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N,*N*-1,2-Benzenedisulfonylimide, a new cyclic leaving group for the stereoselective nucleophilic substitution of amines

Karsten Sørbye, Christoffer Tautermann, Per Carlsen and Anne Fiksdahl *

Organic Chemistry Laboratories, Norwegian University of Science and Technology, N-7034 Trondheim, Norway

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Abstract

We hereby report the preparation and nucleophilic substitutions of the *N*,*N*-1,2-benzenedisulfonylimide derivatives **1a** and **2a** of the chiral amines **1** and **2**. The nucleophilic attack of KNO_2 afforded the respective alcohols **3** and **4** with 84–90% inversion of configuration. Nucleophilic attack by the azide ion afforded the azide products **5** and **6** which were reduced to the corresponding inverted amines **1** and **2** (94–98.5% inversion). The improved leaving group ability of the *N*,*N*-1,2-benzenedisulfonylimides compared with previously reported *N*,*N*-disulfonylimides is discussed. Chiral GLC analysis of all products is summarized and the alternative chiral analysis of product **3** by ^{13}C NMR using heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin as a chiral solvating agent (CSA) is discussed.

1. Introduction

The development of methods for the inversion of configuration of chiral amines for the preparation of new homochiral substances has not received the same attention as other substance groups such as alcohols and their derivatives, epoxides and halides. In our ongoing effort to develop stereoselective transformation reactions for chiral amines we have previously shown[1–5] that some *N*,*N*-disulfonyl derivatives of primary amines — the *N*,*N*-ditosylimides, the *N*,*N*-dimesylimides and the *N*,*N*-dinosylimides — may be transformed by nucleophilic substitution reactions into the corresponding amines or alcohols with inverted stereochemistry. The corresponding alcohols formed with retention of configuration have been prepared via the diazonium intermediate.[4]

In the present study we report the preparation of the new cyclic *N*,*N*-1,2-benzenedisulfonylimide[6] derivatives (**1a** and **2a**) of the primary amines **1** and **2**. The leaving group ability of the disulfonylimide moiety in these compounds was studied by the nucleophilic attack by KNO_2 or the azide ion. The corresponding alcohols **3** and **4** and the azides **5** and **6** were formed. The azides were reduced to the

* Corresponding author. E-mail: Anne.Fiksdahl@chembio.ntnu.no

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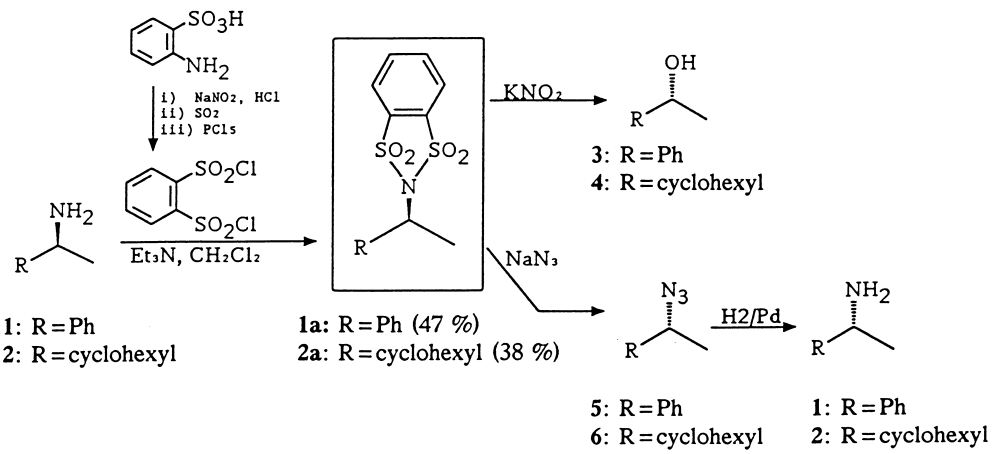
amines **1** and **2**. The stereochemistry of the substitution reactions and the chiral analytical methods are discussed.

