Asymmetric Oxidations

Highly Enantioselective Iron-Catalyzed Sulfide Oxidation with Aqueous Hydrogen Peroxide under Simple Reaction Conditions**

*Julien Legros and Carsten Bolm**

Iron is one of the most abundant metals in the universe.[1] It is inexpensive, environmentally benign, and relatively nontoxic in comparison to other metals. For oxidation reactions the application of iron catalysts[2] in combination with aqueous hydrogen peroxide[3] would be most desirable. Asymmetric oxidations could then be achieved by the use of chiral iron complexes. In this context we recently reported a new enantioselective sulfide oxidation,[4–6] which provides optically active sulfoxides with up to 90% *ee*.[7] The catalysis proceeds under very simple reaction conditions (at room temperature in a capped flask) and utilizes a readily available iron complex generated in situ from $[Fe(acac)_3]$ and Schiff base **3**.[8] Inexpensive and safe 30–35% aqueous hydrogen peroxide serves as terminal oxidant (Scheme 1).

Although the asymmetric induction in this iron-catalyzed sulfoxidation was remarkable, the practicability of the process was limited owing to the low conversion of **1**. Thus, under the conditions required for high enantioselectivities, large amounts of unconverted sulfides remained, and the best yield of sulfoxide **2** was only 44%. We now report on a significant improvement in this iron-catalyzed sulfide oxidation, leading to both higher enantioselectivities (up to 96% *ee*) and better yields (up to 78%).

[*] Dr. J. Legros, Prof. Dr. C. Bolm
Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet-Strasse 1, 52056 Aachen (Germany)
Fax: (+49) 241-809-2391
E-mail: carsten.bolm@oc.rwth-aachen.de

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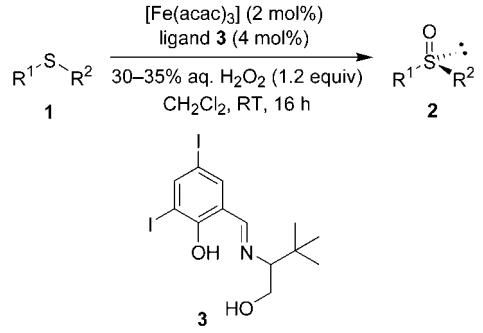


Scheme 1. Iron-catalyzed enantioselective sulfoxidation.

The use of additives is a common and convenient method for the enhancement of the efficiency of metal-catalyzed reactions,[9] as it allows the fine-tuning of the catalyst system without redesigning the ligand.[10] Recently, Jacobsen and co-workers reported the beneficial effects of the presence of substoichiometric amounts of a carboxylic acid in epoxidation reactions with H_2O_2 and the iron complex $[Fe^{II}(mep)(CH_3CN)_2](SbF_6)_2$ (mep = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-ethylene 1,2-diamine).[11] Motivated by these observations we began to investigate the influence of benzoic acid (**AH1**) on the enantioselectivity and the yield of methyl phenyl sulfoxide (**2a**) obtained in the iron-catalyzed oxidation of methyl phenyl sulfide (**1a**). As shown in Figure 1 the

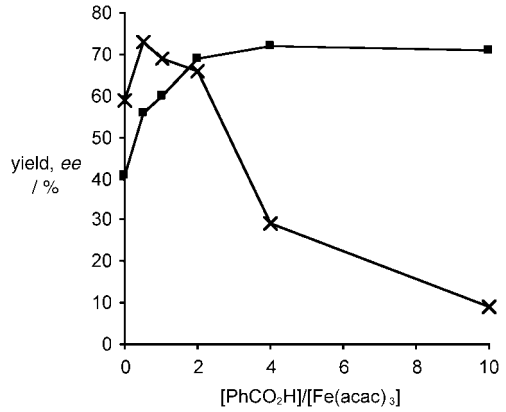
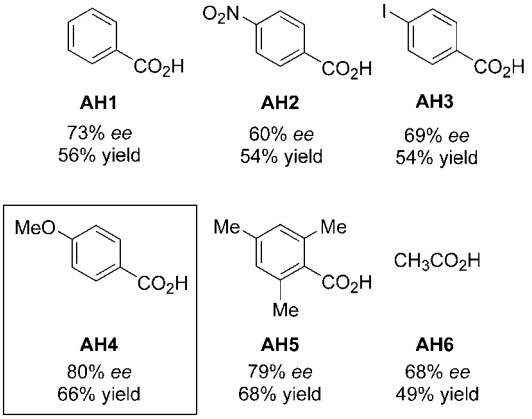


