ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Highly Efficient, Regioselective, and Stereospecific Oxidation of Aliphatic C−H Groups with H_2O_2, Catalyzed by Aminopyridine Manganese Complexes

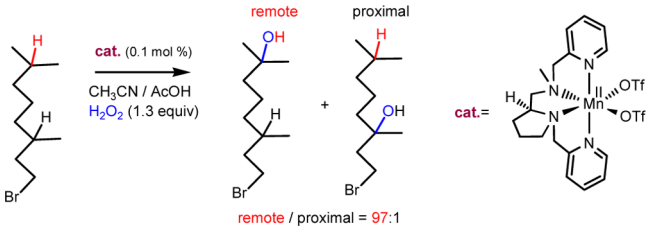
Roman V. Ottenbacher,[†] Denis G. Samsonenko,[‡] Evgenii P. Talsi,[§] and Konstantin P. Bryliakov*[,§]

Novosibirsk State University, Pirogova 2, Novosibirsk 630090, Russian Federation, Nikolaev Institute of Inorganic Chemistry, Pr. Lavrentieva 9, Novosibirsk 630090, Russian Federation, and Boreskov Institute of Catalysis, Pr. Lavrentieva 5, Novosibirsk 630090, Russian Federation

bryliako@catalysis.ru

Received May 3, 2012

ABSTRACT



Aminopyridine manganese complexes $[LMn^{II}(OTf)_2]$ having a similar coordination topology catalyze the oxidation of unactivated aliphatic C−H groups with H_2O_2, demonstrating excellent efficiency (up to TON = 970), site selectivity, and stereospecificity (up to >99%).

Direct C−H transformations have attracted particular interest as valuable tools for the synthesis of natural and unnatural compounds, as well as mechanistic probes for the understanding of the properties of C−H groups.[1] While the oxidations of C−H bonds, catalyzed by enzymes, are widely present in nature, selective, efficient, and environmentally benign C−H oxidation catalyzed by synthetic low-molecular weight compounds remains a great contemporary challenge in synthetic chemistry.[1] To date, a vast number of nonheme iron based catalysts have been developed; some of those can conduct C−H oxidations with H_2O_2 with high selectivity and stereospecificity.[1] Major drawbacks, opposing their wide synthetic application, are the modest turnover numbers sustained by nonheme Fe systems,[2] and the lack of predictable selectivity in the catalytic oxidation of inactivated aliphatic C−H groups.[3]

Nonheme Mn catalyzed C−H oxidations with H_2O_2 have been less represented in the literature, with known examples mainly focusing on Mn complexes with 1,4,7-trimethyl-1,4,7-triazacyclononane (Me_3tacn) or its derivatives.[4]

[†] Novosibirsk State University.
[‡] Nikolaev Institute of Inorganic Chemistry.
[§] Boreskov Institute of Catalysis.

(1) (a) Christmann, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2740. (b) Que, L., Jr.; Tolman, W. *Nature* **2008**, *455*, 333. (c) Shul'pin, G. B. *Mini-Rev. Org. Chem.* **2009**, *6*, 95. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

(2) A notable exception is the Fe complexes with methylpyridine derivatized triazacyclononane ligands or with bulky pinene groups (> 50−100 turnovers).[3d,e]

(3) (a) Chen, M. S.; White, M. K. *Science* **2007**, *318*, 783. (b) Chen, M. S.; White, M. K. *Science* **2010**, *327*, 566. (c) Company, A.; Gómez, L.; Güell, M.; Ribas, X.; Luis, J. M.; Que, L., Jr.; Costas, M. *J. Am. Chem. Soc.* **2007**, *129*, 15766. (d) Company, A.; Gómez, L.; Fontrodona, X.; Ribas, X.; Costas, M. *Chem.—Eur. J.* **2008**, *14*, 5727. (e) Gomez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5720. (f) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 216. (g) Hitomi, Y.; Arakawa, K.; Funabiki, T.; Kodera, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3448. Nonheme iron based catalyst systems for C−H oxidations have been recently overviewed: (h) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939. (i) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (j) Shteinman, A. *Russ. Chem. Rev.* **2008**, *77*, 945. (k) Talsi, E. P.; Bryliakov, K. P. *Coord. Chem. Rev.* **2012**, *256*, 1418.

