_2O_2 ratio of 3:1, and the yield based on **2e** (25–30%) is much higher than that of **I**.

[18] a) T. K. Si, S. Chakraborty, A. K. Mukherjee, M. G. B. Drew, R. Bhattacharyya, *Polyhedron* **2008**, *27*, 2233 – 2242; b) T. K. Si, K. Chowdhury, M. Mukherjee, D. C. Bera, R. Bhattacharyya, *J. Mol. Catal. A* **2004**, *219*, 241 – 247; c) N. Mizuno, K. Kamata, *Coord. Chem. Rev.* **2011**, *255*, 2358 – 2370.

[19] a) P. Mukherjee, A. Bhaumik, R. Kumar, *Ind. Eng. Chem. Res.* **2007**, *46*, 8657 – 8664; b) J. K. Joseph, S. Singhal, S. L. Jain, R. Sivakumaran, B. Kumar, B. Sain, *Catal. Today* **2009**, *141*, 211 – 214; c) G. A. Olah, A. P. Fung, T. Keumi, *J. Org. Chem.* **1981**, *46*, 4305 – 4306.

[20] Although four systems based on H_2O_2 ($RuCl_3$/AcOH, HF/BF_3, vanadyl tetraphenoxyphthalocyanine, and TS-1) with ring/chain ratios of 100:0 have been reported (Table S3), the regioselectivities for *para*-**2g** (14–66%) were lower than that of **I** (77%).

[21] R. Augusti, A. O. Dias, L. L. Rocha, R. M. Lago, *J. Phys. Chem. A* **1998**, *102*, 10723 – 10727.

[22] a) D. M. Jerina, J. W. Daly, B. Witkop, *Biochemistry* **1971**, *10*, 366 – 372; b) B. Meunier, S. P. de Visser, S. Shaik, *Chem. Rev.* **2004**, *104*, 3947 – 3980.

[23] a) E. Hata, T. Takai, T. Yamada, T. Mukaiyama, *Chem. Lett.* **1994**, 1849 – 1852; b) D. M. Jerina, D. R. Boyd, J. W. Daly, *Tetrahedron Lett.* **1970**, *11*, 457 – 460; c) K. H. Mitchell, C. E. Rogge, T. Gierahn, B. G. Fox, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3784 – 3789.

[24] The NIH shift value was investigated for hydroxylation of 4-deuterotoluene (**1g**-d_1). Hydroxylation proceeded with 67% retention and/or migration of deuterium in the formation of *para*-**2g**. This high NIH shift value is in the same range as those observed for hydroxylation of **1g**-d_1 by $[VO(O_2)(pic)(H_2O)_2]$ (70%), $[VO(acac)_2]/O_2$/aldehyde (50%), pyridine *N*-oxide/*hν* (59%), and natural enzymes (68–78%).[12a,22,23]

