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8 Asymmetric Sulfoxidation

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8.1 ASYMMETRIC OXIDATION OF SULFIDES AND KINETIC RESOLUTION OF SULFOXIDES

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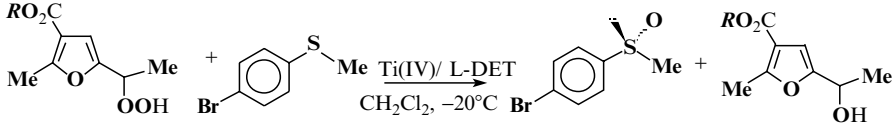
8.1.1 ASYMMETRIC OXIDATION OF 4-BROMOTHIOANISOLE



1 2 (***R***)-**3** **4**

R: Cholestanyl

Materials and equipment

- Anhydrous dichloromethane (99.8 %), 3.5 mL
- 4-Bromothioanisole (97 %), 61 mg, 0.3 mmol
- Titanium(IV) isopropoxide (97 %), 0.09 mL, 0.3 mmol
- Diethyl L-tartrate (99 %), 0.21 mL, 1.2 mmol
- 5-(1-Hydroperoxyethyl)-2-methyl-3-furoic acid 5α-cholestan-3β-yl ester (**1**)[1c] (mixture of diastereo-isomers), 171 mg, 0.3 mmol
- Ethyl acetate, *n*-hexane
- Anhydrous sodium sulfate

- Silica gel 60 (230–400 mesh ASTM)

- One 10 mL round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer
- Refrigerator bath (−22 °C)
- Büchner funnel (6 cm)
- Büchner flask
- Filter paper (589 Blue ribbon)
- Rotary evaporator
- Chromatography column (15 mm diameter)

Procedure

1. In a 10 mL round-bottomed flask equipped with a magnetic stirrer bar were placed, under an argon atmosphere, anhydrous dichloromethane (2 mL) and diethyl L-tartrate (0.21 mL).
2. The mixture was cooled to −22 °C, then titanium(IV) isopropoxide (0.09 mL) and sulfide (61 mg solved in 1.5 mL of anhydrous dichloromethane) were added. Stirring was maintained for 20 minutes and hydroperoxide (171 mg) added to the mixture.
3. The reaction was then continued for 2 hours until completion [monitoring by TLC (eluent: *n*-hexane–ethyl acetate, 5:1. Detector: UV lamp at 254 nm) indicated complete consumption of the hydroperoxide].
4. After completion, water (1.5 mL) was added to the mixture and vigorous stirring continued for 2 hours at room temperature. The resulting white gel was diluted with ethyl acetate and filtered over a filter paper in a Büchner funnel. The solution was dried over sodium sulfate, filtered and concentrated using a rotary evaporator.
5. Purification of the crude mixture was performed by flash chromatography to afford pure 5-(1-hydroxyethyl)-2-methyl-3-furoic acid 5α-cholestan-3β-yl ester (**4**) (90 % yield) and (*R*)-4-bromophenyl methyl sulfoxide (**3**) (61 % yield).

   The ee (92 %) was determined on representative sample by ^{1}H-NMR analysis in the presence of *R*-(−)-(3,5-dinitrobenzoyl)-α-methylbenzyl amine.

   ^{1}H-NMR (200 MHz, $CDCl_3$): 7.68 (d, 2H, J = 8.6 Hz); 7.52 (d, 2H, J = 8.6 Hz); 2.72 (s, 3H).

Table 8.1 Asymmetric oxidation of methylsulfides (**R–S–Me**) with **1**.

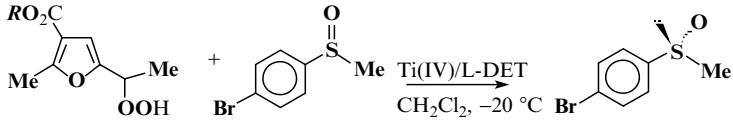
Entry	R	Reac. time (h)	Yield (%)	e.e. (%)
a	4-NO_2-C_6H_4	3	58	>95 (R)
b	2-Br-C_6H_4	7	58	94 (R)
c	4-Cl-C_6H_4	2	63	90 (R)
d	4-Me-C_6H_4	2	74	84 (R)
e	*n*-octyl	2	78	39 (R)

Conclusion

The use of furylhydroperoxides[1] has facilitated an operationally simple procedure, alternative to the one reported by Kagan[2]. Oxidation takes place rapidly and very high e.e.s have been obtained, especially in the case of aryl methyl sulfides, while overoxidation to sulfone can be reduced to a great extent (<3 %) under the proposed experimental conditions.

