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A rare case of facial selectivity inversion for Sharpless asymmetric dihydroxylation in a series of structurally homogeneous substrates: synthesis of non-racemic 3-(nitrophenoxy)-propane-1,2-diols

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ABSTRACT

Asymmetric dihydroxylation of mono nitrophenyl allyl ethers leads to the corresponding non-racemic 3-(nitrophenoxy)-propane-1,2-diols **1a–c**. As this takes place, regardless of the reagent used (AD-mix-α or AD-mix-β), the configuration of the predominant enantiomer for the *para*- and *meta*-nitrosubstituted products is opposite to the configuration of the *ortho*-nitrophenyl derivative. A correlation between the melting points and vibrational spectra of the racemic and enantiopure diols **1a–c** allowed us to establish that all of the chiral substances investigated formed stable racemic compounds in the solid phase.

1. Introduction

Terminal aromatic glycerol ethers Ar-$OCH_2CH(OH)CH_2OH$ (TAGE) are a popular class of organic compounds and include registered drugs such as chlorphenesin, guaifenesin, and mephenesin.[1] The compounds of this series can act as precursors in the synthesis of other registered drugs.[2,3] The ability of the TAGE's glycerol moiety to produce intermolecular hydrogen bonds in a liquid medium has led to thermotropic liquid crystals,[4,5] while also allowing them to act as low molecular weight supramolecular gelling agents.[5–7]

Many, if not all, of the aforementioned TAGE properties depend upon the chirality of the system. In some cases, we were able to relate these features with the type of crystal packing of the compounds investigated.[7,8] In turn, the crystal packing of aromatic glycerol ethers by itself is extremely sensitive to the position and nature of the substituents within the aromatic moiety of the molecule.[7,9] This mutual influence in one form or another was studied for alkyl[7,8,10] and alkoxy[11] substituents, halogens,[12,13] and cyano groups.[12,14] Within the overall strategy of this investigation the mononitro phenyl glycerol ethers **1a–c** (see Scheme 1) are of obvious interest.

Since the nitro group is a strong electron acceptor, it can bring about its own specificity into the intermolecular crystal formative interactions (hydrogen bonding, π–π interactions, etc.), and thus affect the crystallization process for racemic as well as for enantiopure TAGE.

Analysis of the available literature showed that nitrosubstituted aromatic ethers of glycerol represented are of general chemical interest. To date, they have found application in the synthesis of imidazoles useful as antifungal and antibacterial agents,[15] and in the synthesis of substituted sulfonamide derivatives for the preparation of pharmaceuticals.[16] Furthermore, a nitro group can be easily reduced, and used in the synthesis of polymeric acetoacetanilide azo colorants,[17] and in the synthesis of polyesters exhibiting holographic optical properties.[18] It is reasonable to expect that in all of these cases, the use of enantiomeric starting materials will lead to useful changes in the targeted product properties.

Available information with regard to obtaining non-racemic (scalemic) nitrophenoxy-1,2-propanediols is extremely scarce, with only the *meta*-diol (*R*)-**1b** being described.[19] The biocatalytic kinetic resolution of *para*- and *ortho*-nitrophenyl glycidol ethers is also mentioned, with the corresponding diols being obtained in yields of 6% and 38% and enantiomeric excesses of 20% and 28%; no properties of the products are cited.[20]

It is known that *scal*-aryloxypropane-1,2-diols can be prepared from the corresponding allyloxybenzenes using the Sharpless asymmetric dihydroxylation reactions.[21,22] Earlier, using methyl-, methoxy-, chloro-, and cyanosubstituted allyloxybenzenes as an example, Wang et al. found that dihydroxylation of the *para*-substituted phenyl allyl ethers proceeded with satisfactory enantioselectivity (products ee 89–95%). At the same time for the *ortho*-substituted allyloxybenzenes, the asymmetric dihydroxylation enantioselectivity decreases, and the products

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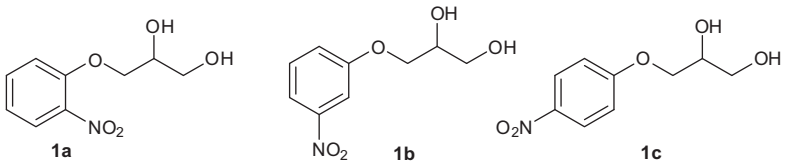


Scheme 1. Mononitrophenyl glycerol ethers.

were obtained with 28–63% ee.[23] It was also found that the use of AD-mix-β as a reagent led to a product with an (*S*)-configuration at C2, and vice versa, (*R*)-TAGEs were obtained by using AD-mix-α. This rule was confirmed for a series of *para*-alkylphenyl allyl ethers.[5]

The asymmetric dihydroxylation of nitro phenyl allyl ethers has not been conducted before. In this regard, our initial aim was to expand upon the asymmetric dihydroxylation procedure to nitro-substituted phenyl allyl ethers. We aimed to obtain a set of mononitro substituted phenyl glycerol ethers **1a–c** in racemic and non-racemic (scalemic) forms with satisfactory chemical yield and a necessary degree of enantiomeric purity. We expected that the analysis of the physicochemical characteristics of the compounds obtained would provide preliminary information on the phase behavior of this family during crystallization.