Figure 1. Effect of benzoic acid (**AH1**) on the *ee* value (×; measured by HPLC on the crude product) and the yield (■; determined by NMR spectroscopic analysis) of (*S*)-**2a** obtained in the asymmetric oxidation of **1a** with H_2O_2 (35%; 1.2 equiv) catalyzed by $[Fe(acac)_3]$ (2 mol%) and (*S*)-**3** (4 mol%).

effect of the acid was remarkable. Its presence improved both the asymmetric induction as well as the yield. The best enantioselectivity was obtained with an **AH1**/$[Fe(acac)_3]$ ratio of 0.5:1. Under those conditions (see footnote in Figure 1), the enantiomeric excess of sulfoxide **2a** increased from 59% *ee* (no additive) to 73% *ee*. Furthermore, the yield of **2a** rose from 41% (no additive) to 56%. The use of larger quantities of benzoic acid afforded **2a** with lower *ee* values, albeit in good yield [for example, an **AH1**/$[Fe(acac)_3]$ ratio of 10:1 gave **2a** with 9% *ee* in 71% yield)].

Next, several other carboxylic acids (**AH2**–**AH6**), which varied in their electronic and steric properties, were applied (Scheme 2). Apparently, the nature of the carboxylic acid and the position of its substituents has a major effect on the sulfide



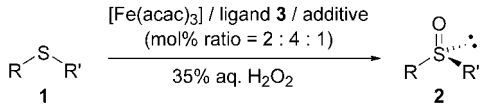
Scheme 2. Effect of various carboxylic acids (**AH1**–**AH6**, 1 mol%) on the yield (determined by NMR spectroscopic analysis) and the *ee* value (measured on the crude product) of (*S*)-**2a** obtained in the asymmetric oxidation of **1a** with H_2O_2 (35%; 1.2 equiv) catalyzed by $[Fe(acac)_3]$ (2 mol%) and (*S*)-**3** (4 mol%).

oxidation. Thus, use of acids with electron-withdrawing substituents (NO_2: **AH2**; I: **AH3**) led to a decrease in the efficiency of the catalysis (relative to the reaction with benzoic acid, **AH1**). In contrast, electron-rich benzoic acids **AH4** and **AH5** (with *p*-MeO-phenyl and mesityl groups) gave very good results and afforded **2a** with 80 and 79% *ee*, respectively. The yields were slightly better as well (56% for **AH1**, 66% for **AH4**, and 68% for **AH5**). Also the presence of acetic acid (**AH6**) resulted in an improvement (with respect to the original conditions), giving **2a** with 68% *ee*.

The fact that the electron-rich carboxylic acids **AH4** and **AH5** led to the best results suggested that the additives acted as coligands, and that the essential characteristic was their chelating properties, not their acidity. Carboxylate salts were therefore expected to increase the efficiency of the reaction further. To our delight we found that this hypothesis was correct. Thus, the use of lithium 4-methoxybenzoate (**ALi4**) in the oxidation of thioanisole **1a** resulted in the formation of sulfoxide **2a** with 90% *ee* (Table 1, entry 1).[12] As shown in Table 1, the effect of the carboxylate in the oxidation of other substrates was similar.

Relative to the original protocol (without any additive), both the enantioselectivity and the yield increased when the sulfide oxidation was performed in the presence of either acid **AH4** or carboxylate **ALi4**. In most cases the latter additive proved to be superior with respect to the former. The best results were observed with *para*-substituted substrates (Table 1, entries 11, 15, 17 and 21), leading to sulfoxides with >92% *ee* (ee_{max} = 96%) in moderate to good yields (up to 78%). Remarkable enantioselectivities were also attained in the oxidation of more-challenging substrates such as phenyl ethyl sulfide (**1b**) and phenyl benzyl sulfide (**1c**), which gave the corresponding sulfoxides with 82 and 79% *ee*, respectively

Table 1: Catalytic enantioselective oxidation of sulfides **1** to sulfoxides **2** with H_2O_2 and a chiral iron complex in the presence of an additive.[a]



