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Asymmetric Autoamplification in the Oxidative Kinetic Resolution of Secondary Benzylic Alcohols Catalyzed by Manganese Complexes

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Abstract

Herewith, chiral Mn-aminopyridine complexes have been shown to catalyze the oxidation of alkylarenes to enantiomerically enriched 1-arylalkanols with hydrogen peroxide. The observed enantiomeric excess values result from the direct enantioselective benzylic C-H hydroxylation, accompanied by stereoconvergent oxidative kinetic resolution of the resulting alcohol. Testing several (*S*,*S*)-bipyrrolidine derived Mn complexes has revealed a novel catalyst (**6**) exhibiting the best kinetic resolution in the series (k_{rel} up to 8.8), along with sufficient reactivity and efficiency (> 1000 TN). The mechanistic study of the Mn mediated alcohol oxidation witnesses electrophilic active species (ρ = -1.2), with rate-limiting H abstraction (k_H/k_D = 2.2), followed by oxygen-rebound and dehydration of the resulting *gem*-diol to form the ketone. Intriguingly, while for the resolution of the relatively bulky 1,2-diphenylethanol, k_{rel} is virtually constant throughout the reaction, for less bulky alcohols, the k_{rel} increases with increasing conversion, in line with the rising optical purity of the 1-arylalkanol. The latter participates in the oxidation as an auxiliary ligand, assisting the chiral recognition. This effect is related to the previously described *asymmetric autocatalysis* and *asymmetric autoinduction*, but is not identical with either of those, which different is being discussed. To unambiguously identify this effect, the term *asymmetric autoamplification* (*chiral autoamplification*) is proposed.

Introduction

Direct catalytic oxygenation of unactivated C-H groups has recently attracted great attention: this approach is foreseen to provide novel efficient methodologies for the introduction of oxygen atom into complex organic molecules at late steps of multistep syntheses.[1] One of the major trends has been the design of bioinspired transition metal (mostly Fe based) catalysts, capable of conducting the C-H oxygenation with environmentally benign oxidants, i.e. H_2O_2 and O_2.[1k] In the last few years, we have shown that Mn aminopyridine complexes with C_2-symmetric bipyrrolidine-derived ligands efficiently oxidize unactivated C-H groups in alkanes with H_2O_2,[2a] and studied the C-H hydroxylation mechanism.[2b,c] The Mn based catalysts have exhibited very good efficiencies (up to 1000 TN), many times higher than for the structurally similar Fe complexes.[2]

The next logical step could be the design of catalyst systems for the asymmetric C-H oxygenation of methylenic groups, aiming at achieving direct enantioselective access to optically pure secondary alcohols from prochiral alkanes. To date, there have been very few reported examples of catalyzed enantioselective C-H oxidations, affording the corresponding non-racemic secondary alcohols. Regarding "green" processes, Simonneaux reported a water-soluble Mn-porphyrin-catalyzed oxygenation of benzylic positions of several arylalkanes with H_2O_2, with moderate enantioselectivities (32 to 57 % *ee*, depending on the alkane).[3a-c] The catalytic protocol required rather high (2.5 mol. %) catalyst loading and a 5-fold excess (relative to alkane) of H_2O_2, thus leaving space for further developments. Very recently, Bietti and Costas with co-workers have published an intriguing Mn-catalyzed enantioselective ketonization of monosubstituted cyclohexanes with H_2O_2, in which the asymmetric center did not coincide with the reaction center (the 2° C atom which underwent catalytic oxidation).[3d]

This work had been initiated with the aim to examine the catalytic behavior of the bioinspired chiral Mn-aminopyridine complexes[2,4] in the stereoselective hydroxylation of prochiral methylenic sites with H_2O_2. However, in the course of catalyzed benzylic oxidation of ethylbenzenes, the asymmetric induction has been found to arise from both enantioselective C-H

hydroxylation and subsequent stereoconvergent kinetic resolution of the resulting alcohols, affording enantiomerically enriched alcohols with up to 61.5 % *ee* (for the oxidation of ethylbenzene). The kinetic resolution step has been studied in detail; the mechanism of the stereoselective alcohol oxidation and ketone formation has been examined, and an important kinetic feature of the oxidative alcohol resolution – *asymmetric autoamplification* – has been observed and rationalized. A new catalyst, bearing 1,1,1-trifluoroethoxy substituents at the ligand pyridine rings has been designed, combining the highest C-H oxidation enantioselectivity and the highest k_{rel} in the family (up to 8.8), and exhibiting good efficiencies (> 1000 TN).

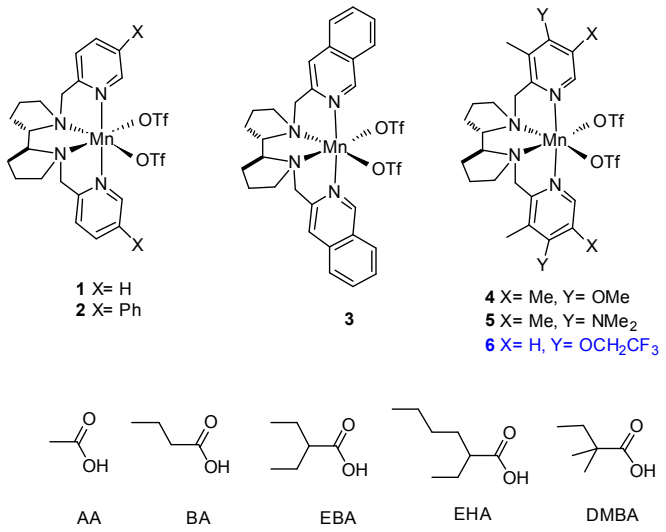
Results and discussion

To examine the catalytic properties of Mn-aminopyridine complexes in the asymmetric oxidation of prochiral CH_2 sites, we have screened a series of complexes **1**-**5**[4e] (Scheme 1), using ethylbenzene as the substrate (Table 1). For Mn-aminopyridine catalyzed epoxidations and C-H oxidations, it is standard to add carboxylic acids as co-catalytic additives (most often it is AcOH), enhancing the catalytic activity, as well as chemo- and stereoselectivity.[2,3d,4,5] In this work, the use of AcOH (AA) as additive has resulted in the formation of alcohol with small optical purity (~0 to 32 % *ee*, entries 1-5 of Table 1). Interestingly, the new catalyst **6** (Figure 1) has demonstrated the highest alcohol yield in the series, along with the highest optical purity (34 % *ee*, entry 6 of Table 1).