2. Results and discussion

2.1. Chemistry

The main method of analysis for the asymmetric dihydroxylation enantioselectivity is 'chiral' HPLC. To obtain reliable results, this method needs a pre-selection of experimental conditions using racemic samples of the test compounds. Racemic nitrophenoxy-1,2-propanediols, *rac*-**1**, can be obtained by reaction of the corresponding phenols with *rac*-glycidol,[17,24] by hydrolysis of racemic arylglycidyl ethers,[15,16,18] and by reaction of the corresponding phenolates with *rac*-3-chloropropane-1,2-diol.[25,26] The latter approach seems preferable because 3-chloropropane-1,2-diol is available in racemic and enantiopure forms. However, using the protocols cited in the literature the desired products are obtained in low yield. Thus, *rac*-**1c** was obtained in 28% yield by a reaction in acetonitrile in the presence of K_2CO_3.[25] Racemic **1b** has been obtained from *meta*-nitrophenol in ethanol in the presence of KOH with a yield of 26%.[19] We have found that the yield of the desired products can be substantially improved upon if the reaction of nitrosubstituted sodium phenolate with a slight excess of chloropropanediol is carried out in toluene with the addition of 0.1 equiv of 15-crown-5 as a phase transfer catalyst (see Scheme 2).

With samples of racemic diols **1a** and **1c** in hand, we chose the conditions under which the individual enantiomers were sufficiently separated on the chromatograms that quantitative analysis could be performed (green curves in Figs. 1 and 2).

However, we were unable to achieve good separation of the enantiomers of *meta*-derivative **1b**, so we treated diol **1b** with a slight excess of thionyl chloride. The mixture of *cis*- and *trans*-diastereomers of the cyclic sulfites was formed quantitatively; each of the diastereomers is represented by two enantiomers, the relative amount of which coincides with that of the initial **1b** (see Scheme 3).

Figure 3 shows a chromatogram of the mixture of cyclic sulfites obtained by derivatization of *rac*-**1b** (green curves). As indicated in the picture, the peaks of all four stereoisomers are well separated; the peak areas of the diastereomeric pairs do not coincide with each other, but the peak areas of the individual enantiomers within every diastereomeric pair are identical (provided that the starting diol is racemic).

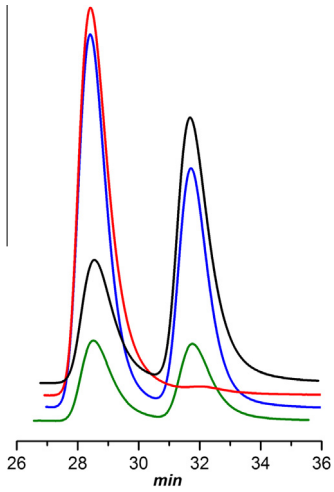


Figure 1. HPLC chromatograms of 3-(2-nitrophenoxy)-propane-1,2-diol **1a**. Green curve—*rac*-**1a**; blue curve—diol **1a** obtained by dihydroxylation of nitrophenyl allyl ether **3a** using AD-mix-β; red curve—(*R*)-**1a**; black curve—diol **1a** obtained by dihydroxylation of nitrophenyl allyl ether **3a** using AD-mix-α.

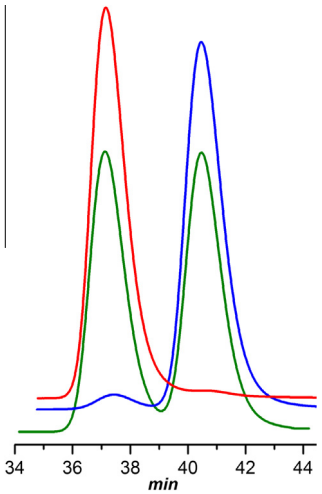


Figure 2. HPLC chromatograms of 3-(4-nitrophenoxy)-propane-1,2-diol **1c**. Green curve: *rac*-**1c**; blue curve: **1c** diol obtained by using AD-mix-β; red curve: (*R*)-**1c**.

With the method of analysis in hand, we next studied the asymmetric dihydroxylation of nitrophenyl allyl ethers **3a–c** (Scheme 4). The use of AD-mix-β as a reagent led to inconsistent results. If the major product of the reaction of *ortho*-nitrophenyl derivative (Fig. 1a, blue curve) was enantiomer of **1a** with a shorter retention time, then for the *para*-nitro analogue (Fig. 2, blue curve) the enantiomer **1c** with a longer retention time dominates among the products. In the case of the *meta*-derivative, the cyclic sulfites obtained from the major enantiomer **1b** change the output order, depending on the type of diastereomer (Fig. 3, blue curve).