1 **2**

Entry	Config. of **3**	**1**	Additive	**2**	Yield [%][b]	*ee* [%][c,d]	Config. of **2**[e]
1	(*S*)	Ph-S-Me (**1a**)	**ALi4**	**2a**	**63**	**90**	(*S*)-(−)
2	(*R*)	Ph-S-Me (**1a**)	**AH4**	**2a**	61	77	(*R*)-(+)
3	(*R*)	Ph-S-Me (**1a**)	**ALi4**	**2a**	**64**	**88**	(*R*)-(+)
4	(*S*)	Ph-S-Et (**1b**)	–	**2b**	30	44	(*S*)-(−)
5	(*S*)	Ph-S-Et (**1b**)	**AH4**	**2b**	51	71	(*S*)-(−)
6	(*S*)	Ph-S-Et (**1b**)	**ALi4**	**2b**	**56**	**82**	(*S*)-(−)
7	(*S*)	Ph-S-Bn (**1c**)	–	**2c**	40	27	(*S*)-(−)
8	(*S*)	Ph-S-Bn (**1c**)	**AH4**	**2c**	**73**	**79**	(*S*)-(−)
9	(*S*)	Ph-S-Bn (**1c**)	**ALi4**	**2c**	64	78	(*S*)-(−)
10	(*S*)	4-MeC_6H_4-S-Me (**1d**)	**AH4**	**2d**	68	78	(*S*)-(−)
11	(*S*)	4-MeC_6H_4-S-Me (**1d**)	**ALi4**	**2d**	**78**	**92**	(*S*)-(−)
12	(*S*)	2-BrC_6H_4-S-Me (**1e**)	**ALi4**	**2e**	48	**66**	(−)
13	(*S*)	4-BrC_6H_4-S-Me (**1f**)	–	**2f**	41	78	(*S*)-(−)
14	(*S*)	4-BrC_6H_4-S-Me (**1f**)	**AH4**	**2f**	55	91	(*S*)-(−)
15	(*S*)	4-BrC_6H_4-S-Me (**1f**)	**ALi4**	**2f**	**59**	**94**	(*S*)-(−)
16	(*S*)	4-ClC_6H_4-S-Me (**1g**)	–	**2g**	32	65	(*S*)-(−)
17	(*S*)	4-ClC_6H_4-S-Me (**1g**)	**AH4**	**2g**	**60**	**92**	(*S*)-(−)
18	(*S*)	4-ClC_6H_4-S-Me (**1g**)	**ALi4**	**2g**	53	92	(*S*)-(−)
19	(*S*)	4-$NO_2C_6H_4$-S-Me (**1h**)	–	**2h**	21	90	(*S*)-(−)
20	(*S*)	4-$NO_2C_6H_4$-S-Me (**1h**)	**AH4**	**2h**	41	91	(*S*)-(−)
21	(*S*)	4-$NO_2C_6H_4$-S-Me (**1h**)	**ALi4**	**2h**	**36**	**96**	(*S*)-(−)
22	(*S*)	2-Naphthyl-S-Me (**1i**)	–	**2i**	44	70	(*S*)-(−)
23	(*S*)	2-Naphthyl-S-Me (**1i**)	**AH4**	**2i**	**67**	**95**	(*S*)-(−)
24	(*S*)	2-Naphthyl-S-Me (**1i**)	**ALi4**	**2i**	63	93	(*S*)-(−)
25	(*S*)	$PhCH_2$-S-Me (**1j**)	**ALi4**	**2j**	64	23	(+)

[a] Reaction conditions: $[Fe(acac)_3]$ (0.02 mmol), ligand **1** (0.04 mmol), **AH4** or **ALi4** (0.01 mmol), sulfide (1 mmol) and aqueous H_2O_2 (35%; 1.2 mmol) in CH_2Cl_2 at room temperature for 16 h. [b] After column chromatography. [c] The *ee* values were measured on the isolated product and determined by HPLC analysis on a chiral stationary phase. [d] In cases in which the *ee* value was $\geq 90\%$, the formation of sulfone (10–15%) was observed; see also comment in reference [13]. [e] The absolute configurations were assigned by comparing optical rotations and/or HPLC elution order with known literature data.