2. Results and discussion

Less vigorous conditions were required for the preparation of the cyclic *N,N*-1,2-benzenedisulfonylimide derivatives **1a** and **2a** from the primary amines **1** and **2** and benzene-1,2-disulfonyl chloride compared with the methods previously reported for the synthesis of *N,N*-disulfonylimides.[1–5] A distinctly lower reaction temperature was needed. Dichloromethane was used as the solvent, while NEt_3 was sufficient as base, compared with NaH in previous methods. Comparable yields of the crystalline imides (% yields, see Scheme 1) were obtained. Purification via crystallization procedures proved as good as or better than chromatographic methods. The *N,N′*-bis-byproduct, the disulfonamide, R–NH–SO_2–Ph–SO_2–NH–R, could also be isolated from all the reactions and identified after characterization. The reagent, benzene-1,2-disulfonyl chloride, was prepared in a three-step procedure (in 21% overall yield) from 2-aminobenzenesulfonic acid by PCl_5 treatment of the diazotization/SO_2 product.[7]



Scheme 1.

Nucleophilic attack on the *N,N*-1,2-benzenedisulfonylimides **1a** and **2a** by KNO_2 and NaN_3 afforded the alcohols **3**, **4** and azides **5**, **6** with 84–90% and 94–98.5% inversion of configuration respectively. (See Table 1 for the % ee and *R* or *S* configuration of the substrates **1a**, **2a** and the products **3**–**6** as well as the % yields.)

As can be seen from Table 1, the benzylic disulphonylimide substrate **1a** is much more easily substituted with both nucleophiles (nitrite and azide) than the corresponding cyclohexyl intermediate **2a**. This is demonstrated by both a lower reaction temperature and a shorter reaction time required for the conversion of **1a** than for **2a** and also compared with our previously reported *N,N*-disulfonylimides.[1–5] This expected difference in reactivity between the benzylic and the cyclohexyl substrate has not been observed with acyclic disulfonylimide leaving groups.[1–5]

Our results show that the highest stereoselectivity was obtained when the reactions were conducted in DMSO as demonstrated by comparing entries 4 and 7. As expected for S_N2 reactions, significantly increased stereoselectivity was obtained by decreasing the reaction temperature (see entries 4–6, 90→20°C), especially in combination with a DMSO based solvent (30% DMF was added in order to

Table 1
Results for the reactions shown in Scheme 1

Substrate, % ee/*R* or *S*	Substitution product, % ee/*R* or *S* (reaction conditions)	Degree of inversion	Yield
1a >99 % ee/*S*			
	Alcohol 3[a]		
entry 1	40 % ee/*R* (KNO_2/18-cr-6, DMF, 20°C, 1h)	70 %	83 %
entry 2	68 % ee/*R* (as above, 30 % DMF/DMSO, 0°C, 24h)	**84 %**	53 %
	Azide 5[b]		
entry 3	44 % ee/*R* (NaN_3, DMF, 0°C, >3d)	72 %	-
entry 4	26 % ee/*R* (NaN_3, DMF, 20°C, 24h)	63 %	-
entry 5	14 % ee/*R* (NaN_3, DMF, 35°C, 20h)	57 %	<20 %
entry 6	0 % ee/*R* (NaN_3, DMF, 90°C, 1h)	50 %	-
entry 7	88 % ee/*R* (NaN_3, dry DMSO, 20°C, 24h)	**94 %**	35 %
entry 8	88 % ee/*R* (NaN_3, 30 % DMF/DMSO, 0°C, >1d)	**94 %**	-
2a >99 % ee/*R*			
	Alcohol 4[c]		
entry 9	80 % ee/*S* (KNO_2/18-cr-6, DMF, 70°C, 13d)	**90 %**	5-10 %
entry 10a	80 % ee/*S* (KNO_2/18-cr-6, DMF, 90°C, 3d)[e]	**90 %**	5-15 %
entry 10b	56 % ee/*S* (as above, entry 10a) alkaline work-up[f]	78 %	27 %
	Azide 6[d]		
entry 11	92 % ee/*S* (NaN_3, DMF, 80°C, 3d)	96 %	25 %
entry 12	97 % ee/*S* (NaN_3, DMSO, 80°C, 4d)	**98.5 %**	53 %

