Asymmetric oxidation of sulfides under solvent-free or highly concentrated conditions

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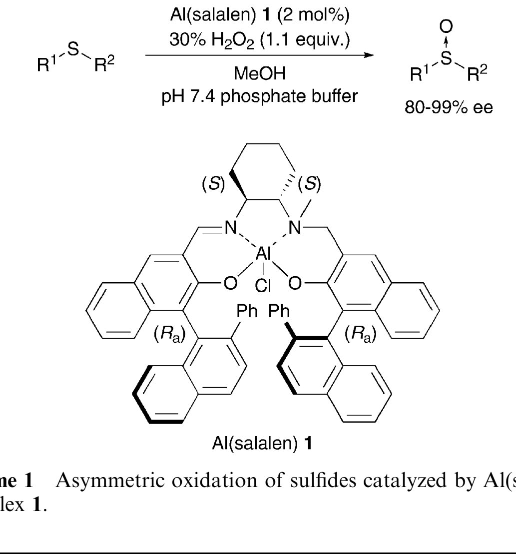
The aluminium(salalen) complex was found to be an efficient catalyst for the asymmetric oxidation of sulfides under solvent-free or highly concentrated conditions, in which an only 0.002–0.01 mol% catalyst loading was sufficient to obtain optically active sulfoxides in high yield with high enantioselectivity.

Organic synthesis has evolved significantly, and many useful methods, reagents and techniques have been developed in the past half-century, so that organic chemists can synthesize most molecules such as complex natural products and sophisticated functional materials.[1] However, modern organic synthesis requires the efficient synthesis of molecules and we must consider many aspects of reactions including practicality, sustainability, waste materials, reaction time, cost, safeness, energy consumption, *etc*. An assessment criterion that measures the efficiency of the reaction is the *E* factor, introduced by Sheldon.[2] The *E* factor is defined as the waste per kg product, and the solvent is a large contributing agent in typical organic syntheses. Thus, solvent-free or highly concentrated reactions can be an effective approach to reduce the *E* factor of a chemical process. Reactions under solvent-free or highly concentrated conditions also have many advantages, such as reducing solvent cost and the enhancement of reaction rate. Therefore, much research effort has been devoted to the development of solvent-free or highly concentrated reactions, and many examples of catalytic asymmetric variants have been reported.[3] To our knowledge, however, highly enantioselective oxidation under these conditions has not been reported, since oxidation is exothermic and the absence of solvent may cause destabilization of reaction conditions.[4]

Recently, we found that chiral aluminium(salalen)[5] complex (R_a,*S*,*S*,R_a)-**1** is an efficient catalyst for asymmetric sulfide oxidation using aqueous hydrogen peroxide as the oxidant (Scheme 1).[6–15] The original conditions required 2 mol% of the catalyst and the reaction was conducted in 0.1 mol L^{-1} substrate concentration at room temperature. While methanol was employed as the solvent, the oxidation of thioanisole in other solvents such as ethanol, ethyl acetate, tetrahydrofuran, dichloromethane and toluene also proceeded with high enantioselectivity. The broad solvent tolerance indicated that substrate sulfides and product sulfoxides might work as solvents without affecting stereoselection. Here, we report the highly enantioselective oxidation of sulfides under solvent-free or highly concentrated conditions.fnoteref †

We first examined effects of substrate concentration in the oxidation of thioanisole using (R_a,*S*,*S*,R_a)-**1** as the catalyst under the conditions, adding aqueous hydrogen peroxide portionwise (Table 1).[16]‡ While a low yield was observed with 0.2 mol% catalyst in 0.1 mol L^{-1} substrate concentration, reactions under more concentrated conditions at lower reaction temperature gave results comparable to that obtained under the original condition (entry 1 *vs.* 5). Further lowering the catalyst load under the conditions diminished yield and enantioselectivity (entries 5–7). To our surprise, however, reaction under solvent-free conditions gave the sulfoxide in 92% yield with 96% ee in the presence of only 0.002 mol% catalyst (entry 8). The significant enhancement of the reaction rate under solvent-free conditions relatively reduced the participation of a non-catalytic sulfur oxidation process in which the catalyst was not involved, so that the high enantioselectivity was obtained.[17]

Next, the scope of sulfides was investigated (Table 2).[18] Oxidation of solid sulfides such as *p*-methoxy- and *p*-chlorophenyl methyl sulfides was conducted in 5 mol L^{-1} sulfide concentration in toluene (entries 3 and 6). Alkyl aryl sulfides were efficiently converted to the sulfoxides with high enantioselectivity in the presence of only 0.002–0.01 mol% catalyst. The electronic nature of the substituents on the aromatic ring slightly affected the reaction progress. The sulfide possessing electron-withdrawing *p*-chloro functionality afforded more sulfone to give a lower yield of the desired sulfoxide than that



Scheme 1 Asymmetric oxidation of sulfides catalyzed by Al(salalen) complex **1**.