(Table 1, entries 6 and 8). The last result is particularly impressive, as the product was obtained with only 27% *ee* in the absence of an additive. Furthermore, the yield of **2c** increased from 44% (no additive) to 73% (with **AH4**).[13]

Although it is difficult to provide a mechanistic rational for the observed improvements at the present stage, the fact that the best results were obtained with 0.5 equivalents of the carboxylic acid (and/or the carboxylate salt) relative to iron suggests that monocarboxylate-bridged diiron(III) complexes similar to those investigated as functional models able to mimic non-heme metalloproteins[2,14] could be involved. Attempts to isolate and to characterize those species formed in situ under the conditions described herein are currently in progress.

In summary, we developed an asymmetric iron-catalyzed sulfide oxidation with hydrogen peroxide as terminal oxidant, which provides sulfoxides with up to 96% *ee* in moderate to good yields (up to 78%). The simplicity of the process (room temperature, aerobic atmosphere) and the high enantioselectivities render this process an attractive alternative to the currently existing methods for metal-catalyzed asymmetric sulfide oxidations.

Experimental Section

$[Fe(acac)_3]$ (7.1 mg, 0.02 mmol) and ligand **3** (18.9 mg, 0.04 mmol) were dissolved in dichloromethane (0.7 mL), and the clear red solution was stirred until it turned clear brown (15 min). This solution was then transferred into a 10-mL flask containing a suspension of either 4-methoxybenzoic acid (**AH4**; 1.5 mg, 0.01 mmol) or lithium salt **ALi4** (1.6 mg, 0.01 mmol) in dichloromethane (0.5 mL), and the resulting mixture was stirred for 10 min. A solution of the sulfide **1** (1 mmol) in dichloromethane (0.8 mL) was then added to the previous solution, followed by the dropwise addition of aqueous H_2O_2 (35%; 1.2 mmol). The flask was then capped, and the reaction mixture was slowly stirred at room temperature (approximately 150 rpm). After 16 h, the aqueous layer was separated, the organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The product was then purified by chromatography on silica gel (pentane/Et_2O 1:2, then ethyl acetate). The *ee* values were determined by HPLC on a chiral stationary phase (Gynkotek apparatus; UV detector UVD 170S (254 nm); 20°C; flow rate 0.5 mL min^{-1}). Retention times [min]: (*R*)-**2a** 26.5, (*S*)-**2a** 31.2 (Chiralcel OD; heptane/*i*PrOH, 9:1); (*R*)-**2b** 22.0, (*S*)-**2b** 27.2 (Chiralcel OD; heptane/*i*PrOH, 9:1); (*R*)-**2c** 28.8, (*S*)-**2c** 36.1 (Chiralcel OD; heptane/*i*PrOH, 9:1); (*R*)-**2d** 24.0, (*S*)-**2d** 26.2 min (Chiralcel OD; heptane/*i*PrOH, 9:1); (−)-**2e** 19.3, (+)-**2e** 28.9 (Chiralcel OB; heptane/*i*PrOH, 8:2); (*S*)-**2f** 25.8, (*R*)-**2f** 35.9 (Chiralcel OB; flow rate, heptane/*i*PrOH, 8:2); (*S*)-**2g** 19.9, (*R*)-**2g** 30.0 (Chiralcel OB; heptane/*i*PrOH, 8:2); (*R*)-**2h** 42.9, (*S*)-**2h** 47.5 (Chiralcel OJ; heptane/*i*PrOH, 7:3); (*R*)-**2i** 37.2, (*S*)-**2i** 40.8 (Chiralcel OD; heptane/*i*PrOH, 9:1); (+)-**2j** = 22.8, (−)-**2j** = 28.4 (Chiralcel OB; heptane/*i*PrOH, 8:2).

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[11] M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194 – 7195.

[12] Sodium, potassium, cesium and tetrabutyl ammonium salts have also been assessed in the oxidation of **2a**: **ANa4**, 90% *ee*; **AK4**, 88% *ee*; **ACs4**, 87% *ee*; **ABu$_4$N4**, 82% *ee*.

[13] In oxidations that give sulfoxides with high *ee* values ($\geq$ 90%) significant amounts of sulfone (ca. 15%) were detected in the crude product. Preliminary studies revealed the existence of a kinetic resolution process that enhances the inherent *ee* value of the sulfoxide. This behavior contrasts that found in the original process (without an additive[7]). Details of these findings will be reported in due course.

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