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Highly Enantioselective C-H Oxidation of Arylalkanes with H_2O_2 in the Presence of Chiral Mn Aminopyridine Complexes

Evgenii P. Talsi,[a,b] *Denis G. Samsonenko,*[a,c] *Roman V. Ottenbacher,*[a,b] *and Konstantin P. Bryliakov*[a,b]*

[a] Prof. Dr. E. P. Talsi, Dr. D. G. Samsonenko, Dr. R. V. Ottenbacher, Prof. Dr. K. P. Bryliakov, Novosibirsk State University, Pirogova 2, Novosibirsk 630090, Russian Federation, E-mail: bryliako@catalysis.ru

[b] Prof. Dr. E. P. Talsi, Dr. R. V. Ottenbacher, Prof. Dr. K. P. Bryliakov, Boreskov Institute of Catalysis, Pr. Lavrentieva 5, Novosibirsk 630090, Russian Federation

[c] Dr. D. G. Samsonenko, Nikolaev Institute of Inorganic Chemistry, Pr. Lavrentieva 3, Novosibirsk 630090, Russian Federation

Abstract

Bioinspired chiral Mn-aminopyridine complexes [((*S,S*)-$LMn^{II}(OTf)_2$] and [((*R,R*)-$LMn^{II}(OTf)_2$] (where (*S,S*)-L = (*2S,2'S*)-1,1'-bis((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-2,2'-bipyrrolidine, and (*R,R*)-L = (*2R,2'R*)-1,1'-bis((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-2,2'-bipyrrolidine) have been shown to efficiently catalyze the benzylic C-H oxidation of arylalkanes with hydrogen peroxide in the presence of carboxylic acid additives, affording enantiomerically enriched 1-arylalkanols and the corresponding ketones. Optically pure additive *N*-Boc-(*L*)-proline, in combination with [((*R,R*)-$LMn^{II}(OTf)_2$] complex, affords 1-arylalkanols having up to 86 % *ee*, which is the highest reported enantioselectivity for direct benzylic hydroxylations with H_2O_2 in the presence of transition metal catalysts. Oxidative kinetic resolution only slightly contributes to the increase of the observed enantiomeric excess over the reaction course. The observed k_H/k_D values (3.5…3.6 for the oxidation of ethylbenzene/d_{10}-ethylbenzene) and competitive oxidation data are consistent with either hydrogen-atom transfer/oxygen rebound, or hydride transfer/oxygen rebound asymmetric hydroxylation mechanism.

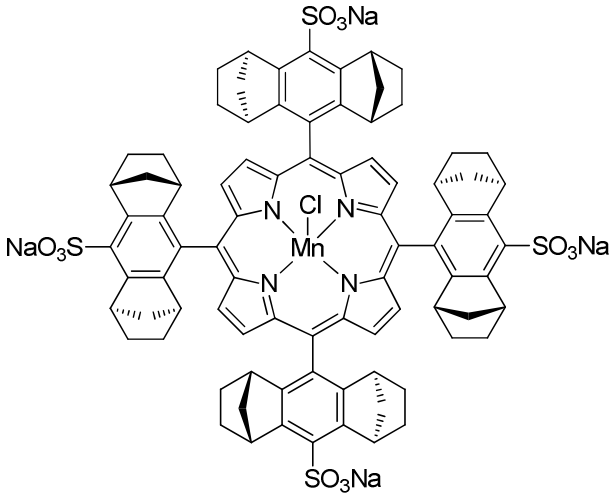
Introduction

The design of biomimetic transition metal based catalyst systems, capable of conducting the selective C-H oxidations, had been continuous attraction for years;[1,2] this interest had been further encouraged by the publications by White and co-workers who showed that bioinspired iron aminopyridine complexes mediate the oxidation of non-activated aliphatic C-H groups in complex organic molecules with environmentally benign oxidant H_2O_2 in a predictably selective fashion.[3] From the practical perspective, the reactivity and site-selectivity are the key factors, determining the possibility of introducing oxygen atoms at particular position of a desired substrate; ideally, development of a variety of transition metal catalysts covering whole range of C-H groups of potential substrates may be the gate to a new era of C-H oxofunctionalization. In recent years, there has been appreciable progress in this direction. For example, the interplay between steric bulk and electronic properties of the elaborate chiral aminopyridine iron catalysts enabled Costas and co-workers to manipulate the oxidation selectivity of complex steroidal substrates, in particular diverting it toward 2° C-H groups over 3° C-H groups.[4] Others have documented the high selectivity and efficiency of manganese based catalysts in catalyzed aliphatic and benzylic C-H oxidations, including the oxidation of arylalkanes and benzylic alcohols.[5]