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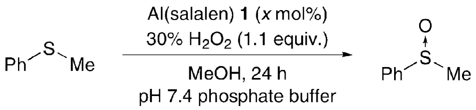
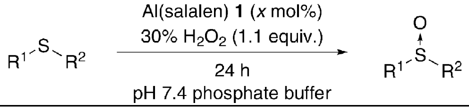
Table 1 Optimization of reaction conditions



Entry	Substrate concentration/mol L^{-1}	x (mol%)	Temperature/°C	Yield (%)[a]	Ee (%)[b]
1	0.1	2	RT	90	98
2	0.1	0.2	RT	52	87
3	1	0.2	RT	88	93
4	1	0.2	0	91	98
5	5	0.2	0	95	97
6	5	0.02	0	92	95
7	5	0.002	0	87	90
8	Solvent-free	0.002	0	92 (86)[c]	96

[a] Determined by ^1H NMR analysis (400 MHz). [b] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OB-H). [c] Isolated yield.

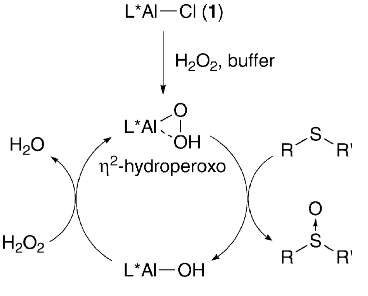
Table 2 Asymmetric oxidation of sulfides under solvent-free or highly concentrated conditions



Entry	R^1	R^2	x (mol%)	Temperature/°C	Yield (%)[a]	Ee (%)
1	p-MeC_6H_4	Me	0.01	−10	86	98[b]
2	o-$MeOC_6H_4$	Me	0.004	0	88	96[b]
3[c]	p-$MeOC_6H_4$	Me	0.01	0	83	99[b]
4	o-ClC_6H_4	Me	0.01	−10	85	>99[b]
5	m-ClC_6H_4	Me	0.01	−10	78	98[b]
6[c]	p-ClC_6H_4	Me	0.01	0	73	99[b]
7	Ph	Et	0.002	0	43	93[d]
8	Ph	Et	0.01	−10	48	97[d]
9	$PhCH_2$	Me	0.01	−10	88	69[b]
10[c]	n-C_8H_{17}	Me	0.01	0	55	78[b]
11[e]	n-C_8H_{17}	Me	0.01	0	31	91[b]

[a] Isolated yield. [b] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OB-H). [c] Substrate concentration: 5 mol L^{-1} in toluene. [d] Determined by chiral HPLC analysis (DAICEL CHIRALCEL OD-H). [e] Substrate concentration: 1 mol L^{-1} in toluene.

with the electron-donating *p*-methoxy group, although ee values of 99% were observed in both cases (entries 3 and 6). While high enantioselectivity was obtained in the reaction of ethyl phenyl sulfide, a significant amount of sulfone was formed and the yield was diminished (entries 7 and 8). Reactions of dialkyl sulfides furnished the sulfoxides with good to high enantioselectivity (entries 9–11). Although the oxidation of methyl *n*-octyl sulfide in 5 mol L^{-1} sulfide concentration was moderately enantioselective, the ee of the sulfoxide was increased under more dilute conditions, due to the accelerated enantiomer-differentiating oxidation of the sulfoxide.[19]



Scheme 2 A plausible catalytic cycle.

A plausible catalytic cycle is illustrated in Scheme 2. Although the precise reaction mechanism is unclear at present, we propose a η^2-hydroperoxo complex as the active species, that is formed by the reaction of the complex **1** and hydrogen peroxide. The hydroperoxo complex oxidizes sulfides to give the sulfoxides along with the formation of an aluminium hydroxide complex. Then, the reaction with hydrogen peroxide regenerates the active hydroperoxo complex.

In summary, we have developed a highly efficient asymmetric oxidation of sulfides under solvent-free or highly concentrated conditions. Under the conditions, optically active sulfoxides were obtained in high yields with high to excellent enantioselectivity in the presence of only 0.002–0.01 mol% catalyst.

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Notes and references

† Typical experimental procedure: a 0.001 mol L^{-1} solution of Al(salalen) complex **1** in toluene (100 μL, 0.002 mol%) was placed in a flask, and then toluene was removed under reduced pressure. Thioanisole (588 μL, 5.0 mmol) and phosphate buffer (20 μL, pH 7.4, 66.7 mol L^{-1}) were added, and the mixture was cooled to 0 °C. 30% hydrogen peroxide (620 μL, 1.1 equiv.) was added in several small portions over 1 h, and then the reaction mixture was stirred. After 24 h, aqueous $Na_2S_2O_3$ and ethyl acetate were added and the organic phase was separated and dried over Na_2SO_4. The crude product was purified by silica gel chromatography (*n*-hexane–ethyl acetate 1 : 1 to 0 : 1) to give the desired sulfoxide (600 mg, 86%). The enantiomeric excess (96% ee) was determined by chiral HPLC (DAICEL CHIRALCEL OB-H, *n*-hexane–*i*-propanol 80 : 20).

‡ **Caution!** Oxidation is usually very exothermic. Oxidant must be carefully added dropwise or in several small portions, even with an efficient cooling system.

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