Complex **6** has been obtained in single-crystalline form; the asymmetric unit of the structure of **6** contains four neutral *cis*-[Mn(dpf)(CF_3SO_3)$_2$] complexes (Figures 1 and S1, SI). Mn(II) atoms are in octahedral coordination environment built with for N atoms of organic ligand and two O atoms of $CF_3SO_3^-$ anions. Mn–N distances are in the range 2.212(10)–2.299(10) Å (average 2.244(25) Å). Mn–O distances are in the range 2.134(10)–2.170(8) Å (average 2.150(13) Å).

For further screening of different carboxylic acids, catalysts **6** and **3** were selected, as affording the alcohol with the highest *ee*s (Table 1, entries 3 and 6). In the case of **3**, the replacement of AA with EHA did not improve the optical purity of the alcohol (entry 7 of Table 1), but deteriorated the alcohol yield. In contrast, the use of EHA instead of AA with catalyst **6** led to

the same alcohol yield and the A/K ratio, and the *ee* increased to 41 % (entry 8 of Table 1). Screening other carboxylic acids, either linear, or branched (Table 1, entries 8-11), resulted in either lower alcohol yields, or in lower enantiomeric purities, or both.



Scheme 1. Structures of Mn(II) aminopyridine complexes (top) and carboxylic acid additives (bottom) used in this study. AA – acetic acid, BA – butyric acid, EBA – 2-ethylbutyric acid, EHA – 2-ethylhexanoic acid, DMBA – 2,2-dimethylbutyric acid.

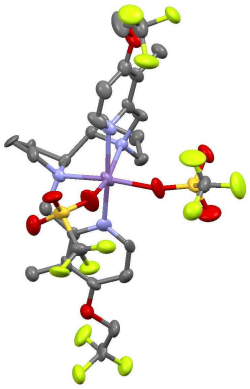
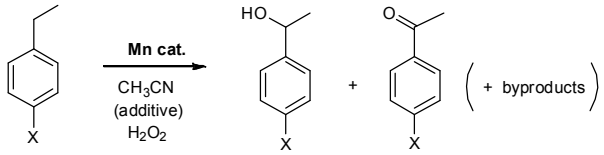


Figure 1. Molecular structure of complex **6**. Thermal ellipsoids drawn at 50 % probability level. Three (out of four) complexes of the asymmetric unit, hydrogen atoms, and rotational disorder of triflates have been omitted for clarity. Full asymmetric unit of **6** is displayed in Figure S2 (SI). CCDC 1455425 (**6**) 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.

Several *p*-substituted ethylbenzenes have been oxidized over catalyst **6** in the presence of EHA (Table 1, entries 9-11). Good substrate conversion and alcohol yield was observed for the oxidation of *p*-ethyltoluene (Table 1, entry 9), and the *ee* was somewhat higher than in the oxidation of ethylbenzene under the same conditions (Table 1, entry 8).

Table 1. Oxidation of *p*-substituted ethylbenzenes with H_2O_2 in the presence of complexes **1**-**6**.[a]



No	X	Catalyst	Additive	Substrate conversion (μmol)	Yield of alcohol / ketone / other [b] (μmol)	A / K [c]	*ee* of alcohol (%)[d]
1	H	**1**	AA	17	10 / 5 / 2	2.0	14
2	H	**2**	AA	12	7 / 3 / 2	2.3	6
3	H	**3**	AA	23	12 / 8 / 3	1.5	32
4	H	**4**	AA	27	12 / 12 / 3	1.0	~0
5	H	**5**	AA	41	11 / 24 / 6	0.4	10
6	H	**6**	AA	37	15 / 19 / 3	0.8	34
7	H	**3**	EHA	13	9 / 4 / −	2.2	32
8	H	**6**	EHA	30	13 / 17 / −	0.8	41
9	CH_3	**6**	EHA	44	25 / 16 / 3	1.6	50
10	OCH_3	**6**	EHA	14	4 / 1.5 / 9	2.6	32
11	Br	**6**	EHA	18	7 / 11 / −	0.6	46
12	H	**6**	−	8.5	2.5 / 6 / −	0.4	62

[a]At 0 °C; [substrate]:[H_2O_2]:[additive]:[Mn] = 200 μmol : 70 μmol : x μmol : 0.1 μmol (x = 600 μmol for AA and BA or 100 μmol for other acids), oxidant added via syringe pump over 30 min and the mixture stirred for an additional 3 h, and analyzed by chiral HPLC. [b] Other products were: esters; traces of (1-hydroperoxyethyl)benzene (entry 5). [c] Alcohol/ketone ratio. [d] Determined by chiral HPLC; (*S*)-absolute configuration.

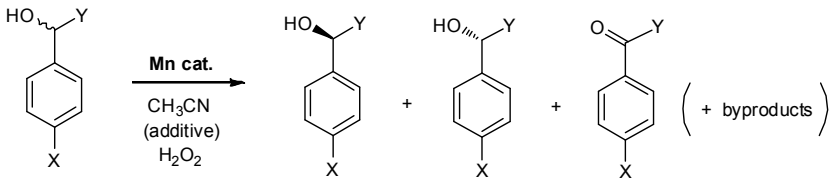
Quite unexpectedly, the catalytic reaction without any additives has afforded (*S*)-1-phenylethanol with significantly higher optical purity (62 % *ee*), albeit with low yield and conversion (entry 12 of Table 1).

This catalytic behavior is quite intriguing, in particular the observation of the highest alcohol *ee*s in the absence of additives. The formation of significant amounts of ketones suggests that there can be kinetic resolution of the initially formed alcohol, affecting the final optical purity of the alcohols. To check this possibility, the oxidation of 1-phenylethanol in the presence of catalyst **6** has been examined (Table 2, entries 1-5). With additives of sterically demanding carboxylic acids (EHA, EBA, DMBA), negligible (or even zero in the case of EHA) kinetic resolution has been documented (Table 2, entries 1-3). This result is evidence that the asymmetric induction in the oxidation of ethylbenzene in the presence of additive EHA (Table 1, entry 8) is generated exclusively at the enantioselective oxidation step, without contribution of kinetic resolution.

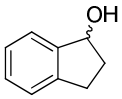
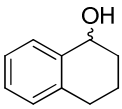
On the contrary, in the presence of AA (Table 2, entry 4) or in the absence of additives (Table 2, entry 5), kinetic resolution takes place, with selectivity factors being significantly higher than 1. Catalysts **1**-**5** have also been tested without additives, all of them exhibiting lower k_{rel}, and in most cases lower conversions than **6** (Table 2, entries 6-10). Oxidation of 1-phenylethanol has been studied at different temperatures (Table 2, entries 5 and 11-15). At -10 °C, the stereodiscrimination was most efficient, so further experiments were conducted at that temperature.