Apparently, next step would be achieving stereoselectivity in "green" C-H oxidations with H_2O_2 mediated by highly efficient metal based catalysts. Until very recently, it was only the manganese porphyrin complex **1** (Figure 1), reported by Simonneaux with co-workers, for which the asymmetric oxidation of prochiral benzylic groups with H_2O_2 had been documented,[6a,b] with the oxidation of *p*-ethyltoluene yielding the corresponding 1-(*p*-tolyl)ethanol with up to 57 % *ee*. The catalytic protocol required rather high (2.5 mol. %) catalyst loading and a 5-fold excess (relative to alkane) of H_2O_2. Costas and Bietti developed a desymmetrization-based protocol for the oxidation of monosubstituted cyclohexanes in the presence of manganese complexes **2a** and **2b** (Figure 1); the oxidation occurred preferentially at the 3rd position, affording the corresponding chiral C3-ketones.[6c] For the best substrates – bulky amide-substituted cyclohexanes – enantiomeric excess

values of 62-96 % *ee* were reported using 2 mol. % of catalyst **2b**, 3.5 equiv. of H_2O_2, and cyclopropanecarboxylic acid as the catalytic additive.[6c]

In a recent paper, mostly dedicated to the kinetic resolution of 1-arylalkanols, we announced the oxidation of ethylbenzene and several *p*-substituted homologues with H_2O_2 in the presence of manganese complex **3** and 2-ethylhexanoic acid, affording chiral 1-arylalkanols with up to 50 % *ee*, the catalyst performing several hundreds of catalytic turnovers.[6d] In this contribution, we are presenting the detailed study of the asymmetric benzylic oxidation of arylalkanes, with substantial improvements of the initial protocol. In particular, it has been found that the chiral environment amplification (the use of chiral catalytic additive *N*-Boc-proline) drastically enhances the oxidation stereoselectivity up to > 80 % *ee*; the asymmetric induction level slightly benefits from the oxidative kinetic resolution of the 1-arylalkanol. The chiral match/mismatch effects and the preliminary mechanistic data are discussed.



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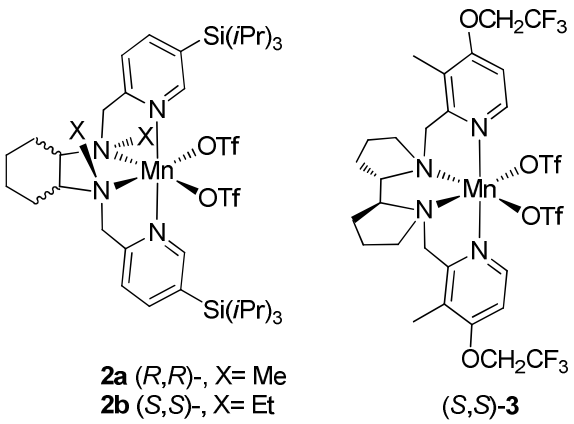


2a (*R*,*R*)-, X= Me
2b (*S*,*S*)-, X= Et

(*S*,*S*)-**3**

Figure 1. Manganese based catalysts for the asymmetric C-H oxidations with H_2O_2.

Results and discussion

The oxidation of ethylbenzene in the presence of manganese complex (*S*,*S*)-**3**[6d] and its enantiomer (*R*,*R*)-**3** (Figure 2), using various carboxylic acids as catalytic additives (Figure 3) has been studied. The results are collected in Table 1. The oxidation in the presence of acetic acid has afforded a mixture of acetophenone and 1-phenylethanol, the latter having 34 % *ee* optical purity (Table 1, entry 1). The use of *n*-butyric acid leads to poor oxidation yield, whereas branched carboxylic acids, with substituents at the α-carbon, usually ensure higher yields and higher enantioselectivities compared with acetic acid (Table 1, entries 3-6), 2-ethylhexanoic and cyclohexanecarboxylic acid demonstrating the highest enantioselectivity and substrate conversion at the same time (entries 5 an 6). Complex (*R*,*R*)-**3** has shown the same catalytic performance with EHA (Table 1, entries 6 and 7). We notice that for the case of EHA, the contribution of oxidative kinetic resolution of the initially formed 1-phenylethanol can be ruled out,[6d] the observed enantioselectivity being solely generated at the asymmetric C-H oxidation step itself.

