Organic Process Research & Development **2002**, *6*, 225−229

Asymmetric Sulfoxidation of an Aryl Ethyl Sulfide: Modification of Kagan Procedure to Provide a Viable Manufacturing Process

Phil J. Hogan,[†] Philip A. Hopes,[‡] William O. Moss,[§] Graham E. Robinson,[†] and Ian Patel*[,‡]

AstraZeneca, Process Research and Development, Silk Road Business Park, Macclesfield SK10 2NA, U.K., AstraZeneca, Process Research and Development, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, U.K., and AstraZeneca, Process Research and Development, Research and Development, Charnwood, Bakewell Road, Loughborough LE11 5RH, U.K.

Abstract:

The asymmetric sulfoxidation of an aryl ethyl sulfide in high enantioselectivity was required as part of a manufacturing route to a candidate drug (ZD3638) within AstraZeneca Pharmaceuticals. The initial discovery process provided small quantities of the required material to satisfy early toxicological work. The optimisation of this sulfoxidation process was required to improve enantioselectivity and therefore yield, and also to improve robustness for manufacturing routinely. Previous studies had indicated that asymmetric sulfoxidation of an aryl ethyl sulfide proceeded with moderate enantioselectivity. Initially, Sharpless conditions which are used for the oxidation of allylic alcohols were employed to effect sulfoxidation in 60% ee; this system was then studied extensively to provide new conditions in 80% ee. Finally, the use of factorial experimental design to explore key parameters in the catalyst formation for these conditions was then studied. This showed the equivalents of the titanium (IV) isopropoxide (0.95 equiv) and (−)-D-diethyl-D-tartrate (1.45 equiv) to be essential factors in controlling enantioselectivity; this has resulted in a viable process with 92% ee in solution, which is improved to greater than 99% ee in the subsequent work-up.

Introduction

Asymmetric sulfoxides are important as intermediates or as active ingredients in the pharmaceutical industry, and their synthesis has been studied extensively in the past.[1,2]

The candidate drug **ZD3638** is an homochiral sulfoxide which was in development from 1993 to 1997 as an atypical antipsychotic agent for the treatment of schizophrenia, and its synthesis has been previously described in this journal.[3] **ZD3638** was required in greater than 99% ee as the minor enantiomer provided an unwanted CNS profile. We report herein the work required to provide an improved asymmetric sulfoxidation from the initial procedure provided by discovery.[4] This had used the standard Sharpless reagent[5] for oxidation of allylic alcohols for the conversion of aryl ethyl sulfide **1** to the corresponding sulfoxide **2** with the (*S*)-(−)-enantiomer as a major product, this being **ZD3638** (but in crude form). The reaction conditions employed also generated the undesired (+)-enantiomer **3**, along with the over-oxidised sulfone **4** (Scheme 1).

The modification of the Sharpless reagent has been utilised successfully by Kagan et al.[6] with enantioselectivity in excess of 90% for some substrates, most notably methyl *p*-tolyl sulfoxide. The work to improve the selectivity started by examination of the Kagan conditions for the oxidation of sulfide **1** and then a more thorough examination of the catalyst system by factorial experimental design,[7]and this is discussed in detail.

Initial Discovery Process

As mentioned, this employed the standard Sharpless conditions whereby titanium (IV) isopropoxide (2 mol equiv) was added to (−)-D-diethyl-D-tartrate (1 mol equiv) in toluene at −25 °C dropwise, followed by addition of the sulfide **1** (1 mol equiv). After cooling to −70 °C, *tert*-butylhydroperoxide (90% w/w, dried over molecular sieves, 1.05 mol equiv) was added, and then the mixture was allowed to warm to −15 °C, where it was held overnight to effect the required oxidation. Aqueous sodium hydroxide was added to quench the reaction, and following the addition of dichloromethane the gelatinous precipitate containing titanium dioxide was filtered through Celite. After phase separation the product was purified by silica gel chromatography. The enantiomeric purity of the isolated solid was measured at 60% ee[8] This was enhanced further by seeding a hot solution of **2** (enriched) in toluene with the racemate[9] of **2**; this then allowed the racemate to crystallise. The liquors were evaporated to dryness to provide a solid **2** at 90% ee. By continuing with this method, material in excess of 99% ee

[†] AstraZeneca, Process Research and Development, Silk Road Business Park, Macclesfield.

