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Stereoselective substitution of (*R*)-2-(sulfonyloxy)nitriles with sulfur nucleophiles[1]

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Abstract

Optically active 2-(4-toluenesulfonyloxy)- and (4-nitrobenzenesulfonyloxy)nitriles (*R*)-**3** and (*R*)-**4**, which were obtained from (*R*)-cyanohydrins (*R*)-**2** by sulfonylation, react with sulfur nucleophiles such as potassium thioacetate, potassium ethylxanthogenate, potassium thiocyanate, as well as thioalcohols and thiophenol in a typical S_N2 manner to give the (*S*)-2-sulfanyl nitriles (*S*)-**7**–**9** and (*S*)-**11**–**13** in good chemical yields and enantiomeric excesses. Even (*R*)-2-methyl-2-(methanesulfonyloxy)hexanenitrile (*R*)-**6**, derived from ketone cyanohydrin (*R*)-**5**, reacts with potassium thioacetate to yield (*S*)-2-acetylthio-2-methylhexanenitrile (*S*)-**10** with 97% *ee*.

1. Introduction

Nucleophilic substitutions of activated α-hydroxycarboxylic acids and esters with O-, N- and S-nucleophiles are well established,[2] but little is known about analogous reactions of cyanohydrins.[3] Optically active 2-(sulfonyloxy)nitriles, easily accessible from the corresponding chiral cyanohydrins by sulfonylation,[4] have a high configurational stability and can therefore be applied as activated cyanohydrins for stereoselective reactions with nucleophiles. With potassium acetate, for example, sulfonylated cyanohydrins, derived from aliphatic aldehydes, react under very mild conditions (room temperature, DMF as solvent) with complete inversion of configuration to yield the corresponding substitution products.[4] Besides reactions with O-nucleophiles, (*R*)-2-(sulfonyloxy)nitriles have also been reacted with various N-nucleophiles such as potassium azide, potassium phthalimide, and amines to give the corresponding substitution products with (*S*)-configuration.[5]

In the present publication we describe substitution reactions of (*R*)-2-(sulfonyloxy)nitriles with various sulfur nucleophiles, especially with respect to the stereochemical outcome of the reactions.

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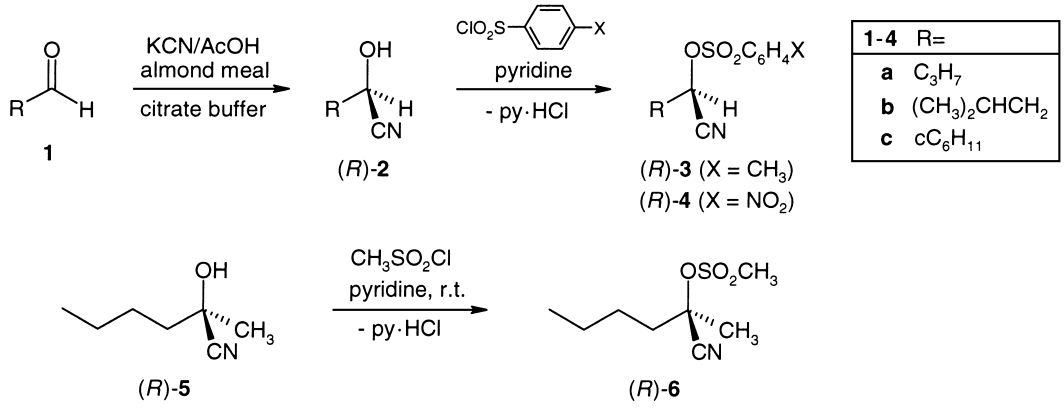
2. Preparation of optically active 2-(sulfonyloxy)nitriles (*R*)-4 and (*R*)-6

While optically active 2-(4-toluenesulfonyloxy)nitriles (*R*)-**3** are known,[4] 2-(4-nitrobenzenesulfonyloxy) nitriles (*R*)-**4** have not been described so far. The starting cyanohydrins (*R*)-**2** were prepared by (*R*)-hydroxynitrile lyase (PaHNL) catalyzed addition of HCN to aldehydes **1** using a slightly modified method developed by Brussee[6] with almond meal as enzyme source. HCN was generated in situ from KCN with acetic acid. Analogously, the ketone cyanohydrin (*R*)-**5** was obtained from butyl methyl ketone. Based on the published procedure[4,7] aldehyde cyanohydrins (*R*)-**2** were reacted with 4-nitrobenzenesulfonyl chloride in the presence of pyridine as a base to yield the corresponding sulfonyloxynitriles (*R*)-**4** (Scheme 1, Table 1).



Scheme 1.

2-(4-Nitrobenzenesulfonyloxy)nitriles (*R*)-**4**, which are solid at room temperature, can be recrystallized for improving enantiomeric excesses.