Several secondary benzylic alcohols, with different electronic properties (modulated by the *p*-substituent X) and steric demand (governed by susbstituent Y) have been resolved (Table 2, cf. entries 13 and 16-24) under the same conditions. In most cases, the selectivity factors have been found inferior as compared with 1-phenylethanol, and the conversions were typically < 50 %. A notable exception is *p*-ethyltoluene, which has been resolved with nearly the same conversion and with a higher k_{rel} = 8.0 (Table 2, entry 16).

Table 2. Kinetic resolution of *p*-substituted 1-phenylethanols in the presence of Mn complexes.[a]

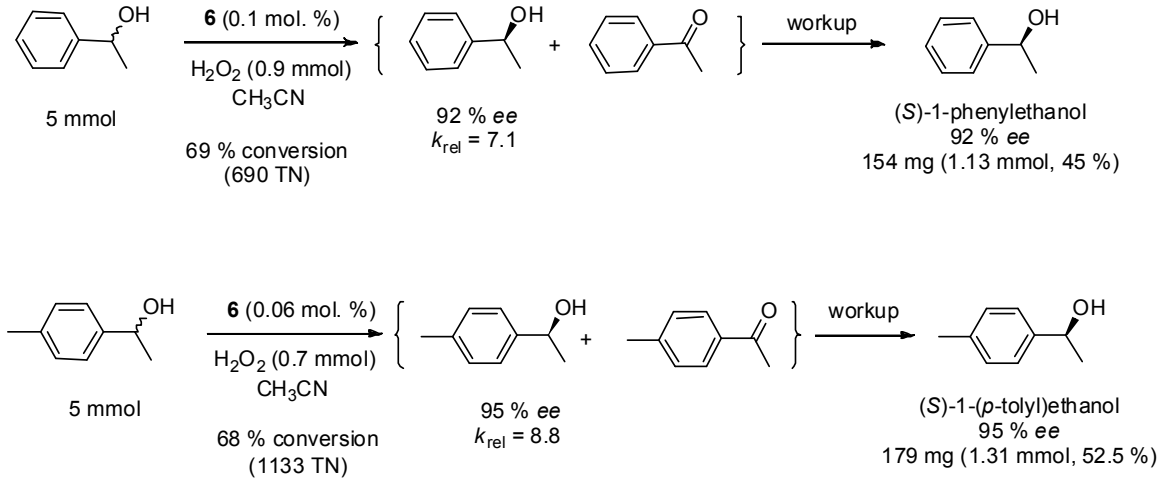


No	X	Y	Catalyst	*T* (°C)	Additive	Conversion (%)	*ee* (%) [b]	k_{rel} [c]

1	H	H	**6**	0	EHA	51	0	1.0
2	H	H	**6**	0	EBA	52	5.5	1.15
3	H	H	**6**	0	DMBA	42	2	1.1
4	H	H	**6**	0	AA	54	32	2.3
5	H	H	**6**	0	–	52	49	4.1
6	H	H	**1**	0	–	22	12	2.7
7	H	H	**2**	0	–	12	0	1.0
8	H	H	**3**	0	–	20	8	2.1
9	H	H	**4**	0	–	54	39	2.8
10	H	H	**5**	0	–	51	22	1.9
11	H	H	**6**	-30	–	48	31	2.7
12	H	H	**6**	-20	–	50	40	3.3
13	H	H	**6**	-10	–	53	61	6.2
14	H	H	**6**	+10	–	53	46	3.7
15	H	H	**6**	+20	–	58	43	2.8
16	CH_3	H	**6**	-10	–	52	65	7.6
17	OCH_3	H	**6**	-10	–	39	27	3.2
18	Cl	H	**6**	-10	–	34	22	3.0
19	F	H	**6**	-10	–	44	29	2.9
20	CF_3	H	**6**	-10	–	59	30	2.0
21	H	CH_3	**6**	-10	–	44	36	3.7
22	H	CH_2Ph	**6**	-10	–	41	34	3.9
23			**6**	-10	–	40	24	2.6
24			**6**	-10	–	44	17	1.8

[a] [substrate]:[H_2O_2]:[additive]:[Mn] = 100 μmol : 60 μmol : x μmol : 0.1 μmol (x = 600 μmol for AA and BA or 100 μmol for other acids). For experiments at $T \geq 0$ °C, oxidant was added via syringe pump over 30 min and the mixture was stirred for additional 3 h. For experiments at $T < 0$ °C, oxidant was added via syringe pump over 60 min and the mixture was stirred overnight. The products were analyzed by chiral HPLC; trace amounts (< 0.2 %) of byproducts ((*R*)- and (*S*)-acetic acid esters) were found in the case of 1-phenylethanol. [b] Determined by chiral HPLC. Entries 1-21: (*S*)-absolute configuration. Entry 22: absolute configuration not assigned. [c] The stereoselectivity factor was calculated as $k_{rel} = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$ (in which c is the conversion of secondary alcohol and ee is the enantiomeric excess of the secondary alcohol).

We notice that this is the first example of kinetic resolution of secondary alcohols in the presence of bioinspired Mn aminopyridine catalysts. To test the synthetic power of the procedure, two semipreparative-scale kinetic resolutions have been performed, using 0.1 and 0.06 mol. % catalyst loadings, to afford (*S*)-arylethanols with 92 and 95 % *ee* (Scheme 2). The isolated yields were not higher than 52.5 %, owing to the relatively small (i.e. < 10) k_{rel} and inescapable product losses during the extraction and separation stages. At the moment, the selectivity factors demonstrated by catalyst **6** are lower than for the most efficient to-date, palladium-sparteine based catalysts systems; for the latter, the k_{rel} for *p*-substituted 1-phelylethanols in some cases exceed 10.[6] On the other hand, taking into account the drawbacks of the Pd-sparteine systems, i.e. high catalyst loadings (5 mol. % Pd and up to 20 mol. % sparteine) and poor reactivity (reaction times of 24 to 192 h at 80 °C and at 1 atm of O_2),[6] we believe that the simple, highly efficient and reactive Mn systems hold a good practical promise; hopefully, with further ligand tuning, improved stereoselection can be achieved.



Scheme 2. 5-mmol scale preparative kinetic resolutions of 1-arylethanols (for details see SI).