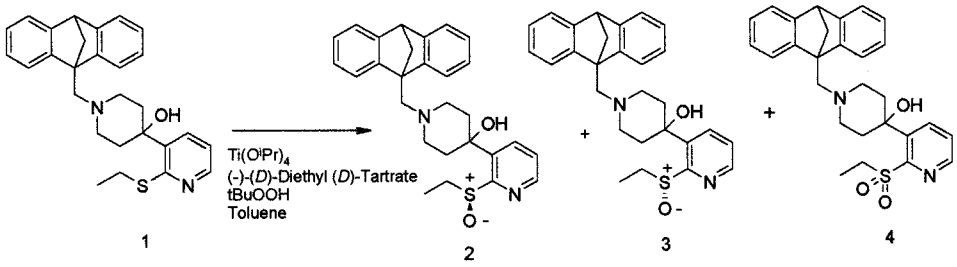
[‡] AstraZeneca, Process Research and Development, Avlon Works, Severn Road, Hallen, Bristol.

[§] AstraZeneca, Process Research and Development, Research and Development Charnwood, Bakewell Road, Loughborough.

(1) Brunel, J. M.; Kagan, H. B. *Bull Soc. Chim. Fr*. **1996**, *133*, 1109−1115 and references therein.
(2) Brunel, J. M.; Kagan, H. B. *Synlett* **1996**, 404−406 and references therein.
(3) Moseley, J. D.; Moss, W. O.; Welham, M. J. *Org. Process Res. Dev.* **2001**, *5*, 491−497.
(4) Trainor, D. A. Zeneca Internal Technology Transfer Report. 1993.
(5) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780 and references therein.
(6) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049−1052,
(7) Carlson, R. *Design and Optimisation in Organic Synthesis*; Elsevier: Amsterdam 1992.
(8) As measured by Ultron ES-ovm 6.0 × 15 cm HPLC and integration of the relative peak areas. The (−)- and (+)-enantiomers had been defined. This was replaced by the more robust Chiralpak AD 25 cm × 4.6 mm during development.
(9) The mixture of (−)- and (+)-enantiomers has been shown to exist as a racemic rather than conglomerate crystal.

10.1021/op0101052 CCC: $22.00
Published on Web 03/20/2002

Scheme 1



could be obtained in an overall 32% yield. For further details see Experimental Section and Method A.

This method was suitable for small quantities of material but clearly required additional work prior to scale-up.

Results and Discussion

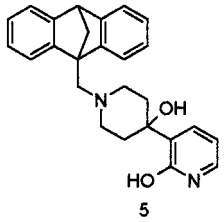
Several features of the discovery process were investigated.

Reaction Temperature. The temperature of *tert*-butylhydroperoxide addition was at −70 °C. The addition at −15 °C did not compromise quality; therefore, a quick modification was allowable.

Availability of *tert*-Butylhydroperoxide and Moisture Content. This was not available in commercial quantities in 90% w/w in the U.K.. The 70% w/w solution in water was extracted into toluene and this was assayed (NaI/$Na_2S_2O_3$) to be typically 3−4 M. To repeat the discovery procedure, this was initially "azeotroped" but was not recommended for further scale-up. Examination of the moisture content of the 3−4 M *tert*-butylhydroperoxide solution revealed this typically contained 2.5% w/w water which corresponded to 0.4 mol equiv. The solvent, toluene, accounted for typically 0.2 mol equiv of water. When this undried mixture was used, the selectivity of the reaction increased from 60 to 75% ee. The addition of 0.5 mol equiv of water was attempted at −20 °C, prior to the addition of the oxidant; unfortunately, the ee of the reaction did not improve. A prior report[10] indicated that the water addition should be carried out at 20 °C, but in the present case this dramatically slowed reaction with beneficial results only obtained if water was added at −20 °C.