In contrast to aldehyde cyanohydrins (*R*)-**2** ketone cyanohydrin (*R*)-**5** (98% *ee*) did not react with toluene- and nitrobenzenesulfonyl chloride, respectively. Only the reaction with methanesulfonyl chloride in pyridine was successful (Scheme 1). After chromatographic purification, mesyl-activated (*R*)-**6** was isolated in 79% yield. Whereas the determination of *ee*-values of sulfonyloxynitriles (*R*)-**4** requires a follow-up reaction (see Table 1), the enantiomeric excess of (*R*)-**6** could be determined directly by gas chromatography to be 98% ($[\alpha]_D^{20}$=+18.9 (*c* 1.0, CH_2Cl_2)). This result indicates that mesylation also proceeds without racemization.

Table 1
2-(4-Nitrobenzenesulfonyloxy)nitriles (*R*)-**4** by reaction of cyanohydrins (*R*)-**2** with 4-nitrobenzenesulfonyl chloride in the presence of pyridine

Cyanohydrins		R.-time	2-(4-Nitrobenzenesulfonyloxy)nitriles			
(*R*)-**2**	*ee* (%)	(h)	(*R*)-**4**	Yield (%)	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)	*ee* (%)[a]
a	(97)	14	**a**	63	+34.7 (1.0)	97
b	(95)	14	**b**	68	+34.7 (1.0)	94
c	(92)	14	**c**	71	+26.8 (1.0)	92

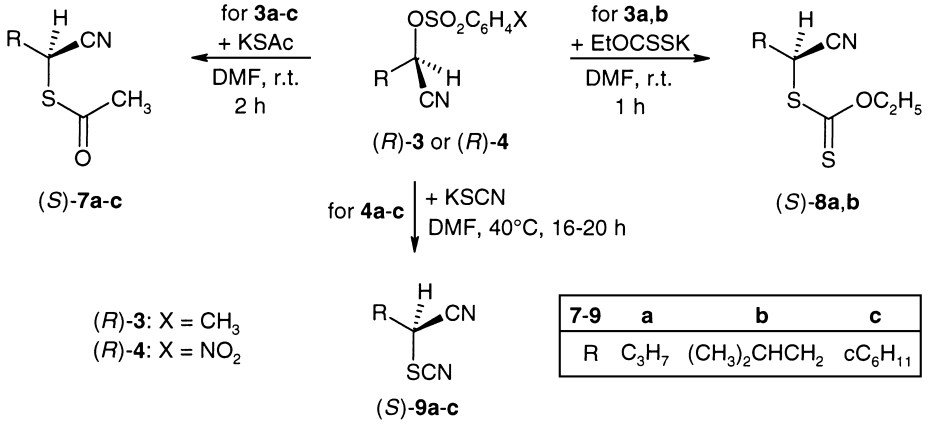
[a] Determined by gas chromatography on a Chiraldex B-TA phase after reaction with potassium thioacetate to 2-acetylthionitriles.

3. Reactions of 2-(sulfonyloxy)nitriles (*R*)-3, (*R*)-4 and (*R*)-6 with various sulfur nucleophiles

Many sulfur nucleophiles are known to react in a typical S_N2 manner with alkylhalides or sulfonates to give the corresponding thio-derivatives.[8] With respect to possible follow-up reactions we have first investigated conversions of the tosyl-activated racemic cyanohydrin (*RS*)-**3a** with various S-nucleophiles under S_N2 reaction conditions.[8a] All attempts failed to react thiourea, hydrogensulfide, sulfite, and thiosulfate with **3a** under reasonable reaction conditions. Thioacetate, xanthogenate, thiocyanate, and some thiols, however, were found to undergo very easily reactions with 2-(sulfonyloxy)nitriles **3** and **4**, respectively.

3.1. Reactions with thioacetate, ethylxanthogenate and thiocyanate

In Scheme 2 the performed nucleophilic substitution reactions of sulfonyl-activated (*R*)-cyanohydrins **3** and **4**, respectively, with sulfur nucleophiles are summarized.



Scheme 2.

Reactions of optically active 2-(sulfonyloxy)nitriles with potassium acetate yielding cyanohydrin acetates with complete inversion of configuration have been investigated intensively.[4] The higher nucleophilicity of thioacetate in comparison to acetate, which is easy to handle[9] and readily soluble in an organic solvent such as DMF, should make S_N reactions possible under mild conditions. Indeed, the reaction conditions used earlier[4b] could be applied successfully to the reactions of 2-(sulfonyloxy)nitriles (*RS*)-**3** and (*R*)-**3**, respectively, with potassium thioacetate (KSAc) (Scheme 2). Due to good solubility of KSAc in DMF, addition of crown ether is not necessary. The conversion was complete after 2 h at room temperature in all cases, and the desired (*S*)-2-acetylthionitriles (*S*)-**7a**–**c** were obtained after chromatographic purification in good chemical yields and high enantiomeric excesses (Table 2). A comparison of the enantiomeric excesses of starting compounds (*R*)-**3** and products (*S*)-**7** shows that the reaction proceeds almost without racemization (Table 2) under complete inversion of configuration as could be proved by follow-up reaction of (*S*)-**7**.[10]

