Iron-Catalyzed Oxidations

Iron-Catalyzed Asymmetric Sulfide Oxidation with Aqueous Hydrogen Peroxide**

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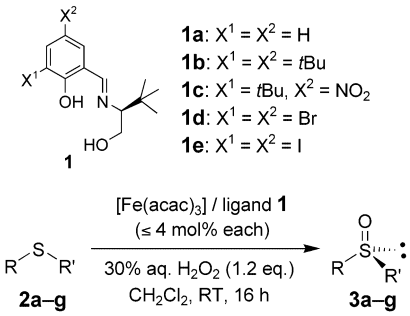
Dedicated to Dr. Jean-Pierre Bégué on the occasion of his 65th birthday

Research concerning new catalytic asymmetric reactions is often focused on the efficiency of the chemical transformation itself (i.e. yield and enantioselectivity) and less so on the practicability of the process and on environmental as well as economic issues. In the development of practical syntheses, however, the latter points become more dominant and aspects such as the simplicity of the process and the availability and toxicity of the reactants play a very significant role.[1] With respect to metal-catalyzed asymmetric oxidation reactions, this means that the choice of metal and terminal oxidant is of primary concern.[2] Along these lines, we now report an iron-catalyzed asymmetric sulfide oxidation, which provides optically active sulfoxides with up to 90% *ee*.[3] The catalysis proceeds under very simple reaction conditions (room temperature in a capped flask) and utilizes a readily available chiral iron complex ($\leqslant$4 mol%) as well as inexpensive and safe 30% aqueous hydrogen peroxide (Scheme 1).[4]



Scheme 1. Iron-catalyzed asymmetric oxidation of sulfides to sulfoxides.

Enantioselective oxidation of sulfides with titanium, manganese, and vanadium complexes has been widely studied.[5,6] Conversely, iron is relatively underrepresented in this field, and the few systems developed so far fail in terms of efficiency and practicability.[5] Most involve structurally complex iron porphyrins and iodosylbenzene[7a–d] or alkyl hydroperoxides[7e] as terminal oxidant, and the enantioselectivities are only moderate (<55% *ee*).[8] The iron complex $[Fe_2O(pb)_4(H_2O)_2](ClO_4)_4$ (pb = (−)-4,5-pinene-2,2′-bipyridine) as a catalyst for sulfide oxidations with H_2O_2 was reported by Fontecave and co-workers but, unfortunately, the enantioselectivity remained rather low (max. 40% *ee*).[9]

We have now found that sulfides can rapidly be oxidized to give chiral sulfoxides (max. 90% *ee*) by using an iron catalyst formed in situ from $[Fe(acac)_3]$ and a Schiff base of type **1** (Scheme 1).[10] The process is synthetically interesting for the following reasons: 1) The oxidation can be performed without particular precautions as the presence of water and air does not affect the outcome. 2) Aqueous hydrogen peroxide (30%, 1.2 equiv) is the most efficient oxidizing agent.[11] 3) Iron is abundant and relatively nontoxic in comparison to other transition metals, and $[Fe(acac)_3]$ is commercially available and inexpensive. 4) Ligands of type **1** are easily prepared from the corresponding aminoalcohol and salicylaldehyde derivatives. Already the first screening with simple ligands revealed that products with high enantioselectivities could be obtained (Table 1). Further ligand adjustments for specific target structures appear to be possible.

The influence of the structure of the ligand on the enantioselectivity of the reaction was studied in the oxidation

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Table 1: Catalytic enantioselective oxidation of sulfides with H_2O_2 and a chiral iron complex.[a]

Entry	Ligand	Sulfide **2**	Sulfoxide	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**1a**	Ph-S-Me (**2a**)	**3a**	27	26	(*S*)-(−)
2	**1b**	Ph-S-Me (**2a**)	**3a**	15	13	(*S*)-(−)
3	**1c**	Ph-S-Me (**2a**)	**3a**	27	23	(*S*)-(−)
4	**1d**	Ph-S-Me (**2a**)	**3a**	30	55	(*S*)-(−)
5	**1e**	Ph-S-Me (**2a**)	**3a**	36	59	(*S*)-(−)
6[e]	**1e**	Ph-S-Me (**2a**)	**3a**	40	51	(*S*)-(−)
7	**1e**	Ph-S-Et (**2b**)	**3b**	30	44	(*S*)-(−)
8	**1e**	Ph-S-Bn (**2c**)	**3c**	40	27	(*S*)-(−)
9	**1e**	*p*-ClPh-S-Me (**2d**)	**3d**	32	65	(*S*)-(−)
10	**1e**	*p*-BrPh-S-Me (**2e**)	**3e**	41	78	(*S*)-(−)
11	**1e**	*p*-NO_2Ph-S-Me (**2f**)	**3f**	21	90	(*S*)-(−)
12	**1e**	2-Naphthyl-S-Me (**2g**)	**3g**	44	70	(−)