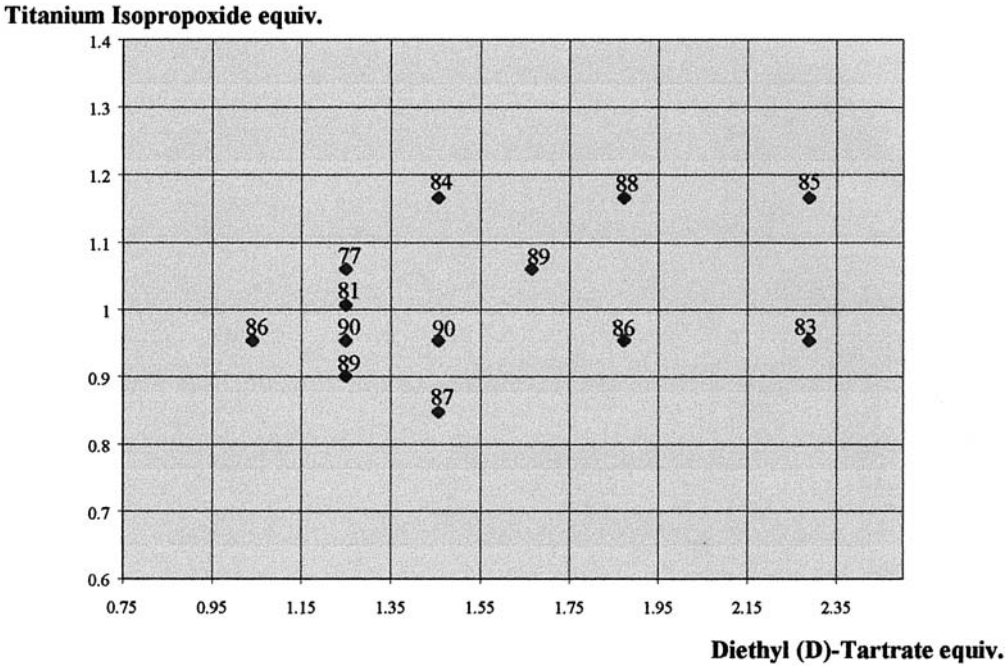
Improving Enantioselectivity. Several modifications were carried out to assess concentration, solvents, stoichiometry of oxidant, alternative chiral ligands, alternative oxidants (e.g., cumene hydroperoxide[11]), reaction temperature,[12] and order of addition of reagents; these led to the process described in the Experimental Section entitled Method B. A combination of concentration, temperature, and most critically, the order of addition of reagents provided the best "step jump" in enantioselectivity from 60 to 80% ee. The led to the following first-generation process being defined: (−)-D-diethyl-D-tartrate and toluene are charged to the reaction vessel first and cooled to −20 °C; this is followed by the controlled addition of titanium (IV) isopropoxide, water, and a toluene solution of sulphide **1** at −20 °C; after a 30 min aging period, *tert*-butylhydroperoxide solution is added at −20 °C.

Work-Up. This was protracted by several isolations being necessary to achieve the required ee in the product **2**. During the reaction the racemate was observed to crystallise; therefore, to aid this the mixture was seeded with the racemate to allow removal of the undesired (+)-enantiomer **3** as a racemate during the work-up in the initial screen. The mass balance of the discovery process was typically in the range of 40−60% for the desired sulfoxide **2**, but the current isolation relied on removal of the undesired (+)-enantiomer **3** as a racemate, and this accounted for a further 30−50% of mass balance. This, although wasteful in yield, did provide product **2** in greater than 99% ee. The need for seeding was eliminated since most of the racemate[13] crystallises in the reaction if the process concentration is increased and also during the quench with titanium dioxide. Following filtration the removal of unreacted sulfide **1** and sulfone **4** could be achieved by selective extraction of the product **2** into acetic acid at pH 3.7−3.75, leaving the impurities in the toluene phase. The product **2** could then be precipitated by sodium hydroxide, after the addition of acetonitrile to aid the physical form to provide **2** in an overall yield of 58% at greater than 99.5% ee. During this procedure some interesting impurities were observed at low levels, and these required control of process conditions to minimise their formation. 2- Hydroxypyridine **5** has been observed as a result of hydrolysis of the

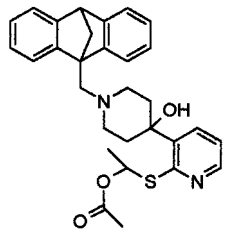


product **2** and is now controlled by the temperature of the work-up. Figures for isolated solids are less than 0.1%, and these are removed in the subsequent final pure recrystallisation. The Pummerer rearrangement product **6** is a potential impurity in the extraction into acetic acid and is controlled by the addition rate and temperature of the pH adjustment to less than 25 °C. Other modifications are described in the Experimental Section of this paper.