Because of their good solubility in polar aprotic solvents and their high nucleophilicity xanthogenates are excellent sulfur nucleophiles. As expected, the reaction of (*R*)-**3a**,**b** with potassium ethylxanthogenate in DMF as solvent was already completed after 1 h yielding the corresponding (*S*)-2-ethylxanthogennitriles (*S*)-**8a**,**b**, but with at least 20% racemization (Table 2). Their purification was

Table 2
(*S*)-2-Acetylthio- and 2-ethylxanthogennitriles (*S*)-**7** and (*S*)-**8** by reaction of (*R*)-2-(4-toluenesulfonyloxy)nitriles (*R*)-**3** with potassium thioacetate and potassium ethylxanthogenate, respectively

Sulfonyloxynitriles		2-Acetylthionitriles **7**				2-Ethylxanthogennitriles **8**		
3	*ee* (%)		Yield (%)	*ee* (%)[a]	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)		Yield (%)	*ee* (%)[a]
(*RS*)-**3a**	–	(*RS*)-**7a**	86	–	–	(*RS*)-**8a**	60	–
(*R*)-**3a**	97 / 95	(*S*)-**7a**	82	97	not determined	(*S*)-**8a**	66	37
(*RS*)-**3b**	–	(*RS*)-**7b**	76	–	–	(*RS*)-**8b**	84	–
(*R*)-**3b**	95 / 92	(*S*)-**7b**	82	94	-96.0 (1.2)	(*S*)-**8b**	69	72
(*RS*)-**3c**	–	(*RS*)-**7c**	55	–	–			
(*R*)-**3c**	92	(*S*)-**7c**	77	91	-50.2 (1.0)			

[a] *ee*-Values determined directly by gas chromatography on a Chiraldex B-TA phase.

difficult and resulted in chemical yields between 66–70% only (Table 2). Due to low thermal stability, xanthogennitriles **8** are not distillable. After chromatography on silica gel compounds **8** contain traces of impurities (GC purity 97%) and decompose at room temperature. The chromatography of small amounts finally afforded pure 2-ethylxanthogennitriles **8** (GC purity >99%) which could be stored at low temperature.

The nucleophilicity of thiocyanate is lower than that of thioacetate under comparable conditions. Consequently, the tosyl-activated cyanohydrin (*R*)-**3a** reacts with potassium thiocyanate (KSCN) in DMF only at temperatures above 60°C. The racemization observed thereby can be explained by an exchange of thiocyanate, which, as pseudohalide, represents both a good leaving group and a relatively good nucleophile. At lower temperatures racemization could be suppressed but the conversion was unsatisfactory.

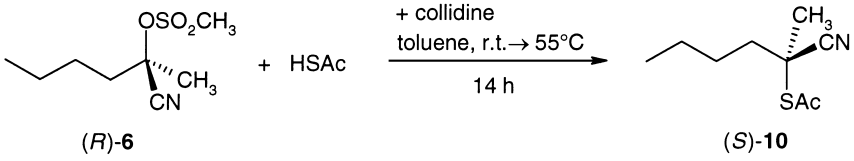
(*R*)-2-(4-Nitrobenzenesulfonyloxy)nitriles (*R*)-**4**, which are more reactive than (*R*)-2-(4-toluenesulfonyloxy)nitriles (*R*)-**3** were therefore applied. The reaction of (*R*)-**4** with KSCN in DMF at 40°C provided the corresponding (*S*)-2-thiocyanatonitriles (*S*)-**9** after chromatography on silica gel in good chemical yields and enantiomeric excesses (Scheme 2, Table 3). Table 3 shows that the reactions proceed almost with complete inversion. A reaction with DMF as nucleophile, as previously described for S_N2 reactions of sulfonyloxynitriles with acetate,[4b] was not observed.

Table 3
(*S*)-2-Thiocyanatonitriles (*S*)-**9** by reaction of (*R*)-2-(4-nitrobenzenesulfonyloxy)nitriles (*R*)-**4** with potassium thiocyanate

Sulfonyloxynitriles		R.-time	(*S*)-2-Thiocyanatonitriles (*S*)-**9**			
(*R*)-**4**	*ee* (%)	(h)		Yield (%)	*ee* (%)[a]	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)
4a	97	20	**9a**	72	94	-34.3 (1.0)
4b	94	20	**9b**	62	91	-33.0 (1.0)
4c	93	16	**9c**	52	- [b]	-20.6 (1.2)

[a] Directly determined by gas chromatography on a Chiraldex B-TA phase. [b] Compound **9c** could not be detected on the used phase.

The reaction of (*R*)-2-methyl-2-(methanesulfonyloxy)hexanenitrile (*R*)-**6**, a ketone cyanohydrin derivative, with thioacetate as nucleophile has also been investigated, as outlined in Scheme 3.