a The % enantiomeric excess of the alcohol product **3** is based on the direct chiral GLC analysis, see Table 2. Chiral ^{13}C NMR analysis carried out at low temperature using heptakis(2,3,6-tri-O-methyl)-ß-cyclodextrin as CSA confirmed the GLC results.

b The % enantiomeric excess of the azide product **5** is based on the direct chiral GLC analysis. Improved chiral GLC analysis of the amine reduction product **1** confirmed the former results, see Table 2.

c The % enantiomer excess of the alcohol product **4** is based on the direct chiral GLC analysis, see Table 2.

d The % enantiomeric excess of the azide product **6** is based on the indirect chiral GLC analysis of the diastereomeric derivatives of the respective amine reduction product **2**. (*S*)-α-methoxyphenylacetyl chloride was used as derivatizing agent.

e Neutral work-up procedure excludes the contribution from the formate ester byproduct (20 % ee *S*).

f Alkaline work-up procedure hydrolyses the formate ester byproduct to the alcohol and includes the contribution from the low optical purity ester (20 % ee *S*), giving lower stereoselectivity and higher yields compared with entry 9a.

avoid freezing, 0°C, see entries 2 and 8). No increase in the degree of inversion was observed when changing the concentrations of the reactants, and no product could be isolated by changing to other solvents.

Reacting the sulfonimides **1a** and **2a** with KNO_2 in DMF, yielded the alcohols **3** and **4** together with the corresponding 1-phenylethyl and 1-cyclohexylethyl formate ester byproducts. The formate ester formation can be rationalized by the competing reaction where DMF functions as an O-nucleophile followed by hydrolysis of the iminium ester intermediate. Especially for the cyclohexyl substrate **2a** the stereoselectivity in the formate ester formation was low (20–25% ee). The formate was isolated and separately hydrolysed to the alcohol product. Alkaline work-up of the crude product mixture hydrolyses the formate ester byproduct to the alcohol and includes the contribution from the formate of low enantiomeric excess, giving lower stereoselectivity and higher yields compared with a neutral work-up for the alcohol **4** (see entries 10a and 10b). For the benzylic substrate **1a**, the stereoselectivity in the formate formation was identical to the alcohol **3**. The formate ester formation was avoided by changing to DMSO as solvent. However, dry solvents were important, otherwise acetophenone was identified as a byproduct for the **1a→3** alcohol reaction and both acetophenone and 1-phenylethanol were formed in addition to the azide main product **5** in the **1a→5** reaction.

2.1. Chiral analysis

The chiral analysis of the products and byproducts was based on GLC chromatography. The cyclohexyl azide product **6** was indirectly analysed after derivatization to the diastereomeric amides of the reduction amine product **2**. The products **3**, **4** and **5** and the formate byproducts were analysed directly using a chiral stationary phase. In Table 2 is shown the chromatographic separation parameters and the chromatographic conditions applied.

