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Asymmetric Catalysis

Asymmetric Oxidation Catalysis by a Chiral Al(salalen) Complex: Highly Enantioselective Oxidation of Sulfides with Aqueous Hydrogen Peroxide**

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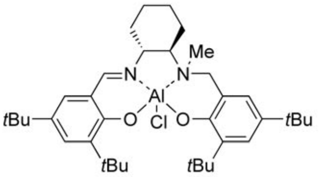
Chiral aluminum complexes have become established as promising Lewis acid catalysts for a wide variety of asymmetric reactions.[1,2] In contrast, asymmetric oxidation catalysis by aluminum complexes has scarcely been developed. As a rare example, Bolm and co-workers reported an Al-catalyzed asymmetric Baeyer–Villiger oxidation with an alkyl hydroperoxide as the oxidant. High enantioselectivity was observed in the reaction, which required anhydrous conditions.[3] To the best of our knowledge, no chiral aluminum catalyst has been reported for a highly enantioselective oxidation with aqueous hydrogen peroxide as the oxidant.[4] Herein, we describe the development of an asymmetric oxidation of sulfides with aqueous hydrogen peroxide in the presence of a chiral Al(salalen) complex.[5–12]

Recently, we reported the first synthesis of the chiral Al(salalen) complex **1** and its asymmetric catalysis of hydrophosphonylation.[13] Reactions with both aldehydes and imines furnished the corresponding products with high to excellent enantioselectivities. We decided to modify and tune the complex to further explore new catalysis of Al(salalen) complexes. During the course of this investigation, we found that the treatment of an Al(salalen) complex with water provided a new water-compatible Al(salalen) complex. Although the complex could not be isolated, it occurred to us that Al(salalen) complexes should serve as catalysts under aqueous conditions. Thus, we investigated the use of the complexes as catalysts for asymmetric oxidation with aqueous hydrogen peroxide as the oxidant.



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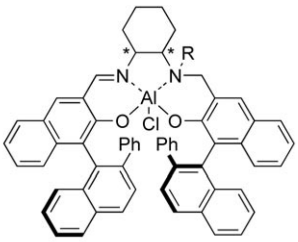
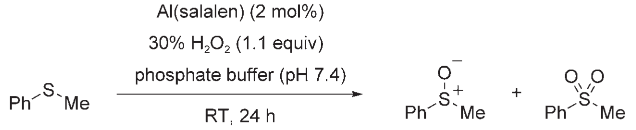


2: (a*R*,*R*,*R*), R = H
3: (a*R*,*R*,*R*), R = Me
4: (a*R*,*S*,*S*), R = H
5: (a*R*,*S*,*S*), R = Me

First, we examined the asymmetric oxidation of thioanisole with 30 % hydrogen peroxide (1.1 equiv) in the presence of Al(salalen) complexes (2 mol %) and found that the structure and configuration of the complexes affected significantly their catalytic and asymmetry-inducing abilities (Table 1). The reaction with complex **1** was only modestly selective and poorly reproducible. In contrast, complexes **2**–**5**, which contain a binol-based salalen ligand (binol = 1,1′-binaphthalene-2,2′-diol), showed higher catalytic activity with good reproducibility in the presence of a phosphate buffer. The reproducibility of the reaction with **1** was not improved by the addition of the phosphate buffer. Asymmetric induction by the (aR,R,*R*) complexes **2** and **3** was modest; however, much higher levels of asymmetric induction

Table 1: Al(salalen)-catalyzed asymmetric oxidation of thioanisole.