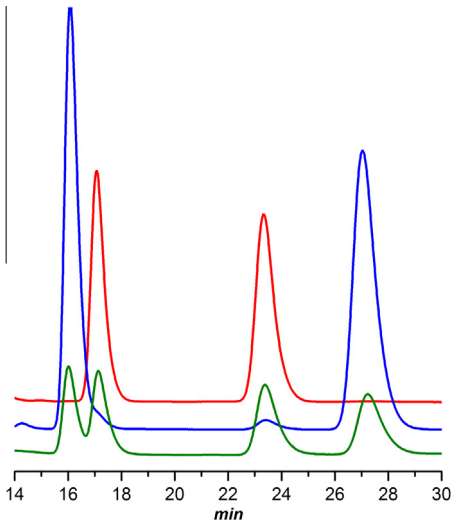
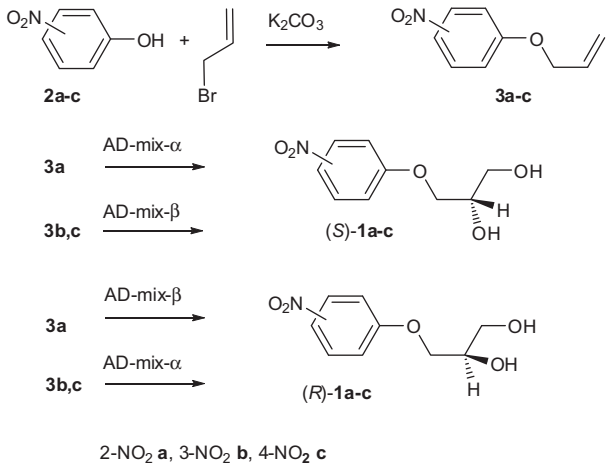


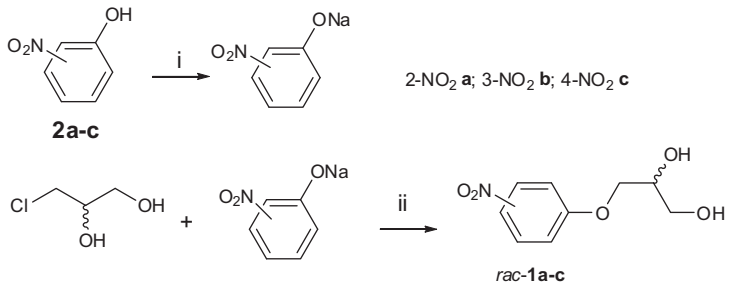
Figure 3. HPLC chromatograms of cyclic sulfites obtained on the basis of 3-(3-nitrophenoxy)-propane-1,2-diols **1b** (see Scheme 3). Green curves: *rac*-**1b** was used as the starting material; blue curves: diol **1b**, obtained by using AD-mix-β, was used as the starting material; red curves: sulfites from (*R*)-**1b**.

We can attribute these results (restricting ourselves to the *ortho*- and *para*-derivatives at this stage) to one of two reasons. The first possibility is that changing the position of the nitro group changes the relative order of output from the chromatographic column for the enantiomers with the same configuration. The second possibility is that a change in substitution pattern of the aromatic moiety qualitatively alters the reaction selectivity, leading to a predominance of the different enantiomers among the products in the case of **1a** and **1c**. Both situations are unusual and have not previously been described for structurally similar compounds.

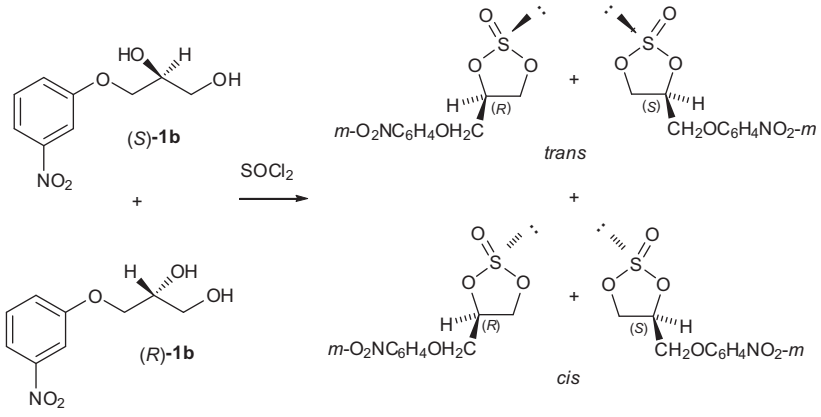


Scheme 4. Asymmetric dihydroxylation of aryl allyl ethers **3a**–**c**.

In order to resolve this problem, we prepared samples of pure diols (*R*)-**1a**–**c** from (*R*)-3-chloropropane-1,2-diol (98% ee) as shown in Scheme 2. From our experience we know that this reaction is accompanied by virtually no racemization and proceeds with retention of the original configuration of the stereogenic center. We have previously reported on the synthesis of non-racemic *ortho*-, *meta*-, and *para*-substituted cyanophenyl glycerol ethers from non-racemic chloropropanediol and have shown that the enantiomeric purity of the products is close to the enantiomeric purity of the starting material.[12] The absolute configuration of the so obtained cyanosubstituted TAGEs was determined by X-ray diffraction using a Flack parameter approach.[14] In all cases, the initial configuration of chloropropanediol was retained in the products. Similar results were obtained for *ortho*-, *meta*-, and *para*-methylphenyl ethers of glycerol.[6,8]



Scheme 2. Reagents and conditions: (i) Na, EtOH; (ii) toluene, 15-crown-5 (0.1 equiv), 90–95 °C, ~30–40 h; isolated yield 60–75%.