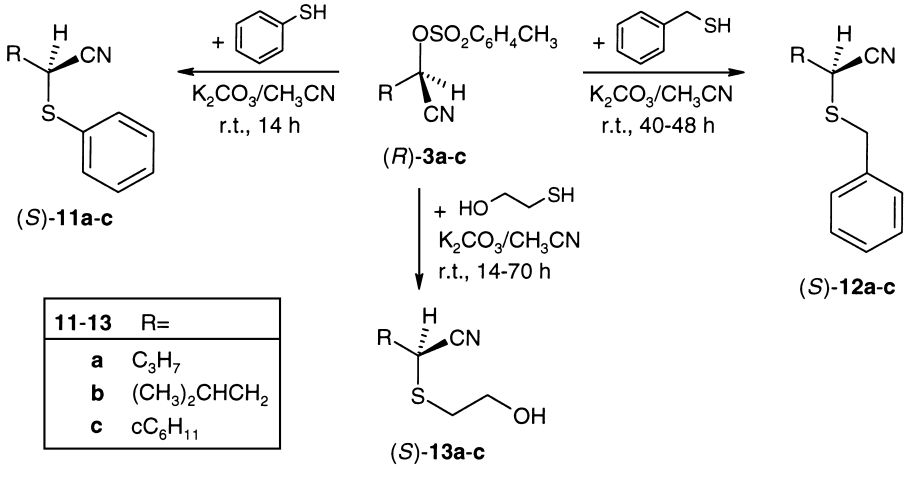


Scheme 3.

Owing to the more bulky methyl group compared to hydrogen and the mesyl group with a lower leaving ability in comparison to the tosyl moiety, (*R*)-**6** should be less reactive than compounds (*R*)-**3** in S_N2 reactions. The conversion of (*RS*)-**6** with potassium thioacetate in DMF was, as expected, very slow, and after 72 h only 35% of the product (*RS*)-**10** was obtained. The reaction was accompanied by side-reactions, resulting in numerous by-products which were not characterized. Comparable results were achieved replacing DMF by toluene as solvent in the presence of crown ether. Thereby the formation of by-products increased at temperatures above 50°C. Satisfying results were obtained, however, by using thioacetic acid and collidine as nucleophilic reagent (Scheme 3). After a reaction time of 14 h at 55°C, (*R*)-**6** (97% *ee*) was converted without racemization to (*S*)-2-acetylthio-2-methylhexanenitrile (*S*)-**10** (97% *ee*, $[\alpha]_D^{20}=-42.5$ (*c* 1.0, CH_2Cl_2)) in 84% yield.

3.2. Reactions with thioalcohols and thiophenol

Scheme 4 illustrates substitution reactions of (*R*)-2-(4-toluenesulfonyloxy)nitriles (*R*)-**3** with thioalcohols and thiophenol.



Scheme 4.

Optically active sulfonylated α-hydroxycarboxylic acid esters are known to undergo nucleophilic substitution reactions with thiophenolate.[2a,11] The published reaction conditions[2a,11] could be applied to the reaction of tosylated cyanohydrins (*R*)-**3** with thiophenol as nucleophile (Scheme 4). The reaction was performed inversely, in which (*R*)-**3** was added to a small excess of thiophenol in a suspension of potassium carbonate/acetonitrile at 0°C. After 14 h reaction time at room temperature, the corresponding (*S*)-2-phenylthionitriles (*S*)-**11** could be isolated in good chemical yields (Table 4). Complete exclusion of oxygen during the reaction is not necessary.

All attempts have failed so far to separate the enantiomers of **11** by gas chromatography. The specific rotations, however, are reproducible, indicating a reaction without racemization.

Table 4
(*S*)-2-Phenyl- and benzylthionitriles (*S*)-**11** and (*S*)-**12** by reaction of tosyloxynitriles (*R*)-**3** with thiophenol and benzyl thiol, respectively

	R.-time	(*S*)-2-Phenylthionitriles (*S*)-**11**			R.-time	(*S*)-2-Benzylthionitriles (*S*)-**12**		
(*R*)-**3**	(h)		Yield (%)	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)[a]	(h)		Yield (%)	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)[a]
3a	14	**11a**	90	-110.3 (1.0)	40	**12a**	86	-260.0 (1.0)
3b	14	**11b**	70	-94.2 (1.0)	40	**12b**	69	-217.7 (1.0)
3c	14	**11c**	70	-96.3 (1.0)	48[b]	**12c**	70	-148.3 (1.0)

[a] A gas chromatographic separation of the enantiomers failed so far. [b] Additionally heating at 40°C for 2 h.