10.1021/ol3015122

Importantly, in many cases Mn catalysts demonstrated higher efficiencies than Fe ones (up to hundreds of turnovers), albeit with lower selectivity.[3k,4]

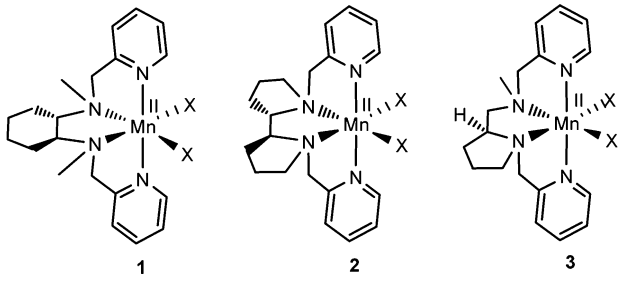


Figure 1. Manganese(II) complexes considered; X = $CF_3SO_3^-$.

Recently, Costas with co-workers reported that complex [(^{H,Me}Pytacn)Mn(CF_3SO_3)$_2$] performed eight catalytic turnovers in the oxidation of *cis*-1,2-dimethylcyclohexane.[3e] We have found that chiral complexes [((*S,S*)-bpmcn)Mn(CF_3SO_3)$_2$] (**1**) and [((*S,S*)-pdp)Mn(CF_3SO_3)$_2$] (**2**) catalyze the enantioselective epoxidation of various olefins with AcOOH and H_2O_2/AcOH with high efficiency (up to 1000 TON);[5] the structure of the aminopyridine ligand and a proper adjustment of reaction conditions were crucial for attaining high efficiency and predictable selectivity. In this work, we present the C−H oxidation reactivity of Mn complexes **1**−**3** (Figure 1): under appropriate conditions, they demonstrate previously unachievable high site selectivities and high efficiencies at the same time.

Complexes **1**,[3e,5a,6] **2**,[7] and [((*S*)-pmpp)Mn(CF_3SO_3)$_2$][8] (**3**, Figure 2) feature a similar *cis*-α-coordination topology, which was earlier shown to be crucial for achieving good catalytic efficiency and high alcohol/ketone selectivity in nonheme iron systems.[9]

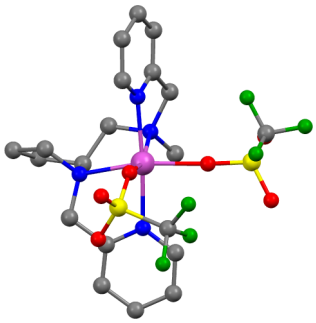
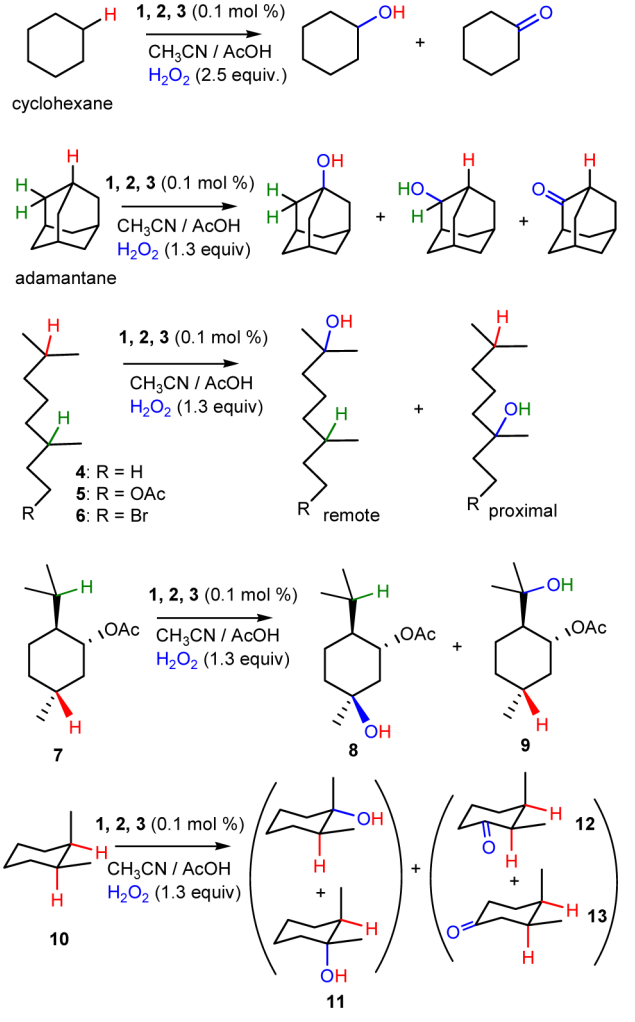


Figure 2. Ball-and-stick plot showing the X-ray structure[8] of complex [((*S*)-pmpp)Mn(CF_3SO_3)$_2$] (**3**). Hydrogen atoms excluded for clarity.