(10) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188.
(11) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135−5144.
(12) It is interesting to note that in the absence of the catalyst the amount of background oxidation under achiral conditions at −19 °C is 1% in 24 h.
(13) The racemate can be recovered for use by washing the cake with dichloromethane, and this can be reduced to sulfide **1** with trifluoroacetic anhydride, sodium iodide, and water using tetrabutylammonium iodide as a phase-transfer catalyst.



Graph 1. **Plot to show area of highest ee.**



6

Use of Diastereomeric Salts To Avoid Product Loss. The work-up procedure relies on removal of the undesired (+)-enantiomer **3** by crystallisation of the racemate, which is wasteful in yield since the desired (−)-enantiomer **2** is also removed. The use of diastereomers formed from the addition of homochiral tartaric acid, malic acid, mandelic acid, and camphorsulfonic acid was evaluated, and an alternative was found (see Method C in the Experimental Section) which provides a viable process in 55% overall yield. This, however, suffered from the addition of a chiral additive and then subsequent removal; on comparison of the yield benefits that had been obtained as a result of improving enantioselectivity in the current process the alternative product isolation was not deemed as attractive.

The Evolution of an Optimised Process by Factorial Experimental Design. Factorial experimental design was used in an attempt to improve the enantiomeric excess of the reaction mixture from 80% to the range of 90%, and this would result in an improved yield for the stage (avoiding the loss of product **2** as racemate).

The process studied in outline for optimisation was the following: titanium (IV) isopropoxide (1.06 equiv) is added to (−)-diethyl-D-tartrate (2.08 equiv) in toluene at −20 °C. Water (1.0 equiv total charge including all reagents) is added, followed by a solution of sulphide **1** (1.0 equiv) in toluene, and *tert*-butylhydroperoxide (1.8 equiv) in toluene, both at −20 °C. After holding for 20 h at −20 °C, the ee of the reaction is typically found to be 80% by chiral HPLC. The mixture is then worked up.

Factorial Experimental Design: Catalyst Formation. To explore the essential factors in the catalyst formation on enantiomeric excess, a 13-factor experimental design was performed.

In this fractional factorial design, the 13 factors investigated in 16 experiments were:

(a) equivalence of (−)-diethyl-D-tartrate (low and high values set at 1.87 equiv and 2.29 equiv)

(b) equivalence of titanium (IV) isopropoxide (low and high values set at 0.95 equiv and 1.17 equiv)

(c) addition time of titanium (IV) isopropoxide (5 and 30 min)

(d) temperature during titanium (IV) isopropoxide addition (−23 and −15 °C)

(e) hold time after titanium (IV) isopropoxide addition (10 and 30 min)

(f) temperature during following hold (−23 and −15 °C)

(g) addition time of water charge (5 s and 5 min)

(h) temperature during water addition (−23 and −15 °C)

(i) temperature during following hold (−23 and −15 °C)

(j) addition time of sulphide **1** solution (15 min and 60 min)

(k) temperature during sulphide **1** addition (−23 and −15 °C)

(l) hold time after sulphide **1** addition (15 and 60 min)

(m) temperature during following hold (−23 and −15 °C)

The addition of the *tert*-butylhydroperoxide was fixed at −20 °C and accomplished in <10 min.

Summary of Results

On the basis of the 16 runs it was possible to analyse the data graphically and by analysis of variance.[14]

The main conclusions were that ee is most influenced by:

(i) equivalence of (−)-diethyl-D-tartrate: lower charges favoured; 3.3% effect within range investigated;

(ii) equivalence of titanium (IV) isopropoxide: lower charges favoured; 1.4% effect within range investigated.

The other factors appear to have negligible effect on ee, although interactions between different parameters may have been significant in this rather fractionated design.

Follow-Up Experiments. The above results paved the way for a response surface design to specifically examine the equivalence of (−)-diethyl-D-tartrate and titanium (IV) isopropoxide. Various combinations of these reagents were tested.

When plotted in Graph 1, it can be seen that there is an area of high ee where (−)-diethyl-D-tartrate = 1.25−1.35 equiv, titanium (IV) isopropoxide = 0.90−0.95 equiv, and sulphide **1** = 1.0 equiv, and this would provide a region of robust charging and high ee (90%). It is also interesting to note how rapidly the ee falls from 90 to 77% in one region.