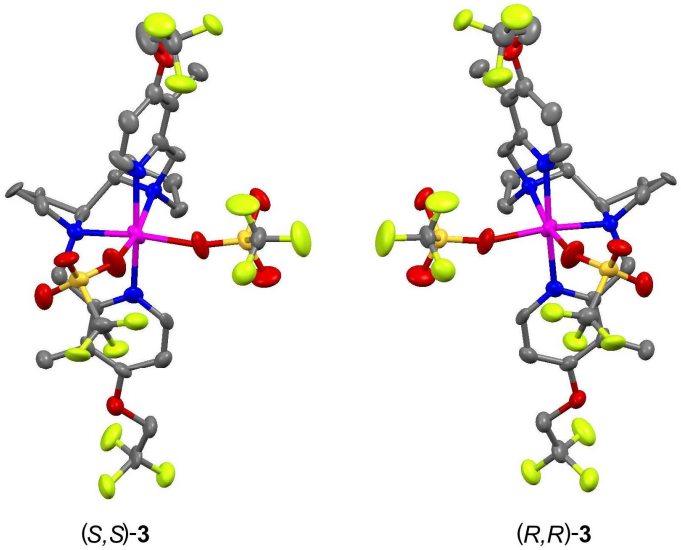


Figure 2. Molecular structures of complex (*S*,*S*)-**3**[6d] and its enantiomer (*R*,*R*)-**3**. Mn magenta, N blue, S orange, F yellow, C grey, O red. Thermal ellipsoids drawn at 50 % probability level. Three (out of four) complexes of the asymmetric unit, hydrogen atoms, and rotational disorder of triflates have been omitted for clarity. Full asymmetric unit of (*R*,*R*)-**3** can be found in Figure S1 (SI).

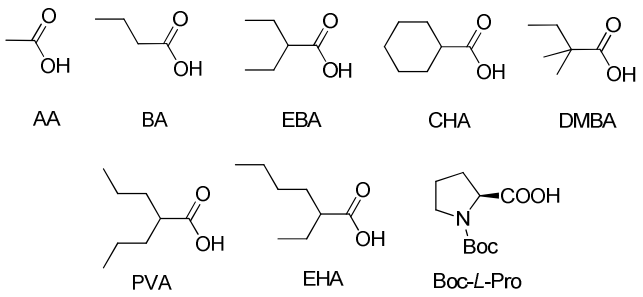
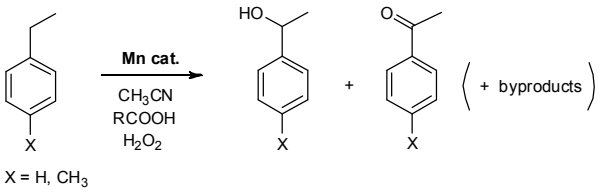


Figure 3. Structure of carboxylic acids used as additives in this work, and the abbreviations used.

Table 1. Oxidation of ethylbenzene and *p*-ethyltoluene with H_2O_2 in the presence of complexes (*S*,*S*)-**3** and (*R*,*R*)-**3**.[a]