Under the optimized reaction conditions (*R*)-**3** reacted with benzyl thiol to give (*S*)-2-benzylthionitriles (*S*)-**12** (Scheme 4, Table 4). Table 4 shows that the yields of (*S*)-**12** are comparable with those of (*S*)-**11**. The reaction times, however, differ markedly. With benzyl thiol, reaction times of ≥40 h are required compared with 14 h using thiophenol. This result is in agreement with experimental data published for reactions of activated α-hydroxycarboxylic acid esters.[2a,11] Possibly, in the heterogeneous system K_2CO_3/acetonitrile, the concentration of deprotonated thiophenol could be higher than that of benzyl thiolate, resulting in an increased total reaction rate. The separation of the enantiomers of **12** by gas chromatography has also failed so far. Follow-up reactions of (*S*)-**12** to (*S*)-5-alkyl-2-thiazolidinones[10] confirm that the substitution of (*R*)-**3** proceeded with complete inversion.

2-Mercaptoethanol has been chosen as sulfur nucleophile since it allows the introduction of an additional functional group. Also 2-mercaptoethanol as primary aliphatic thiol reacts easily under the optimized reaction conditions with (*R*)-**3** to yield (*S*)-2-(2-hydroxyethylthio)nitriles (*S*)-**13** (Scheme 4, Table 5).

Table 5
(*S*)-2-(2-Hydroxyethylthio)nitriles (*S*)-**13** by reaction of (*R*)-**3** with 2-mercaptoethanol

(*R*)-**3**	R.-time (h)	(*S*)-2-(2-Hydroxyethylthio)nitriles (*S*)-**13**	Yield (%)	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)
3a	14[a]	**13a**	88	-66.5 (1.33)
3b	30	**13b**	78	-68.2 (1.0)
3c	70	**13c**	72	-59.3 (1.0)

[a] Additionally heating at 40°C for 3 h.

A reaction of the hydroxy group is very unlikely since both nucleophilicity and acidity of the alcohol group is lower than that of the thiol function. Indeed, only substitution by the thiolate function has been found yielding nitriles **13**. As can be seen from Table 5, the substitution products (*S*)-**13** were obtained in good yields. Owing to the results obtained for 2-phenylthio- and 2-benzylthionitriles (*S*)-**11** and (*S*)-**12**, a substitution reaction with complete inversion of configuration is assumed also in the case of the reaction of mercaptoethanol.

4. Experimental

4.1. Materials and methods

Racemic cyanohydrins were prepared according to a known procedure,[12] racemic 2-(toluenesulfonyloxy)nitriles (*RS*)-**3** are described in the literature.[13] Melting points were determined on a Büchi SMP-20

and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) with TMS as an internal standard. Column chromatography was performed with glass columns of different sizes packed with silica gel S (Riedel–de Haen) or silica gel 60 (Merck), grain size 0.032–0.063 mm. Optical rotations were determined on a Perkin–Elmer polarimeter 241 LC. GC for determination of enantiomeric excess: Hewlett–Packard 6890 Series with FID, 0.9 bar hydrogen, column 30 m×0.32 mm, phase Chiraldex B-TA (ICT).

4.2. Preparation of (R)-cyanohydrins **2** and **5**; general procedure

Defatted almond meal (100 mg/mmol substrate) was soaked in 0.1 mL citrate buffer (20 mM, pH 4.0) for 15 min. A 2 M solution of aldehyde or ketone in *tert*-butyl methyl ether was added, and the reaction mixture was cooled to 0°C. Then a ca. 1 M solution of HCN in *tert*-butyl methyl ether was added portionwise to the vigorously stirred reaction mixture. After being stirred for a further 5 h (aldehydes) or 60 h (ketone), almond meal was filtered off, and the filtrate was dried ($MgSO_4$), and concentrated. The residue was distilled in vacuo.

HCN was generated from KCN as follows: a solution of KCN (2 equiv. with respect to substrate) in water was cooled to 0°C and overlaid with *tert*-butyl methyl ether. After addition of an equimolar amount of glacial acetic acid (with respect to KCN), the aqueous phase was extracted with the *tert*-butyl methyl ether layer to yield a ca. 1 M HCN solution.

4.3. Preparation of 2-(4-nitrobenzenesulfonyloxy)nitriles (R)-**4**; general procedure

To a stirred 1 M solution of (*R*)-**2** and pyridine in dichloromethane at −10°C a solution of 4-nitrobenzenesulfonyl chloride in dichloromethane (0.4 M) was added dropwise within 1 h, and the reaction mixture was allowed to warm to room temperature (14 h). Dichloromethane was removed in vacuo, and the residue was taken up in diethyl ether. After being stirred for 1 h, precipitated pyridinium hydrochloride was filtered off. The filtrate was concentrated, and the residue was chromatographed on silica gel with petroleum ether/ethyl acetate.