Temperature of Catalyst Formation. It has been shown that the temperature during the additions/holds does not significantly affect ee, provided the temperature is approximately −20 °C for the 20 h hold. When the most favourable catalyst stoichiometry is used, for all additions and holds at −15 °C an 89.5% ee is obtained, and for all additions and holds at −23 °C an 90.4% ee is obtained. The practical implication of this is that there is a window of robustness in temperature and also that there is no need to adjust the temperature during additions, that is, the entire catalyst formation sequence can be performed at a single temperature, and this simplifies the process.

The importance of the stoichiometry of water added to the reaction was varied at two levels (0.8 and 1.3 equiv) and resulted in 78 and 86% ee, respectively, suggesting a tolerance to the variation of water, especially at a higher level. It is interesting to note that the rate of reaction was slower using 1.3 equiv H_2O, suggesting some destruction of catalyst.

Use of Hunig's Base (*N,N*-Diisopropylethylamine). The use of a modified Kagan procedure by the introduction of an organic base has been used successfully in the synthesis of esomeprazole.[15,16] To study the impact of a base on the enantioselectivity of the reaction, a solution of sulphide **1** and Hunig's base (1.0 equiv) were added together to the catalyst. The ee at EOR was 93%, with less than 1% sulphone **4** (compared to 85% ee, 5% sulphone **4** for Method B). In an attempt to improve the ee even further a number of variations were attempted:

The use of Hunig's base and conditions from the experimental design (1.45 equiv (−)-D-diethyl-D-tartrate, 0.95 equiv Ti(O^i Pr)$_4$) were combined to give 92% ee (Method D), and although work-up was complicated by extra acetic acid being required for neutralising excess Hunig's base, this resulted in a better crystallisation of **2** in a much improved 73% isolated yield in greater than 99.5% ee. The strength of material was 93% w/w but was mainly attributed to inorganics and processed to give 99.5% strength in pure **ZD3638**.

(14) The data were analysed by using the SAS System, SAS Institute Inc., Cary, NC.

(15) Cotton, H. K.; Larsson, E. M.; Sorenson, H.; Stenhede, U. J.; von Unge, S. Patent WO 9602535AI, Process for Synthesis of Substituted Sulfoxides. 1994.

(16) Cotton, H.; Elebring, T.; Larsson, M.; Lanna, L.; Sorensen, H.; von Unge, S. *Tetrahedron Asymmetry* **2000**, *11*, 3819−3825.

Conclusions

The use of experimental design improved the ee of the sulfoxidation process and aryl ethyl sulfide **1** reaction from 60% (discovery method) to 80% initially (by the order of the addition of reagents) and then 92% by changing the catalyst stoichiometry (1.45 equiv (−)-D-diethyl-D-tartrate, 0.95 equiv Ti(O^iPr)$_4$). This improvement may have been missed if conventional means were employed since the literature suggests a 2:1 ratio of (−)-diethyl-D-tartrate: titanium (IV) isopropoxide; thus, the area examined in follow-up runs may have been ignored. This improvement in ee has established an area of robust operating conditions and an improved yield; this is of considerable importance in routine manufacture and cost savings from raw material tonnage.

Experimental Section

Method A. Titanium (IV) isopropoxide (44.17 mL, 1 mol equiv) is added dropwise to a dry toluene solution of (−)-diethyl-D-tartrate (56.87 g, 2 mol equiv) at −20 °C followed by sulfide **1** (61.05 g, 1 mol equiv). After 60 min at −20 °C, the solution is cooled to −70 °C, and dry *tert*-butylhydroperoxide (90%w/w, 16.18 mL, 1.05 mol equiv, freshly dried over 3 Å sieves) is added dropwise. The reaction is warmed to −15 °C over 3 h and maintained at that temperature for 18 h. Aqueous sodium hydroxide (1.0 M, 1.2 L) is added to quench the reaction mixture, and the gelatinous precipitate is filtered off on a Celite bed after the addition of dichloromethane (500 mL). The cake is washed with dichloromethane (3 × 500 mL), and the filtrates are separated. The product **2** is in the organic layer, and this is evaporated and purified by flash chromatography to provide a mixture of (−)-**2** to (+)-**3** enantiomers in 60% ee. This enriched material is then dissolved in hot toluene, and then seeded with racemate of **2** prior to cooling to allow crystallisation of the racemate. The slurry is filtered, and the mother liquor is evaporated to an oil containing **2** which shows further enrichment to 90% ee. The oil is then taken back into hot toluene and cooled to allow a further crop of racemate to crystallise. This method of enrichment provided material in the mother liquors which on evaporation provided a solid in an overall typical yield of 32% in 99% ee.