No	catalyst	X	additive (μmol)	substrate conversion (μmol)	yield of alcohol / ketone / other [b] (μmol)	A / K [c]	*ee* of alcohol (%)[d]	config.
1	(*S*,*S*)-**3**	H	AA (600)	37	15 / 19 / 3 [e]	0.8	34	(*S*)
2	(*S*,*S*)-**3**	H	BA (100)	7	4 / 2 / 1	2	10	(*S*)
3	(*S*,*S*)-**3**	H	EBA (100)	34	11 / 23 / < 1	0.5	35	(*S*)
4	(*S*,*S*)-**3**	H	DMBA (100)	35	14 / 21 / –	0.7	30	(*S*)
5	(*S*,*S*)-**3**	H	CHA (100)	41	13 / 27 / 1	0.5	41	(*S*)
6	(*S*,*S*)-**3**	H	EHA (100)	43	15 / 27 / 1	0.5	35	(*S*)
7	(*R*,*R*)-**3**	H	EHA (100)	40	15 / 24 / 1	0.6	34	(*R*)
8	(*S*,*S*)-**3**	CH_3	AA (100)	31	20 / 8 / 3	2.6	41	(*S*)
9	(*S*,*S*)-**3**	CH_3	EBA (100)	31	21 / 8 / 2	2.6	40	(*S*)
10	(*S*,S)-**3**	CH_3	DMBA (100)	31	19 / 10 / 2	1.9	44	(*S*)
11	(*S*,*S*)-**3**	CH_3	CHA (100)	27	17 / 8 / 2	2.1	42	(*S*)
12	(*S*,*S*)-**3**	CH_3	EHA (100)	44	25 / 16 / 3 [e]	1.6	50	(*S*)
13	(*S*,*S*)-**3**	CH_3	Boc-*L*-Pro (100)	28	16 / 9 / 3	1.8	50	(*S*)
14	(*R*,*R*)-**3**	CH_3	Boc-*L*-Pro (100)	29	13 / 13 / 3	1.0	86	(*R*)
15	(*R*,*R*)-**3**	CH_3	Boc-*L*-Pro (30)	22	13 / 6 / 3	2.2	80	(*R*)
16	(*S*,*S*)-**3**	H	Boc-*L*-Pro (30)	31	10 / 20 / 1	0.5	49	(*S*)
17	(*R*,*R*)-**3**	H	Boc-*L*-Pro (30)	22	10 / 12 / –	0.8	76	(*R*)

[a] At 0 °C; [substrate]:[H_2O_2]: [Mn] = 200 μmol : 70 μmol : 0.1 μmol, oxidant added via syringe pump over 30 min and the mixture stirred for an additional 3 h, and product yields and *ee*s were determined by analyzing the reaction mixture by chiral HPLC. [b] Other products were: esters; traces

of (1-hydroperoxyethyl)benzene, etc. (see SI for details). [c] Alcohol/ketone ratio. [d] Determined by chiral HPLC. [e] From ref. 6d.

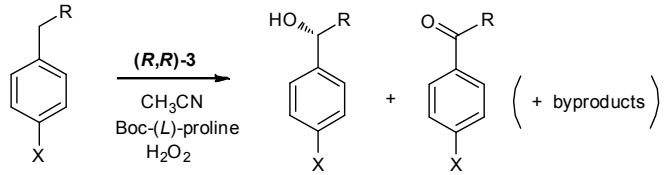
The oxidation of *p*-ethyltoluene in the presence of a variety of carboxylic acids (Table 1, entries 8-12) has shown somewhat different trend: in this case, CHA demonstrated inferior results than DMBA and EHA; the use of EHA ensured the highest substrate conversion and the highest alcohol *ee* at the same time (entries 10-12). In this case, the alcohol/ketone ratios (1.6…2.6, entries 8-12) were higher than for the oxidation of ethylbenzene in the presence of branched acids (0.5…0.7, entries 3-7), apparently, due to somewhat higher reactivity of *p*-ethyltoluene, compared with ethylbenzene (see below).