Previously, we have studied the mechanism of C-H oxidation in the presence of Mn-aminopyridine complexes of the type **1**-**6**, concluding that the reaction proceeded via rate-limiting hydrogen-atom abstraction by the electrophilic, presumably [LMn^{V}=O] active species, followed by oxygen rebound.[2b] It is intriguing to establish whether the mechanism of kinetic resolution embody

the same key step. To address this issue, competitive oxidations of *p*-substituted 1-phenylethanols on catalyst **6** have been conducted. This task is not trivial since in the absence of additives, the Mn catalyst exhibits different reactivities toward the (*R*)- and (*S*)- enantiomers of the substrate. Therefore, for correct kinetic analysis, EHA has been used as additive, to suppress the stereodiscrimination of catalyst **6** (Table 2, entry 5 vs. entry 1) and equalize the reactivities of the active oxygen transferring species toward the (*R*)- and (*S*)- alcohols. The obtained log (k_X/k_H) has shown good linear correlation vs. σ_p (Figure 2), reflecting electrophilic active species (ρ = -1.18). Such ρ value well fits within the typical range reported for the oxidation of benzylic alcohols by high-valent transition metal complexes (-0.8 to -2.0).[7]

The observed Hammett correlation is somewhat different from that for the oxidation of *p*-substituted cumenes, for which log (k_X/k_H) correlated with the polar Brown parameter σ^+_p.[2b] In principle, the absence of correlation with σ^+_p for the alcohol oxidations may argue against hydride-proton transfer (HPT) mechanism, which assumes the formation of protonated ketone intermediate at the rate-limiting step.[8] The hypothesis of hydrogen atom transfer (HAT) mechanism seems more feasible, assuming that the presence of oxygen atom nearby the reaction centre efficiently assists in compensation of the partial positive charge at the rate-limiting (presumably C-H abstraction) step.

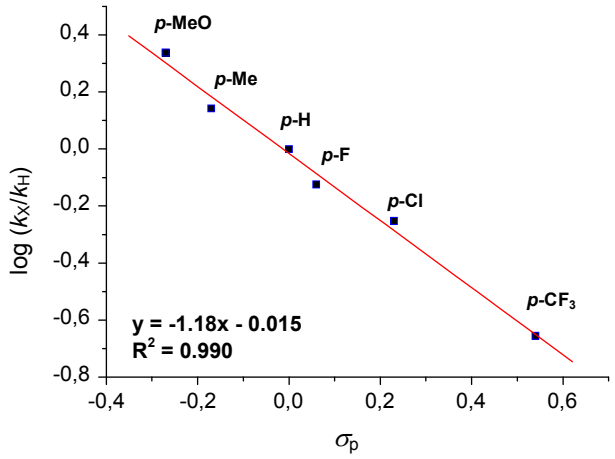
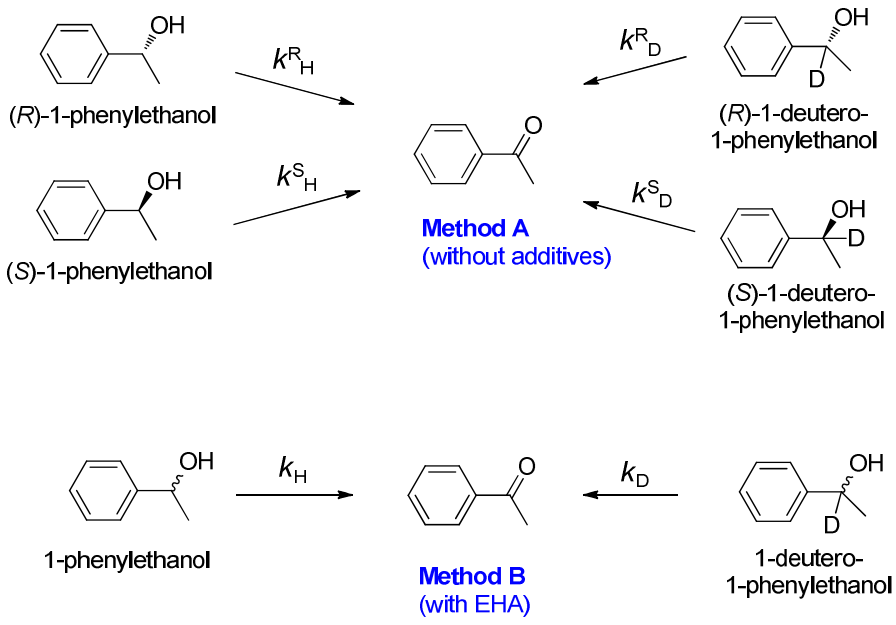


Figure 2. Hammett plot for the oxidation of *p*-substituted 1-phenylethanols with H_2O_2 in the presence of **6**. Conditions: 0 °C, [substrate 1]:[substrate 2]:[H_2O_2]:[EHA]:[Mn] = 0.100 mmol : 0.100 mmol : 0.135 mmol : 0.100 mmol : 0.2 μmol, oxidant was added via syringe pump over 1 h, the mixture was stirred for an additional 3 h and analyzed by NMR and chiral HPLC.

To check whether C-H abstraction is indeed the rate-limiting step, primary kinetic isotope effect was measured. To this end, two alternative approaches have been exploited. The first one (method **A**) is based on the reaction sequence shown in the top of Scheme 3. This approach has afforded a couple of KIE values, k^{R}_{H}/k^{R}_{D}, and k^{S}_{H}/k^{S}_{D} (Table 3; see Supporting Information for details). The latter values are very close, 2.3 and 2.2, respectively (Table 3, entry 1). The alternative approach (method **B**: Scheme 3, bottom) is based on the suppression of stereodiscrimination by using EHA as additive; the resulting k_H/k_D of 2.2 (Table 3, entry 2) very well correspond to the KIE values evaluated by method **A**. With catalyst **4**, a similar k_H/k_D of 2.2 has been revealed (entry 3 of Table 3). Such values are 1.5 times smaller than for the oxidation of C-H bond of cumene, and almost two times smaller than for the oxidation of cyclohexane over Mn-aminopyridine catalysts.[2b] On the other hand, the k_H/k_D values of 2.2 fall within the range (> 1 to ca. 12-15) typical for benzylic alcohol oxidations, proceeding via rate-determining cleavage of the benzylic C-H bond,[7b,7d,7e,8a,9a,b] but are much smaller than the great k_H/k_D (36 to > 50) reported for alcohol oxidations with oxoruthenium(IV)[8b,c] and oxoiron(IV) complexes;[9d] the latter high values required a separate discussion.[9b]



Scheme 3. The formal reaction schemes used for KIE measurements according to methods **A** and **B**. For details see Supporting Information.

