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WO_3–30% H_2O_2–cinchona alkaloids: a new heterogeneous catalytic system for the asymmetric oxidation of sulfides and the kinetic resolution of racemic sulfoxides

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Abstract—WO_3-catalyzed asymmetric oxidation of thioethers and kinetic resolution of sulfoxides with 30% aq. H_2O_2 in the presence of cinchona alkaloids under heterogeneous conditions affords chiral sulfoxides in high yields with moderate to good enantioselectivities.

Chiral sulfoxides have emerged as versatile building blocks and chiral auxiliaries in the synthesis of pharmaceutical products.[1] The asymmetric oxidation of prochiral sulfides with chiral metal complexes has become one of the most effective routes to obtain these chiral sulfoxides.[2] Chiral metal complexes such as Ti-diol/–BINOL,[3] V, Ti and Mn–salen[4] and V–Schiff bases[5] are mainly used as homogeneous catalysts in combination with either alkyl hydroperoxides or expensive chiral hydroperoxides as terminal oxidants, for asymmetric sulfoxidation, often in stochiometric amounts. In recent years, kinetic resolution of racemic sulfoxides[6] has emerged as a promising method to obtain optically pure sulfoxides, as racemic sulfoxides are readily prepared by direct oxidative methods. Although several modified procedures have been reported for both asymmetric sulfoxidations and kinetic resolutions, scant attention has been given to the heterogeneous version of these reactions involving the use of less expensive commercially avialable metal catalysts and chiral ligands.[7] The use of heterogeneous catalysts under ambient conditions offers several advantages compared with their homogeneous counterparts e. g. ease of recovery and recycling and enhanced stability. Further use of aq. H_2O_2 is highly desirable from the viewpoints of atom economy and ecological considerations.

In this communication, we wish to report a new heterogeneous catalytic system (WO_3–30% H_2O_2) which efficiently catalyzes both the asymmetric oxidation of variety of thioethers and kinetic resolution of racemic sulfoxides in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2$–PYR] to produce optically active sulfoxides in high yields and with good enantioselectivities (Schemes 1 and 2).

Table 1 shows the results from the asymmetric oxidations of phenyl benzyl sulphide with 30% H_2O_2 in the presence of a catalytic amount of WO_3 and cinchona alkaloids and it was found that $(DHQD)_2$–PYR in THF gave the best result (70% yield; 53% ee). Among the solvents screened (CH_3OH, CH_2Cl_2, $CHCl_3$, CH_3CN, etc.), THF proved to be the best choice while water and acetic acid were found to be detrimental to the selectivity of the sulfoxidation. Among the various oxidants employed, 30% H_2O_2 as well as H_2O_2–urea complex were found to be effective oxidants, giving excellent yields of sulfoxides with moderate enantioselectivities. After initial optimization studies, combination of WO_3 (5 mol%), chiral cinchona alkaloid (10 mol%) and aq. 30% H_2O_2 (1.1 equiv.) in THF proved to be the best catalytic system for the asymmetric oxidation of aryl alkyl sulfides.

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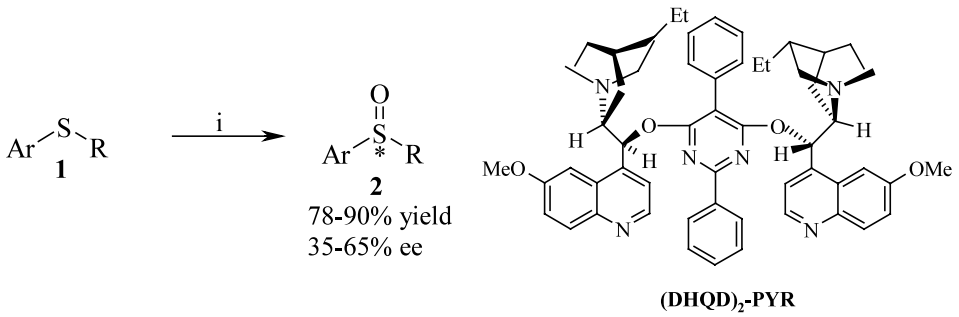


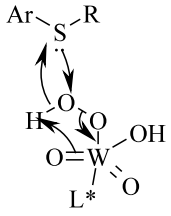
Scheme 1. *Reagents and conditions*: (i) WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF, 0°C.

It is evident from Table 2[†] that a variety of aryl alkyl sulfides **1** underwent oxidation under the reaction conditions to yield the corresponding optically active sulfoxides **2** in 78–90% yields and 35–65% ee. Sulfides possessing benzyl as the R group showed better enantioselectivity than other alkyl groups. Increasing the loading of the ligand (50 mol%) did not have any significant effect on the enantioselectivity of the reactions.

It was also of interest to subject various racemic sulfoxides to WO_3-catalyzed kinetic resolution in the presence of $(DHQD)_2$–PYR as ligand, the results of which are presented in Table 3.[†] Kinetic resolutions were performed at 25°C to afford optically active sulfoxides **4** in 25–44% yield and 44–90% ee along with the corresponding sulfones **5** (Scheme 2).