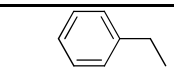
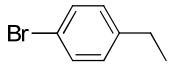
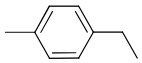
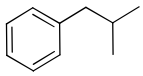
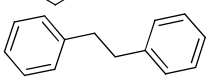
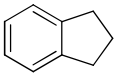
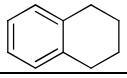
Commercially available 2-ethylhexanoic acid is a racemic mixture of (*R*) and (*S*) enantiomers, which may lead to two diastereomeric catalytically active sites, featuring different stereoselectivities and thus deteriorating the *ee*. One could expect that the use of proper (optically pure) chiral carboxylic acid as additive could positively affect the stereochemical outcome of the C-H oxidation reaction, like it was previously reported for the asymmetric epoxidations of olefins[7] and oxidative kinetic resolution of 1-arylalkanols.[6d] Herewith, the possibility of such *chiral additive amplification* has been tested using optically pure *N*-Boc-(*L*)-proline as the chiral additive (Table 2, entries 13, 14). The oxidation of *p*-ethyltoluene by the system (*S*,*S*)-**3**/Boc-(*L*)-Pro/H_2O_2 has demonstrated the same enantioselectivity as that by the system with (*S*,*S*)-**3**/EHA/H_2O_2 (entries 13 vs. 12). By contrast, the enantioselectivity of the system (*R*,*R*)-**3**/Boc-(*L*)-Pro/H_2O_2 has been much higher than that of (*S*,*S*)-**3**/Boc-(*L*)-Pro/H_2O_2 (cf. entries 14 and 13) at similar substrate conversion levels, thus indicating proper chiral matching between the chiral catalyst and chiral additive. When the amount of added Boc-(*L*)-Pro was reduced from 100 to 30 μmol, the conversion dropped slightly, but the alcohol/ketone ratio increased twice (the yield of alcohol was the same, the yield of ketone being twice smaller) (entry 15 vs. 14). The enantioselectivity was several per cent lower, probably due to smaller contribution of oxidative kinetic resolution (see below). The oxidation of

ethylbenzene by the system (*R*,*R*)-**3**/Boc-(*L*)-Pro/H_2O_2 has also been found much more enantioselective than by (*S*,*S*)-**3**/Boc-(*L*)-Pro/H_2O_2 (76 vs. 49 % *ee*, entries 16 and 17).

The oxidation of several substrates by the system (*R*,*R*)-**3**/Boc-(*L*)-Pro/H_2O_2 has been studied (Table 2). In some cases (*p*-Br-ethylbenzene, *p*-ethyltoluene, isobutylbenzene), enantioselectivities approaching or exceeding 80 % *ee* have been observed. This is much higher than for the asymmetric C-H oxidations with H_2O_2, catalyzed by manganese porphyrin complex **1** (which showed 57 % *ee* at best),[6a,b] catalysts (*S*,*S*)-**3** and (*R*,*R*)-**3** also being much more efficient (performing 200-300 of turnovers under the reaction conditions), and producing 50-160 molecules of chiral alcohol per molecule of catalysts. The oxidant efficiency was moderate, 70 μmol of H_2O_2 affording 10-20 μmol of products (alcohol + ketone, Table 2). Nevertheless, this efficency is comparable with that of the system of Costas and Bietti, which requires 3.5 equiv. of H_2O_2, and is much better than for the Cu/Au nanoparticles-based system of Hua and co-workers, which requires ca. 15 equivalents of H_2O_2.[6e]

Table 2. Oxidation of alkylarenes with H_2O_2 in the presence of complexes (*R*,*R*)-**3**.[a]



No	substrate	substrate conversion (μmol)	yield of alcohol / ketone / other (μmol)	A / K [b]	TON [c]	*ee* of alcohol (%) [d]	config.[d]
1		22	10 / 12 / –	0.8	340	76	(*R*)
2		15	5 / 10 / < 0.5	0.5	250	78	(*R*)
3		22	13 / 6 / 3	2.2	25	80	(*R*)
4		9.5	5.5 / 4 / < 0.5	1.4	135	79	n/a [e]
5		13.5	7 / 6 / 0.5 [f]	1.3	190	70	n/a [e]
6		20	10 / 10 / –	1.0	300	44	(*R*)
7		22	17 / 5 / –	3.4	270	19	(*R*)

[a] At 0 °C; [substrate]:[H_2O_2]:[additive]:[Mn] = 200 μmol : 70 μmol : 30 μmol : 0.1 μmol, oxidant added via syringe pump over 30 min and the mixture stirred for an additional 3 h, and product yields and *ee*s were determined by analyzing the reaction mixture by chiral HPLC. [b] Alcohol/ketone ratio. [c] For this table, turnover numbers, TON, have been calculated as ([A]+2[K])/$[Mn]_0$. [d] Determined by chiral HPLC. [e] Not assigned. [f] Product yields were determined by GS-MS.