Scheme 1. Catalytic Oxidation of Various Aliphatic Alkanes



(4) (a) Lindsay Smith, J. R.; Shul'pin, G. B. *Tetrahedron Lett.* **1998**, *39*, 4909. (b) Shul'pin, G. B.; Lindsay Smith, J. R. *Russ. Chem. Bull.* **1998**, *47*, 2379. (c) Shul'pin, G. B.; Süss-Fink, G.; Lindsay Smith, J. R. *Tetrahedron* **1999**, *55*, 5345. (d) Shul'pin, G. B.; Süss-Fink, G.; Shul'pina, L. S. *J. Mol. Catal. A: Chem.* **2001**, *170*, 17. (e) Shul'pin, G. B.; Nizova, G. V.; Kozlov, Y. N.; Pechenkina, I. G. *New J. Chem.* **2002**, *26*, 1238. (f) Shul'pin, G. B. *J. Mol. Catal. A: Chem.* **2002**, *189*, 39. (g) Nizova, G. V.; Bolm, C.; Ceccarelli, S.; Pavan, C.; Shul'pin, G. B. *Adv. Synth. Catal.* **2002**, *344*, 899. (h) Bennur, T. H.; Sabne, S.; Desphande, S. S.; Srinivas, D.; Sivasanker, S. *J. Mol. Catal. A: Chem.* **2002**, *185*, 71. (i) Ryu, J. Y.; Kim, S. O.; Nam, W.; Heo, S.; Kim, J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1835. (j) Shul'pin, G. B.; Nizova, G. V.; Kozlov, Y. N.; Arutyunov, V. S.; dos Santos, A. C. M.; Ferreira, A. C. T.; Mandelli, D. *J. Organomet. Chem.* **2005**, *690*, 4498. (k) Nizova, G. V.; Shul'pin, G. B. *Tetrahedron* **2007**, *63*, 7997. (l) Shul'pin, G. B.; Matthes, M. G.; Romakh, V. B.; Barbosa, M. I. F.; Aoyagi, J. L. T.; Mandelli, D. *Tetrahedron* **2008**, *64*, 2143. (m) Romakh, V. B.; Rherrien, B.; Süss-Fink, G.; Shul'pin, G. B. *Inorg. Chem.* **2007**, *46*, 1315.

(5) (a) Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. *Inorg. Chem.* **2010**, *49*, 8620. (b) Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. *Adv. Synth Catal.* **2011**, *353*, 558. (c) Lyakin, O. Yu.; Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P. *ACS Catalysis* **2012**, *2*, 1196.

(6) X-ray structure of the (*R,R*)-enantiomer of complex **1** was reported in: Murphy, A.; Dubois, G.; Stack, T. D. P. *J. Am. Chem. Soc.* **2003**, *125*, 5250.

(7) X-ray structure of [((*S,S*)-pdp)Mn(CF_3SO_3)$_2$] (**2**) was reported in the Supporting Information for ref 5b.

(8) CCDC 877672 (Λ-α-[((*S*)-pmpp)Mn(CF_3SO_3)$_2$], complex **3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Additional X-ray data are provided in the Supporting Information.

(9) (a) Chen, K.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 6327. (b) Costas, M.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2002**, *41*, 2179.

Table 1. Cyclohexane Oxidation with H_2O_2 in the Presence of **1**–**3**[a]

	1	**2**	**3**
conversion,[b] %	84	68	72
A/K[c]	5.0	4.9	5.1
TN[d]	144	116	124

[a] Reaction conditions: solvent: 0.4 mL of CH_3CN + 0.08 mL of AcOH, [cyclohexane]/[H_2O_2]/[catalyst] = 400:20:0.1 μmol; 0 °C, oxidant added by syringe pump over 1 h, and reaction mixture stirred for additional 1 h. [b] Based on the oxidant, calculated as 100% × (alcohol + 2 ketone)/$[H_2O_2]_0$. [c] Alcohol/ketone ratio. [d] Turnover number, mol of products (A + K) per mol of catalyst.