Scheme 3. Cyclic sulfite derivatives obtained from 3-(3-nitrophenoxy)-propane-1,2-diol.

Chromatograms of the pure enantiomers (*R*)-**1a**,**c** (and of the corresponding sulfites in the case of (*R*)-**1b**) are shown in Figures 1–3 (red curves). Comparison of these data with the chromatograms of the dihydroxylation products indicates that for *para*- and *meta*-nitro allyloxybenzenes the 'normal' stereoselectivity of the reaction (which was described in the literature[23,5]), in which engagement with AD-mix-β leads predominantly to the (*S*)-enantiomers of the products, is retained. The situation changes for *ortho*-nitro derivatives, when the major product of the same reaction is (*R*)-**1a** (Fig. 1a; the enantiomeric excess of the product is only 22%). To the best of our knowledge, this is the first example of an inversion of the product configuration during an asymmetric dihydroxylation reaction when applying a common reagent to uniformly organized series of arylallyl ethers.

To confirm the disclosed regularity, we carried out the asymmetric dihydroxylation of allyl ethers **3a**–**c** using AD-mix-α as the reagent. The general scheme of the process is illustrated in Scheme 4, and the quantitative characteristics are shown in Table 1; the chromatogram of the 'abnormal' reaction products for *ortho*-nitro derivative is shown in Figure 1 (black curve).

The problem of interpreting and predicting the facial selectivity for asymmetric dihydroxylation reactions remains. Significant progress has been made in the study of the transition state of the reaction, and rules have been developed ('The Mnemonic Device'), linking the stereoselectivity with the relative size of the substituents arranged an oxidizing ethylene moiety.[21,22] Unfortunately, such models are inefficient with respect to monosubstituted ethylenes, which include all aryl allyl ethers. It is difficult to imagine that a change in the position of the substituent in the aromatic ring, which is located at a sufficient distance from the ethylene unit, distorts the steric requirements leading to a reverse in the stereoselectivity. Apparently, a nitro group in the *ortho*-position of a benzene ring takes part in some directional interactions (dipole–dipole, intermolecular hydrogen bond, etc.) with the reagent in the activated complex. However, the proof of this hypothesis is beyond the scope of our work.

2.2. Preliminary solid phase inspection of the mono nitro TAGEs investigated

Table 2 shows some experimental characteristics of the racemic and enantiopure samples of **1a**–**c** obtained from *rac*- and (*R*)-3-chloropropane-1,2-diol respectively.

A comparison of the melting points of racemic and enantioenriched samples of the same chiral compound provides valuable information with regard to the nature of its crystallization. Appreciable excess of the melting point of a racemate over the melting point of enantiopure **1b** strongly suggests that a racemic compound is formed by the enantiomers of this substance in the solid phase. The relationship of the melting temperatures for *rac*-**1a**,**c** and *scal*-**1a**,**c** allows us to exclude, for both compounds, the formation of a normal conglomerate, but leaves the possibility of the formation of continuous or partial solid solutions during crystallization. It is possible to prove or disprove such a possibility by comparison of the IR spectra of crystalline samples for racemic and enantiopure chiral compound. The similarity of the IR spectra is indicative of the similarity of the crystal structure for these samples, and in its turn may indicate that the test substance crystallizes as a conglomerate or a solid solution. In contrast, the IR spectra of the racemic compounds are typically different from those of the corresponding enantiomers.[27,28]

Experimental IR spectra for crystalline samples of **1a**–**c** in KBr tablets, and Pearson correlation coefficients for each pair of 'racemate–scalemate' are shown in Figure 4. Details of the quantitative comparison of the spectra have been described in our previous papers.[5,12]

Both a visual comparison of the spectra and the correlation coefficients between them allow us to establish substantial differences for all *rac*. versus *scal* pairs of **1a**–**c**. Without going into a detailed analysis, we can see that the main differences between the spectra are concentrated in the region of stretching vibrations ν_{OH}. Therefore, for the newly obtained TAGEs, one might expect that a significant difference exists in the system of intermolecular hydrogen bonding in crystals of racemic and enantiomerically pure compounds. Differences in the spectra are also a reliable indication of the formation of stable in solid phase racemic compounds.