Apparently, in the presence of Boc-(*L*)-Pro, kinetic resolution of the initially formed alcohol[6d] could contribute to the observed enantioselectivity. The effect of kinetic resolution on the asymmetric oxidation of ethylbenzene by the system (*R*,*R*)-**3**/Boc-(*L*)-Pro/H_2O_2 has been tested by extending the reaction to higher conversions (Figure 4). One can see that the enantiomeric excess slowly increases from 71 % *ee* at ca. 200 catalyst turnovers to 83 % *ee* at ca. 750 turnovers, which gain is not very significant; the major source of asymmetric induction remains enantioselective oxidation itself. One can see that the yield of 1-phenylethanol approaches its maximum value of ca. 10 μmol and further slowly decreases over the reaction course, while the amount of ketone monotonously grows up, thus becoming the major reaction product.

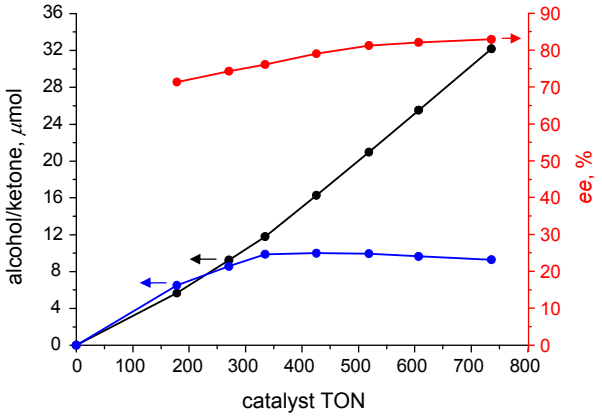


Figure 4. Plot of the amounts of alcohol (blue), ketone (black), and of alcohol *ee* (red) in the course of ethylbenzene oxidation by the system (*R*,*R*)-**3**/Boc-(*L*)-Pro/H_2O_2 ([substrate]:[Mn]:[Boc-(*L*)-Pro] = 200 μmol : 0.1 μmol : 30 μmol) at 0 °C vs. catalyst turnover number, TON, calculated as ([alcohol]+2[ketone])/[(*R*,*R*)-**3**]$_0$.

To get preliminary data on the oxidation mechanism, primary KIE for the oxidation of ethylbenzene/d_{10}-ethylbenzene in the presence of catalysts **3** has been measured. Three experiments,

performed in the presence of different carboxylic acids, have returned very close k_H/k_D values of 3.5...3.6 (similar to those previously documented for the oxidations of cumene/α-D-cumene derivatives in the presence of structurally similar Mn catalysts[5c]), thus corroborating that the benzylic hydrogen lies on the reaction coordinate of the rate-limiting step.

Next, competitive oxidations of *p*-substituted ethylbenzenes have been performed (Figure 5),[8] revealing good linear Brown-Okamoto correlation, with ρ^+ value of ca. -1.4, which fits within typical range for hydroxylations by electron-deficient transition-metal complexes (-1.0…-2.0),[9] and is close to the ρ^+ value of -1.0, reported for the oxidation of *p*-substituted cumenes in the presence of a structurally similar manganese catalyst.[5c] Previously, we proposed the benzylic oxidation (of cumenes) to proceed via rate-limiting hydrogen abstraction, followed by oxygen rebound.[5c] At the same time, keeping in mind (1) the apparently high electrophilicity of the putative oxomanganese(V) species, and (2) the stability of benzylic cations, the Log(k_X/k_H) correlation vs. polar substituent parameter σ_p^+ may as well reflect hydride abstraction mechanism (Figure 6). Hydride transfer mechanism has been previously invoked in oxometal-mediated C-H oxidations.[10] At the moment there is not enough data to reasonably discriminate between the two scenarios; however, this issue will be addressed in a subsequent separate study.