Table 2. Catalytic Oxidation of Cyclohexane and Adamantane with H_2O_2 in the Presence of **1**–**3**[a]

				yield of products, %
substrate	catalyst	conversion, %[b,c]	3°/2°[d]	ketone/alcohol
cyclohexane	**1**	77.8 (778)	–	71.7:6.1
cyclohexane	**2**	87.0 (870)	–	84.2:2.8
cyclohexane	**3**	80.0 (800)	–	75.0:5.0
substrate	catalyst	conversion, %[b,c]	3°/2°[d]	1-ol/2-ol/2-one
adamantane	**1**	10.3 (103)	48	9.7:0.6:–
adamantane	**2**	70.6 (706)	40	65.7:3.2:1.7
adamantane	**3**	36.2 (362)[e]	49	34.1:2.1:–

[a] Reaction conditions: [Cyclohexane]/[H_2O_2]/[catalyst] = 100:250:0.1 μmol, 0 °C, solvent: 0.4 mL of CH_3CN + 0.08 mL of AcOH, oxidant added by syringe pump over 1 h, and reaction mixture stirred for additional 1 h. [Adamantane]/[H_2O_2]/[catalyst] = 100:130:0.1 μmol, 0 °C, solvent: 0.8 mL of CH_3CN + 0.6 mL of CH_2Cl_2 + 0.16 mL of AcOH, oxidant added by syringe pump over 30 min, and reaction mixture stirred for additional 5.5 h. [b] Conversion based on the substrate. [c] Turnover number given in parentheses, in mol of products per mol of catalyst. [d] 3°/2° = 3 × [1-adamantanol]/([2-adamantanol] + [2-adamantanone]). [e] Oxidant added over 2 h.

Cyclohexane is one of the most widely used 'test substrates' for catalyzed C–H oxidations, since it enables free-radical-driven oxidation to be readily distinguished from the metal-based one: in the former case, the observed cyclohexanol/cyclohexanone ratio is expected to be close to 1.0, while, in the latter one, it should be substantially higher than 1.[10] The results of the cyclohexane oxidation (Scheme 1) are presented in Table 1. For all catalysts, the A/K ≈ 5 (clearly indicative of metal-based oxidant) values are the highest ever reported for nonheme manganese catalyzed cyclohexane oxidations with H_2O_2.[3k] Under these model conditions ([H_2O_2] ≪ [substrate], Table 1), **1**–**3** performed 115–144 catalytic turnovers, which is already higher than that for most of the related iron-based catalysts.[3,9] Under practical conditions ([H_2O_2] ≥ [substrate]), the catalytic efficiencies are even more impressive, up to a TON of 870 (Table 2).

At high oxidant/substrate ratios, the reaction yields mainly cyclohexanone (apparently via further oxidation of the initially formed cyclohexanol), which requires two molecules of H_2O_2 per one substrate molecule.

Adamantane oxidation occurs predominately at more electron-rich tertiary C–H groups (3°/2° values of 40–49),[11] despite a 3-fold statistical prevalence of secondary C–H groups, yielding 1-adamantanol as the main product (2-adamantanol and 2-adamantanone are the major and minor byproduct, respectively).

To probe the electronic effects on the oxidation site selectivity, in particular the influence of electron-withdrawing groups, the oxidation of substrates **4**–**6** containing different substituents at the same position has been performed (Table 3). While the oxidation of 2,6-dimethyloctane yields an equimolar mixture of 'remote' and 'proximal' oxidation products, introduction of electron acceptors substantially deactivates the proximal tertiary C–H group. In the case of **6**, the observed remote/proximal ratio varies from 34:1 up to 97:1; to the best of our knowledge, these values are the highest reported for nonheme metal catalysts.[3] The oxidation of tertiary C–H groups in the presence of catalysts **1**–**3** is highly sensitive to the steric environment: (–)-acetoxy-*p*-menthane **7** yields predominately product **8** with all catalysts (Table 4). Complex **2** demonstrates an unprecedented selectivity for **8** over **9** (57:1 at 0 °C; at –10 °C, **8** is formed as the only detectable product).

To test the scalability of the C–H oxidations, larger-scale oxidation of substrates **5**, **6**, and **7** in the presence of catalyst **2** were carried out (Supporting Information); after column chromatography separation, the isolated yields of major oxidation products were 49, 52, and 66%, which is

Table 3. Catalytic Oxidation of Substrates **4**–**6**[a]

			yield of products, %		
substrate	catalyst	conversion, %[b,c]	remote	proximal	remote/proximal
4	**1**	63.5 (635)	31.8	31.8	1:1
4	**2**	68.8 (688)	34.4	34.4	1:1
4	**3**	57.8 (578)	28.9	28.9	1:1
5	**1**	49.1 (491)	43.1	6.0	7:1
5	**2**	53.4 (534)	46.6	6.9	7:1
5	**3**	44.0 (440)	37.6	6.4	6:1
6	**1**	67.7 (677)	56.2	1.5	37:1
6	**2**	74.1 (741)	67.6	2.0	34:1
6	**3**	44.5 (445)	43.5	0.45	97:1

[a] Reaction conditions: solvent: 0.4 mL of CH_3CN + 0.08 mL of AcOH, oxidant added by syringe pump over 30 min, and reaction mixture stirred for additional 2.5 h, [alkane]/[H_2O_2]/[catalyst] = 100:130:0.1 μmol, 0 °C. [b] Conversion based on the substrate. [c] Turnover number given in parentheses, in mol of products per mol of catalyst.