^{1}H NMR (DMSO-d_6 300 MHz): 8.6 (d, 1H), 7.85 (d, 1H), 7.43 (dd, 1H), 7.23 (dd, 4H), 6.91 (m, 4H), 5.54 (s, 1H), 4.31 (s, 2H), 3.04 (m, 1H), 2.67−2.86 (m, 5H), 2.50 (s, 2H + DMSO), 2.20 (m, 1H), 2.02 (d, 1H), 1.66−1.82 (m, 2H), 1.17 (t, 2H).

Melting point: 177−178 °C.

Specific rotation: $[\alpha]_D$ −106 (c = 1.0, MeOH) ((+)-enantiomer specific rotation average +117, c = 1.0, MeOH).

MS: (CI, CH_4) 459 (M + 1), 441 (M + 1 − 18).

Method B. Titanium (IV) isopropoxide (24.8 g, 1.06 mol equiv) in toluene (20 mL) is added dropwise to a solution of (−)-diethyl-D-tartrate (35.31 g, 2.08 mol equiv) in toluene (40 mL) at −20 °C followed by sulfide **1** (36.4 g, 1 mol equiv). After 10 min at −20 °C, water (520 μL, this charge is made such that the total amount of water in the reaction is 1.0 mol equiv including reagents, solvents, and oxidant). After holding for a further 30 min *tert*-butylhydroperoxide in toluene (46 mL, 3.22 M solution in toluene, 1.8 mol equiv) is added dropwise at −20 °C. The reaction is maintained at that temperature for 20 h. Aqueous sodium hydroxide (29.5 g of 47% w/w) is charged to a separate flask, followed by water (205 mL), and this flask is heated to 60 °C in preparation for the reaction quench. The reaction mixture is transferred directly into the aqueous sodium hydroxide solution, and the mixture then held for 1 h at 60 °C. The precipitate is then cooled to 25 °C over 2 h (to aid filterability) and then cooled to 0 °C (at which time an aliquot is taken and filtered so that the liquors can be analysed to ensure that the ee of the solution is greater than 99.5% ee). The slurry is then filtered through a Celite pad, with washing of the cake with toluene (15 mL) and water (15 mL). The phases are allowed to settle and the toluene phase is separated prior to addition of water (245 mL) and glacial acetic acid (21 mL) until the pH is 3.7−3.75. The lower aqueous phase is then separated, and acetonitrile is added (40 mL) prior to the addition of sodium hydroxide (24 mL, 47%w/w) until the pH is greater than 9. The mixture is then cooled to 15 °C, filtered, and washed with water to give the required product **2** in a typical yield of 58% in greater than 99.5% ee.

Method C. In this procedure, the crude reaction mixture is quenched as usual into 4 M NaOH at 60 °C, and toluene (5 vols) is added to help keep the racemate in solution. The reaction mixture is filtered at 60 °C to remove TiO_2, and the filtrate reheated to 60 °C when the aqueous layer is separated off. The toluene layer is washed with brine at 60 °C and the product extracted into water using acetic acid. A solution of L-malic acid (1.05 equiv) in methanol is added over 4 h at 40 °C whereupon the (−)sulphoxide-L-malic acid salt crystallises out. The reaction mixture is ramp-cooled to 0 °C, filtered, washed with methanol, and dried under vacuum at ambient temperature. The isolated yield is 55%, and the de is greater than 99.5%.

Method D. Titanium (IV) isopropoxide (0.95 equiv) is added to (−)-diethyl-D-tartrate (1.45 equiv) in toluene at −20 °C. Water (1.0 equiv total charge including all reagents) is added, followed by a solution of sulphide (**1**, 1.0 equiv) and Hunig's base (1.2 equiv) in toluene and then *tert*-butylhydroperoxide (1.8 equiv) at −20 °C. After holding at −20 °C for 15 h and −15 °C for 3 h, the mixture is worked up as in Method B, outlined above.

The isolated yield is 73%, and the ee is greater than 99.5%.

Acknowledgment

We thank Robert J. Shaw for interpretation of the statistical data with the work reported, and also Thomas Gale for experimental work.

Received for review November 22, 2001.

OP0101052