Table 3. KIE values for oxidation of ethylbenzene/d_{10}-ethylbenzene by catalyst systems **3**/acid/H_2O_2.[a]

No	acid	Catalyst	conversion, μmol	k_H/k_D
1	AA	(*S*,*S*)-**3**	146	3.6
2	PVA	(*S*,*S*)-**3**	137	3.6
3	EHA	(*R*,*R*)-**3**	127	3.5

[a] Conditions: 0 °C, [ethylbenzene]:[d_{10}-ethylbenzene]:[(*R*,*R*)-**3**]:[H_2O_2] = 150 μmol : 300 μmol : 0.2 μmol : 450 μmol), oxidant added via syringe pump over 2 h, the mixture stirred for an additional 3 h; 10 mg of PPh_3 was added to ensure the absence of traces of hydroperoxides, and the mixture was analyzed by NMR and chiral HPLC to provide the yields of alcohols, ketones, and residual alkylarenes. For details see Supporting Information.

10.1002/cctc.201701169

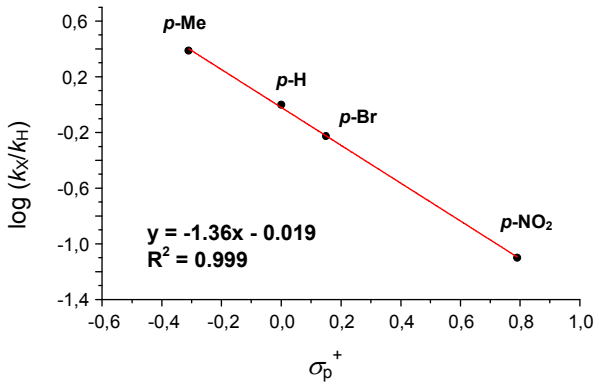


Figure 5. Hammett plot for the competitive oxidation of *p*-substituted ethylbenzenes with H_2O_2.[8] For details see Supporting Information.

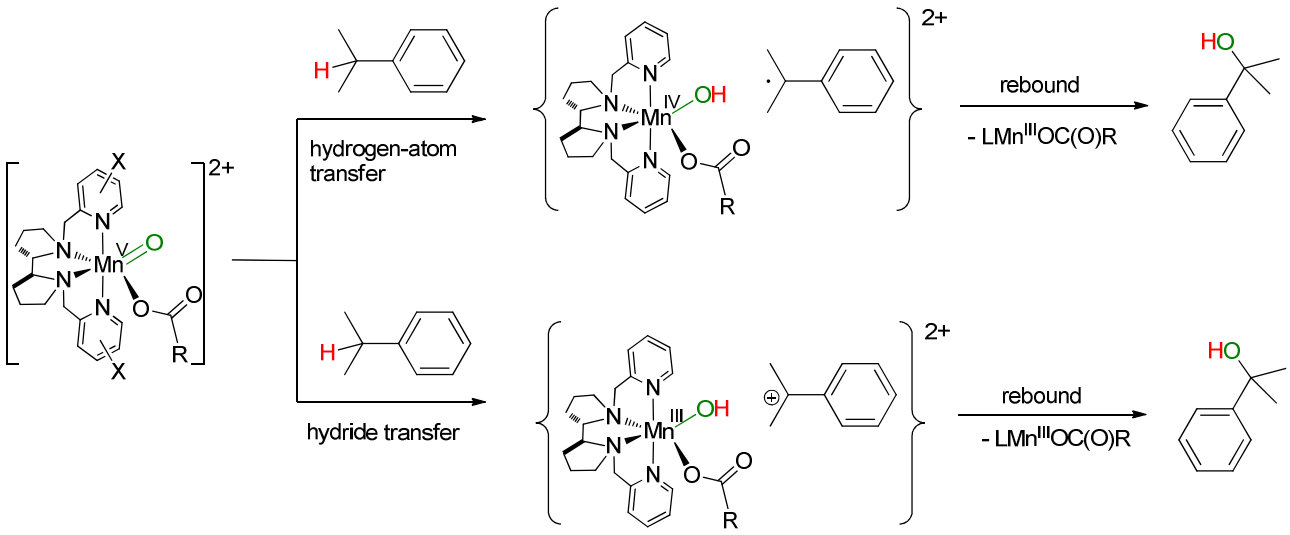


Figure 6. Two alternatives for the proposed mechanism of benzylic C-H oxidation wirh H_2O_2 in the presence of Mn aminopyridine complexes.