A preliminary study of an alternative chiral analytical method was also tested for the alcohol **3**. The method is based on the ^{13}C NMR study of the compound after the addition of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (tri-OMe-β-CD) as a chiral solvating agent (CSA). Cyclodextrins have shown enantiodiscriminating ability toward chiral substrates, and their use as chiral solvating agents for NMR spectroscopy has been proposed.[8] The effect of both the native α-, β-, ɣ-cyclodextrins (CD) and a variety of their derivatives have been explored. Both inclusion complex theories and non-inclusion complexes based on superficial interactions have been discussed. The substrate concentrations are typically 1–100 mM, and the best shift effects are obtained with CD:substrate ratios higher than 1:1 (often 3:1). Increased Δδ values are reported in the NMR spectra at low temperatures. The Δδ values of the signals from either the CD or the substrates have been studied. The sign and the extent of the shift effects are often unpredictable. The highest Δδ values observed are about 0.4–0.5 ppm. However, for an enantiomeric purity (% ee) determination high $\Delta(\Delta\delta)$ values$=\Delta\delta_R-\Delta\delta_S$ are required. Better resolutions ($\Delta\delta_R-\Delta\delta_S$) than have so far been reported are necessary for enantiodeterminations. Alternatively, more simplified NMR signals; singlets instead of multiplets, would allow a better resolution and, consequently, enantiomeric excess determination. Our study is therefore based on ^{13}C NMR spectroscopy instead of ^{1}H NMR. For the quantitative analysis it is necessary that similar nuclei have similar relaxation.

In our preliminary ^{1}H NMR study (using tri-OMe-β-CD:substate ratios 1:1, 2:1 and 3:1 as well as temperatures in the range of +15°C to −50°C), the $\Delta(\Delta\delta)$ values ($\delta_R-\delta_S$) of the 1-methine signal of the alcohol **3** in CD_3OD increased from 0.005 ppm to 0.016 ppm with decreasing temperature. However, because of the quartet nature of the signal, the resolution was not sufficient for an enantiodetermination. Because the *R*- and *S*-signals overlap, the *R*:*S* ratios were not available by integration. No shifts were observed using $CDCl_3$ as the solvent. Improved results were obtained in a ^{13}C NMR study: fully

Table 2
Chiral GLC analysis. Chromatographic separation parameters for *R:S* enantioseparations (column: CP-Chirasil-DEX-CB)

Substance	Column temperature	k' (elution order)	α	R_S
1-Phenylethanol (**3**)	110 °C (isot.)	9.20 (*R*) 10.44 (*S*)	1.13	6.2
1-Phenylethylazide (**5**) (see below (**1**) for improved sep.)	95 °C (isot.)	5.06 (*S*) 5.16 (*R*)	1.02	0.80
1-Phenylethylamine (**1**) (reduction product of **5**)	70°C (5 min.)- 150°(3°/min.)	12.03 (*R*) 12.26 (*S*)	1.02	1.57
1-Phenylethyl formate	110 °C (isot.)	4.4 (*S*) 5.1 (*R*)	1.16	6.2
1-Cyclohexylethanol (**4**)	90 °C (isot.)	22.87 (*R*) 23.13 (*S*)	1.01	0.65
1-Cyclohexylethylazide (**6**)[a]	-	-	-	-
1-Cyclohexylethyl formate	90 °C (isot.)	14.4 (*R*) 17.5 (*S*)	1.22	7.4

[a] Chromatographic separation was obtained by achiral GLC analysis of the diastereomeric amide derivatives[1-3] of the amine reduction product **2**.

decoupled spectra of (i) the racemic and (ii) a 72:28 (*R*:*S*) mixture of the alcohol **3** in CD_3OD with two or three equivalents of tri-OMe-β-CD added showed a splitting of the methyl signal into two (i) 50:50% and (ii) 72:28% signals respectively. These data, confirming the chiral GLC results, prove that there is no difference in relaxation between the two enantiomeric carbons, that is: the two diastereomeric carbons in the two tri-OMe-β-CD complexes. The measured ^{13}C NMR $\Delta(\Delta\delta)$ values were 0.104–0.112 ppm and the resolutions were sufficient for enantiodetermination based on integrals. These preliminary results show that tri-OMe-β-CD used as CSAs in ^{13}C NMR spectroscopy represent an improvement relative to the ^{1}H NMR measurements for the determination of enantiomeric excess. The method will be further investigated.