4.4. Preparation of 2-methyl-2-(methanesulfonyloxy)hexanenitrile (R)-**6**

To a solution of (*R*)-**5** (3.2 g, 25.3 mmol) in pyridine (50 mL) at 0°C methanesulfonyl chloride (3.3 g, 29 mmol) was added dropwise. After being stirred for 18 h, the reaction mixture was poured onto ice and extracted with diethyl ether. The combined extracts were washed with 10% HCl, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate to give 4.1 g (79%) of (*R*)-**6**; 98% *ee*, $[\alpha]_D^{20}$=+18.9 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.96 (t, *J*=7.3 Hz, 3H, CH_3CH_2), 1.37–1.44 (m, 2H, CH_3CH_2), 1.51–1.67 (m, 2H, $CH_2CH_2CH_2$), 1.92 (s, 3H, CH_3), 1.94–2.11 (m, 2H, CCH_2), 3.18 (s, 3H, SO_2CH_3). Anal. calcd for $C_8H_{15}NO_3S$ (205.3): C, 46.81; H, 7.37; N, 6.82; S, 15.62. Found: C, 46.86; H, 7.36; N, 6.78; S, 15.38.

*^{1}H NMR data and elemental analyses of (R)-sulfonyloxynitriles **4***

Compd	^{1}H NMR ($CDCl_3$, δ)
(*R*)-**4a**	1.00 (t, *J* = 7.4 Hz, 3H, CH_3), 1.49-1.61 (m, 2H, CH_2CH_3), 1.90-2.04 (m, 2H, CH_2CH), 5.18 (t, *J* = 6.7 Hz, 1H, CH), 8.15-8.20 (m, 2H, Ph), 8.43-8.48 (m, 2H, Ph)
(*R*)-**4b**	0.98 (t, *J* = 5.9 Hz, 6H, CH_3), 1.79-2.00 (m, 3H, CH_2CH), 5.18-5.22 (dd, *J* = 6.1 Hz, 1H, CH), 8.17-8.19 (m, 2H, Ph), 8.45-8.47 (m, 2H, Ph)
(*R*)-**4c**	1.10-1.97 (m, 11H, C_6H_{11}), 4.98 (d, *J* = 6.2 Hz, 1H, CH), 8.16-8.20 (m, 2H, Ph), 8.44-8.48 (m, 2H, Ph)
	Elemental analysis: mol. formula (mol weight), calculated (found)
(*R*)-**4a**	$C_{11}H_{12}N_2O_5S$ (284.3): C, 46.47 (46.50); H, 4.25 (4.29); N, 9.85 (9.86); S, 11.28 (11.42)
(*R*)-**4b**	$C_{12}H_{14}N_2O_5S$ (298.3): C, 48.32 (48.32); H, 4.73 (4.74); N, 9.39 (9.45); S, 10.75 (10.50)
(*R*)-**4c**	$C_{14}H_{16}N_2O_5S$ (324.4): C, 51.84 (51.88); H, 4.97 (5.00); N, 8.64 (8.59); S, 9.88 (9.90)

*4.5. (S)-2-Acetylthionitriles (S)-**7** and (S)-2-ethylxanthogennitriles (S)-**8** by reaction of (R)-**3** with potassium thioacetate and potassium ethylxanthogenate, respectively; general procedure*

To a solution of (*R*)-**3** in DMF (0.1–0.5 M) at room temperature a solution of KSAc or EtOCSSK (1.0–1.5 equiv.) in DMF was slowly added dropwise. After being stirred for 2 h (for **7**) or 1 h (for **8**), the reaction mixture was hydrolyzed with ice-water, and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and concentrated. The residue was either distilled in vacuo ((*RS*)-**7**) or chromatographed on silica gel with petroleum ether/ethyl acetate ((*S*)-**7** and (*S*)-**8**).

*4.6. (S)-2-Thiocyanatonitriles (S)-**9** by reaction of (R)-**4** with potassium thiocyanate; general procedure*

To a solution of (*R*)-**4** in DMF (5 M) at room temperature a solution of KSCN (1.0–1.4 equiv.) in DMF (ca. 0.05 M) was added dropwise. After being stirred for 16–20 h at 40°C, the reaction mixture was hydrolyzed with ice-water, and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate.

*4.7. Preparation of (S)-2-acetylthio-2-methylhexanenitrile (S)-**10***

To a solution of (*R*)-**6** (1.0 g, 4.87 mmol) and collidine (1 mL) in toluene (15 mL) at room temperature a solution of thioacetic acid (1 mL) in toluene (10 mL) was added dropwise. After being stirred for 14 h at 55°C, the reaction mixture was hydrolyzed with ice-water, and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate to give 762 mg (84%) (*S*)-**10**; 97% *ee*, $[\alpha]_D^{20}$=−42.5 (*c* 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.94 (t, *J*=7.3 Hz, 3H, CH_2CH_3), 1.34–1.43 (m, 2H, CH_2CH_3), 1.50–1.57 (m, 2H, $CH_2CH_2CH_2$), 1.75 (s, 3H, CH_3), 1.79–1.98 (m, 2H, CCH_2), 2.35 (s, 3H, $COCH_3$). $C_9H_{15}NOS$ (185.3): calcd for MH^+ 186.09526. Found: 186.09460. GC–MS (CI, 100 eV) *m/z* (%): 186 (12) [MH^+], 142 (7) [$C_7H_{12}NS^+$], 43 (100) [$C_2H_3O^+$].