Table 3. KIE values for the kinetic resolution of 1-phelylethanol with H_2O_2.[a]

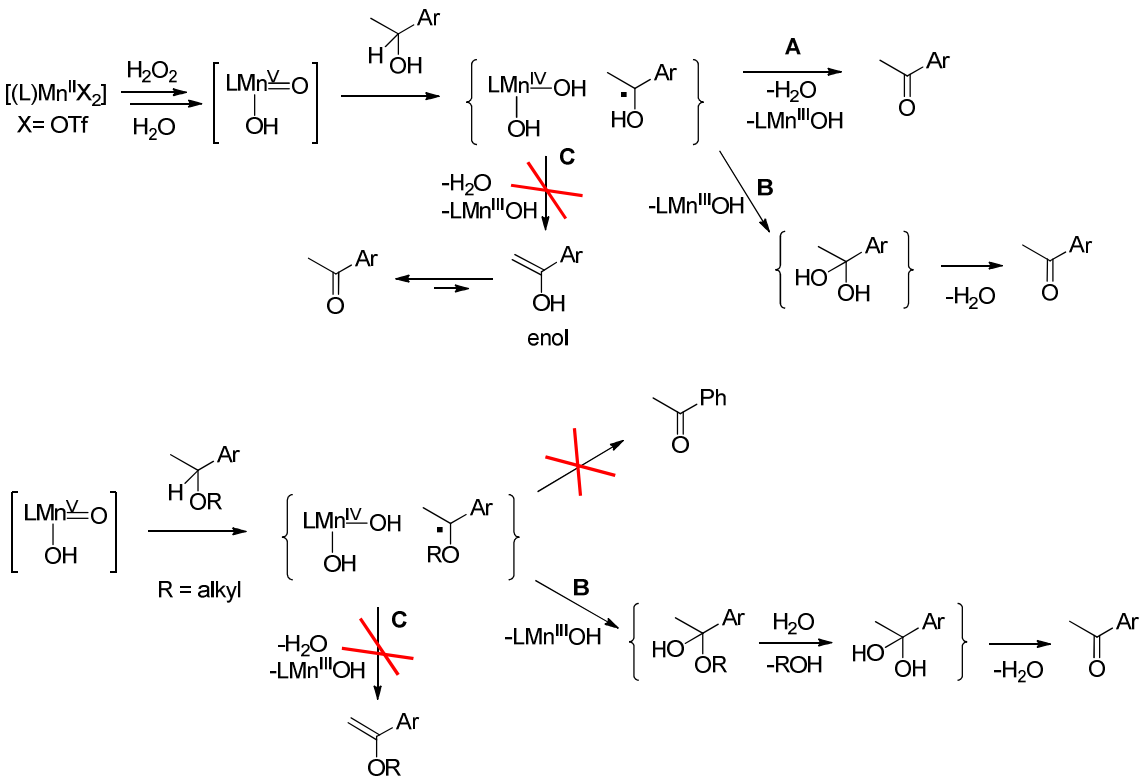
No	method	complex	additive	KIE
1	**A**	**6**	–	$k^R_H/k^R_D = 2.3$; $k^S_H/k^S_D = 2.2$
2	**B**	**6**	EHA (0.2 mmol)	$k_H/k_D = 2.2$
3	**B**	**4**	EHA (0.2 mmol)	$k_H/k_D = 2.2$

[a] Conditions: -10 °C, oxidant added via syringe pump over 1 h, the mixture stirred for an additional 3 h and analyzed by NMR and chiral HPLC. For details see Supporting Information.

Given the rate-determining abstraction of the C-H hydrogen, two major alternative scenarios leading to the corresponding acetophenone may be considered, namely (**A**) second H abstraction (from e.g. OH group) or (**B**) oxygen rebound, followed by dehydration of the resulting unstable intermediate *gem*-diol (Scheme 4, top). Unfortunately, ^{18}O labeling experiments are of little utility for discrimination between these alternatives since ketones readily exchange with water (present in abundance) under our experimental conditions.[2b] Instead, it looks promising to replace hydroxyl hydrogen with alkyl substituent, which would preclude the second H abstraction pathway **A** and leave only pathway **B** available: the intermediate hemiketal is unstable in protic media toward hydrolysis with subsequent dehydration, eventually affording the ketone (Scheme 4, bottom).

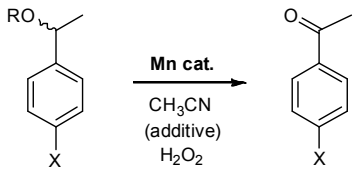
Two different ethers of 1-(*p*-methoxyphenyl)ethanol have been oxidized in the presence of complex **6**: both afforded the corresponding acetophenone (Table 4), thus confirming the feasibility of the H abstraction / oxygen rebound pathway (**B**). This result itself, however, could not be considered as irrefutable evidence against the co-existence of second H abstraction pathway (**A**). At the same time, the 2nd H could also be abstracted from the CH_3 group rather than from the OH group (see pathway (**C**) in Scheme 4, top and bottom), given the 3-fold prevalence of the potentially reactive C-H groups and rather close bond dissociation energies of the C-H and O-H bonds.[10] However, (1-alcoxyethenyl)anisole (pathway (**C**) in Scheme 4, bottom) has not been the reaction product (Table 4), thus excluding 2nd H abstraction from the CH_3 group and leaving pathway **B** as the only route for the ketone formation in the oxidation of 1-arylalkanol ethers. Altogether, these

data give evidence in support of the viability of the hydrogen abstraction / oxygen-rebound / *gem*-diol dehydration mechanism of acetophenone formation.



Scheme 4. Proposed mechanism of alcohols (top) and related ethers (bottom) oxidation in the presence of Mn-aminopyridine catalysts.

Table 4. Oxidation of ethers of 1-phelylethanols with H_2O_2 in the presence of complex **6**.[a]



No	X	R	additive	conversion (%)	yield (%)
1	OMe	*i*Pr	–	6	5
2	OMe	*n*Bu	–	11 [b]	10
3	OMe	*n*Bu	EHA (0.1 mmol)	19 [b]	17

[a] Conditions: 0 °C, [substrate]:[H_2O_2]:[Mn] = 0.100 mmol : 0.55 mmol : 0.1 μmol, oxidant added via syringe pump over 0.5 h, the mixture stirred for an additional 3 h and analyzed by NMR and chiral HPLC. [b] Two sequential additions of H_2O_2 (2×0.55 mmol) were performed.