Entry	Cat.	Solvent	Conv. [%][a]	Yield [%][b] sulfoxide	sulfone	*ee* [%][c,d]
1	**1**	MeOH	40–60	40–60	2–10	20–60 (*S*)
2	**2**	MeOH	70	64	6	46 (*S*)
3	**3**	MeOH	55	51	4	10 (*R*)
4	**4**	MeOH	86	78	8	89 (*S*)
5	**5**	MeOH	99	90	9	98 (*S*)
6	**5**	EtOH	92	78	14	98 (*S*)
7	**5**	AcOEt	85	68	17	97 (*S*)
8	**5**	THF	85	66	18	98 (*S*)
9	**5**	CH_2Cl_2	81	78	13	99 (*S*)
10	**5**	toluene	84	59	25	99 (*S*)
11[e]	**5**	MeOH	33	32	< 1	94 (*S*)

[a] The conversion was determined by ^1H NMR spectroscopic analysis (400 MHz). [b] Yields were determined by ^1H NMR spectroscopic analysis (400 MHz). [c] The *ee* value was determined by HPLC analysis on a chiral phase (Daicel Chiralcel OB-H). [d] The absolute configuration was determined by HPLC analysis by comparison of the elution order of the enantiomers with that of an authentic sample. [e] Reaction time: 1 h.

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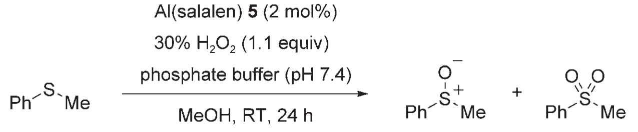
were observed with the (a*R*,*S*,*S*) complexes **4** and **5**.[14] In particular, the reaction with complex **5** proceeded smoothly with high enantioselectivity to give the product with 98 % *ee*. Although excellent enantioselectivity was observed regardless of the solvent used (Table 1, entries 5–10), the reaction in methanol gave the desired sulfoxide in the highest yield accompanied by the smallest amount of the sulfone overoxidation product (entry 5). Although the production of the sulfone was suppressed when the reaction time was decreased, the sulfoxide was then formed in lower yield with a somewhat lower *ee* value (Table 1, entry 11).

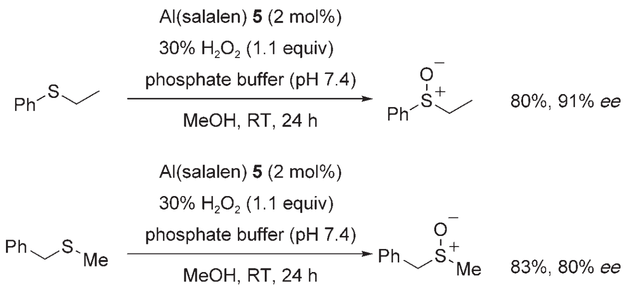
The scope of the reaction with respect to the sulfide substrate was investigated with complex **5** under the optimized conditions (Table 2). All aryl methyl sulfides underwent the reaction to give the desired products in high yield with excellent enantioselectivity, irrespective of the position of the substituent on the aromatic ring and the electronic nature of the aryl substituent. The best *ee* value was observed for the oxidation of methyl *ortho*-methoxyphenyl sulfide, methyl *ortho*-nitrophenyl sulfide, and methyl *meta*-bromophenyl sulfide (Table 2, entries 5–8). In the oxidation of *ortho*-substituted aryl methyl sulfides, the formation of the corresponding sulfone was inhibited significantly (Table 2, entries 5–7). The oxidation could be carried out on a scale as large as 10.0 mmol (Table 2, entry 6). The reaction of ethyl phenyl sulfide also proceeded with high enantioselectivity (Scheme 1), and the oxidation of benzyl methyl sulfide was high yielding, although a slight decrease in enantioselectivity was observed.

Table 2: Asymmetric oxidation of various aryl methyl sulfides with the Al(salalen) complex **5**.[a]



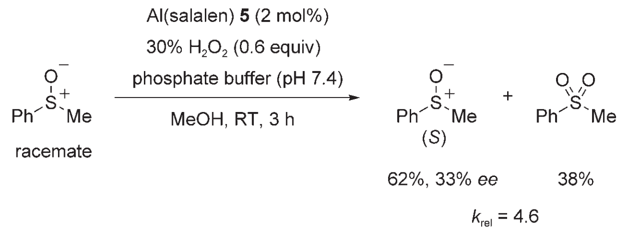
Entry	Ar	Yield [%] sulfoxide[b]	Yield [%] sulfone[c]	*ee* [%][d]
1	C_6H_5	86	9	98 (*S*)[e]
2	*p*-ClC_6H_4	83	9	97 (*S*)[e]
3	*p*-MeC_6H_4	82	9	98 (*S*)[e]
4	*p*-$MeOC_6H_4$	82	8	97 (*S*)[e]
5	*o*-$MeOC_6H_4$	82	1	99 (*S*)[e]
6[f]	*o*-$MeOC_6H_4$	91	<1	99 (*S*)[e]
7	*o*-$NO_2C_6H_4$	84	2	99 (*S*)[g]
8	*m*-BrC_6H_4	81	10	99 (*S*)[e]