As shown in Fig. 1, when the conversion of racemic sulfoxide to sulfone reached 75% for 18 h, the observed optical purity of the recovered sulfoxide with (*R*)-configuration increased to 90% ee.

Mechanistically, it is believed that the electrophilicity of the peroxide oxygen of H_2O_2 is increased by the oxometal (M=O) group coordinated by the chiral ligand, L* **6** so that the asymmetric sulfoxidation of thioethers proceeds readily to give chiral sulfoxides in high yields.



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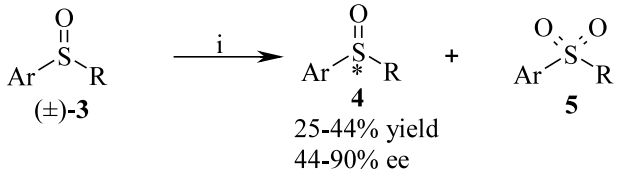
The present methodology was applied to the enantioselective sulfoxidation of **7**[9] to produce antiulcer drug (*R*)-Lansoprazole **8** in 84% yield and 88% ee (Scheme 3).[‡]

In conclusion, the asymmetric oxidation of thioethers as well as kinetic resolution of sulfoxides with 30% H_2O_2 catalyzed by a stable, recyclable and commercially avialable solid WO_3 catalyst provides a simple and effective procedure for the preparation of chiral sulfoxides in good enantiomeric purity.



Scheme 2. *Reagents and conditions*: (i) WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF, 25°C.

[†] *Typical experimental procedure*: A 25 ml round-bottomed flask was charged with WO_3 (0.012 g, 0.05 mmol), $(DHQD)_2$–PYR (0.088 g, 0.1 mmol) and sulfide or racemic sulfoxide (1 mmol) in THF (2 ml). To this reaction mixture was added 30% H_2O_2 (0.12 ml, 1.1 mmol) at a given temperature. The reaction mixture was further stirred for the specified time. The catalyst was filtered off and the filtrate was diluted with EtOAc (10 ml). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography using petroleum ether and EtOAc as eluents to afford optically active sulfoxides.

[‡] **(*R*)-(+)-Lansoprazole 8**: yield 84%; mp 162–165°C (dec.); $[\alpha]_{25}^{D}$ = +250.60 (*c* 0.5, acetone); HPLC: 88% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (*R*)-enantiomer = 18.4 min, (*S*)-enantiomer = 21.3 min. IR (Nujol, cm^{-1}): 3200, 3053, 2950, 2852, 1658, 1559, 1444, 1379, 1267, 1263, 1163, 1037, 1110, 973, 858, 746, 576; ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H), 4.35 (q, *J* = 8.14 Hz, 2H), 4.81 (d, *J* = 6.30 Hz, 2H), 6.64 (d, *J* = 6.30 Hz, 1H), 7.27–7.66 (m, 5H), 8.32 (d, *J* = 6.31 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.08, 30.19, 61.11, 66.25 (q), 107.27, 116.61, 124.66, 148.88, 150.54, 153.52, 163.07; MS *m*/*z* (rel. int.): 369 (M^+, 26), 353 (20), 308 (4), 320 (60), 252 (16), 238 (83), 204 (40), 165 (56), 150 (32), 137 (51), 122 (72), 106 (82), 90 (73), 77 (50), 65 (76), 52 (100). Anal. calcd for $C_{16}H_{14}F_3N_3SO_2$: C, 52.03; H, 3.82; N, 11.38; S, 8.68. Found: C, 52.02; H, 3.72; N, 11.31; S, 8.73%.

Table 1. WO_3-catalyzed asymmetric oxidation of phenyl benzyl sulfide by aq. H_2O_2 in the presence of cinchona alkaloids[a]

Sr. No.	Chiral ligand	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	% ee[c]
1	(−)-Quinine	CH_3CN	0	48	83	29 (*R*)
2	(−)-Quinine	THF	25	4	62	34 (*R*)
3	(−)-Quinine	THF	0	27	88	41 (*R*)
4	DHQD[d]	CH_3CN	0	46	79	27 (*R*)
5	NBCC[e]	CH_2Cl_2–H_2O	25	8	86	13 (*R*)
6	$(DHQD)_2$–PYR[f]	THF	25	5	70	53 (*R*)[h]
7	$(DHQD)_2$–PHAL[g]	THF	25	8	63	22 (*R*)

[a] *Reaction conditions*: WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF.
[b] Isolated yield after column chromatography.
[c] Ee based on comparison of $[\alpha]_D$ values reported in literature,[3,8] as well as by chiral HPLC analysis using Chiralcel OD-H column (conditions: $\lambda = 254$ nm, hexane:2-propanol (9:1), 0.5 ml/min).
[d] Dihydroquinidine.
[e] *N*-Benzyl cinchoninium chloride.
[f] Hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether.
[g] Hydroquinidine 1,4-phthalazinediyl diether.
[h] WO_3 was recovered and recycled at least five times, showing essentially the same conversion and enantioselectivity.