Unexpectedly, when conducting the kinetic resolutions of 1-phenylethanol, we have discovered that the observed k_{rel} is not constant during the reaction but increases in line with

increasing conversion (Figure 3A, black line). The k_{rel} for the resolution of *p*-methyl-1-phenyl ethanol has varied in the same manner (Figure 3A, magenta line). Apparently, such behavior reflects some alteration of the reaction conditions in the course of the reaction. This alteration could not be due to the increase of concentration of H_2O in the mixture, since externally added water (0.56 mmol) caused no effect on k_{rel} and the variation of k_{rel} with conversion. Moreover, the resolution of a bulkier 1,2-diphenylethanol proceeded without significant variation of k_{rel}, which remained in the range 3.9 to 4.1 for conversions between 40 and 70 % (Figure 3A, blue line).

However, there is another parameter which changes monotonously in the course of oxidation – the enantiomeric purity of the chiral alcohol (Figure 3B, black lines, and Figure S2, SI). If the *ee* of the alcohol were connected with the resolution effectiveness, one could expect that the use of non-racemic 1-phenyl ethanol would change the observed dependence of k_{rel} on the conversion. In full agreement with this prediction, this dependence has visibly changed when (*S*)-1-phenylethanol (15.4 % *ee*) has been taken instead of its racemic counterpart (Figure 3B): for the case of non-racemic starting material, the observed k_{rel} were always higher at similar conversions.

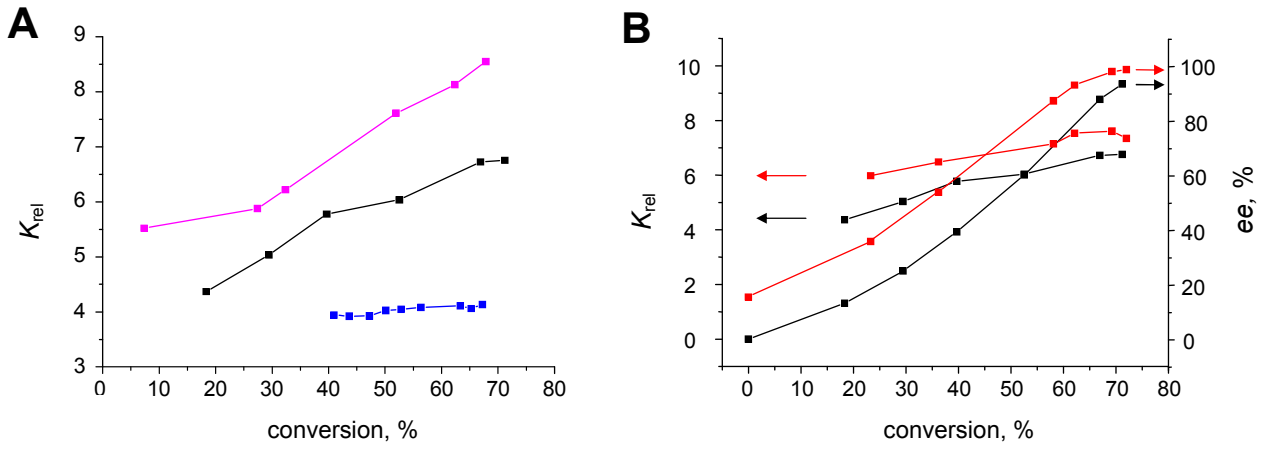
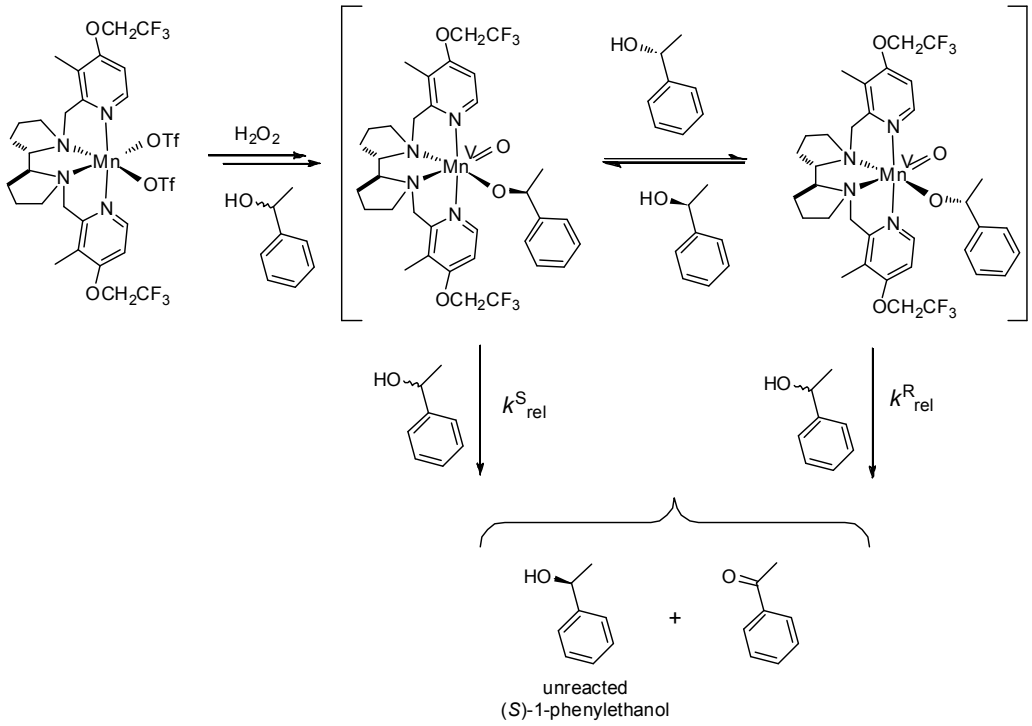


Figure 3. Variation of the k_{rel} vs. conversion for 1-phenylethanol (black), 1-(*p*-methylphenyl)ethanol (magenta), 1,2-diphenylethanol (blue) – (A). Variation of the k_{rel} and *ee* vs. conversion for the resolution of racemic 1-phenylethanol (black) and non-racemic (15.4 % *ee*, (*S*)-configuration) 1-phenylethanol (red) – (B). Conditions: -10 °C, catalyst **6** (0.1 mol %), portionwise addition of oxidant, followed by HPLC analysis after each addition.

The mechanism of the influence of the enantiomeric composition of the substrate on the kinetic resolution is very intriguing. Taking into account the observed effect of added carboxylic acids on the stereoselection (Table 2, entries 1-5), which apparently occurs through coordination of the acid to the catalytically active sites,[4b,e,g] it would be logical to expect that in the absence of acid, the substrate itself may coordinate to the active sites via the hydroxy moieties. Such situation should lead to the generation of a pair of diastereomeric active sites, on default exhibiting different reactivities and stereoselectivities toward the oxidation of 1-arylethanols (Scheme 5). The absence of dependence of k_{rel} for the oxidation of 1,2-diphenylethanol on the conversion may reflect the fact that coordination of the latter to the Mn center is substantially restricted due to steric congestion.