*Physical and spectroscopic data as well as elemental analyses of (S)-**7**-**9***

	bp (°C/Torr)	^{1}H NMR (250 MHz, $CDCl_3$, δ)
7a	64/0.01	0.98 (t, *J* = 7.3 Hz, 3H, CH_3), 1.49-1.64 (m, 2H, CH_2CH_3), 1.76-1.92 (m, 2H, CH_2CH), 2.41 (s, 3H, $COCH_3$), 4.26-4.32 (dd, *J* = 7.7 Hz, 1H, CH)
7b	60/0.001	0.97, 1.00 (each d, *J* = 6.0 Hz, 3H, CH_3), 1.59-1.64 (m, 1H, $(CH_3)_2CH$), 1.83-1.91 (m, 2H, CH_2), 2.41 (s, 3H, $COCH_3$), 4.28-4.31 (m, 1H, CH)
7c	75/0.001	1.14-1.30, 1.61-1.90 (2 m, 11H, C_6H_{11}), 2.41 (s, 3H, CH_3), 4.26 (d, *J* = 5.6 Hz, 1H, CH)
8a	-	1.00 (t, *J* = 7.3 Hz, 3H, CH_3), 1.46 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.54-1.72 (m, 2H, CH_2CH_3), 1.82-2.00 (m, 2H, CH_2CH), 4.44 (t, *J* = 7.3 Hz, 1H, CH), 4.70 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3)
8b	-	0.99, 1.01 (each d, *J* = 6.3 Hz, 3H, CH_3), 1.47 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.64-2.03 (m, 3H, $(CH_3)_2CH$, CH_2CH), 4.42-4.49 (dd, 1H, CH), 4.70 (q, *J* = 7.1 Hz, 2H, CH_2CH_3)
9a	64/0.05	1.04 (t, *J* = 7.3 Hz, 3H, CH_3), 1.57-1.72 (m, 2H, CH_2CH_3), 1.94-2.17 (m, 2H, CH_2CH), 3.09-3.96 (dd, 1H, CH)
9b	61/0.001	1.02, 1.03 (each d, *J* = 6.7 Hz, 3H, CH_3), 1.83-2.09 (m, 3H, $(CH_3)_2CH$, CH_2CH), 3.90-3.93 (dd, 1H, CH)
9c	100/0.005	1.10-1.41, 1.71-2.04 (2 m, 11H, C_6H_{11}), 3.85 (d, *J* = 6.5 Hz, 1H, CH)

	Mol. formula (Mol. weight)	Calculated/found C	H	N	S		Mol. formula (Mol. weight)	Calculated/found C	H	N	S
7a	$C_7H_{11}NOS$	53.47	7.05	8.91	20.39	**8b**	$C_9H_{15}NOS_2$	49.74	6.96	6.44	29.50
	(157.2)	53.48	7.25	9.03	20.50		(217.3)	49.94	7.08	6.44	28.77
7b	$C_8H_{13}NOS$	56.11	7.65	8.18	18.72	**9a**	$C_6H_8N_2S$	51.40	5.75	19.98	22.87
	(171.3)	56.11	7.75	8.19	18.77		(140.2)	51.38	5.89	19.74	22.64
7c	$C_{10}H_{15}NOS$	60.88	7.66	7.10	16.25	**9b**	$C_7H_{10}N_2S$	54.51	6.54	18.16	20.79
	(197.3)	60.98	7.68	7.18	16.23		(154.2)	54.62	6.57	18.39	20.70
8a	$C_8H_{13}NOS_2$	47.26	6.44	6.89	31.54	**9c**	$C_9H_{12}N_2S$	59.97	6.71	15.54	17.78
	(203.3)	47.38	6.49	6.82	31.31		(180.3)	60.03	6.75	15.43	17.72

4.8. Determination of enantiomeric excesses

(i) The enantiomeric excesses of **7**, **8**, **9**, **11** and **12** were determined directly without further reaction (see Tables 2 and 3).

(ii) A solution of **3** or **4** (10 mg) and potassium thioacetate (10 mg) in DMF (100 μL) was reacted for 1 h at room temperature. Water (2 mL) was added, and the reaction mixture extracted with diethyl ether (2 mL). The extract was either dried ($MgSO_4$) or directly used for the determination of enantiomeric excesses.

*4.9. (S)-2-Phenylthio-, (S)-2-benzylthio- and (S)-2-(2-hydroxyethylthio)nitriles (S)-**11**, **12** and **13** by reaction of (R)-**3** with thiophenol, benzyl thiol and 2-mercaptoethanol, respectively; general procedure*

To a suspension of thiophenol, benzyl thiol or 2-mercaptoethanol (1.1 equiv.) and K_2CO_3 (2 equiv.) in acetonitrile at 0°C a solution of (*R*)-**3** (1 equiv.) in acetonitrile (0.4 M) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for the times given in Tables 4 and 5. Then it was hydrolyzed with ice-water and extracted with diethyl ether. The combined extracts, which contain

water because of acetonitrile, were concentrated in vacuo until phase separation. Diethyl ether was added, and the aqueous phase was separated. The organic phase was dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate.