A binary melting phase diagram for chiral compounds forming a normal racemic compound in the solid phase is characterized by two eutectics located on the composition axis symmetrical relative to the racemate.[27,28] The eutectic position on the phase diagram is of considerable practical interest. When samples whose composition lies between eutectics are crystallized, the enantiomeric purity of the crystalline crop drops to ee = 0 inclusive. Conversely, samples with an enantiomeric composition, that lies within the interval between the eutectic and the closest pure enantiomer, through the crystallization sequence can be obtained with the

Table 1
Yield, enantiomeric excess, and some physicochemical characteristics of the products of asymmetric dihydroxylation of allyl ethers **3a**–**c**

Diol	AD-mix-α			AD-mix-β		
	Yield (%)	Configuration, ee (%)	$[\alpha]_{436}^{20}$ (*c* 1, EtOH)	Yield (%)	Configuration, ee (%)	$[\alpha]_{436}^{20}$ (*c* 1, EtOH)
1a	66	(*S*) 42 (38)[a]	+1.7	61	(*R*) 22 (15)[a]	−1.1
1b	49	(*R*) 89[b] (90)[a,b]	−26.8	45	(*S*) 94[b] (94)[a,b]	+29.2
1c	65	(*R*) 89 (>99)[a]	−34.0	66	(*S*) 92 (>99)[a]	+31.6

[a] Ee of diols *scal*-**1a**–**c** after recrystallization from benzene.
[b] Ee was determined after derivatization with thionyl chloride.

Table 2
Yield and some physicochemical characteristics for *rac*- and (*R*)-**1a**–**c**

Diol	*rac*-diol		(*R*)-diol				$\Delta T^{f}_{r,s}$
	Yield (%)	mp (°C)	Yield (%)	mp (°C)	$[\alpha]_{D}^{20}$ (*c* 1, EtOH)	ee (%)	
1a	61	45–46	73	54–55	−0.5 (−4.2)[a]	99.2	−9
1b	68	93–94	63	66–67	−15.0 (−31.1)[a]	99.2[b]	27
1c	75	70–71	70	71–72	−17.4 (−37.2)[a]	>99	−1

[a] Value of $[\alpha]_{436}^{20}$ (*c* 1, EtOH).
[b] Ee was determined after derivatization with thionyl chloride.

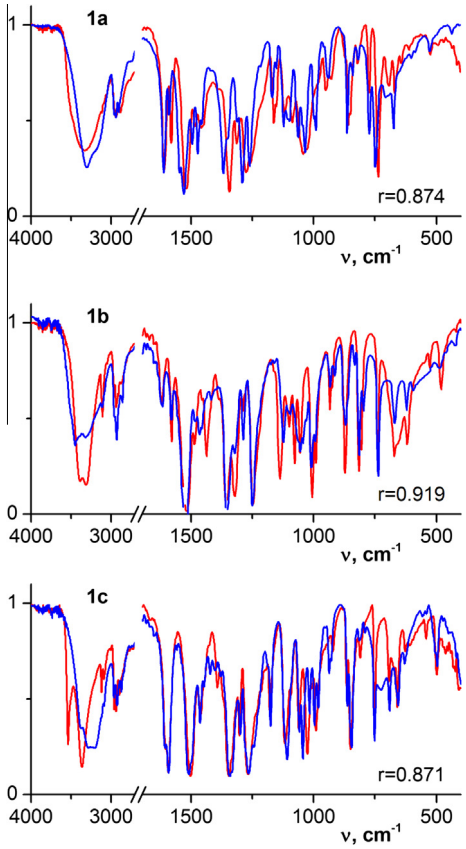


Figure 4. IR spectra of samples of racemic (red curves) and enantiopure (blue curves) **1a–c** and coefficients of correlation between them.

highest enantiomeric purity. It is possible to estimate approximately the eutectic position for compounds **1a–c** from recrystallization results for the products obtained by the asymmetric dihydroxylation (Table 1, columns 3 and 6). As can be seen from the above data, the enantiomeric purity of the samples **1a** and **1b** varies little during the recrystallization. This means that for diol **1a**, the eutectics are obtained with $ee_{eu} \approx 45\%$, and for **1b** $ee_{eu} \approx 90\%$. In contrast, a single recrystallization significantly increases the enantiomeric purity of the sample **1c**, and gives a diol with ee_{eu} <85%.

3. Conclusion

A series of enantiomeric and racemic terminal mononitrophenyl ethers of glycerol **1a** has been synthesized by the asymmetric dihydroxylation of mononitrophenyl allyl ethers and by the reaction of the corresponding nitrophenols with racemic and (*R*)-3-chloropropane-1,2-diol. In the case of *para*- and *meta*-nitrophenyl allyl ethers, the asymmetric dihydroxylation reaction proceeds with good enantioselectivity, and, in accordance with previously known results for different aryl allyl ethers, leads to (*S*)-nitrophenoxypropane-1,2-diols, (*S*)-**1b**,**c** if AD-mix-β is used as the reagent. Using the same reagent during dihydroxylation of *ortho*-nitrophenyl allyl ethers, alongside with a lowering of the reaction enantioselectivity, there is an inversion of facial selectivity, that is, (*R*)-3-(2-nitrophenoxy)-propane-1,2-diol (*R*)-**1a** is obtained. This inversion of the asymmetric dihydroxylation facial selectivity in the ranks of closely-related substrates has not previously been observed.