Scheme 5. Proposed formation of two diastereomeric catalytically active sites upon the coordination of the enantiomers of 1-phenylethanol to the tentative active species. The enhancement of stereoselection with the increase of the *ee* of (*S*)-1-phenylethanol (Figure 3B) suggests $k^{S}_{rel} > k^{R}_{rel}$.

To verify this hypothesis, it would be logical to add an external ligand to the reaction mixture, which would occupy the coordination site of the Mn catalyst; if coordination of 1-

arylethanol enantiomers to Mn is suppressed efficiently enough, the observed amplification of k_{rel} with raising conversion should disappear or at least substantially reduce.

First of all, acetic acid was added (Figure 4, black curve). One can see that in this case, variation of k_{rel} was negligible, the latter remaining in the range 2.5-2.7 at conversions between 30-80 %. Curiously, there was a visible maximum k_{rel} at ca. 48 % conversion.

Next, we attempted the addition of *chiral* external ligands (Boc protected (*L*)- and (*D*)-proline), to probe the chiral environment effects of the stereoselectivity (Figure 4). The observed stereoselectivities were lower than for the same catalyst without additives (cf. Figure 3B). The system with **6**/Boc-(*D*)-proline exhibiting higher k_{rel} of 4.3 up to 4.7 (Figure 4, blue curve), indicating "chiral match". Again the variation of k_{rel} was very small over the reaction course (< 10 %, cf. the 1.5-fold variation (in particular monotonous increase) of k_{rel} in the systems without additives, Figure 3). Like with AcOH, the k_{rel} passed through a maximum at ca. 50 % conversion. For the system **6**/Boc-(*L*)-proline, the observed k_{rel} was lower ("chiral mismatch"), and gradually increased from 1.9 to 2.2 upon the conversion increase from 35 to 81 % (Figure 4, red curve). Overall, the experiments on the addition of external coordinating ligands have provided evidence in support of the proposed mechanism of k_{rel} amplification via interaction with the enantiomers of 1-arylethanol.

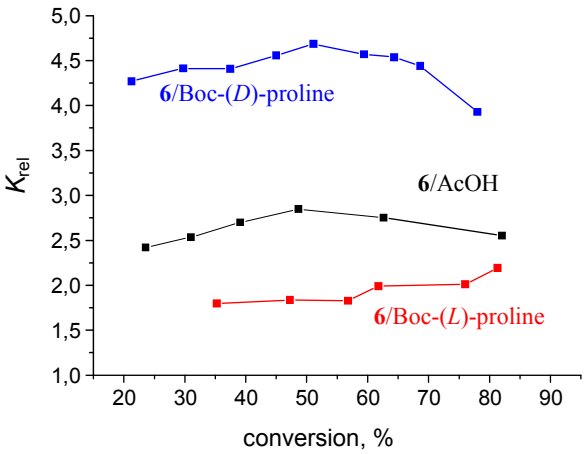


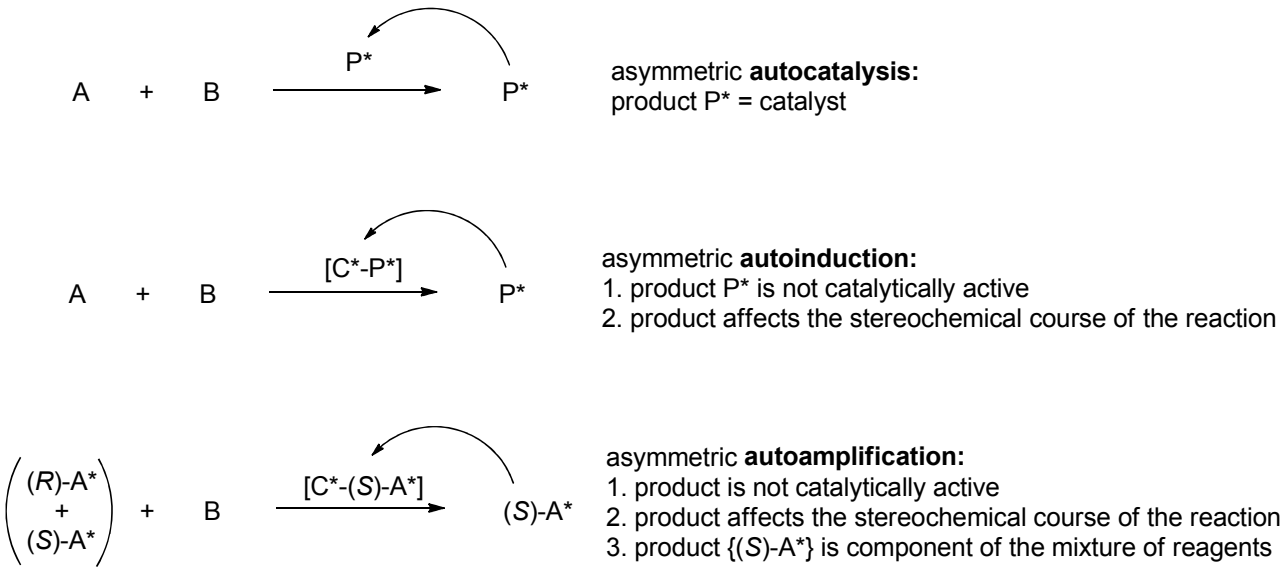
Figure 4. Variation of the k_{rel} vs. conversion for the resolution of 1-phenylethanol by catalyst systems **6**/AcOH (black), **6**/Boc-(*L*)-proline (red), **6**/Boc-(*D*)-proline (blue). For details see Supporting Information.

The origin of the observed maxima of the k_{rel} (Figure 4, black and red curves) is intriguing. Plausible possibility is that the shielding of the catalyst from 1-arylethanol is not perfect, there being a competition between the external ligand and 1-arylethanol for the coordination site of manganese. In effect, with increasing (*S*)-arylethanol/(*R*)-arylethanol ratio over the reaction course, the share of the (most stereoselective) active site [L*Mn^{V}=O·(*S*)-arylethanol)] grows up, thus ensuring gradual increase of the k_{rel}. However, the overall concentration of 1-arylethanol (both (*R*)- and (*S*)-) gradually decreases, so that at some point it becomes insufficient to compete with the added external ligand for the coordination site of Mn. In effect, the k_{rel} goes down, working for its "natural" value (the value which would be expected for the system **6**/external ligand, provided that 1-arylethanol could not coordinate to the Mn center).