Conclusions

Herewith, we have shown that bioinspired chiral Mn-aminopyridine complexes [((*S,S*)-$LMn^{II}(OTf)_2$] and [((*R,R*)-$LMn^{II}(OTf)_2$] (where (*S,S*)-L = (*2S,2'S*)-1,1'-bis((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-2,2'-bipyrrolidine, and (*R,R*)-L = (*2S,2'S*)-1,1'-bis((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)-2,2'-bipyrrolidine) are capable of catalyzing the benzylic oxidation of arylalkanes with hydrogen peroxide, performing several hundreds of catalytic

turnovers, and affording enantiomerically enriched 1-arylalkanols and the corresponding ketones. The choice of carboxylic acid additive is crucial for achieving high alcohol/ketone ratio and high enantioselectivity. While the use of simple achiral or racemic carboxylic acids results in low to moderate enantioselectivities (10-50 % *ee*), optically pure additive *N*-Boc-(*S*)-proline, in combination with [((*R,R*)-LMn^{II}(OTf)$_2$], affords 1-arylalkanols having up to 86 % *ee*. This is the highest reported enantioselectivity level for direct catalyzed benzylic hydroxylations with H_2O_2, and is among the highest enantioselectivities ever reported for transition metal catalyzed benzylic C-H oxidations with other oxidants (2,6-dichloropyridine *N*-oxide and iodosylarenes).[11] In addition, the catalytic efficiency of our catalysts (in mol of chiral alcohol per mol of catalyst) is also among the highest reported values.[6,11]

Oxidative kinetic resolution has relatively small contribution to the amplification of the enantiomeric excess over the reaction course, the major source of asymmetric induction being enantioselective oxidation itself. Currently available mechanistic data (k_H/k_D values of 3.5…3.6 and linear Brown-Okamoto correlations with ρ^+ value of -1.4) may reflect the hydrogen-atom transfer/oxygen rebound or hydride-transfer/oxygen rebound oxidation mechanism. Detailed mechanistic study of Mn-aminopyridine catalyzed asymmetric benzylic C-H oxidations will be reported in a separate study.

At the moment, the major drawback is the pronounced overoxidation of the formed chiral alcohol to the ketone, which makes one use high excess of substrate and stop the reaction at low conversion levels, so that the yield of chiral alcohol is limited to 50-160 molecules per one catalyst molecule, which restricts the immediate synthetic application of the proposed system. This challenging problem will be addressed in further investigations.

Associated content

Supporting information, including description of materials and methods, synthetic procedures, general procedures for C-H oxidations, HPLC separation details, details of KIE and competitive oxidation experiments, and crystal data for complex (*R*,*R*)-**3**. CCDC 1555788 ((*R*,*R*)-**3**) contains the

supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via ww.ccdc.cam.ac.uk/data_request/cif and from the authors.

Acknowledgements

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Keywords

Asymmetric catalysis; C-H hydroxylation; enzyme models; hydrogen peroxide; manganese

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[8] For correct measurements, the catalyst system should be equally reactive toward both prochiral benzylic C-H atoms, i.e. be non-stereoselective. That is why another manganese complex, [((*S,S*)-dpo)$Mn^{II}(OTf)_2$], was taken (see SI for details), together with acetic acid as additive: this particular combination has been previously reported to perform racemoselective benzylic C-H oxidation (see ref 6d).

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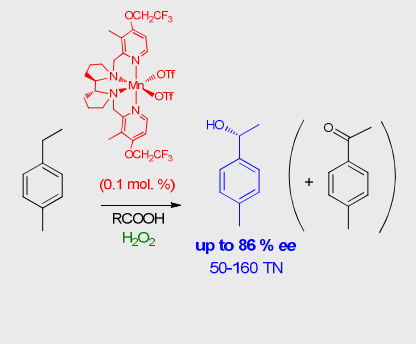
Layout 1:

FULL PAPER

Towards green asymmetric C-H oxidations: catalyst system based on bioinspired Mn aminopyridine complex is presented, which is capable of catalyzing the asymmetric benzylic oxidation of arylalkanes with hydrogen peroxide, affording 1-arylalkanols with up to 86 % *ee*.



*Evgenii P. Talsi, Denis G. Samsonenko, Roman V. Ottenbacher, and Konstantin P. Bryliakov**

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Highly Enantioselective C-H Oxidation of Arylalkanes with H_2O_2 in the Presence of Chiral Mn Aminopyridine Complexes