Comparison of melting points and vibrational spectra of the racemic and enantiopure nitrophenylpropanediols **1a–c** revealed that all of the examined chiral substances formed stable racemic compounds in the solid phase.

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker Avance-400 spectrometer (399.9 MHz for ^{1}H and 100.5 MHz for ^{13}C) in $CDCl_3$ or $(CD_3)_2C{=}O$ with TMS or the signals of the solvent as the internal standard. The IR spectra of the polycrystalline samples of *rac*- and (*S*)-diols **1a–c** under investigations in KBr pellets were recorded on a Bruker Tensor 27 spectrometer. Optical rotations were measured on a Perkin–Elmer model 341 polarimeter (concentration *c* is given as g/100 mL). Melting points for general purposes were determined using a Boëtius apparatus and are uncorrected. The elemental compositions were determined using a EuroVector EA3000 CHN analyzer. Thin-layer chromatography was performed on Silufol UV-254 plates using EtOAc–hexane (4:6) as eluent; TLC plates were visualized under UV light or by treatment with iodine vapor. HPLC analyses were performed on a Shimadzu LC-20AD system controller, UV monitor 275 nm were used as detectors. The columns used, from Daicel, Inc., were Chiralcel OD (0.46 × 25 cm) or Chiralpak AD (0.46 × 25 cm); column temperature 21–23 °C; flow rate: 1.0 mL/min. For the determination of enantiomeric compositions, the columns were calibrated against the corresponding racemic diols **1a–c**.

4.2. Compounds

Racemic 3-chloropropane-1,2-diol (99+%) was purchased from Acros Organics; allyl bromide (99%), 2-nitrophenol (98%), 3-nitrophenol (98+%), 4-nitrophenol (99%), and (*R*)-3-chloropropane-1,2-diol (97%, 98% ee) were purchased from Alfa Aesar. AD-mix-α and AD-mix-β were purchased from Aldrich.

4.2.1. General procedure for the synthesis of aryl allyl ethers 3a–c

Aryl allyl ethers were prepared by analogy with published procedures.[5,29] A stirred suspension of the appropriate phenol **2a–c** (6 mmol), allyl bromide (0.8 g, 6.6 mmol), and ground water-free K_2CO_3 (0.91 g, 6.6 mmol) in anhydrous acetone (10 mL) was refluxed for 12–14 h; the progress of the reaction was monitored by TLC analysis. The reaction mixture was diluted with water (30 mL) and extracted with Et_2O (3 × 40 mL). The collected organic phases were washed with 1 M NaOH (15 mL) and dried over $MgSO_4$. After removal of the solvent, the residual oil **3** was distilled under reduced pressure.

4.2.1.1. 1-(Allyloxy)-2-nitrobenzene, 3a. Yield: 61%, yellow oil [lit.[30,31] yellow oil]; bp 152–153 °C (10 Torr), n_D^{25} 1.5525; R_f = 0.62. ^{1}H NMR ($CDCl_3$) δ 4.71 (ddd, *J* = 1.5, 5.1 Hz; 2H, OCH_2), 5.36 (ddt, *J* = 1.5, 1.5, 10.6 Hz; 1H, CH_2), 5.51 (ddt, *J* = 1.5, 1.5, 17.3 Hz; 1H, CH_2), 6.07 (ddt, *J* = 5.1, 10.6, 17.3 Hz; 1H, CH), 7.05 (ddd, *J* = 1.1, 7.4, 7.7 Hz, 1H, $C^4_{Ar}H$), 7.10 (d, *J* = 8.4 Hz, 1H, $C^6_{Ar}H$), 7.53 (ddd, *J* = 1.7, 7.4, 8.4 Hz; 1H, $C^5_{Ar}H$), 7.86 (dd, *J* = 1.7, 7.7 Hz; 1H, $C^3_{Ar}H$).

4.2.1.2. 1-(Allyloxy)-3-nitrobenzene, 3b. Yield: 61%, yellow oil, which crystallizes upon standing; bp 90–92 °C (0.4 Torr), mp 30–31.5 °C (EtOH), R_f = 0.72. [lit.[32] bright yellow oil; lit.[33] bp 92.2–92.3 °C (0.6 Torr), mp 32–33 °C]. ^{1}H NMR ($CDCl_3$) δ 4.65 (d, *J* = 5.3 Hz; 2H, OCH_2), 5.37 (dd, *J* = 1.3, 10.5 Hz; 1H, CH_2), 5.48 (dd, *J* = 1.3, 17.3 Hz; 1H, CH_2), 6.08 (ddt, *J* = 5.3, 10.5, 17.3 Hz; 1H, CH), 7.26 (d, *J* = 2.2 Hz, 1H, $C^6_{Ar}H$), 7.45 (t, *J* = 8.1 Hz; 1H, $C^5_{Ar}H$), 7.77 (t, *J* = 2.2 Hz; 1H, $C^2_{Ar}H$), 7.85 (dd, *J* = 1.2, 8.1 Hz; 1H, $C^4_{Ar}H$).