(10) (a) Tanase, S.; Bowman, E. In *Advances in Inorganic Chemistry*, Vol. 58; van Eldik, R., Reedijk, J., Eds.; Academic Press: 2006; p 29. (b) Costas, M.; Chen, K.; Que, L., Jr. *Coord. Chem. Rev.* **2000**, *200–202*, 517.

(11) These 3°/2° selectivities are among the highest reported for nonheme Fe and Mn catalysts (up to 48); see refs 10a, 10b.

Table 4. Oxidation of (−)-Acetoxy-*p*-menthane (**7**) and *cis*-1,2-Dimethylcyclohexane (**10**) with H_2O_2 in the Presence of **1**−**3**[a]

			yield of products	
substrate	catalyst	conversion, %[b,c]	**8:9**, %	**8:9**
7	**1**	58.2 (582)	51.5:3.3	16:1
7	**2**	69.5 (695)	68.3:1.2	57:1
7	**3**	64.0 (640)	56.0:4.3	13:1
7	**2**[d]	27.9 (279)	27.9:–	–
substrate	catalyst	conversion, %[b,c]	**11:12:13**, %	RC, %[e]
10	**1**	89.4 (894)	79.7:4.9:4.9	>99
10	**2**	97.0 (970)	92.9:1.7:2.3	>99
10	**3**	84.6 (846)	75.6:4.5:4.5	>99

[a] Reaction conditions: solvent: 0.4 mL of CH_3CN + 0.08 mL of AcOH, oxidant added by syringe pump over 30 min, and reaction mixture stirred for additional 3.5 h, [alkane]/[H_2O_2]/[catalyst] = 100:130:0.1 μmol, 0 °C. [b] Conversion based on the substrate. [c] Turnover number given in parentheses, in mol of products per mol of catalyst. [d] At −10 °C. [e] RC = 100% × [((1*R*,2*R*)-**11** + (1*S*,2*S*)-**11**) − ((1*R*,2*S*)-**11** + (1*S*,2*R*)-**11**)]/[((1*R*,2*R*)-**11** + (1*S*,2*S*)-**11**) + ((1*R*,2*S*)-**11** + (1*S*,2*R*)-**11**)].

comparable or only a few percent lower than those under model conditions (cf. Tables 3 and 4).

Finally, the stereospecificity of catalysts **1**−**3** was probed using *cis*-1,2-dimethylcyclohexane as the test substrate (Table 4). The oxidations yield mainly the tertiary alcohol **11** in good to high yields and with excellent (>99%) retention of the *cis*-configuration, ketones **12** and **13** being minor byproducts

In summary, the oxidation of aliphatic C−H groups with H_2O_2 is efficiently catalyzed by *cis*-α-aminopyridine manganese complexes **1**−**3**, in the presence of acetic acid. All three catalysts demonstrate unprecedented high selectivity and stereospecificity, and high efficiency (up to 970 turnovers) and good oxidant economy at the same time. The reactivity of catalysts **1**−**3** is sufficient to complete the reaction within an acceptable time (2−4 h) at low catalyst loadings (0.1 mol %). The most plausible origin of the much higher efficiency of manganese systems (as compared with iron ones) is their higher reactivity, which allows lower catalyst loadings (0.1 mol % for Mn vs 1.0−15.0 mol % for Fe), thus reducing the catalyst degradation via bimolecular collisions. We believe that the predictable site selectivity and excellent efficiency of aminopyridine manganese complexes will appreciably elevate the area of transition metal catalyzed sustainable regio- and stereoselective C−H oxidations and epoxidations.[5b,c] Further studies will be aimed at the elucidation of the nature of catalytically active species and at the application of the novel catalyst systems for preparative catalytic syntheses of complex molecular structures.

Acknowledgment. This work was supported by the Russian Foundation for Basic Research, Grant 12-03-00782. We thank Dr. O. Yu. Lyakin (Boreskov Institute of Catalysis) for the donation of the (*S,S*)-pdp chiral ligand which was used for the synthesis of complex **2**.

Supporting Information Available. Experimental procedures, copies of ^1H and ^{13}C NMR spectra, and the X-ray data for complex **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.