The described phenomenon represents a very special case of chiral environment amplification,[4g,11] 1-arylethanol acting as both the substrate and the chiral environment, affecting the stereoselectivity. The 1-arylethanol (*S*)-/(*R*)- ratio progressively increases in the course of oxidation, thus increasing the observed k_{rel}. We notice that the less reactive (*S*)-enantiomer is also the desired product of the kinetic resolution reaction, so its ascending effect on the stereoselectivity with increasing conversion can be formally regarded as having autococatalytic-type character. To the best of our knowledge, such phenomenon has not been described asymmetric catalysis. For its unambiguous identification, we propose the term *asymmetric autoamplification (chiral autoamplification)*.

We notice that the reported phenomenon is related to asymmetric autocatalysis[12a,b,d,e] and asymmetric autoinduction,[12c-d] but not identical to them. Scheme 6 illustrates the three concepts. Basically, the difference between asymmetric autocatalysis and asymmetric autoamplification is that in the latter case, the chiral product is not itself catalytically active. At the same time, it can affect the stereochemical course of the reaction, like in the case of asymmetric autoinduction, via complexation with the chiral catalyst. However, the mechanisms of amplification of chirality over

the reaction course in the latter two situations are different. In the case of asymmetric autoinduction, the product is accumulated with time in the reaction mixture, thus increasing the concentration of the [catalyst*·product*] complex, which exhibits higher stereoselectivity than [catalyst*] itself. In the case of asymmetric autoamplification, the chiral product is *not* accumulated in the course of the reaction but is originally present in the reaction as a component of the mixture of enantiomeric reagents. Therefore, the enhancement of the catalyst's stereoselectivity (here characterized by stereodiscrimination, or k_{rel}) with the reaction course is in fact caused by the progressive *decrease* of concentration of the second component of the reagents mixture, which results in increase of the share of the more stereoselective complex between the chiral catalyst and the enantiomeric product [C*-(*S*)-A*] compared with the share of the less stereoselective intermediate [C*-(*R*)-A*] (Scheme 5).



Scheme 6. The difference between asymmetric autocatalysis, asymmetric autoinduction, and asymmetric autoamplification. Asterisks indicate chiral reactants/catalysts/products.

Conclusions

It has been shown that bioinspired chiral Mn-aminopyridine complexes catalyze the oxidation of alkylarenes with H_2O_2 to the corresponding non-racemic 1-arylalkanols and further to ketones, with the hydroxylation enantioselectivity depending on the nature of the externally added carboxylic

acid. 2-Ethylhexanoic acid (EHA) ensures the highest enantioselection in the series, affording substituted 1-phenylethanols with up to 50 % *ee*.

It has been revealed that the enantioselective hydroxylation of alkylarenes is accompanied by the stereoconvergent oxidative kinetic resolution of the resulting benzylic alcohols. The stereoselectivity of the kinetic resolution also depends on the added carboxylic acid, EHA being the least efficient additive of the series, leading to complete loss of stereoselection in the oxidation of 1-phenylethanol. Moreover, the highest k_{rel} were achieved without added acid at all, approaching the value of 8.8 for the resolution of 1-(*p*-methylphenyl)ethanol.

A novel bipyrrolidine derived Mn complex **6** has been synthesized and X-ray characterized, which combines the highest efficiency in the series and the highest stereoselectivity in both the enantioselective oxidation of alkylarenes and kinetic resolution of 1-arylalkanols.

The mechanistic study reveals an electrophilic oxidant (Hammett ρ = -1.2), the observed primary KIE (k_H/k_D = 2.2) for the oxidation of 1-*d*-phenylethanol-1 witnessing rate-limiting C-H abstraction step. The data on the oxidation of ethers of 1-aryl ethanols on catalyst **6** provide evidence in favor of the viability of the C-H abstraction / oxygen-rebound / *gem*-diol dehydration mechanism of acetophenone formation.

For the relatively small alcohols (1-phenylethanol and *p*-methylphenyl-1-ethanol), the observed k_{rel} substantially increases with increasing (*S*)-/(*R*)- substrate ratio, reflecting the participation of the benzylic alcohol in the kinetic resolution. Apparently, this participation is realized via coordination of the enantiomers of the alcohol to the Mn center, resulting in the formation of two diastereomeric active sites, possessing different stereoselectivities. As the reaction proceeds, the (*S*)-/(*R*)- ratio monotonously increases, leading to increasing prevalence of one of the two diastereomeric active sites and hence to monotonous increase of the observed k_{rel} with increasing conversion. To unambiguously distinguish this dynamic substrate-product effect on the stereoselectivity, we propose the term *asymmetric autoamplification (chiral autoamplification)*. Further studies, aimed at designing more stereoselective Mn catalysts, the search for substrates

ensuring higher autoamplification impact on the oxidative resolution, and extended elaboration of the concept of *asymmetric autoamplification* are in progress.

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Keywords

Asymmetric autoamplification; hydrogen peroxide; kinetic resolution; manganese; oxidation

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[10] Cf. e.g. the close (and rather small) C-H and O-H bond energies in •CH_2CH_2-**H** and •CH_2O-**H** radical species (35.7 kcal mol^{-1} and 30.2 kcal mol^{-1}, respectively): S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **2003**, *36*, 255-263. On the other hand, the difference of C-H and O-H bond dissociation energies can be estimated based on the difference of stabilities of the keto end enolic forms of acetophenone, see Figure S3 of the Supporting Information.

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Layout 2:

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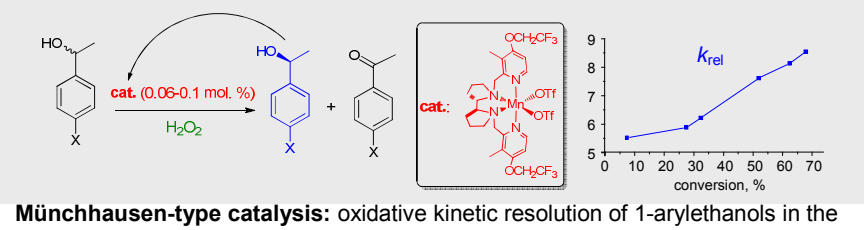

Münchhausen-type catalysis: oxidative kinetic resolution of 1-arylethanols in the presence of chiral Mn-aminopyridine catalysts has been shown to be affected by coordination of the substrate to the catalytically active sites, which results in monotonous increase of the k_{rel} with increasing conversion. To identify this effect, the term *asymmetric autoamplification* is proposed.

*Evgenii P. Talsi, Denis G. Samsonenko, Konstantin P. Bryliakov**

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Asymmetric Autoamplification in the Oxidative Kinetic Resolution of Secondary Benzylic Alcohols Catalyzed by Manganese Complexes