In conclusion, less vigorous conditions were needed both for the preparation and the nucleophilic substitution of the new hereby reported *N,N*-1,2-benzenedisulfonylimides, **1a** and **2a**. The highest degree of inversion (84% for the alcohol **3** and 94% for the azide **5**), for the benzylic substrate **1a** were obtained using a lower reaction temperature (0°C) and a shorter reaction time (24 h) than for the analogous cyclohexyl intermediate **2a** (90% degree of inversion for the alcohol **4** and 98% for the azide **6**) (**2a**→alcohol **4** and azide **6**; 80–90°C, 3–4 days). For the former, DMSO as solvent showed a definitive

positive effect on the stereoselectivity. In the development of heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (tri-OMe-β-CD) as a chiral solvating agent for ^{13}C NMR as an alternative method to the chiral GLC analysis for the determination of enantiomeric excess, our preliminary study seems promising.

3. Experimental

3.1. Chemicals

(*S*)-1-Phenylethylamine **1**, Hexel Chemical Products; (*R*)-1-cyclohexylethylamine **2**, phosphorus pentachloride, 18-crown-6, (*S*)-α-methoxyphenylacetyl chloride from (*S*)-α-methoxyphenylacetic acid, Fluka (purum); 2-aminobenzenesulfonic acid (orthanilic acid), Fluka (pract.); sodium nitrite, Merck (>99%); potassium nitrite, Acros (>97%). Solvents: p.a. quality. DMF and DMSO were dried over activated molecular sieve (4 Å). TLC: DC-Fertigplatten Kieselgel 60 F_{254} (0.25 mm). Detection: UV light at 254 nm or preferentially by 5% alcoholic molybdatophosphoric acid and heating. Flash chromatography: Kieselgel 60 (230–400 mesh) Merck. GLC: Carlo Erba Model 8130; injector: split (100 ml/min, T=300°C), hydrogen, detector: FID (T=270°C), column: Chrompack CP-Sil 5CB fused silica WCOT (25 m). Chiral GLC analysis: Chrompack CP-CHIRADEX-CB fused silica WCOT (25 m, 0.32 mm; 0.32 μm), carrier gas pressure 5–5.5 p.s.i. M.p.s are uncorrected, and were measured on a Büchi apparatus. ^1H NMR: Bruker Avance DPX 300 MHz and 400 MHz NMR spectrometer, chemical shifts are reported in ppm downfield from TMS. MS: AEI MS-902. IR: Nicolet 20SXC FT-IR spectrometer. $[\alpha]_D$: Perkin–Elmer 241 polarimeter (10 cm cell with a total volume of 1 ml).

3.2. Preparation of benzene-1,2-disulfonyl chloride from 2-aminobenzenesulfonic acid[7]

A mixture of orthanilic acid (2-aminobenzenesulfonic acid, 50 g, 0.24 mol, 83% pure), anhydrous sodium carbonate (12.7 g, 0.14 mol) and water (250 ml) was heated and stirred until all the orthanilic acid had dissolved before being cooled to around 15°C. A solution of sodium nitrite (19.8 g, 0.29 mol) in water (50 ml) was added dropwise. The resulting solution was poured onto a mixture of concentrated hydrochloric acid (55 ml) and crushed ice (300 g). Cooling for 1 h and filtering afforded pink crystals of 2-benzendiazonium sulfonate which were immediately dissolved in concentrated hydrochloric acid (300 ml). A suspension of Cu(I)Cl (7 g, 0.07 mol) in sulfur dioxide–acetic acid (475 ml, 30% sulfur dioxide) was added with stirring, and the temperature was slowly raised to 42°C. After 4 h evolution of nitrogen had ceased, and the solvents were stripped off. The resulting solid was stirred and heated with a small amount of saturated sodium chloride (10–20 ml) to yield a green porridge which was cooled, filtered, washed with methanol and dried to yield the disodium salt of 1,2-benzenedisulfonic acid (19 g, 0.67 mol). This material was heated overnight with phosphorus pentachloride (35.1 g, 0.168 mol, 2.5 eq.). The resulting phosphorous oxychloride and excess phosphorus pentachloride were distilled off under vacuum to leave a dry yellowish cake. Chloroform (230 ml) and water (80 ml) were added and the mixture was heated and stirred until all the solid had dissolved. The phases were separated whilst still hot, and the organic phase was concentrated and cooled to afford clear, off-white crystals (13.6 g, 0.05 mol, 21% overall yield from orthanilic acid). M.p. 141–146°C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 2H), 8.47 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 132.3, 136.0, 141.3. MS [m/z (% rel. int.)]: 278/276/274 (M, 0.5/2.0/3.5%), 241 (44%), 239 (100%), 156 (16%), 113 (14%), 111 (38%), 64 (54%). IR (KBr, cm^{-1}): 3106 (w), 1375 (s), 1183 (s), 787 (w), 747 (w), 888 (m), 566 (m), 540 (m).