4.2.1.3. 1-(Allyloxy)-4-nitrobenzene, 3c. Yield: 57.5%, colorless oil [lit.[29] colorless oil]; bp 107–108 °C (0.5 Torr) [lit.[33] bp 105–106 °C (0.4 Torr), lit.[29] bp 126–129 °C (3 Torr)]; n_D^{25} 1.5775; R_f = 0.68. ^{1}H NMR ($CDCl_3$) δ 4.67 (ddd, J = 1.5, 5.3 Hz; 2H, OCH_2), 5.38 (ddt, J = 1.5, 1.5, 10.5 Hz; 1H, CH_2), 5.46 (ddt, J = 1.5, 1.5, 17.3 Hz; 1H, CH_2), 6.07 (ddt, J = 5.3, 10.5, 17.3 Hz; 1H, CH), 6.98–7.02 (m, 2H, $C^{2,6}{}_{Ar}H$), 8.21–8.25 (m, 2H, $C^{3,5}{}_{Ar}H$).

4.2.2. General procedure for the asymmetric dihydroxylation process

Sharpless asymmetric dihydroxylation reactions were carried out according to the literature procedure.[23] A stirred solution of AD-mix (1.4 g) in *t*-BuOH (5 mL) and water (5 mL) was cooled to 0 °C. To the suspension, the corresponding aryl allyl ether **3a–c** (1 mmol) was added and then the reaction mixture was stirred intensively at 0 °C for 24–28 h. Next, Na_2SO_3 (1.5 g) was added and stirred at room temperature for 30 min. The *t*-BuOH layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the product as crystals or an oil. When necessary, the crude product was purified by column chromatography (silica gel, eluent: EtOAc/hexane = 2:1). Yields, configuration, and enantiomeric excess of *scal*-**1a–c** are shown in Table 1.

4.2.3. General procedure for the synthesis of 3-(nitrophenoxy)-propane-1,2-diols 1a–c from 3-chloro-1,2-propanediol

Sodium metal (0.23 g, 10 mmol) was dissolved in 4 mL of absolute ethanol and an appropriate nitrophenol **2a–c** (1.39 g, 10 mmol) in 2 mL of EtOH was added to the resulting solution. The resulting mixture was stirred at room temperature for 30 min, and then the ethanol was removed in vacuo to dryness. Racemic or scalemic 3-chloro-1,2-propanediol **3** (1.44 g, 13 mmol), 15-crown-5 (0.2 g, 0.9 mmol), and toluene (10 mL) were then added to the residue. The resulting mixture was heated with stirring at 90 ± 5 °C for 30–40 h. The reaction was monitored by TLC. Next, toluene was distilled off in vacuo to dryness, after which 15 mL of water were added and extracted with CH_2Cl_2 (5 × 30 mL). The organic phase was dried over $MgSO_4$. The solution was then filtered and concentrated on a rotary evaporator to give an oil (75–90%), which was dissolved in refluxing benzene; nitrodiols **1a–c** (60–75%) precipitated as crystals upon cooling. Analytically pure samples were obtained by recrystallization from hexane or hexane/CH_2Cl_2. The characteristics of the diols are shown below.

4.2.3.1. *rac*-3-(2-Nitrophenoxy)-1,2-propanediol *rac*-1a. Yield: 61%, mp 45–46 °C (hexane) (lit.[26] mp 45 °C; lit.[34] mp 96 °C). ^{1}H NMR ($CDCl_3$) δ: 2.56 (t, J = 5.9 Hz, 1H, OH), 3.24 (d, J = 5.0 Hz, 1H, OH), 3.80–3.94 (m, 2H, CH_2OH), 4.12–4.18 (m, 1H, CHOH), 4.22 (dd, J = 5.8, 9.2 Hz, 1H, OCH_2), 4.28 (dd, J = 4.1, 9.2 Hz, 1H, OCH_2), 7.09 (ddd, J = 1.0, 7.8, 7.8 Hz, 1H, $C^4{}_{Ar}H$), 7.13 (dd, J = 1.0, 7.8 Hz, 1H, $C^6{}_{Ar}H$), 7.57 (ddd, J = 1.7, 7.8, 7.8 Hz, 1H, $C^5{}_{Ar}H$), 7.91 (dd, J = 1.7, 7.8 Hz, 1H, $C^3{}_{Ar}H$). ^{13}C NMR ($CDCl_3$) δ: 63.7 (CH_2OH), 70.2 (CHO), 71.8 (CH_2O), 115.4 ($C^6{}_{Ar}$), 121.5 ($C^4{}_{Ar}$), 126.4 ($C^3{}_{Ar}$), 135.1 ($C^5{}_{Ar}$), 140.1 ($C^2{}_{Ar}$), 152.6 ($C^1{}_{Ar}$). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.41; H, 5.57; N, 6.79.