*Physical and spectroscopic data as well as elemental analyses of (S)-**11-13***

	bp (°C/Torr)	^{1}H NMR (250 MHz, $CDCl_3$, δ)
11a	-	0.97 (t, J = 7.3 Hz, 3H, CH_3), 1.53-1.68 (m, 2H, CH_2CH_3), 1.77-1.89 (m, 2H, CH_2CH), 3.69 (t, J = 7.4 Hz, 1H, CH), 7.36-7.43 (m, 3H, Ph), 7.57-7.65 (m, 2H, Ph)
11b	-	0.96, 0.97 (each d, J = 6.6 Hz, 3H, CH_3), 1.58-2.03 (m, 3H, CH_2CH), 3.68-3.74 (dd, 1H, CH), 7.37-7.44 (m, 3H, Ph), 7.58-7.66 (m, 2H, Ph)
11c	-	1.14-2.04 (m, 11H, C_6H_{11}), 3.57 (d, J = 6.4 Hz, 1H, CH), 7.34-7.43 (m, 3H, Ph), 7.51-7.62 (m, 2H, Ph)
12a	86/0.001	0.89 (t, J = 7.3 Hz, 3H, CH_3), 1.42-1.87 (m, 4H, CH_2CH_3, CH_2CH), 3.25-3.31 (dd, 1H, CH), 3.94 (d, J = 2.3 Hz, 2H, $PhCH_2$), 7.26-7.37 (m, 5H, Ph)
12b	95/0.05	0.84, 0.86 (each d, J = 6.4 Hz, 3H, CH_3), 1.51-1.98 (m, 3H, CH_2CH), 3.26-3.32 (dd, 1H, CH), 3.95 (d, J = 2.5 Hz, 2H, $PhCH_2$), 7.24-7.37 (m, 5H, Ph)
12c	41-43 (mp)	1.09-1.99 (m, 11H, C_6H_{11}), 3.51 (d, J = 6.6 Hz, 1H, CH), 3.92 (s, 2H, $PhCH_2$), 7.29-7.37 (m, 5H, Ph)
13a	84/0.001	0.98 (t, J = 7.2 Hz, 3H, CH_3), 1.48-1.95 (m, 4H, CH_2CH_3, CH_2CH), 2.10 (t, J = 5.6 Hz, 1H, OH), 2.84-3.08 (m, 2H, SCH_2), 3.66-3.72 (dd, 1H, CH), 3.91 (q, J = 5.7 Hz, 2H, CH_2OH)
13b	-	0.97, 0.98 (each d, J = 6.5 Hz, 3H, CH_3), 1.56-1.98 (m, 3H, CH_2CH), 2.33 (t, J = 5.1 Hz, 1H, OH), 2.76-3.08 (m, 2H, SCH_2), 3.69-3.75 (dd, 1H, CH), 3.89 (q, J = 5.1 Hz, 2H, CH_2OH)
13c	-	1.14-1.34 (m, 5H, C_6H_{11}), 1.68-2.14 (m, 6H, C_6H_{11}), 2.83-3.02 (m, 2H, SCH_2), 3.55 (d, 1H, CH), 3.87 (q, J = 5.8 Hz, 2H, CH_2OH)

	Mol. formula (Mol. weight)	Calculated/found C	H	N	S		Mol. formula (Mol. weight)	Calculated/found C	H	N	S
11a	$C_{11}H_{13}NS$	69.07	6.85	7.32	16.76	**12c**	$C_{15}H_{19}NS$	73.42	7.80	5.71	13.07
	(191.3)	68.92	6.92	7.25	16.59		(245.4)	73.51	7.79	5.65	12.99
11b	$C_{12}H_{15}NS$	70.20	7.36	6.82	15.61	**13a**	$C_7H_{13}NOS$	52.79	8.23	8.79	20.13
	(205.3)	70.04	7.32	6.90	15.70		(159.3)	52.60	8.35	8.52	20.08
11c	$C_{14}H_{17}NS$	72.68	7.41	6.05	13.86	**13b**	$C_8H_{15}NOS$	55.45	8.73	8.08	18.50
	(231.4)	72.65	7.48	6.03	13.81		(173.3)	55.40	8.73	7.78	18.55
12a	$C_{12}H_{15}NS$	70.20	7.36	6.82	15.61	**13c**	$C_{10}H_{17}NOS$	60.26	8.60	7.03	16.09
	(205.3)	70.38	7.47	6.71	15.50		(199.3)	59.97	8.79	6.96	16.13
12b	$C_{13}H_{17}NS$	71.19	7.81	6.39	14.61						
	(219.3)	71.07	7.82	6.24	14.59						

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