[a] Reaction conditions: $[Fe(acac)_3]$ (0.02 mmol), ligand (0.04 mmol), sulfide (1 mmol), aqueous H_2O_2 (30%; 1.2 mmol), CH_2Cl_2. [b] Yield of isolated product. [c] The enantiomer ratios were determined by HPLC on a chiral stationary phase. [d] The absolute configurations were assigned by comparing optical rotations and HPLC elution orders with known literature data. [e] Urea–H_2O_2 adduct (UHP, 1.2 mmol) was used instead of aqueous H_2O_2.

of thioanisole (**2a**) (Table 1, entries 1–5). The highest enantioselectivities were obtained with ligands derived from (*S*)-*tert*-leucinol. In contrast to large substituents such as *tert*-butyl (less than 23% *ee* for ligands **1b** and **1c**) on the aryl moiety, halogen atoms such as Br or I (ligands **1d** and **1e**[10d]) increase the enantioselectivity significantly (55 and 59% *ee*, respectively; Table 1, entries 4 and 5).

The chiral iron/H_2O_2 system affords products with particularly high *ee* values in the oxidation of aryl methyl sulfides (59–90% *ee*). Under the conditions described, no sulfones are formed, which indicates that the enantioselectivities are a direct result of the asymmetric sulfide oxidation and not of a kinetic resolution by overoxidation of the resulting sulfoxide.[12] A limitation of the reported catalysis stems from the fact that under the reaction conditions optimized to achieve high enantioselectivities, significant amounts of the substrates remain and the yields do not exceed 44%. All attempts to reach higher sulfide conversions (by increasing the catalyst loading and/or the amount of oxidant,[12] slow addition of the oxidant, or performing the reaction under homogeneous conditions[13]) afforded sulfoxides with lower *ee* values.

The results described herein, albeit not as good as those already reported with chiral complexes of other metals,[5] constitute the basis for a promising new approach and a major step in the ascent of iron-catalyzed asymmetric oxidation in general, and sulfoxidation in particular. Investigations are currently underway to improve the efficiency of the catalysts and to determine which iron species is responsible for the observed enantioselectivity.

Experimental Section

$[Fe(acac)_3]$ (7.1 mg, 0.02 mmol) and ligand **1** (0.04 mmol) were dissolved in dichloromethane (1 mL) in a 10-mL flask, and the clear red solution was stirred until it turned brown (15 min). A solution of the sulfide (1 mmol) in dichloromethane (1 mL) was then added, followed by the dropwise addition of aqueous H_2O_2 (30%; 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, and the organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The product was then purified by flash chromatography on silica gel (pentane/diethyl ether 1:1, then ethyl acetate). The enantiomeric excesses were determined by HPLC on chiral stationary phases (Gynkotek apparatus; UV detector UVD 170S (254 nm); 20°C; flow rate 0.5 mL min^{-1} unless indicated otherwise). Retention times [min]: (*R*)-**3a** 26.6, (*S*)-**3a** 31.7 (Chiralcel OD, heptane/*i*PrOH 9:1); (*R*)-**3b** 20.5, (*S*)-**3b** 25.7 (Chiralcel OD, heptane/*i*PrOH 9:1); (*R*)-**3c** 31.3, (*S*)-**3c** 38.7 (Chiralcel OD, heptane/*i*PrOH 9:1); (*S*)-**3d** 23.2, (*R*)-**3d** 34.3 (Chiralcel OD, heptane/*i*PrOH 9:1); (*S*)-**3e** 26.1, (*R*)-**3e** 35.0 (Chiralcel OB-H, heptane/*i*PrOH 8:2, flow rate 0.4 mL min^{-1}); (*R*)-**3f** 44.2, (*S*)-**3f** 49.7 (Chiralcel OJ, heptane/*i*PrOH 7:3); (+)-**3g** 38.9, (−)-**3g** 43.5 (Chiralcel OD, heptane/*i*PrOH 9:1; optical rotation measured in $CHCl_3$).

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[3] Efficient asymmetric sulfide oxidations are required in various processes towards pharmaceutically relevant molecules. One of the most important is the synthesis of the chiral sulfoxide, omeprazole, which is one of the most sold drugs in the world (sales in 2002: US$6.6 billion). For a summary of recent developments and data, see: A. M. Rouhi, *Chem. Eng. News* **2003**, *81*(19), 56–61.

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[11] Urea–H_2O_2 adduct (UHP) also gives satisfactory results.

[12] After a reaction time of 16 h, a potassium iodide test revealed that no more oxidant was present in the reaction medium. In the presence of a large excess of H_2O_2, complete conversion of sulfide into racemic sulfoxide and sulfone was observed. In independent experiments, it was demonstrated that the sulfoxide to sulfone oxidation proceeded in a non-enantioselective manner.

[13] Attempts to substitute dichloromethane with other solvents such as acetonitrile, acetone, toluene, or *tert*-butyl methyl ether were unsuccessful.