3.3. (S)-N,N-1,2-Benzenedisulfonyl-1-phenylethylamine **1a** from (S)-phenylethylamine **1**

Benzene-1,2-disulfonyl chloride (2.0 g, 7.3 mmol) was dissolved in methylene chloride (200 ml) and brought to reflux. A solution of *S*-(+)-1-phenylethylamine (**1**, 0.93 ml, 7.3 mmol) and triethylamine (2.1 ml, 15 mmol, 2.1 eq.) in methylene chloride (50 ml) was added continuously over 30 h. The reaction was allowed to reflux for at least another 2 h. The solvent was stripped off to yield 4.39 g of solid material which was extracted with hot acetone (30 ml), cooled, filtered and stripped of solvent. The resulting solid was dissolved in hot cyclohexane (150 ml), cooled to ambient temperature and immediately filtered to remove the byproduct *N,N′*-bis((*S*)-1-phenylethyl)-1,2-benzenedisulfonamide. Concentration of the mother liquor, cooling and filtration afforded **1a** (80–90% pure by ^{1}H NMR analysis). By repeating the cyclohexane recrystallization procedure, pure crystalline (*S*)-*N,N*-1,2-benzenedisulfonyl-1-phenylethylamine (**1a**, 1.1 g, 47%) could be obtained. M.p. 105–106°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.08 (d, 3H), 5.43 (q, 1H), 7.38 (m, 3H), 7.60 (m, 2H), 7.88 (m, 2H), 7.95 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 19.4, 56.7, 121.8, 128.1, 128.6, 128.8, 134.6, 135.4, 137.2. MS [m/z (% rel. int.)]: 323 (M, 3%), 308 (12%), 219 (22%), 194 (4%), 180 (3%), 156 (16%), 105 (81%), 104 (100%). IR (KBr, cm^{-1}): 3085 (w), 1498 (w), 1447 (m), 1349 (s), 1195 (m), 1172 (s), 1041 (m), 984 (m), 884 (m), 756 (m), 695 (m). $[\alpha]_D$ −6.3 (c=1, $CHCl_3$).

3.3.1. N,N′-Bis((S)-1-phenylethyl)-1,2-benzenedisulfonamide

6%; m.p. 214–217°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (d, 6H), 4.55 (m, 2H), 6.67 (NH, d, 2H), 6.91 (m, 10H), 7.04 (m, 2H), 7.42 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 23.9, 55.0, 126.1, 127.2, 128.1, 130.4, 131.7, 137.5, 140.7. MS [m/z (% rel. int.)]: 444 (0.02%), 429 (6%), 325 (36%), 308 (8%), 207 (17%), 120 (100%), 105 (86%), 77 (11%). IR (KBr, cm^{-1}): 3305 (s), 3290 (s), 2990 (w), 1458 (m), 1400 (s), 1330 (s), 1322 (s), 1170 (s), 1155 (s), 1080 (m), 1040 (m), 1010 (m), 950 (m), 870 (w). $[\alpha]_D$ +1.5 (c=1.25, $CHCl_3$).