[a] The reaction was carried out on a 0.20-mmol scale, unless otherwise noted. [b] Yield of the isolated sulfoxide. [c] The yield of the sulfone was determined by ^1H NMR spectroscopic analysis (400 MHz). [d] The absolute configuration was determined by HPLC analysis by comparison of the elution order of the enantiomers with that of an authentic sample. [e] The *ee* value was determined by HPLC analysis on a chiral phase (Daicel Chiralcel OB-H). [f] The reaction was carried out on a 10.0-mmol scale. [g] The *ee* value was determined by HPLC analysis on a chiral phase (Daicel Chiralcel OD-H).



Scheme 1. Asymmetric oxidation of sulfides with the Al(salalen) complex **5**.

As already noted, further oxidation of the sulfoxide products was observed in this Al-catalyzed sulfide oxidation. We investigated enantiomer differentiation in the oxidation of racemic methyl phenyl sulfoxide (Scheme 2) and found that the *R* sulfoxide was oxidized preferentially to the sulfone with a relative ratio of 4.6. As the *S* enantiomer was produced selectively in the oxidation of thioanisole, this result explains the gradual increase in the *ee* value of the sulfoxide as the reaction proceeds: The synergistic combination of the initial highly enantioselective oxidation of the sulfide with the following oxidative kinetic resolution process is responsible for the high *ee* values observed for the sulfoxides.[6e,f,15]



Scheme 2. Kinetic resolution of racemic methyl phenyl sulfoxide.

In conclusion, we have introduced the concept of water-compatible aluminum(salalen) complexes and developed a highly enantioselective oxidation of sulfides with aqueous hydrogen peroxide. A variety of sulfides were converted smoothly into the corresponding sulfoxides with good to excellent enantioselectivity. The elucidation of the reaction mechanism and further investigation of the oxidation catalysis of Al(salalen) complexes are in progress.

Experimental Section

5: Diethylaluminum chloride (0.92 M in hexane, 100 μL) was added to a solution of the corresponding salalen ligand (84.5 mg, 0.10 mmol) in dry toluene (1.0 mL) at room temperature. The mixture was stirred at room temperature for 3 h, then the resulting red solution was suspended in hexane. The suspension was filtered through a glass sinter funnel, and the yellow precipitate collected was washed with *n*-hexane to give **5** (79.5 mg, 87 %) as a yellow solid, which was used without further purification. C,H,N analysis (%) calcd for $C_{61}H_{48}N_2O_2AlCl\cdot0.5\,H_2O$: C 79.20, H 5.49, N 3.03; found: C 79.10, H 5.36, N 3.03.

Typical oxidation procedure: Thioanisole (24.8 mg, 0.20 mmol), phosphate buffer (20.0 μL, pH 7.4, 67 mmol L^{-1}), and 30 % aqueous hydrogen peroxide (25.0 mg, 0.22 μmol) were added sequentially to a solution of **5** (3.6 mg, 4.0 mmol) in methanol (2.0 mL), and the resulting solution was stirred at room temperature for 24 h. The mixture was then concentrated in vacuo, and the residue was purified by chromatography on silica gel (*n*-hexane/acetone 4:1–1:1) to give methyl phenyl sulfoxide (24.1 mg, 86 %). The enantiomeric purity of the sulfoxide (98 % *ee*) was determined by HPLC analysis with a Daicel Chiralcel OB-H column (*n*-hexane/*i*PrOH 4:1).

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