Table 2. Asymmetric oxidation of prochiral sulfides by aq. H_2O_2 catalyzed by WO_3–cinchona alkaloids at 0°C[a]

Sr. No.	Ar	R	Chiral ligand	Time (h)	Yield[b] (%)	% ee[c]
1	Ph	Me	$(DHQD)_2$–PYR	49	88	59 (*R*)
		Me	$(DHQ)_2$–PYR[d]	46	83	55 (*S*)
		Et	$(DHQD)_2$–PYR	44	82	51 (*R*)
		^{i}Pr	$(DHQD)_2$–PYR	44	83	45 (*R*)
		^{n}Bu	$(DHQD)_2$–PYR	40	90	35 (*R*)
		C_6H_{11}	$(DHQD)_2$–PYR	36	78	46 (*R*)
		CH_2Ph	$(DHQD)_2$–PYR	24	88	61 (*R*)
2	*p*-Tolyl	Me	$(DHQD)_2$–PYR	44	81	44 (*R*)
		Me	$(DHQ)_2$–PYR	32	87	52 (*S*)
		Et	$(DHQD)_2$–PYR	46	86	43 (*R*)
		CH_2Ph	$(DHQD)_2$–PYR	34	85	65 (*R*)[e]

[a] *Reaction conditions*: WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF, 0°C.
[b] Isolated yield after column chromatography.
[c] Ee based on comparison of $[\alpha]_D$ values reported in the literature, as well as by chiral HPLC analysis using Chiralcel OD-H column (conditions: $\lambda = 254$ nm, hexane:2-propanol (9:1), 0.5 ml/min).
[d] Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether.
[e] WO_3 was recovered by simple filteration and recycled at least five times, essentially showing the same conversion and enantioselectivity.

Table 3. WO_3-catalyzed kinetic resolution of aryl alkyl sulfoxides in presence of $(DHQD)_2$–PYR at 25°C[a]

Sr. No.	Ar	R	Time (h)	Yield[b] (%)		% ee[c] of **4**
				Sulfoxide **4**	Sulfone **5**	
1	Ph	Me	12	40	55	69
		Et	10	39	52	66
		^{i}Pr	12	32	60	60
		^{n}Bu	10	44	48	44
		C_6H_{11}	13	35	62	71
		$C_6H_5CH_2$	20	31	57	82
2	*p*-Tolyl	Me	16	29	66	67
		Et	14	33	67	58
		^{i}Pr	12	28	66	62
		$C_6H_5CH_2$	18	25	72	90

[a] *Reaction conditions*: WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF.
[b] Isolated yield after column chromatography.
[c] Ee based on comparison of $[\alpha]_D$ values reported in literature, as well as by chiral HPLC analysis using Chiralcel OD-H column (conditions: $\lambda = 254$ nm, hexane:2-propanol (9:1), 0.5 ml/min).

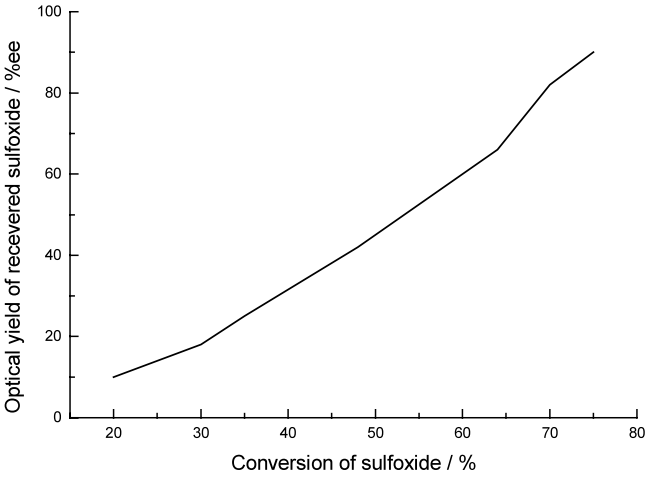
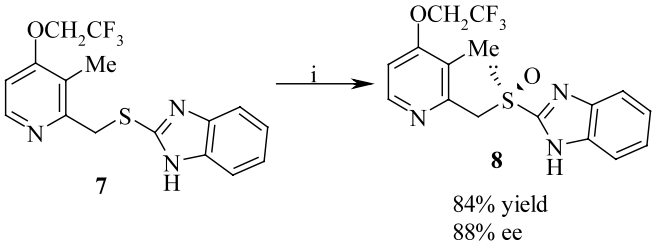


Figure 1. Kinetic resolution of *p*-tolyl benzyl sulfoxide.



Scheme 3. *Reagents and conditions*: (i) WO_3 (5 mol%), $(DHQD)_2$–PYR (10 mol%), aq. 30% H_2O_2 (1.1 equiv.), THF, 0°C, 50 h.

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