3.4. (R)-N,N-1,2-Benzenedisulfonyl-1-cyclohexylethylamine **2a** from (R)-1-cyclohexylethylamine **2**

Benzene-1,2-disulfonyl chloride (2.6 g, 9.5 mmol) was dissolved in methylene chloride (400 ml) and brought to reflux. A solution of *S*-(+)-1-phenylethylamine (**2**, 1.4 ml, 9.5 mmol) and triethylamine (2.6 ml, 19 mmol, 2.0 eq.) in methylene chloride (7.5 ml) was added continuously over 48 h. The reaction was allowed to reflux for at least another 2 h. The solvent was stripped off and the remaining solid material was extracted with hot cyclohexane (2×100 ml) and then continuous Soxhlet extraction with cyclohexane for 20 h. The combined extracts were stripped of solvent to yield 3.3 g of solid material. Repeated recrystallisation from hot cyclohexane (25–30 ml) afforded 1.2 g (38%) pure crystalline **2a**. M.p. 133.5–136°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (d, 3H), 0.9–2.2 (m, 11H), 4.0 (m, 1H), 7.89 (m, 2H), 7.98 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 18.1, 25.5, 25.8, 26.0, 30.4, 30.8, 41.4, 61.3, 121.8, 134.4, 135.7. MS [m/z (% rel. int.)]: 329 (M, 0.2%), 314 (0.3%), 246 (100%), 168 (11%), 110 (17%). IR (KBr, cm^{-1}): 3737 (w), 3101 (w), 2921 (s), 2850 (s), 1446 (m), 1384 (s), 1203 (m), 1161 (m), 1133 (m), 1045 (m), 899 (m), 870 (m), 760 (s), 728 (s), 589 (m), 560 (s). $[\alpha]_D$ −41 (c=1, $CHCl_3$).

3.4.1. N,N′-Bis((S)-1-cyclohexylethyl)-1,2-benzenedisulfonamide

M.p. 112–113°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (d, 6H), 0.8–1.7 (m, 22H), 3.22 (m, 2H), 6.07 (d, NH, 2H), 7.70 (m, 2H), 8.22 (m, 2H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 17.5, 26.0, 26.1, 26.3, 28.4, 28.6, 43.6, 55.3, 131.0, 132.7, 139.0. MS [m/z (% rel. int.)]: 456 (M, 0.06%), 455 (0.1%), 441 (0.8%), 373 (100%), 330 (13%), 263 (55%), 246 (15%), 220 (18%), 168 (9%), 111 (25%). IR (film, cm^{-1}): 3305

(s), 3285 (s), 2920 (s), 2850 (s), 1430 (s), 1345 (s), 1200 (s), 1180 (s), 1125 (m), 1110 (m), 1001 (m), 785 (m), 760 (m), 700 (s). $[\alpha]_D$ +49 (c=1, $CHCl_3$).

*3.5. Nucleophilic substitution reactions for the preparation of (*R*)-1-phenylethanol **3** and (*S*)-1-cyclohexylethanol **4***