4.2.3.2. (*R*)-3-(2-Nitrophenoxy)-1,2-propanediol (*R*)-1a. Yield: 73%, mp 54–55 °C (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = −0.5 (*c* 1, EtOH); $[\alpha]_{436}^{20}$ = −4.2 (*c* 1, EtOH); $[\alpha]_D^{20}$ = −3.0 (*c* 1, hexane:EtOH = 4:1); 99.2% ee [chiral HPLC analysis; Chiralpak AD column; eluent: hexane/2-propanol = 9:1; t_R = 28.4 min (major), t_R = 31.7 min (minor)]. NMR spectra were identical with those cited above for *rac*-**1a**. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.94; H, 5.29; N, 6.65.

4.2.3.3. *rac*-3-(3-Nitrophenoxy)-1,2-propanediol *rac*-1b. Yield: 68%, mp 93–94 °C (hexane/CH_2Cl_2). ^{1}H NMR (acetone-D_6) δ: 3.66–3.76 (m, 2H, CH_2OH), 3.82 (t, J = 5.8 Hz, OH, the signal disappears when adding D_2O), 4.02–4.09 (m, 1H, CHOH), 4.15 (dd, J = 6.1, 9.8 Hz, 1H, OCH_2), 4.20 (d, J = 5.2 Hz, OH, the signal disappears when adding D_2O), 4.27 (dd, J = 4.3, 9.8 Hz, 1H, OCH_2), 7.43 (ddd, J = 0.9, 2.4, 8.3 Hz, 1H, $C^6{}_{Ar}H$), 7.59 (dd, J = 8.3, 8.3 Hz, 1H, $C^5{}_{Ar}H$), 7.79 (dd, J = 2.4, 2.4 Hz, 1H, $C^2{}_{Ar}H$), 7.84 (ddd, J = 0.9, 2.4, 8.3 Hz, 1H, $C^4{}_{Ar}H$). ^{13}C NMR (acetone-D_6) δ: 63.5 (CH_2OH), 70.8 (CHO), 70.9 (CH_2O), 109.4 ($C^2{}_{Ar}$), 115.8 ($C^6{}_{Ar}$), 122.0 ($C^4{}_{Ar}$), 130.8 ($C^5{}_{Ar}$), 149.8 ($C^3{}_{Ar}$), 160.3 ($C^1{}_{Ar}$). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 51.32; H, 4.98; N, 6.09.

4.2.3.4. (*R*)-3-(3-Nitrophenoxy)-1,2-propanediol (*R*)-1b. Yield: 63%, mp 66–67 °C (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ = −15.0 (*c* 1, EtOH); $[\alpha]_{436}^{20}$ = −31.1 (*c* 1, EtOH); {lit.[19] $[\alpha]_D^{20}$ = −12.3 (*c* 1, EtOH)}; 99.2% ee [For reliable ee determination the crude diol was transformed into a diastereomeric mixture of cyclic sulfites via reaction between *scal*-**1b** (1 equiv) and $SOCl_2$ (1.1 equiv) in CH_2Cl_2 at 0 °C. Chiral HPLC analysis of the reaction mixture: Daicel Chiralcel OD column; eluent 2-propanol/hexane = 1:4; t_R = 16.0 min (minor), t_R = 17.1 min (major); t_R = 23.4 min (major), t_R = 27.2 min (minor)]. NMR spectra were identical with those cited above for *rac*-**1b**. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 51.18; H, 5.33; N, 6.33.

4.2.3.5. *rac*-3-(4-Nitrophenoxy)-1,2-propanediol *rac*-1c. Yield: 75%, mp 70–71 °C (hexane) (lit.[25] mp 64 °C; lit.[26] mp 58 °C). ^{1}H NMR (acetone-D_6) δ: 3.66–3.75 (m, 2H, CH_2OH), 3.85 (br s, OH), 4.03–4.09 (m, 1H, CHOH), 4.18 (dd, J = 6.1, 9.8 Hz, 1H, OCH_2), 4.23 (d, J = 4.9 Hz, OH), 4.29 (dd, J = 4.3, 9.8 Hz, 1H, OCH_2), 7.16–7.20 (m, 2H, $C^{2,6}{}_{Ar}H$), 8.21–8.25 (m, 2H, $C^{3,5}{}_{Ar}H$). ^{13}C NMR (acetone-D_6) δ: 63.4 (CH_2OH), 70.7 (CHO), 70.9 (CH_2O), 115.3 ($C^{2,6}{}_{Ar}$), 126.1 ($C^{3,5}{}_{Ar}$), 141.9 ($C^4{}_{Ar}$), 164.9 ($C^1{}_{Ar}$). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.85; H, 5.24; N, 6.58.

4.2.3.6. (*R*)-3-(4-Nitrophenoxy)-1,2-propanediol (*R*)-1c. Yield: 70%, mp 71–72 °C (hexane); $[\alpha]_D^{20}$ = −17.4 (*c* 1, EtOH); $[\alpha]_{436}^{20}$ = −37.2 (*c* 1, EtOH); >99% ee [chiral HPLC analysis; Chiralpak AD column; eluent: hexane/2-propanol = 9:1; t_R = 37.1 min (major), t_R = 40.6 min (minor)]. NMR spectra were identical with those cited above for *rac*-**1c**. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.14; H, 5.32; N, 6.30.

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