Modified catalytic procedures involving the employment of different chiral ligands, such as binaphthol[3], 2,2,5,5-tetramethyl-3,4-hexanediol[4], 1,2-diarylethane-1,2-diols[5] are often less selective and very variable values of e.e.s can be observed.

8.1.2 KINETIC RESOLUTION OF RACEMIC 4-BROMOPHENYL METHYL SULFOXIDE



1 **rac-3** **(*R*)-3**

R: Cholestanyl +sulfone

Materials and equipment

- Anhydrous dichloromethane (99.8 %), 3.5 mL
- Racemic 4-bromophenyl methyl sulfoxide (97 %), 110 mg, 0.5 mmol
- Titanium(IV) isopropoxide (97 %), 0.075 mL, 0.25 mmol
- Diethyl L-tartrate (99 %), 0.175 mL, 1 mmol
- 5-(1-Hydroperoxyethyl)-2-methyl-3-furoic acid 5α-cholestan-3β-yl ester (**1**)[1c] (mixture of diastereoisomers), 228 mg, 0.4 mmol
- Ethyl acetate, *n*-hexane
- Anhydrous sodium sulfate
- Silica gel 60 (230–400 mesh ASTM)

- One 10 mL round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer
- Refrigerator Bath (−22 °C)
- Büchner funnel (6 cm)
- Büchner flask
- Filter paper (589 Blue ribbon)
- Rotary evaporator
- Chromatography column (15 mm diameter)

Procedure

1. In a 10 mL round-bottomed flask equipped with a magnetic stirrer bar were placed, under an argon atmosphere, anhydrous dichloromethane (2 mL) and diethyl L-tartrate (0.21 mL).
2. The mixture was cooled to −22 °C, then titanium(IV) isopropoxide (0.09 mL) and hydroperoxide (228 mg) were added. Stirring was maintained for 10 minutes and racemic sulfoxide (110 mg solved in 1.5 mL of anhydrous dichloromethane) added to the mixture.
3. The reaction was continued for 13 hours until completion [monitoring by TLC (eluent: *n*-hexane–ethyl acetate, 5:1. Detector: UV lamp at 254 nm) indicated complete consumption of the hydroperoxide].
4. After completion, water (1.5 mL) was added to the mixture and vigorous stirring continued for 2 hours at room temperature. The resulting white gel was diluted with ethyl acetate and filtered over a filter paper in a Büchner funnel. The solution was dried over sodium sulfate, filtered and concentrated using a rotary evaporator.
5. Purification of the crude mixture was performed by flash chromatography to afford pure 5-(1-hydroxyethyl)-2-methyl-3-furoic acid 5α-cholestan-3β-yl ester (86% yield), 4-bromophenyl methyl sulfone (59% yield) and (*R*)-4-bromophenyl methyl sulfoxide (34% yield).

   The ee (>95%) was determined on representative sample by ^{1}H-NMR analysis in the presence of *R*-(−)-(3,5-dinitrobenzoyl)-α-methylbenzyl amine.

   Stereoselection factors have been determined according to Kagan's equation[6].

Table 8.2 Kinetic resolution of racemic sulfoxides (**R–SO–Me**) with **1**.

Entry	R	Reac. Time (h)	Yield (%)	e.e. (%)	E
a	*n*-octyl	13	31	94	7.8
b	4-ClC_6H_4	14	29	> 95	> 7.4
c	C_6H_5	23	32	82	5.3
d	4-MeC_6H_4	20	42	83	10
e	4-$NO_2C_6H_4$	14	40	> 95	> 15.7

Conclusion

The above procedure can be exploited for the asymmetric oxidation of racemic sulfoxide[1], and high stereoselection can be frequently observed. Moreover unreacted *R*-sulfoxides were always recovered as the most abundant enantiomers, kinetic resolution and asymmetric oxidation being two enantioconvergent processes. Thus, by the combined routes, higher enantioselectivity can be observed with dialkyl sulfoxides, usually obtained with poor to moderate e.e.s.

Furylhydroperoxides of type **1** or cumyl hydroperoxide can be used according to the particular sulfoxide to be resolved. Other procedures, involv-

ing different chiral auxiliaries[3,4,7] lead to much lower stereoselection factors (≈ 3).

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