The nucleophilic substitution reactions for the preparation of (*R*)-1-phenylethanol **3** from (*S*)-*N*,*N*-1,2-benzenedisulfonyl-1-phenylethylamine **1a** and (*S*)-1-cyclohexylethanol **4** from (*R*)-*N*,*N*-1,2-benzenedisulfonyl-1-cyclohexylethylamine **2a** were carried out using KNO_2/18-crown-6 mainly as described elsewhere.[4] Specific reaction conditions are listed in Table 1, including yields and the degree of inversion. The alcohol products **3** and **4** were characterized by ^{1}H NMR, MS and $[\alpha]_D$, giving data in accordance with data for these substances published previously.[3–5] The alcohol products **3** and **4** coeluted on GLC (both on unpolar methylsilicone and chiral cyclodextrin stationary phases) with the respective alcohols prepared previously and characterized elsewhere.[3–5] The % enantiomeric excesses for the alcohol products **3** and **4** were based on chiral GLC analysis; for chromatographic separation parameters and chromatographic conditions, see Table 2. For alcohol **3** a chiral ^{13}C NMR method using heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (tri-OMe-β-CD) as CSA confirmed the chiral GLC results; to a 70 mM NMR sample in CD_3OD was added 1–3 equivalents of tri-OMe-β-CD. ^{1}H NMR and ^{13}C NMR spectra were recorded at temperatures from +15°C to −50°C and the $\Delta(\Delta\delta)$ values ($\delta_R-\delta_R$) were measured. The $\delta_R-\delta_R$ value for the methine proton quartet in the ^{1}H NMR spectra was 0.005–0.016 ppm, while the respective data for ^{13}C NMR was 0.104–0.112 ppm, the values increasing with a decrease in temperature. For both reactions in DMF the formate ester byproduct could also be isolated by flash chromatography and characterized when the reaction work-up procedure did not include the alcalic treatment as described above. The % ee of the respective formates was 40–68 (identical to the alcohol product **3**) and 20–25 (compared with 80% ee for the alcohol **4**). The isolated formate esters could be hydrolysed (KOH/MeOH) to give the alcohols **3** and **4**. No formate byproduct was observed in the DMSO based reactions (added 30% DMF) at 0°C.

*3.5.1. (*R*)-1-Phenylethyl formate*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 (d, 3H), 6.1 (m, 1H), 7.2–7.4 (m, 5H), 8.1 (s, 1H). MS [m/z (% rel.int.)]: 150 (M, 25%), 120 (6%), 107 (11%), 105 (53%), 104 (100%), 103 (25%), 91 (5%), 77 (37%). IR (film, cm^{-1}): 2983 (w), 2932 (w), 1723 (s), 1173 (s), 761 (m), 699 (m).

*3.5.2. (*S*)-1-Cyclohexylethyl formate*

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.2 (d, 3H), 0.8–1.8 (m, 11H), 4.9 (m, 1H), 8.1 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 17.1, 25.9, 26.0, 26.3, 28.3, 28.4, 42.4, 74.7, 161.0. MS [m/z (% rel.int.)]: 156 (M, 1%), 155 (4%), 127 (8%), 126 (36%), 111 (16%), 109 (43%), 83 (35%), 81 (100%). IR (film, cm^{-1}): 2929 (s), 2855 (m), 1725 (s), 1189 (s).

*3.6. Nucleophilic substitution reactions for the preparation of (*R*)-1-phenylethylazide **5** and (*S*)-1-cyclohexylethylazide **6***

The nucleophilic substitution reactions for the preparation of (*R*)-1-phenylethylazide **5** from (*S*)-*N*,*N*-1,2-benzenedisulfonyl-1-phenylethylamine **1a** and (*S*)-1-cyclohexylethylazide **6** from (*R*)-*N*,*N*-1,2-benzenedisulfonyl-1-cyclohexylethylamine **2a** were carried out using NaN_3 mainly as described elsewhere.[1,2] Specific reaction conditions are listed in Table 1, including yields and the degree of

inversion. The azide products **5** and **6** were characterized by ^{1}H and ^{13}C NMR, MS and IR giving data in accordance with data for these substances published previously.[3–5] Chiral analysis of the azide product **5** could be carried out directly on the chiral cyclodextrin GLC column, see Table 2. The azide product **6** was reduced by hydrogenolysis to the respective amine **2** and chiral analysis was carried out indirectly on an unpolar methylsilicone stationary phase after derivatization with (*S*)-α-methoxyphenylacetyl chloride as described elsewhere.[1–3] The yields and % enantiomeric excess for the azide products **5** and **6** are given in Table 1.

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